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Asymmetric Synthesis of β-Amino-α,α-dimethyl-β-phenylpropionic Acid. The Reactions of Chiral Schiff Bases with Dimethylketene and with Reformatsky Reagent

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Asymmetric synthesis of optically active β-amino-α,α-dimethyl-β-phenylpropionic acid (7) was achieved by the reaction of chiral Schiff bases with dimethylketene or with Reformatsky reagent, in the range of 33—35% optical purities. The specific rotation and configuration of 7 were determined by correlation with authentic *R*(+)-β-benzoylamino-α,α-dimethyl-β-phenylethanol. The steric courses of these reactions are discussed.

Keywords——asymmetric synthesis; β-amino-α,α-dimethyl-β-phenylpropionic acid; chiral Schiff base; dimethylketene; Reformatsky reagent; oxazinone; β-lactam; six-membered ring transition state

Recently, several naturally occurring β-amino acids containing an asymmetric carbon atom have been isolated.[2] Although many studies on asymmetric syntheses of optically active α-amino acids[3] are available, only a few papers have so far appeared on β-amino acids.[4—6] Asymmetric syntheses of β-amino acids were achieved by the addition of chiral amines to C=C compounds,[4,6a] by the reaction of chiral Schiff bases with chiral and achiral Reformatsky reagents,[6b] and by the reduction of enamines.[5,6c]

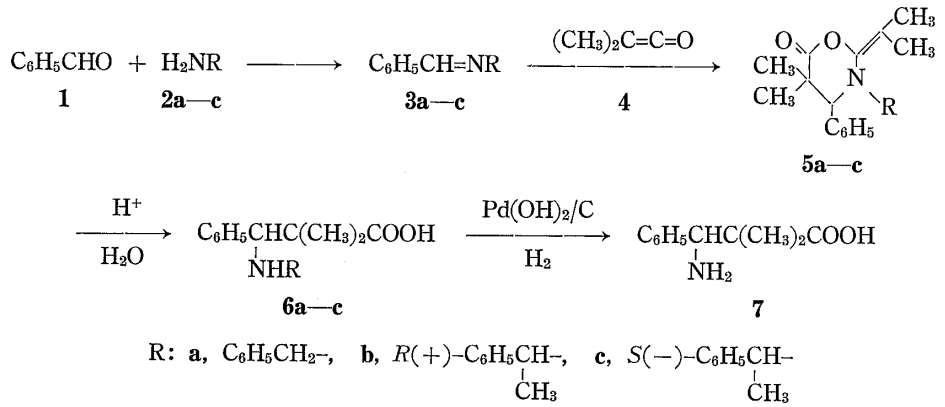


Chart 1. Method A

1) Location: 5-1, *Oe-hon-machi, Kumamoto-shi, 862, Japan.*
2) H.R. Crumpler, C.E. Dent, H. Harris, and R.G. Westall, *Nature* (London), **167**, 307 (1951); N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, *Agr. Biol. Chem.* (Tokyo), **30**, 132 (1966); M. Sato and T. Tatsuno, *Chem. Pharm. Bull.* (Tokyo), **16**, 2182 (1968); S. Kondo, S. Shibahara, S. Takahashi, K. Maeda, H. Umezawa, and M. Ohno, *J. Am. Chem. Soc.*, **93**, 6305 (1971); T. Wakamiya, T. Shiba, and T. Kaneko, *Bull. Chem. Soc. Japan*, **45**, 3668 (1972).
3) J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reaction," Prentice-Hall Inc., New Jersey, 1971.
4) A.P. Terentev, R.A. Gracheva, and T.F. Dendeko, *Dolk. Acad. Nauk. SSSR*, **163**, 674 (1965).
5) K. Achiwa and T. Soga, *Tetrahedron Lett.*, **1978**, 1119.
6) *a*) M. Furukawa, T. Okawara, and Y. Terawaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 1319 (1977); *b*) M. Furukawa, T. Okawara, Y. Noguchi, and Y. Terawaki, *ibid.*, **26**, 260 (1978); *c*) M. Furukawa, T. Okawara, Y. Noguchi, and Y. Terawaki, **27**, 2223 (1979).

One possible route to β-amino acids is the cycloaddition of Schiff bases to ketenes, and this reaction has been investigated by Martin[7] using achiral substrates. We now report the asymmetric synthesis of β-amino-α,α-dimethyl-β-phenylpropionic acid from chiral Schiff bases and dimethylketene. We also examined asymmetric synthesis by the reaction of chiral Schiff bases with Reformatsky reagent prepared from ethyl α-bromoisobutyrate.

The cycloaddition of Schiff bases with ketenes results in the formation of six-membered ring compounds, oxazinones. With chiral Schiff bases, this cycloaddition is expected to proceed stereoselectively. The chiral Schiff bases (**3b** and **c**)[8] used in the reaction were synthesized from benzaldehyde and *R*(+)-α-methylbenzylamine (**2b**) or *S*(−)-α-methylbenzylamine (**2c**). The reaction of **3** with dimethylketene (**4**), prepared from isobutyryl chloride and triethylamine in a solution *in situ*, was successfully carried out in acetonitrile at −30—−40° to afford oxazinones (**5**) in 56—68% yields. Compound **5** was hydrolyzed with 6 N hydrochloric acid under reflux and then treated with infrared (IR) 120 (H^+ form) followed by hydrogenolysis over 10% palladium hydroxide on charcoal to yield β-amino acids (**7**). In the case of the chiral Schiff bases (**3b** and **c**) containing the *R*(+)- and *S*(−)-α-methylbenzylimino moieties, the *R*(+)- and *S*(−)-β-amino acids (**7**) were obtained in optical purities of 47 and 53%, respectively.

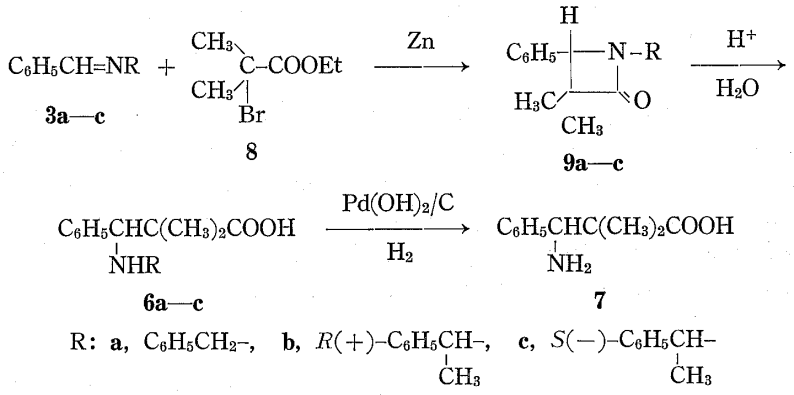


Chart 2. Method B

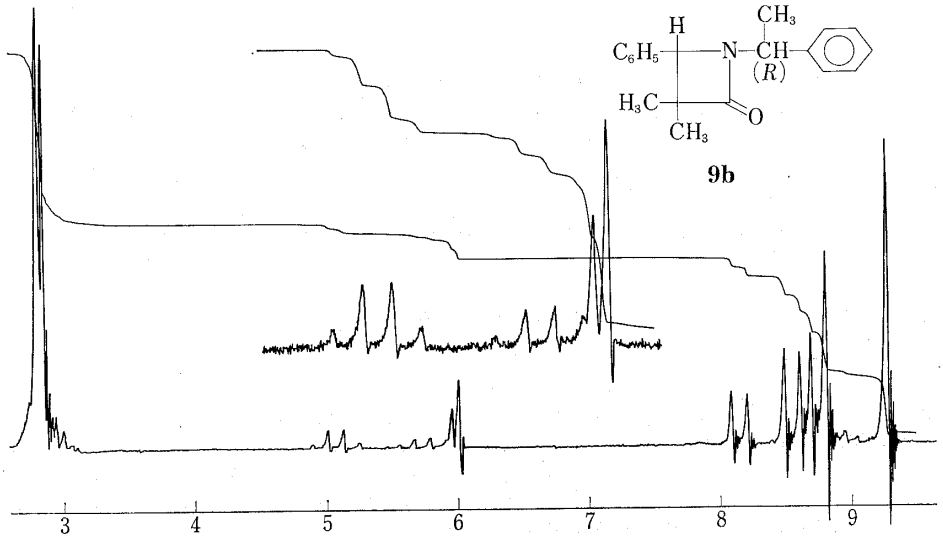


Fig.

7) J.C. Martin, V.A. Hoyle Jr., and K.C. Brannock, *Tetrahedron Lett.*, **1965**, 3589; K.C. Brannock, R.D. Burpitt, P.G. Gott, and V.A. Hoyle Jr., *J. Org. Chem.*, **36**, 2211 (1971).
8) M. Furukawa, T. Okawara, and Y. Terawaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 181 (1977).

Asymmetric synthesis through the formation of a β-lactam by the reaction of **3** with the Reformatsky reagent, prepared from ethyl α-bromoisobutyrate (**8**) and zinc *in situ*, was also examined.

β-Lactam intermediate formation is expected to be highly stereoselective. The reaction was carried out by adding **8** to a boiling solution of **3** in dry benzene containing an excess of zinc powder to give 1-benzyl-3,3-dimethyl-4-oxo-2-phenylazetidines (**9**) in fairly good yields. The ^{1}H–NMR spectrum of **9b** is shown in the figure.

The signals of α-methyl, β-methine, α'-methyl, and α'-methine groups were observed as two singlets, two singlets, two doublets, and two quartets, respectively, indicating the presence of a mixture of the diastereoisomers. The ratio was 65:35 from the integration data.

The β-lactam **9** was, without isolation from the reaction mixture, hydrolyzed with 6 N hydrochloric acid under reflux for 10 hours followed by hydrogenolysis over 10% palladium hydroxide on charcoal to give **7**. In contrast to the case of cycloaddition with dimethylketene, this Reformatsky reaction gave **7** with a configuration different from that of the Schiff base used. Contrary to expectation, the optical purities were only 33 and 36%. Increased optical yields would be expected at lower temperature, but unfortunately the reaction did not proceed under such conditions.

Specific rotations, configurations, optical purities, and overall yields of **7** prepared by these two methods are listed in Table I.

Table I. Optically Active β-Amino-α,α-dimethyl-β-phenylpropionic Acid (7) obtained *via* the Intermediates **5b—c** and **9b—c**

Method	R in **5** and **9**	$[\alpha]_{25}^{D}$ (1N HCl)	Confign. of **7**	Optical purity[c] (%)	Overall yield (%)
A	$R(+)$Me[a]	$+14.5°(c=0.8)$	R	47	21
	$S(-)$Me[b]	$-16.3°(c=1.5)$	S	53	28
B	$R(+)$Me[a]	$-11.0°(c=1.9)$	S	36(30)[d]	35
	$S(-)$Me[b]	$+10.0°(c=2.2)$	R	33(28)[d]	36

a) $R(+)$Me: $R(+)$-$C_6H_5\underset{\displaystyle CH_3}{\underset{|}{CH}}$–. *b*) $S(-)$Me: $S(-)$-$C_6H_5\underset{\displaystyle CH_3}{\underset{|}{CH}}$–.

c) Defined as $([\alpha]_D^{obs}/[\alpha]_D^{pure.}) \times 100$. Optically pure $R(+)$-**7** has $[\alpha]_D^{15}+30.6°$ (c=1.5, 1 N HCl).

d) These optical purities were calculated from the integration data for ^{1}H-NMR spectra of the β-lactams (**9b** and **c**).

In order to determine the specific rotation and the absolute configuration of **7**, stereochemical correlation was performed as shown in Chart 3.

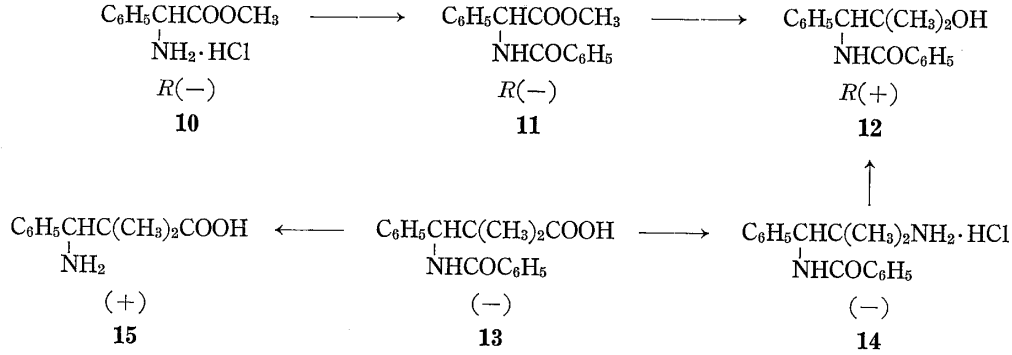
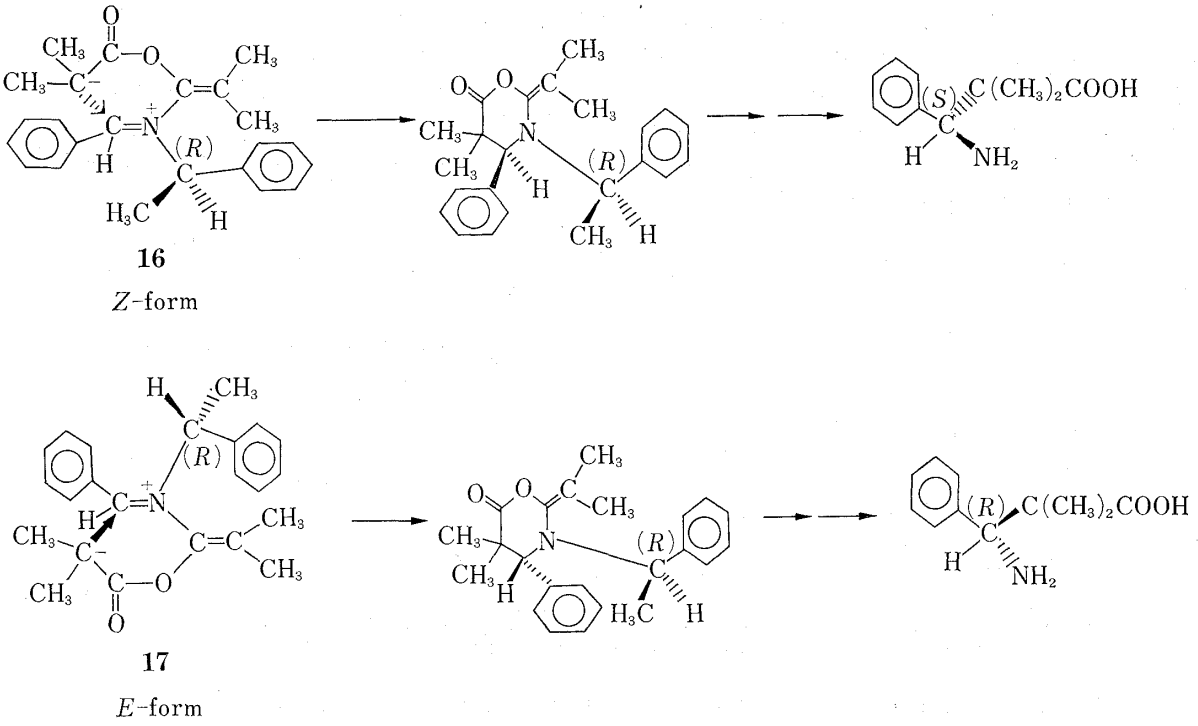


Chart 3

Compound **7** was correlated with an authentic sample of $R(+)$-β-benzoylamino-α,α-dimethyl-β-phenylethanol (**12**), which was prepared by benzoylation of the known compound methyl $R(-)$-phenylglycinate (**10**), followed by Grignard reaction of the resulting N-benzoyl derivatives (**11**) with methylmagnesium iodide. Compound **12** thus obtained showed $[\alpha]_D^{15}$

+12.5° (c=1.4, EtOH). On the other hand, racemic **7** was converted into the N-benzoyl derivative, followed by resolution with cinchonine. The resolution was carried out by fractional crystallization, then treatment of the cinchonine salt with 1 N hydrochloric acid. The resulting optically active compound (**13**) ($[\alpha]_D^{15}$ −24.1°, c=2.0, EtOH) was hydrolyzed with 6 N hydrochloric acid to give optically active **7** showing $[\alpha]_D^{15}$ +30.6° (c=1.5, 1 N HCl). The optical purity of **7** in Table 1 is based on this value. On the other hand, **13** was converted by Schmidt reaction with sodium azide in chloroform in the presence of sulfuric acid as a catalyst into the corresponding amino derivative (**14**), followed by diazotization to **12**, which showed $[\alpha]_D^{15}$ +9.8° (c=1.2, EtOH). On the basis of these results, it is reasonable to conclude that the absolute configuration of (+)-**7** is *R*.

The steric course in the case of the reaction of **3b** with dimethylketene can be presumed to be as shown below.

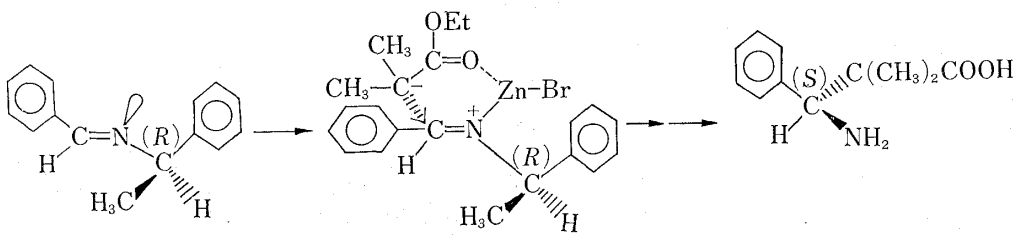


16
Z-form

17
E-form

Chart 4

The reaction proceeds through the formation of the immonium salt, **16** (*Z*-form) or **17** (*E*-form). The attack of a carbanion takes place on the less bulky side of the carbonium ion to afford *S*-**7** in the *Z*-form (**16**), but *R*-**7** in the *E*-form. There is steric repulsion between the phenyl and the methyl groups in the oxazinone from **16**, and acess of carbanion is therefore prevented. However, such repulsion does not exist in the oxazinone from **17**. Therefore, this reaction preferentially proceeds in the *E*-form.



3b
E-form

Chart **5**

The steric course of the reaction of **3b** with the Reformatsky reagent may occur as follows. The reaction proceeds through a six-membered ring transition state from the more stable *E*-form of **3b**, and carbanion attack occurs on the less bulky side of the carbonium ion to give **7** *via* several steps.

Experimental

Hydrogenation was carried out with a Skita and Parr catalytic hydrogenation apparatus. Specific rotations were measured with a Jasco DIP-4 polarimeter using a 10 mm cell. The IR spectra were recorded with a Jasco IRA-1 grating infrared spectrometer. The ^{1}H-NMR spectra were determined with a JEOL C-60H high resolution NMR instrument.

Schiff Bases (3a—c)——These compounds were prepared from benzaldehyde (**1**, 10.6 g, 0.1 mol) and amines (**2a—c**, 0.1 mol) in benzene by the usual method.[8]

3-Alkyl-5,5-dimethyl-2-isopropylidene-4-phenyldihydro-2*H*-1,3-oxazine-6(5*H*)-ones (5a—c)——Triethylamine (9.1 g, 0.09 mol) was gradually added to a stirred solution of isobutyryl chloride (6.4 g, 0.06 mol) in anhydrous acetonitrile (40 ml) at −30——40° and stirring was continued for an additional 10 min. A solution of **3a—c** (0.02 mol) in acetonitrile (10 ml) was slowly added to the mixture with stirring, keeping the temperature at −30—40°, and stirring was continued, allowing the temperature to raise slowly to room temperature. The precipitated triethylamine hydrochloride was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in water (20 ml) and extracted with ether (30 ml). The extract was washed with 1% aq. $NaHCO_3$ (20 ml), 0.1 N HCl (20 ml), and water (20 ml) twice, then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was crystallized by the addition of a small amount of benzene to afford **5a—c**. 3-Benzyloxazinone (**5a**) was recrystallized from benzene, but the other optically active derivatives (**5b** and **c**) were used for subsequent hydrogenolysis without purification. Samples were recrystallized for elemental analyses. Their melting points, yields, specific rotations, elemental analyses, IR and ^{1}H-NMR spectra are listed in Table 2.

***β*-Alkylamino-*α*,*α*-dimethyl-*β*-phcnylpropionic Acids (6a—c)**——1) By Method A: 3-Alkyloxazinone (**5a—c**, 0.005 mol) was refluxed with 6 N HCl (20 ml) for 10 hr. The mixture was extracted with ether (20 ml), and the aqueous layer was evaporated to dryness under reduced preseure. The residue was dissolved in a small amount of water and the solution was applied to an IR 120 column (H^+ form, 2.2×26.5 cm). The column was eluted with 1.5 N aqueous ammonia and the fraction containing **6a—c** was evaporated to dryness under reduced pressure. The residue from **5a** was recrystallized from EtOH to give **6a**: Yield, 0.82 g (55%).

Table II. 3-Alkyl-5,5-dimethyl-2-isopropylidene-4-phenyldihydro-2H-1,3-oxazine-6(5H)-ones (**5a—c**)

	R	Formula	mp (°C)	Analysis (%) Calcd. C	H	N	Found C	H	N
5a	$C_6H_5CH_2$–	$C_{22}H_{25}NO_2H_2O$	160	74.76	7.70	3.96	74.60	7.84	4.16
5b	$R(+)C_6H_5\underset{\displaystyle CH^3}{\overset{\displaystyle |}{C}}H$–	$C_{23}H_{27}NO_2H_2O$	179—181	75.17	7.95	3.81	75.30	7.94	4.13
5c	$S(-)C_6H_5\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}H$–	$C_{23}H_{27}NO_2H_2O$	179—181	75.17	7.95	3.81	75.30	8.01	3.78

	Yield (%)	IR ν_{max}^{KBr} (cm^{-1})	$[\alpha]_D^{25}$(EtOH)	^{1}H-NMR spectra (δ) in $CDCl_3$
5a	58	1718 1602	——	7.30 (s, 5H, arom), 7.14—6.96 (m, 5H, arom), 6.20 (s, 1H, CH), 4.72 (s, 2H, CH_2), 1.39 (s, 6H, 2×CH_3), 1.17 (d, 3H, J=6.0 Hz, CH_3), 0.91 (d, 3H, J=6.0 Hz, CH_3)
5b	56	1728 1570	−1.8(c=2.0)	7.02 (s, 10H, 2×arom), 5.43 (q, 1H, J=7.0 Hz, CH), 3.05 (m, 1H, J=7.0 Hz, CH), 1.86 (d, 3H, J=7.0 Hz, CH_3), 1.48 (d, 6H, J=8.0 Hz, 2×CH_3), 1.36 and 1.22 (d, 6H, J=6.0 Hz, 2×CH_3)
5c	68	1726 1567	+1.7(c=1.8)	7.01 (s, 10H, 2×arom), 5.40 (q, 1H, J=7.0 Hz, CH), 3.02 (m, 1H, J=7.0 Hz, CH), 1.82 (d, 3H, J=8.0 Hz, CH_3), 1.44 (d, 6H, J=8.0 Hz, 2×CH_3), 1.32 and 1.14 (d, 6H, J=6.0 Hz, 2×CH_3)

Table III. 1-Alkyl-3,3-dimethyl-4-oxo-2-phenylazetidines (**9a—c**)

	R	Formula	mp (°C) or bp (mmHg)	Analysis (%) Calcd. C	H	N	Found C	H	N
9a	$C_6H_5CH_2$–	$C_{18}H_{19}NO$	31—32 153—155°(2)	81.47	7.22	5.28	81.51	7.32	5.42
9b	$R(+)C_6H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}H$–	$C_{19}H_{21}NO$	158—160°(2)	81.68	7.58	5.01	81.80	7.81	4.91
9c	$S(-)C_6H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}H$–	$C_{19}H_{21}NO$	158—160°(2)	81.68	7.58	5.01	81.76	7.86	5.00

	Yield (%)	IR ν_{max}^{film} (cm^{-1})	$[\alpha]_D^{25}$(benzene)	^1H-NMR spectra (δ) in $CDCl_3$
9a	73	1740—1760	——	7.09 (s, 5H, arom), 7.07 (s, 5H, arom), 4.30 (q, 2H, J=15.0 Hz, CH_2), 4.07 (s, 1H, CH), 1.33 (s, 3H, CH_3), 0.77 (s, 3H, CH_3)
9b	76	1740—1760	−37.2°(c=2.5)	7.20 (s, 5H, arom), 7.16 (s, 5H, arom), 4.94 and 4.27 (q, 1H, J=7.0 Hz, CH), 4.03 (d, 1H, J=3.0 Hz, CH), 1.86 and 1.45 (d, 3H, J=7.0 Hz, CH_3), 1.25 (d, 3H, J=7.0 Hz, CH_3), 0.75 (s, 3H, CH_3)
9c	75	1740—1760	+35.6°(c=2.0)	7.18 (s, 5H, arom), 7.15 (s, 5H, arom), 4.93 and 4.27 (q, 1H, J=7.0 Hz, CH), 4.02 (d, 1H, J=3.0 Hz, CH), 1.84 and 1.44 (d, 3H, J=7.0 Hz, CH_3), 1.25 (d, 3H, J=6.0 Hz, CH_3), 0.72 (s, 3H, CH_3)

mp 147—148°. IR ν_{max}^{KBr} cm^{-1}: 1590 (COO^-). *Anal.* Calcd. for $C_{18}H_{21}NO_2 \cdot H_2O$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.99; H, 7.81; N, 4.41.

The other optically active derivatives (**6b** and **c**) were used for subsequent hydrogenolysis without isolation in order to avoid fractionation during purification.

2) By Method B: N-Alkylazetidinones (**9a—c**, 0.02 mol) were refluxed with 6 N HCl (20 ml) for 10 hr. The hydrolysates were then worked up as described in Method A. The β-N-benzylamino acid (**6a**) was isolated as the hydrochloride and recrystallized from EtOH. mp 126—127°. Yield, 4.7 g (98%). IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1640 (COOH). *Anal.* Calcd. for $C_{18}H_{22}NO_2Cl$; N, 4.38. Found: N, 4.54.

β-Amino-α,α-dimethyl-β-phenylpropionic Acid (7)——A solution of **6a—c** (0.001 mol) in 50% aqueous EtOH (30 ml) was hydrogenolyzed over 10% palladium hydroxide on charcoal (0.7 g) for 12 hr. When the reaction was over, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was recrystallized from EtOH to give **7**. Racemic **7** (from **6a**): mp 245—246°. Yield, 0.16 g (84%). IR ν_{max}^{KBr} cm^{-1}: 1550—1580 (COO^-). NMR δ (D_2O): 7.38 (s, 5H, arom), 4.27 (s, 1H, OH), 1.28 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). *Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.23; H, 7.93; N, 7.24.

The specific rotations of **6b** and **c** were measured in the crude state without isolation in order to avoid fractionation. Sample of optically active **7** (from **6b**) was recrystallized from EtOH for elemental analysis. mp 243—245°. IR ν_{max}^{KBr} cm^{-1}: 1550—1580 (COO^-). *Anal.* Calcd. for $C_{11}H_{15}NO_2$; C, 68.37; H, 7.82; N, 7.25. Found: C, 68.32; H, 7.93; N, 7.24.

3,3-Dimethyl-4-oxo-2-phenylazetidines (9a—c)——Ethyl α-bromoisobutyrate (**8**, 2.34 g, 0.012 mol) was gradually added with stirring to a boiling solution of **3a—c** (0.01 mol) in dry benzene (30 ml) containing zinc powder (1.34 g, 0.02 gr.at.). The reaction mixture was refluxed for an additional 3 hr, and after cooling, poured with stirring into conc. ammonia solution (20 ml), washed with 1 N HCl (20 ml), 3% $NaHSO_3$ (20 ml), and finally twice with water (20 ml), then dried over anhydrous Na_2SO_4. After removing the solvent, the residue was distilled under reduced pressure. The boiling points, yields, specific rotations, elemental analyses, and IR and ^1H-NMR spectral data are listed in Table 3.

Methyl *R*(−)-N-benzoylphenylglycinate (11)——Methyl *R*(−)-phenylglycinate (10, 10.0 g, 0.05 mol) was benzoylated by the Schotten-Bauman procedure with benzoyl chloride (7.7 g, 0.055 mol) and 1 N NaOH (110 ml) to give **11** (10.3 g, 77%), melting at 90—91°. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1740 ($COOCH_3$), 1660 (CONH). $[\alpha]_D^{15}$ −108.1° (c=2.5, EtOH).

***R*(+)-2-Benzoylamino-1,1-dimethyl-2-phenylethanol (12)**——Compound **11** (5.4 g, 0.02 mol) was converted by Grignard reaction with methyl iodide (14.2 g, 0.1 mol) and magnesium (2.4 g, 0.1 gr.at.) into **12**

(4.0 g, 74%), melting at 134—135° after recrystallization from benzene. $[\alpha]_D^{15}$ +12.5° (c=1.0, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 3330 (NH), 1620 (CONH). *Anal.* Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.75; H, 7.07; N, 5.38. NMR δ ($CDCl_3$): 7.56 (m, 1H, NH), 7.25 (m, 5H, arom), 7.23 (s, 5H, arom), 4.94 (d, 1H, J=9.0 Hz, CH), 2.28 (s, 1H, OH), 1.38 (s, 3H, CH_3), 1.08 (s, 3H, CH_3).

Optically Active β-N-Benzoylamino-α,α-dimethyl-β-phenylpropionic Acid (13)——Racemic 7 (15.6 g, 0.081 mol) was benzoylated with benzoyl chloride (13.6 g, 0.097 mol) and 2 N NaOH (100 ml, 0.2 mol) by the Schotten-Bauman procedure to give racemic **13** (19.0 g, 80%), melting at 174—175° after recrystallization from EtOH. IR ν_{max}^{KBr} cm^{-1}: 3380 (NH), 1660 (COOH), 1655 (CONH). *Anal.* Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.80; H, 6.50; N, 4.67. NMR δ ($CDCl_3$): 8.25—8.10 (broad, 1H, COOH), 7.70 (m, 1H, NH), 7.31 (m, 5H, arom), 7.20 (s, 5H, arom), 5.15 (d, 1H, J=9.0 Hz, CH), 1.50 (s, 3H, CH_3), 1.21 (s, 3H, CH_3).

The racemic **13** (5.9 g, 0.02 mol) and cinchonine (5.9 g, 0.02 mol) were dissolved in 50% aqueous EtOH (60 ml). The solution was allowed to stand for 2 days at room temperature. The separated salt was recrystallized three times from EtOH. mp 174—175°. Yield, 1.6 g (28%). $[\alpha]_D^{15}$ +94.7° (c=2.5, EtOH). *Anal.* Calcd. for $C_{36}H_{41}N_3O_4$: C, 74.56; H, 7.13; N, 7.25. Found: C, 75.05; H, 7.12; N, 6.93.

Treatment of the salt with 1 N HCl followed by extraction with ethyl acetate afforded (−)-**13** showing $[\alpha]_D^{15}$ −23.6° (c=2.0, EtOH). Hydrolysis of (−)-**13** with 6 N HCl gave (+)-**7** with $[\alpha]_D^{15}$ +30.6° (c=1.5, 1 N HCl). mp 233—235°. *Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 67.94; H, 7.90; N, 6.83.

2-Amino-1-benzoylamino-2-methyl-1-phenylpropane Hydrochloride (14)——Sodium azide (0.65 g, 0.01 mol) was added in small portions with stirring to a suspension of **13** (1.5 g, 0.005 mol, $[\alpha]_D^{15}$ −24.1° (c=2.0, EtOH) with 100% sulfuric acid (12 ml) in $CHCl_3$ (20 ml) at 50—55°. The mixture was warmed for 1.5 hr, poured onto crushed ice, made alkaline with sodium carbonate, and extracted with ether (30 ml). The extract was washed twice with water (20 ml) and dried over anhydrous Na_2SO_4. Dry hygrogen chloride was introduced into the dry extract, then the solution was evaporated to one-third of the original volume under reduced pressure. The separated hydrochloride was filtered off and recrystallized from 50% aqueous EtOH. mp 247—249°. Yield, 0.62 g (41%). $[\alpha]_D^{25}$ −31.4° (c=1.0, 50% aqueous EtOH). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH_3^+), 3240 (NH), 1640 (CONH). *Anal.* Calcd. for $C_{17}H_{24}ClN_2O$: C, 66.99; H, 6.95; N, 9.19. Found: C, 67.15; H, 7.20; N, 9.20. NMR δ ($(CD_3)_2SO$): 8.45—8.18 (broad, 3H, NH_3^+), 7.95 (m, 1H, NH), 7.56—7.22 (m, 10H, 2×arom), 5.33 (d, 1H, J=9.0 Hz, CH), 1.36 (s, 6H, 2×CH_3).

3-Benzoylamino-1,1-dimethyl-2-phenylethanol (12) from 14——A solution of sodium nitrite (0.076 g, 0.0011 mol) in water (5 ml) was gradually added with stirring to a suspension of **14** (0.30 g, 0.001 mol, $[\alpha]_D^{25}$ −31.4° (c=1.0, 50% aqueous EtOH)) in 1 N HCl(5 ml) under cooling with ice-water. When the addition was complete, the reaction mixture was stirred for 2 hr at room temperature, then extracted with ether (15 ml). The extract was washed with 1% aq. $NaHCO_3$ (5 ml) and water (5 ml), dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The residue recrystallized from benzene to give (+)-**12** showing $[\alpha]_D^{25}$ +9.8° (c=0.6, EtOH). Yield, 0.031 g (12%). IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 3340 (OH), 1610 (CONH).