A New Synthesis of 1β-Alkylcarbapenems Utilizing Eschenmoser Sulfide Contraction of the Novel Thiazinone Intermediates

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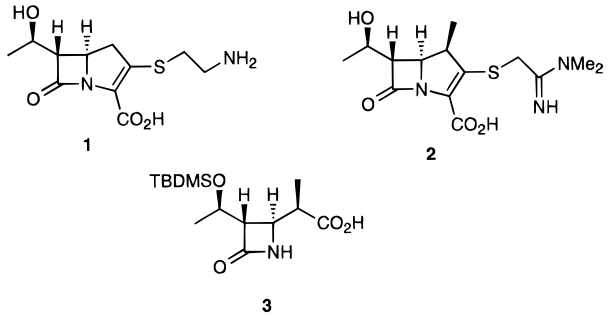
Novel syntheses of the 1β-alkylcarbapenems were achieved on the basis of Eschenmoser sulfide contraction via the new bicyclic 1,3-thiazinone intermediates. 1,3-Thiazinones **7**, **16**, and **25** were effectively prepared from thioesters **5** and **22** using a C4−S bond formation process. The sulfide contraction reactions were performed by treatment of **7**, **16**, and **25** with base (NaH or KO-*t*-Bu) in the presence of triphenylphosphine to generate the corresponding carbapenem enolate **12**, **17**, and **26**, which were trapped by $(PhO)_2POCl$ followed by the reaction with mercaptans to afford carbapenems **10a**, **10b**, **19**, and **28**, respectively.

Introduction

Since the discovery of thienamycin (**1**) in 1976,[1] carbapenems have attracted much attention as novel β-lactam antibiotic agents and intensive efforts have been made to the study of their synthesis.[2] Among them, of paticular note is the report by Christensen et al., which disclosed that introduction of a 1-methyl group in β-orientation to the carbapenem skeleton (e.g., **2**) greatly increased the chemical and metabolic stability.[3] Extensive synthetic studies of 1β-methylcarbapenems have revealed that carboxylic acid **3**, wherein all stereogenic centers were installed, could be an effective intermediate.[4] Carbapenem skeletons with the strained bicyclic systems have been constructed through **3** using methods based on Rh(II)-catalyzed carbene insertion,[5] intramolecular Wittig reaction,[6] and Dieckmann condensation.[7] We have previously reported a preliminary study of the 1β-methylcarbapenems based on ring contraction of bicyclic thiazinone **7** using Eschenmoser's method.[8] Herein we report the details of our method along with the application to the syntheses of the other carbapenem analogs.



It is well documented that the acyl thioglycolates are effectively converted to the corresponding β-keto esters by elimination of the sulfur atom in the presence of phosphine.[9] Although the application of sulfide contraction to the ring contraction is unknown to our knowledge, we anticipated that sulfide contraction of bicyclic thiazinone **A** with an unprecedented ring system could be initiated by intramolecular nucleophilic attack of the anion generated at the carbon α to the ester group on the thioester carbonyl group, followed by sulfur extrusion to give the carbapenem enolate **B** (Scheme 1).

Syntheses of 1β-Methycarbapenems. In this study we initially explored the efficient preparation of the key intermediate 1β-methylthiazinone **7**. This was achieved by intramolecular *S*-alkylation to form the C4−S bond of **7** (Scheme 2). Carboxylic acid **3** was first converted to the corresponding imidazolide, followed by treatment with mercaptan **4**[10] to afford thioester **5** in good yield.[11]

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(1) (a) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B. *16th. Intersci. Conf. Antimicrob. Agents Chemother., Chicago* **1976**, Abstract No. 227. (b) A-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Molin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491. (c) Johnston, D. B. R; Schmitt, S. M.; Bouffard, F. A.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313. (d) Kahan, J. S.; Kahan F. M.; Geogelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1.

(2) For reviews, see: (a) Kametani, T.; Ihara, M. *J. Synth. Org. Chem. Jpn.* **1980**, *38*, 1025. (b) Shibuya, M. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 62. (c) Kametani, T. *Heterocycles* **1982**, *17*, 463. (d) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729.

(3) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

(4) Ito, Y.; Terashima, S. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 606 and references cited therein.

(5) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

(6) (a) Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 8006. (b) Ponsford, R. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1979**, 846. (c) Cama, L.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 2013. (d) Battisitini, C.; Scarafile, C.; Foglio, M.; Franceschi, G. *Tetrahedron Lett.* **1984**, *25*, 2395. (e) Yoshida, A.; Tajima, Y.; Takeda, N.; Oida, S. *Tetrahedron Lett.* **1984**, *25*, 2793.

(7) (a) Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883. (b) Sowin, T. J.; Meyers, A. I. *J. Org. Chem.* **1988**, *53*, 4154. (c) Déziel, R.; Favreau, D. *Tetrahedron Lett.* **1989**, *30*, 1345. (d) Sunagawa, M.; Sasaki, A.; Matsumura, H.; Goda, K.; Tamoto, K. *Chem. Pharm. Bull.* **1994**, *42*, 1381. (e) Kondo, K.; Seki, M.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 1096. (f) Seki, M.; Kondo, K.; Iwasaki, T. *Synlett* **1995**, 315.

(8) Sakurai, O.; Ogiku, T.; Takahashi, M.; Horikawa, H.; Iwasaki, T. *Tetrahedron Lett.* **1994**, *35*, 2187.

(9) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.

(10) Wieland, T.; Sieber, A. *Liebigs Ann. Chem.* **1969**, *722*, 222.

(11) Grais, H.-J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 244.

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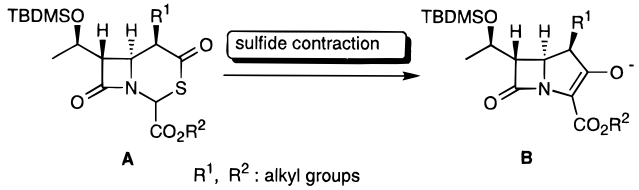
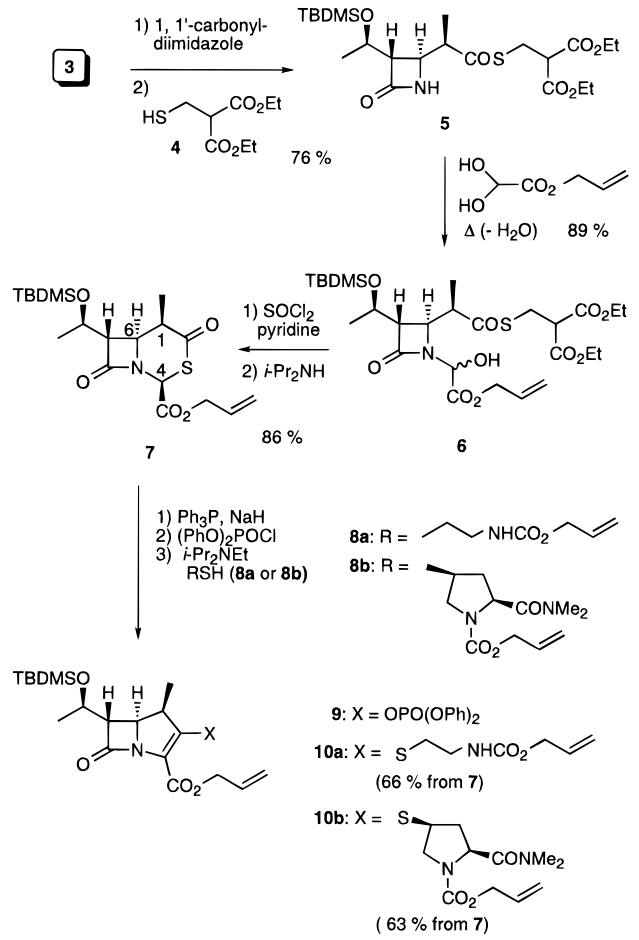
Scheme 1



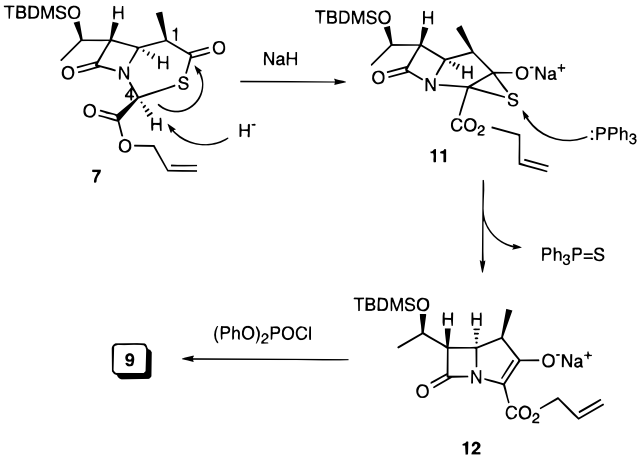
Scheme 2



Thioester **5** was then condensed with allyl glyoxylate in hot toluene to give alcohols **6** as a diastereomeric mixture with a ratio of approximately 1:1, which were subsequently treated with $SOCl_2$ and pyridine to yield the corresponding chlorides.[12] The chlorides were carefully treated with 1 equiv of diisopropylamine in CH_3CN at 0 °C to afford thiazinone **7** as a single diastereomer in good yield. In this reaction, the nucleophilic attack of the thiocarboxylate anion generated by elimination of diethyl methylenemalonate under basic conditions effectively took place on the carbon α to the chlorine atom. The stereochemistry of **7** was unambiguously determined by the NOE experiment; the enhancements were observed between H1 and H4 (1.2%) and between H4 and H6 (0.7%).

With the key intermediate thiazinone **7** in hand, we turned our attention to the key reaction, Eschenmoser sulfide contraction, leading to carbapenems. After trying a variety of conditions, we found that using NaH in DMF as a base−solvent system was effective. Thus, treatment

Scheme 3



of **7** with NaH (1.1 equiv) in DMF at −20 °C in the presence of Ph_3P (1 equiv) followed by addition of $(PhO)_2$-POCl gave enolphosphate **9**. In this reaction, substantial formation of triphenylphosphine sulfide was observed even at −20 °C.[13] This clearly indicated that efficient sulfur extrusion from the thiazinone ring had occurred. Without isolation of **9**, addition of the mercaptans (**8a** or **8b**)[14,15] to the reaction mixture afforded carbapenems **10a**,**b**, respectively, in good yields in one-pot procedure from **7**.[7]

This sulfide contraction is probably initiated by abstraction of H4 in **7** by NaH; this hydrogen atom may be exposed on the convex side of the bicyclic thiazinone (Scheme 3). The resulting carbanion should intramolecularly attack on the carbonyl group in the thiazinone to form thiirane **11**. Subsequently, **11**, subjected to the sulfur extrusion with the aid of Ph_3P, could be converted to enolate **12**, which is effectively trapped *in situ* by $(PhO)_2POCl$ to give **9**.

Synthesis of 1β-Methylcarbapenems Possessing Prodrug-Type Esters. To broaden the synthetic utility of our method, we next investigated the synthesis of the prodrug-type ester analogs which had been widely utilized in penicillins and cephalosporins for oral administration.[16] The preparation of the thiazinone intermediate **16** was similar to that of the allyl ester analog **7**; however, difficulties in obtaining the corresponding glyoxylate ester led us to choose a somewhat indirect route (Scheme 4). Thioester **5** was first acylated with the oxalyl chloride monoester **13**[17] in the presence of pyridine followed by reduction using Zn powder in AcOH[18] to afford alcohols **15** as a diastereomeric mixture in a ratio of approximately 1:1. Conversion of **15** to thiazinone **16** was carried out without difficulty according to the above-described conditions. In this case, the thiazinone obtained was also a single isomer, whose stereochemistry at C4 was determined by the NOE experiment (3.4% between H1 and H4, and 0.8% between H4 and H6).

(12) Scartazzini, R.; Peter, H.; Bickel, H.; Heusler, K.; Woodward, R. B. *Helv. Chim. Acta* **1972**, *55*, 408.

(13) In contrast, the sulfide contraction in the original paper required much higher temperature (over 50 °C). See ref 9.

(14) Shinkai, I.; Liu, T.; Reamer, R.; Sletzinger, M. *Synthesis* **1980**, 924.

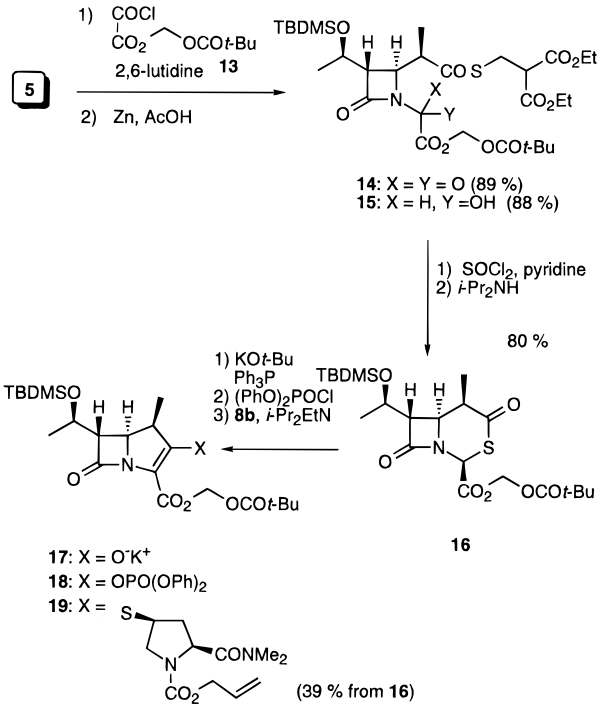
(15) Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiot.* **1990**, *43*, 519.

(16) Ferres, H. *Chem. Ind. (London)* **1980**, 435.

(17) This acyl chloride was prepared from tetrabutylammonium monobenzyl oxalate as follows: (1) (pivaloyloxy)methyl chloride/acetone, (2) hydrogenolysis, (3) oxalyl chloride. See: Japanese Provisional Patent No. 99379, 1987.

(18) Yamamoto, S.; Haga, N.; Aoki, T.; Hayashi, S.; Tanida, H.; Nagata, W. *Heterocycles* **1979**, *8*, 283.

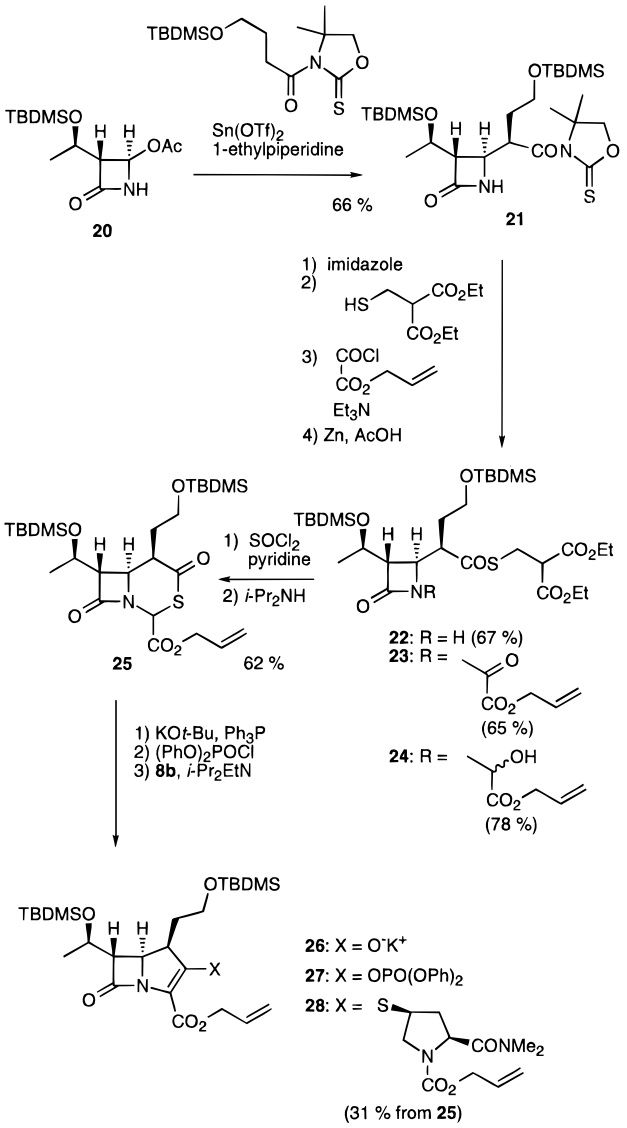
Scheme 4



Our initial attempt to carry out sulfide contraction of **16**, using the above-mentioned conditions (NaH in DMF), ended in the degradation of **16** without any formation of the corresponding enolate. This result would be attributed to the lability of the ester portion of **16** under strongly basic conditions. After the milder conditions were searched, the use of KO-*t*-Bu in toluene was found to be effective. Thus, **16** was treated with KO-*t*-Bu (1.1 equiv) in the presence of Ph_3P in toluene at −40 °C to be smoothly converted to enolate **17**, which was trapped by $(PhO)_2POCl$ to form enolphosphate **18**. Without isolation, **18** was subjected to the reaction with mercaptan **8b** in the presence of diisopropylethylamine in DMF yielded the desired 1β-methylcarbapenem **19**. It is worth noting that our method directly produced a carbapenem with prodrug-type ester without extra steps, usually needed for ester exchange from allyl or *p*-nitrobenzyl group.

Synthesis of 1β-(2-Hydroxyethyl)carbapenem. To develop more potent antibacterial agents, introduction of substituents other than methyl group to the 1β position has been investigated.[19] We also attempted the synthesis of a 1β-(2-hydroxyethyl) analog through our sulfide contraction method (Scheme 5). The introduction of a 4β-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl] moiety to acetoxyazetizinone **20** was achieved by the diastereoselective aldol-type reaction utilizing Sn(II)-enolate with 4,4-dimethyloxazolidine-2-thione auxiliary, giving single product **21**.[20] The obtained azetidinone **21** was then converted to thioester **22** via imidazolide according to Nagao's procedure.[21] Thioester **22** was acylated with (allyloxy)oxalyl chloride[22] followed by reduction with Zn

Scheme 5



in AcOH[18] to give alcohols **24** as an epimeric mixture. Conversion of **24** to the thiazinone was carried out without difficulty using the above conditions ($SOCl_2$/pyridine and then *i*-Pr_2NH) to afford **25** stereoselectively, of which stereochemistry at C4, unfortunately, was not determined despite using either the difference NOE measurement or the 2D-NOESY techniques. Sulfide contraction reaction of thiazinone **25** proceeded smoothly under the modified conditions used for thiazinone **16** (in THF/toluene with ice cooling). The resultant enolate **26** was trapped in situ with $(PhO)_2POCl$ to give enolphosphate **27**,[23] which reacted with mercaptan **8b** to give carbapenem **28**.

Conclusion

Through the novel intermediate thiazinones **7**, **16**, and **25**, 1β-methylcarbapenems **10** and **19** and 1β-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]carbapenem **28** were synthesized by utilizing ring contraction based on Eschenmoser sulfide contraction. It is notable that this is to

(19) (a) Ueda, Y.; Vinet, V. *J. Antibiot.* **1992**, *45*, 940. (b) Remuzon, P.; Bouzard, D.; DiCesare, P.; Essiz, M.; Jacquet, J.-P.; Nicolau, A.; Martel, A.; Menard, M.; Bachand, C. *Tetrahedron* **1995**, *51*, 9657. (c) Bouthillier, G.; Mastalerz, H.; Menard, M. *Tetrahedron Lett.* **1994**, *35*, 4689 and references cited therein.

(20) Déziel, R.; Favreau, D. *Tetrahedron Lett.* **1986**, *27*, 5687.

(21) Nagao, Y.; Kumagai, T.; Nagase, Y.; Tamai, S.; Inoue, Y.; Shiro, M. *J. Org. Chem.* **1992**, *57*, 4232.

(22) Afonso, A.; Fon, F.; Weinstein, J.; Ganguly, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6138.

(23) The stereochemistry of **27** was made sure by the direct comparison of coupling constants of H5 with those of **18**; H5 of **27** appeared as double doublet (J = 10.3, 2.8 Hz) at δ 4.12, while that of **18** did as double doublet (J = 10.4, 3.0 Hz) at δ 4.13 as shown in the Experimental Section.

our knowledge the first example of applying Eschenmoser sulfide contraction to the ring contraction reaction. Furthermore, we demonstrated that **7**, **16**, and **25** were efficiently prepared and sulfide contraction reaction turned out to be especially effective for the "direct" synthesis of carbapenem **19** with a prodrug ester. The application of this method for the synthesis of other types of bicyclic β-lactams, such as penems and cephalosporins, should be possible and will be disclosed in due course.

Experimental Section

(3*S*,4*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-2-[[2,2-bis(ethoxycarbonyl)ethyl]thio]-1-methyl-2-oxoethyl]-2-azetidinone (5). To a stirred dispersion of carboxylic acid **3** (3.0 g, 10 mmol) in dry CH_3CN (50 mL) at rt under N_2 was added 1,1′-carbonyldiimidazole (1.8 g, 11 mmol). After the reaction mixture was stirred for 30 min, mercaptan **4** (2.5 g, 12 mmol) was added and the stirring was continued overnight. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 7:3) to give thioester **5** (3.8 g, 78%) as a colorless solid: $[\alpha]^{26}_D = -37.0°$ (*c* 0.53, $CHCl_3$); IR (KBr) 3080, 1765, 1735, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.87 (9H, s), 1.15 (3H, d, *J* = 6.2 Hz), 1.24 (3H, d, *J* = 6.8 Hz), 1.28 (6H, t, *J* =7.0 Hz), 2.8−3.0 (1H, m), 3.34 (1H, d, *J* = 3.4 Hz), 3.38 (1H, d, *J* = 2.4 Hz), 3.8−3.9 (1H, m), 4.2−4.3 (5H, m), 5.62 (1H, br s); MS (EI) *m*/*z* 432 ($M^+ - 57$); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{39}NO_7SSi$ + H 490.2295 (M^+ + H), found 490.2327.

(3*S*,4*S*)-1-[[(Allyloxy)carbonyl]hydroxymethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-2-[[2,2-bis(ethoxycarbonyl)ethyl]thio]-1-methyl-2-oxoethyl]-2-azetidinone (6). A solution of thioester **5** (3.0 g, 6.12 mmol) and allyl glyoxylate (0.9 g, 6.75 mmol) in toluene (30 mL) was refluxed in a Dean−Stark apparatus for 4 h. After being cooled, the mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 3:1) to give an epimeric mixture of alcohols **6** (3.3 g, 89%) as a brownish syrup: IR (neat) 3470, 1752, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05, 0.07 (6H, each s), 0.87, 0.88 (9H, each s), 1.20−1.32 (12H, m), 2.94−3.10 (2H, m), 3.37 (2H, d, *J* = 7.1 Hz), 3.63 (1H, t, *J* = 7.3 Hz), 4.03−4.27 (7H, m), 4.37, 5.52 (1H, each d, *J* = 8.6, 8.5 Hz), 4.60−4.80 (2H, m), 5.26−5.42 (2H, m), 5.84−6.05 (1H, m); MS (SI) *m*/*z* 587 ($M^+ - 16$), 547 ($M^+ - 56$); HRMS (FAB) *m*/*z* calcd for $C_{27}H_{45}NO_{10}SSi$ + Na 626.2431 (M^+ + Na), found 626.2433.

Allyl (2*S*,5*R*,6*S*,7*S*)-7-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-5-methyl-4,8-dioxo-1-aza-3-thiabicyclo[4.2.0]-octane-2-carboxylate (7). To a solution of alcohols **6** (1.9 g, 3.15 mmol) and pyridine (0.38 mL, 4.72 mmol) in dry THF (40 mL) at −60 °C under N_2 was added dropwise $SOCl_2$ (0.34 mL, 4.72 mmol). After being stirred for 30 min, the mixture was poured into ice−water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give the epimeric mixture of chlorides, which were used for the next step without further purification. To a stirred solution of the crude chlorides in dry CH_3CN (35 mL) with ice cooling was added dropwise a solution of *N*,*N*-diisopropylamine (0.49 mL, 3.46 mmol) in dry CH_3CN (20 mL) over 20 min. After being stirred for 30 min, the reaction mixture was poured into ice−water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 15:1) to give 1,3-thiazinone **7** (1.12 g, 86%) as a colorless syrup: $[\alpha]^{23}_D = -117.9°$ (*c* 1.0, $CHCl_3$); IR (neat) 1779, 1745, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63 (3H, s), 0.78 (3H, s), 0.87 (9H, s), 1.21 (3H, d, *J* = 6.2 Hz), 1.23 (3H, d, *J* = 6.7 Hz), 2.93 (1H, dd, *J* = 4.7, 2.9 Hz), 3.55 (1H, quintet, *J* = 6.7 Hz), 4.12−4.29 (1H, m), 4.55 (1H, dd, *J* = 7.2, 2.9 Hz), 4.60−4.81 (2H, m), 5.23−5.45 (2H, m), 5.84 (1H, s), 5.79−6.02 (1H, m); ^{13}C NMR ($CDCl_3$) −4.90, −4.33, 11.72, 17.91, 22.73, 25.71, 45.10, 53.69, 56.41, 62.42, 64.86, 66.91, 119.6, 130.8, 167.0, 169.4, 197.2; MS (EI) *m*/*z* 356 ($M^+ - 57$); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{31}NO_5SSi$ + H 414.1771 (M^+ + H), found 414.1763.

Sulfide Contraction Reaction of Thiazinone 7 to Carbapenems (10a, 10b). To a stirred solution of thiazinone **7** (300 mg, 0.726 mmol) and Ph_3P (186 mg, 0.726 mmol) in DMF (6 mL) at −20 °C under N_2 was added 60% NaH (32 mg, 0.798 mmol). After the reaction mixture was stirred for 2 h, $(PhO)_2POCl$ (0.165 mL, 0.709 mmol) and DMAP (9 mg, 0.07 mmol) were added to the mixture and the stirring was continued at 0 °C for 2 h. *N*-[(Allyloxy)carbonyl]cysteamine (**8a**) (152 mg, 0.944 mmol) and *i*-Pr_2NEt (0.165 mL, 0.944 mmol) were added to the mixture, which was allowed to stand at 0 °C in the refrigerator for 3 days. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 3:1) to afford **10a** (250 mg, 66%) as a yellowish syrup. The reaction using mercaptan **8b** (188 mg, 0.726 mmol) was carried out in a similar way except for standing in the refrigerator overnight to give carbapenem **10b** (284 mg, 63%) as a yellowish foam.

Allyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-[[[2-[(allyloxy)carbonyl]amino]ethyl]thio]-1-methylcarbapen-2-em-3-carboxylate (10a): $[\alpha]^{26}_D = +58.9°$ (*c* 0.97, $CHCl_3$); IR (KBr) 3350, 1810, 1765, 1718, 1645, 1589, 1522 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.22 (3H, d, *J* = 7.2 Hz), 1.24 (3H, d, *J* = 6.1 Hz), 2.78−3.15 (2H, m), 3.21 (1H, dd, *J* = 5.8, 2.6 Hz), 3.25−3.49 (2H, m), 4.18 (1H, dd, *J* = 9.5, 2.6 Hz), 4.10−4.29 (1H, m), 4.50−4.88 (4H, m), 5.10−5.49 (5H, m), 5.72−6.05 (2H, m); ^{13}C NMR ($CDCl_3$) −4.91, −4.21, 16.79, 18.00, 22.47, 25.77, 31.58, 41.30, 42.91, 55.85, 60.52, 65.63, 65.79, 66.15, 117.9, 118.3, 120.1, 131.7, 132.7, 148.3, 156.2, 160.8, 172.8; MS (SI) *m*/*z* 524 (M^+), 482 ($M^+ - 42$); HRMS (FAB) *m*/*z* calcd for $C_{25}H_{40}N_2O_6SSi$ + H 525.2455 (M^+ + H), found 525.2446.

Allyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-[[(3*S*,5*S*)-5-[(dimethylamino)carbonyl]-pyrrolidin-3-yl]thio]-1-methylcarbapen-2-em-3-carboxylate (10b): $[\alpha]^{22}_D = +46.3°$ (*c* 0.935, $CHCl_3$); IR (neat) 1768, 1709, 1650, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (6H, s), 0.89 (9H, s), 1.24 (3H, d, *J* = 6.0 Hz), 1.25 (3H, d, *J* = 6.0 Hz), 1.85−2.04 (1H, m), 2.50−2.79 (1H, m), 2.97, 2.99 (3H, each s), 3.06, 3.11 (3H, each s), 3.18−3.38 (1H, m), 3.21 (1H, dd, *J* = 5.8, 2.6 Hz), 3.40−3.72 (2H, m), 4.01−4.30 (3H, m), 4.52−4.85 (4H, m), 5.17−5.50 (4H, m), 5.75−6.05 (2H, m); ^{13}C NMR ($CDCl_3$) −4.91, −4.20, 17.07, 17.99, 22.45, 25.77, 35.42, 36.12, 37.01, 40.33, 41.16, 43.89, 54.20, 54.77, 55.81, 60.63, 65.73, 66.13, 76.45, 77.08, 77.72, 117.4, 117.8, 118.4, 126.8, 129.8, 131.6, 132.8, 146.3, 153.5, 154.0, 160.4, 171.0, 172.8; MS (SI) *m*/*z* 622 (M^+ + 1), 606 ($M^+ - 15$), 564 ($M^+ - 57$); HRMS (FAB) *m*/*z* calcd for $C_{30}H_{47}N_3O_7SSi$ + Na 644.2801 (M^+ + Na), found 644.2802.

(3*S*,4*S*)-4-[(1*R*)-2-[[2,2-Bis(ethoxycarbonyl)ethyl]thio]-1-methyl-2-oxoethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-[[[(pivaloyloxy)methyl]oxy]oxalyl]-2-azetidinone (14). To a solution of thioester **5** (1.40 g, 2.87 mmol) and [(pivaloyloxy)methoxy]oxalyl chloride (0.64 g, 2.87 mmol) in dry CH_2Cl_2 (10 mL) with ice cooling was added 2,6-lutidine (0.34 mL, 2.87 mmol). After being stirred for 30 min, [(pivaloyloxy)methoxy]oxalyl chloride (0.64 g, 2.87 mmol) and 2,6-lutidine (0.34 mL, 2.87 mmol) were added to the mixture and stirring was continued for another 30 min. The reaction mixture was poured into cold 0.1 M phosphate buffer (pH 7.0) and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 4:1) to give α-keto ester **14** (1.72 g, 89%) as a colorless syrup: $[\alpha]^{26}_D = -108.4°$ (*c* 1.0, $CHCl_3$); IR (KBr) 1809, 1752, 1732, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.17 (3H, d, *J* = 6.4 Hz), 1.23 (9H, s), 1.28 (6H, t, *J* = 7.0 Hz), 1.29 (3H, d, *J* = 7.0 Hz), 3.26−3.68 (5H, m), 4.16−4.30 (1H, m), 4.25 (4H, q, *J* = 7.0 Hz), 4.41

(1H, dd, J = 5.3, 3.4 Hz), 5.90 (2H, s); MS (EI) m/z 618 (M^+ − 57); HRMS (FAB) m/z calcd for $C_{30}H_{49}NO_{12}SSi$ + Na 698.2642 (M^+ + Na), found 698.2634.

(3*S*,4*S*)-4-[(1*R*)-2-[[2,2-Bis(ethoxycarbonyl)ethyl]thio]-1-methyl-2-oxoethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-[hydroxy[[[(pivaloyloxy)methyl]oxy]carbonyl]methyl]-2-azetidinone (15). To a solution of α-keto ester **14** (1.70 g, 2.53 mmol) in AcOH (10 mL) and CH_2Cl_2 (10 mL) with ice cooling was added Zn powder (5.0 g), and the mixture was stirred vigorously for 30 min. After being passed through a cerite pad, the mixture was poured into ice−water and extracted with CH_2Cl_2. The organic layer was washed successively with saturated aqueous $NaHCO_3$, water, and brine and dried over $MgSO_4$. The solvent was evaporated to give a residue, which was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 3:1) to give an epimeric mixture of alcohols **15** (1.52 g, 88%) as a colorless syrup: IR (KBr) 3460, 1754, 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (6H, m), 0.87 (9H, s), 1.22 (9H, s), 1.22−1.32 (12H, m), 2.90−3.12 (2H, m), 3.38 (2H, dd, J = 7.1, 2.1 Hz), 3.61 (1H, t, J = 7.1 Hz), 4.04−4.28 (7H, m), 4.42 (1H, d, J = 8.8 Hz), 5.30, 5.52 (1H, d, J =8.8 Hz), 5.77−5.91 (2H, m); MS (EI) m/z 620 (M^+ − 57); HRMS (FAB) m/z calcd for $C_{30}H_{51}NO_{12}SSi$ + Na 700.2798 (M^+ + Na), found 700.2765.

(Pivaloyloxy)methyl (2*S*,5*R*,6*S*,7*S*)-7-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4,8-dioxo-5-methyl-1-aza-3-thiabicyclo[4.2.0]octane-2-carboxylate (16). The reaction of alcohols **15** (967 mg, 1.43 mmol) was performed in a similar way to that of alcohols **6** to give thiazinone **16** (557 mg, 80%) as a colorless syrup: $[\alpha]^{26}_D$ = −97.8° (*c* 1.0, $CHCl_3$); IR (KBr) 1775, 1765, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.21 (9H, s), 1.19−1.25 (6H, m), 2.93 (1H, dd, J = 4.6, 3.0 Hz), 3.51 (1H, quintet, J = 6.8 Hz), 4.10−4.30 (1H, m), 4.56 (1H, dd, J = 7.2, 2.9 Hz), 5.82 (1H, d, J = 5.4 Hz), 5.83 (1H, s), 5.91 (1H, d, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) −4.92, −4.33, 11.70, 17.91, 22.70, 25.70, 26.81, 38.77, 45.00, 53.52, 56.39, 62.53, 64.78, 80.30, 166.1, 169.5, 176.7, 196.9; MS (EI) m/z 472 (M^+ − 15), 430 (M^+ − 57); HRMS (FAB) m/z calcd for $C_{22}H_{37}NO_7SSi$ + Na 510.1958 (M^+ + Na), found 510.1923.

Sulfide Contraction of Thiazinone 16 Leading to Carbapenem 19. To a solution of thiazinone **16** (60 mg, 0.123 mmol) and Ph_3P (32 mg, 0.123 mmol) in toluene (2 mL) at −40 °C under N_2 was added KO-*t*-Bu (15 mg, 0.135 mmol), and the reaction mixture was stirred vigorously for 1.5 h. A solution of $(PhO)_2POCl$ (36 mg, 0.135 mmol) in dry CH_3CN (3 mL) was added, and the reaction mixture was gradually warmed to 0 °C and stirred for an additional 3 h to form enolphosphate **18**. The mixture was poured into 0.2 M phosphate buffer (pH 7.0) and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was dissolved in dry DMF (3 mL), and mercaptan **8b** (35 mg, 0.135 mmol) and *i*-Pr_2EtN (26 μL, 0.148 mmol) was added to the mixture with ice cooling under N_2. After standing at 0 °C in the refrigerator for 3 days, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 1:3) to afford carbapenem **19** (33 mg, 39%) as a yellowish gum. Enolphosphate **18** was isolatable (48%) as a yellowish syrup by silica gel column chromatography (elution with *n*-hexane:AcOEt = 6:1).

(Pivaloyloxy)methyl (1*R*,5*R*,6*S*)-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-[(diphenylphosphoryl)oxy]-1-methylcarbapen-2-em-3-carboxylate (18): $[\alpha]^{28}_D$ = +31.1° (*c* 0.51, $CHCl_3$); IR (neat) 1787, 1746, 1635, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 1.18 (3H, d, J = 7.2 Hz), 1.19 (9H, s), 1.22 (3H, d, J = 7.1 Hz), 3.23 (1H, dd, J = 6.3, 3.0 Hz), 3.32−3.53 (1H, m), 4.13 (1H, dd, J = 10.4, 3.0 Hz), 4.09−4.25 (1H, m), 5.78 (1H, d, J = 5.5 Hz), 5.81 (1H, d, J = 5.5 Hz), 7.15−7.43 (10H, m); MS (EI) m/z 687 (M^+), 630 (M^+ − 57).

(Pivaloyloxy)methyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-[[(3*S*,5*S*)-5-[(dimethylamino)carbonyl]pyrrolidin-3-yl]thio]-1-methylcarbapen-2-em-3-carboxylate (19): $[\alpha]^{30}_D$ = +24.0° (*c* 1.01, $CHCl_3$); IR (neat) 1770, 1751, 1709, 1655, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.89 (9H, s), 1.22 (9H, s), 1.12−1.27 (6H, m), 1.80−2.05 (1H, m), 2.54−2.79 (1H, m), 2.97, 2.99 (3H, each s), 3.06, 3.11 (3H, each s), 3.19−4.26 (7H, m), 4.50−4.60 (2H, m), 4.67−4.78 (1H, m), 5.12−5.35 (2H, m), 5.73−6.05 (1H, m), 5.84 (1H, d, J = 5.5 Hz), 5.93 (1H, d, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$) −4.89, −4.26, 17.10, 17.99, 22.49, 25.76, 26.92, 27.33, 29.33, 35.41, 36.12, 37.00, 38.77, 40.37, 41.20, 44.10, 46.63, 51.67, 54.17, 54.73, 55.79, 60.82, 66.10, 66.33, 76.44, 77.07, 77.70, 79.91, 117.9, 128.4, 128.4, 128.6, 132.0, 132.2, 132.8, 148.4, 154.0, 159.3, 170.9, 172.8, 176.8; MS (SI) m/z 696 (M^+ + 1), 680 (M^+ − 15), 638 (M^+ − 57); HRMS (FAB) m/z calcd for $C_{33}H_{53}N_3O_9SSi$ + Na 718.3169 (M^+ + Na), found 718.3208.

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-1-[(4,4-dimethyl-2-thioxooxazolidin-3-yl)carbonyl]propyl]-2-azetidinone (21). To a stirred suspension of $Sn(OTf)_2$ (3.70 g, 9.05 mmol) in dry THF (5 mL) with ice cooling under N_2 was added 1-ethylpiperidine (1.30 mL, 9.40 mmol), and then a solution of 3-[3-[(*tert*-butyldimethylsilyl)oxy]butyroyl]-4,4-dimethyl-2-thioxooxazolidine (2.30 g, 6.96 mmol) in dry THF (5 mL) was added dropwise. After the reaction mixture was stirred for 3 h, a solution of acetoxyazetidinone **20** (1.00 g, 3.48 mmol) in dry THF (5 mL) was added dropwise. After being stirred for an additional 2 h, the mixture was poured into saturated aqueous NH_4Cl, diluted with AcOEt, and stirred vigorously for 10 min. The resultant slurry was passed through a cerite pad to remove the precipitate and washed with AcOEt. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 4:1) to give acyloxazolidine-2-thione **21** (1.28 g, 66%) as a greenish gum: $[\alpha]^{26}_D$ = +32.56° (*c* 0.82, $CHCl_3$); IR (neat) 3260, 1762, 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (6H, s), 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 1.22 (3H, d, J = 6.3 Hz), 1.56 (3H, s), 1.57 (3H, s), 1.59 (9H, s), 1.65−1.83 (1H, m), 1.93−2.17 (1H, m), 3.19−3.27 (1H, m), 3.52−3.75 (2H, m), 3.99 (1H, dd, J = 5.2, 2.0 Hz), 4.11 (1H, d, J = 8.7 Hz), 4.15 (1H, d, J = 8.7 Hz), 4.09−4.27 (1H, m), 5.28−5.37 (1H, m), 6.16 (1H, br s); MS (SI) m/z 559 (M^+ + 1); HRMS (FAB) m/z calcd for $C_{26}H_{50}N_2O_5SSi_2$ + H 559.3057 (M^+ + H), found 559.3039.

(3*S*,4*R*)-4-[(1*R*)-2-[[2,2-Bis(ethoxycarbonyl)ethyl]thio]-1-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-oxoethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-azetidinone (22). To a solution of acyloxazolidine-2-thione **21** (4.53 g, 8.12 mmol) in dry CH_3CN (30 mL) at rt under N_2 was added imidazole (2.76 g, 40.6 mmol), and the mixture was stirred overnight. A solution of mercaptan **4** (1.88 g, 8.93 mmol) in dry CH_3CN (1 mL) was added to the mixture and stirring was further continued for 3 days. The mixture was poured into 1 N HCl and extracted with AcOEt. The organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 4:1) to give thioester **22** (3.46 g, 67%) as a colorless waxy solid: $[\alpha]^{25}_D$ = −11.0° (*c* 1.0, $CHCl_3$); IR (KBr) 3140, 3080, 1766, 1728, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (6H, s), 0.06 (6H, s), 0.86 (9H, s), 0.88 (9H, s), 1.13 (3H, d, J = 6.3 Hz), 1.28 (6H, t, J = 7.0 Hz), 1.60−1.74 (1H, m), 1.84−1.95 (1H, m), 2.86−3.00 (2H, m), 3.28 (1H, d, J = 1.1 Hz), 3.37 (1H, s), 3.45−3.70 (3H, m), 3.83 (1H, dd, J = 6.4, 2.0 Hz), 4.09−4.21 (5H, m), 5.96 (1H, br s); MS (SI) m/z 634 (M^+ + 1), 618 (M^+ − 15), 576 (M^+ − 57); HRMS (FAB) m/z calcd for $C_{29}H_{55}NO_8SSi_2$ + Na 656.3084 (M^+ + Na), found 656.3083.

(3*S*,4*R*)-1-[(Allyloxy)oxalyl]-4-[(1*R*)-2-[[2,2-bis(ethoxycarbonyl)ethyl]thio]-1-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-oxoethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-azetidinone (23). To a solution of thioester **22** (1.00 g, 1.50 mmol) and (allyloxy)oxalyl chloride (0.67 g, 4.50 mmol) in dry CH_2Cl_2 (30 mL) with ice cooling was added dropwise a solution of Et_3N (2.76 g, 40.6 mmol) in dry CH_2Cl_2 (15 mL), and the mixture was stirred overnight. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$,

and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 9:1) to give α-keto ester **23** (0.75 g, 65%) as a yellowish syrup: $[\alpha]^{25}_D$ = −79.5° (*c* 1.0, $CHCl_3$); IR (neat) 1810, 1745, 1728, 1706, 1686, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00−0.11 (12H, m), 0.83−0.89 (18H, m), 1.16−1.30 (9H, m), 1.60−2.10 (2H, m), 3.27−3.69 (8H, m), 4.15−4.30 (4H, m), 4.40−4.48 (1H, m), 4.74−4.85 (2H, m), 5.28−5.50 (2H, m), 5.86−6.06 (1H, m); MS (SI) *m*/*z* 746 (M^+ + 1), 730 (M^+ − 15), 688 (M^+ − 57); HRMS (FAB) *m*/*z* calcd for $C_{34}H_{59}NO_{11}SSi_2$ + H 746.3425 (M^+ + H), found 746.3401.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl]hydroxymethyl]-4-[(1*R*)-2-[[2,2-bis(ethoxycarbonyl)ethyl]thio]-1-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-oxoethyl]-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-azetidinone (24). To a solution of α-keto ester **23** (0.75 g, 1.00 mmol) in AcOH (9 mL) at rt was added Zn powder (4 g), and the reaction mixture was stirred for 2 h and then poured into saturated aqueous $NaHCO_3$. The resultant slurry was passed through a cerite pad and extracted with AcOEt. The combined organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 4:1) to give an epimeric mixture of alcohols **24** (0.58 g, 78%) as a colorless syrup: IR (KBr) 3470, 1760, 1753, 1729, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02−0.05 (12H, m), 0.86, 0.87 (18H, each s), 1.16−1.29 (9H, m), 1.65−1.87 (1H, m), 1.83−2.02 (1H, m), 3.00−3.74 (8H, m), 4.00−4.24 (5H, m), 4.08, 4.49 (1H, d, *J* = 8.2, 10.0 Hz, respectively), 4.55−4.80 (2H, m), 5.28, 5.45 (1H, d, *J* = 8.2, 10.0 Hz, respectively), 5.83−6.00 (1H, m); MS (SI) *m*/*z* 730 (M^+ − 17), 690 (M^+ − 57); HRMS (FAB) *m*/*z* calcd for $C_{34}H_{61}NO_{11}SSi_2$ + Na 770.3401 (M^+ + Na), found 770.3372.

Allyl (2*S*,5*R*,6*S*,7*S*)-5-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-7-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethy]-4,8-dioxo-1-aza-3-thiabicyclo[4.2.0]octane-2-carboxylate (25). Conversion of alcohols **24** (0.90 g, 1.20 mmol) into the thiazinone was carried out in a similar way to that of alcohols **6** except that the formation of the corresponding chloride required the reaction temperature up to 0 °C to give **25** (0.415 g, 62%): $[\alpha]^{24}_D$ = −99.1° (*c* 1.0, $CHCl_3$); IR (neat) 1781, 1744, 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (3H, s), 0.03 (3H, s), 0.05 (3H, s), 0.06 (3H, s), 0.85 (9H, s), 0.88 (9H, s), 1.17 (3H, d, *J* = 6.2 Hz), 1.41−1.57 (1H, m), 1.98−2.14 (1H, m), 2.69 (1H, dd, *J* = 4.8, 2.9 Hz), 3.55−3.77 (3H, m), 4.19 (1H, qd, *J* = 6.2, 5.6 Hz), 4.56 (1H, dd, *J* = 7.3, 2.9 Hz), 4.58−4.75 (2H, m), 5.23−5.36 (2H, m), 5.77−5.97 (1H, m), 5.82 (1H, s); ^{13}C NMR ($CDCl_3$) −4.85, −4.30, 17.95, 18.24, 22.80, 25.74, 25.91, 29.90, 46.59, 53.74, 56.61, 60.36, 62.73, 65.01, 66.92, 119.7, 130.8, 166.7, 169.9, 197.5; MS (SI) *m*/*z* 558 (M^+ + 1), 542 (M^+ − 15), 500 (M^+ − 57); HRMS (FAB) *m*/*z* calcd for $C_{26}H_{47}NO_6SSi_2$ + H 558.2741 (M^+ + H), found 558.2742.

Sulfide Contraction Reaction of Thiazinone 25 to Carbapenem 28. To a stirring solution of thiazinone **25** (100 mg, 0.18 mmol) and Ph_3P (46 mg, 0.18 mmol) in toluene (1 mL) and dry THF (1 mL) was added KO-*t*-Bu (26 mg, 0.226 mmol) with ice cooling under N_2, and the reaction mixture was stirred vigorously for 3 h. $(PhO)_2POCl$ (42 μL, 0.20 mmol) and DMAP (2 mg, 0.02 mmol) were added, and the stirring was continued for additional 2 h to form enolphosphate **27**. The mixture was poured into 0.2 M phosphate buffer (pH 7.0) and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was dissolved in dry DMF (2 mL), and mercaptan **8b** (78 mg, 0.309 mmol) and *i*-Pr_2EtN (54 μL, 0.309 mmol) was added to the mixture with ice cooling under N_2. After standing at 0 °C in the refrigerator overnight, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (elution with *n*-hexane:AcOEt = 1:1) to afford carbapenem **28** (43 mg, 31%) as a yellowish gum. Enolphosphate **27** was isolatable (73 mg, 54%) as a yellowish syrup by silica gel column chromatography (elution with *n*-hexane:AcOEt = 9:1).

Allyl (1*R*,5*R*,6*S*)-1-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-[(diphenylphosphoryl)oxy]carbapen-2-em-3-carboxylate (27): $[\alpha]^{26}_D$ = +35.2° (*c* 1.0, $CHCl_3$); IR (neat) 1784, 1733, 1645, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.07 (6H, s), 0.84 (9H, s), 0.88 (9H, s), 1.27 (3H, d, *J* = 6.1 Hz), 1.50−1.80 (1H, m), 1.90−2.11 (1H, m), 3.15−3.84 (4H, m), 4.12 (1H, dd, *J* = 10.3, 2.8 Hz), 4.10−4.35 (1H, m), 4.64 (2H, d, *J* = 5.3 Hz), 5.16−5.40 (2H, m), 5.76−5.96 (1H, m); MS (SI) *m*/*z* 759 (M^+ + 2), 743 (M^+ − 14), 700 (M^+ − 57); HRMS (FAB) *m*/*z* calcd for $C_{38}H_{56}NO_9PSi_2$ + Na 780.3129 (M^+ + Na), found 780.3171.

Allyl (1*R*,5*S*,6*S*)-1-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-6-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-[[(3*S*,5*S*)-5-[(dimethylamino)carbonyl]pyrrolidin-3-yl]thio]carbapen-2-em-3-carboxylate (28): $[\alpha]^{26}_D$ = +7.14° (*c* 0.70, $CHCl_3$); IR (neat) 1774, 1710, 1660, 1560, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (3H, s), 0.04 (3H, s), 0.06 (3H, s), 0.10 (3H, s), 0.87 (9H, s), 0.90 (9H, s), 1.26 (3H, d, *J* = 4.9 Hz), 1.50−2.10 (3H, m), 2.50−2.68 (1H, m), 2.96, 2.98 (3H, each s), 3.04, 3.09 (3H, each s), 3.00−3.10 (1H, m), 3.42−3.57 (2H, m), 3.60−3.89 (2H, m), 4.02−4.31 (2H, m), 4.50−4.84 (5H, m), 5.16−5.48 (4H, m), 5.75−6.05 (2H, m); ^{13}C NMR ($CDCl_3$) δ −4.83, −4.31, 14.22, 18.04, 18.15, 22.66, 25.85, 29.33, 33.47, 34.98, 36.15, 36.99, 39.67, 40.32, 44.89, 54.48, 55.10, 55.79, 59.88, 60.56, 65.71, 66.04, 66.27, 66.41, 76.41, 77.05, 77.68, 117.8, 118.4, 126.0, 131.7, 132.8, 146.7, 153.3, 153.8, 160.3, 171.0, 172.1; MS (SI) *m*/*z* 767 (M^+ + 2), 708 (M^+ − 57); HRMS-(FAB) *m*/*z* calcd for $C_{37}H_{63}N_3O_8SSi_2$ + Na 788.3772 (M^+ + Na), found 788.3781.

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Supporting Information Available: ^1H NMR spectra (200 MHz) for **5**, **6**, **7**, **10a**, **10b**, **14**, **15**, **16**, **18**, **19**, **21**, **22**, **23**, **24**, **25**, **27**, and **28** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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