

Enantioselective Synthesis of L-Phosphinothricin from L-Methionine and L-Glutamic Acid via L-Vinylglycine¹

Hans-Joachim Zeiss

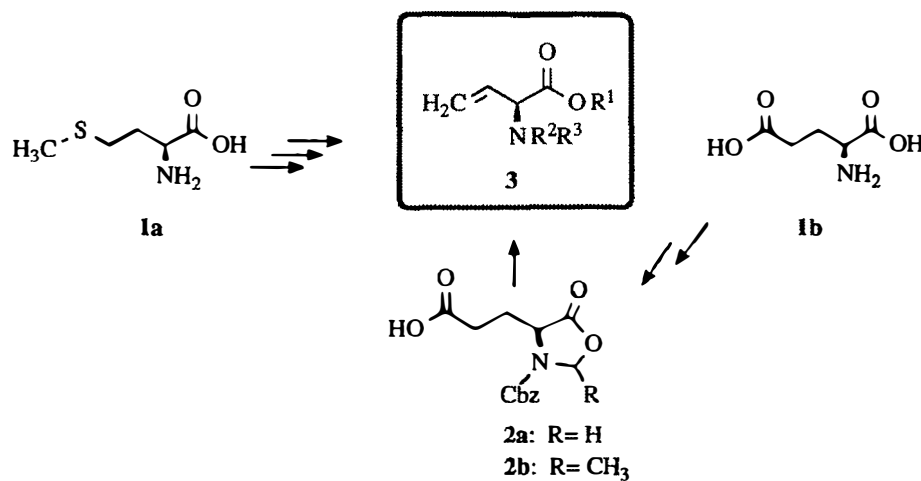
Pflanzenschutzforschung Chemie, Hoechst AG, 6230 Frankfurt 80, FRG

(Received in Germany 26 April 1992)

Key Words: L-Vinylglycine; Regioselective C-P-Bond Formation; L-Phosphinothricin; Glutamine Synthetase Inhibitor

Abstract: L-Phosphinothricin (**6**), a natural occurring amino acid which possesses herbicidal and antibacterial properties by inhibiting the enzyme glutamine synthetase (E.C. 6.3.1.2) in plants and bacteria, can be obtained with 99.4% enantiomeric excess via regioselective addition of alkyl methylphosphinates **4** to protected L-vinylglycine derivatives **3** followed by hydrolysis of the intermediates **5**. L-Vinylglycine derivatives **3** are easily prepared from L-methionine (**1a**) and L-glutamic acid (**1b**). Protected L-vinylglycine derivatives **3** can also be used as starting materials in the enantioselective synthesis of L-2-aminobutyric acids bearing a phosphonate or phosphine oxide moiety in 4-position.

Protected derivatives of L-vinylglycine **3**,² which are readily available from L-methionine (**1a**)³ and L-glutamic acid (**1b**)⁴ represent attractive starting materials for the synthesis of functionalized α -amino acids.⁵



Scheme 1. Synthesis of L-Vinylglycine Derivatives from L-Methionine and L-Glutamic Acid.

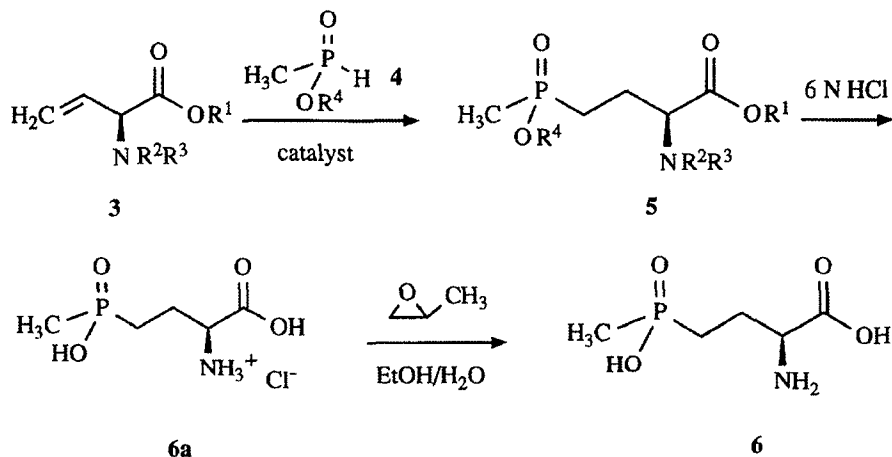
During our continuing efforts⁶ to find new approaches to the synthesis of L-phosphinothricin (**6**), a natural occurring amino acid which exhibits strong herbicidal activity by inhibiting the enzyme glutamine synthetase (E.C. 6.3.1.2) in plants,⁷ we envisaged compounds of type **3** as useful initial building blocks in the preparation of **6**.

Starting from racemic **3a** ($R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = \text{F}_3\text{CCO}$) D,L-**6** had been already synthesized in 77.5% yield via **5a** ($R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = \text{F}_3\text{CCO}$, $R^4 = i\text{-Bu}$).⁸

Enantiomerically enriched **3b** ($R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = \text{Cbz}$) was obtained from **1a** by employing the procedure of Meffre.^{3e} Although the optical rotation indicated this product only to be 69-81% optically pure,⁹ the ee must have been at least 92.6%, as shown by the enantiomeric excess (ee) of **6a** derived from **3b** (vide infra).

Virtually enantiomerically pure **3c** ($R^1, R^2 = \text{CH}_2$, $R^3 = \text{Cbz}$) and **3d** ($R^1, R^2 = \text{CHCH}_3$, $R^3 = \text{Cbz}$) were prepared from **1b** in three steps with a maximum overall yield of 28.0% by following the protocol of Hanessian.^{4a} Although the yield of the key oxidative decarboxylation of **2** mediated by lead(IV)acetate could not be increased to more than 31.5%,¹⁰ this approach was retained because of the simple isolation and the high optical purity of **3** obtained in this way.

Regioselective addition of alkyl methylphosphinates **4** to **3** catalyzed by *tert*-butyl per-2-ethylhexanoate yielded the crude L-phosphinothricin derivatives¹¹ **5** quantitatively (Scheme 2).



Scheme 2. Regioselective Addition of Alkyl Methylphosphinates to Protected L-Vinylglycine.

Intermediate **5** was submitted acidic hydrolysis to furnish the hydrochloride **6a**. The ee of **6a** was determined by HPLC¹³ from the crude products of the saponification, because recrystallization led to an increase of the ee value.^{6b}

The ee of **6a** obtained from **5b** was 92.6%, reflecting the only limited enantiomeric purity of the starting material **3b**. In contrast, the ee of **6a** derived from **5d** reached 97.4%, indicating that at maximum

2.6% racemization could have occurred during five chemical transformations starting from **1b**.¹⁴

Conversion of **6a** into the free amino acid **6** was accomplished by treatment with propene oxide,^{6b} providing almost enantiomerically pure **6** (ee 99.4%).

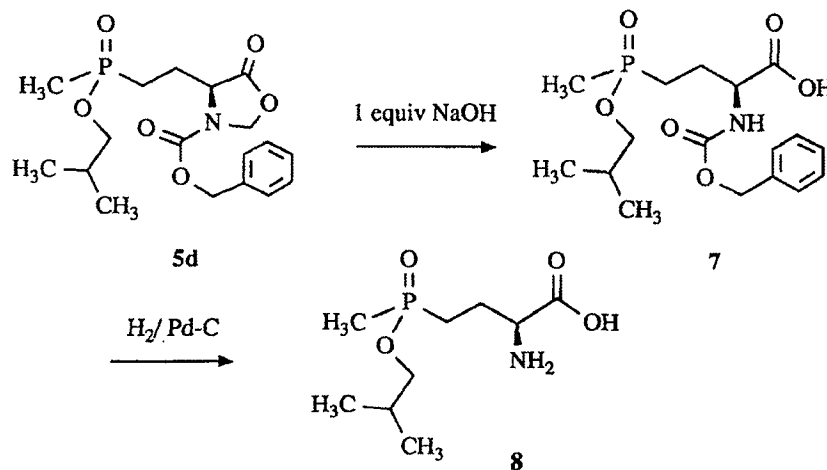
Table 1. Regioselective Addition of Alkyl Methylphosphinates **4** to L-Vinylglycine Derivatives **3**.

Entry	Substrate	L-Phosphinothricin Derivatives 5b-e					Yield ^a [%]	
			R ¹	R ²	R ³	R ⁴		
1	3b	5b	Me		H	Cbz ^b	Et	57.4
2	3c	5c		-CH ₂ -	H	Cbz	Et	97.4
3	3c	5d		-CH ₂ -	H	Cbz	<i>i</i> -Bu	70.3
4	3c	5e		-CH ₂ -	H	Cbz	<i>cyclo</i> -Hexyl	81.6
5	3d	5f		-CHCH ₃ -	H	Cbz	Et	77.4

^a Isolated yield after chromatography on silica gel. Yields of the crude products are almost quantitative.

^b Cbz = Benzyloxycarbonyl

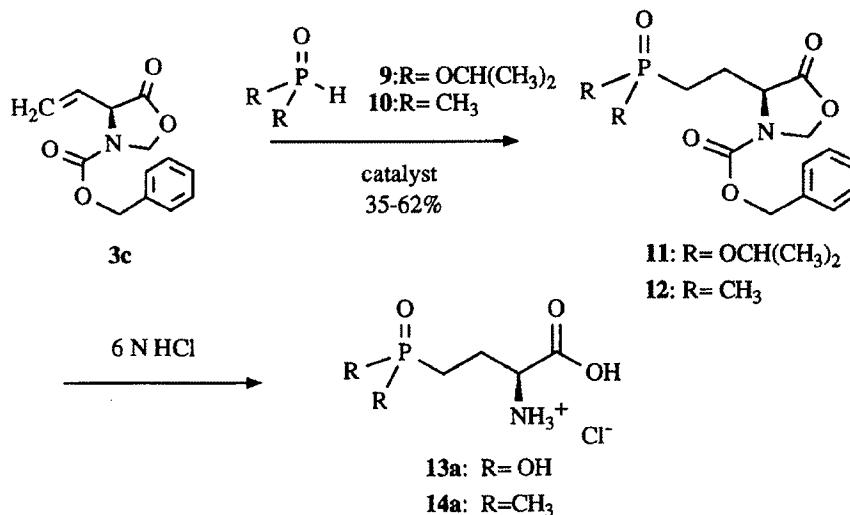
The oxazolidinone **5d** also served as a precursor for partially protected derivatives of **6**. Treatment of **5d** with an equimolar amount of NaOH in THF¹⁵ yielded **7** which could be hydrogenized to **8** (Scheme 3).



Scheme 3. Selective Deprotection of the α -Amino Acid Moiety of **5**.

In contrast to the high-yield addition of **4** to **3**, the *tert*-butyl per-2-ethylhexanoate-catalyzed reaction of diisopropylphosphite (**9**) and dimethylphosphine oxide (**10**) with **3c** afforded the protected phosphonates

11 and phosphine oxides **12** only in moderate yields (Scheme 4). Intermediates **11** and **12** are precursors to the L-2-aminobutyric acids **13** and **14** bearing a phosphonate respectively a phosphine oxide moiety in 4-position. The hydrochlorides **13a** and **14a** were obtained as very hygroscopic crude products by acidic hydrolysis of **11** and **12**. All attempts to purify **13a** and **14a** by recrystallization failed.



Scheme 4. Addition of Dialkylphosphites and Dialkylphosphine Oxides to Protected L-Vinylglycine.

L-2-Amino-4-phosphonobutyric acid (**13**) acts as a L-glutamate antagonist in rat brain synaptic plasma membranes,¹⁶ whereas any biological activity of **14** has not been reported so far.

EXPERIMENTAL SECTION

General. Melting points are not corrected. Concentrations for specific rotations are g/100 mL. The purity of the starting materials **3** was > 97% (GC). tert-Butyl per-2-ethylhexanoate was technical grade and used as obtained from Peroxid-Chemie, Höllriegelskreuth, Germany. Homogeneity of **L-6a** and **L-6** was checked by TLC on silica plates using the solvent system n-BuOH/AcOH/H₂O 5:2:2 and ninhydrin as visualizing agent. ee was determined by analytical HPLC after derivatization with o-phthalaldehyde and N-acetyl-L-cysteine, on a RP 18 column (Hypersil ODS, Shandon).¹³

Methyl (2S)-2-(N-Benzoyloxycarbonyl)aminobut-3-enoate (3b) was obtained as a yellow oil in 9.3 % yield according to the literature procedure:^{3e} [α]_D²³ = - 9.60 ° (c = 0.965, CH₃OH)⁹ [lit.^{3a} [α]_D²⁰ = - 11.80 ° (c = 1.80, CH₃OH) for optically pure material]; ¹³C NMR (75 MHz, CDCl₃) δ 170.873, 155.541, 155.527, 136.222, 132.397, 128.548, 128.221, 128.131, 117.796, 67.161, 56.185, 56.159, 52.710.

(4S)-3-Benzoyloxycarbonyl-4-vinyl-1,3-oxazolidin-5-one (3c) was obtained as low melting solid in 30.0 % yield according to the literature procedure:^{4a} [α]_D²³ = + 91.40 ° (c = 0.641, CHCl₃) [lit.^{4a} [α]_D = + 89.60 ° (CHCl₃)]; ¹³C NMR (75 MHz, CDCl₃) δ 169.828, 152.830, 135.395, 129.423, 128.681, 128.608, 128.344, 119.101, 77.730, 68.086, 56.983; Anal. Calcd for C₁₃H₁₃NO₄: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.9; H, 5.6; N, 5.7.

3-[(2*R,S*)-(4*S*)-3-Benzoyloxycarbonyl-2-methyl-5-oxo-1,3-oxazolidin-4-yl]propanoic Acid (**2b**). 5.60 g (20 mmol) of N-Cbz-L-glutamic acid, 2.30 g (52 mmol) of metacetaldehyde and 0.20 g of p-toluenesulfonic acid were suspended in 150 mL of 1,2-dichloroethane. The mixture was heated to reflux. During 23 h 300 mL of 1,2-dichloroethane were distilled off slowly and instantly replaced by fresh solvent from a dropping funnel so that the volume of the reaction mixture always remained constant. Also, after 7 h a second portion of 2.30 g of metacetaldehyde was added. At the end of the reaction (NMR control) the solvent was distilled off completely, the residue taken up in toluene and the crude product purified by chromatography on silica gel (toluene/diethyl ether 1:1) to yield 3.10 g (50.4%) of **2b** as a pale yellow oil: $[\alpha]_D^{25} = +48.40^\circ$ ($c = 0.411$, CH_3OH); ^1H NMR (100 MHz, CDCl_3) δ 7.36 (s, 5, C_6H_5), 5.80 (q, 1, $J = 5.5$ Hz, NCHCH_3O), 5.18 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.37 (t, 1, $J = 6.3$ Hz, CHNCOO), 2.70-2.04 (m, 4, $\text{HOOCCH}_2\text{CH}_2\text{CH}$), 1.57 (d, 3, $J = 5.5$ Hz, NCHCH_3O); Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.4; H, 5.5; N, 4.4.

(2*R,S*)-(4*S*)-3-Benzoyloxycarbonyl-2-methyl-4-vinyl-1,3-oxazolidin-5-one (**3d**). To a solution of 5.30 g (17 mmol) of **2b** in 150 mL of benzene was added under argon 0.85 g (4.25 mmol) of copper(II)acetate hydrate. The mixture was stirred at room temperature for 1 h, then 7.60 g (17 mmol) of dry lead(IV)acetate was added. The resulting homogeneous solution was refluxed under argon for 7 h. The precipitated lead(II)acetate was filtered off, the filtrate diluted with 50 mL of EtOAc, washed with water (2x50 mL) and brine (1x50 mL), dried (MgSO_4) and concentrated in vacuo. The crude **3d** was purified by chromatography on silica gel (n-heptane/ethyl acetate 6:1) to yield 1.40 g (31.5%) of **3d** as a colorless oil: $[\alpha]_D^{25} = +42.70^\circ$ ($c = 0.517$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) major diastereoisomer δ 7.35 (s, 5, C_6H_5), 6.15-5.62 (m, 2, NCHCH_3O and $\text{H}_2\text{C}=\text{CHCH}$), 5.46 (m, 1, $\text{trans-H}_2\text{C}=\text{CH}$), 5.32 (t, 1, $J = 2$ Hz, $\text{cis-H}_2\text{C}=\text{CH}$), 5.18 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.83 (dt, 1, $J = 5, 2$ Hz, CHNCOO), 1.57 (d, 3, $J = 5.5$ Hz, NCHCH_3O); minor diastereoisomer δ 5.13 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.72 (m, 1, CHNCOO), 1.65 (d, 3, $J = 5.5$ Hz, NCHCH_3O) all other resonances like the major diastereoisomer; Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.0; H, 5.8; N, 5.1.

Methyl 3-[(2*R,S*)-(4*S*)-3-Benzoyloxycarbonyl-2-methyl-5-oxo-1,3-oxazolidin-4-yl]propanoate which is the major byproduct in the oxidative decarboxylation of **2b** can be isolated from the more polar fractions of the chromatography of the crude **3d**: ^1H NMR (100 MHz, CDCl_3) major diastereoisomer δ 7.36 (s, 5, C_6H_5), 5.80 (q, 1, $J = 5.5$ Hz, NCHCH_3O), 5.17 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.35 (t, 1, $J = 6.3$ Hz, CHNCOO), 3.64 (s, 3, COOCH_3), 2.65-2.03 (m, 4, $\text{H}_3\text{COOCCH}_2\text{CH}_2\text{CH}$), 1.55 (d, 3, $J = 5.5$ Hz, NCHCH_3O); minor diastereoisomer δ 5.71 (m, 1, NCHCH_3O), 5.08 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 1.64 (d, 3, $J = 5.5$ Hz, NCHCH_3O) all other resonances like the major diastereoisomer. Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.8; H, 5.9; N, 4.2.

General Procedure for the Addition of Alkyl Methylphosphinates to L-Vinylglycine Derivatives. To 13.2 mmol of alkyl methylphosphinate **4**,¹⁷ preheated to 120 °C (bath temperature), was added under argon during 10 min a solution of 4.4 mmol of protected L-vinylglycine (**3b-d**) in 4 mL of xylene containing a few drops of tert-butyl per-2-ethylhexanoate. The mixture was stirred at 120 °C for 90 min, then concentrated in vacuo (10 Pa) to yield crude **5** almost quantitatively. Purification by rapid chromatography on silica gel (eluent A: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2; eluent B: $\text{CH}_2\text{Cl}_2/\text{MeCN}$ 2:1) afforded **5** as a colorless oil.

Methyl (2*S*)-2-(*N*-Benzoyloxycarbonyl)amino-4-[ethoxy(methyl)phosphinyl]butanoate (**5b**) was obtained as a colorless oil (0.90 g from 1.10 g of **3b** and 1.40 g of ethyl methylphosphinate (**4a**), eluent B, 57.4%); $[\alpha]_D^{25} = +10.90^\circ$ ($c = 0.450$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 7.35 (s, 5, C_6H_5), 5.65 (s, br, 1, CHNHCOO), 5.10 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.42, (m, 1, CHNHCOO), 4.03 (quintet d, 2, $J = 7, 2$ Hz, $\text{H}_3\text{CHH}_2\text{OP}$), 3.75 (s, 3, COOCH_3), 2.39-1.55 (m, 4, $\text{PCH}_2\text{CH}_2\text{CH}$), 1.43 (d, 3, $J = 14$ Hz, PCH_3), 1.30 (dt, 3, $J = 2, 7$ Hz, POCH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 171.374, 155.555, 135.606, 127.722, 127.370, 127.341, 66.225, 59.664, 59.578, 53.509, 53.470, 51.836, 25.762, 24.516, 24.310, 24.279, 16.063, 15.983, 13.707, 12.576; ^{31}P NMR (121 MHz, CDCl_3) δ 54.075.

According to the ^1H NMR spectrum, this sample contained 1 mol of H_2O ¹⁸ which could not be removed by drying over P_2O_5 . Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_6\text{P} \times 1 \text{ H}_2\text{O}$: C, 51.19; H, 6.98; N, 3.73. Found: C, 51.6; H, 6.6; N, 3.4.

(4*S*)-3-Benzoyloxycarbonyl-4-[2-[ethoxy(methyl)phosphinyl]ethyl]-1,3-oxazolidin-5-one (**5c**) was obtained as a colorless oil (2.10 g from 1.50 g of **3c** and 2.00 g of **4a**, eluent A, 97.4%); $[\alpha]_D^{25} = +79.70^\circ$ ($c = 0.488$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 7.38 (s, 5, C_6H_5), 5.53 (d, 1, $J = 5$ Hz, NCH_2O), 5.24 (d, 1, $J = 5$ Hz, NCH_2O), 5.19 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.37 (t, 1, $J = 5.5$ Hz, CHNCOO), 4.03 (quintet d, 2, $J = 7, 1.2$ Hz, $\text{H}_3\text{CCH}_2\text{OP}$), 2.48-1.53 (m, 4, $\text{PCH}_2\text{CH}_2\text{CH}$), 1.43 (d, 3, $J = 14$ Hz, PCH_3), 1.30 (td, 3, $J = 7, 1.2$ Hz, POCH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 170.934, 152.399, 134.823, 134.808, 128.257, 128.216,

127.925, 77.571, 67.733, 60.002, 59.918, 54.607, 54.568, 54.376, 54.337, 25.026, 24.987, 23.777, 23.741, 23.466, 16.372, 16.295, 14.143, 14.054, 12.912, 12.824; ^{31}P NMR (121 MHz, CDCl_3) δ 52.780; Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_6$: C, 54.08; H, 6.24; N, 3.94; P, 8.72. Found: C, 54.2; H, 6.5; N, 3.5; P, 8.1.

(4*S*)-3-Benzoyloxycarbonyl-4-{2-[isobutoxy(methyl)phosphinyl]ethyl}-1,3-oxazolidin-5-one (**5d**) was obtained as a colorless oil (2.18 g from 2.00 g of **3c** and 3.20 g of isobutyl methylphosphinate (**4b**), eluent A, 70.3%); $[\alpha]_{\text{D}}^{19.5} = +72.54^\circ$ ($c = 0.670$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 7.37 (s, 5, C_6H_5), 5.50 (d, 1, $J = 5$ Hz, NCH_2O), 5.23 (d, 1, $J = 5$ Hz, NCH_2O), 5.18 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.37 (t, 1, $J = 5.5$ Hz, CHNCOO), 3.71 (t, 2, $J = 7$ Hz, $(\text{H}_3\text{C})_2\text{CHCH}_2\text{OP}$), 2.46-1.57 (m, 5, $\text{PCH}_2\text{CH}_2\text{CH}$ and $\text{POCH}_2\text{CH}(\text{CH}_3)_2$), 1.41 (d, 3, $J = 14$ Hz, PCH_3), 0.92 (t, 3, $J = 7$ Hz, $\text{POCH}_2\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 171.200, 152.698, 135.071, 128.586, 128.485, 128.255, 77.908, 70.195, 70.105, 68.098, 67.940, 54.946, 54.903, 54.712, 54.668, 29.303, 29.220, 25.271, 24.019, 23.795, 18.806, 18.775, 14.289, 14.192, 13.056, 12.960; ^{31}P NMR (121 MHz, CDCl_3) δ 52.655; Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_6$: C, 56.39; H, 6.84; N, 3.65. Found: C, 56.3; H, 6.8; N, 3.6.

(4*S*)-3-Benzoyloxycarbonyl-4-{2-[cyclohexyloxy(methyl)phosphinyl]ethyl}-1,3-oxazolidin-5-one (**5e**) was obtained as a colorless oil (2.70 g from 2.00 g of **3c** and 3.90 g of cyclohexyl methylphosphinate (**4c**), eluent A, 81.6%); $[\alpha]_{\text{D}}^{21} = +69.40^\circ$ ($c = 0.595$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 7.40 (s, 5, C_6H_5), 5.52 (d, 1, $J = 5$ Hz, NCH_2O), 5.24 (d, 1, $J = 5$ Hz, NCH_2O), 5.19 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.37 (m, 2, CHNCOO and HCOP), 2.41-1.04 (m, 14, $\text{PCH}_2\text{CH}_2\text{CH}$ and cyclo- C_6H_{10}), 1.43 (d, 3, $J = 14$ Hz, PCH_3); ^{31}P NMR (121 MHz, CDCl_3) δ 51.364; Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{NO}_6$: C, 58.67; H, 6.89; N, 3.42; P, 7.57. Found: C, 58.5; H, 6.8; N, 3.2; P, 7.5.

(2*R,S*)-(4*S*)-3-Benzoyloxycarbonyl-4-{2-[ethoxy(methyl)phosphinyl]ethyl}-2-methyl-1,3-oxazolidin-5-one (**5f**) was obtained as a colorless oil (1.20 g from 1.10 g of **3d** and 1.40 g of **4a**, eluent A, 77.4%); $[\alpha]_{\text{D}}^{23} = +58.80^\circ$ ($c = 0.408$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 7.37 (s, 5, C_6H_5), 5.78 (q, 1, $J = 5.5$ Hz, $\text{NCH}_2\text{CH}_3\text{O}$), 5.18 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.35 (t, 1, $J = 5.5$ Hz, CHNCOO), 4.02 (quintet d, 2, $J = 7$, 1.2 Hz, $\text{H}_2\text{CCH}_2\text{OP}$), 2.46-1.53 (m, 4, $\text{PCH}_2\text{CH}_2\text{CH}$), 1.57 (d, 3, $J = 5.5$ Hz, $\text{NCH}_2\text{CH}_3\text{O}$), 1.42 (d, 3, $J = 14$ Hz, PCH_3), 1.30 (td, 3, $J = 7$, 1.2 Hz, POCH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 170.602, 153.054, 135.007, 134.977, 128.498, 128.444, 128.425, 128.071, 86.730, 67.972, 67.945, 60.197, 60.114, 56.042, 55.996, 55.804, 55.758, 25.773, 25.380, 25.355, 25.288, 25.257, 24.527, 22.805, 16.587, 16.509, 14.427, 14.294, 13.198, 13.063; ^{31}P NMR (121 MHz, CDCl_3) δ 53.008, 52.645; Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_6$: C, 55.28; H, 6.55; N, 3.79. Found: C, 55.7; H, 6.5; N, 3.7.

L-Phosphinothricin Hydrochloride (**6a**). **5f** (4.30 g, 11.6 mmol) was dissolved in 120 mL of 6 N HCl and boiled at reflux for 10.5 h. After cooling to room temperature the reaction mixture was extracted with CH_2Cl_2 (2x60 mL). The organic extracts were discarded. Norite[®] (0.20 g) was added to the aqueous phase and the mixture was refluxed for 30 min. The reaction mixture was filtered and the filtrate concentrated in vacuo to yield 2.30 g (91.1%) of crude **6a** as a white solid, which was identical with a sample (TLC, NMR) obtained by enantioselective hydrogenation:^{6b} mp 185-187 °C; $[\alpha]_{\text{D}}^{19.5} = +20.50^\circ$ ($c = 1.976$, 1 N HCl); ee 97.0%.

Following this procedure, saponification of **5b** yielded **6a** with an ee of 92.6%, whereas saponification of **5d** afforded **6a** with an ee of 97.4%.

L-Phosphinothricin (**6**) was obtained by treating **6a** derived from **5f** with propene oxide as described previously:^{6b} mp 208-211; $[\alpha]_{\text{D}}^{19} = +16.00^\circ$ ($c = 0.70$, H_2O); ee 99.4%.

(2*S*)-2-(*N*-Benzoyloxycarbonyl)amino-4-[isobutoxy(methyl)phosphinyl]butanoic Acid (**7**). To 1.66g (4.33 mmol) of **5d** in 40 mL THF was added 4.33 mL of 1 N NaOH. The mixture was stirred at room temperature for 30 min and then concentrated in vacuo. After addition of 5 mL of 1 N HCl the aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield 1.67 g of crude **7** as a colorless oil, which was dissolved in 20 mL of saturated sodium hydrogencarbonate solution. This solution was washed with 20 mL of CH_2Cl_2 . The organic extract was discarded. After acidification with 2 N HCl the aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield 1.26g (78.4%) of **7** as a glasslike substance: $[\alpha]_{\text{D}}^{20} = +32.69^\circ$ ($c = 1.056$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 7.32 (s, 5, C_6H_5), 5.87 (m, 1, CHNHCOO), 5.08 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.38 (m, 1, CHNHCOO), 3.72 (t, 2, $J = 7$ Hz, $(\text{H}_3\text{C})_2\text{CHCH}_2\text{OP}$), 2.40-1.60 (m, 5, $\text{PCH}_2\text{CH}_2\text{CH}$ and $(\text{H}_3\text{C})_2\text{CHCH}_2\text{OP}$), 1.46 (d, 3, $J = 14$ Hz, PCH_3), 0.90 (dd, 6, $J = 7$, 1.2 Hz, $\text{POCH}_2\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 172.955, 172.872, 155.985, 155.955, 136.271, 128.526, 128.085, 128.061, 71.025, 70.932, 67.046, 53.974, 53.754, 29.414, 29.381, 29.332, 29.297, 25.497,

25.339, 25.035, 25.003, 24.245, 24.087, 18.908, 18.875, 14.188, 13.901, 12.957, 12.621; ^{31}P NMR (121 MHz, CDCl_3) δ 58.652, 58.550; Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_6\text{P}$: C, 54.98; H, 7.06; N, 3.77; P, 8.34. Found: C, 54.6; H, 6.8; N, 3.9; P, 7.7.

(2*S*)-2-Amino-4-[isobutoxy(methyl)phosphinyl]butanoic Acid (**8**). To a solution of 1.05 g (2.83 mmol) of **7** in 30 mL of MeOH was added 0.1 g of 10% Pd/C. The reaction bottle was evacuated, flushed with argon and then pressurized with hydrogen (0.30 MPa). After 5 h pressure was released, the catalyst filtered off and the filtrate concentrated in vacuo. The glasslike residue was recrystallized from acetone/water to yield 0.54 g (84.3%) of **8** as a white solid: mp 183–184 °C; $[\alpha]_D^{21} = +11.79^\circ$ ($c = 1.06$, H_2O); ^1H NMR (100 MHz, D_2O) δ 3.81 (m, 3, $\text{CH}(\text{NH}_2)\text{COOH}$ and $(\text{H}_3\text{C})_2\text{CHCH}_2\text{OP}$), 2.38–1.78 (m, 5, $\text{PCH}_2\text{CH}_2\text{CH}$ and $(\text{H}_3\text{C})\text{CHCH}_2\text{OP}$), 1.63 (d, 3, $J = 14$ Hz, PCH_3), 0.94 (d, 6, $J = 7$ Hz, $\text{POCH}_2\text{CH}(\text{CH}_3)_2$); ^{31}P NMR (121 MHz, D_2O) δ 61.614, 61.564; Anal. Calcd for $\text{C}_9\text{H}_{20}\text{NO}_4\text{P} \times 0.5 \text{ H}_2\text{O}$: ^{13}C , 43.90; H, 8.60; N, 5.69; P, 12.56. Found: C, 44.3; H, 8.6; N, 6.2; P, 11.7.

(4*S*)-3-Benzoyloxycarbonyl-4-[2-(diisopropoxyphosphinyl)ethyl]-1,3-oxazolidin-5-one (**11**). To 5.10 g (31 mmol) of freshly distilled diisopropylphosphite (**9**), preheated to 120 °C (bath temperature), was added under argon during 25 min a solution of 1.90 g (7.7 mmol) of **3c** in 4 mL of xylene containing a few drops of tert-butyl per-2-ethylhexanoate. After 60 min stirring at 120 °C another portion of tert-butyl per-2-ethylhexanoate was added and stirring was continued for further 60 min. The mixture was concentrated in vacuo and purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeCN}$ 3:1) to yield 1.12 g (35.1%) of **11** as a colorless oil: $[\alpha]_D^{23} = +69.20^\circ$ ($c = 0.500$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 7.35 (s, 5, C_6H_5), 5.53 (d, 1, $J = 5$ Hz, NCH_2O), 5.22 (d, 1, $J = 5$ Hz, NCH_2O), 5.18, (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.65 (m, 2, $\text{POCH}(\text{CH}_3)_2$), 4.35 (t, 1, $J = 5.5$ Hz, CHNCOO), 2.42–1.45 (m, 4, $\text{PCH}_2\text{CH}_2\text{CH}$), 1.28 (d, 6, $J = 7$ Hz, $\text{POCH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 171.318, 152.833, 135.118, 128.640, 128.590, 128.281, 77.870, 70.464, 70.377, 68.095, 54.898, 54.631, 24.379, 23.963, 23.902, 23.021, 21.102; ^{31}P NMR (121 MHz, CDCl_3) δ 27.767; Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_7\text{P}$: C, 55.20; H, 6.83; N, 3.39; P, 7.49. Found: C, 55.5; H, 6.9; N, 3.1; P, 7.0.

(4*S*)-3-Benzoyloxycarbonyl-4-[2-(dimethylphosphinyl)ethyl]-1,3-oxazolidin-5-one (**12**). Following the general procedure for the synthesis of **5**, 2.20 g (eluent A, 62%) of **12** were obtained as a colorless oil, starting from **3c** (2.70 g, 11 mmol) and dimethylphosphine oxide²⁰ (**10**, 2.55 g, 32.7 mmol): $[\alpha]_D^{23} = +81.70^\circ$ ($c = 0.427$, CHCl_3); ^1H NMR (100 MHz, CDCl_3) δ 7.40 (s, 5, C_6H_5), 5.53 (d, 1, $J = 5$ Hz, NCH_2O), 5.26 (dd, 1, $J = 5$, 1.2 Hz, NCH_2O), 5.21 (s, 2, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.39 (t, 1, $J = 5.5$ Hz, CHNCOO), 2.50–1.63 (m, 4, $\text{PCH}_2\text{CH}_2\text{CH}$), 1.47 (d, 6, $J = 12.5$ Hz, $\text{P}(\text{CH}_3)_2$); ^{31}P NMR (121 MHz, CDCl_3) δ 42.170; Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_5\text{P}$: C, 55.38; H, 6.20; N, 4.31. Found: C, 55.7; H, 6.1; N, 4.0.

(2*S*)-2-Amino-4-phosphonobutanoic Acid Hydrochloride (**13a**). Following the procedure for the synthesis of **6a**, 0.65 g (81.8%) of crude **13a** were obtained as a very hygroscopic glasslike substance from 1.50 g (3.62 mmol) of **11**: $[\alpha]_D^{23} = +14.00^\circ$ ($c = 0.571$, 1 N HCl); ^1H NMR (100 MHz, D_2O) δ 4.13 (t, 1, $J = 5.5$ Hz, CHNCOO), 2.42–1.57 (m, 4, $\text{PCH}_2\text{CH}_2\text{CH}$); ^{13}C NMR (75 MHz, D_2O) δ 174.220, 55.765, 26.769, 26.727, 26.467, 24.651; ^{31}P NMR (121 MHz, D_2O) δ 27.670.

(2*S*)-2-Amino-4-dimethylphosphinylbutanoic Acid Hydrochloride (**14a**). Following the procedure for the synthesis of **6a**, 0.35 g (88.2%) of crude **14a** were obtained as a very hygroscopic glasslike substance from 0.40 g (1.22 mmol) of **12**: $[\alpha]_D^{23} = +17.00^\circ$ ($c = 0.528$, 1 N HCl); ^1H NMR (100 MHz, D_2O) δ 4.20 (t, 1, $J = 5.5$ Hz, CHNCOO), 2.42–1.73 (m, 4, $\text{PCH}_2\text{CH}_2\text{CH}$), 1.58 (d, 6, $J = 10.5$ Hz, PCH_3); ^{13}C NMR (75 MHz, D_2O) δ 173.902, 55.967, 55.757, 28.940, 28.039, 25.327, 17.570, 16.651; ^{31}P NMR (121 MHz, D_2O) δ 55.292.

Acknowledgement. The very able technical assistance of Rita Mosch is gratefully acknowledged.

REFERENCES AND NOTES

- Enantioselective Synthesis of L-Phosphinothricin, Part III. For part II see ref. 6b. Presented in part at the 7. Int. Congr. of Pesticide Chemistry (IUPAC), Hamburg 1990.
- Havlíček, L.; Hanuš, J. *Coll. Czech. Chem. Commun.* **1991**, *56*, 1365.
- (a) Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817. (b) Rajendra, G.; Miller, M.J. *J. Org. Chem.* **1987**, *52*, 4471. (c) Tashiro, T.; Fushiya, S.; Nozoe, S. *Chem. Pharm. Bull.* **1988**, *36*, 893. (d) Mzengcza, S.; Whitney, R.A. *J. Org. Chem.* **1988**, *53*, 4074. (e) Meffre, P.; Vo-Quang, L.; Vo-Quang, Y.; Le Goffic, F. *Synth. Commun.* **1989**, *19*, 3457.

4. (a) Hanessian, S.; Sahoo, S.P. *Tetrahedron Lett.* **1984**, 25, 1425. (b) Barton, D.H.R.; Crich, D.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1985**, 41, 4347. (c) Krol, W.J.; Mao, S.; Steele, D.L.; Townsend, C.A. *J. Org. Chem.* **1991**, 56, 728.
5. (a) Wade, P.A.; Singh, S.M.; Pillay, M.K. *Tetrahedron* **1984**, 40, 601. (b) Cardani, S.; Prati, L.; Tinti, O. *Synthesis* **1986**, 1032. (c) Mzengeza, S.; Yang, C.M.; Whitney R.A. *J. Am. Chem. Soc.* **1987**, 109, 276. (d) Wityak, J.; Gould, S.J.; Hein, S.J.; Keszler, D.A. *J. Org. Chem.* **1987**, 52, 2179. (e) Fushiya, S.; Chiba, H.; Otsubo, A.; Nozoe, S. *Chem. Lett.* **1987**, 2229. (f) Itaya, T.; Shimomichi, M.; Ozasa, M. *Tetrahedron Lett.* **1988**, 29, 4129. (g) Meffre, P.; Vo-Quang, L.; Vo-Quang, Y.; Le Goffic, F. *Tetrahedron Lett.* **1990**, 31, 2291. (h) Kitagawa, O.; Miura, A.; Kobayashi, Y.; Taguchi, T. *Chem. Lett.* **1990**, 1011.
6. (a) Zeiss, H.-J. *Tetrahedron Lett.* **1987**, 28, 1255. (b) Zeiss, H.-J. *J. Org. Chem.* **1991**, 56, 1783. (c) Hoffmann, M.G.; Zeiss, H.-J. *Tetrahedron Lett.* **1992**, 33, 2669.
7. Koecher, H. *BCPC Monogr.* **1989**, 42, 63.
8. Suzuki, A.; Tsuruoka, T.; Mizutani, K.; Inouye, S. *Sci. Reports of Meiji Seika Kaisha* **1981**, 20, 33.
9. The optical rotations of **3b** of comparable chemical purity (> 97%) obtained from different runs ranged from - 8.10 ° to - 9.60 ° [lit.^{3a} $[\alpha]_D^{20} = - 11.80^\circ$]. All of these samples gave **5b** with an identical $[\alpha]_D$ of + 10.90 ° (see experimental part).
10. Cf. ref 3b. Essential amounts (20%) of the methyl ester of **2** (see experimental part for the methyl ester of **2b**) are formed during the oxidative decarboxylation. The formation of this byproduct can be explained by the reaction of a methyl cation, derived from a methyl radical which is produced by oxidative decarboxylation of the acetate moiety of lead(IV)acetate, with the carboxylate anion of **2**. The rest of the crude reaction mixture consisted of unreacted starting material **2**.
11. The oxazolidinone ring of compounds **5c-f** is readily opened even by moderate bases but is somewhat more resistant to acids. This may lead to some difficulties during the purification by chromatography on silica gel. Rapid chromatography or flash chromatography¹² is recommended, otherwise ring-opened *N*-hydroxymethyl derivatives of **5** will be obtained.
12. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923.
13. Lam, S.; Malikin, G. *J. Chromatogr.* **1986**, 368, 413.
14. The ee values of **6a** obtained from **5d** in different experiments ranged from 96.4% - 97.4%. The ee of **6a** derived from **5f** was 97.0%.
15. Itoh, M. *Chem. Pharm. Bull.* **1969**, 17, 1679.
16. Monaghan, D.T.; McMills, M.C.; Chamberlin, A.R.; Cotman, C.W. *Brain Research*, **1983**, 278, 137.
17. (a) Petrov, K.A.; Bliznyuk, N.K.; Studnev, Y.N.; Kolomiets, A.F. *Zh. Obshch. Khim.* **1961**, 31, 179; *Chem. Abstr.* **1961**, 55, 22102c. (b) Sasse, K. In *Houben-Weyl; Methoden der organischen Chemie*; Thieme: Stuttgart, 1963; Vol 12/1, p 323.
18. Derivatives of **6** like **5b**, **7** and **8** may contain 0.5-1.0 mol of water per molecule, depending on the polarity of the protective groups, cf. also ref 6b. Racemic **6** crystallizes as a monohydrate.¹⁹
19. Paulus, E.F.; Grabley, S. *Z. Kristallogr.* **1982**, 160, 39.
20. Kleiner, H.J. In *Houben-Weyl; Methoden der organischen Chemie*; Thieme: Stuttgart, 1982; Vol E1, p 242.