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Syntheses and GABA Receptor Binding Properties of 4-Amino-1-, 2-, and 3-Hydroxybutylphosphinic Acids

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Abstract: Novel racemic 4-amino-1-, 2-, and 3-hydroxybutylphosphinic acids and the corresponding 4-amino-1-, 2-, and 3-hydroxybutyl methylphosphinic acids have been synthesized. The phosphinic acid groups are bioisosteres of the carboxylic acid group, and some of these hydroxy amino acids are $GABA_B$ antagonists. The novel phosphinic acids were evaluated for their $GABA_A$ and $GABA_B$ receptor binding properties using rat brain synaptosomes and were also tested for GABAergic activity in a guinea pig ileum model. None of the phosphinic acids tested were found to be active.

INTRODUCTION

The most widely distributed inhibitory neurotransmitter in the central nervous system (CNS) of vertebrates is 4-aminobutyric acid (GABA). Compounds which affect GABA receptors have pronounced effects on brain function and have either demonstrated or possess potential utility for the treatment of CNS disorders.[1] Three classes of mammalian GABA receptors, denoted $GABA_A$, $GABA_B$ and $GABA_C$, have been identified and characterized so far. [1] $GABA_A$ receptors are ligand-gated Cl^- channels mainly functioning as postsynaptic receptors and mediate fast synaptic inhibition. $GABA_B$ receptors, located predominantly on nerve terminals, mediate slow synaptic inhibition by increasing K^+ and decreasing Ca^{2+} conductances through GTP-binding proteins and intracellular messenger pathways. $GABA_B$ receptors modulate the release of a large number of neurotransmitters. $GABA_C$ receptors are ligand-gated Cl^- channels and are found only in neurons of the retina.[1]

Pharmacologically, $GABA_B$ receptors are characterized by their insensitivity to the specific $GABA_A$ agonists 1,2,3,6-tetrahydropyridin-4-yl-carboxylic acid (isoguvacine) and 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol (THIP), the $GABA_A$ antagonist bicuculline and by their specific affinity for and stereoselective activation by the antispastic muscle relaxant (R)-4-amino-3-(4-chlorophenyl)butyric acid [(R)-baclofen]. In recent years, a number of $GABA_B$ antagonists have been developed among which phosphinic acids occupy a prominent position.[2,3] The most potent and selective $GABA_B$ antagonists described so far are (3-

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aminopropyl)alkylphosphinic acids (**Figure 1**) and further development of these compounds has led to *N*-benzylated $GABA_B$ antagonists with nanomolar receptor affinity.[2,3]

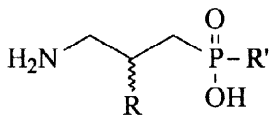


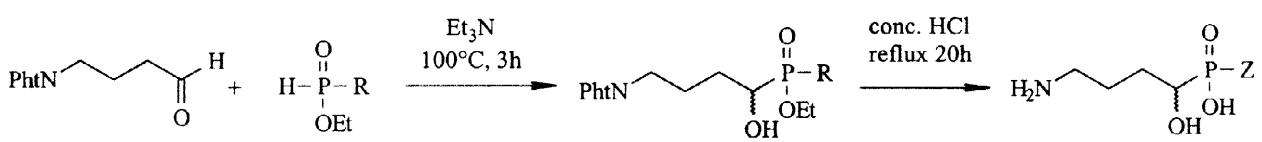
Figure 1. (3-Aminopropyl)alkylphosphinic acid analogues of GABA. R = H or OH.

(R)-4-Amino-3-hydroxybutyric acid (3-OH-GABA) is a $GABA_B$ agonist (IC_{50} value in $GABA_B$ binding = 0.4 μM[4]). Surprisingly however, the homologue, 5-amino-3-hydroxyvaleric acid (3-OH-DAVA), shows no detectable affinity for the GABA-B receptor, whereas 5-amino-(S)-2-hydroxyvaleric acid [(S)-2-OH-DAVA, IC_{50} = 15 μM) and 5-amino-(R)-4-hydroxyvaleric acid [(R)-4-OH-DAVA, IC_{50} = 8 μM] are relatively potent $GABA_B$ antagonists.[4]

Prompted by the observations that the use of phosphinic acid and alkylphosphinic acid as bioisosteric replacements for the carboxylic acid group of GABA and 3-OH-GABA resulted in agonists with increased affinities for the $GABA_B$ receptor by a factor of 5-50, we decided to investigate the effect of similar bioisosteric replacements of the hydroxylated DAVA antagonists.[2,3] As it was shown that the absolute stereochemistry of the OH-substituent is of minor importance for the pharmacology of other hydroxylated alkylphosphinic acid antagonists,[2] we decided to synthesize and characterize the racemates only.

RESULTS AND DISCUSSION

The syntheses of 4-amino-1-hydroxybutylphosphinic acid **4** and (4-amino-1-hydroxybutyl)methylphosphinic acid **5** are outlined in **Figure 2**.



1 **2a, R = CH(OEt)$_2$** **3a, R = CH(OEt)$_2$, 73%** **4, Z = H, 53%**
2b, R = Me **3b, R = Me, 69%** **5, Z = Me, 70%**

Figure 2. Syntheses of 4-amino-1-hydroxybutylphosphinic acid **4** and (4-amino-1-hydroxybutyl)-methylphosphinic acid **5**. Pht = phthaloyl.

The syntheses of **4** and **5** were straightforward from readily available starting materials. Base catalyzed Pudovik addition of the phosphinates **2a**[5,6] and **2b**[7,8] to 4-phthalimidobutyraldehyde **1**[9] gave the amino-protected α-hydroxyphosphinates **3a** and **3b** as 1:1 diastereomeric mixtures. Acidic deprotection and recrystallization gave pure **4** and **5**. The phosphinate **2a** is a masked hypophosphorous acid synthon which has a protected form of hydrogen connected to phosphorus, i.e. a diethoxymethyl group. **2a** and related synthons have proven to be versatile intermediates for the syntheses of phosphinic acids.[5,6]

The syntheses of 4-amino-2-hydroxybutylphosphinic acid **10** and (4-amino-2-hydroxybutyl)methylphosphinic acid **11** are outlined in **Figure 3**. The key step was the regiospecific Lewis acid catalyzed ring opening of *N*-(3,4-epoxybutyl)phthalimide **7**[10] by the *in situ* formed silyl phosphonites **8a**[3,6] or **8b**[3].

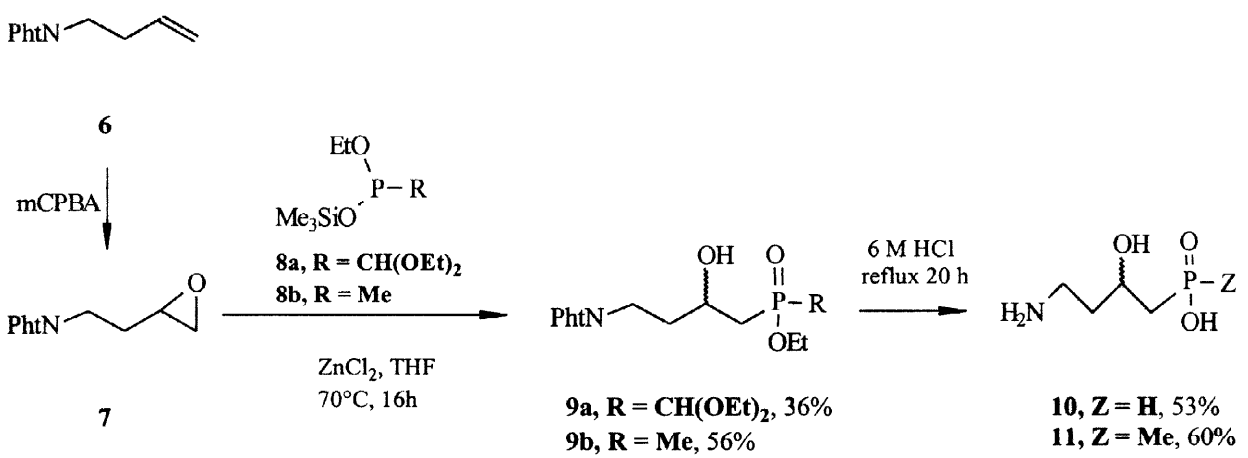


Figure 3. Syntheses of 4-amino-2-hydroxybutylphosphinic acid **10** and (4-amino-2-hydroxybutyl)-methylphosphinic acid **11**. Pht = phthaloyl.

N-(3,4-Epoxybutyl)phthalimide was obtained by epoxidation of *N*-(3-butenyl)phthalimide, **6**[11]. Acidic deprotection of **9a** and **9b** and recrystallization gave pure **10** and **11**. Several attempts to synthesize the protected intermediate **9a** by alkylation of *N*-(2,3-epoxypropyl)phthalimide using the α-lithium salt or the α-lithiocuprate of ethyl (diethoxymethyl)methylphosphinate[6] with or without $BF_3{\cdot}OEt_2$ as catalyst failed, most likely because of cleavage of the phthalimido moiety.

The syntheses of 4-amino-3-hydroxybutylphosphinic acid **14** and (4-amino-3-hydroxybutyl)-methylphosphinic acid **15** are outlined in **Figure 4**. After several unsuccessful attempts, we obtained these compounds from the alkyl-3-butenylphosphinates **12a** and **12b** by Sharpless oxyamination[12,13]. The alkyl-3-butenylphosphinates **12a** and **12b** were synthesized by base catalyzed alkylation of the phosphinates **2a** and **2b** (the Michaelis-Becker reaction[14]) with commercially available 4-bromo-1-butene. The alkylations were very sensitive to the reaction conditions. The use of weak bases like pyridine, triethylamine or potassium carbonate gave no alkylation but led to decomposition of the starting phosphinates. The use of stronger bases, like *tert*-butoxide or lithium diisopropylamide (LDA), gave higher yields of the alkyl-3-butenylphosphinates **12a** and **12b**, but the strength of the base used turned out to be crucial. Thus, whereas the use of *tert*-butoxide gave satisfactory yield of **12a**, less than 10% of impure **12b** was isolated using this base. However, **12b** was isolated in good yields using LDA. The alkylations had to be carried out at low temperature in deoxygenated solvents in an atmosphere of nitrogen, as the anions of **2a** and **2b** are thermally unstable and easily dismutate. A synthesis of **12a** was also attempted by alkylation of the silyl alkylphosphonite **8a** (the silyl-Arbuzov reaction[15]). Although the alkylation went smoothly under reflux conditions (quantitatively according to ^{31}P-NMR), the liberated bromotrimethylsilane caused quantitative deprotection of the resulting ethylester **12a** (the McKenna reaction[16]). Notably, the acetal protecting group of the P-H moiety was not affected under these conditions.

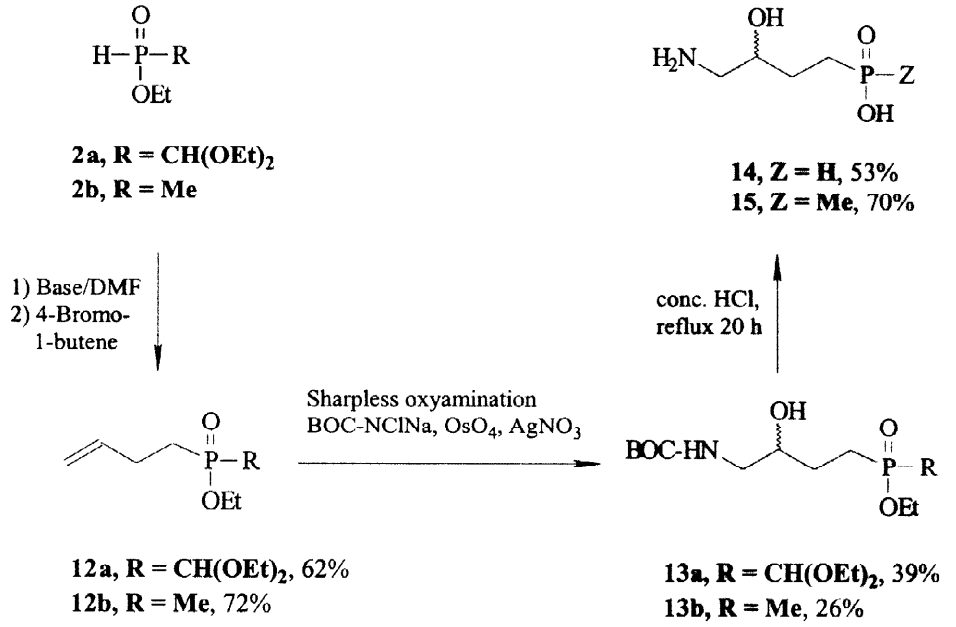


Figure 4. Synthesis of 4-amino-3-hydroxybutylphosphinic acid, **14**, and (4-amino-3-hydroxybutyl)-methylphosphinic acid, **15**.

The oxyamination was first carried out using the chloramine-T procedure,[17-19] but the tosyl protecting group could not be removed without side reactions. Instead, we used the BOC-chloramine procedure[20-22] thereby introducing the readily removable BOC-group. Again, acidic deprotection of **13** and recrystallization gave the pure final products.

The phosphinic acids **4**, **5**, **10** and **14** were tested for affinity for the $GABA_A$ and $GABA_B$ receptors using rat brain synaptosomes.[4,23] Surprisingly however, none of these novel OH-DAVA analogues showed significant affinity (IC_{50} > 100 μM) for the $GABA_A$ or $GABA_B$ receptors. In the guinea pig ileum mode,[4] neither of the analogues showed any GABA agonist (EC_{50} > 1000 μM) or antagonist activity (IC_{50} > 1000 μM).

These results were quite unexpected, and at the present time we do not have any explanations. It has been hypothesized that $GABA_B$ agonist and antagonist binding sites are located within different regions of the G-protein-coupled receptor [2] and, thus, the increased affinities seen for agonistic phosphinic acids [2] does not necessarily apply to antagonists. However, more likely the phosphinic acids do not form the receptor active conformations as readily as their carboxylic acid congeners. An explanation of the molecular basis of these findings must, however, await information about the precise structure of the recently cloned $GABA_B$ receptors[24] and a detailed study of the low-energy conformations of the investigated compounds.

CONCLUSION

Novel hydroxylated 4-aminobutylphosphinic acid analogues of hydroxylated DAVA $GABA_B$ antagonists have been synthesized and tested. None of the novel analogues tested showed affinity for the $GABA_A$ or $GABA_B$ receptors and they did not possess any GABA agonist or antagonist activity.

EXPERIMENTAL

50 % Aqueous phosphinic acid, triethylamine, triethyl orthoformate, anhydrous zinc chloride, potassium *tert*-butoxide, 4-bromo-1-butene, Lithium diisopropylamide (2M in THF), *tert*-butyl carbamate and trifluoroacetic acid were from Fluka. Methyldichlorophosphine was from Hoechst. All other reagents were from Aldrich. Solvents were HPLC grade from LAB-SCAN and were dried over molecular sieves (Grace 4 Å). 4-Phthalimidobutyraldehyde **1**,[9] ethyl (diethoxymethyl)phosphinate **2a**,[25] ethyl methylphosphinate **2b**,[7,8] *N*-(3,4-epoxybutyl)phthalimide **7**[10,11] and *tert*-butyl hypochlorite[26] were prepared by known literature methods. TLC was run on Merck 5554 silica 60 aluminium sheets, column chromatography on Merck 9385 silica 60 (0.040 - 0.063 mm). ^{31}P NMR spectra were run on a JEOL FX 90 Q spectrometer, ^{1}H NMR and ^{13}C NMR spectra on a Varian Unity 400 MHz spectrometer, FAB MS data were obtained on a JEOL HX 110/110 Mass Spectrometer.

Ethyl (diethoxymethyl)phosphinate (2a).

Ethyl (diethoxymethyl)phosphinate **2a**, was made by a sligth modification of the published procedure[25]. 50 % Aqueous phosphinic acid (18.4 ml, 0.5 mol) was added to triethyl orthoformate (170 ml, 0.93 mol) under nitrogen. Trifluoroacetic acid (1.9 ml, 0.025 mol) was added and the reaction mixture stirred under nitrogen at rt for 7 days after which it was evaporated *in vacuo* (bath temperature < 40°C) to constant weight, taken up in chloroform (500 ml), washed with cold saturated sodium hydrogencarbonate (100 ml), dried (anhydrous sodium sulfate) and evaporated *in vacuo* to a clear oil. Distillation *in vacuo* gave ethyl (diethoxymethyl)phosphinate.

Yield: 20.9 g (61%), bp. 55-58°C/0.15 mbar (lit.[25] 65%, bp. 45°C/0.015 mbar). ^{31}P-NMR ($CDCl_3$): 26.1 (dq, $^{1}J_{PH}$ = 554 Hz, $^{2}J_{PH}$ = $^{3}J_{PH}$ = 8 Hz). ^{1}H-NMR ($CDCl_3$): 6.87 (dd, $^{1}J_{HP}$ = 554 Hz, $^{3}J_{HH}$ = 1.7 Hz, 1H, HP), 4.63 (dd, $^{2}J_{HP}$ = 8 Hz, $^{3}J_{HH}$ = 1.7 Hz, 1H, $[EtO]_2CHP$), 4.15 (m, 2H, CH_2O), 3.80 and 3.60 (2 m, 4H, 2 x CH_2O), 1.32 (t, $^{3}J_{HH}$ = 7 Hz, 3H, CH_3), 1.21 (t, $^{3}J_{HH}$ = 7 Hz, 3H, CH_3), 1.20 (t, $^{3}J_{HH}$ = 7 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 100.0 (d, $^{1}J_{PC}$ = 150 Hz, $[EtO]_2CHP$), 65.2 (d, $^{3}J_{PC}$ = 10 Hz, CH_2O), 64.8 (d, $^{3}J_{PC}$ = 10 Hz, CH_2O), 62.8 (d, $^{2}J_{PC}$ = 7 Hz, CH_2OP), 16.1 (d, $^{3}J_{PC}$ = 5 Hz, CH_3), 14.9. FAB^{+}MS: 197.1 ($M+H^{+}$, calcd 197.1).

Ethyl methylphosphinate (2b).

Ethyl methylphosphinate **2b**, was made by a sligth modification of the published procedure[7]. Methyldichlorophosphine (45 ml, 500 mmol) was dissolved in dry diethyl ether (300 ml) under nitrogen in a 3-necked 1 liter flask fitted with reflux condenser, addition funnel and mechanical stirrer and cooled to 0°C (ice bath). Anhydrous ethanol (70 ml, 1.2 mol) and anhydrous triethylamine (70 ml, 500 mmol) were dissolved in dry diethyl ether (100 ml) and the mixture was added during 30 min at 0°C under nitrogen to methyl dichlorophosphine under vigorous stirring. The ice bath was removed and the mixture heated under nitrogen to 60°C for 3 h, then cooled to rt and stirred at rt under nitrogen overnight. The mixture was filtered, the ammonium salt washed with dry diethyl ether (2 x 100 ml), and the solvent removed *in vacuo* to give a clear yellow liquid which was purified by vacuum distillation to give ethyl methylphosphinate as a clear, hygroscopic liquid.

Yield: 43.8 g (81%); bp. 26-30°C/0.8-1. Torr. (lit.[7] 70°C/15 torr.). ^{31}P-NMR ($CDCl_3$): 33.41 (dqt, $^{1}J_{PH}$ = 530 Hz, $^{2}J_{PH}$ = 15 Hz, $^{3}J_{PH}$ = 2 Hz). ^{1}H-NMR ($CDCl_3$): 7.0 (dd, $^{1}J_{HP}$ = 530 Hz, $^{3}J_{HH}$ = 2 Hz, 1H, HP), 4.00-3.80 (m, 2H, CH_2O), 1.35 (dd, $^{2}J_{HP}$ = 15 Hz, $^{3}J_{HH}$ = 2 Hz, 3H, CH_3P), 1.15 (t, $^{3}J_{HH}$ = 7 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 61.8 (d, $^{2}J_{PC}$ = 6 Hz, CH_2OP), 15.7 (d, $^{3}J_{PC}$ = 7 Hz, CH_3), 14.5 (d, $^{1}J_{PC}$ = 95 Hz, CH_3P). GC-MS: 98.5% pure, $[M-H\cdot]^{+}$:107.0 (calcd 107.0).

Ethyl (1-hydroxy-4-*N*-phthalimidobutyl)alkylphosphinate (3a and 3b).

4-Phthalimidobutyraldehyde **1**[9] (4.4 g, 20 mmol), ethyl (diethoxymethyl)phosphinate **2a** (3.9 g, 20 mmol) or ethyl methylphosphinate **2b** (2.16 g, 20 mmol) and dry triethylamine (2.8 ml, 20 mmol) were heated under nitrogen to 100 °C for 3 h, cooled to rt, taken up in DCM (100 ml), washed with ice-cold 4 M HCl (50 ml), saturated sodium hydrogencarbonate (50 ml), brine (50 ml), dried (anhydrous sodium sulfate) and evaporated *in*

vacuo to a clear oil. The product was purified by flash chromatography on silicagel using 5% MeOH in DCM as eluent.

Ethyl (1-hydroxy-4-N-phthalimidobutyl)(diethoxymethyl)phosphinate (3a).
Recrystallization from benzene (30 ml)/petroleumether (50 ml) gave colorless crystals of **3a** as a 1:1 mixture of diastereomers.
Yield: 6.1 g (73%), mp 95-97°C, Rf = 0.23 (95/5; DCM/MeOH). ^{31}P-NMR ($CDCl_3$): 37.89 and 37.37. ^{1}H-NMR ($CDCl_3$): 7.77 and 7.64 (2m, 4H, arom), 4.80 (d, 1H, $^2J_{HP}$ = 8 Hz, $[EtO]_2\underline{C}HP$), 4.18 (2 app. Quint., $^3J_{HH}$ = $^3J_{HP}$ = 6 Hz, 2H, CH_2OP), 3.92 (2m, $^2J_{HP}$ = 10 Hz, 1H, $C\underline{H}[OH]P$), 3.80 (m, 2H, CH_2O), 3.70 (m, 2H, CH_2N), 3.65 (m, 4H, 2 x CH_2O), 3.40 (br. s, 1H, OH), 2.0 and 1.80 (2m, 4H, 2x CH_2), 1.25 (t, $^3J_{HH}$ = 6 Hz, 3H, CH_3), 1.21 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3), 1.20 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 168.0, 133.6, 131.9, 122.9, 100.4 and 100.2 (2 d, $^1J_{PC}$ = 136 Hz, $[EtO]_2\underline{C}HP$), 67.4 and 67.2 (2 d, $^1J_{PC}$ = 102 Hz, $\underline{C}H[OH]P$), 66.0 and 65.9 (2 d, $^3J_{PC}$ = 8 Hz, CH_2O), 65.6 and 65.4 (2 d, $^3J_{PC}$ = 10 Hz, CH_2O), 62.1 and 62.0 (2 d, $^2J_{PC}$ = 7 Hz, CH_2OP), 37.4 (CH_2N), 27.3 and 27.0, 25.1 and 25.0 (2 d, $^2J_{PC}$ = 8 Hz, CH_2), 16.5 and 16.4 (2 d, $^3J_{PC}$ = 5 Hz, CH_3), 15.0 and 14.9. FAB$^+$MS ($M+H^+$): 414.2 (calcd 414.2). Anal. ($C_{19}H_{28}NO_7P$), calcd C: 55.12, H: 6.83, N: 3.39; found C: 55.12, H: 6.54, N:3.33.

Ethyl (1-hydroxy-4-N-phthalimidobutyl)methylphosphinate (3b).
Recrystallization from EtOAc (25 ml)/hexane (10 ml) gave colorless crystals of **3b** as a 1:1 mixture of diastereomers.
Yield: 4.5 g (69%), mp 102-106°C, Rf = 0.40 (95/5; DCM/MeOH). ^{31}P-NMR ($CDCl_3$): 53.53 and 53.12. ^{1}H-(ppm) ($CDCl_3$): 7.77 and 7.64 (2m, 4H, arom), 4.7 (br. s, 1H, OH), 4.18 (dq, $^3J_{HH}$ = 6 Hz, $^3J_{HP}$ = 3 Hz, 2H, CH_2OP), 3.80 (m, 1H, $C\underline{H}[OH]P$), 3.65 (m, 2H, CH_2N), 2.0-1.50 (m, 4H, 2 x CH_2), 1.40 (2d, $^2J_{HP}$ = 10 Hz, 3H, CH_3P), 1.25 (t, $^3J_{HH}$ = 6 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 168.1, 133.7, 131.8, 122.9, 68.6 (d, $^1J_{PC}$ = 111 Hz, $\underline{C}[OH]HP$), 60.8 (2 d, $^2J_{PC}$ = 12 Hz, CH_2OP), 37.2 (CH_2N), 27.6 and 27.5 (2 d, $^3J_{PC}$ = 4 Hz, CH_2P), 25.0 and 24.9 (2 d, $^2J_{PC}$ = 13 Hz, CH_2), 16.4 (d, $^3J_{PC}$ = 5 Hz, CH_3), 10.5 and 9.5 (2 d, $^1J_{PC}$ = 88 Hz, CH_3P). FAB$^+$MS ($M+H^+$): 326.1 (calcd 326.1). Anal. ($C_{15}H_{20}NO_5P$), calcd. C: 55.38, H: 6.20, N: 4.31; found C: 55.43, H: 6.35, N:4.22.

Ethyl (2-hydroxy-4-*N*-phthalimidobutyl)alkylphosphinate (9a and 9b).
In a dry, 100 ml round-bottomed flask under nitrogen ethyl (diethoxymethyl)phosphinate **2a** (9.32 g, 42 mmol) or ethyl methylphosphinate **2b** (4.5 g, 42 mmol) was dissolved in hexamethyl disilazane (10 ml, 48 mmol) and the mixture refluxed under nitrogen for 3 h until ^{31}P-NMR showed almost complete formation of ethyl trimethylsilyl alkylphosphonite (**8a**, **8b**, ^{31}P-NMR: 147 ppm). The mixture was evaporated *in vacuo* to a clear oil and then cooled to rt under nitrogen. *N*-(3,4-Epoxybutyl)phthalimide **7**[10,11] (6.1 g, 28 mmol, dried by evaporation from 40 ml dry MeCN) was dissolved in anhydrous THF (20 ml) and added to ethyl trimethylsilyl alkylphosphonite under nitrogen. Anhydrous zinc chloride (2 g, dried by evaporation from 40 ml dry dioxane) was dissolved in dry THF (20 ml) and added to the reaction mixture under nitrogen. The mixture was heated to 60°C under nitrogen overnight, quenched with 4 M HCl (8 ml), evaporated *in vacuo* to a clear oil, taken up in DCM (100 ml), washed with saturated sodium hydrogencarbonate (50 ml), brine (50 ml), dried (anhydrous sodium sulfate), evaporated *in vacuo* to a clear oil which crystallized upon standing. Recrystallized from EtOAc/hexane.

Ethyl (2-hydroxy-4-N-phthalimidobutyl)(diethoxymethyl)phosphinate (9a).
Yield: 6.2 g (36%), as a 1:1 mixture of diastereomers, mp 102-103°C.
^{31}P-NMR (ppm) ($CDCl_3$): 43.8 and 44.6. ^{1}H-NMR ($CDCl_3$): 7.77 and 7.64 (2m, 4H, arom), 4.65 and 4.60 (2 d, 1H, $^2J_{HP}$ = 8 Hz, $[EtO]_2\underline{C}HP$), 4.18-4.05 (m, 3H, CH_2O + $C\underline{H}[OH]$), 3.80 (m, 4H, 2x CH_2O), 3.65 (m, 2H, CH_2N), 2.10-1.90 (m, 2H, CH_2P), 1.80 (m, 2H, CH_2), 1.25 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3), 1.15 (t, $^3J_{HH}$ = 7 Hz, 6H, 2x CH_3). ^{13}C-NMR ($CDCl_3$): 168.1, 133.6, 131.8, 122.9, 101.0 and 100.8 (2 d, $^1J_{PC}$ = 144 Hz, $[EtO]_2\underline{C}HP$), 65.6

and 65.5 (2 d, $^2J_{PC}$ = 16 Hz, CH[OH]CH_2P), 63.8 (d, $^3J_{PC}$ = 5 Hz, CH_2O), 63.4 (d, $^3J_{PC}$ = 5 Hz, CH_2O), 61.6 and 61.4 (2 d, $^2J_{PC}$ = 15 Hz, CH_2OP), 36.8 and 36.7 (2 d, $^3J_{PC}$ = 1 Hz, CH_2), 34.4 and 34.3 (CH_2N), 32.9 and 32.6 (2 d, $^1J_{PC}$ = 88Hz, CH_2P), 16.4 and 16.3 (2 d, $^3J_{PC}$ = 5 Hz, CH_3), 14.9 and 14.8. FAB$^+$MS ($M+H^+$): 413.9 (calcd 414.2). Anal. ($C_{19}H_{28}NO_7P$, 1/4 H_2O), calcd. C: 54.61, H: 6.87, N: 3.35; found C: 54.83, H: 6.83, N:3.32.

Ethyl (2-hydroxy-4-N-phthalimidobutyl)methylphosphinate (9b).
Yield: 5 g (56%), as a 1:1 mixture of diastereomers, mp 102-106°C. ^{31}P-NMR ($CDCl_3$): 54.6 and 54.0. ^{1}H-NMR ($CDCl_3$): 7.75 and 7.65 (2m, 4H, arom), 4.15 (br. s, 1H, OH), 4.00 (m, 3H, CH_2O + C<u>H</u>[OH]), 3.75 (m, 2H, CH_2N), 1.95-1.70 (m, 4H, CH_2 + CH_2P), 1.45 (2 d, $^2J_{HP}$ = 15 Hz, 3H, CH_3P), 1.25 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 168.2, 133.7, 131.7, 122.9, 63.8 and 63.7 (2 d, $^2J_{PC}$ = 10 Hz, <u>C</u>H[OH]CH_2P), 60.0 and 59.8 (2 d, $^2J_{PC}$ = 18 Hz, CH_2OP), 37.1 and 36.9 (2 d, $^3J_{PC}$ = 2 Hz, CH_2), 36.8 and 35.9 (2 d, $^1J_{PC}$ = 90 Hz, CH_2P), 34.3 and 34.1 (CH_2N), 16.3 and 16.2 (2 d, $^3J_{PC}$ = 4 Hz, CH_3), 15.6 and 14.7 (2 d, $^1J_{PC}$ = 73 Hz, CH_3P). FAB$^+$MS ($M+H^+$): 326.1 (calcd 326.1). Anal. ($C_{15}H_{20}NO_5P$), calcd. C: 55.38, H: 6.20, N: 4.31; found C: 55.12, H: 6.20, N:4.15.

Ethyl 3-butenyl(diethoxymethyl)phosphinate (12a).
Potassium *tert*-butoxide (11.8 g, 105 mmol) was dissolved in anhydrous DMF, the solution deoxygenated by applying vacuum for 1 min (3 times) and the solution cooled to 0°C under nitrogen. Ethyl (diethoxymethyl)phosphinate **2a** (21.3 g, 100 mmol) was added in one portion under nitrogen at 0°C and stirred for 2 min, 4-bromo-1-butene (13.3 ml, 130 mmol) was added in one portion under nitrogen. A white precipitate (KBr) formed immediately and the mixture was stirred under nitrogen at 0°C for 60 min. Diethyl ether (200 ml) was added and the mixture was washed with water (200 ml), brine (50 ml), dried (sodium sulfate) and evaporated *in vacuo* to a clear oil which was purified by vacuum distillation through a 15 cm Vigreux column to give **12a** as a clear oil.
Yield: 15.5 g (62%); bp. 91-96°C/0.6-0.8 mbar. ^{31}P-NMR ($CDCl_3$): 42.50. ^{1}H-NMR ($CDCl_3$): 5.81-5.70 (m, 1H, CH=), 4.95 (dq, 1H, $^2J_{HH\text{-}gem}$ = $^4J_{HH\text{-}allyl}$ = 2 Hz, $^3J_{HH}$ = 17 Hz, CH=), 4.88 (dq, 1H, $^2J_{HH\text{-}gem}$ = $^4J_{HH\text{-}allyl}$ = 2 Hz, $^3J_{HH}$ = 10 Hz, CH=), 4.58 (d, 1H, $^2J_{HP}$ = 7.0 Hz, $[EtO]_2$C<u>H</u>P), 4.20-4.0 (m, 2H, CH_2OP), 3.8 and 3.6 (2m, 4H, 2x CH_2O), 2.30 (m, 2H, CH_2P), 1.80 (m, 2H, CH_2), 1.25 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3), 1.15 (t, $^3J_{HH}$ = 7 Hz, 6H, 2 x CH_3). ^{13}C-NMR ($CDCl_3$): 137.3 (d, $^3J_{CP}$ = 16 Hz), 114.7, 100.8 (d, $^1J_{CP}$ = 142 Hz, $[EtO]_2$<u>C</u>HP), 65.3 (d, $^3J_{CP}$ = 3 Hz, CH_2O), 65.2 (d, $^3J_{CP}$ = 3 Hz, CH_2O), 61.2 (d, $^2J_{CP}$ = 7 Hz, CH_2OP), 24.9 (d, $^2J_{CP}$ = 14 Hz, CH_2), 24.5 (d, $^1J_{CP}$ = 142 Hz, CH_2P), 16. 5 (d, $^3J_{CP}$ = 3 Hz, CH_3), 15.0. FAB$^+$MS ($M+H^+$): 251.1 (calcd 251.1). Anal. ($C_{11}H_{23}O_4P$, ½H_2O), calcd. C: 50.96, H: 9.33; found C: 51.02, H: 9.50.

Ethyl (3-butenyl)methylphosphinate (12b).
Ethyl methylphosphinate, **2b** (4.4 g, 40 mmol) was dissolved in anhydrous THF (40 ml), the solution deoxygenated by applying vacuum for 1 min (3 times) and the solution cooled to -80°C under nitrogen. Lithium diisopropylamide (LDA, 2M/THF; 20 ml, 40 mmol) was added dropwise under nitrogen at -80°C and the mixture stirred for 15 min. 4-Bromo-1-butene (5.0 ml, 60 mmol) was added in one portion at -80°C under nitrogen. A white precipitate formed immediately and the mixture was warmed to 0°C and stirred under nitrogen for 60 min. Diethyl ether (200 ml) was added and the mixture washed with water (200 ml), brine (50 ml), dried (sodium sulfate) and evaporated *in vacuo* to a clear oil which was purified by vacuum distillation through a 15 cm Vigreux column to give **12b** as a clear oil.
Yield: 4.6 g (72%); bp. 52°C/0.4 mbar. ^{31}P-NMR ($CDCl_3$): 53.61. ^{1}H-NMR ($CDCl_3$): 5.81-5.70 (m, 1H, CH=), 4.95 (dq, 1H, $^2J_{HH\text{-}gem}$ = $^4J_{HH\text{-}allyl}$ = 2 Hz, $^3J_{HH}$ = 17 Hz, CH=), 4.88 (ddd, 1H, $^2J_{HH\text{-}gem}$ = $^4J_{HH\text{-}allyl}$ = 2 Hz, $^3J_{HH}$ = 10 Hz, CH=), 4.0 (dq, $^3J_{HH}$ = 7 Hz, $^3J_{HP}$ = 7 Hz, 2H, CH_2OP), 2.25 (m, 2H, CH_2P), 1.75 (m, 2H, CH_2), 1.40 (d, $^2J_{HH}$ = 14 Hz, 3H, CH_3P), 1.25 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 136.6 (d, $^3J_{CP}$ = 15 Hz), 114.7, 59.4 (d, $^2J_{CP}$ = 6 Hz, CH_2OP), 28.5 (d, $^1J_{PC}$ = 94 Hz, CH_2P), 25.6 (d, $^2J_{CP}$ = 3 Hz, CH_2), 16.1 (d, $^3J_{CP}$ = 5 Hz, CH_3), 13.5 (d, $^1J_{CP}$ = 92 Hz, CH_3P). GC-MS: 97% pure, $[M\cdot]^+$: 162 (calcd 162). Anal. ($C_7H_{15}NO_2P$,), calcd. C: 51.85, H: 9.32; found C: 51.45, H: 9.10.

Ethyl (4-*tert*-butoxycarbonylamino-3-hydroxybutyl)alkylphosphinate (13a,b).
tert.-Butyl carbamate (1.64 g; 22.5 mmol) was dissolved in dry MeOH (11.5 ml), cooled to 0°C under nitrogen and freshly made *tert*-butylhypochlorite[26] (2.44 g; 22.5 mmol) was added dropwise under nitrogen at 0 °C. The mixture was stirred under nitrogen at 0°C for 20 min, sodium hydroxide (0.9 g, 22.5 mmol) dissolved in dry MeOH (13 ml) was added dropwise, the icebath removed, the mixture stirred 10 min and then evaporated *in vacuo*. The white powder was suspended in dry MeCN (60 ml), silver nitrate (2.54 g, 15 mmol), ethyl 3-butenyl-(diethoxymethyl)phosphinate **12a** (4.36 g, 15 mmol) or ethyl 3-butenylmethylphosphinate **12b** (2.43 g, 15 mmol), osmium tetroxide (7.5 ml of a 2μmol/ml solution in *tert*-butanol, 0.15 mmol) and water (6 ml) were added and the mixture stirred at rt overnight. The mixture was filtered, 5% sodium bisulfite (40 ml) added and the brown-red solution refluxed for 3 h. The resulting clear solution was evaporated *in vacuo*, diluted with water (50 ml) and extracted with DCM (3 x 50 ml). The combined organic phases were washed with brine (50 ml), dried (sodium sulfate) and evaporated *in vacuo* to a clear yellow oil. The product was purified by flash chromatography on silicagel using as eluent a gradient of MeOH (1-10%) in DCM.

Ethyl (4-tert-butoxycarbonylamino-3-hydroxybutyl)(diethoxymethyl)phosphinate (13a).
Yield: 2.3 g (39%), clear oil; 1:1 mixture of diastereomers. ^{31}P-NMR ($CDCl_3$): 47.14 and 47.06. ^{1}H-NMR ($CDCl_3$): 5.15 (br. s, 1H, NH), 4.62 and 4.60 (2 d, 1H, $^2J_{HP}$ = 7 Hz, $[EtO]_2C\underline{H}P$), 4.20-4.0 (m, 2H, CH_2OP), 3.80-3.60 (m, 6H, 2x CH_2O + CH_2N), 3.25 (m, 1H, $C\underline{H}[OH]$), 2.95 (br. s, 1H, OH), 2.0-1.60 (m, 4H, CH_2 + CH_2P), 1.40 (s, 9H, *tert*-butyl), 1.25 (t, $^3J_{HH}$ = 6 Hz, 3H, CH_3), 1.15 (t, $^3J_{HH}$ = 6 Hz, 6H, 2 x CH_3). ^{13}C-NMR ($CDCl_3$): 156.0, 100.7 (2 d, $^1J_{PC}$ = 143 Hz, $[EtO]_2\underline{C}HP$), 79.1, 70.8 (d, $^3J_{PC}$ = 4 Hz, CHOH), 65.6 and 65.5 (2 d, $^3J_{PC}$ = 5 Hz, CH_2O), 65.4 and 65.3 (2 d, $^3J_{PC}$ = 4 Hz, CH_2O), 61.7 and 61.6 (2 d, $^2J_{PC}$ = 7 Hz, CH_2OP), 53.2 and 46.1 (CH_2N), 28.2 (CH_3-BOC), 26.2 (d, $^2J_{PC}$ = 3 Hz, CH_2), 21.5 and 21.3 (2 d, $^1J_{PC}$ = 89 Hz, CH_2P), 16.5 (d, $^3J_{PC}$ = 3 Hz, CH_3), 15.1 and 15.0. FAB$^+$MS ($M+H^+$): 384.1 (calcd 384.2). Anal. ($C_{16}H_{34}NO_7P$, ½H_2O), calcd. C: 48.97, H: 8.99, N: 3.57; found C: 48.79, H: 8.94, N:3.39.

Ethyl (4-tert-butoxycarbonylamino-3-hydroxybutyl)methylphosphinate (13b).
Yield: 1.15 g (3.9 mmol, 26%), clear oil; 1:1 mixture of diastereomers. ^{31}P-NMR ($CDCl_3$): 56.6 and 56.3. ^{1}H-NMR ($CDCl_3$): 5.15 (br. s, 1H, NH), 4.25 (br. s, 1H, OH), 4.04 and 3.96 (2 q, $^3J_{HH}$ = 7 Hz, 2H, CH_2O), 3.60 (m, 1H, $C\underline{H}OH$), 3.20 and 3.0 (2m, 2H, CH_2N), 1.90-1.60 (m, 4H, CH_2 + CH_2P), 1.39 and 1.38 (2 d, $^2J_{HP}$ = 14 Hz, 3H, CH_3P), 1.35 (s, 9H, *tert*-butyl), 1.10 (2t, $^3J_{HH}$ = 7 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): 170.9, 156.4, 79.0, 70.5 (d, $^3J_{PC}$ = 14 Hz, CHOH), 60.1 (d, $^2J_{PC}$ = 5 Hz, CH_2OP), 45.9 (CH_2N), 28.2 (CH_3-BOC), 26.9 and 26.8 (2 d, $^2J_{PC}$ = 8 Hz, CH_2), 25.8 and 25.7 (2 d, $^1J_{PC}$ = 95 Hz, CH_2P), 16.4 (d, $^3J_{CP}$ = 5 Hz, CH_3), 13.5 and 13.6 (2 d, $^1J_{CP}$ = 92 Hz, CH_3P). FAB$^+$MS ($M+H^+$): 296.1 (calcd 296.1). Anal. ($C_{12}H_{26}NO_5P$, 1/8 H_2O), calcd. C: 48.44, H: 8.89, N: 4.71; found C: 48.59, H: 9.00, N:4.55.

Removal of protecting groups to give the hydrochlorides of 4-amino-1-, 2-, or 3-hydroxybutylphosphinic acids (4, 5, 10, 11, 14 and 15)
The ethyl (4-*N*-protected hydroxybutyl)alkylphosphinate (5 mmol) was dissolved in conc. HCl (50 ml; **3** and **13**) or 6 M HCl (50 ml; **9**) and the clear solution refluxed in an atmosphere of nitrogen for 20 h. The mixture was cooled to 0 °C, filtered, washed with icecold 4 M HCl (2 x 5 ml), the clear solution evaporated *in vacuo* and coevaporated twice with water (10 ml). Recrystallized from. EtOH/diethylether.

4-Amino-1-hydroxybutylphosphinic acid (4).
Recrystallization from abs. EtOH/propylene oxide removed most of the HCl. Yield: 0.82 g (53 %), mp 214-216°C. ^{31}P-NMR (H_2O, DMSO-d_6 ext. lock): 29.3, (dm, $^1J_{PH}$ = 517 Hz). ^{1}H-NMR (D_2O): 6.7 (d, $^1J_{PH}$ = 517 Hz, 1H, HP), 3.50 (dt, $^2J_{PH}$ = 10 Hz, $^3J_{HH}$ = 4 Hz, $C\underline{H}[OH]P$), 3.0 (t, $^3J_{HH}$ = 7 Hz, 2H, CH_2N), 1.85 (m, 1H), 1.75 (m, 2H, CH_2), 1.58 (m, 1H). ^{13}C-NMR (D_2O): 69.5 (d, $^1J_{PC}$ = 110 Hz, CH[OH]P), 39.1 (CH_2N), 25.9 (d, $^3J_{PC}$ = 4

Hz, CH_2), 23.3 (d, $^2J_{PC}$ = 12 Hz, CH_2). FAB$^+$MS ($M+H^+$): 154.0 (calcd 154.0). Anal. ($C_4H_{12}NO_3P$, 0.1HCl), calcd. C: 30.66, H: 7.72, N: 8.93; found C: 31.06, H: 7.48, N: 8.66.

(4-Amino-1-hydroxybuty)methylphosphinic acid hydrochloride (5).
Yield: 0.85 g (85 %), mp 201-203°C. ^{31}P-NMR (D_2O): 49,36 (m). ^{1}H-NMR (D_2O): 3.75 (dt, $^2J_{PH}$ = 10 Hz, $^3J_{HH}$ = 4 Hz, C<u>H</u>[OH]P), 2.98 (t, $^3J_{HH}$ = 7 Hz, 2H, CH_2N), 1.85 (m, 1H), 1.75 (m, 2H, CH_2), 1.58 (m, 1H), 1.40 (d, $^2J_{HP}$ = 14 Hz, CH_3P). ^{13}C-NMR (D_2O): 68.5 (d, $^1J_{PC}$ = 114 Hz, CH[OH]P), 39.0 (CH_2N), 26.3 (d, $^3J_{PC}$ = 4 Hz, CH_2), 23.4 (d, $^2J_{PC}$ = 13 Hz, CH_2), 10.4 (d, $^1J_{CP}$ = 89 Hz, CH_3P). FAB$^+$MS ($M+H^+$): 168.0 (calcd 168.1). Anal. ($C_5H_{14}NO_3P$·0.9HCl), calcd. C: 30.03, H: 7.50, N: 7.00; found C: 29.97, H: 7.20, N: 6.75.

4-Amino-2-hydroxybutylphosphinic acid hydrochloride (10).
Yield: 0.96 g (87%), mp 165-167°C. ^{31}P-NMR (H_2O, DMSO-d_6 ext. lock): 30.3 (ddt, $^1J_{PH}$ = 548Hz, $^2J_{PH}$ = $^3J_{PH}$ = 10 Hz). ^{1}H-NMR (D_2O): 7.0 (d, $^1J_{HP}$ = 548 Hz, 1H, PH), 4.08 (m, 1H, CH[OH]), 3.05 (t, $^3J_{HH}$ = 6 Hz, 2H, CH_2N), 1.95-1.50 (m, 4H, CH_2 + CH_2P). ^{13}C-NMR (D_2O): 64.3 (d, $^2J_{PC}$ = 2 Hz), 37.5, 36.5, 34.6 ($^1J_{PC}$ = 12 Hz). FAB$^+$MS ($M+H^+$): 154.1 (calcd 154.1). Anal. ($C_4H_{12}NO_3P$ HCl), calcd. C: 25.34, H: 6.91, N: 7.39; found C: 24.90, H: 6.81, N: 7.76.

(4-Amino-2-hydroxybutyl)methylphosphinic acid (11).
Recrystallization from abs. EtOH/propyleneoxide removed the HCl.
Yield: 0.25 g (74%), mp 159-162°C. ^{31}P-NMR (D_2O): 41.3 (m). ^{1}H-NMR (D_2O): 4.08 (m, 1H, C<u>H</u>[OH]), 3.10 (br. m, 2H, CH_2N), 2.00-1.70 (m, 4H, CH_2 + CH_2P), 1.23 (d, J = 13 Hz, 3H, CH_3P). ^{13}C-NMR (D_2O): 65.4 (<u>C</u>H[OH]CH_2P), 38.9 (d, $^1J_{PC}$ = 89 Hz, CH_2), 36.8 (CH_2N), 34.7 (d, $^3J_{PC}$ = 10 Hz, CH_2P), 10.7 (d, $^1J_{PC}$ = 93 Hz, CH_3P). FAB$^+$MS ($M+H^+$): 168.0. Anal. ($C_5H_{14}NO_3P$ ¼ H_2O), calcd. C: 34.99, H: 8.51, N: 8.16; found C: 34.88, H: 8.36, N: 8.01.

4-Amino-3-hydroxybutylphosphinic acid hydrochloride (14).
Yield: 0.4g (93%), mp 191-193°C. ^{31}P-NMR (H_2O, DMSO-d_6 ext. lock): 35.6, (dm, $^1J_{PH}$ = 525 Hz). ^{1}H-NMR (D_2O): 7.0 (dt, $^1J_{PH}$ = 525 Hz, $^3J_{HH}$ = 2 Hz, 1H, PH), 3.80 (m, 1H, C<u>H</u>[OH]), 3.05 and 2.90 (2m, 2H, CH_2N), 1.95-1.50 (m, 4H, CH_2 + CH_2P). ^{13}C-NMR) (D_2O): 67.5 (d, $^3J_{PC}$ = 20 Hz, <u>C</u>H[OH]), 44.0 (CH_2N), 25.3, 25.0 (d, $^1J_{PC}$ = 92 Hz, CH_2P). FAB$^+$MS ($M+H^+$): 154.0 (calcd 154.1). Anal. ($C_4H_{12}NO_3P$·HCl), calcd. C: 25.34, H: 6.91, N: 7.39; found C: 25.70, H: 6.74, N: 7.34.

(4-Amino-3-hydroxybutyl)methylphosphinic acid hydrochloride (15).
Yield: 0.25 g (63%), mp 184-186°C. ^{31}P-NMR (D_2O): 56.9 (m). ^{1}H-NMR (D_2O): 3.80 (m, 1H, C<u>H</u>[OH]), 3.05 and 2.90 (m, 2H, CH_2N), 1.95-1.60 (m, 4H, CH_2 + CH_2P), 1.45 (d, J = 14 Hz, 3H, CH_3P). ^{13}C-NMR (D_2O): 67.7 (d, $^3J_{PC}$ = 17 Hz, <u>C</u>H[OH]), 44.0 (CH_2N), 26.3 (d, $^2J_{PC}$ = 3 Hz, CH_2), 25.3 (d, $^1J_{PC}$ = 93 Hz, CH_2P), 13.5 (d, $^1J_{CP}$ = 90 Hz, CH_3P). FAB$^+$MS ($M+H^+$): 168.0 (calcd 168.1). Anal. ($C_5H_{15}ClNO_3P$), calcd. C: 29.50, H: 7.43, N: 6.88; found C: 29.30, H: 7.51, N: 6.83.

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