Synthesis of Racemic (*E*)- and (*Z*)-1-Amino-2-phenylcyclopropanecarboxylic Acid: (*E*)- and (*Z*)-"Cyclopropylphenylalanine"

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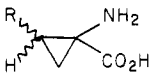
Both *E* and *Z* "cyclopropylogs" of DL-phenylalanine (Δ^E-Phe and Δ^Z-Phe) have been prepared by the cyclopropanation of each 4-benzylidene-2-phenyl-5(4*H*)-oxazolone isomer with diazomethane to form the three-membered ring. Opening of the oxazolone ring to give the benzyl ester followed by debenzoylation using Meerwein's reagent gave the benzyl ester hydrochloride of DL-Δ^Z-Phe. Hydrogenation gave the free amino acid in good yield. Isomerization of the (*Z*)-oxazolone to the *E* isomer followed by cyclopropanation and methyl ester formation gave *N*-Bz-DL-Δ^E-PheOMe. Debenzoylation and conversion to the *N*-Boc methyl ester followed. Saponification of the ester followed by Boc removal (HCl) gave DL-Δ^E-Phe hydrochloride in good yield.

A number of amino acids containing cyclopropane rings occur in nature,[1] and several of these have been synthesized.[2] In recent years the possible value of "cyclopropylogs" of the essential amino acids (Δ-AA) in which the C_α–C_β bond forms one side of the three-membered ring (1) has been recognized by several workers.[3]



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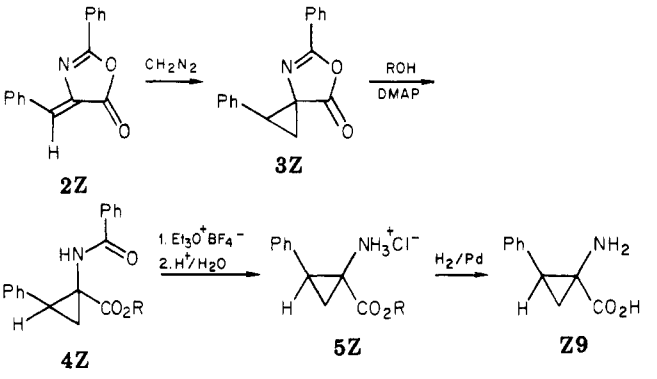
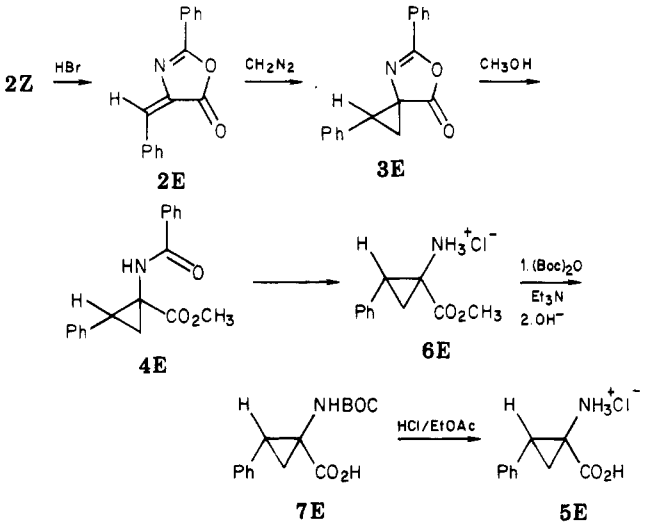
This structure restricts rotation about the C_α–C_β bond so that the β-functionality is fixed in space with respect to the amino and acid moieties as occurs in dehydroamino acid (Δ-AA) residues, but the cyclopropane ring reintroduces chirality into the system. Steric hindrance to reactions at the carbonyl group is expected to be intermediate between that of the α-protio and α-methyl amino acids, so that insertion into a peptide sequence should give amide bonds resistant to hydrolysis. Also, the pseudoconjugation of the amino and carboxyl functions with the β-group may lead to reactivity which is of value in the synthesis of enzyme inhibitors.[3b,c,e,f] Very recently, in fact, it has been shown that the natural unsubstituted compound (1, R = H) reacts readily with a pyridoxal-dependent enzyme, giving α-oxobutyrate and ammonia.[4] For these reasons we have investigated the synthesis of Δ-Phe in conjunction with our work on dehydroamino acids and peptides.

Our synthesis of (*E*)- and (*Z*)-Δ-Phe was accomplished by using, in the early stages, a reaction sequence already in the literature.[3b–e,5] The synthesis of the *Z* isomer **6Z**

Scheme I



Scheme II



(Scheme I) proceeded through the known intermediate **4Z** (R = CH_3 or CH_2Ph) which was then debenzoylated by conversion to an imidate salt by using Meerwein's reagent followed by acid-catalyzed hydrolysis of the salt at room temperature.[6] When **5Z** (R = CH_3) was obtained, attempted basic hydrolysis of the ester function, not surprisingly,[7] gave a mixture of unidentified products. Since

(1) (a) Burroughs, L. F. *J. Sci. Food Agr.* **1960**, *11*, 14. (b) Fowden, L.; Smith, A.; Millington, D. S.; Sheppard, R. C. *Phytochemistry* **1969**, *8*, 437. (c) Ichihara, A.; Shiraishi, K.; Sato, H.; Sakamura, S.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. J. *J. Am.* Chem. *Soc.* **1977**, *99*, 636. (d) Ichihara, A.; Shiraishi, K.; Sakamura, S.; Nishiyama, K. and Sakai, R. *Tetrahedron Lett.* **1977**, 269.

(2) (a) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem.* Soc. **1922**, *121*, 1177. (b) Bregovec, I.; Jakovcic, T. *Monatsh. Chem.* **1972**, *103*, 288. (c) Fujimoto, Y.; Irreverre, F.; Kerle, J. M., Karle, I. L.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3471.

(3) (a) Kaiser, C.; Zirkle, C. L. U.S. Patent 3 313 842, 1967; *Chem. Abstr.* **1965**, *63*, 14979*b*. (b) Pages, R. A.; Burger, A. *J. Med. Chem.* **1967**, *10*, 435. (c) Pages, R. A.; Burger, A. *Ibid.* **1966**, *9*, 766. (d) Bernabe, M.; Fernandez-Alvarez, E.; Ullate, S. P. *An. Quim.* **1972**, *68*, 501, 1005. (e) Bernabe, M.; Cuevas Fernandez O.; Fernandez Alvarez, E. *Eur. J. Med. Chem.* **1979**, *14*, 33. (f) Bernabe, M.; Cuevas Fernandez, O.; Fernandez Alvarez, E. *An. Quim.* **1979**, *75*, 977.

(4) Walsh, C.; Pascal, R. A.; Johnston, M.; Raines, R.; Dikskit, D.; Krantz, A.; Honma, M. *Biochemistry* **1981**, *42*, 7509.

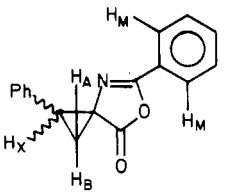
(5) (a) Awad, W. J.; Fateen, A. K.; Zayed, M. A. *Tetrahedron* **1964**, *20*, 891. (b) Hines, J. W.; Breitholle, E. G.; Sato, M.; Stammer, C. H. *J. Org.* Chem. **1976**, *41*, 1466.

(6) (a) Muxfeldt, H.; Rogalski, W. *J. Am. Chem. Soc.* **1965**, *87*, 933. (b) Chen, F. M. F.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 1433.

(7) Walborsky, H. M.; Ronman, P. E. *J. Org. Chem.* **1973**, *38*, 4213. These authors showed that 1-methyl-2,2-diphenylcyclopropylamine was decomposed readily in base, initiated by abstraction of a proton from the amino group.

0022-3263/82/1947-3270$01.25/0

Table I. ^{1}H NMR Spectral Data of Δ-Phenylalanine Derivatives



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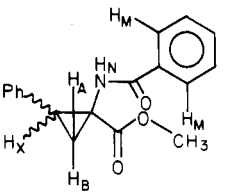

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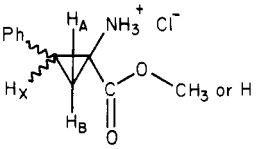


5, 6

compd	chemical shift, δ							coupling constants,[a] Hz		
	H_M	Ar	H_N	H_X	H_A	H_B	CH_3	J_{AB}	J_{AX}	J_{BX}
3Z	7.91-7.93 (m, 2 H)	7.23-7.53 (m, 8 H)		3.22 (m)	2.37 (dd)	2.28 (dd)		-5.4	9.0	9.5
3E	7.91-7.99 (m, 2 H)	7.26-7.58 (m, 8 H)		3.54 (m)	2.41 (dd)	2.39 (dd)		-5.4	9.5	9.5
4Z		7.23-7.46 (m, 10 H)	5.95 (br s)	3.06 (m)	1.88 (dd)	2.35 (dd)	3.77 (s)	-6.1	8.2	9.6
4E	7.84 (m, 2 H)	7.23-7.55 (m, 8 H)	6.86 (br s)	2.99 (m)	1.75 (dd)	2.35 (dd)	3.37 (s)	-5.7	9.8	8.4
5Z		7.43-7.55 (m, 6 H)		3.38 (m)	2.01 (dd)	2.15 (dd)	3.91 (s)	-7.3	8.5	10.0
5E		7.36-7.45 (m, 6 H)		3.24 (m)	1.99 (dd)	2.3 (dd)	3.56 (s)	-6.9	10.3	9.1
6Z		7.43-7.51 (m, 6 H)		3.28 (m)	1.92 (dd)	2.06 (dd)		-6.9	8.3	9.7
6E		7.36-7.43 (m, 6 H)		3.14 (m)	1.92 (dd)	2.18 (dd)		-7.0	10.5	8.7

[a] Theoretical ^{1}H NMR spectra were generated by using the Panic program, (Bruker Instrument Corp.) which applies the Loacoon III algorithm.[11]

the final step in the sequence published by Bernabe[3e] is carried out in strong alkali, some question is raised about that work by these results. Hydrogenation, however, of **5Z** (R = CH_2Ph) gave Δ^Z-Phe (**6Z**) in excellent yield. Even though Burger[3b] reported the synthesis of a "cyclopropyl" thyronine derivative in which an *N*-benzoyl intermediate having the same structural elements as **4Z** was debenzoylated by hydrolysis in boiling HCl/HOAc solution, we[5b] and others[3d] have shown that the cyclopropane ring of **4Z** is unstable under these conditions.

The synthesis of Δ^E-Phe (Scheme II), which has not been previously reported, proceeded similarly from the (*E*)-azlactone **2E** prepared by isomerization of **2Z** with HBr.[8] Since a very useful compound might be the *N*-*tert*-butoxycarbonyl (Boc) acid **7E**, we chose to prepare the methyl esters **4E** and **5E**, converting the latter into the *N*-Boc compound **7E** by N-acylation followed by saponification. Even though the acidity of amide N–H (in Boc-**5E**) must be greater than that of the amino hydrogen atoms of 2,2-diphenylcyclopropylamine investigated by Walborsky,[7] *N*-Boc-**5E** was perfectly stable to the alkaline conditions of ester hydrolysis. It is notable that the NMR methyl peak of **5E** is ~0.4 ppm upfield of that peak in the *Z* isomer due, apparently, to shielding by the face of the benzene ring in the β-position. The *N*-Boc acid **7E** was then readily converted to the amino acid hydrochloride **6E** by anhydrous HCl/EtOAc. This sequence, in which an *N*-Boc methyl ester rather than a benzyl ester intermediate is used, also affords **6Z** as its hydrochloride in good yield.

The configuration of **3Z** was proved by X-ray analysis. Single-crystal X-ray diffractometer data for $C_{17}H_{13}O_2N$ (**3Z**) was collected on a Nonius automated diffractometer. Cell dimensions [a = 5.484 (2) Å, b = 11.101 (6) Å, c = 11.189 (5) Å, α = 85.62 (4)°, β = 82.39 (3)°, γ = 84.50 (4)°, V = 670.64 Å^3] were determined during normal alignment procedures. The structure was solved by direct methods in triclinic space group $P\bar{1}$ (Z = 2, d_{calcd} = 1.305 g cm^{-3}) and refined by full-matrix least-squares methods to a final agreement factor of R = 6.9% by using 2031 observed reflections and unit weights. Hydrogen atoms were located on a difference Fourier map, and their positions were included in final cycles of refinement, but these positions were not varied. The structure (Figure 1) shows the five-membered azlactone ring (C4, O1, C5, C3, N1) to be flat (deviation from planarity averaged 0.009 Å) and to be close to being coplanar with the benzene ring (C6, C7, C8, C9, C10, C11), substituted on carbon 5 (angle between planes 9.20°). The three-membered ring (C1, C2, C3), which includes C-4 of the oxazolone ring, subtends an angle of 87.45° with the plane of that ring and an angle of 71.07° with the plane of the benzene ring (C12, C13, C14, C15, C16, C17). The benzene ring and N1 are shown to be cis to each other with respect to the cyclopropane ring.

Bond distances in the three membered ring are as follows: C2–C3, 1.52 (3) Å; C1–C2, 1.49 (3) Å; C1–C3, 1.54 (1) Å. The angle at C3 (58.3 (3)°) is slightly smaller than the angles at C2 (61.7 (3)°) and C1 (60.0(3)°). This angle appears to be compressed in compensation for the C4–C3–N1 angle of 122.2 (3)°. Bond distances in the oxazolone ring appear normal: C5–N1, 1.28 (3) Å; C3–N1, 1.44 (3) Å; C3–C4, 1.47 (3) Å; C4–O1, 1.40 (2) Å; C5–O1, 1.40 (3) Å.

A careful study of the ^{1}H and ^{13}C spectra of these compounds was made, and the results appear in Tables I and II. The signals due to the protons on the cyclopropyl rings appear as multiplets and doublets of doublets. The lower field signals are assigned to the proton, H_X, on the carbon atom containing the phenyl group. This low-field shift is due to the deshielding of the phenyl ring. The geminal

(8) (a) Tatsuoka, S.; Morimoto, A. *Yakugaku Zasshi* **1950**, *70*, 253. (b) Rao, Y. S.; Filler, R. *Synthesis* **1975**, 749 and references cited herein. (c) The *E* isomer is reconverted to the *Z* compound in laboratory light and must be handled accordingly.

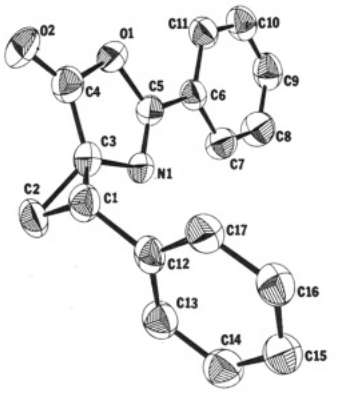
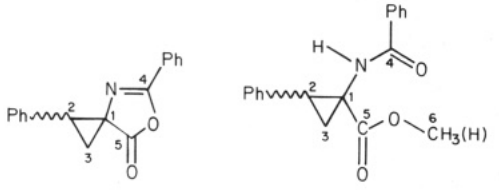


Figure 1. Configuration of **3Z**.

Table II. ^{13}C NMR Spectral Data of Δ-Phenylalanine Derivatives



3 **4-6**

compd	chemical shift, δ					
	C_1	C_2	C_3	C_4	C_5	C_6
3Z	53.93	37.43	24.62	161.8	177.7	
3E	53.81	37.99	23.34	162.0	174.4	
4Z (R = CH_3)	38.66	32.94	21.32	168.2	172.1	52.77
4E	40.83	34.91	20.64	168.3	169.9	51.99
5Z (R = CH_3)	39.27	30.63	17.67		170.9	54.20
5E	40.55	31.77	17.31		168.9	53.70
6Z	39.21	30.36	17.45		172.5	
6E	40.43	31.28	17.11		170.7	

protons, H_A and H_B, which are vicinal to H_X might be assigned by comparisons of their vicinal coupling constants J_{AX} and J_{BX} since it has been found that for vicinal cyclopropyl ring protons J_{cis} is always larger than J_{trans}.[9] However, it was not possible to assign the signals unambiguously to H_A and H_B in **3Z** and **3E** because of the small differences in their coupling constants.

Since the relaxation of a proton may depend significantly on through-space dipole coupling with a second set of protons, its NMR signal intensity may be enhanced when the set of protons which assist in relaxation are saturated by an appropriate irradiation in the NMR spectrometer.[10] This phenomenon, termed the nuclear Overhauser effect, (NOE) is highly dependent on the distance between protons. It is, therefore, possible by NOE studies to identify which protons are cis or trans to H_X. Since a vicinal cis proton is closer to H_X than a vicinal trans proton, the former would be expected to show an NOE enhancement larger than the latter. For example, in **3Z** the irradiation of H_X at 3.22 ppm gave a greater NOE enhancement to the proton signal at 2.28 ppm (assigned as H_B) than to the signal at 2.37 ppm (assigned as H_A). The NOE experiment also allowed us to make an unambiguous assignment of the ring protons in **3E**. Irradiation of H_X at 3.54 ppm gave a greater NOE enhancement to the signal at 2.41 ppm (assigned as H_A) than to that at 2.39 ppm (assigned as H_B). NOE experiments also confirmed the assignments of the ring protons in compounds **4–6** which were made on the basis of chemical shift and coupling constant magnitude.

No very striking trends are clear in the ^{13}C spectra except that both C_1 and C_2 of the *E* isomers appear downfield of these atoms in the *Z* compounds (except in the oxazolones, **3**) while the reverse is true of the carbonyl carbon atoms (C_5) in all cases studied. With further expansion, these data may be useful in the determination of configuration in the future.

Experimental Section

Instrumentation. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer Model 297 recording spectrophotometer with polystyrene as a standard. ^1H NMR spectra were recorded at 400.134 MHz and ^{13}C NMR spectra at 100.2 MHz with a Bruker WH-400 spectrometer with tetramethylsilane or dioxane as internal standards. NOE experiments were carried out with nondegassed 5–10 mM solutions of the samples in $CDCl_3$. NOE effects were measured by using a 4-s gated presaturation pulse and a sweep width of 4000 Hz. A reference spectrum was obtained with the decoupler set at 11 ppm. The NOEs were obtained as the difference between the transformed experimental spectra and the appropriate reference (control) spectrum. NOE signal enhancements of approximately 3–7% were observed. Elemental analyses were provided by Atlantic Microlab, Atlanta, GA.

Thin-layer chromatography was performed on Whatman precoated silica gel plates with the following solvent systems: (I) petroleum ether/ether (2:1), (II) benzene, (III) ether, (IV) $CHCl_3$/MeOH (10:1), (V) $CHCl_3$/MeOH/HOAc (95:5:1), (VI) ether/petroleum ether (1:1), (VII) $CHCl_3$/MeOH (20:1), (VIII) *n*-BuOH/HOAc/H_2O (5:1:4), (IX) EtOAc/$CHCl_3$ (2:1); (X) $CHCl_3$/MeOH/HOAc (25:5:1), (XI) EtOAc/$CHCl_3$ (5:1). Thin-layer plates were visualized by using UV light, 1% ninhydrin/*n*-BuOH w/v, I_2 vapor, and Cl_2/tolidine.

Materials. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), *N*-methylmorpholine, 4-(dimethylamino)pyridine (DMAP), hippuric acid, and benzaldehyde were purchased from Aldrich Chemical Co. and were used without further purification. Collidine and triethylamine were distilled from and stored over CaO. Tetrahydrofuran was distilled from potassium and stored over sodium. Methylene chloride was dried over anhydrous Na_2SO_4. All other solvents were used without purification unless otherwise specified.

(*Z*)-2-Phenyl-4-benzylidene-5-oxazolone (2Z). This compound was prepared by the general method employed by Buck and Ide,[12] and a 72% yield of **2Z** was obtained as yellow needles from benzene: mp 160–165 °C (lit.[13] mp 165–166 °C); R_f (I) = 0.87; NMR ($CDCl_3$) δ 8.4–8.1 (m, 4 H, ortho protons), 7.6–7.2 (m, 7 H, Ar H and HC=C).

(*E*)-2-Phenyl-4-benzylidene-5-oxazolone (2E). A total of 5 g (0.02 mol) of **2Z** was suspended in 90 mL of 48% hydrobromic acid and cooled in an ice bath. The solution was saturated with anhydrous hydrogen bromide gas for 0.5 h and put in the refrigerator overnight. The contents were poured onto crushed ice, and the solid azlactone **2E** was filtered, washed with 300 mL of ice–water, and dried over P_2O_5 to yield 5 g (100%) of **2E** as a yellow solid: mp 147–149 °C (lit.[8] mp 148.5 °C); R_f (I) = 0.80.

(*Z*)-1,5-Diphenyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (3*Z*). A total of 6.0 g (0.024 mol) of **2Z** dissolved in 100 mL of methylene chloride was treated with an ethereal solution of diazomethane (from 21.5 g of Diazald in 200 mL of ether). The mixture was allowed to stand at room temperature overnight, treated with anhydrous $CaCl_2$ to destroy excess diazomethane, filtered, and concentrated in vacuo. The resultant yellow oil was triturated

(9) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: Oxford, 1972; pp 286–288.

(10) Noggle, J. H.; Schirmer, R. E "The Nuclear Overhauser Effect"; Academic Press: New York, 1971.

(11) Castellano, S.; Bothner-By, A. A. *J. Chem. Phys.* 1964, *41*, 3863–3869.

(12) Buck, J. S.; Ide, W. S. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 55.

(13) Carter, H. E. *Org. React.* **1947**, *3*, 198–239.

with ether to give 1.95 g (31%) of **3Z**. Recrystallization from CH_2Cl_2/hexanes gave pure **3Z** as white needles: mp 142–143 °C (lit.[13] mp 142–143 °C); R_f (II) = 0.72; IR (KBr) 1800 (C=O), 1645 cm^{-1} (C=N).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.56; H, 4.94; N, 5.32. Found: C, 77.59; H, 4.96; N, 5.30.

(E)-1,5-Diphenyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-one (3E). A total of 6.0 g (0.024 mol) of **2E** was treated under conditions similar to those used for **2Z** to give 3.4 g (54%) of **3E**. Recrystallization from CH_2Cl_2/hexanes gave an analytical sample of **3E**: mp 115–117 °C; R_f (II) = 0.58; IR (KBr) 1810 (C=O), 1645 cm^{-1} (C=N).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.56; H, 4.94; N, 5.32. Found: C, 77.46; H, 5.00; N, 5.29.

Methyl (Z)-2-Phenyl-1-benzamidocyclopropane-1-carboxylate (4Z, R = CH_3). A total of 0.75 g (2.8 mmol) of **3Z** suspended in 20 mL absolute methanol and 0.35 g (2.8 mmol) of 4-(dimethylamino)pyridine were stirred at room temperature for 30 min. The methanol was removed in vacuo, 30 mL of CH_2Cl_2 and 25 mL of 5% citric acid were added, and the solution was extracted. The aqueous portion was extracted with an additional 30 mL of CH_2Cl_2, and the organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated to give crude **4Z**. Recrystallization from CH_2Cl_2/hexanes gave 0.76 g (90%) of **4Z** as white needles: mp 163–164 °C; R_f (III) = 0.68; IR (KBr) 1715 (C=O), 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{17}O_3N$: C, 73.14; H, 5.75; N, 4.74. Found: C, 73.16; H, 5.80; N, 4.73.

Methyl (E)-2-Phenyl-1-benzamidocyclopropane-1-carboxylate (4E). A total of 2.63 g (0.01 mol) of **3E** underwent methanolysis under exactly the same conditions used in the preparation of **4Z** (R = CH_3) to give 2.87 g (97%) of **4E** as white needles: mp 193–195 °C; R_f (III) = 0.78; IR (KBr) 1730 (C=O), 1640 cm^{-1} (C=O), after recrystallization from CH_2Cl_2/hexanes.

Anal. Calcd for $C_{18}H_{17}O_3N$: C, 73.14; H, 5.75; N, 4.74. Found: C, 73.17; H, 5.80; N, 4.75.

Methyl (Z)-2-Phenyl-1-aminocyclopropane-1-carboxylate Hydrochloride (5Z, R = CH_3). A total of 6.9 g (0.023 mol) of **4Z** dissolved in 50 mL of dry CH_2Cl_2 and 46 mL (0.046 mol) of a 1 M solution of triethyloxonium tetrafluoroborate in CH_2Cl_2 were refluxed under nitrogen overnight. The reaction mixture was extracted with a solution of 8.0 g (0.046 mol) of K_2HPO_4 in 50 mL of water, the aqueous portion was extracted with an additional 50 mL of CH_2Cl_2, and the organic extracts were combined and dried over anhydrous $MgSO_4$. The CH_2Cl_2 was removed in vacuo, and the residual oil was dissolved in 50 mL of ether and cooled in a dry ice–carbon tetrachloride bath. To this was added 20 mL of an HCl-saturated ether solution followed by 100 mL of a 1 N HCl (aq) solution. The reaction mixture was stirred for 30 min at room temperature, filtered to remove any starting material which precipitated, and extracted. The aqueous portion was extracted with an additional 30 mL of ether and evaporated in vacuo. The resultant solid was dissolved in a minimum amount of hot acetonitrile. The solution was dried over anhydrous Na_2SO_4 and filtered, and ether was added until the mixture became cloudy. Crystallization at room temperature afforded 2.17 g of pure **5Z**. The filtrate was stored at 0 °C to provide an additional 0.60 g of **5Z**, for a total 51% yield of **5Z**, as white needles: mp 171 °C dec; R_f (IV) = 0.87; IR (KBr) 3000–2800 (NH), 1740 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{14}O_2NCl$: C, 58.03; H, 6.15; N, 6.15; Cl, 15.58. Found: C, 58.19; H, 6.17; N, 6.11; Cl, 15.39.

Methyl (E)-2-Phenyl-1-aminocyclopropane-1-carboxylate Hydrochloride (5E). A total of 6.0 g (0.02 mol) of **4E** was debenzoylated by the procedure used for preparation of **5Z** to give crude **5E** which was crystallized from 2-propanol/ether to give 1.80 g (39%) of **5E** as a white solid: mp 168–170 °C dec; R_f (IV) = 0.61; IR (KBr) 3000–2800 (NH), 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{14}O_2NCl \cdot 0.5H_2O$: C, 55.82; H, 6.34; N, 5.92; Cl, 14.99. Found: C, 55.78; H, 6.40; N, 5.90; Cl, 14.95.

Benzyl (Z)-2-Phenyl-1-benzamidocyclopropane-1-carboxylate (4Z, R = benzyl). To a solution containing 1.0 g (3.8 mmol) of **3Z** in 25 mL of dry THF and 0.94 mL (9.1 mmol) of benzyl alcohol was added 0.46 g (3.8 mmol) of 4-(dimethylamino)pyridine. The reaction mixture was stirred at room temperature for 48 h, the THF was removed in vacuo, 30 mL of CH_2Cl_2 and 30 mL of 5% citric acid were added, and the solution was extracted. The aqueous layer was extracted with an additional 30 mL of CH_2Cl_2, and the organic layers were combined, washed with saturated NaCl (1 × 15 mL), and dried over anhydrous Na_2SO_4. The CH_2Cl_2 was removed in vacuo and the resultant oil crystallized from CH_2Cl_2/hexanes to give 1.04 g (74%) of **4Z** (R = benzyl) as a white solid: mp 179–180 °C; R_f (VI) = 0.42; IR (KBr) 3300 (NH), 1740 (ester C=O), 1650 cm^{-1} (amide C=O).

Anal. Calcd for $C_{24}H_{21}O_3N$: C, 77.62; H, 5.66; N, 3.77. Found: C, 77.42; H, 5.75; N, 3.72.

Benzyl (Z)-2-Phenyl-1-aminocyclopropane-1-carboxylate Hydrochloride (5Z, R = benzyl). A total of 4.0 g (0.01 mol) of **4Z** (R = benzyl) was debenzoylated as described for **5Z** (R = CH_3), giving crude **5Z** (R = benzyl) which was recrystallized from 2-propanol/ether to afford 0.60 g (19%) of **5Z** (R = benzyl) as small white needles: mp 156–158 °C; R_f (VII) = 0.42.

Anal. Calcd for $C_{17}H_{18}O_2NCl$: C, 67.22; H, 5.93; N, 4.61; Cl, 11.68. Found: C, 67.06; H, 6.00; N, 4.58; Cl, 11.61.

(Z)-2-Phenyl-1-aminocyclopropane-1-carboxylic Acid (6Z). A total of 0.35 g (1.15 mmol) of **5Z** (R = benzyl) dissolved in 30 mL of ethyl acetate was extracted with 5% $NaHCO_3$ (2 × 15 mL). The ethyl acetate extract was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the free amino ester as a colorless oil. It was dissolved in 50 mL of absolute methanol, 50 mg of 10% Pd/C was added, and hydrogen was bubbled through the solution for 30 min. The solution was filtered through Celite, the methanol removed in vacuo, and the resultant oil dissolved in 3 mL of 0.2 M acetic acid. Gel filtration through a Bio-gel P_2 column with a flow rate of 5 mL/h afforded pure **6Z** in fractions 43–49. These fractions were combined and lyophilized to give 165 mg (62%) of **6Z** as a white powder: mp 129–130 °C dec; R_f (VIII) = 0.31.

Anal. Calcd for $C_{10}H_{11}O_2N \cdot 0.5H_2O$: C, 64.51; H, 6.45; N, 7.52. Found: C, 64.46; H, 6.53; N, 7.50.

(E)-2-Phenyl-1-aminocyclopropane-1-carboxylic Acid Hydrochloride (6E). A total of 200 mg (0.72 mmol) of **5E** was dissolved in 15 mL of dry ethyl acetate (distilled from P_2O_5), cooled in an ice bath, and treated with 30 mL of a HCl saturated ethyl acetate solution. The reaction mixture was stirred for 2 h, at which time a white solid precipitated. The precipitate was filtered and washed with 20 mL of ether. The filtrate was evaporated, and the residue was triturated with 30 mL of ether. A total of 140 mg (90%) of **6E** was obtained as a white solid, mp 209 °C dec.

Anal. Calcd for $C_{10}H_{12}O_2NCl$: C, 56.22; H, 5.62; N, 6.55; Cl, 16.60. Found: C, 56.03; H, 5.66; N, 6.53; Cl, 16.53.

Registry No. 2Z, 17606-70-1; **2E**, 15732-43-1; (±)-**3Z**, 66108-19-8; (±)-**3E**, 66108-20-1; (±)-**4Z** (R = CH_3), 82112-02-5; (±)-**4Z** (R = benzyl), 82112-06-9; (±)-**4E**, 82112-03-6; (±)-**5Z** (R = CH_3), 82112-04-7; (±)-**5Z** (R = benzyl), 82112-07-0; (±)-**5E**, 82112-05-8; (±)-**6Z**, 82112-08-1; (±)-**6E**, 82112-09-2; CH_2N_2, 334-88-3.