Synthetic Studies of Carbenem and Penem Antibiotics. V. 1) Efficient Synthesis of the 1β-Methylcarbenem Skeleton

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An efficient synthesis of 1β-methylcarbenem from the 1-(2-oxooazetidinyl)acetate 8 was developed by application of the Dieckmann reaction. Dieckmann-type cyclization of 8 and conversion to the enolphosphate 10 were achieved without epimerization to the 1α-methyl isomer in a one-pot procedure. Treatment with the mercaptan 22 after the phosphorylation resulted in a practical one-pot preparation of the 1β-methyl-carbenem derivative 23 from 8.

Keywords Dieckmann-type cyclization; 1β-methylcarbenem; 1β-methyl-2-oxocarbenem; epimerization; one-pot procedure; meropenem

A novel 1β-methylcarbenem antibiotic, meropenem 1, was discovered during an extensive search for new β-lactam antibiotics at our laboratories.2) Meropenem possesses potent antibacterial activities against a wide range of gram-positive and gram-negative bacteria including Pseudomonas aeruginosa, and is resistant to dehydropeptidase-I (DHP-I). Many methods for synthesizing the key intermediate 2 to 1β-methylcarbenemns have been reported.3) For construction of the 5-membered ring in the carbenem skeleton, the carbene insertion reaction with rhodium catalyst4a,b) and the intramolecular Wittig reaction5a-c) are well-known. However, these methods have some disadvantages for 1β-methylcarbenem synthesis. That is, epimerization at the C-1 position occurred readily during work-up of 1β-methyl-2-oxocarbenem 3,4d) obtained via the carbene insertion reaction. Further, the cyclization yield was rather low in the latter method due to the higher reaction temperature and the longer reaction time.4a) Therefore, we wished to find a superior method to construct the 1β-methyl-carbenem skeleton.

Another approach would be Dieckmann-type cyclization of 1-(2-Oxaoazetidinyl)acetates 4 and 6 could be converted to the carbenem 5 and 1,1-dimethylcarbenem 7 at quite low temperature (−78°C) (Fig. 2).6,7) but this method had not been used widely and had never been applied to the synthesis of 1β-methylcarbenemns. We considered that Dieckmann-type cyclization of 1-(2-oxooazetidinyl)acetate 8 might be a promising method to prepare the 1β-methylcarbenem skeleton, based on the following working hypothesis: 1) highly selective enolization at the 1α-position would be possible compared with the case of 4, since the acidity at the 1α-position was decreased by the substitution with the methyl group and more practical reaction conditions could be applied; 2) the metal enolate 9 could be obtained as a sole product and would be stable enough to prevent epimerization at the C-1 position because of the rigid structure due to chelation; 3) 9 could be converted into the enolphosphate 10 by direct trapping with diphenyl chlorophosphate (DCP) in a one-pot procedure (Chart 1). In this paper, we describe our work to develop an effective and practical synthetic method of 1β-methylcarbenemns, including 1, via Dieckmann-type cyclization of 8 as a key reaction.

Preparation of 1-(2-Oxooazetidinyl)acetates 8 In order to study the synthesis of 1β-methylcarbenemns by Dieckmann-type cyclization, the thioester derivatives 8a–c, 1-[3-1(R)-1-tert-butyldimethylsilyloxyethyl]-4-[(1R)-1-phenylthiocarbonylthethyl]-2-oxooazetidinyl]acet-
tates, were prepared as follows (Chart 2). Compound 12 was obtained by the treatment of (3S,4S)-4-[(1R)-1-benzylxoycarbonylthyl]-3-[(1R)-1-tert-butylidemethylsilyloxyethyl]-2-azetidinone 11 with tert-butyl bromoacetate under the conditions of 50% aqueous NaOH and triethylbenzylammonium chloride in dichloromethane (CH$_2$Cl$_2$) or sodium hydride (NaH) in tetrahydrofuran (THF) in 93% yield and quantitative yield, respectively. Hydrogenolysis of 12 over 10% palladium-carbon in EtOH gave the carboxylic acid 13 in quantitative yield. Compound 13 was transformed to the thioester 8a by treatment with N,N'-carbonyldimidazole or isopropyl chloroformate–triethylamine followed by treatment with thiophenol in quantitative yield. The removal of the tert-butylimethyisilyl (TBS) and tert-butyl groups was achieved by treatment of 8a with titanium tetrachloride and anisole in CH$_2$Cl$_2$ to give the carboxylic acid 14 in 86% yield. The treatment of 14 with p-nitrobenzyl bromide (PNB-Br) and γ-collidine in dimethylformamide (DMF) gave the PNB ester 15 in 93% yield. Silylation of 15 with tert-butylimethyisiloxane or trimethylchlorosilane afforded 8b (96%) or 8c (98%), respectively (Chart 2).

The 1α-methyl derivatives 17a, b were prepared from 4-[(1S)-1-benzylxoycarbonylthyl]-3-[(1R)-1-tert-butylidemethylsilyloxyethyl]-2-azetidinone 16 by means of the same reaction sequences as those from 11 to 8b (Chart 3).

### Dieckmann-Type Cyclization of 8
A preliminary study on the Dieckmann-type cyclization was carried out with regard to base and active ester. It was found that several bases such as sodium hydride (NaH), lithium diisopropylamide (LDA), lithium hexamethydisilazide (LiHMDS), potassium tert-butoxide and sodium methysulfanyl-
methide could be used in the cyclization reaction and that various active esters, i.e., phenylthioester, 2-pyridylthioester, 2,4,5-trichlorophenylester, imidazolide, etc., which were prepared from 11 and 16, could be converted into the cyclized products in the presence of NaH or LiHMDS. Further studies were performed using the phenylthio ester 8b and NaH because of their availability and easy handling. The reaction conditions, such as solvent, reaction temperature, reaction time and so on, were optimized. A typical reaction procedure was as follows: 8b was treated with NaH (2.2 eq) in a 4:1 mixture of toluene and THF for 2 h at -20 °C and usual work-up [quenching with buffer solution (pH 7.0), extraction with ethyl acetate (AcOEt) and concentration] gave the crude product in almost quantitative yield. The crude product was purified by column chromatography on silica gel to give the purified cyclized product in 89% yield. However, it was found that both the crude product and the purified product obtained above were mixtures of 18 and 19 in the ratios of 83:17 and 76:24, respectively, on the basis of the proton nuclear magnetic resonance (1H-NMR) spectra (Fig. 3). We considered that the ratio of 18 and 19 changed during work-up and/or purification judging from the results of analysis by high-performance liquid chromatography (HPLC).

It was confirmed that the epimerization of the methyl group took place not during the reaction but during the work-up, because: 1) the Dieckmann-type cyclization of 8b proceeded stereoselectively to afford the sodium enolate 9b and the cyclization of 17b also gave the sodium enolate 20 stereoselectively; 2) neither the formed sodium enolate 9b nor 20 epimerized at all and there was no tautomerization between the sodium enolate and the corresponding keto form in the reaction mixture, as judged from the 1H-NMR studies described below. First, it was found that the treatment of 8b with NaH in a 4:1 mixture of toluene-d₈ and THF-d₈ under ice-cooling after 1 h gave the sodium enolate 9b as a sole product in quantitative yield and the epimerization of 20 to 9b was not observed at all, even after standing at room temperature for 4 h, based on the 1H-NMR spectrum. Similar treatment of the 1α-methyl isomer 17b gave exclusively the corresponding sodium enolate 20 and the conversion of 20 to 9b was not observed at all. The treatment of 1β-methyl-2-oxocarbenan 18 with NaH under the same conditions was also performed for reference. The 1H-NMR spectrum measured after 1 h revealed a 1:1 mixture of 9b [H-6: δ 3.08 (br d, J=6.3 Hz), H-5: δ 3.92 (br d, J=7.9 Hz)] and 20 [H-6: δ 2.95 (br d, J=6.6 Hz), H-5: δ 3.45 (br d, J=7.6 Hz)] (Chart 4).

Consequently, the Dieckmann-type cyclization could be employed to construct the 1β-methylcarbapenem skeleton if the enolate 9 could be used in the next step, enolphosphorylation, without work-up. After our study was completed and a patent concerning this work was filed, similar Dieckmann-type cyclization with sodium hexamethyldisilazide and epimerization of the 1β-methyl group during purification of the products were reported by two other groups. 9b

Conversion to the Enolphosphate 10 Direct phosphorylation of 9b to the enolphosphate 10b in the Dieckmann-type reaction mixture, without work-up, was attempted by the treatment of the sodium enolate 9b with DCP. In this case, 2 mol eq of DCP should be needed because thiophenoxide ion formed by Dieckmann-type cyclization could also be phosphorylated by DCP. The treatment of 8b in the Dieckmann-type reaction mixture with 2.2 eq of DCP under ice-cooling for 1 h afforded a mixture of the desired product 10b and 21 in 70% and 22% yields, respectively (Chart 5). No 1α-methyl derivatives corresponding to 10b and 21 were observed in the mixture of products. Next, 1 eq of DCP was added first and a further 1 eq of DCP was added after an interval of 30 min. In this case, 10b and 21 were obtained in 41% and 55% yields, respectively. From these results, it was considered difficult to achieve the phosphorylation of 9b by a mere treatment of the reaction mixture with DCP without the formation of 21, which is generated by the reaction between 10b and thiophenoxide ion. Therefore, thiophenoxide ion should be removed completely before the addition of DCP to develop a one-pot procedure. We sought an efficient scavenger of thiophenoxide ion and found that alkylation reagents such as methyl iodide and benzyl bromide gave a good result under the same reaction conditions as used.

![Chart 3](image)

![Chart 4](image)
in the cyclization step. After the treatment of the reaction mixture with benzyl bromide and confirmation of the disappearance of thiophenoxide ion, 1 eq of DCP was added to the reaction mixture to furnish the desired enolphosphate 10b in 90% yield.

**One-Pot Synthesis of Meropenem from 8** The generation of 21 in the phosphorylation described above demonstrated that the reaction of 10b with the mercaptan 22 readily proceeded under the reaction conditions of phosphorylation to afford the 1β-methylcarbapenem 23a, which is protected meropenem (Chart 6). We considered that the synthesis of 23a from 8b by a one-pot procedure might be more facile and might improve the total yield. Therefore, we examined the following reaction sequence in one pot: cyclization, phosphorylation with DCP and treatment with the mercaptan 22. The three-step conversion of 8b was performed using NaH as a base and methyl iodide as a scavenger of thiophenoxide ion in a 4:1 mixture of toluene and THF at -20°C. That is, after the completion of phosphorylation, the mercaptan 22 (1 eq) and NaH (1 eq) were added to the resulting mixture and the whole was stirred for 2 h at the same temperature to afford the product 23a in 57% yield from 8b. The low overall yield of the three-step conversion seemed to be due to the last step, introduction of the C-2 side chain, because the conversion to the enolphosphate 10b was achieved in a quite high yield. Therefore, in order to improve the yield, an appropriate base for the last step was sought. By using 1,8-diazabicyclo[5.4.0]jundec-7-ene (DBU) in place of NaH at the last step, the overall yield from 8b to 23a was eventually increased to 86%.

Finally, we investigated the protecting group of the hydroxy group at the C-8 position. It was found that protection of the 1-hydroxyethyl moiety in the 2-azonetidinone 8 was essential in the Dieckmann-type cyclization because the cyclization of 15, in which the hydroxy group was not protected, failed completely under the same reaction conditions as used for the cyclization of 8. It was considered that the trimethylsilyl (TMS) group could be more appropriate than the TBS group because of its ease of removal and its compatibility with the rest of the chemistry. The three-step conversion of the TMS ether 8c was performed similarly to that of 8b to afford the protected meropenem 23b in 83% yield. The desilylation of 23b proceeded smoothly in an acidic medium (pH 3.0) to provide 23c, the precursor of 1, in 89% yield. The deprotection of PNB and p-nitrobenzylxycarbonyl (PNZ) groups in 23c could be achieved by hydrogenolysis over 10% palladium–carbon in aqueous THF as reported before.

An efficient synthesis of 1β-methylcarbapenem 1 was accomplished by a one-pot procedure consisting of Dieckmann-type cyclization of the 1-(2-oxazetidinyl)acetate 8e, phosphorylation of the formed sodium enolate
9e and successive reaction between the mercapto 22 and the enolphosphate 10c, known as a versatile intermediate for the synthesis of 1,6-methylenecarboxenem antibiotics. The present process should be widely applicable to the practical synthesis of 1,6-methylenecarboxenem antibiotics, including I.

Experimental

Melting points were measured using a Thomas-Hoover capillary melting point apparatus without correction. Infrared (IR) spectral measurements were carried out with a Perkin Elmer 2000 FT IR spectrophotometer. Atoms in acetonitrile (10 ml). After being washed with water, the reaction mixture was diluted with AcOEt and washed with 1 N HCl (20 ml). The aqueous layer was extracted twice with AcOEt. The organic layers were combined, washed with water, dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by silica gel chromatography to give 11 as a colorless solid (1.17 g, 90%). The IR \(\nu\) and \(^1\)H-NMR spectral data were identical with those reported.\(^{40}\)

(35AS)-4-[((1R)-1-Benzoxycarbonyl-3)-(1R,1'-tert-butyldimethylsilyloxy-2)]-azetidine (11) \(K_2\) CO\(_3\) (916 mg, 6.64 mmol) was added to a mixture of 2\(^\circ\) (1.0 g, 3.2 mmol) and benzyl bromide (681 mg, 3.98 mmol) in acetonitrile (10 ml). After being washed with water, the reaction mixture was diluted with AcOEt and washed with 1 N HCl (20 ml). The aqueous layer was extracted twice with AcOEt. The organic layers were combined, washed with water, dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by silica gel chromatography to give 12 as a viscous oil (908 mg, 93%). \(\nu\) and \(^1\)H-NMR spectra were measured with 1 F01, F0X 900 (90 MHz) and F0X 270 (270 MHz) spectrometers, in the designated solvents, using tetramethylsilane as an internal reference (\(\delta\)-values). Mass spectrometry (MS) was taken with a Hitachi M-80B mass spectrometer. Measurements of optical rotation were performed with JASCO DIP-181 and DIP-370 digital polarimeters. Silica gel 60 (70–230 mesh, E. Merck) was used as an adsorbent for column chromatography. Preparative thin layer chromatography (preparative TLC) was performed on Silica gel F\(_{254}\) TLC plates (E. Merck).

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(3S)-3-(1R,1-tert-Butylidimethylsilyloxy)-1-[(p-nitrobenzyl)oxy carbonylmethyl]-4-(1R,1-phenylthiocarbonylmethyl)-2-azetidine (17b) In the same manner as described for the preparation of 8b, 17b was obtained from 14. mp 101–103°C. [α]25 +5.6° (c 0.200, CHCl3). IR (KBr): 1768, 1734, 1696, 1525 cm–1. 1H-NMR (CDCl3): δ 0.04 (3H, s), 0.71 (3H, s), 0.86 (1H, s), 1.27 (3H, d, J = 5.9 Hz), 1.37 (3H, d, J = 7.3 Hz), 2.88 (1H, dd, J = 2.1, 6.4 Hz), 3.01 (1H, m), 3.93–4.3 (4H, m), 5.15–5.23 (2H, m), 7.35–7.5 (7H, m), 8.14 (2H, d, J = 8.6 Hz), 1.37 (3H, d, J = 7.3 Hz). 19F-NMR (CDCl3, δ 0.04 (3H, s), 0.71 (3H, s), 0.86 (1H, s), 1.27 (3H, d, J = 5.9 Hz), 1.37 (3H, d, J = 7.3 Hz), 2.88 (1H, dd, J = 2.1, 6.4 Hz), 3.01 (1H, m), 3.93–4.3 (4H, m), 5.15–5.23 (2H, m), 7.35–7.5 (7H, m), 8.14 (2H, d, J = 8.6 Hz). 1H-NMR (CDCl3, δ 0.08 (3H, s), 0.10 (3H, s), 0.88 (1H, s), 1.21 (3H, d, J = 7.9 Hz), 1.27 (3H, d, J = 6.3 Hz), 2.33 (1H, m), 3.17 (1H, dd, J = 1.7, 5.9 Hz), 3.68 (1H, dd, J = 2.0, 8.3 Hz), 4.30 (1H, m), 4.81 (1H, d, J = 0.7 Hz), 5.29 (2H, m), 7.53 (2H, d, J = 8.9 Hz), 8.24 (2H, d, J = 8.9 Hz). 1H-NMR Study of Dieckmann-Type Cyclization The following experiments were performed in toluene-d8 tubes for 1H-NMR measurement, and the products were observed directly by measurement of the 1H-NMR spectra with a JEOL GX-270 (270 MHz) spectrometer. (a) Dieckmann-Type Cyclization: A solution of 8b (30 mg, 0.055 mmol) in toluene-d8 and THF-d4 (4:1, 1 ml) was treated with 60% NaH (4.4 mg, 0.065 mmol) at 0°C for 1 h under ultrasonic agitation to give a solution of 9b, then the 1H-NMR spectrum was measured. 1H-NMR (toluene-d8, THF-d4 = 4:1) δ: 3.57 (1H, brs, H4), 3.91 (1H, brd, J = ca. 8 Hz, H2). Treatment of 17b (30 mg, 0.05 mmol) by the same procedure gave a solution of 20. 1H-NMR (toluene-d8, THF-d4 = 4:1) δ: 2.91 (1H, brs, H4), 3.44 (1H, brd, J = ca. 8 Hz, H2). (b) Sodium Etolate Formation from 18: A solution of 18 (23 mg, 0.05 mmol), which was prepared by the carbene insertion method, in toluene-d8 and THF-d4 (4:1, 1 ml) was treated with 60% NaH (4.4 mg, 0.065 mmol) at 0°C for 1 h under ultrasonic agitation to give a 1:1 mixture of 9b and 20b. 1H-NMR (toluene-d8, THF-d4 = 4:1) δ: 2.95 (1H, s, brd, J = 6.6 Hz), 3.08 (1H, s, brd, J = 6.3 Hz), 3.45 (1H, s, brd, J = 7.9 Hz), 3.92 (1H, s, brd, J = 7.9 Hz). 1H-NMR (4R,5R,6S)-6-(1R,1-tert-Butylidimethylsilyloxy)-4-methyl-3-dioxy-1-azoxy-3-methyl-4(3H)-oxazolidinone (10b) and 3-diphenylphosphorylazo-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylate (10b) A solution of 8b (69 mg, 0.12 mmol) in dry toluene (0.6 ml) was added dropwise to a suspension of 50% NaH (12.5 mg, 0.26 mmol) in dry THF (0.1 ml) under ice-cooling, and the reaction mixture was stirred for 0.5 h. DCP (67 mg, 0.25 mmol) was added thereto under ice-cooling. The resultant mixture was stirred for 1 h, diluted with AcOEt (10 ml), washed with brine, dried over MgSO4 and K2CO3 (10:1), and concentrated in vacuo. The residue was purified by gel chromatography to give 10b (58 mg, 70%) and 21 (15 mg, 22%). 10b: IR (neat): 1775, 1725, 1518 cm–1. 1H-NMR (CDCl3): δ 0.06 (3H, s), 0.07 (3H, s), 0.86 (9H, s), 1.20 (H, d, J = 7.9 Hz), 1.23 (3H, d, J = 6.6 Hz), 2.39 (1H, d, J = 3.0, 5.6 Hz), 3.43 (1H, m), 4.21 (1H, dd, J = 3.0, 13.2 Hz), 4.22 (1H, m), 5.28 (2H, m), 7.1–7.5 (10H, m), 7.5–7.6 (2H, m), 8.1–8.2 (2H, m). 21: IR (neat): 1765, 1707, 1522 cm–1. 1H-NMR (CDCl3): δ 0.06 (6H, s), 0.08 (4H, s), 0.95 (3H, s), 1.17 (1H, d, J = 6.3 Hz), 3.06 (1H, m), 3.19 (1H, dd, J = 2.9, 5.0 Hz), 4.42 (2H, m), 5.42 (2H, m), 7.3–7.6 (5H, m), 7.69 (2H, d, J = 8.9 Hz), 8.23 (2H, d, J = 8.9 Hz). p-Nitrobenzyl (4R,5R,6S)-6-(1R,1-tert-Butylidimethylsilyloxy)-3-diphenylphosphorylazo-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylate 10b A solution of 8b (117 mg, 0.199 mmol) in a mixture of dry toluene and dry THF (1:1, 1 ml) was added dropwise to a suspension of 50% NaH (22 mg, 0.46 mmol) in a mixture of dry toluene and dry THF (1:1, 0.2 ml) at 20°C, followed by stirring at the same temperature for 1 h. A 2 m solution (0.1 ml) of Mel in THF was added thereto, and stirring was continued for 0.5 h. A solution of DCP (0.21 mmol) in dry toluene (0.1 ml) was added to the mixture at the same temperature, and stirring was continued for 1.5 h. The resultant mixture was diluted with AcOEt (20 ml), washed with brine, dried over MgSO4 and K2CO3 (10:1), and concentrated in vacuo. The residue was purified by gel chromatography to give 10b (95%). This compound (10b) was also prepared by using benzyl bromide instead of Mel as the alkylating reagent (90%). p-Nitrobenzyl (4R,5R,6S)-6-(1R,1-tert-Butylidimethylsilyloxy)-3-(3,3,5,5-tetramethyl-1,4-diazabicyclo[3.2.0]hept-2-en-2-carboxylate (3b) A solution of 8b (415 mg, 0.707 mmol) in a mixture of dry toluene and dry THF (1:1, 4 ml) was added dropwise to a suspension of 50% NaH (75 mg, 1.56 mmol) in a mixture of dry toluene and dry THF (1:1, 0.75 ml) at 20°C, and the whole was stirred at the same
temperature for 1 h. A 0.5 M solution (1.49 ml) of Mel in THF was added thereto, and stirring was continued for 0.5 h. A solution of DCP (218.5 mg, 0.81 mmol) in dry toluene (2.2 ml) was added to the mixture at the same temperature, and stirring was continued for 2 h. Thereafter, (35,55)-5-dimethylaminocarbonyl-3-mercapto-1-(p-nitrobenzoyloxy-carbonyl)pyrrolidine 22) (237.5 mg, 0.67 mmol) and 50% NaH (32.3 mg, 0.67 mmol) were added thereto, and stirring was continued for 2 h. The resultant mixture was diluted with AcOEt (50 ml), washed with brine, dried over MgSO4, and concentrated in vacuo. The residue was purified by silica gel chromatography to give 23a (329 mg, 57%). IR (neat): 1775, 1715, 1660, 1525 cm⁻¹. 1H-NMR (CDCl3) δ: 0.06–0.09 (6H, m), 0.85–0.87 (9H, m), 1.23–1.28 (6H, m), 1.94 (1H, m), 2.71 (1H, m), 2.94–3.10 (6H, m), 3.2–3.8 (4H, m), 4.0–4.4 (3H, m), 4.76 (1H, m), 5.0–5.5 (4H, m), 7.42–7.54 (2H, m), 7.60–7.67 (2H, m), 8.18–8.27 (4H, m).

This product (23a) was also prepared by using benzyl bromide as the alkylation reagent and DBU as a base in the last step (86%). 

p-Nitrobenzyl (4R,5S,6S)-3-[(35,55)-5-Dimethylaminocarbonyl-1-(p-nitrobenzoyloxy carbonyl)pyrrolidin-3-thioyl]-4-methyl-7-oxo-6-[(1R)-1-trimethylsilyloxyethyl]-1-azabicyclo[3.2.0]hept-2-en-2-carboxylate (23b)

Compound 23b was prepared from 8c by a similar procedure to that described for the preparation of 23a by using benzyl bromide as the alkylation reagent and DBU as a base in the last step (83%). [α]D 20 +42.2° (c = 0.200, CHCl₃). IR (KBr): 1775, 1715, 1654, 1522 cm⁻¹. 1H-NMR (CDCl3) δ: 0.06–0.13 (9H, m), 1.26 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 6.3 Hz), 1.95 (1H, m), 2.70 (1H, m), 2.85–3.15 (6H, m), 5.22 (2H, s), 7.35–7.77 (4H, m), 8.1–8.3 (4H, m). MS (SI) m/z: 770 (M⁺).

p-Nitrobenzyl (4R,5S,6S)-3-[(35,55)-5-Dimethylaminocarbonyl-1-(p-nitrobenzoyloxy carbonyl)pyrrolidin-3-thioyl]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylate (23c)

A phosphate buffer solution (pH 3; 8 ml) was added to a solution of 23b (1.0 g, 1.30 mmol) in THF (10 ml), and the resultant mixture was vigorously stirred at room temperature for 2.5 h. The reaction mixture was diluted with AcOEt (50 ml), washed with brine, dried over MgSO4, and concentrated in vacuo to give 23c (808 mg, 89%). The IR and 1H-NMR spectral data were identical with those reported. 23)

References and Notes
4) Other references are cited in the following review, Y. Ito, S. Terashima, Yuki Gosei Kagaku Kyokai Shiki, 47, 606 (1989).
11) Subsequent investigations showed that the hydrolysis of 23b in aqueous THF over 10% palladium-carbon directly provided 1 in a similar yield to that of the hydrolysis of 23c.