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Synthesis of 3-Acylamino-4-hydroxymethyl-2-oxo-1-sulfoazetidines and Related Compounds[1)]

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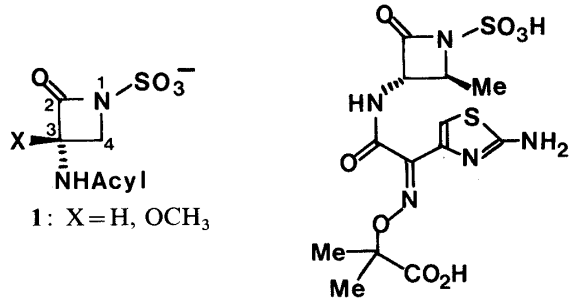
The synthesis of both enantiomers of the *trans*-3-acylamino-4-hydroxymethyl-2-oxo-1-sulfoazetidines **3a**, **b** and **4a**, **b** is described. The enantiomers of 4-hydroxymethyl-2-azetidinone, **7a** and **7b**, were chosen as starting materials, and the latter was synthesized from L-malic acid. For sulfonation at the *N*-1 position, the new amidine-*N*-sulfonic acid **6** was prepared and used. The preparation and antibacterial properties of the 4-acetoxymethyl derivatives **22a**, **b** and **23a**, **b** are described.

Keywords——*N*-sulfoazetidinone; 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]-1-decene-(2,2,4a,7,7-pentamethyl-1,2,3,4,4a,5,6,7-octahydronaphthyridine); sulfonation; 4-hydroxymethyl-2-azetidinone; 4-acetoxymethyl-2-azetidinone; L-malic acid

Recently, various 3-acylamino-2-oxo-1-sulfoazetidines (**1**) have been isolated from certain bacteria.[2)] They have attracted much interest because of their potent antibacterial activities as well as their simple and unique structures. The synthesis of these antibiotics and related compounds has therefore become of major importance and several successful routes have been reported.[3)] Among these antibiotics, compound **2** (SQ-26776), synthesized by the Squibb group, has been selected for clinical studies on the basis of its improved antibacterial activity and stability to β-lactamases.[4)] This synthetic azetidinone, having a methyl group at the *C*-4 position, is an attractive model for structural modification of natural monocyclic β-lactam antibiotics.



1: X=H, OCH_3

2: SQ-26776

Fig. 1

Thus, as a part of a synthetic program aimed at azetidinones having a *C*-4 alkyl group substituted by hetero atoms, we have devised a route to *C*-4-hydroxymethyl azetidinones. The structural convertibility of the hydroxymethyl side chain in these azetidinones makes them attractive intermediates for the synthesis of a variety of new monocyclic β-lactam antibiotics by chemical modification. We report herein the synthesis of (3*R*, 4*S*)-3-acylamino-4-hydroxymethyl-2-oxo-1-sulfoazetidines (**3a**, **4a**) and their 3*S*, 4*R* enantiomers (**3b**, **4b**). For the acyl side chain, 2-methoxyimino-2-(2-amino-4-thiazolyl)acetyl and phenoxyacetyl groups were chosen, since the former was considered to enhance the antibacterial potency in the case of β-lactam antibiotics (*e.g.* the cephalosporins),[5)] and the latter is involved in penicillin V.

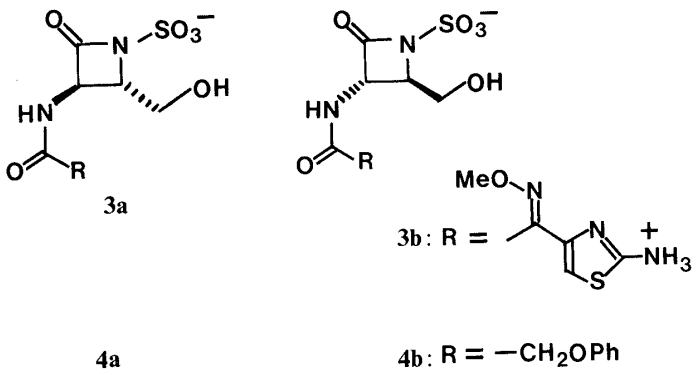


Fig. 2

For preparing our target compounds, the most important step is the sulfonation reaction. We required a sulfonating agent to react at the *N*-1 position under the mild and neutral conditions. The *N*-sulfonic acid obtained should be simultaneously protected, and the protected *N*-sulfonic acids are required to have the following properties: 1) soluble in protic and aprotic organic solvents, 2) stable to many reaction conditions for de-silylation, catalytic hydrogenation, acylation, *etc.*, 3) stable during purification by silica gel chromatography and recrystallization.

Sulfonation procedures based on pyridine–SO_3,[6] dimethylformamide (DMF)–SO_3,[7] dioxane–SO_3,[8] *etc.*[9] were unsatisfactory for our purpose since the products are less soluble in organic solvents. For the sulfonation of azetidinones, the Squibb group developed a procedure[3a-c] which involves sulfonation with pyridine–SO_3 or DMF–SO_3 complex followed by quenching into buffer and ion-pair extraction to give tetra-*n*-butylammonium salts.

In our work, we prepared a new sulfonating agent,[10] the *N*-sulfoamidine **6**, which fully satisfies our requirements. The stable protected *N*-sulfonic acids were produced by simply treating the starting azetidinones with compound **6** in organic solvents.

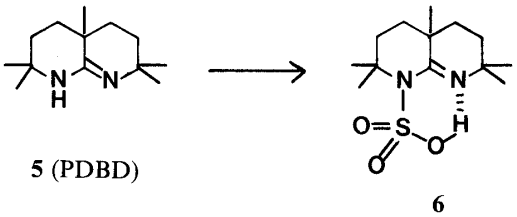
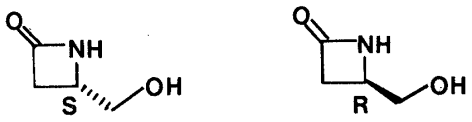


Chart 1

Compound **6** was readily obtained from 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]-1-decene (PDBD) (**5**)[11] by sulfonation with chlorosulfonic acid or pyridine–sulfur trioxide complex in excellent yield. This new sulfonating agent is soluble in most organic solvents and was found to be stable (it could be stored for months without deterioration). The structural assignment of **6** was tentatively made on the basis of its ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra, in which unsymmetrical methyl groups were observed (see the experimental section).

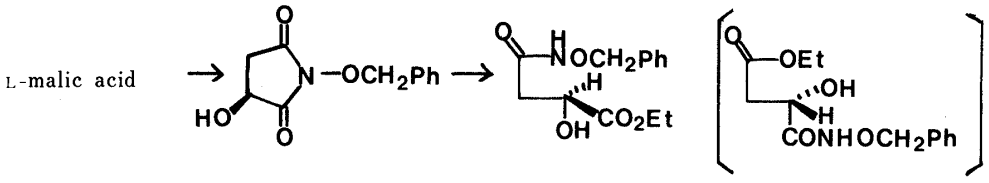
To synthesize our target compounds, we chose (4*S*) and (4*R*)-4-hydroxymethyl-2-azetidinones (**7a** and **7b**) as starting materials. Compound **7a** was prepared from L-aspartic acid by the Merck procedure [12] and compound **7b** was synthesized from readily available L-malic acid as follows.[13]

Treatment of L-malic acid[14] with benzyloxylamine in hot xylene afforded the succinimide **8**[15] in 69% yield. Subsequent treatment of **8** with lithium ethoxide in the presence of *n*-

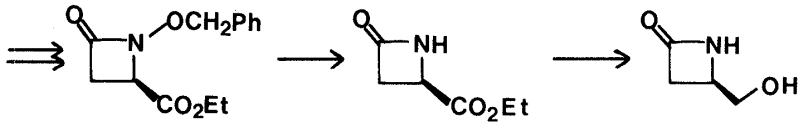


7a 7b

Fig. 3



8 9 10

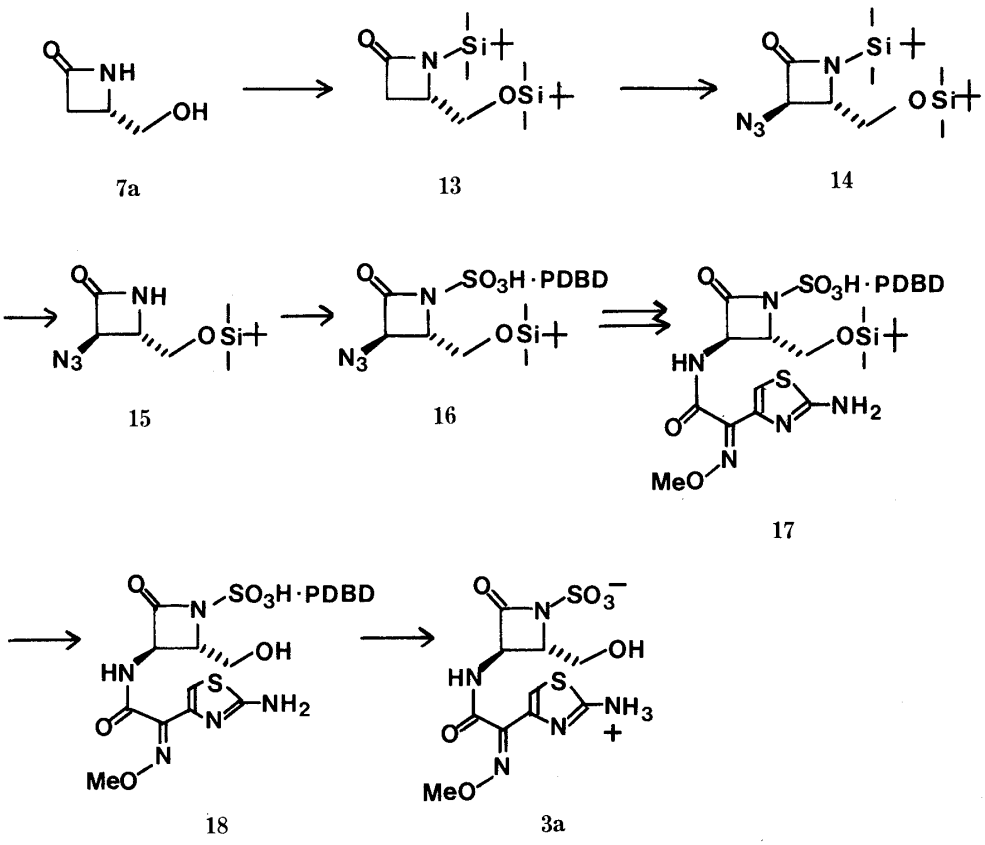


11 12 7b

Chart 2

butyllithium resulted in the regiospecific formation of the hydroxamate **9**[15] in 85% yield. Another possible isomer **10** was not detected in the crude product. The regioselectivity of this ethanolysis can be attributed to the electronic influence of the lithium ion complexation with the hydroxyl group and the adjacent carbonyl group in the starting succinimide **8**. The hydroxamate **9** was cyclized by Miller's method[13,16] using the Mitsunobu reaction[17] to give the azetidinone **11**.[15] Deprotection of **11** by well-documented procedures[13,17] afforded the desired azetidinone **12** which was transformed to the 4-hydroxymethylazetidinone **7b** by reduction with sodium borohydride.

The synthesis of the 1-sulfoazetidinone **3a** is summarized in Chart 3. Both active groups of the starting azetidinone **7a** were protected by silylation with *tert*-butylchlorodimethylsilane and triethylamine in dimethylformamide to afford the disilylate **13**. The introduction of the azido group at the *C*-3 position by use of *p*-toluenesulfonylazide according to Kühlein's method[18] resulted in the stereospecific formation of the *trans* azetidinone **14**, but the yield (*ca.* 49%) was unsatisfactory. However, when the reaction was carried out with 2,4,6-triisopropylbenzenesulfonyl azide,[19] the same azide azetidinone **14** was obtained in good yield. The *trans* relationship of *C*-3H and *C*-4H of **14** is evident from their small coupling constant in the ^{1}H NMR spectrum.[21] Regioselective desilylation of **14** was cleanly achieved with potassium fluoride in cold methanol followed by treatment with acetic acid[20] to give the monosilyl azetidinone **15** in excellent yield. The sulfonation of the azetidinone **15** with the aforementioned PDBD–sulfonic acid **6** at 50—55 °C afforded a crystalline salt of the *N*-sulfoazetidinone **16** in nearly quantitative yield after rapid silica gel column chromatography. The catalytic hydrogenation of **16** using 10% Pd–C in tetrahydrofuran (THF) afforded the amino azetidinone, which was acylated with (*Z*)-2-methoxyimino-2-(2-amino-4-thiazolyl)acetic acid[5] and *N*,*N*′-dicyclohexylcarbodiimide in the presence of a catalytic amount of 1-hydroxybenzotriazole in dimethylformamide to give the desired 3-acylamino azetidinone **17** as a foam in 83% yield from **16**. Deprotection of the silyloxy group in **17** was carried out by treatment with tetra-*n*-butylammonium fluoride in the presence of 1 eq of acetic acid[20] in tetrahydrofuran to afford the desired hydroxy compound **18**. Removal of PDBD

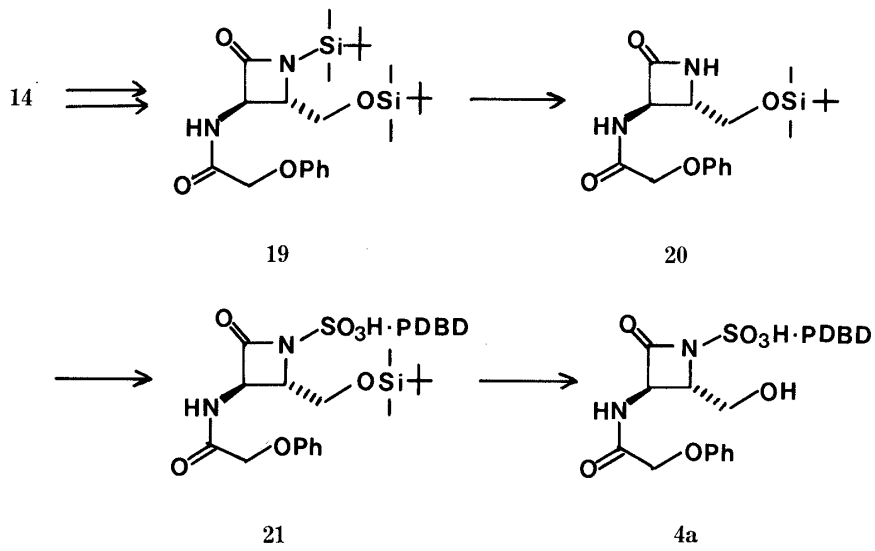


7a 13 14

15 16 17

18 3a

Chart 3



19 20

21 4a

Chart 4

from **18** was readily accomplished by brief treatment with trifluoroacetic acid in dichloromethane to give the desired crystalline zwitterion **3a**.

The phenoxyacetyl derivative **4a** was prepared by an alternative route (Chart 4). The azidoazetidinone **14** was reduced by catalytic hydrogenation followed by acylation with phenoxyacetic acid in the same manner as described above to afford the phenoxyacetyl derivative **19** in good yield. Selective deprotection of **19** followed by sulfonation with **6** gave the sulfonated azetidinone **21** in nearly quantitative yield. The desired hydroxy compound **4a**

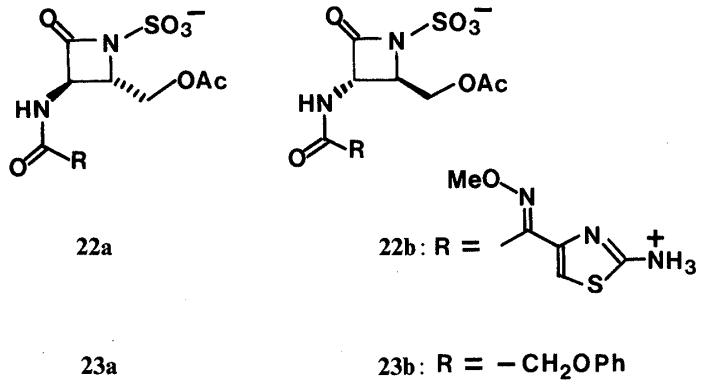


Fig. 4

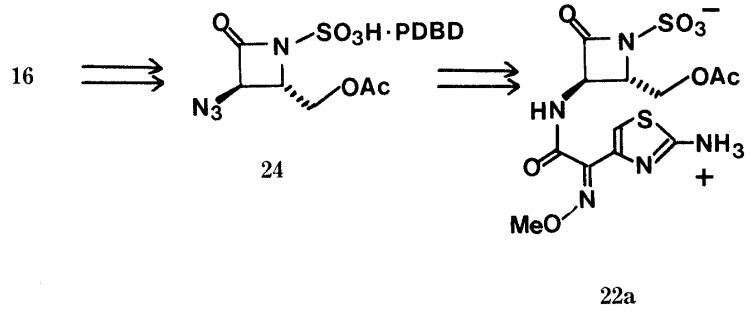


Chart 5

TABLE I. *In Vitro* Antibacterial Activity of (3*R*, 4*S*)- and (3*S*, 4*R*)-4-Acetoxymethyl-3-[(*Z*)-2-(2-amino-4-thiazolyl)-2-methoxyimino-acetamido]-2-oxo-1-sulfoazetidine (**22a** and **22b**)

Organism	Compound	
	22a	**22b**
E. coli 05137	12.5	0.39
Ent. cloacae 03402	3.13	0.10
Ser. marcescens 10100	25.0	0.78
Str. pyogenes G-36	25.0	1.56

MIC: minimum inhibitory concentration (μg/ml).

was obtained by deprotection of **21** with tetra-*n*-butylammonium fluoride in 94% yield as a foam. The enantiomeric azetidinones **3b** and **4b** were also synthesized starting from (4*R*)-4-hydroxymethyl-2-azetidinone **7b** in a manner similar to that mentioned above.

Unfortunately, compounds **3a**, **b** and **4a**, **b** did not show the expected biological activity against Gram-positive and Gram-negative organisms. We therefore turned our attention to modification of the side chain hydroxyl group. For instance, we synthesized the acetates **22a**, **b** and **23a**, **b**. The latter acetates **23a** and **23b** were easily obtained by usual acetylation reactions of **4a** and **4b**, respectively. However, direct acetylations of the zwitterions **3a** and **3b** were unsuccessful. The acetates **22a** and **22b** therefore were synthesized by the alternative route shown in Chart 5, which shows only one enantiomer for convenience. Azidoazetidinone **16** was deprotected with tetra-*n*-butylammonium fluoride and then acetylated with acetic anhydride in pyridine without purification of the intermediate to give the acetate **24** in 89%

yield. Subsequent reduction and acylation of **24** in a manner similar to that mentioned above gave the desired acetate **22a** in 94% yield. Compound **22b** was prepared in a similar manner.

The *in vitro* antibacterial activities of **22** are shown in Table I. The azetidinone **22b** having the 3*S* configuration (as in penicillin) has considerable activities against Gram-negative organisms. It is noteworthy that the 3*R* azetidinone (**22a**) also showed activities, although lower than those of the 3*S* isomer (**22b**).

Experimental

Infrared (IR) spectra were obtained with a JASCO DS-701G spectrometer, and NMR spectra were determined with a JEOL JMS-SP100 spectrometer (^{1}H) and a JEOL JMS FX200 spectrometer (^{13}C) using tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) were recorded on a JEOL JMS-D 300 mass spectrometer using a direct insertion probe. Optical rotations were taken with a Union PM-201 automatic polarimeter. Melting points were determined by the capillary method and are uncorrected.

All experiments were carried out under an argon atmosphere unless otherwise specified. For column chromatography, a 1 : 1 mixture of Merck 70—230 mesh Kieselgel 60 and Mallinckrodt 100 mesh silicic acid was employed.

3,3,6,9,9-Pentamethyl-10-sulfo-2,10-diazabicyclo[4.4.0]-1-decene (6)——a) Chlorosulfonic acid (0.16 ml, 2.41 mmol) was added gradually to a solution of 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]-1-decene **5** (997 mg, 4.79 mmol) in dioxane (14 ml) under ice cooling. The solution was stirred at room temperature for 1 h and was then allowed to stand overnight. After removal of the solvent *in vacuo*, the residue was subjected to silica gel column chromatography. Elution with chloroform/acetone (85 : 15) gave the colorless crystalline sulfonate **6** which was found to be analytically pure. mp 146—147 °C. Yield, 420 mg (61%). *Anal.* Calcd for $C_{13}H_{24}N_2O_3S$: C, 54.14; H, 8.39; N, 9.71. Found: C, 54.01; H, 8.43; N, 9.52. IR ($CHCl_3$): 1607, 1245, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36, 1.38, 1.44, 1.67, 1.77 (each 3H, s, CH_3), 1.20—2.50 (8H, m, CH_2), and 9.47 (1H, br, SO_3H). ^{13}C-NMR ($CDCl_3$) δ: 26.0 (q), 28.5 (q), 29.5 (q), 30.1 (t), 30.6 (t and q), 31.1 (q), 32.1 (t), 35.6 (s), 37.0 (t), 56.2 (s), 63.6 (s), and 168.5 (s). b) Pyridine–sulfur trioxide complex (1.592 g, 10 mmol) was added in one portion to a stirred solution of **5** (2.083 g, 10 mmol) in THF (6 ml) at room temperature, and the mixture was stirred for 1 h. After removal of the solvent *in vacuo*, the residue was purified as above to give the sulfonate **6**. Yield, 2.540 g (88%).

1-Benzyloxy-3-hydroxysuccinimide (8)——A solution of benzyloxylamine (5.489 g, 44.6 mmol) in xylene (35 ml) was added in one portion to a stirred suspension of L-malic acid (4.980 g, 37.1 mmol) in xylene (135 ml) and the suspension was stirred under reflux at 150—160 °C for 6 h. The resulting clear solution was cooled and the precipitate that formed was collected by suction. The precipitate was washed with benzene and recrystallized from THF/isopropyl ether to give colorless needles. mp 125—126 °C. Yield, 5.693 g (69%). *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.95; H, 5.06; N, 6.45. IR (KBr): 3480, 1720 cm^{-1}. NMR (d_6-DMSO) δ: 2.47 (1H, dd, J=17.5 and 4.5 Hz, C_4–H), 3.00 (1H, dd, J=17.5 and 8.5 Hz, C_4–H), 4.47 (1H, dd, J=8.5 and 4.5 Hz, C_3–H), 4.97 (2H, s, OCH_2), 6.20 (1H, br, OH), and 7.40 (5H, m, Ar).

Ethanolysis of 8——A stirred solution of ethyl alcohol (691 mg, 15 mmol) in THF (20 ml) at −78 °C was treated with 12.2 ml (22 mmol) of 1.80 M solution of *n*-butyllithium in *n*-hexane, and subsequently a solution of **8** (2.212 g, 10 mmol) in THF (15 ml) was added dropwise. After being stirred for 15 min at −78 °C, the reaction mixture was warmed to room temperature and stirring was continued for 1 h. The mixture was poured into ice water and extracted with ethyl acetate. The extract was washed with brine, then dried, filtered and concentrated. The residue was chromatographed on silica gel to give the hydroxamate **9**. Yield, 2.265 g (85%). IR ($CHCl_3$): 3700—3100, 1732, 1690 cm^{-1}. NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 2.53 (2H, br, $COCH_2$), 4.13 (2H, q, J=7 Hz, CO_2CH_2), 4.10—4.30 (1H, br, OH), 4.42 (1H, dt, J=5.5 and 5.5 Hz; with D_2O, dd, J=5 and 6.5 Hz, $-C\underline{H}OH$), 4.81 (2H, s, $C\underline{H}_2Ph$), 7.31 (5H, s, Ar), 9.72 (1H, br, NH).

(4*R*)-1-Benzyloxy-4-ethoxycarbonyl-2-azetidinone (11)——A solution of diethyl azodicarboxylate (326 mg, 1.87 mmol) in THF (2 ml) was added to a solution of **9** (500 mg, 1.87 mmol) and triphenylphosphine (491 mg, 1.87 mmol) in THF (9 ml) at 0 °C, then the mixture was warmed to room temperature, and stirred for 4 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give the azetidinone **11** as a colorless oil. Yield, 197 mg (58%). $[\alpha]_D^{22}$ +29.5° (c=2.34, $CHCl_3$). MS m/e: 250.1093. Calcd for $C_{13}H_{16}NO_4$: 250.1079 (M^++H). IR ($CHCl_3$): 1784, 1743 cm^{-1}. NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.68 (1H, dd, J=13.5 and 3 Hz, C_3–H), 2.86 (1H, dd, J=13.5 and 5.5 Hz, C_3–H), 4.07 (1H, dd, J=5.5 and 3 Hz, C_4–H), 4.16 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.98 (2H, s, OCH_2Ph), 7.33 (5H, m, Ar).

(4*R*)-4-Ethoxycarbonyl-2-azetidinone (12)——A suspension of 10% Pd–C (120 mg) in a solution of **11** (612 mg, 2.46 mmol) in methyl alcohol (20 ml) was stirred for 1 h under a current of H_2 at room temperature. After filtration, the residual catalyst was washed thoroughly with methyl alcohol and the combined filtrate and washings were concentrated *in vacuo*. The resulting crude hydroxy compound, without purification, was dissolved in a mixed solvent

of THF (10 ml) and water (22 ml), and sodium acetate (1.208 g, 14.7 mmol) was added. Then aqueous 25% titanium (III) chloride (3.05 ml, 4.91 mmol) was added dropwise to the solution with stirring. The reaction mixture was stirred for 2.5 h at room temperature, and extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate and brine successively, then dried, filtered and concentrated. The residue was chromatographed on silica gel and recrystallized from dichloromethane/isopropyl ether to give colorless plates. mp 32—33 °C. Yield, 188 mg (55%). $[\alpha]_D^{22}$ +46.6° (c=0.90, $CHCl_3$). *Anal.* Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.10; H, 6.22; N, 9.75. IR ($CHCl_3$): 1776, 1742 cm^{-1}. NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, CH_2CH_3), 3.00 (1H, ddd, J=15, 3, and 2 Hz, C_3–H), 3.30 (1H, ddd, J=15, 5.5, and 1.5 Hz, C_3–H), 4.15 (1H, dd, J=5.5 and 3 Hz, C_4–H), 4.20 (2H, q, J=7 Hz, OCH_2), 6.93 (1H, br, NH).

(4*R*)-4-Hydroxymethyl-2-azetidinone (7b)——Sodium borohydride (1.30 g, 34 mmol) was added in one portion to a stirred solution of **12** (4.80 g, 34 mmol) in methyl alcohol (72 ml) under cooling in a water bath at room temperature, and the mixture was stirred for 1 h, then neutralized by adding conc. hydrochloric acid under ice cooling. After evaporation of the solvent *in vacuo*, the residue was suspended in chloroform/methyl alcohol (2 : 1, 80 ml) and dried with magnesium sulfate. The precipitate and drying agent were filtered off and washed thoroughly with the same solvent. The combined filtrate and washings were concentrated *in vacuo*. Chromatography on silica gel followed by recrystallization provided colorless plates. mp 48—49 °C. Yield, 2.82 g (81%). $[\alpha]_D^{22}$ −21.8° (c=1.79, MeOH). *Anal.* Calcd for $C_4H_7NO_2 \cdot 1/2H_2O$: C, 43.63; H, 7.32; N, 12.72. Found: C, 43.82; H, 7.04; N, 12.88. IR ($CHCl_3$): 3400, 1765 cm^{-1}. NMR ($CDCl_3$) δ: 2.65 (1H, dt, J=14.5 and 2 Hz, C_3–H), 2.95 (1H, ddd, J=14.5, 4.5, and 1.5 Hz, C_3–H), 3.40—3.95 (3H, m, C_4–H and C_4–CH_2), 4.44 (1H, t, J=5 Hz, OH), 7.27 (1H, br, NH).

(4*S*)-1-*tert*-Butyldimethylsilyl-3-*tert*-butyldimethylsilyloxymethyl-2-azetidinone (13)——*tert*-Butylchlorodimethylsilane (7.479 g, 49.6 mmol) was added in one portion to a stirred solution of **7a** (2.389 g, 24.6 mmol) and triethylamine (7.25 ml, 52.0 mmol) in DMF (65 ml) at 0 °C. The resulting solution was stirred for 30 min at 0 °C and then 1 h at room temperature. The usual work-up gave a pale yellow oil which was purified by silica gel chromatography to provide a colorless syrup. Yield, 5.884 g (78%). $[\alpha]_D^{22}$ −25.3° (c=0.95, $CHCl_3$). MS m/e: 330.2277. Calcd for $C_{16}H_{36}NO_2Si_2$: 330.2284 (M^++H). IR ($CHCl_3$): 1728 cm^{-1}. NMR ($CDCl_3$) δ: 0.06 (6H, s, 2×$SiCH_3$), 0.23 (6H, s, $SiCH_3$), 0.88 (9H, s, *tert*-Bu), 0.93 (9H, s, *tert*-Bu), 2.75 (1H, dd, J=15 and 2.5 Hz, C_3–H), 3.01 (1H, dd, J=15 and 4.5 Hz, C_3–H), 3.48—3.84 (3H, m, C_4–H and C_4–CH_2). The corresponding 4*R* isomer was obtained by the same procedure as described above from **7b** (2.823 g, 24 mmol), triethylamine (8.56 ml, 53 mmol), and *tert*-butylchlorodimethylsilane (8.838 g, 50 mmol) as a colorless oil. Yield, 7.617 g (97%). $[\alpha]_D^{22}$ +24.5° (c=2.41, $CHCl_3$).

(3*R*, 4*S*)-3-Azido-1-*tert*-butyldimethylsilyl-4-*tert*-butyldimethylsilyloxymethyl-2-azetidinone (14)——A solution of **13** (5 g, 15.2 mmol) in THF (10 ml) was added dropwise over a period of 1.5 h at −78 °C to a stirred solution of freshly prepared lithium diisopropylamide made from *n*-butyllithium (10.4 ml of a 1.75 M solution in *n*-hexane, 18.2 mmol) and diisopropylamine (1.921 g, 19.0 mmol) in 30 ml of THF. Stirring was continued for 50 min at −78 °C, then a solution of 2,4,6-triisopropylbenzenesulfonyl azide (5.163 g, 16.7 mmol) in THF (10 ml) was added over a period of 10 min. Stirring was continued for 20 min at −78 °C, then a solution of chlorotrimethylsilane (3.706 g, 34.1 mmol) in THF (10 ml) was added. The resulting mixture was warmed up to room temperature and stirred for 2 h. The reaction was quenched by adding water. The usual work-up gave an oil, which was purified by column chromatography to give the azidoazetidinone **14** as a colorless oil. Yield, 4.420 g (79%). $[\alpha]_D^{22}$ +68.9° (c=2.09, $CHCl_3$). MS m/e 371.2291. Calcd for $C_{16}H_{35}N_4O_2Si_2$: 371.2298 (M^++H). IR ($CHCl_3$): 2110, 1750 cm^{-1}. NMR ($CDCl_3$) δ: 0.07 (6H, s, $SiMe_2$), 0.22 (3H, s, $SiCH_3$), 0.27 (3H, s, $SiCH_3$), 0.89 (9H, s, *tert*-Bu), 0.95 (9H, s, *tert*-Bu), 3.44—3.92 (3H, m, C_4–H and C_4–CH_2), 4.40 (1H, d, J=2 Hz, C_3–H). The same procedure as described above yielded the corresponding 3*S*, 4*R* isomer from the 4*R* isomer of **13** (3.3 g, 10 mmol), diisopropylamine (1.76 ml, 12.5 mmol), *n*-butyllithium (15.9 ml, 27.8 mmol), 2,4,6-triisopropylbenzenesulfonyl azide (3.411 g, 11.0 mmol), and chlorotrimethylsilane (2.9 ml, 22.5 mmol) as a colorless oil. Yield, 2.290 g (80%). $[\alpha]_D^{22}$ −70.0° (c=2.17, $CHCl_3$).

(3*R*, 4*S*)-3-Azido-4-*tert*-butyldimethylsilyloxymethyl-2-azetidinone (15)——Potassium fluoride (120 mg, 2.07 mmol) was added to a solution of **14** (696 mg, 1.87 mmol) in methyl alcohol (14 ml) at 0 °C. The mixture was stirred at 0 °C for 10 min, then acetic acid (113 mg, 1.88 mmol) was added and the mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel to give the azetidinone **15** as a white solid. Yield, 473 mg (98%). Recrystallization of **15** from isopropyl ether/dichloromethane gave an analytical sample. mp 50—51 °C. $[\alpha]_D^{22}$ +136.7° (c=2.22, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{20}N_4O_2Si$: C, 46.85; H, 7.86; N, 21.85. Found: C, 46.95; H, 8.05; N, 21.92. IR ($CHCl_3$): 3410, 2110, 1780 cm^{-1}. NMR ($CDCl_3$) δ: 0.08 (6H, s, $SiMe_2$), 0.88 (9H, s, *tert*-Bu), 3.50—3.85 (3H, m, C_4–H and C_4–CH_2), 4.40 (1H, t, J=2 Hz, C_3–H), 6.56 (1H, br, NH). By the same procedure as described above, the 3*S*, 4*R* isomer of **15** was obtained from the 3*S*, 4*R* isomer of **14** (5.64 g, 15.2 mmol), potassium fluoride (973 mg, 16.7 mmol), and acetic acid (0.88 ml, 15.2 mmol) as colorless plates. Yield, 3.624 g (93%). $[\alpha]_D^{22}$ −133.3° (c= 2.18, $CHCl_3$).

PDBD–Salt of (3*R*, 4*S*)-3-Azido-4-*tert*-butyldimethylsilyloxymethyl-2-oxo-1-sulfoazetidine (16)——A solution of **15** (147 mg, 0.57 mmol) and the amidine-*N*-sulfonic acid **6** (200 mg, 0.69 mmol) in THF/dioxane (1 : 1, 1.4 ml) was stirred at 50—55 °C (bath temperature) for 1.5 h, then cooled. The mixture was concentrated *in vacuo*, and the residue was purified by silica gel chromatography to provide the sulfonate **16** as a colorless solid. Yield, 303 mg (97%). mp

112—113 °C. $[\alpha]_D^{22}$ +28.4° (c=2.04, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{44}N_6O_5SSi$: C, 50.70; H, 8.14; N, 15.43. Found: C, 50.46; H, 8.25; N, 15.12. IR ($CHCl_3$): 2105, 1769, 1641 cm^{-1}. NMR ($CDCl_3$) δ: 0.09 (6H, s, $SiMe_2$), 0.87 (9H, s, *tert*-Bu), 1.30 (3H, s, CH_3), 1.32 (6H, s, 2×CH_3), 1.37 (6H, s, 2×CH_3), 1.40—2.20 (8H, m, 4×CH_2), 3.85—4.20 (3H, m, C_4–H and C_4–CH_2), 4.49 (1H, d, J=2 Hz, C_3–H), 8.45 (2H, br, SO_3H_2). By the same procedure as described above, the 3*S*, 4*R* isomer of **16** was obtained from the 3*S*, 4*R* isomer of **15** (600 mg, 2.34 mmol) and **6** (810 mg, 2.81 mmol) as a colorless solid. Yield, 1.232 g (97%). $[\alpha]_D^{22}$ −32.8° (c=2.04, $CHCl_3$).

PDBD–Salt of (3*R*,4*S*)-3-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-methoxyiminoacetamido]-4-*tert*-butyldimethylsilyloxymethyl-2-oxo-1-sulfoazetidine (17)——A suspension of 10% Pd–C (481 mg) in a solution of **16** (481 mg, 0.88 mmol) in THF (15 ml) was stirred for 2.5 h under a current of H_2 at room temperature, then filtered. The residual catalyst was washed thoroughly with methyl alcohol and the combined filtrate and washings were concentrated *in vacuo*. The crude amino compound obtained was dissolved in DMF (15 ml), and to this solution, *N*,*N*′-dicyclohexylcarbodiimide (237 mg, 1.15 mmol), 1-hydroxybenzotriazole (48 mg, 0.36 mmol), and (*Z*)-2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid (178 mg, 0.88 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature overnight. The precipitate formed was filtered off and washed thoroughly with acetone. The combined filtrate and washings were concentrated *in vacuo* and the residue obtained was taken up in acetone. The precipitate formed was filtered off and the filtrate was concentrated *in vacuo* to give a pale yellow oil. Column chromatography of this oil on silica gel provided the 3-acylaminoazetidinone **17** as a foam. Yield, 513 mg (83%). This compound showed a positive optical rotation, but the value was too small to measure accurately. IR ($CHCl_3$): 1765, 1670, 1641 cm^{-1}. NMR ($CDCl_3$) δ: 0.11 (6H, s, $SiMe_2$), 0.89 (9H, s, *tert*-Bu), 1.29 (3H, s, CH_3), 1.31 (6H, s, 2×CH_3), 1.30—2.30 (8H, m, 4×CH_2), 3.89 (3H, s, OCH_3), 3.60—4.25 (3H, m, C_4–H and C_4–CH_2), 5.19 (1H, dd, J=8 and 1.5 Hz, C_3–H), 6.06 (2H, br, NH_2), 6.66 (1H, s, Ar), 7.94 (1H, d, J=8 Hz, NH), 8.75 (2H, s, SO_3H_2). By the same procedure as described above, the 3*S*, 4*R* isomer of **17** was obtained as a foam from the 3*S*, 4*R* isomer of **16** (720 mg, 1.32 mmol), 10% Pd–C (720 mg), *N*,*N*′-dicyclohexylcarbodiimide (355 mg, 1.72 mmol), 1-hydroxybenzotriazole (72 mg, 0.53 mmol), and (*Z*)-2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid (266 mg, 1.32 mmol). Yield, 698 mg (75%).

PDBD–Salt of (3*R*,4*S*)-3-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-methoxyiminoacetamido]-4-hydroxymethyl-2-oxo-1-sulfoazetidine (18)——A mixture of **17** (236 mg, 0.34 mmol), tetra-*n*-butylammonium fluoride (159 mg, 0.61 mmol), and acetic acid (20 mg, 0.33 mmol) in THF (4 ml) was stirred overnight at room temperature. After evaporation of the solvent, the residue was chromatographed on silica gel to give the hydroxymethyl azetidinone **18** as a foam. Yield, 160 mg (81%). $[\alpha]_D^{22}$ +9.8° (c=2.04, $CHCl_3$). IR ($CHCl_3$): 1769, 1641 cm^{-1}. NMR ($CDCl_3$) δ: 1.26 (3H, s, CH_3), 1.28 (6H, s, 2×CH_3), 1.33 (6H, s, 2×CH_3), 1.00—2.30 (8H, m, 4×CH_2), 3.86 (3H, s, OCH_3), 3.60—4.30 (3H, m, C_4–H and C_4–CH_2), 4.93 (1H, dd, J=7 and 1.5 Hz, C_3–H), 6.23 (2H, br, NH_2), 6.60 (1H, s, Ar), 8.27 (2H, s, SO_3H_2), 8.59 (1H, d, J=7 Hz, NH). By the same procedure as described for **18**, the corresponding 3*S*, 4*R* isomer was obtained from the 3*S*, 4*R* isomer of **17** (497 mg, 0.71 mmol), tetra-*n*-butylammonium fluoride (334 mg, 1.28 mmol), and acetic acid (43 mg, 0.71 mmol) as a foam. Yield, 333 mg (80%).

(3*R*, 4*S*)-3-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-methoxyiminoacetamido]-4-hydroxymethyl-2-oxo-1-sulfoazetidine (3a)——A solution of trifluoroacetic acid (36 mg, 0.32 mmol) in dichloromethane (2 ml) was added dropwise to a stirred solution of **18** (223 mg, 0.38 mmol) in dichloromethane (5 ml) at −5 °C. The mixture was concentrated *in vacuo* and the residue obtained was taken up in acetone. The precipitate formed was filtered and washed thoroughly with acetone to give the crude zwitterion **3a** as a colorless solid (133 mg). Recrystallization of **3a** from water/acetone gave pure **3a** as colorless prisms. Yield, 58 mg (39%). mp 203—208 °C (dec.). $[\alpha]_D^{22}$ +36.6° (c=1.24, H_2O). *Anal.* Calcd for $C_{10}H_{13}N_5O_7S_2$: C, 30.22; H, 3.80; N, 17.62. Found: C, 30.24; H, 3.44; N, 17.71. IR (KBr): 3300 (br), 1765, 1637 cm^{-1}. NMR (DMSO-d_6) δ: 3.40—4.10 (3H, m, C_4–H and C_4–CH_2), 3.93 (3H, s, OCH_3), 4.73 (1H, dd, J=8 and 1.5 Hz, C_3–H), 5.50 (3H, br, NH_3), 6.92 (1H, s, Ar), 9.49 (1H, d, J=8 Hz, NH). The same procedure as described above gave the 3*S*, 4*R* isomer **3b** from the 3*S*, 4*R* isomer of **18** (333 mg, 0.57 mmol) and trifluoroacetic acid (71 mg, 0.62 mmol) as colorless prisms. Yield, 76 mg (35%). $[\alpha]_D^{22}$ −36.1° (c=0.94, H_2O).

(3*R*, 4*S*)-1-*tert*-Butyldimethylsilyl-4-*tert*-butyldimethylsilyloxymethyl-3-phenoxyacetamido-2-azetidinone (19)——A suspension of 10% Pd–C (212 mg) in a solution of **14** (210 mg, 0.57 mmol) in THF (10 ml) was stirred for 1.5 h under a current of H_2 at room temperature, then filtered. The residual catalyst was washed thoroughly with methyl alcohol and the combined filtrate and washings were concentrated *in vacuo*. The crude amino compound obtained was dissolved in THF (10 ml). To this solution, *N*,*N*′-dicyclohexylcarbodiimide (152 mg, 0.74 mmol), 1-hydroxybenzotriazole (31 mg, 0.23 mmol), and phenoxyacetic acid (95 mg, 0.62 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The precipitate formed was filtered off and washed thoroughly with acetone. The combined filtrate and washings were concentrated *in vacuo*. The crude substance obtained was purified by chromatography on silica gel, giving the amide **19** as a white solid. Yield, 226 mg (83%). mp 121—122 °C. The optical rotation of this compound was near 0°. *Anal.* Calcd for $C_{24}H_{42}N_2O_4Si$: C, 60.20; H, 8.84; N, 5.85. Found: C, 60.40; H, 9.21; N, 5.65. IR ($CHCl_3$): 3410, 1743, 1685 cm^{-1}. NMR ($CDCl_3$) δ: 0.09 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.28 (6H, s, $SiMe_2$), 0.90 (9H, s, *tert*-Bu), 0.98 (9H, s, *tert*-Bu), 3.68—3.90 (3H, m, C_4–H and C_4–CH_2), 4.47 (2H, s, CH_2OPh), 4.71 (1H, dd, J=7 and 2.5 Hz, C_3–H), 6.80—7.45 (6H, m, Ar and NH). By the same procedure as described above, the 3*S*, 4*R* isomer of **19** was obtained from the 3*S*, 4*R* isomer of **14** (467 mg, 1.26 mmol), 10% Pd–C

(467 mg), *N,N'*-dicyclohexylcarbodiimide (338 mg, 1.64 mmol), 1-hydroxybenzotriazole (69 mg, 0.50 mmol), and phenoxyacetic acid (192 mg, 1.39 mmol) as a white solid. Yield, 560 mg (93%).

(3*R*, 4*S*)-4-*tert*-Butyldimethylsilyloxymethyl-3-phenoxyacetamido-2-azetidinone (20)——Potassium fluoride (38 mg, 0.65 mmol) was added to a solution of **19** (280 mg, 0.58 mmol) in methyl alcohol (4 ml) at 0 °C. The mixture was stirred at 0 °C for 15 min, then acetic acid (36 mg, 0.60 mmol) was added and the mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel to give the azetidinone **20** as white crystals. Yield, 207 mg (97%). mp 153—154 °C. $[\alpha]_D^{22}$ +29.7° (*c*=2.05, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{28}N_2O_4Si_2$: C, 59.31; H, 7.74; N, 7.68. Found: C, 59.43; H, 8.06; N, 7.45. IR ($CHCl_3$): 3407, 1773, 1686 cm^{-1}. NMR ($CDCl_3$) δ: 0.06 (6H, s, $SiMe_2$), 0.85 (9H, s, *tert*-Bu), 3.60—3.95 (3H, m, C_4–H and C_4–CH_2), 4.43 (2H, s, $C\underline{H}_2OPh$), 4.82 (1H, dd, *J*=8 and 1.5 Hz, C_3–H), 6.80—7.40 (5H, m, Ar), 7.72 (1H, d, *J*=8 Hz, NH). By the same procedure as described above, the 3*S*, 4*R* isomer of **20** was obtained from the 3*S*, 4*R* isomer of **19** (489 mg, 1.02 mmol), potassium fluoride (66 mg, 1.12 mmol), and acetic acid (62 mg, 1.02 mmol) as colorless crystals. Yield, 367 mg (99%). $[\alpha]_D^{22}$ −29.3° (*c*=2.18, $CHCl_3$).

PDBD–Salt of (3*R*, 4*S*)-4-tert-Butyldimethylsilyloxymethyl-3-phenoxyacetamido-2-oxo-1-sulfoazetidine (21)——A solution of **20** (206 mg, 0.57 mmol) and **6** (196 mg, 0.68 mmol) in tetrahydrofuran/dioxane (1 : 1, 2 ml) was stirred at 50—55 °C (bath temperature) for 1.5 h. The mixture was then cooled and evaporated to dryness *in vacuo*. The residue was purified by silica gel chromatography to provide the sulfonate **21** as a foam. Yield, 362 mg (98%). The optical rotation of this compound was found to be nearly 0°. IR ($CHCl_3$): 1766, 1689, 1641 cm^{-1}. NMR ($CDCl_3$) δ: 0.11 (6H, s, $SiMe_2$), 0.89 (9H, s, *tert*-Bu), 1.32 (9H, s, 3×CH_3), 1.38 (6H, s, 2×CH_3), 1.40—2.20 (8H, m, 4×CH_2), 3.92—4.26 (3H, m, C_4–H and C_4–CH_2), 4.49 (2H, s, $C\underline{H}_2OPh$), 5.21 (1H, dd, *J*=8.5 and 2 Hz, C_3–H), 6.88—7.45 (6H, m, Ar and NH), 8.54 (2H, br, SO_3H_2). By the same procedure as described above, the 3*S*, 4*R* isomer of **21** was obtained from the 3*S*, 4*R* isomer of **20** (330 mg, 0.91 mmol) and **6** (314 mg, 1.09 mmol) as a foam. Yield, 584 mg (99%).

PDBD–Salt of (3*R*, 4*S*)-4-Hydroxymethyl-3-phenoxyacetamido-2-oxo-1-sulfoazetidine (4a)——A mixture of **21** (332 mg, 0.51 mmol) and tetra-*n*-butylammonium fluoride (208 mg, 0.80 mmol) in THF (1.5 ml) was stirred overnight at room temperature. After evaporation of the solvent, the residue was chromatographed on silica gel to give the 4-hydroxymethyl azetidinone **4a** as a foam. Yield, 270 mg (99%). $[\alpha]_D^{22}$ −8.3° (*c*=1.57, $CHCl_3$). IR ($CHCl_3$): 1770, 1689, 1640 cm^{-1}. NMR ($CDCl_3$) δ: 1.33 (9H, s, 3×CH_3), 1.39 (6H, s, 2×CH_3), 1.45—2.20 (8H, m, 4×CH_2), 3.50 (1H, t, *J*=1.5 Hz, OH), 3.70—4.30 (3H, m, C_4–H and C_4–CH_2), 4.47 (2H, s, $C\underline{H}_2OPh$), 4.94 (1H, dd, *J*=7 and 2.5 Hz, C_3–H), 6.80—7.50 (6H, m, Ar and NH), 8.31 (2H, br, SO_3H_2). By the same procedure as that described for **4a**, the 3*S*, 4*R* isomer **4b** was obtained from the 3*S*, 4*R* isomer of **21** (339 mg, 0.52 mmol) and tetra-*n*-butylammonium fluoride (234 mg, 0.94 mmol) as a foam. Yield, 263 mg (94%). $[\alpha]_D^{22}$ +8.9° (*c*=1.12, $CHCl_3$).

PDBD–Salt of (3*R*, 4*S*)-4-Acetoxymethyl-3-azido-2-oxo-1-sulfoazetidine (24)——A mixture of **16** (774 mg, 1.42 mmol), tetra-*n*-butylammonium fluoride (670 mg, 2.56 mmol) and acetic acid (103 mg, 1.71 mmol) in THF (10 ml) was stirred overnight at room temperature, then evaporated to dryness. The residue was dissolved in acetic anhydride (7 ml). Pyridine (3.5 ml) was added to this solution at 0 °C with stirring, and the mixture was allowed to stand overnight, then concentrated *in vacuo*. The residue was chromatographed on silica gel followed by recrystallization from chloroform/ether to afford the acetate **24** as colorless plates. Yield, 578 mg (86%). mp 131—134 °C. $[\alpha]_D^{22}$ +62.6° (*c*=2.03, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{32}N_6O_6S$: C, 48.29; H, 6.83. Found: C, 48.27; H, 6.94. IR ($CHCl_3$): 2110, 1777, 1745, 1642 cm^{-1}. NMR ($CDCl_3$) δ: 1.33 (6H, s, 2×CH_3), 1.36 (3H, s, CH_3), 1.39 (6H, s, 2×CH_3), 1.50—2.30 (8H, m, 4×CH_2), 2.09 (3H, s, Ac), 4.02 (1H, m, C_4–H), 4.42—4.65 (3H, m, C_3–H and C_4–CH_2), 8.36 (2H, br, SO_3H_2). By the same procedure as described above, the corresponding 3*S*, 4*R* isomer of **24** was obtained from the 3*S*, 4*R* isomer of **16**. Yield, 83%. $[\alpha]_D^{22}$ −57.2° (*c*=2.12, $CHCl_3$).

(3*R*, 4*S*)-4-Acetoxymethyl-3-[(*Z*)-2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido]-2-oxo-1-sulfoazetidinone (22a)——A suspension of 10% Pd–C (560 mg) in a solution of **24** (556 mg, 1.17 mmol) in methyl alcohol (18 ml) was stirred for 50 min under a current of H_2 at room temperature, then filtered. The residual catalyst was washed thoroughly with methyl alcohol and the combined filtrate and washings were concentrated *in vacuo*. The crude amino compound obtained was dissolved in dimethylformamide (12 ml). To this solution, *N,N'*-dicyclohexylcarbodiimide (315 mg, 1.53 mmol), 1-hydroxybenzotriazole (64 mg, 0.47 mmol), and (*Z*)-2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid (237 mg, 1.17 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature overnight. The precipitate formed was filtered and the filtrate was concentrated *in vacuo*. The column chromatography of the residue on silica gel provided 585 mg (79% yield) of PDBD–salt of the 3-acylamino-1-sulfoazetidinone as a white solid and 74 mg (15% yield) of the zwitterion **22a** as crystals. A solution of trifluoroacetic acid (114 mg, 0.10 mmol) in dichloromethane (3 ml) was added dropwise to a solution of the former compound in dichloromethane (20 ml) at −5 °C. The solvent was evaporated off and the residue obtained was taken up in acetone. The precipitate formed was filtered and washed thoroughly with acetone to give the spectroscopically pure zwitterion **22a** as a colorless solid. Yield, 224 mg (57%, combined yield, 72%). Recrystallization from chloroform/ether gave an analytical sample. mp >280 °C (dec.) $[\alpha]_D^{22}$ +52.3° (*c*=1.53, H_2O). *Anal.* Calcd for $C_{12}H_{15}N_5O_8S_2 \cdot H_2O$: C, 32.80; H, 3.90. Found: C, 32.93; H, 3.74. IR (KBr): 3300 (br), 1770, 1740, 1630 cm^{-1}. NMR (DMSO-d_6) δ: 2.02 (3H, s, Ac), 3.60—4.60 (3H, m, C_4–H and C_4–CH_2), 3.93 (3H, s, OCH_3), 4.72 (1H, dd, *J*=2.5 and 8.5 Hz, C_3–H), 6.87 (1H, s, Ar), 7.80 (3H, br, NH_3), 9.50 (1H, d, *J*=8.5 Hz, CONH). By the same procedure as described above, the 3*S*, 4*R* isomer **22b** was obtained from the 3*S*, 4*R* isomer of **24**. Yield, 65%. $[\alpha]_D^{22}$ −48.3° (*c*=1.50, H_2O).

PDBD–Salt of (3*R*, 4*S*)-4-Acetoxymethyl-3-phenoxyacetamido-2-oxo-1-sulfoazetidine (23a)——Pyridine (1.5 ml) was added to a solution of **4a** (320 mg, 0.59 mmol) in acetic anhydride (3 ml) at 0 °C with stirring. The mixture was stirred overnight at room temperature, then concentrated *in vacuo*. The residue was chromatographed on silica gel to give the acetate **23a** as a foam. Yield, 320 mg (92%). $[\alpha]_D^{22}$ +8.5° (*c*=2.12, $CHCl_3$). IR ($CHCl_3$): 1775, 1745, 1690, 1640 cm^{-1}. NMR ($CDCl_3$) δ: 1.33 (9H, s, 3×CH_3), 1.37 (6H, s, 2×CH_3), 1.40—2.30 (8H, m, 4×CH_2), 2.07 (3H, s, Ac), 4.20 (1H, m, C_4–H and C_4–CH_2), 4.48 (2H, s, CH_2OPh), 4.50 (2H, ddd, *J*=12, 5, and 3 Hz, C_4–CH_2), 5.03 (1H, dd, *J*=8.5 and 2.5 Hz, C_3–H), 6.83—7.50 (6H, m, Ar and CONH), 8.56 (2H, br, SO_3H_2). By the same procedure as described above, the 3*S*, 4*R* isomer **23b** was obtained from **4b** as a foam. Yield, 90%. $[\alpha]_D^{22}$ −8.4° (*c*=2.15, $CHCl_3$).

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References and Notes

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