β-Lactams. 2. Diastereoselective Alkylative Discrimination of Racemic 3-Substituted 4-Acetoxyazetidin-2-ones and Its Application to the Synthesis of a Chiral Key Intermediate for Carbapenem Syntheses

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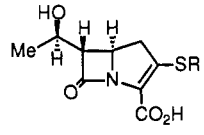
Received June 10, 1991 (Revised Manuscript Received December 2, 1991)

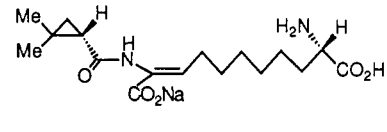
Alkylation of rac 3-substituted 4-acetoxyazetidin-2-one **4** with chiral tin(II) enolate **8** derived from 3-acetyl-(4*S*)-ethyl-1,3-thiazolidine-2-thione (ETT) (**7**) proceeded in a highly diastereoselective manner to give alkylated products **9**, **10**, and **11** in 42%, 20%, and 9% yields, respectively, after chromatographic purification. Similar alkylation of *rac*-**5** with **8** gave **16**, **17**, and **18** in 45%, 29%, and 5% yields, respectively. Compound **9** was readily converted to **33**, a chiral key intermediate for the synthesis of carbapenems. Analytical separation of *rac*-**4** was effectively done with an HPLC technique employing a chiral column packed with A(*S*)MBC.

The fungal metabolite (+)-thienamycin (**1**) has attracted attention as a potential candidate for a new generation of antibiotic drugs because of its high potency, broad spectrum, and stability to metabolism by various β-lactamases.[2]

However, there have been serious problems with the development of a practical drug. (+)-Thienamycin itself is fairly labile in solution, is decomposed by renal dehydropeptidase-I (DHP-I), and is produced in low yields by fermentation methods.[2d,3] Recently, a Merck Sharp & Dohme research group developed the non-natural β-lactam antibiotic imipenem (**2**), a derivative of (+)-thienamycin. It is hoped that **2** will be more chemically stable in solution than **1**.[4] Imipenem is the first carbapenem-type antibiotic drug available; it is used in combination with the DHP-I inhibitor sodium cilastatin **3**.[4] Because of the interest in the use of carbapenems as antibiotics, there have been many papers on carbapenem synthesis.[5-9] Among the various synthetic methods reported so far, alkylation at C-4 of 3-substituted 4-acetoxyazetidin-2-ones has proven to be strikingly efficient for a short synthesis of (+)-thienamycin (**1**) and imipenem.[5y,6d-k,p-r,u,w,y,7a,d,e] In a preliminary paper, we reported a diastereoselective alkylative discrimination method for racemic (rac) 3-substituted 4-acetoxyazetidin-2-one **4**.[10] This method seems promising for asymmetric synthesis of various carbapenems for two reasons. One of the alkylated products (vide infra) can be straightforwardly exploited for carbapenem syntheses, and *rac*-**4** can be readily derived from compound **6**, which is obtained by a simple diketene–imine cycloaddition reaction.[11,12] This racemate discrimination method is also of interest because one of the enantiomers of *rac*-**4** is the matched partner of 3-acyl-(4S)-ethyl-1,3-thiazolidine-2-thiones. Here, we describe details of the alkylative racemate discrimination for *rac*-**4** and **-5**, its



1 R = $(CH_2)_2NH_2$
2 R = $(CH_2)_2NHCH{=}NH{\cdot}H_2O$



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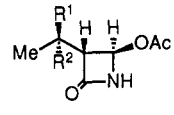
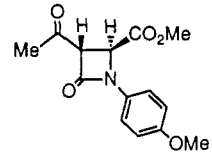


4 R^1 = OSi⁄, R^2 = H
5 R^1 = H, R^2 = OSi⁄



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(1) (a) The University of Tokushima. (b) Lederle (Japan) Ltd. (c) Kyoto University. (d) Daicel Chemical Industries, Ltd.

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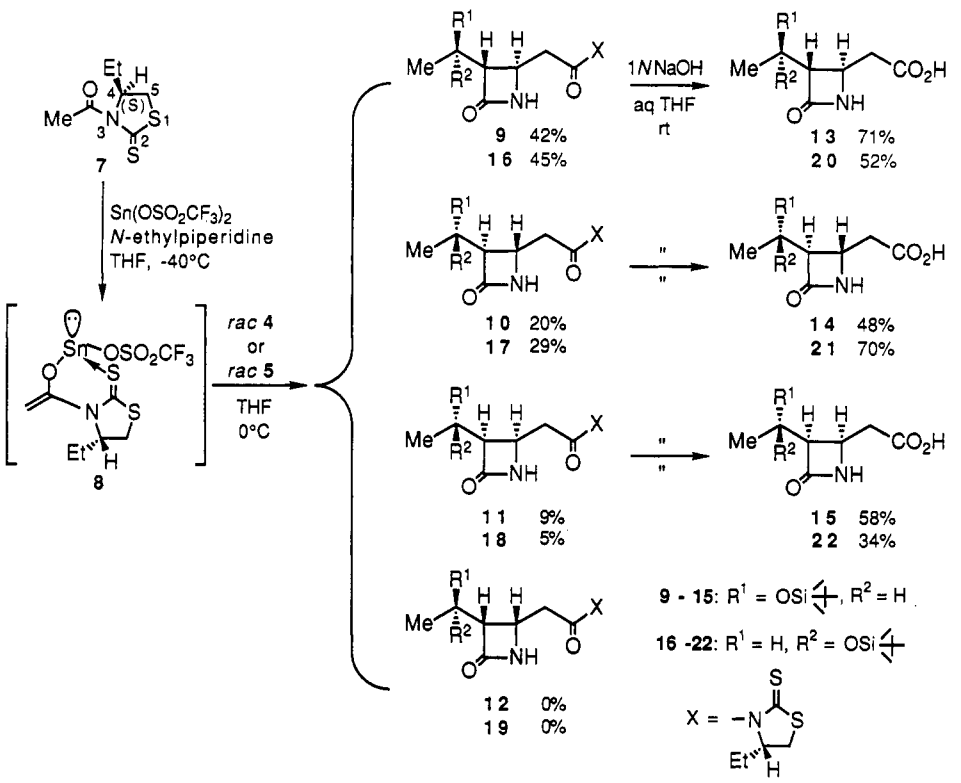
Scheme I



application to synthesis of a chiral key intermediate for carbapenem synthesis, and the analytical separation of *rac*-**4**.

Results and Discussion

Tin(II) enolate **8**, obtained by enolization of 3-acetyl-(4*S*)-ethyl-1,3-thiazolidine-2-thione (**7**)[13] employing Mukaiyama's reaction conditions,[14] was treated with *rac*-**4** at 0 °C for 50 min. Chromatographic separation of the reaction mixture afforded alkylated products **9**, **10**, and **11** in 42%, 20%, and 9% yields, respectively (Scheme I). These three compounds were converted to the corresponding carboxylic acids **13**, **14**, and **15** by simple alkaline hydrolysis with 1 N NaOH in aqueous THF. The antipodal relationship between compound **13** and carboxylic acid **14** was confirmed by their spectroscopic data (^{1}H NMR and IR) and by the opposite signs of their specific rotations. The absolute stereochemistry of compounds **9**, **10**, **13**, and **14** was established by chemical correlation of **9** and **13** with **33**, a key intermediate for (+)-thienamycin synthesis (vide infra). The stereochemistry of **11** was tentatively assigned on the basis of the ^{1}H NMR spectrum of **15** [δ C3-H 3.26 ($CDCl_3$), J = 5.0 Hz (triplet-like)], the combined yield (51%)[15] of **9** and **11**, and general[10,16] mechanistic considerations (Figure 1) (vide infra). The C3-H, C4-H cis compound **12** has never been detected.

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(15) If compound **11** was assigned as C3-H, C4-H β-cis like compound **12** then the combined yield of **9** and **11** should be less than 50%.

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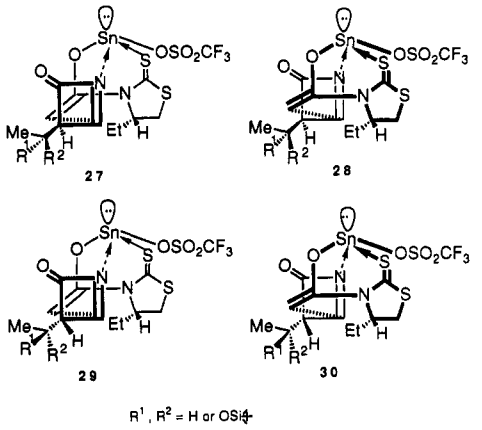
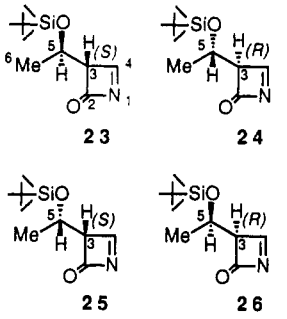


Figure 1. Plausible transition states of alkylation of cyclic acyl imines **23–26** with chiral tin(II) enolate **8**.

The diastereoselective alkylation of *rac*-**5** with chiral tin(II) enolate **8** also furnished three products: **16**, **17**, and **18** in 45%, 29%, and 5% yields, respectively. Alkaline hydrolysis of these (4*S*)-ETT amides with 1 N NaOH in aqueous THF gave the corresponding carboxylic acids **20**, **21**, and **22** in 52%, 70%, and 34% yields, respectively. The C3-H, C4-H cis compound **19** was not isolated. The antipodal relationship between **20** and **21** was confirmed by the fact that their spectroscopic data were identical. The absolute stereochemistry of compounds **16**, **17**, **20**, and **21** was determined by X-ray crystallographic analysis of **20**.[17] The stereochemistry of **18** was tentatively assigned by analysis of the ^{1}H NMR and by consideration of the reaction mechanism, as in the case of **11**. Thus, alkylation of the (3*S*)-cyclic acylimines **23** and **25** with chiral tin(II) enolate **8** of 3-acetyl-(4*S*)-ETT proceeded in an exclusively diastereoselective manner in spite of the difference in C-5 stereochemistry, but similar alkylation of (3*R*)-cyclic acylimines **24** and **26** with **8** resulted in 2.2:1 and 5.8:1 ratios of diastereomers.



The diastereoselectivity of the alkylation of *rac*-**4** and -**5** can be explained by inspecting four plausible six-membered, chelated transition states **27**–**30**[18] for the reaction of tin(II) enolate **8** and cyclic acylimines **23**–**26**.[16] Transition state **27**, which leads to products **9** and **16**, should be tremendously more stable than **28** since the steric interactions between the α-ethyl group of the (4*S*)-ETT moiety and the β-oriented bulky group at C-3 of the cyclic acylimine are absent in **27**. It is not clear whether **29** or **30** would be more stable. Although transition state **30** bears steric repulsion between the α-ethyl group of the (4*S*)-ETT moiety and the cyclic acylimine, it may be somewhat more stable than **29**, in which severe steric repulsion between the enolate moiety and the α-oriented bulky group at C-3 of the cyclic acylimine is vicinal to the reaction center. Therefore, **10** and **17**, obtained via **30**, would be more predominant than **11** and **18**, obtained via **29**. This speculation is supported by the fact that the stereochemistry of the bulky group at C-3 of the cyclic acylimine affects the ratio of diastereomers obtained from alkylation with **8**: 2.2:1 for *rac*-**4** vs 5.8:1 for *rac*-**5**.

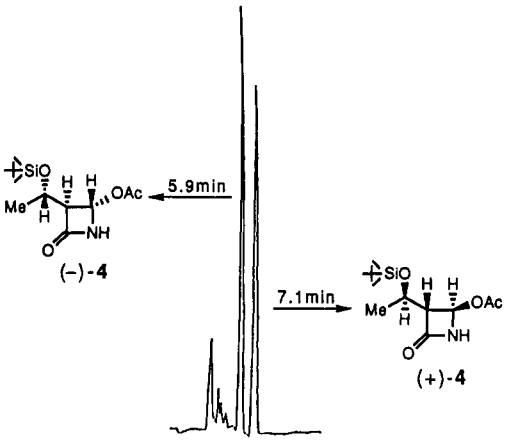
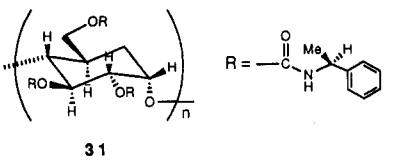


Figure 2. HPLC Chromatogram of *rac*-**4**. Column: A(*S*)-MBC(4.6 mm (i.d.) × 25 cm). Eluent: hexane–EtOH (8:2). Flow rate: 1.0 mL/min. Load: 2 μL. Detect: 220 nm.

A simple determination of the enantiomeric purity of optically active 4-acetoxyazetidin-2-one (**4**) is important not only for an evaluation of its asymmetric synthesis but also for an industrial carbapenem synthesis.[19] Thus, we have investigated an analytical separation of *rac*-**4** by high-performance liquid chromatography (HPLC). We discovered, after several attempts, that *rac*-**4** could be cleanly separated on an amylose (*S*)-methylbenzylcarbamate [A(*S*)MBC] (**31**) column under the conditions shown in Figure 2. The separation factor (α = 1.43) was obtained from the retention time of both enantiomers. The two peaks were assigned by injection of optically pure



(+)-**4**. This analytical result can be applied to preparative optical resolution of *rac*-**4**.[20]

Optically active **9** and its carboxylic acid derivative **13** were readily converted to the key intermediate **33**, which is useful for the syntheses of both (+)-thienamycin (**1**) and imipenem (**2**).[5i] Mono-*p*-nitrobenzyl malonate was treated with $MgCl_2$ in the presence of Et_3N in MeCN to give $Mg(O_2CCH_2CO_2PNB)_2$ in situ.[21] To the solution were added imidazole and (4*S*)-ETT amide **9**. Heating at 55–65 °C afforded the desired β-keto ester **32** in 90% yield. Compound **32** was also obtained in 89% yield by subjecting carboxylic acid **13** to the Masamune procedure[22] employing

(17) Supplementary material is available.

(18) Other transition states[16a] in which the azetidinone carbonyl overlaps the thiazolidine moiety should be disfavored because of the severe 1,3-diaxial steric repulsion between C-3 methylene of the acyl imine and the thiazolidine moiety.

(19) Cf. Nagao, Y.; Kumagai, T.; Yxmada, S.; Fujita, E.; Inoue, Y.; Nagase, Y.; Aoyagi, S.; Abe, T. *J. Chem. Soc., Perkin Trans. 1* 1985, 2361.

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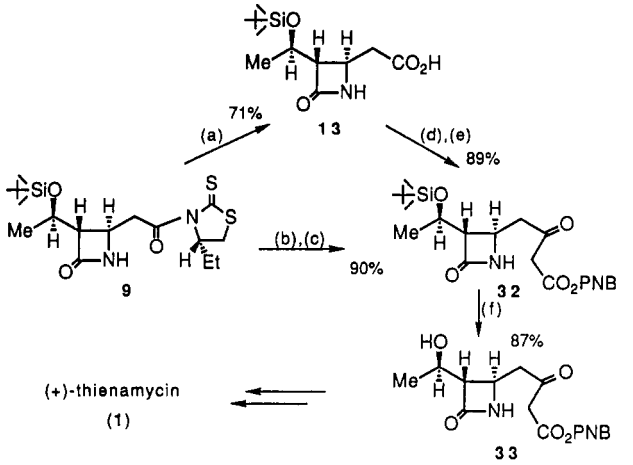
Scheme II[a]



[a] Key: (a) 1 *N* NaOH, aqueous THF, rt; (b) $HO_2CCH_2CO_2PNB$, $MgCl_2$, Et_3N, MeCN, 0 °C; (c) imidazole, 55–65 °C; (d) 1,1′-carbonyldiimidazole, MeCN, rt; (e) $Mg(O_2CCH_2CO_2PNB)_2$, MeCN, 60 °C; (f) HCl, aqueous MeOH, rt.

1,1′-carbonyldiimidazole and $Mg(O_2CCH_2CO_2PNB)_2$. Desilylation of **32** under acidic conditions in aqueous MeOH gave (3*S*,4*R*)-3-[(1*R*)-1-hydroxyethyl]-4-[3-(*p*-nitrobenzyloxycarbonyl)-2-oxopropyl]azetidine-2-one (**33**) in 87% yield. All spectral data of **33** were identical with those reported in the literature.[6v] Since compound **33** has already been converted to (+)-thienamycin (**1**) by Christensen et al.,[5i] this simple synthesis of chiral β-keto ester **33** from *rac*-**4** should be practical for carbapenem synthesis.

From the results of the studies on the diastereoselective alkylative discrimination reactions of *rac*-**4** and -**5**, we also realized that 3-acetyl-(4*S*)-ETT should be the matched partner of (3*S*)-cyclic acylimines **23** and **25** in their alkylation reactions.

Experimental Section

Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded in $CDCl_3$ at 90 or 270 MHz; signals are given in ppm with $SiMe_4$ as an internal standard. Racemic 3-substituted 4-acetoxyazetidin-2-ones **4** and **5** were prepared from **6**, the product of a cycloaddition reaction between diketene and methyl [(4-methoxyphenyl)imino]acetate.[11,12] 3-Acetyl-(4*S*)-ethyl-1,3-thiazolidine-2-thione (**7**) was prepared by our published method.[13] Other general experimental information is discussed in the preceding article.[16a]

Alkylation of *rac*-3-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one (4) with 3-Acetyl-(4*S*)-ethyl-1,3-thiazolidine-2-thione (7). Tin(II) trifluoromethanesulfonate (6.88 g, 16.5 mmol) was dissolved in anhydrous THF (25 mL) under N_2 at rt. To the solution cooled at −40 °C were successively added *N*-ethylpiperidine (3.0 mL, 21.8 mmol) and **7** (2.27 g, 12.0 mmol) in anhydrous THF (10 mL), and the mixture was stirred for 3.5 h at −40 °C to form the tin(II) enolate **8**. To the tin(II) enolate **8** at −40 °C was added a solution of *rac*-**4** (3.16 g, 11.0 mmol) in anhydrous THF (15 mL), and the mixture was stirred at 0 °C for 1 h. A 0.1 M phosphate buffer solution (pH 7.0, 15 mL) and Et_2O (150 mL) were added to the reaction mixture with vigorous stirring. The precipitate was filtered off through Celite, and the filtrate was extracted with three portions Et_2O. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give a yellow viscous oil. Silica gel column chromatography (elution with 20:1 $CHCl_3$–AcOEt) of the oily residue afforded compounds **9** (1.92 g, 42%), **10** (0.92 g, 20%), and **11** (0.41 g, 9%).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]methyl]azetidin-2-one (9): yellow, amorphous solid; mp 103.5–104.5 °C (from $CHCl_3$); $[\alpha]^{25}_D$ +188.8° (*c* 0.93, $CHCl_3$); IR (KBr) 1750, 1695 cm^{-1}; ^1H NMR (90 MHz) δ 0.07 (s, 6 H), 0.87 (s, 9 H), 1.03 (t, 3 H, *J* = 8.0 Hz), 1.23 (t, 3 H, *J* = 6.0 Hz), 1.73–2.05 (m, 2 H), 2.88 (dd, 1 H, *J* = 2.5, 5.0 Hz), 2.96 (dd, 1 H, *J* = 2.0, 12.0 Hz), 3.15 (dd, 1 H, *J* = 10.0, 18.0 Hz), 3.58 (dd, 1 H, *J* = 8.0, 12.0 Hz), 3.90–4.35 (m, 2 H), 4.05 (dd, 1 H, *J* = 3.0, 18.0 Hz), 5.02–5.25 (m, 1 H), 6.05 (br s, 1 H); MS *m*/*z* 416 (M^+). Anal. Calcd for $C_{18}H_{32}N_2O_3S_2Si$: C, 51.89; H, 7.74; N, 6.72. Found: C, 51.93; H, 7.79; N, 6.68.

(3*S*,4*S*)-3-[(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]methyl]azetidin-2-one (10): yellow oil; $[\alpha]^{25}_D$ +47.8° (*c* 1.05, $CHCl_3$); IR (neat) 1750, 1695 cm^{-1}; ^1H NMR (90 MHz) δ 0.07 (s, 6 H), 0.86 (s, 9 H), 1.02 (t, 3 H, *J* = 8.0 Hz), 1.21 (d, 3 H, *J* = 6.0 Hz), 1.66–2.03 (m, 2 H), 2.86 (dd, 1 H, *J* = 2.0, 6.0 Hz), 2.96 (dd, 1 H, *J* = 2.0, 12.0 Hz), 3.46–3.78 (m, 3 H), 3.88–4.08 (m, 1 H), 4.15–4.34 (m, 1 H), 5.03–5.26 (m, 1 H), 6.25 (br s, 1 H); HRMS calcd for $C_{18}H_{32}N_2O_3S_2Si$ MW 416.1623, found *m*/*z* 416.1581.

(3*R*,4*R*)-3-[(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]methyl]azetidin-2-one (11): yellow oil; $[\alpha]^{25}_D$ +187.1° (*c* 0.89, $CHCl_3$); IR (neat) 1755 cm^{-1}; ^1H NMR (90 MHz) δ 0.08 (s, 6 H), 0.86 (s, 9 H), 1.02 (t, 3 H, *J* = 8.0 Hz), 1.32 (d, 3 H, *J* = 6.0 Hz), 1.70–2.02 (m, 2 H), 2.95 (dd, 1 H, *J* = 2.0, 12.0 Hz), 3.23 (dd, 1 H, *J* = 2.0, 6.0 Hz), 3.46–4.48 (m, 5 H), 5.02–5.25 (m, 1 H), 6.05 (br s, 1 H), HRMS calcd for $C_{18}H_{32}N_2O_3S_2Si$ MW 416.1623, found *m*/*z* 416.1634. Anal. Calcd for $C_{18}H_{32}N_2O_3S_2Si$: C, 51.89; H, 7.74; N, 6.72. Found: C, 51.74; H, 7.80; N, 6.18.

Alkaline Hydrolysis of (4*S*)-ETT Amides 9, 10, and 11. To a solution of **9** (1.60 g, 3.84 mmol) in aqueous THF (50%, 40 mL) was added 1 N NaOH (8 mL, 0.13 mmol). The mixture was stirred at rt for 15 min. After evaporation of the solvent in vacuo, water (10 mL) was added. The aqueous solution was washed with $CHCl_3$ and acidified with 1 N HCl. The acidic solution was extracted with AcOEt, and the extract was washed with brine, dried, and evaporated in vacuo. The residue was purified by silica gel column chromatography (elution with 15:1 $CHCl_3$–MeOH) to give carboxylic acid **13** (0.78 g, 71% yield). Similar hydrolyses of compounds **10** (85 mg, 0.20 mmol) and **11** (70 mg, 0.17 mmol) were also performed to give the corresponding carboxylic acids **14** (28 mg, 48%) and **15** (28 mg, 58%).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-(carboxymethyl)azetidin-2-one (13): colorless powder; mp 143.5–144.5 °C (from THF–hexane); $[\alpha]^{25}_D$ +16.7° (*c* 0.23, $CHCl_3$); IR (KBr) 1720 cm^{-1}; ^1H NMR (270 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.87 (s, 9 H), 1.22 (d, 3 H, *J* = 6.3 Hz), 2.55 (dd, 1 H, *J* = 10.7, 17.0 Hz), 2.78 (dd, 1 H, *J* = 3.3, 17.0 Hz), 2.80 (dd, 1 H, *J* = 1.3, 5.3 Hz), 3.95 (ddd, 1 H, *J* = 1.3, 10.7, 13.3 Hz), 4.18 (dq, 1 H, *J* = 5.3, 6.3 Hz), 7.02 (br s, 1 H); HRMS calcd for $C_{13}H_{25}NO_4Si$ MW 287.1553, found *m*/*z* 287.1561. Anal. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.44; H, 8.38; N, 4.96.

(3*R*,4*S*)-3-[(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-(carboxymethyl)azetidin-2-one (14): colorless powder; mp 145–146 °C (from THF–hexane); $[\alpha]^{25}_D$ −16.3° (*c* 0.24, $CHCl_3$); IR (KBr) 1720 cm^{-1}; ^1H NMR (270 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.22 (d, 3 H, *J* = 6.3 Hz), 2.55 (dd, 1 H, *J* = 10.7, 17.0 Hz), 2.80 (dd, 1 H, *J* = 3.0, 17.0 Hz), 2.82 (dd, 1 H, *J* = 2.0, 5.0 Hz), 3.95 (ddd, 1 H, *J* = 2.0, 3.0, 10.7 Hz), 4.19 (dq, 1 H, *J* = 5.0, 6.3 Hz), 7.01 (br s, 1 H); HRMS calcd for $C_{13}H_{25}NO_4Si$ MW 287.1553, found *m*/*z* 287.1576. Anal. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.06; H, 8.71; N, 4.79.

(3*R*,4*R*)-3-[(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-(carboxymethyl)azetidin-2-one (15): colorless powder; mp 120–120.5 °C (from THF–hexane); $[\alpha]^{25}_D$ +68.6° (*c* 0.95, $CHCl_3$); IR (KBr) 1725, 1675 cm^{-1}; ^1H NMR (270 MHz) δ 0.10 (s, 6 H), 0.89 (s, 9 H), 1.20 (d, 3 H, *J* = 6.3 Hz), 2.87 (dd, 1 H, *J* = 3.3, 17.5 Hz), 3.00 (dd, 1 H, *J* = 11.2, 17.5 Hz), 3.26 (dd, 1 H, *J* = 5.0, 5.3 Hz), 4.05 (ddd, 1 H, *J* = 3.3, 5.3, 11.2 Hz), 4.28 (dq, 1 H, *J* = 5.0, 6.3 Hz), 7.31 (br s, 1 H); HRMS calcd for $C_{13}H_{25}NO_4Si$ MW 287.1553, found *m*/*z* 287.1589. Anal. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.02; H, 8.51; N, 4.80.

Alkylation of *rac*-3-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one (5) with 3-Acetyl-(4*S*)-ethyl-1,3-thiazolidine-2-thione (7). The reaction of *rac*-**5** (1.73 g, 6.0 mmol) with tin(II) enolate **8**, obtained from **7** (1.14 g, 6.0

mmol), was carried out as for *rac*-4 and afforded alkylated products 16 (1.14 g, 45%), 17 (0.72 g, 29%), and 18 (0.13 g, 5%) after purification by silica gel column chromatography (elution with 20:1 $CHCl_3$–AcOEt).

(3*S*,4*R*)-3-[(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]methyl]azetidin-2-one (16): yellow oil; $[\alpha]^{25}_D$ +175.0° (*c* 1.23, $CHCl_3$); IR (neat) 1750, 1680 cm^{-1}; ^1H NMR (90 MHz) δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.03 (t, 3 H, *J* = 8.0 Hz), 1.32 (d, 3 H, *J* = 6.0 Hz), 1.73–2.05 (m, 2 H), 2.99 (dd, 1 H, *J* = 2.0, 6.0 Hz), 2.95 (dd, 1 H, *J* = 2.0, 8.0 Hz), 3.59 (dd, 1 H, *J* = 8.0, 12.0 Hz), 3.23 (dd, 1 H, *J* = 10.0, 18.0 Hz), 3.85–4.36 (m, 3 H), 5.03–5.26 (m, 1 H), 6.11 (br s, 1 H); HRMS calcd for $C_{18}H_{32}N_2O_3S_2Si$ MW 416.1623, found *m/z* 416.1636. Anal. Calcd for $C_{18}H_{32}N_2O_3S_2Si$: C, 51.89; H, 7.74; N, 6.72. Found: C, 52.18; H, 7.56; N, 6.54.

(3*R*,4*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]methyl]azetidin-2-one (17): yellow, amorphous solid; mp 112.0–112.5 °C (from $CHCl_3$); $[\alpha]^{25}_D$ +76.2° (*c* 0.9, $CHCl_3$); IR (KBr) 1755, 1690 cm^{-1}; ^1H NMR (90 MHz) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.02 (t, 3 H, *J* = 8.0 Hz), 1.32 (d, 3 H, *J* = 6.0 Hz), 1.60–2.03 (m, 2 H), 2.88–3.05 (m, 2 H), 3.48–3.63 (m, 3 H), 3.83–4.00 (m, 1 H), 4.09–4.33 (m, 1 H), 5.05–5.28 (m, 1 H), 6.05 (br s, 1 H); HRMS calcd for $C_{18}H_{32}N_2O_3S_2Si$ MW 416.1623, found *m/z* 416.1597 (M^+).

(3*R*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]methyl]azetidin-2-one (18): yellow, amorphous solid; mp 132–133 °C (from $CHCl_3$); $[\alpha]^{25}_D$ +69.6° (*c* 0.48, $CHCl_3$); IR (KBr) 1750, 1690 cm^{-1}; ^1H NMR (90 MHz) δ 0.10 (s, 6 H), 0.88 (s, 9 H), 1.03 (t, 3 H, *J* = 8.0 Hz), 1.38 (d, 3 H, *J* = 6.0 Hz), 1.66–2.10 (m, 2 H), 2.96 (dd, 1 H, *J* = 2.0, 12.0 Hz), 3.45 (dd, 1 H, *J* = 12.0, 14.0 Hz), 3.24–3.66 (m, 2 H), 3.96–4.36 (m, 3 H), 5.02–5.31 (m, 1 H), 5.96 (br s, 1 H); HRMS calcd for $C_{18}H_{32}N_2O_3S_2Si$ MW 416.1623, found *m/z* 416.1670 (M^+).

Alkaline Hydrolysis of (4*S*)-ETT Amides 16, 17, and 18. Hydrolysis of 16 (700 mg, 1.68 mmol) with 1 N NaOH was carried out in the same manner as that described for hydrolysis of 9. The crude product which was purified by silica gel column chromatography (elution with 20:1 $CHCl_3$–MeOH) to give carboxylic acid 20 (250 mg, 52%). Hydrolysis of 17 (480 mg, 1.15 mmol) and 18 (163 mg, 0.39 mmol) with 1 N NaOH gave the corresponding carboxylic acids 21 (232 mg, 70%) and 22 (38 mg, 34%).

(3*S*,4*R*)-3-[(1*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-(carboxymethyl)azetidin-2-one (20): colorless solid; mp 137.9–138.0 °C (from THF–hexane); $[\alpha]^{25}_D$ +38.3° (*c* 0.36, $CHCl_3$); IR (KBr) 1710 cm^{-1}; ^1H NMR (270 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.29 (d, 3 H, *J* = 6.3 Hz), 2.57 (dd, 1 H, *J* = 9.9, 17.0 Hz), 2.77 (dd, 1 H, *J* = 4.0, 17.0 Hz), 2.96 (dd, 1 H, *J* = 2.0, 4.0 Hz), 3.87 (ddd, 1 H, *J* = 2.0, 4.0, 9.9 Hz), 4.19 (dq, 1 H, *J* = 4.0, 6.3 Hz), 7.02 (br s, 1 H); MS calcd for $C_{13}H_{25}NO_4Si$ MW 287, found *m/z* 288 ($M^+ + 1$).

(3*R*,4*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-(carboxymethyl)azetidin-2-one (21): colorless solid; mp 133.5–134.0 °C (from THF–hexane); $[\alpha]^{25}_D$ −38.2° (*c* 0.46, $CHCl_3$); IR (KBr) 1710 cm^{-1}; ^1H NMR (270 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.30 (d, 3 H, *J* = 6.3 Hz), 2.60 (dd, 1 H, *J* = 9.6, 17.2 Hz), 2.77 (dd, 1 H, *J* = 4.3, 17.2 Hz), 2.95 (dd, 1 H, *J* = 2.2, 3.8 Hz), 3.88 (ddd, 1 H, *J* = 2.2, 4.3, 9.6 Hz), 4.19 (dq, 1 H, *J* = 3.8, 6.3 Hz), 6.67 (br s, 1 H); MS calcd for $C_{13}H_{25}NO_4Si$ MW 287, found *m/z* 288 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.14; H, 8.40; N, 4.50.

(3*R*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-(carboxymethyl)azetidin-2-one (22): colorless, amorphous solid: mp 112.5–113.0 °C (from THF–hexane); $[\alpha]^{25}_D$ −3.9° (*c* 0.97, $CHCl_3$); IR (KBr) 1725, 1695 cm^{-1}; ^1H NMR (90 MHz) δ 0.10 (s, 6 H), 0.92 (s, 9 H), 1.62 (d, 3 H, *J* = 6.4 Hz), 2.70 (dd, 1 H, *J* = 2.2, 16.4 Hz), 2.96 (dd, 1 H, *J* = 3.2, 16.4 Hz), 3.51 (ddd, 1 H, *J* = 2.4, 3.4, 5.6 Hz), 4.19 (ddd, 1 H, *J* = 2.2, 3.2, 5.6 Hz), 4.55 (dq, 1 H, *J* = 2.4, 6.4 Hz), 6.96 (br s, 1 H); HRMS calcd for $C_{13}H_{25}NO_4Si$ MW 287.1553, found *m/z* 287.1549 (M^+).

(3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[3-(*p*-nitrobenzyloxycarbonyl)-2-oxopropyl]azetidin-2-one (32). (1) Conversion of 13 to 32. 1,1′-Carbonyldiimidazole (352 mg, 2.2 mmol) was added to a solution of 13 (480 mg, 1.7 mmol) in anhydrous MeCN (13 mL) at rt under N_2. The mixture was stirred at rt for 40 min, and then $Mg(O_2CCH_2CO_2PNB)_2$ (835 mg, 1.7 mmol) in anhydrous MeCN (6 mL) was added. After the reaction mixture stirred at 60 °C for 15 min, the solvent was evaporated in vacuo and AcOEt (100 mL) was added. The organic layer was successively washed with 1 N HCl, water, 10% K_2CO_3, and brine. After being dried, the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (elution with 1:1 $CHCl_3$–AcOEt) to give 32 (690 mg, 89%) as a pale yellow oil: $[\alpha]^{25}_D$ +16.7° (*c* 2.49, $CHCl_3$); IR (neat) 1750, 1720, 1520 cm^{-1}; ^1H NMR (90 MHz) δ 0.07 (s, 6 H), 0.86 (s, 9 H), 1.22 (d, 3 H, *J* = 6.0 Hz), 2.69–2.98 (m, 3 H), 3.56 (s, 2 H), 3.79–4.24 (m, 2 H), 5.27 (s, 3 H), 6.05 (br s, 1 H), 7.51 (d, 2 H, *J* = 9.0 Hz), 8.23 (d, 2 H, *J* = 9.0 Hz).

(2) Conversion of 9 to 32. To a solution of $HO_2CCH_2CO_2PNB$ (77.7 mg, 0.33 mmol) in anhydrous MeCN (0.6 mL) at rt was added $MgCl_2$ (15.4 mg, 0.16 mmol) under N_2. The reaction mixture was then cooled to 0 °C. To the resulting suspension was added Et_3N (32.8 mg, 0.33 mmol) in anhydrous MeCN (0.15 mL). The mixture was stirred at 0 °C for 1 h, and then imidazole (20.4 mg, 0.30 mmol) and 9 (111 mg, 0.25 mmol) were added. After the mixture stirred at 55–65 °C for 2 h, the solvent was evaporated in vacuo. To the residue was added AcOEt (10 mL), and then the organic layer was successively washed with 1 N HCl, water, 5% $NaHCO_3$, and brine. After being dried, the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (elution with 95:5 $CHCl_3$–acetone) to give 32 (104 mg, 90%) as a pale yellow oil. This product was identical to 32 obtained from 13.

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-4-[3-(*p*-nitrobenzyloxycarbonyl)-2-oxopropyl]azetidin-2-one (33). To a solution of 32 (1.00 g, 2.15 mmol) in 2:1 water–MeOH (15 mL) at rt was added concd HCl (0.65 mL). After the mixture stirred at rt for 1 h, the solvent was evaporated in vacuo and water (50 mL) was added. The aqueous solution was extracted with AcOEt (2 × 50 mL). The combined organic layer was washed with brine, dried, and evaporated in vacuo. The residue was purified by silica gel column chromatography (elution with 1:10 THF–AcOEt) to give 33 (658 mg, 87%) as colorless needles: mp 126–127 °C (from THF–Et_2O) (lit.[6v] mp 123–124 °C); $[\alpha]^{25}_D$ +21.3° (*c* 0.235, $CHCl_3$) [lit.[6v] $[\alpha]^{25}_D$ +21.0° (*c* 0.189, $CHCl_3$)]; IR (KBr) 1750, 1720, 1710 cm^{-1}; ^1H NMR (270 MHz) δ 1.32 (d, 3 H, *J* = 6.3 Hz), 2.27 (d, 1 H, *J* = 4.0 Hz), 2.83 (dd, 1 H, *J* = 2.3, 6.9 Hz), 2.93 (dd, 1 H, *J* = 7.9, 18.5 Hz), 3.06 (dd, 1 H, *J* = 5.3, 18.5 Hz), 3.59 (s, 2 H), 3.95 (ddd, 1 H, *J* = 2.3, 5.3, 7.9 Hz), 4.14–4.21 (m, 1 H), 5.28 (s, 2 H), 6.01 (br s, 1 H), 7.53 (d, 2 H, *J* = 8.9 Hz), 8.25 (d, 2 H, *J* = 8.9 Hz). Anal. Calcd for $C_{16}H_{18}N_2O_7$: C, 54.86; H, 5.18; N, 8.00. Found: C, 54.82; H, 5.28; N, 7.76.

Acknowledgment. We are sincerely grateful to Professor Emeritus Eiichi Fujita (Kyoto University) and Mr. Kazuyoshi Ogura (R & D Director, Lederle (Japan) Ltd.) for their encouragement throughout this work.

Registry No. 1, 59995-64-1; 2, 64221-86-9; 4, 78963-47-0; 5, 78963-48-1; 7, 101979-44-6; 9, 102832-06-4; 10, 102917-32-8; 11, 102917-33-9; 13, 88669-70-9; 14, 102917-34-0; 15, 102917-35-1; 16, 109361-71-9; 17, 109361-72-0; 18, 109361-73-1; 20, 109361-74-2; 21, 141781-46-6; 22, 133647-14-0; 32, 141686-09-1; 33, 75321-07-2; $Mg(O_2CCH_2CO_2PNB)_2$, 83972-01-4; $HO_2CCH_2CO_2PNB$, 77359-11-6.

Supplementary Material Available: Details of the X-ray diffraction analysis of compound 20 and ^1H NMR spectra for compounds 17, 18, 20, 22, and 32 (12 pages). Ordering information is given on any current masthead page.