Asymmetric Hydrogenation Catalyzed by (Achiral Base)bis(dimethylglyoximato)cobalt(II)-Chiral Cocatalyst System[1)]

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Chiral tertiary amines with a secondary amide group at α- or β-carbon were prepared, and an asymmetric hydrogenation of methyl 2-(acetylamino)acrylate and *N,N'*-dimethyl-5-benzylidenehydantoin catalyzed by achiral base-coordinated bis(dimethylglyoximato)cobalt(II)-chiral cocatalyst system was examined by using each of them as the cocatalyst. The enantiomeric excess of *N,N'*-dimethyl-5-benzylhydantoin reached 79.1% with (*S*)-*N*-[(*R*)-1-phenylethyl]-2-quinuclidinecarboxamide as the cocatalyst. Remarkable differences were observed in the enantioselectivities between the two substrates for the same cocatalysts. Discussion about the conformations of the cocatalysts and substrates led to proposed models of chirality-recognizing transition states.

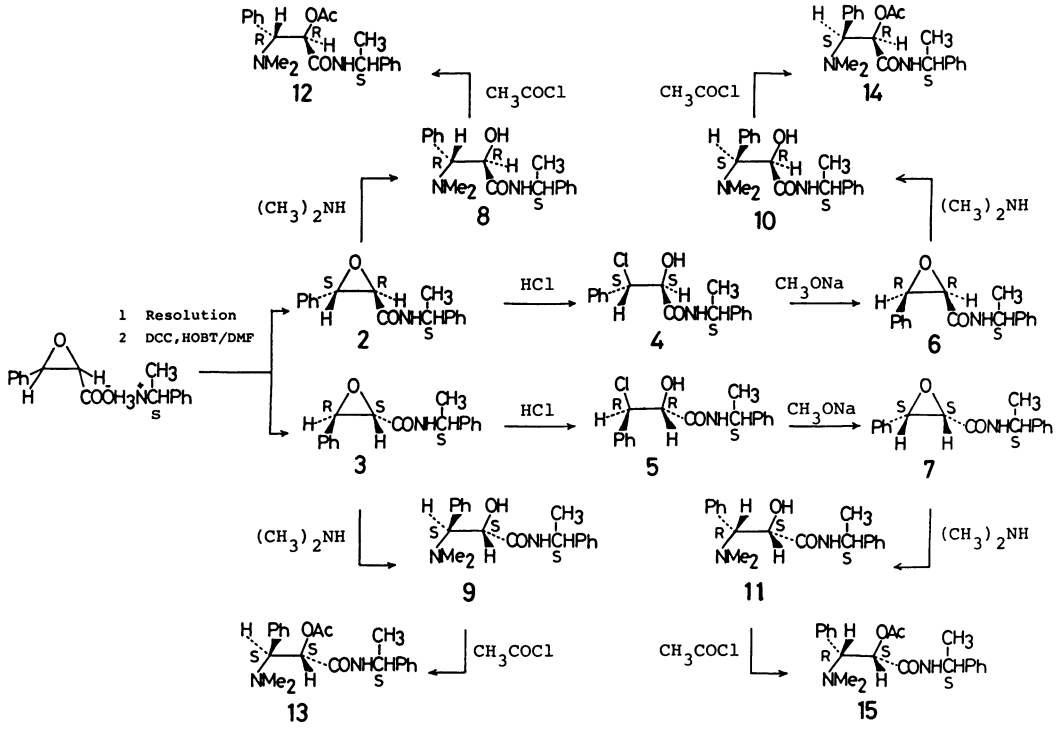
The authors have previously reported the asymmetric hydrogenation catalyzed by the achiral base-coordinated bis(dimethylglyoximato)cabalt(II)-chiral base(cocatalyst) system(hereafter abbreviated as Co(dmgH)$_2$·B-B*; B and B* are achiral and chiral bases respectively). Co(dmgH)$_2$·B-quinine resulted in high optical yields (up to 78%) for α-diketones such as benzil, but in low optical yields (up to 19%) for dehydro amino acid derivatives. A hydrogen bond between the hydroxyl group of cocatalyst(quinine) and the carbonyl group of substrate(benzil) in the chirality-recognizing transition state extremely enhances the enantioselectivity of this system.[2)]

In the preceding paper, the authors reported the asymmetric hydrogenation of methyl 2-(acetylamino)-acrylate with 34.5%ee(enantiomeric excess) using (2*S*, 3*S*)-2-acetoxy-3-dimethylamino-3-pheny-*N*-[(*R*)-1-phenylethyl]propionamide as the cocatalyst and deduced that the hydrogen bond between the amide groups of the substrate and cocatalyst acts as an attractive force to enhance the enantioselectivity.[3)]

Here, we would like to describe the preparation of other new cocatalysts and the asymmetric hydrogenation of 2-(acetylamino)acrylate and *N,N'*-dimethyl-5-benzylidenehydantoin using them as the cocatalysts.

Results and Discussion

Preparation of Cocatalysts. Four diastereoisomers of 2-acetoxy-3-dimethylamino-3-phenyl-[(*S*)-1-phenylethyl]propionamide [**12**(DHP-*OAc*-(2*R*,3*R*)*S*), **13**(DHP-*OAc*-(2*S*,3*S*)*S*), **14**(DHP-*OAc*-(2*R*,3*S*)*S*), and **15**(DHP-*OAc*-(2*S*,3*R*)*S*)] were prepared from (*S*)-1-phenylethylammonium 2,3-epoxy-3-phenylpropionate by the route shown in Scheme 1. Four enantiomers of them [**12'**(DHP-*OAc*-(2*S*,3*S*)*R*), **13'**(DHP-*OAc*-(2*R*, 3*R*)*R*), **14'**(DHP-*OAc*-(2*S*,3*R*)*R*), and **15'**(DHP-*OAc*-(2*R*,3*S*)*R*)] were prepared from (*R*)-1-phenylethyl-



Scheme 1.

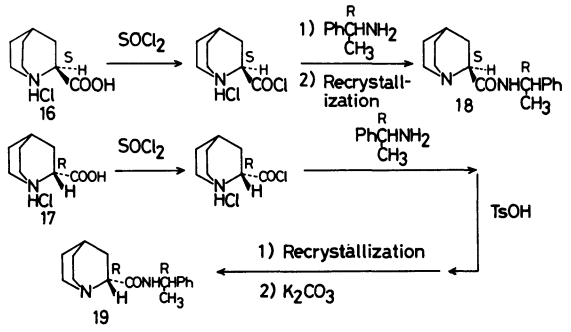
ammonium 2,3-epoxy-3-phenylpropionate by the same procedures (each enantiomer of the compounds in Scheme 1 is expressed as the same number with prime). O-Benzoyl derivative DHP-*OBz*-(2*S*,3*S*)*R* was obtained by benzoylation of **8′**.

Two diastereoisomers of *N*-[(*R*)-1-phenylethyl]-2-quinuclidinecarboxamide [**18**(QC-(*S*)*R*) and **19**(QC-(*R*)*R*)] were prepared from (*S*)- and (*R*)-2-quinuclidinecarboxylic acids (**16** and **17**, respectively) by the route shown in Scheme 2.

(Details are described in the Experimental section).

Asymmetric Hydrogenation of Methyl 2-(acetylamino)-acrylate and N,N′-Dimethyl-5-Benzylidenehydantoin with Co(dmgH)₂·B-chiral Amino Amides. The asymmetric hydrogenation of methyl 2-(acetylamino)acrylate and *N,N′*-dimethyl-5-benzylidenehydantoin with $Co(dmgH)_2$·B-B* was carried out in benzene under an atmospheric pressure of hydrogen at room temperature.

The chiral α- and β-amino amides prepared above were used as the cocatalysts(B*), and quinine and (*S*)-



Scheme 2.

Table 1. The asymmetric hydrogenation of 2-(acetylamino)acrylate with $Co(dmgH)_2$·PPh_3-chiral amino amides[a]

Run	B*	Methyl *N*-acetylalaninate			
		Yield/%	$[\alpha]_D$/°	Config.[b]	% e.e.[c]
1	DHP-*OAc*-(2*S*,3*R*)*R*	60.0	+2.4	*R*	2.6
2	DHP-*OAc*-(2*R*,3*S*)*S*	45.5	−0.5[d]	*S*	0.5
3	DHP-*OAc*-(2*R*,3*S*)*R*	59.3	−0.9	*S*	1.0
4	DHP-*OAc*-(2*S*,3*R*)*S*	43.6	+0.6	*R*	0.7
5	DHP-*OAc*-(2*S*,3*S*)*S*	53.3	+31.3	*R*	34.1
6	DHP-*OAc*-(2*R*,3*R*)*R*	48.6	−33.4	*S*	36.4
7	DHP-*OAc*-(2*S*,3*S*)*R*	45.5	+31.6	*R*	34.5
8	DHP-*OAc*-(2*R*,3*R*)*S*	40.7	−36.0	*S*	39.3
9	DHP-*OBz*-(2*S*,3*S*)*R*	45.5	+39.7	*R*	43.3
10	QC-(*S*)*R*	45.5	+38.0	*R*	41.4
11	QC-(*R*)*R*	65.3	−38.7	*S*	42.2

a) The molar ratio of substrate to cobalt was 10 : 1, while those of PPh_3, the chiral amino amide and its hydrochloride to cobalt were all 1 : 1. Solvent was benzene. b) Configuration. c) See Reference 4). d) Optically pure *S* isomer: $[\alpha]_D$ −91.7° (*c* 2, water).

Table 2. The asymmetric hydrogenation of *N,N′*-dimethyl-5-benzylidenehydantion with $Co(dmgH)_2$·B-chiral bases[a]

Run	B	B*	*N,N′*-dimethyl-5-benzylhydantoin			
			Yield/%	$[\alpha]_D$/°	Config.[b]	% e.e.[c]
1	BA	Quinine	93.0	−12.7	*S*	14.8
2	PPh_3	Quinine	91.0	−49.4	*S*	57.4
3	PPh_3	Pha-*S*,*R*[d]	93.5	−0.8	*S*	0.9
4	PPh_3	Pha-*S*,*S*	93.5	−2.0	*S*	2.3
5	PPh_3	DHP-*OAc*-(2*R*,3*S*)*S*	94.4	−10.0	*S*	11.6
6	PPh_3	DHP-*OAc*-(2*S*,3*R*)*S*	95.0	+10.0	*R*	11.6
7	PPh_3	DHP-*OAc*-(2*R*,3*R*)*R*	91.5	+31.9	*R*	37.1
8	PPh_3	DHP-*OAc*-(2*R*,3*R*)*S*	93.5	+35.5	*R*	41.3
9	PPh_3	DHP-*OBz*-(2*S*,3*S*)*R*	91.0	−37.0	*S*	43.0
10	BA	QC-(*S*)*R*	98.0	−15.6	*S*	18.1
11	PPh_3	QC-(*S*)*R*	93.0	−68.0	*S*	79.1
12	PPh_3	QC-(*R*)*R*	96.5	+60.7	*R*	70.6

a) The molar ratio of substrate to cobalt was 9.3 : 1, while those of PPh_3, BA, the chiral bases and their hydrochlorides to cobalt were all 1 : 1. Solvent was benzene. b) Configuration. c) Optical purity. d) $PhCH_2$-$\overset{S}{C}H(N(CH_3)_2)$-$CONH\overset{R}{C}H(CH_3)Ph$.

N^{α},N^{α}-dimethyl-*N*-[(*R*)-1-phenylethyl]phenylalaninamide(Pha-*S*,*R*) were also used as B* for comparison in the case of *N*,*N*′-dimethyl-5-benzylidenehydantoin. Benzylamine(BA) and triphenylphosphine(PPh_3) were used as the achiral bases(B).

As the specific rotation of enantiomerically pure *N*,*N*′-dimethyl-5-benzylhydantoin was unknown, the enantiomeric excesses shown in Table 2 were determined by the method described in the Experimental section.

The results of the asymmetric hydrogenation are summarized in Table 1 and Table 2.

As can be seen in Table 1, the enantiomeric excesses[4] in runs 5—9 are much higher than those in runs 1—4, and the enantioselectivities are affected by the configurations of the C-2 and C-3 chiral centers of DHP-*OAc* and DHP-*OBz* (the cocatalysts are erythro isomers in runs 5—9 and threo isomers in runs 1—4) but are little affected by that of the chiral center of 1-phenylethylamine moiety.

The most stable conformations of the erythro and the threo isomers may exist as shown in Fig. 1.

In the chirality-recognizing step (*i.e.*, the protonation by the protonated chiral cocatalyst to the carbanion formed through the hydrogenation with $Co(dmgH)_2 \cdot B$[2]), a hydrogen bonding between the amide group of cocatalyst and the functional group of carbanion is possible in the erythro isomer but not in the threo isomer, since in the threo isomer the protonated dimethylamino group and the amide group exist in anti position and cannot interact with the carbanion simultaneously. This explains the difference between enantioselectivity in runs 5—9 and runs 1—4.

As can be seen in Table 2, the enantiomeric excess of *N*,*N*′-dimethyl-5-benzylhydantoin reached 79.1% (run 11), which is the highest value so far attained in the asymmetric hydrogenation of olefinic compounds with $Co(dmgH)_2 \cdot B$-B* system. The configuration of the predominant isomer in every case coincides with that of the chiral center bearing a tertiary amino group of the cocatalyst and the enantioselectivity is not so largely affected by the configuration of the 1-phenylethylamine moiety.

A comparison of Tables 1 and 2 shows that the configurations of *N*,*N*′-dimethyl-5-benzylhydantoin in runs 7, 8, 9, 11 and 12 of Table 2 are opposite to those of methyl *N*-acetylalaninate in runs 6, 8, 9, 10 and 11 of Table 1, respectively, and the enantioselectivities are remarkably increased in runs 11 and 12 of Table 2. The reason for the difference in the enantioselectivity

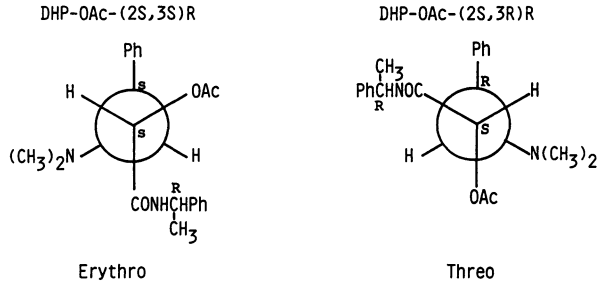


Fig. 1. Conformations of DHP-*OAc*.

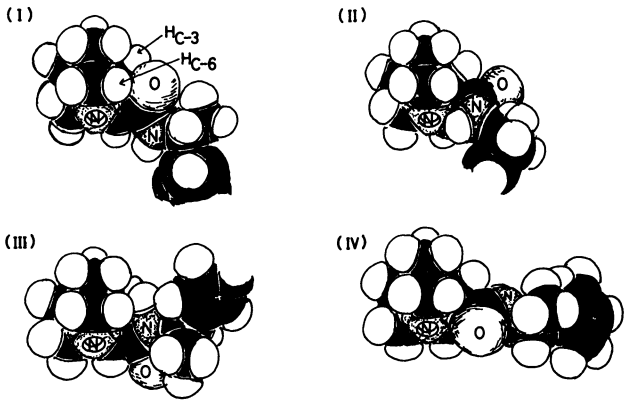


Fig. 2. Conformations of QC-(*S*)*R*.

between the two substrates will be discussed below in the cases of run 10 of Table 1 and run 11 of Table 2.

As the enantioselective recognition is made through the protonation to the carbanions formed from the two substrates by the protonated QC-(*S*)*R*, it is necessary to discuss the interactions between the conformers of the protonated QC-(*S*)*R* and the carbanions. The conformations of QC-(*S*)*R* and the carbanions were considered with CPK's space-filling models.

As C=O and N-H of amide group lie in coplanar anti position, the possible conformers of QC-(*S*)*R* are shown in Fig. 2.

The conformer **III** is very unstable because of a large steric repulsion between the hydrogen atoms attached to C-3 and C-6 of the quinuclidine ($H_{C\text{-}3}$ and $H_{C\text{-}6}$, respectively) and that of N-H of amide group (N-**H**). The conformer **II** and the protonated conformer **IV** are stable because of intramolecular hydrogen bonds (between N-**H** and the nitrogen atom of quinuclidine, and between the carbonyl oxygen and the hydrogen attached to the nitrogen atom of quinuclidine, respectively) and because of small steric repulsions between $H_{C\text{-}3}$, $H_{C\text{-}6}$ and the amide group. Their stabilities, however, will decrease their proton-accepting and proton-donating activities respectively, and will moreover lower their abilities to make an intermolecular hydrogen bond. The protonated conformer **I** (HQC-(*S*)*R*-I) is relatively stable because the steric repulsion between $H_{C\text{-}3}$, $H_{C\text{-}6}$ and the carbonyl oxygen is not so large, and thus can make an intermolecular hydrogen bond between N-**H** of HQC-(*S*)*R*-I and the carbonyl oxygen of the carbanions (the intramolecular hydrogen bonding is impossible).

Therefore, HQC-(*S*)*R*-I is regarded as the best conformer with which to determine the chirality of the carbanions through the intermolecular hydrogen bond in the protonation step.

The possible conformations of the carbanions of (*S*)-*N*,*N*′-dimethyl-5-benzylhydantoin ((*S*)-$DMBH_a$ and (*S*)-$DMBH_b$) and methyl (*R*)-*N*-acetylalaninate ((*R*)-AA) are shown in Fig. 3.

The conformer (*S*)-$DMBH_a$ is more stable irrespective of the relatively large steric repulsion between the hydantoin and benzene rings and is more likely to react with HQC-(*S*)*R*-I than (*S*)-$DMBH_b$, because the electrostatic repulsion between the lone pair on the asym-

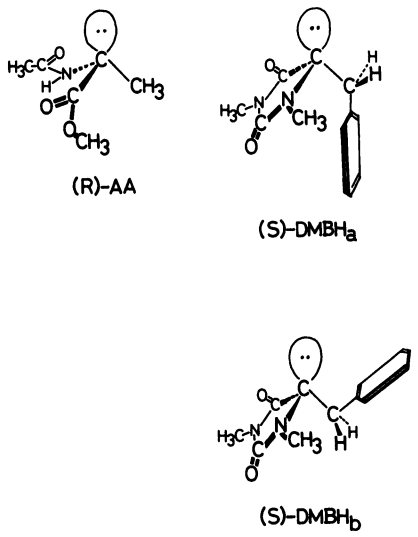


Fig. 3. Conformations of (*R*)-*N*-acetylalaninate and (*S*)-*N*,*N*′-dimethyl-5-benzylhydantoin.

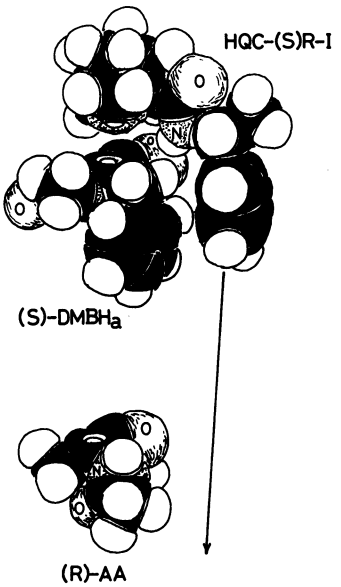


Fig. 4. Models of the protonation by HQC-(*S*)*R*-I to (*S*)-DMBH$_a$ and (*R*)-AA.

metric carbon atom of (*S*)-DMBH$_b$ and the π-electron on the benzene ring is more serious and/or the benzene ring of (*S*)-DMBH$_b$ prevents HQC-(*S*)*R*-I from approaching to the reaction center of (*S*)-DMBH$_b$.

As shown in Fig. 4, HQC-(*S*)*R*-I can approach (*S*)-DMBH$_a$ to make the intermolecular hydrogen bond between N-**H** of HQC-(*S*)*R*-I and the C-4 carbonyl oxygen of (*S*)-DMBH$_a$ without any substantial overlap of their substituents (in Fig. 4, the hydrogen atom attached to the nitrogen atom of quinuclidine and the lone pair on the asymmetric carbon atom of (*S*)-DMBH$_a$ and (*R*)-AA are not depicted for convenience).

On the other hand, if HQC-(*S*)*R*-I approaches (*R*)-DMBH$_a$ without the overlap of their substituents, the intermolecular hydrogen bonding becomes impossible.

Consequently, HQC-(*S*)*R*-I can selectively protonate (*S*)-DMBH$_a$ to give (*S*)-*N*,*N*′-dimethyl-5-benzylhydantoin predominantly with relatively high enantioselectivity.

As can be seen in Fig. 4, HQC-(*S*)*R*-I can approach (*R*)-AA to make the intermolecular hydrogen bond between N-**H** of HQC-(*S*)*R*-I and the carbonyl oxygen of ester group of (*R*)-AA without any substantial overlap of their substituents (if HQC-(*S*)*R*-I in Fig. 4 is shifted in the direction of the arrow and is so placed as to make the hydrogen bond, a plausible model of the transition state of protonation to (*R*)-AA by HQC-(*S*)*R*-I will be made). HQC-(*S*)*R*-I can also approach (*S*)-AA to make the hydrogen bond without a significant overlap of their substituents. However, the approach of HQC-(*S*)*R*-I may occur preferentially to (*R*)-AA rather than to (S)-AA, since the space between $COOCH_3$ and $NHCOCH_3$ is larger than that between CH_3 and $COOCH_3$.

This may explain the opposite and lower enantioselectivity in run 10 of Table 1 in comparison with that of run 11 of Table 2.

Experimental

The melting points were determined by Yanagimoto micro-melting point apparatus and were uncorrected. The IR spectra were recorded on a JASCO A-3 spectrometer. The ^{1}H NMR spectra were obtained on JEOL-FX 200 spectrometer. The optical rotations were measured with a Perkin Elmer 241 polarimeter.

Preparation of Stereoisomers of DHP-OAc and DHP-OBz. As the preparations of **12** and **12′** were described in the preceding paper,[3] the preparation procedures of the other three diastereoisomers and their enantiomers are described below.

*(2R,3S)-2,3-Epoxy-3-phenyl-*N*-[(R)-1-phenylethyl]propionamide (3′) and Its Enantiomer (3).* Starting from 72.1 g of ethyl 2,3-epoxy-3-phenylpropionate, 40.0 g of crystalline (*R*)-1-phenylethylammonium (2*S*,3*R*)-2,3-epoxy-3-phenylpropionate was obtained by Harada's method.[5] The filtrate which contained (*R*)-1-phenylethylammonium (2*R*,3*S*)-2,3-epoxy-3-phenylpropionate(**1′**) was concentrated to dryness *in vacuo* to afford 34.0 g of sirupy residue. This was dissolved in DMF (200 ml) and to the solution was added a solution of DCC (24.6 g, 119 mmol) and 1-hydroxybenzotriazole (16.0 g, 119 mmol) in DMF (150 ml) during 1.5 h on ice-cooling with stirring. Stirring was continued overnight at room tempetature. After filtration of the precipitate, the filtrate was concentrated *in vacuo* at 30—40 °C. The residue was dissolved in ethyl acetate (*ca.* 1300 ml), and the solution was washed successively with a 10% citric acid solution (200 ml), a 4% sodium hydrogencarbonate solution (200 ml), and a sodium chloride solution (300 ml) and then dried (Na_2SO_4). The solution was concentrated to 150—200 ml and the crystals which separated out were dissolved thoroughly on heating. To the solution petroleum ether was added carefully. Crystals (prisms, 17.1 g) were obtained: $[\alpha]_D^{17.5}$ −2.1°; $[\alpha]_{365}^{17.5}$ +46.2° (*c* 0.999, $CHCl_3$).

Its enantiomer(**3**) was likewise prepared from the sirupy residue (33.8 g) containing **1** to give 12.7 g of crystals (prisms): $[\alpha]_D^{25.5}$ +1.6°; $[\alpha]_{365}^{25.5}$ −47.9° (*c* 0.988, $CHCl_3$).

*(2S,3S)-3-Dimethylamino-2-hydroxy-3-phenyl-*N*-[(S)-1-phenylethyl]propionamide (9) and Its Enantiomer (9′).* A suspension of **3** (5.0 g) in a 50% aqueous dimethylamine solution (200 ml) was stirred for 2.5 h at room temperature. The homogeneous solution obtained was evaporated *in vacuo*. A crystalline mass was separated out when water began to evaporate and then was filtered off after water was

added to the solution. After drying, the crystals (5.7 g) were recrystallized from benzene to give 4.2 g of needles: $[\alpha]_D^{20.0}$ −56.1° (*c* 1.016, $CHCl_3$).

Its enantiomer was likewise prepared from **3′** (7.0 g) to give 2.47 g (first crop) and 4.36 g (second crop) of crystals (needles): $[\alpha]_D^{26.0}$ +54.2° (*c* 0.994, $CHCl_3$) and $[\alpha]_D^{21.0}$ +56.1° (*c* 1.007, $CHCl_3$), respectively.

(2S,3S)-2-Acetoxy-3-dimethylamino-3-phenyl-N-[(S)-1-phenylethyl]propionamide (13) and Its Enantiomer (13′). To a solution of **9** (3.8 g, 12.2 mmol) in dry ethyl acetate (200 ml) was added acetyl chloride (1.0 g, 12.2 mmol). The solution was allowed to stand overnight at room temperature. The amorphous solid which separated out was dissolved in water after ethyl acetate was decanted. The aqueous solution was washed with ether, and the aqueous layer was made basic with a sodium hydrogencarbonate solution. The solution was extracted with ethyl acetate. The ethyl acetate layer was dried(Na_2SO_4) and concentrated to yield 3.7 g of crystalline material. This was recrystallized from ethyl acetate–petroleum ether to give 3.23 g of needles: $[\alpha]_D^{27.5}$ −66.8° (*c* 1.003, $CHCl_3$).

Its enantiomer was likewise prepared from **9′** (5.0 g) to give 3.97 g of needles: $[\alpha]_D^{27.0}$ +66.6° (*c* 0.998, $CHCl_3$).

(2S,3S)-3-Chloro-2-hydroxy-3-phenyl-N-[(S)-1-phenylethyl]propionamide (4) and Its Enantiomer (4′). Into a solution of **2** (1.2 g) in 1000 ml of dry benzene was bubbled dry hydrogen chloride gas for 30 min at room temperature with stirring. Stirring was continued for 1 h and then concentrated to dryness to yield 1.2 g of crystalline material.[6] 14.4 g of the crystalline material thus obtained was recrystallized from ethyl acetate (150 ml)– petroleum ether (158 ml) to give 7.7 g of needles: $[\alpha]_D^{20.0}$ +40.8° (*c* 0.500, $CHCl_3$).

Its enantiomer was likewise prepared from **2′** *via* 10.7 g of crystalline material to give 6.1 g of needles: $[\alpha]_D^{27.0}$ −41.1° (*c* 0.506, $CHCl_3$).

(2R,3R)-2,3-Epoxy-3-phenyl-N-[(S)-1-phenylethyl]propionamide (6) and Its Enantiomer (6′). 6.45 g (21.2 mmol) of **4** was dissolved in ethanol (200 ml) while heating. After cooling, 2.12 mol dm^{-1} sodium methoxide solution (10.0 ml) was added dropwise to the solution during 2—3 min with stirring. The solution was allowed to stand for 1.5 h at room temperature and then concentrated. The residue was extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and concentrated to yield 5.5 g of crystalline material. This was recrystallized from ethyl acetate–petroleum ether to give 4.3 g of needles: $[\alpha]_D^{24.0}$ −59.7° (*c* 1.003, $CHCl_3$).

Its enantiomer was likewise prepared from **4′** (5.0 g) to give 4.4 g of needles: $[\alpha]_D^{24.0}$ +60.6° (*c* 1.019, $CHCl_3$).

(2R,3S)-3-Dimethylamino-2-hydroxy-3-phenyl-N-[(S)-1-phenylethyl]propionamide (10) and Its Enantiomer (10′). A suspension of 4.2 g of **6** in a 50% aqueous dimethylamine solution (140 ml) was stirred for 1.5 h at room temperature. The homogeneous solution was treated and purified by the same procedure as **9** to give 4.28 g of needles: $[\alpha]_D^{21.0}$ −125.6° (*c* 1.022, $CHCl_3$).

Its enantiomer was likewise prepared from **6′** (3.5 g) to give 3.2 g of needles: $[\alpha]_D^{20.0}$ +127.1° (*c* 1.036, $CHCl_3$).

(2R,3S)-2-Acetoxy-3-dimethylamino-3-phenyl-N-[(S)-1-phenylethyl]propionamide (14) and Its Enantiomer (14′). These were prepared from **10** (3.6 g) and **10′** (2.9 g) by the same procedure as **13** to give needles (3.4 g and 2.5 g): $[\alpha]_D^{25.0}$ −12.0° (*c* 1.002, $CHCl_3$) and $[\alpha]_D^{27.5}$ +11.9° (*c* 1.003, $CHCl_3$), respectively.

(2R,3R)-3-Chloro-2-hydroxy-3-phenyl-N-[(S)-1-phenylethyl]propionamide (5) and Its Enantiomer (5′). This was prepared from **3** by the same procedure as **4**. The crystalline material (14.5 g) thus obtained was recrystallized from ethyl acetate (100 ml)–petroleum ether (126 ml) to give 5.56 g of prisms. This was again recrystallized from ethyl acetate (25 ml)–petroleum ether (43 ml) to give 4.4 g of prisms: $[\alpha]_D^{20.0}$ −158.3° (*c* 0.504, $CHCl_3$).

Its enantiomer was likewise prepared from **3′**. The product (12.5 g) was recrystallized from ethyl acetate–petroleum ether to give 4.4 g of prisms: $[\alpha]_D^{20.0}$ +156.6° (*c* 0.516, $CHCl_3$).

(2S,3S)-2,3-Epoxy-3-phenyl-N-[(S)-1-phenylethyl]propionamide (7) and Its Enantiomer (7′). These were prepared from **5** (4.1 g) and **5′** (4.0 g) by the same procedure as **6** to give needles (2.5 g and 2.5 g): $[\alpha]_D^{20.5}$ −0.0°; $[\alpha]_{365}^{20.5}$ −16.3° (*c* 1.003, $CHCl_3$) and $[\alpha]_D^{20.5}$ +0.0°; $[\alpha]_{365}^{20.5}$ +15.8° (*c* 1.006, $CHCl_3$), respectively.

(2S,3R)-3-Dimethylamino-2-hydroxy-3-phenyl-N[(S)-1-phenylethyl]propionamide (11) and Its Enantiomer (11′). These were prepared from **7** (3.2 g) and **7′** (3.0 g) by the same procedure as **10** except for recryatallization from ethyl acetate–petroleum ether to give needles (1.82 g and 2.5 g): $[\alpha]_D^{21.0}$ −81.6° (*c* 1.000, $CHCl_3$) and $[\alpha]_D^{20.0}$ +81.6° (*c* 1.002, $CHCl_3$), respectively.

(2S,3R)-2-Acetoxy-3-dimethylamino-3-phenyl-N-[(S)-1-phenylethyl]propionamide (15) and Its Enantiomer (15′). These were prepared from **11** (2.0 g) and **11′** (2.1 g) by the same procedure as **13** except for recrystallization from ether to give needles (1.37 g and 1.25 g): $[\alpha]_D^{27.0}$ −109.8° (*c* 1.001, $CHCl_3$) and $[\alpha]_D^{26.0}$ +110.0° (*c* 1.003, $CHCl_3$), respectively.

(2S,3S)-2-Benzoyloxy-3-dimethylamino-3-phenyl-N-[(R)-1-phenylethyl]propionamide. To a solution of **8′** (1.2 g, 3.8 mmol) in dry ethyl actate (200 ml) was added benzoyl chloride (0.59 g, 4.2 mmol). The solution was allowed to stand for 2 d and then concentrated. The residue was solidified with ether. The solid material was filtered off and recrystallized from methanol–ether to give 0.69 g of prisms: $[\alpha]_D^{15.0}$ +103.3° (*c* 1.002, CH_3OH); IR(KBr) 3500, 3200, 3100, 2800—2400 (amide NH and N^+–H), 1720 (ester C=O) and 1690 cm^{-1} (amide C=O). Found: C, 66.31; H, 6.63; N, 5.95%. Calcd for $C_{26}H_{29}N_2O_3Cl \cdot H_2O$: C, 66.17; H, 6.68; N, 5.80%.

Melting points, elemental analyses, IR spectra and ^1H NMR spectra of the compounds **2**—**15** and their enantiomers **2′**—**15′** are summarized in Tables 3, 4, 5 and 6.

Preparation of QC-(S)R and QC-(R)R. 2-Quinuclidinecarboxylic acid was prepared from 4-pyridinecarbaldehyde and diethyl malonate by the method reported by Långström.[7] Optical resolution of ethyl 2-quinuclidinecarboxylate was caried out by the method reported by Pracejus and Kohl.[8] (*S*)- and (*R*)- quinuclidinecarboxylic acid hydrochlorides, whose optical rotations were $[\alpha]_D^{21.0}$ −96.5° (1.073, water) and $[\alpha]_D^{24.0}$ +97.5° (*c* 1.012, water), respectivety (literature[7]: $[\alpha]_D$ −96.2° (*c* 1, water)) were obtained by hydrolysis of their ethyl esters. QC-(*S*)*R* and QC-(*R*)*R* were prepared by a condensation of **16** and **17** with (*R*)-1-phenylethylamine by the following procedures.[9]

(S)-N-[(R)-1-Phenylethyl]-2-quinuclidinecarboxamide (18).[10] Thionyl chloride (31.5 ml) and **16** (2.95 g, 15.4 mmol) were refluxed for 20 min and the homogeneous solution was concentrated to remove the excess thionyl chloride. To the residue was added dry ether (60 ml) and (*R*)-1-phenylethylamine (8.0 ml, 62 mmol) on ice cooling with stirring. Stirring was continued for 3 h and to the solution was added 50% aqueous potassium carbonate solution untill the water layer became basic. The water layer was extracted with ether three times (300 ml). The ether layer was dried(Na_2SO_4) and concentrated to remove also the excess (*R*)-1-phenylethylamine and to give 3.1 g of oily material which soon crystallized. This was recrystallized from petroleum ether to give 2.33 g of plates: mp 97.0—99.0 °C; $[\alpha]_D^{22.5}$ −3.5°, $[\alpha]_{365}^{22.5}$ +41.1° (*c* 1.004, $CHCl_3$); IR (KBr) 3350 (NH) and 1650 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ=1.47 (3H, d, *J*=7.1 Hz, $C\underline{H}_3$), 1.47 (4H, m), 1.82 (3H, m), 2.62 (2H, q), 2.88 (2H, m), 3.31 (1H, t, *J*= 8.8 Hz, C-2 methine proton), 5.14 (1H, quintet, *J*=7.1 Hz, CH_3-$C\underline{H}$) and 7.30 (6H, m, Ph and $N\underline{H}$). Found: C, 74.38;

TABLE 3. 2,3-EPOXY-3-PHENYL-*N*-(1-PHENYLETHYL)PROPIONAMIDE

No.[a]	mp/°C	Found(Calcd)/%			IR, ν/cm^{-1}		^{1}HNMR, δ in $CDCl_3$			
		C (76.38)	H (6.41)	N (5.24)[b]	NH	C=O (amide)	$C\underline{H}_3$-CH (J_{Hz})	$CH\underline{C}ONH$ (J_{Hz})	$C\underline{H}Ph$ (J_{Hz})	$C\underline{H}$-CH_3
2	169.0—170.0	76.36	6.54	5.57	3280	1670	1.53 d	3.54 d	3.80 d	5.15 q[c]
2′	168.0—169.0	76.12	6.66	5.83			(6.84)	(1.96)	(1.96)	
3	165.0—166.0	76.27	6.42	5.61	3300	1660	1.52 d	3.51 d	3.91 d	5.15 q
3′	166.0—167.0	76.12	6.65	5.71			(6.84)	(1.96)	(1.96)	
6	97.0— 98.0	76.47	6.44	5.50	3340	1640	1.39 d	3.80 d	4.31 d	4.83 q
6′	97.5— 98.0	76.44	6.40	5.32			(6.84)	(4.90)	(4.90)	
7	124.0—126.0	76.37	6.46	5.36	3350	1640	0.81 d	3.78 d	4.35 d	4.82 q
7′	125.0—127.0	76.35	6.44	5.39			(6.84)	(4.90)	(4.90)	

a) Compound number. b) Calculated for $C_{17}H_{17}NO_2$. c) Quintet.

TABLE 4. 3-CHLORO-2-HYDROXY-3-PHENYL-*N*-(1-PHENYLETHYL)PROPIONAMIDE

No.[a]	mp/°C	Found(Calcd)/%			IR, ν/cm^{-1}			^{1}HNMR, δ in $CDCl_3$				
		C (67.21)	H (5.97)	N (4.61)[b]	NH	OH	C=O (amide)	$C\underline{H}_3$-CH (J_{Hz})	$CH\underline{C}ONH$ (J_{Hz})	$O\underline{H}$ (J_{Hz})	$C\underline{H}Ph$ (J_{Hz})	$C\underline{H}$-CH_3
4	166.0—168.0	67.40	6.30	4.99	3400	3280	1640	1.50 d	4.40 dd	3.00 d	5.59 d	5.13 q[c]
4′	164.5—166.5	67.42	6.28	4.96				(6.84)	(6.86, 2.44)	(6.86)	(2.44)	
5	127.0—130.0	67.44	6.02	4.62	3400	3250	1650	1.52 d	4.29 dd	3.10 d	5.55 d	5.13 q
5′	131.0—132.0	67.31	6.00	4.55				(6.84)	(6.86, 2.46)	(6.86)	(2.46)	

a) Compound number. b) Calculated for $C_{17}H_{18}NO_2Cl$. c) Quintet.

TABLE 5. 3-DIMETHYLAMINO-2-HYDROXY-3-PHENYL-*N*-(1-PHENYLETHYL)PROPIONAMIDE

No.[a]	mp/°C	Found(Calcd)/%			IR, ν/cm^{-1}			^{1}HNMR, δ in $CDCl_3$				
		C (73.04)	H (7.74)	N (8.97)[b]	NH	OH	C=O (amide)	$C\underline{H}_3$-CH (J_{Hz})	$N(C\underline{H}_3)_2$	$CH\underline{C}ONH$ (J_{Hz})	$C\underline{H}Ph$ (J_{Hz})	$C\underline{H}$-CH_3
8	156.5—157.5	73.18	7.87	8.83	3400	3300	1650	1.40 d	2.26 s	3.59 d	4.59 d	4.89 q[c]
8′	157.0—157.5	73.23	7.77	8.97				(6.86)		(5.62)	(5.62)	
9	100.5—102.0	71.28	8.05	8.64[d]	3400	3300	1635	0.93 d	2.26 s	3.54 d	4.56 d	4.82 q
9′	100.0—101.0	71.12	8.01	8.63[d]				(6.86)		(5.40)	(5.40)	
10	140.0—142.0	73.01	7.94	8.90	3380	3280	1650	1.46 d	2.12 s	3.60 d	4.34 d	5.05 q
10′	142.0—143.0	73.17	7.91	8.89				(6.96)		(7.34)	(7.34)	
11	100.0—101.0	72.93	7.89	8.81	3280		1658	1.46 d	2.18 s	3.66 d	4.32 d	5.04 q
11′	100.0—101.0	73.10	7.84	8.84				(7.10)		(7.76)	(7.76)	

a) Compound number. b) Calculated for $C_{19}H_{24}N_2O_2$. c) Quintet. d) Calculated for $C_{19}H_{24}N_2O_2 \cdot 1/2H_2O$: C, 71.00; H, 7.84; N, 8.72%.

TABLE 6. 2-ACETOXY-3-DIMETHYLAMINO-3-PHENYL-*N*-(1-PHENYLETHYL)PROPIONAMIDE

No.[a]	mp/°C	Found(Calcd)(%)			IR, ν/cm^{-1}			^{1}HNMR, δ in $CDCl_3$					
		C (71.16)	H (7.39)	N (7.90)[b]	NH	C=O (ester)	C=O (amide)	$C\underline{H}_3$-CH (J_{Hz})	$N(C\underline{H}_3)_2$	$COOC\underline{H}_3$	$CH\underline{C}ONH$ (J_{Hz})	$C\underline{H}Ph$ (J_{Hz})	$C\underline{H}$-CH_3
12	78.0— 82.0	71.14	7.59	7.85	3400	1725	1675	1.44 d	2.21 s	2.02 s	3.88 d	5.79 d	5.02 q[c]
12′	83.0— 84.0	71.28	7.61	7.78				(6.86)			(7.58)	(7.58)	
13	153.0—154.5	71.38	7.57	7.87	3300	1740	1660	1.25 d	2.19 s	1.99 s	3.81 d	5.76 d	5.00 q
13′	152.0—153.5	71.34	7.54	7.86				(6.96)			(7.58)	(7.58)	
14	144.0—145.0	71.30	7.55	7.75	3350 3300	1750	1650 1680	1.23 d	2.26 s	2.14 s	3.78 d	5.60 d	4.97 q
14′	144.0—146.0	71.26	7.60	7.79				(6.86)			(7.10)	(7.10)	
15	127.5—129.0	71.22	7.57	7.86	3300	1740	1650	1.41 d	2.28 s	2.13 s	3.73 d	5.63 d	5.00 q
15′	128.0—130.0	71.25	7.59	7.78				(6.98)			(6.84)	(6.84)	

a) Compound number. b) Calculated for $C_{21}H_{26}N_2O_3$. c) Quintet.

H. 8.58; N, 10.84%. Calcd for $C_{16}H_{22}N_2O$: C, 74.26; H, 8.81; N, 10.76%.

(R)-N[(R)-1-Phenylethyl]-2-quinuclidinecarboxamide (19).[10] This was prepared from **17** (2.3 g) by the procedure used for **20** to yield 2.6 g of oily material which did not crystallize. *p*-Toluenesulfonic acid (1.54 g, 8.1 mmol) and 2.1 g (8.1 mmol) of the oily material were dissolved in methanol (20 ml) and then the solution was concentrated to dryness. To the residue was added dry benzene and the mixture was concentrated (this was repeated 2—3 times). The crystalline material obtained was recrystallized from ethyl acetate (1200 ml) to give 2.2 g of thin plates, which were further recrystallized from ethyl acetate (700 ml) to give 1.8 g of thin plates. These crystals were dissolved in a small amount of water and to the solution was added enough 50% potassium carbonate solution to make the water layer basic. The solution was extracted with ether 2—3 times. The ether layer was dried (Na_2SO_4) and concentrated to give 1.1 g of oil: $[\alpha]_D^{21.5}$ +121.6° (*c* 1.017, $CHCl_3$); IR (NaCl) 3350 (NH) and 1770 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ=1.49 (3H, d, *J*= 6.84 Hz, $C\underline{H}_3$), 1.49 (4H, m), 1.78 (3H, m), 2.75 (2H, t), 2.88 (2H, q), 3.27 (1H, t, *J*=7.8 Hz, C-2 methine proton), 5.51 (1H, quintet, *J*=6.84 Hz, CH_3-C$\underline{H}$), 7.30 (6H, m, Ph and N$\underline{H}$).

Asymmetric Hydrogenation of Methyl 2-(acetylamino)acrylate and N,N'-Dimethyl-5-benzylidenehydantoin with Co(dmgH)$_2$·B-B.* As the procedures of the hydrogenation of methyl 2-(acetylamino)acrylate and the isolation of the hydrogenated product were described in the preceding paper,[3] only those of *N,N'*-dimethyl-5-benzylidenehydantoin in run 11 of Table 2 are given below.

To a methanol solution (10 ml) of $CoCl_2 \cdot 6H_2O$ (0.25 g, 1.05 mmol) was added a hot solution of dimethylglyoxime (0.24 g, 1.05 mmol) in methanol (15 ml) under nitrogen atmosphere with stirring. The solution was stirred for 2—3 min and then 1.0 ml of 2.12 mol dm^{-1} sodium methoxide solution was added to the solution. After 1—2 min, triphenylphosphine (0.275 g, 1.05 mmol) in hot methanol (15 ml) and a methanol solution of equimolar mixture of **18** (0.27 g, 1.05 mmol) and its hydrochloride were added to the solution.

Methanol in the resulting catalyst solution was evaporated *in vacuo*; stirring was continued untill the sample became a wet paste. To this paste 15 ml of degassed benzene was added by a syringe under atmospheric pressure of hydrogen, and the mixture was then evaporated again to wet paste *in vacuo*. To the resulting catalyst was added a degassed benzene solution (60 ml) of *N,N'*-dimethyl-5-benzylidenehydantoin (2.0 g, 9.26 mmol) again with a syringe.

After a theoretical amount of hydrogen was absorbed (for about 3 d), 100 ml of benzene was added to the reaction mixture. Then the solution was washed successively with water, sodium chloride solution, 3 mol dm^{-1} hydrochloric acid solution (100 ml), sodium chloride solution and sodium hydrogencarbonate solution. The benzene layer was dried (Na_2SO_4) and concentrated to give an oily material.

The oily material was adsorbed on a silica-gel column (Wako Gel C-300, 20 g, 1.8ϕ×23 cm), and eluted by benzene (100—150 ml) and then by a mixture of benzene and ethyl acetate (10:1, 200 ml; and then 5:1, 100 ml). Triphenylphosphine was eluted out with 100—150 ml of benzene and 1.89 g of oily material was obtained from the eluates of the mixture of benzene and ethyl acetete (10:1 and 5:1, 300 ml). The oily material was soon crystallized.

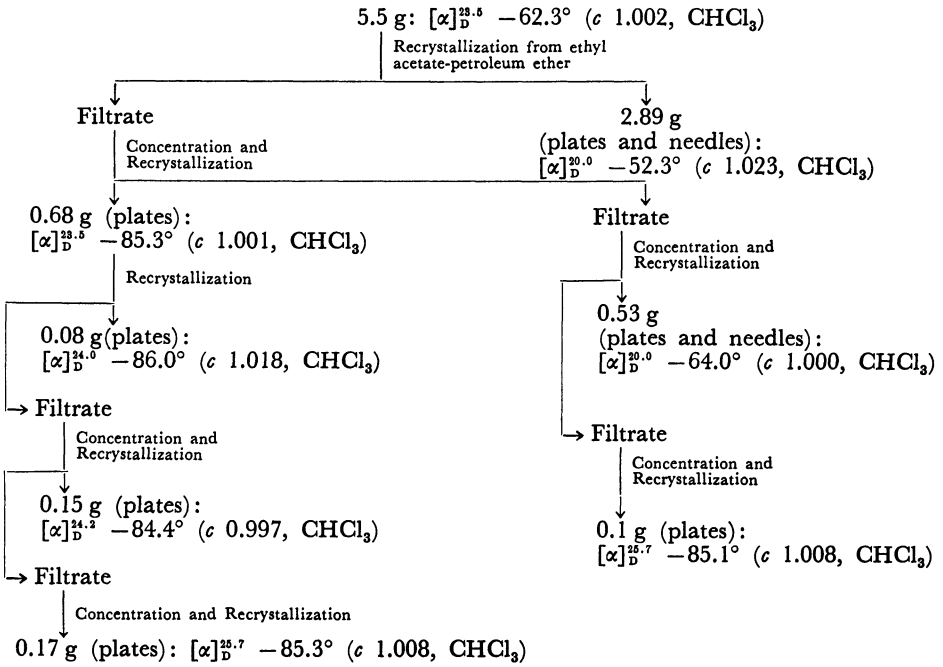
When benzylamine was used as the achiral base, the purification of the product through silica-gel column was not necessary.

Determination of the Specific Rotation of an Enantiomerically Pure (S)-N,N'-Dimethyl-5-benzylhydantoin. (*S*)-5-benzylhydantoin[$[\alpha]_D^{21.0}$ −102.2° (*c* 0.508, 50% C_2H_5OH), literature[11]: $[\alpha]_D$ −96.3° (50% C_2H_5OH)] prepared from (*S*)-phenylalanine was dimethylated by Shin's method[12] as follows.

To a mixture of (*S*)-5-benzylhydantoin (6.0 g) and potassium carbonate (43.8 g) in DMF (180 ml) was added methyl iodide (33 ml) with vigorous stirring; the stirring was continued for 2 d at room temperature. The reaction mixture was poured into water (200 ml) and the solution was extracted with ethyl acetate twice (400 ml). The ethyl acetate layer was washed with sodium chloride solution (200 ml) three times, dried(Na_2SO_4) and then concentrated to give oily material.

The oily material was adsorbed on a silica-gel column (Wako Gel C-300, 60 g, 3.5ϕ×20 cm), and eluted by benzene (600 ml) and then by a mixture of benzene and ethyl acetate (5:1, 700 ml). The eluate of the mixture of benzene and ethyl

TABLE 7. RECRYSTALLIZATION OF *N,N'*-DIMETHYL-5-BENZYLHYDANTOIN OF $[\alpha]_D$ −62.3°



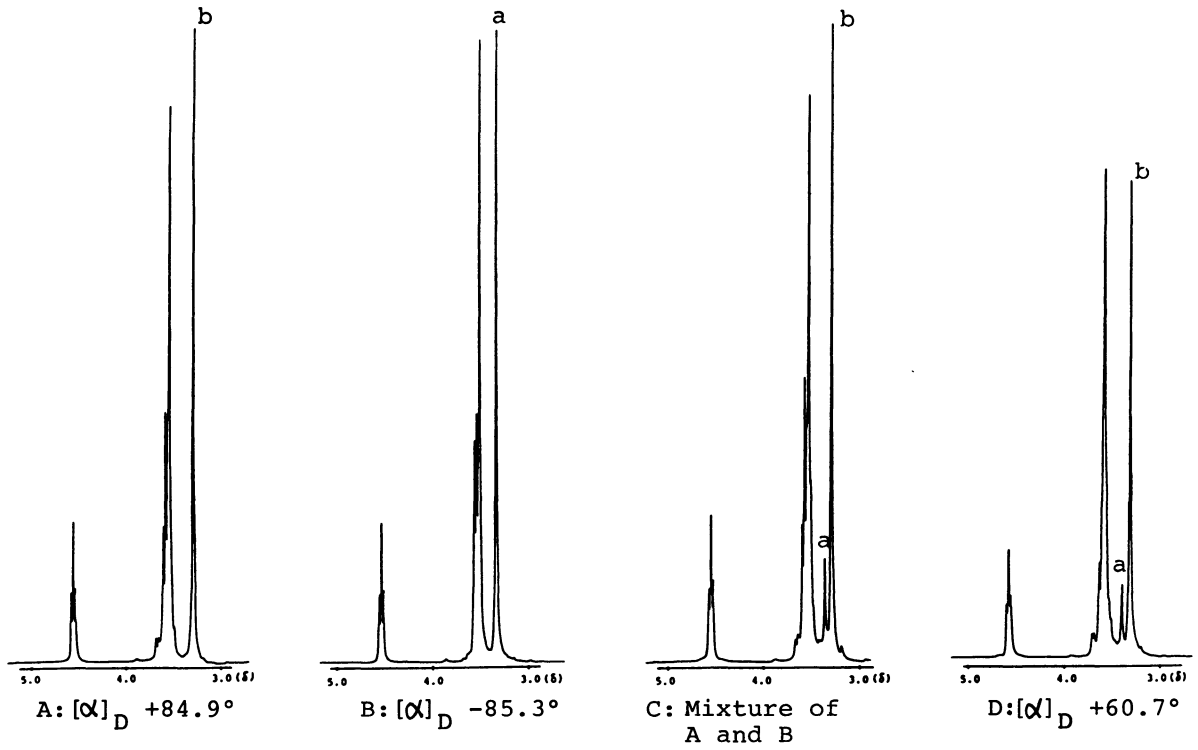


Fig. 5. ^1H NMR spectra of *N,N'*-dimethyl-5-benzylhydantoin in the presence of chiral shift reagent. In each case 45.0—46.0 mg of the sample was dissolved in 860—875 mg of $CDCl_3$ and to the solution 16.0—17.0 mg of the chiral shift reagent was added.

acetate was concentrated to give 5.78 g of oily material which crystallized gradually: $[\alpha]_D^{23.5}$ −62.3° (*c* 1.022, $CHCl_3$).

This was recrystallized from ethyl acetate–petroleum ether to give 2.89 g of crystals in which plates were covered with needles: $[\alpha]_D^{20.0}$ −52.3° (*c* 1.004, $CHCl_3$). The filtrate was concentrated and the crystals obtained were recrystallized from ethyl acetate–petroleum ether to give 0.68 g of long plates: $[\alpha]_D^{23.5}$ −85.3° (*c* 1.001, $CHCl_3$). The long plates were recrystallized repeatedly, as shown in Table 7.

The highest value thus obtained was $[\alpha]_D^{24.0}$ −86.0° (*c* 1.018, $CHCl_3$).

N,N'-dimethyl-5-benzylhydantoin (1.5 g) in run 12 of Table 2 ($[\alpha]_D^{24.0}$+60.7° (*c* 1.004, $CHCl_3$)) was similarly recrystallized from ethyl acetate–petroleum ether to give 0.19 g of long plates as a second crop: $[\alpha]_D^{22.0}$ +84.9° (*c* 1.002, $CHCl_3$).

The ^1H NMR spectra of the samples of $[\alpha]_D$ +84.9° (A), $[\alpha]_D$ −85.3° (B), $[\alpha]_D$ +60.7° (D; of run 12 in Table 2) and the mixture (C) of (A, 39.1 mg) and (B, 6.6 mg) in the presence of tris(3-trifluoroacetyl-d-camphorato)europium(III)[13] are shown in Fig. 5. These ^1H NMR spectra show that signals a and b of each spectrum are those of *S* and *R* enantiomers respectively and that the samples (A) and (B) are approximately enantiomerically pure.[14] Therefore, the highest value detected above ($[\alpha]_D$ −86.0°) must be the one of the enantiomerically pure sample; the enantiomeric excesses in Table 2 were thus calculated from this value.

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