Studies on Angiotensin Converting Enzyme Inhibitors. VI.[1] Synthesis and Angiotensin Converting Enzyme Inhibitory Activities of the Dicarboxylic Acid Derivative of Imidapril and Its Diastereoisomers[2]

Hitoshi KUBOTA,[a] Ken-ichi NUNAMI,*,[a] Kimiaki HAYASHI,[a] Yoshikatsu HASHIMOTO,[b] Noriko OGIKU,[b] Yuzo MATSUOKA,[b] and Ryuichi ISHIDA[b]

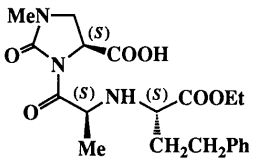
Research Laboratory of Applied Biochemistry[a] and Biological Research Laboratory,[b] Tanabe Seiyaku Co., Ltd., 16–89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan. *Received November 18, 1991*

All possible diastereoisomers of the dicarboxylic acid (10a), the biologically active form of imidapril (1), were synthesized, and their inhibitory activity against angiotensin converting enzyme (ACE) was examined. The *in vitro* ACE inhibitory activity of these compounds greatly depended on the configurations of the three asymmetric carbons in each molecule. The (*S*,*S*,*S*) isomer (10a) showed much more potent activity than the others.

Keywords ACE inhibitor; imidapril; enalapril; biologically active form

Angiotensin converting enzyme (ACE) inhibitors such as enalapril[3] have recently received attention as effective drugs for hypertension. Most of them have three asymmetric carbons, with each carbons being having an *S* configuration. Although the configurations of the three asymmetric carbons would greatly contribute to the inhibitory activity, the structure–activity relationships of all possible diastereoisomers have not yet been systematically studied.

In the series of our synthetic studies on ACE inhibitors, we previously reported that imidapril (**1**), (4*S*)-3-[(2*S*)-2-[*N*-((1*S*)-1-ethoxycarbonyl-3-phenylpropyl)amino]-propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid, is a potent and long-lasting antihypertensive drug for oral use.[4] The biologically active form of imidapril is known to be a dicarboxylic acid derivative (**10a**). In this paper, we wish to report the synthesis and ACE inhibitory activity of all possible diastereoisomers of the biologically active form of imidapril.



imidapril ; **1**

Fig. 1

Chemistry The requisite chiral building blocks for the synthesis of the diastereoisomers of the biologically active form of imidapril were synthesized as shown in Chart 1. The 2-oxoimidazolidine derivatives (**2a, b**) were prepared from L- or D-asparagine according to the reported method.[4] The propionic acid derivatives (**3a, b**) were prepared from D- or L-lactate,[1] and subsequently converted to the requisite acid chlorides (**4a, b**). Both (2*S*) and (2*R*)-2-amino-4-phenylbutyric acid esters (**7a, b**) were enzymatically prepared from *N*-acetyl-2-amino-4-phenylbutyric acid (**5**). Thus, enantioselective deacylation of **5** by using aminoacylase originated from *Aspergillus oryzae* afforded the L-amino acid (**6a**), while the recovered D-acetyl derivative (**5b**) was chemically deacylated to give the D-amino acid (**6b**). Each amino acid was then converted to the corresponding benzyl ester by the usual method.

By using the above three chiral building blocks, all possible diastereoisomers (**10a—h**) of the biologically active form of imidapril were synthesized (Chart 2). Thus,

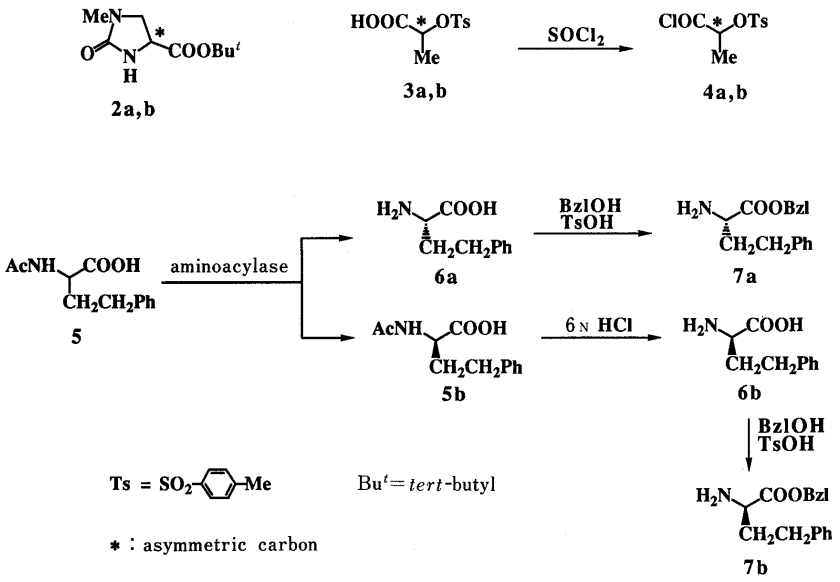


Chart 1

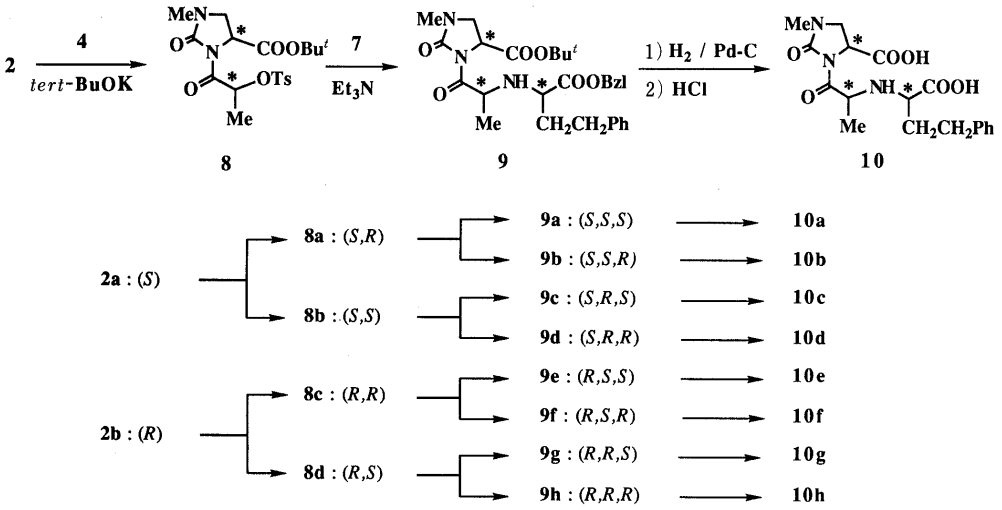
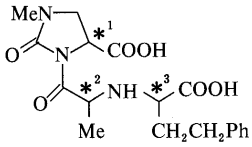


Chart 2

TABLE I. Physical Properties and *in Vitro* ACE Inhibitory Activities of the Dicarboxylic Acids (**10a—h**)



Compound	($*^1$, $*^2$, $*^3$)	Yield (%) (from **9**)	mp (°C)	$[\alpha]_D^{25}$ (c=0.5, solv.[a])	Formula[b]	IC_{50} (M)
10a	(*S*, *S*, *S*)	81	239—241	−90.4 (A)	$C_{18}H_{23}N_3O_6$	1.8×10^{-9}
10b	(*S*, *S*, *R*)	75	197—198	−112.0 (A)	$C_{18}H_{23}N_3O_6$	9.6×10^{-8}
10c	(*S*, *R*, *S*)	60	157—159	−33.2 (A)	$C_{18}H_{23}N_3O_6$	2.3×10^{-5}
10d[c]	(*S*, *R*, *R*)	58	Amorphous powder	−53.2 (B)	$C_{18}H_{23}N_3O_6\cdot HCl$	2.2×10^{-4}
10e[c]	(*R*, *S*, *S*)	60	Amorphous powder	+52.0 (B)	$C_{18}H_{23}N_3O_6\cdot HCl$	4.9×10^{-5}
10f	(*R*, *S*, *R*)	65	158—160	+32.8 (A)	$C_{18}H_{23}N_3O_6$	6.6×10^{-5}
10g	(*R*, *R*, *S*)	72	212—213	+112.5 (A)	$C_{18}H_{23}N_3O_6$	7.2×10^{-4}
10h	(*R*, *R*, *R*)	84	239—240	+89.5 (A)	$C_{18}H_{23}N_3O_6$	$>10^{-3}$
Enalaprilat						2.1×10^{-9}

a) Solvent: A, 5% $NaHCO_3$; B, MeOH. b) All compounds exhibited satisfactory C, H, and N elemental analyses. c) Hydrochloride.

9a was obtained in 58% yield from **2a** according to the method described in the previous paper.[1] The protecting ester residues of **9a** were removed by hydrogenolysis, followed by treatment of the mono carboxylic acid with anhydrous hydrogen chloride in dioxane to afford **10a** in 81% yield. The other isomers (**10b—h**) were also synthesized from **2** by using the same method as described in the preparation of **10a**.

Biological Results The *in vitro* ACE inhibitory activity of the dicarboxylic acid derivatives (**10**) was examined in the presence of hippurylhistidylleucine as a substrate using ACE originated from swine kidney cortex. The results are summarized in Table I. The inhibitory activity of (*S*,*R*,*S*)-**10c** and (*R*,*S*,*S*)-**10e** was 10^4 times less potent than that of (*S*,*S*,*S*)-**10a**, which was comparable to the activity of enalaprilat. Accordingly, both carbons $*1$ and $*2$ should be *S* configurations for exhibiting the inhibitory activity. On the other hand, the inhibitory activity of (*S*,*S*,*R*)-**10b** was only about 50 times less potent than that of **10a**, indicating that the configuration of the carbon $*3$ plays a less important role than carbon $*1$ and $*2$. From the above results, it is concluded that the (*S*,*S*,*S*) isomer showed much more potent activity than the others. Furthermore, these results will give useful information for analysis of the tertiary structure of the active site of ACE.

Experimental

Melting points (mp) were measured by the use of a Yamato MP-21 melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer 1640 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker AC-200 instrument, using tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a Hitachi M-2000A mass spectrometer. Specific rotations were measured with a Perkin-Elmer 243 polarimeter. High-performance liquid chromatography (HPLC) was done on a Shimadzu LC-6A instrument. For silica gel column chromatography, Keselgel 60 (0.040—0.063 mm, E. Merck) was employed.

The synthetic procedure of **10a** is given below as an example. The other compounds were prepared according to this procedure from appropriate starting materials, and yields and physical properties are described.

(2*S*)-2-Amino-4-phenylbutyric Acid (6a) and (2*R*)-2-Amino-4-phenylbutyric Acid (6b) Aminoacylase (1295 mg) obtained from *Aspergillus oryzae* was added to a suspension of **5** (68.1 g, 308 mmol) in water (1980 ml) containing $CoCl_2\cdot6H_2O$ (305 mg). The mixture was adjusted to pH 9.0 with aqueous NaOH and incubated at 37 °C for 24 h. The crystalline precipitates were collected by filtration and washed with water and with MeOH to afford **6a** (20.9 g, 38%) as colorless leaflets. mp >240 °C. $[\alpha]_D^{25}$ +47.5° (c=1, 1 N HCl). IR (KBr): 3400, 1655, 1625, 1582 cm^{-1}. ^{1}H-NMR (D_2O+TFA) δ: 2.10—2.45 (2H, m), 2.68—2.97 (2H, m), 4.10 (1H, t, J=6.3 Hz), 7.20—7.48 (5H, m). MS m/z: 179 (M^+). *Anal.* Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.08; H, 7.26; N, 7.77.

The filtrate after isolation of crystals (**6a**) was acidified with concentrated HCl, and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was recrystallized from AcOEt–MeOH to give **5b** (25.3 g, 37%) as colorless needles. mp 170—172 °C.

A mixture of **5b** (20.0 g, 90.4 mmol) and 6 N HCl (300 ml) was heated under reflux overnight. After cooling, the mixture was concentrated to a half of its original volume, and the resulting mixture was neutralized with concentrated NH_4OH. The crystalline precipitates were collected by filtration and washed with water and with MeOH to afford **6b** (15.5 g, 96%) as colorless leaflets. mp >240 °C. $[\alpha]_D^{26}$ −46.0° ($c=1$, 1 N HCl).

Benzyl (2*S*)-2-Amino-4-phenylbutyrate (7a) A mixture of **6a** (20.5 g, 114 mmol), benzyl alcohol (175 ml), *p*-toluenesulfonic acid monohydrate (28.0 g) and toluene (175 ml) was heated under reflux for 4 h with a Dean-Stark apparatus. After removal of the solvent, a large amount of iso-Pr_2O was added to the residue. The separated crystals were filtered and washed with iso-Pr_2O to afford **7a** *p*-toluenesulfonate (40.0 g, 79%) as colorless needles. mp 139—140 °C. IR (KBr): 1749, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.95—2.18 (2H, m), 2.29 (3H, s), 2.43—2.81 (2H, m), 4.13 (1H, t, $J=6$ Hz), 5.22, 5.28 (2H, ABq, $J=12$ Hz), 7.05—7.56 (14H, m), 8.46 (3H, s). MS *m/z*: 269 (M^+). *Anal.* Calcd for $C_{17}H_{19}NO_2 \cdot C_7H_8O_3S$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.05; H, 6.17; N, 3.15. Compound **7a** *p*-toluenesulfonate dissolved in H_2O was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness to give **7a** as a colorless syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (2H, s), 1.75—2.20 (2H, m), 2.59—2.77 (2H, m), 3.49 (1H, dd, $J=5$, 8 Hz), 5.10, 5.16 (2H, ABq, $J=12$ Hz), 7.05—7.40 (10H, m).

7b *p*-toluenesulfonate: yield 90%; mp 140—142 °C.

***tert*-Butyl (4*S*)-1-Methyl-3-[(2*R*)-2-(4-toluenesulfonyloxy)propionyl]-2-oxoimidazolidine-4-carboxylate (8a)** A mixture of (2*R*)-2-(4-toluenesulfonyloxy)propionic acid (**3a**) (1.15 g, 4.7 mmol), thionyl chloride (1.12 g, 9.4 mmol) and $CHCl_3$ (5 ml) was heated under reflux for 3 h and then concentrated *in vacuo*. The residue was taken up in $CHCl_3$ and the solution was reconcentrated to afford crude (2*R*)-2-(4-toluenesulfonyloxy)-propionyl chloride (**4a**) as a syrup. Potassium *tert*-butoxide (607 mg, 5.4 mmol) was added to a solution of *tert*-butyl (4*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate (**2a**) (1.08 g, 5.4 mmol) in tetrahydrofuran (THF) (12 ml) at −50 °C, and the mixture was stirred at the same temperature for 20 min. After a solution of **4a** in THF (2 ml) was added to the above solution in one portion, stirring was continued for 20 min and then a mixture of AcOEt (6 ml), AcOH (320 mg) and brine (6 ml) was added to the reaction mixture. The organic layer was separated and washed successively with 5% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with $CHCl_3$–AcOEt (2 : 1), and the product was crystallized from hexane to give **8a** (1.48 g, 74%) as colorless needles. mp 78—80 °C. IR (Nujol): 1750, 1735, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.47 (3H, d, $J=7$ Hz), 2.41 (3H, s), 2.87 (3H, s), 3.31 (1H, dd, $J=4$, 9 Hz), 3.70 (1H, t, $J=9$ Hz), 4.50 (1H, dd, $J=4$, 9 Hz), 6.26 (1H, q, $J=7$ Hz), 7.29 (2H, d, $J=7$ Hz), 7.80 (2H, d, $J=7$ Hz). MS *m/z*: 370 (M^+ − isobutene). *Anal.* Calcd for $C_{19}H_{26}N_2O_7S$: C, 53.51; H, 6.14; N, 6.57; S, 7.52. Found: C, 53.37; H, 6.09; N, 6.50; S, 7.44.

8b: Yield 70%; mp 152—153 °C. IR (KBr): 1740, 1730, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.52 (3H, d, $J=7$ Hz), 2.44 (3H, s), 2.88 (3H, s), 3.34 (1H, dd, $J=4$, 10 Hz), 3.72 (1H, t, $J=10$ Hz), 4.67 (1H, dd, $J=4$, 10 Hz), 6.25 (1H, q, $J=7$ Hz), 7.33 (2H, d, $J=8$ Hz), 7.83 (2H, d, $J=8$ Hz). MS *m/z*: 426 (M^+).

8c: Yield 68%; mp 149—151 °C. **8d**: Yield 72%; mp 72 °C.

***tert*-Butyl (4*S*)-3-[(2*S*)-2-[*N*-((1*S*)-1-Benzyloxycarbonyl-3-phenylpropyl)amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate (9a)** A mixture of **8a** (1.00 g, 2.3 mmol), **7a** (0.95 g, 3.5 mmol) and Et_3N (0.36 g, 3.5 mmol) in DMSO (1 ml) was heated under stirring at 80 °C for 18 h. After cooling, the mixture was diluted with AcOEt (10 ml) and brine (3 ml). The separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$–AcOEt (2 : 1) to give **9a** (0.97 g, 79%) as a syrup. IR (film): 3320, 1735, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, $J=7$ Hz), 1.45 (9H, s), 1.8—2.4 (2H, m), 2.5—2.8 (2H, m), 2.82 (3H, s), 3.1—3.7 (3H, m), 4.3—4.9 (2H, m), 5.10 (2H, s), 7.0—7.4 (5H, m), 7.31 (5H, s). MS *m/z*: 523 (M^+). Compound **9a** hydrogen maleate was obtained as colorless needles by treatment with maleic acid in iso-Pr_2O–AcOEt. mp 108—112 °C. *Anal.* Calcd for $C_{29}H_{37}N_3O_6 \cdot C_4H_4O_4$: C, 61.96; H, 6.46; N, 6.57. Found: C, 61.61; H, 6.49; N, 6.53.

9b: Yield 38%; syrup. IR (film): 3350, 1740, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, $J=7$ Hz), 1.44 (9H, s), 1.85—2.13 (2H, m), 2.55—2.80 (2H, m), 2.82 (3H, s), 3.10—3.33 (2H, m), 3.42 (1H, t, $J=10$ Hz), 4.44 (1H, dd, $J=4$, 10 Hz), 4.69 (1H, q, $J=7$ Hz), 5.03, 5.14 (2H, ABq, $J=6$ Hz), 7.08—7.35 (5H, m), 7.35 (5H, s). MS *m/z*: 523 (M^+).

9c: Yield 69%; mp 96—99 °C. IR (KBr): 3340, 1730, 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, d, $J=7$ Hz), 1.43 (9H, s), 1.90—2.10 (2H, m), 2.43—2.85 (2H, m), 2.87 (3H, s), 3.29 (1H, dd, $J=4$, 10 Hz), 3.39 (1H, t, $J=5.5$ Hz), 3.66 (1H, t, $J=10$ Hz), 4.58 (1H, dd, $J=4$, 10 Hz), 4.72 (1H, q, $J=7$ Hz), 5.08, 5.18 (2H, ABq, $J=12$ Hz), 7.05—7.30 (5H, m), 7.34 (5H, s). MS *m/z*: 523 (M^+).

9d: Yield 50%; syrup. IR (film): 3350, 1740, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, $J=7$ Hz), 1.45 (9H, s), 1.75—2.10 (2H, m), 2.59—2.72 (2H, m), 2.87 (3H, s), 3.30 (1H, dd, $J=4$, 10 Hz), 3.40 (1H, t, $J=6$ Hz), 3.67 (1H, t, $J=10$ Hz), 4.59 (1H, dd, $J=4$, 10 Hz), 4.77 (1H, q, $J=7$ Hz), 5.13, 5.21 (2H, ABq, $J=12$ Hz), 7.07—7.46 (10H, m). MS *m/z*: 523 (M^+).

9e: Yield 53%; syrup. **9f**: Yield 63%; mp 99 °C. **9g**: Yield 40%; syrup. **9h**: Yield 75%; syrup.

(4*S*)-3-[(2*S*)-2-[*N*-((1*S*)-1-Carboxy-3-phenylpropyl)amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic Acid (10a) Compound **9a** (1.52 g, 2.9 mmol) dissolved in MeOH (20 ml) was subjected to hydrogenolysis in the presence of 10% palladium on carbon (0.15 g) at room temperature under atmospheric pressure for 2 h. After removal of the catalyst, the filtrate was concentrated *in vacuo*. The residue was dissolved in 4 N HCl in dioxane (20 ml), and the mixture was stirred at room temperature overnight. After the reaction mixture was concentrated *in vacuo*, the crystalline residue was triturated with AcOEt. The resulting crystals were recrystallized from H_2O to afford **10a** (0.89 g, 81%) as colorless needles. IR (KBr): 3470, 1745, 1730, 1695 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.25 (3H, d, $J=7$ Hz), 1.70—1.95 (2H, m), 2.55—2.73 (2H, m), 2.76 (3H, s), 3.15 (1H, t, $J=6$ Hz), 3.38 (1H, dd, $J=4$, 10 Hz), 3.72 (1H, t, $J=10$ Hz), 4.65 (1H, dd, $J=4$, 10 Hz), 4.73 (1H, q, $J=7$ Hz), 7.10—7.34 (5H, m). MS (SIMS) *m/z*: 378 ($M^+ + 1$). *Anal.* Calcd for $C_{18}H_{23}N_3O_6$: C, 57.29; H, 6.14; N, 11.13. Found: C, 56.99; H, 6.09; N, 11.03.

10b: IR (KBr): 3450, 3200, 1745, 1730, 1690, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (3H, d, $J=7$ Hz), 1.70—1.95 (2H, m), 2.43—2.73 (2H, m), 2.76 (3H, s), 3.07 (1H, t, $J=6$ Hz), 3.37 (1H, dd, $J=4$, 10 Hz), 3.70 (1H, t, $J=10$ Hz), 4.53—4.71 (2H, m), 7.12—7.34 (5H, m). MS *m/z*: 377 (M^+).

10c: IR (KBr): 3550, 3410, 1745, 1730, 1695, 1655, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, d, $J=7$ Hz), 1.75—2.00 (2H, m), 2.35—2.80 (2H, m), 2.77 (3H, s), 3.22 (1H, t, $J=5$ Hz), 3.34 (1H, dd, $J=3$, 10 Hz), 3.71 (1H, t, $J=10$ Hz), 4.63 (1H, dd, $J=3$, 10 Hz), 4.77 (1H, q, $J=7$ Hz), 7.10—7.40 (5H, m). MS *m/z*: 359 ($M^+ - H_2O$).

10d Hydrochloride: IR (KBr): 3450, 1740, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.50 (3H, d, $J=7$ Hz), 2.00—2.22 (2H, m), 2.57—2.75 (2H, m), 2.79 (3H, s), 3.46 (1H, dd, $J=3$, 10 Hz), 3.63 (1H, t, $J=6$ Hz), 3.77 (1H, t, $J=10$ Hz), 4.76 (1H, dd, $J=3$, 10 Hz), 5.28 (1H, q, $J=7$ Hz), 7.13—7.40 (5H, m). MS *m/z*: 377 (M^+).

***In Vitro* ACE Inhibitory Activity** The partially purified ACE was prepared from swine kidney cortex by the method of Oshima *et al.*[5] ACE inhibitory activity was determined by the following methods. The reaction mixture contained 1 mM hippurylhistidylleucine, 50 mM NaCl, 50 mM Tris–HCl (pH 7.4), 6 μg enzyme protein (specific activity; 14.2 μmol hippuric acid/mg protein/h) and each final concentration of the samples. Incubation was carried out for 20 min at 37 °C. The reaction was stopped by adding ice cold methanol. After centrifugation of these solutions for 5 min at 3000 rpm, the supernatant was filtrated through a membrane filter (pore size: 0.45 μm). The liberated hippuric acid was measured by the HPLC technique. Column: Nucleosil $5C_{18}$ 4.0 × 200 mm (Chemco), column temperature: 40 °C, mobile phase: 0.01 M KH_2PO_4–H_3PO_4 (pH 3.0) : CH_3CN = 80 : 20, flow rate: 1.0 ml/min, detection wave length: 228 nm, detection sensitivity: 0.04 AUS, injection volume: 10 μl.

Activity was designated in terms of the IC_{50}, which was the molar concentration of the test inhibitor causing 50% inhibition of the control converting enzyme activity.

Acknowledgement We thank Drs. T. Tosa, K. Matsumoto, and T. Iwasaki, of our research laboratory, for their encouragement.

References and Notes

1) Part V: H. Kubota, K. Nunami, M. Yamagishi, S. Nishimoto, and K. Hayashi, *Chem. Pharm. Bull.*, **39**, 1374 (1991).
2) A part of this work was presented at the 111th Annual Meeting of

the Pharmaceutical Society of Japan, Tokyo, Mar. 1991.
3) A. A. Patchett, E. Harris, E. W. Tristram, M. J. Wyvratt, M. T. Wu, D. Taub, E. R. Peterson, T. J. Ikeler, J. ten Broeke, L. G. Payne, D. L. Ondeyka, E. D. Thorsett, W. J. Greenlee, N. S. Lohr, R. D. Hoffsommer, H. Joshua, W. V. Ruyle, J. W. Rothrock, S. D. Aster, A. L. Maycock, F. M. Robinson, R. Hirschmann, C. S. Sweet, E. H. Ulm, D. M. Gross, T. C. Vassil, and C. A. Stone, *Nature* (London), **288**, 280 (1980).
4) K. Hayashi, K. Nunami, J. Kato, N. Yoneda, M. Kubo, T. Ochiai, and R. Ishida, *J. Med. Chem.*, **32**, 289 (1989).
5) G. Oshima, A. Gecse, and E. G. Erdos, *Biochim. Biophys. Acta*, **350**, 26 (1974).