Synthetic Studies of Carbapenem and Penem Antibiotics. V.[1] Efficient Synthesis of the 1β-Methylcarbapenem Skeleton

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An efficient synthesis of 1β-methylcarbapenem from the 1-(2-oxoazetidinyl)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-methylcarbapenem derivative 23 from 8.

Keywords Dieckmann-type cyclization; 1β-methylcarbapenem; 1β-methyl-2-oxocarbapenam; epimerization; one-pot procedure; meropenem

A novel 1β-methylcarbapenem 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-methylcarbapenems have been reported.[3] For construction of the 5-membered ring in the carbapenem skeleton, the carbene insertion reaction with rhodium catalyst[4a,b] and the intramolecular Wittig reaction[5a-c] are well-known. However, these methods have some disadvantages for 1β-methylcarbapenem synthesis. That is, epimerization at the C-1 position occurred readily during work-up of 1β-methyl-2-oxocarbapenam **3**,[4c] 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.[3a] Therefore, we wished to find a superior method to construct the 1β-methylcarbapenem skeleton.

Another approach would be Dieckmann-type cyclization. 1-(2-Oxoazetidinyl)acetates **4** and **6** could be converted to the carbapenam **5** and 1,1-dimethylcarbapenam **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-methylcarbapenems. We considered that Dieckmann-type cyclization of 1-(2-oxoazetidinyl)acetate **8** might be a promising method to prepare the 1β-methylcarbapenem skeleton, based on the following working hypothesis: 1) highly selective enolization at the 1″-position would be possible compared with the case of **4**, since the acidity at the 1′-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-methylcarbapenems, including **1**, *via* Dieckmann-type cyclization of **8** as a key reaction.

Preparation of 1-(2-Oxoazetidinyl)acetates 8 In order to study the synthesis of 1β-methylcarbapenems by Dieckmann-type cyclization, the thioester derivatives (**8a—c**), 1-[3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[(1*R*)-1-phenylthiocarbonylethyl]-2-oxoazetidinyl]ace-

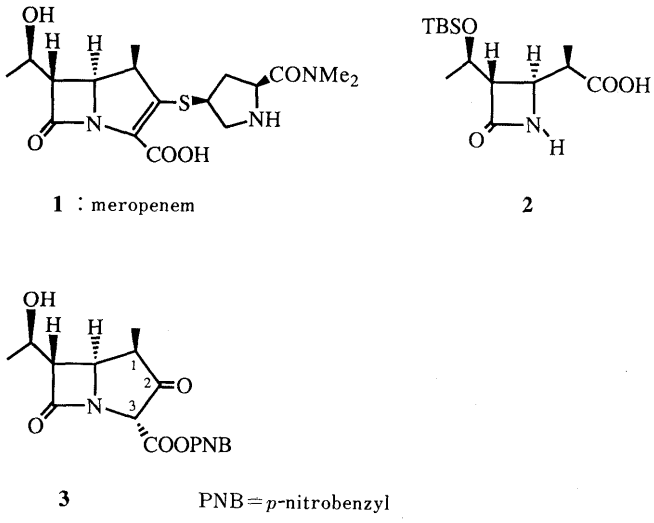


Fig. 1

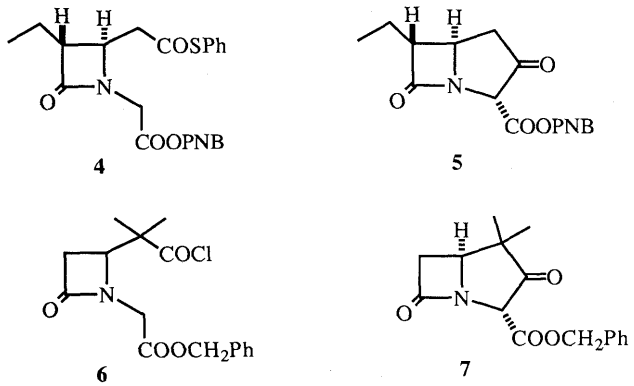
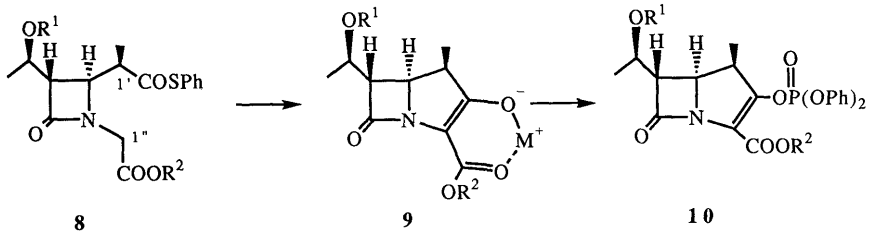


Fig. 2



R^1, R^2 = protecting group
M = metal atom

Chart 1

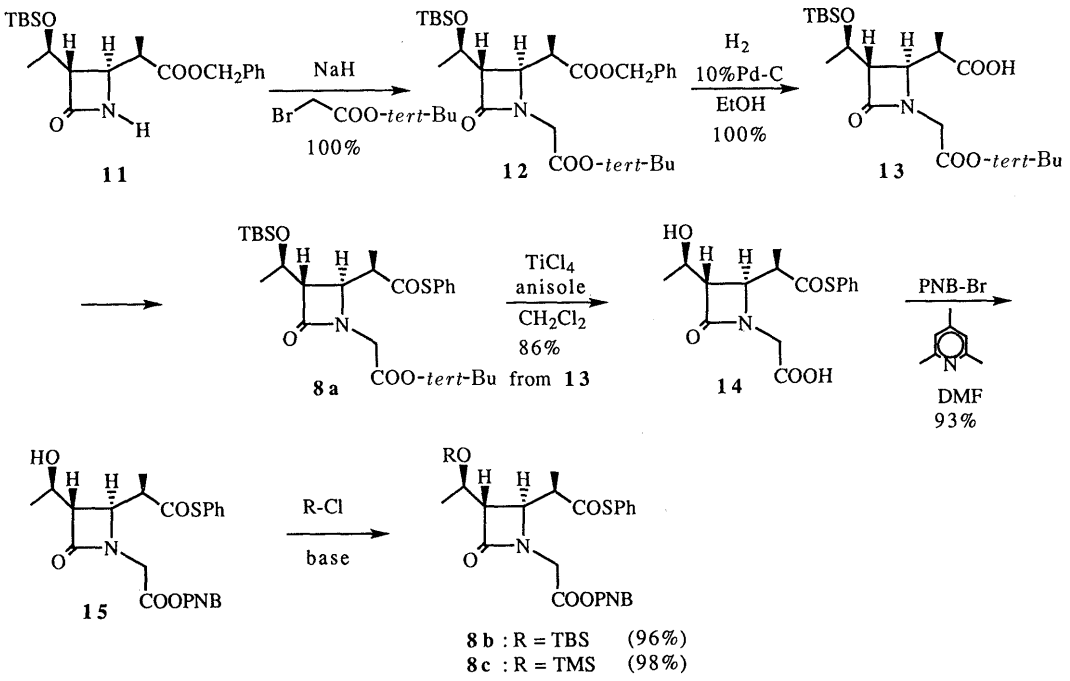


Chart 2

tates, were prepared as follows (Chart 2). Compound **12** was obtained by the treatment of (3*S*,4*S*)-4-[(1*R*)-1-benzyloxycarbonylethyl]-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone **11**[3d,f] with *tert*-butyl bromoacetate under the conditions of 50% aqueous NaOH and triethylbenzylammonium chloride in dichloromethane (CH_2Cl_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*′-carbonyldiimidazole or isopropyl chloroformate–triethylamine followed by treatment with thiophenol in quantitative yeild. The removal of the *tert*-butyldimethylsilyl (TBS) and *tert*-butyl groups was achieved by treatment of **8a** with titanium tetrachloride and anisole in CH_2Cl_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*-butyldimethylchlorosilane or trimethylchlorosilane afforded **8b** (96%) or **8c** (98%), respectively (Chart 2).

The 1α-methyl derivatives **17a, b** were prepared from

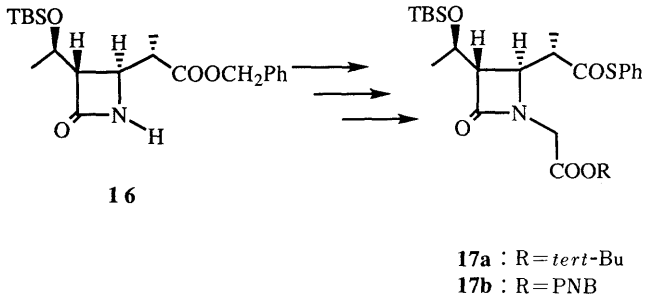


Chart 3

4-[(1*S*)-1-benzyloxycarbonylethyl]-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-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 hexamethyldisilazide (LiHMDS), potassium *tert*-butoxide and sodium methylsulfinyl-

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 (^{1}H-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 ^{1}H-NMR studies described below. First, it was found that the treatment of **8b** with NaH in a 4:1 mixture of toluene-d_8 and THF-d_8 under ice-cooling after 1 h gave the sodium enolate **9b** as a sole product in quantitative yield and the epimerization of **9b** to **20** was not observed at all, even after standing at room temperature for 4 h, based on the ^{1}H-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-oxocarbapenam **18** with NaH under the same conditions was also performed for reference. The ^{1}H-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,[8] 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.[9]

Conversion to the Enolphosphate 10 A 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 alkylating reagents such as methyl iodide and benzyl bromide gave a good result under the same reaction conditions as used

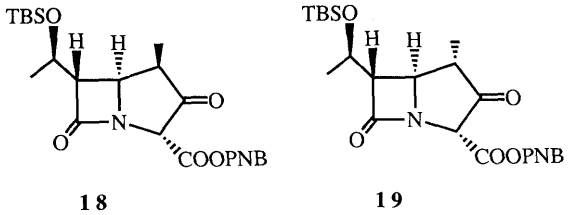


Fig. 3

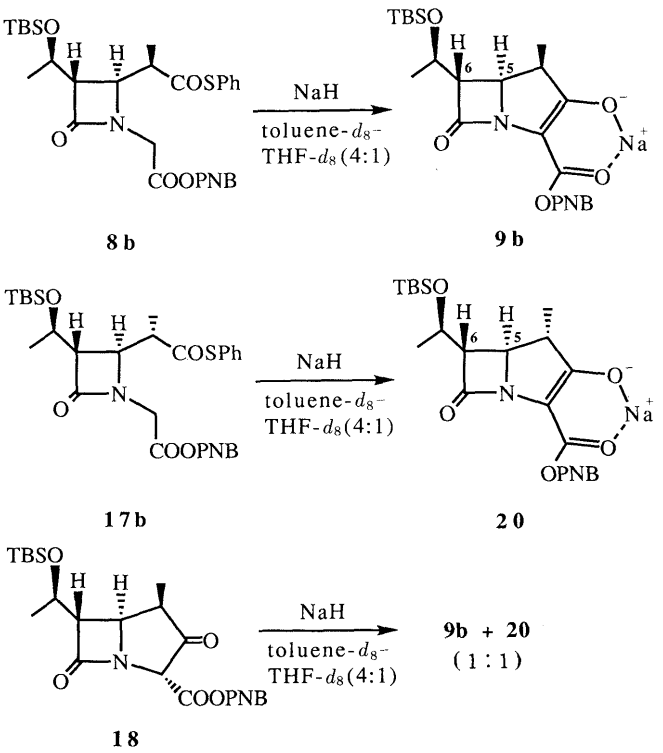


Chart 4

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**[2] 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 $-20\,^{\circ}C$. 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]undec-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-azetidinone **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**,[2] in 89% yield. The deprotection of PNB and *p*-nitrobenzyloxycarbonyl (PNZ) groups in **23c** could be achieved by hydrogenolysis over 10% palladium–carbon in aqueous THF as reported before.[2,10]

An efficient synthesis of 1β-methylcarbapenem **1** was accomplished by a one-pot procedure consisting of Dieckmann-type cyclization of the 1-(2-oxoazetidinyl)-acetate **8c**, phosphorylation of the formed sodium enolate

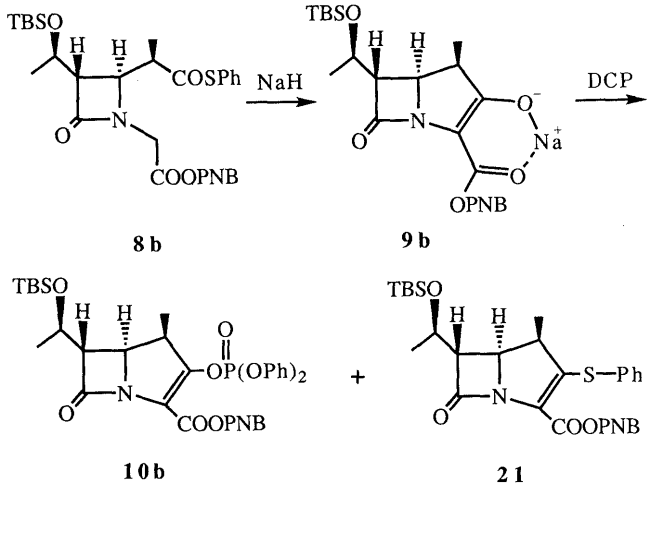


Chart 5

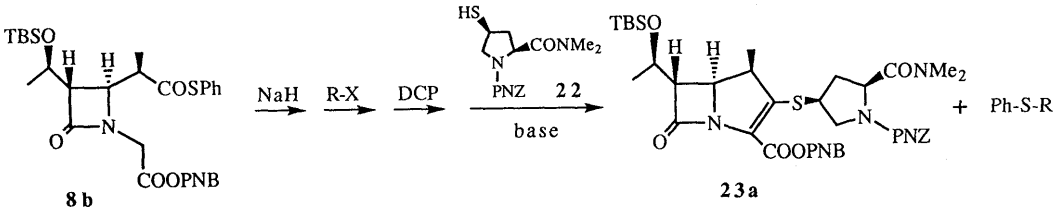


Chart 6

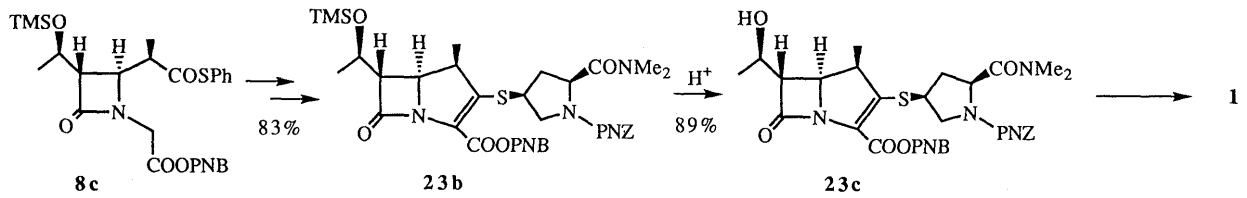


Chart 7

9c and successive reaction between the mercaptan **22** and the enolphosphate **10c**, known as a versatile intermediate for the synthesis of 1β-methylcarbapenem antibiotics. The present process should be widely applicable to the practical synthesis of 1β-methylcarbapenem antibiotics, including **1**.

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 spectrometer. ^{1}H-NMR spectra were measured with JEOL FX-90Q (90 MHz) and GX-270 (270 MHz) spectrometers, in the designated solvent, using tetramethylsilane as an internal reference (δ-values). Mass spectra (MS) were 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 60 F_{254} TLC plates (E. Merck).

(3*S*,4*S*)-4-[(1*R*)-1-Benzyloxycarbonylethyl]-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone (11) K_2CO_3 (916 mg, 6.64 mmol) was added to a solution of **2**[3f] (1.00 g, 3.32 mmol) and benzyl bromide (681 mg, 3.98 mmol) in acetone (10 ml). After being refluxed for 4 h, the reaction mixture was cooled and filtered. The filtrate 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 twice with brine, 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 and ^{1}H-NMR spectral data were identical with those reported.[3d]

(3*S*,4*S*)-4-[(1*R*)-1-Benzyloxycarbonylethyl]-1-(*tert*-butoxycarbonylmethyl)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone (12) To a solution of **11** (755 mg, 1.93 mmol) in CH_2Cl_2 (10 ml) were added successively *tert*-butyl bromoacetate (1.88 g, 9.64 mmol), 50% aqueous NaOH (620 mg), and triethylbenzylammonium chloride (220 mg), and the whole was stirred at room temperature for 2 h. The reaction mixture was diluted with water and Et_2O. The aqueous layer was separated from the organic layer and extracted twice with Et_2O. The extracts were combined with the organic layer, washed with water twice and brine three times, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **12** as a viscous oil (908 mg, 93%). $[\alpha]_D^{24}$ −14.7° (c=0.202, $CHCl_3$). IR (neat): 1755, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (3H, s), 0.07 (3H, s), 0.85 (9H, s), 1.23 (3H, d, J=6.3 Hz), 1.24 (3H, d, J=6.9 Hz), 1.44 (9H, s), 2.90 (1H, qd, J=6.9, 3.6 Hz), 2.99 (1H, dd, J=2.0, 6.6 Hz), 3.83 (2H, m), 5.10 (2H, s), 7.35 (5H, s). MS (FD) m/z: 506 (M^+).

Compound **12** could also be prepared by the folllowing procedure. A solution of **11** (705 mg, 1.80 mmol) and *tert*-butyl bromoacetate (422 mg, 2.2 mmol) in THF (4 ml) was added dropwise to a suspension of 60% NaH (87 mg, 2.2 mmol) in THF (2 ml) at −5 °C, and the whole was stirred at 0 °C for 2 h. The reaction mixture was diluted with water and AcOEt. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **12** (995 mg, quantitative yield).

(3*S*,4*S*)-1-(*tert*-Butoxycarbonylmethyl)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[(1*R*)-1-carboxyethyl]-2-azetidinone (13) A solution of **12** (450 mg, 0.89 mmol) in 99.5% EtOH (6 ml) was subjected to hydrogenation at room temperature in the presence of 10% palladium–carbon (90 mg) under atmospheric pressure, followed by filtration to remove the catalyst. The filtrate was evaporated *in vacuo* to give **13** as a colorless solid (370 mg, quantitative yield). mp 82.5—83.5 °C. $[\alpha]_D^{25}$ −37.5° (c=0.200, $CHCl_3$). IR (neat): 1760, 1740, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.24 (3H, d, J=6.3 Hz), 1.25 (3H, d, J=7.3 Hz), 1.48 (9H, s), 2.94 (1H, qd, J=7.1, 3.0 Hz), 3.04 (1H, dd, J=2.3, 5.5 Hz), 3.98 (2H, m), 4.00 (1H, m), 4.21 (1H, m). *Anal.* Calcd for $C_{20}H_{37}NO_6Si$: C, 57.80; H, 8.97; N, 3.37. Found: C, 57.71; H, 9.36; N, 3.34.

(3*S*,4*S*)-1-(*tert*-Butoxycarbonylmethyl)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[(1*R*)-1-phenylthiocarbonylethyl]-2-azetidinone (8a) A mixture of **13** (1.29 g, 3.10 mmol) and *N*,*N*′-carbonyldiimidazole (604 mg, 3.73 mmol) in dry MeCN (25 ml) was stirred at room temperature for 1 h. To this mixture were added successively a solution of thiophenol (410 mg, 3.73 mmol) in dry MeCN (6 ml) and a solution of triethylamine (Et_3N) (377 mg, 3.73 mmol) in MeCN (6 ml). The reaction mixture was stirred at room temperature for 0.5 h, diluted with AcOEt and dil. HCl, and extracted with AcOEt three times. The extracts were combined, washed with brine twice, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **8a** as a viscous oil (1.60 g, quantitative yield). $[\alpha]_D^{25}$ −52.1° (c=0.200, $CHCl_3$). IR (neat): 1760, 1740, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (3H, s), 0.11 (3H, s), 0.90 (9H, s), 1.27 (3H, d, J=6.9 Hz), 1.43 (9H, s), 3.04 (1H, m), 3.15 (1H, m), 3.7—3.9 (1H, m), 4.05—4.30 (3H, m), 7.37—7.43 (5H, m). MS (FD) m/z: 508 (M^+).

Compound **8a** could also be prepared by the following procedure. Et_3N (283 mg, 2.8 mmol) was added to a solution of **13** (831 mg, 2.0 mmol) in CH_2Cl_2 (3 ml) at 0 °C, and isopropyl chloroformate (343 mg, 2.8 mmol) was added dropwise thereto. The mixture was stirred for 1 h, thiophenol (309 mg, 2.8 mmol) was added, and stirring was continued for 1 h. The reaction mixture was diluted with AcOEt and dil. HCl and extracted with AcOEt three times. The extracts were combined, washed with brine twice, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **8a** (1.02 g, quantitative yield).

(3*S*,4*S*)-1-(Carboxymethyl)-3-[(1*R*)-1-hydroxyethyl]-4-[(1*R*)-1-phenylthiocarbonylethyl]-2-azetidinone (14) Anisole (686 mg, 6.34 mmol) was added to a solution of **8a** (1.02 g, 2.0 mmol) in CH_2Cl_2 (2.5 ml). The reaction mixture was treated with titanium tetrachloride (709 mg, 3.74 mmol) at 0 °C for 1 h, diluted with water at 0 °C and extracted with CH_2Cl_2. The extracts were made alkaline with aqueous Na_2CO_3, diluted with heptane, and filtered over Celite. The aqueous layer was separated, diluted with AcOEt, acidified with HCl at 0 °C, and extracted with AcOEt. The extracts were combined, washed with brine, and concentrated *in vacuo*. The residue was recrystallized from toluene to give **14** (580 mg, 86%). mp 103—105 °C. $[\alpha]_D^{25}$ −93.7° (c=0.200, $CHCl_3$). IR (KBr): 3400 (br), 1729, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=5.9 Hz), 1.33 (3H, d, J=6.9 Hz), 3.1—3.3 (2H, m), 3.75—3.95 (1H, m), 4.15—4.50 (3H, m), 7.3—7.5 (5H, m). *Anal.* Calcd for $C_{16}H_{19}NO_5S$: C, 56.95; H, 5.68; N, 4.15. Found: C, 56.93; H, 5.69; N, 4.16.

(3*S*,4*S*)-3-[(1*R*)-1-Hydroxyethyl]-1-(*p*-nitrobenzyloxycarbonylmethyl)-4-[(1*R*)-1-phenylthiocarbonylethyl]-2-azetidinone (15) γ-Collidine (735 mg, 6.07 mmol) was added dropwise to a solution of **14** (853 mg, 2.53 mmol) and PNB-Br (737 mg, 3.41 mmol) in dry DMF (1.6 ml). The mixture was stirred at 65 °C for 1.5 h, cooled to 0 °C and diluted with toluene–AcOEt (4:1, 20 ml) and dil. HCl. The organic layer was separated and the aqueous layer was extracted again with toluene–AcOEt (4:1, 20 ml). The extracts were combined, washed with aqueous $NaHCO_3$ and dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from toluene to give **15** (1.11 g, 93%). mp 93.2—93.5 °C. $[\alpha]_D^{28}$ −20.0° (c=1.00, $CHCl_3$). IR (KBr): 3430 (br), 1764, 1730, 1702, 1520 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, d, J=6.9 Hz), 2.00 (1H, d, J=4.0 Hz), 3.12 (1H, dd, J=2.3, 6.9 Hz), 3.17 (1H, m), 3.9—4.5 (4H, m), 5.1—5.4 (2H, m), 7.3—7.6 (7H, m), 8.14 (2H, d, J=8.9 Hz). *Anal.* Calcd for $C_{23}H_{24}N_2O_7S$: C, 58.46; H, 5.12; N, 5.93. Found: C, 58.31; H, 5.48; N, 5.88.

(3*S*,4*S*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-1-(*p*-nitrobenzyloxycarbonylmethyl)-4-[(1*R*)-1-phenylthiocarbonylethyl]-2-azetidinone (8b) Imidazole (166 mg, 2.44 mmol) and *tert*-butyldimethylchlorosilane (234 mg, 1.55 mmol) were added to a solution of **15** (524 mg, 1.11 mmol) in dry DMF (2.62 ml), and the mixture was stirred at room temperature for 5 h, then diluted with AcOEt and washed with 20% aqueous NaCl. The aqueous layer was separated from the organic layer and extracted with AcOEt. The extract was combined with the organic layer, washed with 20% aqueous NaCl twice, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **8b** (625 mg, 96%). $[\alpha]_D^{24}$ −18.2° (c=0.196, $CHCl_3$). IR (neat): 1755, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.89 (9H, s), 1.28 (3H, d, J=6.3 Hz), 1.32 (3H, d, J=6.9 Hz), 3.01 (1H, dd, J=2.3, 7.3 Hz), 3.16 (1H, m), 3.9—4.0 (1H, m), 4.10—4.25 (2H, m), 4.25—4.40 (1H, m), 5.1—5.3 (2H, m), 7.3—7.5 (7H, m), 8.12 (2H, m). ^{1}H-NMR (toluene-d_8:THF-d_8=4:1) δ: 0.07 (3H, s), 0.14 (3H, s), 0.95 (9H, s), 1.13 (3H, d, J=7.3 Hz), 1.26 (3H, d, J=5.9 Hz), 2.91 (1H, dd, J=2.3, 7.3 Hz), 3.03 (1H, dq, J=2.3, 7.3 Hz), 3.8—4.3 (4H, m), 4.79 (2H, m), 7.13 (5H, m), 7.26 (2H, m), 7.2—7.4 (2H, m), 7.79 (2H, d, J=8.6 Hz). MS (SI) m/z: 587 (M^+).

(3*S*,4*S*)-1-(*p*-Nitrobenzyloxycarbonylmethyl)-4-[(1*R*)-1-phenylthio-

carbonylethyl]-3-[(1*R*)-1-trimethylsilyloxyethyl]-2-azetidinone (8c) Treatment of **15** with trimethylchlorosilane in the presence of triethylamine in toluene as described for the formation of **8b** gave **8c** (98%). $[\alpha]_D^{23}$ −16.0° (c=0.420, $CHCl_3$). IR (neat): 1760, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.13 (9H, s), 1.29 (3H, d, J=5.9 Hz), 1.30 (3H, d, J=6.9 Hz), 3.04 (1H, dd, J=2.3, 7.3 Hz), 3.15 (1H, dq, J=2.6, 6.9 Hz), 3.85—4.00 (1H, m), 4.05—4.30 (2H, m), 4.3—4.5 (1H, m), 5.10—5.35 (2H, m), 7.3—7.6 (7H, m), 8.12 (2H, m). MS (SI) m/z: 545 (M^+).

(3*S*,4*S*)-4-[(1*S*)-1-Benzyloxycarbonylethyl]-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone (16) Treatment of the 1α-methyl isomer of **2**[3f] with K_2CO_3 and benzyl bromide as described for the formation of **11** gave **16** (90%). The IR and ^{1}H-NMR spectral data were identical with those reported.[3d]

(3*S*,4*S*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-1-(*p*-nitrobenzyloxycarbonylmethyl)-4-[(1*S*)-1-phenylthiocarbonylethyl]-2-azetidinone (17b) In the same manner as described for the preparation of **8b**, **17b** was obtained from **16**. mp 101—103 °C. $[\alpha]_D^{25}$ +5.6° (c=0.200, $CHCl_3$). IR (KBr): 1768, 1734, 1696, 1525 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (3H, s), 0.07 (3H, s), 0.86 (9H, 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), 3.9—4.3 (4H, m), 5.1—5.3 (2H, m), 7.3—7.5 (7H, m), 8.14 (2H, d, J=8.6 Hz). ^{1}H-NMR (toluene-d_8 : THF-d_8=4 : 1) δ: 0.04 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.18 (3H, d, J=6.9 Hz), 1.24 (3H, d, J=5.9 Hz), 2.61 (1H, dd, J=2.3, 7.3 Hz), 2.75 (1H, m), 3.8—4.3 (3H, m), 4.01 (1H, dd, J=2.3, 9.9 Hz), 4.80 (2H, m), 7.10 (5H, m), 7.2—7.4 (2H, m), 7.81 (2H, d, J=8.9 Hz). MS (SI) m/z: 587 (M^+). *Anal.* Calcd for $C_{29}H_{38}N_2O_7SSi$: C, 59.36; H, 6.53; N, 4.77. Found: C, 58.88; H, 6.54; N, 4.75.

***p*-Nitrobenzyl (4*R*,5*R*,6*S*)-6-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptan-2-carboxylate (18)** (a) Carbene Insertion Method: Treatment of (3*S*,4*R*)-4-[(1*R*)-3-diazo-1-methyl-3-(*p*-nitrobenzyloxycarbonyl)-2-oxopropyl]-3-[(1*R*)-1-hydroxyethyl]-2-azetidinone[4c] with imidazole and *tert*-butyldimethylchlorosilane in DMF as described for the formation of **8b** gave the corresponding silyl ether (quantitative yield) as a colorless solid. mp 118—120 °C. $[\alpha]_D^{30}$ −11.4° (c=1.16, $CHCl_3$). IR (KBr): 3484 (br), 1762, 1718, 1654, 1529 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (3H, s), 0.05 (3H, s), 0.84 (9H, s), 1.16 (3H, d, J=6.7 Hz), 1.18 (3H, d, J=6.5 Hz), 2.95 (1H, dd, J=1.3, 4.2 Hz), 3.83—3.97 (2H, m), 4.17 (1H, dt, J=4.2, 6.4 Hz), 5.34 (2H, s), 5.90 (1H, s), 7.53 (2H, d, J=8.9 Hz), 8.25 (2H, d, J=8.9 Hz). *Anal.* Calcd for $C_{23}H_{32}N_4O_7Si$: C, 54.74; H, 6.39; N, 11.10. Found: C, 54.24; H, 6.47; N, 10.52.

The silyl ether (24.1 mg, 0.05 mmol) was dissolved in benzene and treated with rhodium (II) octanoate.[4c] After refluxing for 15 min, the mixture was evaporated *in vacuo* to give crude **18** (23 mg) which was contaminated with a small amount of the 1α-methyl isomer **19** on the basis of the ^{1}H-NMR analysis. This was prepared as a reference compound and the NMR data shown below are only those of **18**. IR (neat): 1766, 1524 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.85 (9H, s), 1.19 (3H, d, J=7.9 Hz), 1.24 (3H, d, J=6.3 Hz), 2.78 (1H, m), 3.23 (1H, dd, J=2.3, 5.3 Hz), 4.24 (1H, dd, J=2.3, 7.9 Hz), 4.31 (1H, m), 4.71 (1H, s), 5.26 (2H, m), 7.50 (2H, d, J=8.4 Hz), 8.22 (2H, d, J=8.6 Hz). ^{1}H-NMR (toluene-d_8 : THF-d_8=4 : 1) δ: 0.05 (3H, s), 0.07 (3H, s), 0.82 (3H, d, J=7.9 Hz), 0.93 (9H, s), 1.07 (3H, d, J=6.3 Hz), 2.32 (1H, m), 2.95 (1H, dd, J=2.6, 5.0 Hz), 4.1—4.2 (2H, m), 4.68 (1H, s), 4.8—5.0 (2H, m), 7.86 (2H, d, J=8.3 Hz).

(b) Dieckmann-Type Cyclization Method: A solution of **8b** (294 mg, 0.50 mmol) in a mixture of dry toluene and dry THF (4 : 1, 2.8 ml) was added dropwise to a suspension of 60% NaH (44 mg, 1.1 mmol) in a mixture of dry toluene and dry THF (4 : 1, 0.5 ml) at −20 °C and the whole was stirred at the same temperature for 2 h. A 0.6 M 4-morpholinepropanesulfonic acid (MOPS) buffer solution (pH 7.0) was added thereto. The resultant mixture was diluted with AcOEt, washed with a phosphate buffer solution (pH 7.0), dried over $MgSO_4$, and concentrated *in vacuo* to give a crude mixture of **18** and **19** in a ratio of 83 : 17 (300 mg). ^{1}H-NMR ($CDCl_3$) δ: 3.17 (1H×0.17, dd, J=1.7, 5.9 Hz), 3.23 (1H×0.83, dd, J=2.6, 5.3 Hz), 3.68 (1H×0.17, dd, J=2.0, 8.3 Hz), 4.24 (1H×0.83, dd, J=2.6, 7.9 Hz), 4.72 (1H×0.83, d, J=0.7 Hz), 4.81 (1H×0.17, d, J=0.7 Hz). The crude mixture was purified by silica gel chromatography to give a mixture of **18** and **19** (213 mg, 89%) in a ratio of 76 : 24 due to the epimerization during the purification. IR (neat): 1766, 1528 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (3H, s), 0.09 (3H, s), 0.87 (9H, s), 1.21 (3H×0.76, d, J=7.9 Hz), 1.27 (3H, d, J=6.3 Hz), 1.30 (3H×0.24, d, J=6.3 Hz), 2.33 (1H×0.24, m), 2.78 (1H×0.76, m), 3.18 (1H×0.24, dd, J=1.7, 5.9 Hz), 3.23 (1H×0.76, dd, J=2.3, 5.3 Hz), 3.68 (1H×0.24, dd, J=1.7, 8.3 Hz), 4.24 (1H×0.76, dd, J=2.3, 7.9 Hz), 4.31 (1H, m), 4.72 (1H×0.76, s), 4.81 (1H×0.24, s), 5.29 (2H, m), 7.53 (2H, d, J=8.6 Hz), 8.24 (2H, d, J=8.6 Hz).

***p*-Nitrobenzyl (4*S*,5*R*,6*S*)-6-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptan-2-carboxylate (19)** Treatment of **17b** with NaH as described for the formation of **18** gave **19** as a sole product (90%). IR (neat): 1766, 1524 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (3H, s), 0.10 (3H, s), 0.88 (9H, 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).

^{1}H-NMR Study of Dieckmann-Type Cyclization The following experiments were performed in sample tubes for ^{1}H-NMR measurement and the products were observed directly by measurement of the ^{1}H-NMR spectra with a JEOL GX-270 (270 MHz) spectrometer.

(a) Dieckmann-Type Cyclization: A solution of **8b** (30 mg, 0.05 mmol) in toluene-d_8 and THF-d_8 (4 : 1, 1 ml) was treated with 60% NaH (4.4 mg, 0.11 mmol) at 0 °C for 1 h under ultrasonic agitation to give a solution of **9b**, then the ^{1}H-NMR spectrum was measured. ^{1}H-NMR (toluene-d_8 : THF-d_8=4 : 1) δ: 3.07 (1H, br s, H_6), 3.91 (1H, br d, J=*ca.* 8 Hz, H_5).

Treatment of **17b** (30 mg, 0.05 mmol) by the same procedure gave a solution of **20**. ^{1}H-NMR (toluene-d_8 : THF-d_8=4 : 1) δ: 2.91 (1H, br s, H_6), 3.44 (1H, br d, J=*ca.* 8 Hz, H_5).

(b) Sodium Enolate Formation from **18**: A solution of **18** (23 mg, 0.05 mmol), which was prepared by the carbene insertion method, in toluene-d_8 and THF-d_8 (4 : 1, 1 ml) was treated with 60% NaH (4.4 mg, 0.11 mmol) at 0 °C for 1 h under ultrasonic agitation gave a 1 : 1 mixture of **9b** and **20**. ^{1}H-NMR (toluene-d_8 : THF-d_8=4 : 1) δ: 2.95 (1H×0.5, br d, J=6.6 Hz), 3.08 (1H×0.5, br d, J=6.3 Hz), 3.45 (1H×0.5, br d, J=7.6 Hz), 3.92 (1H×0.5, br d, J=7.9 Hz).

***p*-Nitrobenzyl (4*R*,5*R*,6*S*)-6-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-3-diphenylphosphoryloxy-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylate (10b) and *p*-Nitrobenzyl (4*R*,5*S*,6*S*)-6-[(1*R*)-*tert*-Butyldimethylsilyloxyethyl]-4-methyl-7-oxo-3-phenylthio-1-azabicyclo[3.2.0]-hept-2-en-2-carboxylate (21)** 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 $MgSO_4$ and K_2CO_3 (10 : 1), and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **10b** (58 mg, 70%) and **21** (15 mg, 22%).

10b: IR (neat): 1775, 1725, 1518 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.86 (9H, s), 1.20 (3H, d, J=7.9 Hz), 1.23 (3H, d, J=6.6 Hz), 3.29 (1H, dd, 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}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.84 (9H, s), 0.95 (3H, d, J=7.3 Hz), 1.17 (3H, d, J=6.3 Hz), 3.06 (1H, m), 3.19 (1H, dd, J=2.9, 5.0 Hz), 4.42 (2H, m), 5.40 (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 (4*R*,5*R*,6*S*)-6-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-3-diphenylphosphoryloxy-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, 1.2 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 MeI in THF was added therero, and stirring was continued for 0.5 h. A solution of DCP (56 mg, 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 $MgSO_4$ and K_2CO_3 (10 : 1), and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give **10b** (115 mg, 81%).

This compound (**10b**) was also prepared by using benzyl bromide instead of MeI as the alkylating reagent (90%).

***p*-Nitrobenzyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-3-[(3*S*,5*S*)-5-dimethylaminocarbonyl-1-(*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylate (23a)** A solution of **8b** (415 mg, 0.707 mmol) in a mixture of dry toluene and dry THF (4 : 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 (4 : 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 MeI 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, (3*S*,5*S*)-5-dimethylaminocarbonyl-3-mercapto-1-(*p*-nitrobenzyloxycarbonyl)pyrrolidine **22**[2] (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 $MgSO_4$, 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}. ^{1}H-NMR ($CDCl_3$) 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 alkylating reagent and DBU as a base in the last step (86%).

***p*-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-Dimethylaminocarbonyl-1-(*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio]-4-methyl-7-oxo-6-[(1*R*)-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 alkylating reagent and DBU as a base in the last step (83%). $[\alpha]_D^{26}$ +42.2° (c=0.200, $CHCl_3$). IR (KBr): 1775, 1715, 1654, 1522 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 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 (4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-Dimethylaminocarbonyl-1-(*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio]-6-[(1*R*)-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 $MgSO_4$, and concentrated *in vacuo* to give **23c** (808 mg, 89%). The IR and ^{1}H-NMR spectral data were identical with those reported.[2]

References and Notes

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