SYNTHESIS OF (-)-*2S,3S,11S,12R*-2,3,11,12-TETRAPHENYL[18]CROWN-6

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Abstract: The synthesis of (-)-*2S,3S,11S,12R*-2,3,11,12-tetraphenyl[18]-crown-6 from (-)-*1S,2S*-hydrobenzoin and *meso*-hydrobenzoin is described. Chemical shifts and vicinal coupling constants of the benzylic protons in the 2*S*,3*S* and 11*S*,12*R* substructures in the free ligands and in complexes with KSCN and 1-phenylethylammonium bromides and a brief discussion of the related conformational changes are also presented. A detailed procedure for the resolution of racemic hydrobenzoin is given.

Chiral crown ethers have found wide interest and applications in stereochemical studies and chiral recognition experiments[1]. Substitution in the 2,3,11 and 12 positions of [18]-crown-6 by four identical substituents gives rise to a set of five diastereomeric structures two of which are pairs of enantiomers. Examples of such a substitution pattern are "dicyclohexano[18]crown-6"[2], [18]-crown-6 tetracarboxylic acid and derivatives thereof[3], and tetraphenyl[18]crown-6. Of the latter, the complete set of stereoisomers including the enantiomers of the *trans-anti-trans*-isomer 8 has been synthesised in our laboratory[4,5]. Their configuration dependent complexing behaviour towards alkali and ammonium cations has been described[4], and a study on the conformations of the three *meso* forms in the free and complexed states was performed based on crystal structure and proton nmr data[4]. The optical active crown ether 8 has only recently been shown to exert a remarkable asymmetric induction in the reduction of aromatic ketones with the borane-ammonia complex[7].

In completion of our studies in this series of crown ethers, we are now reporting the synthesis of the pure (-)-*2S,3S,11S,12R*- enantiomer, (-)-9a.

As a source for chiral 1,2-diphenylethanedioxy units we have recently developed a convenient resolution of racemic hydrobenzoin 1 which enabled us to synthesise the enantiomers of the *trans-anti-trans* isomer 8 by the four centre ring closure of the optically active hydrobenzoins (+)- or (-)-1 and diethyleneglycol ditosylate[5].

Since 9 contains the two diphenylethanedioxy groups in different configurations (*meso* and *R,R* or *S,S*), these have to be introduced in a differentiated manner, e.g. as suitable pairs of diols and ditosylates as shown in Scheme 1. One of the necessary steps is the bis-2-hydroxyethylation of the hydrobenzoins. Attempts to achieve this transformation by the alkylation of (-)-1 with 2-(2-tetrahydropyranyloxy)ethyl tosylate[4] were accompanied by ample racemisation and epimerisation in the

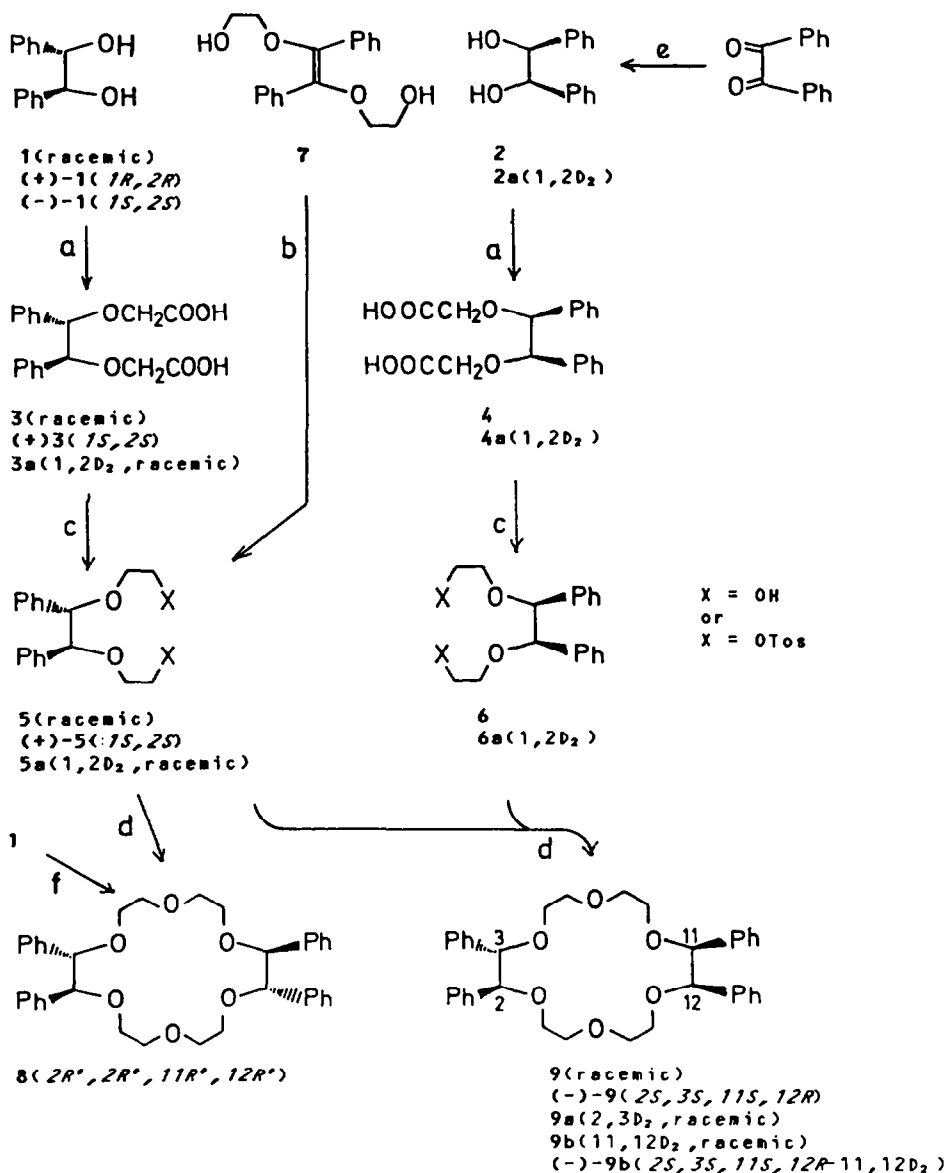diphenylethanedioxy structure. This was surprising with respect to the straightforward synthesis of 8 *without* loss of optical activity. Racemization/epimerisation of hydrobenzoins can be rationalised via the diolate/ketyl equilibrium[8]. In the present case, this may be favoured by the severe steric compression of phenyl, tosyl, and tetrahydropyranyl groups causing *slow* alkylation. In the crown ether ring closure, this undesired side reaction is presumably overcome by the accelerating template effect[9].

Clean alkylation of (-)-1 with complete retention of configuration was eventually accomplished by *tert*-butyl chloroacetate as a more reactive and sterically less demanding alkylating agent[9]. Thus, the hydrobenzoindiacetic acids 3,4 were obtained in high yields, which in turn were cleanly reduced by LiAlH₄ to give the desired optically active, racemic or *meso* diols 5,6. The enantiomeric diols 5 are suitable building blocks for the introduction of optically active 1,2-diphenyldioxy moieties into any crown ether structures.

The complete synthetic scheme is given in Scheme 1 including the preparation of some deuterated derivatives. Ring closure of suitable diols and ditosylates with NaOH in dioxane gave the crown ethers 9,9a,9b in 35-40% yield. The enantiomeric purity (98%+) of the optically active crown ethers (-)-9 and (-)-9b was confirmed by ¹H-nmr spectra in the presence of (+)-*R*-1-phenylethylammonium bromide, 11 (vide infra) within the accuracy of this method. In the series of intermediates containing the *1S,2S*-hydrobenzoin structure, hydrobenzoin itself and the crown ethers 8 and 9 have negative rotations whereas the diacetic acid 3 and the diethanol 5 have positive rotations.

Within the 2,3,11,12-tetraphenyl[18]-crown-6 series, 9 is the only isomer with C_1 symmetry. Therefore, the four benzylic protons are diastereotopic and appear, in the nmr spectrum, as two AB spin systems corresponding to either diphenylethanediyl group. From the spectra of the deuterated crown ethers 9a and 9b, the assignment of the AB-spectra to the *R°,R°* or *R°,S°*

Scheme 1

Ph⋯—OH
Ph⋯—OH

1(racemic)
(+)-1(*1R, 2R*)
(-)-1(*1S, 2S*)

HO—CH₂—O—Ph
Ph—O—CH₂—OH

7

HO⋯Ph
HO⋯Ph

2
2a(1,2D₂)

←e—

O═⟨Ph
O═⟨Ph

a↓

Ph⋯—OCH₂COOH
Ph⋯—OCH₂COOH

3(racemic)
(+)3(*1S, 2S*)
3a(1,2D₂,racemic)

b

HOOCCH₂O⋯Ph
HOOCCH₂O⋯Ph

4
4a(1,2D₂)

a↓

c↓

Ph⋯O⌐X
Ph⋯O⌐X

5(racemic)
(+)-5(:*1S, 2S*)
5a(1,2D₂,racemic)

c↓

X⌐O⋯Ph
X⌐O⋯Ph

6
6a(1,2D₂)

X = OH
or
X = OTos

d↓   f

Ph⋯—O   O—Ph
Ph—O   O⋯Ph

8(*2R*, 2R*, 11R*, 12R**)

d↓

Ph⋯3—O   O—11 Ph
Ph 2—O   O 12 Ph

9(racemic)
(-)-9(*2S, 3S, 11S, 12R*)
9a(2,3D₂,racemic)
9b(11,12D₂,racemic)
(-)-9b(*2S, 3S, 11S, 12R*-11,12D₂)

a)ClCH₂COOtBu,NaOH,18C6-cat,dioxane,r.t;
b)H₂ or D₂/Pd,EtOH;
c)LiAlH₄,THF,r.t.;
d)Dioxane,NaOH-powder,80° C;
e)LiAlH₄ or LiAlD₄,Et₂O;
f)TosOCH₂CH₂OTos, dioxane, NaOH-powder, 80° C.

structural fragments is clear; no assignment, however, is possible to the identity of single protons in each AB spectrum.

Complexation of a potassium ion causes a downfield shift of both AB systems, whereas an upfield shift is observed with 1-phenylethylammonium bromide, 11, as already noted for the other isomers[4]. As expected[11], the interaction of racemic 9 and optically active (+)-*R*-11 gives rise to four AB-quartets which are mutually overlapping. Using the two deuterated crown ethers 9a and 9b, and the two optically active crowns (-)-9 and (-)-9b, a stepwise simplification of the spectrum is achieved so that the four AB systems can be easily identified and assigned to the interactions of the *2R,3R* and *11R,12S* groups in (+)-9 and of the *2S,3S* and *11S,12R* groups in (-)-9, respectively, with (+)-*R*-11. The chemical shifts and vicinal coupling constants of the benzylic protons of the free ligands and their complexes are given in Table 1.

Following our recent study on the conformations of the isomers of 9, a

Table 1:Chemical shifts and vicinal coupling constants of the protons in the diphenylethanedioxy groups in the enantiomers of 9 and its complexes (CDCl₃ solution).

Complexing partner	(+)- -R,R,R,S-9		(-)- S,S,S,R-9	
	2R,3R-H	11R,12S-H	2S,3S-H	11S,12R-H
none	4.59;4.61 (7.54 Hz)	4.73;4.83 (3.88 Hz)	identical	
K⁺ I⁻	4.73;4.78 (8.70)	4.62;5.07 (3.00)	identical	
(+/-)-11	4.37;4.58 (8.67)	4.56;4.68 2.65)	identical	
(+)-R-11	4.29;4.57 (8.63)	4.66;4.68 (2.70)	4.49;4.58 (8.72)	4.46;4.69 (2.59)

Fig. 1: Estimated conformation of (−)-9 in the free state. The curved arrows indicate the conformational motion on complexation; the double arrow marks the preferred complexation site for ammonium ions.
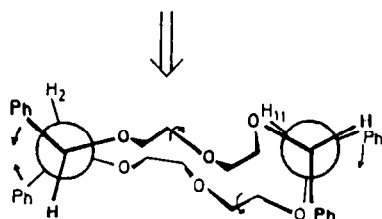
qualitative interpretation of the conformational changes that occur on complexation is possible with these data⁴. The ideal conformation for complexing a cation in the centre of the crown ether ring would require a synclinal-diequatorial array of the 2S,3S phenyl groups and a synclinal-equatorial/axial one for the 11S,12R positions. The values of the vicinal H-H-coupling constants in the free ligand show a deviation from this ideal geometry obviously due to repulsion of the vicinal phenyl groups. The data for the 11S,12R group suggest a close to eclipsed conformation. An estimated conformation of (−)-9 based on the vicinal coupling constants is given in Fig. 1.
By the complexation of a potassium ion in the centre of the crown ether ring, the vicinal oxygen atoms in the diphenylethanediyl groups are forced into the proper synclinal position and, consequently, the coupling constants become larger in the R°,R°-group and smaller in the R°,S°- group thus approaching the values for the ideal geometry⁴.
Similar changes of the coupling constants are observed with 11. Since 9 has diastereotopic faces, preferred complexation from the top face (in Fig 1) is expected because the bottom face is shielded by the axial phenyl

group. As can be seen from the chemical shift data, in the complexes of 9 only *one* proton of each AB system suffers an upfield shift. These protons should then be those standing axial on the complexation site, i.e. protons H₂ and H₁₁ in Fig. 1.

Experimental Section

All chemical preparations were carried out under dry nitrogen. Dioxane was distilled from KOH prior to use. Nmr-spectra were obtained with Varian T 60 or Bruker WM 250 instruments; chemical shift values are given in δ[ppm] vs. TMS in CDCl₃ solution unless otherwise noted.
Optical rotations were measured with a Perkin Elmer Mod. 241 polarimeter. Corrected melting points were taken on a Kofler hot stage microscope. Elementary analyses were carried out in the Microanalytisches Labor der Universität Regensburg.

Resolution of R°,R°-1,2-diphenyl-1,2-ethanediol, 1

To a mixture of (−)-menthoxyacetyl chloride⁵ (50,0 g, 0.2 mol, m.p. 54-55 °C, [α]D²⁵ -91°) and racemic 1¹'² (21.4 g, 0.1 mol) in dichloromethane (200 ml), pyridine (20 ml) is added under stirring and cooling. After stirring overnight, the mixture is heated to reflux for 30 min and poured into cold 6M HCl (500 ml). The organic phase is washed with water and dried to give a slightly tan solid (61 g, 100%, m.p. 70-120 °C) after removal of the solvent. The solid is dissolved in boiling methanol (300 ml) and the solution is allowed to slowly cool to room temperature. Within 2.5 h, 24-26 g of the (−)-1-diester A crystallise as colourless needles which are isolated by suction filtration and washed with cold methanol. The filtrate is concentrated to about 200 ml and any precipitate is dissolved by heating. Upon standing for 12 h at 10 °C, 27-29 g of the (+)-1-diester B have crystallized.

Diastereomer A is purified by two recrystallisions from ethanol: ca. 21 g (35%), m.p.129-31 °C, $[\alpha]_D^{25}$ -49 ° (c = 200 mg/ml in CH_2Cl_2). Diastereomer B is once recrystallised from methanol: ca. 22 g (36%), m.p. 83-85 °, $[\alpha]_D^{25}$ -87° (c= 200 mg/ml in CH_2Cl_2) The mother liquors are not suitable for further crystallisations; they should be hydrolysed for starting material recovery.
$C_{38}H_{54}O_4$ (606.84)

calc.	C 75.21	H 8.90
found	75.19	8.60 (A)
	75.13	8.67 (B)

The ir and nmr spectra of A and B are indistinguishable: [1]H-nmr: 7.0-7.2(m,10H,arom.H);6.14(s, 2H,benzyl-H);4.15,4.09(AB-spectrum,4H J = 16 Hz,O-CH_2-COO-); 0.7-3.2(m,38H, menthyl group).

The enantiomeric hydrobenzoins ((+)-*R,R*-1 from ester A and (-)-*S,S*-1 from ester B) are obtained by alkaline hydrolysis (0.05 mol diester, 200 ml 2M aqueous NaOH, 1000 ml ethanol, 12 h at room temperature). Most of the ethanol is removed *in vacuo*, and the product is extracted with dichloromethane. A single recrystallisation from chloroform/cyclohexane (1:4) gives the enantiomerically pure hydrobenzoins in 85-90% yield with m.p. and optical rotations as described in the literature[13]. (-)Menthoxyacetic acid is recovered from the alkaline hydrolysis solution in >95% yield.

1R,2S-1,2-Dideuterio-1,2-diphenyl-1,2-ethanediol, 2a

Following a literature procedure for *meso*-hydrobenzoin[14], benzil (4.20 g, 20 mmol) was treated with LiAlD4 (0.89 g, 21 mmol) in 50 ml dry ether. Yield: 2.5 g (57%) 2a, m.p. 136-37 °C. ir: v_{C-H} 2120 cm^{-1}; [1]H-nmr: 7.25(s, 10H,arom.H),2.38(broad s,2H,hydroxyl) complete deuteration indicated by the absence of benzylic protons.
$C_{14}H_{12}D_2O_2$ (216.28)

calc.	C 77.75	H/D 7.45
found	77.19	7.68

(+/-)-1*R*,2*R*-2,2'-(1,2-diphenyl-1,2-ethanedioxy-)diethanol, 3a

(corresponding hydrogen compound see ref.[4]) A mixture of 7 (9.00 g, 30 mmol) and 10% Pd/charcoal (Merck, 300 mg) in ethanol (130 ml) was shaken in deuterium atmosphere (Merck, 99.9% isotopic purity) at room temperature and normal pressure until 770 ml (115%) D_2 had been taken up. Usual work-up gave 4.6 g 3a (50%), m.p.85-87 °C. According to nmr, the deuterium content in the benzylic position was 75%. Mass spectrometry showed 56% D_2, 36% DH, and 8% H_2 species.

Stereoisomeric (1,2-diphenyl-1,2-ethanedioxy-)diacetic acids, (+/-)-3,(+)-*1S,2S*-3, 4, 4a

A mixture of the corresponding hydrobenzoin (3.00 g, 14 mmol), *tert*-butyl chloroacetate (8.5 ml, 60 mmol), [18]crown-6 (250 mg) powdered NaOH (12 g) and dioxane (60 ml) is stirred at room temperature for 24 h. The mixture is diluted with water (250 ml) and twice extracted with ether (50 ml). The aqueous phase is acidified and extracted with dichloromethane to give 3.2-3.6 g (70-85%) of the colourless crystalline dicarboxylic acids:
(+/-)-3, m.p.175-179 °C (from benzene); ir: $v_{C=O}$ 1730 cm^{-1}; [1]H-nmr(in $(CD_3)_2C=O$): 7.13(s,10H,arom.H),4.73(s,2H,benzylic H),3.98,4.12(AB-q,4H,J=16Hz,-CH_2-). (+)-*1S,2S*-3, m.p.198-200 °C (from xylene); $[\alpha]_{546}^{25}$ +31.8°, $[\alpha]_{546}^{25}$ +52.6° (c=20.15 mg/ml in ethanol);spectra identical with those of (+/-)-3.

4 and 4a, m.p. 178-180 °C (from water); ir: $v_{C=O}$ 1725,1755 cm^{-1}; [1]H-nmr:7.25(s,10H,arom.H),4.92(s,2H,benzylic H,missing in the spectrum of 4a),3.98,4.12(AB-q,4H,J=16Hz,-CH_2-).
$C_{18}H_{18}O_4$ (330.30)

		calc.	C 65.45	H 5.49
(+/-)-3	found		65.25	4.98
(+)-3			65.10	5.23
4			65.26	5.34

Stereoisomeric 2,2'-(1,2-diphenyl-1,2-ethanedioxy-)diethanols (+/-)-5,(+)-*1S,2S*-5,6,6a

To a suspension of LiAlH4 (0.60 g, 16 mmol) in dry tetrahydrofuran (30 ml) a solution of the corresponding dicarboxylic acid (3 or 4, 2.7 g, 8,0 mmol) in THF (40 ml) is added under stirring at 0 °C. After stirring for 24 h at ambient temperature, the mixture is hydrolysed with 2M aqueous sulfuric acid. The diols are isolated in quantitative yield by extraction with ether.
(+/-)-5 and 6 or 6a had spectroscopic properties as given in ref.[4]. (+)-5: colourless oil; $[\alpha]_{546}^{25}$ +35.8°,$[\alpha]_{546}^{25}$ +24.1° (c = 20.2 mg/ml in ethanol).

Racemate, (-)-enantiomer, and deuterated derivatives of *2R*,*3R*,*11R*,*11S*-2,3,11-12-tetraphenyl[18]crown-6, 9

Suitable combinations of diols 5 or 6 and their corresponding ditosylates, which were prepared as in ref.[4], were employed in the syntheses of the crown ethers 9. Thus, a mixture of diol (1.50 g, 5.0 mmol), ditosylate (3.0 g, 5.0 mmol) and powdered NaOH (4.0 g) in dioxane (20 ml) is stirred for 14 h at 80 °C. The mixture is diluted with water (200 ml) and the product is extracted with dichloromethane to give ca. 2.8 g (98%) of a colourless oil which in turn is stirred with potassium thiocyanate (2.1 g) in dichloromethane (50 ml) for 4h. The mixture is filtered and the crown ether KSCN complex is precipitated with pentane and may be further puri-

fied by dissolving in a small amount
of dichloromethane followed by preci-
pitation with ethyl acetate. Yield:
1.3-1.5 g (40-45%). The free crown
ethers are recovered by dissolution
in dichloromethane and removal of the
KSCN by thorough extraction with
water. Yield: ca. 1.1 g (40%), m.p.
95-96 ° (racemic crown) or 69-70 °C
(optically active crown).
^{1}H-nmr (250 MHz): 7.3-7.0 (m,20H,phe-
nyl groups),4.83,4.73(AB-q,2H, J=3.88
Hz,H_2,H_3(missing in the spectrum of
(+/-)- and (-)-9b), 4.59,4.61(AB-
q,2H,J=7.54 Hz,H_{11},H_{12}(75% diminished
in the spectrum of 9a prepared from
5a),3.5-3.9(m,16H, ethylene groups).
Optical rotations: (-)9:$[\alpha]_{25}^{22}$, -16.1°,
$[\alpha]_{365}^{22}$, -4.3° (c=21.1 mg/ml in CH_2Cl_2)
(-)-9b: $[\alpha]_{25}^{22}$, -12.9°, $[\alpha]_{365}^{22}$, -1.9°
(c= 43.5 mg/ml in CH_2Cl_2.
9: $C_{36}H_{40}O_6$ (568.7)

calc.	C 76.03	H	7.09
found	75.74		7.00

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