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Asymmetric Radical Cyclization Leading to β-Lactams: Stereoselective Synthesis of Chiral Key Intermediates for Carbapenem Antibiotics PS-5 and Thienamycin

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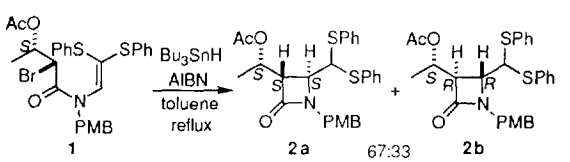
Abstract: A stereoselective synthesis of β-lactams by 4-*exo-trig* radical cyclizations of *N*-[2,2-bis(phenylthio)ethenyl]-α-bromo amides bearing a chiral inductor on the nitrogen atom has been examined. Bromide **8**, upon treatment with Bu_3SnH in the presence of AIBN in boiling benzene, gave a mixture of (4*S*)-2-azetidinone **12a** and its (4*R*)-isomer **12b** in a ratio of 71:29 and 69% combined yield. Similar treatment of α-bromobutanamide **11** with Bu_3SnH afforded *trans*-(4*S*)-2-azetidinone **17a** as the major product along with its (4*R*)-isomer **17b** (70:30, 77% combined yield). Compound **17a** was converted into **24**, a chiral key intermediate in the synthesis of (+)-PS-5 (**25**). The cyclization of bromide **28** bearing an additional stereogenic center [(*S*)-oxygen functionality] at the side chain proceeded with much higher (4*S*)-stereoselectivity to give azetidinone **29a** as the major product together with its (4*R*)-isomer **29b** in a ratio of 78:22 and 40% combined yield. Compound **29a** was converted, via an inversion of the oxygen functionality, into **37**, a chiral key intermediate in the synthesis of (+)-thienamycin (**38**). A possible explanation for the observed diastereoselectivity in radical cyclizations is presented.

Introduction

Stereochemical control in radical addition and cyclization reactions is presently a field of intense research.[1-3] Relative stereochemistry in radical cyclizations induced by *substrate control* has been widely investigated and is now fairly well understood.[2] However, little is known about the asymmetric induction in radical cyclizations induced by *chiral auxiliary control*.[4] A previous paper[5] from our laboratory reported that the *N*-vinylic α-bromo amide **1** bearing a chiral oxygen functionality (*S* configuration) at the side chain, upon treatment with Bu_3SnH in the presence of azobis(isobutyronitrile) (AIBN) in boiling toluene, undergoes 4-*exo-trig* radical cyclization with some degree of diastereoselectivity (67:33) to give (3*S*,4*S*)-2-azetidinone **2a** as the major product along with its (3*R*,4*R*)-isomer **2b** (Scheme 1). This reaction can be classified as a 1,2-asymmetric induction induced by chiral auxiliary control.[6]

Scheme 1

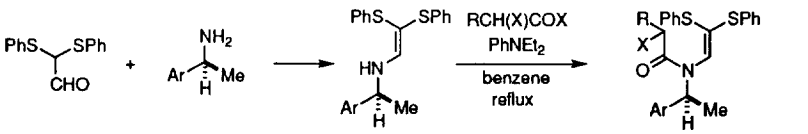


Our interest has now turned to the feasibility of using a chiral inductor on the nitrogen atom of *N*-vinylic α-bromo amides in a 1,3-asymmetric induction in radical cyclization leading to β-lactams. The present paper describes the results with an (*S*)-1-phenylethyl group as a chiral inductor. Applications of the method to the synthesis of chiral key intermediates for the preparation of carbapenem antibiotics PS-5 and thienamycin are also presented.[7]

Results and Discussion

Formal Synthesis of (+)-PS-5. Condensation of bis(phenylthio)acetaldehyde (**3**)[5] with (*S*)-1-phenylethylamine (**4**) followed by *N*-acylation of the resulting enamine **6**[8] with bromoacetyl bromide in boiling benzene in the presence of *N*,*N*-diethylaniline gave *N*-ethenyl-α-bromo amide **8** in 68% yield (Scheme 2). Treatment of **8** with Bu_3SnH in the presence of a catalytic amount of AIBN in boiling benzene gave, in 69% yield, a mixture of (4*S*)- and (4*R*)-2-azetidinones **12a,b** in a ratio of 71:29 (by ^1H NMR spectroscopy) (Scheme 3).

Scheme 2



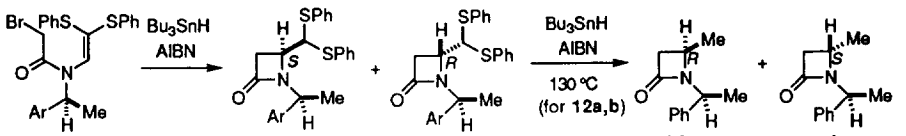
3

4 Ar = Ph
5 Ar = 1-Naph

6 Ar = Ph
7 Ar = 1-Naph

8 R = H, X = Br, Ar = Ph
9 R = H, X = Br, Ar = 1-Naph
10 R = X = Cl, Ar = Ph
11 R = Et, X = Br, Ar = Ph

Scheme 3



8 Ar = Ph
9 Ar = 1-Naph

12a Ar = Ph
13a Ar = 1-Naph

12b Ar = Ph
13b Ar = 1-Naph

14a

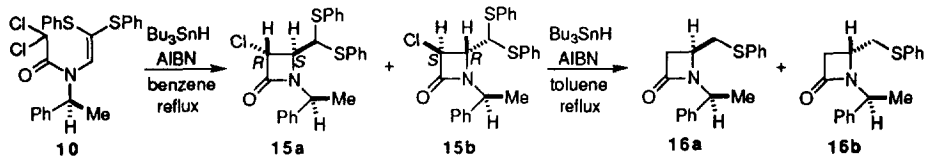
14b

The stereochemistry of **12a** and **12b** was established by conversion to the known compounds **14a** and **14b**, respectively. Thus, heating the mixture of **12a,b** in a large excess of Bu_3SnH at 130 °C in the presence of AIBN[9] afforded, in 66% yield, a new mixture of the completely desulfurized compounds **14a** and **14b** in a ratio of 71:29 (Scheme 3). The literature[10] indicates that in the ^1H NMR spectra (100 MHz, CCl_4) of **14a,b**, the signal due to the methine proton of the *N*-phenethyl group of (*S*)-4-methyl-1-[(*S*)-1-phenylethyl]-2-azetidinone (**14b**) appears at δ 4.65 (q, J = 7 Hz) while the corresponding signal for the (4*R*)-isomer **14a** is located up field at δ *ca.* 4.41. In the ^1H NMR spectrum (300 MHz, CCl_4) of the mixture **14a,b** herein obtained, the signal due to the methine proton of the *N*-phenethyl group of the minor isomer appeared at δ 4.79 (q, J = 6.9 Hz) and the corresponding signal for the major isomer shifted up field at δ 4.52 (q, J = 6.9 Hz). This implies that the major isomer is the (4*R*)-substituted 2-azetidinone **14a**, thereby indicating the *S*-configuration of the C_4 position of the major isomer **12a** obtained by radical cyclization of **8**.

We next examined the cyclization of the enamide **9** bearing a sterically more demanding (*S*)-1-(1-naphthyl)ethyl group on the nitrogen atom. Heating **9** with Bu_3SnH in the presence of AIBN in boiling benzene afforded, in 54% yield, a mixture of (4*S*)-2-azetidinone **13a** and its (4*R*)-isomer **13b** in a ratio of 71:29 (Scheme 3). Thus, no difference between the diastereoselectivity in radical cylization of enamides **8** and **9** was observed. The mixture of **13a,b** could be separated by chromatography on silica gel: pure compounds **13a** and **13b** were obtained in 35 and 8% yields (based on bromide **9**), respectively. The stereochemistry of **13a** and **13b** was deduced by comparing the ^1H NMR spectra with those of **12a,b**: *e. g.*, the signal due to the methine proton of the *N*-naphthylethyl group of **13a** appeared further upfield (δ 5.41) than did the corresponding proton for **13b** (δ 5.73).

Substitution with chlorine atom on the radical center was found to slightly improve the diastereoselectivity in radical cyclization. Thus, treatment of **10** with Bu_3SnH-AIBN in boiling benzene afforded, in 83% yield, a mixture of (3*R*,4*S*)-2-azetidinone **15a** and its (3*S*,4*R*)-isomer **15b** in a ratio of 77:23 (Scheme 4). A small coupling constant between H-3 and H-4 of **15a,b** (both J = 1.7 Hz) established the *trans* relationship between the substituents at C3 and C4.

Scheme 4



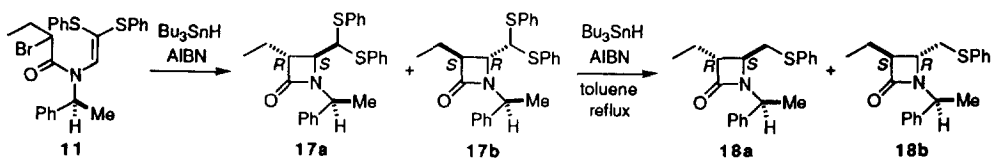
10 **15a** **15b** **16a** **16b**

The absolute configuration of the C3 and C4 positions of **15a,b** was confirmed as follows. Treatment of the mixture of **12a,b** (71:29), whose stereochemistry was established as described above, with Bu_3SnH-AIBN in boiling toluene resulted in partial desulfurization to give a new mixture of lactams **16a** and **16b** in a ratio of *ca.* 3:1. On the other hand, similar treatment of the mixture of **15a,b** with Bu_3SnH gave a mixture of **16a,b** in a ratio of *ca.* 3:1, as a result of dechlorination and partial desulfurization, the major product obtained being identical to the major isomer **16a** obtained from **12a,b**. Hence the absolute configuration of the C-4 position of the major cyclization product **15a** was determined to be *S* and that of C-3 to be *R*.

Encouraged by the observation that the radical cyclizations of *N*-vinylic α-halo amides bearing an (*S*)-1-phenylethyl group on the nitrogen atom gave (4*S*)-substituted 2-azetidinones as the major products, attention was next turned to the synthesis of a chiral intermediate for the preparation of carbapenem antibiotic (+)-PS-5 (**25**).[11]

Bromide **11**, upon treatment with Bu_3SnH-AIBN in boiling benzene, gave a mixture of **17a** and **17b** in a ratio of 70:30 and 77% combined yield (Scheme 5). When a similar reaction was carried out in boiling toluene, the diasteromeric ratio of **17a,b** was improved to 77:23, though the combined yield was slightly lowered to 70%.[12]

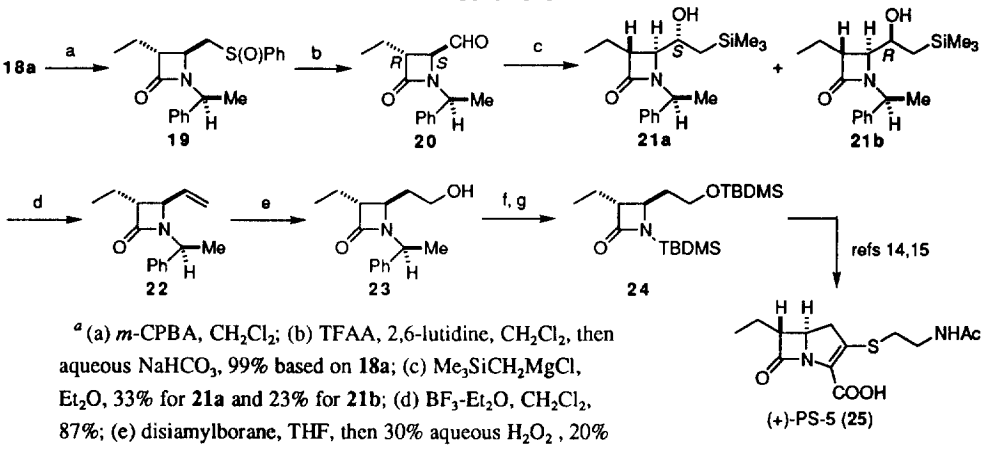
Scheme 5



11 **17a** **17b** **18a** **18b**

Heating the mixture of **17a,b** with Bu_3SnH-AIBN in boiling toluene followed by careful chromatographic separation of the resulting mixture of monophenylthio derivatives afforded **18a** and **18b** in 48 and 9% yields, respectively, along with a mixture of **18a,b** (18%). Oxidation of the major isomer **18a** with *m*-CPBA gave sulfoxide **19**. Treatment of **19** with trifluoroacetic anhydride (TFAA) in the presence of 2,6-lutidine followed by hydrolysis of the resulting Pummerer rearrangement product with aqueous $NaHCO_3$ solution gave the aldehyde **20** in quantitative yield from **18a** (Scheme 6).

Scheme 6[a]



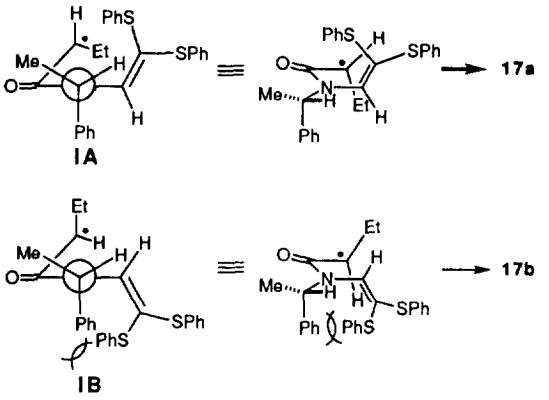
[a] (a) *m*-CPBA, CH_2Cl_2; (b) TFAA, 2,6-lutidine, CH_2Cl_2, then aqueous $NaHCO_3$, 99% based on **18a**; (c) Me_3SiCH_2MgCl, Et_2O, 33% for **21a** and 23% for **21b**; (d) BF_3-Et_2O, CH_2Cl_2, 87%; (e) disiamylborane, THF, then 30% aqueous H_2O_2, 20% aqueous NaOH, 77%; (f) Na, liquid NH_3, THF; (g) TBDMSOTf, 2,6-lutidine, 98% based on **23**.

Grignard coupling of **20** with (trimethylsilyl)methylmagnesium chloride followed by separation of the resulting alcohols gave (*S*)-alcohol **21a** and (*R*)-alcohol **21b** (mp 79-80 °C) in 33 and 23% yields, respectively. X-ray crystallographic analysis of the minor alcohol **21b** established the *R*-configuration of its carbinol and the (3*R*,4*S*) stereochemistry of the parent aldehyde **20**.

The alcohols **21a** and **21b** were combined and then treated with BF_3 etherate in CH_2Cl_2[13] to give olefin **22** in 87% yield. Hydroboration of **22** with disiamylborane followed by oxidation with alkaline H_2O_2 gave alcohol **23** in 77% yield. Removal of the *N*-phenethyl group of **23** with sodium in liquid ammonia followed by *N,O*-disilylation with *tert*-butyldimethylsilyl trifluoromethanesulfonate furnished **24** in 98% yield. The spectral data including the specific rotation [$[\alpha]^{23}_D$ -39.68° (*c* 0.32, $CHCl_3$)] of **24** were identical to the literature values [$[\alpha]^{23}_D$ -39.59° (*c* 2.92, $CHCl_3$)].[14] Since compound **24** has previously been converted into (+)-PS-5 (**25**),[14, 15] the present synthesis of **24**[16] constitutes, in a formal sense, a total synthesis of (+)-PS-5.[17]

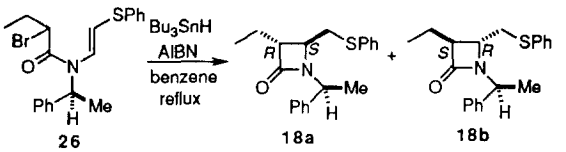
One possible explanation for the observed diastereoselectivity in radical cyclizations is based on the consideration of the Felkin-Anh model for the radical intermediates. The two Felkin-Anh conformers **IA** and **IB**, where the *N*-*C* bond of the amide is regarded as a double bond, can be considered for the radical intermediate generated from bromide **11** (Fig. 1). In conformer **IB** severe steric repulsion between one of the phenylthio groups (*cis* to the nitrogen atom) and the phenyl group of the *N*-phenethyl group becomes evident. We assumed, therefore, that the cyclization might proceed *via* the sterically favored radical intermediate **IA** to give (4*S*)-substituted 2-azetidinone **17a** as the major product.

Fig. 1



Strong support for the above assumption was derived from the result with the enamide **26** which lacked the *cis* phenylthio group. Thus, the cyclization of **26** proceeded with low diastereoselectivity to give **18a** and **18b** in a ratio of 58:42 (Scheme 7).

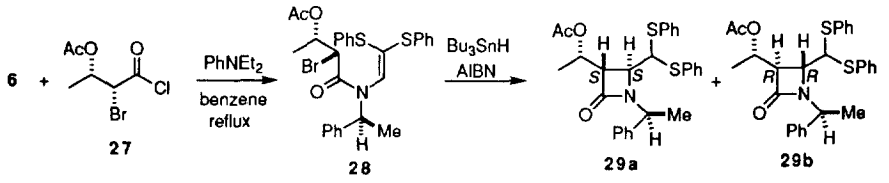
Scheme 7



Asymmetric Radical Cyclization Induced by a Matched Pair of Chiral Inductors: Formal Synthesis of (+)-Thienamycin. As mentioned above, we previously reported that bromide **1** with (*S*)-chirality at the side chain gave (4*S*)-substituted 2-azetidinone **2a** as the major product (1,2-asymmetric induction).[5] The present result indicates that bromide **11** bearing (*S*)-chirality on the nitrogen atom also provides (4*S*)-substituted β-lactam **17a** as the major product (1,3-asymmetric induction). Combining these two methods of asymmetric induction, much higher (4*S*)-stereoselectivity leading to β-lactams might be expected. Therefore, we were encouraged to examine the cyclization of bromide **28** bearing a matched pair of chiral inductors.

Compound **28** was prepared from enamine **6** and (2*R*,3*S*)-3-acetoxy-2-bromobutyryl chloride (**27**)[5] according to the method for the preparation of **8**. Treatment of **28** with Bu_3SnH in the presence of AIBN in

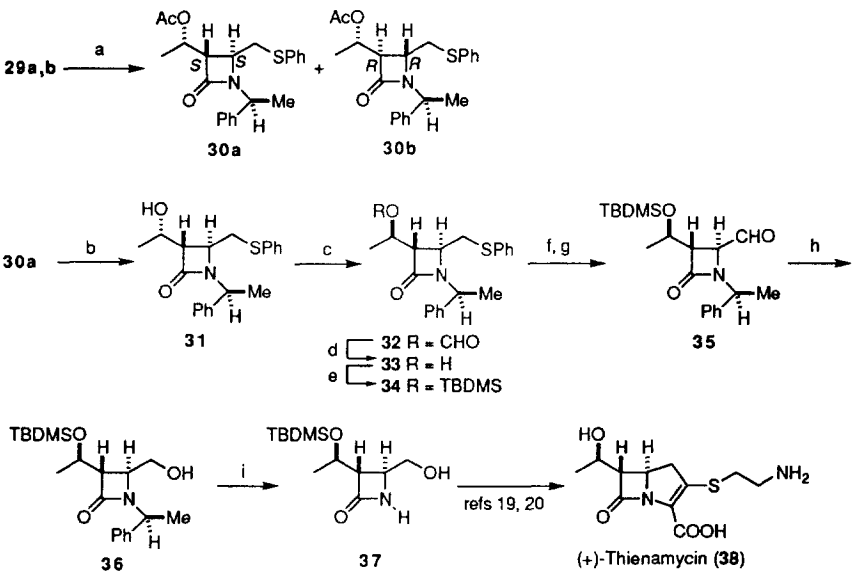
Scheme 8



boiling benzene afforded a mixture of (3*S*,4*S*)-2-azetidinone **29a** and its (3*R*,4*R*)-isomer **29b** in a ratio of 78:22 and in 40% combined yield (Scheme 8). In boiling toluene, an 88:12 mixture of **29a,b** was obtained in 29% yield.[12] Thus, higher diastereoselectivity was observed than in the case of **2a,b** (67:33) from **1** or **17a,b** (77:23) from **11** in boiling toluene.[18]

Partial desulfurization of the mixture of **29a,b** with Bu_3SnH-AIBN in boiling toluene followed by chromatography on silica gel provided pure stereoisomer **30a** in 71% yield together with a trace amount of **30b**. Compound **30a** could be converted into the chiral intermediate **37** for use in the synthesis of (+)-thienamycin (**38**).[19] Thus, hydrolysis of the ester group of **30a** with 1N NaOH in pyridine gave, in 94% yield, (*S*)-alcohol **31**, which was then subjected to the Mitsunobu reaction (diisopropyl azodicarboxylate / formic acid / triphenylphosphine) to give formate **32** in quantitative yield. Acid hydrolysis (96%) of **32** followed by silylation (quantitative) of the resulting (*R*)-alcohol **33** with *tert*-butyldimethylsilyl chloride afforded **34**. In a manner similar to that described above for the preparation of aldehyde **20** from **18a**, compound **34** was converted into aldehyde **35**, which was then subjected to reduction with $NaBH_4$ followed by removal of the *N*-phenethyl group of **36** to furnish **37** [$[\alpha]^{22}_D$ -15.3° (*c* 0.55, $CHCl_3$), lit.[20] $[\alpha]^{22}_D$ -14.1° (c 0.625, $CHCl_3$)]. Since compound **37** has already been transformed into (+)-thienamycin (**38**),[20, 21] the whole sequence of reactions herein described constitutes, in a formal sense, a total synthesis of (+)-thienamycin.[22]

Scheme 9[a]



[a] (a) Bu_3SnH, AIBN, toluene, reflux, 71% for **30a**; (b) 1N NaOH, pyridine, 94%; (c) diisopropyl azodicarboxylate, PPh_3, HCOOH, THF, quantitative; (d) 10% HCl, MeOH, 96%; (e) TBDMSCl, Et_3N, DMF, 99%; (f) *m*-CPBA, CH_2Cl_2; (g) TFAA, 2,6-lutidine, CH_2Cl_2, then aqueous $NaHCO_3$, quantitative based on **34**; (h) $NaBH_4$, EtOH, 52%; (i) Na, liquid NH_3, THF, 62%.

Experimental Section[23]

2-Bromo-*N*-[(*S*)-1-phenylethyl]-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (8). A mixture of bis(phenylthio)acetaldehyde (**3**)[5] (1.0 g, 3.84 mmol) and (*S*)-1-phenylethylamine (**4**) (465 mg, 3.84 mmol) in benzene (40 mL) was heated under reflux with azeotropic removal of water for 2 h. After cooling the mixture containing enamine **6**, *N*,*N*-diethylaniline (573 mg, 3.84 mmol) was added, and the solution was heated again under reflux. To this was added dropwise bromoacetyl bromide (2.33 g, 11.52 mmol) over 5 min, and the mixture was heated under reflux for a further 15 min. The reaction mixture was washed with brine, and the organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **8** (1.26 g, 68%) as an oil: IR (CCl_4) ν 1660 cm^{-1}; ^1H NMR (60 MHz) δ 1.58 (d, J = 7 Hz, 3 H), 3.94 (s, 2H), 5.96 (q, J = 7 Hz, 1 H), 6.18 (s, 1 H), 6.8-7.5 (m, 15 H); HRMS (FAB) calcd for $C_{24}H_{23}BrNOS_2$ ($M+H^+$) 484.0404, found 484.0386.

2-Bromo-*N*-[(*S*)-1-(1-naphthyl)ethyl]-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (9). Using a procedure similar to that described above for **8**, enamine **7**, prepared from **3** (1 g, 3.84 mmol) and (*S*)-1-(1-naphthyl)ethylamine (**5**) (658 mg, 3.84 mmol), was treated with bromoacetyl bromide (1.55 g, 7.68 mmol) in the presence of *N*,*N*-diethylaniline (573 mg, 3.84 mmol) to give **9** (1.72 g, 84%) as an oil: IR (CCl_4) ν 1660 cm^{-1}; ^1H NMR (60 MHz) δ 1.76 (d, J = 7 Hz, 3 H), 3.95 (s, 2 H), 5.90 (q, J = 7 Hz, 1 H), 6.4-8.3 (m, 18 H). Anal. Calcd for $C_{28}H_{24}BrNOS_2$: C, 62.92; H, 4.53; N, 2.62. Found: C, 62.94; H, 4.81; N, 2.99.

2,2-Dichloro-*N*-[(*S*)-1-phenylethyl]-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (10). Using a procedure similar to that described above for **8**, enamine **6** (1.4 g, 3.84 mmol) was treated with dichloroacetyl chloride (1.13 g, 7.68 mmol) in the presence of *N*,*N*-diethylaniline (1.15 g, 7.68 mmol) to give **10** (1.81 g, 100%): mp 88.5-89 °C (hexane/AcOEt); IR (CCl_4) ν 1690 cm^{-1}; ^1H NMR (60 MHz) δ 1.60 (d, J = 7 Hz, 3 H), 5.87 (q, J = 7 Hz, 1 H), 5.98 (s, 1 H), 6.37 (s, 1 H), 6.7-7.6 (m, 15 H). Anal. Calcd for $C_{24}H_{21}Cl_2NOS_2$: C, 60.76; H, 4.46; N, 2.95. Found: C, 60.90; H, 4.43; N, 2.94.

2-Bromo-*N*-[(*S*)-1-phenylethyl]-*N*-[2,2-bis(phenylthio)ethenyl]butanamide (11). Using a procedure similar to that described above for **8**, enamine **6** (698 mg, 1.92 mmol) was treated with 2-bromobutyryl bromide (883 mg, 3.84 mmol) in the presence of *N*,*N*-diethylaniline (573 mg, 3.84 mmol) to give **11** (980 mg, 100%) as an oil: IR (CCl_4) ν 1665 cm^{-1}; ^1H NMR (60 MHz) δ 1.02 (t, J = 7 Hz, 3 H), 1.54, 1.61 (both d, J = 7 Hz, total 3 H), 2.16 (quint, J = 7 Hz, 2 H), 4.40 (t, J = 7Hz, 1 H), 6.00 (q, J = 7 Hz, 1 H), 6.03, 6.43 (both s, total 1 H), 6.6-7.5 (m, 15 H). Anal. Calcd for $C_{26}H_{26}BrNOS_2$: C, 60.93; H, 5.11; N, 2.73. Found: C, 60.57; H, 5.18; N, 2.80.

(4*S*)- and (4*R*)-1-[(*S*)-1-Phenylethyl]-4-[bis(phenylthio)methyl]-2-azetidinones (12a,b). General Procedure for Radical Cyclization. To a boiling solution of **8** (300 mg, 0.62 mmol) in benzene (90 mL) was added a solution of Bu_3SnH (198 mg, 0.68 mmol) and AIBN (12 mg, 0.07 mmol) in benzene (90 mL) *via* a syringe over 4 h, and the mixture was heated under reflux for 1 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 1 h. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 7:1) to give an oily mixture of **12a** and **12b** (173 mg, 69%) in a ratio of 71:29 (determined by ^1H NMR spectroscopy): IR (CCl_4) ν 1760 cm^{-1}; ^1H NMR (270 MHz) δ 1.66 (d, J = 7.3 Hz, Me for **12b**), 1.72 (d, J = 6.9 Hz, Me for **12a**), 2.86-2.90 (m, 2 H), 3.79 (q, J = 3.6 Hz, 1 H), 4.26 (d, J = 3.6 Hz, SCH for **12a**), 4.29 (d, J = 3.6 Hz, SCH for **12b**), 4.54 (q, J = 6.9 Hz, PhC*H* for **12a**), 4.91 (q, J = 7.3 Hz, PhC*H* for **12b**), 7.12-7.44 (m, 15 H); HRMS calcd for $C_{24}H_{23}NOS_2$ 405.1221, found 405.1204.

(4*R*)- and (4*S*)-4-Methyl-1-[(*S*)-1-phenylethyl]-2-azetidinones (14a,b). To the mixture of **12a,b** (71:29) (203 mg, 0.5 mmol) were added Bu_3SnH (5 mL), toluene (1 mL), and AIBN (16 mg, 0.1 mmol), and the whole mixture was heated at 130 °C for 3 days. After cooling the reaction mixture, diethyl ether (20 mL) and 8% aqueous KF (20 mL) were added, and the reaction was stirred vigorouly for 2 h. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 7:1) to give an oily mixture of **14a**[10] and **14b**[10] (62 mg, 66%) in a ratio of 71:29 (determined by ^1H NMR spectroscopy): IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (CCl_4, 300 MHz) δ 1.08 (d, J = 5.9 Hz, C_4-Me for **14a**), 1.21 (d, J = 6.3 Hz, C_4-Me for **14b**), 1.62 (d, J = 6.9 Hz, PhCH*Me* for **14b**), 1.70 (d, J = 6.9 Hz, PhCH*Me* for **14a**), 2.38 (dd, J = 14.2, 2.0 Hz, 1 H, one of H-3 for **14a,b**), 2.90 (dd, J = 14.2, 5.0 Hz, one of H-3 for **14b**), 2.93 (dd, J = 14.2, 5.0 Hz, one of H-3 for **14a**), 3.37-3.54 (m, 1H, H-4 for **14a,b**), 4.52 (q, J = 6.9 Hz, PhC*H* for **14a**), 4.79 (q, J = 6.9 Hz, PhC*H* for **14b**), 7.16-7.29 (m, 5 H).

(4*S*)- and (4*R*)-1-[(*S*)-1-(1)-Naphthylethyl]-4-[bis(phenylthio)methyl]-2-azetidinones (13a,b). Following the general procedure, bromide **9** (400 mg, 0.75 mmol) was treated with Bu_3SnH (240 mg, 0.83 mmol) and AIBN (14 mg, 0.09 mmol) in boiling benzene, and the crude material containing a 71:29 mixture of **13a,b** (by ^1H NMR spectroscopy) was chromatographed on silica gel (hexane/AcOEt, 12:1). The first eluate gave **13b** (27 mg, 8%) as an oil: IR (CCl_4) ν 1755 cm^{-1}; ^1H NMR (270 MHz) δ 1.83 (d, *J* = 6.9 Hz, 3 H), 2.80 (dd, *J* = 15.2, 5.0 Hz, 1 H), 2.87 (dd, *J* = 15.2, 3.0 Hz, 1 H), 3.35 (ddd, *J* = 5.0, 3.6, 3.0 Hz, 1 H), 4.18 (d, *J* = 3.6 Hz, 1 H), 5.73 (q, *J* = 6.9 Hz, 1 H), 6.74-6.79 (m, 2 H), 6.99-7.15 (m, 3 H), 7.25-7.40 (m, 6 H), 7.44-7.55 (m, 3 H), 7.79-7.97 (m, 3 H); HRMS calcd for $C_{28}H_{25}NOS_2$ 455.1406, found 455.1392. The second eluate gave **13a** (115 mg, 35%) as an oil: $[\alpha]^{22}_D$ +32.9° (*c* 1, EtOH); IR (CCl_4) ν 1755 cm^{-1}; ^1H NMR (270 MHz) δ 1.83 (d, *J* = 6.9 Hz, 3 H), 2.93 (d, *J* = 3.6 Hz, 2 H), 3.85 (q, *J* = 3.6 Hz, 1 H), 4.19 (d, *J* = 3.0 Hz, 1 H), 5.41 (q, *J* = 6.9 Hz, 1 H), 6.93-6.97 (m, 2 H), 7.11-7.25 (m, 8 H), 7.37-7.50 (m, 4 H), 7.72-7.85 (m, 2 H). 7.99-8.03 (m, 1 H). Anal. Calcd for $C_{28}H_{25}NOS_2$: C, 73.81; H, 5.53; N, 3.53. Found: C, 73.75; H, 5.53; N, 3.02.

(3*R*,4*S*)- and (3*S*,4*R*)-3-Chloro-1-[(*S*)-1-phenylethyl]-4-[bis(phenylthio)methyl]-2-azetidinones (15a,b). Following the general procedure, chloride **10** (2.11 g, 4.46 mmol) was treated with Bu_3SnH (1.56 g, 5.35 mmol) and AIBN (88 mg, 0.54 mmol) in boiling benzene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1) to give an oily mixture of **15a** and **15b** (1.62 g, 83%) in a ratio of 77:23 (determined by ^1H NMR spectroscopy): IR (CCl_4) ν 1775 cm^{-1}; ^1H NMR for **15a** (270 MHz) δ 1.76 (d, *J* = 6.9 Hz, 3 H), 3.76 (dd, *J* = 3.6, 1.7 Hz, 1 H), 4.23 (d, *J* = 3.6 Hz, 1 H), 4.50 (d, *J* = 6.9 Hz, 1 H), 4.71 (d, *J* = 1.7 Hz, 1 H), 7.15-7.40 (m, 15 H); ^1H NMR for **15b** (270 MHz) δ 1.70 (d, *J* = 7.3 Hz, 3 H), 3.77 (dd, *J* = 4.3, 1.7 Hz, 1 H), 4.16 (d, *J* = 4.3 Hz, 1 H), 4.69 (d, *J* = 1.7 Hz, 1 H), 4.94 (q, *J* = 7.3 Hz, 1 H), 7.15-7.40 (m, 15 H). Anal. Calcd for $C_{24}H_{22}ClNOS_2$: C, 65.51; H, 5.04; N, 3.18. Found: C, 65.13; H, 5.14; N, 3.47.

(4*S*)- and (4*R*)-1-[(*S*)-1-Phenylethyl]-4-[(phenylthio)methyl]-2-azetidinones (16a,b). From 12a,b. To a solution of a mixture of **12a,b** (71:29) (143 mg, 0.35 mmol) in toluene (10 mL) were added Bu_3SnH (308 mg, 1.06 mmol) and AIBN (18 mg, 0.11 mmol), and the mixture was heated under reflux for 4 h. After usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1) to give an oily mixture of **16a,b** (72 mg, 69%) in a ratio of *ca.* 3:1 (determined by ^1H NMR spectroscopy): IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR for **16a** (270 MHz) δ 1.68 (d, *J* = 7.3 Hz, 3 H), 2.57 (dd, *J* = 14.9, 2.3 Hz, 1 H), 2.66 (dd, *J* = 13.9, 8.6 Hz, 1 H), 2.94 (dd, *J* = 13.9, 4.0 Hz, 1 H), 2.97 (dd, *J* = 14.9, 5.0 Hz, 1 H), 3.62 (dddd, *J* = 8.6, 5.0, 4.0, 2.3 Hz, 1 H), 4.69 (q, *J* = 7.3 Hz, 1 H), 7.11-7.40 (m, 10 H); ^1H NMR for **16b** (270 MHz) δ 1.67 (d, *J* = 7.3 Hz, 3 H), 2.56 (dd, *J* = 14.5, 2.3 Hz, 1 H), 2.77 (dd, *J* = 13.5, 9.2 Hz, 1 H), 2.94 (dd, *J* = 14.5, 5.3 Hz, 1 H), 3.15 (dd, *J* = 13.5, 4.0 Hz, 1 H), 3.53 (dddd, *J* = 9.2, 5.3, 4.0, 2.3 Hz, 1 H), 4.90 (q, *J* = 7.3 Hz, 1 H), 7.11-7.40 (m, 10 H). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.69; H, 6.53; N, 5.17.

From 15a,b. In a manner similar to that described above, a mixture of **15a,b** (500 mg, 1.16 mmol) was treated with Bu_3SnH (827 mg, 2.84 mmol) and AIBN (22 mg, 0.14 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1) to give an oily mixture of **16a,b** (244 mg, 72%) in a ratio of ca. 3:1 (determined by ^1H NMR spectroscopy).

(3*R*,4*S*)- and (3*S*,4*R*)-3-Ethyl-1-[(*S*)-1-phenylethyl]-4-[bis(phenylthio)methyl]-2-azetidinones (17a,b). Following the general procedure, bromide **11** (500 mg, 0.98 mmol) was treated with Bu_3SnH (341 mg, 1.17 mmol) and AIBN (19 mg, 0.12 mmol) in boiling benzene, and the crude product was chromatographed on silica gel (hexane/AcOEt, 7:1) to give an oily mixture of **17a** and **17b** (327 mg, 77%) in a ratio of 70:30 (determined by ^1H NMR spectroscopy): IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR (270 MHz) δ 0.93 (t, *J* = 7.3 Hz, CH_2*Me* for **17b**), 0.95 (t, *J* = 7.3 Hz, CH_2*Me* for **17a**), 1.57-1.79 (m, 2 H), 1.64 (d, *J* = 7.3 Hz, CH*Me* for **17b**), 1.71 (d, *J* = 6.9 Hz, CH*Me* for **17a**), 3.08 (td, *J* = 6.9, 2.0 Hz, 1 H), 3.45-3.49 (m, 1 H), 4.27 (d, *J* = 3.6 Hz, SCH for **17a**), 4.34 (d, *J* = 3.6 Hz, SCH for **17b**), 4.51 (q, *J* = 6.9 Hz, PhC*H* for **17a**), 4.93 (q, *J* = 7.3 Hz, PhC*H* for **17b**), 7.06-7.34 (m, 15 H). Anal. Calcd for $C_{26}H_{27}NOS_2$: C, 72.02; H, 6.28; N, 3.23. Found: C, 71.82; H, 6.26; N, 3.23. When a similar reaction on **11** (2.22 g, 4.33 mmol) was carried out in boiling toluene, a 77:23 mixture of **17a,b** (1.31 g, 70%) was obtained.

(3*R*,4*S*)- and (3*S*,4*R*)-3-Ethyl-1-[(*S*)-1-phenylethyl]-4-[(phenylthio)methyl]-2-azetidinones (18a,b). To a solution of a mixture of **17a,b** (77:23) (500 mg, 1.15 mmol) in toluene (15 mL) were added Bu_3SnH (503 mg, 1.73 mmol) and AIBN (23 mg, 0.14 mmol), and the mixture was heated under reflux for 2 h. After usual work-up, the crude product was chromatographed on silica gel (hexane/AcOEt, 15:1). The first eluate gave **18a** (179 mg, 48%) as an oil: $[\alpha]^{21}_D$ -16.9° (*c*, 0.64, EtOH); IR (CCl_4) ν 1745 cm^{-1}; ^1H NMR

(270 MHz) δ 0.95 (t, J = 7.4 Hz, 3 H), 1.49-1.80 (m, 2 H), 1.68 (d, J = 6.9 Hz, 3 H), 2.66 (dd, J = 13.5, 8.9 Hz, 1 H), 2.73 (td, J = 7.6, 2.0 Hz, 1 H), 2.92 (dd, J = 13.5, 4.0 Hz, 1 H), 3.27 (ddd, J = 8.9, 4.0, 2.0 Hz, 1 H), 4.68 (q, J = 6.9 Hz, 1 H), 7.11-7.40 (m, 10 H); HRMS calcd for $C_{20}H_{23}NOS$ 325.1500, found 325.1499. Anal. Calcd for $C_{20}H_{23}NOS$: C, 73.81; H, 7.12; N, 4.30. Found: C, 73.31; H, 6.85; N, 3.97. The second eluate gave a mixture of **18a,b** (64 mg, 18%) as an oil. The third eluate gave **18b** (32 mg, 9%) as an oil: IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (270 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.48-1.73 (m, 2 H), 1.65 (d, J = 7.3 Hz, 3 H), 2.77 (ddd, J = 7.6, 6.3, 2.0 Hz, 1 H), 2.80 (dd, J = 13.9, 10.2 Hz, 1 H), 3.16 (dd, J = 13.9, 4.0 Hz, 1 H), 3.17 (ddd, J = 10.2, 4.0, 2.0 Hz, 1 H), 4.94 (q, J = 7.3 Hz, 1 H), 7.07-7.40 (m, 10 H). Anal. Calcd for $C_{20}H_{23}NOS$: C, 73.81; H, 7.12; N, 4.30. Found: C, 73.75; H, 7.20; N, 4.32.

(2*S*,3*R*)-3-Ethyl-1-[(*S*)-1-phenylethyl]-4-oxo-2-azetidinecarboxaldehyde (20). To an ice cooled solution of **18a** (250 mg, 0.77 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise a solution of *m*-CPBA (80%) (166 mg, 0.77 mmol) in CH_2Cl_2 (15 mL) over 30 min, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was washed with a saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was evaporated off, and the residue containing sulfoxide **19** was dissolved in dry CH_2Cl_2 (10 mL). To this were added successively 2,6-lutidine (165 mg, 1.54 mmol) and TFAA (323 mg, 1.54 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. A saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture and the solution was stirred vigorously for 30 min. The organic layer was separated, the aqueous layer was further extracted with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel (hexane/AcOEt, 4:1) to give **20** (176 mg, 99% based on **18a**) as an oil: IR (CCl_4) ν 1760, 1735 cm^{-1}; ^1H NMR (270 MHz) δ 1.01 (t, J = 7.3 Hz, 3 H), 1.59-1.95 (m, 2 H), 1.68 (d, J = 6.9 Hz, 3 H), 3.02 (ddd, J = 8.3, 5.9, 2.3 Hz, 1 H), 3.64 (dd, J = 4.6, 2.3 Hz, 1 H), 4.91 (q, J = 6.9 Hz, 1 H), 7.26-7.39 (m, 5 H), 9.10 (d, J = 4.6 Hz, 1 H). Due to its lability, this compound was used immediately in the next step.

(3*R*,4*S*)-3-Ethyl-4-[(*S*)- and (*R*)-1-hydroxy-2-(trimethylsilyl)ethyl]-1-[(*S*)-1-phenylethyl]-2-azetidinone (21a,b). To a solution of (trimethylsilyl)methylmagnesium chloride (1 M solution in diethyl ether) (0.71 mL, 0.71 mmol) in diethyl ether (4 mL) was added a solution of **20** (130 mg, 0.59 mmol) in dry diethyl ether (2 mL), and the mixture was heated under reflux for 1.5 h. A saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture, which was then extracted with diethyl ether. The extract was dried over $MgSO_4$ and concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 7:1). The first eluate gave **21b** (26 mg, 23%): mp 79-80 °C (hexane); IR (CCl_4) ν 3580, 3450, 1745 cm^{-1}; ^1H NMR (270 MHz) δ 0.00 (s, 9 H), 0.53-0.65 (m, 2 H), 1.06 (t, J = 7.3 Hz, 3 H), 1.30 (s, 1 H), 1.65-1.87 (m, 2 H), 1.75 (d, J = 6.9 Hz, 3 H), 2.68 (td, J = 7.3, 2.3 Hz, 1 H), 3.19 (dd, J = 7.3, 2.3 Hz, 1 H), 3.61 (dt, J = 13.2, 6.6 Hz, 1 H), 5.06 (q, J = 6.9 Hz, 1 H), 7.30-7.45 (m, 5 H). Anal. Calcd for $C_{18}H_{29}NO_2Si$: C, 67.66; H, 9.15; N, 4.38. Found: C, 67.35; H, 9.17; N. 4.39. The second eluate gave **21a** (38 mg, 33%) as an oil: IR (CCl_4) ν 3580, 3420, 1725 cm^{-1}; ^1H NMR (270 MHz) δ 0.00 (s, 9 H), 0.53 (dd, J = 14.5, 4.6 Hz, 1 H), 0.67 (dd, J = 14.5, 9.6 Hz, 1 H), 1.09 (t, J = 7.3 Hz, 3 H), 1.33 (s, 1 H), 1.66-1.89 (m, 2 H), 1.75 (d, J = 7.3 Hz, 3 H), 3.08 (td, J = 7.3, 2.0 Hz, 1 H), 3.25 (t, J = 2.0 Hz, 1 H), 3.55 (ddd, J = 9.6, 4.6, 2.0 Hz, 1 H), 5.03 (q, J = 7.3 Hz, 1 H), 7.34-7.48 (m, 5 H). Anal. Calcd for $C_{18}H_{29}NO_2Si$: C, 67.66; H, 9.15; N, 4.38. Found: C, 67.33; H, 9.29; N, 4.20.

(3*R*,4*R*)-4-Ethenyl-3-ethyl-1-[(*S*)-1-phenylethyl]-2-azetidinone (22). To an ice cooled solution of a mixture of **21a** and **21b** (24 mg, 0.75 mmol) in CH_2Cl_2 (1 mL) was added BF_3 diethyl etherate complex (0.1 mL), and the mixture was stirred at the same temperature for 2 h. The reaction mixture was washed successively with water and a saturated $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 7:1) to give **22** (15 mg, 87%) as an oil: $[\alpha]^{23}_D$ +38.1° (*c*, 0.32, EtOH); IR (CCl_4) ν 1745 cm^{-1}; ^1H NMR (270 MHz) δ 0.97 (t, J = 7.4 Hz, 3 H), 1.53-1.88 (m, 2 H), 1.71 (d, J = 7.3 Hz, 3 H), 2.76 (ddd, J = 8.6, 5.6, 2.0 Hz, 1 H), 3.56 (dd, J = 8.6, 2.0 Hz, 1 H), 4.51 (q, J = 7.3 Hz, 1 H), 5.10 (dd, J = 9.9, 0.7 Hz, 1 H), 5.16 (dt, J = 17.2, 0.7 Hz, 1 H), 5.65 (ddd, J = 17.2, 9.9, 8.6 Hz, 1 H), 7.22-7.36 (m, 5 H); HRMS (FAB) calcd for $C_{15}H_{20}NO$ ($M+H^+$) 230.1545, found 230.1564.

(2*R*,3*R*)-3-Ethyl-4-oxo-1-[(*S*)-1-phenylethyl]azetidine-2-ethanol (23). 2-Methyl-2-butene (2 M solution in THF) (0.28 mL, 0.56 mmol) was added to a THF solution of borane-THF complex (1 M solution in THF) (0.28 mL, 0.28 mmol) at -15 °C, and the mixture was stirred at 0 °C for 1 h. To the resulting solution of disiamylborane was added dropwise a solution of **22** (26 mg, 0.11 mmol) in THF (3 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. 30% H_2O_2 solution (1 mL) and 20% NaOH solution (1 mL) were added to the mixture at 0 °C, and stirring was continued overnight. The reaction mixture was extracted with AcOEt, and the extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated.

The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **23** (21 mg, 77%) as an oil: $[\alpha]^{21}_D$ -11.1° (*c*, 0.35, EtOH); IR (CCl_4) ν 3640, 3420, 1720 cm^{-1}; ^1H NMR (270 MHz) δ 0.99 (t, *J* = 7.4 Hz, 3 H), 1.38-1.97 (m, 5 H), 1.71 (d, *J* = 7.3 Hz, 3 H), 2.73 (ddd, *J* = 8.3, 6.0, 2.0 Hz, 1 H), 3.30 (ddd, *J* = 9.2, 4.0, 2.0 Hz, 1 H), 3.55 (t, *J* = 6.3 Hz, 2 H), 4.69 (q, *J* = 7.3 Hz, 1 H), 7.23-7.36 (m, 5 H); HRMS calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1577.

(3*R*,4*R*)-1-(*tert*-Butyldimethylsilyl)-4-[2-[(*tert*-butyldimethylsilyl)-oxy]ethyl]-3-ethyl-2-azetidinone (24). Sodium (10 mg, 0.425 mmol) and a solution of **23** (21 mg, 0.085 mmol) in dry THF (2 mL) were added successively to liquid ammonia (2 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 dried ($MgSO_4$) and concentrated to give crude (2*R*,3*R*)-3-ethyl-4-oxo-2-azetidineethanol, which was then dissolved in CH_2Cl_2 (4 mL). To this were added successively 2,6-lutidine (91 mg, 0.85 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (112 mg, 0.425 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. After methanol (0.5 mL) had been added to the reaction mixture, the solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **24**[14] (31 mg, 98% based on **23**) as an oil: $[\alpha]^{24}_D$ -39.68° (*c*, 0.32, $CHCl_3$) [lit.[14] $[\alpha]^{25}_D$ -39.59° (*c*, 2.92, $CHCl_3$)]; IR (CCl_4) ν 1740 cm^{-1}; ^1H NMR (270 MHz) δ 0.05 (s, 6 H), 0.20 (s, 3 H), 0.24 (s, 3 H), 0.89 (s, 9 H), 0.96 (s, 9 H), 1.01 (t, *J* = 7.4 Hz, 3 H), 1.50-1.85 (m, 3 H), 2.08 (dddd, *J* = 13.2, 7.9, 5.9, 3.3 Hz, 1 H), 2.79 (ddd, *J* = 7.6, 6.6, 2.6 Hz, 1 H), 3.37 (dt, *J* = 10.2, 2.6 Hz, 1 H), 3.56-3.74 (m, 2 H). Anal. Calcd for $C_{19}H_{41}NO_2Si_2$: C, 61.39; H, 11.12; N, 3.77. Found: C, 61.12; H, 10.97; N, 3.94.

2-Bromo-*N*-[(*S*)-1-phenylethyl]-*N*-[2-(phenylthio)ethenyl]butanamide (26). (*S*)-1-Phenylethylamine (4) (1.2 g, 9.92 mmol) and $MgSO_4$ (10 g) were added to a solution of (phenylthio)acetaldehyde (1.5 g, 9.92 mmol) in diethyl ether (40 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. $MgSO_4$ was removed by filtration, the filtrate was concentrated *in vacuo*, and the resulting crude imine was dissolved in toluene. *N,N*-Diethylaniline (1.48 g, 9.92 mmol) was added to the solution, and the mixture was cooled to -78 °C. 2-Bromobutyryl bromide (2.96 g, 12.9 mmol) was added to the solution, and the mixture was stirred for 15 h during which time the bath temperature was allowed to warm to room temperature. The reaction mixture was washed with water, and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/AcOEt, 15:1) to give **26** (1.82 g, 47%) as an oil: IR (CCl_4) ν 1665 cm^{-1}; ^1H NMR (300 MHz) δ 1.03 (t, *J* = 7.3 Hz, 3 H x 3/4), 1.04 (t, *J* = 7.3 Hz, 3 H x 1/4), 1.63 (br d, *J* = *ca.* 4.5 Hz, 3 H), 1.98-2.23 (m, 2 H), 4.49 (t, *J* = 7.1 Hz, 1 H x 3/4), 4.51 (t, *J* = 7.1 Hz, 1 H x 1/4), 5.93 (d, *J* = 12.5 Hz, 1 H x 1/4), 5.95 (d, *J* = 13.7 Hz, 1 H x 3/4), 6.05-6.45 (m, 1 H), 6.94-7.10 (m, 2 H), 7.14-7.45 (m, 9 H); HRMS calcd for $C_{20}H_{22}BrNOS$ 403.0606, found 403.0623.

Radical Cyclization of 26. Following the general procedure, compound **26** (252 mg, 0.64 mmol) was treated with Bu_3SnH (206 mg, 0.71 mmol) in the presence of AIBN (12.6 mg, 0,08 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 **18a** and **18b** (50 mg, 24%) in a ratio of 58:42 (determined by ^1H NMR spectroscopy).

(2*R*,3*S*)-3-Acetoxy-2-bromo-*N*-[(*S*)-1-phenylethyl]-*N*-[2,2-bis(phenylthio)ethenyl]butanamide (28). Using a procedure similar to that described above **8**, enamine **6** (5.58 g, 15.36 mmol) was treated with acid chloride **27**[5] (7.5 g, 30.72 mmol) to give for **28** (1.87 g, 21%) as an oil: IR (CCl_4) ν 1745, 1670 cm^{-1}; ^1H NMR (60 MHz) δ 1.3-2.2 (m, 9 H), 4.5-4.8 (m, 1 H), 5.0-5.7 (m, 1 H), 5.8-6.4 (m, 2 H), 6.9-7.6 (m, 15 H). Anal. Calcd for $C_{28}H_{28}BrNO_3S_2$: C, 58.94; H, 4.95; N, 2.45. Found: C, 59.35; H, 5.09; N, 2.94.

(3*S*,4*S*)- and (3*R*,4*R*)-3-[(*S*)-1-Acetoxyethyl]-1-[(*S*)-1-phenylethyl]-4-[bis(phenylthio)-methyl]-2-azetidinones (29a,b). Following the general procedure, bromide **28** (220 mg, 0.39 mmol) was treated with Bu_3SnH (123 mg, 0.42 mmol) and AIBN (8 mg, 0.05 mmol) in boiling benzene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1) to give an oily mixture of **29a** and **29b** (75 mg, 40%) in a ratio of 78:22 (determined by ^1H NMR spectroscopy): IR (CCl_4) ν 1755 cm^{-1}; ^1H NMR for **29a** (270 MHz) δ 1.39 (d, *J* = 6.6 Hz, 3 H), 1.70 (d, *J* = 7.3 Hz, 3 H), 1.90 (s, 3 H), 3.31 (dd, *J* = 3.6, 2.6 Hz, 1 H), 3.56 (dd, *J* = 3.6, 2.6 Hz, 1 H), 4.25 (d, *J* = 3.6 Hz, 1 H), 4.42 (q, *J* = 7.3 Hz, 1 H), 5.15 (qd, *J* = 6.6, 3.6 Hz, 1 H), 7.19-7.45 (m, 15 H). A small peak due to the *O*-acetyl methyl protons of **29b** appeared at δ 1.96 as a singlet. Anal. Calcd for $C_{28}H_{29}NO_3S_2$: C, 68.40; H, 5.94; N, 2.85. Found: C, 68.13; H, 6.05; N, 3.28. When a similar reaction of **28** (207 mg, 0.36 mmol) was carried out in boiling toluene, an 88:12 mixture of **29a,b** (51 mg, 29%) was obtained.

(3*S*,4*S*)-3-[(*S*)-1-Acetoxyethyl]-1-[(*S*)-1-phenylethyl]-4-[(phenylthio)methyl]-2-azetidinone (30a). A solution of **29a,b** (600 mg, 1.22 mmol), Bu_3SnH (426 mg, 1.46 mmol), and AIBN (24 mg, 0.15 mmol) in toluene (10 mL) was heated under reflux for 1 h. After usual work-up, the crude material was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **30a** (334 mg, 71%) as an oil: IR (CCl_4) ν 1755 cm^{-1}; ^1H NMR (270 MHz) δ 1.32 (d, *J* = 6.6 Hz, 3 H), 1.69 (d, *J* = 7.3 Hz, 3 H), 1.96 (s, 3 H), 2.71 (dd, *J* = 13.9, 8.6 Hz, 1 H), 2.92 (dd, *J* = 13.9, 3.6 Hz, 1 H), 2.98 (dd, *J* = 3.6, 2.3 Hz, 1 H), 3.38 (ddd, *J* = 8.6, 3.6, 2.3 Hz, 1 H), 4.57 (q, *J* = 7.3 Hz, 1 H), 5.10 (qd, *J* = 6.6, 3.6 Hz, 1 H), 7.16-7.37 (m, 10 H); HRMS calcd for $C_{22}H_{25}NO_3S_2$ 383.1579, found 383.1567.

(3*S*,4*S*)-3-[(*S*)-1-Hydroxyethyl]-1-[(*S*)-1-phenylethyl]-4-[(phenylthio)methyl]-2-azetidinone (31). To a solution of **30a** (143 mg, 0.37 mmol) in pyridine (1 mL) was added dropwise 0.1 N NaOH solution (1.5 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 solution was extracted with AcOEt. The organic phase was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **31** (119 mg, 94%) as an oil: IR (CCl_4) ν 3440, 1740 cm^{-1}; ^1H NMR (270 MHz) δ 1.25 (d, *J* = 6.3 Hz, 3 H), 1.68 (d, *J* = 7.3 Hz, 3 H), 2.56 (br s, 1 H), 2.68 (dd, *J* = 13.5, 8.9 Hz, 1 H), 2.84 (dd, *J* = 5.9, 2.0 Hz, 1 H), 2.92 (dd, *J* = 13.5, 4.0 Hz, 1 H), 3.50 (ddd, *J* = 8.9, 4.0, 2.0 Hz, 1 H), 3.97 (qd, *J* = 6.3, 5.9 Hz, 1 H), 4.68 (q, *J* = 7.3 Hz, 1 H), 7.12-7.38 (m, 10 H); HRMS calcd for $C_{20}H_{23}NO_2S$ 341.1450, found 341.1443.

(3*S*,4*S*)-3-[(*S*)-1-(Formyloxy)ethyl]-1-[(*S*)-1-phenylethyl]-4-[(phenylthio)methyl]-2-azetidinone (32). A solution of diisopropyl azodicarboxylate (204 mg, 1.01 mmol) in dry THF (1 mL) was added dropwise to a solution of **31** (69 mg, 0.2 mmol), triphenylphosphine (132 mg, 0.51 mmol), and formic acid (9 mg, 0.51 mmol) in dry THF (2 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, 10:1) to give **32** (75 mg, quantitative) as an oil: IR (CCl_4) ν 1750, 1720 cm^{-1}; ^1H NMR (270 MHz) δ 1.34 (d, *J* = 6.3 Hz, 3 H), 1.70 (d, *J* = 7.3 Hz, 3 H), 2.70 (dd, *J* = 13.4, 8.3 Hz, 1 H), 2.97 (dd, *J* = 13.4, 4.0 Hz, 1 H), 3.03 (dd, *J* = 6.3, 2.0 Hz, 1 H), 3.59 (ddd, *J* = 8.3, 4.0, 2.0 Hz, 1 H), 4.64 (q, *J* = 7.3 Hz, 1 H), 5.29 (quint, *J* = 6.3 Hz, 1 H), 7.1-7.4 (m, 10 H), 7.92 (s, 1 H); HRMS calcd for $C_{21}H_{23}NO_3S$ 369.1398, found 369.1395.

(3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-1-[(*S*)-1-phenylethyl]-4-[(phenylthio)methyl]-2-azetidinone (33). To a solution of **32** (90 mg, 0.24 mmol) in methanol (10 mL) was added ten drops of 10% HCl at 0 °C, and the mixture was stirred at room temperature for 5 h. After completion of hydrolysis, brine (25 mL) was added to the reaction mixture, and the solution was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated in vacuo, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **33** (80 mg, 96%): mp 103.5-104.5 °C (hexane/AcOEt); IR (CCl_4) ν 3440, 1745 cm^{-1}; ^1H NMR (270 MHz) δ 1.26 (d, *J* = 6.3 Hz, 3 H), 1.69 (d, *J* = 6.9 Hz, 3 H), 2.01 (br s, 1 H), 2.67 (dd, *J* = 13.9, 8.6 Hz, 1 H), 2.89 (dd, *J* = 5.6, 2.0 Hz, 1 H), 2.96 (dd, *J* = 13.9, 4.0 Hz, 1 H), 3.64 (ddd, *J* = 8.6, 4.0, 2.0 Hz, 1 H), 4.12 (quint, *J* = 5.9 Hz, 1 H), 4.70 (q, *J* = 6.9 Hz, 1 H), 7.11-7.39 (m, 10 H); HRMS calcd for $C_{20}H_{23}NO_2S$ 341.1450, found 341.1469.

(3*S*,4*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-[(*S*)-1-phenylethyl]-4-[(phenylthio)methyl]-2-azetidinone (34). To a solution of **33** (47 mg, 0.14 mmol) in DMF (3 mL) were added successively *tert*-butyldimethylsilyl chloride (104 mg, 0.69 mmol) and triethylamine (98 mg, 0.97 mmol), and the mixture was stirred at room temperature for 6 h. Ethyl acetate (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 **34** (62 mg, 99%): mp 91.5-92.0 °C (hexane); $[\alpha]^{24}_D$ -13.4 ° (*c* 1.4, EtOH); IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR (270 MHz) δ 0.03 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.68 (d, *J* = 7.3 Hz, 3 H), 2.71 (dd, *J* = 13.5, 7.6 Hz, 1 H), 2.84 (dd, *J* = 3.6, 2.0 Hz, 1 H), 2.94 (dd, *J* = 13.5, 4.0 Hz, 1 H), 3.78 (ddd, *J* = 7.6, 4.0, 2.0 Hz, 1 H), 4.18 (qd, *J* = 6.3, 3.6 Hz, 1 H), 4.72 (q, *J* = 7.3 Hz, 1 H), 7.09-7.35 (m, 10 H). Anal Calcd for $C_{26}H_{37}NO_2SSi$: C, 68.52; H, 8.18; N, 3.07. Found: C, 68.22; H, 8.28; N, 2.61.

(2*S*,3*S*)-3-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-[(*S*)-1-phenylethyl]-4-oxo-2-azetidinecarboxaldehyde (35). According to a procedure similar to that described above for the preparation of **20** from **18a**, compound **34** (62 mg, 0.14 mmol) was oxidized with *m*-CPBA (80%) (30 mg, 0.14 mmol), and the resulting sulfoxide was treated successively with TFAA (57 mg, 0.27 mmol) in the presence of 2,6-lutidine (29 mg, 0.27 mmol) and then with a saturated $NaHCO_3$ solution. After workup, the crude material was

chromatographed on silica gel (hexane/AcOEt, 5:1) to give aldehyde **35** (49 mg, quantitative) as an oil: IR (CCl_4) ν 1760, 1730 cm^{-1}; ^1H NMR (270 MHz) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.65 (d, *J* = 6.9 Hz, 3 H), 3.02 (t, *J* = 2.6 Hz, 1 H), 4.12 (dd, *J* = 4.6, 2.6 Hz, 1 H), 4.30 (qd, *J* = 6.3, 2.6 Hz, 1 H), 4.97 (q, *J* = 6.9 Hz, 1 H), 7.28-7.38 (m, 5 H), 9.10 (d, *J* = 4.6 Hz, 1 H); HRMS (FAB) calcd for $C_{20}H_{32}NO_3Si$ ($M+H^+$) 362.2151, found 362.2154.

(2*S*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-[(*S*)-1-phenylethyl]-4-oxo-2-azetidinemethanol (36). To a solution of **35** (53 mg, 0.15 mmol) in ethanol (2 mL) was added sodium borohydride (19 mg, 0.44 mmol) and the mixture was heated at 40 °C for 1.5 h. The mixture was acidified with 5% HCl and the solution was extracted with ethyl acetate. The organic phase was washed successively 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 **36** (28 mg, 52%): mp 91.5-92.5 °C (hexane/AcOEt); $[\alpha]^{22}_D$ -5.4° (*c* 1.4, EtOH); IR (CCl_4) ν 3610, 3420, 1745 cm^{-1}; ^1H NMR (270 MHz) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.19 (d, *J* = 6.3 Hz, 3 H), 1.25 (s, 1 H), 1.66 (d, *J* = 6.9 Hz, 3 H), 2.94 (dd, *J* = 4.6, 2.3 Hz, 1 H), 3.32-3.48 (m, 2 H), 3.79 (td, *J* = 3.7, 2.3 Hz, 1 H), 4.21 (qd, *J* = 6.3, 4.6 Hz, 1 H), 5.01 (q, *J* = 6.9 Hz, 1 H), 7.26-7.43 (m, 5 H); HRMS (FAB) calcd for $C_{20}H_{34}NO_3Si$ ($M+H^+$) 364.2308, found 364.2307.

(2*S*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-oxo-2-azetidinemethanol (37). According to a procedure similar to that described above for the preparation of **24** from **23**, compound **36** (25 mg, 0.07 mmol) was treated with sodium (8 mg, 0.35 mmol) in liquid ammonia (2 m L) and THF (2 mL), and the crude material was chromatographed on silica gel (hexane/AcOEt, 1:2) to give **37**[20] (11 mg, 62%): mp 89.5-90.5 °C (hexane/AcOEt) [lit.[20] mp 89-90 °C]; $[\alpha]^{22}_D$ -15.3° (*c* 0.55, $CHCl_3$)[lit.[20] $[\alpha]^{24}_D$ -14.1° (*c* 0.625, $CHCl_3$)]; IR (CCl_4) ν 3300, 1750 cm^{-1}; ^1H NMR (270 MHz) δ 0.08 (s, 6 H), 0.88 (s, 9 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 2.5-2.7 (br, 1 H), 2.92 (dd, *J* = 4.6, 1.3 Hz, 1 H), 3.60-3.73 (m, 1 H), 3.80-3.88 (m, 2 H), 4.20 (qd, *J* = 6.3, 4.6 Hz, 1 H), 6.21-6.35 (br, 1 H).

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References and Notes

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