CHEMICAL MODIFICATION OF SULFAZECIN

SYNTHESIS OF 4-(SUBSTITUTED METHYL)-2-AZETIDINONE-1-SULFONIC ACID DERIVATIVES†

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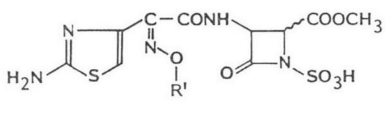
In expectation of improving the antibacterial activity of sulfazecin by chemical modification at the 3- and 4-positions, a number of 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(substituted oxyimino)-acetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonic acids were synthesized. Among various 4-substituents explored, the carbamoyloxymethyl group was found to provide a good effect to the antibacterial activity of these 2-azetidinone derivatives. An extensive study of structure-activity relationships led to selecting (3*S*,4*S*)-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-carboxymethoxyiminoacetamido]-4-carbamoyloxymethyl-2-azetidinone-1-sulfonic acid, AMA-1080 (Ro 17-2301), which has highly potent antibacterial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*, for further biological and subsequent clinical evaluation.

In our previous paper[2], the synthesis and antibacterial activity of 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(substituted oxyimino)acetamido]-4-methoxycarbonyl-2-azetidinone-1-sulfonic acids (**1**) were reported; it was demonstrated that introducing a methoxycarbonyl group at the 4-position of sulfazecin-type derivatives, especially in 3,4-*cis* configuration, significantly enhanced antibacterial activity against Gram-negative bacteria including β-lactamase producing strains. These findings prompted us to synthesize a number of 1-sulfo-2-azetidinones having various kinds of substituents at the 4-position for further improvement of the antibacterial activity. In this paper, the synthesis and antibacterial activity of 4-(substituted methyl)-2-azetidinone-1-sulfonic acid derivatives (**2**) including AMA-1080 (**3**)[1], a clinical candidate of this series, will be reported.

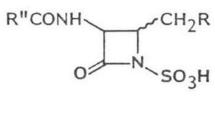
Modification at the 4-Position

Various 3,4-*cis*- and *trans*-4-(substituted methyl)-2-azetidinones (**10** and **13**) were prepared starting from *cis*- and *trans*-3-amino-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-2-azetidinones (**4** and **12**)[2]

Chart 1.



1 $R^1 = CH_3$, $C(CH_3)_2COOH$ *etc.*



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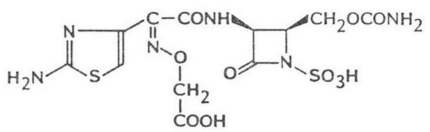
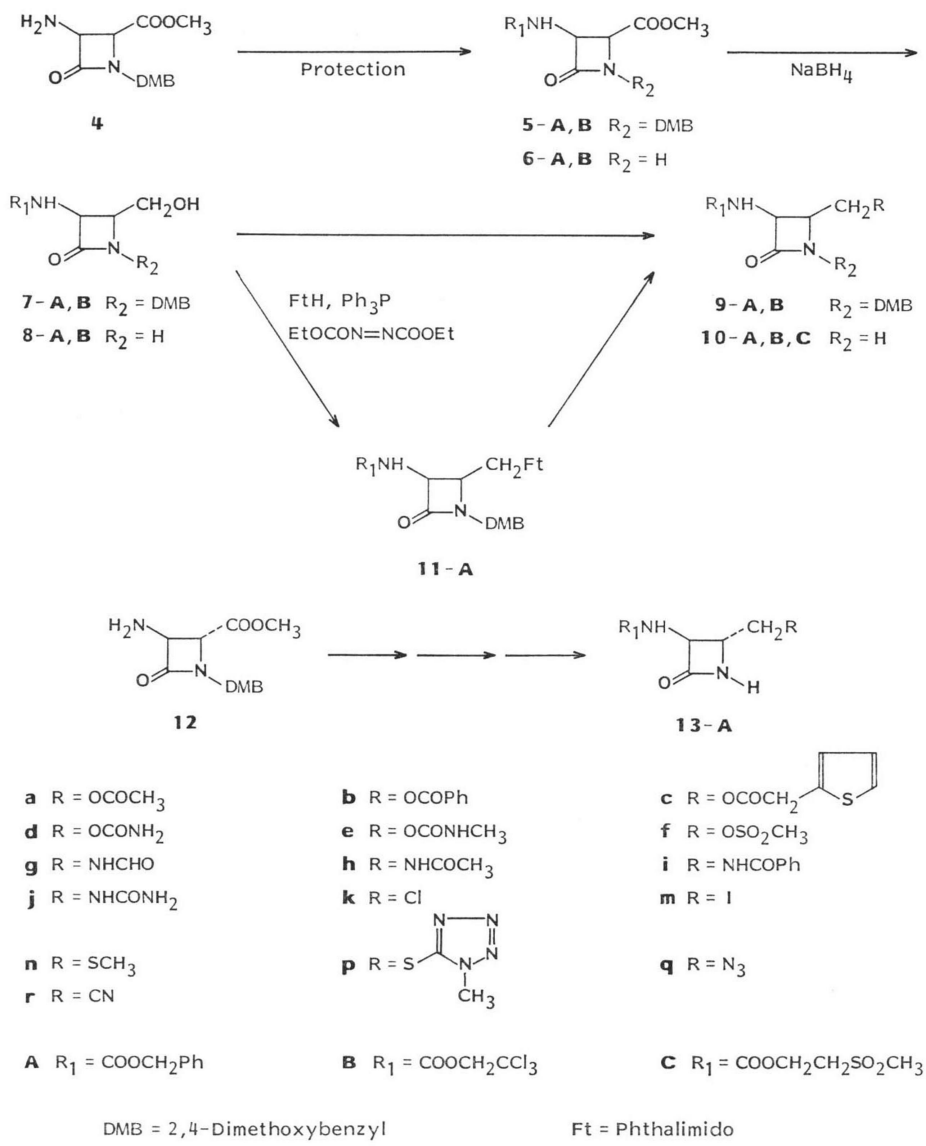


AMA-1080 (Ro 17-2301) (**3**)

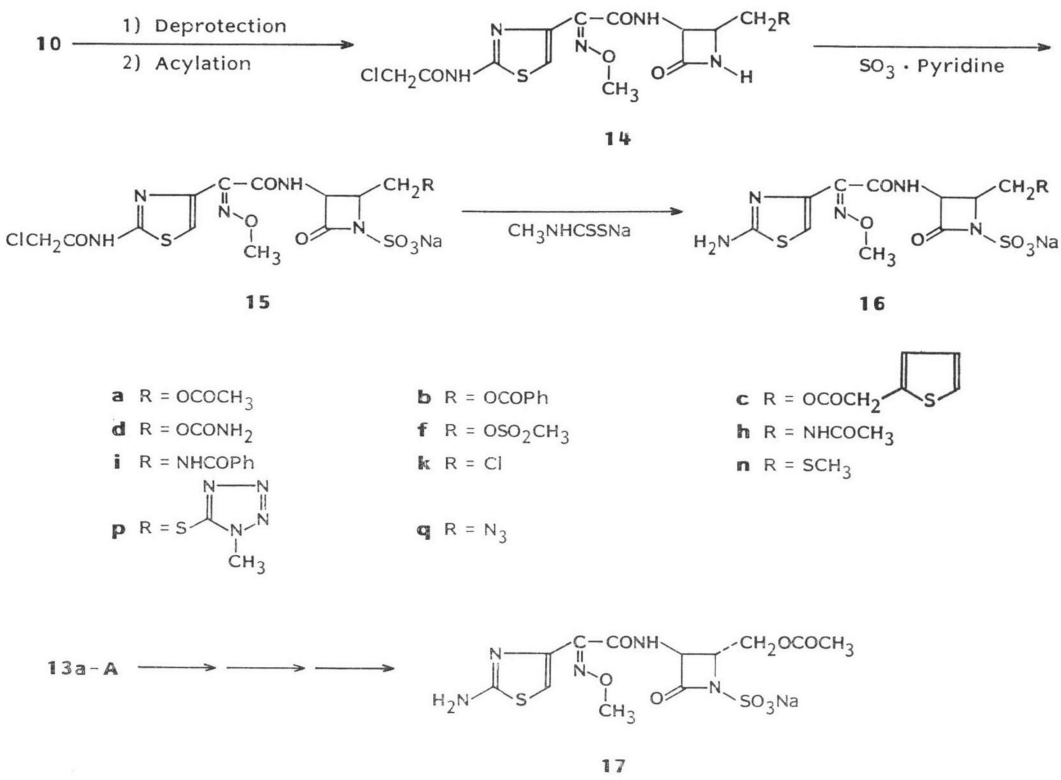
† Part of this paper was reported as a communication[1].

Chart 2.



via the 4-hydroxymethyl compounds (**7**, **8** and their *trans* isomers), which were the key intermediates for the chemical modification in this study (Chart 2). Protection of the 3-amino group of compound **4** gave 3-benzyloxycarbonylamino and 3-(2,2,2-trichloroethoxycarbonylamino) derivatives (**5-A**[2] and **5-B**), and subsequent oxidative cleavage[3] of the 2,4-dimethoxybenzyl group using potassium persulfate afforded the corresponding 1-unsubstituted-2-azetidinones (**6-A**[2] and **6-B**), respectively. Reduction[3] of the 4-methoxycarbonyl groups of **5** and **6** with sodium borohydride gave the *cis*-4-hydroxymethyl compounds (**7** and **8**). The 4-acyloxymethyl (**10a,b-A** and **10c-B**) and 4-carbamoyloxymethyl (**10d,e-A**) derivatives were prepared by treating **7** and **8** with acid chlorides and isocyanates, followed by deprotection in the case of 1-(2,4-dimethoxybenzyl) compounds (**9a,b,d-A**). The 4-acylaminomethyl (**10g,h,i-A**) and 4-carbamoylaminomethyl (**10j-A**) derivatives were synthesized by the following route: the 4-

Chart 3.



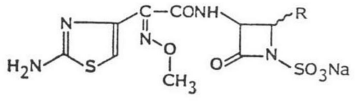
phthalimidomethyl compound (**11-A**), obtained by MITSUNOBU reaction[4] of **7-A** and phthalimide, was treated with hydrazine, and the resultant aminomethyl intermediate was acylated and carbamoylated to give the 4-acylaminomethyl (**9g,h,i-A**) and 4-carbamoylaminomethyl (**9j-A**) derivatives, respectively. Removal of the 2,4-dimethoxybenzyl groups from these compounds afforded **10g,h,i,j-A**. In the meanwhile, mesylation of **7** and **8** gave the 4-mesyloxymethyl compounds (**9f** and **10f**), which were then transformed into the 4-chloromethyl (**10k**) and 4-iodomethyl (**9m** and **10m**) derivatives. The iodomethyl groups of **9m** and **10m** were further converted into various 4-substituents; treatment of the iodides with thiols, sodium azide, and potassium cyanide gave the 4-thiomethyl (**10n,p-B**), 4-azidomethyl (**10q-C**)* and 4-cyanomethyl (**9r-A**) compounds, respectively. Compound **9r-A** was converted into the 1-unsubstituted derivative (**10r-A**) by persulfate oxidation.

Two 3,4-*trans* analogues (**13a,d-A**) were prepared from **12** in a similar manner to that described for the synthesis of the corresponding 3,4-*cis* isomers.

Deprotection of **10** and subsequent acylation with 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetyl chloride[5] gave the 3-acylamino compounds (**14**), which were converted into sodium 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonates (**16**) by sulfonation[6,7] with sulfur trioxide-pyridine complex (SO_3·Pyridine) and removal[5] of the

* In the case of the 4-azidomethyl compound, 2-methylsulfonylethoxycarbonyl group was adopted to protect the 3-amino moiety, because azides are unstable to the reaction conditions used for deprotection of the above two protecting groups.

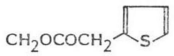
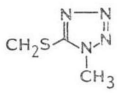
Table 1. Antibacterial activity of compounds **16** and **17**.



16: 3,4-*cis*

17: 3,4-*trans*

MIC (μg/ml)[a]; 10^5 cfu

Compound	R	*Escherichia coli* O-111[b]	*Escherichia coli* T-7[c]	*Serratia marcescens* IFO 12648
16a	CH_2OCOCH_3	<0.1	1.56	0.39
16b	CH_2OCOPh	3.13	12.5	12.5
16c		3.13	12.5	12.5
16d	CH_2OCONH_2	≤0.1	0.39	0.39
16f	$CH_2OSO_2CH_3$	0.2	1.56	1.56
16h	$CH_2NHCOCH_3$	0.2	0.78	0.78
16i	$CH_2NHCOPh$	3.13	12.5	12.5
16k	CH_2Cl	0.2	1.56	0.78
16n	CH_2SCH_3	0.2	1.56	1.56
16p		1.56	12.5	6.25
16q	CH_2N_3	≤0.1	0.78	0.78
17	CH_2OCOCH_3	0.2	12.5	0.78
	$COOCH_3$ (*cis*)	≤0.1	0.39	0.2
	H	0.39	>100	12.5

[a] The MICs were determined by a standard agar dilution method in Trypticase soy agar (BBL).
[b] Cefazolin sensitive strain.
[c] Cefazolin resistant strain.

chloroacetyl groups with sodium *N*-methyldithiocarbamate. The *trans* isomer (**17**)* of the 4-acetoxymethyl compound (**16a**) was similarly prepared from **13a-A**.

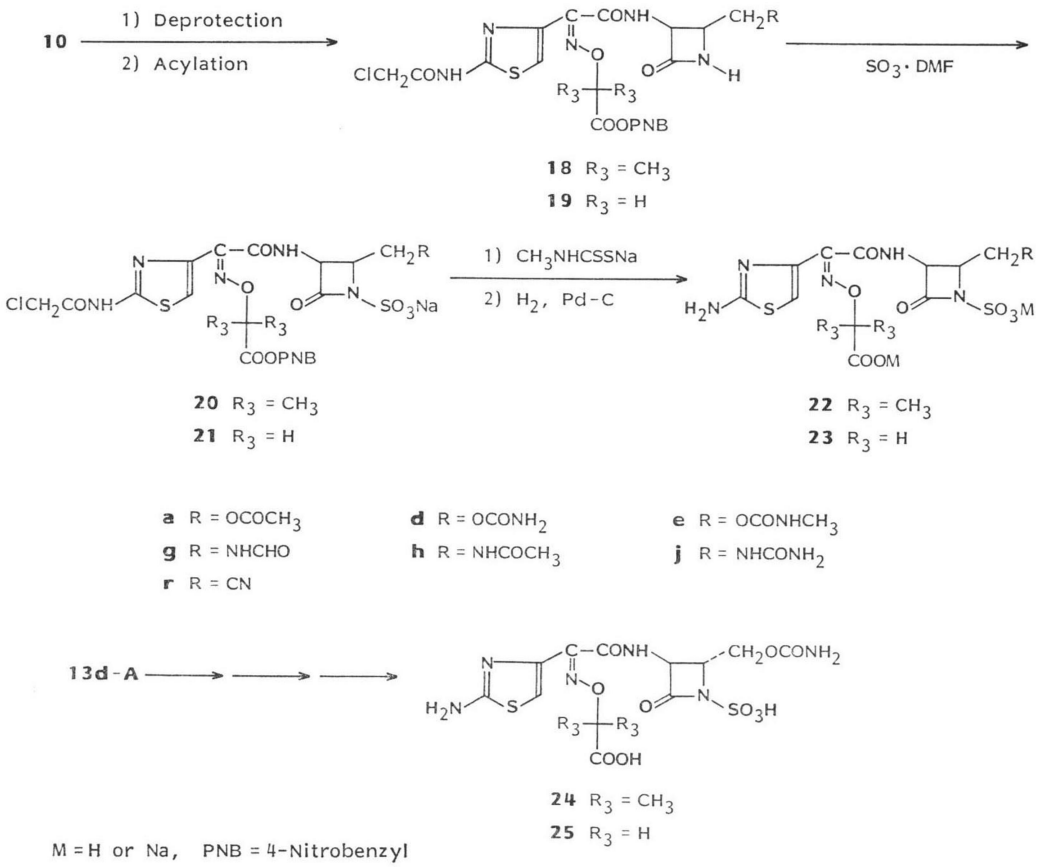
The *in vitro* antibacterial activity of **16** and **17** is shown in Table 1. These 4-(substituted methyl)-1-sulfo-2-azetidinones, as well as the corresponding 4-methoxycarbonyl compounds[2], generally showed good antibacterial activity against Gram-negative bacteria and improved activity against *Escherichia coli* T-7, a producer of the TEM-1 β-lactamase, as compared with the corresponding 4-unsubstituted derivative[7]. However, the potency of the activity varies with the size or lipophilicity of the 4-substituent and tends to decrease when an aromatic ring is introduced as a part of the substituent (compare the activity of **16a**, **16h** and **16n** with that of **16b**, **16i** and **16p**, respectively). Carbamoyloxymethyl, acetoxymethyl, acetamidomethyl and azidomethyl groups were efficient substituents in this series. The *cis*-4-acetoxymethyl compound (**16a**) was more active than the corresponding *trans* isomer (**17**) in analogy with the cases of 4-methoxycarbonyl[2] and 4-methyl[9] derivatives.

Selection of the 3-Acyl Group

In order to examine the effect of the 3-acyl moiety on the antibacterial activity of 4-(substituted methyl)-2-azetidinone-1-sulfonic acids (**2**), the acyl moiety of ceftazidime and an analogous group were

* The (3*S*,4*R*)- and (3*R*,4*S*)-enantiomers of this compound were independently synthesized by SHIBUYA *et al.*[5].

Chart 4.



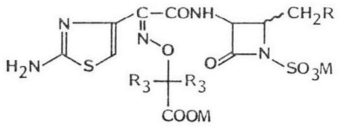
introduced at the 3-position*. Carbamoyloxymethyl, acetoxymethyl and acetamidomethyl groups were selected as representative 4-substituents in this study, and some related groups were also investigated for further improvement of the activity (Chart 4). Deprotection of **10** and subsequent acylation with 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]acetyl chloride[2] and 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-(4-nitrobenzyloxycarbonylmethoxyimino)acetyl chloride** gave the corresponding 3-acylamino derivatives, **18** and **19**, respectively. Sulfonation[6,7] of these compounds with sulfur trioxide-*N*,*N*-dimethylformamide complex (SO_3·DMF) afforded the 1-sulfo-2-azetidinones (**20** and **21**). Removal of the chloroacetyl groups from **20** and **21** by treatment with sodium *N*-methyldithiocarbamate and subsequent catalytic hydrogenolysis of the 4-nitrobenzyl esters gave the deprotected products (**22** and **23**). Two *trans* isomers (**24** and **25**) with a carbamoyloxymethyl group at the 4-position were similarly prepared starting from **13d-A**.

As shown in Table 2, some of these compounds (**22**~**25**) showed good to excellent antibacterial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*. Among four compounds bearing a carbamoyloxymethyl group, the most efficient 4-substituent found in the present study,

* The independent work of SYKES *et al.*[10] led to the development of aztreonam having the ceftazidime side-chain at the 3-position and a methyl group at the 4-position.

** This acid chloride was prepared in a similar manner to that reported for the synthesis of the homologous acid chloride[2].

Table 2. Antibacterial activity of compounds **22**~**25**.



22 and **23**: 3,4-*cis*

24 and **25**: 3,4-*trans*

MIC (μg/ml)[a]; 10^5 cfu

Compound	**22a**	**22d**	**22h**	**22j**	**22r**	**23d**	**23e**	**23g**	**24**	**25**
R_3	CH_3	CH_3	CH_3	CH_3	CH_3	H	H	H	CH_3	H
M	Na	H	H	H	H	H	H	H	H	H
R	$OCOCH_3$	$OCONH_2$	$NHCOCH_3$	$NHCONH_2$	CN	$OCONH_2$	$OCONHCH_3$	NHCHO	$OCONH_2$	$OCONH_2$
Escherichia coli O-111[b]	0.2	0.1	0.2	0.78	$\leq$0.1	<0.1	<0.1	1.56	<0.1	<0.1
E. coli T-7[c]	1.56	1.56	1.56	6.25	1.56	0.39	0.78	6.25	0.39	0.2
Klebsiella pneumoniae TN 1711	1.56	0.39	0.39	3.13	1.56	0.2	0.2	12.5	50	3.13
Serratia marcescens IFO 12648	1.56	0.39	0.39	3.13	0.39	<0.1	0.2	6.25	<0.1	<0.1
Pseudomonas aeruginosa IFO 3455	12.5	6.25	25	6.25	6.25	3.13	3.13	25	3.13	12.5

[a] See the footnote in Table 1.

[b] Cefazolin sensitive strain.

[c] Cefazolin resistant strain.

Chart 5.

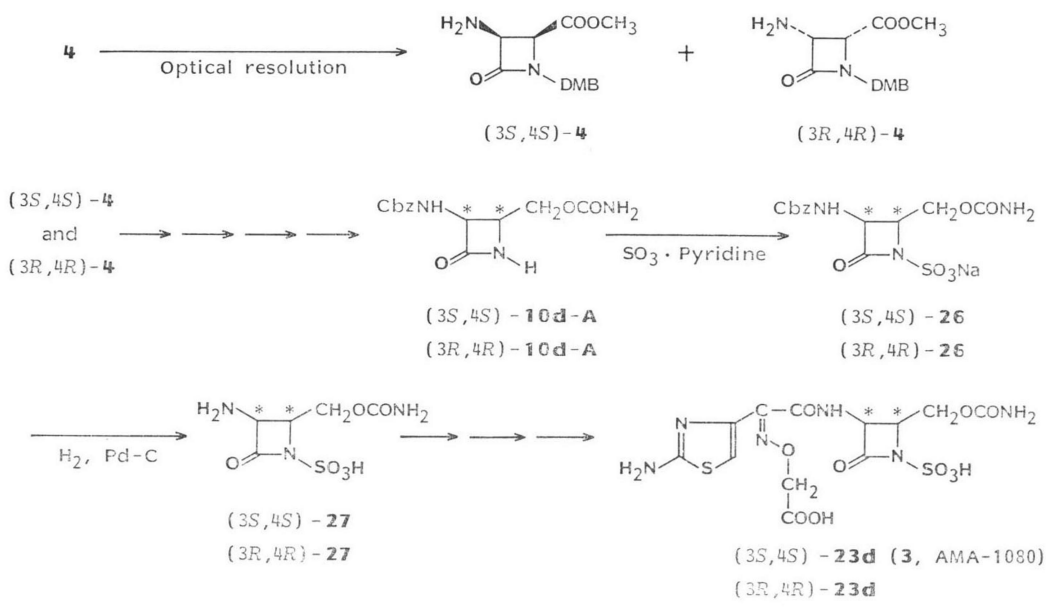
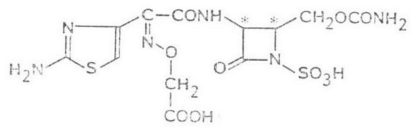


Table 3. Antibacterial activity of (3*S*,4*S*)- and (3*R*,4*R*)-**23d**.



MIC (μg/ml)[a]; 10^5 cfu

Organism	(3*S*,4*S*)-**23d** (**3**, AMA-1080)	(3*R*,4*R*)-**23d**	Aztreonam[b]
Escherichia coli O-111	0.025	12.5	0.025
E. coli T-7	0.2	50	0.39
Klebsiella pneumoniae TN 1711	0.1	>100	25
Enterobacter cloacae IFO 12937	0.78	>100	3.13
Serratia marcescens IFO 12648	0.05	25	0.1
Proteus vulgaris IFO 3988	0.05	25	0.013
Pseudomonas aeruginosa IFO 3455	1.56	>100	3.13
P. aeruginosa GN 3407	6.25	>100	6.25

[a] See the footnote in Table 1.
[b] This reference compound was prepared according to the reported procedure.

cis-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-carboxymethoxyiminoacetamido]-4-carbamoyloxymethyl-2-azetidinone-1-sulfonic acid (**23d**) showed the most promising antibacterial activity.

For further biological evaluation of **23d**, the (3*S*,4*S*)- and (3*R*,4*R*)-enantiomers of this compound were synthesized. The starting materials for the chiral synthesis were obtained by optical resolution of compound **4** using D- and L-di-(4-toluoyl)-tartaric acids, and resultant (3*S*,4*S*)- and (3*R*,4*R*)-**4** were converted into (3*S*,4*S*)- and (3*R*,4*R*)-**10d** in a similar manner to that employed in the racemic series (Chart 5). After sulfonation at the 1-position of these intermediates and subsequent hydrogenolysis of the benzyloxycarbonylamino groups, (3*S*,4*S*)- and (3*R*,4*R*)-isomers of 3-amino-4-carbamoyloxymethyl-2-azetidinone-1-sulfonic acid (**27**) were isolated as colorless crystals, which were then converted into (3*S*,4*S*)-

and (3*R*,4*R*)-**23d**, respectively, by acylation and subsequent deprotection.

As shown in Table 3, the (3*S*,4*S*)-isomer (**3**, AMA-1080) was found to be far more active than the corresponding (3*R*,4*R*)-enantiomer[8], and showed not only potent antibacterial activity against Gram-negative bacteria but also good protective effect on experimental intraperitoneal infection in mice[11]. Compound **3** was also highly resistant to hydrolysis by various types of β-lactamases including those produced by *Klebsiella pneumoniae, Proteus vulgaris* and *Bacteroides fragilis* which hydrolyzed aztreonam and several newer cephalosporins[12]. Investigations on the practical method for the production of AMA-1080 (Ro 17-2301) and its clinical trial are now in progress.

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a Hitachi 215 spectrometer. ^{1}H NMR spectra were taken on a Varian T-60 (60 MHz) or a Varian EM-390 (90 MHz) spectrometer using TMS as an internal standard. Chemical shifts in the NMR spectra are given with proton numbers, absorption patterns, and coupling constants (Hz) in parentheses. Abbreviations are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; ABq, AB quartet; m, multiplet; br, broad. Extracted solutions were dried over sodium sulfate or magnesium sulfate.

cis-1-(2,4-Dimethoxybenzyl)-4-methoxycarbonyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**5-B**)

A solution of 2,2,2-trichloroethyl chloroformate (1.27 g, 6 mmol) in CH_2Cl_2 (1 ml) was added dropwise to a stirred, cooled (0°C) mixture of *cis*-3-amino-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-2-azetidinone (**4**)[2] (1.18 g, 4 mmol) and propylene oxide (2.7 ml) in CH_2Cl_2 (5 ml) over 10 minutes, and the mixture was stirred for 30 minutes at room temp. The mixture was concentrated under reduced pressure and the solid residue was washed with ether to give **5-B** (1.67 g, 89%) as colorless crystals. MP 135~136°C. IR ν_{max}^{KBr} cm^{-1} 1775, 1745. NMR ($CDCl_3$) δ 3.80, 3.84 and 3.86 (each 3H, s), 4.32 (1H, d, 5), 4.48 (2H, ABq, 15), 4.80 (2H, ABq, 12), 5.33 (1H, dd, 5, 8), 5.96 (1H, d, 8), 6.4~6.7 (2H, m), 7.1~7.4 (1H, m).

Anal Calcd for $C_{17}H_{19}Cl_3N_2O_7$: C 43.47, H 4.08, N 5.96.
Found: C 43.43, H 3.99, N 6.19.

General Procedure I: Removal of the 1-(2,4-Dimethoxybenzyl) Group with Potassium Persulfate[2,3]

Potassium persulfate (1.4~4.0 mmol), K_2HPO_4 (1.3~2.0 mmol) and 1-(2,4-dimethoxybenzyl)-2-azetidinone (1.0 mmol) were added to a mixture of acetonitrile and water (2: 1, 30 ml), and the mixture was heated in an oil bath (80~95°C) for 1~3 hours with stirring. After evaporation of the acetonitrile under reduced pressure, the concentrate was extracted with EtOAc. The extract was washed successively with aq $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residue was purified by column chromatography or recrystallization to give 1-unsubstituted-2-azetidinone.

cis-4-Methoxycarbonyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**6-B**)

According to the general procedure I, the 2,4-dimethoxybenzyl group of **5-B** was removed to give **6-B** as colorless crystals. MP 140~141°C. Yield 61%. IR ν_{max}^{KBr} cm^{-1} 1770, 1735. NMR (DMSO-d_6) δ 3.69 (3H, s), 4.5 (1H, d, 6), 4.91 (2H, br s), 5.17 (1H, dd, 6, 10), 8.73 (1H, d, 10), 8.75 (1H, br s).

Anal Calcd for $C_8H_9Cl_3N_2O_5$: C 30.07, H 2.84, N 8.77.
Found: C 30.30, H 2.82, N 8.87.

cis-3-Benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-hydroxymethyl-2-azetidinone (**7-A**) and Its *trans* Isomer

A solution of sodium borohydride (2.65 g, 70 mmol) in water (250 ml) was added to a stirred solution of *cis*-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-2-azetidinone (**5-A**)[2] (12.0 g, 30 mmol) in THF (500 ml) under ice-cooling, and the mixture was stirred for 5 hours at room

temp. After evaporation of the THF under reduced pressure, the concentrate was diluted with water. The resulting precipitate was collected by filtration and washed with water to give **7-A** (9.8 g, 87%) as colorless crystals. MP 129~131°C. IR ν_{max}^{KBr} cm^{-1} 1720. NMR ($CDCl_3$) δ 3.90 (6H, s), 3.5~3.9 (3H, m), 4.33 (2H, s), 5.06 (2H, s), 4.95~5.2 (1H, m), 6.3~6.5 and 7.0~7.3 (3H, m), 7.25 (5H, s).

Anal Calcd for $C_{21}H_{24}N_2O_6$: C 62.99, H 6.04, N 7.00.
Found: C 62.78, H 5.91, N 7.05.

The *trans* isomer of **7-A** was prepared in a similar manner and purified by column chromatography to give a colorless oil. Yield 88%. IR ν_{max}^{Neat} cm^{-1} 1740. NMR ($CDCl_3$) δ 3.3~3.8 (3H, m), 4.1~4.6 (3H, m), 5.1 (2H, s), 5.8 (1H, d, 6), 6.45 and 7.2 (3H, m), 7.32 (5H, s).

cis-1-(2,4-Dimethoxybenzyl)-4-hydroxymethyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**7-B**)

Compound **7-B** was prepared from **5-B** by a method similar to that described above. Colorless crystals. MP 112~114°C. Yield 70%. IR ν_{max}^{KBr} cm^{-1} 1745, 1720. NMR ($CDCl_3$) δ 2.4~2.7 (1H, m), 3.65~4.05 (3H, m), 3.85 and 3.9 (each 3H, s), 4.47 (2H, s), 4.83 (2H, s), 5.25 (1H, dd, 5, 10), 6.44 (1H, d, 10), 6.5~6.7 and 7.25~7.45 (3H, m).

Anal Calcd for $C_{18}H_{19}Cl_3N_2O_6$: C 43.51, H 4.34, N 6.36.
Found: C 43.64, H 4.42, N 6.16.

cis-3-Benzyloxycarbonylamino-4-hydroxymethyl-2-azetidinone (**8-A**)

A solution of sodium borohydride (189 mg, 5 mmol) in water (1.3 ml) was added to a stirred solution of *cis*-3-benzyloxycarbonylamino-4-methoxycarbonyl-2-azetidinone (**6-A**)[2,13] (557 mg, 2 mmol) in THF (2.6 ml) at 0~5°C, and the mixture was stirred for 80 minutes at the same temp. After the excess sodium borohydride had been decomposed with AcOH, the reaction mixture was concentrated under reduced pressure. The concentrate was diluted with brine and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with EtOAc - acetonitrile (4: 1) to give **8-A** (367 mg, 73%) as colorless crystals. MP 103~104°C. IR ν_{max}^{KBr} cm^{-1} 1740. NMR (DMSO-d_6) δ 3.35~3.85 (3H, m), 4.72 (1H, t, 4.5), 4.86 (1H, dd, 4.5, 10), 5.03 (2H, s), 7.33 (5H, s), 7.7 (1H, d, 10), 8.17 (1H, br s).

Anal Calcd for $C_{12}H_{14}N_2O_4$: C 57.59, H 5.64, N 11.19.
Found: C 57.32, H 5.41, N 11.12.

cis-4-Hydroxymethyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**8-B**)

Compound **8-B** was prepared from **6-B** by a method similar to that described above. Colorless crystals. MP 162~164°C. Yield 64%. IR ν_{max}^{KBr} cm^{-1} 1720. NMR (DMSO-d_6) δ 3.35~4.1 (3H, m), 4.82 (2H, ABq, 12), 4.88 (1H, dd, 6, 10), 8.18 (1H, d, 10), 8.1~8.4 (1H, br).

cis-4-Acetoxymethyl-3-benzyloxycarbonylamino-2-azetidinone (**10a-A**) and Its *trans* Isomer (**13a-A**)

(a) Acetyl chloride (2.25 g, 28.7 mmol) was added dropwise to a mixture of **7-A** (5.1 g, 12.7 mmol) and pyridine (3.8 ml) in CH_2Cl_2 (50 ml) at 0~5°C, and the mixture was stirred for 30 minutes at the same temp. After concentration under reduced pressure, the residue was chromatographed on silica gel with EtOAc to give *cis*-4-acetoxymethyl-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-2-azetidinone (**9a-A**) (5.45 g, 96%) as colorless crystals. MP 110~111°C. IR ν_{max}^{KBr} cm^{-1} 1760. NMR ($CDCl_3$) δ 1.95 (3H, s), 3.75 (6H, s), 3.7~4.5 (3H, m), 4.2 (2H, ABq, 15), 5.03 (2H, s), 4.9~5.2 (1H, m), 6.2~6.5 and 6.9~7.3 (3H, m), 7.2 (5H, s).

Anal Calcd for $C_{23}H_{26}N_2O_7$: C 62.43, H 5.92, N 6.33.
Found: C 62.26, H 5.68, N 6.07.

(b) According to the general procedure I, the 2,4-dimethoxybenzyl group of **9a-A** was removed to give **10a-A** as colorless crystals. MP 137~138°C. Yield 53%. IR ν_{max}^{KBr} cm^{-1} 1770, 1750. NMR (DMSO-d_6) δ 1.97 (3H, s), 3.7~4.3 (3H, m), 4.9 (1H, m), 5.03 (2H, s), 7.28 (5H, s), 8.3 (1H, br s).

Anal Calcd for $C_{14}H_{16}N_2O_5$: C 57.53, H 5.52, N 9.59.
Found: C 57.38, H 5.43, N 9.58.

The corresponding *trans* isomer (**13a-A**) was prepared from the *trans* isomer of **7-A** in a similar manner. Colorless crystals. MP 119~121°C. Yield 45%. IR ν_{max}^{KBr} cm^{-1} 1750, 1725. NMR (DMSO-

d_6) δ 2.06 (3H, s), 3.75~4.25 (3H, m), 4.53 (1H, dd, 3, 9), 5.13 (2H, s), 5.57 (1H, d, 9), 6.0~6.5 (2H, br), 7.36 (5H, s).

cis-4-Benzoyloxymethyl-3-benzyloxycarbonylamino-2-azetidinone (**10b-A**)

(a) Using benzoyl chloride in place of acetyl chloride in the above reaction, *cis*-4-benzoyloxymethyl-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-2-azetidinone (**9b-A**) was obtained as colorless crystals. MP 133~134°C. Yield 84%. IR ν_{max}^{KBr} cm^{-1} 1760. NMR ($CDCl_3$) δ 3.74 (6H, s), 3.9~4.7 (5H, m), 5.04 (2H, s), 5.1~5.3 (1H, m), 6.34 and 7.0~8.0 (13H, m).

Anal Calcd for $C_{28}H_{28}N_2O_7$: C 66.65, H 5.59, N 5.55.
Found: C 66.48, H 5.49, N 5.36.

(b) According to the general procedure I, the 2,4-dimethoxybenzyl group of **9b-A** was removed to give **10b-A** as colorless crystals. MP 188~189°C. Yield 44%. IR ν_{max}^{KBr} cm^{-1} 1770. NMR (DMSO-d_6) δ 4.0~4.6 (3H, m), 5.0~5.3 (1H, m), 5.07 (2H, s), 7.34 (5H, s), 7.5~8.2 (5H, m).

Anal Calcd for $C_{19}H_{18}N_2O_5$: C 64.40, H 5.12, N 7.91.
Found: C 64.42, H 4.96, N 7.86.

cis-4-(2-Thienylacetoxymethyl)-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**10c-B**)

Thionyl chloride (424 mg, 3.56 mmol) was added to a solution of 2-thienylacetic acid (468 mg, 3.30 mmol) in CH_2Cl_2 (7 ml), and the mixture was refluxed for 2 hours and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 ml), and the solution was added dropwise to a stirred mixture of **8-B** (800 mg, 2.75 mmol) and triethylamine (416 mg, 4.12 mmol) in CH_2Cl_2 (30 ml) under ice-cooling. The mixture was stirred overnight at room temp, diluted with EtOAc, washed successively with 3 N HCl, aq $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel with EtOAc - hexane (3: 2) to give **10c-B** (600 mg, 53%) as a foam. IR ν_{max}^{KBr} cm^{-1} 1780~1715. NMR ($CDCl_3$) δ 3.92 (2H, s), 3.5~4.6 (3H, m), 4.72 (2H, s), 5.14 (1H, dd, 5, 9), 6.1 (1H, d, 9), 6.4 (1H, br s), 6.8~7.35 (3H, m).

cis-3-Benzyloxycarbonylamino-4-carbamoyloxymethyl-2-azetidinone (**10d-A**) and Its *trans* Isomer (**13d-A**)

(a) Chlorosulfonyl isocyanate (0.09 ml, 1 mmol) was added to an ice-cooled solution of **7-A** (400 mg, 1 mmol) in CH_2Cl_2 (8 ml) with stirring, and the mixture was stirred for 30 minutes under ice-cooling. After further addition of chlorosulfonyl isocyanate (0.09 ml), the mixture was stirred for 10 minutes at the same temp. A solution of sodium sulfite (280 mg) in water (6 ml) was added, and the mixture was stirred for 1 hour at room temp and diluted with CH_2Cl_2. The organic layer was separated, washed with brine, dried and concentrated under reduced pressure. The residue was triturated with ether, and the resulting crystals were collected by filtration to give *cis*-3-benzyloxycarbonylamino-4-carbamoyloxymethyl-1-(2,4-dimethoxybenzyl)-2-azetidinone (**9d-A**) (330 mg, 74%) as colorless crystals. An analytical sample was obtained by recrystallization from EtOAc. MP 172~174°C. IR ν_{max}^{Nujol} cm^{-1} 1760. NMR (DMSO-d_6) δ 3.74 and 3.76 (each 3H, s), 3.7~4.3 (3H, m), 4.2 (2H, ABq, 15), 4.92 (1H, dd, 5, 10), 5.02 (2H, s), 6.35~6.6 (4H, m), 7.05~7.25 (1H, m), 7.35 (5H, s), 7.87 (1H, d, 10).

Anal Calcd for $C_{22}H_{25}N_3O_7$: C 59.58, H 5.68, N 9.47.
Found: C 59.61, H 5.67, N 9.32.

(b) According to the general procedure I, the 2,4-dimethoxybenzyl group of **9d-A** was removed to give **10d-A** as colorless crystals. MP 210~211°C. Yield 67%. IR ν_{max}^{KBr} cm^{-1} 1765. NMR (DMSO-d_6) δ 3.7~4.25 (3H, m), 4.95 (1H, dd, 5, 10), 5.05 (2H, s), 6.47 (2H, br s), 7.33 (5H, s), 7.92 (1H, d, 10), 8.3 (1H, br s).

Anal Calcd for $C_{13}H_{15}N_3O_5$: C 53.23, H 5.15, N 14.32.
Found: C 53.33, H 4.90, N 14.09.

The corresponding *trans* isomer (**13d-A**) was prepared from the *trans* isomer of **7-A** in a similar manner.

(a) The *trans* isomer of **9d-A**: A viscous oil. Yield 30%. IR ν_{max}^{KBr} cm^{-1} 1760~1690. NMR (DMSO-d_6) δ 3.65 (1H, d, 3), 3.73 (3H, s), 3.76 (3H, s), 3.9~4.6 (5H, m), 5.02 (2H, s), 6.4~6.6 (4H, m), 7.1~7.4 (1H, m), 7.32 (5H, s), 8.0 (1H, d, 9).

(b) **13d-A**: Colorless crystals. MP 154~156°C. Yield 69%. IR ν_{max}^{KBr} cm^{-1} 1760, 1720. NMR

(DMSO-d_6) δ 3.6~3.8 (1H, m), 3.8~4.3 (2H, m), 4.38 (1H, dd, 3, 9), 5.03 (2H, s), 6.53 (2H, br s), 7.35 (5H, s), 7.93 (1H, d, 9), 8.15 (1H, br s).

Anal Calcd for $C_{13}H_{15}N_3O_5$: C 53.23, H 5.15, N 14.32.
Found: C 53.09, H 5.03, N 13.95.

cis-3-Benzyloxycarbonylamino-4-methylcarbamoyloxymethyl-2-azetidinone (**10e-A**)

Methyl isocyanate (114 mg, 2 mmol) and triethylamine (101 mg, 1 mmol) were added to a stirred solution of **8-A** (250 mg, 1 mmol) in CH_2Cl_2 (5 ml), and the mixture was stirred for 12 hours at room temp and concentrated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$ - MeOH - EtOAc (85: 10: 5) to give **10e-A** (72 mg, 23%) as colorless crystals. MP 205~207°C. IR ν_{max}^{Nujol} cm^{-1} 1770, 1700. NMR (DMSO-d_6) δ 2.53 (3H, d, 5), 3.6~4.2 (3H, m), 4.93 (1H, dd, 5, 9), 5.03 (2H, s), 6.92 (1H, m), 7.31 (5H, s), 7.9 (1H, d, 9), 8.27 (1H, br s).

Anal Calcd for $C_{14}H_{17}N_3O_5$: C 54.71, H 5.57, N 13.67.
Found: C 54.74, H 5.54, N 14.01.

cis-3-Benzyloxycarbonylamino-4-mesyloxymethyl-2-azetidinone (**10f-A**)

(a) Mesyl chloride (5.15 g, 45 mmol) was added dropwise to an ice-cooled solution of **7-A** (12.0 g, 30 mmol) in pyridine (90 ml). After being stirred for 1 hour at room temp, the reaction mixture was diluted with water (150 ml), THF (150 ml) and EtOAc (150 ml), and adjusted to pH 2 with 6 N HCl. After separation of the organic layer, the aqueous layer was extracted with a mixture of EtOAc - THF (2: 1). The combined extracts were washed successively with water, aq $NaHCO_3$ and brine, dried, and evaporated to dryness. The solid residue was washed with ether to give *cis*-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-mesyloxymethyl-2-azetidinone (**9f-A**) (13.7 g, 96%) as colorless crystals. MP 140~141°C. IR ν_{max}^{KBr} cm^{-1} 1750. NMR ($CDCl_3$) δ 2.87 (3H, s), 3.8 (6H, s), 3.7~4.4 (3H, m), 4.27 (2H, ABq, 15), 4.9~5.1 (1H, m), 5.08 (2H, s), 6.3~6.6 and 7.0~7.3 (3H, m), 7.27 (5H, s).

Anal Calcd for $C_{22}H_{26}N_2O_8S$: C 55.22, H 5.48, N 5.85.
Found: C 55.16, H 5.40, N 5.61.

(b) According to the general procedure I, the 2,4-dimethoxybenzyl group of **9f-A** was removed to give **10f-A** as colorless crystals. MP 138~139°C. Yield 56%. IR ν_{max}^{KBr} cm^{-1} 1770. NMR (DMSO-d_6) δ 3.13 (3H, s), 3.8~4.4 (3H, m), 4.9~5.2 (1H, m), 5.05 (2H, s), 7.28 (5H, s), 8.42 (1H, br s).

Anal Calcd for $C_{13}H_{16}N_2O_6S$: C 47.56, H 4.91, N 8.53.
Found: C 47.50, H 4.91, N 8.47.

cis-4-Mesyloxymethyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**10f-B**)

Compound **10f-B** and the intermediate, *cis*-1-(2,4-dimethoxybenzyl)-4-mesyloxymethyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**9f-B**), were synthesized by a method similar to that described for the synthesis of **10f-A**.

(a) **9f-B**: Colorless crystals. MP 139~140°C. Yield 94%. IR ν_{max}^{KBr} cm^{-1} 1740. NMR ($CDCl_3$) δ 3.0 (3H, s), 3.6~4.05 (1H, m), 3.81 and 3.84 (each 3H, s), 4.3~4.5 (2H, m), 4.4 (2H, ABq, 15), 4.73 (2H, s), 5.06 (1H, dd, 5, 10), 6.3~6.6 and 7.1~7.3 (4H, m).

Anal Calcd for $C_{17}H_{21}Cl_3N_2O_8S$: C 39.28, H 4.07, N 5.39.
Found: C 39.21, H 4.16, N 5.48.

(b) **10f-B**: Colorless crystals. MP 85~86°C. Yield 64%. IR ν_{max}^{KBr} cm^{-1} 1773. NMR (DMSO-d_6) δ 3.15 (3H, s), 3.97 (1H, m), 4.31 (2H, d, 7), 4.72 (2H, ABq, 12), 5.03 (1H, dd, 5, 10), 8.52 (1H, d, 10).

Anal Calcd for $C_8H_{11}Cl_3N_2O_6S$: C 26.00, H 3.00, N 7.58.
Found: C 26.15, H 3.04, N 7.62.

cis-4-Mesyloxymethyl-3-(2-methylsulfonylethoxycarbonylamino)-2-azetidinone (**10f-C**)

A suspension of **10f-A** (3.28 g, 10 mmol) and 5% Pd-C (3.28 g) in EtOH (100 ml) was stirred for 50 minutes at room temp under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated, and the residue was dissolved in a mixture of CH_2Cl_2 (100 ml) and *N*,*N*-dimethylacetamide (15 ml). After addition of propylene oxide (6.99 ml), a solution of 2-methylsulfonylethyl chloroformate (2.79 g) in CH_2Cl_2 (25 ml) was added dropwise to the ice-cooled solution with stirring, and the mixture was stirred for 2 hours at room temp. After removal of the solvent, the residue was dissolved in a mixture of THF - EtOAc (1: 1) and brine, and the organic layer was separated, dried and concentrated

under reduced pressure. The residue was chromatographed on silica gel with EtOAc - EtOH (9: 1) to give **10f-C** (2.16 g, 63%) as colorless crystals. MP 141~142°C. IR ν_{max}^{KBr} cm^{-1} 1790. NMR (DMSO-d_6) δ 3.02 and 3.18 (each 3H, s), 3.47 (2H, t, 6), 3.8~4.2 (1H, m), 4.32 (2H, m), 4.38 (2H, t, 6), 5.03 (1H, dd, 5, 9), 8.16 (1H, d, 9), 8.63 (1H, br s).

Anal Calcd for $C_9H_{16}N_2O_8S_2$: C 31.39, H 4.68, N 8.14.
Found: C 31.34, H 4.76, N 8.34.

cis-3-Benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-phthalimidomethyl-2-azetidinone (**11-A**)

Diethyl azodicarboxylate (0.47 ml, 3 mmol) was added to a stirred mixture of **7-A** (1.0 g, 2.5 mmol), triphenylphosphine (787 mg, 3 mmol) and phthalimide (441 mg, 3 mmol) in THF (20 ml), and the mixture was stirred for 1 hour at room temp. After evaporation of the solvent, the solid residue was washed with EtOAc to give **11-A** (1.16 g, 88%) as colorless crystals. MP 182~184°C. IR ν_{max}^{KBr} cm^{-1} 1775, 1760. NMR (DMSO-d_6) δ 3.5 and 3.66 (each 3H, s), 3.4~4.15 (3H, m), 4.13 (2H, ABq, 15), 4.9 (1H, dd, 5, 9), 5.03 (2H, s), 6.05~6.4 and 6.75~6.95 (3H, m), 7.37 (5H, s), 7.84 (4H, s), 8.25 (1H, d, 9).

cis-3-Benzyloxycarbonylamino-4-formylaminomethyl-2-azetidinone (**10g-A**)

Hydrazine hydrate (3.10 g, 61.2 mmol) was added to a suspension of **11-A** (3.55 g, 6.72 mmol) in EtOH (200 ml), and the mixture was refluxed for 2.5 hours and cooled to 0~5°C. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with water, dried and evaporated to dryness to give the 4-aminomethyl compound as a solid. A mixture of formic acid (4 ml) and acetic anhydride (4 ml) was stirred for 30 minutes at 60°C and allowed to come to room temp. The reaction mixture was added to the solid (the 4-aminomethyl compound) obained above, and the whole mixture was stirred for 2 hours at room temp. The mixture was diluted with EtOAc, washed successively with water, aq $NaHCO_3$ and brine, dried, and concentrated under reduced pressure to give *cis*-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-formylaminomethyl-2-azetidinone (**9g-A**) as a foam, which was used in the subsequent reaction without further purification. According to the general procedure I, the 2,4-dimethoxybenzyl group of **9g-A** was removed to give **10g-A** (367 mg, 20%) as a foam. IR ν_{max}^{KBr} cm^{-1} 1760. NMR (DMSO-d_6) δ 3.1~3.4 (2H, m), 3.55~3.9 (1H, m), 4.87 (1H, dd, 6, 9), 5.06 (2H, s), 7.36 (5H, s), 7.75~8.3 (4H, m).

cis-4-Acetamidomethyl-3-benzyloxycarbonylamino-2-azetidinone (**10h-A**)

(a) The 4-aminomethyl compound, which was prepared from **11-A** (1.059 g, 2 mmol) by the same method as described above, was dissolved in a mixture of CH_2Cl_2 (10 ml) and *N*,*N*-dimethylacetamide (5 ml), and propylene oxide (1.4 ml) and acetyl chloride (0.28 ml, 4 mmol) were added to the stirred solution under ice-cooling. After being stirred for 1 hour at room temp, the reaction mixture was diluted with CH_2Cl_2 (100 ml) and aq $NaHCO_3$ (50 ml). The organic layer was separated, washed successively with water, dil HCl and brine, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$ - acetonitrile (3: 2) to give *cis*-4-acetamidomethyl-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-2-azetidinone (**9h-A**) (651 mg, 74%) as colorless crystals. MP 195~196°C. IR ν_{max}^{KBr} cm^{-1} 1760. NMR (DMSO-d_6) δ 1.76 (3H, s), 3.1~3.4 (2H, m), 3.45~3.7 (1H, m), 3.76 and 3.77 (each 3H, s), 4.22 (2H, ABq, 15), 4.82 (1H, dd, 5, 9), 5.06 (2H, s), 6.4~6.6 and 7.0~7.2 (3H, m), 7.36 (5H, s), 7.6~7.8 (1H, m), 8.04 (1H, d, 9).

Anal Calcd for $C_{25}H_{27}N_3O_6$: C 62.57, H 6.16, N 9.52.
Found: C 62.20, H 6.08, N 9.41.

(b) According to the general procedure I, the 2,4-dimethoxybenzyl group of **9h-A** was removed to give **10h-A** as colorless crystals. MP 226~228°C. Yield 51%. IR ν_{max}^{KBr} cm^{-1} 1765, 1750. NMR (DMSO-d_6) δ 1.79 (3H, s), 3.05~3.25 (2H, m), 3.55~3.85 (1H, m), 4.86 (1H, dd, 5, 9), 5.06 (2H, s), 7.37 (5H, s), 7.6~7.85 (1H, m), 8.04 (1H, d, 9), 8.12 (1H, br s).

cis-4-Benzamidomethyl-3-benzyloxycarbonylamino-2-azetidinone (**10i-A**)

(a) Using benzoyl chloride in place of acetyl chloride in the above reaction, *cis*-4-benzamidomethyl-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-2-azetidinone (**9i-A**) was obtained as colorless crystals. MP 112~115°C. Yield 77%. IR ν_{max}^{KBr} cm^{-1} 1755. NMR (DMSO-d_6) δ 3.35~

3.55 (2H, m), 3.65 (3H, s), 3.71 (3H, s), 3.7~3.9 (1H, m), 4.28 (2H, ABq, 15), 4.89 (1H, dd, 5, 9), 6.2~6.4 and 6.95~7.05 (3H, m), 7.3 (5H, s), 7.4~7.85 (5H, m), 8.15 (1H, d, 9), 8.2~8.4 (1H, m).

(b) According to the general procedure I, the 2,4-dimethoxybenzyl group of **9i-A** was removed to give **10i-A** as colorless crystals. MP 209~211°C. Yield 36%. IR ν_{max}^{KBr} cm^{-1} 1765. NMR (DMSO-d_6) δ 3.3~3.5 (2H, m), 3.65~4.05 (1H, m), 4.92 (1H, dd, 5, 9), 5.06 (2H, s), 7.36 (5H, s), 7.4~8.0 (5H, m), 8.15 (1H, d, 9), 8.23 (1H, br s), 8.2~8.5 (1H, m).

cis-3-Benzyloxycarbonylamino-4-carbamoylaminomethyl-2-azetidinone (**10j-A**)

(a) To a suspension of the 4-aminomethyl compound (3.2 g, 8.01 mmol), which was prepared by a method similar to that described for the synthesis of **9g-A**, in water (150 ml) was added dropwise 10% HCl to give a clear solution (pH 2). Potassium isocyanate (3.2 g, 39.4 mmol) was added to the solution, and the mixture was stirred for 20 minutes at 70~80°C, and cooled to 0~5°C. The resulting crystals were collected by filtration and washed with water and ether to give *cis*-3-benzyloxycarbonylamino-4-carbamoylaminomethyl-1-(2,4-dimethoxybenzyl)-2-azetidinone (**9j-A**) (3.3 g, 93%) as colorless crystals. MP 202~204°C. IR ν_{max}^{KBr} cm^{-1} 1730. NMR (DMSO-d_6) δ 3.0~3.4 (2H, m), 3.4~3.7 (1H, m), 3.77 (3H, s), 3.8 (3H, s), 4.23 (2H, ABq, 15), 4.82 (1H, dd, 6, 9), 5.07 (2H, s), 5.47 (2H, br s), 5.84 (1H, t, 6), 6.4~7.2 (3H, m), 7.39 (5H, s), 8.03 (1H, d, 9).

(b) According to the general procedure I, the 2,4-dimethoxybenzyl group of **9j-A** was removed to give **10j-A** as colorless crystals. MP 218~220°C. Yield 47%. IR ν_{max}^{KBr} cm^{-1} 1740. NMR (DMSO-d_6) δ 3.05~3.3 (2H, m), 3.55~3.8 (1H, m), 4.87 (1H, dd, 6, 9), 5.09 (2H, s), 5.45 (2H, s), 5.87 (1H, t, 6), 7.4 (5H, s), 8.01 (1H, d, 9), 8.16 (1H, s).

Anal Calcd for $C_{13}H_{16}N_4O_4$: C 53.42, H 5.52, N 19.17.
Found: C 53.11, H 5.37, N 19.00.

cis-3-Benzyloxycarbonylamino-4-chloromethyl-2-azetidinone (**10k-A**)

A solution of **10f-A** (657 mg, 2 mmol) in DMF (2.6 ml) was added to a solution of lithium chloride (861 mg, 20.3 mmol) in DMF (7.8 ml). The mixture was stirred for 3 hours at 73°C under an argon atmosphere, allowed to come to room temp, poured into brine (60 ml), and extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with EtOAc - hexane (2: 1) to give **10k-A** (437 mg, 81%) as colorless crystals. MP 147~149°C. IR ν_{max}^{KBr} cm^{-1} 1780. NMR (DMSO-d_6) δ 3.55~4.15 (3H, m), 5.03 (1H, dd, 5, 10), 5.1 (2H, s), 7.35 (5H, s), 8.08 (1H, d, 10), 8.53 (1H, br s).

Anal Calcd for $C_{12}H_{13}ClN_2O_3$: C 53.64, H 4.88, N 10.43.
Found: C 53.49, H 4.81, N 10.35.

cis-4-Iodomethyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**10m-B**)

A mixture of **10f-B** (3.70 g, 10 mmol) and sodium iodide (8.85 g, 59 mmol) in methyl ethyl ketone (130 ml) was refluxed for 3 hours under a nitrogen atmosphere, and concentrated under reduced pressure. The concentrate was dissolved in a mixture of EtOAc and water, and the organic layer was separated, washed with water, dried and evaporated to dryness. The solid residue was washed with ether to give **10m-B** (3.56 g, 89%) as colorless crystals. MP 152~154°C. IR ν_{max}^{KBr} cm^{-1} 1765. NMR ($CDCl_3$+DMSO-d_6) δ 3.35 (2H, d, 7), 4.18 (1H, dt, 5, 7), 4.85 (2H, ABq, 12), 5.12 (1H, dd, 5, 10), 8.07 (1H, br s), 8.39 (1H, d, 10).

Anal Calcd for $C_7H_8Cl_3IN_2O_3$: C 20.95, H 2.01, N 6.98.
Found: C 21.19, H 2.06, N 7.21.

cis-4-Iodomethyl-3-(2-methylsulfonylethoxycarbonylamino)-2-azetidinone (**10m-C**)

Compound **10m-C** was prepared from **10f-C** by a method similar to that described above. Colorless crystals. MP 186~190°C. Yield 85%. IR ν_{max}^{KBr} cm^{-1} 1780. NMR (DMSO-d_6) δ 3.01 (3H, s), 3.43 (2H, t, 6), 3.8~4.2 (1H, m), 4.35 (2H, t, 6), 4.89 (1H, dd, 5, 10), 8.13 (1H, d, 10), 8.54 (1H, br s).

Anal Calcd for $C_8H_{13}IN_2O_5S$: C 25.54, H 3.48, N 7.45.
Found: C 25.64, H 3.53, N 7.34.

cis-4-Methylthiomethyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**10n-B**)

n-Butyllithium (1.37 ml of 1.6 N hexane solution, 2.19 mmol) was added dropwise to a stirred, cool-

ed (0°C) solution of methyl mercaptan (1.49 ml of 4 N THF solution, 5.96 mmol) in THF (10 ml) under a nitrogen atmosphere. After being stirred for 10 minutes under ice-cooling, the mixture was cooled to −45°C, and a solution of **10m-B** (800 mg, 1.99 mmol) in THF (5 ml) was added dropwise. The reaction mixture was stirred for 4 hours at −30~−20°C, and EtOAc and satd aq ammonium chloride were added. The organic layer was separated, washed with brine, dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with EtOAc - hexane (1: 1) to give **10n-B** (500 mg, 78%) as crystals. MP 114~115°C. IR ν_{max}^{KBr} cm^{-1} 1780. NMR (DMSO-d_6) δ 2.06 (3H, s), 2.61 (2H, d, 7), 3.7~4.0 (1H, m), 4.82 (2H, ABq, 12), 4.8~5.05 (1H, m), 8.43 (1H, br s), 8.48 (1H, d, 9).

cis-4-(1-Methyl-1*H*-tetrazol-5-yl)thiomethyl-3-(2,2,2-trichloroethoxycarbonylamino)-2-azetidinone (**10p-B**)

Sodium hydride (65 mg, 2.71 mmol) was added to a stirred, cooled (0°C) solution of 5-mercapto-1-methyl-1*H*-tetrazole (314 mg, 2.71 mmol) in DMF (2 ml), and the mixture was stirred for 10 minutes under ice-cooling and 10 minutes at room temp. To the mixture was added a solution of **10m-B** (724 mg, 1.8 mmol) in DMF (3 ml). After being stirred for 2 days at room temp, the reaction mixture was diluted with EtOAc, washed successively with water and brine, dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with EtOAc - hexane (4: 1) to give **10p-B** (610 mg, 87%) as crystals. MP 67~69°C. IR ν_{max}^{KBr} cm^{-1} 1740. NMR ($CDCl_3$) δ 3.3~3.85 (2H, m), 3.92 (3H, s), 4.05~4.45 (1H, m), 4.78 (2H, ABq, 12), 5.19 (1H, dd, 5, 9), 6.86 (1H, d, 9), 7.42 (1H, br s).

cis-4-Azidomethyl-3-(2-methylsulfonylethoxycarbonylamino)-2-azetidinone (**10q-C**)

A mixture of **10m-C** (1.504 g, 4 mmol) and sodium azide (390 mg, 6 mmol) in DMF (20 ml) was stirred for 66 hours at room temp and 24 hours at 40°C. The mixture was concentrated under reduced pressure, and the concentrate was chromatographed on silica gel with EtOAc - EtOH (9: 1) to give **10q-C** (0.8 g, 69%) as colorless crystals. MP 158~160°C. IR ν_{max}^{KBr} cm^{-1} 2110, 1780. NMR (DMSO-d_6) δ 3.0 (3H, s), 3.3~3.55 (4H, m), 3.55~3.95 (1H, m), 4.35 (2H, t, 6), 4.93 (1H, dd, 5, 10), 8.14 (1H, d, 10), 8.44 (1H, br s).

Anal Calcd for $C_8H_{13}N_5O_5S$: C 32.99, H 4.50, N 24.06.
Found: C 33.15, H 4.74, N 24.22.

cis-3-Benzyloxycarbonylamino-4-cyanomethyl-2-azetidinone (**10r-A**)

(a) *cis*-3-Benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-iodomethyl-2-azetidinone (**9m-A**) was prepared from **9f-A** by a method similar to that described for the synthesis of **10m-B**. Colorless crystals. MP 165~166°C. Yield 80%. IR ν_{max}^{KBr} cm^{-1} 1765. NMR ($CDCl_3$) δ 2.8~3.4 (3H, m), 3.6~3.9 (6H, m), 4.34 (2H, ABq, 15), 5.0 (1H, dd, 5, 9), 5.1 (2H, s), 5.66 (1H, d, 9), 6.3~6.5 and 7.1~7.3 (3H, m), 7.33 (5H, s).

Anal Calcd for $C_{21}H_{23}IN_2O_5$: C 20.95, H 2.01, N 6.98.
Found: C 21.19, H 2.06, N 7.21.

(b) A mixture of **9m-A** (5.1 g, 10 mmol), potassium cyanide (2.6 g, 40 mmol) and 18-crown-6 (50 mg) in DMSO (8 ml) was stirred for 2 days at room temp and 3 hours at 50°C. The mixture was diluted with EtOAc, washed successively with water and brine, dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with EtOAc - hexane (2: 1) to give *cis*-3-benzyloxycarbonylamino-4-cyanomethyl-1-(2,4-dimethoxybenzyl)-2-azetidinone (**9r-A**) (1.64 g, 40%) as a foam. IR ν_{max}^{KBr} cm^{-1} 2240, 1770. NMR ($CDCl_3$) δ 2.48 (2H, d, 6), 3.78 (3H, s), 3.8 (3H, s), 4.32 (2H, ABq, 15), 4.82 (1H, dd, 5, 8), 5.1 (2H, s), 5.96 (1H, d, 8), 6.25~6.55 and 7.05~7.3 (3H, m), 7.31 (5H, s).

(c) According to the general procedure I, the 2,4-dimethoxybenzyl group of **9r-A** was removed to give **10r-A** as crystals. MP 113~115°C. Yield 44%. IR ν_{max}^{KBr} cm^{-1} 2250, 1760. NMR ($CDCl_3$+DMSO-d_6) δ 2.55~2.75 (2H, m), 4.03 (1H, q, 6), 5.11 (1H, dd, 6, 9), 5.14 (2H, s), 7.35 (5H, s), 7.56 (1H, d, 9), 7.85~8.1 (1H, br).

3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(substituted methyl)-2-azetidinones (**14** and Its *trans* Isomer)

Method A: Procedure Starting from **10-A**: A suspension of **10a-A** (1.46 g, 5 mmol) and 5% Pd-C

(500 mg) in EtOH (50 ml) was stirred for 30 minutes at room temp under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of THF (15 ml) and water (15 ml). To the ice-cooled solution were added $NaHCO_3$ (1.05 g, 12.5 mmol) and 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetyl chloride hydrochloride (CATAM-Cl·HCl)[5] (2.0 g, 6 mmol) with stirring. After being stirred for 1 hour under ice-cooling, the resulting precipitate was collected by filtration and washed successively with aq $NaHCO_3$, water and ether to give **14a** (1.86 g, 89%) as colorless crystals.

Compounds **14b,d,f,h,i,k** and *trans* isomer of **14a** were similarly synthesized and the results are shown in Table 4.

Method B: Procedure Starting from **10-B**: Zinc (5.5 g) and 1 M KH_2PO_4 (11 ml) were added to a stirred solution of **10n-B** (643 mg, 2 mmol) in THF (55 ml), and the mixture was stirred for 2 hours at room temp. The zinc was removed by filtration and the filtrate was concentrated under reduced pressure. The concentrate was dissolved in a mixture of THF (20 ml) and water (20 ml). To the stirred, cooled (0°C) solution were added $NaHCO_3$ (588 mg, 7 mmol) and CATAM-Cl·HCl (998 mg, 3 mmol), and the mixture was stirred for 30 minutes under ice-cooling, and diluted with EtOAc. The organic layer was separated, washed with brine, dried and evaporated to dryness. The solid residue was washed with EtOAc - ether (1 : 2) to give **14n** (591 mg, 73%) as colorless crystals.

Compounds **14c,p** were similarly synthesized and the results are shown in Table 4.

Method C: Procedure Starting from **10-C**: Sodium hydroxide (11.4 ml of 0.5 N EtOH solution, 5.7 mmol) was added to an ice-cooled solution of **10q-C** (757 mg, 2.6 mmol) in a mixture of EtOH (60 ml) and DMF (6 ml), and the mixture was stirred for 40 minutes under ice-cooling. After addition of 1 N HCl (5.7 ml), the mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of water (15 ml) and THF (15 ml). To the ice-cooled solution were added $NaHCO_3$ (874 mg, 10.4 mmol) and CATAM-Cl·HCl (1.297 g, 3.9 mmol), and the mixture was stirred for 40 minutes under ice-cooling. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with water and brine, dried and evaporated to dryness. The solid residue was washed with EtOAc and ether to give **14q** (679 mg, 65%) as colorless crystals. The physical data of **14q** are shown in Table 4.

Sodium 3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonates (**15** and Its *trans* Isomer)

General Procedure II: Sulfonation at the 1-Position: To a stirred solution of **14** (1 mmol) in DMF (5~10 ml) was added SO_3·Pyridine (318 mg, 2 mmol), and the mixture was stirred for 48 hours at room temp. After further addition of SO_3·Pyridine (159 mg, 1 mmol), the mixture was stirred for 24 hours. Ether (50~100 ml) was added, and the resulting precipitate was collected by decantation (or filtration) and washed with ether. The precipitate was dissolved (or suspended) in water and treated with Dowex 50W (Na^+) for 1 hour at room temp. After removal of the resin by filtration, the filtrate was concentrated under reduced pressure. The concentrate was chromatographed on Amberlite XAD-2. Gradient elution with aq EtOH (0~20%) and lyophilization of the eluate gave **15** as a powder. The results are shown in Table 5.

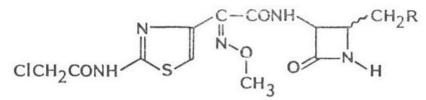
Sodium 3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonates (**16** and Its *trans* Isomer)

General Procedure III: Removal of the Chloroacetyl Group: Sodium *N*-methyldithiocarbamate (129 mg, 1 mmol) was added to a stirred, cooled solution of **15** (1 mmol) in water (20 ml), and the mixture was stirred for 40 minutes at room temp. After further addition of sodium *N*-methyldithiocarbamate (65 mg, 0.5 mmol), the reaction mixture was stirred for 40 minutes, washed with ether and concentrated under reduced pressure. The concentrate was chromatographed on Amberlite XAD-2. Gradient elution with aq EtOH (0~10%) and lyophilization of the eluate gave **16** as a powder. The results are shown in Table 6.

3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]-acetamido]-4-(substituted methyl)-2-azetidinones (**18** and Its *trans* Isomer)

Using 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]-

Table 4. 3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(substituted methyl)-2-azetidinones (**14** and the *trans* isomer of **14a**).



14: 3,4-*cis*

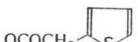
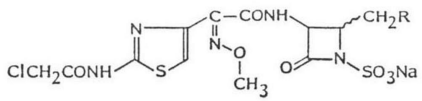
Compound No.	R	Yield (%)	MP (°C)	IR (KBr) (cm^{-1})	NMR, δ (DMSO-d_6)
14a	$OCOCH_3$	89	180~190	1750	2.03 (3H, s), 3.8~4.2 (3H, m), 3.89 (3H, s), 4.35 (2H, s), 5.26 (1H, dd, 4, 9), 7.43 (1H, s), 8.52 (1H, br s), 9.33 (1H, d, 9), 12.83 (1H, br s)
14b	OCOPh	80	210~220	1760	3.83 (3H, s), 4.0~4.5 (3H, m), 4.35 (2H, s), 5.33 (1H, dd, 5, 9), 7.45 (1H, s), 7.5~8.15 (5H, m), 8.67 (1H, br s), 9.48 (1H, d, 9)
14c		58	201~204	1760	3.65~4.6 (3H, m), 3.86 (3H, s), 3.9 (2H, s), 4.32 (2H, s), 5.1~5.4 (1H, m), 6.85~7.6 (3H, m), 7.48 (1H, s), 8.57 (1H, br s), 9.38 (1H, d, 9)
14d	$OCONH_2$	75	185~190	1755	3.88 (3H, s), 3.9~4.45 (3H, m), 5.27 (1H, dd, 5, 9), 6.48 (2H, br s), 7.42 (1H, s), 8.44 (1H, brs), 9.18 (1H, d, 9), 12.75 (1H, br s)
14f	OSO_2CH_3	89	186~189	1770	3.14 (3H, s), 3.92 (3H, s), 4.0~4.3 (3H, m), 4.32 (2H, s), 5.32 (1H, dd, 5, 9), 7.46 (1H, s), 8.7 (1H, br s), 9.34 (1H, d, 9), 12.87 (1H, br s)
14h	$NHCOCH_3$	85	160~165	1760	1.73 (3H, s), 3.1~3.4 (2H, m), 3.6~4.0 (1H, m), 3.9 (3H, s), 4.33 (2H, s), 5.16 (1H, dd, 5, 9), 7.46 (1H, s), 7.5~7.8 (1H, m), 8.2 (1H, br s), 9.37 (1H, d, 9), 12.8 (1H, br s)
14i	NHCOPh	76	145~150	1775	3.3~3.6 (2H, m), 3.7~4.1 (1H, m), 3.87 (3H, s), 4.37 (2H, s), 5.22 (1H, dd, 5, 9), 7.5 (1H, s), 7.3~8.0 (5H, m), 8.1~8.4 (1H, m), 8.36 (1H, br s), 9.52 (1H, d, 9), 12.83 (1H, br s)
14k	Cl	66	212~217	1775	3.55~3.75 (2H, m), 3.8~4.15 (1H, m), 3.9 (3H, s), 4.34 (2H, s), 5.28 (1H, dd, 5, 9), 7.46 (1H, s), 8.72 (1H, br s), 9.33 (1H, d, 9), 12.57 (1H, br s)
14n	SCH_3	73	200~205	1750	2.09 (3H, s), 2.5~2.7 (2H, m), 3.75~4.05 (1H, m), 3.89 (3H, s), 4.34 (2H, s), 5.23 (1H, dd, 5, 9), 7.46 (1H, s), 8.54 (1H, br s), 9.29 (1H, d, 9), 12.93 (1H, br s)
14p		62	195~198	1760	3.42 (2H, d, 7.5), 3.92 (6H, s), 3.68~4.21 (1H, m), 4.33 (2H, s), 5.15~5.4 (1H, m), 7.47 (1H, s), 8.61 (1H, br s), 9.43 (1H, d, 9)
14q	N_3	65	223~230	2110 1760	3.4~3.6 (2H, m), 3.7~4.1 (1H, m), 3.9 (3H, s), 4.34 (2H, s), 5.22 (1H, dd, 5, 9), 7.37 (1H, s), 8.49 (1H, br s), 9.2 (1H, d, 9)
trans isomer of **14a**		79	177~190	1760	2.08 (3H, s), 3.65~3.9 (1H, m), 3.91 (3H, s), 4.05~5.0 (2H, m), 4.35 (2H, s), 4.70 (1H, dd, 3, 9), 7.4 (1H, s), 8.37 (1H, br s), 9.29 (1H, d, 9)

Table 5. Sodium 3-[2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonates (**15** and the *trans* isomer of **15a**).



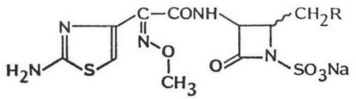
15: 3,4-*cis*

Compound No.	R	Yield (%)	IR (KBr) (cm^{-1})	NMR, δ (DMSO-d_6)	Analysis[a]
15a	$OCOCH_3$	52	1760 1045	1.95 (3H, s), 3.83 (3H, s), 3.8~4.4 (3H, m), 4.3 (2H, s), 5.15 (1H, dd, 4.5, 8), 7.3 (1H, s), 9.3 (1H, d, 8)	$C_{14}H_{15}ClN_5NaO_9S_2 \cdot 2H_2O$
15b	OCOPh	60	1770 1050	3.69 (3H, s), 4.2~4.8 (3H, m), 4.35 (2H, s), 5.32 (1H, dd, 6, 9), 7.35 (1H, s), 7.4~8.2 (5H, m), 9.5 (1H, d, 9), 12.89 (1H, br s)	$C_{19}H_{17}ClN_5NaO_9S_2 \cdot 2H_2O$
15c		37	1765 1050	3.72 (2H, br s), 3.95~4.55 (1H, m), 4.3 (2H, s), 5.25 (1H, dd, 6, 9), 6.8~7.5 (3H, m), 7.41 (1H, s), 9.63 (1H, d, 9)	[b]
15d	$OCONH_2$	41	1770 1060	3.87 (3H, s), 3.95~4.3 (3H, m), 4.33 (2H, s), 5.27 (1H, dd, 5, 9), 6.38 (2H, br s), 7.39 (1H, s), 9.16 (1H, d, 9)	$C_{13}H_{14}ClN_6NaO_9S_2 \cdot 2.5H_2O$
15f	OSO_2CH_3	67	1770 1050	3.1 (3H, s), 3.9 (3H, s), 4.15~4.6 (3H, m), 4.35 (2H, s), 5.33 (1H, dd, 5, 9), 7.41 (1H, s), 9.42 (1H, d, 9), 12.91 (1H, br s)	$C_{13}H_{15}ClN_5NaO_{10}S_2 \cdot 2H_2O$
15h	$NHCOCH_3$	67	1770 1050	1.84 (3H, s), 3.1~3.4 (2H, m), 3.9~4.2 (1H, m), 3.84 (3H, s), 4.4 (2H, s), 5.19 (1H, dd, 5, 9), 7.45~7.65 (1H, m), 7.51 (1H, s), 9.4 (1H, d, 9), 12.65 (1H, br s)	$C_{14}H_{16}ClN_6NaO_8S_2 \cdot 2.5H_2O$
15i	NHCOPh	65	1770 1050	3.3~3.6 (2H, m), 3.92 (3H, s), 4.0~4.3 (1H, m), 4.45 (2H, s), 5.28 (1H, dd, 5, 9), 7.54 (1H, s), 7.4~7.9 (5H, m), 8.4~8.6 (1H, m), 9.49 (1H, d, 9)	$C_{19}H_{15}ClN_6NaO_8S_2 \cdot 2H_2O$
15k	Cl	79	1770 1055	3.65~4.2 (3H, m), 3.89 (3H, s), 4.34 (2H, s), 5.28 (1H, dd, 6, 9), 7.38 (1H, s), 9.37 (1H, d, 9), 12.90 (1H, br s)	$C_{12}H_{12}Cl_2N_5NaO_7S_2 \cdot 1.7H_2O$
15n	SCH_3	75	1760 1050	2.04 (3H, s), 2.7~3.15 (2H, m), 3.87 (3H, s), 3.8~4.2 (1H, m), 4.35 (2H, s), 5.22 (1H, dd, 5, 9), 7.38 (1H, s), 9.32 (1H, d, 9)	$C_{13}H_{15}ClN_5NaO_7S_3 \cdot 2H_2O$
15p		32	1765 1050	3.91 (3H, s), 3.94 (3H, s), 4.05~4.45 (1H, m), 4.34 (2H, s), 5.29 (1H, dd, 6, 9), 7.48 (1H, s), 9.46 (1H, d, 9)	[b]
15q	N_3	64	2110 1765	3.65~3.8 (2H, m), 3.92 (3H, s), 3.8~4.15 (1H, m), 4.25 (2H, s), 5.25 (1H, dd, 5, 9), 7.44 (1H, s), 9.33 (1H, d, 9)	$C_{12}H_{12}ClN_8NaO_7S_2 \cdot 2H_2O$
trans isomer of **15a**		57	1765 1040	2.04 (3H, s), 3.9 (3H, s), 4.3~4.5 (1H, m), 4.35 (2H, s), 4.77 (1H, dd, 3, 8), 7.39 (1H, s), 9.45 (1H, d, 8)	$C_{14}H_{15}ClN_5NaO_9S_2 \cdot H_2O$

[a] All the compounds given the formula were analyzed for C, H and N; analytical results obtained for these elements were within $\pm 0.4\%$ of calculated values.

[b] Not analyzed.

Table 6. Sodium 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonates (**16** and **17**).



16: 3,4-*cis* **17**: 3,4-*trans*

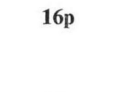
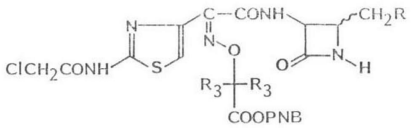
Compound No.	R	Yield (%)	IR (KBr) (cm^{-1})	NMR, δ (DMSO-d_6)	Formula	Analysis Calcd (Found) (%)		
						C	H	N
16a	$OCOCH_3$	74	1760 1050	1.94 (3H, s), 3.78 (3H, s), 3.9~4.4 (3H, m), 5.15 (1H, dd, 4.5, 8), 6.66 (1H, s), 7.1 (2H, br s), 9.2 (1H, d, 8)	$C_{12}H_{14}N_5NaO_8S_2 \cdot 2H_2O$	30.06 (29.81	3.78 4.10	14.61 14.24)
16b	OCOPh	86	1770 1050	3.67 (3H, s), 4.2~4.8 (3H, m), 5.28 (1H, dd, 6, 9), 6.62 (1H, s), 7.12 (2H, br s), 7.4~8.2 (5H, m), 9.38 (1H, d, 9)	$C_{17}H_{16}N_5NaO_8S_2 \cdot 1.5H_2O$	38.34 (38.23	3.60 3.53	13.15 13.15)
16c		77	1770 1050	3.75 (3H, s), 3.82 (2H, ABq, 18), 4.0~4.65 (3H, m), 5.2 (1H, dd, 6, 9), 6.71 (1H, s), 6.8~7.5 (3H, m), 7.14 (2H, br s), 9.22 (1H, d, 9)	$C_{16}H_{16}N_5NaO_8S_3 \cdot 2H_2O$	34.22 (34.42	3.59 3.23	12.47 12.30)
16d	$OCONH_2$	70	1780 1055	3.83 (3H, s), 3.9~4.3 (3H, m), 5.24 (1H, dd, 5, 9), 6.36 (2H, br s), 6.70 (1H, s), 7.1 (2H, br s), 9.10 (1H, d, 9)	$C_{11}H_{13}N_6NaO_8S_2 \cdot 2H_2O$	26.50 (26.51	3.84 3.49	16.80 16.42)
16f	OSO_2CH_3	73	1770 1055	3.1 (3H, s), 3.86 (3H, s), 4.15~4.7 (3H, m), 5.28 (1H, dd, 5, 9), 6.74 (1H, s), 9.3 (1H, d, 9)	$C_{11}H_{14}N_5NaO_9S_2 \cdot 2H_2O$	25.63 (25.64	3.52 3.41	13.59 13.56)
16h	$NHCOCH_3$	77	1765 1050	1.77 (3H, s), 3.2~3.6 (2H, m), 3.86 (3H, s), 3.8~4.1 (1H, m), 5.12 (1H, dd, 5, 9), 6.81 (1H, s), 7.15 (2H, br s), 7.4~7.7 (1H, m), 9.33 (1H, d, 9)	$C_{12}H_{15}N_6NaO_7S_2 \cdot 2H_2O$	30.13 (30.43	4.00 3.63	17.56 17.34)
16i	NHCOPh	86	1765 1050	3.3~3.7 (2H, m), 3.86 (3H, s), 3.9~4.3 (1H, m), 5.23 (1H, dd, 5, 9), 6.82 (1H, s), 7.17 (2H, br s), 7.4~7.7 (5H, m), 8.3~8.5 (1H, m), 9.36 (1H, d, 9)	$C_{17}H_{17}N_6NaO_7S_2 \cdot 2H_2O$	37.78 (37.51	3.92 3.73	15.55 15.67)
16k	Cl	75	1770 1050	3.65~4.25 (3H, m), 3.85 (3H, s), 5.25 (1H, dd, 5, 9), 6.71 (1H, s), 7.14 (2H, br s), 9.24 (1H, d, 9)	$C_{10}H_{11}ClN_5NaO_6S_2 \cdot 2H_2O$	26.35 (26.31	3.32 3.18	15.36 15.33)
16n	SCH_3	96	1760 1050	2.03 (3H, s), 2.7~3.1 (2H, m), 3.81 (3H, s), 3.9~4.2 (1H, m), 5.18 (1H, dd, 6, 9), 6.74 (1H, s), 7.14 (2H, brs), 9.15 (1H, d, 9)	$C_{11}H_{14}N_5NaO_6S_3 \cdot 2H_2O$	28.26 (28.45	3.88 3.63	14.98 14.93)
16p		45	1770 1050	3.5 (2H, d, 6), 3.88 (3H, s), 3.92 (3H, s), 4.0~4.35 (1H, m), 5.22 (1H, dd, 6, 9), 6.75 (1H, s), 7.13 (2H, brs), 9.31 (1H, d, 9)	$C_{12}H_{14}N_6NaO_6S_3 \cdot 2.7H_2O$	26.29 (26.46	3.56 3.59	23.00 22.70)
16q	N_3	92	2110 1765 1050	3.6~3.85 (2H, m), 3.87 (3H, s), 3.85~4.15 (1H, m), 5.2 (1H, dd, 5, 9), 6.75 (1H, s), 7.16 (2H, br s), 9.22 (1H, d, 9)	$C_{10}H_{11}N_8NaO_6S_2 \cdot 2H_2O$	25.98 (26.11	3.27 3.41	24.23 24.34)
17	$OCOCH_3$	75	1765 1050	2.01 (3H, s), 3.7~4.0 (1H, m), 3.83 (3H, s), 4.1~4.55 (2H, m), 4.76 (1H, dd, 3, 8), 6.7 (1H, s), 7.16 (2H, br s), 9.3 (1H, d, 8)	$C_{12}H_{14}N_5NaO_8S_2 \cdot 1.5H_2O$	30.64 (30.66	3.64 3.65	14.89 14.94)

Table 7. 3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-(substituted oxyimino)acetamido]-4-(substituted methyl)-2-azetidinones (**18**, **19** and their *trans* isomers).

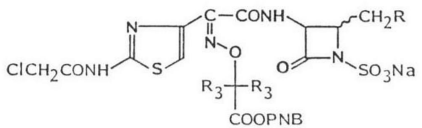


18 and **19**: 3,4-*cis*

Compound No.	R_3	R	Yield (%)	MP (°C)	IR (KBr) (cm^{-1})	NMR, δ (DMSO-d_6)[a]
18a	CH_3	$OCOCH_3$	27	120~123	1740[b]	1.5~1.75 (6H), 2.1 (3H, s), 4.0~4.35 (5H, m), 5.1~5.4 (3H, m), 7.26 (1H, s)
18d	CH_3	$OCONH_2$	90	120~125	1745	1.51 (3H, s), 1.53 (3H, s), 3.8~4.4 (3H, m), 4.37 (2H, s), 5.2~5.45 (3H, m), 6.53 (2H, br s), 7.38 (1H, s), 8.5 (1H, br s), 9.23 (1H, d, 9)
18h	CH_3	$NHCOCH_3$	92	[c]	1780~1730	1.49 (3H, s), 1.51 (3H, s), 1.81 (3H, s), 3.2~4.0 (3H, m), 4.35 (2H, s), 5.2 (1H, dd, 6, 9), 5.32 (2H, s), 7.39 (1H, s), 9.41 (1H, d, 9)
18j	CH_3	$NHCONH_2$	77	145~150	1740	1.55 (6H, s), 3.0~3.5 (2H, m), 3.6~3.9 (1H, m), 4.35 (2H, s), 5.1~5.3 (1H, m), 5.35 (2H, s), 5.78 (2H, br s), 6.1~6.3 (1H, m), 7.39 (1H, s), 8.3 (1H, br s), 9.36 (1H, d, 9)
18r	CH_3	CN	100	[c]	2250 1740	1.55 (6H, s), 2.74 (2H, d, 6), 4.1 (1H, q, 6), 4.33 (2H, s), 5.15~5.5 (1H, m), 5.35 (2H, s), 7.42 (1H, s), 8.76 (1H, br s), 9.38 (1H, d, 9)
trans isomer of **18d**			60	118~120	1740	1.5 (6H, s), 3.6~3.85 (1H, m), 4.0~4.25 (2H, m), 4.32 (2H, s), 4.75 (1H, dd, 3, 9), 5.3 (2H, s), 6.51 (2H, s), 7.35 (1H, s), 8.28 (1H, s), 9.13 (1H, d, 9)
19d	H	$OCONH_2$	81	200~205 (dec)	1760	3.8~4.3 (3H, m), 4.36 (2H, s), 4.86 (2H, s), 5.2~5.45 (1H, m), 5.35 (2H, s), 6.53 (2H, br s), 7.47 (1H, s), 8.49 (1H, br s), 9.3 (1H, d, 9)
19e	H	$OCONHCH_3$	84	225~230 (dec)	1760	2.55 (3H, d, 5), 3.75~4.25 (3H, m), 4.34 (2H, s), 4.83 (2H, s), 5.33 (2H, s), 6.96 (1H, m), 7.43 (1H, s), 8.47 (1H, br s), 9.27 (1H, d, 9)
19g	H	NHCHO	80	[c]	1755	3.7~3.95 (1H, m), 4.35 (2H, s), 4.88 (2H, s), 5.22 (1H, dd, 6, 9), 5.35 (2H, s), 7.5 (1H, s), 8.38 (1H, br s), 9.47 (1H, d, 9)
trans isomer of **19d**			85	210~215 (dec)	1790 1760	3.7~3.85 (1H, m), 4.0~4.2 (2H, m), 4.35 (2H, s), 4.73 (1H, dd, 3, 8), 4.85 (2H, s), 5.35 (2H, s), 6.55 (2H, br s), 7.42 (1H, s), 8.31 (1H, br s), 9.3 (1H, d, 8)

[a] Absorptions of aromatic protons of *p*-nitrobenzyl groups (δ 7.5~8.3) are not given in this table.
[b] Measured in a Nujol mull.
[c] Amorphous.

Table 8. Sodium 3-[2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-(substituted oxyimino)acetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonates (**20**, **21** and their *trans* isomers).



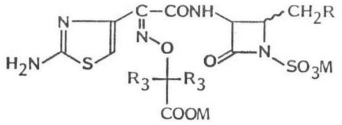
20 and **21**: 3,4-*cis*

Compound No.	R_3	R	Yield (%)	IR (KBr) (cm^{-1})	NMR, δ (DMSO-d_6)[a]	Analysis[b]
20a	CH_3	$OCOCH_3$	74	1760 1050	1.49 (3H, s), 1.50 (3H, s), 1.95 (3H, s), 4.05~4.4 (5H, m), 5.2~5.4 (3H, m), 7.33 (1H, s)	$C_{24}H_{24}ClN_6NaO_{13}S_2 \cdot H_2O$
20d	CH_3	$OCONH_2$	42	1740 1055	1.72 (6H, s), 4.2~4.7 (3H, m), 4.54 (2H, s), 5.5~5.6 (1H, m), 5.53 (2H, s), 7.57 (1H, s)	$C_{23}H_{23}ClN_7NaO_{13}S_2 \cdot 2H_2O$
20h	CH_3	$NHCOCH_3$	73	1785~1730 1050	1.52 (6H, s), 1.81 (3H, s), 3.5~4.2 (3H, m), 4.35 (2H, s), 5.2 (1H, dd, 6, 9), 5.31 (2H, s), 7.37 (1H, s), 9.4 (1H, d, 9), 12.8 (1H, br s)	$C_{24}H_{25}ClN_7NaO_{12}S_2 \cdot 2H_2O$
20j	CH_3	$NHCONH_2$	53	1765 1050	1.53 (6H, s), 3.1~3.5 (2H, m), 4.0~4.2 (1H, m), 4.39 (2H, s), 5.1~5.3 (1H, m), 5.33 (2H, s), 7.37 (1H, s), 9.41 (1H, d, 9), 13.03 (1H, br s)	$C_{23}H_{24}ClN_8NaO_{12}S_2 \cdot H_2O$
trans isomer of **20d**			44	1730 1050	1.5 (6H, s), 4.1~4.4 (2H, m), 4.33 (2H, s), 4.88 (1H, dd, 3, 9), 5.32 (2H, s), 6.3~6.7 (2H, br), 7.34 (1H, s), 8.05 (2H, d, 9), 9.28 (1H, d, 9)	$C_{23}H_{23}ClN_7NaO_{13}S_2 \cdot H_2O$
21d	H	$OCONH_2$	59	1760 1055	4.0~4.3 (3H, m), 4.35 (2H, s), 4.82 (2H, s), 5.2~5.4 (1H, m), 5.35 (2H, s), 6.44 (2H, br s), 7.4 (1H, s), 9.28 (1H, d, 9)	$C_{21}H_{19}ClN_7NaO_{13}S_2 \cdot 3.5H_2O$
21e	H	$OCONHCH_3$	97	1760 1050	3.9~4.4 (3H, m), 4.31 (2H, s), 4.79 (2H, s), 5.2~5.45 (1H, m), 5.35 (2H, s), 6.8~7.15 (1H, m), 7.3 (1H, s), 9.30 (1H, d, 9)	$C_{22}H_{21}ClN_7NaO_{13}S_2 \cdot 3H_2O$
trans isomer of **21d**			40	1760 1050	3.8~4.0 (1H, m), 4.2~4.4 (2H, m), 4.33 (2H, s), 4.8~4.95 (1H, m), 4.84 (2H, s), 5.34 (2H, s), 6.5 (2H, br s), 7.4 (1H, s), 9.43 (1H, d, 8)	$C_{21}H_{19}ClN_7NaO_{13}S_2 \cdot 2.5H_2O$

[a] Absorptions of aromatic protons of *p*-nitrobenzyl groups (δ 7.5~8.3) are not given in this table.

[b] All the compounds given the formula were analyzed for C, H and N; analytical results obtained for these elememts were within $\pm 0.4\%$ of calculated values.

Table 9. 3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(substituted oxyimino)acetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonic acids (**22**, **23**, **24** and **25**).



22 and **23**: 3,4-*cis*

24 and **25**: 3,4-*trans*

Compound No.	R_3	R	M	Yield (%)	IR (KBr) (cm^{-1})	NMR, δ (DMSO-d_6)	Formula	Analysis Calcd (Found) (%) C	H	N
22a	CH_3	$OCOCH_3$	Na	41	1760 1050	1.36 (3H, s), 1.43 (3H, s), 1.93 (3H, s), 3.9~4.25 (2H, m), 4.4~4.65 (1H, m), 5.25 (1H, dd, 5, 9), 6.7 (1H, s), 7.1 (2H, br s), 11.42 (1H, d, 9)	$C_{15}H_{17}N_5Na_2O_{10}S_2\cdot 5H_2O$	28.70 (29.05	4.33 (4.06	11.16 (10.92)
22d	CH_3	$OCONH_2$	H	65	1785 1050	1.46 (6H, s), 3.95~4.4 (3H, m), 5.31 (1H, dd, 4.5, 10), 6.91 (1H, s), 9.14 (1H, d, 10)	$C_{14}H_{18}N_6O_{10}S_2\cdot 1.5H_2O$	32.24 (32.37	4.06 (3.82	16.12 (16.16)
22h	CH_3	$NHCOCH_3$	H	68	1770 1040	1.49 (3H, s), 1.51 (3H, s), 1.8 (3H, s), 3.0~3.9 (3H, m), 5.17 (1H, dd, 6, 9), 7.0 (1H, s), 9.35 (1H, d, 9)	$C_{15}H_{20}N_6O_9S_2\cdot 2.5H_2O$	33.51 (33.70	4.62 (4.75	15.64 (15.33)
22j	CH_3	$NHCONH_2$	H	48	1760 1045	1.51 (6H, s), 3.1~3.6 (2H, m), 3.9~4.1 4.1 (1H, m), 7.04 (1H, s), 9.41 (1H, d, 9)	$C_{14}H_{19}N_7O_9S_2\cdot 2.5H_2O$	31.22 (31.31	4.49 (4.38	18.20 (18.18)
22r	CH_3	CN	H	25[a]	2250 1775 1050	1.56 (6H, s), 2.7~3.3 (2H, m), 4.05~4.55 (1H, m), 5.29 (1H, dd, 6, 9), 7.07 (1H, s), 9.42 (1H, d, 9)	$C_{14}H_{14}N_6O_8S_2\cdot 2.5H_2O$	33.27 (33.57	4.18 (4.01	16.63 (16.28)
23d	H	$OCONH_2$	H	52	1760 1040	4.0~4.4 (3H, m), 4.69 (2H, s), 5.3 (1H, dd, 6, 9), 6.97 (1H, s), 9.37 (1H, d, 9)	$C_{12}H_{14}N_6O_{10}S_2\cdot 1.5H_2O$	29.21 (29.30	3.47 (3.53	17.03 (16.98)
23e	H	$OCONHCH_3$	H	16	1760 1045	2.52 (3H, d, 5), 4.0~4.3 (3H, m), 4.64 (2H, s), 5.3 (1H, dd, 5, 9), 6.91 (1H, s), 9.34 (1H, d, 9)	$C_{13}H_{16}N_6O_{10}S_2\cdot 2H_2O$	30.23 (30.57	3.90 (3.82	16.27 (15.88)
23g	H	NHCHO	H	38[b]	1760 1050	3.25~3.7 (2H, m), 3.8~4.2 (1H, m), 4.72 (2H, s), 5.2 (1H, dd, 6, 9), 7.0 (1H, s), 8.0 (1H, s), 9.46 (1H, d, 9)	$C_{12}H_{14}N_6O_9S_2\cdot 2.1H_2O$	29.52 (29.90	3.75 (3.74	17.21 (16.85)
24	CH_3	$OCONH_2$	H	44	1770 1050	1.47 (6H, s), 3.85~4.0 (1H, m), 4.2~4.35 (2H, m), 4.85 (1H, dd, 3, 9), 6.92 (1H, s), 9.27 (1H, d, 9)	$C_{14}H_{18}N_6O_{10}S_2\cdot 2H_2O$	31.70 (31.51	4.18 (4.11	15.84 (15.69)
25	H	$OCONH_2$	H	57	1760 1050	3.8~3.95 (1H, m), 4.2~4.35 (2H, m), 4.69 (2H, s), 4.83 (1H, dd, 3, 9), 6.98 (1H, s), 9.48 (1H, d, 9)	$C_{12}H_{14}N_6O_{10}S_2\cdot 2H_2O$	28.68 (28.83	3.61 (3.51	16.73 (16.33)

[a] Overall yield from **18r**.

[b] Overall yield from **19g**.

acetyl chloride hydrochloride[2] in place of CATAM-Cl·HCl in Method A described for the synthesis of **14**, **18a,d,h,j,r** and the *trans* isomer of **18d** were obtained from **10a,d,h,j,r** and **13d-A**, respectively. The results are shown in Table 7.

3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-(4-nitrobenzyloxycarbonylmethoxyimino)acetamido]-4-(substituted methyl)-2-azetidinones (**19** and Its *trans* Isomer)

(a) According to the procedure reported for the synthesis of 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]acetyl chloride hydrochloride from 4-nitrobenzyl α-bromoisobutyrate[2], 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-(4-nitrobenzyloxycarbonylmethoxyimino)acetyl chloride hydrochloride was synthesized from 4-nitrobenzyl α-bromoacetate. Colorless crystals. MP 158~161°C. IR ν_{max}^{KBr} cm^{-1} 1780, 1740, 1680.

Anal Calcd for $C_{16}H_{12}Cl_2N_4O_7S \cdot HCl$: C 37.55, H 2.56, N 10.59.
Found: C 37.61, H 2.56, N 10.87.

(b) Using the acid chloride obtained above in place of CATAM-Cl·HCl in Method A described for the synthesis of **14**, **19d,e,g** and the *trans* isomer of **19d** were similarly synthesized. The results are shown in Table 7.

Sodium 3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]acetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonates (**20** and Its *trans* Isomer)

A solution of **19a** (325 mg, 0.52 mmol) in DMF (2 ml) was treated with 1.56 M SO_3·DMF solution (1 ml, 1.56 mmol) at −78°C. After being stirred overnight at 0~5°C, the mixture was treated with pyridine (0.126 ml, 1.56 mmol) and diluted with ether (50 ml). The resulting precipitate was separated by decantation, washed with ether and dissolved in water (15 ml). Dowex 50W (Na^+) (10 ml) was added, and the mixture was stirred for 1 hour at room temp. After removal of the resin by filtration, the filtrate was concentrated under reduced pressure. The concentrate was chromatographed on Amberlite XAD-2 (100 ml). Gradient elution with aq EtOH (0~30%) and lyophilization of the eluate gave **20a** (286 mg, 74%) as a colorless powder.

Compounds **20d,h,j,r** and the *trans* isomer of **20d** were similarly synthesized. Compound **20r** was used in the subsequent reaction without isolation. The results are shown in Table 8.

Sodium 3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-(4-nitrobenzyloxycarbonylmethoxyimino)acetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonates (**21** and Its *trans* Isomer)

Compounds **21d,e,g** and the *trans* isomer of **21d** were prepared from **19d,e,g** and the *trans* isomer of **19d**, respectively, by a method similar to that described above. Compound **21g** was used in the subsequent reaction without isolation. The results are shown in Table 8.

3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(1-carboxy-1-methylethoxyimino)acetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonic Acids (**22** and **24**)

Sodium *N*-methyldithiocarbamate (250 mg, 1.94 mmol) was added to a stirred solution of **20h** (960 mg, 1.26 mmol) in water (10 ml), and the mixture was stirred for 1 hour at room temp. After further addition of sodium *N*-methyldithiocarbamate (150 mg, 1.16 mmol), the reaction mixture was stirred for 1 hour at room temp and washed with ether. The aqueous solution was chromatographed on Amberlite XAD-2 (140 ml). Gradient elution with aq EtOH (0~20%) and lyophilization of the eluate gave a pale yellow powder (762 mg). A suspension of the powder (350 mg) and 10% Pd-C (350 mg) in a mixture of water (20 ml) and THF (20 ml) was stirred for 2 hours at room temp under a hydrogen atmosphere and filtered. The filtrate was treated with Dowex 50W (H^+) (25 ml)* for 1 hour under ice-cooling. After removal of resin by filtration, the filtrate was concentrated under reduced pressure and chromatographed on Amberlite XAD-2 (110 ml). Gradient elution with aq EtOH (0~10%) and lyophilization of the eluate gave **22h** (210 mg, 68%) as a colorless powder.

Compounds **22a,d,j,r** and **24** were similarly synthesized and the results are shown in Table 9.

* Treatment with 2 equiv $NaHCO_3$ instead of Dowex 50W (H^+) gave the disodium salt (**22a**).

3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-carboxymethoxyiminoacetamido]-4-(substituted methyl)-2-azetidinone-1-sulfonic Acids (**23** and **25**)

Compounds **23d,e,g** and **25** were prepared from **21d,e,g** and the *trans* isomer of **21d**, respectively, by a method similar to that described above. The results are shown in Table 9.

(3*R*,4*R*)-3-Benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-2-azetidinone [(3*R*,4*R*)-**5-A**]

(a) The racemic compound **4** (23.1 g, 78.2 mmol) and di-(*p*-toluoyl)-L-tartaric acid (31.6 g, 78.2 mmol) were dissolved in hot acetonitrile (780 ml). After filtration, the filtrate was allowed to stand overnight at room temp. The resulting crystals were collected by filtration and washed with cold acetonitrile to give colorless crystals (30.2 g). The crystals were recrystallized from acetonitrile twice to give the salt (1:1) of (3*R*,4*R*)-**4** and di-(*p*-toluoyl)-L-tartaric acid (17.9 g, 67%) as colorless crystals. MP 166~169°C. $[\alpha]_D^{23}$ −70.2° (*c* 1, MeOH). IR ν_{max}^{Nujol} cm^{-1} 1775, 1720, 1665.

Anal Calcd for $C_{34}H_{36}N_2O_{13}$: C 59.99, H 5.33, N 4.12.
Found: C 59.88, H 5.12, N 4.09.

(b) To a stirred suspension of the salt (17.8 g, 26.2 mmol) obtained above in a mixture of water (100 ml) and THF (200 ml) was added $NaHCO_3$ (6.6 g. 78.6 mmol) followed by addition of carbobenzoxy chloride (5.4 g, 31.6 mmol) under ice-cooling. After being stirred for 1 hour under ice-cooling and another hour at room temp, the mixture was concentrated under reduced pressure, and the concentrate was diluted with water (200 ml) and EtOAc (400 ml). After separation of the organic layer, the aqueous layer was extracted with EtOAc (200 ml). The combined extracts were washed successively with 5% aq $NaHCO_3$, brine, 1 N HCl and brine, dried, and evaporated to dryness. The solid residue was washed with ether and recrystallized from EtOAc - hexane (1:1) to give (3*R*,4*R*)-**5-A** (6.6 g, overall yield 40%) as colorless crystals. MP 120~121°C. $[\alpha]_D^{24.5}$ −24.1° (*c* 1, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1} 1770, 1745, 1695.

Anal Calcd for $C_{22}H_{24}N_2O_7$: C 61.67, H 5.65, N 6.54.
Found: C 61.62, H 5.60, N 6.47.

(3*S*,4*S*)-3-Benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-2-azetidinone [(3*S*,4*S*)-**5-A**]

(a) Compound **4** (50.2 g, 171 mmol) and di-(*p*-toluoyl)-D-tartaric acid (34.5 g, 86.1 mmol) were dissolved in hot acetonitrile (1,280 ml). The solution was filtered and the filtrate was allowed to stand overnight at room temp. The resulting crystals were collected by filtration, washed with cold acetonitrile and recrystallized from acetonitrile to give the salt (1:1) of (3*S*,4*S*)-**4** and di-(*p*-toluoyl)-D-tartaric acid (40.6 g, 70%) as colorless crystals. MP 166~169°C. $[\alpha]_D^{26}$ +70.1° (*c* 0.9, MeOH).

Anal Calcd for $C_{34}H_{36}N_2O_{13}$: C 59.99, H 5.33, N 4.12.
Found: C 59.63, H 5.07, N 4.22.

(b) By a method similar to that described for the synthesis of (3*R*,4*R*)-**5-A**, (3*S*,4*S*)-**5-A** was obtained as colorless crystals. MP 120~121°C. Overall yield 47%. $[\alpha]_D^{25}$ +24.7° (*c* 1, $CHCl_3$).

Anal Calcd for $C_{22}H_{24}N_2O_7$: C 61.67, H 5.65, N 6.54.
Found: C 61.40, H 5.45, N 6.45.

(3*S*,4*S*)-3-Benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-hydroxymethyl-2-azetidinone [(3*S*,4*S*)-**7-A**] and Its Enantiomer [(3*R*,4*R*)-**7-A**]

Compounds (3*S*,4*S*)-**7-A** and (3*R*,4*R*)-**7-A** were synthesized by a method similar to that described for the synthesis of the corresponding racemic compound (**7-A**), and the results are as follows.

(3*S*,4*S*)-**7-A**: Colorless crystals (from EtOAc). MP 137~138°C. Yield 76%. $[\alpha]_D^{25}$ +40.1° (*c* 1, MeOH). IR ν_{max}^{Nujol} cm^{-1} 1740.

Anal Calcd for $C_{21}H_{24}N_2O_6$: C 62.99, H 6.04, N 7.00.
Found: C 62.92, H 5.90, N 7.03.

(3*R*,4*R*)-**7-A**: Colorless crystals. MP 137~138°C. Yield 84%. $[\alpha]_D^{22}$ −39.5° (*c* 1, MeOH).

Anal Calcd for $C_{21}H_{24}N_2O_6$: C 62.99, H 6.04, N 7.00.
Found: C 63.12, H 6.06, N 6.96.

(3*S*,4*S*)-3-Benzyloxycarbonylamino-4-carbamoyloxymethyl-1-(2,4-dimethoxybenzyl)-2-azetidinone [(3*S*,4*S*)-**9d-A**] and Its Enantiomer [(3*R*,4*R*)-**9d-A**]

Compounds (3*S*,4*S*)-**9d-A** and (3*R*,4*R*)-**9d-A** were synthesized by a method similar to that described for the synthesis of the corresponding racemic compound (**9d-A**), and the results are as follows.

(3*S*,4*S*)-**9d-A**: Colorless crystals (from EtOAc - hexane). MP 179~180°C. Yield 78%. $[\alpha]_D^{24.5}$ +34.5° (*c* 0.8, DMSO). IR ν_{max}^{KBr} cm^{-1} 1760, 1710.

Anal Calcd for $C_{22}H_{25}N_3O_7$: C 59.59, H 5.68, N 9.48.
Found: C 59.30, H 5.70, N 9.57.

(3*R*,4*R*)-**9d-A**: Colorless crystals. MP 179~180°C. $[\alpha]_D^{22}$ −34.4° (*c* 1, DMSO).

Anal Calcd for $C_{22}H_{25}N_3O_7$: C 59.59, H 5.68, N 9.48.
Found: C 59.45, H 5.56, N 9.39.

(3*S*,4*S*)-3-Benzyloxycarbonylamino-4-carbamoyloxymethyl-2-azetidinone [(3*S*,4*S*)-**10d-A**] and Its Enantiomer [(3*R*,4*R*)-**10d-A**]

Compounds (3*S*,4*S*)-**10d-A** and (3*R*,4*R*)-**10d-A** were synthesized by a method similar to that described for the synthesis of the corresponding racemic compound (**10d-A**), and the results are as follows.

(3*S*,4*S*)-**10d-A**: Colorless needles. MP 191~192°C. Yield 74%. $[\alpha]_D^{25}$ +60.6° (*c* 1, MeOH). IR ν_{max}^{KBr} cm^{-1} 1755, 1745.

Anal Calcd for $C_{13}H_{15}N_3O_5$: C 53.23, H 5.15, N 14.32.
Found: C 52.83, H 5.02, N 14.26.

(3*R*,4*R*)-**10d-A**: Colorless needles. MP 192~194°C. Yield 74%. $[\alpha]_D^{22}$ −60.4° (*c* 1, MeOH).

Anal Calcd for $C_{13}H_{15}N_3O_5$: C 53.23, H 5.15, N 14.32.
Found: C 53.34, H 5.07, N 14.46.

Sodium (3*S*,4*S*)-3-Benzyloxycarbonylamino-4-carbamoyloxymethyl-2-azetidinone-1-sulfonate [(3*S*,4*S*)-**26**] and Its Enantiomer [(3*R*,4*R*)-**26**]

To a stirred solution of (3*S*,4*S*)-**10d-A** (293 mg, 1 mmol) in dioxane (10 ml) was added SO_3·Pyridine (477 mg, 3 mmol), and the mixture was stirred for 14 hours at room temp. After removal of the solvent, water (20 ml) and Dowex 50W (Na^+) (20 ml) were added, and the mixture was stirred for 1 hour at room temp. After removal of the resin by filtration, the filtrate was concentrated under reduced pressure. The concentrate was chromatographed on Amberlite XAD-2 (200 ml). Gradient elution with aq EtOH (0~10%) and lyophilization of the eluate gave (3*S*,4*S*)-**26** (270 mg, 64%) as a colorless powder. $[\alpha]_D^{25}$ +29.4° (*c* 0.7, H_2O). IR ν_{max}^{KBr} cm^{-1} 1795, 1760. NMR (DMSO-d_6) δ 3.85~4.4 (3H, m), 4.92 (1H, dd, 5, 10), 6.1~6.5 (2H, br), 7.35 (5H, s), 7.98 (1H, d, 10).

Anal Calcd for $C_{13}H_{14}N_2NaO_8S \cdot 1.5H_2O$: C 36.97, H 4.06, N 9.95.
Found: C 37.24, H 4.13, N 10.02.

(3*R*,4*R*)-**26** was similarly synthesized. A colorless powder. Yield 94%. $[\alpha]_D^{22}$ −28.8° (*c* 1, H_2O).

(3*S*,4*S*)-3-Amino-4-carbamoyloxymethyl-2-azetidinone-1-sulfonic Acid [(3*S*,4*S*)-**27**]*

To a solution of (3*S*,4*S*)-**26** (295 mg, 0.7 mmol) in water (8.3 ml) were added 1 N HCl (0.7 ml) and 10% Pd-C (295 mg), and the mixture was stirred for 40 minutes at room temp under a hydrogen atmosphere. After removal of the catalyst, the filtrate was concentrated to *ca.* 5 ml under reduced pressure. To the concentrate was added 1 N HCl (2.8 ml), and the mixture was concentrated again to *ca.* 1 ml and allowed to stand in a refrigerator. The resulting crystals were collected by filtration and washed with cold water (1 ml) to give (3*S*,4*S*)-**27** (101 mg, 60%) as colorless crystals. MP 207~210°C (dec). $[\alpha]_D^{24}$ −62.9° (*c* 0.5, DMSO). IR ν_{max}^{KBr} cm^{-1} 1795, 1775, 1720. NMR (DMSO-d_6) δ 4.0~4.45 (3H, m), 4.67 (1H, d, 5), 6.52 (2H, br s).

Anal Calcd for $C_5H_9N_3O_6S$: C 25.10, H 3.79, N 17.57.
Found: C 25.02, H 3.72, N 17.73.

(3*S*,4*S*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-carboxymethoxyiminoacetamido]-4-carbamoyloxymethyl-2-azetidinone-1-sulfonic Acid (**3**) and Its Enantiomer [(3*R*,4*R*)-**23d**]

(a) A suspension of (3*S*,4*S*)-**26** (422 mg, 1 mmol) and 10% Pd-C (422 mg) in a mixture of water

* The absolute structure of (3*S*,4*S*)-**27** was confirmed by X-ray analysis, and the details will be published elsewhere.

(10 ml) and THF (10 ml) was stirred for 1 hour at room temp under a hydrogen atmosphere. After removal of the catalyst by filtration, $NaHCO_3$ (202 mg, 2.4 mmol) and 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-(4-nitrobenzyloxycarbonylmethoxyimino)acetyl chloride hydrochloride (614 mg, 1.2 mmol) were added to the ice-cooled filtrate, and the mixture was stirred for 30 minutes under ice-cooling. After adjustment to pH 5 with 1 N HCl, the reaction mixture was concentrated to *ca* 30 ml under reduced pressure. The concentrate was diluted with THF (10 ml), and sodium *N*-methyldithiocarbamate (194 mg) was added. The mixture was stirred for 1 hour at room temp, and the same amount of sodium *N*-methyldithiocarbamate was added again. The mixture was stirred for additional 1 hour. After evaporation of the THF, the residual solution was washed with ether and concentrated under reduced pressure. The concentrate was chromatographed on Amberlite XAD-2 (200 ml). Gradient elution with aq EtOH (0~20%) and lyophilization of the eluate gave sodium (3*S*,4*S*)-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(4-nitrobenzyloxycarbonylmethoxyimino)acetamido]-4-carbamoyloxymethyl-2-azetidinone-1-sulfonate (500 mg, 76%) as a pale yellow powder. $[\alpha]_D^{26}$ +10.1° (*c* 1, H_2O). IR ν_{max}^{KBr} cm^{-1} 1760, 1720.

Anal Calcd for $C_{19}H_{18}N_7NaO_{12}S_2 \cdot 2H_2O$: C 34.60, H 3.36, N 14.87.
Found: C 34.44, H 3.10, N 14.82.

(b) A suspension of the powder (500 mg, 0.75 mmol) obtained above, $NaHCO_3$ (71.4 mg) and 10% Pd-C (300 mg) in a mixture of water (20 ml) and THF (21 ml) was stirred for 1.5 hours at room temp under a hydrogen atmosphere. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The concentrate was treated with 3 N HCl (0.83 ml) and chromatographed on Amberlite XAD-2 (140 ml). Gradient elution with aq EtOH (0~5%) and lyophilization of the eluate gave a colorless powder. The powder was suspended in water (4.5 ml) and allowed to stand overnight at 5°C. The resulting crystals were collected by filtration and washed with cold water to give **3** (280 mg, 75%) as colorless crystals. $[\alpha]_D^{24}$ −46.3° (*c* 1, DMSO). IR ν_{max}^{KBr} cm^{-1} 1770, 1655.

Anal Calcd for $C_{12}H_{14}N_6O_{10}S_2 \cdot 2.5H_2O$: C 28.18, H 3.74, N 16.43.
Found: C 28.36, H 4.02, N 16.40.

(3*R*,4*R*)-**23d** was similarly synthesized from (3*R*,4*R*)-**26** in 42% yield. $[\alpha]_D^{20}$ +50.7° (*c* 1, DMSO).

Anal Calcd for $C_{12}H_{14}N_6O_{10}S_2 \cdot 2.5H_2O$: C 28.18, H 3.74, N 16.43.
Found: C 28.35, H 3.46, N 16.54.

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