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LETTERS TO THE EDITOR

Synthesis of Enantiomerically Pure Phosphonic Analog of Natural Aspartic Acid

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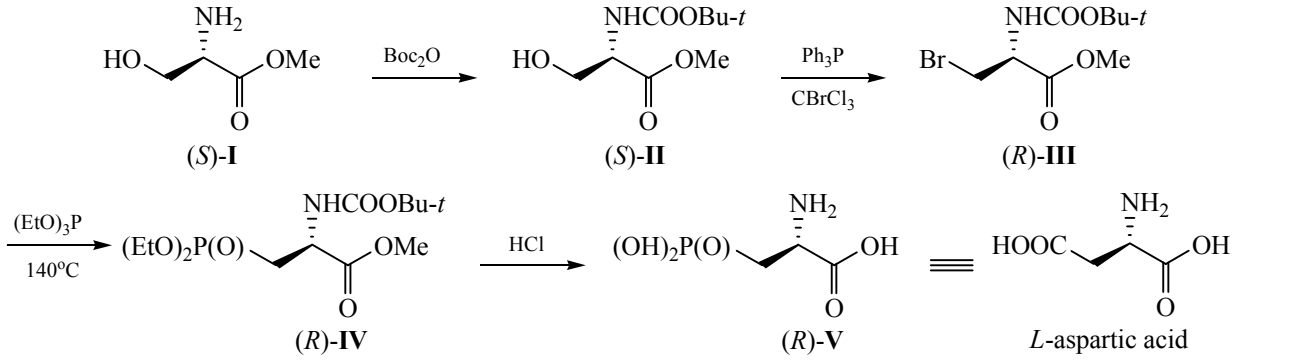
A simple approach to (*R*)-phosphonopropionic acid, phosphonic analog of the natural *L*-aspartic acid, is developed starting from *L*-serine through the Arbuzov reaction as a key stage.



Methyl ester of *L*-serine **I** was Boc-protected at the NH-group [1], then the obtained (*S*)-hydroxyaminocarboxylate **II** was transformed into bromide (*R*)-**III** through reaction with triphenylphosphine and trichlorobromomethane in methylene chloride at 70°C. Bromide **III** was purified by vacuum distillation and brought into the Arbuzov reaction with five-fold excess of triethyl phosphite, the reaction proceeded at 135–140°C over 12 h. After distilling off the volatile reaction product at 0.1 mm Hg at 120°C, the phosphonate **IV** was obtained, which was purified by column chromatography. Its structure was proved by the ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and mass spectrometry. The heating of compound **IV** with hydrochloric acid affords (*R*)-(+)-C-phosphonoaspartic acid **V**. This compound have been earlier obtained by a more complicated method [2]. The physical properties and optical rotation angle coincided with the published data.

Methyl (*S*)-*tert*-buthoxycarbonylamino-3-hydroxypropionate (II). To a solution of 10.5 g (0.05 mol) of (*S*)-methyl serinate hydrochloride in 10 ml of THF was added 15 g of triethylamine at 0°C and this mixture was stirred for 30 min. Then 12 g of Boc_2O was added, and the reaction mixture was warmed to room temperature, stirred for 6 h, and then refluxed for 3 h. Then it was cooled, poured into the saturated aqueous sodium hydrogen bicarbonate solution, extracted with diethyl ether, and concentrated. Yield 90%, $[\alpha]_D^{20}$ 18.0 (MeOH, *c* 5), colorless oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.44 s [9H, $(CH_3)_3C$], 3.77 s (3H, CH_3O), 3.9 m (2H, CH_2), 4.38 m (1H, CHN), 5.57 br.s (1H, NH).

Methyl (*R*)-*tert*-buthoxycarbonylamino-3-bromopropionate (III). To a mixture of 6.5 g (0.03 mol) of compound **II** and 12 g (0.046 mol) of triphenylphosphine in 40 ml of methylene chloride was drop-

wise added 10 g (0.05 mol) of bromotrichloromethane at –80°C. Then the reaction mixture was warmed to room temperature, stirred for 1 h at this temperature, filtered, concentrated, diluted with pentane, again filtered and concentrated. The residue was distilled in a vacuum. Yield 60%, bp 110°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 1.44 s [9H, $(CH_3)_3C$], 3.77 s (3H, CH_3O), 3.78 d.d (1H, BrCH, *J* 3.5, *J* 11.5), 3.90 d.d (1H, BrCH, *J* 3, *J* 11.5), 4.4 m (1H,CHN), 5.57 br.d (1H, NH, *J* 7.5) [3, 4]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J,* Hz): 28.26 [$(CH_3)_3C$], 33.95 ($BrCH_2$), 52.90 (CHN), 54.01 (CH_3O), 80.45 (CO), 154.95 (C=O), 169.65 (C=O). Found, %: C 38.35; H 5.77; Br 28.10. $C_9H_{16}BrNO_4$. Calculated, %: C 38.31; H 5.72; Br 28.32.

Methyl (*R*)-*tert*-buthoxycarbonylamino-3-(diethoxyphosphoryl)propionate (IV). To 7 g (0.025 mol) of bromide **III** was added 20 ml (0.12 mol) of triethyl phosphite. This mixture was heated at 140°C for 24 h. Then triethyl phosphite excess and other volatile products were removed in a vacuum (0.1 mm Hg) at 110–120°C. The spectrally pure phosphonate **IV** was obtained and purified additionally by the column chromatography. R_f 0.50 (1:1, EtOAc–hexane), $[\alpha]_D^{21}$ 12.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 1.31 t (6H, CH_3, *J* 7.2), 1.44 s [9H, $(CH_3)_3C$], 2.33 d (2H, PCH, *J* 13.5), 3.81 s (3H, CH_3O), 4.10 m (4H, OCH_2), 5.78 d (1H, CHN, *J* 8), 6.86 br. s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$),δ_C, ppm (*J,* Hz): 16.4 d (*J* 2.0), 28.0 d (PC, *J* 141.5), 28.3 [$(CH_3)_3C$], 50.0 d (OCH_3, *J* 5.0), 62.1 d (CN, *J* 3.0), 62.0 d (OCH_2, *J* 4.0), 80.0 [$(CH_3)_3C$], 155.0 (C=O), 172 d (C=O, *J* 6.0). ^{31}P NMR spectrum ($CDCl_3$): δ_P 26.5 ppm. Found, %: N 4.11; P 9.21. $C_{13}H_{26}NO_7P$. Calculated, %: N 4.13; P 9.13.

2-*(R)*-Amino-3-phosphonopropionic acid (V). Compound **IV** (0.66 g, 0.02 mol) was refluxed with hydrochloric acid over 12 h. Then water was removed, the residue was washed with ethyl acetate and mixed with propylene oxide. The mixture was stirred overnight at room temperature. The solvent was removed. The residue was recrystalled from aqueous alcohol. Yield 65%, mp >200°C, $[\alpha]_D^{20}$ 15 (*c* 1, 1 N NaOH/H_2O) [2]. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.12 m (1H), 2.3 m (1H), 4.15 m (1H). ^{13}C NMR spectrum (D_2O), δ_C, ppm (*J,* Hz): 28.2 d (PC, *J* 131.0), 49.9 d (CN, *J* 4.5), 172.0 d (C=O, *J* 13.0).

The NMR spectra were recorded on a Varian-300 instrument relative to internal TMS (^{1}H, ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P).

REFERENCES

1. McKillop, A., Taylor, R.J.K., Watson, R.J., and Lewis, N., *Synthesis*, 1994, no. 1, p. 31.
2. Smith, E.C.R., McQuaid, L.A., Paschal, J.W., and DeHoniesto, J., *J. Org. Chem.*, 1990, vol. 55, no. 14, p. 4472.
3. Stocking, E.M., Schwarz, J.N., Senn, H., Salzmann, M., and Silks, L.A., *J. Chem. Soc., Perkin Trans. 1*, 1997, no. 16, p. 2443.
4. Phadnis, P.P. and Mugesh, G., *Org. Biomol. Chem.*, 2005, vol. 3, no. 13, p. 2476.