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Optical Resolution and Absolute Configuration of Axially Dissymmetric 2,2′-Dihydroxy-6,6′-dimethylbiphenyl

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Synopsis. 2,2′-Dihydroxy-6,6′-dimethylbiphenyl (**1**) was successfully resolved into its optically pure forms by the recrystallization of the diastereomeric salts derived from the hydrogenphosphate of **1** and cinchonidine or quinine. The dextrorotatory **1** was determined to have R-configuration.

It is well-known that axially dissymmetric biaryl compounds possess salient ability for chiral recognition. 1,1′-Binaphthyl unit has been very common in the design and construction of chiral auxiliaries,[1)] while biphenyl[2,3)] and 9,9′- or 4,4′-biphenanthryl units[4)] have been applied as well. When biaryl derivatives, even though the nuclei of which are different from each other, have the same functional groups, they serve in most cases as quite similar catalysts for an asymmetric reaction with respect to stereochemistry.[3,5)] In some cases, however, we have observed that the stereochemical outcomes are in disagreement.[3,6)] Inspection of such results might provide an important clue of the consideration on the structure of active species or the steric factors operating in the reaction. It seems, therefore, to be important to compare the chiral catalysts derived from analogous biaryl compounds.

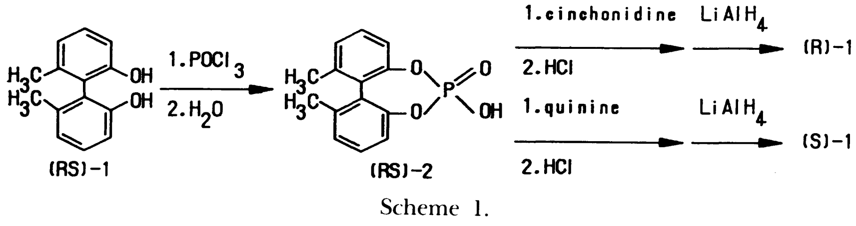
The most famous compound of a series of biaryls is 2,2′-dihydroxy-1,1′-binaphthyl, which is an important intermediate for the preparations of chiral crowns[7)] and the *BINAL-H* reagent[8)] as reported by Cram et al. and Noyori et al., respectively, and for the asymmetric Ullmann reaction as shown by Miyano.[9)] More recently, its biphenanthryl analogs have been resolved on an optically active column in a preparative scale.[4)]

Recently, we have reported briefly a synthesis of optically active 2,2′-dihydroxy-6,6′-dimethylbiphenyl (**1**) as a biphenyl analog and asymmetric reductions of alkyl phenyl ketones by using $LiAlH_4$- and borane-**1** complexes.[5,6)] In this paper, we wish to describe the effective optical resolution of (*RS*)-**1** in more detail. In addition, each resolved **1** was confirmed to be optically pure, and the absolute configuration was determined.

The preparation of (*RS*)-**1** was carried out according to the method described in the literature.[10)] The excellent method for the optical resolution of (*RS*)-2,2′-dihydroxy-1,1′-binaphthyl via its cyclic phosphate has been developed by Jacques et al.[11)] The procedure is essentially applicable to the present case, as shown in the scheme. (*RS*)-**1** was easily converted to (*RS*)-6,6′-dimethylbiphenyl-2,2′-diyl hydrogenphosphate (**2**) by the reaction with phosphoryl chloride followed by hydrolysis in a high yield. We found that cinchonidine or quinine readily forms crystalline salt with the opposite enantiomer of **2** to each other. In the first step, the diastereomeric salts were prepared by mixing equimolar amounts of (*RS*)-**2** and cinchonidine in aqueous methanol. The crystalline salt deposited upon cooling, and the filtration afforded (*R*)-**2**·cinchonidine salt in a satisfactory yield of 45% based on (*RS*)-**2** used. The mother liquor containing the salt of (*S*)-enriched **2** was unsuitable for recrystallization. Crystallinity was greatly improved by employing quinine as a resolving reagent. Simple recrystallization of a mixture of the recovered **2** and an equimolar amount of quinine from aqueous methanol gave (*S*)-**2**·quinine salt in 40% yield. Further recrystallization of both salts of cinchonidine and quinine did not come about noticeable change in optical rotation. Decomposition of each salt with a diluted hydrochloric acid yielded (*R*)-(−)- and (*S*)-(+)-**2** in 42 and 38%, respectively. Each alkaloid used was recovered from the acidic filtrates. Reductive cleavage of (−)- and (+)-phosphates with $LiAlH_4$ yielded optically active **1** in 37 and 33%, respectively (overall yields based on the starting (*RS*)-**1**), whose specific rotations were $[\alpha]_D^{18}$ +91.5° and $[\alpha]_D^{20}$ −91.1° (*c* 1.0, ethanol), respectively.

The optical purity of each **1** thus resolved was determined from the ^{1}H NMR spectrum of the methyl 6,6′-dimethylbiphenyl-2,2′-diyl phosphate (**3**) derived from the intermediate **2**, in the presence of $Eu(tfc)_3$. The spectra are shown in Fig. 1. In the case of racemic **3**, the signals due to the aromatic methyl protons and the ester methyl protons split owing to the diastereomeric lanthanoide induced shift. On the other hand, each of the spectra, measured under the same conditions, of the optically active **3** shows the lack of the peaks due to opposed enantiomer. This fact reveals that each resolved **2** was optically pure.

The (R)-configuration of (+)-**1** was determined by



Scheme 1.

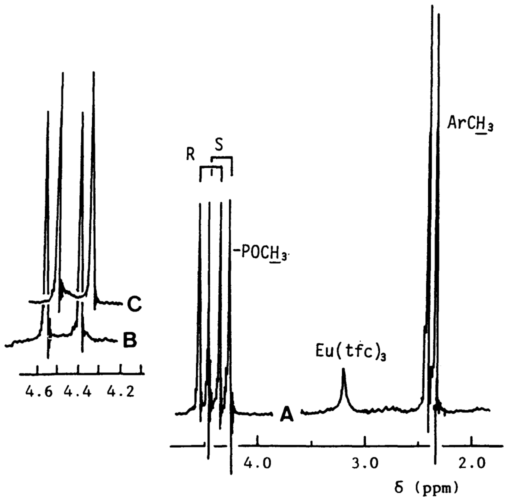


Fig. 1. ^{1}H NMR spectra of **3** (20 mg) in the presence of Eu(tfc)$_3$ (6 mg) in CDCl$_3$ (0.5 ml). A: (*RS*)-**3**, B: (*R*)-**3**, C: (*S*)-**3**.

chemical correlation with (+)-2,2′-diamino-6,6′-dimethylbiphenyl. The absolute configuration of the latter is known to be R from the X-ray crystallography of its *N,N′*-disalicylidene derivative,[12] and Sandmeyer-type reactions of biarylamines are known to proceed in a retention manner.[13] Thus, the optically pure (+)-diamine was treated with NaNO$_2$ in a diluted sulfuric acid. Thermal decomposition of the bis(diazonium) salt in an aqueous medium gave dextrorotatory **2**. The specific rotation ($[\alpha]_D^{19}$ +91.4° (*c* 1.0, ethanol)) is in good agreement with that observed for (+)-**1** resolved. This means that (+)-**1** has R-configuration.

More recently, Okamoto et al. have reported that racemic **1** of our sample can be directly resolved by a high performance liquid chromatography on optically active columns of cellulose tris(phenylcarbamate) derivatives.[14]

Experimental

Melting points are uncorrected. IR and NMR spectra were recorded on a JASCO A-202 and a JEOL JNM-PS-100 (100 MHz) spectrometer, respectively. Optical rotations were measured on a JASCO DIP-SL automatic polarimeter.

Racemic **1** was prepared through six-step reactions from *m*-cresol with slight modification of the reported method.[10] Mp 161.5—162.5 °C (lit,[10] 164 °C). IR (KBr) 3470, 3420, 1180 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=1.85 (s, 6H), 6.6—7.1 (m, 6H), 8.75 (s, 2H).

6,6′-Dimethylbiphenyl-2,2′-diyl Hydrogenphosphate (2). Fifty grams (0.23 mol) of (*RS*)-**1** and phosphoryl chloride (26 ml, 0.28 mol) were mixed in 230 ml of dichloromethane. Triethylamine (80 ml, 0.57 mol) was added dropwise to the stirred mixture under a gentle reflux. Reflux was continued for an additional 3 h. After cooling the precipitates were collected and washed thoroughly with cold water. The remaining solids were chlorophosphate of **1**. Extractive work-up of the filtrate led to an additional yield of the chloride. The combined crude chloride was hydrolyzed in a mixture of tetrahydrofuran (THF) (300 ml) and water (100 ml) with stirring at 50 °C for 3 h. The solution was freed from THF under reduced pressure, and the precipitates were collected. Recrystallization from aqueous methanol gave (*RS*)-**2** (61 g, 94% based on **1** used): mp 285—286 °C; IR (KBr) 3000—2000, 1255, 1215, 1020, 1000 cm^{-1}.

Optical Resolution of (*RS*)-2. All yields were based on (*RS*)-**2** used. Cinchonidine (68 g, 0.23 mol) and (*RS*)-**2** (61 g, 0.22 mol) were dissolved in 500 ml of boiling methanol. After the addition of 100 ml of water the solution was cooled in a refrigerator overnight. The crystals deposited were collected and washed with cold methanol to give (*R*)-**2**·cinchonidine salt (57 g, 45%): mp 185—188 °C (decomp); $[\alpha]_D^{24}$ −155° (*c* 0.5, methanol). The cinchonidine salt was decomposed in 6 mol dm^{-3} HCl (700 ml) with stirring at 50 °C for 1 h. After cooling the precipitates were collected. Recrystallization from aqueous methanol gave (*R*)-**2** (25.5 g, 42%): mp 299—305 °C (decomp); $[\alpha]_D^{19}$ −179° (*c* 0.5, methanol).

The (*S*)-enriched **2** was recovered by evaporating the mother liquor to dryness and subsequently treating the gamy residue with 6 mol dm^{-3} HCl. It was similarly reacted with an equimolar amount of quinine, and recrystallization from aqueous methanol gave (*S*)-**2**·quinine salt: mp 276—278 °C (decomp); $[\alpha]_D^{18}$ −43.0° (*c* 0.5, methanol). Decomposition of the salt followed by recrystallization in a similar way yielded (*S*)-**2** (23 g, 38%): mp 299—304 °C (decomp); $[\alpha]_D^{18}$ +177° (*c* 0.5, methanol).

Methyl 6,6′-Dimethylbiphenyl-2,2′-diyl Phosphate (3). In order to determine the optical purity of each resolved **2**, it was suspended in diethyl ether and treated with a large excess amount of diazomethane in ether. After standing overnight, removal of the solvent and drying under vacuum gave **3** in a nearly quantitative yield. The ^{1}H NMR spectrum of **3** (20 mg) was measured in a CDCl$_3$ solution (0.5 ml) containing Eu(tfc)$_3$ (6 mg) at room temperature. Crystalline **3** was obtained by recrystallizing from chloroform-ether in about 90% yield. (*RS*)-**3**: Mp 219—220 °C; IR (KBr) 2860, 1300, 1235, 1050, 1005 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=2.21 (s, 6H), 3.94 (d, 3H, J_{PH}=11 Hz), 7.0—7.5 (m, 6H). (*R*)-**3**: Mp 227—228 °C; $[\alpha]_D^{20}$ −119° (*c* 0.5, methanol). (*S*)-**3**: Mp 226—228 °C; $[\alpha]_D^{19}$ +117° (*c* 0.5, methanol).

(*R*)-/(*S*)-1. Powdered LiAlH$_4$ (8.4 g, 0.22 mol) was added in portions into a stirred suspension of the above phosphate (−)-**2** (25.5 g, 92 mmol) in dry THF (350 ml) at 0 °C. After the mixture was refluxed for 5 h, the reaction was quenched by successive additions of ethyl acetate, moist ether, and 6 mol dm^{-3} HCl with stirring at 0 °C. The organic layer was separated, washed with dil HCl and brine, and dried over Na$_2$SO$_4$. Evaporation of the solvents followed by recrystallization from benzene-petroleum ether gave (*R*)-**1** (18.4 g, 39% based on (*RS*)-**2** used): Mp 159—160 °C; $[\alpha]_D^{18}$ +91.5° (*c* 1.0, ethanol). Similarly, reduction of (+)-**2** led to (*S*)-**1** (16.5 g, 35%): Mp 159—160 °C; $[\alpha]_D^{20}$ −91.1° (*c* 1.0, ethanol).

Chemical Correlation between (+)-1 and (*R*)-2,2′-Diamino-6,6′-dimethylbiphenyl. A solution of the (*R*)-(+)-diamine (2.0 g, 9.3 mmol) ($[\alpha]_D^{25}$ +50.5° (*c* 1.0, ethanol))[15] in 25% aqueous sulfuric acid (25 ml) was cooled at 0 °C. To this was added an aqueous NaNO$_2$ (1.74 g, 25 mmol) with stirring at 0—5 °C. The resulting solution of the bis(diazonium) salt was occasionally dropped in small portions into a boiling solution of Na$_2$SO$_4$ (80 g) in 18 mol dm^{-3} H$_2$SO$_4$ (100 ml) over a period of 2 h. During the reaction, products were distilled away by bubbling steam into the reaction mixture. The distillate was extracted with ether. The organic layer was decolorized with charcoal and dried over Na$_2$SO$_4$. After the ether was removed, recrystallization gave (+)-**1** (0.17 g, 9%). The selected spectroscopic data were in agreement with those of the authentic sample. *Mp 159—160 °C*, $[\alpha]_D^{19}$ +91.4° (*c* 1.0, ethanol).

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