# Preparation of Optically Active (*S*)-2-Aminoalkylphosphonic Acids from (*S*)-Amino Acids without Racemization

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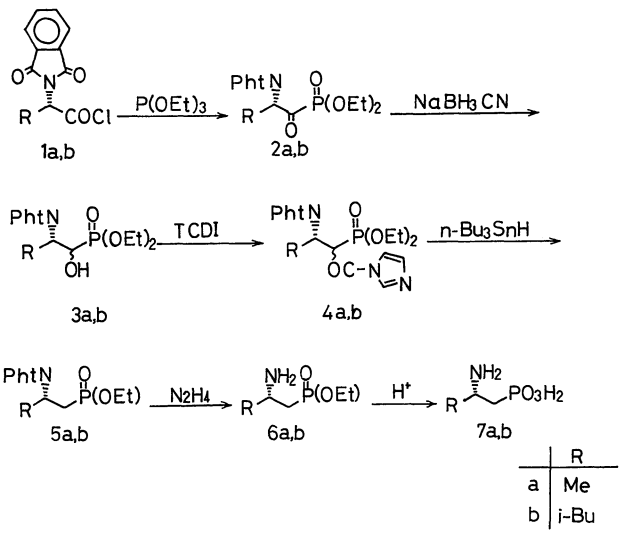
**Synopsis.** Optically active (*S*)-2-aminopropylphosphonic and (*S*)-2-amino-4-methylpentylphosphonic acids were synthesized from commercially available chiral α-amino acids [(*S*)-(+)-alanine and (*S*)-(+)-leucine] without racemization.

Recently, the number of reports concerning the asymmetric synthesis of various amino phosphorus acid derivatives has sharply increased.[1–3] Though several preparative methods of 2-aminoalkylphosphonic acids, which are substances of biochemical interest, analogous to 3-aminoalkylphosphonic acids, were described in previously reported papers,[4] only racemic products were given by the methods. Therefore, optically active 2-aminoalkylphosphonic acids so far been obtained by the optical resolution of prepared racemic 2-aminoalkylphosphonic acids.[5] We have attempted a direct synthesis of chiral 2-aminoalkylphosphonic acid derivatives from commercially available (*S*)-(+)-alanine and (*S*)-(+)-leucine without racemization of the starting optically active amino acids.

2-Phthalimidoalkanoyl chlorides **1a** (R=$CH_3$) and **1b** (R=*i*-Bu) were synthesized from (*S*)-(+)-alanine and (*S*)-(+)-leucine, respsctively, according to previous papers.[6,7] An Arbuzov reaction of triethyl phosphite with acid chlorides **1a** and **1b** afforded compounds **2a** and **2b**, which were converted into 1-hydroxyalkylphosphonates **3a** and **3b** by treatment with sodium cyanoborohydride. Little stereoselectivity for the reduction of the carbonyl group of phosphonate **2** was observed by HPLC analysis. The following deoxygenation reaction of the hydroxyl group of compound **3** was carried out without isolation of the diastereomers of **3a** and **3b**. Several methods for the deoxygenation of the 1-hydroxyl group of alkylphosphonate i.e., direct deoxygenation by diphosphorus tetraiodide[8] and by phosphorus trichloride/metal iodide,[9,10] as well as radical deoxygenation,[3,11] are known. In the present study we attempted either a radical deoxygenation or a direct deoxygenation (phosphorus trichloride/potassium iodide system).




Scheme 1.

4-Imidazolylthiocarbonyloxy derivatives **4a** and **4b** were synthesized from 1-hydroxyalkylphosphonates **3a** and **3b**, respectively, by treatments with thiocarbonyldiimidazole in high yields; thereafter, **4a** and **4b** were treated with tributyltin hydride, affording compounds **5a** and **5b**, respectively, in good yields. On the other hand, direct deoxygenation of 1-hydroxyalkylphosphonate **3a** by using a phosphorus trichloride/potassium iodide system gave compound **7a** in 12% yield. In the latter case, the phthalimido and ester group of phosphonate **3a** were hydrolysed in an acidic medium at the same time as deoxygenation.[9,10] Compounds **5a** and **5b** upon treatment with hydrazine monohydrate lead to 2-aminoalkylphosphonates **6a** and **6b**, respectively. Compounds **6a** and **6b** were hydrolyzed into phosphonic acids **7a** and **7b**, respectively, by treatment with acid.

Compound **6a**, **6b**, **7a**, and **7b**, thus obtained, were confirmed to be in enantiomerically pure forms (>99% e.e.), being analyzed by $^1H$ NMR with a chiral shift reagent, $Eu(tfc)_2$ and further derived them into amino derivative by the action of (*R*)-(+)-2-methoxy-2-(trifluoromethyl)phenylacetic acid (MTPA). These results prove that compounds **6a** and **6b** are optically pure forms retaining the configuration of the starting amino acids and, hence, without racemization in the present process. Compound **3** might show a certain bioactivity because of a strong resemblance of a partial structure to that of KRI-1314,[12] being a medicinally important antihypertensive agent. However, it presently exhibited little activity as a cholinestererase inhibitor.

## Experimental

**Synthesis of Diethyl (*S*)-2-(phthalimido)propionylphosphonate (2a) and (2b); General Procedure:** A mixture of (*S*)-(+)-alanine 10.0 g (112 mmol) and phthalic anhydride 16.7 g (113 mmol) in toluene (60 ml) was refluxed for 12 h; the formed water was collected in a Dean–Stark water trap. Thionyl chloride 14.2 g (120 mmol) was added to the hot toluene solution and the mixture was refluxed for an additional 1.5 h; it was then cooled to room temperature. Removal of excess thionyl chloride and the solvent by an evaporator gave a syrupy product **1a**. Freshly distilled triethyl phosphite 23.2 g (140 mmol) was added dropwise to **1a** with stirring for 1 h at 0 °C; the mixture was then warmed to room temperature. Excess triethyl phosphite was removed from the reaction mixture under reduced pressure, and the obtained residue was separated by column chromatography

on silica gel (eluent: benzene/ethyl acetate=1/1; v/v) to give **2a** (syrup) in 95% yield. $^1$H NMR ($CDCl_3$) $\delta$=1.34 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.75 (d, $J$=7.0 Hz, 3H, CH$_3$), 4.17 [dq, $J_{POCH}$=8.0 Hz, $J_{HH}$=8.0 Hz, 4H, P(OCH$_2$CH$_3$)$_2$], 4.89—5.38 (m, 1H, CH), 7.50—7.84 (m, 4H, aroma). IR (cm$^{-1}$), 1780 and 1710 (C=O), 1250 (P=O).

By the similar manner, diethyl (*S*)-4-methyl-2-(phthalimido)pentanoylphosphonate (**2b**) was synthesized as a syrup in 95% yield. $^1$H NMR ($CDCl_3$) $\delta$=0.91 [d, 6H, $J$=6.6 Hz, CH(CH$_3$)$_2$], 1.32 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.81—2.56 (m, 3H, CH-CH$_2$), 4.16 [dq, $J_{POCH}$=8.0 Hz, $J_{HH}$=8.0 Hz, 4H, P(OCH$_2$CH$_3$)$_2$], 4.78—5.35 (m, 1H, CH), 7.51—7.85 (m, 4H, aroma). IR (cm$^{-1}$), 1780 and 1710 (C=O), 1250 (P=O).

**Synthesis of (*1RS, 2S*)-1-Hydroxy-2-(phthalimido)propylphosphonate (3a); General Procedure:** To a solution of **2a** 0.50 g (1.3 mmol) in anhydrous tetrahydrofuran (20 ml) was added sodium cyanoborohydride 0.40 g (6.5 mmol) by portions; the mixture was then stirred for 24 h at room temperature. Excess hydride was quenched with water (30 ml), and the reaction mixture was neutralized with acetic acid. The aqueous solution was extracted with chloroform (20 ml×3), and the organic layer was washed with brine. The chloroform extract was dried with anhydrous sodium sulfate and concentrated under reduced pressure. Isolation of the product by column chromatography on silica gel (eluent: benzene/ethyl acetate=1/1; v/v) afforded **3a** in quantitative yield. $^1$H NMR ($CDCl_3$) $\delta$=1.26 [t, 8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.53 (d, $J$=7.0 Hz, 3H, CH$_3$), 4.00—5.15 (m, 6H, 2CH, P(OCH$_2$CH$_3$)$_2$], 7.50—7.84 (m, 4H, aroma). IR (cm$^{-1}$), 3300 (OH), 1700 (C=O), 1250 (P=O). HPLC; ratio of the stereoisomer=2/1. $[\alpha]_D^{20}$ −0.8° (*c* 1.45, AcOEt).

Diethyl (1*RS*, 2*S*)-1-hydroxy-4-methyl-2-(phthalimido)-pentylphosphonate (**3b**) (syrup) was synthesized by the same method in 98% yielld. $^1$H NMR ($CDCl_3$) $\delta$=0.98 (d, $J$=4.5 Hz, 6H, 2CH$_3$), 1.25 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.46—2.19 (m, 3H, CH-CH$_2$), 4.33—4.81 [m, 6H, 2CH, P(OCH$_2$CH$_3$)$_2$], 7.54—7.80 (m, 4H, aroma). IR (cm$^{-1}$), 3300 (OH), 1730 (C=O), 1250 (P=O). HPLC; ratio of the stereoisomer=3/1. $[\alpha]_D^{20}$ −5.2° (*c* 0.71, AcOEt).

**Synthesis of Diethyl (*1RS, 2S*)-1-(1-Imidazolylthiocarbonyloxy)-2-(phthalimido)pentylphosphonate (4a); General Procedure:** 1,1-Thiocarbonyldiimidazole 0.30 g (1.8 mmol) was added to a solution of **3a** 0.30 g (0.9 mmol) in dry 1,2-dichloroethane (20 ml). The mixture was heated for 3 h at 70 °C, and cooled to room temperature. The reaction mixture was successively washed with a cold solution of 1 M hydrochloric acid (20 ml×2), 50% sodium hydrogencarbonate (20 ml), and water (20 ml), and the organic layer was dried with anhydrous sodium sulfate. The solvent was removed off under reduced pressure to give **4a** as a syrup in 99 % yield. $^1$H NMR ($CDCl_3$) $\delta$=1.35 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.76 (d, $J$=7.0 Hz, 3H, CH$_3$), 3.91—4.42 [m, 5H, N-CH, P(OCH$_2$CH$_3$)$_2$], 4.79—5.28 (m, 1H, P-CH-O), 6.96 (s, 1H, imida), 7.62—7.87 (m, 4H, aroma), 7.55, 8.25 (2s, 2×1H, imida). $[\alpha]_D^{22}$ −1.2° (*c* 1.55, AcOEt).

Diethyl (1*RS*, 2*S*)-1-(1-imidazolythiocarbonyloxy)-4-methyl-2-(phthalimido)pentylphosphonate (**4b**) was synthesized by the same method in 95 % yield. $^1$H NMR ($CDCl_3$) $\delta$=0.94 (d, $J$=5.0 Hz, 6H, 2CH$_3$), 1.32 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.50—2.61 (m, 3H, CH-CH$_2$), 3.79—4.28 [m, 5H, N-CH, P(OCH$_2$CH$_3$)$_2$], 4.53—5.28 (m, 1H, P-CH-O), 6.92 (s, 1H, imida), 7.62—7.86 (m, 4H, aroma), 7.56, 8.25 (2s, 2×1H, imida). $[\alpha]_D^{22}$ −8.5° (*c* 1.22, AcOEt).

**Synthesis of Diethyl (*S*)-2-(Phthalimido)propylphosphonate (5a); General Procedure:** To a solution of **4a** 0.20 g (0.40 mmol) in anhydrous toluene (20 ml) was added tributyltin hydride 0.20 g (0.70 mmol) through a syringe under a nitrogen atomosphere; the mixture was then refluxed for 2.5 h. The reaction mixture was concentrated, and the residue was apportioned between acetonitrile (20 ml) and hexane (20 ml). The hexane layer was discarded and the acetonitrile layer was washed with hexane (10 ml×3). After removing the acetonitrile under reduced pressure, the residue was separated by preparative thin-layer chromatography on silica gel (eluent: benzene/ethyl acetate=1/1; v/v) to give **5a** as a syrup in 92% yield. $^1$H NMR ($CDCl_3$) $\delta$=1.30 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.59 (d, $J$=7.0 Hz, 3H, CH$_3$), 2.09—2.88 (m, 2H, P-CH$_2$), 4.09 [dq, $J_{POCH}$=8.0 Hz, $J_{HH}$=8.0 Hz, 4H, P(OCH$_2$CH$_3$)$_2$], 4.47—5.01 (m, 1H, N-CH), 7.63—7.85 (m, 4H, aroma). $[\alpha]_D^{20}$ −2.6° (*c* 0.23, AcOEt).

Diethyl (*S*)-4-methyl-2-(phthalimido)pentylphosphonate (**5b**) was synthesized by the same method in 91% yield. $^1$H NMR ($CDCl_3$) $\delta$=0.91 (d, $J$=7.2 Hz, 6H, 2CH$_3$), 1.10—1.58 (m, 3H, CH-CH$_2$), 1.32 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.69—2.05 (m, 2H, P-CH$_2$), 3.99 [dq, $J_{POCH}$=8.0 Hz, $J_{HH}$=8.0 Hz, 4H, P(OCH$_2$CH$_3$)$_2$], 4.51—4.81 (m, 1H, N-CH), 7.63—7.85 (m, 4H, aroma). $[\alpha]_D^{20}$ −0.6° (*c* 0.89, AcOEt).

**Synthesis of Diethyl (*S*)-2-Aminopropylphosphonate (6a); General Procedure:** To a solution of **5a** 0.20 g (0.60 mmol) in methanol (5 ml) was added hydrazine monohydrate (2 ml); the mixture was then stirred for 8 h at room temperature. The reaction mixture was filtered off, and the filtrate was concentrated to yield a residue which was dissolved in chloroform (10 ml); the solution was then washed with water. The organic layer was dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residue gave almost pure compound **6a** as oil in quantitative yield. $^1$H NMR ($CDCl_3$) $\delta$=1.30 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.50 (d, $J$=7.0 Hz, 3H, CH$_3$), 1.95 (br s, 2H,NH$_2$), 1.23—2.20 (m, 2H, P-CH$_2$), 3.43 (m, 1H, N-CH), 4.09 [dq, $J_{POCH}$=8.0 Hz, $J_{HH}$=8.0 Hz, 4H, P(OCH$_2$CH$_3$)$_2$].

Diethyl (*S*)-2-amino-4-methylpentylphosphonate (**6b**) was synthesized quantitatively by the same procedure. $^1$H NMR ($CDCl_3$) $\delta$=0.90 (d, $J$=7.2 Hz, 6H, 2CH$_3$), 1.11—1.58 (m, 3H, CH-CH$_2$), 1.31 [t, $J$=8.0 Hz, 6H, P(OCH$_2$CH$_3$)$_2$], 1.69—2.05 (m, 2H, P-CH$_2$), 1.82 (br s, 2H, NH$_2$), 3.17 (m, 1H, N-CH), 3.99 [dq, $J_{POCH}$=8.0 Hz, $J_{HH}$=8.0 Hz, 4H, P(OCH$_2$CH$_3$)$_2$].

**Synthesis of (*S*)-2-Aminopropylphosphonic Acid (7a).** Compound **6a** 0.20 g (1.0 mmol) in acetic acid (1 ml) was added concd hydrochloric acid (5 ml) and the mixture was refluxed for 8 h. The resulting solution was concentrated in vacuo; the residue was then dissolved in small amount of methanol. The solution was treated with propylen oxide until pH 6 was reached. The precipitate was recrystallized from ethanol–water to afford compound **7a** in 65% yield; mp 276—285 °C [lit,[5] mp 278—284 °C, $[\alpha]_D^{22}$ +4.8° (*c* 0.78, 1 mol dm$^{-3}$ NaOH)].

(*S*)-2-Amino-4-methylpentylphosphonic acid (**7b**) was prepared in 58% yield, mp 229—231 °C, $[\alpha]_D^{26}$ +1.8° (*c* 0.78, 1 mol dm$^{-3}$ NaOH).

**Direct Deoxygenation of 3a.** To a solution of **3a** 0.80 g (2.5 mmol) in chloroform (10 ml) and acetone (5 ml) was added phosphorus trichloride 2.6 g (18.8 mmol) and potassium iodide 4.7 g (28.1 mmol); the reaction mixture was then stirred for 12 h at room temperature. After the solvent was evaporated from the reaction mixture, the product was taken up into water (10 ml). The aqueous solution was then extracted with chloroform (15 ml×3), and the aqueous layer concentrated under reduced pressure. The residue was dissolved into a mixture of conc. hydrochloric acid (15 ml) and acetic acid (10 ml). The solution was then refluxed for 6 h, and the solution extracted with chloroform (10 ml). After concentrating the aqueous solution, the resulting residue was dissolved in methanol (5 ml). The solution was then treated with propylene oxide until pH 6 was reached.

Recrystallization of the product from 90% ethanol afforded **7a** in 12% yield; mp 276—284 °C (lit,[5] mp 278—284 °C), $[\alpha]_D^{22}$ +4.9° (*c* 0.78, 1 mol dm$^{-3}$ NaOH) [lit,[5] $[\alpha]_D^{25}$ +4.9° (1 mol dm$^{-3}$ NaOH)].

All products gave satisfactory microanalyses (C±0.23%, H±0.24%, N±0.21%).

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