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Practical Method for the Synthesis and Optical Resolution of Axially Dissymmetric 6,6′-Dimethylbiphenyl-2,2′-dicarboxylic Acid

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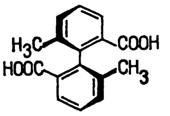
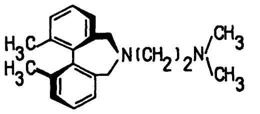
Racemic 6,6′-dimethylbiphenyl-2,2′-dicarboxylic acid (**1**) could be conveniently synthesized and efficiently resolved by the recrystallization of the brucine salts in satisfactory yields. Each enantiomer, thus obtained, was confirmed to be optically pure from a high-performance liquid chromatographic (HPLC) analysis on an optically active column.

N,N- and *N,N*:*N′,N′*-[(Axially dissymmetric biphenyl-2,2′-diyl)dimethylene]-substituted ethylenediamines, such as **2** and **3**, have been found to serve as very efficient chiral ligands for organolithium compounds in the asymmetric polymerization of triphenylmethyl methacrylate[1,2] and the enantioface-differentiating alkylation of aldehydes.[3] A highly asymmetric induction in these reactions is considered to be due to a complementary effect between the high ability of the biphenyl unit for chiral recognition[4] and the flexibility of the tetramethylethylenediamine side-arm for chelation with organolithium compounds.[5] The key intermediate in the syntheses of ligands **2** and **3** is axially dissymmetric 6,6′-dimethylbiphenyl-2,2′-dicarboxylic acid (**1**) as optically pure forms. Therefore, the development of a convenient method for the synthesis and optical resolution of the diacid is practically important from the viewpoint of a ready application of such ligands to asymmetric reactions.


(R)-1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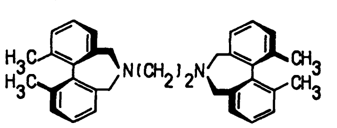
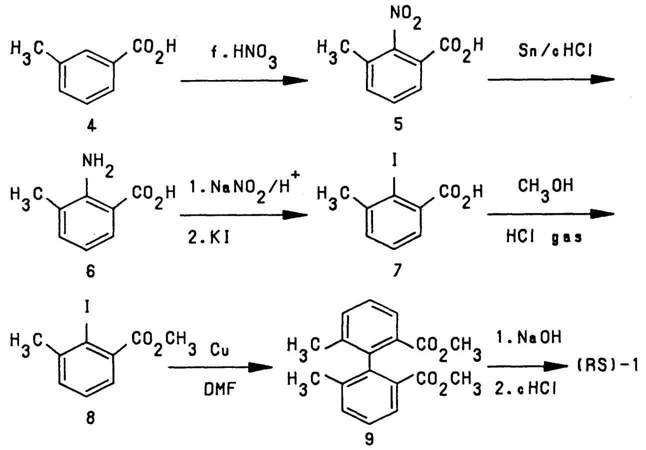

(R,R)-3

Recently, we have reported asymmetric polymerizations of triphenylmethyl methacrylate by using chiral complexes of organolithium with **2** or **3**.[1,2] During the course of these investigations, we intended to develop a more convenient preparation of the chiral ligands. In this paper, we wish to describe a facile synthesis of (*RS*)-**1** and its efficient optical resolution through the recrystallization of the brucine salt. The resolved acids were confirmed to be optically pure by means of a high-performance liquid chromatography (HPLC) with an optically active column.



Scheme 1.

The synthesis of (*RS*)-**1** has been outlined briefly by two research groups.[6,7] However, these papers failed to give the detailed procedures. Our approach to (*RS*)-**1** is represented in the above scheme; details are described in Experimental. The first stage of the synthesis is the nitration of *m*-toluic acid. Even after the optimization of the reaction conditions, the yield was as low as 49%, owing to an inevitable formation of nitrated isomers. However, the poor solubility of 2-nitro-3-methylbenzoic acid (**5**) in cold fuming nitric acid facilitated the separation of **5** from undesirable isomers by a simple suction-filtration. The subsequent steps were conducted in a combination of common procedures, resulting in satisfactory yields.

The first optical resolution of (*RS*)-**1** was carried out with morphine by Bell.[7] Since then, this method has been followed essentially by later investigators.[8,9] However, different specific rotations ranging from +15 to +25° in methanol at 589 nm have been reported for the (+)-acid resolved.[7-9] Moreover, it has been very difficult to obtain optically pure (−)-enantiomer, since the recrystallization of morphine salt of (−)-**1** was not successful.[7]

Bell[7] also reported that an attempt to resolve (*RS*)-**1** with brucine was unsuccessful. We succeeded to resolve the diacid by using this alkaloid.[1] Details of the procedure is as follows. A reaction of (*RS*)-**1** with an equimolar amount of brucine gave a mixture of the diastereomeric salts. In order to effectively separate this mixture into each salt, it was found that solvent systems for recrystallization were extremely important. One recrystallization of the diastereomeric salts from a mixture of methanol–acetone (7/3 v/v) gave levorotatory brucine salt of (*S*)-**1**, the yield of which was 40% based on (*RS*)-**1** used. The optical purity of this salt seemed to be nearly 100%, since further recrystallization did not cause any noticeable change in the optical rotation. Subsequently, when the solvents of the mother liquor were replaced with acetone alone, crystallization of another diastereomeric salt started. The (+)-salt obtained was recrystallized from acetone containing a small amount of methanol to give pure brucine salt of (*R*)-**1** in 43% yield. Further recrystallizations of the last residue remaining in the acetone solution led to additional yields of the individual salts. The decomposition of each salt with diluted hydrochloric acid gave (*S*)- and (*R*)-**1** in 43 and 42% overall yields, respectively; the absolute configuration has been established.[9] As a matter of course, most of the resolving agent was recovered.

Optical purities of (+)- and (−)-**1**, thus resolved, were determined from HPLC analyses of the dimethyl esters **9** derived from the diacids. The column used was an optically active column, **CHIRALCEL OC**, which is commercially available from *Daicel Chemical Industries Ltd.*; the packing material is cellulose tris(phenylcarbamate) coated on a macroporous silica gel.[10] Base-line resolution of racemic **9** was accomplished with this column, using hexane–2-propanol (9/1 v/v) as an eluent.[11] Figure 1 shows the chromatograms of (+)- and (−)-**9** under the same operation conditions as those for the racemate. Each major peak in the curves appeared at a different retention volume, which is nearly in agreement with that of either two peaks in the enantiomeric separation observed for the racemate. An inspection of the curves reveals that each of the samples probably contains a very small amount of the opposite enantiomer. Based on the relative peak area, the optical purities of (+)- and (−)-diesters were estimated to be 99.1 and 99.6%, respectively. From the chromatographic results, each of the diacids **1** resolved in the present study may be regarded as almost optically pure. The completely pure enantiomers, if required, are obtainable by a recrystallization from benzene.

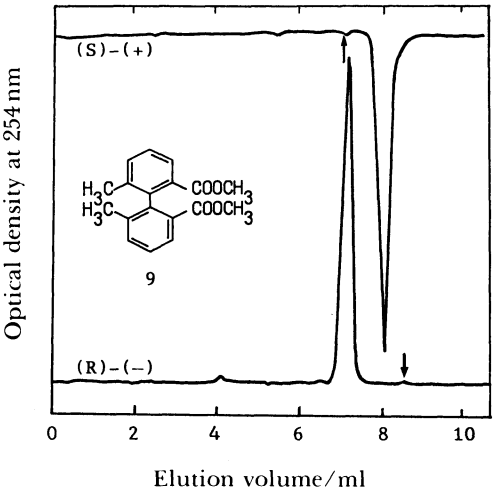


Fig. 1. Chromatograms of the dimethyl esters **9** derived from optically resolved **1**. The peaks marked with arrows are probably due to the minor enantiomers. Column: **CHIRALCEL OC** (*Daicel Chemical Industries Ltd.*), 25×0.46 (i.d.) cm; eluent: hexane–2-propanol (9/1 v/v); flow rate: 0.2 ml min^{-1} at 25 °C; detector: UV at 254 nm.

The present procedure for the optical resolution of (*RS*)-**1** seems advantageous regarding the use of cheaper brucine, an easy access of nicely recrystallizable salts with both enantiomers and, above all, an operational simplicity and high efficiency of the resolution.

Experimental

Melting points are uncorrected. IR and ^{1}H NMR spectra were recorded on a JASCO A-202 and a JEOL JNM-FX-100S (100 MHz) spectrometer, respectively. Optical rotations were measured on a JASCO DIP-360 digital polarimeter. A determination of the optical purities of (+)- and (−)-**9** was performed by using an HPLC on an optically active column, **CHIRALCEL OC** (*Daicel Chemical Industries Ltd.*; 25×0.46 (i.d.) cm). Resolution was carried out with hexane–2-propanol (9/1 v/v) at a flow rate of 0.2 ml min^{-1} at 25 °C.

Preparation of (*RS*)-2,2′-Dimethylbiphenyl-6,6′-dicarboxylic Acid (1). 2-Nitro-3-methylbenzoic Acid (5): *m*-Toluic acid (**4**) (200 g, 1.47 mol) was added in small portions to 500 ml of fuming nitric acid (d=1.52) with stirring at −10 °C. Stirring was continued for an additional 1 h at this temperature. The precipitate was collected by a suction-filtration with a large sintered-glass filter as quickly as possible, and thoroughly washed with water. Recrystallization from ethanol yielded 130 g (49%) of **5**. Mp 218—219 °C (lit,[12] 219 °C); IR (KBr) 3200—2400, 1690, 1550, 1375, and 1300 cm^{-1}; ^{1}H NMR (DMSO-d_6/D_2O) δ=2.32 (s, 3H), 7.5—7.9 (m, 3H).

2-Amino-3-methylbenzoic Acid (6): Tin powder (220 g, 1.85 mol) was suspended in a solution of **5** (120 g, 0.66 mol) in ethanol (500 ml). To the stirred mixture was added dropwise 1.3 l of 9 mol dm^{-3} hydrochloric acid at 50—60 °C. The resulting solution was stirred for 1.5 h at 70 °C, cooled, and then made alkaline by the addition of concd. aqueous NH_3. Inorganic precipitates were removed and the filtrate was freed from ethanol by evaporation under reduced pressure. The resulting solution was acidified with acetic acid (pH=5). The precipitate was collected and dissolved in acetone. After the removal of insoluble materials and then the solvent, recrystallization of the residue from ethanol gave 89 g (89%) of **6**. Mp 174—175 °C (lit,[12] 172 °C); IR (KBr) 3500, 3380, 3200—2400, 1670, 1575, and 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$/D_2O) δ=2.18 (s, 3H), 6.5—7.9 (m, 3H).

2-Iodo-3-methylbenzoic Acid (7): A suspension of **6** (75 g, 0.5 mol) in a mixture of concd. H_2SO_4 (300 ml) and water (600 ml) was stirred for 1 h at room temperature, and then a solution of $NaNO_2$ (45 g, 0.65 mol) in 75 ml of water was added drop by drop at 10 °C. The excess nitrite was decomposed with urea. To the solution were added in one portion a saturated aqueous solution of KI (420 g, 2.5 mol) and a small amount of copper powder,[13] which was prepared by the reduction of copper(II) sulfate with zinc powder. Vigorous stirring was continued for 3 h at about 30 °C, and the mixture was allowed to stand overnight. The supernatant solution was decanted and a brownish precipitate was dissolved in benzene. The benzene solution was decolorized with aqueous $NaHSO_3$, followed by evaporation under reduced pressure. Recrystallization from aqueous ethanol yielded 106 g (81%) of **7**. Mp 143—144 °C (lit,[6] 145—146 °C); IR (KBr) 3200—2400, 1700, and 1290 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.56 (s, 3H), 7.2—7.7 (m, 3H), 9.5 (br s).

Methyl 2-Iodo-3-methylbenzoate (8): A solution of **7** (129 g, 0.49 mol) in 650 ml of methanol was saturated with hydrogen chloride; the gas was then passed through the refluxing solution for 1 h. The usual extractive work-up, followed by distillation under reduced pressure, gave 128 g (94%) of **8**. Bp 130—140 °C (5 mmHg (1 mmHg=133.322 Pa)) (lit,[8] 156.5—157.5 °C (13 mmHg)); IR (liquid film) 1730, 1295, and 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.50 (s, 3H), 3.92 (s, 3H), 7.2—7.4 (m, 3H).

Methyl 6,6′-Dimethylbiphenyl-2,2′-dicarboxylate (9): A solution of **8** (209 g, 0.76 mol) in 210 ml of *N,N*-dimethylformamide was mixed with activated copper powder[14] (100 g), and gently refluxed for 5 h. The copper was filtered off and thoroughly washed with hot benzene. The combined filtrates were washed with water, 1 mol dm^{-3} HCl, aqueous $NaHCO_3$, and then brine. After the solvents were removed, distillation under reduced pressure gave 91 g (80%) of **9**. Bp 150—160 °C (0.05 mmHg) (lit,[8] 197—198 °C (13 mmHg)); IR (liquid film) 1735, 1280, and 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.91 (s, 6H), 3.57 (s, 6H), 7.2—7.9 (m, 6H).

6,6′-Dimethylbiphenyl-2,2′-dicarboxylic Acid (1): The diester **9** (116 g, 0.39 mol) was refluxed in a solution of 150 g of NaOH in 800 ml of water for 5 h. The mixture was acidified by the addition of concd. HCl with cooling and the precipitate was collected. Recrystallization from aqueous ethanol yielded 100 g (95%) of **1**. Mp 240—241 °C (lit,[9] 236—237.5 °C); IR (KBr) 3300—2400, 1700, and 1280 cm^{-1}; ^1H NMR (DMSO-d_6/D_2O) δ=1.81 (s, 6H), 7.3—7.8 (s, 6H). Found: C, 71.06; H, 5.05%. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22%.

Optical Resolution of (*RS*)-1. Brucine (100 g, 0.26 mol) and (*RS*)-**1** (69 g, 0.26 mol) were dissolved in a refluxing mixture of methanol (420 ml) and acetone (180 ml). After the solution was cooled at room temperature overnight, the colorless needles deposited were collected by filtration and washed with cold methanol: Brucine salt of (*S*)-**1**, 68 g (40% yield); $[\alpha]_D^{25}$ −39.2° (*c* 1.0, methanol). When a part of the first crop was recrystallized from acetone, the resulting salt showed a similar rotation of $[\alpha]_D^{25}$ −38.9°. The solvents of the mother liquor were evaporated under reduced pressure and the oily residue was dissolved in 200 ml of acetone on heating. Cooling the solution in a refrigerator overnight gave 78 g of colorless cubics, which showed $[\alpha]_D^{25}$ +37.1° (*c* 1.0, methanol). After the recrystallization of the (+)-salt from acetone containing a small amount of methanol, the resulting (+)-salt showed a slightly higher rotation of $[\alpha]_D^{25}$ +38.1 (*c* 1.0, methanol), and the rotation was not changed by further recrystallization. The yield of brucine salt of (*R*)-**1** was 43% (73 g). Additional recrystallizations of the last residue, in turn from methanol-acetone (7/3 v/v) and acetone alone, gave small amounts of the (−)- and (+)-salts in 5 and 2%, respectively.

The combined (−)-salts (77 g, 0.12 mol) were decomposed in 250 ml of 1 mol dm^{-3} HCl and the equal volume of ethyl acetate with stirring at 50 °C. The organic extracts were washed with 1 mol dm^{-3} HCl and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residual oil, which gradually solidified, was dried under reduced pressure to give 30 g of (*S*)-**1** (43% yield based on (*RS*)-**1** used).[15] It was possible to recrystallize the diacid from benzene. Mp 211—212 °C (lit,[9] 211.5—213.5 °C); $[\alpha]_D^{25}$ +22.1° (*c* 1.0, methanol) (lit,[9] $[\alpha]_D^{25}$ +25° (*c* 1.2)).

The (+)-salt (76 g, 0.11 mol) was similarly converted back to (*R*)-**1** in 42% yield.[15] Mp 213—214 °C (lit,[9] 207—211 °C); $[\alpha]_D^{25}$ −21.3° (*c* 1.0, methanol) (lit,[9] $[\alpha]_D^{23}$ −22° (*c* 1.0)). More than 90% of brucine used were recovered from the acid extracts combined, by the recrystallization from ethanol.

In order to determine the optical purity of the resolved **1**, it was converted to the dimethyl ester **9**. Thus, an ethereal suspension of optically active **1** before recrystallization was treated with a large excess of diazomethane in tetrahydrofuran at room temperature; then, the solvents were removed. The chromatographic sample was purified by a simple distillation of the residue under reduced pressure. The yield of **9** was nearly quantitative. (*R*)-**9**, $[\alpha]_D^{25}$ −55.3° (*c* 2.0, benzene) (lit,[8] $[\alpha]_D^{25}$ −45.1° (*c* 1.3)). (*S*)-**9**, $[\alpha]_D^{25}$ +55.8° (*c* 2.0, benzene) (lit,[8] $[\alpha]_D^{25}$ +55.2° (*c* 2.0)).

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References

1) S. Kanoh, H. Suda, N. Kawaguchi, and M. Motoi, *Makromol. Chem.*, **187**, 53 (1986).

2) S. Kanoh, N. Kawaguchi, T. Sumino, Y. Hongoh, and H. Suda, *J. Polym. Sci., Part A, Polym. Chem.*, **25**, 1603 (1987).

3) When the ligands, (*S*)-**2** and (*S,S*)-**3**, complexed to butyllithium were reacted with, for example, benzaldehyde in dry diethyl ether at −78 °C, according to the Cram's alkylation conditions, (*S*)-enriched 1-phenyl-1-pentanols were obtained in both cases in the optical yields of 56 and 89%, respectively; J.-P. Mazaleyrat and D. J. Cram, *J. Am. Chem. Soc.*, **103**, 4585 (1981).

4) S. Kanoh, N. Kawaguchi, and H. Suda, *Makromol. Chem.*, **188**, 463 (1987).

5) A. W. Langer Jr., *Adv. Chem. Ser.*, **1974**, 1.

6) F. Mayer, *Ber. Dtsch. Chem. Ges.*, **44**, 2298 (1911).

7) F. Bell, *J. Chem. Soc.*, **1934**, 835.

8) G. Wittig and H. Zimmermann, *Chem. Ber.*, **86**, 629 (1953).

9) M. Siegel and K. Mislow, *J. Am. Chem. Soc.*, **80**, 473 (1957).

10) Y. Okamoto, M. Kawashima, and K. Hatada, *J. Chromatogr.*, **363**, 173 (1986).

11) Results of the chromatographic resolution of (*RS*)-**9**:

capacity factors, k_1' (to less retained (*R*)-**9**)=1.22 and k_2'=1.51; separation factor, α=1.24; resolution factor, R_S=1.84; the void volume of the column was estimated to be 3.23 ml with a nonretained compound, 1,3,5-tri-*t*-butylbenzene.

12) W. Findeklee, *Ber. Dtsch. Chem. Ges.*, **38**, 3553 (1905).

13) F. B. Dains and F. Eberly, *Org. Synth.*, Coll. Vol. II, 355 (1943).

14) R. C. Fuson and E. A. Cleveland, *Org. Synth.*, Coll. Vol. III, 339 (1955).

15) It may be recommended that the resolved acid, without recrystallization, is esterified with methanolic hydrogen chloride and the resulting diester **9** is purified by distillation (the yield > 95%).