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Synthesis of 4-Oxo-2-azetidineacetic Acids by Means of Radical Cyclization of *N*-Vinylic α-Bromo Amides

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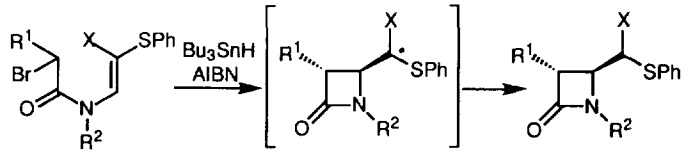
Abstract: Bu_3SnH-mediated radical cyclization of α-bromo amide **8**, bearing phenyl and phenylthio substituents at the terminus of the *N*-vinylic bond, proceeded in a 4-*exo-trig* manner to give β-lactam **9**. Ruthenium tetroxide oxidation of the phenyl group incorporated into the product **9** provided a new synthesis of 4-oxo-2-azetidineacetic acid **13**, a usuful intermediate for (±)-PS-5. Chiral 4-oxo-2-azetidineacetic acids **23** and **36**, key intermediates for the synthesis of (+)-PS-5 and (+)-thienamycin, respectively, were also obtained through the asymmetric radical cyclization of *N*-vinylic α-bromo amides having chiral auxiliaries at the side chain. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

In a series of papers concerning the synthesis of nitrogen-containing heterocycles using Bu_3SnH-mediated radical cyclization of α-halo amides,[1] we reported that α-bromo amides **1** bearing sulfur substituent(s) at the terminus of the *N*-vinylic bond, upon treatment with Bu_3SnH in the presence of azobis(isobutyronitrile) (AIBN), underwent radical cyclization to give β-lactams **3**.[2] Formation of **3** from **1** can be best explained in terms of the 4-*exo-trig* cyclization of the radical intermediate generated from **1** leading to the sulfur-stabilized new radicals **2**. The sulfur-substituent incorporated into the products **3** served as a handle for the elaboration of functionalities required for the synthesis of key intermediates of the carbapenem antibiotics such as PS-5 and thienamycin. In practice, however, it happened that the homologation of the carbon atom in the chemical transformation of **3** was somewhat tedious in terms of the number of step. Therefore, our attention has been turned to the use of the phenyl group in **3** (X = Ph) as a synthetic equivalent of carboxylic acid.[3] The phenyl



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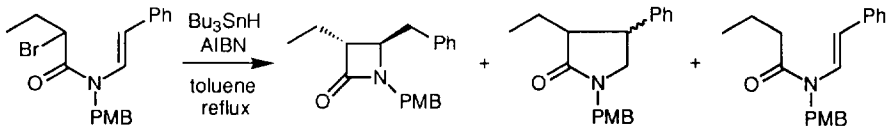
group used would also act as a radical stabilizing group in effecting the 4-*exo-trig* radical cyclization leading to β-lactams. Herein we report an application of this methodology to the synthesis of 4-oxo-2-azetidineacetic acids which are versatile intermediates for the synthesis of many therapeutically important carbapenem antibiotics.[4]

RESULTS AND DISCUSSION

We initiated our investigation by examining the cyclization of *N*-(2-phenylethenyl)-2-bromobutanamide **4**, which was prepared by condensation of phenylacetaldehyde and *p*-methoxybenzylamine followed by *N*-acylation of the resulting imine with 2-bromobutyryl bromide. When bromide **4** was treated slowly with Bu_3SnH in the presence of a catalytic amount of AIBN in boiling toluene, an inseparable mixture containing an approximately equal portion of the expected β-lactam **5** and the 5-*endo-trig* cyclization product **6** was obtained in 31% combined yield. The major product was a simple reduction product **7** (41%) (Scheme 1). The structures of **5** and **6** were deduced from IR [1745 cm^{-1} for **5** and 1685 cm^{-1} for **6**, respectively] and ^1H NMR (see Experimental) spectra of the mixture.[5] This result clearly indicates that the phenyl group alone is insufficient to stabilize the radical intermediate such as **2** formed by 4-*exo-trig* cyclization of bromide **4**.[6]

Scheme 1

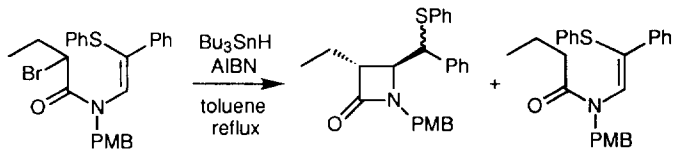


4 **5** **6** **7**

PMB = *p*-Methoxybenzyl

We then examined the cyclization of amide **8** having a phenylthio group as an additional radical stabilizing group. Compound **8**[7] was readily prepared from 2-phenyl-2-(phenylthio)acetaldehyde using a procedure similar to that described for **4**. As expected, the cyclization of **8** proceeded with high efficiency to give the desired β-lactam **9** in 58% yield as a mixture of two diastereoisomers (based on PhS group) in a ratio of 2.7:1; only a trace amount of the reduction product **10** was formed (Scheme 2).

Scheme 2

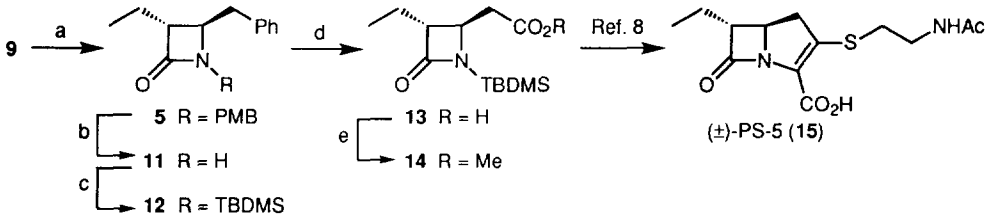


8 **9** **10**

Compound **9** was further treated with Bu3SnH-AIBN in boiling benzene to give the desulfurized β-lactam **5** in 94% yield as a single stereoisomer, which was identical to the compound **5** obtained from **4** (Scheme 3).

Compound **5** could be converted to the key intermediate **14**[8] for the synthesis of carbapenem antibiotic (±)-PS-5 (**15**). Thus, removal of the *N*-*p*-methoxybenzyl group of **5** with ceric ammonium nitrate (CAN) followed by reprotection of the resulting azetidinone **11** with TBDMSCl afforded **12** in 77% yield (based on **5**). The oxidation of the phenyl group of **12** to the corresponding carboxylic acid with RuO_2-$NaIO_4$ was very sluggish, and, after stirring the mixture for 3 days, the desired carboxylic acid **13** was obtained in good yield (72% based on **11**). Finally, compound **13** was esterified with trimethylsilyldiazomethane to give **14** quantitatively. Transformation of **14** to (±)-PS-5 (**15**) has already been described in the literature.[8,9]

Scheme 3[a]

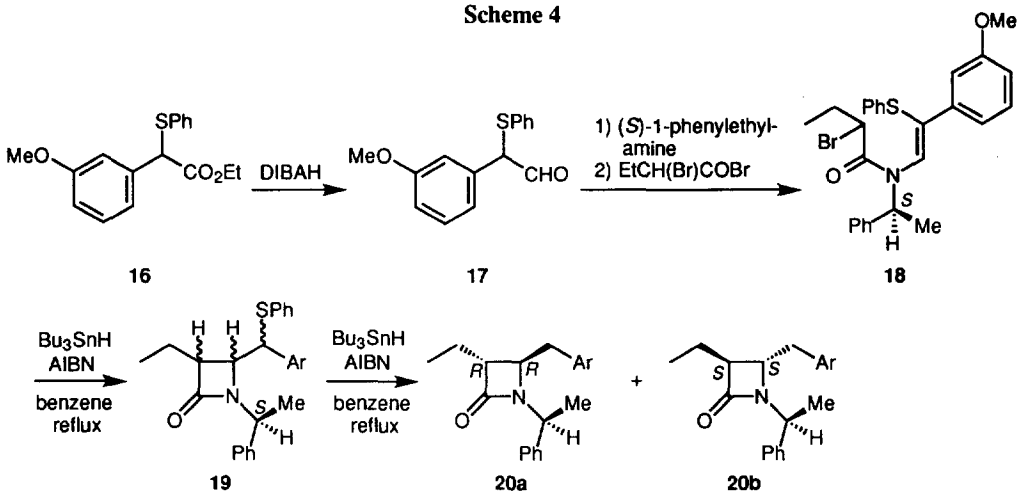


[a] (a) Bu_3SnH, AIBN, benzene, reflux (94%); (b) CAN, CH_3CN-H_2O (1:2), r. t. (77%); (c) TBDMSCl, Et_3N, DMF, r. t. (quant.); (d) RuO_2-H_2O, $NaIO_4$, CCl_4-CH_3CN-H_2O (1:1:1.5), r. t. (72%); (e) Me_3SiCHN_2, benzene-MeOH (4:1), r. t. (quant.).

Asymmetric induction in radical cyclization is currently a field of intense research.[10] A previous paper from our laboratory reported that the radical cyclization of *N*-vinylic α-bromo amide **1** (X = SPh, R^1 = Et) bearing (*S*)-1-phenylethyl group on the nitrogen atom proceeded with some degree of diastereoselectivity (70:30) to give (3*S*,4*R*)-isomer of azetidinone **3** as the major product.[2c] Encouraged by the success of the radical cyclization of **8** having the phenyl group at the terminus of the *N*-vinylic bond and the transformation of the product **9** into 4-oxo-2-azetidineacetic acid **13**, we then examined the diastereoselectivity in radical cyclization of **18** bearing (*S*)-1-phenylethyl group on the nitrogen atom in the hope that it might provide a new route to a chiral intermediate for (+)-PS-5. Since the ruthenium tetroxide oxidation of the phenyl group of **12** required a long reaction time (3 days), more electron-rich *m*-methoxyphenyl group was used as a synthetic equivalent of carboxylic acid.

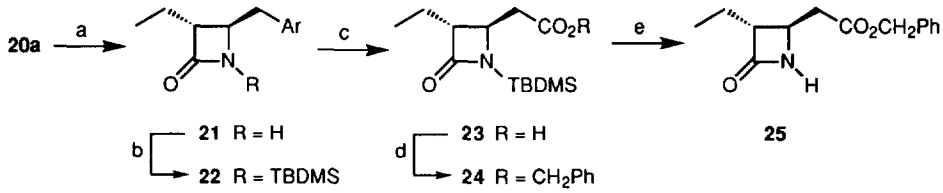
The starting aldehyde **17** was prepared by reduction of the corresponding ester **16** with diisobutylaluminum hydride (DIBAH) (Scheme 4). Treatment of enamide **18**, prepared from **17** and (*S*)-1-phenylethylamine, with Bu_3SnH-AIBN in boiling benzene[11] provided a mixture of four diastereoisomers of **19** in a ratio of 53:24:15:8 and in 56% combined yield. Desulfurization of the mixture **19** with Bu_3SnH-AIBN followed by chromatographic separation of the resulting new mixture provided (3*R*,4*R*)-2-azetidinone **20a** in 61% yield as a single stereoisomer together with its (3*S*,4*S*)-isomer **20b** (25%). The stereochemistry of **20a** was confirmed by its chemical transformation into the known compound **25** (see below). This result indicates that the absolute configuration of the C-3 and C-4 positions of the major isomers of the radical cyclization products **19** to be *R* and *S*, respectively, and hence the (3*R*,4*S*) selectivity of the radical cyclization of **18** giving **19** seems to be (53+15): (24+8) = 68:32.

Scheme 4



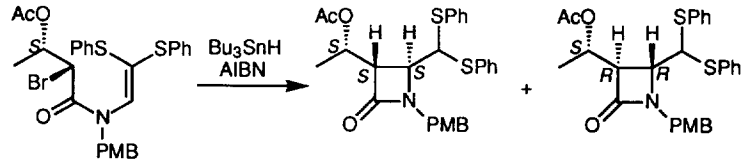
The *N*-phenethyl group of **20a** was removed with sodium in liquid ammonia, and the resulting azetidinone **21** was reprotected with TBDMSCl to give **22** in 91% yield (based on **20a**) (Scheme 5). Compound **22** was then subjected to the ruthenium tetroxide oxidation. As expected, the oxidation of the *m*-methoxyphenyl group of **22** occurred smoothly and was completed within 3 h to give, quantitatively, the desired carboxylic acid **23**. Next, compound **23** was esterified by the Kim's method[12] (benzyloxycarbonyl chloride/Et_3N/DMAP) to give benzyl ester **24**, which was treated with tetrabutylammonium fluoride to remove the silyl group giving the known 4-oxo-2-azetidineacetic acid benzyl ester **25** in 76% yield (based on **23**) [$[\alpha]^{25}_D$ +37.3° (*c* 1.34, $CHCl_3$), lit.[13] $[\alpha]^{25}_D$ +33.7° (*c* 1.11, $CHCl_3$)]. Since the conversion of compound **25** into (+)-PS-5 has previously been reported in the literature,[13,14] the whole sequence of the reactions described above constitutes, in a formal sense, a total synthesis of (+)-PS-5.

Scheme 5[a]



[a] Ar = *m*-methoxyphenyl; (a) Na, NH_3, THF, -78°C (91%); (b) TBDMSCl, Et_3N, DMF, r. t. (quant.); (c) RuO_2-H_2O, $NaIO_4$, CCl_4-CH_3CN-H_2O (1:1:1.5), r. t. (quant.); (d) $PhCH_2OCOCl$, Et_3N, DMAP, CH_2Cl_2, r. t. (76%); (e) Bu_4NF, AcOH, THF, 0°C (quant.).

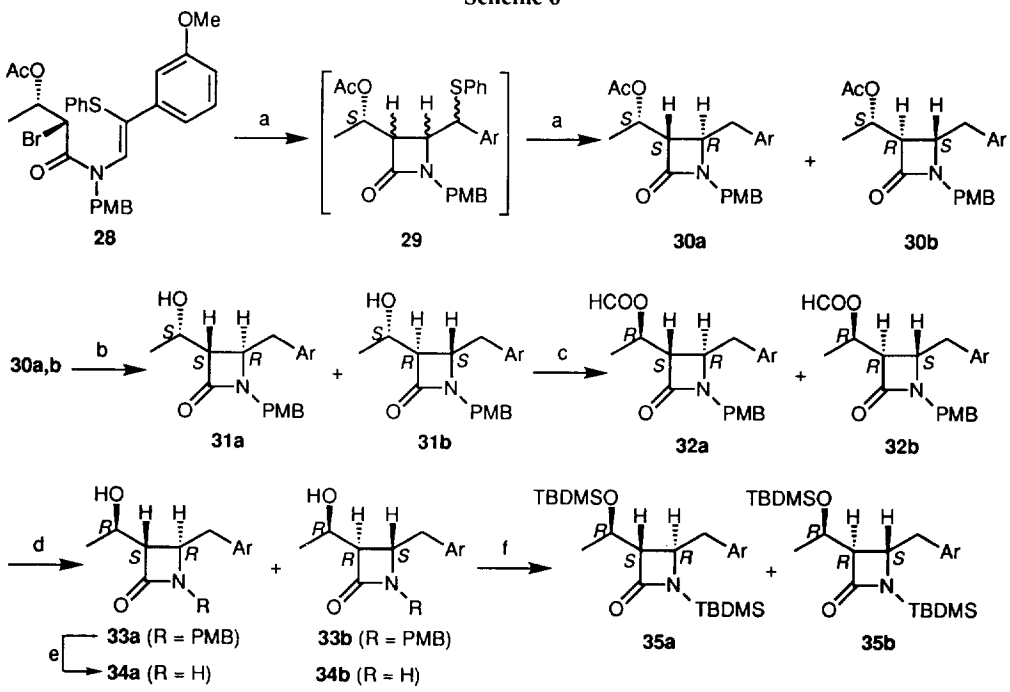
In our previous studies on the asymmetric radical cyclization of α-halo amides, we also reported that bromide **26** bearing an (*S*)-oxygen functionality at the side chain, upon treatment with Bu_3SnH in the presence of AIBN, gave (3*S*,4*S*)-2-azetidinone **27a** as the major product together with its (3*R*,4*R*)-isomer **27b** in a ratio of 67:33.[2a] So we then turned our attention to the diastereoselectivity in cyclization of bromide **28**.



26 **27a** **27b**

Compound **28**[7] was prepared by condensation of aldehyde **17** with *p*-methoxybenzylamine followed by *N*-acylation of the resulting imine with (2*R*,3*S*)-3-acetoxy-2-bromobutyryl chloride.[2a] Treatment of **28** with Bu_3SnH in the presence of AIBN in boiling benzene gave a mixture of four diasteroisomers of β-lactam **29** in

Scheme 6[a]



28 **29** **30a** **30b**

31a **31b** **32a** **32b**

35a **35b**

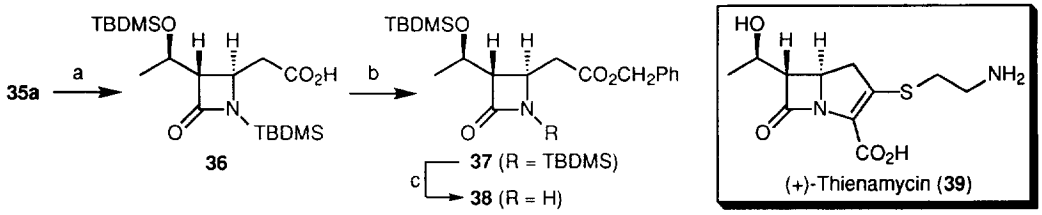
[a] PMB = *p*-methoxybenzyl; Ar = *m*-methoxyphenyl; (a) Bu_3SnH, AIBN, benzene, reflux (66% for **30a,b** from **28**); (b) 1 N NaOH, pyridine, r. t. (95%); (c) (*iso*-PrOCON=)$_2$, PPh_3, HCO_2H, THF, r. t. (81%); (d) 10% HCl, MeOH, r. t. (92%); (e) CAN, CH_3CN-H_2O (1:1), r. t. (50%); (f) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, r. t. (73% for **35a**, 27% for **35b**).

good yield (Scheme 6). However, purification of the mixture containing four isomers by column chromatography on silica gel failed due to the contamination of the side-products. The crude meterial was then treated with Bu_3SnH-AIBN in boiling benzene to give a mixture of the desulfurized (3*S*,4*R*)-2-azetidinone **30a** and its (3*R*,4*S*)-isomer **30b** in 66% combined yield (based on **28**). The ^1H NMR spectrum of the mixture showed the ratio of **30a** and **30b** to be 67:33, which was identical with that of **27a** and **27b**. The absolute configuration of the major product **30a** was established by its chemical transformation to the intermediate **38** for the synthesis of (+)-thienamycin (**39**) (see below).

The major isomer **30a** could be separated from the other by transfoming it to the compound **35a** through inversion of configuration of the oxygen functionality in five steps (Scheme 6). Thus, the ester moiety of **30a,b** was saponified with 1 N NaOH in pyridine to give a mixture of (*S*)-alcohols **31a,b** (69:31) in 95% yield. The Mitsunobu reaction (HCO_2H, diisopropyl azodicarboxylate, PPh_3) of the mixture **31a,b** gave, in 81% yield, a mixure of formates **32a,b** (73:27), which was hydrolyzed with 10% HCl in MeOH to give a mixture of (*R*)-alcohols **33a,b** (76:24) in 92% yield. Deprotection of the *N*-*p*-methoxybenzyl groups of **33a,b** with CAN (50% yield) followed by disilylation of both the OH and lactam NH groups of **34a,b** (76:24) with *tert*-butyldimethylsilyl trifluoromethanesulfonate afforded **35a** and **35b** in 73 and 27% isolated yields, respectively.

Compound **35a** thus obtained as a pure form was converted into the key intermediate **38** for (+)-thienamycin (**39**) in three steps (Scheme 7). The ruthenium tetroxide oxidation of **35a** afforded carboxylic acid **36**, which was then esterified by the Kim's method to give benzyl ester **37** in 51% yield (based on **35a**). Finally, only the *N*-silyl group was deprotected with tetrabutylammonium fluoride in the presence of AcOH to give **38** [mp 91-92 °C, $[\alpha]^{23}_D$ +17.6° (*c* 0.42, $CHCl_3$); lit.[13] mp 92-93 °C, $[\alpha]^{24}_D$ +17.4° (*c* 1.75, $CHCl_3$)]. Compound **38** has already been converted into (+)-thienamycin,[15] and hence we succeeded in a formal synthesis of (+)-thinamycin by using an asymmetric radical cyclization of α-bromo amide.

Scheme 7[a]



[a] (a) RuO_2-H_2O, $NaIO_4$, CCl_4-CH_3CN-H_2O (1:1:1.5), r. t.; (b) $PhCH_2OCOCl$, Et_3N, DMAP, CH_2Cl_2, 0 °C (51% from **35a**); (c) Bu_4NF, AcOH, THF, 0 °C (quant.).

Thus, we revealed that α-bromo amides bearing *m*-methoxyphenyl and phenylthio substituents at the terminus of the *N*-vinylic bond underwent radical cyclization in a 4-*exo*-*trig* manner exclusively to give β-lactams. The ruthenium tetroxide oxidation of the methoxyphenyl group incorporated into the products offers an alternate, useful route to 4-oxo-2-azetidineacetic acid derivatives which are versatile intermediates for the preparation of carbapenem antibiotics.

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, a JEOL JNM-EX 270, 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) were obtained with a Hitachi M-80 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-phenylethenyl)butanamide (4). *p*-Methoxybenzylamine (1.03 g, 7.51 mmol) and $MgSO_4$ (1 g) were added to a solution of phenylacetaldehyde (903 mg, 7.51 mmol) in diethyl ether (50 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h. $MgSO_4$ was filtered off, the filtrate was concentrated *in vacuo*, and the residue containing the crude imine was dissolved in toluene (30 mL). To this solution was added molecular sieves 3A (500 mg) and the mixture was stirred at room temperature for 5 min, then cooled to -78 °C. *N,N*-Diethylaniline (1.12 g, 7.51 mmol) and (±)-2-bromobutyryl bromide (2.59 g, 11.27 mmol) were added successively to the solution at -78 °C, and the mixture was stirred at the same temperature for 1 h and then at room temperature for 2 h. Water was added to the reaction mixture and the whole was extracted with AcOEt. 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, 15:1) to give **4** (1.0 g, 34%) as an oil: IR (CCl_4) ν 1670, 1640 cm^{-1}; ^1H NMR for the major rotamer (300 MHz) δ 1.08 (t, *J* = 7.3 Hz, 3 H), 2.14-2.34 (m, 2 H), 3.78 (s, 3 H), 4.57 (t, *J* = 7.1 Hz, 1 H), 4.90 (d, *J* = 15.4 Hz, 1 H), 5.02 (d, *J* = 15.4 Hz, 1 H), 6.15 (d, *J* = 14.2 Hz, 1 H), 6.81-7.37 (m, 10 H). HRMS (FAB) Calcd for $C_{20}H_{23}{}^{79}BrNO_2$ [(M+H)$^+$]: 388.0912. Found: 388.0896.

(2*R, 3*R**)-3-Ethyl-1-[(4-methoxyphenyl)methyl]-4-phenylmethyl-2-azetidinone (5), 3-Ethyl-1-[4-(methoxyphenyl)methyl]-4-phenyl-2-pyrrolidone (6), and *N*-[(4-Methoxyphenyl)-methyl]-*N*-(2-phenylethenyl)butanamide (7). General Procedure for Radical Cyclization.** To a boiling solution of **4** (171 mg, 0.44 mmol) in toluene (44 mL) was added a solution of Bu_3SnH (154 mg, 0.53 mmol) and AIBN (7 mg, 0.04 mmol) in toluene (44 mL) *via* a syringe over 4 h, and the mixture was 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, 7:1). The first eluent gave **7** (56 mg, 41%) as an oil: IR (CCl_4) ν 1670, 1640 cm^{-1}; ^1H NMR for major rotamer (300 MHz) δ 1.04 (t, *J* = 7.4 Hz, 3 H), 1.73-1.87 (m, 2 H), 2.64 (t, *J* = 7.4 Hz, 2 H), 3.78 (s, 3 H), 4.94 (s, 2 H), 6.00 (d, *J* = 14.2 Hz, 1 H), 6.83-7.36 (m, 10 H). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.30; H, 7.62; N, 4.56.

The second eluent gave a mixture of **5** and **6** (42 mg, 31%) as an oil: IR (CCl_4) ν 1745 (for **5**), 1685 (for **6**) cm^{-1}; ^1H NMR for **5** (300 MHz) δ 0.67 (t, *J* = 7.5 Hz, 3 H), 1.35-1.51 (m, 1 H), 1.57-1.72 (m, 1 H), 2.69 (dd, *J* = 13.5, 7.9 Hz, 1 H, one of CH_2Ph), 2.79 (ddd, *J* = 7.9, 5.6, 1.9 Hz, 1 H, H-3), 2.94 (dd, *J* = 13.5, 6.0 Hz, 1 H, one of CH_2Ph), 3.29 (ddd, *J* = 7.9, 6.0, 1.9 Hz, 1 H, H-4), 3.80 (s, 3 H), 3.86 (d, *J* = 14.9 Hz, 1 H, one of NCH_2), 4.62 (d, *J* = 14.9 Hz, 1 H, one of NCH_2), 6.82 (d, *J* = 8.7 Hz, 2 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 7.06-7.13 (m, 2 H), 7.18-7.32 (m, 3 H); ^1H NMR for the major stereoisomer of **6** (300 MHz) δ 0.93 (t, *J* = 7.4 Hz), 1.75-1.90 (m), 2.52-2.64 (m), 3.05-3.20 (m), 4.39 (d, *J* = 14.4 Hz), 4.41 (d, *J* = 14.4 Hz). A small peak due to the *C*-methyl protons of the minor stereoisomer of **6** appeared at δ 1.22 (t, *J* = 7.5 Hz). The ^1H NMR spectrum of **5** was identical to that of compound **5** obtained by desulfurization of **9** (see below). HRMS Calcd for $C_{20}H_{23}NO_2$: 309.1729. Found: 309.1740.

2-Phenyl-2-(phenylthio)acetaldehyde. 2-Chloro-2-phenylacetyl chloride (1.2 g, 6.33 mmol) was added to absolute ethanol (10 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. To this solution containing ethyl 2-chloro-2-phenylacetate was added a solution of sodium thiophenoxide [prepared from thiophenol (836 mg, 7.6 mmol) and sodium methoxide (444 mg, 8.23 mmol) in absolute ethanol (10 mL)] at 0 °C, and the mixture was stirred at room temperature for 24 h. The precipitated salts were removed by filtration and the filtrate was concentrated *in vacuo*. To the residue was added water (30 mL), and the whole was extracted with diethyl ether. The extract was washed successively with 10% 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, 30:1) to give ethyl 2-phenyl-2-(phenylthio)acetate (1.84 g, quant.) as an oil; ^1H NMR (CCl_4, 60 MHz) δ 1.13 (t, *J* = 7.0 Hz, 3 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 4.87 (s, 1 H), 7.0-7.6 (m, 10 H). HRMS Calcd for $C_{16}H_{16}O_2S$: 272.0871. Found: 272.0886.

To a solution of the above ester (530 mg, 1.95 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise a solution of diisobutylaluminum hydride (DIBAH) [0.93 mol/L in hexane] (2.3 mL, 2.14 mmol) at -50 °C, and

the mixture was stirred at the same temperature for 1 h. MeOH (1 mL) was added to the reaction mixture, and the whole was stirred at room temperature for 10 h. The precipitated salts were removed by filtration, and the remaining salts were dissolved in 10% NaOH solution, and the resulting alkaline solution was extracted with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/AcOEt, 30:1) to give 2-phenyl-2-(phenylthio)acetaldehyde[16] (332 mg, 75%) as an oil; ^1H NMR (60 MHz) δ 4.70 (d, J = 4.5 Hz, 1 H), 6.9-7.5 (m, 10 H), 9.43 (d, J = 4.5 Hz, 1 H).

2-Bromo-*N*-[(4-methoxyphenyl)methyl]-*N*-[2-phenyl-2-(phenylthio)ethenyl]butanamide (8). Using a procedure similar to that described above for **4**, 2-phenyl-2-(phenylthio)acetaldehyde (1.06 g, 4.64 mmol) was treated with *p*-methoxybenzylamine (637 mg, 4.64 mmol), and the resulting imine was treated with (±)-2-bromobutyryl bromide (2.13 g, 9.28 mmol) in the presence of *N,N*-diethylaniline (692 mg, 4.64 mmol) at room temperature. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 12:1) to give **8** (1.61 g, 70%) as an oil: IR (CCl_4) ν 1660 cm^{-1}; ^1H NMR for the major rotamer (270 MHz) δ 0.98 (t, J = 7.1 Hz, 3 H), 2.00-2.14 (m, 2 H), 3.80 (s, 3 H), 4.34 (t, J = 7.3 Hz, 1 H), 4.67 (d, J = 14.5 Hz, 1 H), 5.05 (d, J = 14.5 Hz, 1 H), 6.52 (s, 1 H), 6.86 (d, J = 8.9 Hz, 2 H), 7.02-7.42 (m, 12 H). Anal. Calcd for $C_{26}H_{26}BrNO_2S$: C, 62.90; H, 5.28; N, 2.82. Found: C, 62.65; H, 5.31; N, 3.10.

(3*R,4*R**)-3-Ethyl-1-[(4-methoxyphenyl)methyl]-4-[phenyl(phenylthio)methyl]-2-azetidinone (9).** Following the general procedure, compound **8** (1.64 g, 3.30 mmol) was treated with Bu_3SnH (960 mg, 3.96 mmol) in the presence of AIBN (66 mg, 0.40 mmol) in boiling toluene. After usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 15:1) to give an oily mixture of two diastereoisomers of **9** (794 mg, 58%): IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR for the major isomer (270 MHz) δ 0.55 (t, J = 7.4 Hz, 3 H), 1.20-1.53 (m, 2 H), 2.70-2.79 (m, 1 H, H-3), 3.46 (dd, J = 8.9, 2.1 Hz, 1 H, H-4), 3.83 (s, 3 H), 4.19 (d, J = 8.9 Hz, 1 H, SCH), 4.37 (d, J = 14.8 Hz, 1 H, one of NCH_2), 4.89 (d, J = 14.8 Hz, 1 H, one of NCH_2), 6.90 (d, J = 8.6 Hz, 2 H), 7.09-7.30 (m, 12 H); ^1H NMR for the minor isomer (270 MHz) δ 0.96 (t, J = 7.3 Hz), 1.20-1.53 (m), 3.02-3.10 (m), 3.10 (d, J = 14.9 Hz), 3.51 (dd, J = 8.6, 2.0 Hz), 3.78 (s), 4.18 (d, J = 8.6 Hz), 4.52 (d, J = 14.9 Hz). The ratio of the major and the minor isomers of **9** was estimated to be *ca.* 2.7:1 by an integrated intensity of the peak heights of the signals due to their *O*-methyl protons appeared at δ 3.83 (s) and 3.78 (s), respectively. Anal. Calcd for $C_{26}H_{27}NO_2S$: C, 74.79; H, 6.16; N, 3.35. Found: C, 74.85; H, 6.54; N, 3.36.

Desulfurization of 9. Formation of 5. To a solution of **9** (764 mg, 1.83 mmol) in benzene (10 mL) were added Bu_3SnH (960 mg, 3.96 mmol) and AIBN (46 mg, 0.28 mmol), and the mixture was heated under reflux for 1.5 h. After usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **5** (533 mg, 94%) as an oil, whose ^1H NMR spectrum was identical to that of compound **5** obtained from **4**: IR (CCl_4) ν 1745 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.26; H, 7.89; H, 4.53.

(3*R,4*R**)-3-Ethyl-4-phenylmethyl-2-azetidinone (11).** To a solution of **5** (353 mg, 1.14 mmol) in acetonitrile (10 mL) was added dropwise a solution of ceric ammonium nitrate (CAN) (1.25 g, 2.28 mmol) in water (20 mL) at room temperature, and the mixture was stirred at the same temperature for 4 h. Water (30 mL) was added to the reaction mixture and the whole was extracted with diethy ether. The extract was washed 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, 3:1) to give **11** (167 mg, 77%) as an oil: IR (CCl_4) ν 3420, 3240, 1745 cm^{-1}; ^1H NMR (270 MHz) δ 0.85 (t, J = 7.4 Hz, 3 H), 1.50-1.84 (m, 2 H), 2.77-2.98 (m, 3 H, H-3 and CH_2Ph), 3.51 (ddd, J = 7.9, 6.6, 2.3 Hz, 1 H, H-4), 5.99 (br s, 1 H), 7.15-7.36 (m, 5 H). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.46. Found: C, 76.46; H, 7.83; N, 7.40.

(3*R,4*R**)-1-*tert*-Butyldimethylsilyl-3-ethyl-4-phenylmethyl-2-azetidinone (12).** To a solution of **11** (148 mg, 0.78 mmol) in DMF (6 mL) were added successively *tert*-butyldimethylsilyl chloride (235 mg, 1.56 mmol) and triethylamine (317 mg, 3.13 mmol), and the mixture was stirred at room temperature for 1.5 h. Diethyl ether (20 mL) was added to the reaction mixture, and the solution was washed with water and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **12** (240 mg, quant.) as an oil: IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (270 MHz) δ 0.18 (s, 3 H), 0.22 (s, 3 H), 0.42 (t, J = 7.4 Hz, 3 H), 0.91 (s, 9 H), 1.13-1.34 (m, 1 H), 1.37-1.52 (m, 1 H), 2.47 (dd, J = 12.9, 10.8 Hz, 1 H, one of CH_2Ph), 2.70 (ddd, J = 8.6, 5.9, 2.5 Hz, 1 H, H-3), 3.13 (dd, J = 12.9, 3.7, 1 H, one of CH_2Ph), 3.28 (ddd, J = 10.8, 3.7, 2.5 Hz, 1 H, H-4), 7.05-7.24 (m, 5 H). Anal. Calcd for $C_{18}H_{29}NOSi$: C, 71.23; H, 9.63; N, 4.61. Found: C, 71.37; H, 9.95; N, 4.53.

(2*R,3*R**)-1-*tert*-Butyldimethylsilyl-3-ethyl-4-oxo-2-azetidineacetic Acid (13).** To a solution of **12** (309 mg, 1.02 mmol) in CCl_4 (4.5 mL) and acetonitrile (4.5 mL) were added successively ruthenium dioxide monohydrate (2 mg) and a solution of $NaIO_4$ (4.36 g, 20. 36 mmol) in water (6.8 mL), and the mixture was stirred at room temperature for 3 days. 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 over $MgSO_4$. The solvent was evaporated off to give **13** (200 mg, 72%) as an oil: IR (CCl_4) ν 1740, 1705 cm^{-1}; ^1H NMR (270 MHz) δ 0.20 (s, 3 H), 0.25 (s, 3 H), 0.95 (s, 9 H), 1.00 (t, *J* = 7.4 Hz, 3 H), 1.64-1.87 (m, 2 H), 2.53 (dd, *J* = 15.8, 9.9 Hz, 1 H, one of CH_2COOH), 2.88 (dd, *J* = 15.8, 3.9, 1 H, one of CH_2COOH), 2.94 (dt, *J* = 2.3, 6.9 Hz, 1 H, H-3), 3.60 (ddd, *J* = 9.9, 3.9, 2.3 Hz, 1 H, H-2), 8.2-8.8 (br, 1 H, COOH). This compound was used in the next step without further purification.

Methyl (2*R,3*R**)-1-*tert*-Butyldimethylsilyl-3-ethyl-4-oxo-2-azetidineacetate (14).** To a solution of **13** (15 mg, 0.06 mmol) in benzene (0.35 mL) and methanol (0.1 mL) was added trimethylsilyldiazomethane (8 mg, 0.07 mmol) at room temperature, and the mixture was stirred at the same temperature for 1 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **14**[8] (17 mg, quant.), whose spectroscopic data were identical to the literature values: : IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (270 MHz) δ 0.20 (s, 3 H), 0.25 (s, 3 H), 0.96 (s, 9 H), 1.00 (t, *J* = 7.4 Hz, 3 H), 1.64-1.89 (m, 2 H), 2.50 (dd, *J* = 16.4, 10.0 Hz, 1 H, one of CH_2COOMe), 2.85 (dd, *J* = 16.4, 4.1, 1 H, one of CH_2COOMe), 2.85-2.92 (m, 1 H, H-3), 3.59 (ddd, *J* = 10.0, 4.1, 2.3 Hz, 1 H, H-2), 3.70 (s, 3 H, OMe). HRMS (FAB) Calcd for $C_{14}H_{28}NO_3Si$ [$(M+H)^+$]: 286.1839. Found: 286.1852.

Ethyl 2-(3-Methoxyphenyl)-2-(phenylthio)acetate (16). To a solution of lithium diisopropylamide (LDA) [prepared from diisopropylamine (1.58 g, 15.6 mmol) and butyllithium (1.63 M in hexane) (9.57 mL, 15.6 mmol)] in THF (20 mL) was added a solution of ethyl 2-(3-methoxyphenyl)acetate (1.01 g, 5.20 mmol) in THF (10 mL) at -78°C, and the mixture was stirred at the same temperature for 20 min and then at room temperature for 20 min. To this solution was added a solution of diphenyl disulfide (3.41 g, 15.6 mmol) in THF (10 mL) at -78°C, and the mixture was stirred at the same temperature for 20 min and then at room temperature for 1 h. A saturated NH_4Cl solution was added to the reaction mixture and the whole was extracted with diethyl ether. The organic layer was washed with a saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **16** (1.33 g, 85%) as an oil: IR (CCl_4) ν 1735 cm^{-1}; ^1H NMR (60 MHz) δ 1.13 (t, *J* = 7 Hz, 3 H), 3.73 (s, 3 H), 4.10 (q, *J* = 7 Hz, 2 H), 4.81 (s, 1 H), 6.6-7.5 (m, 9 H). HRMS Calcd for $C_{17}H_{18}O_3S$: 302.0977. Found: 302.0992.

2-(3-Methoxyphenyl)-2-(phenylthio)acetaldehyde (17). Using a procedure similar to that described above for 2-phenyl-2-(phenylthio)acetaldehyde, compound **16** (2.99 g, 9.87 mmol) was treated with DIBAH (0.98 M in hexane) (11.1 mL, 10.86 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 12:1) to give **17** (1.74 g, 68%) as an oil: IR (CCl_4) ν 1720 cm^{-1}; ^1H NMR (60 MHz) δ 3.74 (s, 3 H), 4.63 (d, *J* = 4 Hz, 1 H), 6.7-7.5 (m, 9 H), 9.43 (d, *J* = 4 Hz, 1 H). HRMS (FAB) Calcd for $C_{15}H_{15}O_2S$ [$(M+H)^+$]: 259.0793. Found: 259.0805.

(2*R* and 2*S*)-2-Bromo-*N*-[(*S*)-1-phenylethyl]-*N*-[2-(3-methoxyphenyl)-2-(phenylthio)-ethenyl]butanamides (18). Using a procedure similar to that described above for **4**, aldehyde **17** (1.74 g, 6.74 mmol) was treated with (*S*)-1-phenylethylamine (817 mg, 6.74 mmol), and the resulting imine was treated with (±)-2-bromobutyryl bromide (3.10 g, 13.48 mmol) in the presence of *N*,*N*-diethylaniline (2.01 g, 13.48 mmol) at room temperature. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1) to give **18** (2.03 g, 59%) as an oil: IR (CCl_4) ν 1660 cm^{-1}; ^1H NMR (300 MHz) δ 0.96, 0.99 (both t, *J* = 7.5 Hz, total 3 H), 1.64, 1.65 (both d, *J* = 7.1 Hz, total 3 H), 2.00-2.29 (m, 2 H), 3.67, 3.68 (both s, total 3 H), 4.53, 4.64 (both dd, *J* = 7.9, 6.3 Hz, total 1 H), 6.00, 6.37 (both s, total 1 H), 6.07, 6.15 (both q, *J* = 7.1 Hz, total 1 H), 6.51-7.56 (m, 14 H). HRMS (FAB) Calcd for $C_{27}H_{29}{}^{79}BrNO_2S$ [$(M+H)^+$]: 510.1103. Found: 510.1121.

3-Ethyl-4-[(3-methoxyphenyl)(phenylthio)methyl]-1-[(*S*)-1-phenylethyl]-2-azetidinones (19). Following the general procedure, compound **18** (683 mg, 1.34 mmol) was treated with Bu_3SnH (429 mg, 1.47 mmol) in the presence of AIBN (22 mg, 0.13 mmol) in boiling benzene. After usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1) to give an oily mixture of four diastereoisomers of **19** (323 mg, 56%): IR (CCl_4) ν 1745 cm^{-1}; ^1H NMR for the major isomer (300 MHz) δ 0.65 (t, *J* = 7.5 Hz, 3 H), *ca.* 1.3-1.5 (m, 2 H), 1.85 (d, *J* = 7.2 Hz, 3 H), 2.70-2.76 (m, 1 H, H-3), 3.42 (dd, *J* = 8.1, 2.2 Hz, 1 H, H-4), 3.73 (s, 3 H), 4.16 (d, *J* = 8.1 Hz, 1 H, SCH), 4.92 (q, *J* = 7.2 Hz, 1 H), 6.62-

7.50 (m, 14 H). The ratio of four diastereoisomers of **19** was estimated to be 53:24:15:8 by an integrated intensity of the peak heights of the signals due to their SCH protons appeared at δ 4.16 (d, J = 8.1 Hz), 3.92 (d, J = 8.7 Hz), 4.08 (d, J = 7.8 Hz), and 4.01 (d, J = 7.6 Hz), respectively. Anal. Calcd for $C_{27}H_{29}NO_2S$: C, 75.14; H, 6.77; N, 3.25. Found: C, 74.84; H, 6.98; N, 3.04.

(3*R*,4*R*)-3-Ethyl-4-(3-methoxyphenylmethyl)-1-[(*S*)-1-phenylethyl]-2-azetidinone (20a) and (3*S*,4*S*)-3-Ethyl-4-(3-methoxyphenylmethyl)-1-[(*S*)-1-phenylethyl]-2-azetidinone (20b). To a solution of **19** (549 mg, 1.27 mmol) in benzene (10 mL) were added Bu_3SnH (555 mg, 1.91 mmol) and AIBN (31 mg, 0.19 mmol), and the mixture was heated under reflux for 1.5 h. After usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 12:1). The first eluent gave **20a** (255 mg, 62%) as an oil: $[\alpha]^{24}_D$ +6.7° (*c* 1.16, EtOH)]; IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (300 MHz) δ 0.64 (t, J = 7.4 Hz, 3 H), 1.36-1.49 (m, 1 H), 1.55-1.68 (m, 1 H), 1.74 (d, J = 7.1 Hz, 3 H), 2.46 (dd, J = 13.4, 8.9 Hz, 1 H, one of CH_2Ph), 2.72 (ddd, J = 7.8, 5.6, 2.0 Hz, 1 H, H-3), 2.77 (dd, J = 13.4, 4.9 Hz, 1 H, one of CH_2Ph), 3.30 (ddd, J = 8.9, 4.9, 2.0 Hz, 1 H, H-4), 3.76 (s, 3 H), 4.59 (q, J = 7.1 Hz, 1 H, NCH), 6.54-6.77 (m, 3 H), 7.14-7.38 (m, 6 H). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.83; H, 7.84; N, 4.50.

The second eluent gave **20b** (103 mg, 25%) as an oil: $[\alpha]^{25}_D$ -9.0° (*c* 1.16, EtOH)]; IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (300 MHz) δ 0.55 (t, J = 7.4 Hz, 3 H), 1.25-1.40 (m, 1 H), 1.47-1.60 (m, 1 H), 1.66 (d, J = 7.2 Hz, 3 H), 2.56 (dd, J = 13.2, 9.8 Hz, 1 H, one of CH_2Ar), 2.72 (ddd, J = 8.6, 5.6, 2.0 Hz, 1 H, H-3), 2.99 (dd, J = 13.2, 4.6 Hz, 1 H, one of CH_2Ar), 3.21 (ddd, J = 9.8, 4.6, 2.0 Hz, 1 H, H-4), 3.74 (s, 3 H), 4.91 (q, J = 7.2 Hz, 1 H, NCH), 6.51-6.76 (m, 3 H), 7.12-7.41 (m, 6 H). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.74; H, 7.88; N, 4.53.

(3*R*,4*R*)-3-Ethyl-4-(3-methoxyphenylmethyl)-2-azetidinone (21). Sodium (53 mg, 2.28 mmol) and a solution of **20a** (247 mg, 0.76 mmol) in dry THF (2 mL) were added successively to liquid ammonia (5 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 (3 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 residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **21** (153 mg, 91%) as an oil: $[\alpha]^{21}_D$ -10.4° (*c* 0.78, EtOH)]; IR (CCl_4) ν 3460, 3250, 1750 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 7.4 Hz, 3 H), 1.53-1.84 (m, 2 H), 2.79-2.85 (m, 1 H, H-3), 2,83 (dd, J = 13.1, 7.6 Hz, 1 H, one of CH_2Ar), 2.91 (dd, J = 13.1, 6.0 Hz, 1 H, one of CH_2Ar), 3.50 (ddd, J = 7.6, 6.0, 2.1 Hz, 1 H, H-4), 3.80 (s, 3 H), 5.96 (br s, 1 H, NH), 6.71-6.82 (m, 3 H), 7.24 (t, J = 7.8 Hz, 1 H). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.05; H, 7.83; N, 6.21.

(3*R*,4*R*)-1-*tert*-Butyldimethylsilyl-3-ethyl-4-(3-methoxyphenylmethyl)-2-azetidinone (22). Using a procedure similar to that described above for **12**, compound **21** (78 mg,, 0.36 mmol) was treated with TBDMSCl (107 mg, 0.72 mmol) in the presence of triethylamine (146 mg, 1.44 mmol) in DMF (3 mL). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 15:1) to give **22** (119 mg, quant.) as an oil: $[\alpha]^{24}_D$ -36.8° (*c* 1.11, EtOH)]; IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (300 MHz) δ 0.27 (s, 3 H), 0.32 (s, 3 H), 0.56 (t, J = 7.4 Hz, 3 H), 1.01 (s, 9 H), 1.30-1.46 (m, 1 H), 1.50-1.65 (m, 1 H), 2.54 (dd, J = 13.0, 10.8 Hz, 1 H, one of CH_2Ar), 2.80 (ddd, J = 8.5, 5.8, 2.4 Hz, 1 H, H-3), 3.20 (dd, J = 13.0, 3.8 Hz, 1 H, one of CH_2Ar), 3.39 (ddd, J = 10.8, 3.8, 2.4 Hz, 1 H, H-4), 3.80 (s, 3 H), 6.68-6.80 (m, 3 H), 7.22 (t, J = 7.8 Hz, 1 H). Anal. Calcd for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 68.52; H, 9.55; N, 4.17.

(2*R*,3*R*)-1-*tert*-Butyldimethylsilyl-3-ethyl-4-oxo-2-azetidineacetic Acid (23). Using a procedure similar to that described above for **13**, compound **22** (117 mg, 0.35 mmol) was treated with RuO_2-H_2O (2 mg) and $NaIO_4$ (1.50 g, 7.00 mmol). The reaction was completed within 3 h. Workup gave the carboxylic acid **23** (95 mg, quant.) as an oil, whose IR and ^1H NMR spectra were identical to those of **13** obtained from **12**. HRMS (FAB) Calcd for $C_{13}H_{26}NO_3Si$ [$(M+H)^+$]: 272.1682. Found: 272.1706.

Benzyl (2*R*,3*R*)-1-*tert*-Butyldimethylsilyl-3-ethyl-4-oxo-2-azetidineacetate (24). To an ice-cooled solution of **23** (155 mg, 0.57 mmol) in CH_2Cl_2 (3 mL) were added successively triethylamine (69 mg, 0.69 mmol), *N,N*-dimethylaminopyridine (DMAP) (35 mg, 0.29 mmol), and benzyloxycarbonyl chloride (107 mg, 0.63 mmol), and the mixture was stirred at the same temperature for 1 h. A saturated ammonium chloride solution was added to the reaction mixture, and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 15:1) to give **24** (157 mg, 76%) as an oil: $[\alpha]^{27}_D$ -44.1° (*c* 2.03, EtOH)]; IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (300 MHz) δ 0.19 (s, 3 H), 0.23 (s, 3 H), 0.95 (s, 9 H), 0.96 (t, J = 7.4 Hz, 3

H), 1.60-1.78 (m, 2 H), 2.53 (dd, J = 15.4, 10.0 Hz, 1 H, one of CH_2COOBn), 2.88 (dt, J = 6.9, 2.4 Hz, 1 H, H-3), 2.88 (dd, J = 15.4, 4.1, 1 H, one of CH_2COOBn), 3.59 (ddd, J = 10.0, 4.1, 2.4 Hz, 1 H, H-2), 5.12 (s, 2 H, CH_2Ph), 7.36 (br s, 5 H). HRMS (FAB) Calcd for $C_{20}H_{32}NO_3Si$ [(M+H)$^+$]: 362.2151. Found: 362.2162.

Benzyl (2*R*,3*R*)-3-Ethyl-4-oxo-2-azetidineacetate (25). To an ice-cooled solution of **24** (206 mg, 0.57 mmol) in THF (6.5 mL) were added successively acetic acid (68 mg, 1.14 mmol), and tetrabutylammonium fluoride (TBAF) (1 M in THF) (0.63 mL, 0.63 mmol), and the mixture was stirred at the same temperature for 30 min. Water was added to the reaction mixture, and the whole was extractd with CH_2Cl_2. The organic layer 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, 25:1) to give **25** (143 mg, quant.) as an oil: $[\alpha]^{24}_D$ +37.3° (*c* 1.34, $CHCl_3$) [lit.[13] $[\alpha]^{25}_D$ +33.7° (*c* 1.11, $CHCl_3$)]; IR (CCl_4) ν 3470, 1760, 1730 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.01 (t, J = 7.4 Hz, 3 H), 1.62-1.88 (m, 2 H), 2.64 (dd, J = 16.5, 9.0 Hz, 1 H, one of CH_2COOBn), 2.76-2.82 (m, 1 H, H-3), 2.78 (dd, J = 16.5, 4.8 Hz, 1 H, one of CH_2COOBn), 3.65 (ddd, J = 9.0, 4.8, 2.3 Hz, 1 H, H-2), 5.14 (s, 2 H, CH_2Ph), 6.07 (br s, 1 H, NH), 7.32-7.42 (s, 5 H). HRMS (FAB) Calcd for $C_{14}H_{18}NO_3$ [(M+H)$^+$]: 248.1287. Found: 248.1272.

(2*R*,3*S*)-3-Acetoxy-2-bromo-*N*-(4-methoxyphenylmethyl)-*N*-[2-(3-methoxyphenyl)-2-(phenylthio)ethenyl]butanamide (28). Using a procedure similar to that described above for **8**, aldehyde **17** (1.13 g, 4.36 mmol) was treated with *p*-methoxybenzylamine (599 mg, 4.36 mmol), and the resulting imine was then treated with (2*R*,3*S*)-3-acetoxy-2-bromobutyryl chloride[2a] (3.19 g, 13.09 mmol) in the presence of *N*,*N*-diethylaniline (651 mg, 4.36 mmol). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1) to give **28** (1.95 g, 77%) as an oil: IR (CCl_4) ν 1735, 1665 cm^{-1}; ^{1}H NMR for the major rotamer (300 MHz) δ 1.35 (d, J = 6.3 Hz, 3 H), 2.07 (s, 3 H), 3.71 (s, 3 H), 3.80 (s, 3 H), 4.53 (d, J = 8.7 Hz, 1 H), 4.60 (d, J = 14.4 Hz, 1 H), 5.03 (d, J = 14.4 Hz, 1 H), 5.47 (dq, J = 8.7, 6.3 Hz, 1 H), 6.45 (s, 1 H), 6.76-7.28 (m, 13 H). HRMS (FAB) Calcd for $C_{29}H_{31}{}^{79}BrNO_5S$ [(M+H)$^+$]: 584.1116. Found: 584.1098.

(3*S*,4*R*)- and (3*R*,4*S*)-3-[(*S*)-1-Acetoxyethyl]-1-(4-methoxyphenylmethyl)-4-(3-methoxyphenylmethyl)-2-azetidinones (30a,b). Following the general procedure, bromide **28** (300 mg, 0.51 mmol) was treated with Bu_3SnH (179 mg, 0.61 mmol) and AIBN (10 mg, 0.06 mmol) in boiling benzene. After workup, the crude material containing **29** was dissolved in benzene (5 mL). To this solution were added Bu_3SnH (297 mg, 1.02 mmol) and AIBN (17 mg, 0.1 mmol), and the mixture was heated under reflux for 2 h. After usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 2:1) to give an oily mixture of **30a** and **30b** (134 mg, 66%): IR (CCl_4) ν 1750 cm^{-1}; ^{1}H NMR for **30a** (300 MHz) δ 1.22 (d, J = 6.5 Hz, 3 H), 1.83 (s, 3 H), 2.70 (dd, J = 13.7, 7.6 Hz, 1 H), 2.94 (dd, J = 13.7, 6.0 Hz, 1 H), 3.06 (d, J = 4.1, 2.2 Hz, 1 H, H-3), 3.47 (ddd, J = 7.6, 6.0, 2.2 Hz, 1 H, H-4), 3.76 (s, 3 H), 3.79 (s, 3 H), 3.79 (d, J = 15.1 Hz, 1 H), 4.70 (d, J = 15.1 Hz, 1 H), 5.20 (dq, J = 4.1, 6.5 Hz, 1 H). 6.61-7.24 (m, 8 H). A small peak due to the *O*-acetyl methyl protons of **30b** appeared at δ 1.76 as a singlet. The ratio of **30a** and **30b** was estimated to be 67:33 by an integrated intensity of the peak heights of the signals due to their *O*-acetyl methyl protons appeared at δ 1.83 and 1.76, respectively. Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.24; H, 7.07; N, 3.45.

(3*S*,4*R*)- and (3*R*,4*S*)-3-[(*S*)-1-Hydroxyethyl]-1-(4-methoxyphenylmethyl)-4-(3-methoxyphenylmethyl)-2-azetidinones (31a,b). To an ice-cooled solution of a mixture of **30a,b** (217 mg, 0.55 mmol) in pyridine (2 mL) was added dropwise a 0.1 N NaOH solution (2.7 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 organic layer was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give an oily mixture of **31a** and **31b** (185 mg, 95%): IR (CCl_4) ν 1740 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.98 (d, J = 6.2 Hz, 3 H), 2.46-2.60 (br, 1 H), 2.67 (dd, J = 13.5, 7.7 Hz, 1 H), 2.85-2.94 (m, 2 H, H-3 and one of C_4-CH_2Ar), 3.46 (ddd, J = 7.7, 6.1, 2.2 Hz, 1 H, H-4), 3.76 (s, 3 H), 3.79 (s, 3 H), 3.89 (d, J = 15.1 Hz, 1 H), 4.02-4.11 (m, 1 H), 4.61 (d, J = 15.1 Hz, 1 H), 6.59-7.22 (m, 8 H). A small peak due to the *C*-methyl protons of **31b** appeared at δ 0.93 (d, J = 6.3 Hz). The ratio of **31a** and **31b** was estimated to be 69:31 by an integrated intensity of the peak heights of the signals due to their *C*-methyl protons appeared at δ 0.98 and 0.93, respectively. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.81; H, 7.26; N, 3.78.

(3*S*,4*R*)- and (3*R*,4*S*)-3-[(*S*)-1-Formyloxyethyl]-1-(4-methoxyphenylmethyl)-4-(3-methoxyphenylmethyl)-2-azetidinones (32a,b). A solution of diisopropyl azodicarboxylate (1.35 g, 6.68 mmol) in dry THF (1 mL) was added dropwise to a solution of a mixture of **31a,b** (1.19 g, 3.34 mmol),

triphenylphosphine (1.75 g, 6.68 mmol), and formic acid (307 mg, 6.68 mmol) in dry THF (37 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, 3:1) to give an oily mixture of **32a** and **32b** (1.03 g, 81%): ^{1}H NMR (300 MHz) δ 1.11 (d, *J* = 6.4 Hz, 3 H), 2.63 (dd, *J* = 13.5, 8.0 Hz, 1 H), 2.92 (dd, *J* =13.5, 5.9 Hz, 1 H), 3.01 (dd, *J* = 6.5, 2.2 Hz, 1 H, H-3), 3.62 (ddd, *J* = 8.0, 5.9, 2.2 Hz, 1 H, H-4), 3.77 (m, 3 H), 3.81 (s, 3 H), 3.94 (d, *J* = 15.0 Hz, 1 H), 4.61 (d, *J* = 15.0 Hz, 1 H), 5.15-5.25 (m, 1 H), 6.59-7.25 (m, 8 H), 7.70 (s, 1 H). A small peak due to the formyl proton of **32b** appeared at δ 7.76 as a singlet. The ratio of **32a** and **32b** was estimated to be 73:27 by an integrated intensity of the peak heights of the signals due to their formyl protons appeared at δ 7.70 and 7.76, respectively. HRMS (FAB) Calcd for $C_{22}H_{26}NO_5$ [(M+H)$^+$]: 384.1811. Found: 384.1826.

(3*S*,4*R*)- and (3*R*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-1-(4-methoxyphenylmethyl)-4-(3-methoxyphenylmethyl)-2-azetidinones (33a,b). To a solution of a mixture of **32a,b** (1.03 g, 2.69 mmol) in methanol (23 mL) was added 10% HCl (23 m L) at 0 °C, and the mixture was stirred at room temperature for 24 h. To the reaction mixture was added brine (20 mL), and the whole was extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:2) to give an oily mixture of **33a** and **33b** (877 mg, 92%): IR (CCl_4) ν 1740 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.92 (d, *J* = 6.5 Hz, 3 H), 2.70 (dd, *J* = 13.5, 7.2 Hz, 1 H), 2.75-2.85 (br, 1 H), 2.84-2.92 (m, 2 H, H-3 and one of C_4-C*H*$_2$Ar), 3.72-3.80 (m, 1 H, H-4), 3.73 (s, 3 H), 3.76 (s, 3 H), 3.88 (d, *J* = 15.1 Hz, 1 H), 4.01-4.10 (m, 1 H), 4.58 (d, *J* = 15.1 Hz, 1 H), 6.59-7.22 (m, 8 H). A small peak due to the *C*-methyl protons of **33b** appeared at δ 0.99 (d, *J* = 6.3 Hz). The ratio of **33a** and **33b** was estimated to be 76:24 by an integrated intensity of the peak heights of the signals due to their *C*-methyl protons appeared at δ 0.92 and 0.99, respectively. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.72; H, 7.33; N, 3.93.

(3*S*,4*R*)- and (3*R*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-(3-methoxyphenylmethyl)-2-azetidinones (34a,b). Using a procedure similar to that described above for **11**, a mixture of **33a,b** (75 mg, 0.21 mmol) was treated with CAN (231 mg, 0.42 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 1:2) to give an oily mixture of **34a** and **34b** (25 mg, 50%): IR (CCl_4) ν 3440, 1740 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.09 (d, *J* = 6.3 Hz, 3 H), 2.35-2.50 (br, 1 H), 2.83-2.96 (m, 3 H, H-3 and C*H*$_2$Ar), 3.79 (s, 3 H), 3.88 (ddd, *J* = 7.9, 6.0, 2.2 Hz, 1 H, H-4), 4.10-4.19 (m, 1 H), 6.19 (br s, 1 H), 6.71-6.81 (m, 3 H), 7.23 (t, *J* = 7.8 Hz, 1 H). A small peak due to the *C*-methyl protons of **34b** appeared at δ 1.15 (d, *J* = 6.3 Hz). The ratio of **34a** and **34b** was estimated to be 76:24 by an integrated intensity of the peak heights of the signals due to their *C*-methyl protons appeared at δ 1.09 and 1.15, respectively. HRMS (FAB) Calcd for $C_{13}H_{18}NO_3$ [(M+H)$^+$]: 236.1287. Found: 236. 1306.

(3*S*,4*R*)- and (3*R*,4*S*)-1-*tert*-Butyldimethylsilyl-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-(3-methoxyphenylmethyl)-2-azetidinones (35a,b). To an ice-cooled solution of a mixture of **34a,b** (130 mg, 0.55 mmol) in CH_2Cl_2 (25 mL) were added successively 2,6-lutidine (589 mg, 5.53 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (360 mg, 1.36 mmol), and the mixture was stirred at room temperature for 1 h. MeOH (2 mL) was added to the reaction mixture, and the whole was stirred for 5 min. Water (10 m L) was added to the mixture, and the organic layer was separated, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 10:1). The first eluent gave **35b** (69 mg, 27%) as an oil: [α]$^{23}_D$ +2.6° (*c* 0.69, EtOH)]; IR (CCl_4) ν 1740 cm^{-1}; ^{1}H NMR (300 MHz) δ -0.12 (s, 3 H), -0.07 (s, 3 H), 0.25 (s, 3 H), 0.29 (s, 3 H), 0.83 (s, 9 H), 1.00 (s, 9 H), 1.15 (d, *J* = 6.3 Hz, 3 H), 2.56 (dd, *J* = 13.1, 10.9 Hz, 1 H), 2.87 (dd, *J* = 3.6, 2.8 Hz, 1 H, H-3), 3.17 (dd, *J* = 13.1, 4.0 Hz, 1 H), 3.57 (qd, *J* = 3.6, 6.3 Hz, 1 H), 3.67 (ddd, *J* = 10.9, 4.0, 2.8 Hz, 1 H, H-4), 3.80 (s, 3 H), 6.68-6.79 (m, 3 H), 7.22 (t, *J* = 7.8 Hz, 1 H). HRMS (FAB) Calcd for $C_{25}H_{46}NO_3Si_2$ [(M+H)$^+$]: 464.3017. Found: 464.3014.

The second eluent gave **35a** (186 mg, 73%) as low melting point needles: [α]$^{23}_D$ -31.0° (*c* 1.86, EtOH)]; IR (CCl_4) ν 1740 cm^{-1}; ^{1}H NMR (300 MHz) δ -0.02 (s, 6 H), 0.27 (s, 3 H), 0.29 (s, 3 H), 0.45 (d, *J* = 6.4 Hz, 3 H), 0.83 (s, 9 H), 1.01 (s, 9 H), 2.53 (dd, *J* = 12.9, 10.8 Hz, 1 H), 2.83 (t, *J* = 3.1 Hz, 1 H, H-3), 3.21 (dd, *J* = 12.9, 4.0 Hz, 1 H), 3.79 (ddd, *J* = 10.8, 4.0, 3.1 Hz, 1 H, H-4), 3.80 (s, 3 H), 4.04 (dq, *J* = 3.1, 6.4, Hz, 1 H), 6.69-6.78 (m, 3 H), 7.12 (t, *J* = 7.8 Hz, 1 H). Anal Calcd for $C_{25}H_{45}NO_3Si_2$: C, 64.74, H, 9.78; N, 3.02. Found: C, 64.71; H, 9.96; N, 3.16.

Benzyl (2*R*,3*S*)-1-*tert*-Butyldimethylsilyl-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-oxo-2-azetidineacetate (37). Using a procedure similar to that described above for **13**, compound **35a** (186 mg, 0.40 mmol) was treated with RuO_2-H_2O (2 mg) and $NaIO_4$ (1.72 g, 8.00 mmol). Workup gave crude (2*R*,3*S*)-1-*tert*-butyldimethylsilyl-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-oxo-2-azetidineacetic acid (**36**), which was used in the next step without purification: ^{1}H NMR (300 MHz) δ 0.05 (s, 3 H), 0.08 (s, 3 H),

0.22 (s, 3 H), 0.24 (s, 3 H), 0.88 (s, 9 H), 0.95 (s, 9 H), 1.17 (d, J = 6.2 Hz, 3 H), 2.58 (dd, J = 14.7, 8.7 Hz, 1 H), 2.83 (dd, J = 14.7, 4.3 Hz, 1 H), 3.03 (dd, J = 4.3, 2.6 Hz, 1 H, H-3), 3.98 (ddd, J = 8.7, 4.3, 2.6 Hz, 1 H, H-2), 4.19 (dq, J = 6.2, 4.3 Hz, 1 H).

Thus obtained carboxylic acid **36** was treated according to the procedure described above for **24** with benzyloxycarbonyl chloride (82 mg, 0.48 mmol) in the presence of triethylamine (53 mg, 0.52 mmol) and DMAP (24 mg, 0.24 mmol). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 20:1) to give **37** (100 mg, 51% based on **35a**) as an oil: $[\alpha]^{24}_D$ -41.8° (*c* 1.00, EtOH)]; IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (300 MHz) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.19 (s, 3 H), 0.22 (s, 3 H), 0.87 (s, 9 H), 0.94 (s, 9 H), 1.09 (d, J = 6.3 Hz, 3 H), 2.58 (dd, J = 14.5, 8.7 Hz, 1 H), 2.83 (dd, J = 14.5, 4.5 Hz, 1 H), 2.99 (dd, J = 4.1, 2.7 Hz, 1 H, H-3), 4.00 (ddd, J = 8.7, 4.5, 2.7 Hz, 1 H, H-2), 4.16 (qd, J = 4.1, 6.3 Hz, 1 H), 5.11 (s, 2 H), 7.36 (s, 5 H). HRMS (FAB) Calcd for $C_{26}H_{46}NO_4Si_2$ [(M+H)$^+$]: 492.2966. Found: 492.2964.

Benzyl (2*R*,3*S*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-oxo-2-azetidineacetate (38). Using a procedure similar to that described above for **25**, compound **37** (40 mg, 0.08 mmol) was treated with TBAF (1 M in THF) (0.09 mL, 0.09 mmol) in the presence of AcOH (10 mg, 0.16 mmol). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 3:1) to give **38** (31 mg, quant.): mp 91-92 °C (hexane) [lit.[13] mp 92-93 °C]; $[\alpha]^{23}_D$ +17.6° (*c* 0.42, $CHCl_3$) [lit.[13] $[\alpha]^{24}_D$ +17.4° (*c* 1.75, $CHCl_3$)]; IR (CCl_4) ν 3460, 1765, 1735 cm^{-1}; ^1H NMR (300 MHz) δ 0.067 (s, 3 H), 0.070 (s, 3 H), 0.87 (s, 9 H), 1.19 (d, J = 6.3 Hz, 3 H), 2.62 (dd, J = 16.5, 9.9 Hz, 1 H), 2.79 (dd, J = 16.5, 3.7 Hz, 1 H), 2.81 (dd, J = 4.9, 2.4 Hz, 1 H, H-3), 4.00 (ddd, J = 9.9, 3.7, 2.4 Hz, 1 H, H-2), 4.19 (qd, J = 4.9, 6.3 Hz, 1 H), 5.15 (s, 2 H), 6.04 (br s, 1 H), 7.32-7.42 (m, 5 H). HRMS (FAB) Calcd for $C_{20}H_{32}NO_4Si$ [(M+H)$^+$]: 378.2100. Found: 378.2097.

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