AMINOTHIAZOLYLGLYCYL DERIVATIVES OF CARBACEPHEMS

I. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL CARBACEPHEMS WITH SUBSTITUTED AMINOTHIAZOLYL GROUPS

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A series of new carbacephem compounds which have substituted aminothiazolylglycyl side chain have been prepared starting from corresponding carbacephems with aminothiazolylmethoxyimino group. Among them, the compound having 3,4-dihydroxybenzoyl group showed very sharp activity against *Pseudomonas aeruginosa*. Moreover, the optical resolution of α carbon of aminothiazolylglycyl moiety was carried out through preparation of optically active side chain and the (*S*)-isomer (KT-4380) was found to be the most active against *Pseudomonas* sp. as well as other Gram-negative strains.

The infection caused by antibiotic-resistant bacteria and opportunistic pathogens has been one of major targets of chemotherapy. Many β-lactam antibiotics have been prepared in order to develop broad spectrum antimicrobial compounds with high resistance to β-lactamase enzymes. In a previous paper[1], we reported 1-carbacephems KT-3767 and KT-3937 which possess activity comparable with newer cephalosporins. The acyl group of the 7-position in semisynthetic cephalosporins significantly affects the antibacterial activity. The 2-aminothiazolylmethoxyimino radical is an excellent acyl group and has been successfully employed in many newer cephalosporins[2] such as ceftizoxime, cefotaxime, cefmenoxime and our KT-3767 and KT-3937.

In this paper, we describe the synthesis and antimicrobial activity of compounds which have, as an amido moiety, the aminothiazolylglycyl side chain possessing enhanced anti-pseudomonal activity.

Strong activity against *Pseudomonas* sp. has been found with compounds containing "amido" or "ureido" group, for instance cefoperazone[3], cefpimizole[4], and cefpiramide[5]. These compounds, however, are phenylglycyl derivatives and there are only a few reports relating to compounds with aminothiazolylglycyl side chains[6,7]. We prepared a series of "amido" compounds starting from KT-3767 and KT-3937 which are available in large quantity through the development of a practical synthetic procedure.

Chemistry

The compounds listed in Table 4 were prepared by the method outlined in Scheme 1. Reduction of methoxyimino group of KT-3767 (**1a**) and KT-3937 (**1b**) with zinc powder in acetic acid or aqueous hydrochloric acid gave corresponding aminothiazolylglycyl derivatives **2a** and **2b**, respectively.

Scheme 1.

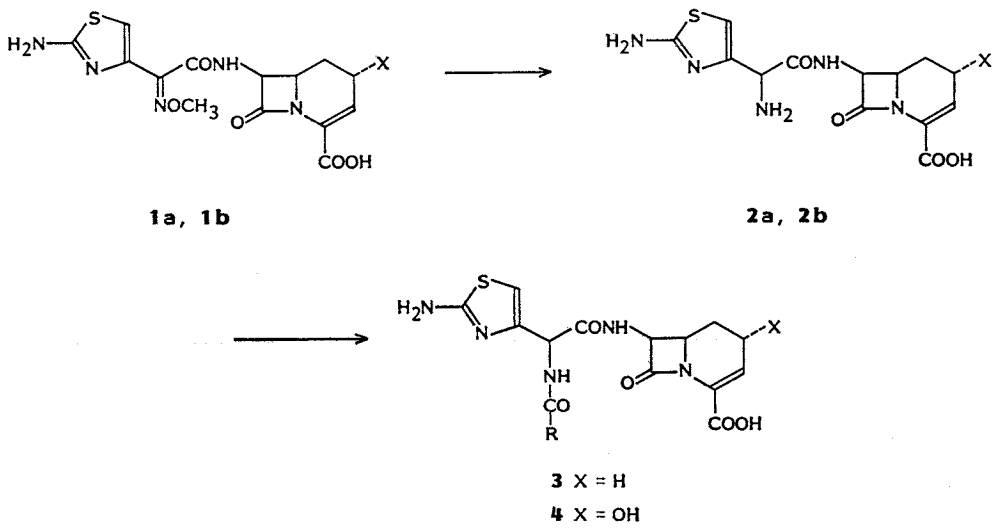
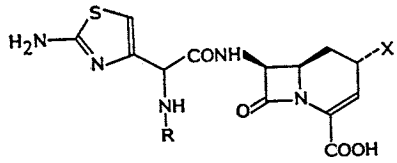
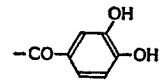


Table 1. Antimicrobial activity of carbacephems (**1**, **2**, **3** and **4**), MIC (μg/ml).



R:	H		CHO					
X:	H **2a**	OH **2b**	H **3a**	OH **4a**	H **3b**	OH **4b**	H **1a**	OH **1b**
Staphylococcus aureus 209-P	1.56	12.5	25	50	1.56	12.5	12.5	25
Escherichia coli Juhl	0.39	0.78	0.01	0.05	0.2	0.2	0.01	0.01
Klebsiella pneumoniae 8045	0.39	0.78	0.02	0.05	0.1	0.2	0.01	0.01
Serratia marcescens T-26	3.13	6.25	0.2	0.78	0.78	0.39	0.2	0.2
Proteus mirabilis 1287	1.56	6.25	0.05	0.39	0.39	0.39	0.01	0.01
P. vulgaris 6897	3.13	12.5	0.05	0.2	0.1	0.2	0.01	0.02
Enterobacter cloacae F 1510	0.78	1.56	0.05	0.1	0.05	0.1	0.1	0.05
Citrobacter freundii F 1526	0.39	0.78	0.02	0.05	0.2	0.1	0.1	0.02
Pseudomonas aeruginosa #1	100	100	100	100	0.78	1.56	12.5	3.13
P. aeruginosa 145	100	100	100	100	0.39	3.13	25	3.13

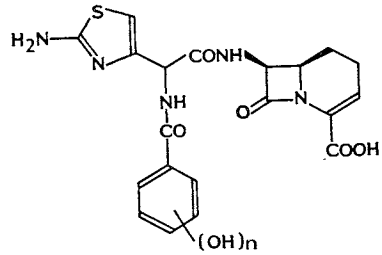
Mueller-Hinton agar dilution method, 10^6 cfu/ml.

Various acyl groups were condensed with amino moiety by the acid chloride, mixed anhydride or active ester methods followed by cleavage of protecting groups where necessary. The compounds obtained were a mixture of approximately equimolecular diastereoisomers.

Antibacterial Activity

The minimum inhibitory concentration (MIC) of 1-carbacephems against Gram-positive and Gram-negative bacteria were determined by the Mueller-Hinton agar dilution method. The results

Table 2. Antimicrobial activity of substituted benzoyl derivatives (3), MIC (μg/ml).



Substituents:	3,4-di-OH **3b**	2,3-di-OH **3c**	2,5-di-OH **3d**	3,5-di-OH **3e**	3,4,5-tri-OH **3f**	4-OH **3g**	3-OH, 4-OCH_3 **3h**
Staphylococcus aureus 209-P	1.56	25	6.25	0.78	25	0.78	3.13
Escherichia coli Juhl	0.2	1.56	0.78	0.2	1.56	0.39	0.2
Klebsiella pneumoniae 8045	0.1	0.78	0.39	0.1	0.78	0.2	0.1
Serratia marcescens T-26	0.78	25	12.5	12.5	6.25	50	25
Proteus mirabilis 1287	0.39	1.56	0.39	0.39	0.78	0.78	0.2
P. vulgaris 6897	0.1	1.56	0.2	0.1	0.78	0.05	0.01
Enterobacter cloacae F 1510	0.05	25	3.13	3.13	6.25	3.13	0.39
Citrobacter freundii F 1526	0.2	3.13	1.56	0.78	1.56	0.78	0.39
Pseudomonas aeruginosa #1	0.78	12.5	50	100	6.25	100	50
P. aeruginosa 145	0.39	25	50	100	6.25	100	100

are listed in Tables 1 and 2. The amino derivatives **2a** and **2b** showed lower activity against Gram-negative bacteria than parent compounds **1a** and **1b**. On the other hand, even in the simplest amido derivatives **3a** and **4a** possess comparative activity with **1a** and **1b**. These result indicate the possible enhancement of the antimicrobial activity by acylation of aminothiazolylglycyl moiety. Among amido compounds thus prepared, **3b** and **4b** which have 3,4-dihydroxybenzoyl group showed strong anti-pseudomonal activity besides broad activity against Gram-negative strains. Concerning carbacephem nuclei, the compound having unsubstituted nucleus revealed stronger activity against Gram-positive and Gram-negative bacteria than 2-hydroxy carbacephems. We synthesized a series of hydroxybenzoyl derivatives along with an acetoxybenzoyl derivative which showed comparative activity to the hydroxybenzoyl derivative due to facile cleavage of acetyl group during the measurement of activity.

As shown in Table 2, most of the compounds did not show activity while 2,3-dihydroxy (**3c**) and 3,4,5-trihydroxy (**3f**) derivatives showed weak activity against *Pseudomonas* sp. Therefore, this anti-pseudomonal activity is specific to 3,4-dihydroxybenzoyl moiety. As described before **3b** is a diastereomeric mixture, so we attempted optical resolution of this compound.

Resolution of Racemic Aminothiazolylglycyl Derivatives

Absolute cofiguration of aminothiazolylglycyl derivatives is still ambiguous, although the separation of two diastereomers using HPLC was reported[8]. We synthesized an optically active side chain through the route shown in Scheme 2 in order to determine the absolute configuration of **2a** as well as to isolate each diastereomer. Methoxyimino ester **5** was reduced into amino ester by catalytic hydrogenation. Two amino groups were protected to form dichloroacetyl compound **6**, and saponification of **6** gave acid **7**. The carboxylic acid **7** was incubated with (L)-amino acid-specific acylase to obtain (L)-amino acid **8** and unhydrolyzed diacyl compound **9b**. Amino acid **8** was again chloroacetylated

Scheme 2.

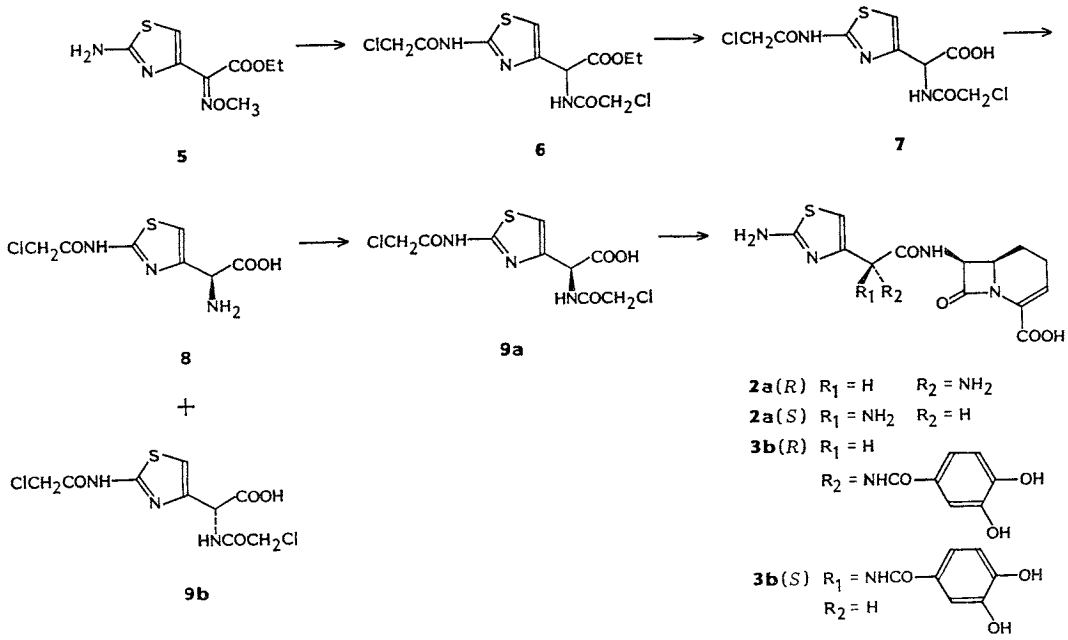
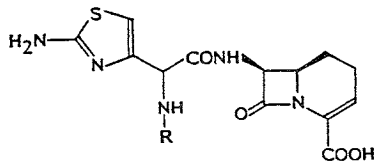


Table 3. Comparative antimicrobial activity of (*R*)- and (*S*)-isomers, MIC (μg/ml).



	R: H		-CO-		Cefoperazone
	2a(*S*)	**2a**(*R*)	**3b**(*S*)	**3b**(*R*)	
Staphylococcus aureus 209-P	12.5	0.78	12.5	3.13	1.56
S. epidermidis	6.25	3.13	12.5	3.13	1.56
Escherichia coli Juhl	0.39	0.78	0.05	0.39	0.1
Klebsiella pneumoniae 8045	0.78	1.56	0.02	0.2	0.05
Serratia marcescens T-26	1.56	12.5	0.2	3.13	1.56
Proteus mirabilis 1287	1.56	3.13	0.2	1.56	0.78
Enterobacter cloacae F 1510	0.78	3.13	0.39	6.25	0.78
Citrobacter freundii F 1526	0.39	1.56	0.05	0.39	0.78
Pseudomonas aeruginosa #1	100	100	0.78	0.78	3.13
P. aeruginosa 145	100	100	0.39	0.39	6.25

to afford **9a**. Each of these compounds was condensed with 3-H carbacephem nucleus by mixed anhydride method followed by deprotection of chloroacetyl groups using thiourea to afford **2a**(*S*) and **2a**(*R*). The 3,4-dihydroxybenzoylation of these compound gave **3b**(*S*) (KT-4380) and **3b**(*R*).

As shown in Table 4, (D)-isomers were more active against Gram-positive bacteria than (L)-isomers, while (L)-isomers were more active against Gram-negative bacteria. This is interesting when

Table 4. Mass, NMR and IR spectral data of **3** and **4**.

	Mass (*m/z*)	IR (KBr)	NMR δ
3a	366 $(M+1)^+$	1770, 1760, 1670, 1650	(CD_3OD); 8.11 (1H, s), 6.63 (1H, s), 6.4 (1H, m), 5.5~5.2 (2H, m), 3.9 (1H, m), 2.3 (2H, m), 1.6 (2H, m)
3b	474 $(M+1)^+$	1770, 1750, 1640, 1605	(D_2O); 7.39~6.94 (3H, m), 6.78 (1H, s), 6.18 (1H, m), 5.59 (1H, s), 5.44 (1H, d), 4.0~3.8 (1H, m), 2.4~1.3 (4H, m)
3c		1770, 1750, 1665, 1645	(D_2O); 7.3~6.7 (3H, m), 6.66 (1H, s), 6.09 (1H, s), 5.52 (1H, s), 5.31 and 5.25 (1H, d), 3.7 (1H, m), 2.2 (2H, m), 1.6 (2H, m)
3d	474 $(M+1)^+$	1770, 1750, 1655, 1640	(D_2O); 7.43 (1H, s), 7.2~6.8 (2H, m), 6.60 (1H, s), 6.03 (1H, m), 5.50 (1H, s), 5.13 (1H, d), 3.7 (1H, m), 2.2 (2H, m), 1.6 (2H, m)
3e	469 $(M)^+$ (Na salt)	1770, 1750, 1640	(D_2O); 6.7 (2H, m), 6.62 (1H, s), 6.5 (1H, m), 5.47 (1H, s), 5.28 and 5.20 (1H, d), 3.75 (1H, m), 2.2 (2H, m), 1.5 (2H, m)
3f*	615 $(M+1)^+$	1795, 1790, 1770, 1645	(CD_3OD); 7.78 (2H, s), 6.50 (1H, s), 5.60 and 5.57 (1H, s), 5.41 and 5.33 (1H, d), 3.8 (1H, m), 2.30 (9H, s), 2.2~1.6 (4H, m)
3g	481 $(M)^+$ (Na salt)	1746, 1637, 1605	(D_2O); 7.69 (2H, d), 6.83 (2H, d), 6.63 (1H, s), 6.12 (1H, m), 5.50 (1H, s), 5.32 and 5.26 (1H, d), 3.8 (1H, m), 2.3~1.6 (4H, m)
3h		1765, 1745, 1670, 1640	(CD_3OD); 7.35 (2H, m), 6.95 (1H, d), 6.53 (1H, s), 6.36 (1H, m), 5.54 (1H, s), 5.30 (1H, d), 3.83 (1H, m), 3.8 (1H, m), 2.4~1.6 (4H, m)
4a		1770, 1760, 1675, 1652	(D_2O); 7.98 (1H, s), 6.60 (1H, s), 6.0 (1H, m), 5.31 (1H, s), 5.23 (1H, s), 4.2 (1H, m), 3.8 (1H, m), 1.6 (2H, m)
4b*		1790, 1785, 1770, 1755, 1660, 1640	(CD_3OD); 7.8 (2H, m), 7.33 (1H, d), 6.56 (1H, s), 6.33 and 6.30 (1H, d), 5.62 and 5.58 (1H, s), 5.50 and 5.43 (1H, d), 3.9 (1H, m), 2.30 (6H, s), 2.0~1.6 (2H, m)

* Data of *O*-acetyl derivative.

compared with the fact that (D)-isomer is more active than (L)-isomer against Gram-positive and Gram-negative bacteria in the case of phenylglycyl derivatives. KT-4380 with (*S*) configuration was strongly active against a broad spectrum of Gram-negative bacteria including *Pseudomonas* sp. Further studies are in progress to evaluate this carbacephem compound.

Experimental

NMR spectra were recorded at 90 MHz on a Varian EM-390 NMR spectrometer and at 100 MHz on a Jeol-FX-100 NMR spectrometer using tetramethylsilane or 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt hydrate as an internal standard. All chemical shifts are reported in ppm. IR spectra were taken on a Jasco IR-810 IR spectrometer. Mass spectra were recorded on a Hitachi M-80B mass spectrometer (secondary ion (SI)-MS). Estimation of purity of analogs was greater than 95% by analytical HPLC.

Antibiotic Susceptibility

All antibacterial activity data are given as the minimum inhibitory concentration (MIC) in μg/ml. MICs were determined by the agar dilution method using Mueller-Hinton agar after incubation at 37°C for 20 hours with an inoculum size of about 10^6 cfu/ml.

(6*R*,7*S*)-7-[2-(2-Aminothiazol-4-yl)-2-aminoacetamido]-1-azabicyclo-[4,2,0]-oct-2-en-8-oxo-2-carboxylic Acid (**2a**)

To a solution of KT-3767 (**1a**, 10 g) in 185 ml of acetic acid was added portionwise 7.0 g of zinc

dust over 30 minutes at room temp. This mixture was stirred for 2 hours and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on Diaion HP-10, eluting with 20% aq MeOH to give 8.1 g of **2a** (76.7%): ^{1}H NMR (D_2O) δ 7.02 (1H, s), 6.53 (1H, m), 5.52, 5.36 (1H, d), 5.23 (1H, s), 3.9 (1H, m), 2.3 (2H, m), 1.9~1.2 (2H, m); SI-MS *m/z* 338 $(M+1)^+$; IR (KBr) cm^{-1} 1775, 1760, 1700, 1650, 1635.

(4*S*,6*R*,7*S*)-7-[2-(2-Aminothiazol-4-yl)-2-aminoacetamido]-4-hydroxy-1-azabicyclo-[4,2,0]-oct-2-en-8-oxo-2-carboxylic Acid (**2b**)

2b was obtained from KT-3937 by a similar procedure as described for the preparation of **2a**: ^{1}H NMR (D_2O) δ 7.01 (1H, s), 6.5 (1H, m), 5.95 (1H, m), 5.56, 5.48 (1H, d), 5.18 (1H, s), 3.9 (1H, m), 1.7 (2H, m); SI-MS *m/z* 354 $(M+1)^+$; IR (KBr) cm^{-1} 1794, 1684, 1624, 1575.

(6*R*,7*S*)-7-[2-(2-Aminothiazol-4-yl)-2-formamidoacetamido]-1-azabicyclo-[4,2,0]-oct-2-en-8-oxo-2-carboxylic Acid (**3a**)

To a solution of 67.4 mg of **2a** in 1 ml of formic acid was added 0.113 ml of acetic anhydride at 0°C. The solution was stirred at 0°C for 1 hour and at room temp for additional 1 hour. The reaction mixture was evaporated, and the product was purified by column chromatography on Diaion HP-10, eluting with 20% aq MeOH to afford 56 mg (76.7%) of **3a**; ^{1}H NMR (CD_3OD) δ 8.11 (1H, s), 6.63 (1H, s), 6.4 (1H, m), 5.5~5.2 (2H, m), 3.9 (1H, m), 2.3 (2H, m), 1.6 (2H, m); SI-MS *m/z* 366 $(M+1)^+$; IR (KBr) cm^{-1} 1770, 1760, 1670, 1650.

General Procedure for the Acylation of **2a**,**2b**

Method A: To a suspension of 0.5 mmol of **2a** or **2b** in 2 ml of tetrahydrofuran (THF) was added 0.5 ml on *N*,*O*-bis(trimethylsilyl)acetamido. The mixture was stirred for 30 minutes at room temp and cooled in an ice bath. To the resulting solution was added 0.6 to 1.0 mmol of acid chloride (hydroxy groups of benzoyl moiety were protected by acetyl group). The reaction mixture was stirred at 0°C for 1 hour and evaporated. The residue was purified by column chromatography on Diaion HP-10, eluting with an aq MeOH, to afford **3** or **4**. In the case of the product which has acetoxy group, removal of protecting group was accomplished by ammonolysis in MeOH. The product was chromatographed on Diaion HP-10 at pH 2 (1 N HCl) or pH 8 ($NaHCO_3$) to give **3** or **4** as free acid or sodium salt, respectively.

Method B: To a solution of 0.5 mmol of **2a** or **2b** in 2 ml of THF and 2 ml of H_2O at pH 8 adjusted with Et_3N was added 0.6 to 1.0 mmol of acid chloride portionwise at 0°C. The mixture was stirred at room temp for 2 hours, acidified to pH 2 with 1 N HCl and concentrated. **3** or **4** was obtained from the residue by a similar procedure as described for method A.

Ethyl 2-(2-Chloroacetamidothiazol-4-yl)-2-chloroacetamido Acetate (**6**)

Ethyl 2-aminothiazol-2-methoxyimino acetate (**5**, 6.75 g) was subjected to hydrogenolysis in 10% HCl - MeOH (160 ml) for 6 hours over 5% Pd-C catalyst (1.0 g) at room temp under atmospheric pressure. The catalyst was filtered and washed with MeOH. The combined filtrate was adjusted to pH 7.8 with Et_3N. Chloroacetylchloride (7.0 ml) was added dropwise to the resulting solution over 20 minutes maintaining to pH 7.5 with Et_3N under ice-cooling and the mixture was stirred for 3 hours at room temp. The reaction mixture was evaporated and the residue was dissolved in EtOAc (200 ml). The solution was washed successively with H_2O, saturated $NaHCO_3$ solution and brine, and then dried over Na_2SO_4. The solvent was evaporated to give the residue, which was crystallized from hexane - EtOAc (1 : 1) to afford **6** as yellow crystals (10.0 g, 96.3%): ^{1}H NMR ($CDCl_3$) δ 7.68 (1H, d), 7.06 (1H, s), 5.68 (1H, d), 4.30 (2H, s), 4.13 (2H, s), 4.2 (2H, q), 1.20 (3H, t); IR (KBr) cm^{-1} 1731, 1703, 1658, 1647.

2-(2-Chloroacetamidothiazol-4-yl)-2-chloroacetamido Acetic Acid (**7**)

To a solution of 10 g of ester **6** and 100 ml of EtOH was added dropwise 35 ml of 2 N KOH under ice-cooling. After 2 hours, the reaction mixture was carefully acidified using 2 N HCl and diluted with water. The solution was extracted twice with EtOAc. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was crystallized from acetone to affored 5.3 g of **7** (58%): ^{1}H NMR (DMSO-d_6) δ 8.73 (1H, d), 7.20 (1H, s),

5.46 (1H, d), 4.33 (2H, s), 4.17 (2H, s); IR (KBr) cm^{-1} 1730, 1685, 1661.

Resolution of **7** Using Enzymatic Deacylation

To a solution of **7** (1.0 g), 10 ml of 1/20 M phosphate buffer (pH 8.0) and 0.2 mM of $CoCl_2$ was added 100 mg of acylase (Amano Pharmaceuticals), and the mixture was incubated at 35°C for 6 hours. The reaction mixture was acidified to pH 2.0 with 2 N HCl and extracted twice with EtOAc. The combined extracts were washed with water and concentrated. The residue was re-incubated in the same manner for 2 days to afford 280 mg of (*R*)-isomer [**9b**, 56%, $[\alpha]_D$ −150.2 (*c* 1, 0.1 N NaOH)]. The aqueous layer was washed with EtOAc and evaporated *in vacuo*. The residue was chromatographed on Diaion HP-10 with eluting by 10% aq MeOH. The eluent containing **8** was concentrated and dissolved in 20 ml of water, 20 ml of THF and Et_3N (pH 8.0). To the solution was added 0.1 ml of chloroacetylchloride with Et_3N under ice-cooling. After stirring 2 hours, the reaction mixture was acidified with 2 N HCl and extracted twice with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was treated by acetone to give **9a** (208 mg, 41.6%) as colorless crystals: $[\alpha]_D$ +145.8 (*c* 1, 0.1 N NaOH).

(6*R*,7*S*)-7-[(*S*)-2-(2-Aminothiazol-4-yl)-2-aminoacetamido]-1-azabicyclo-[4,2,0]-oct-2-en-8-oxo-2-carboxylic Acid **2a**(*S*)

To a solution of **9a** (490 mg) in 15 ml of THF were added 0.214 ml of isobutylchloroformate and 0.181 ml of *N*-methylmorpholine at −10°C. After stirring for 30 minutes, the reaction mixture containing mixed anhydride was used for the following reaction. To a stirred suspention of (6*R*,7*S*)-7-amino-1-azabicyclo-[4,2,0]-oct-2-en-8-oxo-2-carboxylic acid (273 mg) in 15 ml of H_2O and 15 ml of THF was added 0.2 ml of *N*-methylmorpholine. To the resulting solution was added the mixture containing mixed anhydride described above under ice-cooling. Stirring was continued at 0°C for 30 minutes and for 1 hour at room temp. The reaction mixture was adjusted to pH 2 with 1 N HCl. After 30 ml of EtOAc was added, the organic layer was separated, washed with brine and evaporated *in vacuo*. The residue was dissolved in 20 ml dimethylacetamido and 510 mg of thiourea was added to the solution. After stirring for 18 hours, 50 ml of ether was added to the reaction mixture. The precipitates formed were collected by filtration, and dissolved in H_2O with pH 2. The solution was chromatographed on Diaion HP-10 (100 ml) with elution by H_2O and 20% aq MeOH to give **2a**(*S*) (29.8 mg, 56.6%) as colorless powder: ^1H NMR (D_2O) δ 7.02 (1H, s), 6.52 (1H, m), 5.36 (1H, d), 5.21 (1H, s), 3.9 (1H, m), 2.3 (2H, m), 1.8~1.2 (2H, m); IR (KBr) cm^{-1} 1750, 1685, 1653, 1618, 1560.

2a(*R*) was also obtained from **9b** by treatment similar to that described above: ^1H NMR (D_2O) δ 7.01 (1H, s), 6.25 (1H, m), 5.51 (1H, d), 5.20 (1H, s), 3.9 (1H, m), 2.3 (1H, m), 1.8~1.2 (2H, m); IR (KBr) cm^{-1} 1741, 1689, 1618, 1522.

(6*R*,7*S*)-7-[(*S*)-2-(2-Aminothiazol-4-yl)-2-(3,4-dihydroxybenzamido)acetamido]-1-azabicyclo-[4,2,0]-oct-2-en-8-oxo-2-carboxylic Acid **3b**(*S*), KT-4380

To a solution of 400 mg of **2a**(*S*) and 2 ml of bis(trimethylsilyl)acetamide in 5 ml of THF was added 274 mg of 3,4-diacetoxybenzoyl chloride. The reaction mixture was stirred at room temp for 2 hours. After addition of small amount of water, the reaction mixture was acidified to pH 2.0 with 1 N HCl and concentrated. The residue was suspended in 10 ml of MeOH, and two drops of concentrate NH_4OH were added to make a clear solution. The solution was stirred 1.5 hours and concentrated. The residue was purified by column chromatography on Diaion HP-10 at pH 2 to afford 442 mg of **3b**(*S*) (78.9%, KT-4380): ^1H NMR (DMSO-d_6 - CD_3OD) δ 7.3 (2H, m), 6.80 (1H, d), 6.52 (1H, s), 6.35 (1H, m), 5.55 (1H, s), 5.03 (1H, d), 3.83 (1H, m), 2.4 (2H, m), 1.8 (2H, m); IR (KBr) cm^{-1} 1736, 1683, 1642, 1600, 1559.

3b(*R*) was also obtained from **2a**(*R*) by a similar procedure as described for the preparation of **3b**(*S*): ^1H NMR (DMSO-d_6 - CD_3OD) δ 7.3 (2H, m), 6.82 (1H, d), 6.54 (1H, s), 6.35 (1H, m), 5.52 (1H, s), 5.12 (1H, d), 3.8 (1H, m), 2.4 (2H, m), 1.8 (2H, m); IR (KBr) cm^{-1} 1741, 1672, 1627, 1619, 1574.

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