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New Anti-MRSA and Anti-VRE Carbapenems; Synthesis and Structure-activity Relationships of 1β-Metyl-2-(thiazol-2-ylthio)carbapenems

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Discovery of novel antimicrobial agents effective against infections caused by drug-resistant pathogens is an important objective. In order to find a new parenteral carbapenem antibiotic, which has potent antibacterial activity especially against methicillin-resistant staphylococci, vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae*, a series of 1β-methylcarbapenems with thiazol-2-ylthio groups at the C-2 position have been synthesized. Structure-activity relationships were investigated which led to SM-197436 (**27**), SM-232721 (**44**) and SM-232724 (**41**), being selected for further evaluation.

During the last decade, the emergence of multi-drug resistant Gram-positive cocci such as methicillin-resistant staphylococci, vancomycin-resistant enterococci (VRE), and penicillin-resistant *Streptococcus pneumoniae* (PRSP) has become a serious medical problem worldwide, especially in nosocomial settings[1~3]. For treatment of multi-drug resistant Gram-positive bacterial infections, especially methicillin-resistant *Staphylococcus aureus* (MRSA) infection, the glycopeptide antibiotics vancomycin and teicoplanin, and the aminoglycoside antibiotic arbekacin have been used. Several problems, however, such as the spread of teicoplanin- and arbekacin-resistant MRSA[4] and the current emergence of glycopeptide-intermediate *S. aureus* (GISA)[5] are certainly reducing the efficacy of these drugs in the clinic. VRE were first reported in 1986, and identified with increasing frequency in many nations over the past 10 years[6]. Especially vancomycin-resistant *Enterococcus faecium* (VREFm) often show concomitantly high-level resistance to multiple antibacterial classes including β-lactams and aminoglycosides. The emergence of VREFm has been of serious concern because of the limited therapeutic options for treating such infections and their potential to transfer vancomycin-resistant genes to other organism, such as *S. aureus*[6]. Recently, new classes of antibacterial agents such as quinupristin-dalfopristin[7] and linezolid[8] have been approved as effective drugs against these multi-drug resistant Gram-positive bacteria. They both cover VREFm, but their pharmacological profiles such as narrow spectrum, side effects[7], and rapid emergence of bacterial resistance[7,9] might limit their clinical usefulness[10]. It is therefore still very worthwhile to search for new agents that are safe and effective against Gram-positive bacteria, including such multi-drug resistant pathogens, and simultaneously exhibit substantial antibacterial activity against important Gram-negative pathogens.

Carbapenem antibiotics have taken an important position in the field of antibacterial chemotherapy, because of their broad spectrum and high bactericidal activity against many Gram-positive and Gram-negative pathogens compared with other β-lactam antibiotics such as penicillins and cephalosporins. To date, many extensive studies on anti-MRSA carbapenems and also cephalosporins have been reported[11~25], but no interesting β-lactams for treatment of both MRSA and VREFm infections, have been developed, so far.

Previously, we reported that 1β-methyl-2-(4-arylthiazol-2-ylthio)carbapenems, SM-17466 and its analogs, exhibited

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potent anti-MRSA activity in correspondence with their high affinity for penicillin binding protein (PBP)2a in MRSA, and the *in vivo* efficacy of SM-17466 (**1**) against MRSA was confirmed in a mouse systemic infection model[25,26]. However, it was found that the activity against VREFm was insufficient to allow for useful *in vivo* efficacy.

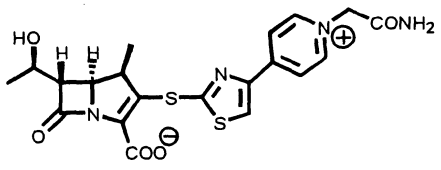
In the search for carbapenems with potent activity against both MRSA and VREFm, successive structural modifications of the thiazole ring substituent in 1β-methyl-2-(4-substituted thiazol-2-ylthio)carbapenem were planned on the basis of the previous SAR studies concerning antibacterial activity, stability against renal dehydropeptidase-I (DHP-I) hydrolysis, binding affinity to human albumin and convulsive activity in mice. In this paper, the synthesis and structure-activity relationships of new series of 1β-methyl-2-(thiazolylthio)carbapenems (Fig. 2), and the detailed profiles of three resulting carbapenems which were selected for further evaluation, are disclosed.

Chemistry

Synthesis of 1β-Methyl-2-(4-aryl-thiazol-2-ylthio)carbapenems (Compounds **7**~**21**) (Type A)

The type A carbapenems were prepared by a coupling reaction of the phosphate intermediate A_1 and 2-mercaptothiazoles B in a similar manner to that reported previously[25] as shown for **7** and **17** (Fig. 3).

Fig. 1.



SM-17466 (1)

4-Aryl-2-mercaptothiazoles $\mathbf{B}_{7\sim17}$ and $\mathbf{B}_{20,21}$, the C-2 side chain unit of the type A carbapenems were also synthesized by similar way to that reported previously[25], except for the preparation of the amidino-phenyl derivatives $\mathbf{B}_{18,19}$, which were synthesized by the method starting from the nitrile $\mathbf{E}_{18,19}$ as shown in Fig. 4.

Synthesis of 1β-Methyl-2-(4-heterocyclyl-thiazol-2-ylthio)-carbapenems (Compounds **22**~**51**) (Type B)

The carbapenems of type B were also prepared by a coupling reaction of the phosphate intermediate A_2 and 2-mercaptothiazoles B as shown in the synthesis of **41** (Fig. 5).

The syntheses of quaternary ammonium carbapenems **33** and **35** were accomplished by quaternization followed by deprotection. *N*-Imidoyl carbapenems **31**, **32**, **36**, **37** and **39** were prepared from the corresponding amino derivatives by a known method[27] (Fig. 6).

The majority of the 2-mercaptothiazoles B were derived from the corresponding chloromethyl ketones H and ammonium dithiocarbamate as shown in the preparation of $\mathbf{B}_{41}$ (Fig. 7).

The synthesis of *N*-methylated 2-mercaptothiazoles was mainly achieved by reduction of the corresponding allyl carbamates utilizing lithium aluminium hydride as shown in the preparation of $\mathbf{B}_{38}$ (Fig. 8). The compounds $\mathbf{B}_{30,34}$, were prepared by sequential quaternization, reduction and aminolysis from the 4-pyridylthiazole derivatives $\mathbf{I}_{30,24}$. This method was also applicable for the preparation of *N*-protected 2-mercaptothiazole $\mathbf{B}_{24}$.

The chloromethylketones H were obtained by the reaction of the corresponding esters **L** with chloromethyl lithium as shown in Fig. 9, except for the preparation of $\mathbf{H}_{23}$.

Fig. 2.

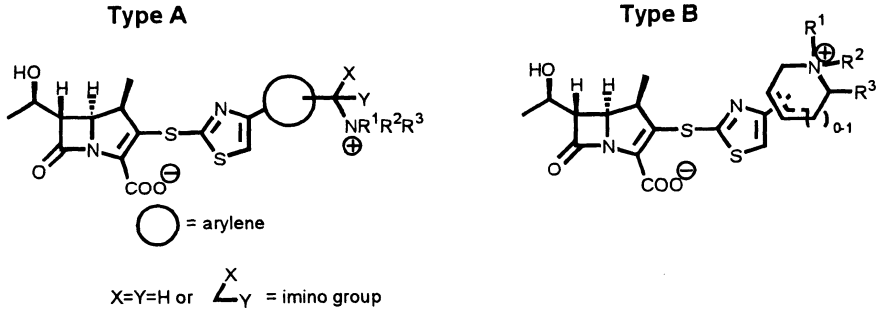


Fig. 3.

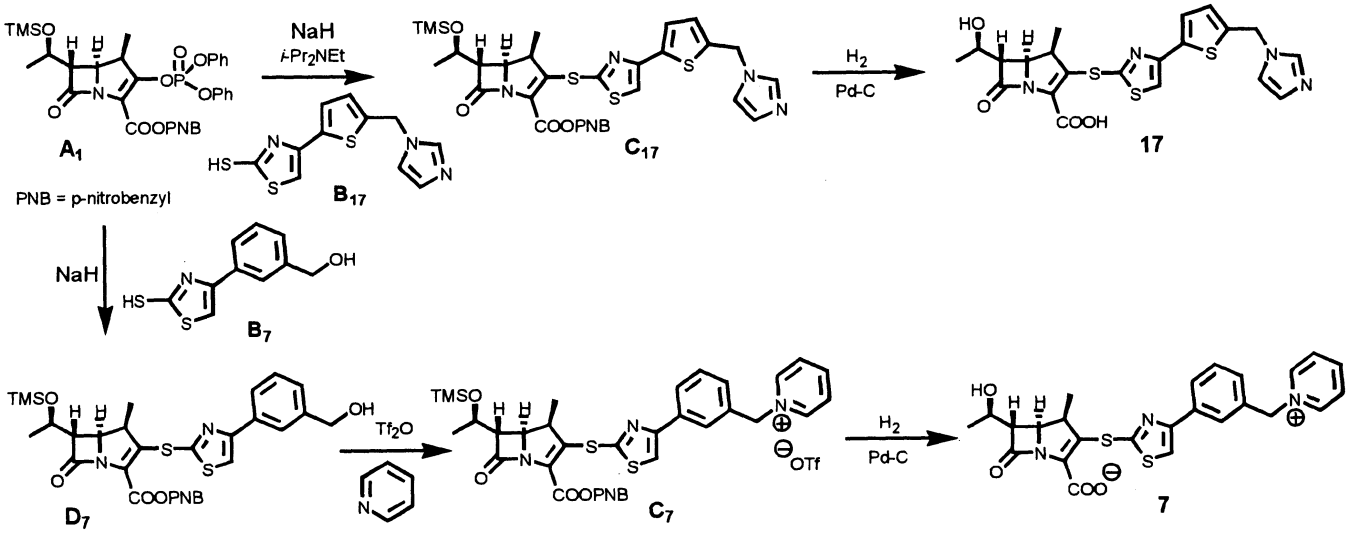


Fig. 4.

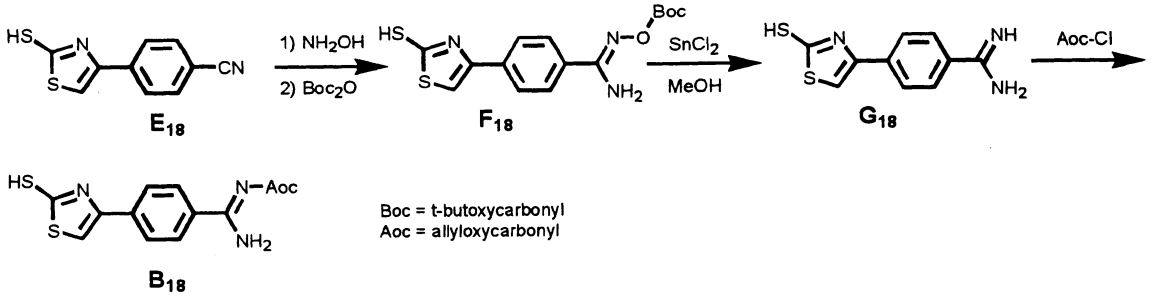


Fig. 5.

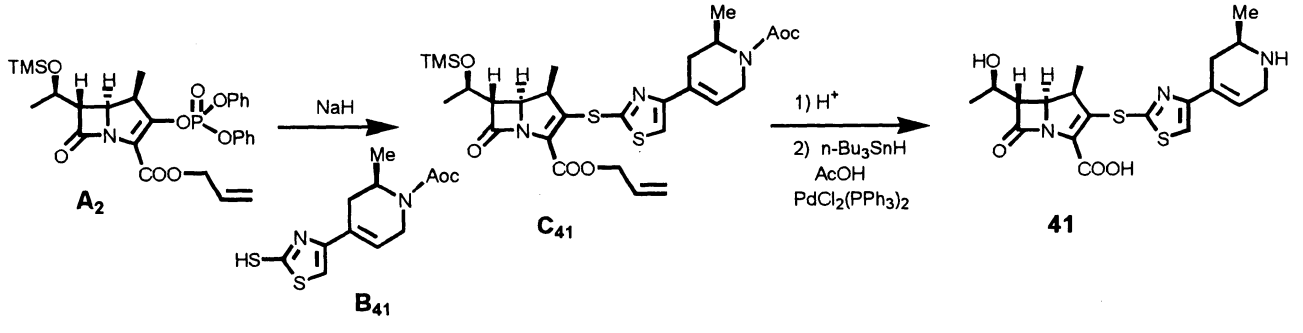


Fig. 6.

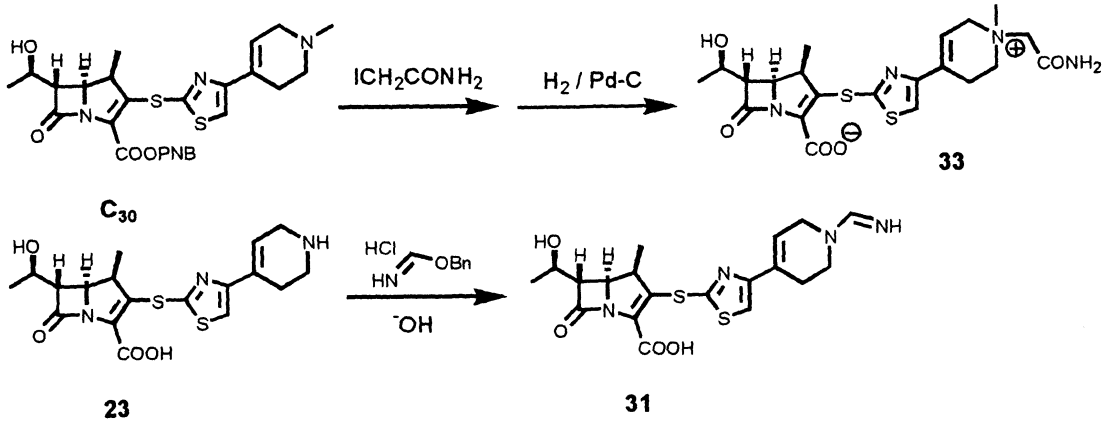


Fig. 7.

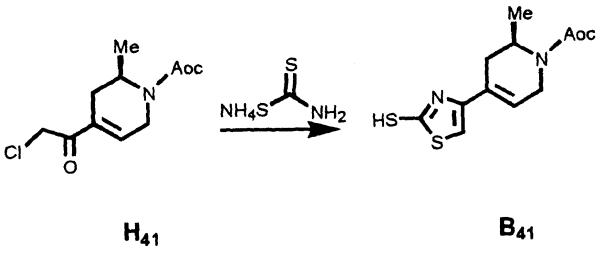


Fig. 8.

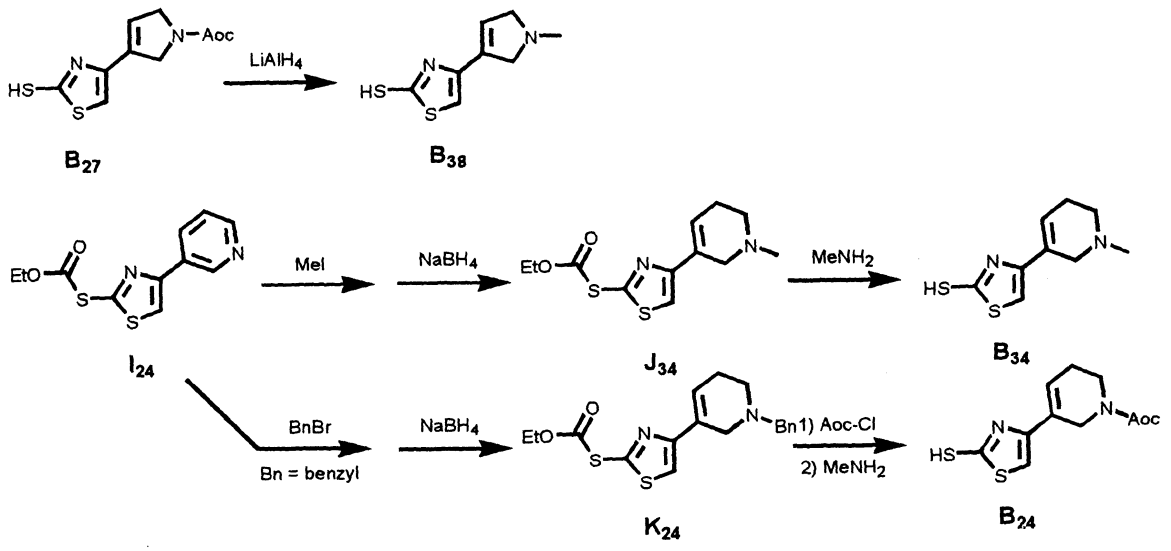


Fig. 9.

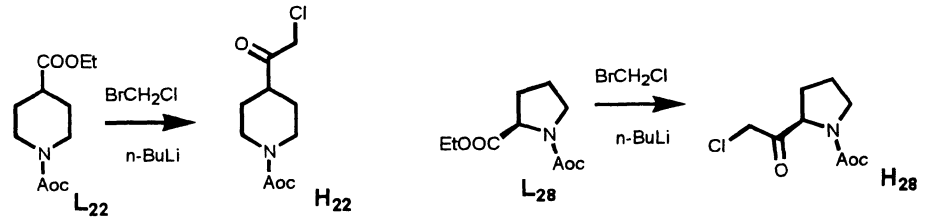


Fig. 10.

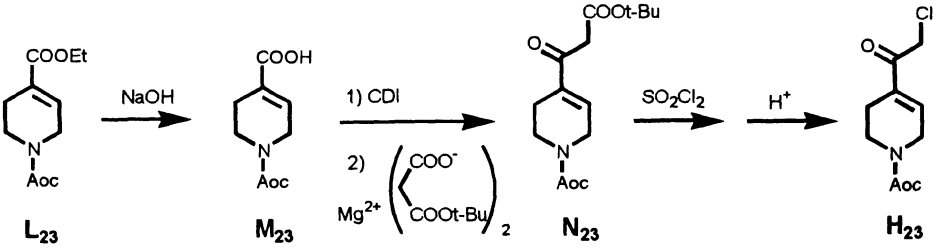
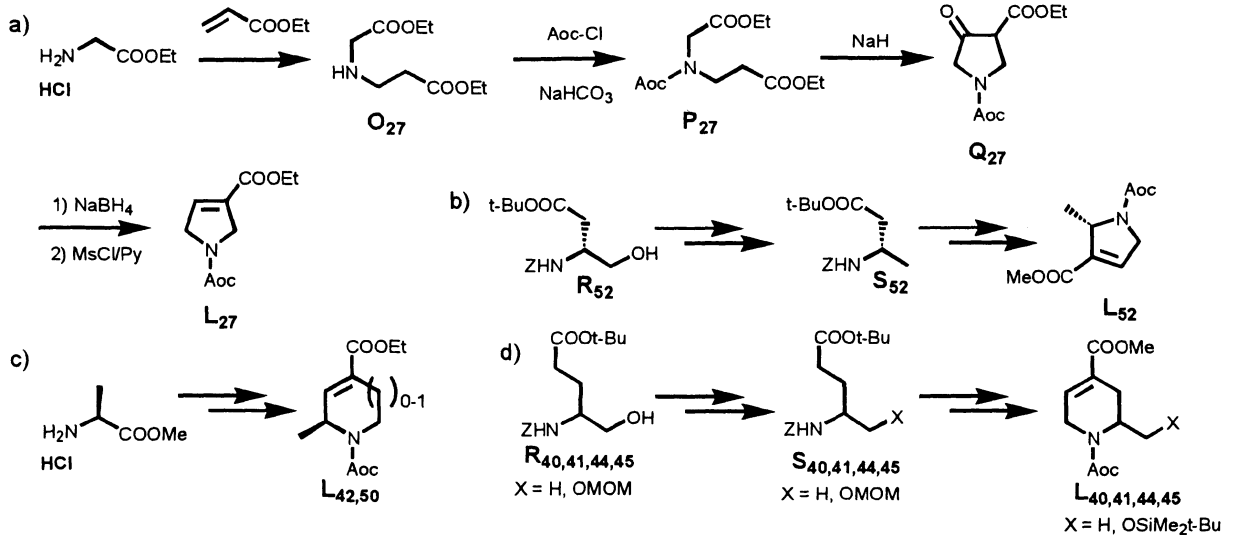


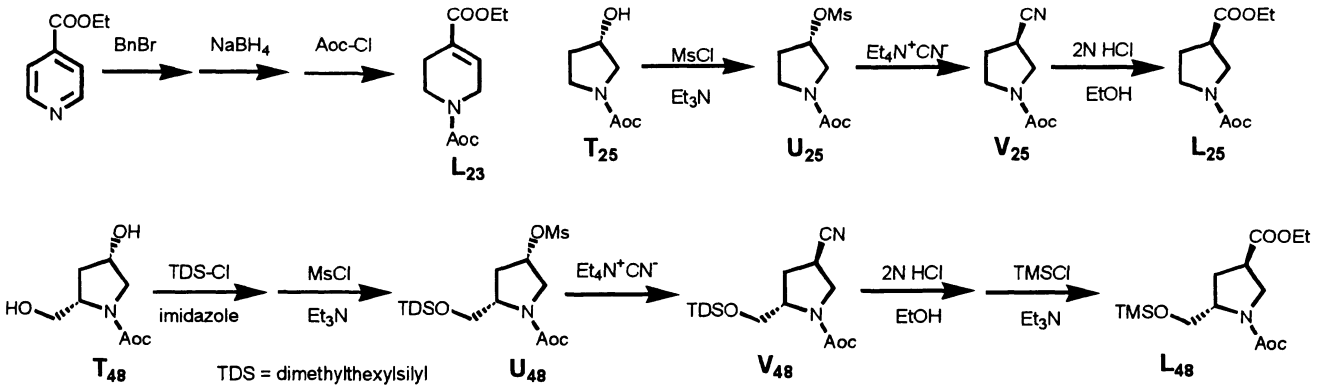
Fig. 11.



The synthesis of $\mathbf{H}_{23}$ was achieved in a stepwise manner from the ester $\mathbf{L}_{23}$ by successive hydrolysis, chain extension by a standard method[28], monochlorination and then acid-catalyzed decarboxylation (Fig. 10).

The majority of the esters L were synthesized from α-amino acid derivatives utilizing the Dieckmann condensation as the key reaction as shown in Fig. 11, except for $\mathbf{L}_{23}$, $\mathbf{L}_{25}$ and $\mathbf{L}_{48,49}$.

Fig. 12.



The ester $\mathbf{L}_{23}$ was prepared from ethyl isonicotinate and pyrrolidine derivatives $\mathbf{L}_{25}$ and $\mathbf{L}_{48,49}$ were prepared in several steps from the pyrrolidinols $\mathbf{T}_{25}$ and $\mathbf{T}_{48,49}$ as shown in Fig. 12.

Biological Results and Discussion

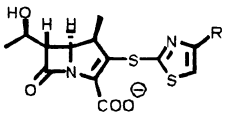
SM-17466 had been designed on the basis of the recognition that the introduction of the 2-mercaptothiazole group at the C-2 position was important for potent anti-MRSA activity. The presence of the cationic moiety in the C-2 side chain effected moderate or low human serum albumin binding and moreover, the relative position of a positive charge in relation to the carbapenem skeleton played an important role in convulsive activity and stability against renal DHP-I rather than anti-MRSA activity[25]. However, because the efficacy against enterococci was not aimed for, by the original design, almost no antibacterial activity data against VREFm, which is essential to design anti-VRE carbapenems, had been determined.

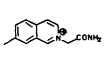
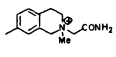
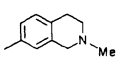
To assess anti-enterococcus potency of a series of 1β-methyl-2-(4-arylthiazol-2-ylthio)carbapenems in this study, we firstly reevaluated several carbapenems synthesized in the earlier work. Table 1 shows the *in vitro* antibacterial activities (MIC; minimum inhibitory concentration, μg/ml) of six carbapenems against key multi-drug resistant Gram-positive pathogens including two vancomycin-susceptible strains *E. faecalis* ATCC 19433 and *E. faecium* ATCC19434, and two clinically isolated *E. faecium* strains VanA E23.8 and VanB E83-10 that exhibited greatly reduced susceptibility to vancomycin and imipenem.

4-Methylthiazole compound (**6**) showed apparently higher antibacterial activity against not only MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE), but also PRSP and the three strains of *E. faecium*, than that of imipenem, suggesting that the introduction of the thiazole ring was effective in providing potent activity against PRSP and VREFm as well as methicillin-resistant staphylococci. Concerning the antienterococcal activities, the increase in the antibacterial activity was remarkably higher against vancomycin-, imipenem-resistant strains of *E. faecium* than against the susceptible strain (16 fold and 4 fold, respectively). In contrast, the MIC against a vancomycin-, imipenem-susceptible *E. faecalis* of **6** decreased 4 fold compared with the MIC of imipenem. The resistance of enterococci to β-lactam antibiotics is considered to be well correlated to the overproduction of low-affinity PBP5 which is a natural component in PBPs of enterococcal species and able to substitute the functions of the susceptible PBPs when these are inhibited by β-lactams[29,30]. Although detailed investigations remain to be carried out, our findings that **6** can inhibit growth of the high-level multi-drug resistant *E. faecium* more effectively, might suggest a significant increase in affinity of this compound for PBP5 of *E. faecium*.

In spite of different anti-MRSA activities, quaternary pyridinium derivatives (SM-17466 and **2**) and the quaternary isoquinolinium derivative (**3**) exhibited MICs against VREFm similar to **6**, but, the introduction of tetrahydroisoquinolinium and quaternary tetrahydro-isoquinolinium groups (**4** and **5**) showed a significant positive impact on both anti-MRSA and VREFm activities. It was also confirmed that the introduction of a cationic

Table 1. *In vitro* antibacterial activity of 2-(4-substituted thiazol-2-ylthio)carbapenems against Gram-positive bacteria.



Compound No.	MIC (μg/ml)[a]							
	1	**2**	**3**	**4**	**5**	**6**		
Organism[b]	R-  SM-17466					—Me	Imipenem	Vancomycin
S. a. 40280[c]	2	2	4	2	1	8	32	2
S. e. MUR275[c]	2	2	4	2	2	8	32	2
S. p. 1/1[d]	<0.125	<0.125	0.125	0.125	0.125	0.125	2	0.25
E. fs. ATCC19433	NT[f]	2	2	1	1	4	1	0.5
E. fm. ATCC19434	0.5	1	0.5	0.25	0.5	1	4	1
E. fm. VanA E23.8[e]	8	8	8	2	2	16	256	256
E. fm. VanB E83-10[e]	8	4	8	4	4	8	128	64

[a] MIC was determined by agar dilution method.
[b] Abbreviations: *S. a. Staphylococcus aureus; S. e., Staphylococcus epidermidis; S. p. , Streptococcus pneumoniae; E. fs., Enterococcus faecalis; E. Fm., Enterococcus faecium*
[c] Methicillin-resistant
[d] Penicillin-resistant
[e] Ampicillin- and vancomycin-resistant
[f] Not tested

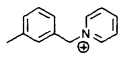
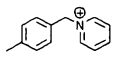
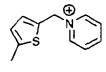
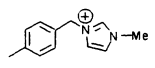
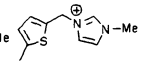
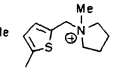
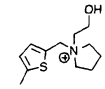
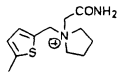
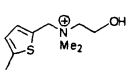
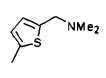
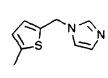
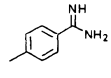
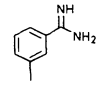
moiety weakened the activity against VREFm in contrast to activity against MRSA. Table 1 also suggests that the position of the positive charge in the C-2 side chain relates to anti-VREFm activity. The nature of the positive-charged aliphatic amine or ammonium might be better for activity than aromatic ammonium as a cationic moiety. On the basis of these findings, we selected type A carbapenems, such as the extended analogues of compounds **3** and **4**, and type B carbapenems as the related aliphatic analogues of compounds **1** and **2** for further SAR studies (Fig. 2).

Table 2 shows the MICs of type A compounds. Most of the 2-arylthiazole derivatives exhibited higher activity than **1** and **2** and comparable to **3** and **4**. Concerning the anti-VREFm activities, it was confirmed that the positional shift of the cationic moiety out of aromatic ring improved activity. But another assumption in the original design was not proven in this series of carbapenems. Type A compounds having aliphatic amine/ammonium (**12**~**17**) as well as type A compounds having aromatic amine/ammonium (**7**~**11**) moieties, exhibited higher anti-VREFm activities than **1** and **2**. The amidino group in compounds **18** and **19** as the cationic moiety also worked equally well for enhancing the anti-VREFm activity. These compounds showed well-balanced *in vitro* antibacterial activity against the Gram-positive bacteria tested, but their water-solubilities were unfortunately very low.

Since the type A compounds seemed promising for further investigations on the basis of their potent antibacterial activity against multi-drug resistant Gram-positive pathogens, we next investigated the neurotoxicity of representative compounds by intraventriculary injection in mice. Neurotoxicity is a major concern of side effect of carbapenem antibiotics. The neurotoxicity of carbapenems, especially the SAR of the C-2 side chain has been extensively studied using meropenem-related derivatives on the above mice model[31,32]. The basicity of the amino group in the C-2 side chain, steric hindrance of the amino group and its distance from carboxyl residue of the carbapenem skeleton, were considered to be important for neurotoxic potential of carbapenems. As we expected, most of the type A compounds (**8**, **9**, **20**, **11**, **21**, **18**) tested in Table 3 exhibited more than threefold lower convulsant activity than imipenem.

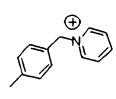
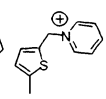
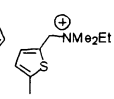
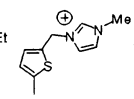
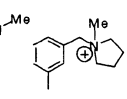
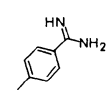
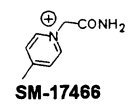
However, these type A compounds showed unexpectedly higher acute toxicity than imipenem when administered intravenously at 250 mg/kg in mice. In contrast to the well studied convulsant activity, so far, no systematic investigation exists with regard to the acute toxicity of

Table 2. *In vitro* antibacterial activity of 2-(4-arylthiazol-2-ylthio)carbapenems against Gram-positive bacteria [Type A].

Compound No.	MIC (μg/ml)[a]						
	7	**8**	**9**	**10**	**11**	**12**	**13**
Organism[b] R-							
S. a. 40280[c]	2	4	2	2	2	2	2
S. e. MUR275[c]	2	4	2	4	2	1	2
S. p. 1/1[d]	0.125	0.125	<0.125	0.125	0.125	0.125	<0.125
E. fs. ATCC19433	2	1	2	2	2	1	2
E. fm. ATCC19434	0.5	0.25	0.25	<0.5	0.25	0.25	0.25
E. fm. VanA E23.8[e]	4	2	2	4	4	4	4
E. fm. VanB E83-10[e]	4	4	2	4	4	4	4
Compound No.	**14**	**15**	**16**	**17**	**18**	**19**	
Organism[b] R-							
S. a. 40280[c]	2	2	2	1	1	2	
S. e. MUR275[c]	2	2	2	1	1	1	
S. p. 1/1[d]	0.125	0.5	0.5	0.125	0.125	0.125	
E. fs. ATCC19433	1	2	2	1	1	0.5	
E. fm. ATCC19434	0.5	0.5	0.25	0.5	0.25	0.125	
E. fm. VanA E23.8[e]	4	4	2	4	2	2	
E. fm. VanB E83-10[e]	4	8	4	4	4	2	

[a] MIC was determined by agar dilution method.
[b] Abbreviations: *S. a. Staphylococcus aureus; S. e., Staphylococcus epidermidis; S. p., Streptococcus pneumoniae; E. fs., Enterococcus faecalis; E. Fm., Enterococcus faecium*
[c] Methicillin-resistant
[d] Penicillin-resistant
[e] Ampicillin- and vancomycin-resistant

Table 3. Toxicological evaluation of selected compounds [Type A].

Compound No.	**8**	**9**	**20**	**11**	**21**	**18**	**1**	
R-							 SM-17466	imipenem
Convulsant activity in mice (ED_{50} ratio to IPM)	5.47	3.32	3.32	3.16	2.84	NT[a]	4.1	1.00
Acute toxicity in mice (death at 250mg/kg)	+	+	+	+	+	-	-	-

[a] Not tested due to low solubility.

carbapenems. Further work on type A compounds was abandoned because it was considered difficult to reduce the acute toxic potential of this series of carbapenems in a rational way.

Table 4 shows MICs of the type B compounds. In this series of carbapenems, the hypothesis according to which an aliphatic amine/ammonium moiety was preferred to an aromatic one with respect to anti-VREFm activity was

Table 4. *In vitro* antibacterial activity of 2-(4-heterocyclyl-thiazol-2-ylthio)carbapenems against Gram-positive bacteria [Type B] Part 1.

Compound No.		MIC (μg/ml)[a]							
		22	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Organism[b]	R-						 SM-197436		
S. a. 40280[c]		2	1	2	2	2	2	8	8
S. e. MUR275[c]		2	2	2	2	2	2	4	4
S. p. 1/1[d]		NT[f]	0.125	0.25	0.25	0.25	0.25	0.25	0.25
E. fs. ATCC19433		2	1	1	2	1	1	1	2
E. fm. ATCC19434		0.25	0.25	0.5	1	0.5	0.5	0.5	0.5
E. fm. VanA E23.8[e]		4	2	4	8	4	4	8	8
E. fm. VanB E83-10[e]		2	2	4	4	4	4	8	8
Compound No.		**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**
Organism[b]	R-								
S. a. 40280[c]		1	2	2	4	2	4	4	1
S. e. MUR275[c]		1	2	4	4	2	4	4	2
S. p. 1/1[d]		0.125	0.25	0.25	0.25	0.125	0.25	0.25	0.125
E. fs. ATCC19433		1	1	2	2	2	1	2	NT
E. fm. ATCC19434		0.5	0.5	0.25	1	0.5	0.5	0.5	0.5
E. fm. VanA E23.8[e]		4	4	4	4	2	4	4	4
E. fm. VanB E83-10[e]		2	4	4	4	4	4	4	4

[a] MIC was determined by agar dilution method.
[b] Abbreviations: *S. a. Staphylococcus aureus; S. e., Staphylococcus epidermidis; S. p., Streptococcus pneumoniae; E. fs., Enterococcus faecalis; E. Fm., Enterococcus faecium*
[c] Methicillin-resistant
[d] Penicillin-resistant
[e] Ampicillin- and vancomycin-resistant
[f] Not tested

proven. Aliphatic 6-member ring derivatives (**22**~**24**) retained high activity against MRSA and MRSE, and exhibited higher anti-VREFm activity than compounds **1** and **2**. Most of the aliphatic 5-member ring derivatives (**25**~**27** and **36**~**39**) also showed enhanced anti-VREFm activities.

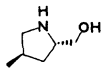
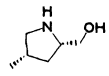
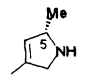
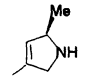
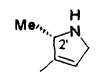
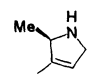
It is difficult to discern meaningful SAR of anti-VREFm activity of the type B compounds in Table 4, because of the lack of significant differences. However, the following three observations can be made. First, there is a minimal distance of the cationic center to the thiazole ring required for potent anti-VREFm activity, since lower activity was observed for compounds **28** and **29** with shorter distance in comparison with the other, more extended analogs. Furthermore the introduction of a double bond-conjugated to the thiazole ring- into the piperidine/pyrrolidine ring (**23** and **27**), which influences both the position of the cationic center, and the basicity, due to inductive effects, showed no significant effects on the anti-VREFm activity. Finally the effect of introduction of *N*-substituents (**30**~**39**) on the anti-VREFm activity is slight and smaller than that on the anti-MRSA activity.

The above findings, which demonstrate that the anti-VREFm activities in this series of derivatives are not significantly changed by minor structural modifications and small changes of steric hindrance around the cationic center, prompted us to introduce a substituent on the carbon neighboring the nitrogen atom in the piperidine and pyrrolidine rings in order to improve the anti-bacterial activity against MRSA, the safety and hopefully physicochemical properties.

As expected, all compounds in which substituents were introduced on the carbon atom neighboring the nitrogen atom in Table 5 retained potent antibacterial activities against VREFm. In addition, their activities against the other bacterial strains tested was not significantly

Table 5. *In vitro* antibacterial activity of 2-(4-heterocyclyl-thiazol-2-ylthio)carbapenems against Gram-positive bacteria [Type B] Part 2.

Organism[b]	Compound No.	R-	MIC (μg/ml)[a]							
			40	41	42	43	44	45	46	47
				 SM-232724			 SM-232721			
S. a. 40280[c]			2	1	2	2	2	2	2	1
S. e. MUR275[c]			1	1	2	2	2	2	4	2
S. p. 1/1[d]			0.125	0.06	0.125	0.06	0.125	NT[f]	NT	NT
E. fs. ATCC19433			1	0.5	1	1	1	1	1	1
E. fm. ATCC19434			< 0.25	< 0.25	< 0.25	< 0.25	< 0.25	0.5	0.25	<0.125
E. fm. VanA E23.8[e]			2	2	4	4	2	4	4	2
E. fm. VanB E83-10[e]			2	2	2	4	4	4	4	2

Organism[b]	Compound No.	R-	48	49	50	51	52	53
								
S. a. 40280[c]			4	2	2	2	2	1
S. e. MUR275[c]			4	2	2	2	2	2
S. p. 1/1[d]			0.25	0.25	0.06	NT	0.06	0.125
E. fs. ATCC19433			2	2	1	1	0.5	1
E. fm. ATCC19434			0.5	0.5	< 0.25	< 0.25	< 0.25	< 0.25
E. fm. VanA E23.8[e]			8	4	4	8	2	4
E. fm. VanB E83-10[e]			8	4	4	4	2	4

[a] MIC was determined by agar dilution method.
[b] Abbreviations: *S. a. Staphylococcus aureus; S. e., Staphylococcus epidermidis; S. p. , Streptococcus pneumoniae; E. fs., Enterococcus faecalis; E. Fm., Enterococcus faecium*
[c] Methicillin-resistant
[d] Penicillin-resistant
[e] Ampicillin- and vancomycin-resistant
[f] Not tested

Table 6. Ring-substituent effects on neurotoxicity in selected compounds from type B series.

Compound No.	23	42	43	41	44	45	30	47	imipenem
Convulsant activity in mice (ED50 ratio to IPM)	1.68	1.89	1.97	3.34	3.05	8.87	1.73	0.91	1.00

influenced by the introduction of methyl, hydroxymethyl *etc.* Although a small change of the MIC against individual Gram-positive bacterium was observed, a clear SAR with resect to antibacterial activity could not be recognized, so far.

On the other hand, a significant substitution effect on the convulsive activity in mice was unexpectedly observed. Unsubstituted tetrahydropyridine compound (**23**) exhibited slightly lower convulsant activity than imipenem. The introduction of a methyl group at C-2′ (**41**) further reduced convulsant activity, although there was no meaningful effect of a methyl group at C-6′ in tetrahydropyridine ring (**42**, **43**) as well as in the case of the introduction of the methyl group on nitrogen (**30**). A similar effect was observed by the introduction of a hydroxymethyl group in both stereoisomers (**44**, **45**). There is significant difference in the substitution effect between **44** and **45**. The convulsant activity of **45** was more than 8-fold weaker than that of imipenem. In contrast to substitution on the carbon neighboring the nitrogen, *N*-methyl substitution in compound **47** canceled out the reduction of the neurotoxic potential by the introduction of the methyl group at C-2′. Although further SAR investigation will be necessary to solve fine substitution effects, these results suggest that

Table 7. Biological properties of the selected compounds.

Compound No.	27	44	41	imipenem	meropenem
Acute toxicity in mice (500mg/kg, n=3)	0/3	NT[c]	0/3	0/3	0/3
DHP-I susceptibility[a]	0.77	1.05	0.75	1.00	0.29
Plasma Protein Binding (%)[b]	28	31	52	ND[d]	9

[a] Rate of hydrolysis by human recombinant DHP-I relative to imipenem
[b] Binding for human plasma at 30μg/ml
[c] Not tested
[d] Not detected

improvement of the convulsant activity without reducing antibacterial activity can be achieved by minor modifications in the piperidine and pyrrolidine rings of type B compounds. The detailed SAR of this type of carbapenems on convulsant activity will be continued.

To clarify the potential of the type B compounds as a series worthy of further investigation, **27**, **44** and **41**, which were assigned as SM-197436, SM-232721 and SM-232724, respectively, were selected for further evaluation of their acute toxicity in mice, stability against human DHP-I, binding affinity for human plasma protein, and antibacterial spectrum against Gram-positive and Gram-negative bacterial strains. In contrast to type A compounds, presented in Table 3, SM-197436 and SM-232724 did not induce any significant toxic symptoms when they were intravenously injected even at 500 mg/kg in mice. Three carbapenems exhibited comparable or higher stability against hydrolysis by human renal DHP-I than imipenem. They showed a slightly higher binding affinity for human plasma protein than imipenem, which was expected, due to the lypophilic properties of the C-2 side chain.

Table 8 shows the antibacterial spectrum of SM-197436, SM-232721 and SM-232724 in comparison with imipenem, meropenem, vancomycin and linezolid. Three novel carbapenems exhibited broad and potent activity against various Gram-positive bacterial strains including MRSA and VREFm with MICs superior to the comparative agents. In terms of anti-Gram-negative activity, these carbapenems, especially SM-197436 show antibacterial activities against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp., *Haemophilus influenzae*, *Moraxella catarrhalis* and *Neisseria* spp., comparable or superior to imipenem, although significant reduction of the MICs was observed against *Enterobacter* spp., *Citrobacter freundii*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*.

Their antibacterial spectra against clinically important multi-drug resistant Gram-positive bacteria and Gram-negative bacteria such as *E. coli*, *K. pneumoniae*, *H. influenzae* and *M. catarrhalis etc.* suggest their clinical usefulness, especially for treatment of serious respiratory infections in nosocomial settings.

In conclusion, a series of carbapenems, with potent activity against highly resistant pathogens such as MRSA and *E. faecium* including VREFm, was discovered by successive structural modifications of SM-17466 and its derivatives. Some of them exhibit attractive profiles with respect to their antibacterial spectrum and safety in the preliminary evaluations. SM-197436, SM-232721 and SM-232724 were advanced to in depth microbiological and pharmacological characterization. Further chemical modifications of 1β-methyl-2-(thiazol-2-ylthio)carbapenem are also underway with the aim to identify carbapenems having even more improved profiles as potential drug candidates.

Experimental

General Analytical Methods

Optical rotations were determined on a Jasco DIP-370 polarimeter. MS spectra were recorded in positive Electron Spray mode (ESP) on an Applied Biosystems API 300 or Waters ZQ2000 instrument, or in Electron Impact mode (EI) on a Finnigan MAT SSQ 7000 instrument. TSP stands for thermal spray. IR spectra were recorded as KBr disc (KBr), as film (FLM), in Nujol (NJL) or under the IR-Microscope (MIR) using on a Perkin Elmer 1600 FTIR,

Table 8. Antibacterial spectrum against standard strains.

Strain No.		MIC (μg/ml)[a]						
		27 (SM-197436)	44 (SM-232721)	41 (SM-232724)	IPM	MEM	VAN	LNZ
S. aureus	ATCC29213	≦0.008	0.016	≦0.008	0.016	0.063	0.5	2
S. aureus[b]	ATCC33591	0.5	1	0.5	16	16	1	1
S. aureus[b]	SP-7928	2	2	1	64	32	0.5	2
S. epidermidis	ATCC14990	≦0.008	0.016	≦0.008	0.016	0.063	1	0.5
S. pyogenes	ATCC12344	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008	0.25	1
S. pyogenes	Cook	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008	0.25	1
S. agalactiae	ATCC13813	≦0.008	0.016	≦0.008	0.016	0.031	0.25	1
S. pneumoniae	ATCC10015	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008	0.25	0.5
S. pneumoniae	ATCC49619	≦0.008	0.016	0.016	0.031	0.063	0.125	1
E. faecalis	ATCC19433	2	2	1	1	8	0.5	4
E. faecalis[c]	ATCC51575	2	2	2	2	8	>128	2
E. faecium	ATCC19434	0.25	0.5	0.25	4	16	0.5	2
E. faecium[c]	ATCC51559	4	4	4	>128	>128	>128	1
E. avium	ATCC14025	0.125	0.125	0.125	0.5	4	0.5	1
M. luteus	ATCC9341	≦0.008	≦0.008	≦0.008	0.031	0.125	0.5	0.5
B. subtilis	ATCC6633	≦0.008	≦0.008	≦0.008	0.016	0.031	0.125	0.5
L. monocytogenes	ATCC15313	≦0.008	0.016	0.016	0.031	0.031	NT[d]	1
E. coli	ATCC25922	0.125	0.5	0.5	0.125	0.016	>128	>128
E. coli	ML1410	0.125	0.5	0.5	0.5	0.016	>128	>128
E. coli	ML1410 RP4	0.5	1	1	0.5	0.016	>128	>128
K. pneumoniae	ATCC10031	0.031	0.125	0.031	0.125	0.016	>128	16
P. mirabiris	GN2425	0.125	0.25	0.5	0.5	0.031	>128	128
P. vulgaris	GN7919	0.5	2	2	1	0.063	>128	>128
E. cloacae	GN7471	4	16	8	0.125	0.031	>128	>128
E. aerogenes	ATCC13048	8	16	16	0.25	0.031	>128	>128
C. freundii	GN346	4	16	16	0.5	0.063	>128	64
S. marcescens	X100	0.5	2	2	0.25	0.031	>128	128
P. aeruginosa	ATCC27853	8	16	16	2	0.25	>128	>128
P. aeruginosa	TL-2666	8	16	16	2	1	>128	>128
P. aeruginosa	TL-2667	16	64	32	16	4	>128	>128
S. maltophilia	IID1275	>128	>128	>128	>128	>128	>128	>128
H. influenzae	ATCC49766	0.016	0.031	0.016	1	0.063	>128	8
H. influenzae	ATCC33533	0.016	0.031	0.016	2	0.063	NT	8
M. catarrharis	ATCC25238	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008	128	4
M. catarrharis	ATCC8176	≦0.008	≦0.008	≦0.008	≦0.008	≦0.008	64	8
N. gonorrhoeae	ATCC49226	≦0.008	0.031	0.016	0.125	0.016	NT	4
N. gonorrhoeae	SP-10017	≦0.008	≦0.008	≦0.008	0.016	≦0.008	NT	4
N. meningitidis	ATCC13077	≦0.008	≦0.008	≦0.008	0.063	≦0.008	>128	8

Abbreviations: IPM, imipenem; MEM, meropenem; VAN, vancomycin; LNZ, linezolid

[a] MIC was determined by agar dilution method.

[b] Methicillin-resistant

[c] Vancomycin-resistant

[d] Not tested

Nicolet FT-IR SX 20, Magna System 550 or 860 Instruments. NMR spectra were recorded on JEOL 270, Bruker 250, 300 or 400 MHz spectrometers as indicated.

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-({4-[3-(Hydroxymethyl)-phenyl]-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 (**D**$_7$)

To a suspension of [3-(2-mercapto-1,3-thiazol-4-yl)phenyl]methanol (**B**$_7$) (1.0 g, 4.5 mmol) in THF (8.0 ml) was added 60% sodium hydride (0.18 g, 4.5 mmol) at 0°C. After 10 minutes, the phosphate (**A**$_1$) (30% in acetonitrile, 9.95 g, 4.5 mmol) was added. After 2 days, the reaction mixture was filtered, and residual solid was washed with cold THF three times. The filtrate was successively washed with satd sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated *in vacuo*. A residual oil (3.67 g) was purified by chromatography on silica gel to give **D**$_7$ (1.75 g, 60%): MS (ESP) *m/z* 640 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (9H, s), 1.01 (3H, d, *J*=7.3 Hz), 1.11 (1H, d, *J*=6.2 Hz), 3.16 (1H, dd, *J*=2.7, 5.7 Hz), 3.47 (1H, dd, *J*=2.6, 9.9 Hz), 4.10~4.18 (2H, m), 4.66 (2H, s), 5.20 (1H, d, *J*=13.7 Hz), 5.40 (1H, d, *J*=13.7 Hz), 7.27 (1H, br d, *J*=7.3 Hz), 7.34 (1H, t, *J*=7.5 Hz), 7.49 (1H, s), 7.56 (2H, d, *J*=9.0 Hz), 7.71 (1H, d, *J*=7.7 Hz), 7.80 (1H, br s), 8.11 (2H, d, *J*=8.8 Hz).

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

To a solution of **D**$_7$ (227 mg, 0.35 mmol) in dichloromethane (7 ml) were added pyridine (112 μl, 1.4 mmol) and trifluoromethanesulfonic anhydride (117 μl, 0.69 mmol) at −70°C. After 1 minute, the mixture was warmed to 0°C. After 40 minutes, satd sodium bicarbonate solution was added to the reaction mixture. EtOAc was added, and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with chloroform and EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residual solid was dissolved in THF (30 ml) and 0.05 M phosphate buffer (pH 7.0, 30 ml), and 10% Pd-C (400 mg) was added. The mixture was stirred under hydrogen atmosphere. After 1.5 hours, the reaction mixture was filtered. Dichloromethane (50 ml) was added to the filtrate, and the mixture was separated into aqueous layer and an organic layer. The aqueous layer was washed with dichloromethane (20 ml). The residual organic solvents in aqueous layer were removed under high vacuum. The aqueous solution was purified by chromatography on MCI gel (CHP-20P) with 3%~12% THF in water. The fraction were combined and lyophilized to give **7** (69.8 mg): IR (KBr) cm^{-1} 3512, 3288, 1757, 1594, 1385.; ^{1}H NMR (300 MHz, D_2O) δ 0.85 (3H, d, *J*=7.3 Hz), 1.05 (3H, d, *J*=6.4 Hz), 3.03 (1H, dd, *J*=7.3, 9.4 Hz), 3.26 (1H, q, *J*=2.7 Hz), 3.97~4.07 (2H, m), 5.72 (2H, s), 7.33 (1H, t, *J*=7.7 Hz), 7.41 (1H, t, *J*=7.4 Hz), 7.70 (1H, d, *J*=7.7 Hz), 7.71 (2H, s), 7.91 (2H, t, *J*=7.4 Hz), 8.39 (1H, d, *J*=7.7 Hz), 8.80 (2H, d, *J*=7.4 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-({4-[4-(Hydroxymethyl)-phenyl]-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 (**D**$_8$)

MS (ESP) *m/z* 640 (M+H); IR (KBr) cm^{-1} 3400, 1770, 1591, 1520, 1346.; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.11 (9H, S), 1.13 (3H, d, *J*=7.3 Hz), 1.27 (3H, d, *J*=6.3 Hz), 3.26 (1H, dd, *J*=3.0, 5.6 Hz), 3.60 (1H, m), 4.25 (2H, m), 4.74 (2H, br s), 5.31 (1H, d, *J*=13.9 Hz), 5.50 (1H, d, *J*=13.9 Hz), 7.44 (2H, d, *J*=8.3 Hz), 7.56 (1H, s), 7.68 (2H, d, *J*=8.6 Hz), 7.89 (2H, d, *J*=8.3 Hz), 8.22 (2H, d, *J*=8.6 Hz).

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

UV nm (H_2O) 318(sh), 279(sh), 268(sh), 261.; IR (KBr) cm^{-1} 3406, 1758, 1599, 1387.; ^{1}H NMR (270 MHz, D_2O) δ 0.94 (3H, d, *J*=7.3 Hz), 1.19 (3H, d, *J*=6.3 Hz), 3.14 (1H, m), 3.38 (1H, dd, *J*=2.6, 5.6 Hz), 4.11 (1H, dd, *J*=2.6, 9.6 Hz), 4.18 (1H, m), 5.86 (2H, s), 7.53 (2H, d, *J*=8.3 Hz), 7.79 (2H, d, *J*=8.3 Hz), 7.82 (1H, s), 8.09 (2H, t, *J*=6.9 Hz), 8.56 (1H, t, *J*=7.9 Hz), 8.98 (2H, d, *J*=6.6 Hz).

[5-(2-Mercapto-1,3-thiazol-4-yl)thien-2-yl]methanol (**B**$_9$)

To a solution of 5-(2-mercapto-1,3-thiazol-4-yl)thiophene-2-carboxylic acid (10.0 g, 41 mmol) in THF (70 ml) and DMF (7 ml) were added triethylamine (9.15 g, 90 mmol) and ethyl chloroformate (9.81 g, 90 mmol) at −78°C. After stirring at the same temperature for 20 minutes, the mixture was slowly warmed to −20°C. To this mixture, sodium borohydride (6.22 g, 164 mmol) in water (12 ml) was added and stirred at 0°C for 1 hour. After the mixture was neutralized with 2 N hydrochloric acid, water and EtOAc were added and separated into an aqueous layer and an organic layer. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give *O*-ethyl *S*-{4-[5-(hydroxymethyl)thien-2-yl]-1,3-thiazol-

2-yl} thiocarbonate (6.52 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, t, J=7.1 Hz), 4.41 (2H, q, J=7.1 Hz), 4.82 (2H, s), 6.96 (1H, d, J=3.7 Hz), 7.32 (1H, d, J=3.7 Hz), 7.48 (1H, s).

To a solution of the thiocarbonate (1.0 g, 3.3 mmol) in MeOH (20 ml) was added methylamine (30% in EtOH, 1.72 g, 17 mmol) at 0°C. After stirring at the same temperature for 2 hours, the mixture was concentrated *in vacuo*. The residual solid was washed with MeOH to give **B_9** (0.76 g) quantitatively: MS (ESP) *m/z* 230 (M+H); ^{1}H NMR (300 MHz, CD_3OD) δ 4.72 (2H, s), 6.84 (1H, s), 6.94 (1H, d, J=3.7 Hz), 7.25 (1H, d, J=3.7 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-({4-[5-(Hydroxymethyl)thien-2-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 (**D_9**)

MS (ESP) *m/z* 646 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.13 (3H, d, J=7.2 Hz), 1.23 (1H, d, J=5.9 Hz), 2.77 (1H, dd, J=5.6, 12.6 Hz), 3.28 (1H, dd, J=2.5, 5.4 Hz), 3.59~3.70 (1H, m), 4.20~4.31 (2H, m), 4.84 (2H, s), 5.31 (1H, d, J=13.7 Hz), 5.51 (1H, d, J=13.7 Hz), 6.98 (1H, br d, J=3.7 Hz), 7.33 (1H, br d, J=3.7 Hz), 7.39 (1H, s), 7.68 (1H, d, J=8.6 Hz), 8.23 (1H, d, J=8.6 Hz).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({4-[5-(pyridinium-1-ylmethyl)thien-2-yl]-1,3-thiazol-2-yl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**9**)

IR (KBr) cm^{-1} 3386, 1757, 1603, 1382, 1278.; ^{1}H NMR (300 MHz, D_2O) δ 0.81 (3H, d, J=6.8 Hz), 1.11 (3H, d, J=6.2 Hz), 2.96~3.05 (1H, m), 3.28 (1H, dd, J=2.4, 5.3 Hz), 3.97~4.02 (1H, m), 4.05~4.13 (1H, m), 5.96 (2H, s), 7.22~7.30 (2H, m), 7.55 (1H, s), 8.02 (2H, t, J=7.9 Hz), 8.49 (1H, t, J=7.9 Hz), 8.94 (2H, d, J=5.7 Hz).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[(4-{4-[(1-methyl-1*H*-imidazol-3-ium-3-yl)methyl]phenyl}-1,3-thiazol-2-yl)thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**10**)

UV nm (H_2O) 315(sh), 266.; IR (KBr) cm^{-1} 3423, 1751, 1653, 1614, 1394.; ^{1}H NMR (270 MHz, D_2O) δ 0.90 (3H, d, J=7.3 Hz), 1.17 (3H, d, J=6.3 Hz), 3.09 (1H, m), 3.30 (1H, dd, J=2.6, 5.6 Hz), 3.89 (3H, s), 4.04 (1H, dd, J=2.6, 9.6 Hz), 4.15 (1H, m), 5.51 (2H, s), 7.43 (2H, d, J=8.3 Hz), 7.45 (1H, br s), 7.73 (2H, d, J=8.3 Hz), 7.75 (1H, s), 8.86 (1H, br s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[(4-{5-[(1-methyl-1*H*-imidazol-3-ium-3-yl)methyl]thien-2-yl}-1,3-thiazol-2-yl)thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**11**)

IR (KBr) cm^{-1} 3375, 1760, 1603, 1454, 1380, 1277.; ^{1}H NMR (300 MHz, D_2O) δ 0.78 (3H, d, J=7.1 Hz), 1.03 (3H, d, J=6.2 Hz), 3.09~3.19 (1H, m), 3.23~3.25 (1H, m), 3.73 (3H, s), 3.97~4.04 (2H, m), 5.45 (2H, s), 7.10 (1H, d, J=3.5 Hz), 7.22 (1H, d, J=3.5 Hz), 7.31 (1H, d, J=1.7Hz s), 7.40 (1H, d, J=1.7Hz s), 7.60 (1H, s), 8.69 (1H, br s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[(4-{5-[(1-methylpyrrolidinium-1-yl)methyl]thien-2-yl}-1,3-thiazol-2-yl)thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**12**)

IR (KBr) cm^{-1} 3424, 1759, 1602, 1386, 1277.; ^{1}H NMR (300 MHz, D_2O) δ 0.83 (3H, d, J=7.1 Hz), 1.05 (3H, d, J=6.2 Hz), 2.10 (4H, br s), 2.91 (3H, s), 3.03~3.13 (1H, m), 3.25 (1H, dd, J=2.8, 5.7 Hz), 3.32~3.39 (2H, m), 3.47~3.56 (2H, m), 3.98~4.07 (2H, m), 7.19 (1H, d, J=3.8 Hz), 7.27 (1H, d, J=3.8 Hz), 7.62 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-{[4-(5-{[1-(2-hydroxyethyl)pyrrolidinium-1-yl]methyl}thien-2-yl)-1,3-thiazol-2-yl]thio}-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**13**)

IR (KBr) cm^{-1} 3321, 2968, 1761, 1603, 1454, 1381.; ^{1}H NMR (300 MHz, D_2O) δ 0.93 (3H, d, J=7.1 Hz), 1.09 (3H d, J=6.1 Hz), 2.09 (4H, br s), 3.13~3.22 (2H, m), 3.30~3.65 (6H, m), 3.96~4.02 (2H, m), 4.04~4.12 (2H, m), 4.72 (2H, s), 7.24 (1H, d, J=3.5 Hz), 7.37 (1H, d, J=3.5 Hz), 7.73 (1H, s).

4-[5-(Pyrrolidin-1-ylmethyl)thien-2-yl]-1,3-thiazole-2-thiol (**B_{14}**)

To a solution of 5-(2-mercapto-1,3-thiazol-4-yl)thiophene-2-carboxylic acid (10.0 g, 41 mmol) in THF (70 ml) and DMF (7 ml) were added triethylamine (9.15 g, 90 mmol) and ethyl chloroformate (9.81 g, 90 mmol) at −60°C. After stirring at −40°C for 1 hour, the mixture was cooled to −60°C. To this mixture, pyrrolidine (6.42 g, 90 mmol) was added at −60°C and then slowly warmed room temperature. To this mixture, 2 N hydrochloric acid was added and resulting precipitate was filtered and washed with MeOH to give 4-[5-(pyrrolidin-1-ylcarbonyl)thien-2-yl]-1,3-thiazole-2-thiol (9.57 g, 79%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.78~2.00 (4H, m), 3.42~3.53 (2H, m), 3.71~3.76 (2H, m), 7.33 (1H, s), 7.58 (1H, d, J=4.0 Hz), 7.59 (1H, d, J=4.0 Hz), 13.82 (1H, br s).

To a mixture of lithium aluminum hydride (0.58 g, 15

mmol) in THF (40 ml) was added solution of the amide (3.0 g, 10 mmol) in THF (20 ml) at 0°C. After stirring for 10 minutes. MeOH was added and the resulting mixture was purified by chromatography on silica gel to give **B_{14}** (3.43 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66~1.73 (4H, m), 2.58~2.61 (4H, m), 3.86 (2H, s), 6.90 (1H, d, J=3.7 Hz), 6.91 (1H, s), 7.28 (1H, d, J=3.7 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({4-[5-(pyrrolidin-1-ylmethyl)thien-2-yl]-1,3-thiazol-2-yl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**D_{14}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, d, J=7.3 Hz), 1.33 (1H, d, J=6.2 Hz), 1.80~1.84 (4H, m), 2.60~2.66 (4H, m), 3.30 (1H, dd, J=2.9, 6.6 Hz), 3.61~3.72 (1H, m), 3.85 (2H, s), 4.20~4.35 (2H, m), 5.30 (1H, d, J=13.5 Hz), 5.53 (1H, d, J=13.7 Hz), 6.90 (1H, d, J=3.5 Hz), 7.31 (1H, d, J=3.5 Hz), 7.36 (1H, s), 7.67 (1H, d, J=8.4 Hz), 8.23 (1H, d, J=8.6 Hz).

(4*R*,5*S*,6*S*)-3-{[4-(5-{[1-(2-Amino-2-oxoethyl)pyrrolidinium-1-yl]methyl}thien-2-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 (**14**)

IR (KBr) cm^{-1} 3398, 1758, 1694, 1600, 1453, 1388.; ^{1}H NMR (300 MHz, D_2O) δ 0.93 (3H, d, J=7.1 Hz), 1.09 (3H d, J=6.4 Hz), 2.08~2.13 (4H, m), 3.14~3.20 (1H, m), 3.32 (1H, dd, J=2.8, 5.7 Hz), 3.56~3.63 (2H, m), 3.73~3.80 (2H, m), 3.92 (2H, s), 4.05~4.10 (2H, m), 4.89 (2H, s), 7.20 (1H, d, J=3.8 Hz), 7.38 (1H, d, J=3.8 Hz), 7.75 (1H, s).

2-[{[5-(2-Mercapto-1,3-thiazol-4-yl)thien-2-yl]methyl}-(methyl)amino]ethanol (**B_{15}**)

To a solution of 5-(2-mercapto-1,3-thiazol-4-yl)thiophene-2-carboxylic acid (23.21 g, 95 mmol) in THF (60 ml) and DMF (70 ml) was added triethylamine (27 ml, 191 mmol) at 0°C. After 15 minutes, *p*-methoxybenzyl chloride (13 ml, 95 mmol) was added. After 35 minutes, the reaction mixture was warmed to room temperature, and the mixture was stirred overnight. 4 N hydrochloric acid was added, and the insoluble materials were filtered off. The filtrate was washed with water several times, and concentrated *in vacuo* to give 5-{2-[(4-methoxybenzyl)thio]-1,3-thiazol-4-yl}-thiophene-2-carboxylic acid (33.06 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (3H, s), 4.47 (2H, s), 6.87 (2H, d, J=8.8 Hz), 7.38 (2H, d, J=8.8 Hz), 7.59 (1H, d, J=3.8 Hz), 7.69 (1H, d, J=3.8 Hz), 8.08 (1H, s).

To a suspension of the carboxylic acid (20.0 g, 55 mmol) and sarcosine ethyl ester hydrochloride (8.44 g, 55 mmol) in chloroform (110 ml) was added triethylamine (7.7 ml, 55 mmol) at −20°C. After 20 minutes, 1,3-dicyclohexylcarbodiimide (11.4 g, 55 mmol) in chloroform (30 ml) was added. After 10 minutes, the mixture was warmed to 0°C. After 1 hour, the mixture was warmed to room temperature, and then stirred overnight. The reaction mixture was filtered through a pad of celite, and filtrate was concentrated *in vacuo*. Water, 1 N hydrochloric acid, brine, EtOAc, and THF were added and the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with EtOAc and THF twice. The organic layer was washed successively with satd sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated *in vacuo* to give ethyl *N*-[(5-{2-[(4-methoxybenzyl)thio]-1,3-thiazol-4-yl}thien-2-yl)carbonyl]-*N*-methylglycinate (26.4 g) quantitatively: MS (ESP) *m/z* 463 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, t, J=7.1 Hz), 3.34 (3H, s), 3.79 (3H, s), 4.25 (2H, q, J=7.1 Hz), 4.28 (2H, s), 4.45 (2H, s), 6.85 (2H, d, J=8.8 Hz), 7.27 (1H, d, J=3.3 Hz), 7.33~7.37 (4H, m).

The amide (26.38 g, 57 mmol) in THF (100 ml) was added dropwise to a suspension of lithium aluminum hydride (6.5 g, 171 mmol) in THF (100 ml) at room temperature. The mixture was stirred for 1 hour. 10% sodium hydroxide was added to the reaction mixture at 0°C. The mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give 2-[[(5-{2-[(4-methoxybenzyl)thio]-1,3-thiazol-4-yl}thien-2-yl)methyl]-(methyl)amino]ethanol (10.49 g, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, s), 2.65 (2H, t, J=5.3 Hz), 3.65 (2H, t, J=5.3 Hz), 3.79 (3H, s), 3.80 (2H, s), 4.44 (2H, s), 6.84 (1H, d, J=3.5 Hz), 6.84 (2H, d, J=8.8 Hz), 7.14 (1H, s), 7.28 (1H, d, J=3.5 Hz), 7.34 (2H, d, J=8.8 Hz).

A solution of the alcohol (10.49 g, 26 mmol) in TFA (50 ml) was refluxed for 9 hours. The solution was concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give trifluoroacetate of **B_{15}** (4.41 g, 43%): MS (ESP) *m/z* 287 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.75 (3H, s), 3.11 (2H, br s), 3.72 (2H, br s), 4.02 (2H, br s), 4.55 (2H, br s), 5.39 (1H, br s), 7.20 (1H, s), 7.31 (1H, d, J=3.7 Hz), 7.58 (1H, d, J=3.7 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-{[4-(5-{[(2-Hydroxyethyl)-(methyl)amino]methyl}thien-2-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 (**D_{15}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 1.13 (3H, d, J=7.3 Hz), 1.20 (3H, d, J=6.0 Hz), 2.30 (3H, s), 2.60~2.66

(2H, m), 3.07~3.12 (1H, m), 3.25 (1H, dd, J=2.9, 5.5 Hz), 3.59~3.63 (2H, m), 3.75~3.79 (2H, m), 3.96~4.37 (2H, m), 5.31 (2H, s), 6.85 (1H, d, J=3.5 Hz), 7.30 (1H, d, J=3.5 Hz), 7.34 (1H, s), 7.65 (2H, d, J=9.0 Hz), 8.15 (2H, d, J=8.9 Hz).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-{[4-(5-{[(2-hydroxyethyl)(dimethyl)ammonio]methyl}thien-2-yl)-1,3-thiazol-2-yl]thio}-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**15**)

IR (KBr) cm^{-1} 3378, 1758, 1670, 1598, 1455, 1386.; ^1H NMR (300 MHz, D_2O) δ 0.91 (3H, d, J=7.1 Hz), 1.08 (3H, d, J=6.2 Hz), 3.03 (6H, s), 3.04~3.20 (3H, m), 3.28~3.34 (1H, m), 3.40 (2H, br s), 4.00 (2H, br s), 4.05~4.11 (2H, m), 7.20~7.27 (1H, m), 7.34~7.37 (1H, m), 7.70~7.72 (1H, m).

4-{5-[(Dimethylamino)methyl]thien-2-yl}-1,3-thiazole-2-thiol (**B_{16}**)

To a suspension of 5-{2-[(4-methoxybenzyl)thio]-1,3-thiazol-4-yl}thiophene-2-carboxylic acid (5.0 g, 14 mmol) and dimethylamine hydrochloride (1.13 g, 14 mmol) in chloroform (30 ml) was added triethylamine (1.92 ml, 14 mmol) at −20°C. After 20 minutes, 1,3-dicyclohexylcarbodiimide (2.84 g, 14 mmol) in chloroform (8 ml) was added. After 30 minutes, the mixture was warmed to 0°C. After 1 hour, the mixture was warmed to room temperature, and then stirred overnight. The reaction mixture was filtered through a pad of celite, and filtrate was concentrated *in vacuo*. Water, 1 N hydrochloric acid, brine, EtOAc, and THF were added, the mixture was separated into an aqueous layer and an organic layer. The aqueous layer was extracted with EtOAc and THF twice. The organic layer was washed successively with satd sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated *in vacuo* to give 5-{2-[(4-methoxybenzyl)thio]-1,3-thiazol-4-yl}-*N*,*N*-dimethylthiophene-2-carboxamide (6.02 g): ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (6H, s), 3.79 (3H, s), 4.45 (2H, s), 6.85 (2H, d, J=8.8 Hz), 7.27 (1H, d, J=3.3 Hz), 7.33~7.37 (4H, m).

The amide (6.0 g, 15.4 mmol) in THF (50 ml) was added dropwise to a suspension of lithium aluminum hydride (1.22 g, 32 mmol) in THF (26 ml) at room temperature. The mixture was stirred for 3 hours. 10% sodium hydroxide and water were added to the reaction mixture. The mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give *N*-[(5-{2-[(4-methoxybenzyl)thio]-1,3-thiazol-4-yl}thien-2-yl)methyl]-*N*,*N*-dimethylamine (2.48 g, 43%): ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (6H, s), 3.64 (2H, s), 3.79 (3H, s), 4.47 (2H, s), 6.82~6.86 (3H, m), 7.13 (1H, s), 7.29 (1H, d, J=3.7 Hz), 7.34 (1H, d, J=8.6 Hz).

A solution of the amine (2.48 g, 3.8 mmol) in TFA (50 ml) was refluxed for 10 hours. The solution was concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give trifluoroacetate of **B_{16}** (1.03 g, 61%): IR (KBr) cm^{-1} 3116, 3025, 2870, 1672, 1468, 1428, 1203, 1050.; ^1H NMR (300 MHz, DMSO-d_6) δ 2.74 (6H, s), 4.50 (2H, s), 7.20 (1H, s), 7.28 (1H, d, J=3.8 Hz), 7.58 (1H, d, J=3.8 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(4-{5-[(Dimethylamino)methyl]thien-2-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_{16}**)

^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.13 (3H, d, J=7.1 Hz), 1.23 (3H, d, J=6.1 Hz), 2.31 (6H, s), 3.27 (1H, dd, J=2.9, 5.5 Hz), 3.57~3.69 (1H, m), 3.64 (2H, s), 4.20~4.30 (2H, m), 5.31 (1H, d, J=13.9 Hz), 5.51 (1H, d, J=13.9 Hz), 6.88 (1H, d, J=3.5 Hz), 7.33 (1H, d, J=3.5 Hz), 7.35 (1H, s), 7.68 (2H, d, J=8.4 Hz), 8.23 (2H, d, J=8.4 Hz).

(4*R*,5*S*,6*S*)-3-[(4-{5-[(Dimethylamino)methyl]thien-2-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 (**16**)

IR (KBr) cm^{-1} 3390, 2969, 1757, 1605, 1389.; ^1H NMR (300 MHz, D_2O) δ 0.92 (3H, d, J=7.1 Hz), 1.09 (3H, d, J=6.2 Hz), 2.70 (6H, s), 3.16 (1H, dd, J=8.8, 10.6 Hz), 3.32 (1H, dd, J=2.7, 6.0 Hz), 4.03~4.13 (2H, m), 4.34 (2H, s), 7.13 (1H, d, J=4.0 Hz), 7.32 (1H, d, J=4.0 Hz), 7.69 (1H, s).

4-[5-(1*H*-Imidazol-1-ylmethyl)thien-2-yl]-1,3-thiazole-2-thiol (**B_{17}**)

To a solution of **B_9** (2.0 g, 8.7 mmol) in dichloromethane (50 ml) and THF (10 ml) were added triethylamine (1.2 ml, 8.7 mmol) and trityl chloride (2.43 g, 8.7 mmol) at room temperature. After 2 hours, the mixture was poured into satd sodium bicarbonate solution, and extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give {5-[2-(tritylthio)-1,3-thiazol-4-yl]thien-2-yl}methanol (4.23 g) quantitatively: ^1H NMR (300 MHz, D_2O) δ 4.80 (2H, s), 6.91 (1H, d, J=3.7 Hz), 7.07 (1H, s), 7.18 (1H, d, J=3.7 Hz), 7.20~7.31 (9H, m), 7.39~7.44 (6H, m).

To a solution of the alcohol (428 mg, 0.91 mmol) in THF

(2.5 ml) was added 1,1'-carbonyldiimidazole (309 mg, 1.9 mmol) and refluxed with stirring. After 1.5 hours, 1,1'-carbonyldiimidazole (309 mg, 1.9 mmol) was added and refluxed for 30 minutes. To this mixture, water was added and extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give 4-[5-(1*H*-imidazol-1-ylmethyl)thien-2-yl]-2-(tritylthio)-1,3-thiazole (359 mg, 76%): ^{1}H NMR (300 MHz, D_2O) δ 5.24 (2H, s), 6.87 (1H, d, J=3.7 Hz), 6.98 (1H, brt, J=1.3 Hz), 7.07 (1H, s), 7.09 (1H, brt, J=1.1 Hz), 7.16 (1H, d, J=3.7 Hz), 7.20~7.31 (9H, m), 7.39~7.44 (6H, m), 7.58 (1H, br s).

TFA was added to the imidazole compound (295 mg, 0.57 mmol) and stirred at 0°C for 5 minutes. After TFA was removed, residue was washed with ether and dried to give **B_{17}** (204.1 mg): ^{1}H NMR (300 MHz, CD_3OD) δ 5.57 (2H, s), 7.16 (1H, d, J=3.7 Hz), 7.36 (1H, d, J=3.7 Hz), 7.46 (1H, brt, J=1.3 Hz), 7.57 (1H, brt, J=1.6 Hz), 7.75 (1H, s), 8.88 (1H, br s).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-({4-[5-(1*H*-Imidazol-1-ylmethyl)thien-2-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 0.12 (9H, s), 1.12 (3H, d, J=7.3 Hz), 1.22 (3H, d, J=6.2 Hz), 3.28 (1H, dd, J=2.9, 5.5 Hz), 3.54~3.68 (1H, m), 4.20~4.30 (2H, m), 5.28 (1H, s), 5.30 (1H, d, J=13.9 Hz), 5.51 (1H, d, J=13.9 Hz), 6.96 (1H, d, J=3.7 Hz), 6.99 (1H, br s), 7.09 (1H, br s), 7.32 (1H, d, J=3.7 Hz), 7.61 (1H, s), 7.67 (2H, d, J=8.6 Hz), 8.22 (2H, d, J=8.6 Hz).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[5-(1*H*-imidazol-1-ylmethyl)thien-2-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**17**)

IR (KBr) cm^{-1} 3428, 2968, 1757, 1604, 1390, 1283.; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (3H, d, J=7.1 Hz), 1.09 (3H, d, J=6.2 Hz), 3.19~3.20 (1H, m), 3.87~3.93 (1H, m), 4.11 (1H, dd, J=3.1, 10.3 Hz), 5.40 (2H, s), 6.90 (1H, s), 7.09 (1H, d, J=3.7 Hz), 7.23 (1H, s), 7.45 (1H, d, J=3.7 Hz), 7.76 (1H, s), 8.02 (1H, s).

N'-[(*tert*-Butoxycarbonyl)oxy]-4-(2-mercapto-1,3-thiazol-4-yl)benzenecarboximidamide (**F_{18}**)

To a solution of 4-(2-mercapto-1,3-thiazol-4-yl)benzonitrile (**E_{18}**) (133 g, 610 mmol) in EtOH (3000 ml) were added hydroxylamine hydrochloride (62 g, 890 mmol) and triethylamine (141 ml, 1000 mmol) and the mixture was heated to reflux for 1 hour. Another hydroxylamine hydrochloride (30 g, 430 mmol) and triethylamine (70 ml, 500 mmol) were added and the mixture was heated to reflux for 2 hours. The mixture was concentrated to volume of 800 ml and EtOAc and water were added. The resulting precipitate was collected by filtration and recrystallized from EtOAc/ethyl ether to give *N'*-hydroxy-4-(2-mercapto-1,3-thiazol-4-yl)benzenecarboximidamide (99.2 g, 65%). To a solution of this material (22.9 g, 91 mmol) in MeOH (1000 ml) was added di-*tert*-butyl-dicarbonate (20.0 g, 92 mmol) and the mixture was stirred at room temperature for 6 hours. The mixture was concentrated and the residue was taken up in dichloromethane and water. The layers were separated and the organic layer was dried over magnesium sulfate, concentrated and purified by chromatography on silica gel followed by crystallization from EtOAc/ethyl ether/hexane to give **F_{18}** (12.5 g, 39%): MS (ESP) *m/z* 352.3 (M+H); IR (NJL) cm^{-1} 1749, 1637.; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.48 (9H, s), 6.80 (2H, br s), 7.50 (1H, br s), 7.77 (2H, d, J=8.5 Hz), 7.85 (2H, d, J=8.5 Hz), 13.75 (1H, br s).

4-(2-Mercapto-1,3-thiazol-4-yl)benzenecarboximidamide (**G_{18}**)

To a solution of **F_{18}** (6.15 g, 17 mmol) in MeOH (250 ml) were added tin(II) chloride (6.18 g, 33 mmol) and molecular sieves 4A (4.0 g) and the mixture was heated to reflux for 1 hour. The solids were removed by filtration and the mother liquor was concentrated. The residue was taken up in water and the pH was adjusted to 7.30. The aqueous layer was washed twice with EtOAc. On standing in the freezer overnight a precipitate forms which was collected by filtration to give **G_{18}** (3.70 g, 90%): MS (ESP) *m/z* 236.2 (M+H); IR (NJL) cm^{-1} 1671.; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.63 (1H, s), 7.88 (2H, d, J=8.5 Hz), 8.02 (2H, d, J=8.5 Hz), 9.10 (2H, br s), 9.40 (2H, br s).

Allyl Imino[4-(2-mercapto-1,3-thiazol-4-yl)phenyl]-methylcarbamate (**B_{18}**)

To a solution of **G_{18}** (1.00 g, 4.2 mmol) in THF (20 ml) was added a solution of sodium hydroxide (0.40 g, 10 mmol) in water (2 ml). To the resulting mixture was added a solution of allyl chloroformate (1.13 g, 9.4 mmol) in THF (5 ml) at 0°C. After stirring for 1.5 hours, the reaction mixture was partitioned between water and EtOAc. The organic layer was washed with brine and the solids were removed by filtration. The organic layer was concentrated to leave 1.32 g of a yellow solid. The solid was taken up in MeOH (5 ml) and a saturated solution of ammonia in MeOH (3 ml) was added and stirred at room temperature for 1 hour. The mixture was concentrated and

the residue was purified by chromatography on silica gel to give **B_{18}** (0.98 g, 72%): *Anal* Calcd for $C_{14}H_{13}N_3O_2S_2$: C 52.65, H 4.10, N 13.16, S 20.08. Found: C 52.70, H 4.13, N 13.04, S 19.86.; ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.57 (2H, d, J=7.2 Hz), 5.15~5.40 (2H, m), 5.90~6.05 (1H, m), 7.53 (1H, s), 7.89 (2H, d, J=8.5 Hz), 8.06 (2H, d, J=8.5 Hz), 9.20 (2H, br s), 13.75 (2H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{4-[{[(Allyloxy)carbonyl]amino}-(imino)methyl]phenyl}-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}**)

To a suspension of **B_{18}** (7.83 g, 25 mmol) in acetonitrile (80 ml) was added sodium hydride (1.07 g, 27 mmol) at 0°C and the mixture was stirred at the same temperature for 30 minutes. To the resulting solution was added the phosphate (**A_2**) (15.6 g, 27 mmol) and the mixture was kept in the freezer at 4°C for 72 hours. The solids were removed by filtration. The mother liquor was partitioned between 10% sodium bicarbonate solution and EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **C_{18}** (10.1 g, 63%): MS (ESP) *m/z* 641.1 (M+H); IR (MIR) cm^{-1} 1774.; ^{1}H NMR (250 MHz, $CDCl_3$) δ −0.11 (9H, s), 1.12 (3H, d, J=7.5 Hz), 1.23 (3H, d, J=6 Hz), 3.20~3.30 (1H, m), 3.49~3.63 (1H, m), 4.14~4.28 (2H, m), 4.60~4.90 (4H, m), 5.20~5.53 (4H, m), 5.90~6.10 (2H, m), 7.70 (1H, s), 7.98 (4H, s).

(4*R*,5*S*,6*S*)-3-[(4-{4-[Amino(imino)methyl]phenyl}-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**)

To a solution of **C_{18}** (3.80 g, 5.9 mmol) in EtOAc (40 ml) was added 0.5 N hydrochloric acid (40 ml) at 0°C and the mixture was stirred at room temperature for 10 minutes. To the resulting mixture was added 60 ml of a 10% sodium bicarbonate solution. The layers were separated and the organic layer was washed with brine, dried over magnesium sulfate, concentrated *in vacuo* and purified by chromatography on silica gel to give allyl (4*R*,5*S*,6*S*)-3-[(4-{4-[{[(allyloxy)carbonyl]amino}(imino)methyl]phenyl}-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 (2.93 g, 87%): MS (ESP) *m/z* 569.4 (M+H); IR (MIR) cm^{-1} 1768.; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18 (3H, d, J=7.5 Hz), 1.36 (3H, d, J=6 Hz), 3.22~3.34 (1H, m), 3.52~3.70 (1H, m), 4.20~4.40 (2H, m), 4.64~4.96 (4H, m), 5.20~5.67 (4H, m), 5.90~6.16 (2H, m), 7.70 (1H, s), 7.97 (4H, s).

To a solution of the hydroxyester (1.00 g, 1.8 mmol) in dichloromethane (100 ml) were added tributyltin hydride (5.11 g, 18 mmol) and bis(triphenylphosphine) palladium (II) dichloride (0.123 g, 0.18 mmol). The mixture was stirred at room temperature for 20 minutes. To the reaction mixture was added a 3 : 1 mixture of water and acetonitrile with stirring. The layers were separated. The aqueous layer was washed 3 times with dichloromethane. The residual organic solvents in aqueous layer were removed under high vacuum. The solid was collected by filtration to give **18** (0.585 g, 75%) with 93% purity by HPLC (area). An analytically pure sample was obtained by chromatography on MCI gel (CHP-20P) with a gradient of water to 30% acetonitrile: MS (ESP) *m/z* 445.3 (M+H); IR (MIR) cm^{-1} 1741.; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (3H, d, J=7.2 Hz), 1.13 (3H, d, J=6.4 Hz), 3.15~3.22 (1H, m), 3.30~3.40 (1H, m), 3.90~4.00 (1H, m), 4.10~4.20 (1H, m), 4.98 (1H, d, J=4.8 Hz), 7.91 (2H, d, J=8.4 Hz), 8.17 (2H, d, J=8.4 Hz), 8.41 (1H, s), 9.20 (2H, br s), 10.50 (2H, br s).

S-{4-[3-((*Z*)-Amino{[(2,2-dimethylpropanoyl)oxy]-imino}methyl)phenyl]-1,3-thiazol-2-yl}2,2-dimethyl-propanethioate (**F_{19}**)

A mixture of 3-(2-mercapto-1,3-thiazol-4-yl)benzonitrile (**E_{19}**) (1.14 g, 5.2 mmol), hydroxylamine hydrochloride (0.53 g, 7.6 mmol) and triethylamine (0.88 g, 8.7 mmol) in EtOH (35 ml) was heated to reflux for 2 hours. To the resulting suspension were added water and EtOAc and the pH was adjusted to 6.8. The solid was removed by filtration. The layers were separated and the organic layer was dried over magnesium sulfate and concentrated. The residue was dissolved in THF (8 ml). To the resulting solution was added a solution of sodium hydroxide (0.35 g, 8.8 mmol) in water (2 ml) at 0°C. To the resulting mixture was added pivaloyl chloride (1.00 g, 8.3 mmol) at 0°C and the mixture was stirred at the same temperature for 1 hour. The mixture was partitioned between water and EtOAc and the organic layer was washed with brine, dried over magnesium sulfate, concentrated *in vacuo* and purified by chromatography on silica gel to give **F_{19}** (0.97 g, 44%): MS (ESP) *m/z* 420.2 (M+H); IR (MIR) cm^{-1} 1740, 1688.; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.26 (9H, s), 1.32 (9H, s), 6.70 (2H, br s), 7.47~7.60 (1H, m), 7.65~7.75 (1H, m), 8.00~8.12 (1H, m), 8.22~8.30 (1H, m), 8.50 (1H, s).

Allyl Imino[3-(2-mercapto-1,3-thiazol-4-yl)phenyl]-methylcarbamate (**B_{19}**)

To a suspension of **F_{19}** (0.95 g, 2.3 mmol) in 2-propanol (20 ml) were added molecular sieve 4A (1.00 g) and tin(II) dichloride (0.85 g, 4.5 mmol) and the mixture was heated to

80°C for 1 hour. The solids were removed by filtration and the mother liquor was concentrated. The residue was taken up in THF (20 ml). To the resulting solution were added 2 N sodium hydroxide (5.64 ml, 11.2 mmol) and a solution of allyl chloroformate (0.60 g, 5.0 mmol) in THF (2 ml) at 0°C. The mixture was stirred at 0°C for 1 hour. The reaction mixture was partitioned between water and EtOAc at a pH of 7.4. The layers were separated and the organic layer was dried over magnesium sulfate and concentrated. The residue was dissolved in MeOH (5 ml). To the resulting solution was added a saturated solution of ammonia in MeOH (5 ml) at 0°C and stirred at same temperature for 30 minutes. The mixture was concentrated and the residue was purified by chromatography on silica gel to give **B_{19}** (0.138 g, 19%): MS (ESP) *m/z* 320.3 (M+H); *Anal* Calcd for $C_{14}H_{13}N_3O_2S_2$: C 52.65, H 4.10, N 13.16. Found: C 52.80, H 4.37, N 12.90.; IR (MIR) cm^{-1} 1619.; ^1H NMR (250 MHz, DMSO-d_6) δ 4.58 (2H, d, J=7.2 Hz), 5.18~5.40 (2H, m), 5.90~6.10 (1H, m), 7.40 (1H, s), 7.50~7.63 (1H, m), 7.85~8.02 (2H, m), 8.22~8.34 (1H, m), 9.20 (2H, br s), 13.75 (2H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{3-[{[(Allyloxy)carbonyl]amino}(imino)methyl]phenyl}-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}**)

MS (ESP) *m/z* 641.4 (M+H); IR (MIR) cm^{-1} 1774.; ^1H NMR (250 MHz, $CDCl_3$) δ 0.11 (9H, s), 1.12 (3H, d, J=7.5 Hz), 1.23 (3H, d, J=6.0 Hz), 3.20~3.30 (1H, m), 3.45~3.60 (1H, m), 4.17~4.30 (2H, m), 4.64~4.90 (4H, m), 5.22~5.52 (4H, m), 5.88~6.10 (2H, m), 7.50~7.60 (1H, m), 7.70 (1H, s), 7.89~7.95 (1H, m), 8.02~8.10 (1H, m), 8.26~8.32 (1H, m).

(4*R*,5*S*,6*S*)-3-[(4-{3-[Amino(imino)methyl]phenyl}-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**)

MS (ESP) *m/z* 445.3 (M+H); IR (MIR) cm^{-1} 1753.; ^1H NMR (400 MHz, DMSO-d_6) δ 1.00 (3H, d, J=7.2 Hz), 1.13 (3H, d, J=6.4 Hz), 3.15~3.25 (1H, m), 3.30~3.45 (1H, m), 3.85~4.00 (1H, m), 4.10~4.20 (1H, m), 5.00 (1H, d, J=4.8 Hz), 7.60~7.85 (2H, m), 8.23 (1H, d, J=8 Hz), 8.32 (1H, s), 8.39 (1H, s).

(4*R*,5*S*,6*S*)-3-{[4-(5-{[Ethyl(dimethyl)ammonio]methyl}thien-2-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 (**20**)

IR (KBr) cm^{-1} 3405, 1759, 1603, 1454, 1385.; ^1H NMR (300 MHz, D_2O) δ 0.82 (3H, d, J=7.1 Hz), 1.03 (3H, d, J=6.2 Hz), 1.27 (3H, t, J=7.2 Hz), 2.90 (3H, s), 3.01~3.11 (1H, m), 3.22~3.29 (3H, m), 3.97~4.05 (2H, m), 4.53 (2H, s), 7.17 (1H, d, J=3.7), 7.26 (1H, d, J=3.7), 7.61 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[(4-{3-[(1-methylpyrrolidinium-1-yl)methyl]phenyl}-1,3-thiazol-2-yl)thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**21**)

IR (KBr) cm^{-1} 3354, 2970, 1756, 1603, 1385.; ^1H NMR (300 MHz, D_2O) δ 0.97 (3H, d, J=7.1 Hz), 1.10 (3H, d, J=6.2 Hz), 2.07~2.18 (4H, m), 2.86 (3H, s), 2.86~2.96 (1H, m), 3.31~3.36 (3H, m), 4.06~4.14 (2H, m), 7.43~7.56 (1H, m), 7.82~7.89 (4H, m).

Allyl 4-(Chloroacetyl)piperidine-1-carboxylate (**H_{22}**)

To a solution of 1-allyl 4-ethyl piperidine-1,4-dicarboxylate (**L_{22}**) (500 mg, 2.1 mmol) and bromochloromethane (0.215 ml, 3.3 mmol) in THF (15 ml) was added a solution of *n*-butyl lithium in hexane (1.6 M, 1.95 ml, 3.1 mmol) at −100°C over 10 minutes. and the mixture was stirred at −100°C for 15 minutes. The reaction was quenched by addition of 460 ml 10% citric acid and extracted with 500 ml EtOAc. The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and purified by chromatography on silica gel to give **H_{22}** (481 mg, 94%): MS (ESP) *m/z* 246 (M+H).; ^1H NMR (250 MHz, $CDCl_3$) δ 1.54~1.68 (2H, m), 1.84~1.89 (2H, m), 2.81~2.95 (3H, m), 4.16 (2H, s), 4.16~4.22 (2H, m), 4.58~4.61 (2H, m), 5.19~5.33 (2H, m), 5.87~6.00 (1H, m).

Allyl 4-(2-Mercapto-1,3-thiazol-4-yl)piperidine-1-carboxylate (**B_{22}**)

To a solution of **H_{22}** (481 mg, 2.0 mmol) in EtOH (20 ml) was added dithiocarbamic acid ammonium salt (216 mg, 2.0 mmol) and the mixture was stirred at room temperature for 1 hour and at reflux for 1 hour. The reaction mixture was partitioned between water and EtOAc and the organic layer was dried over magnesium sulfate, concentrated *in vacuo* and purified by chromatography on silica gel to give **B_{22}** (556 mg) quantitatively: ^1H NMR (250 MHz, $CDCl_3$) δ 1.50~1.63 (2H, m), 1.93~2.02 (2H, m), 2.69~2.91 (3H, m), 4.25~4.31 (2H, m), 4.61 (2H, d, J=5.5), 5.20~5.34 (2H, m), 5.88~6.01 (1H, m), 6.25 (1H, s), 12.49 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{1-[(Allyloxy)carbonyl]piperidin-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_{22}**)

^1H NMR (250 MHz, $CDCl_3$) δ 0.11 (9H, s), 1.05 (3H, d, J=7.5 Hz), 1.24 (1H, d, J=6.0 Hz), 1.55~1.71 (2H, m),

2.02~2.09 (2H, m), 2.88~3.02 (3H, m), 3.22 (1H, dd, J=2.7, 6.4 Hz), 3.35~3.42 (1H, m), 4.09~4.31 (4H, m), 4.60 (2H, d, J=5.7), 4.70~7.48 (2H, m), 5.20~5.50 (4H, m), 5.89~6.03 (2H, m), 7.00 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(4-piperidin-4-yl-1,3-thiazol-2-yl)thio]-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic Acid (**22**)

IR (KBr) cm^{-1} 3413, 1764, 1598, 1386.; ^1H NMR (300 MHz, D_2O) δ 0.96 (3H, d, J=7.1 Hz), 1.17 (3H, d, J=6.4 Hz), 1.77~1.92 (2H, m), 2.15~2.20 (2H, m), 3.04~3.13 (4H, m), 3.37 (1H, dd, J=2.7, 5.5 Hz), 3.42~3.49 (1H, m), 4.10~4.19 (2H, m), 7.34 (1H, s).

1-Allyl 4-Ethyl 3,6-Dihydropyridine-1,4(2*H*)-dicarboxylate ($\mathbf{L_{23}}$)

To a solution of ethyl isonicotinate (14.6 g, 97 mmol) in EtOH (15 ml) was added benzyl bromide (19.8 g, 116 mmol) at 80°C. After 1 hour, heptane (50 ml) was added and the mixture was cooled to 10°C. The precipitate was filtered and washed with heptane and dried. To the solution of this precipitate in EtOH (150 ml) was added sodium borohydride (3.9 g, 103 mmol) in water (40 ml) at 0°C. After stirring at room temperature for 1 hour, water and dichloromethane were added. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give ethyl 1-benzyl-1,2,3,6-tetrahydropyridine-4-carboxylate (23.0 g, 97%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t, J=7.1 Hz), 2.38~2.44 (2H, m), 2.61 (2H, t, J=5.7 Hz), 3.12~3.15 (2H, m), 3.62 (2H, s), 4.19 (2H, q, J=7.1 Hz), 6.86~6.89 (1H, m), 7.25~7.31 (5H, m).

To a solution of the amine (22.8 g, 93 mmol) in chloroform (90 ml) was added allyl chloroformate (12.34 g, 102 mmol) at room temperature. After 1 hour, satd sodium bicarbonate solution was added and the mixture was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give $\mathbf{L_{23}}$ (35.94 g, mixture with benzyl chloride): ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (3H, t, J=7.1 Hz), 2.43 (2H, br s), 3.59 (2H, t, J=5.7 Hz), 4.12~4.15 (2H, m), 4.22 (2H, q, J=7.1 Hz), 4.60~4.65 (2H, m), 5.21~5.34 (2H, m), 5.88~6.01 (1H, m), 6.89 (1H, br s).

1-[(Allyloxy)carbonyl]-1,2,3,6-tetrahydropyridine-4-carboxylic Acid ($\mathbf{M_{23}}$)

To a solution of $\mathbf{L_{23}}$ (5.0 g) in MeOH (5 ml) and water (25 ml) was added a solution of sodium hydroxide (2.5 g, 62.5 mmol) in water (5 ml) at 0°C and stirred at room temperature for 30 minutes. The mixture was washed with chloroform, acidified with 2 N hydrochloric acid and extracted with EtOAc. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give $\mathbf{M_{23}}$ (2.49 g, 88% from ethyl isonicotinate): MS (ESP) *m/z* 212 (M+H); ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (2H, br s), 3.60 (2H, t, J=5.8 Hz), 4.17~4.20 (2H, m), 4.60~4.65 (2H, m), 5.21~5.35 (2H, m), 5.88~6.00 (1H, m), 7.02 (1H, br s).

Allyl 4-(3-*tert*-Butoxy-3-oxopropanoyl)-3,6-dihydropyridine-1(2*H*)-carboxylate ($\mathbf{N_{23}}$)

To a suspension of $Mg(OEt)_2$ (4.23 g, 37 mmol) in THF (40 ml) was added mono *tert*-butyl malonate (11.8 g, 74 mmol) at room temperature. The mixture was stirred at room temperature for 2 hours to give magnesium malonate solution.

To a solution of $\mathbf{M_{23}}$ (13.0 g, 62 mmol) was added 1,1′-carbonyldiimidazole (11.0 g, 68 mmol) at 0°C and stirred for 1 hour. The mixture was added to the magnesium malonate solution and stirred at room temperature for 3 hours. The resulting mixture was concentrated and to this residue 2 N hydrochloric acid and EtOAc were added. The layers were separated and the organic layer was washed with satd sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give $\mathbf{N_{23}}$ (12.4 g, 65%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (9H, s), 2.42 (2H, br s), 3.58 (2H, t, J=5.8 Hz), 3.62 (2H, s), 4.20~4.23 (2H, m), 4.61~4.64 (2H, m), 5.21~5.35 (2H, m), 5.88~6.01 (1H, m), 6.77 (1H, br s).

Allyl 4-(Chloroacetyl)-3,6-dihydropyridine-1(2*H*)-carboxylate ($\mathbf{H_{23}}$)

To a solution of $\mathbf{N_{23}}$ (12.4 g, 40 mmol) in dichloromethane (124 ml) was added SO_2Cl_2 (5.41 g, 40 mmol) at 0°C. After stirring at the same temperature for 10 minutes, satd sodium bicarbonate solution was added to this mixture. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in 1,2-dichlroethane (150 ml) and treated with methanesulfonic acid at 0°C. Then the mixture was heated to 50°C. After stirring for 2 hours, satd sodium bicarbonate solution was added to this mixture. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give $\mathbf{H_{23}}$ (4.87 g, 54%): ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (2H, br s), 3.60 (2H, t, J=5.7 Hz), 4.22~4.25 (2H, m), 4.41 (2H, s), 4.61~4.64 (2H, m), 5.21~5.35 (2H, m), 5.89~6.02 (1H, m), 6.83 (1H, br s).

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

MS (ESP) *m/z* 283 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (2H, br s), 3.68 (2H, t, J=5.7 Hz), 4.18 (2H, d, J=2.9 Hz), 4.63 (2H, d, J=5.7 Hz), 4.61~4.64 (2H, m), 5.21~5.35 (2H, m), 5.89~6.02 (1H, m), 6.17 (1H, br s), 6.42 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{1-[(Allyloxy)carbonyl]-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-carboxylate (**C_{23}**)

MS (ESP) *m/z* 532 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, d, J=6.6 Hz), 1.23 (3H, d, J=7.3 Hz), 2.51 (2H, br s), 3.26 (1H, m), 3.50 (1H, m), 3.69 (2H, m), 4.10 (2H, m), 4.20 (2H, m), 4.60~4.80 (4H, m), 5.00~5.60 (4H, m), 5.80~6.00 (2H, m), 6.66 (1H, s), 7.36 (1H, s).

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

IR (KBr) cm^{-1} 3388, 1762, 1599, 1388.; ^{1}H NMR (300 MHz, D_2O) δ 1.10 (3H, d, J=7.3 Hz), 1.27 (3H, d, J=6.6 Hz), 2.83 (2H, m), 3.32 (1H, m), 3.51 (3H, m), 3.93 (2H, m), 4.26 (2H, m), 6.53 (1H, br s), 7.61 (1H, s).

Allyl 5-{2-[(Ethoxycarbonyl)thio]-1,3-thiazol-4-yl}-3,6-dihydropyridine-1(2*H*)-carboxylate (**J_{24}**)

To a solution of *O*-ethyl *S*-(4-pyridin-3-yl-1,3-thiazol-2-yl)thiocarbonate (**I_{24}**) (5.04 g, 19 mmol) in THF (50 ml) was added benzyl bromide (4.32 ml, 36 mmol) at 70°C. After 2 hours, hexane was added and the mixture was cooled to room temperature. The precipitate was filtered and washed with hexane and dried. To the solution of this precipitate in EtOH (50 ml) was added sodium borohydride (1.40 g, 38 mmol) in water (14 ml) at 0°C. After stirring at room temperature for 1 hour, water and EtOAc were added. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in chloroform (50 ml) and allyl chloroformate (1.9 ml, 18 mmol) was added at room temperature. After 1 hour, satd sodium bicarbonate solution was added and the mixture was extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **J_{24}** (2.43 g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, t, J=7.1 Hz), 2.37 (2H, br s), 3.62 (2H, t, J=5.7 Hz), 4.30~4.36 (2H, m), 4.39 (2H, q, J=7.1 Hz), 4.64~4.66 (2H, m), 5.20~5.36 (2H, m), 5.90~6.03 (2H, m), 6.80 (1H, br s), 7.23 (1H, s).

Allyl 5-(2-Mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**B_{24}**)

To a solution of **J_{24}** (2.43 g, 6.9 mmol) in MeOH (50 ml) was added methylamine (30% in MeOH, 1.4 g, 14 mmol) at 0°C. After stirring at the same temperature for 2 hours, the mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **B_{24}** (1.00 g, 52%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (2H, br s), 3.48 (2H, br s), 4.13 (2H, br s), 4.54~4.57 (2H, m), 5.16~5.32 (2H, m), 5.87~6.00 (2H, m), 6.60 (1H, br s), 6.93 (1H, br s), 12.29 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{1-[(Allyloxy)carbonyl]-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_{24}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.11 (3H, d, J=7.3 Hz), 1.23 (3H, d, J=6.2 Hz), 2.38 (2H, br s), 3.24 (1H, dd, J=3.0, 6.2 Hz), 3.45~3.57 (1H, m), 3.57~3.71 (2H, m), 4.19~4.23 (2H, m), 4.33 (2H, br s), 4.63~4.67 (2H, m), 4.70~4.88 (2H, m), 5.21~5.51 (4H, m), 5.91~6.05 (2H, m), 6.83 (1H, br s), 7.12 (1H, s).

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

IR (KBr) cm^{-1} 3425, 1765, 1595, 1387.; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (3H, d, J=7.1 Hz), 1.09 (3H, d, J=6.4 Hz), 3.13~3.17 (2H, m), 3.87 (2H, br s), 3.88~3.93 (1H, m), 4.05 (1H, dd, J=3.1, 9.7 Hz), 4.96~4.98 (1H, m), 6.69 (1H, br s), 7.60 (1H, s).

Allyl (3*S*)-3-[(Methylsulfonyl)oxy]pyrrolidine-1-carboxylate (**U_{25}**)

To a solution of allyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate (**T_{25}**) (15.0 g, 88 mmol) in dichloromethane (100 ml) was added triethylamine (10.64 g, 105 mmol). The mixture was cooled to 0°C and methanesulfonyl chloride (11.04 g, 96 mmol) was added during 20 minutes with stirring. Stirring was continued for 30 minutes at room temperature. Water was added and the layers were separated. The organic layer was washed successively with 10% citric acid, potassium bicarbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo* to give **U_{25}** (22.72 g) quantitatively: MS (ESP) *m/z* 250.2 (M+H); IR (FLM) cm^{-1} 1702.; ^{1}H NMR (250 MHz, $CDCl_3$-d_6) δ 2.05~2.42 (2H, m), 3.06 (3H, s), 3.48~3.86 (4H, m), 4.61 (2H, d, J=5.5 Hz), 5.20~5.40 (3H, m), 5.84~6.05 (1H, m).

Allyl (3*R*)-3-Cyanopyrrolidine-1-carboxylate ($\mathbf{V_{25}}$)

To a solution of $\mathbf{U_{25}}$ (22.40 g, 90 mmol) in acetonitrile (200 ml) was added tetra ethyl ammonium cyanide (25.84 g, 165 mmol) and the mixture was stirred at 75°C for 18 hours. The product was purified by chromatography on silica gel to give $\mathbf{V_{25}}$ (11.50 g, 71%): MS (TSP) *m/z* 180 (M^+); IR (FLM) cm^{-1} 2245.; ^1H NMR (250 MHz, $CDCl_3$) δ 2.14~2.40 (2H, m), 3.05~3.20 (1H, m), 3.48~3.80 (4H, m), 4.61 (2H, d, J=5.5 Hz), 5.20~5.40 (2H, m), 5.84~6.02 (1H, m). The optical purity of $\mathbf{V_{25}}$ was determined in comparison with its enatiomer $\mathbf{V_{26}}$ by chiral GC on a BGB-174 column 15 m×0.25 mm, NR. 52562 on a HP 5890-4C, Attenuator: RO/A6 using helium at 80 kPa as carrier gas and a temperature program of 3°C/minute from 100~210°C. The ee was found to be 95%.

1-Allyl 3-Ethyl (3*R*)-Pyrrolidine-1,3-dicarboxylate ($\mathbf{L_{25}}$)

A solution of $\mathbf{V_{25}}$ (4.20 g, 23 mmol) in 2 N hydrochloric acid in EtOH (45 ml) was kept at reflux for 18 hours. The reaction mixture was partitioned between water and EtOAc and the organic layer was dried over magnesium sulfate, concentrated *in vacuo* and purified by chromatography on silica gel to give $\mathbf{L_{25}}$ (4.64 g, 88%): MS (EI) *m/z* 227 (M^+); IR (FLM) cm^{-1} 1731.; ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (3H, t, J=7.0 Hz), 2.07~2.24 (2H, m), 2.96~3.17 (1H, m), 3.36~3.77 (4H, m), 4.17 (2H, q, J=7 Hz), 4.60 (2H, d, J=5.5 Hz), 5.20~5.40 (2H, m), 5.84~6.04 (1H, m).

Allyl (3*R*)-3-(Chloroacetyl)pyrrolidine-1-carboxylate ($\mathbf{H_{25}}$)

MS (TSP) *m/z* 231 (M^+); IR (FLM) cm^{-1} 1696.; ^1H NMR (250 MHz, $CDCl_3$) δ 2.07~2.30 (2H, m), 3.40~3.80 (5H, m), 4.16 (2H, s), 4.59 (2H, d, J=5.5 Hz), 5.18~5.38 (2H, m), 5.84~6.04 (1H, m).

Allyl (3*R*)-3-(2-Mercapto-1,3-thiazol-4-yl)pyrrolidine-1-carboxylate ($\mathbf{B_{25}}$)

MS (EI) *m/z* 270 (M^+); IR (FLM) cm^{-1} 1664.; ^1H NMR (250 MHz, $CDCl_3$) δ 1.96~2.20 (1H, m), 2.25~2.42 (1H, m), 3.30~3.70 (4H, m), 3.75~3.95 (1H, m), 4.62 (2H, d, J=5.5 Hz), 5.18~5.40 (2H, m), 5.84~6.04 (1H, m), 6.33 (1H, s), 12.30 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(3*R*)-1-[(Allyloxy)carbonyl]pyrrolidin-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 ($\mathbf{C_{25}}$)

MS (ESP) *m/z* 520.3 (M+H); IR (FLM) cm^{-1} 1772.; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J=7.5 Hz) and 1.09 (d, J=7.5Hz, together 3H), 1.34 (3H, d, J=6 Hz), 1.95~2.30 (3H, m), 3.20~3.30 (1H, m), 3.35~3.72 (5H, m), 3.75~3.85 (1H, m), 4.20~4.30 (2H, m), 4.55~4.65 (1H, m), 4.70~4.80 (1H, m), 4.82~4.92 (1H, m), 5.28~5.50 (4H, m), 5.87~6.04 (2H, m), 7.09, 7.10 (1H, s×2) as mixture of carbamate rotamers.

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({4-[(3*R*)-pyrrolidin-3-yl]-1,3-thiazol-2-yl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**25**)

MS (ESP) *m/z* 396.3 (M+H); IR (MIR) cm^{-1} 1755.; ^1H NMR (250 MHz, D_2O) δ 1.02 (3H, d, J=7 Hz), 1.20 (3H, d, J=6.3 Hz), 2.08~2.30 (1H, m), 2.38~2.58 (1H, m), 3.04~3.22 (1H, m), 3.28~3.80 (5H, m), 4.10~4.30 (2H, m), 7.46 (1H, s).

Allyl (3*R*)-3-[(Methylsulfonyl)oxy]pyrrolidine-1-carboxylate ($\mathbf{U_{26}}$)

To a mixture of methansulfonic acid (16.84 g, 175 mmol) in toluene (100 ml) were added triethylamine (17.73 g, 175 mmol) and triphenylphosphine (47.88 g, 183 mmol) at 0°C with stirring. The mixture was stirred at room temperature for 30 minutes. and the resulting mixture was added to a solution of allyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate ($\mathbf{T_{25}}$) (25.0 g, 146 mmol) in toluene (250 ml). To the resulting mixture was added diisopropyl-azodicarboxylate (38.38 g, 190 mmol) during 10 minutes. and the mixture was heated to 80°C with stirring for 2 hours. The reaction mixture was partitioned between water and EtOAc. The organic layer was washed with 10% citric acid, potassium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and purified by chromatography on silica gel to give $\mathbf{U_{26}}$ (28.2 g, 77%): MS (EI) *m/z* 259 (M^+); IR (MIR) cm^{-1} 1692.; ^1H NMR (250 MHz, $CDCl_3$) δ 2.05~2.42 (2H, m), 3.05 (3H, s), 3.48~3.86 (4H, m), 4.61 (2H, d, J=5.5 Hz), 5.20~5.40 (3H, m), 5.84~6.05 (1H, m). The optical purity of $\mathbf{U_{26}}$ was determined in comparison with its enatiomer $\mathbf{U_{25}}$ by chiral GC on a BGB-174 column 15 m×0.25 mm, NR. 52562 on a HP 5890-4C, Attenuator : RO/A6 using helium at 80 kPa as carrier gas and a temperature program of 3°C/minute from 180~220°C. The ee was found to be 96%.

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(3*S*)-1-[(Allyloxy)carbonyl]pyrrolidin-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 ($\mathbf{C_{26}}$)

MS (ESP) *m/z* 520.3 (M+H); IR (MIR) cm^{-1} 1773.; ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (3H, d, J=7.5 Hz), 1.10 (3H, d, J=6 Hz), 2.00~2.15 (1H, m), 2.20~2.35 (1H, m), 3.30~3.55 (5H, m), 3.56~3.68 (1H, m), 3.69~3.70 (1H,

m), 3.90~4.02 (1H, m), 4.23 (1H, d, J=10.0 Hz), 4.53 (2H, s), 4.65~4.72 (1H, m), 4.75~4.85 (1H, m), 5.04 (1H, d, J=4.8 Hz), 5.17 (1H, d, J=10.4 Hz), 5.20~5.30 (2H, m), 5.44 (1H, d, J=17.0 Hz), 5.88~6.00 (2H, m), 7.70 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({4-[(3*S*)-pyrrolidin-3-yl]-1,3-thiazol-2-yl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**26**)

MS (ESP) *m/z* 396.3 (M+H); IR (MIR) cm^{-1} 1753.; ^1H NMR (250 MHz, D_2O) δ 1.02 (3H, d, J=7.0 Hz), 1.20 (3H, d, J=6.3 Hz), 2.04~2.23 (1H, m): 2.37~2.55 (1H, m), 3.00~3.22 (1H, m), 3.30~3.60 (3H, m), 3.60~3.80 (2H, m), 4.12~4.32 (2H, m), 7.46 (1H, s).

Ethyl *N*-[(Allyloxy)carbonyl]-*N*-(2-ethoxy-2-oxoethyl)-β-alaninate ($\mathbf{P_{27}}$)

To a mixture of ethyl *N*-(2-ethoxy-2-oxoethyl)-β-alaninate (325.2 g, 1.6 mol), dichloromethane (600 ml) and 10% sodium bicarbonate solution (1400 ml) was added allyl chloroformate (195.6 ml, 1.8 mol) at 3°C over 1 hour. Stirring was continued for 1 hour at 3°C. The layers were separated and the organic layer was washed successively with 1 N hydrochloric acid and brine, dried over magnesium sulfate and concentrated *in vacuo* to give $\mathbf{P_{27}}$ (437 g, 95%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.24~1.28 (6H, m), 2.62~2.69 (2H, m), 3.62 (2H, t, J=6.5 Hz), 4.07~4.22 (6H, m), 4.56~4.64 (2H, m), 5.16~5.35 (2H, m), 5.81~6.01 (1H, m).

1-Allyl 3-Ethyl 4-Oxopyrrolidine-1,3-dicarboxylate ($\mathbf{Q_{27}}$)

To a solution of $\mathbf{P_{27}}$ (287.3 g, 1.2 mol) in toluene (1500 ml) and DMF (50 ml) was added *ca.* 5 g of a total amount of sodium hydride (60% in oil, 51.6 g, 1.3 mol). After the initial evolution of hydrogen had stopped, the mixture was heated to 100°C. After stirring at the same temperature for 10 minutes, evolution of hydrogen restarted. The reaction mixture was immediately cooled down to 20°C. The remaining sodium hydride was added portion-wise over period of 0.5 hour while the temperature of the mixture was kept at 20°C. Stirring was continued for 1.5 hours at 20°C, and then, the mixture was poured onto ice/water. Hexane was added and layers were separated. The aqueous layer was washed with hexane and organic layers were back-extracted with water. The pH of the combined aqueous layers was set to 1.5 by the addition of 8 N hydrochloric acid and then extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The remaining oil was crystallized from diethyl ether/Hexane (1 : 3) with stirring at 0°C to give $\mathbf{Q_{27}}$ (234.3 g, 83%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, t, J=7.1 Hz), 4.10~4.30 (6H, m), 4.63 (2H, d, J=5.5 Hz), 5.20~5.37 (2H, m), 5.88~6.03 (1H, m), 10.11 (1H, br s).

1-Allyl 3-Ethyl 2,5-Dihydro-1*H*-pyrrole-1,3-dicarboxylate ($\mathbf{L_{27}}$)

To a solution of $\mathbf{Q_{27}}$ (48.2 g, 200 mmol) in THF (400 ml) and 0.5 M phosphate buffer (pH 7.0, 100 ml) was added portion-wise sodium borohydride (6.81 g, 180 mmol) at 0°C over 40 minutes, the pH of the mixture being kept at 6.5~7.2 by the addition of 1 N phosphoric acid. The mixture was stirred for 1 hour at 0°C and subsequently poured onto 1 N hydrochloric acid/ice. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in pyridine (250 ml) and methanesulfonyl chloride (23.5 ml, 300 mmol) was added to it at 0°C, then the mixture was heated to 90°C for 3 hours. After cooling to 20°C, the mixture was concentrated *in vacuo* and the remaining oil was dissolved in EtOAc. The solution was washed successively with 3 N HCl, 5% sodium bicarbonate solution and brine, and the aqueous layers were back-extracted with EtOAc. The combined organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The remaining oil was purified by chromatography on silica gel to give $\mathbf{L_{27}}$ (29.8 g, 66%): MS (ESP) *m/z* 226 (M+H); ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, t, J=7.1 Hz), 4.24 (2H, d, J=7.1 Hz), 4.38 (4H, s), 4.64 (2H, d, J=5.5 Hz), 5.20~5.37 (2H, m), 5.89~6.03 (1H, m), 6.76 (1H, s).

Allyl 3-(2-Mercapto-1,3-thiazol-4-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate ($\mathbf{B_{27}}$)

MS (ESP) *m/z* 269 (M+H); ^1H NMR (300 MHz, DMSO-d_6) δ 4.23~4.36 (4H, m), 4.54~4.57 (2H, m), 5.19 (2H, d, J=10.4 Hz), 5.25~5.35 (2H, m), 5.88~6.00 (2H, m), 6.52 (1H, br s), 6.99 (1H, s), 13.57 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{1-[(Allyloxy)carbonyl]-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 ($\mathbf{C_{27}}$)

MS (ESP) *m/z* 518 ($M-SiMe_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.10 (3H, d, J=7.1 Hz), 1.23 (3H, d, J=6.2 Hz), 3.25 (1H, dd, J=2.9, 6.2 Hz), 3.47~3.57 (1H, m), 4.16~4.25 (2H, m), 4.40 (2H, br s), 4.53 (2H, br s), 4.67 (2H, br s), 4.71~4.88 (2H, m), 5.22~5.50 (4H, m), 5.91~6.05 (2H, m), 6.44 (1H, br s), 7.12 and 7.15 (1H s×2).

(4*R*,5*S*,6*S*)-3-{[4-(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 (**27**)

IR (KBr) cm^{-1} 3404, 1759, 1600, 1390.; ^1H NMR (300 MHz, D_2O) δ 0.93 (3H, d, J=7.1 Hz), 1.11 (3H, d, J=6.2 Hz), 3.10~3.21 (1H, m), 3.34 (1H, dd, J=2.8, 5.9 Hz), 4.05~4.14 (2H, m), 4.17~4.18 (2H, m), 4.32~4.33 (2H, m), 6.26 (1H, br s), 7.50 (1H, s).

Allyl (2*R*)-2-(Chloroacetyl)pyrrolidine-1-carboxylate (**H_{28}**)

MS (EI) *m/z* 174 (M−Oallyl); IR (MIR) cm^{-1} 1691.; ^1H NMR (400 MHz, $CDCl_3$) δ 1.86~2.07 (3H, m), 2.14~2.24 (1H, m), 3.48~3.65 (2H, m), 4.17~4.37 (2H, m), 4.50~4.65 (3H, m), 5.18~5.37 (2H, m), 5.80~6.00 (1H, m).

Allyl (2*R*)-2-(2-Mercapto-1,3-thiazol-4-yl)pyrrolidine-1-carboxylate (**B_{28}**)

MS (EI) *m/z* 270.1 (M^+); IR (MIR) cm^{-1} 1639.; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93~2.10 (2H, m), 2.17~2.30 (2H, m), 3.40~3.60 (2H, m), 4.54~4.71 (2H, m), 4.80~4.88 (1H, m), 5.20~5.40 (2H, m), 5.86~6.00 (1H, m), 6.29 (1H, s), 11.30 (1H, br s). The optical purity of the compounds **B_{28}** and **B_{29}** were determined by chiral GC on a BGB-172 column 15 m×0.25 mm, NR. 52639 on a HP 5890-2C, Attenuator: RO/A6 using helium at 100 kPa as carrier gas and a temperature program of 1°C/minute from 180~245°C. **B_{28}** had a retention time of 60.77 minutes (100% area), **B_{29}** had a retention time of 59.35 minutes (100% area).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(2*R*)-1-[(Allyloxy)carbonyl]pyrrolidin-2-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_{28}**)

MS (ESP) *m/z* 592.1 (M+H); IR (MIR) cm^{-1} 1783.; ^1H NMR (250 MHz, $CDCl_3$) δ −0.12 (9H, s), 1.06 (3H, d, J=7.5 Hz), 1.14 (3H, d, J=6 Hz), 1.90~2.30 (4H, m), 3.15~3.25 (1H, m), 3.30~3.45 (1H, m), 3.47~3.70 (2H, m), 4.00~4.20 (2H, m), 4.40~4.55 (2H, m), 4.60~4.85 (2H, m), 4.95~5.50 (5H, m), 5.60~6.00 (2H, m), 7.01, 7.14 (1H, s×2) as mixture of carbamate rotamers.

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({4-[(2*R*)-pyrrolidin-2-yl]-1,3-thiazol-2-yl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**28**)

MS (ESP) *m/z* 396.2 (M+H); IR (MIR) cm^{-1} 1759.; ^1H NMR (250 MHz, DMSO-d_6) δ 0.92 (3H, d, J=8 Hz), 1.11 (3H, d, J=6.5 Hz), 1.80~2.20 (3H, m), 2.20~2.40 (1H, m), 3.05~3.45 (5H, m), 3.85~3.98 (1H, m), 4.02~4.18 (1H, m), 4.60~4.73 (1H, m), 7.77 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(2*S*)-1-[(Allyloxy)carbonyl]pyrrolidin-2-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_{29}**)

MS (ESP) *m/z* 592.1 (M+H); IR (MIR) cm^{-1} 1778.; ^1H NMR (250 MHz, $CDCl_3$) δ −0.12 (9H, s), 1.05, 1.06 (totally 3H d, J=7.5 Hz), 1.14 (3H, d, J=6 Hz), 1.90~2.30 (4H, m), 3.15~3.25 (1H, m), 3.30~3.45 (1H, m), 3.47~3.70 (2H, m), 4.00~4.20 (2H, m), 4.40~4.55 (2H, m), 4.60~4.85 (2H, m), 4.95~5.50 (5H, m), 5.60~6.00 (2H, m), 7.01, 7.14 (1H, s×2) as mixture of carbamate rotamers.

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({4-[(2*S*)-pyrrolidin-2-yl]-1,3-thiazol-2-yl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**29**)

MS (ESP) *m/z* 396.2 (M+H); IR (NJL) cm^{-1} 1746.; ^1H NMR (250 MHz, DMSO-d_6) δ 0.94 (3H, d, J=8.0 Hz), 1.12 (3H, d, J=6.5 Hz), 1.80~2.20 (3H, m), 2.20~2.40 (1H, m), 3.05~3.45 (5H, m), 3.85~3.98 (1H, m), 4.02~4.18 (1H, m), 4.60~4.73 (1H, m), 7.77 (1H, s).

O-Ethyl *S*-[4-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-1,3-thiazol-2-yl] Thiocarbonate (**J_{30}**)

To a solution of *O*-ethyl *S*-(4-pyridin-4-yl-1,3-thiazol-2-yl) thiocarbonate (**I_{30}**) (300 mg, 1.1 mmol) in THF (6 ml) was added methyl iodide (0.7 ml, 11 mmol) at room temperature. After stirring for 12 hours, the mixture was concentrated *in vacuo*. The residue was dissolved in EtOH (5 ml) and water (5 ml). To this solution was added sodium borohydride (29 mg, 0.77 mmol) in water (1 ml) at 0°C. After stirring at room temperature for 1 hour, water and toluene were added and aqueous layer was acidified with 2 N hydrochloric acid. Aqueous layer was separated followed by poured into sodium bicarbonate solution and EtOAc. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give **J_{30}** (239 mg, 75%): MS (ESP) *m/z* 285 (M+H); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, t, J=7.1 Hz), 2.41 (3H, s), 2.54~2.59 (2H, m), 2.65~2.70 (2H, m), 3.13~3.16 (2H, m), 4.39 (2H, q, J=7.1 Hz), 6.65 (1H, br s), 7.19 (1H, s).

4-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-1,3-thiazole-2-thiol (**B_{30}**)

MS (ESP) *m/z* 213 (M+H); ^1H NMR (300 MHz, DMSO-d_6) δ 2.29 (3H, s), 2.33 (2H, br s), 2.54~2.58 (2H, m), 3.04 (2H, d, J=3.1 Hz), 6.41 (1H, br s), 6.79 (1H, s).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-{[4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1,3-thiazol-2-yl]thio}-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**C_{30}**)

MS (ESP) *m/z* 557 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, d, *J*=7.4 Hz), 1.33 (1H, d, *J*=6.4 Hz), 2.44 (3H, s), 2.57 (2H, br s), 2.68~2.73 (2H, m), 3.19 (2H, br s), 3.29 (1H, dd, *J*=2.7, 6.6 Hz), 3.53~3.63 (1H, m), 4.20~4.31 (2H, m), 5.29 (1H, d, *J*=13.6 Hz), 5.53 (1H, d, *J*=13.6 Hz), 6.67 (1H, br s), 7.10 (1H, s), 7.67 (2H, d, *J*=8.8 Hz), 8.24 (2H, d, *J*=8.8 Hz).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-{[4-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1,3-thiazol-2-yl]thio}-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**30**)

IR (KBr) cm^{-1} 3423, 1759, 1602, 1388, 1267.; ^{1}H NMR (300 MHz, D_2O) δ 0.91 (3H, d, *J*=7.3 Hz), 1.09 (1H, d, *J*=6.2 Hz), 2.68 (2H, br s), 2.76 (3H, s), 3.08~3.19 (2H, m), 3.29 (2H, br s), 3.32 (1H, dd, *J*=2.6, 5.7 Hz), 3.70 (2H, br s), 4.03~4.11 (2H, m), 6.31 (1H, br s), 7.43 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[1-(iminomethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**31**)

To a solution of **23** (145 mg, 0.36 mmol) in 0.05 M phosphate buffer (pH 8.5, 4 ml) were added benzyl formimidate hydrochloride (494 mg, 2.9 mmol) in three portions at 15 minutes intervals at 0°C. The pH was adjusted to 8.5 by addition of 1 N sodium hydroxide. The product was purified by chromatography on MCI gel (CHP-20P) to give **31**: IR (KBr) cm^{-1} 3401, 1764, 1710, 1596, 1384.; ^{1}H NMR (300 MHz, D_2O) δ 0.98 (3H, d, *J*=7.3 Hz), 1.19 (3H, d, *J*=6.3 Hz), 2.64 (2H, br s), 3.18~3.24 (1H, m), 3.38~3.41 (1H, m), 3.73~3.83 (2H, m), 4.13~4.19 (4H, m), 6.40, 6.45 (1H, s×2), 7.45, 7.46 (1H, s×2), 7.90, 7.91 (1H, s×2).

(4*R*,5*S*,6*S*)-3-{[4-(1-Ethanimidoyl-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 (**32**)

To a solution of **23** (85 mg, 0.21 mmol) in 0.05 M phosphate buffer (pH 8.5, 2 ml) were added ethyl acetimidate hydrochloride (387 mg, 3.1 mmol) in three portions at 15 minutes intervals at 0°C. The pH was adjusted to 8.5 by addition of 1 N sodium hydroxide. The product was purified by chromatography on MCI gel (CHP-20P) to give **32** (32 mg, 34%): IR (KBr) cm^{-1} 3354, 1762, 1603, 1381.; ^{1}H NMR (300 MHz, D_2O) δ 1.05 (3H, d, *J*=7.3 Hz), 1.25 (3H, d, *J*=6.3 Hz), 2.37, 2.41 (3H, s×2), 2.69 (2H, br s), 3.29 (1H, m), 3.47 (1H, m), 3.78~3.83 (2H, m), 4.20~4.34 (4H, m), 6.47 (1H, s), 7.53, 7.54 (1H, s×2).

(4*R*,5*S*,6*S*)-3-({4-[1-(2-Amino-2-oxoethyl)-1-methyl-1,2,3,6-tetrahydropyridinium-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-carboxylate (**33**)

To a solution of **C_{30}** (830 mg, 1.5 mmol) in EtOAc (16 ml) was added iodoacetamide (550 mg, 3.0 mmol) at room temperature. After stirring for 30 minutes, the precipitate was separated by decantation and dried *in vacuo*. This quaternary salt was deprotected by the same way as other carbapenem compounds to give **33** (380 mg, 52%): IR (KBr) cm^{-1} 3378, 1759, 1695, 1599, 1387, 1266.; ^{1}H NMR (300 MHz, D_2O) δ 0.91 (3H, d, *J*=7.1 Hz), 1.09 (1H, d, *J*=6.4 Hz), 2.80 (2H, br s), 3.09~3.20 (2H, m), 3.23 (3H, s), 3.32 (1H, dd, *J*=2.6, 6.0 Hz), 3.63~3.72 (1H, m), 3.80~3.90 (1H, m), 4.01~4.15 (5H, m), 4.28 (1H, br d, *J*=15.6Hz), 6.30 (1H, br s), 7.48 (1H, s).

O-Ethyl *S*-[4-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,3-thiazol-2-yl] Thiocarbonate (**J_{34}**)

MS (ESP) *m/z* 241 (M−OEt), 213 (M−COOEt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, t, *J*=7.1 Hz), 2.36~2.44 (2H, m), 2.46 (3H, s), 2.56~2.59 (2H, m), 3.29~3.31 (2H, m), 4.38 (2H, q, *J*=7.1 Hz), 6.65~6.70 (1H, m), 7.16 (1H, s).

4-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,3-thiazole-2-thiol (**B_{34}**)

MS (ESP) *m/z* 213 (M+H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (2H, br s), 2.32 (3H, s), 2.45~2.49 (2H, m), 3.09~3.10 (2H, m), 6.47 (1H, br s), 6.76 (1H, s).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-{[4-(1-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-carboxylate (**C_{34}**)

MS (ESP) *m/z* 557 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, d, *J*=7.3 Hz), 1.33 (1H, d, *J*=6.2 Hz), 2.39~2.46 (2H, m), 2.47 (3H, s), 2.57~2.62 (2H, m), 3.24~3.33 (3H, m), 3.53~3.63 (1H, m), 4.20~4.31 (2H, m), 5.29 (1H, d, *J*=13.5 Hz), 5.52 (1H, d, *J*=13.5 Hz), 6.67~6.71 (1H, m), 7.07 (1H, s), 7.65~7.69 (2H, m), 8.21~8.26 (2H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-{[4-(1-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 (**34**)

IR (KBr) cm^{-1} 3412, 1761, 1601, 1387, 1275.; ^1H NMR (300 MHz, D_2O) δ 0.92 (3H, d, J=7.5 Hz), 1.09 (1H, d, J=6.2 Hz), 2.50 (2H, br s), 2.82 (3H, s), 3.08~3.25 (3H, m), 3.31~3.34 (1H, m), 3.87~3.93 (2H, m), 4.05~4.12 (2H, m), 6.53 (1H, br s), 7.36 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[1-(2-Amino-2-oxoethyl)-1-methyl-1,2,5,6-tetrahydropyridinium-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 (**35**)

IR (KBr) cm^{-1} 3402, 1757, 1696, 1596, 1387, 1276.; ^1H NMR (300 MHz, D_2O) δ 0.92 (3H, d, J=7.1 Hz), 1.10 (1H, d, J=6.4 Hz), 2.62 (2H, br s), 3.08~3.19 (2H, m), 3.28 (3H, s), 3.33 (1H, dd, J=2.7, 6.0 Hz), 3.52~3.63 (1H, m), 3.73~3.81 (1H, m), 4.04~4.12 (4H, m), 4.29 (1H, br d, J=15.9Hz), 4.52 (1H, br d, J=15.9Hz), 6.60 (1H, br s), 7.42 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(3*R*)-1-Ethanimidoylpyrrolidin-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 (**36**)

To a solution of **25** (0.10 g, 0.25 mmol) in water (1.5 ml) were added ethylacetimidate hydrochloride (0.16 g, 1.3 mmol) in four portions at 15 minutes intervals at room temperature. The pH was adjusted to 7.00 by addition of 1 N sodium hydroxide. The product was purified by chromatography on MCI gel (CHP-20P) to give **36** (0.070 g, 63%): MS (ESP) *m/z* 437.3 (M+H); IR (MIR) cm^{-1} 1753.; ^1H NMR (250 MHz, D_2O) δ 1.10 (3H, d, J=7.0 Hz), 1.21 (3H, d, J=6.3 Hz), 2.10~2.30 (1H, m), 2.25 (3H, s), 2.38~2.58 (1H, m), 3.05~3.22 (1H, m), 3.37~3.45 (1H, m), 3.47~4.10 (5H, m), 7.45 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(3*S*)-1-Ethanimidoylpyrrolidin-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 (**37**)

MS (ESP) *m/z* 437.3 (M+H); IR (MIR) cm^{-1} 1760.; ^1H NMR (250 MHz, D_2O) δ 1.04 (3H, d, J=7 Hz), 1.24 (3H, d, J=6.25 Hz), 2.29 (3H, s), 2.20~2.40 (1H, m), 2.40~2.60 (1H, m), 3.10~3.25 (1H, m), 3.40~4.00 (7H, m), 4.00~4.30 (3H, m), 7.48 (1H, s).

4-(1-Methyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1,3-thiazole-2-thiol (**B_{38}**)

To a suspension of lithium aluminum hydride (70 mg, 1.8 mmol) in THF (3 ml) was added **B_{27}** (200 mg, 0.75 mmol) at room temperature. After stirring for 2 hours, MeOH was added and the mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **B_{38}** (108 mg, 73%): MS (ESP) *m/z* 199 (M+H); ^1H NMR (300 MHz, CD_3OD) δ 2.63 (3H, s), 3.74~3.77 (2H, m), 3.83~3.87 (2H, m), 6.27 (1H, br s), 6.70 (1H, s).

Allyl (4*R*,5*S*,6*S*)-4-Methyl-3-{[4-(1-methyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1,3-thiazol-2-yl]thio}-7-oxo-6-{(1*R*)-1-[(trimethylsilyl)oxy]ethyl}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**C_{38}**)

IR (KBr) cm^{-1} 2968, 1782, 1560, 1490, 1457, 1375, 1322.; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (9H, s), 1.06 (3H, d, J=7.4 Hz), 1.21 (3H, d, J=6.1 Hz), 2.54 (3H, s), 3.21 (1H, dd, J=2.9, 6.4 Hz), 3.45~3.56 (1H, m), 3.63~3.68 (2H, m), 3.76~3.83 (2H, m), 4.14~4.23 (2H, m), 4.67~4.85 (2H, m), 5.25 (1H, dd, J=1.3, 10.4 Hz), 5.44 (1H, dd, J=1.5, 17.0 Hz), 5.96 (1H, ddt, J=5.5, 10.4, 17.0 Hz), 6.37 (1H, br s), 7.04 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-{[4-(1-methyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1,3-thiazol-2-yl]thio}-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**38**)

IR (KBr) cm^{-1} 3422, 1758, 1605, 1396.; ^1H NMR (300 MHz, D_2O) δ 0.93 (3H, d, J=7.0 Hz), 1.10 (3H, d, J=6.4 Hz), 2.78 (3H, s), 3.08~3.20 (1H, m), 3.30~3.34 (1H, m), 3.99~4.21 (6H, m), 6.22 (1H, s), 7.44 (1H, s).

(4*R*,5*S*,6*S*)-3-{[4-(1-Ethanimidoyl-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 (**39**)

Anal Calcd for $C_{19}H_{22}N_4O_4S_2+2H_2O$: C 48.50, H 5.57, N 11.91, S 13.63, H_2O 7.65. Found: C 48.24, H 5.48, N 11.87, S 13.72, H_2O 7.62.; IR (KBr) cm^{-1} 3373, 1758, 1603, 1390.; ^1H NMR (300 MHz, D_2O) δ 1.09 (3H, d, J=7.2 Hz), 1.26 (3H, d, J=6.4 Hz), 2.35, 2.38 (3H, s×2), 3.32 (1H, m), 3.49 (1H, m), 4.24 (2H, m), 4.46 (2H, br s), 4.61, 4.65 (2H, br s×2), 6.46 (1H, m), 7.61 (1H, s).

tert-Butyl (4*S*)-4-{[(Benzyloxy)carbonyl]amino}pentanoate (**S_{40}**)

To a solution of *tert*-butyl (4*R*)-4-{[(benzyloxy)-carbonyl]amino}-5-hydroxypentanoate (**R_{40}**, $[\alpha]_D$ +15.1, c=2.4, $CHCl_3$) (5.0 g, 16 mmol) and carbon tetrabromide (6.2 g, 19 mmol) in dichloromethane (50 ml) was added triphenylphosphine (5.68 g, 22 mmol) at 0°C. After stirring for 30 minutes, ether was added and precipitate was filtered off. The filtrate was concentrated *in vacuo* and the residue

was purified by chromatography on silica gel to give *tert*-butyl (4*R*)-4-{[(benzyloxy)carbonyl]amino}-5-bromopentanoate (4.48 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.84~1.92 (2H, m), 2.23~2.41 (2H, m), 3.50 (1H, dd, J=10.4, 3.5 Hz), 3.57 (1H, dd, J=10.4, 4.4 Hz), 3.86~3.97 (1H, m), 5.04~5.16 (3H, m), 7.27~7.40 (5H, m).

To a solution of the bromide (4.48 g, 12 mmol) and tributyltin hydride (6.2 ml, 23 mmol) in toluene (45 ml) was added 2,2′-azobisisobutyronitrile (0.19 g, 1.2 mmol) and the mixture was stirred at 80°C for 20 minutes. The reaction mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **S$_{40}$** (3.40 g, 95%): MS (ESP) *m/z* 308 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, d, J=6.6 Hz), 1.43 (9H, s), 1.68~1.79 (2H, m), 2.26~2.31 (2H, m), 3.69~3.80 (1H, m), 4.63~4.70 (1H, m), 5.04~5.12 (2H, m), 7.30~7.37 (5H, m).

tert-Butyl (4*S*)-4-[[(Allyloxy)carbonyl](2-methoxy-2-oxoethyl)amino]pentanoate (**P$_{40}$**)

A solution of **S$_{40}$** (3.40 g, 11 mmol) in MeOH (34 ml) was stirred under hydrogen atmosphere in the presence of 10% Pd-C (0.7 g). After 3 hours, catalyst was filtered off and the filtrate was concentrated *in vacuo* to give *tert*-butyl (4*S*)-4-aminopentanoate (1.92 g) quantitatively: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, d, J=6.4 Hz), 1.45 (9H, s), 1.53~1.73 (2H, m), 2.20~2.36 (2H, m), 2.86~2.96 (1H, m).

A solution of the amine (1.92 g, 11 mmol), methyl bromoacetate (1.6 ml, 17 mmol) and *N*,*N*-diisopropylethylamine (2.9 ml, 17 mmol) in MeOH (60 ml) was stirred at 60°C for 3 hours. The reaction mixture was concentrated *in vacuo* followed by dissolved in chloroform (40 ml). To this solution were added allyl chloroformate (2.4 ml, 23 mmol) and *N*,*N*-diisopropylethylamine (36.9 ml, 22 mmol) at 0°C. After stirring for 1 hour, the mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **P$_{40}$** (3.08 g, 84%): MS (ESP) *m/z* 330 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13~1.17 (3H, m), 1.43 (9H, s), 1.64~1.74 (2H, m), 2.25~2.39 (2H, m), 3.69~3.94 (5H, m), 4.18~4.37 (1H, m), 4.56~4.64 (2H, m), 5.15~5.35 (2H, m), 5.81~6.00 (1H, m).

1-Allyl 4-*tert*-Butyl (2*S*)-2-Methyl-5-oxopiperidine-1,4-dicarboxylate (**Q$_{40}$**)

To a suspension of potassium *tert*-butoxide (68 mg, 0.61 mmol) in THF (3.5 ml) was added a solution of **P$_{40}$** (223 mg, 0.68 mmol) in THF (1 ml) at 60°C. After 1 minutes, the mixture was poured into dil hydrochloric acid and extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **Q$_{40}$** (128 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, d, J=6.8 Hz), 1.51 (9H, s), 2.13 (1H, d, J=15.8 Hz), 2.43~2.52 (1H, m), 3.68 (1H, d, J=18.7 Hz), 4.38 (1H, d, J=18.7 Hz), 4.57~4.62 (3H, m), 5.19~5.35 (2H, m), 5.86~6.00 (1H, m), 12.20 (1H, s).

1-Allyl 4-Methyl (2*S*)-2-Methyl-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (**L$_{40}$**)

To a solution of **Q$_{40}$** (2.01 g, 6.8 mmol) and AcOH (0.46 ml, 8.0 mmol) in MeOH (40 ml) was added sodium cyanoborohydride (0.51 g, 8.1 mmol) at room temperature. After 30 minutes, the mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give 1-allyl 4-*tert*-butyl (2*S*)-5-hydroxy-2-methyl-piperidine-1,4-dicarboxylate (1.74 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, d, J=6.9 Hz), 1.47 (9H, s), 1.69~1.87 (2H, m), 2.47~2.56 (1H, m), 2.70~2.80 (1H, m), 3.23 (1H, br s), 3.70~3.87 (1H, m), 4.12~4.28 (1H, m), 4.51 (1H, br s), 4.57~4.60 (2H, m), 5.17~5.33 (2H, m), 5.87~6.00 (1H, m).

To a solution of the alcohol (1.74 g, 5.8 mmol) in dichloromethane (35 ml) were added methanesulfonyl chloride (0.67 ml, 8.7 mmol) and triethylamine (1.62 ml, 12 mmol) at 0°C. After stirring at the same temperature for 20 minutes, water and EtOAc were added to this mixture. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in dichloromethane (9 ml) and toluene (18 ml). 1,8-Diazabicyclo[5.4.0]undec-7-ene (2.6 ml, 17 mmol) was added to this solution at 0°C. After stirring for 1 hour, the mixture was poured into 1 N HCl and extracted with EtOAc. The organic layer was washed successively with satd sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give 1-allyl 4-*tert*-butyl (2*S*)-2-methyl-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (1.26 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, d, J=6.8 Hz), 1.50 (9H, s), 2.30 (1H, d, J=16.8 Hz), 2.42~2.53 (1H, m), 3.73 (1H, d, J=20.3 Hz), 4.44 (1H, d, J=20.3 Hz), 4.61~4.67 (3H, m), 5.19~5.34 (2H, m), 5.88~6.00 (1H, m), 6.78 (1H,

s).

To a solution of the *tert*-butyl ester (0.64 g, 2.3 mmol) in MeOH (10 ml) was added 4 M-hydrogen chloride/MeOH (17.5 ml, 70 mol) at 0°C. After stirring at the same temperature for 10 hours, the mixture was concentrated *in vacuo* to give $\mathbf{L_{40}}$ (0.312 g, 57%): MS (ESP) *m/z* 240 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, d, J=6.8 Hz), 2.33 (1H, d, J=16.8 Hz), 2.44~2.56 (1H, m), 3.70~3.80 (1H, m), 3.74 (3H, s), 4.38~4.50 (1H, m), 4.55~4.70 (3H, m), 5.20 (1H, ddd, J=1.5, 2.7, 10.4 Hz), 5.29 (1H, ddd, J=1.7, 3.1, 17.2 Hz), 5.93 (1H, ddd, J=5.5, 10.4, 17.2 Hz), 6.87 (1H, br s).

Allyl (2*S*)-4-(Chloroacetyl)-2-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate ($\mathbf{H_{40}}$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, d, J=6.8 Hz), 2.43 (2H, br s), 3.77~3.88 (1H, m), 4.35~4.70 (6H, m), 5.21 (1H, ddd, J=1.5, 2.7, 10.4 Hz), 5.29 (1H, ddd, J=1.7, 2.9, 17.2 Hz), 5.93 (1H, ddd, J=5.5, 10.4, 17.2 Hz), 6.81 (1H, br s).

Allyl (2*S*)-4-(2-Mercapto-1,3-thiazol-4-yl)-2-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate ($\mathbf{B_{40}}$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, d, J=6.9 Hz), 2.05~2.14 (1H, m), 2.59~2.70 (1H, m), 3.72~3.84 (1H, m), 4.43~4.74 (4H, m), 5.21 (1H, ddd, J=1.5, 2.7, 10.4 Hz), 5.29 (1H, ddd, J=1.5, 2.9, 17.2 Hz), 5.93 (1H, ddd, J=5.7, 10.4, 17.2 Hz), 6.19 (1H, br s), 6.38 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(2*S*)-1-[(Allyloxy)carbonyl]-2-methyl-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 ($\mathbf{C_{40}}$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (9H, s), 1.10 (3H, d, J=7.1 Hz), 1.18 (3H, d, J=7.0 Hz), 1.21 (3H, d, J=6.2 Hz), 2.28 (1H, d, J=16.3 Hz), 2.67~2.79 (1H, m), 3.22 (1H, dd, J=2.9, 6.2 Hz), 3.46 (1H, dd, J=7.4, 9.9 Hz), 3.75~3.86 (1H, m), 4.15~4.23 (2H, m), 4.42~4.53 (1H, m), 4.59~4.86 (5H, m), 5.16~5.48 (4H, m), 5.88~6.03 (2H, m), 6.64 (1H, br s), 7.08 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(2*S*)-2-methyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**40**)

IR (KBr) cm^{-1} 3392, 2970, 1758, 1599, 1391, 1263.; ^{1}H NMR (300 MHz, D_2O) δ 0.91 (3H, d, J=7.1 Hz), 1.09 (3H, d, J=6.4 Hz), 1.26 (3H, d, J=6.4 Hz), 2.24~2.37 (1H, m), 2.60~2.71 (1H, m), 3.07~3.18 (1H, m), 3.28~3.38 (2H, m), 3.68 (2H, br s), 4.03~4.10 (2H, m), 6.35 (1H, m), 7.39 (1H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(2*R*)-1-[(Allyloxy)carbonyl]-2-methyl-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 ($\mathbf{C_{41}}$)

$\mathbf{C_{41}}$ was synthesized from $\mathbf{R_{41}}$ ($[\alpha]_D$ −15.1, c=2.3, $CHCl_3$) in the same manner to that of $\mathbf{C_{40}}$.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 1.07 (3H, d, J=7.3 Hz), 1.17 (3H, d, J=6.8 Hz), 1.21 (3H, d, J=6.2 Hz), 2.28 (1H, d, J=17.2 Hz), 2.67~2.79 (1H, m), 3.22 (1H, dd, J=2.7, 6.2 Hz), 3.56 (1H, dd, J=7.3, 9.9 Hz), 3.77~3.87 (1H, m), 4.15~4.23 (2H, m), 4.42~4.53 (1H, m), 4.60~4.85 (5H, m), 5.18~5.48 (4H, m), 5.88~6.02 (2H, m), 6.64 (1H, br s), 7.06 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(2*R*)-2-methyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**41**)

IR (KBr) cm^{-1} 3428, 2971, 1758, 1602, 1391, 1263.; ^{1}H NMR (300 MHz, D_2O) δ 0.91 (3H, d, J=7.1 Hz), 1.10 (3H, d, J=6.2 Hz), 1.32 (3H, d, J=6.4 Hz), 2.30~2.45 (1H, m), 2.67~2.78 (1H, m), 3.09~3.18 (1H, m), 3.31~3.34 (1H, m), 3.41~3.52 (1H, m), 3.77 (2H, br s), 4.05~4.13 (2H, m), 6.35 (1H, m), 7.42 (1H, m).

Methyl *N*-[(Allyloxy)carbonyl]-*N*-(4-ethoxy-4-oxobutyl)-*L*-alaninate ($\mathbf{P_{42}}$)

To a suspension of methyl alaninate hydrochloride (100 mg, 0.72 mmol) in DMF (2.5 ml) were added potassium carbonate (500 mg, 3.6 mmol), potassium iodide (60 mg, 0.36 mol) and ethyl 4-bromobutyrate (0.103 ml, 0.72 mmol) and the mixture was stirred at 60°C. After 2 hours, 4-bromobutyrate (0.103 ml, 0.72 mmol) was added again and stirred 2 hours at 60°C. The mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was dissolved in chloroform (5 ml). To this solution were added *N*,*N*-diisopropylethylamine (0.25 ml, 1.44 mmol) and allyl chloroformate (0.15 ml, 1.42 mmol) at room temperature for 1 hour. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give $\mathbf{P_{42}}$ (134 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, t, J=7.1 Hz), 1.49 (3H, d, J=7.4 Hz), 1.80~1.98 (2H, m), 2.30~2.40 (2H, m), 3.12~3.27 (1H, m), 3.38~3.51 (1H, m), 3.71 (3H, s), 4.13 (2H, q, J=7.1 Hz), 4.45~4.62 (3H,

m), 5.18~5.33 (2H, m), 5.81~6.00 (1H, m).

1-Allyl 4-Ethyl (2*S*)-2-Methyl-3-oxopiperidine-1,4-dicarboxylate (**Q_{42}**)

To a suspension of potassium *tert*-butoxide (3.42 g, 30 mol) in THF (50 ml) was added **P_{42}** (4.60 g, 15 mmol) at 60°C and the mixture was stirred for 1 minute. The mixture was poured into 1 M NaH_2PO_4 (50 ml) and pH of the mixture was adjusted to 3.0 with 1 N hydrochloric acid. The mixture was extracted with EtOAc and the extract was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **Q_{42}** (2.03 g, 49%): MS (ESP) *m/z* 270 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, t, *J*=7.1 Hz), 1.40 (3H, d, *J*=7.0 Hz), 2.25~2.42 (2H, m), 2.86~3.08 (1H, m), 4.07~4.28 (1H, m), 4.23 (2H, q, *J*=7.1 Hz), 4.57~4.72 (3H, m), 5.20~5.34 (2H, m), 5.88~6.00 (1H, m), 12.20 (1H, s).

The corresponding methyl ester was also obtained (1.20 g, 31%): MS (ESP) *m/z* 256 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, d, *J*= 6.8 Hz), 2.25~2.42 (2H, m), 2.86~3.03 (1H, m), 3.78 (3H, s), 4.07~4.28 (1H, m), 4.57~4.72 (3H, m), 5.20~5.34 (2H, m), 5.88~6.01 (1H, m), 12.10 (1H, s).

1-Allyl 4-Ethyl (6*S*)-6-Methyl-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (**L_{42}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, d, *J*=7.0 Hz), 1.30 (3H, t, *J*=7.1 Hz), 2.23~2.36 (1H, m), 2.40~2.46 (1H, m), 2.80~2.96 (1H, m), 4.14~4.29 (3H, m), 4.57~4.72 (3H, m), 5.20~5.34 (2H, m), 5.87~6.01 (1H, m), 6.82 (1H, s).

Allyl (6*S*)-4-(Chloroacetyl)-6-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**H_{42}**)

MS (ESP) *m/z* 258 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (3H, d, *J*=7.0 Hz), 2.18~2.31 (1H, m), 2.49~2.56 (1H, m), 2.80~2.94 (1H, m), 4.16~4.31 (1H, m), 4.39 (1H, d, *J*=14.1 Hz), 4.42 (1H, d, *J*=14.1 Hz), 4.60~4.64 (2H, m), 4.74~4.83 (1H, m), 5.20~5.34 (2H, m), 5.86~6.02 (1H, m), 6.73 (1H, s).

Allyl (6*S*)-4-(2-Mercapto-1,3-thiazol-4-yl)-6-methyl-3,6-dihydropyridine-1(2*H*)-carboxylate (**B_{42}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, d, *J*=6.9 Hz), 2.20~2.28 (1H, m), 2.38~2.50 (1H, m), 2.83~3.05 (1H, m), 4.25~4.33 (1H, m), 4.60~4.65 (2H, m), 4.66~4.78 (1H, m), 5.21~5.35 (2H, m), 5.89~6.02 (2H, m), 6.40 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(6*S*)-1-[(Allyloxy)carbonyl]-6-methyl-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_{42}**)

MS (ESP) *m/z* 546 (M−$SiMe_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.06~1.12 (3H, m), 1.24 (3H, d, *J*=6.0 Hz), 1.29~1.32 (3H, m), 2.37~2.45 (1H, m), 2.46~2.59 (1H, m), 3.00~3.12 (1H, m), 3.24 (1H, dd, *J*=6.4, 2.9 Hz), 3.42~3.61 (1H, m), 4.16~4.40 (3H, m), 4.62~4.87 (5H, m), 5.20~5.50 (4H, m), 5.90~6.04 (2H, m), 6.61~6.64 (1H, m), 7.10~7.13 (1H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(6*S*)-6-methyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**42**)

IR (KBr) cm^{-1} 3409, 2971, 1760, 1596, 1390, 1264, 1148, 1028.; ^{1}H NMR (300 MHz, D_2O) δ 0.91 (3H, d, *J*=7.0 Hz), 1.10 (3H, d, *J*=5.7 Hz), 1.32 (3H, d, *J*=6.8 Hz), 2.58~2.63 (2H, m), 3.09~3.26 (2H, m), 3.30~3.34 (1H, m), 3.42~3.51 (1H, m), 4.01~4.11 (3H, m), 6.28 (1H, s), 7.44 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(6*R*)-1-[(Allyloxy)carbonyl]-6-methyl-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_{43}**)

MS (ESP) *m/z* 546 (M−SiMe3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (9H, s), 1.04~1.10 (3H, m), 1.15~1.29 (6H, m), 2.34~2.57 (2H, m), 2.96~3.11 (1H, m), 3.19~3.24 (1H, m), 3.38~3.58 (1H, m), 4.13~4.38 (3H, m), 4.59~4.85 (5H, m), 5.16~5.48 (4H, m), 5.85~6.02 (2H, m), 6.61 (1H, m), 7.08~7.10 (1H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(6*R*)-6-methyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**43**)

IR (KBr) cm^{-1} 3422, 1771.; ^{1}H NMR (300 MHz, D_2O) δ 0.89~0.91 (3H, m), 1.09 (3H, d, *J*=6.4 Hz), 1.33 (3H, d, *J*=7.0 Hz), 2.58~2.67 (2H, m), 3.07~3.35 (3H, m), 3.43~3.53 (1H, m), 4.00~4.12 (3H, m), 6.28 (1H, s), 7.44 (1H, s).

tert-Butyl (4*R*)-4-{[(Benzyloxy)carbonyl]amino}-5-(methoxymethoxy)pentanoate (**S_{44}**)

To a solution of **R_{40}** (15.05 g, 47 mmol) in dichloromethane (150 ml) were added *N*,*N*-diisopropylethylamine (26 ml, 150 mmol), chloromethyl methyl ether (12 ml, 150 mmol) and 4-(dimethylamino)pyridine (120 mg,

1.0 mmol) at 0°C. The mixture was warmed to room temperature and stirred for 10 hours. The resulting mixture was poured into dil hydrochloric acid and extracted with chloroform. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to give **S_{44}** (16.87 g, 99%): MS (ESP) *m/z* 368 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (9H, s), 1.75~1.92 (2H, m), 2.22~2.35 (2H, m), 3.31 (3H, s), 3.47~3.58 (2H, m), 3.75~3.86 (1H, m), 4.58 (2H, s), 5.02 (1H, br d, J=8.1 Hz), 5.07 (2H, s), 7.26~7.37 (5H, m).

tert-Butyl (4*R*)-4-[[(Allyloxy)carbonyl](2-methoxy-2-oxoethyl)amino]-5-(methoxymethoxy)pentanoate (**P_{44}**)

MS (ESP) *m/z* 390 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.78~1.91 (2H, m), 2.31~2.37 (2H, m), 3.33 (3H, s), 3.62 (2H, t, J=6.8 Hz), 3.71 (1.8H, s), 3.72 (1.2H, s), 3.99 (2H, s), 4.22~4.38 (1H, m), 4.52~4.66 (4H, m), 5.15~5.35 (2H, m), 5.81~5.97 (1H, m).

1-Allyl 4-*tert*-Butyl (2*R*)-2-[(Methoxymethoxy)methyl]-5-oxopiperidine-1,4-dicarboxylate (**Q_{44}**)

MS (ESP) *m/z* 358 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (9H, s), 2.29~2.44 (2H, m), 3.33 (3H, s), 3.49~3.76 (3H, m), 4.31~4.48 (1H, m), 4.56~4.70 (5H, m), 5.22 (1H, d, J=10.4 Hz), 5.31 (1H, d, J=17.4 Hz), 5.94 (1H, ddd, J=5.1, 10.4, 17.2 Hz), 12.23 (1H, s).

1-Allyl 4-Methyl (2*R*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}-methyl)-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (**L_{44}**)

MS (ESP) *m/z* 370 (M+H); IR (KBr) cm^{-1} 2953, 1715, 1417, 1251, 1112.; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.01 (6H, s), 0.83 (9H, s), 2.33~2.46 (1H, m), 2.47~2.62 (1H, m), 3.40~3.53 (2H, m), 3.63~3.92 (1H, m), 3.73 (3H, s), 4.33~4.65 (4H, m), 5.20 (1H, dd, J=1.5, 10.4 Hz), 5.29 (1H, d, J=16.7 Hz), 5.92 (1H, ddt, J=5.3, 10.4, 16.7 Hz), 6.78~6.92 (1H, m).

Allyl (2*R*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-(chloroacetyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**H_{44}**)

MS (ESP) *m/z* 388 (M+H); IR (KBr) cm^{-1} 2954, 2858, 1692, 1650, 1414, 1113.; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.02 (6H, s), 0.82 (9H, s), 2.23~2.43 (1H, m), 2.57~2.68 (1H, m), 3.40~3.53 (2H, m), 3.63~3.92 (2H, m), 4.33~4.65 (5H, m), 5.20 (1H, dd, J=1.3, 12.1 Hz), 5.29 (1H, dd, J=1.5, 17.2 Hz), 5.92 (1H, ddt, J=5.3, 12.1, 17.2 Hz), 6.73~6.85 (1H, m).

Allyl (2*R*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-(2-mercapto-1,3-thiazol-4-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**B_{44}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 2.40~2.57 (2H, m), 3.45~3.85 (3H, m), 3.38~3.65 (4H, m), 5.18~5.35 (2H, m), 5.88~6.01 (1H, m), 6.07 (1H, br s), 6.40 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*R*)-1-[(Allyloxy)carbonyl]-2-(hydroxymethyl)-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-carboxylate (**C_{44}**)

IR (KBr) cm^{-1} 3426, 2933, 1772, 1700, 1559, 1457, 1136.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, d, J=7.3 Hz), 1.31 (3H, d, J=6.2 Hz), 2.50 (1H, d, J=17.4 Hz), 2.62~2.73 (1H, m), 3.25 (1H, d, J=2.8, 7.0 Hz), 3.45~3.96 (4H, m), 4.17~4.27 (2H, m), 4.41~4.86 (6H, m), 5.19~5.47 (4H, m), 5.87~6.03 (2H, m), 6.63 (1H, s), 7.11 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(2*R*)-2-(hydroxymethyl)-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 (**44**)

IR (KBr) cm^{-1} 3396, 1752, 1602, 1396.; ^{1}H NMR (300 MHz, D_2O) δ 0.92 (3H, d, J=7.0 Hz), 1.09 (3H, d, J=6.4 Hz), 2.35~2.65 (2H, m), 3.08~3.18 (1H, m), 3.30~3.44 (2H, m), 3.60 (1H, dd, J=6.8, 12.5 Hz), 3.72~3.82 (3H, m), 4.03~4.13 (2H, m), 6.38 (1H, s), 7.41 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*S*)-1-[(Allyloxy)carbonyl]-2-(hydroxymethyl)-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-carboxylate (**C_{45}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, d, J=7.3 Hz), 1.21 (3H, d, J=6.0 Hz), 2.38~2.63 (2H, m), 3.15 (1H, dd, J=2.8, 6.8 Hz), 3.37~3.85 (4H, m), 4.30~4.65 (5H, m), 4.73 (1H, dd, J=5.3, 13.2 Hz), 5.10~5.37 (4H, m), 5.78~5.93 (2H, m), 6.54 (1H, br s), 7.01 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(2*S*)-2-(hydroxymethyl)-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 (**45**)

IR (KBr) cm^{-1} 3379, 1759, 1601, 1388.; ^{1}H NMR (300 MHz, D_2O) δ 0.91 (3H, d, J=7.0 Hz), 1.09 (3H, d, J=6.4 Hz), 2.20~2.33 (1H, m), 2.44~2.53 (1H, m), 3.08~3.73 (7H, m), 4.02~4.13 (2H, m), 6.39 (1H, s), 7.37 (1H, s).

4-[(2*S*)-1,2-Dimethyl-1,2,3,6-tetrahydropyridin-4-yl]-1,3-thiazole-2-thiol (**B_{46}**)

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (3H, d, J=6.4 Hz), 2.04~2.17 (1H, m), 2.63~2.72 (1H, m), 4.01~4.22 (2H, m), 6.38 (1H, s), 6.78 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*S*)-1,2-Dimethyl-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_{46}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 1.05 (3H, d, J=7.1 Hz), 1.21 (6H, d, J=6.2 Hz), 2.24~2.36 (1H, m), 2.41 (3H, s), 2.50~2.61 (1H, m), 2.69~3.00 (2H, m), 3.19~3.22 (1H, m), 3.47~3.53 (1H, m), 4.15~4.20 (2H, m), 4.46~4.85 (3H, m), 5.25 (1H, d, J=10.4 Hz), 5.44 (1H, dd, J=1.4, 17.0 Hz), 5.96 (1H, ddd, J=5.1, 10.4, 17.0 Hz), 6.61 (1H, s), 7.07 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(2*S*)-1,2-Dimethyl-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 (**46**)

IR (KBr) cm^{-1} 3393, 2970, 1749, 1601, 1393, 1266.; ^{1}H NMR (300 MHz, D_2O) δ 0.95 (3H, d, J=7.5 Hz), 1.13 (3H, d, J=6.2 Hz), 1.32 (3H, d, J=6.2 Hz), 2.47~2.58 (1H, m), 2.74~2.88 (1H, m), 2.79 (3H, s), 3.11~3.23 (1H, m), 3.32~3.38 (1H, m), 3.75~3.93 (1H, m), 4.09~4.15 (2H, m), 6.33 (1H, s), 7.47 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-({4-[(2*R*)-1,2-Dimethyl-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_{47}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (9H, s), 1.07 (3H, d, J=7.3 Hz), 1.20 (3H, d, J=6.2 Hz), 1.21 (3H, d, J=6.0 Hz), 2.25~2.34 (1H, m), 2.41 (3H, m), 2.53~2.86 (2H, m), 3.21 (1H, dd, J=2.7, 6.2 Hz), 3.39~3.55 (2H, m), 4.14~4.22 (2H, m), 4.55~4.63 (1H, m), 4.67~4.85 (2H, m), 5.22~5.27 (1H, m), 5.41~5.48 (1H, m), 5.89~6.00 (1H, m), 6.60 (1H, br s), 7.07 (1H, s).

(4*R*,5*S*,6*S*)-3-({4-[(2*R*)-1,2-Dimethyl-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 (**47**)

^{1}H NMR (300 MHz, D_2O) δ 0.93 (3H, d, J=7.1 Hz), 1.11 (3H, d, J=6.4 Hz), 1.32 (3H, br s), 2.46~2.57 (1H, m), 2.73~2.88 (4H, m), 3.10~3.21 (1H, m), 3.33 (1H, dd, J=2.7, 6.2 Hz), 3.45~4.00 (3H, m), 4.05~4.14 (2H, m), 6.31 (1H, m), 7.45 (1H, m).

Allyl (2*S*,4*R*)-4-Cyano-2-({[dimethyl(1,1,2-trimethylpropyl)silyl]oxy}methyl)pyrrolidine-1-carboxylate (**V_{48}**)

To a solution of allyl (2*S*,4*S*)-4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**T_{48}**) (280 g, 1.4 mol) in DMF (2800 ml) was added imidazole (142 g, 2.1 mol). To the resulting solution was added thexyldimethylchlorosilane (248.8 g, 1.4 mol) during 30 minutes at 0°C and then the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was partitioned between hexane and water. The organic layer was washed successively with 10% aq citric acid and brine, dried over magnesium sulfate and concentrated *in vacuo* to constant weight (396.8 g) of which 390 g was dissolved in dichloromethane (3500 ml). To the resulting solution were added triethylamine (137.8 ml, 1.4 mol) and a solution of methanesulfonyl chloride (143 g, 1.2 mol) in dichloromethane (500 ml) during 30 minutes at 0°C. The reaction mixture was then stirred at room temperature for 1 hour and then diluted with water. The layers were separated. The organic layer was washed with 10% aq citric acid and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was dissolved in acetonitrile (2500 ml). To this solition was added tetraethylammonium cyanide (200 g, 1.3 mol) and the mixture was heated to reflux for 18 hours. The reaction mixture was cooled to room temperature and hexane and water was added and the layers were separated. The lighter layer was washed with a 2 : 1 mixture of water and acetonitrile. The aqueous layers were extracted with hexane. The combined hexane fractions were extracted 4 times with acetonitrile and the combined acetonitrile extracts were dried over magnesium sulfate and concentrated *in vacuo* to give **V_{48}** (227 g, 47%): MS (EI) *m/z* 337.2 (M$-CH_3$); IR (FLM) cm^{-1} 2246.; ^{1}H NMR (250 MHz, $CDCl_3$) δ −0.05 (3H, s), −0.03 (3H, s), 0.75~0.90 (12H, m), 1.50~1.65 (1H, m), 2.20~2.45 (2H, m), 3.30~4.20 (6H, m), 4.60 (2H, d, J=5.5 Hz), 5.18~5.40 (2H, m), 5.80~6.00 (1H, m).

1-Allyl 3-Ethyl (3*R*,5*S*)-5-{[(Trimethylsilyl)oxy]methyl}-pyrrolidine-1,3-dicarboxylate (**L_{48}**)

A solution of **V_{48}** (8.0 g, 23 mmol) in 2 M HCl/EtOH (80 ml) was heated to reflux for 18 hours. The reaction mixture was partitioned between water and EtOAc. The organic layer was washed successively with 10% sodium bicarbonate solution and brine then concentrated *in vacuo* to give 1-allyl 3-ethyl (3*R*,5*S*)-5-(hydroxymethyl)pyrrolidine-1,3-dicarboxylate (5.00 g, 86%): MS (EI) *m/z* 258.1 (M+H); IR (MIR) cm^{-1} 1731, 1677.; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (3H, t, J=7.2 Hz), 1.80~2.00 (1H, m), 2.23~2.40 (1H, m), 3.04~3.24 (1H, m), 3.58~3.81 (5H,

m), 4.03~4.21 (1H, m), 4.16 (2H, q, J=7.2 Hz), 4.61 (2H, d, J=8.8 Hz), 5.18~5.40 (2H, m), 5.84~6.04 (1H, m).

A mixture of the alcohol (51.5 g, 200 mmol), hexamethyldisilazane (32.30 g, 200 mmol) and squaric acid (228 g, 2.0 mol) was heated to 75°C for 1 hour. The product was purified by fractional distillation at 110°C and 0.06 mbar to give **L_{48}** (62.34 g, 95%): MS (EI) *m/z* 330.4 (M+H); IR (MIR) cm^{-1} 1734, 1701.; ^1H NMR (250 MHz, $CDCl_3$) δ −0.10 (9H, s), 1.16 (3H, t, J=7.2 Hz), 2.10~2.30 (2H, m), 3.14~3.34 (1H, m), 3.50~3.80 (5H, m), 3.90~4.10 (1H, m), 4.06 (2H, q, J=7.2 Hz), 4.48 (2H, d, J=8.8 Hz), 5.20~5.40 (2H, m), 5.84~6.04 (1H, m).

Allyl (2*S*,4*R*)-4-(2-Mercapto-1,3-thiazol-4-yl)-2-[(pent-4-enoyloxy)methyl]pyrrolidine-1-carboxylate (**B_{48}**)

To a solution of **L_{48}** (20.0 g, 61 mol) and bromochloromethane (15.70 g, 121 mmol) in THF (200 ml) and hexane (100 ml) was added a −78°C cold solution of *n*-butyl lithium in hexane (1.6 M, 75.8 ml, 121 mmol) during 30 minutes at −100°C. The mixture was stirred 15 minutes at −100°C. The reaction mixture was quenched by addition of 10% citric acid. The layers were separated, the organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was taken up in EtOH (200 ml). To the resulting solution was added dithiocarbamic acid ammonium salt (7.81 g, 71 mmol) and the mixture was stirred at room temperature for 30 minutes and then heated to reflux for 2 hours. The reaction mixture was partitioned between water and *tert*-butyl methyl ether at a pH of 10.0. The layers were separated and the aqueous layer was mixed with EtOAc. The pH was adjusted to 5.0 and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated to give slightly yellow foam, which was dissolved in acetonitrile (160 ml). To the resulting solution were added 4-(dimethylamino)-pyridine (6.58 g, 54 mol) and allyl 1-benzotriazolyl carbonate (14.16 g, 65 mmol) and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was partitioned between water and *tert*-butyl methyl ether at a pH of 10.0. The layers were separated and the aqueous layer was mixed with EtOAc. The pH was adjusted to 5.0 and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by chromatography on silica gel to give **B_{48}** (10.98 g, 47%): MS (ESP) *m/z* 385.2 (M+H); IR (MIR) cm^{-1} 1744, 1671.; ^1H NMR (250 MHz, $CDCl_3$) δ 2.17~2.40 (2H, m), 3.40~3.70 (2H, m), 3.74~3.90 (1H, m), 4.17~4.44 (3H, m), 4.57~4.70 (4H, m), 5.20~5.44 (4H, m), 5.84~6.04 (2H, m), 6.31 (1H, s), 11.90 (1H, br s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(3*R*,5*S*)-1-[(Allyloxy)carbonyl]-5-[(pent-4-enoyloxy)methyl]pyrrolidin-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_{48}**)

MS (ESP) *m/z* 706.4 (M+H); IR (MIR) cm^{-1} 1783.; ^1H NMR (250 MHz, $CDCl_3$) δ −0.12 (9H, s), 1.10 (3H, d, J=7.5 Hz), 1.28 (3H, d, J=6.0 Hz), 2.20~2.40 (2H, m), 3.17~3.26 (1H, m), 3.28~3.48 (1H, m), 3.53~3.92 (3H, m), 3.92~4.48 (6H, m), 4.57~5.00 (6H, m), 5.17~5.52 (6H, m), 5.17~5.52 (6H, m), 5.84~6.01 (3H, m), 7.10 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(3*R*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**48**)

Anal Calcd for $C_{18}H_{23}N_3O_5S_2$: C 50.81, H 5.45, N 9.88. Found (corrected for +0.97% H_2O determined by Karl Fischer titration): C 50.89, H 5.42, N 9.85.; MS (EI) *m/z* 426.3 (M+H); IR (MIR) cm^{-1} 1756.; ^1H NMR (250 MHz, D_2O) δ 1.08 (3H, d, J=7.2 Hz), 1.27 (3H, d, J=6.4 Hz), 2.25~2.42 (2H, m), 3.17~3.27 (1H, m), 3.44~3.54 (1H, m), 3.74~4.10 (5H, m), 4.20~4.30 (2H, m), 7.52 (1H, s).

This compound was analyzed by X-ray single crystal analysis and shown to have the assumed stereochemistry.

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(3*S*,5*S*)-1-[(Allyloxy)carbonyl]-5-[(pent-4-enoyloxy)methyl]pyrrolidin-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_{49}**)

MS (ESP) *m/z* 706.5 (M+H); IR (MIR) cm^{-1} 1783.; ^1H NMR (250 MHz, $CDCl_3$) δ −0.12 (9H, s), 1.07 (3H, d, J=7.5 Hz), 1.24 (3H, d, J=6 Hz), 2.09~2.20 (1H, m), 2.50~2.65 (1H, m), 3.20~3.30 (1H, m), 3.32~3.54 (2H, m), 4.00~4.50 (6H, m), 4.55~4.67 (4H, m), 4.68~4.90 (2H, m), 5.18~5.52 (6H, m), 5.84~6.08 (3H, m), 7.10 (1H, s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-({4-[(3*S*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-yl]-1,3-thiazol-2-yl}thio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**49**)

MS (ESP) *m/z* 426.3 (M+H); IR (NJL) cm^{-1} 1762.; ^1H NMR (250 MHz, D_2O) δ 1.08 (3H, d, J=7.2 Hz), 1.27 (3H, d, J=6.4 Hz), 1.95~2.07 (1H, m), 2.55~2.65 (1H, m), 3.15~3.23 (1H, m), 3.35~3.50 (2H, m), 3.75~4.00 (5H, m), 4.20~4.30 (2H, m), 7.52 (1H, s).

1-Allyl 3-Methyl (5*S*)-5-Methyl-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate (**L_{50}**)

MS (ESP) *m/z* 226 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34~1.43 (3H, m), 4.29~4.49 (2H, m), 4.56~4.84 (3H, m), 5.20~5.36 (2H, m), 5.89~6.02 (1H, m), 6.62~6.67 (1H, m).

Allyl (2*S*)-4-(Chloroacetyl)-2-methyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**H_{50}**)

MS (ESP) *m/z* 244 (M+H); IR (KBr) cm^{-1} 1683, 1649, 1629, 1404.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37~1.42 (3H, m), 4.30~4.70 (6H, m), 4.80~4.95 (1H, m), 5.18~5.24 (1H, m), 5.26~5.34 (1H, m), 5.86~5.99 (1H, m), 6.64~6.68 (1H, m).

Allyl (2*S*)-4-(2-Mercapto-1,3-thiazol-4-yl)-2-methyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**B_{50}**)

MS (ESP) *m/z* 283 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34~1.39 (3H, m), 4.32~4.53 (2H, m), 4.61~4.66 (2H, m), 4.72~4.85 (1H, m), 5.22 (1H, d, *J*=10.4 Hz), 5.27~5.35 (1H, m), 5.87~6.09 (2H, m), 6.37 (0.5H, s), 6.40 (0.5H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(5*S*)-1-[(Allyloxy)carbonyl]-5-methyl-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_{50}**)

MS (ESP) *m/z* 532 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06~1.15 (3H, m), 1.35~1.43 (6H, m), 3.26~3.29 (1H, m), 3.47~3.64 (1H, m), 4.20~4.30 (2H, m), 4.43~4.89 (7H, m), 5.24~5.50 (4H, m), 5.92~6.04 (2H, m), 6.37 (1H, br s), 7.12~7.14 (1H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(5*S*)-5-methyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**50**)

IR (KBr) cm^{-1} 3406, 2969, 1760, 1599, 1391.; ^{1}H NMR (300 MHz, D_2O) δ 0.94 (3H, d, *J*=7.3 Hz), 1.12 (3H, d, *J*=6.4 Hz), 1.38 (3H, d, *J*=6.8 Hz), 3.10~3.24 (1H, m), 3.35 (1H, dd, *J*=2.6, 6.0 Hz), 4.05~4.15 (2H, m), 4.23~4.37 (2H, m), 6.25 (1H, s), 7.50 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(5*R*)-1-[(Allyloxy)carbonyl]-5-methyl-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_{51}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (9H, s), 1.08~1.12 (3H, m), 1.22~1.25 (3H, m), 1.37~1.43 (3H, m), 3.24 (1H, dd, *J*=6.2, 2.9 Hz), 3.37~3.58 (1H, m), 4.17~4.24 (2H, m), 4.40~4.87 (7H, m), 5.21~5.50 (4H, m), 5.91~6.05 (2H, m), 6.34~6.38 (1H, m), 7.10~7.14 (1H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(5*R*)-5-methyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**51**)

^{1}H NMR (300 MHz, D_2O) δ 0.92 (3H, d, *J*=7.2 Hz), 1.10 (3H, d, *J*=6.4 Hz), 1.31 (3H, d, *J*=6.8 Hz), 3.10~3.20 (1H, m), 3.32 (1H, dd, *J*=5.9, 2.9 Hz), 4.03~4.28 (4H, m), 6.23 (1H, br s), 7.45 (1H, s).

tert-Butyl (3*S*)-3-{[(Benzyloxy)carbonyl]amino}butanoate (**S_{52}**)

S_{52} was synthesized from **R_{52}** in the same manner to that of **S_{40}**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, d, *J*=6.8 Hz), 1.44 (9H, s), 2.34~2.51 (2H, m), 4.01~4.14 (1H, m), 5.01~5.17 (2H, m), 5.22~5.33 (1H, m), 7.28~7.36 (5H, m).

The optical purity of the compounds **R_{52}** and **R_{53}** were determined by HPLC on a DAICEL CHIRALPAK AD-RH 0.46 i.d.×15 cm, Eluent: H_2O/CH_3CN=2:1, Flow rate: 1.0 ml/minute, Detection: UV 254 nm. **R_{52}** had a retention time of 9.7 minutes (>99% ee), **R_{53}** had a retention time of 13.3 minutes (>99% ee).

tert-Butyl (3*S*)-3-[[(Allyloxy)carbonyl](2-methoxy-2-oxoethyl)amino]butanoate (**P_{52}**)

MS (ESP) *m/z* 316 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22~1.28 (3H, m), 1.43 (9H, s), 2.09~2.64 (2H, m), 3.68~3.73 (5H, m), 4.42~4.55 (1H, m), 4.55~4.66 (2H, m), 5.15~5.38 (2H, m), 5.80~6.02 (1H, m).

1-Allyl 3-*tert*-Butyl (2*S*)-2-Methyl-4-oxopyrrolidine-1,3-dicarboxylate (**Q_{52}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31~1.51 (12H, m), 4.10~4.33 (2H, m), 4.55~4.72 (3H, m), 5.20~5.38 (2H, m), 5.86~6.03 (1H, m), 10.39 (1H, br s).

1-Allyl 3-Methyl (2*S*)-2-Methyl-2,5-dihydro-1*H*-pyrrole-1,3-dicarboxylate (**L_{52}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41~1.47 (3H, m), 3.78 (3H, s), 4.21~4.45 (2H, m), 4.60~4.71 (2H, m), 4.80~4.90 (1H, m), 5.20~5.38 (2H, m), 5.89~6.02 (1H, m), 6.69~6.77 (1H, m).

Allyl (2*S*)-3-(Chloroacetyl)-2-methyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**H_{52}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39~1.44 (3H, m),

4.31~4.58 (4H, m), 4.60~4.71 (2H, m), 4.89~5.00 (1H, m), 5.21~5.38 (2H, m), 5.89~6.02 (1H, m), 6.67~6.87 (1H, m).

Allyl (2*S*)-3-(2-Mercapto-1,3-thiazol-4-yl)-2-methyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**B_{52}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42~1.46 (3H, m), 4.26~4.50 (2H, m), 4.56~4.72 (2H, m), 4.87~5.00 (1H, m), 5.21~5.38 (2H, m), 5.88~6.03 (1H, m), 6.25~6.45 (2H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(2*S*)-1-[(Allyloxy)carbonyl]-2-methyl-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_{52}**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.12 (3H, d, J=7.1 Hz), 1.23 (3H, d, J=6.2 Hz), 1.44~1.50 (3H, m), 3.25 (1H, dd, J=6.0, 2.7 Hz), 3.42~3.58 (1H, m), 4.12~4.48 (4H, m), 4.60~4.89 (4H, m), 4.98~5.08 (1H, m), 5.22~5.51 (4H, m), 5.91~6.05 (2H, m), 6.36~6.37 (1H, m), 7.18~7.26 (1H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(2*S*)-2-methyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**52**)

IR (KBr) cm^{-1} 3417, 2969, 1762, 1602, 1387.; ^{1}H NMR (300 MHz, D_2O) δ 0.92 (3H, d, J=7.1 Hz), 1.07 (3H, d, J=6.4 Hz), 1.35 (3H, d, J=6.6 Hz), 3.02~3.12 (1H, m), 3.31 (1H, dd, J=6.0, 2.7 Hz), 3.97~4.13 (4H, m), 6.20 (1H, s), 7.53 (1H, s).

Allyl (4*R*,5*S*,6*S*)-3-[(4-{(2*R*)-1-[(Allyloxy)carbonyl]-2-methyl-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_{53}**)

C_{53} was synthesized from **R_{53}** (>99% ee) in the same manner to that of **C_{52}**.

MS (ESP) *m/z* 532 (M−SiMe3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s), 1.07~1.10 (3H, m), 1.23~1.26 (3H, m), 1.44~1.50 (3H, m), 3.23~3.30 (1H, m), 3.53~3.62 (1H, m), 4.12~4.48 (4H, m), 4.60~4.89 (4H, m), 4.99~5.08 (1H, m), 5.22~5.51 (4H, m), 5.90~6.05 (2H, m), 6.33~6.37 (1H, m), 7.18~7.26 (1H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-({4-[(2*R*)-2-methyl-2,5-dihydro-1*H*-pyrrol-3-yl]-1,3-thiazol-2-yl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**53**)

IR (KBr) cm^{-1} 3422, 2969, 1760, 1603, 1387.; ^{1}H NMR (300 MHz, D_2O) δ 0.92 (3H, d, J=7.1 Hz), 1.10 (3H, d, J=6.4 Hz), 1.36 (3H, d, J=6.8 Hz), 3.05~3.22 (1H, m), 3.33 (1H, dd, J=5.9, 2.7 Hz), 3.96~4.14 (4H, m), 6.22 (1H, s), 7.53 (1H, s).

Bacterial Strains

Besides standard strains (American Type Culture Collection), clinical isolates from Japanese, American and European hospitals were used. They were identified by standard diagnostic methods and kept as stock cultures at −70°C or below.

Determination of *in Vitro* Antibacterial Activity

Minimum inhibitory concentrations (MICs) were determined by an agar dilution method as recommended by the NCCLS (National Committee for Clinical Laboratory Standards. 1997. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 4th ed. Approved standard M7-A4. National Committee for Clinical Laboratory Standards, Wayne, Pa.).

Determination of Hydrolysis by Human Renal DHP-I

The stability of carbapenems in the presence of human renal DHP-I was determined using purified recombinant human renal DHP-I (rhDHP-I) prepared according to the method of ADACHI[33]. The enzymatic activity of rhDHP-I was spectrophotometrically determined by measuring the hydrolysis of 0.05 mM glycyldehydrophenylalanine as a substrate. The rhDHP-I (approximately 2 milliunits) was used for each of the following reaction. The relative rate of hydrolysis was expressed as a ratio against the rate of imipenem, which was assigned a value of 1.00.

Detection of Binding to Human Plasma Protein

Percent binding to human plasma protein was determined by ultrafiltration method. The concentration of each compound in the flow through fraction was measured by a disk diffusion bioassay using *Bacillus subtilis* ATCC6633.

Testing of Convulsant Activity

Groups of **8~10** male mice intraventicularly 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 convulsant 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.

Testing of Acute Toxicity

After single intravenous injection of 250 or 500 mg/kg of

each compound to 3 mice, mortality was monitored up to 24 hours. The compound that induced death of mice at the dose, was expressed as positive "+" in the tables.

References

1) McGowan, J. E. Jr.: The impact of changing pathogens of serious infections in hospitalized patients. Clin. Infect. Dis. 31 (Suppl. 4): S124~S130, 2000
2) Emori, T. G. & R. P. Gaynes: An overview of nosocomial infections, including the role of the microbiology laboratory. Clin. Microbiol. Rev. 6: 428~442, 1993
3) Jones, R. N. MD: Resistance patterns among nosocomial pathogens. Trends over the past few years. CHEST 119: 397S~404S, 2001
4) Diekema, D. J.; M. A. Pfaller, F. J. Schmits, J. Smayevsky, J. Bell, R. N. Jones, M. Beach & the SENTRY Participants group: Survey of infections due to *Staphylococcus* species: Frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific Region for the SENTRY antimicrobial surveillance program, 1997~1999. Clin. Infect. Dis. 32 (Suppl. 2): S114~S132, 2001
5) Rybak, M. J. & R. L. Akins: Emergence of methicillin-resistant *Staphylococcus aureus* with intermediate glycopepetide resistance: Clinical significance and treatment options. Drugs 61: 1~7, 2001
6) Murray, B. E.: Vancomycin-resistant Enterococcal infections. N. Engl. Med. 342: 710~721, 2000
7) Lamb, H. M.; D. P. Figgitt & D. Faulds: Quinupristin/Dalfopristin. A review of its use in the management of serious gram-positive infections. Drugs 58: 1061~1097, 1999
8) Diekema, D. J. & R. N. Jones: Oxazolidinone antibiotics. Lancet 358: 1975~1982, 2001
9) Gonzales, R. D.; P. C. Schreckenbergar, M. B. Graham, S. Kelkar, K. Denbesten & J. P. Quinn: Infections due to vancomycin-resistant *Enterococcus faecium* resistant to linezolid. Lancet 357: 1179, 2001
10) Livermore, D. M.: Quinupristin/dalfopristin and linezolid: where, when, which and whether to use? J. Antimicrob. Chemother. 46: 347~350, 2000
11) Imamura, H.; N. Ohtake, A. Shimizu, H. Jona, H. Sato, R. Nagano, R. Ushijima, K. Yamada, T. Hashizume & H. Morishima: Structure-activity relationships of *trans*-3,5-disubstituted parrolidinylthio-1β-methylcarbapenems. Part 1: J-111,347 and related compounds. Bioorg. Med. Chem. 10: 109~113, 2000
12) Greenlee, M. L.; J. B. Laub, G. P. Rouen, F. Dininno, M. L. Hammond, J. L. Huber, J. G. Sundelof & G. G. Hammond: Dicationic 2-fluorenonylcarbapenems: potent anti-MRS agents with improved solubility and pharmacokinetic properties. Bioorg. Med. Chem. 9: 3225~3230, 1999
13) Azami, H.; D. Barrett, A. Tanaka, H. Sasaki, K. Matsuda, M. Sakurai, T. Terasawa, F. Shirai, T. Chiba, Y. Matsumoto & S. Tawara: Synthesis and antibacterial activity of novel 4-pyrrolidinylthio carbapenems part IV. 2-Alkyl substituents containing cationic heteroaromatics linked *via* a C–C bond. Bioorg. Med. Chem. 9: 961~982, 2001
14) Imamura, H.; N. Ohtake, H. Jona, A. Shimizu, M. Moriya, H. Sato, Y. Sugimoto, C. Ikeura, H. Kiyonaga, M. Nakano, R. Nagano, S. Abe, K. Yamada, T. Hashizume & H. Morishima: Dicationic dithiocarbamate carbapenems with anti-MRSA activity. Bioorg. Med. Chem. 9: 1571~1578, 2001
15) Hebeisen, P.; I. Heinze-krauss, P. Angehrn, P. Hohl, M. G. P. Page & R. L. Then: *In vitro* and *in vivo* properties of Ro 63-9141, a novel broad-spectrum cephalosporin with activity against methicillin-resistant Staphylococci. Antimicrob. Agents Chemother. 45: 825~836, 2001
16) Ishikawa, T.; K. Kamiyama, Y. Nakayama, Y. Iizawa, K. Okonogi & A. Miyake: Studies on anti-MRSA parenteral cephalosporins. III. Synthesis and antibacterial activity of 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-alkoxyiminoacetamido]-3-[(*E*)-2-(1-alkylimidazo[1,2-*b*]pyridazinium-6-yl)thiovinyl]-3-cephem-4-carboxylates and related compounds. J. Antibiotics 54: 257~277, 2001
17) Yamazaki, H.; Y. Tsuchida, H. Satoh, S. Kawashima, H. Hanaki & K. Hiramatsu: Novel cephalosporins 2. Synthesis of 3-heterocyclic-fused thipyranylthiovinyl cephalosporins and antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*. J. Antibiotics 53: 551~555, 2000
18) Hanaki, H.; H. Akagi, M. Yasui & T. Otani: Structure-activity relationships of 2-thioisocephem against methicillin-resistant *Staphylococcus aureus*. J. Antibiotics 48: 901~903, 1995
19) Cho, A.; T. W. Glinka, M. Ludwikow, A. T. Fan, M. Wang & S. J. Hecker: New anti-MRSA cephalosporins with a basic aminopyridine at the C-7 position. Bioorg. Med. Chem. 11: 137~140, 2001
20) Springer, D. M.; Bing-Yu Luh & J. J. Bronson: Anti-MRSA cephems. Part 1: C-3 substituted thiopyridinium derivatives. Bioorg. Med. Chem. 11: 797~801, 2001
21) Ternansky, R. J.; S. E. Draheim, A. J. Pike, F. W. Bell, S. J. West, C. L. Jordan, C. Y. Ernie Wu, D. A. Preston, W. Alborn, Jr., J. S. Kasher & B. L. Hawkins: Discovery and structure-activity relationships of a series of 1-carba-1-dethiacephem exhibiting activity against methicillin-resistant *Staphylococcus aureus*. J. Med. Chem. 36: 1971~1976, 1993
22) Tsushima, M.; K. Iwamatsu, A. Tamura & S. Shibahara: Novel cephalosporin derivatives possessing a bicyclic heterocycle at the 3-position. Part I: Synthesis and biological activities of 3-(benzothiazol-2-yl)thiocephalosporin derivatives, CP0467 and related compounds. Bioorg. Med. Chem. 6: 1009~1017, 1998
23) Tsushima, M.; K. Iwamatsu, E. Umemura, T. Kudo, Y. Sato, S. Shiokawa, H. Takizawa, Y. Kano, K. Kobayashi, T. Ida, A. Tamura & K. Atsumi: CP6679, a new injectable cephalosporin. Part 1: Synthesis and structure-activity relationships. Bioorg. Med. Chem. 8: 2781~2789, 2000
24) Kanno, O.; Y. Shimoji, S. Ohya & I. Kawamoto: Synthesis and biological evaluation of novel tricyclic carbapenems (trinems). J. Antibiotics 53: 404~414, 2000

25) SHINAGAWA H.; H. YAMAGA, H. HOUCHIGAI, Y. SUMITA & M. SUNAGAWA: Synthesis and biological properties of a new series of anti-MRSA beta-lactams; 2-(thiazol-2-ylthio)carbapenems. Bioorg. Med. Chem. 5: 601~621, 1997

26) SUMITA, Y.; H. NOUDA, K. KANAZAWA & M. FUKUSAWA: Antimicrobial activity of SM-17466, a novel carbapenem antibiotic with potent activity against methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. 39: 910~916, 1995

27) LEANZA, W. J.; K. J. WILDONGER, T. W. MILLER & B. G. CHRISTENSEN: *N*-Acetymidoyl- and *N*-formimidoyl-thienamycin derivatives: antipseudomonal β-lactam antibiotics. J. Med. Chem. 22: 1435~1436, 1979

28) BROOKS, D. W.; L. D.-L. LU & S. MASAMUNE: *C*-Acylation under virtually neutral conditions. Angew. Chem. Int. Ed. Engl. 18: 72~74, 1979

29) HAKENBECK, R. & J. COYETTE: Resistant penicillin-binding proteins. Cell. Mol. Life Sci. 54: 332~340, 1998

30) FONTANA, R.; M. ALDEGHERI, M. LIGOZZI, H. LOPEZ, A. SUCARI & G. SATTA: Overproduction of a low-affinity penicillin-binding protein and high-level ampicillin resistance in *Enterococcus faecium*. Antimicrob. Agents Chemother. 38: 1980~1983, 1994

31) SUNAGAWA, M.; H. MATSUMURA & M. FUKUSAWA: Structure-activity relationships of carbapenem and penem compounds for the convulsive property. J. Antibiotics 45: 1983~1985, 1992

32) SUNAGAWA, M.; H. MATSUMURA, Y. SUMITA & H. NOUDA: Structural features resulting in convulsive activity of carbapenem compounds: effect of C-2 side chain. J. Antibiotics 48: 408~416, 1995

33) ADACHI, H.; T. KATAYAMA, C. INUZUKA, S. OIKAWA, M. TSUJIMOTO & H. NAKAZATO: Identification of membrane anchoring site of human renal dipeptidase and construction and expression of a cDNA for its secretary form. J. Biol. Chem. 246: 15341~15345, 1990