MONOCYCLIC β-LACTAM ANTIBIOTICS: SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 4-(SUBSTITUTED ETHYL)-2-AZETIDINONE-1-SULFONIC ACID DERIVATIVES

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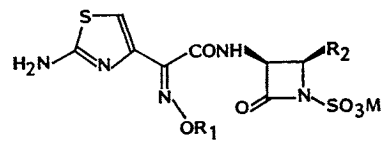
The synthesis and antibacterial activity of sodium (3*S*,4*R*)-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetamido]-2-azetidinone-1-sulfonates having various substituted ethyl groups at the C-4 position are described. Among various substituents explored, the (substituted isothiuronio)ethyl groups were found to have strong antibacterial activity against a variety of Gram-negative bacteria, and moreover, the ethylene isothiuronium derivative exhibited moderate antibacterial activity against *Staphylococcus aureus*.

In our previous paper, we reported on the synthesis and antibacterial activity of sodium (3*S*,4*R*)-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetamido]-4-(2-methoxyethyl)-2-azetidinone-1-sulfonates (**1**)[1]. It has been shown that these compounds have strong antibacterial activity against a variety of Gram-negative bacteria and excellent stability against β-lactamases. However, they showed weak activity against *Pseudomonas aeruginosa*. With the view of further improvement of the antibacterial activity against *P. aeruginosa*, we synthesized a number of 1-sulfo-2-azetidinones having various kinds of substituents at the C-4 position.

In this paper, the synthesis and antibacterial activity of 4-(2-substituted ethyl)-2-azetidinone-1-sulfonic acid derivatives (**2**) are described.

Fig. 1.



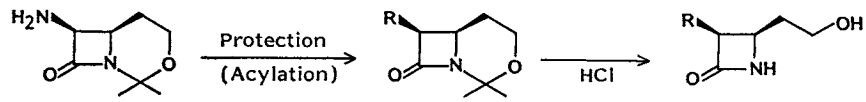
1 $R_1 = CH_2CH_2OCH_3$
$R_2 = CH_3$, CH_2COONa, $C(CH_3)_2COONa$
M = Na

2 R_1 = Substituted ethyl
$R_2 = CH_3$, CH_2COOH
M = Na

Chemistry

The synthesis of the 4-(2-hydroxyethyl) compounds (**5A**[1] ~ **5C**), the key intermediates for various 4-(substituted ethyl)-2-azetidinones, is shown in Scheme 1. Protection of the 7-amino group of (6*R*,7*S*)-7-amino-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (**3**)[1] gave 7-benzyloxycarbonylamino and 7-phthalimido derivatives

Scheme 1.



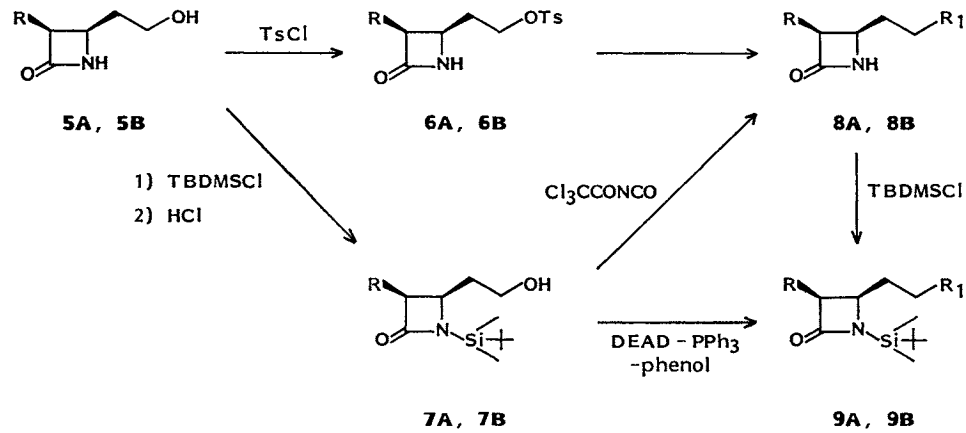
3 4 5

A R = $PhCH_2OCONH-$

B R =

C R = $ClCH_2CONH$ CONH— OCH_3

Scheme 2.



a R_1 = Cl
b R_1 = I
c R_1 = SEt
d R_1 =
e R_1 = $OCONH_2$
f R_1 = OPh
g R_1 = O— —NO_2
h R_1 = O— —NO_2 (NO_2)

A R = $PhCH_2OCONH-$

B R =

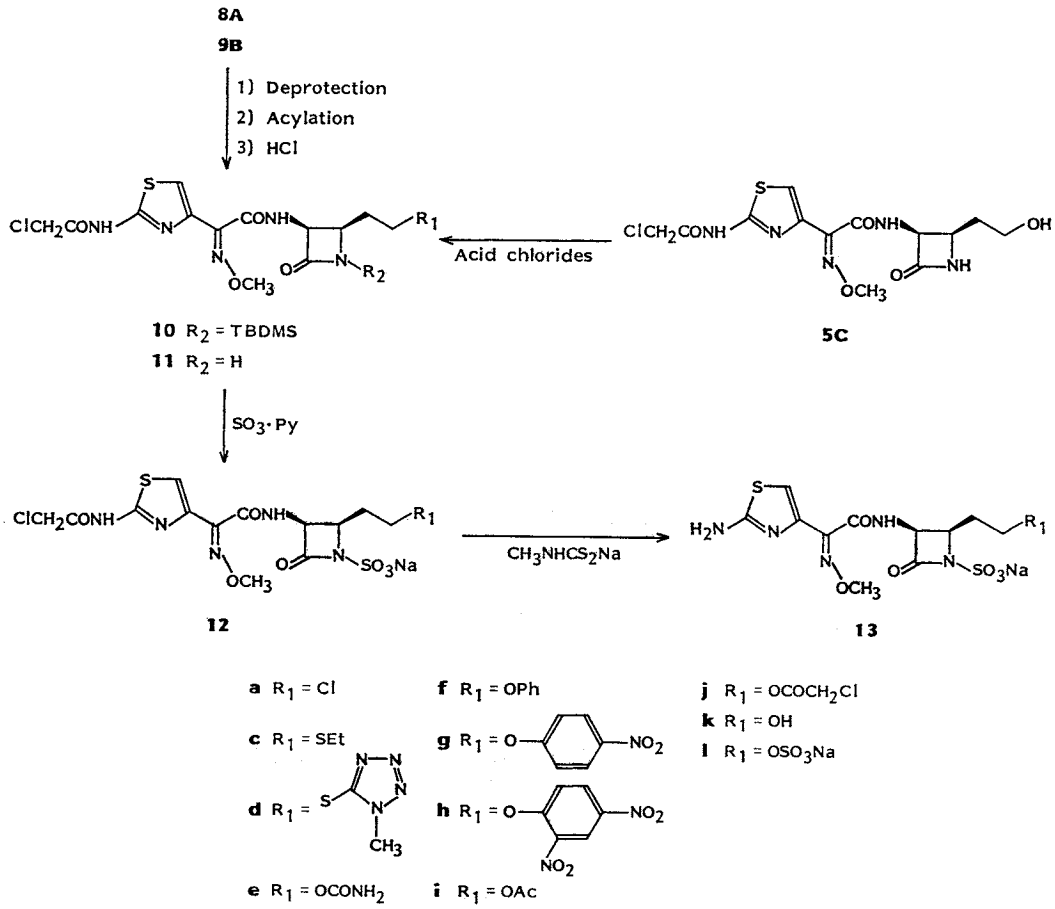
TBDMS = *tert*-Butyldimethylsilyl

(**4A**[1] and **4B**), which were treated with HCl in methanol to provide (4*R*)-4-(2-hydroxyethyl)-2-azetidinones (**5A**[1] and **5B**), respectively. 3-Acylamino-4-(2-hydroxyethyl)-2-azetidinone (**5C**) was similarly prepared by acylation of **3** followed by removal of the acetonide.

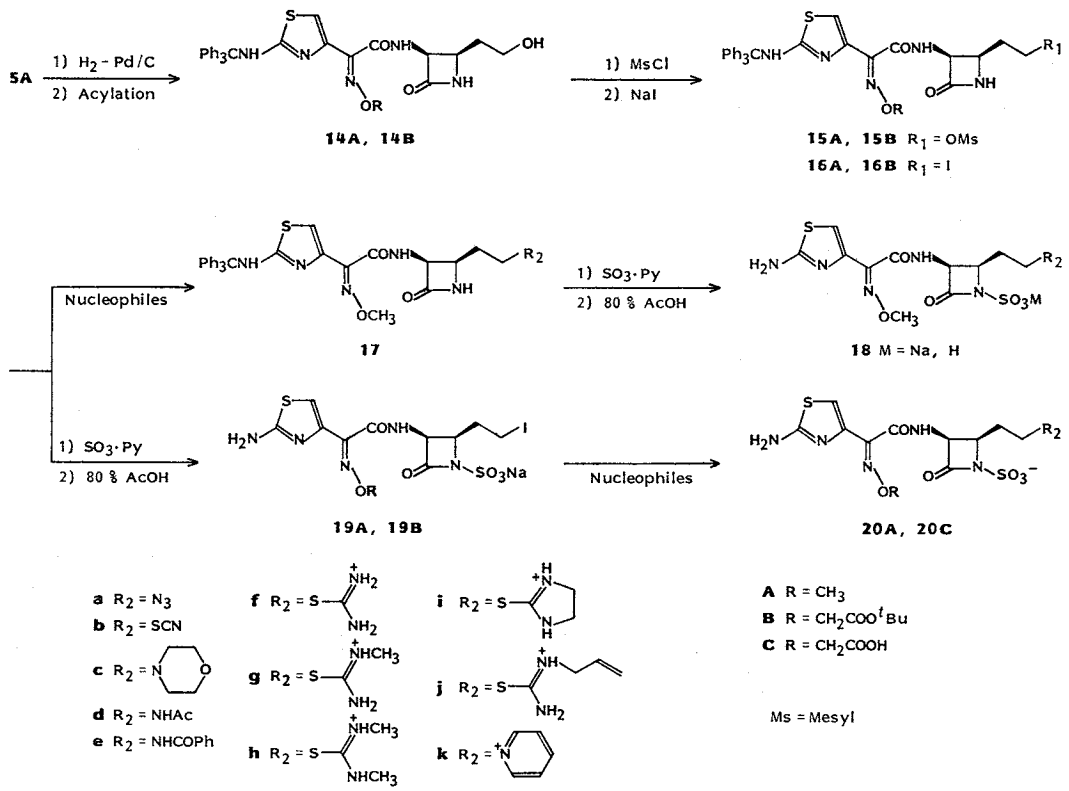
Various 3,4-*cis*-4-(2-substituted ethyl)-2-azetidinone derivatives (**8** and **9**) were prepared from (**5A** and **5B**) by converting the hydroxy group into various substituents (Scheme 2). Tosylation of **5A** and **5B** afforded 4-tosyloxyethyl compounds (**6A** and **6B**), which were subsequently converted into 4-(2-chloroethyl) and 4-(2-iodoethyl) derivatives (**8a-A** and **8b-B**), respectively. Then, compound **8b-B** was treated with thiols followed by silylation with *tert*-butyldimethylchlorosilane to give the 4-(2-substituted thioethyl) derivatives (**9c-B** and **9d-B**). On the other hand, *O*- and *N*-disilylation of **5A** and **5B** followed by regioselective desilylation with HCl in cold methanol gave the *N*-silylated alcohols (**7A** and **7B**), respectively. The 4-(2-carbamoyloxyethyl) derivative (**8e-A**) was prepared by treating **7A** with trichloroacetyl isocyanate followed by desilylation with tetra-*n*-butylammonium fluoride. The 4-(2-phenoxyethyl) derivatives (**9f-B**~**9h-B**) were obtained by the MITSUNOBU reaction[2] of **7B** and phenols.

Deprotection of **8A** and **9B** followed by acylation with the mixed anhydride of 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid[3] and *p*-toluenesulfonyl chloride, followed by desilylation in the case of *N*-silylated compounds (**10**), afforded the 3-acylamino compounds (**11**). The 4-(2-acyloxyethyl) derivatives (**11i** and **11j**) were synthesized by treating **5C** with acetyl chloride and chloroacetyl chloride, respectively. Then, sulfonation of these compounds (**11**) with sulfur trioxide

Scheme 3.



Scheme 4.



pyridine complex (SO_3·Py) gave the 1-sulfo-2-azetidinone derivatives (**12**), which were subsequently converted into sodium 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(2-substituted ethyl)-2-azetidinone-1-sulfonates (**13**) by removing the chloroacetyl group of **12** with sodium *N*-methyldithiocarbamate[3]. The 4-(2-sulfonatoxyethyl) derivative (**13l**) was similarly prepared from **5C** by sulfonation and subsequent deprotection procedure (Scheme 3).

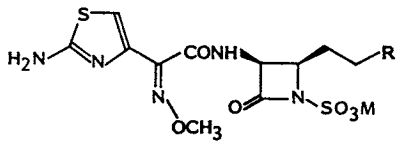
Moreover, various 4-(2-substituted ethyl)-1-sulfo-2-azetidinones (**18** and **20**) were prepared from 4-iodoethyl derivatives (**16A**, **19A** and **19B**) by nucleophilic displacement (Scheme 4). Deprotection of **5A** and subsequent acylation with 2-(2-triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetic acid[4] and dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole gave 3-acylamino-4-(2-hydroxyethyl)-2-azetidinones (**14A** and **14B**). Mesylation of **14A** and **14B** gave the 4-(2-mesyloxyethyl) compounds (**15A** and **15B**), which were then transformed into the 4-(2-iodoethyl) derivatives (**16A** and **16B**). **16A** was treated with sodium azide, potassium cyanide and morpholine to give **17a**, **17b** and **17c**, respectively. Then, **17a** was hydrogenated and subsequently acylated with acetyl chloride and benzoyl chloride to give the 4-(2-acylaminoethyl) derivatives (**17d** and **17e**). Sulfonation of **17** with SO_3·Py and subsequent deprotection of triphenylmethyl group with 80% acetic acid, followed by treating with $NaHCO_3$ in the case of **17a**, **17b**, **17d** and **17e**, gave the deprotected products (**18**). On the other hand, sulfonation and subsequent deprotection of the triphenylmethyl group of **16A** and **16B** gave the sulfonates (**19A** and **19B**), which were treated with thioureas and pyridine, followed by removal of the *tert*-butyl group with HCOOH in the case of **19B**, to give the various 4-(2-isothiuronioethyl) and 4-[2-(1-pyridinio)ethyl] compounds (**20A** and **20C**).

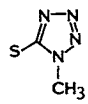
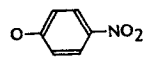
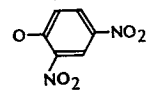
Antibacterial Activity and Conclusions

The MIC values of the 4-(2-substituted ethyl)-1-sulfo-2-azetidinones (**13**, **18** and **20**) against *S. aureus* and a variety of Gram-negative bacteria were determined by the agar dilution method. Aztreonam[5] was used as a reference compound.

Table 1 shows the antibacterial activity of 4-(2-substituted ethyl)-1-sulfo-2-azetidinones (**13**, **18** and **20**). Most of these compounds showed good antibacterial activity against Gram-negative bacteria except *P. aeruginosa*. Among various 4-substituents tested, 4-(2-carbamoyloxyethyl), 4-(2-azidoethyl) and 4-(2-isothiuronioethyl) groups were found to be efficient substituents for the antibacterial activity. Especially, the 4-(2-isothiuronioethyl) derivative (**20f-A**) showed strong antibacterial activity against

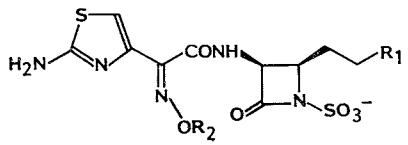
Table 1. Antibacterial activity of compounds **13**, **18**, **19** and **20** (MIC (μg/ml)).



Compound No.	R	M	*S.a.* FDA 209P	*E.c.* NIHJ JC-2	*K.p.* PCI 602	*S.m.* IAM-1184	*E.cl.* 963	*P.m.* IFO 3849	*P.a.* IFO 3445
13a	Cl	Na	>100	0.39	0.025	0.2	0.2	0.05	>100
13c	SEt	Na	>100	3.12	0.05	1.56	0.78	0.2	>100
13d		Na	>100	1.56	0.025	0.78	0.39	0.1	>100
13e	$OCONH_2$	Na	>100	0.39	0.012	0.1	0.1	0.025	>100
13f	OPh	Na	>100	3.12	0.05	1.56	1.56	0.2	50
13g		Na	50	3.12	6.25	6.25	3.12	0.78	100
13h		Na	50	6.25	0.39	12.5	6.25	0.78	>100
13i	OAc	Na	>100	1.56	<0.2	0.78	0.78	<0.2	>100
13k	OH	Na	>100	6.25	3.12	6.25	6.25	6.25	>100
13l	OSO_3Na	Na	>100	0.78	0.39	0.78	0.78	<0.2	>100
18a	N_3	Na	>100	0.39	0.025	0.2	0.1	0.05	>100
18b	SCN	Na	>100	0.78	0.025	0.2	0.2	0.05	>100
18c		—	>100	0.78	0.1	0.78	0.2	0.39	>100
18d	NHAc	Na	>100	0.39	0.05	0.2	0.2	0.1	>100
18e	NHCOPh	Na	>100	12.5	0.2	3.12	3.12	3.12	>100
19-A	I	Na	>100	1.56	0.012	0.39	0.39	0.05	>100
20f-A		—	100	0.1	0.1	0.05	0.1	0.1	50
20k-A		—	>100	0.2	0.2	0.2	0.2	0.2	100

Organisms included in the table are: *S.a.*; *Staphylococcus aureus*, *E.c.*; *Escherichia coli*, *K.p.*; *Klebsiella pneumoniae*, *S.m.*; *Serratia marcescens*, *E.cl.*; *Enterobacter cloacae*, *P.m.*; *Proteus mirabilis*, *P.a.*; *Pseudomonas aeruginosa*.

Table 2. Antibacterial activity of compounds **20** (MIC (μg/ml)).



Organism	Compound:	**20f-A**	**20f-C**	**20g-A**	**20g-C**	**20h-A**	**20i-A**	**20i-C**	**20j-A**	**20j-C**	Aztreonam
	R_1:										
	R_2:	CH_3	CH_2COOH	CH_3	CH_2COOH	CH_3	CH_3	CH_2COOH	CH_3	CH_2COOH	
Staphylococcus aureus FDA 209P		100	>100	25	>100	25	12.5	>100	12.5	>100	>100
S. aureus Terajima		50	>100	12.5	>100	12.5	6.25	>100	12.5	100	—
S. aureus MS 353		50	>100	25	>100	25	6.25	>100	12.5	>100	>100
Escherichia coli NIHJ JC-2		0.1	0.05	0.1	0.025	0.78	0.1	0.05	0.2	0.1	0.05
E. coli K-12 C600		0.1	0.05	0.05	0.025	0.2	0.1	0.05	0.05	0.05	0.1
Rms 823/*E. coli*[a]		0.2	0.05	0.1	0.025	0.78	0.2	0.1	0.2	0.1	—
Klebsiella pneumoniae PCI 602		0.1	0.05	0.05	0.025	0.1	0.1	0.1	0.025	0.05	0.006
Serratia marcescens IAM 1184		0.05	0.012	0.05	0.012	0.78	0.1	0.012	0.1	0.025	0.003
Enterobacter cloacae 963		0.1	0.05	0.05	0.05	0.2	0.05	0.05	0.05	0.1	0.05
E. cloacae GN 5797[b]		0.39	0.1	0.2	0.05	3.12	0.39	0.1	0.39	25	—
Proteus vulgaris OX 19		0.1	0.1	0.1	0.05	0.2	0.1	0.05	0.05	0.1	0.012
P. mirabilis IFO 3849		0.1	0.05	0.05	0.025	0.78	0.05	0.05	0.1	0.05	0.012
Pseudomonas aeruginosa IFO 3445		50	25	100	25	>100	100	50	100	50	1.56
P. aeruginosa NCTC 10490		6.25	3.12	12.5	1.56	50	12.5	3.12	12.5	3.12	0.39
Rms 139/*P. aeruginosa*[a]		50	100	50	50	100	100	25	100	50	—

[a] Penicillinase producing strain, [b] Cephalosporinase producing strain.

a variety of Gram-negative bacteria. In general, as the lipophilicity of the 4-substituent increased, the compounds showed less activity against Gram-negative bacteria. Especially, introduction of an aromatic ring as a part of the substituent significantly decreased the activity against Gram-negative bacteria (**13f**, **13g**, **13h** and **18e**). However, **13l** showed only weak activity in spite of high hydrophilicity. These results agreed with those obtained for C-4-(substituted methyl) monobactams[6~8].

As the isothiuronioethyl group was the most efficient substituent, various 4-(2-substituted isothiuronioethyl)-1-sulfo-2-azetidinones (**20**) were synthesized. The biological results are shown in Table 2. These isothiuronium derivatives showed excellent antibacterial activity. *N*-Monomethylation of the amino group of thiourea resulted in an increase of the antibacterial activity, but *N*,*N*'-dimethylation decreased the activity (compare **20g-A** and **20h-A**). Moreover, interestingly, *N*-alkylated isothiuronium derivatives having the methoxyimino group as a part of the 3-acyl moiety (**20g**~**20i-A** and **20j-A**) showed not only good antibacterial activity against Gram-negative bacteria but also moderate activity against Gram-positive bacteria, *S. aureus*. On the other hand, replacement of the methoxyimino group by the carboxymethoxyimino group resulted in an increase of the activity against Gram-negative bacteria, as expected. The *N*-methylisothiuronium derivative (**20g-C**) was more active than the corresponding 4-(2-methoxyethyl) compound as previously reported[1], and showed nearly the same high activity as aztreonam. However, these isothiuronium derivatives were less active than aztreonam only against *P. aeruginosa*.

Despite the great efforts to introduce various substituents at the C-4 position, no compounds were found to have really sufficient activity against *P. aeruginosa*. However, we have found compounds having moderate activity against *S. aureus* as well as excellent activity against a variety of Gram-negative bacteria except *P. aeruginosa*.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Optical rotations were determined using a Jasco DIP-140 digital polarimeter. IR spectra were obtained on a Jasco IRA-1 or Hitachi 270-30 spectrometer. ^{1}H NMR spectra were recorded on a Hitachi R-20A (60 MHz) or a Hitachi R-90H (90 MHz) spectrometer using TMS or 3-(trimethylsilyl)-propionic acid sodium salt (TSP) as an internal standard. Secondary ion mass spectra (SI-MS) were measured on a Hitachi M-80B mass spectrometer. Silica gel (Wakogel C 200) was used for column chromatography.

In Vitro Antibacterial Activity

MICs were determined by the standard 2-fold agar dilution method[9] using Mueller-Hinton agar (Difco) after 18 hours at 37°C with an inoculum size of 10^6 cfu/ml.

(6*R*,7*S*)-7-Phthalimido-2,2-dimethyl-3-oxa-1-azabicyclo-[4.2.0]octan-8-one (**4-B**)

NEFKENS' reagent[10] (6.56 g, 30 mmol) and triethylamine (NEt_3) (3.04 g, 30 mmol) were added to a solution of **3**[1] (3.40 g, 20 mmol) in DMF (50 ml), and the mixture was stirred overnight at room temp. After further addition of NEFKENS' reagent and NEt_3 (each 10 mmol), stirring was continued for 24 hours at room temp. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (100 ml) and brine (50 ml). The separated organic layer was dried and concentrated under reduced pressure. Ether was added to the residue to give **4-B*** (4.55 g, 77%) as colorless crystals. MP 206~207°C.

* It's IR and NMR spectra supported the structure.

(6*R*,7*S*)-7-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (**4-C**)

A mixture of **3** (170 mg, 1 mmol), 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid[3] (277 mg, 1 mmol), 1-hydroxybenzotriazole (135 mg, 1 mmol) and dicyclohexylcarbodiimide (206 mg, 1 mmol) in DMF (5 ml) was stirred overnight at 0~5°C. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (20 ml) and washed successively with satd $NaHCO_3$ and brine, dried and concentrated under reduced pressure. The residue was crystallized from MeOH - ether - hexane to give **4-C*** (360 mg, 83%) as colorless crystals. MP 180~190°C (dec).

(3*S*,4*R*)-3-Phthalimido-4-(2-hydroxyethyl)-2-azetidinone (**5-B**)

Compound **5-B*** was synthesized from **4-B** by a similar method to that described in preparation of **5-A**[1]. Yield 92%. MP 191~192°C.

(3*S*,4*R*)-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(2-hydroxyethyl)-2-azetidinone (**5-C**)

2 N HCl (2.5 ml) was added to a solution of **4-C** (470 mg, 1.07 mmol) in MeOH (10 ml), and the mixture was stirred for 8 hours at room temp. The resulting precipitate was collected by filtration and washed with MeOH and water to give **5-C*** (338 mg, 81%) as a colorless powder.

(3*S*,4*R*)-3-Benzyloxycarbonylamino-4-(2-*p*-toluenesulfonyloxyethyl)-2-azetidinone (**6-A**)

(3*S*,4*R*)-3-Benzyloxycarbonylamino-4-(2-hydroxyethyl)-2-azetidinone (**5-A**) (1.19 g, 4.5 mmol) was added to a solution of *p*-toluenesulfonyl chloride (1.7 g, 9 mmol) in pyridine (10 ml) at 0~5°C. After being stirred for 3 hours at the same temp, the reaction mixture was poured into EtOAc (50 ml) and ice-water (50 ml) and adjusted to pH 2 with 1 N HCl. Conventional work-up of the organic layer followed by crystallization from benzene - hexane afforded **6-A*** (1.46 g, 77%) as colorless crystals. MP 124~125°C.

(3*S*,4*R*)-3-Phthalimido-4-(2-*p*-toluenesulfonyloxyethyl)-2-azetidinone (**6-B**)

Compound **6-B*** was prepared from **5-B** by a similar method to that described in preparation of **6-A**. Yield 92%. Colorless crystals. MP 93~94°C.

(3*S*,4*R*)-3-Phthalimido-4-(2-hydroxyethyl)-1-*tert*-butyldimethylsilyl-2-azetidinone (**7-B**)

Compound **7-B*** was synthesized from **5-B** by a similar method to that described in preparation of **7-A**[1]. Yield 75%. Colorless crystals. MP 142~143°C.

(3*S*,4*R*)-3-Benzyloxycarbonylamino-4-(2-chloroethyl)-2-azetidinone (**8a-A**)

A mixture of **6-A** (800 mg, 1.9 mmol) and lithium chloride (640 mg, 15 mmol) in Me_2CO (20 ml) was refluxed for 5 hours, and the solvent was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 ml) and brine (25 ml), and the separated organic layer was washed successively with 10% sodium thiosulfate and brine, dried and concentrated under reduced pressure. The residue was washed with ether to give **8a-A*** (502 mg, 93%) as colorless crystals. MP 171~173°C.

(3*S*,4*R*)-3-Phthalimido-4-(2-iodoethyl)-2-azetidinone (**8b-B**)

Compound **8b-B*** was synthesized from **6-B** and sodium iodide by a similar method to that described in preparation of **8a-A**. Pale yellow crystals. Yield 90%. MP 204~207°C (dec).

(3*S*,4*R*)-3-Benzyloxycarbonylamino-4-(2-carbamoyloxyethyl)-2-azetidinone (**8e-A**)

Trichloroacetyl isocyanate (207 mg, 1.1 mmol) was added dropwise to a solution of (3*S*,4*R*)-3-benzyloxycarbonylamino-4-(2-hydroxyethyl)-1-*tert*-butyldimethylsilyl-2-azetidinone (**7-A**)[1] (378 mg, 1 mmol) in CH_2Cl_2 (5 ml) at 0~5°C. After being stirred for 2 hours at room temp, tetra-*n*-butylammonium fluoride·XH_2O (400 mg) was added, and the reaction mixture was stirred for 1 hour at room temp. To this solution was added silica gel (10 g). After 1 hour at room temp, the mixture was chromatographed on silica gel (CH_2Cl_2 - MeOH, 10:1) to give **8e-A*** (270 mg, 88%) as colorless crystals. MP 196~197°C.

(3*S*,4*R*)-3-Phthalimido-4-(2-ethylthioethyl)-1-*tert*-butyldimethylsilyl-2-azetidinone (**9c-B**)

Ethyl mercaptan (250 mg, 4 mmol) was added to a solution of potassium hydroxide (123 mg, 2.2 mmol) in MeOH (5 ml). After being stirred for 30 minutes at 0~5°C, a solution of **8b-B** (740 mg, 2 mmol) in DMF (5 ml) was added, and the resultant mixture was stirred for 30 minutes at the same temp. After being stirred overnight at room temp, AcOH (0.1 ml) was added to the reaction mixture. The solvent was removed under reduced pressure, and the residue was dissolved in DMF (20 ml). After adding *tert*-butyldimethylchlorosilane (600 mg, 4 mmol) and NEt_3 (400 mg, 4 mmol) at 0~5°C, the mixture was stirred overnight at room temp, and diluted with ether (100 ml) and brine (50 ml). Conventional work-up of the separated organic layer followed by chromatography on silica gel (ether - hexane, 1 : 1) gave **9c-B*** (615 mg, 73%) as colorless crystals. MP 99~100°C.

(3*S*,4*R*)-3-Phthalimido-4-[2-(1-methyl-1*H*-tetrazol-5-yl)thioethyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (**9d-B**)

Compound **9d-B*** was similarly synthesized described above by treating **8b-B** with sodium 1-methyl-1*H*-tetrazolyl-5-thiolate (prepared from 1-methyl-1*H*-tetrazolyl-5-thiol and sodium hydride in DMF). Yield 76%. Colorless crystals. MP 147°C.

(3*S*,4*R*)-3-Phthalimido-4-(2-phenoxyethyl)-1-*tert*-butyldimethylsilyl-2-azetidinone (**9f-B**)

To a mixture of **7-B** (374 mg, 1 mmol), triphenylphosphine (315 mg, 1.2 mmol) and phenol (282 mg, 3 mmol) in anhydrous THF (10 ml) was added diethyl azodicarboxylate (209 mg, 1.2 mmol) at 0~5°C under nitrogen, and the mixture was stirred for 1 hour at the same temp. After removing the solvent, the residue was chromatographed on silica gel (ether - hexane, 1 : 1) to give **9f-B*** (245 mg, 54%) as colorless crystals. MP 111~112°C.

Compounds **9g-B** and **9h-B** were similarly prepared.

9g-B*: Yield 67%. Colorless crystals. MP 167~168°C.

9h-B*: Yield 45%. Colorless crystals. MP 171~174°C.

3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(2-substituted ethyl)-2-azetidinones (**11**)

Method A: Procedure starting from **8-A**; a mixture of 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid (180 mg, 0.64 mmol), *p*-toluenesulfonyl chloride (124 mg, 0.65 mmol) and NEt_3 (65 mg, 0.64 mmol) in CH_2Cl_2 (3 ml) was stirred for 50 minutes at 0~5°C. On the other hand, a mixture of **8a-A** (90 mg, 0.32 mmol), 1 N HCl (0.35 ml) and 5% Pd-C (30 mg) in MeOH (5 ml) was stirred for 2 hours at room temp under a hydrogen atmosphere, and the catalyst was filtered off. The filtrate was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (5 ml) containing NEt_3 (65 mg, 0.64 mmol). This solution was added in one portion into the mixed anhydride solution prepared above, and the mixture was stirred for 2 hours at room temp. The resulting precipitate was collected by filtration and washed successively with CH_2Cl_2, water and MeOH to give **11a** (115 mg, 87%) as a colorless powder.

Compound **11e** was prepared from **8e-A** by a similar method to that described above. Results are shown in Table 3.

Method B: Procedure staring from **9-B**; (a) a mixture of **9c-B** (259 mg, 0.6 mmol) and methylhydrazine (276 mg, 6 mmol) in CH_2Cl_2 (10 ml) was stirred for 1 hour at room temp, and the reaction mixture was subjected to chromatography on silica gel (CH_2Cl_2 - MeOH, 20 : 1) to remove excess methylhydrazine. The eluent was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$ (10 ml) and the mixture was stirred for 2 days at room temp. The resulting precipitate was filtered off, and the filtrate was concentrated to give the 3-amino compound (170 mg), which was acylated by a similar method to that described in preparation of **11a** to afford **10c** (170 mg, 54%) as a colorless powder.

Compounds **10d**, **10f**, **10g** and **10h** were similarly prepared described above. These compounds gave satisfactory physical data.

(b) To a solution of **10c** (105 mg, 0.2 mmol) in MeOH (2 ml) was added 1 N HCl (0.4 ml), and the mixture was stirred for 6 hours at room temp. The resulting precipitate was filtered off and washed

Table 3. Spectral and physical data of compounds **11**.

Compound No.	Yield (%)	$[\alpha]_D^{22}$	IR (KBr) β-lactam (cm^{-1})	^1H NMR (solvent) δ (J=Hz)
11a	87[a]	−11.0° (*c* 0.5, DMF)	1755	(DMSO-d_6); 1.75~2.05 (2H, m, 4-CH_2CH$_2$), 3.64 (2H, t, J=7, 4-CH$_2$CH_2), 3.70~4.00 (1H, m, 4-H), 3.89 (3H, s, OCH$_3$), 4.36 (2H, s, ClCH$_2$), 5.19 (1H, dd, J=5, 9, 3-H), 7.43 (1H, s, thiazole-5H), 8.35 (1H, br s, lactam NH), 9.32 (1H, d, J=9, CONH)
11c	39[b]	+4.1° (*c* 1, DMF)	1740	(DMSO-d_6); 1.17 (3H, t, J=8, CH$_2$CH_3), 1.50~1.85 (2H, m, 4-CH_2CH$_2$), 2.40~2.60 (2H, m, 4-CH$_2$CH_2), 2.49 (2H, q, J=8, CH_2CH$_3$), 3.60~3.90 (1H, m, 4-H), 3.89 (3H, s, OCH$_3$), 4.34 (2H, s, ClCH$_2$), 5.17 (1H, dd, J=5, 9, 3-H), 7.39 (1H, s, thiazole-5H), 8.32 (1H, br s, lactam NH), 9.25 (1H, d, J=9, CONH)
11d	56[b]	+1.1° (*c* 1, DMF)	1755	(DMSO-d_6); 1.70~2.10 (2H, m, 4-CH_2CH$_2$), 3.15~3.45 (2H, m, 4-CH$_2$CH_2), 3.80~3.95 (1H, m, 4-H), 3.82 (3H, s, NCH$_3$), 3.91 (3H, s, OCH$_3$), 4.34 (2H, s, ClCH$_2$), 5.19 (1H, dd, J=5, 9, 3-H), 7.39 (1H, s, thiazole-5H), 8.37 (1H, br s, lactam NH), 9.30 (1H, d, J=9, CONH)
11e	69[a]	−1.1° (*c* 1, DMF)	1765	(DMSO-d_6); 1.55~1.95 (2H, m, 4-CH_2CH$_2$), 3.65~3.90 (1H, m, 4-H), 3.88 (3H, s, OCH$_3$), 3.96 (2H, t, J=6, 4-CH$_2$CH_2), 4.38 (2H, s, ClCH$_2$), 5.21 (1H, dd, J=5, 9, 3-H), 6.48 (2H, br s, NH$_2$), 7.44 (1H, s, thiazole-5H), 8.36 (1H, br s, lactam NH), 9.35 (1H, d, J=9, CONH)
11f	42[b]	−5.0° (*c* 1, DMF)	1760	(DMSO-d_6); 1.75~2.10 (2H, m, 4-CH_2CH$_2$), 3.75~3.95 (1H, m, 4-H), 3.84 (3H, s, OCH$_3$), 4.02 (2H, t, J=6, 4-CH$_2$CH_2), 4.36 (2H, s, ClCH$_2$), 5.24 (1H, dd, J=5, 9, 3-H), 6.80~7.00 (3H, m, aromatic H), 7.15~7.40 (2H, m, aromatic H), 7.43 (1H, s, thiazole-5H), 8.42 (1H, br s, lactam NH), 9.38 (1H, d, J=9, CONH)
11g	48[b]	−0.8° (*c* 1, DMF)	1750	(DMF-d_6); 1.90~2.40 (2H, m, 4-CH_2CH$_2$), 3.91 (3H, s, OCH$_3$), 3.95~4.20 (1H, m, 4-H), 4.30 (2H, t, J=6, 4-CH$_2$CH_2), 4.49 (2H, s, ClCH$_2$), 5.37 (1H, dd, J=5.5, 9, 3-H), 7.18 (2H, d, J=9, aromatic H), 7.52 (1H, s, thiazole-5H), 8.20 (2H, d, J=9, aromatic H), 8.37 (1H, br s, lactam NH), 9.22 (1H, d, J=9, CONH)
11h	19[b]	−0.9° (*c* 1, DMF)	1755	(DMF-d_6); 1.95~2.45 (2H, m, 4-CH_2CH$_2$), 3.90~4.30 (1H, m, 4-H), 3.92 (3H, s, OCH$_3$), 4.49 (2H, s, ClCH$_2$), 4.52 (2H, t, J=6, 4-CH$_2$CH_2), 5.40 (1H, dd, J=5, 9, 3-H), 7.50 (1H, s, thiazole-5H), 7.60 (1H, d, J=9, aromatic H), 8.25 (1H, br s, lactam NH), 8.53 (1H, dd, J=3, 9, aromatic H), 8.78 (1H, d, J=3, aromatic H), 9.23 (1H, d, J=9, CONH)
11i	80[c]	−7.2° (*c* 1, DMF)	1750	(DMSO-d_6); 1.65~1.95 (2H, m, 4-CH_2CH$_2$), 2.01 (3H, s, COCH$_3$), 3.70~3.95 (1H, m, 4-H), 3.88 (3H, s, OCH$_3$), 4.04 (2H, t, J=6.5, CH$_2$CH_2), 4.35 (2H, s, ClCH$_2$), 5.18 (1H, dd, J=5, 9, 3-H), 7.43 (1H, s, thiazole-5H), 8.34 (1H, br s, lactam NH), 9.31 (1H, d, J=9, CONH)
11j	67[c]	−3.1° (*c* 1, DMF)	1760	(DMSO-d_6); 1.65~2.00 (2H, m, 4-CH_2CH$_2$), 3.65~3.95 (1H, m, 4-H), 3.87 (3H, s, OCH$_3$), 4.18 (2H, t, J=6, 4-CH$_2$CH_2), 4.35 (2H, s, ClCH$_2$), 4.38 (2H, s, ClCH$_2$), 5.19 (1H, dd, J=5, 9, 3-H), 7.44 (1H, s, thiazole-5H), 8.34 (1H, br s, lactam NH), 9.33 (1H, d, J=9, CONH)

[a] Yield from **8-A**; [b] yield from **9-B**; [c] yield from **5-C**.

Table 4. Spectral and physical data of compounds **12**.

Compound No.	Yield (%)	$[\alpha]_D^{22}$	IR (KBr) β-lactam (cm^{-1})	^1H NMR (solvent) δ (J=Hz)
12a	86	−16.7° (*c* 0.5, 50% EtOH)	1765	(DMSO-d_6); 1.90~2.50 (2H, m, 4-CH_2CH$_2$), 3.73 (2H, t, J=7.5, 4-CH$_2$CH_2), 3.91 (3H, s, OCH$_3$), 3.90~4.15 (1H, m, 4-H), 4.38 (2H, s, ClCH$_2$), 5.17 (1H, dd, J=5.5, 9, 3-H), 7.47 (1H, s, thiazole-5H), 9.48 (1H, d, J=9, CONH)
12c	96	−11.6° (*c* 1, H_2O)	1770	(D_2O); 1.21 (3H, t, J=7, CH$_2$CH_3), 1.70~2.40 (2H, m, 4-CH_2CH$_2$), 2.55 (2H, q, J=7, CH_2CH$_3$), 2.68 (2H, t, J=7, 4-CH$_2$CH_2), 4.03 (3H, s, OCH$_3$), 4.30~4.60 (1H, m, 4-H), 4.41 (2H, s, ClCH$_2$), 5.40 (1H, d, J=5.5, 3-H), 7.48 (1H, s, thiazole-5H)
12d	90	−19.8° (*c* 1, H_2O)	1765	(D_2O); 2.00~2.50 (2H, m, 4-CH_2CH$_2$), 3.40 (2H, t, J=7, 4-CH$_2$CH_2), 3.95 (3H, s, NCH$_3$), 3.96 (3H, s, OCH$_3$), 4.40 (2H, s, ClCH$_2$), 4.40~4.65 (1H, m, 4-H), 5.43 (1H, d, J=5.5, 3-H), 7.40 (1H, s, thiazole-5 H)
12e	79	−32.6° (*c* 1, H_2O)	1760	(DMSO-d_6); 1.80~2.30 (2H, m, 4-CH_2CH$_2$), 3.89 (3H, s, OCH$_3$), 3.90~4.15 (1H, m, 4-H), 4.00 (2H, t, J=7, 4-CH$_2$CH_2), 4.37 (2H, s, ClCH$_2$), 5.17 (1H, dd, J=5, 9, 3-H), 6.46 (2H, br s, NH$_2$), 7.43 (1H, s, thiazole-5H), 9.42 (1H, d, J=9, CONH)
12f	94	−41.5° (*c* 0.5, H_2O)	1765	(D_2O); 2.00~2.60 (2H, m, 4-CH_2CH$_2$), 3.90 (3H, s, OCH$_3$), 4.15 (2H, t, J=7, 4-CH$_2$CH_2), 4.36 (2H, s, ClCH$_2$), 4.40~4.65 (1H, m, 4-H), 5.41 (1H, d, J=5.5, 3-H), 6.85~7.10 (3H, m, aromatic H), 7.20~7.40 (2H, m, aromatic H), 7.40 (1H, s, thiazole-5H)
12g	85	−30.5° (*c* 0.5, 95% Me_2CO)	1760	(CD$_3$COCD$_3$ - D_2O); 2.05~2.55 (2H, m, 4-CH_2CH$_2$), 3.94 (3H, s, OCH$_3$), 4.10~4.50 (3H, m, 4-H and 4-CH$_2$CH_2), 4.38 (2H, s, ClCH$_2$), 5.45 (1H, d, J=5.5, 3-H), 7.06 (2H, d, J=9, aromatic H), 7.43 (1H, s, thiazole-5H), 8.13 (2H, d, J=9, aromatic H)
12h	71	—	—	—
12i	86	−27.0° (*c* 1, H_2O)	1765	(D_2O); 1.80~2.40 (2H, m, CH_2CH$_2$), 2.09 (3H, s, COCH$_3$), 4.01 (3H, s, OCH$_3$), 4.24 (2H, t, J=7, 4-CH$_2$CH_2), 4.40~4.60 (1H, m, 4-H), 4.43 (2H, s, ClCH$_2$), 5.42 (1H, d, J=5, 3-H), 7.49 (1H, s, thiazole-5H)
12j	87	−26.1° (*c* 1, H_2O)	1760	(D_2O); 2.00~2.50 (2H, m, 4-CH_2CH$_2$), 4.01 (3H, s, OCH$_3$), 4.28 (2H, s, ClCH$_2$), 4.30~4.60 (1H, m, 4-H), 4.36 (2H, t, J=7, 4-CH$_2$CH_2), 4.43 (2H, s, ClCH$_2$), 5.42 (1H, d, J=5.5, 3-H), 7.49 (1H, s, thiazole-5H)
12l	97	−27.3° (*c* 1, H_2O)	1770	(D_2O); 1.90~2.60 (2H, m, 4-CH_2CH$_2$), 4.02 (3H, s, OCH$_3$), 4.18 (2H, t, J=6.5, 4-CH$_2$CH_2), 4.30~4.60 (1H, m, 4-H), 4.43 (2H, s, ClCH$_2$), 5.37 (1H, d, J=5.5, 3-H), 7.54 (1H, s, thiazole-5H)

—: Not measured.

Table 5. Spectral and physical data of compounds **13**.

Compound No.	Yield (%)	SI-MS (*m/z*)	$[\alpha]_D^{22}$	IR (KBr) β-lactam (cm^{-1})	^1H NMR (solvent) δ (J=Hz)
13a	64	456 $(M+Na)^+$ 434 $(M+H)^+$	−18.0° (*c* 1, H_2O)	1765	(D_2O); 2.00~2.60 (2H, m, 4-CH_2CH$_2$), 3.74 (2H, t, J=7, 4-CH$_2$CH_2), 4.00 (3H, s, OCH_3), 4.45~4.65 (1H, m, 4-H), 5.37 (1H, d, J=5.5, 3-H), 6.98 (1H, s, thiazole-5H)
13c	72	482 $(M+Na)^+$ 460 $(M+H)^+$	−6.8° (*c* 0.5, H_2O)	1765	(D_2O); 1.24 (3H, t, J=7.5, CH$_2$CH_3), 1.80~2.50 (2H, m, 4-CH_2CH$_2$), 2.59 (2H, q, J=7.5, CH_2CH$_3$), 2.69 (2H, t, J=7, 4-CH$_2$CH_2), 4.00 (3H, s, OCH_3), 4.30~4.60 (1H, m, 4-H), 5.40 (1H, d, J=5.5, 3-H), 6.98 (1H, s, thiazole-5H)
13d	83	536 $(M+Na)^+$ 514 $(M+H)^+$	−18.6° (*c* 1, H_2O)	1765	(D_2O); 2.00~2.60 (2H, m, 4-CH_2CH$_2$), 3.43 (2H, t, J=7, 4-CH$_2$CH_2), 3.92 (3H, s, NCH_3), 3.97 (3H, s, OCH_3), 4.40~4.70 (1H, m, 4-H), 5.42 (1H, d, J=5.5, 3-H), 6.90 (1H, s, thiazole-5H)
13e	74	481 $(M+Na)^+$ 459 $(M+H)^+$	−27.5° (*c* 0.2, H_2O)	1765	(D_2O); 1.90~2.50 (2H, m, 4-CH_2CH$_2$), 3.97 (3H, s, OCH_3), 4.16 (2H, t, J=6.5, 4-CH$_2$CH_2), 4.35~4.55 (1H, m, 4-H), 5.38 (1H, d, J=5.5, 3-H), 6.96 (1H, s, thiazole-5H)
13f	71	514 $(M+Na)^+$ 492 $(M+H)^+$	−21.0° (*c* 0.2, H_2O)	1760	(DMSO-d_6); 1.85~2.45 (2H, m, 4-CH_2CH$_2$), 3.74 (3H, s, OCH_3), 3.90~4.20 (3H, m, 4-H and 4-CH$_2$CH_2), 5.12 (1H, dd, J=5.5, 9, 3-H), 6.68 (1H, s, thiazole-5H), 6.75~6.95 (3H, m, aromatic H), 7.05~7.35 (4H, m, NH_2 and aromatic H), 9.30 (1H, d, J=9, CONH)
13g	45	559 $(M+Na)^+$ 537 $(M+H)^+$	−17.6° (*c* 0.3, H_2O)	1780	(DMSO-d_6); 1.90~2.40 (2H, m, 4-CH_2CH$_2$), 3.78 (3H, s, OCH_3), 4.05~4.40 (3H, m, 4-H and 4-CH$_2$CH_2), 5.19 (1H, dd, J=5, 9, 3-H), 6.72 (1H, s, thiazole-5H), 7.08 (2H, d, J=9, aromatic H), 7.14 (2H, br s, NH_2), 8.14 (2H, d, J=9, aromatic H), 9.40 (1H, d, J=9, CONH)
13h	63	604 $(M+Na)^+$ 582 $(M+H)^+$	−9.8° (*c* 0.2, H_2O)	1765	(DMSO-d_6); 1.90~2.40 (2H, m, 4-CH_2CH$_2$), 3.75 (3H, s, OCH_3), 3.95~4.25 (1H, m, 4-H), 4.35~4.65 (2H, m, 4-CH$_2$CH_2), 5.13 (1H, dd, J=5.5, 9, 3-H), 6.72 (1H, s, thiazole-5H), 7.12 (2H, br s, NH_2), 7.48 (1H, d, J=9, aromatic H), 8.46 (1H, dd, J=3, 9, aromatic H), 8.73 (1H, d, J=3, aromatic H), 9.32 (1H, d, J=9, CONH)
13i	79	480 $(M+Na)^+$ 458 $(M+H)^+$	−25.8° (*c* 1, H_2O)	1765	(D_2O); 1.90~2.50 (2H, m, 4-CH_2CH$_2$), 2.10 (3H, s, $COCH_3$), 3.98 (3H, s, OCH_3), 4.24 (2H, t, J=6.5, 4-CH$_2$CH_2), 4.35~4.60 (1H, m, 4-H), 5.38 (1H, d, J=5.5, 3-H), 6.97 (1H, s, thiazole-5H)
13k	67	[a]	−21.1° (*c* 1, H_2O)	1760	(D_2O); 1.70~2.40 (2H, m, 4-CH_2CH$_2$), 3.76 (2H, t, J=6.5, 4-CH$_2$CH_2), 3.99 (3H, s, OCH_3), 4.30~4.60 (1H, m, 4-H), 5.41 (1H, d, J=5.5, 3-H), 6.99 (1H, s, thiazole-5H)
13l	20	[a]	−30.1° (*c* 0.6, H_2O)	1760	(D_2O); 1.95~2.60 (2H, m, 4-CH_2CH$_2$), 4.00 (3H, s, OCH_3), 4.19 (2H, t, J=6.5, 4-CH$_2$CH_2), 4.30~4.60 (1H, m, 4-H), 5.35 (1H, d, J=5.5, 3-H), 7.00 (1H, s, thiazole-5H)

[a] $(M+Na)^+$ and $(M+H)^+$ peaks were not observed.

with MeOH and ether to give **11c** (65 mg, 74%) as a colorless powder.

Compounds **11d**, **11f**, **11g** and **11h** were similarly prepared and the results are shown in Table 3.

Method C: Procedure starting from **5-C**; to an ice-cold solution of **5-C** (100 mg, 0.26 mmol) in DMF (5 ml) were added pyridine (31 mg, 0.39 mmol) and acetyl chloride (47 mg, 0.6 mmol), and the mixture was stirred for 1 hour at 0~5°C. After being stirred for 30 minutes at room temp, the solvent was evaporated to dryness. The residue was dissolved in EtOAc (10 ml) and cold 1 N HCl (5 ml), and the organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was washed with EtOAc to give **11i** (90 mg, 80%) as a colorless powder.

Compound **11j** was similarly prepared by treating **5-C** with chloroacetyl chloride. The result is shown in Table 3.

Sodium (3*S*,4*R*)-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(2-substituted ethyl)-2-azetidinone-1-sulfonates (**12**)

A mixture of **11a** (90 mg, 0.22 mmol) and $SO_3 \cdot Py$ (70 mg, 0.44 mmol) in DMF (2 ml) and CH_2Cl_2 (2 ml) was stirred for 3 hours at 50°C. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel ($CHCl_3$ - MeOH - H_2O, 100:30:5). The eluent was concentrated, and the residue was dissolved in water (3 ml) and treated with Dowex 50W (Na^+) for 1 hour at room temp. After removal of the resin by filtration, the filtrate was lyophilized to give **12a** (95 mg, 84%), which was used in the next reaction without further purification.

Compounds **12c**~**12j** and **1** were similarly prepared and the results are shown in Table 4.

Sodium (3*S*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(2-substituted ethyl)-2-azetidinone-1-sulfonates (**13**)

To an ice-cooled solution of **12a** (61 mg, 0.12 mmol) in water (2 ml) was added sodium *N*-methyldithiocarbamate (20 mg, 0.15 mmol) and stirred for 90 minutes at room temp. The mixture was diluted with water (5 ml) and washed with ether. The aqueous solution was chromatographed on Diaion HP-20. Elution with water and 10% EtOH, followed by lyophilization, gave **13a** (45 mg, 86%) as a colorless powder.

13c~**13i**, **13k** and **13l** were similarly prepared and the results are shown in Table 5.

(3*S*,4*R*)-3-[2-(2-Triphenylmethylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(2-hydroxyethyl)-2-azetidinone (**14-A**)

Compound **5-A** (1.85 g, 7 mmol) was hydrogenated in MeOH (20 ml) for 5 hours over 5% Pd-C (100 mg) at room temp under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated to dryness. The resulting crystals were treated with 2-(2-triphenylmethylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid (3.41 g, 7.7 mmol)[4], 1-hydroxybenzotriazole (0.95 g, 7 mmol) and dicyclohexylcarbodiimide (1.45 g, 7 mmol) according to the similar method in preparation of **4-C** to give **14-A*** (3.31 g, 85%) as a colorless powder.

(3*S*,4*R*)-3-[2-(2-Triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*tert*-butoxycarbonylmethoxyimino)acetamido]-4-(2-hydroxyethyl)-2-azetidinone (**14-B**)

Using 2-(2-triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*tert*-butoxycarbonylmethoxyimino)acetic acid[4] in place of 2-(2-triphenylmethylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid in the procedure described in preparation of **14-A** and **14-B*** was synthesized. A colorless powder. Yield 88%.

(3*S*,4*R*)-3-[2-(2-Triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetamido]-4-(2-methanesulfonyloxyethyl)-2-azetidinone (**15-A**) and (**15-B**)

According to the procedure described in preparation of **6-A**, compounds **15-A** and **15-B** were synthesized by treating **14-A** and **14-B** with methanesulfonyl chloride.

15-A*: Yield 76%. A colorless powder.

15-B*: Yield 82%. A colorless powder.

(3*S*,4*R*)-3-[2-(2-Triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetamido-4-(2-iodoethyl)-2-azetidinone (**16-A**) and (**16-B**)

According to the procedure described in preparation of **8a-A**, compounds **16-A** and **16-B** were

Table 6. Spectral and physical data of compounds **17** and **18**.

Compound No.	Yield (%)	SI-MS (*m/z*)	$[\alpha]_D^{22}$	IR (KBr) β-lactam (cm^{-1})	^1H NMR (solvent) δ (J=Hz)
17a	80	—	+7.1° (*c* 1, DMF)	2095 (N_3), 1760	($CDCl_3$); 1.60~2.20 (2H, m, 4-CH_2CH$_2$), 3.30~3.50 (2H, m, 4-CH$_2$CH_2), 3.80~4.10 (1H, m, 4-H), 4.00 (3H, s, OCH_3), 5.24 (1H, dd, J=5, 8, 3-H), 6.39 (1H, br s, NH), 6.49 (1H, s, thiazole-5H), 7.27 (15H, s, Ph_3C), 7.42 (1H, br s, NH), 7.42 (1H, d, J=9, CONH)
17b	83	—	+43.6° (*c* 0.2, $CHCl_3$)	1760	($CDCl_3$); 1.90~2.30 (2H, m, 4-CH_2CH$_2$), 2.93 (2H, t, J=7, 4-CH$_2$CH_2), 3.80~4.10 (1H, m, 4-H), 4.00 (3H, s, OCH_3), 5.22 (1H, dd, J=5.5, 7.5, 3-H), 6.48 (1H, s, thiazole-5H), 6.72 (1H, br s, NH), 7.26 (15H, s, Ph_3C), 7.34 (1H, br s, NH), 7.69 (1H, d, J=7.5, CONH)
17c	88	—	+27.5° (*c* 0.6, $CHCl_3$)	1760	($CDCl_3$); 1.60~1.90 (2H, m, 4-CH_2CH$_2$), 2.10~2.60 (6H, m, 4-CH$_2$CH_2 and morpholine), 3.58 (4H, t, J=4.5, morpholine), 3.85~4.10 (1H, m, 4-H), 3.99 (3H, s, OCH_3), 5.35 (1H, dd, J=5.5, 8.5, 3-H), 6.21 (1H, br s, NH), 6.59 (1H, s, thiazole-5H), 7.20 (1H, br s, NH), 7.26 (15H, s, Ph_3C), 7.77 (1H, d, J=8.5, CONH)
17d	50	—	+30.2° (*c* 0.2, $CHCl_3$)	1760	($CDCl_3$); 1.60~2.10 (2H, m, 4-CH_2CH$_2$), 1.85 (3H, s, $COCH_3$), 3.10~3.40 (2H, m, 4-CH$_2$CH_2), 3.70~4.00 (1H, m, 4-H), 3.93 (3H, s, OCH_3), 5.18 (1H, dd, J=5, 8, 3-H), 6.33 (1H, t, J=5, NH), 6.50 (1H, s, thiazole-5H), 7.26 (15H, s, Ph_3C), 7.51 (1H, br s, NH), 8.04 (1H, d, J=8, CONH)
17e	30	—	+28.5° (*c* 0.2, $CHCl_3$)	1755	($CDCl_3$); 1.70~2.05 (2H, m, 4-CH_2CH$_2$), 3.35~3.70 (2H, m, 4-CH$_2$CH_2), 3.70~4.00 (1H, m, 4-H), 3.85 (3H, s, OCH_3), 5.17 (1H, dd, J=5.5, 7.5, 3-H), 6.51 (1H, s, thiazole-5H), 6.95~7.80 (23H, m, Ph_3C, 3×NH and PhCO), 7.86 (1H, d, J=7.5, CONH)
18a	83	463 $(M+Na)^+$ 441 $(M+H)^+$	−27.5° (*c* 0.5, H_2O)	2100 (N_3), 1760	(D_2O); 1.80~2.50 (2H, m, 4-CH_2CH$_2$), 3.52 (2H, t, J=7, 4-CH$_2$CH_2), 3.98 (3H, s), 4.30~4.60 (1H, m, 4-H), 5.38 (1H, d, J=5.5, 3-H), 6.98 (1H, s, thiazole-5H)
18b	67	479 $(M+Na)^+$ 457 $(M+H)^+$	−9.1° (*c* 0.2, H_2O)	1760	(D_2O); 2.05~2.60 (2H, m, 4-CH_2CH$_2$), 3.21 (2H, t, J=7.5, 4-CH$_2$CH_2), 4.02 (3H, s, OCH_3), 4.35~4.55 (1H, m, 4-H), 5.42 (1H, d, J=5.5, 3-H), 6.97 (1H, s, thiazole-5H)
18c	62	463 $(M+H)^+$	−9.0° (*c* 0.2, H_2O)	1765	(D_2O); 2.05~2.40 (2H, m, 4-CH_2CH$_2$), 3.20~3.55 (6H, m, 4-CH$_2$CH_2 and morpholine), 3.85~4.10 (4H, m, morpholine), 3.99 (3H, s, OCH_3), 4.30~4.60 (1H, m, 4-H), 5.39 (1H, d, J=5.5, 3-H), 6.99 (1H, s, thiazole-5H)
18d	51	479 $(M+Na)^+$ 457 $(M+H)^+$	−33.3° (*c* 0.2, H_2O)	1765	(D_2O); 1.80~2.30 (2H, m, 4-CH_2CH$_2$), 1.98 (3H, s, $COCH_3$), 3.30 (2H, t, J=7.5, 4-CH$_2$CH_2), 3.96 (3H, s, OCH_3), 4.30~4.50 (1H, m, 4-H), 5.38 (1H, d, J=5.5, 3-H), 6.96 (1H, s, thiazole-5H)
18e	56	541 $(M+Na)^+$ 519 $(M+H)^+$	−24.9° (*c* 0.2, MeOH)	1770	(DMSO-d_6); 1.80~2.10 (2H, m, 4-CH_2CH$_2$), 3.20~3.60 (2H, m, 4-CH$_2$CH_2), 3.77 (3H, s, OCH_3), 3.95~4.15 (1H, m, 4-H), 5.13 (1H, dd, J=5.5, 9, 3-H), 6.70 (1H, s, thiazole-5H), 7.10 (2H, br s, NH_2), 7.30~7.55 (3H, m, aromatic H), 7.70~7.90 (2H, m, aromatic H), 8.43 (1H, t, J=6, NH), 9.23 (1H, d, J=9, CONH)

—: Not measured.

Table 7. Spectral and physical data of compounds **20**.

Compound No.	Yield (%)	SI-MS (*m/z*)	$[\alpha]_D^{22}$	IR (KBr) β-lactam (cm^{-1})	^1H NMR (solvent) δ (J=Hz)
20f-A	48	452 $(M+H)^+$	+4.5° (*c* 1, 50% MeOH)	1765	(D_2O); 1.95~2.45 (2H, m, 4-CH_2CH_2), 3.15~3.45 (2H, m, 4-CH_2CH_2), 3.98 (3H, s, OCH_3), 4.35~4.55 (1H, m, 4-H), 5.38 (1H, d, J=5.5, 3-H), 6.97 (1H, s, thiazole-5H)
20g-A	67	466 $(M+H)^+$	+21.1° (*c* 1, MeOH)	1765	(DMSO-d_6)[a]; 1.80~2.20 (2H, m, 4-CH_2CH_2), 2.89 (3H, s, NCH_3), 3.83 (3H, s, OCH_3), 3.85~4.15 (1H, m, 4-H), 5.14 (1H, dd, J=6, 8.5, 3-H), 6.73 (1H, s, thiazole-5H), 7.12 (2H, br s, NH_2), 9.10 (3H, br s, SCNH(NH_2)), 9.27 (1H, d, J=8.5, CONH)
20h-A	63	480 $(M+H)^+$	+21.8° (*c* 0.5, 90% MeOH)	1765	(D_2O); 1.95~2.55 (2H, m, 4-CH_2CH_2), 3.03 (6H, s, 2×NCH_3), 3.15~3.45 (2H, m, 4-CH_2CH_2), 3.97 (3H, s, OCH_3), 4.35~4.65 (1H, m, 4-H), 5.38 (1H, d, J=5.5, 3-H), 6.96 (1H, s, thiazole-5H)
20i-A	83	478 $(M+H)^+$	+38.9° (*c* 1, MeOH)	1765	(D_2O); 2.00~2.40 (2H, m, 4-CH_2CH_2), 3.15~3.45 (2H, m, 4-CH_2CH_2), 3.92 (4H, s, CH_2CH_2), 3.97 (3H, s, OCH_3), 4.30~4.60 (1H, m, 4-H), 5.35 (1H, d, J=6, 3-H), 6.96 (1H, s, thiazole-5H)
20j-A	55	492 $(M+H)^+$	+31.1° (*c* 1, MeOH)	1765	(DMSO-d_6)[a]; 1.80~2.20 (2H, m, 4-CH_2CH_2), 3.83 (3H, s, OCH_3), 3.85~4.15 (3H, m, 4-H and NHCH_2), 5.05~5.35 (3H, m, 3-H and CH=CH_2), 5.55~6.05 (1H, m, CH=CH_2), 6.73 (1H, s, thiazole-5H), 7.13 (2H, br s, NH_2), 9.20 (3H, br s, SC(NH_2)=NHCH_2), 9.29 (1H, d, J=8.5, CONH)
20k-A	57	455 $(M+H)^+$	−15.1° (*c* 0.5, H_2O)	1770	(D_2O); 2.30~2.80 (2H, m, 4-CH_2CH_2), 3.80 (3H, s, OCH_3), 4.35~4.60 (1H, m, 4-H), 4.85 (2H, t, J=8, 4-CH_2CH_2), 5.40 (1H, d, J=5.5, 3-H), 6.96 (1H, s, thiazole-5H), 8.10 (2H, dd, J=6.7, 5, pyridinium H), 8.58 (1H, t, J=7.5, pyridinium H), 8.85 (2H, d, J=6, pyridinium H)
20f-C	43	496 $(M+H)^+$	+3.4° (*c* 1, H_2O)	1770	(D_2O); 2.05~2.45 (2H, m, 4-CH_2CH_2), 3.10~3.50 (2H, m, 4-CH_2CH_2), 4.35~4.55 (1H, m, 4-H), 4.60 (2H, s, OCH_2COOH), 5.40 (1H, d, J=5.5, 3-H), 7.04 (1H, s, thiazole-5H)
20g-C	58	510 $(M+H)^+$	+4.5° (*c* 1, H_2O)	1770	(D_2O); 2.00~2.40 (2H, m, 4-CH_2CH_2), 2.97 (3H, s, NCH_3), 3.10~3.40 (2H, m, 4-CH_2CH_2), 4.35~4.55 (1H, m, 4-H), 4.65 (2H, s, OCH_2COOH), 5.37 (1H, d, J=5.5, 3-H), 7.05 (1H, s, thiazole-5H)
20h-C	48	524 $(M+H)^+$	+8.7° (*c* 1, H_2O)	1770	(D_2O); 2.00~2.40 (2H, m, 4-CH_2CH_2), 3.01 (6H, s, 2×NCH_3), 3.10~3.40 (2H, m, 4-CH_2CH_2), 4.35~4.55 (1H, m, 4-H), 4.65 (2H, s, OCH_2COOH), 5.39 (1H, d, J=5.5, 3-H), 7.07 (1H, s, thiazole-5H)
20i-C	56	522 $(M+H)^+$	+29.7° (*c* 1, 50% MeOH)	1765	(D_2O); 2.00~2.40 (2H, m, 4-CH_2CH_2), 3.15~3.45 (2H, m, 4-CH_2CH_2), 3.92 (4H, s, CH_2CH_2), 4.40~4.60 (1H, m, 4-H), 4.65 (2H, s, OCH_2COOH), 5.39 (1H, d, 3-H), 7.09 (1H, s, thiazole-5H)
20j-C	50	536 $(M+H)^+$	+2.7° (*c* 1, 50% MeOH)	1770	(D_2O); 2.00~2.40 (2H, m, 4-CH_2CH_2), 3.15~3.45 (2H, m, 4-CH_2CH_2), 3.95~4.05 (2H, m, NHCH_2), 4.35~4.55 (1H, m, 4-H), 4.60 (2H, s, OCH_2COOH), 5.20~5.45 (3H, m, 3-H and CH=CH_2), 5.65~6.05 (1H, m, CH=CH_2), 7.05 (1H, s, thiazole-5H)

[a] Methylene signal of the C-4 substituent overlapped with that of water in the DMSO-d_6.

synthesized by treating **15-A** and **15-B** with sodium iodide.

16-A*: Yield 92%. Colorless crystals. MP 157~159°C (dec).

16-b*: Yield 93%. A colorless powder.

(3*S*,4*R*)-3-[2-(2-Triphenylmethylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(2-substituted ethyl)-2-azetidinones (**17**)

Method A: A mixture of **16-A** (330 mg, 0.5 mmol) and sodium azide (65 mg, 1 mmol) in DMF (5 ml) was stirred for 2 days at 50°C, and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 ml) and brine, and the separated organic solution was dried and concentrated under reduced pressure. The residue was washed with ether to give **17a** (240 mg, 80%) as a pale yellow powder.

Compounds **17b** and **17c** were similarly prepared by using potassium thiocyanate and morpholine in place of sodium azide in method A, respectively. The physical data of **17a**, **17b** and **17c** are summarized in Table 6.

Method B: Compound **17a** (120 mg, 0.2 mmol) was hydrogenated in DMF (2 ml) for 90 minutes over 5% Pd-C (20 mg) at room temp under a hydrogen atmosphere. The catalyst was filtered off, and to the filtrate was added pyridine (32 mg, 0.4 mmol) and acetyl chloride (31 mg, 0.4 mmol) at 0~5°C. After being stirred for 2 hours at the same temp, the mixture was concentrated under reduced pressure. The residue was subjected to preparative TLC (CH_2Cl_2 - MeOH, 10:1) to give **17d** (60 mg, 50%) as a colorless powder.

Compound **17e** was similarly prepared by using benzoyl chloride in place of acetyl chloride in method B. The physical data of **17d** and **17e** are shown in Table 6.

Sodium (3*S*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(2-substituted ethyl)-2-azetidinone-1-sulfonates (**18**)

General Procedure I: Sulfonation and removal of the triphenylmethyl group: A mixture of compound **17** (0.1~0.2 mmol) and $SO_3 \cdot Py$ (0.5~1 mmol) in DMF (1~2 ml) and CH_2Cl_2 (1~2 ml) was stirred for 3~5 hours at 50°C, and the solvent was evaporated to dryness. The residue was chromatographed on silica gel (CH_2Cl_2 - MeOH, 10:1) to give a crude sulfonated product, which was subsequently dissolved in 80% AcOH (4 ml) and the mixture was stirred for 2 hours at 50°C. The mixture was concentrated under reduced pressure. The concentrate was diluted with water (5 ml), and adjusted to pH 7.5~8.0 with $NaHCO_3$ (this procedure was omitted in the case of **17c**). The solution was washed with ether, and the aqueous solution was chromatographed on Diaion HP-20. Elution with water, 5% EtOH and 10% EtOH, followed by lyophilization, afforded **18** as a colorless powder. The results are shown in Table 6.

Sodium (3*S*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted oxyimino)acetamido]-4-(2-iodoethyl)-2-azetidinone-1-sulfonate (**19-A**) and (**19-B**)

Compounds **19-A** and **19-B** were similarly prepared from **16-A** and **16-B** by a general procedure I.

19-A*: A colorless powder. Yield 58%.

19-B*: A colorless powder. Yield 61%.

(3*S*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-[2-(substituted isothiuronio)-ethyl]-2-azetidinone-1-sulfonates (**20-A**)

General Procedure II: To a solution of **19-A** (105 mg, 0.2 mmol) in EtOH (3 ml) and DMF (0.5 ml) was added thiourea (1 mmol), and the mixture was stirred for 2 days at 50°C. The solvent was removed under reduced pressure, and the residue was chromatographed on Diaion HP-20 after dissolving in water (2 ml). Elution with water, 5%, 10%, and 20% EtOH, followed by lyophilization, afforded **20-A** as a colorless powder. The results are shown in Table 7.

Compound **20k-A** was prepared from **19-A** by using pyridine in place of thiourea in general procedure II, and the result is shown in Table 7.

(3*S*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(carboxymethoxyimino)acetamido]-4-[2-(substituted isothiuronio)ethyl]-2-azetidinone-1-sulfonates (**20-C**)

General Procedure III: Treatment of **19-B** (125 mg, 0.2 mmol) with thiourea (1 mmol) by general

procedure II gave **20-B**, which was dissolved in 99% HCOOH (3 ml) and the mixture was stirred for 90 minutes at 50°C. After removal of the solvent, the residue was chromatographed on Diaion HP-20. Elution with water, 3%, 5% and 10% EtOH, followed by lyophilization, afforded **20-C** as a colorless powder. The results are shown in Table 7.

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