Studies on Angiotensin Converting Enzyme Inhibitors. V.[1] The Diastereoselective Synthesis of 2-Oxoimidazolidine Derivatives[2]

Hitoshi KUBOTA,[a] Ken-ichi NUNAMI,[a] Masafumi YAMAGISHI,[b] Shigeru NISHIMOTO,[b] and Kimiaki HAYASHI*,[a]

Research Laboratory of Applied Biochemistry[a] and Pharmaceutical Technics Division,[b] Tanabe Seiyaku Co., Ltd., 16–89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan. *Received October 15, 1990*

A diastereoselective synthesis of imidapril (1), which is under clinical study as an antihypertensive drug based on its angiotensin converting enzyme (ACE)-inhibitory activity, was established. *N*-Alkylation of (2*S*)-2-amino-4-phenylbutyric acid ester (12) with 3-((2*R*)-2-methane or toluenesulfonyloxypropionyl)-2-oxoimidazolidine derivative (11) diastereoselectively proceeded in an *SN*2 fashion to afford *tert*-butyl (4*S*)-3-[(2*S*)-2-[*N*-[(1*S*)-1-ethoxycarbonyl)-3-phenylpropyl]amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate (13), a precursor of 1. Alternatively, benzyl (2*S*)-2-[*N*-[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propionate (15), which is the key building block of 13, was synthesized by the same strategy. This procedure was also applied to the synthesis of enalapril.

Keywords ACE inhibitor; imidapril; enalapril; racemization; diastereoselective synthesis

Since the discovery that angiotensin converting enzyme (ACE) inhibitors can be effective antihypertensive agents for the treatment of essential and renal hypertension, several synthetic inhibitors have been reported.[3] In our series of synthetic studies on ACE inhibitors, we previously reported that the 2-oxoimidazolidine derivative (**1**), which has (*S,S,S*)-configuration,[4] possesses potent and long-lasting ACE-inhibitory and antihypertensive activities.[1] It was designated as imidapril[5] and has been undergoing clinical trials to evaluate its efficacy in the treatment of hypertension.

In the previous paper,[1] we retro-synthetically divided **1** into three units (A, B and C). As a starting material for the A-unit, (4*S*)-2-oxoimidazolidine-4-carboxylic acid (**2**), which was readily prepared from L-asparagine according to a known procedure,[6] was used. To obtain the C-unit, (2*S*)-2-amino-4-phenylbutyric acid (**6**) was prepared by enantioselective deacylation of the corresponding *N*-acetyl-D,L-amino acid using aminoacylase. We have recently established a more advantageous synthetic procedure for **6** by enzymatic transamination of 2-oxo-4-phenylbutyric acid (**5**) by the use of *Paracoccus denitrificans* with L-aspartic acid as an amino group donor.[7] Meanwhile, 2-bromopropionic acid was adopted as a source of the B-unit. However, *N*-alkylation of the optically active amino acid ester (**12**) with a bromo compound (**7** or **8**) resulted in the formation of diastereomeric mixtures ((*S,S,S*)- and (*S,R,S*)-**13**, or (*S,S*)- and (*R,S*)-**15**), even when optically pure (*S,R*)-**7** or (*R*)-**8** was used. Therefore, an efficient method for stereoselective introduction of the B-unit was required as the key point in the synthesis of (*S,S,S*)-**1**. Now, we wish to report a diastereoselective preparation of (*S,S,S*)-**1** that should be suitable for industrial-scale synthesis.

First, in order to elucidate the nature of the *N*-alkylation reaction, a mixture of (*S,R*)-**7**, **12** and potassium carbonate (K_2CO_3) in hexamethylphosphoramide (HMPA) was stirred at room temperature and the reaction process was investigated periodically by high-performance liquid chromatography (HPLC). Figure 1 shows that (*S,R*)-**7** completely racemized within 5 min under the reaction conditions used, giving a mixture of (*S,R*)-**7** and (*S,S*)-**7**, while the *SN*2-type reaction proceeded much more slowly. This result prompted us to develop a new optically active B-synthon which would hardly racemize under such reaction conditions.

Recently, Iwasaki *et al.*[8] reported the diastereoselective synthesis of ACE inhibitors in which optically active ethyl 2-bromo-4-phenylbutyrate was coupled with dipeptide esters in the presence of a weak base such as ammonium

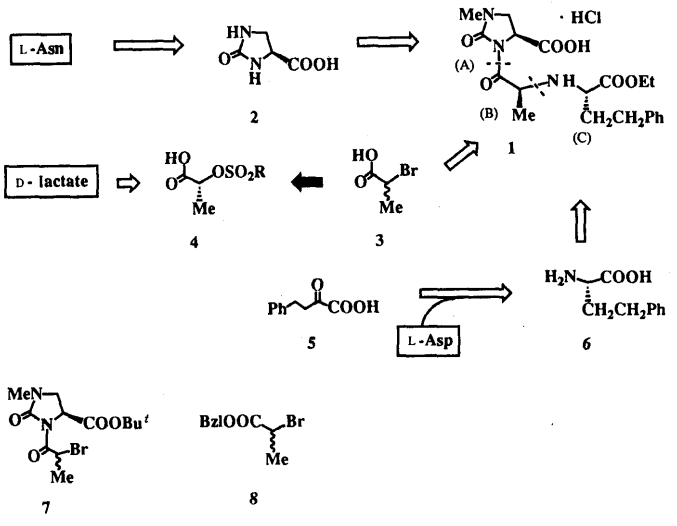

Chart 1

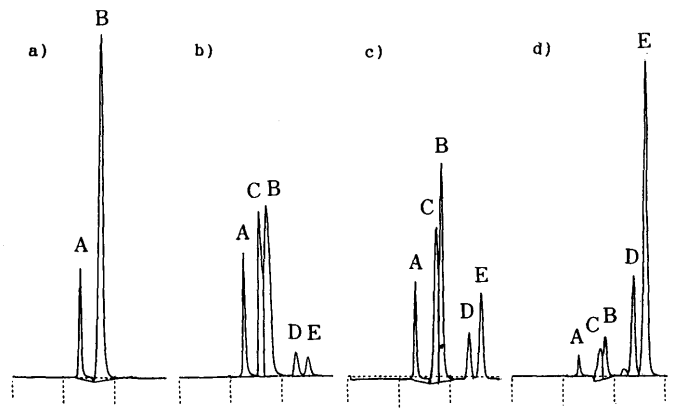

Fig. 1. HPLC Analysis of the Reaction Mixture of (*S,R*)-**7** with **12** in the Presence of K_2CO_3

a) initial; b) 5 min; c) 1 h; d) 24 h. A, **12**; B, (*S,R*)-**7**; C, (*S,S*)-**7**; D, (*S,S,S*)-**13**; E, (*S,R,S*)-**13**.

carbonate by an S_N2 process. However, a small amount of the undesired diastereoisomer was still formed, since the racemization of the bromo compound was not suppressed completely. On the other hand, Effenberger *et al.*[9] prepared several optically active *N*-substituted amino acid esters from 2-trifluoromethanesulfonyloxyalkanoic acid esters and amines. As the reaction proceeded with complete inversion of triflate, this method was supposed to be useful for the diastereoselective synthesis of (*S,S,S*)-**1**. However, triflates are too unstable and expensive to be used on an industrial scale.

Taking the above information into consideration, we chose (2*R*)-2-(4-toluenesulfonyloxy)- or (2*R*)-2-methanesulfonyloxypropionic acid (**4**) as the B-unit synthon. The optically pure tosylate or mesylate derivative (**11**) was synthesized as shown in Chart 2. Namely, the carboxylic acid (**4**) was prepared from D-lactate (**9**) according to the known procedure.[10] Compound **4** was converted to the acid chloride and condensed with a 2-oxoimidazolidine derivative (**10**) in the presence of potassium *tert*-butoxide (*tert*-BuOK) in tetrahydrofuran (THF), affording (*S,R*)-**11** in a good yield.

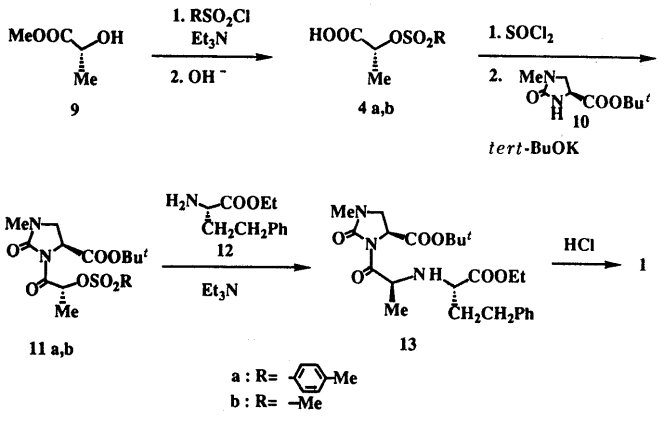

Chart 2

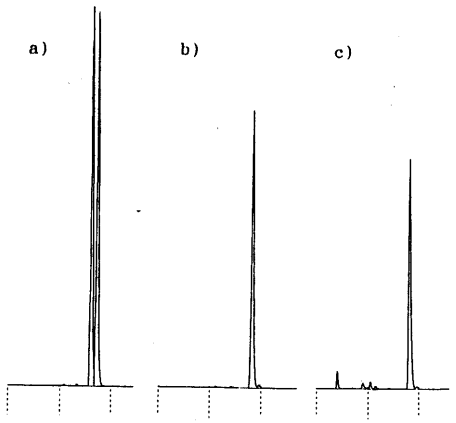

Fig. 2. HPLC Analysis of **11a** in Base-Solvent Systems

a) (*S,R*)-**11a**+(*S,S*)-**11a**; b) (*S,R*)-**11a**–K_2CO_3–HMPA, 25 °C, 24 h; c) (*S,R*)-**11a**–Et_3N–DMSO, 70 °C, 24 h.

TABLE I

$$(S,R)\text{-}\mathbf{11a} + (S)\text{-}\mathbf{12} \xrightarrow[\text{DMSO}]{\text{base}} (S,S,S)\text{-}\mathbf{13}$$

Run	**12** (eq)[a]	Base (eq)[a]	Temp. (°C)	Time (h)	Yield (%)[b]
1	1.0	K_2CO_3 (2.0)	60	5	27
2	1.0	K_2CO_3 (2.0)	60	24	39
3	1.0	Et_3N (1.5)	80	30	61
4	1.5	Et_3N (1.5)	80	24	85
5	1.5	Et_3N (2.0)	80	24	80

a) Molar equivalents to **11a**. *b*) Isolation yield.

The racemization tendency of (*S,R*)-**11** in several base-solvent systems was investigated by HPLC in the same manner as described in the case of the bromo compound ((*S,R*)-**7**) (Fig. 2). No racemization of (*S,R*)-**11a** was observed when K_2CO_3 in HMPA at 25°C or heating in the presence of triethylamine (Et_3N) in dimethyl sulfoxide (DMSO) was used. This result showed that the sulfonate derivative (**11**) was clearly less sensitive to racemization under weakly basic conditions than the bromide (**7**).

Next, the reaction conditions for *N*-alkylation of **12** with (*S,R*)-**11a** were optimized. The results are summarized in Table I. When the reaction was carried out in the presence of K_2CO_3 at room temperature, only the starting materials were recovered. Under heating, the reaction was accompanied with the decomposition of **11a**, resulting in a low yield of expected diester derivative (**13**). Interestingly, the employment of Et_3N instead of K_2CO_3 drastically changed the products. Thus, the reaction smoothly proceeded in the presence of 1.5 eq of Et_3N under heating at 80 °C for 24 h to afford the desired (*S,S,S*)-**13** exclusively in 85% yield (Run 4). The reaction of the mesylate derivative (**11b**) with **12** under the same reaction conditions also afforded (*S,S,S*)-**13**. Removal of the *tert*-butyl group of **13** by treatment with anhydrous hydrogen chloride gave the target compound (**1**).

Next, an alternative method for the preparation of **1** by using optically active tosylate was established in a similar manner (Chart 3). Namely, benzyl (2*R*)-2-(4-toluenesulfonyloxy)propionate (**14**) was submitted to the substitution reaction with **12** in the presence of Et_3N in DMSO to afford

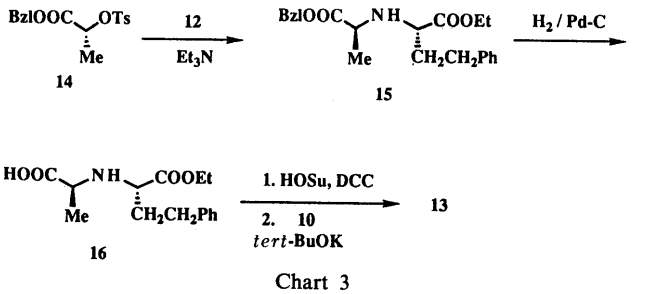

Chart 3

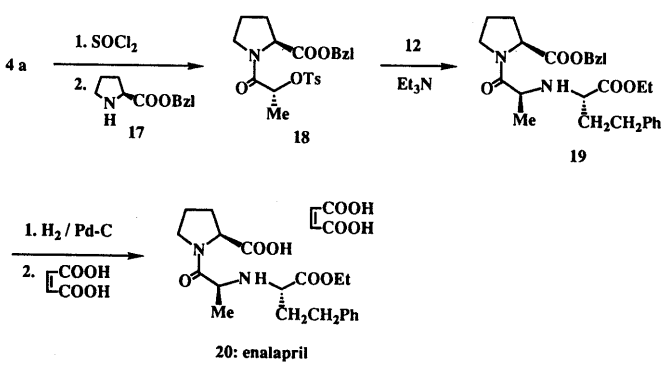

Chart 4

a single diastereoisomer, (*S,S*)-**15**, in 75% yield. Compound **15** was converted to (*S,S,S*)-**13** according to the procedure reported by us.[1)]

Furthermore, this method was extended to the synthesis of enalapril (**20**)[3c)] (Chart 4). The tosylate derivative (**18**), which was obtained from L-proline benzyl ester (**17**), was coupled with **12** under the same reaction conditions, predominantly giving (*S,S,S*)-**19** in 76% yield. The removal of the benzyl group of **19** by hydrogenolysis afforded enalapril.

As described above, we have established practical methods to synthesize the 2-oxoimidazolidine derivative (**1**) having (*S,S,S*) configuration diastereoselectively. Moreover, we have demonstrated that these methods can also be applied to the synthesis of other ACE inhibitors.

Experimental

Melting points (mp) are uncorrected. Infrared (IR) spectra were obtained on a Shimadzu IR-420 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-40 or a Bruker AC-200 instrument, using tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a Hitachi M-60 mass spectrometer. Specific rotations were measured with a Perkin-Elmer 243 polarimeter. HPLC was done on a Shimadzu LC-6A instrument equipped with an ultraviolet detector (SPD-6A, Shimadzu) and a computing integrator (CR-4A, Shimadzu). For silica gel column chromatography, Kieselgel 60 (0.063—0.20 mm, E. Merk) was employed.

HPLC Analysis of the Reaction Mixture of (*S,R*)-7 A mixture of (*S,R*)-**7** (335 mg, 1 mmol), **12** (207 mg, 1 mmol) and K_2CO_3 (138 mg, 1 mmol) in HMPA (1 ml) was stirred at 25 °C. At appropriate time intervals, a portion of the reaction mixture was taken and added to a mixture of Et_2O and H_2O, and the organic layer was analyzed by HPLC. Column, Nucleosil $5C_{18}$ 4.6 × 150 mm (Chemco); eluent, 0.05 N KH_2PO_4–CH_3CN (30 : 70); flow rate, 0.34 ml/min; column temperature, 40 °C; detection, 220 nm.

HPLC Analysis of 11a in a Base-Solvent System A mixture of (*S,R*)-**11** (86 mg, 0.2 mmol) and K_2CO_3 (28 mg, 0.2 mmol) in HMPA (0.2 ml), or (*S,R*)-**11** (200 mg, 0.46 mmol) and Et_3N (94 mg, 0.93 mmol) in DMSO (0.2 ml) was stirred at 25 or 70 °C for 24 h. The reaction mixture was partitioned with Et_2O and H_2O, and the organic layer was analyzed by HPLC. Column, Nucleosil $5C_{18}$ 4.6 × 150 mm (Chemco); eluent, 65% CH_3CN; flow rate, 0.56 ml/min; column temperature, 40 °C; detection, 220 nm.

(2*R*)-2-(4-Toluenesulfonyloxy)propionic Acid (4a) *p*-Toluenesulfonyl chloride (28.7 g, 0.15 mol) was added portionwise to a mixture of **9** (15.6 g, 0.15 mol) and Et_3N (15.2 g, 0.15 mol) in CH_2Cl_2 (100 ml) at 0—5 °C. After being stirred at room temperature overnight, the reaction mixture was washed successively with cold water, 10% HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with hexane–AcOEt (2 : 1) to give methyl (2*R*)-2-(4-toluenesulfonyloxy)propionate (25.5 g, 66%) as a colorless oil. A solution of the above product (12.9 g, 0.05 mol) in 10% NaOH (40 ml) was stirred at 5—10 °C for 15 min and then at room temperature for 45 min. The reaction mixture was washed with CH_2Cl_2, acidified with 1 N HCl, and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was triturated with hexane to give crude crystals (11.3 g, 93%). Recrystallization from hexane–Et_2O gave pure **4a** as colorless needles. mp 106—108 °C. $[\alpha]_D^{25}$ +47.7° (*c* = 5.1, $CHCl_3$). IR (Nujol): 1730, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (3H, d, *J* = 7 Hz), 2.45 (3H, s), 4.97 (1H, q, *J* = 7 Hz), 7.35 (2H, d, *J* = 9 Hz), 7.81 (2H, d, *J* = 9 Hz), 9.62 (1H, s). MS *m/z*: 244 (M^+). *Anal.* Calcd for $C_{10}H_{12}O_5S$: C, 49.17; H, 4.95; S, 13.13. Found: C, 49.12; H, 4.77; S, 13.27.

(2*R*)-2-Methanesulfonyloxypropionic Acid (4b) By the same procedure as described for the preparation of **4a**, **4b** was obtained in 63% yield as colorless needles. mp 71—74 °C. $[\alpha]_D^{25}$ +58.9° (*c* = 2, $CHCl_3$). IR (Nujol): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, d, *J* = 7 Hz), 3.13 (3H, s), 5.16 (1H, q, *J* = 7 Hz), 9.72 (1H, s). MS *m/z*: 123 ($M^+ - CO_2H$). *Anal.* Calcd for $C_4H_8O_5S$: C, 28.57; H, 4.79; S, 19.06. Found: C, 28.60; H, 4.63; S, 19.34.

***tert*-Butyl (4*S*)-1-Methyl-3-[(2*R*)-2-(4-toluenesulfonyloxy)propionyl]-2-oxoimidazolidine-4-carboxylate (11a)** Thionyl chloride (1.12 g, 9.4 mmol) was added to a solution of **4a** (1.15 g, 4.7 mmol) in $CHCl_3$ (5 ml), and the mixture was heated under reflux for 3 h, 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 as a syrup. Potassium *tert*-butoxide (607 mg, 5.4 mmol) was added to a solution of **10** (1.08 g, 5.4 mmol) in THF (12 ml) at −50 °C. The mixture was stirred at the same temperature for 20 min, then a solution of the above acid chloride in THF (2 ml) was added. Stirring was continued at −30 °C for 20 min, and a mixed solution 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 with $CHCl_3$–AcOEt (2 : 1) and the product was crystallized from hexane to give **11a** (1.48 g, 74%) as colorless needles. mp 78—80 °C. $[\alpha]_D^{25}$ −3.0° (*c* = 1, $CHCl_3$). 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). *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.

***tert*-Butyl (4*S*)-1-Methyl-3-[(2*R*)-2-methanesulfonyloxypropionyl]-2-oxoimidazolidine-4-carboxylate (11b)** By the same procedure as described for the preparation of **11a**, **4b** (2.50 g, 14.9 mmol) was converted to **11b** (3.95 g, 76%) as colorless needles. mp 97—100 °C. $[\alpha]_D^{25}$ −3.2° (*c* = 2, $CHCl_3$). IR (Nujol): 1740, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.61 (3H, d, *J* = 7 Hz), 2.89 (3H, s), 3.02 (3H, s), 3.35 (1H, dd, *J* = 4, 10 Hz), 3.73 (1H, t, *J* = 10 Hz), 4.58 (1H, dd, *J* = 4, 10 Hz), 6.35 (1H, q, *J* = 7 Hz). *Anal.* Calcd for $C_{13}H_{22}N_2O_7S$: C, 44.56; H, 6.33; N, 8.00; S, 9.15. Found: C, 44.55; H, 6.31; N, 7.91; S, 8.82.

***tert*-Butyl (4*S*)-3-[(2*S*)-2-[*N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate (13)** A mixture of **11a** (1.00 g, 2.3 mmol), **12** (0.73 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 24 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 with $CHCl_3$–AcOEt (2 : 1) to give **13** (0.92 g, 85%) as a syrup. The product and maleic acid (0.23 g, 2.0 mmol) were dissolved in AcOEt (2 ml) by heating on a water bath. Diisopropyl ether (iso-Pr_2O) (2 ml) was added to the above solution and the mixture was allowed to stand at room temperature for 3 h. The resulting crystals were collected by filtration and washed with AcOEt–iso-Pr_2O (1 : 1) to afford **13** hydrogen maleate as colorless needles (1.09 g, 95%). mp 122—124 °C. $[\alpha]_D^{25}$ −58.2° (*c* = 1, EtOH). IR (Nujol): 3600, 3500, 1740, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, *J* = 7 Hz), 1.47 (9H, s), 1.55 (3H, d, *J* = 6.5 Hz), 2.10—2.45 (2H, m), 2.70—2.93 (2H, m), 2.90 (3H, s), 3.36 (1H, dd, *J* = 4, 9.5 Hz), 3.67—3.95 (2H, m), 4.28 (2H, q, *J* = 7 Hz), 4.68 (1H, dd, *J* = 4, 9.5 Hz), 5.25 (1H, q, *J* = 6.5 Hz), 6.30 (2H, s), 7.15—7.40 (5H, m), 9.12 (3H, br). MS *m/z*: 461 (M^+).

By the same procedure as described above, **11b** (1.0 g, 2.9 mmol) was coupled with **12** (1.04 g, 4.3 mmol) to afford **13** (1.14 g, 86%).

(4*S*)-3-[(2*S*)-2-[*N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic Acid Hydrochloride (1) The diester **13** as the hydrogen maleate (28.9 g, 50 mmol) was suspended in H_2O, basified with K_2CO_3 and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness under reduced pressure. The residue was dissolved in 15% HCl–dioxane solution (140 ml), and the mixture was stirred at room temperature overnight. The crystalline precipitates were collected by filtration and washed with iso-Pr_2O to afford **1** (19.2 g, 90%) as colorless needles. mp 214—216 °C (dec.). $[\alpha]_D^{20}$ −64.1° (*c* = 0.5, EtOH). IR (Nujol): 1735, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3H, t, *J* = 7 Hz), 1.57 (3H, d, *J* = 6.5 Hz), 2.04—2.35 (2H, m), 2.45—2.80 (2H, m), 2.81 (3H, s), 3.45 (1H, dd, *J* = 4, 9.5 Hz), 3.83 (1H, t, *J* = 9.5 Hz), 4.02 (1H, t, *J* = 6.5 Hz), 4.24 (2H, q, *J* = 7 Hz), 4.82 (1H, dd, *J* = 4, 9.5 Hz), 5.23 (1H, q, *J* = 6.5 Hz), 7.20—7.40 (5H, m). MS *m/z*: 405 (M^+).

Benzyl (2*S*)-2-[*N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-propionate (15) A mixture of **14** (1.00 g, 3.0 mmol), **12** (0.62 g, 3.0 mmol), and Et_3N (0.45 g, 4.5 mmol), in DMSO (1 ml) was heated under stirring at 65 °C for 24 h. After cooling, the reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with toluene–AcOEt (10 : 1) to give **15** (0.83 g, 75%) as a colorless oil. IR (film): 3300, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, *J* = 7 Hz), 1.33 (3H, d, *J* = 6.5 Hz), 1.72—2.10 (2H, m), 1.83 (1H, s), 2.68 (2H, t, *J* = 7 Hz), 3.33 (1H, t, *J* = 6.5 Hz), 3.44 (1H,

q, J=6.5 Hz), 4.15 (2H, q, J=7 Hz), 5.12 (2H, s), 7.10—7.40 (10H, m). Compound **15** hydrogen maleate was obtained as colorless needles by treatment with maleic acid in AcOEt–iso-Pr_2O. mp 133—134 °C. $[\alpha]_D^{24}$ +1.1° (c=1, MeOH).

***N*-[(2*R*)-2-(4-Toluenesulfonyloxy)propionyl]-L-proline Benzylester (18)** Thionyl chloride (11.91 g, 0.1 mol) was added to a solution of **4a** (4.89 g, 20 mmol) in $CHCl_3$ (20 ml), and the mixture was heated under reflux for 1 h, then concentrated *in vacuo*. The residue was taken up in $CHCl_3$ and the solution was reconcentrated. The residue was dissolved in $CHCl_3$ (50 ml) and the solution obtained was added to a mixture of **17** (4.11 g, 20 mmol) and Et_3N (3.04 g, 30 mmol) in $CHCl_3$ (100 ml) at 0 °C. After being stirred at room temperature for 30 min, the mixture was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–AcOEt (4 : 1) to give **18** (7.08 g, 82%) as a colorless syrup. IR (film): 1750, 1670, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, d, J=7 Hz), 1.80—2.30 (2H, m), 2.43 (3H, s), 3.30—3.80 (2H, m), 4.35—4.50 (1H, m), 5.00—5.20 (3H, m), 7.20—7.45 (7H, m), 7.79 (2H, d, J=8 Hz).

***N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline Benzylester (19)** A mixture of **18** (2.16 g, 5 mmol), **12** (1.55 g, 7.5 mmol), and Et_3N (1.01 g, 10 mmol) in DMSO (2 ml) was heated under stirring at 75 °C for 8 h. After cooling, the reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–AcOEt (2 : 1) to give **19** (1.78 g, 76%) as a colorless syrup. IR (film): 1740, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.35 (6H, m), 1.80—2.30 (6H, m), 2.55—2.80 (2H, m), 3.24 (1H, t, J=6.5 Hz), 3.40—3.65 (3H, m), 4.17 (2H, q, J=7 Hz), 4.50—4.65 (1H, m), 5.09 (1H, d, J=12 Hz), 5.20 (1H, d, J=12 Hz), 7.10—7.30 (5H, m), 7.34 (5H, s).

***N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-ploline Hydrogen Maleate (20)** Compound **19** (1.15 g, 2.5 mmol) dissolved in EtOH (20 ml) was subjected to hydrogenolysis in the presence of 10% palladium on carbon (0.2 g) at room temperature under atmospheric pressure for 2 h. After removal of the catalyst, the filtrate was concentrated *in vacuo*. The residue and maleic acid (0.29 g, 2.5 mmol) were dissolved in AcOEt (5 ml) by heating. The mixture was allowed to stand at room temperature for 3 h. The resulting crystals were collected by filtration, washed with AcOEt, and recrystallized from acetonitrile to give **20** (1.10 g, 91%) as colorless needles. mp 148—150 °C. $[\alpha]_D^{25}$ −42.2° (c=1, MeOH). IR (Nujol): 1750, 1730, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, J=7 Hz), 1.34 (3H, d, J=7 Hz), 1.80—2.35 (6H, m), 2.45—2.85 (2H, m), 3.30—4.35 (7H, m), 7.15—7.40 (5H, m). *Anal.* Calcd for $C_{24}H_{32}N_2O_9$: C, 58.53; H, 6.55; N, 5.69. Found: C, 58.25; H, 6.42; N, 5.59.

References and Notes

1) Part IV: K. Hayashi, K. Nunami, J. Kato, N. Yoneda, M. Kubo, T. Ochiai, and R. Ishida, *J. Med. Chem.*, **32**, 289 (1989).
2) A part of this work was presented at the Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, Osaka, Nov. 1989.
3) *a*) M. A. Ondetti, B. Rubin, and D. W. Cushman, *Science*, **196**, 441 (1977); *b*) D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, *Biochemistry*, **16**, 5484 (1977); *c*) 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); *d*) E. W. Petrillo and M. A. Ondetti, *Med. Res. Rev.*, **2**, 1 (1982); *e*) M. J. Wyvratt and A. A. Patchett, *ibid.*, **5**, 483 (1985); *f*) J. B. Kostis and E. A. DeFelke (eds.), "Angiotensin Converting Enzyme Inhibitors," Alan R. Liss, Inc., New York, 1987; *g*) H. Gavras, *Circulation*, **81**, 381 (1990).
4) In this paper, the absolute configurations of asymmetric carbons in compounds are represented in parentheses in accordance with the order in the nomenclature: (4*S*)-3-[(2*S*)-2-[*N*-[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid hydrochloride and its (4*S*),(2*R*),(1*S*)-diastereoisomer are (*S*,*S*,*S*)-**1** and (*S*,*R*,*S*)-**1**, respectively.
5) Recommended International Nonproprietary Name (r-INN).
6) T. Shiba, A. Koda, S. Kusumoto, and T. Kaneko, *Bull. Chem. Soc. Jpn.*, **41**, 2748 (1968).
7) M. Senuma, K. Nakamichi, K. Nabe, S. Nishimoto, and T. Tosa, *Appl. Biochem. Biotechnol.*, **22**, 141 (1989).
8) G. Iwasaki, R. Kimura, N. Numao, and K. Kondo, *Chem. Pharm. Bull.*, **37**, 280 (1989).
9) F. Effenberger, U. Burkard, and J. Willfahrt, *Angew. Chem., Int. Ed. Engl.*, **22**, 65 (1983).
10) Daicel Chemical Industries Ltd., Japan Kokai Tokkyo Koho, Japan. Patent 61-210049 [*Chem. Abstr.*, **106**, 66922*r* (1987)].