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Chemical Modification of Sulfazecin. Synthesis of 4-Methoxycarbonyl-2-azetidinone-1-sulfonic Acid Derivatives[1)]

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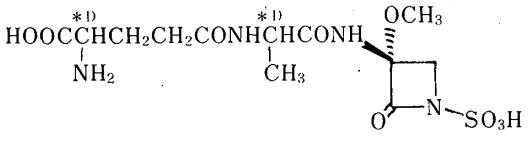
In the course of the chemical modification of sulfazecin, 3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(substituted oxyimino)acetamido]-4-methoxycarbonyl-2-azetidinone-1-sulfonic acids were synthesized starting from *cis*-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-3-phthalimido-2-azetidinone (**2**). These new 4-substituted derivatives showed more potent antimicrobial activities against gram-negative bacteria than did the corresponding 4-unsubstituted compounds, and the derivatives having 3,4-*cis* stereochemistry were more active than the *trans* isomers, especially against *P. aeruginosa* and some β-lactamase-producing bacteria. The reported procedure for the cycloaddition reaction used to prepare **2** was investigated in detail; by the use of a 20% excess of triethylamine, **2** was easily obtained in the yield of 72% as colorless crystals. A possible intermediate of β-lactam formation in this cycloaddition reaction, an acyl iminium salt (**6**), was isolated as crystals and converted into β-lactams by treatment with 1,8-diazabicyclo[5.4.0]-7-undecene.

Keywords——sulfazecin; monocyclic β-lactam; 1-sulfo-2-azetidinone; antibacterial activity; chemical modification; aztreonam; cycloaddition; *cis–trans* isomerization; persulfate oxidation

Recently, a novel monocyclic β-lactam antibiotic, sulfazecin, was discovered in a bacterial culture.[2)] The unique structure of this antibiotic, with a sulfo group on the β-lactam nitrogen, was elucidated by chemical studies[2,3)] and established by X-ray analysis.[4)] Later, Sykes *et al.*[5)] also reported the isolation of several analogous 1-sulfo-2-azetidinone derivatives including sulfazecin. Although sulfazecin has interesting (but moderate) antimicrobial activity, especially against gram-negative bacteria, it seemed necessary from a practical point of view to enhance this activity. Since our earlier observations[6)] revealed that 4-unsubstituted-1-sulfo-2-azetidinone derivatives (**1**) appeared to lack activity against β-lactamase-producing strains of gram-negative bacteria, our efforts have been directed to the synthesis of new derivatives bearing various 4-substituents. In this paper, we report the synthesis and some structure–activity relationships of 4-methoxycarbonyl-1-sulfo-2-azetidinone derivatives. The 4-methoxycarbonyl group is readily convertible[7)] into a variety of other substituents.

When the structural features of penicillins and cephalosporins were taken into consideration, 3,4-*cis* stereochemistry seemed preferable to the *trans* configuration. Therefore,



sulfazecin

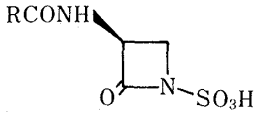


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Chart 1

cis-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-3-phthalimido-2-azetidinone (**2**), first synthesized by Gleason *et al.*,[7] was selected as a starting material, and the synthetic procedure disclosed briefly in patent specifications[7] was investigated in detail. When the reaction of phthalimidoacetyl chloride (**3**) with the imine (**4**) derived from methyl glyoxylate and 2,4-dimethoxybenzylamine was carried out by the slow addition of **3** to a mixture of **4** and an equimolar amount of triethylamine, the *cis* azetidinone (**2**) was isolated in 63% yield as colorless crystals, mp 172—175 °C (Chart 2). However, the isolation procedure was troublesome because the crude reaction product had to be purified by recrystallization from a large quantity of ethyl acetate in order to remove a crystalline by-product, *N*-(2,4-dimethoxybenzyl)phthalimidoacetamide (**5**). The formation of the *trans* isomer (**7**) was not detected by thin layer chromatography (TLC) of the reaction mixture. On the other hand, when triethylamine was added to a mixture of **3** and **4**, no β-lactams were formed, and after the removal of **5** by filtration, an acyl iminium salt, methyl *N*-(2,4-dimethoxybenzyl)-*N*-(phthalimidoacetyl)immonioacetate chloride (**6**), was isolated from the filtrate as a solid in 44% yield. Recrystallization of the crude salt from acetonitrile gave colorless, pure crystals of **6**, mp 187—190 °C, but **6** was fairly unstable and decomposed partly to the amide (**5**) on a silica gel TLC plate. These results suggested that in the former experiment two types of reactions to give **2** and **6** proceeded competitively and then the by-product (**6**) was further converted into **5** under the work-up conditions. The desired compound (**2**) seemed to be formed *via* the ketene (**8**) generated *in situ* from the reaction of **3** and triethylamine; therefore, in order to facilitate the formation of **8**, the amount of triethylamine was increased to 1.2 or 1.5 molar equivalents. As a result, **2** was obtained in the yield of 72 or 69%, respectively. In both cases the formation of the amide (**5**) was clearly reduced and **2** was isolated only by triturating the crude product with a small amount of ethyl acetate. This procedure was convenient for preparing large amounts of the starting material (**2**).

Isolation of the iminium salt (**6**) is of interest in connection with the long-standing question of the cycloaddition mechanism.[8] The structure of **6** was determined on the basis of the elementary analysis, and infrared (IR) and nuclear magnetic resonance (NMR) spectra. In the NMR spectrum taken at room temperature, the resonance due to the methyl group of the ester moiety was split into two singlets and appeared at 3.42 and 3.50 ppm in the ratio of 2 to 1. When the spectrum was measured at 60 °C, the resonance appeared at 3.47 ppm as a singlet. These results supported the presence of a carbon–nitrogen double bond in the molecule. Although intermediary formation of an acyl iminium salt such as **6** has been proposed in some cases of ketene–imine cycloaddition reaction,[8] isolation of this type of intermediate has not previously been reported to our knowledge.

The treatment of **2** with methylhydrazine[9] and the subsequent carbobenzoxylation of the resultant 3-amino intermediate (**9**) afforded *cis*-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-2-azetidinone (**10**) in 88% overall yield. The oxidative deblocking[10] of the ring nitrogen in **10** was carried out conveniently by using 1.4—1.5 molar equivalents of potassium persulfate to give *cis*-3-benzyloxycarbonylamino-4-methoxycarbonyl-2-azetidinone (**11**)[11] in 79% yield. When more than 1.6 molar equivalents of the oxidant were used, *cis*-3-benzyloxycarbonylamino-1-(2,4-dimethoxybenzoyl)-4-methoxycarbonyl-2-azetidinone (**12**) was isolated from the reaction mixture by column chromatography. The 2,4-dimethoxybenzyl moiety was recovered as 2,4-dimethoxybenzaldehyde (**13**) and the corresponding acid (**14**).

Hydrogenolysis of **11** gave *cis*-3-amino-4-methoxycarbonyl-2-azetidinone (**15**),[7] which was then acylated with 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-(substituted oxyimino)acetyl chlorides (**16a—j**) in the presence of sodium bicarbonate. The products (**17a—j**) were sulfonated[6] with sulfur trioxide–pyridine complex ($SO_3 \cdot Py$) or sulfur trioxide–*N*,*N*-dimethylformamide complex ($SO_3 \cdot DMF$), and the resultant 1-sulfo derivatives (**18a—j**) were

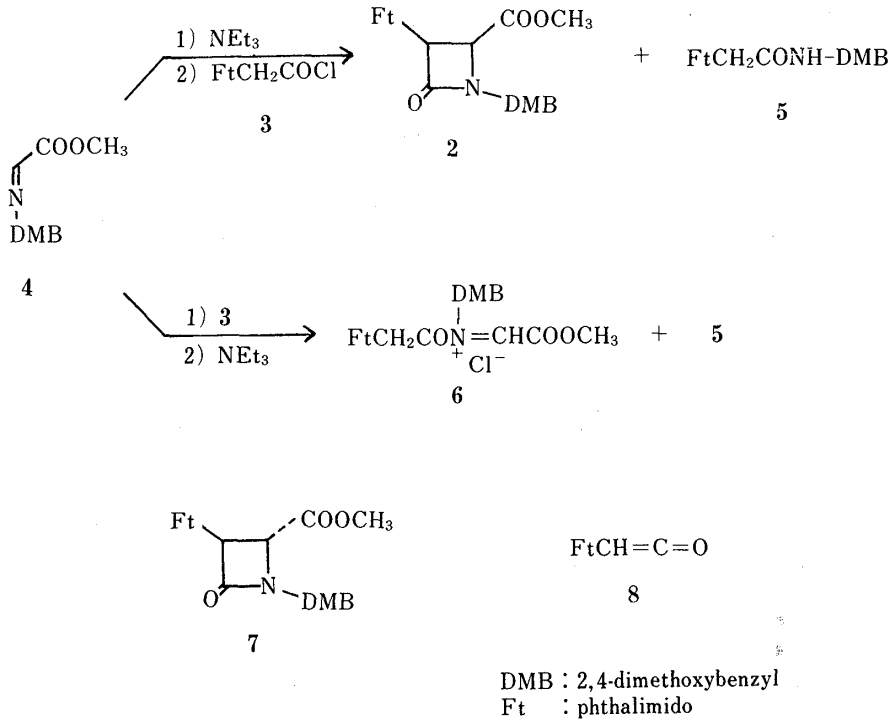


Chart 2

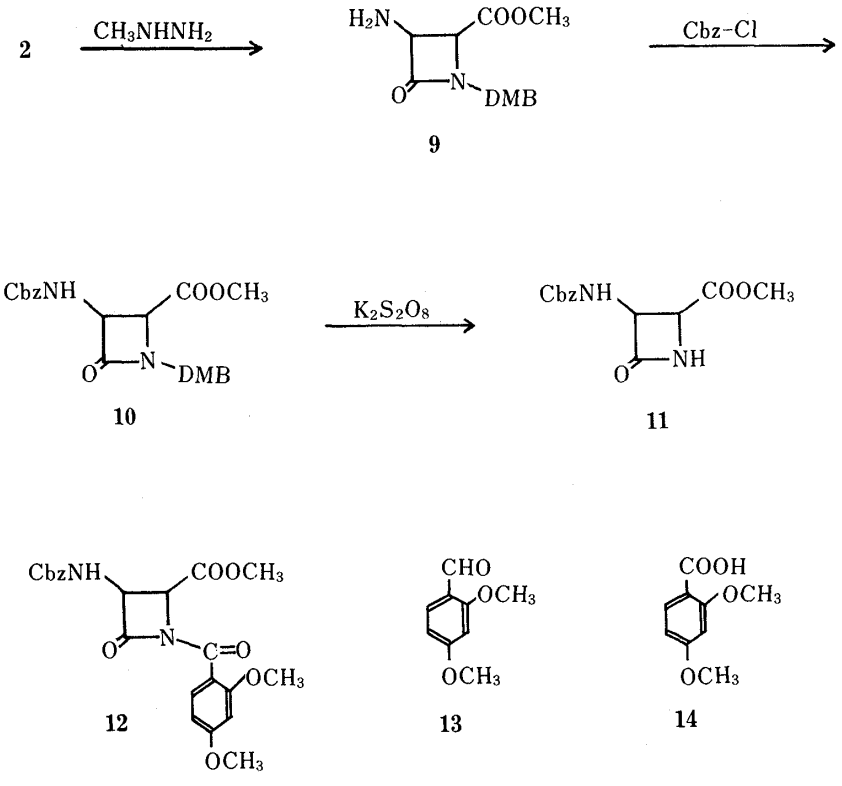
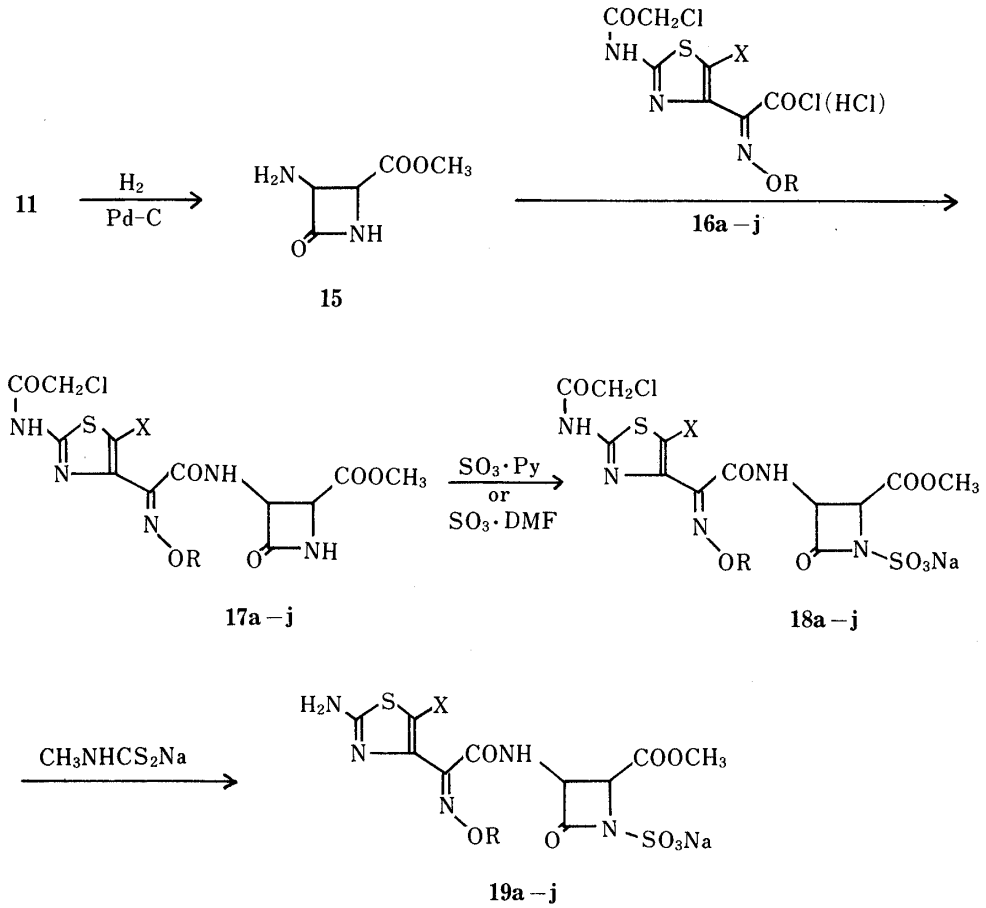


Chart 3

deprotected by treatment[12] with sodium *N*-methyldithiocarbamate to give sodium *cis*-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-(substituted oxyimino)acetamido]-4-methoxycarbonyl-2-azetidinone-1-sulfonates (**19a—j**) (Chart 4).



a: R=methyl, X=H
b: R=ethyl, X=H
c: R=*n*-propyl, X=H
d: R=isopropyl, X=H
e: R=*n*-butyl, X=H
f: R=benzyl, X=H
g: R=allyl, X=H
h: R=CH_2COOCH_3, X=H
i: R=$C(CH_3)_2COOCH_3$, X=H
j: R=methyl, X=Cl

Chart 4

Of these azetidinones, **19a** was the most active compound; its antimicrobial activity against gram-negative bacteria was higher than that of the corresponding 4-unsubstituted analogue,[6] and **19a** was highly active against *Escherichia coli* T-7, a producer of the TEM-1 β-lactamase. In order to confirm the effect of the 3,4-*cis* stereochemistry on the antimicrobial activity, we tried to synthesize the corresponding 3,4-*trans* isomer of **19a**.

Although the acyl iminium salt (**6**) did not react with triethylamine or diisopropylethylamine, it did react with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) to give a mixture of the *trans* β-lactam (**7**), *cis* isomer (**2**), amide (**5**), aldehyde (**13**), and some other compounds. Two major products, **7** and α-chloro-*N*-(2,4-dimethoxybenzyl)-*N*-phthalimidoacetylglycine methyl ester (**20**), were isolated from the reaction mixture by column chromatography in 10 and 8% yields, respectively, but the procedure was not applicable to the large-scale preparation of **7**. Therefore, we tried isomerizing the *cis* β-lactam (**2**). Bose *et al.*[13] reported the efficient conversion of *cis*-1,4-diphenyl-3-phthalimido-2-azetidinone into the corresponding *trans* isomer by heating the benzene solution in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). Although a similar treatment of **2** with DBN gave a poor result (*trans* : *cis* = 2 : 8), the use of DBU resulted in 90% conversion of **2** into **7** after reflux for 2 d. The *trans* isomer (**7**) was isolated directly from the equilibrated reaction mixture by trituration with ethyl acetate in 65% yield, and converted into the 3-acylamino derivative (**21**) (Chart 5). The antibacterial

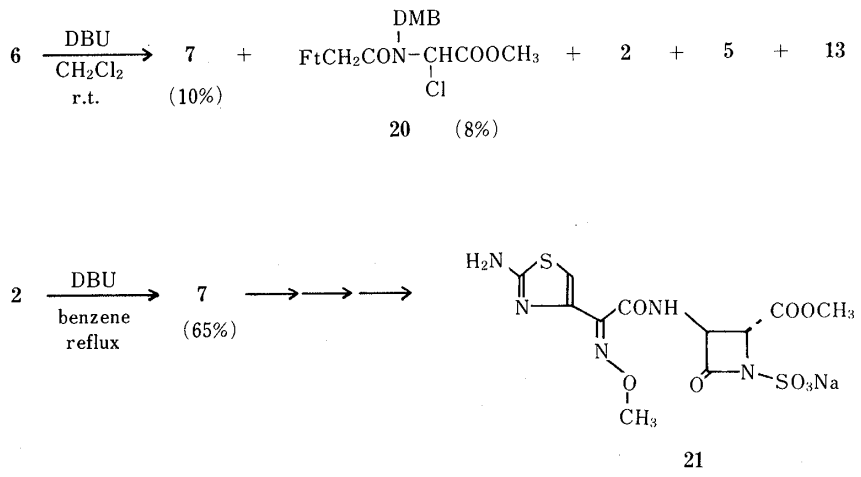
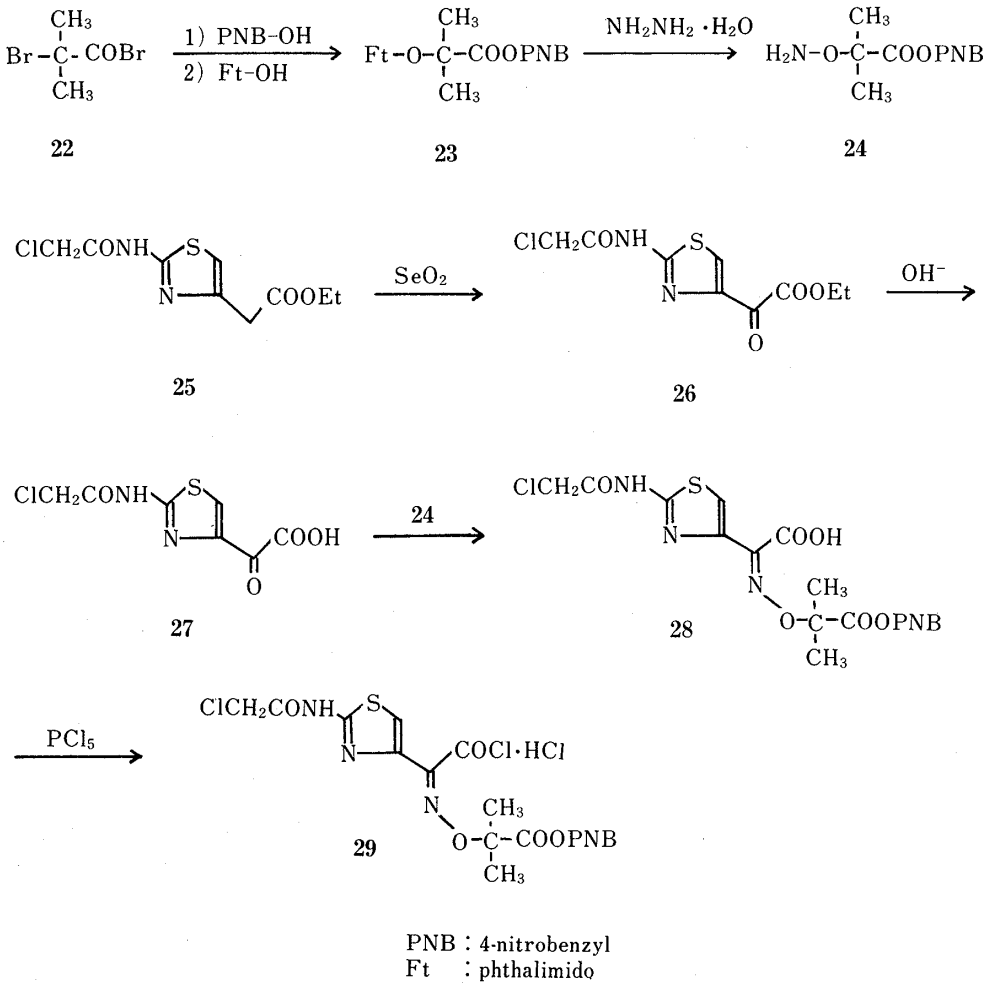


Chart 5



PNB : 4-nitrobenzyl
Ft : phthalimido

Chart 6

activity of **21** was generally lower than that of the corresponding *cis* isomer (**19a**) (Table I).

Since ceftazidime has unique antibacterial activity against gram-negative bacteria including *Pseudomonas aeruginosa*, the same acyl group as in ceftazidime was introduced[14] at the 3-position of **19a** and **21**. The acylating agent (**29**), in which the carboxyl group was conveniently protected as its 4-nitrobenzyl ester, was prepared as shown in Chart 6.

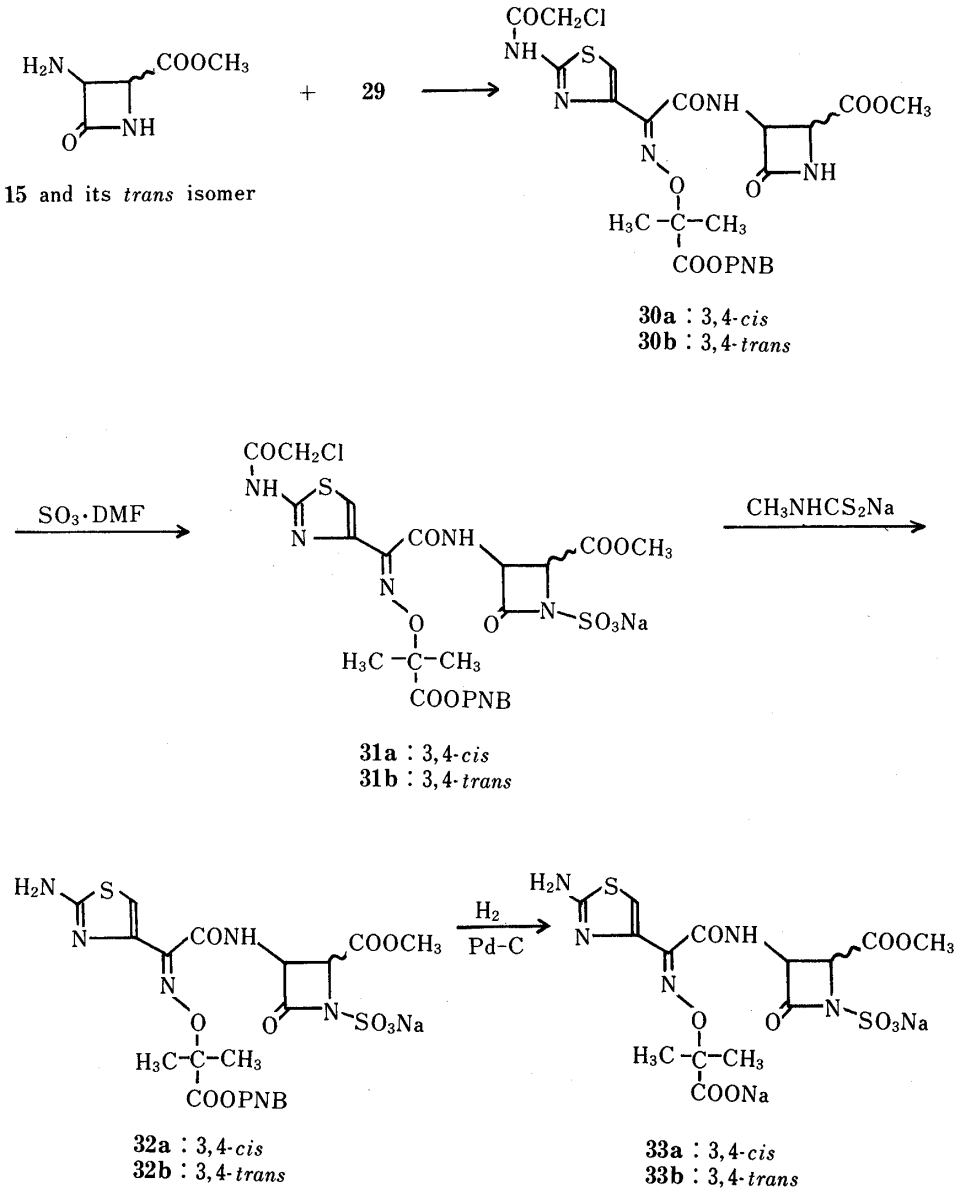


Chart 7

Acylation of **15** and its *trans* isomer with **29** and subsequent sulfonation with $SO_3 \cdot DMF$ gave *cis* and *trans* isomers of sodium 3-{2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]acetamido}-4-methoxycarbonyl-2-azetidinone-1-sulfonate (**31a**, **b**), respectively. After removal of the chloroacetyl groups, the 4-nitrobenzyl esters (**32a**, **b**) were easily hydrogenolyzed in the presence of palladium on carbon, and the products (**33a**, **b**) were isolated in the form of the disodium salts (Chart 7).

Although the *cis* isomer (**33a**) had an improved antibacterial spectrum, the potency was generally lower than that of **19a**. The *trans* isomer (**33b**) was as active as **33a** against many bacterial species tested, but was less active against *Enterobacter cloacae* IFO 12937 and *P. aeruginosa* IFO 3455 (Table I).[15] From these results it is apparent that introduction of a methoxycarbonyl group at the 4-position, especially in a 3,4-*cis* relation, resulted in significant enhancement of the antibacterial activity of 1-sulfo-2-azetidinone derivatives. Further modification at the 4-position starting from compounds **10** and **11** will be reported elsewhere.

TABLE I. Comparison of Antibacterial Activity[a] between 3,4-*cis*- and 3,4-*trans*-1-Sulfo-2-azetidinone Derivatives

(MIC: μg/ml)

Organism	β-Lactamase (Type)	**19a**	**21**	**33a**	**33b**
E. coli NIHJ JC-2		0.1	1.56	1.56	1.56
E. coli T-7	TEM-1[b]	0.78	3.13	1.56	1.56
E. cloacae IFO 12937	Ia[c]	25	25	3.13	25
S. marcescens IFO 12648	Ia[c]	0.2	6.25	1.56	0.78
P. vulgaris IFO 3988	Ic[c]	<0.1	1.56	0.39	0.2
P. aeruginosa IFO 3455	Ia[c]	25	>100	12.5	100

a) Activity was determined by the agar dilution method using an inoculum of 10^8 CFU/ml.
b) Plasmid-mediated β-lactamase.
c) Chromosomal β-lactamase (Richmond classification).

Experimental

Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrophotometer, and mass spectra (MS) with a Hitachi RMU-6D mass spectrometer. ^{1}H-Nuclear magnetic resonance (NMR) spectra were taken on a Varian EM-390 (90 MHz) spectrometer with tetramethylsilane as an internal standard. For some intermediates a Varian T-60 (60 MHz) spectrometer was also used. Chemical shifts are given on the δ scale.

***cis*-1-(2,4-Dimethoxybenzyl)-4-methoxycarbonyl-3-phthalimido-2-azetidinone (2)**——A solution of 2,4-dimethoxybenzylamine[16] (100.2 g, 0.6 mol) in dry dichloromethane (200 ml) was added to a stirred solution of methyl glyoxylate[17] (52.8 g, 0.6 mol) in dry dichloromethane (800 ml) at 0—5 °C. Within a few minutes, water began to separate out. Anhydrous magnesium sulfate ($MgSO_4$) (100 g) was added and the mixture was stirred for 2 h at 0—5 °C. After further addition of $MgSO_4$ (100 g) the whole mixture was stirred for 5 min and filtered. The solid cake was washed with dry dichloromethane (800 ml). The filtrate and washings were combined, and a solution of triethylamine (72.9 g, 0.72 mol) in dry dichloromethane (200 ml) was added at 0—5 °C over 10 min. Subsequently a solution of phthalimidoacetyl chloride (**3**) (134.2 g, 0.6 mol) in dry dichloromethane (600 ml) was added dropwise over 1.5 h and the mixture was stirred overnight at room temperature. After concentration to a half volume, the reaction solution was washed successively with 1 N HCl (2 × 350 ml), water (500 ml), 2% aq. $NaHCO_3$ (2 × 500 ml) and water (500 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. After addition of ethyl acetate (AcOEt) (600 ml) to the solid residue the mixture was warmed in a water bath and then allowed to stand at room temperature. The resulting crystals were collected by filtration to give **2** (182.8 g, 72%), which could be used for the next reaction without further purification. Recrystallization from AcOEt (20 times v/w) gave colorless needles, mp 172—175 °C. *Anal.* Calcd for $C_{12}H_{15}NO_4$: C, 62.26; H, 4.75; N, 6.60. Found: C, 62.22; H, 4.61; N, 6.58. IR ν_{max}^{Nujol} cm^{-1}: 1780, 1755, 1740, 1715. NMR (d_6-DMSO): 3.46 (3H, s, $COOCH_3$), 3.77 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.48 (1H, d, J=6 Hz, C_4–H), 4.48 (2H, q, J=15 Hz, N_1–CH_2), 5.65 (1H, d, J=6 Hz, C_3–H).

***N*-(2,4-Dimethoxybenzyl)phthalimidoacetamide (5) and Methyl *N*-(2,4-Dimethoxybenzyl)-*N*-(phthalimidoacetyl)immonioacetate Chloride (6)**——A solution of 2,4-dimethoxybenzylamine (16.7 g, 0.1 mol) in dry dichloromethane (40 ml) was added to a stirred solution of methyl glyoxylate (8.8 g, 0.1 mol) in dry dichloromethane (120 ml) at 0—5 °C. $MgSO_4$ (40 g) was added and the mixture was stirred for 2 h at 0—5 °C. After further addition of $MgSO_4$ (20 g) the whole mixture was stirred for 5 min and filtered. The solid cake was washed with dry dichloromethane (160 ml). The filtrate and washings were combined, and a solution of **3** (22.3 g, 0.1 mol) in dry dichloromethane (120 ml) was added dropwise at 0—5 °C over 30 min. The mixture was stirred for 20 min at the same temperature. Subsequently a solution of triethylamine (10.1 g, 0.1 mol) in dry dichloromethane (40 ml) was added dropwise over 1 h at room temperature and the reaction solution was stirred overnight. After addition of water (100 ml) the mixture was filtered, and the filtrate was placed in a separatory funnel. The organic layer was separated, washed successively with 0.5 N HCl, water, 2% aq. $NaHCO_3$ and water, then dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated to a half volume under reduced pressure. The resulting crystals were collected by

filtration, washed with a small amount of dichloromethane and recrystallized from acetone to give **5** (5.9 g, 17%) as colorless needles, mp 230—232 °C. *Anal.* Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.68; H, 5.04; N, 7.92. IR ν_{max}^{Nujol} cm^{-1}: 3290, 1770, 1720, 1640. NMR (d_6-DMSO): 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.17 (2H, d, J=6 Hz, $NHCH_2$), 4.24 (2H, s, CH_2CO), 7.90 (4H, s, aromatic protons), 8.43 (1H, t, J=6 Hz, NH).

The filtrate of the crude amide was concentrated under reduced pressure and the residue was subjected to chromatography on a small amount of silica gel. Elution with dichloromethane–AcOEt (20:1 v/v) and recrystallization from acetonitrile gave **6** (10.1 g, 22%) as colorless crystals, mp 187—190 °C. *Anal.* Calcd for $C_{22}H_{21}ClN_2O_7$: C, 57.33; H, 4.59; Cl, 7.69; N, 6.08. Found: C, 57.17; H, 4.53; Cl, 7.61; N, 6.38. IR ν_{max}^{Nujol} cm^{-1}: 1760, 1705, 1685. NMR (d_6-DMSO): 3.42, 3.50 (total 3H, two singlets, $COOCH_3$), 3.78, 3.87 (total 6H, two singlets, 2×OCH_3), 7.92 (4H, s, aromatic protons).

***trans*-1-(2,4-Dimethoxybenzyl)-4-methoxycarbonyl-3-phthalimido-2-azetidinone (7)**——(a) Treatment of **6** with DBU: 1,8-Diazabicyclo[5.4.0]-7-undecene (DBU) (0.8 g, 5 mmol) was added to a suspension of **6** (2.3 g, 5 mmol) in dichloromethane (50 ml), and the mixture was stirred for 5 h at room temperature. The clear reaction solution was washed successively with 1 N HCl (2×50 ml) and water, dried over $MgSO_4$ and concentrated under reduced pressure. AcOEt (40 ml) was added to the residue and the resulting precipitate was filtered off. The filtrate was concentrated under reduced pressure and the residue was subjected to chromatography on silica gel (100 g). Elution with benzene–AcOEt (4:1 v/v) gave α-chloro-*N*-(2,4-dimethoxybenzyl)-*N*-phthalimidoacetylglycine methyl ester (**20**) and **7**. Recrystallization of **7** from AcOEt (11 ml) gave colorless crystals (202 mg, 10%), mp 186—188 °C. *Anal.* Calcd for $C_{22}H_{20}N_2O_7$: C, 62.26; H, 4.75; N, 6.60. Found: C, 62.13; H, 4.64; N, 6.43. IR ν_{max}^{Nujol} cm^{-1}: 1785, 1765, 1745, 1720. NMR (d_6-DMSO): 3.67 (3H, s, $COOCH_3$), 3.77 (6H, s, 2×OCH_3), 4.39 (1H, d, J=3 Hz, C_4–H), 4.40 (2H, q, J=14 Hz, N_1–CH_2), 5.29 (1H, d, J=3 Hz, C_3–H).

Recrystallization of **20** from AcOEt–hexane (2:1 v/v) gave colorless crystals (175 mg, 8%), mp 176—178 °C. *Anal.* Calcd for $C_{22}H_{21}ClN_2O_7$: C, 57.33; H, 4.59; Cl, 7.69; N, 6.08. Found: C, 57.19; H, 4.68; Cl, 7.60; N, 5.94. MS *m/e*: 462, 460 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1765, 1735, 1710, 1685, 1610. NMR ($CDCl_3$): 3.57 (3H, s, $COOCH_3$), 3.81 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.7 (4H, 2×CH_2), 6.30 (1H, s, CH), 6.5, 7.25, 7.80 (total 7H, aromatic protons).

(b) Isomerization of **2**: A mixture of **2** (84.8 g, 0.2 mol) and DBU (30.4 g, 0.2 mol) in benzene (1.5 l) was heated under reflux for 48 h. After evaporation of the benzene under reduced pressure, the residue was dissolved in chloroform (1 l). The solution was washed successively with 1 N HCl (2×400 ml), water (400 ml), 2% aq. $NaHCO_3$ (2×500 ml) and water (400 ml), then dried over $MgSO_4$ and concentrated under reduced pressure. AcOEt (500 ml) was added to the residue, and the mixture was warmed in a water bath, then allowed to stand at room temperature. The resulting crystals were collected by filtration and washed with AcOEt to give **7** (54.7 g, 65%), which could be used for the next reaction without further purification. The IR and NMR spectra of the product were identical with those of **7** obtained above by method (a). The filtrate and washings were combined and concentrated under reduced pressure. Benzene (570 ml) and DBU (11.6 g) were added to the residue and the mixture was heated under reflux for 48 h. Similar work-up and trituration with AcOEt (200 ml) gave another crop of **7** (8.3 g, total 63.0 g, 74%).

***cis*-3-Benzyloxycarbonylamino-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-2-azetidinone (10) and Its *trans* Isomer**——A solution of methylhydrazine (38 ml) in dichloromethane (38 ml) was added dropwise to a stirred solution of **2** (160 g, 0.38 mol) in dichloromethane (1.6 l) over 10 min, and the mixture was stirred for 2 h at room temperature, for 8 h at 35 °C and overnight at room temperature. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in AcOEt and the solution was filtered. The filtrate was extracted with 1 N HCl and the aq. layer was neutralized with aq. $NaHCO_3$. The resulting oily substance was extracted into dichloromethane, and the extract was washed with satd. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to give *cis*-3-amino-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-2-azetidinone (**9**) as an oil, which crystallized in a refrigerator, mp 69—70 °C. The crude amine (**9**) was dissolved in dichloromethane (475 ml). After addition of propylene oxide (254 ml), carbobenzoxy chloride (77.8 g, 0.456 mol) was added dropwise to the stirred solution at 0—5 °C and the mixture was stirred for 1.5 h at room temperature, then concentrated under reduced pressure. Ether (800 ml) was added to the residue and the resulting crystals were collected by filtration to give **10** (143.6 g, 88%), which could be used for the next reaction without further purification. An analytical sample was obtained by chromatography on silica gel and recrystallization from ether as colorless crystals, mp 127—129 °C. *Anal.* Calcd for $C_{22}H_{24}N_2O_7$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.64; H, 5.67; N, 6.49. IR ν_{max}^{KBr} cm^{-1}: 3300, 1770, 1745, 1695. NMR ($CDCl_3$): 3.60 (3H, s, $COOCH_3$), 3.73 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.20 (1H, d, J=5 Hz, C_4–H), 4.37 (2H, q, J=13 Hz, N_1–CH_2), 5.03 (2H, s, CH_2Ph), 5.23 (1H, dd, J=5 and 9 Hz, C_3–H), 5.67 (1H, d, J=9 Hz, C_3–NH), 7.33 (5H, s, aromatic protons).

A similar procedure starting from **7** (10.5 g, 25 mmol) gave the *trans* isomer of **10**. The crude product was subjected to chromatography on silica gel (300 g), and elution with hexane–AcOEt (1:1) gave colorless crystals (9.5 g, 89%), mp 65—68 °C. *Anal.* Calcd for $C_{22}H_{24}N_2O_7$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.84; H, 5.48; N, 6.36. IR ν_{max}^{Nujol} cm^{-1}: 3320, 1770, 1760, 1735, 1725, 1710, 1690. NMR ($CDCl_3$): 3.67 (3H, s, $COOCH_3$), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.93 (1H, d, J=2 Hz, C_4–H), 4.25 (2H, q, J=15 Hz, N_1–CH_2), 4.56 (1H, dd, J=2 and 8 Hz, C_3–H), 5.03 (2H, s, CH_2Ph), 7.34 (5H, s, aromatic protons), 8.19 (1H, d, J=8 Hz, C_3–NH).

***cis*-3-Benzyloxycarbonylamino-4-methoxycarbonyl-2-azetidinone (11) and Its *trans* Isomer**——Compound **10**

(21.4 g, 50 mmol), $K_2S_2O_8$ (18.9 g, 70 mmol) and K_2HPO_4 (11.3 g, 65 mmol) were added to a mixture of acetonitrile (500 ml) and water (250 ml), and the whole was heated in an oil bath (95 °C) under reflux for 2 h. After evaporation of the acetonitrile under reduced pressure, the concentrate was extracted with AcOEt (2 × 100 ml). The extract was washed successively with 2% aq. $NaHCO_3$ (200 ml) and aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (200 g). Gradient elution with hexane–AcOEt (1 : 1→1 : 3 v/v) and subsequent recrystallization from AcOEt–hexane (2 : 1 v/v) gave **11** (8 g) as colorless crystals, mp 127—128 °C. The mother liquor of the first crop was concentrated under reduced pressure. Toluene (50 ml) was added to the residue, and the resulting crystals were collected by filtration and washed with toluene and ether to give another crop of **11** (3.1 g, total 11.1 g, 79%). *Anal.* Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.03; H, 5.01; N, 9.99. IR ν_{max}^{KBr} cm^{-1}: 3300, 1800, 1770, 1740, 1695, 1680. NMR ($CDCl_3$): 3.60 (3H, s, $COOCH_3$), 4.38 (1H, d, J=6 Hz, C_4–H), 5.06 (2H, s, $C\underline{H}_2Ph$), 5.30 (1H, dd, J=6 and 9 Hz, C_3–H), 7.23 (5H, s, aromatic protons).

The *trans* isomer of **11** was obtained in a similar manner as colorless crystals (70%), mp 138—139 °C (from AcOEt–ether). *Anal.* Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.03; H, 5.09; N, 9.85. IR ν_{max}^{Nujol} cm^{-1}: 3260, 1765, 1745, 1720, 1705. NMR (d_6-DMSO): 3.69 (3H, s, $COOCH_3$), 4.11 (1H, d, J=2.5 Hz, C_4–H), 4.58 (1H, dd, J=2.5 and 8 Hz, C_3–H), 5.06 (2H, s, $C\underline{H}_2Ph$), 7.37 (5H, s, aromatic protons), 8.16 (1H, d, J=8 Hz, C_3–NH), 8.60 (1H, s, N_1–H).

***cis*-3-Benzyloxycarbonylamino-1-(2,4-dimethoxybenzoyl)-4-methoxycarbonyl-2-azetidinone (12)**——Compound **10** (21.4 g, 50 mmol), $K_2S_2O_8$ (21.6 g, 80 mmol) and K_2HPO_4 (13.1 g, 75 mmol) were added to a mixture of acetonitrile (500 ml) and water (250 ml), and the mixture was heated in an oil bath (95 °C) under reflux for 2 h. After evaporation of the acetonitrile under reduced pressure, the concentrate was extracted with chloroform. The extract was washed with aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (200 g). Elution with hexane–AcOEt (1 : 1 v/v) gave 2,4-dimethoxybenzaldehyde (**13**) (6.2 g, 75%) and **12**. Recrystallization of **12** from methanol afforded colorless needles (1.0 g, 4.5%), mp 133—135 °C. *Anal.* Calcd for $C_{22}H_{22}N_2O_8$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.75; H, 4.81; N, 6.17. MS *m/e*: 442 (M^+), 165 (2,4-dimethoxyphenyl-C≡O^+). IR ν_{max}^{Nujol} cm^{-1}: 3275, 1815, 1745, 1700, 1680. NMR ($CDCl_3$): 3.73 (3H, s, $COOCH_3$), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.82 (1H, d, J=6 Hz, C_4–H), 5.10 (2H, s, $C\underline{H}_2Ph$), 5.42 (1H, dd, J=6 and 9 Hz, C_3–H), 5.73 (1H, d, J=9 Hz, C_3–NH), 7.36 (5H, s, aromatic protons).

Further elution with hexane–AcOEt (1 : 4 v/v) gave 2,4-dimethoxybenzoic acid (**14**) (68 mg, mp 108—109 °C)[18] and **11** (8.6 g, 62%).

***cis*-3-Amino-4-methoxycarbonyl-2-azetidinone (15) and Its *trans* Isomer**——A suspension of **11** (0.8 g, 2.9 mmol) and 5% Pd–C (50% wet, 0.8 g) in ethanol (20 ml) was stirred for 1 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was allowed to stand in a refrigerator to give **15** (0.38 g, 92%) as colorless crystals, mp 59—61 °C. *Anal.* Calcd for $C_5H_8N_2O_3$: C, 41.66; H, 5.59; N, 19.44. Found: C, 41.54; H, 5.59; N, 19.67. IR ν_{max}^{KBr} cm^{-1}: 3380, 3300, 1760, 1730. NMR ($CDCl_3$): 1.87 (2H, s, NH_2), 3.80 (3H, s, $COOCH_3$), 4.30 (1H, d, J=5 Hz, C_4–H), 4.53 (1H, d, J=5 Hz, C_3–H), 6.70 (1H, br s, N_1–H).

The *trans* isomer of **15** was obtained in a similar manner as colorless crystals (88%) by the use of methanol instead of ethanol. Recrystallization from AcOEt gave colorless needles, mp 135—136 °C. *Anal.* Calcd for $C_5H_8N_2O_3$: C, 41.66; H, 5.59; N, 19.43. Found: C, 41.68; H, 5.53; N, 19.32. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3300, 1760, 1740. NMR ($CDCl_3$): 3.2—3.4 (2H, br s, NH_2), 3.71 (3H, s, $COOCH_3$), 3.91 (1H, d, J=2 Hz, C_4–H), 4.33 (1H, d, J=2 Hz, C_3–H).

***cis*-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-methoxycarbonyl-2-azetidinone (17a)**——A solution of **15** (288 mg, 2 mmol) and $NaHCO_3$ (561 mg, 6.8 mmol) in water (6 ml) was added to a stirred suspension of 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetyl chloride (**16a**) (1.18 g, 4 mmol) in tetrahydrofuran (THF) (10 ml) at 0—5 °C. The mixture was stirred for 2 h at room temperature and then concentrated under reduced pressure. Water was added to the residue. The resulting precipitate was collected by filtration and washed successively with water and ethanol to give **17a** (500 mg, 62%) as colorless crystals, mp 270—275 °C (dec.). Compounds **17b, j** and the *trans* isomer of **17a** were similarly synthesized and the results are shown in Table II.

***cis*-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-(*n*-propoxyimino)acetamido]-4-methoxycarbonyl-2-azetidinone (17c)**——$NaHCO_3$ (729 mg, 8.7 mmol) and 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-(*n*-propoxyimino)acetyl chloride hydrochloride (**16c**) (937 mg, 2.6 mmol) were added to a solution of **15** (250 mg, 1.7 mmol) in a mixture of water (3 ml) and THF (3 ml) at 0—5 °C. The mixture was stirred for 2 h at room temperature and then concentrated under reduced pressure. Water was added to the residue. The resulting precipitate was collected by filtration and washed successively with aq. $NaHCO_3$, water, hexane and ether to give **17c** (650 mg, 87%) as colorless crystals, mp 260—270 °C (dec.). Compounds **17d—i** were similarly synthesized and the results are shown in Table II.

Sodium *cis*-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-methoxycarbonyl-2-azetidinone-1-sulfonate (18a)——A solution of **17a** (202 mg, 0.5 mmol) in *N,N*-dimethylformamide (DMF) (3.5 ml) was treated with SO_3·Py (159 mg, 1 mmol), and the mixture was stirred for 48 h at room temperature. After further addition of SO_3·Py (80 mg, 0.5 mmol), the mixture was stirred for 24 h. Ether (50 ml) was added, and the resulting

TABLE II. Synthesis of Compounds **17**

Compound	Form of **16**	Yield (%)	mp °C (dec.)	Molecular formula	Analysis (%) Calcd (Found) C	H	N	NMR (d_6-DMSO) 4-$COOCH_3$	Th-5-H[a]
17a	Free	62	270—275	$C_{13}H_{14}ClN_5O_6S$	38.66 (38.50	3.49 3.78	17.35 17.25)	3.63	7.24
17b	Free	75	280—290	$C_{14}H_{16}ClN_5O_6S$	40.24 (39.98	3.86 3.80	16.76 16.91)	3.62	7.30
17c	HCl salt	87	260—270	$C_{15}H_{18}ClN_5O_6S \cdot 1/3H_2O$	41.15 (41.26	4.30 4.24	16.00 16.34)	3.63	7.27
17d	HCl salt	49	215—225	$C_{15}H_{18}ClN_5O_6S \cdot 1/3H_2O$	41.15 (41.25	4.30 4.06	16.00 16.04)	3.62	7.26
17e	HCl salt	86	275—280	$C_{16}H_{20}ClN_5O_6S$	43.10 (42.93	4.52 4.45	15.71 15.61)	3.62	7.27
17f	HCl salt	96	275—285	$C_{19}H_{18}ClN_5O_6S$	47.55 (47.31	3.78 3.76	14.59 14.56)	3.54	7.28
17g	HCl salt	78	270—280	$C_{15}H_{16}ClN_5O_6S$	41.91 (41.83	3.75 3.85	16.29 16.37)	3.60	7.29
17h	HCl salt	85	260—265	$C_{15}H_{16}ClN_5O_8S$	39.01 (39.00	3.49 3.58	15.17 15.06)	3.61	7.34
17i	HCl salt	70	212—214	$C_{17}H_{20}ClN_5O_8S$	41.68 (41.47	4.12 4.14	14.30 14.06)	3.66	7.28
17j	Free	71	215—222	$C_{13}H_{13}Cl_2N_5O_6S \cdot 1/3H_2O$	35.14 (35.04	3.10 2.87	15.76 16.23)	3.63	—
trans-**17a**	Free	88	137—139	$C_{13}H_{14}ClN_5O_6S \cdot CH_3OH$[b]	38.57 (38.93	4.16 4.15	16.07 16.04)	3.70	7.35

a) Thiazole-5-H.
b) The crude product was recrystallized from methanol.

precipitate was collected by decantation, washed with ether and dissolved in water (5 ml). The solution was filtered and the filtrate was placed on a column of Dowex 50W (Na). Elution with water and subsequent lyophilization afforded a powder, which was subjected to chromatography on Amberlite XAD-2. Elution with 10% aq. ethanol and subsequent lyophilization gave **18a** (112 mg, 44%) as a colorless powder. Compounds **18b**—**j** and the *trans* isomer of **18a** were similarly synthesized and the results are shown in Table III.

Sodium *cis*-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-methoxycarbonyl-2-azetidinone-1-sulfonate (19a)——A stirred solution of **18a** (850 mg, 1.5 mmol) in water (20 ml) was treated with sodium *N*-methyldithiocarbamate (238.5 mg) at 0—5 °C, and the mixture was stirred for 40 min at room temperature. After further addition of sodium *N*-methyldithiocarbamate (70 mg), the reaction mixture was stirred for 30 min at room temperature and filtered. The filtrate was washed with ether and concentrated under reduced pressure. The residue was subjected to chromatography on Amberlite XAD-2. Elution with water and subsequent lyophilization gave **19a** (400 mg, 56%) as a colorless powder. Compounds **19b**—**j** and **21** were similarly synthesized and the results are shown in Table IV.

***N*-[1-Methyl-1-(4-nitrobenzyloxycarbonyl)ethoxy]phthalimide (23)**——α-Bromoisobutyryl bromide (**22**) (25.3 g, 0.11 mol) was added dropwise to a stirred solution of 4-nitrobenzyl alcohol (15.3 g, 0.1 mol) and pyridine (8.9 ml, 0.11 mol) in dry ether (250 ml) at 0—5 °C. The mixture was stirred for 5 h at room temperature. The resulting precipitate was removed by filtration, and AcOEt (150 ml) was added to the filtrate. The solution was washed successively with dil. HCl, water, aq. $NaHCO_3$ and aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (600 g). Elution with chloroform–hexane (1 : 1 v/v) gave 4-nitrobenzyl α-bromoisobutyrate (29.6 g, 98 mmol) as a yellow oil, which was dissolved in dry DMF (160 ml). *N*-Hydroxyphthalimide (16.0 g, 98 mmol) was added to the above solution with stirring, followed by addition of K_2CO_3 (13.5 g, 98 mmol), and the mixture was stirred for 24 h at room temperature, then concentrated to a half volume under reduced pressure. The concentrate was poured into water (760 ml) and the mixture was stirred for 30 min. The resulting crystals were collected by filtration, washed with water and dissolved in dichloromethane (550 ml). The solution was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The solid residue was triturated with ether–petroleum ether (1 : 1 v/v). The resulting crystals were collected by filtration

TABLE III. Synthesis of Compounds **18**

Compound	Yield (%)	Molecular formula	Analysis (%) Calcd (Found)			NMR (d_6-DMSO)	
			C	H	N	4-$COOCH_3$	Th-5-H[a]
18a	40	$C_{13}H_{13}ClN_5NaO_9S_2 \cdot 3H_2O$	27.88 (28.19	3.42 3.36	12.51 12.49)	3.60	7.23
18b	56	$C_{14}H_{15}ClN_5NaO_9S_2 \cdot 2H_2O$	30.25 (30.01	3.45 3.46	12.60 12.46)	3.62	7.29
18c	68	$C_{15}H_{17}ClN_5NaO_9S_2 \cdot 1/2H_2O$	33.18 (33.19	3.34 3.51	12.90 12.93)	3.60	7.25
18d	53	$C_{15}H_{17}ClN_5NaO_9S_2 \cdot 2H_2O$	31.61 (31.58	3.71 3.65	12.29 12.28)	3.62	7.24
18e	74	$C_{16}H_{19}ClN_5NaO_9S_2 \cdot 2H_2O$	32.91 (32.58	3.97 3.80	11.99 11.83)	3.60	7.25
18f	77	$C_{19}H_{17}ClN_5NaO_9S_2 \cdot H_2O$	38.03 (38.07	3.19 3.27	11.67 11.72)	3.52	7.27
18g	71	$C_{15}H_{15}ClN_5NaO_9S_2 \cdot 3/2H_2O$	32.23 (32.42	3.25 3.30	12.53 12.59)	3.60	7.27
18h	35	$C_{15}H_{15}ClN_5NaO_{11}S_2 \cdot 5/2H_2O$	29.58 (29.49	3.31 3.30	11.50 11.56)	3.60	7.31
18i	84	$C_{17}H_{19}ClN_5NaO_{11}S_2 \cdot 3/2H_2O$	32.99 (33.26	3.58 3.64	11.32 11.14)	3.63	7.27
18j	57	$C_{13}H_{12}Cl_2N_5NaO_9S_2 \cdot 2H_2O$	27.09 (27.42	2.80 2.80	12.15 12.39)	3.63	—
trans-**18a**	41	$C_{13}H_{13}ClN_5NaO_9S_2 \cdot 3/2H_2O$	29.30 (29.11	3.03 3.34	13.14 13.30)	3.70	7.40

a) Thiazole-5-H.

and washed with a small amount of ether to give **23** (29.4 g, 76%), mp 145—146 °C. *Anal.* Calcd for $C_{19}H_{16}N_2O_7$: C, 59.38; H, 4.20; N, 7.29. Found: C, 59.14; H, 4.27; N, 7.26. IR ν_{max}^{KBr} cm^{-1}: 1790, 1740, 1725, 1520, 1345. NMR (d_6-DMSO): 1.61 (6H, s, $2 \times CH_3$), 5.28 (2H, s, $COOCH_2$), 7.59, 8.10 (4H, $2 \times$ d, J=9 Hz, aromatic protons), 7.75 (4H, s, aromatic protons).

***O*-[1-Methyl-1-(4-nitrobenzyloxycarbonyl)ethyl]hydroxylamine (24)**——Hydrazine hydrate (0.97 ml, 20 mmol) was added to a stirred solution of **23** (7.68 g, 20 mmol) in dichloromethane (80 ml) at 0—5 °C, and the mixture was stirred for 2 h at room temperature. After further addition of hydrazine hydrate (0.97 ml, 20 mmol), the reaction mixture was stirred for 3 h. The resulting precipitate was removed by filtration. The filtrate was washed successively with dil. NH_4OH and water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (300 g). Elution with hexane–AcOEt (1 : 1 v/v) gave **24** (4.58 g, 90%) as a yellow oil, which solidified in a refrigerator. The crude product was used for the next reaction without further purification.

Ethyl (2-Chloroacetamidothiazol-4-yl)glyoxylate (26)——Selenium dioxide (28.3 g, 0.255 mol) was added to a solution of ethyl (2-chloroacetamidothiazol-4-yl)acetate[19] (**25**) (53.2 g, 0.20 mol) in a mixture of dioxane (510 ml) and acetic acid (42.6 ml). The mixture was heated under reflux for 4 h at 110—115 °C and then cooled to room temperature. The black precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in AcOEt (3 l), and the solution was washed successively with aq. $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in hot AcOEt (1 l), and hexane (0.8 l) was added to the solution. The resulting yellow needles were collected by filtration to give **26** (35 g, 62.5%), mp 176—178 °C. Recrystallization of the crude product from AcOEt–hexane gave an analytical sample, mp 178—180 °C. *Anal.* Calcd for $C_9H_9ClN_2O_4S$: C, 39.07; H, 3.28; N, 10.12. Found: C, 39.16; H, 3.21; N, 10.13. IR ν_{max}^{KBr} cm^{-1}: 3220, 3000, 1740, 1710, 1680. NMR (d_6-DMSO): 1.31 (3H, t, CH_3), 4.35 (2H, q, $COOCH_2$), 4.40 (2H, s, $ClCH_2$), 8.49 (1H, s, thiazole-5-H).

(2-Chloroacetamidothiazol-4-yl)glyoxylic Acid (27)——A stirred suspension of **26** (35 g, 0.13 mol) in ethanol (646 ml) was treated dropwise with 1 N NaOH (250 ml) at 0—5 °C. The mixture was stirred for 1 h at room temperature, and then concentrated under reduced pressure. The residue was dissolved in water (300 ml) and the solution was washed with AcOEt (400 ml). After treatment with charcoal, the aq. layer was adjusted to pH 1.5 with 10% HCl. The resulting crystals were collected by filtration and washed successively with water and hexane to give **27**

TABLE IV. Synthesis of Compounds **19** and **21**

Compound	Yield (%)	Molecular formula	Analysis (%) Calcd (Found)			NMR (d_6-DMSO)	
			C	H	N	4-COOCH$_3$	Th-5-H[a]
19a	56	$C_{11}H_{12}N_5NaO_8S_2 \cdot 5/2H_2O$	27.85 (27.94)	3.61 3.53	14.76 14.77)	3.61	6.56
19b	70	$C_{12}H_{14}N_5NaO_8S_2 \cdot 2H_2O$	30.06 (30.33	3.78 3.53	14.61 14.76)	3.61	6.56
19c	78	$C_{13}H_{16}N_5NaO_8S_2 \cdot 2H_2O$	31.64 (31.70	4.09 3.81	14.19 14.43)	3.61	6.52
19d	68	$C_{13}H_{16}N_5NaO_8S_2 \cdot 2H_2O$	31.64 (31.92	4.09 3.85	14.19 14.37)	3.62	6.53
19e	62	$C_{14}H_{18}N_5NaO_8S_2 \cdot 2H_2O$	33.13 (33.01	4.37 4.10	13.80 13.85)	3.61	6.54
19f	88	$C_{17}H_{16}N_5NaO_8S_2 \cdot 2H_2O$	37.70 (37.26	3.72 3.37	12.93 12.93)	3.54	6.57
19g	82	$C_{13}H_{14}N_5NaO_8S_2 \cdot 3/2H_2O$	32.36 (32.47	3.55 3.75	14.52 14.46)	3.60	6.56
19h	69	$C_{13}H_{14}N_5NaO_{10}S_2 \cdot 2H_2O$	29.83 (30.14	3.47 3.52	13.38 13.48)	3.60	6.64
19i	74	$C_{15}H_{18}N_5NaO_{10}S_2 \cdot 2H_2O$	32.67 (32.63	4.02 3.96	12.70 12.43)	3.62	6.58
19j	63	$C_{11}H_{11}ClN_5NaO_8S_2 \cdot 2H_2O$	26.43 (26.11	3.02 3.15	14.01 14.13)	3.64	—
21	88	$C_{11}H_{12}N_5NaO_8S_2 \cdot 2H_2O$	28.39 (28.35	3.47 3.63	15.05 15.09)	3.70	6.70

a) Thiazole-5-H.

(26.5 g, 84%). Recrystallization from AcOEt–hexane gave pale yellow prisms, mp 205—210 °C (dec.). *Anal.* Calcd for $C_7H_5ClN_2O_4S$: C, 33.81; H, 2.03; N, 11.27. Found: C, 33.94; H, 2.04; N, 11.23. IR ν_{max}^{KBr} cm^{-1}: 3450, 3200, 1720 (br), 1680. NMR (d_6-DMSO): 4.29 (2H, s, ClCH$_2$), 8.30 (1H, s, thiazole-5-H).

2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]acetic Acid (28)——Compound **24** (1.83 g, 7.2 mmol) was added to a stirred solution of **27** (1.5 g, 6 mmol) in a mixture of water (30 ml) and THF (18 ml). The mixture was adjusted to pH 5.0 with 1 N NaOH, stirred for 12 h at room temperature, then adjusted to pH 7.0 with aq. NaHCO$_3$. THF was evaporated off under reduced pressure. The residual solution was washed with ether, adjusted to pH 2 with dil. HCl and extracted with AcOEt. The extract was washed with aq. NaCl, dried over MgSO$_4$ and concentrated under reduced pressure. The residue was dissolved in ether and the solution was poured into petroleum ether. The resulting powder was collected by filtration to give **28** (2.4 g, 82%), which was used for the next reaction without further purification. IR ν_{max}^{KBr} cm^{-1}: 1740, 1695, 1540, 1520, 1345. NMR (CDCl$_3$): 1.61 (6H, s, 2 × CH$_3$), 4.29 (2H, s, ClCH$_2$), 5.23 (2H, s, COOCH$_2$), 7.26 (1H, s, thiazole-5-H), 7.43, 8.05 (4H, 2 × d, J=9 Hz, aromatic protons).

2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]acetyl Chloride Hydrochloride (29)——PCl$_5$ (686 mg, 3.3 mmol) was added to a stirred solution of **28** (1.5 g, 3 mmol) in dichloromethane (15 ml) at 0—5 °C. The mixture was stirred for 30 min at the same temperature. After addition of hexane (45 ml), the whole was stirred for 30 min. The resulting colorless crystals were collected by filtration and washed with hexane to give **29** (1.53 g, 95%), mp 79—82 °C. *Anal.* Calcd for $C_{18}H_{16}Cl_2N_4O_7S \cdot HCl$: C, 40.05; H, 3.17; N, 10.38. Found: C, 39.80; H, 3.31; N, 10.30. IR ν_{max}^{KBr} cm^{-1}: 2998, 1775, 1735, 1715, 1565, 1520, 1340, 1140.

***cis*-3-{2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]acetamido}-4-methoxycarbonyl-2-azetidinone (30a)**——A suspension of **11** (417 mg, 1.5 mmol) and 5% Pd–C (200 mg) in ethanol (20 ml) was stirred for 30 min at room temperature under a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of THF (15 ml) and water (15 ml), and NaHCO$_3$ (336 mg, 4 mmol) was added to the stirred solution at 0—5 °C. After addition of **29** (972 mg, 1.8 mmol) the mixture was stirred for 30 min at room temperature and extracted with a mixture of AcOEt and THF. The extract was washed successively with aq. NaHCO$_3$ and aq. NaCl, dried over MgSO$_4$ and concentrated under reduced pressure. The residue was triturated with ether–AcOEt (5 : 1), and the resulting crystals were collected

by filtration and washed with ether to give **30a** (704 mg, 77%), mp 198—202 °C (dec.), which was used for the next reaction without further purification. IR ν_{max}^{KBr} cm^{-1}: 3360, 1770, 1745, 1690. NMR (d_6-DMSO): 1.52 (6H, s, 2×CH_3), 3.63 (3H, s, $COOCH_3$), 4.34 (2H, s, $ClCH_2$), 4.47 (1H, d, J=6 Hz, C_4–H), 5.29 (2H, s, $COOCH_2$), 5.48 (1H, dd, J=6 and 9 Hz, C_3–H), 7.23 (1H, s, thiazole-5-H), 7.53, 7.98 (4H, 2×d, J=9 Hz, aromatic protons), 8.64 (1H, br s, N_1–H), 9.28 (1H, d, J=9 Hz, C_3–NH).

The *trans* isomer (**30b**) was similarly synthesized in 86% yield, mp 110—120 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3280, 2980, 2765 (br), 1680. NMR (d_6-DMSO): 1.52 (6H, s, 2×CH_3), 3.72 (3H, s, $COOCH_3$), 4.18 (1H, d, J=3 Hz, C_4–H), 4.32 (2H, s, $ClCH_2$), 4.89 (1H, dd, J=3 and 9 Hz, C_3–H), 5.32 (2H, s, $COOCH_2$), 7.36 (1H, s, thiazole-5-H), 7.62, 8.09 (4H, 2×d, J=9 Hz, aromatic protons), 8.71 (1H, s, N_1–H), 9.30 (1H, d, J=9 Hz, C_3–NH).

Sodium *cis*-3-{2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]-acetamido}-4-methoxycarbonyl-2-azetidinone-1-sulfonate (31a)——A solution of **30a** (550 mg, 0.9 mmol) in DMF (3 ml) was treated with 1.69 M SO_3·DMF solution (1.6 ml, 2.7 mmol) at −78 °C. The mixture was stirred for 24 h at 5 °C. Pyridine (0.22 ml, 2.7 mmol) was added, and the solution was poured into ether (75 ml). The resulting syrupy precipitate was separated by decantation, washed with ether (2×50 ml) and suspended in water (25 ml). Dowex 50W (Na) (20 ml) was added and the mixture was stirred for 1.5 h at room temperature. The resin was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on Amberlite XAD-2 (100 ml). Gradient elution with aq. ethanol (0→30% v/v) and lyophilization of the eluate gave **31a** (505 mg, 77%) as a colorless powder. *Anal.* Calcd for $C_{23}H_{22}ClN_6NaO_{13}S_2 \cdot H_2O$: C, 37.79; H, 3.31; N, 11.50. Found: C, 37.50; H, 3.42; N, 11.69. IR ν_{max}^{KBr} cm^{-1}: 1775, 1740, 1680. NMR (d_6-DMSO): 1.50 (6H, s, 2×CH_3), 3.62 (3H, s, $COOCH_3$), 4.33 (2H, s, $ClCH_2$), 4.51 (1H, d, J=6 Hz, C_4–H), 5.31 (2H, s, $COOCH_2$), 5.52 (1H, dd, J=6 and 9 Hz, C_3–H), 7.25 (1H, s, thiazole-5-H), 7.62, 8.07 (4H, 2×d, J=9 Hz, aromatic protons), 9.33 (1H, d, J=9 Hz, C_3–NH).

The *trans* isomer (**31b**) was similarly synthesized in 60% yield. *Anal.* Calcd for $C_{23}H_{22}ClN_6NaO_{13}S_2 \cdot 2H_2O$: C, 36.88; H, 3.50; N, 11.22. Found: C, 37.02; H, 3.41; N, 11.54. IR ν_{max}^{KBr} cm^{-1}: 1780, 1740, 1680. NMR (d_6-DMSO): 1.53 (6H, s, 2×CH_3), 3.70 (3H, s, $COOCH_3$), 4.15 (1H, d, J=3 Hz, C_4–H), 4.34 (2H, s, $ClCH_2$), 4.89 (1H, dd, J=3 and 8 Hz, C_3–H), 5.34 (2H, s, $COOCH_2$), 7.39 (1H, s, thiazole-5-H), 7.63, 8.10 (4H, 2×d, J=9 Hz, aromatic protons), 9.51 (1H, d, J=8 Hz, C_3–NH).

Sodium *cis*-3-{2-(2-Aminothiazol-4-yl)-(*Z*)-2-[1-methyl-1-(4-nitrobenzyloxycarbonyl)ethoxyimino]acetamido}-4-methoxycarbonyl-2-azetidinone-1-sulfonate (32a)——Sodium *N*-methyldithiocarbamate (241 mg, 1.9 mmol) was added to a stirred solution of **31a** (1.16 g, 1.5 mmol) in water (30 ml). The mixture was stirred for 1 h at room temperature and the same amount of sodium *N*-methyldithiocarbamate was added again. The mixture was stirred for an additional 1 h, then washed with ether and concentrated under reduced pressure. The residue was subjected to chromatography on Amberlite XAD-2 (350 ml). Gradient elution with aq. ethanol (0→20% v/v) and lyophilization of the eluate gave **32a** (710 mg, 69%) as a colorless powder. *Anal.* Calcd for $C_{21}H_{21}N_6NaO_{12}S_2 \cdot 5/2H_2O$: C, 37.01; H, 3.84; N, 12.33. Found: C, 36.99; H, 3.87; N, 12.34. IR ν_{max}^{KBr} cm^{-1}: 1775, 1740, 1680, 1615. NMR (d_6-DMSO): 1.48 (6H, s, 2×CH_3), 3.63 (3H, s, $COOCH_3$), 4.50 (1H, d, J=6 Hz, C_4–H), 5.33 (2H, s, $COOCH_2$), 5.47 (1H, dd, J=6 and 9 Hz, C_3–H), 6.59 (1H, s, thiazole-5-H), 7.24 (2H, br s, NH_2), 7.65, 8.14 (4H, 2×d, J=9 Hz, aromatic protons), 9.18 (1H, d, J=9 Hz, C_3–NH).

The *trans* isomer (**32b**) was similarly synthesized in 77% yield. *Anal.* Calcd for $C_{21}H_{21}N_6NaO_{12}S_2 \cdot 2H_2O$: C, 37.01; H, 3.84; N, 12.33. Found: C, 36.90; H, 3.78; N, 12.30. IR ν_{max}^{KBr} cm^{-1}: 1780, 1740, 1670, 1600. NMR (d_6-DMSO): 1.50 (6H, s, 2×CH_3), 3.69 (3H, s, $COOCH_3$), 4.15 (1H, d, J=3 Hz, C_4–H), 4.82 (1H, dd, J=3 and 9 Hz, C_3–H), 5.33 (2H, s, $COOCH_2$), 6.70 (1H, s, thiazole-5-H), 7.25 (2H, br s, NH_2), 7.65, 8.15 (4H, 2×d, J=9 Hz, aromatic protons), 9.37 (1H, d, J=9 Hz, C_3–NH).

***cis*-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(1-carboxy-1-methylethoxyimino)acetamido]-4-methoxycarbonyl-2-azetidinone-1-sulfonic Acid Disodium Salt (33a)**——A suspension of **32a** (500 mg, 0.73 mmol) and 10% Pd–C (500 mg) in a mixture of water (25 ml) and THF (25 ml) was stirred for 1 h at room temperature under a hydrogen atmosphere. A solution of $NaHCO_3$ (62 mg) in water (25 ml) was added, and the mixture was filtered. The filtrate was washed with AcOEt and concentrated under reduced pressure. The residue was subjected to chromatography on Amberlite XAD-2 (350 ml). Elution with water and lyophilization of the eluate gave **33a** (316 mg, 72%) as a colorless powder. *Anal.* Calcd for $C_{14}H_{15}N_5Na_2O_{10}S_2 \cdot 4H_2O$: C, 28.24; H, 3.89; N, 11.76. Found: C, 28.26; H, 3.68; N, 11.62. IR ν_{max}^{KBr} cm^{-1}: 1775, 1740, 1660, 1630. NMR (d_6-DMSO): 1.36 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.61 (3H, s, $COOCH_3$), 4.53 (1H, d, J=6 Hz, C_4–H), 5.47 (1H, dd, J=6 and 9 Hz, C_3–H), 6.60 (1H, s, thiazole-5-H), 7.13 (2H, br s, NH_2), 11.20 (1H, d, J=9 Hz, C_3–NH).

The *trans* isomer (**33b**) was similarly synthesized in 55% yield. *Anal.* Calcd for $C_{14}H_{15}N_5Na_2O_{10}S_2 \cdot 5H_2O$: C, 27.41; H, 4.11; N, 11.42. Found: C, 27.10; H, 3.90; N, 11.46. IR ν_{max}^{KBr} cm^{-1}: 1780, 1745. NMR (d_6-DMSO): 1.40 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.70 (3H, s, $COOCH_3$), 4.17 (1H, d, J=3 Hz, C_4–H), 4.85 (1H, dd, J=3 and 9 Hz, C_3–H), 6.73 (1H, s, thiazole-5-H), 7.12 (2H, s, NH_2), 11.70 (1H, d, J=9 Hz, C_3–NH).

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