Preparation and Enantiomer Recognition Behaviour of Azophenolic Crown Ethers containing *cis*-Cyclohexane-1,2-diol as the Chiral Centre

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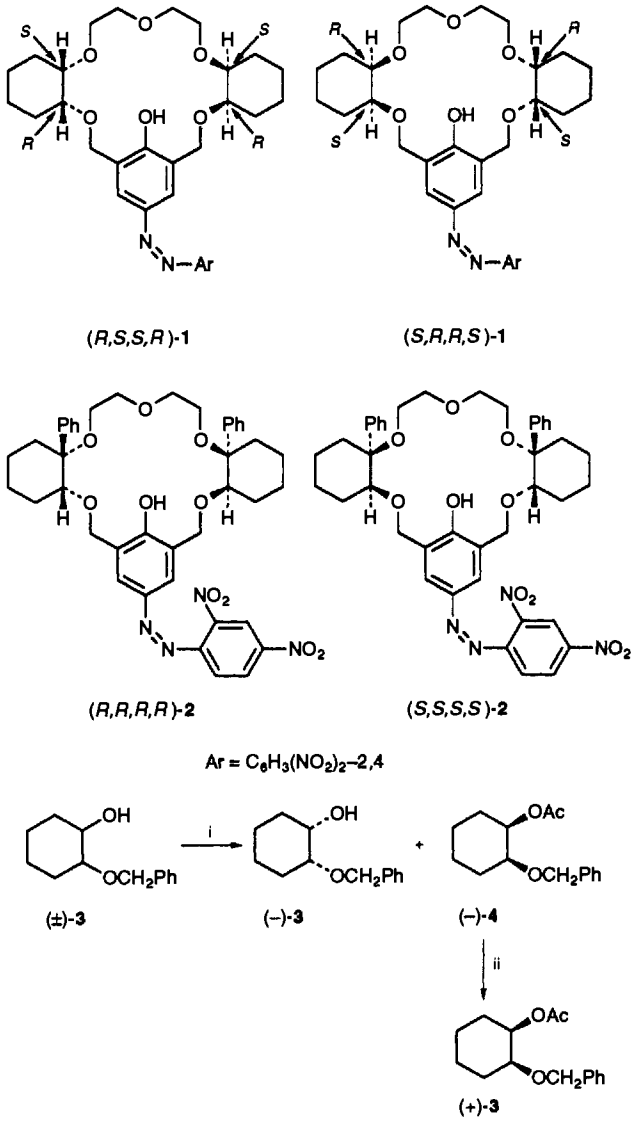
Both enantiomers of the azophenolic crown ether **1** incorporating the *cis*-cyclohexane-1,2-diol residue as the chiral centre have been prepared in enantiomerically pure forms and the chiral recognition behaviour towards 2-aminoethanols and ethylamines has been examined. The observed enantiomer selectivities of the crown ether **1** in complexation with racemic amines have been interpreted on the basis of CPK molecular model examination of the diastereoisomeric complexes.

Various types of natural and synthetic chiral compounds have been used for constructing optically active crown ethers as chiral subunits, and continuing development of chiral building blocks has resulted in the production of a wide variety of optically active crown ethers exhibiting characteristic chiral recognition behaviour.[1] We have also prepared a variety of optically active crown ethers using synthetic chiral subunits[2] and recently reported the preparation and the enantiomer recognition behaviour of crown ethers containing *cis*-1-phenylcyclohexane-1,2-diol and *trans*-1,2-diphenylcyclohexane-1,2-diol, all of which have both the phenyl group and the cyclohexane moiety as chiral barriers on each face of the crown ring.[3,4] The observed association constants for the complex of **2** containing *cis*-1-phenylcyclohexane-1,2-diol with amines suggested that two bulky barriers caused the large steric interactions between the barriers and the guest, resulting in the relative weakness in the binding ability of crown **2** towards the amines bearing the bulky substituent.[4] In this regard, our interest in developing a novel chiral building block for a crown ether led us to prepare the chiral crown ether having the *cis*-cyclohexane-1,2-diol moiety as a chiral centre and to examine the usefulness of this residue as a chiral barrier. Preparations of achiral crown ethers containing *cis*-cyclohexane-1,2-diol have previously been reported,[5] but, as far as we know, no optically active crown ether has been prepared using only this compound as a chiral centre. Herein we report the preparation of the chiral azophenolic crown ether **1** using optically active *cis*-2-benzyloxycyclohexanol **3** as a chiral building block. The enantiomer recognition behaviour of crown **1** is also described and the observed enantiomer selectivities in complexation with chiral amines have been interpreted on the basis of CPK molecular model examination of the diastereoisomeric complexes.

It was our synthetic strategy that *cis*-cyclohexane-1,2-diol would be desymmetrized by conversion of one of the hydroxy groups into a benzyloxy group, and the resulting alcohol **3** was resolved by enzyme-catalysed enantioselective acylation. Ready access to large quantities of both enantiomers of compound **3** in enantiomerically pure forms is a necessary requirement for success in this work. The use of enzymes for the preparation of optically active compounds of synthetic value has been well documented, and particularly useful in this respect are hydrolytic enzymes.[6]

Kinetic resolution of the subunit **3** was achieved by lipase YS (from *Pseudomonas fluorescens*)-catalysed enantioselective acylation of racemate (±)-**3** using vinyl acetate as an acylating agent in diisopropyl ether (see Scheme 1). The progress of the enzymic acylation was monitored by GLC and the reaction was



Scheme 1 *Reagents:* i, lipase YS, CH_2=CHOAc; ii, conc. HCl, MeOH

terminated close to 50% of the esterification point. Chromatographic separation of the product gave (1*R*,2*S*)-(−)-1-acetoxy-2-(benzyloxy)cyclohexane **4**, $[\alpha]_D$ -3.1×10^{-1} deg cm^2 g^{-1} ($CHCl_3$) (>99% e.e.) and alcohol (1*S*,2*R*)-(−)-**3**, $[\alpha]_D$ -16.5×10^{-1} deg cm^2 g^{-1} ($CHCl_3$) (>99% e.e.). Hydrolysis of acetate (−)-**4** with conc. HCl and methanol gave alcohol (1*R*,2*S*)-(+)-**3**, $[\alpha]_D$ $+16.4 \times 10^{-1}$ deg cm^2 g^{-1} ($CHCl_3$). The determination of enantiomeric purities of compounds **3** and **4** was carried out by HPLC analysis using a chiral column, and the absolute configurations of *cis*-cyclohexane-1,2-diol derivatives determined by Mosher's method have been described in the literature.[7]

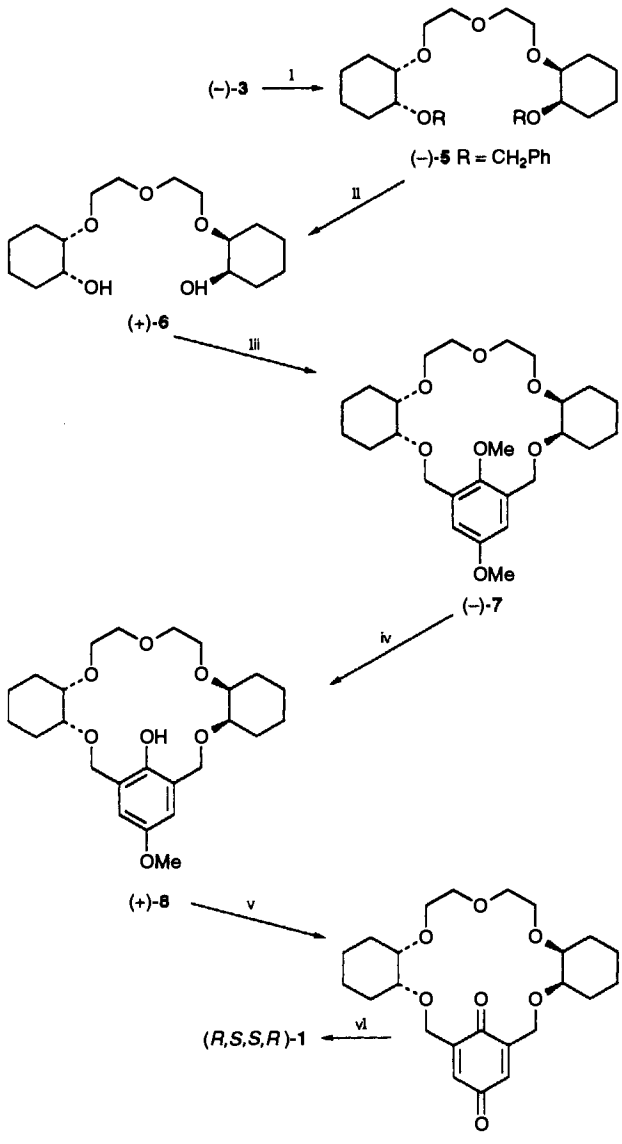
Condensation of alcohol (1*S*,2*R*)-(−)-**3** with diethylene glycol bis(methanesulfonate) in the presence of sodium hydride in dry tetrahydrofuran (THF) gave the polyether (−)-**5**, $[\alpha]_D$ -0.8×10^{-1} deg cm^2 g^{-1} ($CHCl_3$) in 38% yield, which was hydrogenolysed with H_2 and 10% Pd on carbon in 1,4-dioxane to give the diol (+)-**6**, $[\alpha]_D$ $+2.1 \times 10^{-1}$ deg cm^2 g^{-1} ($CHCl_3$) in 61% yield. High-dilution condensation of diol (+)-**6** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in the presence of sodium hydride and potassium tetrafluoroboranuide in dry THF gave the crown ether (−)-**7**, $[\alpha]_D$ -54.2×10^{-1} deg cm^2 g^{-1} ($CHCl_3$) in 47% yield. Treatment of diether (−)-**7** with lithium aluminium hydride in THF resulted in selective cleavage of the inner methoxy group to give the phenolic crown ether (+)-**8**, $[\alpha]_D$ $+9.31 \times 10^{-1}$ deg cm^2 g^{-1} ($CHCl_3$) in 80% yield. Oxidation of the phenol (+)-**8** with cerium(IV) ammonium nitrate (CAN) in acetonitrile–water gave the quinone **9**, which was immediately treated with 2,4-dinitrophenylhydrazine in conc. H_2SO_4–ethanol–dichloromethane followed by column chromatography and recrystallization to afford the azophenolic crown ether (*R*,*S*,*S*,*R*)-**1** as fine orange needles in 72% overall yield for the two steps (Scheme 2). By the same procedure, (*S*,*R*,*R*,*S*)-**1** was prepared from alcohol (1*R*,2*S*)-(+)-**3**. A feature of crown **1** having the phenolate oxygen atom together with the 2,4-dinitrophenylazo group is that it can bind a neutral amine to form a stable complex, and a red shift is observed in the formation of the complex with amines in a UV–VIS spectrum. The observed absorption maximum of crown **1** appeared at 408 nm in its spectrum, and the complexes of crown **1** with chiral and achiral amines showed the absorption maximum in the region 557–588 nm.

The association constants for the complexation of crowns (*R*,*S*,*S*,*R*)-**1** and (*S*,*R*,*R*,*S*)-**1** with chiral and achiral amines were determined by the Benesi–Hildebrand method[8] with the aid of the self-colour-indicating properties of the azophenolic crown ether. The K_a-values together with the λ_{max}-values of complexes are summarized in Table 1.

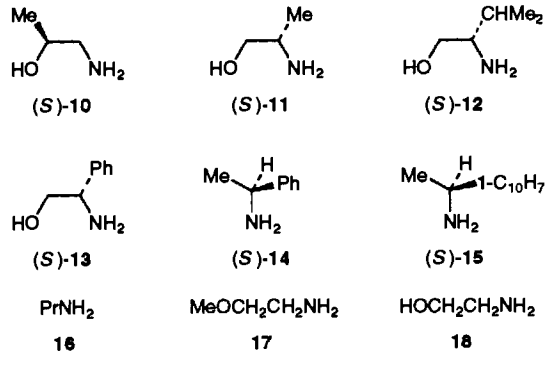
Table 1 demonstrates that the ability of crowns **1** to form complexes with amines examined were higher than that of the azophenolic crown ether **2** containing *cis*-1-phenylcyclohexane-1,2-diol as a chiral centre. As regards the enantiomer recognition behaviour, the marked differences in selectivity between crowns **1** and **2** were found in the complexation with 2-aminoethanols **10**–**12**.

It is our next task to give a reasonable explanation for the observed complexation behaviour on the basis of a CPK molecular model examination of the diastereoisomeric complexes using the assumption that the phenolate oxygen atom necessarily participates in binding the amine[9] and, in the complexes with 2-aminoethanols, the hydroxymethyl group of the guest occupies the area near the phenolate oxygen atom to make the additional hydrogen bond between the phenolate oxygen atom and the hydroxy group of the guest.[4,10]

The observed low selectivity of crowns **1** towards amine (*S*)-**10** may be interpreted on the basis of the predicted geometries **19** and **20**, which are illustrated for the (*R*,*S*,*S*,*R*)-**1**–(*S*)-**10** complex and the (*S*,*R*,*R*,*S*)-**1**–(*S*)-**10** complex, respectively,



Scheme 2 *Reagents:* i, $MsOCH_2CH_2OCH_2CH_2OMs$, NaH; ii, H_2, 10% Pd–C; iii, 1,3-bis(bromomethyl)-2,5-dimethoxybenzene, NaH, KBF_4; iv, $LiAlH_4$; v, CAN; vi, 2,4-dinitrophenylhydrazine, conc. H_2SO_4

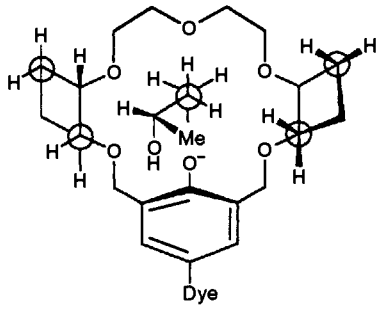


according to the assumption described above. In either geometry, significant steric interactions between the chiral barrier and groups of the guest are not appreciable and hence the difference in stability between two diastereoisomeric complexes was not observed. Thus the cyclohexane moiety did

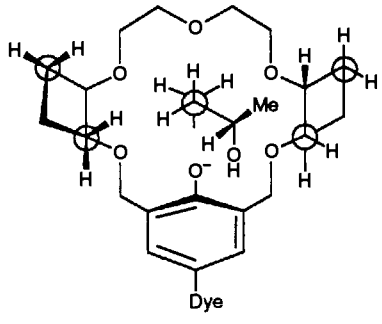
Table 1 Association constants K_a (dm^3 mol^{-1}), the ratio of K_a-values, and absorption maxima of the crown ether **1**–amine complexes

	(*R*,*S*,*S*,*R*)-**1**		(*S*,*R*,*R*,*S*)-**1**		
Amine	K_a (dm^3 mol^{-1})[a]	(λ_{max}/nm)[b]	K_a (dm^3 mol^{-1})	(λ^{1max}/nm)	Relative ratio of K_a-values
(*S*)-**10**	182 ± 2	(569)	184 ± 2	(567)	1/1.01
(*S*)-**11**	151 ± 2	(562)	92.9 ± 1	(558)	1.63/1
(*S*)-**12**	38.5 ± 0.2	(572)	26.1 ± 0.7	(572)	1.48/1
(*S*)-**13**	33.2 ± 0.7	(557)	10.9 ± 1.0	(558)	3.02/1
(*S*)-**14**	14.8 ± 0.5	(566)	23.9 ± 0.3	(558)	1/1.61
(*S*)-**15**	9.2 ± 0.1	(564)	15.0 ± 0.5	(560)	1/1.63
16		420 ± 9	(588)		
17		67.1 ± 11	(588)		
18		328 ± 3	(567)		

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



19 [(*R*,*S*,*S*,*R*)-**1**–(*S*)-**10**]



20 [(*R*,*S*,*S*,*R*)-**1**–(*S*)-**10**]

not function as an effective chiral barrier in complexation with 1-substituted 2-aminoethanols such as **10**.

On the other hand, in the case of complexation with 2-substituted 2-aminoethanols **11**–**13**, the crown ether **1** showed a higher binding ability and a higher enantioselectivity than crown **2**. The combination (*R*,*S*,*S*,*R*)-**1**–(*S*)-**11** leads to the predicted geometries **21** and **22**, but structure **22** is excluded because of steric repulsion between the hydroxymethyl group of the guest and the chiral barrier. Similarly, the geometries **23** and **24** are predicted for the combination (*S*,*R*,*R*,*S*)-**1**–(*S*)-**11**, but in either geometry a steric repulsion between the chiral barrier and the large substituent of the guest made the complex unfavourable. Thus it is understandable that the (*R*,*S*,*S*,*R*)-**1**–(*S*)-**11** complex with the geometry **21** was more stable than its diasteroisomeric complex. The predicted geometry **26** is illustrated for the (*S*,*S*,*S*,*S*)-**2**–(*S*)-**11** complex (K_a 88.3 ± 0.6),[4] and in this case additional steric repulsions between the phenyl substituent and pendant groups of guest (*S*)-**11** made the complex less stable than the (*S*,*R*,*R*,*S*)-**1**–(*S*)-**11** complex with the geometry **23**. In the (*R*,*R*,*R*,*R*)-**2**–(*S*)-**11** complex with the geometry **25**, it is assumed that a large steric repulsion between the phenyl substituent and the hydroxymethyl group markedly decreased the stability of this complex (K_a 78.4 ± 2.3)[4] to result in the least stable of these four complexes.

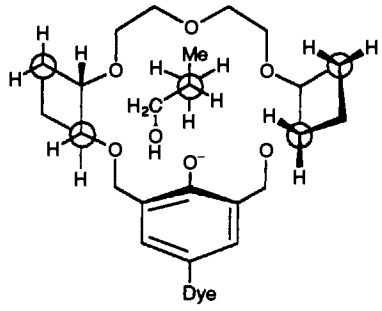
In the case of complexation with 1-substituted ethylamines **14** and **15**, the combination (*S*,*R*,*R*,*S*)-**1**–(*S*)-amine provided the more stable complex. CPK molecular models of the complexes showed that the favourable general geometries **27** and **28** (L and M are the large and the medium-sized group of the amine, respectively) are illustrated for the combination (*R*,*S*,*S*,*R*)-**1**–chiral ethylamine and (*S*,*R*,*R*,*S*)-**1**–chiral ethylamine, respectively. Thus it is obvious that the (*S*,*R*,*R*,*S*)-**1**–(*S*)-**14** complex with the predicted geometry **30**, which matches with the favourable general geometry **28**, was more stable than the (*R*,*S*,*S*,*R*)-**1**–(*S*)-**14** complex with the predicted geometry **29**.

As mentioned above, the results demonstrated that the *cis*-cyclohexane-1,2-diol moiety served as an effective chiral barrier in complexation with 2-aminoethanols and ethylamines having a substituent at the carbon atom bearing the amino group.

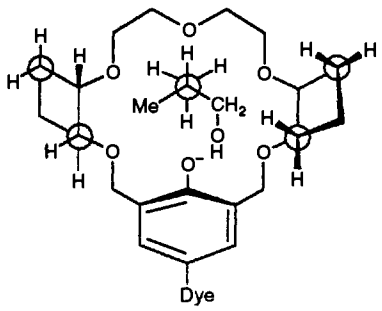
Experimental

General Procedure.—^{1}H NMR spectra were recorded at 270 MHz on a JASCO JNM-MH-270 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. *J* Values are given in Hz. ^{13}C NMR spectra were recorded at 67.8 MHz on a JASCO JNM-MH-270 spectrometer and chloroform (δ_C 77.0) was used as chemical-shift reference. FAB mass spectra were recorded with 3-nitrobenzyl alcohol as a matrix on a JEOL-DX-303-HF spectrometer. Elemental analyses were carried out by Yanagimoto CHN-Corder, Type 2. M.p.s were measured on a Yanagimoto micro melting point apparatus and are uncorrected. UV–VIS spectra were measured on a Hitachi 330 spectrometer. 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 Shimadzu LC-6A using a chiral column Opti-Pak XC (Waters), 250 mm × 4.6 mm [hexane–propan-2-ol (98:2), 2.0 × 10^{-1} cm^3 min^{-1}]. Lipase YS was supplied from the Amano pharmaceutical Co. and used without further purification.

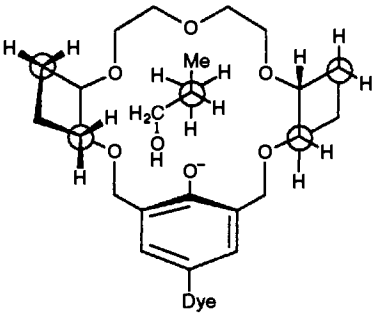
(±)-cis-2-(*Benzyloxy*)*cyclohexanol* **3**.—A solution of *cis*-cyclohexane-1,2-diol[11] (15.0 g, 0.129 mol) in dry THF (300 cm^3) was added dropwise to a stirred and cooled suspension of sodium hydride (3.41 g, 0.142 mol) in dry THF (1200 cm^3) and then the mixture was stirred at room temperature for 1 h. After cooling of the mixture with an ice–water cooling-bath, benzyl bromide (24.3 g, 0.142 mol) was added dropwise to the stirred and cooled reaction mixture. The reaction mixture was stirred at room temperature for 40 h and then methanol was added to decompose the excess of sodium hydride. After removal of the solvent under reduced pressure, the residue was taken up in diethyl ether. The solution was washed with water, dried ($MgSO_4$), and evaporated to give a crude product, which was



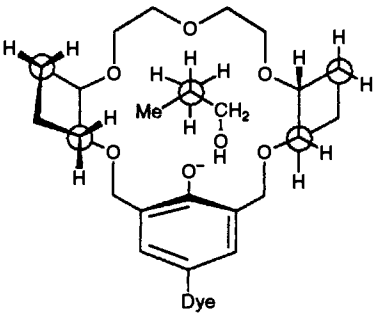
21 [(*R,S,S,R*)-1-(*S*)-11]



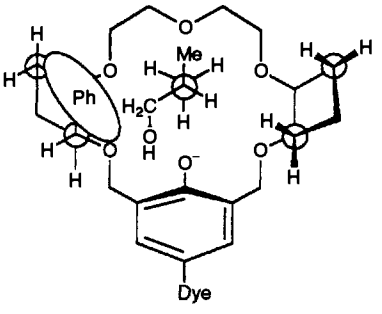
22 [(*R,S,S,R*)-1-(*S*)-11]



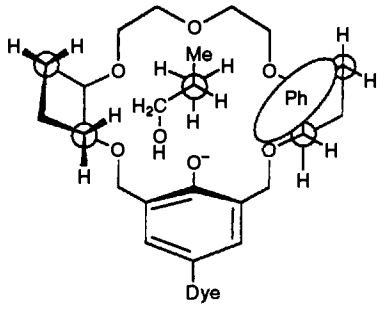
23 [(*S,R,R,S*)-1-(*S*)-11]



24 [(*S,R,R,S*)-1-(*S*)-11]



25 [(*R,R,R,R*)-2-(*S*)-11]



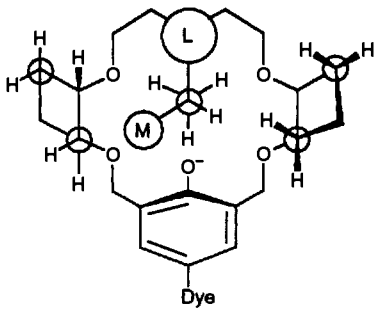
26 [(*S,S,S,S*)-2-(*S*)-11]

chromatographed on silica gel. The fractions eluted with hexane–diethyl ether (9:1) gave *cis*-1,2-bis(benzyloxy)cyclohexane (11.4 g, 30%) as an oil;[12] ν_{max}(neat film)/cm^{-1} 3080, 3060, 3020, 2930, 2855, 1600, 1498, 1455, 1095, 742 and 698. Subsequent fractions eluted with hexane–diethyl ether (5:1) gave *racemate* (±)-**3** (10.6 g, 40%) as an oil; ν_{max}(neat film)/cm^{-1} 3425, 3090, 3070, 3030, 2940, 2870, 1600, 1500, 1455, 1091, 1070, 740 and 698; δ_H 1.23–1.89 (8 H, m, CH_2), 2.49 (1 H, br s, OH), 3.52 (1 H, br s, CH), 3.86 (1 H, br s, CH), 4.51 (1 H, d, *J* 12.4, $ArCH_2$), 4.63 (1 H, d, *J* 12.4, $ArCH_2$) and 7.26–7.36 (5 H, m, ArH) (Found: C, 75.5; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%).

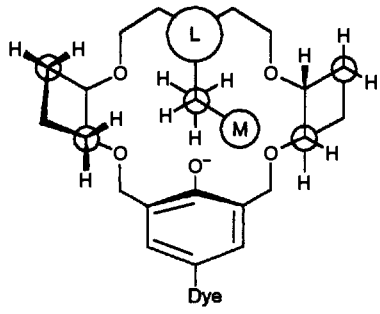
Optical Resolution of (±)-cis-2-(*Benzyloxy*)*cyclohexanol* **3**.—A mixture of racemate (±)-**3** (11.4 g, 55.4 mmol), vinyl acetate (14.4 g, 166 mmol), lipase YS (1.10 g), and diisopropyl ether (280 cm^3) was stirred at room temperature. The progress of the reaction was monitored by GLC (using an SE-52 on Uniport HP, 2 m × 2.6 mm column). After the mixture had been stirred for 50 h, the reaction was terminated close to 50% of the esterification point by filtration off of the enzyme. The volatile materials were evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel. The fractions eluted with hexane gave *acetate* (−)-**4** (6.59 g, 48%) as an oil; $[\alpha]_D^{23}$ −3.1 (*c* 1.00, $CHCl_3$) (>99% e.e.); ν_{max}(neat film)/cm^{-1} 3080, 3060, 3020, 2930, 2850, 1732, 1455, 1230, 1092, 742 and 690 (Found: C, 72.2; H, 8.0. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%). Subsequent fractions eluted with hexane–diethyl ether (5:1) gave *acetate* (−)-**3** (5.60 g, 49%) as an oil; $[\alpha]_D^{23}$ −16.5 (*c* 1.10, $CHCl_3$) (>99% e.e.) (Found: C, 75.4; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%). The enantiomeric purities of compounds **3** and **4** were confirmed by HPLC analysis using a chiral column.

(+)-cis-2-(*Benzyloxy*)*cyclohexanol* **3**.—A solution of acetate (−)-**4** (6.20 g, 25.0 mmol) in methanol (360 cm^3) with a few drops of conc. HCl was stirred at 50 °C for 7 h. After neutralization with sodium hydrogen carbonate, solids were removed by filtration. The solvent was evaporated off under reduced pressure and the residue was taken up in dichloromethane. The solution was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography of the residue on silica gel with hexane–diethyl ether (4:1) as eluent gave *compound* (+)-**3** (4.74 g, 92%); $[\alpha]_D^{23}$ +16.4 (*c* 1.20, $CHCl_3$) (Found: C, 75.3; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%).

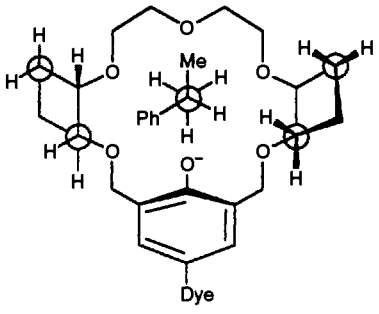
(−)-1,5-*Bis*-[2'-(*benzyloxy*)*cyclohexyloxy*]-3-*oxapentane* **5**.—A solution of compound (−)-**3** (3.24 g, 15.7 mmol) in dry



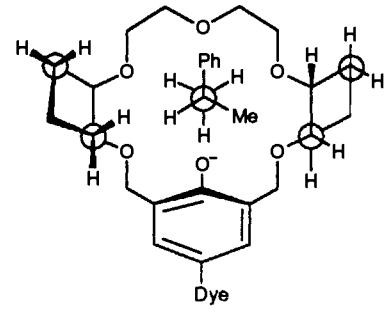
27 [(*R,S,S,R*)-1-chiral ethylamine]



28 [(*S,R,R,S*)-1-chiral ethylamine]



29 [(*R,S,S,R*)-1-(*S*)-14]



30 [(*S,R,R,S*)-1-(*S*)-14]

THF (55 cm^3) was added dropwise to a stirred suspension of sodium hydride (754 mg, 31.4 mmol) in dry THF (55 cm^3) and then the reaction mixture was stirred at room temperature for 1 h. To the reaction mixture was added dropwise a solution of diethylene glycol bis(methanesulfonate) (2.06 g, 7.85 mmol) in dry THF (55 cm^3) and then the reaction mixture was refluxed for 18 h. To the cooled reaction mixture was slowly added methanol to decompose the excess of sodium hydride and then the solvent was removed under reduced pressure. The residue was taken up in chloroform and the solution was washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography on silica gel with hexane–diethyl ether (5:1) as eluent to give compound (−)-**5** (1.44 g, 38%) as an oil; $[\alpha]_D^{24}$ −0.90 (*c* 1.00, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3075, 3050, 3020, 2925, 2850, 1490, 1450, 1092, 732 and 690; δ_H 1.23–1.94 (16 H, m, CH_2), 3.48–3.70 (12 H, m, OCH_2 and CH), 4.56 (2 H, d, *J* 12.6, $ArCH_2$), 4.64 (2 H, d, *J* 12.6, $ArCH_2$) and 7.21–7.38 (10 H, m, ArH); *m/z* (FAB^+) 483 (MH^+) (Found: C, 74.2; H, 8.8. $C_{30}H_{32}O_5$ requires C, 74.65; H, 8.77%).

(+)-1,5-*Bis*-[2'-(*benzyloxy*)*cyclohexyloxy*]-3-*oxapentane* **5**.—By a procedure similar to that described above for (−)-**5**, condensation of compound (+)-**3** (6.00 g, 29.1 mmol) with diethylene glycol bis(methanesulfonate) (3.81 g, 14.5 mmol) followed by column chromatography on silica gel with hexane–diethyl ether (3:1) as eluent gave compound (+)-**5** (2.23 g, 33%); $[\alpha]_D^{24}$ +0.95 (*c* 1.05, $CHCl_3$); *m/z* (FAB^+) 483 (MH^+) (Found: C, 74.4; H, 8.7%).

(+)-2,2'-*Oxybis*(*ethyleneoxy*)*dicyclohexanol* **6**.—A solution of compound (−)-**5** (5.04 g, 10.4 mmol) and toluene-*p*-sulfonic acid monohydrate (190 mg) in 1,4-dioxane (300 cm^3) was vigorously stirred at room temperature over 10% Pd on carbon (350 mg) under 1 atm of hydrogen. After hydrogen uptake had ceased, the catalyst was filtered off. The filtrate was neutralized with sodium hydrogen carbonate and then solids were removed by filtration. The filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the solution was washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography on silica gel, using hexane–ethyl acetate (1:1) as eluent, to give *compound* (+)-**6** (1.94 g, 61%) as an oil; $[\alpha]_D^{23}$ +2.2 (*c* 1.00, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3420, 2930, 2860, 1130 and 1090; δ_H 1.25–1.82 (16 H, m, CH_2), 3.39–3.42 (2 H, m, CH), 3.58–3.75 (8 H, m, OCH_2) and 3.81–3.84 (2 H, m, CH); *m/z* (FAB^+) 303 (MH^+) (Found: C, 63.2; H, 9.8. $C_{16}H_{30}O_5$ requires C, 63.54; H, 10.00%).

(−)-2,2'-*Oxybis*(*ethyleneoxy*)*dicyclohexanol* **6**.—By a procedure similar to that described above for compound (+)-**6**, hydrogenolysis of compound (+)-**5** (4.17 g, 8.63 mmol) over 10% Pd on carbon (290 mg) followed by column chromatography on silica gel with hexane–ethyl acetate (1:1) as eluent gave diol (−)-**6** (1.44 g, 55%); $[\alpha]_D^{24}$ −2.4 (*c* 1.10, $CHCl_3$); *m/z* (FAB^+) 303 (MH^+) (Found: C, 63.5; H, 9.8%).

(8R,9S,17S,22R)-(−)-27,29-*Dimethoxy*-3,10,13,16,23-*pentaoxatetracyclo*[23.3.1.$0^{4,9}$.$O^{17,22}$]*nonacosa*-1(29)^{25,27}-*triene* **7**.—A solution of diol (+)-**6** (880 mg, 2.91 mmol) and 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (945 mg, 2.91 mmol) in dry THF (350 cm^3) was added dropwise to a boiling well stirred mixture of sodium hydride (384 mg, 16.0 mmol), potassium tetrafluoroboranuide (370 mg, 2.94 mmol) and dry THF (135 cm^3) over a period of 10 h. The reaction mixture was heated at reflux under dry nitrogen for a further 4 days and was then cooled. Methanol was slowly added to the cooled reaction mixture and then the mixture was concentrated under reduced pressure. The residue was taken up in diethyl ether and 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–ethyl acetate (1:1) as eluent gave compound (−)-**7** (629 mg, 47%); $[\alpha]_D^{24}$ −54.2 (*c* 1.05, $CHCl_3$); m.p. 90.0–91.5 °C; ν_{max}(KBr)/cm^{-1} 3020, 2930, 2860, 1500, 1460, 1445, 1260, 1130, 1100 and 1060; δ_H 1.23–2.04 (16 H, m, CH_2), 3.34–3.46 (10 H, m, OCH_2 and CH), 3.69–3.72 (2 H, m, CH), 3.80 (3 H, s, OMe), 4.00 (3 H, s, OMe), 4.42 (2 H, d, *J* 11.4, $ArCH_2$), 4.74 (2 H, d, *J* 11.4, $ArCH_2$) and 6.85 (2 H, s, ArH); *m/z* (FAB^+) 464 (MH^+).

(4S,9R,17R,22S)-(+)-27,29-*Dimethoxy*-3,10,13,16,23-*pentaoxatetracyclo*[23.3.1.$0^{4,9}$.$O^{17,22}$]*nonacosa*-1(29)^{25,27}-*triene* **7**.—By a procedure similar to that described above for (−)-**7**, condensation of diol (−)-**6** (1.25 g, 4.13 mmol) with 1,3-bis(bromomethyl)-2,4-dimethoxybenzene (1.34 g, 4.13 mmol) followed by column chromatography on silica gel, using hexane–ethyl acetate (1:2) as eluent, gave compound (+)-**7** (834 mg, 44%); $[\alpha]_D^{23}$ +54.6 (*c* 1.10, $CHCl_3$); m.p. 87.5–88.5 °C; *m*/*z* (FAB$^+$) 464 (MH^+).

(4R,9S,17S,22R)-(+)-29-*Methoxy*-3,10,13,16,23-*pentaoxatetracyclo*[23.3.1.$0^{4,9}$.$0^{17,22}$]*nonacosa*-1(29)^{25,27}-*trien*-29-*ol* **8**.—A solution of compound (−)-**7** (475 mg, 1.04 mmol) in dry THF (50 cm^3) was added dropwise to a stirred and cooled suspension of lithium aluminium hydride (240 mg, 6.30 mmol) in dry THF (95 cm^3) and then the mixture was heated at reflux under dry nitrogen for 15 h. To the cooled reaction mixture were added successively ethyl acetate and water and the mixture was concentrated under reduced pressure. Dil. hydrochloric acid was added to the residue, which was then extracted with chloroform. The extract was washed successively with aq. sodium hydrogen carbonate and water, and was then dried ($MgSO_4$). After removal of the solvent, the product was purified by column chromatography on silica gel with hexane–ethyl acetate (2:1) as eluent, followed by preparative TLC (PLC) on silica gel with hexane–ethyl acetate (2:1) as developer, and gave the phenol (+)-**8** (367 mg, 80%) as an oil; $[\alpha]_D^{24}$ +9.31 (*c* 1.00, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3340, 2980, 2925, 2850, 1490, 1362, 1255, 1100, 1051, 850, 752 and 660; δ_H 1.20–2.04 (16 H, m, CH_2), 3.52–3.77 (12 H, m, OCH_2 and CH), 3.75 (3 H, s, OMe), 4.59 (2 H, d, *J* 11.4, $ArCH_2$), 4.69 (2 H, d, *J* 11.4, $ArCH_2$), 6.73 (2 H, s, ArCH) and 7.72 (1 H, s, OH); *m*/*z* (FAB$^+$) 450 (M^+) (Found: C, 66.2; H, 8.2. $C_{25}H_{38}O_7$ requires C, 66.4; H, 8.50%).

(4S,9R,17R,22S)-(−)-29-*Methoxy*-3,10,13,16,23-*pentaoxatetracyclo*[23.3.1.$0^{4,9}$.$0^{17,22}$]*nonacosa*-1(29)^{25,27}-*trien*-29-*ol* **8**.—By a procedure similar to that described above for compound (+)-**8**, reduction of compound (+)-**7** (372 mg, 0.800 mmol) with lithium aluminium hydride (162 mg, 4.27 mmol) followed by column chromatography on silica gel, using hexane–ethyl acetate (2:1) as eluent, and PLC on silica gel, using hexane–ethyl acetate (2:1) as developer, gave the phenol (−)-**8** (323 mg, 90%); $[\alpha]_D^{24}$ −8.94 (*c* 1.00, $CHCl_3$); *m*/*z* (FAB$^+$) 450 (M^+) (Found: C, 66.2; H, 8.3%).

Azophenolic Crown Ether (R,S,S,R)-**1**.—A solution of the phenol (+)-**8** (727 mg, 1.61 mmol) in acetonitrile (46 cm^3) was added dropwise to a well stirred solution of CAN (2.65 g, 4.84 mmol) in acetonitrile (70 cm^3) and then the mixture was stirred at room temperature for 1.5 h. After the solvent had been evaporated off under reduced pressure, the residue was dissolved in water and extracted with chloroform. The extract was washed with water and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel, using hexane–ethyl acetate (2:1) as eluent, to give the quinone **9** (630 mg, 90%) as a yellow oil, which was used immediately in the next reaction.

To a solution of quinone **9** (630 mg) in ethanol (35 cm^3)–dichloromethane (35 cm^3) was added dropwise a solution of 2,4-dinitrophenylhydrazine (730 mg, 3.68 mmol) in ethanol (20 cm^3) with conc. H_2SO_4 (2 cm^3). The mixture was stirred at room temperature for 1.5 h and was then extracted with chloroform. The extract was washed successively with aq. sodium hydrogen carbonate and water, and was then dried (Na_2SO_4). After removal of the solvent, the product was purified by column chromatography on silica gel, using hexane–ethyl acetate (1:2) as eluent, followed by PLC on silica gel, using hexane–ethyl acetate (2:1) as developer, to give a solid, which was recrystallized from diisopropyl ether–dichloromethane to give (*R*,*S*,*S*,*R*)-**1** (719 mg, 81%) as fine orange needles, m.p. 151–152 °C; ν_{max}(KBr)/cm^{-1} 3340, 2980, 2925, 2850, 1490, 1362, 1255, 1100, 1052, 850, 752 and 660; δ_H 1.22–2.09 (16 H, m, CH_2), 3.56 (2 H, br s, CH), 3.67–3.72 (8 H, m, OCH_2), 3.78 (1 H, br s, CH), 4.65 (1 H, d, *J* 11.1, $ArCH_2$), 4.82 (1 H, d, *J* 11.1, $ArCH_2$), 7.83 (2 H, s, HOAr*H*), 7.83 (1 H, d, *J* 8.9, O_2NArH), 8.48 (1 H, dd, *J* 8.9 and 2.2, O_2NArH), 8.75 (1 H, d, *J* 2.2, O_2NArH) and 9.21 (1 H, br s, OH); δ_C($CDCl_3$) 21.13 (CH_2), 22.61 (CH_2), 26.83 (CH_2), 27.73 (CH_2), 67.80 (OCH_2), 67.82 ($ArCH_2$), 70.44 (OCH_2), 76.52 (CH), 77.48 (CH), 119.98 (HOAr and O_2NAr), 125.88 (4° carbon), 126.15 (O_2NAr), 127.53 (O_2NAr), 145.79 (4° carbon), 146.59 (4° carbon), 146.81 (4° carbon, 149.00 (4° carbon) and 161.60 (4° carbon); λ_{max}-($CHCl_3$)/nm 408; *m*/*z* (FAB$^+$) 615 (MH^+).

Azophenolic Crown Ether (S,R,R,S)-**1**.—By a procedure similar to that described above for (*R*,*S*,*R*,*S*)-**1**, oxidation of the phenol (+)-**8** (246 mg, 0.570 mmol) with CAN (1.15 g, 2.10 mmol) followed by treatment with 2,4-dinitrophenylhydrazine (370 mg, 1.87 mmol) gave a solid, which was purified by column chromatography on silica gel, using hexane–ethyl acetate (1:2) as eluent, followed by PLC on silica gel, using hexane–ethyl acetate (2:1) as developer, to give (*S*,*R*,*R*,*S*)-**1** (166 mg, 39%) as orange needles; m.p. 152–153 °C (from diisopropyl ether–dichloromethane); *m*/*z* (FAB$^+$) 615 (MH^+).

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