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Preparation of phenolic chiral crown ethers and podands and their enantiomer recognition ability toward secondary amines

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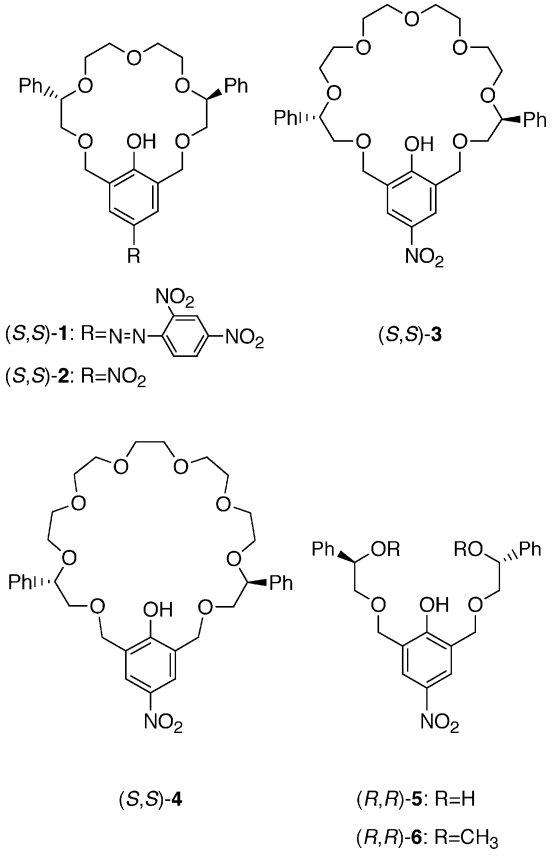
This paper is dedicated to Emeritus Professor Soichi Misumi for his 77th birthday

Abstract—Phenolic pseudo-24-crown-8 (*S*,*S*)-**3**, pseudo-27-crown-9 (*S*,*S*)-**4**, and podands (*R*,*R*)-**5** and (*R*,*R*)-**6** possessing phenyl groups as chiral barriers were prepared and their chiral recognition properties toward secondary neutral amines were examined. Pseudo-24-crown-8 (*S*,*S*)-**3** and podand (*R*,*R*)-**5** showed sufficient binding ability and moderate chiral recognition ability toward secondary amines.

1. Introduction

Enantiomeric recognition of amines and ammonium salts compounds is a topic of considerable significance since these compounds are basic building blocks of biological molecules and a number of them are known to possess potent biological activities which are different from their antipodes.[1] Among the numerous types of host molecules studied, chiral 18-crown-6 derivatives have been recognized as the most successful for chiral discrimination of primary amine-containing compounds. The mechanism of chiral discrimination and molecular design of new chiral 18-crown-6 and their analogs toward chiral primary amine compounds have been well documented. In contrast, little has been reported on chiral recognition of secondary amines despite their synthetic and biological importance. Indeed, there exist many biologically active chiral secondary amines,[2] as exemplified by the well known propranolol, ephedrine, and salbutamol and it has been reported that their activity is frequently different from the corresponding enantiomers.[3] To the best of our knowledge, there are only two reports regarding chiral recognition of secondary amine derivatives, one with chiral binaphthyl derivatives[4a] and the other with a liquid chromatography stationary phase based on a chiral 18-crown-6.[4b] Accordingly, it is important to develop host molecules possessing high chiral recognition ability toward secondary amines.



Herein, we report on the design and synthesis of chiral hosts capable of binding secondary amines and recog-

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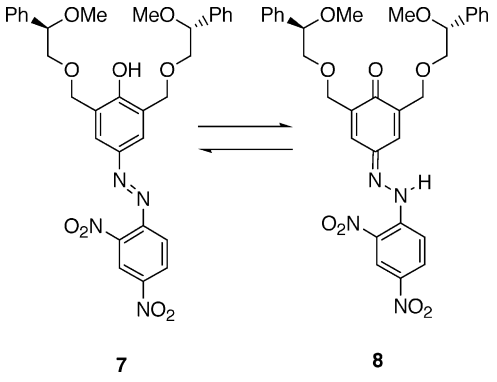
nizing their chirality. Our design is based on pseudo-18-crown-6 (*S*,*S*)-**1** which exhibits not only excellent enantioselectivity toward primary ethanolamine derivatives but also shows a distinct difference in the color developed upon complexation with each guest enantiomer.[5] The salient features 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 hydroxy group which facilitates binding with amines, and (iii) phenyl groups in appropriate positions of the macrocyclic framework as chiral barriers to effect maximum enantiomeric discrimination. The macrocyclic framework of pseudo-18-crown-6 (*S*,*S*)-**1**, is suitable for complexation with primary amines but probably not with secondary amines, since the cavity is too small to form stable complexes with the latter. To achieve sufficient binding with secondary amines, the macrocyclic framework should be larger than that of 18-crown-6. Alternatively, open chain type podands are also possible candidates. Since Stoddart et al. reported that dibenzo-24-crown-8 formed stable complexes with dibenzylammonium and other secondary ammonium ions,[6] we first designed (*S*,*S*)-**3** having a pseudo-24-crown-8 framework. Since the binding site of (*S*,*S*)-**3** is supposed to be smaller than that of dibenzo-24-crown-8, we also planned to prepare pseudo-27-crown-9 (*S*,*S*)-**4** possessing a larger binding site. As open chain hosts, we designed (*R*,*R*)-**5** and its methyl ether (*R*,*R*)-**6**. For comparison, pseudo-18-crown-6 (*S*,*S*)-**2** possessing the same ring size as that of (*S*,*S*)-**1** was also prepared.[7]



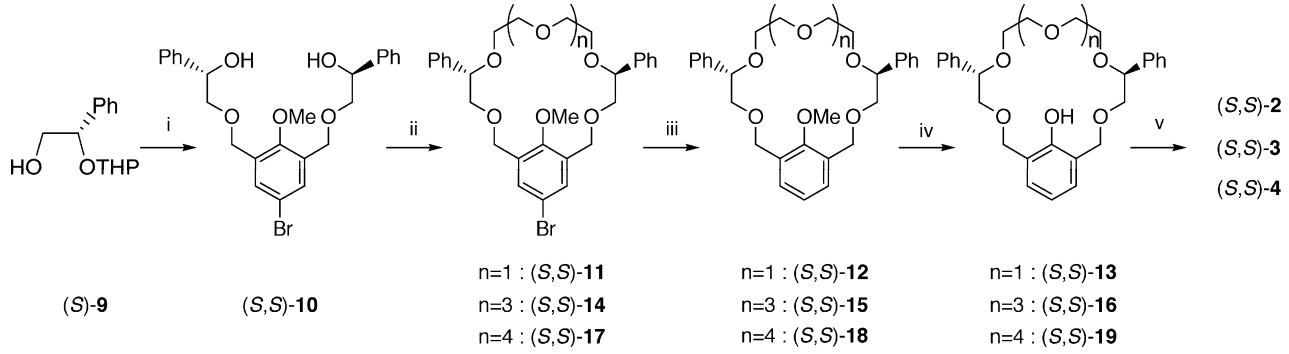
7 **8**

Scheme 1. Equilibrium between azophenol **7** and hydrazone **8** forms of podand **7**.

2. Results and discussion

All receptors designed here possess a nitro group instead of a 2,4-dinitrophenylazo group at the *para* position of the phenolic hydroxy group, as in (*S*,*S*)-**1**, for the following reason. In a preliminary experiment, we prepared podand type host **7** having a 2,4-dinitrophenylazo group, but found, however, that it existed as both the azophenol **7** and its tautomeric hydrazone forms **8** in a ratio of 5:1 in $CDCl_3$ at 30°C (Scheme 1). The nitro group was used in order to avoid this complexity, since its electron-withdrawing properties are almost identical to that of a 2,4-dinitrophenylazo group.[8]

The synthesis of pseudo crown ethers (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*S*,*S*)-**4** is summarized in Scheme 2. The chiral subunit (*S*)-**9** was prepared from (*S*)-(+)-mandelic acid as a mixture of two diastereomers according to the reported procedure.[8,9] Condensation of 2 equiv. of (*S*)-**9** with 5-bromo-1,3-bis(bromomethyl)-2-methoxybenzene[8] in the presence of NaH followed by deprotection with pyridinium *p*-toluenesulfonate in ethanol gave (*S*,*S*)-**10** in 95% overall yield, which was used as a common precursor for preparation of phenolic crown ethers (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*S*,*S*)-**4**. Synthesis of (*S*,*S*)-**2** was initiated from ring closure of (*S*,*S*)-**10** with diethylene glycol di(*p*-toluenesulfonate) in the presence of NaH in THF under high dilution conditions to give (*S*,*S*)-**11** in 44% yield. Reaction of (*S*,*S*)-**11** with *n*-BuLi in hexanes followed by quenching with water at −78°C afforded (*S*,*S*)-**12** in 62% yield. The intra-annular methyl ether of (*S*,*S*)-**12** was selectively cleaved with sodium ethanethiolate in DMF[10] to furnish (*S*,*S*)-**13** in 91% yield. By reaction with HNO_3 and $NaNO_2$,[11] the *para* position to the hydroxy group of (*S*,*S*)-**13** was selectively nitrated to give (*S*,*S*)-**2** in 58% yield. Pseudo-24-crown-8 (*S*,*S*)-**3** and pseudo-27-crown-9 (*S*,*S*)-**4**



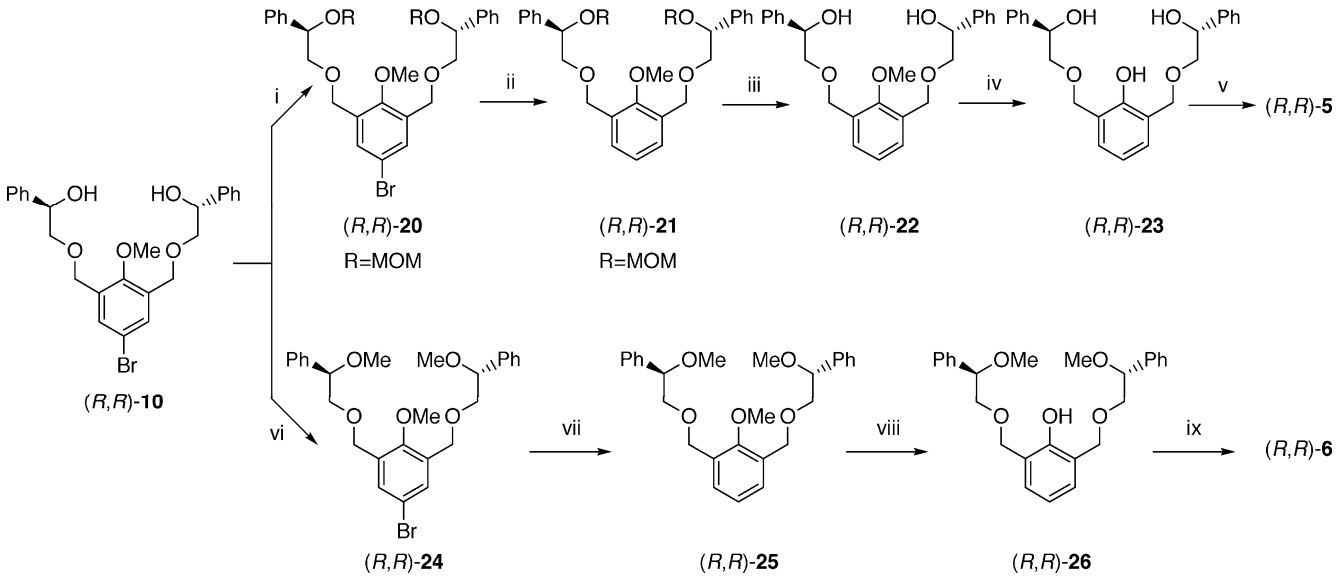
(*S*)-**9** (*S*,*S*)-**10**

n=1 : (*S*,*S*)-**11**
n=3 : (*S*,*S*)-**14**
n=4 : (*S*,*S*)-**17**

n=1 : (*S*,*S*)-**12**
n=3 : (*S*,*S*)-**15**
n=4 : (*S*,*S*)-**18**

n=1 : (*S*,*S*)-**13**
n=3 : (*S*,*S*)-**16**
n=4 : (*S*,*S*)-**19**

Scheme 2. *Reagents and conditions*: (i) a. 5-Bromo-1,3-bis(bromomethyl)-2-methoxybenzene, NaH, b. pyridinium *p*-toluenesulfonate, ethanol, 95% (two steps); (ii) diethylene glycol ditosylate, NaH, 44% ($n=1$), tetraethylene glycol ditosylate, NaH, 36% ($n=3$), pentaethylene glycol ditosylate, NaH, 25% ($n=4$); (iii) *n*-BuLi, then H_2O, 62% ($n=1$), 62% ($n=3$), 68% ($n=4$); (iv) EtSNa, 91% ($n=1$), 86% ($n=3$), 30% ($n=4$); (v) HNO_3, $NaNO_2$, 58% ($n=1$), 34% ($n=3$), 42% ($n=4$).

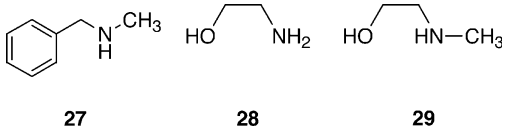


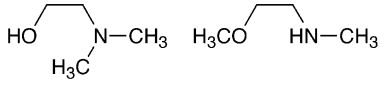
Scheme 3. *Reagents and conditions*: (i) $(CH_3O)_2CH_2$, LiBr, TsOH, 50%; (ii) *n*-BuLi, then H_2O, 71%; (iii) 6N HCl, 72%; (iv) EtSNa, 76%; (v) HNO_3, $NaNO_2$, 25%; (vi) CH_3I, NaH, 86%; (vii) *n*-BuLi, then H_2O, 75%; (viii) EtSNa, 74%; (ix) HNO_3, $NaNO_2$, 58%.

were prepared by essentially the same procedure as that used for the preparation of (*S*,*S*)-**2**. In the case of (*S*,*S*)-**3**, ring closure of (*S*,*S*)-**10** with tetraethylene glycol di(*p*-toluenesulfonate) gave (*S*,*S*)-**14** in 36% yield, which was transformed into (*S*,*S*)-**3** in 18% yield (for three steps) via (*S*,*S*)-**15** and (*S*,*S*)-**16**. Pseudo-27-crown-9 (*S*,*S*)-**4** (through (*S*,*S*)-**17**, (*S*,*S*)-**18**, and (*S*,*S*)-**19**) was prepared from (*S*,*S*)-**10** and pentaethylene glycol di(*p*-toluenesulfonate) in 2.1% overall yield.

For the synthesis of podands, the enantiomerically pure chiral subunit (*R*)-**9** was employed simply by chance (Scheme 3). Thus, treatment of (*R*,*R*)-**10**, derived from (*R*)-**9**, with LiBr, TsOH and formaldehyde dimethyl acetal gave (*R*,*R*)-**20** in 50% yield. Debromination of (*R*,*R*)-**20** afforded (*R*,*R*)-**21** in 71% yield and subsequent deprotection with hydrochloric acid gave (*R*,*R*)-**22** in 72% yield. Demethylation of (*R*,*R*)-**22** followed by nitration at the *para* position of the hydroxy group of the resulting (*R*,*R*)-**23** furnished (*R*,*R*)-**5** in 19% yield for the two steps. For the preparation of (*R*,*R*)-**6**, methylation of the hydroxy groups of (*R*,*R*)-**10** was first carried out to give (*R*,*R*)-**24** in 86% yield. Subsequent reduction, demethylation and nitration via (*R*,*R*)-**25** and (*R*,*R*)-**26** afforded (*R*,*R*)-**6** in 32% yield for three steps.

The binding constants for the complexes were determined by ^{1}H NMR titration in $CDCl_3$ followed by non-linear least-squares curve fitting or by UV–visible titration in $CHCl_3$ followed by Rose–Drago data treatment.[12] As representative examples, the titration curves from the ^{1}H NMR titration method for the complexation of (*S*,*S*)-**3** with amine **32** and graphical expression to appreciate the determined binding constants according to the Rose–Drago method[12b] for the complexation of (*R*,*R*)-**5** with amine **35** are shown in Figs. 1 and 2, respectively. The obtained binding constants are summarized in Tables 1 and 2. For complexation with binding constants of this range (10–10^2 M^{-1}), both the ^{1}H NMR titration and the UV–visible titration methods can be used reliably.[12b,13] In order to check if the data obtained by the different methods are identical within the experimental error, cross experiments were carried out.[14] In the case of (*R*,*R*)-**5**, however, only UV–visible titration method was employed because of its limited solubility in $CDCl_3$.





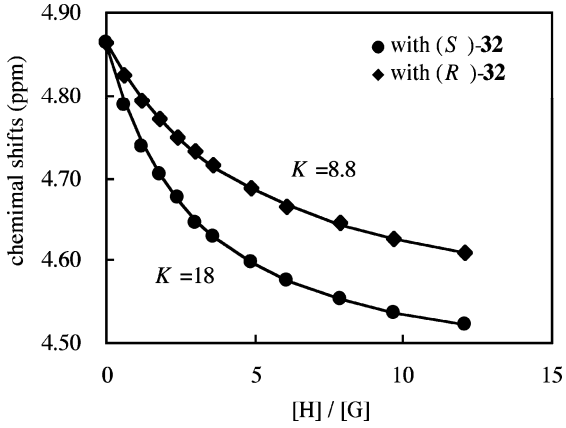


Figure 1. ^{1}H NMR (270 MHz) titration curves for the complexation of (*S*,*S*)-**3** with (*S*)- and (*R*)-**32** in $CDCl_3$ at 15°C.

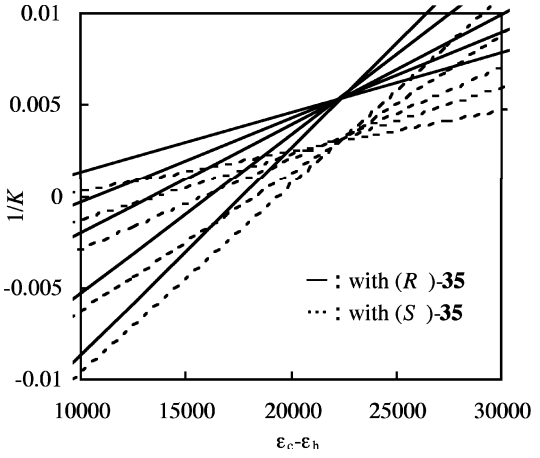


Figure 2. Graph to appreciate the determined binding constant (K) for the complexation of (R,R)-**5** with (S)- and (R)-**35** according to the Rose–Drago method in $CHCl_3$ at 15°C. ε_c: molar extinction coefficient of a complex. ε_h: molar extinction coefficient of a host.

First, the binding ability of the prepared hosts toward secondary amines was investigated using achiral amines **27**–**31**. The binding constants of the hosts with amines **27**–**31** are summarized in Table 1. With *N*-methylbenzylamine (**27**), crown ethers (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*S*,*S*)-**4** form complexes with binding constants of 14, 46, and 22 M^{-1}, respectively at 15°C. Among them, pseudo-24-crown-8 (*S*,*S*)-**3** shows the largest binding constant, suggesting that the cavity of (*S*,*S*)-**2** is too small for **27**, while that of (*S*,*S*)-**4** is too large. In addition, it should be pointed out that the binding constant of podand (*R*,*R*)-**5** with **27** is larger than those of crown ethers (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*S*,*S*)-**4** despite the absence of the cyclic structure.[15] These results suggest that, as we expected, receptors suitable for binding secondary amines should possess macrocyclic rings which are larger than 18-crown-6, or they can be an open chain podand. Since we have reported that pseudo-18-crown-6 like (*S*,*S*)-**1** showed high binding ability and enantiomer selectivity toward primary ethanolamine derivatives,[16] we examined the binding ability toward

Table 1. Binding constants for the complexes of (*S*,*S*)-**2**, (*S*,*S*)-**3**, (*S*,*S*)-**4**, (*R*,*R*)-**5**, and (*R*,*R*)-**6** with **27**, **28**, **29**, **30**, and **31**

	(*S*,*S*)-**2**	(*S*,*S*)-**3**	(*S*,*S*)-**4**	(*R*,*R*)-**5**	(*R*,*R*)-**6**
27	$(1.4\pm0.2)\times10^{a}$	$(4.6\pm0.1)\times10^{a}$	$(2.2\pm0.1)\times10^{a}$	$(1.0\pm0.1)\times10^{2\ b}$	–
28	$(9.9\pm0.5)\times10^{3\ d}$	$(3.7\pm0.1)\times10^{2\ d}$	–	$(3.5\pm0.3)\times10^{d}$	6.2 ± 0.8^{c}
29	$(7.9\pm0.1)\times10^{d}$	$(2.5\pm0.1)\times10^{2\ d}$	$(9.5\pm0.1)\times10^{d}$	$(2.2\pm0.2)\times10^{2\ d}$	$(1.8\pm0.2)\times10^{c}$
30	$<1^{d}$	$<1^{d}$	–	$<1^{d}$	$<1^{d}$
31	–	$(2.1\pm0.1)\times10^{d}$	–	$(8.9\pm0.5)\times10^{d}$	–

[a] Measured by ^{1}H NMR spectroscopy (270 MHz) in $CDCl_3$ at 15°C.
[b] Measured by UV–visible spectroscopy in $CHCl_3$ at 15°C.
[c] Measured by ^{1}H NMR spectroscopy (270 MHz) in $CDCl_3$ at 30°C.
[d] Measured by UV–visible spectroscopy in $CHCl_3$ at 30°C.

Table 2. Binding constants and enantiomer selectivities in complexation of (*S*,*S*)-**2**, (*S*,*S*)-**3**, (*S*,*S*)-**4**, and (*R*,*R*)-**5** with **32**, **33**, **34**, **35**, and **36**

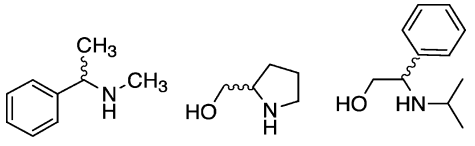
		(*S*,*S*)-**2**[a]	(*S*,*S*)-**3**	(*S*,*S*)-**4**[a]	(*R*,*R*)-**5**[b]
32[c]	K_S	<1	$(1.8\pm0.1)\times10^{a}$	7.5 ± 0.2	$(1.0\pm0.1)\times10^{2}$
	K_R	<1	8.8 ± 0.3^{a}	4.5 ± 0.2	$(7.2\pm0.2)10$
	K_S/K_R	–	2.0	1.7	1.4
33[d]	K_S	–	$(1.6\pm0.1)\times10^{2\ b}$	–	$(9.8\pm0.7)\times10^{2}$
	K_R	–	$(1.3\pm0.1)\times10^{2\ b}$	–	$(8.9\pm0.7)\times10^{2}$
	K_S/K_R	–	1.2	–	1.1
34[c]	K_S	–	$<1^{a}$	–	$(5.3\pm0.2)\times10$
	K_R	–	$<1^{a}$	–	$(4.7\pm0.5)\times10$
	K_S/K_R	–	–	–	1.1
35[c]	K_S	–	$(1.6\pm0.1)\times10^{a}$	–	$(3.1\pm0.2)\times10^{2}$
	K_R	–	$(2.6\pm0.1)\times10^{a}$	–	$(1.8\pm0.1)\times10^{2}$
	K_S/K_R	–	0.6	–	1.7
36[c]	K_S	–	$(5.3\pm0.1)\times10^{a}$	$(1.8\pm0.1)\times10$	$(2.3\pm0.1)\times10^{2}$
	K_R	–	$(3.1\pm0.2)\times10^{a}$	$(1.5\pm0.1)\times10$	$(3.7\pm0.1)\times10^{2}$
	K_S/K_R	–	1.7	1.2	0.6

[a] Measured by ^{1}H NMR spectroscopy (270 MHz) in $CDCl_3$.
[b] Measured by UV–visible spectroscopy in $CHCl_3$.
[c] Measured at 15°C.
[d] Measured at 30°C.

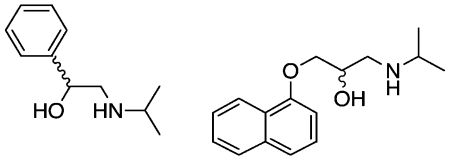
ethanolamine **28**, secondary ethanolamine **29**, and tertiary ethanolamine **30** at 30°C. As we expected, for the primary amine **28**, (*S*,*S*)-**2** exhibits the best binding properties. In the case of secondary amine **29**, pseudo-24-crown-8 (*S*,*S*)-**3** has the best binding properties among the hosts examined. However, none of the hosts bind tertiary amine **30**. Again, the binding constant of podand (*R*,*R*)-**5** toward **29** is similar to that of pseudo-24-crown-8 (*S*,*S*)-**3**. On the other hand, the binding constant of (*R*,*R*)-**6** is very small. The binding constants of the hosts with **29** at 30°C are greater than those with **27** at 15°C, which does not have a hydroxy group, probably due to the steric repulsion of the phenyl group and hydrogen bonding between the phenoxide oxygen of the host and the hydroxy group of **29**.

In order to investigate the effect of the hydroxy group of guest amines, methoxyamine **31** was employed for the complexation of (*S*,*S*)-**3** and (*R*,*R*)-**5**, which showed considerable binding ability toward hydroxyamine **29**. As a result, the binding constant of (*S*,*S*)-**3** with **31** is 10 times smaller than that with **29** and that of (*R*,*R*)-**5** with **31** is less than half of that with **29**. We have reported that the absorption maximum of the more favorable complex of azophenolic pseudo-crown ether such as (*S*,*S*)-**1** with one enantiomer guest appeared at shorter wavelength than that of the less stable complex with the other enantiomer.[17] Indeed, the absorption maxima of the complexes of (*S*,*S*)-**3** with **29** and **31** are 402 and 405 nm, respectively, and those of (*R*,*R*)-**5** are 386 and 389 nm, respectively. These results are consistent with the presence of hydrogen bonding between the hydroxy group of **29** and the phenoxide oxygen of the host.

The binding constants and the enantioselectivity of the hosts were determined for (*S*,*S*)-**3**, (*S*,*S*)-**4**, and (*R*,*R*)-**5** with chiral amines **32**, **33**, **34**, **35**, and **36** (Table 2). The measurements were carried out at 15°C because of the relatively small binding constants at 30°C except in the case of amine **33**. Both enantiomers of **32**, **33**, and **36** are commercially available. Amines **34** and **35** were prepared by *N*-isopropylation of the corresponding primary amines according to the reported procedure.[18] *N*-Isopropylamines were selected because of the ease of preparation of both enantiomers from commercially available materials and because of the fact that many biologically active secondary amines possess this group.[2] First, the binding ability and enantiomer selectivity of (*S*,*S*)-**2**, (*S*,*S*)-**3**, (*S*,*S*)-**4**, and (*R*,*R*)-**5** toward *N*,α-dimethylbenzylamine **32** are compared. While (*S*,*S*)-**2** formed a complex with **27** with a binding constants of 14 M^{-1}, it did not bind *S* and *R* enantiomers of **32** (K <1 M^{-1}). Thus, the introduction of a methyl group in the guest amine reduced the binding ability of (*S*,*S*)-**2** dramatically, suggesting severe steric repulsion between the α-methyl group of **32** and the host. Because of the poor binding ability of (*S*,*S*)-**2** toward a chiral secondary amine, its binding constants with other chiral secondary amine were not determined. With pseudo-24-crown-8 (*S*,*S*)-**3**, although the binding constants with *S* and *R* enantiomers of **32** were considerably reduced (18 and 8.8 M^{-1}, respectively) compared to that with **27**, a moderate degree of enantiomer selectivity was observed ($K_S/K_R=2.0$). Similarly, pseudo-27-crown-9 (*S*,*S*)-**4** exhibited a moderate degree of enantiomer selectivity ($K_S/K_R=1.7$). In contrast with crown ethers (*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*S*,*S*)-**4**, the binding constants of podand (*R*,*R*)-**5** with **32** ($K_S=100$ M^{-1}, $K_R=72$ M^{-1}) decreased only slightly compared to that with achiral amine **27**, resulting in relatively low enantioselectivity ($K_S/K_R=1.4$). The binding constants for pyrrolidinemethanol **33** with pseudo crown ether (*S*,*S*)-**3** and podand (*R*,*R*)-**5** were next examined: in both cases, although the binding constants are larger than those with **32**, the enantiomer selectivities are relatively small. The binding constants toward **34** and **35** were also measured using hosts (*S*,*S*)-**3** and (*R*,*R*)-**5** which showed relatively high binding ability toward **32**. However, (*S*,*S*)-**3** did not bind both enantiomers of α-substituted **34** (K <1 M^{-1}). On the contrary, (*S*,*S*)-**3** formed complexes with *S* and enantiomers of β-substituted **35** with binding constants 16 and 26 M^{-1}, respectively, and moderate degree of enantiomer selectivity ($K_S/K_R=0.6$) was observed. This finding shows a dramatic difference in the binding abilities with regard to the position of the substituent. For podand (*R*,*R*)-**5**, although it binds α-substituted **34**, the enantiomer selectivity is marginal. On the other hand, its binding constants with *S* and *R* enantiomers of β-substituted **35** are considerably large, and a moderate degree of enantiomer selectivity ($K_S/K_R=1.7$) is observed. The relatively low binding abilities of (*S*,*S*)-**3** and (*R*,*R*)-**5** toward **34** suggest a severe steric repulsion between the α-phenyl group and the host. Since (*S*,*S*)-**3** and (*R*,*R*)-**5** showed relatively high binding constants and enantiomer selectivities toward β-substituted ethanolamine **35**, we employed propranolol **36** as a guest, which is one of the well-known bioactive amino alcohols possessing a hydroxy group on a stereogenic center at the β-position of the amino group. In this case, pseudo-27-crown-9 (*S*,*S*)-**4** was also examined in addition to (*S*,*S*)-**3** and (*R*,*R*)-**5**. As we expected, (*S*,*S*)-**3** and (*R*,*R*)-**5** showed relatively high binding ability and a moderate degree of enantiomer selectivity. In the case of (*S*,*S*)-**4**, however, both the binding constant and the enantiomer selectivity are smaller.



32 **33** **34**



35 **36**

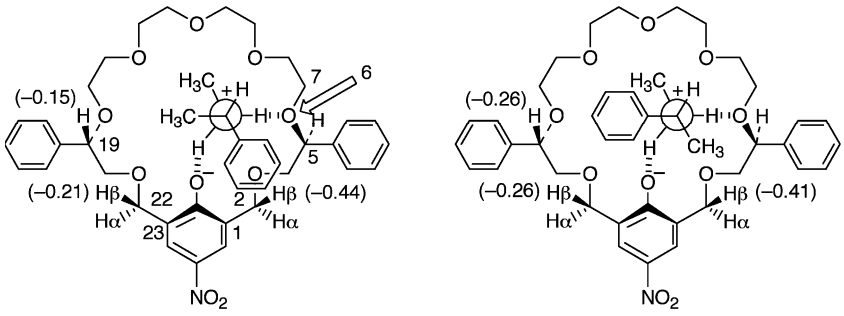


Figure 3. Predicted geometries of complexes **37** and **38**. The values in parenthesis are complexation induced shifts (CISs) of (*S*,*S*)-**3** with (*S*)- and (*R*)-**32**. CISs of H2α, H5, and H22α which are time-averaged with those of H22β, H19, and H2β, respectively, are not shown.

Regarding the predictable *R*/*S*-selectivities of pseudo-18-crown-6 ethers governed by enthalpy,[5c] we have proposed an explanation in terms of steric repulsion between the amine and the hosts on the basis of CPK molecular model examination of the complexes. The enantiomer selectivities of (*S*,*S*)-**3** can be interpreted on the same grounds regardless of the relatively poor enantioselectivity (the maximum selectivity of $K_S/K_R = 2.0$ corresponds to ca. 0.4 kcal/mol), although the host (*S*,*S*)-**3** has a more flexible structure than that of pseudo-18-crown-6. In Fig. 3, predicted geometries **37** and **38** are illustrated for the complexes (*S*,*S*)-**3**:(*S*)-**32** and (*S*,*S*)-**3**:(*R*)-**32**, respectively, assuming the following issues: (i) the phenoxide oxygen atom participates in the binding with the amine; (ii) The phenyl substituents of the host occupy pseudo-equatorial positions,[16c] making the O-6 oxygen (shown by the arrow in Fig. 3) form O···H–N$^+$ hydrogen bond with the ammonium cation nested in the cavity of crown ether; (iii) The protonated amine **32**H$^+$ adopts a conformation in which the bulkiest group is located in the anti position of the *N*-methyl group. On the basis of these assumptions, two hydrogen atoms on the ammonium nitrogen of (*S*)-**32**H$^+$ form hydrogen bonding with the phenoxide oxygen and O-6 oxygen. The position of the methyl group on the nitrogen atom is then on the 11 o'clock position. Consequently, the phenyl group of (*S*)-**32**H$^+$ is located at the anti position of the *N*-methyl group, thereby adopting the 5 o'clock position. Thus, in complex **37**, the α-methyl group of (*S*)-**32**H$^+$ is located at the less hindered 9 o'clock position of (*S*,*S*)-**3**, and the smallest group on the α-position (hydrogen atom) is located at the most congested 2 o'clock position. On the other hand, in the case with (*R*)-**32**H$^+$, the complex must be destabilized because either of the following two requirements cannot be satisfied: (i) the bulkiest phenyl group is located at the *anti* position of the *N*-methyl group; (ii) The smallest group (hydrogen) is located at the 2 o'clock position. The conformer shown as **38**, having the phenyl group at the 9 o'clock position, does not fulfil the second requirement. In order to obtain spectroscopic support for this explanation, complexation induced shifts (CISs) were calculated.[19] Since the equilibrium of the complexation between (*S*,*S*)-**3** and **32** is fast on the ^{1}H NMR time scale even at −50°C, the signals of the protons H5 and H19, H2β and H22α, and H2α and H22β exchange rapidly to each other. The CISs of these protons are shown in Fig. 3. While most of the amine guests exhibited CISs of similar magnitude for H2β and H22β, CIS for H19 is relatively small.[20] Therefore, the proton H19 is suitable to probe the anisotropic shielding effect of the phenyl ring of guest **32**H$^+$. The proton H19 shows a larger upfield shift with (*R*)-**32** than that with (*S*)-**32** (Δ_{R-S}CIS = −0.11), indicating that the proton H19 suffers anisotropic shielding from phenyl ring of (*R*)-**32** more effectively than that from (*S*)-**32**. These results are in agreement with the proposed conformations shown in Fig. 3.[21]

In conclusion, a general class of compounds (*S*,*S*)-**1**–(*R*,*R*)-**6**, were prepared to develop hosts capable of recognizing chirality of secondary amines. Moderate enantiomer recognition of chiral secondary amines was achieved with chiral pseudo-24-crown-8 (*S*,*S*)-**3** and podand type chiral host (*R*,*R*)-**5**. Further works to improve the selectivity and to apply these compounds to chiral chromatography are in progress in our laboratories.

3. Experimental

3.1. General procedure

^{1}H NMR spectra were recorded at 270, 300 or 400 MHz and ^{13}C NMR spectra at 67.8 MHz on a JEOL JNM-GSX-270, a Varian Mercury 300 or a JMN-AL-400 in $CDCl_3$ and with Me_4Si or residual solvent as an internal standard at 30°C. IR spectra were recorded as a KBr disk or a neat film with a JASCO FTIR-410 spectrometer. UV spectra were recorded on a Hitachi 220A or a U-3310 spectrometer. Mass spectral analyses were performed on a JEOL JMS-DX303HF spectrometer or a JEOL JMS-700 spectrometer by EI and FAB ionization. Elemental analyses were performed on a Perkin–Elmer 2400II analyzer. Melting points were measured with a hot-stage apparatus and are uncorrected. Optical rotations were measured using a JASCO

DIP-40 polarimeter at ambient temperature and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography and TLC were performed with Merck silica gel 60 (70–230 mesh ASTM) and Merck silica gel 60 F_{254}, respectively. Preparative HPLC separation was undertaken with a JAI LC-908 chromatograph using 600 mm×20 mm JAIGEL-1H and 2H GPC columns with $CHCl_3$ as an eluent. All reagents were obtained from commercial suppliers and used as received. Solvents were dried (drying agent in parentheses) and distilled prior to use: $CDCl_3$ (P_4O_{10}), DMF (CaH_2) and THF (CaH_2 followed by sodium benzophenone ketyl).

3.2. 5-Bromo-1,3-bis[(4*S*)-4-hydroxy4-phenyl-2-oxabutyl]-2-methoxybenzene, (*S*,*S*)-10

A solution of (*S*)-(+)-2-phenyl-2-(tetrahydropyranyloxy)ethanol (18.6 g, 83.7 mmol) in dry THF (150 mL) which had been prepared from (*S*)-mandelic acid as the mixture of two diastereomers[8,9] was slowly added to a suspension of sodium hydride (60% in mineral oil, 4.69 g, 0.117 mol) in dry THF (300 mL) at room temperature. After being refluxed for 1.5 h, a solution of 5 - bromo - 1,3 - bis(bromomethyl) - 2 - methoxybenzene[8] (12.0 g, 32.2 mmol) in dry THF (150 mL) was added slowly. After additional reflux for 6 h, water (35 mL) was carefully added to the reaction mixture with ice-cooling. Then the solvent was removed under reduced pressure. The residue was extracted with a mixed solvent containing hexane and ethyl acetate, the combined extracts were washed with water and dried over anhydrous $MgSO_4$, and then the solvent was removed under reduced pressure. The residue was stirred with pyridinium *p*-toluenesulfonate (0.966 g, 3.84 mmol) in ethanol (125 mL) for 12 h at 50°C. After the solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$, and washed with water, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (hexane:ethyl acetate) to give (*S*,*S*)-**10** as a yellow oil (14.9 g, 95%): $[\alpha]_D^{25}=+25.1$ (*c* 1.03, $CHCl_3$); IR (neat) 3431, 2871, 1454, 1211, 1105, 757, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.78 (2H, br s, O*H*), 3.53–3.71 (m, 4H, CH_2), 3.73 (3H, s, OCH_3), 4.60 (s, 4H, benzylic CH_2), 4.94 (dd, $J=2.9$, 8.7 Hz, 2H, OC*H*(Ph)CH$_2$), 7.27–7.41 (m, 10H, C$_6H_5$), 7.48 (s, 2H, MeOAr*H*). MS (FAB) *m*/*z* 487 (M+H)$^+$. Anal. calcd for $C_{25}H_{27}O_5Br$: C, 61.61; H, 5.58; Br, 16.39. Found: C, 61.44; H, 5.51; Br, 16.12%.

3.3. (5*S*,13*S*)-19-Bromo-21-methoxy-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(20),17(21),18-triene, (*S*,*S*)-11

A solution of (*S*,*S*)-**10** (1.01 g, 2.06 mmol) and diethylene glycol di(*p*-toluenesulfonate) (858 mg, 2.07 mmol) in dry THF (125 mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 349 mg, 8.73 mmol) in dry THF (85 mL) over a 9 h period at 60°C. After being stirred for 18 h, 20 mL of water was added carefully with ice-cooling and then the solvent was removed under reduced pressure. The residue was extracted with a solvent containing hexane and ethyl acetate, and the combined extract was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (hexane:ethyl acetate) to give (*S*,*S*)-**11** as a colorless powder (500 mg, 44% yield): mp 99–100°C; $[\alpha]_D^{28}=+92.3$ (*c* 1.24, $CHCl_3$); IR (KBr) 2864, 1470, 1430, 1359, 1227, 1096, 1003, 761, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.39–3.71 (m, 12H, CH_2), 4.25 (s, 3H, OCH_3), 4.52 (dd, $J=2.5$, 8.3 Hz, 2H, OC*H*(Ph)CH$_2$), 4.45, 4.69 (AB, $J=7.4$ Hz, $\Delta\nu=65.6$ Hz, 4H, benzylic CH_2), 7.28–7.37 (m, 10H, C$_6H_5$), 7.42 (s, 2H, MeOAr*H*); MS (FAB) *m*/*z* 558 (M+H)$^+$. Anal. calcd for $C_{29}H_{33}O_6Br$: C, 62.48; H, 5.97. Found: C, 62.69; H, 6.12%.

3.4. (5*S*,13*S*)-21-Methoxy-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(20),17(21),18-triene, (*S*,*S*)-12

A 1.6 M solution of *n*-BuLi in hexanes (3.7 mL, 6.1 mmol) was added to a solution of (*S*,*S*)-**11** (2.85 g, 5.11 mmol) in dry THF (40 mL) over a 15 min period at −78°C under nitrogen. After stirring for 1.5 h at the same temperature, water (3 mL) was added dropwise to the reaction mixture at −78°C and the mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was warmed to room temperature and extracted with a solvent containing hexane and ethyl acetate. The combined extracts were washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (hexane:ethyl acetate) to give (*S*,*S*)-**12** as a colorless powder (1.52 g, 62% yield): mp 129–130°C; $[\alpha]_D^{24}=+147.1$ (*c* 0.54, $CHCl_3$); IR (KBr) 2859, 1596, 1453, 1360, 1232, 1095, 995, 955, 790, 762, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.39–3.72 (m, 12H, CH_2), 4.29 (3H, s, OCH_3), 4.52 (dd, $J=2.4$, 8.2 Hz, 2H, OC*H*(Ph)CH$_2$), 4.51, 4.74 (AB, $J=7.1$ Hz, $\Delta\nu=61.6$ Hz, 4H, benzylic CH_2), 7.06 (t, $J=7.4$ Hz, 1H, OMeAr*H*), 7.25–7.35 (m, 12H, OMeAr*H* and C$_6H_5$); MS (FAB) *m*/*z* 479 (M+H)$^+$.

3.5. (5*S*,13*S*)-21-Hydroxy-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(20),17(21),18-triene, (*S*,*S*)-13

To a suspension of sodium hydride (60% in mineral oil, 2.79 g, 69.8 mmol) in dry DMF (70 mL) was added slowly ethanethiol (6.4 mL, 84 mmol) with ice-cooling. After hydrogen evolution ceased, a solution of (*S*,*S*)-**12** (1.66 g, 3.46 mmol) in dry DMF (150 mL) was added to the resulting clear solution. The reaction mixture was stirred for 2 h at 80°C, cooled to 5°C, neutralized with hydrochloric acid and extracted with $CHCl_3$. The combined extract was washed with aqueous solution of sodium hypochlorite, washed with water, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexane:ethyl acetate) followed by recrystallization from hexane to give (*S*,*S*)-**13** as colorless powder (1.47 g, 91% yield): mp 92–94°C; $[\alpha]_D^{21}=+117.1$ (*c* 0.34, $CHCl_3$); IR (KBr) 3366, 2867, 1600, 1467, 1360, 1244, 1097, 754, 703 cm^{-1}; ^{1}H NMR

($CDCl_3$, 400 MHz) δ 3.60–3.80 (m, 12H, CH_2), 4.67 (dd, $J=2.8$, 8.3 Hz, 2H, OCH(Ph)CH_2), 4.76 (s, 4H, benzylic CH_2), 6.81 (t, $J=7.4$ Hz, 1H, phenol ring CH), 7.13 (d, $J=7.4$ Hz, 2H, phenol ring CH), 7.27–7.35 (m, 10H, C_6H_5), 8.14 (s, 1H, phenolic OH); MS (FAB) m/z 465 $(M+H)^+$. Anal. calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.15; H, 7.01%.

3.6. (5*S*,13*S*)-21-Hydroxy-19-nitro-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(20),17(21),18-triene, (*S*,*S*)-2

A solution of sodium nitrite (0.590 g, 8.55 mmol) in water (120 mL) and 0.3N nitric acid (34 mL) was added to a solution of (*S*,*S*)-**13** (1.00 g, 2.15 mmol) in $CHCl_3$ (80 mL) successively. The mixture was then stirred vigorously for 4 h at room temperature. The reaction mixture was neutralized with saturated aqueous solution of sodium hydrogencarbonate and the $CHCl_3$ layer was separated. The organic phase was washed with water and dried over anhydrous $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified by chromatography on alumina (hexane:ethyl acetate then ethanol) to give (*S*,*S*)-**2** as a yellow powder (636 mg, 58% yield): mp 52–54°C; $[\alpha]_D^{21}=+97.2$ (*c* 0.61, $CHCl_3$); IR (KBr) 3319, 2871, 1600, 1520, 1452, 1339, 1091, 749, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.54–3.78 (m, 12H, CH_2), 4.66 (dd, $J=3.7$, 7.2 Hz, 2H, OCH(Ph)CH_2), 4.83 (s, 4H, benzylic CH_2), 7.30–7.38 (m, 10H, C_6H_5), 8.10 (s, 2H, phenol ring CH), 9.20 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 67.8 Hz) 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 $(M+H)^+$; HRMS (FAB) calcd for $C_{28}H_{32}NO_8$ $(M+H)^+$ 510.2128; found 510.2102.

3.7. (5*S*,19*S*)-25-Bromo-27-methoxy-5,19-diphenyl-3,6,9,12,15,18,21-heptaoxabicyclo[21.3.1]heptacosa-1(26),23(27),24-triene, (*S*,*S*)-14

In a manner similar to that described for the preparation of (*S*,*S*)-**11**, treatment of (*S*,*S*)-**10** (6.56 g, 13.5 mmol) with tetraethylene glycol di(*p*-toluenesulfonate) (8.12 g, 16.1 mmol) and sodium hydride (60% in mineral oil, 4.93 g, 123 mmol) gave (*S*,*S*)-**14** (3.14 g, 4.86 mmol, 36% yield) as a colorless oil after chromatography on silica gel (hexane:ethyl acetate) followed by alumina ($CHCl_3$): $[\alpha]_D^{29}=+56.9$ (*c* 1.00, $CHCl_3$); IR (neat) 2867, 1453, 1346, 1216, 1107, 1004, 757, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.46–3.77 (m, 20H, CH_2), 3.93 (s, 3H, OCH_3), 4.63 (dd, $J=3.3$, 8.0 Hz, 2H, OCH(Ph)CH_2), 4.65, 4.70 (AB, $J=11.6$ Hz, $\Delta\nu=13.2$ Hz, 4H, benzylic CH_2), 7.27–7.36 (m, 10H, C_6H_5), 7.51 (s, 2H, phenol ring CH); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 63.13, 67.95, 68.84, 70.60, 70.67, 70.70, 75.33, 82.31, 116.71, 126.75, 127.82, 128.35, 132.25, 133.91, 138.90, 155.66; MS (FAB) m/z 645 $(M+H)^+$, 667 $(M+Na)^+$; HRMS (FAB) calcd for $C_{33}H_{42}O_8Br$ $(M+H)^+$ 642.2043; found 642.2032.

3.8. (5*S*,19*S*)-27-Methoxy-5,19-diphenyl-3,6,9,12,15,18,21-heptaoxabicyclo[21.3.1]heptacosa-1(26),23(27),24-triene, (*S*,*S*)-15

In a manner similar to that described for the preparation of (*S*,*S*)-**12**, treatment of (*S*,*S*)-**14** (541 mg, 0.838 mmol) with a 1.6 M solution of *n*-BuLi in hexanes (1.2 mL, 1.84 mmol) followed by water gave (*S*,*S*)-**15** (294 mg, 0.519 mmol, 62% yield) as a colorless oil after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{30}=+70.7$ (*c* 0.43, $CHCl_3$); IR (neat) 2866, 1452, 1346, 1215, 1100, 1007, 760, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.45–3.79 (m, 20H, CH_2), 3.97 (s, 3H, OCH_3), 4.62 (dd, $J=3.0$, 8.2 Hz, 2H, OCH(Ph)CH_2), 4.68, 4.72 (AB, $J=11.4$ Hz, $\Delta\nu=10.7$ Hz, 4H, benzylic CH_2), 7.10 (t, $J=7.5$ Hz, 1H, MeOArH), 7.27–7.39 (m, 12H, MeOArH and C_6H_5); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 63.32, 68.61, 68.93, 70.67, 70.75, 70.76, 75.28, 82.27, 123.82, 126.80, 127.75, 128.32, 130.13, 131.57, 139.19, 157.10; MS (FAB) m/z 567 $(M+H)^+$, 589 $(M+Na)^+$; HRMS (FAB) calcd for $C_{33}H_{42}O_8Na$ $(M+Na)^+$ 589.2778; found 589.2786.

3.9. (5*S*,19*S*)-27-Hydroxy-5,19-diphenyl-3,6,9,12,15,18,21-heptaoxabicyclo[21.3.1]heptacosa-1(26),23(27),24-triene, (*S*,*S*)-16

In a manner similar to that described for the preparation of (*S*,*S*)-**13**, treatment of (*S*,*S*)-**15** (1.00 g, 1.77 mmol) with sodium ethanethiolate in DMF gave (*S*,*S*)-**16** (838 mg, 86% yield) as a colorless oil after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{26}=+72.1$ (*c* 0.84, $CHCl_3$); IR (neat) 3361, 2866, 1598, 1453, 1347, 1225, 1100, 758, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.51–3.78 (m, 20H, OCH_2), 4.69 (dd, $J=3.7$, 8.6 Hz, 2H, OCH(Ph)CH_2), 4.74, 4.81 (AB, $J=11.9$ Hz, $\Delta\nu=17.7$ Hz, 4H, benzylic CH_2), 6.80 (t, $J=7.7$ Hz, 1H, phenol ring CH), 7.12 (d, $J=7.7$ Hz, 2H, phenol ring CH), 7.27–7.36 (m, 10H, C_6H_5), 8.05 (s, 1H, phenolic OH); ^{13}C NMR ($CDCl_3$, 67.8 Hz) δ 68.75, 70.52, 70.74, 70.76, 70.98, 75.21, 81.64, 119.25, 124.33, 126.89, 127.90, 128.23, 128.38, 138.76, 154.15; MS (FAB) m/z 553 $(M+H)^+$, 575 $(M+Na)^+$, HRMS (FAB) calcd for $C_{32}H_{40}O_8Na$ $(M+Na)^+$ 575.2621; found 575.2623.

3.10. (5*S*,19*S*)-27-Hydroxy-25-nitro-5,19-diphenyl-3,6,9,12,15,18,21-heptaoxabicyclo[21.3.1]heptacosa-1(26),23(27),24-triene, (*S*,*S*)-3

In a manner similar to that described for the preparation of (*S*,*S*)-**2**, treatment of (*S*,*S*)-**16** (660 mg, 1.19 mmol) with sodium nitrite and nitric acid gave (*S*,*S*)-**3** (240 mg, 34% yield) as a yellow oil after chromatography on silica gel (hexane:ethyl acetate) followed by alumina ($CHCl_3$): $[\alpha]_D^{25}=+53.3$ (*c* 1.06, $CHCl_3$); IR (neat) 3277, 2867, 1596, 1521, 1452, 1339, 1097, 751, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.45–3.87 (m, 20H, CH_2), 4.70 (dd, $J=5.8$, 5.8 Hz, 2H, OCH(Ph)CH_2), 4.81, 4.85 (AB, $J=12.9$ Hz, $\Delta\nu=$ 17.9 Hz, 4H, benzylic CH_2), 7.26–7.40 (m, 10H, C_6H_5), 8.08 (s, 2H, phenol ring CH), 9.13 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 68.76, 69.86, 69.87, 70.73, 70.90, 75.50, 81.67, 123.63, 125.26, 126.82, 128.11, 128.49, 138.17, 140.22, 159.56; 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.

3.11. (5*S*,22*S*)-8-Bromo-30-methoxy-5,22-diphenyl-3,6,9,12,15,18,21,24-octaoxabicyclo[24.3.1]triaconta-1(29),26(30),27-triene, (*S*,*S*)-17

In a manner similar to that described for the preparation of (*S*,*S*)-**11**, treatment of (*S*,*S*)-**10** (9.30 g, 19.1 mmol) with pentaethylene glycol di(*p*-toluenesulfonate) (10.4 g, 19.1 mmol) and sodium hydride (60% in mineral oil, 3.85 g, 96.3 mmol) gave (*S*,*S*)-**17** (3.32 g, 25% yield) as a colorless oil after chromatography on silica gel (hexane:ethyl acetate) followed by alumina ($CHCl_3$): $[\alpha]_D^{26}=+56.9$ (*c* 1.10, $CHCl_3$); IR (neat) 2867, 1453, 1347, 1246, 1105, 1003, 857, 759, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.46–3.76 (m, 24H, CH_2), 3.82 (s, 3H, OCH_3), 4.61–4.71 (m, 6H, OC*H*(Ph)CH_2 and benzylic CH_2), 7.27–7.37 (m, 10H, C$_6H_5$), 7.51 (s, 2H, MeOAr*H*); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 62.71, 67.75, 68.79, 70.56, 70.58, 70.69, 70.71, 75.29, 82.14, 116.90, 126.83, 127.84, 128.36, 131.94, 133.87, 139.00, 155.26; MS (FAB) *m*/*z* 689 $(M+H)^+$, 711 $(M+Na)^+$; HRMS (FAB) calcd for $C_{35}H_{45}O_9BrNa$ $(M+Na)^+$ 711.2145; found 711.2158.

3.12. (5*S*,22*S*)-30-Methoxy-5,22-diphenyl-3,6,9,12,15,18,21,24-octaoxabicyclo[24.3.1]triaconta-1(29),26(30),27-triene, (*S*,*S*)-18

In a manner similar to that described for the preparation of (*S*,*S*)-**12**, treatment of (*S*,*S*)-**17** (2.40 g, 3.48 mmol) with a 1.6 M solution of *n*-BuLi in hexanes (3.4 mL, 5.57 mmol) followed by water gave (*S*,*S*)-**18** (1.44 g, 68% yield) as a colorless oil after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{26}=+60.0$ (*c* 1.03, $CHCl_3$); IR (neat) 2866, 1594, 1453, 1347, 1249, 1105, 1006, 950, 788, 760, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.49–3.78 (m, 24H, CH_2), 3.85 (s, 3H, OCH_3), 4.63 (dd, $J=3.2$, 8.2 Hz, 2H, OC*H*(Ph)CH_2), 4.68 (s, 4H, benzylic CH_2), 7.10 (t, $J=7.2$ Hz, 1H, MeOAr*H*), 7.28–7.41 (m, 12H, C$_6H_5$ and MeOAr*H*); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 62.79, 68.31, 68.88, 70.62, 70.63, 70.74, 70.75, 75.22, 82.12, 123.98, 126.85, 127.75, 128.31, 129.65, 131.47, 139.23, 156.53; MS (FAB) *m*/*z* 611 $(M+H)^+$, 633 $(M+Na)^+$; HRMS (FAB) calcd for $C_{35}H_{46}O_9Na$ $(M+Na)^+$ 633.3040; found 633.3021.

3.13. (5*S*,22*S*)-30-Hydroxy-5,22-diphenyl-3,6,9,12,15,18,21,24-octaoxabicyclo[24.3.1]triaconta-1(29),26(30),27-triene, (*S*,*S*)-19

In a manner similar to that described for the preparation of (*S*,*S*)-**13**, treatment of (*S*,*S*)-**18** (1.40 g, 2.29 mmol) with sodium ethanethiolate in DMF gave (*S*,*S*)-**19** as a colorless oil (409 mg, 30% yield) after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{26}=+55.8$ (*c* 1.06, $CHCl_3$); IR (neat) 3361, 2866, 1598, 1453, 1348, 1223, 1104, 758, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.50–3.77 (m, 24H, CH_2), 4.65 (dd, $J=4.0$, 8.2 Hz, 2H, OC*H*(Ph)CH_2), 4.72, 4.76 (AB, $J=12.1$ Hz, $\Delta\nu=12.4$ Hz, 2H, benzylic CH_2), 6.80 (t, $J=7.7$ Hz, 1H, phenol ring C*H*), 7.10 (d, $J=7.7$ Hz, 2H, phenol ring C*H*), 7.28–7.35 (m, 10H, C$_6H_5$), 8.00 (s, 1H, phenolic O*H*); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 68.67, 70.39, 70.59, 70.66, 70.75, 70.81, 75.08, 81.57, 119.25, 124.23, 126.91, 127.88, 128.33, 128.36, 138.83, 154.17; MS (FAB) *m*/*z* 597 $(M+H)^+$, 619 $(M+Na)^+$; HRMS (FAB) calcd for $C_{34}H_{45}O_9$ $(M+H)^+$ 597.3064; found 597.3047.

3.14. (5*S*,22*S*)-30-Hydroxy-8-nitro-5,22-diphenyl-3,6,9,12,15,18,21,24-octaoxabicyclo[24.3.1]triaconta-1(29),26(30),27-triene, (*S*,*S*)-4

In a manner similar to that described for the preparation of (*S*,*S*)-**2**, treatment of (*S*,*S*)-**19** (330 mg, 0.553 mmol) with sodium nitrite and nitric acid gave (*S*,*S*)-**4** (149 mg, 42% yield) as a yellow oil after chromatography on silica gel (hexane:ethyl acetate) followed by alumina ($CHCl_3$ then ethanol): $[\alpha]_D^{27}=+50.5$ (*c* 0.84, $CHCl_3$); IR (neat) 3282, 2868, 1595, 1520, 1453, 1338, 1100, 751, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.49–3.79 (m, 24H, CH_2), 4.67 (dd, $J=4.7$, 6.7 Hz, 2H, OC*H*(Ph)CH_2), 4.75, 4.82 (AB, $J=12.7$ Hz, $\Delta\nu=19.3$ Hz, 4H, benzylic CH_2), 7.27–7.41 (m, 10H, C$_6H_5$), 8.08 (s, 2H, phenol ring C*H*), 9.24 (1H, s, O*H*); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 68.52, 69.60, 70.55, 70.61, 70.68, 75.36, 81.67, 123.91, 125.29, 126.83, 128.08, 128.46, 138.25, 140.18, 159.56; MS (FAB) *m*/*z* 642 $(M+H)^+$, 664 $(M+Na)^+$; HRMS (FAB) calcd for $C_{34}H_{44}NO_{11}$ $(M+H)^+$ 642.2914; found 642.2908.

3.15. 5-Bromo-1,3-bis[(4*R*)-4-hydroxy-4-phenyl-2-oxabutyl]-2-methoxybenzene, (*R*,*R*)-10

In a manner similar to that described for the preparation of (*S*,*S*)-**10**, treatment of (*R*)-(−)-2-phenyl-2-(tetrahydropyranyloxy)ethanol[7,8] (18.3 g, 91.5 mmol) with 5 - bromo - 1,3 - bis(bromomethyl) - 2 - methoxybenzene[7] (14.0 g, 41.6 mmol) and sodium hydride (60% in mineral oil, 4.87 g, 0.122 mol) followed by deprotection gave (*R*,*R*)-**10** (17.2 g, 94%) as a yellow oil after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{26}=-26.3$ (*c* 1.01, $CHCl_3$); IR (neat) 3437, 2903, 1454, 1358, 1212, 1119, 1004, 760, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.91 (bs, 2H, O*H*), 3.53–3.71 (m, 4H, CH_2), 3.70 (3H, s, OCH_3), 4.58 (s, 4H, benzylic CH_2), 4.92 (dd, $J=3.2$, 8.5 Hz, 2H, OC*H*(Ph)CH_2), 7.24–7.38 (m, 10H, C$_6H_5$), 7.47 (s, 2H, OMeAr*H*); MS (FAB) *m*/*z* 487 $(M+H)^+$.

3.16. 5-Bromo-2-methoxy-1,3-bis[(4*R*)-4-methoxymethoxy-4-phenyl-2-oxabutyl]benzene, (*R*,*R*)-20

$LiBr\cdot H_2O$ (4.40 g, 24.6 mmol) and $TsOH\cdot H_2O$ (3.10 g, 30.7 mmol) were added successively to a solution of (*R*,*R*)-**10** in formaldehyde dimethyl acetal (70 mL). After stirring for 2 days at room temperature, the reaction mixture was extracted with ethyl acetate, and combined extracts were washed with water and dried over anhydrous $MgSO_4$. After the solvent was removed under reduced pressure, the residue was chromatographed on silica gel (hexane:ethyl acetate) to give (*R*,*R*)-**20** (3.39 g, 50% yield) as a yellow oil: $[\alpha]_D^{26}=-95.1$ (*c* 0.98, $CHCl_3$); IR (neat) 2890, 1455, 1359, 1212, 1152, 1104, 1035, 919, 760, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.32 (dd, $J=7.7$, 10.4 Hz, 2H, OCH(Ph)CH_2), 3.37 (s, 6H, OCH_2OCH_3), 3.61 (3H, s, OCH_3), 3.76 (dd, $J=4.0$, 10.4 Hz, 2H, OCH(Ph)CH_2), 4.55 (s, 4H, benzylic CH_2), 4.60, 4.65 (AB, $J=6.2$ Hz, $\Delta\nu=11.7$ Hz, 4H, OCH_2OCH_3), 4.86 (dd, $J=4.0$, 7.7 Hz, 2H, OC*H*(Ph)CH_2), 7.23–7.36 (m, 10H, C$_6H_5$), 7.44 (s, 2H, OMeAr*H*); MS (FAB) *m*/*z* 575 $(M+H)^+$.

3.17. 2-Methoxy-1,3-bis[(4*R*)-4-methoxymethoxy-4-phenyl-2-oxabutyl]benzene, (*R*,*R*)-21

In a manner similar to that described for the preparation of (*S*,*S*)-**12**, treatment of (*R*,*R*)-**20** (248 mg, 0.43 mmol) with a 1.6 M solution of *n*-BuLi in hexanes (0.43 mL, 0.65 mmol) followed by water gave (*R*,*R*)-**21** (153 mg, 71% yield) as a yellow oil after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{26}=-103.2$ (*c* 0.64, $CHCl_3$); IR (neat) 2888, 1594, 1455, 1366, 1213, 1152, 1104, 1037, 919, 759, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.35 (s, 6H, OCH_2OCH_3), 3.62 (dd, $J=7.8$, 10.4 Hz, 2H, OCH(Ph)CH_2), 3.65 (3H, s, OCH_3), 3.77 (dd, $J=4.0$, 10.4 Hz, 2H, OCH(Ph)CH_2), 4.59–4.68 (m, 8H, benzylic CH_2 and OCH_2OCH_3), 4.86 (dd, $J=4.0$, 7.8 Hz, 2H, OCH(Ph)CH_2), 7.06 (t, $J=7.5$ Hz, 1H, OMeArH), 7.24–7.34 (m, 12H, OMeArH and C_6H_5); MS (FAB) m/z 519 $(M+Na)^+$.

3.18. 1,3-Bis[(4*R*)-4-hydroxy-4-phenyl-2-oxabutyl]-2-methoxybenzene, (*R*,*R*)-22

A 0.1 mL of 6N HCl was added to a solution of (*R*,*R*)-**21** (898 mg, 1.80 mmol) in methanol with ice-cooling. After being stirred for 2 days at room temperature, an aqueous solution of sodium hydrogencarbonate was added to the reaction mixture. After extraction with ethyl acetate, the extract was washed with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (hexane:ethyl acetate) to give (*R*,*R*)-**22** (535 mg, 72% yield) as a yellow oil: $[\alpha]_D^{26}=-38.5$ (*c* 1.08, $CHCl_3$); IR (neat) 3443, 2863, 1595, 1455, 1359, 1212, 1102, 903, 761, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.93 (s, 2H, OH), 3.55 (dd, $J=8.6$, 9.8 Hz, 2H, OCH(Ph)CH_2), 3.69 (dd, $J=3.2$, 9.8 Hz, 2H, OCH(Ph)CH_2), 3.77 (s, 3H, OCH_3), 4.65 (s, 4H, benzylic CH_2), 4.92 (dd, $J=3.2$, 8.6 Hz, 2H, OCH(Ph)CH_2), 7.13 (t, $J=7.4$ Hz, 1H, OMeArH), 7.24–7.38 (m, 12H, OMeArH and C_6H_5); MS (FAB) m/z 409 $(M+H)^+$.

3.19. 2-Hydroxy-1,3-bis[(4*R*)-4-hydroxy-4-phenyl-2-oxabutyl]benzene, (*R*,*R*)-23

In a manner similar to that described for the preparation of (*S*,*S*)-**13**, treatment of (*R*,*R*)-**22** (465 mg, 1.10 mmol) with sodium ethanethiolate in DMF gave (*R*,*R*)-**23** (341 mg, 76% yield) as a colorless oil after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{26}=-73.1$ (*c* 1.01, $CHCl_3$); IR (neat) 3376, 2864, 1598, 1464, 1358, 1219, 1103, 901, 756, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.50 (dd, $J=8.8$, 10.3 Hz, 2H, OCH(Ph)CH_2), 3.56 (s, 2H, OH), 3.63 (dd, $J=3.2$, 10.3 Hz, 2H, OCH(Ph)CH_2), 4.62, 4.63 (AB, $J=12.4$ Hz, $\Delta\nu=2.3$ Hz, 4H, benzylic CH_2), 4.84 (dd, $J=3.2$, 8.8 Hz, 2H, OCH(Ph)CH_2), 7.07 (d, $J=7.7$, Hz, 2H, phenol ring CH), 7.40 (t, $J=7.7$ Hz, 1H, phenol ring CH), 7.18–7.30 (m, 10H, C_6H_5), 7.94 (s, 1H, phenolic OH); MS (FAB) m/z 395 $(M+H)^+$.

3.20. 2-Hydroxy-1,3-bis[(4*R*)-4-hydroxy-4-phenyl-2-oxabutyl]-5-nitrobenzene, (*R*,*R*)-5

In a manner similar to that described for the preparation of (*S*,*S*)-**2**, treatment of (*R*,*R*)-**23** (750 mg, 1.9 mmol) with sodium nitrite and nitric acid gave (*R*,*R*)-**5** (212 mg, 25% yield) as a yellow powder after chromatography on silica gel (hexane:ethyl acetate) followed by preparative recycling HPLC ($CHCl_3$): mp 52–53°C; $[\alpha]_D^{26}=-29.3$ (*c* 1.01, $CHCl_3$); IR (KBr) 3306, 2868, 1597, 1520, 1454, 1338, 1198, 1099, 909, 750, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.74 (s, 2H, OH), 3.65 (dd, $J=8.6$, 10.1 Hz, 2H, OCH(Ph)CH_2), 3.78 (dd, $J=3.2$, 10.1 Hz, 2H, OCH(Ph)CH_2), 4.77 (s, 4H, benzylic CH_2), 5.00 (dd, $J=3.2$, 8.6 Hz, 2H, OCH(Ph)CH_2), 7.25–7.40 (m, 10H, C_6H_5), 8.09 (s, 2H, phenol ring CH), 8.93 (s, 1H, phenolic OH); MS (FAB) m/z 440 $(M+H)^+$.

3.21. 5-Bromo-2-methoxy-1,3-bis[(4*R*)-4-methoxy-4-phenyl-2-oxabutyl]benzene, (*R*,*R*)-24

A solution of (*R*,*R*)-**10** (2.50 g, 5.10 mmol) in dry THF (50 mL) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 620 mg, 15.5 mmol) in dry THF (50 mL) over a 3 h period at 60°C. After the mixture was cooled to room temperature, iodomethane (2.50 ml, 41.0 mmol) was added dropwise to the reaction mixture. After all the starting material (*R*,*R*)-**10** had been vanished as indicated by TLC, the reaction mixture was neutralized with water and 6N HCl with ice cooling. After excess iodomethane and the solvent were removed under reduced pressure, the residue was extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Chromatography on silica gel (hexane:ethyl acetate) of the residue gave (*R*,*R*)-**24** as a yellow oil (2.30 g, 86% yield): $[\alpha]_D^{26}=-34.7$ (*c* 0.94, $CHCl_3$); IR (neat) 2930, 1455, 1357, 1210, 1106, 1004, 873, 759, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.30 (s, 6H, OCH_3), 3.56 (dd, $J=7.7$, 10.4 Hz, 2H, OCH(Ph)CH_2), 3.63 (3H, s, ArOCH_3), 3.70 (dd, $J=3.8$, 10.4 Hz, 2H, OCH(Ph)CH_2), 4.41 (dd, $J=3.8$, 7.7 Hz, 2H,OCH(Ph)CH_2), 4.51, 4.59 (AB, $J=8.4$ Hz, $\Delta\nu=$ 20.6 Hz, 4H, benzylic CH_2), 7.25–7.40 (m, 10H, C_6H_5), 7.43 (s, 2H, OMeArH); MS (FAB) m/z 515 $(M+H)^+$.

3.22. 2-Methoxy-1,3-bis[(4*R*)-4-methoxy-4-phenyl-2-oxabutyl]benzene, (*R*,*R*)-25

In a manner similar to that described for the preparation of (*S*,*S*)-**12**, treatment of (*R*,*R*)-**24** (500 mg, 0.970 mmol) with a 1.6 M solution of *n*-BuLi in hexanes (0.90 mL, 1.44 mmol) followed by water gave (*R*,*R*)-**25** (290 mg, 75% yield) as a yellow oil after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{26}=-50.4$ (*c* 0.52, $CHCl_3$); IR (neat) 2931, 1455, 1358, 1245, 1103, 1006, 760, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.29 (s, 6H, OCH_3), 3.54 (dd, $J=7.8$, 10.3 Hz, 2H, OCH(Ph)CH_2), 3.67 (3H, s, ArOCH_3), 3.70 (dd, $J=3.9$, 10.3 Hz, 2H, OCH(Ph)CH_2), 4.41 (dd, $J=3.9$, 7.8 Hz, 2H,OCH(Ph)CH_2), 4.57, 4.65 (AB, $J=7.9$ Hz, $\Delta\nu=$ 20.6 Hz, 4H, benzylic CH_2), 7.06 (t, $J=7.6$ Hz,

OMeAr*H*), 7.23–7.35 (m, 12H, OMeAr*H* and C_6H_5); MS (FAB) *m*/*z* 435 (M^+–H).

3.23. 2-Hydroxy-1,3-bis[(4*R*)-4-methoxy-4-phenyl-2-oxabutyl]benzene, (*R*,*R*)-26

In a manner similar to that described for the preparation of (*S*,*S*)-**13**, treatment of (*R*,*R*)-**25** (200 mg, 0.46 mmol) with sodium ethanethiolate in DMF gave (*R*,*R*)-**26** (144 mg, 74% yield) as a colorless oil after chromatography on silica gel (hexane:ethyl acetate): $[\alpha]_D^{26}=-53.5$ (*c* 0.2, $CHCl_3$); IR (neat) 3361, 2865, 2825, 1597, 1492, 1454, 1356, 1223, 1095, 869, 759, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.30 (s, 6H, OCH_3), 3.61 (dd, *J*=7.9, 10.6 Hz, 2H, OCH(Ph)CH_2), 3.70 (dd, *J*=3.7, 10.6 Hz, 2H, OCH(Ph)CH_2), 4.44 (dd, *J*=3.7, 7.9 Hz, 2H,OC*H*(Ph)CH_2), 4.68, 4.72 (AB, *J*=12.4 Hz, $\Delta\nu$=12.1 Hz, 4H, benzylic CH_2), 6.80 (t, *J*=7.4 Hz, phenol ring C*H*), 7.11 (d, *J*=7.7 Hz, 2H, phenol ring C*H*), 7.25–7.38 (m, 10H, C_6H_5), 7.76 (s, 1H, phenolic O*H*); MS (FAB) *m*/*z* 423 $(M+H)^+$.

3.24. 2-Hydroxy-1,3-bis[(4*R*)-4-methoxy-4-phenyl-2-oxabutyl]-5-nitrobenzene, (*R*,*R*)-6

In a manner similar to that described for the preparation of (*S*,*S*)-**2**, treatment of (*R*,*R*)-**26** (173 mg, 0.409 mmol) with sodium nitrite and nitric acid gave (*R*,*R*)-**6** (111 mg, 58% yield) as a yellow oil after chromatography on silica gel (hexane:ethyl acetate) followed by preparative recycling HPLC ($CHCl_3$): $[\alpha]_D^{28}=-71.0$ (*c* 1.07, $CHCl_3$); IR (neat) 3289, 2864, 1597, 1522, 1454, 1338, 1274, 1201, 1090, 869, 816, 760, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MH) δ 3.33 (s, 6H, OCH_3), 3.69 (dd, *J*=7.9, 10.7 Hz, 2H, OCH(Ph)CH_2), 3.73 (dd, *J*=3.8, 10.7 Hz, 2H, OCH(Ph)CH_2), 4.47 (dd, *J*=3.8, 7.9 Hz, 2H,OC*H*(Ph)CH_2), 4.72 (s, 4H, benzylic CH_2), 7.32–7.57 (m, 10H, C_6H_5), 8.10 (s, 2H, phenol ring C*H*), 8.86 (s, 1H, phenolic O*H*); MS (FAB) *m*/*z* 468 $(M+H)^+$. Anal. calcd for $C_{26}H_{29}NO_7$: C, 66.80; H, 6.25; N, 3.00. Found: C, 66.66; H, 6.31; N, 2.78%.

3.25. (*R*)-2-(Isopropylamino)-2-phenylethanol, (*R*)-34

To a solution of (*R*)-2-amino-2-phenylethanol (900 mg, 6.56 mmol) in ethanol (10 mL), acetone (1.2 mL, 10.9 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. After all the starting amine had been consumed as indicated by gas chromatography, sodium borohydride (370 mg, 9.78 mmol) was added with ice-cooling. After being stirred for 30 min, 1N HCl was added dropwise to adjust the solution to pH 1, and the solvent was removed under reduced pressure. 5 M aqueous KOH solution was added to adjust the solution to pH 11, and the mixture was extracted with CH_2Cl_2. The solution was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was recrystallized from hexane to give (*R*)-**34** as colorless prisms (0.98 g, 83%): mp 76–78°C; $[\alpha]_D^{31}=-68.7$ (*c* 1.05, EtOH); IR (KBr) 3270, 1472, 1169, 1134, 1064, 1041, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.02 (d, *J*=6.2 Hz, 3H, CH_3), 1.04 (d, *J*=6.2 Hz, 3H, CH_3), 2.68–2.82 (m, 1H, C*H*(CH_3)$_2$) 3.46 (dd, *J*=8.7, 11 Hz, 1H, CH_2OH), 3.67 (dd, *J*=4.7, 11 Hz, 1H, CH_2OH), 3.86 (dd, *J*=4.7, 8.7 Hz, 1H, C*H*Ph), 7.24–7.38 (m, 5H, C_6H_5); MS (EI) *m*/*z* 148 (M^+–CH_2=OH). Anal. calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.84; H, 9.65; N, 7.87%.

3.26. (*S*)-2-(Isopropylamino)-2-phenylethanol, (*S*)-34

In a manner similar to that described for the preparation of (*R*)-**34**, reaction of (*S*)-2-amino-2-phenylethanol (1.00 g, 7.29 mmol) with acetone followed by sodium borohydride gave (*S*)-**34** (925 mg, 77% yield) as colorless prisms after recrystallization: mp 76–78°C; $[\alpha]_D^{31}=+66.7$ (*c* 0.91, EtOH); IR (KBr) 3270, 1472, 1169, 1134, 1064, 1041, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.02 (d, *J*=6.2 Hz, 3H, CH_3), 1.04 (d, *J*=6.2 Hz, 3H, CH_3), 2.67–2.81 (m, 1H, C*H*(CH_3)$_2$), 3.46 (dd, *J*=8.7, 11 Hz, 1H, CH_2OH), 3.67 (dd, *J*=4.7, 11 Hz, 1H, CH_2OH), 3.86 (dd, *J*=4.7, 8.7 Hz, 1H, C*H*Ph), 7.24–7.38 (m, 5H, C_6H_5); MS (EI) *m*/*z* 148 (M^+–CH_2=OH). Anal. calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.66; H, 9.63; N, 7.91%.

3.27. (*R*)-2-(Isopropylamino)-1-phenylethanol, (*R*)-35

In a manner similar to that described for the preparation of (*R*)-**34**, reaction of (*R*)-2-amino-1-phenylethanol (975 mg, 7.12 mmol) with acetone followed by sodium borohydride gave (*R*)-**35** as colorless needles (904 mg, 71% yield): mp 83–85°C; $[\alpha]_D^{28}=-26.7$ (*c* 1.03, EtOH); IR (KBr) 3293, 2968, 1604, 1450, 1345, 1088, 1062, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.07 (d, *J*=6.2 Hz, 6H, CHCH_3), 2.76–2.87 (m, 1H, C*H*(CH_3)$_2$), 2.65 (dd, *J*=8.9, 12 Hz, 1H, CH_2OH), 2.94 (dd, *J*=3.7, 12 Hz, 1H, CH_2OH), 4.65 (dd, *J*=3.7, 8.9 Hz, 1H, C*H*Ph), 7.23–7.39 (m, 5H, C_6H_5); MS (EI) *m*/*z* 180 (M^+–CH_2=OH). Anal. calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.74; H, 9.70; N, 7.81%.

3.28. (*S*)-2-(Isopropylamino)-1-phenylethanol, (*S*)-35

In a manner similar to that described for the preparation of (*R*)-**34**, reaction of (*S*)-2-amino-1-phenylethanol (979 mg, 7.14 mmol) with acetone followed by sodium borohydride gave (*S*)-**35** as colorless needles after recrystallization (973 mg, 76%): mp 82–83°C; $[\alpha]_D^{28}=+28.3$ (*c* 1.10, EtOH); IR (KBr) 3293, 2968, 1604, 1450, 1345, 1088, 1062, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.07 (d, *J*=6.2 Hz, 6H, CH(CH_3)$_2$), 2.77–2.89 (m, 1H, C*H*(CH_3)$_2$), 2.66 (dd, *J*=8.9, 12 Hz, 1H, CH_2OH), 2.95 (dd, *J*=3.7, 12 Hz, 1H, CH_2OH), 4.66 (dd, *J*=3.7, 8.9 Hz, 1H, C*H*Ph), 7.22–7.39 (m, 5H, C_6H_5); MS (EI) *m*/*z* 180 (M^+–CH_2=OH). Anal. calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.52; H, 9.53; N, 7.82%.

3.29. General procedures for determination of binding constants

The titration experiment for complexation of host (*S*,*S*)-**3** with chiral amine (*S*)-**32** is described here as an example for determination of binding constants by ^1H

NMR spectroscopy. A solution of (*S*,*S*)-**3** (22.3 mM) and a solution of (*S*)-**32** (81.1 mM) each in $CDCl_3$ were prepared. An initial ^1H NMR spectrum of 600 μL of this host (*S*,*S*)-**3** solution was recorded. Samples were made by adding the guest solutions to the host solution. Namely, a 600 μL portion of the host solution and 0.0, 10, 20, 30, 40, 50, 60, 80, 100, 130, 160, and 200 μL portions of the guest (*S*)-**32** solution were mixed. Then, spectra of these samples were recorded. The association constant for the complex of (*S*,*S*)-**3** with (*S*)-**32** was calculated by the non-linear least-squares method following the chemical shift of one of the benzylic protons (Hβ shown in Fig. 3) of (*S*,*S*)-**3**. The titration curve is shown in Fig. 1.

The titration experiment for complexation of host (*R*,*R*)-**5** with chiral amine (*R*)-**35** is described here as an example for determination of binding constants by UV–visible spectroscopy. A solution of (*R*,*R*)-**5** in $CHCl_3$ was prepared and an initial UV spectrum of this solution was recorded. The concentration was calculated to be 0.036 mM based on its molar extinction coefficient. Separately, a solution of (*R*)-**35** in $CHCl_3$ was prepared. Samples were made by adding the guest solution to the host solution and diluted with $CHCl_3$ to make the total volume up to 4.0 mL, so that the concentrations of the guest in each samples were 0.0, 2.0, 5.0, 8.0, 14, 20 mM, respectively. The concentration of the host was kept constant at 0.036 mM in each sample. Then, the spectra of these five different solutions were recorded. The binding constants were calculated from absorption intensity of the complex at the absorption maximum (388 nm) based on the Rose–Drago method using the spreadsheet in Ref. 12b. A graphical expression to appreciate the binding constant is shown in Fig. 2.

The binding constants thus determined are summarized in Tables 1 and 2.

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14. We measured binding constants of (*S*,*S*)-**3** with *S*- and *R*-enantiomers of *N*,α-dimethylbenzylamine (**32**) by the ^1H NMR titration and UV–vis titration methods. The binding constants of (*S*,*S*)-**3** with (*S*)- and (*R*)-**32** obtained by the ^1H NMR titration method were (1.8±0.1)×10 M^{-1} and 8.8±0.3 M^{-1}, respectively ($K_S/K_R = 2.0$), and those determined by the UV–vis titration were (2.1±0.3) and (1.0±0.1)×10 M^{-1}, respectively ($K_S/K_R = 2.1$).
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19. Attempts to measure NOE between the hosts and the guests were unsuccessful.
20. For example, CISs of H2β, H22β, and H19 with isopropylmethylamine are −0.45, −0.24, and −0.08 ppm, respectively. The large negative CISs of H2β and H22β is ascribed to the conformational change of the host (*S*,*S*)-**3** upon complexation.
21. Although the enantiomer selectivities for other host–guest combinations may be similarly explained, we were unable to obtain spectroscopic (NOE and CIS) support for them.