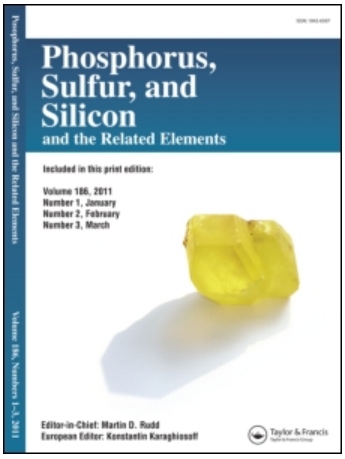

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ORGANIC PHOSPHORUS COMPOUNDS 96.[1] RESOLUTION OF 1-AMINO-2-(4-FLUOROPHENYL)ETHYLPHOSPHONIC ACID AS WELL AS SOME DI- AND TRIPEPTIDES

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ORGANIC PHOSPHORUS COMPOUNDS 96.[1] RESOLUTION OF 1-AMINO-2-(4-FLUOROPHENYL)ETHYLPHOSPHONIC ACID AS WELL AS SOME DI- AND TRIPEPTIDES

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Resolution of racemic 1-amino-2-(4-fluorophenyl)ethylphosphonic acid with dibenzoyltartrate is easily accomplished. In the inhibition of PAL **2b**(−) is about five times as active as **2a**(+). The synthesis of the dipeptides **5a** and **5b**, and of the tripeptides **8a** and **8b** is described and comments are made on their biological activity.

Key words: (+) and (−) 1-Amino-2-(4-fluorophenyl)ethylphosphonic acid; dipeptides; tripeptides; biological activity.

INTRODUCTION

In a previous study[2] it was shown that several 1-amino-2-arylethylphosphonic acids are strong inhibitors of phenylalanine ammonia lyase (PAL) and anthocyanin synthesis and are also quite active botryticides. It seemed of interest to prepare both enantiomers of one of the more active compounds, i.e., 1-amino-2-(4-fluorophenyl)ethylphosphonic acid and furthermore to synthesize some dipeptides and tripeptides.

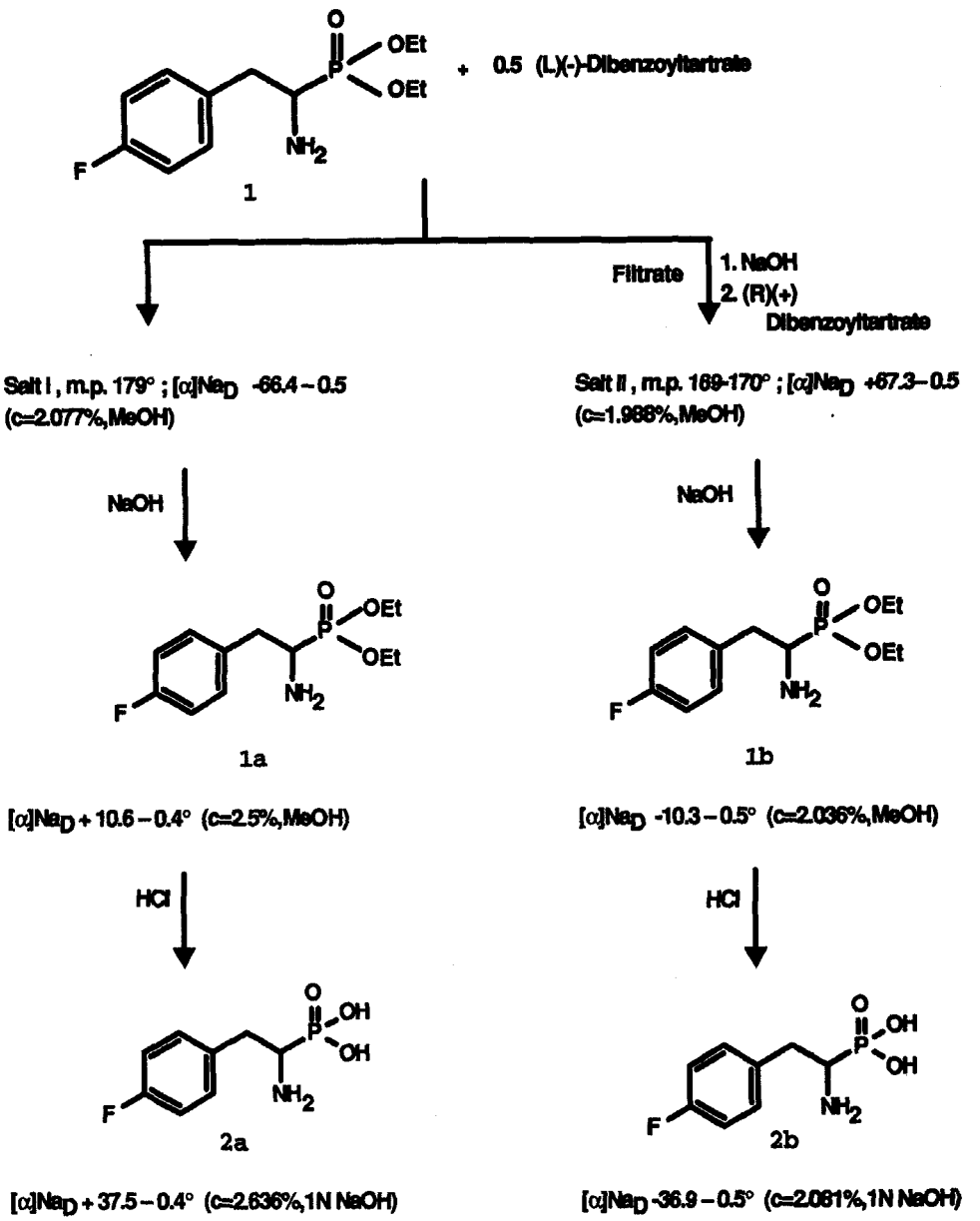
RESULTS AND DISCUSSION

The resolution of racemic 1-amino-2-(4-fluorophenyl)ethylphosphonate, **1** was easily accomplished with (L)(−)dibenzoyl tartrate, similar to that used for the resolution of 1-amino-2-phenylethylphosphonate by Kowalik *et al.*.[3] However, in contrast to Kowalik *et al.*,[3] we also isolated the optically active phosphonate esters and hydrolyzed them to the optically active acids **2a** and **2b**. The pertinent data are summarized in Scheme I.

Peptides containing P-terminal aminophosphonic acids can easily be prepared by coupling N-blocked amino acids or small peptides with free aminoalkane-phosphonic acids or their esters followed by removal of the blocking groups.[4]

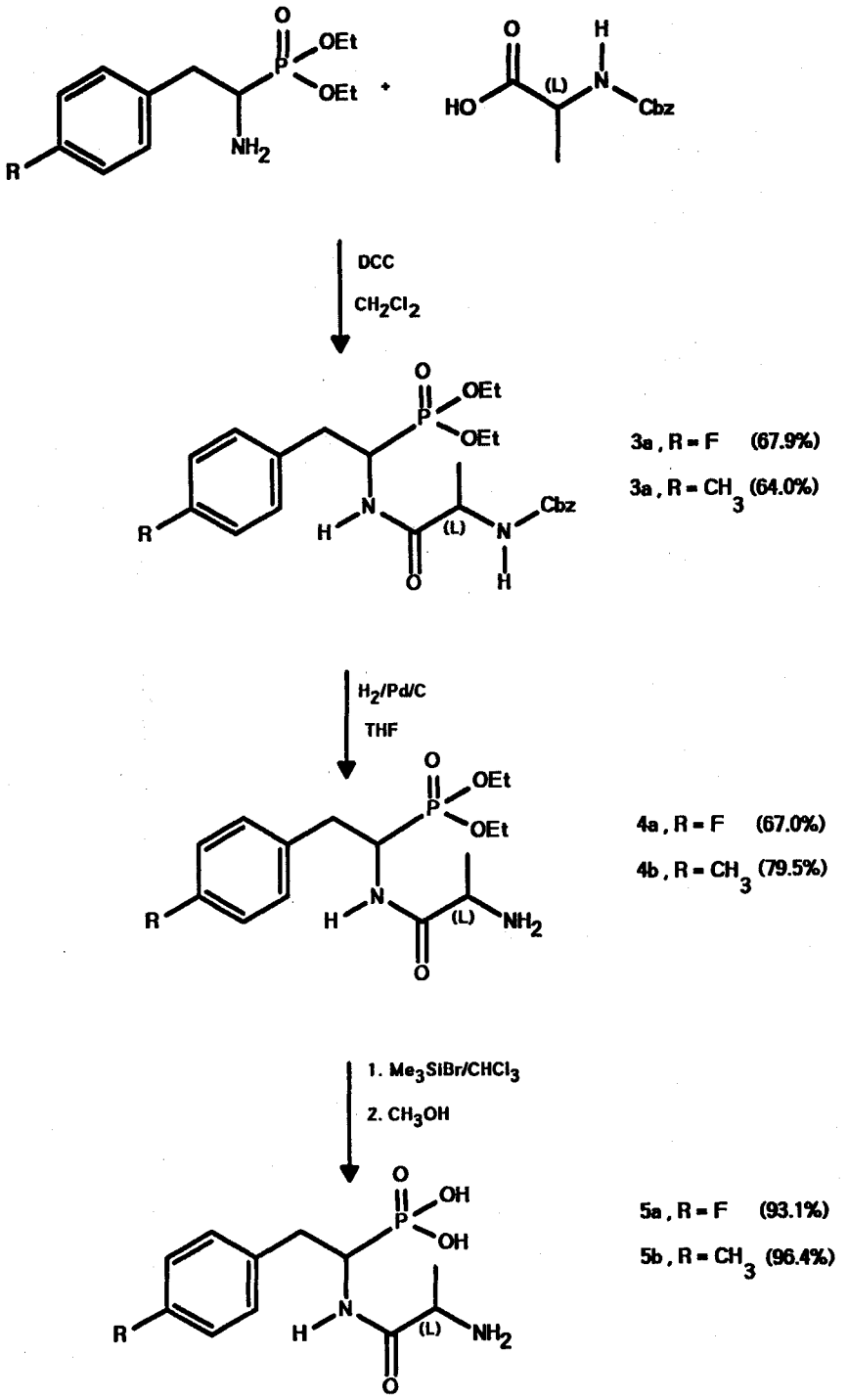
Of the more than fifty coupling procedures known in peptide chemistry only a few of them have been used for phosphonopeptide synthesis.[4]

We have chosen aminophosphonate esters, N-benzyloxy-carbonyl protected aminoacids and dicyclohexylcarbodiimide (DCC, as a condensing agent) for the synthesis of the dipeptides **5a** and **5b** (Scheme II), and the tripeptides **8a** and **8b** (Scheme III).

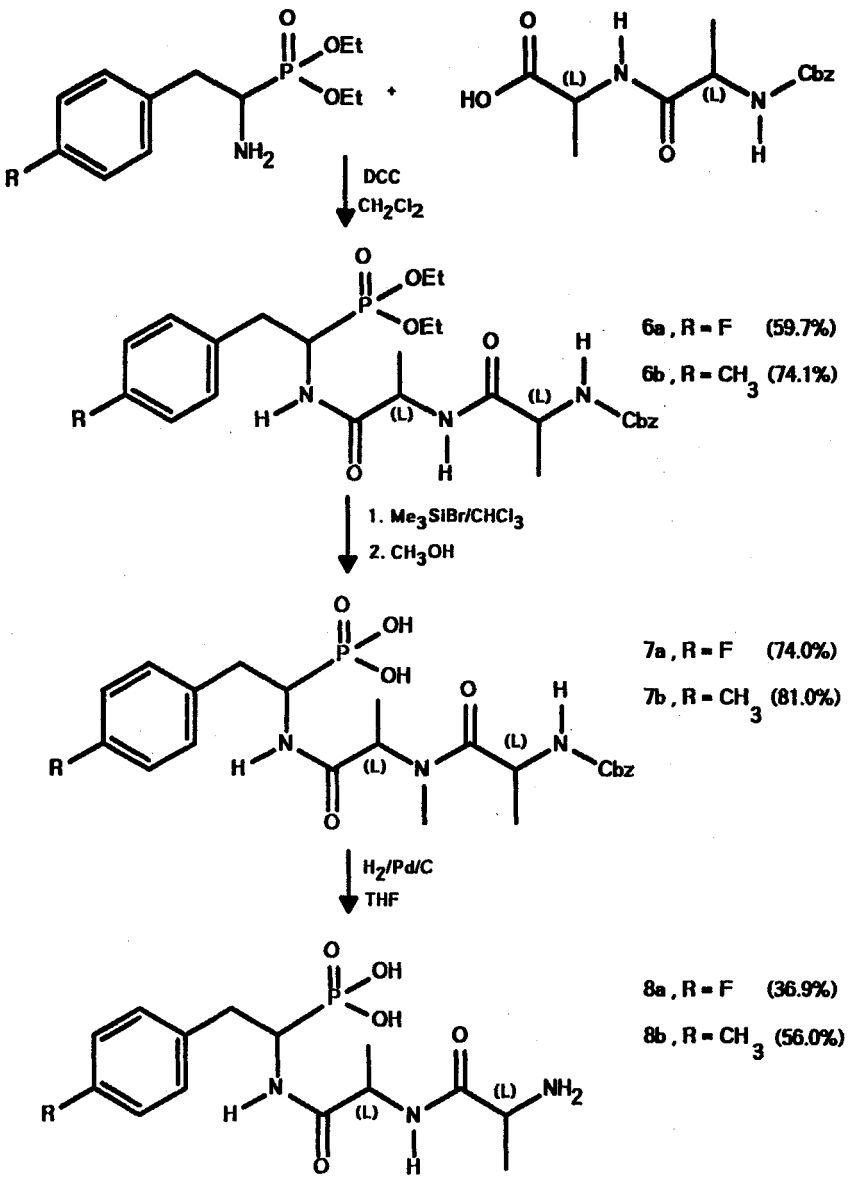


SCHEME I

All steps proceeded with good to excellent yields. Deprotection of the aminoacids was done with H_2 and 5% Pd/C in THF and that of the phosphonate esters with Me_3SiBr in chloroform. Higher yields of the peptides seem to be obtained when the deprotection of the phosphonate esters is done after that of the aminoacids (as in **5a** and **5b**) and not before that of the aminoacids (as in **8a** and **8b**).



SCHEME II



SCHEME III

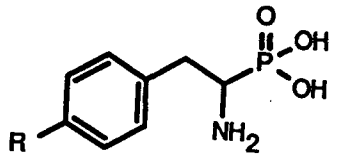
BIOLOGICAL ACTIVITY

As has already been briefly reported,[2] **2a** and **2b** inhibit one of the key enzymes of plant metabolism, i.e., the phenylalanine ammonia lyase (PAL). It was observed that **2b** is about five times as active as **2a**[5] (Table). This conforms with the finding on the unsubstituted compound, 1-amino-2-phenyl-ethylphosphonic acid, where the R(−) derivative was also more active than the S(+).[6]

From these data may be concluded that **2b** very likely has the R and **2a** the S configuration.

TABLE

Inhibition constants for buckwheat PAL and anthocyanin synthesis



R	stereochemical form	Inhibition constant for buckwheat PAL (μM)	Inhibition of anthocyanin synthesis in vivo by 1mM
H	racemate	2.6	83%
	R (-)	1.5	
	S (+)	11.6	
F	racemate	3.5	87%
	(-)	2.8	
	(+)	13.5	

The fungicidal activity of **2a** and **2b** and of the dipeptides **5a** and **5b**, and tripeptides, **8a** and **8b**, was not higher than that of the parent substituted racemic 1-amino-2-(4-fluoro- or 4-methylphenyl)ethylphosphonic acids.

EXPERIMENTAL

Phosphorus NMR-spectra were recorded using a Bruker WP 80 spectrometer at 32.28 MHz (ref. 85% H_3PO_4), and ^{1}H-NMR-spectra were recorded with a Varian EM 360 spectrometer at 60 MHz or a Bruker WM 250/250 MHz spectrometer [ref. $(CH_3)_4Si$]. The chemical shifts are reported in ppm, with negative values being upfield of the standard and positive downfield. All the reactions were run under an atmosphere of argon.

A. (+) and (−) Dibenzoyltartrates of O,O-diethyl-1-amino-2-(4-fluorophenyl)ethylphosphonate Salt I and Salt II.

a) To a solution of 68.82 g (0.125 mol) of **1**[2] in 750 ml of methanol and 750 ml of ethanol is added at room temperature 47.04 g of (L)(−)-dibenzoyl-tartrate × H_2O. After 2 h stirring the white, thick suspension is filtered and the residue dried. Recrystallization twice from ethanol gives 31.5 g (=39.8%) of salt I, m.p. 179°C (dec.); $[\alpha]_D^{20} = -66.4 \pm 0.5°$ (c = 2.077% in CH_3OH).

b) The remaining filtrate from above is evaporated, stirred with 200 ml of 1N NaOH, saturated with NaCl and extracted three times with 400 ml of CH_2Cl_2 each. The organic phase is dried with Na_2SO_4 and evaporated. The remaining brown oil (37.5 g) is dissolved in 400 ml of methanol and 400 ml of ethanol and treated with 25.6 g of (D)(+)-dibenzoyltartrate × H_2O. After 2 h stirring the solid (63 g) is filtered off and recrystallized from 1200 ml of methanol to give 7.2 g of impure salt II. The filtrate is evaporated and the residue recrystallized twice from 500 ml of ethanol each to give 17 g of pure salt II, m.p. 168–170°C (dec.); $[\alpha]_D^{20} = +67.3 \pm 0.5°$ (c = 1.998% in CH_3OH).

1. (+) and (−) O,O-Diethyl-1-amino-2-(4-fluorophenyl)ethylphosphonate, **1a** *and* **1b**.

a) 25.34 g of salt I are treated with 100 ml of 1N NaOH and stirred for 2 h at 20°C. The clear solution

is saturated with NaCl and 200 ml of CH_2Cl_2 is added. The suspension is filtered and the residue washed twice with 200 ml of CH_2Cl_2 each. The organic phases are combined, dried with Na_2SO_4, filtered and evaporated to give 9.1 g (=82.7%) of **1a**, a slightly yellow oil, $[\alpha]_D^{20} = +10.6 \pm 0.4°$ (c = 2.5% in CH_3OH).

^{1}H-NMR (in $CDCl_3$) δ: 1.3 (CH_3, NH_2, 8H); 2.3–3.5 ($PCHCH_2$, 3H); 4.17 (OCH_2, 4H); 7.1 (m, C_6H_4, 4H).

b) Treatment of salt II with 1N NaOH as described above gives 95.9% of **1b**, a slightly yellow oil. $[\alpha]_D^{20} = -10.3 \pm 0.5°$ (c = 2.03% in CH_3OH).

2. (+) and (−) 1-Amino-2-(4-fluorophenyl)ethylphosphonic acid, **2a** *and* **2b**.

a) 5.51 g of **1a** are refluxed for 4 h with 40 ml of a 20% solution of HCl. The solution is evaporated and the residue recrystallized from methanol/propylene oxide to give 3.9 g (=84.5%) of **2a**, m.p. 259–263°C (dec.); $[\alpha]_D^{20} = +37.5° \pm 0.4°$ (c = 2.636% in 1N NaOH).

^{1}H-NMR (in D_2O/NaOD) δ: 2.3–3.1 (m, $PCHCH_2$, 3H); 4.65 (s, OH, NH_2); 6.6–7.17 (m, aryl, 4H).

b) By hydrolysis of **1b** with HCl as described before is obtained **2b** (in 77.6%), m.p. 261–263°C (dec.), $[\alpha]_D^{20} = -36.9 \pm 0.5°$ (C = 2.081% in 1N NaOH).

^{1}H-NMR (in D_2O/NaOD) δ: 2.5–3.4 (m, $PCHCH_2$, 3H); 4.85 (s, OH, NH_2); 6.8–7.4 (m, aryl, 4H).

3. a) O,O-Diethyl-1-N-Cbz-L-alanylamino-2-(4-fluorophenyl)ethylphosphonate, **3a**. To a solution of 13.76 g (0.05 mol) of **1**[2] and 11.16 g of N-Cbz-L-alanine in 100 ml of CH_2Cl_2 is added dropwise with stirring and ice-cooling a solution of 11.35 g of DCC in 100 ml of CH_2Cl_2. A slightly exothermic reaction ensues. After 1 h stirring the white suspension is filtered, the filtrate evaporated and the residue recrystallized from diisopropyl ether to give 16.3 g (=67.9%) **3a**, m.p. 77–81°C.

^{1}H-NMR (in $CDCl_3$) δ: 1.35 (CH_3, 9H); 3.1 (m, CHCHP, 2H); 4.2 (m, OCH_2, CH, COCHN, 6H); 5.1 (S, OCH_2Ph, 2H); 5.9 (s, NH, 1H); 6.7–8.2 (m, Ph, C_6H_4, NH, 10H).

b) O,O-Diethyl-1-N-Cbz-L-alanylamino-2-(4-methylphenyl)ethylphosphonate, **3b**. From 10.85 g (0.04 mol) of O,O-diethyl-1-amino-2-(4-methylphenyl)phosphonate,[2] 8.93 g of N-Cbz-L-alanine and 9.08 g of DCC in CH_2Cl_2 as above was obtained 12.2 g of **3b**, a colorless resin which on recrystallization from diisopropyl ether gave a white solid, 12.2 g (=64%).

^{1}H-NMR (in $CDCl_3$) δ: 1.3 (CH_3, 9H); 2.3 ($ArCH_3$, 3H); 3.1 (m, CHCHP, 2H); 4.1 (m, OCH_2, CH, COCHN, 6H); 5.0 (s, OCH_2Ph, 2H); 5.7 (NH, 1H); 6.9–7.5 (m, 10H).

4. a) O,O-Diethyl-1-L-alanylamino-2-(4-fluorophenyl)ethylphosphonate, **4a**. To 12.01 g (0.025 mol) of **3a** in 200 ml of THF is added 2 g of 5% Pd/C and the mixture hydrogenated at 20°C. After 45 min. H_2-uptake stopped. The catalyst is filtered off, the filtrate evaporated and the residue recrystallized from diisopropyl ether to give 5.8 g (=67%) **4a**, m.p. 76–79°C.

^{1}H-NMR (in $CDCl_3$) δ: 1.0 (d, CH_3); 1.3 (t, CH_3); 1.5 (s, NH_2) (11H); 2.7–3.6 (m, CH_2CHP, 3H); 4.15 (qui, OCH_2, 4H); 4.6 (m, COCHN, 1H); 6.8–7.4 (m, C_6H_4, 4H); 7.6 (d, NH, 1H).

$C_{15}H_{24}FN_2O_4P$ (346.34)	calc:	C 52.02	H 6.99	N 8.09	F 5.49	P 8.95%
	found:	C52.2	H 7.1	N 8.2	F 5.4	P 8.9%

b) O,O-Diethyl-1-L-alanylamino-2-(4-methylphenyl)ethylphosphonate, **4b**. From 8.58 g (0.018 mol) of **3b**, 85 ml of ethanol, 2 g 5% Pd/C and H_2 as above is obtained after recrystallization from isopropyl ether 4.9 g (=79.5%) **4b**, m.p. 68–70°C.

^{1}H-NMR (in $CDCl_3$) δ: 1.3 (m, CH_3, 9H); 1.55 (s, NH_2, 2H); 2.3 (s, $ArCH_3$, 3H); 2.7–3.5 (m, CH_2CHP, 3H); 4.15 (qui, OCH_2, 4H); 4.7 (m, COCHN, 1H); 7.1 (m, C_6H_4, 4H); 7.55 (d, CONH, 1H).

$C_{16}H_{27}N_2O_4P$ (342.37)	calc.:	C 56.13	H 7.95	N 8.18	P 9.05%
	found:	C 56.0	H 8.0	N 8.3	P 9.1%

5. a) 1-(L)Alanylamino-2-(4-fluorophenyl)ethylphosphonic acid, **5a**. To 3.46 g (0.01 mol) of **4a** in 20 ml of $CHCl_3$ is added with stirring 5.18 ml Me_3SiBr and stirring continued for 24 h at 20°C. Then the clear solution is evaporated on a rotavapor. The residue is dissolved in 10 ml CH_3OH, then ether and propylene oxide added. The suspension is filtered and the residue dried to give 2.7 g (=93.1%) **5a**, m.p. 271–273°C (dec.); $[\alpha]_D^{20} = 5.8° \pm 0.5°$ (c = 1.973% in 1N NaOH).

^{1}H-NMR (in D_2O/NaOD) δ: 1.0 (d, CH_3, 3H); 3.15–3.7 (m, CH_2CHP); 5.2 (br, NH, NH_2, OH, CH); 7.2 (m, C_6H_4, 4H).

b) 1-(L)Alanylamino-2-(4-methylphenyl)ethylphosphonic acid, **5b**. From 3.42 of **4b**, 5.18 ml of Me_3SiBr and 20 ml $CHCl_3$ as described above is obtained 3 g (=96.4%) **5b** × 1.37 H_2O m.p. 259–265°C (dec.); $[\alpha]_D^{20}$ = 4.8° ± 0.5° (c = 1.994% in 1N NaOH).

^{1}H-NMR (in D_2O/NaOD) δ: 0.8 (2d, CH_3, 3H); 2.17 (s, $ArCH_3$, 3H); 2.4–3.3 (m, CH_2CHP, 3H); 4.85 (br, NH_2, OH, CH); 7.07 (Ar, 4H).

$C_{12}H_{19}N_2O_4P$ × 1.37 H_2O (310.95)	calc.:	C 46.36	H 7.17	N 9.01	P 9.96	H_2O 7.93%
	found:	C 46.3	H 7.1	N 8.7	P 9.7	H_2O 7.9%

6. a) O,O-Diethyl-1-N-Cbz-L-ala-alanylamino-2-(4-fluorophenyl)ethylphosphonate, **6a**. From 4.68 g of **1**, 5 g of N-Cbz-L-ala-alanine, 3.8 g of DCC in 80 ml of CH_2Cl_2 as described for **3a**, is obtained 5,6 g (=59.7%) **6a**, m.p. 126–135°C (recryst. from ethylacetate).

b) O,O-Diethyl-1-N-Cbz-L-ala-alanylamino-2-(4-methylphenyl)ethylphosphonate, **6b**. From 4.61 g of diethyl-1-amino-2-(4-methylphenyl)phosphonate,[2] 5 g of N-Cbz-L-ala-alanine, 3.86 g of DCC in 80 ml of CH_2Cl_2 as above is obtained 6.9 g (=74.1%) **6b**, a white solid.

7. a) 1-N-Cbz-L-Ala-alanylamino-2-(4-fluorophenyl)ethylphosphonic acid, **7a**. From 5.52 g (0.01 mol) of **6a**, 3.24 mol of Me_3SiBr and 20 ml of $CHCl_3$ as described for **5a** is obtained 3.7 g (=74.7%) **7a**, a white solid.

b) 1-N-Cbz-L-Ala-alanylamino-2-(4-methylphenyl)ethylphosphonic acid, **7b**. From 5.48 g (0.01 mol) of **6b**, 3.24 ml of Me_3SiBr and 20 ml of $CHCl_3$ as described above is obtained 4.0 g (=81.5%) **7b**, a white solid.

8. a) 1-(L)-Ala-alanylamino-2-(4-fluorophenyl)ethylphosphonic acid, **8a**. To 2.97% (0.006 mol) of **7a** in 120 ml of THF is added 3.6 g of 5% Pd/C and the mixture hydrogenated until H_2-uptake stopped. The catalyst is filtered, suspended in 100 ml H_2O and refluxed. Then it is filtered and the filtrate evaporated to give 0.8 g (=36.9%) **8a**, m.p. 245–249°C (dec.); $[\alpha]_D^{20}$ = −31.3° ± 0.5° (c = 2.035% in 1N NaOH).

^{1}H-NMR (D_2O) of diastereomers δ: 0.94 (d, CH_3); 1.25 (d, CH_3); 1.45 (d, CH_3), 1.5 (d, CH_3); 2.7 (2t, PCH); 3.25 (m, CH); 4.0 (m, CH); 4.2 (qu, CHMe); 4.34 (qu, CHMe); 4.85 (s, NH, OH); 7.05 (m) and 7.28 (m) (C_6H_4).

$C_{14}H_{21}FN_3O_5P$ × 1.4 H_2O (386.53)	calc.:	C 43.5	H 6.21	N 10.87	F 4.92	P 8.01%
	found:	C 43.4	H 5.8	N 10.9	F 4.9	P 8.2%

b) 1-(L)-Ala-alanylamino-2-(4-methylphenyl)ethylphosphonic acid, **8b**. From 3.44 g (0.007 mol) of **7b** in 180 ml ethanol, 30 ml H_2O, 2.1 g 5% Pd/C and H_2 as above is obtained 1.4 g (=56%) **8b**, m.p. 243–248°C (dec.); $[\alpha]_D^{20}$ = 0.4° ± 0.4° (c = 2.098% in 1N NaOH).

^{1}H-NMR (D_2O) of diastereomers δ: 0.95 (d, CH_3); 1.25 (d, CH_3); 1.45 (d, CH_3), 1.5 (d, CH_3); 2.3 (s, $ArCH_3$); 2.7 (2t, PCH): 3.25 (m, CH); 4.03 (m, CH); 4.25 (m, CHN); 4.8 (s, OH, NH); 7.18 (s, C_6H_4).

$C_{15}H_{24}N_3O_5P$ × H_2O (375.37)	calc.:	C 48.0	H 6.98	N 11.19	P 8.25%
	found:	C 47.6	H 6.9	N 11.3	P 8.4%

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