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Synthesis of (*E*)-δ-hydroxy-β,γ-dehydro α-amino acids, a new class of vinylglycines by the rearrangement of β-acetoxyallylglycine derivatives

M. Kirihata, M. Fukuari, T. Izukawa, and **I. Ichimoto**

Department of Applied Biochemistry,
College of Agriculture, University of Osaka Prefecture, Osaka, Japan

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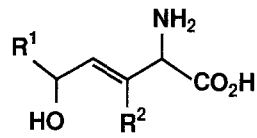
Summary. The efficient synthesis of δ-hydroxy-β,γ-dehydro α-amino acids (**1**) was achieved by the hybrid process, in which the Pd(II)-assisted rearrangement of β-acetoxyallylglycine ester (**6**) afforded the corresponding (*E*)-δ-acetoxyvinylglycine derivatives (**7**) in a moderate yield. The chemo- and stereo-selective hydrolysis of **7** was accomplished by the use of microbial lipase (Amano PS) to afford the allylic alcohol (**8**), which was transformed into **1** in two step sequence.

Keywords: α-Amino acids – β,γ-Dehydro α-amino acids – Vinylglycine derivatives – δ-Hydroxy-β,γ-dehydro α-amino acids – Enzymatic hydrolysis – [3,3]-Sigmatropic rearrangement

Introduction

The γ-substituted β,γ-dehydro α-amino acids (vinylglycines) are worthwhile synthetic targets due to their proven and potential biological activities, e.g. antimicrobial (Girodeau et al., 1986) and enzyme inhibitory activities (Rando, 1975; Walsh, 1982). Particularly, several vinylglycines have been shown to be suicide substrates of B_6-enzyme such as amino acid oxidase (Marcotte and Walsh, 1976) and transaminase (Cooper and Fitzpatrick, 1982). More recently, several (*E*)-γ-alkylated vinylglycines have been proven to be positive modulators of the *N*-methyl-D-aspartate receptor-associated glycine recognition site in synaptic plasma-membrane of rat forebrain (Monahan et al., 1990). Furthermore, (*E*)-γ-hydroxyethylvinylglycines have been shown to be potent inhibitors of glycine binding to the recognition site (Monahan et al., 1990).

The (*E*)-δ-hydroxy-β,γ-dehydro α-amino acids, of the general structure **1** in Scheme 1, are a new class of vinylglycine derivatives. Although a number of vinylglycine derivatives have been synthesized (Greenlee, 1984; Fitzer et al.,



1a~e

a, $R^1 = H$; $R^2 = H$
b, $R^1 = Me$; $R^2 = H$
c, $R^1 = Et$; $R^2 = H$
d, $R^1 = n\text{-}Pr$; $R^2 = H$
e, $R^1 = H$; $R^2 = Me$

Scheme 1

1985; Gastelhano et al., 1986), only a few δ-hydroxy derivatives of γ-substituted vinylglycine have appeared (Agouridas et al., 1985; Williams and Zhai, 1988). This is due to the lability of these substances toward rearrangement of the unsaturated moiety into conjugation with the carbonyl group. Therefore, development of the efficient synthesis of **1** is a challenging task.

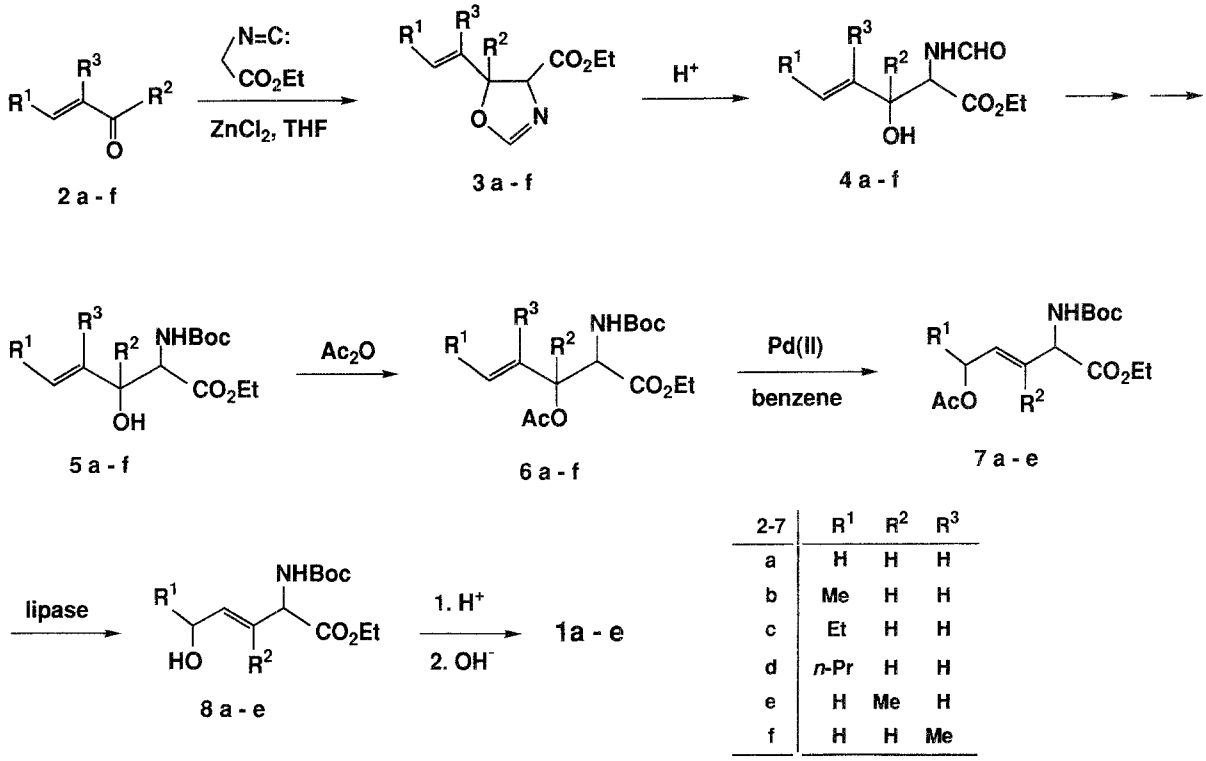
Our initial interest was to prepare the protected γ-hydroxymethylvinylglycine (**8a**) as a synthetic intermediate during the preparation of unusual α-amino acids such as (*E*)-2-amino-5-phosphono-3-pentenoic acid (APPA) (Kirihata et al., 1990) and kainic acid (Kirihata et al., 1991). In this paper, we describe a selective synthesis of (*E*)-δ-hydroxy-β,γ-dehydro α-amino acid (**1**) as depicted in Scheme 2. Our synthesis of **1** based on the Pd(II)-catalyzed rearrangement (Overmann and Knoll, 1979; Kurokawa and Ofune, 1985) of the allylic acetate moiety of **6** and subsequent mild hydrolysis of the migration product (**7**) using microbial lipase.

Results and discussion

The starting compound, oxazoline (**3**) was prepared as a *cis/trans* mixture by the aldol-type condensation of α,β-unsaturated carbonyl compounds (**2**) with ethyl isocyanoacetate according to the modified literature method (Ito et al., 1985). The β-acetoxyallylglycine derivative (**6**), the precursor of the rearrangement, was synthesized in four step sequence; thus, **3** was treated with 90% acetic acid to give the β-hydroxy amino acid ester (**4**) in high yield. Hydrolysis of **4** with 2N hydrochloric acid followed by protection by Boc group in one pot provided *N*-Boc-β-hydroxyallylglycine ester (**5**), which was acetylated with acetic anhydride to give the *syn/anti* mixture of **6** by the usual manner.

[3,3]-Sigmatropic rearrangement of **6a–e** was mediated by bis(acetonitrile)palladium(II) chloride in benzene at 60–80°C under argon to afford the corresponding allylic acetate (**7a–e**), respectively, in 40–60% yield; however, **6f** ($R^1 = R^2 = H$, $R^3 = Me$) was not converted to the corresponding allylic acetate, and recovered from the reaction mixture.

As described in our previous paper (Kirihata et al., 1991), the chemoselective hydrolysis of **7** was successfully achieved by the use of microbial lipase (Amano PS) in phosphate buffer at pH 7.0 at 35–40°C to provide the allylic alcohol **8** without any formation of α,β-unsaturated α-amino acids derivatives. The stereochemistry of the double bond of **8b–d** was readily ascertained by the ^1H NMR examination of the *vicinal* olefinic coupling



2-7	R^1	R^2	R^3
a	H	H	H
b	Me	H	H
c	Et	H	H
d	*n*-Pr	H	H
e	H	Me	H
f	H	H	Me

Scheme 2

constants which were typically J = 15.6~15.9 Hz. In no case, did we find evidences for the formation of any of the corresponding (*Z*)-isomers. In the case of **7b–d**, optically active alcohols (**8b–d**) were formed due to the newly generated chiral center C(5). Finally, **8** was successively treated with 2N hydrochloric acid and sodium hydroxide at room temperature to give the amino acid (**1**). Chromatography through an ion-exchange resine (Dowex 50 × 4, H^+ form) column followed by recrystallization furnished **1**.

In combination with other enzymes *e.g.* aminoacylase or chymotripsin, the present method could be applicable to the elabolation of optically active **1** having higher optical purity and defined stereochemistry.

Methods and materials

Melting points (mp) were determined on a MEL-TEMP II apparatus and are uncorrected. NMR spectra were recorded on a JEOL GSX-270 (270 MHz for ^1H and 67.5 MHz for ^{13}C) spectrometer in $CDCl_3$ as a solvent unless noted otherweise and using TMS as an internal standard. Infrared spectra (IR) were recorded on a Perkin-Elmer 1760X. Mass spectra were obtained with a JMS-AX 500 mass spectrometer. FABMS were obtained using glycerol as a matrix, operating at 6 KV, 20 mA. Flash and open column chromatography was performed on silica gel BW-200 (Fuji Silisia). Distillation under reduced pressure was carried out by a bulb-to-bulb distillation apparatus.

Most chemicals and solvents were analytical grade and used without further purification. Lipase (Amano PS) was perchased from Amano Pharmaceutical Co., Ltd., Nishikinakaku, Nagoya, Japan.

Experimental

*Preparation of oxazoline (**3**)*

The oxazoline **3** was prepared by an aldol-type condensation of the corresponding **2** with ethyl isocyanoacetate in the presence of zinc chloride to give a *cis/trans* mixture of **3** according to the literature method (Ito et al., 1985). The mixture was directly used for the following reactions without further separation of the isomers.

*Preparation of ethyl 2-formylamino-3-hydroxy-4-alkenoate (**4**); general procedure*

A solution of **3** (8 mmol) in 90% acetic acid (10 ml) was stirred for 15 h at room temperature. After being evaporated *in vacuo*, the residue was purified by flash chromatography on silica gel with hexane-EtOAc (1:1) to give practically pure **4** as a *syn/anti* mixture. This material was used for the next reaction without further purification.

*Ethyl 2-formylamino-3-hydroxy-4-pentenoate (**4a**)*

This compound was prepared from **3a** in a 78% yield according to the reported method (Kirihata et al., 1990).

*Ethyl (E)-2-formylamino-3-hydroxy-4-hexenoate (**4b**)*

87% yield, mp 77.5–81°C (EtOAc-Hex). IR ν max (KBr disk) cm^{-1}: 3314, 1729, 1665. ^1H NMR δ 1.29 (3H, t, J = 7.0 Hz), 1.71 (3H, d, J = 6.7 Hz), 3.08 (1H, br. s), 4.23 (2H, q, J = 7.0 Hz), 4.51–4.62 (1H, m), 4.68–4.73 (1H, m), 5.41–5.53 (1H, m), 5.74–5.87 (1H, m), 6.76 (1H, d, J = 8.9 Hz), 8.25 (1H, s). FABMS *m/z*: 202 (MH^+). *Anal.* Found. C, 53.66; H, 7.56; N, 6.90. Calcd. for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96%.

*Ethyl (E)-2-formylamino-3-hydroxy-4-heptenoate (**4c**)*

85% yield, oil. IR ν max (neat) cm^{-1}:3332, 1741, 1669. ^1H NMR δ 0.97 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.99–2.09 (2H, m), 3.84 (1H, br. s, OH), 4.22 (2H, q, J = 7.0 Hz), 4.59–4.62 (1H, m), 4.66 (1H, dd, J = 8.9, 3.1 Hz), 5.45 (1H, dd, J = 15.4, 6.4 Hz), 5.81 (1H, dt, J = 15.3, 6.4 Hz), 6.86 (1H, d, J = 8.9 Hz, NH), 8.21 (1H, s). FABMS *m/z*: 216 (MH^+).

*Ethyl (E)-2-formylamino-3-hydroxy-4-octenoate (**4d**)*

84% yield, oil. IR ν max (neat) cm^{-1}: 3350, 1740, 1669. ^1H NMR δ 0.89 (3H, t, J = 7.3 Hz), 1.30 (3H, t, J = 7.0 Hz), 1.39 (2H, m), 3.16 (1H, br. S, OH), 4.23 (2H, q, J = 7.0), 4,63 (1H, m), 4.69 (1H, d, J = 3.1 Hz), 5.47 (1H, m), 5.78 (1H, m), 6.78 (1H, d, J = 8.9 Hz, NH), 8.24 (1H, s). FABMS m/z: 230 (MH^+).

*Ethyl 2-formylamino-3-hydroxy-3-methyl-4-pentenoate (**4e**)*

83% yield, oil. IR ν max (neat) cm^{-1}: 3354, 1739, 1669, 1520, ^1H MNR δ 1.27–1.37 (6H, m), 2.98 (1H, br. s, OH), 4.15–4.32 (2H, m), 4.63–4.71 (1H, two d, J = 8.2, 9.2 Hz), 5.16–5.22 (1H, m), 5.32–5.41 (1H, m), 5.78–6.01 (1H, m), 6.46–6.57 (1H, br. s, NH), 8.26–8.28 (1H, two s). FABMS *m/z*: 202 (MH^+).

*Ethyl 2-formylamino-3-hydroxy-4-methyl-4-pentenoate (**4f**)*

90% yield, oil. IR ν max (neat) cm^{-1}: 3348, 1738, 1669, 1521. ^1H NMR δ 1.30 (3H, t, J = 7.0 Hz), 1.77 (9H, s), 2.05 (3H, s), 4,24 (2H, q, J = 7.0 Hz), 4.59 (1H, s), 4.87 (1H, dd, J = 9.2, 2.7 Hz), 4.97 (1H, s), 5.08 (1H, s), 6.75 (1H, br. s, NH), 8.19 (1H, s). FABMS *m/z*: 202 (MH^+).

*Preparation of ethyl 3-acetoxy-2-tert-butoxycarbonylamino-4-alkenoate (**6**); general procedure*

A mixture of **4** (8.9 mmol) and 2N hydrochloric acid (25 ml) was stirred for 15 h at ambient temperature. After being evaporated *in vacuo*, the residue was dissolved with dry dichloromethane (30 ml). To the mixture were added triethylamine (2.42 g, 24 mmol) and di-*tert*-butyl dicarbonate (2.53 g, 11.6 mmol) at room temperature. After 12 h additional triethylamine (0.24 g, 2.4 mmol) and di-*tert*-butyl dicarbonate (0.25 g, 1.2 mmol) were added, and the whole was stirred for 8 h. After removal of the solvent *in vacuo*, the resulting oil was extracted with ether (30 ml × 3). The combined extracts were worked up in the usual manner and then chromatographed on silica gel with hexane-EtOAc (1:4) to give **5**. A mixture of **5** (3.67 mmol), 4-*N,N*-dimethylaminopyridine (100 mg) and acetic anhydride (4.71 mmol) in dichloromethane (25 ml) was stirred for 15 h at room temperature. After being evaporated, the residue was extracted with ether (2 × 20 ml). The combined extracts were worked up in the usual manner. The resulting oil was distilled under reduced pressure (120–150°C, 1 mmHg) to give the acetate **6** as a *syn/anti* mixture, which was used directly for the next reaction.

*Ethyl 3-acetoxy-2-tert-butoxycarbonylamino-4-pentenoate (**6a**)*

This compound was prepared in a 65% yield from **4a** according to the literature method (Kirihata et al., 1990).

*Ethyl (E)-3-acetoxy-2-tert-butoxycarbonylamino-4-hexenoate (**6b**)*

74% yield (based on **4b**), oil. IR ν max (neat) cm^{-1}: 3364, 1748, 1718, 1505. ^1H NMR δ 1.26 (3H, t, J = 7.0 Hz), 1.46 (9H, s). 1.71 (3H, d, J = 6.4 Hz), 2.03 (3H, s), 4.12–4.27 (2H, m), 4.46 (1H, dd, J = 3.1, 9.9 Hz), 5.17–5.20 (1H, br. s, NH), 5.42–5.51 (1H, m), 5.67–5.69 (1H, m), 5.78–5.88 (1H, m). FABMS *m/z*: 316 (MH^+).

*Ethyl (E)-3-acetoxy-2-tert-butoxycarbonylamino-4-heptenoate (**6c**)*

69% yield (based on **4c**), mp 38–45°C (EtOAc-hexane). IR ν max (KBr disk) cm^{-1}: 3364, 1741, 1719, 1505. ^1H NMR δ 0.99 (3H, t, J = 7.5 Hz), 1.26 (3H, t, J = 7.0 Hz), 1.46 (9H, s), 2.06 (3H, s), 2.05–2.12 (2H, m), 4.13–4.24 (2H, m), 4.47 (1H, dd, J = 9.8, 3.1 Hz), 5.19 (1H, br. s, NH), 5.43 (1H, ddt, J = 15.3, 6.7, 1.5 Hz), 5.67–5.74 (1H, m), 5.81–5.92 (1H, m). FABMS *m/z*: 330 (MH^+). *Anal.* Found. C, 58.26; H, 8.35; N, 4.17. Calcd. for $C_{16}H_{27}O_6N$: C, 58.34; H, 8.26; N, 4.25%.

*Ethyl (E)-3-acetoxy-2-tert-butoxycarbonylamino-4-octenoate (**6d**)*

65% yield (based on **4d**), oil. IR ν max (neat) cm^{-1}: 3444, 1740, 1723, 1505. ^1H NMR δ 0.88 (3H, t, J = 7.3 Hz), 1.26 (3H, t, J = 7.0 Hz), 1.33–1.41 (2H, m), 1.45 (9H, s), 2.00–2.06 (2H, m), 2.04 (3H, s), 4.14–4.24 (2H, m), 4.48 (1H, dd, J = 9.8, 3.1 Hz), 5.22, (1H, d, J = 9.8 Hz, NH), 5.45 (1H, dd, J = 15.6, 7.0 Hz), 5.81 (1H, dt, J = 15.6, 6.7 Hz). FABMS *m/z*: 344 (MH^+).

*Ethyl 3-acetoxy-2-tert-butoxycarbonylamino-3-methyl-4-pentenoate (**6e**)*

78% yield (based on **4e**), oil. IR ν max (neat) cm^{-1}: 3369, 1733, 1669, 1520. ^1H NMR δ 1.27 (3H, t, J = 7.0 Hz), 1.44 (9H, s), 1.73 (3H, s), 2.05 (3H, s), 4.21 (2H, q, J = 7.0 Hz), 4.63 (2H, d, J = 6.7 Hz), 4.73 (1H, br. s), 5.36 (1H, br. s, NH), 5.67 (1H, t, J = 6.7 Hz). FABMS *m/z*: 316 (MH^+).

*Ethyl 3-acetoxy-2-tert-butoxycarbonylamino-4-pentenoate (**6f**)*

63% yield (based on **4f**), mp 100–110°C (EtOAc). IR ν max (KBr disk) cm^{-1}: 3303, 1746, 1720, 1549. ^1H NMR δ 1.20–1.30 (3H, two t, J = 7.0 Hz), 1.43–1.45 (9H, two s), 1.80–1.83 (3H, two s), 4.18–4.20 (2H, two q, J = 7.0 Hz), 4.64 (1H, dd, J = 9.76, 3.1 Hz), 4.93–4.50 (2H, m), 5.1–5.2 (1H, br. s, NH), 5.58 (1H, m). FABMS *m/z*: 316 (MH^+). *Anal.* Found. C, 57.06; H, 8.08; N, 4.39. Calcd. for $C_{15}H_{25}O_6N$: C, 57.13; H, 7.99; N, 4.44%.

*Preparation of ethyl 2-tert-butoxycarbonylamino-5-hydroxy-3-alkenoate (**8**); general procedure*

A solution of **6** (11.4 mmol) and bis(acetonitrile)palladium(II) chloride (144 mg, 0.56 mmol) in dry benzene was stirred at 60°C for 15 h in argon atmosphere. After being evaporated, the residue was dissolved with ether (30 ml), and then filtered to remove the catalyst. The filtrates were washed with water, dried (Na_2SO_4) and concentrated to afford a dark brown oil. Fractional distillation (120–150°C, 1 mmHg) gave a mixture of **6** and **7**, each of which could be separated by a flash column on silica gel with hexane-EtOAc (1:4) to provide **7**. A mixture of **7** (10 mmol) and Amano PS (100 mg) in 0.1 M phosphate buffer (pH 7, 45 ml) was incubated with gently stirring at 40°C for 10 h. The mixture was extracted with ether (30 ml × 3), and the combined extracts were successively washed with aq. $NaHCO_3$ and water, and dried over Na_2SO_4. After removal of the solvent, the resulting oil was chromatographed on silica gel using hexane-EtOAc (1:1) as eluent.

*Ethyl (E)-2-tert-butoxycarbonylamino-5-hydroxy-3-pentenoate (**8a**)*

This compound was prepared in a 43% yield from **6a** according to the literature procedure (Kirihata et al., 1990). The spectroscopic data (IR and ^1H NMR) of **8a** agreed with those in the literature.

*Ethyl (E)-2-tert-butoxycarbonylamino-5-hydroxy-3-hexenoate (**8b**)*

23% yield (based on **6b**), oil, $[\alpha]_D^{33}$ + 4.82° (c 1.04, MeOH). IR ν max (neat) cm^{-1}: 3374, 1729, 1714, 1511. ^1H NMR δ 1.27 (3H, d, J = 6.1 Hz), 1.29 (3H, t, J = 7.0 Hz), 1.45 (9H, s), 1.78 (1H, br. s, OH), 4.21 (2H, q, J = 7.0 Hz), 4.25–4.37 (1H, m), 4.84 (1H, br. s), 5.21 (1H, br. s , NH), 5.73 (1H, dd, J = 15.6, 4.9 Hz), 5.84 (1H, dd, J = 15.6, 5.5 Hz). FABMS *m/z*: 274 (MH^+).

*Ethyl (E)-2-tert-butoxycarbonylamino-5-hydroxy-3-heptenoate (**8c**)*

24% yield (based on **6c**), oil, $[\alpha]_D^{32}$ + 0.92° (c 1.08, MeOH). IR ν max (neat) cm^{-1}: 3376, 1725, 1714, 1505. ^1H NMR δ 0.90 (3H, t, J = 7.5 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.45 (9H, s), 1.50–1.62 (2H, m), 2.38 (1H, s, OH), 4.03–4.09 (1H, m), 4.20 (2H, q, J = 7.0 Hz), 4.81 (1H, m), 5.68 (1H, m), 5.70 (1H, dd, J = 15.9, 5.2 Hz), 5.80 (1H, dd, J = 15.9, 5.2 Hz). FABMS *m/z*: 288 (MH^+).

*Ethyl (E)-2-tert-butoxycarbonylamino-5-hydroxy-3-octenoate (**8d**)*

12% yield (based on **6d**), oil, $[\alpha]_D^{32}$ − 1.77° (c 1.07, MeOH). IR ν max (neat) cm^{-1}: 3379, 1728, 1714, 1505. ^1H NMR δ 0.92 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.0 Hz), 1.31–1.48 (4H, m), 1.45 (9H, s), 2.06 (1H, br. s, OH), 4.13–4.17 (1H, m), 4.21 (2H, q, J = 7.0 Hz), 4.82 (1H, m), 5.28 (1H, m, NH), 5.70 (1H, dd, J = 15.6, 5.2 Hz), 5.80 (1H, dd, J = 15.6, 4.9 Hz). FABMS *m/z*: 288 (MH^+).

*Ethyl (E)-2-tert-butoxycarbonylamino-5-hydroxy-3-methyl-3-pentenoate (**8e**)*

25% yield (based on **6e**), oil. IR ν max (neat) cm^{-1}: 3375, 1746, 1712, 1504, ^1H NMR δ 1.28 (3H, t, J = 7.0Hz), 1.69 (3H, s), 1.99 (1H, br. s. OH), 4.17–4.25 (4H, m), 4.68 (1H, br. s), 5.43 (1H, br. s, NH), 5.73 (1H, t, J = 6.4Hz) FABMS *m/z:* 278 (MH^+).

*Preparation of δ-hydroxy-β, γ-dehydro α-amino acid (**1**); general procedure*

A mixture of **8** (3.84mmol), 2N hydrochloric acid (5.8ml) and acetic acid (8ml) was stirred for 6h at room temperature. After being evaporated, the residue was treated with 1N sodium hydroxide (11.5ml) for 30min at room temperature. After being acidified with dil. hydrochloric acid, the mixture was applied on an ion-exchange resin (Amberlite IR-120B, H^+) column. The column was washed with water and fractionated using 0.1M pyridine-acetate buffer pH 4.2–4.7, gradient) as eluent. The positive fractions to ninhydrin reagent were combined and concentrated *in vacuo* to dryness. The crude amino acid was further purified by ion-exchange resin column (Dowex 50 × 4, H^+) using 1.5% ammonia as eluent, and then recrystallized from a mixture of water and ethanol to furnish pure **1**.

*(E)-2-Amino-5-hydroxy-3-pentenoic acid (**1a**)*

65%, mp 182°C (decomp.). IR ν max (KBr disk) cm^{-1}: 3468, 3034, 1634, 1489. ^1H NMR (D_2O) δ 4.11 (2H, dd, J = 4.9, 1.2Hz), 4.24 (1H, d, J = 7.9Hz), 5.75 (1H, ddt, J = 15.6, 4.9, 1.5Hz), 6.02 (1H, dt, J = 15.6, 7.9Hz). ^{13}C NMR (D_2O) δ 58.9, 63.8, 125.4, 139.1, 175.7. FABMS *m/z*: 132 (MH^+). Anal. Found. C, 45.86; H, 6.88; N, 10.67. Calcd. for $C_5H_9O_3N$: C, 45.80; H, 6.92; N, 10.68%.

*(E)-2-Amino-5-hydroxy-3-hexenoic acid (**1b**)*

62% yield, mp 181°C (decomp.), $[\alpha]_D^{32}$ + 54.5° (c 1.03, H_2O). IR ν max (KBr disk) cm^{-1}: 3354, 1588, 1515, 1505. ^1H NMR (D_2O) δ 1.35 (3H, d, J = 7.7), 4.35 (1H, d, J = 7.9Hz), 4.46 (1H, m), 5.85 (1H, dd, J = 15.6, 7.9Hz), 6.10 (1H, dd, J = 15.6Hz). ^{13}C NMR (D_2O) δ 21.5, 55.9, 67.1, 121.5, 140.6, 172.9. FABMS *m/z*: 146 (MH^+). *Anal.* Found. C, 49.67; H, 7.66; N, 9.62. Calcd. for $C_6H_{11}O_3N$: C, 49.65; H, 7.64; N, 9.65%.

*(E)-2-Amino-5-hydroxy-3-heptenoic acid (**1c**)*

73% yield, mp 184°C (decomp.), $[\alpha]_D^{32}$ + 5.6° (c 1.04, H_2O). IR ν max (KBr disk) cm^{-1}: 3401, 3014, 1588, 1509. ^1H NMR (D_2O) δ 0.94 (3H, t, J = 7.3Hz), 1.58–1.69 (2H, m), 4.19 (1H, dd, J = 12.5, 6.4Hz), 4.33 (1H, dd, J = 10.1, 2.4Hz), 5.78–5.99 (1H, m), 6.00 (1H, dd, J = 15.6, 5.5). ^{13}C (D_2O) δ 11.6, 31.6, 58.9, 75.4, 125.4, 142.1, 175.7. FABMS *m/z*: 160 (MH^+). *Anal.* Found. C, 52.87; H, 8.30; N, 8.75. Calcd. for $C_7H_{13}O_3N$: C, 53.82; H, 8.23: N, 8.80%.

*(E)-2-Amino-5-hydroxy-3-octenoic acid (**1d**)*

68% yield, mp 175°C (decomp.), $[\alpha]_D^{32}$–22.9° (c 0.98, H_2O). IR ν max (KBr disk) cm^{-1}:3401, 1592, 1505. ^1H NMR (D_2O) δ 0.90 (3H, t, J = 7.3Hz), 1.27–1.44 (2H, m), 1.54, (2H, m), 4.25 (1H, dd, J = 12.8, 6.4Hz), 4.61 (1H, d, J = 7.9Hz), 5.81 (1H, dd, J = 15.5, 7.9Hz), 6.08 (1H, dd, J = 15.5, 5.8Hz). ^{13}C NMR (D_2O) δ 16.0, 20.7, 40.7, 59.0, 73.9, 125.1, 142.5, 175.7. FABMS *m/z*: 172 (MH^+). *Anal.* Found. C, 56.10; H, 7.61; N, 8.12. Calcd. for $C_8H_{15}O_3N$: C, 56.13; H, 7.65; N, 8.18%.

*(E)-2-Amino-5-hydroxy-3-methyl-3-pentenoic acid (***1e***)*

66% yield, mp 185°C (decomp.). IR ν max (KBr disk) cm^{-1}: 3328, 1580, 1523, 1501. ^1H NMR (D_2O) δ 1.66 (3H, s), 4.17 (2H, d, J = 6.5 Hz), 4.20 (1H, s), 5.80 (1H, t, J = 6.6 Hz). ^{13}C NMR (D_2O) δ 14.5, 60.4, 64.4, 134.0, 134.8, 175.5. FABMS *m/z*: 146 (MH^+). *Anal.* Found. C, 49.70; H, 7.69; N, 9.59. Calcd. for $C_6H_{11}O_3N$: C, 49.65; H, 7.64; N, 9.65%.

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References

Agouridas K, Girodeau JM, Pineau R (1985) Synthesis of protected vinylic amino acids by intermolecular Lewis acid catalyzed ene reactions. Tetrahedron Lett 26: 3115–3118

Castelhano AL, Horne S, Billedeau R, Krantz A (1986) Reactions of an electrophilic glycine cation equivalent with Grignard reagent. A simple synthesis of β,γ-unsaturated amino acids. Tetrahedron Lett 27: 2435–2438

Cooper AJL, Fitzpatrick SM (1982) β-Methylene-D,L-aspartic acid: A selective inhibitor of glutamate-aspartate transaminase. J Am Chem Soc 104: 332–334

Fitzner JN, Pratt DV, Hopkins PB (1985) Synthesis of protected racemic β,γ-unsaturated-α-amino acids via γ-phenylseleno-α,β-unsaturated esters. Tetrahedron Lett 26: 1959–1962

Girodeau JM, Agouridas C, Masson M, Pineau R, LeGoffic FJ (1986) The lysine pathway as a target for a new genera of synthetic antibacterial antibiotics. J Med Chem 29: 1023–1030

Greenlee WJ (1984) Synthesis of β,γ-unsaturated amino acids by the Strecker reaction. J Org Chem 49: 2632–2634

Ito Y, Matsuura T, Saegusa T (1985) $ZnCl_2$ and CuCl promoted aldol reactions of isocyanoacetate with α,β-unsaturated carbonyl compounds. Tetrahedron Lett 26: 5781–5784

Kirihata M, Kawahara S, Ichimoto I, Ueda H (1990) An effective synthesis of (±)-(E)-2-amino-5-phosphono-3-pentenoic acid by palladium(II)-assisted migration of the double bond. Agric Biol Chem 54: 753–756

Kirihata M, Kaziwara T, Kawashima Y, Ichimoto I (1991) An efficient synthesis (±)-α-kainic acid using a 3-hydroxyallylglycine derivative as a common building block. Agric Biol Chem 55: 3033–3037

Kurokawa N, Ofune Y (1985) The palladium(II)-assisted synthesis of (±)-α-(methylenecyclopropyl)glycine and (±)-α-(carboxycyclopropyl)glycine, two bioactive amino acids. Tetrahedron Lett 26: 83–84

Marcotte P, Walsh C (1976) Vinylglycine and propargylglycine: complementary suicide substrates for L-amino acid oxidase and D-amino acid oxidase. Biochemistry 15: 3070–3076

Monahan JB, Hood WF, Compton RP, Cordi AA, Williams RM (1990) Identification of a novel structural class of positive modulators of the N-methyl-D-aspartate receptor, with actions mediated through the glycine recognition site. Europ J Pharmacol 189: 373–379

Overmann LE, Knoll FM (1979) Palladium(II)-catalyzed rearrangement of allylic acetates. Tetrahedron Lett 20: 321–324

Rando RR (1975) Mechanisms of action of naturally occuring irreversible enzyme inhibitors. Account Chem Res 8: 281–288

Walsh C (1982) Suicide substrates: mechanism-based enzyme inactivators. Tetrahedron 38: 871–909

Williams RM, Zhai W (1988) Versatile, stereocontrolled, asymmetric synthesis of E-vinylglycine derivatives. Tetrahedron 44: 5425–5430

Authors' address: Dr. M. Kirihata, Department of Applied Biochemistry, College of Agriculture, University of Osaka Prefecture, 1-1 Gakuencho, Sakai, Osaka 593, Japan.

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