Enantioselective complexation of phenolic crown ethers with chiral aminoethanol derivatives: effects of substituents of aromatic rings of hosts and guests on complexation †

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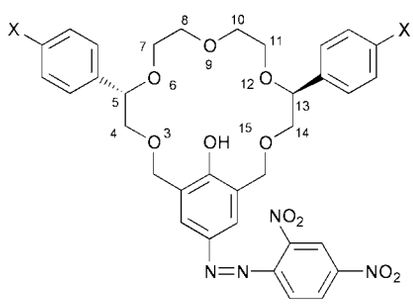
Optically active azophenolic crown ethers having phenyl groups substituted at the respective *para*-position were prepared and their association constants with chiral aminoethanol derivatives, including 2-amino-2-phenylethanols having an electron-donating or an electron-withdrawing group, were determined in chloroform by means of UV-vis titration methods. The enantioselectivities of these crown ethers are estimated from the ratio of the association constants K_R/K_S and the effect of aromatic substituents of both hosts and guests on the binding abilities and enantioselectivities is discussed. The structures of the complexes were investigated on the basis of the ^{1}H NMR and UV-vis spectra.

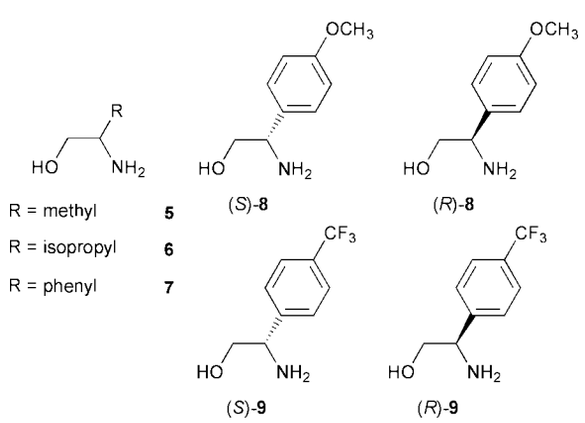
Introduction

Chiral recognition is one of the most important issues in the field of host–guest chemistry and a great deal of chiral host molecules have been developed.[1] We have been investigating the synthesis of chiral phenolic crown ethers having an 18-crown-6-like framework and their complexation ability and enantioselectivity toward chiral amines.[2] The crown ethers of this type bind neutral amines to form phenoxide–ammonium salt complexes, called saltexes,[3] in which the ammonium ion is stabilized by ion–dipole interaction with the surrounding oxygen atoms of the hosts. In order to achieve high enantioselectivity, we have examined the effect of the position of the chiral barriers on the macrocyclic ring,[4] the steric effect of the chiral barriers on C-5 and C-13,[5] and the electronic effect of the substituents on the phenol ring.[6] We found that, among them, crown ether (*S*,*S*)-**1** having phenyl groups as a chiral barrier was capable of binding 2-substituted 2-aminoethanol derivatives with high enantioselectivity.[7]

As an extension of this work, we became interested in the effect of the basicity of the donor oxygen atoms O-6 and O-12, which should strongly participate in the complexation with amines, on the binding and chiral recognition abilities in the complexation with chiral aminoethanols. We expected that the basicity of O-6 and O-12 must be affected by the electronic character, either electron-donating or electron-withdrawing, of a substituent on the *para*-position of the phenyl group of (*S*,*S*)-**1**, though we were not aware of experimental data regarding the effect of *para*-substituents on the basicity of benzylic ethers.[8] In this context, we planned to prepare crown ethers (*S*,*S*)-**2**, having an electron-donating methoxy group, and (*S*,*S*)-**3** and (*S*,*S*)-**4**, having an electron-withdrawing bromo and trifluoromethyl substituent, respectively. Moreover, in connection with the basicity of the donor atoms of the host molecules, we were also interested in investigating the effect of basicity of guest amines. In order to tune the electronic character while keeping the steric environment of the guest unchanged, we employed (*R*) and (*S*) enantiomers of 2-amino-2-phenylethanol derivatives **8**[9] having an electron-donating methoxy group and **9** having an electron-withdrawing trifluoromethyl group, and compared the complexation behaviour toward the above mentioned crown ethers (*S*,*S*)-**1**–(*S*,*S*)-**4** with that of the parent amine **7**. In addition, it should be pointed out that, by changing the aromatic substituents of the hosts and guests, not only the



X = H (*S*,*S*)-**1**
OCH$_3$ (*S*,*S*)-**2**
Br (*S*,*S*)-**3**
CF$_3$ (*S*,*S*)-**4**



R = methyl **5**
R = isopropyl **6**
R = phenyl **7**

(*S*)-**8** (*R*)-**8**

(*S*)-**9** (*R*)-**9**

† Association constants for the complexes of (*S*,*S*)-**1** to (*S*,*S*)-**4** and **43** with amines **5**–**9**, and thermodynamic parameters for the complexes of (*S*,*S*)-**1** to (*S*,*S*)-**4** with amines **5**–**9**, are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/a9/a910171n/

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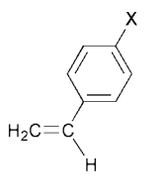
basicities of the donor oxygen atoms of the host and the nitrogen atoms of the guests will be affected, but also the π basicities of both aromatic rings will be altered. Since this would modify the possible aromatic–aromatic interactions between the host and guest, we investigated the spectroscopic data of the complexes.

In this paper, we report the synthesis of crown ethers (*S*,*S*)-**2**–(*S*,*S*)-**4** and the previously unknown chiral guest (*R*)- and (*S*)-**9**, the association constants of (*S*,*S*)-**1**–(*S*,*S*)-**4** with chiral amines **5**–**9** in chloroform, and the spectroscopic (^{1}H NMR and UV-vis spectra) investigation of the complexes.

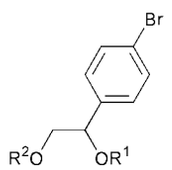
Results and discussion

Synthesis

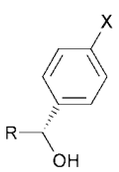
For the preparation of crown ethers (*S*,*S*)-**2**, (*S*,*S*)-**3** and (*S*,*S*)-**4**, it is most important to obtain the chiral diols (*S*)-**10**, (*S*)-**11**, and (*S*)-**12** (see Scheme 1) in an enantiomerically pure form. Diol (*S*)-**11** was prepared by optical resolution of the racemic diols by enantioselective acylation using Lipase QL as an enzyme. On the other hand, chiral ethylene glycols (*S*)-**10** and (*S*)-**12** were prepared by osmium-mediated asymmetric dihydroxylation of the corresponding styrene derivatives **13** and **14**.



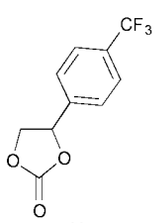
X = OCH_3 **13**
X = CF_3 **14**



R^1 = CH_3CO R^2 = CH_3CO **15**
R^1 = H R^2 = CH_3CO **16**



X = Br R = CH_2OTs **17**
X = Br R = CH_3 **18**
X = CF_3 R = CH_2OTs **19**
X = CF_3 R = CH_3 **20**



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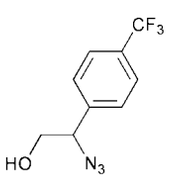

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The enantioselective acylation of (±)-**11**[10] using isopropenyl acetate as an acylating agent and lipase QL from *Alcaligenes* sp. as an enzyme gave diacetate **15** of >99% ee (by HPLC) in 24% yield and monoacetate **16** of 31% ee (by HPLC) in 73% yield. Alkaline hydrolysis of **15** gave diol (+)-**11** in 74% yield. The absolute configuration of (+)-**11** was established by the chemical correlation with (*R*)-(+)-1-(*p*-bromophenyl)ethanol (**18**) of known absolute configuration.[11] Toward this end, the primary hydroxy group of (+)-**11** was selectively tosylated to give (+)-**17** in 60% yield. Treatment of (+)-**17** with $LiAlH_4$ gave (*R*)-(+)-**18** in 81% yield. Accordingly, the absolute configuration of (+)-**11** was assigned to be (*S*).

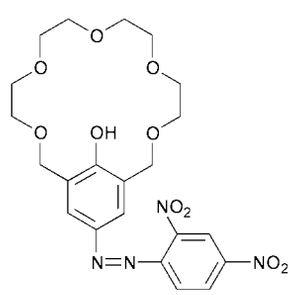
Chiral diol (*S*)-**10** was prepared according to the published procedure,[12] and (*S*)-**12** was prepared using the same method. Namely, asymmetric dihydroxylation of *p*-(trifluoromethyl)-styrene (**14**),[13] which was obtained by methylenation of *p*-(trifluoromethyl)benzaldehyde in 47% yield, gave (*S*)-**12** of >99% ee (by HPLC) in 90% yield. In a manner similar to that described for the case of (*S*)-(+)-**11**, the absolute configuration of (+)-**12** was determinated to be (*S*) by chemical correlation of its antipode, (*R*)-(−)-**12**, prepared by the same method, with (*S*)-(−)-1-[(*p*-trifluoromethyl)phenyl]ethanol (**20**) of known absolute configuration.[14]

Next, the primary hydroxy groups of the diols were protected. Thus, treatment of (*S*)-**11** with chlorotriphenylmethane in the presence of 4-(dimethylamino)pyridine (DMAP) gave regioselectively (*S*)-**22** in 72% yield (Scheme 1). Condensation of two equivalents of (*S*)-**22** with diethylene glycol ditosylate (**24**) in the presence of NaH in THF gave (*S*,*S*)-**26**, which was deprotected with toluene-*p*-sulfonic acid in MeOH to give diol (*S*,*S*)-**29** in 60% overall yield for the two steps. Ring closure of (*S*,*S*)-**29** with the dimethoxybenzene unit **31** in the presence of NaH in THF under high-dilution conditions gave dimethoxy crown ether (*S*,*S*)-**33** in 78% yield. Treatment of (*S*,*S*)-**33** with sodium ethanethiolate in DMF cleaved selectively the inner methoxy group to give (*S*,*S*)-**36** in 94% yield. Oxidation of (*S*,*S*)-**36** with cerium(IV) ammonium nitrate (CAN) in acetonitrile gave (*S*,*S*)-**39**, which was immediately treated with 2,4-dinitrophenylhydrazine in a mixture of EtOH, $CHCl_3$ and concentrated H_2SO_4 to give (*S*,*S*)-**3** in 73% overall yield for the two steps.

Crown ethers (*S*,*S*)-**2** and (*S*,*S*)-**4** were also prepared according to almost the same procedures. The only difference was the fact that it was necessary to use 15-crown-5 ether in the condensation of **21** and **23** with **24** in order to improve the nucleophilicity of the corresponding alkoxide anions, since the yields were much lower otherwise.

Enantioselective complexation

The association constants, K_a, of the complexes of the crown ethers (*S*,*S*)-**1**–(*S*,*S*)-**4** with both enantiomers of chiral amines **5**–**9** were determined on the basis of the UV-vis spectral change upon complex formation in $CHCl_3$ at various temperatures using the Rose–Drago method.[15] As a reference compound, the data for the achiral crown ether **43**[16] having no



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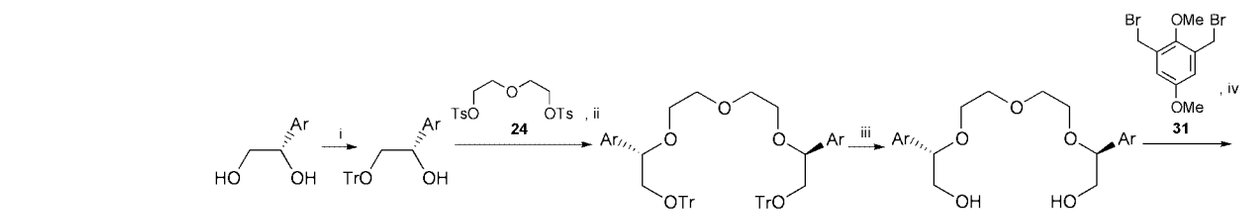
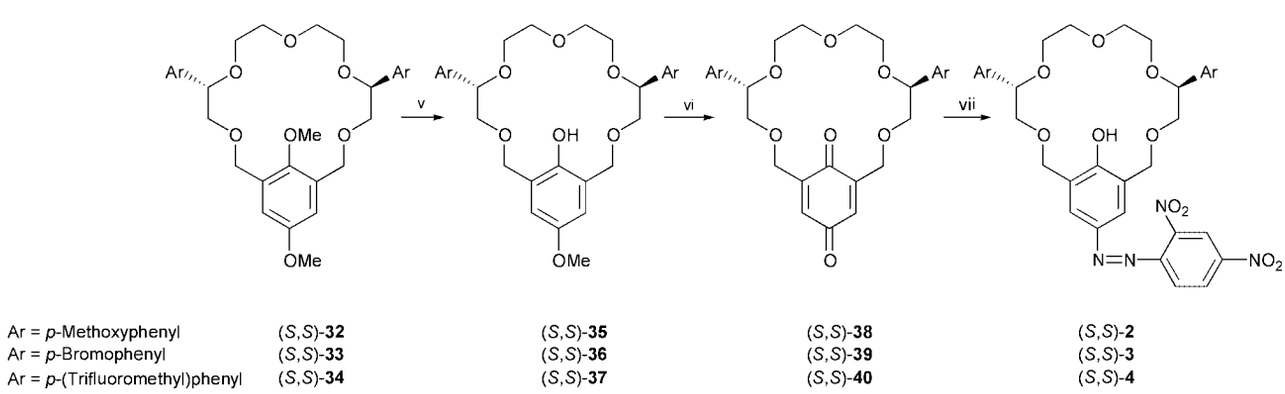
chiral barrier are compared. The observed K_a values at 25 °C are summarised in Table 1. The association constants were determined at five different temperatures and the thermodynamic parameters were calculated based on the van't Hoff plots. These data are summarised in Tables 4 and 5, respectively, which are deposited as Supplementary Material.

The complexation ability of (*S*,*S*)-**2**, which has an electron-donating substituent at the *para*-position of the phenyl group, and those of (*S*,*S*)-**3** and (*S*,*S*)-**4**, which have an electron-withdrawing substituent, are compared to that of (*S*,*S*)-**1**. As shown in Table 1, it turned out that (*S*,*S*)-**2** exhibited larger association constants than (*S*,*S*)-**1** with most of the guest amines. On the other hand, (*S*,*S*)-**3** and (*S*,*S*)-**4** showed smaller binding constants than those of (*S*,*S*)-**1**. This means that the

Table 1 Association constants for the complexes of (*S*,*S*)-**1**–(*S*,*S*)-**4** and **43** with amines **5**–**9** in $CHCl_3$ at 25 °C

Crown ether	Amine	K_R/M^{-1}	K_S/M^{-1}	K_R/K_S
(*S*,*S*)-**1**	**5**	$(3.8 \pm 0.3) \times 10^4$	$(7.8 \pm 0.7) \times 10^3$	4.9
	6	$(7.5 \pm 0.7) \times 10^3$	$(1.7 \pm 0.4) \times 10^3$	4.5
	7	$(2.0 \pm 0.2) \times 10^4$	$(1.7 \pm 0.1) \times 10^3$	12
	8	$(2.9 \pm 0.2) \times 10^4$	$(2.3 \pm 0.2) \times 10^3$	12
	9	$(7.8 \pm 0.3) \times 10^3$	$(4.5 \pm 0.4) \times 10^2$	18
(*S*,*S*)-**2**	**5**	$(3.0 \pm 0.4) \times 10^4$	$(7.8 \pm 0.4) \times 10^3$	3.8
	6	$(8.8 \pm 0.6) \times 10^3$	$(2.0 \pm 0.3) \times 10^3$	4.5
	7	$(2.3 \pm 0.2) \times 10^4$	$(1.8 \pm 0.1) \times 10^3$	11
	8	$(3.7 \pm 0.4) \times 10^4$	$(3.3 \pm 0.5) \times 10^3$	11
	9	$(1.3 \pm 0.1) \times 10^4$	$(6.7 \pm 0.3) \times 10^2$	19
(*S*,*S*)-**3**	**5**	$(1.1 \pm 0.1) \times 10^4$	$(3.2 \pm 0.3) \times 10^3$	3.4
	6	$(3.9 \pm 0.5) \times 10^3$	$(9.1 \pm 0.2) \times 10^2$	4.3
	7	$(1.6 \pm 0.1) \times 10^4$	$(1.0 \pm 0.1) \times 10^3$	15
	8	$(1.7 \pm 0.1) \times 10^4$	$(1.5 \pm 0.1) \times 10^3$	11
	9	$(4.5 \pm 0.3) \times 10^3$	$(2.6 \pm 0.1) \times 10^2$	17
(*S*,*S*)-**4**	**5**	$(8.9 \pm 0.4) \times 10^3$	$(2.3 \pm 0.5) \times 10^3$	3.8
	6	$(2.6 \pm 0.2) \times 10^3$	$(6.1 \pm 0.5) \times 10^2$	4.3
	7	$(7.7 \pm 0.6) \times 10^3$	$(6.2 \pm 0.4) \times 10^2$	12
	8	$(1.4 \pm 0.2) \times 10^4$	$(1.1 \pm 0.1) \times 10^3$	12
	9	$(3.0 \pm 0.4) \times 10^3$	$(1.7 \pm 0.1) \times 10^2$	18
43	**7**	$(7.5 \pm 0.8) \times 10^3$		
	8	$(1.2 \pm 0.1) \times 10^4$		
	9	$(3.1 \pm 0.3) \times 10^3$		





Scheme 1 *Reagents and conditions*: i, Ph_3CCl, DMAP, Et_3N, DMF; ii, NaH, THF, (15-crown-5), 80 °C; iii, *p*-TsOH, MeOH, rt; iv, NaH, THF, 80 °C; v, EtSH, NaH, DMF, 60 °C; vi, CAN, CH_3CN; vii, 2,4-dinitrophenylhydrazine, H_2SO_4, MeOH, $CHCl_3$, rt.

free energy of complexation is dependent on the basicity of O-6 and O-12. The dependence of the basicity of O-6 and O-12 on the substituent was indicated by the ^{1}H NMR chemical shifts of the phenolic protons of (*S*,*S*)-**1**–(*S*,*S*)-**4** in $CDCl_3$, which appeared at 9.14, 9.20, 9.06, and 9.04 ppm, respectively.[17] The chemical shift difference can be ascribed to the strength of the hydrogen bond between the phenolic hydrogen and O-6 and O-12 atoms which in turn is dependent on the basicity of the oxygen atoms. On the other hand, Table 1 also shows that the stabilities of the complexes depend on the basicity of the amines, *i.e.*, the stronger the basicity of amines, the more stable are the complexes as might be expected. Moreover, in all cases, the crown ethers having stereocenters of (*S*) configuration showed (*R*)-selectivity toward the 2-substituted 2-amino-ethanols. Considerably high enanatioselectivity (K_R/K_S = 17–19) was observed for amine **9** having a trifluoromethyl group irrespective of the crown ethers employed. The reason for this significant improvement in the enantioselectivity is not fully understood at this moment.

It is worth noting that the association constants of all chiral crown ethers (*S*,*S*)-**1**–(*S*,*S*)-**4** with the (*R*)-amines are larger than the corresponding K_a for achiral **43**, whereas the K_a values for the complexation of (*S*,*S*)-**1**–(*S*,*S*)-**4** with (*S*)-amines are smaller than those of **43** (or at most similar to them). Since compound **43** has no chiral barrier, the complexes of **43** would not suffer from steric repulsion due to the substituents on the chiral centers. In addition, the basicity of O-6/O-12 atoms must be higher than those of chiral crown ethers (*S*,*S*)-**1**–(*S*,*S*)-**4** having aryl groups, because the aryl groups are inductively electron-withdrawing. Nevertheless, the complexations between

Table 2 Complexation induced shifts (CIS) for the aromatic protons of crown ethers (*S*,*S*)-**1**–(*S*,*S*)-**4** and amines **7**–**9** in $CDCl_3$ at 30 °C

	CIS[a]/ppm			CIS[a]/ppm		
Crown ether	(*R*)-Amine	H_o	$H_{o'}$	(*S*)-Amine	H_o	$H_{o'}$
(*S*,*S*)-**1**	(*R*)-**7**	−0.45	0.60	(*S*)-**7**	—[b]	—[b]
	(*R*)-**8**	−0.43	0.60	(*S*)-**8**	—[b]	0.29
	(*R*)-**9**	−0.49	0.60	(*S*)-**9**	—[b]	0.30
(*S*,*S*)-**2**	(*R*)-**7**	−0.48	0.57	(*S*)-**7**	−0.12	—[b]
	(*R*)-**8**	−0.47	0.57	(*S*)-**8**	−0.12	0.27
	(*R*)-**9**	−0.52	0.61	(*S*)-**9**	−0.14	0.30
(*S*,*S*)-**3**	(*R*)-**7**	−0.47	0.59	(*S*)-**7**	−0.12	—[b]
	(*R*)-**8**	−0.43	0.60	(*S*)-**8**	−0.12	0.27
	(*R*)-**9**	−0.47	0.62	(*S*)-**9**	−0.15	0.28
(*S*,*S*)-**4**	(*R*)-**7**	−0.46	0.60	(*S*)-**7**	−0.11	—[b]
	(*R*)-**8**	−0.44	0.60	(*S*)-**8**	−0.10	0.29
	(*R*)-**9**	−0.48	0.60	(*S*)-**9**	−0.14	0.30

[a] CISs were estimated by measuring the chemical shifts of the relevant protons of appropriate host–guest mixtures and then by extrapolating $\delta_{observed}$ to $\delta_{complex}$ by using the association constants determined by the UV-vis titration method. [b] Not determined because the signal of the relevant protons were concealed by other signals.

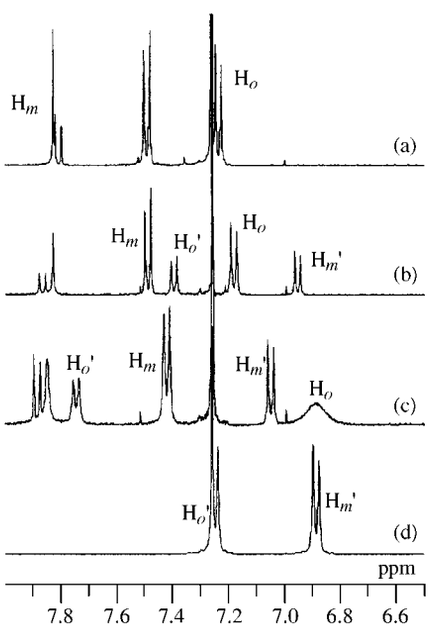


Fig. 1 ^1H NMR spectral change upon complexations of crown ether (*S*,*S*)-**3** with amine **8** (400 MHz, in $CDCl_3$ at 30 °C). (a) (*S*,*S*)-**3** only; (b) [(*S*)-**8**]/[(*S*,*S*)-**3**] = 1.0; (c) [(*R*)-**8**]/[(*S*,*S*)-**3**] = 1.0; (d) **8** (happened to be the (*R*)-enantiomer) only. H_o and H_m mean the *ortho* and *meta* protons of the phenyl group of (*S*,*S*)-**3**, respectively, and $H_{o'}$ and $H_{m'}$ are the corresponding protons of (*R*)- and (*S*)-**8**.

the aryl-substituted crown ethers and the (*R*)-amines are more favorable than those with **43**. This phenomenon can be ascribed to the possible CH–π interaction between the aromatic rings of the hosts and guests, though there is no spectroscopic data to support this idea as described below.

Spectroscopic considerations

To test whether this phenomenon may be ascribed to a CH–π interaction between the aromatic rings of the hosts and guests, an absorption and NMR spectroscopic study was initiated. It is expected that the chemical shifts of the aryl substituents of the host and guest molecule must be affected by each other due to the anisotropy of the aromatic rings, and the complexation induced shifts (CIS) should give valuable information regarding the relative spatial arrangement of the aryl groups of the host and guest molecules. As an example, Fig. 1 shows the aromatic region of the ^1H NMR spectra for the complexation between

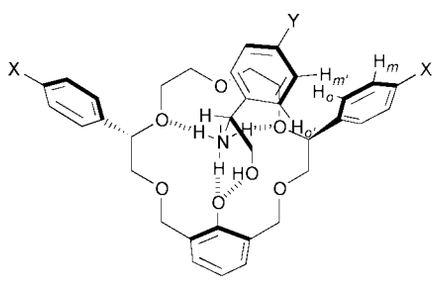


Fig. 2 A model for the complex of a chiral crown ether with an (*R*)-amine. The 2,4-dinitrophenylazo group is omitted for reasons of clarity.

(*S*,*S*)-**3** and (*R*)- and (*S*)-**8** at 30 °C. H_o and H_m denote the *ortho* and *meta* protons of the phenyl group of host (*S*,*S*)-**3**, respectively, and $H_{o'}$ and $H_{m'}$ are the corresponding protons of guests (*R*)- and (*S*)-**8**. As shown in Fig. 1, addition of 1 equivalent of (*R*)-**8** to a solution of (*S*,*S*)-**3** resulted in remarkable changes of the chemical shifts of H_o of (*S*,*S*)-**3** and $H_{o'}$ of (*R*)-**8**, whereas the corresponding change with (*S*)-**8** was relatively small.

By using the association constants for the complexes determined by the UV-vis titration method, the chemical shifts ($\delta_{complex}$) for H_o, H_m, $H_{o'}$ and $H_{m'}$ of the complexes between crown ethers (*S*,*S*)-**1** to (*S*,*S*)-**4** and amines (*R*)- and (*S*)-**7** to **9** were estimated and CISs for these protons were calculated as summarised in Table 2.[18] As shown in Table 2, in general, H_o of the hosts shows a larger upfield shift with the (*R*)-guests (CIS = −0.43 to −0.52 ppm) than with the corresponding (*S*)-guests (CIS = −0.12 to −0.15 ppm) irrespective of their *para*-substituent. Similarly, $H_{o'}$ of the (*R*)-guests shows a larger downfield shift (CIS = 0.57 to 0.62 ppm) than that of the (*S*)-guests (CIS = 0.27 to 0.30 ppm). It seems likely, therefore, that the phenyl rings of (*R*)-guests are located in the spatial arrangement illustrated in Fig. 2, in which the aromatic ring of the hosts suffers from the anisotropic deshielding effect of the phenyl ring of the guest and, in turn, the latter suffers from the shielding effect of the former. However, since there seems to be no relationship between the CIS values and the electronic character of the substituents, it seems difficult to draw a quantitative conclusion from these data regarding the aromatic–aromatic interactions between the hosts and guests.

Next, UV-vis spectra of the complexes were examined. The absorption maxima of the complexes varied from 540 to 568 nm depending on the host–guest combination as shown in Table 3. The $\Delta\lambda_{max}$ values represent the difference between diastereomeric sets of the complexes (λ_{max} (more stable

Table 3 Absorption maxima for the complexes of crown ethers (*S*,*S*)-**1**–(*S*,*S*)-**4** with amines **5**–**9** in $CHCl_3$ at 25 °C

Crown ether	(*R*)-Amine	λ_{max}/nm	(*S*)-Amine	λ_{max}/nm	$\Delta\lambda_{max}$/nm [a]
(*S*,*S*)-**1**	(*R*)-**5**	556	(*S*)-**5**	563	−7
	(*R*)-**6**	560	(*S*)-**6**	560	0
	(*R*)-**7**	555	(*S*)-**5**	567	−12
	(*R*)-**8**	556	(*S*)-**5**	567	−11
	(*R*)-**9**	544	(*S*)-**5**	559	−15
(*S*,*S*)-**2**	(*R*)-**5**	558	(*S*)-**5**	564	−6
	(*R*)-**6**	562	(*S*)-**6**	563	−1
	(*R*)-**7**	556	(*S*)-**5**	567	−11
	(*R*)-**8**	557	(*S*)-**5**	568	−11
	(*R*)-**9**	548	(*S*)-**5**	558	−10
(*S*,*S*)-**3**	(*R*)-**5**	552	(*S*)-**5**	558	−6
	(*R*)-**6**	557	(*S*)-**6**	557	0
	(*R*)-**7**	550	(*S*)-**5**	562	−12
	(*R*)-**8**	551	(*S*)-**5**	563	−12
	(*R*)-**9**	542	(*S*)-**5**	552	−10
(*S*,*S*)-**4**	(*R*)-**5**	549	(*S*)-**5**	556	−7
	(*R*)-**6**	554	(*S*)-**6**	554	0
	(*R*)-**7**	549	(*S*)-**5**	559	−10
	(*R*)-**8**	548	(*S*)-**5**	559	−11
	(*R*)-**9**	540	(*S*)-**5**	551	−11

[a] $\Delta\lambda_{max} = \lambda_{max}$ (more stable complex) − λ_{max} (less stable complex).

complex with (*R*)-amines) − λ_{max} (less stable complex with (*S*)-amines)). In general, the more stable complexes tend to exhibit absorptions at shorter wavelength than the corresponding diastereomeric complexes. This trend is remarkable when 2-aryl-2-aminoethanols **7**–**9** are employed as the guests.

The difference between the absorption maxima of the complexes is explained in terms of the relative stabilisation of the ground and excited states of the dinitrophenylazophenoxide chromophore in connection with the strength of the coulombic interaction between the phenoxide anion and the ammonium ion of the guests.[3,19] Namely, the ground state is highly polarised because the phenolic hydrogen dissociates to form a phenoxide ion upon complexation. It is reasonable to assume that the coulombic interaction between the phenoxide anion and the counter cation would stabilise the ground state of the chromophore. On the other hand, because of the charge transfer character of this chromophore, it may well be anticipated that the excited state is less polarised than the ground state. As a result, the interaction with the ammonium ion would not stabilise the excited state as much as it stabilises the ground state, and accordingly the absorption maximum should shift to a shorter wavelength. The fact that the complexes with (*R*)-amines exhibit shorter λ_{max} than those of the complexes with (*S*)-amines indicates that the ammonium ions of the former complexes interact more strongly with the phenoxide ion than those of the latter.

As can be seen in Table 3, the λ_{max} values shift to shorter wavelength in the order of (*S*,*S*)-**2**, (*S*,*S*)-**1**, (*S*,*S*)-**3**, and (*S*,*S*)-**4** irrespective of the basicity and chirality of the guest amines. This means that with decreasing the basicity of O-6 and O-12 of the crown ethers, the coulombic interaction between the ammonium ion and the phenoxide anion increases, leading to the hypsochromic shift of the absorption. On the other hand, the effect of the substituents of amines is not clear, since the λ_{max} values of the complexes of amines **7** and **8** are almost identical. However, it is worth noting that, in the case of the least basic amines (*R*)- and (*S*)-**9** having a CF_3 group, the absorption maxima appear at shorter wavelength by 8–12 nm than those of the corresponding complexes of the other amines. This suggests that the guest ammonium ion with an electron-withdrawing susbstituent interacts more strongly with the phenoxide ion than the other ammonium ions because it is more positively charged. The UV-vis data of the complexes, however, do not give information regarding the aromatic–aromatic interactions between the hosts and guests.

Conclusions

The association constants between crown ethers (*S*,*S*)-**1**–(*S*,*S*)-**4** and amines **5**–**9** imply that the weaker the basicity of O-6 and O-12 of the crown ethers, the less stable the complexes become. The basicity of amines (*R*)- or (*S*)-**7**–**9** also affects the association constants, and the highest enantioselective complexation was observed in the case of (*S*,*S*)-**2** and **9**. The CIS of the ^1H NMR spectra indicates the most likely arrangement of the complexes with (*R*)-amines shown in Fig. 2, in which one of the aromatic rings of the hosts and the phenyl ring of the guests are orthogonal to each other. The absorption maxima of the complexes well correlate with the basicities of the hosts and guests; the absorption maxima appear at shorter wavelength in the combination of hosts and guests with weaker basicity.

Experimental

General procedure

^1H NMR spectra were recorded at 270, 300 or 400 MHz on a JEOL JNM-GSX-270, a Varian Mercury-300 or a JEOL JNM-AL-400 spectrometer, respectively, in $CDCl_3$ with $SiMe_4$ as internal standard at 30 °C. IR spectra were recorded as a KBr disk or a neat film on a JASCO FTIR-410 spectrometer. Mass spectral analyses were performed on a JEOL JMS-DX303HF spectrometer. Elemental analyses were carried out by a Yanagimoto CHN-Corder Type 2 or a Perkin-Elmer 2400II analyser. Melting points were measured with a hot-stage apparatus and are uncorrected. UV-vis spectra were recorded on a Hitachi 330 spectrometer in $CHCl_3$. 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}. HPLC analyses were carried out on a Shimadzu LC-6A chromatograph using a 250 × 4.6 mm chiral column CHIRAL PAK AD (DAICEL). 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 × 20 mm JAIGEL-1H and 2H GPC columns with $CHCl_3$ as an eluent. The reagents for the Sharpless asymmetric dihydroxylation, AD-mix-α® and AD-mix-β®, were purchased from Aldrich Chemical Company, Inc. Lipase QL (from *Alcaligenes* sp.) was purchased from Meito Sangyo Co. A spectral grade $CHCl_3$ was purchased from Wako Pure Chemical Industries, Ltd and was used without further purification. The chiral

amines (*R*)-**5**, (*S*)-**5**, (*R*)-**6** and (*S*)-**6** were purchased from Aldrich Chemical Company, Inc. and (*R*)-**7** from Tokyo Kasei Kogyo Co., Ltd. These amines were used as purchased. (*S*)-2-Amino-2-phenylethanol (**7**) was purchased from Aldrich Chemical Company, Inc. and was used after recrystallization from benzene–hexane.

Resolution of (±)-11

A mixture of (±)-**11** (25.3 g, 0.117 mol), lipase QL (4.14 g) and isopropenyl acetate (39.5 g, 0.395 mol) in CH_3CN (200 mL) and diisopropyl ether (1000 mL) was stirred for 2 days at 30 °C. The reaction was terminated at the diesterification point of 45% (by GLC) by filtration of the enzyme and volatile materials were evaporated under reduced pressure. Silica gel chromatography (hexane–EtOAc (9 : 1)) of the residue gave diacetate (+)-**15** (8.35 g, 24%, >99% ee by HPLC) and monoacetate (−)-**16** (22.1 g, 73%, 31% ee by HPLC).

A solution of (+)-**15** (9.72 g, 32.3 mmol) and K_2CO_3 (219 mg, 1.59 mmol) in MeOH (20 mL) and water (3 mL) was stirred for 1.5 h at room temperature. After the volatile materials were removed under reduced pressure, the residue was extracted with EtOAc. Customary work-up (*i.e.* washing the extract with water, drying it with anhydrous $MgSO_4$ and evaporating off the solvent under reduced pressure), followed by recrystallization (hexane–EtOAc) of the products gave (*S*)-(+)-**11** (5.18 g, 74%) as a white solid, mp 102–103 °C; $[a]_D^{23}$ +42.9 (*c* 0.896, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3373, 2924, 1092 and 831; δ_H (270 MHz, $CDCl_3$) 1.96 (1H, t, *J* 5.8, primary OH), 2.50 (1H, d, *J* 3.0, secondary OH), 3.61 (1H, m, CH_2), 3.76 (1H, m, CH_2), 4.71 (1H, m, CH), 7.26 (2H, d, *J* 8.4, ArH) and 7.49 (2H, d, *J* 8.4, ArH). The absolute configuration of (+)-**11** was assigned to be (*S*) by its transformation into the known alcohol (*R*)-**18** as described below.

(*S*)-(+)-1-(*p*-Bromophenyl)-2-(*p*-tolylsulfonyloxy)ethanol (*S*)-17

To a solution of (+)-**11** (203 mg, 0.935 mmol) in pyridine (1 mL) was added *p*-TsCl (167 mg, 0.876 mmol) and the mixture was then stirred for 5 h at 0–5 °C. The reaction mixture was poured onto ice–water, acidified (pH 2) with HCl and extracted with $CHCl_3$. Customary work-up, followed by silica gel chromatography (hexane–EtOAc (4 : 1)) gave (+)-**17** (262 mg, 76%), mp 104–106 °C; $[a]_D^{27}$ +35.7 (*c* 1.01, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3533, 3049, 2952, 2870, 1347, 1175 and 819; δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 2.53 (1H, d, *J* 3.4, OH), 4.02 (1H, dd, *J* 10.4, 8.0, CH_2), 4.13 (1H, dd, *J* 11.2, 3.6, CH_2), 4.95 (1H, ddd, *J* 7.9, 3.8, 3.8, CH), 7.19 (2H, d, *J* 8.3, BrArH), 7.33 (2H, d, *J* 8.3, tosyl ArH), 7.45 (2H, d, *J* 8.8, BrArH) and 7.75 (2H, d, *J* 8.3, tosyl ArH); *m*/*z* (FAB) 371 (M^+) (Found: C, 48.44; H, 3.93. $C_{15}H_{15}BrO_4S$ requires C, 48.53; H, 4.07%).

(*R*)-(+)-1-(*p*-Bromophenyl)ethanol (*R*)-18

To a suspension of $LiAlH_4$ (50.0 mg, 1.32 mmol) in dry THF (3 mL) was added a solution of (+)-**17** (180 mg, 0.486 mmol) in dry THF (2 mL) and the mixture was stirred for 1 h at room temperature. To the reaction mixture was carefully added aqueous NH_4Cl with ice-cooling. The deposited solids were removed by filtration and the solvent was evaporated under reduced pressure. Purification was done by preparative TLC (hexane–EtOAc (7 : 3)) to give (+)-**18** (35.0 mg, 36%) as an oil, $[a]_D^{24}$ +34.0 (*c* 0.124, CH_3OH) (lit.,[10] [*a*] +4.1 for (*S*)-**18** of 22.5% ee); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.8, CH_3), 1.75 (1H, d, *J* 3.9, OH), 4.87 (1H, m, CH), 7.25 (1H, d, *J* 8.3, ArH) and 7.47 (1H, d, *J* 6.8, ArH).

(*S*)-(+)-1-(*p*-Bromophenyl)-2-(triphenylmethoxy)ethanol (*S*)-22

To a solution of Et_3N (5.88 g, 0.581 mol) in dry DMF (80 mL) was added successively chlorotriphenylmethane (9.20 g, 33.0 mmol), DMAP (177 mg, 1.45 mmol) and (+)-**11** (6.70 mg, 30.8 mmol) and the resulting mixture was stirred for 15 h at room temperature. After water had been added to the reaction mixture, the reaction mixture was extracted with $CHCl_3$. Customary work-up, followed by silica gel chromatography (hexane–EtOAc (4 : 1)) gave (+)-**22** (11.4 g, 81%), $[a]_D^{23}$ +5.50 (*c* 0.531, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3439, 3058, 2923, 1210, 1070 and 824; δ_H (400 MHz, $CDCl_3$) 2.73 (1H, d, *J* 3.0, OH), 3.24 (1H, dd, *J* 9.8, 7.8, CH_2), 3.32 (2H, dd, *J* 9.8, 3.4, CH_2), 4.70 (1H, m, CH) and 7.11–7.57 (19H, m, *p*-bromophenyl ArH and $C(C_6H_5)_3$); *m*/*z* (EI) 458 (M^+); the high-resolution mass spectrum could not be recorded because of the weak molecular ion peak.

(2*S*,10*S*)-(+)-2,10-Bis(*p*-bromophenyl)-1,11-bis(triphenylmethoxy)-3,6,9-trioxaundecane (*S*,*S*)-26

A solution of (*S*)-**22** (428 mg, 0.932 mmol) in dry DMF (5 mL) was added slowly to a suspension of 60% NaH (170 mg, 4.25 mmol) in dry DMF (10 mL) and the resulting mixture was stirred at 60 °C for 1 h. After the reaction mixture had been cooled to room temperature, a solution of **24** (184 mg, 0.444 mmol) in dry DMF (5 mL) was added dropwise and the reaction mixture was stirred at 60 °C for 1 day under a nitrogen atmosphere. After a small amount of chilled water had been carefully added to the reaction mixture with ice-cooling, the solvent was removed under reduced pressure. The residue was extracted with EtOAc and the combined extracts were washed with water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc (4 : 1)) to give (*S*,*S*)-**26** (367 mg, 84%) as an oil, $[a]_D^{23}$ +5.96 (*c* 0.493, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3057, 2928, 1488, 1069, 1010 and 820; δ_H (400 MHz, $CDCl_3$) 3.12 (2H, dd, *J* 10.9, 5.3, CH_2), 3.38 (2H, dd, *J* 9.5, 6.6, CH_2), 3.48–3.61 (8H, m, CH_2), 4.33 (2H, t, *J* 6.0, CH) and 7.09–7.78 (38H, m, ArH); *m*/*z* (FAB) 986 ($M^+ + 1$) (Found: C, 70.61; H, 5.19. $C_{58}H_{52}Br_2O_5$ requires C, 70.45; H, 5.30%).

(2*S*,10*S*)-(+)-2,10-Bis(*p*-bromophenyl)-3,6,9-trioxaundecane-1,11-diol (*S*,*S*)-29

A solution of (*S*,*S*)-**26** (2.10 g, 2.12 mmol) and *p*-TsOH·H_2O (1.64 g, 8.62 mmol) in MeOH (30 mL) was stirred for 6 h at room temperature. After aqueous $NaHCO_3$ had been added to the reaction mixture, the volatile materials were removed under reduced pressure and the residue was extracted with $CHCl_3$. Customary work-up, followed by silica gel chromatography (EtOAc) of the products gave (*S*,*S*)-**26** (1.06 g, >99%) as a colourless viscous oil, $[a]_D^{23}$ +62.0 (*c* 0.740, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3417, 2870, 1485, 1072, 1010 and 821; δ_H (300 MHz, $CDCl_3$) 3.55–3.74 (12H, m, CH_2), 4.21 (2H, dd, *J* 9.3, 3.9, OH), 4.46 (2H, dd, *J* 8.4, 3.6, CH), 7.21 (4H, d, *J* 8.4, ArH) and 7.48 (4H, d, *J* 8.7, ArH); *m*/*z* (FAB) 505 ($M^+ + 1$); the high-resolution mass spectrum could not be recorded because of the weak molecular ion peak.

(5*S*,13*S*)-(+)-19,21-Dimethoxy-5,13-bis(*p*-bromophenyl)-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(21),17,19-triene (*S*,*S*)-33

A solution of (*S*,*S*)-**29** (938 mg, 1.86 mmol) and **31** (645 mg, 1.99 mmol) in dry THF (100 mL) was slowly added to a suspension of 60% NaH (540 mg, 13.5 mmol) in dry THF (60 mL) over a 26 h period under reflux and the mixture was refluxed for further 18 h under a nitrogen atmosphere. After a small amount of chilled water had been added to the reaction mixture with ice-cooling, the solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ and the combined extracts were washed with water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give (*S*,*S*)-**33** (888 mg, 72%) as a white solid after silica gel chromatography (hexane–EtOAc (4 : 1)), mp 112–114 °C; $[a]_D^{23}$ +119 (*c* 0.404, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2865, 1486, 1229, 1087 and 821; δ_H (400 MHz, $CDCl_3$) 3.38–3.78 (12H, m, CH_2), 3.78

(3H, s, OCH_3), 4.11 (3H, s, OCH_3), 4.45 (2H, m, CH), 4.47 (2H, d, *J* 11.2, benzylic CH_2), 4.68 (2H, d, *J* 11.2, benzylic CH_2), 6.82 (2H, s, ArH), 7.19 (4H, d, *J* 8.4, ArH) and 7.46 (4H, d, *J* 8.0, ArH); *m*/*z* (FAB) 666 (M^+) (Found: C, 54.17; H, 5.05. $C_{30}H_{34}Br_2O_7$ requires C, 54.07; H, 5.14%).

(5*S*,13*S*)-(+)-21-Hydroxy-19-methoxy-5,13-bis(*p*-bromophenyl)-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(21),17,19-triene (*S*,*S*)-36

Ethanethiol (839 mg, 13.5 mmol) was added slowly to a suspension of 60% NaH (584 mg, 14.6 mmol) in dry DMF (10 mL) at 0–5 °C, after which a solution of (*S*,*S*)-**33** (592 mg, 0.888 mmol) in dry DMF (15 mL) was dropwise with ice-cooling. The mixture was heated at 100 °C for 2 h, then cooled to 0–5 °C, and neutralized with HCl and extracted with EtOAc. The combined extracts were washed with water, dried (anhydrous $MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue on silica gel gave (*S*,*S*)-**36** (538 mg, 93%) (hexane–EtOAc (4:1)) as a pale yellow viscous oil, $[\alpha]_D^{26}$ +103 (*c* 0.311, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3390, 2867, 1486, 1255, 1010 and 821; δ_H (300 MHz, $CDCl_3$) 3.56–3.79 (12H, m, CH_2), 3.74 (3H, s, OCH_3), 4.62 (2H, dd, *J* 8.4, 3.3, CH), 4.71 (2H, d, *J* 11.4, benzylic CH_2), 4.73 (2H, d, *J* 11.4, benzylic CH_2), 6.71 (2H, s, HOAr*H*), 7.21 (4H, d, *J* 8.1, ArH) and 7.47 (4H, d, *J* 8.4, ArH); *m*/*z* (FAB) 652 (M^+) (Found: M^+ 652.0555. $C_{29}H_{32}Br_2O_7$ requires 652.0497).

(5*S*,13*S*)-21-Hydroxy-19-(2′,4′-dinitrophenylazo)-5,13-bis-(*p*-bromophenyl)-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(21), 17,19-triene (*S*,*S*)-3

A solution of (*S*,*S*)-**36** (535 mg, 0.820 mmol) in CH_3CN (17 mL) was added to a solution of CAN (481 mg, 0.877 mmol) in CH_3CN (7 mL). The mixture was stirred for 2 h at room temperature and then cooled to 0–5 °C, when it was diluted with water and extracted with EtOAc. The combined extracts were washed with water, dried (anhydrous $MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel ($CHCl_3$) to give the quinone derivative **39** (485 mg, 93%) as a yellow oil, ν_{max}(neat film)/cm^{-1} 3010, 2869, 1658, 1245, 1010 and 820; δ_H (400 MHz, $CDCl_3$) 3.41–3.56 (8H, m, CH_2), 3.61–3.78 (4H, m, CH_2), 4.54 (2H, m, CH), 4.56 (2H, d, *J* 15.3, allylic CH_2), 4.66 (2H, d, *J* 14.7, allylic CH_2), 6.75 (2H, s, quinone CH), 7.19 (4H, d, *J* 8.6, ArH) and 7.48 (4H, d, *J* 8.6, ArH).

To a solution of (*S*,*S*)-**39** (485 mg, 0.762 mmol) in a mixture of $CHCl_3$ (7 mL) and EtOH (5 mL) was added a solution of 2,4-dinitrophenylhydrazine (277 mg, 1.40 mmol) dissolved in a mixture of EtOH (7 mL) and concentrated H_2SO_4 (3 mL). The mixture was stirred for 1.5 h at room temperature, after which it was diluted with water and extracted with $CHCl_3$. The combined extracts were washed with aqueous $NaHCO_3$ and water, dried (anhydrous $MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give a solid (hexane–EtOAc (2:1)), which was further purified by preparative recycling HPLC to give (*S*,*S*)-**3** (307 mg, 49%) as a red amorphous solid, mp 157–158 °C; λ_{max}/($CHCl_3$) 401 nm (ε 2.10×10^4 dm^3 mol^{-1} cm^{-1}); ν_{max}(KBr)/cm^{-1} 3316, 2870, 1535, 1429, 919 and 832; δ_H (400 MHz, $CDCl_3$) 3.55–3.81 (12H, m, CH_2), 4.64 (2H, dd, *J* 7.8, 3.8, CH), 4.84 (4H, s, benzylic CH_2), 7.24 (4H, d, *J* 8.3, ArH), 7.49 (4H, d, *J* 8.3, ArH), 7.81 (1H, d, *J* 9.2, $(NO_2)_2$ArH), 7.83 (2H, s, HOAr*H*), 8.48 (1H, dd, *J* 9.0, 2.2, $(NO_2)_2$ArH), 8.75 (1H, d, *J* 2.0, $(NO_2)_2$ArH) and 9.06 (1H, s, OH); MS (FAB) *m*/*z* 817 ($M^+ + 1$) (Found: C, 49.69; H, 3.90; N, 6.70. $C_{34}H_{32}Br_2N_4O_{10}$ requires C, 50.02; H, 3.95; N, 6.86%).

(*S*)-(+)-1-(*p*-Methoxyphenyl)-2-(triphenylmethoxy)ethanol (*S*)-21

In a manner similar to that described to the preparation of (*S*)-**22**, treatment of (*S*)-**10** (>99% ee) (3.28 g, 19.5 mmol) with chlorotriphenylmethane (5.55 g, 19.9 mmol) gave (*S*)-**21** (6.95 g, 87%) after silica gel chromatography (hexane–EtOAc (9:1)) as a pale yellow viscous oil, $[\alpha]_D^{31}$ +12.7 (*c* 0.810, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3453, 3058, 2925, 1249, 1034, 832 and 705; δ_H (300 MHz, $CDCl_3$) 2.70 (1H, d, *J* 2.6, OH), 3.26 (1H, dd, *J* 9.6, 9.6, CH_2), 3.31 (1H, dd, *J* 9.6, 4.4, CH_2), 3.77 (3H, s, OCH_3), 4.72 (1H, m, CH), 6.82 (2H, d, *J* 8.5, *p*-methoxyphenyl ArH) and 7.16–7.43 (17H, m, *p*-methoxyphenyl ArH and $C(C_6H_5)_3$); *m*/*z* (FAB) 409 ($M^+ - 1$) (Found: M^+ 410.1921. $C_{28}H_{26}O_3$ requires 410.1882).

(2*S*,10*S*)-(+)-2,10-Bis(*p*-methoxyphenyl)-1,11-bis(triphenylmethoxy)-3,6,9-trioxaundecane (*S*,*S*)-25

A solution of (*S*)-**21** (2.96 g, 7.21 mmol) in dry THF (50 mL) was added slowly to a suspension of 60% NaH (479 mg, 20.0 mmol) and 15-crown-5 (1.11 g, 5.03 mmol) in dry THF (35 mL) and the resulting mixture was refluxed for 1 h. After the reaction mixture had been cooled to room temperature, a solution of **24** (1.91 g, 4.61 mmol) in dry THF (40 mL) was added dropwise to the mixture and the reaction mixture was gently refluxed for 6 h under a nitrogen atmosphere. After a small amount of chilled water had been carefully added to the reaction mixture with ice-cooling, the solvent was removed under reduced pressure. The residue was extracted with EtOAc and the combined extracts were washed with water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc (4:1)) to give (*S*,*S*)-**25** (2.62 g, 81%) as an oil, $[\alpha]_D^{32}$ +11.0 (*c* 1.73, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3059, 2929, 1248, 1033, 832 and 706; δ_H (300 MHz, $CDCl_3$) 3.11 (2H, dd, *J* 9.5, 5.3, CH_2), 3.39 (2H, dd, *J* 9.6, 6.9, CH_2), 3.44–3.67 (8H, m, CH_2), 3.77 (6H, s, OCH_3), 4.33 (2H, t, *J* 6.2, CH), 6.81 (4H, d, *J* 8.5, *p*-methoxyphenyl ArH) and 7.14–7.37 (34H, m, *p*-methoxyphenyl ArH and $C(C_6H_5)_3$); the high-resolution mass spectrum could not be recorded because of the weak molecular ion peak.

(2*S*,10*S*)-(+)-2,10-Bis(*p*-methoxyphenyl)-3,6,9-trioxaundecane-1,11-diol (*S*,*S*)-28

In a manner similar to that described for the preparation of (*S*,*S*)-**29**, treatment of (*S*,*S*)-**25** (2.398 g, 2.69 mmol) with MeOH (60 mL) containing $CHCl_3$ (10 mL) and *p*-TsOH·H_2O (107 mg, 0.563 mmol) gave (*S*,*S*)-**28** (1.08 g, >99%) as a white solid after silica gel chromatography (EtOAc), mp 72–73 °C; $[\alpha]_D^{31}$ +91.9 (*c* 0.700, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3384, 2942, 1242, 1096 and 826; δ_H (300 MHz, $CDCl_3$) 3.53–3.76 (12H, m, CH_2), 3.80 (6H, s, OCH_3), 4.46 (2H, dd, *J* 8.9, 3.2, CH), 6.89 (4H, d, *J* 8.8, ArH) and 7.25 (4H, d, *J* 8.5, ArH); *m*/*z* (FAB) 407 ($M^+ + 1$) (Found: C, 64.92; H, 7.47. $C_{22}H_{30}O_7$ requires C, 65.01; H, 7.44%).

(5*S*,13*S*)-(+)-19,21-Dimethoxy-5,13-Bis(*p*-methoxyphenyl)-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(21),17,19-triene (*S*,*S*)-32

By a procedure similar to that described for the preparation of (*S*,*S*)-**33**, reaction of (*S*,*S*)-**28** (908 mg, 2.23 mmol) with **31** (765 mg, 2.36 mmol) followed by silica gel chromatography (hexane–EtOAc (4:1)) gave (*S*,*S*)-**32** (735 mg, 58%) as a white solid, mp 47–48 °C; $[\alpha]_D^{31}$ +118 (*c* 0.536, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2862, 1511, 1248, 1095 and 832; δ_H (300 MHz, $CDCl_3$) 3.35–3.46 (8H, m, CH_2), 3.51 (2H, dd, *J* 10.4, 2.9, CH_2), 3.69 (2H, dd, *J* 10.4, 8.9, CH_2), 3.78 (3H, s, OCH_3), 3.80 (6H, s, OCH_3), 4.18 (3H, s, OCH_3), 4.47 (2H, dd, *J* 8.6, 2.8, CH_2), 4.47 (2H, d, *J* 10.4, benzylic CH_2), 4.70 (2H, d, *J* 10.8, benzylic CH_2), 6.87 (4H, d, *J* 8.8, ArH) and 7.23 (4H, d, *J* 8.5, ArH); *m*/*z* (FAB) 569 (M^+) (Found: C, 67.17; H, 7.15. $C_{32}H_{40}O_9$ requires C, 67.59; H, 7.09%).

(5*S*,13*S*)-(+)-21-Hydroxy-19-methoxy-5,13-bis(*p*-methoxyphenyl)-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(21),17,19-triene (*S*,*S*)-35

In a manner similar to that described for the preparation of (*S*,*S*)-**36**, treatment of (*S*,*S*)-**32** (364 mg, 0.640 mmol) with sodium ethanethiolate in DMF gave (*S*,*S*)-**35** (330 mg, 93%) as a pale yellow viscous oil after silica gel chromatography (hexane–EtOAc (4:1)), $[\alpha]_D^{29}$ +99.8 (*c* 0.713, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3388, 2905, 1513, 1247, 1099 and 833; δ_H (300 MHz, $CDCl_3$) 3.57–3.76 (12H, m, CH_2), 3.74 (3H, s, OCH_3), 3.80 (6H, s, OCH_3), 4.61 (2H, dd, *J* 9.0, 3.0, CH), 4.73 (4H, s, benzylic CH_2), 6.72 (2H, s, HOAr*H*), 6.88 (4H, d, *J* 8.8, ArH), 7.25 (4H, d, *J* 8.5, ArH) and 7.73 (1H, br s, OH); *m*/*z* (FAB) 555 (M^+); the high-resolution mass spectrum could not be recorded because of the weak molecular ion peak.

(5*S*,13*S*)-21-Hydroxy-19-(2′,4′-dinitrophenylazo)-5,13-bis-(*p*-methoxyphenyl)-3,6,9,12,15-pentaoxabicyclo[15.3.1]-henicosa-1(21),17,19-triene (*S*,*S*)-2

In a manner similar to that described for the preparation of (*S*,*S*)-**3**, (*S*,*S*)-**35** was oxidised with CAN (380 mg, 0.693 mmol). Silica gel chromatography of the products ($CHCl_3$) gave (*S*,*S*)-**38** (296 mg, 82%) as a yellow viscous oil, ν_{max}(neat film)/cm^{-1} 2907, 2867, 1512, 1246, 1097, 832 and 754; δ_H (300 MHz, $CDCl_3$) 3.41–3.53 (8H, m, CH_2), 3.62–3.79 (4H, m, CH_2), 3.80 (6H, s, OMe), 4.52 (2H, dd, *J* 8.3, 2.9, CH), 4.58 (2H, d, *J* 14.6, allylic CH_2), 4.67 (2H, d, *J* 14.6, allylic CH_2), 6.77 (2H, s, quinone CH), 6.88 (4H, d, *J* 8.8, ArH) and 7.22 (4H, d, *J* 8.8, ArH).

Treatment of (*S*,*S*)-**38** (289 mg, 0.537 mmol) with 2,4-dinitrophenylhydrazine (304 mg, 1.53 mmol) gave (*S*,*S*)-**2** (191 mg, 49%) as a red solid, mp 74–75 °C; $\lambda_{max}(CHCl_3)$/nm 403 (ε 2.26×10^4 dm^3 mol^{-1} cm^{-1}); ν_{max}(KBr)/cm^{-1} 3385, 2869, 1534, 1345, 1247, 1114 and 833; δ_H (300 MHz, $CDCl_3$) 3.55–3.77 (12H, m, CH_2), 3.80 (6H, s, OMe), 4.64 (2H, dd, *J* 11.8, 4.2, CH), 4.85 (4H, s, benzylic CH_2), 6.89 (4H, d, *J* 8.8, ArH), 7.27 (4H, d, *J* 8.8, ArH), 7.81 (1H, d, *J* 8.8, $(NO_2)_2$ArH), 7.84 (2H, s, HOAr*H*), 8.48 (1H, dd, *J* 8.8, 2.3, $(NO_2)_2$ArH), 8.75 (1H, d, *J* 2.5, $(NO_2)_2$ArH) and 9.20 (1H, s, OH); *m*/*z* (FAB) 718 (M^+ + 1) (Found: C, 59.85; H, 5.07; N, 7.68. $C_{36}H_{38}N_4O_{12}$ requires C, 60.16; H, 5.33; N, 7.80%).

(+)-1-[*p*-(Trifluoromethyl)phenyl]ethane-1,2-diol (*S*)-12

To a solution of AD-mix-*α* (2.51 g) in *t*-BuOH (5 mL) and H_2O (10 mL), *p*-trifluoromethylstyrene (**14**) (312 mg, 1.81 mmol) was added and the solution was stirred at 0 °C for 3 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution, and the mixture was extracted with $CHCl_3$. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was concentrated *in vacuo*, and the solid residue was recrystallized from MeOH to give (*S*)-**12** as a white solid (334 mg, 90%), mp 93–94 °C; $[\alpha]_D^{27}$ +41.3 (*c* 0.828, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3399, 2926, 1324, 1179, 1127, 1066 and 837; δ_H (300 MHz, $CDCl_3$) 2.02 (1H, dd, *J* 6.8, 5.3, OH), 2.65 (1H, d, *J* 3.3, OH), 3.65 (1H, ddd, *J* 11.3, 8.0, 5.0, CH_2), 3.82 (1H, ddd, *J* 11.1, 6.9, 3.4, CH_2), 4.90 (1H, m, CH), 7.51 (2H, d, *J* 8.0, ArH) and 7.63 (2H, d, *J* 8.2, ArH); *m*/*z* (FAB) 206 (M^+) (Found: C, 52.60; H, 4.44. $C_9H_9F_3O_2$ requires C, 52.43; H, 4.40%).

(*R*)-(−)-2-(*p*-Tolylsulfonyloxy)-1-[*p*-(trifluoromethyl)phenyl]-ethanol (*R*)-19

In a manner similar to that described for the preparation of (*S*)-**17**, reaction of (*R*)-**12** (400 mg, 1.94 mmol) with *p*-TsCl (300 mg, 1.57 mmol) in pyridine (5 mL) followed by silica gel chromatography gave (*R*)-**19** (355 mg, 63%) as a white solid, mp 85–87 °C; $[\alpha]_D^{23}$ −35.3 (*c* 0.28, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3493, 3069, 2929, 1329, 1118, 1067 and 818; δ_H (300 MHz, $CDCl_3$) 4.03 (1H, dd, *J* 9.3, 8.7, CH_2), 4.14 (1H, dd, *J* 11.4, 7.2, CH_2), 5.09 (1H, m, CH), 7.34 (2H, d, *J* 7.5, ArH), 7.45 (2H, d, *J* 8.4, ArH), 7.60 (2H, d, *J* 8.1, ArH) and 7.75 (2H, d, *J* 7.5, ArH); *m*/*z* (FAB) 361 (M^+ + 1) (Found: C, 53.34; H, 4.03. $C_{16}H_{15}F_3O_4S$ requires C, 53.33; H, 4.20%).

(*S*)-(−)-1-[*p*-(Trifluoromethyl)phenyl]ethanol (*S*)-20

In a manner similar to that described for the preparation of (*S*)-**18**, reduction of (*R*)-**19** (200 mg, 0.555 mmol) with $LiAlH_4$ (21.0 mg, 0.555 mmol) in THF (5 mL) followed by silica gel chromatography gave (*S*)-**20** (64.0 mg, 60%) as a colourless oil, $[\alpha]_D^{24}$ −27.6 (*c* 1.00, CH_3OH) (lit.,[13] $[\alpha]_D^{24}$ −27.6 (*c* 1.00, CH_3OH)); ν_{max}(neat film)/cm^{-1} 3347, 2978, 2932, 1327, 1068 and 842; δ_H (400 MHz, $CDCl_3$) 1.51 (3H, d, *J* 6.8, CH_3), 1.83 (1H, d, *J* 3.4, OH), 4.97 (1H, m, CH), 7.49 (2H, d, *J* 8.3, ArH) and 7.61 (2H, d, *J* 8.3, ArH).

(*S*)-(+)-1-[*p*-(Trifluoromethyl)phenyl]-2-(triphenylmethoxy)-ethanol (*S*)-23

In a manner similar to that described for the preparation of (*S*)-**22**, treatment of (+)-**12** (>99% ee) (2.03 g, 9.84 mmol) with chlorotriphenylmethane (3.04 g, 10.9 mmol) gave (+)-**23** (3.47 g, 79%) after silica gel chromatography (hexane–EtOAc (9:1)) as a pale yellow viscous oil, $[\alpha]_D^{28}$ +3.86 (*c* 0.495, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3437, 3059, 2923, 1325, 1067, 758 and 705; δ_H (300 MHz, $CDCl_3$) 2.80 (1H, d, *J* 2.7, OH), 3.27 (1H, dd, *J* 9.6, 8.1, CH_2), 3.38 (1H, dd, *J* 9.6, 3.9, CH_2), 4.79 (1H, ddd, *J* 7.1, 3.9, 3.3, CH), 7.21–7.41 (17H, m, ArH and $C(C_6H_5)_3$) and 7.55 (2H, d, *J* 8.0, ArH); *m*/*z* (EI) 448 (M^+ − 1) (Found: M^+ 448.1628. $C_{28}H_{23}F_3O_3$ requires 448.1650).

(2*S*,10*S*)-(+)-2,10-Bis[*p*-(trifluoromethyl)phenyl]-1,11-bis(triphenylmethoxy)-3,6,9-trioxaundecane (*S*,*S*)-27

In a manner similar to that described for the preparation of (*S*,*S*)-**25**, reaction of (*S*)-**23** (3.26 g, 7.28 mmol) with **24** (1.58 g, 3.82 mmol) gave (*S*,*S*)-**27** (1.34 g, 38%) after silica gel chromatography (hexane–EtOAc (9:1)) as a white solid, mp 53–55 °C; $[\alpha]_D^{28}$ +1.12 (*c* 0.623, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3059, 2871, 1325, 1123 and 705; δ_H (300 MHz, $CDCl_3$) 3.15 (2H, dd, *J* 12.8, 7.2, CH_2), 3.42 (2H, dd, *J* 12.8, 8.4, CH_2), 3.50–3.64 (8H, m, CH_2), 4.42 (2H, t, *J* 8.0, CH), 7.15–7.36 (34H, m, ArH and $C(C_6H_5)_3$) and 7.52 (4H, d, *J* 8.0, ArH); *m*/*z* (FAB) 965 (M^+ − 1) (Found: C, 74.11; H, 5.48. $C_{60}H_{52}F_6O_5$ requires C, 74.52; H, 5.42%).

(2*S*,10*S*)-(+)-2,10-Bis[*p*-(trifluoromethyl)phenyl]-3,6,9-trioxaundecane-1,11-diol (*S*,*S*)-30

In a manner similar to that described for the preparation of (*S*,*S*)-**29**, treatment of (*S*,*S*)-**27** (1.186 g, 1.23 mmol) with MeOH (24 mL) containing $CHCl_3$ (6 mL) and *p*-TsOH·H_2O (52 mg, 0.273 mmol) gave (*S*,*S*)-**30** (581 mg, 98%) as a colourless viscous oil after silica gel chromatography (EtOAc), $[\alpha]_D^{28}$ +67.7 (*c* 0.873, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3309, 2876, 1327, 1122, 1067 and 838; δ_H (300 MHz, $CDCl_3$) 3.63–3.77 (12H, m, CH_2), 4.30 (2H, t, *J* 8.0, OH), 4.58 (2H, dd, *J* 9.2, 6.0, CH), 7.47 (4H, d, *J* 8.0, ArH) and 7.62 (4H, d, *J* 8.2, ArH); *m*/*z* (FAB) 483 (M^+ + 1); the high-resolution mass spectrum could not be recorded because of the weak molecular ion peak.

(5*S*,13*S*)-(+)-19,21-Dimethoxy-5,13-bis[*p*-(trifluoromethyl)-phenyl]-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(21),17,19-triene (*S*,*S*)-34

By a procedure similar to that described for the preparation of (*S*,*S*)-**33**, reaction of (*S*,*S*)-**30** (135 mg, 0.280 mmol) with **31** (104 mg, 0.321 mmol) followed by silica gel chromatography (hexane–EtOAc (4:1)) gave (*S*,*S*)-**34** (106 mg, 59%) as a colourless viscous oil, $[\alpha]_D^{28}$ +82.2 (*c* 0.471, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2868, 1326, 1123, 840 and 733; δ_H (300 MHz, $CDCl_3$) 3.41–3.50 (8H, m, CH_2), 3.56 (2H, dd, *J* 14.0, 4.0, CH_2), 3.69 (2H, dd, *J* 14.0, 10.4, CH_2), 3.78 (3H, s, OMe), 4.12 (3H, s, OMe), 4.49

(2H, d, *J* 11.0, benzylic CH_2), 4.57 (2H, dd, *J* 10.4, 4.4, CH), 4.70 (2H, d, *J* 11.0, benzylic CH_2), 6.83 (2H, s, $(MeO)_2ArH$), 7.44 (4H, d, *J* 8.2, ArH) and 7.60 (4H, d, *J* 8.2, ArH); *m*/*z* (FAB) 644 (M^+) (Found: M^+ 644.2222. $C_{32}H_{34}F_6O_7$ requires 644.2209).

(5*S*,13*S*)-(+)-21-Hydroxy-19-methoxy-5,13-bis[*p*-(trifluoromethyl)phenyl]-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosa-1(21),17,19-triene (*S*,*S*)-37

In a manner similar to that described for the preparation of (*S*,*S*)-**36**, treatment of (*S*,*S*)-**34** (444 mg, 0.689 mmol) with sodium ethanethiolate in DMF gave (*S*,*S*)-**37** (249 mg, 57%) as a pale yellow viscous oil after silica gel chromatography (hexane–EtOAc (4:1)), $[a]_D^{29}$ +65.7 (*c* 2.58, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3396, 2871, 1326, 1125, 839 and 760; δ_H (300 MHz, $CDCl_3$) 3.59–3.77 (12H, m, CH_2), 3.74 (3H, s, OMe), 4.71–4.74 (6H, m, CH and benzylic CH_2), 6.72 (2H, s, HOAr*H*), 7.46 (4H, d, *J* 8.2, ArH), 7.59 (4H, d, *J* 8.2, ArH) and 7.61 (1H, s, OH); *m*/*z* (FAB) 630 (M^+) (Found: M^+ 630.2068. $C_{31}H_{32}F_6O_7$ requires 630.2053).

(5*S*,13*S*)-21-Hydroxy-19-(2′,4′-dinitrophenylazo)-5,13-bis[*p*-(trifluoromethyl)phenyl]-3,6,9,12,15-pentaoxabicyclo[15.3.1]-henicosa-1(21),17,19-triene (*S*,*S*)-4

In a manner similar to that described for the preparation of (*S*,*S*)-**3**, (*S*,*S*)-**37** (193 mg, 0.306 mmol) was oxidised with CAN (210 mg, 0.383 mmol). Silica gel chromatography of the products ($CHCl_3$) gave (*S*,*S*)-**40** (174 mg, 92%) as a yellow viscous oil, ν_{max}(KBr)/cm^{-1} 2899, 1647, 1618, 1324, 1124 and 840; δ_H (300 MHz, $CDCl_3$) 3.45–3.71 (12H, m, CH_2), 4.58 (2H, d, *J* 14.6, allylic CH_2), 4.62 (2H, dd, *J* 12.4, 12.4, CH), 4.68 (2H, d, *J* 14.6, allylic CH_2), 6.77 (2H, s, quinone CH), 7.45 (4H, d, *J* 8.0, ArH) and 7.62 (4H, d, *J* 8.2, ArH).

Treatment of (*S*,*S*)-**40** (162 mg, 0.264 mmol) with 2,4-dinitrophenylhydrazine (160 mg, 0.805 mmol) gave (*S*,*S*)-**4** (139 mg, 66%) as a red solid, mp 170–171 °C; λ_{max}($CHCl_3$)/nm 400 (ε 2.19×10^4 dm^3 mol^{-1} cm^{-1}); ν_{max}(KBr)/cm^{-1} 3398, 1536, 1326, 1125 and 834; δ_H (300 MHz, $CDCl_3$) 3.58–3.84 (12H, m, CH_2), 4.75 (2H, dd, *J* 7.0, 7.0, CH), 4.86 (4H, s, benzylic CH_2), 7.49 (4H, d, *J* 8.2, ArH), 7.63 (4H, d, *J* 8.5, ArH), 7.81 (1H, d, *J* 8.8, $(NO_2)_2ArH$), 7.84 (2H, s, HOAr*H*), 8.49 (1H, dd, *J* 9.0, 2.4, $(NO_2)_2ArH$), 8.76 (1H, d, *J* 2.5, $(NO_2)_2ArH$) and 9.04 (1H, s, OH); *m*/*z* (FAB) 795 (M^+ + 1) (Found: C, 54.15; H, 4.06; N, 7.00; F, 14.22. $C_{34}H_{32}N_4F_6O_{10}$ requires C, 54.41; H, 4.06; N, 7.05; F, 14.34%).

(*S*)-(+)-4-[*p*-(Trifluoromethyl)phenyl]-1,3-dioxolan-2-one (*S*)-41

To a solution of (*S*)-**12** (5.51 g, 26.7 mmol) in dimethyl carbonate (65 mL) was added NaOH pellets (2.20 g, 55.0 mmol), and the mixture was stirred at 60 °C for 4 h. A mixture of MeOH and dimethyl carbonate (20–25 mL) was removed by distillation at 90 °C. The remaining suspension was diluted with THF (200 mL), filtered through Celite, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–EtOAc (4:1)) to give (*S*)-**41** (5.58 g, 90%) as a white solid, mp 47–49 °C; $[a]_D^{27}$ +47.5 (*c* 1.01, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3055, 2941, 1820, 1167, 1067 and 844; δ_H (300 MHz, $CDCl_3$) 4.32 (1H, dd, *J* 8.1, 8.1, CH_2), 4.85 (1H, dd, *J* 8.2, 8.2, CH_2), 5.74 (1H, dd, *J* 7.8, 7.8, CH), 7.50 (2H, d, *J* 8.1, ArH) and 7.73 (2H, d, *J* 8.4, ArH); *m*/*z* (FAB) 232 (M^+) (Found: C, 51.74; H, 2.96. $C_{10}H_7F_3O_3$ requires C, 51.74; H, 3.04%).

(*R*)-(−)-2-Azido-2-[*p*-(trifluoromethyl)phenyl]ethanol (*R*)-42

To a solution of (*S*)-**41** (5.50 g, 23.7 mmol) in DMF (50 mL) was added water (0.26 mL, 14.2 mmol) and sodium azide (1.85 g, 28.4 mmol). The mixture was stirred at 110 °C under a nitrogen atmosphere for 3 h. The reaction mixture was diluted with Et_2O (20 mL) and the resulting suspension was filtered through Celite to remove $NaHCO_3$ and excess NaN_3 and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–EtOAc (4:1)) to give (*R*)-**42** (2.32 g, 43%) as a white solid, mp 63–65 °C; $[a]_D^{26}$ −144 (*c* 1.02, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3368, 3064, 2946, 2133, 2082, 1256, 1060 and 836; δ_H (300 MHz, $CDCl_3$) 1.94 (1H, dd, *J* 7.4, 5.6, OH), 3.71–3.85 (2H, m, CH_2), 4.74 (1H, dd, *J* 7.4, 4.8, CH), 7.47 (2H, d, *J* 8.1, ArH) and 7.67 (2H, d, *J* 7.8, ArH); *m*/*z* (FAB) 232 (M^+ + 1) (Found: C, 46.97; H, 3.39; N, 17.94. $C_9H_8F_3N_3O$ requires C, 46.76; H, 3.49; N, 18.18%).

(*R*)-(−)-2-Amino-2-[*p*-(trifluoromethyl)phenyl]ethanol (*R*)-9

To a solution of (*R*)-**42** (1.70 g, 7.35 mmol) in THF (35 mL) was slowly added $LiAlH_4$ (560 mg, 14.7 mmol) at 0 °C. After being stirred at room tempareture for 2 h, the mixture was diluted with Et_2O (50 mL) and quenched with an aqueous solution of KF (1.6 M, 2 mL). The suspension was filtered through Celite, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Recrystallization from hexane–EtOAc afforded (*R*)-**9** (1.07 g, 72%) as white crystals, mp 99–100 °C; $[a]_D^{26}$ −30.5 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3338, 3278, 3131, 2915, 1173, 1071 and 838; δ_H (300 MHz, $CDCl_3$) 1.59 (3H, br s, OH, NH_2), 3.56 (1H, dd, *J* 10.5, 7.8, CH_2), 3.77 (1H, dd, *J* 10.8, 4.5, CH_2), 4.14 (1H, dd, *J* 8.1, 4.5, CH), 7.47 (2H, d, *J* 7.8, ArH) and 7.61 (2H, d, *J* 8.7, ArH); *m*/*z* (FAB) 206 (M^+ + 1) (Found: C, 52.95; H, 4.94; N, 6.77. $C_9H_{10}F_3NO$ requires C, 52.69; H, 4.91; N, 6.83%).

(*R*)-(−)-4-[*p*-(Trifluoromethyl)phenyl]-1,3-dioxolan-2-one (*R*)-41

In a manner similar to that described for the preparation of (*S*)-**41**, reaction of (*R*)-**12** (5.00 g, 24.3 mmol) with NaOH (2.00 g, 50.0 mmol (pellets)) in dimethyl carbonate (60 mL) gave (*R*)-**41** (5.04 g, 89%) as a white solid, mp 47–49 °C; $[a]_D^{27}$ −46.0 (*c* 1.10, $CHCl_3$).

(*S*)-(+)-2-Azido-2-[*p*-(trifluoromethyl)phenyl]ethanol (*S*)-42

In a manner similar to that described for the preparation of (*R*)-**42**, reaction of (*R*)-**41** (4.50 g, 19.3 mmol) with water (0.21 mL, 11.6 mmol) and NaN_3 (1.64 g, 25.2 mmol) in DMF (40 mL) gave (*S*)-**42** (2.29 g, 51%) as a white solid, mp 64–65 °C; $[a]_D^{26}$ +142 (*c* 1.02, $CHCl_3$).

(*S*)-(+)-2-Amino-2-[*p*-(trifluoromethyl)phenyl]ethanol (*S*)-9

In a manner similar to that described for the preparation of (*R*)-**9**, reduction of (*S*)-**42** (1.50 g, 6.49 mmol) with $LiAlH_4$ (490 mg, 12.9 mmol) in THF (40 mL) followed by recrystallization from hexane–EtOAc gave (*S*)-**9** (0.725 g, 55%) as white crystals, mp 99–100 °C; $[a]_D^{26}$ +30.5 (*c* 1.07, $CHCl_3$).

Titration method for determination of association constants

As an example, the titration experiment for complexation of crown ether (*S*,*S*)-**2** with amine (*R*)-**6** is described here. A solution of (*S*,*S*)-**2** in $CHCl_3$ was prepared and an initial UV spectrum of this solution was recorded. The concentration was calculated to be 0.0037 mM based on its molar extinction coefficient. Separately, a 1.22 mM solution of (*R*)-**6** in $CHCl_3$ (prepared by diluting 1.0 mL of a 10.0 mL solution containing 12.89 mg of (*R*)-**6** to 10.0 mL) was prepared. Samples were made by adding the guest solution to the host solution. Namely, a 2.0 mL portion of the host solution, and 0.5, 0.7, 1.0, 1.5, and 2.0 mL portions of the guest solution were mixed, and diluted with $CHCl_3$ to make the total volume up to 4.0 mL. Then, spectra of these five different solutions were recorded. The association constants were calculated from the absorption intensity of the complex at five different wavelengths based on the Rose–Drago method.[15]

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18 The chemical shifts of the complexes, $\delta_{complex}$, were calculated by measuring the chemical shifts of the relevant protons of appropriate host–guest mixtures and then by extrapolating $\delta_{observed}$ to $\delta_{complex}$ by using the association constants determined by the UV-vis titration. The identity of the association constants as well as $\delta_{complex}$ determined by the UV-vis titration in $CHCl_3$ with those obtained by the ^{1}H NMR titration in $CDCl_3$ was checked in several host–guest systems. Where appropriate, K_a at 30 °C was estimated by using the thermodynamic data listed in Table 5 (see Supplementary Material).

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