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A Practical Method for Optical Resolution of 1,1′-Binaphthyl-2,2′-dicarboxylic Acid via 1-Phenylethylamides

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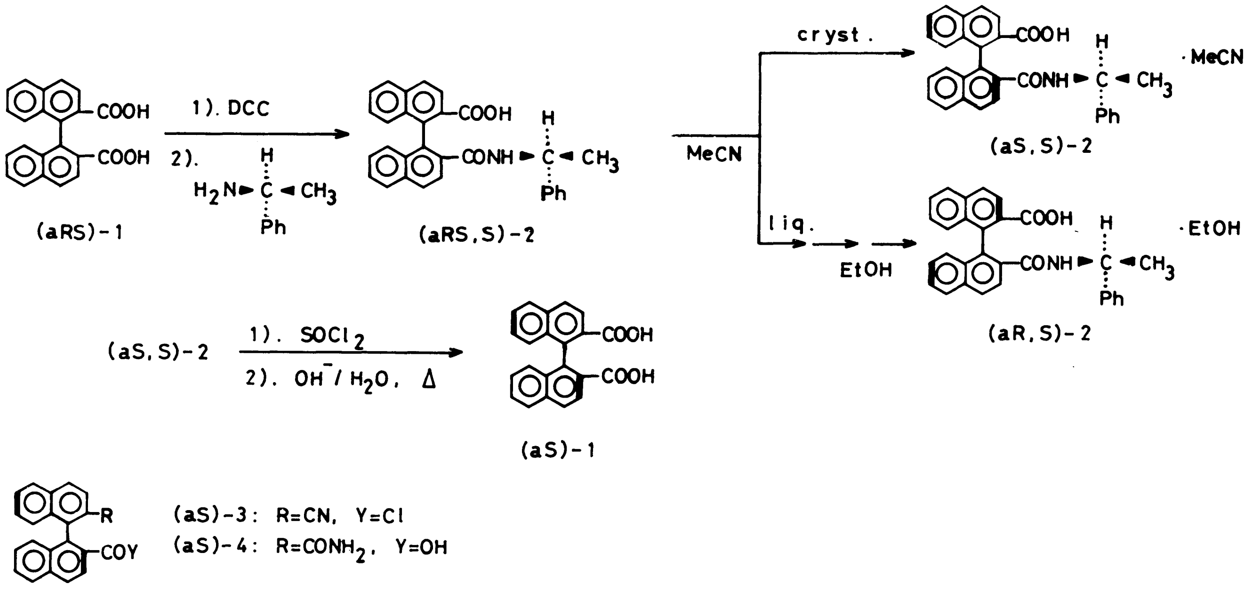
Synopsis. Both enantiomers of 1,1′-binaphthyl-2,2′-dicarboxylic acid (100% ee's by HPLC) were conveniently obtained in high yields (ca. 80% of the theory) via fractional crystallization of the (*S*)-1-phenylethylamide diastereomers of the racemic acid followed by treatment with thionyl chloride and then alkaline hydrolysis.

Since Kuhn and Albrecht first resolved 1,1′-binaphthyl-2,2′-dicarboxylic acid **1** in 1928,[1] optically active **1** has been widely utilized for the preparation of various axially chiral binaphthyl derivatives.[2,3] Recently increasing attention has been centered on **1** as it has become to be known that **1** shows characteristic features not only as chiral host for selective inclusion of enantiomeric alcohols[4] but also as chiral stationary phase for direct discrimination of various enantiomers.[5] The enantiomers of **1** have conventionally been obtained by means of an optical resolution through its quinine salt. But the procedure is rather tedious, and efficiency of resolution was low.[2,6] Quite recently Suda and his co-workers have reported an improved optical resolution of **1**, while it still requires to use highly toxic brucine as the resolving agent.[7]

In this paper, we report another practical method for optical resolution of **1** in substantial quantities via 1-phenylethylamide diastereomers (Scheme 1). Treatment of (a*RS*)-**1**[8] with dicyclohexylcarbodiimide (DCC) gave acid anhydride(s),[9] which in turn allowed to react with ca. 1.2 equiv of (*S*)-1-phenylethylamine to give the pair of the diastereomeric mono amides ((a*R*,*S*)- and (a*S*,*S*)-**2**) in quantitative yield. Upon trying various solvents, we have eventually found that acetonitrile is the specific medium to crystallize (a*S*,*S*)-**2** from the mixture. The (a*S*,*S*)-**2** was obtained as fine crystals of a 1:1 clathrate with acetonitrile; the yield amounted to 86% based on one of the enantiomers of **1** with more than 99% diastereomeric excess (de) as evidenced by HPLC. The filtrate was recrystallized twice from ethanol to give the (a*R*,*S*)-counterpart as a 1:1 clathrate with ethanol in a 81% yield and here again in essentially diastereomerically pure state.

The amide bond of **2** was intact by treatment with aqueous sodium hydroxide or sulfuric acid. Eventually, diastereomeric **2** was first treated with thionyl chloride to give the nitrile **3** (the von Brawn reaction),[10] which was then hydrolyzed to the free diacid ((a*R*)- or (a*S*)-**1**) without any appreciable racemization nevertheless rather severe reaction conditions.

Although the resolution method disclosed here requires amides formation followed by regeneration of the free acids, the procedure is operationally simple and straightforward, and applicable to obtain substantial quantities of optically pure **1**, using rather inexpensive enantiomeric 1-phenylethylamine as the resolving agent. Another merit of the procedure is that diastereomeric purity of **2** is readily checked by HPLC to ensure the obtention of enantiomerically pure **1**.[11]



Scheme 1.

Experimental

Instruments. HPLC measurements were carried out on a JASCO TRIROTAR-III equipped with a JASCO UVIDEC-100-III ultraviolet detector (254 nm). IR spectra were measured on a Shimadzu IR-430 grating spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX 60 instrument with tetramethylsilane as an internal standard. Optical rotations were recorded on a Union PM-101 automatic digital polarimeter in a 1-cm cell at 23—25 °C. Melting points were measured on a Yamato MP-21 apparatus and are uncorrected.

Materials. (a*RS*)-**1** was obtained according to the literature procedure;[2,12] mp 271—272.5 °C; IR (KBr) 3500—2300, 1690, 1280, 1240, and 1130 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=12.2 (2H, br, s, -COOH) and 6.6—8.2 (12H, m, ArH). (*S*)-1-Phenylethylamine ($[\alpha]_D=-38.0$° (*c* 2, ethanol)) and DCC were used as purchased. Thionyl chloride and recrystallization solvents (acetonitrile and ethanol) were distilled before use.

Preparation and Separation of Diastereomeric Amides from (*S*)-1-Phenylethylamine and (a*RS*)-1. To a stirred solution of (a*RS*)-**1** (15.0 g, 43.8 mmol) in THF (150 ml) was added a solution of DCC (9.04 g, 43.8 mmol) in THF (100 ml) at room temperature for 1 h under a nitrogen atmosphere. The mixture was stirred for another 2 h at that temperature, and then heated at reflux for 4 h. After triethylamine (5 ml) and (*S*)-1-phenylethylamine (6.37 g, 52.6 mmol) were added to the hot mixture, it was refluxed for 3 h. The mixture was allowed to cool to room temperature, precipitated *N,N'*-dicyclohexylurea was filtered off, and the solids were rinsed with small portions of THF. The solvent was removed from the filtrate under reduced pressure, and the residue was dissolved in 200 ml of chloroform. The solution was washed with concd HCl (200 ml×2) and then with water (200 ml×4), dried over $MgSO_4$ in the presence of activated charcoal. After filtration, the solvent was evaporated in vacuo to give crude (a*RS,S*)-**2**.

The (a*RS,S*)-**2**, which was contaminated with a small amount of *N,N'*-dicyclohexylurea, was directly dissolved in 1000 ml of acetonitrile, and then 700 ml of the solvent was distilled off under atmospheric pressure. The remaining solution was kept overnight at 4 °C to give 9.14 g (85.8% yield, >99% de by HPLC[13]) of (a*S,S*)-**2** clathrated with 1 mol of acetonitrile; mp 190.5—192 °C; $[\alpha]_D=-123.3$° (*c* 1.04, chloroform); IR (KBr) 3500—2500, 3260, 1703, 1595, and 1565 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=0.99 (3H, d, -CH_3), 2.05 (3H, s, acetonitrile), 4.6 (1H, m, CH), and 6.3—8.5 (18H, m, NH and ArH). Found: C, 79.27; H, 5.67; N, 5.29%. Calcd for $C_{30}H_{23}NO_3\cdot C_2H_3N$: C, 78.99; H, 5.39; N, 5.76%.

The solvent of the mother liquor from the above crystallization was removed under reduced pressure. The residue was dissolved in 260 ml of ethanol with warming, and then 150 ml of which was distilled off under atmospheric pressure. The remaining solution was kept overnight at 4 °C. The precipitated crystals were recovered by filtration (9.12 g), and were again dissolved in 250 ml of ethanol. The solvent was distilled (108 ml) until just prior to causing cloudiness of the solution. The solution was kept overnight at 4 °C to give 8.68 g (80.6% yield, >99% de by HPLC) of (a*R,S*)-**2**; mp 260—261 °C; $[\alpha]_D=+183.2$° (*c* 1.01, chloroform); ^{1}H NMR (DMSO-d_6) δ=0.79 (3H, d, -CH_3), 1.0 (3H, t, ethanol -CH_3), 3.4 (2H, q, ethanol -CH_2-), 4.6 (1H, m, CH), 6.6—8.2 (17H, m, ArH), and 8.3 (1H, d, NH). Found: C, 78.25; H, 6.09; N, 2.91%. Calcd for $C_{30}H_{23}NO_3\cdot C_2H_6O$: C, 78.19; H, 5.95; N, 2.85%.

Regeneration of Axially Homochiral (a*S*)-1. To the 9.14 g (18.8 mmol) of (a*S,S*)-**2** were added 100 ml of thionyl chloride and one drop of DMF, and the mixture was refluxed for 3 h. The excess of thionyl chloride was distilled out, and the residue was dried at 70 °C under vacuum to give (a*S*)-**3**, which was substantiated by IR as methyl ester by treatment with methanol; IR (KBr) 2200 and 1715 cm^{-1}. The crude (a*S*)-**3** was directly dissolved in 130 ml of ethanol with warming, and 10 g of KOH in 30 ml of water was added and then refluxed for 5 h to give amide (a*S*)-**4** as evidenced by IR; (KBr) 3500—2500, 3400, 1700, and 1640 cm^{-1}. After volatiles were removed under reduced pressure, the residue was suspended in a solution of 50 g of NaOH in 400 ml of water and heated at reflux; the mixture became almost clear solution after 10-h heating, and the reaction was continued for another 30 h to ensure complete hydrolysis, while almost all the hydrolysis seemed to be completed by 20-h heating. After cooling to room temperature, 200 ml of water was added and washed with ether (200 ml×2) to remove nonacidic compounds. The aqueous solution was acidified with concd HCl and the precipitate was extracted with ethyl acetate (150 ml×3). The combined organic layer was dried over $MgSO_4$ in the presence of activated charcoal. After filtration, the solvent was evaporated in vacuo and recrystallization from toluene gave 5.84 g (91% yield) of (a*S*)-**1**, which was of essentially 100% ee as evidenced by HPLC; a small sample of the acid was converted to the bis(butylamide) and subjected to HPLC analysis on a chiral stationary phase as reported before;[14] mp 165—167 °C;[15] $[\alpha]_{546}=-126.2$° (*c* 1.05, 0.1 mol dm^{-3} NaOH) (lit,[7] $[\alpha]_{546}=-127$° (*c* 1.0, 0.1 mol dm^{-3} NaOH)).

(a*R*)-2: Similar treatment of 8.68 g (17.7 mmol) of (a*R,S*)-**2** gave 5.69 g (94% yield, 100% ee by HPLC) of (a*R*)-**1**.

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8) The subscript "a" refers to axial chirality.

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