STUDIES ON MONOCYCLIC β-LACTAM ANTIBIOTICS

II. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 3-ACYLAMINO-2-AZETIDINONE-1-OXYSULFONIC ACIDS

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The synthesis and *in vitro* antibacterial and β-lactamase inhibitory activity of the 2-azetidinone-1-oxysulfonic acids having a substituent at C-4 position of the β-lactam ring are described. The influence of C-4 substituents on the antibacterial activity was examined for the compounds having α-ureidoacetyl or α-oxyiminoacetyl group as acyl side chain at C-3 position. The antibacterial activity is correlated with the C-4 substituents and acyl side chain. Especially, 4(*R*)-methyl substituted derivatives exhibited excellent activity against Gram-negative bacteria and 4-dimethyl substituted derivatives exhibited strong activity against resistant Gram-negative bacteria except for *Pseudomonas aeruginosa*. **39** and **40** showed strong inhibitory activity against cephalosporinase of *Enterobacter cloacae* H-27.

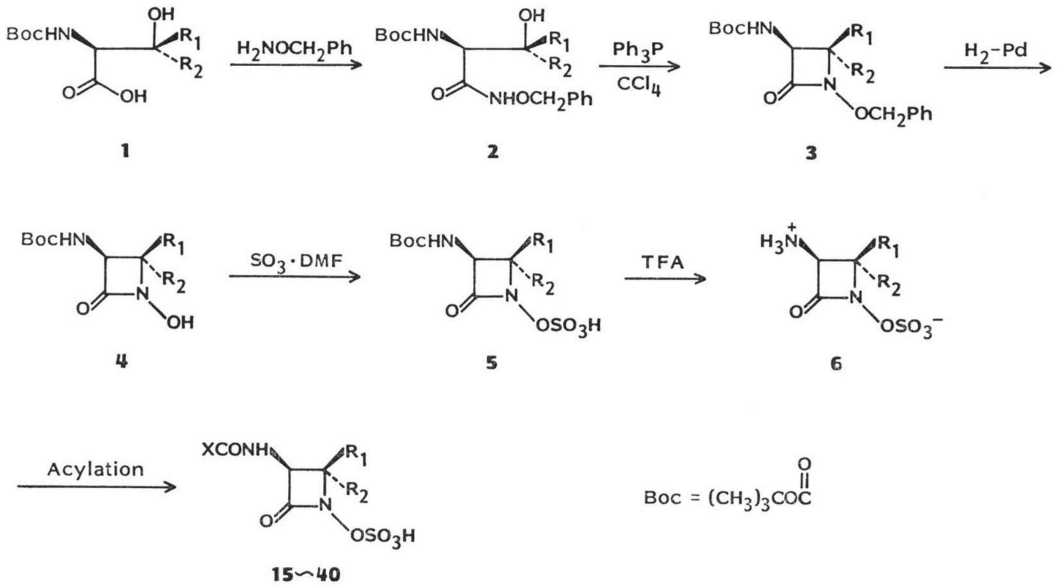
Since the discovery of monocyclic β-lactam antibiotics represented by nocardicin[1] and sulfazecin[2,3] and monobactam[4,5], many of their derivatives have been reported. As a general characteristic of them, they showed strong activity against Gram-negative bacteria and excellent stability against β-lactamase. However, they showed weak activity against Gram-positive bacteria. To overcome this insufficiency, various chemical modifications have been tried at N-1, C-3 and C-4 position of β-lactam. SYKES *et al.*[6,7], and we have independently reported the synthesis and antibacterial activity of the title compounds in a patent literature[8]. In this paper, we report the chemical modification at C-3 and C-4 position, and the interesting results of antibacterial activity and β-lactamase inhibitory activity as well.

Chemistry

Our objective compounds, 3-acylamino-2-azetidinone-1-oxysulfonic acids (**12**, **14**~**40**), were synthesized by the route shown in Schemes 1 and 2. A general synthetic method of β-lactam from β-hydroxyl amino acid through cyclization has already been established by MILLER *et al.*[9]. We modified the method and applied it to the synthesis of 3-*tert*-butoxycarbonyl-1-hydroxy-2-azetidinones (**4**).

Mixed anhydride of *N*-Boc-β-hydroxyamino acids (**1**) coupled with ethylchloroformate was reacted with *O*-benzylhydroxylamine to give hydroxamates (**2**) in good yield. Then, the hydroxamates were cyclized with carbon tetrachloride (CCl_4)-triphenylphosphine (Ph_3P) to give β-lactams (**3**). Since optically inactive amino acids were used as starting materials, the obtained β-lactams (**3e**~**3i**) were a mixture of two diastereomers. *Cis* form (**3e, 3g, 3j**) and *trans* form (**3f, 3h, 3i**) were easily isolated by recrystallization or column chromatography on silica gel. However, the *cis* isomer represented by **3j** was not formed in this cyclization reaction. 1-Hydroxy-2-azetidinones (**4**) were quantitatively ob-

Scheme 1.



1 2 3 4 5 6

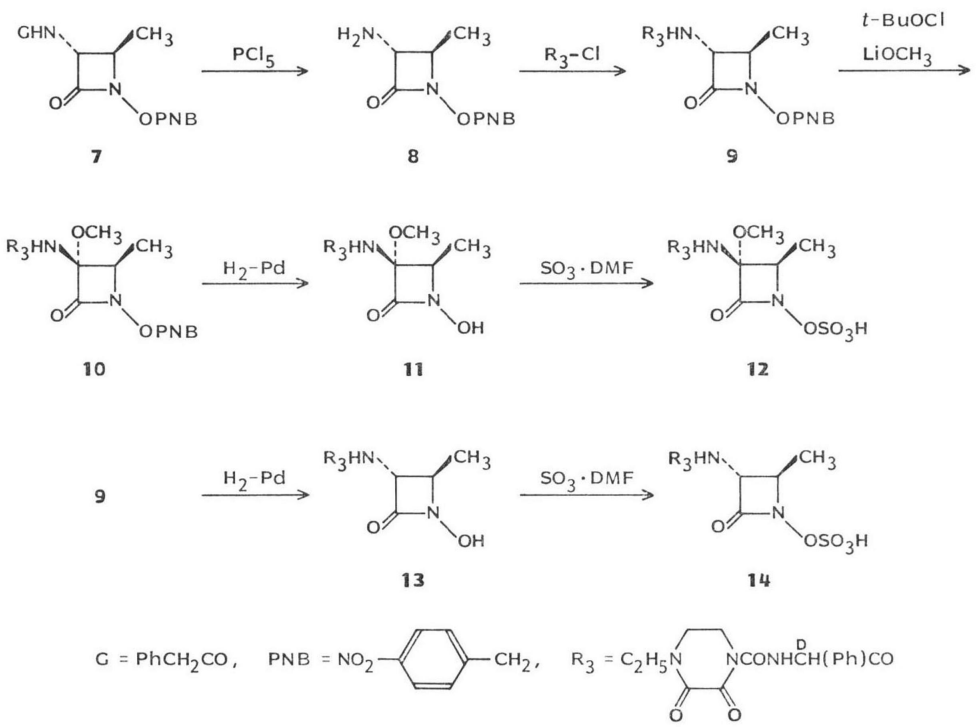
15~40

	a	b	c	d	C-3 *dl*-mixture					
					e	f	g	h	i	j
R_1	H	H	CH_3	CH_3	C_2H_5	H	$CH(CH_3)_2$	H	H	Ph
R_2	H	CH_3	H	CH_3	H	C_2H_5	H	$CH(CH_3)_2$	Ph	H

tained from compounds **3** by hydrogenolysis of benzyl group in MeOH over 5% Pd-C catalyst. **4** was reacted with sulfur trioxide-DMF complex in DMF under ice-cooling for 30 minutes to afford 2-azetidinone-1-oxysulfonic acids (**5**), and subsequently *N*-Boc group was removed by trifluoroacetic acid in dichloromethane under ice-cooling to afford 3-amino-2-azetidinone-1-oxysulfonic acids (**6**), forming zwitterion. However, **6g** was not obtained in good yield, so that we were not able to proceed further steps. After **6** were converted to triethylammonium salts, acyl side chain conventionally employed for semi-synthetic penicillins and cephalosporins were introduced to the amino group of **6** with a condensing agent, for example, *N,N*-dicyclohexylcarbodiimide (DCC). Then, triethylammonium salts of 3-acylamino derivatives were purified by column chromatography on silica gel and converted to sodium salt by Dowex-50W (Na^+ form) or $NaHCO_3$, and then sodium salts were further purified by Amberlite XAD-2 column chromatography. Thus, 3-acylamino-2-azetidinone-1-oxysulfonic acids (**15~40**), as shown in Tables 1~3, were obtained.

On the other hand, we also explored the method[10] to introduce the methoxy group at C-3 position of monobactam derivative. We synthesized **12** by the route shown in Scheme 2. β-Lactam (**7**) (3*R*,4*R*) ($[\alpha]_D$ +20.4°) was synthesized in a similar manner as shown in Scheme 1 using D-threonine as a starting material. Chirality of C-3 and C-4 position of β-lactam (**7**) was determined by NMR spectrum and also from the fact that epimer (3*S*,4*S*) synthesized from L-threonine showed $[\alpha]_D$ −19.25°. **7** was deacylated with phosphorus pentachloride in a conventional manner, and then, it was acylated with α-(ureido)phenylacetyl chloride (R_3=Cl) to afford **9**. **9** was reacted with *tert*-butylhypochlorite and lithium methoxide to afford **10**. Subsequently, PNB group was removed by hydrogenolysis, and

Scheme 2.



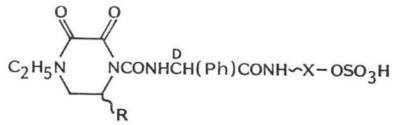
compound **11** thus obtained was reacted with sulfur trioxide-DMF complex in a conventional manner to afford **12**. The chemical structure of thus obtained compounds (**12**, **14**~**40**) were confirmed by IR and NMR spectra.

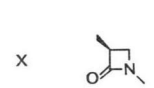
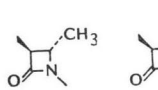
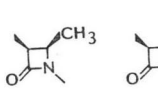
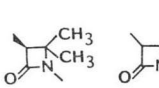
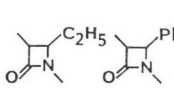
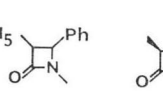
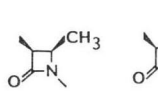
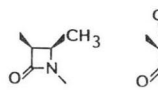
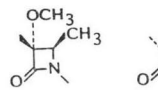
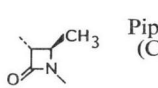
Biological Results and Discussion

The minimum inhibitory concentrations (MICs) of the 3-acylamino-2-azetidinone-1-oxysulfonic acids (**12**, **14**~**40**) against several Gram-positive and Gram-negative bacteria are shown in Tables 1~3. Piperacillin (PIPC)[11] and aztreonam[12] were used as reference compounds. Table 1 shows the structure-activity relationships of 3-(α-ureido)acetamido-2-azetidinone-1-oxysulfonic acids in terms of substitution effect and configuration at C-3 and C-4 position. In this study, there was adopted the same acyl group as that used at 6-position of PIPC.

17, **21** and **22** with 4(R) configuration showed the most excellent activity against Gram-positive bacteria, however, despite of the increase of lipophilicity, **18**, **19** and **20** showed less activity. Interestingly, **21** and **22** showed excellent activity against resistant strain *Staphylococcus aureus* F-137. In general, the effect of substituent at C-4 contributed to the increase of antibacterial activity, as shown in this order $CH_3(R) > CH_3(S) > H >$ di $CH_3 > > CH_2CH_3 >$ phenyl. Some of them showed neally the same antibacterial activity against Gram-negative bacteria as PIPC. Among them, **18** with di CH_3 group at C-4 position and **21** with $CH_3(R)$ group at 6-position of piperazine ring showed excellent activity against β-lactamase-producing bacteria. On the other hand, **12** with the methoxy group at C-3 position lost considerably activity against our expectation, and, as expected, **14** with 3(R) configuration did not show any activity.

Table 1. Antibacterial activity (MIC μg/ml) of 3-(α-ureido)acylamino-2-azetidinone-1-oxysulfonic acids.



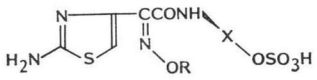
	R	H	H	H	H	H	H	---CH_3	⁻CH_3	H	H	
	X											Piperacillin (Control)
						[3(±)*trans*]						
Organisms[a]		**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**12**	**14**	
S.a. FDA 209P		12.5	6.25	1.56	50	100	>200	1.56	1.56	>200	>200	0.78
E.c. NIHJ JC-2		1.56	0.78	0.78	0.78	1.56	>200	0.78	12.5	12.5	>200	1.56
K.p. Y-50		3.13	0.78	0.78	0.78	1.56	>200	0.78	6.25	50	100	3.13
E.cl. IID 977		6.25	6.25	6.25	3.13	25	>200	12.5	100	12.5	>200	6.25
S.m. IID 620		6.25	3.13	1.56	0.78	3.13	>200	1.56	6.25	50	100	0.78
P.mi. T-111		12.5	1.56	0.78	0.78	6.25	>200	0.78	12.5	100	200	0.78
Ps.a. IFO 3445		25	12.5	6.25	6.25	25	>200	6.25	50	>200	>200	6.25
S.a. F-137*		50	50	12.5	50	200	>200	6.25	3.13	>200	>200	200
E.c. TK-3*		50	12.5	25	25	12.5	>200	6.25	>200	100	>200	>200
E.c. GN 5482**		100	50	50	1.56	100	>200	25	200	12.5	>200	6.25
K.p. Y-4*		50	6.25	12.5	6.25	12.5	>200	6.25	100	>200	>200	50
S.m. W-8**		>200	200	>200	12.5	200	>200	>200	>200	>200	>200	>200
P.v. GN 76**		6.25	0.78	1.56	0.78	3.13	>200	3.13	12.5	6.25	>200	1.56
Ps.a. GN 3379*		50	12.5	6.25	12.5	100	>200	6.25	100	>200	>200	25

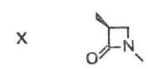
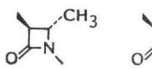
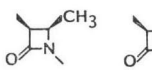
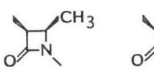
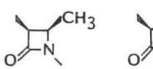
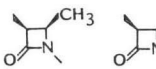
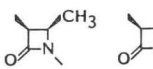
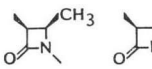
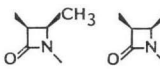
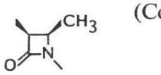
[a] Organisms included in the Table are: *S.a., Staphylococcus aureus*; *E.c., Escherichia coli*; *K.p., Klebsiella pneumoniae*; *E.cl., Enterobacter cloacae*; *S.m., Serratia marcescens*; *P.mi., Proteus mirabilis*; *Ps.a., Pseudomonas aeruginosa*; *P.v., Proteus vulgaris*.

* Penicillinase producer.

** Cephalosporinase producer.

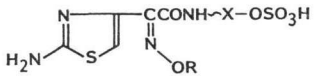
Table 2. Antibacterial activity (MIC μg/ml) of 3-(α-oxyimino)acetamido-2-azetidinone-1-oxysulfonic acids.

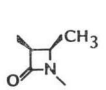
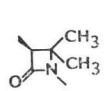
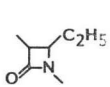
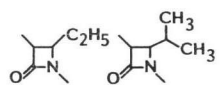
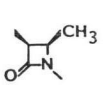
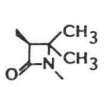
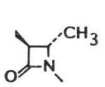
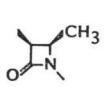


R	CH_3	CH_3	CH_3	H	C_2H_5	$CH(CH_3)_2$	$C(CH_3)_3$		CH_2Ph	Ph	Aztreonam (Control)
X											
Organisms[a]	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	
S.a. FDA 209P	25	50	12.5	1.56	6.25	6.25	6.25	3.13	1.56	3.13	>200
E.c. NIHJ JC-2	1.56	≦0.1	≦0.1	0.78	≦0.1	0.2	0.39	0.39	1.56	1.56	0.2
K.p. Y-50	12.5	0.2	0.2	1.56	0.2	0.2	0.39	0.39	3.13	1.56	≦0.1
E.cl. IID 977	100	12.5	1.56	1.56	3.13	0.78	3.13	3.13	3.13	3.13	3.13
S.m. IID 620	25	0.2	≦0.1	0.78	0.2	0.78	0.78	0.78	6.25	3.13	≦0.1
P.mi. T-111	12.5	0.39	≦0.1	1.56	≦0.1	0.39	0.39	0.78	3.13	1.56	0.1
Ps.a. IFO 3445	50	25	12.5	25	6.25	6.25	6.25	6.25	12.5	6.25	3.13
S.a. F-137*	12.5	50	12.5	1.56	6.25	6.25	6.25	3.13	1.56	3.13	>200
E.c. TK-3*	>200	100	12.5	200	6.25	3.13	6.25	25	25	12.5	≦0.1
E.c. GN 5482**	100	12.5	6.25	6.25	6.25	3.13	3.13	3.13	3.13	6.25	6.25
K.p. Y-4*	100	6.25	3.13	6.25	1.56	1.56	6.25	6.25	12.5	6.25	0.2
S.m. W-8**	>200	>200	25	200	25	12.5	25	6.25	6.25	12.5	6.25
P.v. GN 76**	50	3.13	1.56	25	0.39	0.78	0.78	0.78	1.56	0.39	≦0.1
Ps.a. GN 3379*	100	50	25	50	6.25	6.25	12.5	6.25	25	6.25	6.25

[a] See the footnotes in Table 1.

Table 3. Antibacterial activity (MIC μg/ml) of 3-(α-oxyimino)acetamido-2-azetidinone-1-oxysulfonic acids.



	R	$CH(CH_3)_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	CH_2COOH	CH_2COOH	$C(CH_3)_2COOH$	$C(CH_3)_2COOH$	
	X										Aztreonam (Control)
				[3(±)*cis*]	[3(±)*trans*]						
Organisms[a]		**28**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	
S.a. FDA 209P		6.25	100	100	100	100	200	>200	>200	>200	>200
E.c. NIHJ JC-2		0.2	0.78	1.56	0.78	6.25	0.2	0.39	0.78	0.78	0.2
K.p. Y-50		0.2	0.39	0.78	1.56	3.13	0.2	0.2	0.78	0.78	≦0.1
E.cl. IID 977		0.78	1.56	1.56	6.25	6.25	1.56	0.39	6.25	6.25	3.13
S.m. IID 620		0.78	1.56	3.13	6.25	12.5	≦0.1	≦0.1	0.2	≦0.1	≦0.1
P.mi. T-111		0.39	1.56	3.13	3.13	12.5	≦0.1	≦0.1	≦0.1	≦0.1	≦0.1
Ps.a. IFO 3445		6.25	50	25	100	200	6.25	50	6.25	6.25	3.13
S.a. F-137*		6.25	50	100	50	200	200	>200	>200	>200	>200
E.c. TK-3*		3.13	0.78	12.5	3.13	6.25	3.13	0.39	50	6.25	≦0.1
E.c. GN 5482**		3.13	0.39	6.25	12.5	1.56	25	0.78	50	50	6.25
K.p. Y-4*		1.56	3.13	6.25	6.25	25	1.56	0.78	25	3.13	0.2
S.m. W-8**		12.5	0.39	12.5	12.5	1.56	25	1.56	100	0.2	6.25
P.v. GN 76**		0.78	≦0.1	12.5	0.39	1.56	0.2	≦0.1	3.13	50	≦0.1
Ps.a. GN 3379*		6.25	100	100	100	>200	12.5	100	25	6.25	6.25

[a] See the footnotes in Table 1.

Tables 2 and 3 show the structure-activity relationships of many monocyclic β-lactam derivatives bearing the oxyiminoacetyl side chain which have been often used in conventional cephalosporins. While the substituents at C-4 position being fixed $CH_3(R)$, the substitution effect (H and CH_3) at C-4 position and the effect of lipophilicity of substituents in alkoxyimino group were investigated, and the result is shown in Table 2. The effect of substituents at C-4 position showed that the compound with 4(*R*) configuration, one of *cis* form, showed better result against Gram-positive and Gram-negative bacteria, as shown in the following order 4-$CH_3(R)$>4-$CH_3(S)$>H. As the lipophilicity of alkoxyimino side chain increased, compounds showed stronger activity against *S. aureus* (**30**, **31**, **32**). However, **26** showed excellent activity despite of low lipophilicity. On the other hand, they tended to show stronger antibacterial activity against Gram-negative bacteria in an inverse proportion to the increase of lipophilicity. As compared with α-ureidoacetyl derivatives, α-oxyiminoacetyl derivatives showed a little less effect against Gram-positive bacteria (shown in Table 1), however, possesed relatively broad spectrum of activity against Gram-negative bacteria and resistant strains. Among them, **28** with α-isopropyloxyimino side chain showed the best activity. Then, while α-propyloxyimino, carboxymethoxyimino and 1-carboxy-1-methylethoxyimino group being fixed as a moiety of acyl side chain, the effect of alkyl group at C-4 position was studied on synthesized compounds.

As the chain length of alkyl group at C-4 position extended, all compounds showed less activity against both Gram-positive bacteria and *P. aeruginosa* as shown in Table 1. However, interestingly, **33** and **38** showed excellent antibacterial activity against resistant strains. Replacement of alkyl group with an acidic substituents in compounds (**37**~**40**) contributed to the significant decrease of activity against *S. aureus*, but, to the increase of activity against *Proteus mirabilis* and *Serratia marcescens*. They showed a little less activity against Gram-negative bacterial than aztreonam.

Table 4. β-Lactamase inhibitory activity.

Compound	I_{50} (μg/ml)	
	Cephalosporinase	Penicillinase
39	0.25	>500
40	0.02	>500
Aztreonam	0.02	>500
Sulbactam	14	16

Aztreonam has been reported to have strong β-lactamase inhibitory activity. The inhibitory activity on cephalosporinase and penicillinase, which were produced from *E. cloacae* H-27 and *Escherichia coli* TK-3, respectively, were investigated on compounds *in vitro*, and their respective I_{50} values were determined (Table 4). Two tested compounds (**39**, **40**) showed excellent cephalosporinase inhibitory activity, however, showed no penicillinase inhibitory activity. Antibacterial activity against cephalosporinase producing strains showed no correlation with cephalosporinase inhibitory activity.

Thus, it was found that 3-acylamino-2-azetidinone-1-oxysulfonic acids have several characteristics. Their affinity with PBPs and permeability to membrane remain to be elucidated in further study. It is expected that further studies may lead to the finding of the compound with broader spectrum and strong activity.

Experimental

The reference compounds, aztreonam and sulbactam[13], were synthesized in our laboratory for comparison. Melting points are uncorrected. IR spectra were recorded on a Hitachi model 260-30 Spectrophotometer. NMR spectra were recorded on a Hitachi R-24 (60 MHz) Spectrometer using

TMS as an internal standard. Organic solvents were dried over anhydrous $MgSO_4$, and all concentration and evaporation of solvents were carried out under reduced pressure. Column chromatography was carried out on Wako silica gel (C-200).

Determination of *In Vitro* Antibacterial Activity

All the *in vitro* antibacterial activities are given as the MIC in μg/ml. MICs were determined by the agar dilution method using heart infusion agar (Eiken) after incubation at 37°C for 20 hours and an inoculum size of about 10^4 cfu/ml.

Determination of *In Vitro* β-Lactamase Inhibitory Activity (I_{50} Values)

I_{50} values were determined by the method of MAK *et al*[14]. β-Lactamases were used penicillinase (from *E. coli* TK-3) and cephalosporinase (from *E. cloacae* H-27). Various concentration of inhibitors were mixed with the same volume (about 20~100 μl) of the β-lactamase-liquor. And the mixture were pre-incubated for 5 minutes at 30°C. Further, the mixture was added to 3 ml of 100 μM benzylpenicillin or cephaloridin as the substrate.

Compounds **2(a~c)~5(a~c)** and **6(a~c)** were prepared as reported in the reference[6,7,15,16]. **5a~5c**, **6b**, **15~17**, **23~25** and **39** were reported in the patent literature[7,8].

Preparation of Hydroxamate (**2d**)

To a solution of (L)-*N*-Boc-β-hydroxyvaline (**1d**) (20 g, 85.7 mmol) in CH_2Cl_2 (100 ml) was added *N*-methyl morpholine (9.71 ml, 88.3 mmol) under ice-cooling. $ClCO_2Et$ (8.6 ml, 90 mmol) in CH_2Cl_2 (20 ml) was added dropwise to the resulting solution at −30~−20°C over 15~20 minutes and the mixture was stirred at −20~−15°C for 1 hour. H_2NOCH_2Ph (10.66 g, 86.6 mmol) in CH_2Cl_2 (20 ml) was added dropwise to the resulting mixture at −30~−20°C over 15~20 minutes and the mixture was stirred at −15~5°C for 1 hour. Water (100 ml) was dropped into the reaction mixture, and the mixture was extracted with CH_2Cl_2.

The organic layer was washed successively with saturated $NaHCO_3$ solution and brine, and then dried. The solvent was evaporated to give the residue, which was crystallized from diisopropyl ether to afford **2d** as colorless crystals (26 g, 89.7%). MP 81~83°C. IR $\nu_{C=O}^{KBr}$ 1665 cm^{-1}.

Other hydroxamates (**2e~2i**) were synthesized from the corresponding *N*-Boc amino acid in a similar manner as in **2d**.

General Preparation of β-Lactams (**3**)

To a solution of hydroxamates (**2**) (20 mmol), Ph_3P (40 mmol) and CCl_4 (40 mmol) in CH_3CN (140~160 ml) were added Et_3N (45 mmol) at 35~40°C, and the resulting mixture was stirred at 20~30°C for 1.5 hours. The reaction mixture was evaporated and the residue was dissolved in EtOAc (200 ml). The solution was washed successively with H_2O and brine, and then dried. The solvent was evaporated to give the residue, which was purified by column chromatography on silica gel (benzene - EtOAc, 10: 1) to afford **3**. Results of **3** are summarized in Table 5.

Preparation of 1-Hydroxy-2-azetidinone (**4d**)

β-Lactam (**3d**) (3.6 g, 11.25 mmol) was subjected to hydrogenolysis in MeOH (180 ml) for 30 minutes over 5% Pd-C catalyst (400 mg) at room temp under 5 atmospheric pressure. The catalyst was filtered and washed with MeOH. The combined filtrate was evaporated to give the residue, which was triturated with IPE to afford **4d** as white powders (2.3 g, 98%). MP 139~142°C (dec). IR $\nu_{C=O}^{KBr}$ 1775, 1695 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (3H, s), 1.48 (3H, s), 1.55 (9H, s), 4.38 (1H, d, J=10.0 Hz), 7.82 (1H, d, J=10.0 Hz), 10.25 (1H, br s).

Crude 1-hydroxy-2-azetidinone (**4d**) was used in subsequent steps without a further purification. Other 1-hydroxy-2-azetidinones (**4e~4i**) were synthesized from the corresponding β-lactams.

Preparation of 2-Azetidinone-1-oxysulfonate, Pyridinium Salt (**5d**)

To a solution of 1-hydroxy-2-azetidinone (**4d**) (2.2 g, 9.5 mmol) in DMF (4~6 ml) was added sulfur trioxide-DMF complex (8.47 ml, 10.5 mmol) (1.24 mol solution in DMF) under ice-cooling and the mixture was stirred at the same temp for 30 minutes. Pyridine (0.93 ml, 11.5 mmol) was added to the

Table 5. Yield, MP, and IR data of β-lactams (**3d**~**3i**).

Compound	Yield (%)	MP (°C)	^{1}H NMR δ (J=Hz) (Solvent)	IR $\nu_{C=O}$ (cm^{-1})
3d	64	Amorphous	(DMSO-d_6); 1.22 (3H, s), 1.34 (3H, s), 1.46 (9H, s), 4.36 (1H, d, 9), 5.06 (2H, s), 7.59 (5H, s), 7.88 (1H, d, 9), 7.88 (1H, d, 9)	1770, 1720 (CH_2Cl_2)
3e	81.2	110~111	($CDCl_3$); 0.86 (3H, t, 7), 1.25~1.61 (11H, m), 3.50 (1H, m), 4.64 (1H, dd, 5, 8), 4.87 (2H, s), 5.41 (1H, d, 8), 7.26 (5H, s)	1780, 1695 (KBr)
3f	75.4	122~123	($CDCl_3$); 0.92 (3H, t, 7), 1.25~1.70 (11H, m), 3.36 (1H, m), 4.06 (1H, dd, 2.7), 4.88 (2H, s), 5.40 (1H, d, 7), 7.21 (5H, s)	1780, 1680 (KBr)
3g	66.7	118~119	($CDCl_3$); 0.80 (3H, d, 6), 1.07 (3H, d, 6), 1.47 (9H, s), 1.87 (1H, m), 3.34 (1H, dd, 5, 5), 4.88 (1H, dd, 5, 9), 5.14 (2H, s), 5.57 (1H, d, 9), 7.57 (5H, s)	1780, 1680 (KBr)
3h	79.5	151~152	($CDCl_3$); 1.01 (3H, d, 6), 1.07 (3H, d, 6), 1.51 (9H, s), 2.00 (1H, m), 3.46 (1H, dd, 2, 6), 4.40 (1H, dd, 2, 8), 5.18 (2H, s), 5.47 (1H, d, 8), 7.62 (5H, s)	1775, 1680 (KBr)
3i	46.8	129~130	($CDCl_3$); 1.44 (9H, s), 4.22 (1H, dd, 2.5, 7), 4.53 (1H, d, 2.5), 4.94 (2H, s), 5.53 (1H, d, 7), 7.24 (10H, s)	1780, 1680 (KBr)

resulting mixture, and the mixture was stirred for 5 minutes. Solvent was evaporated and the obtained residue was triturated with Et_2O to afford **5d** as colorless crystals (3.6 g, 97.3%), which was used in subsequent steps without a further purification. MP 153~157°C (dec). IR $\nu_{C=O}^{KBr}$ 1765, 1710, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6+D_2O) δ 1.40 (15H, s), 4.35 (1H, m), 7.99~9.10 (5H, m).

Other 2-azetidinone-1-oxysulfonate, pyridinum salts (**5e**~**5i**) were synthesized from the corresponding 1-hydroxy-2-azetidinones.

General Preparation of 3-Amino-2-azetidinone-1-oxysulfonic Acids (**6**)

To a solution of TFA (1.5 ml) in 1,2-dichloroethane (3.5 ml) was added 2-azetidinone-1-oxysulfonate, pyridinium salts (**5**) (8 mmol) under ice-cooling, and the mixture was stirred at the same temp for 2 hours. The precipitate was collected by filtration, washed with 1,2-dichloroethane, and dried over P_2O_5 to afford **6**. Results of **6** are summarized in Table 6.

General Procedure for the Acylation of 3-Amino-2-azetidinone-1-oxysulfonic Acids

Synthesis of 3-(α-Ureido)acetamido-2-azetidinone-1-oxysulfonic Acids

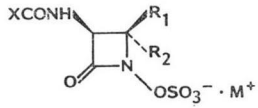
(Method A) Preparation of **18**, **19** and **20**: To a mixture of 3-amino-2-azetidinone-1-oxysulfonic acids (**6**) (1 mmol) in CH_2Cl_2 (2~3 ml) was added Et_3N (2.2 mmol) at −40°C. D(−)-α-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)phenylacetyl chloride[17] (1.1 mmol) was added to the solution at the same temp. And the mixture was stirred for 30 minutes at −15~−5°C, and further for an additional 1 hour at room temp.

Table 6. Yield, MP, IR and analytical data of 3-amino-2-azetidinone-1-oxysulfonic acids (**6d**~**6i**).

Compound	Yield (%)	MP (°C, dec)	IR $\nu_{C=O}$ (cm^{-1})	*Anal*[a]
6d	82.5	140~142	1805, 1780	$C_5H_{10}N_2O_5S$
6e	76.4	130	1780	$C_5H_{10}N_2O_5S$
6f	78.2	130	1790	$C_5H_{10}N_2O_5S$
6h	84.9	114~117	1800, 1765	$C_6H_{12}N_2O_5S$
6i	78.8	105	1770	$C_9H_{10}N_2O_5S$

[a] All the compound given the formular were analyzed for C, H, and N; analytical results obtained for these elements were within ±0.4% of calculated values.

Table 7. MP, ^{1}H NMR and IR data of 3-acylamino-2-azetidinone-1-oxysulfonic acids.



Compound	M	MP (°C, dec)	^{1}H NMR δ (J=Hz) (Solvent)	IR $\nu_{C=O}$ (cm^{-1})
18	Et_3N	150	(DMSO-d_6); 0.8~1.4 (18H, m), 2.8~4.0 (12H, m), 4.44 (1H, d, 7.5), 5.56 (1H, d, 7.5), 7.30 (5H, s), 9.26 (1H, d, 7.5), 9.73 (1H, d, 7.5)	1770, 1715, 1670
19	Et_3N	130	(DMSO-d_6); 0.80 (3H, t, 7), 1.00~1.33 (14H, m), 2.97~4.15 (13H, m), 4.50 (1H, dd, 2, 7), 5.65 (1H, d, 8), 7.56 (5H, s), 9.86 (1H, d, 7), 10.10 (1H, d, 8)	1775, 1715, 1675
20	Et_3N	118	($CDCl_3$); 1.02~1.26 (12H, m), 3.05 (6H, q, 7), 3.27~4.12 (6H, m), 4.69 & 4.77 (1H, d, 2)*, 5.09 & 5.20 (1H, dd, 2, 8)*, 5.53 (1H, d, 8), 6.60 (1H, d, 8), 7.29~7.50 (10H, m), 9.85 (1H, d, 8)	1780, 1715, 1670
21	Et_3N	164	(DMSO-d_6); 1.82 (3H, d, 7), 1.01~1.33 (15H, m), 3.00~4.08 (10H, m), 4.23 (1H, m), 4.55~5.13 (2H, m), 5.65 (1H, d, 8), 7.56 (5H, s)	1775, 1715, 1675
22	Et_3N	165	(DMSO-d_6); 0.80 (3H, d, 6), 1.00~1.34 (15H, m), 3.00~3.96 (10H, m), 4.21 (1H, m), 4.58~5.15 (2H, m), 5.66 (1H, d, 8), 7.58 (5H, s), 9.47 (1H, d, 8), 10.13 (1H, d, 8)	1775, 1710, 1675
26	H	165	(DMSO-d_6); 1.28 (3H, d, 2), 4.27 (1H, m), 5.01 (1H, dd, 2, 8), 5.85~6.55 (4H, m), 6.75 (12H, s), 9.42 (1H, d, 8)	1770, 1660, 1640
27	Na	110	(DMSO-d_6); 1.02~1.40 (6H, m), 3.07 (2H, q, 7), 4.31 (1H, d, 5), 5.01 (1H, d, 6.5), 6.68 (1H, s)	1770, 1660
28	Na	153	(DMSO-d_6); 1.00~1.35 (9H, m), 34.13 (1H, q, 7), 4.42 (1H, m), 5.10 (1H, dd, 6, 8), 6.85 (1H, s), 7.33 (2H, br s), 9.43 (1H, d, 8)	1765, 1655
29	H	130~135	(DMSO-d_6); 1.25 (12H, s), 4.34 (1H, m), 4.98 (1H, m), 6.68 (1H, s), 7.20 (3H, br s), 9.17 (1H, d, 8)	1770, 1660
30	Na	Amorphous	(DMSO-d_6); 1.0~1.8 (11H, m), 4.40 (1H, m), 4.73 (1H, m), 5.00 (1H, m), 6.78 (1H, s), 7.30 (2H, br s), 9.35 (1H, d, 8)	1780, 1650
31	Et_3N	145	(DMSO-d_6); 1.02~1.33 (12H, m), 3.17 (6H, q, 7), 4.36 (1H, m), 5.13 (1H, dd, 6, 8), 5.26 (2H, s), 6.90 (1H, s), 7.37 (2H, br s), 7.54 (5H, s), 9.56 (1H, d, 8)	1770, 1670
32	Na	164	(DMSO-d_6); 1.34 (3H, d, 5), 4.47 (1H, m), 5.20 (1H, m), 6.85 (1H, s), 7.25 (2H, br s), 7.40 (5H, s), 9.85 (1H, d, 8)	1770, 1660
33	Na	126~134	(DMSO-d_6); 1.20 (6H, d, 6), 1.33 (3H, s), 1.47 (3H, s), 4.48 (1H, q, 6), 4.72 (1H, d, 7), 6.82 (1H, s), 7.38 (2H, br s), 9.58 (1H, d, 7)	1770, 1660
34	Et_3N	158	(DMSO-d_6); 1.0~1.5 (18H, m), 2.6~3.5 (8H, m), 3.70 (1H, m), 4.41 (1H, m), 5.25 (1H, m), 6.82 (1H, s), 7.35 (2H, br s), 9.67 (1H, d, 8)	1770, 1655
35	Et_3N	Amorphous	(DMSO-d_6); 0.96~1.38 (18H, m), 2.75~3.45 (9H, m), 3.84 (1H, m), 4.60 (1H, m), 6.81 (1H, s), 7.39 (2H, br s), 9.52 (1H, d, 8)	1775, 1660
36	Et_3N	136~137	(DMSO-d_6+D_2O); 0.87~1.32 (21H, m), 2.00 (1H, m), 3.10 (6H, q, 7), 3.84 (1H, m), 4.30 (1H, q, 6), 4.63 (1H, d, 2), 6.68 (1H, s)	1775, 1660
37	Na	Amorphous	(DMSO-d_6+D_2O); 1.23 (3H, d, 5), 4.25~4.65 (3H, m), 5.12 (1H, d, 5), 6.92 (1H, s)	1770, 1665
38	Na	145~148	(DMSO-d_6+D_2O); 1.35 (3H, s), 1.54 (3H, s), 4.55 (2H, s), 4.73 (1H, s), 6.88 (1H, s)	1770, 1690
40	Na	154~156	(DMSO-d_6+D_2O); 1.1~1.7 (9H, m), 4.15 (1H, m), 4.95 (1H, m), 6.7 (1H, s)	1770, 1670

* Diastereomer mixture.

Dil brine (5 ml) and THF (10 ml) were added to the reaction mixture, and the mixture was adjusted to pH 7.5 with Et_3N. The organic layer was separated, washed with brine, then dried. The solvent was evaporated to give the residue, which was purified by column chromatography on silica gel ($CHCl_3$ - EtOH, 5: 1) to afford the Et_3N salts of **18**~**20** in 60~70% yield.

(Method B) Preparation of **21** and **22**: To a solution of **6c** (1.5 mmol) in DMF (5 ml) was added Et_3N (0.21 ml) under ice-cooling. D(−)-α-[(6*R* or 6*S*)-4-Ethyl-6-methyl-2,3-dioxo-1-piperazinecarboxamido]phenylacetic acid[18] (1.35 mmol) and DCC (1.5 mmol) was added to the solution. And the mixture was stirred for 2 hours at room temp. The insolubles were filtered off and the filtrate was evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$ - EtOH, 5: 1) to afford the Et_3N salts of **21** and **22** in 54.2 and 50.2% yield, respectively.

Synthesis of 3-(α-Oxyimino)acetamido-2-azetidinone-1-oxysulfonic Acids

(Method C) Preparation of **26**~**30**, **32** and **33**: To a solution of **6** (1 mmol) in DMF (5 ml) was added Et_3N (1 mmol) under ice-cooling. 2-(2-Triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*O*-substituted alkoxyimino)acetic acid (0.95 mmol), 1-hydroxybenzotriazole hydrate (1 mmol), molecular sieves 4A (1 g) and DCC (1 mmol) were added to the solution at the same temp and the mixture was stirred overnight at room temp. The insolubles were filtered off and the filtrate was dropped into IPE (300 ml). The solvent was removed by decantation and the obtained precipitate was purified by column chromatography on silica gel ($CHCl_3$ - EtOH, 5: 1) to afford the Et_3N salts of 3-[2-(2-triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*O*-substituted alkoxyimino)acetamido]-2-azetidinone-1-oxysulfonic acids as an amorphous or oily substance in 60~80% yield. Thus obtained compounds were dissolved in THF (3 ml) and 50% aq HCOOH (3 ml), and kept at 45~50°C for 30 minutes. The solvent was evaporated to give the colorless oil, which was applied to a column of Dowex-50W (Na^+ form) ion-exchange resin (10 ml) (eluant; H_2O) to afford crude sodium salts. Sodium salt of each compound was purified by column chromatography on Amberlite XAD-2 (30 ml) (nonionic polymeric adsorbent) (eluant; H_2O) to afford the sodium salts of **27**, **28**, **30**, **32** and **33** as white powders in 40~50% yield.

The coloress oil obtained above was directly purified by column chromatography on Amberlite XAD-2 without the application of Dowex column to afford **26** and **29** as white powders in 50% yield, respectively.

(Method D) Preparation of **31**, **34**, **35** and **36**: 3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted alkoxyimino)acetamido]-2-azetidinone-1-oxysulfonic acids were synthesized directly from 2-(2-aminothiazol-4-yl)-(*Z*)-2-(*O*-substituted alkoxyimino)acetic acid in place of 2-(2-triphenylmethylaminothiazol-4-yl)-(*Z*)-2-(*O*-substituted alkoxyimino)acetic acid in a similar manner as in Method C. The title compounds were obtained as white powders in 50~65% yield.

(Method E) Preparation of **37**, **38** and **40**: Triethylammonium 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(1-*tert*-butoxycarbonyl-1-methylethoxyimino)acetamido or (1-*tert*-butoxycarbonyl-1-ethoxyimino)-acetamido]-2-azetidinone-1-oxysulfonate obtained in a similar manner as in Method C was dissolved in CH_2Cl_2 (15 ml). TFA (10 ml) was added to the solution under ice-cooling, and reacted for 2 hours. 20 ml of IPE was added to the reaction mixture. The formed precipitate was filtered, washed with IPE, and dried under reduced pressure over P_2O_5. The obtained substances were subjected to Dowex-50W and Amberlite XAD-2 column chromatography in a similar manner as in Method C to afford respective sodium salt in 40~50% yield.

(3*R*,4*R*)-4-Methyl-1-(*p*-nitrobenzyloxy)-3-phenylacetamido-2-azetidinone (**7**)

The title compound was obtained from *N*-phenylacetyl-D-threonine in a similar manner as in **3**. Yield 88.8%. MP 141~142°C; $[\alpha]_D^{25}$ +20.4° (*c* 2, MeOH); IR $\nu_{C=O}^{KBr}$ 1780, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.33 (3H, d, J=6.0 Hz), 3.54 (2H, s), 3.72 (1H, m), 4.12 (1H, dd, J=2.0 Hz, J=7.0 Hz), 5.04 (2H, s), 6.87 (1H, d, J=7.0 Hz), 7.25 (5H, s), 7.57 (2H, d, J=9.0 Hz), 8.17 (2H, d, J=9.0 Hz).

(3*R*,4*R*)-3-Amino-4-methyl-1-(*p*-nitrobenzyloxy)-2-azetidinone (**8**)

To a solution of **7** (10 g, 27 mmol) in CH_2Cl_2 (100 ml) and *N*,*N*-dimethylaniline (6.86 ml, 54.2 mmol) was added portionwise PCl_5 (7.33 g, 35.2 mmol) with stirring over 20 minutes at −50~−45°C.

After stirring for 15 minutes at −25°C, MeOH (50 ml) was added dropwise to the mixture at −30°C over 15 minutes, and then reaction temp was raised to −15°C. Water (100 ml) and IPE (100 ml) were added to the resulting mixture. And the separated aqueous layer was adjusted to pH 7.2 with saturated $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine, and dried. The solvent was evaporated to afford the title compound (**8**) as a pale yellow oil, 5.8 g (85%). Crude **8** was used in subsequent steps without a further purification. HCl salt of **8**: MP 173°C (dec); IR $\nu_{C=O}^{KBr}$ 1770 cm^{-1}.

Anal Calcd for $C_{11}H_{14}N_3O_4Cl$: C 45.92, H 4.90, N 14.61.
Found C 45.64, H 4.81, N 14.80.

(3*R*,4*R*)-3-[D(−)-α-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)phenylacetamido]-4-methyl-1-(*p*-nitrobenzyloxy)-2-azetidinone (**9**)

The title compound was synthesized in a similar manner as in Method A. Yield 75.3%. MP 125°C (dec); IR $\nu_{C=O}^{KBr}$ 1775, 1715, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.07 (3H, t, J=7.0 Hz), 1.10 (3H, d, J=6.0 Hz), 3.23~4.08 (7H, m), 4.31 (1H, dd, J=2.0 Hz, J=7.0 Hz), 5.24 (2H, s), 5.60 (1H, d, J=7.0 Hz), 7.53 (5H, s), 7.90 (2H, d, J=9.0 Hz), 8.43 (2H, d, J=9.0 Hz), 9.45 (1H, d, J=7.0 Hz), 10.14 (1H, d, J=7.0 Hz).

(3*R*,4*R*)-3-[D(−)-α-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)phenylacetamido]-3-methoxy-4-methyl-1-(*p*-nitrobenzyloxy)-2-azetidinone (**10**)

To a solution of **9** (2 g, 3.62 mmol) in CH_2Cl_2 (40 ml) and MeOH (1 ml) was added dropwise $LiOCH_3$ (2.73 ml) (2.655 N solution in MeOH) at −80~−70°C, and then *tert*-BuOCl (0.47 g, 4.33 mmol). After stirring for 15 minutes at the same temp, AcOH (0.41 ml) and H_2O (20 ml) were added to the resulting mixture.

The separated organic layer was washed successively with H_2O and brine, and dried. The solvent was evaporated to give the residue, which was purified by column chromatography on silica gel (benzene - EtOAc, 1: 1) to afford the title compound **10** as white powders, 0.5 g (24%). MP 145°C (dec); IR $\nu_{C=O}^{KBr}$ 1775, 1720, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.78 (3H, d, J=6.0 Hz), 1.14 (3H, t, J=7.0 Hz), 3.38 (3H, s), 3.38~4.22 (7H, m), 5.23 (2H, s), 5.77 (1H, d, J=7.0 Hz), 7.62 (5H, s), 7.92 (2H, d, J=9.0 Hz), 8.43 (2H, d, J=9.0 Hz), 9.30 (1H, s), 10.13 (1H, d, J=7.0 Hz).

(3*R*,4*R*)-3-[D(−)-α-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)phenylacetamido]-1-hydroxy-3-methoxy-4-methyl-2-azetidinone (**11**)

The title compound was synthesized by hydrogenolysis in EtOH in a similar manner as in **4**. Yield 99%. MP 145~150°C; IR $\nu_{C=O}^{KBr}$ 1770, 1725~1710, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.74 (3H, d, J=6.0 Hz), 1.12 (3H, t, J=7.0 Hz), 3.29~4.11 (10H, m), 5.72 (1H, d, J=7.0 Hz), 7.54 (5H, m), 9.69 (1H, s), 10.07 (1H, d, J=7.0 Hz), 10.50 (1H, br s).

(3*R*,4*R*)-3-[D(−)-α-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)phenylacetamido]-1-hydroxy-4-methyl-2-azetidinone (**13**)

The title compound was synthesized in a similar manner as in **4**. Yield 95%. MP 135~138°C (dec); IR $\nu_{C=O}^{KBr}$ 1765, 1710, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.09 (3H, t, J=7.0 Hz), 1.31 (3H, d, J=5.5 Hz), 3.25~4.05 (7H, m), 4.02 (1H, dd, J=2.0 Hz, J=7.0 Hz), 5.48 (1H, dd, J=2.0 Hz, J=8.0 Hz), 7.43 (5H, s), 9.28 (1H, dd, J=2.0 Hz, J=8.0 Hz), 9.92 (1H, dd, J=2.0 Hz, J=7.0 Hz), 10.36 (1H, br s).

Sodium (3*R*,4*R*)-3-[D(−)-α-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)phenylacetamido]-3-methoxy-4-methyl-2-azetidinone-1-oxysulfonate (**12**)

The title compound was synthesized in a similar manner as in **5**. Yield 77%. MP 142°C (dec); IR $\nu_{C=O}^{KBr}$ 1780, 1710, 1670 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.78 (3H, d, J=5.5 Hz), 1.1 (3H, t, J=7.0 Hz), 3.37 (3H, s), 3.2~4.1 (6H, m), 4.2 (1H, d, J=5.5 Hz), 5.68 (1H, d, J=7.0 Hz), 7.44 (5H, s), 9.6 (1H, s), 9.87 (1H, d, J=7.0 Hz).

Sodium (3*R*,4*R*)-3-[D(−)-α-(4-Ethyl-2,3-dioxo-1-piperadinecarboxamido)phenylacetamido]-4-methyl-2-azetidinone-1-oxysulfonate (**14**)

The title compound was synthesized in a similar manner as in **5**. Yield 80%. MP 145°C (dec); IR $\nu_{C=O}^{KBr}$ 1775, 1715, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.07 (3H, t, J=7.0 Hz), 1.33 (3H, d, J=6.0 Hz), 3.13~4.04 (7H, m), 4.23 (1H, dd, J=2.0 Hz, J=7.0 Hz), 5.43 (1H, d, J=7.0 Hz), 7.27 (5H, s), 9.33 (1H, d, J=7.0 Hz), 9.75 (1H, d, J=7.0 Hz).

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