# Practical Synthesis of Optically Active 6,6′-Dichloro-2,2′-dipfenic Acid and Its Dimethyl Ester

Seitaro SAEKI,* Tomoko OKA, Takeshi HAYAKAWA and Kiyoshi SAKAI

*Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812, Japan.* *Received January 10, 1989*

**A practical synthetic route to optically active 6,6′-dichloro-2,2′-diphenic acid (III) and its dimethyl ester (IV) was developed.**

**Keywords** diphenyl; diazo coupling reaction; (*R*)-(+)-6,6′-dichloro-2,2′-diphenic acid; (*S*)-(−)-6,6′-dichloro-2,2′-diphenic acid; (*R*)-(+)-dimethyl 6,6′-dichloro-2,2′-diphenate; (*S*)-(−)-dimethyl 6,6′-dichloro-2,2′-diphenate; optical resolution

Recently, much attention has been centered on asymmetric synthesis by the use of axially chiral biaryls as chiral auxiliaries. For example, the 2,2′-bis(diphenylphosphino)-1,1′-dinaphthyl (BINAP)-coordinated Rh(I) and Ru(II) complexes have shown to be efficient catalysts for asymmetric hydrogenation of olefins and ketones.[1a,b] Their application to the asymmetric synthesis of natural products has been reported.[2a,b] Furthermore, these chiral complexes play a very important role in the industrial synthesis of (−)-menthol.[3a,b]

We have investigated the synthesis of optically active 6,6′-dichloro-2,2′-diphenic acid and its derivatives as potential chiral reagents and chiral auxiliaries.

Christie *et al.*[4] have reported the synthesis of dimethyl 6,6′-dichloro-2,2′-diphenate from 2-amino-3-methylnitrobenzene *via* nine steps, but the yield was not described. Considering that the diazonium salt coupling reaction gave tetrachlorodiphenic acid in good yield,[5] we undertook the synthesis of 6,6′-dichloro-2,2′-diphenic acid starting from the commercially available 3-chloro-2-nitrobenzoic acid (I), as shown in Chart 1.

3-Chloro-2-nitrobenzoic acid (I) was subjected to reduction by using NaBH$_4$–NiCl$_2$[6] to give the anilino compound (II) in 85% yield. The diazonium salt prepared from (I) with sodium nitrite underwent a reductive coupling reaction in the presence of cuprous cation to afford crude 6,6′-dichloro-2,2′-diphenic acid (III) in quantitative yield. Because of the difficulty of purification, this acid (III) was converted by dimethyl sulfate treatment to dimethyl 6,6′-dichloro-2,2′-diphenate (IV), which was recrystallized from hexane to give the pure ester as fine white crystals, mp 161 °C. Hydrolysis of the pure ester (IV) with KOH in methanol–water (3 : 1) gave the pure acid (III), mp 157 °C. The overall yield from the starting material (I) was 76%.

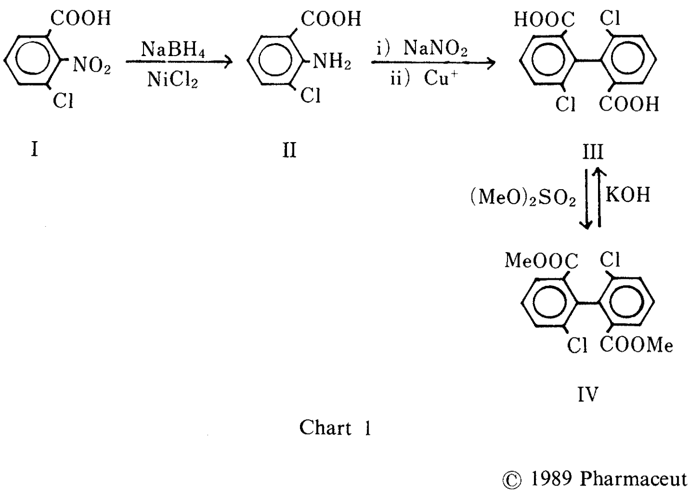

Chart 1

The optical resolution of 6,6′-dichloro-2,2′-diphenic acid has already been reported by Christie *et al.*[4] We reexamined their method. A mixture of the acid (III) and brucine·2H$_2$O (1 : 3, w/w) in methanol was allowed to stand at room temperature overnight and the precipitate obtained was separated into hot methanol-soluble and -insoluble fractions. Recrystallization of the insoluble salt from methanol gave the pure (*R*)-(+)-6,6′-dichloro-2,2′-diphenic acid brucine salt, mp 228 °C, $[\alpha]_D^{22}$ +4.79° ($c$=1.58, CHCl$_3$). The same treatment of the soluble salt gave the pure (*S*)-(−)-6,6′-dichloro-2,2′-diphenic acid brucine salt, mp 169 °C, $[\alpha]_D^{22}$ −60.32° ($c$=1.74, CHCl$_3$). The yields were 92% and 49.7%, respectively.

Treatment of each brucine salt with 10% KOH aqueous solution gave (*R*)-(+)-6,6′-dichloro-2,2′-diphenic acid ((*R*)-(+)-III), mp 264 °C, $[\alpha]_D^{19}$ +7.3° ($c$=0.83, MeOH) and (*S*)-(−)-6,6′-dichloro-2,2′-diphenic acid ((*S*)-(−)-III), mp 259 °C, $[\alpha]_D^{21}$ −7.2° ($c$=0.81, MeOH).

In order to determine its optical purity, each acid was esterified by using dimethyl sulfate as above to give (*R*)-(+)-dimethyl 6,6′-dichloro-2,2′-diphenate ((*R*)-(+)-IV), mp 106°, $[\alpha]_D^{22}$ +16.5° ($c$=0.94, CHCl$_3$) and (*S*)-(−)-dimethyl 6,6′-dichloro-2,2′-diphenate ((*S*)-(−)-IV), mp 107 °C, $[\alpha]_D^{23}$ −14.8° ($c$=1.03, CHCl$_3$), respectively. Determination of the optical purity of the esters (*R*)-(+)-IV and (*S*)-(−)-IV was done by proton nuclear magnetic resonance ($^1$H-NMR) spectroscopy with the aid of a chiral lanthanide shift reagent, tris[fluorobutyryl-(+)-camphorato]europium (III), [Eu(hfc)$_3$].

The ester methyl proton signals of the racemic ester (±)-

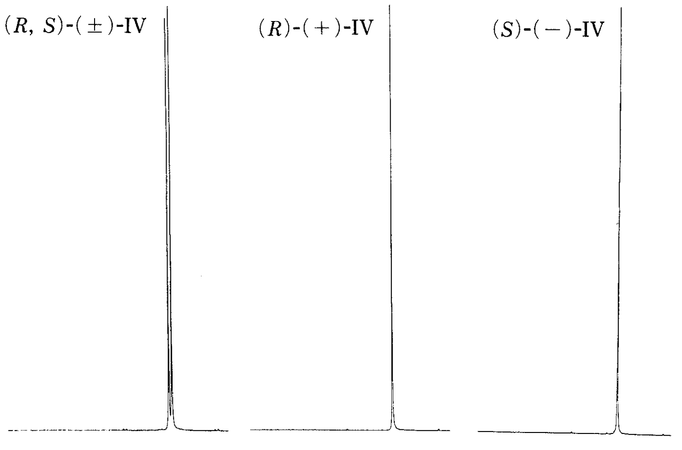

Fig. 1. $^1$H-NMR Spectra of (±)-(IV), (+)-(IV) and (−)-(IV) in the Presence of Eu(hfc)$_3$

(IV) appeared at 3.844 and 3.825 ppm in $CDCl_3$ containing 1.44 molar ratio of $[Eu(hfc)_3]$, those of (*R*)-(+)-IV and (*S*)-(−)-IV appeared at 3.829 ppm and at 3.806 ppm, respectively, in the same solvent containing 1.37 molar ratio of $[Eu(hfc)_3]$. With each of (*R*)-(+)-IV and (*S*)-(−)-IV, no signal due to the enantiomer was observed. Therefore, it can be concluded that the enantiomeric excesses of (*R*)-(+)-IV and (*S*)-(−)-IV are over 99%.

The absolute configurations of the enantiomers have already been assigned by Mislow *et al.*[7] In conclusion, we have developed a novel and convenient synthetic method for optically active 6,6′-dichloro-2,2′-diphenic acid and its dimethyl ester from commercially available 3-chloro-2-nitrobenzoic acid (I) in reasonable yield.

## Experimental

All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-202 spectrometer. Nuclear magnetic resonance (NMR) spectra were measured on JEOL JNM PS-100 and GX-270 spectrometers using tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) were obtained on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-4 polarimeter.

**2-Amino-3-chlorobenzoic Acid (II)** A mixture of 8 g of 3-chloro-2-nitrobenzoic acid and 19 g of $NiCl_2 \cdot 6H_2O$ in 15 ml of 99% MeOH was treated with 6 g of $NaBH_4$ under ice cooling. The solution was stirred for 1 h at room temperature. The solvent was distilled off *in vacuo*, and the black residue thus obtained was washed with concentrated HCl solution and then extracted with AcOEt. The extract was dried over $MgSO_4$ and the solvent was distilled off. Recrystallization from EtOH–$H_2O$ (1 : 1) gave 5.75 g (85%) of 2-amino-3-chlorobenzoic acid (II), mp 189 °C, white leaflets. *Anal.* Calcd for $C_7H_6ClNO_2$: C, 48.98; H, 3.49; N, 8.16. Found: C, 48.80; H, 3.46; N, 7.98. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3480, 3370 (NH), 2600—2300 ($NH_3^+$), 1670 (C=O). MS *m/z*: 171 ($M^+$).

**6,6′-Dichloro-2,2′-diphenic Acid (III)** 2-Amino-3-chlorobenzoic acid (3 g, 0.018 mol) was dissolved in a solution of 0.9 g (0.023 mol) of NaOH in 50 ml of $H_2O$. To this solution was added 1.32 g (0.019 mol) of $NaNO_2$, and the mixture was cooled to 10 °C. Seven milliliters of concentrated HCl solution and 14 ml of $H_2O$ were placed in a flask and cooled below 5 °C. The cold solution of sodium 2-amino-3-chlorobenzoate and $NaNO_2$ was then added to the HCl solution below 5 °C. Stirring was continued for 30 min, then 237 mg of $NaNO_2$ was added to complete the diazotization. On the other hand, 7.55 g of $CuSO_4 \cdot H_2O$ was dissolved in 30 ml of $H_2O$ and then 13 ml of concentrated $NH_4OH$ was added. A solution of 2.93 g of $(NH_2OH)_2 \cdot H_2SO_4$ in 14 ml of $H_2O$ was prepared. To the $(NH_2OH)_2 \cdot H_2SO_4$ solution was added 5.9 ml of 6 N NaOH solution under cooling. This $NH_2OH$ solution was immediately added to the ammoniacal cupric sulfate solution. To the solution containing the reducing reagent prepared above, the diazo solution was added under a nitrogen stream. After the completion of the reaction, the solution was heated at 80—90 °C for 1 h, and then acidified with concentrated HCl solution. The product was collected by filtration, and dissolved in AcOEt; this solution was dried over $MgSO_4$, and evaporated to leave the crude 6,6′-dichloro-2,2′-diphenic acid (2.7 g, 99.2%).

**Dimethyl 6,6′-Dichloro-2,2′-diphenate (IV)** A mixture of 400 mg (1.28 mmol) of 6,6′-dichloro-2,2′-diphenic acid (III), 350 mg (2.77 mmol) of dimethyl sulfate and 310 mg (2.24 mmol) of $K_2CO_3$ in 30 ml of anhydrous acetone was refluxed for 2—3 h. The solvent was distilled off, ice was added, and the whole was extracted with $CH_2Cl_2$. The extract was dried over $MgSO_4$ and concentrated. Recrystallization of the residue from hexane–$CH_2Cl_2$ gave 410 mg (94%) of dimethyl 6,6′-dichloro-2,2′-diphenate (IV), mp 161 °C (lit.[4] 156 °C), white columns. *Anal.* Calcd for $C_{16}H_{12}Cl_2O_4$: C, 56.64; H, 3.54. Found: C, 56.51; H, 3.60. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1725 (C=O). $^1$H-NMR ($CDCl_3$) $\delta$: 3.62 (3H, s, $CH_3$), 7.39 (2H, t, $J=8$ Hz, $C_4$-H), 7.64 (2H, dd, $J_{3,4}=8$ Hz, $J_{4,5}=3$ Hz, $C_5$-H), 7.99 (2H, dd, $J_{3,4}=8$ Hz, $J_{3,5}=3$ Hz, $C_3$-H). MS *m/z*: 338 ($M^+$, 31.2), 340 ($M^+ + 2$, 22.0).

**Hydrolysis of Dimethyl 6,6′-Dichloro-2,2′-diphenate (IV)** A mixture of 3 g (8.8 mmol) of powdered dimethyl 6,6′-dichloro-2,2′-diphenate (IV) and 1.62 g (28.9 mmol) of KOH in 400 ml of MeOH–$H_2O$ (3 : 1) was refluxed for 4—5 h. The solvent was distilled off, and the residue was dissolved in a small amount of water; the resulting solution was aciditied with concentrated HCl solution. The precipitate was filtered off and dissolved in AcOEt; this solution was dried over $MgSO_4$ and evaporated to leave 2.6 g (95%) of pure 6,6′-dichloro-2,2′-diphenic acid, white solid, mp 263—265 °C. *Anal.* Calcd for $C_{14}H_8Cl_2O_4$: C, 54.01; H, 2.57. Found: C, 53.99; H, 2.66. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1685 (C=O). MS *m/z*: 310 ($M^+$, 252), 312 ($M^+ + 2$, 170).

**The Optical Resolution of 6,6′-Dichloro-2,2′-diphenic Acid (III)** A solution of 3 g (6.97 mmol) of brucine · $2H_2O$ in 10 ml of MeOH was added to a solution of 1 g (3.21 mmol) of acid (III) in 10 ml of MeOH. The mixture was allowed to stand overnight at room temperature to give 3.6 g of precipitated brucine salt. This salt was dissolved in 50 ml of MeOH with heating and separated into the hot methanol-soluble and -insoluble fractions. (*R*)-(+)-6,6′-Dichloro-2,2′-diphenic acid brucine salt was obtained as a white powder from the insoluble fraction (yield 2.25 g). On cooling of the MeOH solution, 1.2 g of (*S*)-(−)-6,6′-dichloro-2,2′-diphenic acid brucine salt was obtained. Recrystallization of the (+)-salt gave 1.7 g (92%) of the pure salt, mp 228 °C (lit.[4] 235 °C), white needles, $[\alpha]_D^{22}$ +4.79° ($c=1.58$, $CHCl_3$) (lit.[4] +1.97°, $c=1.23$, $CHCl_3$). *Anal.* Calcd for $C_{14}H_8Cl_2O_4 \cdot 2C_{23}H_{26}O_4N_2 \cdot 2H_2O$: C, 63.43; H, 5.63; N, 4.93. Found: C, 63.62; H, 5.62; N, 4.75. Recrystallization of the (−)-salt gave 900 mg (49.7%) of the pure (−)-salt, mp 169 °C (lit.[4] 163 °C), white needles, $[\alpha]_D^{22}$ −60.32° ($c=1.74$, $CHCl_3$) (lit.[4] −58.62°, $c=1.16$, $CHCl_3$). *Anal.* Calcd for $C_{14}H_8Cl_2O_4 \cdot 2C_{23}H_{26}O_4N_2 \cdot 4H_2O$: C, 61.48; H, 5.80; N, 4.78. Found: C, 61.67; H, 5.62; N, 4.82.

**(*R*)-(+)- and (*S*)-(−)-6,6′-Dichloro-2,2′-diphenic Acid [(*R*)-(+)-III and (*S*)-(−)-III]** Five hundred milligrams of the powdered (+)-brucine salt was added to a mixture of 30 ml of benzene and 6 ml of 10% KOH solution and stirred for 30 min. The aqueous layer was separated and made acidic with concentrated HCl. The precipitated acid was extracted with AcOEt. The extract was dried over $MgSO_4$ and evaporated to give 120 mg of (*R*)-(+)-6,6′-dichloro-2,2′-diphenic acid ((*R*)-(+)-III), mp 264 °C (lit.[4] 259°), $[\alpha]_D^{19}$ +7.3° ($c=0.83$, MeOH). *Anal.* Calcd for $C_{14}H_8Cl_2O_4$: C, 54.01; H, 2.57. Found: C, 54.03; H, 2.56.

The same treatment of 500 mg of the (−)-brucine salt gave 115 mg of (*S*)-(−)-6,6′-dichloro-2,2′-diphenic acid ((*S*)-(−)-III), mp 259 °C (lit.[4] 259 °C), $[\alpha]_D^{21}$ −6.3° ($c=0.81$, MeOH). *Anal.* Calcd for $C_{14}H_8Cl_2O_4$: C, 54.01; H, 2.57. Found: C, 53.89; H, 2.50.

**(*R*)-(+)- and (*S*)-(−)-Dimethyl 6,6′-Dichloro-2,2′-diphenate [(*R*)-(+)-IV and (*S*)-(−)-IV]** A mixture of 365 mg (1.17 mmol) of (*R*)-(+)-6,6′-dichloro-2,2′-diphenic acid, 319 mg (2.53 mmol) of dimethyl sulfate and 348 mg (2.52 mmol) of $K_2CO_3$ in 30 ml of acetone was refluxed for 1.5—2 h. The solvent was distilled off, ice was added to the residue and the whole was extracted with $CH_2Cl_2$. The extract was dried over $MgSO_4$ and evaporated, and recrystallization of the residue from hexane gave 350 mg of the (*R*)-(+)-methyl ester ((*R*)-(+)-IV), mp 106 °C, $[\alpha]_D^{22}$ +16.5° ($c=0.94$, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{12}Cl_2O_4$: C, 56.64; H, 3.53. Found: C, 56.90; H, 3.41.

The same treatment of 360 mg (1.15 mmol) of (*S*)-(−)-6.6′-dichloro-2,2′-diphenic acid gave 340 mg of the (*S*)-(−)-methyl ester ((*S*)-(−)-IV), mp 109 °C, $[\alpha]_D^{23}$ −14.8° ($c=1.03$, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{12}Cl_2O_4$: C, 56.64; H, 3.54. Found: C, 56.94; N, 3.52.

## References and Notes

1) *a*) T. Ohta, H. Takaya, M. Kitamura, K. Nagai and R. Noyori, *J. Org. Chem.*, **52**, 3174 (1987); *b*) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya and R. Noyori, *J. Am. Chem. Soc.*, **110**, 629 (1988).

2) *a*) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta and H. Takaya, *J. Am. Chem. Soc.*, **108**; 7117 (1986); *b*) H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara and R. Noyori, *ibid.*, **109**, 1596 (1987).

3) *a*) K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Takemori, H. Takaya, A. Miyashita and R. Noyori, *J. Chem. Soc., Chem. Commun.*, **1982**, 600; *b*) K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, A. Miyashita, R. Noyori and S. Otsuka, *J. Am. Chem. Soc.*, **106**, 5208 (1984).

4) G. H. Christie, C. W. James and J. Kenner, *J. Chem. Soc.*, **1923**, 1948.

5) E. R. Atkinson, D. M. Murphy and J. E. Lufkin, *Org. Synth.*, **31**, 96 (1951); E. R. Atkinson and H. J. Lawler, *J. Am. Chem. Soc.*, **62**, 1704 (1940).

6) A. Nose and T. Kudo, *Chem. Pharm. Bull.*, **29**, 1159 (1981).

7) *a*) P. Newman, P. Rutkin and K. Mislow, *J. Am. Chem. Soc.*, **80**, 465 (1958); *b*) K. Mislow and M. Siegel, *ibid.*, **80**, 473 (1958).

8) According to IUPAC rules, compounds III and IV were nominated as [1,1′-biphenyl]-6,6′-dichloro-2,2′-dicarboxylic acid and dimethyl [1,1′-biphenyl]-6,6′-dichloro-2,2′-dicarboxylate, respectively.