1β-Methyl-2-(5-substituted pyrrolidin-3-ylthio)carbapenems; 1. Synthesis and Antibacterial Activity of BO-2502A and Its Related Compounds†

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The synthesis and biological activity of (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-substituted pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid, in which lactams and cyclic amines are introduced as substituents, are described. They showed potent antibacterial activity against Gram-positive and Gram-negative bacteria including *P. aeruginosa*. Among them, BO-2502A (**4h-1**) was selected for further evaluation.

Imipenem,[2] the first marketed carbapenem antibiotic, is highly valued in the clinic for its efficacy against serious bacterial infections. However, due to its instability to renal dehydropeptidase-I (DHP-I), it is used in combination with cilastatin, a DHP-I inhibitor.

In 1984, it was reported by Merck researchers[3] that the installment of a methyl group on the 1β-position of the carbapenem nucleus resulted in the great improvement of both the chemical and metabolic stability. L-646-591 (**1**), a representative 1β-methyl carbapenem, indicated the possibility of clinical use as a single entity without cilastatin, due to its greatly improved stability to DHP-I. These findings prompted many research groups in the world to identify new parenteral 1β-methyl carbapenem analogues. Following the discovery of L-646-591 (**1**), meropenem (**2**)[4,5] and biapenem (**3**)[6,7] were reported to be in development as a single agent.

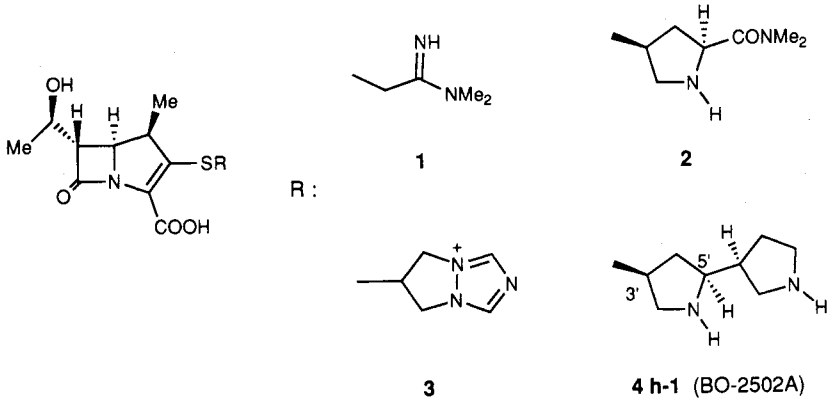
As part of our program directed toward a new parenteral 1β-methyl carbapenem agent with improved properties including antibacterial activity and stability to DHP-I, 1β-methyl-2-(5-substituted pyrrolidin-3-ylthio)-carbapenems, bearing a variety of lactams or cyclic amines as substituents, were prepared.

This paper describes the synthesis of new 1β-methyl carbapenems, their biological activities, and in addition the in-depth evaluation of the most active BO-2502A (**4h-1**).

Chemistry

Our general synthetic route leading to new carbapenems involved preparation of appropriately protected bicyclic side chain thiols and their coupling reaction

Fig. 1.



† See ref. 1.

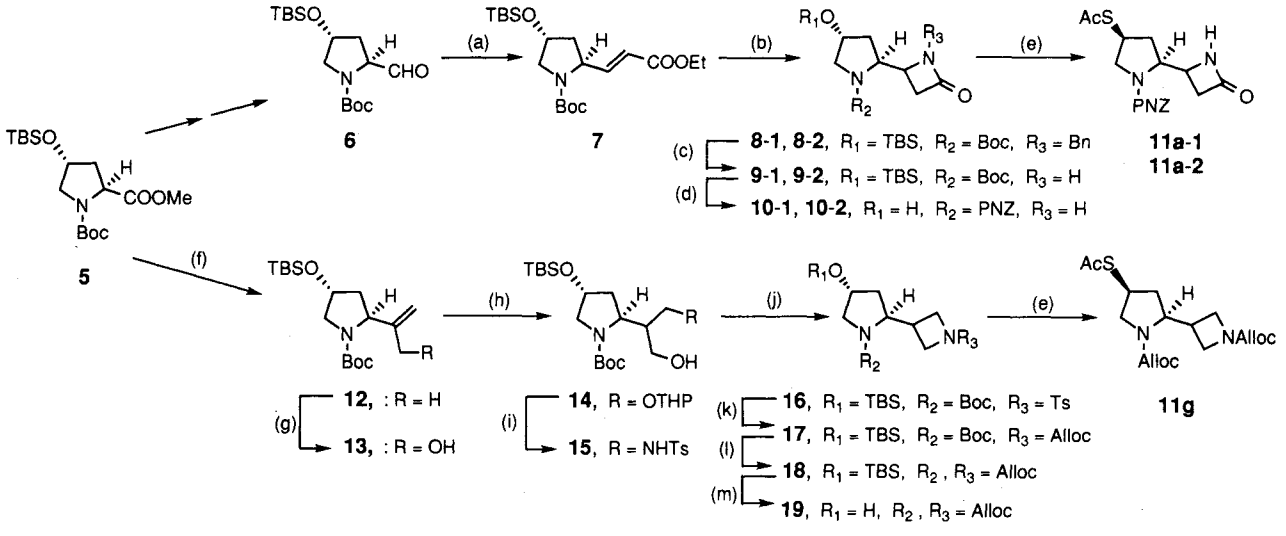
with the carbapenem diphenylphosphates (**39**[3], **40**[8]), followed by deprotection of the resulting protected carbapenems (**41**) in a usual manner.

In the preparation of new bicyclic pyrrolidine thiols, we selected the protected hydroxyproline methylester (**5**)[9] as a starting material, which was easily derived from commercially available (2*S*,4*R*)-L-hydroxyproline. Introduction of an additional ring moiety into the C-2 position of the pyrrolidine ring was performed by multi-step functionalization of the ester moiety.

Scheme 1 through 3 summarized the preparation of representative thiols such as azetidinyl, pyrrolidinyl and piperidinyl pyrrolidine derivatives. Scheme 1 showed the preparation of the azetidinone and azetidine derivatives (**11a** and **11g**). Michael addition of benzylamine to α,β-unsaturated ester (**7**), derived from the aldehyde (**6**)[9], followed by basic hydrolysis and cyclization of the resulting amino acid using OHNO's method[10], furnished the β-lactams [**8-1** (polar isomer) and **8-2** (less polar isomer)] in a ratio of 2:1, after separation by silica gel column chromatography. Debenzylation of **8-1** and **8-2** by Birch reduction (Na, liquid NH_3, $-78°C$) gave **9-1** and **9-2**, respectively. **9-1** and **9-2** were transformed to **10-1** and **10-2**, respectively, in the following manner: (1) TFA-anisole, (2) PNZS [4,6-dimethyl-2-(*p*-nitrobenzyloxycarbonylthio)pyrimidine], and (3) 46% hydrofluoric acid. Conversion of the hydroxyls of **10-1** and **10-2** to the corresponding thioacetates with inversion were carried out by Mitsunobu reaction using thioacetic acid[11] to give **11a-1** and **11a-2**.

Preparation of azetidine derivative (**11g**) was started from **5**. Addition of methylmagnesium bromide followed by dehydration with thionyl chloride gave the isopropenyl pyrrolidine (**12**) in 58% yield. Oxidation of the allylic methyl moiety of **12** by selenium dioxide gave the allyl alcohol (**13**) in a moderate yield. Protection of the alcohol moiety as a tetrahydropyranyl ether followed by hydroboration with 9-BBN gave the alcohol (**14**), after oxidative work-up. The alcohol (**14**) was converted to the tosylamide (**15**) by a five step sequence: (1) mesylation with MsCl (methanesulfonyl chloride) and TEA (triethylamine), (2) substitution of the mesylate with sodium azide in DMF, (3) reduction of the azide group with triphenylphosphine-H_2O, (4) protection of the resulting amine with *p*-toluenesulfonyl chloride, and (5) selective deprotection of the tetrahydropyranyl ether under mild acidic condition [PPTS (pyridinium *p*-toluenesulfonate) in MeOH at 40°C]. Azetidine ring formation of **15** was easily accomplished by the treatment of the corresponding mesylate with sodium hydride in DMF to give the tosylazetidine (**16**) in a good yield. The *N*-protecting groups of **16** were converted to the corresponding *N*-allyloxycarbonyl groups to give **18** by the following method: (1) deprotection of the tosyl group

Scheme 1.



(a) $(EtO)_2POCH_2CO_2Et$, 60% NaH, THF, 4 °C, (b); 1) $BnNH_2$, 2) 1 N NaOH, EtOH, 3) PPh_3, $(2\text{-PyS})_2$, CH_3CN, 80 °C, (c) Na, *t*-BuOH, THF, liq. NH_3, −78 °C, (d); 1) TFA, anisole, CH_2Cl_2, 4 °C, then PNZS, TEA, THF, 2) 46% aq. HF, CH_3CN, (e) DEAD, PPh_3, AcSH, THF, 4 °C, (f); 1) MeMgBr, THF, −20 °C, 2) $SOCl_2$, Py, CH_2Cl_2, −50 °C, (g); SeO_2, *t*-BuOOH, CH_2Cl_2, (h); 1) DHP, PPTS, CH_2Cl_2, 2) 9-BBN, THF, then Na_2BO_4, (i); 1) MsCl, TEA, THF, 4 °C, 2) NaN_3, DMF, 50 °C, 3) PPh_3, H_2O, THF, 4) TsCl, TEA, THF, r.t., 5) PPTS, MeOH, 40 °C, (j); 1) MsCl, TEA, THF, 4 °C, 2) 60% NaH, DMF, (k) Na, *t*-BuOH, THF, liq. NH_3, −78°C, then AllocCl, TEA, THF, 4 °C, (l) TMSOTf, 2,6-lutidine, CH_2Cl_2, 4 °C, then AllocCl, TEA, CH_2Cl_2, (m) TBAF, THF.

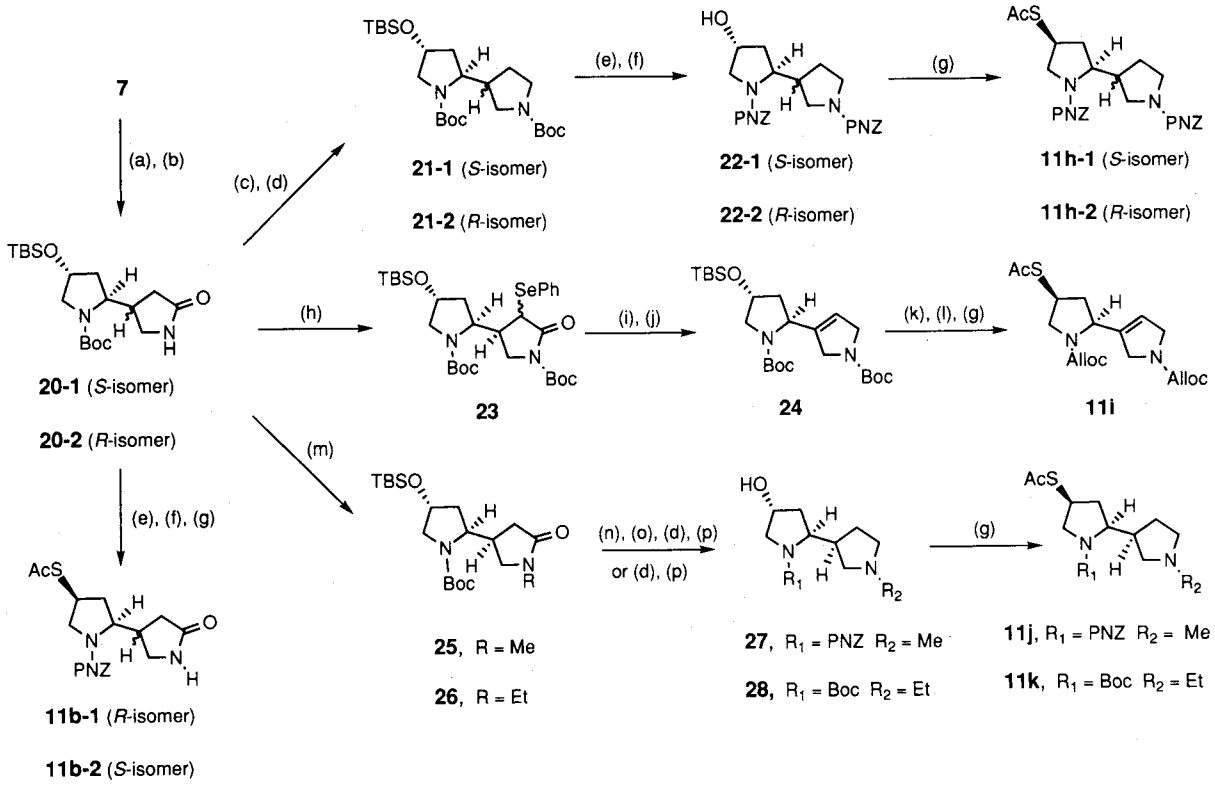
by Birch reduction and the subsequent protection with AllocCl (allyl chloroformate), (2) deprotection of the Boc group with TMSOTf (trimethylsilyl trifluoromethanesulfonate) and 2,6-lutidine[12] followed by the treatment with AllocCl. Finally deprotection of the silyl ether with TBAF (*tetra-n*-butylammonium fluoride) gave **19**, which was converted to the thioacetate (**11g**) by Mitsunobu reaction.

Next we prepared the pyrrolidone and pyrrolidine derivatives (**11b**, **11h**, **11i**, **11j**, and **11k**) as shown in Scheme 2. The pyrrolidone (**20**), a versatile intermediate leading to various pyrrolidine derivatives, was prepared from **7** as follows: Michael addition of nitromethane to **7** in the presence of *N*,*N*,*N*′,*N*′-tetramethylguanidine, followed by reduction of the nitro group with Raney nickel. The pyrrolidone (**20**) was obtained as a mixture of diastereomers in a ratio of 1 : 1, which was separated by fractional crystallization from heptane to give **20-1** (4′*S*-isomer) and **20-2** (4′*R*-isomer). The lactam nitrogens of **20-1** and **20-2** were protected with a Boc group by reaction with di-*t*-butyl dicarbonate in the presence of DMAP (dimethylaminopyridine), and the subsequent reduction with $BH_3 \cdot SMe_2$ furnished **21-1** and **21-2**, respectively, in good yields. Deprotection of **21-1** and **21-2** followed by reprotection with PNZCl (*p*-nitrobenzyl chloroformate) afforded the alcohols (**22-1** and **22-2**), which were converted to the corresponding thioacetates (**11h-1** and **11h-2**) in a similar manner described for the preparation of **11g**. Alternatively, acetylthiolation of **22-1** and **22-2** were achieved by substitution of the corresponding mesylates with potassium thioacetate in DMF at 60～70°C.

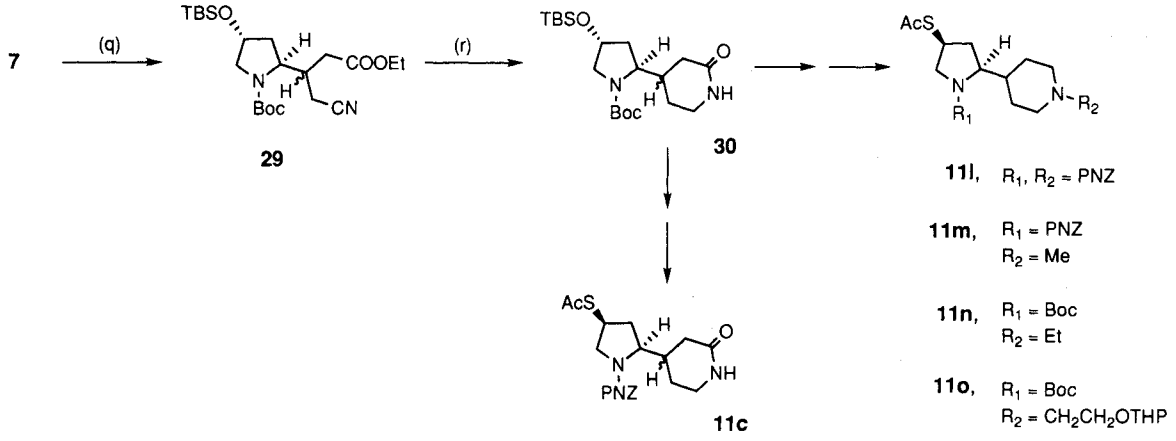
The 3-pyrroline derivative (**11i**) was prepared from **20-1**. Treatment of the di-*t*-butoxycarbonyl pyrrolidone, obtained from **20-1**, with lithium hexamethyldisilazide at −78°C and the subsequent addition of phenylselenyl chloride gave **23** in 74% yield. Careful reduction of the lactam moiety of **23** with $BH_3 \cdot SMe_2$ and the subsequent oxidation with *m*-chloroperbenzoic acid afforded the pyrroline (**24**). Conversion of **24** to the thioacetate (**11i**) was achieved by an usual method.

Preparation of the *N*-alkylpyrrolidine derivatives (**11j** and **11k**) were initiated with **20-1**, which was treated with sodium hydride and iodoalkanes such as iodomethane and iodoethane at room temperature, giving the *N*-alkylpyrrolidone (**25** and **26**). The *N*-methyl derivative (**11j**) was prepared as follows. **25** was converted to **27** in a four step sequence: (1) deprotection of Boc group, (2) reprotection with PNZCl, (3) reduction of the lactam moiety with $BH_3 \cdot SMe_2$, and (4) deprotection of the silyl group with TBAF. Transformation of **27** to **11j** was achieved as described above for the preparation of **11h**.

Scheme 2.

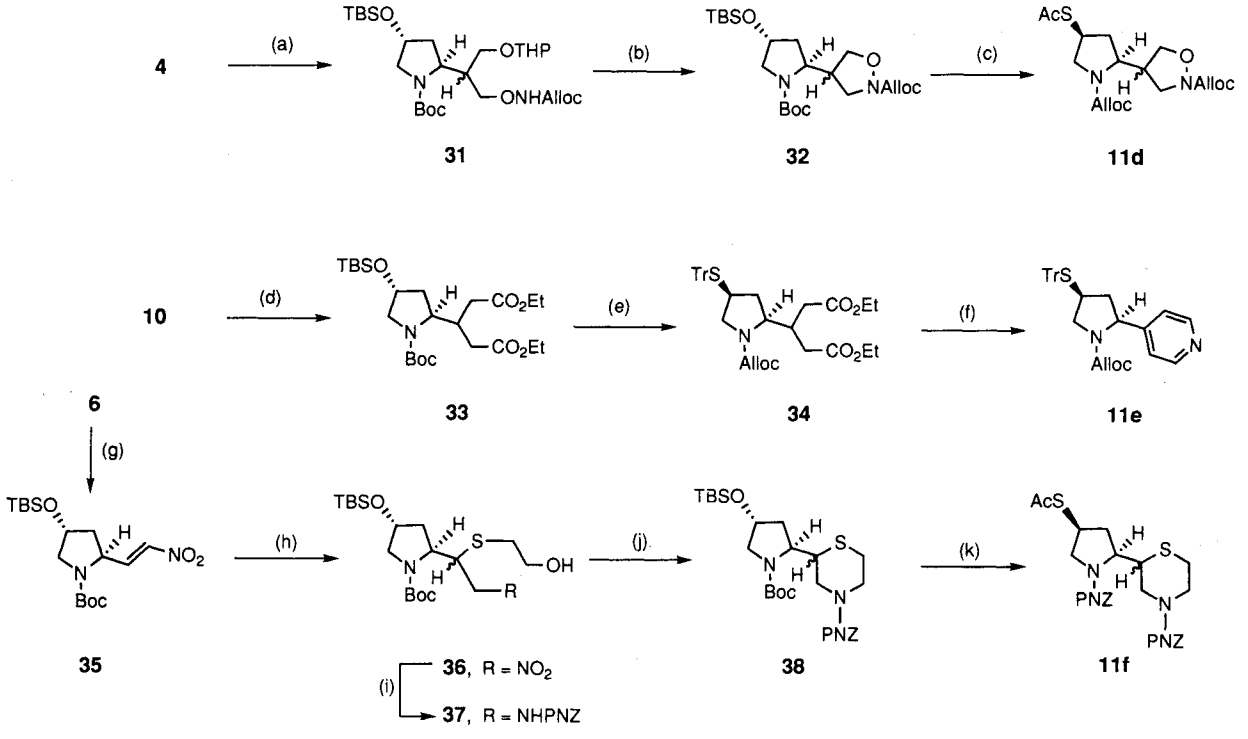


Scheme 3.



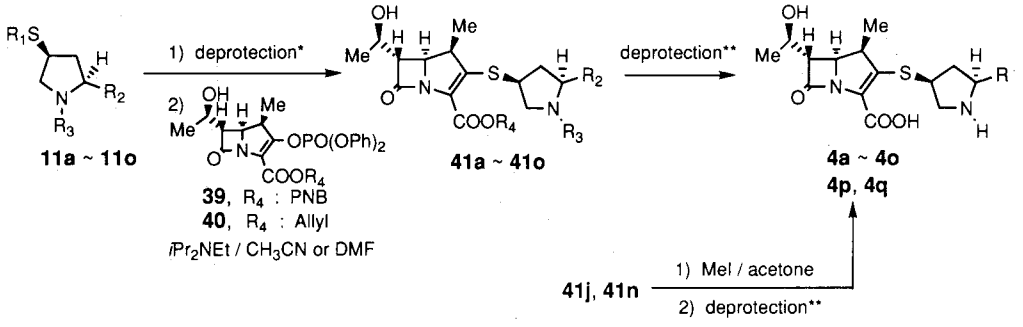
(a) $MeNO_2$, TMG, (b) Raney Ni, H_2, EtOH, then reflux, benzene, (c) Boc_2O, DMAP, MeCN, (d) BH_3·SMe_2, THF, reflux, (e) HCl-MeOH, (f) PNZCl, Na_2CO_3, dioxane–H_2O, 4 °C, (g) AcSH, DEAD, PPh_3, THF, 4 °C, or 1) MsCl, TEA, THF, 4 °C, 2) AcSK, DMF, 60~70 °C, (h) $LiN(TMS)_2$, PhSeCl, THF, –78 °C, (i) BH_3·SMe_2, THF, 55 °C, (j); mCPBA, CH_2Cl_2, (k) TMSOTf, 2,6-lutidine, CH_2Cl_2, 4 °C, then AllocCl, TEA, CH_2Cl_2, (l) 46% aq. HF, MeCN, (m) 60% NaH, RI, THF, r.t. to reflux, (n) TFA, CH_2Cl_2, 4 °C, (o) PNZCl, TEA, CH_2Cl_2, 4 °C, (p) TBAF, THF, 4 °C, (q) $NCCH_2CO_2Et$, 60% NaH, n-Bu_4NBr, THF, 50 °C, (r) Raney Ni, H_2 (3 atm), EtOH.

Scheme 4.



(a); 1) N-hydroxyphthalimide, DEAD, PPh_3, THF, 4 °C, 85%, 2) NH_2NH_2·H_2O, EtOH, 3) AllocCl, TEA, CH_2Cl_2, 75%, (b); 1) PPTS, EtOH, 40 °C. 75%, 2) DEAD, PPh_3, THF, 4 °C, 70%, (c); 1) HCl–MeOH, 2) AllocCl, TEA, CH_2Cl_2, 4 °C, 3) DEAD, PPh_3, AcSH, THF, 4 °C, 85%, (d); 1) Diethyl malonate, 60% NaH, THF, 50 °C, 2) NaCl, DMSO, 140°C, 70%, (e); 1) TFA, CH_2Cl_2, 4 °C, 2) AllocCl, TEA, CH_2Cl_2, 4 °C, 3) HCl–MeOH, 4) MsCl, TEA, THF, 4 °C, 5) TrSH, 60% NaH, DMF, 65%, (f); 1) DIBAL-H, –78 °C, 2) NH_2OH, AcOH, 100 °C, 10%, (g); 1) $MeNO_2$, TEA, 65 %, 2) $SOCl_2$, TEA, –50 °C, CH_2Cl_2, 81%, (h) $HSCH_2CH_2OH$, EtOH, 100%, (i); 1) LAH, Et_2O, 4 °C, 2)PNZCl, TEA, $CHCl_3$, 72%, (j); 1) MsCl, TEA, THF, 4 °C, 2) 10% Pd-C, H_2, EtOH, 3) PNZCl, TEA, $CHCl_3$, 27%, (k); 1) HCl–MeOH, 2) PNZCl, TEA, dioxane-H_2O, 3) MsCl, TEA, THF, 4 °C, 100%, 4) AcSK, DMF, 70 °C, 84%.

Scheme 5.



* Et_3SiH / TFA, CH_2Cl_2, 1 N NaOH / MeOH, or HCl / MeOH.
** (a); 10 % Pd-C, H_2, THF, MOPS buffer, EtOH, or $(PPh_3)_2PdCl_2$, nBu_3SnH, CH_2Cl_2, H_2O, (b); RP-18 column chromatography.

On the other hand **11k** was easily prepared without replacing the Boc group by a PNZ group. Reduction of the lactam moiety of **26** with $BH_3 \cdot SMe_2$ followed by deprotection of the silyl group with TBAF gave **28**, which was converted to the thioacetate (**11k**) in the usual manner in a good yield.

A similar methodology was applied to the preparation of the piperidine derivatives as shown in Scheme 3. Michael addition of ethyl cyanoacetate to the α,β-unsaturated ester (**7**) followed by deethoxycarbonylation in the presence of sodium chloride and H_2O in DMSO at 140°C furnished cyanoester (**29**)[13] in 75% yield, which was treated with Raney nickel under a hydrogen pressure (3 kg/cm^2), affording the piperidone (**30**). Transformation of **30** to the piperidone and piperidine derivatives (**11c**, **11l**, **11m**, **11n**, and **11o**) were carried out by similar methods as shown in Scheme 2.

Other pyrrolidine derivatives carrying cyclic amine moieties such as isoxazolidine, pyridine, and thiomorpholine (**11d**, **11e**, and **11f**) were prepared as shown in Scheme 4.

Thus, the acetylthio and tritylthio derivatives (**11a**~**11o**) obtained above, were converted to the corresponding thiols including the *N*-unprotected thiol derived from **11k** with HCl-MeOH. They were coupled with the appropriately protected enol phosphates (**39** and **40**) in the presence of diisopropylethylamine in CH_3CN or DMF at 0~5°C to afford the protected carbapenem derivatives (**41a**~**41o**) in moderate to good yields, after purification by silica gel column chromatography. Deprotection of **41a**~**41o** were carried out either by catalytic hydrogenation in the case of *p*-nitrobenzyl protection, or bis(triphenylphosphine)palladium(II)dichloride and tributyltin hydride[14] in the case of allyl protection, giving the carbapenems (**4a**~**4o**), after purification by reversed phase column chromatography. **4p** and **4q** were prepared from **41j** and **41n**, respectively, by treatment of **41j** and **41n** with excess iodomethane followed by deprotection of the resulting quaternary ammonium salts.

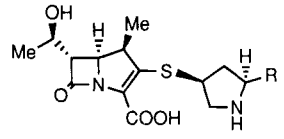
Biological Properties

Table 1 shows the antibacterial activity and stability to porcine renal DHP-I of the novel carbapenems prepared above, together with those of imipenem and meropenem as reference compounds.

First we looked at the effects of lactams and cyclic amines introduced into the C-5′ of the pyrrolidinylthio side chain. When four to six membered lactams were introduced, the resulting carbapenems (**4a**, **4b**, and **4c**) showed potent antibacterial activity and good stability to DHP-I. **4b-1**, a representative of the lactam series, exhibited better activity than that of meropenem against *S. aureus* including MRSA and comparable activity against *P. aeruginosa*. Its stability to DHP-I was superior to that of meropenem. On the other hand, introduction of the cyclic amine moieties into the C-5′ position, resulted in the great enhancement of antipseudomonal activity, while retaining the well balanced potent antibacterial activity against *S. aureus* and *E. coli*. Furthermore their stability to DHP-I was generally improved compared to that of meropenem.

In the correlation of the antipseudomonal activity with the ring size, the five and six membered rings (**4h** and **4l**) were preferable to the corresponding four membered ring (**4g**). As to the amino substitution, the antipseudomonal activity was maximum when the ring amines were unsubstituted, and generally decreased as the degree and size of the alkyl group were increased as shown in

Table 1. *In vitro* antibacterial activity (MIC, μg/ml) and DHP-I stability of carbapenem compounds.



Organism / R	4a-1	4a-2	4b-1***	4b-2***	4c-1***	4c-2***	4d-1***	4d-2***
S.aureus 209P NIHJ JC1	0.05	0.025	0.025	0.012	0.025	0.025	0.025	0.025
S.aureus BB5939*	12.5	12.5	6.25	6.25	6.25	12.5	12.5	12.5
S.aureus pMS520/Smith	12.5	12.5	6.25	6.25	6.25	25	25	25
E.coli NIHJ JC2	0.025	0.05	0.05	0.05	0.05	0.05	0.05	0.05
P.aeruginosa MB5002	12.5	12.5	3.13	6.25	6.25	6.25	6.25	6.25
P.aeruginosa MB5178	12.5	12.5	6.25	6.25	12.5	12.5	12.5	12.5
P.aeruginosa AKR17*	6.25	3.13	1.56	3.13	6.25	3.13	3.13	3.13
DHP-I susceptibility**	<0.1	<0.1	0.07	0.08	0.13	0.12	<0.05	<0.05

Organism / R	4e	4f	4g	4h-1 (BO-2502A)***	4h-2***	4i	4j	4k
S.aureus 209P NIHJ JC1	<0.006	0.012	0.025	0.012	0.012	0.012	0.012	0.012
S.aureus BB5939*	3.13	3.13	6.25	3.13	6.25	3.13	6.25	3.13
S.aureus pMS520/Smith	6.25	6.25	12.5	6.25	12.5	12.5	6.25	6.25
E.coli NIHJ JC2	0.012	0.05	0.05	0.05	0.1	0.05	0.1	0.05
P.aeruginosa MB5002	25	0.78	1.56	0.78	1.56	3.13	0.78	0.78
P.aeruginosa MB5178	12.5	6.25	6.25	1.56	3.13	6.25	3.13	6.25
P.aeruginosa AKR17*	6.25	6.25	3.13	0.78	1.56	3.13	1.56	1.56
DHP-I susceptibility**	0.05	0.06	<0.05	0.09	0.07	0.11	0.05	0.05

Organism / R	4l	4m	4n	4o	4p	4q	IPM	MEPM
S.aureus 209P NIHJ JC1	0.006	0.012	0.012	0.012	0.025	0.012	<0.006	0.05
S.aureus BB5939*	3.13	3.13	3.13	3.13	6.25	3.13	6.25	12.5
S.aureus pMS520/Smith	6.25	3.13	6.25	6.25	12.5	12.5	25	25
E.coli NIHJ JC2	0.1	0.1	0.05	0.05	0.1	0.1	0.1	0.012
P.aeruginosa MB5002	0.78	0.78	0.78	0.78	0.78	0.78	1.56	1.56
P.aeruginosa MB5178	1.56	6.25	6.25	6.25	12.5	6.25	12.5	6.25
P.aeruginosa AKR17*	1.56	1.56	1.56	1.56	1.56	1.56	3.13	3.13
DHP-I susceptibility**	0.07	0.12	<0.05	<0.05	<0.05	0.05	1.0	0.20

* β-lactamase producing strain. ** Relative to imipenem, porcine renal DHP-I. *** -1: polar isomer, -2: less polar isomer.

Table 1. As a result, the unsubstituted cyclic amines (**4h** and **4l**) were superior to the corresponding tertially and quaternarized congeners.

The pyrrolidine derivative (**4h-1**) showed better antipseudomonal activity than the diastereomer (**4h-2**), indicating that the configuration of the additional amine moiety also influenced the activity. In addition, the fact that pyrrolidine and the piperidine derivatives (**4h** and **4l**) with strong basicity showed better antipseudomonal activity than the isoxazolidine and pyridine derivatives (**4d** and **4e**) and the lactam derivatives (**4a**, **4b**, and **4c**), suggested that the basicity of the additional cyclic amines plays an important role in enhancing the antipseudomonal activity.

Among these compounds, **4h-1** (BO-2502A) was selected for further evaluation owing to its good stability to DHP-I and antibacterial activity. Table 2 shows the *in vitro* antibacterial activity of BO-2502A against clinical isolates consisting of Gram-positive and Gram-negative bacteria including MRSA and imipenem-resistant *P. aeruginosa*. As expected, BO-2502A exhibited the potent antibacterial activity against the isolates tested, especially the isolates of MSSA and *P. aeruginosa*, showing the MIC_{90} of 3.13 μg/ml or below, which were superior to those of meropenem. BO-2502A showed the good *in vivo* efficacy for the experimental systemic infections in mice (Table 3). In particular, BO-2502A had exquisite *in vivo* activity against the infectants of MRSA and *P. aeruginosa*, which well reflected the potent *in vitro* activity as described above and better pharmacokinetics in mice than those of imipenem and meropenem (Table 4).

Table 2. Comparative *in vitro* activities against clinical isolates.

Organisms (no. of isolates)	Compounds	MIC (μg/ml)*			
		Range	G-Mean	50%	90%
S. aureus (27) MSSA	BO-2502A	0.025 - 0.39	0.063	0.05	0.2
	MEPM	0.1 - 0.78	0.22	0.2	0.78
	IPM	0.012 - 0.10	0.029	0.025	0.1
S. aureus (23) MRSA	BO-2502A	3.13 - 12.5	5.71	6.25	12.5
	MEPM	6.25 - 25	14.50	12.50	25
	IPM	1.56 - 25	8.45	6.25	25
E. faecalis (25)	BO-2502A	0.39 - 3.13	1.36	1.56	1.56
	MEPM	0.78 - 6.25	4.01	6.25	6.25
	IPM	0.2 - 0.78	0.66	0.78	0.78
E. coli (27)	BO-2502A	0.02 - 0.1	0.038	0.05	0.05
	MEPM	0.012 - 0.025	0.02	0.025	0.025
	IPM	0.1 - 0.39	0.12	0.1	0.2
P. mirabilis (27)	BO-2502A	0.1 - 0.39	0.16	0.2	0.2
	MEPM	0.025 - 0.05	0.046	0.05	0.05
	IPM	0.2 - 6.25	0.47	0.39	1.56
P. vulgaris (27)	BO-2502A	0.05 - 3.13	0.27	0.39	0.78
	MEPM	0.025 - 0.39	0.072	0.1	0.2
	IPM	0.2 - 6.25	1.31	1.56	1.56
E. cloacae (27)	BO-2502A	0.05 - 0.20	0.062	0.05	0.1
	MEPM	0.025 - 0.39	0.056	0.05	0.2
	IPM	0.1 - 0.78	0.29	0.2	0.39
S. marcescens (27)	BO-2502A	0.1 - 3.13	0.34	0.2	3.13
	MEPM	0.025 - 6.25	0.21	0.05	6.25
	IPM	0.2 - 3.13	0.50	0.39	1.56
P. aeruginosa (102) IPM-susceptible (<6.25 μg/ml)	BO-2502A	0.05 - 1.56	0.16	0.2	0.39
	MEPM	0.05 - 12.5	0.50	0.39	3.13
	IPM	0.39 - 6.25	1.36	1.56	3.13
P. aeruginosa (20) IPM-resistant (>12.5 μg/ml)	BO-2502A	0.39 - 100	1.99	1.56	3.13
	MEPM	0.78 - >100	8.84	6.25	25.00
	IPM	12.5 - >100	25.00	25.00	50.00

* Agar dilution method using Mueller-Hinton agar and inoculum size of 10^6 cfu/ml.

Table 3. Therapeutic effect against experimental systemic infection in mice*.

Organisms (Infection dose; cfu/mouse)	Compounds	MIC (μg/ml)	ED_{50} (95% confidence limit)**
S. aureus 4970 ($1.6x10^6$)	BO-2502A	0.025	0.05 (0.02-0.09)
	MEPM	0.10	3.33 (1.86-6.33)
	IPM	0.025	0.07 (0.03-0.12)
S. aureus pMS520/Smith*** ($2.9x10^7$)	BO-2502A	3.13	2.11 (0.94-4.35)
	MEPM	12.50	43.1 (undefined)
	IPM	6.25	16.1 (undefined)
E. coli ML4707 ($1.1x10^4$)	BO-2502A	0.05	2.81(1.49-5.05)
	MEPM	0.025	43.5 (22.9-106)
	IPM	0.10	98.1 (undefined)
P. aeruginosa BB5935 ($5.6x10^5$)	BO-2502A	0.78	1.37 (0.76-2.56)
	MEPM	1.56	13.1 (6.89-31.9)
P. aeruginosa BB5746 ($2.9x10^4$)	BO-2502A	0.2	0.44 (0.19-0.87)
	MEPM	0.39	2.41 (0.76-6.72)
	IPM	0.39	1.19 (0.44-2.80)

* DDY male mice.
** Antibiotics were administered subcutaneously at 1 hr after infection and ED values were calculated by probit method (n=7 or 8).
*** Methicillin-resistant strain.

Table 4. Pharmacokinetics of carbapenems after s.c. administration of a 20 mg/kg to mice (n = 3).

Compounds	Pharmacokinetic parameters			Urinary recovery
	Cmax (μg/ml)	T1/2 (hr)	AUC (μg·hr/ml)	0-6hr (%)
BO-2502A	26.5	0.17	12.9	55.8
MEPM	22.9	0.10	7.9	22.8
IPM	21.5	0.12	9.5	21.5

Experimental

MIC Determination

MICs were determined by an agar dilution method using Mueller-Hinton medium. The culture grown overnight at 37°C for 20 hours was diluted to 3×10^6 CFU/ml, and about 10^4 CFU/ml was spotted onto the agar plates containing serial two-fold dilutions of antibiotics with a replicating device (Microplanter; Sakuma Seisakusyo, Tokyo, Japan). The plates were incubated at 37°C for 20 hours. The MIC was defined as the lowest concentration of antibiotics, at which visible growth was inhibited.

DHP-I Stability

Susceptibility of carbapenems to hydrolysis by DHP-I was determined by using partially purified porcine renal DHP-I (specific activity, 0.3 U/mg of protein). One unit of activity was defined as the amount of enzyme hydrolyzing 1 μmol of glycyldehydrophenylalanine per minute

when the substrate and 0.04 U of DHP-I per ml was incubated at 35°C in 50 mM MOPS buffer (pH 7.0). Hydrolysis was monitored spectrophotometrically, and expressed as the relative hydrolysis rate, taking the hydrolysis rate of imipenem as 1.0.

Determination of Antibiotic Levels in Mouse Plasma and Urine

Groups of three mice each were injected subcutaneously with 20 mg of each carbapenem per kg of body weight. The levels of carbapenems were determined by biological assay with a paper disk method using *Bacillus subtilis* ATCC 12432 as the indicator organism. The inoculated agar plates (antibiotic medium No. 1; Difco) were incubated at 37°C for 16 hours. The contents of the disk were calculated from a standard curve.

Systemic Infection

DDY male mice, 4 weeks old, were intraperitoneally infected with Gram-positive and Gram-negative bacteria, which were suspended in 5% gastric mucin. Antibiotics were subcutaneously administered to the mice once at 1 hour after injection. The therapeutic efficacy (ED_{50}) was calculated by probit method from the survival rate on the day 4 after treatment.

General Methods

Melting points were taken on a Yanaco micromelting point apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-200 spectrometer. ^{1}H NMR spectra were taken with Varian XL-200 and GEM-300 FT spectrometer in the designated solvent, using tetramethylsilane or residual DOH (δ 4.80) as an internal reference. Mass spectra were obtained on JEOL JMS-SX102A. Optical rotations were determined on a Jasco DIP-370 digital polarimeter. Column chromatography was carried out on WAKO gel C-300. Reversed phase column chromatography was carried out on YMC-gel ODS-AQ 120-S50. Reactions under anhydrous conditions were carried out using anhydrous solvents, dried over Molecular Sieves type 4A, under a nitrogen atmosphere.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[(*E*)-2-ethoxycarbonylvinyl]pyrrolidine (**7**)

To a mixture of 60% NaH (1.0 g, 25 mmol) in THF (100 ml) was added diethyl ethoxycarbonyl-methylphosphonate (6.0 g, 27 mmol) dropwise at 4°C and the mixture was stirred for 30 minutes at the same temperature. (2*S*,4*R*)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-formylpyrrolidine **6** (8.0 g, 24 mmol) in THF (20 ml) was added dropwise below 5°C, and the mixture was further stirred for 1 hour. The mixture was poured into H_2O, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **7** (9.4 g, 98%): $[\alpha]_D^{20}$ −23.2° (*c* 1.0, $CHCl_3$); IR (KBr) 1701, 1396, 1167 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.88 (9H, s), 1.30 (3H, d, J=7.0 Hz), 1.44 (9H, br s), 1.84 (1H, m), 2.10 (1H, m), 3.48 (2H, m), 4.12 (2H, q, J=7.0 Hz), 4.35 (1H, m), 5.88 (1H, br d, J=16.0 Hz), 6.86 (1H, m); HRFAB-MS *m/z* Calcd for $C_{24}H_{46}NO_7Si$ $(M+H)^+$ 488.3013; Found 488.3028.

(2*S*,4*R*)-2-(*N*-Benzyl-2-azetidinon-4-yl)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxypyrrolidine (**8-1**, **8-2**)

1) A mixture of **7** (2.2 g, 5.5 mmol) and benzylamine (1.2 ml, 11 mmol) was stirred for 5 days at room temperature. The mixture was purified by column chromatography to give ethyl 3-benzylamino-3-[(2*S*,4*R*)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxypyrrolidin-2-yl]propionate (2.0 g, 71%).

2) To a solution of the above compound (2.0 g, 3.9 mmol) in EtOH (30 ml) was added 1 N aqueous NaOH (4.3 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was neutralized with 1 N HCl (4.3 ml), and concentrated *in vacuo* to give the residue, which was taken up with THF (50 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude carboxylic acid (1.8 g).

3) To a solution of the above residue in CH_3CN (380 ml) were added triphenylphosphine (1.2 g, 4.6 mmol) and 2,2'-dipyridyl disulfide (1.0 g, 4.6 mmol), and the mixture was stirred for 4.5 hours at 80°C. The mixture was concentrated *in vacuo* to give the residue, which was diluted with EtOAc. The organic layer was washed with 0.1 N aqueous NaOH and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give **8-1** (1.1 g, 61%, polar isomer) and **8-2** (0.47 g, 27%, less polar isomer).

8-1: IR (KBr) 1730, 1690, 1390 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.88 (9H, s), 1.50 (9H, br s), 2.54 (1H, br d, J=14.0 Hz), 2.93 (1H, dd, J=4.0 and 14.0 Hz), 3.16 (1H, dd, J=4.0 and 12.0 Hz), 7.35 (5H, m).

8-2: IR (KBr) 1760, 1700, 1400 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.85 (9H, s), 1.45 (9H, br s), 1.84 (2H, m), 2.58 (1H, br d, J=16.0 Hz), 2.92 (2H, m), 3.44 (1H, m), 3.95~4.30 (4H, m), 4.60 (1H, m), 7.30

(5H, m).

(2*S*,4*R*)-2-(2-Azetidinon-4-yl)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxypyrrolidine (**9-1**, **9-2**)

To a solution of **8-1** (470 mg, 0.98 mmol) in THF (10 ml), *t*-BuOH (1 ml) and liquid NH_3 (30 ml) was added sodium metal (100 mg, 4.4 mmol) in portions at −78°C. After being stirred for 15 minutes at the same temperature, ammonium chloride (470 mg, 8.7 mmol) was added, and the mixture was warmed to room temperature to remove liquid NH_3. The residue was diluted with EtOAc, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$ and, concentrated *in vacuo*. The residue was purified by column chromatography to give **9-1** (340 mg, 89%).

9-1: IR (KBr) 1750, 1700, 1380 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.87 (9H, s), 1.47 (9H, s), 1.61 (1H, m), 2.02 (1H, m), 2.62 (1H, br d, J=6.0 Hz), 3.02 (1H, d, J=6.0 and 16.0 Hz), 3.33 (1H, m), 3.50 (2H, m), 4.05 (1H, m), 4.30 (1H, m).

9-2 was prepared in 88% yield as described for the preparation of **9-1**.

9-2: IR (KBr) 1760, 1690, 1390 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.47 (9H, s), 1.93 (2H, m), 2.66 (1H, d, J=16.0 Hz), 2.97 (1H, ddd, J=2.0, 5.0, and 16.0 Hz), 3.26 (1H, dd, J=5.0 and 12.0 Hz), 3.55 (1H, m), 4.00~4.30 (3H, m).

(2*S*,4*R*)-2-(2-Azetidinon-4-yl)-4-hydroxy-*N*-(*p*-nitrobenzyloxycarbonyl)pyrrolidine (**10-1**, **10-2**)

To an ice-cooled solution of **9-1** (340 mg, 0.88 mmol) in CH_2Cl_2 (3 ml) was added TFA (3 ml), and the mixture was stirred for 1 hour at 4°C, and then the mixture was concentrated *in vacuo*. To a solution of the residue in THF (5 ml) was added TEA (1.2 ml, 8.6 mmol) and PNZS (280 mg, 0.88 mmol), and the mixture was stirred for 1.5 hours at room temperature. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with 0.1 N aqueous NaOH and brine, dried over $MgSO_4$, and concentrated *in vacuo*. To the residue in CH_3CN (5 ml) was added 46% hydrofluoric acid (0.5 ml), and the mixture was stirred for 1.5 hours at room temperature. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give **10-1** (177 mg, 60%).

10-1: IR (KBr) 1750, 1700, 1520 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.72 (1H, m), 2.14 (1H, m), 2.64 (1H, d, J=14.0 Hz), 3.06 (2H, m), 3.57 (1H, m), 3.74 (1H, m), 4.12 (1H, m), 4.44 (1H, m), 5.22 (2H, br s), 7.52 (2H, d, J=8.0 Hz), 8.22 (2H, d, J=8.0 Hz).

10-2 was prepared in 61% yield as described for the preparation of **10-1**.

10-2: IR (KBr) 1740, 1670, 1520 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.06 (2H, s), 2.70 (1H, d, J=16.0 Hz), 3.02 (1H, d, J=16.0 Hz), 3.47 (1H, m), 3.76 (1H, m), 4.16 (1H, m), 4.34 (1H, m), 4.50 (1H, m), 5.26 (2H, br s), 7.54 (2H, d, J=8.0 Hz), 8.24 (2H, d, J=8.0 Hz).

(2*S*,4*S*)-4-Acetylthio-2-(2-azetidinon-4-yl)-*N*-(*p*-nitrobenzyloxycarbonyl)pyrrolidine (**11a-1**, **11a-2**)

To an ice-cooled solution of **10-1** (180 mg, 0.53 mmol) in THF (10 ml) was added triphenylphosphine (350 mg, 1.3 mmol) and diethyl azodicarboxylate (0.21 ml, 0.13 mmol). After being stirred for 30 min at 4°C, thioacetic acid (95 μl, 0.13 mmol) was added, and the mixture was further stirred for 3 hours at the same temperature. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give **11a-1** (77 mg, 37%): **11a-1**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.65 (1H, m), 2.38 (3H, s), 3.08 (1H, dd, J=4.0 and 14.0 Hz), 3.30 (1H, t, J=9.0 Hz), 3.64~4.28 (4H, m), 5.25 (2H, br s), 7.55 (2H, d, J=8.0 Hz), 8.26 (2H, d, J=8.0 Hz).

11a-2 was prepared in 49% yield as described for the preparation of **11a-1**.

11a-2: ^1H NMR (200 MHz, $CDCl_3$) δ 1.87 (1H, m), 2.36 (3H, s), 2.52 (1H, m), 3.04 (1H, br d, J=12.0 Hz), 3.18 (1H, t, J=10.0 Hz), 3.80~4.32 (4H, m), 5.26 (2H, br s), 7.54 (2H, d, J=8.0 Hz), 8.23 (2H, d, J=8.0 Hz).

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-(propen-2-yl)pyrrolidine (**12**)

1) To a solution of **5** (10 g, 28 mmol) in THF (100 ml) was added a 1.0 M solution of methylmagnesium bromide in ether (98 ml) at −20°C, and the mixture was stirred for 1 hour at the same temperature. The reaction was quenched by adding saturated aqueous NH_4Cl solution, and the mixture was poured into H_2O and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give (2*S*,4*R*)-*N*-*t*-butoxycarbonyl-4-*t*-butyl-dimethylsilyloxy-2-(2-hydroxypropan-2-yl)pyrrolidine (8.2 g, 82%).

2) To a solution of the above compound (3.0 g, 8.4 mmol) in toluene (50 ml) were added TEA (2.3 ml, 17 mmol) and thionyl chloride (0.92 ml, 12.5 mmol) drop-

wise at $-50°C$. After being stirred for 30 minutes at the same temperature, the reaction temperature was raised to $-10°C$ and the reaction was quenched with aqueous NH_4Cl solution. The mixture was extracted with EtOAc, and the organic layer was washed with 1 N aqueous NaOH solution and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography gave **12** (2.0 g, 71%): IR (KBr) 1701, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.88 (9H, s), 1.35~1.55 (9H, m), 1.65 (3H, br s), 1.83 (1H, m), 2.00 (1H, m), 3.40~3.53 (2H, m), 4.33 (2H, m), 4.79 (2H, m); FAB-MS *m/z* 342 $(M+H)^+$.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-(1-hydroxypropen-2-yl)pyrrolidine (**13**)

To a solution of **12** (500 mg, 1.5 mmol) in CH_2Cl_2 (10 ml) were added *t*-butyl hydroperoxide (0.6 ml, 4.4 mmol) and selenium dioxide (86 mg, 0.77 mmol), and the mixture was stirred for 20 hours at room temperature. Evaporation of the mixture gave the residue, which was poured into H_2O, and extracted with EtOAc. The extract was washed with 1 N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. To the residue in EtOAc (10 ml) were added dimethylsulfide (0.75 ml, mmol) and AcOH (0.25 ml, mmol), and the mixture was stirred for 1.5 hours at room temperature. The mixture was diluted with EtOAc and washed with 1 N aqueous NaOH solution and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the residue, which was purified by silica gel column chromatography affording **13** (190 mg, 36%): IR (KBr) 3435, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.87 (9H, s), 1.44 (9H, s), 1.64 (1H, m), 2.08 (1H, m), 3.46 (2H, m), 4.09 (2H, ABq, $J=11.5$ Hz), 4.32~4.60 (2H, m), 4.99 (1H, s), 5.03 (1H, br s); FAB-MS *m/z* 358 $(M+H)^+$.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[*N*-(*p*-toluenesulfonyl)azetidin-3-yl]pyrrolidine (**16**)

To an ice-cooled solution of **15** (912 mg, 1.73 mmol) in THF (15 ml) were added TEA (0.29 ml, 2.1 mmol) and MsCl (0.15 ml, 2.0 mmol) dropwise, and the mixture was stirred for 40 minutes at the same temperature. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. To the residue in DMF (80 ml) was added 60% NaH (97 mg, 2.4 mmol) and the mixture was stirred for 4 hours at room temperature. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **16** (680 mg, 77%): mp 98~99.5°C (heptane); $[\alpha]_D^{20}$ $-23.2°$ (*c* 1.0, $CHCl_3$); IR (KBr) 1701, 1159 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.82 (9H, s), 1.41 (9H, s), 1.58 (1H, m), 1.87 (1H, m), 2.46 (3H, s), 2.76 (1H, m), 3.15 (1H, m), 3.42 (2H, m), 3.73 (3H, m), 3.90 (1H, m), 4.22 (1H, m), 7.38 (2H, d, $J=8$ Hz), 7.73 (2H, d, $J=8$ Hz); HRFAB-MS *m/z* Calcd for $C_{25}H_{43}N_2O_5SSi$ $(M+H)^+$ 511.2662; Found 511.2667.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-2-[*N*-allyloxycarbonylazetidin-3-yl]-4-*t*-butyldimethylsilyloxypyrrolidine (**17**)

To a solution of **16** (2.0 g, 3.9 mmol) in THF (15 ml), *t*-BuOH (1.1 ml) and liquid NH_3 (30 ml) was added sodium metal (410 mg, 18 mmol) in portions at $-78°C$, and the mixture was stirred for 30 minutes at the same temperature. The reaction mixture was warmed to room temperature to remove liquid NH_3 and then the resulting mixture was concentrated *in vacuo*. To an ice-cooled solution of the residue in THF (30 ml) was added TEA (2.2 ml, 15.7 mmol) and AllocCl (0.83 ml, 7.8 mmol), and the mixture was further stirred for 30 minutes at the same temperature. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography gave **17** (1.7 g, 99%): ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.85 (9H, s), 1.44 (9H, s), 1.96 (1H, m), 2.94 (1H, m), 3.26 (1H, dd, $J=4.0$ and 11.5 Hz), 3.45~3.75 (2H, m), 3.80~4.05 (3H, m), 4.17 (1H, m), 4.30 (1H, m), 4.54 (2H, dd, $J=1.3$ and 7.0 Hz), 5.92 (1H, m).

(2*S*,4*R*)-*N*-Allyloxycarbonyl-2-[*N*-allyloxycarbonylazetidin-3-yl]-4-*t*-butyldimethylsilyloxypyrrolidine (**18**)

To an ice-cooled solution of **17** (1.46 g, 3.3 mmol) in CH_2Cl_2 (30 ml) were added 2,6-lutidine (0.69 ml, 5.9 mmol) and TMSOTf (0.99 ml, 5.0 mmol), and the mixture was stirred for 30 minutes at the same temperature. After the addition of MeOH (5 ml), the mixture was further stirred for 30 minutes, and then concentrated *in vacuo*. To an ice-cooled solution of the residue in CH_2Cl_2 (30 ml) were added TEA (1.0 ml, 7.2 mmol) and AllocCl (0.70 ml, 6.7 mmol), and the mixture was stirred for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue was poured into H_2O and with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was

purified by silica gel chromatography to give **18** (1.4 g, 99%): IR (KBr) 1707, 1408, 1111 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.83 (9H, s), 1.73 (1H, m), 2.00 (1H, m), 2.93 (1H, m), 3.34 (1H, dd, J=4.0 and 11.5 Hz), 3.50~3.70 (2H, m), 3.80~4.05 (3H, m), 4.21 (1H, m), 4.32 (1H, m), 4.32 (1H, m), 4.45~4.62 (4H, m), 5.14~5.39 (4H, m), 5.80~5.95 (2H, m); FAB-MS m/z 425 $(M+H)^+$.

(2*S*,4*R*)-*N*-Allyloxycarbonyl-2-(*N*-allyloxycarbonylazetidin-3-yl)-4-hydroxy-pyrrolidine (**19**)

To an ice-cooled solution of **18** (2.8 g, 6.6 mmol) in THF (40 ml) was added a 1.0 M solution of tetra-*n*-butylammonium fluoride in THF (7.54 ml) dropwise, and the mixture was stirred for 3 hours at the same temperature. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography gave **19** (2.0 g, 99%): IR (KBr) 3440, 1693, 1410 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (1H, m), 2.13 (1H, m), 3.00 (1H, m), 3.43 (1H, m), 3.69 (2H, m), 3.80~4.10 (3H, m), 4.27 (1H, q, J=7.6 Hz), 4.45 (1H, m), 4.50~4.65 (4H, m), 5.15~5.37 (4H, m), 5.82~6.02 (2H, m); HRFAB-MS m/z Calcd for $C_{15}H_{23}N_2O_5$ $(M+H)^+$ 311.1607; Found 311.1635.

(2*S*,4*S*)-4-Acetylthio-*N*-allyloxycarbonyl-2-(*N*-allyloxycarbonylazetidin-3-yl)pyrrolidine (**11g**)

To an ice-cooled solution of **19** (2.0 g, 6.45 mmol) in THF (40 ml) were added triphenylphosphine (2.2 g, 8.4 mmol) and diethyl azodicarboxylate (1.3 ml, 8.4 mmol). After being stirred for 30 minutes at the same temperature, thioacetic acid (0.69 ml, 9.7 mmol) was added, and the mixture was further stirred for 1 hour. Evaporation of the mixture gave the residue, which was purified by silica gel column chromatography affording **11g** (2.2 g, 92%): IR (KBr) 1703, 1549, 1408 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (1H, m), 1.64 (1H, m), 2.34 (3H, s), 2.55 (1H, m), 3.00 (1H, m), 3.15 (1H, dd, J=8.5 and 11.4 Hz), 3.70 (1H, br t, J=7.3 Hz), 3.86 (1H, m), 3.95~4.04 (2H, m), 4.06~4.20 (2H, m), 4.53~4.60 (4H, m), 5.18~5.34 (4H, m), 5.85~5.96 (2H, m); HRFAB-MS m/z Calcd for $C_{17}H_{25}N_2O_5S$ $(M+H)^+$ 369.1484; Found 369.1492.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-(2-pyrrolidon-4-yl)pyrrolidine (**20**)

1) To a solution of **7** (9.0 g, 23 mmol) in nitromethane (33 ml) was added *N*,*N*,*N*′,*N*′-teramethylguanidine (5.8 ml, 46 mmol) at room temperature and the mixture was stirred overnight. Evaporation of the mixture gave the residue, which was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give (2*S*,4*R*)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[3-ethoxycarbonyl-1-nitropropan-2-yl)pyrrolidine (10.1 g, 97%).

2) To a solution of the above compound (3.6 g, 7.8 mmol) in EtOH (50 ml) was added Raney nickel (W-2, 3.0 ml) and the mixture was stirred overnight under a hydrogen atmosphere. The catalyst was filtered off and washed with EtOH. The combined filtrate and washings were concentrated *in vacuo*. A solution of the residue in benzene (50 ml) was stirred overnight at reflux temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography to give **20** (1.87 g, 62%).

20 (10.8 g, 22.3 mmol) was dissolved in hexane (75 ml) at 40°C, and the insoluble was removed by filtration. After standing overnight at room temperature, the resulting precipitates were collected by filtration and dried to give (2*S*,4*R*)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[(4*S*)-2-pyrrolidon-4-yl]pyrrolidine **20-1** (3.7 g, 35%). The filtrate was concentrated *in vacuo*, and the residue was dissolved in hexane (70 ml) with heating. The similar operation was repeated to give (2*S*,4*R*)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[(4*R*)-2-pyrrolidon-4-yl]pyrrolidine **20-2** (1.9 g, 17%).

20-1: mp 92~95°C; $[\alpha]_D^{20}$ −39.0° (c 1.0, $CHCl_3$); IR (KBr) 1685, 1395, 1250, 1175 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.46 (9H, s), 1.72~1.97 (2H, m), 2.20 (1H, dd, J=8.0 and 18.0 Hz), 2.41 (1H, dd, J=8.0 and 18.0 Hz), 2.90~3.80 (5H, m), 4.15 (1H, br), 4.32 (1H, br), 6.06 (1H, br); HRFAB-MS m/z Calcd for $C_{19}H_{36}NO_4SiNa$ $(M+Na)^+$ 407.2342; Found 407.2371.

Anal Calcd for $C_{19}H_{36}N_2O_4Si \cdot H_2O$:
C 56.68, H 9.51, N 6.96.
Found:
C 56.96, H 9.41, N 6.90.

20-2: mp 97~100°C; $[\alpha]_D^{20}$ −57.4° (c 1.0, $CHCl_3$); IR (KBr) 1685, 1385, 1255, 1160 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.46 (9H, s), 1.70~1.95 (2H, m), 2.04 (1H, dd, J=8.0 and 16.0 Hz), 2.32 (1H, dd, J=8.0 and 16.0 Hz), 2.90~3.60 (5H, m), 4.10 (1H, br), 4.32 (1H, br), 6.00 (1H, br); HRFAB-MS m/z Calcd for $C_{19}H_{37}N_2O_4Si$ $(M+H)^+$ 385.2523; Found 385.2523.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[(3*S*)-*N*-*t*-butoxycarbonylpyrrolidin-3-yl]pyrrolidine (**21-1**)

1) To a solution of **20-1** (4.80 g, 12.5 mmol) in CH_3CN (50 ml) were added 4-dimethylaminopyridine (790 mg, 6.5 mmol) and di-*t*-butyldicarbonate (4.1 g, 19 mmol), and the mixture was stirred for 4 hours at room temperature. The mixture was concentrated *in vacuo* and the residue was poured into H_2O and extracted with EtOAc. The organic layer was washed with 5% aqueous citric acid solution and brine, dried over $MgSO_4$, and concentrated *in vacuo*. To the residue in THF (75 ml) was added $BH_3 \cdot SMe_2$ (2.5 ml, 25 mmol) dropwise and the mixture was refluxed for 1 hour. The reaction was cooled to 4°C and quenched by adding excess MeOH (5 ml). The mixture was concentrated *in vacuo* to give the residue, which was purified by silica gel column chromatography affording **21-1** (5.8 g, 98%): mp 80~81.5°C; IR (KBr) 1695, 1398, 1169 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.86 (9H, s), 1.44 (18H, m), 1.56~2.04 (4H, m), 3.02~3.70 (6H, m), 4.00 (1H, m), 4.34 (1H, m); FAB-MS *m/z* 471 $(M+H)^+$.

(2*S*,4*R*)-4-Hydroxy-*N*-(*p*-nitrobenzyloxycarbonyl)-2-[(3*S*)-*N*-(*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-yl]pyrrolidine (**22-1**)

To a solution of **21-1** (5.7 g, 12.1 mmol) in MeOH (20 ml) was added a 3 N solution of hydrogen chloride in MeOH (20 ml). After being stirred for 3 hours at room temperature, the mixture was concentrated *in vacuo*. To an ice-cooled solution of the residue in dioxane (50 ml) and H_2O (25 ml) was added Na_2CO_3 (2.8 g, 27 mmol) and PNZCl (5.5 g, 25 mmol). After being stirred for 3 hours at the same temperature, the mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **22-1** (5.3 g, 85%). IR (KBr) 3452, 1691, 1408, 1120 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.50~2.15 (4H, m), 2.73 (1H, m), 3.10 (1H, br t, J=10.3 Hz), 3.30~3.90 (5H, m), 4.23 (1H, m), 4.48 (1H, m), 5.21 (4H, br s), 7.51 (4H, d, J=8.6 Hz), 8.21 (4H, d, J=8.6 Hz); HR-MS Calcd for $C_{24}H_{27}N_4O_9$ $(M+H)^+$ 515.1778; Found 515.1766.

(2*S*,4*S*)-4-Acetylthio-*N*-(*p*-nitrobenzyloxycarbonyl)-2-[(3*S*)-*N*-(*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-yl]pyrrolidine (**11h-1**)

To an ice-cooled solution of **22-1** (2.2 g, 4.28 mmol) in THF (30 ml) were added TEA (0.89 ml, 6.42 mmol) and MsCl (0.41 ml, 5.35 mmol), and the mixture was stirred for 30 minutes at the same temperature. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. A mixture of the mesylate and potassium thioacetates (1.5 g, 13 mmol) in DMF (30 ml) was stirred for 6 hours at 60~70°C. The reaction mixture was cooled to room temperature, poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography gave **11h-1** (1.70 g, 73%): $[\alpha]_D^{20}$ −45.0° (*c* 1.0, $CHCl_3$); IR (KBr) 1705, 1522, 1406, 1346, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58~2.10 (3H, m), 2.35 (3H, s), 2.50 (1H, m), 2.77 (1H, m), 3.07~3.20 (2H, m), 3.34 (1H, m), 3.45~3.67 (2H, m), 3.85 (1H, m), 4.10 (1H, m), 4.22 (1H, m), 5.21 (4H, br s), 7.51 (4H, d, J=8.6 Hz), 8.24 (4H, m); HRFAB-MS *m/z* Calcd for $C_{26}H_{29}N_4O_9S$ $(M+H)^+$ 573.1656; Found 573.1644.

(2*S*,4*S*)-4-Acetylthio-*N*-(*p*-nitrobenzyloxycarbonyl)-2-[(3*R*)-*N*-(*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-yl]pyrrolidine (**11h-2**)

11h-2 was prepared from **20-2** as described for the preparation of **11h-1**.

11g-2: $[\alpha]_D^{20}$ −16.0° (*c* 1.0, $CHCl_3$); IR (KBr) 1705, 1520, 1408, 1346, 1109 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.55~1.80 (2H, m), 1.92 (1H, m), 2.35 (3H, s), 2.45~2.70 (2H, m), 3.06~3.45 (3H, m), 3.52~3.68 (2H, m), 3.87 (1H, m), 4.08 (1H, m), 4.24 (1H, m), 5.21 (4H, s), 7.51 (4H, br d, J=8.6 Hz), 8.20 (4H, m); HRFAB-MS *m/z* Calcd for $C_{26}H_{29}N_4O_9S$ $(M+H)^+$ 573.1656; Found 573.1674.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[(4*S*)-*N*-*t*-butoxycarbonyl-3-phenylselenyl-2-pyrrolidon-4-yl]pyrrolidine (**23**)

To a solution of lithium hexamethyldisilazide in THF (40 ml), prepared from hexamethyldisilazane (1.5 ml, 7.0 mmol) and a 1.6 M solution of *n*-BuLi in hexane (4.2 ml), was added (2*S*,4*R*)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[(4*R*)-*N*-*t*-butoxycarbonyl-2-pyrrolidon-4-yl]pyrrolidine (2.5 g, 5.2 mmol) in THF (20 ml) dropwise at −78°C. After being stirred for 30 minutes at the same temperature, phenylselenyl chloride (1.5 g, 7.8 mmol) in THF (15 ml) was added, and the mixture was further stirred for 1 hour. The reaction was quenched by adding saturated aqueous NH_4Cl solution and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and con-

centrated *in vacuo*. The residue was purified by silica gel column chromatography to give **23** (2.5 g, 74%): IR (KBr) 1778, 1545, 1693, 1549, 1394 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.84 (9H, s), 1.40~1.60 (10H, m), 1.87 (1H, m), 2.77 (1H, quint, J=4.7 Hz), 3.17 (1H, m), 3.20~3.80 (4H, m), 4.00~4.25 (2H, m), 7.25~7.40 (3H, m), 7.67 (2H, d, J=6.7 Hz); FAB-MS m/z 663 $(M+Na)^+$.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-(*N*-*t*-butoxycarbonyl-3-pyrrolin-4-yl]pyrrolidine (**24**)

1) To a solution of **23** (2.3 g, 3.5 mmol) in THF (30 ml) was added $BH_3 \cdot SMe_2$ (0.53 ml, 5.3 mmol) and the mixture was stirred at 55°C for 45 minutes. The reaction was quenched by adding excess MeOH (3 ml) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give (2*S*,4*R*)-*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[(4*R*)-*N*-*t*-butoxycarbonyl-3-phenylselenylpyrrolidin-4-yl]pyrrolidine (1.54 g, 70%): IR (KBr) 1695, 1396, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.85 (9H, s), 1.42, 1.46 (9H, each s), 1.56 (1H, m), 1.85 (1H, m), 2.47~2.80 (1H, m), 2.90~3.20 (2H, m), 3.30~3.70 (4H, m), 3.87 (1H, m), 4.21 (2H, m), 7.29 (3H, m), 7.54 (2H, d, J=6.7 Hz); FAB-MS m/z 649 $(M+Na)^+$.

2) To a solution of the above compound (1.4 g, 2.3 mmol) in CH_2Cl_2 (25 ml) was added *m*-chloroperbenzoic acid (400 mg, 2.3 mmol), and the mixture was stirred overnight at room temperature. Evaporation of the mixture gave the residue, which was poured into H_2O, and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **24** (860 mg, 81%): IR (KBr) 1709, 1408, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.87 (9H, s), 1.43, 1.46 (9H, each s), 1.87 (1H, m), 2.03 (1H, m), 3.35~3.50 (2H, m), 3.97~4.13 (H, m), 4.34 (1H, m), 4.40~4.68 (1H, m), 5.50 (1H, br s); FAB-MS m/z 491 $(M+Na)^+$.

(2*S*,4*S*)-4-Acetylthio-*N*-allyloxycarbonyl-2-(*N*-allyloxycarbonyl-3-pyrrolin-4-yl)pyrrolidine (**11i**)

11i was prepared from **24** as described for the preparation of **11g**.

11i: IR (KBr) 1707, 1547, 1408 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.86 (1H, m), 2.34 (3H. s), 2.58 (1H, m), 3.26 (1H, dd, J=8.0 and 12.0 Hz), 3.98 (1H, m), 4.06~4.30 (5H, m), 4.63 (4H, m), 5.14~5.40 (4H, m), 5.62 (1H, m), 5.76~6.08 (2H, m); HRFAB-MS m/z Calcd for $C_{18}H_{25}N_2O_5S$ $(M+H)^+$ 381.1484; Found 381.1457.

Ethyl 3-[(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxypyrrolidin-2-yl]-4-cyanobutyrate (**29**)

To a suspension of 60% NaH (1.0 g, 25 mmol) in THF (50 ml) was added ethyl cyanoacetate (2.7 ml, 25 mmol) at 4°C. After being stirred for 30 minutes at the same temperature, tetra-*n*-butylammonium bromide (0.81 g, 2.5 mmol) and **7** (10 g, 25 mmol) in THF (15 ml) were added, and the mixture was further stirred overnight at 50°C. The reaction was quenched with 1.5 N hydrochloric acid, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of the residue in DMSO (65 ml) was added NaCl (1.5 g, 25 mmol) and H_2O (0.9 ml, 50 mmol), and the mixture was heated at 140°C for 1 hour. The mixture was cooled to room temperature, poured into H_2O, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **29** (7.4 g, 67%): IR (KBr) 2247, 1734, 1693, 1392 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.28 (3H, d, J=7.0 Hz), 1.46 (9H, s), 1.64~2.08 (2H, m), 2.30~2.70 (4H, m), 2.79 (1H, m), 3.20 (1H, m), 3.54 (1H, m), 4.11 (1H, m), 4.18 (2H, q, J=7.0 Hz), 4.34 (1H, br s); FAB-MS m/z 441 $(M+H)^+$.

(2*S*,4*R*)-*N*-*t*-Butoxycarbonyl-4-*t*-butyldimethylsilyloxy-2-[2-piperidon-4-yl]pyrrolidine (**30**)

To a solution of **29** (50.0 g, 0.11 mol) in EtOH (800 ml) was added Raney nickel (W-2, 50 ml), and the mixture was stirred for 22 hours under a hydrogen pressure (3.0 kg/cm^2) at room temperature. The catalyst was removed by filtration and washed with EtOH. The combined filtrate and washings were concentrated *in vacuo* to give the residue, which was purified by silica gel column chromatography affording **30** (34 g, 75%) as a colorless crystal: mp 124~126°C (heptane); IR (KBr) 1691, 1645, 1402, 1165 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.86 (9H, s), 1.45 (9H, s), 1.71~1.97 (4H, m), 2.21~2.47 (2H, m), 3.11~3.55 (5H, m), 3.99 (1H, m), 4.31 (1H, m), 5.91 (1H, m); HRFAB-MS m/z Calcd for $C_{20}H_{39}N_2O_4Si$ $(M+H)^+$ 399.2679; Found 399.2664.

(2*S*,4*S*)-4-Acetylthio-*N*-(*p*-nitrobenzyloxycarbonyl)-2-[*N*-(*p*-nitrobenzyloxycarbonyl)piperidin-4-yl]pyrrolidine (**11l**)

11l was prepared from **30** as described for the preparation of **11h-1**.

11l: $[\alpha]_D^{20}$ −47.8° (*c* 1.0, $CHCl_3$); IR (KBr) 1701, 1520, 1348, 1109 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.07~1.35 (2H, m), 1.45~1.84 (3H, m), 2.10~2.46 (5H, m), 2.76 (2H, m), 3.00 (1H, t, J=10.0 Hz), 3.80 (1H, m), 3.98 (1H, m), 4.26 (3H, m), 5.23 (4H, s), 7.52 (2H, d, J=8.0 Hz), 7.54 (2H, d, J=8.0 Hz), 8.23 (2H, d, J=8.0 Hz), 8.24 (2H, d, J=8.0 Hz). HRFAB-MS *m/z* Calcd for $C_{27}H_{31}N_4O_9S$ $(M+H)^+$ 587.1811; Found 587.1805.

The following compounds were prepared, and their spectral data were shown below.

11b-1: IR (KBr) 1705, 1695, 1520, 1345 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.74 (2H, m), 2.00~2.60 (4H, m), 2.34 (3H, s), 3.00~3.50 (3H, m), 3.84 (1H, m), 4.00~4.30 (2H, m), 5.22 (2H, s), 6.02 (1H, br), 7.52 (2H, d, J=8.0 Hz), 8.24 (2H, d, J=8.0 Hz).

11b-2: IR (KBr) 1750, 1700, 1520, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.68 (2H, m), 2.04~2.64 (4H, m), 2.35 (3H, s), 3.18 (2H, m), 3.42 (1H, m), 3.84 (1H, m), 4.04~4.34 (2H, m), 5.23 (2H, s), 5.97 (1H, br), 7.53 (2H, d, J=8.0 Hz), 8.25 (2H, d, J=8.0 Hz).

11d: ^1H NMR (200 MHz, $CDCl_3$) δ 1.75 (1H, m), 2.34 (3H, s), 2.40 (1H, m), 3.05~3.17 (1H, m), 3.30~3.59 (2H, m), 3.74~4.23 (6H, m), 4.56~4.68 (4H, m), 5.20~5.40 (4H, m), 5.77~6.03 (2H, m).

11e: ^1H NMR (200 MHz, $CDCl_3$) δ 1.62 (1H, m), 2.38 (1H, m), 2.88 (1H, m), 3.14 (1H, m), 4.12 (1H, m), 4.15~4.65 (2H, m), 4.90 (1H, m), 5.10~5.38 (2H, m), 5.86 (1H, m), 7.05 (2H, d, J=7.0 Hz), 7.12~7.58 (15H, m), 8.50 (2H, d, J=7.0 Hz).

11f: IR (KBr) 1700, 1520, 1345 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.10 (1H, m), 2.30 (1H, m), 2.32 (3H, s), 2.64 (1H, m), 2.94 (1H, m), 3.08 (1H, m), 3.58 (1H, m), 3.90 (4H, m), 4.60 (4H, m), 4.96 (1H, m), 5.28 (4H, m), 5.92 (2H, m).

11j: ^1H NMR (200 MHz, $CDCl_3$) δ 1.48~2.03 (3H, m), 2.26~3.04 (12 H, m), 3.13 (1H, t, J=10.0 Hz), 3.82 (1H, quint, J=8.0 Hz), 4.10 (1H, q, J=8.0 Hz), 4.26 (1H, dd, J=8.0 and 11.0 Hz), 5.24 (2H, s), 7.54 (2H, d, J=8.0 Hz), 8.24 (2H, d, J=8.0 Hz).

11k: IR (KBr) 1700, 1390 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (3H, d, J=9.0 Hz), 1.48 (9H, s), 1.80~2.30 (2H, m), 2.52 (2H, m), 2.60~3.10 (6H, m), 3.22 (2H, m), 3.80 (1H, m), 4.10 (2H, m).

11m: ^1H NMR (200 MHz, $CDCl_3$) δ 1.20~2.20 (8H, m), 2.34 (6H, s), 2.66 (1H, m), 2.88~3.08 (3H, m), 3.78 (1H, m), 3.98 (1H, m), 4.26 (1H, m), 5.23 (2H, br s), 5.92 (2H, m), 7.52 (2H, d, J=8.0 Hz), 8.24 (2H, d, J=8.0 Hz).

The final carbapenems (**4a~4q**) were prepared by the following procedures using the S-protected side chains (**11a~11o**) and the carbapenem diphenylphosphates (**39** and **40**).

Procedure 1

(1) To an ice-cooled solution of **11a-1** (90 mg, 0.23 mmol) in MeOH (5 ml) was added a 1 N aqueous NaOH solution (0.23 ml). After being stirred for 15 minutes at the same temperature, 1 N hydrochloric acid (0.23 ml) was added, and the mixture was concentrated *in vacuo*. The residue was poured into H_2O, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude thiol, which was used for the next reaction without further purification.

(2) To a mixture of the above crude thiol and **39** (150 mg, 0.26 mmol) in CH_3CN (10 ml) was added diisopropylethylamine (0.048 ml, 0.28 mmol) at 0°C, and the mixture was stirred overnight at that temperature. The mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to give *p*-nitrobenzyl (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-(2-azetidinon-4-yl)-*N*-(*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (**41a-1**) (128 mg, 80%): IR (KBr) 1760, 1700, 1520, 1340 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (3H, d, J=7.0 Hz), 1.34 (3H, d, J=6.0 Hz), 1.91 (2H, m), 2.44~3.10 (3H, m), 3.17~3.46 (2H, m), 3.66 (1H, m), 4.00~4.36 (5H, m), 5.24 (3H, m), 5.50 (1H, d, J=14.0 Hz), 7.52 (2H, d, J=8.0 Hz), 7.65 (2H, d, J=8.0 Hz), 8.21 (2H, d, J=8.0 Hz), 8.23 (2H, d, J=8.0 Hz).

(3) A mixture of **41a-1** (128 mg, 0.18 mmol) and 10% Pd-C (60 mg) in THF (14 ml), EtOH (4 ml) and 0.1 M MOPS buffer (pH 7.0, 14 ml) was stirred for 2 hours at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration, and washed with 50% THF-H_2O. The combined filtrate and washings were concentrated *in vacuo* to *ca.* 10 ml. After the insoluble in the aqueous layer was removed by filtration, the filtrate was subjected to reversed phase column chromatography, which was eluted with 10% MeOH-H_2O. The fractions detected by HPLC were combined, concentrated *in vacuo* and lyophilized to give sodium (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-(2-azetidinon-4-yl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (**4a-1**) (28.5 mg, 36%): IR (KBr) 3400, 1755, 1590 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.25 (3H, d,

J=8.0 Hz), 1.35 (3H, d, J=7.0 Hz), 1.84 (1H, m), 2.76 (1H, dd, J=8.0 and 15.0 Hz), 2.89 (1H, dd, J=2.0 and 15.0 Hz), 3.19~3.56 (4H, m), 3.87~4.40 (5H, m).

The following compounds were prepared according to the procedure 1.

4a-2 (23%): IR (KBr) 3400, 1750, 1590 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.25 (3H, d, J=8.0 Hz), 1.32 (3H, d, J=7.0 Hz), 1.65 (1H, m), 2.70 (1H, dd, J=8.0 and 15.0 Hz), 2.74 (1H, br d, J=15.0 Hz), 3.20~3.54 (4H, m), 3.62 (1H, d, J=6.0 and 12.0 Hz), 3.76 (1H, q, J=8.0 Hz), 3.85~4.14 (2H, m), 4.20~4.40 (2H, m).

4b-1 (38%): IR (KBr) 3400, 1760, 1580 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.23 (3H, d, J=8.0 Hz), 1.30 (3H, d, J=7.0 Hz), 1.67 (1H, m), 2.35 (1H, dd, J=8.0 and 17.0 Hz), 2.58 (2H, m), 2.94 (1H, m), 3.20~3.52 (4H, m), 3.55~3.80 (3H, m), 4.02 (1H, m), 4.20~4.34 (2H, m).

4b-2 (21%): IR (KBr) 3400, 1760, 1580 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.22 (3H, d, J=8.0 Hz), 1.30 (3H, d, J=7.0 Hz), 2.28 (1H, dd, J=8.0 and 17.0 Hz), 2.58~2.90 (2H, m), 2.95 (1H, m), 3.26~3.54 (4H, m), 3.58~3.84 (3H, m), 4.02 (1H, m), 4.20~4.36 (2H, m).

4c-1 (27%): IR (KBr) 3400, 1760, 1590 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.22 (3H, d, J=7.0 Hz), 1.29 (3H, d, J=6.0 Hz), 1.63 (1H, m), 1.77 (1H, m), 2.02 (1H, br d, J=13.0 Hz), 2.16 (1H, dd, J=10.5 and 17.0 Hz), 2.31 (1H, m), 2.53 (1H, dd, J=5.0 and 17.0 Hz), 2.79 (1H, m), 3.28~3.60 (7H, m), 3.68 (1H, dd, J=7.0 and 13.0 Hz), 4.03 (1H, m), 4.24 (2H, m); FAB-MS m/z 410 $(M+H)^+$.

4c-2 (25%): IR (KBr) 3400, 1760, 1590 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.23 (3H, d, J=7.0 Hz), 1.30 (3H, d, J=6.0 Hz), 1.63 (1H, m), 1.81 (1H, m), 1.98 (1H, br d, J=13.0 Hz), 2.20~2.40 (2H, m), 2.58 (1H, br d, J=13.0 Hz), 2.84 (1H, m), 3.30~3.50 (6H, m), 3.58 (1H, q, J=8.0 Hz), 3.70 (1H, dd, J=7.0 and 12.0 Hz), 4.04 (1H, m), 4.23 (2H, m); FAB-MS m/z 410 $(M+H)^+$.

4f (15%): IR (KBr) 3450, 1740, 1600, 1490 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.20 (3H, d, J=7.0 Hz), 1.29 (3H, d, J=6.0 Hz), 1.52 (1H, m), 1.98 (1H, m), 2.62 (2H, m), 2.90~3.50 (10H, m), 3.80 (1H, m), 4.20 (2H, m); HRFAB-MS m/z Calcd for $C_{18}H_{28}N_3O_5S_2$ $(M+H)^+$ 414.1522; Found 414.1532.

4h-2 (27%): IR (KBr) 1750, 1590, 1390 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.26 (3H, d, J=7.2 Hz), 1.33 (3H, d, J=6.2 Hz), 1.80~1.94 (2H, m), 2.38 (1H, m), 2.78~2.95 (2H, m), 3.16 (1H, br t, J=10.2 Hz), 3.32~3.83 (5H, m), 3.63~3.85 (3H, m), 4.09 (1H, m), 4.24~4.33 (2H, m); FAB-MS m/z 382 $(M+H)^+$;

Anal Calcd for $C_{18}H_{27}N_3O_4S \cdot HCl \cdot 2H_2O$:
C 47.62, H 7.11, N 9.26, S 7.06.
Found:
C 47.77, H 7.24, N 9.14, S 7.00.

4j (42%): IR (KBr) 1760, 1590, 1380 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.21 (3H, d, J=7 Hz), 1.30 (3H, d, J=6 Hz), 1.53 (1H, m), 1.92 (1H, m), 2.94 (3H, s), 3.91 (1H, m), 4.23 (2H, m); HRFAB-MS m/z Calcd for $C_{19}H_{30}N_3O_4S$ $(M+H)^+$ 396.1957; Found 396.1956.

4l (21%): IR (KBr) 3425, 1755, 1590 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.19 (3H, d, J=7.0 Hz), 1.26 (3H, d, J=6.0 Hz), 1.28~1.58 (3H, m), 1.70 (1H, m), 1.85~2.15 (2H, m), 2.46 (1H, m), 2.78~3.18 (5H, m), 3.40 (4H, m), 3.76 (1H, m), 4.22 (2H, m); FAB-MS m/z 396 $(M+H)^+$;

Anal Calcd for $C_{19}H_{29}N_3O_4S \cdot 5H_2O$:
C 46.99, H 8.10, N 8.65, S 6.60.
Found:
C 47.16, H 8.45, N 8.55, S 6.40.

4m (60%): $[\alpha]_D^{20}$ +1.6° (c 1.0, H_2O); IR (KBr) 1750, 1590, 1380 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.21 (3H, d, J=7.0 Hz), 1.29 (3H, d, J=6.0 Hz), 1.32~1.82 (6H, m), 1.84~2.16 (2H, m), 2.53 (1H, m), 2.74 (3H, s), 2.76~3.12 (3H, m), 3.14~3.50 (4H, m), 3.90 (1H, m), 4.13~4.32 (2H, m); FAB-MS m/z 410 $(M+H)^+$;

Anal Calcd for $C_{20}H_{31}N_3O_4S \cdot HCl \cdot 3H_2O$:
C 48.04, H 7.66, N 8.40, S 6.41.
Found:
C 48.35, H 8.02, N 8.65, S 6.28.

Procedure 2

To a solution of **41j** (2.14 g, 3.0 mmol) in acetone (15 ml) was added iodomethane (15 ml), and the mixture was stirred overnight at room temperature. The mixture was concentrated *in vacuo* to give **41p** (2.37 g, 92%), which was used for the next reaction without further purification.

4p was prepared in 48% yield from **41p** as described for the preparation of **4a** (procedure 1-(3)).

4p: IR (KBr) 1750, 1590, 1380 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.20 (3H, d, J=8.0 Hz), 1.29 (3H, d, J=7.0 Hz), 2.12 (1H, m), 2.44 (2H, m), 3.17 (3H, s), 3.24 (3H, s), 3.77 (2H, m), 4.22 (2H, m); FAB MS m/z 410 $(M+H)^+$.

Anal Calcd for $C_{20}H_{31}N_3O_4S \cdot HCl \cdot 2.5H_2O$:
C 48.92, H 7.60, N 8.56, S 6.53.
Found:
C 48.88, H 7.79, N 8.54, S 6.92.

4q was prepared in 69% yield from **41m** according to the procedure 2.

4q: IR (KBr) 1750, 1590, 1380 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.21 (3H, d, J=7.0 Hz), 1.29 (3H, d, J=6.0 Hz), 1.20~1.50 (2H, m), 1.63~2.15 (6H, m), 2.54 (1H, m), 3.08 (3H, s), 3.15 (3H, s), 2.84~3.60 (7H, m),

3.78 (1H, m), 4.20 (2H, m); FAB MS *m/z* 424 $(M+H)^+$.

Procedure 3

1) **11k** (17 g, 41 mmol) was dissolved in a 1.2 M solution of hydrogen chloride in MeOH (100 ml) and the mixture was stirred for 4 hours at 60°C. Evaporation of the mixture *in vacuo* gave the residue, which was crystallized from EtOH (30 ml) affording (2*S*,4*S*)-2-(*N*-ethylpyrrolidin-3-yl)-4-mercaptopyrrolidine·dihydrochloride (9.9 g %): IR (KBr) 3400, 2930, 2690, 1450 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.23 (3H, d, J=9.0 Hz), 1.60 (1H, m), 1.80~2.40 (2H, m), 2.52 (1H, m), 2.95 (1H, m), 3.15 (4H, m), 3.20~3.70 (7H, m).

2) To a solution of **39** (13.8 g, 23.1 mmol) in CH_3CN (150 ml) was added *N*,*N*-diisopropylethylamine (13.4 ml, 77 mmol) and the above thiol (7.0 g, 26 mmol) in DMF (40 ml) at −20°C. After being stirred overnight at that temperature, the reaction mixture was concentrated *in vacuo*. The resulting precipitates were collected by filtration and washed with CH_3CN and diisopropyl ether to give **41k** (10.1 g, 72%) as a crystalline solid. mp 216°C (decomp.); IR (KBr) 3350, 1770, 1700, 1605 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.18 (3H, d, J=8.0 Hz), 1.19 (3H, d, J=8.0 Hz), 1.24 (3H, t, J=9.0 Hz), 1.60 (2H, m), 1.80~2.30 (2H, m), 5.28, 5.50 (2H, ABq, J=16.0 Hz), 7.75 (2H, d, J=8.0 Hz), 8.27 (2H, d, J=8.0 Hz).

3) A mixture of **41k** (10 g, 18 mmol) and 10% Pd-C (10 g) in THF (500 ml), 0.5 M MOPS buffer (pH 7.0, 500 ml) and EtOH (150 ml) was stirred for 2 hours under a hydrogen atmosphere at room temperature. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to *ca.* 100 ml. After the insoluble was filtered off, the filtrate was subjected to HP-20SS (250 ml), which was eluted with 30% MeOH-H_2O. The fractions containing the desired compound were combined, and the solution was concentrated *in vacuo* to give (1*R*,5*S*,6*S*)-2-{(3*S*,5*S*)-5-[(3*R*)-*N*-ethylpyrrolidin-3-yl]pyrrolidin-3-ylthio}-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carba-pen-2-em-3-carboxylic acid (**4k**, 3.4 g, 45%) as a crystalline solid: IR (KBr) 3220, 1745, 1675, 1580 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.18 (3H, d, J=8.0 Hz), 1.19 (3H, d, J=8.0 Hz), 1.24 (3H, t, J=9.0 Hz), 2.20~3.00 (6H, m), 3.05~3.20 (2H, m), 3.40~4.20 (10H, m).

The following compounds were prepared according to the procedure 3.

4n (44%): IR (KBr) 1750, 1590, 1390 cm^{-1}; ^1H NMR (200 MHz, D_2O+DCl) δ 1.23 (3H, d, J=7 Hz), 1.29 (3H, d, J=7 Hz), 1.31 (3H, t, J=7.5 Hz), 1.50~1.85 (3H, m), 2.00~2.20 (3H, m), 2.80 (1H, m), 3.00 (2H, m), 3.20 (2H, m), 3.30~3.60 (4H, m), 3.67 (3H, m), 4.05 (1H, m), 4.25 (2H, m).

4o (31%): IR (KBr) 3300, 1755, 1595 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.23 (3H, d, J=7.0 Hz), 1.30 (3H, d, J=6.0 Hz), 1.60~1.85 (3H, m), 2.00~2.20 (3H, m), 2.79 (1H, dt, J=7.0 and 14.0 Hz), 3.11 (2H, m), 3.27~3.60 (H, m), 3.62~3.75 (3H, m), 3.93 (2H, t, J=5.0 Hz), 4.05 (1H, m), 4.25 (2H, m); HRFAB-MS *m/z* Calcd for $C_{21}H_{34}N_3O_5S$ $(M+H)^+$ 440.2219; Found 440.2231.

Procedure 4

1) To an ice-cooled solution of **11i** (350 mg, 0.92 mmol) in MeOH (10 ml) was added 1 N NaOH aqueous solution (0.92 ml), and the mixture was stirred for 15 minutes at that temperature. After the addition of 1 N HCl (0.92 ml), the mixture was concentrated *in vacuo* to give the residue, which was poured into H_2O, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude thiol, which was used in the next reaction without further purification.

2) To a stirred mixture of **40** (500 mg, 1.0 mmol) and the above thiol (310 mg, 0.92 mmol) in CH_3CN (25 ml) was added *N*,*N*-diisopropylethylamine (0.16 ml, 0.92 mmol) dropwise at −10°C. After being stirred overnight at 4°C, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **41i** (205 mg, 38%): IR (KBr) 1780, 1710, 1410, 1330 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, d, J=7.0 Hz), 1.36 (3H, d, J=6.0 Hz), 1.88 (1H, m), 2.62 (1H, m), 3.18~3.48 (3H, m), 3.64 (1H, m), 5.12~5.53 (6H, m), 5.64 (1H, m), 5.78~6.10 (3H, m).

3) To an ice-cooled solution of **41i** (205 mg, 0.35 mmol) in CH_2Cl_2 (7.5 ml) was successively added H_2O (31 μl), bis(triphenylphosphine)palladium(II)chloride (12.3 mg, 0.017 mmol) and tri-*n*-butyltin hydride (0.375 ml, 1.39 mmol). After being stirred for 20 minutes at the same temperature, the temperature was raised to room temperature and the mixture was further stirred for 20 minutes. The mixture was extracted with H_2O, and the aqueous layer was washed with $CHCl_3$ (×2) and concentrated *in vacuo* to *ca.* 10 ml. After the insoluble was removed by filtration, the aqueous layer was subjected to reversed phase column chromatography, which was eluted with 20% MeOH-H_2O. The fractions detected by HPLC were combined, and the solution was concentrated *in vacuo*, and lyophilized to give (1*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-1-methyl-2-[(3*S*,5*S*)-5-(3-pyrrolin-3-yl)pyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylic acid (**4i**, 54 mg, 45%): IR (KBr) 1760, 1590, 1390 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.21 (3H, d, J=7.0 Hz),

1.29 (3H, d, J=6.0 Hz), 1.54 (1H, m), 2.60 (1H, m), 2.99 (1H, dd, J=3.0 and 12.0 Hz), 3.18~3.43 (3H, m), 3.82 (2H, m), 4.13 (4H, s), 4.23 (2H, m), 5.83 (1H, br s).

The following compounds were prepared according to the procedure 4.

4d-1 (20%): IR (KBr) 3430, 1760, 1600, 1390 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.20 (3H, d, J=7.0 Hz), 1.28 (3H, d, J=6.0 Hz), 1.77 (1H, m), 2.72~2.85 (2H, m), 3.10 (1H, m), 3.30~3.48 (4H, m), 3.65~3.85 (3H, m), 4.01 (2H, m), 4.24 (2H, m); FAB-MS m/z 384 $(M+H)^+$.

4d-2 (20%): IR (KBr) 3430, 1760, 1590, 1380 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.21 (3H, d, J=7.0 Hz), 1.28 (3H, d, J=6.0 Hz), 1.74 (1H, m), 2.77 (1H, m), 2.85 (1H, m), 3.11 (1H, m), 3.30~3.48 (4H, m), 3.63~3.78 (3H, m), 4.03 (2H, m), 4.24 (2H, m); FAB-MS m/z 384 $(M+H)^+$.

4e (23%): IR (KBr) 3400, 1750, 1600, 1390 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.25 (3H, d, J=7.0 Hz), 1.31 (3H, d, J=6.0 Hz), 2.10 (1H, m), 3.12 (1H, dt, J=8.0 and 13.0 Hz), 3.30~3.62 (3H, m), 3.90 (1H, dd, J=8.0 and 12.0 Hz), 4.10~4.35 (3H, m), 4.90 (1H, m), 7.58 (2H, d, J=7.0 Hz), 8.65 (2H, d, J=7.0 Hz); HRFAB-MS m/z Calcd for $C_{19}H_{24}N_3O_5S$ $(M+H)^+$ 390.1487; Found 390.1497.

4g (15%): IR (KBr) 3400, 1750, 1600, 1390 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.21 (3H, d, J=7.0 Hz), 1.29 (3H, d, J=6.0 Hz), 1.48 (1H, m), 2.68 (1H, m), 3.14 (1H, dd, J=4.0 and 12.0 Hz), 3.25~3.50 (4H, m), 3.75~4.10 (6H, m), 4.20 (2H, m); FAB-MS m/z 368 $(M+H)^+$.

Preparation of **4h-1** (BO-2502A)

1) *p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-1-methyl-2-{(3*S*,5*S*)-*N*-(*p*-nitrobenzyloxycarbonyl)-5-[(3*S*)-*N*-(*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-yl]-pyrrolidin-3-ylthio}-1-carbapen-2-em-3-carboxylate (**41h-1**) was prepared according to the procedure 1-(1) (79%): IR (KBr) 1780, 1700, 1520, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (3H, d, J=7.0 Hz), 1.37 (3H, d, J=6.0 Hz), 1.60~2.15 (4H, m), 2.55 (1H, m), 2.78 (1H, m), 4.04~4.35 (3H, m), 5.24 (5H, m), 5.53 (1H, d, J=14.0 Hz), 7.54 (4H, br d, J=8.0 Hz), 7.67 (2H, d, J=8.0 Hz), 8.24 (6H, br d, J=8.0 Hz).

2) A mixture of **41h-1** (36.5 g, 41.7 mmol) and 10% Pd-C (15.0 g) in THF (1.5 liters) and 0.1 M sodium acetate buffer (pH 5.8, 1.5 liters) was stirred for 5 hours under a hydrogen pressure (3 kg/cm^2) at 27°C. The catalyst was filtered off and washed with 50% THF-H_2O. The combined filtrate and washings were concentrated *in vacuo* to *ca.* 2 liters. The aqueous layer was adjusted to pH 9.0 with 6 N NaOH and subjected to HP-20, which was eluted with 20% MeOH-H_2O. The fractions containing the desired compound were combined, and the pH of the solution was adjusted to 6.0 with 2 N HCl. The resulting solution was concentrated *in vacuo*, and lyophilized to give a colorless powder, which was recrystallized from 90% H_2O-MeOH affording (1*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-1-methyl-2-{(3*S*,5*S*)-5-[(3*S*)-pyrrolidin-3-yl]pyrrolidin-3-ylthio}-1-carbapen-2-em-3-carboxylic acid·hydrochloride (**4h-1**) (6.0 g, 36%) as a colorless crystalline solid: $[\alpha]_D^{20}$ +1.4° (c 1.0, H_2O); IR (KBr) 1701, 1520, 1348, 1109 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.24 (3H, d, J=7.2 Hz), 1.32 (3H, d, J=6.1 Hz), 1.71~1.96 (2H, m), 2.31~2.49 (1H, m), 2.72~2.91 (2H, m), 3.10 (1H, br t, J=9.6 Hz), 3.32~3.83 (8H, m), 4.08 (1H, m), 4.21~4.35 (2H, m); FAB-MS m/z 382 $(M+H)^+$;

Anal Calcd for $C_{18}H_{27}N_3O_4S \cdot HCl \cdot 0.75H_2O$:
C 50.11, H 6.89, N 9.74.
Found:
C 50.36, H 6.72, N 9.75.

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