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Amino Acids and Peptides. XXVIII.[1] A New Synthesis of α-Amino Acid Derivatives by Alkylation of Schiff Bases derived from Glycine and Alanine[2]

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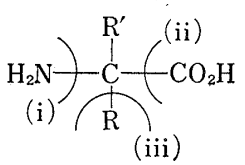
The Schiff base (I) from glycine *tert*-butyl ester and benzaldehyde was treated with lithium diisopropylamide to give the corresponding α-carbanion. Alkylation of the α-carbanion with benzyl or butyl halide followed by removal of benzylidene group yielded phenylalanine or norleucine *tert*-butyl ester (IIa or IIb), accompanied by dialkylated product (IIIa or IIIb). The Schiff base (IV) from alanine *tert*-butyl ester and (−)-menthone (VI) was also treated as above to furnish α-methylphenylalanine or α-methyl-β-(3,4-dimethoxyphenyl)alanine *tert*-butyl ester (Va or Vb) in 21 or 24% asymmetric yield.

Keywords——alkylation; α-carbanion; amino acid; asymmetric synthesis; Schiff base

For the synthesis of α-amino acids and their derivatives we have already reported two methods based on the electrophilic attack to carbanions: (i) amination of α-metalated carboxylic acids[4] and amides,[5] and (ii) carboxylation of α-metalated amine derivatives.[5] We here report the third method based on the alkylation of carbanions derived from glycine or alanine, depicted as (iii)[6]:

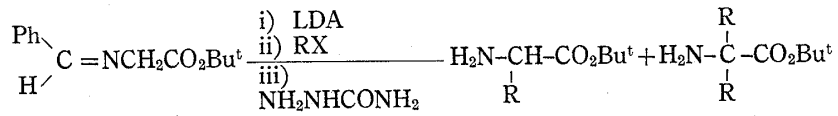


R′=H or CH₃

When glycine is converted to the other α-amino acids by alkylation, both amino and carboxyl groups of glycine should be protected with functions which are not attacked with lithium diisopropylamide (LDA), a carbanion generator. Thus, *tert*-butyl benzylideneaminoacetate (I), easily prepared from glycine *tert*-butyl ester and benzaldehyde, was chosen as a starting material. The α- carbanion of I was generated by the action of LDA. Alkylation with either benzyl or butyl halides followed by treatment with semicarbazide gave a mixture of mono and dialkyl derivatives (II and III), whose results are summarized in Table I. Lowering the reaction temperature decreased the formation of dialkyl derivative (III) while changing the leaving group(Cl→Br→I) increased the yield of monoalkyl derivatives (II).[7]

1) Part XXVII: K. Murato, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 1559 (1977).
2) A part of this work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1975, Abstracts of Papers, II, p. 4.
3) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan.*
4) S. Yamada, T. Oguri, and T. Shioiri, *J. Chem. Soc. Chem. Commun.*, **1972**, 623; T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 167 (1975).
5) T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 173 (1975).
6) For previous trials, see *a*) M. Saito, K. Okawa, and S. Akabori, *Bull. Chem. Soc. Japan*, **30**, 937 (1957); *b*) S. Akabori and T. Otani, *Arch. Biochem. Biophys.*, **83**, 1 (1959); *c*) K. Harada and J. Oh-hashi, *J. Org. Chem.*, **32**, 1103 (1967); *d*) A. Nakahara, S. Nishikawa, and J. Mitani, *Bull. Chem. Soc. Japan*, **40**, 2212 (1967); *e*) K. Rühlmann and G. Kuhrt, *Angew. Chem. Int. Ed. Engl.*, **7**, 809 (1968); *f*) U. Schöllkopf, D. Hoppe, and R. Jentsch, *Angew. Chem. Int. Ed. Engl.*, **10**, 331 (1971); *g*) J.Y. Chenard, D. Commereuc, and Y. Chauvin, *J. Chem. Soc. Chem. Commun.*, **1972**, 750; *h*) M. Suzuki, K. Matsumoto, T. Iwasaki, and K. Okumura, *Chem. Ind.* (London), **1972**, 687; *i*) B. Angelo, *C.R. Acad. Sci.* (*C*), **278**, 383 (1974); *j*) D. Hoppe, *Angew. Chem. Int. Ed. Engl.*, **14**, 426 (1975); *k*) A.P. Krapcho and E.A. Dundulls, *Tetrahedron Lett*, **1976**, 2205.
7) Recently G. Stork, *et al.* have also reported the benzylidene derivative of glycine ethyl ester can be used in mono- or sequential dialkylation leading to syntheses of α-amino esters and acids: G. Stork, A.Y.W. Leong, and A.M. Touzin, *J. Org. Chem.*, **41**, 3491 (1976).

Table I.

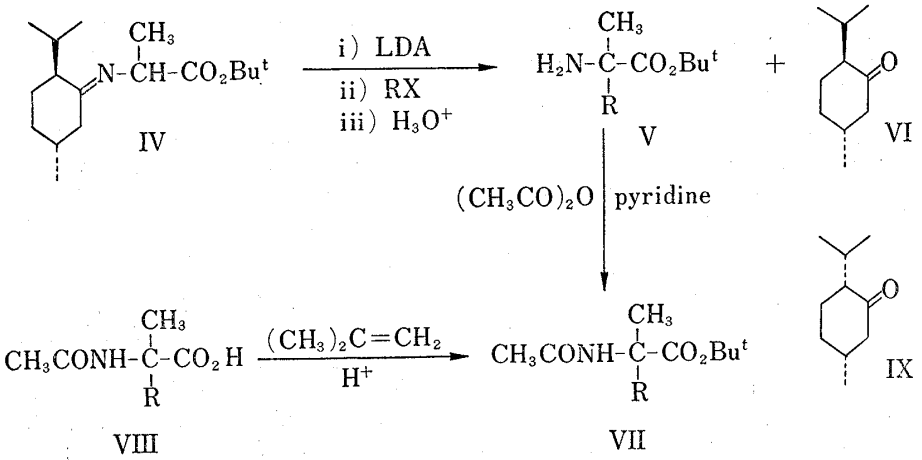


I IIa,b IIIa,b

RX	Reaction temp (°C)	Reaction time (hr)	Yield (%) of IIa,b	Yield (%) of IIIa,b
$PhCH_2Cl$	−72 → Room temp.	0.5 → 21	25	6
$PhCH_2Br$	−74 → Room temp.	2 → overnight	50[a]	11[a]
$PhCH_2Br$	−74	3.5	76	4
BuBr	−5 → Room temp.	0.5 → 7	25	3
BuI	−74	24	51	trace

a) Phenyl hydrazine was used for removal of benzylidene group.
a: R=benzyl, b: R=butyl.

On the basis of these facts, we next investigated the asymmetric alkylation[6g,h] of the Schiff base(IV) prepared from DL-alanine *tert*-butyl ester and easily available (−)-menthone (VI), as shown in Chart 1. The Schiff base(IV) was converted to its carbanion with LDA, and alkylated with benzyl bromide. The resulting Schiff base was hydrolyzed with aqueous citric acid to give (*S*)-α-methylphenylalanine *tert*-butyl ester(*S*–Va) in 55% yield. The asymmetric yield of the reaction was calculated to be 21% by the comparison of the optical rotation of the acetyl derivatives(*S*–VIIa) of *S*–Va with that of *R*–VIIa prepared from (*R*)-N-acetyl-α-methylphenylalanine[8] (*R*–VIIIa). When 3,4-dimethoxybenzyl bromide was used in place of benzyl bromide, the (*S*)-3,4-dimethoxy derivative (*S*–Vb) was obtained in 72% yield with 24% asymmetric yield which was determined by the comparison of the optical rotation of the acetyl derivative (*S*–VIIb) with that of *R*–VIIb prepared from (*R*)-N-acetyl-α-methyl-β-(3,4-dimethoxyphenyl)alanine[9](*R*-VIIIb).



a: R=benzyl
b: R=3, 4-dimethoxybenzyl

Chart 1

8) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1138 (1966).
9) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 1399 (1965).

Since (−)-menthone(VI) was recovered in 60% yield in the latter asymmetric alkylation, the chiral source may be used for recycling purpose, hence it enables to proliferate the asymmetry. However, (+)-isomenthone(IX), 2-epimerized compound, was also obtained in 12% yield. It has not been known yet where epimerization occurred.

The investigation on the more efficient system for the asymmetric alkylation is now under way.[10]

Experimental

Unless otherwise stated, mp's were measured on a hot stage apparatus and uncorrected; bp's were uncorrected; infrared (IR) spectra were measured in KBr tablets for crystals and in liquid films for oils; proton magnetic resonance (NMR) spectra (60 or 100 MHz) were measured in carbon tetrachloride or deuterochloroform and chemical shifts (δ) are given in ppm relative to internal tetramethylsilane; mass spectra (MS) were measured at 70 eV. Silica gel (Wakogel C-200) was used for column chromatography. PLC refers to preparative thick layer chromatography on Merck Kieselgel GF_{254} plates. The organic solutions were dried over sodium sulfate before vacuum evaporation.

***tert*-Butyl Benzylideneaminoacetate (I)**——A mixture of glycine *tert*-butyl ester[11] (7.81 g, 59.6 mmol), benzaldehyde (6.30 g, 59.6 mmol), and magnesium sulfate (5 g) in benzene (50 ml) was stirred at room temperature for 24 hr, and filtered. The filtrate was washed with ice-cooled saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried, and evaporated. The residue was distilled at 103—106° (0.02 mmHg) to give a colorless oil of I (7.48 g, 57%). IR ν_{max} cm^{-1}: 2990, 1732, 1644, 1583, 1455, 1386, 1372, 1150, 848, 757, 694. NMR δ 1.42 (9H, singlet, $(CH_3)_3C$), 4.14 (2H, singlet, CH_2), 7.2—7.5 (3H, multiplet, *m*- and *p*-protons of benzene), 7.6—7.9 (2H, multiplet, *o*-protons of benzene), 8.13 (1H, singlet, CH). MS *m/e*: 219 (M^+), 204, 163, 162, 119, 118, 91. *Anal.* Calcd. for $C_{13}H_{17}NO_2$ (molecular weight 219.1259): C, 71.20; H, 7.82; N, 6.39. Found: 219.1255 (by mass measurement); C, 70.49; H, 7.83; N, 6.27.

A General Procedure for α-Anion Formation of I——To a stirred diisopropylamine (210 mg, 2×1.05 mmol) in tetrahydrofuran (5 ml) was added butyl lithium in hexane (1.2 ml, 2×1.05 mmol) below 0° under nitrogen, and the mixture was stirred at 5° for 15 min. The Schiff base (I) (439 mg, 2 mmol) in tetrahydrofuran (1 ml) was added to the above LDA solution at −70——74°, and the mixture was stirred for 50 min to form a yellow clear solution of the α-anion.

Benzylation of α-Anion of I. (i) With Benzyl Chloride——To the α-anion (2 mmol) of I obtained as above was added benzyl chloride (277 mg, 2×1.1 mmol) in tetrahydrofuran (1 ml) at −70——74°, and the mixture was stirred at −72° for 0.5 hr and then at room temperature for 21 hr. The mixture was filtered with the aid of celite, and the filtrate was evaporated to give a yellow oil (678 mg). This yellow oil (281 mg, 0.83 mmol) and semicarbazide hydrochloride (101 mg, 0.83×1.1 mmol) was dissolved in ethanol (1.5 ml), and ammonia gas was introduced to the stirred solution with ice-cooling for 5 min. The mixture was stirred at room temperature for 3 hr. The white precipitates were filtered, and the filtrate was evaporated to the residue, which was washed with diethyl ether. The washings were evaporated to give a yellow oil (145 mg), which was subjected to a PLC with diethyl ether–benzene (1: 1). The upper fraction gave DL-phenylalanine *tert*-butyl ester (IIa) (45 mg, 25%) as a colorless oil, which was identified with the sample prepared according to the literature.[11]

The lower fraction gave DL-2-benzylphenylalanine *tert*-butyl ester (IIIa) (15 mg, 6%) as a colorless oil, IR ν_{max} cm^{-1}: 3378, 3320, 1726, 1601, 1499, 1457, 1372, 1150, 705. NMR δ 1.23 (11H, singlet, $(CH_3)_3C$ and NH_2), 2.94 (4H, quartet, $J=13$ Hz, $2\times CH_2$), 7.12 (10H, singlet, $2\times C_6H_5$). Reaction with phenylisocyanate as usual afforded the phenylurea derivative as colorless needles, mp 146—147° (recrystallized from hexane–benzene), IR ν_{max} cm^{-1}: 3345, 1735, 1655, 1600, 1545, 1498, 1224, 1153, 700. *Anal.* Calcd. for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51. Found: C, 75.45; H, 7.03; N, 6.70.

(ii) With Benzyl Bromide-a——To the α-anion (2 mmol) of I obtained as above was added benzyl bromide (410 mg, 2×1.2 mmol) in tetrahydrofuran (1 ml) at −74°, and the mixture was stirred at −74° for 2 hr and then at room temperature overnight. The mixture was evaporated, the residue was suspended in benzene (10 ml), and the precipitates were filtered. After addition of phenylhydrazine (216 mg, 2 mmol) to the filtrate, the mixture was stirred at room temperature for 3 hr and filtered. The filtrate was evaporated to give a yellow oil (869 mg), 130 mg of which was subjected to a PLC with methylene chloride. The upper fraction was eluted with methylene chloride to give IIa (33 mg, 50%) as a yellow oil. The lower fraction gave IIIa (10 mg, 11%).

(iii) With Benzyl Bromide-b——To the α-anion (3 mmol) of I obtained according to the general procedure was added benzyl bromide (617 mg, 3×1.2 mmol), and the mixture was stirred at −74° for 3.5 hr. Quench-

10) A preliminary account along this line was already communicated: S. Yamada, T. Oguri, and T. Shioiri, *J. Chem. Soc. Chem. Commun.*, **1976**, 136.

11) G.W. Anderson and F.M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).

ing with water (a few drops) followed by evaporation gave the residue, which was dissolved in ethanol (5 ml). After addition of semicarbazide hydrochloride (666 mg, 3×2 mmol), ammonia gas was introduced to the ice-cooled mixture for 1 min. The mixture was stirred at room temperature for 1 hr. The precipitates were filtered, and the filtrate was dissolved in benzene (40 ml). The benzene solution was extracted with 15% aqueous citric acid, and the aqueous extracts were basified with potassium carbonate and extracted with benzene. Drying of the benzene layer followed by evaporation afforded a yellow oil (539 mg), which was identified with a mixture of IIa and IIIa, whose integral ratio of benzyl protons of the nuclear magnetic resonance (NMR) spectrum was determined to be 1: 0.047. Thus the yield of IIa and IIIa was calculated to be 76% for IIa and 4% for IIIa.

Butylation of α-Anion of I. (i) **With Butyl Bromide**——To the α-anion (3 mmol) of I obtained as above was added butyl bromide (450 mg, 3×1.1 mmol) in tetrahydrofuran (1 ml) at −5°, and the mixture was stirred at −5° for 30 min and then at room temperature for 1 hr. After addition of sodium iodide (*ca.* 10 mg), the mixture was stirred at room temperature for 6 hr and quenched with a few drops of water. The evaporated residue was dissolved in methanol (5 ml), and semicarbazide hydrochloride (666 mg, 3×2 mmol) was added. Ammonia gas was introduced to the ice-cooled mixture for 5 min, and the mixture was stirred at room temperature for 1 hr and evaporated. Diethyl ether–hexane was added to the residue, and the precipitates were filtered. The filtrate was evaporated to give a yellow oil, which was dissolved in benzene (30 ml) and extracted with 15% aqueous citric acid (10 ml×5). The aqueous extracts were basified with potassium carbonate and extracted with benzene (20 ml×6). After washing of the benzene extracts with saturated aqueous sodium chloride, the benzene was evaporated to give a yellow oil (240 mg), which was fractionated with silica gel (20 g) column chromatography with diethyl ether–hexane (1: 2). The first fraction to be eluted was 2-butylnorleucine *tert*-butyl ester (IIIb) (23 mg, 3%) as a colorless oil, IR ν_{max} cm^{-1}: 3380, 3300, 1735, 1364, 1140, 845; NMR δ 0.7—1.9 (18H, multiplet, 2×*n*-C_4H_9), 1.38 (9H, singlet, $(CH_3)_3C$), 1.66 (2H, broad singlet, exchangeable with D_2O, NH_2).

The second fraction to be eluted was norleucine *tert*-butyl ester (IIb) (140 mg, 25%) as a yellow oil, IR ν_{max} cm^{-1}: 3378, 3305, 1732, 1373, 1250, 1157, 853; NMR δ 0.60—1.70 (9H, multiplet, *n*-C_4H_9), 1.40 (9H, singlet, $(CH_3)_3C$), 1.53 (2H, singlet, exchangeable with D_2O, NH_2), 3.14 (1H, multiplet, CH). Reaction of IIb with phenyl isocyanate afforded 5-butyl-3-phenylhydantoin as colorless needles (recrystallized from benzene–hexane), mp 112—113°, IR ν_{max} cm^{-1}: 3220, 3110, 1700, 1502, 1430, 1176; NMR δ 0.7—2.2 (9H, multiplet, *n*-C_4H_9), 4.12 (1H, multiplet, CH), 7.12 (1H, broad singlet, exchangeable with D_2O after standing for 1 day, NH), 7.42 (5H, singlet, benzene H). *Anal.* Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.33; H, 6.96; N, 12.22.

(ii) **With Butyl Iodide**——To the α-anion (3 mmol) of I was added butyl iodide (662 mg, 3×1.2 mmol) and hexamethylphosphortriamide (535 mg, 3 mmol) at −74°, and the mixture was stirred at −74° for 24 hr. The evaporated residue was dissolved in benzene (30 ml), and washed with water (20 ml). The benzene layer was dried and evaporated to give a yellow oil (749 mg), which was dissolved in ethanol (5 ml). Semicarbazide hydrochloride (666 mg, 3×2 mmol) was added, and ammonia gas was introduced to the ice-cooled mixture for 5 min. The mixture was stirred at room temperature for 1 hr, and filtered. The filtrate was evaporated to the residue, which was suspended in hexane and filtered again. The residual oil (560 mg) after evaporation was fractionated over silica gel (30 g) with diethyl ether–hexane (1: 2) to give IIb (285 mg, 51%) as a colorless oil. Only a minute amount of IIIb was detected by thin-layer chromatography of the fractions before IIb.

The Schiff Base (IV) from DL-Alanine *tert*-Butyl Ester and (−)-Menthone (VI)——A mixture of DL-alanine *tert*-butyl ester[12] (3.64 g, 25 mmol) and (−)-menthone (VI) (3.85 g, 25 mmol) in toluene (50 ml) was refluxed for 5 days using a Cope apparatus. After evaporation, the residue was distilled at 95—96° (0.07 mmHg) to give IV (3.3 g, 47%) as a colorless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1734, 1650, 1457, 1374, 1166, 850; NMR δ 0.7—2.5 (21H, multiplet), 1.40 (9H, singlet, $(CH_3)_3C$), 4.03 (1H, quartet, J=6 Hz, CHN); MS *m/e*: 281 (M^+), 239, 225. Molecular weight (by accurate mass measurement): Calcd. for $C_{17}H_{31}NO_2$, 281.2354; Found: 281.2381.

3,4-Dimethoxybenzyl Bromide——3,4-Dimethoxybenzyl alcohol (16.8 g, 0.1 mol) in benzene (150 ml) was shaken with 47% aqueous hydrobromic acid (51.6 g). The benzene layer was washed with saturated aqueous sodium chloride, dried over potassium carbonate, and evaporated to give 3,4-dimethoxybenzyl bromide (17.3 g, 75%) as a white solid. This crude material was washed with diethyl ether, and the washings were allowed to stand in a freezer to give white precipitates. The mother liquor was concentrated, and cooled in a freezer to give colorless needles, which were recrystallized again to give the pure bromide, mp 58—58.5°; NMR δ 3.75 (6H, singlet, 2×CH_3O), 4.31 (2H, singlet, CH_2), 6.5—6.9 (3H, multiplet, benzene H). *Anal.* Calcd. for $C_9H_{11}BrO_2$: C, 46.77; H, 4.80. Found: C, 46.47; H, 4.75.

Benzylation of the Schiff Base (IV). (*S*)-α-Methylphenylalanine *tert*-Butyl Ester (*S*-Va) and Its N-Acetyl Derivative (*S*-VIIa)——To LDA (3×1.1 mmol) in tetrahydrofuran (5 ml) was added the Schiff base (IV) (844 mg, 3 mmol) in tetrahydrofuran (1 ml) at −72° under nitrogen, and the mixture was stirred at −72°

12) R.W. Roeske, *Chem. Ind.* (London), **1959**., 1121.

for 45 min. Benzyl bromide (1.025 g, 3×2 mmol) in tetrahydrofuran (1 ml) was added to the above yellow α-anion solution at −72°——60°, and the mixture was stirred at −74° for 24 hr. The mixture was quenched with 15% aqueous citric acid (24 ml), and stirred at room temperature overnight. Benzene was added, and the benzene layer was extracted with 15% aqueous citric acid (5 ml×3). The combined aqueous layer was basified with potassium carbonate, and extracted with benzene. The benzene extracts were washed with saturated aqueous sodium chloride, dried, and evaporated. The resultant oil (480 mg) was purified by silica gel (25 g) column chromatography with diethyl ether–benzene (1: 1) to give *S*-Va (387 mg, 55%) as a yellowish oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380, 2990, 1725, 1604, 1458, 1376, 1156, 1112, 852; NMR δ 1.25 (3H, singlet, α-CH_3), 1.38 (2H, singlet, NH_2), 1.40 (9H, singlet, $(CH_3)_3C$), 2.82 (2H, quartet, J=12 Hz, CH_2), 7.13 (5H, singlet, benzene H).

This ester (*S*-Va) (363 mg, 1.55 mmol) was dissolved in pyridine (1 ml), followed by the addition of acetic anhydride (190 mg, 1.55×1.2 mmol) with water-cooling. The mixture was stirred at room temperature for 24 hr, and diluted with benzene (30 ml). The benzene solution was successively washed with 15% aqueous citric acid (2 ml×8), saturated aqueous sodium bicarbonate (1 ml×2), and saturated aqueous sodium chloride (1 ml×2). Drying followed by evaporation gave *S*-VIIa (410 mg, 96.5%) as colorless needles, mp 107—108°, $[\alpha]_D^{25}$ +11.4° (c=2.06, chloroform). Its spectral and chromatographic behavior was identical with that of *R*-VIIa obtained below. The optical purity of *S*-VIIa was calculated to be 21%.

(*R*)-N-Acetyl-α-methylphenylalanine *tert*-Butyl Ester (*R*-VIIa)——To a solution of (*R*)-N-acetyl-α-methylphenylalanine[8] (*R*-VIIIa) (800 mg, 3.61 mmol) in dioxane (30 ml) containing concentrated aqueous sulfuric acid (200 mg) was introduced isobutene until the increase of the volume reached 20 cm^3, and the mixture was stirred in a stoppered flask at room temperature for a week. The mixture was poured into saturated aqueous sodium bicarbonate, followed by extraction with benzene (70 ml×2). The benzene extracts were washed with saturated aqueous sodium chloride, dried, and evaporated to give *R*-VIIa (151 mg, 15%). Recrystallization from benzene–hexane afforded colorless plates, mp 132—133°, $[\alpha]_D^{25}$ −53.3° (c=0.98, chloroform) IR ν_{max} cm^{-1}: 3365, 1710, 1668, 1530, 1460, 1370, 1293, 1169, 1124; NMR δ 1.44 (9H, singlet, $(CH_3)_3C$), 1.60 (3H, singlet, α-CH_3), 1.90 (3H, singlet, CH_3CO), 3.34 (2H, quartet, J=14 Hz, CH_2), 6.18 (1H, broad singlet, NH), 7.17 (5H, singlet, benzene H). *Anal.* Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.24; H, 8.55; N, 5.21.

3,4-Dimethoxybenzylation of the Schiff Base (IV). (*S*)-α-Methyl-β-(3,4-dimethoxyphenyl)alanine *tert*-Butyl Ester (*S*-Vb) and Its N-Acetyl Derivative (*S*-VIIb)——To the α-anion derived from IV (3 mmol) as above was added 3,4-dimethoxybenzyl bromide (1.38 g, 3×2 mmol) in tetrahydrofuran (2 ml) at −76°——−70°, and the mixture was stirred at −72° for 24 hr under nitrogen. After the mixture was quenched with 15% aqueous citric acid (24 ml), and stirred at room temperature overnight. The work-up similar to the case of Va followed by silica gel (50 g) column chromatography of the basic fraction with diethyl ether afforded Vb (640 mg, 72%) as a colorless oil, IR ν_{max} cm^{-1}: 3370, 3310, 2980, 1728, 1517, 1262, 1157, 1032, 853; NMR δ 1.19 (3H, singlet, α-CH_3), 1.26 (2H, singlet, NH_2), 1.36 (9H, singlet, $(CH_3)_3C$), 2.75 (2H, quartet, J=14 Hz, CH_2), 3.75 (6H, singlet, CH_3O×2), 6.61 (3H, singlet, benzene H).

This ester (*S*-Vb) (340 mg, 1.15 mmol) was dissolved in pyridine (1 ml), followed by the addition of acetic anhydride (141 mg, 1.15×1.2 mmol) with ice-cooling. The mixture was stirred at room temperature for 20 hr, diluted with benzene (30 ml), and washed with 15% aqueous citric acid (2 ml×8), saturated aqueous sodium bicarbonate (1 ml×2), and aqueous sodium chloride (1 ml×2). Drying followed by evaporation gave *S*-VIIb (340 mg, 88%) as colorless needles, mp 139—147°, $[\alpha]_D^{24}$ +13.8° (c=1.04, chloroform). Its spectral and chromatographic behavior was identical with that of *R*-VIIb obtained below. The optical purity of *S*-VIIb was calculated to be 24%.

The neutral benzene extracts from the above work-up of *S*-Vb were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried, and evaporated to give a yellow oil (1.267 g). The silica gel (70 g) column chromatography of this oil with diethyl ether–hexane (1: 20) afforded (−)-menthone (VI) (275 mg, 60%) as the first fraction, which was identified with the authentic sample, $[\alpha]_D^{20}$ −30.7° (c=1.22, chloroform) (lit.[13] $[\alpha]_D^{20}$ −31.1° (c=2.0, chloroform)).

The second fraction to be eluted was (+)-isomenthone (IX) (54 mg, 12%) as a colorless oil, $[\alpha]_D^{20}$ +108.9° (c=0.68, chloroform) (lit.[13] $[\alpha]_D^{20}$ +111.3° (c=2.0, chloroform).

(*R*)-N-Acetyl-α-methyl-β-(3,4-dimethoxyphenyl)alanine *tert*-Butyl Ester (*R*-VIIb)——To a solution of (*R*)-N-acetyl-α-methyl-β-(3,4-dimethoxyphenyl)alanine[9] (*R*-VIIIb) (900 mg, 3.38 mmol) in dioxane (30 ml) containing concentrated aqueous sulfuric acid (200 mg) was introduced isobutene (20 ml), and the mixture was stirred in a stoppered flask at room temperature for a week. Work-up as in the case of *R*-VIIa afforded *R*-VIIb (483 mg, 43%), which was recrystallized from benzene–hexane to give colorless needles, mp 131—131.5°, $[\alpha]_D^{24}$ −58.5° (c=1.02, chloroform), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3305, 1725, 1673, 1516, 1372, 1260, 1157; NMR δ 1.48 (9H, singlet, $(CH_3)_3C$), 1.62 (3H, singlet, α-CH_3), 1.90 (3H, singlet, CH_3CO), 3.30 (2H, quartet, J=14 Hz, CH_2), 3.81 (6H, singlet, 2×CH_3O), 6.18 (1H, broad singlet, NH), 6.64 (3H, doublet, benzene H). *Anal.* Calcd. for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.06; N, 4.15. Found: C, 64.17; H, 8.23; N, 4.19.

13) Y. Naves, *Helv. Chim. Acta*, **31**, 932 (1948).