Preparation and Enantiomer Recognition Behaviour of Crown Ethers containing *cis*-1-Phenylcyclohexane-1,2-diol and *trans*-1,2-Diphenylcyclohexane-1,2-diol as a Chiral Subunit[1]

Koichiro Naemura,* Hajime Miyabe, Yasuhiro Shingai and Yoshito Tobe
Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

Pig liver esterase-mediated hydrolysis of (±)-*cis*-2-acetoxy-1-phenylcyclohexanol **5** gave (+)-*cis*-1-phenylcyclohexane-1,2-diol **4** of high optical purity, from which (−)-*trans*-1,2-diphenylcyclohexane-1,2-diol **8** has been prepared. Using these diols (+)-**4** and (−)-**8** as a chiral subunit, chiral crown ethers (−)-**1**, (−)-**2** and (−)-**3** have been prepared and their chiral recognition behaviour toward (±)-1,2-diphenylethylamine hydrochloride and methyl (±)-phenylglycinate hydrochloride in enantiomer differential transport has been examined. The enantiomer selectivities of these crown ethers in complexation with racemic ammonium salts have been interpreted on the basis of CPK molecular model examination of the diastereoisomeric complexes.

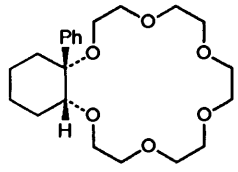
A large number of optically active crown ethers exhibiting enantiomer recognition for chiral alkylammonium salts have been prepared and various kinds of natural and synthetic optically active compounds have been used for constructing these compounds as chiral building blocks.[2] Our interest in developing a novel chiral building block for a crown ether[3] prompted us to prepare optically active crown ethers containing *cis*-1-phenylcyclohexane-1,2-diol **4** and *trans*-1,2-diphenylcyclohexane-1,2-diol **8** as a chiral subunit. The structural features of these crown ethers is that conformational flexibility of the chiral centre bearing the phenyl group is reduced compared to that of crown ethers containing an open-chain subunit such as 1,2-diphenylethane-1,2-diol.

The use of enzymes for the preparation of optically active compounds of synthetic value has been well documented.[4] Particularly useful in this respect are hydrolytic enzymes and in this study we have used them for the enantioselective hydrolysis of the acetate of a racemic diol which is a convenient starting point for the preparation of optically active subunits.

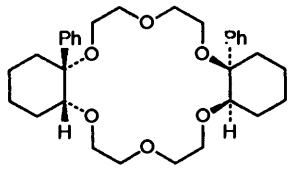
Herein we report the kinetic resolution of the diol **4** by enzyme-catalysed enantioselective hydrolysis of its acetate **5** and the preparation of enantiomerically pure crown ethers (−)-**1**, (−)-**2** and (−)-**3**. The enantiomer recognition behaviour of these crowns is also described and their observed enantiomer selectivities in complexation with 1,2-diphenylethylamine hydrochloride and methyl phenylglycinate hydrochloride have been interpreted on the basis of CPK molecular model examination of the structures of diastereoisomeric complexes.

Ready access to large quantities of the enantiomerically pure diol **4** is a necessary requirement for success in this work. Although preparation of (−)-**4** from (−)-1,2-epoxy-1-phenylcyclohexane has been described,[5] we attempted to prepare optically active **4** conveniently in large quantities by enzyme-catalysed kinetic resolution of (±)-**5**. First, treatment of (±)-**4** with acetic anhydride gave exclusively (±)-**5**, enzyme-catalysed hydrolysis of which was performed in phosphate buffer solution using pig liver esterase (PLE), porcine pancreas lipase (PPL) and lipase from *Candida cylindracea* (CCL). The progress of the reaction was monitored by GLC and the reaction was terminated at, or close to, 50% of the hydrolysis point by extraction with $CHCl_3$. The results of preliminary experiments of kinetic resolution of (±)-**5** are summarised in Table 1.

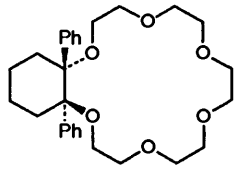
Since, as can be seen from Table 1, the hydrolysis of (±)-**5** with PLE proceeded at a rate acceptable for preparative purposes to give products with high optical purity, the kinetic resolution of (±)-**5** in a preparative scale was performed using



(−)-(*R*, *R*)-**1**



(−)-(*R*, *R*)(*R*, *R*)-**2**



(−)-(*R*, *R*)-**3**

Table 1 Enzyme-catalysed enantioselective hydrolysis of the racemic acetate **5**

Enzyme	Reaction time (h)	Product	Yield (%)	e.e. (%)
PLE	11	(+)-(1*R*,2*R*)-**4**	46	84
		(−)-(1*S*,2*S*)-**5**	46	85
PPL	114	(+)-(1*R*,2*R*)-**4**	47	56
		(−)-(1*S*,2*S*)-**5**	53	57
CCL	97	(−)-(1*S*,2*S*)-**4**	46	27
		(+)-(1*R*,2*R*)-**5**	46	26

PLE. The absolute values of specific rotations of (+)-**4** and (−)-**5** were unambiguously determined to be $[\alpha]_D$ + 19.3* (benzene) and $[\alpha]_D$ − 118.8 (benzene), respectively, by HPLC analysis using a chiral column; the absolute configuration of **4** has been described as (+)-(1*R*,2*R*)-**4** in the literature.[5] Although the maximal e.e. values of (+)-**4** and (−)-**5** obtained by the hydrolysis with PLE were 93 and 81%, respectively, the optical purity of (+)-**4** was easily improved by recrystallisation from hexane, enantiomerically pure **4** being obtained (> 99% e.e. by HPLC). Hydrolysis of (−)-**5**, $[\alpha]_D$ − 96.2 with methanolic KOH gave (−)-**4**, $[\alpha]_D$ − 15.7 and the result determined

* Throughout, $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}.

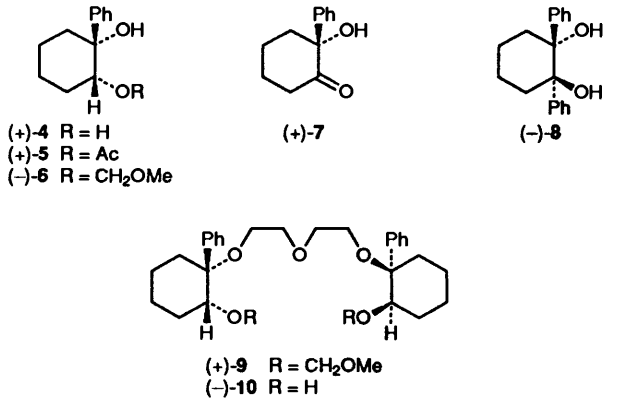


Table 2 Differential transport of enantiomeric molecules through bulk liquid membranes containing chiral crown ethers

Host	Guest[a]	Time (h)	Transport (%)	Configuration of dominant enantiomer	Optical purity (%)
(–)-**1**	a	3.0	9.3	*S*	38
(–)-**1**	b	8.5	10.2	*S*	3
(–)-**2**	a	7.3	9.8	*S*	70
(–)-**2**	b	8.0	10.0	*S*	16
(–)-**3**	a	4.8	9.6	*S*	81
(–)-**3**	b	6.0	9.9	*S*	14

[a] a = (±)-1,2-Diphenylethylamine hydrochloride and b = methyl (±)-phenylglycinate hydrochloride.

eventually the absolute configuration of **5** to be (–)-(1*S*,2*S*)-**5**.

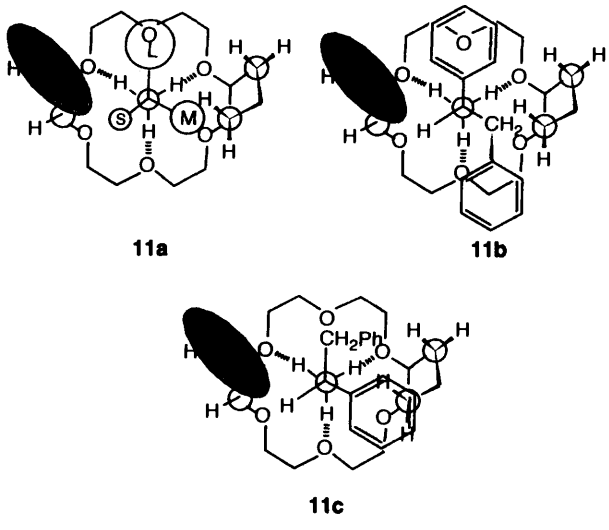
Next our task was the preparation of the optically active diol **8** as a chiral subunit of C_2 symmetry like *threo*-1,2-diphenylethane-1,2-diol. Following unsuccessful attempts to resolve (±)-**8** by enzymatic hydrolysis of its acetate, the enantiomerically pure diol **8** was derived from (+)-**4** as follows. Oxidation of (+)-**4** (>99% e.e.) with *N*-chlorosuccinimide, dimethyl sulfide and triethylamine in toluene[6] gave (–)-**7**, treatment of which with phenyllithium[7] gave exclusively (–)-(1*R*,2*R*)-**8**, $[\alpha]_D$ – 83.2 in 48% yield for two steps, the optical purity of which was confirmed to be >99% e.e. by its HPLC analysis.

Next we turned our attention to the preparation of the crown ethers. High dilution condensation of (+)-**4** (>99% e.e.) with pentaethyleneglycol bis(toluene-*p*-sulfonate) in the presence of NaH and KBF_4 in dry tetrahydrofuran (THF) under reflux followed by chromatographic purification gave (–)-(*R*,*R*)-**1**, $[\alpha]_D$ – 7.75 in 62% yield and, similarly, (–)-(*R*,*R*)-**3**, $[\alpha]_D$ –37.2 was prepared from (–)-**8** (>99% e.e.) in 15% yield. The low yield of the latter was due to the decreased reactivity of **8**. The latter arises because both tertiary hydroxy groups are attached to the carbon atom bearing the bulky substituent and the phenyl groups are forced to take an axial position in the *trans*-1,2-diphenylcyclohexane-1,2-diol moiety, when **8** is incorporated into a 18-crown-6 framework.

The key intermediate in the preparation of **2**, which has two building blocks of the same chirality and a C_2 axis lying in the plane of the macro ring, is the diol **10** of C_2 symmetry. Treatment of (+)-**4** (>99% e.e.) with dimethoxymethane, LiBr and toluene-*p*-sulfonic acid gave regiospecifically (–)-**6**, $[\alpha]_D$ –41.2 in 88% yield as the sole product. Treatment of (–)-**6** with diethyleneglycol bis(methanesulfonate) and NaH in dry THF gave (+)-**9**, $[\alpha]_D$ + 10.8, which was treated with hydrochloric acid and MeOH to afford (–)-**10**, $[\alpha]_D$ – 7.50 in 60% yield for two steps. High dilution condensation of (–)-**10** with diethyleneglycol bis(methanesulfonate) under the same conditions for the preparation of (*R*,*R*)-**1** provided (–)-(*R*,*R*), (*R*,*R*)-**2**, $[\alpha]_D$ – 22.6 in 52% yield.

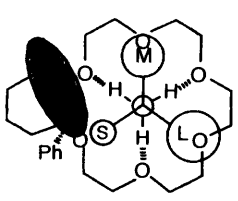
The enantiomer recognition properties of these crown ethers were evaluated on the basis of their behaviour in enantiomer differential transport[8] of (±)-1,2-diphenylethylamine hydrochloride and methyl (±)-phenylglycinate hydrochloride through bulk liquid membranes containing the crown ethers and the results are given in Table 2. The crown ethers (*R*,*R*)-**1**, (*R*,*R*)(*R*,*R*)-**2** and (*R*,*R*)-**3** transported preferentially (*S*)-1,2-diphenylethylamine hydrochloride and methyl (*S*)-phenylglycinate hydrochloride.

It is our next task to give a reasonable explanation for the observed chiral recognition behaviour on the basis of the structures of the diastereoisomeric complexes. Judging from a CPK molecular model of the C_2 crown ether (*R*,*R*)(*R*,*R*)-**2**, the phenyl groups fixed nearly vertical to the macro ring provide the most effective chiral barrier, the axial hydrogen atoms at C-3 of the cyclohexane moieties providing the smaller chiral barrier. Each side of (*R*,*R*)(*R*,*R*)-**2** possesses a bulky phenyl barrier which with the smaller axial hydrogen barrier create the three well-defined areas shown in the general structure **11a**, 'sideness' problems being thus avoided. CPK molecular model examination predicts that the (*R*,*R*)(*R*,*R*)-

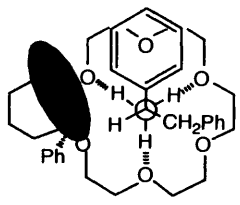


2-(*S*)-1,2-diphenylethylamine complex **11b** is more stable than its diastereoisomeric complex **11c**, because the 'large' phenyl group of the guest is allowed to occupy the 'L-area'. In addition, attractive arene–arene secondary interaction[9] provides further stability to **11b**. In **11c**, the phenyl group is forced into the 'M-area' which tends to destabilise the complex. Consequently, (*R*,*R*)(*R*,*R*)-**2** transported preferentially (*S*)-1,2-diphenylethylamine hydrochloride with high enantiomer selectivity.

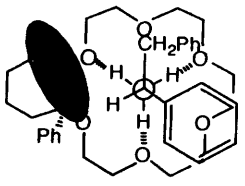
In the C_2 crown ether (*R*,*R*)-**3**, the two phenyl groups, which are fixed nearly vertical to the plane of the macro ring, are the effective steric barrier on each side of the molecule, the cyclohexane moiety providing no chiral barrier. CPK molecular model examination shows that the general structure **12a**, on steric grounds, has the more favourable arrangement of three ligands attached to a chiral centre of one enantiomer of a guest. The (*R*,*R*)-**3**-(*S*)-1,2-diphenylethylamine complex **12b**, in which the 'large' phenyl group and the 'medium sized' benzyl group of the guest occupy the 'M-area' and the 'L-area', respectively, is mismatched. But the difference in the stability between complex **12b** and its diastereoisomeric complex **12c**, on steric grounds, is rather small, the difference in the steric environment between the 'L-area' and the 'M-area' thus being insignificant. Arene–arene secondary interaction between the phenyl group and the



12a



12b

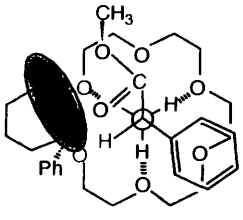


12c

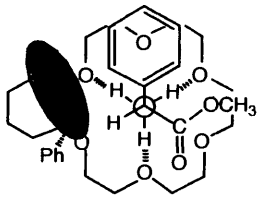
phenyl barrier is presumed to stabilise the complex **12b** and hence (*S*)-1,2-diphenylethylamine hydrochloride was preferentially transported by (*R*,*R*)-**3**.

It is understandable that the enantioselectivity of the crown ether (*R*,*R*)-**1** towards both guests is low since well-defined chiral recognition is not expected in the complex formed by attachment of a guest to the side possessing no bulky phenyl barrier.

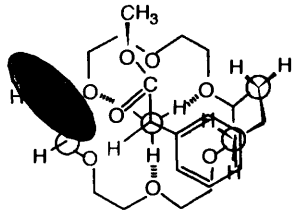
Substitution of CO_2Me for CH_2Ph as a 'medium sized' group in the guest decreased chiral recognition. This effect is attributable to the π-acid to π-base secondary interaction between the ester group and the phenyl barrier[10] as well as the arene–arene secondary interaction. It is understandable that the (*R*,*R*)-**3**-methyl (*S*)-phenylglycinate complex **13a**, in which the 'large' phenyl group and the 'medium sized' ester group occupy the 'L-area' and the 'M-area', respectively, is more stable than its diastereoisomeric complex **13b**. In (*R*,*R*)(*R*,*R*)-**2**-methyl phenylglycinate complexes, the (*R*,*R*)(*R*,*R*)-**2**-(*R*)-guest complex **14b** is, on steric ground, more favourable than the (*R*,*R*)(*R*,*R*)-**2**-(*S*)-guest complex **14a**. On the other hand, **14a** is presumed to be stabilised by π-acid to π-base secondary interaction. Therefore, (*R*,*R*)(*R*,*R*)-**2** would transport preferentially methyl (*S*)-phenylglycinate hydrochloride, but its enantioselectivity is low.



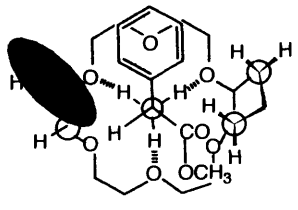
13a



13b



14a



14b

As mentioned above, the results demonstrated that the diols **4** and **8** are effective as a chiral subunit for a crown ether. The enantiomer selectivities of the crown ethers **2** and **3** on complexation with 1,2-diphenylethylamine hydrochloride and methyl phenylglycinate hydrochloride are interpreted on the basis of CPK molecular model examination of the structures of the diastereoisomeric complexes.

Experimental

General Procedure.—^{1}H NMR spectra were obtained on a JASCO JNM-MH-100 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. *J* Values are given in Hz. Mass spectroscopic analyses were carried out on a JEOL-DX-303-HF spectrometer. Elemental analyses were carried out by Yanagimoto CHN-Corder, Type 2. 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}. CD spectra were collected with a JASCO J-500 spectropolarimeter. UV spectra were measured on a Hitachi 220A spectrometer. Gas chromatography was performed on a Shimadzu GS 8A chromatograph using a SE-52 on Uniport HP, 2 m × 2.6 mm column and a PEG 20M on Chromosorb W, 2 m × 2.6 mm column. HPLC analyses were carried out on a Shimadzu LC-6A chromatograph using a chiral column Opti-Pak XC (Waters), 250 mm × 4.6 mm.

Pig liver esterase (Boehringer Mannheim Gmbh Co.), porcine pancreas lipase (Sigma Chemical Co.), and CCL (lipase from *Candida cylindracea*, Sigma Chemical Co.) were used as received without further purification. (±)-*cis*-1-Phenylcyclohexane-1,2-diol **4** was prepared according to literature procedures.[11]

(±)-cis-2-*Acetoxy*-1-*phenylcyclohexanol* **5**.—To a chilled solution of (±)-**4** (1.64 g, 8.54 mmol) in dry pyridine (10 cm^3) was added acetic anhydride (4.30 g, 42.2 mmol) and the mixture was stirred at room temperature for 12 h. The reaction mixture was then poured into ice–water, acidified with HCl and extracted with diethyl ether. Customary work-up followed by silica gel chromatography of the product gave (±)-**5** (hexane–20% diethyl ether as eluent) (1.96 g, 98%), m.p. 118–119 °C (from hexane); ν_{max}(KBr)/cm^{-1} 3525, 1715, 1250, 760 and 695; δ_H 1.40–2.00 (8 H, m, CH_2), 1.79 (3 H, s, Me), 2.30 (1 H, s, OH), 5.25 (1 H, dd, *J* 8.5 and 6.5, CH) and 7.20–7.50 (5 H, m, ArH) (Found: C, 71.95; H, 7.8. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74).

PLE-*Catalysed Hydrolysis of* (±)-**5**.—Preliminary experiment. To a solution of (±)-**5** (300 mg, 1.28 mmol) in EtOH (6 cm^3) was added phosphate buffer solution (0.1 mol dm^{-3}, pH 8.0; 600 cm^3) followed by PLE (1.8 mg, 100 units mg^{-1}). The mixture was stirred for 11 h at room temperature and then extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated and silica gel chromatography of the residue gave (−)-**5** (hexane–20% diethyl ether as eluent), $[\alpha]_D^{20}$ − 101.0 (*c* 0.310, benzene) (138 mg, 46%) and (+)-**4** (hexane–30% diethyl ether as eluent), $[\alpha]_D^{23}$ + 16.2 (*c* 0.325, benzene) (114 mg, 46%).

Preparative scale. By a procedure similar to that described above, (−)-**5**, $[\alpha]_D^{22}$ − 96.2 (*c* 0.350, benzene) (1.15 g, 50%) and (+)-**4**, $[\alpha]_D^{23}$ + 18.0 (*c* 0.410, benzene) (868 mg, 46%) were prepared from (±)-**5** (2.30 g, 9.81 mmol) using PLE (6 mg). Recrystallisation of (+)-**4** from hexane yielded (+)-**4**, $[\alpha]_D^{22}$ + 19.3 (*c* 0.380, benzene) (>99% e.e. by HPLC), m.p. 121–121.5 °C {lit.[5] $[\alpha]_D$ − 19.4 (benzene), m.p. 121.5–122 °C} (Found: C, 74.9; H, 8.35. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%).

PPL-Catalysed Hydrolysis of (±)-**5**.—A mixture of (±)-**5** (100 mg, 0.427 mmol) and PPL (2.0 g) in phosphate buffer solution (pH 7.5; 700 cm^3) was stirred for 114 h at room temperature. After work-up similar to that described above, silica gel chromatography of the product gave (−)-**5**, $[\alpha]_D^{23}$ −67.7 (*c* 0.332, benzene) (54 mg, 53%) and (+)-**4**, $[\alpha]_D^{23}$ +10.9 (*c* 0.333, benzene) (40 mg, 47%).

CCL-*Catalysed Hydrolysis of* (±)-**5**.—A mixture of (±)-**5** (100 mg, 0.427 mmol) and CCL (400 mg) in phosphate buffer solution (pH 7.5; 200 cm^3) was stirred for 97 h at room temperature. A work-up similar to that described above followed by silica gel chromatography gave (+)-**5**, $[\alpha]_D^{20}$ + 30.8 (*c* 0.320, benzene) (46 mg, 46%) and (−)-**4**, $[\alpha]_D^{24}$ − 5.21 (*c* 0.334, benzene) (38 mg, 46%).

Hydrolysis of (−)-**5**.—A solution of (−)-**5** {$[\alpha]_D$ − 96.2; 1.10 g, 4.70 mmol} in 5% methanolic KOH (60 cm^3) was stirred for 12 h at room temperature. The reaction mixture was then neutralized with HCl and concentrated under reduced pressure and the residue was extracted with diethyl ether. Customary work-up, followed by silica gel chromatography of the product gave (−)-**4** (hexane–20% diethyl ether as eluent) (773 mg, 86%) $[\alpha]_D^{23}$ − 15.6 (*c* 0.424, benzene), which was recrystallized from hexane to give (−)-**4**, $[\alpha]_D^{23}$ − 19.3 (> 99% e.e. by HPLC).

Oxidation of (+)-**4**.—To a chilled mixture of *N*-chlorosuccinimide (2.69 g, 0.0201 mmol), dimethyl sulfide (1.67 g, 20.7 mmol) and dry toluene (65 cm^3) was added a solution of (+)-**4** {$[\alpha]_D$ + 19.2; 2.55 g, 13.3 mmol} in dry toluene (170 cm^3) at −25 °C followed by a solution of triethylamine (2.04 g, 20.6 mmol) in toluene (4 cm^3). The mixture was then stirred at room temperature for 1.5 h after which it was washed successively with 1% HCl, saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel) to give (−)-**7** (hexane-10% diethyl ether as eluent) (1.48 g, 58%), $[\alpha]_D^{25}$ − 185.9 (*c* 1.81, $CHCl_3$) as a solid; ν_{max}/cm^{-1} 3450, 1710, 760 and 700; δ_H 1.60–2.15 (5 H, m, CH_2), 2.46 (2 H, m, CH_2), 2.97 (1 H, m, CH_2), 3.40 (1 H, br s, OH) and 7.28–7.32 (5 H, m, ArH) (Found: C, 75.55; H, 7.5. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%).

(−)-trans-1,2-*Diphenylcyclohexane*-1,2-*diol* **8**.—A solution of (−)-**7** (788 mg, 4.10 mmol) in dry benzene (15 cm^3) was added to a solution of phenyllithium, prepared from Li (460 mg, 66.3 mmol) and bromobenzene (5.18 g, 32.5 mmol) in dry diethyl ether (10 cm^3), after which the mixture was refluxed for 23 h. It was then chilled and 10% HCl added to it. The organic layer was separated, the aqueous layer was extracted with benzene and the combined organic solutions were worked up. The product was chromatographed (silica gel) to give a solid (hexane–5% diethyl ether as eluent), which was recrystallised from hexane–benzene to give (−)-**8** (906 mg, 82%); $[\alpha]_D^{25}$ − 83.2 (*c* 0.394, benzene); m.p. 133–134 °C [lit.,[7] (±)-**8**; m.p. 121–122 °C] (Found: C, 80.65; H, 7.6. $C_{18}H_{20}O$ requires C, 80.56; H, 7.51%).

(−)-cis-2-(*Methoxymethoxy*)-1-*phenylcyclohexanol* **6**.—A mixture of (+)-**4** (2.25 g, 11.7 mmol), dimethoxymethane (40 cm^3), $LiBr{\cdot}H_2O$ (480 mg) and toluene-*p*-sulfonic acid (220 mg) was heated under reflux for 9.5 h and then diluted with water. The organic layer was separated, the aqueous layer was extracted with diethyl ether and the combined organic solutions were worked up. The product was chromatographed (silica gel) to give a solid (hexane–10% diethyl ether as eluent) which upon recrystallisation from hexane gave (−)-**6** (1.72 g, 62%); $[\alpha]_D^{26}$ − 41.2 (*c* 1.14 $CHCl_3$); m.p. 57.5–58 °C; δ_H 1.40–2.00 (9 H, m, OH and CH_2), 2.83 (3 H, s, OMe), 3.93 (1 H, dd *J* 9.5 and 4.5, OCH), 4.29 (1 H, d *J* 3.2, OCH_2O), 4.30 (1 H, d *J* 3.2, OCH_2O) and 7.15–7.55 (5 H, m, ArH) (Found: C, 71.0; H, 8.45. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%).

2,2′-*Oxydiethylenedioxybis*(2-*phenylcyclohexanol*) **10**.—To a mixture of (−)-**6** (1.00 g, 4.23 mmol), NaH (155 mg, 4.64 mmol) and dry THF (25 cm^3) was added a solution of diethyleneglycol bis(methanesulfonate) (580 mg, 2.21 mmol) in dry THF (45 cm^3) and the mixture was then refluxed for 5 h. After excess of NaH had been decomposed with water, the reaction mixture was concentrated under reduced pressure and the residue was extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$) and evaporated and silica gel chromatography of the residue gave a solid (hexane–10% diethyl ether as eluent). This was recrystallised from hexane to give 2,2′-oxydiethylenedioxybis(2-phenylcyclophenylethyl methyl ether) (+)-**9** (536 mg, 47%); $[\alpha]_D^{24}$ + 10.8 (*c* 0.528, $CHCl_3$); m.p. 112.5–113 °C; δ_H 1.40–2.20 (16 H, m, CH_2), 2.86 (6 H, s, Me), 3.30–3.60 [8 H, m, $O(CH_2)_2O$], 3.73 (2 H, t *J* 5.5, OCH), 4.10 (2 H, d *J* 5.0, OCH_2O), 4.11 (2 H, d *J* 5.0, OCH_2O) and 7.15–7.50 (10 H, m, ArH) Found: C, 70.9; H, 8.6. $C_{32}H_{46}O_7$ requires C, 70.82; H, 8.54%).

A solution of (+)-**9** (497 mg, 0.916 mmol) in MeOH (140 cm^3) with a small amount of HCl was stirred at 50 °C for 3 h after which the solvent was removed. The residue was dissolved in CH_2Cl_2 and worked up, silica gel chromatography of the product giving (−)-**10** [hexane–diethyl ether (1:1) as eluent] (411 mg, 98%) as a semisolid; $[\alpha]_D^{23}$ − 7.50 (*c* 0.374, $CHCl_3$) (Found: C, 73.7; H, 8.4. $C_{28}H_{38}O_5$ requires C, 73.98; H, 8.42%).

cis-4a-*Phenyloctahydro*-5,8,11,14,17,20-*hexaoxabenzocyclooctadecane* (−)-(R,R)-**1**.—A solution of (+)-**4** (576 mg, 3.00 mmol) and pentaethyleneglycol bis(toluene-*p*-sulfonate) (1.64 g, 3.00 mmol) in dry THF (100 cm^3) was slowly added to a boiling mixture of NaH (160 mg, 6.67 mmol) and KBF_4 (378 mg, 3.00 mmol) in dry THF (100 cm^3) over an 8 h period and the reaction mixture was then refluxed for 30 h. After excess of NaH had been decomposed with water and the mixture concentrated under reduced pressure the residue was dissolved in $CHCl_3$. The solution was washed with water, dried ($MgSO_4$) and concentrated. Silica gel chromatography of the product gave (−)-**1** (diethyl ether–20% hexane as eluent) (727 mg, 62%) as a colourless viscous oil; $[\alpha]_D^{25}$ − 7.75 (*c* 1.17, $CHCl_3$) (Found: M^+, 394.2334. $C_{22}H_{34}O_6$ requires *M*, 394.2355).

cis-4a,11a-*Diphenyldecahydro*-5,8,11,14,17,20-*hexaoxadibenzo*[a,j]*cyclooctadene* (−)-(*R*,*R*)(*R*,*R*)-**2**.—A solution of (−)-**10** (367 mg, 0.807 mmol) and diethyleneglycol bis(methanesulfonate) (235 mg, 0.897 mmol) in dry THF (90 cm^3) was slowly added to a boiling mixture of NaH (58 mg, 2.4 mmol) and KBF_4 (102 mg, 0.810 mmol) in dry THF (30 cm^3) over an 8 h period and the reaction mixture was then refluxed for 32 h. After a work-up similar to that described above, silica gel chromatography of the product gave (−)-**2** (diethyl ether–30% hexane as eluent) (218 mg, 52%) as a colourless viscous oil; $[\alpha]_D^{24}$ −22.6 (*c* 0.901, $CHCl_3$) (Found: M^+, 524.3136. $C_{33}H_{44}O_6$ requires *M*, 524.3138).

trans-4a,20a-*Diphenyloctahydro*-5,8,11,14,17,20-*hexaoxabenzocyclooctadene* (−)-(*R*,*R*)-**3**.—By a procedure similar to that described for the preparation of (−)-**1**, high dilution condensation of (−)-**8** (474 mg, 1.79 mmol) with pentaethyleneglycol bis(toluene-*p*-sulfonate) (968 mg, 1.77 mmol) followed by silica gel chromatography (diethyl ether–20% hexane as eluent) gave (−)-**3** (124 mg, 15%); $[\alpha]_D^{22}$ − 37.2 (*c* 0.673, $CHCl_3$); m.p. 95 °C (from MeOH) (Found: M^+, 470.2661. $C_{28}H_{38}O_6$ requires *M*, 470.2668).

Enantiomer Differential Transport.—Enantiomer differential transport was carried out in an apparatus which consisted of an outer cylindrical glass vessel (24.5 mm inner diam.) and a central glass tube (15.5 mm inner diam.). The chloroform solution of an optically active crown ether (0.005 mol dm^{-3}) separated the inner aqueous phase (0.01 mol dm^{-3} HCl) and the outer aqueous phase (0.08 mol dm^{-3} HCl) containing $LiPF_6$ (0.2 mol dm^{-3}) and (±)-1,2-diphenylethylamine hydrochloride (0.04 mol dm^{-3}) or methyl (±)-phenylglycinate hydrochloride (0.04 mol

dm^{-3}). The organic layer was stirred at a constant speed (60 rpm) at 25 ± 22 °C. Transport was monitored by UV spectroscopy and the e.e. value of the guest molecule transported was monitored by circular dichroism.

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