Renin Inhibitors. III. Synthesis and Structure–Activity Relationships of Transition-State Inhibitors Containing Dihydroxyethylene Isostere at the P_1–$P_{1'}$ Site[1)]

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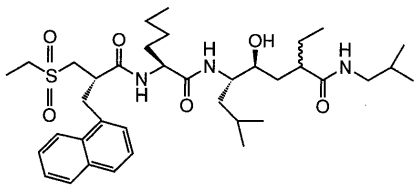
The design, synthesis and structure–activity relationships of transition-state inhibitors containing the dihydroxyethylene isostere at the scissile site are described. The compounds with (2*S*,3*R*,4*S*)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol at the P_1–$P_{1'}$ site are potent renin inhibitors. (2*S*,3*R*,4*S*)-4-[*N*-[(2*S*)-3-Ethylsulfonyl-2-(1-naphthylmethyl)propionyl]-L-norleucyl]amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (2) (BW-175), which is the most potent inhibitor (IC_{50}: 3.3 nM against human renin) in this series, poorly inhibits cathepsin D (IC_{50}: 26000 nM) and pepsin (IC_{50}: >100000 nM), and thus it is specific for renin. Compound 2 contains only one amino acid and showed an oral bioavailability of 2.8% at 10 mg/kg and 9.7% at 30 mg/kg in rats. The interaction between renin and inhibitor 2 is discussed on the basis of molecular modeling studies.

Keywords renin inhibitor; antihypertensive agent; dihydroxyethylene isostere; structure–activity relationship

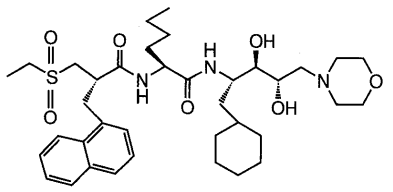
The renin-angiotensin system (RAS) plays a central role in the regulation of blood pressure. Renin is an aspartic protease which catalyzes the first and rate-limiting step in the RAS, and angiotensinogen is the only known natural substrate of renin. Therefore, in principle, renin inhibitors could be better antihypertensive agents than inhibitors of angiotensin converting enzyme, which hydrolyzes several natural substrates. While a large number of renin inhibitors have been investigated,[2)] none have good oral bioavailability with a long duration of action.

We have reported that compound **1** (BW-146), containing a homostatine analogue at the P_1–$P_{1'}$ site, is a potent renin inhibitor *in vitro*, but it has low oral bioavailability (0.73% at 8.4 mg/kg in rats).[1)] As a result of further investigation involving modification at the C-terminus in **1**, we developed a novel renin inhibitor **2** (BW-175), which is a non-peptide, orally active, low-molecular-weight inhibitor with a dihyroxyethylene isostere, (2*S*,3*R*,4*S*)-4-amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (ACMP), as the C-terminal fragment (Fig. 1).[3)] In this paper, we describe the design, synthesis and structure–activity relationships of renin inhibitors which contain the dihydroxyethylene isostere at the P_1–$P_{1'}$ site.[4)]

The literature describing potent renin inhibitors which have leucinal[5)] or difluorostatone[6)] at the scissile site of the substrate prompted us to synthesize peptide diketones such as compound **6**. Aldehyde and difluoroketone were postulated to bind renin as the corresponding hydrated form B, as shown in Fig. 2. The hydrated form B was thought to mimic the tetrahedral intermediate during the hydrolysis of the amide bonds.[7)] Difluorostatone derivatives are more potent than statone derivatives, due to the electron-withdrawing fluorine atom, which facilitates the hydration of the ketone. In addition, Angelastro *et al.*[8)] demonstrated that the carbonyl group proximal to nitrogen in the α-diketone **3**, which is a potent inhibitor of α-chymotrypsin, undergoes hydration in dimethyl sulfoxide-d_6 (DMSO-d_6) with added D_2O, using ^{13}C-NMR. Therefore, we designed the α-diketo derivative **6** as a renin inhibitor. On the other hand, Hanson *et al.*[9)] and Matsueda *et al.*[5b)] reported that peptide diols such as compounds **4** and **5** showed inhibitory activities against

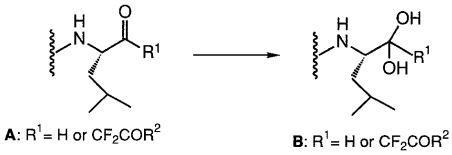


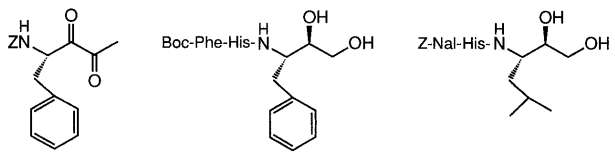
1 (BW-146)



2 (BW-175)

Fig. 1





3 **4** **5**

Fig. 2

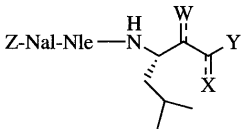
renin with the IC_{50} values of 5.2 and 2.6 μM, respectively. The diol group in **4** and **5** was thought to be bioisosteric with aldehyde. For that reason, the α-diol **8** was also synthesized. As shown in Table I, compound **6** wealky inhibited renin, with an IC_{50} of 5.6 μM, and its derivative, the α-hydroxyketone **7**, was slightly more potent. The α-diol compound **8** was the most potent inhibitor, with an IC_{50} of 0.46 μM, among these three isosteres. A similar result was obtained with compounds **9** and **10**. Since two hydroxyl groups of **8** or **10** were thought to interact with two aspartyl residues at the active site or with the other sites of renin,[4] we explored the α-diol series.

Synthesis The compounds prepared for this study are shown in Tables I—IV.

Compounds **6**—**8** were synthesized as shown in Chart 1. The synthesis of their N-terminal fragment, *N*-[*N*-benzyloxycarbonyl-3-(1-naphthyl)-L-alanyl]-L-norleucine (Z–Nal–Nle–OH), has already been reported.[10] The β-ketoester **13** was prepared from (2*RS*)-norstatine **11** (2*S*,3*S*:2*R*,3*S*=2:3)[11] by *N*,*O*-diprotection followed by Masamune's C-acylation[12] using benzyl magnesium malonate. After alkylation of **13** with ethyl bromide and potassium *tert*-butoxide, hydrogenolysis of the resulting mixture of the product and the starting material gave a mixture of decarboxylation products **14** and **15**. These could be separated by silica gel chromatography to give pure **14** and **15** in 54% and 30% yields, respectively. Treatment of **15** with 4 M HCl–dioxane followed by coupling of the resulting amine with Z–Nal–Nle–OH using diphenylphosphorazidate (DPPA) yielded inhibitor **7**. Inhibitors **6** and **8** were prepared from **7** by Swern oxidation (in this reaction, epimerization of C-4 was observed and yielded a 2:1 mixture of diastereomers) or sodium borohydride ($NaBH_4$) reduction. Inhibitors **9** and **10** were synthesized from **14** by methods similar to those described for **7** and **8**.

Most of the diol compounds listed in Tables II—IV were synthesized by essentially the same methods. In this paper, we describe the synthetic routes to compounds **2**, **24** and their isomers at the second hydroxyl group (Chart 2). Compound **16** was prepared from statine by the method previously reported,[13] and **17** was synthesized from *N*-benzyloxycarbonyl-3-cyclohexyl-L-alanine methyl ester (Z–CHA–OMe) following the method described by Weber *et al.*[14] Treatment of **16** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane gave the epoxide **18** as a 1—2:1 mixture of diastereomers, and the *S*-isomer was predominant. Compound **18** was also prepared from norstatine aldehyde **20**, derived from L-leucine according to the method described previously,[10] by reaction with trimethylsulfoxonium iodide in the presence of sodium hydride. The epoxide **19** was synthesized by the same method as that described for **18**. The regiospecific epoxide opening of **18** with propylmagnesium bromide in the presence of cuprous iodide gave the diastereomeric mixture. These diastereomers could be separated by silica gel chromatography, to afford **22** and **23** in 44.9% and 25.0% yields from the olefin **16**, respectively. After deprotection of **22**, the resulting amine was condensed

TABLE I. Renin-Inhibitory Activities



No.	W	X	Y	IC_{50} (nM)
6	O[a]	O	Me	5600
7	OH(*RS*)	O	Me	2600
8	OH(*RS*)	OH(*RS*)	Me	460
9	OH(*RS*)	O	Pr	870
10	OH(*S*)	OH(*RS*)	Pr	69

a) Mixture (4*S*:4*R*=2:1) of stereisomers.

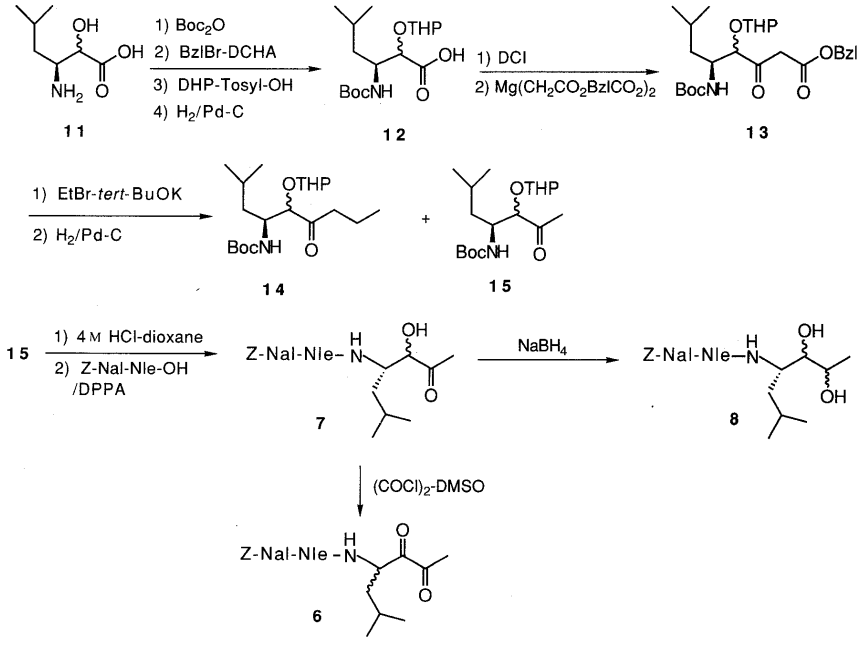


Chart 1

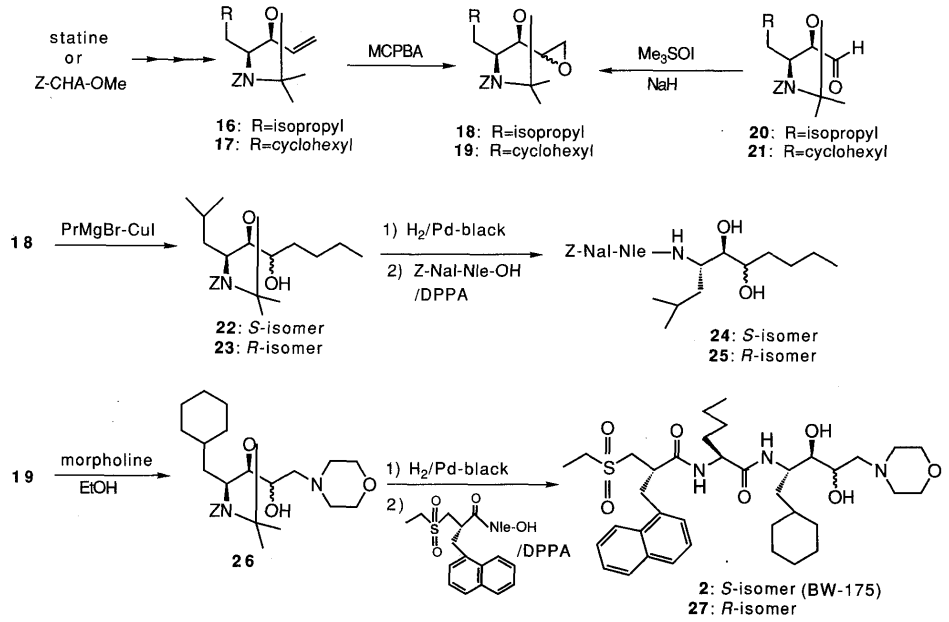
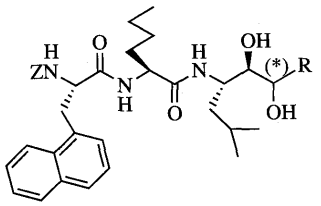


Chart 2

TABLE II. Renin-Inhibitory Activities of α-Diol Compounds



No.	(*)	R	IC_{50} (nM)
10	*RS*	Pr	69
24	*S*	Bu	73
25	*R*	Bu	13.8%[a]
28	*S*	1-Methylpropyl	1500
29	*S*	Benzyl	1000
30	*S*	Morpholinomethyl	31
31	*S*	2-(2-Pyridyl)ethylaminomethyl	4100
32	*S*	(4-Methylpiperazin-1-yl)methyl	2300

a) Percent inhibition at 100 μM.

with Z–Nal–Nle–OH using DPPA to yield inhibitor **24** in a 58% yield. Its isomer **25** was prepared by the same method from **23** in a 47% yield.

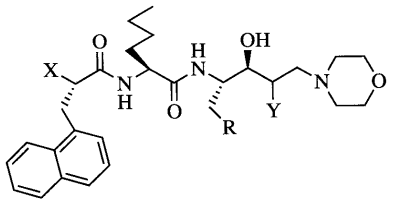
Treatment of the epoxide **19** with morpholine in ethanol afforded **26** quantitatively. Afrer hydrogenolysis of **26**, coupling of the resulting amine with *N*-[(2*S*)-2-(1-naphthylmethyl)-3-ethylsulfonylpropionyl]-L-norleucine[13] by the DPPA method gave a mixture of diastereomers. These diastereomers were readily separable by silica gel chromatography, and gave **2** (BW-175) and **27** in 43% and 37% yields, respectively. Stereospecific synthesis of ACMP has already been reported,[15] and the configuration of the carbon atom bonding the second hydroxyl group of **2** was determined to be *S*.

Structure–Activity Relationships The renin-inhibitory potencies of the compounds synthesized in this study were measured with human plasma renin by the method described previously,[10] and the IC_{50} values are summarized in Tables II, III, and IV.

Table II shows the results of modification of the C-terminus of **10**. Compound **24**, with a butyl group at the C-terminus, was less potent than **10**. Replacement of the propyl group of **10** with the more bulky substituent, 1-methylpropyl, or the aromatic group, benzyl, resulted in loss of potency (compounds **28** and **29**). In order to improve the aqueous solubility of the inhibitors, introduction of basic alkyl groups into the C-terminus was investigated. Compound **30**, containing a morpholinomethyl group, was slightly more potent than **10**, but others (compounds **31** and **32**) were less potent.

We selected **30** and tried to modify its N-terminus and the P_1 side chain in order to improve the activity. The results are shown in Table III. As described previously,[1] introduction of the ethylsulfonylmethyl group instead of the benzyloxycarbonylamino group increased the potency in homostatine-containing inhibitors. In these compounds with the diol isostere, similar results were obtained (compound **30** *vs.* compound **35** and compound **33** *vs.* compound **2**). Compound **34** with the acetoxymethyl group at the same site showed a potency intermediate between those of **33** and **2**. Although replacement of the isobutyl group of **30** with the cyclohexylmethyl group gave a slightly less potent inhibitor (compound **33**), the same substitution in **35** increased potency (compound **2**). This result was consistent with the P_1–P_3–P_4 combination which we reported previously.[10] Removal of the second hydroxyl group of **35** gave a 15-fold decrease in potency (compound **36**). In addition, compound **27**, an isomer of **2**, was eighty times less potent than **2**. These results indicate that the additional second hydroxyl group plays an important role in the inhibitory activity, and computer-modeling studies afforded an explanation for this, as discussed below. The corresponding sulfoxide derivatives (compounds **37** and **38**) were less potent than the sulfone **2**, and the diastereomers at the sulfoxide portion showed different potency (the configuration was

Table III. Renin-Inhibitory Activities of N-Terminally Modified α-Diol Compounds



No.	X	R	Y	IC_{50} (nM)
30	ZNH–	iso-Pr	OH(*S*)	31
33	ZNH–	Cyclohexyl	OH(*S*)	46
34	$AcOCH_2$–	Cyclohexyl	OH(*S*)	10
35	$EtSO_2CH_2$–	iso-Pr	OH(*S*)	8.4
36	$EtSO_2CH_2$–	iso-Pr	H	140
2	$EtSO_2CH_2$–	Cyclohexyl	OH(*S*)	3.3
27	$EtSO_2CH_2$–	Cyclohexyl	OH(*R*)	290
37[a]	$EtSOCH_2$–	Cyclohexyl	OH(*S*)	6.1
38[a]	$EtSOCH_2$–	Cyclohexyl	OH(*S*)	12
39	$EtSCH_2$–	Cyclohexyl	OH(*S*)	18

a) Diastereomer at the sulfoxide residue. The absolute configurations were not determined.

not determined). Furthermore, the sulfide derivative **39** was less potent than sulfoxides.

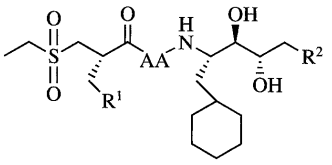
Table IV shows the results of the modification of the C-terminus, P_2 and P_3 sites of **2**. In compounds **40**—**47**, modification of the morpholino residue of **2** gave the following interesting results. 1) Tertiary amine was more potent than secondary amine (compounds **42**, **43** *vs.* the others). The reason for this is unclear. 2) The oxygen atom was necessary for high potency (compound **2** *vs.* compound **40** and compound **44** *vs.* compound **45**). 3) Ring closure was quite effective for obtaining higher potency, possibly by fixing the conformation (compound **2** *vs.* compound **45**, and compound **40** *vs.* compound **44**). 4) Surprisingly, *N*-oxidation of the morpholino residue of **2** did not affect the potency (compound **46**), and *N*-methylation of the same part resulted in a slight loss of the potency (compound **47**). These results indicated that the basic nature of the morpholino residue was not essential for potency.

At the P_2 site, substitution of norleucine with histidine gave an equipotent inhibitor (compound **48**), but introduction of serine resulted in a 100-fold decrease in potency (compound **49**). At the P_3 site, replacement of the naphthylmethyl group with less lipophilic alkyl groups, benzyl or cyclohexylmethyl decreased the potency (compounds **50** and **51**).

Enzyme Specificity Table V shows the specificity of these diol compounds for inhibition of related aspartic proteases. Although the contribution of histidine at the P_2 site to the specificity has been described,[16] these diol compounds containing norleucine instead of histidine showed high selectivity for renin. Comparison of the selectivity of inhibitors containing ACMP with that of inhibitors **1** and **24** suggests that the morpholino residue of ACMP might play an important role in the specificity.

Modeling Studies In order to investigate the role of the two hydroxyl groups and the morpholino group, we modeled renin complexed with inhibitor **2**. Modeling of the complex was performed as previously reported.[1] In the course of modeling, one conformation of the inhibitor was obtained in which both hydroxyl groups faced the

Table IV. Reinin-Inhibitory Activities of C-Terminally Modified Compounds



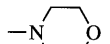
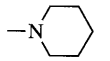
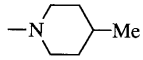
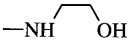
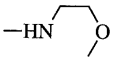
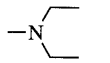
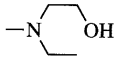
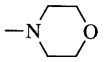
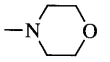
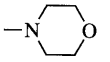
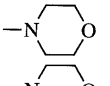
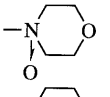
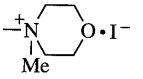
No.	R^1	AA	R^2	IC_{50} (nM)
2	1-Naphthyl	Nle		3.3
40	1-Naphthyl	Nle		45
41	1-Naphthyl	Nle		400
42	1-Naphthyl	Nle		524
43	1-Naphthyl	Nle		250
44	1-Naphthyl	Nle		128
45	1-Naphthyl	Nle		39
46	1-Naphthyl	His		4.2
47	1-Naphthyl	Ser		300
48	Phenyl	Nle		10
49	Cyclohexyl	Nle		14
50	1-Naphthyl	Nle		2.8
51	1-Naphthyl	Nle		20

Table V. Enzyme Specificity

No.	Renin (human)	IC_{50} (nM) Cathepsin D (bovine)	Pepsin (porcine)
1[a]	0.5	15	260
2	3.3	26000	$>1\times10^5$
24	73	210	270
33	46.0	15000	46.4%[b]
36	140	21000	4%[b]
37	6.1	64000	19.0%[b]
39	18.0	34000	20.1%[b]
46	2.8	2600	<10%[b]
47	20.0	66000	<10%[b]
48	4.2	0%[c]	0%[c]
50	10.0	16000	14.6%[b]
51	14.0	22000	13.6%[b]

a) Ref. 1. *b*) Percent inhibition at 100 μM. *c*) Percent inhibition at 10 μM.

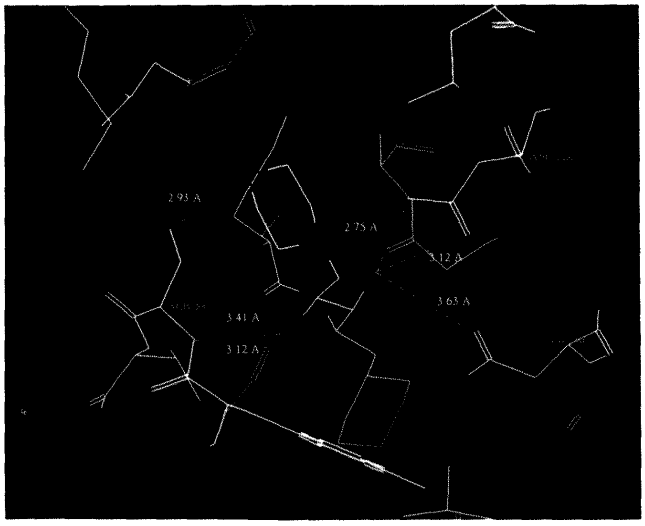


Fig. 3. Hydrogen Bonding Network around the C-Terminal Region of Compound **2**

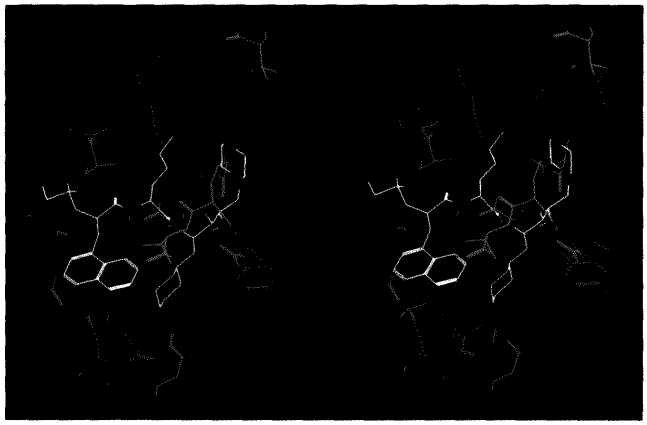


Fig. 4. Stereo View of Compound **2** and Its Surrounding Residues of Renin

Hydrophobic residues are colored in magenta and hydrophilic ones in cyan.

active site aspartic residues (Asp^{38} and Asp^{226}) (data not shown). This conformation is similar to those reported by Luly *et al.*[4e] However, this conformation was energetically less favorable than the other conformation in which the (3*R*)-hydroxyl group of ACMP faced the active site aspartic residues while the other hydroxyl group faced the carbonyl group of the amide bond in the inhibitor. The latter conformation is similar to those found in other renin inhibitors containing an α-diol group which are complexed with pepsin.[17] Therefore we analyzed the model of the latter conformation of compound **2** complexed with renin.

The (3*R*)-hydroxyl group of ACMP is directed toward the carboxyl groups of Asp^{226} and Asp^{38} in the active site of renin and the distances between the oxygen atom of the hydroxyl group and the aspartic oxygen atoms are favorable for hydrogen bonding (Fig. 3). The hydrogen bonding pattern is similar to that seen in other renin inhibitors containing norstatine or homostatine analogues complexed with renin.[18,19] The other hydroxyl group is directed toward the carbonyl group of the amide bond between the P_1 and P_2 sites. The amide hydrogen of Ser^{84} in the flap region of renin is directed toward this hydroxyl oxygen of the inhibitor. Consequently, the two hydroxyl groups maintain a hydrogen bonding network not only with the aspartic residue in the active site and the flap region of renin but also with the inhibitor itself.

As for the morpholino group in the inhibitor, the oxygen atom in the six-membered ring occupies a favorable position for making a hydrogen bond with the hydroxyl group in the side chain of Ser^{84}. Deletion of this oxygen or deformation of the ring structure would make it difficult to form a hydrogen bond with the flap region of renin. Furthermore, the morpholino ring is located in the hydrophobic area where the alkyl chain of norleucine exists (Fig. 4). These features are likely to contribute to hydrophobic interactions between the inhibitor and renin, just like the counterparts, the naphthyl and cyclohexyl groups in the P_1 and P_3 regions. The morpholino ring is so rigid that the relative location of the oxygen atom and the methylene groups are restricted. When the oxygen atom in the morpholino ring makes a hydrogen bond with the hydroxyl group of Ser^{84}, methylene groups in the ring are close to the butyl group of norleucine in the inhibitor. The resultant hydrocarbon cluster is located in the S_2 site and seems to be stabilized by hydrophobic interaction. The nitrogen atom in the morpholino ring does not seem to

TABLE VI. Characterization of Renin Inhibitors

No.	t_R (min)[a]	Purity (%)	Formula	FAB-MS[b]	
				Calcd	Found
2	8.54	97	$C_{37}H_{57}N_3O_7S$	688.3995	688.4014
6	6.77[c]	91	$C_{35}H_{43}N_3O_6$	602.3230	602.3210
7	5.52, 7.02[c]	94	$C_{35}H_{45}N_3O_6$	604.3387	604.3372
8	4.91, 5.28[c]	92	$C_{35}H_{47}N_3O_6$	606.3543	606.3519
9	7.12[c]	78	$C_{37}H_{49}N_3O_6$	632.3700	632.3704
10	5.65, 6.44[c]	97	$C_{37}H_{51}N_3O_6$	634.3856	634.3871
24	6.95[c]	97	$C_{38}H_{53}N_3O_6$	648.4012	648.3937
25	7.39[c]	99	$C_{38}H_{53}N_3O_6$	648.4012	648.3946
27	7.89	92	$C_{37}H_{57}N_3O_7S$	688.3995	688.3994
28	6.91[c]	92	$C_{35}H_{47}N_3O_6$	606.3543	606.3519
29	6.83[c]	98	$C_{41}H_{51}N_3O_6$	682.3856	682.3881
30	9.32	90	$C_{39}H_{54}N_4O_7$	691.4071	691.4048
31	8.74	94	$C_{42}H_{55}N_5O_6$	726.4230	726.4144
32	9.72	96	$C_{40}H_{57}N_5O_6$	704.4387	704.4402
33	14.74	95	$C_{42}H_{58}N_4O_7$	731.4384	731.4092
34	10.19	96	$C_{37}H_{55}N_3O_7$	654.4118	654.4116
35	5.60	98	$C_{34}H_{53}N_3O_7S$	648.3682	648.3680
36	5.77	98	$C_{34}H_{53}N_3O_6S$	632.3733	632.3752
37	8.93	99	$C_{37}H_{57}N_3O_6S$	672.4046	672.4042
38	9.10	96	$C_{37}H_{57}N_3O_6S$	672.4046	672.4070
39	19.00	97	$C_{37}H_{57}N_3O_5S$	656.4097	656.4084
40	8.29	96	$C_{38}H_{59}N_3O_6S$	686.4203	686.4181
41	9.27	96	$C_{39}H_{61}N_3O_6S$	700.4359	700.4363
42	6.34	91	$C_{35}H_{55}N_3O_7S$	662.3839	662.3828
43	6.77	87	$C_{36}H_{57}N_3O_7S$	676.3995	676.4017
44	7.09	96	$C_{37}H_{59}N_3O_6S$	674.4203	674.4225
45	6.82	93	$C_{37}H_{59}N_3O_7S$	690.4152	690.4137
46	6.67	99	$C_{37}H_{57}N_3O_8S$	704.3945	704.3932
47	7.06	98	$C_{38}H_{60}N_3O_7S$	702.4152	702.4150
48	6.37	98	$C_{37}H_{53}N_5O_7S$	712.3744	712.3740
49	6.50	82	$C_{34}H_{51}N_3O_8S$	662.3475	662.3451
50	5.94	94	$C_{33}H_{55}N_3O_7S$	638.3839	638.3854
51	8.43	94	$C_{33}H_{61}N_3O_7S$	644.4308	644.4291

a) See the experimental section for conditions. *b*) For $[M+H]^+$. *c*) Solvent: MeOH : H_2O = 7 : 1.

function as a hydrogen bond acceptor and there is a little space between the nitrogen atom and surrounding residues, where an oxygen atom or methyl group could be introduced. We should be able to make further modifications around the morpholino group considering the interaction mentioned above.

Biological Results of Inhibitor 2 From among these inhibitors, we selected inhibitor **2** (BW-175) and examined its bioavailability in rats and the hypotensive effect in furosemide-treated, normotensive marmosets.[3a] Compound **2** showed an oral bioavailability of 2.8% at 10 mg/kg and 9.7% at 30 mg/kg in rats. Oral administration of 30 mg/kg of **2** to furosemide-treated, normotensive marmosets resulted in a reduction of 5—20 mmHg of mean blood pressure for 4 h.

In conclusion, further modification at the C-terminus in **1** (BW-146) in conjunction with structure–activity studies led to inhibitor **2** (BW-175). This compound, which was specific for renin, had improved oral bioavailability and induced lowered blood pressure after oral administration.

Experimental

Melting points were determined with a Yanagimoto melting point apparatus without correction. Infrared (IR) spectra were measured with a Hitachi 270-30 IR spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian VXR-300 (300 MHz) or a Hitachi R-24 (60 MHz) spectrometer in deuteriochloroform ($CDCl_3$). Chemical shifts are reported relative to residual protons of deuterated NMR solvents. Fast atom bombardment mass spectra (FAB-MS) were obtained with a JEOL JMS-DX 300 mass spectrometer. Optical rotations were determined with a Horiba SEPA-200 high-sensitivity polarimeter. Analytical high-performance liquid chromatography (HPLC) was performed on a Hitachi L-6200 system, using a packed column, Chromatorex ODS (5 μm, 4.6 × 250 mm), and MeOH–10 mM $AcONH_4$ (5 : 1) for elution unless otherwise stated (flow rate, 1 ml/min), with ultraviolet (UV) detection at 254 nm (Hitachi L-4000 UV detector). Thin-layer chromatography (TLC) was conducted with E. Merck 0.25-mm glass plates precoated with Silica gel 60 F_{254} (Art. 5715). Column chromatography was done on Kieselgel 60 (E. Merck, 70-230 mesh). The organic solutions were dried over $MgSO_4$ before vacuum evaporation.

(2*RS*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-5-methyl-2-(tetrahydro-2-pyranyl)oxyhexanoic Acid (12) Triethylamine (0.17 ml, 1.2 mmol) and *O*-*tert*-butyl-*S*-(4,6-dimethylpyrimidine-2-yl)thiocarbonate (BOC-S) (213 mg, 0.89 mmol) were added to a solution of (2*RS*)-norstatine (2*S*,3*S* : 2*R*,3*S* = 2 : 3)[11b] (130 mg, 0.81 mmol) in water (1.0 ml). After being stirred at room temperature overnight, the mixture was poured into water and extracted with ethyl acetate (AcOEt). The aqueous layer was adjusted to pH 2 with 1 N HCl and extracted with AcOEt. The organic layer was washed with 1 N HCl, water and brine, then dried and evaporated to afford *N*-Boc-norstatine (188 mg, 89%) as a colorless oil. This oil was dissolved in a mixture of dimethylformamide (DMF) (1.5 ml) and dichloromethane (CH_2Cl_2) (1.5 ml), and then dicyclohexylamine (0.17 ml, 0.85 mmol) and benzyl bromide (0.1 ml, 0.84 mmol) were added. The mixture was stirred at room temperature overnight, water was added and then extraction was performed with AcOEt. The organic layer was washed with 10% citric acid, 4% $NaHCO_3$, water and brine. Drying and evaporation yielded the benzyl ester derivative (240 mg, 95%) as a colorless oil. A solution of benzyl ester compound (240 mg, 0.68 mmol) in CH_2Cl_2 (2.5 ml) was treated with dihydropyran (0.2 ml, 2.58 mmol) and *p*-toluenesulfonic acid monohydrate (0.1 mg). This mixture was stirred at room temperature for 4 h, then ether was added and the mixture was washed with 4% $NaHCO_3$ water and brine. Drying followed by evaporation and purification by silica gel chromatography (hexane : AcOEt = 10 : 1) gave the tetrahydropyran (THP) derivative (228 mg, 77%) as a colorless oil. A suspension of this residue (240 mg, 0.52 mmol) and 10% Pd–C (23 mg) in EtOH (6 ml) was stirred under a hydrogen atmosphere overnight at room temperature. The catalyst was filtered off and the filtrate was concentrated to give the title compound (186 mg, 100%) as a colorless oil. *Rf* 0.40 (benzene : MeOH : AcOH = 10 : 1 : 0.5). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.78—1.06 (6H, m), 1.38 (9H, s), 1.20—1.35 (9H, m), 3.25—5.14 (5H, m), 7.94 (1H, br s).

(4*RS*,5*S*)-5-(*tert*-Butoxycarbonyl)amino-7-methyl-3-oxo-4-(tetrahydro-2-pyranyl)oxyoctanoic Acid Benzyl Ester (13) A solution of **12** (311 mg, 0.90 mmol) in anhydrous tetrahydrofuran (THF) (5 ml) was treated with *N*,*N*-dicarbonyldiimidazole (DCI), (156 mg, 1.0 mmol). The mixture was stirred for 6 h at room temperature, then benzyl magnesium malonate (397 mg, 0.97 mmol) was added. Stirring was continued overnight at room temperature, then the mixture was poured into 10% citric acid and extracted with AcOEt. The organic layer was washed with 4% $NaHCO_3$, water and brine. Drying followed by evaporation and purification by silica gel chromatography (hexane : AcOEt = 10 : 1) gave the title compound (361 mg, 84%) as a colorless oil. *Rf* 0.38 and 0.44 (hexane : AcOEt = 3 : 1). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.78—1.09 (6H, m), 1.38 (9H, s), 1.09—1.99 (9H, m), 3.30—4.81 (7H, m), 5.14 (2H, s), 7.29 (5H, s). FAB-MS *m*/*z*: 478 $[M+H]^+$.

(5*RS*,6*S*)-6-(*tert*-Butoxycarbonyl)amino-8-methyl-5-(tetrahydro-2-pyranyl)oxynonan-4-one (14) and (3*RS*,4*S*)-4-(*tert*-Butoxycarbonyl)-amino-6-methyl-3-(tetrahydro-2-pyranyl)oxyheptan-2-one (15) Potassium *tert*-butoxide (68 mg, 0.61 mmol) and ethyl bromide (0.6 ml, 8.0 mmol) were added to a solution of **13** (291 mg, 0.61 mmol) in *tert*-BuOH (4.5 ml). After being stirred overnight at 50 °C, the mixture was poured into 10% citric acid. The mixture was extracted with ether and the organic layer was washed with water and brine. Drying and evaporation gave a residue as a pale yellow oil. A suspension of the residue and 10% Pd–C (31 mg) in EtOH (7 ml) was stirred under a hydrogen atmosphere overnight at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by silica gel chromatography (hexane : AcOEt = 10 : 1) to afford **14** (122 mg, 54%) and **15** (63 mg, 30%). Compound **14**: colorless oil. *Rf* 0.48 (hexane : AcOEt = 3 : 1). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.72—1.05 (9H, m), 1.38 (9H, s), 1.21—2.05 (11H, m), 2.28—2.55 (2H, m), 3.25—4.30 (4H, m), 4.52 (1H, br s). FAB-MS *m*/*z*: 372 $[M+H]^+$. Compound **15**: colorless oil. *Rf* = 0.35 (hexane : AcOEt = 3 : 1). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.76—1.07 (6H, m), 1.39 (9H, s), 1.21—1.91 (9H, m), 2.13 (3H, s), 3.16—4.34 (4H, m), 4.58 (1H, br s). FAB-MS *m*/*z*: 344 $[N+H]^+$.

(3*RS*,4*S*)-4-[*N*-[*N*-Benzyloxycarbonyl-3-(1-naphthyl)-L-alanyl]-L-norleucyl]amino-3-hydroxy-6-methyl-2-heptanone (7) Compound **15** (63 mg, 0.18 mmol) was dissolved in 4 M HCl–dioxane (1 ml). The solution was stirred for 1.5 h at 0 °C, then evaporated to give a colorless oil. A solution of the oil in DMF (0.6 ml) was added to a solution of Z–Nal–Nle–OH (868 mg, 0.15 mmol), DPPA (49 μl, 0.23 mmol) and triethylamine (53 μl, 0.38 mmol) in DMF (2 ml) at −15 °C. The whole was stirred overnight at room temperature, diluted with AcOEt and washed with 10% citric acid, 4% $NaHCO_3$, water and brine. Drying followed by evaporation and purification by silica gel chromatography ($CHCl_3$: MeOH = 50 : 1) gave the title compound (47 mg, 42%) as a white solid. mp 102.0—108.0 °C. *Rf* = 0.50 ($CHCl_3$: MeOH = 40 : 1). ^{1}H-NMR ($CDCl_3$) δ: 0.77—1.03 (9H, m), 1.03—1.90 (9H, m), 2.27 (3/2H, s), 2.30 (3/2H, s), 3.43—3.65 (2H, m), 4.05—4.15 (1H, m), 4.15—4.31 (2H, m), 4.38—4.63 (2H, m), 4.99—5.15 (2H, m), 5.25—5.39 (1H, m), 7.18—7.41 (7H, m), 7.42—7.61 (1H, m), 8.17 (1H, br s). FAB-MS *m*/*z*: $[M+H]^+$ Calcd for $C_{35}H_{46}N_3O_6$: 604.3387. Found: 604.3372.

(2*RS*,3*RS*,4*S*)-4-[*N*-[*N*-Benzyloxycarbonyl-3-(1-naphthyl)-L-alanyl]-L-norleucyl]amino-2,3-dihydroxy-6-methylheptane (8) A solution of **7** (20.3 mg, 0.034 mmol) and $NaBH_4$ (2.7 mg, 0.071 mmol) in EtOH (1.5 ml) was stirred for 1 h at room temperature. The mixture was diluted with AcOEt and washed with water and brine. Drying followed by evaporation gave the title compound (22 mg, quant.) as a shite solid, mp 170.0—173.0 °C. *Rf* 0.080, 0.12, 0.16 and 0.21 ($CHCl_3$: MeOH = 40 : 1). FAB-MS *m*/*z*: $[M+H]^+$ Calcd for $C_{35}H_{48}N_3O_6$: 606.3548. Found: 606.3519.

(4*RS*)-4-[*N*-[*N*-Benzyloxycalbonyl-3-(1-naphthyl)-L-alanyl]-L-norleucyl]amino-6-methylheptane-2,3-dione (6) A solution of oxalyl chloride (4 μl, 0.05 mmol) in CH_2Cl_2 (0.1 ml) was treated with DMSO (7 μl) at −78 °C. The mixture was stirred at the same temperature for 10 min, then a solution of **7** (11 mg, 0.018 mmol) in CH_2Cl_2 (0.2 ml) at −78 °C was added. Stirring was continued for 1 h at −30 °C, then triethylamine (14 μl) was added. After 30 min, the reaction mixture was diluted with AcOEt and washed with 4% $NaHCO_3$, water and brine. Drying followed by evaporation and purification by silica gel chromatography ($CHCl_3$: MeOH = 30 : 1) afforded the title compound (8.6 mg, 80%) as a white solid. *Rf* 0.25 ($CHCl_3$: MeOH = 30 : 1).

^{1}H-NMR ($CDCl_3$) δ: 0.74—1.85 (18H, m), 2.32 (3H × 1/3, s), 2.35 (3H × 2/3, s), 3.39—3.69 (2H, m), 4.10—4.20 (1/3H, m), 4.20—4.35 (2/3H, m), 4.49—4.65 (1H, m), 4.80—4.95 (1H, m), 5.03 (2H, br s), 5.29—5.42 (1H, m), 6.12—6.28 (1H, m), 7.18—7.45 (7H, m), 7.45—7.67 (2H, m), 7.77 (1H, d, J=7.09 Hz), 7.88 (1H, d, J=7.9 Hz), 8.15 (1H, d, J=7.9 Hz). FAB-MS m/z: $[M+H]^+$ Calcd for $C_{35}H_{44}N_3O_6$: 602.3230. Found: 602.3210. This compound was a 2:1 mixture of diastereomers at C-4.

(4*S*,5*R*)-3-Benzyloxycarbonyl-4-isobutyl-2,2-dimethyl-5-[(2*RS*)-2-oxiranyl]oxazolidinone (18) From Compound **16**: MCPBA (1.2 g, 70% purity) was added to a solution of **16** (0.5 g, 1.58 mmol) in CH_2Cl_2 (5 ml) at 0 °C. The mixture was stirred for 90 h at room temperature, then diluted with AcOEt and washed with 10% $NaHSO_3$, saturated Na_2CO_3 water and brine. Drying followed by evaporation gave the title compound (589 mg, quant.) as a colorless oil. This compound was a 4:3 mixture of diastereomers, in which the *S*-isomer was predominant. It was used without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.65—1.15 (6H, m), 1.25—1.90 (9H, m), 2.55—2.65 (1H, m), 2.80 (3/7H, t, J=4.4 Hz), 2.87 (4/7H, t, J=4.4 Hz), 3.02—3.12 (1H, m), 3.60, 3.83, 3.95 (sum 2H, m), 5.02—5.25 (2H, m), 7.25—7.50 (5H, m).

From Compound **20**: A mixture of sodium hydride (0.29 g, 7.2 mmol, 60% in oil) and trimethylsulfoxonium iodide (1.58 g, 7.2 mmol) in DMSO (8 ml) was stirred for 2 h at room temperature, then a solution of **20** (1.91 g, 5.98 mmol) in DMSO (10 ml) was added. The whole was stirred for 2 h at room temperature, then poured into water. The mixture was extracted with ether and the organic layer was washed with brine. Drying followed by evaporation and purification by silica gel chromatography (hexane : AcOEt = 5 : 1) gave **18** (0.98 g, 49%) as a pale yellow oil. This compound was a 2:1 mixture of diastereomers, in which the *S*-isomer was predominant.

(4*S*,5*R*)-3-Benzyloxycarbonyl-4-cyclohexylmethyl-3,3-dimethyl-5-[(2*RS*)-2-oxiranyl]oxazolidinone (19) The title compound was prepared from **17** or **21** by a procedure similar to that described for **18**.

From **17**: Quantitative yield as a pale yellow oil. This compound was a 3:2 mixture of diastereomers, in which the *S*-isomer was predominant. It was used without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.65—1.95 (19H, m), 2.56—2.65 (1H, m), 2.83 (2/5H, t, J=4.5 Hz), 2.87 (3/5H, t, J=4.4 Hz), 3.02—3.12 (1H, m), 3.61 (1H, m), 3.70—4.20 (2H, m), 5.00—5.27 (2H, m), 7.20—7.55 (5H, m).

From **21**: 40% yield as a pale yellow oil after purification by silica gel chromatography (hexane : AcOEt = 5 : 1). This compound was a 1:1 mixture of diastereomers.

(4*S*,5*R*)-3-Benzyloxycarbonyl-5-[(1*S*)-1-hydroxypentyl]-4-isobutyl-2,2-dimethyloxazolidine (22) and (4*S*,5*R*)-3-Benzyloxycarbonyl-5-[(1*R*)-1-hydroxypentyl]-4-isobutyl-2,2-dimethyloxazolidine (23) A suspension of cuprous iodide (36 mg, 0.18 mmol) in THF (1 ml) was treated with propylmagnesium bromide (1.05 ml, 2.1 mmol, 2 M THF solution) at −30 °C. This mixture was stirred for 5 min at the same temperature, and a solution of **18** (235 mg, 0.71 mmol, prepared from **16**) in THF (2 ml) was added at −30 °C. The reaction mixture was stirred for 2 h at room temperature and poured into saturated NH_4Cl. The whole was extracted with AcOEt, and the organic layer was washed with 1 N HCl, saturated $NaHCO_3$, water and brine. Drying followed by evaporation and purification by silica gel chromatography (toluene : AcOEt = 20 : 1) afforded **22** and **23**. Compound **22**: 45% yield from **16** as a white solid, mp 97.5—99.5 °C. *Rf* 0.67 (toluene : AcOEt = 15 : 1). IR (neat): 3466, 1686 cm^{-1}. $[\alpha]_D^{20}$ +6.0° (c=0.933, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.65—1.05 (9H, m), 1.20—1.90 (15H, m), 3.45—3.68 (2H, m), 4.11 (1H, m), 5.07, 5.18 (2H, ABq, J=12.5 Hz), 7.20—7.45 (5H, m). FAB-MS m/z: $[M+H]^+$ Calcd for $C_{22}H_{36}NO_4$: 378.2645. Found: 378.2638. Compound **23**: 25% yield from **16** as a colorless oil. Rf=0.60 (toluene : AcOEt = 15 : 1). IR (neat): 3500, 1716 cm^{-1}. $[\alpha]_D^{20}$ +23.7° (c=0.987, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.60—1.10 (9H, m), 1.15—1.80 (15H, m), 3.38—3.50 (1H, m), 3.64 (1H, dd, J=2.1, 7.8 Hz), 3.70—4.00 (1H, m), 5.07, 5.19 (2H, ABq, J=12.0 Hz), 7.18—7.45 (5H, m). FAB-MS m/z: $[M+H]^+$ Calcd for $C_{22}H_{36}NO_4$: 378.2645. Found: 378.2662. The absolute configurations of the new chiral carbons were estimated from the biological activities of compounds **24** and **25**.[3a]

(4*S*,4*R*,6*S*)-4-[*N*-[*N*-Benzyloxycarbonyl-3-(1-naphthyl)-L-alanyl]-L-norleucyl]amino-5,6-dihydroxy-2-methyldecane (24) A suspension of **22** (64 mg, 0.17 mmol) and Pd–black was stirred under a hydrogen atmosphere overnight at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in DMF (0.7 ml) and Z–Nal–Nle–OH (52 mg, 0.11 mmol), DPPA (30 ml) and triethylamine (20 ml, 0.14 mmol) were added at −15 °C. The mixture was stirred for 2 h at the same temperature and further stirred at room temperature overnight. After dilution with AcOEt, the mixture was washed with 10% citric acid, 4% $NaHCO_3$, water and brine. Drying followed by evaporation and purification by silica gel chromatography ($CHCl_3$: MeOH = 100 : 1) gave **24** (42 mg, 58%) as a white solid, mp 184.0—185.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.75—0.98 (12H, m), 0.98—1.95 (15H, m), 3.20 (2H, br s), 3.46 (1H, dd, J=7.8, 14.4 Hz), 3.62 (1H, dd, J=5.9 Hz), 4.15—4.37 (2H, m), 4.43—4.55 (1H, m), 5.03 (2H, br s), 5.31 (1H, d, J=3.6 Hz), 6.11 (1H, d, J=6.6 Hz), 6.53 (1H, d, J=7.8 Hz), 7.20—7.45 (7H, m), 7.45—7.65 (2H, m), 7.80 (1H, d, J=7.8 Hz), 7.88 (1H, d, J=8.1 Hz), 8.11 (1H, d, J=7.5 Hz). FAB-MS m/z: $[M+H]^+$ Calcd for $C_{38}H_{54}N_3O_6$: 648.4012. Found: 648.3937.

(4*S*,5*R*,6*R*)-4-[*N*-[*N*-Benzyloxycarbonyl-3-(1-naphthyl)-L-alanyl]-L-norleucyl]amino-5,6-dihydroxy-2-methyldecane (25) The title compound was prepared from **23** by a procedure similar to that described for **24** and purified by silica gel chromatography ($CHCl_3$: MeOH = 100 : 1); 47% yield as a white solid, mp 200.0—203.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, J=7.2 Hz), 0.88—1.10 (9H, m), 1.17—2.00 (15H, m), 3.32—3.40 (1H, m), 3.45—3.70 (3H, m), 4.01 (1H, m), 4.14 (1H, m), 4.53 (1H, m), 5.01, 5.11 (2H, ABq, J=12.1 Hz), 5.39 (1H, m), 6.02 (1H, m), 4.45 (1H, m), 7.18—7.45 (7H, m), 7.48—7.65 (2H, m), 7.79 (1H, d, J=8.1 Hz), 7.87 (1H, d, J=7.8 Hz), 8.15 (1H, d, J=7.5 Hz). FAB-MS m/z: $[M+H]^+$ Calcd for $C_{38}H_{54}N_3O_6$: 648.4012. Found: 648.3946.

(4*S*,5*R*)-3-Benzyloxycarbonyl-4-cyclohexylmethyl-5-[(1*RS*)-1-hydroxy-2-morpholino]ethyl-2,2-dimethyloxazolidine (26) A solution of **19** (198 mg, 0.53 mmol, prepared from **17**) and morpholine (0.6 ml) in EtOH (3 ml) was refluxed for 2 h. Evaporation followed by purification by silica gel chromatography (hexane : AcOEt = 1 : 1) afforded **26** (209 mg, 96% from **17**) as a pale yellow oil. IR (neat): 3466, 1710 cm^{-1}. $[\alpha]_D^{20}$ −9.7° (c=0.963, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.65—1.90 (19H, m), 2.25—2.75 (6H, m), 3.45—3.90 (6H, m), 4.05—4.30 (1H, m), 4.98—5.25 (2H, m), 7.15—7.55 (5H, m). FAB-MS m/z: $[M+H]^+$ Calcd for $C_{26}H_{41}N_2O_5$: 461.3015. Found: 461.3033.

(2*S*,3*R*,4*S*)-4-[*N*-[(2*S*)-3-Ethylsulfonyl-2-(1-naphthylmethyl)propionyl]-L-norleucyl]amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (2) and (2*R*,3*R*,4*S*)-4-[*N*-[(2*S*)-3-Ethylsulfonyl-2-(1-naphthylmethyl)propionyl]-L-norleucyl]amino-5-cyclohexyl-1-morpholino-2,3-pentanediol (27) A suspension of **26** (281 mg, 0.61 mmol) and Pd–black in EtOH (5 ml) was stirred under a hydrogen atmosphere overnight. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in MeOH (5 ml) and 1 N HCl (1.2 ml) was added. Evaporation gave a hydrochloride salt (221 mg, quant.) as an amorphous compound. A solution of the hydrochloride salt (122 mg, 0.31 mmol) and triethylamine (55 μl, 0.38 mmol) in DMF (1 ml) was added to a solution of *N*-[(2*S*)-2-(1-naphthylmethyl)-3-ethylsulfonylpropionyl]-L-norleucine (100 mg, 0.21 mmol), DPPA (62 μl, 0.26 mmol) and triethylamine (40 μl, 0.26 mmol) in DMF (0.9 ml) at −15 °C. The mixture was stirred for 2 h at the same temperature and further stirred at room temperature overnight. After dilution with AcOEt, the mixture was washed with water and brine. Drying followed by evaporation and purification by silica gel chromatography ($CHCl_3$: MeOH = 100 : 1) gave **2** and **27**. Compound **2** (BW-175): 43% yield as a white solid, mp 163.0—166.0 °C. *Rf* 0.34 ($CHCl_3$: MeOH = 20 : 1). ^{1}H-NMR ($CDCl_3$) δ: 0.81—0.96 (3H, m), 1.20 (3H, t, J=7.6 Hz), 1.12—1.85 (19H, m), 2.41—2.57 (2H, m), 2.57—2.91 (6H, m), 3.03 (1H, dd, J=3.4, 13.7 Hz), 3.26—3.78 (11H, m), 4.19—4.34 (2H, m), 4.60 (1H, br s), 6.01 (1H, d, J=7.9 Hz), 6.09 (1H, d, J=6.3 Hz), 7.32—7.50 (2H, m), 7.50—7.69 (2H, m), 7.82 (1H, d, J=7.9 Hz), 7.92 (1H, d, J=7.9 Hz), 8.03 (1H, d, J=7.9 Hz). FAB-MS m/z: $[M+H]^+$ Calcd for $C_{37}H_{58}N_3O_7S$: 688.3995. Found: 688.4014. Compound **27**; 37% yield as a white solid, mp 94.0—97.0 °C. *Rf* 0.34 ($CHCl_3$: MeOH = 20 : 1). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.8 Hz), 0.90—1.90 (19H, m), 2.30—2.90 (8H, m), 2.98 (1H, dd, J=4.0, 14.2 Hz), 3.20—3.75 (12H, m), 4.05 (1H, m), 4.19 (1H, m), 6.10 (1H, d, J=8.6 Hz), 6.25 (1H, d, J=7.1 Hz), 7.30—7.48 (7H, m), 7.50—7.65 (2H, m), 7.80 (1H, d, J=7.9 Hz), 7.89 (1H, d, J=7.9 Hz), 8.02 (1H, d, J=7.9 Hz). FAB-MS m/z: $[M+H]^+$ Calcd for $C_{37}H_{58}N_3O_7S$: 688.3995. Found: 688.3994.

References and Notes

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