Formation of Styrylglycine and Derivatives from Cyclopropylogs of Phenylalanine and Dihydroxyphenylalanine. Authentic Styrylglycine

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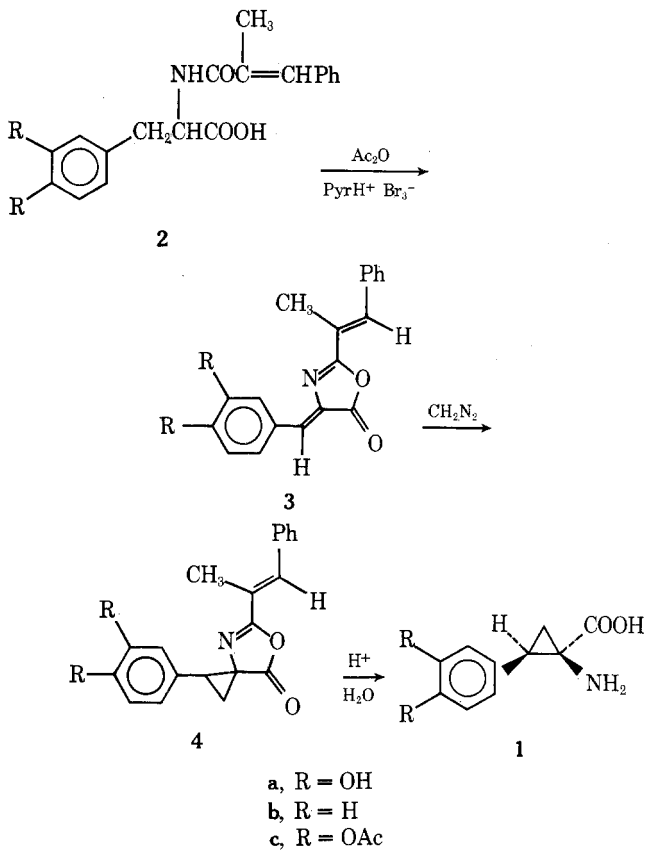
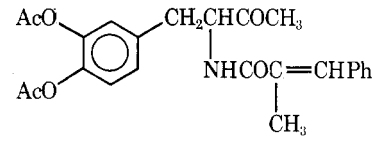
Much research has been devoted to the synthesis of compounds capable of inhibiting the enzymes associated with the biosynthesis of catecholamines. α-Methyldihydroxyphenylalanine (α-methyl-Dopa) is a potent Dopa decarboxylase inhibitor[3] while cyclopropane derivatives of metabolites such as histidine[4] and phenethylamine[5] are also enzyme inhibitors. In view of our recent work[6] on α,β-unsaturated azlactones and the fact that these may serve as intermediates[4,7] in the synthesis of "cyclopropylogs" of amino acids, we investigated an approach to the synthesis of "cyclopropyl Dopa" (**1a**). Our reaction sequence (Scheme I)

Scheme I



was much shorter than that described in a 1965 patent by Kaiser[8] in that we were to obtain **1** directly from Dopa rather than by the complex process described by Kaiser. Our procedure gave the azlactone **3c** in 45% overall yield from Dopa and, in the second stage, **3c** was cyclopropylated with diazomethane giving **4c** in 45% yield. The structure of **4c** was secured by the presence of the cyclopropyl proton absorptions[7] at δ 3.04 (1 H) and 2.10 (2 H) and the styryl methyl group absorption at δ 2.08 (3 H) in its NMR spectrum. Interestingly, a by-product of the oxidation procedure was isolated by high-pressure liquid chromatography and proved to be ketone **5**, formed, apparently, by a Dakin–West[9] acetylation–decarboxylation reaction. We had not previously observed products of this type in our development of this oxidation procedure but, in 1968, Steglich[10]



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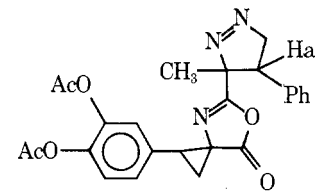
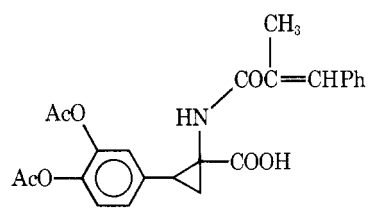


6

did report the conversion of an alanine azlactone into a ketone at ambient temperatures under conditions similar to those which led to the formation of **5**. Apparently, the Dakin–West reaction competes successfully, in some cases, with the double dehydrohalogenation which leads to **3**. From the cyclopropylation step, a crystalline by-product was also isolated in small yield by HPLC. This material proved to be the result of the addition of diazomethane to the styryl group in **4c** forming a pyrazoline ring. Of the two possible isomeric pyrazolines, **6** was established as the correct structure by the fact that the benzylic proton (H_a) appeared as a triplet due to coupling with the adjacent methylene group. ^{13}C spectroscopy established the purity of this compound even though it might be expected to be a mixture of diastereomers and did show a very broad melting point, apparently owing to thermolysis. It was interesting that only small amounts of **6** were formed even though a large excess of diazomethane was used. The methylenation reaction was much more selective than expected.

In spite of the careful exclusion of oxygen, all attempts to hydrolyze **4c** under basic conditions gave colored complex mixtures even though the literature[4,7] reports that similar cyclopropanes had been obtained this way. Long refluxing of a solution of **4c** in acidic aqueous acetone afforded only a 38% yield of the expected acid (**7**), the remainder



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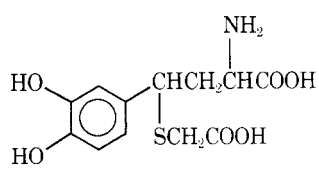

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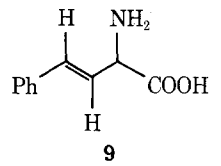
of the starting azlactone being recovered unchanged. This extreme resistance to hydrolysis of the azlactone ring was apparently due to steric hindrance exhibited by the trisubstituted a-carbon atom. Attempts to hydrolyze **4c** to the cyclopropyl amino acid in refluxing 6 N HCl led to complete decomposition as shown by TLC and NMR spectroscopy. When the hydrolysis was carried out in the presence of the antioxidant mercaptoacetic acid, a high-melting substance was obtained which, by elemental and spectral analysis, appeared to be a 1:1 combination of mercaptoacetic acid and **1**. The NMR spectrum indicated the presence of four different kinds of aliphatic protons consistent with structure **8**

in which the cyclopropane ring had been destroyed by reaction with the mercaptan.

Since oxidative decomposition is always a complicating factor in the synthesis of Dopa derivatives, we undertook the synthesis of cyclopropylphenylalanine (**1b**) in order to further investigate the hydrolysis in the absence of this complication. In 1964, Awad[7] reported the synthesis of *N*-benzoylcyclopropylphenylalanine but did not report its conversion into the free amino acid. By methods analogous to those just described, **2b** was converted into the unsaturated azlactone **3b** which was cyclopropanated to give the spiroazlactone **4b** in 39% yield. Using 6 N HCl, we hydrolyzed **4b** and obtained a small yield of an amino acid which was clearly not cyclopropylphenylalanine. This product was isomeric with the expected product, ninhydrin positive, and showed two coupled vinyl protons in its NMR spectrum. All the physical data were consistent with this product being styrylglycine (**9**), which had been reported by Pinner[11a] in 1889 and by later workers[11b] to have a melting point in the range of 240–250 °C. Since our product melted at 196–199 ° C, we synthesized authentic **9** by a new procedure which confirmed the melting point and the spectral data obtained for **9**.

The key intermediate in the Pinner synthesis of **9** was the hydantoin **10a** which was prepared by acid-catalyzed ring closure of the ureidonitrile **11**. Workers in the penicillin field[11b] reported that direct hydrolysis of **11** also gave **9**.



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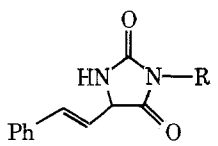
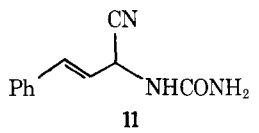


10a, R = H
b, R = C_2H_5



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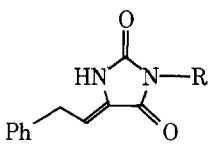
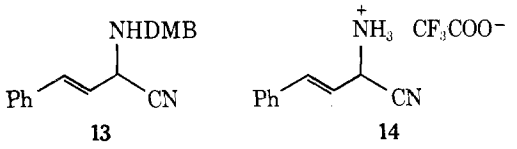


12a, R = H
b, R = C_2H_5

In our hands, the latter procedure gave an amino acid, mp 216–218 °C, which, by NMR spectroscopy, could not be **9**. We showed that this product was actually γ-phenyl-α-aminobutyric acid by comparison with an authentic sample prepared by hydrogenation of our styrylglycine (**9**). Pinner had obtained **9** by basic hydrolysis of what he thought was the *N*-ethylhydantoin, **10b.** He obtained **10b** by ethylation of either hydantoin **10a,** mp 172 °C, or its "cis isomer", mp 198 °C. We found that the "cis isomer" of **10a** was actually the conjugated isomer, **12a,** and that the N-ethylated compound was the conjugated isomer, **12b.** The treatment of **10a** with base during ethylation had rearranged the double bond into the more conjugated position. In our hands, basic hydrolysis of either **12a** or **12b** gave no amino acid of melting point 240–250 °C as reported by Pinner, and this approach to **9** was not further investigated.

Our synthesis of DL-styrylglycine is outlined below. Cinnamaldehyde, on treatment with 2,4-dimethoxybenzylamine and sodium cyanide, gave an excellent yield of the oily cyano amine **13** which was converted to a crystalline hydrochloride for characterization. Direct hydrolysis of **13** in concentrated hydrochloric acid gave **9** in an overall yield from the aldehyde of 13%. However, when **13** was treated with trifluoroacetic acid in the presence of dimethoxybenzene as scavenger, the nitrile salt **14** was obtained in 67% yield and **14** was hydrolyzed to **9** in 39% yield. Further development showed that when **14** was first converted to an imino ester, hydrolysis of this compound afforded **9** in 70% yield. The pure DL-styrylglycine obtained by our procedure showed a melting point of 198–200 °C, in disagreement with all previous reports, and showed the required spectral characteristics.



13 **14**

DMB = 2,4-dimethoxybenzyl

The formation of DL-styrylglycine (**9**) during the hydrolysis of **4b** and the formation of the sulfide **8** from **4c** are an indication of the acid lability of 1-aminocyclopropanecarboxylic acids. Even though earlier workers[4] have not observed this, our work indicates that these compounds are not always readily accessible by acid hydrolysis of their *N*-acyl derivatives.

Experimental Section

Instrumentation. Melting points were determined on a Nalge Model Y6 micro hot stage and are uncorrected. Infrared spectra (Nujol mull and KBr pellet) were taken on a Perkin-Elmer 257 recording spectrophotometer with polystyrene as the standard, and proton NMR spectra were obtained on Perkin-Elmer R-20 and Varian HA-100 spectrometers with Me_4Si as the internal standard. Carbon-13 NMR spectra were obtained on a JEOL PFT-100 spectrometer with Me_4Si as the internal standard. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Ga.

Materials. β-3,4-Dihydroxy-DL-phenylalanine was purchased from Sigma Chemical Co., and used as received. (*E*)-α-Methylcinnamic acid was prepared according to Johnson[12] and converted to the acid chloride by refluxing in thionyl chloride.

***N*-[(*E*)-α-Methylcinnamoyl]-β-3,4-dihydroxy-DL-phenylalanine (2a).** A suspension of sodium metaborate (44.5 g, 116.6 mmol) in 100 ml of water in a 2-l. three-necked round-bottomed flask fitted with a magnetic stirrer, delivery funnel with nitrogen inlet, and an electrode connected to a Corning Model 10C pH control unit was stirred under nitrogen for 20 min. β-3,4-Dihydroxy-DL-phenylalanine (25.0 g, 126.7 mmol) was added and the mixture stirred for 30 min under nitrogen at room temperature. The mixture was then cooled in an ice bath, sodium dithionite (1.0 g) and 200 ml of 1,2-dimethoxyethane (DME) added, and the pH brought to 10 with 1.0 N NaOH. A solution of (*E*)-α-methylcinnamoyl chloride (21.0 g, 116 mmol) in 200 ml of DME was added dropwise over a period of 30 min while the pH was maintained at 10 by the addition of 1.0 N NaOH. The reaction mixture was stirred for 3 h at room temperature and filtered, and the yellow filtrate was acidified with concentrated HCl to pH 1. The acidic solution was extracted with five 200-ml portions of ethyl acetate, and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to yield a sticky solid. The solid was stirred with 100 ml of fresh ethyl acetate and filtered, and the resulting white solid was dried under vacuum to yield 32.2 g (81%) of crude **2.** The crude material was recrystallized from acetone–hexane to yield 28.7 g (72%) of **2a:** mp 196–198 °C; ir (Nujol) 3510 (OH), 3360 (NH), 1710 (acid C=O), 1650 and 1600 cm^{-1} (amide C=O and C=C); uv (95% ethanol) 264 nm (ε 19 350); NMR (acetone-d_6) δ 7.16–8.00 (3 H, broad, NH and OH), 7.36 (5 H, s, C_6H_5), 7.24 (1 H, m, PhC**H**=), 6.81–6.64 [3 H, m, Ar**H**$(OH)_2$], 4.78 (1 H, m, C**H**NH), 3.04 (2 H, m, ArCH_2), 2.04 ppm (3 H, d, CH_3C=).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.79; H, 5.78; N, 4.16.

2-[(*E*)-1-Methylstyryl]-4-(3,4-diacetoxybenzylidene)-5-oxazolone (3c). A solution of **2a** (25.0 g, 73.24 mmol) in 100 ml of

acetic anhydride and 1 ml of pyridine in a 250-ml round-bottomed flask fitted with a drying tube was stirred for 1 h in an ice bath. Pyridine hydrobromide perbromide (20.0 g, 83.71 mmol) was added and the mixture stirred for 2 h. Pyridine (20 ml) was then added and the mixture stirred for an additional 2 h at room temperature. The solvents were removed in vacuo to yield a yellow semisolid which was rinsed into ice–water with a small amount of acetone and rapidly stirred for 1.5 h. The resulting amorphous yellow solid was filtered, dried under vacuum, and crystallized from absolute ethanol to yield 18.3 g (62%) of **3a**, mp 148–152 °C. An analytical sample was recrystallized from benzene–hexane: mp 150.5–151.5 °C; ir (Nujol) 1805 (oxazolone C=O), 1765 and 1755 (acetoxy C=O), 1650 (C=N), 1610 and 1600 cm^{-1} (C=C); uv (CH_2Cl_2) 291 nm (ϵ 11 900), 377 (45 900); NMR ($CDCl_3$) δ 8.02–7.22 (8 H, m, aromatic), 7.63 (1 H, m, styryl), 7.00 (1 H, s, benzylidene), 2.32 (3 H, d, CH_3 C=), 2.30 (3 H, s, CH_3COO), 2.27 (3 H, s, CH_3COO); ^{13}C NMR ($CDCl_3$) 166.9 and 166.7 (CH_3COO), 166.2 and 164.9 (oxazolone C=O and C=N), 143.2, 141.5, 139.0, 134.7, 133.6, 131.5, 129.9, 129.4, 128.3, 127.8, 126.0, 123.0, and 122.6 (aromatic and vinyl), 20.4 (CH_3COO), 13.5 ppm (CH_3C=).

Anal. Calcd for $C_{23}H_{19}NO_6$: C, 68.14; H, 4.72; N, 3.45. Found: C, 68.01; H, 4.77; N, 3.40.

Isolation of 3-[(*E*)-α-Methylcinnamamido]-4-(3,4-diacetoxyphenyl)-2-butanone (5). A mixture of **2a** (15.0 g, 43.9 mmol) in 50 ml of acetic anhydride and 5 ml of pyridine in a 200-ml round-bottomed flask fitted with a drying tube was stirred for 1 h at room temperature. The solution was filtered, the filtrate was cooled in an ice bath, and pyridine hydrobromide perbromide (10.5 g, 43.9 mmol) added. The mixture was stirred for 1.5 h, 20 ml of pyridine was added, and the mixture stirred for an additional 1 h at room temperature. The mixture was then filtered, and the filtrate was concentrated in vacuo to yield a yellow semisolid. The residue was rinsed into ice–water with a small amount of acetone and the mixture was rapidly stirred for 1 h. The amorphous yellow solid was filtered, dried under vacuum, and crystallized from absolute ethanol to yield 8.3 g (47%) of **3c**. Evaporation of the mother liquor gave a yellow oil which partially crystallized on standing. The oil was triturated with a small amount of acetone and filtered to give 3.1 g (23%) of crude **5**. Recrystallization of the crude material several times from ethyl acetate–hexane gave 1.7 g (13%) of pure **5**: mp 136.5–137.5 °C; ir (Nujol) 3345 and 3290 (NH), 1765 (acetoxy C=O), 1725 (ketone C=O), 1645 (amide C=O), 1620 (C=C), 1515 cm^{-1} (amide II); NMR ($CDCl_3$) δ 7.46–6.94 (10 H, m, NH, PhC**H**=, aromatic), 4.85 (1 H, m, C**H**NH), 3.11 (2 H, m, ArCH_2), 2.24, 2.20, and 2.18 (9 H, 3 s, CH_3COO and CH_3CO), 2.02 (3 H, d, CH_3C=).

Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31. Found: C, 68.36; H, 5.56; N, 3.32.

Cyclopropanation of 3c. Synthesis of 1-(3,4-Diacetoxyphenyl)-5-[(*E*)-1-methylstyryl]-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (4c) and 1-(3,4-Diacetoxyphenyl)-5-(*cis*-3-methyl-4-phenyl-1-pyrazolin-3-yl)-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (6). A solution of **3c** (8.0 g, 19.7 mmol) in 250 ml of $CHCl_3$ was treated with a solution of diazomethane in 250 ml of ether, prepared from 21.5 g (0.1 mol) of Diazald (Aldrich Chemical Co.), in a 1-l. Erlenmeyer flask fitted with a rubber stopper and drying tube. After the reaction mixture was stirred for 16 h at room temperature, the excess diazomethane was removed under a stream of dry nitrogen, and the solvents were evaporated in vacuo to yield a yellow oil. The oil was crystallized from ethyl acetate–hexane to yield 3.7 g (45%) of **4c**, mp 137–140 °C. An analytical sample was prepared by several recrystallizations from ethyl acetate–hexane: mp 142–144 °C; ir (Nujol) 1805 (oxazolone C=O), 1770 (acetoxy C=O), 1635 (C=N), 1610 cm^{-1} (C=C); uv (CH_2Cl_2) 291 nm (ϵ 28 860); NMR ($CDCl_3$) δ 7.46–6.96 [9 H, m, PhC**H**=, Ph, Ar**H**$(OH)_2$], 3.18 (1 H, m, cyclopropyl CH), 2.40 (2 H, m, cyclopropyl CH_2), 2.21 (6 H, s, CH_3COO), 2.08 (3 H, s, CH_3C=).

Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.82; H, 5.09; N, 3.31.

High-pressure liquid chromatography of the mother liquor on an 8 ft × 0.375 in. silica gel (18–32 μ) column eluting with 2:3 ethyl acetate–hexane gave an additional 1.7 g (total yield 54%) of **4c** as the first component. The second component was collected and rechromatographed on a 4 ft × 0.375 in. Porasil B (37–75 μ) column eluting with 2:3 $CHCl_3$–hexane. The second component was collected and the solvents evaporated in vacuo to yield a colorless oil which crystallized on standing. This material was recrystallized from ethyl acetate–hexane to yield 0.107 g (1.6%) of **6**: mp 116–140 °C; ir (KBr) 1815 (oxazolone C=O), 1770 (acetoxy C=O), 1640 cm^{-1} (C=N); NMR ($CDCl_3$) δ 7.28–6.78 [8 H, m, Ph and Ar**H**$(OH)_2$], 4.91 (2 H, m, pyrazoline CH_2), 3.70 (1 H, m, pyrazoline CH), 3.10 (1 H, m, cyclopropyl CH), 2.28 (6 H, s, CH_3COO), 2.23 (2 H, m cyclopropyl CH_2), 1.20 (3 H, d, pyrazoline CH_3).

Anal. Calcd for $C_{25}H_{23}NO_6$: C, 65.06; H, 5.02; N, 9.10. Found: C, 64.74; H, 5.02; N, 8.94.

1-[(*E*)-α-Methylcinnamamido]-2-(3,4-diacetoxyphenyl)cyclopropanecarboxylic Acid (7). A suspension of **4c** (0.5 g, 1.2 mmol) in 30 ml of acetone containing 10 ml of water and a few drops of trifluoroacetic acid was refluxed for 5 days in a 50-ml round-bottomed flask fitted with a condenser. The acetone was evaporated in vacuo, and the resulting mixture extracted with two 50-ml portions of ethyl acetate. The combined extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo to yield a glass. The residue was recrystallized from acetone–hexane to give 200 mg (38%) of **7**, mp 186–195 °C. An analytical sample was prepared by several recrystallizations from acetone–hexane: mp 194–197 °C; ir (KBr) 3330 (NH), 3440–2300 (carboxyl OH), 1765 (acetoxy C=O), 1705 (acid C=O), 1650 (amide C=O), 1625 (C=C), 1505 cm^{-1} (amide II); NMR (Me_2SO-d_6) δ 7.48–6.82 [10 H, m, Ph, CH=, NH, Ar**H**$(OH)_2$], 3.01 (1 H, m, cyclopropyl CH), 2.45 (2 H, m, cyclopropyl CH_2), 2.21 (6 H, s, CH_3COO), 1.78 (3 H, s, CH_3C=).

Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.89; H, 5.30; N, 3.20. Found: C, 65.95; H, 5.31; N, 3.18.

2-Amino-4-(carboxymethylthio)-4-(3,4-dihydroxyphenyl)-butanoic Acid (8). A suspension of **4c** (1.0 g, 2.38 mmol) in 50 ml of 6.0 N HCl containing 2 ml of mercaptoacetic acid in a 100-ml round-bottomed flask was refluxed for 14 h under a nitrogen atmosphere. The clear yellow solution was cooled in an ice bath, and the resulting solid was filtered, 255 mg (67%) of (*E*)-α-methylcinnamic acid. The yellow filtrate was concentrated in vacuo at room temperature to yield a light brown oil. The oil was dissolved in 50 ml of water and the solution was extracted with six 50-ml portions of ether. The aqueous layer was again concentrated under high vacuum at room temperature to yield a viscous brown oil. The oil was dissolved in a minimum of absolute ethanol, and the solution was added dropwise with rapid stirring to 500 ml of anhydrous ether. The mixture was centrifuged, and the resulting hygroscopic solid was washed several times with anhydrous ether and dried in vacuo to yield 0.7 g (97%) of crude **8**. Chromatography of the crude material on a 1 × 80 cm column of Sephadex G-10 eluting with 0.001 M β-mercaptoethanol in water gave 415 mg (60%) of pure **8**: mp 300 °C dec; ir (Nujol) 3600–2300 (OH), 1720 (acid C=O), 1605 cm^{-1} (carboxylate); NMR (D_2O) δ 7.00–6.80 [3 H, m, Ar**H**$(OH)_2$], 4.06 (1 H, m, C**H**NH), 3.83 (1 H, m, PhC**H**), 3.18 (2 H, s, $-SCH_2COO$), 2.46 (2 H, m, $CHCH_2CH$).

Anal. Calcd for $C_{12}H_{15}NO_6S$: C, 47.83; H, 5.02; N, 4.65. Found: C, 47.71; H, 5.21; N, 4.61.

1-Phenyl-5-[(*E*)-1-methylstyryl]-6-oxa-4-azaspiro[2.4]-hept-4-en-7-one (4b). To a solution of 3.0 g (10.4 mmol) of **3b**[6] in 75 ml of chloroform was added 100 ml of ethereal diazomethane, prepared from 21.5 g (0.1 mol) of Diazald (Aldrich Chemical Co.), in a 250-ml Erlenmeyer flask fitted with a rubber stopper and a drying tube. After stirring at room temperature for 15 h, the excess diazomethane was removed in a stream of dry nitrogen. Evaporation of the solvents in vacuo gave a yellow, oily residue. Preparative chromatography of part of the oily residue on 3-mm silica gel plates in a 3:2 *n*-hexane–chloroform system followed by crystallization from 1:1 *n*-hexane–ethyl acetate gave pure **4b**, mp 93–97 °C. Using a seed crystal a total of 1.22 g (39%) of **4b** was obtained: mp 95–98 °C; ir (Nujol) 1802, 1780 (C=O), 1630 (C=N), 1603 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.11 (s, 3 H, CH_3C=), 2.00–2.31 (m, 2 H, CH_2), 3.00–3.22 (m, 1 H, cyclopropyl CH), 7.10–7.38 (m, 10 H, ArH), 7.45 ppm (m, 1 H, C_6H_5CH=C).

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.17; H, 5.65; N, 4.62. Found: C, 79.19; H, 5.66; N, 4.57.

5-(2-Phenylethylidine)hydantoin (12a). One-half gram of **10a**[11a] (mp 172 °C) was dissolved in 10 ml of 10% NaOH. After a few minutes the solution was acidified with dilute HCl and the precipitate was collected, washed with H_2O, and dried to give 0.47 g (94%) of colorless **12a**: mp 198–200 °C; ir (Nujol) 3220 (NH), 1790 (C=O), 1735 (C=O), 1685 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 3.50 (2 H, d, J = 8 Hz, $-CH_2-$), 5.62 (1 H, t, J = 8 Hz, $-CH$=), 7.24 (5 H, s, Ph), 10.36 (1 H, s, NH), 10.96 ppm (1 H, s, NH).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.42; H, 4.99; N, 13.89.

3-Ethyl-5-(2-phenylethylidene)hydantoin (12b). Using the literature[11a] procedure, 13.5 g of **10a** was ethylated to give 3 g of colorless prisms (**12b**): mp 166–168 °C; ir (Nujol) 3220 (NH), 1780 (C=O), 1720 (C=O), 1680 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.19 (3 H, t, J = 7 Hz, CH_2CH_3), 3.54 (2 H, d, J = 8 Hz, $-CH_2CH$=), 3.58

(2 H, q, J = 7 Hz, $-CH_2CH_3$), 6.04 (1 H, t, J = 8 Hz, -CH=), 7.22 (5 H, s, Ph), 9.15 (1 H, s, NH).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.77; H, 6.18; N, 12.11.

2-(2,4-Dimethoxybenzylamino)-4-phenyl-3-butenonitrile (13). To an ice-cold stirred solution of cinnamaldehyde (2.64 g) and 2,4-dimethoxybenzylamine hydrochloride (4.07 g) in 40 ml of MeOH, a solution of NaCN (1.0 g) in 10 ml of H_2O was added. The mixture was stirred for an additional 45 min at 5–10 °C, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give 5.9 (96%) of crude **13** as a colorless oil: ir (neat) 3340 (NH), 2240 (C≡N), 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.1 (NH), 3.77 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 3.66–4.12 (2 H, d, $-NHCH_2$), 4.36 (1 H, d, d, J = 5, 2 Hz, NHCHCH=), 6.14 (1 H, d, d, J = 5, 15 Hz, =CHCHN), 6.3–7.5 ppm [9 H, m, $C_6H_3(OCH_3)_2$, C_6H_5, and PhCH=CH–). A small portion of the crude oil was dissolved in hexane–dry ether (1:1) and dry HCl was passed into the solution to precipitate **13** HCl. Recrystallization from absolute ethanol–hexane gave colorless crystals, mp 113–115 °C dec.

Anal. Calcd for $C_{19}H_{21}N_2O_2Cl$: C, 66.17; H, 6.14; N, 8.12. Found: C, 65.93; H, 6.19; N, 8.00.

2-Amino-4-phenyl-3-butenonitrile Trifluoroacetate (14). Crude **13** (5.54 g) and *m*-dimethoxybenzene (5 g) were dissolved in 40 ml of CF_3COOH with ice cooling, and the mixture was allowed to stand at room temperature for 15 h. After evaporation of CF_3COOH in vacuo, 20 ml of MeOH was added to the residue and the mixture was evaporated in vacuo. The residual oil was washed with petroleum ether and crystallized from benzene–hexane. The crystal were collected and washed with benzene to give 3.5 g (67%) of **14** as pale yellow prisms, mp 122–125 °C. Recrystallization from EtOAc–hexane gave an analytical sample: mp 122–124 °C dec; ir (KBr) 2260 cm^{-1} (C≡N); NMR (CF_3COOH) δ 5.23 (1 H, d, J = 6 Hz, -CHNH), 6.15 (1 H, d, d, J = 6, 15 Hz, =CHCH), 7.02 (1 H, d, J = 15 Hz, PhCH=), 7.22 ppm (5 H, m, C_6H_5).

Anal. Calcd for $C_{12}H_{11}N_2O_2F_3$: C, 52.94; H, 4.07; N, 10.29. Found: C, 52.79; H, 4.12; N, 10.45.

Styrylglycine (9). A. Direct Hydrolysis of 13. Crude aminonitrile **13**, prepared from 264 mg of cinnamaldehyde, was dissolved in 5 ml of MeOH and added to 30 ml of concentrated HCl and the solution was refluxed for 3 h. The reaction mixture was filtered to remove some resinous product, washed twice with $CHCl_3$, and evaporated to dryness giving a crystalline residue. The crude product was dissolved in a minimum amount of H_2O, and the pH was adjusted to 6.5 with dilute NaOH. After cooling, the precipitate was collected, washed with a small amount of H_2O and EtOH, successively, and dried to give 50 mg (overall yield 13%) of **9** as pale orange crystals, mp 178–183 °C dec. Recrystallization from H_2O gave colorless leaves: mp 198–200 °C dec; ir (Nujol) 3050–2650 (NH_3^+), 1655 cm^{-1} (COO^-); NMR (CF_3COOH) δ 5.06 (m, 1 H, -CHCOOH), 6.25 (1 H, d, d, J = 16, 6 Hz, PhCH=CH–), 7.06 (1 H, d, J = 16 Hz, PhCH=), 7.40 (5 H, s, C_6H_5–), 7.58 ppm (3 H, broad s, NH_3^+).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.87; H, 6.37; N, 7.84.

B. Hydrolysis of 14. Three hundred milligrams of **14** was dissolved in 15 ml of concentrated HCl and the solution was refluxed for 3 h. Evaporation of the reaction mixture gave a solid which was dissolved in H_2O. The solution was filtered to remove insoluble material and neutralized with dilute NaOH. After cooling, the precipitate was collected, washed with H_2O and EtOH, successively, and dried to give 75 mg (35%) of **9** as colorless crystals, mp 180–185 °C dec. The ir spectrum was identical with that of the product obtained by method A.

C. Hydrolysis of 14 via the Imino Ester. A solution of **14** (2.91 g) in 30 ml of absolute MeOH was saturated with dry HCl at 0 °C. After 2 h at room temperature, the reaction mixture was diluted with 300 ml of concentrated HCl and refluxed for 2 h. Using the same work-up procedure, 1.31 g (70%) of **9** as colorless crystals was obtained, mp 185–190 °C. The spectrum was identical with that of **9** obtained by method A.

D. From 4b. A solution of 0.92 g (3 mmol) of **4b** in 35 ml of glacial acetic acid and 35 ml of 6 N HCl was refluxed for 24 h. The dark reaction mixture was extracted with three 20-ml portions of diethyl ether and the aqueous solution was concentrated to 4–6 ml on a vacuum pump. After diluting with 20 ml of water, the aqueous solution was clarified with Norit and again evaporated in vacuo giving an extremely hygroscopic residue. The residue was redissolved in 15 ml of water, and the solution was adjusted to pH 5.0–6.0 with 10% ammonium hydroxide solution. After cooling to 0 °C, the precipitated amino acid was filtered and dried in vacuo, giving 0.215 g (41%) of crude product, mp 155–168 °C. Recrystallization from an ammonium acetate buffered solution gave 0.13 g (24%) of **9**, mp 181–190 °C dec (recrystallization raised the melting point to 196–199 °C), identical in all respects with authentic sample.

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References and Notes

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A Facile Preparation of Highly Fluorinated Diamines

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Most highly fluorinated amines and diamines are prepared by lithium aluminum hydride reduction of the corresponding amides[1] or by high-pressure (1000 psi) catalytic hydrogenation of nitriles.[2] The former class of compounds often gives highly explosive reaction mixtures,[1] while the latter reaction is inconvenient and involves an additional dehydration step in the synthesis. Both methods proceed in only moderate yield. Previous attempts to employ the easily obtained 2,2,3,3,4,4-hexafluoropentane 1,5-di-*p*-toluenesulfonate (**1**) with ammonia, methylamine, or diethylamine gave only tarry mixtures from which no amine could be isolated.[1] In one instance,[3] reaction of 1,1-di-*H*-heptafluorobutyl *p*-toluenesulfonate with aniline at 230 °C for 24 h gave a 68% yield of the desired amine, but reaction with ammonia gave only tars.

It has now been found that reaction of **1** with an excess of sodium azide takes place readily to give an almost quantitative yield of diazide **3** when hexamethylphosphoric triamide (HMPA) is employed as solvent. Azide formation was not observed when DMF was used as solvent. The