[Chem. Pharm. Bull. 31(6)1874—1884(1983)]

Synthesis and Antibacterial Activity of 3-Acylamino-2-azetidinone-1-sulfonic Acid Derivatives[1)]

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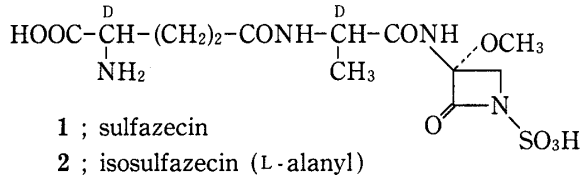
(Received November 12, 1982)

Sulfazecin (**1**) is a monocyclic β-lactam antibiotic isolated from strain G-6302, *Pseudomonas acidophila*. As a key intermediate for the synthesis of sulfazecin derivatives, 3-amino-2-azetidinone (**16**) was synthesized from penicillins, and various new compounds were synthesized by acylation and sulfonation of **16**. Some of these new compounds showed potent antibacterial activity.

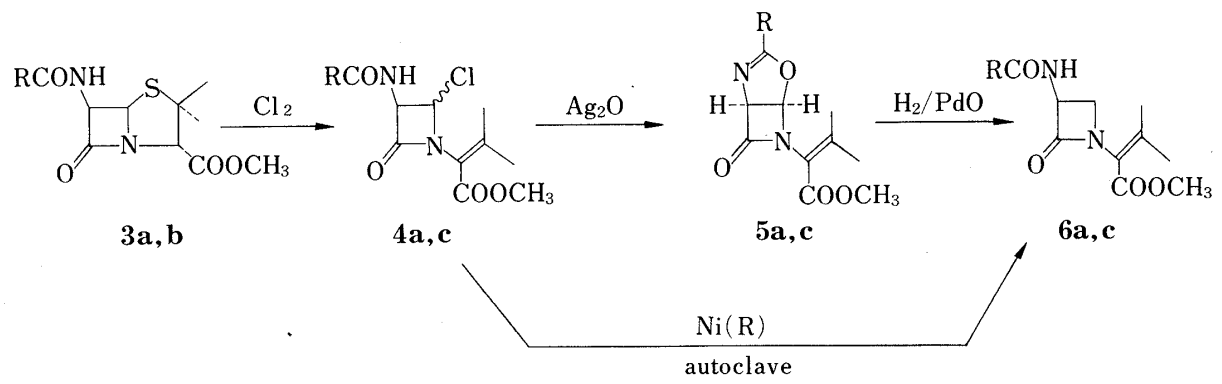
Keywords——monocyclic β-lactam; sulfazecin; 3-amino-2-azetidinone; sulfonation; 3-acylamino-2-azetidinone; antibacterial activity

Imada *et al.*[2a)] first reported that novel monocyclic β-lactam antibiotics, sulfazecin (**1**) and isosulfazecin (**2**), are produced by new species of *Pseudomonas*. The isolation of some other monocyclic β-lactam antibiotics having structures closely related to that of sulfazecin was later reported by Sykes *et al.*[2b)] These compounds are novel monocyclic β-lactam antibiotics of unique structure, and the 1-sulfo-2-azetidinone moiety appears to be essential for the antibacterial activity. From the practical standpoint, it was desirable to improve and/or enhance the antibacterial activity of sulfazecin (**1**) or isosulfazecin (**2**). Therefore, extensive chemical modification studies have been carried out on these compounds. In this paper the synthesis and antibacterial activity of various 3-acylamino-2-azetidinone-1-sulfonic acid derivatives (**21**) will be described.

The 4-unsubstituted azetidinone derivatives (**6**) were synthesized by the sequence of reactions shown in Charts 1 and 2. By analogy with the reaction reported by Kukolja,[3)] the 4-chloro azetidinone derivative (**4a**) was synthesized by treating penicillin methyl esters (**3a**) with three equivalents of chlorine. In the case of **3b**, the 4-chloro derivative (**4b**) could not be



1 ; sulfazecin
2 ; isosulfazecin (L-alanyl)



3a,b **4a,c** **5a,c** **6a,c**

a: R=$C_6H_5CH_2$–, **b**: R=$C_6H_5OCH_2$–, **c**: R=*p*-Cl-$C_6H_4OCH_2$–

Chart 1

obtained under similar reaction conditions and four equivalents of chlorine were necessary for the completion of the reaction which, however, led only to the dichlorinated compound (**4c**). Removal of the chloro substituent with silver oxide followed by purification by column chromatography gave the oxazoline derivatives (**5a, c**), which were converted into the 4-unsubstituted azetidinone derivatives (**6a, c**) by catalytic reduction with palladium oxide.[4] Treatment of **4c** with Raney nickel in ethyl acetate or tetrahydrofuran in an autoclave afforded an alternative and direct route to **6c** (yields; 35 and 45%, respectively). Similar treatment of **4a**, however, resulted in the formation of unidentified decomposition compounds probably due to the instability of the chloro compound **4a** under these reaction conditions (Chart 1).

As shown in Chart 2, the desulfurization reaction[5] was successfully extended to the synthesis of the desired compounds (**6**). Monitoring of the reaction of the compounds **9** with Raney nickel by thin layer chromatography suggested an intermediary formation of the symmetrical disulfide derivatives (**11**). The symmetrical disulfides (**11**) which were prepared either by the treatment of the disulfide derivatives (**9**)[6a] with Raney nickel or by the treatment of the thiazoline derivatives (**10**)[6b] with iodine[6c] were proved to give the 4-unsubstituted azetidinone derivatives (**6**) on further treatment with Raney nickel. On the other hand, the 4-methylthio derivative (**12a**)[7] was found to be rather resistant to the desulfurization reaction compared with the disulfide compound **11a**.

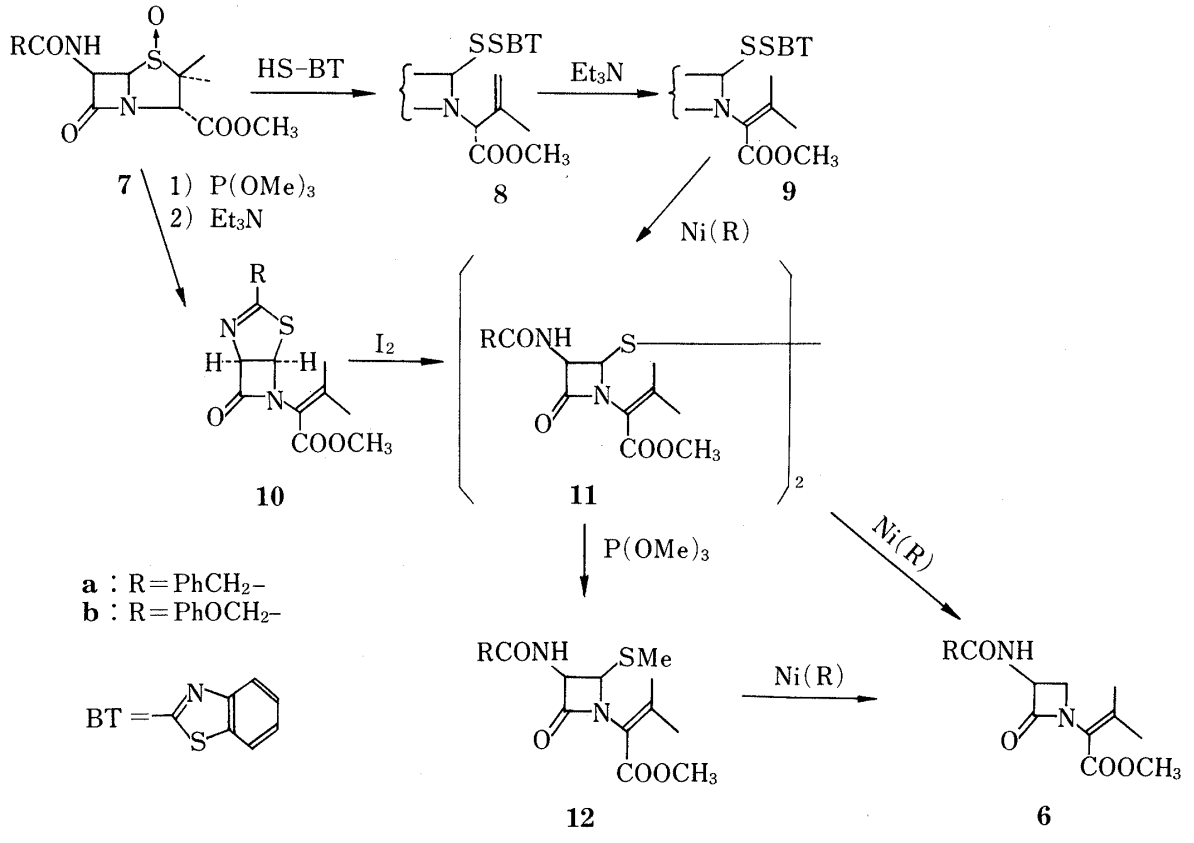


Chart 2

The 3-acylamino-2-azetidinone-1-sulfonic acid derivatives (**21**) were obtained by means of the reactions shown in Chart 3. The 3-benzyloxycarbonylamino derivative (**14**) was synthesized by acylation of the 3-amino derivative (**13**) with benzyloxycarbonyl chloride. The compound **14** was ozonized followed by solvolysis[8] to give 3-benzyloxycarbonylamino-2-azetidinone (**15**). This compound **15** was treated with 10% palladium on carbon in ethyl alcohol to obtain an important intermediate, 3-amino-2-azetidinone (**16**). After removal of the substituent at the 1-position from **6**, compound **17** was obtained. However, attempts to

deacylate **17** to yield **16** have so far been unsuccessful. Acylation of **16** was carried out by the mixed anhydride, acid chloride or dicyclohexylcarbodiimide (DCC) method to yield 3-acylamino-2-azetidinone derivatives (**18**).[9] Sulfonation of **18** with sulfur trioxide–pyridine (SO_3–pyridine) or sulfur trioxide–dimethylformamide (SO_3–DMF) complex in dimethylformamide gave the 3-acylamino-2-azetidinone-1-sulfonic acid derivatives (**21**). The compounds **21** were also synthesized by the sulfonation of **15** followed by deprotection and acylation (Chart 3).

The *in vitro* antibacterial activities of the newly synthesized 3-acylamino-2-azetidinone-1-sulfonic acid derivatives (**21**) against several bacteria are shown in Tables I and II. From Table I it is apparent that the 3-amino derivative (**20**) has no significant antibacterial activity, but the 3-acylamino derivatives show potent activity. Table II indicates the effect of the acyl group and variations at the oxyimino moiety on the antibacterial activity. Variation of the acyl group (**21b,i,j** and **k**) caused changes in activity. Compounds (**21m, n** and **p**)[10] showed remarkable activity, especially against Gram-negative bacteria.

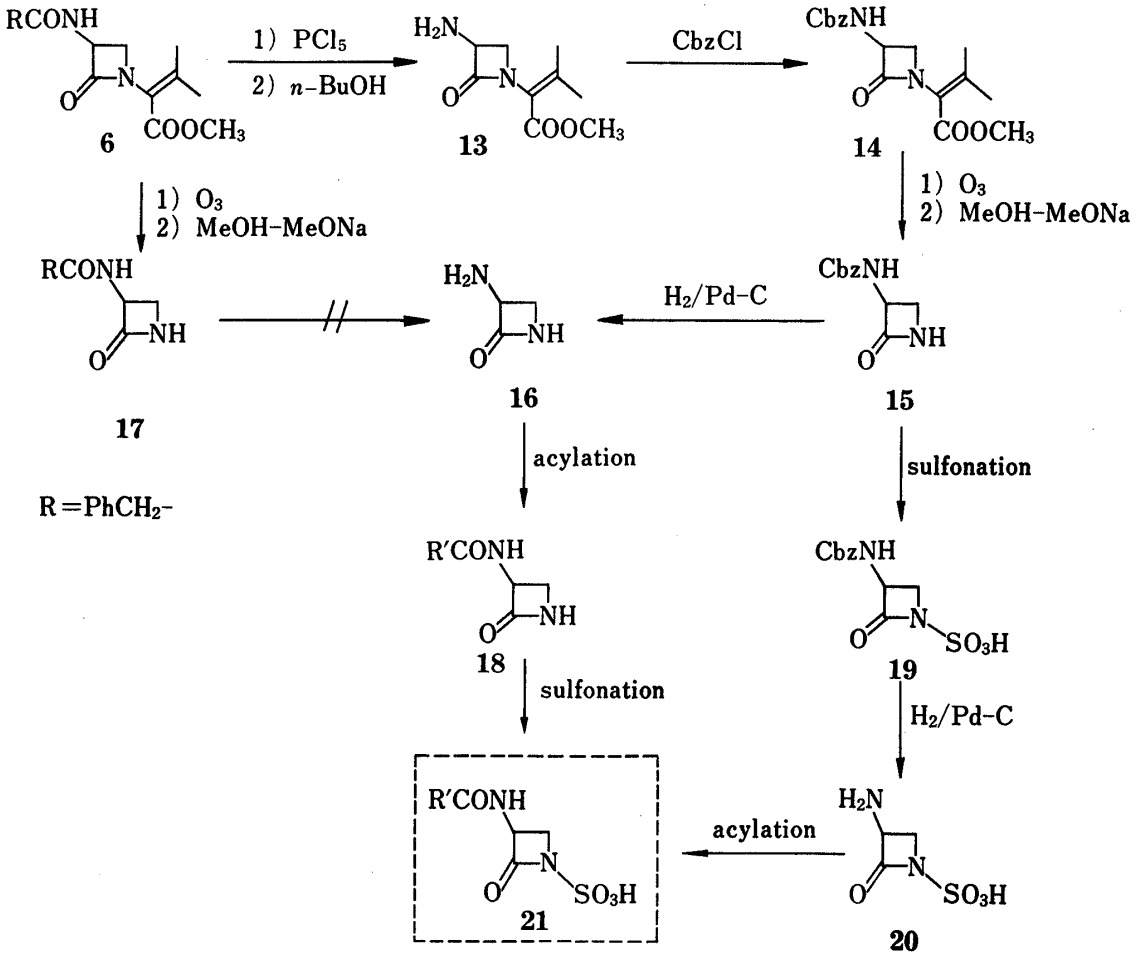


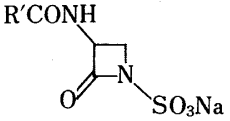
Chart 3

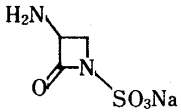
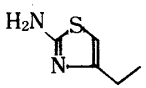
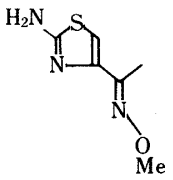
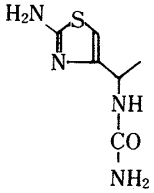
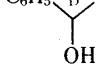
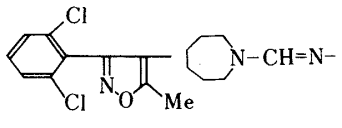
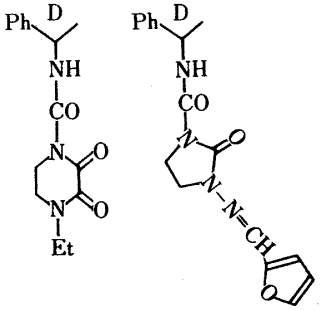
Experimental

All melting points were taken with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a Hitachi type 260-10 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a Varian HA-100 or T-60 spectrometer using tetramethylsilane as a standard. Abbreviations are as follows; s=singlet, br s=broad singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet. Column chromatography was carried out on Kieselgel (0.05—0.2 mm, Merck).

Methyl 3-Benzyl-α-(1-methylethylidene)-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-ene-6-acetate (5a)—— A solution of chlorine (21.3 g) in CCl_4 (250 ml) was added dropwise to a coole d(−10——15°C) solution of

TABLE I. Effect of the 3-Acyl Group[a] on Antibacterial Activity (MIC: μg/ml)[b]



Compound / Organism	R' =  **20**	 **21a**	 **21b**	 **21c**	 **21d**	 **21e**	 **21f**	**21g**	**21h**
S. aureus FDA 209P	>100	25	50	100	25	12.5	100	6.25	6.25
S. aureus 308 A-1	>100	12.5	25	50	50	12.5	100	3.13	3.13
E. coli O-111	>100	50	0.39	12.5	>100	>100	12.5	0.2	3.13
E. coli T-7	>100	>100	>100	25	>100	>100	>100	>100	>100
S. marcescens IFO 12648	>100	50	12.5	12.5	>100	>100	>100	3.13	1.56
P. vulgaris IFO 3988	>100	>100	1.56	25	>100	>100	>100	0.1	0.2

a) Acyl groups were prepared according to the literature.[9]

b) Inoculum size: 10^8 CFU/ml.

TABLE II. Effect of the 3-α-Oxyiminoacetamido Group[a] on Antibacterial Activity (MIC: $z2\mu g/ml$)[b]

Compound	R				R'			
Organism	**21b**	**21i**	**21j**	**21k**	**21m**	**21n**	**21p**
S. aureus FDA 209P	50	50	50	50	25	>100	>100
S. aureus 308 A-1	25	25	50	25	25	>100	>100
E. coli O-111	0.39	6.25	100	25	6.25	0.2	≦0.1
E. coli T-7	>100	>100	>100	>100	>100	6.25	12.5
S. marcescens IFO 12648	12.5	25	100	100	0.39	12.5	1.56
P. vulgaris IFO 3988	1.56	25	100	50	0.78	0.78	≦0.1
P. aeruginosa IFO 3455	6.25	50	>100	>100	3.13	12.5	0.78

a) Acyl groups were prepared according to the literature.[9]

b) Inoculum size: 10^8 CFU/ml.

methyl 6-phenylacetamido-2,2-dimethylpenam-3-carboxylate (**3a**, 34.8 g) in CH_2Cl_2 (400 ml) with stirring and the mixture was stirred for 1 h at the same temperature. Sodium bicarbonate (38 g) in water (400 ml) was added to the reaction mixture and the separated organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed to give the crude chloro derivative **4a** (43 g) as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s, OCH_3), 4.92 (1H, dd, J=1.5 and 7 Hz, CH), 5.82 (1H, d, J=1.5 Hz, CH), 7.26 (5H, s, aromatic-H).

A mixture of the chloro derivative **4a** (4.3 g) and Ag_2O (2.55 g) in CH_3CN (40 ml) was stirred at room temperature for 1.5 h. After removal of the precipitate, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with AcOEt: *n*-hexane (4: 1—2: 3) to give **5a** (2.27 g, 72.3% from **3a**) as pale yellow needles (Et_2O), mp 120—122°C. *Anal.* Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.54; H, 5.80; N, 8.72. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1720, 1655, 1620. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s, OCH_3), 5.14 (1H, d, J=3.5 Hz, CH), 5.92 (1H, d, J=3.5 Hz, CH), 7.26 (5H, s, aromatic-H).

Methyl 3-(4-Chlorophenoxymethyl)-α-(1-methylethylidene)-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-ene-6-acetate (5c)——Similar treatment of the dichloro derivative (**4c**), which was prepared from methyl 6-phenoxyacetamido-2,2-dimethylpenam-3-carboxylate (**3b**, 10.8 g) and 4 eq of chlorine, with Ag_2O afforded the corresponding oxazoline derivative **5c** (2.93 g, 27.1%) as a foam. IR ν_{max}^{KBr} cm^{-1}: 1787, 1725, 1655, 1498, 1230. ^{1}H-NMR ($CDCl_3$) δ: 3.72 (3H, s, OCH_3), 5.26 (1H, d, J=4 Hz, CH), 6.10 (1H, d, J=4 Hz, CH), 6.86 (2H, d, J=9 Hz, aromatic-H), 7.23 (2H, d, J=9 Hz, aromatic-H).

(3*S*)-1-(1-Methoxycarbonyl-2-methylprop-1-enyl)-3-phenylacetamido-2-azetidinone (6a)——(a) A mixture of **5a** (75.5 g) and PdO (9.8 g) in AcOEt (1.2 l) was vigorously stirred under an H_2 atmosphere for 7 h at room temperature. After removal of the catalyst, the filtrate was concentrated under reduced pressure. The residue was treated with Et_2O to give **6a** (67.5 g, 88.9%) as colorless needles (Et_2O), mp 115.5—117°C. *Anal.* Calcd for $C_{17}H_{20}N_2O_4$: C, 64.57; H, 6.37; N, 8.86. Found: C, 64.50; H, 6.40; N, 8.77. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1765, 1725, 1645, 1530. ^{1}H-NMR ($CDCl_3$) δ: 3.4—3.8 (2H, m, C_4–H), 3.68 (3H, s, OCH_3), 4.7—5.0 (1H, m, C_3–H), 7.26 (5H, s, aromatic-H).

(b) A mixture of **11a** (12 g) and $P(OCH_3)_3$ (7 ml) in dry benzene (30 ml) was heated at 100°C for 45 min. After removal of the solvent, the residue was purified by silica gel column chromatography eluted with AcOEt: *n*-hexane (1: 1) to give the 4-methylthio derivative **12a**[7] (5.5 g, 43.9%) as colorless prisms (benzene–*n*-hexane). *Anal.* Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.55; H, 6.01; N, 7.82. $[\alpha]_D^{24}$ −4.7° (c=1.01, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1763, 1722, 1678. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, s, SCH_3), 3.77 (3H, s, OCH_3), 5.09 (1H, d, J=5 Hz, C_4–H), 5.51 (1H, dd, J=5 and 9 Hz, C_3–H), 7.35 (5H, s, aromatic-H).

A mixture of **12a** (0.13 g) and Raney nickel (1 ml) in dry tetrahydrofuran (THF) (5 ml) was refluxed for 6 h. After removal of the catalyst, the product was purified by silica gel column chromatography to give **6a** (0.028 g, 24.8%) and the starting material **12a** (0.054 g, 41.5%).

(c) A mixture of the disulfide derivative (**11a**, 6.95 g) and Raney nickel (35 ml) in EtOH (100 ml) was vigorously stirred at 50°C for 30 min. A procedure similar to that described in (a) gave **6a** (4.82 g, 76.2%).

(3*S*)-3-(4-Chlorophenoxy)acetamido-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-2-azetidinone (6c) and (3*S*)-4-Phenoxyacetamido-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-2-azetidinone (6b)——(a) A reaction similar to that described for the synthesis of **6a** [(a)] afforded the corresponding **6c** (0.85 g, 84.2%) as colorless needles (AcOEt–*n*-hexane) starting from **5c** (1 g), mp 138—140°C. *Anal.* Calcd for $C_{17}H_{19}ClN_2O_5$: C, 55.67; H, 5.22; N, 7.64. Found: C, 55.89; H, 5.11, N, 7.44. IR ν_{max}^{KBr} cm^{-1}: 1750, 1715, 1680. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (1H, dd, J=2.5 and 5 Hz, C_4–H), 3.73 (3H, s, OCH_3), 3.90 (1H, d, J=5 Hz, C_4–H), 5.10 (1H, m, C_3–H), 6.82 (2H, d, J=9 Hz, aromatic-H), 7.26 (2H, d, J=9 Hz, aromatic-H).

(b) A mixture of the chloro derivative (**4c**, 1.7 g) and Raney nickel (5 ml) in THF (40 ml) was stirred under an H_2 atmosphere in an autoclave (150 kg/cm², 100°C, 2 h). After removal of the catalyst, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **6c** (0.70 g, 45%).

(c) A mixture of the disulfide derivative (**11b**, 1g) and Raney nickel (5 ml) in EtOH (15 ml) was vigorously stirred at 55°C for 20 min. A procedure similar to that described for the synthesis of **6a** gave **6b** as colorless needles in almost quantitative yield, mp 153—154°C (dec.). *Anal.* Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.41; H, 6.01; N, 8.45. IR ν_{max}^{KBr} cm^{-1}: 1740, 1708, 1680. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, CH_3), 2.10 (3H, s, CH_3), 3.60 (1H, dd, J=2.5 and 5 Hz, C_4–H), 3.73 (3H, s, OCH_3), 3.86 (1H, d, J=5 Hz, C_4–H), 4.50 (2H, s, CH_2), 4.90—5.20 (1H, m, C_3–H), 6.80—7.60 (5H, m, aromatic-H).

Synthesis of Symmetrical Disulfide Derivatives (11a, b)——(a) A mixture of **9b** (1 g) and Raney nickel (2 ml) in EtOH (15 ml) was stirred at room temperature for 1 h. After removal of the catalyst, the filtrate was concentrated under reduced pressure to give the residue, which was purified by silica gel column chromatography. Elution with AcOEt: *n*-hexane (1: 1—1: 2) afforded **11b** (0.624 g, 91.1%) as colorless needles (AcOEt–pet. ether), mp 108—109°C (dec.). *Anal.* Calcd for $C_{34}H_{38}N_4O_{10}S_2$: C, 56.19; H, 5.27, N, 7.71. Found: C, 55.82; H, 5.17; N, 7.51. IR ν_{max}^{KBr} cm^{-1}: 1775, 1725, 1690. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, CH_3), 2.26 (3H, s, CH_3), 3.63 (3H, s, OCH_3), 4.63 (2H, s, CH_2), 5.16 (1H, d, J=4 Hz, CH), 5.30 (1H, dd, J=4 and 8 Hz, CH), 6.80—7.40 (5H, m, aromatic-H), 7.60 (1H, d, J=8 Hz, NH).

(b) A solution of I_2 (11 g) in THF (20 ml) was added dropwise with stirring to an ice-cooled solution of **10b** (30.4 g) in THF (140 ml)–H_2O (20 ml). After being stirred at 4°C for 1 h, the reaction mixture was treated with aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The separated organic layer was concentrated to give the residue, which was purified by silica gel column chromatography. Elution with CH_2Cl_2–AcOEt (3: 1—1: 1) afforded **11b** (22 g, 69%).

(c) A procedure similar to that [(a) or (b)] described for the synthesis of **11b** provided **11a**. Purification was carried out by silica gel column chromatography [AcOEt: *n*-hexane (5: 1)]. IR ν_{max}^{KBr} cm^{-1}: 3310, 1770,

1721, 1673, 1525. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.67 (2H, s, CH_2), 3.79 (3H, s, OCH_3), 4.80 (1H, dd, J=4 and 8 Hz, CH), 5.02 (1H, d, J=4 Hz, CH), 6.54 (1H, d, J=8 Hz, NH), 7.37 (5H, s, aromatic-H).

(3*S*)-3-Amino-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-2-azetidinone (13)——Pyridine (71.2 g) and pulverized PCl_5 (93.7 g) were added to a cooled (−40°C) solution of **6a** (47.5 g) in CH_2Cl_2 (750 ml), and the reaction mixture was allowed to warm up gradually to 0°C, then stirred for 70 min. *n*-Butyl alcohol (150 ml) was added to this reaction mixture with stirring at −40°C and the whole was stirred at 0°C for 1 h. The reaction mixture was poured into ice-water (300 ml) and extracted with CH_2Cl_2. The aqueous layer was adjusted to pH 6.2, and extracted with CH_2Cl_2 several times, and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed to obtain **13** (26.8 g, 90.1%) as colorless prisms (Et_2O), mp 48—50°C. *Anal.* Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.40; H, 6.94; N, 13.92. $[\alpha]_D^{24}$ −2.1° (c=1.025, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3300, 1750, 1720. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (2H, br s, NH_2), 3.2—3.9 (2H, m, C_4–H), 3.73 (3H, s, OCH_3), 4.28 (1H, m, C_3–H).

(3*S*)-3-Benzyloxycarbonylamino-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-2-azetidinone (14)——Benzyloxycarbonyl chloride (56.3 g) was added dropwise to a solution of **13** (58 g) and propylene oxide (120 ml) in CH_2Cl_2 (240 ml) at 4°C. The reaction mixture was allowed to warm up gradually to room temperature then stirred for 30 min. After removal of the solvent, the residue was treated with Et_2O to afford **14** (82.6 g, 84.9%) as colorless fine needles (MeOH–H_2O), mp 139—140°C. *Anal.* Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.35; H, 6.02; N, 8.31. $[\alpha]_D^{24}$ −18.9° (c=1.02, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3280, 1738, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.95 (3H, s, CH_3), 2.19 (3H, s, CH_3), 3.4—3.9 (2H, m, C_4–H), 3.74 (3H, s, OCH_3), 4.89 (1H, m, C_3–H), 5.12 (2H, s, CH_2),

(3*S*)-3-Benzyloxycarbonylamino-2-azetidinone (15)——A solution of **14** (0.3 g) in dry CH_2Cl_2 (30 ml) was ozonized at −78°C in an acetone-dry ice bath, until the solution turned bluish-green, at which time the ozone was replaced by a stream of dry nitrogen gas. After treatment with Me_2S (1 ml), the solution was allowed to come to room temperature over 1 h. The solution was evaporated to dryness and the residue was dissolved in MeOH (10 ml). A catalytic amount of NaOMe in MeOH was added to this methanol solution and the solution was stirred at room temperature for 5 min. After addition of a few drops of AcOH to the reaction mixture, the solvent was evaporated off under reduced pressure. Water was added to the residue to yield **15** (0.15 g, 75.4%) as a solid (MeOH–H_2O), mp 164—165°C. *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.50; N, 12.72. Found: C, 59.62; H, 5.45; N, 12.52. $[\alpha]_D^{24}$ −28.5° (c=0.995, dimethylsulfoxide (DMSO)). IR ν_{max}^{KBr} cm^{-1}: 3350, 1740, 1725, 1700. ^{1}H-NMR (DMSO-d_6) δ: 3.08 (1H, dd, J=3 and 6 Hz, C_4–H), 3.40 (1H, t, J=6 Hz, C_4–H), 4.63 (1H, ddd, J=3, 6 and 8 Hz, C_3–H), 5.00 (2H, s, CH_2), 7.28 (5H, s, aromatic-H), 7.80 (1H, s, NH).

(3*S*)-3-Amino-2-azetidinone (16)——A mixture of **15** (0.22 g) and 10% Pd–C (0.4 g) in EtOH (12 ml) was stirred vigorously under an H_2 gas stream. After 30 min, the catalyst was filtered off and the filtrate was concentrated to give **16** (0.076 g, 88.4%) as colorless hygroscopic needles. *Anal.* Calcd for $C_3H_6N_2O$–1/10H_2O: C, 41.00; H, 7.11; N, 31.87. Found. C, 40.88; H, 6.87; N, 31.73. $[\alpha]_D^{24}$ −7.9° (c=1.06, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 3300, 1760. ^{1}H-NMR (DMSO-d_6) δ: 2.63 (2H, br s, NH_2), 2.80 (1H, dd, J=3 and 6 Hz, C_4–H), 3.33 (1H, t, J=6 Hz, C_4–H), 4.00 (1H, m, C_3–H), 7.63 (1H, s, NH).

(3*S*)-3-Phenylacetamido-2-azetidinone (17)——A procedure similar to that described for the synthesis of **15** provided the title compound **17** (80%) as colorless fine needles (MeOH), mp >270°C. *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.45; H, 5.83; N, 13.69. IR ν_{max}^{Nujol} cm^{-1}: 3330, 3270, 1780, 1720, 1655. ^{1}H-NMR (DMSO-d_6) δ: 3.05 (1H, dd, J=3 and 5 Hz, C_4–H), 3.40 (1H, t, J=5 Hz, C_4–H), 3.46 (2H, s, CH_2), 4.36 (1H, ddd, J=3, 5 and 8 Hz, C_3–H), 7.28 (5H, s, aromatic–H), 7.93 (1H, br s, NH), 8.67 (1H, d, J=8 Hz, NH).

(3*S*)-3-Amino-2-azetidinone-1-sulfonic Acid (20)——(a) A solution of (3*S*)-3-benzyloxycarbonylamino-2-azetidinone (**15**, 0.44 g) and SO_3–pyridine complex (0.32 g) in DMF (2 ml) was allowed to stand at room temperature for 2 d, and then Et_2O (50 ml) was added to this reaction mixture. The resulting powdery precipitate was collected by filtration and washed with Et_2O, then with EtOH to give pyridinium (3*S*)-3-benzyloxycarbonylamino-2-azetidinone-1-sulfonate (**19**, 0.613 g, 80.9%) as light-yellow needles, mp 134—138°C (dec.). *Anal.* Calcd for $C_{16}H_{17}N_3O_6S$: C, 50.65; H, 4.52; N, 11.08. Found: C, 50.57; H, 4.51; N, 11.04. IR ν_{max}^{KBr} cm^{-1}: 3320, 1760, 1695, 1530, 1270, 1240, 1055. ^{1}H-NMR (DMSO-d_6) δ: 3.30 (1H, d, J=6 Hz, C_4–H), 3.62 (1H, dd, J=2 and 6 Hz, C_4–H), 4.64 (1H, ddd, J=2, 6 and 8 Hz, C_3–H), 5.05 (2H, s, CH_2), 8.10, 8.62 and 8.94 (5H, m, aromatic-H).

(b) A mixture of **19** (0.13 g) and 10% Pd–C (0.13 g) in 60% EtOH (4.5 ml) was stirred under an H_2 gas stream at room temperature for 1.5 h. The catalyst was filtered off and the filtrate was concentrated to give (3*S*)-3-amino-2-azetidinone-1-sulfonic acid (**20**, 0.056 g, 98%) as a foam. IR ν_{max}^{KBr} cm^{-1}: 3400, 1750, 1240, 1050. ^{1}H-NMR (D_2O) δ: 3.56 (1H, dd, J=3 and 6 Hz, C_4–H), 4.05 (1H, t, J=6 Hz, C_4–H), 4.45 (1H, dd, J=3 and 6 Hz, C_3–H).

(c) A solution of phenylacetyl chloride (0.069 g) in THF (1 ml) and $NaHCO_3$ (0.101 g) were added to an ice-cooled solution of **20** (0.05 g) in water (1 ml). After being stirred at room temperature for 30 min, the reaction mixture was adjusted to pH 5.8 with phosphoric acid. The aqueous layer was chromatographed on an Amberlite XAD-2 column followed by lyophilization to give sodium (3*S*)-3-phenylacetamido-2-azetidi-

none-1-sulfonate (0.042 g, 27.8%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3310, 1780, 1670, 1300—1200, 1080, 1065. ^{1}H-NMR (DMSO-d_6) δ: 3.27 (1H, dd, J=3 and 6 Hz, C_4–H), 3.46 (2H, s, CH_2), 3.60 (1H, t, J=6 Hz, C_4–H), 4.84 (1H, ddd, J=3, 6 and 8 Hz, C_3–H), 7.29 (5H, s, aromatic-H), 8.83 (1H, d, J=9 Hz, NH).

Sodium (3*S*)-3-[2-(2-Aminothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonate (21a)——(a) (2-Chloroacetamidothiazol-4-yl) acetyl chloride HCl salt (1.3 g) and $NaHCO_3$ (0.63 g) were added to a cooled (4°C) solution of **16** (0.438 g) in THF (6 ml)–water (6 ml). The reaction mixture was stirred at room temperature for 2 h, and the resulting crystalline substance was collected, washed with water, and dried over P_2O_5, to give (3*S*)-3-[2-(2-chloroacetamidothiazol-4-yl)acetamido]-2-azetidinone (**18a**, 0.543 g, 35.3%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 1740, 1725, 1703, 1655. ^{1}H-NMR (DMSO-d_6) δ: 3.09 (1H, dd, J=3 and 5 Hz, C_4–H), 3.42 (1H, t, J=5 Hz, C_4–H), 3.54 (2H, s, CH_2), 4.36 (2H, s, $ClCH_2$–), 4.86 (1H, ddd, J=3, 5 and 8 Hz, C_3–H), 6.97 (1H, s, thiazole-H), 7.96 (1H, s, NH), 8.65 (1H, d, J=8 Hz, NH).

(b) A mixture of **18a** (0.515 g) and SO_3–pyridine complex (0.325 g) in DMF (20 ml) was allowed to stand at room temperature for 2 d. After addition of Et_2O, the resulting oily substance was dissolved in water and treated with Dowex-50W (Na^+) and chromatographed on an Amberlite XAD-2 column. Elution with water followed by lyophilization gave sodium (3*S*)-3-[2-(2-chloroacetamidothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonate (0.569 g, 82.6%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3430, 1760, 1660, 1550, 1260, 1150, 1050. ^{1}H-NMR (DMSO-d_6) δ: 3.30 (1H, dd, J=3 and 6 Hz, C_4–H), 3.60 (1H, t, J=6 Hz, C_4–H), 4.34 (2H, s, $ClCH_2$–), 4.85 (1H, ddd, J=3, 6 and 8 Hz, C_3–H), 6.97 (1H, s, thiazole-H), 8.74 (1H, d, J=8 Hz, NH).

(c) A solution of sodium *N*-methyldithiocarbamate (0.154 g) in water (2 ml) was added with stirring to an ice-cooled solution of sodium (3*S*)-3-[2-(2-chloroacetamidothiazol-4-yl)acetamido]-2-azetidinone-1-sulfonate (0.486 g) in water (6 ml).[11] The mixture was stirred for 3 h, then insoluble material was filtered off and the filtrate was chromatographed on an Amberlite XAD-2 column. Elution with water followed by lyophilization gave **21a** (0.144 g, 36.6%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3400, 3270, 1760, 1650, 1610, 1270, 1235, 1200, 1050. ^{1}H-NMR (DMSO-d_6) δ: 3.25 (1H, dd, J=3 and 6 Hz, C_4–H), 3.62 (1H, t, J=6 Hz, C_4–H), 4.85 (1H, ddd, J=3, 6 and 8 Hz, C_3–H), 6.25 (1H, s, thiazole-H), 6.82 (2H, s, NH_2), 8.66 (1H, d, J=8 Hz, NH).

Sodium (3*S*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone-1-sulfonate (21b)——(3*S*)-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone (**18b**) and the title compound **21b** were synthesized by a procedure similar to that described for the synthesis of **21a**.

(a) **18b**: Powder (76.5%). IR ν_{max}^{KBr} cm^{-1}: 1740, 1690, 1660. ^{1}H-NMR (DMSO-d_6) δ: 3.14 (1H, dd, J=3 and 5 Hz, C_4–H), 3.49 (1H, t, J=5 Hz, C_4–H), 3.90 (3H, s, OCH_3), 4.37 (2H, s, $ClCH_2$–), 4.99 (1H, ddd, J=3, 5 and 8 Hz, C_3–H), 7.43 (1H, s, thiazole-H), 8.02 (1H, s, NH), 9.22 (1H, d, J=8 Hz, NH).

(b) Sodium (3*S*)-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone-1-sulfonate: Powder (81.7%). IR ν_{max}^{KBr} cm^{-1}: 3430, 1760, 1690, 1650, 1140. ^{1}H-NMR (D_2O) δ: 3.95 (1H, dd, J=3 and 6 Hz, C_4–H), 4.12 (3H, s, OCH_3), 4.15 (1H, t, J=6 Hz, C_4–H), 4.93 (2H, s, $ClCH_2$–), 5.22 (1H, dd, J=3 and 6 Hz, C_3–H), 7.52 (1H, s, thiazole-H).

(c) **21b**: Powder (37.7%). IR ν_{max}^{KBr} cm^{-1}: 3450, 1770, 1670, 1610, 1260, 1050. ^{1}H-NMR (D_2O) δ: 3.89 (1H, dd, J=4 and 6 Hz, C_4–H), 4.03 (3H, s, OCH_3), 4.09 (1H, t, J=6 Hz, C_4–H), 5.16 (1H, dd, J=4 and 6 Hz, C_3–H), 7.01 (1H, s, thiazole-H).

Sodium (3*S*)-3-[2-(2-Aminothiazol-4-yl)-2-ureidoacetamido]-2-azetidinone-1-sulfonate (21c)——(3*S*)-3-[2-Chloroacetamidothiazol-4-yl)-2-ureidoacetamido]-2-azetidinone (**18c**), its sodium 1-sulfonate derivative and the title compound (**21c**) were synthesized by a procedure similar to that described for the synthesis of **21a**.

(a) **18c**: Powder (59%). IR ν_{max}^{KBr} cm^{-1}: 1750.

(b) Sodium (3*S*)-3-[2-(2-Chloroacetamidothiazol-4-yl)-2-ureidoacetamido]-2-azetidinone-1-sulfonate: Powder (33%). IR ν_{max}^{KBr} cm^{-1}: 1755, 1660, 1520, 1230, 1045. ^{1}H-NMR (DMSO-d_6) δ: 4.35 (2H, s, $ClCH_2$–), 4.82 (1H, m, C_3–H), 5.74 (2H, s, NH_2), 7.00 (1H, s, thiazole-H).

(c) **21c**: Powder (89%). IR ν_{max}^{KBr} cm^{-1}: 1755, 1660, 1520, 1235, 1045. ^{1}H-NMR (DMSO-d_6+D_2O) δ: 3.43 (1H,dd, J=3 and 6 Hz, C_4–H), 3.68 (1H, t, J=6 Hz, C_4–H), 4.82(1H, m, C_3–H), 6.62 (1H s, thiazole-H).

Sodium (3*S*)-(D-2-Hydroxy-2-phenylacetamido)-2-azetidinone-1-sulfonate (21d)——(a) A mixture of **16** (0.1 g), D-(−)-mandelic acid *tert*-butyldimethylsilylether (0.266 g) and DCC (0.23 g) in DMF (4 ml) was stirred at room temperature for 1 h. After removal of insoluble material, the filtrate was concentrated under reduced pressure to give the residue, which was treated with THF–AcOEt–brine. The separated organic layer was evaporated to give (3*S*)-3-(D-2-*tert*-butyldimethylsilyloxy-2-phenylacetamido)-2-azetidinone (**18d**, 0.262 g, 67.7%) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 3300, 1760, 1670, 1510, 1253, 1100, 860, 838. ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.13 and 0.98 (15H, each s, CH_3), 3.27 (1H, dd, J=3 and 6 Hz, C_4–H), 3.62 (1H, t, J=6 Hz, C_4–H), 5.01 (1H, m, C_3–H), 6.44 (1H, br s, NH), 7.3—7.7 (5H, m, aromatic-H).

(b) A mixture of **18d** (0.462 g) and SO_3–pyridine complex (0.44 g) in DMF (4 ml) was allowed to stand at room temperature for 1 d. Treatment similar to that described for the preparation of **21a** afforded sodium (3*S*)-3-(D-2-*tert*-butyldimethylsilyloxy-2-phenylacetamido)-2-azetidinone-1-sulfonate (0.295 g, 48.9%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3400, 1758, 1670, 1503, 1245, 1190, 1050, 835. ^{1}H-NMR (DMSO-d_6) δ: 0.02, 0.08 and 0.90 (15H, each s, CH_3), 3.25 (1H, dd, J=3 and 6 Hz, C_4–H), 3.58 (1H, t, J=6 Hz, C_4–H), 4.85 (1H, ddd, J=3, 6 and 9 Hz, C_3–H), 7.23—7.53 (5H, m, aromatic-H), 8.64 (1H, d, J=9 Hz, NH).

(c) A solution of the silylether derivative (0.145 g) obtained above (b) and (n-Bu)$_4$NF·3H_2O (0.28 g) in MeOH (3 ml) was stirred at room temperature overnight. Water (3 ml) was added to the reaction mixture

and the solution was treated with Dowex-50W (Na^+). The resulting solution was purified by Amberlite XAD-2 column chromatography to give **21d** (0.03 g, 28%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3300, 1755, 1663, 1520, 1243, 1045. ^{1}H-NMR (DMSO-d_6) δ: 3.31 (1H, dd, J=3 and 6 Hz, C_4–H), 3.55 (1H, t, J=6 Hz, C_4–H), 4.80 (1H, ddd, J=3,6 and 9 Hz, C_3–H), 4.93 (1H, d, J=5 Hz, CH), 6.09 (1H, d, J=5 Hz, OH). 7.2—7.5 (5H, m, aromatic-H), 8.71 (1H, d, J=9 Hz, NH).

Sodium (3*S*)-3-[[3-(2,6-Dichlorophenyl)-5-methylisoxazol-4-yl]carbonylamino]-2-azetidinone-1-sulfonate (21e)——Treatment similar to that described for the preparation of **21a** afforded **21e**.

(a) (3*S*)-3-[[3-(2,6-Dichlorophenyl)-5-methylisoxazol-4-yl]carbonylamino]-2-azetidinone (**18e**): Powder (78.3%). IR ν_{max}^{KBr} cm^{-1}: 1760, 1660. ^{1}H-NMR (DMSO-d_6) δ: 2.68 (3H, s, CH_3), 3.07 (1H, dd, J=2 and 5 Hz, C_4–H), 3.39 (1H, t, J=5 Hz, C_4–H), 4.87 (1H, ddd, J=2, 5 and 8 Hz, C_3–H), 7.53 (3H, s, aromatic-H).

(b) **21e**: Powder (76.3%). IR ν_{max}^{KBr} cm^{-1}: 1762, 1665, 1250. ^{1}H-NMR (DMSO-d_6) δ: 2.77 (3H, s, CH_3), 3.25 (1H, dd, J=2 and 6 Hz, C_4–H), 3.57 (1H, t, J=6 Hz, C_4–H), 4.86 (1H, ddd, J=1, 6 and 8 Hz, C_3–H), 7.53 (3H, s, aromatic-H), 8.74 (1H, d, J=8 Hz, NH).

Sodium (3*S*)-3-[(Hexahydro-1*H*-azepin-1-yl)methyleneamino]-2-azetidinone-1-sulfonate (21f)——(a) A solution of 1-hexamethyleneiminocarboxaldehyde dimethylacetal (0.693 g) in CH_2Cl_2 (6 ml) was added to a solution of **16** (0.344 g) in DMF (6 ml)–CH_2Cl_2 (6 ml), and the reaction mixture was stirred at room temperature for 1 h. The mixture was treated with water–CH_2Cl_2, and the separated organic layer was evaporated to give (3*S*)-3-[(hexahydro-1*H*-azepin-1-yl)methyleneamino]-2-azetidinone (**18f**, 0.2 g, 25.6%) as a solid. IR ν_{max}^{KBr} cm^{-1}: 3180, 2430, 1700, 1620. ^{1}H-NMR (DMSO-d_6) δ: 1.64—3.40 (12H, m, CH_2), 3.36 (1H, t, J=6 Hz, C_4–H), 3.90 (1H, dd, J=2 and 6 Hz, C_4–H), 4.40 (1H, dd, J=2 and 6 Hz, C_3–H), 7.46 (1H, s, –CH=N).

(b) A solution of **18f** (0.172 g) and SO_3–pyridine complex (0.183 g) in DMF (1 ml) was allowed to stand at room temperature for 2 d, and treatment similar to that described for the preparation of **21a** afforded **21f** (0.056 g, 21.4%) as a foam. IR ν_{max}^{KBr} cm^{-1}: 1762, 1684, 1270, 1242, 1042. ^{1}H-NMR (DMSO-d_6) δ: 1.4—1.9 (12H, m, CH_2), 3.72 (1H, t, J=6 Hz, C_4–H), 4.90 (1H, dd, J=3 and 6 Hz, C_3–H), 8.19 (1H, s, –CH=N).

Sodium (3*S*)-3-[D-2-(4-Ethyl-2,3-dioxo-1-piperazinecarbonylamino)-2-phenylacetamido]-2-azetidinone-1-sulfonate (21g)——(3*S*)-3-[D-2-(4-Ethyl-2,3-dioxo-1-piperazinecarbonylamino)-2-phenylacetamido]-2-azetidinone (**18g**) and the title compound **21g** were synthesized by a procedure similar to that described for the synthesis of **21a**.

(a) **18g**: Solid (58%). $[\alpha]_D^{25}$ −59.7° (c=0.385, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3290, 1760, 1710, 1670. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, t, J=7 Hz, CH_3), 3.02 (1H, dd, J=3 and 6 Hz, C_4–H), 3.39 (1H, t, J=6 Hz, C_4–H), 3.41 (2H, q, J=7 Hz, CH_2), 4.86 (1H, ddd, J=3 and 8 Hz, C_3–H), 5.46 (1H, d, J=8 Hz, CH), 7.2—7.5 (5H, m, aromatic-H), 8.00 (1H, s, NH).

(b) **21g**: Powder (61%). *Anal.* Calcd for $C_{18}H_{20}N_5NaO_8S \cdot 2H_2O$: C, 41.15; H, 4.60; N, 13.33; S, 6.09. Found: C, 41.33; H, 4.39; N, 13.22; S, 5.84. IR ν_{max}^{KBr} cm^{-1}: 3470, 3280, 1760, 1705, 1670, 1510, 1250, 1190, 1050. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, t, J=7 Hz, CH_3), 3.13 (1H, dd, J=3 and 6 Hz, C_4–H), 3.41 (2H, q, J=7 Hz, CH_2), 3.59 (1H, t, J=6 Hz, C_4–H), 4.85 (1H, ddd, J=3, 6 and 8 Hz, C_3–H), 5.45 (1H, d, J=8 Hz, CH), 7.2—7.5 (5H, m, aromatic-H).

Sodium (3*S*)-3-[D-2-(3-Furfurylideneamino-2-oxoimidazolidin-1-yl)carbonylamino-2-phenylacetamido]-2-azetidinone-1-sulfonate (21h)——(3*S*)-3-[D-2-(3-Furfurylideneamino-2-oxoimidazolidin-1-yl)carbonylamino-2-phenylacetamido]-2-azetidinone (**18h**) and the title compound **21h** were synthesized by a procedure similar to that described for the synthesis of **21a**.

(a) **18h**: Powder (81%). IR ν_{max}^{KBr} cm^{-1}: 3300, 1750, 1720, 1660.

(b) **21h**: Powder (17%) IR ν_{max}^{KBr} cm^{-1}: 3450, 3300, 1755, 1720, 1665, 1520, 1470, 1410, 1270, 1230, 1050. ^{1}H-NMR (DMSO-d_6) δ: 3.12 (1H, dd, J=3 and 6 Hz, C_4–H), 3.58 (1H, t, J=6 Hz, C_4–H), 4.86 (1H, ddd, J=3, 6 and 8 Hz, C_3–H), 5.45 (1H, d, J=8 Hz, CH), 6.5—7.9 (8H, m, aromatic-H), 7.75 (1H, s, –CH=N), 9.04 and 9.24 (each 1H, each d, J=8 Hz, NH).

Sodium (3*S*)-3-[2-(2-Furyl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone-1-sulfonate (21i)——(3*S*)-3-[2-(2-Furyl)-(*Z*)-2-methoxyiminoacetamido]-2-azetidinone (**18i**) and the title compound **21i** were synthesized by a procedure similar to that described for the synthesis of **21a**.

(a) **18i**: Solid (81.2%). IR ν_{max}^{KBr} cm^{-1}: 3240, 1760, 1670. ^{1}H-NMR (DMSO-d_6) δ: 3.19 (1H, dd, J=3.5 and 6 Hz, C_4–H). 3.28 (3H, s, OCH_3), 3.48 (1H, t, J=6 Hz, C_4–H), 4.7—5.1 (1H, m, C_3–H), 6.63 and 7.78 (3H, m, aromatic-H), 7.98 (1H, br s, NH), 9.27 (1H, d, J=8 Hz, NH).

(b) **21i**: Powder (15%). *Anal.* Calcd for $C_{10}H_{10}N_3NaO_7S \cdot 2.5\,H_2O$: C, 31.25; H, 3.93; N, 10.93. Found: C, 31.49; H, 4.00; N, 10.55. IR ν_{max}^{KBr} cm^{-1}: 1770, 1700, 1685, 1250, 1055. ^{1}H-NMR (D_2O) δ: 3.91 (1H, dd, J=3.5 and 6 Hz, C_4–H), 4.13 (1H, t, J=6 Hz, C_4–H), 4.10 (3H, s, OCH_3), 5.22 (1H, dd, J=3.5 and 6 Hz, C_3–H), 6.72 and 7.79 (3H, m, aromatic-H).

Sodium (3*S*)-3-((*Z*)-2-Methoxyimino-2-thienylacetamido)-2-azetidinone-1-sulfonate (21j)——(3*S*)-3-((*Z*)-2-Methoxyimino-2-thienylacetamido)-2-azetidinone (**18j**) and the title compound **21j** were synthesized by a procedure similar to that described for the synthesis of **21a**.

(a) **18j**: Foam (76.1%). IR ν_{max}^{KBr} cm^{-1}: 1760, 1652, 1528.

(b) **21j**: Powder (76.2%). IR ν_{max}^{KBr} cm^{-1}: 1758, 1643, 1523, 1280, 1223, 1045. ^{1}H-NMR (DMSO-d_6) δ: 3.48 (1H, dd, J=3 and 6 Hz, C_4–H), 3.65 (1H, t, J=6 Hz, C_4–H), 4.07 (3H, s, OCH_3), 4.95 (1H, ddd, J=3, 6 and 8 Hz, C_3–H).

Sodium (3*S*)-3-((*Z*)-2-Methoxyimino-2-phenylacetamido)-2-azetidinone-1-sulfonate (21k)——(3*S*)-3-((*Z*)-2-Methoxyimino-2-phenylacetamido)-2-azetidinone (**18k**) and the title compound **21k** were synthesized by a procedure similar to that described for the synthesis of **21a**.

(a) **18k**: Foam (68.5%). ^{1}H-NMR ($CDCl_3$) δ: 3.26 (1H, dd, J=2 and 5 Hz, C_4–H), 3.52 (1H, t, J=5 Hz, C_4–H), 3.92 (3H, s, OCH_3), 4.96 (1H, ddd, J=2, 5 and 8 Hz, C_3–H), 6.47 (1H, br s, NH), 7.2—7.7 (5H, m, aromatic-H).

(b) **21k**: Powder (82.4%). *Anal.* Calcd for $C_{12}H_{12}N_3NaO_6S \cdot 1/2H_2O$: C, 40.23; H, 3.66; N, 11.73. Found: C, 40.02; H, 3.89; N, 12.02. IR ν_{max}^{KBr} cm^{-1}: 1760, 1660, 1530, 1250. ^{1}H-NMR (DMSO-d_6) δ: 3.67 (1H, t, J=5.5 Hz, C_4–H), 3.90 (3H, s, OCH_3), 4.95 (1H, ddd, J=2, 5.5 and 8 Hz, C_3–H), 7.3—7.7 (5H, m, aromatic-H), 9.38 (1H, d, J=8 Hz, NH).

Sodium (3*S*)-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-isopropoxyiminoacetamido]-2-azetidinone-1-sulfonate (21m)——A procedure similar to that described for the preparation of **21a** afforded **21m**.

(a) (3*S*)-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-isopropoxyiminoacetamido]-2-azetidinone (**18m**): Powder (68.5%). IR ν_{max}^{KBr} cm^{-1}: 3250, 1750, 1655, 1540. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=6 Hz, CH_3), 3.13 (1H, dd, J=2 and 6 Hz, C_4–H), 3.46 (1H, t, J=6 Hz, C_4–H), 4.33 (2H, s, $ClCH_2$–), 4.33 (1H, q, uintet J=6 Hz, CH), 5.0 (1H, m, C_3–H), 7.36 (1H, s, thiazole-H), 8.0 (1H, br s, NH), 9.10 (1H, d, J=8 Hz, NH).

(b) Sodium (3*S*)-3-[2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-isopropoxyiminoacetamido]-2-azetidinone-1-sulfonate: Powder (81.2%). IR ν_{max}^{KBr} cm^{-1}: 1755, 1700, 1540, 1250, 1050. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=6 Hz, CH_3), 3.66 (1H, t, J=6 Hz, C_4–H), 4.33 (1H, q, uinted J=6 Hz, CH), 4.33 (2H, s, $ClCH_2$–), 4.96 (1H, m, C_3–H), 7.36 (1H, s, thiazole-H), 9.23 (1H, d, J=8 Hz, CH).

(c) **21m**: Powder (71.6%). $[\alpha]_D^{24}$ −6.1° (c=0.99, MeOH) IR ν_{max}^{KBr} cm^{-1}: 1760, 1660, 1620, 1525, 1250, 1050. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=6 Hz, CH_3), 3.66 (1H, t, J=6 Hz, C_4–H), 4.33 (1H, q, uinted J=6 Hz, CH), 4.96 (1H, m, C_3–H), 7.36 (1H, s, thiazole-H), 9.23 (1H, d, J=8 Hz, NH).

(3*S*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*) -2- carboxymethoxyiminoacetamido] -2- azetidinone -1- sulfonic Acid (21n)——(a) A mixture of 2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-(2-trimethylsilylethoxycarbonylmethoxyimino)acetic acid HCl salt (1.72 g), pyridine (0.218 g), *N*-hydroxybenzotriazole (HOBT) (0.421 g) and DCC (0.62 g) in DMF (15 ml) was stirred at room temperature for 1.5 h. (3*S*)-3-Amino-2-azetidinone (**16**, 0.215 g) was added to the above suspension and the mixture was stirred at room temperature for 15 h. After removal of insoluble material, the solvent was evaporated off to give the residue. Purification was carried out by silica gel column chromatography to obtain the corresponding 2-azetidinone derivative (1.21 g, 74.3%) as a foam. IR ν_{max}^{KBr} cm^{-1}: 3280, 2960, 1760, 1675, 1515, 1250, 1202. ^{1}H-NMR (DMSO-d_6) δ: 0.05 (9H, s, CH_3), 3.08 (1H, dd, J=3 and 5 Hz, C_4–H), 3.38 (1H, t, J=5 Hz, C_4–H), 4.86 (1H, m, C_3–H), 6.74 (1H, s, thiazole-H), 7.26—7.50 (15H, m, aromatic-H), 7.96 (1H, s, NH), 8.76 (1H, s, NH), 8.97 (1H, d, J=8 Hz, NH).

(b) A solution of SO_3–DMF complex (0.805 g) in DMF (3.15 ml) was added to a solution of the 2-azetidinone derivative (1.15 g) obtained above (a) in DMF (7 ml) at −70°C. The mixture was stirred at 0°C for 15 h, then pyridine (0.417 g) was added, and treatment as described for the preparation of **21a** [(b)] gave sodium (3*S*)-3-[2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-(2-trimethylsilylethoxycarbonylmethoxyimino)acetamido]-2-azetidinone-1-sulfonate (0.859 g, 64.8%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3400, 1755, 1675, 1515, 1275, 1246, 1050. ^{1}H-NMR (DMSO-d_6) δ: 0.05 (9H, s, CH_3), 3.37 (1H, dd, J=3 and 6 Hz, C_4–H), 3.62 (1H, t, J=6 Hz, C_4–H), 4.88 (1H, m, C_3–H), 6.73 (1H, s, thiazole-H), 7.17—7.50 (15H, m, aromatic-H), 8.77 (1H, s, NH), 9.16 (1H, d, J=8 Hz, NH).

(c) A mixture of the 2-azetidinone-1-sulfonate derivative (0.70 g) obtained above (b) and (n-Bu)$_4$NF·$3H_2O$ (0.73 g) in DMF (7 ml) was stirred at room temperature for 40 min. After removal of the solvent, the residue was treated with AcOEt–water. The separated organic layer was concentrated to give an oily residue, which was dissolved in MeOH (100 ml). The methanol solution was stirred with Dowex 50W (H^+, 50 ml) for 5 h at room temperature. After removal of the resin and MeOH, the aqueous solution was purified by Amberlite XAD-2 column chromatography followed by lyophilization to obtain **21n** (0.124 g, 34.2%) as a powder. *Anal.* Calcd for $C_{10}H_{11}N_5O_8S_2 \cdot H_2O$: C, 29.20; H, 3.19; N, 17.03. Found: C, 29.38; H, 3.56; N, 16.54. IR ν_{max}^{KBr} cm^{-1}: 3350, 1755, 1660, 1630, 1268—1228, 1200, 1043. ^{1}H-NMR (DMSO-d_6) δ: 3.34 (1H, dd, J=3 and 6 Hz, C_4–H), 3.68 (1H, t, J=6 Hz, C_4–H), 4.71 (2H, s, CH_2), 4.96 (1H, m, C_3–H), 7.04 (1H, s, thiazole-H), 9.48 (1H, d, J=8 Hz, NH).

Sodium (3*S*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-(1-carboxy-1-methylethoxyimino)acetamido]-2-azetidinone-1-sulfonate (21p)——(a) Diphosgene (0.104 ml) was added to a solution of DMF (0.097 g) in CH_2Cl_2 (5 ml) at −10°C with stirring, and the reaction mixture was stirred at room temperature for 30 min. A solution of 2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-(2-trimethylsilylethoxycarbonyl)-1-methylethoxyimino]acetic acid (0.494 g) and Et_3N (0.145 g) in CH_2Cl_2 (15 ml) was added dropwise to the solution prepared above at −25—−20°C. The whole was stirred at the same temperature for 2 h, then Et_3N (0.145 g) and a solution of (3*S*)-3-amino-2-azetidinone (**16**, 0.095 g) in *N*,*N*-dimethylacetamide (4 ml) were added at −70°C. The reaction mixture was stirred at 0°C for 1 h, then the organic solvent was removed and the resulting oil was purified by silica gel column chromatography to obtain (3*S*)-3-[2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-(2-trimethylsilylethoxycarbonyl)-1-methylethoxyimino]-2-azetidinone (**18p**, 0.286 g, 50.3%) as a solid. IR ν_{max}^{KBr} cm^{-1}: 3275, 2940, 1740, 1700, 1680, 1660, 1565, 1142. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (2H, t, J=8.5 Hz, CH_2), 1.62 (6H, s, CH_3), 3.45 (1H, dd, J=3 and 5 Hz, C_4–H), 3.71 (1H, t, J=5 Hz, C_4–H), 4.20 (2H, t, J=8.5 Hz, CH_2), 4.25 (2H,

s,CH_2), 5.18(1H,m, C_3–H), 6.56 (2H, s, NH), 7.41 (1H, s, thiazole-H), 8.12(1H, d, J=8Hz, NH), 10.71 (1H, s, NH).

(b) A solution of SO_3–DMF complex (0.459 g) in DMF (1.8 ml) was added to a solution of the 2-azetidinone derivative (0.517 g) obtained above (a) in DMF (4 ml) at −70°C. The mixture was stirred at 0°C for 1.5 h, then pyridine (0.238 g) was added and work-up as described for the preparation of **21a** [(b)] gave sodium (3*S*)-3-[2-(2-chloroacetamidothiazol-4-yl)-(*Z*)-2-[1-(2-trimethylsilylethoxycarbonyl)-1-methylethoxyimino]-acetamido]-2-azetidinone-1-sulfonate (0.441 g, 71.3%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3450, 3270, 2950, 1755, 1662, 1538, 1270, 1245, 1145, 1048. ^{1}H-NMR (DMSO-d_6) δ: 0.03 (9H, s, CH_3), 1.47 (6H, s, CH_3), 3.31 (1H, dd, J=3 and 6 Hz, C_4–H), 3.68 (1H, t, C_4–H), 4.98 (1H, m, C_3–H), 7.38 (1H, s, thiazole-H), 9.14 (1H, d, J=8 Hz, NH), 12.83 (1H, br s, NH).

(c) A solution of sodium *N*-methyldithiocarbamate (0.101 g) in water (1.5 ml) was added to a cooled (0°C) solution of the 2-azetidinone-1-sulfonate derivative (0.372 g) obtained above (b) in DMF (4 ml). After the reaction mixture had been stirred at room temperature for 2 h, DMF was removed to give an oily residue, which was purified by Amberlite XAD-2 column chromatography to obtain the corresponding aminothiazole-2-azetidinone-1-sulfonate derivative (0.239 g, 73.3%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3430, 3325, 1760, 1666, 1620, 1530, 1280, 1250, 1150, 1052. ^{1}H-NMR (DMSO-d_6) δ: 0.03 (9H, s, CH_3), 1.43 (6H, s, CH_3), 3.40 (1H, dd, J=3 and 6 Hz, C_4–H), 3.64 (1H, t, J=6 Hz, C_4–H), 4.93 (1H, m, C_3–H), 6.70 (1H, s, thiazole-H), 7.20 (2H, br s, NH_2), 8.98 (1H, d, J=8 Hz, NH).

(d) A mixture of the above aminothiazole derivative (0.10 g) and $(n\text{-Bu})_4NF\cdot 3H_2O$ (0.5 g) in DMF (2 ml) was stirred at room temperature for 1 h. After removal of the solvent, water (5 ml) and Dowex-50W (Na^+, 8 ml) were added to the residue. The mixture was stirred at room temperature for 2 h, then the resin and the solvent were removed to obtain a resinous product. Purification was carried out by Amberlite XAD-2 column chromatography to give **21p** (0.0375 g, 42%) as a powder. IR ν_{max}^{KBr} cm^{-1}: 3390, 1755, 1658, 1620, 1522, 1265, 1240, 1200, 1048. ^{1}H-NMR (DMSO-d_6) δ: 1.43 (6H, s, CH_3), 3.32 (1H, dd, J=3 and 6 Hz, C_4–H), 3.67 (1H, t, J=6 Hz, C_4–H), 4.96 (1H, m, C_3–H), 6.72 (1H, s, thiazole-H), 7.16 (2H, s, NH_2), 9.48 (1H, d, J=8 Hz, NH).

Acknowledgement The authors thank Dr. K. Morita of the Central Research Division for his advice and encouragement. Thanks are also due to Dr. M. Kondo for the biological evaluation.

References and Notes

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