Resolution and Deblocking of Racemic *N*-(Benzyloxycarbonyl)cyclopropylphenylalanine

Hitoshi Kimura and Charles H. Stammer*

Department of Chemistry, University of Georgia, Athens, Georgia 30602

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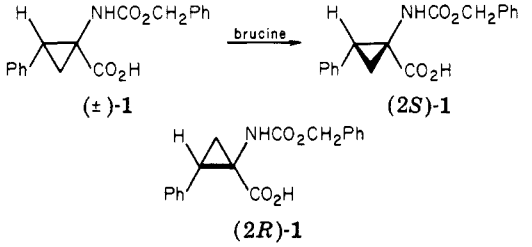
We recently published[1] the synthesis of both diastereomers of "cyclopropylphenylalanine", designated as ∇^ZPhe and ∇^EPhe.[2] In order to incorporate these new amino acids into peptides, we investigated the resolution and chemistry of the isomer of greatest interest. Previously, we prepared several peptides containing dehydrophenylalanine (ΔPhe) residues,[3] and, due to the greater stability of the *Z* isomer[4] (Δ^ZPhe), no peptides having the Δ^EPhe isomer have been reported. For this reason, we chose to investigate the ∇^EPhe isomer first, so that peptides containing a conformationally restricted Phe residue having the *E* configuration might be obtained.

With use of the classical method of resolution, *N*-(benzyloxycarbonyl)-(2*RS*)-∇^E-phenylalanine [Z-(2*RS*)-∇^EPhe·OH] (1) was converted into a mixture of diastereomeric brucine salts, and, after two recrystallizations from aqueous ethanol, the more insoluble diastereomer gave, after conversion back to the free acid, the (−) isomer, $[\alpha]^{22}_D$ −120.1°, of Z-∇^EPhe·OH in about 60% yield. The mother liquor afforded the (+) enantiomer, $[\alpha]^{20}_D$ +115°, in 38% yield.



In order to obtain the amino acid enantiomers from (2*S*)-1 and (2*R*)-1, we studied the deblocking of these benzyloxycarbonyl derivatives. It is well-known that catalytic hydrogenolysis is the method of choice for removal of the benzyloxycarbonyl protecting group in peptide synthesis. In our recent work[1] on the preparation of cyclopropylphenylalanine, we reported that the hydrogenolysis of ∇^ZPheOBzl over 10% Pd/C afforded the free amino acid in good yield without affecting the cyclopropane ring.[5] On the basis of this, we incorrectly assumed that the benzyloxycarbonyl protecting group of Z-∇^EPhe (1) could be removed under these same conditions. We found, however, that the ring-opened compound 2-amino-4-phenylbutyric acid (2) is formed in almost quantitative yield under these conditions. Interestingly, when the optically active isomers ($[\alpha]^{25}_D$ ±118°) of 1 were treated in the same manner, partially active ([α] −3.5° and 6.5°) products were obtained. Since we have now determined the absolute configurations of the enantiomers of 1, vide infra, and the absolute configurations have recently been reported[6] for the enantiomers of 2, we can deduce that the ring cleavage occurred with ~8% and ~15% retention of configuration,[7] respectively.

Table I. Hydrogenolysis of Z-∇^E- and Z-∇^ZPhe

	catalyst[a]	time	yield, %	proportion[c] 3	2
(*Z*)∇^EPhe	10% Pd/C	30 min		40	60[d]
		1 h	98	0	100
	5% Pd/C	20 min		100	0[d]
		1 h	62	60	40
	5% Pd/C pyridine[b]	1.5 h	65	100	0
(*Z*)∇^ZPhe	10% Pd/C	1 h	44	0	100[d]
	5% Pd/C	1 h	42	0	100[d]
	5% Pd/C pyridine[b]	1.5 h	24	0	100[d]

[a] 40 mg of catalyst/mmol of substrate in 40 mL of ethanol. [b] 1 molar equiv. [c] The product precipitated during reduction and was extracted from the catalyst with 1 N HCl/EtOH. [d] Starting material was identified in the ethanol filtrate by TLC.

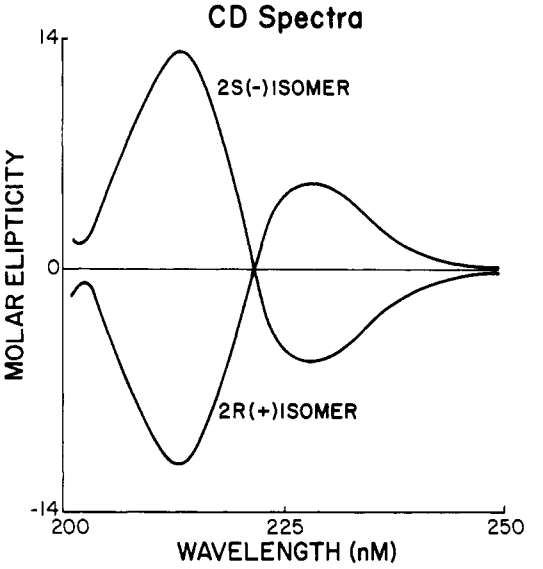
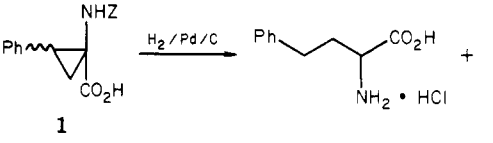


Figure 1. CD curves on the enantiomeric hydrochlorides of ∇^EPhe 3 in water.



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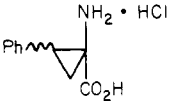

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(1) King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270.

(2) The *Z* isomer is a mixture of the 2*S*,3*S* and 2*R*,3*R* and the *E* isomer consists of the 2*S*,3*R* and 2*R*,3*S* enantiomers. Since the configurations (and conformations) of the *Z* and *E* amino acids are most important to the discussion of peptides containing these compounds, we shall use the ∇^Z and ∇^E nomenclature, designating only the configuration at C-2 (numbering the carbon chain as an amino acid, not as a cyclopropane) by the RS system; i.e., (2*S*)∇^EPhe or (2*R*)∇^ZPhe.

(3) (a) English, M. L.; Stammer, C. H. *Biochem. Biophys. Res. Commun.* **1978**, *85*, 780. (b) Grim, M. D.; Chauhan, V.; Shimohigashi, Y.; Kolar, A. J.; Stammer, C. H. *J. Org. Chem.* **1981**, *46*, 2671. (c) Fisher, G. H.; Berryer, P.; Ryan, J. W.; Chauhan, V.; Stammer, C. H. *Arch. Biochem. Biophys.* **1981**, *211*, 269. (d) Nitz, T. J.; Lindsey, J.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 4029. (e) King, S. W.; Stammer, C. H. *Ibid.* **1981**, *46*, 4780.

(4) Nitz, T. J.; Holt, E. M.; Rubin, B.; Stammer, C. H. *J. Org. Chem.* **1981**, *46*, 2667.

(5) See Stewart: (Stewart, F. H. C. *Aust. J. Chem.* **1981**, *34*, 2431) for an example of the hydrogenolysis of cyclopropylalanine derivatives and Witiak et al. (Witiak, D. T.; Lee, H. J.; Goldman, H. D.; Zwilling, B. S. *J. Med. Chem.* **1978**, *21*, 1194) for successful hydrogenolytic deblocking of benzyloxycarbonyl diaminocyclopropanes.

(6) Weller, H. N.; Gordon, E. M. *J. Org. Chem.* **1982**, *47*, 4160.

(7) Cushman et al. (Cushman, B. M.; Earnest, S. E.; Brown, D. B. *J. Organomet. Chem.* **1978**, *159*, 431) have studied reactions of cyclopropanes with Pt, but we know of no reports of Pd-catalyzed reductive ring openings on optically active compounds.

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In order to investigate the deblocking further, we examined the catalytic hydrogenolysis of both ∇^EPhe and ∇^ZPhe derivatives with several palladium catalysts. The results, summarized in Table I, showed that 5% Pd/C deactivated with pyridine selectively removed the benzyloxycarbonyl group from the *E* isomer but was completely nonselective in deblocking the *Z* isomer. Thus, none of the three catalysts selectively removed the benzyloxycarbonyl protecting group.

The (-)- and (+)-∇^EPhe hydrochlorides were obtained from the blocked amino acid enantiomers (1) by hydrogenolysis over 5% Pd/C attenuated with pyridine. Their CD spectra (Figure 1) showed[8] that the (-) isomer of 3 had a large positive Cotton effect at 214 nm while the (+) isomer showed a similar curve opposite in sign, indicating these to be the 2*S* and 2*R* enantiomers, respectively. Potentiometric titration gave average pK_as of 3.11 (CO_2H) and 8.04 (NH_2) in water solution, somewhat different from phenylalanine itself [pK_a[9] 2.58 (CO_2H) and 9.24 (NH_2)].

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. The ^{1}H NMR spectra were recorded on a Varian EM-390 90-MHz NMR spectrometer with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 infrared spectrophotometer with polystyrene as the standard. Elemental analyses were carried out by Atlantic Microlab, Atlanta, GA.

Z-∇^EPhenylalanine (1). A suspension of ∇^Ephenylalanine methyl ester hydrochloride (456 mg, 2 mmol) and carbobenzyloxy chloride (95%, 0.40 g, 2.2 mmol) in 5% $NaHCO_3$ (10 mL) was stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate (20 mL × 3). The extract was washed with 5% citric acid (20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was suspended in 2 N NaOH (5 mL) and methanol (5 mL) and stirred overnight at room temperature. The reaction mixture was condensed under reduced pressure to one-half its volume, diluted with water (20 mL), and washed with ethyl acetate. The aqueous solution was acidified with 2 N HCl and extracted with ethyl acetate, and this extract was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was crystallized from ethyl acetate–hexane to give 450 mg (72%) of 1 as colorless needles: mp 124–125 °C; IR (KBr) ν_{max} cm^{-1} 3300 (NH), 3150–2800 (OH), 1700 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.35–1.66 (1 H, br, CH), 1.95–2.20 (1 H, br, CH), 2.73–3.05 (1 H, br, PhCH), 5.20 (2 H, s, $PhCH_2$), 7.00–7.45 (10 H, m, ring H), 10.46 (1 H, s, CO_2H).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.66; H, 5.66; N, 4.51.

Z-∇^ZPhenylalanine. Following the same procedure described above, ∇^Zphenylalanine (1.14 g, 5 mmol), carbobenzyloxy chloride (95%, 0.95 g, 5.5 mmol), and 5% $NaHCO_3$ (20 mL) gave Z-∇^ZPhe·OMe, which was treated with 2 N NaOH (10 mL) and methanol (10 mL) and gave 0.98 g (62%) of Z-∇^ZPhe·OH as a white solid: mp 168–169 °C (ethyl acetate–hexane); IR (KBr) ν_{max} cm^{-1} 3280 (OH), 1695 (C=O); ^{1}H NMR ($CDCl_3$ 20% Me_2SO-d_6) δ 1.63–1.87 (1 H, m, CH), 1.93–2.16 (1 H, m, CH), 3.08 (1 H, t, *J* = 9 Hz, PhCH), 5.07 (2 H, s, $PhCH_2$), 5.97 (1 H, s, NH), 7.33 (10 H, s, ring H).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.41; H, 5.52; N, 4.48.

Resolution of Z-(2*RS*)-∇^EPhenylalanine (1). A solution of 1 (6.22 g, 0.02 mol) and brucine·2H_2O (8.64 g, 0.02 mol) in 100 mL of ethanol–water (1:1) was allowed to stand at room temperature for 4 days. The precipitated crystals were collected by suction and recrystallized twice from ethanol–water (1:1) to give 5.64 g of a brucine salt; $[\alpha]^{20}_D$ -59.3° (*c* 1.03, MeOH). This salt was suspended in 5% NaOH (100 mL), and the suspension was stirred for 10 min. The precipitated crystals were filtered and washed three times with water. The filtrate was acidified with concentrated HCl and extracted with ethyl acetate. After the solution was dried over Na_2SO_4, the extract was evaporated in vacuo and the crystals were recrystallized from ethyl acetate–hexane to give 1.91 g (59.3%) of (-)-1 as colorless leaves: mp 153–154 °C; $[\alpha]^{22}_D$ -120.1° (*c* 1.03, MeOH).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.44; H, 5.53; N, 4.48.

The mother liquor, containing the other optical isomer, was evaporated to dryness in vacuo, and the residue was suspended in 5% NaOH (100 mL) and stirred for 10 min. The precipitated crystals were filtered and washed three times with water. The filtrate was acidified with concentrated HCl and extracted with ethyl acetate. After the solution was dried over anhydrous Na_2SO_4, the extract was evaporated in vacuo and the crystalline residue was recrystallized from ethyl acetate–hexane to give 1.22 g (37.9%) of (+)-1 as colorless leaves: mp 153–154 °C; $[\alpha]^{20}_D$ +114.8° (*c* 1.0, MeOH).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.52; H, 5.52; N, 4.46.

(-)-(2*S*)-∇^EPhenylalanine (-)-3. A suspension of (-)-1 (3.11 mg, 1 mmol), 5% Pd/C (Engelhard) (30 mg) and pyridine (80 mg, 1 mmol) in absolute EtOH (30 mL) was stirred under hydrogen for 1.5 h at room temperature. The precipitated catalyst and crystals were collected on a filter, washed with ether, and extracted with 20 mL of ethanol–1 N HCl (10:1). The extract was evaporated in vacuo, and the residue was recrystallized from AcOEt–EtOH to give 137 mg (67%) of (-)-3·HCl: mp 219–220 °C dec; $[\alpha]^{25}_D$ -74.6° (*c* 1.0, H_2O).

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.29; H, 5.67; N, 6.53. IR and NMR spectra were identical with those previously reported for the racemic compound.

(+)-(2*R*)-∇^EPhenylalanine (+)-3. Following the same procedure, Z-(2*R*)-∇^EPhe (187 mg, 0.6 mmol), 5% Pd/C (20 mg), pyridine (50 mg, 0.6 mmol) and absolute EtOH (20 mL) gave 82 mg (64%) of (+)-3·HCl: mp 221–222 °C dec; $[\alpha]^{25}_D$ +74.4° (*c* 1.0, H_2O).

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.28; H, 5.70; N, 6.52.

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Registry No. (±)-*trans*-1, 86014-29-1; (-)-1, 86087-19-6; (+)-1, 86087-20-9; (±)-*trans*-1 methyl ester, 86014-30-4; (±)-*cis*-1, 86014-31-5; (-)-1 brucine salt, 86116-64-5; (-)-3, 86087-21-0; (+)-3, 86087-22-1; (±)-*trans*-3 methyl ester, 82112-05-8; (±)-∇^Z-phenylalanine, 82112-08-1; carbobenzyloxy chloride, 501-53-1; brucine, 357-57-3.

(8) See Yamada et al. (Yamada, S.; Achiwa, K.; Terashima, S.; Mizuno, H.; Takamura, N.; LeGrant, M. *Chem. Pharm. Bull.* **1969**, *17*, 2608) for references to ORD/CD studies on α-methyl amino acids.

(9) "The Merck Index", 9th ed.; Merck: Rahway, NJ, 1976; p 7072.

Base-Catalyzed Conversion of 2,5-Dicarbomethoxy-3,4-diazacyclopentadienone 3,4-Dioxide to 3,5-Dicarbomethoxy-4-hydroxyisoxazole

Jeremiah P. Freeman* and James A. Kassner

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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Since the establishment of the structure by Freeman et al. some years ago,[1] abortive efforts have been made to carry out base-catalyzed reactions to functionalize the

(1) Freeman, J. P.; Gannon, J. J.; Surbey, D. L. *J. Org. Chem.* **1969**, *34*, 187–194.

0022-3263/83/1948-2441$01.50/0