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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 $[RuCl_2 {(R)-biphemp}]$ [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 acetonide 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 needing 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'-binaphtalene], 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 [RuCl₂(PPh₃){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 [RuCl₂{(R)-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 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-diphenyl-propan-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

- 1. Kobayashi, T.; Kakimoto, M.; Imai, Y. Polym. J. 1993, 25, 741.
- 2. Bakos, J.; Toth, I.; Heil, B. Tetrahedron Lett. 1984, 25, 4965.
- 3. Ito, K.; Harada, T.; Tai, A. Bull. Chem. Soc. Jpn. 1980, 53, 3367.
- Sayo, N.; Saito, T.; Kumobayashi, H.; Akutagawa, S.; Noyori, R.; Takaya, H. Eur. Pat. Appl. EP 297,752 (1989).
- 5. Yamamoto, K.; Ando, H.; Chikamatsu, H. J. Chem. Soc. Chem. Commun. 1987, 334.
- 6. Pini, D.; Iuliano, A.; Salvadori, P. Tetrahedron : Asymmetry. 1992, 3, 693.
- 7. Mezzetti, A.; Consiglio, G. J. Chem. Soc. Chem. Commun. 1991, 1675.

- 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.; Crameri, 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.}).
- 10. Pirkle, W.H.; Mahler, G.S.; Pochapsky, T.C.; Hyun, M.H. J.Chromatogr. 1987, 388, 307.
- 11. 0.46 cm $\phi \times 25$ 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 $R_s = 2.7$.
- 12. Rosini, C.; Scamuzzi, S.; Uccello-Barretta, G.; Salvadori, P.; J. Org. Chem. 1994, 59, 7395.
- 13. NMR data for (4) in CDCl₃. ¹H-NMR δ 1.54 (s, 6H), 2.26 (t, J = 7.8 Hz, 2H), 5.02 (t, J = 7.8 Hz, 2H), 7.15-7.50 (m, 10H). ¹³C-NMR δ 24.96, 41.51, 68.49, 101.10, 125.74, 127.23, 128.30, 142.35.
- Harada, N.; Nakanishi, K. "Circular Dichroic Spectroscopy-Exciton Coupling in Organic Chemistry", Oxford Press, 1983.
- 15. MMX routine; program PCModel, Serena Software.

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