Synthesis and Enantiomer Recognition of Crown Ethers containing Cyclohexane-1,2-diol Derivatives as the Chiral Centre and Enzymatic Resolution of the Chiral Subunits

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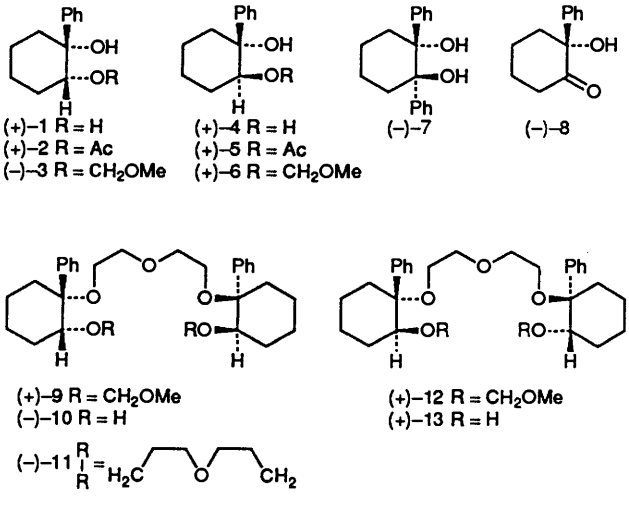
The cyclohexane-1,2-diol derivatives **1** and **4** of high optical purity have been prepared by enantioselective hydrolysis of their acetates (±)-**2** and (±)-**5** using pig liver esterase. The enantiomer recognition behaviour of the chiral crown ethers **11**, **14**, **15** and **16** containing the cyclohexane-1,2-diol derivatives as a chiral subunit has also been examined.

The use of enzymes for the preparation of optically active compounds of synthetic value has been well studied.[1] Especially attractive in this regard are hydrolytic enzymes, which operate without requiring expensive co-enzymes, and in the present study we have used them for the enantioselective hydrolysis of acetates of racemic diols which are a convenient starting point for the preparation of optically active diols. Our interest in developing a novel chiral subunit for a crown ether[2] prompted us to prepare optically active crown ethers containing the cyclohexane-1,2-diol derivatives as a chiral subunit and to resolve the sub-units by an enzymatic method. Here we report the kinetic resolution of the diols **1** and **4** by enantioselective enzyme-catalysed hydrolysis of their acetates and the preparation of optically active crown ethers (−)-**11**, (−)-**14**, (−)-**15** and (−)-**16**. The enantiomer recognition behaviour of the latter is also described.

Treatment of (±)-**1**[3] and (±)-**4**[3] with acetic anhydride and pyridine gave exclusively (±)-**2**, m.p. 118–119 °C, and (±)-**5**, m.p. 98.5–99.5 °C, respectively. Enzyme-catalysed hydrolyses of (±)-**2** and (±)-**5** were performed in phosphate buffer solution at room temperature and terminated at, or close to, 50%-of-hydrolysis point.

The e.e. values of **1** and **4** were unambiguously determined by HPLC analysis [using a chiral column; Opti-Pak XC (Waters)] and the absolute configurations of (+)-(1*R*,2*R*)-**1**[4] and (−)-(1*S*,2*R*)-**4**[5] are described in the literature. The absolute configurations and the e.e. values of (−)-**2** and (+)-**5** were confirmed by conversion into (−)-**1** and (+)-**4**, respectively.



The results of enzyme-catalysed hydrolysis are given in Table 1. As can be seen from Table 1, the diols **1** and **4** of high optical purity were prepared more simply with the enzymatic method than with the chemical method.[4,5]

Oxidation of (+)-**1** with *N*-chlorosuccinimide, dimethyl sulphide and triethylamine in toluene gave (−)-**8**, treatment of which with phenyllithium gave exclusively (−)-(1*R*,2*R*)-**7** (≥98% e.e.) in 48% overall yield.

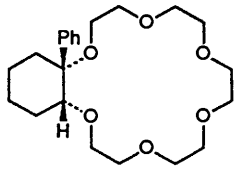
Table 1 Enzyme-catalysed hydrolysis of the racemic acetates **2** and **5**

Substrate	Enzyme[a]	Reaction time (h)	Product	Yield (%)	E.e. (%)
2	PLE (pH 8.0)	11	(+)-(1*R*,2*R*)-**1**	46	84
			(−)-(1*S*,2*S*)-**2**	46	85
2	PPL (pH 7.5)	114	(+)-(1*R*,2*R*)-**1**	47	56
			(−)-(1*S*,2*S*)-**2**	53	57
2	CCL (pH 7.5)	97	(−)-(1*S*,2*S*)-**1**	46	27
			(+)-(1*R*,2*R*)-**2**	46	26
5	PLE (pH 8.0)	10	(−)-(1*S*,2*R*)-**4**	47	78
			(+)-(1*R*,2*S*)-**5**	50	82
5	PPL (pH 7.5)	246	(−)-(1*S*,2*R*)-**4**	41	78
			(+)-(1*R*,2*S*)-**5**	49	72
5	CCL (pH 7.5)	194	(−)-(1*S*,2*R*)-**4**	54	25
			(+)-(1*R*,2*S*)-**5**	38	60

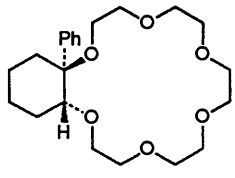
[a] PLE = pig liver esterase (Boehringer Mannheim Gmbh Co.); PPL = porcine pancreas lipase (Sigma chemical Co.); CCL = lipase from *Candida cylindracea* (Sigma chemical Co.)

Next we turned our attention to the preparation of the crown ethers. Treatment of (+)-**1** and (+)-**4** with dimethoxymethane, LiBr and toluene-*p*-sulphonic acid gave (−)-**3** (88% yield) and (+)-**6** (87% yield), respectively. Condensation of (−)-**3** with diethyleneglycol bis(methanesulphonate) and NaH in tetrahydrofuran (THF) followed by treatment with HCl in MeOH gave (−)-**10** (60% yield), and similarly (+)-**6** was converted into (+)-**13** (47% yield).

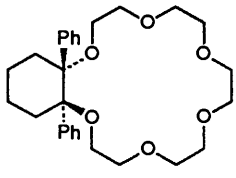
High dilution condensation of (−)-**10** with diethyleneglycol bis(methanesulphonate) in the presence of NaH and KBF_4 in THF under reflux gave (−)-**11**, $[\alpha]_D$ −22.6° in 52% yield. But, reaction of (+)-**13** with diethyleneglycol bis(methanesulphonate) under conditions similar to those described above did not provide any cyclised products. Reaction of (+)-**1**, (−)-**4** and (−)-**7** with pentaethyleneglycol bis(toluene-*p*-sulphonate) in the presence of NaH and KBF_4 in THF under reflux followed by chromatographic purification gave (−)-**14** (oil, 62% yield); $[\alpha]_D$ −7.75°, (−)-**15** (oil, 25% yield); $[\alpha]_D$ −54.4° and (−)-**16** (m.p. 95 °C, 15% yield); $[\alpha]_D$ −37.2°, respectively.



(−)-14



(−)-15



(−)-16

Table 2 lists the enantiomer recognition behaviour of these crown ethers. The noteworthy feature of the results is that the crown ether (−)-**16** showed high enantiomer selectivity toward (±)-1,2-diphenylethylamine hydrochloride. In CPK molecular model of (−)-**16**, both phenyl groups prefer to take an axial position in the *trans*-1,2-diphenylcyclohexane-1,2-diol moiety and are fixed nearly vertical to the plane of the macro ring, when the subunit **7** is incorporated into a 18-crown-6 framework. The high enantiomer selectivity exhibited by (−)-**16** demonstrated that the phenyl groups of the subunit **7** function efficiently as a chiral steric barrier.

Table 2 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 (%)
(−)-**11**	a	7.3	9.8	S	70
(−)-**11**	b	8.0	10.0	S	16
(−)-**14**	a	3.0	9.3	S	38
(−)-**14**	b	8.5	10.2	S	3
(−)-**15**	a	2.0	9.6	S	30
(−)-**15**	b	8.0	10.6	S	8
(−)-**16**	a	4.8	9.6	S	81
(−)-**16**	b	6.0	9.9	S	14

[a] Carried out in conventional apparatus which consisted of an outer cylindrical glass vessel (24.5 mm inner diam.) and a central glass tube (15.5 mm inner diam.). A $CHCl_3$ solution of the host (0.01 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) which contained $LiPF_6$ (0.4 mol dm^{-3}) and the racemic guest (0.08 mol dm^{-3}). The organic layer was stirred at a constant speed (60 r.p.m.) at room temperature. [b] a = (±)-1,2-diphenylethylamine hydrochloride and b = methyl (±)-phenylglycinate hydrochloride.

Experimental

PLE-catalysed Hydrolysis of Acetates.—To a solution of (±)-**2** (300 mg, 1.28 mmol) in EtOH (6 ml) was added 600 ml of phosphate buffer solution (0.1 mol dm^{-3}; pH 8.0). After PLE (1.8 mg, 100 Units/mg) was added to the solution, the mixture was stirred for 11 h at room temperature and extracted with $CHCl_3$. Silica gel chromatography of the product gave (−)-**2**, $[\alpha]_D^{20}$ −118.8° (*c* 0.310, benzene) (138 mg, 46% yield) and (+)-**1**, $[\alpha]_D^{23}$ + 16.2° (*c* 0.325, benzene) (114 mg, 46%) which was recrystallized from hexane to give (+)-**1**, $[\alpha]_D^{22}$ +19.2° (≥98% e.e.), m.p. 121–121.5 °C. Hydrolysis of (−)-**2** with KOH in MeOH gave (−)-**1**, $[\alpha]_D^{25}$ −16.5° (*c* 0.325, benzene). Similarly, PLE-catalysed hydrolysis of (±)-**5** provided (+)-**5**, $[\alpha]_D^{25}$ + 34.0° (*c* 0.387, benzene) (50%) and (−)-**4**, $[\alpha]_D^{27}$ −40.3° (*c* 0.365, benzene) (47%), recrystallization (hexane) of which gave (−)-**4**, $[\alpha]_D^{23}$ − 52.8° (≥98%), m.p. 79–79.5 °C.

(−)-trans-1,2-*Diphenylcyclohexane*-1,2-*diol* **7**.—To a mixture of *N*-chlorosuccinimide (2.69 g, 0.0201 mol), dimethyl sulphide (1.67 g, 20.7 mmol) and dry toluene (65 ml) was added a solution of (+)-**1** (2.55 g, 13.3 mmol) in dry toluene (170 ml) at −25 °C. A solution of triethylamine (2.04 g, 20.6 mmol) in toluene (4 ml) was added to the mixture which was then stirred for 1.5 h at room temperature. After work-up, the product was chromatographed (silica gel) to give (−)-**8**, $[\alpha]_D^{25}$ −185.9° (*c* 1.81, $CHCl_3$) (1.48 g, 58%). A solution of (−)-**8** (788 mg, 4.10 mmol) in dry benzene (15 ml) was added to a solution of phenyllithium, prepared from Li (460 mg, 66.3 mmol) and bromobenzene (5.10 g, 32.5 mmol) in dry ether (10 ml), after which the mixture was refluxed for 23 h. After work-up, recrystallization of the product from hexane–benzene gave (−)-**7**, $[\alpha]_D^{25}$ −83.2° (*c* 0.394, benzene), m.p. 133–134 °C and (±)-**7**, m.p. 121–122 °C[6] (906 mg, 82%) (Found: C, 80.65; H, 7.6. $C_{18}H_{20}O_2$ requires C, 80.56; H, 7.51%).

(−)-*Crown Ether* **11**.—To a mixture of (−)-**3** {$[\alpha]_D^{26}$ −41.2° (*c* 1.14, $CHCl_3$), m.p. 57.5–58 °C} (1.00 g, 4.23 mmol), NaH (155 mg, 4.64 mmol) and dry THF (25 ml) was added a solution of diethylene glycol bis(methanesulphonate) (580 mg, 2.21 mmol) in dry THF (45 ml); the mixture was then refluxed for 5 h. Chromatography (silica gel) followed by recrystallization

(hexane) of the product gave (+)-**9** (696 mg, 61%), $[\alpha]_D^{24}$ +10.8° (*c* 0.528, $CHCl_3$), m.p. 112.5–113 °C (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 ml) with a small amount of HCl was stirred for 3 h at 50 °C to give (−)-**10** (411 mg, 98%), $[\alpha]_D^{23}$ −7.50° (*c* 0.374, $CHCl_3$) as a semisolid. A solution of (−)-**10** (367 mg, 0.807 mmol) and diethylene glycol bis-(methanesulphonate) (235 mg, 0.896 mmol) in dry THF (90 ml) 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 ml). The mixture was refluxed for 32h and then worked up, chromatography of the product giving (−)-**11** (218 mg, 52%), $[\alpha]_D^{24}$ −22.6° (*c* 0.901, $CHCl_3$) as a viscous oil (Found: M^+, 524.3136. $C_{33}H_{44}O_6$ requires M, 524.3138).

Similarly, from (+)-**4**, (+)-**6**, $[\alpha]_D^{22}$ +64.8° (*c* 1.01, $CHCl_3$), m.p. 44 °C (recrystallized from hexane), (+)-**12**, $[\alpha]_D^{23}$ +86.3° (*c* 0.315, $CHCl_3$) and (+)-**13**, $[\alpha]_D^{20}$ +35.5° (*c* 0.155, $CHCl_3$) were prepared.

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