Chem. Pharm. Bull.
34(4)1434—1446(1986)

A Formal Total Synthesis of Thienamycin from 4-Propargyl-2-azetidinone[1]

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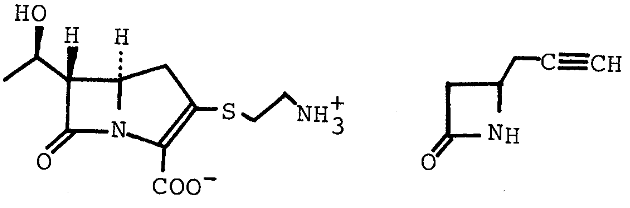
(Received July 18, 1985)

A mild and efficient method for the conversion of propiolic esters to β-keto esters was developed. Initially, propiolic esters were converted to β-phenylthio-α,β-unsaturated esters, which were treated with *N*-bromoacetamide in an aqueous solvent followed by reductive debromination with an aqueous solution of sodium sulfite, affording β-keto esters in good yields. Using this new method, a formal total synthesis of (±)-thienamycin from 4-propargyl-2-azetidinone was accomplished.

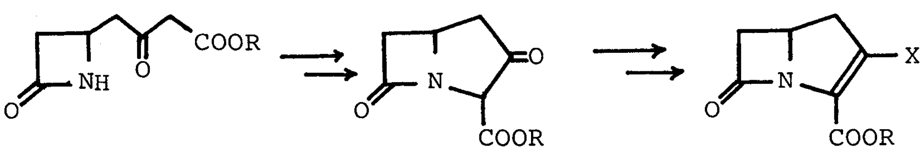
Keywords——β-lactam antibiotic; carbapenem; propiolic ester; β-keto ester; thiophenol; β-phenylthio-α,β-unsaturated ester; *N*-bromoacetamide; α,α-dibromo-β-keto ester; (±)-thienamycin

Since the discovery of thienamycin (**1**), many attempts have been made to synthesize carbapenem antibiotics.[3] In the preceding paper,[4] we have reported an efficient synthesis of 4-propargyl-2-azetidinone (**2**) and described the novel reactivities of **2** with organostannanes. However, low selectivity in the conversion to the key intermediate for the synthesis of the carbapenem skeleton led us to investigate another route for the synthesis of the key intermediate from **2**. Namely, efficient transformation of the versatile intermediate (**2**) to 4-(3-alkoxycarbonyl-2-oxopropyl)-2-azetidinone (**3**), a key intermediate for the synthesis of carbapenem β-lactams by the Merck approach,[5] (Chart 1), was undertaken.



1 **2**

Fig. 1



3 **4**

Chart 1

Firstly, **8** was prepared from **2** for the investigation of regioselective hydration. After the *tert*-butyldimethylsilylation of **2** under standard conditions, **5** was converted to lithium acetylide (**6**) by reaction with lithium diisopropylamide (LDA) in tetrahydrofuran (THF).

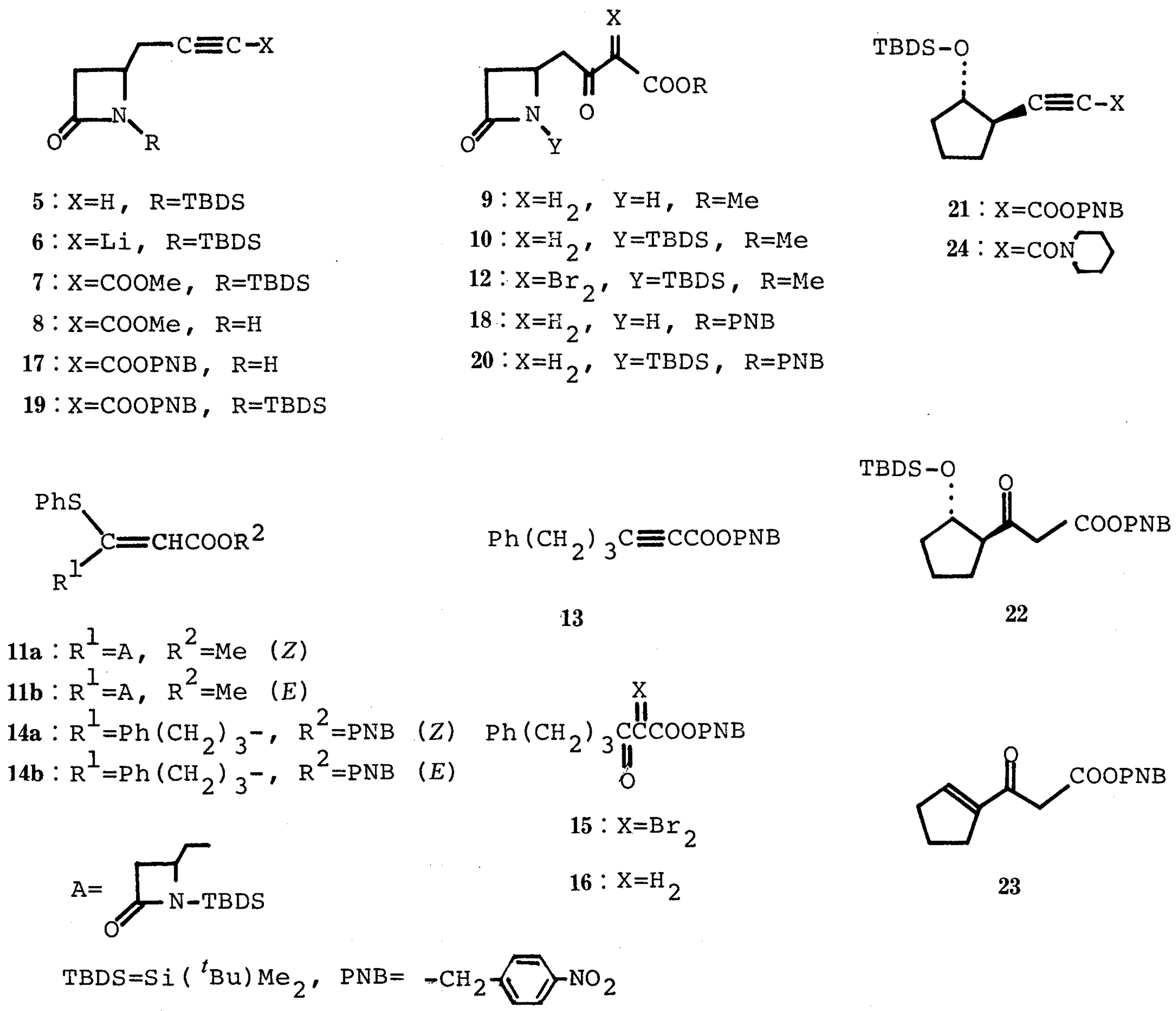


Fig. 2

Addition of methyl chloroformate to **6** gave a complex reaction mixture, whereas dropping the solution of **6** into a THF solution of methyl chloroformate afforded **7** in good yield. Acid treatment of **7** gave desilylated **8** efficiently. Initially, the regioselective hydration of **8** was attempted in aqueous methanol–sulfuric acid in the presence of mercuric acetate, giving the desired β-keto ester (**9**) in only 28% yield with competitive decomposition of **9**. Accordingly we turned our attention toward the hydration of the β-phenylthio-α,β-unsaturated ester (**11**). The vinyl sulfide (**11a**) was readily obtained as a major product by the reaction of **7** with thiophenol in the presence of triethylamine, and the stereochemistry of **11a** and **11b** around the double bond was determined by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy (see Experimental). However, the hydration of **11a** catalyzed by mercury(II) salts[6] or titanium tetrachloride[7] in aqueous media did not give the desired product. On the other hand, the reaction of **11a** with *N*-bromoacetamide (NBA) in aqueous THF gave a single product.[8,9] Although the structure of the initial product could not be confirmed because of its instability, we anticipated the product to be the α,α-dibromo-β-keto ester (**12**) from both the mechanistic point of view (Chart 2) and the ^{1}H-NMR spectrum, which showed no vinylic or aromatic protons. Subsequently, the dibromide (**12**) was subjected to reduction with sodium sulfite in aqueous media, and the desired product (**10**) was obtained in 73% yield.

To confirm the presence of the dibromide (**12**) as an initial product, the simple propiolic ester (**13**) was converted to the vinyl sulfides **14a** and **14b**, and then **14** (a mixture of **14a** and

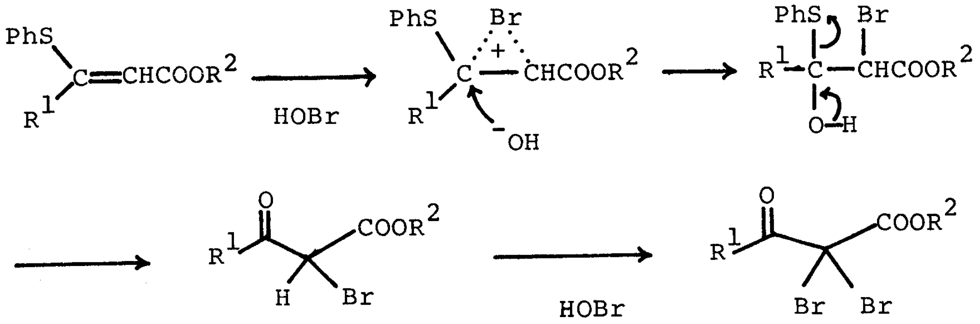


Chart 2

14b) was allowed to react with NBA in aqueous dioxane to give the dibromide (**15**). In the ^{1}H-NMR spectrum of **15**, isolated by a usual extractive work-up procedure, aromatic protons (due to the phenylthio group) observed in the spectrum of **14** had disappeared and methylenic protons were greatly shifted downfield (δ 2.02, 2.68 and 3.01). More convincing evidence was obtained from the mass spectrum (MS) which clearly exhibited molecular ion peaks at *m/e* 501, 499 and 497. Again, the dibromide (**15**) could be converted to the β-keto ester (**16**) by treatment with sodium sulfite (62% yield from **14**). As a result, we concluded that this transformation proceeded *via* the α,α-dibromo-β-keto esters.

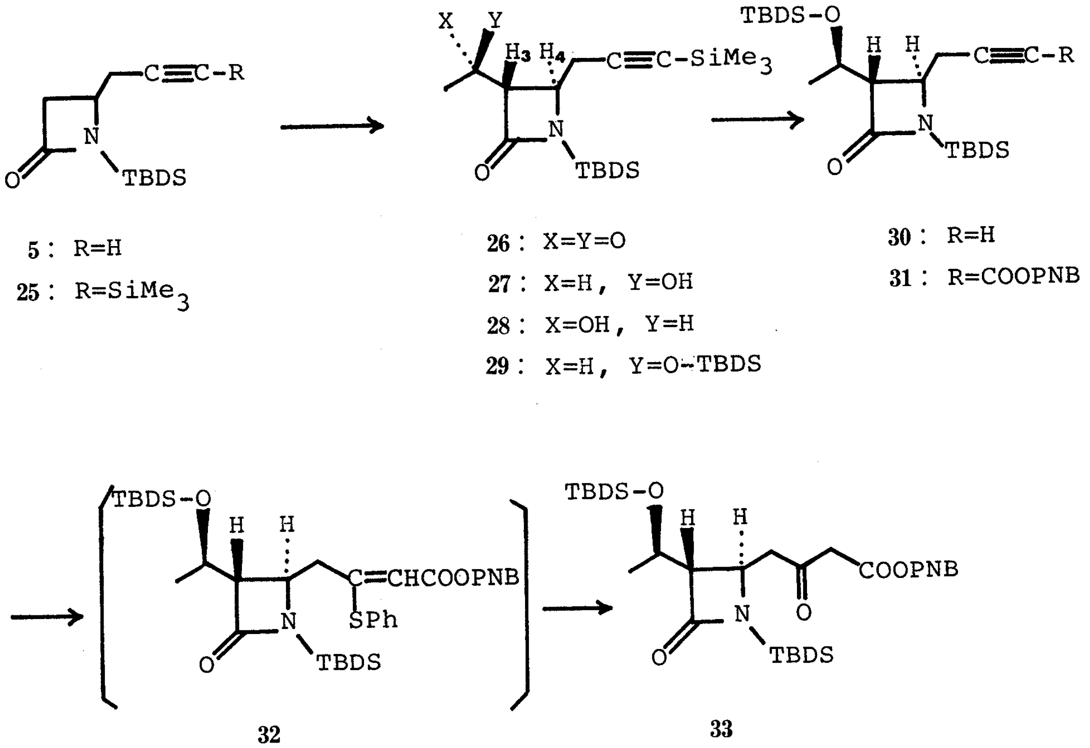
Subsequently, this new method for the conversion of propiolic esters to β-keto esters was applied to several substrates which contain acid- or base-sensitive functionalities. The results are shown in Table I (method A) compared with the results obtained under Bestmann and Geismann's conditions for similar transformation *via* the piperidine enamine (method B).10) In run 1, methods A and B gave almost the same results and the desired β-keto ester (**18**) was prepared in good yield. On the other hand, the propiolic ester (**19**) was converted to the β-keto ester (**20**) in only 30% yield by method B which may reflect steric hindrance surrounding the triple bond and instability of **20** under the hydrolysis conditions, whereas **20** was obtained in good yield by method A. In the case of **21**, which would afford the fairly unstable β-keto ester (**22**), the transformation employing method B gave the unsaturated β-keto ester (**23**) as the major product (50% yield) together with **24** (13% yield), and none of the desired product was obtained. On the other hand, **22** was obtained in 68% yield by method A, showing the mildness of the present method.11)

TABLE I. Conversion of Propiolic Esters to β-Keto Esters

Run	Substrate	Method$^{a)}$	Product (Yield, %)$^{b)}$
1	**17**	A	**18** (66)
		B	(71)
2	**19**	A	**20** (79)
		B	(30)
3	**21**	A	**22** (68)
		B	**23** (50)
			24 (13)

a) Method A: i) PhSH, Et$_3$N in THF; ii) NBA, (4—5 eq) in aq. dioxane; iii) aq. Na$_2$SO$_3$. Method B: i) piperidine, benzene, refluxing; ii) oxalic acid in EtOH–water. *b*) Isolate yield.

Since this mild method for the conversion of propiolic esters to β-keto esters was in hand, our interest was next focused on a synthesis of (±)-thienamycin as an application of this method (Chart 3).



5 : R=H
25 : R=SiMe$_3$

26 : X=Y=O
27 : X=H, Y=OH
28 : X=OH, Y=H
29 : X=H, Y=O-TBDS

30 : R=H
31 : R=COOPNB

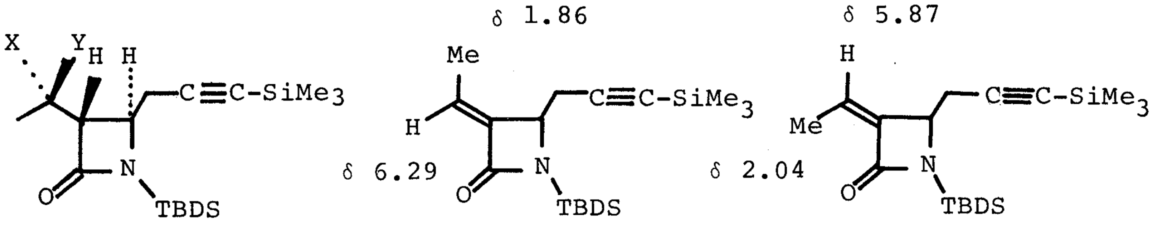
32

33

Chart 3

For the synthesis of (±)-thienamycin, the β-keto ester (**33**), a well-known intermediate[12] for the thienamycin, was required. Toward this end, the acetylation of **19** by reaction with the lithium enolate of **19** and acetylimidazole was attempted. However, the desired product was not obtained because of the instability of **19** under the strongly basic conditions. On the other hand, the acetylation of the lithium enolate generated from **25**, in which the terminal acetylene is protected by a trimethylsilyl group, with acetylimidazole proceeded smoothly to give 3-acetylazetidinone (**26**) as a single stereoisomer. The stereochemistry of **26** was assigned as *trans* by ^{1}H-NMR spectroscopy ($J_{5,6}=2.5$ Hz). Reduction of the acetyl group in **26** with sodium borohydride gave a mixture of the diastereomers (**27** and **28**) in the ratio of 1 : 1.1 (Table II). In order to assign the relative configuration of the side chain,[13] each isomer was converted to the ene-lactam (**36** and **37**) by mesylation followed by *E*2-elimination (Fig. 3). In the ^{1}H-NMR spectrum of **36**, which was derived from **27** *via* **34**, a vinylic proton was seen at lower field than that of **37** which was obtained from **28** *via* **35**. On the other hand, an allylic methyl signal of **36** was shown in higher field than in that of **37**. Considering the deshielding effect of the β-lactam carbonyl group, it can be concluded that the stereochemistry around the double bond of **36** is *E* and that of **37** is *Z*. On the assumption that *trans*-elimination of methanesulfonic acid occurs, the configuration of the carbon atom carrying the hydroxy group in **27** is R^* and that in **28** is S^*. Several attempts at the stereoselective reduction of **26** were carried out, and the results are listed in Table II.

The desired **27** was obtained as the major product in the reduction using lithium selectride in ether in the presence of potassium iodide. It is noteworthy that the reduction of **26** employing diisobutylaluminum 2, 6-*tert*-butyl-4-methylphenoxide[14] afforded the alcohol (**28**) with high stereoselectivity. After protection of the hydroxy group as a silyl ether, the trimethylsilyl group linked to the acetylenic moiety was removed selectively by means of Schmidt's reaction[15] in 88% yield from **27**; **29** was treated successively with silver nitrate and potassium cyanide in aqueous ethanol. The acetylene (**30**) was allowed to react with LDA in THF to afford the corresponding lithium acetylide. A solution of the acetylide was dropped



34: X=H, Y=OMs
35: X=OMs, Y=H

36

37

Fig. 3

TABLE II. Reduction of Acetyl Group in **26**

Run	Reagent	Solvent	Temp. (°C)	Yield (%)	Ratio[a] **27**:**28**
1	$NaBH_4$ (4 eq)	MeOH	0	85	1:1.1[b]
2	Aluminum phenoxide[c] (10 eq)	Toluene	−78	99	100:0
3	L-Selectride (2 eq)	THF	−78	93	1:3.0
4	$ZnCl_2$–L-Selectride (1.5 eq)	Ether	−78	70	1:1.6
5	KI–L-Selectride (2 eq)	THF	−78	82	1:3.8
6	KI–L-Selectride (1.5 eq)	Ether	−78	87	1.7:1

a) Determined by ^1H-NMR spectroscopy. *b*) Determined by isolation of the product. *c*) Diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide.

into a THF solution of 4-nitrobenzyl chloroformate, giving the propiolic ester (**31**) in 46% yield along with recovered **30** (32%). Finally, the crucial transformation of **31** to the β-keto ester (**33**) was carried out as described above; **31** was converted to **32** by reaction with thiophenol and triethylamine in THF, and then **32** was treated with NBA in aqueous dioxane. The reaction was quenched by the addition of a saturated aqueous solution of sodium sulfite, and **33** was isolated in 37% yield from **31**. The spectral data of **33** showed good agreement with the reported values.

Since an efficient synthesis of thienamycin from the β-keto ester (**33**) has been established by the Merck group,[12] we have now succeeded in a formal total synthesis of (±)-thienamycin.

Experimental

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a Hitachi 215 grating infrared spectrometer. ^1H-NMR spectra were recorded on a Varian EM360A NMR spectrometer or a Varian XL-100-12 NMR spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Low-resolution MS were recorded on a JEOL JMS-D300 mass spectrometer and high-resolution MS on a JEOL JMS-OISG-2 mass spectrometer. Thin layer chromatography (TLC) was carried out on silica gel plates (Merck Art 5715) and all *Rf* values refer to silica gel plates. In general, reactions were carried out under an argon atmosphere unless otherwise mentioned. Reaction products were isolated by extraction with the indicated solvent, followed by washing with brine, drying over anhydrous sodium sulfate or magnesium sulfate, and evaporation of the solvent.

Methyl 1-*tert*-Butyldimethylsilyl-4-oxo-2-azetidine-α-butynoate (7)——A THF (20 ml) solution of 1-*tert*-butyldimethylsilyl-4-propargyl-2-azetidinone (**5**)[4] (1.96 g, 8.79 mmol) was added to a THF solution of LDA [prepared from diisopropylamine (1.48 ml, 10.6 mmol) and *n*-BuLi (1.4 M, hexane solution, 7.2 ml, 10.4 mmol)] at −78 °C with stirring, and the mixture was stirred for 20 min under the same conditions. The lithium acetylide solution thus obtained was dropped into a THF (20 ml) solution of methyl chloroformate (2 ml, 8.79 mmol) at −78 °C using a stainless steel cannulā. After stirring of the mixture for 1 h, the reaction was quenched by the addition of saturated aqueous ammonium chloride (sat. NH_4Cl) and the whole was warmed to room temperature. The product was extracted with ether (30 ml, 3 times) and the combined extracts were washed with brine, dried over magnesium sulfate ($MgSO_4$), and concentrated *in vacuo*. Purification by silica gel column chromatography (50 g, AcOEt–*n*-hexane (1 : 5—1 : 3)) gave 1.82 g (74%) of **7**. mp 62—63.3 °C (AcOEt–*n*-hexane). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2950, 2925, 2850, 2225, 2750 (shoulder), 1735, 1700, 1320, 1265, 1180, 840. ^{1}H-NMR δ (ppm): 0.24 (3H, s), 0.28 (3H, s), 0.98 (9H, s), 2.59 (1H, dd, J= 17, 7 Hz), 2.81 (1H, dd, J= 17, 4 Hz), 2.85 (1H, dd, J= 15.5, 3 Hz), 3.27 (1H, dd, J= 15.5, 5 Hz), 3.77 (4H, s and overlapped m). MS *m/e*: 282, 281 (M^+), 225, 224, 223, 191, 158, 155, 142, 116, 100, 93, 89; *m/e*: 281.1468 (Calcd for $C_{14}H_{23}NO_3Si$, 281.1447, M^+).

Methyl 4-Oxo-2-azetidine-α-butyrate (8)——A 10% HCl solution (5 ml) was added to a methanol (20 ml) solution of **7** (414 mg, 1.47 mmol) and the mixture was stirred for 3.7 h at 0 °C. After the addition of sat. $NaHCO_3$, the methanol was removed *in vacuo*. The crude product was extracted with AcOEt and the combined extracts were washed with brine, dried, and concentrated. Purification of the residue by silica gel column chromatography (25 g, ether) gave pure **8** (214 mg, 87%) as pale yellow crystals, which were recrystallized from ether–AcOEt. mp 62—63 °C. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3450, 2230, 1760, 1710, 1358, 1265, 1200, 1078. ^{1}H-NMR δ (ppm): 2.70 (2H, d, J= 7 Hz), 2.78 (1H, br d, J= 15 Hz), 3.17 (1H, ddd, J= 15, 5.5, 3 Hz), 3.79 (3H, s), 3.88 (1H, m), 6.30 (1H, br). MS *m/e*: 168 (M^+ + 1), 136, 126, 124, 98, 94, 93; *m/e*: 167.0592 (Calcd for $C_8H_9NO_3$, 167.0582, M^+). *Anal.* Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.48; N, 8.38. Found: C, 57.52; H, 5.45; N, 8.24.

$Hg(OAc)_2$-Catalyzed Hydration of 8——A methanol (1 ml) solution of **8** (23 mg, 0.14 mmol) was treated with 0.2 ml of 10% aq. sulfuric acid in the presence of mercuric acetate (catalytic amount) at 6 °C for 13 h. After the addition of 2 ml of sat. $NaHCO_3$, the product was extracted with AcOEt. The combined extracts were washed with brine, dried, and concentrated to give a residue. Separation by silica gel column chromatography (15 g, ether–AcOEt (10 : 1—10 : 2), then AcOEt) gave 10 mg (44%) of **8** and 7 mg (28%, or 49% based on the recovered starting material) of methyl 4,β-dioxo-2-azetidinebutyrate (**9**). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3425, 1750, 1735 (shoulder), 1710, 1438, 1380, 1230, 1170. ^{1}H-NMR δ (ppm): 2.63 (1H, ddd, J= 15, 3, 1 Hz), 2.86 (1H, dd, J= 18, 9 Hz), 3.06 (1H, dd, J= 18, 5 Hz), 3.19 (1H, ddd, J= 15, 5, 2 Hz), 3.52 (2H, s), 3.78 (3H, s), 3.93 (1H, m), 6.02 (1H, br). MS *m/e*: 185 (M^+), 142, 116, 112, 101 (base), 70; *m/e*: 185.0698 (Calcd for $C_8H_{11}NO_4$, 185.0688, M^+).

Methyl (*Z*)-1-*tert*-Butyldimethylsilyl-4-oxo-β-phenylthio-2-azetidine-α-butenoate (11a) and Its *E*-Isomer (11b)——Triethylamine (52 μl, 0.37 mmol) and thiophenol (38 μl, 0.37 mmol) were added to a methanol (2 ml) solution of **7** (94 mg, 0.33 mmol), and the mixture was stirred for 30 min at room temperature. After evaporation of the methanol, the residue was chromatographed over silica gel (10 g, AcOEt–petr. ether (1 : 4)) to give 9 mg (7%) of **11b** as the less polar product (*Rf*= 0.59, AcOEt–petr. ether (1 : 2)) and 111 mg (85%) of **11a** as the more polar product (*Rf*= 0.47).

11b: IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3000, 2940, 2850, 1738 (shoulder), 1725, 1600 (shoulder), 1575, 1190, 1173, 1118, 1080, 1000, 838, 820. ^{1}H-NMR δ (ppm): 0.28, 0.31 (6H, two s), 0.99 (9H, s), 2.85 (1H, dd, J= 13, 11 Hz), 3.12 (2H, d, J= 4 Hz), 3.60 (3H, s), 3.63 (1H, dd, J= 13, 4 Hz), 3.91 (1H, qd, J= 10, 4 Hz), 5.25 (1H, s), 7.43 (5H, s). MS *m/e*: 391 (M^+), 374, 333, 291, 259, 217, 202, 109, 100, 89, 73; *m/e*: 391.1635 (Calcd for $C_{20}H_{29}NO_3SSi$, 391.1637, M^+).

11a: mp 89—92 °C (ether–*n*-hexane). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3000, 2950, 2925, 2850, 1738 (shoulder), 1725, 1600 (shoulder), 1575, 1340, 1330, 1180, 838, 820. ^{1}H-NMR δ (ppm): −0.11 (6H, s), 0.76 (9H, s), 2.11 (1H, dd, J= 15, 11 Hz), 2.61 (1H, dd, J= 16, 2 Hz), 2.84 (1H, dd, J= 15, 4 Hz), 3.12 (1H, dd, J= 16, 5 Hz), 3.58 (1H, m), 3.75 (3H, s), 5.79 (1H, s), 7.31—7.62 (5H, m). MS *m/e*: 391 (M^+), 390, 375, 333, 259, 217, 202, 89, 73; *m/e*: 391.1642 (Calcd for $C_{20}H_{29}NO_3SSi$, 391.1637, M^+). *Anal.* Calcd for $C_{20}H_{29}NO_3SSi$: C, 61.36; H, 7.47; N. 3.58. Found: C, 61.36; H, 7.47; N, 3.57.

Conversion of 11a to the Dibromide (12)——NBA (recrystallized from $CHCl_3$–*n*-hexane, 12 mg, 0.09 mmol) was added to a solution of **11a** (15 mg, 0.04 mmol) in aq. THF (THF–water (5 : 1), 0.5 ml). The mixture was stirred for 45 min at 0 °C, then further NBA (11 mg, 0.08 mmol) was added. After being stirred for 15 min, the mixture was diluted with water (*ca.* 10 ml) and the product was extracted with ether (15 ml, 3 times). The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave methyl α,α-dibromo-1-*tert*-butyldimethylsilyl-4,β-dioxo-2-azetidinebutyrate (**12**), which showed the following signals in the ^{1}H-NMR spectrum δ (ppm): 0.24, 0.27 (6H, two s), 0.98 (9H, s), 2.81 (1H, dd, J= 16, 3 Hz), 3.12 (1H, dd, J= 17, 11 Hz), 3.36 (1H, dd, J= 16, 5 Hz), 3.59 (1H, dd, J= 17, 4 Hz), 3.93 (3H, s), 3.98 (1H, m).

Conversion of 11a to 10——NBA (221 mg, 1.60 mmol) was added to a solution of **11a** (126 mg, 0.32 mmol) in aq. dioxane (dioxane–water (10 : 1), 3 ml) with stirring at 0 °C. Stirring was continued for 45 min, then 6 ml of sat. Na_2SO_3 was added, and the mixture was stirred for 20 min at 0 °C. The product was extracted with AcOEt and the combined extracts were washed with brine, dried, and concentrated to leave a residue. Purification by silica gel column chromatography (20 g, *n*-hexane–AcOEt (2 : 1)) gave 70 mg (73%) of methyl 1-*tert*-butyldimethylsilyl-4, β-dioxo-2-azetidinebutyrate (**10**). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2940, 2860, 1755 (shoulder), 1720, 1655, 1630, 1320, 1290, 1255, 1188, 1085, 1005, 838, 822, 810. ^{1}H-NMR δ (ppm): 0.20 (3H, s), 0.25 (3H, s), 0.97 (9H, s), 2.65 (1H, dd, J= 16, 2 Hz), 2.76 (1H, dd, J= 18, 9 Hz), 3.16 (1H, dd, J= 18, 4 Hz), 3.34 (1H, dd, J= 16, 5 Hz), 3.47 (2H, s), 3.75 (3H, s), 3.90 (1H, m). MS *m/e*: 300 (M^+ + 1), 284, 268, 242, 210, 173, 168, 101, 100 (base), 89; *m/e*: 300.1628 (Calcd for $C_{14}H_{26}NO_4Si$, 300.1631, M^+ + 1).

4-Nitrobenzyl 6-Phenyl-2-hexynoate (13)——A solution of 5-phenyl-1-pentyne (332 mg, 2.31 mmol) [prepared by the reaction of 1-bromo-3-phenylpropane with lithium acetylide-*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) complex in DMSO] in THF was treated with *n*-BuLi (1.5 M, hexane solution, 2.3 ml, 3.47 mmol) at −70 °C for 20 min. The lithium acetylide solution thus obtained was added to a THF (20 ml) solution of 4-nitrobenzyl chloroformate (884 mg, 4.10 mmol) at −70 °C, and the whole was stirred for 30 min at the same temperature. The reaction was quenched by the addition of sat. NH_4Cl, and the product was extracted with ether. Usual work-up and silica gel column chromatography (35 g, petr. ether–AcOEt (10 : 1)) afforded 449 mg (60%) of **13**. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3080, 3020, 2940, 2855, 2220, 1708, 1605, 1520, 1345, 1240, 1065, 850, 745, 696. ^{1}H-NMR δ (ppm): 1.91 (2H, quintet-like, J=8 Hz), 2.60 (2H, t, J=7 Hz), 2.75 (2H, t, J=8 Hz), 5.29 (2H, s), 7.24 (5H, m), 7.55 (2H, d, J=9 Hz), 8.24 (2H, d, J=9 Hz). MS *m*/*e*: 323 (M$^+$), 306, 253, 197, 187, 153, 136, 106, 91, 78 (base), 57; *m*/*e*: 323.1156 (Calcd for $C_{19}H_{17}NO_4$, 323.1157, M$^+$).

4-Nitrobenzyl (*Z*)-3-Phenylthio-6-phenyl-2-hexenoate (14a) and Its *E*-Isomer (14b)——The propiolate (**13**, 167 mg, 0.52 mmol) was allowed to react with thiophenol (0.09 ml, 0.88 mmol) in the presence of triethylamine (0.13 ml, 1.93 mmol) in THF (5 ml) for 2 d at room temperature. After removal of the volatile material *in vacuo*, the crude product was purified by silica gel column chromatography (40 g, petr. ether–AcOEt (10 : 1)) to give 43 mg of **14a** and 34 mg of **14b**, along with a mixture of both isomers (122 mg, **14a** : **14b** = 1.6 : 1), 88% in total.

14a: IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 2940, 2860, 1699, 1608, 1580, 1528, 1350, 1182, 1175, 855, 830, 690. ^{1}H-NMR δ (ppm): 1.68 (2H, quintet-like, J=7 Hz), 2.18 (2H, t, J=7.5 Hz), 2.38 (2H, t, J=7.5 Hz), 5.31 (2H, s), 5.94 (1H, s), 7.00 (2H, m), 7.20 (2H, m), 7.25—7.72 (8H, m), 8.24 (2H, d, J=8.5 Hz). MS *m*/*e*: 435, 434, 433 (M$^+$), 398, 329, 147, 91; *m*/*e*: 433.1318 (Calcd for $C_{25}H_{23}NO_4S$, M$^+$).

14b: IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3070, 3030, 3010, 2940, 2860, 1710, 1595, 1525, 1350, 1180, 1145, 862, 850, 699, 690. ^{1}H-NMR δ (ppm): 2.03 (2H, m), 2.73 (2H, t, J=8.5 Hz), 2.94 (2H, t, J=8.5 Hz), 5.15 (2H, s), 5.28 (1H, s), 7.25 (5H, br s), 7.48 (7H, br s), 8.19 (2H, d, J=9 Hz). MS *m*/*e*: 435, 434, 433 (M$^+$), 420, 418, 329, 149, 147, 136, 134, 91; *m*/*e*: 433.1347 (Calcd for $C_{25}H_{23}NO_4S$, M$^+$).

Reaction of 14 with NBA——A mixture of **14a** and **14b** (**14a** : **14b** = 1.6 : 1, 79 mg, 0.18 mmol) was dissolved in aq. dioxane (dioxane–water (10 : 1), 2 ml) and the solution was cooled to 0 °C with stirring. Then 101 mg (0.73 mmol) of NBA was added and the mixture was stirred for 2.8 h and allowed to warm gradually to room temperature. Then 22 mg (0.16 mmol) of NBA was added and the mixture was stirred for a further 10 min at room temperature. After dilution with ether (*ca.* 50 ml), the mixture was washed with water (15 ml, 3 times), dried, and concentrated *in vacuo* to give crude 4-nitrobenzyl 2,2-dibromo-3-oxo-6-phenylhexanoate (**15**). ^{1}H-NMR δ (ppm): 2.02 (2H, quintet-like, J=8 Hz), 2.68 (2H, t, J=8 Hz), 3.01 (2H, t, J=7.5 Hz), 5.39 (2H, s), 7.23 (5H, m), 7.56 (2H, d, J=8 Hz), 8.25 (2H, d, J=8 Hz). MS *m*/*e*: 501 (M$^+$), 499 (M$^+$), 497 (M$^+$), 421, 420, 419, 418, 403, 402, 401 (base), 400, 365, 363, 362, 341, 340.

Then, crude **15** was dissolved again in aq. dioxane (dioxane–water (10 : 1)) and 6 ml of sat. Na_2SO_3 was added. After stirring of the mixture for 50 min, the product was extracted with AcOEt. The combined extracts were washed with brine, dried, and concentrated to give a residue (66 mg). Purification by silica gel column chromatography (20 g, AcOEt–petr. ether (1 : 5)) gave 39 mg (62%) of 4-nitrobenzyl 3-oxo-6-phenylhexanoate (**16**). mp 58—59 °C (ether). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3025, 2945, 1748, 1719, 1610, 1525, 1352, 1320, 860, 700. ^{1}H-NMR δ (ppm): 1.98 (2H, quintet-like, J=7 Hz), 2.56 (2H, t, J=8 Hz), 2.65 (2H, t, J=7 Hz), 3.52 (2H, s), 5.28 (2H, s), 7.24 (5H, m), 7.53 (2H, d, J=9 Hz), 8.23 (2H, d, J=9 Hz). MS *m*/*e*: 342, 341 (M$^+$), 323, 237, 136, 117 (base); *m*/*e*: 341.1257 (Calcd for $C_{19}H_{19}NO_5$, 341.1263, M$^+$).

4-Nitrobenzyl 1-*tert*-Butyldimethylsilyl-4-oxo-2-azetidine-α-butynoate (19)——A THF (5 ml) solution of **5** (518 mg, 2.32 mmol) was added to a THF (10 ml) solution of LDA [prepared from *n*-BuLi (1.55 M hexane solution, 1.6 ml, 2.48 mmol) and diisopropylamine (0.35 ml, 2.50 mmol)] at −78 °C, and the whole was stirred for 20 min at the same temperature. A THF solution of the acetylide **6** thus obtained was added to a THF (10 ml) solution of 4-nitrobenzyl chloroformate (767 mg, 3.56 mmol) at −78 °C. Stirring was continued for 2 h at the same temperature, then the reaction was quenched by addition of sat. NH_4Cl. The mixture was warmed to room temperature, and THF was removed *in vacuo*. The crude product was extracted with ether, and the combined extracts were washed with brine, dried, and concentrated. Chromatographic purification (silica gel, 120 g, AcOEt–petr. ether (1 : 4—1 : 1)) gave 633 mg (68%) of **19** as yellow crystals, and 159 mg of **5** was recovered. mp 80—82 °C (ether). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 2230, 1735, 1720, 1610, 1528, 1350, 1255, 842. ^{1}H-NMR δ (ppm): 0.23 (3H, s), 0.26 (3H, s), 0.96 (9H, s), 2.69 (1H, dd, J=17, 7 Hz), 2.83 (1H, dd, J=17, 4 Hz), 2.90 (1H, dd, J=16, 3 Hz), 3.28 (1H, dd, J=16, 5 Hz), 3.82 (1H, m), 5.30 (2H, s), 7.55 (2H, d, J=8 Hz), 8.23 (2H, d, J=8 Hz). MS *m*/*e*: 402 (M$^+$), 345, 136; *m*/*e*: 403.1693 (Calcd for $C_{20}H_{27}N_2O_5Si$, 403.1689, M$^+$+1). *Anal.* Calcd for $C_{20}H_{26}N_2O_5Si$: C, 59.68; H, 6.52; N, 6.96. Found: C, 59.40; H, 6.37; N, 7.10.

4-Nitrobenzyl 4-Oxo-2-azetidine-α-butynoate (17)——A THF (10 ml) solution of **19** (633 mg, 1.57 mmol) was treated with 10% aq. HCl, and the mixture was stirred for 9 h at room temperature. After neutralization with sat. $NaHCO_3$, the crude product was extracted with AcOEt. The combined extracts were washed with brine, dried, and concentrated. Purification by silica gel column chromatography (30 g, AcOEt–petr. ether (1 : 2—3 : 1, finally 5 : 1)) gave 294 mg (65%) of **17** as a colorless solid. mp 117.5—118 °C (AcOEt). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3425, 3000, 2230, 1768, 1713, 1605, 1525, 1350, 1260, 1075. ^{1}H-NMR δ (ppm): 2.74 (2H, d, J=6 Hz), 2.78 (1H, ddd, J=15, 3, 1 Hz), 3.18 (1H, ddd, J=15, 6, 3 Hz), 3.90 (1H, dtd, J=6, 6, 3 Hz), 5.29 (2H, s), 6.30 (1H, br), 7.55 (2H, d, J=9 Hz), 8.24

(2H, d, $J=9$ Hz). MS *m/e*: 289, 288 (M^+), 246, 153; *m/e*: 288.0736 (Calcd for $C_{14}H_{12}N_2O_5$, 288.0746, M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_5$: C, 58.32; H, 4.20; N, 9.72. Found: C, 58.38; H, 4.21; N, 9.80.

4-Nitrobenzyl *trans*-3-(2-*tert*-Butyldimethylsilyloxycyclopentyl)propiolate (21)——*n*-BuLi (1.55 M, hexane solution, 1.5 ml, 2.33 mmol) was added to a THF (20 ml) solution of *trans*-(2-*tert*-butyldimethylsilyloxycyclopentyl)-ethyne,[16] (500 mg, 2.23 mmol) at −72 °C with stirring. The whole was stirred at the same temperature for 20 min, then allowed to stand for 3 min without a cooling bath. After recooling to −72 °C, the acetylide solution was added to a THF (20 ml) solution of 4-nitrobenzyl chloroformate (501 mg, 2.33 mmol). The mixture was stirred at −50—−40 °C for 40 min. The reaction was quenched by the addition of sat. NH_4Cl, then the whole was warmed to room temperature. The crude product was extracted with ether. The combined extracts were washed with brine, dried, and concentrated to give a residue, which was purified by silica gel column chromatography (35 g, AcOEt–petr. ether (1 : 7)) to give 681 mg (76%) of **21** as a yellow oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 2225, 1710, 1608, 1520, 1350, 1220. ^{1}H-NMR δ (ppm): 0.09 (6H, s), 0.89 (9H, s), 1.42—2.38 (6H, m), 2.72 (1H, m), 4.28 (1H, m), 5.29 (2H, s), 7.66 (2H, d, $J=8.5$ Hz), 8.24 (2H, d, $J=8.5$ Hz). MS *m/e*: 403 (M^+), 402, 340; *m/e*: 404.1835 (Calcd for $C_{21}H_{30}NO_5Si$, 404.1893, $M^+ + 1$).

General Procedure for the Conversion of Propiolic Esters to β-Keto Esters——Method A: A mixture of propiolic ester and thiophenol (1.1 eq) in THF was stirred in the presence of triethylamine (1.1 eq) at room temperature for 2—4 h. The solvent was removed *in vacuo*, and the residue was dissolved in aq. dioxane (dioxane–water (10 : 1)). NBA (recrystallized from $CHCl_3$–petr. ether, 4—5 eq) was added to this solution, and the mixture was stirred for 20 min—2 h. Sat. Na_2SO_3 (excess) was added to the mixture, and the whole was stirred for 20 min at room temperature. The crude product was extracted with AcOEt and the combined extracts were washed with brine, dried, and concentrated to give a residue, which was purified by silica gel column chromatography.

Method B: A solution of propiolic ester and piperidine (1.1 eq) in benzene was refluxed. After evaporation of the benzene, the resultant crude enamine was dissolved in ether and treated with an ether–ethanol (1 : 10) solution of oxalic acid·$2H_2O$ (1.2 eq) at room temperature. The product was extracted with AcOEt and the combined extracts were washed with brine, dried, and concentrated to give a residue, which was purified by silica gel column chromatography.

Conversion of 17 to 18——Method A: A solution of **17** (57 mg) in THF (1 ml) was allowed to react with thiophenol and triethylamine at room temperature for 2.5 h to give the vinyl sulfides (a mixture of stereoisomers). The vinyl sulfides were dissolved in aq. dioxane (2 ml) and treated with NBA (5 eq, 0 °C—room temperature, 2.5 h). After reduction and usual work-up, 40 mg (66%) of 4-nitrobenzyl 4,β-dioxo-2-azetidinebutyrate (**18**) was obtained as a pale yellow powder. mp 53—54 °C (CH_2Cl_2–petr. ether). IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3430, 1755, 1720, 1660, 1630, 1610, 1528, 1350. ^{1}H-NMR δ (ppm): 2.68 (1H, ddd, $J=15, 2, 1$ Hz), 2.88 (1H, dd, $J=18.5, 8.5$ Hz), 3.07 (1H, dd, $J=18.5, 4.5$ Hz), 3.19 (1H, ddd, $J=15, 5, 2$ Hz), 3.59 (2H, s), 3.99 (1H, m), 5.29 (2H, s), 6.56 (1H, br), 7.54 (2H, d, $J=9$ Hz), 8.24 (2H, d, $J=9$ Hz). MS *m/e*: 307, 306 (M^+), 265; *m/e*: 306.0868 (Calcd for $C_{14}H_{14}N_2O_6$, 306.0852, M^+).

Method B: A solution of **17** (46 mg) in benzene (2 ml) was refluxed for 12 h in the presence of piperidine. Hydrolysis and usual work-up gave 35 mg (72%) of **18**.

Conversion of 19 to 20——Method A: A mixture of **19** (201 mg, 0.50 mmol), thiophenol and triethylamine in THF (2.8 ml) was stirred for 3.3 h. Vinyl sulfides (a mixture of stereoisomers) thus obtained were allowed to react with NBA (5 eq) in aq. dioxane (4 ml) at 0 °C for 45 min. After reduction and usual work-up, 166 mg (79%) of 4-nitrobenzyl 1-*tert*-butyldimethylsilyl-4,β-dioxo-2-azetidinebutyrate (**20**) was obtained as a colorless oil. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1730, 1660, 1630, 1610, 1527, 1350, 840. ^{1}H-NMR δ (ppm) 0.19, 0.22 (6H, two s), 0.95 (9H, s), 2.64 (1H, dd, $J=18, 10$ Hz), 3.15 (1H, dd, $J=18, 4$ Hz), 3.34 (1H, dd, $J=16, 5.5$ Hz), 3.58 (2H, s), 3.88 (1H, m), 5.29 (2H, s), 7.54 (2H, d, $J=9$ Hz), 8.23 (2H, d, $J=9$ Hz). MS *m/e*: 421 ($M^+ + 1$), 405, 363, 153, 136; *m/e*: 421.1809 (Calcd for $C_{20}H_{29}N_2O_6Si$, 421.1794, $M^+ + 1$).

Method B: A solution of **19** (106 mg) in benzene (3 ml) was refluxed for 17 h in the presence of piperidine. Hydrolysis and usual work-up gave 33 mg (30%) of **20**.

Conversion of 21 to 22——Method A: A mixture of **21** (106 mg), thiophenol and triethylamine in THF (1.5 ml) was stirred at room temperature overnight. Vinyl sulfides (a mixture of stereoisomers) thus obtained were allowed to react with NBA (4 eq) in aq. dioxane (3 ml) at 0 °C for 30 min. After reduction and usual work-up, 75 mg (68%) of 4-nitrobenzyl *trans*-3-(2-*tert*-butyldimethylsilyloxycyclopentyl)-3-oxopropanoate (**22**) was obtained. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 2940, 1742, 1708, 1640 (shoulder), 1602, 1520, 1340, 1248, 830, 722. ^{1}H-NMR δ (ppm): 0.04 (6H, s), 0.87 (9H, s), 1.36—2.20 (6H, m), 2.95 (1H, m), 3.64 (2H, s), 4.31 (1H, m), 5.28 (2H, s), 7.55 (2H, d, $J=8$ Hz), 8.23 (2H, d, $J=8$ Hz). MS *m/e*: 422, 421 (M^+), 403, 365; *m/e*: 422.2000 (Calcd for $C_{21}H_{32}NO_6Si$, 422.1999, $M^+ + 1$).

Method B: A mixture of **21** (118 mg) in benzene (3 ml) was refluxed for 48 h in the presence of piperidine (1.1 eq). After addition of another 1.1 eq of piperidine, the mixture was refluxed for 8 h. Hydrolysis followed by work-up gave 43 mg (50%) of 4-nitrobenzyl 3-(1-cyclopentenyl)-3-oxopropanoate (**23**) and 14 mg (14%) of 1-[3-(*trans*-2-*tert*-butyldimethylsilyloxycyclopentyl)propynoyl]piperidine (**24**).

23: IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 2940, 1740, 1655, 1580, 1520, 1340. ^{1}H-NMR δ (ppm): 1.95 (2H, quintet, $J=8$ Hz), 2.60 (4H, t, $J=8$ Hz), 3.82 (2H, s), 5.29 (2H, s), 6.82 (1H, s), 7.54 (2H, d, $J=8$ Hz), 8.22 (2H, d, $J=8$ Hz). MS *m/e*: 290, 289 (M^+), 205, 153, 137, 95, 93 (base); *m/e*: 289.0941 (Calcd for $C_{15}H_{15}NO_5$, 289.0950, M^+).

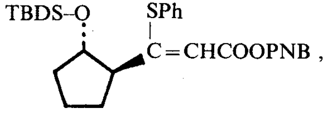
24: IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 2210, 1620, 1430, 1260. ^{1}H-NMR δ (ppm): 0.06 (6H, s), 0.87 (9H, s), 1.30—2.30 (12H, m), 2.64

Table III. Characteristic Signals in the ^{1}H-NMR Spectra of Vinyl Sulfides

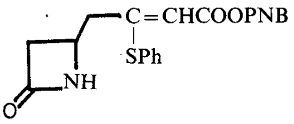
Compound[a,b]	Chemical shift, δ (ppm), (multiplicity)		
	Vinylic H	$-S-C_6H_5$	Allylic or propargylic H
13	—	—	2.60 (t)
14a (MP)	5.94 (s)	7.35—7.73 (m)	2.18 (t)
14b (LP)	5.28 (s)	7.48 (s)	2.73 (t)
21	—	—	2.69 (t)
38a (MP)	5.91 (s)	7.23—7.71 (m)	2.57 (m)
38b (LP)	5.22 (s)	7.46 (s)	4.42 (m)
7	—	—	2.59 (dd), 2.81 (dd)
11a (MP)	5.79 (s)	7.31—7.62 (m)	2.11 (dd), 2.84 (dd)
11b (LP)	5.25 (s)	7.43 (s)	2.85 (dd), 3.63 (dd)
17	—	—	2.74 (d)
39a (MP)	5.95 (s)	7.24—7.69 (m)	2.43 (dd), 2.53 (dd)
39b (LP)	5.14 (s)	7.48 (s)	3.09 (dd), 3.38 (dd)

a) MP, more polar isomer; LP, less polar isomer.

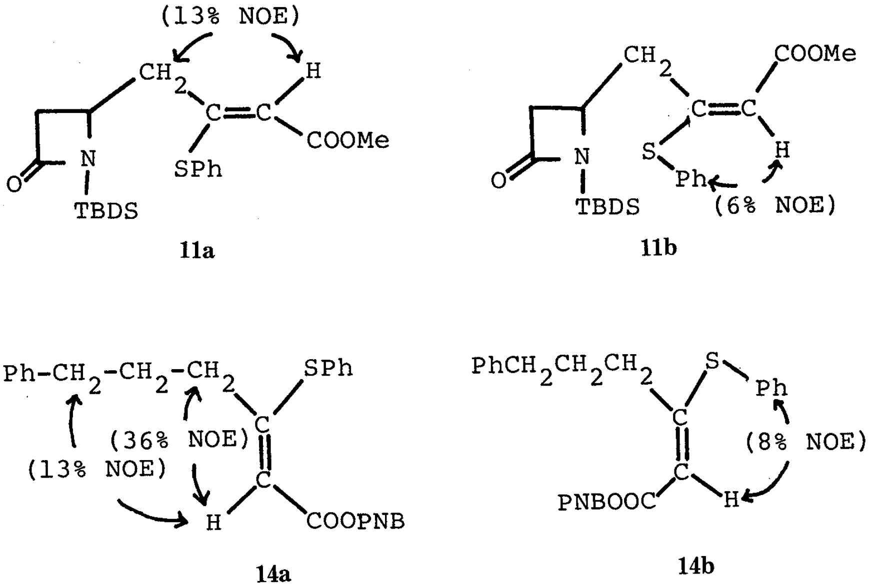
b)



38a: (*Z*)
38b: (*E*)



39a: (*Z*)
39b: (*E*)



11a **11b**

14a **14b**

Fig. 4

(1H, m), 3.62 (4H, m), 4.26 (1H, m). MS *m*/*e*: 336, 335 (M$^+$), 320, 279, 278; *m*/*e*: 335.2278 (Calcd for $C_{19}H_{33}NO_2S$, 335.2280, M$^+$).

Stereochemistry of Vinyl Sulfides——Characteristic signals in the ^{1}H-NMR spectra of vinyl sulfides are listed in Table III. In the Table, MP and LP mean "more polar" and "less polar" isomer, respectively, of vinyl sulfides on TLC analysis (silica gel, AcOEt-*n*-hexane). The following differences can be pointed out in the ^{1}H-NMR spectra of MP and LP isomers; 1) the vinylic protons of MP isomers have chemical shifts at lower field (δ 5.79—5.95) than those of LP isomers (δ 5.14—5.28); 2) the aromatic protons of the phenylthio group in MP isomers appear as complex multiplets, whereas those of LP isomers are singlets; 3) the allylic protons of LP isomers are found at lower field (δ 2.73—4.42) than those of MP isomers (δ 2.11—2.84). Considering the anisotropic effect of the phenylthio group and alkoxycarbonyl group, it can be concluded that the configuration of the MP isomers is *Z* and that of LP isomers is *E*. These assignments are supported by the nuclear Overhauser effect (NOE) observations, as shown in Fig. 4.

The configurational difference of vinyl sulfides had no apparent effect on the reaction with NBA.

1-*tert*-Butyldimethylsilyl-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (25)——A THF (10 ml) solution of LDA [prepared from *n*-BuLi (1.51 M, hexane solution, 1.8 ml, 2.72 mmol) and diisopropylamine (0.38 ml, 2.71 mmol)] was dropped into a THF (10 ml) solution of **5** (553 mg, 2.48 mmol) at $-78\,^{\circ}$C. The whole was stirred for 15 min at the same temperature, then trimethylchlorosilane (0.4 ml, 3.70 mmol) was added to the mixture. After stirring of the mixture for 10 min, the reaction was quenched by the addition of sat. NH_4Cl, and the whole was warmed to room temperature. The crude product was extracted with ether (30 ml, 3 times) and the combined extracts were washed with brine, dried, and concentrated to give a residue. Purification by silica gel column chromatography (45 g, AcOEt–petr. ether (1 : 15)) gave 585 mg (81%) of **25**. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2950, 2925, 2855, 2170, 1729, 1322, 1252, 840. ^{1}H-NMR δ (ppm): 0.14 (9H, s), 0.22 (3H, s), 0.24 (3H, s), 0.97 (9H, s), 2.53 (1H, dd, $J=17$, 6 Hz), 2.66 (1H, dd, $J=17$, 3 Hz), 2.91 (1H, dd, $J=15$, 3 Hz), 3.15 (1H, dd, $J=15$, 5 Hz), 3.50 (1H, m). MS *m/e*: 296, 295 (M^+), 238, 169; *m/e*: 296.1857 (Calcd for $C_{15}H_{30}NOSi_2$, 296.2866, $M^+ + 1$).

(3*S,4*R**)-3-Acetyl-1-*tert*-butyldimethylsilyl-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (26)**——A THF (20 ml) solution of LDA [prepared from *n*-BuLi (1.51 M, hexane solution, 3.3 ml, 4.98 mmol) and diisopropylamine (0.7 ml, 4.99 mmol)] was dropped into a stirred THF (20 ml) solution of **25** (589 mg, 2.00 mmol) through a stainless steel cannula at $-78\,^{\circ}$C, and the whole was stirred for 15 min at the same temperature. Then the lithium enolate solution was dropped into a THF (20 ml) solution of acetylimidazole (440 mg, 3.99 mmol) at $-78\,^{\circ}$C for 15 min, and the mixture was stirred for 15 min at the same temperature. The reaction was quenched by addition of sat. NH_4Cl, then warmed to room temperature. After removal of THF *in vacuo*, the crude product was extracted with ether (50 ml). The combined extracts were washed with brine, dried, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (70 g, AcOEt–petr. ether (1 : 2)) to give 537 mg (79%) of **26** as a colorless waxy solid. mp 52.5—53.5 °C (petr. ether). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2955, 2930, 2170, 1745, 1712, 1325, 1255, 1170, 845. ^{1}H-NMR δ (ppm): 0.15 (9H, s), 0.21 (3H, s), 0.27 (3H, s), 0.96 (9H, s), 2.30 (3H, s), 2.62 (2H, d, $J=5$ Hz), 4.14 (1H, m), 4.21 (1H, d, $J=2.5$ Hz). MS *m/e*: 338, 337 (M^+), 336, 322, 280; *m/e*: 337.1925 (Calcd for $C_{17}H_{31}NO_2Si_2$, 337.1893, M^+). *Anal.* Calcd for $C_{17}H_{31}NO_2Si_2$: C, 60.50; H, 9.27; N, 4.15. Found: C, 60.52; H, 9.18; N, 4.37.

(3*S,4*R**)-1-*tert*-Butyldimethylsilyl-3-[(*R**)-1-hydroxyethyl]-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (27) and (3*S**,4*R**)-1-*tert*-butyldimethylsilyl-3-[(*S**)-1-hydroxyethyl]-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (28)**——Sodium borohydride (18 mg, 0.48 mmol) was added to a methanol (3 ml) solution of **26** (160 mg, 0.48 mmol) and the mixture was stirred for 1 h at 0 °C. The reaction was quenched by addition of acetone (4 ml) and sat. NH_4Cl (4 ml). The methanol was removed *in vacuo*, and the crude product was extracted with AcOEt. The combined extracts were washed with brine, dried, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50 g, petr. ether–AcOEt (5 : 1)) to give 65 mg (40%) of **27** as the more polar product and 73 mg (45%) of **28** as the less polar product.

27: mp 87—88 °C (petr. ether). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3650—3250, 2960, 2930, 2860, 2170, 1740 (shoulder), 1730, 1330, 1255, 1028, 845, 825, 810. ^{1}H-NMR δ (ppm): 0.15 (9H, s), 0.21 (3H, s), 0.27 (3H, s), 0.97 (9H, s), 1.33 (3H, d, $J=7$ Hz), 2.52 (1H, dd, $J=17$, 7.5 Hz), 2.74 (1H, dd, $J=17$, 3.5 Hz), 3.11 (1H, dd, $J=5$, 2.5 Hz), 3.79 (1H, ddd, $J=7.5$, 3.5, 2.5 Hz), 4.23 (1H, dq, $J=7$, 5 Hz). MS *m/e*: 340 ($M^+ + 1$), 324, 284; *m/e*: 340.2111 (Calcd for $C_{17}H_{34}NO_2Si_2$, 340.2128, $M^+ + 1$).

28: mp 66.5—67.5 °C (petr. ether). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3625—3250, 2960, 2930, 2860, 2170, 1728, 1335, 1255, 1175, 1025, 843, 825, 812. ^{1}H-NMR δ (ppm): 0.16 (9H, s), 0.22 (3H, s), 0.26 (3H, s), 0.98 (9H, s), 1.34 (3H, d, $J=6.5$ Hz), 2.38 (1H, br s), 2.50 (1H, dd, $J=17$, 8 Hz), 2.73 (1H, dd, $J=17$, 4 Hz), 3.09 (1H, dd, $J=7$, 2.5 Hz), 3.56 (1H, ddd, $J=8$, 4, 2.5 Hz), 4.10 (1H, dq, $J=7$, 6.5 Hz). MS *m/e*: 340 ($M^+ + 1$), 324, 282; *m/e*: 333.2039 (Calcd for $C_{17}H_{33}NO_2Si_2$, 339.2050, M^+). *Anal.* Calcd for $C_{17}H_{33}NO_2Si_2$: C, 60.14; H, 9.80; N, 4.13. Found: C, 59.98; H, 9.70; N, 4.17.

Determination of the Configuration of the Side Chain (A—D). A. (3*S,4*R**)-1-*tert*-Butyldimethylsilyl-3-[(*R**)-1-methanesulfonyloxyethyl]-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (34)**——Triethylamine (47 l, 0.34 mmol) and methanesulfonyl chloride (18 l, 0.23 mmol) were added to a stirred CH_2Cl_2 (2 ml) solution of **27** (38 mg, 0.11 mmol) in an ice bath. The mixture was stirred for 3 h. The reaction temperature was gradually raised to room temperature. Then the mixture was diluted with ether and the separated organic layer was washed with water, sat. $NaHCO_3$, and brine successively. After drying, evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (30 g, petr. ether–AcOEt (6 : 1)) to give the mesylate **34**, 39 mg (83%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2955, 2930, 2855, 2770, 1740, 1358, 1338, 1255, 1178, 908, 843, 825. ^{1}H-NMR δ (ppm): 0.15 (9H, s), 0.23 (3H, s), 0.27 (3H, s), 0.89 (9H, s), 1.58 (3H, d, $J=6.5$ Hz), 2.55 (1H, dd, $J=17$, 7 Hz), 2.73 (1H, dd, $J=17$, 3.5 Hz), 3.02 (3H, s), 3.29 (1H, dd, $J=4.5$, 2.5 Hz), 3.84 (1H, ddd, $J=7$, 3.5, 2.5 Hz), 4.64 (1H, dq, $J=6.5$, 4.5 Hz). MS *m/e*: 418 ($M^+ + 1$), 402, 360, 306; *m/e*: 418.1930 (Calcd for $C_{18}H_{36}NO_4SSi_2$, 418.1903, $M^+ + 1$).

B. (3*S,4*R**)-1-*tert*-Butyldimethylsilyl-3-[(*S**)-1-methanesulfonyloxyethyl]-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (35)**——The alcohol **28** (40 mg, 0.12 mmol) was stirred with methanesulfonyl chloride (19 μl, 0.25 mmol) and triethylamine (49 μl, 0.35 mmol) in CH_2Cl_2 (2 ml) for 3 h (0 °C—room temperature). Extractive work-up as described above and silica gel column chromatography (25 g, petr. ether–AcOEt (6 : 1)) gave 44 mg (90%) of **35**. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2960, 2930, 2860, 2170, 1743, 1365, 1255, 1175, 910, 843, 825. ^{1}H-NMR δ (ppm): 0.16 (9H, s), 0.23 (3H, s), 0.28 (3H, s), 0.99 (9H, s), 1.62 (3H, d, J = 6.5 Hz), 2.56 (1H, dd, J = 17.5, 6.5 Hz), 2.71 (1H, dd, J = 17.5, 4 Hz), 3.07 (1H, ddd, J = 6.5, 4, 2.5 Hz), 5.11 (1H, dq, J = 6.5, 4.5 Hz). MS m/e: 418 (M^+ + 1), 402, 360, 306; m/e: 417.1796 (Calcd for $C_{18}H_{35}NO_4SSi_2$, 417.1825, M^+).

C. **1-*tert*-Butyldimethylsilyl-3-[(*E*)-ethylidene]-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (36)**——A mixture of **34** (39 mg, 0.09 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 42 μl, 0.28 mmol) in 1 ml of toluene was stirred for 40 min at room temperature, then at 52 °C for 4 h. After cooling, the reaction mixture was diluted with ether and the whole was washed with water, and brine successively. The dried solution was concentrated to give a residue, which was purified by silica gel column chromatography (5 g, petr. ether–AcOEt (15 : 1)) to afford 16 mg (54%) of **36**. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2960, 2930, 2855, 2170, 1740 (shoulder), 1730, 1710 (shoulder), 1302, 1255, 1145, 1027, 845, 828. ^{1}H-NMR δ (ppm): 0.14 (9H, s), 0.25 (3H, s), 0.28 (3H, s), 0.98 (9H, s), 1.68 (3H, d, J = 7.5 Hz), 2.62 (1H, dd, J = 17.5, 6.5 Hz), 2.75 (1H, dd, J = 17.5, 4.5 Hz), 4.27 (1H, br t, J = 5.5 Hz), 6.29 (1H, dq, J = 7.5, 1.5 Hz). MS m/e: 322, 321 (M^+), 306, 264 (base); m/e: 321.1948 (Calcd for $C_{17}H_{31}NOSi_2$, 321.1944, M^+).

D. **1-*tert*-Butyldimethylsilyl-2-[(*Z*)-ethylidene]-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (37)**——A mixture of **35** (36 mg, 0.09 mmol) and DBU (40 μl, 0.27 mmol) was stirred at room temperature for 30 min, then at 52 °C for 2 h. After cooling, the mixture was diluted with ether. The ether solution was washed with water, and brine successively. The dried solution was concentrated to give a residue, which was purified by silica gel column chromatography (5 g, petr. ether–AcOEt (15 : 1)) to give 10 mg (37%) of **37**. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 2960, 2935, 2860, 2170, 1738 (shoulder), 1730 (shoulder), 1720, 1335, 1255, 1143, 1010, 842. ^{1}H-NMR δ (ppm): 0.15 (9H, s), 0.23 (3H, s), 0.26 (3H, s), 0.97 (9H, s), 2.04 (3H, d, J = 7.5 Hz), 2.46 (1H, dd, J = 16.5, 8 Hz), 2.72 (1H, dd, J = 16.5, 4.5 Hz), 4.08 (1H, dd, J = 8, 4.5 Hz), 5.87 (1H, q, J = 7.5 Hz). MS m/e: 322, 321 (M^+), 306, 265 (base), 264; m/e: 321.1944 (Calcd for $C_{17}H_{31}NOSi_2$, 321.1944, M^+).

Stereoselective Reduction of 26——The results shown in Table II (run 2 through run 6) were obtained from the following experiments. The ratio of the reduction products (**27** and **28**) was determined by integration of the H_3 signal of each isomer (δ 3.79 for **27** and δ 3.56 for **28**) in the ^{1}H-NMR spectrum.

Reduction of 26 with Diisobutylaluminum 2,6-Di-*tert*-butyl-4-methylphenoxide (Run 2)——Diisobutylaluminum hydride (1.2 M, toluene solution, 1 ml, 1.20 mmol) was added to a toluene (6 ml) solution of 2,6-di-*tert*-butyl-4-methylphenol (529 mg, 2.40 mmol) at 0 °C and the mixture was stirred for 1 h at the same temperature. The solution was cooled to −78 °C, a toluene (1 ml) solution of **26** (40 mg, 0.12 mmol) was added, and the whole was stirred at the same temperature for 2 h. Then the reaction was quenched by the addition of sat. NH_4Cl and the product was extracted with AcOEt. The combined extracts were washed with brine, dried, and concentrated to give a residue, which was purified by silica gel column chromatography (20 g, AcOEt–petr. ether (1 : 3)), giving 40 mg (99%) of **28**.

Reduction of 26 with Lithium Tri-*sec*-butylborohydride (L-Selectride) (Run 3)——L-Selectride (1 M THF solution, 0.12 ml, 0.12 mmol) was added to a THF (5 ml) solution of **26** (20 mg, 0.06 mmol) with stirring at −78 °C and the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of sat. NH_4Cl and the product was extracted with AcOEt. The combined extracts were washed with brine, dried, and concentrated to give a residue, which was purified by silica gel column chromatography (10 g, petr. ether–AcOEt (1 : 3)) to give a mixture of **27** and **28**, 19 mg (93%). The ratio of **27** and **28** was determined to be 1 : 3.0 by ^{1}H-NMR spectroscopy.

Reduction of 26 with $ZnCl_2$–L-Selectride (Run 4)——L-Selectride (1 M THF solution, 0.09 ml, 0.09 mmol) was added to a mixture of **26** (20 mg, 0.06 mmol) and zinc chloride (80 mg, 0.59 mmol) in ether (5 ml) with stirring at −78 °C. The reaction mixture was stirred at the same temperature for 1 h, then stirred without a cooling bath for 30 min, and quenched by addition of sat. NH_4Cl at −78 °C. The work-up described above gave a mixture of **27** and **28**, 14 mg (70%). The ratio of **27** and **28** was estimated to be 1 : 1.6 by ^{1}H-NMR spectroscopy.

Reduction of 26 with KI–L-Selectride in THF (Run 5)——L-Selectride (1 M THF solution, 0.12 ml, 0.12 mmol) was added to a mixture of **26** (20 mg, 0.06 mmol) and potassium iodide (148 mg, 0.89 mmol) in THF (5 ml) with stirring at −78 °C. After stirring for 2 h at the same temperature, the reaction was quenched and the work-up described above gave a mixture of **27** and **28**, 16 mg (82%). The ratio of **27** and **28** was estimated to be 1 : 3.8 by ^{1}H-NMR spectroscopy.

Reduction of 26 with KI–L-Selectride in Ether (Run 6)——L-Selectride (1 M THF solution, 0.09 ml, 0.09 mmol) was added to a solution of **26** (20 mg, 0.06 mmol) and potassium iodide (152 mg, 0.09 mmol) in ether (5 ml) at −78 °C with stirring. The mixture was stirred at the same temperature for 1 h, then stirred without a cooling bath for 30 min. After quenching of the reaction, usual work-up gave a mixture of **27** and **28**, 17 mg (87%). The ratio of **27** and **28** was estimated to be 1.7 : 1 by ^{1}H-NMR spectroscopy.

(3*S,4*R**)-1-*tert*-Butyldimethylsilyl-3-[(*R**)-1-*tert*-butyldimethylsilyloxyethyl]-4-(3-trimethylsilyl-2-propynyl)-2-azetidinone (29)**——A mixture of **27** (93 mg, 0.27 mmol), imidazole (33 mg, 0.49 mmol), and *tert*-butyldimethylchlorosilane (73 mg, 0.49 mmol) in 0.3 ml of DMF was stirred for 12.5 h at room temperature. Water (10 ml) was added to this mixture and the product was extracted with ether (20 ml, 3 times). The combined extracts were washed with brine, dried, and concentrated to give a residue which was used for the next reaction without further purification.

The following data were obtained for a purified sample of **29**. mp 78—81 °C (petr. ether). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2950, 2925, 2850, 2170, 1735, 1252, 839. ^{1}H-NMR δ (ppm): 0.05 (3H, s), 0.07 (3H, s), 0.14 (9H, s), 0.21 (3H, s), 0.24 (3H, s), 0.92 (9H, s), 0.96 (9H, s), 1.24 (3H, d, J=6.5 Hz), 2.56 (1H, dd, J=17, 6.5 Hz), 2.69 (1H, dd, J=17, 4 Hz), 3.06 (1H, dd, J=4, 2.5 Hz), 3.81 (1H, ddd, J=6.5, 4, 2.5 Hz), 4.25 (1H, dq, J=6.5, 4 Hz). MS *m/e*: 453 (M$^+$), 452, 396; *m/e*: 453.2897 (Calcd for $C_{23}H_{47}NO_2Si_3$, 453.2913, M$^+$).

(3*S,4*R**)-1-*tert*-Butyldimethylsilyl-3-[(*R**)-1-*tert*-butyldimethylsilyloxyethyl]-4-(2-propynyl)-2-azetidinone (30)**——An aq. ethanol (water–ethanol (1 : 3), 1 ml) solution of silver nitrate (72 mg, 0.42 mmol) was added to an ethanol (1 ml) solution of crude **29** (described above), and the whole was stirred for 25 min at room temperature. Then cooled in an ice bath. An aq. solution of potassium cyanide (127 mg, 1.95 mmol, in 1 ml of water) was added to the reaction mixture and the whole was stirred for another 10 min, then the reaction was diluted with water (10 ml). The product was extracted with AcOEt. The combined extracts were washed with brine and dried. Concentration of this solution, followed by purification by silica gel column chromatography (20 g, AcOEt–petr. ether (1 : 15)) gave 92 mg (88% from **27**) of **30**. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3320, 2950, 2925, 2850, 1738, 1725 (shoulder), 1255, 839. ^{1}H-NMR δ (ppm): 0.07 (3H, s), 0.09 (3H, s), 0.25 (6H, s), 0.90 (9H, s), 0.98 (9H, s), 1.25 (3H, d, J=6.5 Hz), 2.06 (1H, dd, J=2.5, 2.5 Hz), 2.58 (2H, m), 3.09 (1H, dd, J=4.5, 2.5 Hz), 3.80 (1H, ddd, J=6.5, 4, 2.5 Hz), 4.22 (1H, dq, J=6.5, 4 Hz). MS *m/e*: 382, 381 (M$^+$), 366, 324; *m/e*: 382.2611 (Calcd for $C_{20}H_{40}NO_2Si_2$, 382.2597, M$^+$ + 1).

4-Nitrobenzyl (2*R,3*S**)-1-*tert*-Butyldimethylsilyl-3-[(*R**)-1-*tert*-butyldimethylsilyloxyethyl]-4-oxo-2-azetidine-α-butynoate (31)**——A THF (5 ml) solution of **30** (96 mg, 0.25 mmol) was added to a stirred THF (10 ml) solution of LDA [prepared from *n*-BuLi (1.51 M, hexane solution, 0.3 ml, 0.45 mmol) and diisopropylamine (64 μl, 0.46 mmol)] at −78 °C. After being stirred for 17 min at the same temperature, the lithium acetylide solution thus obtained was dropped into a THF (10 ml) solution of 4-nitrobenzyl chloroformate (109 mg, 0.51 mmol) at −78 °C through a stainless steel cannula over 3 min. The mixture was stirred at the same temperature for 30 min, then quenched by the addition of sat. NH_4Cl. The mixture was warmed to room temperature, THF was removed *in vacuo*, and the crude product was extracted with AcOEt (50 ml, 3 times). The combined extracts were washed with brine, dried, and concentrated. Purification of the residue by silica gel column chromatography (25 g, petr. ether–AcOEt (10 : 1)) gave 67 mg (46%) of **31**, along with 31 mg of **30**. mp 125—126 °C (ether–petr. ether). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2955, 2930, 2855, 2230, 1745, 1730 (shoulder), 1720 (shoulder), 1608, 1528, 1350, 1258, 1078, 840. ^{1}H-NMR δ (ppm): 0.05 (3H, s), 0.08 (3H, s), 0.23 (3H, s), 0.25 (3H, s), 0.88 (9H, s), 0.96 (9H, s), 1.23 (3H, d, J=6 Hz), 2.70 (1H, dd, J=17.5, 6.5 Hz), 2.81 (1H, dd, J=17.5, 4.5 Hz), 3.04 (1H, dd, J=4.5, 3 Hz), 3.85 (1H, ddd, J=6.5, 4, 2.5 Hz), 4.21 (1H, dq, J=6, 4.5 Hz), 5.30 (2H, s), 7.55 (2H, d, J=8.5 Hz), 8.77 (2H, d, J=8.5 Hz). MS *m/e*: 561, 560 (M$^+$), 559, 545, 507; *m/e*: 561.2814 (Calcd for $C_{28}H_{45}N_2O_6Si_2$, 561.2816, M$^+$ + 1).

4-Nitrobenzyl (2*R,3*S**)-1-*tert*-Butyldimethylsilyl-3-[(*R**)-1-*tert*-butyldimethylsilyloxyethyl]-4,β-dioxo-2-azetidinebutyrate (33)**——The propiolate **31** (39 mg, 0.07 mmol) was dissolved in THF (0.5 ml) and allowed to react with thiophenol (8 μl, 0.08 mmol) in the presence of triethylamine (11 μl, 0.08 mmol) for 4 h at room temperature. When the reaction was completed, THF was removed *in vacuo* to afford the residue, which was dissolved in aq. dioxane (dioxane–water (10 : 1)) with stirring in an ice bath. To this, 62 mg (0.45 mmol) of NBA was added and the mixture was stirred for 2.5 h at the same temperature. Then sat. Na_2SO_3 (6 ml) was added to the mixture and stirring was continued for 25 min. The product was extracted with AcOEt, and the combined extracts were washed with brine, and dried. The solvent was removed *in vacuo*, and purification of the residue by silica gel column chromatography (20 g, AcOEt–petr. ether (1 : 11—1 : 4)) gave 15 mg (37%) of **33**. mp 113—113.2 °C (ether–petr. ether). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2950, 2930, 2855, 1732, 1650, 1623, 1608, 1525, 1348, 1255, 1145, 838. ^{1}. ^{1}H-NMR δ (ppm): 0.05 (3H, s), 0.07 (3H, s), 0.20 (6H, s), 0.88 (9H, s), 0.95 (9H, s), 1.18 (3H, d, J=6.5 Hz), 2.85 (1H, dd, J=17, 8 Hz), 2.86 (1H, dd, J=4.5, 2.5 Hz), 3.03 (1H, dd, J=17, 5 Hz), 3.57 (2H, s), 4.03 (1H, ddd, J=8, 5, 2.5 Hz), 4.15 (1H, dq, J=6, 4.5 Hz), 5.30 (2H, s), 7.56 (2H, d, J=9 Hz), 8.27 (2H, d, J=9 Hz). MS *m/e*: 579, 578 (M$^+$), 577, 563, 521, 503; *m/e*: 578.2841 (Calcd for $C_{28}H_{46}N_2O_7Si_2$, 578.2843, M$^+$). *Anal.* Calcd for $C_{28}H_{46}N_2O_7Si_2$: C, 58.10; H, 8.02; N, 4.84. Found: C, 58.32; H, 7.97; N, 4.74.

Acknowledgements We thank Misses Megumi Moriyama and Kazumi Nakano for their technical assistance and also Misses Keiko Takahashi and Miyuki Nakamura for NMR and mass spectral measurements. Partial financial support of this research by a grant from the Japan Research Foundation for Optically Active Compounds and by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, is gratefully acknowledged.

References and Notes

1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday, in recognition of his outstanding contribution to asymmetric synthesis and related areas of chemistry.
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