Sulfur-Directed Regioselective Radical Cyclization Leading to β-Lactams: Formal Synthesis of (±)-PS-5 and (+)-Thienamycin

Hiroyuki Ishibashi,* Chisato Kameoka, Hiroko Iriyama, Kazuya Kodama, Tatsunori Sato, and Masazumi Ikeda*

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Received October 10, 1994[⊗]

A new method for the synthesis of β-lactams by tributyltin hydride (Bu_3SnH)-mediated radical cyclizations of *N*-ethenyl-α-bromo amides bearing sulfur-substituent(s) at the terminus of the *N*-vinylic bond is described. *N*-[2-(Phenylthio)ethenyl]-α-bromoacetamide (**11**), upon treatment with Bu_3SnH in the presence of azobis(isobutyronitrile) (AIBN) in boiling toluene, underwent radical cyclization in a 4-*exo-trig* manner to give β-lactam **13**, but in low yield (22%), whereas *N*-[2,2-bis-(phenylthio)ethenyl] congener **23** cyclized with a high degree of effeciency to give β-lactam **25** and a partially desulfurized lactam **13** in 70% combined yield. The effectiveness of the 4-*exo* cyclization of **23** can be explained in terms of the high stability of the intermediate of radical **19b**. Similar treatment of α-bromobutanamide **24** with Bu_3SnH afforded, in 58% yield, β-lactam **26**, which was transformed, via aldehyde **31**, into the key intermediate **35** for the synthesis of (±)-PS-5 (**36**). 1,2-Asymmetric induction in radical cyclizations leading to β-lactams was then examined. Cyclization of (2*S*,3*R*)-3-acetoxy-2-bromo-*N*-[2-(phenylthio)ethenyl]butanamide (**38**) proceeded with no diastereoselectivity to give β-lactams **40a** and **40b** in approximately equal amounts. However, 2,2-bis-(phenylthio) congener **39** provided (3*R*,4*R*)-2-azetidinone **41a** and its (3*S*,4*S*)-isomer **41b** in a ratio of ca. 2:1. Similarly, (2*R*,3*S*)-butanamide **47** afforded **48a** as a major product. Saponification of **48a** followed by partial desulfurization of **49** gave alcohol **50**, which was then subjected to Mitsunobu inversion to afford **52**. This compound was converted into the key intermediate **56** for the synthesis of (+)-thienamycin (**58**). Reversibility of the radical cyclization leading to the β-lactams is discussed.

Introduction

In a series of papers[1] concerning the use of radical cyclizations of α-haloamides in the synthesis of nitrogen-containing heterocyclic molecules, we reported that *N*-vinylic α-chloroacetamides **1a** and **1b** underwent radical cyclization in different manners.[2] Enamide **1a** derived from 2-tetralone, upon treatment with tributyltin hydride (Bu_3SnH) in the presence of azobis(isobutyronitrile) (AIBN), cyclized in a 4-*exo-trig* manner to give β-lactam **2**, whereas enamide **1b** derived from 2-benzosuberone cyclized in a 5-*endo-trig* manner to give γ-lactam **3**. The difference between the modes of cyclization of **1a** and **1b** was explained by assuming the electronic stability of radical intermediates **5** and **6**. Thus, inspection of molecular models indicates that radical **5a**, generated by 4-*exo-trig* cyclization of carbamoylmethyl radical **4a**, should be well-stabilized due to an excellent overlapping of the *p*-orbital of the radical center with the neighboring aromatic π-system, while the corresponding *p*-orbital of radical **5b** is almost perpendicular to the aromatic π-system in its most stable conformation. Therefore, radical **4a** is expected to cyclize so as to form more stabilized benzylic radical **5a** in preference to α-acylamino radical **6a**, while radical **4b** cyclizes to α-acylamino radical **6b** in preference to the less stabilized benzylic radical **5b**.

Shortly after our publication, Belletire et al.[3] reported that enamide **7** bearing two phenyl groups at the terminus of the *N*-vinylic bond, upon treatment with Bu_3SnH, gave β-lactam **9**. The highly stable intermediate radical **8**, which is flanked by two phenyl groups, would play a crucial role in effecting the 4-*exo* cyclization. Our interest has now turned to the feasibility of using a sulfur substituent as a radical stabilizing group in the radical cyclizations leading to monocyclic β-lactams. We found that enamides bearing two phenylthio groups at the terminus of the *N*-vinylic bond such as **23** and **24** underwent radical cyclization with high efficiency to give β-lactams in good yields. The high regioselectivity of the cyclization coupled with the versatility of having sulfur substituents in the products make the method useful for the synthesis of many therapeutically important β-lactam antibiotics. This paper describes the results of our work in this area, including studies on diastereoselectivity in the radical cyclization of enamides bearing a chiral functionality. Applications of the methods to the formal synthesis of carbapenem antibiotics (±)-PS-5 and (+)-thienamycin are also presented.[4]

Results and Discussion

Radical Cyclizations of *N*-[2-(Phenylthio)ethenyl]-α-bromoamides. We initiated our investigation by examining the cyclization of enamides **11** and **12** having a phenylthio group at the terminus of the *N*-vinylic bond.

[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1995.

(1) (a) Sato, T.; Wada, Y.; Nishimoto, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 879. (b) Ishibashi, H.; So, T. S.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M. *J. Org. Chem.* **1991**, *56*, 95. (c) Sato, T.; Ishida, S.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 353. (d) Sato, T. Tsujimoto, K.; Matsubayashi, K.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1992**, *40*, 2308. (e) Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Org. Chem.* **1993**, *58*, 2360.

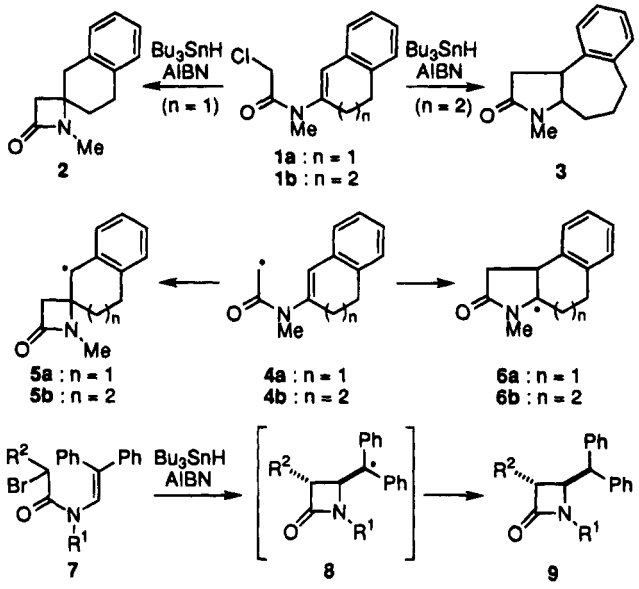
(2) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399.

(3) Fremont, S. L.; Belletire, J. L.; Ho, D. M. *Tetrahedron Lett.* **1991**, *32*, 2335.

(4) For a preliminary account of a portion of this work, see: Ishibashi, H.; Kameoka, C.; Yoshikawa, A.; Ueda, R.; Kodama, K.; Sato, T.; Ikeda, M. *Synlett* **1993**, 649.

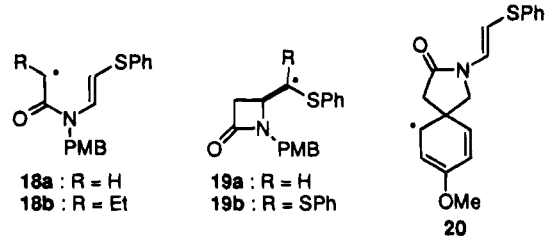
0022-3263/95/1960-1276$09.00/0

Scheme 1



Enamides **11** and **12** were prepared by condensation of (phenylthio)acetaldehyde with *p*-methoxybenzylamine followed by *N*-acylation of the resulting imine **10** with bromoacetyl bromide or 2-bromobutyryl bromide at −78 °C and then at room temperature in the presence of *N,N*-diethylaniline.

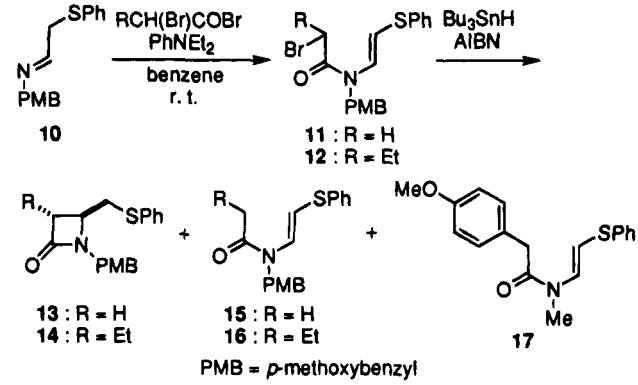
A toluene solution of Bu_3SnH (1.1 equiv) and AIBN (0.1 equiv) was added slowly to a boiling solution of **11** in toluene (0.01 M) over 3 h, and the mixture was further heated for additional hours until any starting material was not detected by TLC (General Procedure). After workup, the crude material was chromatographed on silica gel to give β-lactam **13** in 22% yield; a reduction product **15** and a rearrangement product **17** were also obtained in 40 and 6% yields, respectively. This result clearly indicates that the phenylthio group is capable of stabilizing the radical center of **19a** formed by 4-*exo-trig* cyclization of carbamoylmethyl radical **18a**. Formation of an unexpected product **17** from **11** may involve an intramolecular ipso attack of carbamoylmethyl radical **18a**[5] on the *p*-methoxyphenyl group to give spiro radical **20**. This step is then followed by ring opening, with concomitant rearomatization, to give **17**.



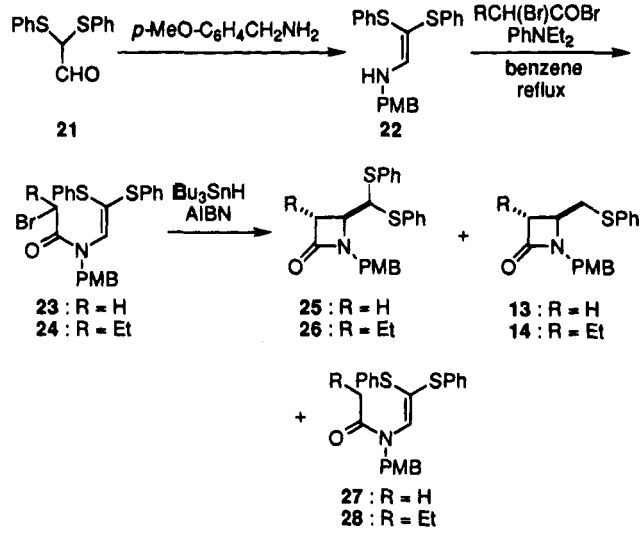
On the other hand, the cyclization of 2-bromobutanamide **12** proceeded more smoothly to give β-lactam **14** in 45% yield along with the reduction product **16** (14%). We previously noticed that alkyl-substituted carbamoylmethyl radicals show higher reactivity toward olefin cyclization than do nonsubstituted radicals.[1a] This is the case for the radicals **18a,b**.

It should be noted that β-lactam **14** was obtained as a single stereoisomer. ^1H NMR spectra of **14**, which showed a small coupling constant (J = 2.1 Hz) between

Scheme 2



Scheme 3



H-3 and H-4, established a trans relationship between the substituents at C_3 and C_4.

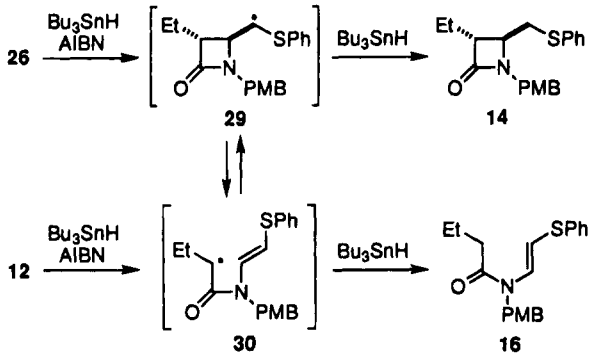
Bis(phenylthio)-substituted enamides **23** and **24** were prepared by condensation of bis(phenylthio)acetaldehyde with *p*-methoxybenzylamine followed by *N*-acylation of the resulting enamine **22** (not imine)[6] with bromoacetyl bromide or 2-bromobutyryl bromide in refluxing benzene in the presence of *N,N*-diethylaniline.

Enamide **23** was found to cyclize with high efficiency to give β-lactam **25** in 46% yield together with a partially desulfurized compound **13** (24%); only a 7% yield of the reduction product **27** was produced. The high combined yields (70%) of β-lactams **25** and **13** might be attributable to the high stability of radical intermediate **19b** which is flanked by two phenylthio groups. Similarly, enamide **24** afforded **26** (58%) and **14** (trace), along with the reduction product **28** (14%). Interestingly, when 2 equiv of Bu_3SnH were used in the cyclization of **24**, compound **16** was obtained in 15% yield together with **26** (27%), **14** (18%), and **28** (14%). Since enamide **28** was not desulfurized with Bu_3SnH–AIBN, formation of compound **16** from **24** may be explained as follows. Attack of tributyltin radical ($Bu_3Sn^•$) on the phenythio group of β-lactam **26**, formed by 4-*exo* cyclization of **24**, gives the radical

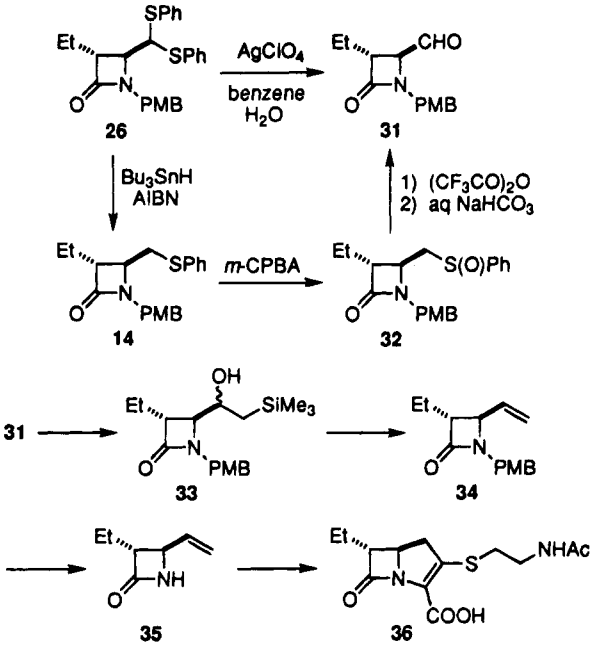
(5) Ishibashi, H.; Nakamura, N.; Ito, K.; Kitayama, S.; Ikeda, M. *Heterocycles* **1990**, *31*, 1781.

(6) ^1H NMR for **22** ($CDCl_3$, 60 MHz) δ 3.72 (s, 3 H), 4.15 (d, J = 6 Hz, 2 H), 5.0–5.7 (br, 1 H), 6.7–7.5 (m, 15 H). Formation of enamines of type **22** from bis(ethylthio)acetaldehyde and primary amines was reported, see: Bates, G.S.; Ramaswamy, S. *Can. J. Chem.* **1983**, *61*, 2466.

Scheme 4



Scheme 5



intermediate **29**, which is then reduced by Bu_3SnH to afford the normal desulfurized lactam **14**. On the other hand, ring-opening of the four-membered radical **29** provides new radical **30**, which is then reduced by Bu_3SnH to provide **16**. In fact, when a boiling solution of **26** in toluene was treated slowly with Bu_3SnH–AIBN, compound **16** was obtained in 7% yield along with the desulfurized lactam **14** (27%).[7] The result also suggested the ring-opening and cyclization between **29** and **30** to be reversible,[8] because radical **29** is an intermediate for the cyclization of bromide **12** leading to β-lactam **14**.

Formal Synthesis of (±)-PS-5. PS-5 (**36**) is a carbapenem antibiotic against Gram-positive and Gram-negative bacteria including β-lactamase-producing organisms.[9] We examined a transformation of the radical cyclization product **26** into the key intermediate **35** for the synthesis of (±)-PS-5.

Treatment of **26** with $AgClO_4$ in aqueous benzene[10] afforded aldehyde **31**, but in low yield (39%). We decided to prepare **31** by using the mono(phenylthio) derivative **14**. Although compound **14** could be obtained directly by radical cyclization of **12**, the partial desulfurization of **26** seemed to be the best choice for the preparation of **14**, since the overall yield of **26** from enamine **22** was much higher than was that of **14** from imine **10**. As noted above, a slow addition of Bu_3SnH into the solution of **26** resulted in the formation of the ring-opening product **16** as a byproduct together with the desired **14**. However, heating **26** in boiling benzene in the presence of 2 equiv of Bu_3SnH and a catalytic quantity of AIBN afforded **14** in excellent yield (86%). This may be because the radical intermediate **29** was immediately attacked by a large excess of Bu_3SnH under the reaction conditions employed.

Oxidation of **14** with *m*-chloroperbenzoic acid (*m*-CPBA) gave sulfoxide **32**. Treatment of **32** with trifluoroacetic anhydride (TFAA) in the presence of 2,6-lutidine afforded the Pummerer rearrangement product, which was then hydrolyzed with a saturated $NaHCO_3$ solution to give aldehyde **31** in 73% yield from **14**. Aldehyde **31** was converted to olefin **34** by employing a Peterson olefination.[11] Thus, Grignard coupling of **31** with trimethylsilylmethylmagnesium chloride in refluxing diethyl ether afforded, in 53% yield, a ca. 1:1 mixture of two diastereoisomers of alcohol **33**. Treatment of **33** with boron trifluoride diethyl etherate gave olefin **34** in 95% yield. Removal of the *p*-methoxybenzyl group was accomplished by treatment with ceric ammonium nitrate to give **35**[12] in 53% yield. Since compound **35** is convertible into (±)-PS-5,[12,13] the present synthesis of **35** is a formal synthesis of (±)-PS-5.[14]

1,2-Asymmetric Induction: Formal Synthesis of (+)-Thienamycin. Recently, great interest has been devoted to the controlling stereochemistry in radical addition and cyclization reactions.[15,16] Our attention was

(7) *N*-Ethenyl-*N*-[(4-methoxyphenyl)methyl]butanamide was also obtained in 24% yield (see Experimental Section). This compound might arise from **16**, since compound **16** was desulfurized with Bu_3SnH in the presence of AIBN in good yield (67%). The uneffectiveness of desulfurization of **28** giving **16** with Bu_3SnH is probably due to the steric reason.

(8) Reversibility of cyclization of 4-pentenyl radicals has frequently been discussed, see: Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 287. Park, S.-U.; Varick, T. R.; Newcomb, M. *Tetrahedron Lett.* **1990**, *31*, 2975. Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719. Ogura, K.; Sumitani, N.; Kayano, A.; Iguchi, H.; Fujita, M. *Chem. Lett.* **1992**, 1487.

(9) Okamura, K.; Hirata, S.; Koki, A.; Hori, K.; Shibamoto, N.; Okumura, Y.; Okabe, M.; Okamoto, R.; Kouno, K.; Fukagawa, Y.; Shimauchi, Y.; Ishikura, T. *J. Antibiot.* **1979**, *32*, 262. Sakamoto, M.; Iguchi, H.; Okamura, K.; Hori, S.; Fukagawa, Y.; Ishikura, T. *J. Antibiot.* **1979**, *32*, 272. Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, N.; Okamura, K.; Shimauchi, Y.; Ishikura, T. *J. Antibiot.* **1980**, *33*, 796.

(10) Mukaiyama, T.; Kobayashi, S.; Kamio, K.; Takei, H. *Chem. Lett.* **1972**, 237.

(11) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. Hudrick, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2263.

(12) Mukai, C.; Kataoka, O.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 563.

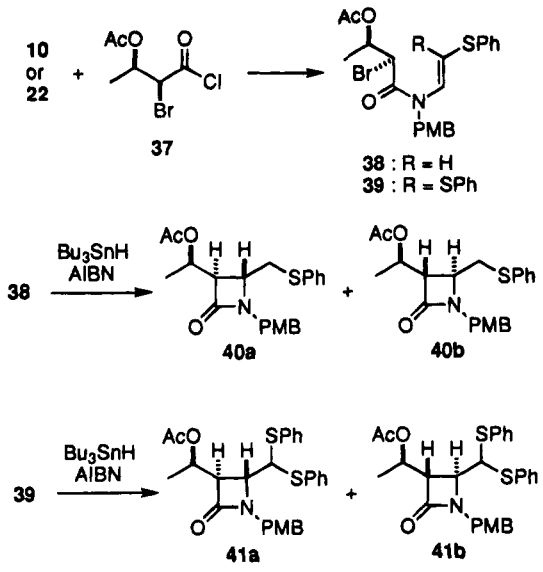
(13) Favara, D.; Omodei-Sale, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.* **1982**, *23*, 225.

(14) For a review on the synthesis of PS-5 and related carbapenem compounds, see: Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Ed.; Springer-Verlag: Berlin-Heidelberg, 1990; pp 565–612.

(15) For reviews, see: Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. Smadja, W. *Synlett* **1994**, 1.

(16) For recent references to the studies on controlling stereochemistry in radical addition and cyclization reactions, see: Thoma, G.; Curran, D. P.; Geib, S. V.; Giese, B.; Damm, W.; Wetterich, F. *J. Am. Chem. Soc.* **1993**, *115*, 8585. Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464. Giese, B.; Hoffmann, U.; Roth, M.; Velt, A. Wyss, C.; Zehnder, M.; Zipse, H. *Tetrahedron Lett.* **1993**, *34*, 2445. Giese, B.; Damm, W.; Wetterich, F.; Zeltz, H.-G.; Rancourt, J.; Gulndon, Y. *Tetrahedron Lett.* **1993**, *34*, 5885. Curran, D. P.; Sun, S. *Tetrahedron Lett.* **1993**, *34*, 6184. Curran, D. P.; Abraham, A. C. *Tetrahedron* **1993**, *49*, 4821. Curran, D. P.; Ramamoorthy, P. S. *Tetrahedron* **1993**, *49*, 4841. Beckwith, A. L. J.; Chai, C. L. L. *Tetrahedron* **1993**, *49*, 7871. Renaud, P.; Carrupt, P.-A.; Gerster, M.; Schenk, K. *Tetrahedron Lett.* **1994**, *35*, 1703. Curran, D. P.; Geib, S. J.; Lin, C.-H. *Tetrahedron Asymmetry* **1994**, *5*, 199. Zahouily, M.; Journet, M.; Malacria, M. *Synlett* **1994**, 366.

Scheme 6

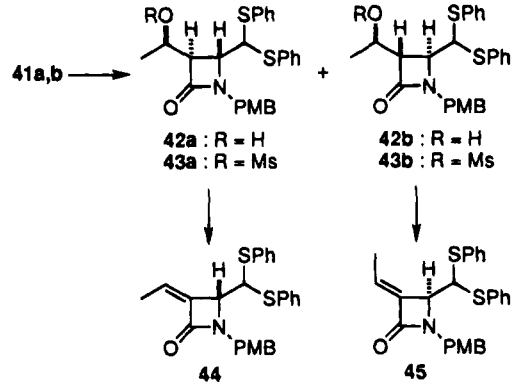


next turned to the 1,2-asymmetric induction in radical cyclizations of enamides **38** and **39** bearing a chiral oxygen functionality at the side chain, in the hope that a new route to carbapenem antibiotic (+)-thienamycin (**58**) might result. Thienamycin possesses a wide spectrum of antibacterial activity,[17] and the enormous commercial potential of thienamycin has resulted in intense and diverse synthetic effort.[18]

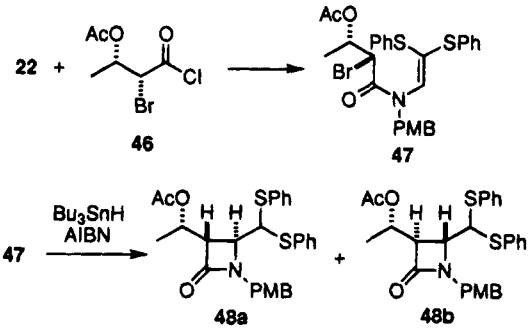
Enamides **38** and **39** were synthesized by reaction of **10** or **22** with (2*S*,3*R*)-3-acetoxy-2-bromobutyryl chloride (**37**),[19] prepared from L-threonine, by using a procedure similar to that described above for **11** or **23**, respectively.

Treatment of **38** with Bu_3SnH in the presence of AIBN gave a ca. 1:1 mixture of β-lactams **40a** and **40b** in 39% combined yield. Thus, no diastereoselectivity was observed for the formation of β-lactams **40a,b** from **38**. We found, however, that bis(phenylthio) congener **39** provided a ca. 2:1 mixture of β-lactams **41a** and **41b**. The combined yield of **41a,b** was also improved to 64%. The stereochemistries of (3*R*,4*R*)-isomer **41a** and (3*S*,4*S*)-isomer **41b** were confirmed according to a protocol reported by the Merck group.[20] Thus, the mixture of **41a,b** was saponified by 0.1 N NaOH in pyridine at room temperature to give the corresponding alcohols **42a** and **42b** in 49 and 23% yields, respectively, after separation by chromatography on silica gel. The major alcohol **42a** was then treated with methanesulfonyl chloride, and the resulting methanesulfonate **43a** was heated with $NaHCO_3$ in refluxing methanol to give (*Z*)-olefin **44**. A similar sequence of reactions of the minor alcohol **42b** afforded (*E*)-olefin **45**. ^1H NMR spectra showed that the olefinic proton signal of **44** appeared at δ 5.93, whereas the resonance of the corresponding proton of **45** shifted down

Scheme 7



Scheme 8



field to δ 6.23 due to the deshielding effect of the neighboring lactam carbonyl group. This was also the case for the methyl protons of **44** (δ 2.04) and **45** (δ 1.73). Since the base-promoted elimination of **43a,b** has to proceed via an E2 mechanism, the stereochemistries of methanesulfonates giving **44** and **45** were assigned as **43a** and **43b**, respectively, as depicted in Scheme 7, thereby confirming the stereochemistries of the original acetates **41a** and **41b**. The exact reason for the predominant formation of **41a** from **39**, however, is not clear at the moment.

Three stereocenters in **41b** have the identical configuration to those in (+)-thienamycin (**58**), but, unfortunately, compound **41b** was a minor product of the radical cyclization of **39**. Therefore, we examined the cyclization of enamide **47** having (3*S*)-acetoxy group. The expected major product **48a** (an enantiomer of **41a**) might be convertible to the key intermediate **57**[21,22] for the synthesis of (+)-thienamycin, through inversion of the oxygen functionality at the side chain.

The requisite acid chloride **46** for the synthesis of (2*R*,3*S*)-butanamide **47** was prepared from D-threonine according to the reported procedure for the synthesis of **37** from L-threonine.[19] Enamine **22** was then *N*-acylated with **46** to give enamide **47** in 79% yield. Treatment of **47** with Bu_3SnH in the presence of AIBN afforded a mixture of β-lactams **48a** and **48b** in a ratio of ca. 2:1 and in 58% combined yield. Saponification of **48a,b** with

(17) Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. S.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491. Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, C.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1.

(18) For a review of enantioselective synthesis of carbapenem antibiotics including (+)-thienamycin, see: Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729.

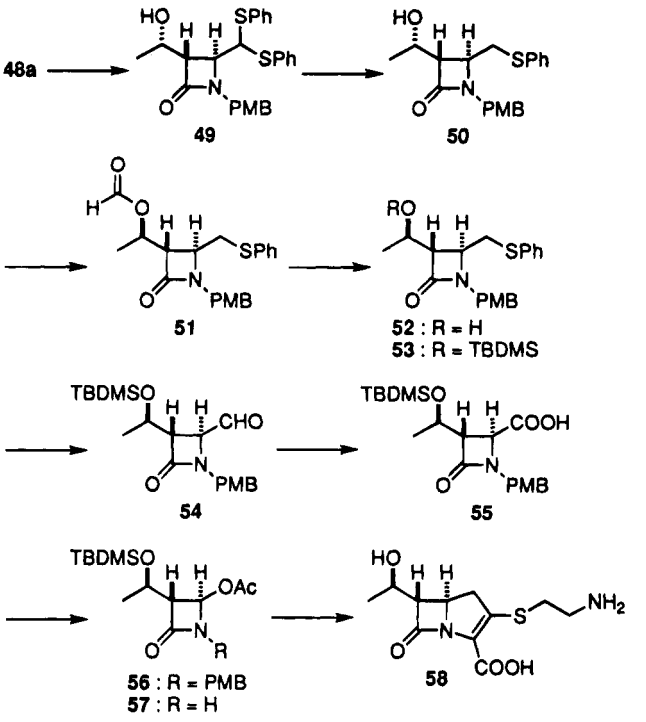
(19) Shiozaki, M.; Hiraoka, T. *Tetrahedron* **1982**, *38*, 3457.

(20) Johnston, D. B. R.; Schmitt, S. M.; Bouffard, F. A.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313. See also Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.

(21) Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 379. Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293.

(22) Recently, highly diastereoselective syntheses of 1β-methylcarbapenems from **57** have been reported, see: Murayama, T.; Yoshida, A.; Kobayashi, T.; Miura, T. *Tetrahedron Lett.* **1994**, *35*, 2271. Choi, W.-B.; Churchill, H. R. O.; Lynch, J. E.; Thompson, A. S.; Humphrey, G. R.; Volante, R. P.; Reider, P. J.; Shinkai, I. *Tetrahedron Lett.* **1994**, *35*, 2275. Uyeo, S.; Itani, H. *Tetrahedron Lett.* **1994**, *35*, 4377. Hirai, K.; Iwano, Y.; Mikoshiba, I.; Koyama, H.; Nishi, T. *Heterocycles* **1994**, *38*, 277.

Scheme 9



0.1 N NaOH gave a mixture of the corresponding alcohols. Although the mixture of alcohols could be separated by careful chromatography on silica gel, fractional recrystallization of the mixture from hexane/AcOEt was found to readily provide the major alcohol **49** in good yield (56%). One of the phenylthio groups of **49** was removed by treatment with Bu_3SnH in the presence of AIBN (97%), and the resulting alcohol **50** was subjected to the Mitsunobu reaction with diisopropyl azodicarboxylate/PPh_3/formic acid to give formate **51** in 79% yield. Acid hydrolysis of **51** gave (*R*)-alcohol **52** in 96% yield. Conversion of **52** into the known acetate **56** was achieved in a straightforward manner as outlined in Scheme 9. Protection of alcohol **52** with a TBDMS group gave **53**. Oxidation of **53** with *m*-CPBA followed by Pummerer rearrangement/hydrolysis of the resulting sulfoxide in a manner similar to those described for the preparation of **31** from **32** provided aldehyde **54** in 96% yield from **53**. Oxidation of **54** with alkaline $KMnO_4$ followed by treatment of the resulting carboxylic acid **55** with lead tetraacetate gave acetate **56**[23] in 65% yield from **54**. Since removal of the *p*-methoxybenzyl group of **56** leading to **57** has been reported,[23] the whole sequence of reactions herein described constitutes, in a formal sense, a total synthesis of (+)-thienamycin.

In conclusion, we have shown that the sulfur atom can act as an effective radical stabilizing group for the 4-*exo-trig* cyclization of *N*-ethenyl-α-bromo amides leading to β-lactams. The (phenylthio)methyl group incorporated into the cyclization products serves as a handle for the elaboration of functionalities required for the synthesis of therapeutically important carbapenem antibiotics. The present results also offer a useful methodology for controlling regiochemistry in radical addition and cyclization reactions onto enamines. Such work is now in progress.

Experimental Section

Melting points and boiling points are uncorrected. IR spectra were recorded with a JASCO IR-A-100 spectrophotometer. ^1H and ^{13}C 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 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.

(Phenylthio)acetaldehyde. To an ice cooled solution of sodium ethoxide (8.98 g, 0.132 mol) in ethanol (60 mL) was slowly added thiophenol (14.54 g, 0.132 mol), and the mixture was stirred for 15 min. Bromoacetaldehyde diethyl acetal (20.81 g, 0.11 mol) was then added and the mixture was heated under reflux for 2 h. After the precipitated salt had been removed by filtration, the solvent was evaporated off, the residue was dissolved in water (50 mL), and the solution was extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and the solvent was evaporated off to give crude (phenylthio)acetaldehyde diethyl acetal (22.77 g, 91%) as an oil: ^1H NMR (60 MHz) δ 1.16 (t, J = 7 Hz, 6 H), 3.12 (d, J = 6 Hz, 2 H), 3.35–3.9 (m, 4 H), 4.66 (t, J = 6 Hz, 1 H), 7.1–7.5 (m, 5 H). The acetal so obtained (22.6 g, 0.1 mol) was added to a mixture of 1% HCl (200 mL) and acetone (100 mL), and the mixture was heated under reflux for 1.5 h. Acetone was removed by evaporation, the residual aqueous layer was neutralized with a saturated $NaHCO_3$ solution, and the solution was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvent was evaporated off, and the residue was distilled under reduced pressure to give (phenylthio)acetaldehyde[24] (11.86 g, 78%): bp 105 °C (7 Torr); ^1H NMR (60 MHz) δ 3.57 (d, J = 3 Hz, 2 H), 7.29 (s, 5 H), 9.51 (t, J = 3 Hz, 1H).

α-Bromo-*N*-[(4-methoxyphenyl)methyl]-*N*-[2-(phenylthio)ethenyl]acetamide (11). *p*-Methoxybenzylamine (686 mg, 5 mmol) and $MgSO_4$ (10 g) were added to a solution of (phenylthio)acetaldehyde (761 mg, 5 mmol) in diethyl ether (20 mL) at 0 °C, and the mixture was stirred at the same temperature for 2 h. $MgSO_4$ was removed by filtration, the filtrate was concentrated in vacuo, and the resulting crude imine **10** was dissolved in toluene (20 mL). *N,N*-Diethylaniline (746 mg, 5 mmol) was added to the solution, and the mixture was cooled to −78 °C. Bromoacetyl bromide (1.01 g, 5 mmol) was added dropwise 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, 10:1) to give **11** (841 mg, 44%) as an oil: ^1H NMR (60 MHz) δ 3.74 (s, 3 H), 3.97, 4.20 (both s, total 2 H), 4.84 (s, 2 H), 5.69 (d, J = 14 Hz, 1 H), 6.6–7.4 (m, 10 H). Anal. Calcd for $C_{18}H_{18}BrNO_2S$: C, 55.11; H, 4.62; N, 3.57. Found: C, 55.03; H, 4.61; N, 3.51.

2-Bromo-*N*-[(4-methoxyphenyl)methyl]-*N*-[2-(phenylthio)ethenyl]butanamide (12). Using a procedure similar to that described above for **11**, imine **10** was treated with 2-bromobutyryl bromide to give **12** (30%) as an oil: ^1H NMR (60 MHz) δ 0.7–1.15 (m, 3 H), 1.8–2.4 (m, 2 H), 3.70 (s, 3 H), 4.0–5.0 (m, 3 H), 5.63 (d, J = 13.5 Hz, 1 H), 6.5–7.4 (m 10 H). Anal. Calcd for $C_{20}H_{22}BrNO_2S$: C, 57.15; H, 5.28; N, 3.33. Found: C, 56.83; H, 5.26; N, 3.32.

Radical Cyclization of 11. General Procedure. To a boiling solution of **11** (524 mg, 1.38 mmol) in toluene (150 mL) was added a solution of Bu_3SnH (442 mg, 1.52 mmol) and AIBN (23 mg, 0.14 mmol) in toluene (75 mL) via a syringe during 3 h, and the mixture was heated under reflux for 2 h. After the solvent had been evaporated off, diethyl ether (20 m L) 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). The first eluate gave *N*-methyl-*N*-[2-

(23) Maruyama, H.; Shiozaki, M.; Hiraoka, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3264.

(24) Toyoshima, K.; Okuyama, T.; Fueno, T. *J. Org. Chem.* **1978**, *43*, 2789.

(phenylthio)ethenyl]-4-methoxyphenylacetamide (**17**) (26 mg, 6%) as an oil: IR (CCl_4) ν 1675 cm^{-1}; ^1H NMR (60 MHz) δ 3.14 (s, 3 H), 3.76 (s, 5 H), 5.56 (d, J = 13 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 2 H), 6.9–7.5 (m, 8 H). Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 69.01; H, 6.22; N, 4.21. The second eluate gave *N*-[(4-methoxyphenyl)methyl]-*N*-[2-(phenylthio)ethenyl]acetamide (**15**) (174 mg, 40%) as an oil: IR (CCl_4) ν 1680 cm^{-1}; ^1H NMR (60 MHz) δ 2.30 (s, 3 H), 3.76 (s, 3 H), 4.86 (br s, 2 H), 5.56 (d, J = 14 Hz, 1 H), 6.7–7.5 (m, 10 H); exact mass calcd for $C_{18}H_{19}NO_2S$ 313.1137, found 313.1118. The third eluate gave 1-[(4-methoxyphenyl)methyl]-4-[(phenylthio)methyl]-2-azetidinone (**13**) (95 mg, 22%) as an oil: IR (CCl_4) ν 1755 cm^{-1}; ^1H NMR (270 MHz) δ 2.65 (dd, J = 14.8, 1.7 Hz, 1 H), 2.89 (dd, J = 13.7, 7.4 Hz, 1 H), 2.99 (dd, J = 14.8, 4.9 Hz, 1 H), 3.10 (dd, J = 13.7, 4.8 Hz, 1 H), 3.59–3.67 (m, 1 H), 3.81 (s, 3 H), 4.05 (d, J = 14.8 Hz, 1 H), 4.52 (d, J = 14.8 Hz, 1 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.17 (d, J = 8.6 Hz, 2 H), 7.25, 7.26 (both s, total 5 H); exact mass calcd for $C_{18}H_{19}NO_2S$ 313.1136, found 313.1137.

Radical Cyclization of 12. Following the general procedure, enamide **12** (500 mg, 1.2 mmol) was treated with Bu_3SnH and AIBN, and the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1). The first eluate gave *N*-[(4-methoxyphenyl)methyl]-*N*-[2-(phenylthio)ethenyl]butanamide (**16**) (57 mg, 14%) as an oil: IR (CCl_4) ν 1665 cm^{-1}; ^1H NMR (60 MHz) δ 0.7–2.7 (m, 7 H), 3.76 (s, 3 H), 4.84 (br s, 2 H), 5.53 (d, J = 13 Hz, 1 H), 6.7–7.6 (m, 10 H). Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10. Found: C, 70.19; H, 6.77; N, 3.64. The second eluate gave (3*R**,4*S**)-3-ethyl-1[(4methoxyphenyl)methyl]-4-[(phenylthio)methyl]-2-azetidinone (**14**) (183 mg, 45%) as an oil: IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR (300 MHz) δ 0.94 (t, J = 7.5 Hz, 3 H), 1.49–1.82 (m, 2 H), 2.82 (ddd, J = 8.0, 6.2, 2.1 Hz, 1 H), 2.91 (dd, J = 13.5, 7.6 Hz, 1 H), 3.12 (dd, J = 13.5, 4.8 Hz, 1 H), 3.27 (ddd, J = 7.6, 4.8, 2.1 Hz, 1 H), 3.81 (s, 3 H), 4.01 (d, J = 14.9 Hz, 1 H), 4.57 (d, J = 14.9 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.17 (d, J = 8.7 Hz, 2 H), 7.17–7.29 (m, 5 H); ^{13}C NMR (75.4 MHz) δ 11.5, 21.4, 36.7, 44.1, 55.3, 55.9, 57.3, 114.2, 126.6, 127.9, 129.1, 129.5, 129.7, 135.3, 159.2, 169.7. Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10. Found: C, 70.49; H, 6.68; N, 3.91.

Bis(phenylthio)acetaldehyde (21). Diisobutylaluminum hydride (1.0 mol solution in hexane) (26.3 mL, 26.3 mmol) was added slowly to a solution of ethyl bis(phenylthio)acetate[25] (7.28 g, 23.92 mmol) in CH_2Cl_2 (70 mL) at −50 °C, and the mixture was stirred at the same temperature for 2 h. Methanol (5.5 mL) was added to the reaction mixture, and the solution was stirred at room temperature overnight. The precipitated salt was removed by filtration, and the residual mass was washed thoroughly with CH_2Cl_2. The combined organic phases were concentrated in vacuo, and the residue was chromatographed on silica gel (hexane/AcOEt, 15:1) to give bis(phenylthio)acetaldehyde in 60–80% yield: ^1H NMR (60 MHz) δ 4.69 (d, J = 4 Hz, 1 H), 7.0–7.6 (m, 10 H), 9.20 (d, J = 4 Hz, 1 H). This compound must be stored in a refrigerator because of its lability.

α-Bromo-*N*-[(4-methoxyphenyl)methyl]-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (23). A mixture of bis(phenylthio)acetaldehyde (**21**) (260 mg, 1 mmol) and *p*-methoxybenzylamine (137 mg, 1 mmol) in benzene (10 mL) was heated under reflux with azeotropical removal of water for 2 h. After cooling the mixture containing enamine **22**, *N*,*N*-diethylaniline (149 mg, 1 mmol) was added, and the solution was heated again under reflux. To this was added dropwise bromoacetyl bromide (404 mg, 2 mmol) during 5 min, and the mixture was heated under reflux for further 10 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, 7:1) to give **23** (461 mg, 92%) as an oil: IR (CCl_4) ν 1670 cm^{-1}; ^1H NMR (60 MHz) δ 3.76 (s, 3 H), 3.86 (s, 2 H), 4.73 (s, 2 H), 6.55 (s, 1 H), 6.80 (d, J = 9 Hz, 2 H), 6.8–7.4 (m, 12 H). Anal. Calcd for $C_{24}H_{22}BrNO_2S_2$: C, 57.60; H, 4.43; N, 2.80. Found: C, 57.63; H, 4.41; N, 2.75.

2-Bromo-*N*-[(4-methoxyphenyl)methyl]-*N*-[2,2-bis(phenylthio)ethenyl]butanamide (24). Using a procedure similar to that described above for **23**, enamine **22** was treated with 2-bromobutyryl bromide to give **24** (90%) as an oil: IR (CCl_4) ν 1675 cm^{-1}; ^1H NMR (60 MHz) δ 1.0 (t, J = 7 Hz, 3 H), 1.8–2.4 (m, 2 H), 3.75 (s, 3 H), 4.29 (t, J = 7 Hz, 1 H), 4.80 (br s, 2 H), 6.59 (s, 1 H), 6.80 (d, J = 9 Hz, 2 H), 6.8–7.5 (m, 12 H). Anal. Calcd for $C_{26}H_{26}BrNO_2S_2$: C, 59.09, H, 4.96; N, 2.65. Found: C, 58.69; H, 4.84; N, 2.43.

Radical Cyclization of 23. Following the general procedure, enamide **23** (220 mg, 0.44 mmol) was treated with Bu_3SnH and AIBN, and the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1). The first eluate gave *N*-[(4-methoxyphenyl)methyl]-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (**27**) (13 mg, 7%) as an oil: IR (CCl_4) ν 1665 cm^{-1}; ^1H NMR (60 MHz) δ 2.13 (s, 3 H), 3.80 (s, 3 H), 4.80 (s, 2 H), 6.7–7.5 (m, 15 H). Anal. Calcd for $C_{24}H_{23}NO_2S_2$: C, 68.38; H, 5.50; N, 3.32. Found: C, 68.52; H, 5.70; N, 3.63. The second eluate gave 4-[bis(phenylthio)methyl]-1-[(4-methoxyphenyl)methyl]-2-azetidinone (**25**) (85 mg, 46%) as an oil: IR (CCl_4) ν 1760 cm^{-1}; ^1H NMR (270 MHz) δ 2.92 (d, J = 3.6 Hz, 2 H), 3.78–3.85 (m, 1 H), 3.79 (s, 3 H), 3.90 (d, J = 14.8 Hz, 1 H), 4.40 (d, J = 4.6 Hz, 1 H), 4.63 (d, J = 14.8 Hz, 1 H), 6.82 (d, J = 8.6 Hz, 2 H), 7.13 (d, J = 8.6 Hz, 2 H), 7.25–7.40 (m, 10 H). Anal. Calcd for $C_{24}H_{23}NO_2S_2$: C, 63.38; H, 5.50; N, 3.32. Found: C, 68.75; H, 5.68; N, 3.40. The third eluate gave **13** (44 mg, 24%) which was identical with that obtained from **11**.

Radical Cyclization of 24. With 1.1 Equiv of Bu_3SnH. Following the general procedure, enamide **24** (821 mg, 1.55 mmol) was treated with Bu_3SnH and AIBN, and the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1). The first eluate gave *N*-[(4-methoxyphenyl)methyl]-*N*-[2,2-bis(phenylthio)ethenyl]butanamide (**28**) (97 mg, 14%) as an oil: IR (CCl_4) ν 1665 cm^{-1}; ^1H NMR (60 MHz) δ 0.93 (t, J = 7 Hz, 3 H), 1.3–1.9 (m, 2 H), 2.35 (t, J = 7 Hz, 2 H), 3.79 (s, 3 H), 4.83 (s, 2 H), 6.7–7.5 (m, 15 H). Anal. Calcd for $C_{26}H_{27}NO_2S_2$: C, 69.45; H, 6.05; N, 3.12. Found: C, 69.52; H, 6.15; N, 3.16. The second eluate gave (3*R**,4*S**)-3-ethyl-4-[bis(phenylthio)methyl]-1-[(4-methoxyphenyl)methyl]-2-azetidinone (**26**) (405 mg, 58%) as an oil: IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR (300 MHz) δ 0.94 (t, J = 7.4 Hz, 3 H), 1.55–1.78 (m, 2 H), 3.12 (dddd, J = 7.5, 6.5, 2.1, 0.9 Hz, 1 H), 3.49 (dd, J = 4.7, 2.1 Hz, 1 H), 3.80 (s, 3 H), 3.82 (dd, J = 14.9, 0.9 Hz, 1 H), 4.43 (d, J = 4.7 Hz, 1 H), 4.67 (d, J = 14.9 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 7.11 (d, J = 8.7 Hz, 2 H), 7.25–7.35 (m, 10 H). Anal. Calcd for $C_{26}H_{27}NO_2S_2$: C, 69.45; H, 6.05; N, 3.12. Found: C, 69.31; H, 6.05; N, 3.10. The third eluate gave **14** (trace) which was identical with that obtained from **12**.

With 2 Equiv of Bu_3SnH. Following the general procedure, enamide **24** (580 mg, 1.1 mmol) was treated with Bu_3SnH (640 mg, 2.2 mmol) and AIBN, and the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1). The first eluate gave **16** (58 mg, 15%). The second eluate gave **28** (71 mg, 14%). The third eluate gave **26** (133 mg, 27%). The fourth eluate gave **14** (66 mg, 18%).

Formation of 16 From 26. Following the general procedure, β-lactam **26** (384 mg, 0.85 mmol) was treated with Bu_3SnH (373 mg, 1.28 mmol) and AIBN (21 mg, 0.128 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1). The first eluate gave **16** (21 mg, 7%). The second eluate gave *N*-ethenyl-*N*-[(4-methoxyphenyl)methyl]butanamide (47 mg, 24%) as an oil, whose ^1H NMR spectrum showed the presence of two rotamers in a ratio of ca. 4:1: ^1H NMR for major rotamer (270 MHz) δ 1.00 (t, J = 6.6 Hz, 3 H), 1.64–1.82 (m, 2 H), 2.52 (t, J = 7.3 Hz, 2 H), 3.77 (s, 3H), 4.31 (d, J = 9.2 Hz, 1 H), 4.47 (d, J = 15.5 Hz, 1 H), 4.82 (s, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.88 (dd, J = 15.5, 9.2 Hz, 1 H), 7.12 (d, J = 8.6, 2 H); exact mass calcd for $C_{14}H_{19}NO_2$ 233.1415, found 233.1437. The third eluate gave **14** (78 mg, 27%).

Synthesis of 14 from 26. To a solution of **26** (125 mg, 0.28 mmol) in benzene were added Bu_3SnH (178 mg, 0.61 mmol) and AIBN (5 mg, 0.03 mmol), and the mixture was heated under reflux for 2 h. After usual workup, the crude material

(25) Campbell, M. M.; Jigajnni, V. B.; MacLean, K. A.; Wightman, R. H. *Tetrahedron Lett.* **1980**, *21*, 3305.

was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **14** (82 mg, 86%), which was identical with that obtained from **12**.

(2S*,3R*)-3-Ethyl-1-[(4-methoxyphenyl)methyl]-4-oxo-2-azetidinecarboxaldehyde (31). From 26. $AgClO_4$ (370 mg, 1.6 mmol) was added to a mixture of **26** (181 mg, 0.4 mmol) in benzene (1 mL) and water (0.08 mL), and the solution was stirred at room temperature in the dark. After stirring for 24 h, additional $AgClO_4$ (100 mg, 0.48 mmol) was added, and stirring was continued for a further 1 h. Diethyl ether (10 mL) was added to the reaction mixture, and inorganic materials were removed by filtration. The filtrate was washed successively with aqueous ammonia, brine, and water and then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **31** (39 mg, 39%) as an oil: IR (CCl_4) ν 1760, 1725 cm^{-1}; ^1H NMR (270 MHz) δ 1.00 (t, J = 7.3 Hz, 3 H), 1.60–1.95 (m, 2 H), 3.12 (ddd, J = 8.3, 5.9, 2.6 Hz, 1 H), 3.59 (dd, J = 3.3, 2.6 Hz, 1 H), 3.80 (s, 3 H), 4.29 (d, J = 14.7 Hz, 1 H), 4.53 (d, J = 14.7 Hz, 1 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.15 (d, J = 8.6 Hz, 2 H), 9.42 (d, J = 3.3 Hz, 1 H); exact mass calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1191.

From 14. To an ice cooled solution of **14** (407 mg, 1.19 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise a solution of *m*-CPBA (257 mg, 1.19 mmol) in CH_2Cl_2 (15 mL) during 40 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 **32** was dissolved in dry CH_2Cl_2. 2,6-Lutidine (255 mg, 2.38 mmol) and TFAA (500 mg, 2.38 mmol) were added successively to the solution at 0 °C, and the mixture was stirred at room temperature for 1 h. A saturated $NaHCO_3$ solution (10 mL) was then 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, 1:1) to give **31** (214 mg, 73% based on **14**) which was identical with that obtained from **26**.

(3R*,4S*)-3-Ethyl-4-[(R*)- and (S*)-1-hydroxy-2-(trimethylsilyl)ethyl]-1-[(4-methoxyphenyl)methyl]-2-azetidinones (33). To a solution of (trimethylsilyl)methylmagnesium chloride (1 M solution in diethyl ether) (0.99 mL, 0.99 mmol) in dry diethyl ether (6.5 mL) was added a solution of **31** (203 mg, 0.82 mmol) in dry diethyl ether (3.7 mL), and the mixture was heated under reflux for 3 h. A saturated NH_4Cl solution (5 mL) was added to the reaction 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, 2:1) to give **33** (146 mg, 53%) as an oil: IR (CCl_4) ν 3575, 3400, 1745, 1720 cm^{-1}; ^1H NMR spectral property (60 MHz), which exhibited two pairs of an AB quartet centered at δ 4.30 (J = 15 Hz) and 4.41 (J = 15 Hz) ascribed to the benzylic protons, indicated that compound **33** was a mixture of two diasteroisomers in a ratio of ca. 1:1. This mixture was used immediately in the next step.

(3R*,4R*)-4-Ethenyl-3-ethyl-1-[(4-methoxyphenyl)methyl]-2-azetidinone (34). Boron trifluoride diethyl etherate (462 mg, 0.33 mmol) was added to a solution of **33** (91 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred at the same temperature for 16 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, 3:1) to give **34** (63 mg, 95%) as an oil: IR (CCl_4) ν 1750 cm^{-1}; ^1H NMR (270 MHz) δ 0.95 (t, J = 7.3 Hz, 3 H), 1.57–1.83 (m, 2 H), 2.83 (ddd, J = 7.9, 6.3, 2.0 Hz, 1 H), 3.52 (dd, J = 8.3, 2.0 Hz, 1 H), 3.80 (s, 3 H), 3.87 (d, J = 14.8 Hz, 1 H), 4.62 (d, J = 14.8 Hz, 1 H), 5.20 (d, J = 10.2 Hz, 1 H), 5.23 (d, J = 17.2 Hz, 1 H), 5.75 (ddd, J = 17.2, 10.2, 8.3 Hz, 1 H), 6.85 (d, J = 8.6 Hz, 2 H), 7.15 (d, J = 8.6 Hz, 2 H); exact mass calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1413.

(3R*,4R*)-4-Ethenyl-3-ethyl-2-azetidinone (35). A solution of CAN (473 mg, 0.82 mmol) in water (5.4 mL) was added to a solution of **34** (67 mg, 0.27 mmol) in acetonitrile (2.7 mL) at 0 °C, and the mixture was stirred at the same temperature for 4 h and then at room temperature for 13 h. 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 brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 3:1) to give **35** (18 mg, 53%) as an oil, whose spectral properties were identical with those described in the literature:[12] IR (CCl_4) ν 3420, 3240, 1750 cm^{-1}; ^1H NMR (270 MHz) δ 1.04 (t, J = 7.6 Hz, 3 H), 1.64–1.93 (m, 2 H), 2.85 (dddd, J = 8.3, 5.9, 2.3, 1.0 Hz, 1 H), 3.81 (ddd, J = 6.9, 2.3, 1.2 Hz, 1 H), 5.17 (d, J = 10.1 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1 H), 5.94 (ddd, J = 17.2, 10.1, 6.9 Hz, 1 H), 6.16 (br s, 1 H).

(2S,3R)-3-Acetoxy-2-bromo-N-[(4-methoxyphenyl)methyl]-N-[(2-phenylthio)ethenyl]butanamide (38). According to a procedure similar to that described above for **11**, imine **10** (1.79 g, 6.61 mmol) was treated with (2*S*,3*R*)-3-acetoxy-2-bromobutyryl chloride (**37**)[19] (3.23 g, 13.2 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 12:1) to give **38** (1.04 g, 33%) as an oil: IR (CCl_4) ν 1745, 1670 cm^{-1}; ^1H NMR (60 MHz) δ 1.1–1.5 (m, 3 H), 1.82, 1.93, 2.05 (both s, total 3 H), 3.78 (br s, 3 H), 4.3–5.0 (m, 3 H), 5.2–6.4 (m, 2 H), 6.6–7.5 (m, 10 H). This compound was used immediately in the next step.

(3R,4R)- and (3S,4S)-3-[(R)-1-Acetoxyethyl]-1-[(4-methoxyphenyl)methyl]-4-[(phenylthio)methyl]-2-azetidinones (40a,b). Following the general procedure, enamide **38** (268 mg, 0.56 mmol) was treated with Bu_3SnH and AIBN in boiling toluene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 3:1) to give an oily mixture of **40a** and **40b** (88 mg, 39%) in a ratio of ca. 1:1: IR (CCl_4) ν 1755, 1740 cm^{-1}; ^1H NMR (300 MHz) for one isomer (probably **40a**): δ 1.313 (d, J = 6.5 Hz, 3 H), 1.92 (s, 3 H), 2.94 (dd, J = 13.7, 7.7 Hz, 1 H), 3.05–3.10 (m, 1 H), 3.13 (dd, J = 13.7, 4.7 Hz, 1 H), 3.40 (ddd, J = 7.7, 4.7, 2.1 Hz, 1 H), 3.80 (s, 3 H), 3.83 (d, J = 14.9 Hz, 1 H), 4.64 (d, J = 14.9 Hz, 1 H), 5.10 (qd, J = 6.5, 4.0 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 2 H), 7.15–7.30 (m, 7 H); ^1H NMR (300 MHz) for another isomer (probably **40b**): δ 1.308 (d, J = 6.4 Hz, 3 H), 1.96 (s, 3 H), 2.96 (dd, J = 13.7, 7.1 Hz, 1 H), 3.05–3.10 (m, 1 H), 3.13 (dd, J = 13.7, 4.7 Hz, 1 H), 3.62 (ddd, J = 7.1, 4.7, 2.1 Hz, 1 H), 3.81 (s, 3 H), 3.94 (d, J = 14.9 Hz, 1 H), 4.61 (d, J = 14.9 Hz, 1 H), 5.16 (quint, J = 6.4 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.15–7.30 (m, 7 H). Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.50; H, 6.18; N, 3.52.

(2S,3R)-3-Acetoxy-2-bromo-N-[(4-methoxyphenyl)methyl]-N-[2,2-bis(phenylthio)ethenyl]butanamide (39). According to a procedure similar to that described above for **23,** enamine **22** (973 mg, 2.56 mmol) was treated with acid chloride **37**[19] (1.25 g, 5.12 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1) to give **39** (1.1 g, 73%) as an oil: IR (CCl_4) ν 1745, 1670 cm^{-1}; ^1H NMR (60 MHz) δ 1.38 (d, J = 7 Hz, 3 H), 2.07 (s, 3 H), 3.77 (s, 3 H), 4.47 (d, J = 9 Hz, 1 H), 4.60, 4.83 (AB q, J = 14 Hz, 1 H each), 5.2–5.7 (m, 1 H), 6.39 (br s, 1 H), 6.78 (d, J = 8.5 Hz, 2H), 6.9–7.4 (m, 12H). This compound was used immediately in the next step.

(3R,4R)- and (3S,4S)-3-[(R)-1-Acetoxyethyl]-1-[(4-methoxyphenyl)methyl]-4-[bis(phenylthio)methyl]-2-azetidinones (41a,b). Following the general procedure, enamide **39** (957 mg, 1.63 mmol) was treated with Bu_3SnH and AIBN in boiling toluene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 5:1) to give an oily mixture of **41a** and **41b** (543 mg, 64%) in a ratio of ca. 2:1: IR (CCl_4) ν 1755, 1740 cm^{-1}; ^1H NMR for **41a** (300 MHz) δ 1.36 (d, J = 6.5 Hz, 3 H), 1.87 (s, 3 H), 3.33 (dd, J = 3.6, 2.4 Hz, 1 H), 3.60 (dd, J = 4.8, 2.4 Hz, 1 H), 3.68 (d, J = 14.9 Hz, 1 H), 3.79 (s, 3 H), 4.44 (d, J = 4.8 Hz, 1 H), 4.70 (d, J = 14.9 Hz, 1 H), 5.13 (qd, J = 6.5, 3.6 Hz, 1 H), 6.80 (d, J = 8.7 Hz, 2 H), 7.12 (d, J = 8.7 Hz, 2 H), 7.2–7.5 (m, 10 H); ^1H NMR for **41b** (300 MHz) δ 1.33 (d, J = 6.4 Hz, 3 H), 1.92 (s, 3 H), 3.40 (dd, J = 6.4, 2.3 Hz, 1 H), 3.67 (d, J = 15.1 Hz, 1 H), 3.81 (s, 3 H), 3.85 (dd, J = 3.4, 2.3 Hz, 1 H), 4.42 (d, J = 3.4 Hz, 1 H), 4.66 (d, J = 15.1 Hz, 1 H), 5.17 (quint, J = 6.4 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 2 H), 7.12 (d, J = 8.8 Hz, 2 H), 7.2–7.5 (m, 10 H).

Anal. Calcd for $C_{28}H_{29}NO_4S_2$: C, 66.25; H, 5.76; N, 2.76. Found: C, 66.67; H, 5.44; N, 2.79.

(3*R*,4*R*)- and (3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-1-[(4-methoxyphenyl)methyl]-4-[bis(phenylthio)methyl]-2-azetidinones (42a,b). To a solution of **41a,b** (319 mg, 0.64 mmol) in pyridine (0.93 mL) was added dropwise a 0.1 N NaOH solution (1.8 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, 6:1). The first eluate gave **42a** (112 mg, 49%): mp 128–128.5 °C (hexane/AcOEt); $[\alpha]^{24}_D$ −3.8° (*c* 1, EtOH); IR (CCl_4) ν 3460, 1750 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.30 (d, J = 6.4 Hz, 3 H, CMe), 2.07–2.17 (br, 1 H), 3.23 (dd, J = 5.8, 2.1 Hz, 1 H), 3.76 (dd, J = 4.6, 2.1 Hz, 1 H), 3.79 (s, 3 H), 3.83 (d, J = 15.1 Hz, 1 H), 3.96–4.07 (m, 1 H), 4.41 (d, J = 4.6 Hz, 1 H), 4.67 (d, J = 15.1 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 2 H), 7.13 (d, J = 8.7 Hz, 2 H), 7.22–7.33 (m, 10 H). Anal. Calcd for $C_{26}H_{27}NO_3S_2$: C, 67.07; H, 5.84; N, 3.01. Found: C, 67.02; H, 5.87; N, 3.14. The second eluate gave **42b** (62 mg, 23%) containing a small quantity of **42a**: IR (CCl_4) ν 3200–3700, 1750 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.27 (d, J = 6.4 Hz, 3 H), 2.05–2.15 (br, 1 H), 3.29 (dd, J = 6.1, 2.1 Hz, 1 H), 3.79 (s, 3 H), 3.81 (d, J = 15.1 Hz, 1 H), 3.89 (dd, J = 3.8, 2.1 Hz, 1 H), 4.14 (quint, J = 6.2 Hz, 1 H), 4.44 (d, J = 3.8 Hz, 1 H), 4.67 (d, J = 15.1 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 2 H), 7.12 (d, J = 8.7 Hz, 2 H), 7.20–7.35 (m, 10 H); exact mass calcd for $C_{26}H_{27}NO_3S_2$ 465.1430, found 465.1416.

(4*R*)-(*Z*)-3-Ethylidene-1-[(4-methoxyphenyl)methyl]-4-[bis(phenylthio)methyl]-2-azetidinone (44). To a solution of **42a** (40 mg, 0.086 mmol) and triethylamine (35 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (39 mg, 0.344 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:1). The first eluate gave **43a** (26 mg, 53%) [δ 2.73 (s, 3 H, SO_2Me)]. The second eluate gave recovered **42a** (15 mg, 38%).

To a solution of **43a** (35 mg, 0.067 mmol) in methanol (3 mL) was added $NaHCO_3$ powder (150 mg), and the mixture was heated under reflux for 5 h. Inorganic materials were removed by filtration, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2, and the solution was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **44** (18 mg, 63%) as an oil: IR (CCl_4) ν 1745 cm^{-1}; ^{1}H NMR (60 MHz) δ 2.04 (d, J = 7 Hz, 3 H), 3.77 (s, 3 H), 4.06 (d, J = 15.5 Hz, 1 H), 4.19 (br s, 1 H), 4.42 (d, J = 4 Hz, 1 H), 4.69 (d, J = 15.5 Hz, 1 H), 5.90 (q, J = 7 Hz, 1 H), 6.73 (d, J = 8.5 Hz, 2 H), 7.08 (d, J = 8.5 Hz, 2 H), 7.22, 7.25 (both s, total 10 H). Anal. Calcd for $C_{26}H_{25}NO_2S_2$: C, 69.77; H, 6.03; N, 3.13. Found: C, 69.57; H, 5.71; N, 3.11.

(4*S*)-(*E*)-3-Ethylidene-1-[(4-methoxyphenyl)methyl]-4-[bis(phenylthio)methyl]-2-azetidinone (45). According to a procedure similar to that described above for **42a**, lactam **42b** (123 mg, 0.26 mmol) containing a small quantity of **42a** was treated with methanesulfonyl chloride (60 mg, 0.53 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **43b** (132 mg, 92%) [δ 2.83 (s, 3 H, SO_2Me)]. Following a procedure similar to that described above for **43a**, a solution of **43b** (72 mg, 0.13 mmol) in methanol was heated in the presence of $NaHCO_3$. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 3:1). The first eluate gave **44** (8 mg, 14%) derived from **42a**. The second eluate gave **45** (35 mg, 59%): mp 89.5–92 °C (hexane/AcOEt); IR (CCl_4) ν 1755 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.73 (d, J = 7 Hz, 3 H), 3.76 (s, 3 H), 4.13 (d, J = 15.5 Hz, 1 H), 4.40 (br s, 1 H), 4.54 (d, J = 2 Hz, 1 H), 4.77 (d, J = 15.5 Hz, 1 H), 6.23 (br q, J = 7 Hz, 1 H), 6.77 (d, J = 8.5 Hz, 2 H), 7.13 (d, J = 8.5 Hz, 2 H), 7.24 (s, 10 H). Anal. Calcd for $C_{26}H_{25}NO_2S_2$: C, 69.77; H, 6.03; N, 3.13. Found: C, 69.99; H, 5.77; N, 3.17.

(2*R*,3*S*)-3-Acetoxy-2-bromo-*N*-[(4-methoxyphenyl)methyl]-*N*-[2,2-bis(phenylthio)ethenyl]butanamide (47). According to a procedure similar to that described above for **23**, enamine **22** (3.02 g, 7.9 mmol) was treated with acid chloride **46** (for preparation, see text) (3.33 g, 15.8 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 7:1) to give **47** (3.67 g, 79%) as an oil: IR (CCl_4) ν 1745, 1670 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.38 (d, J = 7 Hz, 3 H), 2.07 (s, 3 H), 3.77 (s, 3 H), 4.47 (d, J = 9 Hz, 1 H), 4.60, 4.83 (ABq, J = 14 Hz, 1 H each), 5.2–5.7 (m, 1 H), 6.39 (br s, 1 H), 6.78 (d, J = 8.5 Hz, 2 H), 6.9–7.4 (m, 12 H). Anal. Calcd for $C_{28}H_{28}BrNO_4S_2$: C, 57.34; H, 4.81; N, 2.39. Found: C, 57.10; H, 4.93; N, 2.56.

(3*S*,4*S*)- and (3*R*,4*R*)-3-[(*S*)-1-Acetoxyethyl]-1-[(4-methoxyphenyl)methyl]-4-[bis(phenylthio)methyl]-2-azetidinones (48a,b). Following the general procedure, enamide **47** (720 mg, 1.2 mmol) was treated with Bu_3SnH and AIBN in refluxing toluene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 5:1) to give an oily mixture of **48a** and **48b** (372 mg, 60%) in a ratio of ca. 2:1. IR and ^{1}H NMR spectra were essentially the same as those of a mixture of **41a** and **41b**. Anal. Calcd for $C_{28}H_{29}NO_4S_2$: C, 66.25; H, 5.76; N, 2.76. Found: C, 66.22; H, 5.87; N, 2.94.

(3*S*,4*S*)-3-[(*S*)-1-Hydroxyethyl]-1-[(4-methoxyphenyl)methyl]-4-[bis(phenylthio)methyl]-2-azetidinone (49). According to a procedure similar to that described above for **42a,b**, a mixture of **48a,b** (316 mg, 0.62 mmol) was treated with 0.1 N NaOH in pyridine, and the crude material containing alcohol **49** and the corresponding (3*R*,4*R*)-isomer was recrystallized from hexane/AcOEt to give pure **49** (163 mg, 56%): mp 129.5–130 °C (hexane/AcOEt); $[\alpha]^{24}_D$ +3.8° (*c* 1, EtOH). IR and ^{1}H NMR spectra were essentially the same as those of **42a**. Anal. Calcd for $C_{26}H_{27}NO_3S_2$: C, 67.07; H, 5.84; N, 3.01. Found: C, 66.75; H, 5.78; N, 3.24.

(3*S*,4*S*)-3-[(*S*)-1-Hydroxyethyl]-1-[(4-methoxyphenyl)methyl]-4-[(phenylthio)methyl]-2-azetidinone (50). Bu_3SnH (828 mg, 2.8 mmol) and AIBN (38 mg, 0.23 mmol) were added to a solution of **49** (353 mg, 0.76 mmol) in toluene (50 mL), and the mixture was heated under reflux for 14 h. After usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 2:1) to give **50** (262 mg, 97%): mp 70–72 °C (hexane/AcOEt); $[\alpha]^{24}_D$ +45.0° (*c* 1, EtOH); IR (CCl_4) ν 3450, 1740 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.24 (d, J = 6.3 Hz, 3 H), 2.56–2.65 (br s, 1 H), 2.90 (dd, J = 13.9, 7.6 Hz, 1 H), 2.92 (dd, J = 7.3, 2.0 Hz, 1 H), 3.09 (dd, J = 13.9, 4.6 Hz, 1 H), 3.50 (ddd, J = 7.6, 4.6, 2.0 Hz, 1 H), 3.78 (s, 3 H), 3.90–4.01 (m, 1 H), 4.01 (d, J = 15.2 Hz, 1 H), 4.55 (d, J = 15.2 Hz, 1 H), 6.84 (d, J = 8.6 Hz, 2 H), 7.15–7.27 (m, 7 H). Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 66.93; H, 6.66; N, 3.80.

(3*S*,4*S*)-3-[(*R*)-1-(Formyloxy)ethyl]-1-[(4-methoxyphenyl)methyl]-4-[(phenylthio)methyl]-2-azetidinone (51). A solution of diisopropyl azodicarboxylate (121 mg, 0.6 mmol) in dry THF (0.6 mL) was added dropwise to a solution of **50** (107 mg, 0.3 mmol), triphenylphosphine (157 mg, 0.6 mmol), and formic acid (28 mg, 0.6 mmol) in dry THF 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 **51** (91 mg, 79%) as an oil: $[\alpha]^{22}_D$ +58.4° (*c* 2, EtOH); IR (CCl_4) ν 1755, 1725 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.35 (d, J = 6.5 Hz, 3 H), 2.93 (dd, J = 13.9, 6.9 Hz, 1 H), 3.11 (dd, J = 6.5, 2.0 Hz, 1 H), 3.14 (dd, J = 13.9, 4.8 Hz, 1 H), 3.60 (ddd, J = 6.9, 4.8, 2.0 Hz, 1 H), 3.81 (s, 3 H), 3.96 (d, J = 14.9 Hz, 1 H), 4.58 (d, J = 14.9 Hz, 1 H), 5.27 (quint, J = 6.5 Hz, 1 H), 6.87 (d, J = 8.6 Hz, 2 H), 7.14–7.30 (m, 7 H), 7.92 (s, 1 H). Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found: C, 65.38; H, 5.85; N, 3.70.

(3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-1-[(4-methoxyphenyl)methyl]-4-[(phenylthio)methyl]-2-azetidinone (52). To a solution of **51** (91 mg, 0.24 mmol) in methanol (1 mL) was added two drops of 10% HCl at 0 °C, and the mixture was stirred at room temperature for 4 h. After completion of hydrolysis, brine (5 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, 2:1) to give **52** (81 mg, 96%): mp 90–90.5 °C (hexane/AcOEt); $[\alpha]^{23}_D$ +34.4° (*c* 1, EtOH); IR (CCl_4) ν 3600, 1735 cm^{-1}; ^1H NMR (270 MHz) δ 1.25 (d, J = 6.3 Hz, 3 H), 1.91 (br d, J = 4.6 Hz, 1 H), 2.91 (dd, J = 13.9, 7.6 Hz, 1 H), 2.96 (br dd, J = ca. 5.5, 2.0 Hz, 1 H), 3.13 (dd, J = 13.9, 4.6 Hz, 1 H), 3.65 (ddd, J = 7.6, 4.6, 2.0 Hz, 1 H), 3.80 (s, 3 H), 4.02 (d, J = 14.8 Hz, 1 H), 4.11 (br sextet, J = 5.5 Hz, 1 H), 4.58 (d, J = 14.8 Hz, 1 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.15–7.30 (m, 7 H). Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.48; N, 3.92. Found: C, 66.85; H, 6.57; N, 3.77.

(3*S*,4*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-[(4-methoxyphenyl)methyl]-4-[(phenylthio)methyl]-2-azetidinone (53). To a solution of **52** (218 mg, 0.61 mmol) in DMF (7.6 mL) were added successively *tert*-butyldimethylsilyl chloride (257 mg, 1.7 mmol) and imidazole (291 mg, 4.3 mmol), and the mixture was stirred at room temperature overnight. 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, 4:1) to give **53** (259 mg, 90%) as an oil: $[\alpha]^{22}_D$ +16.3° (*c* 1, EtOH); IR (CCl_4) ν 1755 cm^{-1}; ^1H NMR (270 MHz) δ −0.01 (s, 3H), 0.03 (s, 3H), 0.81 (s, 9 H), 1.18 (d, J = 6.3 Hz, 3 H), 2.90–2.94 (m, 1 H), 2.95 (dd, J = 13.9, 6.6 Hz, 1 H), 3.07 (dd, J = 13.9, 5.3 Hz, 1 H), 3.76 (ddd, J = 6.6, 5.3, 2.0 Hz, 1 H), 3.81 (s, 3 H), 4.09–4.19 (m, 1 H), 4.11 (d, J = 15.2 Hz, 1 H), 4.49 (d, J = 15.2 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2 H), 7.15–7.30 (m, 7 H). Anal. Calcd for $C_{26}H_{37}NO_3SSi$: C, 66.20; H, 7.91; N, 2.97. Found: C, 65.86; H, 7.58; N, 2.70.

(2*S*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-[(4-methoxyphenyl)methyl]-4-oxo-2-azetidinecarboxaldehyde (54). According to a procedure similar to that described above for the preparation of **31** from **14**, compound **53** (238 mg, 0.51 mmol) was oxidized with *m*-CPBA (80%) (109 mg, 0.51 mmol), and the resulting sulfoxide was treated successively with TFAA (212 mg, 1.01 mmol) in the presence of 2,6-lutidine (108 mg, 1.01 mmol) and then with aqueous $NaHCO_3$ solution. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 5:1) to give aldehyde **54** (189 mg, 99% based on **53**) as an oil: $[\alpha]^{22}_D$ +11.0° (*c* 0.39, EtOH); IR (CCl_4) ν 1765, 1730 cm^{-1}; ^1H NMR (270 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9 H), 1.19 (d, J = 6.3 Hz, 3 H), 3.11 (br t, J = ca. 3.0 Hz, 1 H), 3.80 (s, 3 H), 4.04 (br t, J = ca. 3.0 Hz, 1 H), 4.1–4.4 (m, 1 H), 4.37, 4.45 (ABq, J = 14.5 Hz, 1 H each), 6.85 (d, J = 8.6 Hz, 2 H), 7.17 (d, J = 8.6 Hz, 2 H), 9.40 (d, J = 3.3 Hz, 1 H). Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.63; H, 8.28; N, 3.71. Found: C, 63.31; H, 8.44; N, 3.78.

(2*S*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-[(4-methoxyphenyl)methyl]-4-oxo-2-azetidinecarboxylic Acid (55). A mixture of $KMnO_4$ (179 mg, 1.13 mmol) and K_2CO_3 (235 mg, 1.7 mmol) in water (3 mL) was added to a solution of **54** (107 mg, 0.28 mmol) in THF (4 mL), and the mixture was stirred at room temperature for 15 h under a nitrogen atmosphere. The precipitated inorganic materials were filtered off, and THF was removed by evaporation. Water (5 mL) was added to the residue, and the solution was washed with diethyl ether to remove neutral compounds. The aqueous phase was acidified to pH 4 with 6 N HCl, and the solution was extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give **55** (108 mg, 97%): mp 104.5–105 °C (hexane) [lit.[23] mp 107–109 °C]; $[\alpha]^{22}_D$ +17.5° (*c* 0.4, EtOH); IR (KBr) ν 1755, 1715 cm^{-1}; ^1H NMR (270 MHz) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.83 (s, 9 H), 1.21 (d, J = 6.3 Hz, 3 H), 3.27 (dd, J = 3.3, 2.3 Hz, 1 H), 3.79 (s, 3 H), 4.11 (d, J = 2.3 Hz, 1 H), 4.16 (d, J = 14.5 Hz, 1 H), 4.29 (qd, J = 6.3, 3.3 Hz, 1 H), 4.71 (d, J = 14.5 Hz, 1 H), 6.85 (d, J = 8.6 Hz, 2 H), 7.19 (d, J = 8.6 Hz, 2 H). Anal. Calcd for $C_{20}H_{31}NO_5Si$: C, 61.04; H, 7.94; N, 3.56. Found: C, 60.58; H, 8.00; N, 3.53.

(3*R*,4*R*)-4-Acetoxy-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-[(4-methoxyphenyl)methyl]-2-azetidinone (56). To a solution of **55** (56 mg, 0.14 mmol) in DMF (3 mL) were added successively acetic acid (0.75 mL) and $Pb(OAc)_4$ (90%) (700 mg, 1.42 mmol), and the mixture was heated at 65 °C for 2 h under a nitrogen atmosphere. Water (7 mL) was added to the reaction mixture, and the solution was extracted with diethyl ether. The organic phase was washed with 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, 10:1) to give **56**[23] (39 mg, 67%) as an oil, whose spectral properties were virtually identical to those reported in the literature:[23] $[\alpha]^{22}_D$ +7.7° (*c* 0.4, EtOH); IR (CCl_4) ν 1770, 1750 cm^{-1}; ^1H NMR (270 MHz) δ 0.01 (s, 3H), 0.05 (s, 3H), 0.83 (s, 9 H), 1.22 (d, J = 6.3 Hz, 3 H), 1.89 (s, 3H), 3.12 (br d, J = 3.6 Hz, 1 H), 3.79 (s, 3 H), 4.18 (qd, J = 6.3, 3.6 Hz, 1 H), 4.26, 4.36 (AB q, J = 15.2 Hz, 1 H each), 6.07 (br s, 1H), 6.84 (d, J = 8.6 Hz, 2 H), 7.21 (d, J = 8.6 Hz, 2 H).

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

Supplementary Material Available: ^1H NMR spectra of **13**, **15**, *N*-ethenyl-*N*-[(4-methoxyphenyl)methyl]butanamide, **31**, **33**, **34**, **35**, **38**, **39**, **42b**, and **56** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO941695N