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# A Practical and Stereocontrolled Synthesis of a Versatile 1$\beta$-Methylcarbapenem Intermediate

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**$S$-[2-(Dialkylaminocarbonyl)phenyl](2$R$)-2-[(3$S$,4$S$)-3-[(1$R$)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (11), useful intermediates for the synthesis of 1$\beta$-methylcarbapenems including 1$\beta$-methylthienamycin, were prepared in a highly stereoselective manner by the reaction of $E$-1-(*tert*-butyldimethylsilyloxy)-1-[2-(dialkylaminocarbonyl)phenylthio]-1-propene (10) with commercially available (3$S$,4$R$)-3-[(1$R$)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-acetoxyazetidin-2-one (6) in the presence of zinc chloride catalyst. The diethylaminocarbonyl derivative (11b) was particularly convenient for practical production because of its highly crystalline nature.**

**Key words** 1$\beta$-methylcarbapenem; silyl enolate; 4-acetoxyazetidinone; zinc chloride

Since 1$\beta$-methylcarbapenems (**1a**, **1b**) were discovered by a Merck research group,[1] a lot of attention has been focused on the 2-substituted analogue, because the 1$\beta$-methyl group proved to impart enhanced chemical and metabolic stability while still maintaining excellent antimicrobial activity compared with non-methylated carbapenems.

Among hundreds of reports and reviews concerning synthetic works of 1$\beta$-methylcarbapenems,[2] Merck's pioneering research was notable for the synthesis of 2-thio derivatives of 1$\beta$-methylcarbapenems *via* carboxylic acid (**2**) which are versatile in structure–activity relationship studies. We have been interested in the practical synthesis of 1$\beta$-methylcarbapenems and designed a new retrosynthetic plan of protected 1$\beta$-methylcarbapenems (**3**) as follows: (i) side chain substitution reaction of $S$-oxide derivative (**4**) with required functionalized mercaptan (RSH); (ii) construction of carbapenem's bicyclic skeleton by intramolecular Wittig-type reaction[3] of a derivative of **5** and the following oxidation of sulfide; (iii) stereospecific formation of $\beta$-methyl thioester (**5**) from an enolate of a thiopropionate derivative and 4-acetoxyazetidinone (**6**) (Chart 2).

A unique characteristic of this scheme is that an auxiliary $R^1$ for stereoselective introduction of the $\beta$-methyl group works once again as a leaving group to incorporate a functionalized 2-alkylthio side chain. In this paper, the stereocontrolled preparation of **11b** which may be applicable to large-scale production of 1$\beta$-methylcarbapenems is described.

## Results and Discussion

A precursor for silyl enolate was easily prepared from 2,2′-dithiobenzamide (**8**), which was obtained from commercially available 2,2′-dithiobenzoic acid (**7**) *via* its acid chloride.[4] Reduction of **8** with zinc powder in the presence of propionic anhydride gave the desired $S$-aryl thiopropionate (**9**) directly. The thiopropionate was converted into silyl enolate (**10**) using an internal quench methodology[5] in order to avoid the fragmentation reaction

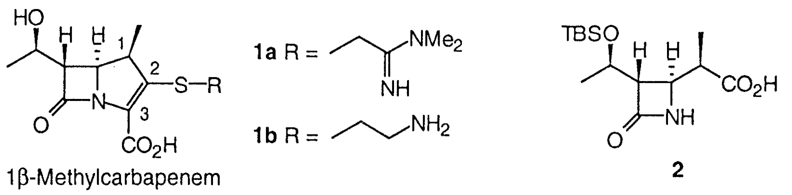

Chart 1

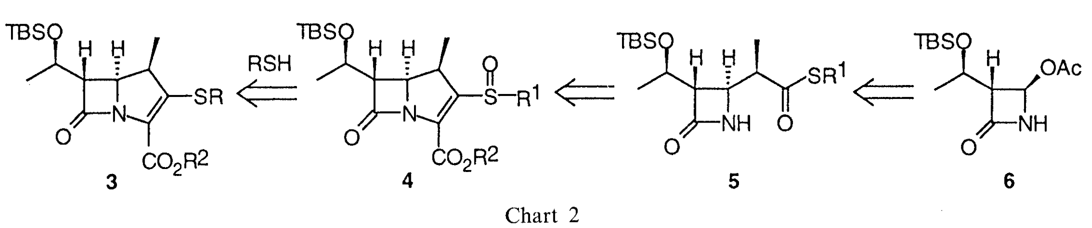

Chart 2

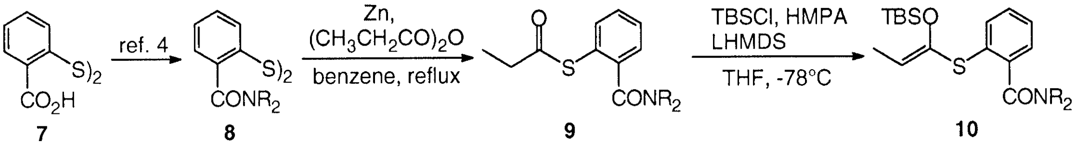

Chart 3

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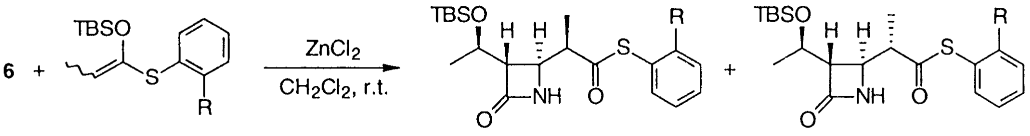
of lithium enolate intermediate into ketene and the lithium salt of mercaptan. Namely a tetrahydrofuran (THF) solution of lithium bis(trimethylsilyl)amide (LHMDS) was added to the cooled mixture of **9**, *tert*-butyldimethylsilyl chloride (TBSCl) and hexamethylphosphoric triamide (HMPA) (2 eq) (Chart 3). The HMPA was added in order to accelerate the reaction between the silyl chloride and the lithium enolate. The silyl enolates prepared by this procedure were generally rich in *E*-isomer, and the *E*/*Z* ratio varied from 60/40 to 88/12. The stereochemistry and the ratio were deduced from the $^1$H-NMR spectra by using the resonance signal of the allylic protons (1.7—1.8 ppm).

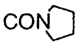
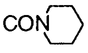
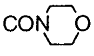
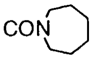
The coupling reaction with acetoxyazetidinone (**6**) was performed by employing 2 eq of the silyl enolate (**10**) in the presence of $ZnCl_2$ (2 eq) in $CH_2Cl_2$ at room temperature. Diastereomeric *β*- and *α*-methyl products (**11**, **12**) were separated using silica gel flash column chromatography, and a *β*-methyl isomer was always polar than the corresponding *α*-methyl isomer. The ratio of isomers was determined based on the weight of the isolated isomers. The stereochemistry of each product was assigned by the coupling constant between the C-4 proton on the azetidinone ring and the C-2 proton of the propionate side chain in the $^1$H-NMR spectrum.[6)] The results are listed in Table 1. As was shown in the table, the total yields of the coupling reactions were generally high. Silyl enolates (**10j**, **10k**) in which a hydrogen and an isopropyl group were the substituents on the phenyl ring, respectively, gave undesirable *α*-isomer predominantly. On the other hand, silyl enolate having a dialkylaminocarbonyl group as a substituent on the phenyl ring yielded preferable *β*-isomer as the major product, and it was determined that a coordinating group to zinc metal was necessary for the predominant production of *β*-isomer. Among the *β*-isomers of the products, those carrying a cyclic amino group (entries 6—9) were all amorphous including the *β*-isomer (**11i**) that was formed with the best diastereoselectivity. On the other hand, the *β*-isomers containing an acyclic amino group (**11a**—**11d**) were obtained as crystalline solids. This is one of the most important aspects for practical production because the isolation and purification of the product is simplified by recrystallization. The silyl enolate (**10b**) was chosen to optimize the coupling reaction conditions, because it revealed the highest diastereoselectivity among silyl enolates yielding crystalline products.

In order to clarify the influence of the geometry of silyl enolate on the diastereoselectivity of coupling products, *E*- and *Z*-isomers of **10b** were separated by preparative reverse phase HPLC (acetonitrile/$H_2O$ = 90/10). The molar ratio of silyl enolate (**10b**) and acetoxyazetidinone (**6**) in their coupling reaction was reduced from 2/1 to 1.2/1 in order to minimize the kinetic effect. The amount of $ZnCl_2$ was also cut down to a catalytic amount (0.2 eq) without affecting the yield. In this case, raising the reaction temperature to the boiling point of $CH_2Cl_2$ was necessary for a reasonable reaction rate. The *E*-silyl enolate (*E*-**10b**) ($E/Z = 95/5$) afforded selectively *β*-isomer (**11b**) ($\beta/\alpha = 95/5$) in 88% yield in contrast to the fact that the *Z*-silyl enolate (*Z*-**10b**) ($E/Z = 4/96$) showed opposite stereoselectivity ($\beta/\alpha = 10/90$) in a slightly lower yield of 65%. From these results, we proposed a transition state of the coupling reaction depicted in Chart 4, in which the azetidinone ring and silyl enolate are arranged properly by mediacy of zinc metal. In entry 5, lower selectivity of the formation of *β*-isomer was observed. This result was explained by the weaker coordination between zinc and

Table 1. The Coupling Reaction of Silyl Enolate (**10**) with Acetoxyazetidinone (**6**)



**10a**—**k** **11a**—**k** **12a**—**k**

| Entry | | R | Silyl enolate **10** *E*/*Z* ratio[a)] | Yield (%) | Isolated yield (%) | | | Ratio of **11**/**12** | mp (°C) of **11** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **11** | **12** | Total | | |
| 1 | **a** | $CONMe_2$ | 80/20 | 85 | 79 | 16 | 95 | 83/17 | 99—101 |
| 2 | **b** | $CONEt_2$ | 81/19 | 88 | 82 | 10 | 92 | 89/11 | 130.5—132 |
| 3 | **c** | $CONPr_2$ | 68/32 | 88 | 74 | 21 | 95 | 78/22 | 112—113 |
| 4 | **d** | $CON(iso\text{-}Bu)_2$ | 60/40 | 85 | 50 | 38 | 88 | 57/43 | 144—146 |
| 5 | **e** | CON(Me)Ph | 88/12 | 87 | 64 | 25 | 89 | 72/28 | Amorphous |
| 6 | **f** |  | 86/14 | 94 | 85 | 12 | 97 | 88/12 | Amorphous |
| 7 | **g** |  | 73/27 | 94 | 75 | 16 | 91 | 82/18 | Amorphous |
| 8 | **h** |  | 84/16 | 99 | 83 | 11 | 94 | 88/12 | Amorphous |
| 9 | **i** |  | 73/27 | 86 | 87 | 9 | 96 | 91/ 9 | Amorphous |
| 10 | **j** | H | 83/17 | 63 | b) | b) | 97 | 9/91[c)] | |
| 11 | **k** | iso-Pr | >20/ 1 | 88 | b) | b) | 99 | 5/95 | |

*a*) Determined by peak area ratio of $^1$H-NMR spectrum. *b*) **11** and **12** were inseparable by silica gel column chromatography. *c*) Similar results was reported by Martel *et al.*[6a)] the oxygen atom. The presence of a phenyl substituent on the aminocarbonyl moiety reduced the electron density of carbonyl oxygen. Martel *et al.* found that a *β*-methyl thiopropionate was obtained stereoselectively by $ZnCl_2$-mediated reaction between **6** and the silyl enolate derived from *S*-(3-methyl-2-pyridylmethyl) thiopropionate.[6a] A similar reaction using *S*-(3-methyl-2-pyridyl) thiopropionate was reported by Hirai *et al.*[6b] It was mentioned in both papers that zinc chelation between nitrogen and sulfur atoms in the silyl enolate molecule is crucial for the high stereoselectivity. They observed that both *E*- and *Z*-silyl enolate yielded predominantly *β*-isomer, which was quite different from our case where *E*- and *Z*-isomers gave *β*- and *α*-isomers, respectively. Although Martel's or Hirai's silyl enolate bearing a pyridyl group gave better stereoselectivity for the formation of *β*-isomer, silyl enolate with a dialkylaminocarbonyl group (*e.g.* **10b**) was obviously more suitable for our purpose because *N*-oxidation would be inevitable to a certain extent in the presence of a pyridine ring in the subsequent oxidation step of sulfide to *S*-oxide (**4**).

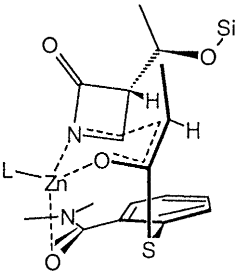
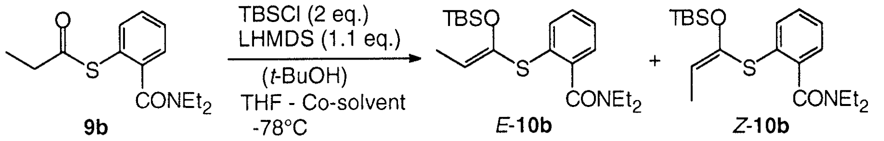


Chart 4

We next focused on the stereoselective preparation of silyl enolate (*E*-**10b**) which gave the desirable *β*-isomer **11b** (Table 2). It is well known that *E*-silyl enolates are obtained by deprotonation and silylation using HMPA as the co-solvent in THF.[7] Indeed, *E*/*Z*-selectivity in our compound also increased up to 93/7 (entry 3) by increasing the proportion of HMPA to 33% (v/v). When a catalytic amount of *tert*-butyl alcohol was added to promote thermodynamic equilibrium of lithium enolate prior to silylation, an *E*/*Z* ratio of 94/6 was obtained in spite of a low proportion of HMPA (entry 2). However, a substitute for HMPA was necessary for practical use because of its toxicity. Use of *N*,*N*-dimethylformamide (DMF) as the co-solvent was most successful. An *E*/*Z* selectivity of >95/5 was attained (entry 7), which was the same level as that obtained by preparative HPLC separation.

Table 2. Selective Preparation of *E*-Silyl Enolate



| Entry | Co-solvent[a] | Co-solvent/THF[b] (v/v) | *tert*-BuOH | **10b** *E*/*Z* ratio[c] |
|---|---|---|---|---|
| 1 | HMPA | 1/3—1/6 | — | 84/16 |
| 2 | HMPA | 1/3—1/6 | 0.1 | 94/ 6 |
| 3 | HMPA | 1/2—1/3 | — | 93/ 7 |
| 4 | DMPU | 1/4—1/8 | — | 58/42 |
| 5 | DMPU | 1/4—1/8 | 0.04 | 84/16 |
| 6 | DMA | 1/1—1/2 | — | 82/18 |
| 7 | DMF | 1/1—1/2 | — | >95/ 5 |

*a*) DMPU: *N*,*N*′-dimethylpropyleneurea, DMA: *N*,*N*-dimethylacetamide. *b*) The proportion of co-solvent decreased, as the THF solution of LHMDS was added. *c*) The ratio was determined by the peak area ratio in the $^1$H-NMR spectrum of crude product.

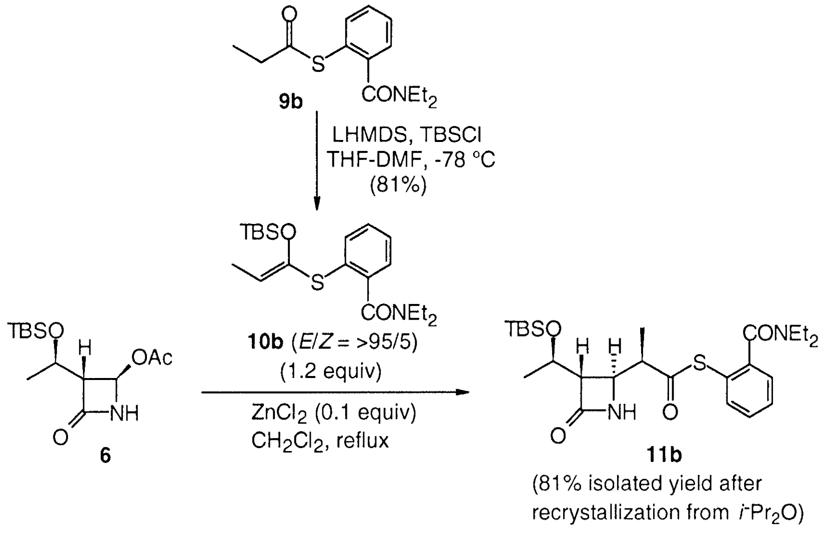


Chart 5

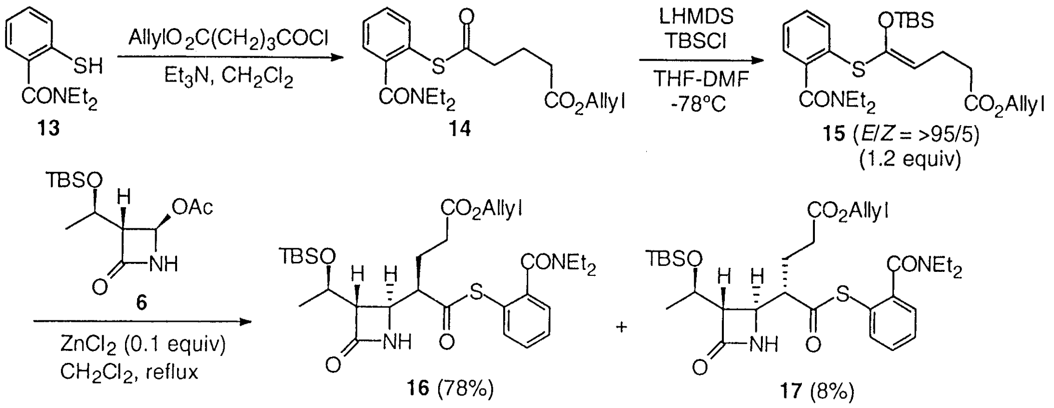


Chart 6

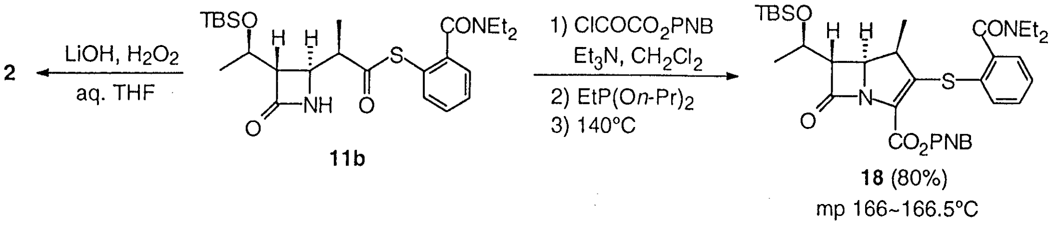


Chart 7

The practical synthesis of **11b** was performed using 1.2 eq of silyl enolate ($E$-**10b**) obtained using the above improved conditions and 0.1 eq of ZnCl$_2$. After conventional treatment of the reaction mixture, crystallization of a crude product from isopropyl ether afforded the desired **11b** in 81% yield (Chart 5). In this experiment, the entire stereoselectivity was **11b**/**12b** ($\beta/\alpha$) = 92 : 8.

This diethylaminocarbonylphenylthio auxiliary also effected stereoselective introduction of the other $\beta$-configured alkyl side chain at the C-1 position of the carbapenem skeleton. For example, introduction of a protected 3-propionate moiety was demonstrated as shown in Chart 6. The silyl enolate (**15**) was prepared from the corresponding thioester (**14**) using co-solvent of 50% (v/v) DMF in THF. The geometry of the silyl enolate obtained in this procedure was again $E$-isomer ($E/Z$ = >95/5). Reaction of this silyl enolate with **6** gave predominantly the $\beta$-isomer of the thioester (**16**) in 78% yield accompanied by 8% yield of the $\alpha$-isomer (**17**). The stereochemistry of each product was assigned similarly as was done for the assignment of **11** and **12**. The product (**16**) would be a useful intermediate for the synthesis of carbapenems which have a functionalized alkyl group at the 1$\beta$-position.

Finally, the versatility of **11b** is shown in Chart 7. Hydrolysis of **11b** with alkaline hydrogen peroxide gave the versatile key intermediate **2**. In addition, **11b** was converted to a new 1$\beta$-methyl-2-arylthiocarbapenem (**18**) as follows: $N$-acylation of **11b** with $p$-nitrobenzyloxyoxalyl chloride, formation of ylide by reacting with dipropyl ethylphosphonite, and finally thermal intramolecular cyclization.[3,8] A successful application of the substitution reaction of a sulfoxide derived from **18** to form, *e.g.*, 1$\beta$-methylthienamycin will be announced in a forthcoming paper.

## Conclusion

A practical route for the industrial-scale production of a key intermediate of 1$\beta$-methylcarbapenems was developed.

### Experimental

Reagents were used as purchased except for ZnCl$_2$ which was dried by heating to melting under reduced pressure. Anhydrous THF was used as purchased from Aldrich Chemical Co., Ltd. Other solvents for anhydrous reactions were dried over 4A molecular sieves before use. Chromatography columns were prepared with Aluminum oxide 90 (70—230 mesh) or Silica gel 60 (230—400 mesh) from E. Merck Co., Ltd. Reactions were carried out under nitrogen atmosphere. IR spectra were recorded on a JASCO A-102, FT/IR-5300 or FT/IR-8300 spectrometer. $^1$H-NMR spectra were recorded on a JEOL JNM-EX-270 (270 MHz) spectrometer. Chemical shifts are shown in ppm downfield from internal tetramethylsilane in CDCl$_3$. The abbreviation used in $^1$H-NMR data are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Mass spectra (MS) were obtained on a JEOL JMS-01SG, JMS-D300, JMS-AX505H (EI) or JMS-SX/SX102A (FAB and high resolution mass spectra (HR-MS)) spectrometer. 2,2′-Disulfanediyldibenzamide derivatives (**8a**—**i**) were prepared from commercial 2,2′-disulfanediyldibenzoic acid according to the literature.[4]

***S*-[2-(Dimethylaminocarbonyl)phenyl]thiopropionate (9a)** A typical experimental procedure for the preparation of **9** is described below. A mixture of 2,2′-disulfanediyldibenzoic acid bisdimethylamide (**8a**) (5.31 g, 14.7 mmol), zinc powder (1.56 g, 23.9 mmol), and propionic anhydride (8.8 ml, 68.6 mmol) in benzene (20 ml) was refluxed for 2 h. After being cooled to room temperature, the solution was diluted with EtOAc (100 ml). Insoluble precipitate was separated by filtration and washed with EtOAc. The combined filtrate was further diluted with EtOAc and the solution was washed with water and brine in turn, dried over anhydrous MgSO$_4$, and concentrated. The oily residue was purified by silica gel column chromatography (acetone/hexane = 1/2) to give **9a** (6.43 g, 92%) as a pale yellow oil. IR (film): 1709, 1639, 1396, 1096, 927 cm$^{-1}$. $^1$H-NMR $\delta$: 1.17 (3H, t, $J$ = 7.3 Hz), 2.65 (2H, q, $J$ = 7.3 Hz), 2.75 (3H, s), 3.07 (3H, s), 7.17—7.55 (4H, m). MS (EI) $m/z$: 238 (M$^+$ + 1), 181, 136.

$S$-[2-(Diethylaminocarbonyl)phenyl]thiopropionate (**9b**): Pale yellow oil IR (film): 1709, 1634, 1430, 1293, 1106, 928 cm$^{-1}$. $^1$H-NMR $\delta$: 1.02 (3H, t, $J$ = 7.3 Hz), 1.20 (3H, t, $J$ = 7.3 Hz), 1.23 (3H, t, $J$ = 7.3 Hz), 2.66 (2H, q, $J$ = 7.3 Hz), 3.00—3.10 (2H, br), 3.20—3.35 (1H, br), 3.75—3.90

(1H, br), 7.30—7.33 (1H, m), 7.42—7.50 (3H, m). MS (EI) $m/z$: 265 (M$^+$), 209, 176, 137.

*S*-[2-(Dipropylaminocarbonyl)phenyl]thiopropionate (**9c**): 96% yield. Colorless oil. IR (film): 1709, 1635, 1424, 1253, 1107, 929 cm$^{-1}$. $^1$H-NMR $\delta$: 0.72 (3H, t, $J=7.3$ Hz), 0.98 (3H, t, $J=7.3$ Hz), 1.20 (3H, t, $J=7.3$ Hz), 1.45 (2H, m), 1.69 (2H, m), 2.66 (2H, q, $J=7.3$ Hz), 2.90—3.00 (2H, br), 3.10—3.80 (2H, br), 7.29—7.33 (1H, m), 7.40—7.50 (3H, m). MS (EI) $m/z$: 293 (M$^+$), 237, 204, 137.

*S*-[2-(Diisobutylaminocarbonyl)phenyl]thiopropionate (**9d**): 99% yield. Colorless oil. IR (film): 1713, 1637, 1425, 1280, 1112, 930 cm$^{-1}$. $^1$H-NMR $\delta$: 0.74 (6H, d, $J=6.6$ Hz), 1.01 (6H, d, $J=6.6$ Hz), 1.19 (3H, t, $J=7.3$ Hz), 1.81 (1H, m), 2.14 (2H, m), 2.66 (2H, q, $J=7.3$ Hz), 2.85—2.90 (2H, m), 3.10—3.18 (1H, m), 3.56—3.65 (1H, m), 7.29—7.33 (1H, m), 7.40—7.49 (3H, m). MS (EI) $m/z$: 321 (M$^+$), 265, 222, 209, 137.

*S*-[2-(*N*-Methyl-*N*-phenylaminocarbonyl)phenyl]thiopropionate (**9e**): 96% yield. Colorless oil. IR (film): 1707, 1645, 1496, 1372, 1108, 927 cm$^{-1}$. $^1$H-NMR $\delta$: 1.23 (3H, t, $J=7.3$ Hz), 2.70 (2H, q, $J=7.3$ Hz), 3.12 (0.6H, br s), 3.51 (2.4H, s), 6.98—7.50 (9H, m). MS (EI) $m/z$: 299 (M$^+$), 243, 193, 137.

*S*-[2-(Pyrrolidinocarbonyl)phenyl]thiopropionate (**9f**): 94% yield. Pale yellow oil. IR (film): 1703, 1630, 1420, 1016, 927 cm$^{-1}$. $^1$H-NMR $\delta$: 1.20 (3H, t, $J=7.3$ Hz), 1.77—1.99 (4H, m), 2.67 (2H, q, $J=7.3$ Hz), 3.15 (2H, t, $J=6.6$ Hz), 3.62 (2H, t, $J=6.6$ Hz), 7.35—7.38 (1H, m), 7.42—7.52 (3H, m). MS (EI) $m/z$: 263 (M$^+$), 207, 164, 137.

*S*-[2-(Piperidinocarbonyl)phenyl]thiopropionate (**9g**): 98% yield. Colorless oil. IR (film): 1703, 1632, 1429, 1283, 1000, 926 cm$^{-1}$. $^1$H-NMR $\delta$: 1.21 (3H, t, $J=7.3$ Hz), 1.40—1.46 (2H, m), 1.59—1.69 (4H, m), 2.68 (2H, q, $J=7.3$ Hz), 3.02—3.21 (2H, m), 3.58—3.66 (1H, m), 3.77—3.83 (1H, m), 7.28—7.32 (1H, m), 7.41—7.51 (3H, m). MS (EI) $m/z$: 277 (M$^+$), 221, 137.

*S*-[2-(Morpholinocarbonyl)phenyl]thiopropionate (**9h**): 89% yield. Colorless oil. IR (film): 1702, 1637, 1428, 1380, 1114, 1283, 1015, 927 cm$^{-1}$. $^1$H-NMR $\delta$: 1.22 (3H, t, $J=7.3$ Hz), 2.69 (2H, q, $J=7.3$ Hz), 3.18—3.22 (2H, m), 3.44—3.90 (6H, m), 7.29—7.33 (1H, m), 7.43—7.53 (3H, m). MS (EI) $m/z$: 279 (M$^+$), 223, 179, 137.

*S*-[2-(2*H*-1,3,4,5,6,7-Hexahydroazepinocarbonyl)phenyl]thiopropionate (**9i**): 99% yield. Colorless oil. IR (film): 1708, 1633, 1422, 1302, 1012, 929 cm$^{-1}$. $^1$H-NMR $\delta$: 1.20 (3H, t, $J=7.3$ Hz), 1.50—1.90 (8H, br), 2.67 (2H, q, $J=7.3$ Hz), 3.10—3.22 (2H, br), 3.60—3.72 (2H, br), 7.28—7.32 (1H, m), 7.41—7.52 (3H, m). MS (EI) $m/z$: 291 (M$^+$), 235, 202, 137.

*S*-(2-Isopropylphenyl)thiopropionate (**9k**): Propionic anhydride (0.52 ml, 4.1 mmol) was added to a mixture of 2-isopropylthiophenol (580 mg, 3.43 mmol) and pyridine (0.34 ml, 4.1 mmol) in toluene (7 ml), and the mixture was stirred for 15 h at room temperature. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography ($CH_2Cl_2$/hexane = 1/1) to give **9k** (727 mg, 99%) as a colorless oil. $^1$H-NMR $\delta$: 1.20 (6H, d, $J=6.8$ Hz), 1.23 (3H, t, $J=7.3$ Hz), 2.69 (2H, q, $J=7.3$ Hz), 3.30 (1H, m), 7.18—7.24 (1H, m), 7.37—7.43 (3H, m).

**Synthesis of 9b in Preparative Scale** A small portion (about 5%) of 2,2′-disulfanediyldibenzoic acid bis-diethylamide (**8b**) (87.1 g, 0.209 mol) was added to a mixture of zinc powder (14.36 g, 0.220 mol) and propionic anhydride (80.0 ml, 0.624 mol), and the mixture was heated at 100 °C for 5 min. Then a solution of the remaining **8b** in benzene (100 ml) was added dropwise to the reaction mixture at the same temperature over a period of 20 min, and the mixture was refluxed for 200 min. After being cooled to room temperature, precipitate was separated by filtration and washed with EtOAc. The combined filtrate was further diluted with EtOAc and the solution was washed with water and brine in turn, dried over anhydrous $MgSO_4$, and concentrated. The oily residue was purified by distillation to give **9b** (106.97 g, 96%) as a pale yellow oil. bp 167 °C (0.95 mmHg)—170 °C (1.1 mmHg).

**(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(diethylaminocarbonyl)phenylthio]-1-propene (*E*-10b) and Its (*Z*)-Isomer (*Z*-10b) (Method A)** A typical experimental procedure for the preparation of **10** is described below. A 1.0 M THF solution of LHMDS (3.0 ml, 3.0 mmol) was added to a solution of **9b** (729 mg, 2.75 mmol), TBSCl (832 mg, 5.52 mmol) and HMPA (621 mg, 3.47 mmol) in THF (6 ml) at −78 °C over a period of 7 min. The reaction mixture was stirred for 10 min, and then quenched by adding 2 ml of saturated aqueous $NaHCO_3$. After being diluted with hexane, the solution was washed twice with water, with saturated brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by alumina column chromatography ($CH_2Cl_2$/hexane = 1/1) to give a mixture of *E*,*Z*-isomers of **10b** (922 mg, 88%) as a colorless oil. The *E*/*Z* ratio was 81/19 by peak area ratio in the $^1$H-NMR spectrum. $^1$H-NMR $\delta$: *E*-**10b**: 0.11 (6H, s), 0.89 (9H, s), 1.07 (3H, t, $J=7.3$ Hz), 1.27 (3H, t, $J=7.3$ Hz), 1.70 (3H, d, $J=6.6$ Hz), 3.11—3.22 (2H, m), 3.50—3.65 (2H, br), 5.35 (1H, q, $J=6.6$ Hz), 7.11—7.20 (2H, m), 7.22—7.32 (1H, m), 7.38-7.44 (1H, m). *Z*-**10b**: 0.10 (6H, s), 0.80 (9H, s), 1.07 (3H, t, $J=7.3$ Hz), 1.27 (3H, t, $J=7.3$ Hz), 1.78 (3H, d, $J=6.6$ Hz), 3.11—3.22 (2H, m), 3.50—3.65 (2H, br), 5.35 (1H, q, $J=6.6$ Hz), 7.11—7.20 (2H, m), 7.22—7.32 (1H, m), 7.38—7.44 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(dimethylaminocarbonyl)phenylthio]-1-propene (*E*-**10a**) and Its (*Z*)-Isomer (*Z*-**10a**): 85% yield, the *E*/*Z* ratio was 80/20. Colorless oil. $^1$H-NMR $\delta$: *E*-**10a**: 0.11 (6H, s), 0.89 (9H, s), 1.70 (3H, d, $J=6.6$ Hz), 2.88 (3H, s), 3.12 (3H, s), 5.35 (1H, q, $J=6.6$ Hz), 7.15—7.20 (2H, m), 7.24—7.33 (1H, m), 7.40—7.47 (1H, m). *Z*-**10a**: 0.10 (6H, s), 0.79 (9H, s), 1.78 (3H, d, $J=6.6$ Hz), 2.88 (3H, s), 3.12 (3H, s), 5.33 (1H, q, $J=6.6$ Hz), 7.15—7.20 (2H, m), 7.24—7.33 (1H, m), 7.40—7.47 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(dipropylaminocarbonyl)phenylthio]-1-propene (*E*-**10c**) and Its (*Z*)-Isomer (*Z*-**10c**): 88% yield, the *E*/*Z* ratio was 68/32. Colorless oil. $^1$H-NMR $\delta$: *E*-**10c**: 0.11 (6H, s), 0.73 (3H, t, $J=7.3$ Hz), 0.89 (9H, s), 1.00 (3H, t, $J=7.3$ Hz), 1.43—1.60 (2H, m), 1.62—1.80 (2H, m), 1.70 (3H, d, $J=6.6$ Hz), 3.01—3.10 (2H, m), 3.40—3.53 (2H, br), 5.35 (1H, q, $J=6.6$ Hz), 7.10—7.19 (2H, m), 7.22—7.31 (1H, m), 7.36—7.43 (1H, m). *Z*-**10c**: 0.10 (6H, s), 0.73 (3H, t, $J=7.3$ Hz), 0.81 (9H, s), 1.00 (3H, t, $J=7.3$ Hz), 1.43—1.60 (2H, m), 1.62—1.80 (2H, m), 1.77 (3H, d, $J=6.6$ Hz), 3.01—3.10 (2H, m), 3.40—3.53 (2H, br), 5.37 (1H, q, $J=6.6$ Hz), 7.10—7.19 (2H, m), 7.22—7.31 (1H, m), 7.36—7.43 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(diisobutylaminocarbonyl)-phenylthio]-1-propene (*E*-**10d**) and Its (*Z*)-Isomer (*Z*-**10d**): 85% yield, the *E*/*Z* ratio was 60/40. Colorless oil. $^1$H-NMR $\delta$: *E*-**10d**: 0.12 (6H, s), 0.75 (6H, d, $J=6.6$ Hz), 0.90 (9H, s), 1.03 (6H, d, $J=7.3$ Hz), 1.71 (3H, d, $J=6.6$ Hz), 1.80—1.95 (1H, m), 2.10—2.22 (1H, m), 2.97—3.04 (2H, m), 3.10—3.70 (2H, br), 5.36 (1H, q, $J=6.6$ Hz), 7.09—7.22 (2H, m), 7.23—7.30 (1H, m), 7.34—7.42 (1H, m). *Z*-**10d**: 0.12 (6H, s), 0.77 (6H, d, $J=6.6$ Hz), 0.82 (9H, s), 1.03 (6H, d, $J=7.3$ Hz), 1.76 (3H, d, $J=6.6$ Hz), 1.80—1.95 (1H, m), 2.10—2.22 (1H, m), 2.97—3.04 (2H, m), 3.10—3.70 (2H, br), 5.42 (1H, q, $J=6.6$ Hz), 7.09—7.22 (2H, m), 7.23—7.30 (1H, m), 7.34—7.42 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(*N*-methyl-*N*-phenylaminocarbonyl)phenylthio]-1-propene (*E*-**10e**) and Its (*Z*)-Isomer (*Z*-**10e**): 87% yield, the *E*/*Z* ratio was 88/12. Colorless oil. $^1$H-NMR $\delta$: *E*-**10e**: 0.15 (6H, s), 0.92 (9H, s), 1.69 (3H, d, $J=6.6$ Hz), 3.46 (3H, br s), 5.34 (1H, q, $J=6.6$ Hz), 6.85—7.27 (8H, m), 7.31—7.38 (1H, m). *Z*-**10e**: 0.10 (6H, s), 0.84 (9H, s), 1.79 (3H, d, $J=6.6$ Hz), 3.46 (3H, br s), 5.39 (1H, q, $J=6.6$ Hz), 6.85—7.27 (8H, m), 7.31—7.38 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(pyrrolidinocarbonyl)phenylthio]-1-propene (*E*-**10f**) and Its (*Z*)-Isomer (*Z*-**10f**): 94% yield, the *E*/*Z* ratio was 86/14. Colorless oil. $^1$H-NMR $\delta$: *E*-**10f**: 0.10 (6H, s), 0.88 (9H, s), 1.69 (3H, d, $J=6.6$ Hz), 1.81—2.02 (4H, m), 3.25 (2H, t, $J=6.6$ Hz), 3.65 (2H, t, $J=6.6$ Hz), 5.36 (1H, q, $J=6.6$ Hz), 7.12—7.33 (3H, m), 7.39—7.45 (1H, m). *Z*-**10f**: 0.10 (6H, s), 0.79 (9H, s), 1.79 (3H, d, $J=6.6$ Hz), 1.81—2.02 (4H, m), 3.25 (2H, t, $J=6.6$ Hz), 3.65 (2H, t, $J=6.6$ Hz), 5.33 (1H, q, $J=6.6$ Hz), 7.12—7.33 (3H, m), 7.39—7.45 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(piperidinocarbonyl)phenylthio]-1-propene (*E*-**10g**) and Its (*Z*)-Isomer (*Z*-**10g**): 94% yield, the *E*/*Z* ratio was 73/27. Colorless oil. $^1$H-NMR $\delta$: *E*-**10g**: 0.11 (6H, s), 0.89 (9H, s), 1.40—1.73 (6H, br), 1.69 (3H, d, $J=6.6$ Hz), 3.20—3.26 (2H, m), 3.55—3.95 (2H, br), 5.34 (1H, q, $J=6.6$ Hz), 7.10—7.19 (2H, m), 7.22—7.32 (1H, m), 7.39—7.45 (1H, m). *Z*-**10g**: 0.10 (6H, s), 0.80 (9H, s), 1.40—1.73 (6H, br), 1.77 (3H, d, $J=6.6$ Hz), 3.20—3.26 (2H, m), 3.55—3.95 (2H, br), 5.34 (1H, q, $J=6.6$ Hz), 7.10—7.19 (2H, m), 7.22—7.32 (1H, m), 7.39—7.45 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(morpholinocarbonyl)phenylthio]-1-propene (*E*-**10h**) and Its (*Z*)-Isomer (*Z*-**10h**): 99% yield, the *E*/*Z* ratio was 84/16. Colorless oil. $^1$H-NMR $\delta$: *E*-**10h**: 0.11 (6H, s), 0.89 (9H, s), 1.70 (3H, d, $J=6.6$ Hz), 3.29 (2H, br s), 3.64 (2H, br s), 3.79 (4H, br s), 5.35 (1H, q, $J=6.6$ Hz), 7.13—7.21 (2H, m), 7.25—7.36 (1H, m), 7.41—7.46 (1H, m). *Z*-**10h**: 0.10 (6H, s), 0.79 (9H, s), 1.78 (3H, d, $J=6.6$ Hz), 3.29 (2H, br s), 3.64 (2H, br s), 3.79 (4H, br s), 5.34 (1H, q, $J=6.6$ Hz), 7.13—7.21 (2H, m), 7.25—7.36 (1H, m), 7.41—7.46 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[2-(2*H*-1,3,4,5,6,7-hexahydroazepinocarbonyl)phenylthio]-1-propene (*E*-**10i**) and Its (*Z*)-Isomer (*Z*-**10i**):

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86% yield, the *E*/*Z* ratio was 73/27. Colorless oil. *E*-**10i**: $^{1}$H-NMR $\delta$: 0.12 (6H, s), 0.90 (9H, s), 1.55—1.67 (6H, m), 1.69 (3H, d, $J$=6.6 Hz), 1.80—1.90 (2H, m), 3.24—3.31 (2H, m), 3.65—3.73 (2H, m), 5.34 (1H, q, $J$=6.6 Hz), 7.10—7.19 (2H, m), 7.21—7.33 (1H, m), 7.38—7.45 (1H, m). *Z*-**10i**: $^{1}$H-NMR $\delta$: 0.10 (6H, s), 0.79 (9H, s), 1.55—1.67 (6H, m), 1.78 (3H, d, $J$=6.6 Hz), 1.80—1.90 (2H, m), 3.24—3.31 (2H, m), 3.65—3.73 (2H, m), 5.33 (1H, q, $J$=6.6 Hz), 7.10—7.19 (2H, m), 7.21—7.33 (1H, m), 7.38—7.45 (1H, m).

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1-[(2-isopropylphenyl)thio]-1-propene (*E*-**10k**): 88% yield, the *E*/*Z* ratio was >95/5. Colorless prism. $^{1}$H-NMR $\delta$: 0.08 (6H, s), 0.88 (9H, s), 1.21 (6H, d, $J$=6.8 Hz), 1.69 (3H, d, $J$=6.8 Hz), 3.28 (1H, m), 5.17 (1H, q, $J$=6.8 Hz), 7.10—7.25 (3H, m), 7.34—7.37 (1H, m).

**HPLC Separation of Geometric Isomers of Silyl Enolate, *Z*-10b and *E*-10b** The *E*- and *Z*-isomers were separated using preparative reverse-phase HPLC (Shiseido: Capsel Pac C18 SG-120, 20 mm$\phi$*250 mmL, acetonitrile/$H_2O$=90/10, flow rate 5 ml/min). *Z*-**10b** (less retained isomer): $^{1}$H-NMR $\delta$: 0.10 (6H, s), 0.80 (9H, s), 1.07 (3H, t, $J$=7.3 Hz), 1.27 (3H, t, $J$=7.3 Hz), 1.78 (3H, d, $J$=6.6 Hz), 3.18 (2H, q, $J$=7.3 Hz), 3.50—3.65 (2H, br), 5.35 (1H, q, $J$=6.6 Hz), 7.15—7.19 (2H, m), 7.23—7.29 (1H, m), 7.38—7.41 (1H, m). *E*-**10b** (more retained isomer): $^{1}$H-NMR $\delta$: 0.11 (6H, s), 0.89 (9H, s), 1.07 (3H, t, $J$=7.3 Hz), 1.27 (3H, t, $J$=7.3 Hz), 1.70 (3H, d, $J$=6.6 Hz), 3.16 (2H, q, $J$=7.3 Hz), 3.50—3.63 (2H, br), 5.35 (1H, q, $J$=6.6 Hz), 7.14—7.18 (2H, m), 7.25—7.31 (1H, m), 7.41—7.44 (1H, m).

**Stereoselective Preparation of *E*-10b (Method B)** A 1.0 M THF solution of LHMDS (75.5 ml, 75.5 mmol) was added to a solution of **9b** (20.01 g, 75.4 mmol), TBSCl (22.33 g, 148 mmol) in THF and DMF (1 : 1 (v/v), 150 ml) at < −65 °C over a period of 20 min. The reaction mixture was stirred for 30 min, and then quenched by being poured into water. The mixture was extracted with hexane, and the organic extract was washed twice with water and brine in turn, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane=1/9—3/7) to give the desired *E*-isomer of **10b** (23.25 g, 81%) as a colorless oil. The *E*/*Z* ratio was calculated as >95/5 by peak area ratio in the $^{1}$H-NMR spectrum.

***S*-[2-(Diethylaminocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (11b) and Its (2*S*)-Isomer (12b) (Method C)** A typical experimental procedure for the coupling reaction is described below. Anhydrous $ZnCl_2$ (330 mg, 2.42 mmol) was added to a solution of **10b** (*E*/*Z*=81/19) (911 mg, 2.40 mmol) and **6** (347 mg, 1.21 mmol) in $CH_2Cl_2$ (12 ml), and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc and the solution was washed with water and saturated brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane=1/1—7/3), to give the 2*S*-isomer (**12b**) (61 mg, 10%) as a colorless crystalline solid from the less polar fraction, and the 2*R*-isomer (**11b**) (487 mg, 82%) as a colorless crystalline solid from the more polar fraction. **11b**: mp 130.5—132 °C (iso-$PrO_2$). $[\alpha]_D^{26}$ −36.4° ($c$=1.2, $CHCl_3$). IR (KBr): 1762, 1700, 1637, 1140, 1102, 965 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.08 (6H, s), 0.87 (9H, s), 1.03 (3H, t, $J$=7.3 Hz), 1.21 (3H, d, $J$=6.6 Hz), 1.27 (3H, d, $J$=6.6 Hz), 1.28 (3H, t, $J$=7.9 Hz), 2.96—3.15 (4H, m), 3.20—3.85 (2H, br), 3.96 (1H, dd, $J$=2.1, 4.1 Hz), 4.19 (1H, quintet, $J$=6.6 Hz), 6.07 (1H, br s), 7.30—7.35 (1H, m), 7.41—7.51 (3H, m). MS (EI) *m*/*z*: 492 (M$^{+}$), 435, 226, 209. *Anal.* Calcd for $C_{25}H_{40}N_2O_4SSi$: C, 60.94; H, 8.18; N, 5.69; S, 6.51. Found: C, 60.85; H, 8.10; N, 5.62; S, 6.50. **12b**: mp 124—125 °C (iso-$PrO_2$). $[\alpha]_D^{25}$ +57.0° ($c$=1.1, $CHCl_3$). IR (KBr): 1765, 1711, 1629, 1296, 1256, 1103, 953 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.06, 0.07 (6H, each s), 0.87 (9H, s), 1.05 (3H, t, $J$=6.9 Hz), 1.26 (3H, d, $J$=5.9 Hz), 1.27 (3H, t, $J$=5.9 Hz), 1.28 (3H, d, $J$=5.9 Hz), 2.71—2.83 (2H, m), 3.00—3.21 (2H, m), 3.35—3.80 (2H, br), 3.63 (1H, d, $J$=9.9 Hz), 4.14 (1H, quintet, $J$=5.9 Hz), 7.15 (1H, br s), 7.30—7.35 (1H, m), 7.42—7.53 (3H, m). MS (EI) *m*/*z*: 492 (M$^{+}$), 435, 226, 209. *Anal.* Calcd for $C_{25}H_{40}N_2O_4SSi$: C, 60.94; H, 8.18; N, 5.69; S, 6.51. Found: C, 60.72; H, 8.01; N, 5.70; S, 6.57.

*S*-[2-(Dimethylaminocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**11a**) and Its (2*S*)-Isomer (**12a**): **11a**: 79% yield from the more polar fraction. Colorless needles. mp 99—101 °C (EtOAc–hexane). $[\alpha]_D^{25}$ −31.7° ($c$=1.2, $CHCl_3$). IR (KBr): 1763, 1703, 1638, 1398, 1137, 1100, 962 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, $J$=6.6 Hz), 1.29 (3H, d, $J$=6.6 Hz), 2.79 (3H, s), 2.96—3.08 (2H, m), 3.10 (3H, s), 3.94 (1H, dd, $J$=4.6, 2.6 Hz), 4.19 (1H, qd, $J$=6.6, 4.6 Hz), 6.15 (1H, br s), 7.31—7.36 (1H, m), 7.40—7.70 (3H, m). MS (EI) *m*/*z*: 465 (M$^{+}$+H), 407, 226, 181. *Anal.* Calcd for $C_{23}H_{36}N_2O_4SSi$: C, 59.45; H, 7.81; N, 6.03; S, 6.90. Found: C, 59.67; H, 8.04; N, 5.89; S, 6.94. **12a**: 16% yield from the less polar fraction. Colorless needles. mp 118.5—119 °C (EtOAc–hexane). $[\alpha]_D^{25}$ +60.1° ($c$=1.1, $CHCl_3$). IR (KBr): 1763, 1712, 1635, 1398, 1255, 1171, 1103, 953 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.08 (6H, s), 0.87 (9H, s), 1.25 (3H, d, $J$=6.6 Hz), 1.27 (3H, d, $J$=7.3 Hz), 2.72—2.89 (2H, m), 2.84 (3H, s), 3.11 (3H, s), 3.64 (1H, dd, $J$=10.0, 1.9 Hz), 4.17 (1H, quintet, $J$=6.6 Hz), 7.02 (1H, br s), 7.32—7.36 (1H, m), 7.45—7.54 (3H, m). MS (EI) *m*/*z*: 465 (M$^{+}$+H), 407, 226, 181. *Anal.* Calcd for $C_{23}H_{36}N_2O_4SSi$: C, 59.45; H, 7.81; N, 6.03; S, 6.90. Found: C, 59.53; H, 7.86; N, 5.94; S, 7.07.

*S*-[2-(Dipropylaminocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**11c**) and Its (2*S*)-Isomer (**12c**): **11c**: 74% yield from the more polar fraction. Colorless needles. mp 112—113 °C (EtOAc–hexane). $[\alpha]_D^{26}$ −33.2° ($c$=1.1, $CHCl_3$). IR (KBr) 1762, 1694, 1641, 1137, 1096, 963 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.08 (6H, s), 0.72 (3H, t, $J$=7.3 Hz), 0.88 (9H, s), 1.00 (3H, t, $J$=7.3 Hz), 1.21 (3H, d, $J$=5.9 Hz), 1.22—1.33 (3H, br), 1.46 (2H, m), 1.70 (2H, m), 2.92—3.05 (2H, m), 3.10—3.80 (2H, br), 3.96 (2H, dd, $J$=4.3, 2.2 Hz), 4.19 (1H, quintet, $J$=5.9 Hz), 6.07 (1H, br s), 7.32—7.35 (1H, m), 7.40—7.52 (3H, m). MS (EI) *m*/*z*: 520 (M$^{+}$), 463, 237, 226. *Anal.* Calcd for $C_{27}H_{44}N_2O_4SSi$: C, 62.27; H, 8.52; N, 5.38; S, 6.16. Found: C, 62.04; H, 8.52; N, 5.32; S, 6.44. **12c**: 21% yield from the less polar fraction. Colorless needles. mp 123—124 °C (EtOAc–hexane). $[\alpha]_D^{26}$ +56.2° ($c$=1.1, $CHCl_3$). IR (KBr): 1766, 1709, 1636, 1252, 1170, 955 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.05, 0.06 (3H, each s), 0.73 (3H, t, $J$=7.3 Hz), 0.87 (9H, s), 1.01 (3H, t, $J$=7.3 Hz), 1.26 (6H, d, $J$=6.6 Hz), 1.48 (2H, m), 1.70 (2H, m), 2.71—2.82 (2H, m), 2.88—3.08 (2H, m), 3.30—3.66 (3H, br), 4.14 (1H, quintet, $J$=6.6 Hz), 7.16 (1H, br s), 7.32—7.35 (2H, m), 7.44—7.50 (3H, m). MS (EI) *m*/*z*: 520 (M$^{+}$), 463, 237, 226. *Anal.* Calcd for $C_{27}H_{44}N_2O_4SSi$: C, 62.27; H, 8.52; N, 5.38; S, 6.16. Found: C, 62.44; H, 8.53; N, 5.35; S, 6.44.

*S*-[2-(Diisobutylaminocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**11d**) and Its (2*S*)-Isomer (**12d**): **11d**: 50% yield from the more polar fraction. Colorless needles. mp 144—146 °C (EtOAc–hexane). $[\alpha]_D^{26}$ −29.0° ($c$=1.1, $CHCl_3$). IR (KBr): 1766, 1705, 1623, 1171, 1060, 952 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.08 (6H, s), 0.74 (6H, d, $J$=6.6 Hz), 0.87 (9H, s), 1.02 (6H, d, $J$=6.6 Hz), 1.21 (3H, d, $J$=5.9 Hz), 1.20—1.40 (3H, br), 1.81 (1H, m), 2.12 (1H, m), 2.80—3.06 (4H, m), 3.20—3.57 (2H, br), 3.98 (1H, br s), 4.13—4.28 (1H, m), 5.95—6.15 (1H, br), 7.29—7.35 (1H, m), 7.42—7.50 (3H, m). MS (EI) *m*/*z*: 549 (M$^{+}$+1), 491, 265, 226. *Anal.* Calcd for $C_{29}H_{48}N_2O_4SSi$: C, 63.46; H, 8.82; N, 5.10; S, 5.84. Found: C, 63.56; H, 8.86; N, 5.04; S, 5.99. **12d**: 38% yield from the less polar fraction. Colorless needles. mp 139—140 °C (EtOAc–hexane). $[\alpha]_D^{26}$ +48.4° ($c$=1.0, $CHCl_3$). IR (KBr): 1763, 1708, 1623, 1255, 1105, 951 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.08 (6H, s), 0.73 (3H, d, $J$=6.6 Hz), 0.78 (3H, d, $J$=6.6 Hz), 0.86 (9H, s), 1.00 (3H, d, $J$=6.6 Hz), 1.02 (3H, d, $J$=6.6 Hz), 1.26 (6H, d, $J$=5.9 Hz), 1.81 (1H, septet, $J$=6.6 Hz), 2.11 (1H, m), 2.72—3.02 (4H, m), 3.26—3.75 (3H, m), 4.11—4.28 (1H, m), 7.13 (1H, br s), 7.30—7.35 (1H, m), 7.43—7.52 (3H, m). MS (EI) *m*/*z*: 549 (M$^{+}$+1), 491, 265, 226; *Anal.* Calcd for $C_{29}H_{48}N_2O_4SSi$: C, 63.46; H, 8.82; N, 5.10; S, 5.84. Found: C, 63.59; H, 8.74; N, 5.10; S, 5.98.

*S*-[2-(*N*-Methyl-*N*-phenylaminocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**11e**) and Its (2*S*)-Isomer (**12e**): **11e**: 64% yield from the more polar fraction. Colorless gum. $[\alpha]_D^{26}$ −23.5° ($c$=1.0, $CHCl_3$). IR (film): 1768, 1698, 1641, 1377, 1255, 1105, 960 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.08, 0.09 (3H, each s), 0.88 (9H, s), 1.23 (3H, d, $J$=5.9 Hz), 1.34 (3H, d, $J$=6.6 Hz), 3.01—3.12 (2H, m), 3.49 (3H, s), 4.04 (1H, br s), 4.21 (1H, quintet, $J$=5.9 Hz), 6.14 (1H, br s), 6.99—7.46 (9H, m); MS (EI) *m*/*z* 469 (M$^{+}$−*tert*-Bu), 243, 226. *Anal.* Calcd for $C_{28}H_{38}N_2O_4SSi$: C, 63.84; H, 7.27; N, 5.32; S, 6.09. Found: C, 63.54; H, 7.22; N, 5.33; S, 6.13. **12e**: 25% yield from the less polar fraction. Colorless needles. mp 158—159.5 °C (EtOAc–hexane). $[\alpha]_D^{25}$ +13.0° ($c$=1.1, $CHCl_3$). IR (KBr): 1761, 1701, 1652, 1379, 953 cm$^{-1}$. $^{1}$H-NMR $\delta$: 0.08 (6H, s), 0.87 (9H, s), 1.28 (3H, d, $J$=5.9 Hz), 1.31 (3H, d, $J$=5.9 Hz), 2.77—2.90 (2H, m), 3.49 (3H, s), 3.71 (1H, d, $J$=9.9 Hz), 4.18 (1H, quintet, $J$=5.9 Hz), 7.04—7.36 (10H, m). MS (EI) *m*/*z*: 527 (M$^{+}$+1), 469, 243, 226. *Anal.* Calcd for $C_{28}H_{38}N_2O_4SSi$: C, 63.84; H, 7.27; N, 5.32; S, 6.09. Found: C, 63.02; H, 7.31; N, 5.23; S, 6.26.

*S*-[2-(Pyrrolidinocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**11f**)

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and Its (2*S*)-Isomer (**12f**): **11f**: 85% yield from the more polar fraction. Colorless foam. $[\alpha]_D^{26}$ −33.1° ($c$=1.1, $CHCl_3$). IR (film): 1760, 1695, 1622, 1253, 1098, 958 cm$^{-1}$. $^1$H-NMR $\delta$: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, $J$=6.6 Hz), 1.29 (3H, d, $J$=6.6 Hz), 1.75—2.00 (4H, m), 2.95—3.06 (2H, m), 3.18 (2H, t, $J$=6.6 Hz), 3.60 (2H, t, $J$=6.6 Hz), 3.96 (1H, dd, $J$=4.4, 2.2 Hz), 4.20 (1H, quintet, $J$=6.6 Hz), 6.16 (1H, br s), 7.37—7.53 (4H, m). MS (EI) $m/z$: 491 ($M^+$+1), 433, 226, 207. FAB-HR-MS $m/z$: 513.2206 (Calcd for $C_{25}H_{38}N_2O_4SSiNa$ ($M^+$+Na): 513.2219). **12f**: 12% yield from the less polar fraction. Colorless viscous oil. $[\alpha]_D^{26}$ +52.4° ($c$=1.2, $CHCl_3$). IR (film): 1758, 1695, 1618, 1255, 1143, 957 cm$^{-1}$. $^1$H-NMR $\delta$: 0.08 (6H, s), 0.87 (9H, s), 1.25 (6H, d, $J$=6.6 Hz), 1.83—2.00 (4H, m), 2.72—2.83 (2H, m), 3.10—3.34 (2H, m), 3.53—3.70 (3H, m), 4.16 (1H, quintet, $J$=6.6 Hz), 7.24 (1H, br s), 7.38—7.52 (4H, m). MS (EI) $m/z$: 491 ($M^+$+1), 433, 226, 207. FAB-HR-MS $m/z$: 513.2198 (Calcd for $C_{25}H_{38}N_2O_4SSiNa$ ($M^+$+Na): 513.2219).

*S*-[2-(Piperidinocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**11g**) and Its (2*S*)-Isomer (**12g**): **11g**: 75% yield from the more polar fraction. Colorless foam. $[\alpha]_D^{25}$ −32.1° ($c$=1.0, $CHCl_3$). IR (nujol): 1757, 1698, 1622, 1282, 1263, 958 cm$^{-1}$. $^1$H-NMR $\delta$: 0.07, 0.08 (6H, each s), 0.87, 0.88 (9H, each s), 1.21—1.23 (3H, m), 1.28, 1.33 (3H, each d, $J$=6.6 Hz), 1.42—1.48 (2H, m), 1.60—1.72 (4H, br), 2.97—3.23 (4H, m), 3.50—3.58 (1H, m), 3.82—3.98 (3H, m), 4.15—4.25 (1H, m), 6.04, 6.11 (1H, each br s), 7.31—7.35 (1H, m), 7.45—7.52 (3H, m). MS (EI) $m/z$: 504 ($M^+$), 447, 227, 221. *Anal.* Calcd for $C_{26}H_{40}N_2O_4SSi$: C, 61.87; H, 7.99; N, 5.55; S, 6.35. Found: C, 61.71; H, 7.85; N, 5.45; S, 6.38. **12g**: 16% yield from the less polar fraction. Colorless viscous oil. $[\alpha]_D^{24}$ +51.5° ($c$=1.1, $CHCl_3$). IR (film): 1757, 1698, 1622, 1282, 1263, 958 cm$^{-1}$. $^1$H-NMR $\delta$: 0.06, 0.09 (6H, each s), 0.86, 0.89 (9H, each s), 1.26 (6H, d, $J$=6.6 Hz), 1.45—1.75 (6H, m), 2.72—2.83 (2H, m), 3.10—3.43 (2H, m), 3.60—3.94 (3H, m), 4.09—4.22 (1H, m), 6.75, 7.19 (1H, each br s), 7.30—7.37 (1H, m), 7.43—7.53 (3H, m). MS (EI) $m/z$: 504 ($M^+$), 447, 221. FAB-HR-MS $m/z$: 513.2368 (Calcd for $C_{26}H_{40}N_2O_4SSiNa$ ($M^+$+Na): 527.2376).

*S*-[2-(Morpholinocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**11h**) and Its (2*S*)-Isomer (**12h**): **11h**: 83% yield from the more polar fraction. Colorless foam. $[\alpha]_D^{26}$ −40.5° ($c$=1.1, $CHCl_3$). IR (nujol): 1758, 1698, 1636, 1264, 1115, 960 cm$^{-1}$. $^1$H-NMR $\delta$: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, $J$=6.6 Hz), 1.27—1.36 (3H, m), 2.98—3.07 (2H, m), 3.12—3.30 (2H, m), 3.50—3.80 (4H, m), 3.97 (1H, br s), 4.17—4.24 (1H, m), 5.90—6.10 (1H, br), 7.32—7.37 (1H, m), 7.47—7.51 (3H, m). MS (EI) $m/z$: 506 ($M^+$), 449, 226, 223. FAB-HR-MS $m/z$: 529.2160 (Calcd for $C_{25}H_{38}N_2O_5SSiNa$ ($M^+$+Na): 529.2168). **12h**: 11% yield from the less polar fraction. Colorless foam. $[\alpha]_D^{26}$ +54.6° ($c$=1.2, $CHCl_3$). IR (nujol): 1759, 1697, 1623, 1262, 1113, 952 cm$^{-1}$. $^1$H-NMR $\delta$: 0.07 (6H, s), 0.87 (9H, s), 1.26 (3H, d, $J$=5.9 Hz), 1.28 (3H, d, $J$=5.9 Hz), 2.75—2.86 (2H, m), 3.15—3.43 (2H, m), 3.58—3.94 (7H, m), 4.12—4.24 (1H, m), 6.77, 6.97 (1H, each br s), 7.32—7.36 (1H, m), 7.45—7.55 (3H, br). MS (EI) $m/z$: 506 ($M^+$), 449, 226, 223. FAB-HR-MS $m/z$: 529.2140 (Calcd for $C_{25}H_{38}N_2O_5SSiNa$ ($M^+$+Na): 529.2168).

*S*-[2-(2*H*-1,3,4,5,6,7-Hexahydroazepinocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**11i**) and Its (2*S*)-Isomer (**12i**): **11i**: 87% yield from the more polar fraction. Colorless viscous oil. $[\alpha]_D^{26}$ −26.7° ($c$=1.1, $CHCl_3$). IR (nujol): 1761, 1700, 1629, 1374, 1140, 954 cm$^{-1}$. $^1$H-NMR $\delta$: 0.08 (6H, s), 0.88 (9H, s), 1.22 (3H, d, $J$=5.9 Hz), 1.20—1.36 (3H, br), 1.52—1.90 (8H, br), 2.99—3.06 (2H, m), 3.10—3.30 (2H, br), 3.45—3.86 (2H, br), 3.95—3.97 (1H, m), 4.18 (1H, quintet, $J$=5.9 Hz), 6.07—6.22 (1H, br), 7.31—7.35 (1H, m), 7.43—7.51 (3H, m). MS (EI) $m/z$: 518 ($M^+$), 461, 235, 226. FAB-HR-MS $m/z$: 541.2545 (Calcd for $C_{27}H_{42}N_2O_4SSiNa$ ($M^+$+Na): 541.2533). **12i**: 9% yield from the less polar fraction. Colorless viscous oil. $[\alpha]_D^{26}$ +50.1° ($c$=1.1, $CHCl_3$). IR (film): 1758, 1702, 1620, 1255, 1143, 953 cm$^{-1}$. $^1$H-NMR $\delta$: 0.07 (6H, s), 0.87 (9H, s), 1.26 (6H, d, $J$=5.9 Hz), 1.52—1.90 (8H, br), 2.64—2.83 (2H, m), 3.12—3.30 (2H, br), 3.50—3.72 (2H, m), 3.81 (1H, td, $J$=13.9, 5.9 Hz), 4.09—4.17 (1H, m), 7.25—7.36 (2H, m), 7.43—7.52 (3H, m). MS (EI) $m/z$: 518 ($M^+$), 461, 235, 226. FAB-HR-MS 519.2732 (Calcd for $C_{27}H_{43}N_2O_4SSi$ ($M^+$+H): 519.2713).

*S*-(2-Isopropylphenyl) (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]thiopropionate (**12k**): The $\alpha$ and $\beta$ isomer were inseparable by silica gel column chromatography. The ratio of **11k** to **12k** was determined to be 5/>95 based on peak area ratio in the $^1$H-NMR spectra. **12k**: $^1$H-NMR $\delta$: 0.07 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.20 (6H, d, $J$=6.8 Hz), 1.25 (3H, d, $J$=6.4 Hz), 1.38 (3H, d, $J$=7.3 Hz), 2.81—2.95 (2H, m), 3.25 (1H, m), 3.77 (1H, dd, $J$=9.8, 2.0 Hz), 4.15—4.23 (1H, m), 6.03 (1H, br s), 7.20—7.25 (1H, m), 7.35—7.43 (3H, m).

**Synthesis of 11b from *E*-10b Using a Catalytic Amount of $ZnCl_2$ (Method D)** Anhydrous $ZnCl_2$ (756 mg, 5.55 mmol) was added to a solution of *E*-**10b** ($E/Z$=>95/5) (23.25 g, 61.24 mmol) and **6** (14.67 g, 51.04 mmol) in $CH_2Cl_2$ (250 ml), and the mixture was stirred under refluxing for 140 min. After the solvent was evaporated, the residue was dissolved in EtOAc, and the solution was washed three times with water and brine in turn, dried over anhydrous $MgSO_4$ and concentrated. The oily residue was diluted with iso-$PrO_2$ (240 ml) and allowed to stand overnight. The crystalline product was collected and dried, to give **11b** (20.44 g, 81%) as colorless needles. The stereochemical purity of the product was shown to be **11b**/**12b**=98.3/1.7 by HPLC analysis (YMC: AQ312 (ODS), 6 mm$\phi$*150 mmL, acetonitrile/$H_2O$=80/20, flow rate 1.5 ml/min). The mother liquor was concentrated and the residue was purified by silica gel column chromatography (EtOAc/hexane=1/1—7/3), to give **12b** (1.85 g, 7%) and additional **11b** (1.29 g, 5%). The stereoselectivity of this reaction was deduced to be **11b**/**12b**=92/8.

***S*-[2-(Diethylaminocarbonyl)phenyl] 4-(2-Propenyloxycarbonyl)thiobutyrate (14)** Compound **14** was obtained as a colorless oil. IR (film): 1734, 1705, 1634 1430, 1293, 1158, 992 cm$^{-1}$. $^1$H-NMR $\delta$: 1.02 (3H, t, $J$=7.2 Hz), 1.23 (3H, t, $J$=7.1 Hz), 2.01 (2H, quintet, $J$=7.3 Hz), 2.42 (2H, t, $J$=7.3 Hz), 2.72 (2H, t, $J$=7.3 Hz), 3.00—3.12 (2H, m), 3.15—3.85 (2H, m), 4.58 (2H, d of t, $J$=5.8, 1.4 Hz), 5.24 (1H, dq, $J$=10.4, 1.4 Hz), 5.32 (1H, dq, $J$=17.1, 1.4 Hz), 5.91 (1H, ddt, 17.1, 10.4, 5.8 Hz), 7.30—7.33 (1H, m), 7.42—7.50 (3H, m). MS (EI) $m/z$: 364 ($M^+$+1), 335, 306, 209.

**2-Propenyl (*E*)-5-(*tert*-Butyldimethylsilyloxy)-5-[2-(diethylaminocarbonyl)phenylthio]-4-pentenoate (15)** Compound **14** was treated as described in the preparation of *E*-**10b** from **9b** by method B to give **15** in 81% yield. The $E/Z$ ratio was >95/5. IR (film): 1738, 1636, 1426, 1258, 1165, 1107, 1053 cm$^{-1}$. $^1$H-NMR $\delta$: 0.11 (6H, s), 0.88 (9H, s), 1.07 (3H, t, $J$=7.1 Hz), 1.26 (3H, t, $J$=7.1 Hz), 2.40—2.54 (4H, m), 3.15 (2H, q, $J$=7.1 Hz), 3.50—3.61 (2H, m), 4.59 (2H, dt, $J$=5.8, 1.4 Hz), 5.20—5.36 (3H, m), 5.91 (1H, ddt, $J$=17.2, 10.4, 5.8 Hz), 7.15—7.17 (2H, m), 7.25—7.31 (1H, m), 7.39 (1H, d, $J$=7.9 Hz).

***S*-[2-(Diethylaminocarbonyl)phenyl] (2*R*)-2-[(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-oxo-4-azetidinyl]-4-(2-propenyloxycarbonyl)thiobutyrate (16) and (2*S*)-Isomer (17)** Compound **15** was treated as described in the preparation of **11b** by method D. **16**: 78% yield from the more polar fraction. Colorless gum. $[\alpha]_D^{24}$ −20.1° ($c$=1.3, $CHCl_3$). IR (film): 1765, 1740, 1700, 1634, 1256, 1173, 957 cm$^{-1}$. $^1$H-NMR $\delta$: 0.07 (6H, s), 0.87 (9H, s), 1.03 (3H, t, $J$=7.1 Hz), 1.20 (3H, d, $J$=6.3 Hz), 1.26 (3H, t, $J$=7.1 Hz), 1.86—2.13 (2H, m), 2.36—2.60 (2H, br), 2.96—3.15 (4H, m), 3.35—3.63 (2H, br), 3.92 (1H, dd, $J$=5.4, 2.0 Hz), 4.21 (1H, qd, $J$=6.3, 4.1 Hz), 4.60 (2H, dt, $J$=5.8, 1.4 Hz), 5.25 (1H, dq, $J$=10.3, 1.4 Hz), 5.33 (1H, dq, $J$=17.2, 1.4 Hz), 5.91 (1H, ddt, 17.2, 10.3, 5.8 Hz), 6.02 (1H, br s), 7.32—7.35 (1H, m), 7.45—7.49 (3H, m). MS ($FAB^+$) $m/z$: 591 ($M^+$+1). FAB-HR-MS $m/z$: 613.2739 (Calcd for $C_{30}H_{46}N_2O_6SSiNa$ ($M^+$+Na): 613.2744). **17**: 8% yield from the less polar fraction. Colorless gum. $[\alpha]_D^{24}$ +8.0° ($c$=1.1, $CHCl_3$). IR (film): 1767, 1740, 1707, 1622, 1256, 1167, 949 cm$^{-1}$. $^1$H-NMR $\delta$: 0.06, 0.07 (6H, each s), 0.86 (9H, s), 1.06 (3H, t, $J$=7.1 Hz), 1.27 (3H, t, $J$=7.1 Hz), 1.28 (3H, d, $J$=6.1 Hz), 1.97 (2H, q, $J$=7.1 Hz), 2.36—2.54 (2H, m), 2.72—2.84 (2H, m), 3.02—3.18 (2H, m), 3.41—3.70 (3H, m), 4.07—4.16 (1H, m), 4.61 (2H, dt, $J$=5.7, 1.4 Hz), 5.26 (1H, dq, $J$=10.3, 1.4 Hz), 5.34 (1H, dq, $J$=17.4, 1.4 Hz), 5.92 (1H, ddt, 17.4, 10.3, 5.8 Hz), 7.32—7.35 (1H, m), 7.42—7.51 (4H, m). MS ($FAB^+$) $m/z$: 591 ($M^+$+1). FAB-HR-MS $m/z$: 613.2726 (Calcd for $C_{30}H_{46}N_2O_6SSiNa$ ($M^+$+Na): 613.2744).

**(3*S*,4*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-carboxyethyl]azetidin-2-one (2)** A 0.43 M aqueous solution of LiOH (2.4 ml, 1.0 mmol) was added to a solution of **11b** (324 mg, 0.658 mmol) and 3% aqueous $H_2O_2$ (1.5 ml, 1.3 mmol) in THF (10 ml) at 0 °C over a period of 5 min. After being stirred for 2 h, the solution was diluted with 1 M $NaH_2PO_4$ (20 ml) and extracted with ether. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Recrystallization of a crude product gaive **2** (189 mg, 63%) as colorless needles. mp 147—148.5 °C (dec.) (EtOAc–hexane). {lit.[1a)] mp 140—143 °C, lit.[9a)] mp 143.5—144 °C, lit.[9b)] mp 145—146 °C, lit.[9c)] mp 148—149 °C}, $[\alpha]_D^{26}$ −31.6° ($c$=0.505, MeOH). {lit.[9a)] $[\alpha]_D^{25}$ −36.9° ($c$=0.469, MeOH), lit.[9b)] $[\alpha]_D^{20}$ −34° ($c$=0.37, MeOH), lit.[9c)] $[\alpha]_D^{20}$ −32.4° ($c$=1.07, MeOH)}.

**4-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[2-(diethylaminocarbonyl)phenylthio]-1-methylcarbapen-2-em-3-carboxylate (18)** *p*-Nitrobenzyloxyoxalyl chloride (729 mg, 3.00 mmol) was added in one portion to an ice-cooled solution of **11b** (493 mg, 1.00 mmol) and triethylamine (0.42 ml, 3.0 mmol) in $CH_2Cl_2$ (7 ml). After stirring for 15 min, excess reagent was quenched by slow addition of 2-propanol (0.23 ml, 3.0 mmol). After being diluted with EtOAc, the solution was washed twice with cold water and brine in turn, dried over anhydrous $MgSO_4$, and concentrated. Freshly prepared EtP(O*n*-Pr)$_2$ (1.07 g, 6.00 mmol) was added to the crude oily product (1.18 g), and stirred for 150 min at room temperature. After excess reagent was evaporated *in vacuo*, the residue was dissolved in xylene (60 ml) and refluxed for 6 h. The solution was concentrated and the oily residue was purified by silica gel column chromatography (EtOAc/hexane = 1/2) to give **18** (536 mg, 80%) as colorless needles. mp 166—166.5 °C (EtOAc–hexane). $[\alpha]_D^{26}$ +146.3° ($c$ = 1.2, $CHCl_3$). IR (KBr): 1763, 1696, 1630, 1341, 1212, 1140, 990 cm$^{-1}$. $^1$H-NMR $\delta$: 0.06 (6H, s), 0.84 (9H, s), 1.01 (3H, t, $J$ = 7.2 Hz), 1.16 (3H, t, $J$ = 6.2 Hz), 0.95—1.15 (6H, m), 3.40—3.85 (1H, br), 4.21—4.30 (2H, m), 5.28 (1H, d, $J$ = 13.9 Hz), 5.44 (1H, d, $J$ = 13.9 Hz), 7.27—7.65 (4H, m), 7.67 (2H, d, $J$ = 8.9 Hz), 8.21 (2H, d, $J$ = 8.9 Hz). MS (EI) $m/z$: 667 (M$^+$), 611, 480, 467, 208. *Anal.* Calcd for $C_{34}H_{45}N_3O_7SSi$: C, 61.14; H, 6.79; N, 6.29; S, 4.80. Found: C, 61.09; H, 6.82; N, 6.24; S, 5.02.

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