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Enantioselective Synthesis And CD Assignment Of Absolute Configuration Of (-)-1,3-Diphenylpropane-1,3-Diol.

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Abstract: Highly stereoselective hydrogenation of dibenzoylmethane in the presence of $[\text{RuCl}_2\{(\text{R})\text{-biphemp}\}]$ [biphemp = 2,2'-bis(diphenylphosphino)-6,6'-dimethyl-1,1'-biphenyl], in ethanol-dichloromethane, gives enantiomerically pure (-)-1,3-diphenylpropane-1,3-diol (**2**) (70% yield); analysis of the CD spectra of the corresponding acetone allows the absolute configuration of the diol to be established as (S,S). The direct HPLC separation of the enantiomers of (**2**) is also reported.

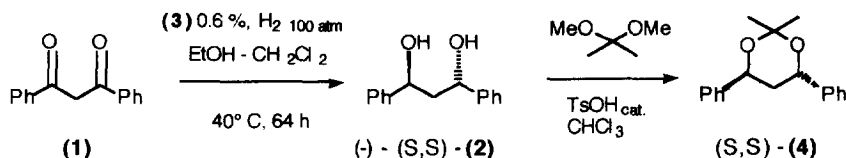
Despite the usefulness of optically active 1,3-diols as chiral auxiliaries and synthetic intermediates, few high yielding methods are available for obtaining these substances in enantiomerically pure form. (-)-1,3-Diphenylpropane-1,3-diol (**2**), used as starting material in the preparation of chiral polyesters¹ and as precursor of a 1,3-diphosphinite², was first synthesized by asymmetric hydrogenation of dibenzoylmethane (**1**) over Raney nickel catalyst modified with (R,R)-tartaric acid and NaBr (TA-NaBr-MRNi)³; however, because of the need of repeated crystallizations of the product to eliminate the meso diol (R*,S*)-(**2**), the yield was rather low (15-20%). Recently (-)-(**2**) has been prepared by enantioselective hydrogenation in the presence of binap complexes of ruthenium [binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene], but few experimental details were reported^{1,4}.

Little attention has also been paid to the elucidation of the absolute stereochemistry of (**2**), previous assignments depending upon somewhat questionable comparisons on chemical or spectroscopic ground. Tai *et Al.*³ inferred the (R,R) configuration for (-)-(**2**) obtained by asymmetric hydrogenation in the presence of (R,R)-TA-NaBr-MRNi, in analogy with the observed enantioselectivity in the reduction of 2,4-pentanedione and other β -dicarbonyl compounds and on the basis of lanthanide-induced shifts in ¹H-nmr spectra. However, because of a mistake in the assignment by Cahn-Ingold-Prelog priorities, these arguments effectively suggest an (S,S) configuration of (-)-(**2**). Subsequently Yamamoto *et Al.*⁵ proposed the same (-)-(S,S) correlation comparing the CD spectra of monoacetate of (+)-(**2**) with that of acetate of α -phenylethanol, though without quoting any detail of such comparison.

We wish to report here an efficient synthesis of (**2**) and a reliable determination of its absolute stereochemistry established in the course of our studies on the chemistry of pentacoordinate silicon compounds⁶.

As Consiglio *et Al.*⁷ reported that $[\text{RuCl}_2(\text{PPh}_3)\{\text{biphemp}\}]$ is an efficient catalyst in the enantioselective hydrogenation of 2,4-pentanedione to 2,4-pentanediol, we reasoned that the reduction of (**1**) in the presence of the analogous complex $[\text{RuCl}_2\{(\text{R})\text{-biphemp}\}]$ (**3**)⁸ could occur with high extent of enantioselectivity.

Scheme 1



Indeed under the conditions of Scheme 1 we were able to isolate, by simple filtration, the desired diol (-)-(2) in 70% yield, as colorless crystals separated from solution during the reaction⁹. GLC analysis of the diacetate of the product showed the presence of a single diastereoisomer, the one having C₂ symmetry, that was also optically pure as evaluated by comparison of its rotatory power with that of enantiomerically pure (2)³. Because of the drawbacks of enantiomeric excess determination by polarimetry, we looked for an independent determination by HPLC using a chiral stationary phase. Although in the literature only separations of derivatives of the enantiomers of (2) have been reported^{5,10} we found that the (R,R) and (S,S)-diols themselves could be directly resolved using a Chiralcel OJ column¹¹. The *meso* form (R*,S*)-(2) coeluted with the more retained enantiomer that turned out to be the (-)-diol, allowing us to confirm easily the complete enantiomeric purity of the product in our hands.

The stereoselectivity of the hydrogenation step was evaluated, in a separate run, on the whole crude material by means of the techniques reported above, resulting in a stereoisomeric composition (S,S) : (R,R) : (R*,S*) = 88 : 6 : 6; HPLC showed also only trace amounts of the mono-hydrogenation product (1,3-diphenylpropan-3-ol-1-one) and unreacted (1).

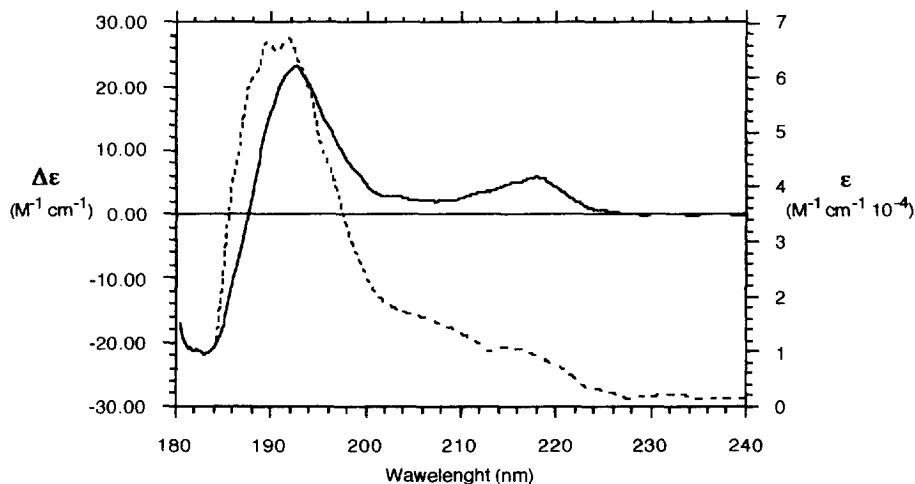


Figure 1. UV (broken line) and CD spectra (solid line) of ketal (4) (1.5 × 10⁻³ M in MeCN).

The determination of the absolute configuration of the diol was performed following a recently developed method¹². (-)-(2) was easily converted into the corresponding acetone ketal (4)¹³ and the CD spectrum of (4)

was recorded between 180 and 300 nm (Figure 1). The presence of a positive couplet centered at 187 nm, corresponding to the exciton coupling between the transition dipoles polarized along the phenyl long axes, is allied to a positive chirality in the arrangement of aromatic chromophores of (4)¹⁴.

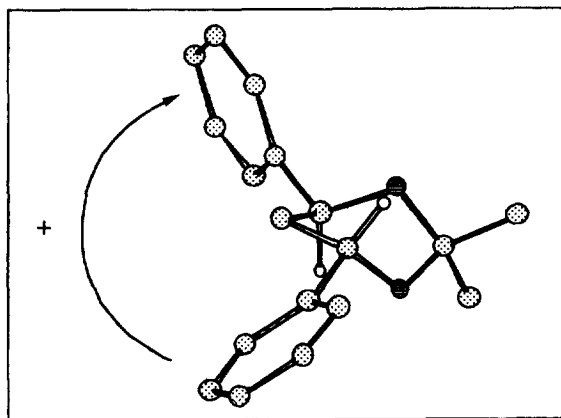


Figure 2. MMX most stable conformation of ketal (S,S)-(4). Only hydrogen atoms at stereogenic centers shown for clarity.

Molecular mechanic calculations¹⁵ showed that the phenyl groups of the (S,S) enantiomer of (4) in the most stable conformation (Figure 2) effectively describe a positive chirality, allowing us to conclude that such a configuration has to be assigned to (-)-(2) sample under investigation.

Conformational analysis also showed that the chirality defined by Ph groups of (S,S)-(4) remains positive through a large series of conformational changes, unless considering a highly unfavorable structure with both aromatic rings in pseudo-axial position, making very reliable our assignment.

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References and Notes

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8. The complex (**3**) was prepared treating (R)-(biphemp)Ru(OAc)₂ with 2 equivalents of HCl in methanol, stirring at r.t. for 2.5 hrs and eliminating volatiles under reduced pressure. See also Heiser, B.; Broger, E.A.; Cramer, Y. *Tetrahedron : Asymmetry*. **1991**, 2, 51.
9. Dibenzoylmethane (**1**) (22.3 mmol) was hydrogenated in EtOH-CH₂Cl₂ (10 ml) for 64 hrs at 40°C, under an initial hydrogen pressure of 100 atm (101300 hPa), in the presence of (**3**) (0.14 mmol). Filtration of the colorless crystals obtained afforded (-)-(**2**) having $[\alpha]^{20}_D = -74.4$ (C 0.97 EtOH_{ass.}) in 70% yield. Concentration of the mother liquors gave a second crop of crystals (16%) with $[\alpha]^{20}_D = -41.8$ (C 0.88 EtOH_{ass.}).
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11. 0.46 cm ϕ \times 25 cm by Daicel Chemical Industries, Ltd. 0.6 ml / min hexane : isopropyl alcohol = 90 : 10; in these conditions the k' values resulted : (R,R) = 4.1, (S,S) = (R*,S*) = 4.7 and the resolution R_s = 2.7.
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