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Synthesis of a Chiral 1β-Methylcarbapenem Key Intermediate Using Radical Cyclization of *N*-Vinylic α-Bromo Amides

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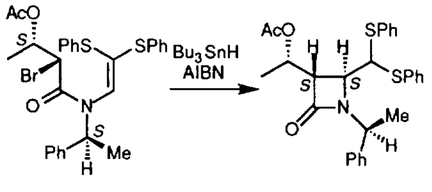
Abstract: The chiral 1β-methylcarbapenem key intermediate **5** was synthesized by using radical cyclization of *N*-vinylic α-bromo amide **18** as a key step. © 1997 Elsevier Science Ltd.

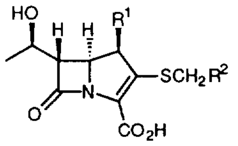
INTRODUCTION

Recently, great interest has been devoted to control the stereochemistry in radical addition and cyclization reactions.[1] In a series of papers[2] concerning the diastereoselective radical cyclization of α-halo amides, we reported that (2*R*,3*S*)-3-acetoxy-2-bromo-*N*-vinylbutanamide **1** bearing an (*S*)-1-phenylethyl group on the nitrogen atom, upon treatment with Bu_3SnH/azobisisobutyronitrile (AIBN) in boiling toluene, gave (3*S*,4*S*)-2-azetidinone **2** as the major product with high degree of diastereoselectivity (88:12).[2b] In view of the fact that the chirality at the carbon adjacent to the bromine atom led to no chiral induction,[2b] the predominant formation of **2** from **1** might be a result of the high level of stereoselection induced by a matched pair of chiral inductors, *i. e.*, an (*S*)-oxygen functionality at the side chain and an (*S*)-1-phenylethyl group on the nitrogen atom of **1**. The synthetic utility of the method was verified by transforming **2** to a chiral key intermediate for the synthesis of the therapeutically important carbapenem antibiotic (+)-thienamycin (**3**).



1

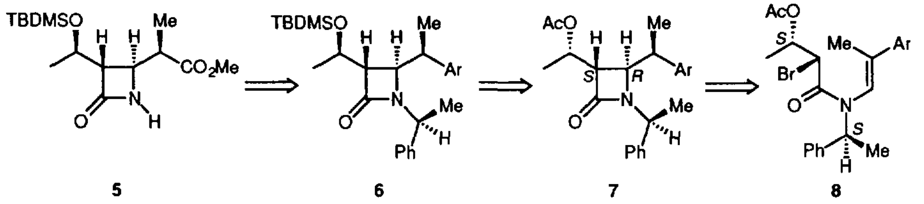
2 (major)



3: R^1 = H, R^2 = CH_2NH_2
4: R^1 = Me, R^2 = C(=NH)NMe_2

As an extension of the above methodology, we have now examined a diastereoselective synthesis of a chiral key intermediate for the synthesis of 1β-methylcarbapenems (*e. g.*, **4**)[3] according to the strategy outlined in retrosynthetic format depicted in Scheme I. We envisioned that the aryl group at the terminus of the *N*-vinylic bond of the radical precursor **8** would act both as a radical-stabilizing group in effecting the 4-***exo-trig*** cyclization of **8** and as a synthetic equivalent of carboxylic acid.[2c] A key step in the synthesis involves a diastereoselective radical cyclization of **8** induced by a matched pair of chiral inductors employed for **1** to lead to the formation of (3*S*,4*R*)-2-azetidinone **7**. An inversion of configuration of the oxygen functionality of the product **7** followed by ruthenium tetroxide oxidation of the aryl group at the C-4 side chain of **6** would provide **5**. Herein we report the result of our works based on this strategy.[4]

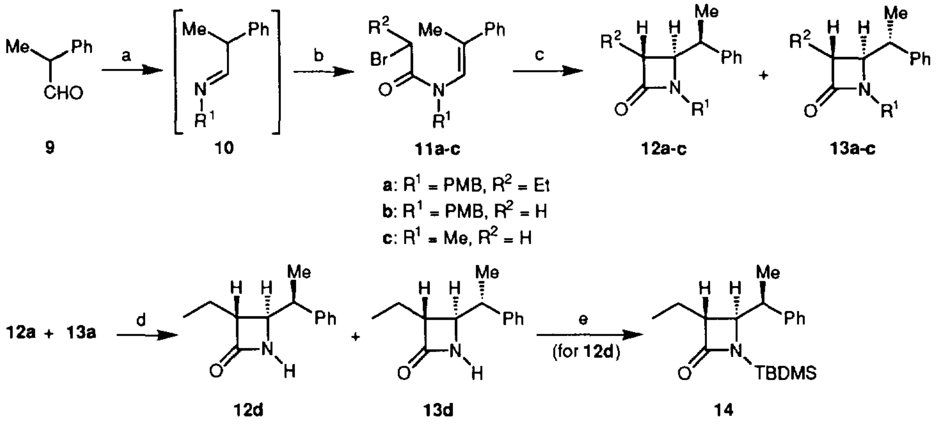
Scheme I



RESULTS AND DISCUSSION

The most important problem in the present synthesis is how to control the desired stereochemistry of the methyl group at the C-4 side chain of **7**. Therefore, we initiated our investigation by examining the diastereoselectivity in radical cyclization of α-bromo amides **11a-c**. Compounds **11a-c** were prepared by condensation of 2-phenylpropionaldehyde (**9**) with an appropriate amine followed by *N*-acylation of the resulting imine **10** with 2-bromobutyryl bromide or 2-bromoacetyl bromide.

Scheme II[a]



[a] a) R^1NH_2, benzene, reflux; b) $EtCH(Br)COBr$ or $BrCH_2COBr$, *N,N*-diethylaniline, benzene, reflux; c) Bu_3SnH, AIBN, toluene, reflux; d) CAN, CH_3CN-H_2O (1:2), r. t. (43% for **12d**, 9% for **13d**); e) TBDMSCl, Et_3N, DMF, r. t. (97%).

Treatment of **11a** with Bu_3SnH in the presence of AIBN in boiling toluene afforded an inseparable mixture of two diastereoisomers **12a** and **13a** in 63% combined yield and in a ratio of 2.7:1 (determined by ^1H NMR spectroscopy). *N*-Deprotection of the mixture of **12a** and **13a** with ceric ammonium nitrate (CAN) followed by careful chromatographic separation of the resulting lactams afforded **12d** and **13d** in 43 and 9% yields, respectively. The stereochemistry of **12d** was determined by an X-ray crystallographic analysis (Fig 1) of the crystalline derivative **14** derived from **12d**. This result clearly indicates that the methyl group of the major cyclization product **12a** has the same relative stereochemistry as that in 1β-methylcarbapenem.

Compound **11b**, upon treatment with Bu_3SnH and AIBN in boiling toluene, gave an inseparable mixture of two diastereoisomers **12b** and **13b** in combined 57% yield and in a ratio of 5.1:1. The major isomer was assigned the structure **12b** by the chemical transformation to **12a**. Thus, alkylation of the above mixture with LDA and ethyl iodide gave a mixture of **12a** and **13a** in a ratio of 2.2:1 (determined by ^1H NMR spectroscopy), along with the recovered mixture of **12b** and **13b** (in a ratio 3.8:1).

When *N*-methyl derivative **11c** was treated with Bu_3SnH and AIBN in boiling toluene, two diastereoisomers **12c** and **13c** were obtained in 49% combined yield and in a ratio of *ca.* 3:2, whose stereochemistries were not determined.

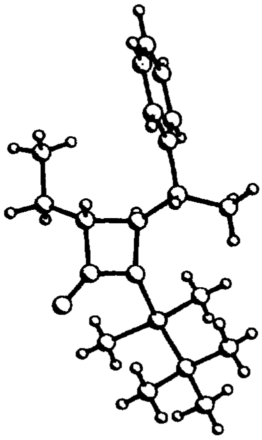
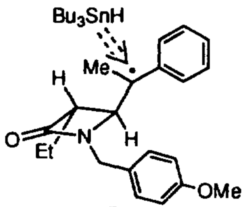
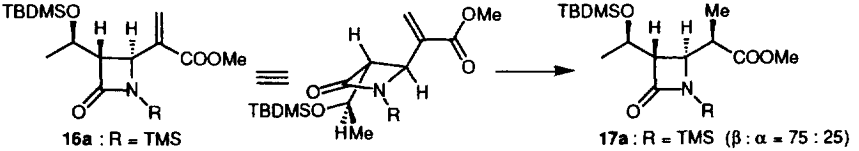


Figure 1. X-ray structure of β-lactam **14**

One possible rationalization for the predominant formation of **12a** from **11a** would involve the intermediate **15**, in which the sterically more demanding phenyl group at the C-4 side chain is in an *exo* orientation relative to the azetidinone ring to avoid the steric interaction with the hydrogen atom at the C-3 position. In this intermediate, the front-face (β-face) of the radical center must be sterically hindered by the presence of the *p*-methoxybenzyl (PMB) group on the nitrogen atom, so that Bu_3SnH preferentially attacks on the radical center from the less hindered back-face (α-face) of the radical to give the major product **12a**. According to this model, the presence of the ethyl group at the C-3 position may have the reverse effect: *i. e.*, the approach of Bu_3SnH from the back-side is hindered, although the effect is not large enough to overweigh the steric effect of the PMB group on the nitrogen atom. Therefore, if the ethyl group at the C-3 position is removed, the diastereoselectivity is expected to be improved. Indeed, the ratio of two diastereoisomers **12b** and **13b** obtained from **11b** was found to be 5.1:1. In contrast, if the PMB group is replaced by a smaller methyl group, the approach of Bu_3SnH from the front-face may become somewhat favored. Thus, lower diastereoselectivity of **11c** (the ratio of **12c** and **13c** was 3:2) was not unexpected. There is an analogy for this type of reaction found in the catalytic hydrogenation of the unsaturated ester **16a**.[5] Thus, the hydrogenation of **16a** having a trimethylsilyl group on the nitrogen atom afforded the β-methyl derivative **17a** as the major product, while the compound **16b** bearing no substituent on the nitrogen atom yielded the α-methyl derivative **17b** as the major product.[6]



15



16a : R = TMS
16b : R = H

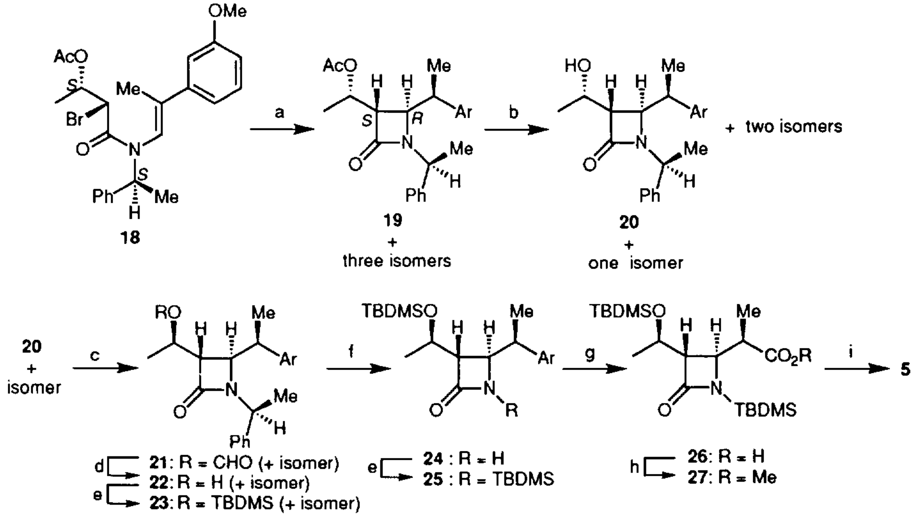
17a : R = TMS (β : α = 75 : 25)
17b : R = H (β : α = 35 : 65)

Also intriguing is that the radical cyclization of **11a** took place more smoothly than did the bromide having no methyl group at the teminus of the *N*-vinylic bond which gave only a small quantity of β-lactam.[2c] The result indicates that the methyl group introduced at the terminus of the *N*-vinylic bond of **11a**, which is essential for the present purpose, acts also as an effective radical-stabilizing group for the formation of the radical intermediate **15**.

Encouraged by the observation that the radical cyclization of **11a** gave **12a** as the major product, the synthesis of **5** was next examined according to the strategy outlined in Scheme I.

Taking into account the earlier observation that the ruthenium tetroxide oxidation of the phenyl group was rather sluggish,[2c] we chose an electron-rich (readily oxidizable) *m*-methoxyphenyl group as an equivalent of carboxylic acid. Compound **18** was prepared by condensation of 2-(*m*-methoxyphenyl)propionaldehyde and (*S*)-1-phenylethylamine followed by *N*-acylation of the resulting imine with (2*R*,3*S*)-3-acetoxy-2-bromobutyryl chloride.[2a] The radical cyclization of **18** proceeded cleanly to give a mixture of **19** and other three diastereoisomers in a ratio of 57:21:20:2 and in 78% combined yield. The stereochemistry of the major product **19** was determined by transforming it to the target molecule **5** through isolation of compound **24** as a pure form. Thus, the mixture of the cyclization products was treated with 1N NaOH in pyridine to give a mixture of (*S*)-alcohol **20** and its stereoisomer in a ratio of 73:27 and in 58% yield, along with an additional mixture of other two isomers. The former mixture was then subjected to the Mitsunobu reaction (HCO_2H / diisopropyl azodicarboxylate / PPh_3) and the resulting mixture containing formate **21** was hydrolyzed with 10% HCl in methanol to give a mixture of (*R*)-alcohol **22** and its isomer. *O*-Silylation of the mixture with TBDMSCl followed by *N*-deprotection of the resulting mixture containing **23** with sodium in liquid ammonia afforded **24** in 50% yield as a pure form after recrystallization of the crude material from hexane.

Scheme III[a]



[a] (a) Bu_3SnH, AIBN, toluene, reflux (78%); (b) 1N NaOH, pyridine, r. t. (58% for **20** and its isomer); (c) HCO_2H, diisopropyl azodicarboxylate, PPh_3, THF, r. t.; (d) 10% HCl, MeOH, r. t.; (e) TBDMSCl, Et_3N, DMF, r. t. [92% for **23** (+ isomer) from **20** (+ isomer), quantitative for **25** from **24**]; (f) Na, liquid NH_3, THF, -78 °C (50%); (g) RuO_2-H_2O, $NaIO_4$, CH_3CN-CCl_4-H_2O (1:1:1.5), r. t., 3 h; (h) $TMSCHN_2$, benzene-MeOH (4:1), r. t. (62% from **25**); (i) Bu_4NF, AcOH, THF, 0 °C (quantitative).

Reprotection of **24** with TBDMSCl afforded **25** quantitatively. As expected, the ruthenium tetroxide oxidation of **25** occurred smoothly within 3 h to give carboxylic acid **26**. Treatment of **26** with trimethylsilyldiazomethane followed by deprotection of the *N*-TBDMS group of the resulting ester **27** with tetrabutylammonium fluoride furnished the target molecule **5** {mp 118.5-119 °C, $[\alpha]_D^{24}$ −20.9° (*c* 0.45, CH_2Cl_2): lit.[7] mp 120-121 °C, $[\alpha]_D^{24}$ −21.0° (*c* 2.09, CH_2Cl_2)}.

Thus, we revealed that two chiral inductors, an (*S*)-oxygen functionality at the side chain and an (*S*)-1-phenylethyl group on the nitrogen atom of **1**, used for the diastereoselective synthesis of (+)-thienamycin also acted as a good pair of chiral inductors in radical cyclization of *N*-vinylic α-bromo amide **18** to lead to a new method of constructing four continuous stereocenters of 1β-methylcarbapenem.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded with a JASCO IR-A-100 spectrophotometer. ^1H NMR spectra were measured on a JEOL JNM-PMX 60 or a Varian XL-300 spectrometer for solutions in $CDCl_3$. δ Values quoted are relative to tetramethylsilane. Optical rotations were measured with a JASCO DIP-360 polarimeter. High resolution mass spectra (HRMS) (EI and FAB mass spectra) were obtained with a JEOL-SX 102A instrument at 20 eV. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure.

2-Bromo-*N*-[(4-methoxyphenyl)methyl]-*N*-(2-phenylprop-2-enyl)butanamide (11a). A mixture of 2-phenylpropionaldehyde (**9**) (1.11 g, 8.27 mmol) and *p*-methoxybenzylamine (1.13 g, 8.27 mmol) in benzene (50 mL) was heated under reflux with azeotropic removal of water for 2 h. After cooling, *N,N*-diethylaniline (1.23 g, 8.27 mmol) was added to the mixture, and the whole was again heated under reflux. To this was added slowly (±)-2-bromobutyryl bromide (2.28 g, 9.92 mmol), and the mixture was heated for further 1 h. Water was added to the reaction mixture and the whole was extracted with benzene. The extract was washed successively with 1% HCl, a saturated $NaHCO_3$ solution, and brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **11a** (2.42 g, 73%) as an oily mixture of two geometric isomers: IR (CCl_4) ν 1665 cm^{-1}; ^1H NMR for the major isomer (300 MHz) δ 0.98 (t, *J* = 7.3 Hz, 3 H), 1.90 (d, *J* = 1.5 Hz, 3 H), 1.96-2.29 (m, 2 H), 3.79 (s, 3 H), 4.36 (t, *J* = 7.3 Hz, 1 H), 4.61 (d, *J* = 13.9 Hz, 1 H), 4.76 (d, *J* = 13.9 Hz, 1 H), 6.30 (q, *J* = 1.5 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 7.14-7.38 (m, 7 H). A peak due to the *C*-methyl protons of the minor isomer appeared at δ 0.79 (t, *J* = 7.3 Hz), whose integrated intensity showed the ratio of two isomers to be *ca.* 2.1:1. HRMS (FAB) Calcd for $C_{21}H_{25}{}^{79}BrNO_2$ $[(M+H)^+]$: 402.1069. Found: 402.1073.

2-Bromo-*N*-[(4-methoxyphenyl)methyl]-*N*-(2-phenylprop-2-enyl)acetamide (11b). According to a procedure similar to that described above for the preparation of **11a**, the imine prepared from **9** (1.34 g, 10 mmol) and *p*-methoxybenzylamine (1.37 g, 10 mmol) was treated with bromoacetyl bromide (2.42 g, 12 mmol) in the presence of *N,N*-diethylaniline (1.79 g, 12 mmol). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **11b** (2.51 g, 67%) as an oily mixture of two geometric isomers: ^1H NMR for the major isomer (300 MHz) δ 1.86 (d, *J* = 1.5 Hz, 3 H), 3.80 (s, 3 H), 3.87 (s, 2 H), 4.66 (s, 2 H), 6.30 (q, *J* = 1.5 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 7.36

(s, 5 H). A peak due to the methyl protons on the alkenic bond of the minor isomer appeared at δ 1.82 (d, *J* = 1.5 Hz), whose integrated intensity showed the ratio of two isomers to be *ca.* 5:1. HRMS (FAB) Calcd for $C_{19}H_{21}{}^{79}BrNO_2$ $[(M+H)^+]$: 374.0755. Found: 374.0745.

2-Bromo-*N*-methyl-*N*-(2-phenylprop-2-enyl)acetamide (11c). According to a procedure similar to that described above for the preparation of **11a**, the imine prepared from **9** (1.34 g, 10 mmol) and methylamine (large excess) was treated with bromoacetyl bromide (2.42 g, 12 mmol) in the presence of *N,N*-diethylaniline (1.79 g, 12 mmol). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 3:1) to give **11c** (1.23 g, 46%) as an oil, whose ^{1}H NMR spectrum indicated it to be a single geometric isomer: ^{1}H NMR (300 MHz) δ 2.08 (d, *J* = 1.5 Hz, 3 H), 3.13 (s, 3 H), 3.87 (s, 2 H), 6.54 (q, *J* = 1.5 Hz, 1 H), 7.36-7.45 (m, 5 H). HRMS (FAB) Calcd for $C_{12}H_{15}{}^{79}BrNO$ $[(M+H)^+]$: 268.0337. Found: 268.0348.

(3*R,4*R**)-3-Ethyl-1-[(4-methoxyphenyl)methyl]-4-[(*R**)-1-phenylethyl]-2-azetidinone (12a) and (3*R**,4*R**)-3-Ethyl-1-[(4-methoxyphenyl)methyl]-4-[(*S**)-1-phenylethyl]-2-azetidinone (13a): General Procedure for Radical Cyclization.** To a boiling solution of **11a** (211 mg, 0.52 mmol) in toluene (50 mL) was added a solution of Bu_3SnH (198 mg, 0.68 mmol) and AIBN (9 mg, 0.05 mmol) in toluene (50 mL) *via* a syringe over 4 h, and the mixture was further heated under reflux for 2 h. After evaporating off the solvent, diethyl ether (20 mL) and 8% aqueous KF (20 mL) were added to the residue, and the mixture was stirred vigorously at room temperature for 5 h. The organic layer was separated, dried ($MgSO_4$), and concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 10:1) to give an oily mixture of **12a** and **13a** (106 mg, 63%): IR (CCl_4) ν 1745 cm^{-1}; ^{1}H NMR for **12a** (300 MHz) δ 0.61 (t, *J* = 7.4 Hz, 3 H), 1.25-1.55 (m, 2 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 2.66-2.73 (m, 1 H, H-3), 2.81-2.95 (m, 1 H), 3.19 (dd, *J* = 7.5, 2.2 Hz, 1 H, H-4), 3.81 (s, 3 H), 3.98 (d, *J* = 15.1 Hz, 1 H), 4.80 (d, *J* = 15.1 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 7.06-7.37 (m, 7 H). A small peak due to the *C*-methyl protons at the C-3 position of **13a** appeared at δ 0.93 (t, *J* = 7.4 Hz), whose integrated intensity showed the ratio of **12a** and **13a** to be *ca.* 2.7:1. *Anal.* Calcd for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.55; H, 7.85; N, 4.30.

(4*R)-1-[(4-methoxyphenyl)methyl]-4-[(*R**)-1-phenylethyl]-2-azetidinone (12b) and (4*R**)-1-[(4-methoxyphenyl)methyl]-4-[(*S**)-1-phenylethyl]-2-azetidinone (13b).** Following the general procedure, compound **11b** (191 mg, 0.51 mmol) was treated with Bu_3SnH (178 mg, 0.61 mmol) in the presence of AIBN (10 mg, 0.06 mmol) in boiling toluene (50 mL). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 2:1) to give an oily mixture of **12b** and **13b** (75 mg, 57%): ^{1}H NMR for **12a** (300 MHz) δ 1.32 (d, *J* = 7.0 Hz, 3 H), 2.55 (dd, *J* = 14.8, 2.5 Hz, 1 H), 2.76 (dd, *J* = 14.8, 5.1 Hz, 1 H), 2.91 (quint, *J* = 7.0 Hz, 1 H), 3.60 (ddd, *J* = 7.0, 5.1, 2.5 Hz, 1 H), 3.80 (s, 3 H), 4.03 (d, *J* = 15.1 Hz, 1 H), 4.78 (d, *J* = 15.1 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 7.05-7.35 (m, 7 H). A small peak due to the *C*-methyl protons of **13b** appeared at δ 1.18 (t, *J* = 7.0 Hz), whose integrated intensity showed the ratio of **12b** and **13b** to be *ca.* 5.1:1. HRMS (FAB) Calcd for $C_{19}H_{22}NO_2$ $[(M+H)^+]$: 296.1651. Found: 296.1667.

Alkylation of 12b and 13b: Formation of 12a and 13a. To a solution of lithium diisopropylamide (LDA) [prepared from diisopropylamine (67 mg, 0.66 mmol), a 1.6 mol/L hexane solution of BuLi (0.38 mL, 0.60 mmol) and THF (0.5 mL)] was added a solution of a mixture of **12b** and **13b** (160 mg, 0.55 mmol) and hexamethylphosphoric triamide (HMPA) (186 mg, 1.04 mmol) in THF (0.5 mL) at -78°C, and the mixture was stirred at the same temperature for 1 h. Ethyl iodide (315 mg, 2.02 mmol) was added to this solution and the stirring was continued at -20 °C for 1.5 h. A saturated NH_4Cl solution (2 mL) was added to the reaction mixture, and the whole was extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane/AcOEt, 2:1). The first eluent gave a mixture of **12a** and **13a** (41 mg, 23 %), whose ^{1}H NMR spectrum showed the ratio of **12a** and **13a** to be 2.2:1. The second eluent gave a mixture of the recovered compounds **12b** and **13b** (50 mg, 28%) in a ratio of 3.8:1.

(4*R)-1-Methyl-4-[(*R**)-1-phenylethyl]-2-azetidinone (12c) and (4*R**)-1-Methyl-4-[(*S**)-1-phenylethyl]-2-azetidinone (13c).** Following the general procedure, compound **11c** (138 mg, 0.52 mmol) was treated with Bu_3SnH (180 mg, 0.62 mmol) in the presence of AIBN (10 mg, 0.06 mmol) in boiling toluene (50 mL). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 2:1) to give an oily mixture of **12c** and **13c** (48 mg, 49%): ^{1}H NMR for the major isomer (300 MHz) δ 1.42 (d, *J* = 7.0 Hz, 3 H), 2.50 (dd, *J* = 14.8, 2.4, 1.0 Hz, 1 H), 2.78 (dd, *J* = 14.8, 5.0 Hz, 1 H), 2.90 (s, 3 H), 2.95 (quint, *J* = 7.0 Hz, 1 H), 3.63 (ddd, *J* = 7.0, 5.0, 2.4 Hz, 1 H), 7.15-7.45 (m, 5 H). A small peak due to the *C*-methyl protons of the minor isomer appeared at δ 1.25 (d, *J* = 7.0 Hz), whose integrated intensity showed the ratio of the major isomer and the minor one to be *ca.* 3:2. HRMS (FAB) Calcd for $C_{12}H_{16}NO$ [$(M+H)^+$]: 190.1232. Found: 190.1243.

(3*R,4*R**)-3-Ethyl-4-[(*R**)-1-phenylethyl]-2-azetidinone (12d) and (3*R**,4*R**)-3-Ethyl-4-[(*S**)-1-phenylethyl]-2-azetidinone (13d).** To a solution of the mixture of **12a** and **13a** (469 mg, 1.45 mmol) in acetonitrile (14 mL) was added slowly a solution of ceric ammonium nitrate (2.52 g, 4.36 mmol) in water (28 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. Water was added to the reaction mixture and the whole was extracted with AcOEt. The extract was washed successively with a saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 5:1). The first eluent gave **13d** (26 mg, 9%) as an oil, which solidified on standing in a refrigerator: IR (CCl_4) ν 3450, 1750 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.06 (t, *J* = 7.3 Hz, 3 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 1.66-1.91 (m, 2 H), 2.77 (dq, *J* = 9.5, 7.0 Hz, 1 H), 2.79-2.84 (m, 1 H, H-3), 3.34 (dd, *J* = 9.5, 2.0 Hz, 1 H, H-4), 5.56 (br s, 1 H), 7.16-7.38 (m, 5 H). HRMS (FAB) Calcd for $C_{13}H_{18}NO$ [$(M+H)^+$]: 204.1388. Found: 204.1404.

The second eluent gave **12d** (126 mg, 43%): mp 124-125 °C (hexane/AcOEt); IR (CCl_4) ν 3450, 1750 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.56 (t, *J* = 7.3 Hz, 3 H), 1.32-1.47 (m, 1 H), 1.34 (d, *J* = 7.0 Hz, 3 H), 1.50-1.65 (m, 1 H), 2.69-2.75 (m, 1 H, H-3), 2.78 (dq, *J* = 9.0, 7.3 Hz, 1 H), 3.35 (dd, *J* = 9.0, 2.1 Hz, 1 H, H-4), 6.60-6.75 (br, 1 H), 7.17-7.35 (m, 5 H). HRMS (FAB) Calcd for $C_{13}H_{18}NO$ [$(M+H)^+$]: 204.1388. Found: 204.1399.

(3*R,4*R**)-1-*tert*-Butyldimethylsilyl-3-ethyl-4-[(*R**)-1-phenylethyl]-2-azetidinone (14).** To a solution of **12d** (95 mg, 0.47 mmol) in DMF (3 mL) were added successively triethylamine (189 mg, 1.88 mmol) and *tert*-butyldimethylsilyl chloride (141 mg, 0.94 mmol) at room temperature, and the mixture was stirred for 3 h. Water was added to the reaction mixture and the whole was extracted with diethyl ether. The extract was washed with brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 15:1) to give **14** (144 mg, 97%): mp 100.5-101 °C (hexane); IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (300 MHz) δ 0.27 (s, 3 H), 0.29 (s, 3 H), 0.80 (t, *J* = 7.4 Hz, 3 H), 1.00 (s, 9 H), 1.36 (d, *J* = 7.0 Hz, 3 H), 1.40-1.67 (m, 2 H), 2.63 (ddd, *J* = 8.3, 6.0, 2.4 Hz, 1 H, H-3), 2.99 (quint, *J* = 7.0 Hz, 1 H), 3.37 (dd, *J* = 7.0, 2.4 Hz, 1 H, H-4), 7.17-7.33 (m, 5 H). *Anal.* Calcd for $C_{19}H_{31}NOSi$: C, 71.87; H, 9.84; N, 4.41. Found: C, 71.56; H, 9.84; N, 4.60.

2-(3-Methoxyphenyl)propionaldehyde. A solution of ethoxymethyltriphenylphosphonium chloride (6.85 g, 19.95 mmol) in dimethyl sulfoxide (10 mL) was added to a solution of sodium methylsulfinylmethylide (19.95 mmol) in dimethyl sulfoxide (5 mL) at 0 °C, and the mixture was stirred at the same temperature for 15 min. To this was added a solution of *m*-methoxyacetophenone (2.9 g, 13.32 mmol) in dimethyl sulfoxide (20 mL), and the mixture was stirred at room temperature for 1 h. Water was added to the reaction mixture and the whole was extracted with diethyl ether. The extract was dried ($MgSO_4$), the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane/AcOEt, 20:1) to give 3-methoxy-1-(2-methoxy-1-methylethenyl)benzene (1.96 g, 83%) as an oily mixture of *E*- and *Z*-isomers in a ratio of *ca.* 1:1: IR (CCl_4) ν 1650 cm^{-1}; ^1H NMR (60 MHz) δ 1.90, 1.98 (both br s, total 3 H), 3.64, 3.70 (both s, total 3 H), 3.79 (s, 3 H), 6.08, 6.40 (both br s, total 1 H), 6.50-7.37 (m, 4 H). HRMS Calcd for $C_{11}H_{14}O_2$: 178.0994. Found: 178.0982.

The above Wittig reaction product (1.96 g, 11.01 mmol), water (7 mL), and *p*-toluenesulfonic acid monohydrate (130 mg, 0.68 mmol) were successively added to dioxane (35 mL), and the mixture was heated under reflux for 10 h. Water was added to the reaction mixture and the whole was extracted with diethyl ether. The extract was dried ($MgSO_4$), the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane/AcOEt, 20:1) to give 2-(3-methoxyphenyl)propionaldehyde (1.68 g, 94%) as an oil: IR (CCl_4) ν 1720 cm^{-1}; ^1H NMR (60 MHz) δ 1.41 (d, *J* = 7 Hz, 3 H), 3.56 (q, *J* = 7 Hz, 1 H), 3.76 (s, 3 H), 6.6-7.5 (m, 4 H), 9.58 (s, 1 H). HRMS Calcd for $C_{10}H_{12}O_2$: 164.0837. Found: 164.0839.

(2*R*,3*S*)-3-Acetoxy-2-bromo-*N*-[2-(3-methoxyphenyl)-1-propen-1-yl]-*N*-[(*S*)-1-phenylethyl]butanamide (18). According to a procedure similar to that described above for **11a**, 2-(3-methoxyphenyl)propionaldehyde (1.11 g, 6.82 mmol) was allowed to react with (*S*)-1-phenylethylamine (827 mg, 6.82 mmol), and the resulting imine was treated with (2*R*,3*S*)-3-acetoxy-2-bromobutyryl chloride[2a] (3.33 g, 13.64 mmol) in the presence of *N*,*N*-diethylaniline (1.01 g, 6.82 mmol). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **18** (2.91 g, 92%) as an oily mixture of more than four geometric isomers: IR (CCl_4) ν 1745, 1660 cm^{-1}; ^1H NMR (60 MHz) δ [0.73 (d, *J* = 7 Hz), 1.3-2.2 (m), total 12 H], 3.73 (br s, 3 H), 4.2-4.4 (m, 1 H), 4.9-5.6 (m, 1 H), 5.6-6.2 (m, 2 H), 6.7-7.5 (m, 9 H). HRMS (FAB) Calcd for $C_{24}H_{29}{}^{79}BrNO_4$ [$(M+H)^+$]: 474.1280. Found: 474.1289.

(3*S*,4*R*)-3-[(*S*)-1-Acetoxyethyl]-4-[(*R*)-1-(3-methoxyphenyl)ethyl]-1-[(*S*)-1-phenylethyl)]-2-azetidinone (19) and Its Stereoisomers. Using a procedure similar to that described above for **11a**, bromide **18** (597 mg, 1.26 mmol) was treated with Bu_3SnH (367 mg, 1.64 mmol) and AIBN (25 mg, 0.15 mmol) in boiling toluene. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 5:1) to give an oily mixture of **19** and its three diastereoisomers (387 mg, 78%): IR (CCl_4) ν 1745 cm^{-1}; ^1H NMR for **19** (300 MHz) δ 1.20 (d, *J* = 6.5 Hz, 3 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.80 (d, *J* =

7.3 Hz, 3 H), 1.89 (s, 3 H), 2.86 (dd, J = 3.7, 2.6 Hz, 1 H, H-3), 2.9 (quint, J = 6.8 Hz, 1 H), 3.34 (dd, J = 6.4, 2.6 Hz, 1 H, H-4), 3.80 (s, 3 H), 4.52 (q, J = 7.3 Hz, 1 H), 4.87 (dq, J = 3.7, 6.5 Hz, 1 H, OCH), 6.59-6.83 (m, 3 H), 7.03-7.40 (m, 6 H). Small peaks due to the *O*-acetyl methyl protons of other three diastereoisomers appeared at δ 1.87, 1.88, 1.90 as singlets, respectively. The GLC analysis of the mixture showed the ratio of four diastereoisomers to be 57:21:20:2. *Anal.* Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.79; H, 7.55; N, 3.45.

(3*S*,4*R*)-3-[(*S*)-1-Hydroxyethyl]-4-[(*R*)-1-(3-methoxyphenyl)ethyl]-1-[(*S*)-1-phenylethyl)]-2-azetidinone (20) and Its Stereoisomers. To an ice-cooled solution of the mixture of **19** and its three stereoisomers (366 mg, 0.93 mmol) in pyridine (4 mL) was added dropwise a 0.1 N NaOH solution (5 mL) over a period of 15 min, and the mixture was stirred at room temperature overnight. A saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture, and the whole was extracted with AcOEt. The extract was washed with water, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 5:1). The first eluent gave an oily mixture of **20** and its one diastereoisomer (189 mg, 58%): IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR for **20** (300 MHz) δ 0.94 (d, J = 6.4 Hz, 3 H), 1.23 (d, J = 7.0 Hz, 3 H), 1.78 (d, J = 7.2 Hz, 3 H), 2.50-2.60 (br, 1 H, OH), 2.72 (dd, J = 7.1, 2.2 Hz, 1 H, H-3), 2.87 (quint, J = 6.9 Hz, 1 H), 3.35 (dd, J = 6.6, 2.2 Hz, 1 H, H-4), 3.68-3.80 (m, 1 H, OCH), 3.77 (s, 3 H), 4.58 (d, J = 7.2 Hz, 1 H), 6.57-6.82 (m, 3 H), 7.02-7.40 (m, 6 H). A small peak due to the *C*-methyl protons of the *N*-phenethyl group of another stereoisomer appeared at δ 1.65 (d, J = 7.2 Hz), whose integrated intensity showed the ratio of **20** and its stereoisomer to be 73:27. *Anal.* Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.77; H, 7.80; N, 4.00.

The second eluent gave an oily mixture of other two stereoisomers (93 mg, 28%).

(3*S*,4*R*)-3-[(*R*)-1-Formyloxyethyl]-4-[(*R*)-1-(3-methoxyphenyl)ethyl]-1-[(*S*)-1-phenylethyl)]-2-azetidinone (21) and Its Stereoisomer. A solution of diisopropyl azodicarboxylate (214 mg, 1.06 mmol) in dry THF (1 mL) was added dropwise to a solution of the mixture of **20** and its isomer (188 mg, 0.53 mmol), triphenylphosphine (279 mg, 1.06 mmol), and formic acid (49 mg, 1.06 mmol) in dry THF (6 mL) at room temperature, and the mixture was stirred at the same temperature for 2 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 7:1) to give an oily mixture of **21** and its isomer (202 mg, quantitative): IR (CCl_4) ν 1740, 1725 cm^{-1}; ^1H NMR for **21** (300 MHz) δ 1.08 (d, J = 6.4 Hz, 3 H), 1.26 (d, J = 7.1 Hz, 3 H), 1.79 (d, J = 7.2 Hz, 3 H), 2.89 (dd, J =5.6, 2.3 Hz, 1 H, H-3), 2.91 (quint, J = 7.1 Hz, 1 H), 3.49 (dd, J = 6.1, 2.3 Hz, 1 H, H-4), 3.79 (s, 3 H), 4.54 (q, J = 7.2 Hz, 1 H), 5.15 (dq, J = 6.4, 5.6 Hz, 1 H, OCH), 6.58-6.83 (m, 3 H), 7.04-7.40 (m, 6 H), 7.76 (s, 1 H, CHO). A small peak due to the *C*-methyl protons of the *N*-phenethyl group of another stereoisomer appeared at δ 1.67 (d, J = 7.2 Hz), whose integrated intensity showed the ratio of **21** and its stereoisomer to be 77:23. HRMS Calcd for $C_{23}H_{27}NO_4$: 381.1940. Found: 381.1954.

(3*S*,4*R*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*R*)-1-(3-methoxyphenyl)ethyl]-1-[(*S*)-1-phenylethyl)]-2-azetidinone (22) and Its Stereoisomer. To a solution of the mixture of **21** and its stereoisomer (202 mg, 0.53 mmol) in methanol (5 mL) was added 10% HCl (4 m L) at 0 °C, and the mixture was stirred at room temperature for 24 h. Brine (20 mL) was added to the reaction mixture, and the whole was extracted with diethyl ether. The extract was dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 1:2) to give an oily mixture of **22** and its stereoisomer (187 mg, quantitative): IR (CCl_4) ν 3450, 1720 cm^{-1}; ^1H NMR for **22** (300 MHz) δ 0.93 (d, J = 6.4 Hz, 3 H), 1.23 (d, J = 7.1 Hz, 3 H), 1.76 (d, J = 7.2 Hz, 3 H), 2.0-2.15 (br, 1 H, OH), 2.77 (dd, J = 4.9, 2.2 Hz, 1 H, H-3), 2.88 (quint, J = 7.0 Hz, 1 H), 3.59 (dd, J = 6.2, 2.2 Hz, 1 H, H-4), 3.77 (s, 3 H), 3.91-4.01 (m, 1 H, OCH), 4.60 (q, J = 7.2 Hz, 1 H), 6.58-6.80 (m, 3 H), 7.04-7.38 (m, 6 H). A small peak due to the *C*-methyl protons of the *N*-phenethyl group of another stereoisomer appeared at δ 1.65 (d, J = 7.3 Hz), whose integrated intensity showed the ratio of **22** and its stereoisomer to be 75:25. *Anal.* Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.52; H, 7.68; N, 3.94.

(3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-(3-methoxyphenyl)ethyl]-1-[(*S*)-1-phenylethyl)]-2-azetidinone (23) and Its Stereoisomer. To a solution of the mixture of **22** and its stereoisomer (789 mg, 2.23 mmol) in DMF (18 mL) were added successively *tert*-butyldimethylsilyl chloride (1.68 g, 11.15 mmol) and triethylamine (1.56 g, 15.61 mmol), and the mixture was stirred at room temperature for 1.5 h. Diethyl ether (60 mL) was added to the reaction mixture, and the solution was washed with water and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 15:1) to give an oily mixture of **23** and its stereoisomer (965 mg, 92%): IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR for **23** (300 MHz) δ 0.01 (s, 3 H), 0.04 (s, 3 H), 0.87 (s, 9 H), 0.88 (d, J = 6.3 Hz, 3 H), 1.19 (d, J = 7.1 Hz, 3 H), 1.71 (d, J = 7.2 Hz, 3 H), 2.75 (dd, J = 5.0, 2.2 Hz, 1 H, H-3), 2.81-2.90 (m, 1 H), 3.66 (dd, J = 5.6, 2.2 Hz, 1 H, H-4), 3.77 (s, 3 H), 3.98-4.06 (m, 1 H), 4.62 (q, J = 7.2 Hz, 1 H), 6.62-6.79 (m, 3 H), 7.16-7.37 (m, 6 H). A small peak due to the *C*-methyl protons of the *N*-phenethyl group of another stereoisomer appeared at δ 1.62 (d, J = 7.2 Hz), whose integrated intensity showed the ratio of **23** and its stereoisomer to be 76:24. HRMS (FAB) Calcd for $C_{28}H_{42}NO_4Si$ [$(M+H)^+$]: 468.2934. Found: 468.2937.

(3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-(3-methoxyphenyl)ethyl]-2-azetidinone (24). Sodium (187 mg, 8.16 mmol) and a solution of the mixture of **23** and its isomer (1.27 g, 2.72 mmol) in dry THF (6 mL) were added successively to liquid ammonia (15 mL) at –78 °C, and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by addition of ammonium chloride, and the mixture was allowed to warm to room temperature to remove any excess ammonia. A saturated ammonium chloride solution (9 mL) was added to the residue, and the whole mixture was extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated off and the residual solid was recrystallized from hexane to give **24** (491 mg, 50%): mp 104–105 °C; $[\alpha]_D^{23}$ –7.8° (*c* 4.10, EtOH); IR (CCl_4) ν 3450, 3250, 1755 cm^{-1}; ^1H NMR (300 MHz) δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.58 (d, J = 6.4 Hz, 3 H), 0.85 (s, 9 H), 1.35 (d, J = 7.0 Hz, 3 H), 2.74-2.84 (m, 2 H), 3.72 (dd, J = 8.5, 2.1 Hz, 1 H, H-4), 3.80 (s, 3 H), 4.07 (dq, J = 3.3, 6.4 Hz, 1 H, OCH), 6.35-6.45 (br, 1 H), 6.74-6.81 (m, 3 H), 7.24 (t, J = 7.8 Hz, 1 H). *Anal.* Calcd for $C_{20}H_{33}NO_3Si$: C, 66.07; H, 9.15; N, 3.85. Found: C, 65.93; H, 9.27; N, 4.16.

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-(3-methoxyphenyl)ethyl]-2-azetidinone (25). Using a procedure similar to that described for the preparation of **14**, compound **24** (491 mg, 1.35 mmol) was treated with *tert*-butyldimethylsilyl chloride (610 mg, 4.05 mmol) in the presence of triethylamine (820 mg, 8.10 mmol). After work-up, the crude material was chromatographed on silica gel (hexane/AcOEt, 25:1) to give **25** (644 mg, quantitative) as an oil: $[\alpha]_D^{21}$ –47.2° (*c* 1.0, EtOH); IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (300 MHz) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.27 (s, 3 H), 0.28

(s, 3 H), 0.89 (s, 9 H), 0.94 (d, J = 6.2 Hz, 3 H), 0.99 (s, 9 H), 1.37 (d, J = 7.1 Hz, 3 H), 2.71 (dd, J = 6.3, 2.5 Hz, 1 H, H-3), 3.03 (dq, J = 7.1, 5.0 Hz, 1 H), 3.65 (dd, J = 5.0, 2.5 Hz, 1 H, H-4), 3.79 (s, 3 H), 3.96 (quint, J = 6.2 Hz, 1 H, OCH), 6.72-6.81 (m, 3 H), 7.16-7.23 (m, 1 H). *Anal.* Calcd for $C_{26}H_{47}NO_3Si_2$: C, 65.35; H, 9.91; N, 2.93. Found: C, 65.34; H, 10.03; N, 2.89.

(2*R*)-2-{(2*R*,3*S*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-oxoazetidin-2-yl}propanoic Acid (26). To a solution of **25** (67 mg, 0.14 mmol) in CCl_4 (1.5 mL) and acetonitrile (1.5 mL) were added syccessively ruthenium dioxide monohydrate (2 mg) and a solution of sodium metaperiodate (612 mg, 2.8 mmol) in water (2.3 mL), and the mixture was stirred at room temperature for 3 h. To the reaction mixture was added 0.01 N HCl, and the whole was extracted with diethyl ether. The extract was washed three times with a saturated $NaHCO_3$ solution, and the alkaline solution was acidified to pH 3 with 10% HCl, then extracted with diethyl ether. The organic layer was washed with brine, and dried ($MgSO_4$). The solvent was evaporated off to give **26** as an oil: ^1H NMR (300 MHz) δ 0.06 (s, 3 H), 0.10 (s, 3 H), 0.21 (s, 3 H), 0.27 (s, 3 H), 0.89 (s, 9 H), 0.96 (s, 9 H), 1.23 (d, J = 7.2 Hz, 3 H), 1.27 (d, J = 6.1 Hz, 3 H), 2.95 (dq, J = 3.8, 7.2 Hz, 1 H), 3.31 (dd, J = 7.0, 2.5 Hz, 1 H, H-3), 3.71 (dd, J = 3.8, 2.5 Hz, 1 H, H-4), 4.06 (quint, J = 6.6 Hz, 1 H, OCH): the peak due to the carboxylic acid was not observed. This compound was used in the next step without further purification.

Methyl (2*R*)-2-{(2*R*,3*S*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-oxoazetidin-2-yl}propanoate (27). The above compound **26** was dissolved in benzene (0.7 mL) and methanol (0.2 mL). To this was added trimethylsilyldiazomethane (2 M in hexane) (0.09 mL, 0.18 mmol), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **27** (38 mg, 62% based on **25**) as an oil: $[\alpha]_D^{22}$ −59.0° (*c* 0.98, EtOH); IR (CCl_4) ν 1740 cm^{-1};^1H NMR (300 MHz) δ 0.06 (s, 3 H), 0.09 (s, 3 H), 0.19 (s, 3 H), 0.26 (s, 3 H), 0.89 (s, 9 H), 0.96 (s, 9 H), 1.19 (d, J = 7.1 Hz, 3 H), 1.26 (d, J = 6.2 Hz, 3 H), 2.93 (dq, J = 3.8, 7.1 Hz, 1 H), 3.27 (dd, J = 7.2, 2.5 Hz, 1 H, H-4), 3.67 (dd, J = 3.8, 2.5 Hz, 1 H), 3.68 (s, 3 H), 3.99-4.09 (m, 1 H). *Anal.* Calcd for $C_{21}H_{43}NO_4Si_2$: C, 58.69; H, 10.08; N, 3.26. Found: C, 58.79; H, 10.21; N, 3.19.

Methyl (2*R*)-2-{(2*R*,3*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-oxoazetidin-2-yl}propanoate (5). To an ice-cooled solution of **27** (38 mg, 0.09 mmol) in dry THF (1 mL) were added successively acetic acid (5 mg, 0.18 mmol) and tetrabutylammonium fluoride (TBAF) (1 M in THF) (0.1 mL, 0.1 mmol), and the mixture was stirred at room temperature for 30 min. Water was added to the reaction mixture, and the whole was extracted with CH_2Cl_2. The extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 40:1) to give **5** (28 mg, quantitative): mp 118.5–119 °C (hexane) [lit.[7] mp 120–121 °C]; $[\alpha]_D^{24}$ −20.9° (*c* 0.45, CH_2Cl_2) {lit.[7] $[\alpha]_D^{24}$ −21.0° (*c* 2.09, CH_2Cl_2)}; IR (CCl_4) ν 3560, 3360, 1760, 1745 cm^{-1};^1H NMR (300 MHz) δ 0.068 (s, 3 H), 0.071 (s, 3 H), 0.87 (s, 9 H), 1.16 (d, J = 6.3 Hz, 3 H), 1.23 (d, J = 7.1 Hz, 3 H), 2.70 (quint, 1 H), 2.99 (dd, J = 4.2, 2.2 Hz, 1 H, H-3), 3.70 (s, 3 H), 3.88 (dd, J = 6.1, 2.2 Hz, 1 H, H-2), 4.20 (dq, J = 4.2, 6.3 Hz, 1 H), 6.13 (br s, 1 H, NH). *Anal.* Calcd for $C_{15}H_{29}NO_4Si$: C, 57.11; H, 9.26; N, 4.44. Found: C, 57.30; H, 9.35; N, 4.47.

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