β-Lactams. 1. Highly Diastereoselective Alkylation of 4-Acetoxyazetidin-2-one Useful for 1β-Methylcarbapenem Synthesis

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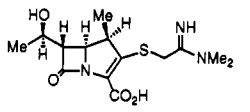
On the basis of the principle of hard and soft acids and bases, a highly diastereoselective "asymmetric soft acid–soft base imine alkylation" was developed. 4-Acetoxyazetidin-2-one (**5**) was alkylated with the tin(II) enolates of 3-acyl-(4*S*)-ethyl(and isopropyl)-1,3-thiazolidine-2-thiones **7a,b** and **21a,b**. The resultant alkylation products (**9a,b** and **24a,b**) could be converted to **17**, the key intermediate for the syntheses of both thienamycin (**2**) and imipenem (**3**), and to **35**, the key intermediate for the synthesis of 1β-methylcarbapenem.

Introduction

Since the discovery of 1β-methylcarbapenem (**1**), which possesses fairly strong stability against renal dehydropeptidase-I (DHP-I) and chemical stability,[2] numerous stereoselective carbon–carbon bond formation methods have been developed for construction of the chiral C-1 in the 1β-substituted carbapenems.[2a,3,4] In a preliminary paper in 1986, we reported a highly diastereoselective method for alkylation of 4-acetoxyazetidin-2-ones employing tin(II) enolates of *C*-4-chiral 3-acyl-1,3-thiazolidine-2-thiones.[3a] We now describe the details of the alkylation of 4-acetoxyazetidin-2-one (**5**) with tin(II) enolates of 3-acyl-1,3-thiazolidine-2-thiones **7a,b** and **21a,b** and the use of the chiral alkylation products for syntheses of optically active **17**, the key intermediate for the syntheses of both thienamycin (**2**)[5] and imipenem (**3**), and **35**, the key intermediate for 1β-methylcarbapenem (**1**) synthesis.

Imipenem (**3**), developed by a Merck Sharp & Dohme research group, has recently appeared on the drug market as the first carbapenem-type antibiotic.[6] However, **3** must be used with the DHP-I inhibitor sodium cilastain (**4**).[6] 1β-Methylcarbapenems seem to have more potential as candidates for new-generation antibiotics because all of them can directly resist metabolism by renal DHP-I without an enzyme inhibitor **4**.[2] Although an attractive 1β-methylcarbapenem (**1**) was disclosed by the Merck Sharp & Dohme research group in 1984,[2] no one reported a highly stereoselective method for the introduction of a methyl group at the 1β-position of the carbapenem until our work was published in 1986.[3a] Extensive research in our group led to the development of a highly diastereoselective synthesis of 4-alkylated azetidin-2-ones.



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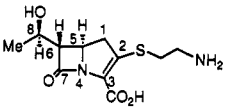

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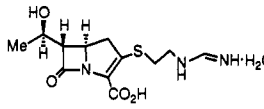

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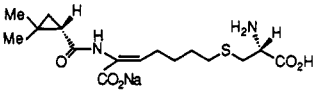

4

In carbapenem synthesis, carbon–carbon bond formation at C-4 of azetidin-2-ones is remarkably intriguing, and various reactions have been developed to date.[4b,7] However, there has been no report of a facile and efficient method for asymmetric alkylation of achiral azetidin-2-ones such as **5**. Carbon alkylation of simple imines with metal enolates is generally not easy. However, there are some examples of alkylations with lithium[8a–c] and boryl[8d] enolates, silyl enolates in the presence of Lewis acid,[8e] and some tin(II) enolates.[8f] However, cyclic *N*-acylimine **6**, readily obtained from **5** by removal of acetic acid, reacts with soft anions such as silyl enolates in the presence of zinc halides,[4b] CN^-,[7a] aluminum enolates,[7b,c] and tetraallyl tin.[7d] The reactivity of **6** with these soft bases can be rationalized in terms of the soft acidity of C-4 when the imine is in conjugation with a carbonyl group. We adopted

(1) (a) The University of Tokushima. (b) Lederle (Japan) Ltd. (c) Rigaku Corporation.

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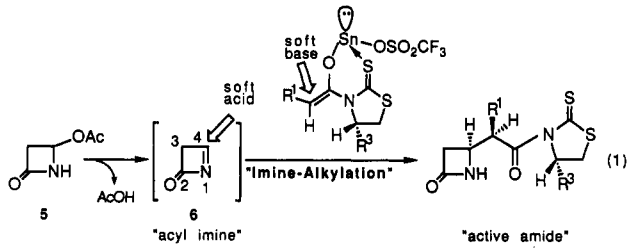
the tin(II) enolates of *C*-4-chiral 3-acyl-1,3-thiazolidine-2-thiones as our soft base and designed an "asymmetric soft acid–soft base imine alkylation" as represented by eq 1. This alkylation method can be used for the asymmetric



synthesis of not only 1β-methylcarbapenems but also various other 1β-substituted carbapenems by changing the R^1 group of the 3-acylthiazolidines.[9]

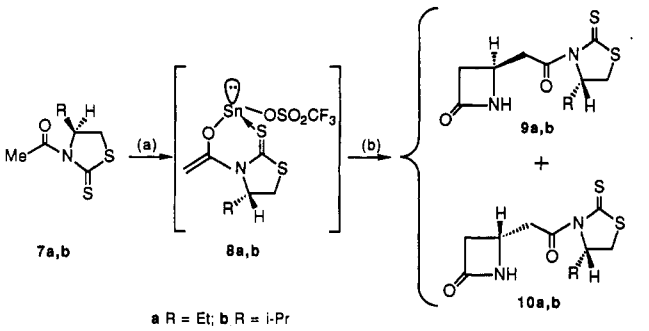
Results and Discussion

Asymmetric alkylations of 4-acetoxyazetidin-2-one (**5**)[10] with 3-acyl derivatives of (4*S*)-ethyl-1,3-thiazolidine-2-thione [(4*S*)-ETT][11] and (4*S*)-isopropyl-1,3-thiazolidine-2-thione [(4*S*)-IPTT][11] were carried out as follows (Scheme I). To a THF solution of tin(II) trifluoromethanesulfonate[12] at −40 °C were added *N*-ethylpiperidine[12] and a THF[13] solution of the 3-acetyl derivative of (4*S*)-ETT (**7a**), and then the mixture was stirred at −40 °C for 3–4 h to form the tin(II) enolate **8a**. After addition of **5** in THF, the mixture was kept at 0 °C for 1 h with stirring to afford C-4-alkylated azetidin-2-ones **9a** and **10a** in a 95:5 ratio by HPLC analysis.[14] Pure **9a** was isolated in 82% yield from the mixture of **9a** and **10a** by chromatographic separation on a silica gel column. Asymmetric alkylation of **5** with the 3-acetyl derivative of (4*S*)-IPTT (**7b**) was performed similarly to give **9b** in a highly diastereoselective manner (96% diastereomeric excess[14]) and in 85% isolated yield.

The absolute configuration of **9a** was established by its chemical conversion to known compound **11**,[15] which was obtained from L-aspartic acid (Scheme II). The stereochemistry of **9b** was determined by its chemical conversion to carboxylic acid **14**, which was derived from **9a**. Both **9a** and **9b** were converted to **14** by the procedure shown in Scheme II. Treatment of **9a** or **b** with TBDMS chloride–Et_3N in DMF gave the TBDMS derivative **12a** or **12b** in 98% and 91% yield, respectively. Since simple alkaline hydrolysis of **12a** with 10% NaOH resulted in its decomposition, **12a** was subjected to alcoholysis with the sodium salt of benzyl alcohol to furnish benzyl ester **13** in 44% yield. Hydrogenolysis of the benzyl group of **13** gave carboxylic acid **14** in 87% yield. A more attractive procedure for the transformation of **12a** to carboxylic acid **14** was a mild aminolysis[16] of the active amide functionality of **12a**. Compound **12a** was treated with a small excess of imidazole in THF at room temperature. Subsequent acidification of the resultant imidazolide (**15**) with 10% citric acid gave **14** in 76% overall yield from **12a**. Compound **12b** was also subjected to the aminolysis–hydrolysis procedure to give **14** in 67% overall yield (Scheme II).

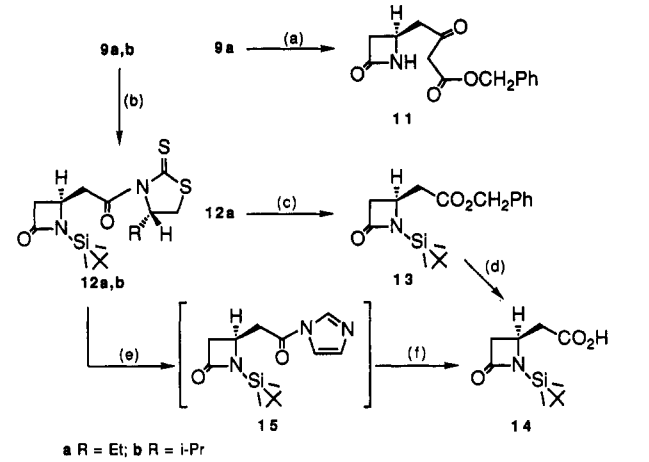
Subsequently, **14** was successfully converted to (hydroxyethyl)azetidin-2-one derivative **17**, which should be useful for the syntheses of both thienamycin (**2**) and imipenem (**3**) (Scheme III). The first attempt at acetylation

Scheme I[a]



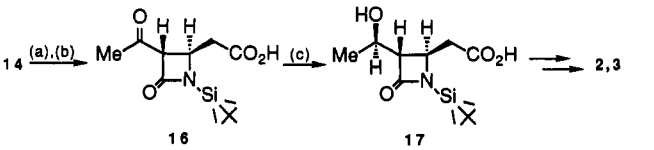
[a] Key: (a) $Sn(OSO_2CF_3)_2$, *N*-ethylpiperidine, THF, −40 → 0 °C; (b) compound **5**, THF, 0 °C (**5** → **9a**: 82%) (**5** → **9b**: 85%).

Scheme II[a]



[a] Key: (a) benzyl acetate, LDA, THF, −78 °C (26%); (b) TBDMSCl, Et_3N, DMF, 0 °C (**9a** → **12a**: 98%) (**9b** → **12b**: 91%); (c) $PhCH_2ONa$, toluene, 0 °C → rt (44%); (d) H_2, 5%-Pd–C, MeOH, rt (87%); (e) imidazole, THF, rt; (f) 10% citric acid, rt (**12a** → **15** → **14**: 76%) (**12b** → **15** → **14**: 67%).

Scheme III[a]



[a] Key: (a) LDA, MeCHO, THF, −30 → 0 °C; (b) $K_2Cr_2O_7$, aqueous H_2SO_4, Et_2O–petroleum ether (2:1), −20 °C (36%); (c) $(i\text{-}Pr)_2NH{\cdot}BH_3$, $Mg(CF_3CO_2)_2$, Et_2O, −78 °C (60%).

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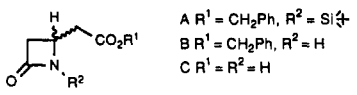
(13) Although the diastereoselectivity was the same as that of the reaction in THF, the same reaction in CH_2Cl_2 gave low chemical yields of major products **9a,b**.

(14) To determine the HPLC retention time of the diastereoisomers, an authentic mixture of the diastereomeric alkylation products was prepared as follows. Racemic carboxylic acid **14**, obtained by alkylation of **5** with the tin(II) enolate of 3-acetylthiazolidine-2-thione and subsequent *N*-silylation with TBDMSCl and imidazole, was treated with benzyl alcohol in the presence of $EtN{=}C{=}N(CH_2)_3N(Me)_2{\cdot}HCl$ and DMAP in CH_2Cl_2 to give compound **A**. Desilylation (46% HF in MeCN) of **A** and subsequent debenzylation (H_2, Pd–C in MeOH) of the resultant **B** gave compound **C**. Dehydrative condensation of **C** with (4*S*)-ETT or (4*S*)-IPTT afforded the corresponding mixture of **9a** and **10a** or **9b** and **10b**.



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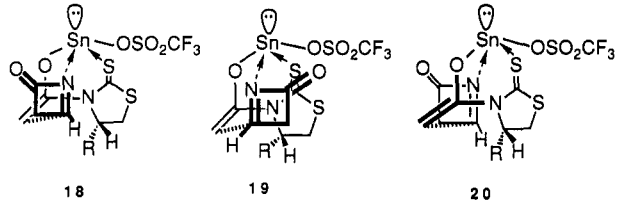
(16) Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; and Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 841.

of the dianionic lithium enolate of **14** with acetylimidazole resulted in decomposition of **14**. Therefore, the dianionic lithium enolate was treated with excess acetaldehyde, and subsequent Beckmann oxidation[17] of the diastereomeric mixture of the aldol products gave the desired acetyl derivative **16** in 36% overall yield. Reduction of **16** with diisopropylamine–borane complex in the presence of magnesium trifluoroacetate[18] gave (*R*)-(hydroxyethyl)azetidin-2-onecarboxylic acid **17** in 60% yield (Scheme III).

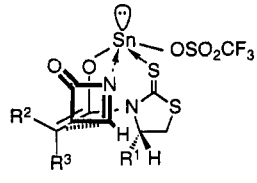
The high *re*-face selectivity of the reaction between presumed acylimine **6** and tin(II) enolates **8a,b** can be rationalized in terms of six-membered transition state **18** involving tin(II) chelation.[11] Because of the severe 1,3-diaxial steric repulsion between the C-3 methylene protons of the acylimine and the thiazolidine moiety in structure **19**, compound **6** must approach tin(II) enolates **8a,b** from the less hindered β-side away from the α-R (Et, *i*-Pr) group of the thiazolidine moiety to form **18** predominantly. The contribution of transition state **20**, corresponding to *si*-face selectivity, should be very minor because of the large steric repulsion between the R (Et, *i*-Pr) group of the thiazolidine and the acylimine. These mechanistic speculations are consistent with experimental outcomes.



18 19 20

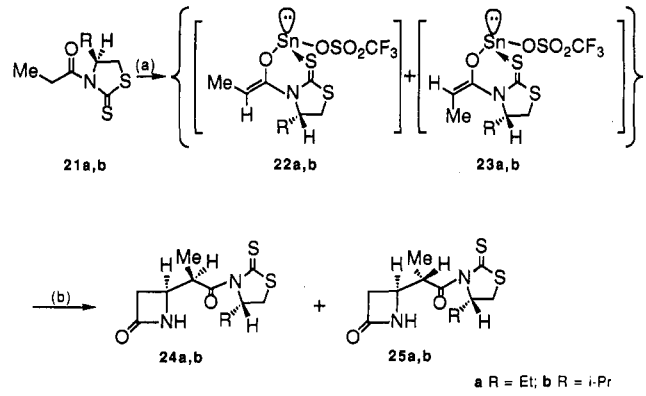
Formulae 18 - 20

Based on the excellent results of the reactions between **8a,b** and **5**, similar alkylations of **5** with the 3-propionyl derivatives of (4*S*)-ETT (**21a**) and (4*S*)-IPTT (**21b**) were investigated (Scheme IV). Treatment of tin(II) enolates **22a,b** and **23a,b** with **5** afforded the corresponding alkylation products (**24a,b**) and (**25a,b**) with high diastereoselectivity (**24a**:**25a** = 90:10; **24b**:**25b** = 95:5 by HPLC analysis).[19] The major products (**24a,b**) were purified by chromatography in good yields (82% for **24a** and 85% for **24b**). The stereochemistry of **24a,b** was confirmed to be the desired (4*S*,5*R*) configuration by X-ray crystallographic analysis[3a] of carboxylic acid **28**, which was derived from **24a,b** as shown in Scheme V. To determine their absolute configuration, the minor products (**25a,b**) were purified by repeated chromatography and recrystallization. Crystalline compound **25b** was subjected to X-ray crystallographic analysis[20] to prove its stereochemistry to be a (4*S*,5*S*) configuration. The stereochemical outcome of this highly diastereoselective alkylation can be rationalized as follows. The major products **24a,b** could be obtained via tin(II)-chelated, six-membered transition state **30**, generated by the highly stereoselective approach of **6** to *Z*-enolates **22a,b** in a manner similar to that for the case of **6** and **8a,b**. The minor products **25a,b** might be formed via a similar six-membered transition state **31**, presumably formed by the stereocontrolled approach of **6** to *E*-enolates **23a,b**.[19]



30 R^1 = Et,*i*-Pr; R^2 = Me; R^3 = H
31 R^1 = Et,*i*-Pr; R^2 = H; R^3 = Me

Scheme IV[a]

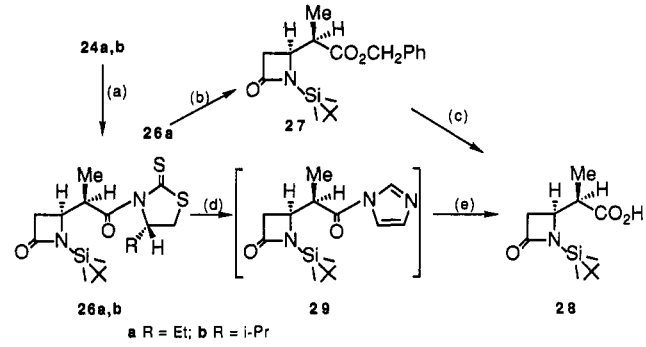


21a,b **22a,b** **23a,b** **24a,b** **25a,b**

a R = Et; b R = *i*-Pr

[a] Key: (a) $Sn(OSO_2CF_3)_2$, *N*-ethylpiperidine, THF, −50 °C; (b) compound **5**, THF, −50–0 °C (**5** → **24a**: 82%) (**5** → **24b**: 85%).

Scheme V[a]

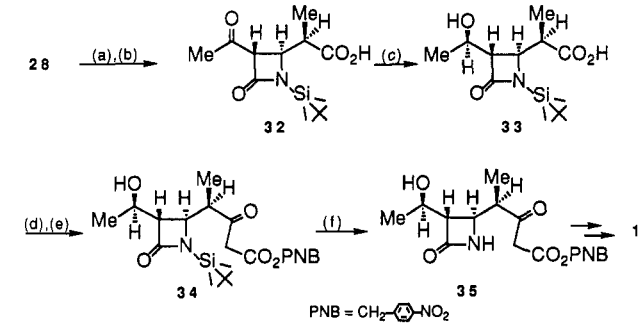


24a,b **26a** **27** **26a,b** **29** **28**

a R = Et; b R = *i*-Pr

[a] Key: (a) TBDMSCl, Et_3N, DMF, 0 °C (**24a** → **26a**: 99%) (**24b** → **26b**: 91%); (b) $PhCH_2ONa$, toluene, 0 °C → rt (40%); (c) H_2, 5%Pd–C, MeOH, rt (99%); (d) imidazole, THF, rt; (e) 10% citric acid, rt (**26a** → **29** → **28**: 76%), (**26b** → **29** → **28**: 70%).

Scheme VI[a]



28 **32** **33** **34** **35**

PNB = CH_2–C$_6$H$_4$–NO_2

[a] Key: (a) LDA, THF, −40 °C; (b) acetylimidazole, THF, −78 °C → rt (83%); (c) $(i\text{-Pr})_2NH{\cdot}BH_3$, $Mg(CF_3CO_2)_2$, Et_2O, −78 °C (71%); (d) 1,1′-carbonyldiimidazole, MeCN, rt; (e) $Mg(O_2CCH_2CO_2PNB)_2$, 50 °C (39%); (f) 6 *N* HCl, MeOH, rt (81%).

Compound **28** was readily converted to **35**, a key intermediate in Shih's synthesis of (−)-1β-methylcarbapenem (**1**) (Scheme VI).[2] Compound **28** was treated with LDA in THF and then with acetylimidazole to give the 3α-acetylazetidin-2-one derivative **32**. Stereoselective re-

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(19) The other two possible diastereomers were not detected under our HPLC conditions.

(20) Supplementary material is available.

duction of the acetyl group of **32** was done with diisopropylamine–borane complex in the presence of magnesium trifluoroacetate[18] to afford (hydroxyethyl)azetidin-2-onecarboxylic acid **33** in 59% overall yield from **28**. Compound **33** was subjected to the Masamune method[21] for preparation of β-keto esters to give compound **34** in 39% yield. Deprotection of the TBDMS group of **34** with 6 N HCl in MeOH gave the desired compound **35** in 82% yield. Compound **35** should be useful for asymmetric syntheses of various 1β-methylcarbapenems. Thus, we have demonstrated that tin(II) enolates of various 3-acyl derivatives of (4*S*)-IPTT and (4*S*)-ETT can be useful for efficient synthesis of chiral 4-alkylated azetidin-2-ones.

Experimental Section

Melting points were determined on a micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded in $CDCl_3$ at 90 MHz unless otherwise noted; signals are given in ppm with $SiMe_4$ as internal standard. Low-resolution mass spectra and high-resolution mass spectra are abbreviated to MS and HRMS, respectively. All reactions were monitored by thin-layer chromatography with 0.25-mm silica gel plates. Preparative thin-layer chromatography was performed on 0.5-mm × 20-cm × 20-cm silica gel plates. Column chromatographic separations were carried out on Wako gel C-200 (particle size 74–149 μm, Wako Pure Chem. Ind.). Organic extracts were generally dried over $MgSO_4$ or Na_2SO_4. 4-Acetoxyazetidin-2-one (**5**) was synthesized by the known method.[10] (4*S*)-Isopropyl-1,3-thiazolidine-2-thione [(4*S*)-IPTT] and (4*S*)-ethyl-1,3-thiazolidine-2-thione [(4*S*)-ETT] were prepared according to the method reported by us.[11] Tin(II) trifluoromethane sulfonate was prepared according to the literature procedures.[12,22]

Reaction of 4-Acetoxyazetidin-2-one (5) with 3-Acetyl-(4*S*)-ethyl(or isopropyl)-1,3-thiazolidine-2-thione (7a or 7b). Tin(II) trifluoromethanesulfonate (5.06 g, 12.1 mmol) was dissolved in anhydrous THF (20 mL) at rt under N_2. To the solution cooled at −40 °C were successively added *N*-ethylpiperidine (1.75 mL, 12.7 mmol) and **7a** (1.778 g, 9.4 mmol) in anhydrous THF (10 mL), and the mixture was then stirred for 3–4 h at 0 °C to form the tin(II) enolate **8a**. To the tin(II) enolate **8a** at 0 °C was added a solution of **5** (0.87 g, 6.7 mmol) in anhydrous THF (10 mL), and then the mixture was stirred at 0 °C for 1 h. A 0.1 M phosphate buffer solution (pH 7.0, 20 mL) and Et_2O (200 mL) were added to the reaction mixture with vigorous stirring. The precipitate was filtered off through Celite, and the filtrate was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried, and evaporated in vacuo to give a yellow, viscous oil. HPLC analysis (column, Partisil-10 ODS 4.6-mm i.d. × 25 cm; eluent, 35:65 MeOH–H_2O; flow rate, 1.5 mL/min; detection, UV 305 nm) of the oil showed the presence of **9a** and **10a** in a 95:5 ratio. Silica gel column chromatography of the residue (elution with 3:1 $CHCl_3$–AcOEt) afforded pure **9a** (1.42 g, 82%). A small quantity of **10a** was obtained by column chromatography of the combined **10a**-rich fractions collected from the repeated reactions. The reaction of **5** (0.297 g, 2.3 mmol) with the tin(II) enolate **8b**, obtained from 3-acetyl-(4*S*)-isopropyl-1,3-thiazolidine-2-thione (**7b**) (0.653 g, 3.2 mmol) as discussed above, afforded a mixture of **9b** and **10b** in a 98:2 ratio (HPLC analysis). Purification of the mixture of **9b** and **10b** by silica gel column chromatography gave pure **9b** (0.532 g, 85%).

(4*S*)-4-[[((4*S*)-4-Ethyl-2-thioxo-1,3-thiazolidin-3-yl)-carbonyl]methyl]azetidin-2-one (9a): yellow oil; $[\alpha]^{20}_D$ +261.9° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1740, 1680 cm^{-1}; ^{1}H NMR δ 1.03 (t, 3 H, *J* = 8.0 Hz), 1.73–2.07 (m, 2 H), 2.70 (dd, 1 H, *J* = 2.0, 15.0 Hz), 2.90–3.45 (m, 3 H), 3.60 (dd, 1 H, *J* = 7.0, 12.0 Hz) 3.88–4.14 (m, 2 H), 5.05–5.28 (m, 1 H), 6.10 (br s, 1 H); HRMS calcd for $C_{10}H_{14}N_2O_2S_2$ MW 258.0497, found *m*/*z* 258.0483 (M$^+$).

(4*R*)-4-[[((4*S*)-4-Ethyl-2-thioxo-1,3-thiazolidin-3-yl)-carbonyl]methyl]azetidin-2-one (10a): yellow oil; IR ($CHCl_3$) 1750, 1690 cm^{-1}; ^{1}H NMR δ 1.00 (t, 3 H, *J* = 7.5 Hz), 1.07–2.15 (m, 2 H), 2.00–3.27 (m, 4 H), 3.60 (dd, 1 H, *J* = 7.5, 12.0 Hz), 3.85–4.05 (m, 1 H), 4.30–4.50 (m, 1 H), 5.10–5.32 (m, 1 H), 6.20 (br s, 1 H); HRMS calcd for $C_{10}H_{14}N_2O_2S_2$ MW 258.0497, found *m*/*z* 258.0476 (M$^+$).

(4*S*)-4-[[((4*S*)-4-Isopropyl-2-thioxo-1,3-thiazolidin-3-yl)-carbonyl]methyl]azetidin-2-one (9b): yellow needles; mp 82–84 °C (from AcOEt–hexane); $[\alpha]^{25}_D$ +346.6° (*c* 1.3, $CHCl_3$); IR (KBr) 1750, 1700 cm^{-1}; ^{1}H NMR δ 0.97 (d, 3 H, *J* = 7.0 Hz), 1.06 (d, 3 H, *J* = 7.0 Hz), 2.15–2.45 (m, 1 H), 2.56–2.68 (m, 1 H), 3.02 (dd, 1 H, *J* = 2.0, 12.0 Hz), 3.05–3.40 (m, 2 H), 3.53 (dd, 1 H, *J* = 7.5, 12.0 Hz), 3.80–4.15 (m, 2 H), 5.07–5.24 (m, 1 H), 6.15 (br s, 1 H); HRMS calcd for $C_{11}H_{16}N_2O_2S_2$ MW 272.0654, found *m*/*z* 272.0660 (M$^+$). Anal. Calcd for $C_{11}H_{16}N_2O_2S_2$: C, 48.50; H, 5.92; N, 10.28. Found: C, 48.33; H, 5.65; N, 10.36.

(4*R*)-4-[3-(Benzyloxycarbonyl)-2-oxopropyl]azetidin-2-one (11). To a solution of diisopropylamine (0.1 mL, 0.71 mmol) in anhydrous THF (1.4 mL) at −78 °C was added an 1.5 M solution of *n*-butyllithium in hexane (0.47 mL, 0.71 mmol) with stirring under argon atmosphere. The mixture was stirred at 0 °C for 0.5 h and then cooled to −78 °C. A solution of benzyl acetate (106.8 mg, 0.71 mmol) in anhydrous THF (0.5 mL) was added dropwise. After the reaction mixture was kept at −78 °C for 1 h, a solution of **9a** (175 mg, 0.68 mmol) in anhydrous THF (0.5 mL) was added dropwise. The mixture was stirred at −78 °C for 5 min, treated with saturated aqueous NH_4Cl, and extracted with AcOEt. The extract was washed with brine, dried, and evaporated in vacuo. The residue was purified on a silica gel column impregnated with 5% $AgNO_3$ (elution with 3:1 $CHCl_3$–acetone) to give known compound **11** (45.2 mg, 26%) as a pale yellow oil: $[\alpha]^{20}_D$ +41.4° (*c* 0.86, benzene) (lit.[15] $[\alpha]^{20}_D$ +43.2° (*c* 0.37, benzene)).

(4*R*)-1-(*tert*-Butyldimethylsilyl)-4-[[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]methyl]azetidin-2-one (12a). To a solution of **9a** (461.4 mg, 1.79 mmol) in anhydrous DMF (10 mL) at 0 °C were added TBDMSCl (539.1 mg, 3.58 mmol) and Et_3N (0.995 mL, 7.14 mmol). The mixture was stirred at 0 °C for 0.5 h. After benzene (75 mL) and hexane (75 mL) were added, the organic layer was washed with water, dried, and evaporated under reduced pressure to give an oily residue. The residue was purified by silica gel column chromatography (elution with 9:1 $CHCl_3$–AcOEt) to afford **12a** (650 mg, 98%) as yellow needles: mp 67–69 °C (from $CHCl_3$–AcOEt); IR (KBr) 1730, 1690 cm^{-1}; ^{1}H NMR δ 0.24 (s, 6 H), 0.96 (s, 9 H), 1.03 (t, 3 H, *J* = 8.0 Hz), 1.68–2.03 (m, 2 H), 2.73 (dd, 1 H, *J* = 2.0, 16.0 Hz), 2.90–4.00 (m, 5 H), 5.03–5.26 (m, 1 H). Anal. Calcd for $C_{16}H_{28}N_2O_2S_2Si$: C, 51.57; H, 7.57; N, 7.52. Found: C, 51.35; H, 7.55; N, 7.57.

(4*R*)-1-(*tert*-Butyldimethylsilyl)-4-[[((4*S*)-4-isopropyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]methyl]azetidin-2-one (12b). Reaction of **9b** (27.2 mg, 0.10 mmol) with TBDMSCl (30 mg, 0.20 mmol) by the procedure described above gave **12b** (35.1 mg, 91%) as a yellow oil: IR ($CHCl_3$) 1730, 1685 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.24 (s, 6 H), 0.95–0.98 (s, 12 H), 1.07 (d, 3 H, *J* = 7.0 Hz), 2.04–2.37 (m, 2 H), 2.72 (dd, 1 H, *J* = 2.5, 15.5 Hz), 3.04 (dd, 1 H, *J* = 2.0, 12.0 Hz), 3.34–3.56 (m, 3 H), 3.83–4.14 (m, 2 H), 5.15–5.21 (m, 1 H); HRMS calcd for $C_{17}H_{30}N_2O_2S_2Si$ MW 386.1518, found *m*/*z* 386.1509 (M$^+$).

(4*S*)-4-[(Benzyloxycarbonyl)methyl]-1-(*tert*-butyldimethylsilyl)azetidin-2-one (13). To a solution of **12a** (1.364 g, 3.66 mmol) in toluene (10 mL) at 0 °C was added sodium benzyl oxide (476 mg, 3.66 mmol). The mixture was stirred at 0 °C for 1 h and at rt for 0.5 h. The reaction was quenched with 10% citric acid, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and brine and dried. After evaporation of the solvent, the residue was purified by silica gel column chromatography (elution with 4:1 hexane–AcOEt) to give **13** (531 mg, 44%) as a pale yellow oil: $[\alpha]^{20}_D$ −61.6° (*c* 1.06, $CHCl_3$); IR (film) 1750 cm^{-1}; ^{1}H NMR δ 0.20 (s, 3 H), 0.23 (s, 3 H), 0.95 (s, 9 H), 2.29 (dd, 1 H, *J* = 10.5, 15.0 Hz), 2.73 (dd, 1 H, *J* = 3.0, 15.0 Hz), 2.70 (dd, 1 H, *J* = 4.5, 15.0 Hz), 3.05 (dd, 1 H, *J* = 6.0, 15.0 Hz), 3.76–4.15 (m, 1 H), 5.12 (s, 2 H), 7.34 (s, 5 H).

(4*S*)-1-(*tert*-Butyldimethylsilyl)-4-(carboxymethyl)azetidin-2-one (14). (1) Conversion of 13 to 14. A mixture of **13** (296.7 mg, 0.89 mmol) and 5% Pd–C (60 mg) in MeOH (5 mL)

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was stirred for 18 h under H_2. After removal of the catalyst, the solvent was evaporated under reduced pressure to give **14** (187.4 mg, 87%) as a colorless solid: mp 88–91 °C (from CH_2Cl_2–acetone); $[\alpha]^{25}_D$ –72.9° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$) 1725, 1680 cm^{-1}; ^1H NMR δ 0.23 (s, 3 H), 0.26 (s, 3 H), 0.96 (s, 9 H), 2.47 (dd, 1 H, *J* = 12.0, 15.0 Hz), 2.78 (dd, 1 H, *J* = 3.0, 15.0 Hz), 2.90 (dd, 1 H, *J* = 4.5, 15.0 Hz), 3.33 (dd, 1 H, *J* = 6.0, 15.0 Hz), 3.90 (m, 1 H), 8.20 (br s, 1 H); HRMS calcd for $C_{11}H_{21}NO_3Si$ MW 243.1291, found *m/z* 243.1300 (M^+).

(2) Conversion of 12a to 14. To a solution of **12a** (15.32 g, 41.2 mmol) in anhydrous THF (240 mL) was added imidazole (16.3 g, 239.4 mmol). The mixture was stirred at rt for 5 h, and then 10% citric acid (410 mL) was added. After being stirred vigorously for 2 h, the reaction mixture was extracted with AcOEt. The extract was washed with brine, dried, and evaporated in vacuo. The residue was purified by silica gel column chromatography (elution with 4:1 CH_2Cl_2–AcOEt) to give **14** (7.6 g, 76%) as a colorless solid: mp 88–91 °C (from CH_2Cl_2–acetone). This compound was identical to the product obtained from hydrogenolysis of **13**.

(3) Conversion of 12b to 14. Reaction of **12b** and imidazole on a 0.84 mmol scale according to procedure 2 gave compound **14** (67%).

(3*S*,4*R*)-3-Acetyl-1-(*tert*-butyldimethylsilyl)-4-(carboxymethyl)azetidin-2-one (16). To a solution of diisopropylamine (202 mg, 2 mmol) in anhydrous THF (5 mL) at –30 to –40 °C was added an 1.6 M solution of *n*-butyllithium in hexane (1.28 mL, 2.1 mmol). After the solution was stirred for 0.5 h at –30 °C, a solution of **14** (243 mg, 1.0 mmol) in anhydrous THF (5 mL) was added. The mixture was stirred at –30 °C for 0.5 h and then treated with CH_3CHO (1 mL). After being stirred for 0.5 h at 0 °C, the reaction was quenched by the addition of 10% citric acid (20 mL). The aqueous solution was extracted with Et_2O, and the extract was washed with water and brine and dried. After evaporation of the solvent, the residue was purified by silica gel column chromatography (elution with 9:1 $CHCl_3$–acetone) to give the 3-hydroxyethyl compound. To a solution of the 3-hydroxyethyl compound (206 mg, 0.72 mmol) in 2:1 Et_2O–petroleum ether (15 mL) at –20 °C was added $K_2Cr_2O_7$–H_2SO_4 solution (2.5 mL) [$K_2Cr_2O_7$ (5 g) was dissolved in concd H_2SO_4 (6.6 g), and water was added dropwise to bring the volume to 25 mL].[17] The mixture was stirred at –20 °C for 1.5 h, and then chilled water (10 mL) was added. The aqueous solution was extracted with Et_2O, and the extract was washed with brine, dried, and evaporated in vacuo. The residue was purified by silica gel column chromatography (elution with 9:1 $CHCl_3$–acetone) to give **16** (102 mg, 36%) as a yellow oil: $[\alpha]^{25}_D$ –22.2° (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 1740, 1710 cm^{-1}; ^1H NMR δ 0.23 (s, 3 H), 0.27 (s, 3 H), 0.96 (s, 9 H), 2.55 (dd, 1 H, *J* = 9.0, 15.0 Hz), 2.89 (dd, 1 H, *J* = 4.5, 15.0 Hz), 4.10–4.40 (m, 2 H), 7.50 (br s, 1 H); MS *m/z* 285 (M^+).

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(1*R*)-1-hydroxyethyl]-4-(carboxymethyl)azetidin-2-one (17). To a solution of **16** (75.4 mg, 0.26 mmol) in anhydrous Et_2O (5 mL) at –78 °C was added a 1 M solution of $Mg(CF_3CO_2)_2$ in Et_2O (1.3 mL, 1.30 mmol) with stirring. After the solution was stirred at –78 °C for 5 min, $(i\text{-}Pr)_2NH{\cdot}BH_3$ (0.079 mL, 0.53 mmol) in anhydrous Et_2O (1 mL) was added. The mixture was stirred at –78 °C for 1.5 h and then 10% citric acid was added. After separation of the organic layer, the aqueous layer was extracted with Et_2O, and then the combined organic layer was washed with brine, dried, and evaporated in vacuo. Purification of the residue by silica gel column chromatography (elution with 4:1 $CHCl_3$–acetone) gave compound **17** (45.6 mg, 60%) as colorless needles: mp 75–77 °C (from $CHCl_3$–acetone); $[\alpha]^{25}_D$ –65° (*c* 0.4, $CHCl_3$); IR (KBr) 1730, 1690 cm^{-1}; ^1H NMR δ 0.23 (s, 3 H), 0.27 (s, 3 H), 0.96 (s, 9 H), 1.33 (d, 3 H, *J* = 6.0 Hz), 2.52 (dd, 1 H, *J* = 10.5, 16.5 Hz), 2.96 (dd, 1 H, *J* = 2.5, 7.5 Hz), 3.40 (dd, 1 H, *J* = 4.5, 16.5 Hz), 3.60–3.90 (m, 1 H), 3.95–4.25 (m, 1 H), 5.05 (br s, 1 H); HRMS calcd for $C_{13}H_{25}NO_4Si$ MW 287.1552, found *m/z* 287.1537 (M^+). Anal. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.55; H, 8.50; N, 4.93.

Reaction of 4-Acetoxyazetidin-2-one (5) with 3-Propionyl-(4*S*)-ethyl(or isopropyl)-1,3-thiazolidine-2-thione (21a or 21b). Tin(II) trifluoromethanesulfonate (7.50 g, 18.0 mmol) was dissolved in anhydrous THF (30 mL) under N_2 at rt. To the solution cooled at –50 °C were successively added *N*-ethylpiperidine (2.6 mL, 19.0 mmol) and **21a** (2.85 g, 14.0 mmol) in anhydrous THF (15 mL), and the mixture was then stirred for 4 h at –50 °C to form the tin(II) enolate **22a**. After addition of **5** (1.29 g, 10.0 mmol) in anhydrous THF (15 mL) at –50 °C, the mixture was stirred at 0 °C for 1 h. Workup of the reaction mixture gave a yellow, viscous oil. HPLC analysis of the oily residue under conditions similar to those used for **7a** showed **24a** and **25a** in a 90:10 ratio. Silica gel column chromatography of the residue (elution with 9:1 $CHCl_3$–acetone) afforded pure **24a** (2.24 g, 82%). A minor product, **25a**, was also isolated in a manner similar to that used for **10a**. The reaction between **5** (0.434 g, 3.36 mmol) and **21b** (1.023 g, 4.71 mmol) was performed as discussed above to afford compounds **24b** and **25b** in a 95:5 ratio (HPLC analysis). Silica gel column chromatography of the mixture of **24b** and **25b** gave pure **24b** (0.816 g, 85%).

(4*S*)-4-[(1*R*)-1-[((4*S*)-4-Ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (24a): yellow needles; mp 121–122 °C (from $CHCl_3$–hexane); $[\alpha]^{25}_D$ +266.7° (*c* 0.2, $CHCl_3$); IR (KBr) 1760 cm^{-1}; ^1H NMR δ 1.01 (t, 3 H, *J* = 7.4 Hz), 1.24 (d, 3 H, *J* = 6.8 Hz), 1.66–2.10 (m, 2 H), 2.73–3.20 (m, 3 H), 3.52 (dd, 1 H, *J* = 7.5, 12.0 Hz), 3.90–4.05 (m, 1 H), 4.85–5.30 (m, 2 H), 6.20 (br s, 1 H); HRMS calcd for $C_{11}H_{16}N_2O_2S_2$ MW 272.0653, found *m/z* 272.0614 (M^+). Anal. Calcd for $C_{11}H_{16}N_2O_2S_2$: C, 48.50; H, 5.92; N, 10.28. Found: C, 48.80; H, 5.94; N, 10.27.

(4*S*)-4-[(1*S*)-1-[((4*S*)-4-Ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (25a): pale yellow oil; IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR δ 1.01 (t, 3 H, *J* = 7.6 Hz), 1.28 (d, 3 H, *J* = 6.9 Hz) 1.70–2.10 (m, 2 H), 2.67 (dd, 1 H, *J* = 2.3, 15.1 Hz), 2.93 (d, 1 H, *J* = 11.3 Hz), 3.05–3.23 (m, 1 H), 3.63 (dd, 1 H, *J* = 7.6, 11.3 Hz), 3.73–4.03 (m, 1 H), 4.23–4.55 (m, 1 H), 5.00–5.27 (m, 1 H), 6.45 (br s, 1 H); HRMS calcd for $C_{11}H_{16}N_2O_2S_2$ MW 272.0653, found *m/z* 272.0665 (M^+).

(4*S*)-4-[(1*R*)-1-[((4*S*)-4-Isopropyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (24b): yellow needles; mp 150.5–151.5 °C (from $CHCl_3$–hexane); $[\alpha]^{25}_D$ +414.4° (*c* 0.5, $CHCl_3$); IR (KBr) 1740 cm^{-1}; ^1H NMR δ 0.97 (d, 3 H, *J* = 6.9 Hz), 1.06 (d, 3 H, *J* = 6.9 Hz), 1.19 (d, 3 H, *J* = 6.9 Hz), 2.14–2.52 (m, 1 H), 2.73–3.17 (m, 3 H), 3.50 (dd, 1 H, *J* = 7.8, 11.6 Hz), 3.89–4.04 (m, 1 H), 4.87–5.21 (m, 2 H), 6.24 (br s, 1 H); HRMS calcd for $C_{12}H_{18}N_2O_2S_2$ MW 286.0810, found *m/z* 286.0819 (M^+). Anal. Calcd for $C_{12}H_{18}N_2O_2S_2$: C, 50.32; H, 6.33; N, 9.78. Found: C, 50.34; H, 6.31; N, 9.70.

(4*S*)-1-(*tert*-Butyldimethylsilyl)-4-[(1*R*)-1-[((4*S*)-4-ethyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (26a). To a solution of **24a** (4.05 g, 14.8 mmol) in anhydrous DMF (14.9 mL) at 0 °C were added TBDMSCl (4.47 g, 29.7 mmol) and Et_3N (8.29 mL, 59.5 mmol) under N_2. After the mixture was stirred at 0 °C for 0.5 h, AcOEt was added. The usual workup afforded **26a** (5.71 g, 99%) as yellow crystals: mp 94–95 °C (from hexane); $[\alpha]^{25}_D$ +71.9° (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 1735, 1705 cm^{-1}; ^1H NMR δ 0.20 (s, 3 H), 0.26 (s, 3 H), 0.95 (s, 9 H), 1.02 (t, 3 H, *J* = 7.5 Hz), 1.25 (d, 3 H, *J* = 7.0 Hz), 1.72–2.03 (m, 2 H), 2.95 (dd, 1 H, *J* = 10.0, 15.0 Hz), 3.10–3.20 (m, 2 H), 3.52 (dd, 1 H, *J* = 7.0, 12.0 Hz), 3.65–3.80 (m, 1 H), 4.97–5.30 (m, 2 H); HRMS calcd for $C_{17}H_{30}N_2O_2S_2Si$ MW 386.1518, found *m/z* 386.1526 (M^+). Anal. Calcd for $C_{17}H_{30}N_2O_2S_2Si$: C, 52.81; H, 7.82; N, 7.24. Found: C, 52.40; H, 7.69; N, 7.18.

(4*S*)-1-(*tert*-Butyldimethylsilyl)-4-[(1*R*)-1-[((4*S*)-4-isopropyl-2-thioxo-1,3-thiazolidin-3-yl)carbonyl]ethyl]azetidin-2-one (26b). Similar reaction of **24b** (28.6 mg, 0.10 mmol) with TBDMSCl (30 mg, 0.20 mmol) gave **26b** (36.3 mg, 91%) as a yellow oil: IR ($CHCl_3$) 1735, 1700 cm^{-1}; ^1H NMR (270 MHz) δ 0.20 (s, 3 H), 0.26 (s, 3 H), 0.96 (s, 9 H), 0.99 (d, 3 H, *J* = 6.9 Hz), 1.06 (d, 3 H, *J* = 6.9 Hz), 1.25 (d, 3 H, *J* = 6.9 Hz), 2.30–2.44 (m, 1 H), 3.00 (dd, 1 H, *J* = 1.0, 11.6 Hz), 3.07–3.15 (m, 2 H), 3.45 (dd, 1 H, *J* = 8.3, 11.5 Hz), 3.71–3.77 (m, 1 H), 5.11–5.24 (m, 2 H); HRMS calcd for $C_{18}H_{32}N_2S_2O_2Si$ MW 400.1675, found *m/z* 400.1672 (M^+).

(4*S*)-4-[(1*R*)-1-(Benzyloxycarbonyl)ethyl]-1-(*tert*-butyldimethylsilyl)azetidin-2-one (27). Alcoholysis of **26a** (3.86 g, 10.0 mmol) with sodium benzyl oxide (1.69 g, 13.0 mmol) was carried out in toluene (50 mL) as with **12a** to give **27** (1.39 g, 40%) as a pale yellow oil: IR (neat) 1740 cm^{-1}; ^1H NMR δ 0.15 (s, 3 H), 0.19 (s, 3 H), 0.93 (s, 9 H), 1.17 (d, 3 H, *J* = 7.0 Hz), 2.70–3.12 (m, 3 H), 3.63–3.80 (m, 1 H), 5.03 (d, 1 H, *J* = 12.0 Hz), 5.17 (d, 1 H, *J* = 12.0 Hz), 7.35 (s, 5 H); HRMS calcd for $C_{19}H_{29}NO_3Si$

MW 347.1917, found m/z 347.1953 (M^+).

(4*S*)-4-[(1*R*)-1-Carboxyethyl]-1-(*tert*-butyldimethylsilyl)azetidin-2-one (28). (1) Conversion of 27 to 28. A mixture of **27** (1.000 g, 2.88 mmol) and 5% Pd–C (200 mg) in MeOH (18 mL) was stirred at rt for 14 h under H_2. The usual workup gave **28** (735 mg, 99%) as colorless needles: mp 128–129 °C (from $CHCl_3$–hexane); $[\alpha]^{26}_D$ –54.6° (c 0.6, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 0.22 (s, 3 H), 0.27 (s, 3 H), 0.97 (s, 9 H), 1.18 (d, 3 H, J = 7.0 Hz), 2.81–3.17 (s, 3 H), 3.60–3.81 (m, 1 H); MS m/z 258 (M^+ + 1). Anal. Calcd for $C_{12}H_{23}NO_3Si$: C, 55.99; H, 9.01; N, 5.44. Found: C, 55.87; H, 8.88; N, 5.50.

(2) Conversion of 26a to 28. To a solution of **26a** (37.3 g, 96.5 mmol) in anhydrous THF (400 mL) was added imidazole (26.4 g, 387.8 mmol). The mixture was stirred at rt for 4 h, and then 10% citric acid (1000 mL) was added. After being stirred vigorously at rt for 2 h, the mixture was treated as usual to give **28** (18.95 g, 76%) as colorless needles: mp 128–129 °C (from $CHCl_3$–acetone). This product was found to be identical to **28** obtained from **27**.

(3) Conversion of 26b to 28. Reaction of **26b** and imidazole on a 0.09 mmol scale according to procedure **2** gave **28** (70%) identical with **28** obtained from **27**.

(3*S*,4*S*)-3-Acetyl-1-(*tert*-butyldimethylsilyl)-4-[(1*R*)-1-carboxyethyl]azetidin-2-one (32). To a solution of diisopropylamine (669 mg, 6.6 mmol) in anhydrous THF (10 mL) at 0–5 °C was added an 1.56 M solution of n-butyllithium in hexane (4.2 mL, 6.6 mmol). The mixture was stirred at 0 °C for 15 min and then cooled to –40 °C. A solution of **28** (540 mg, 2.1 mmol) in anhydrous THF (10 mL) was added, and the mixture was stirred at –40 °C for 15 min. After the reaction mixture was cooled to –78 °C, acetylimidazole (484 mg, 4.4 mmol) in anhydrous THF (15 mL) was added. The mixture was stirred at rt for 15 min and then quenched by addition of 10% citric acid. The aqueous layer was extracted with AcOEt, and the extract was washed with water and brine, dried, and evaporated in vacuo. The residue was purified by silica gel column chromatography (elution with 9:1 $CHCl_3$–acetone) to give **32** (521 mg, 83%) as a pale yellow oil: IR (neat) 1740, 1710 cm^{-1}; ^1H NMR δ 0.23 (s, 3 H), 0.28 (s, 3 H), 0.93 (s, 9 H), 1.18 (d, 3 H, J = 7.0 Hz), 2.32 (s, 3 H), 2.92–3.14 (m, 1 H), 4.11 (dd, 1 H, J = 3.0, 5.0 Hz), 4.61 (d, 1 H, J = 3.0 Hz), 8.53 (br s, 1 H).

(3*S*,4*S*)-1-(*tert*-Butyldimethylsilyl)-3-[(1*R*)-1-hydroxyethyl]-4-[(1*R*)-1-carboxyethyl]azetidin-2-one (33). To a solution of **32** (436.5 mg, 1.46 mmol) in anhydrous Et_2O (15 mL) at –78 °C was added a 1 M solution of $Mg(CF_3CO_2)_2$ in Et_2O (7.3 mL, 7.29 mmol). After the solution was stirred for 20 min at –78 °C, $(i\text{-}Pr)_2NH{\cdot}BH_3$ (0.4 mL, 2.68 mmol) was added. The mixture was then stirred at –78 °C for 1 h. The reaction was quenched with 10% citric acid, and the aqueous layer was extracted with AcOEt. The organic extract was washed with water and brine, dried, and evaporated in vacuo. The residue was purified by silica gel column chromatography (elution with 7:3 $CHCl_3$–acetone) to give **33** (313.9 mg, 71%) as colorless crystals: mp 130–132 °C (from $CHCl_3$–acetone); $[\alpha]^{26}_D$ –54.6° (c 0.5, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 0.23 (s, 3 H), 0.28 (s, 3 H), 0.96 (s, 9 H), 1.22 (d, 3 H, J = 6.0 Hz), 1.30 (d, 3 H, J = 6.0 Hz), 2.82–3.10 (m, 1 H), 3.43 (dd, 1 H, J = 2.0, 5.0 Hz), 3.76 (dd, 1 H, J = 2.0, 5.0 Hz), 4.03–4.30 (m, 1 H), 6.65 (br s, 2 H). Anal. Calcd for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65. Found: C, 55.72; H, 8.97; N, 4.56.

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(1*R*)-1-hydroxyethyl]-4-[(1*R*)-1-methyl-3-(*p*-nitrobenzyloxycarbonyl)-2-oxopropyl]azetidin-2-one (34). 1,1'-Carbonyldiimidazole (31.9 mg, 0.20 mmol) was added to a solution of **33** (49 mg, 0.16 mmol) in anhydrous MeCN (3 mL). The mixture was stirred at rt for 0.5 h, and then $Mg(O_2CCH_2CO_2PNB)_2$ (87.4 mg, 0.17 mmol) was added. After the reaction mixture was stirred at 50 °C for 18 h, the solvent was evaporated in vacuo and AcOEt was added. The organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. After being dried, the solvent was evaporated in vacuo to give a residue. Preparative TLC (4:1 $CHCl_3$–AcOEt) of the residue afforded compound **34** (30.3 mg, 39%) as a yellow, amorphous powder: IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR δ 0.10 (s, 6 H), 0.80 (s, 9 H), 1.03 (d, 3 H, J = 8.5 Hz), 1.15 (d, 3 H, J = 6.0 Hz), 2.75–2.95 (m, 1 H), 3.06 (dd, 1 H, J = 3.0, 6.0 Hz), 3.43 (s, 2 H), 3.48–3.60 (m, 1 H), 3.78–4.03 (m, 1 H), 5.08 (s, 2 H), 7.35 (d, 2 H, J = 8.5 Hz), 8.06 (d, 2 H, J = 8.5 Hz).

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-4-[(1*R*)-1-methyl-3-(*p*-nitrobenzyloxycarbonyl)-2-oxopropyl]azetidin-2-one (35). To a solution of **34** (6.5 mg, 0.01 mmol) in MeOH (0.1 mL) was added 6 N HCl (7 μL). The mixture was stirred at rt for 1.5 h. After addition of 0.1 M phosphate buffer solution (pH 7.0), the mixture was adjusted to pH 6–7 with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated in vacuo. Preparative TLC (AcOEt) of the residue yielded compound **35** (4.0 mg, 81%) as a colorless solid: mp 95–97 °C (from Et_2O), [lit.[2] mp 94–96 °C (from Et_2O)]; $[\alpha]^{25}_D$ –8.1° (c 0.9, CH_2Cl_2), [lit.[2] $[\alpha]^{21}_D$ –8.0° (c 2.5, CH_2Cl_2)]; IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR δ 1.26 (d, 3 H, J = 7.0 Hz), 1.30 (d, 3 H, J = 7.0 Hz), 2.80–3.05 (m, 2 H), 3.65 (s, 2 H), 3.85 (m, 1 H), 4.10 (m, 1 H), 5.30 (s, 2 H), 6.83 (s, 1 H), 7.55 (d, 2 H, J = 8.0 Hz), 8.25 (d, 2 H, J = 8.0 Hz).

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Registry No. **1**, 90822-26-7; (±)-**5**, 64804-09-7; **7a**, 101979-44-6; **7b**, 101979-45-7; (+)-**9a**, 102851-16-1; (+)-**9b**, 102831-93-6; **10a**, 102831-96-9; (+)-**11**, 76144-20-2; **12a**, 141585-76-4; **12b**, 141585-77-5; (–)-**13**, 102832-00-8; (–)-**14**, 77856-54-3; (±)-**14**, 85798-33-0; **16**, 102832-03-1; **17** (isomer 1), 75321-05-0; **17** (isomer 2), 141660-95-9; **21a**, 102831-91-4; **21b**, 102831-92-5; (+)-**24a**, 102831-94-7; (+)-**24b**, 102831-95-8; **25a**, 141660-96-0; **25b**, 141660-97-1; (+)-**26a**, 102831-99-2; **26b**, 141585-78-6; **27**, 102832-01-9; (–)-**28**, 102832-02-0; **32**, 102832-04-2; (–)-**33**, 102917-31-7; **34**, 141585-79-7; (–)-**35**, 141585-80-0; $CH_3C(O)OCH_2Ph$, 140-11-4; $Mg(O_2CCH_2CO_2PNB)_2$, 84854-29-5; thienamycin, 59995-64-1; imipenem, 64221-86-9.

Supplementary Material Available: Details of the X-ray diffraction analysis of compound **25b** and ^1H NMR spectra for compounds **9a**, **10a**, **12b**, **13**, **14**, **16**, **25a**, **26b**, **27**, **32**, **34**, and **35** (18 pages). Ordering information is given on any current masthead page.