Use of Axially Chiral 2′-Methoxy-1,1′-binaphthyl-2-carboxylic Acid as Chiral Derivatizing Agent for Discrimination of Enantiomeric Alcohols and Amines by ^{1}H NMR

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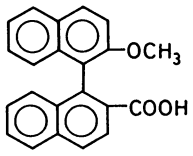
Axially chiral 2′-methoxy-1,1′-binaphthyl-2-carboxylic acid (**1**) was effectively utilized as chiral derivatizing agent for discrimination of enantiomeric alcohols and amines by ^{1}H NMR with the aid of Eu(fod)$_3$. Among a pair of the diastereomeric esters or amides prepared from (a*S*)-**1** and an α-chiral alcohol or amine, the methoxyl protons of the (a*S*,*R*)-diastereomer showed the larger lanthanoid-induced downfield shift than those of the (a*S*,*S*)-counterpart. Thus, addition of up to 0.5—1.0 equiv amount of Eu(fod)$_3$ caused base-line separation of those protons, allowing determination of the enantiomeric purities and assignment of the absolute configurations of the enantiomeric alcohols and amines. An X-ray crystallographic analysis of the amide ((a*S*,*S*)-**2**) obtained from (a*S*)-**1** and (*S*)-1-phenylethylamine showed structural resemblance between the amides and esters of **1**. Steric models which explain the NMR behavior of the diastereomeric esters and amides are presented based on X-ray analyses. Also reported are two methods to regenerate free acid **1** from amide **2** to afford axially homochiral **1**.

Recently a variety of chiral derivatizing agents have been developed for determination of absolute configurations and enantiomeric purities of optically active compounds,[1] among which Mosher's α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) has been most widely used for discrimination by NMR.[2] In our previous paper[3] we have reported the optical resolution of 2′-methoxy-1,1′-binaphthyl-2-carboxylic



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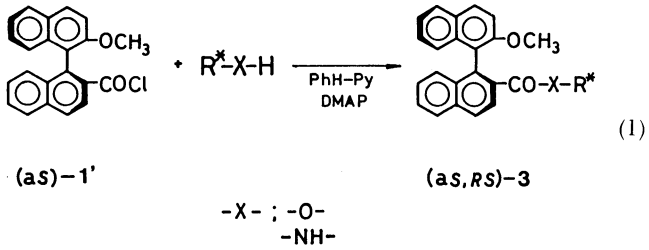
acid (**1**) and the use of atropisomeric **1** as highly efficient chiral derivatizing agent for differentiation of enantiomeric alcohols and amines by high-performance liquid chromatography (HPLC). In our continuing efforts to extend the scope and the utility of **1** as a chirality-recognizing element, we have studied ^{1}H NMR behavior of the diastereomeric esters and amides of **1**. Herein we wish to report that the methoxyl group serves as a chiral probe, as the MeO protons of a pair of the diastereomeric esters or amides were nicely separated at 60 MHz by addition of up to 0.5 to 1.0 equiv amount of Eu(fod)$_3$ (tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium). Also reported are alternative procedures for optical resolution of **1** by fractional crystallization of the diastereomeric *N*-(1-phenylethyl)amides (**2**).

Results and Discussion

^{1}H NMR Study of the Diastereomeric Esters and Amides of (a*S*)-1.[4] The preparation of the samples of



(1)

diastereomeric esters or amides of (a*S*)-**1** from partially active alcohols or amines has been reported in the previous paper unless otherwise noted (Eq. 1).[3] NMR measurements of those samples showed that the shift differences of respective ^{1}H absorptions of a pair of the diastereomers were not always large enough to enable quantitative analysis at 60 MHz (Table 1). However, it was found that the lanthanoid-induced downfield shifts of the MeO signals of the (a*S*,*R*)-diastereomers were consistently larger than those of the corresponding (a*S*,*S*)-isomers, causing base-line separation of those signals by addition of up to 0.5 to 1 equiv amount of Eu(fod)$_3$. Results summarized in Table 1 show that axially chiral **1** is useful as chiral derivatizing agent for discrimination of enantiomeric alcohols and amines not only by HPLC but also by ^{1}H NMR. A potential problem of kinetic resolution by use of **1** has been discussed in the previous paper.[3] Emphasis should be placed on the discrimination of the amide diastereomers (vide infra). As a typical example, Fig. 1 shows the induced shift of the MeO signals of *N*-[(*R*)- and (*S*)-1-methylhexyl]amide of (a*S*)-**1** ((a*S*,*R*)- and (a*S*,*S*)-**4**)) by successive addition of Eu(fod)$_3$. It should be noted that addition of Eu(fod)$_3$ did not apparently cause collapse of the MeO signals; although the lanthanoid-induced shift (LIS) method

Table 1. Chemical Shifts of MeO Protons of the Diastereomers Derived from (aS)-**1** and Enantiomeric Alcohols and Amines[a)]

Run	Substrate	Chemical shift of MeO (δ)			
				Eu(fod)$_3$ added (1 equiv)	
		(a*S*,*R*)	(a*S*,*S*)	(a*S*,*R*)	(a*S*,*S*)
1	Me HO-CH-Ph	3.15	3.19	4.84	4.42
2	Menthol	3.28	3.23	4.70	4.00
3	Borneol	3.27	3.25	4.58	4.37
4	Me HO-CH-Et	3.23	3.22	4.99	4.79
5	Me HO-CH-CHMe$_2$	3.11	3.13	5.18	4.71
6	Me HO-CH-C$_6$H$_{13}$	3.27	3.23	5.07	4.71
7	α-Tetralol	3.09	3.23	5.00	4.82
8	Me H$_2$N-CH-Ph	3.04	3.12	5.47	5.19
9	Me H$_2$N-CH-(1-Naphthyl)	2.86	2.97	4.97	4.56
10	Me H$_2$N-CH-(2-Naphthyl)	3.00	3.09	5.06	4.89
11	Me H$_2$N-CH-Et	3.17	3.19	5.04	4.81
12	Me H$_2$N-CH-C$_5$H$_{11}$	3.19	3.19	5.43	4.99
13	Me H$_2$N-CH-C$_6$H$_{13}$	3.20	3.18	5.91	4.92
14	Bornylamine	3.21	3.20	5.12	4.65
15	Isobornylamine	3.19	3.21	6.11	5.16
16	Me H$_2$N-CH-⬡	3.19	3.19	6.52	5.22
17	CH$_2$Ph H$_2$N-CH-CH$_2$OMe	3.28	3.20	5.00	4.72
18	Me H$_2$N-CH$_2$-CH-Ph	3.10	3.10	6.13	5.50
19	Et H$_2$N-CH$_2$-CH-C$_4$H$_9$	3.21	3.21	5.26	5.13
20	3-(Aminomethyl)pinane	3.21	3.21	5.86	5.36

a) Measured in C_6D_6 using TMS as internal standard at 60 MHz.

has been successfully applied to diastereomeric MTPA esters for discrimination of a wide range of alcohols,[2,5)] it has rarely been used for MTPA amides because of the broadening of the signals by addition of Eu(fod)$_3$.[6)] Table 1 also contains the examples of the discrimination of β-chiral amines[7)] (Runs 18—20).

X-Ray Crystallographic Analysis of (a*S*,*S*)-2. Figure 2 shows an ORTEP drawing of (a*S*,*S*)-**2**. It was shown that the dihedral angle θ between the two naphthalene rings is 97.5°, and that the -CO-NH-CH- atoms are almost on a same plane, the -CO-NH- linkage being *s*-trans conformation and the dihedral angle ϕ of C_1-C_2-C=O being 52.6° as schematically depicted in Fig. 3. The structure is similar to that of (−)-menthyl ester of (a*S*)-**1** except that the plane which contains the ester linkage -CO-O-CH- is almost on the same plane of the relevant naphthalene ring (ϕ=0—10°).[3)] In case of the amide, the deviation of the dihedral angle ϕ from coplanarity with the naphthalene ring seems to be caused by the steric repulsion between the amide proton and the other naphthalene ring (Fig. 3). In any event, these X-ray analyses suggest the structural resemblance between the amides and the esters derived from axially chiral **1**.

Configuration Correlation Models to Explain the Lanthanoid-Induced Shifts. The lanthanoid-induced shifts of the diastereomeric MTPA esters have been rationalized in terms of the steric interactions for the

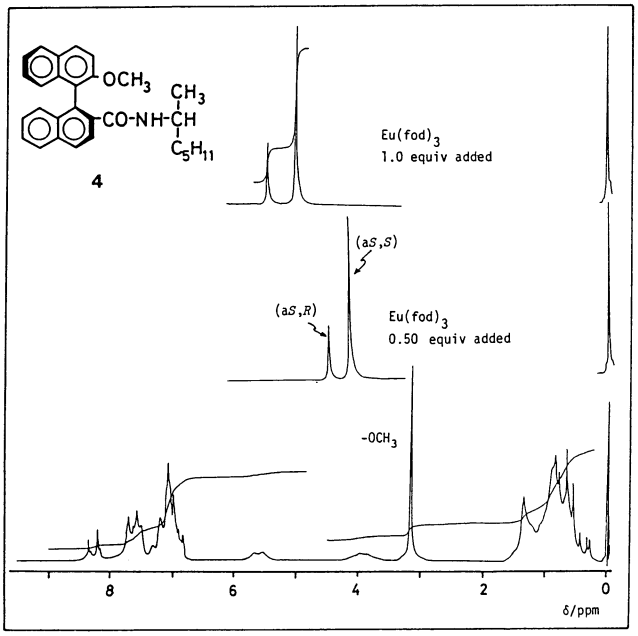


Fig. 1. ^{1}H NMR spectra of a pair of the diastereomeric amides prepared from (*S*)-2-heptanamine (50% ee) and (a*S*)-**1** in the presence or absence of Eu(fod)$_3$.

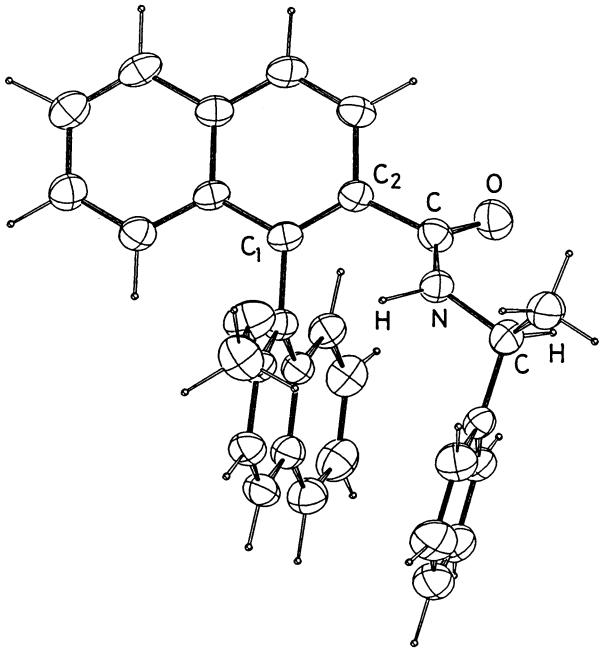


Fig. 2. ORTEP drawing of (a*S*,*S*)-**2**.

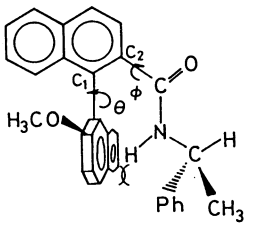
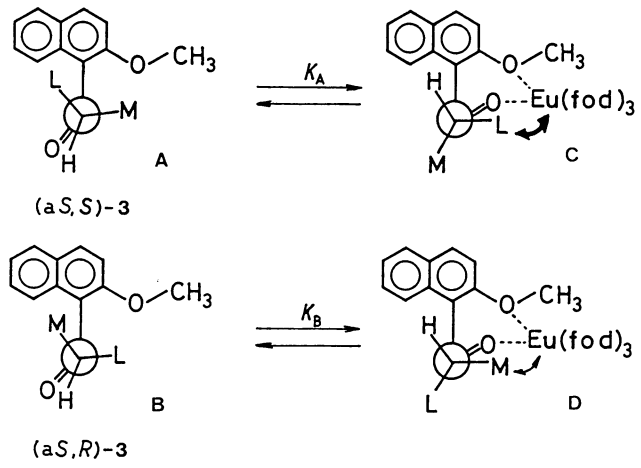
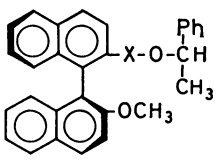


Fig. 3. Schematic view of crystal structure of (a*S*,*S*)-**2**.



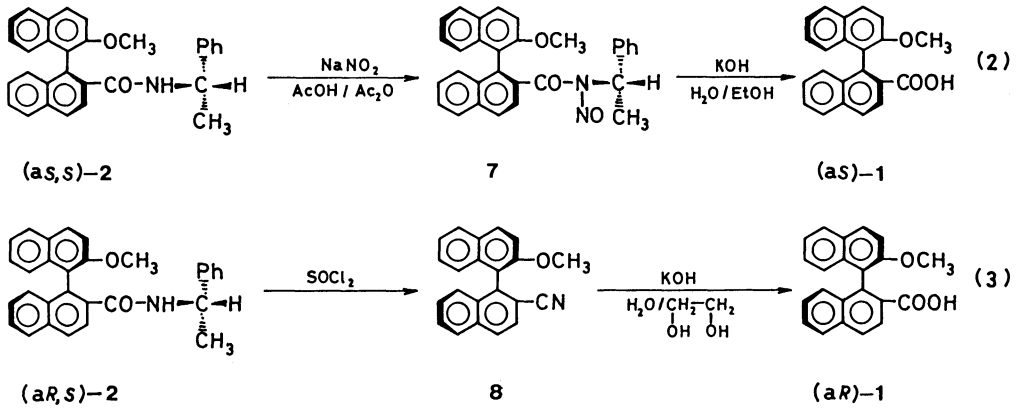
Scheme 1.

complex formation between the esters and Eu(fod)$_3$.[2,5] Application of the models with slight modifications to the diastereomers of α-chiral esters and amides of **1** (**3**) also explains the shift behavior listed in Table 1 (Scheme 1): On the basis that preferred conformations of these diastereomers in solutions are deducible from the X-ray crystallographic analyses as suggested in the previous paper,[3] the conformations of (a*S*,*S*)- and (a*S*,*R*)-**3** are schematically depicted as structures **A** and **B**, respectively, where L and M stand for the largest and the medium substituent on the carbinyl (C-1) carbon of the original alcohol or amine. Structures **C** and **D** represent empirical models of the complexes of **3** with Eu(fod)$_3$, where the esters or amides coordinate to Eu(fod)$_3$ by virtue of the two oxygen atoms from the methoxyl and carbonyl group of the (a*S*)-2′-methoxy-1,1′-binaphthylcarboxylic acid moiety. In the complex **C**, the largest ligand L is arrayed toward the Eu-metal, while in the complex **D** the medium ligand M directs toward the metal-center posing less steric repulsions. Thus, the complexation constant K_A for the formation of **C** may be smaller than that (K_B) for the formation of **D**, inducing the larger downfield shifts of the MeO signals for the (a*S*,*R*)-**3** complexes as are observed. The reasoning could not be applied to 1-methoxy-3-phenyl-2-propanamine (Run 17); the steric bulk of methoxymethyl group is seemingly smaller than that of benzyl group, which does not agree with the priority order of the two groups by the *R* and *S* designation. However, this exceptional behavior of the amine may be



(a*S*,*RS*)-**5** ; -X- = -CO-

(a*S*,*RS*)-**6** ; -X- = -CH$_2$-



explained by assuming that the 1-methoxyl group of the (a*S*,*S*)-amide effectively competes with the binaphthyl 2′-methoxyl group for the coordination site of Eu (**C**; L=CH_2OMe), thus reducing the magnitude of the lanthanoid-induced shift of the latter MeO protons.

To demonstrate the importance of the coordination to Eu(fod)$_3$ by the carbonyl oxygen as well as the 2′-methoxyl oxygen, the shift behavior of ester diastereomers **5** was compared with that of the ether counterparts **6**. As Table 1 shows, methoxyl groups of diastereomeric **5** are good probes for discrimination of the 1-phenylethyl moiety with the aid of Eu(fod)$_3$. On the other hand, the magnitude of the induced shifts of the MeO protons of (a*S*,*S*)- and (a*S*,*R*)-**6** were not only small but also almost identical on addition of up to 2 equiv amounts of Eu(fod)$_3$ (see Experimental).

Optical Resolution of 1 via *N*-(1-Phenylethyl)-amides. Racemic **1** was converted into the acid chloride (**1′**), which was then treated with (*S*)-1-phenylethylamine to give the mixture of diastereomeric amides ((a*S*,*S*)- and (a*R*,*S*)-**2**)) in quantitative yield. The mixture was crystallized twice from hexane-ethyl acetate to give diastereomerically pure (a*S*,*S*)-**2** as fine cubic crystals in a 55% yield based on one enantiomer present in the racemate; suitable one of the crystals was used for X-ray analysis (vide supra). Subsequent column chromatography of the mother liquor readily afforded (a*R*,*S*)-**2** of 100% diastereomeric excess (de) in a 63% yield as the first eluting component.

The amide bond of **2** was highly resistant to acidic or alkaline hydrolysis,[8] but regeneration of the axially chiral acids was achieved by either of the two routes without racemization. These are, 1) nitrosation to *N*-nitroso amide **7** followed by alkaline hydrolysis (Eq. 2),[9] and 2) conversion into nitrile **8** by treatment with thionyl chloride (the von Brawn reaction)[10] followed by alkaline hydrolysis (Eq. 3).[11] Although **1** can be resolved by column-chromatographic separation of the diastereomeric esters,[3] it should be pointed out that the amide routes disclosed here enable treatment of a larger amount of the diastereomeric mixture because of the crystallization out of one of the diastereomers and better separability of the amides on silica-gel column than that of the ester diastereomers.[12]

Experimental

Instruments and materials were those disclosed previously unless otherwise noted.[3] Partially active (*R*)-2-phenyl-1-propanamine was prepared by referring to a literature procedure;[13] IR (KBr) 3500—3300 (br) and 900—800 (br); $[\alpha]_D$ +8.0° (*c* 1.38, EtOH) (lit,[14] $[\alpha]_D$ max +34.0° (*c* 1.0, EtOH)). Commercial (*S*)-3-(aminomethyl)pinane (HCl salt) and (*S*)-2-ethyl-1-hexanamine (HCl salt) were allowed to react with partially active (a*S*)-**1′** (ca. 50% ee) as before[3] to prepare diastereomeric amide samples for ^{1}H NMR measurements.

NMR Shift Studies. Discrimination of 2-heptanamine enantiomers is representative. Partially active (*S*)-2-heptanamine (prepared to be ca. 50% ee by mixing (*S*)-isomer with the racemate) was treated with (a*S*)-**1′** as before to give a mixture of the diastereomeric amides ((a*S*,*S*)- and (a*S*,*R*)-**4**).[3] A part of the sample (15 mg, 0.035 mmol) was dissolved in ca. 0.40 ml of C_6D_6. ^{1}H NMR spectra of the sample were taken with successive addition of 1 M† solution of Eu(fod)$_3$ in C_6D_6, and the magnitudes of the induced shift of MeO signals were recorded (Fig. 1). The further shifted, smaller MeO signal was readily assigned to (a*S*,*R*)-**4** by comparing the peak areas, and the diasteromeric composition was calculated to be 49.7% de by integrating those MeO signals.

Preparation of (a*S*,*RS*)-6 and Its Shift Study. Diastereomerically pure (−)-menthyl ester of (a*S*)-**1**[3] (0.17 g, 0.36 mmol) was boiled with $LiAlH_4$ (0.30 g) in ether (10 ml) for 3 h. The reaction was worked up as usual, and TLC on silica gel/$CHCl_3$ gave 92 mg of (a*S*)-2-hydroxymethyl-2′-methoxy-1,1′-binaphthyl (**9**) (81%); $[\alpha]_D^{23}$ +75.0° (*c* 1.09, $CHCl_3$) (lit,[15] for (a*R*)-isomer of 96% ee, $[\alpha]_D$−71.4° (*c* 0.15, $CHCl_3$)). To a solution of **9** (90 mg, 0.29 mmol) in acetic acid (15 ml) was added dropwise 0.80 ml of 48% HBr at 80 °C for 30 min, and the mixture was stirred at this temperature for another 30 min. The mixture was diluted with 70 ml of water, and treated as usual. Volatiles were removed in vacuo to give (a*S*)-2-bromomethyl-2′-methoxy-1,1′-binaphthyl (104 mg, 94%), which was dissolved in DMF (5 ml). This was added dropwise to a solution of sodium (*S*)-1-phenylethoxide in 5 ml of DMF (prepared from (*S*)-1-phenylethanol of ca. 30% ee (35 mg, 0.29 mmol) and NaH). The mixture was stirred overnight at ambient temperature,

† 1 M=1 mol dm^{-3}.

and then heated at 80 °C for 10 h. After a usual work-up, (a*S*,*RS*)-**6** enriched in (a*S*,*S*)-isomer was obtained by TLC on silica gel/$CHCl_3$ (70 mg, 61%); ^{1}H NMR δ=1.20 and 1.25 (3H, d, J=6.9 Hz, C-CH_3), 3.04 and 3.12 (3H, s, O-CH_3), 3.8—4.6 (3H, m, CH and CH_2), and 6.8—8.2 (17H, m, Ar-H).

The methoxyl protons of (a*S*,*R*)-**6** which appeared at δ 3.04 shifted to δ 3.12 and 3.17 on addition of 1 and 2 equiv amounts of Eu(fod)$_3$, respectively. On the other hand, those of (a*S*,*S*)-**6** which appeared at δ 3.12 shifted to δ 3.20 and 3.24 on addition of 1 and 2 equiv Eu(fod)$_3$, respectively.

Preparation and Resolution of 2. To a stirred solution of (*S*)-1-phenylethylamine (12.9 g, 107 mmol) and 4-dimethylaminopyridine (1.25 g) in benzene (250 ml) was added dropwise a solution of acid chloride **1′** (prepared from 16.7 g of (±)-**1** (50.9 mmol)) in benzene (250 ml) under a nitrogen atmosphere at ambient temperature. The mixture was stirred at this temperature for 5 h, and then heated at 60 °C for 3 h. The reaction mixture was diluted with benzene, washed successively with 2 M HCl, 1 M Na_2CO_3, and water, and dried over Na_2SO_4. Evaporation of volatiles under reduced pressure gave 22.8 g of a crude mixture of the diastereomeric amides (104%). HPLC of the mixture on a silica-gel column eluting with hexane-2-propanol (3%) showed two peaks of (a*S*,*R*)- and (a*S*,*S*)-**2** in the ratio of 50.06:49.94 (by absorptions at 254 nm) in the order of increasing retention volume. The mixture was crystallized from hexane-ethyl acetate (8/5) to give 7.85 g of (a*S*,*S*)-**2** of 93% de, and recrystallization of which from the same solvent system afforded 6.08 g of diastereomerically pure (a*S*,*S*)-**2** (55% based on one of the enantiomers of **1**). Concentration of the recrystallization mother liquor gave additional 1.09 g of (a*S*,*S*)-**2** (98.4% de) as crystals, and 0.50 g of (a*S*,*S*)-**2** of 0.8% de was recovered from the filtrate.

The mother liquor of the initial crystallization was concentrated and subjected to column chromatography on silica gel (825 g) eluting with hexane-ethyl acetate with varing the composition of the eluent from 5/1 to 5/3, to give five fractions as follows: (1) 6.86 g (63% yield), (a*R*,*S*), 100% de; (2) 1.32 g, (a*R*,*S*), 86.0% de; (3) 2.16 g, (a*S*,*S*), 12.6% de; (4) 1.24 g, (a*S*,*S*), 65.4% de; (5) 0.14 g, (a*S*,*S*), 93.4% de. Total recovery of optically active **2** amounted to 89% yield based on the starting (±)-**1**.

(a*S*,*S*)-2: mp 161—163 °C; $[\alpha]_D^{23}$ +72.7° (c 1.0, $CHCl_3$); IR (KBr) 3475, 1642, 1510, and 1246 cm^{-1}; ^{1}H NMR (C_6D_6, TMS) δ=0.89 (3H, d, J=6.7 Hz, CH_3), 3.12 (3H, s, OCH_3), 4.8—5.2 (1H, m, CH), 6.2—6.5 (1H, br, NH), and 6.5—8.4 (12H, m, Ar-H).

(a*R*,*S*)-2: mp 61—65 °C; $[\alpha]_D^{23}$+122.4° (c 1.0, $CHCl_3$); IR (KBr) 3395, 1654, 1505, and 1247 cm^{-1}; ^{1}H NMR (C_6D_6, TMS) δ=0.67 (3H, d, J=6.7 Hz, CH_3), 3.04 (3H, s, OCH_3), 4.7—5.3 (1H, m, CH), 5.9—6.4 (1H, br, NH), and 6.5—8.4 (12H, m, Ar-H).

Regeneration of 1 from 2. Typical examples are as follows.

Method A: To a stirred mixture of 5.87 g of (a*S*,*S*)-**2** (13.6 mmol) in acetic acid (13.6 ml) and acetic anhydride (68.0 ml) was added portionwise 24.4 g of $NaNO_2$ (0.299 mol) over 5 h at 0 °C, followed by stirring for another 5 h at this temperature. After the mixture was allowed to stand for 20 h at ambient temperature, it was heated at 40 °C for 4 h. The mixture was diluted with water (150 ml), extracted with portions of ether. The combined organic layers were washed with 5% aq Na_2CO_3 and then with water, and dried over Na_2SO_4. Evaporation of volatiles in vacuo left *N*-nitroso amide **7** (5.5 g), which was directly boiled for 3 h in a solution of KOH (30 g) in ethanol (300 ml) and water (30 ml). The mixture was diluted with 0.5 M NaOH (1 dm^{-3}) and extracted with portions of ether. The aqueous layer was made acidic by addition of concd HCl, and precipitated solid was taken into ether and worked up as usual to give 3.40 g of (a*S*)-**1** (76%): $[\alpha]_D^{23}$ −24.6° (c 1.05, THF) (lit,[16] $[\alpha]_D^{25}$ −25.98° (c 1.22, THF)); IR (KBr) 3045 (br), 1685, and 1260 cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS) δ=3.60 (3H, s, OCH_3), 6.5—8.2 (12H, m, Ar-H), and 12.2 (1H, br, COOH). The sample was more than 99.5% ee as evidenced by HPLC on Pirkle column as methyl ester eluting with hexane-2-propanol (2%).

Method B: A sample of 670 mg of (a*R*,*S*)-**2** (1.55 mmol, >99.5% de) was boiled in ca. 5 ml of thionyl chloride for 3 h. After careful evaporation of excess thionyl chloride, the residue was diluted with ether, washed successively with 2 M NaOH, 2M HCl, and then water, and dried over Na_2SO_4. Trap-to-trap distillation gave a small amount of (*R*)-1-phenylethyl chloride, $[\alpha]_D^{23}$ +1.6° (c 6.84, $CHCl_3$), leaving 2-cyano-2′-methoxy-1,1′-binaphthyl **8** as the residue, IR (KBr) 2300 cm^{-1}. The residue was boiled for 6 h in a solution of KOH (10 g) in 45 ml of a 8:1 mixture of ethylene glycol and water. After the reaction, the mixture was diluted with water and extracted with ether. The aqueous phase was made acidic by addition of concd H_2SO_4. White precipitate was extracted with ether and worked up as usual to give 0.34 g of (a*R*)-**1** (67%), IR (KBr) 1685 cm^{-1}, which was enantiomerically pure as evidenced by HPLC on Pirkle column as above.

Crystal Structure Determination of (a*S*,*S*)-2. A colorless crystal of (a*S*,*S*)-**2** with the dimensions of 0.10×0.20×0.25 mm was used for the data collection on a Rigaku-Denki automated four-circle diffractometer (Rigaku AFC-5R), equipped with a rotating anode (40 kV, 200 mA), using graphite monochromated Cu $K\alpha$ radiation (λ=1.5418 Å). Crystal data are as follows: M.F.=$C_{30}H_{25}NO_2$, M.W.=431.5, orthorhombic space group $P2_12_12_1$, a=10.119(1), b=24.581(3), c=9.250(1) Å, V=2300.8(5) Å^3, Z=4, D_{calcd}=1.25 g cm^{-3}, μ(Cu $K\alpha$)=5.724 cm^{-1}. A total of 1921 reflections within 2θ=126° were collected by the θ-2θ scan mode at a 2θ scan rate of 4° min^{-1}. The structure was solved by the direct method using RANTAN81 program with some modifications.[17] After the block-diagonal least-squares refinement for non-hydrogen atoms with anisotropic temperature factors, hydrogen atoms were almost located from the difference Fourier map, some methyl hydrogen atoms were calculated, and then included in the refinement with isotropic temperature factors. The final R factor was 0.060 (R_w=0.064) for 1781 reflections with $|F_o|>3\sigma(|F_o|)$.

The atomic scattering factors from the International Tables for X-ray Crystallography[18] were used. All the computations were carried out by a ACOS 2000 computer using the applied library program of UNICS III system.[19]

Tables of final atomic coordinates, temperature factors, bond lengths and bond angles, and the F_o–F_c structure factors are kept at the Chemical Society of Japan (Document No.8907).

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