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LETTERS TO THE EDITOR

Synthesis of Phosphonic Analog of Glutamic Acid

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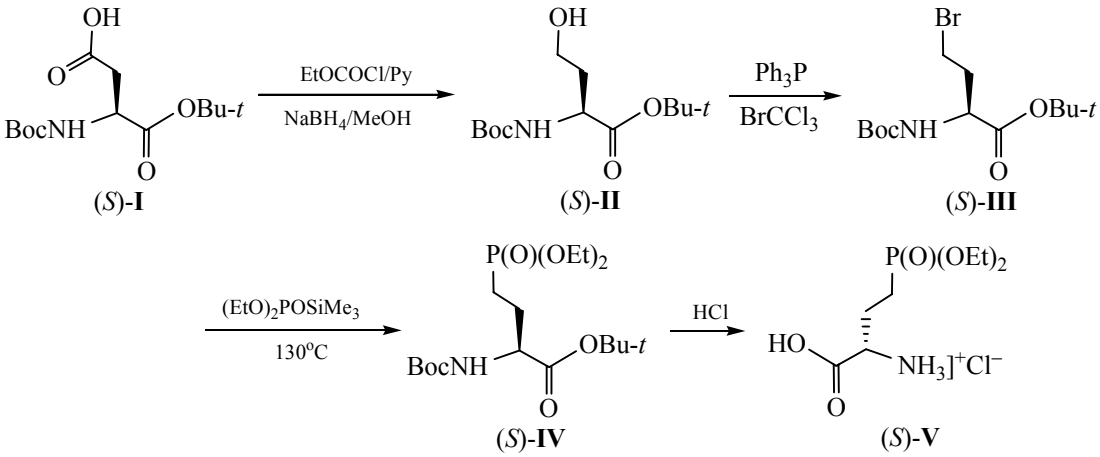
A scheme for the synthesis of phosphonic analog of glutamic acid starting from *tert*-butyl *N*-*tert*-butoxycarbonylaspartate **I** was developed. The latter was obtained from aspartic acid by the previously described method [1, 2]. The carboxy group of compound **I** was acylated with ethyl chloroformate and reduced with sodium borohydride in methanol to give *tert*-butyl-(*S*)-*N*-(*tert*-butoxycarbonyl)homoserine (*S*)-**II** [2]. The latter was converted to the bromide (S)-**III** via the reaction with triphenylphosphine and bromotrichloromethane [3]. Bromide **III** was introduced into the Arbuzov reaction with trimethylsilyldiethylphosphite to yield phosphonate **IV**, deprotection of which with diluted hydrochloric acid resulted in the phosphorus analog of glutamic acid **V**.

***tert*-Butyl-(*S*)-*N*-(*tert*-butoxycarbonyl)homoserine (II).** To a solution of *tert*-butyl *N*-*tert*-butoxycarbonylaspartate **I** [2] (5.8 g, 0.02 mol) in 15 ml of THF with stirring and cooling to from –10 to –20°C was successively added dropwise pyridine (2.4 g, 0.03 mol) and ethyl chloroformate (2.4 g, 0.022 mol). After stirring for 15 min the resulting precipitate was filtered off. Then the obtained solution was added dropwise to a solution of sodium borohydride (1.17 g, 0.03 mol) in 15 ml of methanol with stirring and cooling to 0°C. The reaction mixture was stirred for 1 h. Then to the reaction mixture was added 20 ml of 1 N HCl and 70 ml of diethyl ether. The organic phase was washed with 1 N hydrochloric acid, 5% aqueous sodium hydrogen carbonate solution and water, dried with anhydrous sodium sulfate. The solvent was removed under vacuum. Yield 5.00 g (90%), colorless oil, $[\alpha]_D^{20}$ –38 (*c* 1.0, EtOH) [2]. ^{1}H NMR spectrum, ($CDCl_3$), δ_H, ppm, (*J*, Hz): 1.40 s (9H, CH_3C), 1.42 s (9H, CH_3C), 2.08–2.10 m (1H, CH_2), 2.33–2.36 m (1H, CH_2), 3.67 m (2H, CH_2O), 3.93 m (1H, CHN), 4.90 br.d (1H, NH, J_{HH} 7). ^{13}C NMR spectrum, ($CDCl_3$), δ_C, ppm: 28.10 ($\underline{C}H_3C$), 28.50 ($\underline{C}H_3C$), 37.60 (CH_2), 54.20 (CN), 59.10 (CH_2O), 79.70 ($CH_3\underline{C}$), 82.00 ($CH_3\underline{C}$), 156.00 (C=O), 171.40 (C=O).

***tert*-Butyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]bromobutanoate (III).** To a solution of **II** (5.5 g, 0.02 mol)



in 15 ml of methylene chloride at –70°C was added a solution of bromotrichloromethane (6.0 g, 0.03 mol) in 3.2 ml of methylene chloride and a solution of triphenylphosphine (8.1 g, 0.031 mol) in 5 ml of methylene chloride. The mixture was stirred for 2 h at room temperature. The solvent was evaporated in a vacuum. To the residue diethyl ether and hexane were added. The precipitated triphenylphosphine oxide was filtered off. The filtrate was evaporated in a vacuum. The residue was distilled in a vacuum. Yield 80%, colorless oil, bp 140°C (0.08 mm Hg), $[\alpha]_D^{20}$ –11 (*c* 1, $CHCl_3$). ^{1}H NMR spectrum, ($CDCl_3$), δ_H, ppm, (*J*, Hz): 1.41 s (9H, CH_3C), 1.43 s (9H, CH_3C), 2.35 and 2.15 m (2H, CH_2), 3.40 m (2H, CH_2Br), 4.30 m (1H, CHN), 5.00 br.d (1H, NH, J_{HH} 7.0). ^{13}C NMR spectrum, ($CDCl_3$), δ_C, ppm: 28.09 (CH_3C), 28.50 (CH_3C), 30.81 (CH_2Br), 34.73 (CH_2), 56.67 (CN), 79.61 ($\underline{C}CH_3$), 82.68 ($\underline{C}CH_3$), 153.14 (C=O), 175.58 (C=O). Found, %: C 46.25; H 7.18; Br 24.02. $C_{13}H_{24}BrNO_4$. Calculated, %: C 46.16; H 7.15; Br 23.62.

***tert*-Butyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-(diethoxyphosphoryl)butanoate (IV).** Compound **III** (3.4 g, 0.01 mol) was heated with an excess trimethylsilyldiethylphosphite (8.4 g, 0.04 mol) at 100–120°C for several hours, monitoring the reaction progress by NMR. Then the volatiles were removed in a vacuum, the residue was purified by the column chromatography. Yield 60%, $[\alpha]_D^{20}$ –10.0 (*c* 1, $CHCl_3$). ^{1}H NMR spectrum, ($CDCl_3$), δ_H, ppm, (*J*, Hz): 1.26 t (6H, CH_3, J_{HH} 7), 1.43 s (9H, CH_3C), 1.41 s (9H, CH_3C), 2.15–2.16 m (CH_2), 2.32 m (CH_2), 4.00 m (4H, OCH_2), 4.42 m (1H, CHN), 5.68 br.s (1H, NH). ^{13}C NMR spectrum, ($CDCl_3$), δ_C, ppm, (*J*, Hz): 15.80 (CH_3CH_2), 23.00 d (PC, J_{CP} 145), 27.24 (PC$\underline{C}$), 28.10 (CCH_3), 28.50 (CCH_3), 55.55 (CN), 61.25 (PO$\underline{C}$), 79.80, 82.70 ($CH_3\underline{C}$), 156.03 (C=O), 174.50 (C=O). ^{31}P NMR spectrum, ($CDCl_3$): δ_P 32 ppm. Found, %: C 51.50; H 8.68; P 7.95. $C_{17}H_{34}NO_7P$. Calculated, %: C 51.64; H 8.67; P 7.83.

(*S*)-2-Amino-4-(diethylphosphono)butanoic acid hydrochloride (V). Phosphonate **IV** (3.95 g, 0.01 mol) was treated with 10 ml of hydrochloric acid for 1 h at weak heating. The solvent was removed under vacuum, and the residue was washed with diethyl ether and dried under vacuum to give a solid product. Yield 50%. ^{1}H NMR spectrum, (D_2O), δ_H, ppm, (*J*, Hz): 1.25 t (6H, CH_3, J_{HH} 7), 1.90–2.10 m (4H, CH_2), 3.87 m (1H, CHN), 4.00 m (4H, CH_2O), 6.50 br.s (3H, NH_3). ^{13}C NMR spectrum, (D_2O), δ_C, ppm, (*J*, Hz): 16.41, 16.47 (CH_3), 21.00 d (PC, J_{CP} 145), 25.00 d (CH_2, *J* 5), 50.50 d (CN, *J* 5) 61.20 d (POC, *J* 6), 173 (C=O). ^{31}P NMR spectrum, ($CDCl_3$): δ_P 31.00 ppm [4]. Found P, %: 10.99. $C_8H_{19}ClNO_5P$. Calculated P, %: 11.24.

NMR spectra were taken on a Bruker 170 Avance (500 MHz) instrument relative to internal TMS (^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P).

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