Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for support. Palladium chloride was kindly provided by Engelhard Industries.

Registry No. $Ph(PPh_3)_4$, 14221-01-3; (*E*)-1-chloro-2-iodoethylene, 28540-81-0; (*E*)-1-chloro-1-decen-3-yne, 90320-86-8; (*E*)-1-chloro-1-nonen-3-yne, 77973-37-6; (*e*)-1-chloro-5-methyl-1,5-hexadien-3-yne, 90320-87-9; (*E*)-1-chloro-4-phenyl-1-buten-3-yne, 18685-03-5; (*E*)-1-chloro-1-dodecene-3,5-diyne, 90320-88-0; 1,3-decadiyne, 55682-66-1; 4-phenyl-1,3-butadiyne, 5701-81-5; 1-decen-3-yne, 33622-26-3; 1,2-dibromo-3-decyne, 90320-89-1; 1-phenyl-1,3-pentadiyne, 4009-22-7; 2,4-undecadiyne, 90320-90-4; 1-(trimethylsilyl)-1,3-decadiyne, 84751-17-7; 1-(trimethylsilyl)-4-phenyl-1,3-butadiyne, 38177-56-9; acetylene, 74-86-2; 1-octyne, 629-05-0; 1-heptyne, 628-71-7; 2-methyl-1-buten-3-yne, 78-80-8; phenylethyne, 536-74-3; 1-sodio-4-phenyl-1,3-butadiyne, 90320-91-5; vinyl bromide, 593-60-2.

Synthesis of β,γ-Unsaturated Amino Acids by the Strecker Reaction

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In recent years, numerous studies of β,γ-unsaturated amino acids have been reported. These are of interest not only for their antibiotic[1] and enzyme inhibitory properties[2] but also as synthetic intermediates.[3] Synthetic routes to a number of such amino acids have been reported.[4] Conceptually, many β,γ-unsaturated amino acids could be prepared readily from α,β-unsaturated aldehydes by use of a Stecker condensation. The low yields of vinylglycine and β-methylenenorvaline obtained by using this approach (<1%)[5] have perhaps discouraged its use. We now report a versatile route to β,γ-unsaturated amino acids which utilizes a Strecker reaction.

Treatment of α,β-unsaturated aldehydes with primary amines in the presence of molecular sieves (Scheme I) afforded the corresponding imines **2**.[6] These, without isolation, were subjected to the action of trimethylsilyl cyanide,[7] which, by 1,2-addition, produced β,γ-unsaturated aminonitriles **3**. These could be isolated and purified, but due to their instability on silica gel, they were usually treated directly with aqueous HCl (6 N), providing, after ion-exchange chromatography, the β,γ-unsaturated amino acids **4**.

In initial attempts to prepare N-unsubstituted β,γ-unsaturated amino acids, ammonium acetate was used as the amine component. Thus treatment of (*E*)-2-methyl-3-butenal with NH_4OAc and KCN in ethanol for 4–5 h afforded an aminonitrile, which, when subjected to acidic hydrolysis and then ion-exchange chromatography, afforded pure amino acid **4e**. However, the presence of impurities in the aminonitrile **3** (R = H) (several spots by

Scheme I

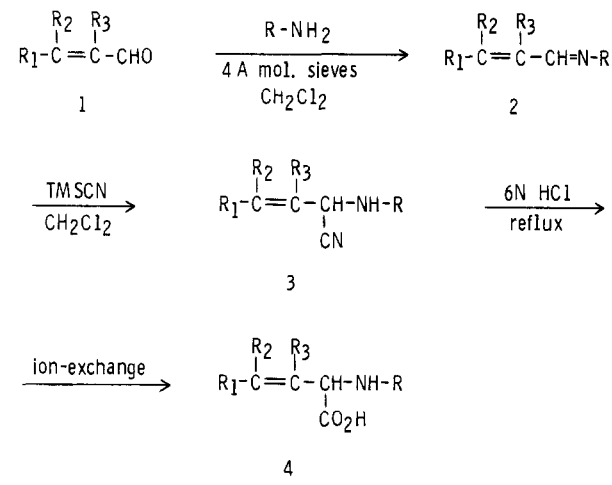
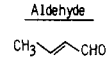
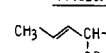
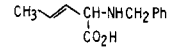
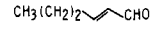
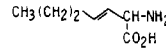
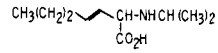
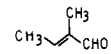
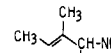
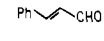
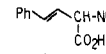
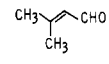
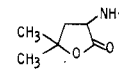
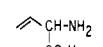


Table I. Preparation of β,γ-Unsaturated Amino Acids

Aldehyde	Amine	Product	Yield (%)
	5	 4a	48
	$PhCH_2NH_2$	 4b	43
	5	 4c	45
	$(CH_3)_2CH-NH_2$	 4d	68
	5 NH_4OAc	 4e	44 27
	5	 4f	15
	$PhCH_2NH_2$	 6	68
	5	 4g	7

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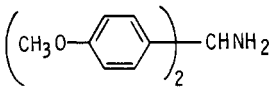
0022-3263/84/1949-2632$01.50/0

TLC) and the low yield of **4e** (27%) illustrated the limitations of this approach.[8] More advantageous was the use of 4,4'-dimethoxybenzhydrylamine (**5**) as the amine component. With **5**, preparation of pure aminonitriles **3** (R = 4,4'-dimethoxybenzhydryl) was possible (as judged by TLC and NMR). Rapid removal of the dimethoxybenzhydryl (DMB) group under the conditions of the acidic hydrolysis step[9] allowed isolation of amino acids **4** (R = H) after purification by ion-exchange chromatography.



5

The examples in Table I illustrate the scope and limitations of the method. While the yields of **4f** and **4g**, prepared from cinnamaldehyde[10] and acrolein[11] were low, the overall yields are generally good. Preparation of γ,γ-disubstituted-β,γ-unsaturated amino acids by this method was not possible: acidic hydrolysis of the aminonitrile **3** prepared from 3,3-dimethylacrolein afforded lactone **6**.[12] Amino acids **4a** and **4b** were shown by NMR to contain small amounts (3–5%) of the *Z* isomer. All others in the table were exclusively the *E* isomer as judged by the NMR coupling constants of the olefinic protons (J_{ab} = 16 Hz).

Experimental Section

Proton magnetic resonance spectra (NMR) were recorded on a Varian Associates XL-200 spectrometer. Chemical shifts are reported in δ units (ppm) relative to an internal standard (sodium 2,2-dimethyl-2-silapentane-5-sulfonate). Melting points (mp) were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra (MS) were recorded by Mr. J. Smith, MSDRL, using a Varian 731 spectrometer at 70 eV; those marked FAB were performed by using the fast atom bombardment method. Analyses were carried out by Mr. J. Gilbert and his associates, MSDRL. Molecular sieves were powdered immediately before use. 3,3-Dimethylacrolein was a generous gift of BASF Corporation. The other aldehydes were purchased from Aldrich Chemical Co. or from Fluka, A. G. Crotonaldehyde (Aldrich; stabilized with 15% H_2O) was dried (Na_2SO_4) and distilled immediately before use. Thin-layer chromatography (TLC) was performed on silica gel plates coated with 250 μM of silica gel GF (Whatman). The following abbreviations are used for chromatography solvents: EBAW = EtOAc:BuOH:H_2O:AcOH, CMWA = $CHCl_3$:CH_3OH:H_2O:AcOH.

4,4'-Dimethoxybenzyhydrylamine (5). A solution of 4,4'-dimethoxydiphenylmethanol (16.9 g, 0.244 mol) in ether (200 mL) was saturated with anhydrous HCl. Concentration left a pink-colored residue which was redissolved in ether and dried ($NaSO_4$). The resulting pink solid (12.8 g), mp 82–84 °C, was added to liquid ammonia (200 mL) under a dry ice condenser. The mixture was stirred for 6 h and then ammonia was allowed to evaporate. The residue was extracted with ether and the combind organic portions were washed with H_2O and brine and dried (Na_2SO_4). The residue after evaporation was chromatographed on 50 g of silica gel (Woelm, Act 1), giving a white solid, mp 61–62 °C (lit.[9] mp 58–59 °C).

(*E*)-2-Amino-3-heptenoic Acid (4c). A mixture of *trans*-2-hexenal (0.196 g, 2.00 mmol), amine **5** (0.438 g, 2.00 mmol), and 4 Å-molecular sieves (0.60 g) in CH_2Cl_2 (4 mL) was stirred under nitrogen for 90 min. Trimethylsilyl cyanide (0.29 mL, 2.2 mmol) was added and stirring continued for 90 min. The mixture was added and stirring continued for 90 min. The mixture was filtered and evaporated to a colorless oil. This was combined with 6 N HCl (50 mL) and the mixture warmed at reflux for 18 h. The mixture was cooled, extracted with CH_2Cl_2 (3 × 10 mL), treated with activated charcoal, and then evaporated to a light-yellow solid.

The crude product was purified on DOWEX 50W-X4 (4 g), pure amino acid being eluted with H_2O:CH_3OH:py (100:100:8). Recrystallization from CH_3OH provided the analytical sample: mp 227–228 °C dec; NMR (1 N DCl in D_2O) δ 0.67 (3 H, t, J = 7), 1.23 (2 H, m), 1.92 (2 H, q, J = 8), 4.44 (1 H, d, J = 8), 5.3–5.5 (1 H, m), 5.94 (1 H, dt, J = 16, 8); MS (FAB), m/e 144 (M^+ + 1); TLC (3:1:1:1 EBAW) R_f 0.6. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.70; H, 9.11; N, 9.73.

The following were prepared in a similar manner from the starting materials indicated in Table I.

(*E*)- and (*Z*)-2-Amino-3-pentenoic acid (4a): recrystallized from CH_3OH–H_2O; mp 201–202 °C (lit.[16] mp 202 °C); NMR (D_2O) *E* isomer 2.00 (3 H, dd, J = 6,1), 4.65 (1 H, d, J = 8), 5.76 (1 H, ddq, J = 16, 8, 1), 6.41 (1 H, dq, J = 16.6); *Z* isomer (5% of mixture by integration) 1.48 (3 H, dd, J = 6, 2); 4.86 (1 H, d, J = 10); MS(FAB), m/e 116 (M^+ + 1); TLC (3:1:1:1 EBAW) R_f 0.4. Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.88; H, 7.96; N, 12.06.

(*E*)- and (*Z*)-2-(Benzylamino)-3-pentenoic acid (4b): recrystallized from H_2O–CH_3OH, mp 197–198 °C dec; NMR (1 N DCl in D_2O) *E* isomer 1.54 (3 H, dd, J = 7,1), 3.97 (2 H, AB, J_{AB} = 13, δ_{AB} = 36), 4.18 (1 H, d, J = 8), 5.30 (1 H, ddq, J = 16, 8, 1), 5.96 (1 H, dt, J = 16, 7), 7.4–7.6 (5 H, m); *Z* isomer (3% of mixture by integration) 1.47 (3 H, dd, J = 7, 1); MS (FAB), m/e 206 (M^+ + 1); TLC (100:20:3:0.5 CMWA) R_f 0.7. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.55; H, 7.63; N, 6.64.

(*E*)-2-(Isopropylamino)-3-heptenoic acid (4d): recrystallized from CH_3OH, mp 236–237 °C dec; NMR (1 N DCl in D_2O) 0.66 (3 H, t, J = 7), 1.08 (3 H, d, J = 6), 1.13 (3 H, d, J = 6), 1.22 (2 H, m) 1.92 (2 H, q, J = 8), 3.2–3.3 (1 H, m), 4.43 (1 H, d, J = 8), 5.1–5.4 (1 H, m), 6.04 (1 H, dt, J = 16, 8); MS, m/e 185 (M^+); TLC (3:1:1:1 EBAW) R_f 0.7. m/e 185 (M^+). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 65.51; H, 10.10; N, 7.61.

(*E*)-2-Amino-3-methyl-3-pentenoic acid (4e): recrystallized from CH_3OH; mp (sealed capillary) 263–264 °C dec; lit.[17] mp 236 °C dec; NMR (D_2O) 1.66 (3 H, s), 1.68 (3 H, d, J = 8), 4.22 (1 H, s), 5.82 (1 H, q, J =); TLC (3:1:1:1 EBAW) R_f 0.4. MS(FAB), m/e 130 (M^+ + 1).

(*E*)-2-Amino-4-phenyl-3-butenoic Acid (4f). A mixture of cinnamaldehyde (2.00 mmol, 0.264 g), amine **5** (2.00 mmol, 0.438 g), and 4-Å molecular sieves (0.60 g) in CH_2Cl_2 (4 mL) was stirred for 90 min and then trimethylsilyl cyanide (2.20 mmol; 0.29 ml) was added. Stirring was continued for 90 min, and then the mixture was filtered and concentrated. The residue was dissolved in CH_3OH (30 mL) and the cooled solution (ice bath) was saturated with anhydrous HCl. After 3 h at 0 °C, the mixture was evaporated to dryness and the residue combined with 6 N HCl (30 mL). The mixture was heated at reflux for 18 h, cooled, and

(8) Preparation of amino acid **4e** by a Strecker reaction (NH_4Cl, NaCN) in unspecified yield has been reported.[13] Assignment of the *E* configuration to the product was confirmed by a stereospecific synthesis of the *Z* isomer by another method. Synthesis of 1-cyclohexenylglycine by Strecker (NH_4Cl, NaCN; 25% yield) and Bucherer ($(NH_4)_2CO_3$, KCN; 27% yield) reactions has been reported.[14]

(9) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451 and references cited therein.

(10) The aminonitrile **3f** in this case is pure by TLC and NMR. The low yield seems to be due to decomposition during the hydrolysis step.[18]

(11) Private communication from Dr. D. Taub: The 6 N HCl hydrolysis time was 2 h and the vinylglycine was isolated by chromatography on DOWEX 50W-X4 eluting with 30:1 H_2O:pyridine. Further elution with 1 M NH_4OH (aq) gave crude 2,4-diaminobutyric acid (TLC). While the yield of vinylglycine is low, this essentially one-step procedure may be more convenient for the preparation of small quantities than the previously reported multistep procedures.[15]

(12) Lactone formation under acidic conditions was observed in a previously reported synthesis of β,γ-unsaturated amino acids: Ben-Ishai, D.; Moshenberg, R.; Altman, J. *Tetrahedron* **1977**, *33*, 1533.

(13) Cahill, R.; Crout, D. H. G.; Mitchell, M. B.; Muller, U. S. *J. Chem. Soc., Chem. Commun.* **1980**, 419.

(14) Asako, T.; Soma, T.; Masuya, H.; Harukawa, T.; Miki, T. U.S. Patent 3 824 237, 1974; 3 937 699, 1976, Takeda Chem. Ind. Ltd., Japan.

(15) Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817. Baldwin, J. E.; Haber, S. B.; Hoskins, C.; Kruse, L. I. *Ibid.* **1977**, *43*, 1239. Rando, R. R. *Biochemistry* **1974**, *13*, 3859. Hurdlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251. Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085.

(16) Marcotte, P.; Walsh, C. *Biochemistry* **1978**, *17*, 5620.

(17) Heinzer, F.; Bellus, D. *Helv. Chim. Acta* **1981**, *64*, 2279.

extracted with CH_2Cl_2 (3 × 10 mL) and then treated with activated charcoal. The resulting colorless solution was evaporated to dryness. The residue was slurried in H_2O and the solid collected on a filter and rinsed several times with cold H_2O. This material and a second crop obtained after concentration of the filtrate provided pure **4f** (64.0 mg, 0.30 mmol, 15%): mp 198–200 °C dec (lit.[18] mp 198–200 °C); TLC (3:1:1:1 EBAW) R_f 0.6; NMR (1 N DCl in D_2O) 4.59 (1 H, d, J = 10), 6.06 (1 H, dd, J = 16, 10), 6.72 (1 H, d, J = 10), 7.1–7.3 (5 H, m); MS(FAB), m/e 178 ($M^+ + 1$). Anal. Calcd for $C_{10}H_{11}NO_2 \cdot {}^1/_4H_2O$: C, 66.10; H, 6.38; N, 7.70. Found: C, 65.81; H, 6.24; N, 7.62.

Preparation of Amino Acid 4e from NH_4OAc. A mixture of (*E*)-2-methyl-2-butenal (0.168 g, 2.0 mmol), NH_4OAc (0.442 g, 6.0 mmol) and KCN (0.130 g, 2.0 mmol) in EtOH (4 mL) was stirred for 5 h under nitrogen. The reaction mixture was evaporated to dryness and the residue combined with 6 N HCl (30 mL). The solution was heated at reflux for 18 h and then treated as described above for **4c**, affording pure amino acid (69.4 mg, 0.538 mmol, 27%), identical with that prepared as described above.

2-(Benzylamino)-5,5-dimethylbutyrolactone Hydrochloride (6). A mixture of 3,3-dimethylacrolein (1.00 g, 11.9 mmol), benzylamine (1.28 g, 11.9 mmol), and 4-Å molecular sieves (2.0 g) in CH_2Cl_2 (25 mL) was stirred under nitrogen for 1 h. Then trimethylsilyl cyanide (1.75 mL, 13.1 mmol) was added and stirring was continued for 1 h. The mixture was filtered and evaporated to dryness. The residue was combined with concentrated HCl (80 mL) and the mixture heated at reflux for 18 h. The mixture was diluted with H_2O (100 mL) and treated, while still warm, with activated charcoal. Filtration and cooling of the solution gave a white solid, which was collected and rinsed with H_2O. This and a second crop obtained upon concentration of the filtrate provided 2.08 g (8.16 mmol, 68%) of lactone: mp 258–260 °C dec; TLC (50:1 CH_2Cl_2:CH_3OH) R_f 0.2; NMR (CD_3OD) 1.48 (3 H, s), 1.56 (3 H, s), 2.23 (1 H, t, J = 13), 2.74 (1 H, dd, J = 13, 8), 4.43 (2 H, AB, J_{AB} = 12, δ_{AB} = 52), 4.75 (1 H, dd, J = 13, 8), 7.5–7.7 (5 H, m); MS, m/e 176 ($M^+ + 1 - CO_2$). Anal. Calcd for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.05; H, 7.09; N, 5.48; Cl, 13.86. Found: C, 61.15; H, 7.16; N, 5.35; Cl, 13.81.

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Registry No. **3** (R = $PhCH_2$; R_1 = R_2 = Me; R_3 = H), 90461-23-7; (*E*)-**3** (R = $CH(C_6H_4$-*p*-$OMe)_2$; R_1 = Me; R_2 = R_3 = H), 90481-27-9; (*E*)-**4** (R = R_2 = R_3 = H; R_1 = Ph), 90461-24-8; (*E*)-**4a**, 90528-90-8; (*Z*)-**4a**, 90528-91-9; (*E*)-**4b**, 90461-20-4; (*Z*)-**4b**, 90461-21-5; (*E*)-**4c**, 90461-19-1; (*E*)-**4d**, 90461-22-6; (*E*)-**4e**, 80744-99-6; (*E*)-**4f**, 90528-92-0; **4g**, 56512-51-7; **5**, 19293-62-0; **6**, 77694-17-8; $NH_3 \cdot HOAc$, 631-61-8; $PhCH_2NH_2$, 100-46-9; $CH_3CH{=}CHCHO$, 4170-30-3; $(CH_3)_2CHNH_2$, 75-31-0; $CH_2{=}CHCHO$, 107-02-8; $(p\text{-}MeOC_6H_4)_2CHCl$, 7525-23-7; 4,4'-dimethoxydiphenylmethanol, 728-87-0; *trans*-2-hexenal, 6728-26-3; *trans*-cinnamaldehyde, 14371-10-9; (*E*)-2-methyl-2-butenal, 497-03-0; 3,3-dimethylacrolein, 107-86-8.

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Synthesis of 6β-(Bromoacetoxy)cortisol 21-Bromoacetate: A Novel Reagent for Labeling the Catalytic Site of Enzymes

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Earlier, we synthesized the first steroid with two alkylating functional groups, 2,4-bis(bromomethyl)-3-hydroxy1,3,5(10)-estradien-17-one, and found it to be a long-acting antiestrogen.[1] 2,4-Bis(bromomethyl)estradiol, prepared by reduction of this compound, was a long-acting estrogen and it also irreversibly inactivated the enzyme human placental 17β-estradiol dehydrogenase.[2] Several radioactive (bromoacetoxy)progesterone derivatives were synthesized and found to be useful for radiolabeling amino acids at the catalytic site of the enzyme 3α,20β-hydroxysteroid dehydrogenase (3α,20β-HSD).[3-6] 16α-(Bromoacetoxy)progesterone, 11α-(bromoacetoxy)progesterone, and 19-nortestosterone 17-bromoacetate terminated pregnancy in rats.[7,8] Medroxyprogesterone 17-bromoacetate maintained pregnancy in rats although it was equal to 16α-(bromoacetoxy)progesterone both in its chemical reactivity and also its capacity to inactivate 3α,20β-HSD by the mechanism of affinity alkylation.[9,10] The many intriguing and useful properties of these novel steroids inspired us to design an even more versatile bromoacetoxy steroid derivative for biochemical and reproductive biological experiments. This led to the present synthesis of 6β-(bromoacetoxy)cortisol 21-bromoacetate.

In general, the solubility in water of the various (bromoacetoxy)progesterones prepared by us[3-8] has been found to be about 0.1 mM, or approximately one-tenth that of progesterone. We assumed that the addition of two bromoacetoxy groups to progesterone would reduce its water solubility by as much as 2 orders of magnitude which would render a bis(bromoacetoxy)progesterone analogue unusable for experiments with enzymatic proteins. Enzymes are generally soluble and stable only in aqueous, buffer solutions. Therefore, to enhance its water solubility for use in enzyme experiments, a suitable bis(bromoacetoxy) steroid had to contain two free hydroxy groups. The polarity and hydrogen-bonding capability of the hydroxy groups were expected to compensate for the hydrophobicity of the two bromoacetoxy groups thus enhancing the water solubility of the steroid.

The main synthetic problem was the stepwise introduction of two bromoacetoxy groups at specific positions on a steroid molecule which contained four hydroxy groups (**4**, Scheme I). Furthermore, a progesterone analogue in which one bromoacetoxy group is at the C-6β position and the other group is at the C-21 position was required for extension of our previous work. These positional and configurational requirements were necessary for comparing the biochemical and biological properties of the new steroid with those of 6β-(bromoacetoxy)progesterone and 21-(bromoacetoxy)progesterone from our earlier enzymological[2,4,6] and reproductive biological studies.[7,8] This report describes the synthesis of **7** which had the desired structure and also enhanced water solubility.

Results and Discussion

Synthesis. Cortisol (**1**) was heated under reflux in a mixture of 2,2-dimethoxypropane, dimethylformamide, and a catalytic amount of *p*-toluenesulfonic acid and gave a 75% yield of the crude dienol methyl ether acetonide (**2**). The acetonide group in **2** blocked both the C-17 and C-21 hydroxy groups and the conjugated dienol function in the

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