Chem. Pharm. Bull. 26(3) 803—808 (1978)

UDC 547.446.22.04 : 542.953.4.04

Amino Acids and Peptides. XXIX.[1] A New Efficient Asymmetric Synthesis of α-Amino Acid Derivatives with Recycle of a Chiral Reagent—Asymmetric Alkylation of a Chiral Schiff Base from Glycine[2]

Tomei Oguri, Nobutaka Kawai,[3] Takayuki Shioiri,[3a] and Shun-ichi Yamada[3]

Faculty of Pharmaceutical Sciences, University of Tokyo[3]

(Received July 26, 1977)

An efficient asymmetric synthesis of D-α-amino acid derivatives (VI) has been achieved by alkylation of the Schiff base (III), prepared from glycine *tert*-butyl ester and (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one (II), followed by hydrolytic cleavage of the alkylated Schiff base (V). The chiral source (II) was also recovered in good yield, allowing the proliferation of the asymmetry according to the cycle of the amino acid asymmetric synthesis shown in Chart 1.

Keywords——amino acid; asymmetric synthesis; chiral reagent; alkylation; Schiff base; proliferation of the asymmetry; carbanion; α-pinene; lithium diisopropylamide

We have disclosed, in a previous paper of the series,[4] a new synthesis of α-amino acid derivatives by alkylation of Schiff bases derived from glycine and alanine. In the latter case, (—)-menthone was used for a chiral source and the asymmetric synthesis of α-alkylamino acids was achieved in *ca.* 20% asymmetric yield. We here describe a much more efficient asymmetric synthesis of α-amino acid derivatives by analogous processes, which may offer a new system for the asymmetric carbon-carbon bond formation.

The chiral reagent used here is (1*S*,2*S*,5*S*)-(—)-2-hydroxypinan-3-one(II) easily prepared by permanganate oxidation of (1*R*,5*R*)-(+)-α-pinene(I) according to the method of Carlson and Pierce.[5] Condensation of the ketol (II) with glycine *tert*-butyl ester in refluxing benzene containing boron trifluoride etherate smoothly afforded the chiral Schiff base(III). The infrared spectrum of a molar solution of the Schiff base(III) in carbon tetrachloride shows two hydroxyl absorptions at 3542 and 3400 cm^{-1}. These can be ascribed to the intra and intermolecular hydrogen bonds, respectively, since the latter peak diminishes with decreasing the concentration while the former unchanges, as shown in Fig. 1.

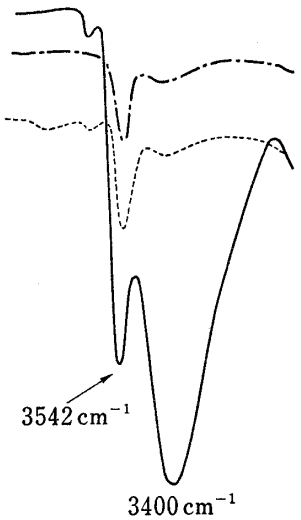

Fig. 1. The Hydroxyl Infrared Absorption of the Schiff Base (III) in Carbon Tetrachloride

———: 1 M solution.
– – –: 0.1 M solution.
·····: 0.01 M solution.

1) Part XXVIII: T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 2287 (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; Preliminary Communication, S. Yamada, T. Oguri, and T. Shioiri, *Chem. Commun.*, **1976**, 136.
3) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan*; *a*) Present address: *Faculty of Pharmaceutical Sciences, Nagoya City University, 3-1, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan.*
4) *Cf.*, S. Yamada, T. Oguri, and T. Shioiri, *Chem. Commun.*, **1972**, 623; T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 167 (1975); T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 173 (1975).
5) R.G. Carlson and J.K. Pierce, *J. Org. Chem.*, **36**, 2319 (1971).

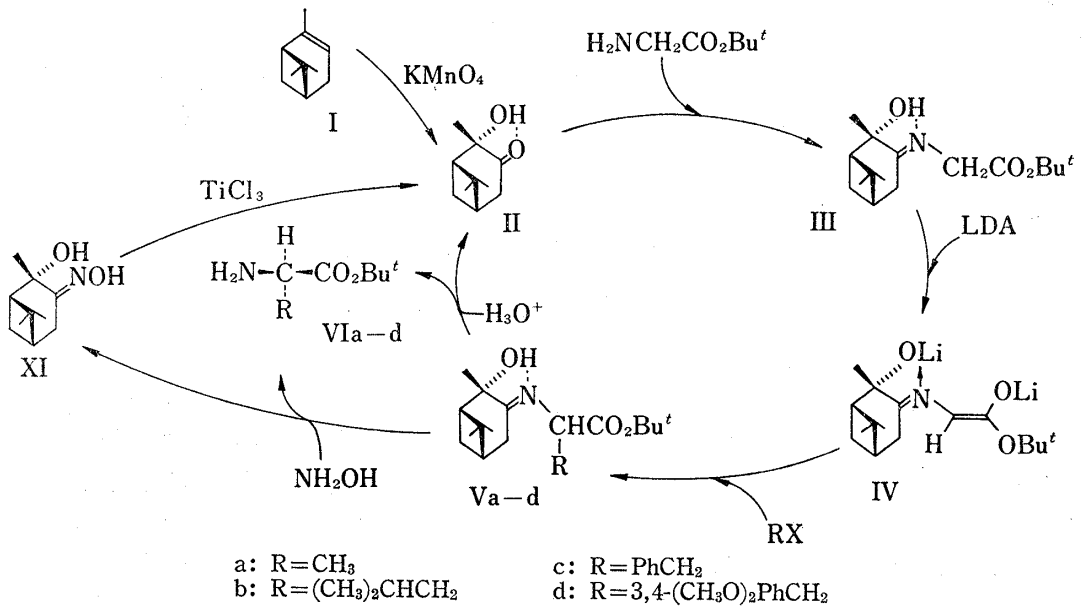

Chart 1. Amino Acid Asymmetric Synthesis Cycle

Action of 2 equivalents of lithium diisopropylamide (LDA) to the Schiff base(III) afforded the dianion whose structure may be depicted as IV.[6] Treatment of IV with methyl iodide furnished the methylated Schiff base(Va) which was directly hydrolyzed with aqueous citric acid. The ketol(II) used as the chiral source was recovered in good yield. Alanine *tert*-butyl ester(VIa) desired was obtained as an ethereal solution, to which hydrogen chloride was introduced to give alanine hydrochloride in 52% yield based on III. Benzoylation of the ester (VIa) furnished N-benzoylalanine *tert*-butyl ester which was proved to have D-configuration and to be 83% optical purity by comparisons with the optical rotation of optically pure N-benzoyl-L-alanine *tert*-butyl ester prepared from L-alanine *tert*-butyl ester.

The results of the other asymmetric alkylation of the lithiated Schiff base(IV) using isobutyl iodide, benzyl bromide, and 3,4-dimethoxybenzyl bromide are summarized in Table I. Hydrolysis of the isobutylated Schiff base(Vb) with aqueous citric acid followed by benzoylation yielded N-benzoyl-D-leucine *tert*-butyl ester in 50% overall yield with 83% optical purity which was estimated by comparison with the optical rotation of optically pure N-benzoyl-L-leucine *tert*-butyl ester.

Table I. The Results of the Asymmetric Alkylation

Alkylating agent RX	Product[a]	Overall yield (%)[b]	Optical yield (%)[c]
CH_3I	H-D-Ala-OH·HCl	52	83
$(CH_3)_2CHCH_2I$	Bz-D-Leu-OBu^t	50	83
$PhCH_2Br$	H-D-Phe-OBu^t	79	72
$3,4\text{-}(CH_3O)_2PhCH_2Br$	H-D-3,4-$(CH_3O)_2$Phe-OBu^t	62	66

a) Symbols and abbreviations of amino acid derivatives are in accordance with the recommendations of the IUPAC-IUB Commision on Biochemical Nomenclature, *Pure Appl. Chem.*, **40**, 315 (1974).
b) Based on the Schiff base (III).
c) Based on products purified, without attempted resolution, by use of a silica gel column.

6) *Cf.* M.W. Rathke and D.F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973); See also, A.I. Meyers, C. Knaus, K. Kamata, and M.E. Ford, *J. Am. Chem. Soc.*, **98**, 567 (1976).

Since the hydrolysis with aqueous citric acid of the amino acid derivatives(Vc and Vd) containing aromatic residues sluggishly proceeded, the cleavage was carried out with hydroxylamine acetate to give *tert*-butyl esters of D-phenylalanine (VIc) and its 3,4-dimethoxy-analog(VId) in good chemical and optical yields. The latter(VId) was further converted to its N-acetyl derivative(D-VII) with 66% optical purity which was estimated by comparison with the optically pure L-analog(L-VII) prepared as follows: N-Formyl-3-(3,4-dimethoxyphenyl)-L-alanine[7] (VIII) was subjected to acid hydrolysis to give 3-(3,4-dimethoxyphenyl)-L-alanine(IX) which was treated with acetic anhydride to furnish the N-acetyl derivative(X). Further treatment with isobutene afforded the optically pure L-VII, as shown in Chart 2.

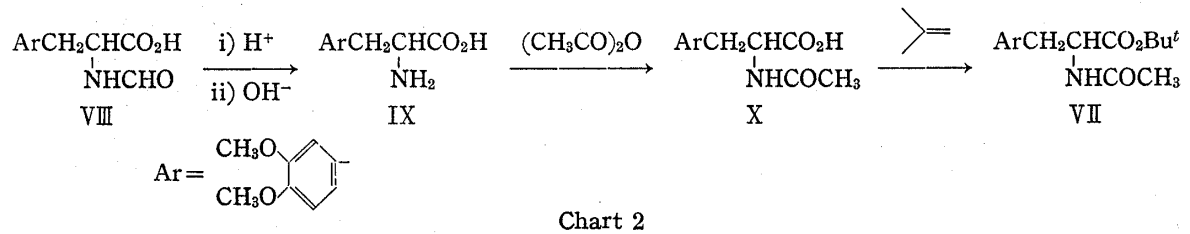

Chart 2

The ketol (II) was also recovered as the corresponding oxime (XI), which was readily converted to II, without any loss of optical purity, with aqueous titanium trichloride[8] in good yield. Thus the cycle of the amino acid asymmetric synthesis has been completed in every case, allowing the proliferation of the asymmetry using the ketol (II) as a chiral source. It is worthy of note that no dialkylation occurred in any case even when an excess of alkylating agents was used. Furthermore the method may allow the asymmetric synthesis of both D- and L-isomers, because α-pinene(I), and consequently the ketol(II), is available from natural sources in both optically active forms.[9]

Experimental

Unless otherwise stated, mp's were measured on a hot stage apparatus and uncorrected; bp's were uncorrected; infrared spectra were measured in nujol for crystals and in chloroform for oils; nuclear magnetic resonance 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 were measured at 70 eV. Silica gel (Wakogel C-200) was used for column chromatography. The organic solutions were dried over magnesium sulfate before vacuum evaporation.

Lithium diisopropylamide (LDA) was prepared in tetrahydrofuran according to the procedure described in our previous paper.[1]

(1*S*,2*S*,5*S*)-(−)-2-Hydroxypinan-3-one (II)——i) Prepared from (1*R*,5*R*)-(+)-α-pinene (I, $[\alpha]_D^{20}$ +22.5° (neat), 44% optical purity) according to the literature.[5] The crude ketol (II) was purified by column chromatography over silica gel (40 parts) using ethyl acetate–hexane (1: 10), followed by distillation to give a colorless oil, bp_{15} 118—119° (lit.[5] bp_{17} 113—115°), $[\alpha]_D^{25}$ −17.6° (c=1.31, chloroform). Thus the optical rotation of the optically pure ketone (II) may be estimated to be −40°.

ii) Prepared from (1*R*,5*R*)-(+)-α-pinene (I, $[\alpha]_D^{20}$ +47.5° (neat), 93% optical purity) by the procedure in reference 6 except that the reaction temperature was held at −7°. The crude ketol (II) was recrystallized four times from pentane to give colorless prisms, mp 31—32°, $[\alpha]_D^{25}$ −38.9° (c=2.64, chloroform). The optical purity of the ketol (II) may be estimated to be at least 97%.[10]

The Schiff Base (III) from Glycine *tert*-Butyl Ester and the Ketol (II)——A mixture of glycine *tert*-butyl ester[11] (8.66 g, 33×2 mmol) and the ketol (II) (5.55 g, 33 mmol) in benzene (80 ml) containing boron trifluoride etherate (0.1 g) was refluxed for 4 hr using a Cope apparatus (molecular sieve type 4A) under nitrogen. Evaporation followed by distillation afforded a slightly yellow oil (7.7 g, 83%), $bp_{0.2}$ 120—122°,

7) A.W. Schrecker and J.L. Hartwell, *J. Am. Chem. Soc.*, **79**, 3827 (1957).
8) G.H. Timms and E. Wildsmith, *Tetrahedron Lett.*, **1971**, 195.
9) Mechanistic interpretation of the asymmetric alkylation should await further investigations.
10) M. Delépine, A. Horeau, and M. Grandperrin-Harispe, *Ann. Chim.* (France), **18**, 250 (1943), reported the preparation of the ketol (II) with $[\alpha]_D$ −41.2° (c=0.04, chloroform) from (+)-α-pinene (I), $[\alpha]_D$ +45.9° (neat).
11) G.W. Anderson and R.M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).

$[\alpha]_D^{20}$ −0.54° (c=1.48, chloroform), $[\alpha]_D^{20}$ −10.0° (c=1.47, benzene). IR ν_{max} cm^{-1}: 3540, 3310, 1736, 1650, 1373, 1155. NMR 0.84 (3H, singlet, CH_3), 1.31 (3H, singlet, CH_3), 1.40 (3H, singlet, CH_3), 1.44 (9H, singlet, $(CH_3)_3C$), 1.5—2.6 (6H, multiplet), 2.95 (1H, singlet, OH), 4.0 (2H, singlet, CH_2N). Molecular weight for $C_{16}H_{27}NO_3$: 281.1991. Found: 281.2006 (by mass measurement).

Alkylation of the Schiff Base (III) with Methyl Iodide——i) To LDA (2×2.2 mmol) in tetrahydrofuran (2 ml) was added the Schiff base (III) (563 mg, 2 mmol) in tetrahydrofuran (1.5 ml) at −74° under nitrogen, and the mixture was stirred for 30 min to form the dianion (IV). After the addition of methyl iodide (567 mg, 2×2 mmol), the mixture was stirred at −74° for 2 hr 45 min. Benzene (30 ml) and 15% aqueous citric acid (3.2 ml) were added, and the benzene layer was washed with saturated aqueous sodium chloride (2 ml). Evaporation of the benzene at room temperature afforded the residue, which was dissolved in tetrahydrofuran (14 ml). After the addition of 15% aqueous citric acid (6 ml, 2×2 mmol), the mixture was stirred at room temperature for 34 hr. The tetrahydrofuran was evaporated at room temperature, benzene (40 ml) was added, and the benzene layer, containing the ketol (II), was extracted with 15% aqueous citric acid (3 ml×3). The combined aqueous layer was basified with potassium carbonate, and extracted with diethyl ether (15 ml×9). The ethereal extracts containing alanine *tert*-butyl ester (VIa) were washed with saturated aqueous sodium chloride, dried, and concentrated to *ca.* 5 ml at room temperature. Benzoyl chloride (365 mg, 2×1.3 mmol) and pyridine (206 mg, 2×1.3 mmol) were added to the concentrate with ice-cooling and stirring. The mixture was stirred with ice-cooling for 1 hr, and then at room temperature for 2 hr. Diethyl ether (50 ml) was added, and the mixture was successively washed with 15% aqueous citric acid (2 ml×3), 2.8% aqueous ammonia (2 ml×3), 15% aqueous citric acid (1 ml×1), saturated aqueous sodium bicarbonate (2 ml×2), and saturated aqueous sodium chloride (2 ml×2). Drying followed by evaporation gave a yellow oil which was purified by column chromatography over silica gel (25 g) using diethyl ether–hexane (1: 3) to give N-benzoyl-D-alanine *tert*-butyl ester (260 mg, 52%) as a colorless solid, mp 62—67°, $[\alpha]_D^{25}$ −32.3° (c=1.04, chloroform), whose spectral and thin-layer chromatographic behavior was identical with that of L-isomer obtained below.

The benzene layer, obtained after hydrolysis of the methylated Schiff base (Va) as above, was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. Drying followed by evaporation gave a yellow oil (305 mg), 290 mg of which was purified by column chromatography over alumina (10 g) using diethyl ether–hexane (1: 2) to give a slightly yellow solid of the ketol (II) (239 mg, 75%), $[\alpha]_D^{25}$ −37.0° (c=2.62, chloroform).

ii) In the same manner as above, there was obtained the ethereal extracts (*ca.* 140 ml) containing alanine *tert*-butyl ester (VIa). Hydrogen chloride was introduced for 2 min, and the ether was evaporated to give a yellow solid of D-alanine hydrochloride (208 mg), the yield of which was estimated to be 52% by an amino acid analysis.

L-Alanine *tert*-Butyl Ester——To an ice-cooled solution of carbobenzoxy-L-alanine (13 g, 58.2 mmol) in methylene chloride (100 ml) containing concentrated aqueous sulfuric acid (0.64 ml, 12 mmol) 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 60 hr. The mixture was poured into water (120 ml) containing sodium bicarbonate (830 mg). The organic layer was washed with saturated aqueous sodium chloride. Drying followed by evaporation gave a slightly yellow oil (14.7 g), 12.6 g of which was catalytically hydrogenated over 5% palladium-carbon (0.5 g) in ethanol (80 ml) during 20 hr. The mixture was filtered, evaporated, and distilled at 61—64° (21 mmHg) to give L-alanine *tert*-butyl ester (3.7 g), which was directly used for benzoylation below. A part of this ester (200 mg) was converted to its hydrochloride by the treatment with hydrogen chloride in anhydrous diethyl ether. Recrystallization from chloroform–diethyl ether afforded colorless needles of L-alanine *tert*-butyl ester hydrochloride (200 mg, 80%), mp 163° (dec.).[12]

N-Benzoyl L-Alanine *tert*-Butyl Ester——To L-alanine *tert*-butyl ester (218 mg, 1.5 mmol) in diethyl ether (5 ml) were added benzoyl chloride (232 mg, 1.5×1.1 mmol) and pyridine (130 mg, 1.5×1.1 mmol) with stirring and ice-cooling, and the mixture was stirred with ice-cooling for 1 hr and then at room temperature for 2 hr.

Diethyl ether (45 ml) was added, and the mixture was successively washed with 15% aqueous citric acid (2 ml×3), 2.8% aqueous ammonia (2 ml×2), 15% aqueous citric acid (1 ml×1), saturated aqueous sodium bicarbonate (2 ml×2), and saturated aqueous sodium chloride (2 ml×2), and dried. The evaporated residue (330 mg) was purified by column chromatography over silica gel (25 g) using diethyl ether–benzene (1: 3) to give colorless prisms of N-benzoyl-L-alanine *tert*-butyl ester (320 mg, 86%). Recrystallization from diethyl ether–hexane afforded colorless prisms, mp 58—59°, $[\alpha]_D^{25}$ +38.9° (c=1.06, chloroform). IR ν_{max} cm^{-1} 3358, 1747, 1647, 1515, 1160. NMR 1.42 (3H, singlet, CH_3), 1.50 (9H, singlet, $(CH_3)_3C$), 4.63 (1H, multiplet, CH), 7.4, 7.8 (5H, two multiplets, C_6H_5CO), 7.0 (1H, broad doublet, NH). *Anal.* Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.54; H, 7.90; N, 5.79.

Alkylation of the Schiff Base (III) with Isobutyl Iodide——To LDA (2×2.2 mmol) in tetrahydrofuran (2 ml) was added the Schiff base (III) (563 mg, 2 mmol) in tetrahydrofuran (1.5 ml) at −78°——70° under

12) R.W. Roeske (*Chem. and Ind.*, **1959**, 1121) describes this hydrochloride decomposes without melting.

nitrogen, and the mixture was stirred at −78° for 10 min. Hexamethylphosphortriamide (0.72 ml, 2×2 mmol) was added, and the mixture was stirred for 30 min to form the dianion (IV). After the addition of isobutyl iodide (732 mg, 2×2 mmol), the mixture was stirred at −74° for 2 hr and then at −45° for 22 hr. The reaction mixture was poured into 15% aqueous citric acid (3.2 ml) with ice-cooling, and extracted with benzene (50 ml). The benzene layer was washed with water (2 ml×4), and evaporated at room temperature. The residue was dissolved in a mixture of 15% aqueous citric acid (6 ml) and tetrahydrofuran (10 ml), and the mixture was stirred at room temperature for 70 hr. The tetrahydrofuran was evaporated, benzene (40 ml) was added, and the benzene layer was extracted with 15% aqueous citric acid (3 ml×3). The combined aqueous layer was basified with potassium carbonate, and extracted with diethyl ether (20 ml×5). The ethereal extracts were washed with saturated aqueous sodium chloride (2 ml×2) and dried to give 124 ml of the solution containing D-leucine *tert*-butyl ester (VIb), 60 ml of which was used for benzoylation. Benzoyl chloride (422 mg, 3 mmol) and pyridine (237 mg, 3 mmol) were added to this ice-cooled ethereal solution (60 ml), and the mixture was stirred with ice-cooling for 2 hr and then at room temperature for 1 hr. The reaction mixture was successively washed with 15% aqueous citric acid (3 ml×3), 2.8% aqueous ammonia (3 ml×3), 15% aqueous citric acid (1 ml×1), saturated aqueous sodium bicarbonate (2 ml×3), and saturated aqueous sodium chloride (2 ml×2). Drying followed by evaporation afforded a white solid (260 mg), which was purified by column chromatography over silica gel (25 g) using diethyl ether–hexane (1: 3) to give N-benzoyl-D-leucine *tert*-butyl ester (140 mg, 50%), mp 92—96°, $[\alpha]_D^{25}$ −21.7° (c=1.16, chloroform), whose spectral and thin-layer chromatographic behavior was identical with that of the L-isomer obtained below.

N-Benzoyl-L-leucine *tert*-Butyl Ester——Prepared from L-leucine *tert*-butyl ester[11] (562 mg, 3 mmol), benzoyl chloride (464 mg, 3×1.1 mmol), and pyridine (261 mg, 3×1.1 mmol) in a similar manner as above preparation of N-benzoyl-L-alanine *tert*-butyl ester. The yield was 802 mg (92%). Recrystallization from diethyl ether–hexane afforded colorless needles, mp 99—100°, $[\alpha]_D^{25}$ +26.2° (c=1.15, chloroform). IR ν_{max} cm^{-1}: 3380, 1746, 1648, 1520, 1152. NMR 0.95 (6H, doublet, J=6 Hz, $(C\underline{H}_3)_2CH$), 1.47 (9H, singlet, $(CH_3)_3C$), 1.6 (2H, multiplet, $C\underline{H}_2CH$), 4.66 (1H, multiplet, CHN), 6.7 (1H, broad doublet, NH), 7.3 and 7.7 (5H, two multiplets, C_6H_5CO). *Anal.* Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.07; H, 8.68; N, 4.90.

Alkylation of the Schiff Base (III) with Benzyl Bromide——To LDA (2×2.2 mmol) in tetrahydrofuran (2 ml) was added the Schiff base (III) (562 mg, 2 mmol) in tetrahydrofuran (1.5 ml) at −70° under nitrogen, and the mixture was stirred at −74° for 10 min. Hexamethylphosphortriamide (0.72 ml, 2×2 mmol) was added, and the mixture was stirred for 30 min. After the addition of benzyl bromide (1.026 g, 2×3 mmol), the mixture was stirred at −74°——70° for 3 hr and poured into 7.5% aqueous citric acid (12 ml) with ice-cooling. After the extraction with benzene (50 ml), the benzene layer was washed with water (2 ml×5), dried, and evaporated to give 1.56 g of the residue, 890 mg of which was fractionated by column chromatography over silica gel (60 g) using benzene and then diethyl ether to give the crude benzylated Schiff base (Vc) (450 mg). An ethanolic solution of hydroxylamine acetate (0.5 M, 3.2 ml, 1.6 mmol) was added to the Schiff base (Vc), and the mixture was stirred at room temperature for 12 hr. After the addition of more ethanolic hydroxylamine acetate (3 ml, 1.5 mmol), the mixture was stirred for 26 hr. The evaporated residue was dissolved in benzene (50 ml), and the solution was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. Drying followed by evaporation afforded a yellow oil (450 mg), 400 mg of which was fractionated by column chromatography over silica gel (60 g) using diethyl ether–hexane (1: 1). The first fraction to be eluted was the oxime (XI) of the ketol (130 mg, 65%), mp 115—116°, identified with the sample of XI obtained below.

The second fraction to be eluted was D-phenylalanine *tert*-butyl ester (VIc) (189 mg, 79%) as a slightly yellow oil, $bp_{0.04}$ 120—130° (bath temperature), $[\alpha]_D^{25}$ −23.4° (c=1.95, ethanol), identified with the sample of VIc prepared according to the literature.[11] $[\alpha]_D^{25}$ −25.9° (neat) (lit.[11] $[\alpha]_D^{25}$ −24.8°), $[\alpha]_D^{30}$ −32.6° (c=1.90, ethanol)).

Alkylation of the Schiff Base (III) with 3,4-Dimethoxybenzyl Bromide——The reaction was carried out in the same scale and method as the preparation of VIc except that 3,4-dimethoxybenzyl bromide[4] was used as the alkylating agent. The reaction temperature was −74°, and the reaction time was 5.5 hr. The desired 3-(3,4-dimethoxyphenyl)-D-alanine *tert*-butyl ester (VId) was obtained as a colorless viscous oil in 62% yield. IR ν_{max} cm^{-1}: 3345, 3280, 1730, 1583, 1519, 1466, 1373, 1258, 1155, 1029, 846. NMR 1.25 (2H, singlet, NH_2), 1.36 (9H, singlet, $(CH_3)_3C$), 2.8 (2H, multiplet, CH_2), 3.4 (1H, multiplet, CH), 3.75 (6H, singlet, 2×CH_3O), 6.58 (3H, singlet, benzene). MS m/e: 281 (M^+), 180, 151.

A mixture of the ester (VId) (165 mg, 0.586 mmol), acetic anhydride (72 mg, 0.586×1.2 mmol), and pyridine (0.5 ml) was stirred at room temperature for 20 hr. Diethyl ether (50 ml) was added, and the mixture was successively washed with 15% aqueous citric acid (2 ml×3), saturated aqueous sodium bicarbonate (2 ml×1), and saturated aqueous sodium chloride (2 ml×2). Drying followed by evaporation gave a slightly yellow oil (130 mg), which was purified by column chromatography over silica gel (8 g) using diethyl ether–hexane (1: 1) and then diethyl ether to give a slightly yellow oil of N-acetyl-3-(3,4-dimethoxyphenyl)-D-alanine *tert*-butyl ester (70 mg, 37%), $[\alpha]_D^{25}$ −44.3° (c=1.24, chloroform). IR ν_{max} cm^{-1}: 3400, 1733, 1670, 1510, 1270, 1160. NMR 1.42 (9H, singlet, $(CH_3)_3C$), 1.88 (3H, singlet, CH_3CO), 2.92 (2H, doublet, J=6 Hz,

NH), 3.74 (6H, singlet, $2\times CH_3O$), 4.5 (1H, multiplet, CH), 6.62 (3H, singlet, benzene), whose spectral and thin-layer chromatographic behavior was identical with that of the L-isomer (VII).

(1*S*,2*S*,5*S*)-2-Hydroxypinan-3-one Oxime (XI)——A mixture of the ketol (II) (300 mg, 1.79 mmol) and ethanolic hydroxylamine acetate (0.5 M, 7.1 ml, 1.79×2 mmol) were stirred at room temperature for 2 days. After the ethanol was removed *in vacuo*, benzene (30 ml) was added. The benzene solution was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, and dried. The evaporated residue was purified by column chromatography over silica gel (25 g) using diethyl ether–benzene (1: 3), followed by recrystallization from hexane to give colorless prisms of the oxime (XI), mp 117—118°, $[\alpha]_D^{22}$ +16.6° (c=3.0, chloroform). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3555, 3300, 1475, 1426, 1378, 1363, 1160, 1086, 927. NMR 0.88 (3H, singlet, CH_3), 1.34 (3H, singlet, CH_3), 1.53 (3H, singlet, CH_3), 1.6—2.5 (4H, multiplet), 2.71 (2H, singlet, $CH_2C{=}N$), 4.17 (1H, singlet, OH), 9.83 (1H, singlet, OH). *Anal.* Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.54; H, 9.36; N, 7.60.

Deoximation of the Oxime (XI)——To ammonium acetate (3.65 g) in water (12 ml) was added 20% aqueous titanium trichloride (6 ml, 3×2.5 mmol) with ice-cooling under argon. The oxime (XI) (550 mg, 3 mmol) in dioxane (6 ml) was added, and the mixture was stirred with ice-cooling for 6 hr. The mixture was extracted with diethyl ether (50 ml × 7), and the ethereal extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. Drying followed by evaporation afforded a yellow oil (435 mg). On the other hand, the aqueous layer after the above extraction with diethyl ether was acidified with 20% aqueous hydrochloric acid. The mixture was stirred at room temperature overnight, and extracted with diethyl ether (50 ml × 4). The ethereal extracts were treated as above to give a colorless oil (25 mg). The combined colorless oil (460 mg) was purified by column chromatography over silica gel (50 g) using ethyl acetate–hexane (1: 4) to give the ketol (II) (352 mg, 70%), $[\alpha]_D^{25}$ −38.5° (c=2.52, chloroform), whose spectral and thin-layer chromatographic behavior was identical with that of the ketol (II) prepared from I.

3-(3,4-Dimethoxyphenyl)-L-alanine (IX)——A mixture of N-formyl-3-(3,4-dimethoxyphenyl)-L-alanine[7] (VIII) (8.40 g, 33 mmol) and 10% aqueous hydrochloric acid (28 ml) was refluxed for 30 min. After evaporation, the residue was dissolved in water, and the pH of the solution was adjusted to 6 to give colorless precipitates. Recrystallization from water (*ca.* 620 ml) afforded colorless needles of IX (5.98 g, 82%), mp 218—219° (dec.), $[\alpha]_D^{20}$ −5.0° (c=2.0, 2 N hydrochloric acid). IR ν_{max} cm^{-1}: 3168, 1615, 1593, 1510, 1403. NMR in trifluoroacetic acid, 3.51 (2H, multiplet, CH_2), 3.94 (6H, singlet, $2\times CH_3O$), 4.67 (1H, multiplet, CH), 7.06 (3H, singlet, benzene), 7.44 (3H, singlet, NH_3^+). *Anal.* Calcd. for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.63; H, 6.67; N, 6.05.

N-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine (X)——To 3-(3,4-dimethoxyphenyl)-L-alanine (IX) (2.25 g, 10 mmol) in water (5.5 ml) was added simultaneously 20 N aqueous sodium hydroxide (3.5 ml, 70 mmol) and acetic anhydride (2.84 ml, 30 mmol) during 2 hr with stirring and ice-cooling. After the mixture was stirred for 15 min, concentrated aqueous hydrochloric acid (7.09 g, 70 mmol) was added to give white needles of X (1.84 g, 70%). Recrystallization from water furnished colorless needles (1.48 g, 56%), mp 149—151° (lit.[13] 149—150°), $[\alpha]_D^{20}$ +46.3° (c=5.0, methanol) (lit.[13] $[\alpha]_D^{20}$ +46.2° (c=5, methanol)). IR ν_{max} cm^{-1}: 3320, 1650, 1648, 1520. NMR in tetradeuteromethanol, 1.90 (3H, singlet, CH_3CO), 3 (2H, triplet, J=7 Hz, CH_2), 3.75 (6H, singlet, CH_3O), 4.6 (1H, quartet, J=7 Hz, CH), 6.80 (3H, singlet, benzene).

N-Acetyl-3-(3,4-dimethoxyphenyl)-L-alanine *tert*-Butyl Ester (L-VII)——To an ice-cooled solution of the acid (X) (2 g, 7.5 mmol) in dioxane (70 ml) containing concentrated aqueous sulfuric acid (0.1 ml) was introduced isobutene until saturation. The mixture was stirred at room temperature for 3 days in a stoppered flask, poured into an ice-cooled saturated aqueous sodium bicarbonate, and extracted with diethyl ether (300 ml). The ethereal extracts were washed with saturated aqueous sodium chloride, dried, and evaporated. The residue was purified by column chromatography over silica gel (95 g) using ethyl acetate–benzene (1: 1) to give a slightly brown oil of VII (690 mg, 29% yield), which was crystallized with hexane. Repeated recrystallizations from diethyl ether–hexane afforded colorless needles, mp 79.5—81°, $[\alpha]_D^{25}$ +67.6° (c=1.24, chloroform), whose spectral and thin-layer chromatographic behavior was identical with that of the D-isomer obtained by the asymmetric alkylation. *Anal.* Calcd. for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.18; H, 7.73; N, 4.31.

Acknowledgement We thank Dr. G.C. Anderson of Hercules Incorporated, Wilmington, Delaware for a gift of (+)-α-pinene.

13) A. Nakamoto, M. Aburatani, and M. Inagaki, *J. Med. Chem.*, **14**, 1021 (1971).