nitrile)palladium dichloride, and the mixture was heated at 80 °C for 3 h. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5:1 hexane/EtOAc) to yield **17a**, 0.068 g (40.0%), as a white crystalline solid: mp 47–48 °C; IR ($CHCl_3$) 1714, 1609, 1596, 1460, 1421, 1374, 1306, 1282, 1141, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (d, J = 9.1 Hz, 1 H), 7.37 (d, J = 2.6 Hz, 1 H), 7.11 (dd, J = 2.6, 9.1 Hz, 1 H), 6.49 (s, 1 H), 3.64 (sept, 1 H), 2.77 (s, 3 H), 1.31 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{14}H_{14}F_3NO_4S$: C, 48.14; H, 4.04. Found: C, 47.93; H, 3.97.

***N*-Acetyl-2-*n*-butyl-5-[(trifluoromethyl)sulfonyl]indole (17b).** To a solution of 0.144 g (0.396 mmol) of *N*-acetyl-2-hexyn-1-yl-4-[(trifluoromethyl)sulfonyl]aniline in acetonitrile (4 mL) was added 0.010 g (0.058 mmol) of bis(acetonitrile)palladium dichloride, and the mixture was heated at 80 °C for 2.5 h. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5:1 hexane/EtOAc) to yield **17b**, 0.093 g (64.6%), as a white crystalline solid: mp 69–70 °C; IR ($CHCl_3$) 1706, 1450, 1415, 1362, 1304, 1132, 1095, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (d, J = 9.2 Hz, 1 H), 7.35 (d, J = 2.6 Hz, 1 H), 7.11 (dd, J = 2.6, 9.2 Hz, 1 H), 6.43 (s, 1 H), 2.97 (t, 2 H), 2.73 (s, 3 H), 1.70 (quin, 2 H), 1.45 (sext, 2 H), 0.96 (t, 3 H). Anal. Calcd for $C_{15}H_{16}F_3NO_4S$: C, 49.58; H, 4.44. Found: C, 49.75; H, 4.46.

***N*-Acetyl-2-phenyl-5-[(trifluoromethyl)sulfonyl]indole (17c).** To a solution of 0.091 g (0.237 mmol) of *N*-acetyl-2-(phenylethynyl)-4-[(trifluoromethyl)sulfonyl]aniline in acetonitrile (3 mL) was added 6 mg (0.024 mmol) of bis(acetonitrile)palladium dichloride, and the mixture was heated at 80 °C for 3.5 h. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5:1 hexane/EtOAc) to yield **17c**, 0.048 g (52.7%), as a white crystalline solid: mp 87–87.5 °C; IR ($CHCl_3$) 1702, 1449, 1437, 1411, 1360, 1301, 1292, 1130, 1088, 939 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (d, J = 8.9 Hz, 1 H), 7.48 (s, 5 H), 7.47 (d, J = 2.5 Hz, 1 H), 7.23 (dd, J = 2.5, 8.9 Hz, 1 H), 6.65 (s, 1 H), 2.06 (s, 3 H). Anal. Calcd for $C_{17}H_{12}F_3NO_4S$: C, 53.27; H, 3.16. Found: C, 53.37; H, 3.16.

***N*-Acetyl-2-*n*-butyl-4-[(trifluoromethyl)sulfonyl]indole (18a).** To a solution of 0.137 g (0.38 mmol) of *N*-acetyl-2-hexyn-1-yl-3-[(trifluoromethyl)sulfonyl]aniline in acetonitrile (3 mL) was added 10 mg (0.038 mmol) of bis(acetonitrile)palladium dichloride, and the mixture was heated at 80 °C for 4 h. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5:1 hexane/EtOAc) to yield **18a**, 0.031 g (22.6%), as an oil: IR (film) 1718, 1424, 1304, 1181, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 1 H), 7.25 (t, J = 8.2, 8.3 Hz, 1 H), 7.18 (d, J = 8.2 Hz, 1 H), 6.50 (s, 1 H), 2.97 (t, 2 H), 2.75 (s, 3 H), 1.71 (quin, 2 H), 1.44 (sext, 2 H), 0.97 (t, 3 H); HRMS calcd for $C_{15}H_{16}F_3NO_4S$ 363.0752, found 363.0761.

***N*-Acetyl-2-phenyl-4-[(trifluoromethyl)sulfonyl]indole (18b).** To a solution of 0.141 g (0.37 mmol) of *N*-acetyl-2-(phenylethynyl)-3-[(trifluoromethyl)sulfonyl]aniline in acetonitrile (4 mL) was added 10 mg (0.037 mmol) of bis(acetonitrile)palladium dichloride, and the mixture was heated at 80 °C for 4 h. The solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5:1 hexane/EtOAc) to yield **18b**, 0.045 g (31.9%), as a white crystalline solid: mp 79.5–81 °C; IR ($CHCl_3$) 1712, 1458, 1422, 1370, 1304, 1246, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.36 (d, J = 8.3 Hz, 1 H), 7.48 (s, 5 H), 7.36 (t, J = 8.2, 8.3 Hz, 1 H), 7.22 (envelope, 1 H), 6.71 (s, 1 H), 2.07 (s, 3 H). Anal. Calcd for $C_{17}H_{12}F_3NO_4S$: C, 53.27; H, 3.16. Found: C, 53.16; H, 3.19.

Acknowledgment. This work was supported by an NIH Postdoctoral Fellowship (GM11862-01) to D.E.R. and an NSF grant (CHE-8703218). The palladium was provided under the Johnson-Matthey Metal Loan Program.

Registry No. 1, 614-76-6; **2a**, 90585-00-5; **2b**, 123027-90-7; **2c**, 116491-53-3; **2d**, 26385-33-1; **2e**, 123027-91-8; **2f**, 110598-59-9; **2g**, 123027-92-9; **2h**, 123027-93-0; **2i**, 123027-94-1; **2j**, 61403-29-0; **3a**, 90585-31-2; **3b**, 123051-57-0; **3c**, 116491-55-5; **3d**, 78388-91-7; **4**, 123027-98-5; **5**, 123027-99-6; **6**, 123028-02-4; **7a**, 123028-05-7; **7b**, 123028-06-8; **7c**, 123028-07-9; **7d**, 123028-08-0; **7e**, 123028-09-1; **8a**, 123028-10-4; **8b**, 123028-11-5; **8c**, 123028-12-6; **8d**, 123028-13-7; **9a**, 123028-14-8; **9b**, 123028-15-9; **9c**, 104683-00-3; **9d**, 123028-16-0; **9e**, 123028-17-1; **9f**, 123028-18-2; **10a**, 123028-19-3; **10b**, 123028-20-6; **10c**, 123028-21-7; **10d**, 123028-22-8; **11a**, 123028-23-9; **11b**, 123051-58-1; **11c**, 123028-24-0; **12a**, 123028-25-1; **12b**, 123028-26-2; **13a**, 123028-27-3; **13b**, 123028-28-4; **13c**, 123028-29-5; **14a**, 123028-30-8; **14b**, 123028-31-9; **14c**, 123051-59-2; **14d**, 123028-32-0; **15a**, 123028-33-1; **15b**, 123028-34-2; **15c**, 104683-04-7; **15d**, 123028-35-3; **15e**, 123028-36-4; **15f**, 123028-37-5; **16a**, 123028-38-6; **16b**, 123028-39-7; **16c**, 123028-40-0; **16d**, 123028-41-1; **17a**, 123028-42-2; **17b**, 123028-43-3; **17c**, 123028-44-4; **18a**, 123028-45-5; **18b**, 123028-46-6; $HC{\equiv}C(CH_2)_2OSi(Me)_2Bu$-t, 78592-82-2; $Bu_3SnC{\equiv}C(CH_2)_2OSi(Me)_2Bu$-t, 98155-22-7; $HC{\equiv}C(CH_2)_3OSi(Me)_2Bu$-t, 61362-77-4; $Br(CH_2)_3OSi(Me)_2Bu$-t, 89031-84-5; $Bu_3SnC{\equiv}C(CH_2)_3OSi(Me)_2Bu$-t, 123027-88-3; $HC{\equiv}C(CH_2)_4C{\equiv}CTMS$, 83182-85-8; $Bu_3SnC{\equiv}C(CH_2)_4C{\equiv}CTMS$, 123027-89-4; $Bu_3SnC{\equiv}C(CH_2)_3CH_3$, 86633-17-2; $Bu_3SnC{\equiv}CCH(CH_3)_2$, 58064-11-2; $Bu_3SnC{\equiv}C(CH_2)_3CH_3$, 35864-20-1; $Bu_3SnC{\equiv}CPh$, 3757-88-8; $Bu_3SnC{\equiv}CCH_2OTHP$, 109669-44-5; $Bu_3SnC{\equiv}CTMS$, 81353-38-0; *cis*-$Bu_3SnC{\equiv}CCH{=}CHOMe$, 123027-95-2; $Bu_3SnC{\equiv}CCH_2OMe$, 113794-24-4; $(CH_3CN)_2PolCl_2$, 14592-56-4; 1-butyn-4-ol, 927-74-2; 3-bromopropanol, 627-18-9; lithium acetaldehyde, 7447-41-8; 1,7-octadiyne, 871-84-1; 4-carbomethoxyphenyl trifluoromethanesulfonate, 17763-71-2; 2-nitro-4-carbomethoxyphenyl trifluoromethanesulfonate, 123027-96-3; 2-amino-4-carbomethoxyphenyl trifluoromethanesulfonate, 123027-97-4; 4-methoxy-2-nitroaniline, 96-96-8; 4-bromo-3-nitroanisole, 5344-78-5; 2-bromo-5-methoxyaniline, 59557-92-5; 2-bromo-4-chloroaniline, 873-38-1; *N*-acetyl-2-bromo-4-chloroaniline, 57045-85-9; 3-bromo-4-nitrophenol, 5470-65-5; 3-bromo-4-nitrophenyl trifluoromethanesulfonate, 123028-00-2; 2-bromo-4-[(trifluoromethyl)sulfonyl]aniline, 123028-01-3; 2-bromo-3-[(trifluoromethyl)sulfonyl]aniline, 123028-03-5; *N*-acetyl-2-bromo-3-[(trifluoromethyl]sulfonyl]-aniline, 123028-04-6; *N*-acetyl-2-bromo-4-methylaniline, 614-83-5.

Synthesis of (±)-2,3-Methanovaline and (±)-2,3-Methanoleucine

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The synthesis of racemic 2,3-methanovaline and 2,3-methanoleucine have been accomplished by dipolar addition of the appropriate diazocompounds to dehydroalanine derivatives followed by decomposition of the resulting pyrazolines. Both chemical and NMR evidence allowed assignment of configuration to the *E* and *Z* isomers of 2,3-methanoleucine.

The two aliphatic amino acids, valine and leucine, occupy an important place in peptide structure and function. They are often in conformation-controlling positions in peptide hormones such as angiotensin II and may appear at crucial enzymatic cleavage sites such as the Leu-Val site in human angiotensinogen, which affords angiotensin I. In our studies of the synthesis of conformationally constrained cyclopropane-containing amino acids, we felt it

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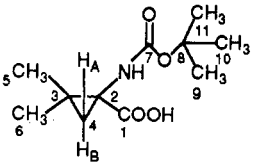
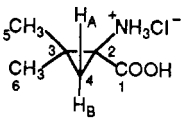
Table I. ^1H NMR and ^{13}C NMR Spectral Data of 2,3-Methanovaline



5a



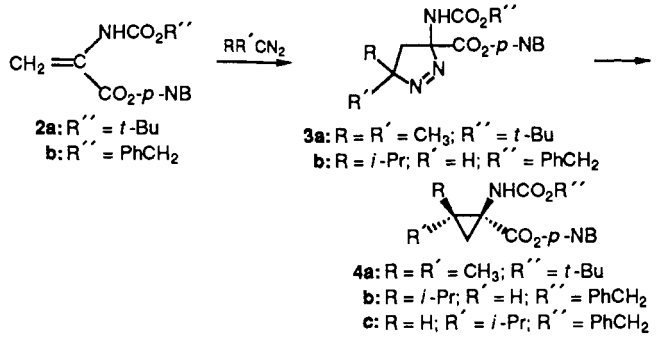
1a

compd.	^1H NMR chemical shift[a]						
	CH_3	CH_3	H_A	H_B	$(CH_3)_3C$	NH	COOH
5a[b]	1.23 (s)		0.86 (br s)	1.52 (br s)	1.43 (s)	6.38 (br s)	11.68 (s)
1a[c]	1.28 (s)	1.33 (s)	1.30 (d, J = 6.9 Hz)	1.63 (d, J = 6.9 Hz)			

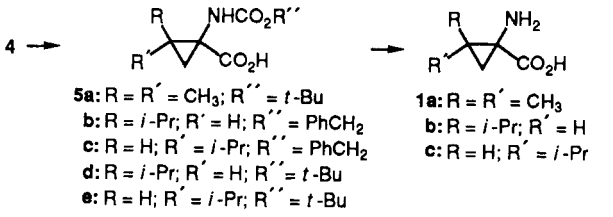
compd	^{13}C NMR chemical shift								
	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_{9-11}
5a[b]	172.6	41.65	26.14	21.01	18.63		155.57	77.9	27.2
1a[c]	171.55	42.39	26.40	25.15	20.02	19.10			

[a] Recorded on a Bruker WM 300 spectrometer. [b] Solvent $CDCl_3$ + $(CD_3)_2SO$; internal reference $CDCl_3$. [c] Solvent D_2O; internal reference *p*-dioxane.

Scheme I



Scheme II



important to synthesize these new methano amino acids, not only for their probable ability to stabilize[1] adjacent peptide linkages, but also to examine the possibility that peptides containing them might be enzyme inhibitors.[2]

The simplest and most direct approach to the synthesis of 2,3-methano amino acids, although not operationally the safest, is the "diazo addition" method[3] in which a diazo compound is added to a dehydroalanine derivative. This method often gives *both* diastereomers of the desired amino acid in one step, thus obviating the necessity to develop separate syntheses for the *E* and *Z* isomers. We used the *p*-nitrobenzyl esters (**2**, Scheme I) in this work because dehydroalanine *p*-nitrobenzyl esters, in contrast to aliphatic esters, were found to be crystalline compounds stable indefinitely to storage at room temperature. Scheme I shows the sequence of reactions leading to the formation of the cyclopropane ring in good to excellent yields. In the 2,3-methanovaline synthesis, the *tert*-butoxycarbonyl group was used to block the amino function while the methanoleucines were prepared using the *N*-benzyloxycarbonyl protecting group. The pyrazoline **3a**, formed by addition of 2-diazopropane to **2a**, was cleanly converted into the cyclopropane **4a** by pyrolysis. The intermediate pyrazoline, **3b**, resulting from addition of diazoisobutane to **2b**, was shown to be a single entity by HPLC and ^{13}C NMR spectroscopy, although its configuration remains unknown. It was converted to the cyclopropanes **4b** and **4c** by both pyrolysis and photolysis, the former method giving both diastereomers while the latter gave, as expected,[4] a single isomer, which was assigned the *E* configuration. Surprisingly, the diastereomeric mixture obtained pyrolytically appeared to be a single entity by both thin-layer chromatography and ^1H NMR (90 MHz) spectroscopy until examined carefully by HPLC, the *Z* isomer having the longer retention time. Luckily, these isomers were easily separated by recrystallization of the mixture from ethanol, the *Z* isomer being the more insoluble.

As shown in Scheme II, the cyclopropanes were deblocked by hydrolysis of the ester functions, giving the acids **5**, followed by removal of the nitrogen blocking groups. Racemic 2,3-methanovaline **4a** was formed in excellent yield using these methods, while some decomposition apparently occurred during the hydrolysis steps in the methanoleucine series. Hydrogenolysis of the benzyloxycarbonyl group proceeded without complication and the free amino acids, **1b** and **1c**, were obtained in excellent yields. Hydrogenolysis of both protecting groups followed by treatment with *tert*-butoxycarbonyl anhydride gave the *N*-Boc derivatives of both methanoleucines (**5d**, **5e**) in good yield, indicating the excellent stability of the cyclopropane ring to hydrogenation using 5% Pd/C as catalyst. In our work with these compounds, we find that only those with aromatic substituents on the cyclopropane ring may be cleaved during catalytic hydrogenation.[5]

NMR Studies. A careful study of the NMR spectra of these two amino acids was carried out in order to fully characterize these ring systems in both the protected and free amino acids.

In the valine series, **5a** and **1a**, the lack of diastereoisomerism simplified the spectra, but they were, nevertheless, interesting (Table I). In the N-blocked compound,

(1) Kimura, H.; Stammer, C. H.; Shimohigashi, Y.; Ren-Lin, C.; Stewart, J. *Biochem. Biophys. Res. Commun.* **1983**, *115*, 112.

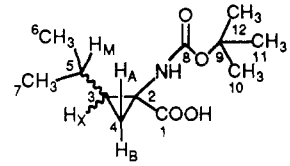
(2) Ner, S. K.; Suckling, C. H.; Bell, A. R.; Wrigglesworth, R. *J. Chem. Soc., Chem. Commun.* **1987**, 480.

(3) (a) Suzuki, M.; Gooch, E. E.; Stammer, C. H. *Tetrahedron Lett.* **1983**, *24*, 3839. (b) Bregovec, I.; Jacovcic, T. *Monatsh. Chem.* **1972**, *103*, 288.

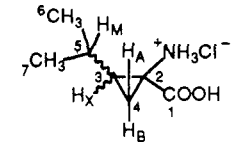
(4) (a) Engel, P. S. *Chem. Rev.* **1980**, *80*, 99. (b) Van Auken, T. V.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3736.

(5) Kimura, H.; Stammer, C. H. *J. Org. Chem.* **1983**, *48*, 2440.

Table II. ^{1}H NMR Spectral Data of 2,3-Methanoleucine Derivative



5d,e



1b,c

compd	chemical shift							
	CH_3	CH_3	H_A	H_B	H_X	H_M	$(CH_3)_3C$	COOH
5d[a,c] (*Z*)	1.05 (d, *J* = 3 Hz)	1.10 (d, *J* = 3 Hz)		2.20 (m)		2.40 (m)	1.43 (s)	8.7 (s)
5e[a,c] (*E*)	1.15 (d, *J* = 3 Hz)	1.20 (m)		2.36 (m)		2.71 (m)	1.47 (s)	8.8 (s)
1b[b,d] (*Z*)	0.82 (d, *J* = 6.6 Hz)	0.87 (d, *J* = 6.6 Hz)	0.97 (m)	1.46 (m)		1.15 (m)		
1c[b,d] (*E*)	1.01 (d, *J* = 6.6 Hz)	0.99 (d, *J* = 6.6 Hz)		1.58 (m)		1.69 (m)		

[a] Solvent $CDCl_3$; internal reference TMS group. [b] Solvent D_2O; internal reference *p*-dioxane. [c] Recorded on a JEOL FX 270Q spectrometer. [d] Recorded on a Brucker AM 500 spectrometer.

Table III. ^{13}C NMR Chemical Shifts of 2,3-Methanoleucine Derivatives (ppm)[a]

compd	C_1	C_2	C_3	C_4	C_5	C_6 & C_7	C_8	C_9	C_{10-12}
5d[b]	175.6	38.4	28.0	22.1	36.1	21.8	157.0	27.9	80.0
5e[b]	177.5	38.7	26.7	22.1	37.5	22.0	157.2	28.2	80.1
1b[c]	172.6	38.0	27.5	21.7	33.9	21.4			
1c[c]	171.8	38.2	26.3	21.8	35.8	21.5			

[a] Recorded on a JEOL FX 270Q spectrometer. [b] Solvent $CDCl_3$; internal reference $CDCl_3$ 77.0 ppm. [c] Solvent D_2O; internal reference *p*-dioxane, 66.5 ppm.

5a, both the ^{1}H and ^{13}C NMR spectra showed the geminal methyl groups having identical chemical shifts in spite of their apparent different magnetic environments, while the H_A and H_B protons differed by an unexpectedly large 0.66 ppm with a very small coupling constant. In the free amino acid (**1a**), however, both protons and carbon atoms of the methyl groups are distinguishable by chemical shift and the H_A and H_B protons show a large geminal coupling (J = 6.9 Hz). The H_A peak assignment was made by the observation that the more upfield proton peak (δ 0.86 ppm) was shifted most downfield (Δ 0.44 ppm) when the positively charged ammonium group was formed during deblocking. Logically, the H_B proton was assigned to the more downfield peak (1.52 ppm) because of the expected deshielding effect of the proximal carbonyl function.

The ^{1}H and ^{13}C NMR assignments of **5d,e** and **1b,c** are summarized in Tables II and III. When we attempted to make configurational assignments to these diastereomers by careful NMR studies, we found that the necessary unambiguous peak assignments to the cyclopropane protons, H_A, H_B, and H_X, were difficult because of poor resolution and complex coupling patterns. The ^{1}H spectrum of **1b** did show a multiplet at δ 0.97 assignable to H_A because of its upfield position[6] and the appearance of cross connectivity between this peak and that of the H_B/H_X multiplet in the ^{1}H–^{1}H COSY spectrum. The methine proton, H_M, of the isopropyl group in both **1b** and **1c** was assigned by selective irradiation of the proton multiplet at δ 1.15 in **1b** and δ 1.69 in **1c** which caused decoupling of the isopropyl methyl protons at δ 0.82, 0.87 (**1b**) and δ 1.01, δ 0.9 (**1c**). Further confirmation of this assignment was given by the ^{1}H–^{1}H COSY spectrum of **1b**, which revealed that the H_M peak at δ 1.15 had a second off-diagonal cross-connectivity at δ 1.46, which was then assigned to H_X. The H_M proton showed no cross-peaks with the H_A/H_B multiplet in the NOESY spectrum because, according to models, it is beyond the maximum 0.3–0.5 Å NOE distance. As expected, H_M and the isopropyl protons in the *E* isomers, **1c** and **5e** (Table II), are downfield of those in the *Z* compounds, **1b** and **5d**, due to deshielding by the adjacent carbonyl group. Interestingly, the same trends of chemical shift values are evident in the ^{13}C NMR data (Table III), when the isopropyl carbons C_5, C_6, and C_7 of the *E* isomers appeared downfield of those in the *Z* compounds.

Chemical corroboration of these configurational assignments was obtained from a very important qualitative observation of the striking difference in the hydrolysis rates[7] of the esters; i.e., **4b**, $\sim$10 × **4c**. This large rate differential undoubtedly results from the steric effect of the proximal bulky isopropyl group on the approach of a nucleophile to the carbonyl function of the *E* isomer. This same effect might be expected to appear vis á vis peptide bond hydrolysis.

Experimental Section

Materials and Methods. Carbobenzoxy chloride, *p*-nitrobenzyl bromide, isobutylamine, isobutyl chloroformate, *N*-methylmorpholine (NMM), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide (EDC) were purchased from Aldrich Chemical Co. and were used without further purification except NMM, which was distilled from CaO. Triethylamine (TEA) was purchased from Eastman Kodak Co. and was distilled from CaO. DL-Serine, L-phenylalanine, and EDC were purchased from Sigma Chemical Co. and were used without further purification.

Melting points were recorded on a Thomas Hoover "Unimelt" capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out using the following solvent systems: (I) $CHCl_3$; (II) hexanes–EtOAc, 3:1, v/v; (III) BuOH–HOAc–H_2O, 4:1:5, v/v/v; (IV) $CHCl_3$–MeOH–AcOH, 90:10:1, v/v/v. All infrared spectra were recorded on a Perkin-Elmer Model 295 infrared spectrometer using KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX270Q spectrometer at frequencies of 270 and 67.5 MHz, respectively. One- and two-dimensional proton spectra were obtained on a Brucker AM 500 (at 500 MHz) and a Brucker AM 300 (at 300 MHz) spectrometer. Samples (0.3 M) in D_2O solution were degassed by several

(6) For examples of other methanoamino acid NMR spectra, see: (a) Mapelli, C.; Turocy, G.; Switzer, F. L.; Stammer, C. H. *J. Org. Chem.* **1989**, *54*, 145. (b) King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270.

(7) Malcolm Roberts, Master's Thesis, University of Georgia, 1984, Synthesis of Carbobenzoxy-(*E*)- and -(*Z*)-cyclopropaneleucine, p 23.

freeze–thaw cycles and sealed in NMR tubes under argon atmosphere. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) for ^1H NMR spectra and to $CDCl_3$ or *p*-dioxane for ^{13}C NMR spectra. Methylene, methyne, and quaternary carbon atoms of the cyclopropane ring were assigned by DEPT 135 °C experiments. Two-dimensional homonuclear spectroscopy and NOE correlated spectroscopy were carried out using ^1H–^1H COSY and NOESY pulse sequences (Bruker).

Photochemical reactions were carried out using a 450-W Hanovia high-pressure mercury arc lamp and quartz cell. TLC was carried out using Whatman MK6F silica gel (40A) TLC plates, which were visualized by UV and chlorine/*o*-tolidine. HPLC was carried out using a Waters Associates Liquid Chromatograph system comprising a Model 6000A solvent delivery system, a Model U6K universal liquid chromatograph injector, a Model 440 Absorbance Detector and a normal-phase μ-Porasil silica gel column (30 × 0.78 cm). Elemental analyses were carried out by Atlantic Microlab, Atlanta, GA.

***N*-Boc-dehydroalanine *p*-Nitrobenzyl Ester (2a).** To a solution of *N*-(*tert*-butoxycarbonyl)-DL-serine *p*-nitrobenzyl ester (3.0 g, 9 mmol) in $CHCl_3$ (90 mL) was added CuCl (0.9 g, 9 mmol) and EDC (2.07 g, 11 mmol). After stirring at room temperature for 6 h, 60 mL of water was added, and the mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 2.6 g (92%) of **2a** as white crystals: mp 95–96 °C; R_f (I) 0.61; ^1H NMR ($CDCl_3$) δ 8.5–8.2 and 7.7–7.4 (q, 4 H, Ar *H*), 7.1–6.9 (br s, 1 H, NH), 6.3 (s, 1 H, vinyl), 5.9 (s, 1 H, vinyl), 5.3 (s, 2 H, OCH_2), 1.4 (s, 9 H, $C(CH_3)_3$).

Anal. Calcd for $C_{15}H_{18}N_2O_6$: C, 55.90; H, 5.63; N, 8.69. Found: C, 55.85; H, 5.67; N, 8.65.

***N*-(Benzyloxycarbonyl)dehydroalanine *p*-Nitrobenzyl Ester (2b).** The ester **2b** was prepared in the manner described above from *N*-(benzyloxycarbonyl)-DL-serine *p*-nitrobenzyl ester (33.18 g, 0.08 mol), and the crude product was crystallized from ethyl acetate–hexanes followed by percolation in 3:1 hexanes–ethyl acetate solution through a sintered-glass funnel containing silica gel (60–200 mesh, 60 g). The solvent was removed in vacuo, and the oily residue was crystallized from ethyl acetate–hexanes to give 14.03 g (44.4%) of **2b** as pale yellow prisms; mp 86–88 °C; R_f (II) 0.52; ^1H NMR ($CDCl_3$) δ 8.30–7.41 (dd, 4 H, $PhNO_2$), 7.38 (s, 5 H, Ph), 7.26 (br s, 1 H, NH), 6.32 (m, 1 H, vinyl), 5.88 (m, 1 H, vinyl proton), 5.39 (s, 2 H, CH_2PhNO_2), 5.20 (s, 2 H, CH_2Ph).

Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.48; H, 4.54; N, 7.81.

***N*-Boc-3-amino-3-(4-nitrobenzyloxycarbonyl)-5,5-dimethyl-1-pyrazoline (3a).** An etheral solution of 2-diazopropane,[8] prepared from 15 g (0.21 mol) of acetone hydrazone,[9] was distilled into a receiving flask containing a solution of **2a** (9.5 g, 0.03 mol) in ether (300 mL) and cooled in a dry ice–acetone bath. When the generation of 2-diazopropane was complete, the flask was separated from the apparatus, fitted with a Drierite tube, placed in an ice bath, and kept in the dark. After 3 h, TLC (hexane/EtOAc, 9:1) showed the absence of starting material. A few drops of acetic acid were added, and the solvent was removed in vacuo, leaving **3a** as a solid: 7.63 g (63%); mp 98.5–99 °C dec; NMR ($CDCl_3$) δ 8.20 and 7.50 (dd, 4 H, Ar H), 6.80 (br, s, 1 H, NH), 5.25 (s, 2 H, OCH_2), 2.35 (s, 6 H, CH_3 × 2), 2.20 (s, 2 H, CH_2), 1.35 (s, 9 H, Boc). The analytical sample was recrystallized from ether.

Anal. Calcd for $C_{18}H_{24}N_4O_6$: C, 55.10; H, 6.17; N, 14.28. Found: C, 55.18; H, 6.20; N, 14.25.

***N*-Boc-2,3-methanovaline *p*-Nitrobenzyl Ester (4a).** A solution of 7.13 g (0.018 mol) of **3a** in toluene (200 mL) was placed in a 500-mL round-bottomed flask fitted with a thermometer and reflux condenser and heated in an oil bath at 120 °C. N_2 was rapidly evolved when the internal temperature reached 100 °C, and the flask was removed from the oil bath. TLC (hexane/EtOAc, 9:1) showed the absence of starting material. The toluene was removed in vacuo, and the solid residue was recrystallized from hot hexane–EtOAc to give 5.74 g (88%) of **4a** as white crystals, mp 114.5–116 °C. A sample was purified by silica gel chromatography (Chromatotron, hexane–EtOAc, 9:1) and recrystallized from hot hexane: mp 118–118.5 °C; NMR ($CDCl_3$) δ 8.20 and 7.50 (dd, 4 H, ArH), 5.10 (s, 2 H, OCH_2), 4.90 (br s, 1 H, NH), 1.35 (s, 9 H, Boc), 1.30 (s, 2 H, CH_2), 1.25 (s, 6 H, CH_3 × 2).

Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.42; H, 6.66; N, 7.67.

***N*-Boc-2,3-methanovaline (5a).** A solution of sodium dithionite (0.94 g, 5.4 mmol) and sodium carbonate (0.57 g, 5.4 mmol) in H_2O (15 mL) was added to a solution of **4a** (0.517 g, 14 mmol) in CH_3CN (15 mL) and after 23 h at reflux temperature, only traces of starting material remained (TLC, $CHCl_3$/MeOH/AcOH, 95:5:1). The CH_3CN was removed in vacuo, and the aqueous phase was acidified to pH 3 (10% citric acid) and extracted with Et_2O (2 × 40 mL). The organic layer was washed with 10% citric acid (3 × 20 mL) and 5% $NaHCO_3$ (3 × 30 mL), and the combined basic extract was washed with Et_2O (30 mL), acidified to pH 3 with 10% citric acid, and extracted with Et_2O (3 × 30 mL). The organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo to give **5a** as a white solid, 0.25 g (75%), mp 187.5–188 °C dec.

Anal. Calcd for $C_{11}H_{19}N_2O_4$: C, 57.56; H, 8.34; N, 6.22. Found: C, 57.59; H, 8.38; N, 6.07.

2,3-Methanovaline Hydrochloride (1a). To a solution of **5a** (0.22 g, 1.0 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added 4 N HCl in dioxane (2.5 mL), and the reaction mixture was stirred at room temperature for 2.0 h. The solvent was evaporated in vacuo, and the residue was crystallized from methanol–ether to yield 0.14 g (85%) of **1a**: mp 220–222 °C dec; R_f (III) 0.67.

Anal. Calcd for $C_6H_{12}NO_2Cl$: C, 43.51; H, 7.31; N, 8.46. Found: C, 43.60; H, 7.34; N, 8.42.

***p*-Nitrobenzyl 3-[(Benzyloxycarbonyl)amino]-5-isopropyl-1-pyrazoline-3-carboxylate (3b).** A solution of ethereal diazoisobutane[10] was added over 30 min to a stirred solution of **2b** (1.02 g, mmol) in CH_2Cl_2 (20 mL) at −15 to −12 °C. The reaction mixture was stirred cold for 1 h, the solvent was removed in vacuo and the yellow oily residue was dissolved in hexanes–ethyl acetate (3:1) and passed through a 60-mL sintered-glass funnel filled with silica gel (60–200 Å, 20 g). The solvent was removed in vacuo to give a yellow oil, which solidified on standing and was recrystallized from ethyl acetate–hexanes to give 0.94 g (74.6%) of **3b** as colorless needles: mp 91–92 °C dec; HPLC (hexanes–ethyl acetate, 3:1; flow rate 1 mL/min) 1 peak, t_R 37 min; R_f (II) 0.36; ^1H NMR ($CDCl_3$) δ 8.21–7.45 (dd, 4 H, $PhNO_2$), 7.33 (s, 5 H, Ph), 6.53 (br s, 1 H, NH), 5.32 (s, 2 H, CH_2PhNO_2), 5.03 (d, 3 H, CH_3), 0.97 (d, 3 H, CH_3); IR (KBr) 3350 ($NHCO_2$), 1740 (COOR), 1720 (NHCO), 1540 (N=N), 1510 (NO_2) cm^{-1}.

Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.91; H, 5.53; N, 12.68.

***N*-(Benzyloxycarbonyl)-2,3-methanoleucine *p*-Nitrobenzyl Ester (4b,c). (A) Pyrolysis.** The pyrazoline **3b** (0.69 g, 1.57 mmol) was dissolved in benzene, and the solution was refluxed for 4.5 h. On cooling, the solvent was removed in vacuo, and the yellow residue was recrystallized from ethyl acetate–hexanes to give 0.59 g (91.3%) of **4b,c** as white crystals: mp 120–123 °C; HPLC (hexanes–ethyl acetate, 3:1; flow rate 1/mL/min), two peaks, t_R 25, 25.7 min; R_f (II) 0.42; ^1H NMR ($CDCl_3$) δ 8.17–7.40 (dd, 4 H, $PhNO_2$), 7.31 (s, 5 H, Ph), 5.18 (s, 2 H, CH_2PhNO_2), 5.10 (s, 2 H, CH_2Ph), 1.93–1.22 (m, 4 H, $CHMe_2$, CH, and CH_2 of cyclopropane ring), 1.09–0,80 (m, 6 H, $(CH_3)_2CH$); IR (KBr) 3340 (NHCO), 1725 (COOR), 1700 (NHCO) cm^{-1}.

The ester mixture (**4b,c**, 4.0 g, 9.70 mmol) was dissolved in the minimum amount of hot absolute ethanol, and the solution was allowed to stand at room temperature overnight. The resulting crystals were collected by filtration, and the procedure was repeated three more times to give a total of 1.26 g (31.5%) of **4b** as colorless needles: mp 133–134 °C; HPLC (hexanes–ethyl acetate, 3:1; flow rate 1 mL/min) one peak, t_R 25.7 min. The recrystallization mother liquors were combined and evaporated in vacuo, and the yellow residue was recrystallized from ethyl acetate–hexanes to give 2.02 g (50.5%) of **4c** as a white solid: mp 87–89 °C; HPLC (hexanes–ethyl acetate, 3:1; flow rate 1 mL/min) one peak, t_R 25.0 min ^1H NMR ($CDCl_3$) (**4b**) δ 8.18–7.40 (dd, 4 H, $PhNO_2$), 7.31 (s, 5 H, Ph), 5.23 (br s, 1 H, NH), 5.19 (s, 2 H,

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CH_2PhNO_2), 5.12 (d, 2 H, CH_2Ph), 1.95–1.24 (m, 4 H, $CHMe_2$, CH, and CH_2 of cyclopropane ring), 1.05 (d, 3 H, CH_3), 0.99 (d, 3 H, CH_3); (**4c**) δ 8.13–7.42 (dd, 4 H, $PhNO_2$), 7.31 (s, 5 H, Ph), 5.35 (br s, 1 H, NH), 5.19 (s, 2 H, CH_2PhNO_2), 5.12 (d, 2 H, CH_2Ph), 1.78–1.21 (m, 4 H, $CHMe_2$, CH, and CH_2 of cyclopropane ring), 1.00 (d, 3 H, CH_3), 0.84 (d, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) (**4b**) δ 172.59 (C_1 of CH_2Ph), 128.50, 128.24, 127.79, 123.69, 67.11, (CH_2PhNO_2), 65.42 (CH_2Ph), 38.76 (cyclopropane ring), 36.94 ($CHMe_2$), 28.16 (CH of cyclopropane ring), 23.36 (CH_2 of cyclopropane ring), 22.63 (CH_3), 22.18, (CH_3); (**4c**) δ 171.29 (COOR), 156.40 (NHCO), 147.56 (C-NO_2), 143.07 (C_1 of $PhNO_2$), 136.18, 128.50, 128.11, 123.75, 66.92 (CH_2PhNO_2), 65.49 (CH_2Ph), 40.58 ($CHMe_2$), 39.21 (quat C of cyclopropane ring), 26.66 (CH of cyclopropane ring), 23.80 (CH_2 of cyclopropane ring), 22.18 (CH_3), 22.04 (CH_3).

Anal. Calcd for $C_{22}H_{24}N_2O_6$ (**4b,c**): C, 64.07; H, 5.87; N, 6.79. Found: (**4b**) C, 63.99; H, 5.90; N, 6.76; (**4c**) C, 64.14; H, 5.89; N, 6.77.

(B) Photolysis (ii). A stirred soluton of **3b** (0.2 g, 0.45 mmol) in toluene (700 mL) was irradiated in a quartz cell using a 450-W high-pressure mercury lamp at −18 to −15 °C for 15 min. The solvent was removed in vacuo, and the oily residue was crystallized from ethyl acetate–hexanes to give 0.08 g (42.7%) of **4c** as a white solid; mp 83–84 °C; HPLC (hexanes–ethyl acetate, 3:1; flow rate 1 mL/min) one peak, t_R 25.0 min; ^1H NMR ($CDCl_3$) δ 8.19–7.40 (dd, 4 H, $PhNO_2$), 7.31 (s, 5 H, Ph), 5.36 (br s, 1 H, NH), 5.19 (s, 2 H, CH_2PhNO_2), 5.12 (d, 2 H, CH_2Ph), 1.78–1.20 (m, 4 H, $CHMe_2$, CH, and CH_2 of cyclopropane ring), 1.00 (d, 3 H, CH_3), 0.84 (d, 3 H, CH_3).

Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.9; H, 5.91; N, 6.75.

***N*-(Benzyloxycarbonyl)-(*Z*)-2,3-methanoleucine (5b).** To a stirred solution of **4b** (1.26 g, 3.06 mmol) in methanol (20 mL) at room temperature was added dropwise 3 N KOH (10.2 mL). The reaction mixture was stirred at room temperature for 24 h, and the methanol was removed in vacuo. The residual aqueous solution was washed with ethyl acetate (3 × 10 mL) and acidified to pH 2 with concentrated HCl, and the precipitate was extracted into ethyl acetate (2 × 25 mL). The organic layer was washed with saturated NaCl solution (1 × 5 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo to yield a yellow oil. The crude product was crystallized from ethyl acetate–hexanes to give 0.30 g (35.4%) of **4b** as colorless crystals: mp 114–115 °C; ^1H NMR ($CDCl_3$) δ 9.47 (br s, 1 H, COOH), 7.31 (s, 5 H, Ph), 5.27 (br s, 1 H, NH), 5.13 (s, 2 H, CH_2Ph), 1.97–1.23 (m, 4 H, $CHMe_2$, CH, and CH_2 of cyclopropane ring), 1.05 (d, 3 H, CH_3), 0.99 (d, 3 H, CH_3).

Anal. Calcd for $C_{15}H_{19}NO_{14}$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.05; H, 6.95; N, 5.02.

***N*-(Benzyloxycarbonyl)-(*E*)-2,3-methanoleucine (5c).** The ester **4c** (1.80 g, 4.36 mmol) was hydrolyzed in the manner described above to yield a yellow oil, which was dissolved in ether (10 mL) to which dicyclohexylamine (0.79 g, 4.36 mmol) was added. The resulting white precipitate was collected by filtration, washed with ethyl acetate, and dissolved in 3 N KOH (10 mL). The solution was diluted with water (25 mL) and washed with ethyl acetate (3 × 10 mL), and the aqueous layer was acidified to pH 2 with concentrated HCl. The precipitate was extracted with ethyl acetate (2 × 25 mL), and the organic layer was washed with saturated NaCl solution (1 × 5 mL), dried over Na_2SO_4 (anhydrous), and evaporated in vacuo to yield an amorphous solid, which stood 4 days under hexanes at 4 °C to give 0.21 g (17%) of **5c** as a white solid: mp 96–97 °C; ^1H NMR ($CDCl_3$) δ 8.94 (br s, 1 H, COOH), 7.32 (s, 5 H, Ph), 5.52 (br s, 1 H, NH), 5.13 (s, 2 H, CH_2Ph), 1.89–1.21 (m, 4 H, $CHMe_2$, CH, CH_2 of cyclopropane ring), 1.00 (d, 6 H, CH_3 of i-Pr).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.09; H, 6.95; N, 5.03.

Saponification of 4a and 4b. To stirred solutions of **4a** and **4b** (0.01 g, 0.24 mmol) in methanol 1 mL) and THF (0.1 mL) was added 3 N KOH (0.8 ml) at room temperature. The reactions were followed by TLC using hexanes–ethyl acetate, 3:1, as eluant. The spot as R_f 0.42 for **4a** disappeared within 5 min and for **4b** within 60 min.

***N*-Boc-(*Z*)-2,3-methanoleucine (5d).** To a solution of **4b** (2.0 g, 0.048 mol) in N_2-purged methanol (200 mL) was added 5% Pd/C (20 mg). Hydrogen was bubbled into the solution at atmospheric pressure and room temperature, for 4.0 h. The catalyst was filtered, the solvent was evaporated under reduced pressure, and the crude product, R_f (III) 0.75, was used in the next step.

A solution of crude (*Z*)-2,3-methanoleucine (0.65 g, 4.8 mmol) and 2 N NaOH (2.4 mL) in dioxane–water (50%) (4.8 mL) was chilled to 0 °C, and di-*tert*-butyl dicarbonate (1.57 g, 7.2 mmol) was added in two aliquots with vigorous stirring. The reaction mixture was stirred at 0 °C for 2.0 h and then at room temperature overnight. The solvent was removed under reduced pressure, and the residue was diluted with water. The solution was acidified by addition of 10% $KHSO_4$ to pH 2 and extracted with ethyl acetate. The extracts were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The oily residue was crystallized from ethyl acetate–hexane to yield 0.86 g (73%) of **5d**: mp 210 °C; R_f (IV) 0.45.

Anal. Calcd for $C_{12}H_{21}O_4N$: C, 59.25; H, 8.64; N, 5.76. Found: C, 59.59; H, 8.79; H, 5.83.

***N*-Boc-(*E*)-2,3-methanoleucine (5e).** The *E* isomer was prepared from **4c** (2.0 g, 4.8 mmol) in the same manner as the *Z* isomer to give 0.9 g (76.3%) of **5e**: mp 200–202 °C; R_f (IV) 0.45.

Anal. Calcd for $C_{12}H_{21}O_4N$: C, 59.25; H, 8.64; N, 5.76. Found: C, 59.09; H, 8.76; N, 5.92.

(*Z*)-2,3-Methanoleucine Hydrochloride (1b). To a solution of **5d** (0.36 g, 1.5 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added 4 N HCl in dioxane (2.0 mL). The reaction mixture was stirred for 2.0 h at room temperature, the solvent was evaporated under reduced pressure, and the oily residue was triturated with anhydrous ether to afford a white solid, which was recrystallized from anhydrous methanol–ether to yield 0.2 g (74.2%) of **1b**: mp 187–189 °C dec; R_f (III) 0.76.

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.79; H, 7.79; N, 7.79. Found: C, 46.82; H, 7.87; N, 7.74.

(*E*)-2,3-Methanoleucine Hydrochloride (1c). This compound was prepared in the same manner as the *Z* isomer from **5e** (0.36 g, 1.5 mmol) to give 0.20 g (73%) of **1c**: mp 175 °C dec; R_f (III) 0.76.

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.79; H, 7.79; N, 7.79. Found: C, 46.89; H, 7.83; N, 7.69.

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Registry No. **1a**·HCl, 123311-22-8; **1b**·HCl, 95474-42-3; **1c**·HCl, 123311-23-9; **2a**, 88950-54-3; **2b**, 52715-73-8; **3a**, 123311-13-7; **3b**, 123311-14-8; **4a**, 123311-15-9; **4b**, 123311-16-0; **4c**, 123311-17-1; **5a**, 123311-18-2; **5b**, 123311-19-3; **5c**, 123311-20-6; **5d**, 123311-21-7; **5e**, 88950-67-8; BOC-DL-Ser-OpNB, 123311-11-5; Cbz-DL-Ser-OpNB, 123311-12-6; $Me_2C{=}N_2$, 2684-60-8; (*i*-Pr)$HC{=}N_2$, 763-36-0.