Synthesis of azophenolic crown ethers of C_s symmetry incorporating *cis*-1-phenylcyclohexane-1,2-diol residues as a steric barrier and diastereotopic face selectivity in complexation of amines by their diastereotopic faces [1]

Koichiro Naemura,*[,a] Sachiko Takeuchi,[a] Masaki Asada,[a] Koji Ueno,[a] Keiji Hirose,[a] Yoshito Tobe,[a] Takahiro Kaneda[b] and Yoshiteru Sakata[b]

[a] *Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan*
[b] *The Institute of Scientific and Industrial Research, Osaka University, Mihoganoka, Ibaraki, Osaka 567, Japan*

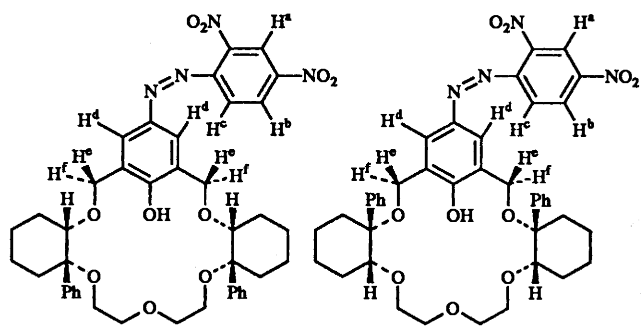
Azophenolic crown ethers **1** and **2** of C_s symmetry incorporating *cis*-1-phenylcyclohexane-1,2-diol residues as a steric barrier have been prepared. Diastereotopic face selectivity in complexation with 2-methoxyethylamine, *n*-propylamine and ethanolamine was examined using temperature-dependent ^{1}H NMR spectroscopy. Both bind ethanolamine stereoselectively to one of their diastereotopic faces; the prediction of which diastereoisomeric complex was preferentially formed is made on the basis of a CPK molecular-model examination of the complexes.

Introduction

Many chiral and achiral crown ethers have been prepared and their complexation with neutral and ionic molecules has been widely investigated.[2] Most of them contain at least one C_2 axis and have homotopic faces to avoid 'sidedness' problems in complexation with a guest molecule. However, diastereotopic face selectivity in the complexation of a crown ether having diastereotopic faces with a guest molecule is of interest. The complexation of alkylammonium cations with chiral crown ethers having diastereotopic faces has been reported,[3] but, as far as we know, there has been no report of diastereotopic face selectivity in complexation of alkylamine and alkylammonium cations by the diastereotopic faces of a crown ether of the *meso*-type. Herein we report the preparation of *meso*-azophenolic crown ethers **1** and **2** which contain *cis*-1-phenylcyclohexane-1,2-diol residues as a steric barrier. The plane of symmetry is perpendicular to the crown ring and hence the faces of the crown rings are diastereotopic. Diastereotopic face selectivity in complexation of hosts *meso*-**1** and *meso*-**2** with achiral alkylamines is also described and the prediction of which diastereoisomeric complex is formed preferentially is made on the basis of temperature-dependent ^{1}H NMR spectroscopy and an examination of CPK molecular models.

Results and discussion

Treatment of diol (±)-**3**[4] with dimethoxymethane gave exclusively the monoprotected alcohol (±)-**4**, and condensation of compound (±)-**4** with diethylene glycol bis(methanesulfonate) in the presence of sodium hydride in dry tetrahydrofuran (THF) gave the polyether **5** as a mixture of *meso*-**5** and (±)-**5**. The ^{1}H NMR spectrum consisted of two sets of signals. One set of signals coincided with that of compound (−)-**5** previously prepared from diol (−)-**3** *via* intermediate (+)-**4**.[5] All attempts to separate *meso*-**5** from the mixture of diastereoisomeric polyethers were unsuccessful, and the mixture was used in the following reactions. After treatment of the mixture of polyethers **5** with conc. HCl and methanol, the resulting diol **6** was condensed with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in the presence of sodium hydride and potassium tetrafluoroboranuide in dry THF to give a mixture of diastereoisomeric crown ethers, which was separated into *meso*-

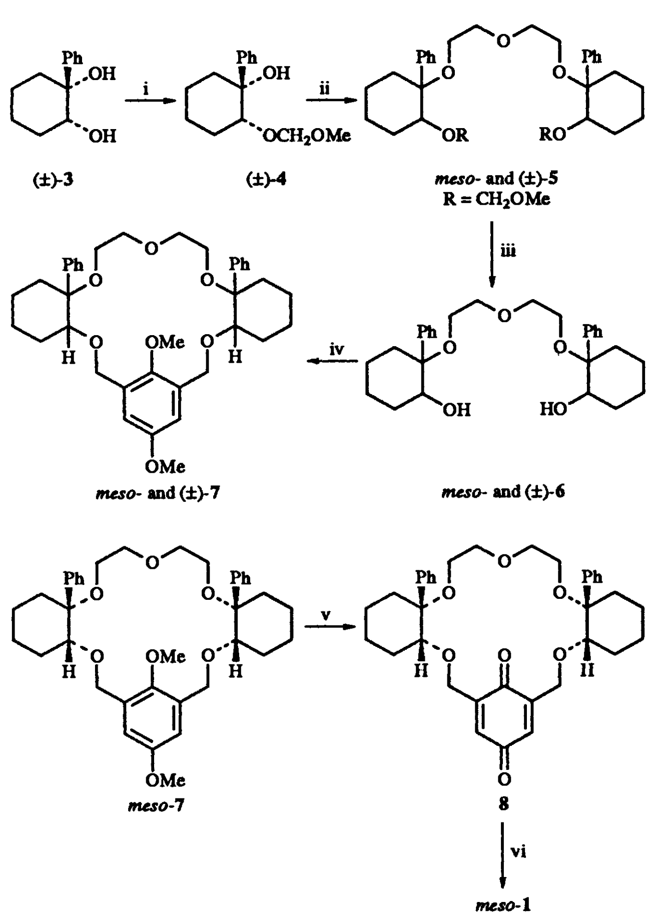


meso-**1** *meso*-**2**

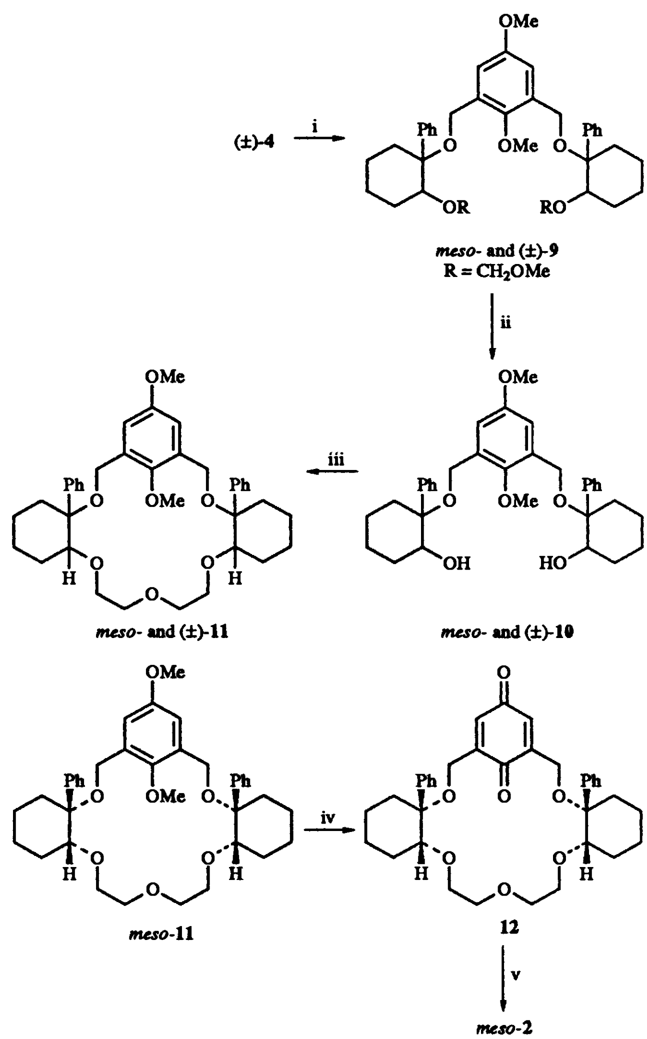
7 (24%) and (±)-**7** (25%) by chromatography on silica gel. The structure of racemate (±)-**7** was unambiguously identified by comparison of its spectral data with those of crown (+)-**7**[5] prepared from compound (−)-**5**. Oxidation of *meso*-**7** with cerium(IV) ammonium nitrate (CAN) in acetonitrile–water gave the quinone **8**, which was immediately treated with 2,4-dinitrophenylhydrazine in conc. H_2SO_4–ethanol to give *meso*-**1** as an orange solid (Scheme 1). By the similar manner, condensation of racemate (±)-**4** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene gave a mixture of compounds *meso*-**9** and (±)-**9**. The ^{1}H NMR spectrum consisted of two sets of signals. The mixture was used in the following reactions without further separation. Hydrolysis of the mixture of compounds **9** gave the diol **10**, which was treated with diethylene glycol bis(methanesulfonate) to give the mixture of diastereoisomeric crown ethers **11**. Chromatographic separation of the mixture gave *meso*-**11** (17%) and (±)-**11** (19%) and the structure of the latter was confirmed by comparison of its spectral data with those of crown (−)-**11**. Oxidation of *meso*-**11** followed by treatment with 2,4-dinitrophenylhydrazine provided *meso*-**2** as an orange solid (Scheme 2).

The optically active crown ether (−)-**11** was prepared from (1*S*,2*S*)-(−)-**3**, $[\alpha]_D$ −19.3† (> 99% ee) by the same procedure as for the preparation of racemate (±)-**11**. After the conversion

† Units for $[\alpha]_D$-values are 10^{-1} deg cm^2 g^{-1}.



Scheme 1 *Reagents*: i, $(MeO)_2CH_2$, LiBr, TsOH; ii, $(MsOCH_2CH_2)_2O$, NaH; iii, conc. HCl, MeOH; iv, 1,3-bis(bromomethyl)-2,5-dimethoxybenzene, NaH, KBF_4; v, CAN; vi, 2,4-dinitrophenylhydrazine, conc. H_2SO_4



Scheme 2 *Reagents*: i, 1,3-bis(bromomethyl)-2,5-dimethoxybenzene, NaH; ii, conc. HCl, MeOH; iii, $(MsOCH_2CH_2)_2O$, NaH, KBF_4; iv, CAN; v, 2,4-dinitrophenylhydrazine, conc. H_2SO_4

Table 1 Association constants[a] and absorption maxima[b] of the complexes

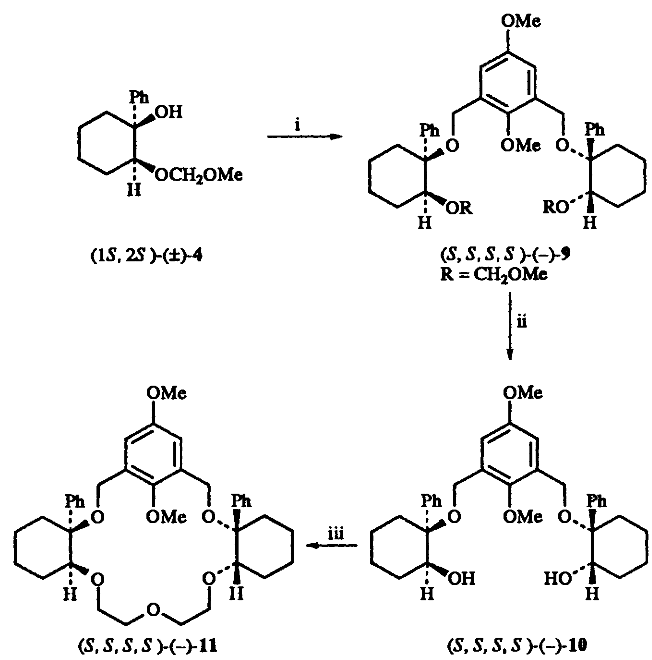
Amine	Crown ether	K_a/dm^3 mol^{-1}	λ_{max}/nm
Ethanolamine	**1**	2.97×10^4	585
Ethanolamine	**2**	9.88×10^3	589

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

of (−)-**3** into the alcohol (1*S*,2*S*)-(+)-**4**, reaction of compound (+)-**4** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene followed by hydrolysis gave diol (−)-**10** *via* intermediate (−)-**9**. Condensation of diol (−)-**10** with diethylene glycol bis(methanesulfonate) gave crown (*S,S,S,S*)-(−)-**11**, $[\alpha]_D$ −41.3 ($CHCl_3$) (Scheme 3).

A feature of crown ethers **1** and **2** which have C_s symmetry and a phenolate oxygen atom together with the 2,4-dinitrophenylazo group is that they can bind neutral amines to form diastereoisomeric α- and/or β-complexes; the red shift observed on formation of the complex with amines can be detected in UV and visible spectra. The observed absorption maximum of hosts **1** and **2** appeared at 414 and 416 nm, respectively, and their complexes with ethanolamine showed the absorption maximum in the region 585–589 nm.

The association constants for the complexation of crown ethers **1** and **2** with amines in $CHCl_3$ were determined by the Benesi–Hildebrand method[6] with the aid of their self-colour-



Scheme 3 *Reagents*: i, 1,3-bis(bromomethyl)-2,5-dimethoxybenzene, NaH; ii, conc. HCl, MeOH; iii, $(MsOCH_2CH_2)_2O$, NaH, KBF_4

Table 2 ^1H NMR chemical shifts of selected protons of the mixture of host **1** and 2-methoxyethylamine (in $CDCl_3$; *J* in Hz)

	Host/guest	Host/guest	Host/guest
Protons[a]	1/0.5 (at 35 °C)	1/0.5 (at −50 °C)	1/1.5 (at −50 °C)
H[a]	8.66 d, *J* 2.0	8.85 d, *J* 2.5 (h)[b]	
		8.67 d, *J* 2.0 (ma.)[b]	8.67 d (ma.)
		8.65 d, *J* 2.5 (mi.)[b]	8.65 d (mi.)
H[b]	8.37 dd, *J* 2.0 and 9.0	8.57 dd, *J* 10.0 and 2.5 (h)	
		8.33 dd, *J* 9.5 and 2.0 (ma.)	8.33 dd (ma.)
		8.23 dd, *J* 10.5 and 2.5 (mi.)	8.23 dd (mi.)
H[c]	7.84 d, *J* 9.0	7.90 d, *J* 9.5 (ma.)[c]	7.90 d (ma.)
		7.94 d, *J* 10.5 (mi.)	7.94 d (mi.)

[a] In this table, signals unambiguously assigned are listed. [b] (h), signal for the host; (ma.), signal for the major complex; (mi.), signal for the minor complex. [c] The peaks for the host are overlapping resonances.

indicating properties[7] and the observed K_a-values of the complexes are listed in Table 1. The rather large K_a-values for the complexes suggested that the hydroxy group of ethanolamine was bound to the phenolate oxygen of the hosts by additional hydrogen bonding to make these complexes stable.[8]

We next examined diastereotopic face selectivity in complexation of achiral amines by the diastereotopic faces of hosts **1** and **2** by using temperature-dependent ^1H NMR spectroscopy in $CDCl_3$. The ^1H NMR spectrum of the mixture of host **1** and 0.5 mol equiv. of 2-methoxyethylamine showed signals for H^a, H^b and H^c at δ 8.66, 8.37 and 7.84, respectively, at 35 °C and, on cooling down to −50 °C, each signal separated well into high- (δ 8.67, 8.33 and 7.90, respectively) and low- (δ 8.65, 8.23 and 7.94, respectively) intensity signals for the complexes and those (δ 8.85 and 8.57) for the host. When 1.5 mol equiv. of the amine was added to host **1**, signals for the host disappeared completely and two sets of signals for the complexes were observed in the low-temperature ^1H NMR spectrum of the mixture. ^1H NMR chemical shifts of these protons are listed in Table 2. These observations indicated that host **1** bound 2-methoxyethylamine to both of its diastereotopic faces to form the diastereoisomeric complexes in the ratio ~2:1 as judged from the intensity of signals.

Similarly, the low-temperature ^1H NMR spectrum of the mixture of host **1** and 1.5 mol equiv. of *n*-propylamine showed high- (δ 8.67, 8.34 and 7.99 due to H^a, H^b and H^c, respectively) and low- (δ 8.65, 8.23 and 7.93 due to H^a, H^b and H^c, respectively) intensity signals for the complexes, and signals for the host which were observed in the spectrum of the mixture of **1** and 0.5 mol equiv. of the amine had completely disappeared (Table 3). The results demonstrated that *n*-propylamine was also bound to both faces of host **1** to furnish the diastereoisomeric complexes in the ratio ~2:1.

In the case of complexation of hosts **1** and **2** with ethanolamine, calculation on the basis of the temperature-dependent ^1H NMR spectra of the complexes showed that compounds **1** and **2** were almost quantitatively converted into complexes **13** and **14**, respectively, in $CDCl_3$ solution at low temperature. When less than one mol equiv. of ethanolamine was added to host **1**, the ^1H NMR spectrum of the mixture showed high- (δ 8.53, 8.40, 8.02, 6.70, 3.06 and 5.19 due to H^a, H^b, H^c, H^d, H^e and H^f, respectively) and low- (δ 8.81, 8.53, 7.82, 7.59, 4.28 and 4.89 due to H^a, H^b, H^c, H^d, H^e and H^f, respectively) intensity signals in the 'high'/'low' ratio of δ ~ 5:2 and the signals with low intensity were identified as those of the host (Table 4). The spectrum of the mixture of **1** with an excess of the amine showed only one set of signals for the complex even at low temperature (Table 5). The results provided evidence for the exclusive formation of one of the diastereoisomeric complexes.

Next, the prediction of which diastereoisomeric complex of host **1** with ethanolamine was exclusively formed was made on the basis of ^1H NMR spectra and examination of CPK molecular models of the complexes. In the spectrum of the complex of compound **1** with ethanolamine, signals for H^d and H^e were shifted upfield by ~0.95 and ~1.35 ppm compared with their respective chemical shifts in the spectrum of host **1**. The upfield shifts observed showed that two phenyl substituents were oriented over these protons in the α-complex **13α**; that is, complexation occurred at the α-face of compound **1**. CPK molecular models of the complexes show that H^d and H^e are shielded by the phenyl barriers in complex **13α**, but not in the β-complex **13β**. The CPK molecular model of complex **13β** suggested that two cyclohexane residues are brought close

Table 3 ^1H NMR chemical shifts of selected protons of the mixture of host **1** and *n*-propylamine (in $CDCl_3$ at −50 °C; *J* in Hz)

	Host/guest	Host/guest
Protons[a]	1/0.5	1/1.5
H[a]	8.85 d, *J* 2.5 (h)[b]	
	8.67 d, *J* 2.5 (ma.)[b]	8.67 d (ma.)
	8.65 d, *J* 2.5 (mi.)[b]	8.65 d (mi.)
H[b]	8.57 dd, *J* 10.0 and 2.5 (h)	
	8.34 dd, *J* 9.5 and 2.5 (ma.)	8.34 dd (ma.)
	8.23 dd, *J* 9.5 and 2.5 (mi.)	8.23 dd (mi.)
H[c]	7.99 d, *J* 9.5 (ma.)[c]	7.99 d (ma.)
	7.93 d, *J* 9.5 (mi.)	7.93 d (mi.)

[a] In this table, signals unambiguously assigned are listed. [b] (h), signal for the host; (ma.), signal for the major complex; (mi.), signal for the minor complex. [c] The peaks for the host are overlapping resonances.

Table 4 ^1H NMR chemical shifts of selected protons of host **1** and a mixture of host **1** and ethanolamine (host/guest = 1.4/1.0) (in $CDCl_3$, at − 20 °C; *J* in Hz)

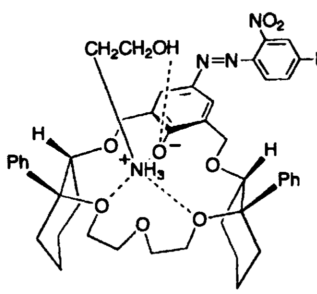
Protons[a]	1	Mixture
H[a]	8.81 d, *J* 2.2	8.81 d (h)[b]
		8.53 d (com.)[b]
H[b]	8.53 dd, *J* 8.9 and 2.5	8.53 dd (h)
		8.40 dd (com.)
H[c]	7.82 d, *J* 8.9	7.82 d (h)
		8.02 d (com.)
H[d]	7.57 br	7.59 br (h)
		6.70 s (com.)
H[e]	4.26 br	4.28 br (h)
		3.06 d (com.)
H[f]	4.89 d, *J* 10.4	4.89 d (h)
		5.19 d (com.)

[a] In this table, signals unambiguously assigned are listed. [b] (h), signal for the host; (com.), signal for the complex.

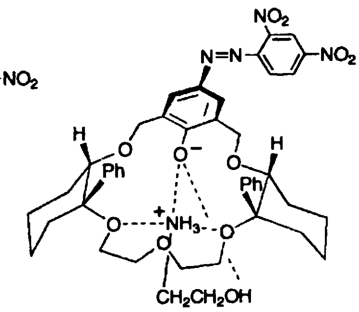
together on the α-face of complex **13β**, and so the high α-face selectivity in complexation is assumed to arise from steric repulsions between these residues which make complex **13β** less stable than complex **13α**. On the other hand, the steric repulsions between two cyclohexane residues and the guest bound to the α-face in complex **13α** is presumed to be small, because ethanolamine is the less sterically demanding guest.

In the low-temperature ^1H NMR spectrum of the mixture of host **2** with an excess of ethanolamine, one set of signals for the complex was observed and signals for the host were not found (Table 6). The results indicated that compound **2** was quantitatively converted into one of the diastereoisomeric complexes. In this case, it was concluded that the amine was preferentially bound to the β-face, because no upfield shift of the signals for H^d and H^e was observed in the spectrum of the β-complex **14β**. Protons H^d and H^e in the α-complex **14α** should be oriented within the shielding zones of the phenyl groups. A CPK molecular model of complex **14α** suggests that two phenyl substituents and the phenol moiety are brought close together on the β-face of complex **14α** and the high stereoselectivity of binding to the β-face may be ascribed to large steric repulsions by these groups. Although complex **14β** is energetically more favourable than complex **14α**, the K_a-value for complex **14β** is reduced to one-third that for complex **13α**. The relatively small K_a-value for complex **14β** may be ascribed to steric repulsions by two cyclohexane moieties on the α-face of complex **14β**, which make this complex less stable than complex **13α**.

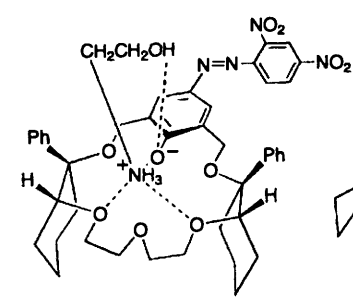
Observed singlet signals for H^d and H^e in complexes **13α** and **14β** at 35 °C showed that two H^d and H^e protons were, respectively, homotopic because of free rotation about the C–N bond of the azophenolic residue at this temperature. However, on cooling down to −50 °C, each signal separated into two peaks of equal intensity. Similarly, H^d protons in crown ether **15** were homotopic even at −50 °C, but their signals in the complex of host **15** with ethanolamine separated into two peaks of equal intensity at −50 °C (Table 7). From these results, we assume that restricted rotation about the C–N bond resulting from a contribution of the quinoid structure of the phenolate moiety in the complex with ethanolamine made these protons heterotopic at low temperature.



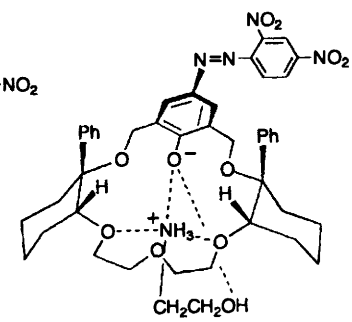
13β



13α



14β



14α

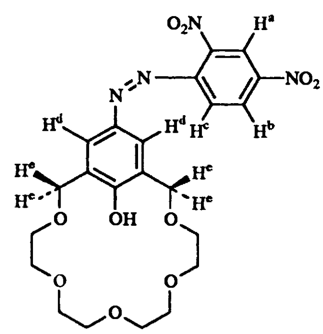


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Table 5 ^1H NMR chemical shifts of selected protons of a mixture of host **1** and ethanolamine (host/guest = 1/3) (in $CDCl_3$)

Protons[a]	At 35 °C	At −30 °C
H^a	8.58 d	8.65 d
H^b	8.34 dd	8.41 dd
H^c	7.95 d	8.04 d
H^d	6.79 s	6.68 s, 6.69 s
H^e	3.11 d	3.04 d, 3.09 d
H^f	5.19 d	5.19 d

[a] In this table, signals unambiguously assigned are listed.

Experimental

General procedure

Mps were measured on a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a JASCO JNM-MH-270 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. *J* Values are given in Hz. FAB mass spectra were recorded with 3-nitrobenzyl alcohol as a matrix on a JEOL-DX-303-HF spectrometer. Elemental analyses were carried out on a Yanagimoto CHN-Corder, Type 2. UV–visible spectra were measured on a Hitachi 330

Table 6 ^1H NMR chemical shifts of selected protons of host **2** and a mixture of host **2** and ethanolamine (host/guest = 1/3) (in $CDCl_3$; *J* in Hz)

	2		Mixture	
Protons[a]	At 35 °C	At −50 °C	At 35 °C	At −50 °C
H^a	8.71 d, *J* 2.2	8.85 d	8.59 d	8.69 d
H^b	8.44 dd, *J* 8.9 and 2.2	8.55 dd	8.29 dd	8.36 dd
H^c	7.76 d, *J* 8.9	7.78 d	7.93 d	8.09 d
H^d	7.54 s	*b*	7.85 br s	7.85 d, 8.05 d
H^e	4.35 d, *J* 10.9	4.22 br s	4.17 d	4.10 d, 4.12 d
H^f	4.52 d, *J* 10.9	4.73 br s	4.75 d	4.80 d, 4.86 d

[a] In this table, signals unambiguously assigned are listed. [b] The peaks of H^d for the host are overlapping resonances.

Table 7 ^1H NMR chemical shifts of selected protons of host **15** and a mixture of host **15** and ethanolamine (host/guest = 1/3) (in $CDCl_3$; J in Hz)

	15		Mixture	
Protons[a]	At 35 °C	At −50 °C	At 35 °C	At −50 °C
H[a]	8.75 d, J 2.2	8.87 d	8.59 d	8.69 d
H[b]	8.48 dd, J 8.9 and 2.2	8.59 dd	8.33 dd	8.42 dd
H[c]	7.81 d, J 8.9	7.85 d	7.91 d	7.95 d
H[d]	7.81 s	7.89 s	7.84 s	7.83 s, 7.95 s
H[e]	4.76 s	4.76 s	4.55 br	5.03 d, 5.19 d[b]

[a] In this table, signals unambiguously assigned are listed. [b] The two other peaks of H[e] are overlapping resonances at δ 3.9–4.1.

spectrometer. IR spectral data were obtained on a Hitachi 260-10 spectrophotometer. Optical rotations were measured using a JASCO DIP-40 polarimeter and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}.

(±)-2-Methoxymethoxy-1-phenylcyclohexanol 4

A mixture of (±)-cis-1-phenylcyclohexane-1,2-diol **3**[4] (15.0 g, 78.1 mmol), dimethoxymethane (230 g, 3.02 mol), lithium bromide hydrate (2.88 g), and toluene-*p*-sulfonic acid monohydrate (TsOH) (1.47 g) was refluxed for 9 h and then diluted with water. An organic layer was separated, washed successively with saturated aq. $NaHCO_3$ and water, and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on silica gel with hexane–diethyl ether (9:1) as eluent to give *title compound* (±)-**4** (9.80 g, 53%) as a solid, mp 56–57 °C; ν_{max}(neat film)/cm^{-1} 3450s, 3050w, 3020w, 2930s, 2855m, 1595w, 1445m, 1155m, 1135m, 1095m, 1030s, 985m, 760s and 700s; δ_H 1.35–1.98 (8 H, m, CH_2), 2.65 (1 H, br s, OH), 2.85 (3 H, s, OMe), 3.96 (1 H, dd, J 4.7 and 10.9, CH), 4.16 (1 H, d, J 6.9, OCH_2O), 4.47 (1 H, d, J 6.9, OCH_2O) and 7.18–7.52 (5 H, m, ArH) (Found: C, 71.0; H, 8.5. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%).

***meso*- and (±)-1,5-Bis(2′-methoxymethoxy-1′-phenylcyclohexyloxy)-3-oxapentane 5**

A solution of compound (±)-**4** (5.00 g, 21.2 mmol) in dry THF (37 cm^3) was added dropwise to a suspension of sodium hydride (1.02 g, 42.5 mmol) in dry THF (37 cm^3) and then the mixture was heated at 50 °C for 1 h. After cooling of this mixture to room temp., a solution of diethylene glycol bis(methanesulfonate) (2.75 g, 10.5 mmol) in dry THF (40 cm^3) was added to the mixture, which was then refluxed for 19 h. After the reaction mixture had been cooled in an ice-bath, a small amount of water was slowly added to the reaction mixture to decompose the excess of sodium hydride and then the solvent was removed under reduced pressure. The residue was diluted with water and extracted with methylene dichloride. The extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane–diethyl ether (4:1) as eluent to give the mixture of *poly ethers meso*- and (±)-**5** (2.01 g, 35%) as an oil, which solidified in a refrigerator; mp 113–114 °C; ν_{max}(KBr)/cm^{-1} 3080w, 3052w, 3020w, 2950s, 2902m, 2860m, 2830m, 1600w, 1450m, 1220m, 1150m, 1135m, 1100m, 1085m, 1043s, 760m and 700m; δ_H 1.34–2.16 (m, CH_2, *meso* and ±), 2.89 (s, OMe, ±), 2.90 (s, OMe, *meso*), 3.35–3.50 (m, OCH_2CH_2O and CH, *meso* and ±), 3.89 (d, J 6.9, OCH_2, ±), 3.90 (d, J 6.9, OCH_2, *meso*), 4.38 (d, J 6.9, OCH_2, *meso* and ±), 7.18–7.24 (m, ArH, *meso* and ±), 7.27–7.36 (m, ArH, *meso* and ±) and 7.43–7.48 (m, ArH, *meso* and ±) (Found: C, 70.7; H, 8.5. $C_{32}H_{46}O_7$ requires C, 70.82; H, 8.54%).

(−)-1,5-Bis(2′-methoxymethoxy-1′-phenylcyclohexyloxy)-3-oxapentane 5

By the same treatment as described above, compound (+)-**4**, $[\alpha]_D$ +47.0 ($CHCl_3$) (5.00 g, 21.2 mmol), reacted with diethylene glycol bis(methanesulfonate) (2.75 g, 10.5 mmol) to give *title compound* (−)-**5** (1.56 g, 27%), mp 113 °C (from hexane); $[\alpha]_D^{23}$ −9.9 (c 1.00, $CHCl_3$); δ_H 1.6–2.17 (16 H, m, CH_2), 2.89 (6 H, s, OMe), 3.37–3.52 (8 H, m, OCH_2CH_2O), 3.75 (2 H, dd, J 5.68 and 5.44, CH), 3.89 (2 H, d, J 6.93, OCH_2), 4.38 (2 H, d, J 6.93, OCH_2), 7.21 (2 H, tt, J 1.2 and 7.5, ArH), 7.31 (4 H, t, J 7.7, ArH) and 7.46 (4 H, dd, J 1.2 and 7.7, ArH) (Found: C, 70.5; H, 8.6%).

***meso*- and (±)-2,2′-Diphenyl-2,2′-[oxybis(ethyleneoxy)]-dicyclohexanol 6**

A solution of the mixture of polyethers *meso*-**5** and (±)-**5** (1.90 g, 3.51 mmol) in methanol (220 cm^3) with a few drops of conc. HCl was stirred at 50 °C for 4 h and then was extracted with methylene dichloride. The extract was washed successively with saturated aq. $NaHCO_3$ and water, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, silica gel chromatography of the product with hexane–diethyl ether (2:1) as eluent gave a mixture of *diols meso*-**6** and (±)-**6** (1.51 g, 95%) as a viscous oil, ν_{max}(neat film)/cm^{-1} 3400s, 3080w, 3052w, 3020w, 2950s, 2870m, 1600w, 1450m, 1095s, 760m and 700m; δ_H 1.36–2.20 (m, CH_2, *meso* and ±), 3.21–3.41 (m, OCH_2CH_2O, *meso* and ±), 3.50–3.58 (m, OCH_2CH_2O, *meso* and ±), 3.65–3.74 (m, OCH_2CH_2O, *meso* and ±), 3.89–3.91 (m, CH, *meso* and ±), 4.00 (br s, OH, *meso* and ±), 7.24–7.30 (m, ArH, *meso* and ±), 7.33–7.39 (m, ArH, *meso* and ±) and 7.47–7.53 (m, ArH, *meso* and ±) (Found: C, 73.8; H, 8.4. $C_{28}H_{38}O_5$ requires C, 73.98; H, 8.42%).

***meso*- and (±)-2,5-Dimethoxy-1,3-bis(2′-methoxymethoxy-1′-phenylcyclohexyloxymethyl)benzene 9**

A solution of racemate (±)-**4** (5.52 g, 23.4 mmol) in dry THF (45 cm^3) was added dropwise to a suspension of sodium hydride (910 mg, 38.0 mmol) in dry THF (45 cm^3) and then the mixture was stirred for 1 h at room temp. To the mixture was added a solution of 1,3-bis(bromomethyl)-2,5-dimethoxybenzene[9] (3.24 g, 10.0 mmol) in dry THF (45 cm^3) and then the mixture was refluxed under nitrogen for 24 h. After cooling to room temperature, the reaction mixture was treated with a small amount of water added slowly and then was concentrated under reduced pressure. The residue was taken up in chloroform and the solution was washed with water and dried ($MgSO_4$). The solvent was evaporated off under reduced pressure and column chromatography of the residue on silica gel with hexane–diethyl ether (4:1) as eluent gave a mixture of *title compound meso*-**9** and (±)-**9** (3.73 g, 59%) as an oil, ν_{max}(neat film)/cm^{-1} 3055w, 2950s, 2860m, 1600m, 1450m, 1220m, 1110m, 1045s, 760m and 700m; δ_H 1.44–2.23 (m, CH_2, *meso* and ±), 3.57 (br s, CH, *meso* and ±), 2.94 (s, OMe, ±), 2.95 (s, OMe, *meso*), 3.57 (s, ArOMe, *meso*), 3.58 (s, ArOMe, ±), 3.86 (s, ArOMe, *meso* and ±), 3.99 (d, J 6.9, OCH_2, *meso* and ±), 4.29 (d, J 11.8, ArCH_2, ±), 4.30 (d, J 11.8, ArCH_2, *meso*), 4.43 (d, J 6.9, OCH_2, *meso* and ±), 4.45 (d, J 12.1, ArCH_2, *meso* and ±), 7.16 [s, Ar(OMe)*H*, *meso* and ±], 7.24–7.27 (m, ArH, *meso* and ±), 7.31–7.37 (m, ArH, *meso* and ±) and 7.51–7.57 (m, ArH, *meso* and ±) (Found: C, 71.7; H, 7.8. $C_{38}H_{50}O_8$ requires C, 71.90; H, 7.94%).

***meso*- and (±)-2″,6″-Dimethoxy-2,2′-diphenyl-2,2′-[*m*-phenylenebis(methyleneoxy)]dicyclohexanol 10**

A solution of the mixture of polyethers *meso*-**9** and (±)-**9** (3.70 g, 5.84 mmol) in methanol (450 cm^3) with a few drops of conc. HCl was stirred at 50 °C for 3 h. After cooling to room temperature, the reaction mixture was neutralized (to pH ~7, pH paper) with aq. $NaHCO_3$. The solvent was evaporated off under reduced pressure and the residue was taken up in methylene dichloride. The solution was washed with water and dried ($MgSO_4$). After removal of the solvent, column chromatography of the residue on silica gel with hexane–diethyl ether (1:1) as eluent gave a mixture of *diols meso*-**10** and (±)-**10** (3.00 g, 94%) as a glass, ν_{max}(KBr)/cm^{-1} 3400s, 2940s, 2855m, 1600m, 1445s, 1215m, 1150m, 1060s, 755m and 700s; δ_H 1.54–2.21 (m, CH_2, *meso* and ±), 3.74–3.77 (m, CH, *meso* and ±), 3.53 (s, OMe, ±), 3.55 (s, OMe, *meso*), 3.83 (s, OMe, *meso* and ±), 4.17 (d, *J* 11.6, ArCH_2, *meso*), 4.18 (d, *J* 11.6, ArCH_2, ±), 4.45 (d, *J* 11.6, ArCH_2, *meso* and ±), 6.98 [s, Ar(OMe)*H*, *meso*], 6.99 [s, Ar(OMe)*H*, ±], 7.00 (s, OH, *meso* and ±), 7.26–7.32 (m, ArH, *meso* and ±), 7.36–7.41 (m, ArH, *meso* and ±) and 7.49–7.52 (m, ArH, *meso* and ±) (Found: C, 74.4; H, 7.6. $C_{34}H_{42}O_6$ requires C, 74.69; H, 7.74%).

***meso*-Crown ether 7 and (±)-crown ether 7**

A solution of the mixture of diols *meso*-**6** and (±)-**6** (1.50 g, 3.30 mmol) and 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (1.07 g, 3.30 mmol) in dry THF (370 cm^3) was added dropwise to a boiling mixture of sodium hydride (320 mg, 13.3 mmol), potassium tetrafluoroboranuide (416 mg, 3.30 mmol) and dry THF (180 cm^3) over a 10 h period and then the mixture was refluxed for an additional 20 h under dry nitrogen. After the reaction mixture had been cooled in an ice-bath, a small amount of water was slowly added and the solvent was evaporated off under reduced pressure. The residue was diluted with water and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel. Early fractions eluted with hexane–diethyl ether (4:1) gave *crown ether meso*-**7** (492 mg, 24%) as a solid, mp 175–177 °C, and subsequent fractions eluted with the same solvent gave *racemate* (±)-**7** (517 mg, 25%) as a glass.

For *meso*-**7**; ν_{max}(KBr)/cm^{-1} 3050w, 3025w, 2945s, 2855m, 1610m, 1482m, 1442m, 1320m, 1240m, 1110m, 1095s, 755m and 700m; δ_H 1.39–2.05 (16 H, m, CH_2), 3.06–3.12 (4 H, m, OCH_2), 3.26–3.34 (4 H, m, OCH_2), 3.63 (3 H, s, OMe), 4.09 (3 H, m, OMe), 3.87 (2 H, dd, *J* 2.8 and 8.5, CH), 4.01 (2 H, d, *J* 10.1, ArCH_2), 5.00 (2 H, d, *J* 10.1, ArCH_2), 6.57 [2 H, s, Ar$(OMe)_2$*H*], 7.37 (4 H, dd, *J* 1.5 and 8.2, ArH) and 7.18–7.34 (6 H, m, ArH); *m/z* (FAB^+) 616 (M^+) (Found: C, 73.7; H, 7.6. $C_{38}H_{48}O_7$ requires C, 74.00; H, 7.84%).

For (±)-**7**; ν_{max}(KBr)/cm^{-1} 3050w, 3020w, 2950s, 2860m, 1610m, 1490m, 1450m, 1320m, 1250m, 1120m, 1100s, 760m and 700m; δ_H 1.30–2.05 (16 H, m, CH_2), 2.90–3.30 (8 H, m, OCH_2), 3.73 (3 H, s, OMe), 3.97 (3 H, m, OMe), 3.85–4.10 (2 H, m, CH), 4.35 (2 H, d, *J* 10.2, ArCH_2), 4.71 (2 H, d, *J* 10.2, ArCH_2), 6.72 [2 H, s, Ar$(OMe)_2$*H*] and 7.10–7.45 (10 H, m, ArH); *m/z* (FAB^+) 616 (M^+) (Found: C, 73.7; H, 7.5%).

***meso*-Crown ether 11 and (±)-crown ether 11**

A solution of the mixture of diols *meso*-**10** and (±)-**10** (4.93 g, 9.03 mmol) and diethylene glycol bis(methanesulfonate) (2.60 g, 9.92 mmol) in dry THF (1000 cm^3) was slowly added to a boiling mixture of sodium hydride (820 mg, 34.2 mmol), potassium tetrafluoroboranuide (1.14 g, 9.05 mmol), and dry THF (300 cm^3) over a 22 h period and then the reaction mixture was refluxed for an additional 22 h under dry nitrogen. After work-up as described above, the product was chromatographed on silica gel. Early fractions eluted with hexane–diethyl ether (3:1) gave *crown ether meso*-**11** (930 mg, 17%) as a solid, and subsequent fractions eluted with the same solvent gave *crown ether* (±)-**11** (1.04 g, 19%) as a glass.

For *meso*-**11**; ν_{max}(KBr)/cm^{-1} 3050w, 2940s, 2855m, 1600m, 1485m, 1375m, 1218m, 1150m, 1100s, 1065s, 760m and 705m; δ_H 1.10–2.20 (16 H, m, CH_2), 3.20–3.70 (10 H, m, CH and OCH_2CH_2O), 3.44 (3 H, s, OMe), 3.77 (3 H, s, OMe), 4.20 (2 H, d, *J* 10.9, ArCH_2), 4.40 (2 H, d, *J* 10.9, ArCH_2), 6.84 (2 H, s, ArH) and 7.25–7.65 (10 H, m, ArH); *m/z* (FAB^+) 616 (M^+) (Found: C, 73.7; H, 7.5%).

For (±)-**11**; ν_{max}(KBr)/cm^{-1} 3050w, 2930s, 2855m, 1600w, 1475m, 1442m, 1370m, 1318w, 1220m, 1140m, 1110s, 1055s, 755m, 700m and 690s; δ_H 1.08–2.42 (16 H, m, CH_2), 3.30–3.85 (10 H, m, CH and OCH_2CH_2O), 3.43 (3 H, s, OMe), 3.73 (3 H, s, OMe), 4.04 (2 H, d, *J* 10.9, ArCH_2), 4.36 (2 H, d, *J* 10.9, ArCH_2), 6.66 (2 H, s, ArH) and 7.24–7.60 (10 H, m, ArH); *m/z* (FAB^+) 616 (M^+) (Found: C, 73.7; H, 7.8%).

***meso*-Azophenolic crown ether 1**

A solution of crown ether *meso*-**7** (600 mg, 0.973 mmol) in a mixture of acetonitrile (15 cm^3) and methylene dichloride (4 cm^3) was added to a solution of CAN (2.70 g, 4.92 mmol) in a mixture of acetonitrile (7 cm^3) and water (5 cm^3) and then the mixture was stirred at room temperature for 2 h and at 50 °C for an additional 0.5 h. After the reaction mixture was diluted with water and extracted with chloroform, the extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Silica gel chromatography of the residue gave the quinone **8** [hexane–ethyl acetate (5:1) as eluent] (395 mg, 69%) as a yellow glass, which was dissolved in methylene dichloride (1 cm^3) and ethanol (20 cm^3). To the solution was added a solution of 2,4-dinitrophenylhydrazine (515 mg, 0.671 mmol) in a mixture of conc. H_2SO_4 (2 cm^3) and ethanol (20 cm^3) and the mixture was stirred at room temp. for 1.5 h. The reaction mixture was extracted with chloroform and the extract was worked up as usual. The product was chromatographed on silica gel to give *crown ether meso*-**1** [hexane–ethyl acetate (4:1) as eluent] (190 mg, 25%) as an orange solid, which was recrystallized from ethanol, mp 75 °C; λ_{max}($CHCl_3$)/nm 414; ν_{max}(KBr)/cm^{-1} 3400s, 3080w, 3050w, 2920s, 2860m, 1600s, 1525s, 1455m, 1350s, 1290m, 1142s, 1110s, 1090s, 760w and 700w; δ_H 1.37–2.07 (16 H, m, CH_2), 3.33–3.79 (8 H, m, OCH_2CH_2O), 3.84–3.91 (2 H, m, CH), 4.41 (2 H, d, *J* 10.9, H^e), 4.89 (2 H, d, *J* 10.9, H^f), 7.20–7.48 (10 H, m, ArH), 7.63 (2 H, s, H^d), 7.80 (1 H, d, *J* 8.9, H^c), 8.46 (1 H, dd, *J* 8.9 and 2.2, H^b), 8.73 (1 H, d, *J* 2.2, H^a) and 9.69 (1 H, s, OH); *m/z* (FAB^+) 767 (MH^+) (Found: C, 65.5; H, 6.0; N, 7.2. $C_{42}H_{46}N_4O_{10}$ required C, 65.78; H, 6.05; N, 7.31%).

***meso*-Azophenolic crown ether 2**

By a similar method to that described above, oxidation of crown ether *meso*-**11** (560 mg, 0.908 mmol) with CAN (2.49 g, 4.54 mmol) followed by silica gel chromatography gave the quinone **12** [hexane–ethyl acetate (5:1) as eluent] (337 mg, 37%) as a yellow glass. Treatment of compound **12** (337 mg, 0.574 mmol) with 2,4-dinitrophenylhydrazine (270 mg, 1.36 mmol) followed by silica gel chromatography gave *crown ether meso*-**2** [hexane–ethyl acetate (5:1) as eluent] (216 mg, 24%) as an orange solid, λ_{max}($CHCl_3$)/nm 416; ν_{max}(KBr)/cm^{-1} 3400s, 2920s, 2850m, 1590s, 1525s, 1455m, 1420m, 1340s, 1285m, 1125m, 1110s, 1060m, 755w and 695w; δ_H 1.21–2.24 (16 H, m, CH_2), 3.50–3.88 (10 H, m, CH and OCH_2CH_2O), 4.35 (2 H, d, *J* 10.9, H^e), 4.52 (2 H, d, *J* 10.9, H^f), 7.31–7.57 (10 H, m, ArH), 7.54 (2 H, s, H^d), 7.76 (1 H, d, *J* 8.9, H^c), 8.44 (1 H, dd, *J* 8.9 and 2.2, H^b), 8.71 (1 H, d, *J* 2.2, H^a) and 10.10 (1 H, s, OH); *m/z* (FAB^+) 767 (MH^+) (Found: C, 65.4; H, 6.1; N, 7.2%).

(−)-2″,5″-Dimethoxy-2,2′-diphenyl-2,2′-[*m*-phenylenebis(methyleneoxy)]dicyclohexanol 10

By the similar manner to that described for the preparation of the mixture of *meso*-**10** and (±)-**10**, the alcohol (1*S*, 2*S*)-(+)-**4**, $[\alpha]_D$ +47.0 ($CHCl_3$); mp 57–57.5 °C (3.50 g, 14.8 mmol) prepared from diol (1*S*, 2*S*)-(−)-**3**, $[\alpha]_D$ −19.3 ($CHCl_3$) (>99% ee)[4] was converted into *compound* (−)-**9** (3.87 g, 94%), $[\alpha]_D$ −33.7 ($CHCl_3$) as an oil, ν_{max}(neat film)/cm^{-1} 3100w, 3060w, 3050w, 2950s, 2860m, 1600m, 1450m, 1105m, 1042s, 760m, 705m and 690s; δ_H 1.44–2.23 (16 H, m, CH_2), 3.57 (2 H, br s, CH), 2.94 (6 H, s, OMe), 3.58 (3 H, s, ArO*Me*), 3.86 (3 H, s, ArOMe), 3.99 (2 H, d, *J* 6.9, OCH_2), 4.29 (2 H, d, *J* 11.8, $ArCH_2$), 4.43 (2 H, d, *J* 6.9, OCH_2), 4.44 (2 H, d, *J* 12.1, $ArCH_2$), 7.16 [2 H, s, Ar(OMe)*H*], 7.24 (2 H, tt, *J* 1.5 and 7.2, ArH), 7.34 (4 H, t, *J* 7.2, ArH) and 7.52 (4 H, dd, *J* 1.5 and 8.2, ArH) (Found: C, 71.8; H, 7.8. $C_{38}H_{50}O_8$ requires C, 71.90; H, 7.94%).

Treatment of compound (−)-**9** (3.50 g, 5.50 mmol) with HCl–methanol gave *diol* (−)-**10** (2.59 g, 86%), mp 147.5–148.5 °C (recrystallized from hexane–benzene); $[\alpha]_D^{23}$ −35.9 (*c* 1.05, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3400s, 3050w, 3010w, 2940s, 2890m, 2855m, 1600m, 1475m, 1460m, 1440m, 1205m, 1110m, 1058m, 1030m, 1008m, 760m and 700s; δ_H 1.16–2.46 (16 H, m, CH_2), 3.52 (3 H, s, OMe), 3.61–3.89 (2 H, m, CH), 3.83 (3 H, s, OMe), 4.26 (4 H, dd, *J* 10.9 and 9.1, $ArCH_2$), 6.96 (2 H, s, ArH), 7.14–7.57 (10 H, m, *Ar*CH) and 9.69 (2 H, s, OH); *m/z* (FAB^+) 546 (M^+) (Found: C, 74.7; H, 7.7. $C_{34}H_{42}O_6$ required C, 74.69; H, 7.74%).

(*S*,*S*,*S*,*S*)-(−)-Crown ether 11

By a similar manner to that described for the preparation of the mixture of crown ethers *meso*-**11** and (±)-**11**, diol (−)-**10** (2.00 g, 3.70 mmol) was treated with diethylene glycol bis(methanesulfonate) (1.05 g, 4.00 mmol) to give *title crown ether*(−)-**11** (910 mg, 40%) as a glass, $[\alpha]_D^{24}$ −41.3 (*c* 0.95, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3050w, 2930s, 2855m, 1600w, 1478m, 1442m, 1372m, 1320w, 1220m, 1140m, 1110s, 1055s, 755m, 700m and 690s; δ_H 1.08–2.40 (16 H, m, CH_2), 3.31–3.84 (10 H, m, CH and OCH_2CH_2O), 3.43 (3 H, s, OMe), 3.73 (3 H, s, OMe), 4.21 (4 H, dd, *J* 21.0 and 10.9, $ArCH_2$), 6.66 (2 H, s, ArH) and 7.26–7.66 (10 H, m, *Ar*CH); δ_C($CDCl_3$ [δ_C 77.00]; 67.8 MHz) 22.32 (2° carbon), 22.46 (2°), 26.77 (2°), 33.30 (2°), 55.40 (1°), 61.08 (2°), 62.30 (1°), 68.68 (2°), 70.68 (2°), 81.02 (4°), 81.53 (3°), 114.41 (3°), 126.99 (3°), 127.68 (3°), 127.93 (3°), 133.90 (4°), 142.74 (4°), 150.89 (4°) and 154.92 (4°); *m/z* (FAB^+) 616 (M^+) (Found: C, 73.7; H, 7.8. $C_{38}H_{48}O_7$ required C, 74.00; H, 7.84%).

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