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2-(Alkylthio)penem-3-carboxylic Acids. III. Synthesis of 6-Ethylpenems[1]

Akira Yoshida, Teruo Hayashi, Noriko Takeda, Sadao Oida,* and Eiji Ohki

Central Research Laboratories, Sankyo Co., Ltd., Hiromachi, Shinagawa-ku, Tokyo, 140 Japan

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An N-protected derivative of 4-phenylthio-2-azetidinone (**3b**) was ethylated to give **3c**, which was converted into the phosphorane **5d** by the standard procedure. Intramolecular Wittig reaction of **5d** afforded 6-ethylpenem esters **8a** and **9a** which were transformed *via* manipulation of the side chain to the amino acids **8d** and **9d** and subsequently to the acetamido derivatives **8e** and **9e**, which are 1-thia analogs of the antibiotic PS-5.

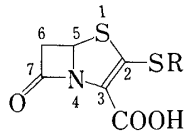
Keywords——antibiotics; β-lactam; 6-ethylpenem-3-carboxylic acid; PS-5 analog; intramolecular Wittig reaction of trithiocarbonate; manipulation of penem side chain

In preceding papers,[1-3] we reported the synthesis of 6-unsubstituted penem-3-carboxylic acids (**1**) having various kinds of alkylthio side chains at the C-2 position, and showed them to possess remarkable antibacterial activity against gram-positive and gram-negative bacteria.[4] In the course of this study, Okamura *et al.*[5] announced that a new antibiotic, PS-5, had been isolated from a fermentation broth of a subspecies of *Streptomyces cremeus* and exhibited wide-spectrum antibacterial activity. Its structure was elucidated as a 6-ethyl-1-carbapenem compound (**2**), making the preparation of its penem analogs even more attractive on the basis of the contribution of the 6-ethyl substituent to bioactivity. We would like to describe here the synthesis of 6-ethyl-substituted penems and their antibacterial activities.

4-Phenylthio-2-azetidinone[6] (**3a**) was silylated with *tert*-butyldimethylchlorosilane and triethylamine in N,N-dimethylformamide to provide the N-protected azetidinone **3b** quantitatively. **3b** was lithiated with lithium hexamethyldisilylazide in THF at −78 °C and then treated with ethyl iodide in the presence of hexamethylphosphoramide to afford a 74% yield of a single ethylated azetidinone **3c**. Based on the coupling constant ($J_{3,4}$=2 Hz) of the nuclear magnetic resonance (NMR) spectrum of **3c**, *trans* stereochemistry was assigned. Conversion of **3c** into the sulfone **4a** was carried out in 83% yield by oxidation with peracetic acid in the presence of a catalytic amount of manganese(III) acetylacetonate.[7] Deblocking of the sulfone **4a** with tetrabutylammonium fluoride gave the 4-phenylsulfonyl-2-azetidinone **4b** quantitatively.

The sulfone **4b** was treated with sodium trithiocarbonate, prepared *in situ* by mixing equimolar amounts of sodium isopropoxide, 2-(*tert*-butyldimethylsilyloxy)ethylmercaptan and carbon disulfide, in isopropanol at 0 °C to give a 53% yield of a *cis/trans* mixture of the azetidinone trithiocarbonate **5a** in a 1:4 ratio (based on NMR).

The trithiocarbonate **5a** was alternatively synthesized as follows. According to the method of Clauss *et al.*,[6] treatment of a 1:1 *cis/trans* mixture of 1-butenyl acetate[8] with chlorosulfonyl isocyanate followed by reductive hydrolysis afforded a 1:1 *cis/trans* mixture of 3-ethyl-4-acetoxyazetidinone (**6a**). The latter 1:1 mixture of **6a** was also obtained by treatment of the (phenylthio)azetidinone **3b** with mercuric acetate in acetic acid at room temperature and removal of the N-protecting group of the resulting acetoxyazetidinone **6b** (*cis/trans* 1:1) with tetrabutylammonium fluoride. The 3-ethyl-4-acetoxyazetidinone **6a** thus obtained was more reactive than the (phenylsulfonyl)azetidinone **4b** to sodium trithiocarbonate and was transformed more efficiently into the azetidinone trithiocarbonate **5a** with a *cis/trans* ratio of 1:4 in 83% yield.



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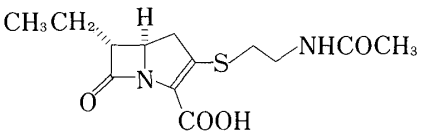

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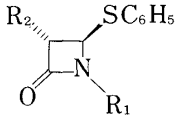
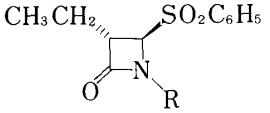
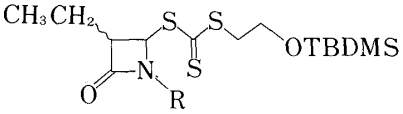


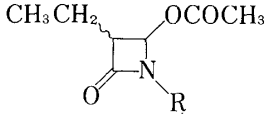
3a : $R_1=R_2=H$
3b : $R_1=$TBDMS, $R_2=H$
3c : $R_1=$TBDMS, $R_2=CH_2CH_3$



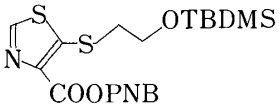
4a : R=TBDMS
4b : R=H



5a : R=H
5b : R=CH(OH)COOPNB
5c : R=CHClCOOPNB
5d : $R=C(P(C_6H_5)_3)COOPNB$



6a : R=H
6b : R=TBDMS



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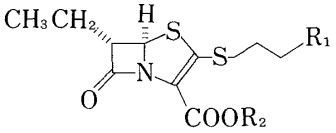
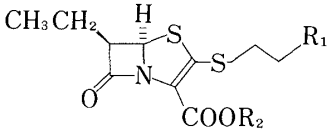


8a : $R_1=$OTBDMS, $R_2=$PNB
8b : $R_1=$OH, $R_2=$PNB
8c : $R_1=N_3$, $R_2=$PNB
8d : $R_1=NH_2$, $R_2=H$
8e : $R_1=NHCOCH_3$, $R_2=$Na
8f : $R_1=$OH, $R_2=$Na



9a : $R_1=$OTBDMS, $R_2=$PNB
9b : $R_1=$OH, $R_2=$PNB
9c : $R_1=N_3$, $R_2=$PNB
9d : $R_1=NH_2$, $R_2=H$
9e : $R_1=NHCOCH_3$, $R_2=$Na

TBDMS: *tert*-butyldimethylsilyl
PNB: *p*-nitrobenzyl

Chart 1

Conversion of the trithiocarbonate **5a** into the phosphorane **5d** was carried out according to the same procedure as described in our preceding papers.[1-3] Reflux of the trithiocarbonate **5a** with *p*-nitrobenzyl glyoxylate in benzene quantitatively gave a diastereomeric mixture of the hemiaminal **5b**, whose treatment with thionyl chloride and purification by silica gel chromatography gave the chloroacetate **5c** in high yield. In a practical procedure, the hemiaminal **5b** was transformed into the phosphorane **5d** in 68% yield, without isolation of the intermediate chloroacetate **5c**, by successive treatment with thionyl chloride and triphenylphosphine in the presence of 2,6-lutidine.

Thiazoline ring formation by an intramolecular Wittig reaction of **5d** to provide the penem ester **8a** was easily conducted by heating at 120—130 °C in xylene for 6—8 hours under a nitrogen atmosphere. The reaction mixture was chromatographed over silica gel, giving an inseparable 1: 1 mixture of the penem esters **8a** and **9a** in 43% yield along with a small amount of a thiazole carboxylate **7**. The NMR spectrum of the mixture of the penem esters thus obtained exhibited a singlet absorption at δ 5.42 and a doublet at δ 5.74 (J=4 Hz), in a relative intensity of 1: 1, assignable to H-5 protons of the *trans* penem **8a** and the *cis* penem **9a**, respectively. Formation of the thiazole **7** would be explained by thermal cleavage of the β-lactam ring of the penem esters with removal of ethylketene. It is interesting to note that the *trans*- and *cis*-penem ester, **8a** and **9a**, were formed in a 1: 1 ratio, which was not in accord with the 4: 1 composition of the starting material **5d**. Interconversion between the *trans*- and *cis*-penem esters

Table I. Antibacterial *in Vitro* Activities of 2-(Alkylthio)-6-ethylpenem-3-carboxylic Acids

Microorganism	MIC, μg/mL[a]				
	8d	9d	8e	9e	8f
Staphylococcus aureus FDA 209P JC	≦0.1	≦0.1	0.4	0.8	0.2
Staphylococcus aureus 56 (PCase$^+$)	≦0.1	0.2	1.5	3.1	0.8
Escherichia coli NIHJ JC-2	25	6.2	25	25	6.2
Escherichia coli 609 (CSase$^+$)	50	50	25	>100	12.5
Shigella flexneri IID 642	25	12.5	25	12.5	12.5
Pseudomonas aeruginosa 1001	>200	>100	>100	>100	>100
Klebsiella pneumoniae 806	25	12.5	25	50	6.2
Klebsiella sp. 846	50	25	>100	>100	50
Proteus vulgaris 1430	50	12.5	25	12.5	12.5
Salmonella enteritidis G	25	12.5	25	12.5	6.2

a) MIC values were determined in nutrient agar.

by thermal epimerization at the C-5 position will be discussed in a forthcoming paper in which more reliable experimental evidence will be presented.

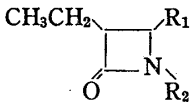
Desilylation of the mixture of penem esters, **8a** and **9a**, was carried out by treatment with tetrabutylammonium fluoride in tetrahydrofuran in the presence of acetic acid to give a mixture of the penem alcohols whose separation by chromatography provided the *trans* alcohol **8b** ($J_{5,6}$=0 Hz) and the *cis* alcohol **9b** ($J_{5,6}$=4 Hz) as crystals. Both penem alcohols **8b** and **9b** were treated with hydrogen azide in the presence of triphenylphosphine and diethyl azodicarboxylate[1,9] to give the corresponding azides **8c** and **9c** in good yields. Following the procedure described in our preceding paper,[3] hydrogenolysis of the penem alcohol **8b** and the penem azides, **8c** and **9c**, with 10% palladium-charcoal in a mixture of tetrahydrofuran/phosphate buffer solution (pH 7.1) followed by purification on Diaion HP 20AG afforded the sodium salt of a hydroxy acid, **8f**, and the amino acids ,**8d** and **9d**, respectively. Acetylation of the penem amino acids **8d** and **9d** with acetic anhydride in a solution of sodium bicarbonate provided the sodium salts of the corresponding acetamido acids, **8e** and **9e**, penem analogs of PS-5, respectively.

The antibacterial activities of these 6-ethyl penem carboxylic acids are shown in Table I. They exhibited antibacterial properties against gram-positive and gram-negative bacteria; however, except for the enhanced activities against *Staphylococci*, their activities against most microorganisms were decreased compared to those of the corresponding 6-unsubstituted penem acids reported earlier.[2] There seemed to be little difference in biological activity between the *trans* and *cis* isomers except for the susceptibility of the *cis* isomers to β-lactamase-producing strains.

Experimental

Melting points are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer and ultraviolet spectra (UV) on a Cary 14 CM-50 (Serial 1258) spectrometer. Proton magnetic resonance spectra (NMR) were obtained on a Varian A-60, a Hitachi-Perkin-Elmer R-24 or a Varian XL 100A-15 spectrometer, unless otherwise specified, tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel $60F_{254}$ precoated, layer thickness 0.25 mm (E. Merck) and spots were made visible by UV irradiation, by spraying with vanadic acid-sulfuric acid followed by heating, or by iodine treatment. Chromatography columns were prepared with Wakogel C-200 (Wako Pure Chemical Industries, Ltd.) and preparative TLC was carried out on plates of Silica gel $60F_{254}$ (E. Merck). The amount of silica gel used and the developing solvents are shown in parenthesis. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; td, triplet of doublets; t, triplet; m, multiplet; br., broad; sh., shoulder.

TABLE II. 3-Ethyl-2-azetidinone Derivatives (3—6)



Compd.	R_1[a]	R_2[a]	*cis*/*trans* ratio	IR ν_{max} cm^{-1} (state or solvent)	NMR δ[b] (60 MHz, $CDCl_3$)	Formula	Analysis (%) Calcd (Found) C	H	N	S
3c	SC_6H_5	TBDMS	*trans*	1735, 1528 ($CHCl_3$)	0.28 (6H, s), 0.85 (3H, t, 7), 0.96 (9H, s), 1,68 (2H, quintet, 7), 3.15 (1H, td, 7, 2), 4.59 (1H, d, 2), 7.2—7.7 (5H, m)	$C_{17}H_{27}NOSSi$	63.55 (63.54	8.41 8.44	4.36 4.61	9.97 10.12)
4a	$SO_2C_6H_5$	TBDMS	*trans*	1767, 1584 (Nujol)	0.30 (3H, s), 0.34 (3H, s), 0.60 (3H, t, 6), 1.2—1.7 (2H, m), 3.05 (1H, ddd, 8, 6, 2), 4.14 (1H, d, 2), 7.5—8.1 (5H, m)	$C_{17}H_{27}NO_3SSi$	57.75 (57.48	7.70 7.64	3.96 3.84	9.22 9.22)
4b	$SO_2C_6H_5$	H	*trans*	3320, 1722, 1584 (Nujol)	0.89 (3H, t, 7), 1.70 (2H, m), 3.36 (1H, ddd, 8, 7, 2), 4.59 (1H, d, 2), 7.5—8.2 (5H, m)	$C_{11}H_{13}NO_3S$	55.21 (55.06	5.48 5.38	5.85 5.75	13.40) 13.42
5a	$SCS(CH_2)_2OTBDMS$ ‖ S	H	1/4	3410, 1770, 1721, 1600 ($CHCl_3$)	0.06 (6H, s), 0.89 (9H, s), 1.04 (3H, t, 7), 1.81 (2H, quintet, 7), 3.0—3.3 (1H, m), 3.3—4.0 (4H, m), 5.33 (4/5H, d, 2), 5.81 (1/5H, d, 5), 6.08 (1H, br. s)	$C_{14}H_{27}NO_2S_3Si$	45.99 (45.71	7.44 7.49	3.83 3.77	26.30 26.43)
5b	$SCS(CH_2)_2OTBDMS$ ‖ S	CHOH | COOPNB	1/4[c]	3540, 1772, 1756, 1523 ($CHCl_3$)	0.06 (6H, s), 0.85 (9H, s), 0.97 (3H, t, 7), 1.79 (2H, quintet, 7), 3.0—4.0 (5H, m), 5.26 (1H, s), 5.32 (1H, s), 5.72 and 5.83 (1:1, 4/5H, d, 2), 6.10 and 6.20 (1:1, 1/5H, d, 5), 7.55 (2H, d), 8.25 (2H, d)	$C_{23}H_{34}N_2O_7S_3Si$	48.06 (47.88	5.96 5.92	4.87 4.71	16.73 16.57)
5c	$SCS(CH_2)_2OTBDMS$ ‖ S	CHCl | COOPNB	1/4[c]	—	0.08 (6H, s), 0.88 (9H, s), 1.03 (3H, t, 7), 3.2—4.0 (5H, m), 5.29 and 5.35 (2:3, 2H, s), 5.99 and 6.06 (1:1, 4/5H, d, 2), 6.07 and 6.17 (1:1, 1H, s), 6.31 and 6.35 (1:1, 1/5H, d, 5), 7.50 (2H, d), 8.21 (2H, d)	$C_{23}H_{33}ClN_2O_6S_3Si$	—	—	—	—
5d	$SCS(CH_2)_2OTBDMS$ ‖ S	$C{=}P(C_6H_5)_3$ | COOPNB	1/4	1750, 1619, 1602, 1516 ($CHCl_3$)	—	$C_{41}H_{47}N_2O_6PS_3Si$	60.12 (59.67	5.78 5.74	3.42 3.37)	—
6a	$OCOCH_3$	H	1/1	3290, 1775, 1760 sh. (liq.)	0.98 (3H, t, 7), 1.70 (2H, quintet, 7), 2.05 (3H, s), 3.0—3.4 (1H, m), 5.54 (1/2H, br. s), 5.87 (1/2H, d, 4), 7.3 (1H, br. s)	$C_7H_{11}NO_3$	53.49 (53.47	7.05 7.22	8.91 8.58)	—
6b	$OCOCH_3$	TBDMS	1/1	1760, 1735 sh. (liq.)	0.21 (5H, s), 0.92 (9H, s), 0.95 (3H, t, 7), 1.3—1.9 (2H, m), 1.99 (3H, s), 2.90 (1/2H, t, 7), 3.18 (1/2H, td, 7, 4), 5.61 (1/2H, br. s), 6.05 (1/2H, d, 4)	$C_{13}H_{25}NO_3Si$[d]	—	—	—	—

a) TBDMS, *tert*-butyldimethylsilyl; PNB, *p*-nitrobenzyl. b) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses.
c) Both *cis* and *trans* isomers were 1:1 diastereomeric mixtures as judged from the NMR spectrum. d) MS *m/e*: 271 (M^+), 227 (M^+-CO), 211 (M^+-CH_3COOH).

1-(*tert*-Butyldimethylsilyl)-4-phenylthio-2-azetidinone (3b)——*tert*-Butyldimethylchlorosilane (2.78 g, 18.4 mmol) was added to an ice-cold solution of 4-phenylthio-2-azetidinone[6] (**3a**, 3.00 g, 16.8 mmol) and triethylamine (1.86 g, 18.4 mmol) in DMF (18 ml) with stirring under an N_2 atmosphere. After being stirred for 1.5 h at the same temperature, the mixture was diluted with a 1:1 mixture of benzene–hexane (120 ml) and washed with water. The washings were extracted with the same solvent mixture and the organic layer and extracts were combined, dried and evaporated *in vacuo*. The residue (5.2 g) was chromatographed (25 g, benzene) to give **3b** (4.82 g, 98%) as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1759, 1584. NMR ($CDCl_3$) δ: 0.29 (6H, s), 0.95 (9H, s), 2.95 (1H, dd, $J=15$, 3 Hz), 3.43 (1H, dd, $J=15$, 5 Hz), 4.87 (1H, dd, $J=5$, 3 Hz), 7.36 (5H, s). *Anal.* Calcd for $C_{15}H_{23}NOSSi$: C, 61.38; H, 7.90; N, 4.77; S, 10.92. Found: C, 61.32; H, 8.07; N, 4.63; S, 11.31.

3,4-*trans*-1-(*tert*-Butyldimethylsilyl)-3-ethyl-4-phenylthio-2-azetidinone (3c)——A 15% solution of *n*-butyllithium in hexane (1.45 ml, 2.38 mmol) was added to an ice-cold and stirred solution of hexamethyldisilazane (384 mg, 2.39 mmol) in THF (11.6 ml) under an N_2 atmosphere. The mixture was cooled at −78°C and a solution of **3b** (582 mg, 1.99 mmol) in THF (1 ml) was added with stirring. The mixture was stirred for 2 min, then ethyl iodide (0.33 ml, 3.96 mmol) and HMPA (0.3 ml) were added, and the whole was allowed to warm gradually to −50°C over a period of 2 h. Acetic acid (286 mg, 4.77 mmol) was added to halt the reaction and the mixture was diluted with benzene, washed with water three times, dried and evaporated off *in vacuo*. The residue (599 mg) was chromatographed (10 g, benzene–AcOEt, 30:1) to give **3c** (469 mg, 74%) as an oil. Elementary analysis and spectral data are given in Table II.

3,4-*trans*-1-(*tert*-Butyldimethylsilyl)-3-ethyl-4-phenylsulfonyl-2-azetidinone (4a)——Anhydr. sodium acetate (120 mg, 1.46 mmol), 5.9 M peracetic acid (1.49 ml, 8.79 mmol) and manganese(III) acetylacetonate (15 mg, 0.042 mmol) were successively added to an ice-cold solution of **3c** (469 mg, 1.46 mmol) in AcOEt (9.2 ml) with stirring, and stirring was continued at the same temperature for 2.5 hr. The mixture was diluted with AcOEt, washed with aq. $NaHSO_3$, then with $NaHCO_3$, dried and evaporated to dryness, leaving a crystalline mass (533 mg) which was recrystallized from MeOH to give **4a** (302 mg) as prisms, mp 117—118°C. The mother liquor was evaporated off and the residue was chromatographed (5 g, benzene–AcOEt, 30—20:1) to give a second crop (126 mg). The total yield was 428 mg (83%). See Table II.

3,4-*trans*-3-Ethyl-4-phenylsulfonyl-2-azetidinone (4b)——A solution of tetrabutylammonium fluoride (360 mg, 1.38 mmol) and acetic acid (165 mg, 2.75 mmol) in THF (1 ml) was added to a solution of **4a** (423 mg, 1.20 mmol) in THF (1 ml) with ice-cooling and stirring. After being stirred for 1.5 h at 0°C, the mixture was worked up. The crystalline product was recrystallized from hexane–acetone, giving **4b** (239 mg) as needles, mp 165—166°. The mother liquor was evaporated to dryness and the residue was subjected to preparative TLC (benzene–AcOEt, 15:1) to give a second crop (19 mg). The total yield was 258 mg (90%). See Table II.

4-Acetoxy-1-(*tert*-butyldimethylsilyl)-3-ethyl-2-azetidinone (6b)——A mixture of **3c** (1.00 g, 3.12 mmol), mercuric acetate (1.10 g, 3.46 mmol), AcOEt (1.5 ml) and acetic acid (1.5 ml) was kept at room temperature for 1 hr. The mixture was then evaporated to dryness *in vacuo* and the residue was partitioned between hexane and water and filtered through Celite. The filtrate was washed with 5% aq. $NaHCO_3$, then with brine and dried. After removal of the solvent, the residue was chromatographed (10 g, benzene–AcOEt, 20—10:1), giving **6b** (741 mg, 88%) as an oil which was found to be a 1:1 mixture of 3,4-*cis* and *trans* isomers by NMR analysis. See Table II.

4-Acetoxy-3-ethyl-2-azetidinone (6a)——(i) Chlorosulfonyl isocyanate (3.72 g, 26 mmol) was added dropwise to a solution of 1-butenyl acetate[8] (*cis*/*trans* 1:1 mixture, 3.00 g, 26 mmol) in CH_2Cl_2 (10 ml) below 10°C with stirring. After being stirred for 3 h at room temperature, the mixture was slowly poured into ice-water (10 ml) containing $NaHCO_3$ (6 g) and Na_2SO_3 (2.1 g). The mixture was stirred for 30 min and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated. The residue was chromatographed (50 g, benzene–AcOEt, 6—5:1) to give a 1:1 *cis*/*trans* mixture of **6a** (757 mg, 18.3%) as an oil. See Table II.

(ii) As described for the preparation of **4b**, treatment of **6b** with tetrabutylammonium fluoride in THF in the presence of acetic acid afforded a 1:1 *cis*/*trans* mixture of **6a** quantitatively.

2-(*tert*-Butyldimethylsilyloxy)ethylmercaptan——A solution of 2-mercaptoethanol (2.69 g, 34.5 mmol), imidazole (3.52 g, 51.8 mmol) and *tert*-butyldimethylchlorosilane (5.71 g, 37.9 mmol) in CH_2Cl_2 (60 ml) was stirred at room temperature overnight. The mixture was worked up and the product was purified by distillation, bp_7 64—65°C. Yield, 3.17 g (48%). NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.85 (9H, s), 2.57 (2H, t, $J=6$ Hz), 3.70 (2H, t, $J=6$ Hz). *Anal.* Calcd for $C_8H_{20}OSSi$: C, 49.94; H, 10.48; S, 16.67. Found: C, 50.11; H, 10.52; S, 16.58.

4-[[[[2-(*tert*-Butyldimethylsilyloxy)ethyl]thio]thiocarbonyl]thio]-3-ethyl-2-azetidinone (5a)——i) 2-(*tert*-Butyldimethylsilyloxy)ethylmercaptan (88 mg, 0.46 mmol) and then carbon disulfide (35 mg, 0.46 mmol) were added to an ice-cold sodium isopropoxide solution prepared by dissolving Na (10 mg, 0.43 mmol) in isopropanol (2 ml) with stirring, and the mixture was stirred for 5 min with cooling. Then, **4b** (115 mg, 0.50 mmol) was added and stirring was continued for 1 hr with cooling. Work-up in the usual manner followed by preparative TLC (benzene–AcOEt, 5:1) of the product afforded a *cis*/*trans* 1:4 isomeric mixture of **5a** (89 mg, 53%) as an oil. See Table II.

ii) Proceeding exactly as described above, a sodium trithiocarbonate solution was prepared from Na (105 mg, 4.59 mmol), isopropanol (12 ml), carbon disulfide (366 mg, 4.81 mmol) and 2-(*tert*-butyldimethylsilyloxy)ethylmercaptan (925 mg, 4.81 mmol). After addition of a solution of **6a** (800 mg, 5.10 mmol) in THF (4 ml) at 0°C under an N_2 atmosphere, the mixture was stirred for 45 min with cooling, and then, after addition of a small amount of acetic acid, worked up as described above. Chromatography of the product afforded a *cis*/*trans* 1: 4 isomeric mixture of **5a** (1.55 g, 83%) as an oil.

***p*-Nitrobenzyl 2-[4-[[[[2-(*tert*-Butyldimethylsilyloxy)ethyl]thio]thiocarbonyl]thio]-3-ethyl-2-oxo-1-azetidinyl]-2-hydroxyacetate (5b)**——A mixture of **5a** (390 mg, 1.07 mmol), *p*-nitrobenzyl glyoxylate (hydrate, 340 mg, 1.45 mmol) and benzene (4 ml) was refluxed for 2 h. The solvent was evaporated off *in vacuo* and the residue was chromatographed (10 g, benzene–AcOEt, 10—8: 1), giving a diastereomeric mixture of **5b** (567 mg, 92%) as an oil. See Table II.

***p*-Nitrobenzyl 2-[4-[[[[2-(*tert*-Butyldimethylsilyloxy)ethyl]thio]thiocarbonyl]thio]-3-ethyl-2-oxo-1-azetidinyl]-2-chloroacetate (5c)**——2,6-Lutidine (61 mg, 0.57 mmol) and then thionyl chloride (60 mg, 0.50 mmol) were added to an ice-cold and stirred solution of **5b** (200 mg, 0.357 mmol) in THF (4 ml) under an N_2 atmosphere. The mixture was stirred for 30 min with cooling, then the resulting 2,6-lutidine hydrochloride was filtered off using Celite and washed with benzene. The filtrate and washings were combined and evaporated to dryness *in vacuo*. The residue was chromatographed (4 g, benzene–AcOEt, 40—20: 1) to give **5c** (192 mg, 93%) as an oil. See Table II.

***p*-Nitrobenzyl 2-[4-[[[[2-(*tert*-Butyldimethylsilyloxy)ethyl]thio]thiocarbonyl]thio]-3-ethyl-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetate (5d)**——Thionyl chloride (141 mg, 1.18 mmol) was added to a solution of **5b** (567 mg, 0.99 mmol) and 2,6-lutidine (132 mg, 1.23 mmol) in THF (10 ml) at −5°C with stirring, and stirring was continued for 20 min at the same temperature. Then, triphenylphosphine (518 mg, 1.98 mmol) and 2,6-lutidine (211 mg, 1.97 mmol) were added and the mixture was heated at 70°C for 4.5 h with stirring under an N_2 atmosphere. After the disappearance of **5c** had been confirmed by TLC, the mixture was diluted with AcOEt and worked up as usual. The product (1.13 g) thus obtained was chromatographed (15 g, 40—30: 1) to give the crude phosphorane **5d** (623 mg), which was further chromatographed (10 g, hexane–acetone, 4—3.5: 1) to yield a *cis*/*trans* 1: 4 isomeric mixture of **5d** (558 mg, 68%) as a foam.

***p*-Nitrobenzyl 5,6-*trans*-3-[[2-(*tert*-Butyldimethylsilyloxy)ethyl]thio]-6-ethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8a) and it 5,6-*cis* Isomer (9a)**——A solution of **5d** (3.00 g, 3.67 mmol) and hydroquinone (210 mg, 1.91 mmol) in xylene (300 ml) was heated at 120—130°C (bath temp.) for 6.5 h under an N_2 atmosphere with stirring. Removal of the solvent by evaporation *in vacuo* followed by chromatography of the residue (32 g, benzene–acetone, 50: 1) gave a 1: 1 mixture of **8a** and **9a** (817 mg, 42%) as a crystalline mass, mp 111—120°C (from MeOH). UV λ_{max}^{EtOH} nm (ε): 263 (15700), 333 (10000). *Anal.* Calcd for $C_{23}H_{32}N_2O_6S_2Si$: C, 52.65; H, 6.15; N, 5.34; S, 12.46. Found: C, 52.81; H, 6.14; N, 5.18; S, 12.46. Other spectral data are given in Table III. Further elution of the column (benzene–acetone, 30: 1) gave unchanged **5d** (1.60 g, 53%) and then the thiazole **7** (45 mg, 2.7%) as needles, mp 93—94°C (from hexane–AcOEt). IR ν_{max}^{Nujol} cm^{-1} for **7**: 1700, 1603, 1520, 1346. NMR ($CDCl_3$) δ: for **7**: 0.06 (6H, s), 0.84 (9H, s), 3.11 (2H, t, J= 6 Hz), 3.88 (2H, t, J=6 Hz), 5.47 (2H, s), 7.74 (2H, d), 8.23 (2H, d), 8.64 (1H, s). *Anal.* Calcd for $C_{19}H_{26}N_2O_5S_2Si$: C, 50.20; H, 5.76; N, 6.16; S, 14.10. Found: C, 50.11; H, 5.77; N, 6.09; S, 14.27.

***p*-Nitrobenzyl 5,6-*trans*-6-Ethyl-3-[(2-hydroxyethyl)thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8b) and its 5,6-*cis* Isomer (9b)**——Acetic acid (250 mg, 4.17 mmol), tetrabutylammonium fluoride (541 mg, 2.07 mmol) and anhydr. magnesium sulfate (4.0 g) were added to an ice-cold solution of **8a** (417 mg, 0.796 mmol) in THF (2 ml) with stirring. After being stirred at 10°C for 1 h, the mixture was diluted with AcOEt, followed by aqueous work-up. Liquid chromatography of the product over a Lobar column-B (E. Merck, Darmstadt) ($CHCl_3$–AcOEt, 4: 1) gave the *cis*-isomer **9b** (135 mg) as needles, mp 137—139.5°C (from ether–AcOEt) and then the *trans*-isomer **8b** (140 mg) as needles, mp 105—106°C (from ether–AcOEt). The total yield was 84%. *Anal.* Calcd for $C_{17}H_{18}N_2O_6S_2$: C, 49.75; H, 4.42; N, 6.82; S, 15.62. Found for **8b**: C, 49.85; H, 4.56; N, 6.76; S, 15.48; for **9b**: C, 49.85; H, 4.45; N, 6.90; S, 15.90. Spectral data for **8b** and **9b** are given in Table III.

***p*-Nitrobenzyl 5,6-*trans*-3-[(2-Azidoethyl)thio]-6-ethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8c) and Its 5,6-*cis* Isomer (9c)**——A 1.7 M solution of hydrogen azide in benzene (0.37 ml, 0.65 mmol), triphenylphosphine (150 mg, 0.572 mmol) and diethyl azodicarboxylate (100 mg, 0.572 mmol) were added successively to a stirred solution of the *trans* isomer **8b** (157 mg, 0.382 mmol) in THF (4 ml). The mixture was left to stand for 30 min, then diluted with AcOEt. Work-up as usual and chromatography of the product (6 g, benzene–AcOEt, 40—20: 1) gave **8c** (124 mg, 75%) as needles, mp 107—109° (from acetone–ethanol). *Anal.* Calcd for $C_{17}H_{17}N_5O_5S_2$: C, 46.89; H, 3.93; N, 16.08. Found: C, 46.72; H, 4.00; N, 16.01.

Analogous treatment of the *cis*-isomer **9b** gave the corresponding azide **9c** as an oil in 42% yield. See Table III.

5,6-*trans*-3-[(2-Aminoethyl)thio]-6-ethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (8d) and its 5,6-*cis* Isomer (9d)——A mixture of **8c** (81 mg), THF (5.7 ml), 0.1 M phosphate buffer solution (pH 7.1, 4.0 ml) and 10% palladium-charcoal (180 mg) was shaken under an H_2 atmosphere at room temperature for 4 h. After addition of the same buffer solution (5 ml), the catalyst was filtered off using Celite and washed with the buffer solution (5 ml). The filtrate and washings were combined, washed with AcOEt and concen-

TABLE III. 3-(Alkylthio)-6-ethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid Derivatives (**8**, **9**)

Compd.	R_1[a]	R_2[b]	5,6-Stereochemistry	IR ν_{max} cm^{-1} (state or solvent)	NMR δ[c] (60 MHz, $CDCl_3$)
8a + **9a**	OTBDMS	PNB	*cis*/*trans* 1/1 mixture	1789, 1682, 1610 (Nujol)	0.07 (6H, s), 0.90 (9H, s), 1.08 (3H, t, 6), 1.7—2.1 (2H, m), 3.0—3.3 (2H, m), 3.6—4.0 (3H, m), 5.22 (1H, d, 14), 5.42 (1/2H, s), 5.48 (1H, d, 14), 5.74 (1/2H, d, 4), 7.64 (2H, d), 8.24 (2H, d)[d]
8b	OH	PNB	*trans*	3500, 3400, 1760, 1680, 1598 (Nujol)	1.01 (3H, t, 7), 1.84 (2H, quintet, 7), 2.6—4.0 (5H, m), 5.13 (1H, d, 14), 5.42 (1H, s), 5.45 (1H, d, 14), 7.60 (2H, d), 8.19 (2H, d)
8c	N_3	PNB	*trans*	2120, 1775, 1690, 1672, 1604 (Nujol)	1.04 (3H, t, 7), 1.84 (2H, quintet, 7), 2.9—3.3 (2H, m), 3.3—3.8 (2H, m), 3.68 (1H, td, 7, 1), 5.14 (1H, d, 14.5), 5.43 (1H, d, 1), 5.46 1H, d, 14.5), 7.60 (2H, d), 8.20 (2H, d)
8d	NH_2	H	*trans*	3410, 1770, 1570 (KBr)	1.02 (3H, t, 8), 1.86 (2H, quintet, 8), 2.9—3.5 (4H, m), 3.86 (1H, td, 8, 1), 5.57 (1H, d, 1)[e]
8e	$NHCOCH_3$	Na	*trans*	3400, 1760, 1640, 1585 (KBr)	0.96 (3H, t, 7), 1.80 (2H, quintet, 7), 1.93 (3H, s), 2.8—3.2 (2H, m), 3.42 (2H, t, 6), 3.73 (1H, td, 7, 1), 5.45 (1H, d, 1)[e]
8f	OH	Na	*trans*	3400, 1762, 1600 (KBr)	1.01 (3H, t, 8), 1.85 (2H, quintet, 8), 2.9—3.2 (2H, m), 3.82 (2H, t, 6), 5.53 (1H, s)[e]
9b	OH	PNB	*cis*	3520, 3400, 1782, 1765, 1680 (Nujol)	0.96 (3H, t, 7), 1.8—2.1 (2H, m), 3.0—4.0 (5H, m), 5.14 (1H, d, 13), 5.44 (1H, d, 13), 5.72 (1H, d, 4), 7.61 (2H, d), 8.18 (2H, d)
9c	N_3	PNB	*cis*	2060, 1780, 1682, 1600 ($CHCl_3$)	0.98 (3H, t, 6.5), 1.6—2.2 (2H, m), 2.9—3.7 (4H, m), 3.85 (1H, ddd, 9, 8, 4), 5.14 (1H, d, 14), 5.46 (1H, d, 14), 5.76 (1H, d, 4), 7.59 (2H, d), 8.14 (2H, d)
9d	NH_2	H	*cis*	3410, 1775, 1580 (KBr)	0.96 (3H, t, 8), 1.6—2.1 (2H, m), 2.8—3.6 (4H, m), 3.95 (1H, ddd, 10, 8, 4), 5.83 (1H, d, 4)[e]
9e	$NHCOCH_3$	Na	*cis*	3400, 1760, 1640, 1580 (KBr)	0.91 (3H, t, 7), 1.7—2.0 (2H, m), 1.93 (3H, s), 2.8—3.2 (2H, m), 3.2—3.6 (2H, m), 3.75 (1H, m), 5.71 (1H, d, 4)[e]

a) TBDMS, *tert*-butyldimethylsilyl.
b) PNB, *p*-nitrobenzyl.
c) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses.
d) At 100 MHz.
e) At 100 MHz in D_2O solution using Me_4Si as an external standard.

trated *in vacuo* to about 2 ml. The concentrate was charged on Diaion HP 20AG (Mitsubishi Chemical Industries, Ltd., 8 ml), washed with water and eluted with 5—10% acetone–water. The fractions were collected and lyophilized to give **8d** (29.4 mg, 58%) as an amorphous powder. UV $\lambda_{max}^{H_2O}$ nm (ε): 252 (4800), 319 (6300). Other spectral data are given in Table III.

Analogously, the *cis* azide ester **9c** was hydrogenated to give the amino acid **9d** as an amorphous powder in 38% yield. UV $\lambda_{max}^{H_2O}$ nm (ε): 249 (4300), 316 (5500). Other spectral data are given in Table III.

Sodium 5,6-*trans*-6-Ethyl-3-[(2-hydroxyethyl)thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8f)——A mixture of **8b** (62 mg), THF (3.9 ml), 0.1 M phosphate buffer solution (pH 7.2, 2.8 ml) and 10% palladium charcoal (76 mg) was shaken under an H_2 atmosphere for 3.5 h. After addition of the same buffer solution (2 ml), the catalyst was filtered off using Celite and washed with the buffer solution (5 ml). The combined filtrate and washings were washed with AcOEt and concentrated *in vacuo* to about 2 ml. The concentrate was charged on Diaion HP 20AG (7 ml), eluted with water and lyophilized to give the sodium salt **8f** (32.8 mg, 73%) as an amorphous powder. UV $\lambda_{max}^{H_2O}$ nm (ε): 253 (5600), 322 (7400). Other spectral data are given in Table III.

Sodium 5,6-*trans*-3-[(2-Acetamidoethyl)thio]-6-ethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8e) and its 5,6-*cis* Isomer (9e)——Sodium bicarbonate (5.8 mg, 0.069 mmol) and acetic anhydride (4.2 mg, 0.041 mmol) were added to an ice-cold mixture of **8d** (9.4 mg, 0.034 mmol), THF (1 ml) and water (1 ml) with stirring. After being stirred for 30 min, the mixture was diluted with 0.1 M phosphate buffer solution (5 ml), washed with AcOEt and concentrated *in vacuo* to about 2 ml. The concentrate was charged

on Diaion HP 20AG (8 ml), washed with water and eluted with 2—5% acetone–water. The fractions were collected and lyophilized to give **8e** (4.5 mg, 39%) as an amorphous powder.

Analogously, the *cis* amino acid **9d** was transformed to the *cis* acetamido acid sodium salt **9e**, an amorphous powder, in 74% yield.

Spectral data for **8e** and **9e** are given in Table III.

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