Palladium(0)-Catalyzed Isomerization Reactions of Aziridines Bearing an α,β-Unsaturated Ester Group: A Thermodynamic Preference for Chiral Alkyl (2*E*)-4,5-*cis*-4,5-Epimino-*N*-(alkyl- or arylsulfonyl) 2-Enoates over the Other Three Stereoisomers

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Palladium(0)-catalyzed reactions of five sets of four stereoisomeric 4,5-epimino-*N*-(methanesulfonyl) or -*N*-(arylsulfonyl) 2-enoates reveal that 4,5-*cis*-(2*E*)-isomers are thermodynamically more stable than other isomers, in accord with calculations. A highly stereoselective synthesis of (*E*)-alkene dipeptide isosteres having the desired stereochemistries from unwanted stereoisomeric 4,5-epimino-*N*-(arylsulfonyl) 2-enoates is also presented.

Backbone modification of amide bonds in bioactive peptides has attracted much attention over the years.[1] Among the known isosteric units, the (*E*)-double bond has been a topic of continuing interest in the synthetic,[2] theoretical,[3] and biological[4] fields because the (*E*)-CH=CH double bond closely resembles the three-dimensional structure of the parent amide bond in peptides.[5] Recently, we[6] and others[7−10] have reported that small peptides containing (*E*)-alkene isosteres exhibit various types of biological activities. It has also been shown that peptide analogues involving (*Z*)-alkene dipeptide isosteres are considerably less bioactive than peptide mimics involving an (*E*)-alkene isostere.[11] In addition, it has been reported that the stereochemistry at the α-carbon center in dipeptide isosteres is one of the essential factors for enzyme inhibition.[4a] While many different synthetic routes to alkene dipeptide isosteres have been developed,[12,13] recently we[14] and Wipf[15] have described convenient and highly stereoselective synthesis of (*E*)-alkene dipeptide isosteres **5** and **6** *via* an organocopper-mediated S_N2' reaction of *N*-activated 4,5-epimino 2-enoates (**1** and **2**) and (**3** and **4**), respectively (Scheme 1).

In our continuing synthetic and biological studies, we required a practical procedure for the synthesis of isosteres of type **5** because small peptides containing (*E*)-alkene isosteres of type **6** showed undesired and/or low

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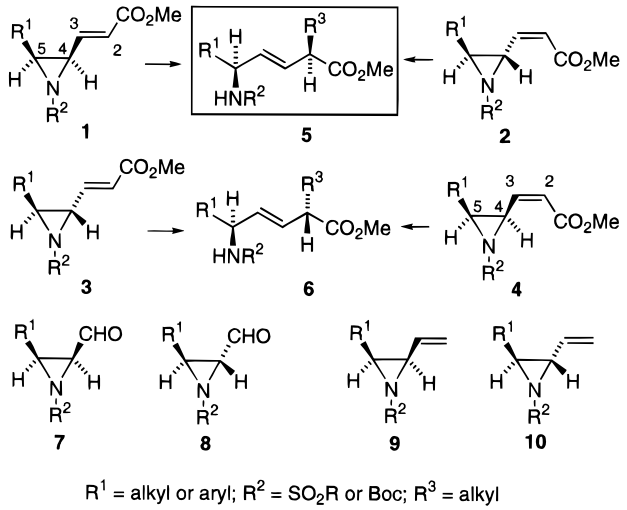
Scheme 1[a]



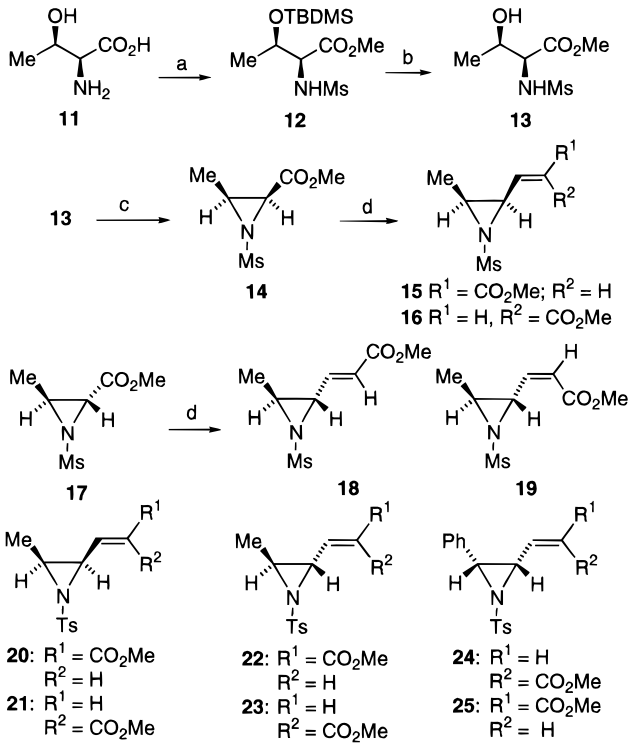
biological activities.[16] However, the highly stereoselective synthesis of **1** or **2** from chiral aldehyde **7** or **8** has hitherto been difficult. Reaction of aldehydes **7** and **8** with [(alkoxycarbonyl)methylene]triphenylphosphorane always yields a mixture of enoates (**1** and **4**) and (**2** and **3**), respectively. Consequently, development of practical and facile methods for isomerizing unwanted aziridines such as **3** and **4** into required stereoisomers is desired.

It was our expectation that palladium(0)-catalyzed isomerization of undesired enoates **3** and **4** into the desired **1** could occur *via* π-allylpalladium complexes. Taking advantage of recent Pd(0)-catalyzed equilibration reactions of vinylaziridines **9** and **10**,[17] we decided to investigate equilibration reactions of various aziridines bearing an α,β-unsaturated ester group with $Pd(PPh_3)_4$. We are aware of no systematic investigation of Pd(0)-catalyzed equilibrations in these systems, although some *N*-activated 4,5-epimino 2-enoates are known to undergo Pd(0)-formic acid-mediated ring-opening reactions yielding alkene isosteres.[18,19] We now describe a study involving the palladium(0)-catalyzed equilibration of five sets of 4,5-epimino 2-enoates.[20]

Results and Discussion

Synthesis of Five Sets of Four Stereoisomeric Alkyl 4,5-Epimino-*N*-(alkyl- and arylsulfonyl)-2-alkenoates. For the present palladium(0)-catalyzed isomerization study, it seemed that activation by the introduction of a strong electron-withdrawing group on the nitrogen atom of the aziridine was desirable. The methanesulfonyl (Ms) or arylsulfonyl [e.g., *p*-toluenesulfonyl (Ts) and 2-mesitylenesulfonyl (Mts)] group serves as an effective activating group. The choice of Mts as a protecting group was based primarily on its ease of deprotection.

Scheme 2[a]



[a] Reagents: (a) (i) $SOCl_2$−MeOH, (ii) MsCl-*N*,*N*-diisopropylethylamine, (iii) TBDMSCl−imidazole; (b) HF−MeCN−MeOH−H_2O; (c) PPh_3−diethyl azodicarboxylate; (d) (i) DIBAL, (ii) $Ph_3P{=}CHCO_2Me$.

The requisite homochiral enoates **15** and **16** were prepared from L-threonine (**11**) (Scheme 2). Threonine **11** was sequentially treated with thionyl chloride−methanol, methanesulfonyl chloride in the presence of diisopropylethylamine, and *tert*-butyldimethylsilyl chloride and imidazole to afford the silyl ether **12** in a 45% yield after the usual extractive workup followed by flash chromatography over silica gel. Removal of the silyl group with 48% HF solution in acetonitrile afforded the hydroxy ester **13**. It should be noted that the water-soluble hydroxy ester **13** poses serious problems with respect to product isolation. The usual extractive workup leads to considerable loss of **13**. Consequently, after deprotection of the silyl group in **12**, the reaction mixture was made alkaline with 28% ammonium hydroxide and concentrated to dryness under reduced pressure to leave a semisolid, which was directly flash chromatographed over silica gel. In this way, **13** was obtained in 92% yield from **12**. Cyclization of **13** with PPh_3 and diethyl azodicarboxylate afforded the aziridine **14**, which was successively reacted with diisobutylaluminum hydride (DIBAL) and [(methoxycarbonyl)methylene]triphenylphosphorane to yield a separable mixture of enoates **15** and **16**. In a similar manner, the known aziridine carboxylate **17**[17] was converted into the two isomeric enoates **18** and **19**. In this way, a set of four stereoisomeric enoates **15** (4,5-*cis*-2*E*), **16** (4,5-*cis*-2*Z*), **18** (4,5-*trans*-2*E*), and **19** (4,5-*trans*-2*Z*) were synthesized. Other *N*-tosylaziridine enoates **20**−**25** (Scheme 2) were readily prepared following literature procedures.[14]

Synthesis of a set of four stereoisomeric enoates **31**−**34** bearing a 2-mesitylenesulfonyl group at the aziridine nitrogen is shown in Scheme 3. L-Threonine (**11**) was sequentially treated with $SOCl_2$−MeOH and 2-mesitylenesulfonyl chloride-Et_3N to afford the hydroxy mesity-

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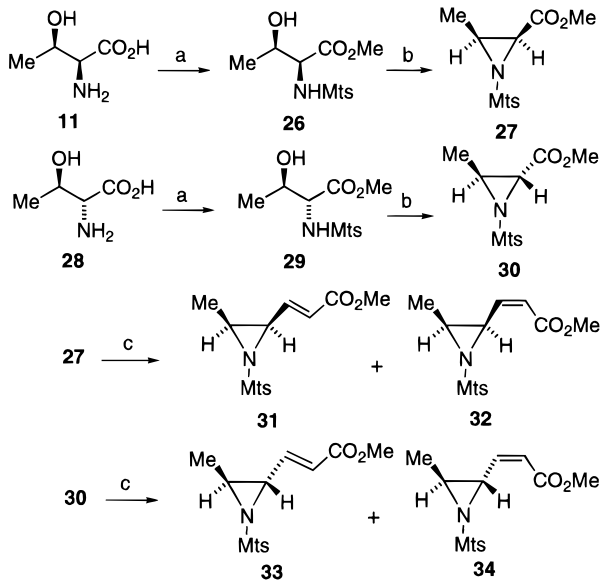
Scheme 3[a]



[a] Reagents: (a) (i) $SOCl_2$−MeOH, (ii) 2-mesitylenesulfonyl chloride−Et_3N; (b) PPh_3-diethyl azodicarboxylate; (c) (i) DIBAL, (ii) $Ph_3P{=}CHCO_2Me$.

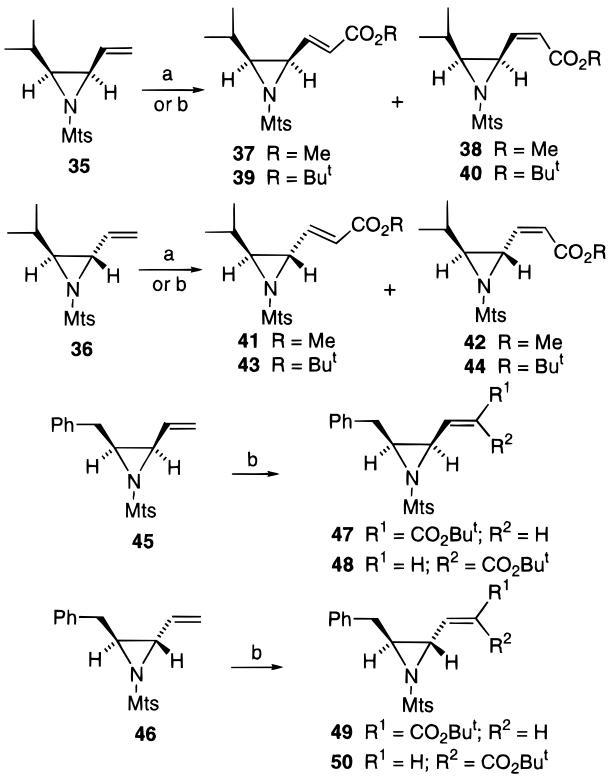
lenesulfonamide **26**, which on treatment with triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran (THF) yielded the 2,3-*cis*-aziridine **27**. Successive treatment of **27** with DIBAL and [(methoxycarbonyl)methylene]triphenylphosphorane gave a separable mixture of two products. Flash chromatographic separation yielded the enoates **31** (23% yield) and **32** (61% yield) (Scheme 3). In the same manner, D-*allo*-threonine (**28**) was converted in good overall yields into (2*E*)- and (2*Z*)-enoates **33** and **34** via the hydroxy ester **29** and the *N*-(mesitylenesulfonyl) carboxylate **30** (see the Experimental Section).

Starting from the known 2-vinylaziridines[17] **35**, **36**, **45**, and **46**, three sets of four isomeric enoates (**37**, **38**, **41**, and **42**), (**39**, **40**, **43**, and **44**), and (**47**, **48**, **49**, and **50**) bearing an isopropyl or benzyl group on the aziridine ring were prepared (Scheme 4). Ozonolysis of the 3-isopropyl-2-vinylaziridine **35** followed by exposure to [(methoxycarbonyl)methylene]triphenylphosphorane afforded the (2*E*)- and (2*Z*)-enoates **37** (29%) and **38** (53%) after flash chromatographic separation. In the same manner, other requisite enoates shown in Scheme 4 were readily prepared in good yields.

Space restrictions prevent detailed description; however, the 4,5-*cis*/*trans* and *E*/*Z* configurations of all of the required homochiral α,β-enoates shown in Schemes 2−4 were unambiguously assigned on the basis of ^{1}H NMR spectral analyses (see the Experimental Section).

Relative Thermodynamic Stabilities of Two Sets of Four Stereoisomeric α,β-Enoates (15, 16, 18, and 19) and (20, 21, 22, and 23): Palladium (0)-Catalyzed Equilibration Reactions. Despite their potential usefulnesses for the synthesis of various natural products such as alkaloids[21] antibiotics,[22] and heterocycles,[23] to date 4,5-epimino 2-enoates have scarcely been studied

Scheme 4[a]



[a] Reagents: (a) (i) ozone, (ii) PPh_3, (iii) $Ph_3P{=}CHCO_2Me$; (b) (i) ozone, (ii) zinc powder, (iii) $Ph_3P{=}CHCO_2Bu^t$.

from the viewpoint of relative thermodynamic stabilities.[24] Consequently, both theoretical and experimental aspects of this study were carried out with two sets of four stereoisomeric 2-enoates, (**15**, **16**, **18**, and **19**) and (**20**, **21**, **22**, and **23**).

We initiated our study to determine the relative stabilities of four stereoisomeric 2-enoates bearing a methanesulfonyl group on the nitrogen **15**, **16**, **18**, and **19**. Would the enoate **15**, **16**, **18**, or **19** be expected to be the most thermodynamically stable compound? In order to gain an understanding of the relative stabilities of these four isomeric enoates, we undertook calculations at the PM3, HF/3-21G**, and HF/4-31G** levels.[25] The optimized geometries **15-A**, **16-A**, **18-A**, and **19-A** of the four isomeric enoates **15**, **16**, **18**, and **19** as well as relative energies are shown in Figure 1. In addition, two energy minima **18-B** and **19-B** of the nitrogen invertomers of **18-A** and **19-A**, respectively, are also shown in

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(25) For the PM3 level of theory, see: Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 210. All optimizations were carried out by using the PM3 method, and stationary points were also confirmed by vibrational analysis on the PM3 potential surface. Single-point energy calculations were done at the HF/3-21G** and HF/4-31G** levels of theory. All calculations were performed using the program GAUSSIAN 92 on a CRAY Y-MP2E/264 at the Supercomputer Laboratory, Institute for Chemical Research, Kyoto University. GAUSSIAN 92, Revision C: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Forseman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1992.

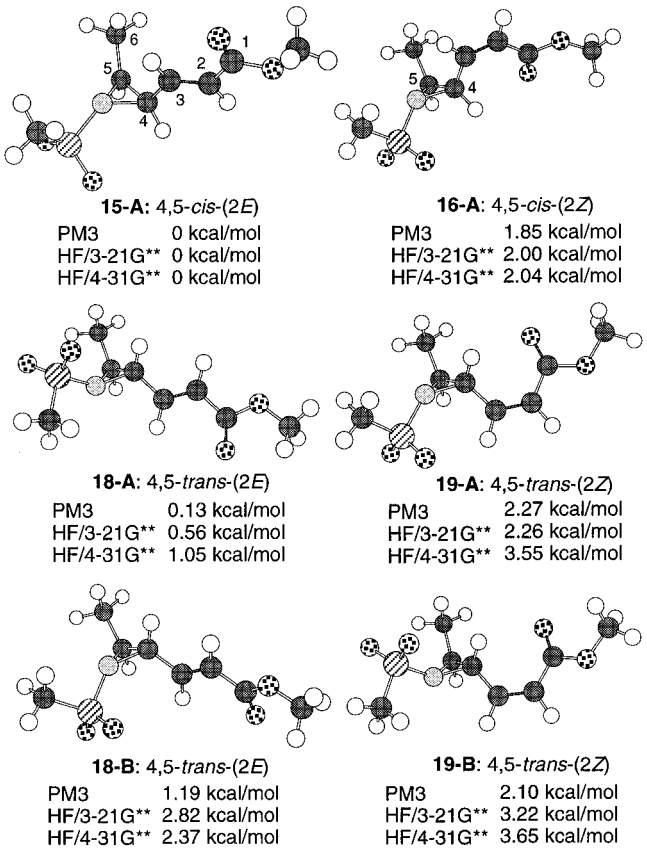

Figure 1. PM3 optimized geometries of four stereoisomeric methyl 4,5-epimino-*N*-(methanesulfonyl)hex-2-enoates **15**, **16**, **18**, and **19**. Energies are relative to the lowest energy at the PM3, HF/3-21G**, and HF/4-31G** levels, respectively.[25] **15-A**, **16-A**, **18-A**, and **19-A**: the lowest energy geometries of **15**, **16**, **18**, and **19**, respectively. **18-B** and **19-B**: the lowest energy geometries of the nitrogen invertomers of **18-A** and **19-A**, respectively.

Figure 1. As one might expect, for 4,5-*cis* enoates **15-A** and **16-A**, the methanesulfonyl group is *trans* with respect to substituents at the C-4 and C-5 positions, for presumably steric reasons.

From the calculations it is apparent that among the four stereoisomers **15**, **16**, **18**, and **19** the most stable and unstable enoates are predicted to be 4,5-*cis*-(2*E*)-enoate **15** and 4,5-*trans*-(2*Z*)-enoate **19**, respectively (Figure 1). Calculations also suggest that the energy minimum **15-A** of 4,5-*cis*-(2*E*) enoate **15** is favored by 1.05 kcal mol^{-1} over the global energy minimum **18-A** of the 4,5-*trans*-(2*E*)-isomer **18** at the HF/4-31G** level. Generally, it is well documented that in disubstituted alkenes the (*E*)-isomer is more stable than the (*Z*).[26] In accord with this, the (*E*)-enoates **15** and **18** are calculated to be more stable than the corresponding (*Z*)-enoates **16** and **19**.

As can be seen from Figure 1, the order of decreasing relative thermodynamic stabilities for the four stereoisomeric α,β-enoates **15**, **16**, **18**, and **19** were predicted to be as follows: 4,5-*cis*-(2*E*) (**15**) > 4,5-*trans*-(2*E*) (**18**) > 4,5-*cis*-(2*Z*) (**16**) > 4,5-*trans*-(2*Z*) (**19**). The relative energy differences among the four isomeric enoates are calculated to give an approximately 87:11:2:0.1 mixture of **15**, **18**, **16**, and **19** at 0 K at equilibrium in the gas phase. As will be described below, this prediction proved to be close to the experimental results obtained in solution. The relative stabilities of the four stereoisomers are summarized in Scheme 5.

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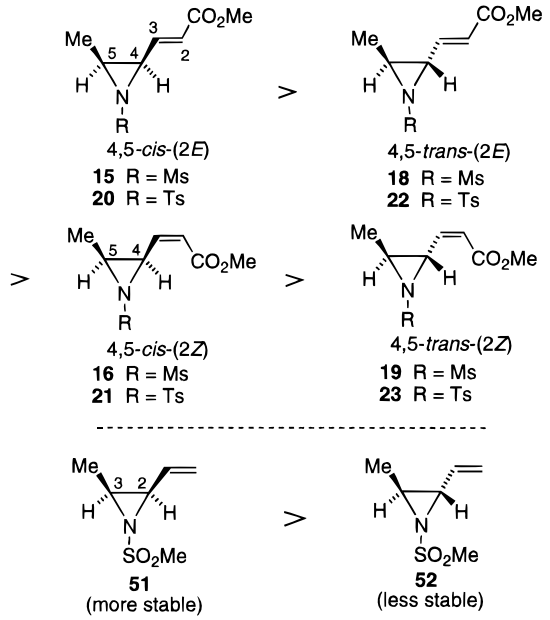
Scheme 5. Relative Stabilities of Two sets of Four Stereoisomeric α,β-Enoates (15, 16, 18, and 19) and (20, 21, 22, and 23)[a]



[a] The order of decreasing relative thermodynamic stabilities of four stereoisomeric α,β-enoates (**15**, **16**, **18**, and **19**) and (**20**, **21**, **22**, and **23**) were predicted as follows: 4,5-*cis*-(2*E*) (**15**) > 4,5-*trans*-(2*E*) (**18**) > 4,5-*cis*-(2*Z*) (**16**) > 4,5-*trans*-(2*Z*) (**19**). 4,5-*cis*-(2*E*) (**20**) > 4,5-*trans*-(2*E*) (**22**) > 4,5-*cis*-(2*Z*) (**21**) > 4,5-*trans*-(2*Z*) (**23**). Our results of an earlier study of the relative stabilities of vinylaziridines **51** and **52** are included for comparison (see ref 17).

In accord with calculations, the 4,5-*trans*-(2*Z*)-enoate **19** did give an 88.89:7.67:3.45:<0.01 equilibrium mixture of **15**, **18**, **16**, and **19** by exposure to 4 mol % of $Pd(PPh_3)_4$ (entry 4, Table 1). The rather low combined isolated yield can be attributed to competing decomposition of products, since the isolated yield of an equilibrated mixture of products is maximized within 24 h or less at 0–25 °C. To establish the observed equilibration results from **19** as a general trend, the same Pd(0)-catalyzed reactions were carried out for the other stereoisomers **15**, **16**, and **18**. It is found that the enoates **15**, **16**, and **18** gave comparable results (entries 1–3, Table 1).

From the above results, it is evident that palladium-(0)-catalyzed reactions lead to equilibrium ratios of all possible stereoisomers as a function of their relative stabilities. The stereochemical outcomes of these palladium-catalyzed isomerizations could be rationalized by considering π-allylpalladium complexes **A**, **B**, **C**, and **D** generated by oxidative addition of 4,5-epimino-*N*-(methanesulfonyl) 2-enoates **15**, **16**, **18**, and **19** to the Pd(0) complex shown in Figure 2.

Next, both theoretical and experimental studies were carried out with the four stereoisomeric 2-enoates **20**–**23** bearing a tosyl group as an activating moiety. Figure 3 shows optimized geometries **20-A**, **21-A**, **22-A**, and **23-A** for the four stereoisomeric methyl 4,5-epimino-*N*-(4-methylbenzenesulfonyl)hex-2-enoates **20**, **21**, **22**, and **23**. The calculations suggest that the energy minimum **20-A** of 4,5-*cis*-(2*E*)-enoate **20** is favored by 0.67 kcal mol^{-1} over the energy minimum **22-A** of the 4,5-*trans*-(2*E*)-isomer **22** at the HF/4-31G** level. Likewise, the optimized geometry **21-A** of 4,5-*cis*-(2*Z*) enoate **21** was predicted to

Table 1. Pd(PPh$_3$)$_4$-Catalyzed Equilibrated Reactions of *N*-(Methanesulfonyl)- or *N*-(Arylsulfonyl)-γ,δ-epimino α,β-Enoates[a]

entry	substrate	Pd(PPh$_3$)$_4$ (mol %)	conds (*T* (°C), time (h))		product ratio *cis*-(*E*):*cis*-(*Z*):*trans*-(*E*):*trans*-(*Z*)	combined isolated yield (%)
1	**15**	4	0	16	**15**:**16**:**18**:**19** = 89.17:3.39:7.43:<0.01	87%
2	**16**	4	25	16	**15**:**16**:**18**:**19** = 89.00:3.24:7.75:<0.01	65%
3	**18**	4	25	16	**15**:**16**:**18**:**19** = 88.23:3.46:8.30:<0.01	56%
4	**19**	4	25	16	**15**:**16**:**18**:**19** = 88.89:3.45:7.67:<0.01	64%
5	**20**	2	15	15	**20**:**21**:**22**:**23** = 85.74:5.02:9.24:<0.01	93%
6	**21**	2	15	15	**20**:**21**:**22**:**23** = 87.00:4.70:8.30:<0.01	86%
7	**22**	2	15	15	**20**:**21**:**22**:**23** = 85.09:5.12:9.79:<0.01	84%
8	**23**	2	15	15	**20**:**21**:**22**:**23** = 87.86:5.70:6.44:<0.01	88%
9	**31**	2	20	15	**31**:**32**:**33**:**34** = 90.40:3.89:5.71:<0.001	87%
10	**32**	2	20	15	**31**:**32**:**33**:**34** = 91.23:3.17:5.60:<0.001	90%
11	**33**	2	20	15	**31**:**32**:**33**:**34** = 90.91:3.57:5.52:<0.001	96%
12	**34**	2	20	15	**31**:**32**:**33**:**34** = 90.54:3.85:5.61:<0.001	96%
13	**37**	4	0	24	**37**:**38**:**41**:**42** = 94.13:0.43:5.44:<0.001	97%
14	**38**	4	0	24	**37**:**38**:**41**:**42** = 94.12:0.51:5.47:<0.001	98%
15	**41**	2	0	24	**37**:**38**:**41**:**42** = 94.03:0.50:5.47:<0.001	97%
16	**42**	2	0	24	**37**:**38**:**41**:**42** = 94.06:0.56:5.38:<0.001	96%
17	**47**	4	30	3	**47**:**48**:**49**:**50** = 90.22:4.04:4.79:0.95	90%
18	**48**	4	30	3	**47**:**48**:**49**:**50** = 89.40:3.70:5.79:1.11	70%
19	**49**	4	30	3	**47**:**48**:**49**:**50** = 88.51:3.42:5.44:2.63	94%
20	**50**	4	28	3	**47**:**48**:**49**:**50** = 88.61:3.62:6.32:1.45	93%

[a] All reactions were carried out in dry THF (ca. 0.05 M solution) under slight positive argon pressure. Except for entries 17−20, product ratios were determined by reverse phase HPLC (Cosmosil 5C18-AR, MeOH:H_2O = 42−10:58−90). Product ratios (entries 17−20) were determined by HPLC (Cosmosil 10SL, hexane:THF = 92:8).

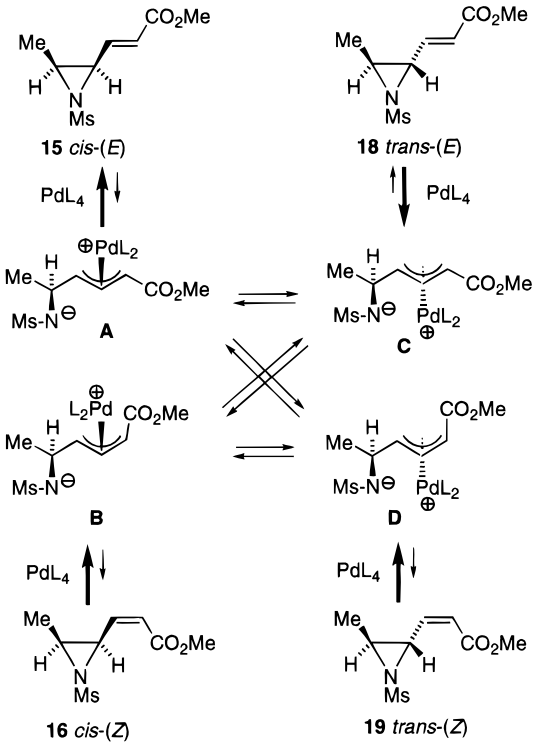


Figure 2. Palladium(0)-catalyzed equilibrated reaction.

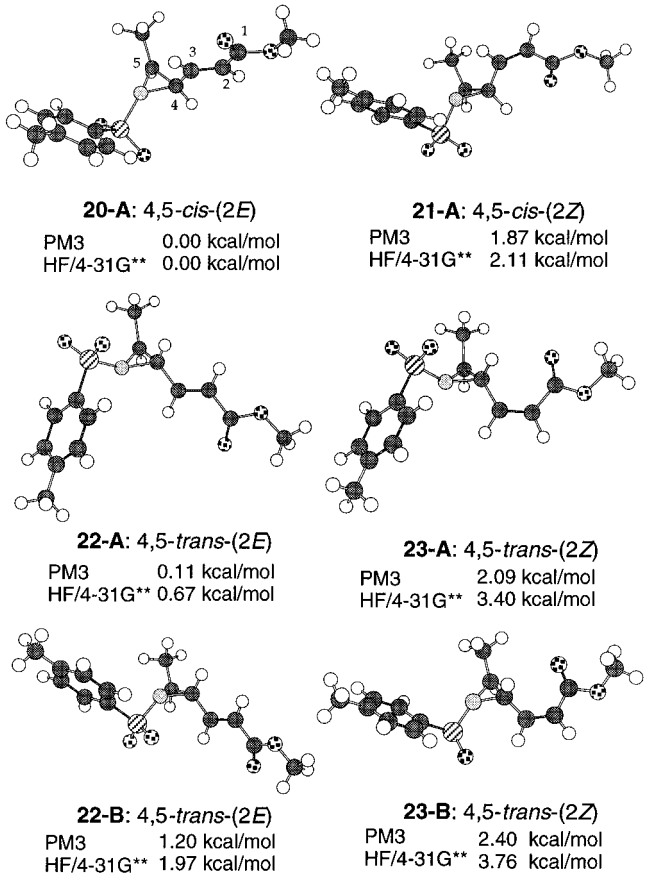


Figure 3. PM3-optimized geometries of four stereoisomeric methyl 4,5-epimino-*N*-(4-methylbenzenesulfonyl)hex-2-enoates **20**−**23**. Energies are relative to the lowest energy at the PM3 and HF/4-31G** levels, respectively.[25] **20-A**, **21-A**, **22-A**, and **23-A**: the lowest energy geometries of **20**, **21**, **22**, and **23**, respectively. **22-B** and **23-B**: the lowest energy geometries of the nitrogen invertomers of **22-A** and **23-A**, respectively.

be more stable by 1.29 kcal mol^{-1} than the energy minimum **23-A** of the isomeric 4,5-*trans*-(2*Z*)-enoate **23**. Optimized conformations **22-B** and **23-B** are the nitrogen invertomers of **22-A** and **23-A**. It is evident that **22-A** and **23-A** are energetically favored over these nitrogen invertomers **22-B** and **23-B**. The order of decreasing relative thermodynamic stabilities for the four 2-enoates **20**−**23** was predicted to be as follows: 4,5-*cis*-(2*E*) (**20**) > 4,5-*trans*-(2*E*) (**22**) > 4,5-*cis*-(2*Z*) (**21**) > 4,5-*trans*-(2*Z*) (**23**). These trends are in good accord with the results depicted in Figure 1.

In actuality, the *N*-tosyl 2-enoate **23** did afford an 87.86:6.44:5.70:<0.01 mixture of **20**, **22**, **21**, and **23** in 88% combined isolated yield upon exposure to Pd(PPh$_3$)$_4$ (2 mol %) in THF at 15 °C (entry 8, Table 1). Within the limits of experimental error, essentially identical results

were obtained following treatment of the isomeric enoates **20**−**22** under the same reaction conditions (entries 5−7, Table 1).

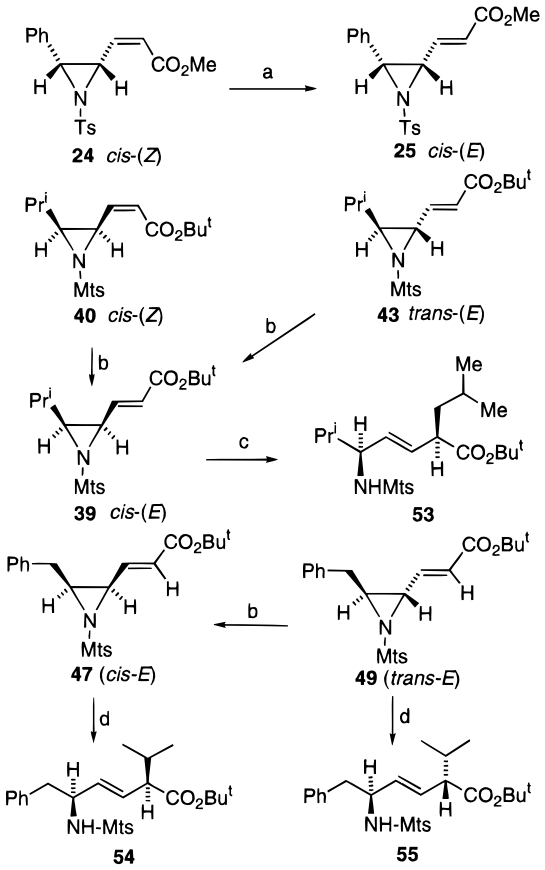
This Pd(0)-catalyzed reaction was successfully carried out on three other sets of four stereoisomeric 2-enoates (**31**, **32**, **33**, and **34**), (**37**, **38**, **41**, and **42**), and (**47**, **48**, **49**, and **50**). The desired 4,5-*cis*-(2*E*)-products **31**, **37**, and **47** were obtained with a selectivity as high as ca. 9:1 [**31**:(**32** + **33** + **34**), **37**:(**38** + **41** + **42**), and **47**:(**48** + **49** + **50**)] when a catalytic amount of $Pd(PPh_3)_4$ was employed in the equilibrated reactions (entries 9−20, Table 1). Thus, good agreement was observed between computationally predicted and experimental results, thereby providing feedback about the reliability of the calculation procedure.

Clearly the thermodynamic stabilities of the 4,5-*cis*-4,5-epimino (2*E*)-enoates **15**, **20**, **31**, **37**, and **47** are higher than those of the corresponding 4,5-*trans*-4,5-epimino (2*E*)-enoates **18**, **22**, **33**, **41**, and **49**. In addition, it is apparent from entries 9−12 and 13−16 in Table 1 that the greater steric bulk of the nitrogen protecting group (Mts) and the alkyl group (*i*-Pr) on the aziridine ring tended to afford considerably higher ratios of the desired 4,5-*cis*-4,5-epimino (2*E*)-enoates **31** and **37**.

Although the actual basis for the thermodynamic preference of 4,5-*cis*-(2*E*)-enoates over the other corresponding stereoisomers is still not clear, we speculate that the origin of this energy difference might lie in a delicate balance of steric and electronic factors. Steric interaction between the alkyl group and the α,β-enoate group at the aziridine-ring carbons would be of less importance because the 4,5-*cis*-(2*E*)-enoate **37** bearing a bulky isopropyl group and a relatively large 2-mesitylenesulfonyl group on the nitrogen atom was obtained in higher ratios (entries 13−16, Table 1).

Synthetic Application to the Synthesis of (*E*)-Alkene Dipeptide Isosteres. The equilibrated reactions illustrated below demonstrate how the undesired 2-enoates **24**, **40** and **43**, and **49** were transformed into the desired 2-enoates **25**, **39**, and **47** (Scheme 6). Thus, chiral *cis*-(*Z*)-enoate **24** bearing a phenyl group can be converted into diastereomerically pure *cis*-(*E*)-enoate **25** as follows. Exposure of **24** to $Pd(PPh_3)_4$ (4 mol %) in dry THF at 20 °C for 18 h was followed by filtration through a short pad of silica gel with *n*-hexane−EtOAc (1:1). Concentration under reduced pressure gave a crystalline residue. Recrystallization from MeOH gave essentially pure *cis*-(*E*)-enoate **25** as silky needles in 75% yield. The mother liquor was concentrated to a semisolid, which was again treated with $Pd(PPh_3)_4$ (4 mol %) in dry THF. Workup as described above gave additional **25** in 6% yield. The total combined yield of **25** amounted to 81%. In the same manner, both *cis*-(*Z*)- and *trans*-(*E*)-enoates **40** and **43** were converted into the desired enoate **39** having a *cis*-(*E*)-configuration in 84 and 87% isolated yields. Reaction of **39** with *i*-BuCu(CN)MgCl in THF at −78 °C for 30 min gave the required isostere **53** in 95% isolated yield as a single isomer. Likewise, the enoate **49** gave an isomeric enoate **47** in 78% isolated yield by treatment with a catalytic amount (4 mol %) of $Pd(PPh_3)_4$ followed by flash chromatography or recrystallization from *n*-hexane−Et_2O (9:1). Space restrictions prevent detailed descriptions of all results; however, it is apparent that the Pd(0)-catalyzed reactions give very satisfactory results. Exposure of the enoates **47** and **49** to *i*-PrCu(CN)MgCl gave the Phe-Ψ[(*E*)-CH=CH]-Val isosteres **54** and **55**, respectively, in high yields.

Scheme 6[a]



[a] Reagents: (a) $Pd(PPh_3)_4$ (4 mol %); (b) $Pd(PPh_3)_4$ (2 mol %); (c) *i*-BuCu(CN)MgCl; (d) *i*-PrCu(CN)MgCl.

In summary, it has been shown herein that palladium-catalyzed equilibrated reactions of various 4,5-epimino 2-enoates afford mixtures of four possible stereoisomers in which the desired *cis*-(*E*)-isomers predominate over other stereoisomers. Ready access to desired α,β-enoates from unwanted α,β-enoates and subsequent transformation into highly useful dipeptide isosteres in a regio- and stereoselective manner are attractive features of this approach.

Experimental Section

General Methods. The instrumentation has already been described.[2e,17] All reactions were carried out under a positive pressure of argon. All glassware and syringes were dried in an electric oven at 100 °C prior to use. All melting points are uncorrected. For flash chromatographies, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed. For HPLC, Cosmosil-5SL (10 × 200 mm, Nacalai Tesque) was employed.

Methyl (2*S*,3*R*)-*O*-(*tert*-Butyldimethylsilyl)-*N*-(methanesulfonyl)-L-threoninate (12). Thionyl chloride (14.64 mL, 0.2 M) was added dropwise to a stirred solution of (2*S*,3*R*)-threonine **11** (16 g, 0.134 M) in MeOH (160 mL) at −78 °C, and the mixture was allowed to warm to rt and stirred at this temperature for 18 h. Concentration under reduced pressure gave an oily residue. To a solution of the oily residue in a mixed solvent of DMF (20 mL) and $CHCl_3$ (30 mL) at −78 °C were added *N*,*N*-diisopropylethylamine (81.5 mL, 0.469 M) and methanesulfonyl chloride (15.6 mL, 0.2 M) with stirring, and stirring was continued for 5 h at 0 °C. Imidazole (36.48 g, 0.536 M) and *tert*-butyldimethylsilyl chloride (24.13 g, 0.161 M) were added to the mixture at 0 °C with stirring, and stirring was continued for 18 h, followed by quenching with aqueous 5% $NaHCO_3$ (40 mL). The mixture was extracted

with EtOAc−Et_2O (3:1), and the extract was washed successively with water, 10% citric acid, water, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Usual workup followed by flash chromatography over silica gel with *n*-hexane−EtOAc (2:1) gave 19.6 g (45% yield) of the title compound **12** as a colorless oil: $[\alpha]^{31}_D$ −31.8 (*c* 0.886, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 3 H), 0.10 (s, 3 H), 0.84 (s, 9 H), 1.29 (d, *J* = 6.2 Hz, 3 H), 3.00 (s, 3 H), 3.78 (s, 3 H), 3.99 (dd, *J* = 10.5, 1.5 Hz, 1 H), 4.45 (ddd, *J* = 10.5, 4.3, 1.5 Hz, 1 H), 5.06 (d, *J* = 10 Hz, 1 H); LRMS (FAB) *m*/*z* 326 (MH^+), 310, 268 (base peak), 208, 194, 159, 73.

Methyl (2*S*,3*R*)-*N*-(Methanesulfonyl)-L-threoninate (13). To a stirred solution of **12** (2.5 g, 7.67 mmol) in a mixed solvent of MeCN (8 mL), MeOH (3 mL), and water (0.6 mL) was added 1.5 mL of 46% aqueous HF, and the mixture was stirred at 50 °C for 1 h. The mixture was made basic with 28% NH_4OH at 0 °C and concentrated under reduced pressure to leave a colorless semisolid. The semisolid was purified by flash chromatography over silica gel eluting with *n*-hexane−EtOAc (1:2.5) to give 1.49 g (92% yield) of the title compound **13** as a colorless crystalline mass. Recrystallization from Et_2O−EtOAc (3:1) gave colorless crystals: mp 117 °C; $[\alpha]^{25}_D$ −38.3 (*c* 0.99, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.5 Hz, 3 H), 2.12 (d, *J* = 5.7 Hz, 1 H), 3.01 (s, 3 H), 3.84 (s, 3 H), 4.02 (dd, *J* = 9.7, 2.7 Hz, 1 H), 4.36 (dddd, *J* = 11.9, 6.2, 6.2, 2.4 Hz, 1 H), 5.38 (d, *J* = 9.5 Hz, 1 H). Anal. Calcd for $C_6H_{13}NO_5S$: C, 34.12; H, 6.20; N, 6.63. Found: C, 33.95; H, 6.00; N, 6.58.

Methyl (2*S*,3*S*)-*N*-(Methanesulfonyl)-3-methyl-2-aziridinecarboxylate (14). Triphenylphosphine (484 mg, 1.84 mmol) and diethyl azodicarboxylate (0.338 mL, 2.12 mmol) were added to a stirred solution of the ester **13** (300 mg, 1.42 mmol) in 10 mL of $CHCl_3$ at 0 °C, and the mixture was stirred at this temperature for 6 h. The mixture was concentrated under reduced pressure to an oil, which was flash chromatographed on a silica gel column. Elution with *n*-hexane−EtOAc−$CHCl_3$ (2:1:3) gave 207 mg (75%) of the title compound **14** as a colorless oil: $[\alpha]^{30}_D$ −84.2 (*c* 1.04, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.40 (d, *J* = 5.9 Hz, 3 H), 3.04−3.14 (m, 1 H), 3.13 (s, 3 H), 3.40 (d, *J* = 7.6 Hz, 1 H), 3.81 (s, 3 H); LRMS (FAB) *m*/*z* 194 (MH^+, base peak), 162, 134, 114; HRMS (FAB) *m*/*z* calcd for $C_6H_{12}NO_4S$ (MH^+) 194.0487, found 194.0489.

Methyl (4*R*,5*S*,2*E*)-4,5-Epimino-*N*-(methanesulfonyl)-hex-2-enoate (15) and Methyl (4*R*,5*S*,2*Z*)-4,5-Epimino-*N*-(methanesulfonyl)hex-2-enoate (16). To a stirred solution of **14** (1.30 g, 6.73 mmol) in toluene (8 mL) at −78 °C under argon was added dropwise diisobutylaluminum hydride (1 M solution in toluene; 6.73 mL, 6.73 mmol). After 2 h, saturated aqueous NH_4Cl (2 mL) and [(methoxycarbonyl)methylene]-triphenylphosphorane (4.5 g, 13.46 mmol) were added to the solution with stirring at −78 °C. The mixture was stirred for 1 h, during which time it was allowed to warm to room temperature. The mixture was made acidic with 20% citric acid and extracted with EtOAc−$CHCl_3$ (4:1). The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to an oil, which was flash chromatographed on silica gel eluting with *n*-hexane−EtOAc (2:3) to give the *cis*-enoate **16** (770 mg, 52% yield). Continued elution gave the *trans*-enoate **15** (278 mg, 19% yield). **15**: colorless crystals from Et_2O; mp 56 °C; $[\alpha]^{20}_D$ −180 (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* = 5.8 Hz, 3 H), 3.05 (s, 3 H), 3.11 (m, 1 H), 3.38 (ddd, *J* = 7.5, 6.8, 1.0 Hz, 1 H), 3.77 (s, 3 H), 6.21 (dd, *J* = 15.6, 1.0 Hz, 1 H), 6.74 (dd, *J* = 15.6, 6.8 Hz, 1 H). Anal. Calcd for $C_8H_{13}NO_4S$: C, 43.82; H, 5.98; N, 6.39. Found: C, 43.70; H, 6.03; N, 6.36. **16**: colorless oil; $[\alpha]^{30}_D$ −96.5 (*c* 0.904, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (d, *J* = 5.9 Hz, 3 H), 3.06 (s, 3 H), 3.17 (m, 1 H), 3.77 (s, 3 H), 4.32 (ddd, *J* = 7.8, 7.8, 1.0 Hz, 1 H), 5.97 (dd, *J* = 11.6, 8.1 Hz, 1 H), 6.12 (dd, *J* = 11.6, 1.0 Hz, 1 H). LRMS (FAB) *m*/*z* 220 (MH^+), 219 (M^+), 188, 140 (base peak), 110, 109, 99; HRMS (FAB) *m*/*z* calcd for $C_8H_{14}NO_4S$ (MH^+) 220.0643, found 220.0637.

Methyl (4*S*,5*S*,2*E*)-4,5-Epimino-*N*-(methanesulfonyl)-hex-2-enoate (18) and Methyl (4*S*,5*S*,2*Z*)-4,5-Epimino-*N*-(methanesulfonyl)hex-2-enoate (19). By a procedure identical with that described for the preparation of the enoates **15** and **16** from **14**, the aziridine **17** (0.98 g, 5.07 mmol) was converted into the enoates **18** (435 mg, 39% yield) and **19** (220 mg, 20% yield). **18**: colorless oil; $[\alpha]^{28}_D$ +49.2 (*c* 1.19, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.58 (d, *J* = 5.9 Hz, 3 H), 2.96 (m, 1 H), 3.08 (s, 3 H), 3.20 (dd, *J* = 8.9, 4.3 Hz, 1 H), 3.76 (s, 3 H), 6.20 (d, *J* = 15.4 Hz, 1 H), 6.83 (dd, *J* = 15.4, 8.9 Hz, 1 H); LRMS (FAB) *m*/*z* 220 (MH^+), 219 (M^+), 188, 140 (base peak), 110, 109, 99; HRMS (FAB) *m*/*z* calcd for $C_8H_{14}NO_4S$ (MH^+) 220.0643, found 220.0641. **19**: colorless oil; $[\alpha]^{28}_D$ −113.6 (*c* 0.83, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.55 (d, *J* = 5.7 Hz, 3 H), 2.97 (m, 1 H), 3.77 (s, 3 H), 3.08 (s, 3 H), 4.36 (dd, *J* = 8.9, 3.8 Hz, 1 H), 6.07 (d, *J* = 11.6 Hz, 1 H), 6.19 (dd, *J* = 11.6, 8.9 Hz, 1 H); LRMS (FAB) *m*/*z* 220 (MH^+), 219 (M^+), 188, 140 (base peak), 110, 109, 99; HRMS (FAB) *m*/*z* calcd for $C_8H_{14}NO_4S$ (MH^+) 220.0643, found 220.0647.

Methyl (2*S*,3*R*)-*N*-[(2,4,6-Trimethylphenyl)sulfonyl]threoninate (26). Thionyl chloride (8.65 mL, 0.12 M) was added dropwise to a stirred solution of (*S*)-threonine (**11**) (11.9 g, 0.1 M) in MeOH (100 mL) at −78 °C, and the mixture was allowed to warm to rt and stirred at this temperature for 18 h. Concentration under reduced pressure gave an oily residue. To a solution of the residual oil in a mixed solvent of DMF (30 mL) and $CHCl_3$ (50 mL) at 0 °C were added Et_3N (40 mL) and 2,4,6-trimethylbenzenesulfonyl chloride (21.87 g) with stirring, and stirring was continued for 2 h followed by quenching with 5% $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc, and the extract was washed successively with water, 10% citric acid, water, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Usual workup followed by recrystallization from Et_2O−$CHCl_3$ (10:1) gave 15 g (48% yield) of the title compound **26** as colorless crystals: mp 120 °C; $[\alpha]^{20}_D$ −20.3 (*c* 1.82, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.3 Hz, 3 H), 2.29 (s, 3 H), 2.64 (s, 6 H), 3.52 (s, 3 H), 3.74 (dd, *J* = 9.6, 3.3 Hz, 1 H), 4.10 (m, 1 H), 5.58 (d, *J* = 9.6 Hz, 1 H), 6.95 (s, 2 H). Anal. Calcd for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.20; H, 6.91; N, 4.37.

Methyl (2*S*,3*S*)-3-Methyl-*N*-[(2,4,6-trimethylphenyl)-sulfonyl]-2-aziridinecarboxylate (27). By a procedure identical with that described for the preparation of the aziridine **14** from **13**, the ester **26** (8.1 g, 25.7 mmol) was converted into the aziridine **27** (6.2 g, 81% yield): mp 76−77 °C (*n*-hexane−Et_2O = 1:1) ; $[\alpha]^{20}_D$ −41.6 (*c* 2.74, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (d, *J* = 5.9 Hz, 3 H), 2.31 (s, 3 H), 2.70 (s, 6 H), 3.13 (m, 1 H), 3.79 (d, *J* = 7.3 Hz, 1 H), 3.73 (s, 3 H), 6.97 (s, 2 H). Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.52; H, 6.62; N, 4.65.

Methyl (2*R*,3*R*)-*N*-[(2,4,6-Trimethylphenyl)sulfonyl]allothreoninate (29). By a procedure identical with that described for the preparation of **26** from (2*S*,3*R*)-threonine (**11**), D-allothreonine (**28**) (8 g, 67 mmol) was converted into the title compound **29** (17 g, 81% yield): colorless prisms from EtOAc−$CHCl_3$ (2:1); mp 143 °C; $[\alpha]^{20}_D$ +3.2 (*c* 0.754, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.6 Hz, 3 H), 2.29 (s, 3 H), 2.53 (d, *J* = 8.6 Hz, 1 H), 2.64 (s, 6 H), 3.52 (s, 3 H), 3.84 (dd, *J* = 8.9, 4.3 Hz, 1 H), 4.03 (m, 1 H), 5.69 (d, *J* = 8.9 Hz, 1 H), 6.96 (s, 2 H). Anal. Calcd for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.20; H, 6.87; N, 4.41.

Methyl (2*R*,3*S*)-3-Methyl-*N*-[(2,4,6-trimethylphenyl)-sulfonyl]-2-aziridinecarboxylate (30). By a procedure identical with that described for the preparation of the aziridine **27** from the hydroxy ester **26**, the hydroxy ester **29** (7.635 g, 24.2 mmol) was converted into the title compound **30** (6.15 g, 88% yield) by treatment with PPh_3 (7.6 g, 29 mmol) and diethyl azodicarboxylate (4.6 mL, 29 mmol) in THF (50 mL) followed by flash chromatography over silica gel with *n*-hexane−EtOAc (3:1): colorless prisms from *n*-hexane−Et_2O (2:1); mp 71 °C; $[\alpha]^{20}_D$ +18.8 (*c* 1.52, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.70 (d, *J* = 5.9 Hz, 3 H), 2.29 (s, 3 H), 2.72 (s, 6 H), 3.12 (m, 1 H), 3.34 (d, *J* = 4.0 Hz, 1 H), 3.69 (s, 3 H), 6.95 (s, 2 H). Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.58; H, 6.51; N, 4.76.

Methyl (4*R*,5*S*,2*E*)-4,5-Epimino-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (31) and Methyl (4*R*,5*S*,2*Z*)-4,5-Epimino-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (32). By a procedure identical with that described for the preparation of the enoates **15** and **16** from **14**, the aziridine **27** (4.35 g, 14.64 mmol) was converted into the enoates **31** (1.1

g, 23% yield) and **32** (2.91 g, 61% yield). **31**: colorless oil; $[\alpha]^{20}_D$ −68.8 (*c* 1.44, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (d, J = 5.9 Hz, 3 H), 2.31 (s, 3 H), 2.68 (s, 6 H), 3.12 (m, 1 H), 3.43 (t, J = 7.3 Hz, 1 H), 6.05 (d, J = 15.8 Hz, 1 H), 6.68 (dd, J = 15.8, 6.6 Hz, 1 H), 6.91 (s, 2 H); LRMS (FAB) *m/z* 324 (MH^+), 183, 167, 140 (base peak), 119; HRMS (FAB) *m/z* calcd for $C_{16}H_{22}NO_4S$ (M^+) 324.1269, found 324.1261. **32**: colorless crystals from *n*-hexane−Et_2O (1:1); mp 97 °C; $[\alpha]^{20}_D$ +23.3 (*c* 1.51, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.22 (d, J = 5.9 Hz, 3 H), 2.30 (s, 3 H), 2.68 (s, 6 H), 3.18 (m, 1 H), 3.74 (s, 3 H), 4.38 (t, J = 7.6 Hz, 1 H), 5.88 (dd, J = 11.9, 7.6 Hz, 1 H), 5.98 (d, J = 11.9 Hz, 1 H), 6.95 (s, 2 H). Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55; N, 4.33. Found: C, 59.19; H, 6.48; N, 4.12.

Methyl (4*S*,5*S*,2*E*)-4,5-Epimino-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (33) and Methyl (4*S*,5*S*,2*Z*)-4,5-Epimino-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (34). By a procedure identical with that described for the preparation of the enoates **31** and **32** from **27**, the aziridine **30** (5.91 g, 20 mmol) was converted into the enoates **33** (2.4 g, 37.3% yield) and **34** (1.9 g, 30% yield) by treatment with diisobutylaluminum hydride (1 M solution in *n*-hexane; 24.5 mL, 24 mmol, 1.2 equiv) followed by [(methoxycarbonyl)-methylene]triphenylphosphorane (7.45 g, 22 mmol, 1.1 equiv). **33**: colorless oil; $[\alpha]^{20}_D$ +25.6 (*c* 1.70, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.52 (d, J = 5.9 Hz, 3 H), 2.30 (s, 3 H), 2.68 (s, 6 H), 3.00 (m, 1 H), 3.20 (dd, J = 8.9, 4.0 Hz, 1 H), 3.71 (s, 3 H), 6.04 (d, J = 15.5 Hz, 1 H), 6.86 (dd, J = 15.5, 8.9 Hz, 1 H), 6.94 (s, 2 H); LRMS (FAB) *m/z* 324 (MH^+), 322, 183, 167, 140 (base peak), 119, 109; HRMS (FAB) *m/z* calcd for $C_{16}H_{22}NO_4S$ (MH^+) 324.1269, found 324.1270. **34**: colorless oil; $[\alpha]^{20}_D$ −18.8 (*c* 0.84, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.48 (d, J = 5.6 Hz, 3 H), 2.29 (s, 3 H), 2.68 (s, 6 H), 3.00 (m, 1 H), 3.73 (s, 3 H), 4.43 (dd, J = 9.6, 4.0 Hz, 1 H), 5.98 (d, J = 11.6 Hz, 1 H), 6.22 (dd, J = 11.6, 9.6 Hz, 1 H), 6.94 (s, 2 H); LRMS (FAB) *m/z* 324 (MH^+), 322, 183, 167, 140, 119 (base peak), 109; HRMS (FAB) *m/z* calcd for $C_{16}H_{22}NO_4S$ (MH^+) 324.1269, found 324.1268.

Methyl (4*R*,5*S*,2*E*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (37) and Methyl (4*R*,5*S*,2*Z*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (38). Ozone was bubbled through a solution of the vinylaziridine **35** (2.0 g, 6.82 mmol) in CH_2Cl_2 (30 mL) at −78 °C until a blue color persisted. The solution was stirred for 30 min, during which time it was allowed to warm to 0 °C. To the mixture at 0 °C were added triphenylphosphine (893 mg, 3.41 mmol) and [(methoxycarbonyl)-methylene]triphenylphosphorane (3.41 g, 10.23 mmol, 1.5 equiv), and the mixture was stirred for 18 h. The mixture was concentrated under reduced pressure to leave a semisolid, which was purified by flash chromatography over silica gel eluting with *n*-hexane−EtOAc (5:1) to give the (*Z*)-enoate **38** (1.26 g, 53% yield). Continued elution gave the (*E*)-enoate **37** (690 mg, 29% yield). **37**: colorless crystals from *n*-hexane−Et_2O (2:1); mp 78 °C; $[\alpha]^{20}_D$ −80.8 (*c* 1.17, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.79 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 1.40 (m, 1 H), 2.31 (s, 3 H), 2.66 (dd, J = 9.9, 7.3 Hz, 1 H), 2.70 (s, 6 H), 3.48 (t, J = 7.2 Hz, 1 H), 3.73 (s, 3 H), 6.09 (dd, J = 15.5, 1.0 Hz, 1 H), 6.72 (dd, J = 15.5, 6.9 Hz, 1 H), 6.96 (s, 2 H). Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.53; H, 7.19; N, 3.94. **38**: colorless oil; $[\alpha]^{20}_D$ −41.7 (*c* 1.08, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 1.39 (m, 1 H), 2.30 (s, 3 H), 2.70 (s, 6 H), 2.74 (dd, J = 9.9, 7.6 Hz, 1 H), 3.75 (s, 3 H), 4.46 (t, J = 7.3 Hz, 1 H), 5.93 (dd, J = 11.9, 7.3 Hz, 1 H), 6.00 (d, J = 11.9 Hz, 1 H), 6.95 (s, 2 H); LRMS (FAB) *m/z* 352 (MH^+), 350, 254 (base peak), 183, 168, 153, 119; HRMS (FAB) *m/z* calcd for $C_{18}H_{26}NO_4S$ (MH^+) 352.1582, found 352.1574.

***tert*-Butyl (4*R*,5*S*,2*E*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (39) and *tert*-Butyl (4*R*,5*S*,2*Z*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (40).** Ozone was bubbled through a solution of the vinylaziridine **35** (1.3 g, 4.436 mmol) in AcOEt (15 mL) at −78 °C until a blue color persisted. Zinc powder (0.7 g) was added to the solution, and the mixture was stirred for 30 min, during which time it was allowed to warm to 0 °C. To the mixture at 0 °C was added [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane (3.3 g, 8.87 mmol, 2.0 equiv), and the mixture was stirred for 1 h. The mixture was concentrated under reduced pressure to leave a semisolid, which was purified by flash chromatography over silica gel eluting with *n*-hexane−EtOAc (4:1) to give the (*Z*)-enoate **40** (760 mg, 44% yield). Continued elution gave the (*E*)-enoate **39** (950 mg, 55% yield). **39**: colorless crystals; mp 118 °C (*n*-hexane−Et_2O = 2:1); $[\alpha]^{20}_D$ −54.7 (*c* 1.64, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), 1.36−1.50 (m, 1 H), 1.47 (s, 9 H), 2.31 (s, 3 H), 2.63 (dd, J = 10.0, 7.2 Hz, 1 H), 2.70 (s, 6 H), 3.47 (ddd, J = 7.2, 7.2, 1.0 Hz, 1 H), 6.02 (dd, J = 15.6, 1.0 Hz, 1 H), 6.59 (dd, J = 15.6, 7.2 Hz, 1 H), 6.96 (s, 2 H). Anal. Calcd for $C_{21}H_{31}NO_4S$: C, 63.93; H, 8.18; N, 3.55. Found: C, 63.65; H, 8.06; N, 3.38. **40**: colorless oil; $[\alpha]^{20}_D$ −54.2 (*c* 1.84, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 1.37 (m, 1 H), 1.50 (s, 9 H), 2.30 (s, 3 H), 2.69 (s, 6 H), 2.70 (dd, J = 9.9, 7.6 Hz, 1 H), 4.42 (dd, J = 7.6, 6.4 Hz, 1 H), 5.82 (dd, J = 11.6, 6.4 Hz, 1 H), 5.88 (d, J = 11.6 Hz, 1 H), 6.941 (s, 1 H), 6.943 (s, 1 H); LRMS (FAB) *m/z* 394 (MH^+), 338, 320, 254 (base peak), 154, 119; HRMS (FAB) *m/z* calcd for $C_{21}H_{32}NO_4S$ (MH^+) 394.2052, found 394.2057.

Methyl (4*S*,5*S*,2*E*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (41) and Methyl (4*S*,5*S*,2*Z*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (42). By a procedure identical with that described for the preparation of the enoates **37** and **38** from **35**, the 2-vinylaziridine **36** (2.4 g, 8.19 mmol) was converted into the enoates **41** (2.15 g, 75% yield) and **42** (740 mg, 19% yield). **41**: colorless oil; $[\alpha]^{20}_D$ −12.8 (*c* 1.10, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.76 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 1.57 (m, 1 H), 2.30 (s, 3 H), 2.69 (s, 6 H), 2.89 (dd, J = 7.6, 4.0 Hz, 1 H), 3.14 (dd, J = 9.9, 4.0 Hz, 1 H), 3.74 (s, 3 H), 6.13 (d, J = 15.8 Hz, 1 H), 6.94 (s, 2 H), 7.16 (dd, J = 15.8, 9.9 Hz, 1 H); LRMS (FAB) *m/z* 352 (MH^+), 350, 254, 183, 168 (base peak), 153, 119; HRMS (FAB) *m/z* calcd for $C_{18}H_{26}NO_4S$ (MH^+) 352.1582, found 352.1589. **42**: colorless oil; $[\alpha]^{20}_D$ −121 (*c* 0.975, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.73 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 1.58 (m, 1 H), 2.30 (s, 3 H), 2.69 (s, 6 H), 2.85 (dd, J = 7.7, 4.3 Hz, 1 H), 4.50 (dd, J = 10.0, 4.3 Hz, 1 H), 6.03 (d, J = 11.6 Hz, 1 H), 6.61 (dd, J = 11.6, 10.0 Hz, 1 H), 6.94 (s, 2 H); LRMS (FAB) *m/z* 352 (MH^+), 350, 254, 183, 168 (base peak), 153, 119; HRMS (FAB) *m/z* calcd for $C_{18}H_{26}NO_4S$ (MH^+) 352.1582, found 352.1581.

***tert*-Butyl (4*S*,5*S*,2*E*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (43) and *tert*-Butyl (4*S*,5*S*,2*Z*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (44).** By a procedure identical with that described for the preparation of the enoates **39** and **40** from **35**, **36** (760 mg, 2.59 mmol) was converted into the enoates **43** (800 mg, 79% yield) and **44** (180 mg, 18% yield). **43**: colorless oil; $[\alpha]^{20}_D$ +6.0 (*c* 1.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J = 6.7 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 1.48 (s, 9 H), 1.59 (m, 1 H), 2.29 (s, 3 H), 2.69 (s, 6 H), 2.90 (dd, J = 7.6, 4.1 Hz, 1 H), 3.08 (dd, J = 10.0, 4.1 Hz, 1 H), 6.00 (dd, J = 15.4, 0.4 Hz, 1 H), 6.93 (s, 2 H), 7.01 (dd, J = 15.4, 10.0 Hz, 1 H); LRMS (FAB) *m/z* 394 (MH^+), 338, 320, 210, 154, 119 (base peak); HRMS (FAB) *m/z* calcd for $C_{21}H_{32}NO_4S$ (MH^+) 394.2052, found 394.2044. **44**: colorless oil; $[\alpha]^{20}_D$ −94.0 (*c* 0.723, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 1.48 (s, 9 H), 1.58 (m, 1 H), 2.30 (s, 3 H), 2.70 (s, 6 H), 2.82 (dd, J = 7.4, 4.2 Hz, 1 H), 4.48 (ddd, J = 10.0, 4.2, 1.0 Hz, 1 H), 5.92 (dd, J = 11.6, 1.0 Hz, 1 H), 6.46 (dd, J = 11.6, 10.0 Hz, 1 H), 6.94 (s, 2 H); LRMS (FAB) *m/z* 394 (MH^+), 338, 320, 282, 254 (base peak), 154, 119; HRMS (FAB) *m/z* calcd for $C_{21}H_{32}NO_4S$ (MH^+) 394.2052, found 394.2045.

***tert*-Butyl (4*R*,5*S*,2*E*)-4,5-Epimino-6-phenyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (47) and *tert*-Butyl (4*R*,5*S*,2*Z*)-4,5-Epimino-6-phenyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (48).** By a procedure identical with that described for the preparation of the enoates **39** and **40** from **35**, the 2-vinylaziridine **45** (570 mg, 1.67 mmol)

was converted into the enoates **47** (256 mg, 35% yield) and **48** (332 mg, 45% yield). **47**: colorless crystals (*n*-hexane−Et_2O = 4:1); mp 92 °C; $[\alpha]^{35}_D$ −52.9 (*c* 0.85, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 2.30 (s, 3 H), 2.56 (s, 6 H), 2.62 (dd, *J* = 14.3, 8.1 Hz, 1 H), 2.77 (dd, *J* = 14.3, 5.1 Hz, 1 H), 3.15 (m, 1 H), 3.55 (ddd, *J* = 7.0, 7.0, 1.1 Hz, 1 H), 6.10 (dd, *J* = 15.7, 1.1 Hz, 1 H), 6.73 (dd, *J* = 15.7, 6.5 Hz, 1 H), 6.85 (s, 2 H), 6.91−7.14 (m, 5 H); LRMS (FAB) *m*/*z* 442 (MH^+), 386, 368, 258, 202, 186, 156, 119 (base peak), 91; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{32}NO_4S$ (MH^+) 442.2052, found 442.2054. **48**: colorless oil; $[\alpha]^{31}_D$ −73.6 (*c* 0.78, $CHCl_3$); ^1H NMR (2700 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 2.29 (s, 3 H), 2.57 (s, 6 H), 2.60 (dd, *J* = 14.8, 8.1 Hz, 1 H), 2.80 (dd, *J* = 14.8, 4.9 Hz, 1 H), 3.22 (ddd, *J* = 8.1, 8.1, 4.9 Hz, 1 H), 4.49 (m, 1 H), 5.97 (m, 2 H), 6.85 (s, 2 H), 6.90−7.14 (m, 5 H); LRMS (FAB) *m*/*z* 442 (MH^+), 386, 368, 302 (base peak), 202, 186, 156, 119, 91; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{32}NO_4S$ (MH^+) 442.2052, found 442.2046.

***tert*-Butyl (4*S*,5*S*,2*E*)-4,5-Epimino-6-phenyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (49) and *tert*-Butyl (4*S*,5*S*,2*Z*)-4,5-Epimino-6-phenyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (50).** By a procedure identical with that described for the preparation of the enoates **43** and **44** from **36**, the 2-vinylaziridine **46** (450 mg, 1.32 mmol) was converted into the enoates **49** (427 mg, 73% yield) and **50** (50 mg, 9% yield). **49**: colorless crystals from *n*-hexane−EtOAc (2:1); mp 100 °C; $[\alpha]^{35}_D$ 27.9 (*c* 0.96, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.46 (s, 9 H), 2.30 (s, 3 H), 2.57 (s, 6 H), 2.84 (dd, *J* = 14.3, 5.9 Hz, 1 H), 3.02 (dd, *J* = 14.3, 5.7 Hz, 1 H), 3.22 (m, 2 H), 6.01 (d, *J* = 15.4 Hz, 1 H), 6.87 (dd, *J* = 15.4, 9.2 Hz, 1 H), 6.89 (s, 2 H), 6.95−7.19 (m, 5 H). Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 67.00; H, 7.08; N, 3.17. Found: C, 67.30; H, 7.04; N, 3.19. **50**: colorless oil; $[\alpha]^{35}_D$ −34.1 (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.53 (s, 9 H), 2.30 (s, 3 H), 2.67 (dd, *J* = 14.0, 7.3 Hz, 1 H), 3.04−3.19 (m, 2 H), 4.64 (ddd, *J* = 9.7, 3.5, 0.5 Hz, 1 H), 5.94 (dd, *J* = 11.3, 0.5 Hz, 1 H), 6.34 (dd, *J* = 11.3, 10, 0 Hz, 1 H), 6.85 (s, 2 H), 6.90−7.14 (m, 5 H); LRMS (FAB) *m*/*z* 442 (MH^+), 386, 302 (base peak), 202, 183, 119, 91, 57; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{32}NO_4S$ (MH^+) 442.2052, found 442.2055.

Methyl (4*S*,5*R*,2*E*)-4,5-Epimino-5-phenyl-*N*-[(4-methylphenyl)sulfonyl]pent-2-enoate (25) from 24. To a stirred solution of *cis*-(*Z*)-enoate **24** (107 mg, 0.3 mmol) in THF (3 mL) at 20 °C under argon was added by syringe a solution of $Pd(PPh_3)_4$ (13.9 mg, 4 mol %) in 2 mL of THF. After 18 h, the mixture was filtered through a short pad of silica gel with *n*-hexane−EtOAc (1:1). Concentration under reduced pressure gave a crystalline residue. Recrystallization from MeOH gave 80 mg (75% yield) of pure *cis*-(*E*)-enoate **25** as silky needles. The mother liquor was concentrated to a semisolid, which was treated with $Pd(PPh_3)_4$ (4 mol %) in dry THF. The same workup as described above gave 7 mg (6% yield) of **25**. The total yield of **25** amounted to 81%: colorless silky needles from MeOH; mp 146 °C; $[\alpha]^{20}_D$ −44.3 (*c* 1.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 3.63 (s, 3 H), 3.68 (m, 1 H), 6.09 (dd, *J* = 15.7, 0.6 Hz, 1 H), 6.33 (dd, *J* = 15.7, 7.7 Hz, 1 H), 7.19−7.36 (m, 5 H), 7.86−7.87 (m, 2 H). Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.95; H, 5.33; N, 3.69.

***tert*-Butyl (4*R*,5*S*,2*E*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (39) from *tert*-Butyl (4*R*,5*S*,2*Z*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (40).** To a stirred solution of the enoate **40** (1.1 g, 2.8 mmol) in 7 mL of dry THF at 0 °C under argon was added by syringe a solution of $Pd(PPh_3)_4$ (64.6 mg, 0.056 mmol, 2 mol %) in 3 mL of dry THF, and the mixture was stirred at 15 °C for 15 h. Concentration under reduced pressure at 0 °C followed by flash chromatography over silica gel with *n*-hexane−EtOAc (4:1) gave 1.08 g of a crystalline mass. Recrystallization from *n*-hexane gave 690 mg (62.7% yield) of the (2*E*)-isomer **39** as colorless crystals. The mother liquor was concentrated under reduced pressure to leave 410 mg of a colorless semisolid. The semisolid was treated with 24 mg of $Pd(PPh_3)_4$ in 5 mL of dry THF for 16 h at 15 °C. Usual workup followed by flash chromatography over silica gel with *n*-hexane−EtOAc (5:1) and recrystallization from *n*-hexane gave 230 mg (20.9% yield) of the enoate **39**. The product **39** thus obtained amounts to 920 mg (83.6% yield): mp 118 °C (from *n*-hexane); $[\alpha]^{26}_D$ −54.8° (*c* 0.945, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 1.36−1.50 (m, 1 H), 1.47 (s, 9 H), 2.31 (s, 3 H), 2.63 (dd, *J* = 10.0, 7.2 Hz, 1 H), 2.70 (s, 6 H), 3.47 (ddd, *J* = 7.2, 7.2, 1.0 Hz, 1 H), 6.02 (dd, *J* = 15.6, 1.0 Hz, 1 H), 6.59 (dd, *J* = 15.6, 7.2 Hz, 1 H), 6.96 (s, 2 H). Anal. Calcd for $C_{21}H_{31}NO_4S$: C, 63.93; H, 8.18; N, 3.55. Found: C, 64.00; H,8.11; N, 3.59.

***tert*-Butyl (4*R*,5*S*,2*E*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (39) from *tert*-Butyl (4*S*,5*S*,2*E*)-4,5-Epimino-6-methyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hept-2-enoate (43).** By a procedure identical with that described for the preparation of the enoates **39** from **40**, the 4,5-*trans*-enoate **43** was converted into the enoate **39** (86.7% yield): mp 118 °C (from *n*-hexane); $[\alpha]^{26}_D$ −55.1° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 1.36−1.50 (m, 1 H), 1.47 (s, 9 H), 2.31 (s, 3 H), 2.63 (dd, *J* = 10.0, 7.2 Hz, 1 H), 2.70 (s, 6 H), 3.47 (ddd, *J* = 7.2, 7.2, 1.0 Hz, 1 H), 6.02 (dd, *J* = 15.6, 1.0 Hz, 1 H), 6.59 (dd, *J* = 15.6, 7.2 Hz, 1 H), 6.96 (s, 2 H). Anal. Calcd for $C_{21}H_{31}NO_4S$: C, 63.93; H, 8.18; N, 3.55. Found: C, 64.01; H,8.21; N, 3.60.

***tert*-Butyl (2*R*,5*S*,3*E*)-6-Methyl-2-(2-methylpropyl)-5-[[(2,4,6-trimethylphenyl)sulfonyl]amino]-3-heptenoate (53) from 39.** To a stirred solution of CuCN (916 mg, 10.2 mmol) and LiCl (860 mg, 20.4 mmol) in 20 mL of dry THF under argon was added by syringe isobutylmagnesium chloride (1.1 M solution in THF; 9.27 mL, 10.2 mmol) at −78 °C, and the mixture was allowed to warm to 0 °C and stirred at this temperature for 10 min. The enoate **39** (1.0 g, 2.544 mmol) in 10 mL of dry THF was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 30 min followed by quenching with 20 mL of a 1:1 saturated NH_4Cl−28% NH_4OH solution. The mixture was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was flash chromatographed on silica gel eluting with *n*-hexane−EtOAc (4:1) to give the title compound **53** (1.091g, 95% yield) as a crystalline mass. Recrystallization from *n*-hexane gave colorless crystals: mp 108 °C; $[\alpha]^{20}_D$ −42.1 (*c* 1.35, $CHCl_3$); $\Delta\epsilon$ −4.75 (219 nm in isooctane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, *J* = 6.4 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.98 (m, 1 H), 1.28−1.48 (m, 2 H), 1.38 (s, 9 H), 1.74 (m, 1 H), 2.28 (s, 3 H), 2.61 (s, 6 H), 2.69 (m, 1 H), 3.47 (m, 1 H), 4.48 (d, *J* = 7.8 Hz, 1 H), 5.18 (m, 2 H), 6.91 (s, 2 H). Anal. Calcd for $C_{25}H_{41}NO_5S$: C, 66.48; H, 9.15; N, 3.10. Found: C, 66.43; H, 9.09; N, 3.14.

***tert*-Butyl (4*R*,5*S*,2*E*)-4,5-Epimino-6-phenyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (47) from *tert*-Butyl (4*S*,5*S*,2*E*)-4,5-Epimino-6-phenyl-*N*-[(2,4,6-trimethylphenyl)sulfonyl]hex-2-enoate (49).** By a procedure identical with that described for the preparation of the enoate **39** from **40**, the enoate (**49**) was converted into the isomeric enoate **47** (78% yield). **47**: colorless crystals from *n*-hexane−Et_2O (2:1); mp 92 °C; $[\alpha]^{35}_D$ −46.2 (*c* 1.17, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 2.30 (s, 3 H), 2.56 (s, 6 H), 2.62 (dd, *J* = 14.3, 8.1 Hz, 1 H), 2.77 (dd, *J* = 14.3, 5.1 Hz, 1 H), 3.15 (m, 1 H), 3.55 (ddd, *J* = 7.0, 7.0, 1.1 Hz, 1 H), 6.10 (dd, *J* = 15.7, 1.1 Hz, 1 H), 6.73 (dd, *J* = 15.7, 6.5 Hz, 1 H), 6.85 (s, 2 H), 6.91−7.14 (m, 5 H). Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 67.99; H, 7.08; N, 3.17. Found: C, 67.80: H, 7.15: N, 3.14.

***tert*-Butyl (2*S*,5*S*,3*E*)-2-(2-Methylethyl)-6-phenyl-5-[[(2,4,6-trimethylphenyl)sulfonyl]amino]-3-hexenoate (55).** To a stirred solution of CuCN (81 mg, 0.89 mmol) and LiCl (76.5 mg, 1.81 mmol) in 2 mL of dry THF under argon was added by syringe isopropylmagnesium chloride (0.89 M solution in THF; 1.0 mL, 0.89 mmol) at −78 °C, and the mixture was allowed to warm to 0 °C and stirred at this temperature for 10 min. The enoate **49** (100 mg, 0.226 mmol) in 2 mL of dry THF was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 30 min followed by quenching with 2 mL of a 1:1 saturated NH_4Cl−28% NH_4OH solution. The mixture was extracted with EtOAc,

and the extract was successively washed with water, 5% citric acid, 5% $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was flash chromatographed on silica gel eluting with *n*-hexane−EtOAc (4:1) to give the title compound **55** (88 mg, 80% yield) as a colorless oil: $[\alpha]^{33}_D$ +2.65 (*c* 1.08, $CHCl_3$); $\Delta\epsilon$ +3.37 (219 nm in isooctane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.66 (d, J = 6.8 Hz, 3 H), 0.81 (d, J = 6.5 Hz, 3 H), 1.43 (s, 9 H), 1.75 (m, 1 H), 2.25 (s, 3 H), 2.41 (t, J = 8.4 Hz, 1 H), 2.49 (s, 6 H), 2.80 (m, 2 H), 3.92 (m, 1 H), 4.46 (d, J = 6.2 Hz, 1 H), 5.27−5.50 (m, 2 H), 6.88 (s, 2 H), 7.01−7.26 (m, 5 H); LRMS (FAB) *m*/*z* 486 (MH^+), 484, 470, 384, 338, 302, 231, 185, 129, 119 (base peak), 91, 57; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{40}NO_4S$ (MH^+) 486.2678, found 486.2669.

***tert*-Butyl (2*R*,5*S*,3*E*)-6-Phenyl-2-(2-methylethyl-5-[[(2,4,6-trimethylphenyl)sulfonyl]amino]-3-hexenoate (54).** By a procedure identical with that described for the preparation of the enoate **55** from **49**, the enoate **47** was converted into the title compound **54** as a colorless oil (90% yield): $[\alpha]^{33}_D$ −64.0 (*c* 0.85, $CHCl_3$); $\Delta\epsilon$ −4.89 (227 nm in isooctane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.73 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 6.5 Hz, 3 H), 1.40 (s, 9 H), 1.80 (m, 1 H), 2.28 (s, 3 H), 2.39−2.48 (m, 1 H), 2.49 (s, 6 H), 2.81 (m, 2 H), 3.91 (m, 1 H), 4.46 (d, J = 7.0 Hz, 1 H), 5.30−5.47 (m, 2 H), 6.87 (s, 2 H), 7.00−7.26 (m, 5 H); LRMS (FAB) *m*/*z* 486 (MH^+), 484, 470, 384, 338, 302, 231, 185, 129, 119 (base peak), 91, 57; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{40}NO_4S$ (MH^+) 486.2678, found 486.2661.

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Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **12**, **14**, **16**, **18**, **19**, **31**, **33**, **34**, **38**, **40**−**44**, **47**, **48**, **50**, **54**, and **55** are available (19 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.

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