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SM-216601, a Novel Parenteral 1β-Methylcarbapenem: Structure-activity Relationships of Antibacterial Activity and Neurotoxicity in Mice

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Abstract It has been reported that 2-(4-substituted thiazol-2-ylthio)-1β-methyl-carbapenems exhibit potent activity against methicillin-resistant staphylococci (MRS) and vancomycin-resistant enterococci (VRE). In order to develop a novel broad-spectrum carbapenem, the structure-activity relationships of a series of 2-(4-tetrahydropyridinylthiazol-2-ylthio)-1β-methylcarbapenems and 4-dihydropyrrolyl thiazole analogs were investigated with regard to their activity against Gram-positive and especially Gram-negative bacteria and also their convulsant activity, which is a major side effect concern of carbapenems. The introduction of substituent(s) on the dihydropyrrole moiety did not cause remarkable changes in anti-MRS and VRE activities, but tended to lower the anti-Gram-negative bacterial activity except in some cases of methyl group introduction. These substitutions did however cause a reduction of the convulsant activity, which was affected by the size and also the configuration of the substituent. In the case of SM-216601 (**6**), introduction of a methyl group brought about significant reduction in neurotoxicity while maintaining favorable anti-Gram-negative bacterial activity.

Keywords 1β-methylcarbapenem, structure-activity relationship, antibacterial activity, neurotoxicity

Introduction

The emergence of multidrug-resistant Gram-positive cocci such as methicillin-resistant staphylococci (MRS), vancomycin-resistant enterococci (VRE), and penicillin-intermediate/penicillin-resistant *Streptococcus pneumoniae* have reduced the value of antibacterial chemotherapy and is a great concern especially in nosocomial settings [1～3]. Therefore, there is an urgent need for new antibacterial agents effective against these resistant pathogens. For this purpose, improvements of the existing class of antibacterial agents has been extensively pursued and β-lactam antibiotics are good candidates owing to their potent bactericidal activity and excellent safety profiles [4]. In the field of carbapenem antibiotics, a large number of derivatives have been synthesized and investigated from the 1990s [5].

Previously, we have reported that a series of 1β-methylcarbapenems possessing a thiazol-2-ylthio group as the C-2 side chain exhibited the potent activity against MRS [6, 7]. A representative compound SM-17466 (Fig. 1) achieved potent *in vitro* and *in vivo* activities against methicillin-resistant *Staphylococcus aureus* (MRSA), which was comparable to those of vancomycin. In addition, this carbapenem exhibited the more than 8-fold improved activity against *Enterococcus faecium* in comparison with existing carbapenems (MIC_{90} values of SM-17466, imipenem, and meropenem against 11 strains of clinically isolated *E. faecium* were 12.5, >100, and >100 μg/ml, respectively) [8]. Although the activity was still insufficient for clinical application, it suggested the possibility of finding novel carbapenems with potent activity against both MRSA and VRE. Based on a structure-activity relationship (SAR) study focusing on these multidrug-resistant Gram-

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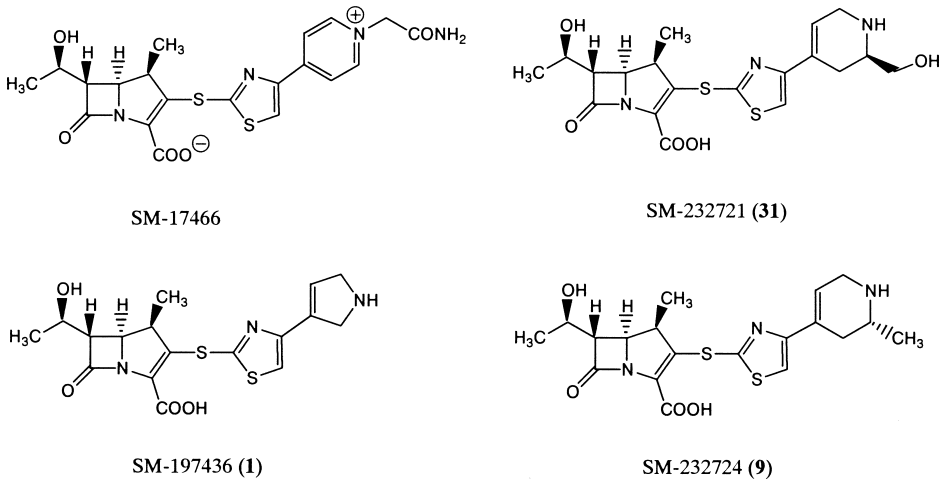


Fig. 1 Carbapenem antibiotics having 2-(thiazol-2-ylthio) group at *C*-2 position.

positive bacteria, a 2-(4-dihydropyrrolylthiazol-2-ylthio)-1β-methyl carbapenem SM-197436 (**1**) and two 2-(4-tetrahydopyridinylthiazol-2-ylthio)-1β-methylcarbapenems, SM-232721 (**31**) and SM-232724 (**9**) were identified as candidates as anti-MRSA and anti-VRE carbapenems (Fig. 1) [9]. Moreover, detailed microbiological studies revealed that these three carbapenems exhibited substantial activity against Gram-negative pathogens and the activity of SM-197436 was significantly superior to those of the other two carbapenems [10], although the convulsant activity of SM-197436 was also the highest [9].

The preferable antibacterial profile of new β-lactams targeting multidrug-resistant Gram-positive bacteria has been debated. Two approaches, one aiming at broad-spectrum activity covering Gram-negative pathogens and the other having relatively narrow-spectrum of activity similar to, for example, that of glycopeptides, have been reported mainly concerning cephalosporin derivatives [11～14]. Although we have aimed to select candidates based on their activity against resistant Gram-positive bacteria, the clinical importance of the existing carbapenems prompted us to consider the development of a broad-spectrum antibacterial agent from SM-197436 type derivatives. Thus, the 2-(thiazol-2-ylthio)-1β-methylcarbapenems having a tetrahydropyridinyl or dihydropyrrolyl moiety have been reevaluated from a viewpoint of their activity against Gram-negative bacteria and their convulsant activity. Since SM-197436 has already achieved the acceptable activity against most Gram-negative bacteria, the reduction of the convulsant effect as well as increasing the antibacterial activity was considered to be an important issue for further investigation.

In this paper, we describe the SAR of a series of 2-(4-tetrahydropyridinylthiazol-2-ylthio)-1β-methylcarbapenems and 4-dihydropyrrolylthiazole analogs, which consisted of previously disclosed compounds [9] and newly synthesized ones, with regard to their antibacterial activities, especially against Gram-negative bacteria, and their convulsant activity in mice. The results of this SAR led us to select SM-216601 (**6**) for further evaluation.

Chemistry

A series of carbapenems were prepared by a conventional coupling reaction of the phosphate intermediate **A** and 2-mercaptothiazoles **B**. Subsequent deprotection and purification by column chromatography gave the desired products as solids after lyophilization. A representative example is shown in Fig. 2.

Most of the 2-mercaptothiazoles **B** were synthesized from diesters **G**～**I** which were prepared from the appropriate α-amino acid derivatives by known methods [9] (Fig. 3).

The heterocyclic esters **D**, the precursors of **B**, were synthesized using the Dieckmann condensation as the key reaction as shown in Fig. 4. The chlorination of the carbinol $\mathbf{D_{21,22,38}}$ was achieved by the triphenylphosphine-carbon tetrachloride method. Finally, the thiazole ring was constructed by a classical method as shown for $\mathbf{B_{10}}$ (Fig. 5).

The synthesis of *N*-methylated 2-mercaptothiazoles $\mathbf{B_{12,31,32}}$ was achieved by reduction of the corresponding allyl carbamates using lithium aluminium hydride and $\mathbf{B_{24}}$ was prepared from $\mathbf{B_{22}}$ using *p*-methoxybenzyl (PMB) as a thiol-protecting group (Fig. 6).

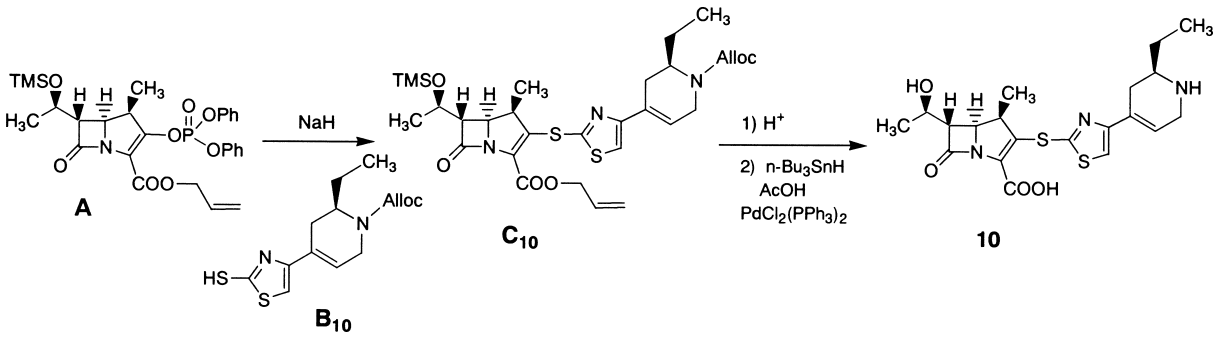


Fig. 2 Synthesis of 2-(4-substituted thiazol-2-ylthio)-1β-methylcarbapenems.

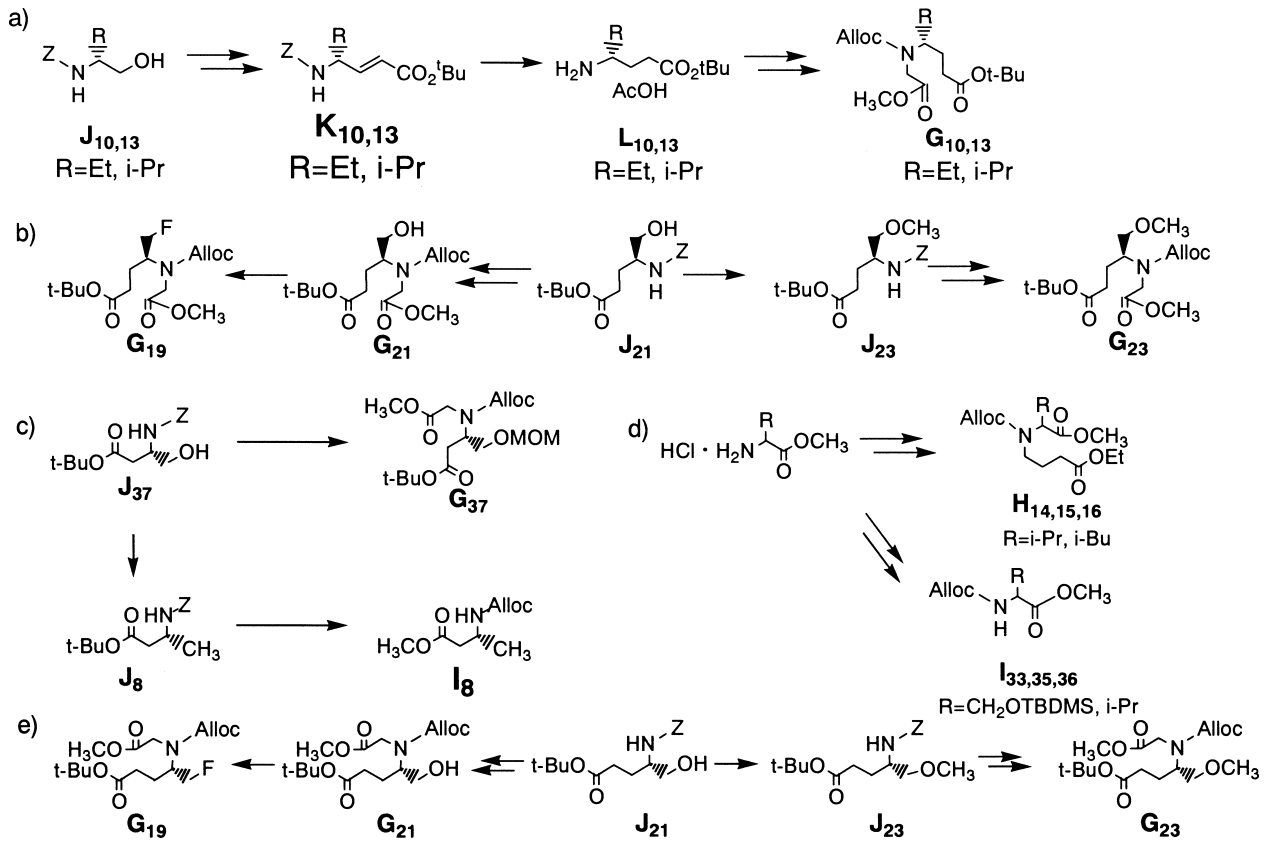


Fig. 3 Synthesis of diesters G~I.

Biological Results and Discussion

MIC, convulsant activity as a relative value of ED_{50} to that of imipenem (IPM), calculated p*K*a (cp*K*a) of the amino group in the C-2 side chain, and calculated log P (clog P) of 2-(thiazol-2-ylthio)-1β-methylcarbapenem derivatives **1**~**38** are listed in Tables 1~5. For comparison, those of IPM and panipenem (PAPM) are also listed in Table 1.

Antibacterial Activity

It has been confirmed, as reported previously, that the activities against multidrug-resistant Gram-positive bacteria in this series of derivatives *i.e.* **1**~**38** were not changed significantly by the introduction of an alkyl group on the carbon α to the nitrogen atom in the tetrahydropyridine (*e.g.* **2** *vs.* **9**) or dihydropyrrole ring (**1** *vs.* **4** *etc.*) [9]. Most of the derivatives **4**~**25** showed MIC_{90} values ranging from 2 to 4 μg/ml against both clinical isolates of MRSA and

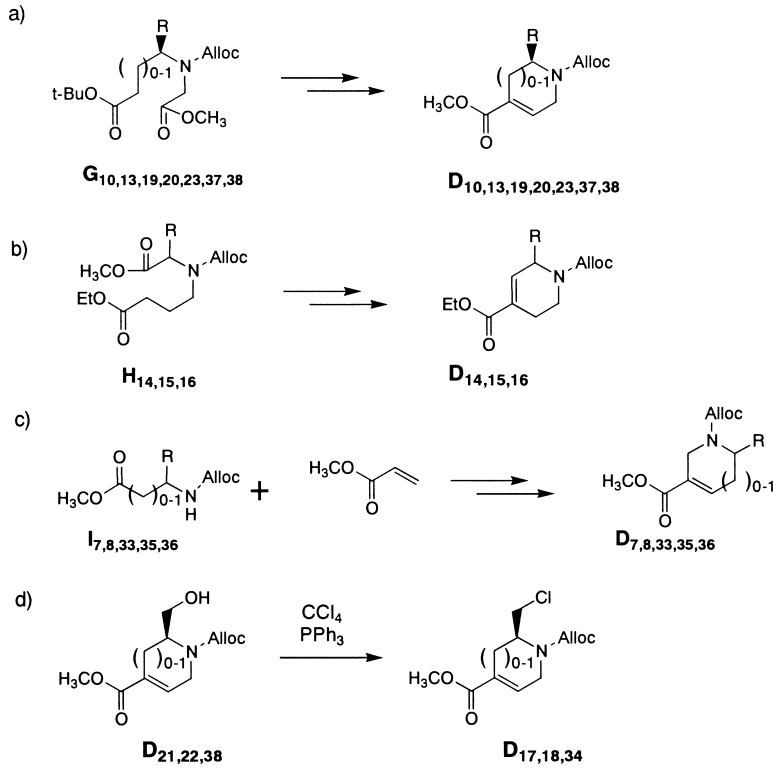


Fig. 4 Synthesis of heterocyclic esters D.

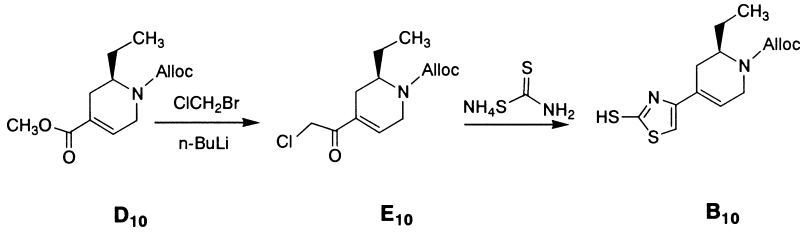


Fig. 5 Preparation of 2-mercaptothiazoles B.

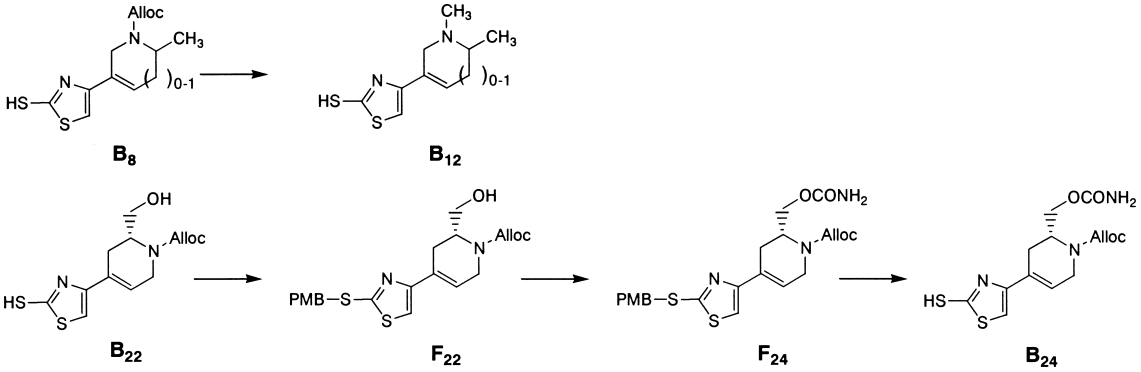
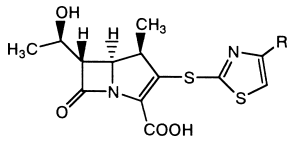
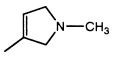


Fig. 6 Modifications of 2-mercaptothiazoles B.

Table 1 *In vitro* antibacterial activity and convulsant activity of 2-(4-substituted-thiazol-2-ylthio)carbapenems [Part I]

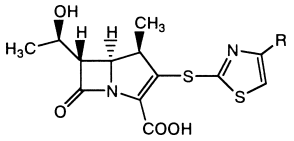


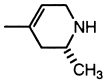
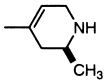
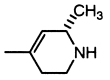
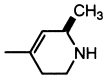
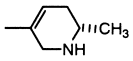
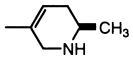
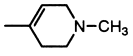
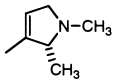
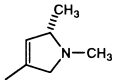
Compound No.	R-	cp*Ka*	clog P	MIC$_{90}$ (μg/ml)[a]		MIC (μg/ml)[b]								Convulsant activity[c]
				S.a.	*E.fm.*	*E.c.*	*K.p.*	*P.m.*	*P.v.*	*S.m.*	*E.cl.*	*C.f.*	*P.a.*	
	$C_{17}H_{19}N_3O_4S_2$													
1	 SM-197436	8.48	−0.149	2	4	0.125	0.031	0.125	0.5	2	8	8	2	0.63*
	$C_{18}H_{21}N_3O_4S_2$													
2		9.10	0.181	2	2	0.25	0.031	0.125	1	4	8	8	4	1.68*
3		8.90	0.341	4	4	0.5	0.063	0.25	1	4	8	8	4	1.22
4		8.54	0.343	2	4	0.25	0.063	0.25	2	4	8	8	4	1.68
5		8.54	0.343	4	2	0.125	0.031	0.125	0.5	2	8	4	4	3.81
6	 SM-216601	8.54	0.343	2	4	0.125	≤0.016	0.125	0.5	2	8	8	4	3.88
7		8.54	0.343	4	8	0.125	0.031	0.25	0.5	4	8	8	4	3.15
8		7.23	−0.403	2	4	1	0.125	1	2	16	32	16	32	0.64
	Imipenem	10.37	−2.784	32	>32	0.5	0.125	0.25	1	0.25	0.125	0.5	1	1.00
	Panipenem	12.57	−3.692	32	>32	0.25	0.063	0.5	0.5	0.25	0.125	0.25	4	2.09

[a] MIC$_{90}$ was determined by the agar dilution method agasint 17 clinical isolates of methicillin-resistant *Staphylococcus aureus* (*S.a.*) and 20 isolates of vancomycin-resistant *Enterococcus faecium* (*E.fm.*). [b] MIC was determined by the agar dilution method using the following bacterial strains; *E.c.*, *Escherichia coli* ML1410; *K.p.*, *Klebsiella pneumoniae* ATCC10031; *P.m.*, *Proteus mirabilis* GN2425; *P.v.*, *Proteus vulgaris* GN7919; *S.m.*, *Serratia marcescens* GN6473; *E.cl.*, *Enterobacter cloacae* GN7471; *C.f.*, *Citrobacter freundii* GN346; *P.a.*, *Pseudomonau aeruginosa* IFO3451. [c] ED$_{50}$ ratio relative to imipenem. * the ED$_{50}$ value has been reported [9].

vancomycin-resistant *E. faecium* (VREFm) except for **7**, **15**, and **17**, the MIC$_{90}$ of which against VREFm were 8 μg/ml. The effect of *N*-methylation on the activity especially against MRSA was also not significant (**1** *vs.* **8**). In the cases of introduction of a substituted methyl group, the activity decreased from fluoro (**28**), to chloro (**34**), and to hydroxy group (**35**, **36**) substitutions. Consequently, effective substituents to significantly improve the activity

Table 2 *In vitro* antibacterial activity and convulsant activity of 2-(4-substituted-thiazol-2-ylthio)carbapenems [Part II]



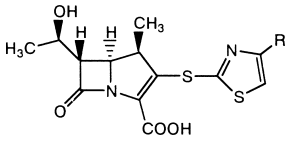
Compound No.	R-	cp*K*a	clog P	MIC$_{90}$ (μg/ml)[a]		MIC (μg/ml)[b]								Convulsant activity[c]
				S.a.	*E.fm.*	*E.c.*	*K.p.*	*P.m.*	*P.v.*	*S.m.*	*E.cl.*	*C.f.*	*P.a.*	
	$C_{19}H_{23}N_3O_4S_2$													
9	 SM-232724	9.16	0.673	2	4	0.25	0.031	0.25	2	8	16	16	4	3.34*
10		9.16	0.673	2	2	0.5	0.063	0.5	4	8	16	16	8	1.14
11		9.16	0.673	2	4	0.25	0.031	0.25	2	8	16	16	8	1.89*
12		9.16	0.673	2	4	0.25	0.031	0.25	2	8	16	16	8	1.97*
13		8.96	0.833	4	4	1	0.063	0.5	2	8	16	16	16	3.34
14		8.96	0.833	2	4	1	0.031	0.5	2	16	16	16	16	—[d]
15		7.99	−0.661	4	8	1	0.063	1	4	16	16	16	16	1.75
16		7.30	0.089	2	4	1	0.063	1	4	16	16	16	16	1.00
17		7.30	0.089	2	8	1	0.063	1	2	16	16	16	32	1.25

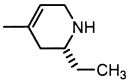
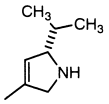
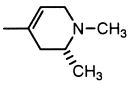
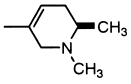
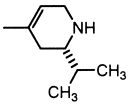
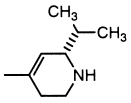
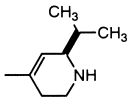
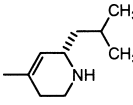
[a] MIC$_{90}$ was determined by the agar dilution method agasint 17 clinical isolates of methicillin-resistant *Staphylococcus aureus* (*S.a.*) and 20 isolates of vancomycin-resistant *Enterococcus faecium* (*E.fm.*). [b] MIC was determined by the agar dilution method using the following bacterial strains; *E.c.*, *Escherichia coli* ML1410; *K.p.*, *Klebsiella pneumoniae* ATCC10031; *P.m.*, *Proteus mirabilis* GN2425; *P.v.*, *Proteus vulgaris* GN7919; *S.m.*, *Serratia marcescens* GN6473; *E.cl.*, *Enterobacter cloacae* GN7471; *C.f.*, *Citrobacter freundii* GN346; *P.a.*, *Pseudomonau aeruginosa* IFO3451. [c] ED$_{50}$ ratio relative to imipenem. [d] Not tested. * the ED$_{50}$ value has been reported [9].

against MRSA and VREFm compared with the unsubstituted tetrahydropyridine derivative **2**, **3** or dihydropyrrole derivative **1** could not be found.

Regarding Gram-negative bacteria, the MICs of **1** (SM-197436) against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *P. vulgaris* were comparable or better than those of IPM. Meanwhile, the MICs against *Serratia marcescens*, *Enterobacter cloacae*, and *Citrobacter freundii* were higher than those of IPM and PAPM. The MIC against *Pseudomonas aeruginosa* was 2 μg/ml, which was higher than that of IPM, but lower than that of PAPM. These high activities of **1** were surprising because of its much higher lipophilicity (clog P value) than that of IPM or PAPM. It has been well known that anti-Gram-negative bacterial activity of carbapenems is affected by physicochemical properties such as lipophilicity, p*K*a, and so on, which reflected the outer-membrane permeability, as well as the chemical structure itself. It was considered that

Table 3 *In vitro* antibacterial activity and convulsant activity of 2-(4-substituted-thiazol-2-ylthio)carbapenems [Part III]



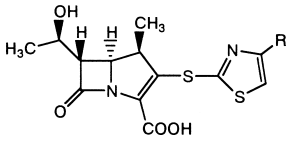
Compound No.	R-	cp*K*a	clog P	MIC_{90} (μg/ml)[a]		MIC (μg/ml)[b]								Convulsant activity[c]
				S.a.	*E.fm.*	*E.c.*	*K.p.*	*P.m.*	*P.v.*	*S.m.*	*E.cl.*	*C.f.*	*P.a.*	
$C_{20}H_{25}N_3O_4S_2$														
18		9.16	1.204	2	4	1	0.031	1	4	16	16	16	8	1.34*
19		8.41	1.222	4	4	1	0.031	1	4	8	32	16	32	4.63
20		8.00	−0.147	2	2	—[d]	—	—	—	—	—	—	—	0.91*
21		7.86	0.742	4	4	2	0.063	2	4	16	16	16	16	2.97
$C_{21}H_{27}N_3O_4S_2$														
22		9.03	1.552	4	4	2	0.063	4	16	32	16	16	32	3.17
23		9.03	1.552	2	2	—	—	—	—	—	—	—	—	1.06*
24		9.03	1.552	4	2	2	0.063	4	8	16	16	16	16	—[c]
$C_{22}H_{29}N_3O_4S_2$														
25		9.16	2.083	4	4	4	0.063	8	16	32	32	16	32	1.00

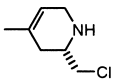
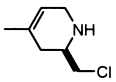
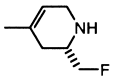
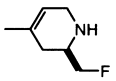
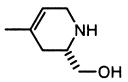
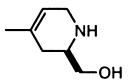
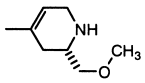
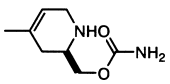
[a] MIC_{90} was determined by the agar dilution method agasint 17 clinical isolates of methicillin-resistant *Staphylococcus aureus* (*S.a.*) and 20 isolates of vancomycin-resistant *Enterococcus faecium* (*E.fm.*). [b] MIC was determined by the agar dilution method using the following bacterial strains; *E.c.*, *Escherichia coli* ML1410; *K.p.*, *Klebsiella pneumoniae* ATCC10031; *P.m.*, *Proteus mirabilis* GN2425; *P.v.*, *Proteus vulgaris* GN7919; *S.m.*, *Serratia marcescens* GN6473; *E.cl.*, *Enterobacter cloacae* GN7471; *C.f.*, *Citrobacter freundii* GN346; *P.a.*, *Pseudomonau aeruginosa* IFO3451. [c] ED_{50} ratio relative to imipenem. [d] Not tested. * the ED_{50} value has been reported [9].

the anti-Gram-negative bacterial activity of our thiazole carbapenems could be affected especially by their lipophilicities, because the log P value of the lead compound (**1**) was high enough to effect membrane permeability.

As hypothesized, the correlation between lipophilicity and antibacterial activity was apparent by the comparison of **1**, the non-substituted derivatives **2** and **3**, and the *C*-alkylated derivatives **4**∼**7**, **9**∼**14**, **18**, **19**, **22**∼**25**. Their cp*K*a values ranged from 8.48 to 9.16 and, in such a cp*K*a

Table 4 *In vitro* antibacterial activity and convulsant activity of 2-(4-substituted-thiazol-2-ylthio)carbapenems [Part IV]

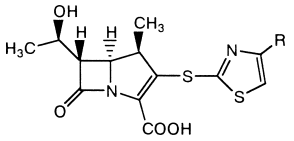


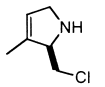
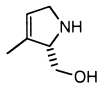
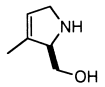
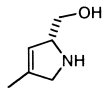
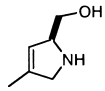
Compound No.	R-	cp*K*a	clog P	MIC$_{90}$ (μg/ml)[a]		MIC (μg/ml)[b]								Convulsant activity[c]
				S.a.	*E.fm.*	*E.c.*	*K.p.*	*P.m.*	*P.v.*	*S.m.*	*E.cl.*	*C.f.*	*P.a.*	
26		8.03	0.644	2	4	2	≤0.016	2	8	16	16	16	16	5.68
27		8.03	0.644	2	4	2	0.031	4	8	32	16	16	16	0.62
28		7.94	0.257	4	8	—[d]	—	—	—	—	—	—	—	11.95
29		7.94	0.257	4	4	2	≤0.016	2	8	32	32	32	32	6.56
30		8.41	−0.683	2	4	0.25	0.031	0.25	2	4	16	16	8	8.87*
31 SM-232721		8.41	−0.683	2	4	0.25	0.031	0.25	2	4	16	16	8	3.05*
32		8.41	−0.061	4	4	1	0.063	2	8	16	16	32	32	6.57
33		7.99	−0.661	4	4	2	0.063	4	8	16	16	32	16	3.17

[a] MIC$_{90}$ was determined by the agar dilution method agasint 17 clinical isolates of methicillin-resistant *Staphylococcus aureus* (*S.a.*) and 20 isolates of vancomycin-resistant *Enterococcus faecium* (*E.fm.*). [b] MIC was determined by the agar dilution method using the following bacterial strains; *E.c.*, *Escherichia coli* ML1410; *K.p.*, *Klebsiella pneumoniae* ATCC10031; *P.m.*, *Proteus mirabilis* GN2425; *P.v.*, *Proteus vulgaris* GN7919; *S.m.*, *Serratia marcescens* GN6473; *E.cl.*, *Enterobacter cloacae* GN7471; *C.f.*, *Citrobacter freundii* GN346; *P.a.*, *Pseudomonau aeruginosa* IFO3451. [c] ED$_{50}$ ratio relative to imipenem. [d] Not tested. * the ED$_{50}$ value has been reported [9].

range, a significant correlation between the activity and the cp*K*a values could not be observed. On the other hand, the antibacterial activities appeared to depend on the molecular formula (*i.e.* the number of carbon atoms and hydrogen atoms), which reflected the lipophilicity of the molecule. The derivatives **2**∼**7**, the molecular formulae of which were identical and their molecular weights were higher than **1** by the addition of a single CH_2 unit, revealed similar antibacterial activities with each other and their activities were close to those of **1**. The addition of two CH_2 units showed a tendency to decrease the activities against some of the bacteria and in the cases of derivatives with more than three CH_2 units, an apparent reduction of the antibacterial activities against all Gram-negative bacteria

Table 5 *In vitro* antibacterial activity and convulsant activity of 2-(4-substituted-thiazol-2-ylthio)carbapenems [Part V]



Compound No.	R-	cp*K*a	clog P	MIC_{90} (μg/ml)[a]		MIC (μg/ml)[b]								Convulsant activity[c]
				S.a.	*E.fm.*	*E.c.*	*K.p.*	*P.m.*	*P.v.*	*S.m.*	*E.cl.*	*C.f.*	*P.a.*	
34		7.37	0.334	8	8	2	0.031	2	4	32	32	32	32	1.06
35		7.76	−0.705	4	8	0.5	0.125	0.5	2	8	32	32	8	5.94
36		7.76	−0.705	4	2	0.125	0.031	0.063	1	4	8	8	4	4.86
37		7.76	−0.705	4	4	0.125	0.031	0.063	0.5	4	8	8	8	9.96
38		7.76	−0.705	4	4	0.25	0.063	0.25	1	4	8	8	8	9.96

[a] MIC_{90} was determined by the agar dilution method agasint 17 clinical isolates of methicillin-resistant *Staphylococcus aureus* (*S.a.*) and 20 isolates of vancomycin-resistant *Enterococcus faecium* (*E.fm.*). [b] MIC was determined by the agar dilution method using the following bacterial strains; *E.c., Escherichia coli* ML1410; *K.p., Klebsiella pneumoniae* ATCC10031; *P.m., Proteus mirabilis* GN2425; *P.v., Proteus vulgaris* GN7919; *S.m., Serratia marcescens* GN6473; *E.cl., Enterobacter cloacae* GN7471; *C.f., Citrobacter freundii* GN346; *P.a., Pseudomonau aeruginosa* IFO3451. [c] ED_{50} ratio relative to imipenem. * the ED_{50} value has been reported [9].

tested was observed. It was suggested that there was a boarder line clog P value, of around 1 to1.2, below which compounds maintain high anti-Gram-negative bacterial activities in this series of *C*-alkylated derivatives.

As for the *N*-methyl derivatives **8**, **15**, **16**, **17**, **20**, and **21**, their antibacterial activities were lower than those of the corresponding derivatives with the same molecular formula in spite of their relatively low clog P values. This could be considered due to their low cp*K*a values, which ranged from 7.2 to 8.0.

In the series of substituted methyl derivatives **26**∼**38** in Table 4 and Table 5, both clog P and cp*K*a values seemed to correlate with the anti-Gram negative bacterial activities. The reduced activities of chloromethyl derivatives **26**, **27**, and **34** could be explained by their high lipophilicities. The similar activities of hydroxylmethyl derivatives **30**, **31**, **35**∼**38** to the corresponding methyl derivatives could be understood by considering both the lipophilicity and basicity. The relatively low antibacterial activities of **32** and **33** suggested that basicity rather than lipophilicity might be a dominant factor in determining the antibacterial activity if the cp*K*a is below the borderline discussed above. Thus, a good correlation between the activity of 2-(thiazol-2-ylthio)-1β-methylcarbapenems against Gram-negative bacteria and their physicochemical properties was observed although other factors, *e.g.* affinity for bacterial PBPs, which affects antibacterial activity as well, could not be excluded.

Convulsant Activity in Mice

Based on the biological and physicochemical data of the 38 compounds in this study, a significant correlation between the convulsant activity and lipophilicity (clog P) was not found unlike the correlation observed between the anti-Gram-negative bacterial activity and lipophilicity as discussed above. In addition, a clear relationship between the activity and cp*K*a values could not been found in this study. It is possible that the SAR of the convulsant activity is very subtle because of the differing activity amongst **1**, **2**, and **3**, the chemical structures of which were closely

related.

It was also difficult to interpret the effects of substituents introduced on the tetrahydropyridine or dihydropyrrole ring, on the convulsant activity. In the case of 4-tetrahydropyridine derivative **2**, the introduction of a methyl group only at the 2′*R*-position (**9**), but not the 2′*S*- (**10**), 6′*S*- (**11**), or 6′*R*- (**12**) positions nor at the nitrogen atom (**15**), revealed a significant substituent effect that lowered the convulsant activity although the possibility of reducing the neurotoxicity by a substituent effect had been previously suggested [9]. This type of effect was observed upon the introduction of an ethyl and isopropyl group at the 2′*R*-position (**18**, **22**) whereas the introduction of an isopropyl or *sec*-butyl group at the 6′*S*-position enhanced rather than lowered the convulsant activity (**23**, **25**). On the other hand, the introduction of a substituted methyl group at the 2′*R*- and even 2′*S*-positions significantly lowered the convulsant activity in all derivatives synthesized except the 2′*S*-chloromethyl derivative (**27**) although the substituent effect at the 2′*S*-position was obviously low. The substituent effect of the fluoromethyl group was particularly pronounced in **28** and **29**.

As described above, the convulsant activity of **2** was not affected by *N*-methylation (**15**), but *N*-methylation of **3** annulled the substituent effect of the 2′*R*-methyl group and enhanced the convulsant activity. The convulsant activity of **13** was more than 2-fold lower than unsubstituted derivative **3**. This suggested that the substituent introduced also affected the convulsant activity in our series of 3-tetrahydropyridinyl derivatives although only a limited number of derivatives had been investigated so far.

The substituent effect in dihydropyrrole derivative **1** seemed to be more pronounced and different from that of tetrahydropyridine derivative **2**. All of the substituted dihydropyrrole compounds (**4**～**7**, **19**, **34**～**38**) synthesized except *N*-methylated ones (**8**, **16**, **17**) had the reduced convulsant activities compared with that of **1**, although the levels of reduction were different. In the case of the *C*-methylated derivatives (**4**～**7**), a significant effect was observed not only at the 2′*R*-position, which corresponded to the 2′*R*-position in the 4-tetrahydropyridineium ring, but also at the 5′*S*- and 5′*R*-positions. The convulsant reducing effect of the methyl group at the 5′*S*-position was also observed with the isopropyl group (**19**), while chloromethylation at the 2′*S*-position did not effectively lower the convulsant activity (**34**). As for hydroxymethylation at the carbon α to the nitrogen atom, this was also effective in all compounds (**35**～**38**) and the introduction at the 5′*S*- and 5′*R*-positions was preferable. Meanwhile, *N*-methylation of **1** did not affect the convulsant activity (**8**), but *N*-methylation of *C*-methylated compounds **16** and **17** annulled the *C*-methylation effect observed in the tetrahydropyridine series.

It has been reported that the convulsant activity of carbapenems is related to the basicity of the C2-side chain, distance between the carboxylic acid in the carbapenem skeleton and basic/cationic moiety in the C-2 side chain [15, 16], and the steric hindrance around the basic nitrogen atom. No clear relationship between the convulsant activity and basicity was found in the limited range of differences of the basicity in this study. It was also difficult to find a relationship between the distance described above because of structural flexibility since there is almost free rotation of the tetrahydropyridine and dihydropyrrole rings, which was calculated by a preliminary study using MOPAC6/PM3. Based on the substituent effects observed in this study, it appears that the convulsant activity was affected by a subtle difference of the steric hindrance around the nitrogen atom, but a clear explanation including that for differences between the tetrahydropyridine and dihydropyrrole rings was not possible. Further investigations will be required to clarify the SAR.

Conclusion

The SAR of a series of 2-(4-tetrahydropyridinylthiazol-2-ylthio)-1β-methylcarbapenems and 4-dihydropyrrolyl-thiazole analogs on the antibacterial activity and the convulsant activity in mice were clarified. Most of the substitutions in the tetrahydropyridine and dihydropyrrole rings tended to diminish the antibacterial activity against Gram-negative bacteria; however, it is noteworthy that the reduction of the activity was not observed in some dihydropyrrole derivatives. In particular, the compounds bearing a methyl group on the carbon α to the nitrogen atom (**4**～**7**) maintained potent activities similar to those of the unsubstituted derivative **1** against most of Gram-negative bacteria. In terms of convulsant activity, the introduction of a substituent in the carbon α to the nitrogen atom was an effective approach to lowering their neurotoxicities, especially in the dihydropyrrole derivatives. Amongst the derivatives tested in this study, SM-216601 (**6**) was selected because the methyl group introduced at the 5′*S*-position brought about significant reduction of the convulsant activity while maintaining favorable activity against both multidrug-resistant Gram-positive bacteria and Gram-negative bacteria. Further detailed microbiological and pharmacological evaluations of SM-216601 are underway as a possible candidate for broad-spectrum carbapenem antibiotics.

Experimental

General Analytical Methods

IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. NMR spectra were recorded on JEOL JNM-LA300 or Bruker 400 MHz spectrometers and chemical shifts are reported in δ values (ppm) relative to internal standard TMS for organic solvents, and unreferenced in D_2O. The low-resolution MS spectra were recorded in positive Electron Spray mode (ESP) on Waters ZQ2000 instrument and the high-resolution mass studies were conducted on QSTAR mass spectrometer.

Methyl (3*S*)-3-{[(Allyloxy)carbonyl]amino}butanoate ($\mathbf{I_7}$)

To a solution of *tert*-butyl (3*S*)-3-{[(benzyloxy)carbonyl]-amino}butanoate (5.63 g, 19.2 mmol) in methanol (28 ml) was added a hydrochloric acid solution which was prepared by acetyl chloride (41 ml, 577 mmol) and methanol (78 ml, 1.93 mol). After stirring at 0°C for 10 hours, the solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give methyl ester intermediate (3.61 g). To a solution of this intermediate in methanol (72 ml) was added 10% Pd–C (1.13 g) and the mixture was stirred under hydrogen atmosphere for 3 hours. The catalyst was filtered off and the solvent was removed under reduced pressure and the residue was dissolved in THF (30 ml). To this solution were added allyl chloroformate (1.60 ml, 15.0 mmol) and diisopropylethylamine (2.62 ml, 15.0 mmol) and the mixture was stirred at 0°C for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give $\mathbf{I_7}$ (2.06 g, 53%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, d, J=6.8 Hz), 2.54 (2H, d, J=5.5 Hz), 3.67 (3H, s), 4.05~4.18 (1H, m), 5.06~5.13 (2H, m), 5.15~5.24 (1H, m), 7.28~7.39 (5H, m). MS (ESP) m/z 202 (M+H).

1-Allyl 3-Methyl (6*S*)-6-Methyl-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate ($\mathbf{D_7}$)

To a solution of $\mathbf{I_7}$ (2.06 g, 10.2 mmol) and methyl acrylate (1.11 ml, 10.2 mmol) in toluene (25 ml) was added NaH (60% in oil, 0.41 g, 10.2 mmol) at 45°C and the mixture was stirred for 2 hours. The mixture was partitioned between ethyl acetate and 1 N HCl. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in methanol (40 ml). To this solution were added acetic acid (0.70 ml, 12.2 mmol) and sodium cyanoborohydride (0.77 g, 12.2 mmol) and the mixture was stirred for 1 hour. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give hydroxyester intermediate (1.21 g). The intermediate was dissolved in dichloromethane (24 ml) and to this solution was added methanesulfonyl chloride (0.52 ml, 6.7 mmol) and triethylamine (1.24 ml, 8.9 mmol). After stirring for 30 minutes, the mixture was diluted with ethyl acetate, washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in toluene (12 ml) and dichloromethane (6 ml). To this solution was added DBU (2.0 ml, 13.4 mmol) at 0°C and the mixture was stirred for 5 minutes. The mixture was partitioned between ethyl acetate and dil. HCl. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give $\mathbf{D_7}$ (278 mg, 11%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, d, J=6.8 Hz), 1.31 (3H, t, J=7.1 Hz), 2.04~2.13 (1H, m), 2.53~2.64 (1H, m), 3.70~3.79 (1H, m), 3.77 (3H, s), 4.55~4.68 (4H, m), 5.19~5.34 (2H, m), 5.89~6.02 (1H, m), 7.00~7.04 (1H, m).

Allyl (2*S*)-5-(Chloroacetyl)-2-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate ($\mathbf{E_7}$)

To a solution of $\mathbf{D_7}$ (232 mg, 0.97 mmol) and bromochloromethane (0.10 ml, 1.55 mmol) in THF (7 ml) was added *n*-BuLi (1.56 M, 0.93 ml, 1.49 mmol) at −100°C and the mixture was stirred for 10 minutes. The mixture was partitioned between ethyl acetate and water. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give $\mathbf{E_7}$ (85 mg, 34%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, d, J=7.0 Hz), 2.13~2.24 (1H, m), 2.66~2.75 (1H, m), 3.71~3.79 (1H, m), 4.36~4.46 (2H, m), 4.60~4.71 (4H, m), 5.20~5.34 (2H, m), 5.88~6.01 (1H, m), 6.96~6.99 (1H, m). MS (ESP) m/z 258 (M+H).

Allyl (2*S*)-5-(2-Mercapto-1,3-thiazol-4-yl)-2-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate ($\mathbf{B_7}$)

To a solution of $\mathbf{E_7}$ (141 mg, 0.55 mmol) in methanol (3 ml) was added ammonium dithiocarbamate (72 mg, 0.65 mmol) at 0°C and the mixture was stirred for 30 minutes. The mixture was concentrated and the residue was dissolved in ethanol (6 ml). This solution was refluxed for 2 hours and

concentrated. The residue was purified by chromatography on silica gel to give **B_7** (160 mg, 99%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, d, J=7.0 Hz), 2.08～2.18 (1H, m), 2.60～2.70 (1H, m), 3.71～3.79 (1H, m), 4.52～4.65 (4H, m), 5.22～5.34 (2H, m), 5.89～6.01 (1H, m), 6.18～6.20 (1H, m), 6.42 (1H, s), 10.66 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(6*S*)-1-[(Allyloxy)carbonyl]-6-methyl-1,2,5,6-tetrahydropyridin-3-yl}-1,3-thiazol-2-yl)thio]-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_7)

To a solution of **B_7** (160 mg, 0.54 mmol) in THF (6.4 ml) was added lithium bis(trimethylsilyl)amide (1.0 M, 0.54 ml, 0.54 mmol) at 0°C and the mixture was stirred for 30 minutes. To this mixture was added a solution of **A** (30% in acetonitrile, 1.54 g, 0.81 mmol) and the mixture was stirred at 0°C for 16 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give **C_7** (175mg, 52%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.10 (3H, d, J=7.1 Hz), 1.19 (3H, d, J=6.8 Hz), 1.24 (3H, d, J=6.2 Hz), 2.09～2.17 (1H, m), 2.62～2.70 (1H, m), 3.25 (1H, dd, J=3.5, 6.2 Hz), 3.51～3.61 (1H, m), 3.88～3.94 (1H, m), 4.17～4.25 (2H, m), 4.64～4.88 (6H, m), 5.21～5.51 (4H, m), 5.91～6.04 (2H, m), 6.73～6.76 (1H, m), 7.12 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(6*S*)-6-methyl-1,2,5,6-tetrahydropyridin-3-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (7)

To a solution of **C_7** (175 mg, 0.28 mmol) in THF (3.5 ml) and water (1.7 ml) was added 1 N HCl at 0°C and the mixture was stirred for 30 minutes. The mixture was partitioned between ethyl acetate and sat. sodium bicarbonate solution. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (3.5ml). To this solution were added tributyltin hydride (0.69 ml, 2.19 mmol), acetic acid (0.041 ml, 0.72 mmol) and dichlorobis(triphenylphosphine)palladium (20 mg, 0.028 mmol). After stirring for 1 hour, the mixture was extracted with water and the aqueous layer was washed with dichloromethane. The aqueous solution was purified by polymer gel chromatography and lyophilized to give **7** (70 mg, 59%).

IR (KBr) cm^{-1} 3404, 2971, 1758, 1597, 1456, 1389, 1265, 1148, 1028, 767. ^{1}H-NMR (300 MHz, D_2O) δ 0.95 (3H, d, J=7.7 Hz), 1.13 (3H, d, J=6.2 Hz), 1.31 (3H, d, J=6.4Hz), 2.20～2.31 (1H, m), 2.52～2.62 (1H, m), 3.14～3.20 (1H, m), 3.33～3.37 (1H, m), 3.41～3.51 (1H, m), 3.96～4.01 (2H, m), 4.09～4.15 (2H, m), 6.53～6.65 (1H, m), 7.41 (1H, s). MS (ESP) m/z 422 (M+H). HR-MS 422.1204 (M+H) (calcd for $C_{19}H_{24}N_3O_4S_2$ 422.1202).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(6*R*)-1-[(Allyloxy)carbonyl]-6-methyl-1,2,5,6-tetrahydropyridin-3-yl}-1,3-thiazol-2-yl)thio]-4-methyl-7-oxo-6-{(1R)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_8)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 1.11 (3H, d, J=7.3 Hz), 1.17 (3H, d, J=6.8 Hz), 1.21 (3H, d, J=6.1 Hz), 2.04～2.15 (1H, m), 2.58～2.71 (1H, m), 3.18～3.24 (1H, m), 3.37～3.48 (1H, m), 3.82～3.93 (1H, m), 4.06～4.21 (2H, m), 4.62～4.86 (6H, m), 5.15～5.48 (4H, m), 5.87～6.03 (2H, m), 6.71 (1H, br s), 7.11 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(6*R*)-6-methyl-1,2,5,6-tetrahydropyridin-3-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (8)

IR (KBr) cm^{-1} 3428, 2970, 1759, 1599, 1392. ^{1}H-NMR (300 MHz, D_2O) δ 0.95 (3H, d, J=7.3 Hz), 1.12 (3H, d, J=6.0 Hz), 1.31 (3H, d, J=6.4 Hz), 2.18～2.33 (1H, m), 2.50～2.64 (1H, m), 3.10～3.49 (3H, m), 3.95～4.16 (4H, m), 6.54 (1H, s), 7.41 (1H, s).

***tert*-Butyl (2*E*,4*R*)-4-{[(Benzyloxy)carbonyl]amino}hex-2-enoate (K_{10})**

To a suspension of benzyl (1*R*)-1-(hydroxymethyl)-propylcarbamate (**J_{10}**) (9.46 g, 42.4 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy (0.143 g, 0.85 mmol) and sodium bromide (4.36 g, 42 mmol) in toluene, (125 ml), water (21 ml) and ethyl acetate (125 ml) were added sodium bicarbonate (10.3 g) followed by sodium hypochlorite solution (5%, 316 ml, 212 mmol) at 0°C. The organic layer was separated and washed successively with 10% aqueous potassium hydrogen sulfate solution, 10% aqueous sodium thiosulfate solution and brine. The solvent was removed under reduced pressure and the residue was dissolved in THF (60 ml). After stirring at room temperature for 90 minutes, the mixture was concentrated and purified by chromatography on silica gel to give **K_{10}** (9.73 g).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, t, J=7.5 Hz), 1.46 (9H, s), 1.42～1.68 (2H, m), 4.20～4.32 (1H, m), 3.65～3.73 (1H, m), 5.07 (1H, d, J=15.8 Hz), 5.11 (1H, d, J=15.8 Hz), 5.82 (1H, d, J=15.6 Hz), 6.71 (1H, dd, J=5.7, 15.6 Hz), 7.28～7.37 (5H, m). MS (ESP) m/z 320 (M+H).

***tert*-Butyl (4*R*)-4-Aminohexanoate Acetate (L_{10})**
A solution of K_{10} (9.73 g, 30.5 mmol) in methanol (200 ml) was stirred under hydrogen atmosphere in the presence of 10% Pd–C (3.2 g). After 7 hours, the catalyst was filtered off and the filtrate was concentrated *in vacuo* to give L_{10} (7.5 g) quantitatively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, t, J=7.5 Hz), 1.46 (9H, s), 1.53～1.63 (2H, m), 1.68～1.92 (2H, m), 2.35 (2H, t, J=7.5 Hz), 2.90～2.98 (1H, m).

***tert*-Butyl (4*R*)-4-[[(Allyloxy)carbonyl](2-methoxy-2-oxoethyl)amino]hexanoate (G_{10})**
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.3 Hz), 1.41 (9H, s), 1.37～1.79 (4H, m), 2.21～2.42 (2H, m), 3.66～3.77 (5H, m), 3.90～4.20 (1H, m), 4.50～4.63 (2H, m), 5.13～5.32 (2H, m), 5.78～5.97 (1H, m). MS (ESP) *m*/*z* 344 (M+H).

1-Allyl 4-Methyl (2*R*)-2-Ethyl-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (D_{10})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.4 Hz), 1.32～1.57 (2H, m), 2.44～2.47 (2H, m), 3.63～3.79 (1H, m), 3.76 (3H, s), 4.35～4.65 (4H, m), 5.19～5.34 (2H, m), 5.88～6.01 (1H, m), 6.88 (1H, br s). MS (ESP) *m*/*z* 254 (M+H).

Allyl (2*R*)-4-(Chloroacetyl)-2-ethyl-3,6-dihydropyridine-1(2*H*)-carboxylate (E_{10})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.3 Hz), 1.32～1.57 (2H, m), 2.34～2.46 (1H, m), 2.50～2.57 (1H, m), 3.70～3.82 (1H, m), 4.34～4.48 (1H, m), 4.39 (1H, d, J=14.1), 4.43 (1H, d, J=14.1), 4.60～4.65 (1H, m), 5.19～5.34 (2H, m), 5.88～6.01 (1H, m), 6.81 (1H, br s).

Allyl (2*R*)-2-Ethyl-4-(2-mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (B_{10})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.4 Hz), 1.37～1.66 (2H, m), 2.17～2.24 (1H, m), 2.58～2.68 (1H, m), 3.65～3.79 (1H, m), 4.43～4.67 (4H, m), 5.21～5.34 (2H, m), 5.89～6.01 (1H, m), 6.08 (1H, br s), 6.39 (1H, s), 10.94 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(2*R*)-1-[(Allyloxy)carbonyl]-2-ethyl-1,2,3,6-tetrahydropyridin-4-yl}-1,3-thiazol-2-yl)thio]-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{10})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 0.91 (3H, t, J=6.7 Hz), 1.09 (3H, d, J=7.1 Hz), 1.24 (3H, d, J=6.2 Hz), 1.41～1.69 (2H, m), 2.35～2.42 (1H, m), 2.67～2.76 (1H, m), 3.24 (1H, dd, J=2.9, 6.2 Hz), 3.51～3.63 (1H, m), 3.70～3.81 (1H, m), 4.17～4.24 (2H, m), 4.45～4.68 (4H, m), 4.70～4.87 (2H, m), 5.18～5.50 (4H, m), 5.90～6.05 (2H, m), 6.64 (1H, br s), 7.09 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(2*R*)-2-Ethyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (10)
IR (KBr) cm^{-1} 3248, 2969, 1760, 1599, 1392, 1264, 1028. ^{1}H-NMR (300 MHz, D_2O) δ 0.94 (3H, t, J=7.5 Hz), 0.95 (3H, d, J=6.1 Hz), 1.12 (3H, d, J=6.2 Hz), 1.59～1.81 (2H, m), 2.35～2.46 (1H, m), 2.72～2.81 (1H, m), 3.13～3.22 (1H, m), 3.25～3.37 (2H, m), 3.76～3.80 (2H, m), 4.08～4.14 (2H, m), 6.37～6.40 (1H, m), 7.46 (1H, s). MS (ESP) *m*/*z* 436 (M+H). HR-MS 436.1371 (M+H) (calcd for $C_{20}H_{26}N_3O_4S_2$ 436.1359).

4-[(6*R*)-1,6-Dimethyl-1,2,5,6-tetrahydropyridin-3-yl]-1,3-thiazole-2-thiol (B_{12})
To a suspension of lithium aluminum hydride (25 mg, 0.66 mmol) in THF (0.6 ml) was added a suspension of B_8 (65.2 mg, 0.22 mmol) in THF (0.6 ml) at 0°C. The mixture was warmed to room temperature and stirred for 1 hour. Methanol was added and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel to give B_{12} (17.6 mg, 35%).

^{1}H-NMR (300 MHz, CD_3OD) δ 1.23 (3H, br s), 2.10～2.29 (1H, m), 2.54 (3H, br s), 2.80 (2H, br s), 3.50～3.70 (2H, m), 6.38 (1H, br s), 6.71 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(6*R*)-1,6-Dimethyl-1,2,5,6-tetrahydropyridin-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{12})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, d, J=7.3 Hz), 1.16 (3H, d, J=6.4 Hz), 1.29 (3H, d, J=6.4 Hz), 2.17～2.30 (2H, m), 2.46 (3H, s), 2.64～2.76 (1H, m), 3.21～3.25 (1H, m), 3.32～3.43 (1H, m), 3.48～3.61 (2H, m), 4.15～4.27 (2H, m), 4.71 (1H, dd, J=5.7, 13.4 Hz), 4.83 (1H, dd, J=5.3, 13.4 Hz), 5.26 (1H, d, J=10.4 Hz), 5.44 (1H, d, J=17.2 Hz), 5.96 (1H, dddd, J=5.3, 5.7, 10.4, 17.2 Hz), 6.60 (1H, s), 7.07 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(6*R*)-1,6-Dimethyl-1,2,5,6-tetrahydropyridin-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (12)
IR (KBr) cm^{-1} 3400, 2968, 1764, 1602, 1386. ^{1}H-NMR (300 MHz, D_2O) δ 0.95 (3H, d, J=7.3 Hz), 1.12 (3H, d, J=6.4 Hz), 1.28 (3H, d, J=6.6 Hz), 2.27～2.40 (1H, m), 2.58～2.72 (1H, m), 2.83 (3H, s), 3.13～3.38 (4H, m),

3.90～4.14 (3H, m), 6.52 (1H, s), 7.40 (1H, s).

***tert*-Butyl (2*E*,4*R*)-4-{[(Benzyloxy)carbonyl]amino}-5-methylhex-2-enoate (K_{13})**

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, d, J=7.0 Hz), 0.92 (3H, d, J=6.8 Hz), 1.46 (9H, s), 1.78～1.92 (1H, m), 4.16～4.26 (1H, m), 4.76 (1H, d, J=9.7 Hz), 5.07 (1H, d, J=13.9 Hz), 5.11 (1H, d, J=12.1 Hz), 5.83 (1H, dd, J=1.3, 15.5 Hz), 6.73 (1H, dd, J=5.5, 15.5 Hz), 7.28～7.37 (5H, m). MS (ESP) m/z 334 (M+H).

***tert*-Butyl (4*S*)-4-Amino-5-methylhexanoate (L_{13})**

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, d, J=7.0 Hz), 0.95 (3H, d, J=6.8 Hz), 1.41 (9H, s), 1.63～1.91 (3H, m), 2.28～2.47 (2H, m), 2.83 (1H, dt, J=4.4, 8.8 Hz).

***tert*-Butyl (4*S*)-4-[[(Allyloxy)carbonyl](2-methoxy-2-oxoethyl)amino]-5-methylhexanoate (G_{13})**

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, J=6.6 Hz), 0.97 (3H, d, J=6.6 Hz), 1.35～1.65 (2H, m), 1.42 (9H, s), 1.88～2.02 (1H, m), 2.26～2.52 (2H, m), 3.59～3.93 (5H, m), 4.51～4.68 (2H, m), 5.18～5.31 (2H, m), 5.78～5.96 (1H, m). MS (ESP) m/z 358 (M+H).

1-Allyl 4-Methyl (2*S*)-2-isopropyl-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (D_{13})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.4 Hz), 1.60～1.72 (1H, m), 2.28～2.40 (1H, m), 2.67 (1H, d, J=17.6 Hz), 3.55～3.77 (1H, m), 3.74 (3H, s), 3.93～4.13 (1H, m), 4.41～4.65 (3H, m), 5.19 (1H, ddd, J=1.5, 2.8, 10.4 Hz), 5.28 (1H, d, J=17.2 Hz), 5.92 (1H, ddt, J=5.5, 10.4, 17.2 Hz), 6.86 (1H, br s). MS (ESP) m/z 268 (M+H).

Allyl (2*S*)-4-(Chloroacetyl)-2-isopropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (E_{13})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.6 Hz), 1.50～1.64 (1H, m), 2.21～2.34 (1H, m), 2.78 (1H, d, J=17.4 Hz), 3.64～3.75 (2H, m), 4.33～4.44 (2H, m), 4.50～4.70 (3H, m), 5.17～5.32 (2H, m), 5.85～5.99 (1H, m), 6.80 (1H, br s).

Allyl (2*S*)-2-Isopropyl-4-(2-mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (B_{13})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, J=6.6 Hz), 0.92 (3H, d, J=6.6 Hz), 1.67～1.83 (1H, m), 2.38～2.58 (2H, m), 3.57～3.80 (1H, m), 3.97～4.18 (1H, m), 4.44～4.68 (3H, m), 5.21 (1H, dd, J=1.3, 10.4 Hz), 5.29 (1H, dd, J=1.4, 17.2 Hz), 5.93 (1H, ddt, J=5.5, 10.4, 17.2 Hz), 6.03 (1H, br s), 6.38 (1H, br s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(2*S*)-2-isopropyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (13)

IR (KBr) cm^{-1} 3434, 2969, 1753, 1598. ^{1}H-NMR (300 MHz, D_2O) δ 0.95 (6H, d, J=6.8 Hz), 0.97 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=6.4 Hz), 1.95～2.07 (1H, m), 2.47～2.76 (2H, m), 3.16～3.36 (3H, m), 3.82 (2H, br s), 4.08～4.15 (2H, m), 6.38 (1H, br s), 7.48 (1H, s). MS (ESP) m/z 450 (M+H).

Methyl *N*-[(Allyloxy)carbonyl]-*N*-(4-ethoxy-4-oxobutyl)-L-valinate (H_{14})

To a solution of L-val-OMe hydrochloride (11.47 g, 68.4 mmol) in DMF (235 ml) were added potassium carbonate (37.81 g, 274 mol), ethyl 4-bromobutyrate (19.6 ml, 137 mmol) and potassium iodide (4.38 g, 27.3 mmol). The mixture was stirred at 60°C for 2 hours. The resulting mixture was cooled and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in chloroform. To this solution were added diisopropylethylamine (24 ml, 138mmol) and allyl chloroformate (14.5 ml, 137 mmol) at 0°C and stirred for 1 hour. The mixture was partitioned between chloroform and water. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give **H_{14}** (18.5 g, 82%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, d, J=6.8 Hz), 0.96 (3H, d, J=6.4 Hz), 1.21～1.27 (3H, m), 1.80～2.50 (5H, m), 3.22～3.33 (1H, m), 3.45 (2H, t, J=7.7 Hz), 3.69 (3H, s), 4.07～4.16 (2H, m), 4.53～4.62 (2H, m), 5.16～5.43 (2H, m), 5.83～5.98 (1H, m). MS (ESP) m/z 330 (M+H).

1-Allyl 4-Ethyl (6*S*)-6-Isopropyl-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (D_{14})

To a solution of potassium *t*-butoxide (4.45 g, 40 mmol) in THF (200 ml) was added a solution of **H_{14}** (6.53 g, 20 mmol) in THF (52 ml) at 60°C and the mixture was stirred for 2 hours. The mixture was partitioned between ethyl acetate and 1 N HCl. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in methanol (50 ml). To this solution were added acetic acid (1.37 ml, 24 mmol) and sodium cyanoborohydride (1.51 g, 24 mmol) and the mixture was stirred for 1 hour. The solvent was removed under reduced

pressure and the residue was purified by chromatography on silica gel to give the hydroxyester intermediate (4.6 g). The intermediate was dissolved in dichloromethane (20 ml) and to this solution was added methanesulfonyl chloride (1.8 ml, 23 mmol) and triethylamine (4.3 ml, 31 mmol). After stirring for 1 hour, the mixture was diluted with dichloromethane (30 ml) and to this solution was added DBU (3.5 ml, 23 mmol) at 0°C and the mixture was stirred for 13 hours. The mixture was partitioned between ethyl acetate and 1 N HCl. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give **D_{14}** (1.60 g, 29%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, d, J=6.8 Hz), 1.00 (3H, d, J=6.8 Hz), 1.28 (3H, t, J=7.1 Hz), 1.94 (1H, sesq, J=6.8 Hz), 2.22～2.43 (2H, m), 2.78～2.94 (1H, m), 4.13～4.41 (4H, m), 4.53～4.62 (2H, m), 5.19 (1H, dd, J=1.3, 10.2 Hz), 5.27 (1H, dd, J=1.5, 17.2 Hz), 5.91 (1H, ddd, J=5.0, 10.2, 17.2 Hz), 6.99 (1H, br s). MS (ESP) m/z 282 (M+H).

Allyl (6*S*)-4-(Chloroacetyl)-6-isopropyl-3,6-dihydropyridine-1(2*H*)-carboxylate (E_{14})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, d, J=6.8 Hz), 0.98 (3H, d, J=6.8 Hz), 1.95 (1H, sesq, J=6.8 Hz), 2.09～2.25 (1H, m), 2.36～2.44 (1H, m), 2.75～2.93 (1H, m), 4.13～4.58 (6H, m), 5.15 (1H, dd, J=1.3, 10.4 Hz), 5.23 (1H, ddd, J=1.6, 3.1, 17.0 Hz), 5.87 (ddd, J=5.1, 10.4, 17.0 Hz), 6.88 (1H, br s). MS (ESP) m/z 286 (M+H).

Allyl (6*S*)-6-Isopropyl-4-(2-mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (B_{14})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, d, J=6.8 Hz), 1.04 (3H, d, J=6.7 Hz), 1.92～2.05 (1H, m), 2.17～2.28 (1H, m), 2.35～2.56 (1H, m), 2.88～3.15 (1H, m), 4.19～4.48 (2H, m), 4.52～4.69 (2H, m), 5.22 (1H, ddt, J=1.2, 1.3, 10.4 Hz), 5.31 (1H, ddt, J=1.5, 1.5, 17.2 Hz), 5.86～6.00 (1H, m), 6.21 (1H, br s), 6.40 (1H, br s), 10.70 (1H, br s). MS (ESP) m/z 325 (M+H).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(6*S*)-1-[(Allyloxy)carbonyl]-6-isopropyl-1,2,3,6-tetrahydropyridin-4-yl}-1,3-thiazol-2-yl)thio]-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{14})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.00 (9H, s), 0.88～1.00 (9H, m), 1.11～1.14 (3H, m), 1.87 (1H, sesq, J=7.3 Hz), 2.22～2.48 (2H, m), 2.88～3.14 (2H, m), 3.27～3.47 (1H, m), 3.97～4.77 (8H, m), 5.06～5.38 (4H, m), 5.77～5.93 (2H, m), 6,71 (1H, br s), 6.99 (1H, br s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(6*S*)-6-isopropyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (14)

IR (KBr) cm^{-1} 3362, 2968, 1760, 1599, 1390. ^{1}H-NMR (300 MHz, D_2O) δ 0.90～0.95 (9H, m), 1.09 (3H, d, J=6.4 Hz), 1.93 (1H, sesq, J=6.6 Hz), 2.59～2.67 (2H, m), 3.06～3.23 (2H, m), 3.29～3.34 (1H, m), 3.46～3.53 (1H, m), 3.72～3.77 (1H, m), 4.04～4.11 (2H, m), 6.40 (1H, s), 7.45 (1H, s). MS(ESP) m/z 450 (M+H). HR-MS 450.1518 (M+H) (calcd for $C_{21}H_{28}N_3O_4S_2$ 450.1515).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(6*R*)-6-isopropyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (15)

IR (KBr) cm^{-1} 3412, 2968, 1755, 1599, 1393. ^{1}H-NMR (300 MHz, D_2O) δ 0.92～0.98 (9H, s), 1.12 (3H, d, J=6.4 Hz), 1.90～2.03 (1H, m), 2.62～2.73 (2H, m), 3.09～3.38 (3H, m), 3.48～3.65 (1H, m), 3.77～3.83 (1H, m), 4.04～4.16 (2H, m), 6.42 (1H, s), 7.48 (1H, m).

Ethyl *N*-[(Allyloxy)carbonyl]-*N*-(4-ethoxy-4-oxobutyl)-L-leucinate (H_{16})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, d, J=6.4 Hz), 0.96 (3H, d, J=6.6 Hz), 1.24～1.30 (6H, m), 1.48～2.00 (5H, m), 2.25～2.43 (2H, m), 3.06～3.13 (1H, m), 3.33～3.52 (1H, m), 4.08～4.22 (4H, m), 4.31～4.41 (1H, m), 4.52～4.65 (2H, m), 5.17～5.35 (2H, m), 5.82～6.00 (1H, m).

1-Allyl 4-Ethyl (6*S*)-6-Isobutyl-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (D_{16})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.94 (6H, d, J=6.4 Hz), 1.26 (3H, d, J=7.1 Hz), 1.35～1.52 (2H, m), 1.57～1.74 (1H, m), 2.22～2.43 (2H, m), 2.75～2.96 (1H, m), 4.06～4.30 (3H, m), 4.50～4.75 (3H, m), 5.19 (1H, ddt, J=1.3, 1.5, 10.4 Hz), 5.27 (1H, ddt, J=1.5, 1.7, 17.0 Hz), 5.91 (1H, ddt, J=5.7, 10.4, 17.0 Hz), 6.86 (1H, br s).

Allyl (6*S*)-4-(Chloroacetyl)-6-isobutyl-3,6-dihydropyridine-1(2*H*)-carboxylate (E_{16})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96 (6H, d, J=6.4 Hz), 1.37～1.54 (2H, m), 1.63～1.73 (1H, m), 2.16～2.34 (1H, m), 2.39～2.49 (1H, m), 2.74～2.96 (1H, m), 4.12～4.39 (3H, m), 4.52～4.87 (3H, m), 5.17～5.33 (2H, m), 5.92 (1H, ddt, J=5.7, 10.4, 17.2 Hz), 6.79 (1H, br s).

Allyl (6*S*)-6-Isobutyl-4-(2-mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (B_{16})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.37～1.54 (2H, m), 1.63～

1.75 (1H, m), 2.13～2.24 (1H, m), 2.34～2.50 (1H, m), 2.88～3.07 (1H, m), 4.14～4.37 (1H, m), 4.53～4.80 (3H, m), 5.17～5.23 (1H, m), 5.29 (1H, ddt, *J*=1.5, 1.7, 17.2 Hz), 5.92 (1H, ddt, *J*=5.7, 10.4, 17.2 Hz), 6.11 (1H, br s), 6.37 (1H, br s).

(4R,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(6*S*)-6-isobutyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (16)

IR (KBr) cm^{-1} 3386, 2966, 1756, 1600, 1388. ^{1}H-NMR (300 MHz, D_2O) δ 0.86 (6H, d, *J*=6.2 Hz), 0.95 (3H, d, *J*=7.7 Hz), 1.12 (3H, d, *J*=6.2 Hz), 1.50～1.79 (3H, m), 2.63～2.70 (2H, m), 3.13～3.37 (3H, m), 3.47～3.65 (2H, m), 3.98～4.15 (2H, m), 6.39 (1H, br s), 7.47 (1H, s).

1-Allyl 4-Methyl (2*S*)-2-(chloromethyl)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (D_{17})

To a solution of 1-allyl 4-methyl (2*S*)-2-(hydroxymethyl)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (**D_{21}**) (310 mg, 1.21 mmol) in carbon tetrachloride (6.2 ml) was added triphenylphosphine (410 mg, 1.56 mmol) and stirred at reflux for 2 hours. Ethyl acetate was added to this mixture and insoluble materials were filtered off. The filtrate was concentrated and purified by chromatography on silica gel to give **D_{17}** (197 mg, 59%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.45～2.73 (2H, m), 3.35～3.46 (2H, m), 3.65～3.84 (1H, m), 3.75 (3H, s), 4.40～4.84 (4H, m), 5.21 (1H, ddd, *J*=1.4, 2.7, 10.4 Hz), 5.30 (1H, d, *J*=17.0 Hz), 5.93 (ddd, *J*=5.0, 10.4, 17.0 Hz), 6.88 (0.5H, br s), 6.92 (0.5H, br s).

Allyl (2*S*)-4-(Chloroacetyl)-2-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (E_{17})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.37～2.48 (1H, m), 2.68 (1H, d, *J*=17.9 Hz), 3.37 (2H, d, *J*=7.9 Hz), 3.70～3.88 (1H, m), 4.29～4.85 (6H, m), 5.18 (1H, ddd, *J*=1.3, 2.6, 10.4 Hz), 5.26 (1H, d, *J*=17.2 Hz), 5.88 (1H, ddd, *J*=5.7, 10.4, 17.2 Hz), 6.81 (1H, br s).

Allyl (2*S*)-2-(Chloromethyl)-4-(2-mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (B_{17})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.48～2.70 (2H, m), 3.45 (1H, dd, *J*=8.2, 11.0 Hz), 3.52 (1H, dd, *J*=7.1, 11.0 Hz), 3.71～3.90 (1H, m), 4.42～4.85 (4H, m), 5.23 (1H, dd, *J*=1.3, 10.4 Hz), 5.31 (1H, dd, *J*=1.3, 17.0 Hz), 5.93 (1H, ddd, *J*=5.7, 10.4, 17.0 Hz), 6.22 (1H, br s), 6.44 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*S*)-1-[(Allyloxy)carbonyl]-2-(chloromethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{17})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.11 (9H, s), 1.07 (3H, d, *J*=7.4 Hz), 1.21 (3H, d, *J*=6.0 Hz), 2.68～2.75 (2H, m), 3.22 (1H, dd, *J*=2.7, 6.4 Hz), 3.47～3.60 (3H, m), 3.73～3.90 (1H, m), 4.15～4.22 (2H, m), 4.42～4.86 (6H, m), 5.20～5.35 (3H, m), 5.45 (1H, dd, *J*=1.5, 17.2 Hz), 5.88～6.03 (2H, m), 6.65 (1H, br s), 7.12 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(2*S*)-2-(Chloromethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (17)

IR (KBr) cm^{-1} 3398, 2968, 1760, 1601, 1389, 1264. ^{1}H-NMR (300 MHz, D_2O) δ 0.91 (3H, d, *J*=7.1 Hz), 1.08 (3H, d, *J*=6.2 Hz), 2.67～2.75 (2H, m), 3.14 (1H, dd, *J*=7.3, 9.7 Hz), 3.31 (1H, dd, *J*=2.8, 5.9 Hz), 3.75～3.95 (5H, m), 4.02～4.11 (2H, m), 6.37 (1H, m), 7.43 (1H, m). MS (ESP) *m*/*z* 456 (M+H). HR-MS 456.0821 (M+H) (calcd for $C_{19}H_{23}ClN_3O_4S_2$ 456.0813).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*R*)-1-[(Allyloxy)carbonyl]-2-(chloromethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{18})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.13 (3H, d, *J*=7.1 Hz), 1.23 (3H, d, *J*=6.2 Hz), 2.71～2.76 (2H, m), 3.25 (1H, dd, *J*=2.9, 6.0 Hz), 3.45～3.63 (3H, m), 3.76～3.91 (1H, m), 4.18～4.26 (2H, m), 4.45～4.88 (6H, m), 5.22～5.50 (4H, m), 5.90～6.04 (2H, m), 6.68 (1H, br s), 7.15 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(2*R*)-2-(Chloromethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (18)

IR (KBr) cm^{-1} 3412, 2968, 1758, 1600, 1393, 1264, 1028. ^{1}H-NMR (300 MHz, D_2O) δ 1.02 (3H, d, *J*=7.1 Hz), 1.19 (3H, d, *J*=6.4 Hz), 2.64～2.82 (2H, m), 3.19～3.28 (1H, m), 3.40～3.43 (1H, m), 3.69～4.00 (5H, m), 4.13～4.20 (2H, m), 6.47～6.50 (1H, m), 7.51 (1H, s). MS (ESP) *m*/*z* 456 (M+H). HR-MS 456.0820 (M+H) (calcd for $C_{19}H_{23}ClN_3O_4S_2$ 456.0813).

***tert*-Butyl (4*S*)-4-[[(Allyloxy)carbonyl](2-methoxy-2-oxoethyl)amino]-5-fluoropentanoate (G_{19})**

To a solution of *tert*-butyl (4*S*)-4-[[(allyloxy)carbonyl](2-

methoxy-2-oxoethyl)amino]-5-hydroxypentanoate (**G_{21}**) (2.38 g, 6.9 mmol) in dichloromethane (72 ml) were added methanesulfonyl chloride (0.81 ml, 10.4 mmol) and triethylamine (1.45 ml, 10.4 mmol) at 0°C, and stirred for 10 minutes. The mixture was partitioned with water and ethyl acetate, and the aquous layer was extracted twice with ethyl acetate. The organic layers were combined and washed successively with 1 N HCl, sat. sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in acetonitrile and to this solution was added tetrabutylammonium fluoride. The mixture was stirred at 80°C for 30 minutes, then added to water and extracted with ethyl acetate. The organic layers were combined and washed with 1 N HCl, sat. sodium bicarbonate solution and brine, followed by dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give **G_{19}** (0.47 g, 20%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.75～1.99 (2H, m), 2.31～2.36 (2H, m), 3.69～3.77 (3H, m), 3.88～4.14 (2H, m), 4.20～4.73 (5H, m), 5.18～5.33 (2H, m), 5.80～5.99 (1H, m).

1-Allyl 4-Methyl (2*S*)-2-(fluoromethyl)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (D_{19})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.48～2.60 (2H, m), 3.77 (3H, s), 3.78～3.90 (1H, m), 4.24～4.91 (6H, m), 5.21～5.36 (2H, m), 5.89～6.01 (1H, m), 6.91 (1H, br s).

Allyl (2*S*)-4-(Chloroacetyl)-2-(fluoromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (E_{19})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.44～2.53 (1H, m), 2.64 (1H, d, *J*=17.9 Hz), 3.87～4.00 (1H, m), 4.18～4.91 (8H, m), 5.21～5.36 (2H, m), 5.89～6.02 (1H, m), 6.85 (1H, br s).

Allyl (2*S*)-2-(Fluoromethyl)-4-(2-mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (B_{19})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.37～2.46 (1H, m), 2.52～2.63 (1H, m), 3.79～3.84 (1H, m), 4.24～4.91 (6H, m), 5.22～5.37 (2H, m), 5.89～6.02 (1H, m), 6.13 (1H, br s), 6.45 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*S*)-1-[(Allyloxy)carbonyl]-2-(fluoromethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{19})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.10 (3H, d, *J*=7.3 Hz), 1.24 (3H, d, *J*=6.0 Hz), 2.57 (1H, d, *J*=16.7 Hz), 2.69～2.80 (1H, m), 3.24 (1H, dd, *J*=6.2, 2.9 Hz), 3.49～3.60 (1H, m), 3.78～3.94 (1H, m), 4.08～4.99 (10H, m), 5.22～5.50 (4H, m), 5.90～6.04 (2H, m), 6.69 (1H, br s), 7.14 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(2*S*)-2-(Fluoromethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (19)

^{1}H-NMR (300 MHz, D_2O) δ 0.92 (3H, d, *J*=7.3 Hz), 1.10 (3H, d, *J*=6.2 Hz), 2.24～2.33 (1H, m), 2.43～2.49 (1H, m), 3.12～3.19 (1H, m), 3.30～3.33 (1H, m), 3.53～3.56 (2H, m), 4.05～4.12 (2H, m), 4.31～4.39 (1H, m), 4.46～4.54 (1H, m), 6.40～6.43 (1H, m), 7.36 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*R*)-1-[(Allyloxy)carbonyl]-2-(fluoromethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{20})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.13 (3H, d, *J*=7.3 Hz), 1.24 (3H, d, *J*=6.0 Hz), 2.57 (1H, d, *J*=16.9 Hz), 2.69～2.80 (1H, m), 3.25 (1H, dd, *J*=6.2, 2.7 Hz), 3.44～3.59 (1H, m), 3.78～3.94 (1H, m), 4.11～5.00 (10H, m), 5.22～5.50 (4H, m), 5.90～6.05 (2H, m), 6.68 (1H, br s), 7.15 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(2*R*)-2-(Fluoromethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (20)

^{1}H-NMR (300 MHz, D_2O) δ 0.92 (3H, d, *J*=7.1 Hz), 1.10 (3H, d, *J*=6.2 Hz), 2.38～2.50 (1H, m), 2.55～2.63 (1H, m), 3.09～3.19 (1H, m), 3.31～3.34 (1H, m), 3.48～3.62 (1H, m), 3.68～3.72 (2H, m), 4.04～4.12 (2H, m), 4.40～4.45 (1H, m), 4.55～4.61 (1H, m), 6.39～6.42 (1H, m), 7.40 (1H, s). MS(ESP) *m*/*z* 440 (M+H). HR-MS 440.1118 (M+H) (calcd for $C_{19}H_{23}FN_3O_4S_2$ 440.1108).

***tert*-Butyl (4*S*)-4-{[(Benzyloxy)carbonyl]amino}-5-methoxypentanoate (J_{23})**

To a solution of *tert*-butyl (4*S*)-4-{[(benzyloxy)carbonyl]-amino}-5-hydroxypentanoate (**J_{21}**) (4.0 g, 12.4 mmol) in acetonitrile were added silver (I) oxide (14.3 g, 61.7 mmol) and iodomethane (7.7 ml, 124 mmol), and stirred for 19 hours. Insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give **J_{23}** (2.98 g, 71%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.75～1.91 (2H, m), 2.28～2.33 (2H, m), 3.33 (3H, s), 3.36～3.42 (2H,

m), 3.75～3.85 (1H, m), 4.99～5.03 (1H, m), 5.09 (2H, s), 7.27～7.37 (5H, m).

***tert*-Butyl (4*S*)-4-[[(Allyloxy)carbonyl](2-methoxy-2-oxoethyl)amino]-5-methoxypentanoate (G_{23})**

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.74～1.92 (2H, m), 2.27～2.33 (2H, m), 3.24～3.25 (3H, m), 3.38～3.53 (2H, m), 3.68～3.73 (3H, m), 3.91～4.07 (2H, m), 4.20～4.36 (1H, m), 4.54～4.65 (2H, m), 5.16～5.34 (2H, m), 5.81～5.59 (1H, m).

1-Allyl 4-methyl (2*S*)-2-(Methoxymethyl)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (D_{23})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.40～2.56 (2H, m), 3.23～3.40 (2H, m), 3.33 (3H, s), 3.66～3.84 (1H, m), 3.77 (3H, s), 4.42～4.82 (4H, m), 5.20～5.38 (2H, m), 5.89～6.01 (1H, m), 6.89 (1H, s).

Allyl (2*S*)-4-(Chloroacetyl)-2-(methoxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (E_{23})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.18～2.65 (2H, m), 3.21～3.38 (2H, m), 3.31 (3H, s), 3.65～3.90 (2H, m), 4.41 (1H, d, J=14.1 Hz), 4.43 (1H, d, J=14.1 Hz), 4.50～4.80 (3H, m), 5.20～5.36 (2H, m), 5.89～6.02 (1H, m), 6.83 (1H, s).

Allyl (2*S*)-4-(2-Mercapto-1,3-thiazol-4-yl)-2-(methoxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (B_{23})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.42 (2H, d, J=16.8 Hz), 2.52～2.63 (1H, m), 3.21～3.43 (2H, m), 3.34 (3H, s), 3.65～3.86 (1H, m), 4.43～4.82 (4H, m), 5.21～5.36 (2H, m), 5.89～6.02 (1H, m), 6.10 (1H, br s), 6.43 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*S*)-1-[(Allyloxy)carbonyl]-2-(methoxymethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{23})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.09 (3H, d, J=7.3 Hz), 1.24 (3H, d, J=6.2 Hz), 2.54 (1H, d, J=16.8 Hz), 2.63～2.73 (1H, m), 3.24 (1H, dd, J=6.2, 2.9 Hz), 3.39～3.48 (2H, m), 3.34 (3H, s), 3.50～3.64 (1H, m), 3.70～3.87 (1H, m), 4.18～4.26 (2H, m), 4.48～4.88 (6H, m), 5.20～5.51 (4H, m), 5.90～6.04 (2H, m), 6.68 (1H, br s), 7.12 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(2*S*)-2-(methoxymethyl)-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (23)

^{1}H-NMR (300 MHz, D_2O) δ 0.91 (3H, d, J=7.1 Hz), 1.09 (3H, d, J=6.4 Hz), 2.38～2.49 (1H, m), 2.59～2.66 (1H, m), 3.09～3.20 (1H, m), 3.30 (3H, s), 3.31～3.33 (1H, m), 3.48～3.65 (3H, m), 3.73 (2H, br s), 4.03～4.12 (2H, m), 6.37 (1H, s), 7.40 (1H, s). MS (ESP) m/z 452 (M+H). HR-MS 452.1317 (M+H) (calcd for $C_{20}H_{26}N_3O_5S_2$ 452.1308).

Allyl (2*R*)-2-(Hydroxymethyl)-4-{2-[(4-methoxybenzyl)thio]-1,3-thiazol-4-yl}-3,6-dihydropyridine-1(2*H*)-carboxylate (F_{22})

To a solution of [(2*R*)-4-(2-mercapto-1,3-thiazol-4-yl)-1-methyl-1,2,3,6-tetrahydropyridin-2-yl]-Methanol (**B_{22}**) (218 mg, 0.7 mmol) in THF (3 ml) were added 4-methoxybenzylchloride (0.95 ml, 0.70 mmol) and triethylamine (0.98 ml, 0.70 mmol) at 0°C, and stirred for 3 hours followed by warm to room temperature. Resulting mixture was diluted with ethyl acetate and washed with sat. sodium bicarbonate solution and brine respectively. The organic layer was dried and concentrated under reduced pressure. The residue was purified by thin layer chromatography to give **F_{22}** (150 mg, 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.40 (1H, d, J=16.7 Hz), 2.53～2.65 (1H, m), 3.50～3.80 (3H, m), 3.69 (3H, s), 4.29～4.67 (2H, m), 4.30 (2H, s), 4.56 (2H, d, J=5.5 Hz), 5.13 (1H, dd, J=1.5, 10.4 Hz), 5.23 (1H, dd, J=1.5, 17.2 Hz), 5.87(1H, ddd, J=5.5, 10.4, 17.2 Hz), 6.56 (1H, s), 6.75 (2H, d, J=8.6 Hz), 6.81 (1H, s), 7.21 (2H, d, J=8.6 Hz).

Allyl (2*R*)-2-{[(Aminocarbonyl)oxy]methyl}-4-{2-[(4-methoxybenzyl)thio]-1,3-thiazol-4-yl}-3,6-dihydropyridine-1(2*H*)-carboxylate (F_{24})

To a solution of **F_{22}** (75 mg, 0.17 mmol) in chloroform (1 ml) was added chlorosulfonyl isocyanate (0.017 ml, 0.20 mmol) at 0°C, and the mixture was stirred for 3 hours. To this mixture was added chlorosulfonyl isocyanate (0.010 ml, 0.11 mmol) and stirred for 3 hours. Water was added and extracted with ethyl acetate. The organic layer was washed with brine, dried, concentrated and purified by thin layer chromatography to give **F_{24}** (74.5 mmg, 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.37～2.45 (1H, m), 2.61～2.78 (1H, m), 3.72～4.95 (9H, m), 3.77 (3H, s), 4.38 (2H, s), 5.21 (1H, dd, J=1.3, 10.4 Hz), 5.31 (1H, d, J=17.2 Hz), 5.95 (1H, ddd, J=5.5, 10.4, 17.2 Hz), 6.64 (1H, br s), 6.83 (2H, d, J=8.6 Hz), 6.88 (1H, s), 7.29 (2H, d, J=8.6 Hz).

Allyl (2*R*)-2-{[(Aminocarbonyl)oxy]methyl}-4-(2-mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (B_{24})

To a solution of F_{24} (74.5 mg, 0.16 mmol) and anisole (35 ml, 0.32 mmol) in trifluoroacetic acid (6 ml) was added thioisonicotinamide (3 mg) and stirred at 80°C for 4 hours. The mixture was concentrated and the residue was dissolved in 1 N-NaOH solution, and washed with hexane. The aqueous layer was acidified with 6 N-HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give B_{24} (37.3 mg, 67%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.21～2.70 (2H, m), 3.73～4.65 (8H, m), 4.80 (1H, br s), 5.18 (1H, d, J=10.3 Hz), 5.26 (1H, d, J=17.2 Hz), 5.88 (1H, ddd, J=5.1, 10.3, 17.2 Hz), 6.22 (1H, br s), 6.40 (1H, s).

(4*R*,5*S*,6*S*)-3-{[4-((2R)-2-{[(Aminocarbonyl)oxy]methyl}-1,2,3,6-tetrahydropyridin-4-yl)-1,3-thiazol-2-yl]thio}-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (24)

IR (KBr) cm^{-1} 3406, 2969, 1759, 1728, 1602, 1391, 1264, 1087. ^{1}H-NMR (300 MHz, D_2O) δ 0.95 (3H, d, J=7.3 Hz), 1.12 (3H, d, J=6.0 Hz), 2.49～2.92 (2H, m), 3.14～3.20 (1H, m), 3.33～3.35 (1H, m), 3.82～3.85 (2H, m), 4.08～4.23 (2H, m), 4.30～4.37 (1H, m), 6.39～6.42 (1H, m), 7.46 (1H, s). MS(ESP) *m*/*z* 481 (M+H). HR-MS 481.1206 (M+H) (calcd for $C_{20}H_{25}N_4O_6S_2$ 481.1210).

4-[(5*S*)-1,5-Dimethyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazole-2-thiol (B_{31})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, d, J=6.4 Hz), 2.49 (3H, s), 3.43～3.59 (2H, m), 3.97～4.03 (1H, m), 5.89 (1H, br s), 6.30 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(5*S*)-1,5-Dimethyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{31})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.11～0.12 (9H, m), 1.04～1.09 (3H, m), 1.17～1.28 (6H, m), 2.52 (3H, s), 2.55～2.63 (1H, m), 3.21～3.25 (1H, m), 3.49～3.62 (3H, m), 4.09～4.25 (3H, m), 4.60～4.87 (3H, m), 5.17～5.50 (4H, m), 5.85～6.04 (1H, m), 6.28～6.30 (1H, m), 7.05～7.27 (1H, m).

(4*R*,5*S*,6*S*)-3-({4-[(5*S*)-1,5-Dimethyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (31)

^{1}H-NMR (300 MHz, D_2O) δ 0.93 (3H, d, J=7.1 Hz), 1.11 (3H, d, J=6.2 Hz), 1.34 (3H, d, J=6.8 Hz), 2.81 (3H, s), 3.13～3.18 (1H, m), 3.34 (1H, dd, J=6.2, 2.8 Hz), 4.03～4.14 (3H, m), 4.21～4.30 (1H, m), 4.38～4.45 (1H, m), 6.22 (1H, s), 7.47 (1H, s).

4-[(2*R*)-1,2-Dimethyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazole-2-thiol (B_{32})

^{1}H-NMR (300 MHz, $CDCl_3$-CD_3OD) δ 1.33 (3H, d, J=6.4 Hz), 2.57 (3H, s), 6.20～6.22 (1H, m), 6.43 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*R*)-1,2-dimethyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{32})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.11 (9H, s), 1.08 (3H, d, J=7.4 Hz), 1.25 (3H, d, J=6.2 Hz), 1.30 (3H, d, J=6.2 Hz), 2.53 (3H, s), 3.23 (1H, dd, J=6.6, 2.7 Hz), 3.39～3.47 (1H, m), 3.53～3.63 (1H, m), 3.80～3.98 (2H, m), 4.16～4.26 (2H, m), 4.56～4.87 (2H, m), 5.25～5.50 (2H, m), 5.87～6.04 (1H, m), 6.29～6.31 (1H, m), 7.18 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(2*R*)-1,2-Dimethyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (32)

^{1}H-NMR (300 MHz, D_2O) δ 0.94 (3H, d, J=7.3 Hz), 1.12 (3H, d, J=6.4 Hz), 1.37 (3H, d, J=6.6 Hz), 2.80 (3H, s), 3.13～3.23 (1H, m), 3.35 (1H, dd, J=6.0, 2.9 Hz), 3.84～3.89 (1H, m), 4.06～4.15 (2H, m), 4.21～4.27 (1H, m), 4.45～4.51 (1H, m), 6.21 (1H, s), 7.55 (1H, s).

Methyl *N*-[(Allyloxy)carbonyl]-L-valinate (I_{33})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, J=6.8 Hz), 0.94 (3H, d, J=7.0 Hz), 2.07～2.19 (1H, m), 3.72 (3H, s), 4.27 (1H, dd, J=4.7, 9.0 Hz), 4.55 (2H, d, J=5.5 Hz), 5.15～5.33 (3H, m), 5.90 (1H, ddt, J=5.5, 10.6, 17.2 Hz).

1-Allyl 3-Ethyl (5*S*)-5-isopropyl-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate (D_{33})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, d, J=6.9 Hz), 0.97～1.00 (3H, m), 1.29～1.34 (3H, m), 2.29～2.54 (1H, m), 4.20～4.31 (3H, m), 4.43～4.75 (4H, m), 5.20～5.37 (2H, m), 5.91～6.01 (1H, m), 6.66～6.72 (1H, m).

Allyl (2*S*)-2-Isopropyl-4-(2-mercapto-1,3-thiazol-4-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (B_{33})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, d, J=6.8 Hz), 1.00 (3H, d, J=7.0 Hz), 2.29～2.55 (1H, m), 4.23～4.33 (1H, m), 4.45～4.76 (4H, m), 5.18～5.35 (2H, m), 5.87～6.02 (1H, m), 6.16～6.24 (1H, m), 6.36～6.43 (1H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(5*S*)-5-isopropyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (33)
^{1}H-NMR (300 MHz, D_2O) δ 0.91～0.96 (9H, m), 1.11 (3H, d, J=6.4 Hz), 1.93～2.05 (1H, m), 3.11～3.22 (1H, m), 3.34 (1H, dd, J=2.7, 6.0 Hz), 4.05～4.13 (2H, m), 4.25～4.42 (3H, m), 6.35 (1H, s), 7.51 (1H, s).

1-Allyl 3-Methyl (2*R*)-2-(Chloromethyl)-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate (D_{34})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.70 (3H, s), 3.92～4.06 (2H, m), 4.17～4.38 (2H, m), 4.52～4.58 (2H, m), 5.00～5.07 (1H, m), 5.11～5.17 (1H, m), 5.18～5.25 (1H, m), 5.76～5.92 (1H, m), 6.81～6.88 (1H, m).

Allyl (2*R*)-3-(Chloroacetyl)-2-(chloromethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (E_{34})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.98～4.03 (1H, m), 4.09～4.34 (1H, m), 4.37～4.61 (4H, m), 4.63～4.68 (2H, m), 5.22～5.36 (3H, m), 5.88～6.02 (1H, m), 6.95～7.03 (1H, m).

Allyl (2*R*)-2-(Chloromethyl)-3-(2-mercapto-1,3-thiazol-4-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (B_{34})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.73～3.80 (1H, m), 4.26～4.43 (1H, m), 4.62～4.68 (4H, m), 5.24～5.38 (4H, m), 5.89～6.02 (1H, m), 6.48～6.54 (2H, m).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*S*)-1-[(Allyloxy)carbonyl]-2-(chloromethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{34})
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 9 H), 1.07 (d, 3H, J=7.3 Hz), 1.21 (d, 3H, J=6.2 Hz), 3.23, (dd, 1H, J=2.9, 6.0 Hz), 3.33～3.46 (m, 1H), 3.96～4.01 (m, 1H), 4.16～4.48 (m, 5H), 4.60～4.85 (m, 4H), 5.20～5.49 (m, 5H), 5.91～6.05 (m, 2H), 6.45 (s, 1H), 7.34 and 7.41 (each s, total 1H).

(4*R*,5*S*,6*S*)-3-({4-[(2*R*)-2-(Chloromethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (34)
IR (KBr) cm^{-1} 3410, 2971, 1760, 1600, 1392, 1283, 1147, 1030, 771. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.93 (d, 3H, J=7.3 Hz), 1.09 (d, 3H, J=6.4 Hz), 3.10 (td, 1H, J=7.3, 16.9 Hz), 3.32 (dd, 1H, J=2.9, 6.0 Hz), 3.92 (dd, 1H, J=4.8, 13.3 Hz), 4.00～4.11 (m, 3H), 4.15 (br s, 1H), 4.17～4.24 (m, 1H), 5.21 (br s, 1H), 6.40～6.43 (m, 1H), 7.65 (s, 1H). MS(ESP) m/z 442 (M+H). HR-MS 442.0654 (M+H) (calcd for $C_{18}H_{22}N_3O_5S_2$ 442.0656).

Methyl *N*-[(Allyloxy)carbonyl]-*O*-[*tert*-butyl(dimethyl)silyl]serinate (I_{35})
To a solution of alloc-ser-OMe (0.50 g, 2.46 mmol) in DMF (5 ml) ware added *t*-butyldimethylchlorosilane (0.445 g, 2.92 mol), imidazole (0.251 g, 3.69 mmol). The mixture was stirred for 1 hour and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give $\mathbf{I_{35}}$ (0.785 g) quantitatively.
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.03 (3H, s), 0.86 (9H, s), 3.75 (3H, s), 3.84 (1H, dd, J=10.1, 3.1 Hz), 4.06 (1H, dd, J=10.1, 2.6 Hz), 4.39～4.43 (1H, m), 4.58～4.61 (2H, m), 5.21～5.37 (2H, m), 5.52～5.57 (1H, m), 5.87～6.00 (1H, m).

1-Allyl 3-Methyl (5*R*)-5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate (D_{35})
$\mathbf{D_{35}}$ was synthesized from $\mathbf{I_{35}}$ as described for the preparation of $\mathbf{D_7}$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.03 (3H, s), 0.86 (9H, s), 3.65～3.85 (1H, m), 3.78 (3H, s), 3.89～3.96 (1H, m), 4.23～4.31 (1H, m), 4.40～4.50 (1H, m), 4.60～4.63 (2H, m), 4.67～4.77 (1H, m), 5.20～5.35 (2H, m), 5.88～6.01 (1H, m), 6.75～6.77 (1H, m).

Allyl (2*R*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-(chloroacetyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (E_{35})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.04 (3H, s), 0.85 (9H, s), 3.89～3.96 (1H, m), 3.70～4.00 (2H, m), 4.27～4.55 (4H, m), 4.60～4.65 (2H, m), 4.78～4.89 (1H, m), 5.21～5.36 (2H, m), 5.88～6.01 (1H, m), 6.79～6.80 (1H, m).

Allyl (2*R*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-(2-mercapto-1,3-thiazol-4-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (B_{35})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 3.67～3.87 (1H, m), 3.90～3.96 (1H, m), 4.28～4.35 (1H, m), 4.40～4.55 (1H, m), 4.61～4.66 (2H, m), 4.70～4.78 (1H, m), 5.21～5.37 (2H, m), 5.89～6.02 (1H, m), 6.15 (1H, br s), 6.37～6.40 (1H, m).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(5*R*)-1-[(Allyloxy)carbonyl]-5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{35})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, d, J=7.3 Hz), 1.32 (3H, d, J=6.5 Hz), 3.28 (1H, dd, J=7.0, 2.9 Hz), 3.52～3.62 (1H, m), 3.70～3.76 (1H, m), 3.89～3.94 (1H, m), 4.19～4.35 (2H, m), 4.45～4.77 (6H, m), 4.82～4.89 (1H, m), 4.93～4.98 (1H, m), 5.24～5.50 (4H, m), 5.90～6.05 (1H, m), 6.28～6.30 (1H, m), 7.21 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(5*R*)-5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (35)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, d, J=7.3 Hz), 1.20 (3H, d, J=6.2 Hz), 3.19～3.30 (1H, m), 3.34 (1H, dd, J=6.1, 2.7 Hz), 3.84 (1H, dd, J=12.6, 5.0 Hz), 3.95 (1H, dd, J=12.6, 3.3 Hz), 4.13～4.22 (2H, m), 4.38～4.50 (2H, m), 6.27 (1H, s), 7.62 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(5*S*)-1-[(Allyloxy)carbonyl]-5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{36})

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, d, J=7.3 Hz), 1.34 (3H, d, J=6.2 Hz), 3.28 (1H, dd, J=7.0, 2.9 Hz), 3.46～3.58 (1H, m), 3.71～3.77 (1H, m), 3.92～3.96 (1H, m), 4.22～4.31 (2H, m), 4.45～4.78 (6H, m), 4.83～4.90 (1H, m), 4.94～4.99 (1H, m), 5.26～5.51 (4H, m), 5.92～6.06 (2H, m), 6.27～6.30 (1H, m), 7.20 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(5*S*)-5-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (36)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, d, J=7.3 Hz), 0.98 (3H, d, J=6.4 Hz), 3.13～3.19 (1H, m), 3.33 (1H, dd, J=6.1, 2.9 Hz), 3.71 (1H, dd, J=12.5, 5.1 Hz), 3.82 (1H, dd, J=12.5, 3.4 Hz), 4.06～4.13 (2H, m), 4.28～4.33 (2H, m), 6.18 (1H, s), 7.51 (1H, s).

***tert*-Butyl (3*S*)-3-[[(Allyloxy)carbonyl](2-methoxy-2-oxoethyl)amino]-4-(methoxymethoxy)butanoate (G_{37})**

To a solution of *tert*-butyl (3*S*)-3-amino-5-(methoxymethoxy)pentanoate (9.7 g, 44 mmol) in methanol (300 ml) were added diisopropylethylamine (15.5 ml, 88 mmol) and methyl bromoacetate (8.3 ml, 88 mmol), and stirred at 60°C for 2 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in chloroform (100 ml). To this solution were added diisopropylethylamine (15.5 ml, 88 mmol) and allyl chloroformate (9.4 ml, 88 mmol) at 0°C, and the mixture was stirred at room temperature for 10 hours. The mixture was partitioned between ethyl acetate and water, and the organic layer was separated and washed with brine then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to give $\mathbf{G_{37}}$ (11.7 g, 71%).

^{1}H-NMR (300 MHz, $CDCl_3$) d 1.43 (9H, s), 2.54～2.75 (2H, m), 3.33 (3H, s), 3.54～3.82 (5H, m), 4.04～4.09 (2H, m), 4.50～4.71 (5H, m), 5.15～5.38 (2H, m), 5.80～6.02 (1H, m). MS (ESP) *m*/*z* 376 (M+H).

1-Allyl 3-Methyl (2*S*)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate (D_{37})

$\mathbf{D_{37}}$ was synthesized from $\mathbf{G_{37}}$ in the same manner to that of $\mathbf{D_{14}}$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ −0.08 (3H, s), −0.07 (3H, s), 0.78 (9H, s), 3.75 (3H, s), 3.84～4.42 (4H, m), 4.58～4.64 (2H, m), 4.77～4.84 (1H, m), 5.18～5.23 (1H, m), 5.29 (1H, dt, J=1.7, 17.2 Hz), 5.92 (1H, ddd, J=5.5, 10.4, 17.2 Hz), 6.77～6.84 (1H, m). MS (ESP) *m*/*z* 356 (M+H).

Allyl (2*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-(chloroacetyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (E_{37})

^{1}H-NMR (300 MHz, $CDCl_3$) δ −0.08 (3H, s), −0.06 (3H, s), 0.78 (9H, s), 3.86～4.13 (2H, m), 4.23～4.63 (6H, m), 4.87～4.96 (1H, m), 5.21 (1H, dd, J=2.9, 10.4 Hz), 5.29 (1H, d, J=17.0 Hz), 5.92(1H, ddd, J=5.7, 10.4, 17.0 Hz), 6.79 (0.5H, br s), 6.85 (0.5H, br s). MS (ESP) *m*/*z* 374 (M+H).

Allyl (2*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-(2-mercapto-1,3-thiazol-4-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (B_{37})

^{1}H-NMR (300 MHz, DMSO-d_6) δ −0.15 (3H, s), −0.12 (3H, s), 0.76 (9H, s), 3.90～4.13 (3H, m), 4.23～4.34 (1H, m), 4.49～4.70 (2H, m), 4.88～4.95 (1H, m), 5.16～5.34 (2H, m), 5.86～5.99 (1H, m), 6.56 (0.6H, br s), 6.59 (0.4H, br s), 7.06 (1H, s). MS (ESP) *m*/*z* 413 (M+H).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*S*)-1-[(Allyloxy)carbonyl]-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{37})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, d, J=7.3 Hz), 1.32 (3H, d, J=6.1 Hz), 3.22～3.28 (1H, m), 3.53～3.64 (1H, m), 3.72～3.80 (1H, m), 3.93～4.47 (6H, m), 4.58～4.88 (4H, m), 5.12～5.48 (4H, m), 5.80～6.05 (2H, m), 6.38 (1H, s), 7.31 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(2*S*)-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (37)
^{1}H-NMR (300 MHz, D_2O) δ 0.92 (3H, d, J=6.8 Hz), 1.10 (3H, d, J=5.7 Hz), 3.12～3.19 (1H, m), 3.30～3.35 (1H, m), 3.73～4.13 (7H, m), 6.36 (1H, s), 7.55 (1H, s). MS (ESP) m/z 424 (M+H). HR-MS 424.0986 (M+H) (calcd for $C_{18}H_{22}N_3O_5S_2$ 424.0995).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*R*)-1-[(Allyloxy)carbonyl]-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (C_{38})
^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, d, J=7.1 Hz), 1.33 (3H, d, J=6.2 Hz), 3.27 (1H, dd, J=6.9, 2.7 Hz), 3.42～3.60 (1H, m), 3.76～4.50 (7H, m), 4.66～4.89 (4H, m), 5.06～5.50 (5H, m), 5.91～6.05 (2H, m), 6.43～6.46 (1H, m), 7.35～7.40 (1H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(2*R*)-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (38)
^{1}H-NMR (300 MHz, D_2O) δ 0.94 (3H, d, J=7.3 Hz), 1.09 (3H, d, J=6.4 Hz), 3.05～3.16 (1H, m), 3.32 (1H, dd, J=6.0, 2.9 Hz), 3.81～3.93 (2H, m), 4.03～4.19 (4H, m), 4.87～4.90 (1H, m), 6.36 (1H, s), 7.60 (1H, s).

Calculation of cp*K*a and clog P

The values of cp*K*a and clog P were calculated by ACD/PhysChem Batch Version 7.0.

Other Antibiotics

Imipenem (IPM) and panipenem (PAPM) were purified from imipenem-cilastatin (Banyu Pharmaceutical Co., Ltd., Tokyo, Japan) and panipenem-betamipron (Sankyo, Tokyo, Japan), respectively, in the laboratories of Sumitomo Pharmaceuticals Research Division.

Bacterial Strains

Standard strains (American Type Culture Collection, IFO, and GN) and clinical isolates from Japanese, American and European hospitals were bacterial collection in our laboratory. They were identified by standard diagnostic methods and kept as stock cultures at −70°C or below.

Determination of *In Vitro* Antibacterial Activity

MIC was determined by the twofold serial agar dilution method, with Mueller-Hinton agar (Difco, Detroit, MI). Cells of test strains were grown in Mueller-Hinton broth (Difco) at 37°C, overnight, and diluted with phosphate buffered saline supplemented with 0.01% gelatin to give a final concentration of approximately 10^6 CFU/ml. A portion (5 μl) of the dilution was placed onto a drug-containing agar surface with a Microplanter® (Sakuma Seisakusho, Tokyo). The plates were incubated at 37°C overnight The MIC was defined as the lowest antibiotic concentration that completely prevented visible growth.

Testing of Convulsant Activity

Male slc : ICR mice were purchased from Japan SLC (Sizuoka, Japan). Groups of ten mice intracerebroventricularly received each dose (0.3～100 μg/head) of compounds. Immediately after injection, incidence of clonic and tonic convulsion and mortality were recorded for 30 minutes. The convulsive activity (ED_{50}) was estimated using the method of probit analysis and expressed as the multiplicity of the ED_{50} to that of imipenem, which was assigned a value of 1.00. All animal procedures were performed in accordance with the institution's guidelines for the humane handling, care, and treatment of research animals.

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