Poststatin, a New Inhibitor of Prolyl Endopeptidase

VIII. Endopeptidase Inhibitory Activity of Non-peptidyl Poststatin Analogues

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Non-peptidyl poststatin analogues, (*S*)-*N*-substituted-2-[2-(1-acylpyrrolidinyl)]-2-oxoacetamides were synthesized and examined for their inhibitory activity against prolyl endopeptidase and cathepsin B *in vitro*. Many compounds showed stronger activity than natural poststatin, a pentapeptide. Among them, (*S*)-*N*-cyclohexyl-2-oxo-2-[2-(1-(3-phenoxybenzoyl)pyrrolidinyl)]acetamide (**22**) and (*S*)-*N*-cyclohexyl-2-[2-(1-(2-naphthoyl)pyrrolidinyl)]-2-oxoacetamide (**19**) indicated IC_{50} value of 5.8 and 8.2 ng/ml for prolyl endopeptidase inhibition respectively. None of these compounds possess significant inhibitory activities against cathepsin B, a cysteine protease. These results indicate that these compounds are more selective inhibitors against prolyl endopeptidase than is natural poststatin.

Prolyl endopeptidase (PEP)[EC 3.4.21.26] is a serine protease[1] that is highly active in the brain and degrades proline-containing oligopeptides such as oxytocin, neurotensin, substance P, thyrotropin releasing hormone, bradykinin, and angiotensin II[2~7]. PEP also degrades vasopressin which has been suggested to play an important role in learning and memory[8~10]. Moreover, PEP may be involved in processing the *C*-terminal portion of the amyloid precursor protein in ALZHEIMER's disease[11].

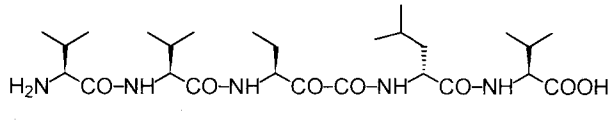
Recently, many potent inhibitors such as benzyloxycarbonyl(Z)-Gly-Pro-CH_2Cl[1], Z-Pro-prolinal[12], 1-(*N*-(4-phenylbutyryl)-Pro)-pyrrolidine[13], and related compounds[13~19] have been studied, and peptidyl aldehydes and pyrrolidine derivatives have been reported to ameliorate the experimental amnesia induced by scopolamine in rats[13,16].

In the course of our study, poststatin (PST, Fig. 1) was isolated as a PEP inhibitor (IC_{50} = 0.030 μg/ml) from a *Streptomyces* culture filtrate[20~22]. Many peptidyl PST analogues which contain a (*S*)-3-amino-2-oxovaleryl moiety in the P_1 position were synthesized for determination of the structure-activity relationships[23]. In the preceding paper we have described a potent and selective PEP inhibitor series containing a (*S*)-2-oxo-2-(2-pyrrolidinyl)acetyl (ProCO) moiety in the P_1 position. We have also found that P'_1 in the ProCO containing inhibitors was exchangeable to the cyclohexyl (cHx) amine moiety without significant loss of inhibitory activity[24]. These results encouraged us to design even smaller PEP inhibitors by eliminating the P_2-amino acid residue, and our attention was focused on conversion to lower molecular weight and non-peptidyl structures. In this paper, we report the synthesis of the new series of PEP inhibitors with a general formula (R_2-ProCO-R_1(R_2 = acyl group, R_1 = amine)) and their inhibitory activity is contrasted with that of cathepsin B *in vitro*.

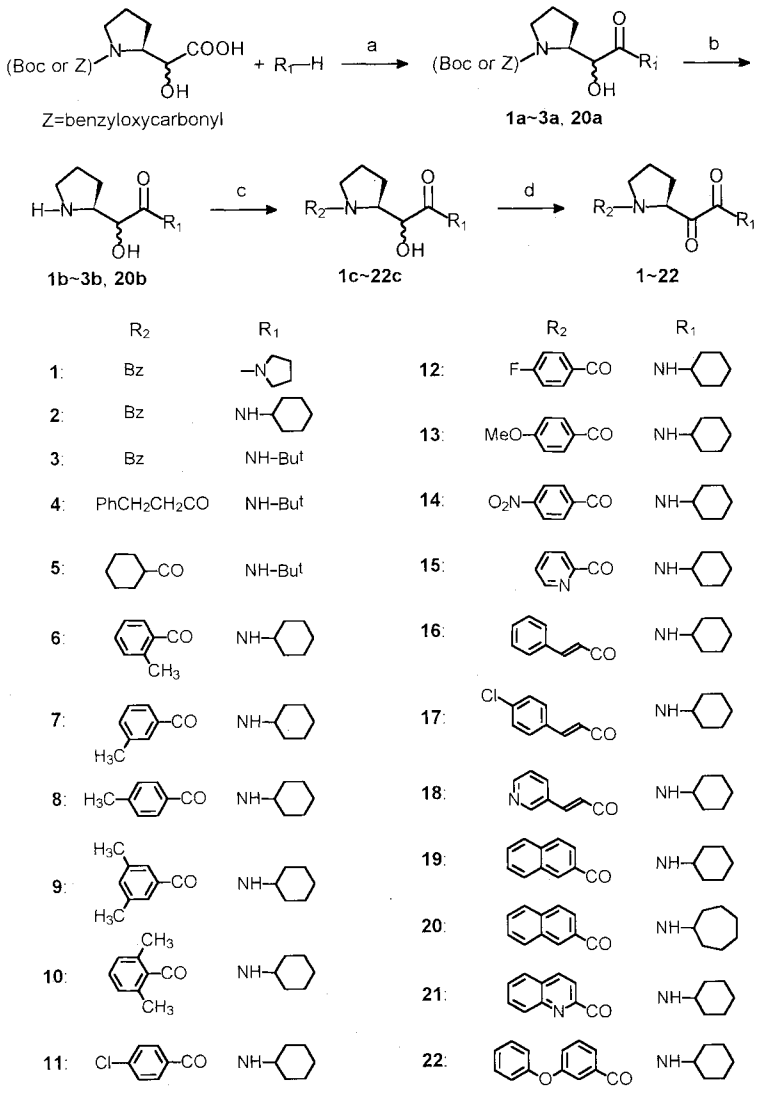
Chemistry

The synthetic route is outlined in scheme 1. Starting *N*-Boc- or *N*-Z-(*RS*)-2-hydroxy-2-((*S*)-2-pyrrolidinyl)-acetic acid (Boc- or Z-H_2ProCO) was prepared from Z-L-proline in five steps according to the procedure described in the previous paper[24]. The coupling reaction of these acid components with various amine components was performed by the 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)-1-hydroxybenzotriazole (HOBt) method[25,26]. Removal of the protective

Fig. 1. Structure of poststatin.



Scheme 1.



a: EDC·HCl, HOBt, b: 1) 4 N HCl-dioxane (for Boc), 2) Et_3N, or H_2, Pd-black (for Z),
c: R_2-Cl, Et_3N, or R_2-OH, EDC·HCl, HOBt,
d: EDC·HCl, DMSO, pyridinium trifluoroacetate, or Ac_2O, DMSO.

group was performed by acid treatment for the Boc-group and hydrogenation for the Z-group. Introduction of the acyl group was performed by the acid chloride method or the EDC-HOBt method. Oxidation of the hydroxyl group of the diastereomeric H_2ProCO residue to ketone was performed by the Pfitzner-Moffatt[27] or the Albright-Goldman[28] method.

Results and Discussion

The results obtained are summarized in Table 1.

Previously we reported the effect of introduction of a cycloalkylamine component on PEP inhibition in aldehyde-type inhibitors[24]. To estimate the effect of the P'_1 cycloalkylamine moiety in the non-peptidyl structure, we prepared compounds having three different types of amine (cyclic amine (pyrrolidine (**1**)), cycloalkylamine (cyclohexylamine (**2**)), and bulky alkylamine (*t*-butylamine (**3**~**5**))). Among them, the P'_1 cycloalkylamino group was found to be most effective for PEP inhibition and showed no significant inhibitory activity for cathepsin B. Thus we selected **2** as a further lead compound, and the P_2 acyl group of **2** was widely varied.

Comparison of the compounds having mono- and di-substituted benzoyl groups (*o*-methyl (**6**), *m*-methyl (**7**), *p*-methyl (**8**), 3,5-dimethyl (**9**), and 2,6-dimethyl (**10**)) indicated that the *para* substituted benzoyl group was most potent in this series.

Introduction of different types of substituents for the *para*-benzoyl position of compound **8** (chloro- (**11**),

Table 1. Inhibitory activities of poststatin and **1**~**22**.

Compound	IC_{50} (μg/ml)	
	Prolyl endopeptidase	Cathepsin B
Poststatin	0.030	2.1
1	3.9	>100
2	0.060	>100
3	0.16	>100
4	0.16	>100
5	0.62	>100
6	0.17	>100
7	0.050	>100
8	0.022	>100
9	0.026	>100
10	0.062	>100
11	0.024	>100
12	0.12	>100
13	0.026	>100
14	0.054	>100
15	0.032	>100
16	0.017	>100
17	0.043	>100
18	0.085	>100
19	0.0082	>100
20	0.0092	>100
21	0.010	>100
22	0.0058	>100

fluoro- (**12**), methoxy- (**13**), and nitro- (**14**)) indicated that **11** and **13** were equipotent, **14** was 2.5-fold less potent and **12** was 5.5-fold less potent than parental **8** in PEP inhibition. The heterocyclic bioisostere of **2** (picolinoyl (**15**)) was less potent than **8**.

We tried to introduce more bulky hydrophobic groups than benzoyl (cinnamoyl (**16**), 2-naphthoyl (**19**, **20**), and 3-phenoxybenzoyl (**22**)) since we hoped to enhance a putative van der Waals interaction with a S_2 subsite of the enzyme. All these compounds gave a 3.5~10-fold increase in potency over parental **2**, but introduction of both a basic nitrogen into the aromatic ring (**18** *vs* **16** and **21** *vs* **19**) and a *p*-chloro group into cinnamoyl group (**17** *vs* **16**) decreased the inhibitory activity.

In summary, a series of acyl-ProCO-amide type compounds showed potent inhibitory activity against PEP in spite of their non-peptidyl and low molecular weight structures and their possession of only one asymmetric center. Among them the compounds having a cycloalkylamine component in the P'_1 position was preferable and introduction of 3-phenoxybenzoyl or 2-naphthoyl group in the P_2 position was effective.

Experimental

General

Melting points were determined with a micro melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were recorded at 400 MHz or 270 MHz with a JEOL JNM-GX400 or a JNM-EX270 spectrometer, respectively. FAB-MS spectra were measured with a JEOL JMS-SX102 mass spectrometer. TLC was carried out on Merck precoated silica gel $60F_{254}$ plates.

Enzyme Assay

Inhibitory activities of PEP and cathepsin B were measured by the procedure described in the previous paper[20].

Synthesis

1-[(*RS*)-2-Hydroxy-2-((*S*)-2-pyrrolidinyl)acetyl]pyrrolidine Hydrochloride (**1b**·HCl)

1b·HCl was prepared from 1-{2-[(*S*)-2-(1-*t*-butoxycarbonylpyrrolidinyl)]-(*RS*)-2-hydroxyacetyl}pyrrolidine (**1a**) according to the procedure described in the previous paper[24].

N-Cyclohexyl-(*RS*)-2-hydroxy-2-((*S*)-2-pyrrolidinyl)-acetamide Hydrochloride (**2b**·HCl)

2b·HCl was prepared from *N*-cyclohexyl-2-[(*S*)-2-(1-*t*-butoxycarbonylpyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**2a**) according to the procedure described in the previous paper[24].

N-Cycloheptyl-(*RS*)-2-hydroxy-2-((*S*)-2-pyrrolidinyl)acetamide Hydrochloride (**20b**·HCl)

20b·HCl was prepared from *N*-cycloheptyl-2-[(*S*)-2-(1-*t*-butoxycarbonylpyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**20a**) according to the procedure described in the previous paper[24].

N-*t*-Butyl-2-[(*S*)-2-(1-benzyloxycarbonylpyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**3a**)

To an ice-cold solution of Z-H_2ProCO[24] (745.6 mg, 2.67 mmol), *t*-butylamine (301 μl, 2.83 mmol) and HOBt (541.8 mg, 4.01 mmol) in DMF (5 ml) was added EDC·HCl (716.5 mg, 3.74 mmol), and the mixture was stirred in an ice bath for 2 hours and then at room temperature for 4 hours. The mixture was diluted with EtOAc (50 ml), and the mixture was washed with 4% aq $NaHCO_3$, saturated aq NaCl, 1% aq citric acid, saturated aq NaCl (each 30 ml), and dried (Na_2SO_4). After removal of the solvent, the product was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (7:1) to give **3a** as a solid, 399.6 mg (44.8%): Rf 0.60 (CH_2Cl_2-EtOAc, 7:1), FAB-MS *m/z* 335 $(M+H)^+$, 291, 245, 201, 160, 91, 70, 57.

N-*t*-Butyl-2-[(*S*)-2-(1-benzoylpyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**3c**) and Its Analogues (**4c** and **5c**)

To a solution of **3a** (349.5 mg, 1.01 mmol) in MeOH (5 ml) was added 97% palladium-black catalyst (15.2 mg). The mixture was hydrogenated at room temperature under a hydrogen atmosphere for 7 hours. The

catalyst (11.3 mg) was added and hydrogenation was continued for 16 hours. The catalyst was filtered off, evaporation of the solvent gave *N*-*t*-butyl-(*RS*)-2-hydroxy-2-((*S*)-2-pyrrolidinyl)acetamide (**3b**) as a solid, 204.2 mg (97.7%).

To a solution of **3b** (47.5 mg, 0.237 mmol) in anhydrous THF (1.0 ml) was added triethylamine (42 μl, 0.300 mmol), and the solution was treated dropwise with benzoyl chloride (34 μl, 0.293 mmol) in anhydrous THF (1.5 ml) over a period of 30 minutes. The mixture was stirred for additional 2 hours at room temperature, and the solvent was evaporated. To the mixture was added 1 N HCl (1.5 ml), and the mixture was extracted thrice with EtOAc (each 2 ml). The combined extracts were washed with saturated aq $NaHCO_3$ (6 ml) and saturated aq NaCl (6 ml), and dried (Na_2SO_4). After removal of the solvent, the product was purified by Sephadex LH-20 column chromatography with MeOH to give **3c** as a solid, 71.2 mg (98.6%): Rf 0.36, 0.42 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 305 $(M+H)^+$, 287, 232, 204, 174, 105, 70, 57.

The compound **4c** and **5c** were prepared from **3b** by a similar procedure using 3-phenylpropionyl chloride and cyclohexylcarbonyl chloride, respectively.

N-*t*-Butyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(3-phenylpropionyl)pyrrolidinyl)]acetamide (**4c**): Yield 98.1%; Rf 0.51 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 333 $(M+H)^+$, 315, 260, 232, 202, 201, 91, 70, 57.

N-*t*-Butyl-2-[(*S*)-2-(1-cyclohexylcarbonylpyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**5c**): Yield 99.2%; Rf 0.47 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 311 $(M+H)^+$, 293, 238, 210, 201, 180, 83, 70.

1-{2-[(*S*)-2-(1-Benzoylpyrrolidinyl)]-(*RS*)-2-hydroxyacetyl}pyrrolidine (**1c**) and Its Analogues (**2c**, **6c**~**8c**, **11c**~**14c** and **16c**): General Acid Chloride Method

To a mixture of the HCl salt of the amine component (**1b**·HCl or **2b**·HCl, 1 equiv) in anhydrous THF was added triethylamine (2.2~2.4 equiv), and the solution was treated dropwise with the corresponding acid chloride (1.1~1.2 equiv) in anhydrous THF over a period of 30 minutes. The mixture was stirred for additional 2~5.5 hours at room temperature, and the solvent was evaporated. The mixture was acidified with 1 N HCl, and the mixture was extracted thrice with EtOAc. The combined extracts were washed with saturated aq $NaHCO_3$ and saturated aq NaCl, and dried (Na_2SO_4). After removal of the solvent, the product was purified by silica gel column chromatography with CH_2Cl_2-MeOH (120:1~40:1) elution.

1c: Yield 75.8%; Rf 0.30 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 303 $(M+H)^+$, 232, 204, 174, 105.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(2-methylbenzoyl)pyrrolidinyl)]acetamide (**6c**): Yield 92.0%; Rf 0.48 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 345 $(M+H)^+$, 246, 218, 188, 119, 91.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(3-methylbenzoyl)pyrrolidinyl)]acetamide (**7c**): Yield 95.8%; Rf 0.45, 0.51 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 345 $(M+H)^+$, 327, 246, 218, 188, 119, 100, 91, 70.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(4-methylbenzoyl)pyrrolidinyl)]acetamide (**8c**): Yield 95.1%; Rf 0.37, 0.41 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 345 $(M+H)^+$, 327, 246, 218, 188, 119, 100, 91, 70.

N-Cyclohexyl-2-[(*S*)-2-(1-(4-chlorobenzoyl)pyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**11c**): Yield 93.9%; Rf 0.36, 0.42 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 365 $(M+H)^+$, 331, 266, 238, 208, 139, 70.

N-Cyclohexyl-2-[(*S*)-2-(1-(4-fluorobenzoyl)pyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**12c**): Yield 78.4%; Rf 0.53, 0.55 (CH_2Cl_2-MeOH, 10:1); FAB-MS *m/z* 349 $(M+H)^+$, 331, 250, 222, 192, 123, 100, 70.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(4-methoxybenzoyl)pyrrolidinyl)]acetamide (**13c**): Yield 73.6%; Rf 0.61, 0.65 (CH_2Cl_2-MeOH, 10:1); FAB-MS *m/z* 361 $(M+H)^+$, 343, 262, 234, 204, 135, 70.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(4-nitrobenzoyl)pyrrolidinyl)]acetamide (**14c**): Yield 95.4%; Rf 0.27, 0.35 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 376 $(M+H)^+$, 360, 346, 277, 249, 227, 219, 150, 120, 100, 70.

N-Cyclohexyl-2-[(*S*)-2-(1-cinnamoylpyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**16c**): Yield 87.7%; Rf 0.44 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 357 $(M+H)^+$, 258, 230, 200, 131.

N-Cyclohexyl-2-[(*S*)-2-(1-benzoylpyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**2c**) was prepared by the similar method using dioxane as a solvent instead of THF: Yield 84.3%; Rf 0.34, 0.44 ($CHCl_3$-MeOH, 20:1).

N-Cyclohexyl-2-[(*S*)-2-(1-(3,5-dimethylbenzoyl)pyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**9c**) and Its Analogues (**10c**, **15c** and **17c**~**22c**): General Carbodiimide Method

To the HCl salt of the amine component (**1b**·HCl or **20b**·HCl, 1 equiv) was added corresponding acid component (1.1 equiv), and HOBt (2 equiv) in DMF. Triethylamine (1 equiv) and EDC·HCl (1.4 equiv) was added under ice cooling, and the mixture was stirred in an ice bath for 2 hours and at room temperature for 3~21 hours. The completion of the reaction was monitored by TLC. The mixture was diluted with EtOAc, and the mixture was washed with 4% aq $NaHCO_3$, saturated aq NaCl, 1~10% aq citric acid (this operation was omitted in case of basic compound), and saturated aq NaCl, and dried (Na_2SO_4). After removal of the solvent, the product was purified by silica gel column chromatography with CH_2Cl_2-MeOH (120:1~50:1 (CH_2Cl_2-MeOH-Et_3N, 120~150:1:1 in case of basic compound)) elution.

9c: Yield 89.4%; Rf 0.46, 0.54 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 359 $(M+H)^+$, 341, 260, 232, 202, 133, 105, 70.

N-Cyclohexyl-2-[(*S*)-2-(1-(2,6-dimethylbenzoyl)pyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**10c**): Yield

96.3%; Rf 0.35 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 359 $(M+H)^+$, 260, 232, 202, 133.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-picolinoylpyrrolidinyl)]acetamide (**15c**): Yield 85.9%; Rf 0.22 (CH_2Cl_2-MeOH-Et_3N, 30:1:0.5); FAB-MS *m/z* 332 $(M+H)^+$, 233, 205, 175.

N-Cyclohexyl-2-[(*S*)-2-(1-(*p*-chlorocinnamoyl)pyrrolidinyl)]-(*RS*)-2-hydroxyacetamide (**17c**): Yield 91.3%; Rf 0.43 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 391 $(M+H)^+$, 292, 264, 234, 165.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-{(*S*)-2-[1-(*trans*-3-(3-pyridyl)acryloyl)pyrrolidinyl]}acetamide (**18c**): Yield 92.8%; Rf 0.39 (CH_2Cl_2-MeOH-Et_3N, 20:1:0.5); FAB-MS *m/z* 358 $(M+H)^+$, 259, 231, 201, 132.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(2-naphthoyl)pyrrolidinyl)]acetamide (**19c**): Yield 98.4%; Rf 0.42, 0.50 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 381 $(M+H)^+$, 363, 282, 254, 224, 155, 127.

N-Cycloheptyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(2-naphthoyl)pyrrolidinyl)]acetamide (**20c**): Yield 93.9%; Rf 0.41, 0.49 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 395 $(M+H)^+$, 282, 254, 224.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(2-quinolinecarbonyl)pyrrolidinyl)]acetamide (**21c**): Yield 99.1%; Rf 0.28 (CH_2Cl_2-MeOH-Et_3N, 30:1:0.5); FAB-MS *m/z* 382 $(M+H)^+$, 364, 255, 225, 128.

N-Cyclohexyl-(*RS*)-2-hydroxy-2-[(*S*)-2-(1-(3-phenoxybenzoyl)pyrrolidinyl)]acetamide (**22c**): Yield 97.4%; Rf 0.37, 0.47 (CH_2Cl_2-MeOH, 20:1); FAB-MS *m/z* 423 $(M+H)^+$, 405, 324, 296, 266, 197.

Pfitzner-Moffatt Oxidation (Synthesis of **2**~**18**)

A mixture of H_2ProCO residue-containing precursor (**2c**~**18c**, 1 equiv), pyridinium trifluoroacetate (0.5 equiv), EDC·HCl (3 equiv) and anhydrous DMSO (0.5~1.3 ml/100 mg of substrate) in benzene was stirred at room temperature for 5~17 hours. The completion of the reaction was monitored by TLC. The reaction mixture was diluted with EtOAc (10-fold excess of DMSO), and the mixture was washed with water, and dried (Na_2SO_4). After removal of the solvent, the product was purified by the following method.

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-benzoylpyrrolidinyl)]-2-oxoacetamide (**2**) was purified by silica gel column chromatography with $CHCl_3$-EtOAc (30:1) to give **2** (90.0% yield): Rf 0.21 ($CHCl_3$-MeOH, 20:1); mp 63.5~65.5°C (crystallized from EtOAc-heptane); $[\alpha]_D^{26}$ −51.7° (*c* 0.85, $CHCl_3$); FAB-MS *m/z* 329 $(M+H)^+$, 247, 202, 174, 105; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.09~1.17 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.55~2.10 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb(ProCO)), 2.45 (1H, m, CHa*Hb*(ProCO)), 3.50~3.90 (3H, m, NCH_2, N-CH), 5.42 (1H, dd, *J*=6.2, 8.1 Hz, NCHCOCO), 6.81(1H, br d, *J*=7.9 Hz, NH), 7.25~7.62 (5H, m, aromatic protons).

Crude (*S*)-*N*-*t*-butyl-2-[2-(1-benzoylpyrrolidinyl)]-2-oxoacetamide (**3**) was purified by silica gel column chromatography with CH_2Cl_2~CH_2Cl_2-EtOAc (15:1) to give **3** as crystals (74.2% yield): Rf 0.31 (CH_2Cl_2-MeOH, 40:1); mp 99~100°C; $[\alpha]_D^{24}$ −41.3° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 303 $(M+H)^+$, 247, 202, 174, 105, 70, 57; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (9H, s, Bu^t), 1.85~2.10 (3H, m, CH_2C*Ha*Hb(ProCO)), 2.44 (1H, m, CHa*Hb*(ProCO)), 3.58 (1H, m, NC*Ha*Hb), 3.67 (1H, m, NCHa*Hb*), 5.40 (1H, dd, *J*=6.3, 8.3 Hz, NCHCOCO), 6.74 (1H, br s, NH), 7.35~7.65 (5H, m, Ph).

Crude (*S*)-*N*-*t*-butyl-2-oxo-2-[2-(1-(3-phenylpropionyl)pyrrolidinyl)]acetamide (**4**) was purified by silica gel column chromatography with CH_2Cl_2~CH_2Cl_2-EtOAc (20:1) to give **4** (80.9% yield): Rf 0.26 (CH_2Cl_2-MeOH, 30:1); mp 96~97°C (crystallized from EtOAc-hexane); $[\alpha]_D^{26}$ −59.9° (*c* 1.2, $CHCl_3$); FAB-MS *m/z* 331 $(M+H)^+$, 275, 230, 202, 199, 143, 91,70, 57; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.40 (9H, s, Bu^t), 1.85~2.08 (3H, m, CH_2C*Ha*Hb(ProCO)), 2.30 (1H, m, CHa*Hb*(ProCO)), 2.50~2.70 (2H, m, CH_2CO), 2.96 (2H, dd, *J*=7.6, 8.3 Hz, PhCH_2), 3.43 (1H, m, NC*Ha*Hb), 3.56 (1H, m, NCHa*Hb*), 5.24 (1H, dd, *J*=5.3, 8.6 Hz, NCHCOCO), 6.73 (1H, br s, NH), 7.15~7.35 (5H, m, Ph).

Crude (*S*)-*N*-*t*-butyl-2-[2-(1-cyclohexylcarbonylpyrrolidinyl)]-2-oxoacetamide (**5**) was purified by silica gel column chromatography with CH_2Cl_2~CH_2Cl_2-EtOAc (20:1) to give **5** as crystals (71.0% yield): Rf 0.38 (CH_2Cl_2-MeOH, 40:1); mp 114~116°C; $[\alpha]_D^{25}$ −64.3° (*c* 0.93, $CHCl_3$); FAB-MS *m/z* 309 $(M+H)^+$, 253, 208, 199, 180, 143, 83, 70, 57; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.14~2.12 (13H, m, CH_2C*Ha*Hb(ProCO), $CH_2\times5$ (cHx)), 1.38 (9H, s, Bu^t), 2.22~2.45 (2H, m, CHa*Hb*(ProCO), CH(cHx)), 3.53~3.78 (2H, m, NCH_2), 5.15 (1H, dd, *J*=5.9, 8.9 Hz, NCHCOCO), 6.69 (1H, br s, NH).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(2-methylbenzoyl)pyrrolidinyl)]-2-oxoacetamide (**6**) was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (50:2)~CH_2Cl_2-EtOAc-MeCN (50:2:5) to give **6** (88.9% yield): Rf 0.43 (CH_2Cl_2-MeOH, 40:1); mp 132~134°C (crystallized from CH_2Cl_2-hexane); $[\alpha]_D^{26}$ −37.0° (*c* 2.8, $CHCl_3$); FAB-MS *m/z* 343 $(M+H)^+$, 216, 188, 119, 91; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02~1.50 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.52~2.12 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb(ProCO)), 2.38 (3H, s, CH_3), 2.44 (1H, m, CHa*Hb*(ProCO)), 3.19~3.46 (2H, m, NCH_2), 3.78 (1H, m, N-CH), 5.45 (1H, dd, *J*=5.9, 8.9 Hz, NCHCOCO), 6.81 (1H, br d, *J*=7.6 Hz, NH), 7.10~7.36 (4H, m, aromatic protons).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(3-methylbenzoyl)pyrrolidinyl)]-2-oxoacetamide (**7**) was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (25:1)~CH_2Cl_2-EtOAc-MeCN (25:1:1) to give **7** as crystals (91.9% yield): Rf 0.34 (CH_2Cl_2-MeOH, 40:1); mp 102~103°C; $[\alpha]_D^{24}$ −45.9° (*c* 1.1, $CHCl_3$); FAB-MS *m/z* 343 $(M+H)^+$, 216, 188, 119, 91; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.04~1.49 (5H, m, $CH_2\times2$, C*Ha*Hb (cHx)), 1.54~2.11 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb(ProCO)), 2.37 (3H, s, CH_3), *ca.* 2.43 (1H,

m, overlapping, CHa*Hb*(ProCO)), 3.50~*ca.* 3.73 (2H, m, overlapping, NCH_2), 3.77 (1H, m, N-CH), 5.41 (1H, dd, J=6.1, 8.1 Hz, NCHCOCO), 6.79 (1H, br d, J=7.9 Hz, NH), 7.15~7.45 (4H, m, aromatic protons).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(4-methylbenzoyl)-pyrrolidinyl)]-2-oxoacetamide (**8**) was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (25:1) to give **8** (92.7% yield): Rf 0.30 (CH_2Cl_2-MeOH, 40:1); mp 137~138°C (crystallized from EtOAc-hexane); $[\alpha]_D^{26}$ −49.6° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 343 $(M+H)^+$, 188, 119; ^1H NMR (270 MHz, $CDCl_3$) δ 1.05~1.48 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.53~2.10 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb(ProCO)), 2.38 (3H, s, CH_3), *ca.* 2.41 (1H, m, overlapping, CHa*Hb*(ProCO)), 3.50~3.88 (3H, m, NCH_2, N-CH), 5.41 (1H, dd, J=6.1, 7.7 Hz, NCHCOCO), 6.78 (1H, br d, J=8.2 Hz, NH), 7.21, 7.47 (4H, two d, aromatic protons).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(3,5-dimethylbenzoyl)pyrrolidinyl)]-2-oxoacetamide (**9**) was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (50:2)~CH_2Cl_2-EtOAc-MeCN (50:2:5) to give **9** (61.1% yield): Rf 0.39 (CH_2Cl_2-MeOH, 40:1); mp 43~44°C (amorphous solid); $[\alpha]_D^{25}$ −41.2° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 357 $(M+H)^+$, 230, 202, 133, 105; ^1H NMR (270 MHz, $CDCl_3$) δ 1.07~1.50 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.54~2.11 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb(ProCO)), 2.33 (6H, s, $CH_3\times2$), 2.42 (1H, m, CHa*Hb*(ProCO)), 3.50~*ca.* 3.73 (2H, m, overlapping, NCH_2), 3.77 (1H, m, N-CH), 5.40 (1H, dd, J=6.3, 8.3 Hz, NCHCOCO), 6.78 (1H, br d, J=8.6 Hz, NH), 7.06 (1H, s, aromatic proton), 7.15 (2H, s, aromatic protons).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(2,6-dimethylbenzoyl)pyrrolidinyl)]-2-oxoacetamide (**10**) was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (25:1)~CH_2Cl_2-EtOAc-MeCN (25:1:2) to give **10** as crystals (74.7% yield): Rf 0.64 (CH_2Cl_2-MeOH, 20:1); mp 132~134°C; $[\alpha]_D^{25}$ −37.5° (*c* 1.1, $CHCl_3$); FAB-MS *m/z* 357 $(M+H)^+$, 230, 202, 133, 105; ^1H NMR (270 MHz, $CDCl_3$) δ 1.08~1.50 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.55~2.13 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb(ProCO)), 2.32 (3H, s, CH_3), 2.33 (3H, s, CH_3), *ca.* 2.44 (1H, m, overlapping, CHa*Hb*(ProCO)), 3.21~3.47 (2H, m, NCH_2), 3.78 (1H, m, N-CH), 5.43 (1H, dd, J=5.9, 8.9 Hz, NCHCOCO), 6.82 (1H, br d, J=8.3 Hz, NH), 7.02 (2H, m, aromatic protons), 7.14 (1H, m, aromatic proton).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(4-chlorobenzoyl)-pyrrolidinyl)]-2-oxoacetamide (**11**) was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (25:1) to give **11** (97.4% yield): Rf 0.51 (CH_2Cl_2-MeOH, 40:1); mp 109~110°C (crystallized from EtOAc-hexane); $[\alpha]_D^{27}$ −44.4° (*c* 1.1, $CHCl_3$); FAB-MS *m/z* 363 $(M+H)^+$, 329, 208, 139; ^1H NMR (270 MHz, $CDCl_3$) δ 1.04~1.50 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.54~2.12 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb (ProCO)), 2.45 (1H, m, CHa*Hb*(ProCO)), 3.57 (1H, m, NC*Ha*Hb), 3.67 (1H, m, NCHa*Hb*), 3.76 (1H, m, N-CH), 5.40 (1H, dd, J=6.1, 8.1 Hz, NCHCOCO), 6.78 (1H, br d, J=7.6 Hz, NH), 7.39 (2H, m, aromatic protons), 7.52 (2H, m, aromatic protons).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(4-fluorobenzoyl)pyrrolidinyl)]-2-oxoacetamide (**12**) was purified by silica gel column chromatography with CH_2Cl_2~CH_2Cl_2-EtOAc (25:1) to give **12** (86.8% yield): Rf 0.39 (CH_2Cl_2-MeOH, 40:1); mp 151~152°C (crystallized from CH_2Cl_2-hexane); $[\alpha]_D^{28}$ 0° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 347 $(M+H)^+$, 220, 192, 123; ^1H NMR (270 MHz, $CDCl_3$) δ 1.00~1.50 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.54~2.15 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb (ProCO)), 2.45 (1H, m, CHa*Hb*(ProCO)), 3.59 (1H, m, NC*Ha*Hb), 3.68 (1H, m, NCHa*Hb*), 3.76 (1H, m, N-CH), 5.41 (1H, dd, J=5.9, 7.9 Hz, NCHCOCO), 6.78 (1H, br d, J=7.9 Hz, NH), 7.10 (2H, m, aromatic protons), 7.59 (2H, m, aromatic protons).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(4-methoxybenzoyl)-pyrrolidinyl)]-2-oxoacetamide (**13**) was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (50:1~10:1) to give **13** (82.5% yield): Rf 0.33 (CH_2Cl_2-MeOH, 40:1); mp 153~154°C (crystallized from CH_2Cl_2-hexane); $[\alpha]_D^{30}$ −21.6° (*c* 1.1, $CHCl_3$); FAB-MS *m/z* 359 $(M+H)^+$, 232, 204, 135; ^1H NMR (270 MHz, $CDCl_3$) δ 1.05~1.48 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.53~2.14 (8H, m, $CH_2\times2$, C*Ha*Hb(cHx), CH_2C*Ha*Hb (ProCO)), 2.44 (1H, m, CHa*Hb*(ProCO)), 3.52~*ca.* 3.93 (3H, m, overlapping, NCH_2, N-CH), 3.84 (3H, s, CH_3O), 5.41 (1H, dd, J=6.1, 7.8 Hz, NCHCOCO), 6.78 (1H, br d, J=7.9 Hz, NH), 6.91 (2H, m, aromatic protons), 7.57 (2H, m, aromatic protons).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(4-nitrobenzoyl)pyrrolidinyl)]-2-oxoacetamide (**14**) was purified by silica gel column chromatography with CH_2Cl_2~CH_2Cl_2-EtOAc (8:1) to give **14** (95.6% yield): Rf 0.42 (CH_2Cl_2-MeOH, 40:1); mp 150~152°C (crystallized from EtOAc-hexane); $[\alpha]_D^{28}$ −47.0° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 374 $(M+H)^+$, 360, 344, 225, 150, 120, 70; ^1H NMR (270 MHz, $CDCl_3$) δ 1.00~1.50 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.54~2.15 (8H, m, $CH_2\times2$, C*Ha*Hb (cHx), CH_2C*Ha*Hb(ProCO)), 2.49 (1H, m, CHa*Hb* (ProCO)), 3.51 (1H, m, NC*Ha*Hb), 3.64 (1H, m, NCHa*Hb*), 3.76 (1H, m, N-CH), 5.44 (1H, dd, J=5.9, 8.3 Hz, NCHCOCO), 6.79 (1H, br d, J=7.9 Hz, NH), 7.73 (2H, m, aromatic protons), 8.29 (2H, m, aromatic protons).

Crude (*S*)-*N*-cyclohexyl-2-oxo-2-[2-(1-picolinoylpyrrolidinyl)]acetamide (**15**) was purified by silica gel column chromatography with $CHCl_3$-MeCN-AcOH (100:2:0.3~100:18:0.3) to give **15** as gum (91.2% yield): Rf 0.50 (CH_2Cl_2-MeOH, 20:1); $[\alpha]_D^{23}$ +22.0° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 330 $(M+H)^+$, 203, 175, 106; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12~1.54 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.55~1.87 (3H, m, CH_2, C*Ha*Hb (cHx)), 1.88~2.12 (5H, m, CH_2(cHx), CH_2C*Ha*Hb (ProCO)), 2.35 (1H, m, CHa*Hb*(ProCO)), 3.71~3.94 (2H, m, NC*Ha*Hb, N-CH), 4.00 (1H, m, NCHa*Hb*), 5.89

(1H, dd, J=2.7, 9.0 Hz, NCHCOCO), 6.98 (1H, d, J=8.3 Hz, NH), 7.31 (1H, m, aromatic proton), 7.79 (1H, m, aromatic proton), 8.16 (1H, d, aromatic proton), 8.24 (1H, d, aromatic proton).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-cinnamoylpyrrolidinyl)]-2-oxoacetamide (**16**) was purified by silica gel column chromatography with CH_2Cl_2-EtOAc (100:4)~CH_2Cl_2-EtOAc-MeCN (100:4:5) to give **16** (90.3% yield): Rf 0.50 (CH_2Cl_2-MeOH, 30:1); mp 184~185°C (crystallized from EtOAc-CH_2Cl_2-hexane); $[\alpha]_D^{27}$ −38.6° (*c* 1.1, $CHCl_3$); FAB-MS *m/z* 355 $(M+H)^+$, 228, 200, 131; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.08~1.49 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.55~2.19 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb(ProCO)), 2.39 (1H, m, CHa*Hb*(ProCO)), 3.67~3.94 (3H, m, NCH_2, N-CH), 5.40 (1H, dd, J=5.6, 8.9 Hz, NCHCOCO), 6.74 (1H, d, J=15.5 Hz, olefinic proton), 6.79 (1H, br d, overlapping, NH), 7.30~7.59 (5H, m, Ph), 7.68 (1H, d, J=15.5 Hz, olefinic proton).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(*p*-chlorocinnamoyl)-pyrrolidinyl)]-2-oxoacetamide (**17**) was purified by silica gel column chromatography with CH_2Cl_2-MeCN (100:1~100:7) to give **17** (83.5% yield): Rf 0.49 (CH_2Cl_2-MeOH, 30:1); mp 178~180°C (crystallized from CH_2Cl_2-hexane); $[\alpha]_D^{26}$ −16.6° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 389 $(M+H)^+$, 262, 234, 225, 165; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13~1.46 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.53~1.80 (3H, m, CH_2, CHa*Hb*(cHx)), 1.81~2.18 (5H, m, CH_2(cHx), CH_2C*Ha*Hb(ProCO)), 2.37 (1H, m, CHa*Hb*(ProCO)), 3.67~3.91 (3H, m, NCH_2, N-CH), 5.37 (1H, dd, J=5.9, 8.8 Hz, NCHCOCO), 6.69 (1H, d, J=15.4 Hz, olefinic proton), 6.74 (1H, br d, J=7.8 Hz, NH), 7.33 (2H, m, aromatic protons), 7.43 (2H, m, aromatic protons), 7.61 (1H, d, J=15.4 Hz, olefinic proton).

Crude (*S*)-*N*-cyclohexyl-2-oxo-2-{2-[1-(*trans*-3-(3-pyridyl)acryloyl)pyrrolidinyl]}acetamide (**18**) was purified by silica gel column chromatography with $CHCl_3$-MeOH (300:1~100:1) to give **18** (89.4% yield): Rf 0.41 ($CHCl_3$-MeOH, 20:1); mp 181~182°C (crystallized from CH_2Cl_2); $[\alpha]_D^{22}$ −14.9° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 356 $(M+H)^+$, 201; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.07~1.50 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.55~2.21 (8H, m, $CH_2\times2$, CHa*Hb*(cHx), CH_2C*Ha*Hb(ProCO)), 2.40 (1H, m, CHa*Hb*(ProCO)), 3.67~3.95 (3H, m, NCH_2, N-CH), 5.42 (1H, dd, J=5.6, 8.9 Hz, NCHCOCO), 6.79 (1H, br d, overlapping, NH), 6.82 (1H, d, J=15.5 Hz, olefinic proton), 7.32 (1H, dd, J=5.0, 7.9 Hz, aromatic proton), 7.67 (1H, d, J=15.5 Hz, olefinic proton), 7.82 (1H, m, aromatic proton), 8.59 (1H, br d, aromatic proton), 8.77 (1H, br s, aromatic proton).

Albright-Goldman Oxidation (Synthesis of **1** and **19~22**)

A mixture of H_2ProCO residue-containing precursor (**1c** or **19c~22c**, 1 equiv), anhydrous DMSO (0.3 ml~1.0 ml/100 mg of substrate) and Ac_2O (20 equiv) was stirred at room temperature for 22~24 hours. The reaction mixture was diluted with H_2O (20-fold excess of DMSO) and stirred for 30 minutes. The mixture was extracted thrice with CH_2Cl_2 or EtOAc, and the combined extracts were dried (Na_2SO_4). After removal of the solvent, the product was purified by the following method.

Crude (*S*)-1-{2-[2-(1-benzoylpyrrolidinyl)]-2-oxoacetyl}pyrrolidine (**1**) was purified by silica gel column chromatography with CH_2Cl_2-MeCN (100:7~10:1) to give **1** as a syrup (75.3% yield): Rf 0.38 (CH_2Cl_2-MeOH, 30:1); $[\alpha]_D^{22}$ −91.8° (*c* 1.2, $CHCl_3$); FAB-MS *m/z* 301 $(M+H)^+$, 230, 222, 174, 70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76~2.01 (5H, m, 4-C*Ha*Hb(ProCO), $CH_2\times2$ (pyrrolidinyl)), 2.11 (1H, m, 4-CHa*Hb*(ProCO)), 2.24 (1H, m, 3-C*Ha*Hb(ProCO), 2.50 (1H, m, 3-CHa*Hb*(ProCO)), 3.40~3.60, 3.64~3.80 (3H, 3H, two m, NCH_2, H_2C-NCH_2), 7.29 (1H, t, J=8.1 Hz, NCHCOCO), 7.35~7.60 (5H, m, Ph).

Crude (*S*)-*N*-cyclohexyl-2-[2-(1-(2-naphthoyl)pyrrolidinyl)]-2-oxoacetamide (**19**) was purified by silica gel column chromatography with CH_2Cl_2-MeCN (25:1) to give **19** (97.7% yield): Rf 0.54 (CH_2Cl_2-MeOH, 40:1); mp 132.5~133.5°C (crystallized from EtOAc-hexane); $[\alpha]_D^{27}$ −31.4° (*c* 1.1, $CHCl_3$); FAB-MS *m/z* 379 $(M+H)^+$, 252, 224, 155, 127; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.00~1.85 (8H, m, $CH_2\times4$(cHx)), 1.85~2.15 (5H, m, CH_2(cHx), CH_2C*Ha*Hb(ProCO)), 2.49 (1H, m, CHa*Hb*(ProCO)), 3.57~3.95 (3H, m, NCH_2, N-CH), 5.48 (1H, dd, J=6.3, 8.3 Hz, NCHCOCO), 6.82 (1H, br d, J=8.3 Hz, NH), 7.43~7.72 (3H, m, aromatic protons), 7.72~7.96 (3H, m, aromatic protons), 8.07 (1H, s, aromatic proton).

Crude (*S*)-*N*-cycloheptyl-2-[2-(1-(2-naphthoyl)pyrrolidinyl)]-2-oxoacetamide (**20**) was purified by silica gel column chromatography with CH_2Cl_2-MeCN (25:1~100:7) to give **20** (88.8% yield): Rf 0.57 (CH_2Cl_2-MeOH, 40:1); mp 114~115°C (crystallized from EtOAc-hexane); $[\alpha]_D^{24}$ −30.6° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 393 $(M+H)^+$, 252, 224, 155, 127; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20~1.80 (10H, m, $CH_2\times5$ (cycloheptyl)), 1.84~2.12 (5H, m, CH_2 (cycloheptyl)), CH_2C*Ha*Hb(ProCO)), 2.48 (1H, m, CHa*Hb*(ProCO)), 3.65 (1H, m, NC*Ha*Hb), 3.76 (1H, m, NCHa*Hb*), 3.96 (1H, m, N-CH), 5.47 (1H, dd, J=6.6, 8.1 Hz, NCHCOCO), 6.87 (1H, br d, J=8.3 Hz, NH), 7.45~7.60 (2H, m, aromatic protons), 7.64 (1H, m, aromatic proton), 7.74~7.95 (3H, m, aromatic protons), 8.06 (1H, s, aromatic proton).

Crude (*S*)-*N*-cyclohexyl-2-oxo-2-[2-(1-(2-quinolinecarbonyl)pyrrolidinyl)]acetamide (**21**) was purified by silica gel column chromatography with CH_2Cl_2-MeCN-AcOH (100:2:0.3~100:6:0.3) to give **21** (60.6% yield): Rf 0.30 (CH_2Cl_2-MeOH, 40:1); mp 160~161°C (crystallized from CH_2Cl_2-hexane); $[\alpha]_D^{24}$ −39.3° (*c* 1.0, $CHCl_3$); FAB-MS *m/z* 380 $(M+H)^+$, 224, 128; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02~1.51 (5H, m, $CH_2\times2$, C*Ha*Hb(cHx)), 1.59~1.84 (3H, m, CH_2, CHa*Hb*(cHx)), 1.85~2.18 (5H, m, CH_2(cHx), CH_2C*Ha*Hb(ProCO)),

2.48 (1H, m, CHa*Hb*(ProCO)), 3.80~3.98 (2H, m, NC*Ha*Hb, N-CH), 4.03 (1H, m, NCHa*Hb*), 6.39 (1H, dd, J=3.9, 9.3 Hz, NCHCOCO), 6.95 (1H, d, J=8.3 Hz, NH), 7.56 (1H, m, aromatic proton), 7.63 (1H, m, aromatic proton), 7.80 (1H, d, aromatic proton), 7.89 (1H, d, aromatic proton), 8.22 (1H, d, aromatic proton), 8.28 (1H, d, aromatic proton).

Crude (*S*)-*N*-cyclohexyl-2-oxo-2-[2-(1-(3-phenoxybenzoyl)pyrrolidinyl)]acetamide (**22**) was purified by silica gel column chromatography with CH_2Cl_2 - MeCN (50 : 1 ~ 50 : 3) to give **22** (75.6% yield): Rf 0.51 (CH_2Cl_2 - MeOH, 40 : 1); mp 40~42°C (amorphous solid); $[\alpha]_D^{23}$ −34.4° (*c* 1.1, $CHCl_3$); FAB-MS *m/z* 421 $(M+H)^+$, 294, 266, 197; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06~1.50 (5H, m, CH_2×2, C*Ha*Hb(cHx)), 1.55~2.19 (8H, m, CH_2×2, C*Ha*Hb(cHx)), CH_2C*Ha*Hb(ProCO)), 2.43 (1H, m, CHa*Hb*(ProCO)), 3.50~3.89 (3H, m, NCH_2, N-CH), 5.39 (1H, dd, J=6.0, 7.7 Hz, NCHCOCO), 6.76 (1H, br d, J=7.8 Hz, NH), 6.89~7.50 (9H, m, aromatic protons).

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