Studies on Angiotensin Converting Enzyme Inhibitors. 4. Synthesis and Angiotensin Converting Enzyme Inhibitory Activities of 3-Acyl-1-alkyl-2-oxoimidazolidine-4-carboxylic Acid Derivatives[1]

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(4*S*)-1-Alkyl-3-[[*N*-(carboxyalkyl)amino]acyl]-2-oxoimidazolidine-4-carboxylic acid derivatives (**3**) were prepared by two methods. Their angiotensin converting enzyme (ACE) inhibitory activities and antihypertensive effects were evaluated, and the structure–activity relationships were discussed. The dicarboxylic acids **3a–n** possessing *S,S,S* configuration showed potent in vitro ACE inhibitory activities with IC_{50} values of 1.1×10^{-8}–1.5×10^{-9} M. The most potent compound in this series, monoester **3p**, had an ID_{50} value of 0.24 mg/kg, po for inhibition of angiotensin I induced pressor response in normotensive rats and produced a dose-dependent decrease in systolic blood pressure of spontaneously hypertensive rats (SHRs) at doses of 1–10 mg/kg, po.

In the last decade, angiotensin converting enzyme (ACE) inhibitors[2] have received much attention as a new type of antihypertensive drugs, and their clinical efficacy has been well established.[3]

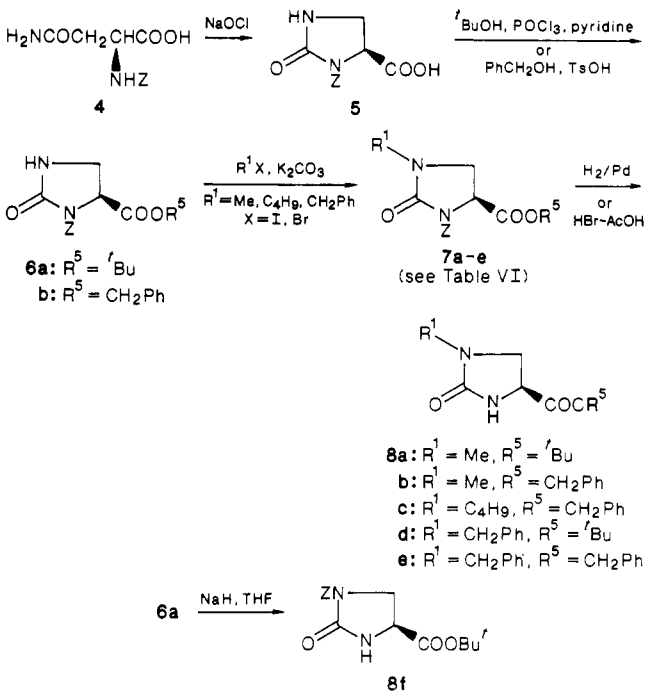
During our synthetic studies on ACE inhibitors, we observed that *N*-[(carboxyethyl)carbamoyl]tetrahydroisoquinoline derivatives **1** showed potent ACE inhibitory activities and the ureido carbonyl group played a favorable role as a hydrogen-bond acceptor which would interact with the enzyme.[4]

From the above information, we expected that a cyclic imino acid moiety incorporating a ureido group in the ring would be effective as the C-terminal of ACE inhibitors, and therefore, we aimed at introduction of a 2-oxoimidazolidine-4-carboxylic acid moiety.

In order to examine the effectiveness of this imino acid moiety, the in vitro ACE inhibitory activities of (4*S*)-1-substituted-3-L-alanyl-2-oxoimidazolidine-4-carboxylic acids (**2a** and **2b**) were evaluated in comparison with L-alanyl-L-proline and L-valyl-L-tryptophan,[5] which are known to be potent simple dipeptide inhibitors without strong ligands to zinc ion such as the mercapto group. As shown in Figure 1, compounds **2a** and **2b** indicated potencies almost comparable to that of L-valyl-L-tryptophan. These results prompted us to attempt the modification of **2** with the expectation of more potent inhibitory activities.

In this paper, we describe the syntheses and pharmacological activities of a series of 1-alkyl-3-[[*N*-(carboxyalkyl)amino]acyl]-2-oxoimidazolidine-4-carboxylic acid derivatives (**3**).

Scheme I[a]



[a] Z = $COOCH_2Ph$.

Chemistry

The target 2-oxoimidazolidine derivatives **3** were synthesized according to the routes shown in Schemes I–IV.

First, (4*S*)-3-(benzyloxycarbonyl)-2-oxoimidazolidine-4-carboxylic acid (**5**) was prepared by Hoffman rearrangement of *N*-(benzyloxycarbonyl)-L-asparagine (**4**) according to the literature procedure.[6] After acid **5** was esterified, N-alkylation with alkyl halide was carried out in the presence of potassium carbonate (K_2CO_3) to afford (4*S*)-1-substituted-3-(benzyloxycarbonyl)-2-oxoimidazolidine-4-carboxylates (**7**). Removal of the benzyloxycarbonyl group of **7** by hydrogenolysis or acidolysis with hydrogen bromide in acetic acid gave (4*S*)-1-substituted-2-oxoimidazolidine-4-carboxylic acid *tert*-butyl or benzyl esters (**8**), respectively. *tert*-Butyl (4*S*)-1-(benzyloxycarbonyl)-2-oxoimidazolidine-4-carboxylate (**8f**) was obtained via migration of the benzyloxycarbonyl group of *tert*-butyl (4*S*)-3-(benzyloxycarbonyl)-2-oxoimidazolidine-4-carboxylate (**6a**) by use of sodium hydride

(1) A part of this work was presented at Japan Symposium on Peptide Chemistry, Kobe, September 28–October 2, 1987.
(2) (a) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *196*, 441. (b) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, *16* 5484. (c) Mita, I.; Iwao, J.; Oya, M.; Chiba, T.; Iso, *J. Chem. Pharm. Bull.* **1978**, *26*, 1333. (d) Patchett, A. A.; et al. *Nature (London)* **1980**, *288*, 280. (e) Kaplan, H. R.; et al. *Pharmacologist* **1982**, *24*(3), 176. (f) Teetz, V.; Geiger, R.; Henning, R.; et al. *Arzneim-Forsch Drug Res.* **1984**, *34*, 1399. (g) Attwood, M. R.; et al. *FEBS Lett.* **1984**, *165*, 201. (h) Stanton, J. L.; et al. *J. Med. Chem.* **1985**, *28*, 1603. (i) Johnson, A. L.; et al. *J. Med. Chem.* **1985**, *28*, 1596.
(3) (a) Gavras, H.; Brunner, H. R.; Turini, G. A.; et al. *New Engl. J. Med.* **1978**, *298*, 991. (b) Gavras, H.; Biollaz, J.; Waeber, B.; et al. *Lancet.* **1981**, *2*, 543. (c) Jenkins, A. C.; Dreslinski, G. R.; Tadross, S. S. *J. Cardiovasc. Pharmacol.* **1985**, *7*, S96.
(4) (a) Hayashi, K.; Nunami, K.; Sakai, K.; Ozaki, Y.; Kato, J.; Kinashi, K.; Yoneda, N. *Chem. Pharm. Bull.* **1983**, *31*, 3553. (b) Hayashi, K.; Nunami, K.; Sakai, K.; Ozaki, Y.; Kato, J.; Kinashi, K.; Yoneda, N. *Chem. Pharm. Bull.* **1985**, *33*, 2011.
(5) Cheung, H. S.; Wang, F. L.; Ondetti, M. A.; Sabo, E. F.; Cushman, D. W. *J. Biol. Chem.* **1980**, *255*, 401.
(6) Shiba, T.; Koda, A.; Kusumoto, S.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2748.

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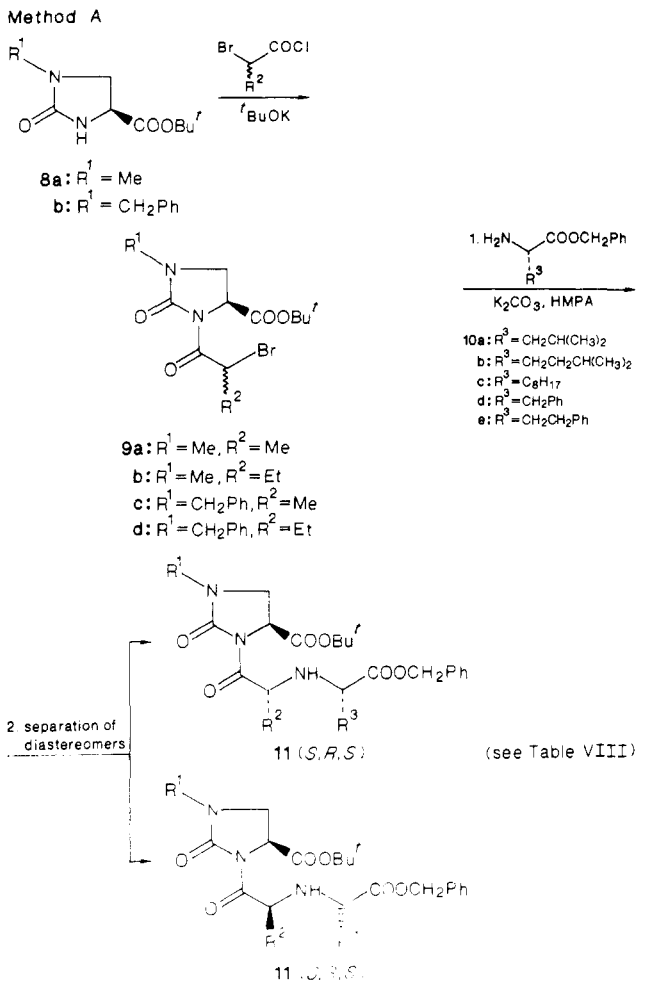
Scheme II

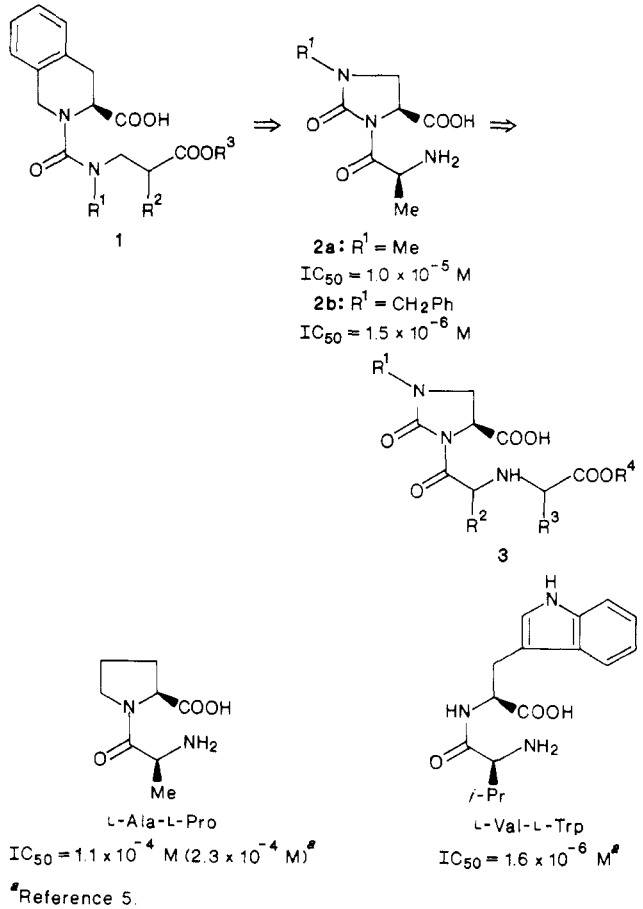


(NaH) according to a reported method.[7]

Diester compounds **11** were prepared from **8** as shown in Scheme II (method A). After compounds **8** were treated with potassium *tert*-butoxide (*t*-BuOK) in tetrahydrofuran (THF), condensation with α-bromoacyl chlorides afforded (4*S*)-1-substituted-3-(2-bromoacyl)-2-oxoimidazolidine-4-carboxylates (**9**) as a diastereomeric mixture. Since compounds **9** were easily racemized under conditions of subsequent reaction, separation of the diastereomers was not adequate at this stage.

Meanwhile, optically active (*S*)-α-amino acid benzyl esters **10** were prepared from the corresponding *N*-acetyl-DL-amino acids by an enzymatic method using aminoacylase obtained from *Aspergillus oryzae* followed by a usual esterification using benzyl alcohol and *p*-toluenesulfonic acid. Condensation of **9** and **10** in the presence of K_2CO_3 in hexamethylphosphoramide (HMPA) gave diesters **11** as a mixture of diastereomers (*S,R,S* and *S,S,S*); the diastereomeric ratio was approximately 3.6–15.3:1 in favor of the undesired *S,R,S* isomer. These diastereomers were separated by column chromatography using silica gel. The absolute configuration of the asymmetric carbon bearing the R^2 substituent in the side chain of these isomers was determined by comparison with the products prepared by the following method.

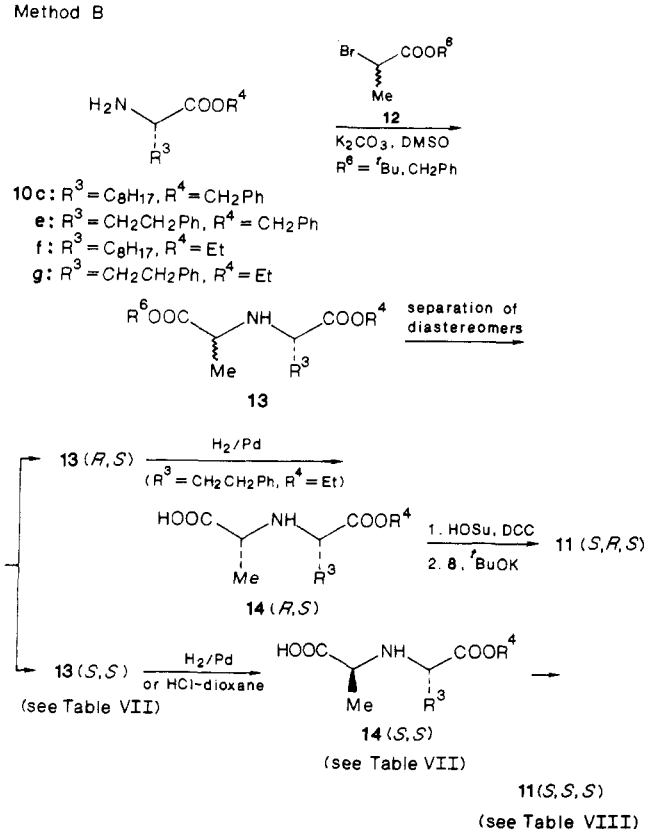
A method for the predominant formation of diester compounds possessing the desired configuration (*S,S,S*-**11**) was developed as method B shown in Scheme III. N-Alkylation of **10** with α-bromopropionate **12** in the presence



[a] Reference 5.

Figure 1.

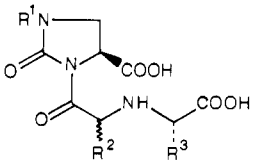
Scheme III



of K_2CO_3 in dimethyl sulfoxide (DMSO) gave *N*-[1-(alkoxycarbonyl)alkyl]amino acid esters **13** as a mixture of diastereomers (*S,S* and *R,S*) in good yields. The diaste-

(7) Saijo, S.; Wada, M.; Himizu, J.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *28*, 1459.

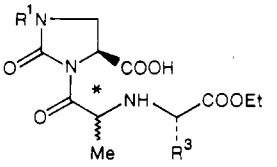
Table I. Physical Properties and in Vitro ACE Inhibitory Activities of Dicarboxylic Acid Derivatives **3a–n**



compd	R^1	R^2 (config)	R^3	mp, °C	$[\alpha]_D$, deg (*c*, solv,[a] °C)	formula[b]	IC_{50}, M
3a	H	Me (*S*)	CH_2CH_2Ph	213–214 dec	−92.4 (0.5, B, 24)	$C_{17}H_{21}N_3O_6$	3.5×10^{-9}
3b[c]	Me	Me (*R*)	C_8H_{17}	135–136	−6.6 (1, A, 25)	$C_{18}H_{31}N_3O_6$·HCl	2.4×10^{-6}
3c	Me	Me (*S*)	C_8H_{17}	204–205 dec	−84.7 (1, B, 19)	$C_{18}H_{31}N_3O_6$	1.6×10^{-9}
3d	Me	Et (*S*)	C_8H_{17}	105–110 dec	−85.4 (1, B, 19)	$C_{19}H_{33}N_3O_6$	2.4×10^{-9}
3e	Me	Me (*S*)	CH_2CH_2Ph	239–241 dec	−88.4 (1, B, 19)	$C_{18}H_{23}N_3O_6$	1.7×10^{-9}
3f	C_4H_9	Me (*S*)	CH_2CH_2Ph	192–195 dec	−74.7 (1, B, 24)	$C_{21}H_{29}N_3O_6$	6.7×10^{-9}
3g	CH_2Ph	Me (*S*)	$CH_2CH(CH_3)_2$	141–142 dec	−60.2 (0.5, C, 24)	$C_{20}H_{27}N_3O_6$	2.1×10^{-9}
3h	CH_2Ph	Me (*S*)	$CH_2CH_2CH(CH_3)_2$	208–209 dec		$C_{21}H_{29}N_3O_6$	3.3×10^{-9}
3i	CH_2Ph	Me (*S*)	C_8H_{17}	211–215 dec	−64.3 (1, B, 19)	$C_{24}H_{35}N_3O_6$	1.5×10^{-9}
3j	CH_2Ph	Et (*S*)	C_8H_{17}	183–185 dec		$C_{25}H_{37}N_3O_6$	2.1×10^{-9}
3k	CH_2Ph	Me (*S*)	CH_2Ph	184–185 dec	−50.4 (0.5, C, 26)	$C_{23}H_{25}N_3O_6$	1.1×10^{-8}
3l[c]	CH_2Ph	Me (*R*)	CH_2CH_2Ph	164–165 dec	+65.8 (1, A, 27)	$C_{24}H_{27}N_3O_6$·HCl	2.4×10^{-6}
3m	CH_2Ph	Me (*S*)	CH_2CH_2Ph	223–225 dec	−62.7 (1, B, 19)	$C_{24}H_{27}N_3O_6$	1.7×10^{-9}
3n	CH_2Ph	Et (*S*)	CH_2CH_2Ph	173–175 dec	−31.4 (1, A, 25)	$C_{22}H_{29}N_3O_6$	2.3×10^{-9}
enalaprilat[d]							2.9×10^{-9}

[a] Solvent: A, 1 N HCl–MeOH = 1:4; B, 5% $NaHCO_3$; C, MeOH. [b] All compounds exhibited satisfactory C, H, and N elemental analyses and exhibited IR and NMR spectra consistent with the structure. [c] Hydrochloride. [d] Literature 2d: $IC_{50} = 3.8 \times 10^{-9}$ M.

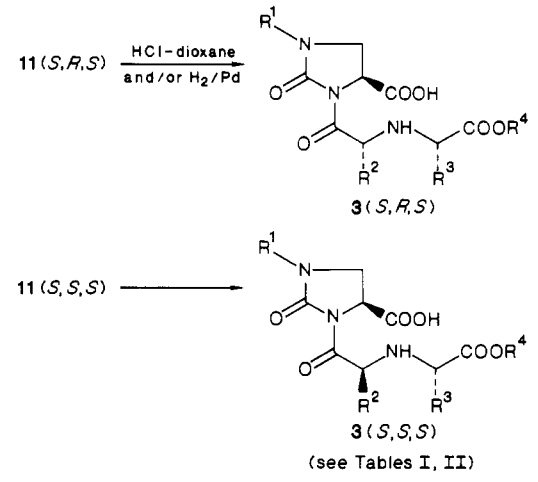
Table II. Physical Properties and in Vitro ACE Inhibitory Activities of Monoester Derivatives **3o–s**



compd	R^1	R^3	config (*)	mp, °C	$[\alpha]^{20}_D$, deg (*c* 0.5, EtOH)	formula[a]	IC_{50}, M
3o	Me	C_8H_{17}	*S*	85–86	−77.5	$C_{20}H_{35}N_3O_6$	5.1×10^{-6}
3p[b]	Me	CH_2CH_2Ph	*S*	214–216 dec	−64.1	$C_{20}H_{27}N_3O_6$·HCl	9.9×10^{-6}
3q[b]	Me	CH_2CH_2Ph	*R*	175–176 dec	+10.6	$C_{20}H_{27}N_3O_6$·HCl	
3r	CH_2Ph	C_8H_{17}	*S*	86–88	−59.7	$C_{26}H_{39}N_3O_6$	2.2×10^{-6}
3s	CH_2Ph	CH_2CH_2Ph	*S*	56–57	−53.4	$C_{26}H_{31}N_3O_6 \cdot {}^1/_4H_2O$	7.9×10^{-6}

[a] All compounds exhibited satisfactory C, H, and N elemental analyses and exhibited IR and NMR spectra consistent with the structure. [b] Hydrochloride.

Scheme IV



reomers of **13** were easily separated by column chromatography using silica gel or by crystallization of the maleic acid salt; the ratio of *R,S*:*S,S* was 1:1.24–1.75.

To determine the absolute configuration of the asymmetric carbon bearing the R^3 substituent of **13**, we achieved the alternative synthesis of **13** as follows. In the case of **13d** and **13e** ($R^3 = CH_2CH_2Ph$, $R^4 = Et$, $R^6 = CH_2Ph$), L-alanine benzyl ester was condensed with ethyl 2-bromo-4-phenylbutyrate in the same manner described above to afford the diastereomers with *S,R* and *S,S* configuration (**13f** and **13e**), which were separated by column chromatography using silica gel. The product obtained from the early fractions showed the same physical constants as those of **13d** except for optical rotation and that from the later fraction was identical with that of **13e**. In this way, the configurations of **13d**, **13e**, and **13f** were determined to be *R,S*, *S,S*, and *S,R*, respectively. The absolute configurations of the other compounds (**13a–c**) synthesized by method B were assigned on the basis of their chromatographic characteristics related to those observed in **13d** and **13e**. After removal of the ester residue (R^6) of **13**, N-substituted α-amino acids **14** were converted to *N*-succinimidyl esters by use of *N*-hydroxysuccinimide (HOSu) and dicyclohexylcarbodiimide (DCC) and subsequently condensed with the potassium salt of **8** to give diesters **11** in good yield. Physical constants of the *S,R,S* isomer (**11f**) and *S,S,S* isomer (**11g**) ($R^1 = Me$, $R^2 = Me$, $R^3 = CH_2CH_2Ph$, $R^4 = Et$) derived by this method were identical with those of the major isomer and the minor one in the method A, respectively. The stereochemical assignment of the other diesters (**11a,b**, **11d**, **11i,j**, **11m–p**,

Table III. Inhibitory Effects of Dicarboxylic Acids **3c**, **3e**, **3i**, and **3m** on Angiotensin I Induced Pressor Responses in Anesthetized Normotensive Rats[a]

compd	max % inhibn (dose: 10 μg/kg, iv; N^b = 5)
3c	53.4 ± 4.4
3e	62.4 ± 3.3
3i	41.0 ± 5.1
3m	39.0 ± 3.9
enalaplilat	54.5 ± 4.5

[a] See the Experimental Section. [b] Number of animals.

Table IV. Inhibitory Effects of Dicarboxylic Acids **3c** and **3e** and Monoesters **3o** and **3p** on Angiotensin I Induced Pressor Responses in Anesthetized Normotensive Rats[a]

compd	dose, mg/kg, po	N^b	max % inhibn
3c	1.0	5	18.4 ± 9.2
3o	1.0	5	56.2 ± 7.4
3e	0.2	4	−7.2 ± 2.0
	0.5	6	16.5 ± 13.3
	1.0	4	26.3 ± 8.4
3p	0.2	6	52.0 ± 7.2
	0.5	6	62.7 ± 2.6
	1.0	6	69.8 ± 2.2
enalapril	0.2	6	42.9 ± 5.4
	0.5	7	50.5 ± 6.3
	1.0	6	69.8 ± 4.6
vehicle[c]		7	−27.8 ± 9.5

[a] See the Experimental Section. [b] Number of animals. [c] Pure water.

and **11r**) synthesized by method A was made by analogy with the chromatographic characteristics of **11f** and **11g**.

The ester residues (R^5) of **11** were removed by treatment of anhydrous hydrogen chloride in dioxane and/or then hydrogenolysis to afford the final dicarboxylic acids and monoesters **3**. The physical constants of these compounds are listed in Tables I and II.

Biological Results and Discussion

The in vitro ACE inhibitory activities of dicarboxylic acids **3a–n** were determined with use of ACE obtained from pig renal cortex and hippurylhistidylleucine as a substrate. The results are shown in Table I. All of the compounds having the R^2 substituent with *S* configuration showed potent inhibitory activities with IC_{50} values of 1.1×10^{-8}–1.5×10^{-9} M. These values with the exception of **3f** and **3k** were comparable or superior to that of enalaprilat as the reference. The results suggest that the coplanarity between the 2-oxoimidazolidine ring and the amide carbonyl in the side chain could be held in a geometry suitable for effective binding with the active site of ACE and that the ureido carbonyl in the ring could provide an additional binding site to the enzyme through hydrogen bonding. In order to enhance the inhibitory activity, we chose substituents R^3 possessing a suitable hydrophobicity on the basis of the finding in the studies on *N*-[(carboxyethyl)carbamoyl]tetrahydroisoquinoline series 1. As a result, all of the substituents (R^3) were effective. Introduction of the R^1 substituent at the nitrogen of 2-oxoimidazolidine ring did not markedly affect the activity, but that of the methyl or benzyl group was more favorable.

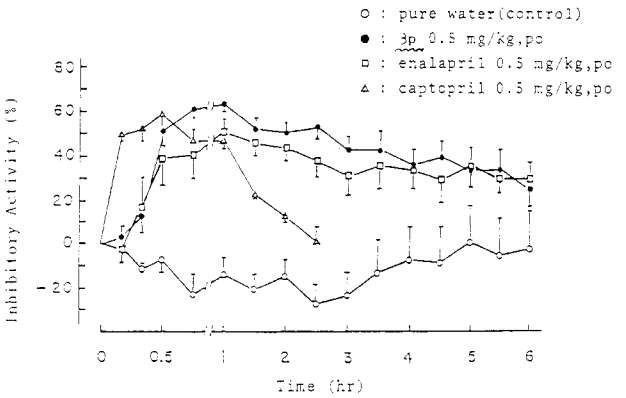


Figure 2. Time courses of inhibitory effects of **3p**, enalapril, and captopril on angiotensin I induced pressor responses in anesthetized rats (N = 6–7).

Dicarboxylic acids **3c**, **3e**, **3i**, and **3m** were selected as more active compounds in the in vitro screening, and their ACE inhibitory activities by intravenous administration were evaluated in anesthetized rats. As summarized in Table III, all the compounds markedly inhibited angiotensin I (300 ng/kg, iv) induced pressor response at a dose of 10 μg/kg intravenously. Furthermore, the relative inhibitory potencies of these compounds were found to be in the order **3e** > **3c** = enalaprilat > **3i** = **3m**.

In addition, ACE inhibitory activities of **3c** and **3e** were compared with those of monoesters **3o** and **3p** as prodrugs by oral administration. Monoesters **3o** and **3p** inhibited more markedly angiotensin I induced pressor response than **3c** and **3e**, respectively, as shown in Table IV. Among these four compounds, compound **3p** was the most active and dose-dependently inhibited angiotensin I induced pressor response at doses of 0.1–1.0 mg/kg, po. The inhibitory ID_{50} value was 0.24 mg/kg, po, whereas that of enalapril was 0.30 mg/kg.

Time courses of the inhibitory effects of **3p**, enalapril, and captopril after oral administration of 0.5 mg/kg are shown in Figure 2. The inhibitory effects of **3p** and enalapril reached the maximum about 1 h after administration and lasted for not less than 6 h, whereas that of captopril reached the maximum after about 30 min and disappeared 2 h after dosing.

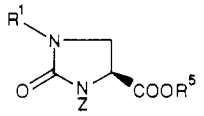
The antihypertensive effect of compound **3p** was also evaluated in spontaneously hypertensive rats (SHRs) in

Table V. Antihypertensive Effects of **3p** and Enalapril in SHRs[a]

			systolic blood pressure (mmHg)				
compd	dose, mg/kg, po	N^b	initial (mean ± SE)	max effect (mean ± SE)	time,[c] h	change ± SE	duration,[d] h
3p	1	6	190.0 ± 3.4	172.5 ± 5.0#	3	−17.5 ± 7.2	
	2	6	190.8 ± 2.7	165.8 ± 2.7###**	3	−25.0 ± 3.7	
	5	7	191.4 ± 1.8	164.3 ± 2.5###***	6	−27.1 ± 2.1	>9
	10	6	192.5 ± 2.1	154.2 ± 4.2###***	6	−38.3 ± 5.4	>9
enalapril	1	6	190.8 ± 3.3	178.3 ± 2.1##	3	−12.5 ± 2.8	
	2	7	192.9 ± 3.9	168.6 ± 3.0###**	3	−24.3 ± 3.0	
	5	6	190.0 ± 3.4	166.7 ± 3.1###**	3	−23.3 ± 3.3	>9
	10	8	193.3 ± 2.1	165.0 ± 5.2###**	6	−28.3 ± 5.0	>9
vehicle	4 mL/kg	7	191.4 ± 2.8	185.0 ± 3.8		−6.4 ± 2.8	

[a] See the Experimental Section. [b] Number of animals. [c] The time of the maximal fall in blood pressure. [d] The duration time of hypotensive effect showing statistically significant difference from initial value. #: statistically significant difference from initial value, $p < 0.05$; ##, $p < 0.01$; ###, $p < 0.001$. **: statistically significant difference from vehicle, $p < 0.01$; ***, $p < 0.001$.

Table VI. Yields and Physical Data of 7



compd[a]	R^1	R^5	yield, %	mp, °C	$[\alpha]^{23}_D$, deg (c 1, MeOH)	IR (Nujol), cm^{-1}	^1H NMR ($CDCl_3$) δ
7a	Me	*t*-Bu	89.8	102–103	−67.2	1790, 1775, 1735	1.43 (9 H, s), 2.87 (3 H, s), 3.32 (1 H, dd, *J* = 9.5, 4 Hz), 3.66 (1 H, t, *J* = 9.5 Hz), 4.57 (1 H, dd, *J* = 9.5, 4 Hz), 5.3 (2 H, s), 7.3–7.5 (5 H, m)
7b	Me	CH_2Ph	65.7	120–122	−45.8	1785, 1740	2.83 (3 H, s), 3.28 (1 H, dd, *J* = 9.5, 4 Hz), 3.63 (1 H, t, *J* = 9.5 Hz), 4.7 (1 H, dd, *J* = 9.5, 4 Hz), 5.17 (2 H, s), 5.23 (2 H, s), 7.2–7.5 (10 H, m)
7c	C_4H_9	CH_2Ph	30.1	syrup		1785, 1740	0.8–1.0 (3 H, m), 1.1–1.6 (4 H, 7), 3.1–3.9 (4 H, m), 4.73 (1 H, dd, *J* = 9.5, 4 Hz), 5.17 (2 H, s), 5.26 (2 H, s), 7.2–7.5 (10 H, m)
7d	CH_2Ph	*t*-Bu	75.6	103–105	−14.2	1790, 1740, 1715	1.48 (9 H, s), 3.16 (1 H, dd, *J* = 9.5, 4 Hz), 3.54 (1 H, t, *J* = 9.5 Hz), 4.28, 4.55 (2 H, AB q, *J* = 15 Hz), 4.5 (1 H, dd, *J* = 9.58 4 Hz), 5.28 (2 H, s), 7.2–7.5 (10 H, m)
7e	CH_2Ph	CH_2Ph	90.4	102–103	−28.6	1780, 1760	3.13 (1 H, dd, *J* = 9.5, 4 Hz), 3.5 (1 H, t, *J* = 9.5 Hz), 4.4 (2 H, s), 4.65 (1 H, dd, *J* = 9.5, 4 Hz), 5.07 (2 H, s), 5.2 (2 H, s), 7.2–7.5 (15 H, m)

[a] All compounds exhibited satisfactory C, H, and N elemental analyses.

comparison with that of enalapril. As shown in Table V, both compounds significantly and dose-dependently decreased the systolic blood pressure at 1 mg/kg or more orally. Compound **3p** was almost as potent as enalapril in the dose ratio.

As described above, compound **3p** was found to be a potential agent for treatment of hypertension. More detailed pharmacological and clinical studies will be reported elsewhere.

Experimental Section

Melting points are uncorrected. Infrared (IR) spectra were obtained on a Shimazu IR-27G spectrophotometer. Nuclear magnetic resonance (^1H NMR) spectra were recorded on a Hitachi R-20A 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. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60F-254 plates.

***tert*-Butyl (4*S*)-3-(Benzyloxycarbonyl)-2-oxoimidazolidine-4-carboxylate (6a).** Phosphorus oxychloride (82 g, 0.535 mol) was added dropwise to a solution of **5**[6] (118 g, 0.447 mol) in pyridine (220 mL), *tert*-butyl alcohol (340 mL), and $CHCl_3$ (590 mL) with stirring at −10 °C. After being stirred at −5 to 0 °C for 30 min and then at room temperature for 4 h, the mixture was washed successively with water, cold 1% HCl, saturated aqueous $NaHCO_3$, and water. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crystalline residue was recrystallized from AcOEt to give **6a** (127.5 g, 89.2%) as colorless needles: mp 145–147 °C; $[\alpha]^{23}_D$ −78.6° (*c* 1, MeOH); IR (Nujol) 3270, 1790, 1760, 1740, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (9 H, s), 3.35 (1 H, dd, *J* = 9.5, 4 Hz), 3.68 (1 H, t, *J* = 9 Hz), 4.64 (1 H, dd, *J* = 9.5, 4 Hz), 5.26 (2 H, s), 6.90 (1 H, br s), 7.30–7.45 (5 H, m). Anal. ($C_{16}H_{20}N_2O_5$) C, H, N.

Benzyl (4*S*)-3-(Benzyloxycarbonyl)-2-oxoimidazolidine-4-carboxylate (6b). A mixture of **5** (40 g, 0.15 mol), benzyl alcohol (40 g, 0.37 mol), *p*-toluenesulfonic acid monohydrate (6 g, 0.03 mol), and benzene (400 mL) was heated under reflux for 16 h with a Dean–Stark trap. The benzene solution was washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. The residue was crystallized from hexane to give **6b** (45.7 g, 85.2%) as colorless needles: mp 109–110 °C; $[\alpha]^{24}_D$ −59.5° (*c* 1, MeOH); IR (Nujol) 3300, 1780, 1750, 1700, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.32 (1 H, dd, *J* = 9.5, 4 Hz), 3.68 (1 H, t, *J* = 9.5 Hz), 4.63 (1 H, dd, *J* = 9.5, 4 Hz), 5.10 (2 H, s), 5.14 (2 H, s), 6.85–7.0 (1 H, m), 7.20–7.40 (10 H, m). Anal. ($C_{19}H_{18}N_2O_5$) C, H, N.

Typical Procedure for the Preparation of (4*S*)-1-Substituted-3-(benzyloxycarbonyl)-2-oxoimidazolidine-4-carboxylic Acid Esters (7a–e). *tert*-Butyl (4*S*)-3-(Benzyloxycarbonyl)-1-methyl-2-oxoimidazolidine-4-carboxylate (7a). A mixture of **6a** (9.6 g, 30 mmol), K_2CO_3 (8.3 g), and methyl iodide (14.2 g, 100 mmol) in Me_2CO (150 mL) was stirred at room temperature for 3 days. The insoluble materials were filtered off, and the filtrate was concentrated in vacuo. The residue was dissolved in AcOEt and the solution was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was crystallized from *n*-hexane to give **7a** (9.0 g, 89.8%) as colorless needles.

Other compunds **7b–e** were prepared by a similar method. The results are summarized in Table VI.

***tert*-Butyl (4*S*)-1-Methyl-2-oxoimidazolidine-4-carboxylate (8a).** A mixture of **7a** (8.5 g, 25.4 mmol) in MeOH (200 mL) was hydrogenolyzed in the presence of palladium black (0.1 g) under atmospheric pressure at room temperature for 3 h. After the catalyst was filtered off, the filtrate was concentrated to dryness in vacuo. The crystalline residue was triturated with hexane to afford **8a** (5.0 g, 98.2%) as colorless leaflets: mp 135–136 °C; $[\alpha]^{23}_D$ +24.9° (*c* 1, MeOH); IR (Nujol) 3300, 1735, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (9 H, s), 2.78 (3 H, s), 3.50–3.78 (2 H, m), 4.12 (1 H, t, *J* = 8 Hz), 5.48 (1 H, br s). Anal. ($C_9H_{16}N_2O_3$) C, H, N.

Compound **8d** was obtained similarly in 94.3% yield: mp 105–108 °C; $[\alpha]^{23}_D$ +41.4° (*c* 1, MeOH); IR (Nujol) 3250, 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (9 H, s), 3.32–3.65 (2 H, m), 3.98–4.20 (1 H, m), 4.36 (2 H, s), 5.80 (1 H, br s), 7.10–7.40 (5 H, m). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

Benzyl (4*S*)-1-Benzyl-2-oxoimidazolidine-4-carboxylate (8e). Compound **7e** (26.8 g, 60 mmol) was dissolved in 25% hydrogen bromide–acetic acid solution (100 mL) and the mixture was stirred for 20 min at room temperature. After the mixture was concentrated in vacuo, the residue was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was crystallized from diisopropyl ether to give **8e** (15.2 g, 81.1%) as colorless leaflets: mp 116–117 °C; $[\alpha]^{20}_D$ +29.6° (*c* 1, MeOH); IR (Nujol) 3420, 1720, 1700, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42–3.60 (3 H, m), 4.10–4.30 (1 H, m), 4.35 (2 H, s), 5.17 (2 H, s), 5.33 (1 H, br s), 7.20–7.40 (10 H, m). Anal. ($C_{18}H_{18}N_2O_3$) C, H, N.

Compounds **8b** and **8c** were prepared in the same manner as described above. The yields and physical data are as follows.

8b: yield 83.3%; mp 94–95 °C; $[\alpha]^{20}_D$ +10.7° (*c* 1, MeOH); IR (Nujol) 3250, 1745, 1710, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75 (3 H, s), 3.45–3.80 (2 H, m), 4.05–4.40 (1 H, m), 5.08, 5.25 (2 H, AB t, *J* = 10 Hz), 5.66 (1 H, br s), 7.20–7.40 (5 H, m). Anal. ($C_{12}H_{14}N_2O_3$) C, H, N.

8c: yield 57.0%; mp 53–54 °C; $[\alpha]^{23}_D$ +13.5° (*c* 1, MeOH); IR (Nujol) 3200, 1745, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, t, *J* = 6.5 Hz), 1.10–1.75 (4 H, m), 3.21 (2 H, t, *J* = 6.5 Hz), 3.60–3.82 (2 H, m), 4.28 (1 H, t, *J* = 8 Hz), 5.24 (2 H, s), 5.32 (1

H, br s), 7.38 (5 H, s). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

***tert*-Butyl (4*S*)-1-(Benzyloxycarbonyl)-2-oxoimidazolidine-4-carboxylate (8f).** A slurry of 62% NaH (4.26 g, 110 mmol) was added portionwise to a solution of **6a** (32 g, 100 mmol) in THF (400 mL) at 0 °C, and the mixture was stirred for 1 h at 10 °C. The mixture was neutralized with acetic acid (6.6 mL), concentrated in vacuo, and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to dryness. The residue was purified by column chromatography on silica gel with $CHCl_3$–AcOEt (5:1) to give crude product (23 g, 71.9%). Recrystallization from AcOEt–diisopropyl ether gave pure **8f** as colorless needles: mp 99–101 °C; $[\alpha]^{24}_D$ +53.2° (*c* 1, MeOH); TLC ($CHCl_3$–AcOEt, 1:1) R_f 0.47; IR (Nujol) 3350, 3200, 1800, 1780, 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (9 H, s), 3.90–4.15 (3 H, m), 5.23 (2 H, s), 6.25 (1 H, br s), 7.20–7.45 (5 H, m). Anal. ($C_{16}H_{20}N_2O_5$) C, H, N.

(4*S*)-3-[(2*S*)-Aminopropionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic Acid (2a). Potassium *tert*-butoxide (9.1 g, 81 mmol) was added portionwise to a solution of **8a** (16.2 g, 81 mmol) in THF (200 mL) with stirring at −50 °C. After being stirred for 10 min at the same temperature, a solution of *N*-succinimidyl *N*-(benzyloxycarbonyl)-L-alaninate (25.9 g, 81 mmol) in THF (70 mL) was added dropwise to the above mixture. The mixture was stirred at −30 to −20 °C for 30 min and then poured into a mixture of 2% acetic acid (240 mL) and Et_2O (240 mL) in one portion. The organic layer was separated, washed with water, 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 *tert*-butyl (4*S*)-3-[(2*S*)-2-[*N*-(benzyloxycarbonyl)amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate (19.3 g, 60.4%) as colorless crystals. It was homogeneous by TLC ($CHCl_3$–AcOEt 4:1, R_f 0.49) and used directly without further purification: mp 87–90 °C; IR (Nujol) 3310, 1715, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (3 H, d, *J* = 7 Hz), 1.46 (9 H, s), 2.86 (3 H, s), 3.20–3.80 (2 H, m), 4.50–4.80 (1 H, m), 5.09 (2 H, s), 5.20–5.55 (1 H, m), 7.32 (5 H, s); MS, *m/e* 391 (M^+).

HCl–dioxane solution (14%; 150 mL) was added to the above material (15 g, 38 mmol), and the mixture was stirred at room temperature overnight. The mixture was concentrated to dryness in vacuo, and the residue was triturated with Et_2O and collected by filtration to give crystalline precipitates. The product dissolved in MeOH (90 mL) was hydrogenolyzed in the presence of 10% palladium on carbon (0.5 g) under atmospheric pressure at room temperature for 3 h. After the catalyst was filtered off, the solvent was removed in vacuo. The resulting residue was crystallized from hot EtOH and collected by filtration to give **2a** (5.75 g, 72.2%) as colorless fine needles: mp 174–175 °C dec; $[\alpha]^{26}_D$ −128.2° (*c*, 1, $^1/_{10}$ N HCl); IR (Nujol) 3500, 3350, 1720, 1690, 1630 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 1.84 (3 H, d, *J* = 7 Hz), 3.04 (3 H, s), 3.77 (1 H, dd, *J* = 9.5, 4 Hz), 4.07 (1 H, t, *J* = 9.5 Hz), 5.15 (1 H, dd, *J* = 9.5, 4 Hz), 5.50–5.80 (1 H, m). Anal. ($C_8H_{13}N_3O_4$), C, H, N.

Compound **2b** was obtained similarly: mp 177–178 °C dec; $[\alpha]^{20}_D$ −77.7° (*c* 0.8, MeOH); IR (Nujol) 3500, 3350, 1730, 1690, 1630, 1600 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 1.92 (3 H, d, *J* = 7 Hz), 3.50–4.20 (2 H, m), 4.54, 4.68 (2 H, AB q, *J* = 9 Hz), 5.14 (1 H, dd, *J* = 9.5, 4 Hz), 5.52–5.95 (1 H, m), 7.20–7.66 (5 H, m). Anal. ($C_{14}H_{17}N_3O_4$) C, H, N.

Typical Procedure for the Preparation of (4*S*)-1-Substituted-3-(2-bromoacyl)-2-oxoimidazolidine-4-carboxylic Acid Esters (9a–d). *tert*-Butyl (4*S*)-1-Benzyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate (9c). Potassium *tert*-butoxide (3.1 g) was added portionwise to a solution of **8d** (7.5 g, 27.1 mmol) in THF (70 mL) at −50 °C. After being stirred at the same temperature for 20 min, 2-bromopropionyl chloride (6.7 g, 39.1 mmol) was added dropwise to the above mixture. Stirring was continued at −30 °C for 1 h, and then the reaction mixture was poured into a mixture of Et_2O (50 mL), AcOH (1.7 g), and brine (50 mL). The organic phase was separated and washed successively with brine, 2% aqueous K_2CO_3, and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel with toluene–AcOEt (15:1) to afford a mixture of diastereomers of **9c** as colorless crystals: mp 105–110 °C; TLC (toluene–AcOEt, 4:1) R_f 0.67, 0.47; IR (Nujol) 1735, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40, 1.46 (9 H, 2 s), 1.85 (3 H, d, *J* = 7 Hz), 3.0–3.45 (1 H, m), 3.46–3.75 (1 H, m), 4.08–4.78 (3 H, m), 5.75–6.10 (1 H, m), 7.30 (5 H, s). Anal. ($C_{18}H_{23}BrN_2O_4$), C, H, N.

Other compounds **9a**, **9b**, and **9d** were prepared similarly. The yields and the physical data are as follows.

9a (diastereomeric mixture): yield 71.5%; mp 90–95 °C; TLC (toluene–AcOEt, 4:1) R_f 0.41, 0.23; IR (Nujol) 1740, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (9 H, s), 1.71–1.92 (3 H, m), 2.90 (3 H, s), 3.18–3.90 (2 H, m), 4.43–4.67 (1 H, m), 5.68–6.08 (1 H, m). Anal. ($C_{12}H_{19}BrN_2O_4$) C, H, N.

9b (diastereomeric mixture): yield 81.1%; mp 62–62 °C; TLC (toluene–AcOEt, 4:1) R_f 0.49, 0.28; IR (Nujol) 1740, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92–1.17 (3 H, m), 1.47 (9 H, s), 1.85–2.30 (2 H, m), 2.90 (3 H, s), 3.29 (1 H, dd, *J* = 9.5, 4 Hz), 3.70 (1 H, t, *J* = 9.5 Hz), 4.66 (1 H, dd, *J* = 9.5, 4 Hz), 5.78 (1 H, t, *J* = 6.5 Hz). Anal. ($C_{13}H_{21}BrN_2O_4$), C, H, N.

9d (diastereomeric mixture): yield 69.3%; mp 105–107 °C; TLC (toluene–AcOEt, 4:1) R_f 0.80, 0.58; IR (Nujol) 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.25 (3 H, m), 1.43, 1.45 (9 H, 2 s), 1.85–2.30 (2 H, m), 3.0–4.80 (5 H, m), 5.77 (1 H, m), 7.29 (5 H, s). Anal. ($C_{19}H_{25}BrN_2O_4$) C, H, N.

Preparation of L-α-Amino Acid Esters 10a–g. Benzyl (2*S*)-2-Aminodecanoate (10c). 2-Bromodecanoic acid (32 g, 27 mmol) was dissolved in 28% aqueous ammonia (200 mL), and the mixture was allowed to stand at room temperature for 1 week. The mixture was concentrated under reduced pressure to a small volume and adjusted to pH 6.5 with concentrated HCl. The resulting crystalline precipitates were collected by filtration and washed with Et_2O to afford 2-aminodecanoic acid (15 g, 62.9%), mp 264–265 °C (lit.[8] mp 264–265 °C).

2-Aminodecanoic acid (13.3 g, 7.1 mmol) was acetylated by the Schotten-Baumann method using acetic anhydride: yield; 15 g (92.1%); mp 105–106 °C.

Aminoacylase (162.5 mg) obtained from *Aspergillus oryzae* (10 mL) was added to a suspension of the acetylated material (14.5 g, 63.2 mmol) and water (120 mL) containing $CoCl_2$ (5 mM). The mixture was adjusted to pH 7.0 with aqueous NaOH and incubated at 37 °C for 3 days. The crystalline precipitates were collected by filtration and washed with Et_2O to afford (2*S*)-2-aminodecanoic acid (5.62 g, 47.5%) as colorless leaflets: mp 265–267 °C; $[\alpha]^{24}_D$ +27.8° (*c* 1, 1 N HCl–MeOH = 1:1).

A mixture of the above (*S*)-amino acid (5.43 g, 2.9 mmol), benzyl alcohol (8 ml), *p*-toluenesulfonic acid monohydrate (6.6 g), and benzene (100 mL) was heated under reflux for 6 h with a Dean–Stark trap. After removal of the solvent, the residue was triturated with Et_2O. The resulting crystals were filtered and washed with Et_2O to afford **10c** *p*-toluenesulfonate (12.15 g, 93.1%) as colorless needles: mp 165–166 °C; $[\alpha]^{25}_D$ −7.2° (*c* 1, MeOH); IR (Nujol) 1750, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, t, *J* = 6 Hz), 0.95–1.40 (12 H, m), 1.50–1.90 (2 H, m), 2.28 (3 H, s), 4.0 (1 H, m), 4.92, 5.13 (2 H, AB q, *J* = 12 Hz), 7.05 (2 H, d, *J* = 8 Hz), 7.23 (5 H, s), 7.74 (2 H, d, *J* = 8 Hz), 8.20 (3 H, br s). Anal. ($C_{17}H_{27}NO_2 \cdot C_7H_8O_3S$) C, H, N.

Compounds **10b** and **10e** were prepared by the same procedure as described for the preparation of **10c**. Compounds **10a** and **10d** were obtained from the commercially available L-amino acids. Ethyl esters **10f** and **10g** were prepared by esterification of the corresponding L-amino acids with thionyl chloride in EtOH. The physical data of compounds are as follows.

10b *p*-toluenesulfonate: mp 138–140 °C; $[\alpha]^{25}_D$ −10.6° (*c* 1, MeOH). Anal. ($C_{14}H_{21}NO_2 \cdot C_7H_8O_3S$) C, H, N.

10e *p*-toluenesulfonate: mp 139–140 °C; $[\alpha]^{24}_D$ +12.7° (*c* 1, MeOH). Anal. ($C_{17}H_{19}NO_2 \cdot C_7H_8O_3S$) C, H, N.

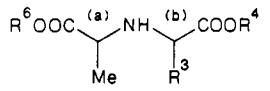
10f hydrochloride: mp 104–105 °C; $[\alpha]^{24}_D$ +14.9° (*c*, 1, MeOH). Anal. ($C_{12}H_{25}NO_2 \cdot HCl$) C, H, N.

10g hydrochloride: mp 155–157 °C; $[\alpha]^{24}_D$ +38.7° (*c* 1, H_2O) [lit.[2i] mp 157–158 °C; $[\alpha]^{24}_D$ +40.0° (*c* 1.04, EtOH)].

Typical Procedure for the Preparation of *N*-[1-(Alkoxycarbonyl)alkyl]amino Acid Esters 13a–f. Benzyl 2-[*N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propionate (13d and 13e). Benzyl 2-bromopropionate (10.1 g, 41.5 mmol) was added to a mixture of **10g** (6 g, 28.9 mmol), K_2CO_3 (4 g), and DMSO (15 mL) with stirring and ice cooling. After being stirred at room temperature for 30 h, the reaction mixture was diluted

(8) Stork, G.; et al. *J. Org. Chem.* **1976**, *41*, 3491.

Table VII. Yields and Physical Data of **13** and **14**



compd	R^3	R^4	R^6	config (a, b)	yield, %	mp, °C	$[\alpha]^{24}_D$, deg (c 1, MeOH)	formula[a]	IR (Nujol), cm^{-1}
13a[b]	C_8H_{17}	CH_2Ph	*t*-Bu	*S,S*	37.9	100–101	−16.3	$C_{24}H_{39}NO_4 \cdot C_4H_4O_4$	3300, 1740[e]
13b[b]	C_8H_{17}	Et	CH_2Ph	*S,S*	36.7	109–110	−7.9	$C_{22}H_{35}NO_4 \cdot C_4H_4O_4$	3300, 1740[e]
13c[b]	CH_2CH_2Ph	CH_2Ph	*t*-Bu	*S,S*	40.8	136–137	+1.1	$C_{24}H_{31}NO_4 \cdot C_4H_4O_4$	1745, 1730, 1600[f]
13d[c]	CH_2CH_2Ph	Et	CH_2Ph	*R,S*	27.8	124–125	+36.5	$C_{22}H_{27}NO_4 \cdot HCl$	3300, 1740[e]
13e[b]	CH_2CH_2Ph	Et	CH_2Ph	*S,S*	43.6	133–134	+1.1	$C_{22}H_{27}NO_4 \cdot C_4H_4O_4$	3300, 1740[e]
13f[c]	CH_2CH_2Ph	Et	CH_2Ph	*S,R*	15.9[d]	125–126	−37.1	$C_{22}H_{27}NO_4 \cdot HCl$	3300, 1740[e]
14a	C_8H_{17}	CH_2Ph	H	*S,S*	73.4	136–140	−13.0	$C_{20}H_{31}NO_4$	1750, 1630
14b	C_8H_{17}	Et	H	*S,S*	83.3	127–128	+9.9	$C_{15}H_{29}NO_4$	1750, 1620
14c	CH_2CH_2Ph	CH_2Ph	H	*S,S*	94.0	161–162	+7.6	$C_{20}H_{23}NO_4$	1745, 1620
14d	CH_2CH_2Ph	Et	H	*R,S*	95.1	135–138	+28.0	$C_{15}H_{21}NO_4$	3200, 1740, 1650
14e[g]	CH_2CH_2Ph	Et	H	*S,S*	96.0	150–151	+28.1	$C_{15}H_{21}NO_4$	3250, 1745, 1735, 1600

[a] All compounds exhibited satisfactory C, H, and N elemental analyses. [b] Melting points and specific rotations refer to maleate. [c] Melting points and specific rotations refer to hydrochloride. [d] Yield refers to the reaction of benzyl L-alaninate with ethyl 2-bromo-4-phenylbutyrate. [e] Taken by film. [f] IR spectrum refers to maleate. [g] Literature 9: mp 148–149 °C, $[\alpha]^{20}_D$ + 28.0° (*c* 1, MeOH).

with Et_2O (50 mL). The insoluble materials were filtered off, and the filtrate was washed with water, dried over $MgSO_4$, filtered, and evaporated to afford a crude diastereomeric mixture. The diastereomers were separated by column chromatography on silica gel with toluene–AcOEt (10:1) as an eluent to give **13d** (*R,S* diastereomer, 2.97 g, 27.8%) from the first fraction and **13e** (*S,S* diastereomer, 4.66 g, 43.6%) from the second fraction, each as a colorless oil. **13d**: TLC (toluene–AcOEt, 9:1) R_f 0.55; ^1H NMR ($CDCl_3$) δ 1.23 (3 H, t, *J* = 7 Hz), 1.30 (3 H, d, *J* = 6.5 Hz), 1.80–2.10 (2 H, m), 2.20 (1 H, br), 2.71 (2 H, t, *J* = 7 Hz), 3.27 (1 H, t, *J* = 6.5 Hz), 3.38 (1 H, q, *J* = 6.5 Hz), 4.13 (2 H, q, *J* = 7 Hz), 5.10 (2 H, s), 7.10–7.40 (10 H, m). **13d** hydrochloride was obtained by treatment with ethanolic HCl solution and recrystallized from EtOH–diisopropyl ether as colorless needles. **13e**: TLC (toluene–AcOEt, 9:1) R_f 0.34; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, t, *J* = 7 Hz), 1.33 (3 H, d, *J* = 6.5 Hz), 1.72–2.10 (2 H, m), 1.83 (1 H, s), 2.68 (2 H, t, *J* = 7 Hz), 3.33 (1 H, t, *J* = 6.5 Hz), 3.44 (1 H, q, *J* = 6.5 Hz), 4.15 (2 H, q, *J* = 7 Hz), 5.12 (2 H, s), 7.10–7.40 (10 H, m). **13e** maleate was obtained by treatment with maleic acid in AcOEt–diisopropyl ether as colorless needles.

To confirm the configuration of **13d** and **13e**, the reaction of benzyl L-alaninate (8.95, 50 mmol) with ethyl 2-bromo-4-phenylbutyrate (20.4 g, 75 mmol) was carried out by the same procedure. The diastereomers were separated by column chromatography on silica gel with toluene–AcOEt (10:1) to afford the minor diastereomer **13f** (3.86 g, 15.9%) from the first fraction and to afford the major diastereomer **13e** (7.31 g, 30.1%) from the second fraction. The physical constants of the major diastereomer were identical with those of **13e** which was prepared from **10g** and benzyl 2-bromopropionate. IR and ^1H NMR spectra of the minor diastereomer **13f** were identical with those of **13d**. Accordingly **13d**, **13e**, and **13f** possess the *R,S*, *S,S*, and *S,R* configuration, respectively.

The results of other compounds are summarized in Table VII.

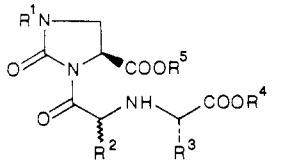
Typical Procedure for the Preparation of *N*-[1-(Alkoxycarbonyl)alkyl]amino Acids 14a–e. (2*S*)-2-[*N*-[(1*S*)-1-(Benzyloxycarbonyl)-3-phenylpropyl]amino]propionic Acid (14c). **13c** (13.5 g, 34 mmol) was dissolved in 15% HCl–dioxane solution (300 mL). After being stirred at room temperature overnight, the mixture was concentrated to dryness in vacuo. The residue was dissolved in H_2O (50 mL) and adjusted to pH 5.5 with saturated aqueous $NaHCO_3$. The resulting crystalline precipitates were collected by filtration and dried to give **14c** (10.9 g, 94.0%). Recrystallization from AcOEt afforded colorless fine needles: ^1H NMR ($CDCl_3$) δ 1.35 (3 H, t, *J* = 6.5 Hz), 1.80–2.20 (2 H, m), 2.50–2.90 (2 H, m), 3.17–3.62 (2 H, m), 5.17 (2 H, s), 6.48 (2 H, br), 7.10–7.45 (10 H, m).

(2*S*)-2-[*N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propionic Acid (14e). Compound **13e** (36.9 g, 0.1 mol) dissolved in EtOH (300 mL) was hydrogenolyzed in the presence of palladium black (2 g) at room temperature under atmospheric pressure for 3 h. After removal of the catalyst, the filtrate was concentrated to dryness in vacuo. The crystalline residue was recrystallized from $CHCl_3$–diisopropyl ether to afford **14e** (26.8 g, 96.0%) as colorless needles: ^1H NMR ($CDCl_3$) δ 1.28 (3 H, t, *J* = 7 Hz), 1.34 (3 H, d, *J* = 6.5 Hz), 1.80–2.10 (2 H, m), 2.60–2.85 (2 H, m), 3.34 (1 H, q, *J* = 6.5 Hz), 3.42 (1 H, t, *J* = 6.5 Hz), 4.18 (2 H, q, *J* = 7 Hz), 5.47 (2 H, br), 7.15–7.35 (5 H, m).

Typical Procedure for the Preparation of Diesters 11a–s. Method A. *tert*-Butyl (4*S*)-1-Benzyl-3-[2-[*N*-[(1*S*)-1-(benzyloxycarbonyl)-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylate (11o and 11p). A mixture of **9c** (8.9 g, 21.6 mmol), **10e** (5.9 g, 21.9 mmol), and K_2CO_3 (3.0 g) in HMPA (20 mL) was stirred at room temperature for 2 days. The mixture was diluted with AcOEt and water. The separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The oily residue was chromatographed on silica gel, eluting with toluene–AcOEt (6:1) to give **11p** (*S,S,S* diastereomer, 1.4 g, 10.1%) from the first fraction and **11o** (*S,R,S* diastereomer, 8.4 g, 60.4%) from the second fraction, each as a colorless syrup. **11o**: TLC (toluene–AcOEt, 4:1) R_f 0.23; ^1H NMR ($CDCl_3$) δ 1.38 (3 H, d, *J* = 6.5 Hz), 1.39 (9 H, s), 1.85–2.20 (2 H, m), 2.35 (1 H, s), 2.50–2.90 (2 H, m), 3.0–3.52 (2 H, m), 3.53 (1 H, t, *J* = 9.5 Hz), 4.22, 4.63 (2 H, AB q, *J* = 15 Hz), 4.35–4.85 (2 H, m), 5.14 (2 H, s), 7.10–7.40 (15 H, m). **11p**: TLC (toluene–AcOEt, 4:1) R_f 0.48; ^1H NMR ($CDCl_3$) δ 1.39 (3 H, d, *J* = 6.5 Hz), 1.42 (9 H, s), 1.75–2.15 (2 H, m), 2.20 (1 H, s), 2.40–2.80 (2 H, m), 3.0–3.52 (3 H, m), 4.05–4.90 (4 H, m), 5.12 (2 H, s), 7.10–7.40 (15 H, m).

Method B. *tert*-Butyl (4*S*)-3-[(2*S*)-2-[*N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylate (11g). A solution of DCC (10.5 g, 51 mmol) in THF (21 mL) was added dropwise to a suspension of **14e** (14 g, 50 mmol) and *N*-hydroxysuccinimide (5.9 g, 51 mmol) in THF (120 mL) at 5 °C. The mixture was stirred at room temperature overnight. The insoluble materials were filtered off, and the filtrate was concentrated in vacuo to afford crude *N*-succinimidyl (2*S*)-2-[*N*-[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propionate as a syrup. Potassium *tert*-butoxide (6.2 g, 55 mmol) was added portionwise to a solution of **8a** (11 g, 55 mmol) in THF (100 mL) at −50 °C. After being stirred at the same temperature for 20 min, a solution of the above activated ester in THF (20 mL) was added in one portion. Stirring was continued at −30 °C for 20 min and then the reaction mixture was poured into a mixture of AcOEt (70 mL), AcOH (3.3 g), and brine (70 mL). The organic phase was separated and washed successively with brine, 5% aqueous K_2CO_3, and brine. After the organic layer was dried over $MgSO_4$, the solvent was removed in vacuo to give crude **11g** as a syrup. The product and maleic acid (5.8 g, 50 mmol) were dissolved in AcOEt (100 mL) by heating on a water bath. Diisopropyl ether (75 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–diisopropyl ether (1:1) to afford **11g** maleate (23.9 g, 82.6%) as colorless needles: mp 118–120 °C; $[\alpha]^{24}_D$ −57.7° (*c* 1, EtOH); ^1H NMR ($CDCl_3$) δ 1.32 (3 H, t, *J* = 7 Hz), 1.47 (9 H, s), 1.55 (3 H, d, *J* = 6.5 Hz), 2.10–2.45 (2 H, m),

Table VIII. Yields and Physical Data of Diesters 11a–s



compd	R^1	R^2 (config)	R^3	R^4	R^5	prepn method	yield, %	IR (film), cm^{-1}	MS, m/e (M^+)
11a	Me	Me (*R*)	C_8H_{17}	CH_2Ph	*t*-Bu	A	64.4	3320, 1740, 1680	531
11b	Me	Me (*S*)	C_8H_{17}	CH_2Ph	*t*-Bu		14.0	3320, 1735, 1680	531
11c	Me	Me (*S*)	C_8H_{17}	Et	CH_2Ph	B	66.7	3320, 1735, 1680	503
11d	Me	Et (*S*)	C_8H_{17}	CH_2Ph	*t*-Bu	A	2.9	3320, 1740, 1680	545
11e[a]	Me	Me (*S*)	CH_2CH_2Ph	CH_2Ph	*t*-Bu	B	81.3	3650, 3500, 1740, 1700[b]	523
11f	Me	Me (*R*)	CH_2CH_2Ph	Et	*t*-Bu	B	85.0	3320, 1735, 1680	461
						A	52.8		
11g[a]	Me	Me (*S*)	CH_2CH_2Ph	Et	*t*-Bu	B	82.6	3600, 3500, 1740, 1690[b]	461
						A	13.9		
11h	Bu	Me (*S*)	CH_2CH_2Ph	CH_2Ph	CH_2Ph	B	58.4	3320, 1735, 1685	599
11i	CH_2Ph	Me (*S*)	$CH_2CH(CH_3)_2$	CH_2Ph	*t*-Bu	A	10.8	3320, 1735, 1685	551
11j	CH_2Ph	Me (*S*)	$CH_2CH_2CH(CH_3)_2$	CH_2Ph	*t*-Bu	A	18.9	3320, 1735, 1685	565
11k	CH_2Ph	Me (*S*)	C_8H_{17}	CH_2Ph	CH_2Ph	B	70.2	3320, 1735, 1680	641
11l	CH_2Ph	Me (*S*)	C_8H_{17}	Et	CH_2Ph	B	61.6	3320, 1730, 1690	579
11m	CH_2Ph	Et (*S*)	C_8H_{17}	CH_2Ph	*t*-Bu	A	5.3	3320, 1740, 1680	621
11n	CH_2Ph	Me (*S*)	CH_2Ph	CH_2Ph	*t*-Bu	A	9.7	3300, 1750, 1720, 1680	585
11o	CH_2Ph	Me (*R*)	CH_2CH_2Ph	CH_2Ph	*t*-Bu	A	60.4	3300, 1725, 1680	599
11p	CH_2Ph	Me (*S*)	CH_2CH_2Ph	CH_2Ph	*t*-Bu		10.1	3300, 1725, 1680	599
11q	CH_2PH	Me (*S*)	CH_2CH_2Ph	Et	CH_2Ph	B	63.4	3300, 1730, 1680	571
11r	CH_2Ph	Et (*S*)	CH_2CH_2Ph	CH_2Ph	*t*-Bu	A	4.9	3320, 1735, 1680	613
11s[a]	CO_2CH_2Ph	Me (*S*)	CH_2CH_2Ph	CH_2Ph	*t*-Bu	B	84.7	3650, 1805, 1745, 1720[b]	643

[a] Maleate. **11e** maleate: mp 114–115 °C; $[\alpha]^{25}_D$ −59.2° (*c* 1, MeOH). Anal. ($C_{29}H_{37}N_3O_6 \cdot C_4H_4O_4$) C, H, N. **11s** maleate: mp 140–141 °C; $[\alpha]^{25}_D$ −27.0° (*c* 1, MeOH). Anal. ($C_{36}H_{41}N_3O_8 \cdot C_4H_4O_4$) C, H, N. [b] Taken in Nujol.

2.70–2.93 (2 H, m), 2.90 (3 H, s), 3.36 (1 H, dd, *J* = 9.5, 4 Hz), 3.67–3.95 (2 H, m), 4.28 (2 H, q, *J* = 7 Hz), 4.68 (1 H, dd, *J* = 9.5, 4 Hz), 5.25 (1 H, q, *J* = 6.5 Hz), 6.30 (2 H, s), 7.15–7.40 (5 H, m), 9.12 (3 H, br). Anal. ($C_{24}H_{35}N_3O_6 \cdot C_4H_4O_4$) C, H, N.

The yields and the physical data of the other compounds are summarized in Table VIII.

Typical Procedure for the Preparation of Dicarboxylic Acids 3a–n. (4*S*)-1-Benzyl-3-[2-[*N*-[(1*S*)-1-carboxy-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylic Acid (3m). Compound **11p** (1.2 g, 2 mmol) was dissolved in 15% HCl–dioxane solution (20 mL). After being stirred at room temperature overnight, the mixture was concentrated in vacuo. The residue was dissolved in water and adjusted to pH 5.5 with saturated aqueous $NaHCO_3$. The solution was extracted three times with AcOEt, and the combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure to afford (4*S*)-1-benzyl-3-[(2*S*)-2-[*N*-[(1*S*)-1-(benzyloxycarbonyl)-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylic acid (1.0 g) as colorless viscous oil. The product dissolved in MeOH (20 mL) was hydrogenolyzed with palladium black (50 mg) at room temperature under atmospheric pressure for 2 h. After removal of the catalyst by filtration, the filtrate was concentrated to dryness in vacuo. The residue was triturated with Et_2O to afford **3m** (0.7 g, 77.2%) as colorless crystals: IR 3150, 1740, 1700 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 1.84 (3 H, d, *J* = 6.5 Hz), 2.40–2.78 (2 H, m), 2.80–3.15 (2 H, m), 3.50–4.30 (3 H, m), 4.53 (2 H, s), 4.85–5.20 (1 H, m), 5.53 (1 H, q, *J* = 6.5 Hz), 7.15–7.50 (10 H, m).

(4*S*)-1-Benzyl-3-[2-[*N*-[(1*S*)-1-carboxy-*n*-nonyl]amino]-propionyl]-2-oxoimidazolidine-4-carboxylic Acid (3i). Compound **11k** (4.3 g, 6.7 mmol) dissolved in MeOH (100 mL) was hydrogenolyzed in the presence of palladium black (0.2 g) at room temperature under atmospheric pressure for 2 h. After removal of the catalyst, the filtrate was concentrated to dryness in vacuo. The crystalline residue was recrystallized from MeOH to give **3i** (2.81 g, 90.9%) as colorless crystals: IR (Nujol) 3150, 1740, 1700 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 0.85–2.35 (20 H, m), 3.50–4.30 (3 H, m), 4.58 (2 H, s), 5.0–5.25 (1 H, m), 5.80–5.95 (1 H, m), 7.30–7.44 (5 H, m).

Typical Procedure for the Preparation of Monoesters 3o–s. (4*S*)-3-[(2*S*)-2-[*N*-[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic Acid (3p). Diester **11g** maleate (28.9 g, 50 mmol) suspended in H_2O was basified with K_2CO_3 and extracted with AcOEt. The extracts were 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, washed with diisopropyl ether, and dried to afford **3p** hydrochloride (19.2 g, 90%) as colorless crystals: IR (Nujol) 1735, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.26 (3 H, t, *J* = 7 Hz), 1.57 (3 H, d, *J* = 6.5 Hz), 2.04–2.35 (2 H, m), 2.45–2.80 (2 H, m), 2.81 (3 H, s), 3.45 (1 H, dd, *J* = 9.5, 4 Hz), 3.83 (1 H, t, *J* = 9.5 Hz), 4.02 (1 H, t, *J* = 6.5 Hz), 4.24 (2 H, q, *J* = 7 Hz), 4.82 (1 H, dd, *J* = 9.5, 4 Hz), 5.23 (1 H, q, *J* = 6.5 Hz), 7.20–7.40 (5 H, m).

(4*S*)-1-Benzyl-3-[2-[*N*-[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylic Acid (3s). Compound **11q** (2.6 g, 4.5 mmol) dissolved in EtOH (50 mL) was hydrogenolyzed in the same manner as described for the preparation of **3i**. Crystallization from H_2O afforded **3s** 0.25-hydrate (1.97 g, 89.1%) as colorless crystals: IR (Nujol), 3450, 1735, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3 H, t, *J* = 7 Hz), 1.47 (3 H, d, *J* = 6.5 Hz), 1.95–2.30 (2 H, m), 2.55–2.90 (2 H, m), 3.22–3.65 (3 H, m), 4.16 (2 H, q, *J* = 7 Hz), 4.20–4.50 (2 H, m), 4.52–5.03 (2 H, m), 6.90 (2 H, br s), 7.05–7.32 (10 H, m).

In Vitro ACE Inhibitory Activity. ACE was prepared from swine renal cortex by the method of Oshima et al.[10] ACE inhibitory activity was determined by the following methods. The reaction mixture contained: Tris·HCl (pH 7.4), 60 μmol; sodium chloride, 60 μmol; hippurylhistidylleucine, 0.5 μmol; testing inhibitor and converting enzyme (6 μg of protein) in a final volume of 0.5 mL. Incubation was carried out for 20 min at 37 °C. The reaction was stopped by placing the tubes in ice water. Histidylleucine formed was measured microbiologically by the use of *Leuconostoc mesenteroides* P-60.[11] Each sample was run in duplicate and the average of the two readings obtained was

(9) Urbach, H.; Henning, R. *Tetrahedron Lett.* **1984**, *25*, 1143.
(10) Oshima, G.; Geese, A.; Erdos, E. G. *Biophys. Acta* **1974**, *350*, 26.
(11) Itoh, H.; Kawashima, K.; Chibata, I. *Agric. Biol. Chem.* **1973**, *37*, 2227.

calculated. A standard curve of histidylleucine was always prepared with each assay.

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

Inhibitory Effect on Angiotensin I Induced Pressor Response in Anesthetized Rats. Male Wistar slc rats, weighing 300–400 g, were used after fasting for 18–20 h. Under urethane anesthesia (1.2 g/kg, sc) the arterial cannula inserted into the left carotid was connected to a pressure transducer (Nihon Kohden, MPU-0.5), and the blood pressure was recorded by carrier amplifier (Nihon Kohden, RP-3 and RM-150). Angiotensin I (300 ng/kg) dissolved in 0.9% physiological saline was injected through a cannula which had been inserted into the left femoral vein. After the constant elevation of blood pressure by angiotensin I was confirmed, the test compounds dissolved in distilled pure water were administered intravenously or orally. Angiotensin I induced pressor responses were measured, at fixed intervals, up to 6 h after oral administration of the test compounds. The inhibitory percentages of the test compounds were calculated by the following formula: [1 – (mean blood pressure induced by angiotensin I after the test compound/mean blood pressure induced by angiotensin I before the test compound)] × 100. ID_{50} (50% inhibitory dose) was graphically calculated by the linear regression curve.

Antihypertensive Effect in SHRs. Eighteen to 22 week old male NCrj SHRs (Charles River Japan, Inc.), weighing about 350 g, with 180–200 mmHg of systolic blood pressure were used. Systolic blood pressure was measured by a rat tail plethysmograph (Ueda, USM-105-R). The test compounds were dissolved in distilled pure water and administered orally after fasting for 18–20 h.

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Registry No. **2a**, 117581-62-1; **2a** (protected), 117560-20-0; **2b**, 117560-21-1; **2b** (protected), 117560-26-6; **3a**, 117560-10-8; **3b**, 89460-21-9; **3b** (free base), 117605-20-6; **3c**, 89384-26-9; **3d**, 89371-74-4; **3e**, 89371-44-8; **3f**, 89371-87-9; **3g**, 89708-53-2; **3h**, 89371-62-0; **3i**, 89371-52-8; **3j**, 89371-71-1; **3k**, 89371-67-5; **3l**, 39396-97-4; **3l** (free base), 97549-58-1; **3m**, 89371-51-7; **3n**, 89371-76-6; **3o**, 89371-41-5; **3p**, 89396-94-1; **3p** (free base), 89371-37-9; **3q**, 117605-19-3; **3q** (free base), 117676-68-3; **3r**, 89371-49-3; **3s**, 89371-48-2; **5**, 59760-01-9; **6a**, 77999-24-7; **6b**, 89384-29-2; **7a**, 83056-78-4; **7b**, 89371-89-1; **7c**, 89371-94-8; **7d**, 83057-00-5; **7e**, 89371-88-0; **8a**, 83056-79-5; **8b**, 89371-35-7; **8c**, 89371-95-9; **8d**, 83057-01-6; **8e**, 89371-46-0; **8f**, 117560-19-7; **9a** (isomer 1), 117605-24-0; **9a** (isomer 2), 117605-25-1; **9b** (isomer 1), 117605-26-2; **9b** (isomer 2), 117605-27-3; **9c** (isomer 1), 117605-28-4; **9c** (isomer 2), 117605-29-5; **9d** (isomer 1), 117605-30-8; **9d** (isomer 2), 117605-31-9; **10a** *p*-toluenesulfonate, 16652-76-9; **10b** *p*-toluenesulfonate, 117560-22-2; **10c** *p*-toluenesulfonate, 117560-23-3; **10d** *p*-toluenesulfonate, 1738-78-9; **10e** *p*-toluenesulfonate, 117560-24-4; **10f**·HCl, 113889-70-6; **10f** (acid), 84277-81-6; (±)-**10f** (acid), 35237-35-5; **10g**·HCl, 90891-21-7; **10g** (acid), 943-73-7; **11a**, 89397-13-7; **11b**, 89371-81-3; **11c**, 89371-40-4; **11d**, 89371-73-3; **11e**, 117605-21-7; **11f**, 117605-22-8; **11g**, 117605-23-9; **11g** (free base), 89371-38-0; **11h**, 89371-86-8; **11i**, 89655-62-9; **11j**, 89371-60-8; **11k**, 89384-28-1; **11l**, 89384-27-0; **11m**, 89371-69-7; **11n**, 89371-65-3; **11o**, 89396-95-2; **11p**, 89371-55-1; **11q**, 89371-47-1; **11r**, 89371-75-5; **11s**, 117560-18-6; **12** (R = CH_2Ph), 117560-25-5; **12** (R = Bu-*t*), 32821-07-1; **13a**, 117560-12-0; **13a** (free base), 117560-11-9; **13b**, 117560-13-1; **13b** (free base), 89371-90-4; **13c**, 117560-15-3; **13c** (free base), 117560-14-2; **13d**, 111542-00-8; **13d** (free base), 93841-86-2; **13e**, 97457-39-1; **13e** (free base), 82717-95-1; **13f**, 117560-16-4; **13f** (free base), 90315-81-4; **14a**, 89371-45-9; **14b**, 89371-39-1; **14c**, 89371-42-6; **14d**, 85196-26-5; **14d** (succinimidyl ester), 89371-34-6; **14e**, 82717-96-2; *N*-succinimidyl *N*-(benzyloxycarbonyl)-L-alaninate, 3401-36-3; 2-bromopropionyl chloride, 71425-59-7; 2-bromobutyryl chloride, 38188-35-1; 2-bromodecanoic acid, 2623-95-2; (2*S*)-2-aminodecanoic acid, 84277-81-6; (±)-*N*-acetyl-2-aminodecanoic acid, 5440-41-5; benzyl L-alaninate, 17831-01-5; ethyl 2-bromo-4-phenylbutyrate, 82586-61-6; (4*S*)-1-benzyl-3-[(2*S*)-[*N*-(1*S*)-(benzyloxycarbonyl)-3-phenylpropyl]-amino]propionyl]-2-oxoimidazolidine-4-carboxylic acid, 89371-56-2.

Synthesis and Radioprotective Activity of Dipeptide Cysteamine and Cystamine Derivatives

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Some *N*-(dipeptidyl)-*S*-acetylcysteamine and *N,N'*-(dipeptidyl)cystamine salt derivatives were synthesized and evaluated as canditate radioprotector agents. Toxicity and radioprotective activity as the dose reduction factor (DRF) were determined in vivo on mice and compared to *N*-glycyl-*S*-acetylcysteamine trifluoroacetate. One of the most interesting compounds of this series was *N*-glycylglycyl-*S*-acetylcysteamine trifluoroacetate (**8**).

We have recently shown[1] that conjugation of an amino acid with *S*-acetylcysteamine and with cystamine lead us to a class of low-toxicity radioprotectors.

Furthermore the lead compound of this series, i.e., *N*-glycyl-*S*-acetylcysteamine trifluoroacetate (**1**), was shown to afford preferential radioprotection for certain normal tissues as opposed to tumors.[2]

TFA, $H_2NCH_2CONH(CH_2)_2SCOCH_3$
1

These data prompted us to extend this approach to some dipeptide derivatives in order to evaluate the influence of the extension of the amino acid conjugation on the biological response.

Chemistry

As the most promising amino acids have been shown to be glycine and L-alanine,[1] we focused first on some dipeptides corresponding to those two amino acids.

The synthesis of **5–7** (Table I) was accomplished by coupling reactions between N-protected dipeptide (glycylglycine (**2**), glycyl-L-alanine (**3**), L-alanylglycine (**4**)) and *S*-acetylcysteamine. These coupling reactions can be

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(1) Oiry, J.; Pue, J. Y.; Imbach, J. L.; Fatome, M.; Sentenac-Roumanou, H.; Lion, C. *J. Med. Chem.* **1986**, *29*, 2217.
(2) Lespinasse, F.; Oiry, J.; Fatome, M.; Ardouin, P.; Imbach, J.; Malaise, E. P.; Guichard, M. *Int. J. Radiat. Oncol. Biol. Phys.* **1985**, *11*, 1035.

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