Synthesis of a Homostatine-Containing Renin Inhibitor Which Incorporates a Sulfonemethylene Isostere at Its *N*-Terminus

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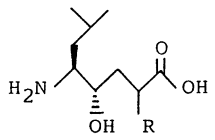
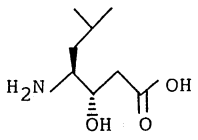
A homostatine analogue, (2*RS*,4*S*,5*S*)-*N*-isobutyl-5-amino-2-ethyl-4-hydroxy-7-methyloctanamide, was synthesized starting from natural statine. The modified Horner-Wadsworth-Emmons reaction of (4*S*,5*R*)-3-benzyloxycarbonyl-5-formyl-4-isobutyl-2,2-dimethyloxazolidine is a key reaction for the synthesis of a homostatine analogue. Stereoselective and stereospecific syntheses of a *N*-terminal precursor, *N*-[(2*R*)-3-hydroxy-2-(1-naphthylmethyl)propionyl]-L-norleucine *t*-butyl ester and a total synthesis of a highly active renin inhibitor, (2*RS*,4*S*,5*S*)-*N*-isobutyl-5-[[*N*-[(2*S*)-2-(1-naphthylmethyl)-3-(2-pyrimidinylsulfonyl)propionyl]-L-norleucyl]amino]-2-ethyl-4-hydroxy-7-methyloctanamide are described.

Renin, a rate-limiting enzyme in the renin-angiotensin system, is thought to play an important role in the regulation of blood pressure and sodium homeostasis, and the synthetic study of its inhibitor has been investigated intensively in this decade. Among inhibitors synthesized so far, compounds containing homostatine analogue **1** turned out to show potent inhibitory activities against human plasma renin.[1] Homostatine analogue **1** is a dipeptide analogue in which the peptide bond at the scissile site is replaced by a 1-hydroxy-1,2-ethanediyl bond (hydroxyethylene isostere), and syntheses of it have been achieved previously by various methods. Although several synthetic methods of a homostatine starting from an L-amino acid were reported, all of them failed to control the stereochemistry of the position-4 in homostatine, resulting only in a mixture of the stereoisomers.[2-8,11,14,17] Actually, however, we ensured that the stereostructure of natural (3*S*,4*S*)-statine (**2**) could be transformed into the corresponding (4*S*,5*S*)-homostatine analogue (**1**) without any epimerization of its chiralities. We have tried to remove the peptide bond in a renin inhibitor in order to improve the oral bioavailavility and to prevent proteolytic hydrolysis.[9] As the result, we found that the replacement of the amide bond by a sulfonemethylene isostere at the *N*-terminus of homostatine-containing inhibitor enhanced its renin-inhibitory activity. We selected a 2-pyrimidinylsulfonyl derivative, (2*RS*,4*S*,5*S*)-*N*-isobutyl-5-[[*N*-[(2*S*)-2-(1-naphthylmethyl)-3-(2-pyrimidinylsulfonyl)propionyl]-L-norleucyl]amino]-2-ethyl-4-hydroxy-7-methyloctanamide (**26**) as a target compound, which is shown in Fig 1.[10,11] It was quite expected that the introduction of such a *N*-heteroarylsulfonyl compound would be a good analogy to the structure of -Pro^7- in angiotensinogen (P_4 site[1]) of substrate). Here we report a modified synthetic approach of a homostatine analogue **14** starting from statine (**2**) and a total synthesis of a homostatine-containing renin inhibitor **26** which incorporates a sulfonemethylene isostere at its *N*-terminus.

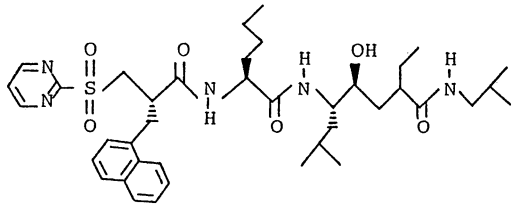


1 homostatine analogue



2 statine

[hydroxyethylene dipeptide isostere]



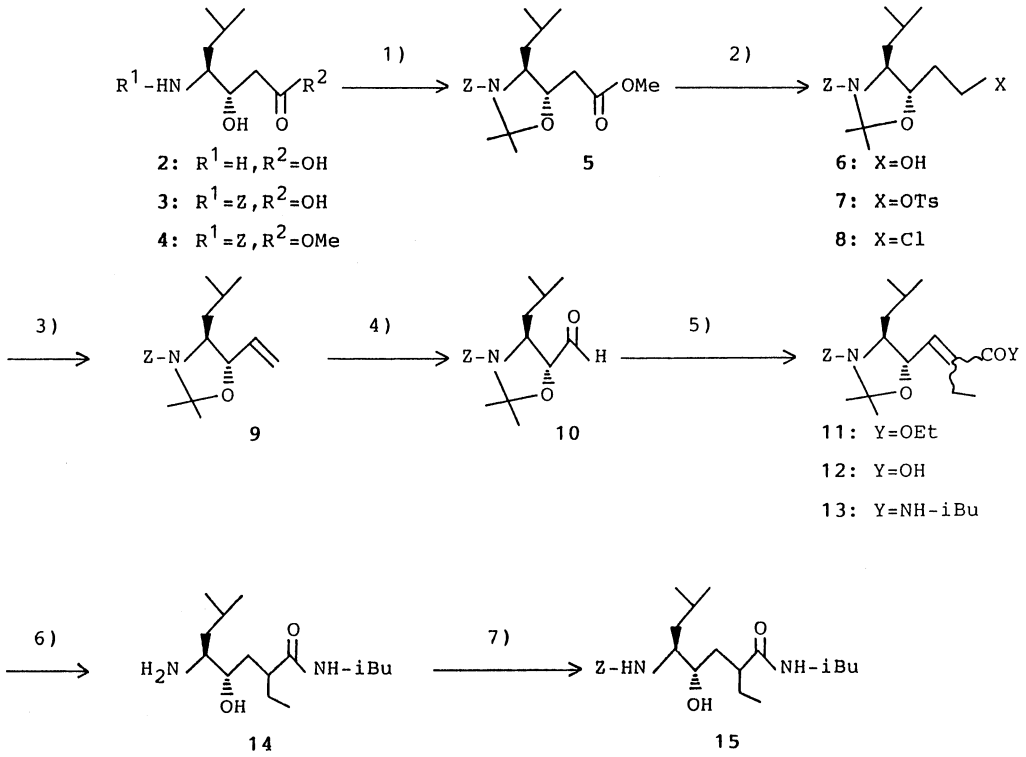
IC_{50}(nM, human plasma renin) 0.17

Fig. 1. A highly active renin inhibitor, (2*RS*, 4*S*, 5*S*)-*N*-isobutyl-5-[[*N*-[(2*S*)-2-(1-naphthylmethyl)-3-(2-pyrimidinylsulfonyl)propionyl]-L-norleucyl]-amino]-2-ethyl-4-hydroxy-7-methyloctanamide (**26**).

Results and Discussions

Our new method for a synthesis of homostatine analogue (**1**) has a characteristic of using two chiral centers (3*S*,4*S*) of statine (**2**) which was easily obtained from hydrolysis of pepstatin (isovaleryl-Val-Val-Sta-Ala-Sta), a natural aspartic protease inhibitor. Pepstatin was highly produced (4 mg ml^{-1}) by actinomycetes in media containing various sources, as reported before.[12] Pepstatin was hydrolyzed in concentrated hydrochloric acid at 30—40 °C for several days. By sequential chromatographical separations of the mixture, pure statine (**2**) was obtained in about 50% yield. Thus, it has become possible to supply a large amount of statine (**2**) from hydrolysis of pepstatin.

Scheme 1 illustrates a synthetic pathway to a homostatine analogue (**14**). Treatment of statine (**2**)

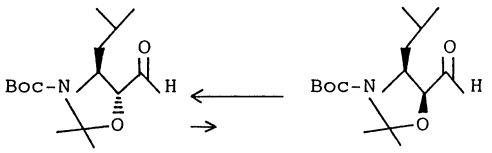


Reagents: 1) $(MeO)_2C(CH_3)_2$, TsOH; 2) a. $NaBH_4$ b. TsCl, pyridine c. LiCl; 3) $KOBu^t$; 4) OsO_4, $NaIO_4$; 5) $(EtO)_2PO$-CH(Et)-COOEt, Et_3N, LiCl; 6) Pd, H_2; 7) Z-S-Reagent, Et_3N.

Abbreviation: Z=benzyloxycarbonyl, *i*Bu=isobutyl, Bu^t=*t*-butyl, Et=ethyl.

Scheme 1. Synthesis of a homostatine analogue.

with *O*-benzyl *S*-(4,6-dimethyl-2-pyrimidinyl)carbonothioate gave *N*-*Z*-statine (**3**) in 93% yield. Esterification with methanolic hydrogen chloride, followed by *N*,*O*-isopropylidenation with 2,2-dimethoxypropane afforded fully-protected statine **5** as colorless syrup in 91% yield. Reduction of **5** with sodium borohydride in ethanol gave an alcohol **6** quantitatively. Treatment of **6** with *p*-toluenesulfonyl chloride in pyridine gave the tosylate **7**, together with the chloride **8** as a minor product. A mixture of **7** and **8** was treated with lithium chloride in *N*,*N*-dimethylformamide (DMF) without separation to afford a single product **8** in 80% yield. The chloride **8** was treated with potassium *t*-butoxide in DMSO and benzene (1 : 1) to afford a vinyl compound **9** quantitatively. A key intermediate, (4*S*,5*R*)-3-benzyloxycarbonyl-5-formyl-4-isobutyl-2,2-dimethyloxazolidine (**10**) was obtained from the Lemieux-Johnson oxidation[13] of **9** in 94% yield. The elongation of the C-terminus was carried out with aldehyde **10** and diethyl phosphonate, $(EtO)_2$-$POCH(R^1)COR^2$. An epimerization at the α-position of the formyl group in the aldehyde **10** is likely to occur under drastic conditions, and we observed in fact that a Horner-Wadsworth-Emmons reaction using sodium hydride as a base resulted in partial epimerization. In addition to that, Thaisrivongs et al.[14] reported that the diastereomeric mixture of (4*S*,5*RS*)-3-*t*-butoxycarbonyl-5-formyl-4-isobutyl-

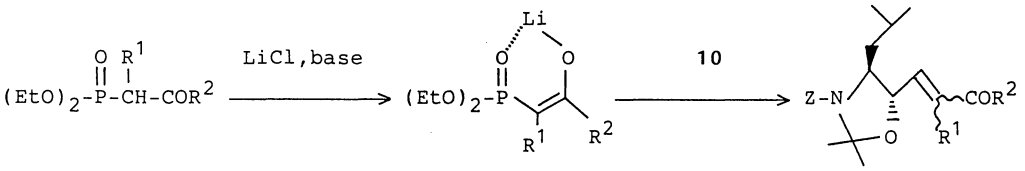


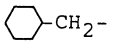
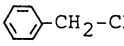
(4*S*, 5*R*) (4*S*, 5*S*)

Scheme 2. Base-catalyzed equilibration between (4*S*, 5*R*)- and (4*S*,5*S*)-5- formyloxazolidine derivatives.[14]

oxazolidine which was prepared from an (2*S*)-amino aldehyde derivative, can be equilibrated to the favorable (4*S*,5*R*)-isomer rather than unfavorable(4*S*,5*S*)-isomer [10 : 1<(4*S*,5*R*) : (4*S*,5*S*)] (Scheme 2). However, we found that under the modified reaction conditions,[15,16] where the reaction proceeded smoothly in the presence of lithium chloride and triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) instead of a strong base such as butyllithium or metal alkoxide, no epimerization was observed. Thus, Emmons condensation product **11** containing an alkyl substituent at the position-2 was prepared in good yield as an *E*/*Z* mixture in a 50 : 50—60 : 40 ratio, as shown in Table 1. Ethyl (diethoxyphosphinyl) acetate (Entry 1, Table 1) was allowed to react with **10** in the presence of triethylamine. However, ethyl 2-(diethoxyphosphinyl)-alkanoate needed more stong base such as DBU than

Table 1. Modified Horner-Wadsworth-Emmons Reactions

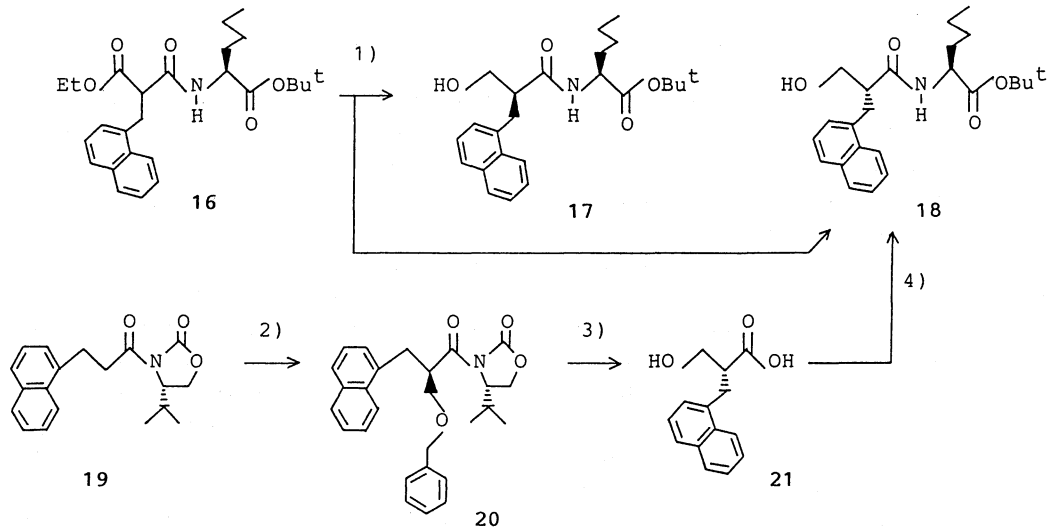


Entry	R^1	R^2	Base	Yield/%	$(E:Z)^{a)}$
1	H	OEt	Et_3N	82	100:0
2	*i*-Bu	OEt	Et_3N	27	50:50
3	*i*-Bu	OEt	DBU	65	60:40
4	*i*-Bu	NH-*i*-Bu	DBU	0	—
5	*i*-Pr	OEt	DBU	60	35:65
6	Et	OEt	DBU	88	52:48
7		OEt	DBU	68	61:39
8		OEt	DBU	83	58:42
9	THP-O-$(CH_2)_3$-	OEt	DBU	84	60:40

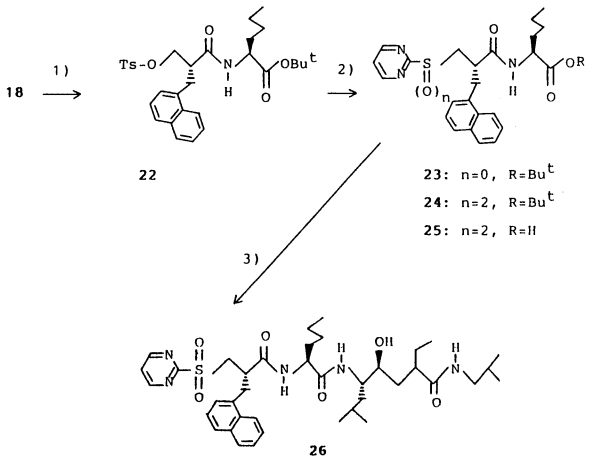
Et: ethyl, *i*-Bu: isobutyl, *i*-Pr: isopropyl, DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene, THP: tetrahydropyranyl. a) Determined by HPLC analysis.

triethylamine (Entry 2 and 3). In the case of Entry 4 in Table 1, *N*-isobutyl-4-methyl-2-(diethoxyphosphinyl)-pentanamide failed to react with **10** under the same conditions. Therefore, the ester **11** obtained under the conditions of Entry 6 was converted via **12** into an amide **13** as follows. The ester **11** was hydrolyzed with sodium hydroxide in aqueous ethanol prior to hydrogenolysis of the double bond and hydrogenolytic removal of the protecting groups, in order to prevent a lactone formation. The resulted carboxylic acid **12** was condensed with isobutylamine to yield an *E/Z* mixture of *N*-isobutyl-3-[(4*S*,5*S*)-3-benzyloxycarbonyl-4-isobutyl-2,2-dimethyl-5-oxazolidinyl]-2-ethyl-2-propenamide (**13**) which could be separated by silica-gel column chromatography to afford (*Z*)-isomer (**13a**) and (*E*)-isomer (**13b**). But even as in an *E/Z* mixture, compound **13** was allowed to be reduced over palladium black under the atmospheric pressure of hydrogen to give a homostatine isobutylamide **14** as a 1:1 mixture of stereoisomers at the position-2. After conversion of **14** into a *N*-benzyloxycarbonyl compound **15**, the stereoisomers at the position-2 of **15** were separated by HPLC. The separated **15a** and **15b** were debenzyloxycarbonylated by a usual manner to give a chiral homostatine **14a** and **14b**, respectively.

Wuts et al. reported that an isomerization of the double bond was observed when an ester of the Horner-Emmons product such as **11** was hydrogenated over palladium carbon.[17] However, in the course of this study, we did not observe any epimerization at the position-4 in homostatine or the formation of the carbonyl compound reported by Wuts et al.



Scheme 3. 1) $NaBH_4$; 2) LDA, $BnOCH_2Br$; 3) a. LiOOH, b. cyclohexene/ethanol, Pd, reflux; 4) L-Nle-OBu^t, HOBT, DCC.



Scheme 4. 1) TsCl, pyridine; 2) 2-pyrimidinethiol, NaH, DMF; 3) a: H_2O_2, Na_2WO_4, b: TFA-CH_2Cl_2, c. homostatine (**14**), DPPA, Et_3N.

This may be due to the conversion of ester **11** into the stable amide **13** before reduction of the double bond and removal of *N,O*-isopropylidene group. Thus we have ensured an efficient synthesis of a homostatine analogue **14** starting from natural statine.

Schemes 3 and 4 illustrate a synthetic pathway to the N-terminus of **26**. We have led *N*-[(2*RS*)-ethoxycarbonyl-3-(1-naphthyl)propionyl]-L-norleucine *t*-butyl ester (**16**) into a N-terminal precursor of our renin inhibitor, which is the modification of *N*-benzyloxycarbonyl-3-(1-naphthyl)-L-alanine,[18] a typical N-terminus of previous inhibitors.[19] Compound **16** was readily prepared from condensation between racemic 2-ethoxycarbonyl-3-(1-naphthyl)propionic acid and L-norleucine *t*-butyl ester by DPPA[25] or DCC-HOBT method. Borohydride reduction of **16** afforded a diastereomeric mixture which was separated by silica-gel column chromatography to afford **17** and **18**. The stereostructure of the diastereomers **17** and **18** were determined by an asymmetric alkylation of **19** to afford **20**. Acylation of lithium salt of Evans chiral auxiliary, (4*S*)-isopropyl-2-oxazolidinone with 3-(1-naphthyl)propionyl chloride gave **19**.[20] The asymmetric alkylation[21] was accomplished by the treatment of **19** with LDA and bromomethyl benzyl ether which was generated in situ from chloromethyl benzyl ether.[4] Hydroxy acid **21** could be obtained by a treatment of **20** with lithium hydrogen peroxide,[22] followed by catalytic transfer hydrogenation using palladium black and cyclohexene as the hydrogen doner.[23] When the hydrolysate of **20** was treated with a usual hydrogenation over palladium black under the atmospheric pressure of hydrogen, it afforded the unfavorable tetralin compound. The chiral acid **21** was coupled with L-norleucine *t*-butyl ester to afford **18**, and any detectable amount of **17** was not included in the **18** obtained from **21**. We made use of not only **16** but also **21** in order to provide **18** efficiently. Compound **18** was treated with tosyl chloride in pyridine by usual manner to afford **22**. Compound **22** was treated with sodium thiolate which was prepared from sodium hydride and 2-pyrimidinethiol in DMF to afford **23**. Oxidation of **23** with hydrogen peroxide in the presence of sodium tungstate afforded **24**. Thus, by means of versatile nucleophilicity of the thiolate anion followed by subsequent oxidation, various sulfonyl compounds were synthesized.[10] During the conversion of **18** into **24** (Scheme 4), little epimerization took place at the α-position of the 2-(1-naphthylmethyl)propionyl moiety.[24] After **24** was treated with trifuloroacetic acid to deprotect *t*-butyl ester, the resulting **25** was coupled with a homostatine analogue **14** (as a 1 : 1 mixture of (2*R*)- and (2*S*)-isomer) to afford a highly active renin inhibitor **26**. According to the results of our assay, the 2-pyrimidinylsulfonyl compound **26** revealed a quite potent inhibitory activity against human plasma renin (0.17 nM, IC_{50}). The structure-activity relationship at the 2-position in homostatine analogue (**1**) is under investigation.

Experimental

General. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined with a HORIBA SEPA-200 HIGH SENSITIVE POLARIMETER. IR spectra were recorded on a HITACHI 270-30 Infrared Spectrophotometer. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a VARIAN VXR-300 spectrometer. High-performance liquid chromatography (HPLC) was carried out by a Jasco 880-PU intelligent HPLC pump (JAPAN SPECTROSCOPIC CO.,LTD.) and a SSC UVDETECTOR 3000 (SENSHU SCIENTIFIC Co., Ltd.). Mass spectra were obtained with JEOL JMS-DX300 mass spectrometer. Elemental analyses were measured by a service at Sumika Chemical Analysis Service, Ltd. Thin-layer chromatography was conducted with E. Merck 0.25-mm glass plates precoated with silica-gel 60 F_{254}(Art. 5715). For column chromatography, E. Merck silica-gel 60, 70—230 mesh (Art. 7734) was used.

Statine (2), (Hydrolysis of Pepstatin). Pepstatin was obtained from a culture of actinomycetes , as described before.[12] Pepstatin (110 g) was dissolved in concentrated hydrochloric acid (1 l)and hydrolyzed at 37—40 °C for two days. The solution was diluted with 25% water-containing methanol (30 l) and then passed through a column of Dowex 50W (H^+-type, 50—100 mesh, 2.5 l). The column was washed with 1 M ammonium hydroxide (18 l) (1 M=1 mol dm^{-3}). The eluate was concentrated in vacuo to obtain crude powder (45 g) which was dissolved in formate buffer (0.2 M pyridine-formic acid, pH 3.0) and charged on a column of Dowex 50W (pyridine-type, 200—400 mesh, 1.2 l). The column was washed with (pH 3.0, 1.5 l and then pH 4.0, 3.0 l) and eluted with (pH 5.0, 4.5 l) the same formate buffer. Statine-containing fractions were collected and concentrated in vacuo to obtain statine (28 g, 50%): mp 200-201 °C (decomp); $[\alpha]_D^{20}$ −19° (*c* 0.5, H_2O).

***N*-(Benzyloxycarbonyl)statine (3)** To a solution of statine (3.0 g, 17 mmol) in aqueous dioxane (1 : 1, 90 ml) were

added 5.2 g (19 mmol) of *O*-benzyl *S*-(4,6-dimethyl-2-pyrimidinyl) carbonothioate (*Z*-*S*-Reagent) and triethylamine (3.6 ml, 26 mmol). The mixture was stirred at 30 °C overnight and concentrated in vacuo. The residue was dissolved in 3% aqueous sodium hydrogencarbonate (100 ml) and washed with diethyl ether. After the organic layer was removed, the aqueous layer was adjusted to pH 4 by a dropwise additon of 1 M hydrochloric acid and extracted with ethyl acetate (2×150 ml). The extracts were combined and washed with 0.5 M hydrochloric acid and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 4.9 g (93 %) of **3** as pale yellow powder. Recrystallized with diethyl ether–hexane afforded pure **3**: mp 118—121 °C; $[\alpha]_D^{20}$ −43.9° (*c* 0.9, $CHCl_3$). Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53%. Found: C, 62.17; H, 7.58; N, 4.36%.

Methyl [(4*S*,5*S*)-3-Benzyloxycarbonyl-4-isobutyl-2,2-dimethyl-5-oxazolidinyl] Acetate (5). To a solution of **3** (2.88 g, 9.3 mmol) in anhydrous methanol (15 ml) was added 10% dry hydrogen chloride in methanol (0.1 ml) and the mixture was allowed to stand at room temperature for 24 h. An additional 10% dry hydrogen chloride in methanol (0.1 ml) was added and it was warmed at 40 °C for 24 h. Volatiles were removed in vacuo and the residue was dissolved in a mixture of dichloromethane and toluene, concentrated, and dried azeotropically in vacuo to give methyl ester **4** as yellow syrup: ^{1}H NMR ($CDCl_3$) δ=0.89—0.97 (m, 6H), 1.37 (m, 1H), 1.50—1.75 (m, 2H), 2.50—2.57 (m, 2H), 3.27 (br, 1H), 3.65—3.74 (m, 4H), 4.04 (m, 1H), 4.99 (d, 1H, *J*=9 Hz), 5.10 (s, 2H), and 7.32—7.38 (m, 5H). To a solution of the methyl ester **4** in 2,2-dimethoxypropane (15 ml) was added dry *p*-toluenesulfonic acid (83 mg, 0.48 mmol) and it was stirred at room temperature for 2 h and then at 38 °C for 1 h. The resultant mixture was diluted with diethyl ether (300 ml) and washed successively with 4% aqueous sodium hydrogencarbonate and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (20 : 1 toluene–ethylacetate) to afford 3.08 g (91%) of **5** as colorless syrup: $[\alpha]_D^{20}$ +8.7° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1700 and 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.75—1.01 (m, 6H), 1.44—1.68 (m, 9H), 2.63 (m, 2H), 3.70 (s, 3H), 3.83 (m, 1H), 4.34 (br t, 1H, *J*=6.9 Hz), 5.08 (br m, 1H), 5.18 (d, 1H, *J*=12.0 Hz), and 7.32—7.38 (m, 5H).

HRMS(FAB) Found: *m/z* 364.2139. Calcd for $C_{20}H_{29}NO_5$: M+H, 364.2124.

(4*S*,5*S*)-3-Benzyloxycarbonyl-5-(2-hydroxyethyl)-4-isobutyl-2,2-dimethyloxazolidine (6). To a stirred solution of **5** (3.02 g, 8.31 mmol) in ethanol (75 ml) was added sodium borohydride (630 mg, 16.7 mmol) and the mixture was stirred for 8 h. After sodium borohydride (945 mg) was added and it was stirred for 24 h, an additional sodium borohydride (945 mg) was added and it was stirred for 16 h. The mixture was concentrated in vacuo to give a suspension which was dissolved in chloroform (250 ml). After addition of water (150 ml), 1 M hydrochloric acid (50 ml) was added dropwise into the two-phase solution with vigorous stirring to decompose excess sodium borohydride. The organic layer was adjusted to pH 5, separated from the aqueous layer, washed with 4% aqueous hydrogencarbonate and then brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 2.78 g (99.7%) of **6** as colorless oil: $[\alpha]_D^{20}$ +6.8° (*c* 0.84, $CHCl_3$); IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.75—1.00 (m, 6H), 1.42—1.71 (m, 8H), 1.71—2.00 (m, 3H), 3.71—3.86 (m, 3H), 4.10 (m, 1H), 5.09 (br d, 1H, *J*=12.5 Hz), 5.18 (d, 1H, *J*=12.5 Hz), and 7.33—7.40 (m ,5H).

HRMS(FAB) Found: *m/z* 336.2187. Calcd for $C_{19}H_{29}NO_4$: M+H, 336.2175.

(4*S*,5*S*)-3-Benzyloxycarbonyl-5-(2-chloroethyl)-4-isobutyl-2,2-dimethyloxazolidine (8). To a solution of **6** (3.89 g, 11.6 mmol) in anhydrous pyridine (15 ml) was added *p*-toluenesulfonyl chloride (2.65 g, 13.9 mmol) and the mixture was allowed to stand at room temperature overnight. The resultant mixture was concentrated in vacuo and the resulted crystals were filtered off and washed with a small amount of toluene. The combined filtrate was concentrated in vacuo and was purified by silica-gel column chromatography (30 : 1 benzene–ethyl acetate) to give a mixture (4.47 g) of **7** and **8** as syrup. To a solution of this syrup in anhydrous DMF (30 ml) was added dry lithium chloride (1.16 g, 27.4 mmol) and the mixture was allowed to stand at room temperature overnight. After the mixture was concentrated in vacuo, the residue was dissolved in chloroform (300 ml). The solution was washed with water, 2% aqueous potassium hydrogensulfate, 4% aqueous sodium hydrogencarbonate, and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 3.30 g (80%) of **8** as colorless syrup: $[\alpha]_D^{20}$ −8.6° (*c* 1.3, $CHCl_3$); ^{1}H NMR($CDCl_3$); δ=0.75—1.04 (m, 6H), 1.45—1.67 (m, 9H), 1.94 (m, 1H), 2.09 (m, 1H), 3.56—3.85 (m, 3H), 4.12 (m, 1H), 5.09 (m, 1H), 5.18 (d, 1H, *J*=12.0 Hz), and 7.29—7.31 (m, 5H).

Calcd for $C_{19}H_{28}ClNO_3$: C, 64.49; H, 7.97; N, 3.96; Cl, 10.02%. Found: C, 64.57; H, 7.91; N, 3.98; Cl, 10.08%.

(4*S*,5*S*)-3-Benzyloxycarbonyl-5-ethenyl-4-isobutyl-2,2-dimethyloxazolidine (9). To a stirred and cooled solution of **8** (610 mg, 1.72 mmol) in dry benzene (3.6 ml) was added a solution of potassium *t*-butoxide (390 mg, 3.48 mmol) in dimethyl sulfoxide (3.6 ml). The mixture was warmed to room temperature and stirred for 10 minutes. The solution was directly charged on a column of silica gel and eluted with benzene–ethyl acetate (30 : 1). The eluate was concentrated in vacuo to afford 540 mg (99%) of **9** as colorless syrup: $[\alpha]_D^{20}$ +13.3°(*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.73—1.00 (m, 6H), 1.45—1.72 (m, 9H), 3.85 (br, 1H), 4.30 (dd, 1H, *J*=3.8 Hz, 7.0 Hz), 5.09 (d, 1H, *J*=12.4 Hz), 5.17 (d, 1H, *J*=12.3 Hz), 5.21 (d, 1H, *J*=10.2 Hz), 5.32 (d, 1H, *J*=17.0 Hz), 5.94 (ddd, 1H, *J*=7.1 Hz, 10.2 Hz, 17.2 Hz), and 7.29—7.38 (m, 5H).

HRMS(FAB) Found: *m/z* 318.2079. Calcd for $C_{19}H_{27}NO_3$: M+H, 318.2069.

(4*S*, 5*R*)-3-Benzyloxycarbonyl-5-formyl-4-isobutyl-2,2-dimethyloxazolidine (10). To a solution of **9** (535 mg, 1.69 mmol) in dioxane (3.5 ml) was added a solution of osmium tetraoxide (30 mg, 0.12 mmol) in dioxane (3 ml) at room temperature. The mixture was stirred in the dark for 15 minutes. The resulted mixture was diluted with water (7 ml) and aqueous sodium periodate (720 mg, 3.37 mmol in 4 ml) was added dropwise over a period of 1 h. After being stirred for additional 1 h, the precipitate was removed by filtration. The filtrate was extracted with ethyl acetate (80 ml) and the extract was washed with 5% aqueous sodium sulfide and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was further dried under the reduced pressure to afford 477 mg (94 %) of **10** as crude syrup: IR (KBr) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=9.8 (s, 1H). Melting point and optical rotation were measured by

its 2,4-dinitrophenylhydrazone derivative.

(4*S*,5*R*)-3-Benzyloxycarbonyl-5-formyl-4-isobutyl-2,2-dimethyloxazolidine 2,4-dinitrophenylhydrazone: mp 36—42 °C; $[\alpha]_D^{20}$ −82.4°(*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.85—1.05 (m, 6H), 1.5—1.7 (m, 9H), 4.37 (br, 1H), 4.63 (dd, 1H, *J*=2.0 Hz, 4.7 Hz), 5.16 (s, 2H), 7.37 (m, 5H), 7.53 (d, 1H, *J*=4.7 Hz), 7.83 (br, 1H), 8.28 (br, 1H), 9.12 (d, 1H, *J*=2.4 Hz), and 11.07 (s, 1H); HRMS (FAB) Found: *m/z* 500.2162. Calcd for $C_{24}H_{29}N_5O_7$: M+H, 500.2145.

Ethyl 2-(diethoxyphosphinyl)butanoate. Sodium hydride (856 mg, 60% dispersion in mineral oil, 21.5 mmol) was washed with hexane to separate the oil. After dried under a nitrogen stream, the powdered sodium hydride was suspended in DMF (7.2 ml). To the ice-cooled and stirred suspension was added dropwise ethyl (diethoxyphosphinyl)-acetate (4.26 ml, 21.5 mmol) over a period of 1 h and the mixture was stirred at room temperature for 1 h and then it was recooled in an ice bath. To the mixture was added bromoethane (1.92 ml, 25.7 mmol) and the mixture was stirred at 55 °C overnight. The resultant mixture was poured into water (40 ml) and extracted with ethyl acetate (3×20 ml). The extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (4:1 hexane–acetone) to afford 2.76 g (51%) of the title compound as oil: ^1H NMR ($CDCl_3$) δ=0.98 (t, 3H *J*=7.0 Hz), 1.29—1.33 (m, 12H), 1.88—2.08 (m, 2H), 2.84 (ddd, 1H, *J*=22.6 Hz, 10.5 Hz, 4.4 Hz), 4.08—4.29 (m, 6H); FAB MS *m/z* 253 $(M+H)^+$.

Ethyl 3-[(4*S*,5*S*)-3-benzyloxycarbonyl-4-isobutyl-2,2-dimethyl-5-oxazolidinyl]-2-ethyl-2-propenoate (11). To a stirred suspension of lithium chloride (72 mg, 1.70 mmol) in 5 ml of dry tetrahydrofuran (THF) in an argon atmosphere were added a solution of ethyl 2-(diethoxyphosphinyl)-butanoate (426 mg, 1.69 mmol) in dry THF (0.6 ml) and a 50% dry THF solution containing DBU (323 mg, 2.12 mmol). After being stirred at room temperature for 10 min, a solution of **10** (450 mg, 1.41 mmol) in dry THF (1.0 ml) was added into the mixture and it was stirred at room temperature overnight. The resultant mixture was neutralized with 1 M hydrochloric acid with cooling in an ice bath and then extracted successively with ethyl acetate. The combined extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual syrup was purified by silica-gel column chromatography(10:1 benzene–ethyl acetate) to give (518 mg, 88%) of **11** as colorless syrup: ^1H NMR ($CDCl_3$) δ=0.65—0.96 (m, 6H), 1.01 (m, 3H), 1.26 (t, 3H, *J*=7.1 Hz), 1.4—1.7 (m, 9H), 2.22—2.44 (m, 2H), 3.74 (br, 0.5H), 3.82 (br, 0.5H), 4.18 (m, 2H), 4.58 (dd, 0.5H *J*=2.7 Hz, 9.0 Hz), 5.00—5.18 (m, 2.5H), 5.83 (d, 0.5H, *J*=9.0 Hz), 6.67 (d, 0.5H, *J*=9.0 Hz), and 7.3 (m, 5H).

HRMS(FAB) Found: *m/z* 418.2601. Calcd for $C_{24}H_{35}NO_5$: M+H, 418.2594.

***N*-Isobutyl-3-[(4*S*,5*S*)-3-benzyloxycarbonyl-4-isobutyl-2,2-dimethyl-5-oxazolidinyl]-2-ethyl-2-propenamide (13).** Compound of **11** (517 mg, 1.24 mmol) was dissolved in 2 M potassium hydroxide (3.1 ml, 6.2 mmol) in aqueous ethanol (EtOH–water 9:1) and the solution was stirred for 3 h at room temperature. The reaction mixture was adjusted to pH 2 with 1 M hydrochloric acid with cooling in an ice bath, diluted with water (24 ml), and extracted with ethyl acetate (3×20 ml). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford 3-[(4*S*,5*S*)-3-benzyloxycarbonyl-4-isobutyl-2,2-dimethyl-5-oxazolidinyl]-2-ethyl-2-propenoic acid (**12**) as crude syrup. To a cooled (−10 °C) and stirred solution of the crude **12** in dry DMF (1.0 ml) were added successively isobutylamine (0.15 ml, 1.48 mmol) and 0.32 ml (1.48 mmol) of diphenyl phosphorazidate (DPPA),[25] and triethylamine (0.21 ml, 1.50 mmol). The mixture was stirred at −10 °C for 1 h and then stirred at room temperature overnight. The resultant mixture was diluted with ethyl acetate (60 ml), washed with 10% aqueous citric acid, 4% aqueous sodium hydrogencarbonate, and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (5:1 hexane–ethyl acetate) to afford 204 mg (37%) of (2*Z*)-*N*-isobutyl-3-[(4*S*,5*S*)-3-benzyloxycarbonyl-4-isobutyl-2,2-dimethyl-5-oxazolidinyl]-2-ethyl-2-propenamide (**13a**) as a solid and 151 mg (27%) of (2*E*)-*N*-isobutyl-3-[(4*S*, 5*S*)-3-benzyloxycarbonyl-4-isobutyl-2,2-dimethyl-5-oxazolidinyl]-2-ethyl-2-propenamide (**13b**) as colorless syrup.

Z-Isomer **13a**: mp 86—87 °C; $[\alpha]_D^{20}$ −63.2°(*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.82 (m, 1H), 2.26 (m, 1H), 2.40 (m, 1H), 3.19 (m, 2H), 3.81 (br, 1H), 4.51 (dd, *J*=2.6 Hz, 8.7 Hz, 1H), 5.10 (br d,*J*=12.3 Hz, 1H), 5.19 (d, *J*=12.2 Hz, 1H), 5.61 (d, *J*=8.8 Hz, 1H), 6.54 (br, 1H), and 7.36 (m, 5H).

Calcd for $C_{26}H_{40}N_2O_4$: C, 70.24; H, 9.07; N, 6.30%. Found: C, 70.14; H, 9.23; N, 6.47%.

E-Isomer **13b**: $[\alpha]_D^{20}$ −40.8° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.82 (m, 1H), 2.42 (m, 2H), 3.14 (dt, *J*=1.5 Hz, 5.0 Hz, 2H), 3.83 (br, 1H), 4.60 (dd *J*=2.8 Hz, 8.9 Hz, 1H), 5.09 (br d, *J*=11.7 Hz, 1H), 5.18 (d, *J*=11.8 Hz, 1H), 5.76 (br, 1H), 6.08 (d, *J*=9.0 Hz, 1H), and 7.3—7.4 (m, 5H).

Calcd for $C_{26}H_{40}N_2O_4$: C, 70.24; H, 9.07; N, 6.30%. Found: C, 70.16; H, 9.11; N, 6.74%.

(2*RS*,4*S*,5*S*)-*N*-Isobutyl-5-amino-2-ethyl-4-hydroxy-7-methyloctanamide (14). A solution of **13** (1:1 mixture of *E* and *Z*, 578 mg, 1.30 mmol) in methanol (10 ml) was hydrogenated under the atmospheric pressure of hydrogen over palladium black. During 4 h, 1.4 ml of 1 M hydrochloric acid (7×0.2 ml, 1.4 mmol) was added dropwise into the solution to maintain the pH (ca. 5). Then the palladium black was filtered off and the filtrate was concentrated in vacuo. A solution of the residual syrup in a mixture of dichloromethane–benzene was concentrated and dried under reduced pressure to afford 361 mg (90%) of **14** as amorphous hydrochloride salt. The crude **14** could be coupled with an acid component without any purification. The pure **14a** and **14b** [(2*R*)-isomer or (2*S*)-isomer] were obtained as hygroscopic solids by catalytic (over 10% palladium carbon) hydrogenation of **15a** and **15b**, respectively. Their spectral data are shown as follows.

Isomer **14a** (derived from **15a**): IR (KBr) 3350, 3080, 2970, 2870, 2720, 1650, 1600, 1550, and 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.8—1.0 (m, 15H), 1.13—1.38 (m, 2H), 1.50—1.87 (m, 5H), 2.2—2.5 (m, 3H), 2.59 (m, 1H), 3.03 (m, 1H), 3.13 (m, 1H), 3.30 (m, 1H), and 6.34 (br, 1H); ^{13}C NMR ($CDCl_3$) δ=11.8, 20.0 (2C), 21.4, 23.6, 24.6, 25.2, 28.3, 37.1, 43.4, 45.8, 46.6, 53.6, 72.6, and 176.0.

Isomer **14b** (derived from **15b**): IR (KBr) 3330, 2960, 2880, 1650, 1580, 1550, and 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.80—1.05 (m, 15H), 1.10—1.50 (m, 3H), 1.62—1.89 (m, 3H), 2.2—2.5 (m, 3H), 2.54 (m, 1H), 2.99—3.22 (m, 3H), and 6.24

(br,1H); ^{13}C NMR ($CDCl_3$) δ=12.2, 20.1 (2C), 21.4, 23.7, 24.7, 26.3, 28.4, 37.5, 43.6, 45.7, 46.7, 53.9, 71.6, and 175.5.

(2*R* or 2*S*,4*S*,5*S*)-*N*-Isobutyl-5-benzyloxycarbonylamino-2-ethyl-4-hydroxy-7-methyloctanamide (15a) and (2*S* or 2*R*,4*S*,5*S*)-*N*-isobutyl-5-benzyloxycarbonylamino-2-ethyl-4-hydroxy-7-methyloctanamide (15b). A (2*RS*,4*S*, 5*S*)-stereomixture of **15** (410 mg,73%) was obtained from **14** (425 mg) by the same method used for the preparation of **3** from **2**. The mixture (200 mg) was separated by HPLC to afford **15a** (77 mg) and **15b** (49 mg). The conditions were given as follows. Column: Senshu Pak Silica-1151-N (ϕ10×300 mm); solvent:100 : 20 : 5 hexane-ethyl acetate-methanol (flow rate 3.0 ml min^{-1}); detection: 254 nm; retention time 20.0 min (**15a**) and 22.8 min (**15b**).

Isomer **15a**: mp 122—123 °C; $[\alpha]_D^{20}$ +8.4° (*c* 1.2, $CHCl_3$); IR (KBr) 3480, 3360, 3340, 2960, 2930, 2870, 1670, 1650, 1550, 1470, 1390, 1360, 1270, 1230, and 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.83 (t, *J*=7.4 Hz, 3H), 0.90 (m, 12H), 1.2—1.9 (m, 8H), 2.15 (m, 1H), 2.96 (m ,1H), 3.11 (m, 1H), 3.55 (m, 1H), 3.69 (m, 1H), 3.74 (d, *J*=5.1 Hz, 1H), 5.07 (m, 2H), 5.34 (d, *J*=9.6 Hz, 1H), and 6.04 (br t, *J*=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=11.6, 20.0 (2C), 22.1, 23.0, 24.5, 26.6, 28.3, 36.7, 41.8, 46.0, 46.7, 52.5, 66.4, 72.0, 127.7, 127.8, 128.3, 136.6, 156.7, and 176.2.

Calcd for $C_{23}H_{38}N_2O_4$: C, 67.95; H, 9.42; N, 6.89%. Found: C, 68.10; H, 9.42; N, 7.08%.

Isomer **15b**: mp 150—152 °C; $[\alpha]_D^{20}$ −35.0° (*c* 1.0, $CHCl_3$); IR (KBr) 3460, 3330, 2960, 2940, 2870, 1680, 1630, 1550, 1470, 1390, 1270, 1120, 1070, and 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.9 (m, 15H), 1.25—1.8 (m, 8H), 2.29 (m, 1H), 3.00 (m, 1H), 3.11 (m, 1H), 3.64 (br, 3H), 5.00 (br d, *J*=8.4 Hz, 1H), 5.09 (s, 2H), 5.92 (br t, *J*=5.1 Hz, 1H), and 7.27—7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=12.2, 20.0 (2C), 22.0, 23.1, 24.7, 25.1, 28.4, 36.8, 41.7, 45.7, 46.8, 53.6, 66.5, 70.4, 127.7, 127.9, 128.3, 136.5, 156.8, and 176.3.

Calcd for $C_{23}H_{38}N_2O_4$: C, 67.95; H, 9.42; N, 6.89%. Found: C, 68.00; H, 9.55; N, 7.09%.

***N*-[(2*S*)-3-Hydroxy-2-(1-naphthylmethyl)propionyl]-L-norleucine *t*-Butyl Eser (17) and *N*-[(2*R*)-3-hydroxy-2-(1-naphthylmethyl)propionyl]-L-norleucine *t*-Butyl Ester (18).** Compound **16** (2.45 g, 5.6 mmol) was prepared from racemic 2-ethoxycarbonyl-3-(1-naphthyl)propionic acid and L-norleucine *t*-butyl ester by DPPA[25] method. To a stirred solution of **16** in ethanol (60 ml) was carefully added sodium borohydride (1.48 g, 39 mmol) and the mixture was stirred at room temperature for 3.5 h. An additional sodium borohydride (0.5 g, 13 mmol) was added and stirred for 2 h. The resultant mixture was concentrated in vacuo (<40 °C) to afford paste which was suspended in ethyl acetate (250 ml). The solution was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (1 : 1 hexane-ethyl acetate) to afford **17** (0.97 g, 44%) and **18** (0.74 g, 33%) as white amorphous solids.

Compound **17**: mp 92—94 °C; $[\alpha]_D^{20}$ −72.6° (*c* 1.0, $CHCl_3$); IR (KBr) 3260, 3100, 2960, 2870, 1750, 1660, and 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.84 (t, *J*=7.4 Hz, 3H), 0.92 (m, 2H), 1.17 (m, 2H), 1.35—1.55 (m, 2H), 1.43 (s, 9H), 2.79 (m, 1H), 3.26 (m, 2H), 3.48 (dd, *J*=9.0 Hz, 14.1 Hz, 1H), 3.86 (t, *J*=6.5 Hz, 2H), 4.36 (m, 1H), 5.74 (br d, *J*=7.8 Hz, 1H), 7.36 (m, 2H), 7.51 (m, 2H), 7.73 (m, 1H), 7.86 (dd, *J*=1.5 Hz, 8.1 Hz, 1H), and 8.02 (dd, *J*=1.0 Hz, 7.8 Hz, 1H).

Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51%. Found: C, 72.01; H, 8.28; N, 3.51%.

Compound **18**: mp 94—95 °C; $[\alpha]_D^{20}$ +50.5° (*c* 1.0, $CHCl_3$); IR (KBr) 3380, 2960, 2870, 1720, 1650, and 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.86 (t, *J*=7.1 Hz, 3H), 1.13—1.15 (m, 4H), 1.43 (s, 9H), 1.62 (m, 1H), 1.77 (m, 1H), 2.77 (m, 2H), 3.33 (dd, *J*=7.7 Hz, 13.9 Hz, 1H), 3.49 (dd, *J*=7.5 Hz, 13.8 Hz, 1H), 3.82 (m, 1H), 4.37 (ddd, *J*=5.6 Hz, 7.1 Hz, 12.9 Hz, 1H), 6.12 (br d, *J*=7.2 Hz, 1H), 7.38 (d, *J*=5.1 Hz, 2H), 7.52 (m, 2H), 7.73 (dd, *J*=3.0 Hz, 6.6 Hz, 1H), 7.86 (dd, *J*=1.5 Hz, 8.1 Hz, 1H), and 8.05 (dd, *J*=0.9 Hz, 8.4 Hz, 1H).

Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51%. Found: C, 72.09; H, 8.27; N, 3.79%.

(4*S*)-3-[(2*R*)-3-Benzyloxy-2-(1-naphthylmethyl)propionyl]-4-isopropyl-2-oxazolidinone (20). Prior to the asymmetric alkylation, bromomethyl benzyl ether was generated from chloromethyl benzyl ether and used in the reaction immediately. To a solution of dry lithium bromide (3.23 g, 37 mmol) in THF (10 ml) under a dry argon atmosphere was added dropwise a solution of chloromethyl benzyl ether (5.56 g, 36 mmol) in dry THF (10 ml) at room temperature. The solution was stirred for 1 h. To the reaction vessel was attached a vacuum line which was filled with anhydrous calcium chloride. After almost of the THF was evaporated through the vacuum line under the reduced pressure, dry pentane was added via syringe and the solution was stirred for a few minutes. The precipitated lithium chloride was filtered off in an argon atmosphere. The filtrate was concentrated in vacuo under a dry argon stream to afford slightly brown bromomethyl benzyl ether. The crude solution was allowed to be stored in a dry argon and used in the alkylation as soon as possible. A magnetically stirred and cooled (−78 °C) solution of lithium diisopropylamide which was prepared from diisopropylamine (164 mg, 1.62 mmol) in dry THF (2 ml) and butyllithium (1.48 M in hexane, 1.09 ml, 1.61 mmol) was used to enolize **19**[20] (475 mg, 1.52 mmol) in dry THF (2 ml). After being stirred at −78 °C for 0.5 h, bromomethyl benzyl ether (0.8 ml) prepared as above was added via syringe. The mixture was stirred at −40 °C for 1 h, and stirred at 0 °C for 3 h, and it was quenched by addition of 10% aqueous ammonium chloride (20 ml). Volatiles were removed in vacuo and the product was extracted into ethyl acetate (30 ml). The extract was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford yellow oil which was purified by flash column chromatography (silica-gel, 6 : 1 hexane-ethyl acetate) to afford 470 mg (71%) of **20** as colorless oil: $[\alpha]_D^{20}$ +51.7° (*c* 0.9, $CHCl_3$); IR (KBr) 1780, 1700, 1390, 1300, and 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.75 (d, *J*=6.9 Hz, 3H), 0.85 (d, *J*=7.2 Hz, 3H), 2.28 (m, 1H), 3.38 (dd *J*=7.4 Hz, 14.0 Hz, 1H), 3.48 (dd, *J*=7.8 Hz, 13.8 Hz, 1H), 3.66 (dd, *J*=5.4 Hz, 9.3 Hz, 1H), 3.82 (dd, *J*=6.8 Hz, 8.9 Hz, 1H), 3.86 (t, *J*=8.6 Hz, 1H), 4.03 (dd, *J*=3.0 Hz, 9.0 Hz, 1H), 4.28 (m, 1H), 4.50 (m, 2H), 4.69 (m, 1H), 7.27—7.39 (m, 7H), 7.49 (m, 2H), 7.72 (dd, *J*=3.0 Hz, 6.6 Hz, 1H), 7.83 (m, 1H), and 8.09 (m, 1H).

HRMS(FAB) Found: *m/z* 432.2181. Calcd for $C_{27}H_{29}NO_4$: M+H, 432.2175.

(2*R*)-3-Hydroxy-2-(1-naphthylmethyl)propionic Acid (21). To a solution of **20** (200 mg, 0.46 mmol) in aqueous THF (9.6 ml, 3 : 1 THF-water) cooled in an ice bath were added 30% hydrogen peroxide (0.26 ml, 5 equiv) and lithium hydroxide monohydrate (43.5 mg, 1.04 mmol). The mixture was stirred at room temperature for 6.5 h and then

cooled (0 °C). To the cooled mixture was added dropwise 1.5 M aqueous sodium sulfite (1.7 ml). After being stirred at room temperature for 1.5 h, volatiles were evaporated in vacuo and the resultant aqueous solution was adjusted pH 3 with 2 ml of 1 M sulfuric acid. The product was extracted with ethyl acetate (20 ml), washed with 1 M sulfuric acid and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 140 mg of crude (2*R*)-3-benzyloxy-2-(1-naphthylmethyl)propionic acid as oil. To a solution of the oil in ethanol (4 ml) were added freshly distilled cyclohexene (2 ml) and palladium black and the mixture was refluxed for 4 h. The catalyst was filtered off and the filtrate was purified by silica-gel column (50:1:0.05 toluene-ethanol-acetic acid) to afford a solid. It was recrystallized with benzene to afford pure crystals of **21** (85 mg, 80%): mp 96—99 °C; $[\alpha]_D^{20}$ +34.8° (*c* 1.2, $CHCl_3$); IR (KBr) 3400, 3060, 2960, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.06 (m, 1H), 3.29 (dd, *J*=9.3 Hz, 14.1 Hz, 1H), 3.64 (dd, *J*=5.6 Hz, 14.0 Hz, 1H), 3.74 (dd, *J*=6.2 Hz, 11.6 Hz, 1H), 3.82 (dd, *J*=3.6 Hz, 11.1 Hz, 1H), 7.36—7.43 (m, 2H), 7.51 (m, 2H), 7.76 (dd, *J*=2.7 Hz, 6.6 Hz, 1H), 7.87 (m, 1H), and 8.08 (dd, *J*=1.0 Hz, 8.1 Hz, 1H).

Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13%. Found: C, 72.90; H, 6.25%.

***N*-[(2*R*)-3-Hydroxy-2-(1-naphthylmethyl)propionyl]-L-norleucine *t*-Butyl Ester (18) from 21.** Compound **21** was coupled with an equivalent amount of L-norleucine *t*-butyl ester by usual DCC-HOBT method in DMF to afford **18** (90%) which was identical with the sample **18** prepared from **16**.

***N*-[(2*R*)-2-(1-Naphthylmethyl)-3-(*p*-toluenesulfonyloxy)-propionyl]-L-norleucine *t*-Butyl Ester (22).** Compound **18** (488 mg) was tosylated by a usual procedure (tosyl chloride in pyridine) to afford 636 mg (94%) of **22** as colorless oil: $[\alpha]_D^{20}$ +25.8° (*c* 0.9, $CHCl_3$); IR (KBr) 3390, 2960, 2930, 1740, 1680, 1670, and 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.87 (t, *J*=7.1 Hz, 3H), 1.05—1.35 (m, 4H), 1.38 (s, 9H), 1.52 (m, 1H), 1.70 (m, 1H), 2.43 (s, 3H), 2.95 (m, 1H), 3.27 (m, 2H), 4.18 (dd, *J*=5.4 Hz, 10.2 Hz, 1H), 4.29 (m, 2H), 5.79 (br d, *J*=7.6 Hz, 1H), 7.20—7.38 (m, 5H), 7.52 (m, 2H), 7.71 (m, 1H), 7.86 (dd, *J*=1.5 Hz, 8.1 Hz, 1H), and 7.93 (dd, *J*=0.9 Hz, 8.4 Hz, 1H).

HRMS(FAB) Found: *m/z* 554.2574. Calcd for $C_{31}H_{39}NO_6S$: M+H, 554.2576.

***N*-[(2*S*)-2-(1-Naphthylmethyl)-3-(2-pyrimidinylthio)-propionyl]-L-norleucine *t*-Butyl Ester (23).** To a stirred suspension of sodium hydride (80 mg, 3.3 mmol) in dry DMF (0.5 ml) was added a solution of 2-pyrimidinethiol (560 mg, 5.0 mmol) in DMF (4 ml) and the mixture was stirred at room temperature for 1 h. The solution described as above (0.5 ml, 0.56 mmol) was added dropwise into a solution of **22** (52 mg, 94 μmol) in DMF (0.5 ml). After the mixture was stirred for 4 h, water (1 ml) was added. The product was extracted with ethyl acetate (20 ml) and the extract was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by silica-gel column (3:1 hexane-ethyl acetate) to afford 41 mg (88%) of **23** as white amorphous solids: mp 82 °C; $[\alpha]_D^{20}$ −33.7° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.85 (t, *J*=7.1 Hz, 3H), 1.11—1.35 (m, 4H), 1.37 (s, 9H), 1.56 (m, 1H), 1.75 (m, 1H), 3.04 (m, 1H), 3.38 (dd, *J*=6.2 Hz, 14.0 Hz, 1H), 3.47 (m, 2H), 4.36 (m, 1H), 6.13 (br d, *J*=7.5 Hz, 1H), 6.96 (t, *J*=5.0 Hz, 1H), 7.31—7.42 (m, 2H), 7.42—7.48 (m, 2H), 7.70 (br dd, *J*=1.5 Hz, 7.5 Hz ,1H), 7.83 (m, 1H), 8.13 (m, 1H), and 8.45 (d, *J*=4.2 Hz, 2H).

HRMS(FAB) Found: *m/z* 494.2455. Calcd for $C_{28}H_{35}N_3O_3S$: M+H, 494.2477.

***N*-[(2*S*)-2-(1-Naphthylmethyl)-3-(2-pyrimidinylsulfonyl)-propionyl]-L-norleucine *t*-Butyl Ester (24).** To a solution of **23** (38 mg, 77 μmol) in methanol (1 ml) were added sodium tungstate dihydrate (20 mg, 61 μmol) and 30% hydrogen peroxide (0.25 ml, 2.2 mmol). The mixture was stirred at room temperature overnight. The resultant mixture was diluted with ethyl acetate (20 ml), washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 29 mg (76%) of **24** as white solids. This crude compound was conducted to the next step without any more purification. Compound **24**: mp 50—54 °C; $[\alpha]_D^{20}$ −7.0° (*c* 1.0, $CHCl_3$); IR (KBr) 1730, 1670, 1570, and 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.87 (t, *J*=7.1 Hz, 3H), 1.16—1.37 (m, 4H), 1.40 (s, 9H), 1.62 (m, 1H), 1.74 (m, 1H), 3.23—3.39 (m, 2H), 3.50 (dd, *J*=7.5 Hz, 13.5 Hz, 1H), 3.72 (dd, *J*=3.2 Hz, 14.9 Hz, 1H), 4.13 (dd, *J*=8.0 Hz, 15.2 Hz, 1H), 4.29 (m, 1H), 6.08 (br d, *J*=7.5 Hz, 1H), 7.27—7.38 (m, 3H), 7.50 (m, 2H), 7.70 (br d, *J*=8.1 Hz, 1H), 7.82 (m, 1H), 7.96 (m, 1H), and 8.63 (d, *J*=4.8 Hz, 2H).

HRMS (FAB) Found: *m/z* 526.2401. Calcd for $C_{28}H_{35}N_3O_5S$: M+H, 526.2375.

(2*RS*,4*S*,5*S*)-*N*-Isobutyl-5-[[*N*-[(2*S*)-2-(1-naphthylmethyl)-3-(2-pyrimidinylsulfonyl)propionyl]-L-norleucyl]amino]-2-ethyl-4-hydroxy-7-methyloctanamide (26). To a solution of **24** (27 mg, 51 μmol) in dichloromethane (0.5 ml) was added trifluoroacetic acid (0.5 ml) and the mixture was allowed to stand at room temperature for 3 h. The mixture was concentrated in vacuo and the residue which was dissolved in benzene was dried by azeotropical concentration in vacuo to afford **25** as white solids. To a cooled (−15 °C) and stirred solution of the resulted solid in dry DMF (0.4 ml) were added triethylamine (21 μl) and DPPA (14 μl, 65 μmol) successively. After 5 minutes, a solution of **14** (27 mg, 87 μmol) and triethylamine (15 μl) in DMF (0.5 ml) was added into the reaction mixture. The mixture which was stirred at −15 °C for 1 h and stirred at 5 °C overnight was diluted with ethyl acetate (20 ml). The solution was washed with water, 4% aqueous sodium hydrogencarbonate, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by silica-gel column (40:1 chloroform-methanol) to afford 31 mg (85%) of **26** as white solid: mp 164—168 °C; IR (KBr) 3300, 2960, 2870, 1740, 1650, 1560, and 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.20 (m, 0.5H), 2.30 (m, 0.5H), 2.88—3.05 (m, 1H), 3.12 (m, 1H), 3.28 (m, 2H), 3.50 (m, 1H), 3.61 (m, 1H), 3.70 (dd, *J*=2.6 Hz, 14.9 Hz, 1H), 3.86 (m, 1H), 4.04 (m, 1H), 4.22 (m, 1H), 5.85 (m, 1H), 6.20 (m, 1H), 6.42 (m, 1H), 7.28 (m, 2H), 7.37 (m, 1H), 7.50 (m, 2H), 7.72 (br d, *J*=7.8 Hz, 1H), 7.83 (m, 1H), 7.91 (m, 1H), 8.55 (d, *J*=4.2 Hz, 1H), and 8.56 (d, *J*=4.2 Hz, 1H).

HRMS (FAB) Found: *m/z* 724.4100. Calcd for $C_{39}H_{57}N_5O_6S$: M+H, 724.4108.

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