Chem. Pharm. Bull.
29(10)2899—2909(1981)

2-(Alkylthio)penem-3-carboxylic Acids. IV.[1] Synthesis of (Hydroxyethyl)-azetidinone Precursors to 1-Thia Analogs of Thienamycin[2]

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

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

(Received April 25, 1981)

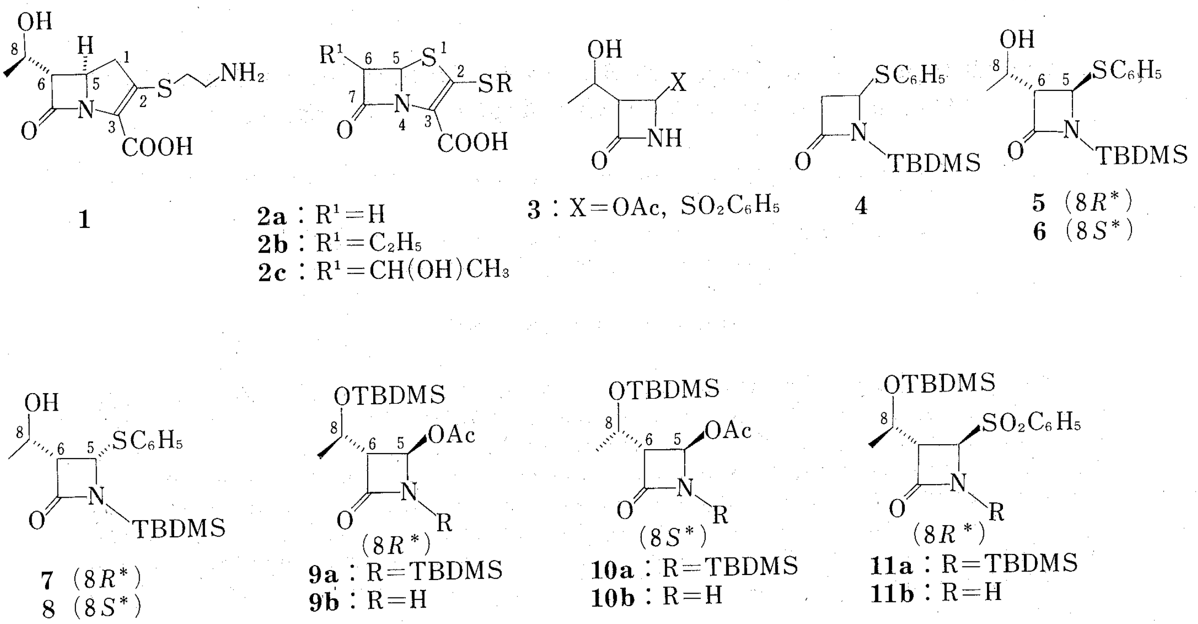
The synthesis of hydroxyethylazetidinone precursors to 1-thia analogs of thienamycin is described. An N-protected azetidinone **4** was hydroxyethylated *via* an aldol reaction to give four diastereomers **5**—**8**, which were converted to the diastereomeric pair of racemic 8*R* and 8*S* *trans* azetidinones **9b** and **10b**. Stereochemical assignment was achieved by correlation of **9b** with the optically active azetidinone **16** which was obtained from the hydroxyethylpenicillanate **14a** with known stereochemistry. The optically active 8*R* and 8*S* azetidinones **16** and **27** were synthesized more efficiently starting from the penicillin-derived bromo compound **19** in a series of steps including stereochemical inversion at the C-8 position.

Keywords——antibiotics; β-lactam; hydroxyethylazetidinones; aldol reaction; aluminum enolate of β-lactam; stereochemical inversion; triphenylphosphine/diethyl azodicarboxylate system; penicillin degradation

Viewed in the light of antibacterial potency and spectral breadth, thienamycin (**1**) is the most remarkable of the naturally occurring β-lactam antibiotics found in the past decade. Its chemical structure has been elucidated as a 1-carbapenem (**1**) with the absolute stereochemistry 5*R*, 6*S*, 8*R*.[3] Several successful efforts to construct its novel framework with the desired stereochemistry have already been reported.[4] Recently, we synthesized 6-unsubstituted 2-(alkylthio)penem-3-carboxylic acids[5] **2a** and the 6-ethyl analogs[1] **2b**, starting from 4-acetoxy- or 4-phenylthio-2-azetidinone, which were found to be intrinsically active as antibiotics against gram-positive and gram-negative bacteria.[1,6] Consequently, it was considered that the penem-3-carboxylic acids **2c** having a 1-hydroxyethyl group at the C-6 position, *i.e.* 1-thia analogs of thienamycin, form a most attractive synthetic target in view of their antibacterial activity.[7] This paper deals with synthetic approaches directed at the (hydroxyethyl)azetidinones **3** having a suitable substituent for a subsequent displacement reaction, such as an acetoxy or phenylsulfonyl group at the C-4 position, which can serve as precursors for the synthesis of 6-(1-hydroxyethyl)penem-3-carboxylic acids **2c**. These functionalized azetidinones **3** can also be utilized as intermediates for the synthesis of thienamycin itself and related carbapenem antibiotics by applying the reported methodology which involves C–C bond formation at the C-4 position of the β-lactam ring as a key reaction.[8]

Method A

For access to the title compounds, we first attempted to introduce the hydroxyethyl side chain into the monocyclic β-lactam *via* an aldol reaction as follows. The N-*tert*-butyldimethylsilyl(TBDMS) derivative **4**[1] of (±)-4-phenylthio-2-azetidinone was lithiated with lithium diisopropylamide in tetrahydrofuran (THF) and then treated with acetaldehyde at −78°C to give a quantitative yield of a mixture of four diastereomers **5**—**8**.[9,10] Separation by liquid chromatography afforded one *trans* isomer **5** (34% yield) as crystals [nuclear magnetic resonance spectrum (NMR): δ 4.71 (d, $J=2$ Hz, H-5), 2.85 (dd, $J=4.5$, 2 Hz, H-6)], the other *trans* isomer **6** (27% yield) as an oil [NMR: δ 4.51 (d, $J=2$ Hz, H-5), 2.87 (dd, $J=6$, 2 Hz, H-6)] and an inseparable mixture of *cis* isomers **7** and **8** (34% yield) [NMR: δ 4.81 (d, $J=5$ Hz, H-5)]. The stereochemical relationships at C-5 and C-6 of these diastereomers were assigned



1

2a : $R^1=H$
2b : $R^1=C_2H_5$
2c : $R^1=CH(OH)CH_3$

3 : $X=OAc, SO_2C_6H_5$

4

5 (8*R**)
6 (8*S**)

7 (8*R**)
8 (8*S**)

(8*R**)
9a : R=TBDMS
9b : R=H

(8*S**)
10a : R=TBDMS
10b : R=H

(8*R**)
11a : R=TBDMS
11b : R=H

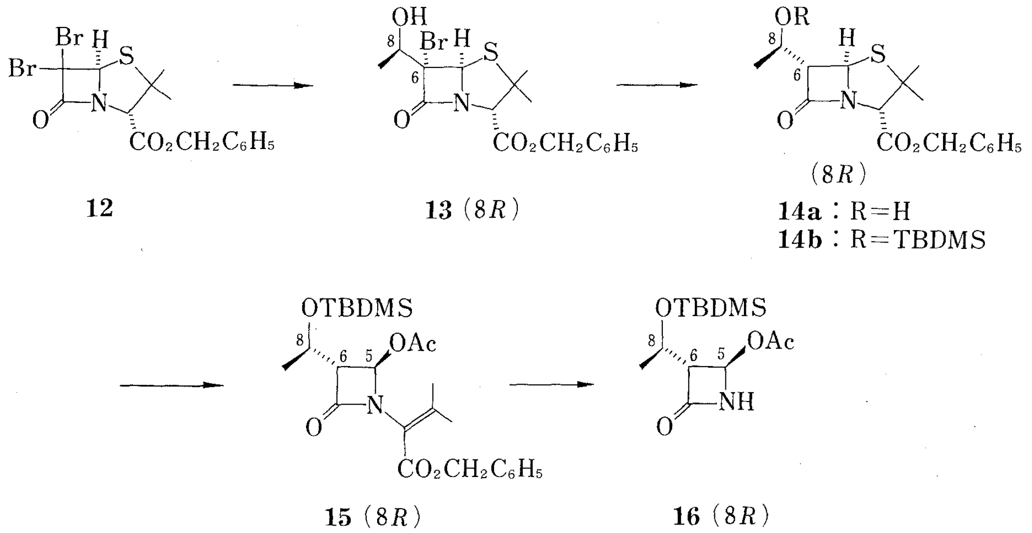
TBDMS: *tert*-butyldimethylsilyl

Chart 1

based on the coupling constants ($J_{5,6}$), as *cis* β-lactams have larger coupling constants than *trans* β-lactams. Each of the *trans* isomers **5** and **6** was silylated to the N,O-diTBDMS derivative and then treated with mercuric acetate in acetic acid at room temperature to give the *trans* acetoxyazetidinones **9a** [NMR: δ 6.15 (d, $J=1$ Hz, H-5)] and **10a** [NMR: δ 5.77 (d, $J=1$ Hz, H-5)], respectively, in high yields. Analogously, the *cis* diastereomeric mixture (**7** and **8**) was silylated and treated with mercuric acetate to afford a 1: 3 mixture of **9a** and **10a**, whose separation was difficult. The pure acetoxyazetidinones **9a** and **10a**, obtained from **5** and **6** respectively, were treated with one equivalent of tetrabutylammonium fluoride in THF in the presence of acetic acid. This resulted in the selective removal of the N-TBDMS group, giving the O-protected azetidinones **9b**, mp 78—80°C, and **10b**, mp 81.5—82°C, respectively. Since 4-(phenylsulfonyl)azetidinone is also a feasible compound for a displacement reaction with sodium alkyl trithiocarbonate,[1)] a sulfone such as **11b** seemed to be another attractive material as a precursor to 6-(hydroxyethyl)penems. Thus, the N,O-diTBDMS derivative of **5** was oxidized with peracetic acid in the presence of a catalytic amount of manganese(III) acetylacetonate[11)] to give the protected sulfone **11a**. Selective removal of the N-silyl group of **11a** in a manner similar to that described above provided the sulfone **11b** in 65% overall yield from **5**. Evidence for the assignment of the side chain stereochemistry of the azetidinones mentioned above was obtained by correlation with samples alternatively prepared from penicillin *via* the route described below (Methods B and C). Hydroxyethylation of **4** *via* the lithium enolate occurred non-stereoselectively to yield a mixture of four diastereomers which could be converted into almost equal amounts of the pair of *trans* diastereomers **9b** and **10b**; however, the separation of each diastereomer by liquid chromatography was inefficient.

Method B

For the structural assignment of **9b**, an alternative synthesis to obtain the optically active compound was performed as follows. In 1977, DiNinno *et al.*[12)] reported that transmetallation between 6,6-dibromopenicillanate (**12**) and Grignard reagent followed by reaction with acetaldehyde afforded predominantly 6α-bromo-6β-[(*R*)-hydroxyethyl]penicillanate (**13**) whose reduction with a zinc-silver couple gave almost exclusively 6α-[(*R*)-hydroxyethyl]penicillanate (**14a**). We followed their method, without separating the diastereomers formed in each step,



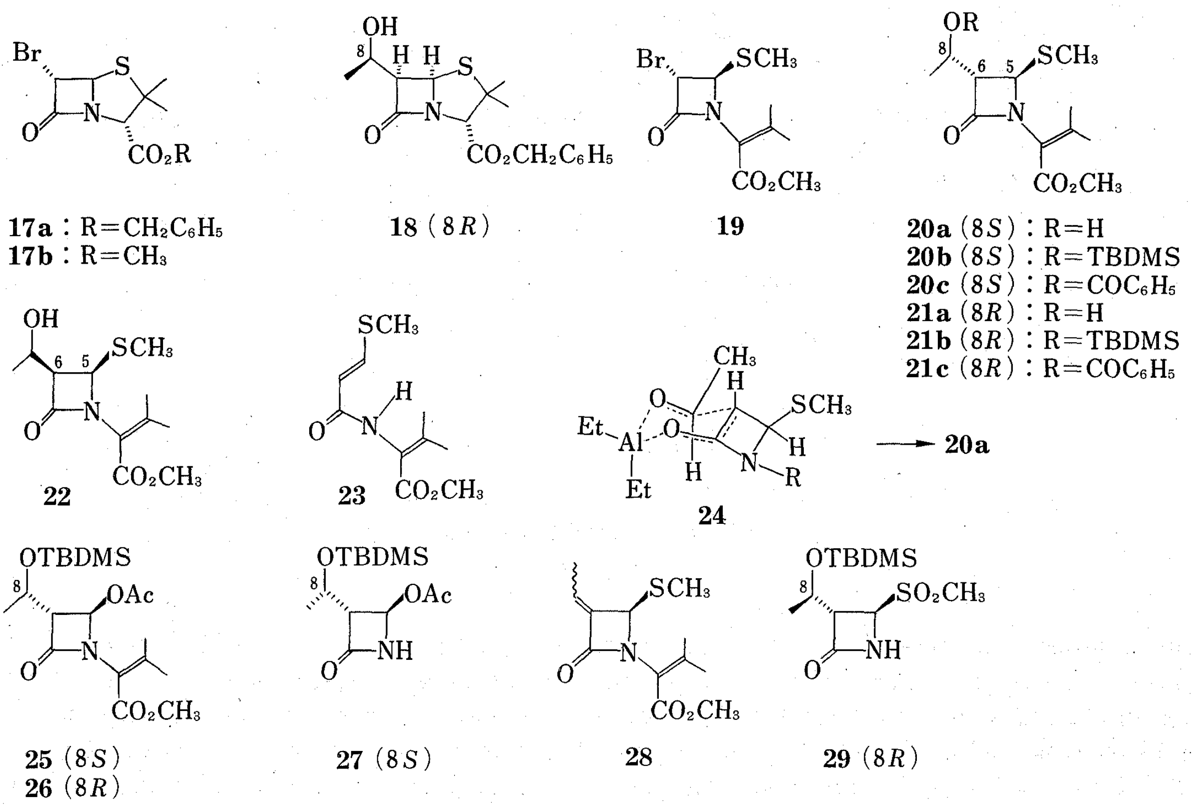
TBDMS: *tert*-butyldimethylsilyl

Chart 2

and obtained a mixture of 6-(hydroxyethyl)penicillanates considerably enriched in **14a**. The mixture was silylated and the product containing **14b** as a major diastereomer was treated with mercuric acetate in acetic acid at 90°C, giving the monocyclic *trans* β-lactam mixture enriched in **15** in good yield. Removal of the N-substituent was accomplished by treatment with a catalytic amount of potassium permanganate and an excess of sodium periodate in a mixture of acetone and phosphate buffer solution (pH 7.1). This provided an 88% yield of the N-unsubstituted azetidinone from which pure, crystalline *trans* 6*R*, 8*R* diastereomer **16**, mp 104—106°C, $[\alpha]_D$ +48.8° ($CHCl_3$), was obtained as a major product in 41% yield. The NMR, IR and TLC properties of **16** were identical with those of the racemic azetidinone **9b**. The azetidinone **16** has the same configurations at C-6 and C-8 as thienamycin and the approach described above seems to be an efficient method for preparing a precursor to optically active penem analogs related to thienamycin. However, there are still some difficulties in Method B; for example, a somewhat low yield in preparing the starting material **12** from 6-aminopenicillanic acid (6-APA), the requirement for a low reaction temperature for the metallation of **12** and the lack of reproducibility experienced in large-scale reductive debromination of **13**. Therefore, other approaches to the key intermediate **16** were sought.

Method C

6β-Bromopenicillanate can be obtained from 6-APA in a higher yield than the 6,6-dibromo derivative.[13] DiNinno *et al.*[12] reported that metallation of 6-halopenicillanate with Grignard reagent at −78°C followed by the condensation of the anion with acetaldehyde resulted in the formation of a diastereomeric mixture of hydroxyethylpenicillanates with low stereoselectivity. Considering that the reaction course of the aldol reaction would be influenced by the nature of the solvent and type of metal cation present,[14] we studied the aldol reaction using the aluminum enolate which should be formed from 6-bromopenicillanate **17a** according to the method of Maruoka *et al.*[15] Thus, treatment of **17a** with diethylaluminum chloride and activated zinc[16] in THF at room temperature generated the supposed aluminum enolate which reacted immediately with the coexisting acetaldehyde to give a 60% yield of a mixture of hydroxyethylated products, whose NMR spectrum was compared with the data reported by DiNinno *et al.*[12] It turned out that the configuration of the major product **18** (more than 60% of the mixture) was 6*R*, 8*R*. The reason for the preferential attack of the acetaldehyde at the hindered β-face of the penicillin enolate, which was also observed in the aforementioned hydroxyethylation of **12** to **13**, is not clear; however, it seemed to be a usual process in the bicy-



TBDMS: *tert*-butyldimethylsilyl

Chart 3

clic penam system. It was, however, expected that aluminum enolates of monocyclic β-lactams would react with electrophiles on the less hindered side, giving products with *trans* β-lactam stereochemistry.

Monocyclic bromosecopenicillin **19** was obtained in 66% yield, according to a procedure described by Dennerley *et al.*,17) by treatment of methyl 6α-bromopenicillanate13) (**17b**) with trimethyloxonium tetrafluoroborate followed by reaction of the resulting sulfonium salt with sodium carbonate. Hydroxyethylation of **19** was carried out by treatment with diethylaluminum chloride and activated zinc in the presence of an excess of acetaldehyde in THF at room temperature to give, after separation by silica gel chromatography, a 60% yield of a 3:1 mixture of *trans* diastereomers **20a** [NMR: δ 4.92 (d, J=3 Hz, H-5)] and **21a** [NMR: δ 5.05 (d, J=3 Hz, H-5)], and a 5% yield of a single *cis* isomer **22** [NMR: δ 5.05 (d, J=5.5 Hz, H-5)]. The ring-opened by-product **23** was obtained in 6% yield. As expected, hydroxyethylation occurred preferentially at the sterically less hindered α-face of the monocyclic β-lactam enolate. The C-8 stereochemistry of the major *trans* diastereomer **20a** was inferred as *S* by considering the cyclic transition state for the aldol reaction as depicted by **24**, in which the methyl group of an incoming acetaldehyde molecule takes the equatorial position with the pro-*S* configuration. Confirmation of the assignment of the side chain configuration was obtained as follows. The mixture of **20a** and **21a** was silylated to the O-TBDMS derivatives **20b** and **21b**, which were then treated with mercuric acetate in acetic acid to give a mixture of the *trans* acetoxyazetidinones **25** and **26**, and oxidative removal of the N-substituent with the aforementioned KMnO$_4$/NaIO$_4$ system gave a 3:1 mixture of **27** and **16**. Recrystallization of the mixture afforded the pure 8*S* azetidinone **27**, mp 49—50.5°C, $[\alpha]_D$ +67.9° (CHCl$_3$), which was a diastereomer of **16** obtained earlier. Spectroscopic data and TLC behavior of **27** were identical with those of the aforementioned racemic azetidinone **10b**.

Conversion of the 8*S* hydroxyethylsecopenicillin **20a** into the 8*R* isomer **21a** by an inversion reaction at the C-8 position was attempted. The conversion was eventually successfully achieved under mild conditions by using a triphenylphosphine and diethyl azodicarboxylate system.[18] Bose *et al.*[19] carried out the inversion of a sterol configuration in a stereospecific manner using the above reagent system in the presence of an acid nucleophile. According to their method, the 3: 1 mixture of **20a** and **21a** described above was treated with two equivalents each of triphenylphosphine and diethyl azodicarboxylate in the presence of two equivalents of benzoic acid, affording a 1: 3 mixture of the 8*S* and 8*R* benzoates **20c** and **21c** in 71% yield. This mixture underwent debenzoylation with methanolic sodium methoxide to give a 1: 3 mixture of **20a** and **21a** in 87% yield. In the above displacement reaction, a mixture of (*E*/*Z*)-ethylidene *β*-lactams **28** was obtained as a by-product whose formation was increased when a smaller amount of benzoic acid was used. Proceeding exactly as described above, the 1: 3 mixture of **20a** and **21a** was silylated and treated with mercuric acetate and then with $KMnO_4/NaIO_4$ to yield the 1: 3 mixture of N-unsubstituted 8*S* and 8*R* azetidinones **27** and **16**, in 73% yield over the three steps, from which the pure 6*R*, 8*R* diastereomer **16** was readily obtained by recrystallization (38% overall yield from the 1: 3 mixture of **20a** and **21a**). Since it had been demonstrated that the 4-alkylsulfonyl group of azetidinone as well as the 4-acetoxy group was easily displaced by various other nucleophiles,[20] the (methylsulfonyl)azetidinone **29** was also synthesized. The 1: 3 mixture of **20b** and **21b** described above was oxidized with a $KMnO_4/NaIO_4$ system to yield a diastereomeric mixture of N-unsubstituted (methylsulfonyl)-azetidinones from which the major 8*R* isomer **29** was obtained as crystals. The azetidinone **29** was later found to be less reactive than the corresponding acetoxyazetidinones. Attempted displacement reaction of **29** with sodium alkyl trithiocarbonate afforded an undesired complex mixture.

In the above reaction sequence to synthesize **16** and **27**, a *p*-nitrobenzyloxycarbonyl group was used instead of the TBDMS group for protection of the C-8 hydroxy group, because it can be easily removed under mild hydrogenolytic conditions together with other *p*-nitrobenzyl-derived protecting groups for the carboxy or amino function at the final step of the synthesis of penemcarboxylic acids. However, it was found to be difficult to separate the derived mixture of 8*R* and 8*S* diastereomers at any step. Thus, it was concluded that protection of the C-8 hydroxy function with *p*-nitrobenzyloxycarbonyl group was not superior in our case to that with the TBDMS group.

The way was now open for the production, starting from 6-APA, of the optically active key intermediates **16** and **27** to the thienamycin-related penem compounds. Conversion of these acetoxyazetidinones into 1-thia analogs of thienamycin will be described in the following paper.

Experimental

Melting points are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer and proton magnetic resonance spectra (NMR) on a Varian A-60 or a Hitachi-Perkin-Elmer R-24 spectrometer in $CDCl_3$ using Me_4Si as an internal standard. Mass spectra (MS) were obtained on a JEOL 01SG spectrometer. Rotations were determined on a Perkin-Elmer 141 spectrometer at 25°C. 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 parentheses. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; qd, quartet of doublets; m, multiplet; br., broad; sh., shoulder.

(±)-1-(*tert*-Butyldimethylsilyl)-3-1(-hydroxyethyl)-4-phenylthio-2-azetidinones (5—8)——A solution of (±)-1-(*tert*-butyldimethylsilyl)-4-phenylthio-2-azetidinone[1] (4) (1.0 g, 3.41 mmol) in THF (2.5 ml) was added to a stirred solution of lithium diisopropylamide (4.26 mmol) in THF (25 ml) at 78°C. After being stirred for 2 min, a solution of acetaldehyde (freshly distilled, 0.30 g, 6.81 mmol) in THF (2.5 ml) was added at the same temperature. The mixture was stirred for 5 min and then acidified by addition of acetic acid

Table I. Spectral Data for (±)-3-(1-Hydroxyethyl)-2-azetidinone Derivatives (**5**—**11**)

Compd.	IR $\nu_{\max}$ cm^{-1} (state or solvent)	NMR $\delta^{a)}$ (60 MHz)
5	3350, 1720 (KBr)	0.02 (6H, s), 0.72 (9H, s), 0.78 (3H, d, 7), 2.07 (1H, br. s), 2.85 (1H, dd, 4.5, 2), 3.8 (1H, m), 4.71 (1H, d, 2), 7.1 (5H, m)
6	3450 (br.), 1738, 1581 ($CHCl_3$)	0.02 (6H, s), 0.70 (9H, s), 0.90 (3H, d, 6), 1.77 (1H, br. d, 5), 2.87 (1H, dd, 6, 2), 3.76 (1H, m), 4.51 (1H, d, 2), 7.11 (5H, m)
7+**8** (1 : 3)$^{b)}$	3500, 1740, 1581 ($CHCl_3$)	0.02 (6H, s), 0.73 (9H, s), 1.10 (3H, d, 6), 2,61 (1H, br. d, 3), 3.31 (1H, t, 5), 4.0 (1H, m), 4.81 (1H, d, 5), 7.11 (5H, s)
9a	1755 ($CHCl_3$)	0.10 (6H, s), 0.18 (3H, s), 0.26 (3H, s), 0.89 (9H, s), 0.97 (9H, s), 1.24 (3H, d, 6), 2.07 (3H, s), 3.12 (1H, dd, 3, 1), 4.23 (1H, qd, 6, 3), 6.21 (1H, d, 1)
9b	3170, 3130, 1785, 1748 (Nujol) 3430, 1790, 1750 ($CHCl_3$)	0.07 (6H, s), 0.88 (9H, s), 1.25 (3H, d, 6.5), 2.13 (3H, s), 3.20 (1H, dd, 3.5, 1.5), 4.3 (1H, m), 5.98 (1H, d, 1.5), 7.24 (1H, br.)
10a	1755 ($CHCl_3$)	0.10 (6H, s), 0.18 (3H, s), 0.26 (3H, s), 0.89 (9H, s), 0.97 (9H, s), 1.30 (3H, d, 6), 2.07 (3H, s), 3.12 (1H, dd, 3, 1), 4.34 (1H, qd, 6, 3), 5.83 (1H, d, 1)
10b	3330, 1764, 1739 (sh.), 1729 (Nujol) 3420, 1788, 1745 ($CHCl_3$)	0.08 (6H, s), 0.88 (9H, s), 1.31 (3H, d, 6), 2.13 (3H, s), 3.24 (1H, dd, 3.5, 1.5), 4.3 (1H, m), 5.82 (1H, d, 1.5), 6.8 (1H, br.)
11a	1759, 1582 (Nujol)	0.01 (6H, s), 0.41 (6H, s), 0.45 (3H, d, 7), 0.86 (9H, s), 1.09 (9H, s) 3.32 (1H, t, 2.5), 4.2 (1H, m), 4.74 (1H, d, 2.5), 7.6—8.2 (5H, m)
11b	3180, 1773, 1737 (Nujol)	0.00 (6H, s), 0.81 (9H, s), 1.09 (3H, d, 7), 3.41 (1H, t, 2), 4.27 (1H, m), 4.70 (1H, d, 2), 6.7 (1H, br. s), 7.6—8.2 (5H, m)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses.
b) The ratio was determined by NMR analysis after conversion of the mixture to a diastereomeric mixture of **9a** and **10a**.

(0.51 g, 8.50 mmol) with cooling. The mixture was diluted with benzene–hexane (1: 1), washed with water, dried and evaporated to dryness *in vacuo*. The residue was chromatographed (4 g, benzene–AcOEt, 5: 1) to give a diastereomeric mixture of **5**—**8** (1.23 g). The product was injected into a Lobar column-B (E. Merck, Darmstadt) and eluted with $CHCl_3$–AcOEt (10: 1), yielding a mixture of 3,4-*cis* isomers **7** and **8** (393 mg, 34%) as an oil, one 3,4-*trans* isomer **6** (310 mg, 27%) as an oil and the other 3,4-*trans* isomer **5** (390 mg, 34%) as needles, mp 66—69°C (from hexane), in that order of elution. IR and NMR data are shown in Table I. *Anal.* Calcd for $C_{17}H_{27}NO_2SSi$: C, 60.49; H, 8.06; N, 4.15. Found for **5**: C, 60.48; H, 8.08; N, 4.24. MS *m/e* for **6** or a mixture of **7** and **8**: 228 [$M^+(337)-SC_6H_5$], 210 ($M^+-SC_6H_5-H_2O$), 141.

(±)-4β-Acetoxy-1-(*tert*-butyldimethylsilyl)-3α-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinones (9a and 10a)——i) Imidazole (101 mg, 1.49 mmol) and *tert*-butyldimethylchlorosilane (223 mg, 1.48 mmol) were added to a solution of **5** (227 mg, 0.67 mmol) in N,N-dimethylformamide (DMF, 2 ml) at room temperature and the mixture was stirred for 5 h. Aqueous work-up and purification of the product by chromatography (5 g, benzene–AcOEt, 20: 1) gave an N,O-diTBDMS derivative of **5** (285 mg, 94%) as an oil. IR $\nu_{\max}^{CHCl_3}$ 1753 cm^{-1}. MS *m/e*: 436 [M^+ (451, $C_{23}H_{41}NO_2SSi_2$)$-CH_3$], 394 ($M^+-C_4H_9$).

The N,O-diTBDMS derivative (275 mg, 0.61 mmol) thus obtained was dissolved in a mixture of acetic acid (0.4 ml) and AcOEt (0.4 ml) and then mercuric acetate (300 mg, 0.94 mmol) was added. The mixture was stirred for 1 h at room temperature, then partitioned between hexane and water, and filtered. The organic layer was washed with water and the solvent was removed. The product was chromatographed (5 g, benzene–hexane, 1: 1—benzene–AcOEt, 10: 1) to give **9a** (227 mg, 93%) as an oil.

Following the procedure described above, the other *trans* isomer **6** was transformed to **10a** in 87% yield over two steps. Spectral data for **9a** and **10a** are given in Table I.

ii) Similarly, a mixture of *cis* isomers **7** and **8** obtained as above was silylated to N,O-diTBDMS derivatives and then treated with mercuric acetate in a mixture of acetic acid and AcOEt to afford an inseparable mixture of **9a** and **10a** (1: 3 on the basis of NMR analysis) as an oil in 90% overall yield over two steps.

(±)-1-(*tert*-Butyldimethylsilyl)-3α-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4β-phenylsulfonyl-2-azetidinone (11a)——The N,O-diTBDMS derivative of **5** (210 mg, 0.46 mmol) was treated with a mixture of 40%

peracetic acid (0.44 ml, 2.57 mmol), AcONa·3H_2O (58 mg, 0.43 mmol), manganese(III) acetylacetonate (6 mg, 0.02 mmol) and AcOEt (4 ml) at 0°C for 5 h. The mixture was diluted with AcOEt and excess peracid was decomposed by addition of dil. $NaHSO_3$ solution. The organic layer was collected, washed with dil. $NaHCO_3$ solution and water, dried and evaporated to dryness *in vacuo*. The product was purified by chromatography (5 g, benzene–AcOEt, 10: 1) to give **11a** (180 mg, 81%) as prisms, mp 116—116.5°C (from MeOH). *Anal.* Calcd for $C_{23}H_{41}NO_4SSi_2$: C, 57.10; H, 8.54; N, 2.90; S, 6.63. Found: C, 57.09; H, 8.59; N, 2.72; S, 6.85. Spectral data are given in Table I.

(±)-3*α*-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4*β*-phenylsulfonyl-2-azetidinone (11b)——A solution of tetrabutylammonium fluoride (93 mg, 0.36 mmol) and acetic acid (43 mg, 0.72 mmol) in THF (0.25 ml) was added to an ice-cold solution of **11a** (150 mg, 0.31 mmol) in THF (1 ml). After being stirred for 1 h and 15 min, the mixture was diluted with AcOEt, washed successively with dil. $NaHCO_3$ solution and water, dried and evaporated to dryness *in vacuo*. The residue was chromatographed (5 g, benzene–AcOEt, 5: 1) to afford the sulfone **11b** (95 mg, 83%) as needles, mp 145.5—146.5°C (from hexane–MeOH). *Anal.* Calcd for $C_{17}H_{27}NO_4SSi$: C, 55.25; H, 7.36; N, 3.79. Found: C, 55.15; H, 7.38; N, 3.64. Spectral data are given in Table I.

(±)-4*β*-Acetoxy-3*α*-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinones (9b and 10b)——A solution of tetrabutylammonium fluoride (190 mg, 0.73 mmol) and acetic acid (88 mg, 1.47 mmol) in THF (1 ml) was added to a solution of **9a** (243 mg, 0.61 mmol) in THF (1 ml). The mixture was stirred for 30 min at room temperature and then partitioned between water and AcOEt. The organic layer was collected, washed successively with dil. $NaHCO_3$ solution and brine, dried and evaporated to dryness *in vacuo*. Chromatography (5 g, benzene–AcOEt, 6: 1) of the residue gave **9b** (149 mg, 100%) as a crystalline mass. Recrystallization from hexane afforded an analytical sample, mp 78—80°C.

Analogous treatment of the diastereomer **10a** gave the corresponding N-desilylated azetidinone **10b**, mp 81.5—82°C (from hexane), in a quantitative yield. *Anal.* Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found for **9b**: C, 54.22; H, 8.73; N, 4.90; for **10b**: C, 54.15; H, 8.74; N, 4.92. Spectral data for **9b** and **10b** are given in Table I.

Benzyl 6*α*-[(*R*)-1-Hydroxyethyl]penicillanate (14a) and Its O-TBDMS Derivative (14b)——(Hydroxyethyl)-penicillanate was obtained as a diastereomeric mixture containing **14a** as a main component according to the procedure of DiNinno *et al.*[12] as follows. A 2.5 mM ethereal solution of methylmagnesium iodide (1 ml, 2.5 mmol) was added dropwise to a solution of benzyl 6,6-dibromopenicillanate **12** (898 mg, 2.0 mmol) at −78°C with stirring. The mixture was stirred for 20 min at the same temperature, then acetaldehyde (0.6 ml, 10 mmol) was added and stirring was continued for 20 min with cooling. After addition of an NH_4Cl saturated solution (5 ml), the mixture was partitioned between AcOEt and water. The organic layer was collected, washed with brine and evaporated to dryness *in vacuo*. The residue was chromatographed (10 g, benzene–AcOEt, 5: 1) to give a diastereomeric mixture of benzyl 6-bromo-6-(1-hydroxyethyl)penicillanates enriched in **13** (754 mg, 91%) as an oil. NMR δ: 1.26 and 1.44 (2: 1, d, $J=6$ Hz, $\underline{CH_3}CH$–), 1.40 (s, 2α-CH_3), 1.63 (s, 2β-CH_3), 2.55 (d, $J=5$ Hz, OH), 4.25 (m, CH_3–C$\underline{H}$–O), 4.55 (s, H-3), 5.23 (s, $\underline{CH_2}C_6H_5$), 5.52 and 5.62 (1: 2, s, H-5), 7.4 (s, C_6H_5).

The 6-bromo-6-(1-hydroxyethyl)penicillanates mixture (1.98 g, 4.8 mmol) obtained above was dissolved in MeOH (50 ml) and added in one portion to a stirred suspension of zinc-silver couple[21] (2 g) in MeOH (10 ml) at room temperature. The mixture was stirred for 10 min, filtered and worked up as usual. The product was chromatographed (20 g, benzene–AcOEt, 20: 1—7: 1) to give a diastereomeric mixture of benzyl 6-(hydroxyethyl)penicillanates (1.18 g, 74%) which contained the 5,6-*trans* 8*R* isomer **14a** and the 5,6-*trans* 8*S* isomer as main components in approximately a 7: 3 ratio (based on NMR analysis). NMR δ: 1.33 and 1.35 (7: 3, d, $J=6$ Hz, $\underline{CH_3}CH$–O), 1.40 (s, 2α-CH_3), 1.61 (s, 2β-CH_3), 2.4 (m, OH), 3.31 (7/10H, dd, $J=6.5$, 2 Hz, H-6β), 3.40 (3/10H, dd, $J=5$, 2 Hz, H-6β), 4.25 (m, CH_3C$\underline{H}$–O), 4.52 (s, H-3), 5.22 (s, $\underline{CH_2}C_6H_5$), 5.25 and 5.34 (3: 7, d, $J=2$ Hz, H-5), 7.4 (s, C_6H_5).

The 6-(1-hydroxyethyl)penicillanates mixture (261 mg, 0.78 mmol) obtained as above was dissolved in DMF (1.3 ml), and *tert*-butyldimethylchlorosilane (164 mg, 10.9 mmol) and imidazole (74 mg, 10.9 mmol) were added. The mixture was stirred for 5 h at room temperature, then diluted with AcOEt, washed with water, dried and evaporated to dryness. The product was purified by chromatography (5 g, benzene–AcOEt, 10: 1) to give the O-TBDMS derivative (310 mg, 89%) as an oil containing the 5,6-*trans* 8*R* isomer **14b** as a main component and the 5,6-*trans* 8*S* isomer as the second component. IR ν_{max}^{liq} cm^{-1}: 1780, 1750. NMR δ: 0.05 (s, Si($CH_3)_2$), 0.85 (s, Si-*t*-C_4H_9), 1.25 and 1.32 (7: 3, d, $J=7$ Hz, $\underline{CH_3}CH$–O), 1.40 (s, 2α-CH_3), 1.60 (s, 2β-CH_3), 3.24 (7/10H, dd, $J=5$, 2 Hz, H-6β), 3.36 (3/10H, dd, $J=4.5$, 2 Hz, H-6β), 4.2 (m, CH_3C$\underline{H}$–O), 4.49 and 4.51 (7: 3, s, H-3), 5.21 (s, $\underline{CH_2}C_6H_5$), 5.23 and 5.30 (3: 7, d, $J=2$ Hz, H-5), 7.4 (s, C_6H_5).

(3*R*,4*R*)-4-Acetoxy-1-(1-benzyloxycarbonyl-2-methyl-1-propenyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-2-azetidinone (15)——The diastereomeric mixture of the O-TBDMS derivatives (630 mg, 1.40 mmol) containing **14b** as a main component, obtained above, was dissolved in acetic acid (6 ml) and mercuric acetate (893 mg, 2.80 mmol) was added. The mixture was stirred for 1.5 h at 90°C, then the acetic acid was removed *in vacuo*. AcOEt was added to the residue. The solution was washed with dil.$NaHCO_3$, dried and concentrated *in vacuo*. The product was purified by chromatography (15 g, benzene–AcOEt, 30: 1) to give a diastereomeric mixture of the 8*R* isomer **15** and its 8*S* isomer (7: 3 based on NMR analysis, 628 mg, 94%)

as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1760 (sh.), 1725, 1635. NMR δ: 0.05 (6H, br. s), 0.90 (9H, s), 1.14 and 1.30 (3: 7, 3H, d, $J=6$ Hz), 1.98, 2.01 and 2.25 (3H each, s), 3.21 (7/10H, dd, $J=7$, 1.5 Hz), 3.31 (3/10H, dd, $J=5$, 1.5 Hz), 4.1 (1H, m), 5.24 (2H, s), 6.19 and 6.23 (3: 7, 1H, d, $J=1.5$ Hz), 7.4 (5H, s).

Aldol Reaction of Aluminum Enolate Generated from 6-Bromopenicillanate 17a——A solution of **17a** (200 mg, 0.54 mmol) and freshly distilled acetaldehyde (80 mg, 1.8 mmol) in THF (2 ml) was added dropwise to a stirred mixture of activated zinc[16] (53 mg, 0.82 mmol), a 15% solution of diethylaluminum chloride in hexane (0.54 ml, 0.54 mmol) and THF (1.5 ml) at 15°C over a period of 40 min. After being stirred for 1.5 h, the mixture was diluted with AcOEt and then treated with water. The precipitates were filtered off using Celite and the filtrate was washed with brine, dried and evaporated to dryness *in vacuo*. The residue was chromatographed (5 g, benzene–AcOEt, 5: 1) to give a diastereomeric mixture of benzyl 6-(1-hydroxyethyl)-penicillanates (110 mg, 61%) containing the diastereomer **18** as a main component (>60% based on NMR) and apparently two minor diastereomers. NMR data for the main component in the mixture are given below, and were in good accord with those reported for **18**.[12] NMR δ: 1.21 (d, $J=6$ Hz, $C\underline{H}_3CH$–O), 1.40 (s, 2α-CH_3), 1.63 (s, 2β-CH_3), 3.47 (dd, $J=9$, 5 Hz, H-6α), 4.2 (m, $CH_3C\underline{H}$–O), 4.48 (s, H 3), 5.21 (s, $C\underline{H}_2C_6H_5$), 5.40 (d, $J=5$ Hz, H-5), 7.4 (s, C_6H_5).

(3*S*,4*R*)-3-Bromo-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-4-methylthio-2-azetidinone (**19**)——Trimethyloxonium tetrafluoroborate (4.52 g, 30.6 mmol) was added to an ice-cold solution of **17b**[13] (8.56 g, 30.4 mmol) in nitromethane (61 ml) with stirring under an N_2 atmosphere. After being stirred for 10 min, the mixture was kept at 5°C for 48 h. The resulting precipitates were dissolved by further addition of nitromethane (60 ml) and the mixture was stirred with pulverized Na_2CO_3 (11.3 g, 107 mmol) at room temperature for 2 h. The mixture was diluted with AcOEt, washed successively with water, dil.HCl and dil.$NaHCO_3$ solution, dried and evaporated to dryness *in vacuo*. The residue was charged on a column packed with alumina (Woelm B, activity I, 100 g) and eluted with AcOEt to give **19** (5.96 g, 66%) as a powder. The analytical sample was obtained by recrystallization from isopropyl ether–hexane as a powder, mp 55—56°C. *Anal.* Calcd for $C_{10}H_{14}BrNO_3S$: C, 38.97; H, 4.58; Br, 25.93; S, 10.40. Found: C, 38.85; H, 4.54; N, 4.37; Br, 26.14; S, 10.57. NMR data are given in Table II.

TABLE II. NMR Data for Azetidinones (**19**—**22**, **25**, **26** and **29**)

Compd.	NMR δ[a] (60 MHz)
19	2.00 (3H, s), 2.16 (3H, s), 2.27 (3H, s), 3.80 (3H, s), 4.85 (1H, d, 2), 5.13 (1H, d, 2)
20a	1.30 (3H, d, 6), 1.93 (3H, s), 2.05 (3H, s), 2.15 (3H, s), 3.14 (1H, dd, 6, 3), 3.72 (3H, s), 4.12 (1H, m), 4.92 (1H, d, 3)
20b	0.10 (6H, s), 0.84 (9H, s), 1.28 (3H, d, 6), 1.92 (3H, s), 2.05 (3H, s), 2.16 (3H, s), 3.20 (1H, dd, 5, 3), 3.71 (3H, s), 4.23 (1H, m), 4.96 (1H, d, 3)
20c	1.52 (3H, d, 6), 1.95 (3H, s), 2.03 (3H, s), 2.17 (3H, s), 3.38 (1H, t, 3), 3.74 (3H, s), 4.96 (1H, d, 3), 5.63 (1H, m), 7.5 (3H, m), 8.1 (2H, m)
21a	1.26 (3H, d, 6), 1.93 (3H, s), 2.05 (3H, s), 2.15 (3H, s), 3.10 (1H, dd, 6, 3), 3.72 (3H, s), 4.23 (1H, m), 5.05 (1H, d, 3)
21b	0.10 (6H, s), 0.84 (9H, s), 1.23 (3H, d, 6), 1.92 (3H, s), 2.05 (3H, s), 2.16 (3H, s), 3.05 (1H, dd, 5, 3), 3.71 (3H, s), 4.23 (1H, m), 5.09 (1H, d, 3)
21c	1.49 (3H, d, 6), 1.95 (3H, s), 2.03 (3H, s), 2.17 (3H, s), 3.33 (1H, dd, 7, 3), 3.74 (3H, s), 5.14 (1H, d, 3), 5.63 (1H, m), 7.5 (3H, m), 8.1 (2H, m)
22	1.35 (3H, d, 6), 1.95 (3H, s), 2.05 (3H, s), 2.18 (3H, s), 3.42 (1H, dd, 5.5, 4.5), 3.72 (3H, s), 4.2 (1H, m), 5.05 (1H, 5.5)
25	0.10 (6H, s), 0.90 (9H, s), 1.34 (3H, d, 6), 1.94 (3H, s), 2.06 (3H, s), 2.22 (3H, s), 3.34 (1H, dd, 5.5, 1.5), 3.80 (3H, s), 4.3 (1H, m), 6.25 (1H, d, 1.5)
26	0.10 (6H, s), 0.90 (9H, s), 1.32 (3H, d, 6), 1.94 (3H, s), 2.06 (3H, s), 2.22 (3H, s), 3.23 (1H, dd, 6, 1.5), 3.80 (3H, s), 4.3 (1H, m), 6.32 (1H, d, 1.5)
29	0.09 (6H, s), 0.87 (9H, s), 1.26 (3H, d, 6), 2.97 (3H, s), 3.58 (1H, m), 4.35 (1H, m), 4.75 (3H, d, 2.5), 7.1 (1H, br.)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses.

(3*S*,4*R*)-3-(1-Hydroxyethyl)-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-4-methylthio-2-azetidinones (20a and 21a) and Its (3*R*,4*R*)-Isomer 22——A solution of **19** (1.96 g, 6.38 mmol) and freshly distilled acetaldehyde (843 mg, 19.2 mmol) in THF (20 ml) was added dropwise to a mixture of activated zinc[16] (625 mg, 9.62 mmol), a 15% solution of diethylaluminum chloride in hexane (6.68 ml, 6.68 mmol) and THF (15 ml) at 15—20°C with stirring over a period of 40 min. After being stirred for 1 h, the mixture was diluted with AcOEt and then treated with water. The precipitates were removed by filtration through Celite and the organic layer was washed with water, dried and evaporated to dryness *in vacuo*. The crude product (2.05 g) was chromatographed (30 g, $CHCl_3$–AcOEt, 5: 1—5: 2) to give 190 mg of a mixture of the ring-opened product **23** and a single *cis* isomer **22** and 1.04 g (60% yield) of a mixture of *trans* isomers **20a** and **21a**. Preparative TLC ($CHCl_3$–AcOEt, 5: 2) of the mixture of **22** and **23** afforded pure **22** (89 mg, 5%) as an oil and **23** (90 mg, 6%) as crystals. The ratio of **20a** and **21a** in the mixture obtained above was determined as 3: 1 by NMR analysis.

Data for a mixture of **20a** and **21a**: IR $\nu_{max}^{liq.}$ cm^{-1}: 3450, 1760, 1710. *Anal.* Calcd for $C_{12}H_{19}NO_4S$: C, 52.72; H, 7.01; N, 5.13; S, 11.73. Found: C, 52.81; H, 7.21; N, 5.43; S, 11.78. NMR data are given in Table II.

Data for **22**: IR $\nu_{max}^{liq.}$ cm^{-1}: 3400, 1755, 1720, 1622. NMR data are given in Table II.

Data for **23**: mp 138—139°C (from benzene–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3170, 1730, 1630, 1577. NMR δ: 1.75, 2.04, 2.24 and 3.68 (3H each, s), 5.80 (1H, d, $J=15$ Hz), 7.0 (1H, br.), 7.67 (1H, d, $J=15$ Hz). *Anal.* Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11; S, 13.98. Found: C, 52.57; H, 6.57; N, 6.14; S, 13.96.

Inversion of Side Chain Stereochemistry of the Alcohol 20a——A solution of diethyl azodicarboxylate (338 mg, 1.94 mmol) in THF (2.5 ml) was added dropwise to a stirred solution of the 3: 1 mixture of **20a** and **21a** (262 mg, 0.96 mmol) obtained above, triphenylphosphine (503 mg, 1.92 mmol) and benzoic acid (234 mg, 1.92 mmol) in THF (5 ml) at 20°C over a period of 10 min, and stirring was continued for 1.5 h. The mixture was evaporated to dryness *in vacuo* and the residue was dissolved in benzene–AcOEt (6: 1, 7 ml) and allowed to stand with cooling. The resulting precipitates were filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue (1.0 g) was chromatographed (10 g, benzene–AcOEt, 10: 1) to give a mixture of benzoates **20c** and **21c** (300 mg) contaminated by the dehydrated product **28**. Further purification by repeated preparative TLC (benzene–AcOEt, 5: 1) afforded pure dehydrated product **28**, the less polar *E*-isomer (20 mg, 9%) and the polar *Z*-isomer (13 mg, 6%), and a 1: 3 mixture of **20c** and **21c** (258 mg, 71%) as an oil whose ratio was determined by NMR analysis. In a practical procedure, the mixture contaminated with **28** was used for the next debenzoylation reaction without further purification as follows.

Data for a mixture of **20c** and **21c**: IR $\nu_{max}^{liq.}$ cm^{-1}: 1765, 1720. *Anal.* Calcd for $C_{19}H_{23}NO_5S$: C, 60.48; H, 6.10; N, 3.71; S, 8.49. Found: C, 59.20; H, 6.36; N, 3.52; S, 8.68. NMR data are given in Table II.

Data for **28**: the *E*-isomer; mp 83—84°C (needles from benzene–hexane). IR ν_{max}^{KBr} cm^{-1}: 1745, 1720, 1625. NMR δ: 1.99, 2.02, 2.23 and 3.77 (3H each, s), 2.10 (3H, d, $J=7$ Hz, $C\underline{H}_3CH=$, protons deshielded by lactam carbonyl), 5.47 (1H, q, $J=1$ Hz), 5.75 (1H, qd, $J=7$, 1 Hz). *Anal.* Calcd for $C_{12}H_{17}NO_3S$: C, 56.44; H, 6.71; N, 5.49; S, 12.56. Found: C, 56.85; H, 6.71; N, 5.38; S, 12.57; the *Z*-isomer; mp 109—110°C (needles from benzene–hexane). IR ν_{max}^{KBr} cm^{-1}: 1755, 1730, 1635. NMR δ: 1.90 (3H, d, $J=7$ Hz), 1.99, 2.02, 2.23 and 3.77 (3H each, s), 5.57 (1H, br. s), 6.42 (1H, qd, $J=7$, 1.5 Hz, $CH_3C\underline{H}=$, proton deshielded by lactam carbonyl). *Anal.* Found: C, 56.66; H, 6.68; N, 5.26; S, 12.36.

The mixture of benzoates **20c** and **21c** (455 mg) containing the by-product **28** as described above was dissolved in MeOH (3 ml), and a 1 M methanolic sodium methoxide solution (1.67 ml, 1.67 mmol) was added at 0°C. The mixture was stirred at room temperature for 5 h. After acidification by addition of acetic acid, the solution was diluted with AcOEt, washed with water, dried and evaporated to dryness *in vacuo*. The residue was chromatographed (10 g, benzene–AcOEt, 10: 1) to afford the unchanged **28** (*E*/*Z* mixture, 50 mg) and further elution with hexane–acetone (2: 1) afforded a 1: 3 mixture of **20a** and **21a** (247 mg, 62% over two steps). The ratio of two diastereomers thus obtained was determined by NMR analysis of the mixture. *Anal.* Calcd for $C_{12}H_{19}NO_4S$: C, 52.72; H, 7.01; N, 5.13; S, 11.73. Found: C, 53.03; H, 7.33; N, 4.68; S, 11.39.

(3*S*,4*R*)-3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-4-methylthio-2-azetidinones (20b and 21b)——i) The diastereomeric 3: 1 mixture of **20a** and **21a** (1.59 g, 5.82 mmol) obtained by aldol reaction of the aluminum enolate generated from **19** was dissolved in DMF (7.5 ml) and treated with imidazole (0.52 g, 7.68 mmol) and *tert*-butyldimethylchlorosilane (1.05 g, 6.98 mmol) at room temperature for 3 h. The mixture was diluted with benzene (50 ml), washed with water, dried and evaporated to dryness *in vacuo*. The residue was chromatographed (30 g, benzene–AcOEt, 10: 1) to give a 3: 1 mixture of the O-TBDMS derivatives **20b** and **21b** (2.00 g, 89%) as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1766, 1724, 1625. *Anal.* Calcd for $C_{18}H_{33}NO_4SSi$: C, 55.77; H, 8.58; N, 3.61; S, 8.27. Found: C, 55.44; H, 8.70; N, 3.42; S, 8.45. NMR data for both the isomers **20b** and **21b** are given in Table II.

ii) The diastereomeric 1: 3 mixture of **20a** and **21a** (5.69 g, 20.8 mmol) obtained above by inversion of the side chain stereochemistry was similarly treated with imidazole (2.54 g, 37.3 mmol) and *tert*-butyldimethylchlorosilane (5.33 g, 35.3 mmol) in DMF (110 ml) at room temperature overnight. The mixture was worked up as usual and chromatography of the product gave a 1: 3 mixture of **20b** and **21b** (7.95 g, 94%) as an oil.

(3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-methylsulfonyl-2-azetidinone (29)——The diastereomeric 1: 3 mixture of **20b** and **21b** (218 mg, 0.56 mmol) described above was dissolved in a mixture of sodium periodate (600 mg, 2.8 mmol), potassium permanganate (8 mg, 0.05 mmol), 0.1 M phosphate buffer solution (pH 7.1, 20 ml) and acetone (20 ml). The mixture was stirred at room temperature overnight and the precipitates were filtered off. The filtrate was concentrated *in vacuo* to half the initial volume, saturated with NaCl and extracted with benzene. The extract was dried and evaporated to dryness *in vacuo*. The residue was purified by chromatography (5 g, benzene–AcOEt, 10: 1) to give a crystalline mass which was recrystallized from benzene–hexane to provide the pure *R* diastereomer **29** (93 mg, 54%) as needles, mp 102—103°C, $[\alpha]_D$ +3.5° (*c*=0.48, THF). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3320, 1790, 1780. *Anal.* Calcd for $C_{12}H_{25}NO_4SSi$: C, 46.87; H, 8.20; N, 4.56; S, 10.43. Found: C, 45.87; H, 8.21; N, 4.54; S, 10.57. NMR data are given in Table II.

(3*R*,4*R*)-4-Acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-azetidinones (25 and 26)——i) The diastereomeric 3: 1 mixture of **20b** and **21b** (1.97 g, 5.09 mmol) obtained above was treated with mercuric acetate (3.25 g, 10.2 mmol) in acetic acid (20 ml) at 90—100°C for 30 min, then cooled. The solvent was evaporated off *in vacuo* and the residue was partitioned between water and AcOEt. The organic layer was collected, washed with water and evaporated to dryness *in vacuo*. The residue was chromatographed (15 g, benzene–AcOEt, 10: 1) to give a 3: 1 mixture of **25** and **26** (1.94 g, 94%) as an oil. IR $\nu_{\max}^{\mathrm{liq.}}$ cm^{-1}: 1780, 1755, 1725, 1630. *Anal.* Calcd for $C_{19}H_{33}NO_6Si$: C, 57.11; H, 8.32; N, 3.51. Found: C, 56.80; H, 8.44; N, 3.29. NMR data for both the isomers **25** and **26** are given in Table II.

ii) The diastereomeric 1: 3 mixture of **20b** and **21b** (3.85 g, 9.95 mmol) described above was similarly treated with mercuric acetate (5.08 g, 15.9 mmol) in acetic acid (38 ml) at 95—100°C for 20 min. Work-up as described above and chromatography of the product gave a 1: 3 mixture of **25** and **26** (1.94 g, 95%) as an oil. IR $\nu_{\max}^{\mathrm{liq.}}$ cm^{-1}: 1780, 1755, 1725, 1630. *Anal.* Calcd for $C_{19}H_{33}NO_6Si$: C, 57.11; H, 8.32; N, 3.51. Found: C, 56.77; H, 8.38; N, 3.36.

(3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (16)——i) The diastereomeric 7: 3 mixture of the 8*R* isomer **15** and its 8*S* isomer (3.21 g, 8.06 mmol) previously obtained was dissolved in acetone (350 ml) and added to an ice-cold solution of sodium periodate (8.62 g, 40.3 mmol) and potassium permanganate (100 mg, 0.63 mmol) in 0.05M phosphate buffer solution (pH 7.1, 350 ml). The mixture was stirred at room temperature for 5 h and the precipitates were filtered off. The filtrate was concentrated *in vacuo* to half the initial volume and extracted with benzene. The extract was dried and evaporated to dryness *in vacuo*. The crystalline residue was chromatographed (20 g, benzene–AcOEt, 10: 1) to give a 7: 3 mixture of **16** and **27** (2.03 g, 88%) which was crystallized from cold hexane to yield **16** (949 mg, 41%) as needles, mp 104—106°C, $[\alpha]_D$ +48.8° (*c*=0.41, $CHCl_3$). *Anal.* Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.04; H, 8.79; N, 4.71. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3175, 1783, 1743. NMR and TLC properties of **16** were identical with those of the racemic material **9b**.

ii) The diastereomeric 1: 3 mixture of **25** and **26** (3.00 g, 7.5 mmol) obtained above was similarly oxidized by treatment with sodium periodate (6.43 g, 30.1 mmol) and potassium permanganate (120 mg, 0.76 mmol) in a mixture of acetone (300 ml) and 0.05 M phosphate buffer solution (pH 7.1, 300 ml) at room temperature for 5 h. The mixture was worked up as described above and extracted with benzene. Removal of the solvent and chromatography of the residue afforded a crystalline material (1.77 g, 82%) which was shown to be a 3: 1 mixture of **16** and **27** by NMR analysis. Recrystallization from cold hexane gave the pure azetidinone **16** (928 mg, 43%) as needles, mp 104—106°C, which had the same physical properties, including optical rotation, as the sample obtained above.

(3*R*,4*R*)-4-Acetoxy-3-[(*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (27)——The diastereomeric 3: 1 mixture of **25** and **26** (1.50 g, 3.76 mmol) described above was dissolved in acetone (120 ml) and added to an ice-cold solution of sodium periodate (4.00 g, 18.7 mmol) and potassium permanganate (50 mg, 0.32 mmol) in 0.05 M phosphate buffer solution (pH 7.1, 120 ml). The mixture was stirred at room temperature for 5 h and worked up as described above. Chromatography (10 g, benzene–AcOEt, 10: 1) of the residue gave a 3: 1 mixture of **27** and **16** (852 mg, 79%) as an oil which was dissolved in hexane and cooled for crystallization to afford **27** (421 mg, 39%) as crystals, mp 49—50.5°C, $[\alpha]_D$ +67.9° (*c*=1.02, $CHCl_3$). IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3380, 3250, 1790, 1780, 1740. *Anal.* Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.15; H, 8.74; N, 4.92. NMR and TLC properties of **27** were identical with those of the racemic material **10b**.

References and Notes

1) Part III: A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, **29**, 1854 (1981).
2) Some of the investigations described in this and the subsequent paper were presented at the Second International Symposium on β-Lactam Antibiotics at Cambridge on July 2, 1980. See S. Oida, "Recent Advances in the Chemistry of β-Lactam Antibiotics," (2nd International Symposium), ed. by G.I. Gregory, Special Publication No. 38, The Royal Society of Chemistry, 1981, p. 330.
3) G. Albers-Schönberg, B.H. Arison, O.D. Hensens, J. Hirshfield, K. Hoogsteen, E.A. Kaczka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratcliffe, E. Walton, L.J. Ruswinkel, R.B. Morin, and B.G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).
4) *a*) D.B.R. Johnston, S.M. Schmitt, F.A. Bouffard, and B.G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978); *b*) R.J. Ponsford and R. Southgate, *Chem. Comm.*, **1980**, 1085; *c*) T. Kametani, S.-P. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, *J. Am. Chem. Soc.*, **102**, 2060 (1980); *d*) T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen, and F.A. Bouffard, *J. Am. Chem. Soc.*, **102**, 6161 (1980); *e*) D.G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, *Tetrahedron Lett.*, **21**, 2783 (1980); *f*) M. Shiozaki and T. Hiraoka, *Tetrahedron Lett.*, **21**, 4473 (1980).

5) S. Oida, A. Yoshida, T. Hayashi, N. Takeda, and E. Ohki, *Chem. Pharm. Bull.*, **28**, 3232, 3258 (1980).
6) S. Oida, A. Yoshida, T. Hayashi, N. Takeda, T. Nishimura, and E. Ohki, *J. Antibiotics*, 33, 107 (1980).
7) Recently, racemic 2-unsubstituted 6-(hydroxyethyl)penem-3-carboxylic acids have been synthesized and their antibacterial activities reported: H.R. Pfaendler, J. Gosteli, and R.B. Woodward, *J. Am. Chem. Soc.*, **102**, 2039 (1980).
8) S. Oida, A. Yoshida, and E. Ohki, *Chem. Pharm. Bull.*, **28**, 3494 (1980) and references cited therein.
9) Numbering corresponds to that of thienamycin.
10) Compounds **4**—**11** are racemic and their structural formulas and stereochemical designations refer to the enantiomer related to thienamycin.
11) A.R. Doumaux, Jr., J.E. McKeon, and D.J. Trecker, *J. Am. Chem. Soc.*, **91**, 3992 (1969); A.R. Doumaux, Jr. and D.J. Trecker, *J. Org. Chem.*, **35**, 2121 (1970).
12) F. DiNinno, T.R. Beattie, and B.G. Christensen, *J. Org. Chem.*, **42**, 2960 (1977).
13) J.P. Clayton, *J. Chem. Soc. (C)*, **1969**, 2123.
14) J.A. Aimetti and M.S. Kellogg, *Tetrahedron Lett.*, **1979**, 3805.
15) K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 7705 (1977).
16) Refer to C.R. Hauser and D.S. Breslow, "Organic Synthesis," Coll. Vol. III, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 408.
17) P.M. Dennerley and E.J. Thomas, *Tetrahedron Lett.*, **1977**, 71; *idem*, *J. Chem. Soc. Perkin I*, **1979**, 3175.
18) O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Jpn.*, **40**, 2380 (1967); O. Mitsunobu and E. Eguchi, *ibid.*, **44**, 3427 (1971).
19) A.K. Bose, B. Lal, W.A. Hoffman, and M.S. Manhas, *Tetrahedron Lett.*, **1973**, 1619.
20) K. Clauss, D. Grimm, and G. Prossel, *Justus Liebigs Ann. Chem.*, **1974**, 539.
21) C.H. Heathcock and R.D. Clark, *J. Org. Chem.*, **41**, 636 (1976).