SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 2-AZETIDINONE-1-SULFONIC ACID DERIVATIVES WITH A HETEROATOM-BOUND SUBSTITUENT AT THE 4-POSITION†

NORIYOSHI NOGUCHI, HIROTOMO MASUYA, TOHORU SUGAWARA, YASUHIKO KAWANO, TAISUKE MATSUO (deceased) and MICHIHIKO OCHIAI

Central Research Division, Takeda Chemical Industries, Ltd.
Juso, Yodogawa-ku, Osaka 532, Japan

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The synthesis and antibacterial activity of 3-[(*Z*)-2-alkoxyimino-2-(2-aminothiazol-4-yl)-acetamido]-2-azetidinone-1-sulfonic acid derivatives with a heteroatom-bound substituent at the 4-position are described. The effect of various 4-substituents on the antibacterial activity was examined. Some of these compounds showed excellent antibacterial activity especially against Gram-negative bacteria, including β-lactamase-producing strains.

Our earlier chemical modification of sulfazecin[1,2] revealed that although some of the 4-unsubstituted 2-azetidinone-1-sulfonic acid derivatives with various 3-acylamino groups had improved antibacterial activity, these compounds generally lack the activity against β-lactamase-producing strains.

To correct for this deficiency we explored new derivatives having various 4-heteroatom-bound substituents††. This paper deals with the synthesis and the antibacterial activity of 3-[(*Z*)-2-alkoxyimino-2-(2-aminothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonic acid derivatives with 4-heteroatom-bound substituents.

Chemistry

Reactions of the 4β-methylsulfonyl compound (**2Bb**)[5], or the 4α-acetoxy compound (**2Aa**) which is obtainable by hydrogenolysis of 3-benzyloxycarbonylamino derivative (**1**)[6,7] over Pd-black followed by tritylation with trityl chloride and triethylamine, with various nucleophiles (Y^-) gave mixtures of the 4α-substituted-2-azetidinone derivatives (**2Ac**～**h**) and the 4β-isomers (**2Bc**～**h**).

The 4-methoxycarbonylmethylthio derivatives (**2Ae** and **2Be**) were converted into 4-carbamoylmethylthio derivatives (**2Ai** and **2Bi**) by treatment with ammonia, and the 4β-azido compound (**2Bh**) was transformed to the 4β-triazolyl compounds (**2Bj** and **2Bk**) by the 1,3-dipolar cycloaddition reaction[5] with methyl propiolate.

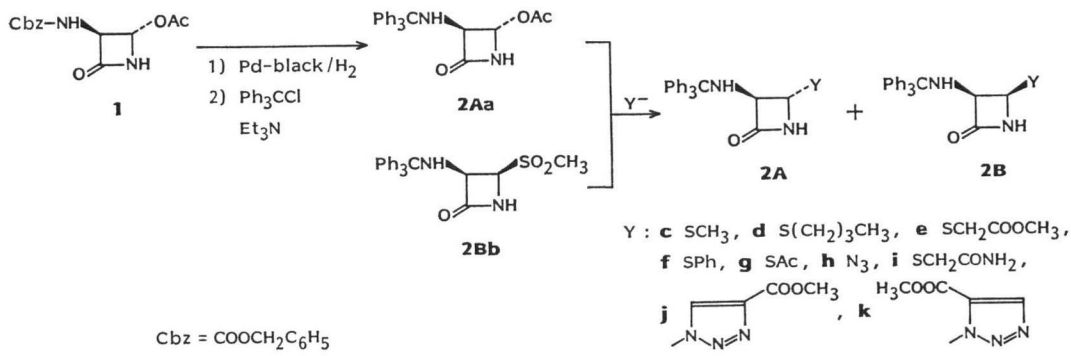
3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-substituted-2-azetidinone-1-sulfonic acid derivatives (**7a**～**k**) were synthesized from these 3-tritylamino compounds (**2A** and **2B**) as shown in Chart 2.

Removal of the trityl group of **2a**～**k** with *p*-toluenesulfonic acid monohydrate gave the 3-amino

† A part of this paper was presented at the 2nd Symposium of French-Japanese Society for Medicinal and Fine Chemistry. Sept. 20～23, Montsoult, 1982.

†† Carumonam (AMA-1080)[3] having a carbamoyloxymethyl group at the 4β-position was synthesized in our laboratory as a result of a similar exploration, and is active, like aztreonam[4], against β-lactamase-producing strains of Gram-negative bacteria.

Chart 1.



derivatives (**3a**~**k**), which were directly converted into the 2-azetidinone derivatives (**5a**~**k**) by acylation with 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetyl chloride monohydrochloride (**4**)[9]. Sulfonation of **5a**~**k** with SO_3·dimethylformamide complex (SO_3·DMF)[8,10] followed by treatment with pyridine and then with Dowex 50W ion exchange resin (Na^+ form) afforded the sodium salts (**6a**~**k**). The chloroacetyl groups of **6a**~**g**, **6i** and **6j** were removed by reaction with sodium *N*-methyldithiocarbamate[9] to give **7a**~**g**, **7i** and **7j**, respectively.

However, treatment of the 4-azido derivatives (**6Ah** and **6Bh**) with sodium *N*-methyldithiocarbamate caused decomposition of the β-lactam ring. 4-Azido compounds (**7Ah** and **7Bh**) were smoothly obtained *via* the 2-formamidothiazolyl compounds (**9** and **10**) as shown in Chart 2. Deprotection of the formyl group of **10Ah** and **10Bh** with aqueous HCl in methanol followed by treatment with sodium hydrogen carbonate gave **7Ah** and **7Bh**, respectively.

Since 4-azido derivatives (**7Ah** and **7Bh**) and 4β-carbamoylmethylthio derivative (**7Bi**) showed potent antibacterial activity against Gram-negative bacteria (Table 1), we introduced carboxylic acid moieties into the methoxyimino function in the 3-acyl side chain of these derivatives expecting to improve the antibacterial activity (Chart 3).

Reaction of **11** with bromo compounds (**12** and **17**) in the presence of potassium carbonate followed by catalytic reduction and subsequent treatment with aqueous HCl gave carboxylic acid monohydrochlorides (**13** and **18**, respectively). An active ester obtained by treatment of carboxylic acid (**13**) with 1-hydroxybenztriazole (HOBT) in the presence of pyridine and dicyclohexylcarbodiimide (DCC) was reacted with the amino compounds (**3Ah** and **3Bh**) to afford **14Ah** and **14Bh**. Sulfonation of **14Ah** and **14Bh** gave **15Ah** and **15Bh**, respectively. The 2-trimethylsilylethyl (TMSE) group of **15Ah** and **15Bh** was deprotected by reaction with tetrabutylammonium fluoride[11] and then the trityl group was removed by treatment with Dowex 50W ion exchange resin (H^+ form) to give **16Ah** and **16Bh**.

By a similar procedure, the 4-azido derivatives (**21Ah** and **21Bh**) and the 4β-carbamoylmethylthio derivative (**21Bi**) with a 2-carboxyprop-2-oxyimino group were synthesized using **18** in place of **13**.

Antibacterial Activity

The antibacterial activity of 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido] derivatives (**7a**~**k**) is given in Table 1. The compounds (**7Ac**, **7Bc**, **7Ah**, **7Bh**, **7Ai** and **7Bi**) having methylthio, azido, and carbamoylmethylthio groups, respectively, at the 4-position exhibited high antibacterial

Chart 2.

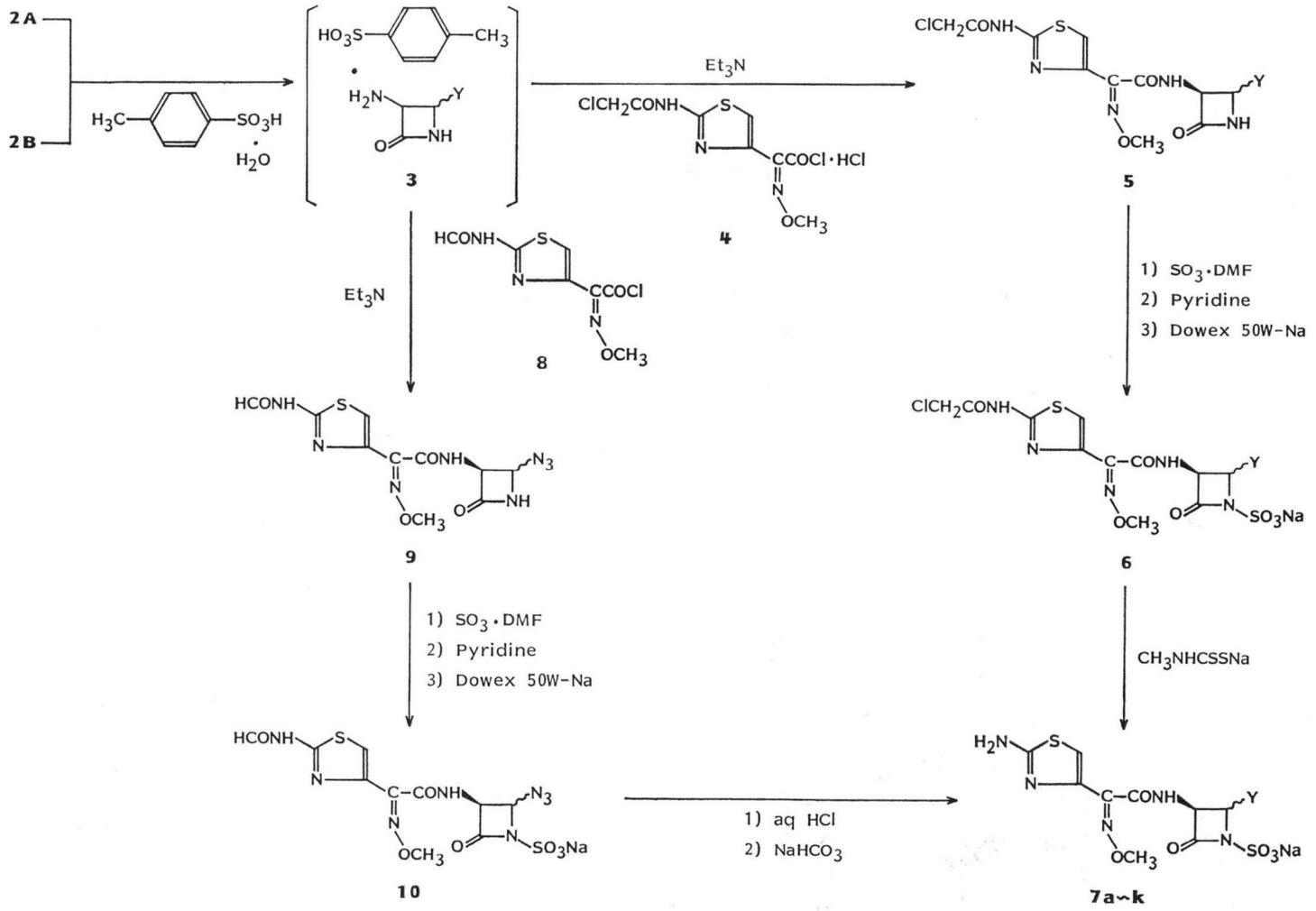
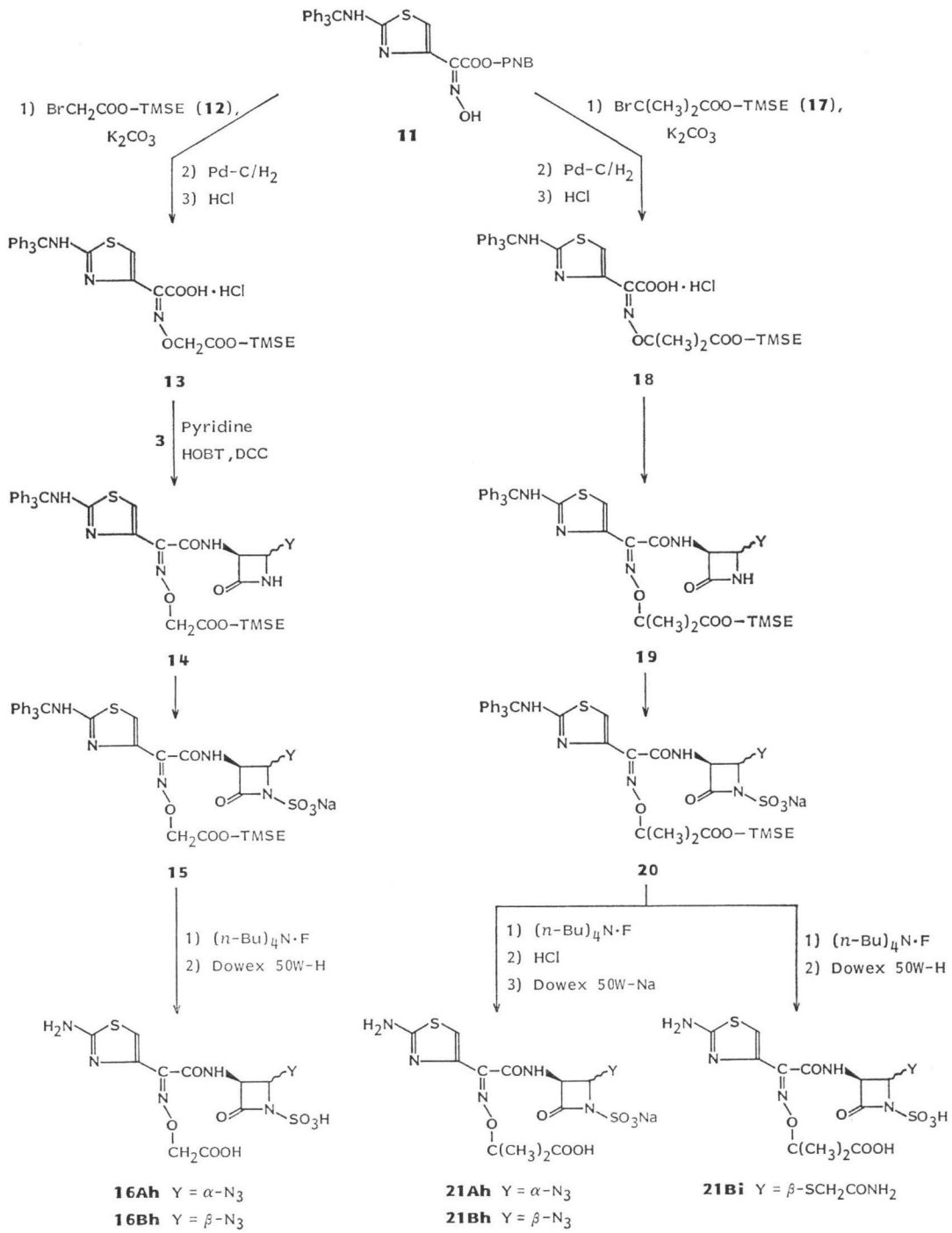

2A
2B
HO_3S
CH_3
H_2N
Y
NH
O
3
H_3C
SO_3H
H_2O
Et_3N
$ClCH_2CONH$
S
N
$CCOCl \cdot HCl$
OCH_3
4
5
C–CONH
1) $SO_3 \cdot DMF$
2) Pyridine
3) Dowex 50W-Na
HCONH
CCOCl
8
9
N_3
6
SO_3Na
10
1) aq HCl
2) $NaHCO_3$
$CH_3NHCSSNa$
7a~k

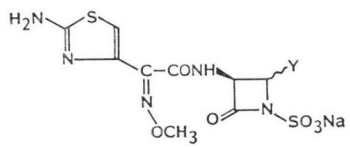
Chart 3.

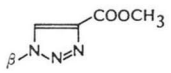
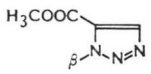


TMSE = $CH_2CH_2Si(CH_3)_3$ HOBT = 1-Hydroxybenztriazole

PNB = *p*-Nitrobenzyl DCC = Dicyclohexylcarbodiimide

Table 1. Antibacterial activity of 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-substituted-2-azetidinone-1-sulfonic acid derivatives (**7**).



Compound	Y	MIC (μg/ml)[a]					
		E.c.-2	*E.c.*-7	*E.cl.*	*S.m.*	*P.v.*	*P.a.*
7Aa	α-OAc	50	>100	>100	100	50	>100
7Bb	β-SO_2CH_3	>100	>100	>100	>100	>100	>100
7Ac	α-SCH_3	1.56	1.56	25	1.56	0.78	>100
7Bc	β-SCH_3	0.78	1.56	12.5	0.78	0.39	>100
7Ad	α-$S(CH_2)_3CH_3$	100	50	50	>100	12.5	>100
7Bd	β-$S(CH_2)_3CH_3$	50	50	100	>100	12.5	>100
7Ae	α-SCH_2COOCH_3	6.25	12.5	>100	12.5	>100	>100
7Be	β-SCH_2COOCH_3	1.56	1.56	50	3.15	50	>100
7Af	α-SPh	>100	>100	>100	>100	>100	>100
7Ag	α-SAc	>100	>100	>100	>100	>100	>100
7Bg	β-SAc	>100	>100	>100	>100	>100	>100
7Ah	α-N_3	6.25	12.5	>100	25	6.25	50
7Bh	β-N_3	0.78	0.78	25	1.56	0.39	12.5
7Ai	α-SCH_2CONH_2	3.13	6.25	12.5	12.5	12.5	>100
7Bi	β-SCH_2CONH_2	<0.1	0.2	0.78	0.39	0.39	50
7Bj		>100	>100	>100	>100	>100	>100
7Bk		12.5	6.25	25	50	3.13	>100

[a] The MICs were determined by a standard dilution method in Trypticase soy agar (BBL).
Inoculum size: 10^8 cfu/ml.
Test organisms and abbreviations: *E.c.*-2; *Escherichia coli* NIHJ JC-2, *E.c.*-7; *E. coli* T-7, *E.cl.*; *Enterobacter cloacae* IFO 12937, *S.m.*; *Serratia marcescens* IFO 12648, *P.v.*; *Proteus vulgaris* IFO 3988, *P.a.*; *Pseudomonas aeruginosa* IFO 3455.

activity against *Escherichia coli* and *Proteus vulgaris*, and the compounds (**7Ae**, **7Be**, **7Bk**, **7Ad**, **7Bd** and **7Aa**) having methoxycarbonylmethylthio, 5-methoxycarbonyltriazolyl, *n*-butylthio, and acetoxyl groups, respectively, at the 4-position showed moderate antibacterial activity. The 4β-isomers (derivatives having 3,4-*cis* stereochemistry) were more active than the corresponding 4α-isomers.

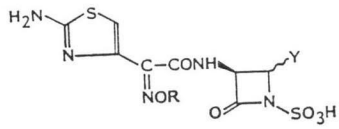
Table 2 shows that the introduction of carboxylic acid moieties into the methoxyimino function in the 3-acyl side chain enhanced activity against *Pseudomonas aeruginosa*; the 4-carbamoylmethylthio derivative (**21Bi**) was the most active compound among these 4-substituted derivatives*.

Experimental

IR spectra were taken on a Hitachi type 260-10 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian HA-100 or T-60 spectrometer using tetramethylsilane as a standard. Optical rotations were measured with Jasco DPI-181 polarimeter. Melting points are uncorrected.

* Recently Squibb group reported the synthesis of the 4-carbamoylmethylthio derivative (**21Bi**)[12].

Table 2. Antibacterial activity of 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-carboxymethoxyiminoacetamido]-4-substituted-2-azetidinone-1-sulfonic acid derivatives (**16**) and 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(2-carboxyprop-2-oxyimino)acetamido]-4-substituted-2-azetidinone-1-sulfonic acid derivatives (**21**).



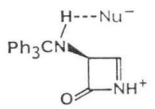
Compound	R	Y	MIC (μg/ml)[a]					
			E.c.-2	*E.c.*-7	*E.cl.*	*S.m.*	*P.v.*	*P.a.*
16Ah	CH_2COOH	α-N_3	6.25	12.5	>100	25	6.25	50
16Bh	CH_2COOH	β-N_3	0.39	0.78	25	1.56	0.39	12.5
21Ah[b]	$C(CH_3)_2COOH$	α-N_3	3.13	3.13	>100	6.25	0.39	25
21Bh[b]	$C(CH_3)_2COOH$	β-N_3	0.78	1.56	6.25	3.13	0.2	6.25
21Bi	$C(CH_3)_2COOH$	β-SCH_2CONH_2	0.39	0.78	1.56	0.39	0.39	1.56

[a] See the footnote in Table 1.
[b] Sodium salt.

Table 3. Reaction of nucleophiles with **2Aa** or **2Bb**.

Run	Nucleophiles	Starting material	Temp (°C)	Time (hours)	Products	Yield (%)	Ratio[a]
							2A[b]/**2B**[b]
1	$NaSCH_3$	**2Aa** or **2Bb**	20~25	1	**2c**	81	1:1
2	$NaS(CH_2)_5CH_3$	**2Aa** or **2Bb**	20~25	1	**2d**	92	1:1
3	$NaSCH_2COOCH_3$	**2Aa**	20~25	1	**2e**	76	4:5
4	NaSPh	**2Bb**	20~25	1	**2f**	93	1:1
5	KSAc	**2Aa**	55~60	0.5	**2g**	84	7:3
6	NaN_3	**2Aa** or **2Bb**	40~50	1.5	**2h**	82	3:2

[a] Ratio of **2A** to **2B** was determined by isolated yields after silica gel column chromatography or HPLC.
It was supposed that the formation of *cis*-isomers (4,3-isomers) (**2B**) in unexpectedly high ratio was caused by the steric approach control of 3-tritylamino founction forming an ion pair like **23**.
(Reactions of 3-phtalimido or 3-methyl-4-acetoxy-2-azetidinone with nucleophiles gave *trans*-isomers predominantly[13,14].)



23

[b] **A** and **B** mean *trans* and *cis* configuration of 3- and 4-substituents, respectively.

(3*S*,4*S*)-4-Acetoxy-3-tritylamino-2-azetidinone (**2Aa**)

A mixture of (3*S*,4*S*)-4-acetoxy-3-benzyloxycarbonylamino-2-azetidinone (**1**)[6,7] (18 g) and Pd-black (4 g) in THF (300 ml) was stirred under a H_2 gas atmosphere at room temp for 1.5 hours. The catalyst was filtered off and the filtrate was concd to about 70 ml under reduced pressure. To this solution were added CH_2Cl_2 (100 ml) and triethylamine (6.9 g), and then a solution of trityl chloride (18.5 g) in CH_2Cl_2 (120 ml) was added dropwise at 0°C to the above solution. After being stirred at room temp for 3 hours, the reaction mixture was concd under reduced pressure. The residue was dissolved in EtOAc and the resulting solution was washed with H_2O and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel and eluted with a mixture of EtOAc - hexane (1:2) to afford an oil of **2Aa**, which was treated with Et_2O to give 23.8 g (87%) of **2Aa**·1/2 Et_2O as a crystal: mp 90~92°C; $[\alpha]_D^{25}$ −198° (*c* 1.12, MeOH); IR (KBr) 3320, 1775, 1735, 1230, 1030 cm^{-1}; NMR ($CDCl_3$) δ 1.85 (3H, s), 2.90 (1H, br s), 4.27 (1H, m), 4.87 (1H, d, *J*=1 Hz), 6.58 (1H, br s), 7.27~7.77 (15H, m).

Anal Calcd for $C_{24}H_{22}N_2O_3 \cdot 1/2C_4H_{10}O$: C 73.74, H 6.42, N 6.61.
Found: C 73.52, H 6.30, N 6.56.

Table 4. 3-Tritylamino-4-substituted-2-azetidinone derivatives (**2**).

Compound	Y	IR ν_{max}^{KBr} cm^{-1}	$[\alpha]_D^{25}$ (MeOH)	NMR ($CDCl_3$, δ)			
				C(3)-H 1H, dd (Hz)	C(4)-H 1H, d (Hz)	CONH 1H, s	Y
2Ac	α-SCH_3	1750	−172°	4.00~4.20 (m)		5.93	1.74 (3H, s)
2Bc	β-SCH_3	1752	+21.8°	4.42 (J=5, 8)	4.18 (J=5)	6.16	1.80 (3H, s)
2Ad	α-$S(CH_2)_3CH_3$	1750	—	4.07~4.25 (m)		6.90	0.70~1.05 (3H, m), 1.15~1.60 (4H, m), 2.07~2.40 (2H, m)
2Bd	β-$S(CH_2)_3CH_3$	1755	—	4.45 (J=5, 8)	4.25 (J=5)	6.80	0.73~1.07 (3H, m), 1.27~1.70 (4H, m), 2.05~2.40 (2H, m)
2Ae	α-SCH_2COOCH_3	1760~1725	−138°	3.90~4.20 (m)		6.55	2.93 (2H, s), 3.57 (3H, s)
2Be	β-SCH_2COOCH_3	1760~1725	+69.9°	4.42 (J=6, 9)	4.43 (J=6)	6.67	2.96 (2H, ABq, J=15, 27 Hz), 3.61 (3H, s)
2Af	α-SPh	1755	—	4.00 (J=2, 9)	4.33 (J=2)	6.52	7.10~7.70 (5H, m)
2Bf	β-SPh[a]	1755	+168°	4.58 (J=5, 8)	4.77 (J=5)	6.08	7.17~7.65 (5H, m)
2Ag	α-SAc	1760	—	4.23 (m)	4.66 (J=2)	6.77	2.15 (3H, s)
2Bg	β-SAc	1775, 1765	—	4.77 (m)	5.13 (J=5)	6.57	2.30 (3H, s)
2Ah	α-N_3	1765	−174°	3.98~4.20 (m)		6.40	
2Bh	β-N_3[b]	1782	+111°	4.40 (J=4, 9)	4.26 (J=4)	6.30	

[a] mp 173~175°C, [b] mp 166~168°C.

General Procedure for the Preparation of 4-Substituted-2-azetidinone Derivatives (**2c~h**)

To a solution of (3*R*,4*R*)-4-methylsulfonyl-3-tritylamino-2-azetidinone (**2Bb**) or **2Aa** (10 mM) in MeOH (70 ml) were added nucleophile (12~13 mM) and H_2O (10 ml) at 0°C. After being stirred under the conditions shown in Table 3, the mixture was concd under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with H_2O and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the resulting residue was chromatographed on silica gel and eluted with a mixture of EtOAc-hexane to give **2A** and **2B** (Table 4). The structure of **2c~h** were confirmed on the basis of IR and ^1H NMR spectral data shown in Table 4.

(3*R*,4*S*)-4-Carbamoylmethylthio-3-tritylamino-2-azetidinone (**2Ai**)

To a solution of (3*R*,4*S*)-4-methoxycarbonylmethylthio-3-tritylamino-2-azetidinone (**2Ae**) (0.447 g) in EtOH (5 ml) was added 28% aq ammonia (1 ml). After being stirred at room temp for 2 days, the reaction mixture was concd under reduced pressure. The residue was chromatographed on silica gel and eluted with a mixture of EtOAc - $CHCl_3$ - MeOH (8: 8: 1) to afford **2Ai** (0.173 g, 41%) as a crystal: mp 160~163°C (dec); IR (KBr) 3415, 3310, 3180, 1740, 1670 cm^{-1}; NMR (DMSO-d_6) δ 2.81 (2H, s), 3.71 (1H, dd, J=2, 10 Hz), 4.22 (1H, d, J=10 Hz), 4.27 (1H, d, J=2 Hz), 6.99 (2H, br s), 7.10~7.57 (15H, m), 8.29 (1H, s).

Anal Calcd for $C_{24}H_{23}N_3O_2S$: C 69.04, H 5.55, N 10.06, S 7.68.
Found: C 69.04, H 5.60, N 10.07, S 7.65.

(3*R*,4*R*)-4-Carbamoylmethylthio-3-tritylamino-2-azetidinone (**2Bi**)

The title compound (**2Bi**) was prepared in 43% yield using **2Be** in an analogous way described above: IR (KBr) 3420, 3285, 3150~3075, 1745, 1666 cm^{-1}; NMR (DMSO-d_6) δ 2.89 (2H, ABq, J= 14, 17 Hz), 3.47 (1H, d, J=9 Hz), 4.28 (1H, dd, J=5, 9 Hz), 4.48 (1H, d, J=5 Hz), 7.15~7.57 (15H, m), 8.37 (1H, s).

(3*S*,4*R*)-4-(4-Methoxycarbonyl-1,2,3-triazol-1-yl)-3-tritylamino-2-azetidinone (**2Bj**) and (3*S*,4*R*)-4-(5-Methoxycarbonyl-1,2,3-triazol-1-yl)-3-tritylamino-2-azetidinone (**2Bk**)

Methyl propiolate (1.14 g) was added to a solution of (3*S*,4*R*)-4-azido-3-tritylamino-2-azetidinone (**2Bh**) (2.0 g) in toluene (35 ml). The mixture was refluxed for 2 hours and concd under reduced pressure. Chromatography of the residue on silica gel [EtOAc - hexane (1: 2) as eluant] gave two fractions.

The first eluted fraction gave **2Bk** (0.818 g, 33.5%) as a powder: IR (KBr) 3330, 1780, 1730, 1256 cm^{-1}; NMR (DMSO-d_6) δ 3.87 (3H, s), 3.90 (1H, d, J=12 Hz), 4.97 (1H, dd, J=4, 12 Hz), 6.36 (1H, d, J=4 Hz), 7.21 (15H, s), 8.13 (1H, s), 8.80 (1H, s).

The second eluted fraction gave **2Bj** (1.258 g, 51.5%) as a crystalline solid: mp 193~195°C; IR (KBr) 3340, 3275, 1785, 1712, 1237 cm^{-1}; NMR (DMSO-d_6) δ 3.87 (3H, s), 4.07 (1H, d, J=10 Hz), 4.89 (1H, dd, J=4, 10 Hz), 5.84 (1H, d, J=4 Hz), 7.20 (15H, s), 8.57 (1H, s), 8.86 (1H, s).

Anal Calcd for $C_{26}H_{23}N_5O_3$: C 68.86, H 5.11, N 15.44.
Found: C 68.65, H 5.15, N 15.36.

3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-substituted-2-azetidinone Derivatives (**5**)

To a solution of **2** (1 mM) in acetone (5 ml) was added *p*-toluenesulfonic acid monohydrate (1.1 mM) at 0°C. The mixture was stirred at room temp for 1 hour and evaporated under reduced pressure. The residue was treated with Et_2O to give **3** as a powder. To a suspension of **4** (1.2 mM) in CH_2Cl_2 (12 ml) were added triethylamine (3.5 mM), **3** and propylene oxide (1 ml) at −78°C, and the mixture was allowed to warm up to room temp. After being stirred at room temp for 30 minutes, the reaction mixture was concd under reduced pressure. The residue was purified by silica gel column chromatography to afford **5** as a powder (Table 5).

Sodium 3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-substituted-2-azetidinone-1-sulfonate Derivatives (**6**)

A solution of SO_3·DMF (3 mM) in anhydrous DMF (3 ml) was added at −78°C to a solution of

Table 5. 3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-substituted-2-azetidinone derivatives (**5**).

Compound	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	NMR (DMSO-d_6, δ)			
			C(3)-H 1H, dd (Hz)	C(4)-H 1H, d (Hz)	β-Lactam-NHCO 1H, s	Thiazole-5H 1H, s
5Aa	71	1770, 1740	4.90 (*J*=2, 8)	5.93 (*J*=2)	9.30	7.52
5Bb	70	1790	5.57 (*J*=5, 9)	4.93 (*J*=5)	9.40	7.53
5Ac	49	1758	4.57~4.90 (m)		8.80	7.40
5Bc	89	1760	5.40 (*J*=4, 9)	4.93 (*J*=4)	8.84	7.50
5Ad	90	1762	4.68 (*J*=2, 9)	4.68 (*J*=2)	8.81	7.40
5Bd	86	1758	5.38 (*J*=5, 9)	4.98 (*J*=5)	8.81	7.49
5Ae	78	1763	4.75 (*J*=2, 8)	4.82 (*J*=2)	8.81	7.41
5Be	77	1762	5.40 (*J*=4, 8)	5.09 (*J*=4)	8.80	7.48
5Af	72	1752	4.69 (*J*=2, 8)	4.98 (*J*=2)	9.04	7.34
5Bf	22	1755	5.58 (*J*=5, 9)	5.36 (*J*=5)	9.01	7.34
5Ag	65	1752	4.93 (*J*=2, 8)	5.21 (*J*=2)	8.97	7.42
5Bg	35	1770~1755	5.36 (*J*=5, 8)	5.68 (*J*=5)	8.99	7.56
5Ah	74	1755	4.70 (*J*=2, 8)	5.13 (*J*=2)	9.13	7.45
5Bh	73	1768	5.18~5.40 (m)		9.07	7.34
5Ai	80	1756	4.74 (*J*=2, 8)	4.84 (*J*=2)	8.74	7.43
5Bi	78	1763	5.38 (*J*=5, 8)	5.11 (*J*=5)	8.76	7.50
5Bj	89	1785	5.70 (m)	6.55 (*J*=4)	8.75	7.07
5Bk	45	1782	5.75 (*J*=4, 9)	6.72 (*J*=4)	8.42	7.17

Table 6. Sodium 3-[2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-substituted-2-azetidinone-1-sulfonate derivatives (**6**).

Compound	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	NMR (DMSO-d_6, δ)		
			C(3)-H 1H, dd (Hz)	C(4)-H 1H, d (Hz)	Thiazole-5H 1H, s
6Aa	73	1780, 1750	4.77 (*J*=2, 9)	6.10 (*J*=2)	7.34
6Bb	67	1785	5.71 (*J*=5, 9)	5.15 (*J*=5)	7.53
6Ac	42	1765	4.71 (*J*=2, 8)	4.79 (*J*=2)	7.40
6Bc[a]	63	1765	5.50 (*J*=4)	5.26 (*J*=4)	7.65
6Ad	47	1765	4.66 (*J*=3, 8)	4.80 (*J*=3)	7.38
6Bd	65	1792	5.35 (*J*=6, 9)	5.16 (*J*=6)	7.51
6Ae	77	1763	4.74 (*J*=2, 8)	5.01 (*J*=2)	7.40
6Be	77	1778	5.37 (*J*=5, 8)	5.36 (*J*=5)	7.49
6Af	64	1765	4.55 (*J*=3, 8)	4.98 (*J*=3)	7.29
6Ag	59	1770	4.95 (*J*=2, 8)	5.33 (*J*=2)	7.44
6Bg	67	1770	5.34 (*J*=5, 8)	5.87 (*J*=5)	7.70
6Ah	71	1775	4.57 (*J*=2, 8)	5.22 (*J*=2)	7.46
6Bh	68	1780	5.22 (*J*=4, 8)	5.45 (*J*=4)	7.43
6Ai[a]	41	1762	4.92 (*J*=2)	5.25 (*J*=2)	7.65
6Bi	44	1765	5.41 (*J*=5, 8)	5.18 (*J*=5)	7.54
6Bj[b]					
6Bk	87	1790	5.72 (*J*=5, 8)	7.11 (*J*=5)	7.14

[a] DMSO-d_6+D_2O, [b] not isolated.

5 (1 mM) in anhydrous DMF (2 ml). After being kept standing at 0°C for 1~3 days, pyridine (3 mM) was added to this solution and then the solvent was evaporated under reduced pressure. The residue, after washed with Et_2O, was dissolved in 50% aq EtOH (20 ml) and treated with Dowex 50W ion exchange resin (N^+-form, 10 ml) at room temp for 1 hour. The resin was filtered off and the filtrate

Table 7. Sodium 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-substituted-2-azetidinone-1-sulfonate derivatives (**7**).

Compound	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	NMR (DMSO-d_6, δ)		
			C(3)-H 1H, dd (Hz)	C(4)-H 1H, d (Hz)	Thiazole-5H 1H, s
7Aa	65	1780, 1770	4.71 (J=2, 8)	6.07 (J=2)	6.71
7Bb	61	1782	5.70 (J=5, 8)	5.16 (J=5)	6.98
7Ac	45	1765	4.68 (J=2, 8)	4.74 (J=2)	6.70
7Bc[a]	25	1760	5.43 (J=4)	5.23 (J=4)	7.03
7Ad	36	1765	4.62 (J=3, 8)	4.81 (J=3)	6.66
7Bd	44	1765	5.32 (J=6, 8)	5.14 (J=6)	6.90
7Ae	60	1763	4.67 (J=2, 8)	4.98 (J=2)	6.70
7Be	32	1767	5.88 (J=5, 8)	5.28 (J=5)	6.85
7Af	64	1768	4.52 (J=3, 9)	4.99 (J=3)	6.58
7Ag	35	1768	4.90 (J=2, 8)	5.33 (J=2)	6.79
7Bg	19	1770			
7Ai	66	1757	4.71 (J=2, 9)	4.98 (J=2)	6.75
7Bi	62	1765	5.24~5.50 (m)		6.88
7Bj	60	1795	5.67 (m)	6.57 (J=5)	6.13
7Bk	65	1785	5.65 (J=5, 8)	7.06 (J=5)	6.30

[a] DMSO-d_6+D_2O.

was concd under reduced pressure. The residue was purified by column chromatography on Amberlite XAD-2 to give **6** as a powder (Table 6).

Sodium 3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-substituted-2-azetidinone-1-sulfonate Derivatives (**7**)

General Procedure: To a solution of **6** (1 mM) in 50% aq MeOH (20 ml) was added sodium *N*-methyldithiocarbamate (1.2~1.5 mM) at 0°C. After the mixture was stirred at room temp for 50 minutes, MeOH was removed under reduced pressure. The separated precipitate was filtered off and the filtrate was purified by column chromatography on Amberlite XAD-2 to afford **7** as a powder (Table 7).

Sodium (3*S*,4*S*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-azido-2-azetidinone-1-sulfonate (**7Bh**): A solution of diphosgene (0.195 ml) in CH_2Cl_2 (2 ml) was added dropwise at 0°C to a solution of DMF (0.748 g) in CH_2Cl_2 (15 ml). After being stirred at room temp for 30 minutes, a mixture of 2-(2-formamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid[15] (0.687 g) and triethylamine (0.355 g) in CH_2Cl_2 (15 ml) was added to the solution at −78°C. The mixture was stirred at −25~−20°C for 1.5 hours and then cooled to −78°C. To the resulting solution were added triethylamine (0.658 g), **3Bh** [which was prepared by reaction of (3*S*,4*R*)-4-azido-3-tritylamino-2-azetidinone (**2Bh**) (0.924 g) with *p*-toluenesulfonic acid monohydrate (0.547 g)] and propylene oxide (2 ml). The mixture was allowed to warm up to room temp for 1 hour and evaporated under reduced pressure. The residue was treated with CH_2Cl_2 to give (3*S*,4*R*)-4-azido-3-[2-(2-formamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone (**9Bh**) (0.658 g, 77.9%) as a powder: IR (KBr) 3230, 2102, 1770, 1660, 1540, 1280, 1048 cm^{-1}; NMR (DMSO-d_6) δ 3.91 (3H, s), 5.20~5.40 (2H, m), 7.40 (1H, s), 8.50 (1H, s), 9.02 (1H, s), 9.54 (1H, d, J=8 Hz).

According to the procedure employed for the conversion of **5** to **6**, **9Bh** (0.60 g) was sulfonated to afford sodium (3*S*,4*S*)-4-azido-3-[2-(2-formamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone-1-sulfonate (**10Bh**) (0.60 g, 76.4%): IR (KBr) 3480, 3280, 2112, 1775, 1660, 1540, 1280, 1248, 1053 cm^{-1}; NMR (DMSO-d_6) δ 3.90 (3H, s), 5.21 (1H, dd, J=5, 8 Hz), 5.45 (1H, d, J=5 Hz), 7.42 (1H, s), 8.50 (1H, s), 9.50 (1H, d, J=8 Hz), 12.55 (1H, s).

To a solution of **10Bh** (0.25 g) in MeOH (2 ml) was added 1 N HCl (1.7 ml) at 0°C. After being stirred at room temp for 2.5 hours, H_2O (5 ml) and sodium hydrogen carbonate (0.144 g) were added

to this solution. Organic solvent was removed under reduced pressure. The residue was purified by column chromatography on Amberlite XAD-2 to give **7Bh** (0.104 g, 44.4%) as a powder: $[\alpha]_D^{25}$ +30.9° (*c* 0.515, H_2O); IR (KBr) 3410, 3315, 3270, 2112, 1780, 1650, 1518, 1265, 1048 cm^{-1}; NMR (DMSO-d_6) δ 3.85 (3H, s), 5.17 (1H, dd, J=5, 8 Hz), 5.44 (1H, d, J=5 Hz), 6.77 (1H, s), 7.18 (2H, s), 9.48 (1H, d, J=8 Hz).

Anal Calcd for $C_9H_9N_8NaO_8S_2 \cdot 2H_2O$: C 24.11, H 2.92, N 24.99, S 14.30.
Found: C 24.13, H 2.77, N 25.03, S 14.19.

Sodium (3*S*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-azido-2-azetidinone-1-sulfonate (**7Ah**): (3*S*,4*S*)-4-Azido-3-[2-(2-formamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone (**9Ah**) and sodium (3*S*,4*R*)-4-azido-3-[2-(2-formamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone-1-sulfonate (**10Ah**) and the title compound (**7Ah**) were synthesized by a procedure similar to that described for the synthesis of **7Bh**.

9Ah (84.2%): IR (KBr) 3235, 2102, 1772, 1655, 1530, 1268, 1040 cm^{-1}; NMR (DMSO-d_6) δ 3.91 (3H, s), 4.69 (1H, dd, J=2, 8 Hz), 5.16 (1H, d, J=2 Hz), 7.42 (1H, s), 8.51 (1H, s), 9.09 (1H, s), 9.39 (1H, d, J=8 Hz), 12.56 (1H, s).

10Ah (48.8%): IR (KBr) 3475, 3250, 2112, 1775, 1668, 1540, 1275, 1050 cm^{-1}; NMR (DMSO-d_6) δ 3.91 (3H, s), 4.57 (1H, dd, J=2, 8 Hz), 5.25 (1H, d, J=2 Hz), 7.45 (1H, s), 8.51 (1H, s), 9.48 (1H, d, J=8 Hz), 12.56 (1H, s).

7Bh (20.7%): $[\alpha]_D^{25}$ −30.6° (*c* 0.265, H_2O); IR (KBr) 3420, 3300, 2115, 1778, 1665, 1615, 1525, 1275, 1250, 1052 cm^{-1}; NMR (DMSO-d_6) δ 3.85 (3H, s), 4.51 (1H, dd, J=2, 8 Hz), 5.23 (1H, d, J=2 Hz), 6.78 (1H, s), 7.17 (2H, br s), 9.36 (1H, d, J=8 Hz).

(*Z*)-2-[2-(2-Trimethylsilylethoxycarbonyl)prop-2-oxyimino]-2-(2-tritylaminothiazol-4-yl)acetic Acid Monohydrochloride (**18**)

To a solution of *p*-nitrobenzyl (*Z*)-2-hydroxyimino-2-(2-tritylaminothiazol-4-yl)acetate (**11**) (28.3 g) in DMF (100 ml) were added potassium carbonate (13.8 g) and 2-trimethylsilylethyl 2-bromo-2-methylpropanoate (**17**) (16 g). After being stirred at room temp for 2 hours, the mixture was partitioned between EtOAc (500 ml) and ice-water (800 ml). The organic layer was washed with H_2O (200 ml×3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column and eluted with a mixture of EtOAc - CH_2Cl_2 (1: 6) to give *p*-nitrobenzyl 2-[2-(2-trimethylsilylethoxycarbonyl)prop-2-oxyimino]-(*Z*)-2-(2-tritylaminothiazol-4-yl)acetate (27.75 g, 73.9%): IR (KBr) 3400, 2948, 1735, 1520, 1345, 1282, 1166 cm^{-1}.

A mixture of *p*-nitrobenzyl 2-[2-(2-trimethylsilylethoxycarbonyl)prop-2-oxyimino]-(*Z*)-2-(2-tritylaminothiazol-4-yl)acetate (20 g) and 10% palladium carbon (4.5 g) in THF (200 ml) was stirred under a H_2 gas atmosphere at room temp for 3 hours. Then 10% palladium carbon (2.5 g) was added and the mixture was stirred under a H_2 atmosphere for additional 4 hours. The catalyst was filtered off and the filtrate was concd under reduced pressure. The residue was partitioned between EtOAc (200 ml) and 1 N HCl (500 ml). The organic layer was washed with brine (200 ml), dried ($MgSO_4$) and evaporated. The resulting residue was treated with Et_2O to afford **18** (14.76 g, 85%) as a powder: IR (KBr) 3060, 2950, 1735, 1590, 1535, 1156, 1140 cm^{-1}.

(*Z*)-2-(2-Trimethylsilylethoxycarbonyl)methoxyimino-2-(2-tritylaminothiazol-4-yl)acetic Acid Monohydrochloride (**13**)

The title compound (**13**) was prepared in 65% yield in analogous way described above using 2-trimethylsilylethyl 2-bromoacetate (**12**): IR (KBr) 3060, 2950, 1755, 1730, 1595, 1570, 1247, 1185 cm^{-1}.

(3*S*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-carboxymethoxyiminoacetamido]-4-azido-2-azetidinone-1-sulfonic Acid (**16Ah**)

To a solution of **13** (1.37 g) in DMF (8 ml) were added pyridine (0.174 g), HOBT (0.337 g) and DCC (0.496 g). After the mixture was stirred at room temp for 1 hour, pyridine (0.174 g) and **3Ah** [which was prepared by reaction of **2Ah** (0.739 g) with *p*-toluenesulfonic acid monohydrate (0.418 g)] were added to the suspension and then the resulting mixture was stirred at room temp for 20 hours. Insoluble material was filtered off and the filtrate was concd under reduced pressure to give a residue,

which was chromatographed on silica gel and eluted with a mixture of EtOAc - hexane (2: 3) to give (3*S*,4*S*)-4-azido-3-[(*Z*)-2-(2-trimethylsilylethoxycarbonyl)methoxyimino-2-(2-tritylaminothiazol-4-yl)-acetamido]-2-azetidinone (**14Ah**) (1.11 g, 79.6%) as a powder: IR (KBr) 3270, 2955, 2110, 1782, 1740, 1680, 1527, 1250 cm^{-1}; NMR (DMSO-d_6) δ 0.04 (9H, s), 0.97 (2H, t, J=8 Hz), 4.18 (2H, t, J=8 Hz), 4.55 (1H, dd, J=2, 8 Hz), 4.60 (2H, s), 4.91 (1H, d, J=2 Hz), 6.87 (1H, s), 7.17~7.40 (15H, m), 8.74 (1H, s), 8.99 (1H, s), 9.12 (1H, d, J=8 Hz).

According to the procedure employed for the conversion of **5** to **6**, **14Ah** (1.0 g) was sulfonated to afford sodium (3*S*,4*R*)-4-azido-3-[(*Z*)-2-(2-trimethylsilylethoxycarbonyl)methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonate (**15Ah**) (0.671 g, 58.8%) as a powder: IR (KBr) 3410, 2115, 1780, 1735, 1675, 1528, 1270, 1250, 1052 cm^{-1}; NMR (DMSO-d_6) δ 0.05 (9H, s), 0.98 (2H, t, J=8 Hz), 4.19 (2H, t, J=8 Hz), 4.46 (1H, dd, J=2, 8 Hz), 4.62 (2H, s), 5.18 (1H, d, J=2 Hz), 6.78 (1H, s), 7.19~7.46 (15H, m), 8.78 (1H, s), 9.28 (1H, d, J=8 Hz).

Tetrabutylammonium fluoride trihydrate (0.52 g) was added to a solution of **15Ah** (0.60 g) in DMF (5 ml) at room temp. The mixture was stirred at room temp for 40 minutes and concd under reduced pressure. The residue was partitioned between EtOAc and H_2O. Evaporation of the organic layer gave a residue which was dissolved in 50% aq MeOH (50 ml). To this solution was added Dowex 50W ion exchange resin (H^+ form, 30 ml). The resulting suspension was stirred at room temp for 3 hours. The resin was filtered off and the filtrate was concd under reduced pressure to give a residue, which was purified by column chromatography on Amberlite XAD-2 (5% aq EtOH as eluant) to afford **16Ah** (0.149 g, 46%) as a powder: $[\alpha]_D^{25}$ −79.2° (*c* 0.255, DMSO); IR (KBr) 3300, 3120, 2120, 1778, 1660, 1630, 1250, 1045 cm^{-1}; NMR (DMSO-d_6) δ 4.56 (1H, d, J=2, 8 Hz), 4.70 (2H, s), 5.29 (1H, d, J=2 Hz), 7.04 (1H, s), 9.53 (1H, d, J=8 Hz).

Anal Calcd for $C_{10}H_{10}N_8O_5S_2 \cdot H_2O$: C 26.55, H 2.67, N 24.77.
Found: C 26.47, H 2.87, N 24.55.

(3*S*,4*S*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-carboxymethoxyiminoacetamido]-4-azido-2-azetidinone-1-sulfonic Acid (**16Bh**)

(3*S*,4*R*)-4-Azido-3-[(*Z*)-2-(2-trimethylsilylethoxycarbonyl)methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone (**14Bh**) and sodium (3*S*,4*S*)-4-azido-3-[(*Z*)-2-(2-trimethylsilylethoxycarbonyl)methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonate (**15Bh**) and the title compound (**16Bh**) were prepared in an analogous way described above.

14Bh (74.8%): IR (KBr) 3275, 2950, 2110, 1785, 1735, 1680, 1515, 1250 cm^{-1}; NMR (DMSO-d_6) δ 0.05 (9H, s), 0.98 (2H, t, J=8 Hz), 4.19 (2H, t, J=8 Hz), 4.60 (2H, s), 5.28 (1H, dd, J=4, 8 Hz), 5.33 (1H, d, J=4 Hz), 6.76 (1H, s), 7.18~7.43 (15H, m), 8.74 (1H, s), 8.98 (1H, s), 9.31 (1H, d, J=8 Hz).

15Bh (57.4%): IR (KBr) 3375, 2125, 1775, 1690, 1525, 1285, 1250, 1052 cm^{-1}; NMR (DMSO-d_6) δ 0.06 (9H, s), 1.00 (2H, t, J=8 Hz), 4.20 (2H, t, J=8 Hz), 4.62 (2H, s), 5.14 (1H, dd, J=5, 8 Hz), 5.45 (1H, d, J=5 Hz), 6.81 (1H, s), 7.20~7.46 (15H, m), 8.85 (1H, s), 9.28 (1H, d, J=8 Hz).

16Bh (52.5%): $[\alpha]_D^{25}$ +53.0° (*c* 0.30, DMSO); IR (KBr) 3280, 3110, 2115, 1771, 1670, 1635, 1275~1250, 1042 cm^{-1}; NMR (DMSO-d_6) δ 4.70 (2H, s), 5.20 (1H, dd, J=5, 8 Hz), 5.54 (1H, d, J=5 Hz), 7.70 (1H, s), 9.56 (1H, d, J=8 Hz).

Anal Calcd for $C_{10}H_{10}N_8O_5S_2 \cdot H_2O$: C 26.55, H 2.67, N 24.77, S 14.17.
Found: C 26.57, H 2.90, N 24.61, S 13.50.

(3*R*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(2-carboxyprop-2-oxyimino)acetamido]-4-carbamoylmethylthio-2-azetidinone-1-sulfonic Acid (**21Bi**)

(3*R*,4*R*)-4-Carbamoylmethylthio-3-[(*Z*)-2-[2-(2-trimethylsilylethoxycarbonyl)prop-2-oxyimino]-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone (**19Bi**) and sodium (3*R*,4*R*)-4-carbamoylmethylthio-3-[(*Z*)-2-[2-(2-trimethylsilylethoxycarbonyl)prop-2-oxyimino]-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonate (**20Bi**) and the title compound (**21Bi**) were obtained by a procedure similar to that described for the synthesis of **16Ah**.

19Bi (62.5%): IR (KBr) 3280, 2955, 1772, 1735, 1675, 1528 cm^{-1}; NMR (DMSO-d_6) δ 0.03 (9H, s), 0.95 (2H, m), 1.41 (6H, s), 3.15 (2H, s), 4.13 (2H, m), 5.11 (1H, dd, J=5 Hz), 5.33 (1H, dd,

J=5, 8 Hz), 6.79 (1H, s), 7.16~7.50 (15H, m), 8.75 (1H, s), 9.12 (1H, d, J=8 Hz).

20Bi (16.4%): IR (KBr) 3440~3380, 1765, 1725, 1670, 1520, 1275, 1248, 1045 cm^{-1}; NMR (DMSO-d_6) δ 0.03 (9H, s), 0.95 (2H, m), 1.74 (6H, s), 3.40 (2H, ABq, J=11, 17 Hz), 4.14 (2H, m), 5.17~5.43 (2H, m), 6.78 (1H, s), 7.15~7.50 (15H, m), 8.74 (1H, s), 9.23 (1H, m).

21Bi (66.8%): IR (KBr) 3440~3300, 1770, 1660, 1280~1240, 1150, 1050 cm^{-1}; NMR (DMSO-d_6) δ 1.43 (3H, s), 1.45 (3H, s), 3.41 (2H, ABq, J=13, 18 Hz), 5.27~5.55 (2H, m), 6.82 (1H, s), 7.05 (1H, s), 7.17 (2H, s), 7.46 (1H, s), 9.83 (1H, d, J=8 Hz).

Anal Calcd for $C_{14}H_{18}N_6O_9S_3 \cdot 4H_2O$: C 28.86, H 4.50, N 14.43, S 16.51.
Found: C 28.92, H 3.86, N 14.27, S 16.09.

Sodium (3*S*,4*S*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(2-carboxyprop-2-oxyimino)acetamido]-4-azido-2-azetidinone-1-sulfonate (**21Bh**)

(3*S*,4*R*)-4-Azido-3-[(*Z*)-2-[2-(2-trimethylsilylethoxycarbonyl)prop-2-oxyimino]-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone (**19Bh**) and sodium (3*S*,4*S*)-4-azido-3-[(*Z*)-2-[2-(2-trimethylsilylethoxycarbonyl)prop-2-oxyimino]-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonate (**20Bh**) were synthesized by a procedure similar to that described for the synthesis of **16Ah**.

19Bh (58.3%): IR (KBr) 3350~3280, 2112, 1780, 1730, 1675, 1520 cm^{-1}; NMR ($CDCl_3$) δ 0.03 (9H, s), 0.97 (2H, t, J=9 Hz), 1.95 (3H, s), 1.97 (3H, s), 4.21 (2H, t, J=9 Hz), 5.33 (1H, d, J=4 Hz), 5.56 (1H, dd, J=4, 8 Hz), 6.75 (1H, s), 6.83 (1H, s), 6.93 (1H, s), 7.31 (15H, m), 8.15 (1H, d, J=8 Hz).

20Bh (74%): IR (KBr) 3380, 2115, 1778, 1728, 1676, 1512, 1282, 1245, 1050 cm^{-1}; NMR (DMSO-d_6) δ 0.05 (9H, s), 0.95 (2H, t, J=8 Hz), 1.40 (3H, s), 4.13 (2H, t, J=8 Hz), 5.14 (1H, dd, J=5, 8 Hz), 5.44 (1H, d, J=5 Hz), 6.70 (1H, s), 7.15~7.53 (15H, m), 8.73 (1H, s), 9.08 (1H, d, J=8 Hz).

To a solution of **20Bh** (0.30 g) in DMF (3 ml) was added tetrabutylammonium fluoride trihydrate (0.34 g) at 0°C. After being stirred at room temp for 30 minutes, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with H_2O. Evaporation of the solvent gave a residue, to which MeOH (4 ml) and 1 N HCl (2.67 ml) were added. The mixture was stirred at room temp for 4 hours. To this solution were added MeOH (10 ml) and Dowex 50W ion exchange resin (Na^+ form, 30 ml) at room temp. After 1 hour, the resin (20 ml) was added and the suspension was stirred for additional 1 hour. The resin was filtered off and the filtrate was concd under reduced pressure to give a residue, which was purified by column chromatography on Amberlite XAD-2 to afford **21Bh** (0.089 g, 51%) as a powder: $[\alpha]_D^{25}$ +19.0° (c 0.29, H_2O); IR (KBr) 3400, 2120, 1780, 1662, 1585, 1530, 1276, 1260, 1055 cm^{-1}; NMR (DMSO-d_6) δ 1.43 (3H, s), 1.46 (3H, s), 5.27 (1H, dd, J=5, 8 Hz), 5.56 (1H, d, J=5 Hz), 6.74 (1H, s), 7.14 (2H, s), 10.99 (1H, d, J=8 Hz).

Anal Calcd for $C_{12}H_{13}N_5NaO_9S_2 \cdot 4H_2O$: C 25.90, H 3.77, N 20.13.
Found: C 25.37, H 3.67, N 19.97.

Sodium (3*S*,4*R*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(2-carboxyprop-2-oxyimino)acetamido]-4-azido-2-azetidinone-1-sulfonate (**21Ah**)

(3*S*,4*S*)-4-Azido-3-[(*Z*)-2-[2-(2-trimethylsilylethoxycarbonyl)prop-2-oxyimino]-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone (**19Ah**) and sodium (3*S*,4*R*)-4-azido-3-[(*Z*)-2-[2-(2-trimethylsilylethoxycarbonyl)prop-2-oxyimino]-2-(2-tritylaminothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonate (**20Ah**) and the title compound (**21Ah**) were prepared in an analogous way described above.

19Ah (73.7%): IR (KBr) 3290, 2105, 1785, 1730, 1678, 1522, 1150 cm^{-1}; NMR (DMSO-d_6) δ 0.03 (9H, s), 0.94 (2H, t, J=8 Hz), 1.40 (6H, s), 4.13 (2H, t, J=8 Hz), 4.57 (1H, dd, J=2, 8 Hz), 4.92 (1H, d, J=2 Hz), 6.70 (1H, s), 7.10~7.50 (15H, m), 8.74 (1H, s), 8.98 (1H, d, J=8 Hz), 9.00 (1H, s).

20Ah (72%): IR (KBr) 3360, 2110, 1782, 1730, 1662, 1522, 1250, 1182, 1150, 1050 cm^{-1}; NMR (DMSO-d_6) δ 0.03 (9H, s), 0.95, (2H, t, J=8 Hz), 1.46 (6H, s), 4.14 (2H, t, J=8 Hz), 4.48 (1H, dd, J=2, 8 Hz), 5.15 (1H, d, J=2 Hz), 6.70 (1H, s), 7.15~7.50 (15H, m), 8.40 (1H, s), 9.08 (1H, d, J=8 Hz).

21Ah (64%): $[\alpha]_D^{25}$ −26.4° (c 0.235, H_2O); IR (KBr) 3390, 2115, 1775, 1655, 1585, 1525, 1270, 1245, 1052 cm^{-1}; NMR (DMSO-d_6) δ 1.43 (6H, s), 4.61 (1H, dd, J=2, 8 Hz), 5.18 (1H, d, J=2 Hz),

6.76 (1H, s), 7.14 (2H, s), 11.42 (1H, d, J=8 Hz).

Anal Calcd for $C_{12}H_{13}N_8NaO_8S_2 \cdot 4H_2O$: C 25.90, H 3.77, N 20.13.
Found: C 25.85, H 3.64, N 20.19.

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References

1) MATSUO, T.; T. SUGAWARA, H. MASUYA, Y. KAWANO, N. NOGUCHI & M. OCHIAI: Synthesis and antibacterial activity of 3-acylamino-2-azetidinone-1-sulfonic acid derivatives. Chem. Pharm. Bull. 31: 1874~1884, 1983
2) MATSUO, T.; H. MASUYA, T. SUGAWARA, Y. KAWANO, N. NOGUCHI & M. OCHIAI: Synthesis and antibacterial activity of 3-acylamino-3-methoxy-2-azetidinone-1-sulfonic acid derivatives. Chem. Pharm. Bull. 31: 2200~2208, 1983
3) KISHIMOTO, S.; M. SENDAI, S. HASHIGUCHI, M. TOMIMOTO, Y. SATOH, T. MATSUO, M. KONDO & M. OCHIAI: Synthesis of sulfazecin-type 2-azetidinones with a carbon substituent at the 4-position. J. Antibiotics 36: 1421~1424, 1983
4) SYKES, R. B.; D. P. BONNER, K. BUSH & N. H. GEORGOPAPADAKOU: Azthreonam (SQ 26,776), a synthetic monobactam specifically active against aerobic Gram-negative bacteria. Antimicrob. Agents Chemother. 21: 85~92, 1982
5) BRAIN, E. G.; J. EGLINGTON, J. H. C. NAYLER, M. J. PEARSON & R. SOUTHGATE: Syntheses based on 1,2-secopenicillins. 1. Oxidation. J. Chem. Soc. Perkin I 1976: 447~451, 1976
6) MATSUO, T.; H. MASUYA, N. NOGUCHI & M. OCHIAI (Takeda Chemical Ind., Ltd.): 2-Oxoazetidine derivatives, their production and use. Japan Kokai 57-131,759, 1982
7) BEVILACQUA, P. & J. L. ROBERTS: Studies on the reactivity of 4-acetoxy-3-acylamino-2-azetidinones: Stereospecific *trans* carbon-carbon bond formation. Syn. Commn. 13: 797~808, 1983
8) WILLNER, D.; A. M. JELENEVSKY & L. C. CHENEY: Cyclo-addition of acetylenes to 7-acylamino-3-azidomethyl-3-cephem-4-carboxylic acid. J. Med. Chem. 15: 948~951, 1972
9) OCHIAI, M.; A. MORIMOTO, T. MIYAWAKI, Y. MATSUSHITA, T. OKADA, H. NATSUGARI & M. KIDA: Synthesis and structure-activity relationships of 7β-[2-(2-aminothiazol-4-yl)acetamido]cephalosporin derivatives. V. Synthesis and antibacterial activity of 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-cephalosporin derivatives and related compounds. J. Antibiotics 34: 171~185, 1981
10) FLOYD, D. M.; A. W. FRITZ, J. PLUSCEC, E. R. WEAVER & C. M. CIMARUSTI: Monobactams. Preparation of (*S*)-3-amino-2-oxoazetidine-1-sulfonic acids from L-α-amino-β-hydroxy acid *via* their hydroxamic esters. J. Org. Chem. 47: 5160~5167, 1982
11) GERLACH, H.: 2-(Trimethylsilyl)äthylester als Carboxylschutzgruppe; Anwendung bei der Synthese des (−)-(*S*)-Curvularins. Helv. Chim. Acta 60: 3039~3044, 1977
12) CIMARUSTI, C. M. & R. B. SYKES: Monocyclic β-lactam antibiotics. Med. Res. Rev. 4: 1~24, 1984
13) SUARATO, A.; P. LOMBARDI, C. GALLIANI & G. FRANCESCHI: A new rout to optically active 4-acyloxy azetidin-2-ones. Tetrahedron Lett. 1978: 4059~4062, 1978
14) CLAUSS, K.; D. GRIMM & G. PROSSEL: β-Lactam mit über Heteroatome gebundenen Substituenten. Ann. Chem. 1974: 539~560, 1974
15) TAKAYA, T.; H. TAKASUGI, T. MASUGI, T. CHIBA, H. KOCHI, T. TAKANO & H. NAKANO: Structure-activity relationships of sodium 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate (ceftizoxime) and its related compounds. Nippon Kagaku Kaishi 1981: 785~804, 1981