Synthesis and Enantiomer Recognition of Crown Ethers containing the *cis*-4b,5,6,10b,11,12-Hexahydrochrysene and the *cis*-4b,5,9b,10-Tetrahydroindeno[2,1-*a*]-indene Subunit as the Chiral Centre

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The absolute configurations of the diols (−)-(**1**) and (+)-(**4**) of C_2 symmetry have been established and the enantiomer recognition behaviour of the novel optically active crown ethers (−)-(**3**) and (+)-(**6**) prepared from (−)-(**1**) and (+)-(**4**), respectively, has been examined.

A large number of optically active crown ethers have been prepared by using various types of chiral molecules as the subunit. Recently, we have described the preparation and enantiomer recognition behaviour of optically active crown ethers incorporating chiral molecules of C_2 symmetry as the source of chirality.[1] Here we report the synthesis of two novel crown ethers (−)-(**3**) and (+)-(**6**) containing the *cis*-4b,5,6,10b,11,12-hexahydrochrysene and *cis*-4b,5,9b,10-tetrahydroindeno[2,1-*a*]indene molecular framework as the chiral subunit of C_2 symmetry, respectively, and their enantiomer recognition behaviour. A structural feature of the crown ethers (−)-(**3**) and (+)-(**6**) is that two aromatic rings of the chiral centre overhang the polyether ring and form a chiral barrier.

The absolute configuration of 3,4-diphenyladipic acid (**12**) was unambiguously determined by chemical correlation with 2,3-diphenylsuccinic acid (**9**) of known absolute configuration. (+)-(2*S*,3*S*)-2,3-Diphenylsuccinic acid (**9**),[2] $[\alpha]_D^{24}$ +302.3° (EtOH), m.p. 234—236 °C, was converted into (+)-(**10**), $[\alpha]_D^{21}$ +2.1° (EtOH), by esterification followed by $LiAlH_4$ reduction. Tosylation followed by treatment with sodium cyanide in *N*,*N*-dimethylformamide converted (+)-(**10**) into the cyanide (**11**),† $[\alpha]_D^{22}$ + 20.3° ($CHCl_3$), m.p. 125—126 °C, which was hydrolysed with KOH in ethylene glycol at 100 °C to give (−)-(3*S*,4*S*)-(**12**), $[\alpha]_D^{22}$ −11.0° (EtOH), m.p. 198—199 °C. For preparative purpose, optical resolution of (±)-(**12**) was accomplished *via* the brucine salt to give (+)-(3*R*,4*R*)-(**12**), $[\alpha]_D^{22}$ +13.1° (EtOH), m.p. 200—201 °C {lit.[3] $[\alpha]_D$ +14.4° (EtOH), m.p. 200—201 °C}. The dicarboxylic acid (+)-(**12**) was converted, with thionyl chloride and a trace of pyridine in dry benzene, into (**13**), which was then treated with aluminium chloride in dry benzene at room temperature to afford a 62% overall yield of (−)-(**7**),‡ which was recrystallized from methanol to provide optically pure (−)-(**7**), $[\alpha]_D^{19}$ −317° (EtOH),§ m.p. 127.5—128 °C. We assigned the (4b*R*,10b*R*)-configuration to (−)-(**7**) on the basis of the absolute configuration of (+)-(3*R*,4*R*)-(**12**).

(+)-(4b*S*,9b*S*)-*cis*-4b,5,9b,10-Tetrahydroindeno[2,1-*a*]-indene-5,10-dione (**8**), $[\alpha]_D^{23}$ +51.2° (EtOH), m.p. 253—254 °C {lit.[4] $[\alpha]_D$ +51.1° (EtOH), m.p. 253—254.5 °C}, whose absolute configuration has been established,[4] was reduced with $NaBH_4$ in methanol at room temperature to give a mixture of diols. Fractional recrystallization from benzene furnished (+)-(**4**), $[\alpha]_D^{25}$ +265° (EtOH), m.p. 199.5—201 °C

† Satisfactory elemental analyses and i.r. and ^1H n.m.r. spectral data were obtained for all new compounds.

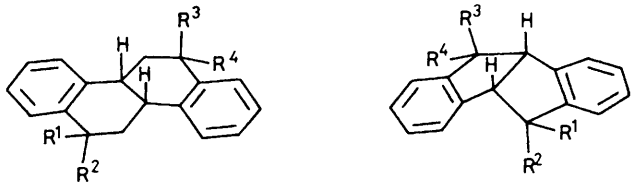
‡ The racemate (**7**) has been prepared by Ramage and Robinson.[5]

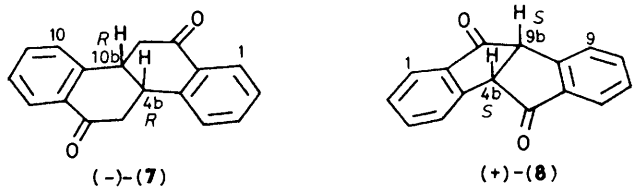
§ The optical purity was analysed by h.p.l.c. with a column packed with (+)-poly(triphenylmethyl methacrylate).[6]

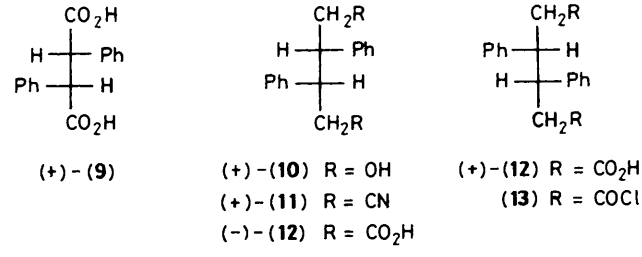
Table 1. Differential transport (ref. 7) of enantiomeric molecules through bulk liquid membranes containing chiral crown ethers.[a]

Host	Guest[b]	Time/h	Transport/%	Configuration of dominant enantiomer	Optical purity/%
(−)-(**3**)	a	0.5	11.2	*S*	23
	b	2.0	9.5	*R*	10
	c	17.0	10.0	*R*	7
(+)-(**6**)	a	4.0	10.5	*S*	40
	b	9.0	9.8	*R*	22
	c	3.4	10.0	*R*	15

[a] Carried out in conventional apparatus (ref. 8) which consisted of an outer cylindrical glass vessel (24.5 mm inner diameter) and a central glass tube (15.5 mm inner diameter). An 0.01 M $CHCl_3$ solution of the host separated the inner aqueous phase (0.01 M HCl) and the outer aqueous phase (0.08 M HCl) which contained $LiPF_6$ (0.4 M) and the racemic guest (0.08 M). The organic layer was stirred at a constant speed (60 rev. min^{-1}) at 25 °C. [b] a (±)-1,2-Diphenylethylamine hydrochloride, b (±)-2-aminotetralin hydrochloride, c methyl (±)-phenylglycinate hydrochloride.







(57%), and (+)-(**5**), $[\alpha]_D^{20}$ +145° (EtOH), m.p. 181—182.5 °C (12%). In the ^1H n.m.r. spectra (CD_3SOCD_3), the methine protons at C-5 and C-10 of the major diol appear as a doublet (2H, *J* 7.5 Hz) at δ 5.25 and those of the minor diol appear as a singlet (1H) at δ 5.16 and a doublet (1H, *J* 7.5 Hz) at δ 5.35. On the basis of these spectral data, we assigned the C_2-symmetric structure (**4**) to the major diol and the C_1-symmetric structure (**5**) to the minor diol.

Reduction of (−)-(**7**) with $NaBH_4$ in methanol afforded a mixture of (**1**) and (**2**), recrystallization of which from benzene furnished (−)-(**1**), $[\alpha]_D^{19}$ −102° (EtOH), m.p. 183—184.5 °C, in 40% yield. Attempts to purify the minor product (**2**) were unsuccessful. By analogy with the reduction of (+)-(**8**), we assigned the C_2-symmetric structure (**1**) to the major product and its ^1H n.m.r. spectrum¶ is in agreement with the structure.

Reaction of (−)-(**1**) with 3,6,9,12-tetraoxatetradecane-1,14-diyl bis(toluene-*p*-sulphonate) (pentaethyleneglycol ditosylate) in a mixture of NaH and tetrahydrofuran (THF) (refluxed and stirred under nitrogen for 62 h) gave (−)-(**3**) in 57% yield after chromatography on alumina (eluted with $CHCl_3$) as an oil, $[\alpha]_D^{22}$ −19.3° ($CHCl_3$). Condensation of (+)-(**4**) with pentaethyleneglycol ditosylate (NaH–THF) followed by chromatography (Al_2O_3; $CHCl_3$) provided (+)-(**6**) in 50% yield as an oil, $[\alpha]_D^{21}$ +120° ($CHCl_3$).

Table 1 lists the enantiomer recognition behaviour of these crown ethers with (±)-1,2-diphenylethylamine, (±)-2-aminotetralin, and methyl (±)-phenylglycinate hydrochloride. Table 1 shows that (+)-(**6**) possessing a conformationally rigid chiral subunit has a higher enantiomer selectivity than (−)-(**3**) towards the three guest substrates. The results appear to suggest that a conformationally flexible chiral subunit reduces the enantiomer selectivity of crown ethers of this type.

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¶ ^1H N.m.r. (CD_3SOCD_3) δ 1.6—2.2 (4H, m, CH_2), 3.15 (2H, dd, *J* 14 and 3 Hz, CH), 3.91 (2H, s, OH), 4.78 (2H, dd, *J* 10.5 and 7 Hz, H–C–O), and 7.1—7.7 (8H, m, ArH).