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SYNTHESIS OF (+)-2R,3R,11R,12R- AND (-)-2S,3S,11S,12S-TETRAPHENYL-18-CROWN-6

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Abstract: The synthesis of the title crown ethers starting from optically active hydrobenzoins is described. R(+)-**1**,in $CDCl_3$,preferentially extracts R(+)-phenylglycine methyl ester hydroperchlorate from an aqueous solution of the racemate with a chiral recognition factor of 1.5 as shown by nmr measurements.

Several types of optically active crown ether ligands derived from natural or synthetic chiral precursors have been prepared in recent years [1] with the main goal of studying the chiral recognition of enantiomers and the structural requirements of this phenomenon [2].

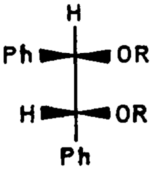
Recently, we have reported the syntheses of all diastereomeric forms of 2,3,11,12-tetraphenyl-18-crown-6 which consist of three achiral meso forms and two pairs of enantiomers [3]. Of the latter, the R^*,R^*,R^*,R^*-isomer **1** (trans-anti-trans structure) is of particular interest as a chiral host compound since it has homotopic faces due to its D_2 symmetry. We describe in this communication an effective synthesis of both enantiomers of **1** and preliminary results on their chiral recognition properties.
The chirality of **1** is based on the simple chiral structure of the hydrobenzoins R(+)-**2** and S(-)-**2** which hence are the starting materials of choice. Although **2** is a well known example of a racemate which spontaneously forms enantiomorphic crystals separable by hand [4], its enantiomers, to our knowledge, have not been used as a chiral source in the construction of crown ethers, conceivably due to the facile epimerization/racemization of the hydrobenzoins in basic media [5].

In our approach, dl-**2** prepared from trans-stilbene epoxide [6] or meso-1,2-dibromo-1,2-diphenylethane [7] was transferred into the diastereomeric bis-(-)-menthoxyacetates [8] **3a,b** which were easily separated by fractional crystallization from ethanol. **3a** and **3b** were treated with ethanolic sodium hydroxide to give pure R(+)- and S(-)-**2** [9] in 72% combined yield.

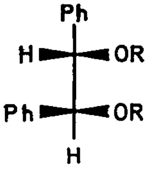
Reaction of R(+)-**2** or S(-)-**2** with diethyleneglycol ditosylate and powdered sodium hydroxide in dioxane for 12 h at 80 °C gave (+)-**1** and (-)-**1**, respectively in 25-30% yield each. No racemization or epimerization of the hydrobenzoins occurred under these conditions. With the known absolute configurations of the hydrobenzoins [6], the R-configuration at all four chiral centers of (+)-**1** is established.

When equal amounts of R(+)-**1** and S-(-)-**1** are combined in ethanol, racemic crystals, m.p. 151 °C, are formed. This material is identical with one of the isomers prepared earlier [3] which, however, had erroneously been associated with the achiral trans-syn-trans structure [10]. Correspondingly, the ring closure of racemic hydrobenzoin gives a mixture of racemic **1** and the trans-syn-trans isomer, m.p. 190 °C, whose structure is herewith confirmed. Starting from meso-hydrobenzoin a mixture of the cis-syn-cis and cis-anti-cis isomers, m.p. 111 and 214 °C is obtained as expected [3].

R(+)-**1** and S(-)-**1** were also obtained following the synthesis described in our previous communication [3] with a chromatographic resolution of the dibenzoate of racemic bis-(2-hydroxyethoxy-)-1,2-diphenylethane on cellulose triacetate [11] as a key step.

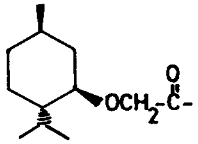


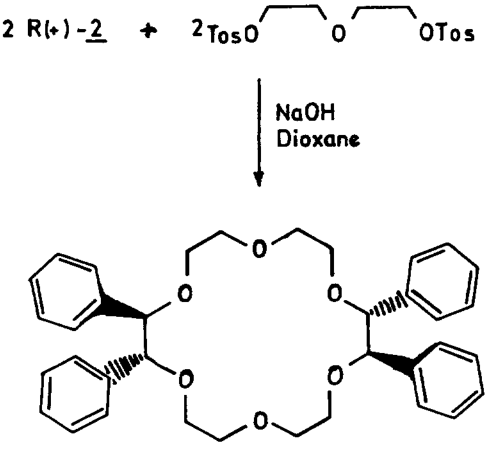
3a: R = (-)-MEA
R(+)-**2**: R = H



3b: R = (-)-MEA
S(-)-**2**: R = H

(-)-MEA =

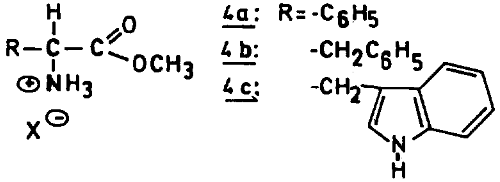




R(+)-**1**

	R(+)-1	S(-)-1	3a[14]	3b[14]
m.p.(°C)	113-14	113-14	83-5	135-36
$[\alpha]_D^{20}$ (°)	+14	-14	-87	-49

Table: Proton nmr chemical shifts of complexes of racemic/optically active pairs of crown ethers **1** and ammonium salts **4a-c** (X=SCN); δ, vs.TMS in $CDCl_3$, concentrations 0.1 **M** each.



Complex	Chemical shifts of **1**		Chemical shifts of **4**
	$-OCH_2CH_2O-$	-OCH-Ph	$-COOCH_3$
(+)-**1**/rac.**4a**	3.33-3.80(m)	4,56(s)	3.93(s),3.96(s)
rac.**1**/(-)-**4a**	same	4.48(s),4.46(s)	3.94(s)
(+)-**1**/rac.**4b**	3.36-3.86(m)	4.68(s)	3.78(s),3.80(s)
rac.**1**/(-)-**4b**	same	4.69(s)	3.79(s)
(+)-**1**/rac.**4c**	3.28-3.93(m)	4.51(s)	3.84(s),3.91(s)
rac.**1**/(-)-**4c**	same	4.45(s),4.58(s)	3.88(s)

The ability of the optically active crown ethers **1** for chiral recognition was tested by extraction experiments monitored by proton nmr with the methyl esters **4a-c** of N-protonated amino acids. Mutual enantiodifferentiation in all cases was manifested by signal splittings in the nmr spectra (see Table) due to the equilibrium formation of diastereomeric complexes [12]. In the combinations racemic crown/optically active salt, splitting of the crown benzylic protons occurred in cases **4a** and **4c**; splitting of the methyl ester protons was observed in all cases with optically active crown and racemic salt.

In the case of phenylglycine, **4a**, the signal of the ester methyl group is sufficiently separated from the methylene proton signals of the crown ether as to allow the determination of the chiral recognition factor (CRF) directly from the integration of the splitted signal in the 250 MHz spectrum. Thus, R(+)-**1**, in $CDCl_3$, selectively extracts R(-)-**4a** from concentrated aqueous solutions. The CRF is 1.2 for the hydrothiocyanate and 1.5 for the hydroperchlorate at 25 °C. These values are in the same range as those reported for dibinaphthyl-22-crown-6 [13].

As a special feature of the new crown ethers R(+)-**1** and S(-)-**1** we feel that the free para positions of the phenyl rings should offer convenient and versatile functionalization which may allow the attachment to solid supports for chromatographic or catalytic purposes. Further work in this direction is in progress.

References and Notes

[1] For a recent review see: S.T.Tolley, J.Bradshaw and R.M.Izatt, J.Heterocyclic Chem. **19,** 3(1982).

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[8] (-)-Menthoxyacetic acid, m.p. 54-5 °C, $[\alpha]_D^{20}$ -91°(EtOH), was conveniently prepared by stirring a mixture of (-)-menthol (0.3 mol), sodium hydride (0.35 mol) and sodium chloroacetate (0.3 mol) in DMSO/THF(1000 ml, 1:1 vv) at 25 °C for 12 h; yield 85% after aqueous work up and recrystallization from pentane (confer also: P.F.Newton and G.H.Whithen, J.C.S.Perkin I **1979,** 3072). Conversion into the acid chloride and esterification with dl-hydrobenzoin was achieved following usual procedures.

[9] Physical data as in ref. [4].

[10] An nmr study of the behavior of **all** diastereomers of **1** in the presence of optically active 1-phenylethylammonium hydrobromide which will show the reason for our wrong assignment will be published separately.

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[14] The spectroscopic properties of R(+)-**1** and S(-)-**1** are identical with those of the racemate [3].

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