SYNTHESIS AND STRUCTURE OF (4R,5R)-α,α,α',α'-2,2-HEXAPHENYL-4,5-DIMETHANOL-1,3-DIOXOLANE

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Abstract: We report the synthesis of the 1,4-diol **2** (4R,5R)-α,α,α',α'-2,2-hexaphenyl-4,5-dimethanol-1,3-dioxolane from dimethyl-L-tartrate and benzophenone. The X-ray and the IR structural studies on **2** show that this compound has a preferred conformation with OH···Ph interactions which are different from related compounds.

L-Tartrate derived 1,1,4,4-tetraphenyl-1,4-diols have been used in asymmetric synthesis as chiral ligands for some metals such as titanium or aluminium in chiral Lewis acid catalysis[1]. Recently, the advantages of chiral auxiliary reagents possessing C_2-symmetry in asymmetric processes[2,3], have been reported. Because of the high enantioselectivity reported[4] in asymmetric Diels-Alder reactions using the 1,4-diol **1**, we decided to attempt the synthesis of the 1,4-diol **2** and to study its behaviour as chiral auxiliary in this reaction. Furthermore, few X-ray structural studies have been carried out with this kind of diols[5,6,7,8], which almost all of them are host-guest derivatives of **3**, **4** and **5**. Only one structure of an isolated diol (**3**) has been reported[6]. We present here the synthesis and the structural study of **2** by X-ray diffraction and IR and we compare the results with the previously described for diol **3**.

During the performance of this work, the 1,4-diol **2** was published[5], but reported physical data differ from ours. It has also been referred to in a patent[9].

R^1 = Ph, R^2 = CH_3	**1**
R^1 = R^2 = Ph	**2**
R^1 = R^2 = CH_3	**3**
R^1-R^2 = $(CH_2)_5$	**4**
R^1-R^2 = $(CH_2)_4$	**5**
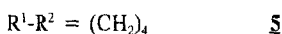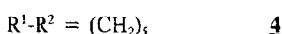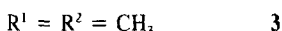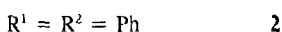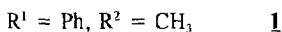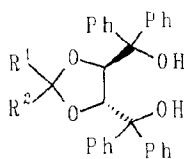
Results and Discussion:

The synthesis of **2** was accomplished by the method commonly used for these systems (Scheme 1). Transacetalization of the dimethyl acetal of benzophenone **6** with commercial dimethyl-L-tartrate **7** provided the dioxolane **8** in 82% yield[10]. Treatment of **8** with excess phenylmagnesium bromide gave the 1,4-diol **2** in 65% yield, and e.e. ≥98%[11].
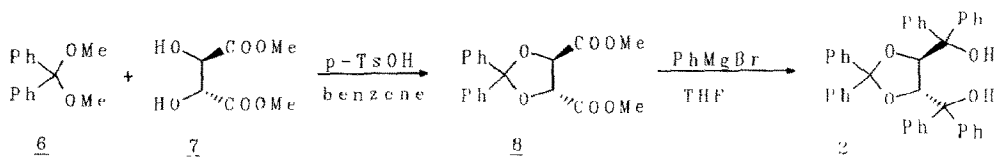
Scheme 1

The crystallographic labelling scheme used for molecules is shown in Figure 1. All the covalent parameters are within the normal range. The space group is P2₁, consistent with the chirality of the compound. A summary of the crystal data and experimental parameters is given in Table 1. In the solid state, diol **2** has two molecules in the asymmetric unit having different conformations **2I** and **2II** (Figure 2). The basic difference between these conformations is the disposition of the phenyl rings around the C_{ipso}-C_{para} axis (Figure 1). In each pair of phenyl rings attached to the same carbon atom, one of them differs only slightly while the other one does so more significantly (Table 2).
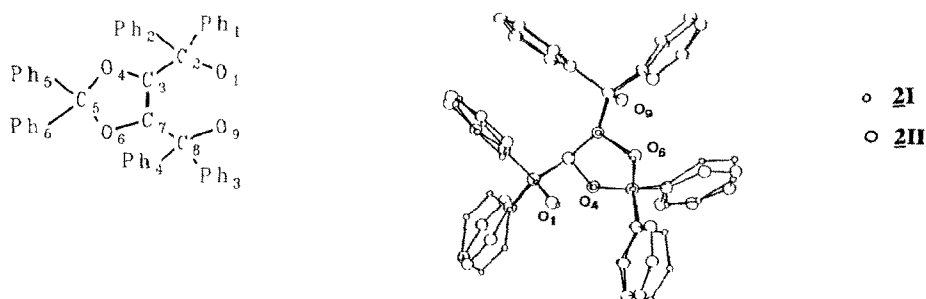
Figure 1: Crystallographic numbering of **2** and Best Molecular Fit[11] of the two conformations of **2**

Table 1: Crystal and diffraction data for **2**

Formula	$C_{41}H_{34}O_4$	Z	4
Molecular Weight	590.72	$\mu(mm^{-1})$ (Mo Kα)	0 711
Crystal System	monoclinic	F(000)	1248
Space Group	P2₁(4)	Unique reflections	5964
a(Å)	10.560(1)	Observed reflections	2640
b(Å)	15.822(1)	$(I \leq 2.5\sigma(I))$	
c(Å)	19.868(5)	hkl range	-12/12 0/18 0/23
$\alpha(°)$	90	R	0.0391
$\beta(°)$	100.37(2)	R_w	0.0422
$\gamma(°)$	90	$w = 1(\sigma^2(F) + kF^2)$	0.0024
V(Å³)	3265.3(9)	Parameters	683
Dc(g/cm³)	1.2016	Residual electron density (eÅ⁻³)	0.14/-0.15

The structure of molecule **2** shows the presence of a C_2 symmetry. The conformation I shows just a little deviation from this symmetry (asymmetry parameter[13] $\Delta C_2^5 = 0.82$). In contrast, the dioxolane ring in the conformation II shows a greater deviation from this symmetry transmitted to the rest of the molecule ($\Delta C_2^5 = 13.36$).
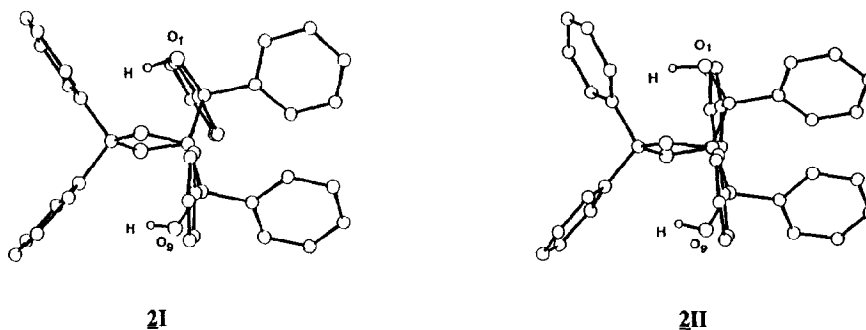

2I   **2II**

Figure 2: Conformations of **2**. Drawing with the OH$\cdots$Ph interactions of **2I** and **2II**

Table 2: Distances (Å) between phenyl carbons of the two conformers of **2** after matching (Best Molecular Fit[12])

	C_{ipso}	C_{orto}	$C_{orto'}$	C_{meta}	$C_{meta'}$	C_{para}
Ph$_1$	0.102	0.637	0.438	0.651	0.424	0.128
Ph$_2$	0.102	2.478	2.277	2.560	2.198	0.260
Ph$_3$	0.045	0.147	0.191	0.151	0.196	0.071
Ph$_4$	0.190	2.649	2.184	2.772	2.068	0.461
Ph$_5$	0.688	0.396	0.282	0.529	0.204	0.298
Ph$_6$	0.181	2.618	2.195	2.734	2.078	0.397

Table 3: Selected Torsion Angles (°) of **2I** and **2II**

	2I	**2II**
$C_2-C_3-C_7-C_8$	-144.4(4)	-137.2(5)
$O_4-C_3-C_7-C_8$	97.7(5)	101.4(5)
$C_2-C_3-C_7-O_6$	96.4(4)	106.9(5)
$O_4-C_3-C_7-O_6$	-21.4(5)	-14.6(5)
$C_5-O_4-C_3-C_7$	17.7(5)	17.3(5)
$O_6-C_5-O_4-C_3$	-6.9(5)	-13.0(5)
$C_7-O_6-C_5-O_4$	-7.8(5)	3.0(5)
$C_3-C_7-O_6-C_5$	18.4(5)	7.3(5)

In both conformations, the two hydroxyl groups are bended over the dioxolane ring, forming a OH$\cdots$phenyl hydrogen bond (Figure 2, Table 4). This fact contrasts with previously described structures, in

which OH$\cdots$OH bonds are always formed irrespective of the presence or absence of guest compounds. In the case of **3** intra and intermolecular hydrogen bonds are formed, and dimeric association is observed[6].

The IR spectrum of the solid compound **2** shows a sharp band at 3540 cm^{-1} assigned to the OH$\cdots\pi$ hydrogen bond and just a very weak broad band at 3400 cm^{-1} assigned to intermolecular OH$\cdots$OH bond. IR spectra in chloroform show a unique, concentration independent band at 3540 cm^{-1} for concentrations up to 0.02 M. Above this value a weak broad band at 3400 cm^{-1} is observed. Similar wave number values for OH$\cdots\pi$ hydrogen bonds have been described in alkyl substituted bis(hydroxyphenyl)alkanes[14] and in 2,2'-dihydroxybiphenyl[15].

Although this OH$\cdots\pi$ hydrogen bond is weaker than the OH$\cdots$OH one, an extra interaction OH$\cdots$O with the oxygens of the dioxolane ring O_4, O_6 may help to stabilize the conformation of **2**. This kind of OH$\cdots$O hydrogen bonds have been described in cyclic acetal isomers of glycerol[16]. The dioxolane ring is more planar in **2** than in **3**, and the half-axial/half-equatorial arrangement of phenyl groups described for **3** and host-guest compounds of **3**, **4** and **5** is not observed.(Figure 2).

Table 4: Hydrogen Bonding. OH$\cdots$Ph and OH$\cdots$O contact distances (Å)

	2I			**2II**		
	d(O$\cdot\cdot$C)	d(O-H)	d(H$\cdot$C)	d(O$\cdot$C)	d(O-H)	d(H$\cdot$C)
O_1-H$\cdot\cdot$Ph$_{5(ipso)}$	3.056(5)	0.90(7)	2.27(6)	3.051(6)	1.17(9)	2.27(9)
O_1-H$\cdot\cdot$Ph$_{5(orto)}$	3.299(6)	0.90(7)	2.40(7)	3.326(6)	1.17(9)	2.76(8)
O_9-H$\cdot\cdot$Ph$_{6(ipso)}$	3.104(6)	0.84(8)	2.44(8)	3.323(6)	0.97(10)	2.48(10)
O_9-H$\cdot\cdot$Ph$_{6(orto)}$	3.293(6)	0.84(8)	2.47(8)	3.272(5)	0.97(10)	2.72(10)

In conclusion, all the above data reveal that compound **2** has the same basic conformation in chloroform solution and in crystal, and this conformation is very different from that described for similar compounds.

EXPERIMENTAL SECTION

General: Melting points were obtained on a Büchi-Tottoli melting point apparatus and are uncorrected. Boiling points are also uncorrected. IR spectra were recorded on a Perkin-Elmer 683 Spectrophotometer. ^{1}H-NMR were recorded on a Perkin-Elmer R-24 spectrometer at 60 MHz. All NMR spectra were recorded in CDCl$_3$ and are reported relative to $(CH_3)_4Si(\delta=0.0$ ppm). Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 1 dm polarimeter cell. Mass spectra were obtained on a Hewlett-Packard 5995 AGC MS spectrometer. Elemental analysis were obtained on a Carlo-Erba CHNS-O/EA 1108 apparatus. TLC analyses were carried out on Kieselgel 60 F254 Merck plates. Tetrahydrofuran (THF), toluene and benzene were distilled over Na.

X-Ray structure analysis: A suitable monocrystal was grown from a chloroform solution and mounted on an Enraf-Nonius CAD4 diffractometer. Graphite monochromated Mo-K_α radiation, ($\lambda = 0.71069$ Å) was used. Lattice parameters were obtained from least-squares refinement of 25 well centered reflections. Intensity measurements were done at room temperature using the $\omega/2\Theta$ scan technique. Standard reflections monitored every 200 measurements showed no significant decay. Lorentz and polarization corrections were applied but no absorption corrections were made. The structure was solved by direct methods using the SHELXS[17] program and was refined anisotropically by the least-squares method[18]. Block matrices were used because of the great number of parameters to be refined. The atomic scattering factors were taken from the International Tables for X-Ray Crystallography. The positions of all hydrogen atoms bound to carbon were calculated and refined with an overall isotropic temperature factor. The hydrogen atoms bound to oxygen were located in difference Fourier maps and refined with a different overall isotropic temperature factor. The full set of coordinates, anisotropic thermal parameters and additional geometrical data have been deposited at the Cambridge Crystallographic Data Centre.

(4R,5R)-2,2-Diphenyl-4,5-dimethoxycarbonyl-1,3-dioxolane $\underline{8}$: To a 80 mL benzene solution of dimethyl-L-tartrate (7.30 g, 41 mmol) and dimethoxydiphenylmethane (9.35 g, 41 mmol) is added a catalytic amount of p-toluenesulfonic acid. The mixture is heated to reflux to remove the liberated methanol azeotropically (bp 58.3°C, 60.5% benzene:39.5% methanol) with occasional addition of benzene until the boiling point reaches 80.5°C. The mixture is washed with saturated aqueous $NaHCO_3$ solution (2x50 mL) and then with brine (2x50 mL) and is dried over $MgSO_4$. The solvent is removed under reduced pressure and the white solid obtained is recrystallized from hexane to obtain the pure white crystalline product (11.5 g, 82% yield): mp 80-81°C; $[\alpha]_D^{20}$ +54.2 (c = 0.964, $CHCl_3$); IR (KBr) 3060, 2945, 1750, 1590, 1490, 1385, 1250, 1220, 1120, 760, 705 cm^{-1}; ^{1}H-NMR 7.50-7.13 (m, 10H, aromatic CH), 4.93 (s, 2H, -CH<), 3.62 (s, 6H, -CH$_3$); MS, *m/z (rel.int. %)* 343 (1.0%), 342 (4.3%), 283 (10.3%), 265 (100%), 165 (6.2%), 152 (1.6%), 105 (34.4%) 77 (14.2%); Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66%; H, 5.30% Found: C, 66.72%; H, 5.20%

(4R,5R)-$\alpha,\alpha,\alpha',\alpha'$-2,2-Hexaphenyl-4,5-dimethanol-1,3-dioxolane $\underline{2}$: The phenylmagnesium bromide is prepared in the usual manner by adding bromobenzene (26.1 mL, 39.23 g, 250 mmol) dissolved in 90 mL of dry THF dropwise to stirred magnesium turnings (6.08 g, 250 mmol) and a small I_2 crystal if it is necessary. The resulting mixture is heated to reflux for 30 minutes. The mixture is cooled to 0°C and the acetal $\underline{8}$ (17.10 g, 50 mmol) dissolved in 100 mL of dry THF is added dropwise. The reaction mixture is stirred at room temperature overnight and then heated to reflux for 2 hours. A saturated aqueous NH_4Cl solution (500 mL) is added. Organic materials are extracted with ethyl acetate (3x200 mL), and the organic layer is washed with brine (2x200 mL) and dried over $MgSO_4$. The solvent is removed under reduced pressure and the residue is purified by column cromatography over silicagel using benzene:hexane 1:2 and $CHCl_3$ as eluents. The separated product is dissolved in hot hexane and a small portion of 2-propanol is added to the mixture with stirring. A white crystalline solid is formed slowly (product:2-propanol 1:1). The solid is filtered and dissolved in benzene. 2-Propanol is removed azeotropically with benzene several times by evaporation under reduced pressure. The pure product is obtained as an oil which crystallizes to give a white crystalline solid (19.2 g, 65% yield): mp 156-157°C, $[\alpha]_D^{20}$ +187.7 (c = 0.505, $CHCl_3$); IR (KBr) 3540, 3400, 3060, 2970, 1600, 1495, 1225, 1100, 1025, 760, 750, 695 cm^{-1}; ^{1}H-NMR 7.49-6.70 (m, 30H, aromatic CH), 5.43

(s, 2H, -CH<), 1.94 (s, 2H, OH); MS *m/z (rel.int. %)* 513 (0.4%), 407 (6.9%), 365 (14.4%), 225 (4.4%), 207 (29.0%), 183 (100), 165 (5.7%), 152 (1.4%), 105 (73.3%), 77 (21.9). Anal. Calcd for $C_{41}H_{34}O_4$: C, 83.37%; H, 5.80% Found: C, 83.38%; H, 5.96%

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