(m, 1 H), 4.57 (m, 1 H), 6.88 (d, 2 H, *J* = 7.3 Hz), 7.05 (d, 2 H, *J* = 8.1 Hz); mass spectrum, *m/e* (relative intensity) 448 (1.2), 375 (1.1), 347 (2.4), 234 (43.4), 70 (100). Anal. Calcd for $C_{24}H_{36}N_2O_6$: C, 64.3; H, 8.1; N, 6.2. Found: C, 63.4; H, 8.1; N, 6.0.

p-Nitrophenyl 4-Methyl-3-[4′β-[[[*N′*-[(*tert*-butyloxy)-carbonyl]-L-prolyl]amino]ethyl]phenoxy]pentanoate (9). A mixture of the acid 8 (340 mg, 0.76 mmol) and *p*-nitrophenyl trifluoroacetate[10] (270 mg, 1.14 mmol) in 15 mL of pyridine was stirred for 14 h at room temperature. After evaporation, the residue was dissolved in 50 mL of ethyl acetate and washed with 1 M HCl (3 × 25 mL), 50% saturated NaHCO₃ (5 × 25 mL), and saturated NaCl (1 × 10 mL), dried, and evaporated. The resulting yellow oil was chromatographed (SiO₂, 50 g; EtOAc/toluene, 2/1) to give 9 (413 mg, 95%) as an equal mixture of diastereomers: NMR δ 1.04 (d, 6 H, *J* = 6.6 Hz), 1.42 (s, 9 H), 1.5–2.4 (m, 4 H), 2.6–3.0 (m, 5 H), 3.2–3.6 (m, 4 H), 4.22 (m, 1 H), 4.68 (m, 1 H), 6.25 (s, 1 H), 6.92 (d, 2 H, *J* = 8.8 Hz), 7.11 (d, 2 H, *J* = 8.8 Hz), 7.13 (d, 2 H, *J* = 9.5 Hz), 8.20 (d, 2 H, *J* = 9.5 Hz).

cyclo-[[4-Methyl-3-[4′β-[(aminoethyl)phenyl]oxy]penta-noyl]-L-prolyl]; (5*S*,9*R*)-9-Isopropyl-5,6-trimethylene-8-deamino-1,2-dihydro-*p*-phencyclopeptine (4). The active ester 9 (521 mg, 0.91 mmol) was dissolved in 15 mL of anhydrous TFA at 0 °C. After 1 h the solvent was removed in vacuo to give an oil (776 mg) which was dissolved in 575 mL of *N,N*-dimethyl-

acetamide. This solution was added by a metering pump over a period of 50 h to 600 mL of pyridine, mechanically stirred and maintained at 90 °C. The solution was stirred and heated an additional 10 h, the solvent was evaporated, and the residue was dissolved in methanol and passed through a mixed-bed ion-exchange resin. The first 100 mL of eluant was collected, evaporated, and chromatographed on Sephadex LH-20 (200 g, MeOH). Fractions 1 (47 mg), 2 (187 mg), and 3 (65 mg) were collected. Fraction 3 was sublimed at 120 °C (0.02 mm) to give 62 mg of a yellow glass. Following TLC (CHCl₃/MeOH, 20/1) two bands were isolated with *R_f*'s of 0.65 and 0.56 in a 5/1 mass ratio. the *R_f* 0.65 band was cyclopeptide 4 (52 mg, 18% yield from total educt). The minor component (*R_f* 0.56) was not a 14-membered-ring cyclopeptide and was not further characterized. For cyclopeptide 4: ¹H NMR, summarized in Table I and Figure 1; UV λ_max 271 nm (ε 614), 276 (564); low-resolution mass spectrum, *m/e* (relative intensity) 331 (3.3), 330 (14.8), 211 (12.2), 70 (100); high-resolution mass spectrum calcd for $C_{19}H_{26}N_2O_3$ *m/e* 330.1943, found *m/e* 330.1945; IR (CHCl₃) 1678, 1612 cm⁻¹.

Registry No. 3d, 69100-22-7; **4**, 75266-53-4; **5**, 68898-89-5; **6**, 75266-54-5; **7a**, 75266-55-6; (*E*)-**7b**, 75266-56-7; (*Z*)-**7b**, 75266-57-8; **8** (isomer 1), 75266-58-9; **8** (isomer 2), 75266-59-0; **9** (isomer 1), 75266-60-3; **9** (isomer 2), 75266-61-4; 3-methyl-1-butyne, 598-23-2; benzyl chloroformate, 501-53-1.

L-Vinylglycine

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Optically pure L-vinylglycine (1) has been synthesized from L-methionine in 54% overall yield. The process consists in first preparing *N*-[(benzyloxy)carbonyl]methionine methyl ester (9) which is then oxidized to methyl 2-[[(benzyloxy)carbonyl]amino]-4-(methylsulfinyl)butyrate (10). Thermal syn elimination followed by acid hydrolysis then gives L-vinylglycine.

Vinylglycine (1), which has been isolated in the partially racemized D form from mushrooms,[2] has been the subject of numerous biochemical studies and has been postulated as an intermediate in the enzymatic conversions of homoserine to threonine[3] and α-ketobutyrate.[4] It was first synthesized in 1974[5] as the racemic material in very poor yield and partially resolved to D-vinylglycine with L-amino acid oxidase or baker's yeast.[5a] Subsequently, in a related approach, the synthesis of racemic 1 was described from acrolein in an overall yield of 15%.[6] In this report, we present a convenient and high-yield synthesis of optically pure L-vinylglycine and some of its derivatives.

One of the early[7] methods for the synthesis of unsaturated amino acid derivatives makes use of olefin formation through syn elimination from selenoxides.[8] Thus dehydroalanine derivatives were prepared from selenocysteine derivatives, and similarly, α,β-unsaturated amino acid derivatives and dehydropeptides have been prepared by syn elimination of sulfoxides[9] (2 → 3 → 4). The relatively

mild conditions effective in the latter instances (80–140 °C) presumably result from the ease of removal of the α-proton.

Y = Se, S   R₂, R₃ = H, alkyl
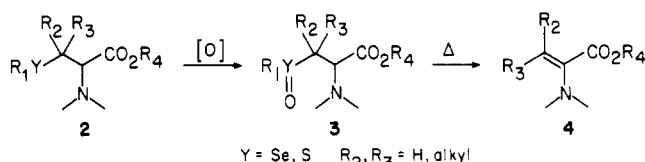
When sulfoxide elimination was applied to the formation of β,γ-unsaturated amino acid derivatives where the reactivity of the α-proton could not be exploited, much more drastic conditions were used.[8] Thus methyl 2-[[(*tert*-butyloxy)carbonyl]amino]-3-butenoate (6) was obtained by
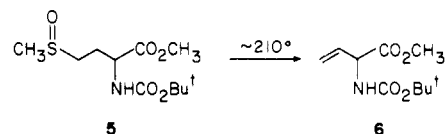
passing a dilute solution of sulfoxide 5 in xylene through a hot tube at 200–210 °C; no optical activity data were reported for product 6.

Our interest in vinylglycine required a method for the preparation of optically pure material and on a scale compatible with its use as a synthetic intermediate. Therefore we undertook a study of its formation from

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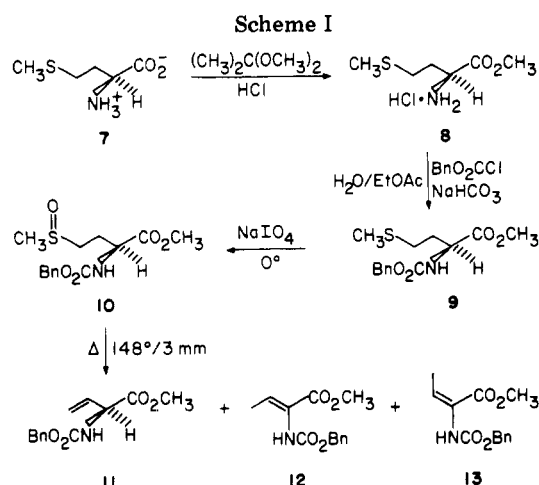(4) Posner, B. I.; Flavin, M. *J. Biol. Chem.* 1972, *247*, 6402.

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Scheme I

Table I. Dehydrosulfenylation of Methyl 2-[[(Benzyloxy)carbonyl]amino]-4-(methylsulfinyl)butyrate (10)

|	temp,	pressure,	% olefinic products[a]		
expt	°C	mmHg	11	12	13
1	180	3	80	14	6
2	160	3	90	10	0
3	148	3	95	5	0
4	148	0.02	10[b]	0	0

[a] Yield and ratio of olefinic products as determined by gas chromatography. [b] The remaining 90% is unchanged sulfoxide 10 which is highly volatile under these conditions.

methionine under milder, nonracemizing conditions.

Although we were able to effect dehydrosulfenylation of sulfoxide 5 under milder conditions (Kugelrohr distillation at 140 °C (5 mm)), the relatively high volatility of 5 always led to a substantial amount of unchanged sulfoxide 5 as an accompanying impurity in olefin 6. Higher temperatures and pressures decreased this impurity but caused increased thermal isomerization to the α,β-unsaturated isomer.

A more effective way to suppress the volatility of 5 was to substitute a benzyl group for the *tert*-butyl group in 5. Thus, L-methionine (7) was converted to its methyl ester hydrochloride 8 (Scheme I) in practically quantitataive yield by refluxing in methanolic hydrogen chloride or by stirring at room temperature a 2,2-dimethoxypropane solution of 7 with concentrated hydrochloric acid.[10] Treatment of ester 8 with benzyl chloroformate under Schotten–Baumann conditions afforded the N-[(benzyloxy)carbonyl] ester 9 in 95% yield as white needles, mp 42–43 °C. Oxidation of 9 was accomplished in quantitative yield by treatment with sodium metaperiodate to give the sulfoxide 10, isolated as amorphous white solid.

Pyrolysis of methyl 2-[[(benzyloxy)carbonyl]amino]-4-(methylsulfinyl)butyrate (10) by Kugelrohr distillation led to the desired β,γ-unsaturated product 11, accompanied by some of the Z and E α,β-unsaturated isomers 12 and 13.[11] The best conditions [148 °C (3 mm), Table I] resulted in an olefinic product which was 95% β,γ and 5%

Scheme II
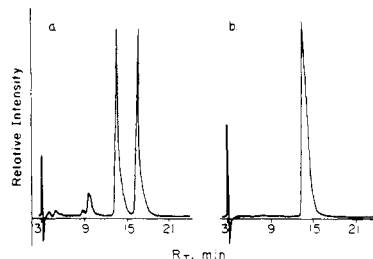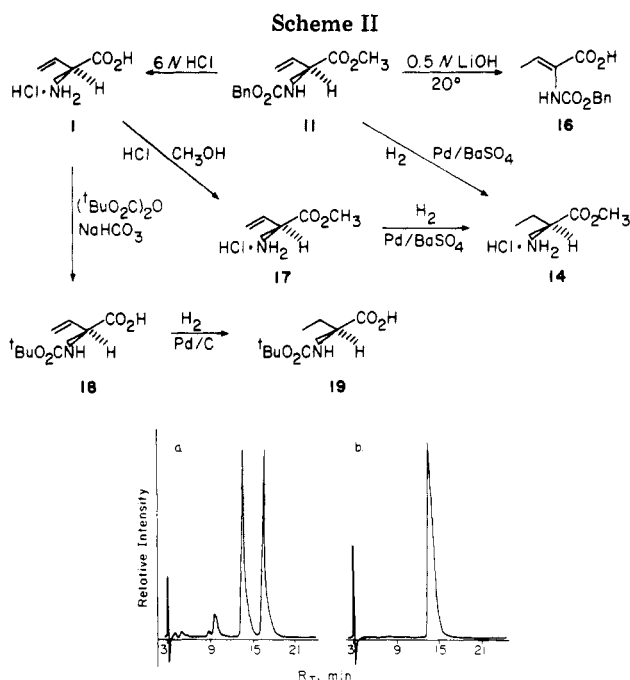
Figure 1. High-pressure liquid chromatogram of (a) amides 15 obtained from racemic α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride and racemic methyl 2-aminobutanoate and (b) amide 15 obtained from (+)-acid chloride and methyl 2-aminobutanoate (14) originating from vinylglycine derivative 11.

(Z)-α,β isomer. Simple chromatography then removed some unidentified sulfur-containing byproducts and gave the protected vinylglycine 11 in 80% isolated yield for this elimination step. The β,γ-unsaturated derivative 11 is very base sensitive and is converted to its (Z)-α,β isomer 12 quantitatively by stirring a solution of 11 in an organic solvent with triethylamine or N-methylmorpholine.

The optical purity of the protected vinylglycine 11 was determined by conversion first to methyl 2-aminobutanoate (14), Scheme II, by hydrogenolysis and hydrogenation at atmospheric pressure. Reaction of 14 with (+)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride[12] then afforded the amide 15 as a colorless viscous oil. To obtain a reference sample, we carried out the above reaction with (±)-methyl 2-aminobutanoate [prepared from (±)-methionine under the same conditions used to prepare 11] and (±)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride to give the diastereoisomeric mixture of amides 15. High-pressure liquid chromatography gave complete separation of these diastereomeric amides 15. When these conditions were applied to the amide 15 originating from vinylglycine derivative 11, only a single amide was detected, establishing that 11 was optically pure (Figure 1). It is of interest that the NMR spectra of the diastereomeric methyl ester amides 15 show a marked chemical shift difference (0.15 ppm) in the absorptions of the α-methoxy protons. This is in contrast to the practically identical chemical shifts found for these protons when derivatizing simple amines.[12]

Alkaline hydrolysis of 11 even under very mild conditions resulted in migration of the double bond as well as hydrolysis of the methyl ester to form the α,β-unsaturated acid 16. However, acid hydrolysis of 11 gave vinylglycine (1) in greater than 90% yield, isolated and characterized as its hydrochloride salt. The vinylglycine so obtained was shown to be optically pure by conversion to 2-amino-

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(11) Configurations were assigned to the α,β-unsaturated isomers on the basis of their NMR spectra, (Z)-12 showing an absorption at δ 1.8 (C=CCH₃) in comparison to that of (E)-13 at δ 2.05. The latter is obtained along with 11 and 12 when sulfoxide 10 is Kugelrohr distilled at 180 °C. Support for these assignments of geometrical isomers of α,β-unsaturated α-amino acid derivatives is found in: (a) Srinivasan, A.; Richards, K. D.; Olsen, R. K. *Tetrahedron Lett.* 1976, 891; (b) Poisel, H. *Chem. Ber.* 1977, *110*, 948; (c) ref 9.

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* 1969, *34*, 2543.

butyrate **14** through vinylglycine methyl ester **17** and analysis as the amide with (+)-acid chloride. Finally, the (*tert*-butyloxy)carbonyl derivative **18** of vinylglycine (**1**) was also obtained in high yield by treatment of the latter with di-*tert*-butyl dicarbonate in aqueous dioxane. Whereas optical purities previously were established through methyl 2-aminobutanoate (**14**) and analysis as amides **15** with α-methoxy-α-[(trifluoromethyl)phenyl]-acetyl chloride, the Boc acid **18** was analyzed by derivatization through the carboxyl group. Hydrogenation gave α-[[(*tert*-butyloxy)carbonyl]amino]butanoic acid (**19**) which was converted to amides **20** with both optically active and racemic α-phenylethylamine via the mixed carbonic anhydride method.[13] High-pressure LC analysis established that **18** was >99% optically pure.

Thus this method of preparation provides optically pure L-vinylglycine as the amino acid hydrochloride **1**, the methyl ester hydrochloride **17**, the N-protected acid **18**, and the N-protected ester **11**.

Experimental Section

Melting points were determined on a Buchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. ^{1}H NMR (internal Me$_4$Si) spectra were taken on a Varian T60 or Varian EM-390 instrument. High-pressure LC analysis was carried out on an Altex Model 110 instrument using a Lichrosorb Si-60, 3.2 × 250 mm, 5-μm silica column. All preparative column chromatography was carried out by using E. Merck, 70–230-mesh, A57M silica gel 60. Organic solutions were dried over MgSO$_4$ and evaporated on a Berkeley rotary evaporator. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

L-Methionine methyl ester hydrochloride (8) was prepared as directed:[10] 95% yield; mp 145–146 °C (lit.[10] mp 147–150 °C).

N-[(Benzyloxy)carbonyl]-L-methionine Methyl Ester (9). To an ice-cold solution of **8** (2.00 g, 10 mmol) and potassium bicarbonate (5 g) in 50 mL each of water and ethyl acetate was added dropwise benzyl chloroformate (1.87 g, 11 mmol) over a period of 30 min. After the mixture was stirred for 4 h, the organic layer was separated, washed with dilute hydrochloric acid and then water, dried, and evaporated to a colorless oily residue. Kugelrohr distillation [120 °C (0.05 mm)] and crystallization from petroleum ether gave 2.7 g (90% yield) of **9**: mp 42–43 °C; [α]$^{20}_D$ +16.9° (*c* 4, CHCl$_3$); NMR (CDCl$_3$) δ 2.01 (m, 5 H), 2.41 (m, 2 H), 3.68 (s, 3 H), 4.4 (m, 1 H), 5.02 (s, 2 H), 7.23 (s, 5 H). Anal. Calcd for C$_{14}$H$_{19}$NO$_4$: C, 56.6; H, 6.4; N, 4.7. Found: C, 56.7; H, 6.4; N, 4.7.

Methyl L-2-[[(Benzyloxy)carbonyl]amino]-4-(methylsulfinyl)butanoate (10). A solution of sodium metaperiodate (2.22 g, 10.4 mmol) in 12 mL of water was added dropwise to a vigorously stirred ice-cold solution of sulfide **9** (2.97 g, 10 mmol) in 30 mL of methanol. The reaction mixture was stirred for an additional 3 h, the precipitated iodate was filtered off and washed with methanol, and the combined filtrates were concentrated to 10 mL and then extracted several times with chloroform. The combined CHCl$_3$ extracts were washed with water, dried, and evaporated, and the oily residue was Kugelrohr distilled at 120 °C (0.03 mm) to give 2.95 g (95% yield) of sulfoxide **10**: NMR (CDCl$_3$) δ 2.47 (s, 3 H), 2.63 (t, 2 H), 3.66 (s, 3 H), 5.03 (s, 2 H), 6.16 (br d, 1 H, *J* = 8 Hz), 7.1 (s, 5 H). Anal. Calcd for C$_{14}$H$_{19}$NO$_5$S: C, 53.7; H, 6.1; N, 4.5. Found: C, 53.8; H, 6.2; N, 4.4.

Pyrolysis of Sulfoxide 10. Methyl L-2-[[(benzyloxy)carbonyl]amino]-4-(methylsulfinyl)butanoate (**10**; 3.13 g, 10 mmol) was Kugelrohr distilled at 148 °C (3 mm). The yellowish brown oily distillate was chromatographed on a column of silica gel by eluting with an 85/15 mixture of *n*-hexane/ethyl acetate to give 2.05 g (80% yield) of **11** as a light yellow oil contaminated with

2% of its (Z)-α,β isomer **12**. A second column chromatography with 9/1 *n*-hexane/ethyl acetate afforded analytically pure N-[(benzyloxy)carbonyl]-L-vinylglycine methyl ester (**11**) in quantitative recovery as a colorless oil: [α]$^{20}_D$ –11.8° (*c* 1.8, CH$_3$OH); NMR (CDCl$_3$) δ 3.61 (s, 3 H), 4.8 (m, 1 H), 5.0 (s, 2 H), 5.1 (m, 1 H), 5.25 (dd, 1 H, *J* = 6 Hz, *J'* = 1 Hz), 5.6–6 (m, 2 H). Anal. Calcd for C$_{13}$H$_{15}$NO$_4$: C, 62.5; H, 6.0; N, 5.6. Found: C, 62.6; H, 6.1; N, 5.6.

Isomerization of 11 to 12. Triethylamine (600 mg, 6 mmol) was added to a solution of **11** (250 mg, 1 mmol) in methanol (10 mL), and the solution was stirred at room temperature for 3 h. The solution was evaporated, the residue was dissolved in 20 mL of CH$_2$Cl$_2$, the CH$_2$Cl$_2$ was washed twice with 10% hydrochloric acid and then with water, dried, and evaporated, and the residue was crystallized from ether/petroleum ether to give 200 mg (80% yield) of **12**:[11] mp 69–70 °C; NMR (CDCl$_3$) δ 1.8 (d, 2 H, *J* = 6 Hz), 3.65 (s, 3 H), 5.4 (br s, 1 H), 6.7 (q, 1 H, *J* = 6 Hz), 7.25 (s, 5 H). Anal. Calcd for C$_{13}$H$_{15}$NO$_5$: C, 62.6; H, 6.0; N, 5.6. Found: C, 62.6; H, 6.0; N, 5.7.

Hydrolysis of 11 to 16. A solution of **11** (500 mg, 2 mmol) in 10 mL each of acetone and 0.5 M lithium hydroxide was stirred at room temperature for 30 min. After the acetone was evaporated, the aqueous solution was acidified with concentrated HCl and extracted with ether (3 × 25 mL). The combined ether extracts were washed with brine, dried, and evaporated to leave 450 mg (96% yield) of a crystalline residue of **16**: mp 185–186 °C (from hexane/ether); NMR (acetone-d$_6$) δ 1.8 (d, *J* = 7 Hz, 3 H), 5.1 (s, 2 H), 6.65 (q, *J* = 7 Hz, 1 H), 7.3 (s, 5 H). Anal. Calcd for C$_{12}$H$_{13}$NO$_4$: C, 61.3; H, 5.5; N, 5.9. Found: C, 61.1; H, 5.6; N, 5.9.

Conversion of Methyl L-2-[[(Benzyloxy)carbonyl]amino]-3-butenoate [N-[(Benzyloxy)carbonyl]-L-vinylglycine Methyl Ester (11)] to Methyl L-2-Aminobutanoate (14). Hydrogen was bubbled through a vigorously stirred mixture of **11** (2.50 g, 10 mmol) in 50 mL of methanol containing 2 g of 5% Pd/BaSO$_4$. After 45 min, the mixture was filtered, the catalyst was washed with CH$_3$OH, and the combined filtrate and methanol washings were evaporated to an oily residue which was Kugelrohr distilled at 20 °C (0.03 mm) to give 0.95 g (81% yield) of **14**, characterized as its hydrochloride salt: mp 145–146 °C (lit.[14] mp 116–117 °C; [α]$^{20}_D$ +14.1° (*c* 1, 95% AcOH) [lit.[14] [α]$^{24}_D$ +13.8° (*c* 1, 95% AcOH)]; NMR (D$_2$O) δ 0.82 (t, 3 H), 1.83 (q, 2 H), 3.53 (s, 3 H), 3.96 (t, 1 H). Anal. Calcd for C$_5$H$_{12}$ClNO$_2$: C, 39.1; H, 7.8; N, 9.1. Found: C, 39.0; H, 8.0; N, 9.2.

N-[1-(Methoxycarbonyl)propyl]-α-methoxy-α-[(trifluoromethyl)phenyl]acetamide (15). A solution of (+)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride[11] (252 mg, 1 mmol) in 2 mL of carbon tetrachloride was added dropwise to a stirred solution of methyl (–)-2-aminobutanoate (**14**; 117 mg, 1 mmol) and triethylamine (200 mg, 2 mmol) in 5 mL of carbon tetrachloride, with the temperature of the reaction mixture maintained at 20 °C. The solution was stirred at 20 °C for 2 h, washed successively with 10% hydrochloric acid, H$_2$O, 5% NaHCO$_3$, and water, dried, and evaporated to give amide **15** as a colorless oil: NMR (CDCl$_3$) δ 0.86 (t, 3 H), 1.8 (m, 2 H), 3.53 (d, 3 H, *J* = 2 Hz, α-OCH$_3$), 3.7 (s, 3 H), 4.53 (m, 1 H), 7.2 (m, 5 H). Amide **15** prepared from (+)-acid and (–)-amine **14** has a retention time of 13.2 min on analytical high-pressure LC, eluting with a 91/9 mixture of *n*-hexane/ethyl acetate with a flow rate of 0.75 mL/min.

The above reaction was repeated with racemic acid and amine, and the oily product had the following characteristics: NMR (CDCl$_3$) δ 0.87 (t, 6 H), 1.79 (m, 4 H), 3.38 (d, 3 H, *J* = 2 Hz, α-OCH$_3$), 3.52 (d, 3 H, *J* = 2 Hz, α-OCH$_3$), 3.7 (s, 6 H), 4.55 (m, 2 H), 7.22 (m, 10 H). On high-pressure LC under the conditions described above, two equal peaks appeared with retention times of 13.2 and 16.5 min, respectively.

L-Vinylglycine Hydrochloride (1). A mixture of methyl L-2-[[(benzyloxy)carbonyl]amino]-3-butenoate (**11**; 2.50 g, 10 mmol) in 50 mL of 6 N hydrochloric acid was refluxed for 1 h. The solution was cooled, washed with chloroform (2 × 20 mL), and evaporated to dryness. Crystallization of the residue was achieved by refluxing in 50 mL of acetone to give L-vinylglycine

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hydrochloride (1): 1.22 g (88% yield); mp 175–177 °C dec; $[\alpha]^{20}_D$ +78.5° (c 1.9, H_2O), +96° (c 1, 2 N HCl); NMR (D_2O) δ 4.6 (d, 1 H, J = 6 Hz), 5.35–6.1 (m, 3 H). Anal. Calcd for $C_4H_8ClNO_2$: C, 34.4; H, 5.7; N, 10.0. Found: C, 34.9; H, 5.5; N, 9.9.

The vinylglycine hydrochloride (1) obtained above was proved to be optically pure as follows. A solution of 1 (275 mg, 2 mmol) in 20 mL of dry methanol saturated with HCl gas was refluxed for 4 h with the use of dry ice condenser. Evaporation left 250 mg (85% yield) of the hydrochloride 17 as an amorphous residue: $[\alpha]^{20}_D$ +81.4° (c 2, CH_3OH); NMR (free base, $CDCl_3$) δ 3.63 (s, 3 H), 3.95 (m, 1 H), 5.0–6.1 (m, 3 H). Anal. Calcd for $C_5H_{10}ClNO_2 \cdot {}^1/_3H_2O$: C, 38.1; H, 6.8; N, 8.9. Found: C, 38.0; H, 6.8; N, 8.7.

A solution of 200 mg of 17 in 10 mL of methanol was shaken with H_2 at 40 psi in the presence of $Pd/BaSO_4$ for 4 h. The catalyst was removed, the solvent was evaporated, and the residue was crystallized from acetone, affording methyl 2-aminobutanoate (14), identical in all respects with 14 obtained from hydrogenation of 11. Treatment of 14 with (+)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride gave ester amide 15 which showed a single peak, R_T = 13.2 min, on high-pressure LC as above.

L-2-[(tert-Butyloxy)carbonyl]amino]-3-butenoic Acid (18). A solution of L-vinylglycine hydrochloride (1; 275 mg, 2 mmol), di-tert-butyl dicarbonate (575 mg, 2.1 mmol), and sodium bicarbonate (335 mg, 4 mmol) in 12 mL each of dioxane and water was refluxed for 2 h. The dioxane was evaporated, and the aqueous solution was acidified with dilute hydrochloric acid and extracted with chloroform (3 × 15 mL). The combined chloroform extracts were washed with saturated sodium bicarbonate and then water, dried, and evaporated to give 450 mg (87% yield) of 18

as a colorless oil: NMR ($CDCl_3$) δ 1.46 (s, 9 H), 3.7 (m, 1 H), 4.73 (br d, 1 H), 5.1–6.05 (m, 3 H), 10.3 (s, 1 H); $[\alpha]^{20}_D$ +2.8° (c 4, CH_3OH). Anal. Calcd for $C_8H_{15}NO_4$: C, 53.7; H, 7.5; N, 7.0. Found: C, 53.5; H, 7.8; N, 6.7.

The optical purity of acid 18 was determined by hydrogenating a solution of 18 (200 mg, 1 mmol) in 10 mL of methanol with H_2 at 40 psi in the presence of 150 mg of 10% Pd/C for 16 h. The catalsyt was removed, the solvent was evaporated, and to the residue of 19 as a solution in 10 mL THF at –20 °C were added isobutyl chloroformate (137 μL, 1 mmol) and N-methylmorpholine (112 μL, 1 mmol). After the mixture was stirred for 10 min at –20 °C, (+)-α-phenylethylamine (130 μL, 1 mmol) was added and stirring continued for 20 min. Extraction in the usual way gave the L-2-[[(tert-butyloxy)carbonyl]amino]butanoyl-d-α-phenylethylamide (20) as a colorless oil in quantitative yield. The above procedure was repeated with acid 19 and (±)-α-phenylethylamine. The diastereomeric amides 20 from the latter reaction on high-pressure LC (10/1 hexane/ethyl acetate, 1.5 mL/min) showed two equal peaks (R_T = 9.6 and 11.1 min); the amide 20 from the former reaction showed only the single peak of R_T = 9.6 min.

Registry No. 1, 75266-38-5; 8, 2491-18-1; 9, 56762-93-7; 10, 75266-39-6; 11, 75266-40-9; 12, 60027-61-4; 13, 60027-55-6; 14, 56545-22-3; (±)-14, 7682-18-0; 15, 70363-18-7; (±)-15 (isomer 1), 75330-84-6; (±)-15 (isomer 2), 75330-85-7; 16, 72015-57-7; 17, 75266-41-0; 18, 75266-42-1; 19, 34306-42-8; 20 (isomer 1), 75266-43-2; 20 (isomer 2), 75266-44-3; benzyl choroformate, 501-53-1; (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4; (±)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 64312-89-6; di-tert-butyl dicarbonate, 691-64-5; (+)-α-phenethylamine, 3886-69-9; (±)-α-phenethylamine, 618-36-0.

Synthetic Studies toward Verrucarol. 1. Synthesis of the AB Ring System

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A synthetic route to the AB ring system of verrucarol is described. After two routes employing intramolecular cyclization failed, the Diels–Alder reaction of methyl coumalate and isoprene afforded bicyclic lactone 13. Transformation of 13 into hydroxy lactone 16 involved cuprate addition, hydroxylation, and oxidation. The conversion of 16 into desired keto alcohol 14 was accomplished by enol ether formation, reduction of the lactone and ester, and hydrolysis of the enol ether. The successful nine-step sequence proceeded in an overall yield of 7.9% from methyl coumalate.

Verrucarol (1) is the sesquiterpene portion of several macrocyclic dilactones which exhibit potent anticancer activity.[1] Certain derivatives of verrucarol are active in inhibiting viral infections.[2] Anguidin (2), a related com-
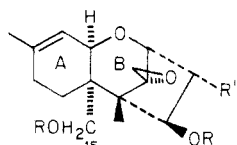
1, R = R' = H
2, R = $COCH_3$; R' = OH

pound, shows inhibitory activity against several cancers.[3] As a result of their biological activity and novel structures,

Scheme I
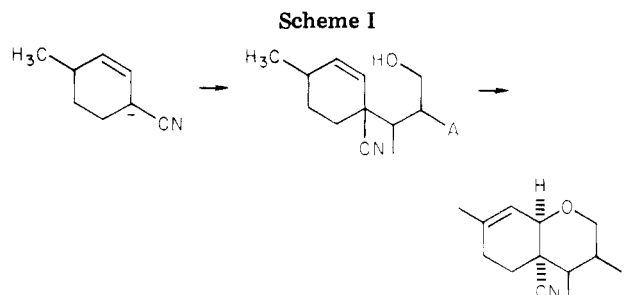
verrucarol and related compounds have been the objects of intense synthetic activity. The total synthesis of trichodermol (15-deoxyverrucarol) has been reported by both Colvin[4] and Still.[5] Syntheses of certain precursors and aromatic analogues[6] have also been reported. Trost and

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