A Short-Step Synthesis of Orally Active Carbapenem Antibiotic CS-834[1)]

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An orally bioavailable carbapenem CS-834, which is a pivaloyloxymethyl (POM) ester-type prodrug and has (*R*)-5-oxopyrrolidin-3-ylthio moiety at the C-2 position of the 1β-methylcarbapenem skeleton, is currently under clinical trial. We accomplished a short-step synthesis of CS-834 by using phosphorus ylide from the intramolecular Wittig-type reaction in the key step for cyclization to the bicyclic carbapenem system. The POM ester group was found to be suitable for the cyclization conditions.

Key words carbapenem; synthesis; intramolecular Wittig-type reaction; pivaloyloxymethyl ester; diethyl ethylphosphonite; prodrug

Carbapenem antibiotics such as imipenem,[2)] panipenem[3)] and meropenem[4)] have been widely used for treatment of severe infectious diseases. These compounds have been developed for parenteral use, and no carbapenem has yet been used for the purpose of oral administration. Recently, orally active antibiotics with potent activity are of much interest in the clinical realm because oral administration with lower dosage is sometimes therapeutically advantageous. The title compound, CS-834[5)] is now under clinical study as an oral antiinfective drug as are GV118819[6)] and L-084.[7)] CS-834 is a pivaloyloxymethyl (POM) ester-type prodrug of the active metabolite R-95867 that possesses a 1β-methylcarbapenem skeleton with a (*R*)-5-oxopyrrolidin-3-ylthio substituent at the C-2 position as shown in Chart 1 and exhibits highly potent antibacterial activity.

Synthesis of the active component, R-83201, which is a sodium salt of R-95867, was initially performed according to the conventional procedure developed by Merck researchers[8)] starting from the carboxylic acid **1**[9)] *via* the reaction sequence **2**→**3**→**5**→**6** as shown in Chart 2.[5)] The carboxy group of R-83201 thus obtained was esterified with POM iodide[10)] in *N*,*N*-dimethylacetamide to give the POM ester, CS-834. In order to obtain CS-834 by a shorter route based on the Merck procedure, some attempts to provide the intermediate POM ester corresponding to the *p*-nitrobenzyl (PNB) ester **2** or **3** were tried, but all failed.[11)] Then, our attention was focused on finding an alternative method for efficient synthesis of CS-834. One method we found was an intramol-

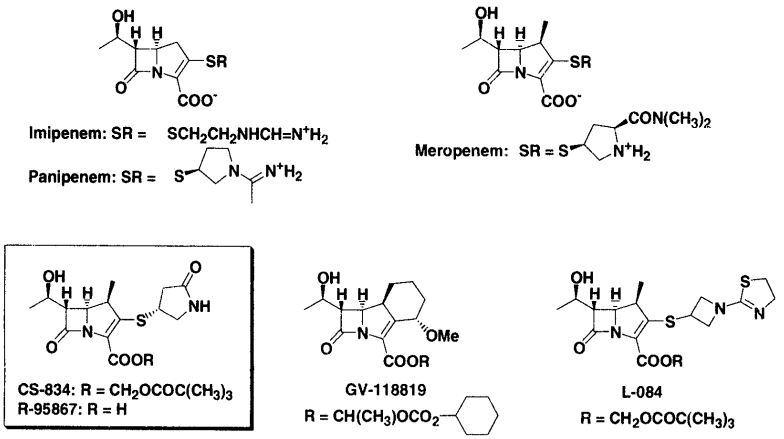

Chart 1

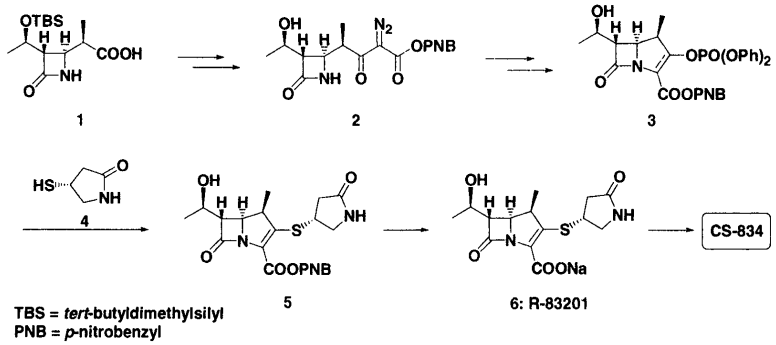

Chart 2

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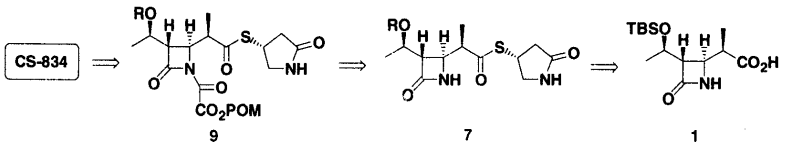

Chart 3

ecular Wittig-type reaction developed at our laboratories for construction of the carbapenem skeleton.[12]

In this paper, we wish to report a short-step synthesis of CS-834 by application of the procedure involving an intramolecular Wittig-type reaction in which the carboxy group is protected as a POM ester.

Results and Discussion

A new synthetic route to CS-834 based on the Wittig-type reaction for the construction of its skeleton is shown in Chart 3. Efficient synthesis of POM ester-type prodrugs, such as CS-834, is achieved by utilizing the POM group as a protecting group of carboxylic acid at an early stage of the synthesis.

We first tested the feasibility of the intramolecular Wittig-type reaction to construct the carbapenem skeleton with an oxopyrrolidinylthio moiety at the C-2 position using a PNB ester as the protecting group of the carboxylic acid (Chart 4). The thioester **7a** was prepared by condensation of the acid **1** and the mercaptan **4**[5] using *N*,*N*-carbonyldiimidazole (CDI) in acetonitrile (CH_3CN) in 86% yield. Initial attempts to form the oxalimide **9a** by treatment of **7a** with 1 eq of *p*-nitrobenzyloxyoxalyl chloride in the presence of triethylamine (Et_3N) resulted in formation of the undesired product **8**. *N*-Oxalylation occurred only at the γ-lactam of **7a**, not at the β-lactam. Therefore, it was necessary to mask the NH group of the γ-lactam before oxalylation. Selective *N*-silylation of the γ-lactam ring and subsequent *N*-oxalylation of the β-lactam ring were successfully carried out as follows. The thioester **7a** was treated with 1 eq of trimethylsilyl chloride (TMSCl) in the presence of Et_3N in CH_2Cl_2 at 0 °C, followed by addition of 2.5 eq of *p*-nitrobenzyloxyoxalyl chloride at −20 °C and then an aqueous workup to afford the desired product **9a** in 73% yield. The oxalimide **9a** was treated with 10 eq of triethyl phosphite in toluene at 60 °C for 3 h under a nitrogen atmosphere to afford the ylide **10a**. After removal of excess triethyl phosphite and solvent under reduced pressure, **10a** was heated in mesitylene at 163 °C for 8 h to give the desired compound **11a** in 71% yield. Instead of triethyl phosphite, diethyl ethylphosphonite[13a,b] was examined for the cyclization of **9a**. Formation of the ylide **10b** easily occurred by treatment of **9a** with 4 eq of diethyl ethylphosphonite at room temperature for 0.5 h, and subsequent cyclization of **10b** to **11a** was more readily achieved by heating in mesitylene at 163 °C for 3 h in 81% yield.

From the above results, we were convinced that the Wittig-type reaction was utilizable for a more straightforward synthesis of CS-834. Thus, the *tert*-butyldimethylsilyl (TBS) group in **7a** was exchanged *via* the alcohol **7b** to the TMS or triethylsilyl (TES) group as in **7c** or **7d** with the intention of more easily deprotecting this group after construction of the carbapenem skeleton (Chart 5). Treatment of **7b** with TMSCl and TESCl in the presence of Et_3N in *N*,*N*-dimethylformamide (DMF) afforded **7c** and **7d** in 89% and 79% yield, respectively. [(Pivaloyloxy)methyloxy]oxalyl chloride (**13**) was prepared from oxalic acid in two steps as follows.[14] Treatment of oxalic acid with POM iodide in the presence of Et_3N gave pivaloyloxymethyl oxalic acid mono-ester **12** as a crude oil. The unreacted oxalic acid and the crystalline by-product, bis(pivaloyloxymethyl) oxalate, were easily removed by washing with water and filtration, respectively. The acid **12** was treated with oxalyl chloroide in CH_2Cl_2 to give the acid chloride **13**. Selective oxalylation on the β-lactam ring of **7c** to **9b** using **13** was initially performed in a manner similar to

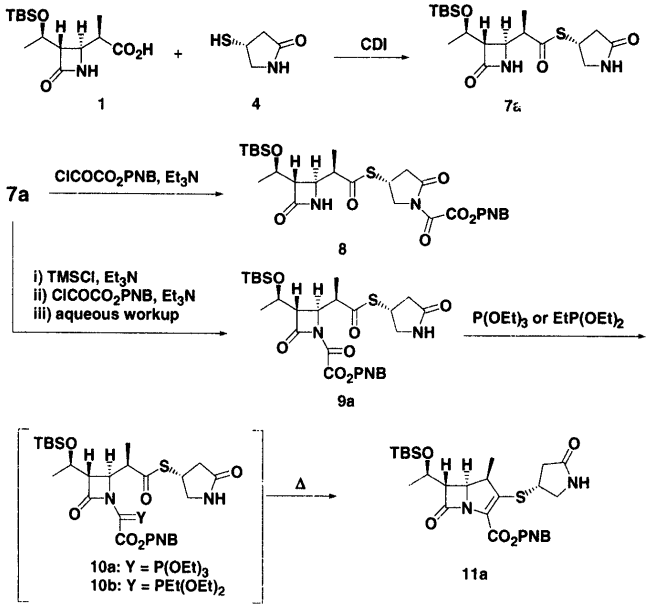

Chart 4

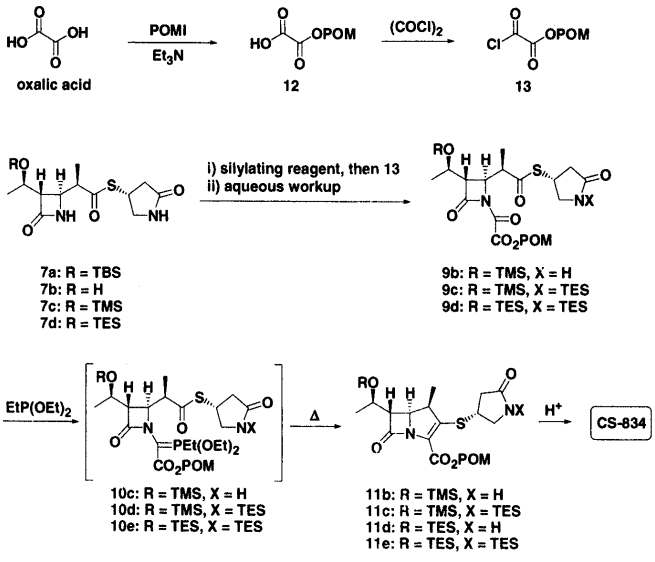

Chart 5

that described for **9a**. Reaction of **7c** with 1 eq of TMSCl in the presence of Et_3N in CH_2Cl_2 at 0 °C, followed by treatment with 3 eq of **13** at −20 °C afforded **9b** in 58% yield. The same reaction using TESCl instead of TMSCl gave the *N*-silylated oxalimide **9c** in 58% yield. The N–TES bond in **9c** was found to be stable during the usual aqueous workup and silica gel chromatography. In order to simplify the procedure to prepare **9b** from the alcohol **7b**, a one-pot synthesis was examined. Treatment of **7b** with 2 equivalents of TMSCl in a mixed solvent of DMF and CH_2Cl_2, followed by addition of **13**, provided **9b** in 43% yield. The yield was, however, lower than the stepwise preparation (**7b**→**7c**→**9b**, 52%). We observed partial hydrolysis of the N–oxalyl bond of **9b** and **9c** during chromatography on silica gel, and this appears to be the reason for the relatively low isolated yields of **9b** and **9c**. On the other hand, the oxalimide **9d** was stable on silica gel and prepared in a high yield (88% from **7d**). The imide **9d** possesses a relatively bulky substituent, a (triethylsilyloxy)ethyl group, at the C-3 position of the β-lactam ring, which might retard hydrolysis of the N–oxalyl bond and contribute to stabilization of the molecule.

With the oxalimides **9b**—**d** in hand, we subjected them to the intramolecular Wittig-type reaction to construct the skeleton of CS-834. In a way similar to that described for cyclization of **9a** to **11a**, the oxalimides **9b**—**d** were treated with 6 eq of triethyl phosphite in toluene at 60 °C for 3 h under a nitrogen atmosphere to afford the corresponding triethoxy phosphorus ylides, whose heating in mesitylene at 163 °C gave, contrary to our expectations, only the complex mixture. The functionality of the POM ester was found not to be stable under these reaction conditions when the ylide was derived from triethyl phosphite. After this, a more efficient reagent for the Wittig-type reaction, diethyl ethylphosphonite, was examined for the cyclization of **9b**. Formation of the ylide **10c** occurred easily by treating **9b** with 3 eq of diethyl ethylphosphonite at room temperature for 0.5 h, and subsequent cyclization of **10c** readily proceeded by heating in mesitylene at 163 °C for 3 h to give **11b** in 86% yield. Hydrolysis of **11b** with 1 N HCl in CH_3CN at 0 °C for 5 min afforded a crude solid, which was recrystallized from ethyl acetate, to afford CS-834 in 88% yield. Oxalimides **9c** and **9d**, of which nitrogen atoms of the γ-lactam rings are protected with a TES group, were similarly treated with diethyl ethylphosphonite, and the resulting ylides **10d** and **10e** were cyclized by heating to give the carbapenems **11c** and **11e**, respectively, which were accompanied by the respective *N*-desilylated compounds **11b** and **11d**. These carbapenems were desilylated by treatment with 1 N HCl in CH_3CN at 0 °C to give the crude product, of which recrystallization afforded CS-834 in a pure form in 74% and 84% yield from the oxalimides **9c** and **9d**, respectively.

Conclusion

Application of the intramolecular Wittig-type reaction to the POM ester oxalimide intermediate enabled shortening of the synthetic route to CS-834 starting from the carboxylic acid **1** (45% overall yield in 6 steps), whereas the original route to CS-834 from **1** *via* **3** (as shown in Chart 2) required 8 steps and the overall yield was *ca.* 25%.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX-270 (270 MHz) spectrometer. Chemical shifts are shown in ppm downfield from internal tetramethylsilane in $CDCl_3$ or sodium 2,2-dimethyl-2-silapentane-5-sulfonate in D_2O. The abbreviations used in ^{1}H-NMR data are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dq, doublet of quartets; br, broad; m, multiplet. Infrared (IR) spectra were recorded on a JASCO A-102, FT/IR-8300 or FT/IR-8900 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 spectrometer at 25 °C. Mass spectra (MS) were obtained on a JEOL JMS-D300 or JMS-AX505H spectrometer. Chromatography columns were prepared with Silica gel 60 (230—400 mesh, E. Merck) or Cosmosil 75C_{18}-PREP (Nacalai Tesque). Flash chromatography on silica gel was carried out using a Lobar® pre-packed glass column Size A (LiChroprep® Si60, E. Merck).

(3*S*,4*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-[[(*R*)-2-oxopyrrolidin-4-ylthio]carbonyl]ethyl]-2-azetidinone (7a) A suspension of **1** (1.04 g, 3.45 mmol) and CDI (567 mg, 3.50 mmol) in CH_3CN (20 ml) was stirred at room temperature for 1 h. To the resulting clear solution was added a solution of **4** (404 mg, 3.45 mmol) in CH_3CN (2 ml) at 0 °C and the mixture was stirred at the same temperature for 15 h. After the solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate, and the solution was washed successively with water, a saturated aqueous solution of sodium hydrogen carbonate and brine. The organic layer was dried over magnesium sulfate and filtered. After evaporation under reduced pressure, the residual crude product was purified by recrystallization from ethyl acetate–diisopropyl ether to give **7a** (1.18 g, 86%) as colorless crystals, mp 139—141 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 1.16 (3H, d, J=6.6 Hz), 1.26 (3H, d, J=7.3 Hz), 2.31 (1H, dd, J=17.2, 5.9 Hz), 2.81 (1H, dd, J=17.2, 8.6 Hz), 2.88 (1H, m), 3.00 (1H, dd, J=4.3, 1.7 Hz), 3.30 (1H, dd, J=9.9, 5.3 Hz), 3.85—3.95 (2H, m), 4.10—4.30 (2H, m), 5.90 (1H, br s), 5.97 (1H, br s). IR (KBr) cm^{-1}: 3188, 3112, 1754, 1681. $[\alpha]_D$ −20° (c=0.66, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{32}N_2O_4SSi$: C, 53.97; H, 8.05; N, 6.99; S, 8.00. Found: C, 53.74; H, 8.19; N, 7.01; S, 8.07. MS (EI) *m/z*: 401 (M^++1), 385 (M^+-CH_3), 343 ($M^+-C_4H_9$).

(3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*R*)-1-[[(*R*)-2-oxopyrrolidin-4-ylthio]carbonyl]ethyl]-2-azetidinone (7b) A solution of **7a** (814 mg, 2.03 mmol) and boron trifluoride diethyl etherate (750 μl, 6.10 mmol) in CH_3CN (15 ml) was stirred at room temperature for 3 h, and then quenched with a saturated aqueous solution of sodium hydrogen carbonate. After removal of the solvent under reduced pressure, the residue was subjected to reversed phase column chromatography on a Cosmosil 75C_{18}-PREP (50 g) using a mixture of water and methanol (1 : 0 to 1 : 1) as the eluent. Collected fractions were concentrated under reduced pressure to give **7b** (522 mg, 90%) as needles, mp 164—165 °C (dec.). ^{1}H-NMR (D_2O) δ: 1.21 (3H, d, J=6.4 Hz), 1.25 (3H, d, J=7.0 Hz), 2.41 (1H, dd, J=17.7, 5.2 Hz), 2.96 (1H, dd, J=17.7, 8.9 Hz), 3.11 (1H, quintet, J=7.0 Hz), 3.20 (1H, dd, J=5.0, 2.0 Hz), 3.38 (1H, dd, J=11.3, 4.5 Hz), 3.80 (1H, dd, J=7.0, 2.0 Hz), 3.94 (1H, dd, J=11.3, 7.6 Hz), 4.15 (1H, dq, J=6.4, 5.0 Hz), 4.24 (1H, m). IR (KBr) cm^{-1}: 3378, 3317, 3203, 1746, 1702, 1673, 1655. $[\alpha]_D$ −44° (c=0.49, H_2O). *Anal.* Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.33; H, 6.34; N, 9.78; S, 11.20. Found: C, 50.37; H, 6.21; N, 9.57; S, 11.17. MS (EI) *m/z*: 287 (M^++1).

(3*S*,4*S*)-4-[(*R*)-1-[[(*R*)-2-Oxopyrrolidin-4-ylthio]carbonyl]ethyl]-3-[(*R*)-1-(trimethylsilyloxy)ethyl]-2-azetidinone (7c) To a solution of **7b** (65.9 mg, 2.30×10^{-4} mol) in DMF (3 ml) was added Et_3N (65 μl, 4.6×10^{-4} mol) and TMSCl (59 μl, 4.6×10^{-4} mol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. After a saturated aqueous solution of sodium hydrogen carbonate was added to the mixture, the product was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous solution of ammonium chloride, water and brine, and then dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel using a mixture of hexane, ethyl acetate and methanol (1 : 1 : 0→0 : 1 : 0→0 : 10 : 1) as the eluent to give **7c** (73.1 mg, 89%) as colorless needles, mp 124 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.12 (9H, s), 1.19 (3H, d, J=5.9 Hz), 1.25 (3H, d, J=7.3 Hz), 2.30 (1H, dd, J=17.2, 5.9 Hz), 2.81 (1H, dd, J=17.2, 9.2 Hz), 2.86 (1H, m), 3.01 (1H, dd, J=5.3, 2.0 Hz), 3.31 (1H, dd, J=9.9, 5.3 Hz), 3.80 (1H, dd, J=5.9, 2.0 Hz), 3.88 (1H, dd, J=9.9, 7.6 Hz), 4.05—4.25 (2H, m), 6.13 (1H, br s), 6.16 (1H, br s). IR (KBr) cm^{-1}: 3177, 3107, 1750, 1679. $[\alpha]_D$ −22° (c=0.51, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{26}N_2O_4SSi$: C, 50.25; H, 7.31; N, 7.81; S, 8.94. Found: C, 50.10; H, 7.16; N, 7.82; S, 9.20. MS *m/z*: 343 (M^+-CH_3).

(3*S*,4*S*)-4-[(*R*)-1-[[(*R*)-2-Oxopyrrolidin-4-ylthio]carbonyl]ethyl]-3-[(*R*)-1-(triethylsilyloxy)ethyl]-2-azetidinone (7d) To a solution of **7b**

(120 mg, 4.19×10^{-4} mol) in DMF (3 ml) was added Et_3N (70 μl, 5.0×10^{-4} mol) and TESCl (77 μl, 4.6×10^{-4} mol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. After a saturated aqueous solution of sodium hydrogen carbonate was added to the mixture, the product was extracted with ethyl acetate. The extract was washed successively with a saturated aqueous solution of ammonium chloride, water and brine, and then dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel using a mixture of ethyl acetate and methanol (1 : 0 to 10 : 1) as the eluent to give **7d** (133 mg, 79%) as colorless crystals, mp 139—141 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.60 (6H, q, J=7.9 Hz), 0.95 (9H, t, J=7.9 Hz), 1.18 (3H, d, J=6.6 Hz), 1.26 (3H, d, J=7.3 Hz), 2.31 (1H, dd, J=17.2, 6.6 Hz), 2.81 (1H, dd, J=17.2, 8.6 Hz), 2.88 (1H, m), 2.99 (1H, dd, J=4.3, 2.0 Hz), 3.30 (1H, dd, J=10.6, 4.6 Hz), 3.86 (1H, dd, J=5.9, 2.0 Hz), 3.89 (1H, dd, J=10.6, 6.9 Hz), 4.10—4.25 (2H, m), 6.20 (1H, br s), 6.30 (1H, br s). IR (KBr) cm^{-1}: 3180, 3110, 1760, 1717, 1685. $[\alpha]_D$ −19° (c=0.55, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{32}N_2O4SSi$: C, 53.97; H, 8.05; N, 6.99. Found: C, 53.70; H, 8.20; N, 7.03. MS (EI) *m/z*: 401 (M^++1), 371 ($M^+-C_2H_5$).

[(Pivaloyloxy)methyloxy]oxalyl Chloride (13) To a solution of oxalic acid (8.00 g, 88.8 mmol) and Et_3N (24.8 ml, 178 mmol) in DMF (100 ml) was added POM iodide (21.5 g, 89.0 mmol) at room temperature and the reaction mixture was stirred for 18 h. After addition of ethyl acetate (400 ml) the mixture was washed with water and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure. To this was added diisopropyl ether and the insoluble materials were filtered off. The filtrate was concentrated under reduced pressure to give the crude [(pivaloyloxy)methyloxy]oxalic acid **12** (7.96 g, 43 %) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s), 5.29 (2H, s), 8.06 (1H, br s). IR (neat) cm^{-1}: 3193, 2979, 1759. The crude acid **12** (254 mg, 1.25 mmol) thus obtained was dissolved in CH_2Cl_2 (1.5 ml), and oxalyl chloride (0.13 ml, 1.5 mmol) and a catalytic amount of DMF (*ca.* 0.05 ml) were added at 0 °C. This mixture was stirred at room temperature for 2 h, and concentrated under reduced pressure to give a crude **13** as a pale yellow oil (280 mg), which was immediately used without further purification for the next reaction. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s), 5.94 (2H, s).

(3*S*,4*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-[[(*p*-nitrobenzyl)oxy]oxalyl]-4-[(*R*)-1-[[(*R*)-2-oxopyrrolidin-4-ylthio]carbonyl]ethyl]-2-azetidinone (9a) To a solution of **7a** (220 mg, 5.50×10^{-4} mol) and Et_3N (84 μl, 6.0×10^{-4} mol) in CH_2Cl_2 (2 ml) was added TMSCl (76 μl, 6.0×10^{-4} mol) at 0 °C and the mixture was stirred at the same temperature for 10 min. After the reaction mixture was cooled at −20 °C, Et_3N (195 μl, 1.40 mmol) and a solution of *p*-nitrobenzyloxyoxalyl chloride (340 mg, 1.40 mmol) in CH_2Cl_2 (1 ml) were added. After being stirred at −20 °C for 20 min, a saturated aqueous solution of ammonium chloride was added to the reaction mixture and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, successively, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel using a 1 : 2 mixture of hexane and ethyl acetate as the eluent, giving **9a** (238 mg, 73%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: −0.05 (3H, s), 0.05 (3H, s), 0.78 (9H, s), 1.19 (3H, d, J=6.6 Hz), 1.28 (3H, d, J=7.3 Hz), 2.25 (1H, dd, J=17.2, 5.9 Hz), 2.76 (1H, dd, J=17.2, 8.6 Hz), 3.25 (1H, dd, J=10.6, 5.3 Hz), 3.50—3.65 (2H, m), 3.81 (1H, dd, J=10.6, 7.3 Hz), 4.16 (1H, m), 4.30 (1H, m), 4.42 (1H, dd, J=4.6, 3.3 Hz), 5.37 (1H, d, J=13.2 Hz), 5.43 (1H, d, J=13.2 Hz), 5.60 (1H, br s), 7.58 (1H, d, J=8.6 Hz), 8.24 (1H, d, J=8.6 Hz). IR ($CHCl_3$) cm^{-1}: 3214, 1807, 1759, 1704. $[\alpha]_D$ −88° (c=0.56, $CHCl_3$). *Anal.* Calcd for $C_{26}H_{37}N_3O_9SSi$: C, 52.42; H, 6.26; N, 7.05; S, 5.38. Found: C, 52.63; H, 6.29; N, 6.80; S, 5.09.

(3*S*,4*S*)-4-[(*R*)-1-[[(*R*)-2-Oxopyrrolidin-4-ylthio]carbonyl]ethyl]-1-[[(pivaloyloxy)methyloxy]oxalyl]-3-[(*R*)-1-(trimethylsilyloxy)ethyl]-2-azetidinone (9b) To a solution of **7c** (150 mg, 4.18×10^{-4} mol) and Et_3N (60 μl, 4.3×10^{-4} mol) in CH_2Cl_2 (1 ml) was added TMSCl (54 μl, 4.3×10^{-4} mol) at 0 °C and the mixture was stirred at the same temperature for 15 min. After the reaction mixture was cooled at −20 °C, Et_3N (180 μl, 1.29 mmol) and a solution of **13** (280 mg) in CH_2Cl_2 (1 ml) were added to the reaction mixture. After being stirred at −20 °C for 30 min, a saturated aqueous solution of ammonium chloride was added to the reaction mixture and extracted with ethyl acetate. The extract was washed successively with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel using a 1 : 2 mixture of hexane and ethyl acetate as the eluent, giving **9b** (132 mg, 58%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (9H, s), 1.21 (3H, d, J=6.7 Hz), 1.23 (9H, s), 1.26 (3H, d, J=6.7 Hz), 2.26 (1H, dd, J=17.2, 5.3 Hz), 2.79 (1H, dd, J=17.2, 8.6 Hz), 3.25 (1H, dd, J=10.6, 5.8 Hz), 3.50—3.65 (2H, m), 3.90 (1H, dd, J=10.6, 6.6 Hz), 4.10—4.30 (2H, m), 4.32 (1H, dd, J=4.6, 3.3 Hz), 5.89 (2H, s), 6.16 (1H, br s). IR ($CHCl_3$) cm^{-1}: 3445, 1810, 1755, 1700. $[\alpha]_D$ −89° (c=0.75, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{36}N_2O_9SSi$: C, 50.72; H, 6.66; N, 5.14. Found: C, 50.59; H, 6.86; N, 5.10.

(3*S*,4*S*)-4-[(*R*)-1-[[(*R*)-2-Oxo-1-(triethylsilyl)pyrrolidin-4-ylthio]carbonyl]ethyl]-1-[[(pivaloyloxy)methyloxy]oxalyl]-3-[(*R*)-1-(trimethylsilyloxy)ethyl]-2-azetidinone (9c) To a solution of **7c** (150 mg, 4.18×10^{-4} mol) and Et_3N (60 μl, 4.3×10^{-4} mol) in CH_2Cl_2 (1 ml) was added TESCl (73 μl, 4.3×10^{-4} mol) at 0 °C and the mixture was stirred at the same temperature for 15 min. After the reaction mixture was cooled at −20 °C, Et_3N (180 μl, 1.29 mmol) and a solution of **13** (280 mg) in CH_2Cl_2 (1 ml) were added. After being stirred at −20 °C for 30 min, a saturated aqueous solution of ammonium chloride was added to the reaction mixture and extracted with ethyl acetate. The extract was washed successively with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel using a 1 : 1 mixture of hexane and ethyl acetate as the eluent, giving **9c** (160 mg, 58%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (9H, s), 0.75—0.87 (6H, m), 0.96 (9H, t, J=7.3 Hz), 1.20 (3H, d, J=6.6 Hz), 1.23 (9H, s), 1.28 (3H, d, J=6.6 Hz), 2.34 (1H, dd, J=17.2, 6.6 Hz), 2.82 (1H, dd, J=17.2, 7.9 Hz), 3.27 (1H, dd, J=11.2, 5.3 Hz), 3.40—3.55 (1H, m), 3.52 (1H, br t, J=3.8 Hz), 3.80 (1H, dd, J=11.2, 7.3 Hz), 4,11 (1H, m), 4.25(1H, dq, J=6.6, 3.8 Hz), 4.34 (1H, dd, J=4.7, 3.8 Hz), 5.90 (2H, s). IR ($CHCl_3$) cm^{-1}: 1810, 1760, 1700, 1680. $[\alpha]_D$ −87° (c=0.56, $CHCl_3$). *Anal.* Calcd for $C_{29}H_{50}N_2O_9SSi_2$: C, 52.86; H, 7.65; N, 4.25. Found: C, 52.62; H, 7.40; N, 4.31.

(3*S*,4*S*)-4-[(*R*)-1-[[(*R*)-2-Oxo-1-(triethylsilyl)pyrrolidin-4-ylthio]carbonyl]ethyl]-1-[[(pivaloyloxy)methyloxy]oxalyl]-3-[(*R*)-1-(triethylsilyloxy)ethyl]-2-azetidinone (9d) To a solution of **7d** (170 mg, 4.24×10^{-4} mol) and Et_3N (63 μl, 4.5×10^{-4} mol) in CH_2Cl_2 (1 ml) was added TESCl (75 μl, 4.5×10^{-4} mol) at 0 °C and the mixture was stirred at the same temperature for 15 min. After the reaction mixture was cooled at −20 °C, Et_3N (180 μl, 1.29 mmol) and a solution of **13** (280 mg) in CH_2Cl_2 (1 ml) were added. After being stirred at −20 °C for 30 min, a saturated aqueous solution of ammonium chloride was added to the reaction mixture and extracted with ethyl acetate. The extract was washed successively with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using a 1 : 1 mixture of hexane and ethyl acetate as the eluent, giving **9d** (261 mg, 88%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.57 (6H, q, J=7.9 Hz), 0.75—0.85 (6H, m), 0.92 (9H, t, J=7.9 Hz), 0.96 (9H, t, J=7.9 Hz), 1.20 (3H, d, J=6.6 Hz), 1.23 (9H, s), 1.28 (3H, d, J=7.3 Hz), 2.34 (1H, dd, J=17.2, 6.6 Hz), 2.81 (1H, dd, J=17.2, 8.6 Hz), 3.27 (1H, dd, J=11.2, 5.3 Hz), 3.45—3.55 (1H, m), 3.53 (1H, br t, J=4.0 Hz), 3.80 (1H, dd, J=11.2, 7.3 Hz), 4.13 (1H, m), 4.30 (1H, m), 4.40 (1H, dd, J=4.6, 4.0 Hz), 5.89 (2H, s). IR ($CHCl_3$) cm^{-1}: 1810, 1755, 1700, 1675. $[\alpha]_D$ −82° (c=0.60, $CHCl_3$). *Anal.* Calcd for $C_{32}H_{56}N_2O_9SSi_2$: C, 54.83; H, 8.05; N, 4.00; S, 4.57. Found: C, 54.14; H, 7.95; N, 4.09; S, 4.46.

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methyl-2-[(*R*)-2-oxopyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate (11a)** a) A solution of **9a** (25.0 mg, 4.20×10^{-5} mol) and triethyl phosphite (70 mg, 4.2×10^{-4} mol) in toluene (0.1 ml) was stirred at 60 °C for 3 h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in mesitylene (5 ml), and refluxed for 8 h under a nitrogen atmosphere. After the solvent was removed *in vacuo*, the residue was subjected to column chromatography on silica gel (1 g) using ethyl acetate as the eluent to give **11a** (17.2 mg, 71%) as a solid.

b) A solution of **9a** (25.0 mg, 4.20×10^{-5} mol) and diethyl ethylphosphonite (purchased from Zeneca Inc., 25 mg, 1.7×10^{-4} mol) in toluene (0.3 ml) was stirred at room temperature for 0.5 h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in mesitylene (5 ml), and refluxed for 3 h under a nitrogen atmosphere. After the solvent was removed *in vacuo*, the residual crude product was purified by recrystallization from ethyl acetate–diisopropyl ether to give **11a** (19.5 mg, 81%), mp 186—191 °C (dec.) as pale yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (3H, s), 0.09 (3H, s), 0.87 (9H, s), 1.25 (3H, d, J=6.6 Hz), 1.28 (3H, d, J=7.3 Hz), 2.42 (1H, dd, J=17.3, 5.3 Hz), 2.81 (1H, dd, J=17.2, 7.9 Hz), 3.20—3.30 (2H, m), 3.35 (1H, dd, J=9.9, 5.3 Hz), 3.83 (1H, dd, J=10.6, 7.9 Hz), 4.04 (1H, m), 4.20—4.35 (2H, m), 5.25 (1H, d, J=13.9 Hz), 5.45 (1H, d, J=13.9 Hz), 5.49 (1H, br s), 7.65 (2H,

d, J=8.6 Hz), 8.22 (2H, d, J=8.6 Hz). IR (KBr) cm^{-1}: 3392, 1770, 1707. *Anal.* Calcd for $C_{27}H_{37}N_3O_7SSi$: C, 56.33; H, 6.48; N, 7.30. Found: C, 56.05; H, 6.36; N, 7.07.

(Pivaloyloxy)methyl (1*R*,5*S*,6*S*)-1-Methyl-2-[(*R*)-2-oxo-1-pyrrolidin-4-ylthio]-6-[(*R*)-1-(trimethylsilyloxy)ethyl]-1-carbapen-2-em-3-carboxylate (11b) A solution of **9b** (50.0 mg, 4.20×10^{-5} mol) and diethyl ethylphosphonite (33 mg, 1.7×10^{-4} mol) in toluene (0.3 ml) was stirred at room temperature for 0.5 h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in mesitylene (5 ml), and refluxed for 3 h under a nitrogen atmosphere. After being cooled, the reaction mixture was passed through a short column of silica gel (500 mg) using a 10 : 1 mixture of ethyl acetate and methanol as the eluent. The eluate was concentrated under reduced pressure and left the crude product, which was purified by recrystallization from diisopropyl ether–hexane to give **11b** (40.5 mg, 86%) as colorless crystals, mp 74—76 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.14 (9H, s), 1.22 (9H, s), 1.27 (6H, d, J=6.6 Hz), 2.40 (1H, dd, J=17.2, 5.3 Hz), 2.80 (1H, dd, J=17.2, 8.6 Hz), 3.21 (1H, dd, J=6.6, 2.6 Hz), 3.24 (1H, m), 3.35 (1H, dd, J=9.9, 5.3 Hz), 3.82 (1H, dd, J=9.9, 7.9 Hz), 4.03 (1H, m), 4.16 (1H, dd, J=9.6, 2.6 Hz), 4.21 (1H, m), 5.56 (1H, br s), 5.85 (1H, d, J=5.3 Hz), 5.94 (1H, d, J=5.3 Hz). IR (KBr) cm^{-1}: 3272, 1780, 1755, 1702. $[\alpha]_D$ +46° (c=0.20, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{36}N_2O_7SSi$: C, 53.88; H, 7.08; N, 5.46. Found: C, 53.73; H, 6.96; N, 5.27. MS (EI) *m/z*: 512 (M^+).

(Pivaloyloxy)methyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*R*)-2-oxo-1-pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate (CS-834) a) To a solution of **11b** (35.0 mg, 6.83×10^{-5} mol) in CH_3CN (0.5 ml) was added 1 N HCl (70 μl) at 0 °C. After stirring at 0 °C for 5 min, the mixture was treated with a saturated aqueous solution of sodium hydrogen carbonate, and the product was extracted with CH_2Cl_2, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by recrystallization from ethyl acetate to give CS-834 (26.5 mg, 88%) as colorless crystals, mp 188—190 °C (dec.).

b) A solution of **9c** (112 mg, 1.70×10^{-4} mol) and diethyl ethylphosphonite (75 mg, 5.0×10^{-4} mol) in toluene (0.5 ml) was stirred at room temperature for 30 min under a nitrogen atmosphere. The mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in mesitylene (10 ml), and refluxed for 3 h under a nitrogen atmosphere. After being cooled, the reaction mixture was passed through a short column of silica gel (1 g) using a 10 : 1 mixture of ethyl acetate and methanol as the eluent. The eluate was concentrated under reduced pressure to give an oily residue, which was dissolved in CH_3CN (1 ml), and 1 N HCl (0.3 ml) was added at 0 °C. After stirring at 0 °C for 30 min, the mixture was treated with a saturated aqueous solution of sodium hydrogen carbonate, and the product was extracted with CH_2Cl_2, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by recrystallization from ethyl acetate to give CS-834 (62.9 mg, 84%) as colorless crystals, mp 188—190 °C (dec.).

c) A solution of **9d** (94.5 mg, 1.35×10^{-4} mol) and diethyl ethylphosphonite (60 mg, 4.0×10^{-4} mol) in toluene (0.5 ml) was stirred at room temperature for 30 min under a nitrogen atmosphere. The mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in mesitylene (10 ml), and refluxed for 3 h under a nitrogen atmosphere. After being cooled, the reaction mixture was passed through a short column of silica gel (1 g) using a 10 : 1 mixture of ethyl acetate and methanol as the eluent. The eluate was concentrated under reduced pressure to give an oily residue, which was dissolved in CH_3CN (1 ml), and 1 N HCl (0.3 ml) was added at 0 °C. After stirring at 0 °C for 30 min, the mixture was treated with a saturated aqueous solution of sodium hydrogen carbonate, and the product was extracted with CH_2Cl_2, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by recrystallization from ethyl acetate to give CS-834 (44.1 mg, 74%) as colorless crystals, mp 188—190 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (9H, s), 1.28 (3H, d, J=7.3 Hz), 1.35 (3H, d, J=6.6 Hz), 2.32 (1H, br s), 2.40 (1H, dd, J=17.2, 5.8 Hz), 2.81 (1H, dd, J=17.2, 7.9 Hz), 3.26 (1H, dd, J=7.3, 2.6 Hz), 3.35 (1H, dd, J=10.6, 5.2 Hz), 3.84 (1H, dd, J=10.6, 9.5 Hz), 4.03 (1H, m), 4.15—4.30 (2H, m), 5.83 (1H, d J=5.5 Hz), 5.97 (1H, d, J=5.5 Hz), 6.09 (1H, br s). IR (KBr) cm^{-1}: 3335, 1763, 1752, 1717, 1692. $[\alpha]_D$ +40° (c=0.54, CH_3OH). *Anal.* Calcd for $C_{20}H_{28}N_2O_7S$: C, 54.53; H, 6.41; N, 6.36. Found: C, 54.31; H, 6.56; N, 6.22.

References and Notes

1) Some of the investigations described in this paper were presented at the 16th Symposium on Medicinal Chemistry, Nov. 1996, Toyama, Japan, the Pharmaceutical Society of Japan. See: Oida S., Mori M., Japan. Kokai Tokkyo Koho JP 96-59663, 5 Mar. 1996 [*Chem. Abstr.*, **124**, 316873*g* (1996)].
2) Leanza W. J., Windonger K. J., Miller T. M., Christensen B. G., *J. Med. Chem.*, **22**, 1435—1436 (1979).
3) Miyadera T., Sugimura Y., Hashimoto T., Tanaka T., Iino K., Shibata T., Sugawara S., *J. Antibiotics.*, **36**, 1034—1039 (1983).
4) Sunagawa M., Matsumura H., Inoue T., Fukasawa M., Kato M., *J. Antibiotics.*, **43**, 519—532 (1990).
5) Miyauchi M., Endo R., Hisaoka M., Yasuda H., Kawamoto I., *J. Antibiotics.*, **50**, 429—439 (1997).
6) Gaviraghi G., *Eur. J. Med. Chem.*, **30** (suppl.), 467s—478s (1995).
7) Abe T., Hayashi K., Mihira A., Satoh C., Tamai S., Yamamoto S., Hikida M., Kumagai T., Kitamura M., The 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, Sept. 1998, Abstr. No. F64, p. 249, American Society of Microbiology.
8) Shih D. H., Baker F., Cama L., Christensen B. G., *Heterocycles*, **21**, 29—40 (1984).
9) Berks A. H., *Tetrahedron*, **52**, 331—375 (1996) and references cited therein.
10) Bodor N., Sloan K. B., Kaminski J. J., Shih C., Pogany S., *J. Org. Chem.*, **48**, 5280—5284 (1983).
11) Recently another research group reported the synthesis of intermediate **3** in which the carboxyl and the hydroxyl groups were protected as POM ester and TBS ether forms, respectively. See: Sakurai O., Ogiku T., Takahashi M., Hayashi M., Yamanaka T., Horikawa H., Iwasaki T., *J. Org. Chem.*, **61**, 7889—7894 (1996).
12) Yoshida A., Tajima Y., Takeda N., Oida S., *Tetrahedron Lett.*, **25**, 2793—2796 (1984).
13) *a*) Budt K.-H., Fischer G., Hörlein R., Kirrstetter R., Lattrell R., *Tetrahedron Lett.*, **33**, 5331—5334 (1992); *b*) Budt K.-H., Hörlein R., Lattrell R., Wollmann T., Eur. Pat. Appl. EP476649, 25 Mar. 1992 [*Chem. Abstr.*, **116**, 255398*s* (1992)].
14) Another procedure for preparation of **13** is reported: Kaye R. L., Volkmann R. A., Lindner D. L., Eur. Pat. Appl. EP223397, 27 May 1987 [*Chem. Abstr.*, **109**, 92641*e* (1988)].