S_N2'-Reactions of Peptide Aziridines. A Cuprate-Based Approach to (*E*)-Alkene Isosteres†

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Alkenylaziridines were prepared from allylic alcohols via Sharpless epoxidation, oxirane to aziridine conversion under modified Staudinger conditions, and Wittig chain extension. Alternatively, β-hydroxy α-amino acids such as threonine can serve as readily available precursors. The corresponding *N*-acyl, -peptidyl-, -carbamoyl-, and -sulfonylaziridines underwent a high-yielding *anti*-S_N2' alkylation with organocopper/BF_3 complex to give (*E*)-alkene peptide isosteres in 62 to >98% de. The stereoselectivity of the addition process was studied by ^1H and ^{19}F NMR as well as chemical degradation. Alkene isosteres are important nonhydrolyzable and rigidified analogs of peptide bonds in biologically active peptides. This new methodology considerably facilitates the synthesis and the study of these peptide mimetics, since alkenylaziridines are readily prepared and side-chain modification is simplified by the wide range of functionalized organocopper reagents that are available.

Peptide analogs are widely employed in elucidating structure–activity relationships, and replacement of the peptide backbone by thiomethylene, hydroxymethylene, ketomethylene, α-aza, and other amino acid isosteres has led to significant increases in bioavailability and oral activity.[2] The amide bond in peptides and proteins is a prime target for enzymatic degradation, and backbone modifications are therefore crucial for improving metabolic stability. Alkenes are ideal isosteric replacements of amides, since the (*E*)-CR=CH group closely resembles the three-dimensional structure (bond length, bond angle, and rigidity) of the parent amide (Figure 1).

The use (*E*)-alkene isosteres as mimetics of dipeptide units in biologically active peptides requires the preparation of two asymmetric centers at the α- and δ-positions of 5-amino-3-pentenoic acids. Among the reported synthetic procedures for this class of compounds,[3] stereocontrolled protocols[4] are relatively rare, and a general stereoselective synthesis of alkene isosteres would considerably increase their application in drug discovery and development.

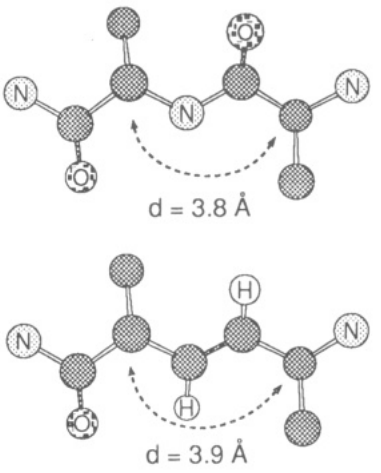

Figure 1.

We have recently reported on the preparation of peptide aziridines by the Mitsunobu reaction.[5] As an extension of these studies, we were interested in the use of aziridines of type **1** as peptide mimetics. Specifically, S_N2'-reaction of cuprates with **1** would provide a versatile route to (*E*)-alkene dipeptide isosteres (Figure 2). In the past years, reactions of allylic derivatives with organocuprate reagents have been extensively studied.[6] Al-

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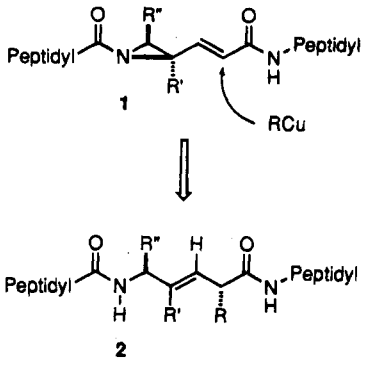

Figure 2.

though S_N2'-alkylation of alkenyl aziridines has escaped this attention,[7] there is ample precedence for this transformation in a highly stereoselective anti-S_N2' fashion with allylic esters,[8] sulfonates,[9] oxiranes,[10] phosphates,[11] halides,[6a,12] and carbonates.[13]

Preparation of Alkenyl Aziridines. A variety of routes to scalemic aziridines is available.[14] We envisioned several synthetic schemes for the preparation of peptidyl aziridines **1**. Epoxy alcohols **4**, obtained by Sharpless asymmetric epoxidation[15] of allylic alcohols **3** in the presence of (+)-diisopropyl tartrate (DIPT), were oxidized under Swern conditions,[16] and the resulting aldehydes were subjected to a Wittig chain extension with (carbalkoxymethylene)triphenylphosphorane (69–88% yield for two steps, Scheme 1). Stereoselective epoxide ring opening at C(4) of **5** was achieved in 45–85% yield by treatment with 3.0 equiv of sodium azide and 3.0 equiv of ammonium chloride in refluxing ethanol[17] for 3 h or less. Under these reaction conditions, generally less than 5% of the epimeric azide **7** was isolated. Any increase

Scheme 1

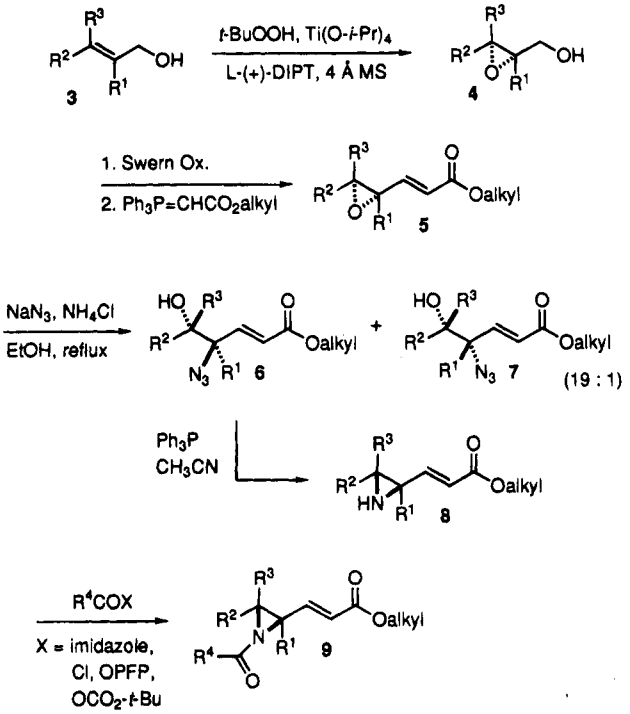

Table 1. Preparation of Alkenylaziridines 9 from Epoxy Alcohols 4 According to Scheme 1

	alkenylaziridines 9					
entry	R^1	R^2	R^3	R^4	no.	yield[a] (%)
1	H	CH_3	H	Ph	**9a**	27
2	H	CH_3	H	$EtO_2CCH_2CH_2$	**9b**	42
3	H	CH_3	H	$PhCH_2OC(O)NHCH_2$	**9c**	39
4	H	CH_3	H	*t*-BuO	**9d**	47
5	CH_3	H	CH_3	*t*-BuO	**9e**	24

[a] Yields are not optimized and are based on epoxy alcohol **4** and aziridines **9**. Aziridines were purified by column chromatography on silica gel; **9a–d** contained ≤5% of the corresponding (2*S*)-diastereomer.

in reaction time led to a significant decrease in the ratio of **6**:**7**, possibly as a consequence of a nonstereoselective [3,3]sigmatropic allylic azide shift.[18] Staudinger reaction[19] of β-azido alcohol **6** proceeded in 65–82% yield and resulted in aziridine formation via inversion of the configuration at C(5).[20] Subsequent *N*-acylation of **8** with acylimidazoles, acid chlorides, pentafluorophenyl esters (OPFP), or mixed anhydrides yielded 57–98% of the desired alkenylaziridines **9**. A summary of the *N*-acylaziridines that were prepared via this route and the overall yield from epoxy alcohol **4** are given in Table 1.

The Sharpless asymmetric epoxidation protocol provides epoxy alcohols **4** in various degrees of optical purity, depending on the substitution pattern of the alkene.[15] Crystallization of appropriate derivatives can also be used to improve the enantiomeric excess.[21] We used epoxy alcohols **4a** and **4e** in 84% and 60% ee, as determined by comparison of $[\alpha]_D$ with literature data

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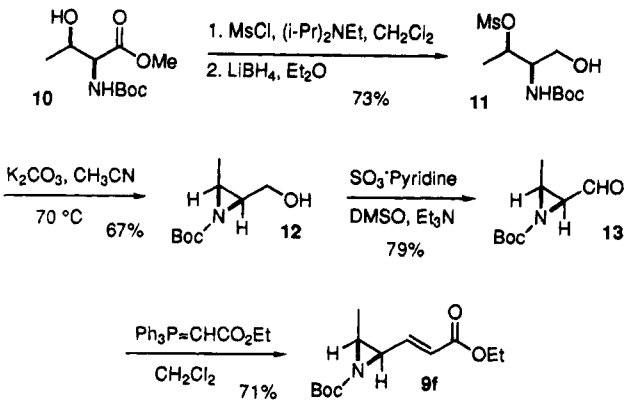
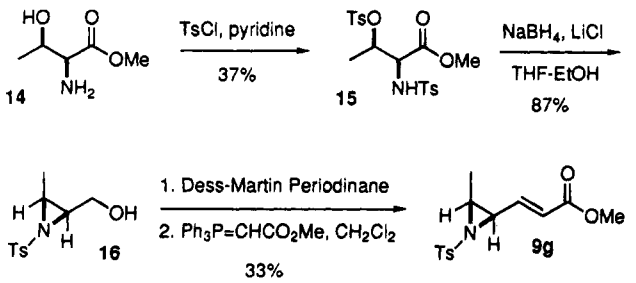
Scheme 2



Scheme 3



and integration of the ^{19}F NMR of the Mosher ester[22] derivatives. Alternatively, optically pure peptide aziridines can be obtained from β-hydroxy amino acids.[5a,23] Sequential treatment of Boc-threonine methyl ester (**10**) with 1 equiv of mesyl chloride in CH_2Cl_2 and lithium borohydride in Et_2O provided alcohol **11** in 73% overall yield (Scheme 2). Cyclization of **11** in hot CH_3CN in the presence of potassium carbonate was followed by Parikh–Doering oxidation[24] to aldehyde **13**. The Wittig reaction with (carbethoxymethylene)triphenylphosphorane gave the *N*-Boc protected alkenylaziridines **9f** in 71% yield. In a related sequence of reactions, the *N*-tosylated derivative **9g** was prepared in four steps from threonine methyl ester (**14**) (Scheme 3). Reduction of *N,O*-ditosylated ester **15** with $NaBH_4$ in the presence of LiCl[25] resulted in concomitant aziridine ring formation.

Cuprate Additions to Alkenylaziridines. Several electrophilic sites on alkenylaziridines of type **9** are potential points of attack for organocuprate reagents (Figure 3). The desired α-alkylation product **17** was obtained by S_N2'-reaction of the organocuprate. Generally, the formation of **17** was accompanied by S_N2-(γ-alkylation) and reduction products **20** and **18**. Single electron transfer from the copper(I) species followed by H· abstraction or enolization of the transient α-Cu(III) species could account for the reduction product that is a frequent side product in organocuprate substitution and addition reactions.[6c] Another generally observed side

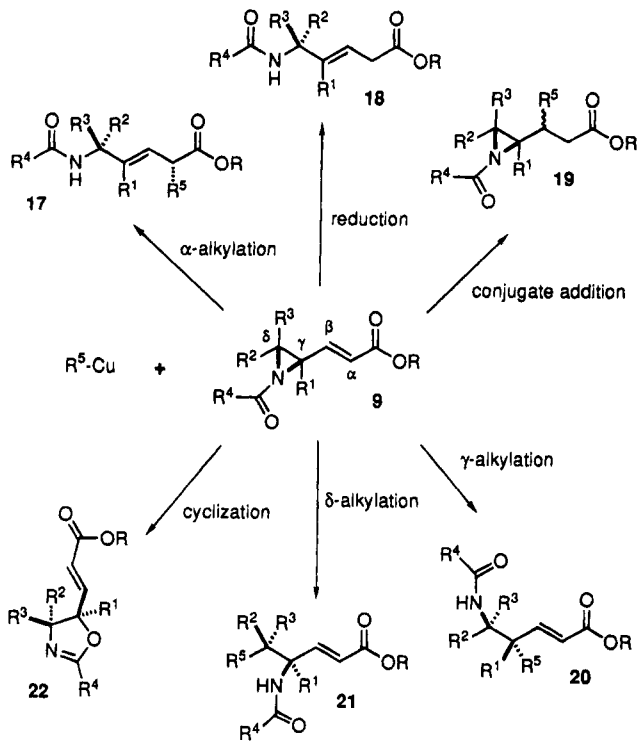


Figure 3.

product was *trans*-oxazoline **22**; this compound was formed as the only detectable product with $PhCu{\cdot}BF_3$ in Et_2O.[26] No δ-alkylation or conjugate addition products **21** or **19** were observed. Table 2 summarizes the results of organocuprate additions to alkenylaziridines.

The balance between S_N2'-reaction products of alkenylaziridines and side products of this process depends strongly on the type of cuprate reagent used. The best results were obtained with alkylcopper reagents derived from CuI or CuCN and alkyl lithium in the presence of boron trifluoride–diethyl ether (Yamamoto-type[6a] cuprates). The nature of the electron-withdrawing acyl group (R^4CO) on the aziridine ring nitrogen was also found to have a profound effect on the efficiency and the regioselectivity of the addition reaction. The yield of dipeptide isosteres **17** was highest (70–90%) with *N*-sulfonated or Boc-protected azirdines **9g**, **9f**, and **9e** (Table 1, entries 17–22). Nucleophilic attack on the *N*-benzoylated substrate **9a** as well as the succinate derivative **9b** and the Cbz-glycyl tripeptide **9c** led to significant amounts of γ-alkylation and, consequently, decreased amounts (<70%) of α-alkylation products.

The stereoselectivity of the S_N2'-alkylation of alkenylaziridines **9** appeared, according to high-field NMR, uniformly high in favor of *anti* attack. This result is in agreement with the vast majority of allylic displacements involving organocopper reagents.[6,10] Corey and Boaz suggested orbital symmetry, e.g. the interaction of a filled d^{10} copper orbital with both the π^* and the σ^* antibonding orbitals of the allylic leaving group, to be the reason for this preference.[27] In order to obtain NMR-independent quantitative information on the degree of *anti*-selectivity of the S_N2' process, alkene peptide isosteres **17** were chemically degraded to short-chain alcohols (Scheme 4). Reduction of the ester **17** to the primary alcohol **23** with $LiBH_4$ was followed by *O*-benzylation, Johnson–Lemieux

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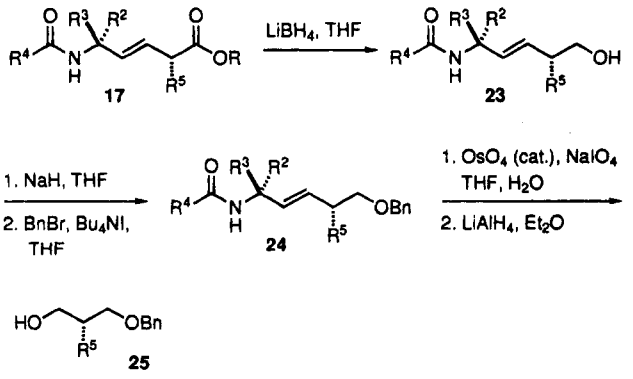
Table 2. Product Distribution and Yield of Organocuprate Additions to Alkenylaziridines 9

entry	cuprate (additive)	aziridine	products [% yield][a] 17	18	20	22	R^5
1	Me_2CuLi	**9a**	ND	**18a** (53)	**20aa** (21)	ND	Me
2	$Me_2Cu(CN)Li_2$ (BF_3·OEt_2)	**9a**	ND	**18a** (44)	**20aa** (7)	ND	Me
3	$Me_2Cu(CN)Li_2$	**9a**	ND	**18a** (46)	**20aa** (3)	ND	Me
4	Me_2CuLi_2 (TMS-Cl)	**9a**	**17aa** (24)	**18a** (43)	**20aa** (4)	ND	Me
5	MeCu (BF_3)	**9a**	**17aa** (62)	**18a** (<1)	**20aa** (6)	3	Me
6	MeCu(CN)Li (BF_3)	**9a**	**17aa** (60)	**18a** (<1)	**20aa** (3)	5	Me
7	MeCu(CN)Li[b] (BF_3)	**9a**	**17aa** (65)	**18a** (<1)	**20aa** (2)	5	Me
8	BuCu[c] (BF_3)	**9a**	**17ab** (69)	**18a** (<1)	**20ab** (14)	ND	Bu
9	PhCu (BF_3)	**9a**	**17ac** (32)[d]	**18a** (<1)	ND	7	Ph
10	PhCu[e,f] (BF_3)	**9a**	ND	ND	ND	53	Ph
11	MeCu (BF_3)	**9b**	**17ba** (53)	ND	**20ba** (6)	ND	Me
12	MeCu[b] (BF_3)	**9c**	**17ca** (51)	**18c** (10)	**20ca** (7)	ND	Me
13	MeCu(CN)Li[e] (BF_3)	**9c**	**17ca** (50)	**18c** (24)	**20ca** (15)	ND	Me
14	MeCu[b] (BF_3)	**9d**	**17da** (45)	ND	**20da** (8)	ND	Me
15	MeCu(CN)Li[e] (BF_3)	**9d**	**17da** (45)	ND	**20da** (11)	ND	Me
16	BuCu[c] (BF_3)	**9d**	**17db** (44)	ND	**20db** (8)	ND	Bu
17	MeCu(CN)Li (BF_3)	**9e**	**17ea** (71)	**18e** (15)	ND	ND	Me
18	BuCu(CN)Li (BF_3)	**9e**	**17eb** (90)	ND	ND	ND	Bu
19	*i*-BuCu(CN)Li (BF_3)	**9e**	**17ed** (83)	ND	ND	ND	*i*-Bu
20	MeCu(CN)Li (BF_3)	**9f**	**17fa** (68)	ND	**20fa** (9)	ND	Me
21	MeCu(CN)Li (BF_3)	**9g**	**17ga** (74)	**18g** (8)	ND	ND	Me
22	BuCu(CN)Li (BF_3)	**9g**	**17gb** (86)	ND	ND	ND	Bu

[a] Yields are not optimized and are based on aziridine and chromatographically purified product; the ratios of chromatographically inseparable **17** and **20** were determined by integration in ^1H NMR; ND = not detected. [b] 1.2 equiv of organocopper reagent were used. [c] 2 equiv of organocopper reagent were used. [d] 63% based on recovered starting material. [e] 3 equiv of organocopper reagent were used. [f] This reaction was performed in Et_2O.

Scheme 4



oxidation[28] of the internal double bond, and reduction with $LiAlH_4$ to give 3-(benzyloxy)-2-alkyl-1-propanol **25**. The overall yields of these transformations are given in Table 3.

The chirality and the optical purity of alcohols **25** were analyzed by comparison of their $[\alpha]_D$ with literature data[29] and ^{19}F NMR after conversion to the corresponding Mosher esters. Based on these data, the optical purity of the starting materials as well as integration of high-field NMR spectra, the diastereoselectivity of the S_N2'-reaction of organocuprates with alkenylaziridines was determined to vary between 62 and >98% de, depending on the nature of the *N*-acyl substituent R^4 and the organocuprate (Figure 4, Table 4).[30] Sulfonamides, carbamates, and benzamides gave superior results to succinate **9b**, where the remote ethyl ester is potentially interfering as a metal chelator with the stereoselectivity of the addition process. Cuprates derived from CuCN appear to be slightly more selective than reagents derived from CuI.

Conclusion. The addition of organocopper/BF_3 complex to alkenylaziridines of type **1** occurs with high *anti* S_N2'-selectivity and provides a versatile route to peptidyl (*E*)-alkene isosteres **2**. Conventional peptide protective groups (Boc, Cbz, sulfonamides) and even amino acid

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(29) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292.

(30) The stereoselectivities for the S_N2' additions were calculated as follows: %de in S_N2'-addition = (%ee of **25** or %de of the Mosher ester of **25**)/(%ee of Sharpless epoxidation × %de of oxirane to aziridine conversion).

Table 3. Degradation of (*E*)-Alkenes According to Scheme 4

	(*E*)-alkene **17**					alcohol **25**		
entry	R^2	R^3	R^4	R^5	no.	R^5	no.	yield[a] (%)
1	CH_3	H	Ph	CH_3	**17aa**	CH_3	**25a**	26
2	CH_3	H	Ph	Bu	**17ab**	Bu	**25b**	24
3	CH_3	H	Ph	Ph	**17ac**	Ph	**25c**	21
4	CH_3	H	$EtO_2CCH_2CH_2$	CH_3	**17ba**	CH_3	**25a**	16
5	CH_3	H	*t*-BuO	CH_3	**17da**	CH_3	**25a**	21
6	H	CH_3	*t*-BuO	CH_3	**17fa**	CH_3	**25a**	23

[a] Yields are not optimized and are based on (*E*)-alkenes **17** and chromatographically purified product.

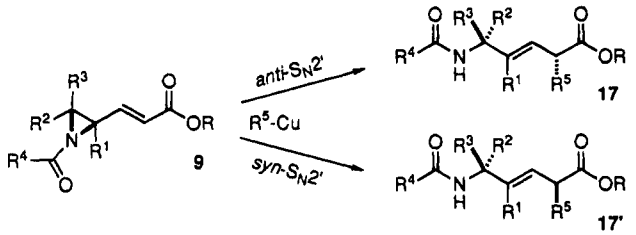

Figure 4.

Table 4. Stereoselectivity of Organocuprate Additions to Alkenylaziridines

			(*E*)-alkene **17**	
entry	aziridine **9**	organocuprate	no.	anti/syn ratio
1	**9a**	MeCu(CN)Li·BF_3	**17aa**	98/2[a]
2	**9a**	BuCu·BF_3	**17ab**	99/1[b]
3	**9a**	PhCu·BF_3	**17ac**	95/5[b]
4	**9b**	MeCu·BF_3	**17ba**	81/19[a]
5	**9d**	MeCu·BF_3	**17da**	95/5[c]; 93/7[a]
6	**9d**	MeCu(CN)Li·BF_3	**17da**	99/1[c]
7	**9e**	MeCu(CN)Li·BF_3	**17ea**	>98/2[c]
8	**9e**	BuCu(CN)Li·BF_3	**17eb**	93/7[c]
9	**9e**	*i*-BuCu(CN)Li·BF_3	**17ed**	>99/1[c]
10	**9f**	MeCu(CN)Li·BF_3	**17fa**	99/1[a]
11	**9g**	MeCu(CN)Li·BF_3	**17ga**	>99/1[c]
12	**9g**	BuCu(CN)Li·BF_3	**17gb**	>99/1[c]

[a] Determined by measurement of the $[\alpha]_D$ of the corresponding alcohol **25**. [b] Determined by integration of the ^{19}F NMR spectrum of the Mosher ester derivative of the corresponding alcohol **25**. [c] Determined by integration of the ^1H NMR spectra of crude **17da**, **17ea**, **17eb**, **17ed**, **17ga**, and **17gb**, respectively.

segments are tolerated as acyl components on the aziridine nitrogen. This allows the direct incorporation of (*E*)-alkene amide bond isosteres in extended peptide segments and the efficient preparation of a range of side-chain analogs of a given peptide for SAR studies. Alkenylaziridines **1** are readily prepared from epoxy alcohols or β-hydroxy α-amino acid precursors. Due to the ease of preparation of scalemic alkenylaziridines and the wide variation of available functionalized organocopper reagents, it is expected that this new methodology for the preparation of (*E*)-alkene peptide mimetics will considerably facilitate their use in receptor mapping and drug discovery.

Experimental Section

General Methods. IR spectra were recorded on a IBM IR/32 spectrophotometer. NMR spectra were recorded on Bruker AM-500 or AM-300 spectrometers in $CDCl_3$ unless otherwise noted. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectra were obtained on a VG-70-70 HF. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. Oxalyl chloride and trifluoroborane etherate were distilled before use. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere. Analytical TLC used Merck silica gel 60 F-254 plates, and flash chromatography was used to separate and purify the crude reaction mixtures.

(2*S*,3*S*)-2,3-Epoxy-1-butanol (4a). A solution of 1.96 mL (9.3 mmol) of L-(+)-diisopropyl tartrate, 2.31 mL (7.75 mmol) of titanium(IV) isopropoxide, and 4.6 g of powdered 4-Å molecular sieves in 300 mL of CH_2Cl_2 was stirred at −22 °C for 15 min. After addition of 13.2 mL (155 mmol) of *trans*-2-buten-1-ol, the solution was stirred for 15 min and 103 mL (310 mmol) of *tert*-butyl hydroperoxide (3.0 M in 2,2,4-trimethylpentane) was added dropwise over 10 min. The reaction mixture was kept at −20 °C overnight, quenched by the slow addition of 38.6 mL (155 mmol) of tributylphosphine over a 30 min time at −22 °C, and treated with a solution of 10% acetone/Et_2O containing 1.49 g (7.75 mmol) of anhydrous citric acid. The solution was allowed to warm to room temperature, filtered (Celite 545), and concentrated under reduced pressure, and the residue was distilled (aspirator vacuum, 60 °C) and chromatographed on SiO_2 (40%−60% EtOAc/hexanes) to afford 9.466 g (69%) of epoxy alcohol **4a** as an oil: $[\alpha]^{23}_D$ −46.0° (*c* 0.9, CH_2Cl_2) [lit.[31] $[\alpha]^{24}_D$ −55° (*c* 0.22, C_6H_6)], IR (neat) 3412, 1452, 1383, 1103, 1039 cm^{-1}; ^1H NMR δ 3.95−3.85 (m, 1 H), 3.66−3.55 (m, 1 H), 3.04 (dq, 1 H, *J* = 2.1, 5.1 Hz), 2.90−2.85 (m, 1 H), 2.18 (b, 1 H), 1.33 (d, 3 H), *J* = 5.2 Hz); ^{13}C NMR δ 61.6, 59.5, 51.9, 16.9.

(2*S*,3*R*)-2-Methyl-2,3-epoxy-1-butanol (4e). A solution of angelic acid methyl ester (12.0 mL, 100 mmol) in 48 mL of Et_2O was slowly added at 0 °C to a stirred suspension or $LiAlH_4$ (10.0 g, 250 mmol) in 76 mL of Et_2O. The reaction mixture was warmed to room temperature, stirred for 1 h, and treated with more $LiAlH_4$ (3.0 g, 75 mmol) and 50 mL of Et_2O. After 30 min, the reaction was quenched by the sequential addition of 13.0 mL of H_2O, 13.0 mL of 15% aqueous NaOH, and 39.0 mL of H_2O. After filtration, the solution was dried ($MgSO_4$) and concentrated in vacuo. Kugelrohr distillation (60−80 °C, water aspirator vacuum) afforded 6.42 g (75%) of allylic alcohol **3e** as an oil: IR (neat) 3341, 1458, 1375, 1246, 1005 cm^{-1}; ^1H NMR δ 5.27 (q, 1 H, *J* = 6.9 Hz), 4.03 (s, 2 H), 3.17 (s, 1 H), 1.70 (s, 3 H), 1.55 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 134.7, 121.1, 59.7, 20.5, 12.3; MS (EI) *m/e* (rel intensity) 86 (M^+, 55), 71 (100); HRMS *m/e* calcd for $C_5H_{10}O$ 86.0732, found 86.0745.

A suspension of 1.05 g (4.47 mmol) of L-(+)-diisopropyl tartrate, 1.11 mL (3.73 mmol) of titanium(IV) isopropoxide, and 2.3 g of powdered 4-Å molecular sieves in 150 mL of CH_2Cl_2 at −22 °C was stirred for 15 min, treated with 6.42 g (155 mmol) of **3e**, stirred for 15 min, and treated dropwise over 10 min with 50.0 mL (149 mmol) of *tert*-butyl hydroperoxide (3.0 M in 2,2,4-trimethylpentane). The reaction mixture was kept at −20 °C overnight and quenched by the slow addition of 18.56 mL (74.5 mmol) of tributylphosphine over a 30 min period while the temperature was maintained at −22 °C, followed by the addition of 110 mL of a 10% acetone/Et_2O solution containing 0.72 g (3.73 mmol) of anhydrous citric acid. The solution was allowed to warm to room temperature, filtered (Celite 545), and concentrated in vacuo. Kugelrohr distillation of the crude reaction mixture (70−90 °C, water aspirator vacuum), followed by chromatography on SiO_2 (40%−60% EtOAc/hexanes) afforded 4.80 g (63%) of epoxy alcohol **4e** as an oil: $[\alpha]^{21}_D$ +11.7° (*c* 1.0, CH_2Cl_2); IR (neat) 3416, 1448, 1377, 1115, 1080, 1037 cm^{-1}; ^1H NMR δ 3.65 (s, 2 H), 2.97 (q,

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1 H, J = 5.6 Hz), 2.44 (b, 1 H), 1.36 (s, 3 H), 1.32 (d, 3 H, J = 5.6 Hz); ^{13}C NMR δ 63.1, 60.6, 59.8, 19.4, 13.1.

Ethyl (2*E*,4*S*,5*S*)-4,5-Epoxy-2-hexenoate (5a). To a solution of 0.87 mL (9.96 mmol) of oxalyl chloride in 110 mL of CH_2Cl_2 at −60 °C was added dropwise 1.41 mL (19.92 mmol) of DMSO. The solution was stirred for 10 min and a solution of 731.4 mg (8.30 mmol) of epoxy alcohol **4a** in 5.0 mL of CH_2Cl_2 was added. After 20 min at −60 °C, 3.47 mL (24.9 mmol) of Et_3N was added. After 5 min, the reaction mixture was allowed to warm to room temperature during 30 min. A solution of 7.63 g (20.8 mmol) of (carbethoxymethylene)-triphenylphosphorane in 10 mL of CH_2Cl_2 was added and the reaction mixture was stirred for 24 h, quenched with aqueous NH_4Cl, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and purified by chromatography on SiO_2 to afford 723.1 mg (56%) of **5a** and 92.3 mg (7.1%) of ethyl (2*Z*,4*S*,5*S*)-4,5-epoxy-2-hexenoate as oils.

5a: $[\alpha]^{23}_D$ −13.8° (*c* 1.3, CH_2Cl_2); IR (neat) 1720, 1304, 1261, 1240, 1188, 1142, 1034 cm^{-1}; ^{1}H NMR δ 6.67 (dd, 1 H, J = 15.5, 7.1 Hz), 6.13 (d, 1 H, J = 15.6 Hz), 4.20 (q, 3 H, J = 7.1 Hz), 3.18 (dd, 1 H, J = 7.1, 1.8 Hz), 2.97 (dq, 1 H, J = 5.1, 1.9 Hz), 1.39 (d, 3 H, J = 5.1 Hz), 1.29 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 165.6, 144.6, 123.7, 60.5, 57.4, 57.2, 17.5, 14.2.

Methyl (2*E*,4*S*,5*R*)-4,5-Epoxy-4-methyl-2-hexenoate (5e). To a solution of 0.84 mL (9.6 mmol) of oxalyl chloride in 108 mL of CH_2Cl_2 was added at −60 °C 1.36 mL (19.2 mmol) of DMSO. The solution was stirred for 10 min, treated with a solution of 817 mg (8.0 mmol) of **4e** in 4.0 mL of CH_2Cl_2, stirred for 20 min, and treated with 3.35 mL (24.0 mmol) of Et_3N. After 5 min at −60 °C, the reaction mixture was allowed to warm to room temperature over 30 min and a solution of 5.35 g (16.0 mmol) of (carbmethoxymethylene)triphenylphosphorane in 20 mL of CH_2Cl_2 was added. The reaction mixture was stirred overnight at room temperature, diluted with CH_2Cl_2, extracted with saturated aqueous NH_4Cl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (12% EtOAc/hexanes) afforded 1.099 g (88%) of **5e** as an oil: $[\alpha]^{21}_D$ +54.9° (*c* 2.0, CH_2Cl_2); IR (neat) 1726, 1655, 1437, 1329, 1273, 1217, 1170 cm^{-1}; ^{1}H NMR δ 6.88 (d, 1 H, J = 15.7 Hz), 6.02 (d, 1 H, J = 15.5 Hz), 3.75 (s, 3 H), 3.10 (q, 1 H, J = 5.5 Hz), 1.46 (s, 3 H), 1.24 (d, 3 H, J = 5.5 Hz); ^{13}C NMR δ 165.4, 145.2, 122.5, 61.5, 58.8, 50.8, 20.4, 13.1.

Ethyl (2*E*,4*R*,5*S*)-4-Azido-5-hydroxy-2-hexenoate (6a). A solution of 3.923 g (25.11 mmol) of epoxy ester **5a** in 55 mL of EtOH was added to a mixture of 4.029 g (75.33 mmol) of NH_4Cl and 4.897 g (75.33 mmol) of NaN_3. The solution was slowly warmed to reflux over 1.5 h, heating at reflux was continued for 50 min, and then the solution was allowed to cool to room temperature. The reaction mixture was filtered, the solid residue was washed with EtOH, and the solvents were evaporated. The residue was dissolved in Et_2O (220 mL) and washed with H_2O (60 mL), and the aqueous layer was extracted with Et_2O (2 × 60 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Chromatography on SiO_2 (30% EtOAc/hexanes) afforded 4.271 g (85%) of a 19:1 mixture of **6a** and its (4*S*,5*S*)-epimer **7a** as an oil. Chromatographic separation of **6a** and **7a** was not possible at this stage. The ratio of **6a**:**7a** was determined by integration of the crude ^{1}H NMR of the corresponding aziridines **9a** and (2*S*)-**9a** (resonances at 6.56 and 6.92 ppm). The structure of **7a** was assigned on the basis of its fully characterized aziridine derivative (2*S*)-**9a**.

6a: $[\alpha]^{23}_D$ −35.4° (*c* 1.2, CH_2Cl_2); IR (neat) 3447, 1718, 1371, 1273, 1182, 1095 cm^{-1}; ^{1}H NMR δ 6.87 (dd, 1 H, J = 15.8, 7.1 Hz), 6.11 (dd, 1 H, J = 15.8, 0.9 Hz), 4.23 (q, 2 H, J = 7.1 Hz), 4.10−4.05 (m, 1 H), 3.95−3.88 (m, 1 H), 2.05 (d, 1 H, J = 4.5), 1.31 (t, 3 H, J = 7.1 Hz), 1.20 (d, 3 H, J = 6.3 Hz); ^{13}C NMR δ 165.6, 140.9, 125.0, 69.0, 67.9, 60.8, 18.4, 14.0; MS (EI) *m/e* (rel intensity) 154 (5), 127 (8), 109 (10), 98 (40); HRMS *m/e* calcd for $C_6H_8N_3O_2$ (M − C_2H_5O) 154.0617, found 154.0621.

Characteristic peaks for **7a**: ^{1}H NMR δ 6.80 (q, 1 H); ^{13}C NMR δ 170.3, 141.2, 125.0, 68.7, 66.8, 61.2, 19.3, 14.0.

(2*R*,3*R*)-2-[(*E*)-2-(Ethoxycarbonyl)ethenyl]-3-methylaziridine (8a). To a solution of 724.0 mg (3.63 mmol) of a 19:1 mixture of azido alcohol **6a** and its (4*S*,5*S*)-epimer **7a** in 16 mL of CH_3CN was added over 30 min 1.047 g (3.99 mmol) of triphenylphosphine. The reaction was heated at reflux for 3 h. The solvents were evaporated, and the residue was dissolved in Et_2O. After addition of hexane, the precipitates were filtered off, and the solution was evaporated. Kugelrohr distillation (90 °C, 0.1 Torr) afforded 462.1 mg (82%) of a 19:1 mixture of **8a** and its (2*S*,3*R*)-epimer as an oil.

8a: $[\alpha]^{23}_D$ +96.6° (*c* 1.3, CH_2Cl_2); IR (neat) 3287, 3230, 1707, 1647, 1367, 1340, 1232, 1157, 1095, 978 cm^{-1}; ^{1}H NMR δ 6.43 (b, 1 H), 6.05 (d, 1 H, J = 15.5 Hz), 4.19 (q, 2 H, J = 7.2), 2.27 (d, 1 H, J = 8.7), 2.12 (b, 1 H), 1.30−1.26 (m, 6 H); ^{13}C NMR δ 165.8, 148.5, 121.3, 60.1, 38.7, 35.6, 18.3, 14.0; MS (EI) *m/e* (rel intensity) 155 (M$^+$, 1), 126 (11), 112 (40), 82 (100); HRMS *m/e* calcd for $C_6H_8NO_2$ (M − C_2H_5) 126.0555, found 126.0563.

(2*R*,3*S*)-2-[(*E*)-2-(Methoxycarbonyl)ethenyl]-2,3-dimethylaziridine (8e). To a solution of 840.5 mg (5.38 mmol) of **5e** in 12 mL of MeOH at room temperature were added 1.049 g (16.14 mmol) of NaN_3 and 863.3 mg (16.14 mmol) of NH_4Cl. The reaction mixture was stirred at 55−60 °C for 5.5 h, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 (20% EtOAc/hexanes) afforded 796.0 mg of a crude mixture of two products. This mixture was dissolved in 18 mL of CH_3CN and 1.154 g (4.40 mmol) of triphenylphosphine were added. The reaction mixture was stirred at room temperature for 15 min until evolution of N_2 subsided and then heated at 75−78 °C for 6.5 h. The solution was cooled to room temperature, and the solvents were evaporated in vacuo. Chromatography on SiO_2 (60% EtOAc/hexanes, then 100% EtOAc/hexanes), followed by Kugelrohr distillation (100−110 °C, 0.2 Torr) afforded 237 mg (28%) of **8e** as an oil: $[\alpha]^{22}_D$ −92.6° (*c* 1.6, CH_2Cl_2); IR (neat) 3285, 1724, 1647, 1313, 1174 cm^{-1}; ^{1}H NMR δ 6.81 (d, 1 H, J = 15.6 Hz), 6.00 (d, 1 H, J = 15.6 Hz), 3.74 (s, 3 H), 2.20 (q, 1 H, J = 5.8 Hz), 1.40 (s, 3 H), 1.21 (b, 3 H); ^{13}C NMR δ 165.2, 148.9, 120.2, 50.1, 40.5, 37.7, 21.3, 13.5; MS (EI) *m/e* (rel intensity) 154 ([M − H]$^+$, 22), 141 (10), 128 (12).

(2*R*,3*R*)-*N*-Benzoyl-2-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3-methylaziridine (9a). A solution of 1.22 g (10.0 mmol) of benzoic acid in 5.0 mL of THF was treated portionwise with 1.622 g (10.0 mmol) of 1,1′-carbonyldiimidazole and stirred for 30 min. A solution of 1.552 g (10.0 mmol) of a 19:1 mixture of aziridine **8a** and its (2*S*,3*R*) diastereomer in 5.0 mL of THF was added, and stirring was continued for 24 h at 39 °C. After addition of Et_2O, the mixture was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. Purification by chromatography on SiO_2 (20% EtOAc/hexanes) afforded 1.483 g (57%) of a 19:1 mixture of **9a** and its (2*S*,3*R*)-diastereomer as an oil. A sample of this mixture was separated by repeated chromatography on SiO_2 (15% EtOAc/hexanes) to give pure (2*S*)-**9a**.

9a: $[\alpha]^{23}_D$ −57.3° (*c* 1.1, CH_2Cl_2); IR (neat) 1718, 1674, 1344, 1298, 1261, 1190, 1140 cm^{-1}; ^{1}H NMR δ 7.99−7.94 (m, 2 H), 7.56−7.50 (m, 1 H), 7.46−7.38 (m, 2 H), 6.56 (dd, 1 H, J = 15.5, 8.3 Hz), 6.16 (d, 1 H, J = 15.6 Hz), 4.16 (q, 2 H, J = 7.1 Hz), 3.10 (dd, 1 H, J = 8.3, 2.7 Hz), 2.86 (dq, 1 H, J = 5.5, 2.8 Hz), 1.32 (d, 3 H, J = 5.6 Hz), 1.26 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 176.8, 165.5, 144.0, 133.3, 132.8, 128.9, 128.4, 124.1, 60.5, 44.0, 42.5, 16.4, 14.1; MS (EI) *m/e* (rel intensity) 259 (M$^+$,1), 215 (4), 154 (12), 131 (6), 105 (100); HRMS *m/e* calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1234.

(2*S*)-**9a**: $[\alpha]^{23}_D$ +99.6° (*c* 0.5, CH_2Cl_2); IR (neat) 1718, 1290, 1178, 1111 cm^{-1}; ^{1}H NMR δ 7.99−7.94 (m, 2 H), 7.60−7.54 (m, 1 H), 7.46−7.38 (m, 2 H), 6.92 (dd, 1 H, J = 15.6, 7.0 Hz), 6.22 (d, 1 H, J = 15.7 Hz), 4.25 (q, 2 H, J = 7.1 Hz), 3.24 (t, 1 H, J = 6.7 Hz), 2.97−2.87 (m, 1 H), 1.41 (d, 3 H, J = 5.7 Hz), 1.26 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 178.9, 165.6, 141.7, 132.9, 132.6, 129.1, 128.4, 125.7, 60.6, 41.4, 40.1, 14.2, 13.4; MS (EI) *m/e* (rel intensity) 259 (M$^+$,1), 232 (5), 215 (3), 154 (12), 131 (6), 105 (100); HRMS *m/e* calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1208.

(2*R*,3*R*)-*N*-[3-(Ethoxycarbonyl)propanoyl]-2-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3-methylaziridine (9b). To a solution of 200.0 mg (1.29 mmol) of a 19:1 mixture of aziridine **8a** and its (2*S*,3*R*)-diastereomer and 115 μL (1.42 mmol)

pyridine in 3.0 mL of THF was added at 0 °C 191.5 μL (1.29 mmol) of ethyl succinyl chloride. After 10 min, the reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O (3 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography on SiO_2 (30% EtOAc/hexanes) afforded 233.2 mg (64%) of a 19:1 mixture of **9b** and its (2*S*,3*R*)-diastereomer as an oil.

9b: $[\alpha]^{22}_D$ +4.9° (*c* 1.2, CH_2Cl_2); IR (neat) 1722, 1693, 1423, 1369, 1261, 1192, 1140; ^1H NMR δ 6.51 (dd, 1 H, *J* = 15.4, 8.6 Hz), 6.14 (d, 1 H, *J* = 15.5 Hz), 4.21–4.08 (m, 4 H), 2.95 (dd, 1 H, *J* = 8.5, 2.5 Hz), 2.74–2.45 (m, 5 H), 1.38 (d, 3 H, *J* = 5.5 Hz), 1.29–1.02 (m, 6 H); ^{13}C NMR δ 181.4, 172.6, 165.4, 143.8, 124.3, 60.6, 60.5, 43.5, 41.5, 31.7, 28.9, 16.3, 14.1; MS (CI) *m/e* (rel intensity) 284 (M^+, 100).

(2*R*,3*R*)-*N*-(Cbz-glycyl)-2-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3-methylaziridine (9c). A solution of 199.0 mg (1.08 mmol) of pentafluorophenol in 2.0 mL of CH_2Cl_2 was treated with 226 mg (1.08 mmol) of Cbz-glycine and cooled to 0 °C, and a solution of 222.8 mg (1.08 mmol) of 1,3-dicyclohexylcarbodiimide in 1.0 mL of CH_2Cl_2 was added. After 3 h at room temperature, a solution of a 19:1 mixture of aziridine **8a** and its (2*S*,3*R*)-diastereomer in 1.0 mL of CH_2Cl_2 was added and stirring was continued for 12 h. The reaction mixture was diluted with 7.0 mL of CH_2Cl_2, filtered (Celite 545), and concentrated in vacuo. Purification by chromatography on SiO_2 (40% EtOAc/hexanes) afforded 254.4 (82%) of a 19:1 mixture of **9c** and its (2*S*,3*R*)-diastereomer as an oil.

9c: $[\alpha]^{22}_D$ −2.7° (*c* 0.6, CH_2Cl_2); IR (neat) 3315, 1714, 1522, 1498, 1429, 1365, 1165, 980, cm^{-1}; ^1H NMR δ 7.36–7.27 (m, 5 H), 6.47 (dd, 1 H, *J* = 15.5, 8.3 Hz), 6.13 (d, 1 H, 15.5 Hz), 5.75 (b, 0.7 H), 5.08 (s, 2 H), 4.15 (q, 2 H, *J* = 7.1 Hz), 4.05 (dd, 1 H, *J* = 17.7, 5.1 Hz), 3.87 (dd, 1 H, *J* = 18.0, 4.2 Hz), 2.95 (dd, 1 H, *J* = 8.4, 2.5 Hz), 2.75–2.60 (m, 1 H), 1.36 (d, 3 H, *J* = 6.2 Hz), 1.25 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 179.1, 165.3, 156.4, 143.1, 135.8, 127.9, 127.3, 123.8, 66.3, 60.2, 44.7, 42.8, 41.1, 15.5, 13.4; MS (EI) *m/e* (rel intensity) 346 (M^+, 2), 224 (6), 211 (1), 172 (5), 166 (5), 154 (30), 110 (25), 91 (100); HRMS *m/e* calcd for $C_8H_{12}NO_2$ [M − (Cbz-Gly)] 154.0868, found 154.0868.

(2*S*,3*R*)-*N*-Boc-2-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3-methylaziridine (9d). To a solution of 52.2 mg (0.336 mmol) of a 19:1 mixture of aziridine **8a** and its (2*R*,3*R*)-diastereomer in 1.0 mL of THF were added 54 μL (0.386 mmol) of Et_3N and a solution of 140.6 mg (0.644 mmol) of di-*tert*-butyl dicarbonate in 1.0 mL of THF. After 2 h, the reaction mixture was diluted with 7 mL of Et_2O and washed with H_2O (2 mL). The aqueous layer was extracted with Et_2O (2 × 3 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and purified by chromatography on SiO_2 (15% EtOAc/hexanes) to afford 85.5 mg (100%) of a 19:1 mixture of **9d** and its (2*S*,3*R*)-diastereomer as an oil.

9d: $[\alpha]^{22}_D$ +5.8° (*c* 1.0, CH_2Cl_2); IR (neat) 1718, 1655, 1369, 1304, 1257, 1157 cm^{-1}; ^1H NMR δ 6.48 (dd, 1 H, *J* = 15.6, 8.7 Hz), 6.13 (d, 1 H, *J* = 15.6 Hz), 4.27–4.11 (m, 2 H), 2.78 (dd, 1 H, *J* = 8.5, 2.8 Hz), 2.55 (dq, 1 H, *J* = 5.7, 3.1 Hz), 1.46 (s, 9 H), 1.33 (d, 3 H, *J* = 5.6 Hz), 1.29 (t, 3 H, *J* = 5.0); ^{13}C NMR δ 165.5, 159.9, 144.0, 123.9, 81.6, 60.4, 43.9, 41.4, 27.8, 16.1, 14.1; MS (EI) *m/e* (rel intensity) 182 (3), 154 (6), 112 (16); HRMS *m/e* calcd for $C_9H_{12}NO_3$ (M − C_4H_9O) 182.0817, found 182.0827.

(2*R*,3*S*)-*N*-Boc-2-[(*E*)-2-(methoxycarbonyl)ethenyl]-2,3-dimethylaziridine (9e). A solution of 783 mg (3.59 mmol) of di-*tert*-butyl dicarbonate in 3.0 mL of THF was added to a solution of 278.7 mg (1.80 mmol) of **8e** and 300 μL (2.15 mmol) of Et_3N in 5.0 mL of THF. The reaction mixture was stirred overnight, diluted with Et_2O, and washed with H_2O. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Chromatography on SiO_2 (12% EtOAc/hexanes) afforded 452.4 mg (98%) of **9e** as an oil: $[\alpha]^{21}_D$ −146.6° (*c* 1.5, CH_2Cl_2); IR (neat) 1724, 1660, 1441, 1369, 1273, 1163, 1113, 987 cm^{-1}; ^1H NMR δ 6.78 (d, 1 H, *J* = 15.6 Hz), 6.07 (d, 1 H, *J* = 15.6 Hz), 3.75 (s, 3 H), 2.53 (q, 1 H, *J* = 5.7 Hz), 1.46 (s, 9 H), 1.41 (s, 3 H), 1.18 (d, 3 H, *J* = 5.8 Hz); ^{13}C NMR δ 165.9, 159.9, 145.6, 123.0, 80.5, 51.1, 45.5, 45.1, 27.5, 19.0, 13.2; MS (EI) *m/e* (rel intensity) 255 (M^+, 1), 199 (2), 182 (6), 154 (40), 129 (17), 122 (12), 112 (20); HRMS *m/e* calcd for $C_9H_{12}NO_3$ (M − C_4H_9O) 182.0817, found 182.0830.

***N*-[(1*R*,2*R*)-1-(Hydroxymethyl)-2-(methanesulfonyloxy)ethyl]-1-(1,1-dimethylethoxy)methanamide (11).** A solution of 4.50 mL (58.15 mmol) of methanesulfonyl chloride in 20 mL of CH_2Cl_2 was added at 0 °C to a stirred solution of 7.53 g (32.30 mmol) of Boc-threonine methyl ester (**10**) and 10.13 mL (58.15 mmol) of *N*,*N*-diisopropylethylamine in 35 mL of CH_2Cl_2. After 40 min, the reaction mixture was poured into ice water (70 g) and extracted with CH_2Cl_2. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of solvent afforded the mesylate as an amber oil which was used immediately without further purification. A solution of the crude mesylate in 100 mL of Et_2O was treated portionwise with a total of 985 mg (45.2 mmol) of $LiBH_4$. The reaction mixture was warmed to room temperature over 15 min, cooled to 0°C, and carefully quenched with saturated aqueous NH_4Cl (90 mL) followed by addition of 15 mL of 10% HCl. The aqueous layer was washed with Et_2O (2 × 75 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on SiO_2 (60% EtOAc/hexanes) afforded 7.31 g (73%) of **11** as an oil: $[\alpha]^{22}_D$ +7.4° (*c* 0.6, CH_2Cl_2); IR (neat) 3383, 1695, 1522, 1346, 1250, 1172, 1061, 978 cm^{-1}; ^1H NMR δ 5.11 (d, 1 H, *J* = 6.2 Hz), 4.83 (d, 1 H, *J* = 8.5 Hz), 3.88–3.70 (m, 2H), 3.60 (dd, 1 H, *J* = 10.9, 7.7 Hz), 3.00 (s, 3 H), 2.7–2.4 (b, 1 H), 1.49–1.45 (m, 12 H); ^{13}C NMR δ 155.5, 79.5, 76.1, 60.7, 54.7, 37.6, 27.7, 17.1; MS (EI) *m/e* (rel intensity) 252 (3), 210 (4), 196 (4), 160 (10), 152 (40), 100 (30); HRMS *m/e* calcd for $C_9H_{18}NO_5S$ (M − CH_3O) 252.0906, found 252.0926.

(2*S*,3*S*)-*N*-Boc-2-(hydroxymethyl)-3-methylaziridine (12). A slurry of 283.3 mg (1.0 mmol) of **11** and 276.5 mg (2.0 mmol) of finely pulverized K_2CO_3 in 4.5 mL of CH_3CN was stirred for 7.5 h at 75 °C and then cooled to room temperature. Insoluble material was removed by filtration, and the filtrate and washings were concentrated in vacuo. Purification of the residue by chromatography on SiO_2 (40% EtOAc/hexanes) afforded 98.0 mg (52%) of **12** and 62.1 mg (22%) of recovered starting material **11**.

12: $[\alpha]^{21}_D$ −1.9° (*c* 0.7, CH_2Cl_2); IR (neat) 3427, 1720, 1456, 1394, 1369, 1238, 1163, 1043 cm^{-1}; ^1H NMR δ 3.68–3.64 (m, 2 H), 2.86 (b, 1 H), 2.61–2.50 (m, 2 H), 1.41 (s, 9 H), 1.23 (d, 3 H, *J* = 5.5 Hz); ^{13}C NMR δ 162.5, 81.3, 60.1, 42.3, 37.2, 27.8, 12.9; MS (EI) *m/e* (rel intensity) 114 (6), 87 (4); HRMS *m/e* calcd for $C_5H_8NO_2$ (M − C_4H_9O) 114.0555, found 14.0558.

(2*R*,3*S*)-*N*-Boc-2-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3-methylaziridine (9f). A solution of 82.8 mg (0.442 mmol) of alcohol **12** in 3.3 mL of CH_2Cl_2 was treated with 246 μL (1.768 mmol) of Et_3N, cooled to 0 °C, treated with a solution of 216 mg (1.33 mmol) of pyridine·SO_3 complex in 1.33 mL of DMSO, and stirred for 1 h at 0 °C. The reaction mixture was partitioned between hexanes/Et_2O (2:1, 55 mL) and saturated aqueous $NaHCO_3$ (17 mL). The aqueous layer was extracted with hexanes/Et_2O (2:1, 7 mL), and the combined organic extracts were washed with 1 M NaH_2PO_4 solution (35 mL) and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (15% EtOAc/hexanes) afforded 64.4 mg (79%) of aldehyde **13** that was used without further purification. A solution of 180 mg (0.490 mmol) of (carbethoxymethylene)-triphenylphosphorane in 1.0 mL of CH_2Cl_2 was added to a solution of 36.3 mg (0.196 mmol) of **13** in 1.0 mL of CH_2Cl_2 and the reaction mixture was stirred overnight at room temperature. The solution was diluted with 40 mL of CH_2Cl_2 and extracted with H_2O (7 mL), brine (7 mL), and saturated aqueous $CuSO_4$ (7 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography on SiO_2 (10% EtOAc/hexanes) afforded 35.7 mg (71%) of **9f** as a solid: mp 34 °C (EtOAc/hexanes); $[\alpha]^{22}_D$ −177.3° (*c* 3.0, CH_2Cl_2); IR (neat) 1724, 1392, 1369, 1228, 1161, 1043 cm^{-1}; ^1H NMR δ 6.74 (dd, 1 H, *J* = 6.8, 15.6 Hz), 6.13 (d, 1 H, *J* = 15.5 Hz), 4.20 (q, 2 H, *J* = 7.1 Hz), 3.03 (dd, 1 H, *J* = 6.6, 6.7 Hz), 2.73 (m, 1 H), 1.45 (s, 9 H), 1.30 (t, 3 H, *J* = 7.1 Hz), 1.22 (d, 3 H, *J* = 5.6 Hz); ^{13}C NMR δ 165.5, 161.6, 141.7, 125.0, 81.2, 60.3, 41.1, 39.8, 27.7, 14.0, 13.2; MS (EI) *m/e* (rel intensity) 182 (3), 155 (6), 112 (15); HRMS *m/e* calcd for $C_9H_{12}NO_3$ (M − C_4H_9O) 182.0818, found 182.0810.

***N,O*-Ditosyl-L-threonine Methyl Ester (15).** To a solution of 4.25 g (25.0 mmol) of L-threonine methyl ester hydrochloride in 25 mL of pyridine was added at 0 °C portionwise over 30 min 15.0 g (79 mmol) of tosyl chloride. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 4.5 h. After addition of 0.4 g (21 mmol) of tosyl chloride and continued stirring overnight, the reaction mixture was poured into 160 g of ice water, stirred, and then filtered. The crude dark purple solid was dissolved in EtOAc and hexane was added to precipitate a purple crystalline solid. Purification by chromatography on SiO_2 (30–60% EtOAc/hexanes) afforded 4.10 g (37%) of **15** as a pale orange crystalline soild: mp 142–144 °C (EtOAc/hexanes); $[\alpha]^{22}_D$ +19.3° (*c* 1.2, CH_2Cl_2); IR (neat) 3283, 1751, 1437, 1340, 1290, 1163, 1093, 1061 cm^{-1}; ^1H NMR δ 7.73 (d, 2 H, J = 8.3 Hz), 7.68 (d, 2 H, J = 8.3 Hz), 7.34 (d, 2 H, J = 8.4 Hz), 7.29 (d, 2 H, J = 8.1 Hz), 5.24 (d, 1 H, J = 9.8 Hz), 5.04 (dq, 1 H, J = 2.3, 6.4 Hz), 3.97 (dd, 1 H, J = 2.3, 9.8 Hz), 3.45 (s, 3 H), 2.45 (s, 3 H), 2.42 (s, 3 H), 1.34 (d, 3 H, J = 6.4 Hz); ^{13}C NMR δ 168.2, 144.9, 143.7, 136.2, 133.1, 129.7, 129.4, 127.6, 126.9, 77.8, 59.4, 52.6, 21.4, 21.3, 17.7; MS (EI) *m/e* (rel intensity) 382 (4), 242 (40), 210 (10), 155 (75), 132 (50), 114 (60), 91 (100); HRMS *m/e* calcd for $C_{17}H_{20}NO_5S_2$ (M − $C_2H_3O_2$) 382.0783, found 382.0815.

(2*S*,3*S*)-*N*-Tosyl-2-(Hydroxymethyl)-3-methylaziridine (16). A solution of 2.41 g (5.46 mmol) of **15** in 24.0 mL of THF/EtOH (1:2) was treated at room temperature with 0.70 g (16.38 mmol) of anhydrous LiCl and 0.64 g (16.38 mmol) of $NaBH_4$. The reaction mixture was stirred overnight and quenched by the slow addition of acetone followed by 5% HCl until the reaction mixture became clear. The solution was extracted with Et_2O (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography on SiO_2 (40% EtOAc/hexanes) afforded 1.15 g (87%) of **16** as a white solid: mp 68–70 °C (EtOAc/hexanes), $[\alpha]^{22}_D$ +5.3° (*c* 0.6, CH_2Cl_2); IR (neat) 3512, 1597, 1450, 1404, 1321, 1244, 1159, 1091, 1045 cm^{-1}; ^1H NMR δ 7.80 (d, 2 H, J = 8.3 Hz), 7.32 (d, 2 H, J = 8.0 Hz), 3.72, (dd, 1 H, J = 4.5, 11.9 Hz), 3.59 (dd, 1 H, J = 6.5, 12.0 Hz), 3.01–2.89 (m, 2 H), 2.42 (s, 3 H), 1.75 (b, 1 H), 1.22 (d, 3 H, J = 5.7 Hz); ^{13}C NMR δ 144.6, 134.7, 129.7, 127.8, 59.2, 44.8, 40.0, 21.6, 12.1; MS (CI) *m/e* (rel intensity) 242 ([M + 1]$^+$, 100).

(2*R*,3*S*)-*N*-Tosyl-2-[(*E*)-2-(Methoxycarbonyl)ethenyl]-3-methylaziridine (9g). A solution of 1.15 g (4.76 mmol) of alcohol **16** in 24 mL of CH_2Cl_2 was added to a suspension of 2.35 g (5.71 mmol) of Dess–Martin reagent[32] in 24 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 h and chromatographed on SiO_2 (28% EtOAc/hexanes) to afford 0.91 g (80%) of aziridine aldehyde. This compound was treated with a solution of 2.54 g (7.60 mmol) of (carbmethoxymethylene)triphenylphosphorane in 25 mL of CH_2Cl_2. The solution was stirred for 3 h at room temperature, diluted with 200 mL of CH_2Cl_2, washed with 75 mL of saturated aqueous NH_4Cl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (25% EtOAc/hexanes) afforded 0.695 g (52%) of a 4.5:1 mixture of *trans*- and *cis*-alkenylaziridines. Further purification by chromatography on SiO_2 (20% EtOAc/hexanes and 40% Et_2O/hexanes) afforded pure *trans*-alkenylaziridine **9g** as a white solid: mp 87.5–88.5 °C (EtOAc/hexanes); $[\alpha]^{21}_D$ −80.7° (*c* 2.2, CH_2Cl_2); IR (neat) 1722, 1659, 1437, 1325, 1269, 1161, 1045 cm^{-1}; ^1H NMR δ 7.83 (d, 2 H, J = 8.3 Hz), 7.35 (d, 2 H, J = 8.4 Hz), 6.67 (dd, 1 H, J = 6.6, 15.5 Hz), 6.08 (dd, 1 H, J = 0.9, 15.5 Hz), 3.73 (s, 3 H), 3.41 (dd, 1 H, J = 6.8, 6.8 Hz), 3.14 (m, 1 H), 2.46 (s, 3 H), 1.22 (d, 3 H, J = 5.8 Hz); ^{13}C NMR δ 165.4, 144.6, 139.1, 134.7, 129.7, 127.6, 125.8, 51.6, 43.3, 41.4, 21.5, 12.2; MS (CI) *m/e* (rel intensity) 296 ([M + 1]$^+$, 65).

General Procedure A for the Reaction of MeCu·BF_3 or MeCu(CN)Li·BF_3 with Alkenylaziridines. Ethyl (2*R*,3*E*,5*R*)-2-Methyl-5-(phenylmethanamido)-3-hexenoate (17aa). To a slurry of 95.2 mg (0.500 mmol) of CuI or 44.8 mg (0.500 mmol) of CuCN in 3.0 mL of THF at −30 °C was added 0.35 mL (0.500 mmol) of a solution of methyllithium (1.4 M in Et_2O). The reaction mixture was warmed to 0 °C for 5 min and then cooled to −70 °C, and 61.5 μL (0.500 mmol) of BF_3·OEt_2 was added. After 5 min, a solution of 129.7 mg (0.500 mmol) of a 19:1 mixture of aziridine **9a** and its C(2)-epimer in 2.0 mL of THF was added and the reaction mixture was stirred for 10 min, quenched by addition of 5.0 mL of saturated aqueous NH_4Cl, and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 afforded 91.6 mg (68%) of a 10.3:1 mixture of **17aa** (and its (2*S*,5*R*)-diastereomer **17aa'**) and **20aa** as an oil.

17aa: $[\alpha]^{23}_D$ −19.5° (*c* 1.2, CH_2Cl_2); IR (neat) 3300, 1732, 1635, 1537, 1275, 1182 cm^{-1}; ^1H NMR δ 7.82–7.76 (m, 2 H), 7.53–7.40 (m, 3 H), 6.06 (d, 1 H, J = 7.8 Hz), 5.77 (dd, 1 H, J = 15.8, 7.3 Hz), 5.66 (dd, 1 H, J = 15.7, 4.8 Hz), 4.86–4.74 (m, 1 H), 4.13 (q, 2 H, J = 7.2 Hz), 3.15 (p, 1 H, J = 6.9 Hz), 1.34 (d, 3 H, J = 6.8 Hz), 1.29–1.22 (m, 6 H); ^{13}C NMR δ 174.4, 166.5, 134.5, 132.6, 131.3, 129.1, 128.3, 126.8, 60.5, 46.2, 42.3, 20.4, 17.0, 14.0; MS (EI) *m/e* (rel intensity) 275 (M$^+$, 4), 202 (15), 174 (20), 105 (100); HRMS *m/e* calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1521.

Characteristic peaks for **20aa**: ^1H NMR δ 6.98 (dd, 1 H, J = 7.6, 15.5 Hz), 5.92 (d, 1 H, J = 15.5 Hz), 4.40–4.30 (m, 1 H), 2.70–2.60 (m, 1 H).

General Procedure B for the Reaction of Me_2CuLi or $Me_2Cu(CN)Li_2$ with Alkenylaziridines To Yield Reduced Product. Ethyl (3*E*,5*R*)-5-(Phenylmethanamido)-3-hexenoate (18a). To a slurry of 102.6 mg (0.500 mmol) of CuBr·Me_2S or 44.8 mg (0.500 mmol) of CuCN in 3.0 mL of THF at −35 °C was added 0.71 mL (1.00 mmol) of a solution of methyllithium (1.4 M in Et_2O). The reaction mixture was warmed to −23 °C for 15 min and then cooled to −70 °C. A solution of 129.7 mg (0.500 mmol) of a 19:1 mixture of aziridine **9a** and its C(2)-epimer in 2.0 mL of THF was added and the reaction mixture was stirred for 5 min, quenched by addition of 5.0 mL of saturated aqueous NH_4Cl and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 (30% EtOAc/hexanes) afforded 46–53% of **18a** as an oil: $[\alpha]^{23}_D$ +0.3° (*c* 0.7, CH_2Cl_2); IR (neat) 3308, 1734, 1639, 1579, 1533, 1489, 1369, 1273, 1176, 97 cm^{-1}; ^1H NMR δ 7.78–7.84 (m, 2 H), 7.52–7.40 (m, 3 H), 6.11 (d, 1 H, J = 7.4 Hz), 5.78 (dt, 1 H, J = 15.9, 6.6 Hz), 5.69 (dd, 1 H, J = 15.8, 4.7 Hz), 4.84–4.76 (m, 1 H), 4.14 (q, 2 H, J = 7.1 Hz), 3.08 (d, 2 H, J = 6.1 Hz), 1.36 (d, 3 H, J = 6.8 Hz), 1.26 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 171.5, 166.5, 135.1, 134.5, 131.3, 128.3, 126.8, 122.2, 60.6, 46.3, 37.5, 20.3, 14.0; MS (EI) *m/e* (rel intensity) 261 (M$^+$, 5), 188 (18), 174 (5), 156 (25), 105 (100); HRMS *m/e* calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1353.

General Procedure C for the Addition of n-BuCu·BF_3 to Alkenylaziridines. Ethyl (2*R*,3*E*,5*R*)-2-Butyl-5-(phenylmethanamido)-3-hexenoate (17ab). To a slurry of 65.9 mg (0.346 mmol) of CuI in 3.0 mL of THF was added at −35 °C 0.15 mL (0.346 mmol) of a solution of *n*-butyllithium (2.3 M in hexanes). The reaction mixture was stirred for 5 min, cooled to −70 °C, treated with 42.5 μL (0.346 mmol) of BF_3·OEt_2, and stirred for 5 min. A solution of 45.0 mg (0.173 mmol) of a 19:1 mixture of aziridine **9a** and its C(3)-epimer in 2.0 mL of THF was added and the reaction mixture was stirred for 10 min, quenched by addition of 5.0 mL of saturated aqueous NH_4Cl, and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography on SiO_2 (20% EtOAc/hexanes) afforded 45.7 mg (83%) of a 4.7:1 mixture of **17ab** and its (2*S*,5*R*)-epimer and ethyl (4*S*)-4-[(1*R*)-1-(phenylmethanamido)ethyl]-2-octenoate (**20ab**) as an oil. Full characterization of **17ab** was provided at the level of its reduced derivative **23ab**.

17ab: ^1H NMR δ 7.78–7.70 (m, 2 H), 7.53–7.27 (m, 3 H), 6.07 (d, 1 H, J = 8.1 Hz), 5.67–5.65 (m, 2 H), 4.85–4.74 (m, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 3.02–2.94 (m, 1 H), 1.77–1.70 (m, 1 H), 1.56–1.46 (m, 1 H), 1.40–1.22 (m, 10 H), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR δ 174.1, 166.4, 134.6, 133.6, 131.2, 128.3, 128.1, 126.8, 60.3, 48.8, 46.2, 32.1, 29.1, 22.2, 20.6, 14.1, 13.8. Characteristic peaks for **20ab**: ^1H NMR δ 6.83 (dd, 1

(32) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

H, J = 9.5, 15.6 Hz), 5.92 (d, 1 H, J = 15.6 Hz), 4.43–4.33 (m, 1 H), 2.5–2.4 (m, 1 H).

General Procedure D for the Reaction of PhCu·BF_3 with Alkenylaziridines. Ethyl (2*S*,3*E*,5*R*)-2-Phenyl-5-(phenylmethanamido)-3-hexenoate (17ac). To a slurry of 95.2 mg (0.500 mmol) of CuI in 3.0 mL of THF at −40 °C was added 0.28 mL (0.500 mmol) of a solution of phenyllithium (1.8 M in cyclohexane/Et_2O). The reaction mixture was stirred for 15 min, cooled to −70 °C, treated with 61.5 μL (0.500 mmol) of BF_3·OEt_2, and stirred for 5 min. A solution of 129.7 mg (0.500 mmol) of a 19:1 mixture of aziridine **9a** and its C(2)-epimer in 2.0 mL of THF was added and the reaction mixture was stirred for 15 min, quenched by addition of 5.0 mL of saturated aqueous NH_4Cl, and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 (20% EtOAc/hexanes) afforded 63.1 mg (49%) of recovered starting material **9a** and 53.2 mg (32%) of **17ac** as a colorless solid: $[\alpha]^{21}_D$ +21.9° (*c* 0.8, CH_2Cl_2); IR (neat) 3306, 1732, 1637, 1578, 1541, 1491, 1271, 1155 cm^{-1}; ^1H NMR δ 7.77–7.74 (m, 2 H), 7.50–7.40 (m, 4 H), 7.37–7.25 (m, 4 H), 6.05 (dd, 1 H, J = 15.5, 8.2 Hz), 6.00 (d, 1 H, J = 8.3 Hz), 5.70 (dd, 1 H, J = 15.6, 5.0 Hz), 4.90–4.80 (m, 1 H), 4.31 (d, 1 H, J = 8.2 Hz), 4.20–4.10 (m, 2 H), 1.36 (d, 3 H, J = 6.8 Hz), 1.24 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 172.3, 166.5, 138.0, 134.5, 134.2, 131.3, 128.7, 128.6, 128.4, 127.7, 127.2, 126.8, 61.0, 54.3, 46.2, 20.3, 14.0; MS (CI) *m/e* (rel intensity) 338 (M^+, 100).

(4*R*,5*S*)-4-Methyl-5-[(*E*)-2-(ethoxycarbonyl)ethenyl]-2-phenyl-Δ²-oxazoline (22a). According to general procedure D, except that Et_2O was used as solvent, 291.4 mg (1.53 mmol) of CuI, 0.85 mL (1.53 mmol) of phenyllithium (1.8 M in Et_2O), 188 μL (1.53 mmol) of BF_3·OEt_2, and 132.3 mg (0.510 mmol) of a 19:1 mixture of aziridine **9a** and its C(3)-epimer provided 74.4 mg (56%) of **22a** as a solid: mp 27 °C (EtOAc/hexanes); $[\alpha]^{21}_D$ −91.5° (*c* 0.5, CH_2Cl_2); IR (neat) 1720, 1663, 1450, 1321, 1288, 1238, 1180 cm^{-1}; ^1H NMR δ 7.98–7.95 (m, 2 H), 7.54–7.40 (m, 3 H), 6.99 (d, 1 H, J = 15.5, 5.5 Hz), 6.10 (dd, 1 H, J = 15.7, 1.4 Hz), 4.77–4.72 (m, 1 H), 4.22 (q, 2 H, J = 7.1 Hz), 4.12 (p, 1 H, J = 6.9 Hz), 1.43 (d, 3 H, J = 6.7), 1.30 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 165.7, 162.4, 144.1, 131.5, 128.3, 128.2, 127.2, 121.6, 84.7, 68.0, 60.6, 20.9, 14.1; MS (EI) *m/e* (rel intensity) 259 (M^+, 3), 214 (5), 156 (10), 154 (20), 131 (100); MS (CI) *m/e* (rel intensity) 300 (5), 260 ([M + 1]$^+$, 100).

Ethyl 3-(*N*-((1*R*,2*E*,4*R*)-4-(Ethoxycarbonyl)-1-methyl-2-pentenyl)carbamoyl)propanoate (17ba). According to the general procedure A, 133.3 mg (0.70 mmol) of CuI, 0.50 mL (0.700 mmol) of methyllithium (1.4 M in Et_2O), 86 μL (0.70 mmol) of BF_3·OEt_2, and 198.1 mg of a 19:1 mixture of **9b** and its C(2)-epimer afforded 123.3 mg (59%) of an 8.8:1 mixture of **17ba** and **20ba** as an oil.

17ba: $[\alpha]^{22}_D$ +22.1° (*c* 1.3, CH_2Cl_2); IR (neat) 3298, 1732, 1659, 1631, 1537, 1178 cm^{-1}; ^1H NMR δ 5.73–5.53 (b, 1 H), 5.65 (dd, 1 H, J = 15.5, 7.1 Hz), 5.54 (dd, 1 H, J = 15.6, 4.9 Hz), 4.6–4.5 (m, 1 H), 4.18–4.10 (m, 4 H), 3.07–3.02 (m, 1 H), 2.69–2.62 (m, 2 H), 2.46 (t, 2 H, J = 6.7 Hz); 1.30–1.18 (m, 9 H); ^{13}C NMR δ 174.6, 173.0, 170.4, 132.6, 129.0, 60.7, 60.6, 45.8, 42.4, 31.2, 29.6, 20.5, 17.2, 14.2 (2C); MS (EI) *m/e* (rel intensity) 299 (M^+, 4), 254 (7), 226 (25), 198 (30), 170 (38), 156 (24), 129 (100); HRMS *m/e* calcd for $C_{13}H_{20}NO_4$ (M − C_2H_5O) 254.1392, found 254.1412.

Characteristic peaks for **20ba**: ^1H NMR δ 6.87 (dd, 1 H), 5.99 (d, 1 H, J = 15.6 Hz).

Ethyl (2*R*,3*E*,5*R*)-2-Methyl-5-(Cbz-glycylamino)-3-hexenoate (17ca) and Ethyl (3*E*,5*R*)-5-(Cbz-glycylamino)-3-hexenoate (18c). According to the general procedure A, 146.7 mg (0.77 mmol) of CuI, 0.55 mL (0.77 mmol) of methyllithium (1.4 M in Et_2O), 95 μL (0.77 mmol) of BF_3·OEt_2, and 224.1 mg (0.64 mmol) of a 19:1 mixture of **9c** and its C(2)-epimer afforded 181.4 mg of a mixture of **17ca**, **18c**, and **20ca**. Further attempts to purify this material by chromatography on SiO_2 afforded a mixture of **17ca** and **20ca** as well as 26.4 mg (10%) of pure **18c** as oils.

17ca: $[\alpha]^{23}_D$ +7.7° (*c* 1.2, CH_2Cl_2); IR (neat) 3319, 1732, 1651, 1537, 1454, 1373, 1250, 1182 cm^{-1}; ^1H NMR δ 7.37 (s, 5 H), 5.88 (b, 1 H), 5.69 (dd, 1 H, J = 15.3, 7.1 Hz), 5.53 (dd, 1 H, J = 15.5, 5.2 Hz), 5.41 (b, 1 H), 5.14 (s, 2 H), 4.58 (m, 1 H), 4.13 (q, 2 H), J = 7.1 Hz), 3.86 (d, 2 H, J = 5.7 Hz), 3.11 (p, 1 H, 7.1 Hz), 1.29–1.22 (m, 9 H); ^{13}C NMR δ 174.3, 168.0, 156.5, 135.9, 132.2, 128.8, 128.2, 127.9, 127.7, 66.7, 60.4, 45.8, 44.2, 42.0, 20.2, 16.9, 13.8 cm^{-1}; MS (EI) *m/e* (rel intensity) 362 (M^+, 3), 289 (6), 271 (5), 180 (16), 170 (28), 153 (14), 127 (11), 108 (21); HRMS *m/e* calcd for $C_{19}H_{26}N_2O_5$ 362.1842, found 362.1816.

18c: $[\alpha]^{21}_D$ +15.7° (*c* 1.0, CH_2Cl_2); IR (neat) 3314, 1727, 1663, 1250, 1162, 1049 cm^{-1}; ^1H NMR δ 7.36 (s, 5 H), 5.94 (b, 1 H), 5.70 (dt, 1 H, J = 15.4, 6.6 Hz), 5.55 (dd, 1 H, J = 15.4, 4.8 Hz), 5.43 (b, 1 H), 5.14 (s, 2 H), 4.57 (sx, 1 H, J = 6.9 Hz), 4.14 (q, 2 H, J = 7.2 Hz), 3.86 (d, 2 H, J = 6.7 Hz), 1.31–1.23 (m, 6 H); ^{13}C NMR δ 171.6, 168.0, 156.6, 136.1, 134.8, 128.5, 128.2, 128.0, 122.2, 67.0, 60.7, 46.1, 44.5, 37.5, 20.2, 14.1; MS (EI) *m/e* (rel intensity) 348 (M^+, 3), 257 (5), 240 (7), 194 (15), 166 (85), 156 (30), 141 (20), 127 (25), 108 (70), 91 (100); HRMS *m/e* calcd for $C_{11}H_{17}N_2O_5$ (M − C_7H_7) 257.1137, found 257.1116.

Characteristic peaks for **20ca**: ^1H NMR δ 6.88 (dd, 1 H, J = 8.1, 16.0 Hz), 2.60–2.45 (m, 1 H).

Ethyl (2*R*,3*E*,5*R*)-5-[(1,1-Dimethylethoxy)methanamido]-2-methyl-3-hexenoate (17da). According to the general procedure A, 91.4 mg (0.48 mmol) of CuI, 0.34 mL (0.48 mmol) of methyllithium (1.4 M in Et_2O), 59 μL (0.48 mmol) of BF_3·OEt_2, and 103.3 mg of a 19:1 mixture of **9d** and its C(2)-epimer afforded 65.7 mg of a 4.7:1 mixture of **17da** and ethyl (2*E*,3*R*,5*R*)-5-[(1,1-dimethylethoxy)methanamido]-3-methyl-2-hexenoate (**20da**). Complete characterization of **17da** was provided at the level of its alcohol derivative **23da**.

17da: IR (neat) 3360, 1713, 1514, 1452, 1367, 1248, 1174, 1047, 974 cm^{-1}; ^1H NMR δ 5.64 (ddd, 1 H, J = 15.7, 7.5, 1.3 Hz), 5.53 (dd, 1 H, J = 15.4, 4.3 Hz), 4.45 (b, 1 H), 4.25–4.18 (m, 1 H), 4.13 (q, 2 H, J = 7.1 Hz), 3.11 (p, 1 H, J = 7.1 Hz), 1.45 (s, 9 H), 1.31–1.21 (m, 9 H); ^{13}C NMR δ 174.5, 155.0, 133.3, 128.4, 79.1, 60.4, 47.1, 42.3, 28.2, 20.8, 17.1, 14.0; MS (EI) *m/e* (rel intensity) 215 (12), 155 (17), 142 (25), 128 (10), 114 (15); HRMS *m/e* calcd for $C_{10}H_{17}NO_4$ (M-C_4H_8) 215.1158, found 215.1169.

Characteristic peaks for **20da**: ^1H NMR δ 6.90 (dd, 1 H, J = 7.8, 15.6 Hz), 5.85 (d, 1 H, J = 15.6 Hz), 2.55–2.40 (m, 1 H).

Methyl (3*E*,2*R*,5*S*)-5-[(1,1-Dimethylethoxy)methanamido]-2,4-dimethyl-3-hexenoate (17ea). A solution of 1.32 mL (1.636 mmol) of methyllithium (1.24 M in Et_2O) was added at −30 °C to a slurry of 146.5 mg (1.636 mmol) of CuCN in 9.0 mL of THF. The reaction mixture was warmed to −5 °C over a 10-min period, cooled to −70 °C, treated with 201 μL (1.636 mmol) of BF_3·OEt, and stirred for 10 min. A solution of 139.2 mg (0.545 mmol) of **9e** in 2.0 mL of THF was added. The reaction mixture was slowly warmed to −20 °C, kept at this temperature for 1.25 h, quenched with saturated aqueous NH_4Cl (7 mL), and extracted with Et_2O (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography on SiO_2 (16% EtOAc/hexanes) afforded 21 mg (15%) of reduced product **18e** and 105 mg (71%) of **17ea** as an oil.

17ea: $[\alpha]^{22}_D$ −61.4° (*c* 1.4, CH_2Cl_2); IR (neat) 3480, 1750, 1710, 1510, 1460, 1370, 1250, 1175 cm^{-1}; ^1H NMR δ 5.37 (d, 1 H, J = 9.3 Hz), 4.55–4.45 (m, 1 H), 4.1–4.0 (m, 1 H), 3.66 (s, 3 H), 3.39–3.29 (m, 1 H), 1.65 (s, 3 H), 1.43 (s, 9 H), 1.23–1.18 (m, 6 H); ^{13}C NMR δ 175.3, 154.9, 138.4, 123.3, 78.8, 51.9, 51.5, 38.3, 28.2, 19.6, 17.7, 13.4; MS (EI) *m/e* (rel intensity) 256 (7), 215 (7), 171 (27), 156 (30), 139 (25), 128 (28), 120 (20), 105 (22); HRMS *m/e* calcd for $C_{10}H_{17}NO_4$ (M − C_4H_8) 215.1158, found 215.1163.

18e: ^1H NMR δ 5.54 (t, 1 H, J = 7.1 Hz), 4.52 (bs, 1 H), 4.20–4.15 (m, 1 H), 3.68 (s, 3 H), 3.08 (d, 2 H, J = 6.9 Hz), 1.64 (s, 9 H), 1.21 (d, 3 H, J = 6.8 Hz).

Ethyl (3*E*,2*R*,5*S*)-2-Methyl-5-[*N*-(*tert*-butoxycarbonyl)-amino]-3-hexenoate (17fa). A solution of 0.96 mL (1.185 mmol) of methyllithium (1.24 M in Et_2O) was added at −30 °C to a slurry of 106.1 mg (1.185 mmol) of CuCN in 3.3 mL of THF. The solution was warmed to 0 °C over 10 min, cooled to −70 °C, treated with 146 μL (1.185 mmol) of BF_3·OEt, stirred for 10 min, and then warmed to −35 °C. A solution of 100.8 mg (0.395 mmol) of **9f** in 1.2 mL of THF was added. The reaction mixture was stirred for 10 min at −35 °C, quenched with saturated aqueous NH_4Cl (4.0 mL) and extracted with

Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography on SiO_2 (10% EtOAc/hexanes) afforded 82.0 mg (77%) of an 8:1 mixture of **17fa** and γ-alkylation product **20fa** as an oil.

17fa: IR (neat) 3364, 1716, 1518, 1454, 1390, 1367, 1250, 1174, 1049, 970 cm^{-1}; ^1H NMR δ 5.67 (dd, 1 H, J = 7.1, 16.0 Hz), 5.52 (dd, 1 H, J = 4.8, 15.6 Hz), 4.43 (b, 1 H), 4.25–4.1 (m, 1 H), 4.12 (q, 2 H, J = 7.1 Hz), 3.15–3.05 (m, 1 H), 1.44 (s, 9 H), 1.38–1.19 (m, 9 H); ^{13}C NMR δ 174.3, 154.9, 133.2, 128.4, 78.9, 60.3, 47.1, 42.3, 28.2, 20.7, 17.1, 14.0; MS (EI) *m/e* (rel intensity) 215 (7), 155 (18), 142 (25), 128 (10), 114 (15); HRMS *m/e* calcd for $C_{10}H_{17}NO_4$ (M − C_4H_8) 215.1158, found 215.1171. Characteristic peaks for **20fa**: ^1H NMR δ 6.88 (dd, 1 H, J = 8.1, 15.6 Hz), 5.83 (d, 1 H, J = 15.6 Hz), 2.60–2.45 (m, 1 H).

Methyl (3*E*,2*R*,5*S*)-2-Methyl-5-tosylamido-3-hexenoate (17ga). A solution of 0.35 mL (0.430 mmol) of methyllithium (1.24 M in Et_2O) was added at −30 °C to a slurry of 38.5 mg (0.430 mmol) of CuCN in 2.0 mL of THF. The solution was warmed to 0 °C over 10 min, cooled to −70 °C, treated with 53 μL (0.430 mmol) of BF_3·OEt, and stirred for 10 min. A solution of 42.4 mg (0.143 mmol) of **9g** in 1.0 mL of THF was added. The reaction mixture was stirred for 10 min at −70 °C, quenched with saturated aqueous NH_4Cl (1.5 mL), and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography on SiO_2 (25% EtOAc/hexanes) afforded 26.8 mg (74%) of **17ga** as an oil, 3.0 mg (8.0%) reduced product **18g**, and 7.6 mg (18%) of recovered **9g**.

17ga: $[\alpha]^{22}_D$ −54.1° (*c* 0.8, $CDCl_3$); IR (neat) 3277, 1736, 1454, 1433, 1329, 1161, 1091, 968 cm^{-1}; ^1H NMR δ 7.74 (d, 2 H, J = 8.3 Hz), 7.28 (d, 2 H, J = 8.1 Hz), 5.53 (dd, 1 H, J = 7.6, 16.0 Hz), 5.32 (dd, 1 H, J = 6.5, 16.1 Hz), 4.54 (d, 1 H, J = 7.5 Hz), 3.89 (m, 1 H), 3.65 (s, 3 H), 3.02–2.93 (m, 1 H), 2.42 (s, 3 H), 1.19 (d, 3 H, J = 6.7 Hz), 1.10 (d, 3 H, J = 7.1 Hz); ^{13}C NMR δ 174.6, 143.2, 137.9, 132.3, 129.9, 129.5, 127.1, 51.9, 51.0, 42.1, 21.7, 21.5, 16.9; MS (EI) *m/e* (rel intensity) 296 (100), 264 (30), 252 (65), 224 (75), 198 (30), 155 (75), 140 (20), 124 (10); HRMS *m/e* calcd for $C_{14}H_{18}NO_4S$ (M − CH_3) 296.0957, found 296.0963.

18g: ^1H NMR δ 7.74 (d, 2 H, J = 8.3 Hz), 7.30 (d, 2 H, J = 8.3 Hz), 5.60 (dt, 1 H, J = 15.5, 6.9 Hz), 5.37 (dd, 1 H, J = 15.5, 6.0 Hz), 4.33 (d, 1 H, J = 6.5 Hz), 3.95–3.85 (m, 1 H), 3.68 (s, 3 H), 2.94 (d, 2 H, J = 6.9 Hz), 2.44 (s, 3 H), 1.19 (d, 3 H, J = 6.7 Hz).

Ethyl (2*R*,3*E*,5*R*)-2-Butyl-5-[(1,1-Dimethylethoxy)methanamido]-3-hexenoate (17db). According to the general procedure C, 114.3 mg (0.600 mmol) of CuI, 0.26 mL (0.600 mmol) of *n*-butyllithium (2.3 M in hexanes), 73.8 μL (0.600 mmol) of BF_3·OEt_2, and 76.6 mg of a 19:1 mixture of **9d** and its C(3)-epimer afforded 48.9 mg of a 5.5:1 mixture of **17db** and ethyl (2*E*,4*S*,5*R*)-4-butyl-5-[(1,1-dimethylethoxy)methanamido]-2-hexenoate (**20db**).

17db: IR (neat) 3366, 1714, 1516, 1365, 1248, 1174 cm^{-1}; ^1H NMR δ 5.61–5.43 (m, 2 H), 4.43 (b, 1 H), 4.25–4.1 (m, 1 H), 4.13 (q, 2 H, J = 7.1), 2.99–2.91 (m, 1 H), 1.78–1.62 (m, 1 H), 1.55–1.45 (m, 1 H), 1.44 (s, 9 H), 1.33–1.28 (m, 10 H), 0.88 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 174.2, 155.0, 134.4, 127.4, 79.1, 60.3, 48.8, 32.2, 29.4, 28.3, 22.3, 20.9, 14.1, 13.8; MS (EI) *m/e* (rel intensity) 257 (15), 195 (15), 184 (13), 140 (11), 114 (12); HRMS *m/e* calcd for $C_{13}H_{23}NO_4$ (M − C_4H_8) 257.1627, found 257.1621.

Characteristic peaks for **20db**: ^1H NMR δ 6.76 (dd, 1 H, J = 9.7, 15.6 Hz), 5.84 (d, 1 H, J = 15.6 Hz), 2.25–2.15 (m, 1 H).

Methyl (3*E*,2*R*,5*S*)-2-Butyl-5-(1,1-dimethoxymethanamido)-4-methyl-3-hexenoate (17eb). A solution of 1.32 mL (1.636 mmol) of *n*-butyllithium (2.50 M in hexanes) was added at −40 °C to a slurry of 123.6 mg (1.380 mmol) of CuCN in 5.0 mL of THF. The solution was stirred for 10 min, cooled to −70 °C, treated with 170 μL (1.380 mmol) of BF_3·OEt, and stirred for 5 min. A solution of 117.5 mg (0.460 mmol) of **9e** in 2.0 mL of THF was added. The reaction mixture was stirred for 15 min at −70 °C, quenched with saturated aqueous NH_4Cl (7 mL), and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography on SiO_2 (20% EtOAc/hexanes) afforded 129.0 mg (90%) of **17eb** as an oil: $[\alpha]^{21}_D$ −63.9° (*c* 1.2, CH_2Cl_2); IR (neat) 3370, 1726, 1691, 1502, 1448, 1363, 1240, 1159, 1099, 1061 cm^{-1}; ^1H NMR δ 5.33 (d, 1 H, J = 9.7 Hz), 4.55–4.45 (m, 1 H), 4.13–4.03 (m, 1 H), 3.65 (s, 3H), 3.21 (q, 1 H, J = 7.2 Hz), 1.75–1.55 (m, 1 H), 1.65 (s, 3 H), 1.55–1.15 (5 H), 1.43 (s, 9 H), 1.19 (d, 3 H, J = 6.8 Hz), 0.85 (t, 3 H, J = 6.8 Hz); ^{13}C NMR δ 174.8, 154.8, 138.8, 122.4, 78.7.52.0, 51.3, 44.2, 32.4, 28.9, 28.1, 22.2, 19.5, 13.7, 13.4. MS (EI) *m/e* (rel intensity) 314 ([M + 1]$^+$, 1), 258 (7), 199 (30), 165 (18), 155 (10), 140 (25), 129 (20), 110 (18); MS (CI) *m/e* (rel intensity) 314 ([M + 1]$^+$, 13), 197 (100).

Methyl (3*E*,2*R*,5*S*)-2-Butyl-5-tosylamido-3-hexenoate (17gb). A solution of 0.51 mL (0.747 mmol) of *n*-butyllithium (1.47 M in hexanes) was added at −40 °C to a slurry of 66.9 mg (0.747 mmol) of CuCN in 3.0 mL of THF. The solution was stirred for 10 min, cooled to −70 °C, treated with 92 μL (0.747 mmol) of BF_3·OEt, and stirred for 10 min. A solution of 73.5 mg (0.249 mmol) of **9g** in 1.0 mL of THF was added. The reaction mixture was stirred for 10 min at −70 °C, quenched with saturated aqueous NH_4Cl (3 mL), and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography on SiO_2 (25% EtOAc/hexanes) afforded 75.6 mg (86%) of **17gb** as an oil: $[\alpha]^{22}_D$ −65.3° (*c* 1.9, CH_2Cl_2); IR (neat) 3279, 1732, 1433, 1377, 1329, 1161, 1093, 1020, 970 cm^{-1}; ^1H NMR δ 7.72 (d, 2 H, J = 8.2 Hz), 7.25 (d, 2 H, J = 8.2 Hz), 5.44–5.27 (m, 2 H), 5.04 (d, 1 H, J = 6.7 Hz), 3.89–3.79 (m, 1 H), 3.60 (s, 3 H), 2.83–2.76 (m, 1 H), 2.39 (s, 3 H), 1.60–1.50 (m, 1 H), 1.34–1.07 (m, 5 H), 1.12 (d, 3 H, J = 6.7 Hz), 0.82 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 174.3, 143.0, 138.0, 133.3, 129.4, 128.7, 127.0, 51.6, 51.0, 48.4, 32.0, 29.0, 22.2, 21.7, 21.4, 13.7; MS (EI) *m/e* (rel intensity) 338 (22), 224 (26), 198 (90), 182 (40), 166 (10), 155 (68), 91 (100); HRMS *m/e* calcd for $C_{17}H_{24}NO_4S$ (M − CH_3): 338.1426, found: 338.1403.

Methyl (3*E*,2*R*,5*S*)-5-[(1,1-Dimethylethoxy)methanamido]-2-(2-methylpropyl)-4-methyl-3-hexenoate (17ed). A solution of 0.45 mL (1.13 mmol) of isobutyllithium (2.50 M in Et_2O) was added at −50 °C to a slurry of 101.2 mg (1.13 mmol) of CuCN in 6.0 mL of THF. The solution was stirred for 10 min, cooled to −70 °C, treated with 139 μL (1.13 mmol) of BF_3·OEt, and stirred for 5 min. A solution of 96.2 mg (0.377 mmol) of **9e** in 2.0 mL of THF was added. The reaction mixture was stirred for 25 min at −70 °C, quenched with saturated aqueous NH_4Cl (7 mL), and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Chromatography on SiO_2 (15% EtOAc/hexanes) afforded 98.0 mg (83%) of **17ed** as an oil: $[\alpha]^{21}_D$ −68.8° (*c* 2.2, CH_2Cl_2, 21 °C); IR (neat) 3375, 1734, 1516, 1367, 1325, 1244, 1170, 1113, 1062 cm^{-1}; ^1H NMR δ 5.28 (d, 1 H, J = 9.6 Hz), 4.55–4.45 (m, 1 H), 4.1–4.0 (m, 1 H), 3.63 (s, 3 H), 3.34–3.26 (m, 1 H), 1.65 (s, 1 H, 1.65–1.30 (m, 3 H), 1.41 (s, 9 H), 1.17 (d, 3 H, J = 6.8 Hz), 0.89 (d, 3 H, J = 6.4 Hz), 0.84 (d, 3 H, J = 6.3 Hz); ^{13}C NMR δ 175.1, 155.0, 138.8, 122.8, 79.1, 52.1, 51.6, 42.5, 41.8, 28.3, 25.6, 22.6, 22.2, 19.7, 13.7; MS (EI) *m/e* (rel intensity) 257 (6), 213 (10), 198 (18), 139 (20), 128 (30); HRMS *m/e* calcd for $C_{13}H_{23}NO_4$ (M − C_4H_8) 257.1627, found 257.1637.

General Procedure E for $LiBH_4$ Reduction of Esters. *N*-((1*R*,2*E*,4*R*)-4-(Hydroxymethyl)-1-methyl-2-octenyl)-benzamide (23ab). To a solution of 9.3 mg (0.425 mmol) of $LiBH_4$ in 0.4 mL of THF was added 45.0 mg (0.141 mmol) of a solution of a 4.7:1 mixture of **17ab** and ethyl (4*S*)-4-[(1*R*)-1-(phenylmethanamido)ethyl]-2-octenoate (**20ab**) in 0.4 mL of THF. The reaction was monitored by TLC and quenched after 20 h by addition of a few drops of saturated aqueous NH_4Cl. After addition of $MgSO_4$, the reaction mixture was stirred for 10 min and filtered and the solvent was removed in vacuo. Purification of the residue by chromatography on SiO_2 (45% EtOAc/hexanes) afforded 24.3 mg (76%) of alcohol **23ab** as an oil: $[\alpha]^{22}_D$ −18.2° (*c* 1.8, CH_3OH); IR (neat) 3321, 1632, 1576, 1539, 1429, 1057, 970 cm^{-1}; ^1H NMR ($CDCl_3$/CD_3OD) δ 7.73–7.70 (d, 2 H), 7.44–7.32 (m, 3 H), 7.17 (d, 1 H, J = 7.3 Hz), 5.45 (dd, 1 H, J = 15.5, 5.9 Hz), 5.33 (dd, 1 H, J = 15.5, 8.4 Hz), 4.58 (sx, 1 H, J = 6.6 Hz), 3.87 (b, 1 H), 3.47 (dd, 1 H, J = 10.8, 4.7 Hz), 3.30 (dd, 1 H, J = 10.7, 8.4 Hz), 2.12–2.02 (m, 1 H), 1.26 (d, 3 H, J = 6.8 Hz), 1.25–1.10 (m, 7 H), 0.80 (t,

3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 167.6, 134.1, 132.8, 132.4, 131.1, 128.1, 126.7, 65.2, 47.1, 45.0, 30.3, 28.9, 22.3, 20.4, 13.5; MS (EI) *m/e* (rel intensity) 275 (M^+, 1), 174 (7), 148 (7), 122 (30), 105 (100); MS (CI) *m/e* (rel intensity) 276 ([M + 1]$^+$, 100), 258 (7), 245 (6), 145 (5), 122 (18), 105 (10), 69 (4).

***N*-((1*R*,2*E*,4*R*)-5-Hydroxy-1,4-dimethyl-2-pentenyl)benzamide (23aa).** According to the general procedure E, 9.3 mg (0.428 mmol) of $LiBH_4$ and 39.3 mg (0.143 mmol) of **17aa** afforded 23.0 mg (70%) of **23aa** as an oil: $[\alpha]^{24}_D$ +9.86° (*c* 0.7, CH_2Cl_2); IR (neat) 3308, 1637, 1578, 1541, 1491, 1035 cm^{-1}; ^1H NMR δ 7.76 (d, 2 H, J = 7.2 Hz), 7.51–7.38 (m, 3 H), 6.34 (d, 1 H, J = 7.1 Hz), 5.57–5.50 (m, 2 H), 4.71–4.65 (m, 1 H), 3.49 (dd, 1 H, J = 10.7, 5.3 Hz), 3.38 (dd, 1 H, J = 10.4, 7.9 Hz), 2.49 (b, 1 H), 2.40–2.30 (m, 1 H), 1.33 (d, 3 H, J = 6.8 Hz), 0.97 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 166.9, 134.7, 133.6, 132.6, 131.5, 128.8, 126.9, 67.1, 47.4, 39.6, 21.0, 16.4; MS (EI) *m/e* (rel intensity) 215 (2), 203 (9), 148 (7), 131 (15), 122 (30), 105 (100); HRMS *m/e* calcd for $C_{13}H_{17}NO$ (M – CH_2O) 203.1310, found 203.1286.

***N*-((1*R*,2*E*,4*S*)-5-Hydroxy-1-methyl-4-phenyl-2-pentenyl)benzamide (23ac).** According to the general procedure E, 6.8 mg (0.310 mmol) of $LiBH_4$ and 35.0 mg (0.103 mmol) of **17ac** afforded 20.9 mg (69%) of **23ac** as a solid: $[\alpha]^{21}_D$ +17.7° (*c* 1.3, CH_3OH); IR (neat) 3308, 1637, 1578, 1541, 1491, 1452, 1340, 1035 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 7.79–7.76 (m, 2 H), 7.51–7.42 (m, 3 H), 7.33–7.28 (m, 2 H), 7.25–7.19 (m, 3 H), 6.92 (d, 1 H, J = 7.5 Hz), 5.87 (dd, 1 H, J = 15.5, 7.3 Hz), 5.61 (dd, 1 H, J = 15.5, 6.1 Hz), 4.71 (sx, 1 H, J = 6.8 Hz), 3.80–3.73 (m, 2 H), 3.51–3.43 (m, 1 H), 1.32 (d, 3 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 167.7, 140.9, 134.1, 133.0, 131.2, 130.7, 128.2, 128.1, 127.4, 126.7, 126.3, 65.6, 50.9, 46.9, 20.0; MS (EI) *m/e* (rel intensity) 277 (2), 174 (7), 156 (5), 144 (60), 129 (20), 122 (10), 115 (10), 105 (100); HRMS *m/e* calcd for $C_{11}H_{12}NO$ (M – C_8H_9O) 174.0919, found 174.0926.

***N*-((1*R*,2*E*,4*R*)-5-Hydroxy-1,4-dimethyl-2-pentenyl)-4-hydroxybutanamide (23ba).** According to the general procedure E, 10.9 mg (0.502 mmol) of $LiBH_4$ and 34.0 mg (0.114 mmol) of **17ba** afforded 14.8 mg (61%) of a 75:25 mixture of **23ba** and its (1*R*,4*S*)-epimer as determined by ^{13}C NMR.

23ba: IR (neat) 3289, 1647, 1547, 1456, 1377, 1037 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 7.75 (d, 1 H, J = 6.1 Hz), 5.45 (s, 2 H), 4.45–4.35 (m, 1 H), 3.58–3.50 (m, 2 H), 3.38–3.32 (m, 2 H), 2.32–2.20 (m, 3 H), 1.88–1.78 (m, 2 H), 1.18–1.10 (m, 3 H), 0.98–0.92 (m, 3 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 172.9, 132.2, 130.7, 66.1, 60.4, 45.8, 38.3, 32.0, 27.8, 19.4, 15.3; MS (EI) *m/e* (rel intensity) 200 (1), 185 (22), 166 (15), 138 (37), 128 (10), 112 (40), 104 (62); HRMS *m/e* calcd for $C_{10}H_{19}NO_2$ (M – CH_2O) 185.1416, found 185.1417.

***N*-((1*R*,2*E*,4*R*)-5-Hydroxy-1,4-dimethyl-2-pentenyl)(1,1-dimethylethoxy)methanamide (23da).** According to the general procedure E, 22.4 mg (1.03 mmol) of $LiBH_4$ and 93. mg (0.343 mmol) of a 4.7:1 mixture of **17da** and **20da** afforded 45.6 mg (70%) of **23da** as an oil: $[\alpha]^{22}_D$ +34.9° (*c* 1.1, CH_2Cl_2); IR (neat) 3337, 1689, 1524, 1392, 1367, 1248, 1172, 1045 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 5.42–5.30 (m, 2 H), 4.93 (b, 1 H), 4.01 (b, 1 H), 3.4–3.25 (m, 3 H), 2.3–2.2 (m, 1 H), 1.36 (s, 9 H), 1.11 (d, 3 H, J = 6.6 Hz), 0.89 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 155.6, 132.7, 79.4, 66.7, 48.1, 39.2, 28.2, 20.9, 16.2; MS (FAB) *m/e* (rel intensity) 252 ([M + Na]$^+$, 30), 230 ([M + H]$^+$, 20), 219 (10).

***N*-((1*S*,2*E*,4*R*)-5-Hydroxy-1,4-dimethyl-2-pentenyl)(1,1-dimethylethoxy)methanamide (23fa).** To a solution of 18.1 mg (0.829 mmol) of $LiBH_4$ in 1.0 mL of THF was added 75.0 mg (0.276 mmol) of a solution of an 8:1 mixture of **17fa** and **20fa** in 0.5 mL of THF. The reaction was monitored by TLC and quenched after 6 h by addition of a few drops of saturated aqueous NH_4Cl. After addition of $MgSO_4$, the reaction mixture was stirred for 10 min and filtered and the solvent was removed in vacuo. Purification of the residue by chromatography on SiO_2 (45% EtOAc/hexanes) afforded 42.6 mg (75%) of alcohol **23fa** as an oil: $[\alpha]^{22}_D$ –7.4° (*c* 1.5, CH_2Cl_2); IR (neat) 3337, 1689, 1524, 1454, 1390, 1365, 1248, 1172, 1045, 970 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 5.52–5.38 (m, 2 H), 4.13 (b, 1 H), 3.47 (dd, 1 H, J = 5.5, 10.7 Hz), 3.35 (dd, 1 H, J = 7.5, 10.7 Hz), 2.33 (m, 1 H), 2.21 (b, 1 H), 1.42 (s, 9 H), 1.19 (d, 3 H, J = 6.7 Hz), 0.97 (d, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 155.2, 132.9, 132.1, 79.3, 67.0, 39.1, 28.3, 21.0, 16.2; MS (EI) *m/e* (rel intensity) 199 (2), 158 (5), 143 (50), 132 (30), 114 (18); HRMS *m/e* calcd for $C_7H_{13}NO_2$ (M – $C_5H_{10}O$) 143.0946, found 143.0933.

General Procedure F for Benzylation, Johnson–Lemieux Oxidation, and Reduction of Homoallylic Alcohols 23. (2*R*)-3-(Benzyloxy)-2-butyl-1-propanol (25b). To a solution of 29.5 mg (0.076 mmol) of a crude sample of alcohol **23ab** in 0.5 mL of THF was added 5.1 mg (0.128 mmol) of NaH (60% dispersion in mineral oil). The reaction mixture was stirred for 10 min, treated with 38.2 μL (0.321 mmol) of benzyl bromide and 39.5 mg (0.107 mmol) of tetrabutylammonium iodide, and monitored by TLC. After 2 h, the solution was quenched by addition of a few drops of saturated aqueous NH_4Cl and diluted with 2.0 mL of THF, and ca. 50 mg of $MgSO_4$ was added. The reaction mixture was stirred for 10 min, filtered, and concentrated under reduced pressure. Chromatography on SiO_2 (30% EtOAc/hexanes) afforded 45.9 mg (117%) of crude benzyl ether **24ab**. This compound was dissolved in 2.0 mL of THF/H_2O (4:1), and 34 μL (0.005 mmol) of OsO_4 (4% weight in H_2O) was added. After 5 min, 68.7 mg (0.321 mmol) of $NaIO_4$ was added in three portions over 10 min. The reaction mixture was stirred for 3 h, diluted with Et_2O, and washed with H_2O. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 (12% EtOAc/hexanes) afforded 16.8 mg of a crude aldehyde that was dissolved in 0.75 mL of Et_2O and added at 0 °C to a slurry of 3.7 mg (0.092 mmol) of $LiAlH_4$ (95%) in 0.75 mL of Et_2O. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and quenched by sequential addition of 3 μL of H_2O, 3 μL of 15% aqueous NaOH, and 9 μL of H_2O. After addition of ca. 50 mg of $MgSO_4$, the heterogeneous solution was stirred for an additional 10 min, filtered, and concentrated in vacuo. Chromatography on SiO_2 (20% EtOAc/hexanes) afforded 5.6 mg (31%) of alcohol **25b** as an oil: $[\alpha]^{20}_D$ +16.5° (*c* 0.5, CH_2Cl_2); IR (neat) 3418, 1454, 1097, 1028 cm^{-1}; ^1H NMR δ 7.39–7.30 (m, 5 H), 4.57–4.49 (m, 2 H), 3.76–3.70 (m, 1 H), 3.66–3.50 (m, 2 H), 3.47 (t, 1 H), 2.68–2.64 (m, 1 H), 1.98–1.85 (m, 1 H), 1.29–1.26 (m, 7 H), 0.90 (t, 3 H, J = 6.5 Hz); ^{13}C NMR δ 128.4, 127.7, 127.6, 74.3, 73.4, 66.5, 40.5, 29.4, 27.7, 22.9, 14.0; MS (EI) *m/e* (rel intensity) 222 (M^+, 5), 147 (9), 120 (6), 107 (80), 95 (10), 91 (100); HRMS *m/e* calcde for $C_{14}H_{22}O_2$ 222.1620, found 222.1620.

(2*R*)-3-(Benzyloxy)-2-methyl-1-propanol (25a) from 23aa. According to the general procedure F, 22.8 mg (0.099 mmol) of **23aa**, 4.8 mg (0.119 mmol) of NaH (60% dispersion in mineral oil), 35.3 μL (0.297 mmol) of benzylbromide, 36.6 mg (0.99 mmol) of tetrabutylammonium iodide, 33.4 μL (0.005 mmol) of OsO_4 (4% weight in H_2O), 67.4 mg (0.315 mmol) of $NaIO_4$, and 1.8 mg (0.045 mmol) of $LiAlH_4$ (95%) afforded 6.6 mg (37%) of **25a** as an oil: $[\alpha]^{22}_D$ +12.6° (*c* 0.5, CH_2Cl_2) [lit.[29] $[\alpha]^{21}_D$ –17.6° (*c* 4.53, $CHCl_3$)].

From 23ba. According to general procedure F, 14.8 mg (0.069 mmol) of **23ba**, 6.6 mg (0.166 mmol) of NaH (60% dispersion in mineral oil), 49 μL (0.414 mmol) of benzylbromide, 25.5 mg (0.69 mmol) of tetrabutylammonium iodide, 14.9 μL (0.002 mmol) of OsO_4 (4% weight in H_2O), 30.2 mg (0.141 mmol) of $NaIO_4$, and 1.1 mg (0.027 mmol) of $LiAlH_4$ (95%) afforded 3.3 mg (27%) of **25a** as an oil: $[\alpha]^{22}_D$ +8.1° (*c* 0.5, CH_2Cl_2).

From 23da. According to general procedure F, 22.8 mg (0.099 mmol) of **23da**, 6.8 mg (0.169 mmol) of NaH (60% dispersion in mineral oil), 50.7 μL (0.426 mmol) of benzylbromide, 52.5 mg (0.142 mmol) of tetrabutylammonium iodide, 46.1 μL (0.007 mmol) of OsO_4 (4% weight in H_2O), 93.0 mg (0.435 mmol) of $NaIO_4$, and 3.7 mg (0.093 mmol) of $LiAlH_4$ (95%) afforded 7.5 mg (30%) of **25a** as an oil: $[\alpha]^{22}_D$ +10.7° (*c* 0.4, CH_2Cl_2); ^1H NMR δ 7.39–7.25 (m, 5 H), 4.53 (s, 3 H), 3.65–3.55 (m, 3 H), 3.44 (t, 1 H, J = 8.3 Hz), 2.57–2.51 (m, 1 H), 2.15–2.04 (m, 1 H), 0.89 (d, 3 H, J = 6.9 Hz).

From 23fa. According to general procedure F, 30.0 mg (0.130 mmol) of **23fa**, 6.3 mg (0.157 mmol) of NaH (60% dispersion in mineral oil), 46 μL (0.390 mmol) of benzylbromide, 48 mg (0.130 mmol) of tetrabutylammonium iodide, 35

μL (0.005 mmol) of OsO_4 (4% weight in H_2O), 69.9 mg (0.327 mmol) of $NaIO_4$, and 4.3 mg (0.108 mmol) of $LiAlH_4$ (95%) afforded 7.9 mg (34%) of **25a** as an oil: $[\alpha]^{22}_D$ +17.3° (*c* 0.8, CH_2Cl_2).

(2*R*)-3-(Benzyloxy)-2-phenyl-1-propanol (25c). According to general procedure F, 20.9 mg (0.071 mmol) of **23ac**, 3.4 mg (0.085 mmol) of NaH (60% dispersion in mineral oil), 25 μL (0.213 mmol) of benzylbromide, 26.2 mg (0.99 mmol) of tetrabutylammonium iodide, 19 μL (0.003 mmol) of OsO_4 (4% weight in H_2O), 38 mg (0.177 mmol) of $NaIO_4$, and 9.4 mg (0.236 mmol) of $LiAlH_4$ (95%) afforded 5.2 mg (30%) of **25c** as an oil: $[\alpha]^{21}_D$ +13.0° (*c* 0.2, CH_2Cl_2); IR (neat) 3400, 1495, 1452, 1097, 1028 cm^{-2}; ^1H NMR δ 7.45–7.22 (m, 10 H), 4.57 (s, 2 H), 4.08–4.0 (m, 1 H), 3.92–3.77 (m, 3 H), 3.3–3.2 (m, 1 H), 2.45–2.40 (m, 1 H); ^{13}C NMR δ 128.7, 128.5, 128.0, 127.8, 127.7, 127.1, 73.7, 73.5, 66.6, 47.8; MS (EI) *m/e* (rel intensity) 242 (M^+, 3), 194 (6), 121 (40), 104 (100); HRMS *m/e* calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1310.

General Procedure G for the Preparation of Mosher Esters. (2*S*)-2-[(Benzyloxy)methyl]hexyl (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. To a solution of 3.5 mg (0.0157 mmol) of **25b** in 0.3 mL of CH_2Cl_2 were added ca. 120 mg of pyridine and ca. 60 mg of (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride. The reaction was monitored by TLC and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride was added until the reaction had gone to completion. After addition of 0.3 mL of H_2O, the solution was extracted with 2 mL of Et_2O, washed with 10% HCl, saturated aqueous Na_2CO_3, and H_2O, and dried (Na_2SO_4). Purification by chromatography on SiO_2 (7% EtOAc/hexanes) afforded 6.4 mg (93%) of the Mosher ester of **25b** as an oil: ^1H NMR δ 7.53–7.50 (m, 10 H), 4.93–4.31 (m, 4), 3.53 (s, 3 H), 3.50–3.30 (m, 2 H), 2.06–1.99 (m, 1 H), 1.50–1.15 (m, 6 H), 0.90–0.87 (m, 3 H); ^{19}F NMR δ −70.9 (s, 2.64 F), −70.9 (s, 0.36 F).

(2*S*)-3-(Benzyloxy)-2-phenylpropyl (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. According to general procedure G, 1.6 mg (0.0066 mmol) of **25c** afforded 2.8 mg (93%) of the corresponding Mosher ester as an oil: ^1H NMR δ 7.36–7.20 (m, 15 H), 4.76–4.70 (m, 1 H), 4.63–4.57 (m, 1 H), 4.50–4.47 (m, 2 H), 3.69–3.66 (m, 2 H), 3.38 (s, 2.49 H), 3.35 (s, 0.51 H); ^{19}F NMR δ −71.3 (s, 2.52 F), −71.3 (s, 0.48 H).

Supplementary Material Available: NMR spectra (44 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.