Syntheses and Biological Activities of Renin Inhibitors Containing Statine Analogues

Takahide NISHI,*[,a] Fujio SAITO,[a] Hitoshi NAGAHORI,[a] Mitsuru KATAOKA,[a] Yasuhiro MORISAWA,*[,a] Yuichiro YABE,[b] Mitsuya SAKURAI,[b] Susumu HIGASHIDA,[b] Machiko SHOJI,[b] Yoichi MATSUSHITA,[b] Yasuteru IIJIMA,[b] Kiyoshi OHIZUMI[c] and Hiroyuki KOIKE*[,c]

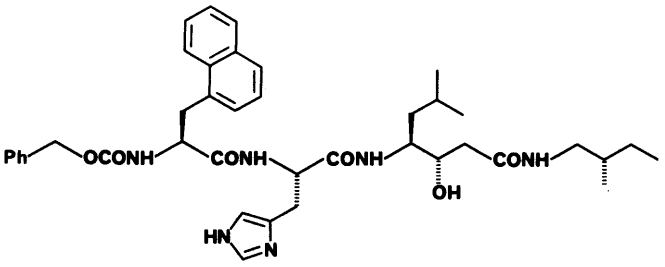
Medicinal Chemistry Research,[a] New Lead Research,[b] and Biological Research[c] Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan. *Received May 22, 1989*

Syntheses and biological activities of dipeptide renin inhibitors that contain statine analogues are described. The key steps of the synthetic approach to dipeptide renin inhibitors are the asymmetric synthesis of 2(*R*)-substituted-3-aminocarbonylpropionic acids and the diastereoselective syntheses of (3*S*,4*S*)-statine analogues. These inhibitors (2, 14—40) inhibited human renin in the 3—140 nM range. Inhibitor ES 6864 (2) was found to be a highly potent inhibitor of human renin (IC_{50}: 4.6×10^{-9} M) and showed high enzyme specificity. Oral administration of ES 6864 at 3 mg/kg to conscious, sodium-depleted marmosets inhibited plasma renin activity (PRA) more than 80% after 1 h.

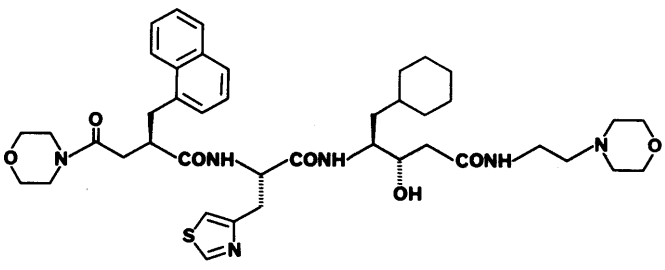
Keywords renin inhibitor; ES 6864; oral administration; 2(*R*)-substituted-3-aminocarbonylpropionic acid; statine analogue

Renin is an aspartic proteinase and it plays a key role in the renin angiotensin system. In principle, renin inhibitors should provide a means of controlling blood pressure. Therefore, the development of renin inhibitors is expected to provide effective antihypertensive agents. In recent years, research for renin inhibitors has been intensified in many laboratories.[1] The most notable renin inhibitors found so far are (1) natural substrate analogues,[2] (2) transition-state analogues containing statine and its analogues,[3] and (3) peptides having new chemical groups, such as hydroxyethylene dipeptide isostere, in place of the scissile bond of the substrate.[4] In attempting to prepare therapeutically useful renin inhibitors, the most important and difficult problems are obtaining high inhibitory potency, high specificity, metabolic stability, and oral efficacy with a long duration of action.

In previous work from our laboratories, a new potent low-molecular-weight renin inhibitor derived from an angiotensinogen transition-state analogue, ES 254 (1) (Z–Nal(1)–His–(3*S*,4*S*)-Sta–2(*S*)-methylbutylamide) was disclosed.[5] ES 254 was found to be highly potent and specific for human renin (IC_{50}: 4.5×10^{-7} M). However, this inhibitor has not shown good oral activity. We have therefore initiated a program with the aim of overcoming the poor oral absorption.



1 (ES 254)



2 (ES 6864)

Fig. 1

Herein, we report the design and a practical synthesis of orally active renin inhibitors that contain statine analogues, and we describe their biological activities. The strategies used for designing new renin inhibitors based on ES 254 were as follows (Fig. 1): (1) the transformation of the histidine group to another more potent amino acid residue, (2) the transformation of Z–Nal(1) to other acyl groups that have a retro-inverso amide bond,[6] to provide resistance to various proteases and increased hydrophilicity, (3) the transformation of statine amide to more potent and water-soluble analogues.

On the basis of the above strategies, we synthesized appropriate elements as follows.

Chemistry

First, the transformation of the histidine segment in ES 254 was investigated. A renin-inhibitory effect was retained, even though histidine at the P_2 position was replaced by other amino acids. In particular, 3-(4-thiazolyl)-L-alanine and 3-(5-isoxazolyl)-L-alanine were as effective or more effective than histidine. These amino acids were easily prepared by known methods[7] followed by optical resolution by acylase. Biological activities are presented later.

Second, we examined the N-terminal element in place of *N*-benzyloxycarbonyl-3-(1-naphthyl)-L-alanine. The N-terminal part of a renin inhibitor is very significant for oral absorption (water solubility) and stability to various proteases, not to mention the renin-inhibitory activity. Therefore many effective N-terminal sequences have been designed in several laboratories.[8] Among them, a 2(*R*)-substituted-3-aminocarbonylpropionyl group is effective, for example 3-morpholinocarbonyl-2(*R*)-(1-naphthyl)-methylpropionic acid, which was first synthesized as a racemate by Kissei's group.[6a] That is considered to be a substitute for the Pro–Phe moiety. We investigated the asymmetric syntheses independently,[9] and an asymmetric synthetic route to these groups was established as depicted in Chart 1. The key step of this synthetic method is diastereoselective alkylation by application of Evans's methodology.[10]

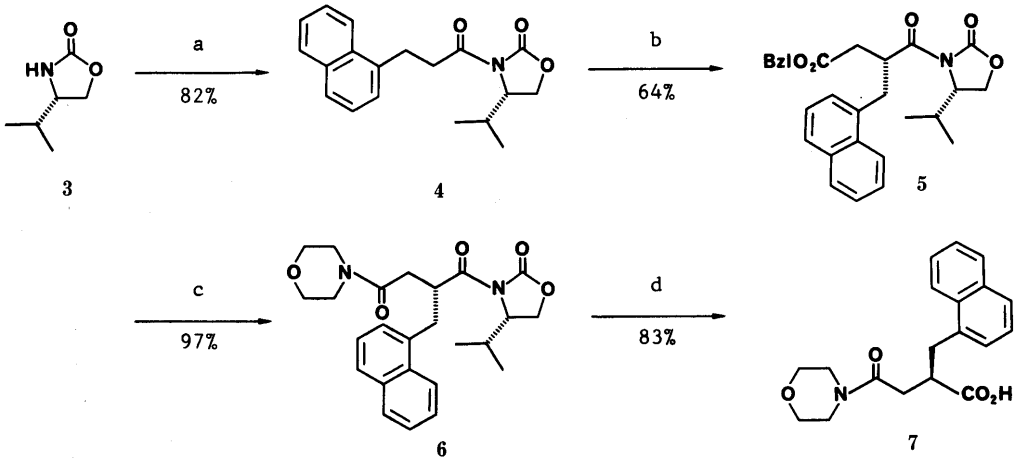
Acylation of the lithium salt of an optically active oxazolidinone with acyl halide gave **4**. Treatment of **4** with lithium diisopropylamide followed by alkylation with benzyl bromoacetate afforded **5** in high diastereoselectivity. Removal of the benzyl group by 10% Pd–C-catalyzed hydrogenolysis, and condensation with morpholine by diethylphosphoryl cyanide (DEPC)[11] and triethylamine afforded **6** in a good yield. The stereochemistry of **6** was confirmed by X-ray analysis. Hydrolysis of **6** with lithium hydroxide gave the enantiomerically pure carboxylic acid **7**. In the same manner, we were able to synthesize the optically active 2(*R*)-substituted-3-aminocarbonylpropionic acids. The renin-inhibitory activities of compounds including these groups as the N-terminal sequence are summarized in Table I.

Last, we describe the statine analogues. Statine is an unusual β-hydroxy-γ-amino acid, which was found by Umezawa *et al.*, as a component of pepstatin.[12] Statine and its analogues are also important elements of renin inhibitors from a transition-state analogue point of view. Furthermore, Boger *et al.* reported that (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACHPA) is more potent than statine in renin-inhibitory effect.[13] In view of this physiological significance, a practical and highly stereoselective synthetic method is desirable. In particular, construction of the desired (3*S*,4*S*) absolute configuration is critical. As a result of our work, some highly stereoselective synthetic methods were confirmed. One approach is the diastereoselective epoxidation of *cis*-amino allylic alcohol by *m*-chloroperbenzoic acid (*m*-CPBA).[14] A second method involves homogeneous asymmetric hydrogenation catalyzed by 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)–Ru complexes.[15] Moreover, starting from diacetone-D-glucose as a chiral auxiliary, we established an effective synthetic route.[16]

In this paper we describe the second method, which is shown in Chart 2. The commercially available *N-tert*-butoxycarbonyl(Boc)-L-phenylalanine was converted to the β-ketoester **9** in a good yield. Homogeneous asymmetric hydrogenation of the chiral β-ketoester **9** catalyzed by $RuBr_2$[(*R*)-binap][17] gave the desired *threo* isomer **10** in high diastereoselectivity (>99:1), through double stereodifferentiation. The enantiomeric purity of the product was determined by high performance liquid chromatography (HPLC) analysis of its diastereomeric thiourea derivative (no racemization occurred under the reaction conditions). After hydrolysis of the ethyl ester **10**, catalytic hydrogenation by Rh on Al_2O_3 gave the (3*S*,4*S*)-*N*-Boc–ACHPA (**11**). In conclusion, we were able to develop a short and highly stereoselective synthetic route to statine analogues.

As mentioned above, practical synthetic methods leading to each component of dipeptide renin inhibitors were established. The desired dipeptide renin inhibitors, such as ES 6864 (**2**), were prepared by standard amide coupling procedures (Chart 3).

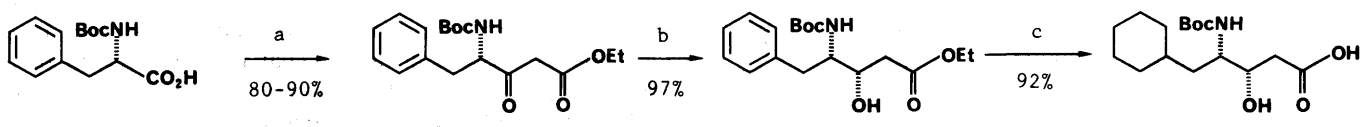
Condensation of 4-(2-aminoethyl)morpholine with (3*S*,4*S*)-*N*-Boc–ACHPA (**11**) gave **12** in 96% yield. After removal of the Boc group, acylation with *N*-Boc-3-(4-thiazolyl)-L-alanine yielded **13**. Furthermore, deprotection of **13** and coupling with 3-morpholinocarbonyl-2(*R*)-(1-naphthyl)methylpropionic acid **7** using DEPC and triethylamine afforded ES 6864 (**2**) in a good yield. In this synthetic method, the stereochemistry at the newly formed asymmetric centers was controlled completely. Therefore it was not necessary to separate the diastereomers by column chromatography. In this way, a practi-



3 4 5 6 7

a) i) *n*-BuLi, ii) 3-(1-naphthyl)propionyl chloride, THF, −78°C. b) i) LDA, ii) benzyl (Bzl) bromoacetate, THF, −78°C → 0°C. c) i) H_2/Pd–C, EtOH, ii) morpholine, DEPC, NEt_3, THF, 0°C. d) LiOH, aqueous THF, 0°C.

Chart 1

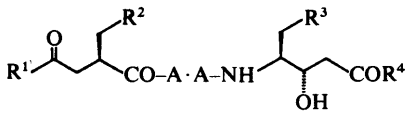


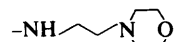
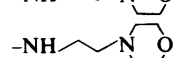
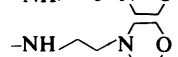
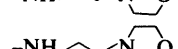
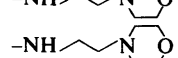
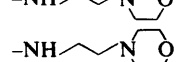
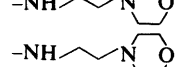
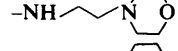
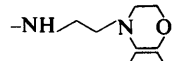
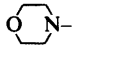
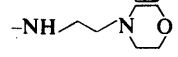
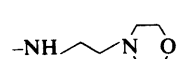
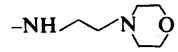
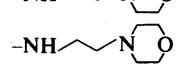
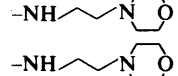
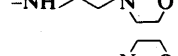
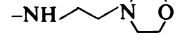
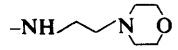
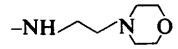
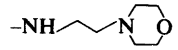
8 9 10 11

a) i) *N*,*N*′-carbonyldiimidazole, THF, ii) $(EtO_2CCH_2CO_2)_2Mg$ or $LiCH_2CO_2Et$. b) H_2(100 atm)/$RuBr_2$ [(*R*)-binap], EtOH, room temperature. c) i) KOH, aqueous dioxane, ii) H_2/Rh on Al_2O_3, EtOH.

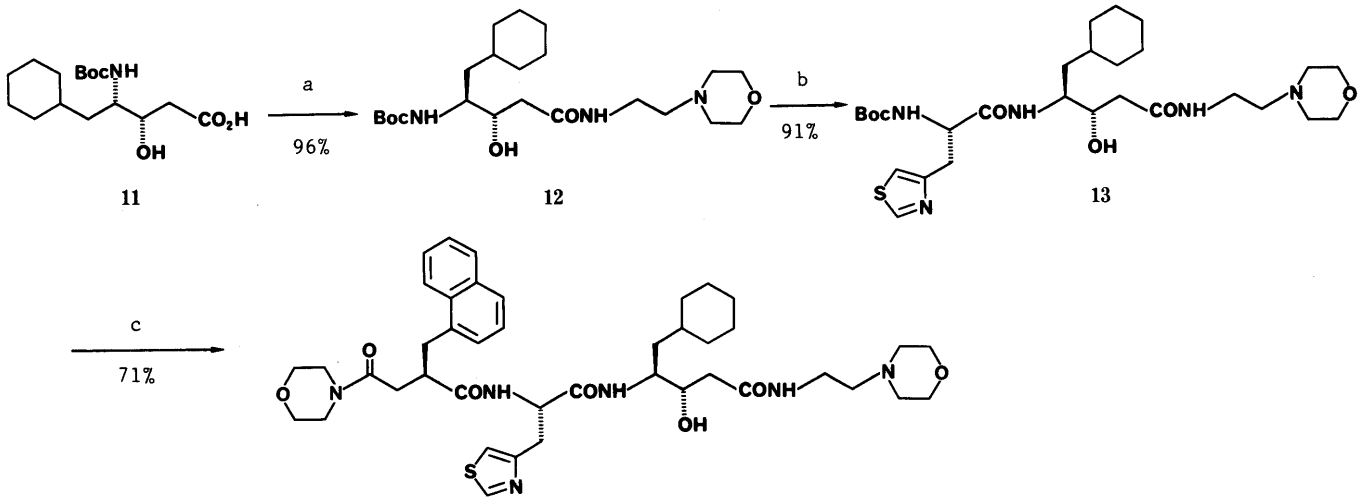
Chart 2

TABLE I. Structures and Renin Inhibitory Activities



No.	R^1	R^2	A-A	R^3	R^4	IC_{50} (nM)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	S
2		1-Naphthyl	Thia(L)[b]	Cyclohexyl		4.6	$C_{42}H_{58}N_6O_7S \cdot H_2O$	62.35 (62.09)	7.48 (7.39)	10.39 (10.25)	3.96 (3.74)
14		1-Naphthyl	His(L)	Cyclohexyl		20	$C_{42}H_{59}N_7O_7 \cdot 2.5H_2O$	61.59 (61.65)	7.88 (7.65)	11.97 (11.73)	— (—)
15		1-Naphthyl	Isox(L)[c]	Cyclohexyl		3.1	$C_{42}H_{57}N_6O_8 \cdot H_2O$	63.70 (63.75)	7.51 (7.19)	10.61 (10.41)	— (—)
16		1-Naphthyl	Thie(L)[d]	Cyclohexyl		16	$C_{43}H_{59}N_5O_7S \cdot 2.5H_2O$	61.85 (61.74)	7.73 (7.50)	8.39 (8.18)	3.84 (3.62)
17		1-Naphthyl	Phe(L)	Cyclohexyl		22	$C_{45}H_{61}N_5O_7 \cdot 2.5H_2O$	65.19 (65.06)	8.02 (7.87)	8.45 (8.25)	— (—)
18		1-Naphthyl	Leu(L)	Cyclohexyl		23	$C_{42}H_{63}N_5O_7 \cdot 2H_2O$	64.18 (63.82)	8.59 (8.31)	8.91 (8.81)	— (—)
19		1-Naphthyl[e]	Thia(L)	Cyclohexyl		>1000	$C_{42}H_{58}N_6O_7S \cdot H_2O$	62.35 (62.13)	7.48 (7.61)	10.39 (10.05)	3.96 (3.81)
20		Phenyl	Thia(L)	Cyclohexyl		50	$C_{38}H_{56}N_6O_7S \cdot 2H_2O$	58.74 (58.38)	7.78 (7.83)	10.82 (10.53)	4.13 (3.92)
21		1-Naphthyl	Thia(L)	Isopropyl		140	$C_{38}H_{52}N_6O_7S \cdot H_2O$	60.92 (60.75)	7.34 (7.23)	10.93 (10.75)	4.17 (4.02)
22		1-Naphthyl	Thia(L)	Phenyl		240	$C_{42}H_{52}N_6O_7S \cdot H_2O$	62.82 (62.68)	6.78 (6.52)	10.47 (10.41)	3.99 (3.63)
23		1-Naphthyl	Thia(L)	Cyclohexyl		5.2	$C_{46}H_{60}N_6O_6S \cdot 1.5H_2O$	64.84 (64.85)	7.45 (7.26)	9.86 (9.64)	3.76 (3.64)
24		1-Naphthyl	Thia(L)	Cyclohexyl		2.8	$C_{45}H_{64}N_6O_6S \cdot H_2O$	64.72 (64.52)	7.97 (7.81)	10.06 (9.81)	3.84 (3.92)
25		1-Naphthyl	Thia(L)	Cyclohexyl		1.5	$C_{46}H_{62}N_6O_6S \cdot H_2O$	65.38 (65.30)	7.63 (7.53)	9.94 (9.94)	3.79 (3.90)
26		1-Naphthyl	Thia(L)	Cyclohexyl		29	$C_{43}H_{61}N_7O_6S \cdot 2H_2O$	61.48 (61.56)	7.80 (7.82)	11.67 (11.52)	3.82 (3.87)
27		1-Naphthyl	Thia(DL)	Cyclohexyl		7.0	$C_{43}H_{60}N_6O_6S \cdot H_2O$	63.99 (63.85)	7.74 (7.78)	10.41 (10.68)	
28		1-Naphthyl	Thia(DL)	Cyclohexyl		9.0	$C_{42}H_{58}N_6O_6S_2 \cdot 2.5H_2O$	59.20 (59.23)	7.45 (7.22)	9.86 (9.66)	7.52 (7.82)
29		1-Naphthyl	Thia(DL)	Cyclohexyl		6.3	$C_{44}H_{62}N_6O_7S \cdot 4.5H_2O$	58.71 (58.73)	7.95 (7.72)	9.34 (9.51)	3.56 (3.60)
30		1-Naphthyl	Thia(DL)	Cyclohexyl		3.7	$C_{48}H_{63}N_7O_6S \cdot H_2O$	65.21 (65.36)	7.41 (7.51)	11.09 (11.22)	3.63 (3.39)
31		1-Naphthyl	Thia(DL)	Cyclohexyl		30	$C_{42}H_{58}N_6O_6S \cdot 2.5H_2O$	61.51 (61.42)	7.74 (7.39)	10.25 (10.29)	3.91 (3.75)
32	Et_2N–	1-Naphthyl	Thia(DL)	Cyclohexyl		13	$C_{42}H_{60}N_6O_6S \cdot 2.5H_2O$	61.36 (61.45)	7.97 (7.79)	10.22 (10.10)	3.90 (3.88)
33		1-Naphthyl	Thia(DL)	Cyclohexyl		14	$C_{45}H_{58}N_6O_6S \cdot 1.5H_2O$	64.49 (64.43)	7.34 (7.03)	10.03 (9.82)	3.83 (3.82)
34	n-C_3H_7NH–	1-Naphthyl	Thia(DL)	Cyclohexyl		66	$C_{41}H_{58}N_6O_6S \cdot 0.5H_2O$	63.79 (63.70)	7.70 (7.62)	10.89 (10.66)	4.15 (4.05)
35		1-Naphthyl	Thia(L)	Cyclohexyl		45	$C_{43}H_{61}N_7O_6S \cdot 3H_2O$	60.19 (60.02)	7.86 (7.53)	11.43 (11.16)	3.74 (4.00)
36		1-Naphthyl	Thia(L)	Cyclohexyl		8.0	$C_{43}H_{58}N_6O_7S \cdot 2H_2O$	61.55 (61.74)	7.45 (7.43)	10.02 (9.77)	3.82 (3.97)
37		1-Naphthyl	Thia(L)	Cyclohexyl		62	$C_{42}H_{58}N_6O_6S \cdot 4H_2O$	59.50 (59.21)	7.85 (7.55)	9.92 (9.68)	3.79 (4.00)
38		1-Naphthyl	Thia(DL)	Cyclohexyl		30	$C_{42}H_{60}N_6O_6S \cdot 2.5H_2O$	61.36 (61.49)	7.97 (7.74)	10.22 (9.94)	3.90 (3.60)
39		1-Naphthyl	Thia(DL)	Cyclohexyl		41	$C_{43}H_{60}N_6O_6S \cdot 1.5H_2O$	63.29 (63.50)	7.78 (7.58)	10.30 (10.07)	3.93 (3.70)
40		1-Naphthyl	Thia(DL)	Cyclohexyl		26	$C_{43}H_{60}N_6O_7S \cdot H_2O$	62.75 (62.73)	7.59 (7.56)	10.21 (10.04)	3.90 (3.61)

a) Inhibitory potencies IC_{50} were determined using sheep angiotensinogen, as reported previously. *b*) Thia = 3-(4-thiazolyl)alanine. *c*) Isox = 3-(5-isoxazolyl)-alanine. *d*) Thie = 3-(2-thienyl)alanine. *e*) 2(*S*)-(1-Naphthyl)methyl.



a) 2-(4-aminoethyl)morpholine, DEPC, NEt_3, THF, 0°C. b) i) 4 N HCl/dioxane, ii) *N*-Boc-3-(4-thiazolyl)-L-alanine, DEPC, NEt_3, THF, 0°C. c) i) 4 N HCl/dioxane, ii) **7**, DEPC, NEt_3, THF, 0°C.

Chart 3

cal, straightforward, and stereoselective synthetic route to dipeptide renin inhibitors was accomplished. Most of the inhibitors listed in Table I were synthesized by essentially the same methods.

Biological Results and Discussion

Structure–activity relationships for this novel dipeptide series of renin inhibitors were examined. The renin inhibitory potencies of the compounds were measured with a human renin-sheep substrate assay system, and the IC_{50} values are summarized in Table I. Compounds **14**—**18** explore the variation of the amino acid moiety (A-A). Among them, inhibitors that contain 3-(4-thiazolyl)-L-alanine (**2**) and 3-(5-isoxazolyl)-L-alanine (**15**) are more potent than the histidine-containing inhibitor (**14**), and they are superior in terms of ease of purification and higher yield of the inhibitors. We therefore proceeded with several A-A = Thia (Thia = 3-(4-thiazolyl)-L-alanine) inhibitors, because resubstitution of His with Thia gives a nearly 5-fold more potent inhibitor. Replacement of the 2(*R*)-(1-naphthyl)methyl group with a 2(*S*)-isomer (**19**) resulted in a remarkable loss of activity. The effect of replacing the 1-naphthyl ring by a phenyl ring, compound **20**, was a *ca.* 10-fold loss of activity. These results suggest that the stereochemistry of the asymmetric center in the N-terminal element is very important. Reduced potency is generally observed for significant changes in the P_1 site. Namely, replacement of ACHPA with statine (**21**) or (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) (**22**) causes a loss of activity. Structure–activity relationships at the N-terminal elements were demonstrated with compounds **23**—**34**. The replacement of the 4-(2-aminoethyl)-morpholine group by other polar amino groups (compounds **35**—**40**) did not seriously affect the potency.

Among these dipeptide inhibitors, we examined the biological effects of oral administration using salt-depleted marmosets. Oral administrations of compounds **2** (ES 6864), **15**, and **27** were investigated, and the percent inhibition of plasma renin activity (PRA) was measured 0.5, 1, 2, 3, and 5 h after administration of test compounds to salt-depleted marmosets at a dose of 3 mg/kg (Table II). These compounds inhibited PRA more than 80% after 1 h. The longest duration was observed with ES 6864. In a previous *in vivo* evaluation of ES 6864, a corresponding inhibition of PRA and a reduction of blood pressure at doses of 3, 10, and 30 mg/kg were found.[18] Mean blood pressure tended to decrease at ES 6864 doses of 3 and 10 mg/kg. At a dose of 30 mg/kg, mean blood pressure decreased significantly, and it remained lowered for 5 h.

TABLE II. *In Vivo* Plasma Renin Inhibition in Salt-Depleted Marmosets[a]

Compound	Dose (mg/kg)	% inhibition of PRA[b]				
		0.5	1	2	3	5 (h)
2 (ES 6864)	3	69±12	83±10	61±15	79±1	66±6
15	3	95	95	85	51	0
27	3	91	83	35	0	0

a) The *in vivo* test procedures were carried out as described in the experimental section. *b*) Tabulated results indicate the percent inhibition of plasma renin activity measured 0.5, 1, 2, 3, and 5 h after administration of the test compound to salt-depleted marmosets.

ES 6864 was resistant to the proteolytic actions of the enzymes in rat tissue homogenates (liver, kidney, pancreas, and small intestine), but it was degraded by about 20% by liver homogenate in a 1 h incubation period. Furthermore, ES 6864 did not inhibit cathepsin D, pepsin, trypsin, chymotrypsin, angiotensin converting enzyme (ACE), or urinary kallikrein at a concentration of 10^{-5} M.

In conclusion, structure–activity studies with tripeptide ES 254 as a starting material led to the dipeptide inhibitor ES 6864. This compound was a very potent inhibitor of human renin, and effectively inhibited PRA and lowered blood pressure after oral administration at doses of 3—30 mg/kg. Further investigations are in progress.

Experimental

Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO A-302 or Nic 5SXC FT IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in deuteriochloroform, with tetramethylsilane as an internal reference with a JEOL JNM-

GX 270 FT NMR spectrometer. Mass spectra (MS) were obtained with a JEOL JMS-01SG or JMS-D300 mass spectrometer. Column chromatography was done on Kieselgel 60 F_{254} (Merck, 70—230 mesh). In general, reactions were carried out under a nitrogen stream.

***N*-(*tert*-Butoxycarbonyl)-3-(4-thiazolyl)-L-alanine** 3-(4-Thiazolyl)-DL-alanine dihydrochloride[7a] (10.00 g, 40.8 mmol) was dissolved in 1 N NaOH (122.4 ml), and then acetic anhydride (4.23 ml, 44.8 mmol) and 1 N NaOH (44.8 ml) were added to the solution at 0 °C. After stirring for 2 h, this solution was adjusted to pH 7.5 with 1 N NaOH and acylase (1.00 g) was added to this solution. After stirring for 3 d at 37 °C, this reaction mixture was filtered through Celite, then dioxane (300 ml) and triethylamine (2.85 ml, 20.4 mmol) were added to the filtrate. To this solution, di-*tert*-butyl dicarbonate (4.91 g, 22.5 mmol) was added at 0 °C. This reaction mixture was stirred overnight and washed with AcOEt, and the aqueous layer was adjusted to pH 2 with 10% citric acid at 0 °C. This solution was extracted with AcOEt and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Elution with 5—10% MeOH in CH_2Cl_2 (v/v) afforded *N*-(*tert*-butoxycarbonyl)-3-(4-thiazolyl)-L-alanine (5.13 g, 47%) as crystals. mp 111—113 °C, $[\alpha]_D^{20}$ −4.5° (c=1, MeOH). *Anal.* Calcd for $C_{11}H_{16}NO_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.77. Found : C, 48.40; H, 6.09; N, 9.96; S, 11.80. IR (KBr): 1698, 1684 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H), 3.25—3.65 (m, 2H), 4.56 (m, 1H), 5.58 (br s, 1H), 7.13 (s, 1H), 8.90 (s, 1H). MS m/z: 272 (M^+), 127, 99, 57.

The enantiomeric excess was determined to be >98% by HPLC analysis of the corresponding methyl ester (column, CHIRALCEL OC (Daicel) 4.6 × 250 mm; eluent, 85 : 15 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of L-form, 16.5 min; t_R of D-form, 20.2 min).

4(*S*)-Isopropyl-3-[3-(1-naphthyl)-1-oxopropyl]-2-oxazolidinone (4) A solution of 4(*S*)-isopropyl-2-oxazolidinone **3** (10.75 g, 83.2 mmol) in dry tetrahydrofuran (THF) (200 ml) was added dropwise to *n*-BuLi (1.6 M solution in *n*-hexane, 62.4 ml) at −78 °C under nitrogen. The mixture was stirred for 30 min, then a solution of 3-(1-naphthyl)propionyl chloride (21.82 g, 99.9 mmol) in dry THF (100 ml) was added dropwise over a period of 10 min. This reaction mixture was stirred for 1 h. Next, the reaction mixture was quenched by the addition of 1 N HCl (100 ml) and brine (100 ml). This solution was extracted with AcOEt and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography. Elution with 10—20% AcOEt in *n*-hexane (v/v) afforded **4** (23.19 g, 82%) as crystals. Recrystallization from isopropyl ether gave an analytical sample, mp 80—82 °C, $[\alpha]_D^{20}$ +61.3° (c=1, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.28; H, 6.74; N, 4.47. IR (Nujol): 1770, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.85 and 0.90 (d, each 3H, J=7 Hz), 2.39 (m, 1H), 3.3—3.6 (m, 4H), 4.20 (m, 2H), 4.43 (m, 1H), 7.3—8.2 (m, 5H). MS m/z: 311 (M^+), 154, 141.

3-[3-Benzyloxycarbonyl-2(*R*)-(1-naphthyl)methyl-1-oxopropyl]-4(*S*)-isopropyl-2-oxazolidinone (5) A solution of **4** (10.00 g, 32.1 mmol) in dry THF (50 ml) was added to a stirred solution of lithium diisopropylamide (LDA) (prepared from diisopropylamine (5.4 ml) and *n*-BuLi (1.6 M solution in *n*-hexane, 22.06 ml)) at −78 °C. The mixture was stirred for 1 h, and then a solution of benzyl bromoacetate (15.26 ml, 96.3 mmol) in dry THF (50 ml) was added. The reaction mixture was stirred for 5 h at −78 °C→0 °C. After neutralization with 1 N HCl and brine, this solution was extracted with AcOEt and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography. Elution with 10—20% AcOEt in *n*-hexane (v/v) afforded **5** (9.45 g, 64%) as crystals. Recrystallization from ethyl ether gave an analytical sample, mp 145—146 °C, $[\alpha]_D^{20}$ +79.8° (c=1, $CHCl_3$). *Anal.* Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 72.77; H, 6.06; N, 3.04. IR (Nujol): 1770, 1730, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 and 0.85 (d, each 3H, J=7 Hz), 2.27 (m, 1H), 2.40 (dd, 1H, J=16.9, 4.6 Hz), 3.02 (dd, 1H, J=16.9, 10.3 Hz), 3.15 (dd, 1H, J=13.5, 8.6 Hz), 3.51 (dd, 1H, J=13.5, 7.3 Hz), 3.82 (dd, 1H, J=8.8, 8.8 Hz), 4.05 (dd, 1H, J=8.8, 2.4 Hz), 4.20 (m, 1H), 4.79 (m, 1H), 5.03 (ABq, 2H, J=12.5 Hz, Δ=0.06 ppm), 7.2—8.3 (m, 12H). MS m/z: 459 (M^+), 368, 221, 130, 91.

The diastereomeric ratio was determined to be 95 : 5 by HPLC analysis (column, Senshu Pak ODS-1251-SH 4.6 × 250 mm; eluent, 65 : 35 CH_3CN–H_2O mixture; flow rate, 1.0 ml/min; t_R of **5**, 20.4 min; t_R of the 2(*S*)-isomer, 23.3 min).

Independent Preparation and Separation of 5 and Its Diastereomer 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.12 ml, 0.80 mmol) was added to a solution of **5** (180 mg, 0.39 mmol) in dry benzene (5 ml), and this solution was refluxed for 6 h. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Separation of the two isomers was achieved by HPLC under the above conditions, and the ratio of **5** and its diastereomer was 3.3 : 1.

4(*S*)-Isopropyl-3-[4-morpholino-2(*R*)-(1-naphthyl)methyl-1,4-dioxobutyl]-2-oxazolidinone (6) The benzyl ester **5** (1.80 g, 3.92 mmol) in EtOH (180 ml) was hydrogenated with 10% Pd–C (500 mg) at room temperature under a hydrogen atmosphere overnight. Filtration and removal of the solvent gave the carboxylic acid. This product was dissolved in dry THF (100 ml). To this solution, morpholine (0.57 ml, 4.47 mmol), DEPC (0.72 ml, 4.47 mmol), and triethylamine (0.66 ml, 4.73 mmol) were added dropwise under nitrogen at 0 °C. The reaction mixture was stirred for 2 h at the same temperature. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Elution with 20—30% AcOEt in *n*-hexane (v/v) afforded **6** (1.67 g, 97%) as crystals. Recrystallization from isopropyl ether gave an analytical sample, mp 127—129 °C, $[\alpha]_D^{20}$ +99.4° (c=1, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.33; H, 6.70; N, 6.42. IR (Nujol): 1760, 1700, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 and 0.91 (d, each 3H, J=7 Hz), 2.28 (dd, 1H, J=16.2, 4.4 Hz), 2.34 (m, 1H), 2.94 (dd, 1H, J=16.2, 10.4 Hz), 3.16 (dd, 1H, J=13.4, 9.0 Hz), 3.1—3.7 (m, 9H), 3.82 (dd, 1H, J=9.0, 9.0 Hz), 4.06 (dd, 1H, J=9.0, 2.6 Hz), 4.20 (m, 1H), 4.83 (m, 1H), 7.3—8.3 (m, 7H). MS m/z: 438 (M^+), 310, 129.

3-Morpholinocarbonyl-2(*R*)-(1-naphthyl)methylpropionic Acid (7) The amide **6** (3.87 g, 8.83 mmol) was dissolved in aqueous THF (20% H_2O in THF (v/v), 100 ml). Next, lithium hydroxide monohydrate (741 mg, 17.7 mmol) was added at 0 °C, and the solution was stirred for 3 h. The solvent was removed *in vacuo* and the residue was dissolved in 10% NaOH. This solution was washed with CH_2Cl_2, and then the aqueous layer was acidified with ice-cold 1 N HCl. This solution was extracted with CH_2Cl_2 and the extract was dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography. Elution with 5—10% MeOH in CH_2Cl_2 (v/v) afforded **7** (2.40 g, 83%) as an amorphous solid. $[\alpha]_D^{20}$ −37.9° (c=1, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.88; H, 6.41; N, 4.45. IR ($CHCl_3$): 1710, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.34—2.71 (m, 2H), 3.15—3.73 (m, 11H), 7.25—8.14 (m, 7H). MS m/z: 327 (M^+), 240, 141.

The enantiomeric excess of **7** was determined to be >98% by HPLC analysis of the corresponding methyl ester (column, CHIRALCEL OC (Daicel) 4.6 × 250 mm; eluent, 50 : 50 *n*-hexane–2-propanol mixture; flow rate, 1.5 ml/min; t_R of methyl ester of **7**, 13.1 min; t_R of the 2(*S*)-isomer, 21.2 min).

The authentic enantiomer of **7** was synthesized in the same manner, starting from (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone as the chiral auxiliary.

(4*S*)-4-(*N*-*tert*-Butoxycarbonyl)amino-3-oxo-5-phenylpentanoic Acid Ethyl Ester (9) A solution of *N*,*N*′-carbonyldiimidazole (6.72 g, 41.4 mmol) in dry THF (30 ml) was added to a solution of *N*-(*tert*-butoxycarbonyl)-L-phenylalanine (10.00 g, 37.7 mmol) in dry THF (20 ml), and this reaction mixture was stirred for 30 min. To this solution, magnesium ethyl malonate in dry THF solution and dimethyl sulfoxide (80 ml) were added and the whole was stirred for 4 h at room temperature. After acidification with 1 N HCl, this solution was extracted with ethyl ether. The organic layer was washed with water, saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography. Elution with 10—15% AcOEt in *n*-hexane (v/v) afforded **9** (9.80 g, 78%) as crystals. Recrystallization from *n*-hexane gave an analytical sample, mp 64—65 °C, $[\alpha]_D^{20}$ −58.5° (c=1, MeOH). *Anal.* Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.21; H, 7.31; N, 4.14. IR (KBr): 1747, 1723, 1684 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 3H, J=7 Hz), 1.40 (s, 9H), 2.98 (dd, 1H, J=14, 8 Hz), 3.15 (dd, 1H, J=14, 6 Hz), 3.47 (ABq, 2H, J=16 Hz, Δ=0.05 ppm), 4.17 (q, 2H, J=7 Hz), 4.57 (m, 1H), 5.03 (br d, 1H), 7.1—7.4 (m, 5H). MS m/z: 335 (M^+), 120, 57.

(3*S*,4*S*)-4-(*N*-*tert*-Butoxycarbonyl)amino-3-hydroxy-5-phenylpentanoic Acid Ethyl Ester (10) A solution of **9** (20.00 g, 59.7 mmol) in degassed anhydrous EtOH (40 ml) was placed in an 80 ml Schlenk tube and degassed by means of three freeze-thaw cycles. $RuBr_2$[(*R*)-binap] (100 mg, 0.113 mmol) was then added to this solution under argon, and the catalyst was dissolved with the aid of an ultrasonicator. The resulting light brown solution was degassed by means of two freeze-thaw cycles. Using a cannula, this was then transferred to a glass vessel placed in a 100 ml stainless steel autoclave. Hydrogen was introduced to 100 atm, and the solution was stirred at 20 °C for 145 h. The solvent was removed under reduced pressure, and the remaining solid was purified by silica gel column chromatography. Elution with 50% AcOEt in *n*-hexane (v/v) afforded **10** (19.5 g, 97%) as a >99 : 1 (3*S*,4*S*)–(3*R*,4*S*) mixture. Recrystallization from *n*-hexane gave an analytical sample, mp 88—89 °C, $[\alpha]_D^{20}$ −36.9° (c=

1, MeOH). *Anal.* Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.88; H, 7.99; N, 4.18. IR (KBr): 1730, 1682 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, 3H, J=7 Hz), 1.41 (s, 9H), 2.37 (dd, 1H, J=17, 3 Hz), 2.59 (dd, 1H, J=17, 10 Hz), 2.91 (d, 2H, J=8 Hz), 3.48 (br s, 1H), 3.73 (m, 1H), 3.99 (m, 1H), 4.13 (q, 2H, J=7 Hz), 4.94 (br d, 1H), 7.15—7.35 (m, 5H). MS m/z: 338 (M^++1), 246, 146, 100, 57.

The diastereomeric ratio was determined to be >99:1 by HPLC analysis (column, Senshu Pak ODS-1251-SH 4.6×250 mm; eluent, 55:45 H_2O–CH_3CN mixture; flow rate, 1.0 ml/min; t_R of (3*S*,4*S*), 18.6 min; t_R of (3*R*,4*S*), 15.8 min).

The enantiomeric excess of **9** was determined to be 99% ee by HPLC analysis of the corresponding 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) derivatives. The hydrogenation product was converted to the corresponding free base by trifluoroacetic acid treatment and condensed with GITC by a reported method.[17] The resulting thiourea was analyzed as a 99.5:0.5 diastereomeric mixture by HPLC analysis (column, Senshu Pak Silica-1251-N; eluent, 93:7 *n*-hexane–2-propanol mixture; flow rate, 1.0 ml/min; t_R of (3*S*,4*S*)-isomer, 12.7 min; t_R of (3*R*,4*R*)-isomer, 10.9 min).

(3*S*,4*S*)-4-(*N*-*tert*-Butoxycarbonyl)amino-5-cyclohexyl-3-hydroxypentanoic Acid (11) The ester **10** (10.00 g, 29.6 mmol) was dissolved in 20% H_2O in dioxane (v/v) (300 ml). To this solution, potassium hydroxide (8.31 g, 0.15 mol) in aqueous solution was added at 0 °C. The reaction mixture was stirred for 8 h. The solvent was removed *in vacuo*, and the resulting solid was dissolved in 1 N NaOH. The aqueous solution was washed with ethyl ether, and then acidified with 10% citric acid. A white precipitate was extracted with ethyl ether and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the resulting oil was triturated with *n*-hexane, giving (3*S*,4*S*)-*N*-Boc-4-amino-3-hydroxy-5-phenylpentanoic acid (8.80 g, 96%) as a white powder. This acid was hydrogenated in EtOH (200 ml) with 5% Rh on Al_2O_3 (1.0 g) for 16 h at 4—5 atm of H_2. The reaction mixture was filtered through Celite, and the filtrate was removed *in vacuo*. The resulting solid was crystallized from *n*-hexane, giving **11** (8.60 g, 92% from **10**) as white crystals. mp 108—110 °C, $[\alpha]_D^{20}$ −36.7° (c=1, MeOH). *Anal.* Calcd for $C_{16}H_{29}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 60.65; H, 9.15; N, 4.36. IR (KBr): 1722, 1667 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—2.0 (m, 13H), 1.45 (s, 9H), 2.55 (m, 2H), 3.65 (m, 1H), 4.00 (m, 1H), 4.81 (d, 1H, J=9.5 Hz), 5.84 (d, 1H, J=9.5 Hz). MS m/z: 316 (M^++1), 170, 126, 57.

(3*S*,4*S*)-4-(*N*-*tert*-Butoxycarbonyl)amino-5-cyclohexyl-3-hydroxy-*N*-(2-morpholinoethyl)pentanamide (12) **11** (5.00 g, 15.9 mmol) and 4-(2-aminoethyl)morpholine (2.29 ml, 17.4 mmol) were dissolved in dry THF (100 ml). To this solution, DEPC (2.65 ml, 17.5 mmol) and triethylamine (2.43 ml, 17.4 mmol) were added dropwise under nitrogen at 0 °C. The reaction mixture was stirred for 6 h at the same temperature. After 6 h, the solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Elution with 5—10% MeOH in CH_2Cl_2 (v/v) afforded **12** (6.49 g, 96%) as crystals. Recrystallization from isopropyl ether gave an analytical sample, mp 50—53 °C. $[\alpha]_D^{20}$ −38.2° (c=1, MeOH). *Anal.* Calcd for $C_{22}H_{41}N_3O_5$: C, 61.80; H, 9.67; N, 9.83. Found: C, 61.47; H, 9.64; N, 9.51. IR (KBr): 1710, 1689, 1647 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.9 (m, 13H), 1.45 (s, 9H), 2.2—2.7 (m, 8H), 3.37 (m, 2H), 3.55—3.80 (m, 6H), 3.95 (br d, 1H), 4.75 (br d, 1H), 6.25 (br s, 1H). MS m/z: 427 (M^+), 201, 100.

(3*S*,4*S*)-4-[*N*-Boc-3-(4-thiazolyl)-L-alanyl]amino-5-cyclohexyl-3-hydroxy-*N*-(2-morpholinoethyl)pentanamide (13) The amide **12** (3.00 g, 7.02 mmol) was added to 4 N HCl/dioxane solution (40 ml), and this solution was stirred for 30 min under nitrogen at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with diethyl ether. The residue was dried *in vacuo* for 8 h. This solid was suspended in dry THF (50 ml). To this solution, *N*-Boc-3-(4-thiazolyl)-L-alanine (2.10 g, 7.71 mmol), DEPC (1.17 ml, 7.71 mmol), and triethylamine (3.23 ml, 23.2 mmol) were added at 0 °C under nitrogen. The reaction mixture was stirred for 6 h at the same temperature, then the solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography. Elution with 5—10% MeOH in CH_2Cl_2 (v/v) afforded **13** (3.72 g, 91%) as crystals. Recrystallization from isopropyl ether gave an analytical sample, mp 106—109 °C, $[\alpha]_D^{20}$ −33.0° (c=1, MeOH). *Anal.* Calcd for $C_{28}H_{47}N_5O_6S \cdot 0.5\ H_2O$: C, 56.92; H, 8.19; N, 11.85; S, 5.42. Found: C, 57.25; H, 8.16; N, 11.45; S, 5.54. IR (KBr): 1687, 1675, 1632 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.8 (m, 13H), 1.44 (s, 9H), 2.16 (dd, 1H, J=15.0, 2.9 Hz), 2.3—2.6 (m, 7H), 3.15—3.50 (m, 4H), 3.65—3.80 (m, 4H), 3.8—4.0 (m, 2H), 4.43 (m, 1H), 6.38 (br s, 1H), 6.48 (br d, 2H), 7.12 (d, 1H, J=2.2 Hz), 8.79 (d, 1H, J=2.2 Hz). MS m/z: 581 (M^+), 201, 113, 100.

(3*S*,4*S*)-5-Cyclohexyl-3-hydroxy-4-{*N*-[2(*R*)-(1-naphthyl)methyl-3-morpholinocarbonylpropionyl]-3-(4-thiazolyl)-L-alanyl}amino-*N*-(2-morpholinoethyl)pentanamide (ES 6864) (2) Compound **13** (200 mg, 0.34 mmol) was added to 4 N HCl/dioxane solution (5 ml), and this solution was stirred for 30 min under nitrogen at room temperature. The solvent was removed *in vacuo*, and the remaining solid was evaporated with diethyl ether. The residue was dried *in vacuo* for 8 h, then suspended in dry THF (10 ml). To this suspension, the carboxylic acid **7** (113 mg, 0.35 mmol), DEPC (0.06 ml, 0.35 mmol), and triethylamine (0.21 ml, 1.51 mmol) were added at 0 °C under nitrogen. The reaction mixture was stirred for 8 h at the same temperature. The solvent was removed *in vacuo*, and the residue was purified by preparative thin layer chromatography (CH_2Cl_2: MeOH=10:1). The obtained solid was crystallized from isopropyl ether to afforded **2** (193 mg, 71%) as crystals. mp 78—81 °C, $[\alpha]_D^{20}$ −23.0° (c=1, MeOH). *Anal.* Calcd for $C_{42}H_{58}N_6O_7S \cdot H_2O$: C, 62.35; H, 7.48; N, 10.39; S, 3.96. Found: C, 62.09; H, 7.39; N, 10.25; S, 3.74. IR (KBr): 1647 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.9 (m, 13H), 2.1—2.8 (m, 10H), 3.0—4.1 (m, 12H), 4.68 (m, 1H), 6.85 (br s, 3H), 7.17 (d, 1H, J=2.2 Hz), 7.2—8.3 (m, 7H), 8.67 (d, 1H, J=2.2 Hz). MS m/z: 772 (M^++1−H_2O), 573, 349, 141, 113, 100.

***In Vivo* Activity** Male marmosets (270—380 g) were fed only fruit for 7—10 d before the experiment. The animals were anesthetized with Saffan (Glaxo), 24 mg/kg i.m., and the left femoral artery was cannulated. The other end of the cannula was led under the skin and exteriorized at the root of the tail. The end of the cannula was closed by applying heat, and furosemide 10 mg/kg i.m. was administered. The next day each animal was placed in a Bollman cage. The femoral cannula was connected to a pressure transducer (Nihon Kohden, TP-200T) to measure blood pressure. An animal was allowed 3 h for the blood pressure to stabilize. Blood samples for PRA assay were collected at 30 min before and 0.5, 1, 2, 3, 5 h after the drug was administered by gavage at a dose of 3 mg/kg. PRA was determined with a kit purchased from Dainabot Labs.

Acknowledgement We are grateful to Prof. Tatsuo Kokubu and Prof. Kunio Hiwada for useful discussions throughout this work.

References and Notes

1) J. Boger, *Trans. Pharmacol. Sci.*, **8**, 370 (1987); W. J. Greenlee, *Pharm. Res.*, **4**, 364 (1987), and references cited therein.
2) *a*) K. Poulsen, J. Burton and E. Haber, *Biochemistry*, **12**, 3877 (1973); *b*) J. Burton, K. Poulsen and E. Haber, *ibid.*, **14**, 3892 (1975); *c*) K. Poulsen, E. Haber and J. Burton, *J. Biochim. Biophys. Acta*, **452**, 533 (1976); *d*) R. J. Cody, J. Burton, G. Evin, K. Poulsen, J. A. Herd and E. Haber, *Biochem. Biophys. Res. Commun.*, **97**, 230 (1980).
3) *a*) M. G. Bock, R. M. DiPardo, B. E. Evans, K. E. Rittle, J. S. Boger, R. M. Freidinger and D. F. Veber, *J. Chem. Soc., Chem. Commun.*, **1985**, 109; *b*) H. L. Sham, C. A. Rempel, H. Stein and J. Cohen, *ibid.*, **1987**, 683; *c*) K. Y. Hui, W. D. Carlson, M. S. Bernatowicz and E. Haber, *J. Med. Chem.*, **30**, 1287 (1987); *d*) M. G. Bock, R. M. DiPardo, B. E. Evans, K. E. Rittle, J. Boger, M. Poe, B. I. LaMont, R. J. Lynch, E. H. Ulm, G. P. Vlasuk, W. J. Greenlee and D. F. Veber, *ibid.*, **30**, 1853 (1987); *e*) J. Maibaum and D. H. Rich, *ibid.*, **31**, 625 (1988).
4) *a*) S. Thaisrivongs, D. T. Pals, L. T. Kroll, S. R. Turner and F-S. Han, *J. Med. Chem.*, **30**, 976 (1987); *b*) D. J. Kempf, E. de Lara, H. H. Stein, J. Cohen and J. J. Plattner, *ibid.*, **30**, 1978 (1987).
5) R. Matsueda, Y. Yabe, H. Kogen, S. Higashida, H. Koike, Y. Iijima, T. Kokubu, K. Hiwada, E. Murakami and Y. Imamura, *Chem. Lett.*, **1985**, 1041.
6) *a*) K. Iizuka, T. Kamijo, T. Kubota, K. Akahane, H. Umeyama and Y. Kiso, *J. Med. Chem.*, **31**, 701 (1988); *b*) K. Iizuka, T. Kamijo, H. Harada, K. Akahane, T. Kubota, I. Shimaoka, H. Umeyama and Y. Kiso, *Chem. Pharm. Bull.*, **36**, 2278 (1988).
7) *a*) H. Watanabe, S. Kuwata, T. Sakata and K. Matsumura, *Bull. Chem. Soc. Jpn.*, **39**, 2473 (1966); *b*) S. H. Rosenberg, J. J. Plattner, K. W. Woods, H. H. Stein, P. A. Marcotte, J. Cohen and T. J. Perun, *J. Med. Chem.*, **30**, 1224 (1987).
8) *a*) S. Thaisrivongs, D. T. Pals, D. W. Harris, W. M. Kati and S. R. Turner, *J. Med. Chem.*, **29**, 2088 (1986); *b*) S. Thaisrivongs, D. T. Pals, J. A. Lawson, S. R. Turner and D. W. Harris, *ibid.*, **30**, 536 (1987); *c*) D. Nisato, C. Lacour, A. Roccon, R. Gayrand, C. Cazaubon and C. Carlet, *J. Hypertens.* **5** (Suppl. 5), S23—S25 (1987); *d*) S. Thaisrivongs, D. T. Pals, S. R. Turner and L. T. Kroll, *J. Med. Chem.*, **31**, 1369 (1988); *e*) P. Bühlmayer, A. Caselli, W. Fuhren, R. Göschke, V. Rasetti, H. Rüeger, J. L. Stanton, L. Criscione and J. M.

Wood, *ibid.*, **31**, 1839 (1988); *f*) J. J. Plattner, P. A. Marcotte, H. D. Kleinert, H. H. Stein, J. Greer, G. Bolis, A. K. L. Fung, B. A. Bopp, J. R. Luly, H. L. Sham, D. J. Kempf, S. H. Rosenberg, J. F. Dellaria, B. De, I. Merits and T. J. Perun, *ibid.*, **31**, 2277 (1988); *g*) T. M. Zydowsky, J. F. Dellaria, Jr. and H. N. Nellans, *J. Org. Chem.*, **53**, 5607 (1988).
9) T. Nishi, M. Sakurai, S. Sato, M. Kataoka and Y. Morisawa, *Chem. Pharm. Bull.*, **37**, 2200 (1989).
10) D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, **104**, 1737 (1982).
11) S. Yamada, Y. Kasai and T. Shioiri, *Tetrahedron Lett.*, **1973**, 1595.
12) H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, H. Hamada and T. Takeuchi, *J. Antibiot.*, **23**, 259 (1970).
13) J. Boger, L. S. Payne, D. S. Perlow, N. S. Lohr, M. Poe, E. H. Blaine, E. H. Ulm, T. W. Schorn, B. I. LaMont, T-Y. Lin, M. Kawai, D. H. Rich and D. F. Veber, *J. Med. Chem.*, **28**, 1779 (1985).
14) H. Kogen and T. Nishi, *J. Chem. Soc., Chem. Commun.*, **1987**, 311.
15) T. Nishi, M. Kitamura, T. Ohkuma and R. Noyori, *Tetrahedron Lett.*, **29**, 6327 (1988).
16) H. Yanagisawa, T. Kanazaki and T. Nishi, *Chem. Lett.*, **1989**, 687.
17) *a*) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta and H. Takaya, *J. Am. Chem. Soc.*, **108**, 7117 (1986); *b*) T. Ohta, H. Takaya and R. Noyori, *Inorg. Chem.*, **27**, 566 (1988).
18) K. Hiwada, T. Kokubu, E. Murakami, S. Muneta, Y. Morisawa, Y. Yabe, H. Koike and Y. Iijima, *Hypertension*, **11**, 708 (1988).