An Effective Synthesis of ($\pm$)-(*E*)-2-Amino-5-phosphono-3-pentenoic Acid by Palladium(II)-assisted Migration of the Double Bond

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A new approach for the synthesis of ($\pm$)-(*E*)-2-amino-5-phosphono-3-pentenoic acid (*E*-APPA) is described. The key intermediate, (*E*)-5-acetoxy-3,4-dehydronorvaline derivative **8**, was prepared by [3,3]-sigmatropic rearrangement of allyl acetate **7** in the presence of Pd(II) catalyst. The acetoxy group in **8** was transformed into the phosphonyl group to furnish (*E*-APPA in a moderate yield.

Unusual amino acids which possess specific functions in their side chains are frequently found as constituents of biologically active peptides.¹⁾ There is significant interest in both the organic chemistry and biological aspects of these compounds. An aminophosphonic acid, (*Z*)-2-amino-5-phosphono-3-pentenoic acid (*Z*-APPA) was isolated first by Sakai *et al.*²⁾ as a constituent of plumbemicines, a threonine antimetabolite from *Streptomyces plumbeus*. Recently, Rapp *et al.* have reported that APPA was a constitutional amino acid of rhizocticines, and antifungal oligopeptide from *Bacillus subtilis*.³⁾ However, a D-configuration for APPA was assumed in plumbemicines, whereas rhizocticines contained L-APPA.

Although Natchev reported a synthesis of ($\pm$)-(*E*)-APPA **I**, the geometric isomer of natural APPA, starting from (*E*)-4-bromo-2-butenal,⁴⁾ there has remained the need to develop a simpler and more efficient synthesis of **I**. In this paper, we describe a new synthesis of ($\pm$)-(*E*)-APPA **I** by the effective route shown in the schemes.

The synthetic strategy for **I** is based on the features of Scheme 1. 5-Hydroxy-3,4-dehydronorvaline **1** was anticipated to be a reasonable precursor of **I**, since the hydroxy group of **1** can be converted into the phosphono group in the usual manner. It was expected that **1** could be constructed by an allylic rearrangement from 3-hydroxyallyl-

Scheme 1.

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glycine derivative **2**, which would be readily available from oxazoline **3**.

The starting material, oxazoline **3** (*trans/cis*=2:1), prepared by an aldol reaction of ethyl isocyanoacetate **4** with acrolein⁵⁾ in the presence of zinc chloride, was hydrolyzed with acetic acid to give *N*-formyl-3-hydroxyallylglycine ethyl ester **5** in a 97% yield. Allyl acetate **7** was synthesized from **5** by the sequence shown in Scheme 2, compound **5** being hydrolyzed with 2*N*-hydrochloric acid to give 3-hydroxyallylglycine ethyl ester, which was *N*-protected with di-*t*-butyl dicarbonate to give **6**, and then *O*-acetylated with acetic anhydride to afford allyl acetate **7**.

The Pd(II)-catalyzed [3,3]-sigmatropic rearrangement of allylic acetate **8** was achieved according to the method reported by Ofune *et al.*⁶⁾ Acetate **7** was treated with a catalytic amount of bis(acetonitrile)palladium(II) dichloride (0.05 mol eq) in benzene at 60°C under an argon atmosphere for 8 hr to give the (*E*)-olefin **8** in a 55% yield.

In an attempt to remove the acetyl group of **8**, mild hydrolysis of **8** with potassium carbonate unexpectedly gave the conjugated olefin **12** (Fig. 1) as the main product. After several unsuccessful trials, we employed lipase (Amano P) to remove the acetyl group, compound **8** being treated with Amano P in phosphate buffer (pH 6.8) at 35–40°C for 4 hr to give alcohol **9** quantitatively. Chlorination of **9**

Fig. 1.

was effected with triphenylphosphine and tetrachloromethane under neutral conditions, and then an Arbuzov reaction of **10** with triethyl phosphite in benzene at 60°C in the presence of sodium iodide gave phosphonate **11** in a 25% yield, 75% of **10** being recovered. The deprotection of **11** was achieved with 6*N*-hydrochloric acid at 120°C for 12 hr to give crude **I**, which was purified by ion-exchange resin (Dowex 120, H⁺ form) chromatography.

In conclusion, a simple and efficient synthesis of (±)-(*E*)-APPA **I** was accomplished via [3,3]-sigmatropic rearrangement of the allyl acetate as the key step.

Experimental

All melting points (mp) were determined on a micro-hot-stage Yanaco MP-S3 and are uncorrected. The IR spectra were recorded with a JASCO FT/IR 5000, and NMR spectra were determined with a JEOL-MH GSX 270 spectrometer. Unless otherwise stated, tetramethylsilane was used as the internal standard. The high-resolution mass spectra were obtained with a JMS-AX 500 mass spectrometer. Flash and open column chromatography were performed on silica gel Kieselgel 60 and Wacogel C-200, respectively.

4-Carboethoxy-5-ethenyloxazoline (3).⁵¹ To a stirred solution of ethyl isocyanoacetate **4** (2.26 g, 20 mmol) in 25 ml of anhyd. THF was added anhyd. zinc chloride (2.73 g, 20 mmol, dried over phosphorus pentoxide) at once at 0°C with ice cooling. The solution was stirred for 15 min, and then a solution of acrolein (1.34 g, 24 mmol) in 5 ml of anhyd. THF was added dropwise at 0°C. After stirring had been continued for 3 hr at the same temperature, the solution was allowed to warm to room temperature and stirred for a further 12 hr. The mixture was poured into a saturated sodium hydrogencarbonate solution (30 ml) and filtered by suction, the filtrate was extracted with ether (30 ml $\times$ 2). The combined extract was dried over anhyd. sodium sulfate and evaporated to give a crude oil. Fractional distillation *in vacuo* afforded 1.44 g of **3** as a diastereomeric mixture (*trans/cis* = 2:1, from GLC, 43%), bp 100–110°C/0.1 mHg (bulb to bulb). IR $\nu_{\max}$ (KBr, film) cm^{-1} : 2900, 1720, 1600, 1090; NMR δ_{H} (CDCl_3): 1.32 and 1.27 (3H, two t), 4.25 and 4.31 (2H, two q), 4.41 and 4.31 (1H, two dd, J = 10.7 and 2.1 Hz for *trans*-oxazoline, J = 7.5 and 2.1 Hz for *cis*-oxazoline), 5.10–5.16 (1H, m), 5.30–5.46 (2H, m), 5.73–5.95 (1H, m).

Ethyl 2-formylamino-3-hydroxy-4-pentenoate (5). A solution of oxazoline **1** (3.5 g, 20 mmol) in 20 ml of 95% acetic acid was stirred at room temperature for 12 hr. After the mixture had been concentrated to dryness under reduced pressure, the residue was purified over silica gel column to afford 3.6 g of **5** as a colorless oil (97%). *Anal.* Found: C, 51.40; H, 7.05; N, 7.56. Calcd. for $\text{C}_8\text{H}_{13}\text{O}_4\text{N}$: C, 51.33; H, 7.00; N, 7.68. IR $\nu_{\max}$ (KBr film) cm^{-1} : 3300, 1730, 1680, 1280, 1210. NMR δ_{H} (CDCl_3): 1.30 (3H, t, J = 7.0 Hz), 3.47 (1H, broad s, OH), 4.25 (2H, q, J = 14.3 Hz), 4.70–4.84 (2H, m), 5.34–5.41 (2H, dd, J = 17.4, 10.2 Hz), 5.78–5.92 (1H, m), 6.84 (1H, d, J = 8.9 Hz, NH), 8.22 (1H, s).

Ethyl 2-tert-butyloxycarbonylamino-3-hydroxy-4-pentenoate (6). A solution of **5** (2 g, 10.7 mmol) in 20 ml of 2N-hydrochloric acid was stirred at room temperature for 20 hr. The reaction mixture was concentrated *in vacuo* to give an oil. This resulting residue was dissolved in methanol and then concentrated *in vacuo*, this treatment being repeated more than five times to afford the ammonium salt in a quantitative yield. To a solution of the resulting oil (2.1 g) in 20 ml of methylene chloride were added triethylamine (2.92 g, 29 mmol) and di-*tert*-butyl dicarbonate (3.03 g, 13.9 mmol) at room temperature with vigorous stirring. After the stirring had been continued for 40 hr, the mixture was evaporated *in vacuo* and the residue was extracted with ether. The usual workup and chromatography gave pure *N*-Bocamino ester **6**, as a colorless oil in a 1.97 g yield (71%). *Anal.* Found: C, 55.63; H, 8.21; N, 5.31. Calcd. for $\text{C}_{12}\text{H}_{21}\text{O}_5\text{N}$: C, 55.58; H, 8.21; N, 5.40. IR $\nu_{\max}$ (KBr film) cm^{-1} : 3444, 2984, 1723, 1694, 1506, 1371, 1160. NMR δ_{H} (CDCl_3): 1.30 (1H, t, J = 7.0 Hz), 1.44 (9H, s), 2.53 (1H, broad s, OH), 4.24 (2H, q, J = 14.4 Hz)

4.36–4.62 (2H, m), 5.24–5.41 (2H, dd, J = 17.1, 10.7 Hz), 5.33 (1H, broad s, NH), 5.85–5.96 (1H, m).

Ethyl 3-acetoxy-2-tert-butyloxycarbonylamino-4-pentenoate (7). To a solution of **6** (5.5 g, 21.2 mmol) and 4-*N,N*-dimethylaminopyridine (78 mg, 32 mmol) in 60 ml of dry dichloromethane was added a solution of acetic anhydride (3.26 g, 32 mmol) in 5 ml of dry dichloromethane at room temperature. After stirring for 4 hr under nitrogen, the reaction mixture was concentrated to dryness *in vacuo*. The residue was extracted with ether (20 ml $\times$ 2), and the combined ether extracts were washed with water and dried over sodium sulfate. Removal of the solvent gave an oil, which was purified by fractional distillation (bulb to bulb) *in vacuo* to afford 6.07 g of **7** (95%), bp 125°C/0.1 mHg, mp 50–54°C; yield 6.07 g (95%). *Anal.* Found: C, 55.88; H, 7.65; N, 4.60. Calcd. for $\text{C}_{14}\text{H}_{23}\text{O}_6\text{N}$: C, 55.80; H, 7.69; N, 4.60. IR $\nu_{\max}$ (KBr film) cm^{-1} : 2984, 1750, 1721, 1506, 1371, 1166. NMR δ_{H} (CDCl_3): 1.27 (3H, t, J = 7.0 Hz), 1.45 (3H, s), 2.06 (3H, s), 4.21 (2H, q, J = 14.3 Hz), 4.54 (1H, dd, J = 2.4, 7.3 Hz), 5.19 (1H, d, J = 9.5 Hz), 5.28–5.38 (2H, dd, J = 15.6, 9.5 Hz), 5.58–5.89 (2H, m).

(*E*)-Ethyl 5-acetoxy-2-tert-butyloxycarbonylamino-3-pentenoate (8). A solution of **7** (1 g, 3.3 mmol) and bis-(acetonitrile)palladium dichloride (4.3 mg, 0.17 mmol) in 25 ml of dry benzene was stirred at 50–60°C under an argon atmosphere. After the solvent had been removed under reduced pressure, the residue was treated with ether (10 ml) and then filtered to remove the catalyst. The filtrate was washed with water and dried over magnesium sulfate. Removal of the solvent gave an oil, which was purified by flash chromatography (silica gel, 20% ethyl acetate/*n*-hexane) to afford pure **8**, yield 0.55 g (1.8 mmol, 55%). *Anal.* Found: C, 55.60; H, 7.65; N, 4.70. Calcd. for $\text{C}_{14}\text{H}_{23}\text{O}_6\text{N}$: C, 55.80; H, 7.69; N, 4.65. IR $\nu_{\max}$ (KBr film) cm^{-1} : 2980, 1750, 1721, 1506, 1371, 1166. NMR δ_{H} (CDCl_3): 1.29 (3H, t, J = 7.0 Hz), 1.45 (9H, s), 2.07 (3H, s), 4.23 (2H, q, J = 12.8 Hz), 4.58 (2H, d, J = 4.8 Hz), 4.88 (1H, broad s), 5.21 (1H, broad s), 5.84–5.91 (2H, m). NMR δ_{C} (CDCl_3): 13.83, 20.54, 28.00, 54.62, 61.51, 63.46, 79.78, 126.72, 128.55, 154.75, 170.23. Starting material **7** (0.4 g, 1.3 mmol) was recovered.

(*E*)-Ethyl 2-tert-butyloxycarbonylamino-5-hydroxy-3-pentenoate (9). A mixture of **8** (2 g, 6.7 mmol) and lipase (Amano P, 0.5 g) in 0.1 M phosphate buffer (pH 6.8, 20 ml) was stirred at 30°C for 4 hr. The resultant homogeneous solution was extracted with ether (30 ml $\times$ 2), and the combined ether extracts were washed with saturated sodium hydrogen carbonate and water, and dried over anhyd. magnesium sulfate. Removal of the solvent gave alcohol **9** in a pure state; yield 1.69 g (98%). *Anal.* Found: C, 39.60; H, 8.28; N, 5.54. Calcd. for $\text{C}_{12}\text{H}_{21}\text{O}_5\text{N}$: C, 39.67; H, 8.16; N, 5.40. IR $\nu_{\max}$ (KBr film) cm^{-1} : 3484, 1715, 1682, 1408, 1386, 1168. NMR δ_{H} (CDCl_3): 1.29 (3H,

t, $J=7.0$ Hz), 1.45 (9H, s), 2.06 (1H, broad s, OH), 4.16–4.27 (4H, m), 4.84 (1H, broad s), 5.34 (1H, broad s), 5.73–5.81 (1H, dd, $J=5.5$, 15.6 Hz), 5.94 (1H, ddd, $J=4.9$, 5.5, 15.6 Hz). NMR δ_c (CDCl₃): 14.0, 28.2, 54.9, 61.7, 62.2, 80.2, 125.2, 132.4, 155.0, 170.8.

(*E*)-Ethyl 2-*tert*-butyloxycarbonylamino-5-chloro-3-pentenoate (**10**). A mixture of **9** (3.1 g, 12 mmol) and triphenylphosphine (3.47 g, 13.2 mmol) in anhyd. tetrachloromethane (40 ml, dried over calcium oxide) was refluxed under nitrogen for 6 hr in an oil bath. After the reaction mixture had been concentrated under reduced pressure, the residue was chromatographed over silica gel column (10% ether/*n*-hexane) to afford 2.5 g of **10** as a colorless oil (71%). IR $\nu_{\max}$ (KBr film) cm⁻¹: 2982, 1715, 1506, 1394, 1361, 1166. NMR δ_H (CDCl₃): 1.29 (3H, t, $J=7.0$ Hz), 1.45 (9H, s), 4.05 (2H, d, $J=9.2$ Hz), 4.21 (2H, q, $J=14.0$ Hz), 4.84 (1H, broad s), 5.21 (1H, broad s), 5.80–5.98 (2H, m). HR-MS: found, m/z 277.2818; Calcd for C₁₂H₂₀O₄NCl, 277.2836.

(*E*)-Ethyl 2-*tert*-butyloxycarbonylamino-5-diethylphosphono-3-pentenoate (**11**). A mixture of **10** (2 g, 7.6 mmol), triethylphosphite (1.4 g, 8.2 mmol) and sodium iodide (0.1 g, 0.7 mmol) was stirred in a nitrogen stream at 50–60°C in an oil bath for 6 hr. The clear, pale yellow mixture was cooled to room temperature, diluted to about a tenfold volume with ether, and washed twice with water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give crude phosphonate **11** as a pale yellow oil. This oil was chromatographed over silica gel column (50% ethyl acetate/*n*-hexane) to afford 690 mg of pure **11** (25%). Anal. Found. C, 50.66; H, 8.01; N, 3.69; P, 8.08. Calcd. for C₁₆H₃₀O₇NP: C, 50.65; H, 7.97; N, 3.69; P, 8.16. IR $\nu_{\max}$ (KBr film) cm⁻¹: 3270, 2982, 1746, 1715, 1506, 1394, 1361, 1166. NMR δ_H (CDCl₃): 1.26–1.33 (9H, three t), 1.45 (9H, s), 2.61 (2H, dd, $J=6.5$, 21.6 Hz), 4.06–4.25 (6H, three q), 4.83 (1H, broad s), 5.28 (1H, d, $J=7.6$ Hz), 5.67–5.85 (2H, m). Pure chloride **10** (1.4 g, 5.3 mmol) was recovered.

(*E*)-2-Amino-5-phosphono-3-pentenoic acid (**I**). A mixture of **11** (1 g, 26 mmol) in 6*N*-hydrochloric acid was heated at 120°C with stirring in a nitrogen stream for 20 hr. After the reaction mixture had been cooled to room temperature, it was diluted with water (300 ml) and extracted with ethyl acetate. The aqueous layer was concentrated *in vacuo* to give a colorless oil, which was applied to an ion-exchange resin column (Dowex 50 × 4, 200–400 mesh, H⁺ form). The amino acid **I** was eluted with water. The fractions containing **I** were combined and concentrated *in vacuo* to give a colorless solid, which was recrystallized from water and ethanol to furnish 457 mg of **I** (90%), mp 180°C. Anal. Found: C, 30.80; H, 5.16; N, 7.25; P, 15.91. Calcd. for C₅H₁₀O₅NP: C, 30.78; H, 5.16; N, 7.18; P, 15.87. IR $\nu_{\max}$ (KBr pellet) cm⁻¹: 3450, 3200, 3100, 2364, 1727, 1624, 1506, 1404. NMR δ_H (D₂O): 2.59 (2H, dd, $J=14.9$, 21.2 Hz), 4.52 (1H, d, $J=8.4$ Hz), 5.72–5.77 (1H, m), 6.00–6.09 (1H, dd, $J=7.6$, 21.2 Hz). NMR δ_c (D₂O): 32.94 (d), 55.72 (d), 124.43 (d), 132.79 (d), 171.94 (d).

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