bound hydroxide ions can also act as general bases, but this possibility has not been experimentally demonstrated yet. The present study of the hydrolysis of 1 in the presence of Cu(II) ion is the first evidence obtained for the general base catalysis by metal-bound hydroxide ions.

In many metalloenzymes, metal ions act as Lewis acids.[52] In the action of such a metalloenzyme, the metal-bound water molecule and the metal-bound hydroxide ion as well as the metal ion itself can act as catalytic functional groups. The nucleophilic attack by metal-bound water[17] or hydroxide ion[20-25] has been demonstrated in model systems. The general-base action of metal-bound hydroxide ion demonstrated in the present study expands the repertoire of the catalytic roles of metal ions in metalloenzymes.

(52) Vallee, B. L.; Wacker, W. E. C. *Handbook of Biochemistry and Molecular Biology*; 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, 1976; Vol. II, pp 276-292.

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A Highly Stereoselective Synthesis of (*E*)-Alkene Dipeptide Isosteres via Organocyanocopper–Lewis Acid Mediated Reaction

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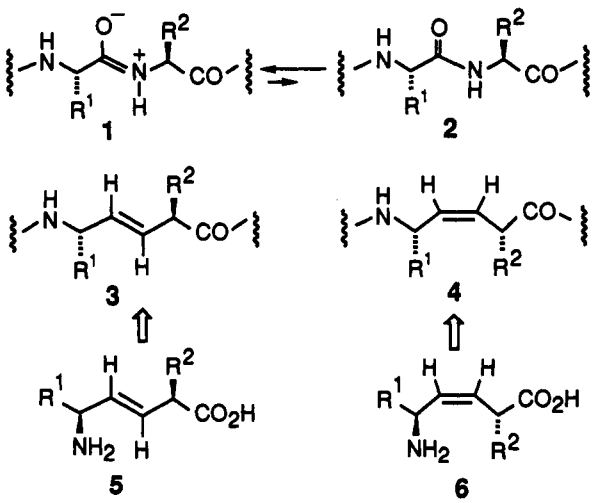
A stereoselective synthesis of protected (*E*)-alkene dipeptide isosteres by the reaction of the mesylates of homochiral δ-aminated γ-hydroxy (*E*)-α,β-enoates with either RCu(CN)Li·BF_3 or RCu(CN)MgX·BF_3 reagent is described. The degree of diastereoselectivity has been found to be uniformly high except for the serine- and threonine-derived acetonides **77** and **81**. The synthesis permits the introduction of sterically hindered appendages such as isopropyl and *tert*-butyl groups at the α position to the ester group. This methodology provides a new route to a wide range of modified (*E*)-alkene peptide mimics that may have biological importance.

In recent years, increasing interest has been shown in the backbone modification of amide bonds in biologically active peptides.[1] The major purpose in this area deals with stabilizing a given peptide toward enzymatic degradation by in vivo proteases or imparting enzyme inhibitory activity to the synthesized peptide mimic.[2] The peptide bond in polypeptides and proteins generally assumes the trans amide bond configuration **1**, since its cis counterpart induces unfavorable steric interactions.[3a-c] In fexible peptides, a proline-generated cis configurational isomer generally accounts for up to 30% of the total cis/trans population.[3d] Consequently, free rotation around the CO–NH bond axis is retarded (Scheme I).[3]

The (*E*)-CH=CH bonding in a peptide mimic (**3**) closely resembles the three-dimensional structure (bond length, bond angle, and rigidity) of the parent amide (**1** and **2**).[2,3] Thus, replacement of an amide bond by a (*E*)-CH=CH bond should not significantly alter the overall conformation

Scheme I



of a peptide molecule, and, hence, its biological activity, provided that the replaced amide bond is not directly involved in either the secondary or tertiary structure of the peptide or the mechanism whereby the biological response is elicited.[2] It has recently been shown that peptide analogues **4** having a (*Z*)-alkene dipeptide isostere (**6**) were considerably less bioactive than peptide mimics **3** involving an (*E*)-alkene isostere (**5**).[4] The interest in these (*E*)-

(1) (a) Spatola, A. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. 7, p 267. (b) According to IUPAC rules, the structure inside the bracket following ψ is the unit substituting for the amide bond. For nomenclature, see: IUPAC-IUB Joint Commission on Biochemical Nomenclature, *Eur. J. Biochem.* **1984**, *138*, 9.

(2) Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc., Chem. Commun.* **1980**, 234. Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc., Perkin Trans. I* **1982**, 307.

(3) (a) Dickerson, R. E.; Geis, I. In *The Structure and Action of Proteins*; Harper & Row: New York, Evanston, London, 1969; p 13. (b) Schulz, G. E.; Schirmer, R. H. In *Principles of Protein Structure*; Springer-Verlag: New York, Heidelberg, Berlin, 1979; p 18. (c) Sukumaran, D. K.; Prorok, M.; Lawrence, D. S. *J. Am. Chem. Soc.* **1991**, *113*, 706 and references cited. (d) London, R. E.; Matwiyoff, N. A.; Stewart, J. M.; Cann, J. R. *Biochemistry* **1978**, *17*, 2277.

(4) Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenberg, A. D. *J. Med. Chem.* **1990**, *33*, 838.

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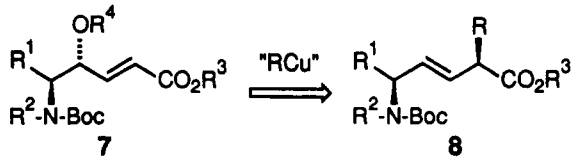
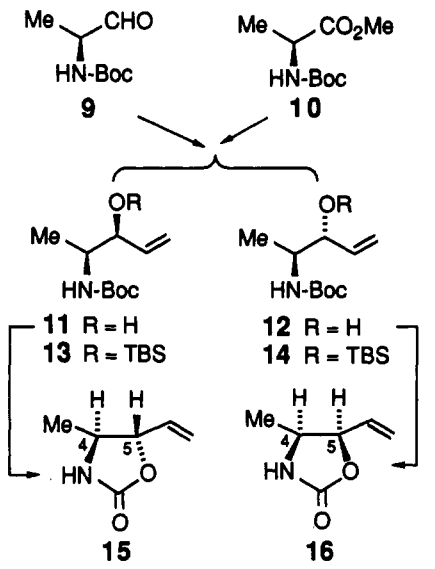
Scheme II



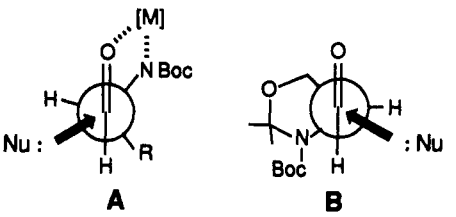
alkene isosteres has provoked a large number of synthetic studies.[5,6] Because it has been reported that α-carbon stereochemistry was one of the essential factors for enzyme inhibition,[7] the stereocontrolled synthesis of (*E*)-alkene dipeptide isosteres would be highly valuable. Except in two synthetic routes reported by Hopkins and his co-workers,[8a,b] and by Whitesell and Lawrence,[8c] published synthetic routes to such (*E*)-alkene dipeptide isosteres give unsatisfactory results with regard to double-bond geometry and/or stereochemistry at the α position to the carboxyl group. The synthetic method developed by Hopkins and his co-workers[8a,b] has been successfully applied by de Gaeta and his co-workers to the synthesis of protected forms of the highly functionalized dipeptide isosteres, Asnψ[(*E*)-CH=CH]Val and Serψ[(*E*)-CH=CH]Asn.[7b] In our continuing synthetic study of biologically important polypeptides,[9] we were in need of a practical and highly stereoselective synthetic route to possibly generate more specific, highly active alkene isosteres in which the olefinic geometry was exclusively *E*.

Therefore, we sought to study these stereochemical problems and to develop a general and flexible route to (*E*)-alkene isosteres by the regio- and stereospecific reaction of organocopper reagents to δ-aminated γ-oxy α,β-unsaturated esters. Until now, an organocopper–Lewis acid assisted reaction of δ-aminated γ-oxy α,β-enoates for

Scheme III



Scheme IV



constructing (*E*)-alkene isosteres has no precedent as far as we are aware.[10] Detailed here is an efficient and general method for the synthesis of (*E*)-alkene dipeptide isosteres of defined stereochemistry.[11]

Results and Discussion

It was our expectation to be able to synthesize stereochemically pure (*E*)-alkene isosteres 8 by employing recent advances in organocopper-mediated *anti*-S_N2' reactions of γ-oxygenated α,β-unsaturated esters 7.[12] In these substrates, the amino group was protected with the *tert*-butoxycarbonyl (Boc) group, which can withstand a wide range of chemical manipulations and yet be easily removed by treatment with trifluoroacetic acid under mild conditions (Scheme II).

The requisite δ-aminated γ-hydroxy (*E*)-α,β-enoates **19**, **20**, **23**, **24**, **36**, **37**, **38**, **39**, **49**, and **50** were readily prepared in acceptable yields from natural (*S*)-α-amino acids.

Reaction of Boc-(*S*)-alaninal (**9**)[13] with vinylmagnesium

(5) (a) Cox, M. T.; Heaton, D. W.; Horbury, J. *J. Chem. Soc., Chem. Commun.* **1980**, 799. (b) Johnson, R. L. *J. Med. Chem.* **1984**, *27*, 1351. (c) Miles, N. J.; Sammes, P. G.; Kennewell, P. D.; Westwood, R. *J. Chem. Soc., Perkin Trans. I* **1985**, 2299. (d) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399. (e) Shue, Y.-K.; Carrera, G. M.; Nadzan, A. M. *Tetrahedron Lett.* **1987**, *28*, 3225. (f) Shue, Y.-K.; Tufano, M. D.; Nadzan, A. M. *Tetrahedron Lett.* **1988**, *29*, 4041. (g) Precigoux, G.; Benkoulouche, M.; Geoffre, S.; Hospital M. In *Peptides 1988*; Jung, G., Bayer, E., Eds.; Walter de Gruyter: Berlin & New York, 1989; p 525. (h) Tourwe, D.; de Cock, E.; van Marsenille, M.; van der Auwera, L.; van Binst, G.; Viville, R.; Degelaen, J.; Scarso, A. In *Peptides 1988*; Jung, G., Bayer, E., Eds.; Walter de Gruyter: Berlin & New York, 1989; p 562. (i) Elseviers, M.; Jaspers, H.; Delaet, N.; De Vadder, S.; Depermans, H.; Tourwe, D.; van Binst, G. In *Peptides: Chemistry Structure, and Biology*; Rivier, J. E., Marshall, G. R., Eds.; ESCOM: Reiden, 1990; p 198. (j) Allemendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7297. (k) Thompson, W. J.; Tucker, T. J.; Schwering, J. E.; Barnes, J. L. *Tetrahedron Lett.* **1990**, *31*, 6819.

(6) For incorporation of CH=CH isosteres into peptides, see: (a) Cox, M. T.; Gormley, J. J.; Hayward, C. F.; Petter, N. N. *J. Chem. Soc., Chem. Commun.* **1980**, 800. (b) Natarajan, S.; Condon, M.; Nakane, M.; Reid, J.; Gordon, E.; Cushman, D.; Ondetti, M. In *Peptides: Synthesis, Structure, and Function*; Rich, D. H., Gross, E., Eds.; Pierce Chemical Co.: Rockford, IL, 1981; p 429. (c) Precigoux, G.; Ouvrard, E.; Geoffre, S. In *Peptides: Structure and Function*; Deber, C. M., Hruby, V. J., Kopple, K. D., Eds.; Pierce Chemical Co.: Rockford, IL, 1985; p 763. (d) Allemendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301.

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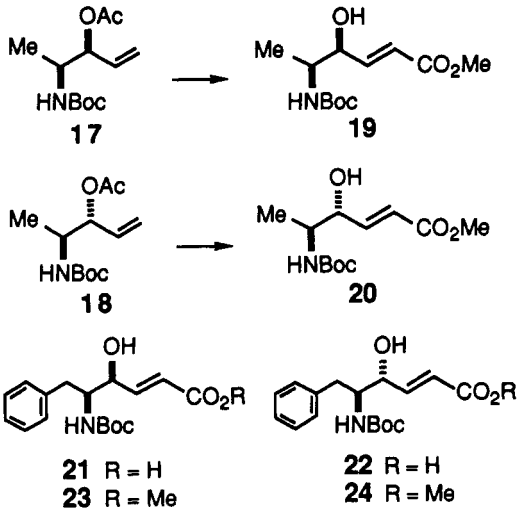
(10) Very recently, an independent report on the synthesis of dipeptide isostere(s) via an organocopper-mediated reaction of γ-mesyloxy α,β-enoates by an American group has appeared. Wang, X. C.; Kempf, D. J. *Abstracts of Papers*, 200th National Meeting of the American Chemical Society, Washington, DC, August 26–31, 1990; American Chemical Society: Washington, DC, 1990; ORGN 60.

(11) For a preliminary communication of a portion of this work, see: Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801.

(12) (a) Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420. (b) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1596. (c) Ibuka, T.; Akimoto, N.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 4055. (d) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864. (e) Ibuka, T.; Tanaka, M.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 967. (f) Marino, J. O.; Viso, A. *J. Org. Chem.* **1991**, *56*, 1349.

(13) (a) Stanfield, C. F.; Parker, J. E.; Kanellis, P. *J. Org. Chem.* **1981**, *46*, 4797. (b) Colebiowski, A.; Jacobsson, U.; Jurczak, J. *Tetrahedron* **1987**, *43*, 3063.

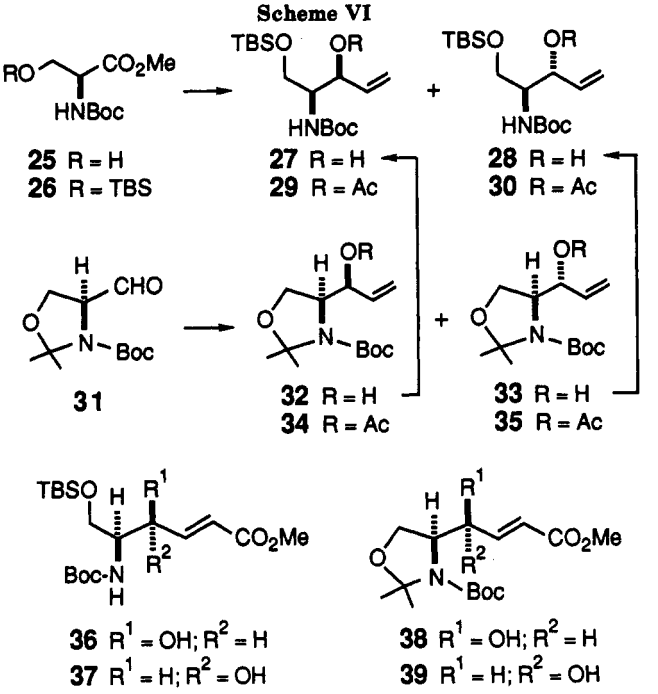
Scheme V



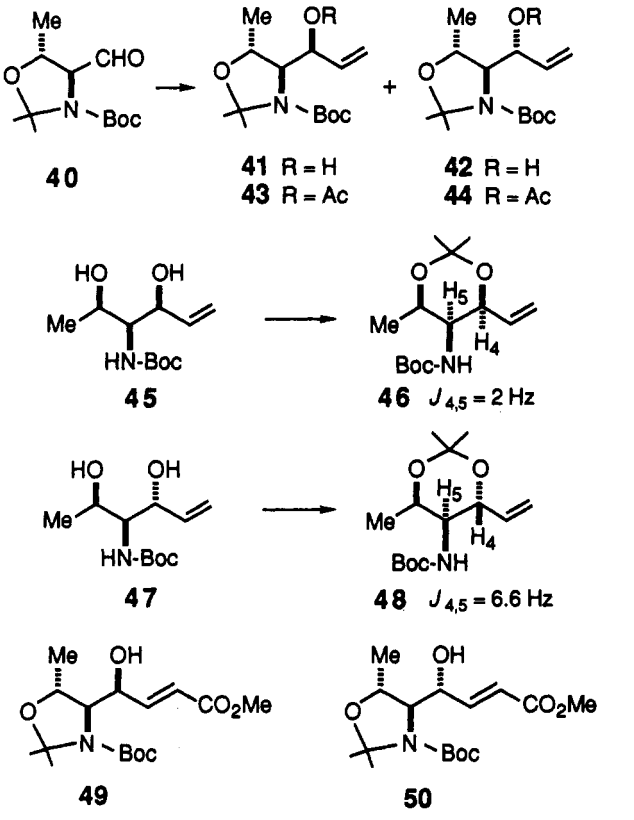
chloride[14] (THF, −70 to 0 °C) gave a mixture (7:3) of syn and anti vinyl alcohols 11 and 12 in 53% combined yield[15] (Scheme III). Perhaps the diastereoselectivity of the reaction of aldehyde with the vinylmagnesium halide is dependent on the presence of the NH group. The syn diastereoselectivity observed with NHBoc aldehyde could be explained by the chelation-controlled Cram cyclic model A (M = MgX)[16] as shown in Scheme IV. Thus, attack by vinylmagnesium chloride occurs from the less hindered side of the transition state A to give the syn vinyl alcohol 11 as the major product. In agreement with this explanation, the HNBoc amino ester 10 was successively treated with diisobutylaluminum hydride (DIBAL) and vinylmagnesium chloride[14] in a one-pot reaction[17] to predominantly yield the syn vinyl alcohol 11 (diastereoselection, >15:1; 60% combined yield), presumably due to the transition state A (M = AlR_2) (Scheme IV).

The mixture of 11 and 12 showed a single spot on thin layer chromatography, and attempts to separate individual isomers by flash chromatography failed at this stage. However, the mixture of *tert*-butyldimethylsilyl ethers 13 and 14, derived from the mixture of 11 and 12, was easily separated by flash chromatography, and the treatment of the silyl ethers 13 and 14 with 18% hydrofluoric acid in acetonitrile regenerated the pure alcohols 11 and 12, respectively. Both pure alcohols 11 and 12 were desired for purposes of biological evaluation of (*E*)-alkene isosteres that could be synthesized from 11 and 12, because when incorporated into polypeptides the *R* or *S* configuration at the α carbon to the carboxyl group may be critical for enzymatic inhibition.[7] Stereochemical assignments for diastereomers 11 and 12 were made by conversion to oxazolidone derivatives 15 and 16 by treatment with sodium hydride in DMF. The compound 16 derived from 12 showed a $J_{4,5}$ value (J = 8.06 Hz) larger than that of the isomer 15 (J = 7.1 Hz). The C-5 proton in 15 resonates

Scheme VI



Scheme VII



at higher field (δ 4.48) than those of the isomer 16 (δ 5.04). The data are in agreement with ^{1}H NMR data for related compounds.[18] The optical purity of chiral alcohols 11 and 12 was easily demonstrated by conversion of 11 and 12 to the corresponding Mosher esters,[19] and analysis by ^{1}H

(14) The use of vinylmagnesium bromide in place of the chloride gave a mixture of the allylic alcohols 3 and 4 in a very low yield.

(15) The notations syn and anti are used as defined in the following: Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

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(17) (a) Bolis, G.; Fung, A. K. L.; Greer, J.; Kleinert, H. D.; Marcotte, P. A.; Perum, T. J.; Plattner, J. J.; Stein, H. H. *J. Med. Chem.* **1987**, *30*, 1729. (b) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Chem. Pharm. Bull.* **1989**, *37*, 2867.

(18) (a) Karlsson, J. O.; Rundblad, A.; Malm, B.; Nilsson, I.; Nitenberg, T.; Starke, I.; Sörensen, H.; Westerlund, C. *Tetrahedron Lett.* **1989**, 30. (b) Dondoni A.; Fantin, G.; Fogagnolo, M.; Pedrine, P. *J. Org. Chem.* **1990**, *55*, 1439. (c) Sham, H. L.; Rempel, C. A.; Stein, H.; J. Cohen, J. *J. Chem. Soc., Chem. Commun.* **1990**, 904. (d) Patel, D. V.; R.-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587.

NMR and/or by high performance liquid chromatography (HPLC) indicated that both Mosher esters were essentially optically pure (>98% de).

Acetylation of **11** gave the acetate **17**, which was successively treated with ozone at −78 °C in CH_2Cl_2, (carbomethoxymethylene)triphenylphosphorane at −78 to 0 °C in CH_2Cl_2, and sodium carbonate in methanol[5e] to yield the γ-hydroxy (*E*)-α,β-enoate **19** in 36% overall yield after flash chromatography over silica gel (Scheme V). In the same manner, the vinyl acetate **18** was converted to the isomeric enoate **20** in 86% overall yield. The *E* geometry of **19** and **20** was easily established from the coupling constant (ca. J = 15.7 Hz) of the two olefinic protons by ^{1}H NMR analyses.

The requisite γ-hydroxy (*E*)-α,β-enoates **23** and **24** for the synthesis of isosteres involving (*S*)-phenylalanine were prepared from the known hydroxy acids **21**[5d] and **22**,[5d] respectively, by methylation with diazomethane.

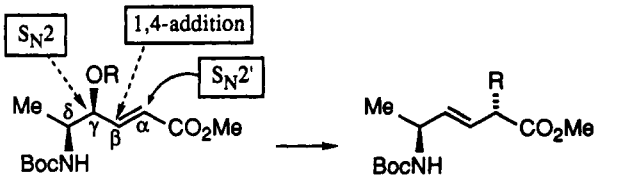
Synthesis of δ-aminated γ-hydroxy α,β-enoates from (*S*)-serine and (*S*)-threonine was as follows (Schemes VI and VII). Boc-(*S*)-serine methyl ester (**25**)[20] was converted into the *tert*-butyldimethylsilyl ether **26**, which was successively treated with DIBAL and vinylmagnesium bromide in a one-pot reaction to yield a separable 74:26 mixture of syn and anti vinyl alcohols **27** and **28** in 58% combined yield.

Alternatively, the reaction of *N*-Boc-(*S*)-serinal acetonide (**31**)[21,22] with vinylmagnesium chloride gave a separable 1:5.3 mixture of the known vinyl alcohols **32**[21] and **33**[21] in 67.5% combined yield. The anti diastereoselectivity observed in the reaction of *N*-Boc-serine aldehyde (**31**) with vinylmagnesium chloride may be ascribed to the predominance of the Felkin–Anh conformation **B**[23] of aldehydes **31** (Scheme IV) and to the attack of reagent from the less hindered *re* face. Stereochemical assignments for the above vinyl alcohols **27** and **28** were made by direct comparison of spectral data of **27** and **28** with those of authentic samples prepared from the known alcohols **32**[21] and **33**[21] by treatment with 5% hydrochloric acid in aqueous methanol followed by selective *tert*-butyldimethylsilylation. The vinyl alcohols **27**, **28**, **32**, and **33** were transformed into the desired γ-hydroxy (*E*)-α,β-enoates **36**, **37**, **38**, and **39**, respectively, by a sequence of reactions (**27**–**29**–**36**, **28**–**30**–**37**, **32**–**34**–**38**, and **33**–**35**–**39**) identical with that described for the synthsis of the γ-hydroxy (*E*)-α,β-enoate **19**.

N-Boc-(*S*)-threoninal acetonide (**40**)[22b] was transformed into δ-aminated γ-hydroxy (*E*)-α,β-enoates **49** and **50**, respectively, as shown in Scheme VII. Thus, the reaction of aldehyde **40** with vinylmagnesium chloride gave a separable 49:51 mixture of the vinyl alcohols **41** and **42** in 74% combined yield. Stereochemical assignments for diastereomers **41** and **42** were made by transforming them into the six-membered cyclic acetonides **46** and **48** via the diols **45** and **47**, respectively. The acetonide **46** showed a $J_{4,5}$ value (J = 1.7 Hz) smaller than that of the isomer **48** ($J_{4,5}$ = 6.59 Hz). The data are in agreement with ^{1}H NMR data for related compounds.[21,24] The alcohols **41** and **42** were converted to the desired substrates **49** and **50**, respectively, by a sequence of reactions (**41**–**43**–**49** and **42**–**44**–**50**) identical with that described for the synthesis of γ-hydroxy (*E*)-α,β-enoate **19**.

At first glance, reaction of γ-oxygenated (*E*)-α,β-enoates with organocoppers to provide the corresponding α-alkyl (*E*)-β,γ-enoates (alkene isosteres) would appear to pose several significant problems. Four possible different reaction products from (*E*)-α,β-enoates with a leaving group at the γ position could be envisioned. All four reactivity patterns have been reported on relatively simple allylic systems. Thus, the S_N2 reaction of substrates with organocopper reagents at the γ position generates a γ-alkylated product,[25] conjugate addition at the β position provides

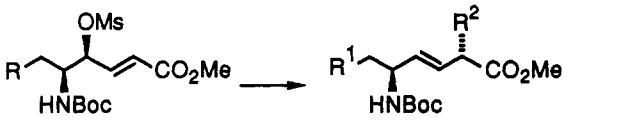
Scheme VIII



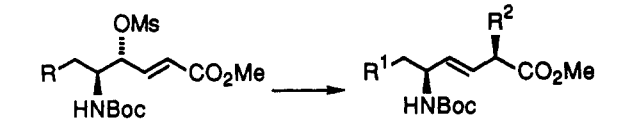
51 R = Ac
52 R = Ms

53 R = Me (*anti*-S_N2' product)
54 R = H (reduction product)

Scheme IX



52 R = H	**53** R^1 = H;	R^2 = Me
	55 R^1 = H;	R^2 = *iso*-Pr
	56 R^1 = H;	R^2 = CH_2Ph
57 R = OTBS	**58** R^1 = OTBS;	R^2 = Me
	59 R^1 = OTBS;	R^2 = *iso*-Bu
	60 R^1 = OTBS;	R^2 = *iso*-Pr
61 R = Ph	**62** R^1 = Ph;	R^2 = Me
	63 R^1 = Ph;	R^2 = *iso*-Bu
	64 R^1 = Ph;	R^2 = *iso*-Pr
	65 R^1 = Ph;	R^2 = *tert*-Bu



66 R = H	**67** R^1 = H;	R^2 = Me
	68 R^1 = H;	R^2 = *iso*-Pr
	69 R^1 = H;	R^2 = CH_2Ph
70 R = OTBS	**71** R^1 = OTBS;	R^2 = Me
	72 R^1 = OTBS;	R^2 = *iso*-Bu
73 R = Ph	**74** R^1 = Ph;	R^2 = Me
	75 R^1 = Ph;	R^2 = *iso*-Bu
	76 R^1 = Ph;	R^2 = *iso*-Pr

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(20) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037.
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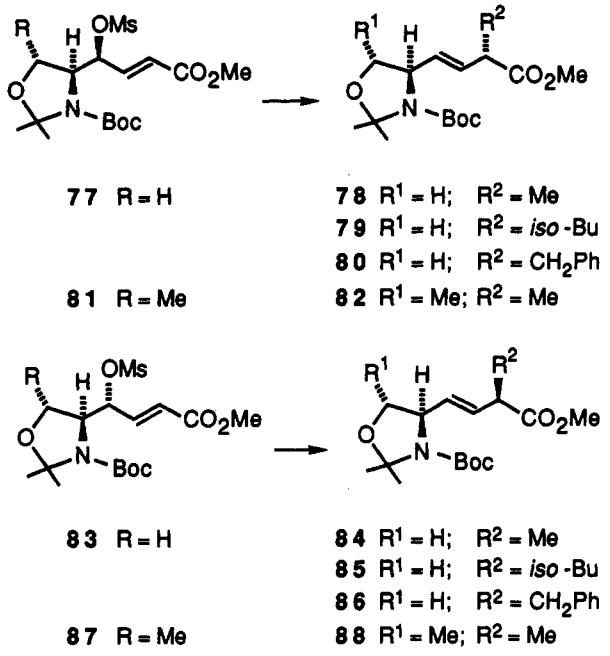
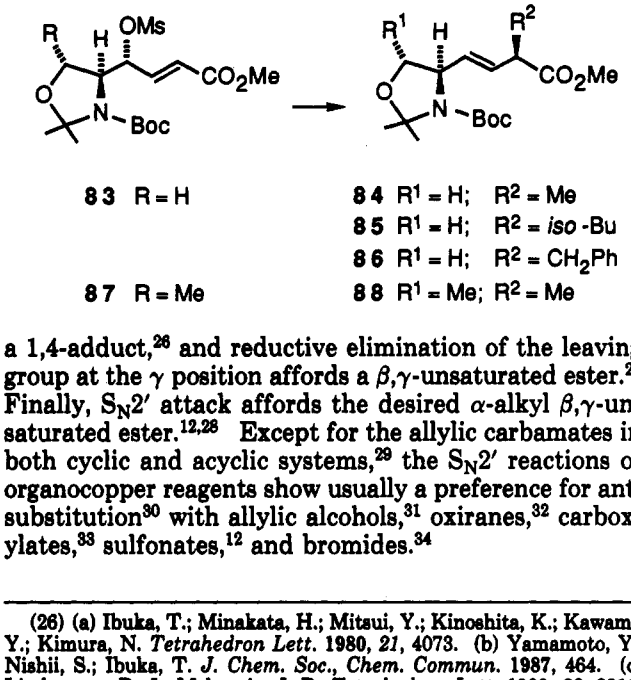
Scheme X



77 R = H; 78 R^1 = H; R^2 = Me; 79 R^1 = H; R^2 = *iso*-Bu; 80 R^1 = H; R^2 = CH_2Ph; 81 R = Me; 82 R^1 = Me; R^2 = Me



83 R = H; 84 R^1 = H; R^2 = Me; 85 R^1 = H; R^2 = *iso*-Bu; 86 R^1 = H; R^2 = CH_2Ph; 87 R = Me; 88 R^1 = Me; R^2 = Me

a 1,4-adduct,[26] and reductive elimination of the leaving group at the γ position affords a β,γ-unsaturated ester.[27] Finally, S_N2' attack affords the desired α-alkyl β,γ-unsaturated ester.[12,28] Except for the allylic carbamates in both cyclic and acyclic systems,[29] the S_N2' reactions of organocopper reagents show usually a preference for anti substitution[30] with allylic alcohols,[31] oxiranes,[32] carboxylates,[33] sulfonates,[12] and bromides.[34]

It was assumed that the γ-acetoxy α,β-enoate **51** derived from **19** would provide an *anti*-S_N2' reaction product, though we have not completely eliminated the possibility of an unpredictable influence of the HNBoc group at the δ position. However, this was not to be the case, since the reaction of the acetate **51** with MeCu(CN)Li in THF at −78 °C recovered unchanged started material (Scheme VIII). When the same reaction was run in ether, the α-methylated product **53** was obtained in a very low yield (13%) along with a large amount (~83%) of the reduction product **54**. Similar reductive elimination reactions of simple cyclic γ-oxygenated α,β-enoates[27] and γ-oxygenated enones[35] with organocopper reagents have been previously reported. Generally, the reactivity of cuprates can be enhanced by certain additives such as $BF_3{\cdot}Et_2O$ and $(Me)_3SiCl$.[36] For reasons unknown, however, we did not detect any alkylation product by treatment of the acetate **51** with 4 molar equiv of MeCu(CN)Li·BF_3 in THF at −78 °C for 30 min. The only compound isolated was the starting material. Thus, efficient and regiocontrolled α-alkylation of the acetate **51** with MeCu(CN)Li or its Lewis acid complex proved troublesome.

On the other hand, treatment of the mesylate **52** with MeCu(CN)Li·BF_3 in a mixed solvent involving THF cleanly and rapidly afforded protected dipeptide isostere **53** in 93% isolated yield (diastereoselection, >99:1) following flash chromatographic purification (Table I, entry 1). Examination of the vinylic proton region of a 200-MHz ^1H NMR spectrum of the crude reaction material revealed that the product was stereochemically homogeneous; the *E* product had been exclusively produced. The desired *E* stereochemistry of the products was inferred from the ca. 15.6-Hz coupling constant of the two olefinic protons. The factors for clean reactions were quite similar to that recently described,[12] and the following points were found to be necessary to ensure the success of the preparation of homochrial dipeptide isosteres (Table I, Schemes IX and X). (1) A γ-mesyloxy leaving group is essential for clean reactions. Consequently, all γ-hydroxy α,β-enoates (**19**, **20**, **23**, **24**, **36**, **37**, **38**, **39**, **49**, and **50**) were converted into the corresponding mesylates. (It is expected that, although not performed, α,β-enoates with a γ-tosyloxy group would lead to the same results.) (2) Except for the serine- and threonine-derived acetonides **77** and **81**, satisfactory chemical and optical yields were obtained by reaction of γ-mesyloxy α,β-enoates with organocopper–Lewis acid reagents prepared from CuCN,[37] RLi or RMgX, and

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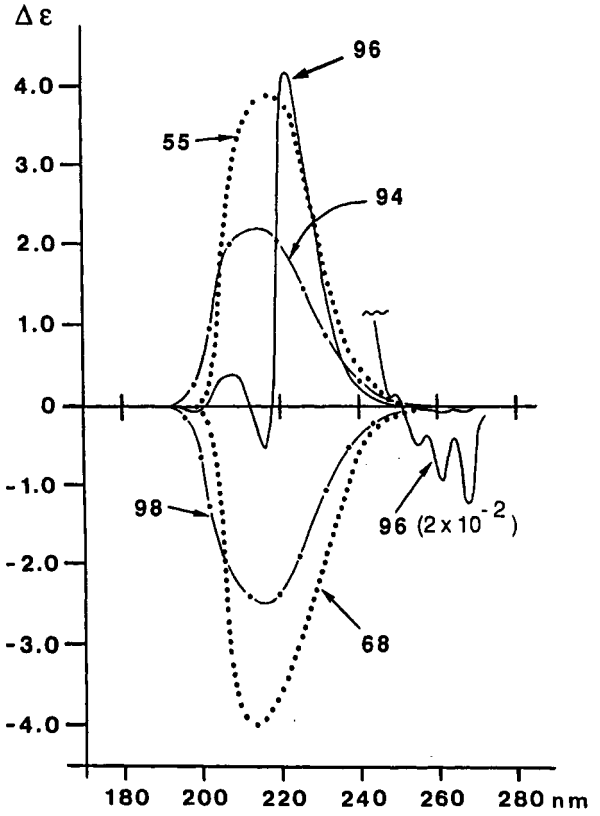
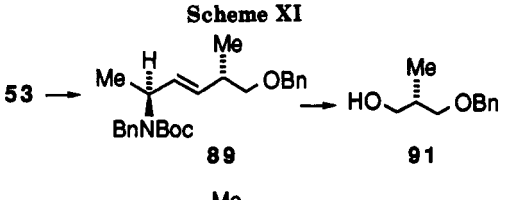


Figure 1. CD spectra of methyl esters **55** and **68** (in isooctane), amino acids **94** and **98** (in methanol), and protected tripeptide isostere **96** (in isooctane) at 25–30 °C.

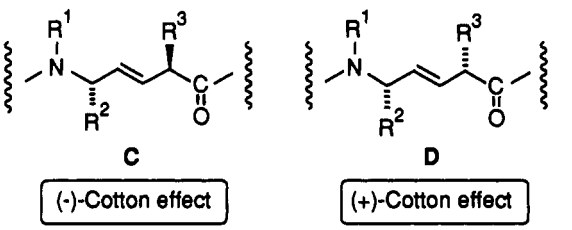
BF_3·Et_2O. Thus, lower order organocyanocopper·BF_3 complexes, RCu(CN)Li·BF_3 (R = primary, secondary, and tertiary) and RCu(CN)MgX·BF_3 (R = primary, secondary, and tertiary), could be used equally as well. As can be seen from Table I (entries 36 and 37), if the reaction is performed in the absence of BF_3·Et_2O, a substantial amount of a reductive elimination product is obtained as a by-product. (3) There is a solvent effect in the organocyanocopper·BF_3-mediated reaction.[38] Tetrahydrofuran (THF) or mixed solvents involving THF [e.g., THF:Et_2O (ca. 10:2) or THF:*n*-hexane (ca. 10:2)] is the solvent of choice since reaction in Et_2O, a poorer Lewis base than THF,[39] is rather slow to undergo the desired reaction with MeCu(CN)Li·BF_3 (LiBr).

Compared with the usual 1,4-addition reaction of organocopper reagents to α,β-unsaturated carbonyl compounds,[40] the present reaction of γ-mesyloxy α,β-enoates

Scheme XI



Scheme XII



with organocyanocopper·BF_3 reagents in THF or mixed solvents involving THF was significantly faster and usually attained completion in short periods of reaction time, even at −78 °C.

As illustrated in Table I, except for the serine- and threonine-derived substrates **77** and **81** (entries 25, 27, and 29), these results exhibit both high levels of diastereoselectivity and an impressive degree of generality. The purity of all synthesized protected (*E*)-alkene isosteres shown in Table I was determined by capillary gas chromatography (0.2 mm × 50 m) and/or 200-, 300-, or 400-MHz ^{1}H NMR spectroscopy. At the outset of this work, we had not completely eliminated the possiblity that the racemization at the α position to the ester group was introduced during the preparation of the isostere. However, the reaction conditions used did not cause any isomerization. This was demonstrated by subjecting pure **53** to the organocyanocopper·BF_3 treatment at −78 °C for 1 h. No sign of isomerization was detected by ^{1}H NMR and capillary GC. Homochiral α-alkyl (*E*)-β,γ-enoates are usually configurationally stable up to at least 140 °C (1 mmHg). Consequently, the protected isostere **53** could be Kügelrohr distilled without any racemization.

In addition, the following points should be clearly noted: (1) the presence of a HNBoc group at the δ position in the substrates (**52**, **57**, **61**, **66**, **70**, and **73**; Table I, entries 1–23) does not exert any influence on the course of the anti S_N2' reaction; (2) although synthesis of isosteres involving either a secondary or tertiary group at the α position by the base-catalyzed alkylation was rather difficult,[7b] excellent results were obtained by the reaction of γ-mesyloxy α,β-enoates with *i*-PrCu(CN)MgCl·BF_3, *t*-BuCu(CN)Li·BF_3, or *t*-BuCu(CN)MgCl·BF_3 (Table I, entries 2, 8, 11–13, 15, and 23); and (3) for reasons unclear at present, although serine- and threonine-derived anti substrates **83** and **87** usually gave satisfactory results (Table I, entries 30–36), the syn substrates **77** and **81** gave the α-alkylation products with low diastereoselectivity in low chemical yields by treatment with MeCu(CN)MgBr·BF_3 (Table I, entries 25, 27, and 29).[41] However, this drawback could be com-

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Table I. Isolated Chemical Yields and Diastereoselectivity in the Reaction of δ-Aminated γ-Oxygenated (*E*)-α,β-Enoates with Organocopper Reagents

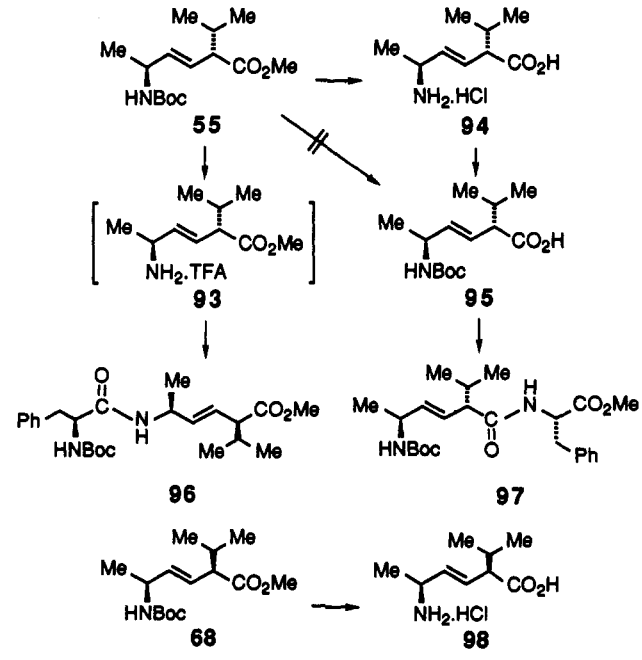
entry	substr	reagent	product (chem yield, %)	diastereoselectivity[a] (abs confgn at C-2)	$[\alpha]_D$, deg cm^2 g^{-1} (in $CHCl_3$)
1	52	MeCu(CN)Li·BF_3[b]	53 (93)	99:1 (*S*)	+2.74
2	52	*i*-PrCu(CN)MgCl·BF_3	55 (85)	99:1 (*S*)	+21.5
3	52	$PhCH_2$Cu(CN)MgCl·BF_3	56 (80)	99:1 (*S*)	+20.5
4	57	MeCu(CN)Li·BF_3[b]	58 (92)	99:1 (*S*)	+33.7
5	57	MeCu(CN)MgBr·BF_3	58 (93)	99:1 (*S*)	+34.2
6	57	*i*-BuCu(CN)Li·BF_3	59 (93)	99:1 (*S*)	+44.1
7	57	*i*-BuCu(CN)MgCl·BF_3	59 (94)	99:1 (*S*)	+44.2
8	57	*i*-PrCu(CN)MgCl·BF_3	60 (95)	99:1 (*S*)	+35.3
9	61	MeCu(CN)Li·BF_3[b]	62 (96)	99:1 (*S*)	+36.4
10	61	*i*-BuCu(CN)Li·BF_3	63 (97)	99:1 (*S*)	+49.6
11	61	*i*-PrCu(CN)MgCl·BF_3	64 (96)	99:1 (*S*)	+43.4
12	61	*t*-BuCu(CN)Li·BF_3	65 (89)	99:1 (*R*)	+34.3
13	61	*t*-BuCu(CN)MgCl·BF_3	65 (86)	99:1 (*R*)	+34.2
14	66	MeCu(CN)Li·BF_3[b]	67 (90)	99:1 (*R*)	−64.0
15	66	*i*-PrCu(CN)MgCl·BF_3	68 (90)	99:1 (*R*)	−88.5
16	66	$PhCH_2$Cu(CN)MgCl·BF_3	69 (81)	99:1 (*R*)	−87.6
17	70	MeCu(CN)Li·BF_3[b]	71 (91)	97:3 (*R*)	−17.1
18	70	MeCu(CN)MgBr·BF_3	71 (92)	97:3 (*R*)	−16.8
19	70	*i*-BuCu(CN)Li·BF_3	72 (94)	97:3 (*R*)	−39.8
20	70	*i*-BuCu(CN)MgCl·BF_3	72 (93)	97:3 (*R*)	−39.8
21	73	MeCu(CN)Li·BF_3[b]	74 (98)	99:1 (*R*)	−18.5
22	73	*i*-BuCu(CN)Li·BF_3	75 (96)	99:1 (*R*)	−42.6
23	73	*i*-PrCu(CN)MgCl·BF_3	76 (98)	99:1 (*R*)	−33.5
24	77	MeCu(CN)Li·BF_3[b]	78 (94)	97:3 (*S*)	+27.1
25	77	MeCu(CN)MgBr·BF_3	78 (54)[c]	54:46 (*S*)	*g*
26	77	*i*-BuCu(CN)Li·BF_3	79 (97)	97:3 (*S*)	+40.3[h]
27	77	$PhCH_2$Cu(CN)Li·BF_3	80 (73)	85:15 (*S*)	+29.8[h]
28	81	MeCu(CN)Li·BF_3[b]	82 (66)	99:1 (*S*)	+29.5
29	81	MeCu(CN)MgBr·BF_3	82 (52)[d]	80:20 (*S*)	*g*
30	83	MeCu(CN)Li·BF_3[b]	84 (98)	99:1 (*R*)	−31.6
31	83	MeCu(CN)MgBr·BF_3	84 (93)[e]	99:1 (*R*)	*g*
32	83	*i*-BuCu(CN)Li·BF_3	85 (97)	99:1 (*R*)	−62.1
33	83	*i*-BuCu(CN)MgCl·BF_3	85 (98)	99:1 (*R*)	−61.2
34	83	$PhCH_2$Cu(CN)Li·BF_3	86 (97)	99:1 (*R*)	−73.5
35	87	MeCu(CN)Li·BF_3[b]	88 (79)	99:1 (*R*)	−26.7
36	87	MeCu(CN)MgBr·BF_3	88 (90)	99:1 (*R*)	*g*
37	87	MeCu(CN)MgBr	88 (23)[f]	99:1 (*R*)	*g*

[a] Determined by capillary gas chromatography (0.20 mm × 50 m) and/or 200-, 300-, or 400-MHz ^{1}H NMR spectyroscopy. [b] Prepared from ethereal MeLi (as complexed with LiBr). Substrate 81 and 87 gave comparable results by treatment with MeCu(CN)Li·BF_3 prepared from ethereal MeLi as the LiI complex as for the entries 28 and 35. [c] Obtained along with ca. 46% of reductive elimination product. [d] Obtained along with ca. 32% of reductive elimination product. [e] Obtained along with ca. 5.5% of reductive elimination product. [f] Obtained along with ca. 72% of reductive elimination product. [g] Not determined. [h] Value of the isolated pure major diastereomer (purity >99%).

pensated by the use of the HNBoc substrates such as **57** and **70** (Table I, entries 5 and 18).

The absolute configuration of the α position, although clear from the reaction course of the *anti*-S_N2' attack of organocopper reagents[42] and from the *E* geometry of the β,γ double bond of the products, could be determined by chemical degradation (Scheme XI). For example, the protected isostere **53** was treated with DIBAL followed by sodium hydride and benzyl bromide in DMF to yield the benzyl ether **89** in 67% yield. Ozonolysis of the benzyl ether **89** followed by reduction with DIBAL at −78 °C gave the known alcohol **91**[43] in 57% yield. The above reaction sequence was also performed by starting from the protected isostere **84**, leading to the known alcohol **92**[43] via

Scheme XIII



the benzyl ether **90** (see Experimental Section). A similar chemical method for the determination of the absolute

(41) As a possible mechanistic explanation for an atypical *syn*-S_N2' addition of RCu(CN)MgX·BF_3 to the syn substrates **77** and **81**, one of the reviewers kindly suggested that the alkylmagnesio cuprate(s) might be directed to the α position of the γ-mesyloxy α,β-unsaturated esters via a seven-membered-ring chelated transition state involving the sulfoxide oxygen atom, the nitrogen atom of the Boc group, and the magnesium atom.

(42) For a *syn*-S_N2' reaction with organocopper reagents, see: Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1987**, *52*, 1106. See also: Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.

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configuration has recently been reported by Kishi[43a] and Marshall.[43b,c]

More conveniently, the absolute configuration of the alkylated carbon center in (E)-alkene isosteres can be determined by a circular dichroism measurement[44] (Scheme XII and Figure 1). Whereas compounds with a partial structure (C) show a negative n → π* Cotton effect around 220 nm, compounds with a partial structure (D) exhibit a positive n → π* Cotton effect near 220 nm as exemplified in Figure 1 (for structures **54**, **68**, **94**, **96**, and **98**, see Scheme XIII). Thus, given the sign of the n → π* Cotton effect, one can determine the absolute configuration at the α position in the (E)-alkene isosteres. The presence of aminated group at the δ position does not exert any influence on the sign of n → π* Cotton effect.

For the synthesis of pseudopolypeptides, it is necessary to substitute a transition-state mimic (E)-alkene dipeptide isostere for a natural dipeptide segment in the interior position or at either the amino or carboxylic acid terminus of polypeptides.

After removal of the Boc protecting group from **55** by treatment with trifluoroacetic acid (TFA), the TFA salt of **93** was neutralized with 5% $NaHCO_3$ and extracted with CH_2Cl_2. The compound **93** in CH_2Cl_2 was coupled with (S)-Boc-phenylalanine and DCC to yield the protected pseudotripeptide **96**.

With the intension of preparing the Boc-Ala-ψ[(E)-CH=CH]-D-Val (**95**), the protected isostere **55** was treated with 1 N NaOH under the usual conditions used in peptide chemistry. However, the reaction is quite slow and the prolonged reaction at room temperature gave an inseparable mixture of products. On the other hand, treatment of **55** with 3 N HCl under reflux yielded the amino acid hydrochloride **94** in 78.4% isolated yield. The reaction condition did not cause any isomerization. The optical purity (>99%) of **94** was easily demonstrated by its HPLC and ^1H NMR data, which were distinctively different from those of the diastereomer **98** derived from **68** using the same reaction conditions. The amino group **94** was protected in the usual way to yield **95**, which was transformed into the pseudotripeptide **97** by reaction with DCC followed by (S)-phenylalanine methyl ester in the presence of 1-hydroxybenzotriazole (HOBt). Thus, it is apparent from this result that all protected dipeptide isosteres could be used for the coupling with amino acid derivatives at both amino and carboxylic acid termini.

In summary, the described methodology involving the organocyanocopper·BF_3-mediated reaction clearly has several advantages over the other method in terms of mildness, selectivity, efficiency, and convenience. This strategy also allows flexibility in introducing substituents, including sterically hindered groups such as isopropyl and *tert*-butyl groups at the α position to the ester group merely by the change of organocyanocopper·BF_3 reagent. The dipeptide mimics are available in both stereoisomeric forms with defined stereochemistry by the choice of starting syn or anti amino alcohol. The absolute configuration at the α position of synthesized dipeptide isosteres could be determined by either chemical degradation or circular dichroism measurement. This methodology provides a new efficient route to a wide range of modified peptide mimics that may have biological significance.

Experimental Section

General Methods. All reactions were carried out under a positive pressure of argon. All glassware and syringes were dried in an electric oven at 110 °C prior to use. Ethereal MeLi (as complex with LiBr) was purchased from Aldrich. *i*-PrMgCl and *i*-BuLi were prepared by reaction of isopropyl chloride with magnesium and isobutyl chloride with metallic Li, respectively, in the usual way. *t*-BuLi and *t*-BuMgCl were purchased from Kanto Chemicals. CuCN was obtained from Mitsuwa Chemicals and dried in an Abderhalden under vacuum at 50 °C. All melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Infrared spectra were obtained on a Shimadzu Model IR-400 spectrometer. Nominal and exact mass spectra were recorded on a JEOL JMS-01SG-2 mass spectrometer. The ^1H spectra were recorded on a JEOL FX-200 (200 MHz for ^1H), Varian XL 300 (300 MHz for ^1H), and/or a Bruker AM-400 (400 MHz for ^1H) spectrometer. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet). Optical rotations were meaured with a JASCO DIP-360 digital polarimeter. Circular dichroism spectra were measured with a JASCO J-500A spectrometer at 25–30 °C. 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.

(2*S*,3*S*)-2-Amino-*N*-[(*tert*-butyloxy)carbonyl]-3-hydroxy-4-pentene (11) and Its 2*S*,3*R* Isomer (12). To a stirred solution of 4.06 g (20 mmol) of ester **10** in CH_2Cl_2 (15 mL) at −78 °C under argon was added dropwise 23.5 mL (40 mmol) of a 1.7 M solution of DIBAH in *n*-hexane, and the mixture was stirred for 3 h at −78 °C. The mixture was allowed to warm to −20 °C and stirring was continued for 30 min. The mixture was recooled to −78 °C, where a 2.0 M solution of vinylmagnesium chloride in THF (30 mL, 60 mmol) was added dropwise with stirring. The mixture was allowed to warm to 0 °C and to stir at this temperature for an additional 2 h. The mixture was made acidic with 5% HCl at −30 °C and extracted with Et_2O. The usual workup and flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) gave 2.4 g (60% yield) of a mixture of **11** and **12** as a colorless oil. To the above oil (2.4 g, 11.9 mmol) in a mixture of CH_2Cl_2 (50 mL) and DMF (10 mL) at 0 °C were added imidazole (4.08 g, 60 mmol) and *tert*-butyldimethylsilyl chloride (3.62 g, 24 mmol), and the mixture was stirred for 24 h at room temperature. The usual workup and flash chromatography over silica gel with *n*-hexane–EtOAc (7:1) gave 144 mg (4% yield) of *tert*-butyldimethylsilyl ether **14** and further elution gave 2.208 g (58% yield) of *tert*-butyldimethylsilyl ether **13**. *tert*-Butyldimethylsilyl ether **13**: a colorless oil; Kugelrohr distillation, 130 °C (1 mm Hg); $[\alpha]^{20}_D$ −31.9° (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3440, 2970, 2950, 2880, 1702. 1498, 1370, 1254, 1166, 1102, 1056, 1028, 1007, 996, 931, 889, 859, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.07 (s, 3 H), 0.91 (s, 9 H), 1.11 (d, J = 6.59 Hz, 3 H), 1.44 (s, 9 H), 3.67 (m, 1 H), 4.08 (m, 1 H), 4.58 (m, 1 H), 5.18 (m, 2 H), 5.18 (m, 2 H), 5.82 (ddd, J = 17.33, 10.50, 6.10 Hz, 1 H). Anal. Calcd for $C_{16}H_{33}NO_3Si$: C, 60.90; H, 10.54; N, 4.44. Found: C, 61.11; H, 10.64; N, 4.56. *tert*-Butyldimethylsilyl ether **14**: a colorless oil; Kugelrohr distillation, 130 °C (1 mmHg); $[\alpha]^{20}_D$ −18.35° (*c* 0.719, $CHCl_3$); IR ($CHCl_3$) 3440, 2970, 2950, 2880, 1702, 1498, 1370, 1254, 1166, 1102, 1056, 1028, 1007, 996, 931, 889, 859, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.02 (s, 3 H), 0.05 (s, 3 H), 0.92 (s, 9 H), 1.02 (d, J = 6.82 Hz, 3 H), 1.44 (s, 9 H), 3.66 (m, 1H), 4.27 (m, 1 H), 4.55 (m, 1 H), 5.20 (m, 2 H), 5.78 (ddd, J = 17.34, 10.50, 5.73 Hz, 1 H). Anal. Calcd for $C_{16}H_{33}NO_3Si$: C, 60.90; H, 10.54; N, 4.44. Found: C, 61.13; H, 10.76; N, 4.41.

To a stirred solution of silyl ether **13** (3 g, 9.5 mmol) in 15 mL of CH_3CN was added dropwise 10 mL of 46% HF at −20 °C, and the mixture was stirred for 1.25 h with warming to 0 °C. The mixture was made alkaline with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was successively washed

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with 5% $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil, which was flash chromatographed over silica gel with *n*-hexane–EtOAc (3:1) to yield **11** (1.91 g, 94% yield) as a colorless oil: $[\alpha]^{25}_D$ −41.58° (*c* 1.41, $CHCl_3$); IR ($CHCl_3$) 3450, 2980, 2950, 2860, 1695, 1504, 1458, 1398, 1374, 1340, 1245, 1165, 1100, 1052, 1028, 998, 985, 937, 875, 850, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.84 Hz, 3 H), 1.44 (s, 9 H), 2.72 (m, 1 H), 3.69 (m, 1 H), 4.02 (m, 1 H), 5.17–5.35 (m, 2 H), 5.88 (ddd, *J* = 17.21, 10.37, 5.98 Hz, 1 H). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.41; H 9.73; N, 7.02. The optical purity (>98% de) of **11** was demonstrated by conversion of **11** to the Mosher ester and analysis by ^1H NMR ($CDCl_3$) and HPLC (column, μ-Bondashere, 5-μm, SiO_2; eluent, 5% THF–*n*-hexane). To a stirred solution of vinyl alcohol **11** (25 mg, 0.124 mmol) in $CHCl_3$ (4 mL) were added successively pyridine (0.5 mL), 4-(dimethylamino)pyridine (5 mg), and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (102 mg, 0.404 mmol) at room temperature. The mixture was stirred for 16 h at ambient temperature. To the stirred mixture was added 5 mL of saturated $NaHCO_3$ at −20 °C followed by stirring for 30 min at 0 °C. The mixture was extracted with Et_2O, and the extract was washed successively with saturated citric acid, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to yield 44 mg (85% yield) of the Mosher ester of **11** as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.84 Hz, 3 H), 1.42 (s, 9 H), 3.54 (m, 3 H), 3.95 (br s, 1 H), 4.42 (m, 1 H), 5.39 (m, 2 H), 5.49 (m, 1 H), 5.85 (ddd, *J* = 17.33, 10.5, 7.08 Hz, 1 H), 7.35–7.55 (m, 5 H).

By a procedure identical with that described for the preparation of **11** from its *tert*-butyldimethylsilyl ether **13**, 2.5 g (7.92 mmol) of *tert*-butyldimethylsilyl ether **14** was converted into 1.14 g (72% yield) of the title compound **12**: mp 54–57 °C (*n*-hexane); $[\alpha]^{25}_D$ −14.49° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3450, 3010, 2960, 1695, 1502, 1459, 1399, 1373, 1164, 1110, 1084, 1052, 1032, 994, 935, 877, 840 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.84 Hz, 3 H), 1.45 (s, 9 H), 3.83 (m, 1 H), 4.20 (m, 1 H), 4.66 (m, 1 H), 5.21–5.38 (m, 2 H), 5.86 (ddd, *J* = 16.84, 10.25, 5.98 Hz, 1 H). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.40; H, 9.49; N, 6.93. The optical purity (>98% de) of the Mosher ester of **12** was easily demonstrated by its ^1H NMR ($CDCl_3$) and HPLC (column, μ-Bondashere, 5-μm SiO_2; eluent, 5% THF–*n*-hexane). To a stirred solution of vinyl alcohol **12** (14 mg, 0.070 mmol) in $CHCl_3$ (2 mL) were added successively pyridine (1 mL), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)acetyl chloride (100 mg, 0.396 mmol), and 4-(dimethylamino)pyridine (2 mg) at room temperature, and the mixture was stirred for 12 h at 0 °C. Saturated $NaHCO_3$ (5 mL) was added dropwise to the above mixture at 0 °C with stirring, and stirring was continued for 30 min at room temperature. The mixture was extracted with Et_2O, and the extract was washed successively with water, saturated citric acid, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–AcOEt (4:1) to yield 24 mg (83% yield) of the Mosher ester of **12** as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (d, *J* = 7.08 Hz, 3 H), 1.45 (s, 9 H), 3.53 (s, 3 H), 3.91 (br s, 1 H), 4.39 (m, 1 H), 5.31 (m, 2 H), 5.60 (m, 1 H), 5.75 (ddd, *J* = 16.91, 10.51, 6.11 Hz, 1 H), 7.35–7.58 (m, 5 H).

(4*S*,5*S*)-4-Methyl-5-vinyl-2-oxazolone (15). To a stirred suspension of 60 mg of sodium hydride in 1 mL of DMF at 0 °C was added 150 mg (0.75 mmol) of alcohol **11** in 1 mL of DMF. The stirring was continued for 16 h at 0 °C, followed by quenching with 3 mL of 5% NH_4Cl. The mixture was extracted with Et_2O and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give 75 mg (79% yield) of the title compound **15** as a colorless oil: Kugelrohr distillation, 140 °C (1 mmHg); $[\alpha]^{26}_D$ −45.6° (*c* 0.899, $CHCl_3$); IR ($CHCl_3$) 3450, 3250, 2990, 1750, 1385, 1323, 1304, 1285, 1232, 1208, 1127, 1090, 1018, 986, 938 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.1 Hz, 3 H), 3.67 (m, 1 H), 4.48 (tt, *J* = 7.1, 0.98 Hz, 1 H), 5.30–5.47 (m, 2 H), 5.90 (ddd, *J* = 17.09, 10.26, 6.84 Hz, 1 H). Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.44; H, 7.38; N, 10.88.

(5*R*,4*S*)-4-Methyl-5-vinyl-2-oxazolone (16). By a procedure identical with that described for the preparation of **15** from **11**, 150 mg (0.75 mmol) of alcohol **12** was converted into 88.6 mg (93% yield) of the title compound **16** as colorless crystals (*n*-hexane): mp 61 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.59 Hz, 3 H), 4.03 (m, 1 H), 5.04 (ddt, *J* = 8.06, 6.83, 1.22 Hz, 1 H), 5.35–5.51 (m, 2 H), 5.87 (ddd, *J* = 17.09, 10.25, 6.84 Hz, 1 H). Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.67; H, 7.29; N, 10.96.

(2*S*,3*S*)-3-Acetoxy-2-amino-*N*-[(*tert*-butyloxy)carbonyl]-4-pentene (17). To a stirred solution of alcohol **11** (3.59 g, 17.9 mmol) in a mixture of pyridine (7 mL), 4-(dimethylamino)pyridine (50 mg), and CH_2Cl_2 (20 mL) was added 7 mL of acetic anhydride at 0 °C. The solution was allowed to stand at 25 °C for 48 h. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) gave 4.21 g (97% yield) of acetate **17** as a colorless oil: Kugelrohr distillation, 115 °C (1 mmHg); $[\alpha]^{20}_D$ −47.3° (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 3455, 2980, 2950, 1733, 1710, 1505, 1453, 1372, 1162, 1053, 1024, 988, 942, 907, 852 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.84 Hz, 3 H), 1.44 (s, 9 H), 2.10 (s, 3 H), 3.91 (br s, 1 H), 4.55 (br s, 1 H), 5.19–5.33 (m, 3 H), 5.80 (ddd, *J* = 17.09, 10.25, 6.59 Hz, 1 H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.25; H, 8.96; N, 5.65.

Methyl (4*S*,5*S*,2*E*)-5-Amino-*N*-[(*tert*-butyloxy)carbonyl]-4-hydroxy-2-hexenoate (19). To a solution of 4.02 g (20 mmol) of acetate **17** in 30 mL of CH_2Cl_2 was bubbled ozone at −78 °C until a blue color persisted. The solution was warmed to 0 °C and stirred for 10 min. To the above solution were added 5.24 g (20 mmol) of PPh_3 and 13.36 g (40 mmol) of (carbomethoxymethylene)triphenylphosphorane at −78 °C, and the mixture was stirred for 2 h at 0 °C. The mixture was concentrated under reduced pressure to an oil, which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (3:1) gave 4.6 g of a colorless oil. Powdered Na_2CO_3 (8.1 g) was added to a solution of 4.6 g of the above oil in 38 mL of MeOH under stirring at room temperature and the mixture was stirred for 18 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to leave a slightly yellow oil, which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (3:1) gave 1.75 g (34% yield) of the title compound **19** as a colorless oil: $[\alpha]^{30}_D$ −54.5° (*c* 0.955, $CHCl_3$): IR ($CHCl_3$) 3450, 2980, 2960, 1709, 1504, 1453, 1440, 1397, 1372, 1316, 1163, 1052, 983, 931, 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.84 Hz, 3 H), 1.43 (s, 9 H), 3.74 (s, 3 H), 4.26 (td, *J* = 4.67, 1.51 Hz, 1 H), 4.68 (m, 1 H), 6.13 (dd, *J* = 15.7, 1.65 Hz, 1 H), 6.95 (dd, *J* = 15.7, 4.70 Hz, 1 H); nominal mass spectrum, *m/z* 260 (MH^+), 244, 204, 186, 172, 144, 116, 88, 57, 44 (base peak); exact mass, *m/z* calcd for $C_{12}H_{21}NO_5H^+$ 260,1498, found 260.1499.

Methyl (4*S*,5*S*,2*E*)-5-Amino-*N*-[(*tert*-butyloxy)carbonyl]-4-hydroxy-6-phenyl-2-hexanoate (23). To a stirred solution of 160 mg (0.5 mmol) of carboxylic acid **21** in 5 mL of MeOH was added a solution of ethereal diazomethane at 0 °C until a yellow color persisted. Excess diazomethane was decomposed with acetic acid, and the mixture was extracted with Et_2O. The extract was washed successively with 5% $NaHCO_3$ and water and dried over $MgSO_4$. Concentration under reduced pressure gave a crystallne residue, which was flash chromatographed on a silica gel column with *n*-hexane–EtOAc (5:1) to yield 162 mg (97% yield) of hydroxy ester **23** as colorless silky needles from *n*-hexane–Et_2O (1:1): mp 118–119 °C; $[\alpha]^{20}_D$ −65.3° (*c* 1.56, $CHCl_3$); IR ($CHCl_3$) 3450, 3000, 1712, 1499, 1456, 1439, 1396, 1370, 1311, 1286, 1250, 1169, 984 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 9 H), 2.95 (d, *J* = 7.52 Hz, 2 H), 3.72 (s, 3 H), 3.82 (m, 1 H), 4.31 (m, 1 H), 4.84 (d, *J* = 8.55 Hz, 1 H), 6.10 (dd, *J* = 15.65, 1.79 Hz, 1 H), 6.94 (dd, *J* = 15.65, 4.23 Hz, 1 H), 7.18–7.35 (m, 5 H). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.22; H, 7.67; N, 4.20.

Methyl (2*S*)-2-Amino-*N*-[(*tert*-butyloxy)carbonyl]-3-(*tert*-butyldimethylsiloxy)propionate (26). *tert*-Butyldimethylsilyl chloride (13.1 g, 86.7 mmol) was added portionwise to a stirred solution of 19 g (86.7 mmol) of methyl (2*S*)-*N*-[(*tert*-butyloxy)carbonyl]-2-amino-3-hydroxypropionate (**25**) in a mixture of 100 mL of CH_2Cl_2 and 11.8 g (173.4 mmol) of imidazole at 0 °C, and the mixture was stirred for 48 h. The usual

workup led to a colorless oil, which was flash chromatographed over a silica gel column. Elution with *n*-hexane–EtOAc (3:1) gave 20.2 g (70% yield) of silyl ether **26** as a colorless oil: Kugelrohr distillation, 125 °C (1 mmHg); $[\alpha]^{20}_D$ +21.6° (*c* 1.39, $CHCl_3$); IR ($CHCl_3$) 3450, 2980, 2960, 2890, 1750, 1710, 1500, 1445, 1377, 1358, 1301, 1260, 1168, 1104, 1073, 841 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 1.45 (s, 9 H), 3.74 (s, 3 H), 3.81 (dd, *J* = 10.01, 2.93 Hz, 1 H), 4.04 (dd, *J* = 10.01, 2.44 Hz, 1 H), 4.35 (m, 1 H), 5.34 (d, *J* = 7.08 Hz, 1 H). Anal. Calcd for $C_{15}H_{31}NO_5Si$: C, 54.02; H, 9.37. Found: C, 53.88; H, 9.61.

(2*S*,3*S*)-2-Amino-1-(*tert*-butyldimethylsiloxy)-*N*-[(*tert*-butyloxy)carbonyl]-3-hydroxy-4-pentene (27) and Its 3*R*,2*S* Isomer (28). To a solution of 3.33 g (10 mmol) of ester **26** in a mixture of 15 mL of CH_2Cl_2 and 15 mL of toluene at −78 °C was added dropwise 11.8 mL (20 mmol) of a 1.7 M solution of DIBAH in *n*-hexane, and the mixture was stirred for 3 h at −78 °C. The mixture was allowed to warm to −20 °C and stirring was continued for 30 min. The mixture was recooled to −78 °C, where a 1.0 M solution of vinylmagnesium bromide (20 mL, 20 mmol) in THF was added dropwise with stirring. The mixture was stirred for 2 h with warming to −20 °C, and then the reaction was quenched with 15 mL of a saturated NH_4Cl solution with vigorous stirring. The usual workup and flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) gave 1.45 g (43% yield) of 2*S*,3*S* isomer **27**, and further elution gave 0.503 g (15% yield) of 3*R*,2*S* isomer **28**. **27**: a colorless oil; Kugelrohr distillation, 135 °C (1 mmHg); $[\alpha]^{25}_D$ +7.97° (*c* 0.979, $CHCl_3$); IR ($CHCl_3$) 3450, 2980, 2960, 2780, 1704, 1496, 1396, 1372, 1259, 1168, 1102, 1081, 936, 840 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 6 H), 0.91 (s, 9 H), 1.44 (s, 9 H), 3.61 (m, 1 H), 3.70–3.90 (m, 2 H), 4.46 (m, 1 H), 5.17 (m, 1 H), 5.19 (dt, *J* = 10.50, 1.46 Hz, 1 H), 5.34 (dt, *J* = 17.09, 1.46 Hz, 1 H), 5.86 (ddd, *J* = 17.09, 10.50, 5.38 Hz, 1 H). Anal. Calcd for $C_{16}H_{33}NO_4Si$: C, 57.97; H, 10.03; N, 4.22. Found: C, 58.09; H, 10.21; N, 4.20. **28**: a colorless oil; Kugelrohr distillation, 135 °C (1 mmHg); $[\alpha]^{25}_D$ +29.3° (*c* 1.173, $CHCl_3$); IR ($CHCl_3$) 3450, 2980, 2960, 2780, 1704, 1492, 1396, 1372, 1259, 1168, 1096, 1074, 936, 843 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.068 (s, 3 H), 0.073 (s, 3 H), 0.90 (s, 9 H), 1.45 (s, 9 H), 3.61 (m, 1 H), 3.74 (dd, *J* = 10.25, 2.93 Hz, 1 H), 3.93 (dd, *J* = 10.50, 2.93 Hz, 1 H), 4.27 (m, 1 H), 5.24 (dt, *J* = 10.50, 1.46 Hz, 1 H), 5.27 (m, 1 H), 5.38 (dt, *J* = 17.09, 1.71 Hz, 1 H), 5.93 (ddd, *J* = 17.09, 10.75, 4.88 Hz, 1 H). Anal. Calcd for $C_{16}H_{33}NO_4Si$: C, 57.97; H, 10.03; N, 4.22. Found: C, 58.05; H, 10.36; N, 4.29.

(2*S*,3*S*)-3-Acetoxy-2-amino-1-(*tert*-butyldimethylsiloxy)-*N*-[(*tert*-butyloxy)carbonyl]-4-pentene (29). To a stirred solution of 600 mg (1.81 mmol) of alcohol **27** in a mixture of 4 mL of pyridine, 10 mg of 4-(dimethylamino)pyridine, and 5 mL of CH_2Cl_2 at 0 °C was added 2 mL of acetic anhydride. The mixture was stirred for 2 h with warming to room temperature. The usual workup and flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) gave 661 mg (98% yield) of acetate **29** as a colorless oil: Kugelrohr distillation, 150 °C (1 mmHg); $[\alpha]^{30}_D$ +0.2° (*c* 0.996, $CHCl_3$); IR ($CHCl_3$) 3450, 2970, 2940, 2860, 1735, 1709, 1492, 1370, 1161, 1108, 1021, 939, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.89 (s, 9 H), 1.44 (s, 9 H), 2.07 (s, 3 H), 3.54 (dd, *J* = 10.25, 6.10 Hz, 1 H), 3.68 (dd, *J* = 10.25, 3.91 Hz, 1 H), 3.83 (m, 1 H), 4.78 (d, *J* = 9.76 Hz, 1 H), 5.25 (dt, *J* = 10.3, 1.46 Hz, 1 H), 5.30 (dt, *J* = 17.09, 1.46 Hz, 1 H), 5.49 (t, *J* = 6.26 Hz, 1 H), 5.82 (ddd, *J* = 17.09, 10.50, 6.35 Hz, 1 H). Anal. Calcd for $C_{18}H_{35}NO_5Si$: C, 57.87; H, 9.45; N, 3.75. Found: C, 58.16; H, 9.75; N, 3.99.

(2*S*,3*S*)-2-Amino-*N*-[(*tert*-butyloxy)carbonyl]-1,3-dihydroxy-1,2-*O*,*N*-isopropylidene-4-pentene (32) and Its 2*S*,3*R* Isomer (33). To a stirred solution of 11.45 g (50 mmol) of aldehyde **31** in 30 mL of THF at −78 °C was added by syringe 27.5 mL (55 mmol) of 2 M vinylmagnesium chloride in THF, and the mixture was allowed to warm to −40 °C and to stir at this temperature for 1 h. The excess reagent was decomposed with 5 mL of a 5% NH_4Cl solution at −20 °C. The mixture was extracted with Et_2O, and the extract was washed successively with 5% HCl, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless residue, which was flash chromatographed over silica gel with *n*-hexane–EtOAc (4:1) to yield, in order of elution, 7.3 g (56.8% yield) of **33** and 1.38 g (10.7% yield) of **32**. **32**: colorless crystals from *n*-hexane; mp 82–83 °C; $[\alpha]^{20}_D$ −51.1° (*c* 0.76, $CHCl_3$); ^1H NMR (200 MHz, d_6-DMSO) δ 1.35 (s, 3 H), 1.42 (s, 9 H), 1.44 (s, 3 H), 3.83–3.97 (m, 3 H), 4.34 (br s, 1 H), 5.06–5.22 (m, 3 H), 5.82 (ddd, *J* = 16.84, 10.25, 6.34 Hz, 1 H). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.41; H, 9.17; N, 5.50. **33**: colorless oil, Kugelrohr distillation, 120 °C (1 mmHg); $[\alpha]^{20}_D$ −11.6° (*c* 0.80, $CHCl_3$); ^1H NMR (200 MHz, d_6-DMSO) δ 1.40 (s, 12 H), 1.47 (s, 3 H), 3.60–4.13 (m, 4 H), 4.95–5.20 (m, 2 H), 5.15 (ddd, *J* = 16.84, 1.95, 1.50 Hz, 1 H), 5.81 (ddd, *J* = 16.84, 10.25, 6.1 Hz, 1 H); nominal mass spectrum, *m*/*z* 257 (M^+), 242, 200, 184, 144, 100, 83, 57 (base peak); exact mass, *m*/*z* calcd for $C_{13}H_{23}NO_4$ 257.1626, found 257.1621. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.39; H, 8.12; N, 5.38.

(2*S*,3*S*)-3-Acetoxy-2-amino-*N*-[(*tert*-butyloxy)carbonyl]-1-hydroxy-1,2-*O*,*N*-isopropylidene-4-pentene (34). To a stirred solution of 950 mg (3.7 mmol) of **32** in a mixture of 10 mL of CH_2Cl_2, 20 mg of 4-(dimethylamino)pyridine, and 3 mL of pyridine was added 1 mL of acetic anhydride, and the mixture was stirred at 0 °C for 18 h. The usual workup and flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) gave 1.095 g (99% yield) of acetate **34** as a colorless oil: Kugelrohr distillation, 130 °C (1 mmHg); $[\alpha]^{25}_D$ −39.6° (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) 2990, 2950, 2910, 1738, 1692, 1481, 1458, 1390, 1382, 1370, 1172, 1102, 1085, 1059, 1048, 1024, 988, 940, 848 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 3 H), 1.50 (s, 9 H), 1.56 (d, *J* = 5.0 Hz, 3 H), 2.07 (s, 3 H), 3.90–4.18 (m, 3 H), 5.28–5.36 (m, 2 H), 5.64 (m, 1 H), 5.77–5.92 (m, 1 H). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.88; H, 8.51; N, 4.73.

Methyl (4*S*,5*S*,2*E*)-5-Amino-6-(*tert*-butyldimethylsiloxy)-*N*-[(*tert*-butyloxy)carbonyl-4-hydroxy-2-hexenoate (36). To a solution of 1.3 g (3.5 mmol) of acetate **29** in 15 mL of CH_2Cl_2 was bubbled ozone at −78 °C until a blue color persisted. The solution was allowed to warm to 0 °C and stirring was continued for 10 min. To the above solution at −78 °C were added 1 g (0.41 mmol) of PPh_3 and 3 g (8.98 mmol) of (carbomethoxymethylene)triphenylphosphorane, and the mixture was stirred for 2 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 (3:1) gave 1.5 g of a colorless oil. Powdered Na_2CO_3 (3 g) was added to a stirred solution of 1.5 g of the above oil in 30 mL of MeOH at room temperature and the mixture was stirred for 20 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to leave a slightly yellow oil, which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (3:1) gave 740 mg (55% yield) of the title compound **36** as a colorless oil: $[\alpha]^{30}_D$ −3.8° (*c* 0.628, $CHCl_3$); IR ($CHCl_3$) 3450, 2980, 2960, 2880, 1725, 1711, 1498, 1442, 1372, 1263, 1171, 1101, 986, 843 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 6 H), 0.91 (s, 9 H), 1.42 (s, 9 H), 3.66–3.70 (m, 2 H), 3.74 (s, 3 H), 3.89 (m, 2 H), 4.66 (m, 1 H), 5.07 (d, *J* = 8.06 Hz, 1 H), 6.14 (dd, *J* = 15.62, 1.71 Hz, 1 H), 6.91 (dd, *J* = 15.62, 3.91 Hz, 1 H); nominal mass spectrum, *m*/*z* 390 (MH^+), 389 (M^+), 316, 276, 218, 174, 158, 140, 116, 96, 73, 57; exact mass, *m*/*z* calcd for $C_{18}H_{35}NO_6Si$ 389.2233, found 389.2220.

(2*R*,3*R*,4*S*)-3-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2,4-dihydroxy-2,3-*O*,*N*-isopropylidene-5-hexene (41) and Its 2*R*,3*R*,4*R* Isomer (42). To a stirred solution of 2 g (8.23 mmol) of (*S*)-Boc-threoninal acetonide (**40**) in 10 mL of THF at −78 °C was added dropwise 6.86 mL (16.5 mmol) of a 2.4 M solution of vinylmagnesium chloride in THF. The mixture was stirred for 1 h with warming to 0 °C, and then the reaction was quenched with 10 mL of a saturated NH_4Cl solution with vigorous stirring at −20 °C. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) gave 812 mg (36% yield) of **42** and further elution gave 844 mg (38% yield) of **41**. **41**: colorless oil, Kugelrohr distillation, 160 °C (1 mmHg); ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.35 Hz, 3 H), 1.43 (s, 9 H), 1.44 (s, 3 H), 3.50 (ddd, *J* = 10.49, 1.71, 1.71 Hz, 1 H), 4.08–4.18 (m, 1 H), 4.40–4.49 (m, 1 H), 4.98 (d, *J* = 10.01 Hz, 1 H), 5.17–5.38 (m, 2 H), 5.80 (ddd, *J* = 17.33, 10.49, 4.88 Hz, 1 H). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29; N, 5.16. Found: C, 61.77; H, 9.24; N, 5.17. **42**: colorless oil, Kugelrohr distillation, 160 °C (1 mmHg); ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 3 H), 1.48 (s, 9 H), 1.57 (s, 3 H), 3.60–3.70 (m, 1 H), 3.71–4.06 (m, 2 H), 5.21–5.37 (m, 2 H), 5.82 (ddd, *J* = 17.33, 10.50, 6.35 Hz, 1 H). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29; N, 5.16. Found: C, 61.80; H, 9.45; N, 5.18.

(2*R*,3*S*,4*S*)-3-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2,4-dihydroxy-5-hexene (45). To a stirred solution of 200 mg (0.738 mmol) of **41** in 2 mL of MeOH was added 0.1 mL of 5% HCl, and the mixture was stirred for 1 h. The mixture was made alkaline with a saturated $NaHCO_3$ solution and concentrated under reduced pressure to an oil, which was extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) gave 160 mg (94% yield) of the title compound **45** as a colorless oil: Kugelrohr distillation, 145 °C (1 mmHg); $[\alpha]^{30}_D$ −39.6° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3450, 2990, 2950, 2910, 1704, 1498, 1457, 1397, 1370, 1320, 1300, 1172, 1095, 1064, 994, 936, 896, 862 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.35 Hz, 3 H), 1.44 (s, 9 H), 3.21 (s, 2 H), 3.51 (d, *J* = 8.79 Hz, 1 H), 4.14 (m, 1 H), 4.42 (m, 1 H), 5.15–5.38 (m, 3 H), 5.91 (ddd, *J* = 17.09, 10.49, 5.37 Hz, 1 H); nominal mass spectrum, *m/z* 231 (M^+), 186, 174, 169, 158, 130, 118, 86, 74, 57 (base peak); exact mass, *m/z* calcd for $C_{11}H_{21}NO_4$ 231.1470, found 231.1463.

(2*R*,3*S*,4*S*)-3-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2,4-(isopropylidenedioxy)-5-hexene (46). To a stirred solution of 100 mg (0.433 mmol) of **45** in a mixture of 2 mL of CH_2Cl_2 and 2 mL of 2,2-dimethoxypropane at 0 °C was added 0.05 mL of $BF_3{\cdot}Et_2O$, and the mixture was stirred for 15 min. The mixture was made alkaline with a saturated $NaHCO_3$ solution and extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil, which was flash chromatographed over silica gel with *n*-hexane–EtOAc (3:1) to give 98 mg (84% yield) of the title compound **46** as a colorless oil: Kugelrohr distillation, 140 °C (1 mmHg); $[\alpha]^{30}_D$ −28.1° (*c* 0.762, $CHCl_3$); IR ($CHCl_3$) 3450, 2990, 2950, 2910, 1700, 1495, 1383, 1370, 1352, 1322, 1303, 1262, 1165, 1109, 1077, 1023, 1000, 987, 975, 946, 897, 845 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.35 Hz, 3 H), 1.43 (s, 9 H), 1.44 (s, 3 H), 1.49 (s, 3 H), 3.50 (dt, *J* = 10.25, 1.70 Hz, 1 H), 4.12 (ddd, *J* = 12.70, 6.35, 1.70 Hz, 1 H), 4.46 (ddd, *J* = 4.48, 3.18, 1.70 Hz, 1 H), 4.99 (d, *J* = 10.01 Hz, 1 H), 5.16–5.38 (m, 2 H), 5.80 (ddd, *J* = 17.33, 10.49, 4.88 Hz, 1 H); nominal mass spectrum, *m/z* 271 (M^+), 256, 200, 157, 140, 114, 101, 57 (base peak); exact mass, *m/z* calcd for $C_{14}H_{25}NO_4$ 271.1783, found 271.1779.

(2*R*,4*R*,3*S*)-3-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2,4-dihydroxy-5-hexene (47). By a procedure identical with that described for the synthesis of **45**, 200 mg (0.738 mmol) of **42** was converted into 158 mg (93% yield) of **47** as a colorless oil: Kugelrohr distillation, 160 °C (1 mmHg); $[\alpha]^{30}_D$ −3.18° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3450, 2990, 2950, 2910, 1698, 1498, 1457, 1397, 1370, 1300, 1280, 1168, 1089, 987, 935, 878 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.59 Hz, 3 H), 1.45 (s, 9 H), 3.29 (s, 2 H), 3.45 (m, 1 H), 4.26 (m, 1 H), 4.37 (m, 1 H), 5.22–5.45 (m, 3 H), 5.94 (ddd, *J* = 17.09, 10.5, 5.13 Hz, 1 H); nominal mass spectrum, *m/z* 231 (M^+), 174, 158, 130, 118 113, 101, 86, 73, 57 (base peak); exact mass, *m/z* calcd for $C_{11}H_{21}NO_4$ 231.1470, found 231.1451.

(2*R*,4*R*,3*S*)-3-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2,4-(isopropylidenedioxy)-5-hexene (48). By a procedure identical with that described for the synthesis of **46**, 200 mg (0.866 mmol) of **47** was reacted with 2 mL of 2,2-dimethoxypropane in 2 mL of CH_2Cl_2 in the presence of 0.1 mL of $BF_3{\cdot}Et_2O$ at 0 °C for 10 min. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) gave 25 mg (10.6% yield) of **48** and further elution gave 204 mg (87% yield) of **42**. **48**: colorless oil, Kugelrohr distillation, 140 °C (1 mmHg); $[\alpha]^{30}_D$ +25.0° (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 3450, 2990, 2950, 2910, 1708, 1500, 1457, 1396, 1371, 1328, 1053, 990, 930, 895, 869, 848 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (d, *J* = 7.08 Hz, 3 H), 1.38 (s, 3 H), 1.39 (s, 3 H), 1.44 (s, 9 H), 3.76 (ddd, *J* = 10.25, 6.59, 3.9 Hz, 1 H), 3.94 (dddd, *J* = 6.59, 5.37, 1.47, 1.47 Hz, 1 H), 4.15 (ddd, *J* = 13.18, 6.59, 4.15 Hz, 1 H), 4.83 (d, *J* = 10.26 Hz, 1 H), 5.17–5.38 (m, 2 H), 5.99 (ddd, *J* = 17.33, 10.49, 5.12 Hz, 1 H). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.27; N, 5.16. Found: C, 61.96; H, 9.40; N, 5.11. The ^1H NMR (200 MHz, $CDCl_3$) and IR ($CHCl_3$) spectra of *N,O*-acetonide **42** were identical with authentic spectra of **42**. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.27; N, 5.16. Found: C, 61.69; H, 9.47; N, 5.15.

Methyl (4*S*,5*S*,2*E*)-4-Acetoxy-5-amino-*N*-[(*tert*-butyloxy)carbonyl]-2-hexenoate (51). To a stirred solution of 400 mg (1.54 mmol) of alcohol **19** in a mixture of pyridine (1.87 mL), 4-(dimethylamino)pyridine (19 mg), and CH_2Cl_2 (5 mL) was added 2 mL of acetic anhydride. The mixture was allowed to stand at room temperature for 18 h. The usual workup followed by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) gave a crystalline residue. Recrystallization from *n*-hexane gave 423 mg (91% yield) of acetate **51** as a colorless oil: Kugelrohr distillation, 150 °C (1 mmHg); $[\alpha]^{21}_D$ −41.5° (*c* 0.597, $CHCl_3$); IR ($CHCl_3$) 3450, 1724, 1712, 1503, 1453, 1442, 1372, 1316, 1288, 1165, 1052, 1032, 984 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.84 Hz, 3 H), 1.43 (s, 9 H), 2.14 (s, 3 H), 3.74 (s, 3 H), 4.00 (br s, 1 H), 4.53 (m, 1 H), 5.43 (ddd, *J* = 5.61, 4.15, 1.71 Hz, 1 H), 5.95 (dd, *J* = 15.87, 1.71 Hz, 1 H), 6.87 (dd, *J* = 15.87, 5.13 Hz, 1 H). Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.58; H, 7.97; N, 4.61.

Methyl (4*S*,5*S*,2*E*)-5-Amino-*N*-[(*tert*-butyloxy)carbonyl]-4-[(methylsulfonyl)oxy]-2-hexenoate (52). To a stirred solution of 1.57 g (6.06 mmol) of alcohol **19** in a mixture of 6 mL of pyridine and 10 mL of CH_2Cl_2 at −78 °C was added dropwise 2 mL of methanesulfonyl chloride, and the mixture was stirred for 18 h with warming to 0 °C. The mixture was poured into a cold solution of 25 mL of 5% $NaHCO_3$ and extracted with a mixed solvent of Et_2O–CH_2Cl_2 (4:1). The extract was washed successively with 5% citric acid, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure below 25 °C yielded an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give a crystalline residue. Recrystallization from a mixed solvent of *n*-hexane–Et_2O (1:1) gave 2.025 g (99% yield) the title compound **52** as a colorless oil: $[\alpha]^{18}_D$ −25.3° (*c* 0.978, $CHCl_3$); IR ($CHCl_3$) 3440, 2980, 1715, 1501, 1453, 1440, 1369, 1315, 1285, 1175, 1095, 974, 954, 926 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.97 Hz, 3 H), 1.43 (s, 9 H), 3.08 (s, 3 H), 3.76 (s, 3 H), 4.03 (br s, 1 H), 4.63 (d, *J* = 8.2 Hz, 1 H), 5.22 (ddd, *J* = 5.48, 3.82, 1.44 Hz, 1 H), 6.16 (dd, *J* = 15.71, 1.49 Hz, 1 H), 6.91 (dd, *J* = 15.71, 5.59 Hz, 1 H); nominal mass spectrum, *m/z* 337 (M^+), 322, 282, 264, 206, 194, 186, 168, 144, 115, 110, 88, 83, 57, 44 (base peak); exact mass, *m/z* calcd for $C_{13}H_{23}NO_7S$ 337.1195, found 337.1188.

General Procedure Using RCu(CN)Li·BF_3 (R = Me, *i*-Bu, *t*-Bu). The following procedure is representative for all reactions of δ-aminated γ-mesyloxy (*E*)-α,β-enoates with MeCu(CN)Li·BF_3, *i*-BuCu(CN)Li·BF_3, or *t*-BuCu(CN)Li·BF_3.

Methyl (2*S*,5*S*,3*E*)-5-Amino-*N*-[(*tert*-butyloxy)carbonyl]-2-methyl-3-hexenoate (53). To a stirred slurry of CuCN (72 mg, 0.8 mmol) in 5 mL of dry THF at −78 °C was added by syringe 0.533 mL (0.8 mmol) of 1.5 M MeLi–LiBr in Et_2O, and the mixture was allowed to warm to −20 °C and to stir at this temperature for 10 min. $BF_3{\cdot}Et_2O$ (0.1 mL, 0.8 mmol) was added to the above mixture at −78 °C and the mixture was stirred for 5 min. A solution of α,β-enoate **52** (67.4 mg, 0.2 mmol) in dry THF (2 mL) was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 30 min followed by quenching with 3 mL of a 2:1 satuated NH_4Cl–28% NH_4OH solution. The mixture was extracted with Et_2O and the extract was washed successively with 5% citric acid, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **53** (47 mg, 93% yield) as a colorless syrup of better than 99% optical purity (capillary gas chromatography and ^1H NMR): Kugelrohr distillation, 125 °C (1 mmHg); $[\alpha]^{15}_D$ +2.74° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 3440, 2980, 2940, 2880, 1722, 1710, 1494, 1453, 1438, 1395, 1378, 1369, 1168, 1070, 1049, 969 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.75 Hz, 3 H), 1.25 (d, *J* = 7.05 Hz, 3 H), 1.45 (s, 9 H), 3.14 (m, 1 H), 3.68 (s, 3 H), 4.22 (br s, 1 H), 4.45 (br s, 1 H), 5.56 (dd, *J* = 15.68, 4.74 Hz, 1 H), 5.66 (ddd, *J* = 15.68, 7.46, 1.27 Hz, 1 H); nominal mass spectrum, *m/z* 257 (M^+), 201, 186, 142, 141, 114, 70 (base peak), 57; exact mass, *m/z* calcd for $C_{13}H_{23}NO_4$ 257.1626, found 257.1630.

Methyl (5*S*,3*E*)-5-Amino-*N*-(*tert*-butoxycarbonyl)-3-hexenoate (54). To a stirred slurry of CuCN (72 mg, 0.8 mmol) in 5 mL of dry Et_2O at −20 °C was added by syringe 0.533 mL of 1.5M MeLi–LiBr in Et_2O, and the mixture was stirred for 10 min. A solution of acetate **51** (60 mg, 0.2 mmol) in 2 mL of Et_2O was added dropwise to the above reagent at −78 °C with stirring and the stirring was continued for 30 min followed by quenching with 3 mL of a 2:1 saturated NH_4Cl–28% NH_4OH solution. The

mixture was extracted with Et_2O, and the extract was washed successively with 5% citric acid, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was flash chromatographed over silica gel with *n*-hexane–EtOAc (4:1) to give 6.7 mg (13.3% yield) of **53** and further elution gave 40 mg (83% yield) of the title compound **54**. **54**: colorless oil, Kugelrohr distillation, 150 °C (1 mmHg); $[\alpha]^{25}_D$ −29.6° (*c* 0.965, $CHCl_3$); IR ($CHCl_3$) 3460, 2990, 2950, 2910, 1730 (shoulder), 1709, 1496, 1454, 1440, 1372, 1164, 1071, 972, 911, 851 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.84 Hz, 3 H), 1.44 (s, 9 H), 3.05 (s, 1 H), 3.08 (s, 1 H), 3.69 (s, 3 H), 4.20 (m, 1 H), 4.43 (m, 1 H), 5.55 (dd, *J* = 15.62, 4.64 Hz, 1 H), 5.63–5.77 (m, 1 H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.40; H, 8.97; N, 5.64.

General Procedure Using RCu(CN)MgX·BF_3 (R = Me, *i*-Pr, *i*-Bu, and *t*-Bu). The following procedure is representative for all reactions of δ-aminated γ-mesyloxy (*E*)-α,β-enoates with MeCu(CN)MgBr·BF_3, *i*-PrCu(CN)MgCl·BF_3, *i*-BuCu(CN)-MgCl·BF_3, or *t*-BuCu(CN)MgCl·BF_3.

Methyl (2*S*,5*S*,3*E*)-5-Amino-*N*-[(*tert*-butyloxy)-carbonyl]-2-isopropyl-3-hexenoate (55). To a stirred slurry of CuCN (1.89 g, 21 mmol) in 20 mL of dry THF was added by syringe 15 mL (21 mmol) of 1.4 M *i*-PrMgCl in THF, and the mixture was allowed to warm to 0 °C and to stir at this temperature for 15 min. $BF_3·Et_2O$ (2.58 mL, 21 mmol) was added to the above mixture at −78 °C and the mixture was stirred for 5 min. A solution of α,β-enoate **52** (1.77 g, 5.25 mmol) in dry THF (8 mL) was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 30 min followed by quenching with 8 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 a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) followed by recrystallization from *n*-hexane to yield **55** (1.28 g, 85% yield) as colorless crystals of better than 99% optical purity (capillary gas chromatography and ^1H NMR): mp 50 °C; $[\alpha]^{20}_D$ +21.5° (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3430, 2960, 2910, 1725, 1709, 1495, 1451, 1436, 1366, 1165, 1067, 1050, 1024, 974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.73 Hz, 3 H), 0.90 (d, *J* = 6.64 Hz, 3 H), 1.20 (d, *J* = 6.75 Hz, 3 H), 1.44 (s, 9 H), 1.98 (m, 1 H), 2.68 (m, 1 H), 3.68 (s, 3 H), 4.23 (br s, 1 H), 4.45 (br s, 1 H), 5.47–5.61 (m, 2 H). Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 62.89; H, 9.74; N, 4.87.

(2*S*,5*S*,3*E*)-5-Amino-*N*-benzyl-1-(benzyloxy)-*N*-[(*tert*-butyloxy)carbonyl]-2-methyl-3-hexene (89). To a stirred solution of 140 mg (0.545 mmol) of ester **53** in 6 mL of a mixture of CH_2Cl_2–THF (1:1) at −78 °C was added 1.28 mL (2.18 mmol) of 1.7 M DIBAL in *n*-hexane, and the mixture was stirred for 3 h with warming to −50 °C. The excess reagent was decomposed with 5 mL of 5% NH_4Cl at 0 °C. The inorganic salts were removed by filtration through Celite. The usual workup of the filtrate led to a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to yield an alcohol (100 mg, 80% yield) as a colorless oil. To a stirred suspension of NaH (82 mg of 50% sodium hydride in mineral oil, 1.72 mmol) in dry DMF (2 mL) was added a solution of the above alcohol (100 mg) in 2 mL of dry DMF at 0 °C with stirring. Benzyl bromide (0.3 mL) was added to the above mixture and the mixture was stirred for 18 h at room temperature. The mixture was poured into ice–water and extracted with Et_2O. The extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (10:1) gave 150 mg (84% yield) of benzyl ether **89** as a colorless syrup: $[\alpha]^{20}_D$ −23.1° (*c* 1.47, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2880, 1679, 1457, 1409, 1371, 1332, 1162, 1118, 1020, 978, 908, 867 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.59 Hz, 3 H), 1.17 (d, *J* = 7.08 Hz, 3 H), 1.40 (s, 9 H), 2.42 (m, 1 H), 3.24 (m, 2 H), 4.29 (br s, 2 H), 4.47 (s, 2 H), 5.47 (m, 2 H), 7.13–7.35 (m, 10 H); nominal mass spectrum, *m*/*z* 409 (M^+), 354, 353, 352, 294, 268, 247, 228, 218, 204, 188, 178, 160, 134, 91 (base peak); exact mass spectrum, *m*/*z* calcd for $C_{26}H_{35}NO_3$ 409.2616, found 409.2627.

(4*R*)-*N*-[(*tert*-Butyloxy)carbonyl]-2,2-dimethyl-4-[(3*R*,1*E*)-4-(benzyloxy)-3-methyl-1-butenyl]oxazolidine (90). To a stirred solution of 100 mg (0.32 mmol) of ester **84** in 6 mL of a mixture of CH_2Cl_2–THF (1:1) was added 0.752 mL (1.28 mmol) of 1.7 M DIBAL in *n*-hexane at −78 °C, and the mixture was stirred for 3 h at −50 °C. The excess reagent was decomposed with 5 mL of 5% NH_4Cl at 0 °C. The inorganic salts were removed by filtration through Celite. The usual workup of the filtrate led to a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to yield 81 mg (89% yield) of an alcohol as a colorless oil. To a stirred suspension of NaH (34 mg, 0.71 mmol) in dry DMF (2 mL) was added a solution of the above alcohol (81 mg) in 2 mL of dry DMF at 0 °C with stirring. Benzyl bromide (0.3 mL) was added to the above mixture and the mixture was stirred for 18 h at room temperature. The mixture was poured into ice–water and extracted with Et_2O. The extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (5:1) gave 75 mg (63% yield) of benzyl ether **90** as a colorless syrup: $[\alpha]^{20}_D$ −5.08° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 2990, 2950, 2880, 1691, 1479, 1456, 1391, 1382, 1371, 1172, 1102, 1057, 970, 857, 703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.84 Hz, 3 H), 1.43 (s, 9 H), 1.50 (s, 3 H), 1.60 (d, *J* = 1.55 Hz, 3 H), 2.51 (m, 1 H), 3.33 (m, 2 H), 3.72 (dd, *J* = 8.79, 2.28 Hz, 1 H), 4.01 (dd, *J* = 8.79, 5.86 Hz, 1 H), 4.24 (br s, 1 H), 4.50 (s, 2 H), 5.40–5.62 (m, 2 H), 7.21–7.39 (m, 5 H); nominal mass spectrum, *m*/*z* 375 (M^+), 360, 319, 275, 260 (base peak), 246, 218, 198, 144, 100, 91, 57; exact mass, *m*/*z* calcd for $C_{22}H_{33}NO_4$ 375.2409, found 375.2405.

(2*S*)-3-(Benzyloxy)-2-methyl-1-propanol (91). Benzyl ether **89** (115 mg, 0.281 mmol) was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to −78 °C. Ozone was bubbled into the solution until a blue color persisted. The solution was stirred for 30 min with warming to 0 °C. To the above mixture at −78 °C was added dropwise 4 mL (6.8 mmol) of a 1.7 M *n*-hexane solution of DIBAL, and the mixture was stirred for 2 h at −20 °C. Saturated NH_4Cl (2 mL) was added with vigorous stirring at −78 °C. The mixture was allowed to warm to 0 °C and the stirring was continued for 30 min. The mixture was made acidic with 5% HCl at −30 °C and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to leave a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to yield 29 mg (57% yield) of the title compound **91** as a colorless syrup: Kugelrohr distillation (140 °C/10 mmHg); $[\alpha]^{20}_D$ −17.2° (*c* 0.801, $CHCl_3$); IR ($CHCl_3$) 3500, 2980, 2950, 2880, 1458, 1365, 1091, 1031, 991, 962, 906 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.84 Hz, 3 H), 2.09 (m, 1 H), 2.53 (br s, 1 H), 3.38–3.66 (m, 4 H), 4.52 (s, 3 H), 7.26–7.41 (m, 5 H); nominal mass spectrum, *m*/*z* 180 (M^+), 162, 161, 107, 92, 91 (base peak), 79, 65; exact mass, *m*/*z* calcd for $C_{11}H_{16}O_2$ 180.1149, found 180.1153.

(2*R*)-3-(Benzyloxy)-2-methyl-1-propanol (92). By a procedure identical with that described for the preparation of alcohol **91** from **89**, 70 mg (0.187 mmol) of benzyl ether **90** was converted into 13 mg (39% yield) of alcohol **92** as a colorless syrup: Kugelrohr distillation (140 °C/10 mmHg); $[\alpha]^{22}_D$ +17.2° (*c* 0.512, $CHCl_3$); IR ($CHCl_3$) 3500, 2980, 2950, 2880, 1458, 1365, 1091, 1031, 991, 962, 906 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.84 Hz, 3 H), 2.09 (m, 1 H), 2.17 (br s, 1 H), 3.38–3.66 (m, 4 H), 4.52 (s, 3 H), 7.26–7.41 (m, 5 H); nominal mass spectrum, *m*/*z* 180 (M^+), 162, 161, 107, 91 (base peak), 79, 65; exact mass, *m*/*z* calcd for $C_{11}H_{16}O_2$ 180.1149, found 180.1151.

H-Ala-ψ[(*E*)-CH=CH]-D-Val-OH Hydrochloride (94). To a stirred solution of 245 mg (0.859 mmol) of **55** in 5 mL of CH_2Cl_2 were added anisole (2 mL) and trifluoroacetic acid (TFA) (2.5 mL) at 0 °C, and the mixture was allowed to stand at 0 °C for 18 h. The solvent, anisole, and TFA were removed under reduced pressure to leave a colorless oil. To the above oil was added 20 mL of 3 N HCl, and the mixture was heated under reflux for 3 h. The mixture was concentrated under reduced pressure to leave a colorless semisolid, which was recrystallized from Et_2O–Me_2CO (1:1) to give 118 mg (78.4% yield) of the title compound **94** as colorless crystals: mp 170 °C; $[\alpha]^{20}_D$ +45.38° (*c* 1.159, MeOH); IR (KBr) 3470, 3300, 3280, 3240, 1725, 1674, 1615, 1578, 1502, 1466, 1448, 1384, 1368, 1263, 1215, 1175, 1155, 1121, 1099, 971, 942, 899, 873, 845, 828, 817, 667 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 0.92 (d, *J* = 6.83 Hz, 3 H), 0.97 (d, *J* = 6.59 Hz, 3 H), 1.39 (d, *J* = 6.59 Hz, 3 H), 2.00 (m, 1 H), 2.74 (t, *J* = 8.55 Hz, 1 H), 3.90 (m, 1 H), 5.62 (dd, *J* = 15.63, 7.08 Hz, 1 H), 5.89 (dd, *J* = 15.63,

9.52 Hz, 1 H). Anal. Calcd for $C_9H_{17}NO_2$·HCl: C, 52.04; H, 8.74; N, 6.74. Found: C, 51.84; H, 8.62; N, 6.78.

Boc-Ala-ψ[(*E*)-CH=CH]-D-Val-OH (95). To a stirred solution of 90 mg (0.433 mmol) of **94** in water (4 mL) was added a mixture of 0.12 mL (0.867 mmol) of Et_3N, 104 mg (0.476 mmol) of $(Boc)_2O$ and 5 mL of dioxane at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The mixture was concentrated under reduced pressure to leave a colorless residue, which was made acidic (pH 2.0) with 1 N HCl at 0 °C. The mixture was extracted with EtOAc and the extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a crystalline residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:2). Recrystallization from *n*-hexane–Et_2O (2:1) gave 71 mg (60.4% yield) of the title compound **95** as colorless crystals: mp 65 °C; $[\alpha]^{26}_D$ +26.84° (*c* 0.499, $CHCl_3$); IR ($CHCl_3$) 3450, 2990, 2960, 1705, 1503, 1457, 1397, 1371, 1168, 1051, 976 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.84 Hz, 3 H), 0.96 (d, *J* = 6.59 Hz, 3 H), 1.21 (d, *J* = 6.59 Hz, 3 H), 1.44 (s, 9 H), 2.03 (m, 1 H), 2.69 (m, 1 H), 4.20 (br s, 1 H), 4.51 (br s, 1 H), 5.56 (m, 2 H); nominal mass spectrum, *m/z* 271 (M^+), 256, 215, 200, 169, 156, 155, 154, 128, 114, 112, 110, 88, 70, 57 (base peak); exact mass, *m/z* calcd for $C_{14}H_{25}NO_4$ 271.1784, found 271.1790.

Boc-Phe-Ala-ψ[(*E*)-CH=CH]-D-Val-OMe (96). To a stirred solution of 100 mg (0.377 mmol) of (*S*)-Boc-Phe-OH in 5 mL of CH_2Cl_2 was added 85.6 mg (0.415 mmol) of dicyclohexylcarbodiimide, and the mixture was stirred for 1 h at 0 °C. Twenty-five milligrams (0.134 mmol) of H-Ala-ψ[(*E*)-CH=CH]-D-Val-OMe in 5 mL of CH_2Cl_2 was added to the above mixture at 0 °C, and the mixture was allowed to stand for 48 h. The mixture was filtered and the filtrate was diluted with 30 mL of Et_2O. The solution was washed successively with 1 N HCl, water, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure gave a crystalline residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) to give 31 mg (53% yield) of a crystalline residue. Recrystallization from *n*-hexane–Et_2O (1:1) gave the title compound **96** as colorless crystals: mp 103 °C; $[\alpha]^{20}_D$ +21.84° (*c* 0.458, $CHCl_3$); IR ($CHCl_3$) 3440, 2980, 2950, 2910, 1728, 1710, 1677, 1498, 1458, 1439, 1373, 1164, 1121, 1085, 1055, 1024, 977, 861 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.84 Hz, 3 H), 0.88 (d, *J* = 6.59 Hz, 3 H), 1.14 (d, *J* = 6.84 Hz, 3 H), 1.42 (s, 9 H), 1.95 (m, 1 H), 2.61 (t, *J* = 8.54 Hz, 1 H), 2.99 (dd, *J* = 15.14, 7.81 Hz, 1 H), 3.10 (dd, *J* = 15.14, 5.86 Hz, 1 H), 3.67 (s, 3 H), 4.26 (m, 1 H), 4.48 (m, 1 H), 5.07 (m, 1 H), 5.31 (dd, *J* = 15.62, 4.39 Hz, 1 H), 5.44 (dd, *J* = 15.62, 8.3 Hz, 1 H), 5.62 (m, 1 H), 7.16–7.35 (m, 5 H); nominal mass spectrum, *m/z* 432 (M^+), 389, 376, 359, 315, 285, 272, 241, 220, 184, 164, 120 (base peak), 57; exact mass, *m/z* calcd for $C_{24}H_{36}N_2O_5$ 432.2623, found 432.2609.

Boc-Ala-ψ[(*E*)-CH=CH]-D-Val-Phe-OMe (97). To a stirred solution of 20 mg (0.0074 mmol) of **95** in DMF (10 mL) were added successively DCC (16.7 mg, 0.0811 mmol), 1-hydroxybenzotriazole (12.4 mg, 0.0811 mmol), and phenylalanine methyl ester hydrochloride (47.7 mg, 0.221 mmol) in a mixture of Et_3N (0.029 mL, 0.221 mmol) and DMF (10 mL) at 0 °C, and the mixture was allowed to stand at 0 °C for 2 days. Concentration under reduced pressure gave a semisolid, which was dissolved in EtOAc. The solution was washed successively with 5% HCl, water, 5% $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) gave 20 mg (63% yield) of the title compound **97** as colorless crystals from CH_2Cl_2–Et_2O (1:10): mp 113–115 °C; $[\alpha]^{20}_D$ +44.8° (*c* 0.429, $CHCl_3$); IR ($CHCl_3$) 3440, 2980, 2950, 2880, 1738, 1705, 1676, 1662, 1496, 1451, 1370, 1235, 1170, 1071, 1049, 1028, 976 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.84 Hz, 3 H), 0.85 (d, *J* = 6.59 Hz, 3 H), 1.17 (d, *J* = 6.84 Hz, 3 H), 1.45 (s, 9 H), 2.05 (m, 1 H), 2.47 (m, 1 H), 3.07 (dd, *J* = 13.91, 6.59 Hz, 1 H), 3.16 (dd, *J* = 13.91, 5.86 Hz, 1 H), 3.71 (s, 3 H), 4.17 (m, 1 H), 4.40 (m, 1 H), 4.86 (m, 1 H), 5.50 (m, 2 H), 6.02 (m, 1 H), 7.08–7.34 (m, 5 H); nominal mass spectrum, *m/z* 432 (M^+), 399, 389, 376, 333, 288, 272, 246, 214, 206, 171, 162, 146, 131, 120, 110 (base peak), 88, 70, 57; exact mass, *m/z* calcd for $C_{24}H_{36}N_2O_5$ 432.2623, found 432.2619.

(2*R*,5*S*,3*E*)-5-Amino-2-isopropyl-3-hexenoic Acid Hydrochloride (98). A mixture of 192 mg (0.673 mmol) of ester **68** in 3.5 mL of 3 N HCl was heated under reflux for 5 h. The mixture was concentrated under reduced pressure to leave a colorless semisolid, which was recrystallized from H_2O–THF–MeCN (1:20:20) to give 116 mg (83% yield) of amino acid hydrochloride **98** as colorless crystals: mp 172–174 °C; $[\alpha]^{21}_D$ –67.6° (*c* 1.379, MeOH); IR (KBr) 3400, 1710, 1620, 1482, 1378, 1366, 1350, 1260, 1215, 1205, 1090, 1058, 975, 800, 668 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 0.94 (d, *J* = 6.84 Hz, 3 H), 0.98 (d, *J* = 6.59 Hz, 3 H), 1.39 (d, *J* = 6.59 Hz, 3 H), 2.00 (m, 1 H), 2.74 (t, *J* = 8.54 Hz, 1 H), 3.89 (m, 1 H), 5.64 (dd, *J* = 15.62, 6.83 Hz, 1 H), 5.89 (dd, *J* = 15.62, 9.28 Hz, 1 H). Anal. Calcd for $C_9H_{18}NO_2Cl$: C, 52.05; H, 8.74; N, 6.74. Found: C, 51.98; H, 8.92; N, 6.72.

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Supplementary Material Available: Synthetic methods and spectral data [$[\alpha]_D$, IR, ^1H NMR, ^{13}C NMR (in part), and MS] for **18**, **20**, **24**, **30**, **35**, **37–39**, **43**, **49**, **50**, and **56–88** and ^1H NMR spectra of **11–20**, **23–24**, **26–30**, **32–39**, **41–92**, and **94–98** (105 pages). Ordering information is given on any current masthead page.