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Mechanism of Phosphorus–Carbon Bond Formation in the Amidoalkylation of Phosphonous Carboxylic Acids

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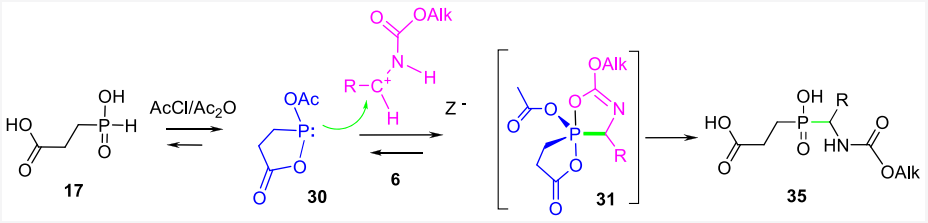


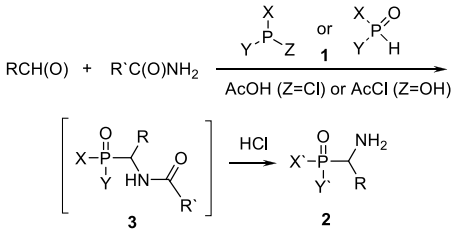
ABSTRACT: An unusual greater reactivity of phosphonous propionic acids was found in comparison with phosphonous propionic esters in carbamate version of Kabachnik–Fields reaction. Compounds of tricoordinated phosphorus generated *in situ* during the amidoalkylation of hydrophosphorylic compounds in acetyl chloride/acetic anhydride mixture were found by ^{31}P NMR analysis. A hypothesis is proposed about the generation of spirophosphoranes *in situ* to explain the mechanism for the formation of the phosphorus–carbon bond in the reaction under study.

INTRODUCTION

Studies of the carbamate version of the Kabachnik–Fields reaction in recent years indicate its growing preference over the amide and classical versions of this method for construction of the α-aminophosphorylic function.[1−3]

The amide version of the reaction for trivalent phosphorus chlorides **1** in acetic acid (Oleksyszyn reaction) was initially proposed with the aim for synthesis of α-aminoalkylphosphorylic compounds **2** (usually without isolation of N-protected amino acids **3**) (Scheme 1).[4]

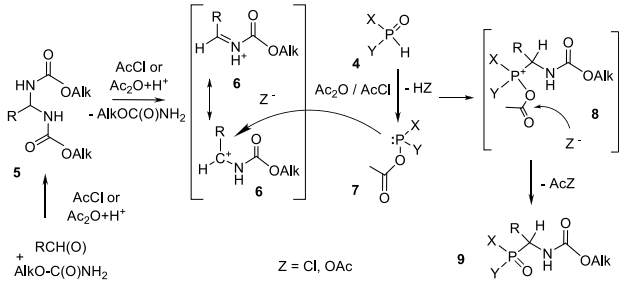
Scheme 1. Amide Version of the Kabachnik–Fields Reaction



The reaction was further modified into the amidoalkylation of dialkyl phosphites **1** in acetyl chloride or in a mixture of acetic acid and thionyl chloride with the participation of carbonyl compounds, amides (R′ = Alk), or carbamates (R′ = OAlk, Scheme 1).[5] Acetyl chloride and acetic anhydride are effective solvents for carrying out the three-component amide version of the Kabachnik–Fields reaction.[5−7]

The milder amidoalkylation conditions of hydrophosphorylic compounds **4** in acetic anhydride at room temperature compared to acetyl chloride made it possible to detect greater reactivity of alkyl carbamates in comparison with amides.[2] Under these conditions, for the first time, it was possible to isolate *N,N′*-alkylidenebiscarbamates **5** (Scheme 2) as stable intermediate reaction products.[2] Previously, related compounds, bisamides,[7] and amidoalkylacetates[8] have been proposed as intermediates in the Oleksyszyn reaction.

Scheme 2. Formation of Phosphorus–Carbon Bond by Arbuzov-Type Reaction



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Biscarbamates **5** are a source of acyliminium cations **6**, charged Schiff bases which are formed under conditions of acid catalysis and are highly reactive electrophilic component of the reaction (Scheme 2).[2,9] Intermediate **7**, containing a P^{III}−OAc anhydride fragment (Scheme 2), was proposed as nucleophilic component directly involved in the formation of a phosphorus−carbon bond.[2,9] It was confirmed by experiments with using presynthesized acetyldiethylphosphite and also tetraethylpyrophosphite for generation *in situ* of acetyldiethylphosphite.[10]

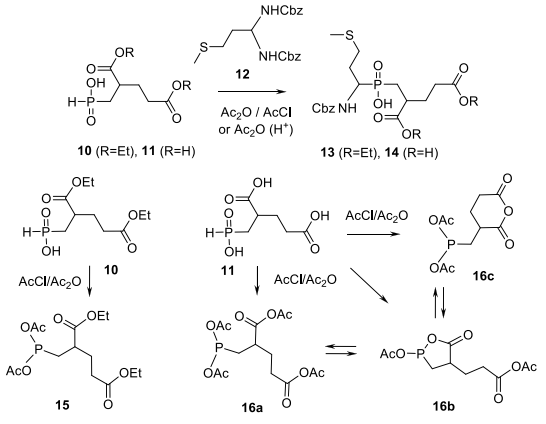
Thus, a phosphorus−carbon bond formation mechanism was proposed in accordance with the Arbuzov reaction resulting from a nucleophilic attack of acetyloxyderivative **7** on a positively charged carbon atom of iminium cation **6** (Scheme 2) which are generated *in situ* in AcCl/Ac_2O, from hydrophosphorylic compound **4** and *N,N′*-alkylidenebis(alkylcarbamate) **5**, respectively.[2,9] The transformation of formed phosphonium ion **8** with the subsequent formation of α-aminoalkylphosphorylic compound **9** proceeds in accordance with the second stage of the Arbuzov reaction (Scheme 2).

The amidoalkylation of hydrophosphorylic compounds, containing an isoster of amino acid, is a convenient approach to the synthesis of phosphinic pseudopeptides, which are structural analogues of natural peptides, in the molecule of which two amino acid components are linked by methylenephosphorylic $CH_2P(O)(OH)$ fragment that mimics the peptide NHC(O)−bond in the transition state of peptide hydrolysis with a tetra-coordinated carbon atom.[11] Therefore, phosphinic peptides are potent inhibitors of matrix metalloproteinases (MMPs), which are a family of zinc-containing endoproteases involved in diverse biological processes.[12]

The currently prevailing NP+C strategy for the synthesis of phosphinic dipeptides[11,12] is based on studies by Ciba-Geigy[13] devoted to methods for the synthesis of N,P-protected building blocks, which are phosphonous isosteres of natural amino acid. The Michael−Pudovik addition of the latter to the corresponding α-substituted acrylates leads to the formation of target phosphinic dipeptides.[11,12] We are developing a promising shorter N+PC strategy for the synthesis of phosphinic peptides with reverse order of construction of desired molecule,[2,9,14] which includes the step of amidoalkylation of phosphonous acids (PC-component), containing isostere of the corresponding amino acid, for example, glutamic acid **10** and **11** (Scheme 3). The using of corresponding aldehydes and carbamates or presynthesized *N,N′*-alkylidenebiscarbamates, for example, *N,N′*-methylthiopropylidene-bis(benzylcarbamate) **12** leads to the formation of *N*-protected aminophosphinic acids, for example, pseudomethionylglutamates **13** and **14** (Scheme 3).[15a] In accordance with this synthetic strategy, bis(acetyl)phosphonite **15** (Scheme 3), generated *in situ* from phosphonous PC-component **10**, is proposed as a nucleophilic component directly involved in the formation of a phosphorus−carbon bond by the Arbuzov-type reaction.[2,15] However, attempts for amidoalkylation of phosphonous acids **10** containing two ester functions using benzyl carbamate and methylthiopropionic aldehyde in accordance with the three-component carbamate version of the Kabachnik−Fields reaction unexpectedly proved to be less effective.[15a] Nonetheless, the use of presynthesized biscarbamate **12** allowed us to carry out the synthesis of pseudomethionylglutamate **14** by amidoalkylation of phosphonous dicarboxylic acid **11**.[15a] On the contrary, the use of phosphonous acid **10** containing ester groups showed lower results. The study for the synthesis of pseudoprolylglutamate by cyclic amidoalkylation of phosphonous acids **10** and **11** also showed the higher reactivity of diacid **11** compared to that of diester **10**.[15b,c]

We suggested that phosphonous dicarboxylic acid **11** is capable of generating three possible P^{III}−OAc intermediates, **16a,c**, *in situ* in AcCl/Ac_2O medium (Scheme 3).[15] In turn, diethyl ether **11** under these conditions can generate *in situ* only one intermediate, **15**, the nucleophilicity of which should be close to the nucleophilicity of intermediate **16a**. Therefore, the contribution to the reactivity of the PC-component is probably due to intermediates **16b** or **16c**. Previously, we assumed[15] that *in situ* generated intermediate **16c** containing a glutaric anhydride ring is source for a noticeable increase in the reactivity of PC-component **11**. In this regard, it is of interest to study the amidoalkylation of PC-component containing only one carboxylic function.

Scheme 3. Synthesis of Phosphinic Met−Glu−Peptide

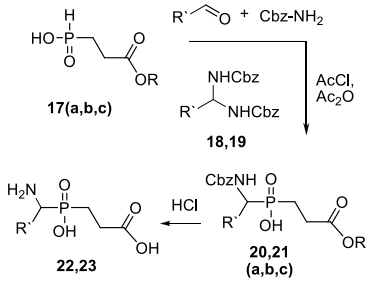


RESULTS AND DISCUSSION

This work is devoted to the study of the amidoalkylation of phosphonous PC-component **17** containing a glycine isoster and one carboxylic function in the form of esters and acid form (Scheme 4).

Two- and three-component reaction versions involving benzylcarbamate and isobutyric and isovaleric aldehydes or presynthesized *N,N′*-*i*-butylidene-bis(benzylcarbamate) **18** and *N,N′*-*i*-amylidene-bis(benzylcarbamate) **19** with the formation of phosphinic *N*-Cbz-pseudovalylglycines **20** and *N*-Cbz-

Scheme 4. Two- and Three-Component Carbamate Versions of the Kabachnik−Fields Reaction



R = H (a), Et (b), Bn (c); R`= i-Pr (18,20,22), i-Bu (19,21,23)

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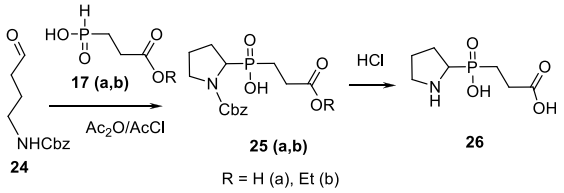
pseudoleucylglycines **21** were studied, and pseudopeptides **22** and **23** in free form were obtained (Scheme 4). Also, a two-component cyclic version of the reaction using 4-*N*-Cbz-aminobutyraldehyde **24** with the formation of phosphinic *N*-Cbz-pseudoprolylglycine **25** was studied, and free pseudoprolylglycine **26** was obtained (Scheme 5).

Scheme 5. Two-Component Cyclic Version of the Kabachnik–Fields Reaction



We found that amidoalkylation in AcCl and in a AcCl/Ac_2O mixture (1:1–3) at room temperature proceeds extremely rapidly; the formation of target phosphinic acids and the disappearance of starting phosphonous PC-component **17** occur within a few minutes. However, carrying out the reaction under milder conditions, in a mixture AcCl/Ac_2O (1:4–7), revealed higher reactivity of the PC-component containing an acidic carboxylic function as compared to the phosphonous component with an ester function (Supporting Information part 1).

This regularity was observed in the three-component version of amidoalkylation (compare entry 1 with entries 2 and 3 and entry 6 with entries 7 and 8 in Table 1) and in the two-component reaction of biscarbamates **18** and **19** with phosphonous acid **17a** and its esters **17b,c** (entries 4 and 5, as well as 9/10 and 11/12 in Table 1). A difference of reactivity of carboxylic acid **17a** and ester **17b** in the cyclic version of amidoalkylation was also noted (entries 13 and 14, also entries 15 and 16 in Table 1).

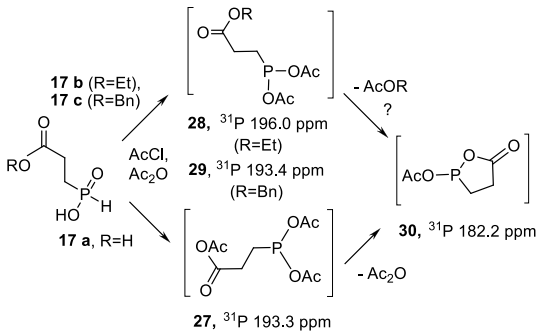
Table 1. Study of Amidoalkylation of Phosphonous Propionic Acid 17a and Its Esters 17b,c

entry	AcCl/Ac_2O (v)	electrophilic component	PC-component/product	time (h)[d]	conversion (%)[e]
1	1:4	*i*-Pr[a]	**17a/20a**	1.0	77
2	1:4	*i*-Pr[a]	**17b/20b**	2.0	46
3	1:7	*i*-Pr[a]	**17b/20b**	2.0	7
4	1:7	**18**[b]	**17a/20a**	2.0	85
5	1:7	**18**[b]	**17b/20b**	2.0	16
6	1:6	*i*-Bu[a]	**17a/21a**	3.0	70
7	1:6	*i*-Bu[a]	**17b/21b**	3.0	26
8	1:6	*i*-Bu[a]	**17c/21c**	3.0	14
9	1:4	**19**[b]	**17a/21a**	0.7	98
10	1:4	**19**[b]	**17c/21c**	0.7	75
11	1:7	**19**[b]	**17a/21a**	3.0	90
12	1:7	**19**[b]	**17c/21c**	3.0	55
13	1:4	**24**[c]	**17a/25a**	1.5	98
14	1:4	**24**[c]	**17b/25b**	1.5	76
15	1:6	**24**[c]	**17a/25a**	3.0	94
16	1:6	**24**[c]	**17b/25b**	3.0	59

[a]Three-component reaction version. [b]Two-component reaction version. [c]Cyclic reaction version. [d]The duration of the reaction, from the mixing of all reagents to the analysis of the mixture by ^{13}P NMR. [e]The content of reaction products in the reaction mixture was determined by using of integrating for signals in the range of 50–70 ppm of ^{13}P NMR spectrum (Supporting Information part 1).

In addition, at the initial stage of the reaction, we were able to fix the formation of bisacetylphosphonites **27–29** with characteristic peaks for derivatives of trivalent phosphorus in the region of 193–196 ppm (Scheme 6 and Supporting Information part 1).

Scheme 6. *In Situ* Generated POAc Derivatives of Phosphonous Carboxylic Acid 17a and Its Esters 17b,c



Moreover, we found that phosphonous propionic acid **17a**, in contrast to esters **17b,c**, is capable of generating two derivatives of three-coordinated phosphorus (Scheme 6). We assume that diacetylphosphonite **27** is *in situ* converted into cyclic phospholactone **30** with liberation of Ac_2O. The possible formation of lactone **30** from esters **17b,c** and then from phosphonites **28** and **29** with liberation of AcOR seems less likely that confirmed by the absence of significant quantity of dealkylated reaction products.

The nucleophilicity of diacetylphosphonite **27** generated from **17a** should not noticeably differ from the nucleophilicity of diacetylphosphonites **28** and **29**, which generated from ester PC-component, regardless of the ester radical (R). This can be explained by the close structure of these intermediates, which differ only the ester function at the periphery of the P^{III}-containing molecule, which can indirectly confirm by close chemical shifts of diacetylphosphonites **27–29** (δ_P 193–196 ppm).

It is very likely that phospholactone **30** (δ_P 182 ppm) may be responsible for increasing the reactivity of phosphonous propionic acid **17a** in comparison with phosphonous acids **17b,c** containing ester functions. Nevertheless, it seems difficult to explain the greater reactivity of lactone **30** compared to noncyclic acetylphosphonites **27–29**, based on the structural features of intermediates and their proposed nucleophilicity.

We propose a hypothesis of spirophosphorane formation to explain the results of this study. *N*-Protected phosphinic pseudopeptides are unique compounds containing both *β*-carboxylic function and *β*-carbamide fragments, which as shown earlier by Yiotakis and colleagues,[16,17] can facilitate the successful reaction at the phosphorylic center by *in situ* generating unstable phosphoranes[18] containing the corresponding five-membered cycles with participation of oxygen atoms of propionic[16] or carbamide functions.[17]

The apical-equatorial orientation of two five-membered rings in the trigonal-bipyramidal structure will be facilitated to the formation of spirophosphoranes **31** (Scheme 7). This corresponds to the rules of electronegativity of radicals,[19] as well as the rigidity of cycles[20] for compounds of five-

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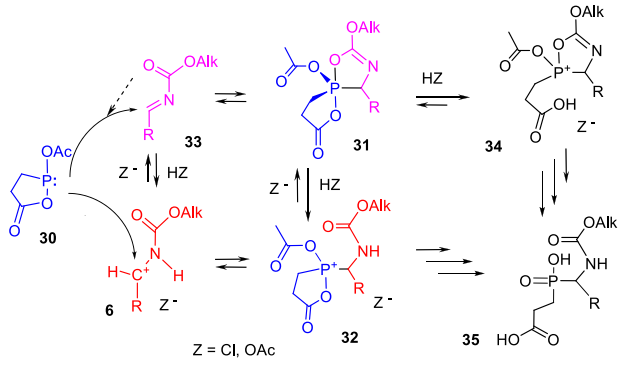
Scheme 7. Spirophosphorane Hypothesis in the Mechanism of Phosphorus−Carbon Bond Formation



coordinated phosphorus. We suggest that the formation of spirophosphoranes **31** is possible as result of nucleophilic attack of phospholactone **30** on charged Schiff cation **6** followed by the formation of phosphonium ion **32**, which can be converted to spirophosphorane **31**.

The formation of spirophosphoranes **31** can also occur as result of 1,4-cycloaddition of lactone **30** to the nitrogen analogue of α,β-unsaturated carbonyl compound, imine **33**, which in turn can be formed from Schiff cation **6** under the conditions of reaction (Scheme 7). It is known that cyclic esters of trivalent phosphorus acids react easily with α,β-unsaturated carbonyl compounds to form spirophosphoranes.[21]

It is likely that phospholactone **30** with a three-coordinated phosphorus atom may be more reactive in the 1,4-cycloaddition to *N*-alkyloxycarbonyl-imine **33** (Scheme 7) with the formation of spirophosphorane **31** compared to diacetylphosphonites **27**−**29**. Further transformation of spirophosphorane **31** can take place with the formation of phosphonium ions **32** or **34** or others related intermediates.

The general picture of possible transformations of unstable intermediates of the spirophosphorane structure can probably be more complicated by the existence of a spirophosphorane−bipolar structure equilibrium, formed during the reversible disclosure of the phospholene or phospholane cycles,[21,22] which are not shown in the scheme. Apparently, subsequent final breakdown of phosphorus−oxygen apical bonds of the spirophosphorane leads to formation of N-protected α-aminophosphinic propionic acids **35** (Scheme 7).

CONCLUSIONS

An unusually greater reactivity of phosphonous propionic acids was found in comparison with that of phosphonous propionic esters. Compounds of tricoordinated phosphorus generated *in situ* during the amidoalkylation of hydrophosphorylic compounds in a mixture of acetyl chloride and acetic anhydride were found. A hypothesis is proposed concerning the generation of unstable spirophosphoranes *in situ* to explain the mechanism for the formation of phosphorus−carbon bonds in the reaction under study.

EXPERIMENTAL SECTION

Materials and Methods. All reagents used in the reactions described in this manuscript are commercial, were purchased from Acros Organics Ltd., Aldrich Chemical Co. Ltd., and Alfa Aesar companies, and were used without additional purification. The exception is isobutyric and isovaleric aldehydes, which were used as freshly distilled. Reactions described in this paper were controlled using ^{31}P NMR spectroscopy and (or) thin layer chromatography (TLC). All of the compounds for which spectral and analytical data are given were gomogenous by TLC. Analytical TLC was carried out on silica-coated aluminum plates (silica gel Silufol-254, starch cohesive) using a UV light as visualizing agent (254 nm) and flame heat for control visualization. Chromatograms were visualized in iodine vapor; the analysis and visualization of the free amino phosphinic acids was carried out using ninhydrin solution. Column chromatography was performed on silica gel L100/160 (Chemapol) or silica gel 60 (Alfa Aesar) or silica gel 60 (Merck). All other reagents and solvents (acetic anhydride, acetyl chloride, dichloromethane, toluene, and others) were used dry. All reactions were performed under an atmosphere of argon with magnetic stirring. Melting points were determined on a Boetius PHMK apparatus or in open glass capillaries and are uncorrected.

^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer ^{31}P and ^{13}C NMR spectra are fully proton decoupled; an DEPT ^{13}C NMR experiment was carried out if necessary. ^{31}P NMR chemical shifts are reported on a δ scale (parts per million, ppm) downfield from 85% H_3PO_4. Tetramethylsilane (TMS) was used as an internal standard (^{1}H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.25 ppm, DMSO at 2.49 ppm, CH_3OD at 3.30 ppm, H_2O at 4.75 ppm; ^{13}C NMR: $CDCl_3$ at 77.00 ppm, DMSO-d_6 at 39.50 ppm, CD_3OD at 49.0 ppm).

Negative-mode high-resolution mass spectra (HRMS) were acquired using an Orbitrap Exactive (Thermofisher Scientific, Bremen) mass spectrometer. A custom-built electrospray ion source with the etched silica emitter was used,[23] the electrospray voltage was applied to the metal union connecting the plastic capillary with the silica emitter. The sample was injected via syringe pump with the flow rate of 1 μL/min. The samples were dissolved in acetonitrile at concentration ~1 mg/mL, with 0.5% formic acid, and then they were diluted in acetonitrile again 50-fold for the analysis. Mass spectra of all samples in the negative mode contained the (M − H) ion peaks; the measured m/z and the isotopic patterns were compared with the theoretical ones. The experimental m/z values for (M − H) peaks correspond to the theoretical calculated values; the discrepancies are <0.001 Da.

Synthesis of Starting Materials. Phosphonous acids (**17a**−**c**) were synthesized in according to the procedures reported earlier[14] with minor modifications.

2-Ethyloxycarbonyl-ethylphosphonous Acid ***17b***. Ammonium hypophosphite (24.9 g, 0.3 mol) and hexamethydisilazane (96.8 g, 0.6 mol) under argon atmosphere were stirred for 2 h at 130−140 °C on oil bath. Ethylacrylate (10.9 mL, 10.0 g, 0.1 mol) at 30−40 °C during 1−1.5 h was added slowly dropwise to the *in situ* formed bis(trimethylsilyl)hypophosphite. The reaction mixture was stirred at 25−40 °C for 5 h and then was cooled at 5−10 °C. A water−dioxane solution (25 mL, 1.4 mol of H_2O/10 mL of dioxane) was slowly added dropwise to the formed solution, and reaction mixture was evaporated *in vacuo*. The residue was partitioned between ethyl acetate (100 mL) and water solutions (50 mL, pH ~3). The water phase was additionally twice extracted with ethyl acetate (100 mL). Organic extracts were combined, dried over sodium sulfate, and evaporated *in vacuo*. A residue representing ester **17b** was isolated as colorless oil (23.7 g, 0.164 mol, 47% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 12.02 (s, 1H), 7.15 (d, $^{1}J_{PH}$ = 561.2 Hz, 1H), 4.11 (q, 2H), 2.45−2.70 (m, 2H), 1.90−2.15 (m, 2H), 1.22 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$) δ = 35.87. Anal. Calcd for $C_5H_{11}O_4P$;%: C, 36.15; H, 6.67; P, 18.65. Found: C, 35.84; H, 6.98; P, 18.37.

Phosphonous Propionic Acid, 2-Hydroxycarbonyl-ethylphosphonous Acid ***17a***. Hydrolysis of ethyl ester **17b** (10.0 g, 60.2 mmol) with 60 mL of 3 N HCl after 4 h reflux gave free phosphonous carboxylic acid **17a** as a very viscous, almost glassy substance in 95% yield (7.9 g). The spectral data of **17a** did not differ significantly from those previously published.[24] ^{1}H NMR (200 MHz, D_2O) δ = 6.95 (d, $^{1}J_{PH}$ = 558.6 Hz, 1H), 2.35−2.60 (m, 2H), 1.75−2.00 (m, 2H).

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$^{31}P\{^{1}H\}$ NMR (81 MHz, D_2O) δ = 36.49. Anal. Calcd for $C_3H_7O_4P$, %: C, 26.10; H, 5.11; P, 22.43. Found: C, 25.86; H 5.35; P, 22.17.

2-(Benzyloxycarbonyl)ethylphosphonous Acid ***17c.*** Synthesis of 2-(benzyloxycarbonyl)ethylphosphonous acid **17c** was carried out by the addition of *in situ* generated ammonium or potassium hypophosphite (0.3 mol) bis(trimethylsilyl)hypophosphite to a benzyl ester of acrylic acid (0.1 mol) in accordance with the above procedure for the synthesis of ethyl ester **17b**.[14]

Yield for **17c**: 17.3 g, 76%. Low-melting crystals, off-white. Mp 36−37 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 11.71 (s, 1H), 7.30−7.40 (m, 5H), 7.17 (d, $^{1}J_{PH}$ = 561.8 Hz, 1H), 5.12 (s, 2H), 2.55−2.80 (m, 2H), 1.90−2.20 (m, 2H). $^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$) δ = 35.70. $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ = 171.5 (d, $^{3}J_{PC}$ = 13.3 Hz), 135.3, 128.3, 128.1, 128.0, 66.5, 25.83 (d, $^{2}J_{PC}$ = 2.2 Hz), 24.12 (d, $^{1}J_{PC}$ = 95.5 Hz). Anal. Calcd for $C_{10}H_{13}O_4P$, %: C, 52.64; H, 5.74; P, 13.57. Found: C, 52.32; H, 5.96; P, 13.30.

General Synthesis of N,N′-Alkylidenebiscarbamates ***18*** *and* ***19.*** Synthesis of the title compounds was carried out in accordance with the procedure previously described,[9] with minor modification and simplification.

TFA (0.05 mmol) and the corresponding aldehyde (2.5 mmol) were then slowly added dropwise under stirring to a solution of benzyl carbamate (5.0 mmol) in acetic anhydride (5 mL) at room temperature. The stirring was continued for 10 h. Precipitated crystals were filtered off and were flushed with acetic anhydride (1−2 mL) and then petroleum ether (1−2 mL). Biscarbamates **18** and **19** were recrystallized from diethyl ether−ethanol mixture.

The yields and constants, as well as ^{1}H, ^{13}C, and ^{31}P NMR spectral data, of biscarbamates **18** and **19** did not differ significantly from those previously published.[9b]

4-(N-Benzyloxycarbonyl) aminobutyraldehyde ***24.*** The title compound was synthesized from 4-amino-butyraldehyde dimethyl acetal according to the acylation procedure previously described.[25]

Amidoalkylation of Phosphonous Acid ***17a*** *and Its Esters* ***17b,c.*** It should be noted that dried 2-hydroxycarbonyl-ethylphosphonous acid **17a** is a very viscous, almost glassy substance; it could not quickly dissolve in acetic anhydride. Only a mixture of acetic anhydride and acetyl chloride allowed **17a** to dissolve very fast.

Procedures for the Synthesis of Phosphinic Pseudopeptides. *General Procedure A (Three-Component Reaction Version).* The corresponding aldehyde (1.7 mmol, ∼1.1 equiv) in one portion and then immediately acetyl chloride (1−4 mL) were added to a stirred mixture of phosphonous propionic acid (**17a**), the ethyl ester (**17b**) (1.5 mmol), or the benzyl ester (**17c**) (1.5 mmol) phosphonous propionic acid and benzylcarbamate (1.5 mmol) in acetic anhydride (4−7 mL).

The resulting mixture was stirred for 1−2 h (in the case of acid **17a**) or for ∼20 h (in the case of esters **17b** and **17c**), and the progress of the reaction was monitored by ^{31}P NMR spectroscopy. After completion of the reaction, 10 mL of water was added to the reaction mass; the resulting mixture was stirred for 1 h and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (eluent: chloroform−methanol (or *i*-propanol) (from 2 to 10%).

General Procedure B (Two-Component Reaction Version). The corresponding *N,N′*-alkylidene-bis(benzylcarbamate) **18** or **19** (1.5 mmol) in one portion and then immediately 1−4 mL of acetyl chloride were added to a stirred mixture of phosphonous propionic acid (**17a**) (1.5 mmol), a solution of ethyl ester (**17b**) (1.5 mmol), or a solution of the benzyl ester (**17c**) (1.5 mmol) in 4−7 mL of acetic anhydride at room temperature. The resulting mixture was stirred for 1−2 h (in the case of acid **17a**) or for ∼20 h (in the case of esters **17b** and **17c**); the progress of the reaction was monitored by ^{31}P NMR spectroscopy. After completion of the reaction, 10 mL of water was added to the reaction mass; the resulting mixture was stirred for 1 h and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (eluent: chloroform−methanol (or *i*-propanol) (from 2 to 10%).

General Procedure C (Cyclic Two-Component Reaction Version). Phosphonous propionic acid (**17a**) (1.5 mmol) or the ethyl ester of phosphonous propionic acid (**17b**) (1.5 mmol) in one portion and immediately then acetyl chloride (1−4 mL) were added to the stirred solution of 4-(*N*-benzyloxycarbonyl)-aminobutyraldehyde **24** (1.5 mmol) in 4−7 mL acetic anhydride.

The resulting mixture was stirred for 1−2 h (in the case of acid **17a**) or for ∼20 h (in the case of ester **17b**), and the progress of the reaction was monitored by ^{31}P NMR spectroscopy. After completion of the reaction, 10 mL of water was added to the reaction mass, the resulting mixture was stirred for an hour and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (eluent: chloroform−methanol (or *i*-propanol) (2−7%).

Characterization of N-Protected Pseudopeptides 20, 21, and 25. N-Protected pseudodipeptides are a mixture of conformers. This is probably due to (a) the presence of a chiral carbon center of the aminophosphorylic fragment and (b) the presence of an amide nitrogen atom and the inhibition of free rotation of the *N*-Cbz fragment relative to the time scale of NMR. This manifests itself to varying degrees in the NMR spectra under various conditions. The presence of a five-membered pyrrolidine ring in the form of a nonplanar cycle introduces additional elements of asymmetry, manifested in the NMR spectra of proline-containing compounds. In this regard, the ^{1}H, ^{31}P, and ^{13}C spectra of *N*-Cbz-protected pseudopeptides were recorded in various solvents. Hereafter, signals marked with an asterisk refer to minor conformer forms.

1-(Benzyloxycarbonylamino)-2-methyl-propyl-2′-(hydroxycarbonyl)-ethylphosphinic Acid ***(20a).*** Yield: 0.23 g, 44% (procedure A); 0.32 g, 63% (procedure B). White solid; mp 164−167 °C. R_f = 0.10−0.15 ($CHCl_3$/EtOH ∼ 95:5). ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.48 (d, J = 10.2 Hz, 1H), 7.20−7.50 (m, 5H), 5.06 (AB − system, 2H), 3.45−3.70 (m, 1H), 2.25−2.50 (m, 2H), 2.0−2.25 (m, 1H), 1.65−1.95 (m, 2H), 0.85−1.00 (2d, J = 4.4 Hz, 6H). $^{31}P\{^{1}H\}$ NMR (81 MHz, DMSO-d_6) δ 47.26, 46.90*, 46.64*. $^{13}C\{^{1}H\}$ NMR (50 MHz, DMSO-d_6) δ 173.6 (d, J = 16.1 Hz), 156.7 (d, J = 5.5 Hz), 137.2, 128.4, 127.7, 127.4, 65.5, 55.0 (d, J = 104.7 Hz), 27.5, 26.4, 22.9 (d, J = 90.4 Hz), 20.8 (d, J = 8.1 Hz), 18.7 (d, J = 5.1 Hz). ^{1}H NMR (200 MHz, $CDCl_3$ + drop of TFA) δ 7.25−7.50 (m, 5 H), 6.61*(∼30%) (d, J = 9.8 Hz, 1H), 5.77 (∼70%) (d, J = 10.3 Hz, 1H), 5.21* (s, 2H), 5.16 (s, 2H), 3.90−4.25 (m, 1H), 2.50−2.90 (m, 2H), 1.90−2.45 (m, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 5.9 Hz, 3H). $^{31}P\{^{1}H\}$ NMR (81 MHz, $CDCl_3$ + drop of TFA) δ 59.03 (∼70%), 58.15* (∼30%). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$ + drop of TFA) δ 177.8 (d, J = 7.7 Hz), 158.3* (d, J = 2.4 Hz), 157.7 (d, J = 2.9 Hz), 135.2, 134.6*, 129.0, 128.8, 128.6, 128.5, 127.9, 69.1*, 68.4, 55.6* (d, J = 103.2 Hz), 54.5 (d, J = 105.4 Hz), 27.9*, 27.8, 26.1, 25.9*, 22.0 (d, J = 89.3 Hz), 21.8* (d, J = 89.7 Hz), 20.5* (d, J = 10.1 Hz), 20.4 (d, J = 10.3 Hz), 17.5 (d, J = 2.2 Hz), 17.3* (d, J = 1.9 Hz). Anal. Calcd for $C_{15}H_{22}NO_6P$;%: C, 52.48; H, 6.46; P, 9.02. Found: C, 52.18; H, 6.58; P, 8.70.

1-(Benzyloxycarbonylamino)-2-methyl-propyl-2′-(ethyloxycarbonyl)-ethylphosphinic Acid ***(20b).*** Yield 0.30 g, 54% (procedure A); 0.41 g, 73% (procedure B). White solid; mp 86−88°C. R_f = 0.15 ($CHCl_3$/$CO(CH_3)_2$ 4:1). ^{1}H NMR (200 MHz, CD_3OD) δ 7.20−7.45 (m, 5H), 5.12 (AB − system, 2H), 4.12 (q, 2H), 3.79 (dd, J = 5.1 Hz, 1H), 2.45−2.65 (m, 2H), 2.15−2.35 (m, 1H), 1.85−2.10 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H) 1.02 (d, J = 4.2 Hz, 3H), 1.00 (d, J = 4.7 Hz, 3H). $^{31}P\{^{1}H\}$ NMR (81 MHz, CD_3OD) δ 49.22, 48.43*. $^{13}C\{^{1}H\}$ NMR (50 MHz, CD_3OD) δ 173.9 (d, J = 15.7 Hz), 159.0 (d, J = 5.5 Hz), 138.2, 129.5, 129.0, 128.8, 67.9, 62.0, 56.1 (d, J = 106.1 Hz), 29.2 (d, J = 1.5 Hz), 27.6 (d, J = 2.6 Hz), 23.9 (d, J = 91.5 Hz), 21.2 (d, J = 9.1 Hz), 18.8 (d, J = 5.1 Hz), 14.5. ^{1}H NMR (200 MHz, $CDCl_3$ + drop TFA) δ 7.25−7.45 (m, 5H, Ph), 6.59* (∼35%) (d, J = 10.0 Hz, 1H, NH), 5.89 (∼65%) (d, J = 10.6 Hz, 1H), 5.21* (s, 2H), 5.15 (s, 2H), 3.90−4.30 (m, 3H), 2.55−2.90 (m, 2H), 2.00−2.50 (m, 3H), 1.95−2.45 (m, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.03 (d, J = 4.1 Hz, 3H), 1.00 (d, J = 5.3 Hz, 3H). $^{31}P\{^{1}H\}$ NMR δ (81 MHz, $CDCl_3$ + drop TFA) δ 57.32 (∼65%), 56.96* (∼35%). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$ + drop TFA) δ 175.0 (d, J = 9.2 Hz), 174.5*

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(35%) (d, J = 9.9 Hz), 158.4* (d, J = 5.2 Hz), 157.8 (d, J = 5.9 Hz), 135.1, 134.6*, 128.9, 128.8, 128.6, 128.5, 127.9, 69.2*, 68.4, 62.6, 62.5*, 55.5* (d, J = 104.7 Hz), 54.4 (d, J = 105.8 Hz), 27.9* (d, J = 1.4 Hz), 27.8 (d, J = 1.5 Hz), 26.4 (d, J = 5.5 Hz), 26.3* (d, J = 5.5 Hz), 22.0 (d, J = 87.7 Hz), 21.7* (d, J = 88.5 Hz), 20.5* (d, J = 11.1 Hz), 20.4 (d, J = 10.7 Hz), 17.5 (d, J = 4.1 Hz), 17.3* (d, J = 4.1 Hz), 13.7. Anal. Calcd for $C_{17}H_{26}NO_6P$, %: C, 54.98; H, 7.06; P, 8.34. Found: C, 54.80; H 7.23; P, 8.17.

*1-(Benzyloxycarbonylamino)-2-methyl-butyl-2′-(hydroxycarbonyl)ethylphosphinic Acid (**21a**).* Yield 0.28 g, 53% (procedure A); 0.38 g, 71% (procedure B). White solid; mp 183−185 °C. R_f = 0.15 ($CHCl_3$/EtOH ∼ 95:5). ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.52 (d, J = 9.1 Hz, 1H, NH), 7.20−7.40 (m, 5H), 5.04 (AB − system, 2H), 3.55−3.85 (m, 1H), 2.25−2.55 (m, 2H), 1.65−1.90 (m, 2H), 1.30−1.70 (m, 3H), 0.87 (d, J = 6.1 Hz, 3H), 0.80 (d, J = 6.1 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, DMSO-d_6) δ 47.40, 46.72*. ^{13}C{^{1}H} NMR (50 MHz, DMSO-d_6) δ 173.6 (d, J = 15.7 Hz), 156.2 (d, J = 4.0 Hz), 137.2, 128.4, 127.8, 127.5, 65.5, 48.2 (d, J = 106.5 Hz), 35.6, 26.4, 24.0 (d, J = 11.3 Hz), 23.3, 21.7 (d, J = 86.0 Hz), 20.8. ^{1}H NMR (200 MHz, CD_3OD) δ 7.20−7.45 (m, 5H), 5.10 (AB − system, 2H), 3.90−4.10 (m, 1H), 2.45−2.70 (m, 2H), 1.85−2.10 (m, 2H), 1.45−1.80 (m, 3H), 0.95 (d, J = 6.1 Hz, 3H), 0.89 (d, J = 6.1 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, CD_3OD) δ 51.54, 50.54*. ^{1}H NMR (200 MHz, $CDCl_3$ + drop of TFA) δ = 7.20−7.45 (m, 5 H), 6.47*(∼35%) (d, J = 9.8 Hz, 1H), 5.61 (∼65%) (d, J = 9.8 Hz, 1H), 5.23* (s, 2H), 5.15 (s, 2H), 4.10−4.35 (m, 1H), 2.60−2.90 (m, 2H), 2.00−2.35 (m, 2H), 1.40−1.85 (m, 3H), 0.96 (d, J = 6.1 Hz, 3H), 0.93* (d, J = 6.1 Hz, 3H), 0.88 (d, J = 6.1 Hz, 3H), 0.81* (d, J = 6.1 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$ + drop of TFA) δ 61.03, 60.47* (∼35%). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$ + drop of TFA) δ 178.8* (∼35%), 178.0, 158.1*, 157.4, 135.1, 134.4*, 129.1, 128.7, 128.0, 69.3*, 68.5, 49.2* (d, J = 105.8 Hz), 48.3 (d, J = 103.5 Hz), 36.0*, 35.7, 26.0, 25.85*, 24.3 (d, J = 10.6 Hz), 23.1, 23.0*, 20.8 (d, J = 91.1 Hz), 20.5* (d, J = 90.0 Hz), 20.59, 20.47*. Anal. Calcd for $C_{16}H_{24}NO_6P$, %: C, 53.78; H, 6.77; P, 8.67. Found: C, 53.56; H 6.95; P, 8.49. HRMS (ESI) calcd for $C_{16}H_{23}NO_6P$ m/z: [M − H]$^-$ 356.1258. Found 356.1248.

*1-(Benzyloxycarbonylamino)-3-methyl-butyl-2′-(ethyloxycarbonyl)-ethylphosphinic Acid (**21b**).* Yield: 0.32 g, 55% (procedure A); 0.36 g, 63% (procedure B). White solid; mp 110−112 °C. R_f = 0.2 ($CHCl_3$/$CO(CH_3)_2$ 4:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.69 (s, broad, 1H), 7.20−7.40 (m, 5H), 5.16 (d, J = 11.0 Hz, 1H), 5.10 (s, 2H), 4.12 (q, 2H), 3.95−4.20 (m, 1H), 2.45−2.70 (m, 2H), 1.90−2.15 (m, 2H), 1.40−1.80 (m, 3H), 1.22 (t, 3H), 0.93 (d, J = 5.9 Hz, 3H), 0.90 (d, J = 5.9 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$) δ 55.68, 54.33*. ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 172.2 (d, J = 15.4 Hz), 156.1 (d, J = 4.4 Hz), 136.2, 128.5, 128.2, 128.0, 67.3, 61.0, 47.7 (d, J = 106.5 Hz), 36.2, 26.3 (d, J = 2.6 Hz), 24.3 (d, J = 11.3 Hz), 23.4, 21.6 (d, J = 92.6 Hz), 21.04, 14.14. Anal. Calcd for $C_{18}H_{28}NO_6P$, %: C, 56.10; H, 7.32; P 8.04. Found: C, 55.83, 55.70; H, 7.54, 7.58; P 7.78, 7.74.

*1-(Benzyloxycarbonylamino)-3-methyl-butyl-2′-(benzyloxycarbonyl)-ethylphosphinic Acid (**21c**).* Yield: 0.34 g, 51% (procedure A); 0.45 g, 67% (procedure B). White solid; mp 105−107 °C. R_f = 0.2 ($CHCl_3$/$CO(CH_3)_2$ 4:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.19 (s, broad, 1H), 7.20−7.40 (m, 10H), 5.00−5.15 (m, 5H, $2CH_2$), 3.85−4.20 (m, 1H), 2.50−2.80 (m, 2H), 1.90−2.20 (m, 2H), 1.35−1.80 (m, 3H), 0.91 (d, J = 5.5 Hz, 3H), 0.89 (d, J = 6.1 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$) δ = 55.91, 54.58*. ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 171.9 (d, J = 16.1 Hz), 156.1 (d, J = 4.6 Hz), 136.1, 135.6, 128.7, 128.5, 128.2, 128.0, 67.2, 66.7, 47.7 (d, J = 106.6 Hz), 36.1, 26.3 (d, J = 2.3 Hz), 24.3 (d, J = 11.1 Hz), 23.4, 21.5 (d, J = 92.8 Hz), 21.0. ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ 129.2, 129.0, 128.7, 128.4, 67.7, 67.2, 48.1 (d, J = 106.5 Hz), 36.5, 26.8 (d, J = 2.7 Hz), 24.8 (d, J = 11.5 Hz), 23.9, 22.0 (d, J = 92.3 Hz), 21.5. ^{1}H NMR (200 MHz, $CDCl_3$ + drop TFA) δ 7.20−7.45 (m, 10H, Ph), 6.47* (∼30%) (d, J = 9.8 Hz, 1H), 5.72 (∼70%) (d, J = 9.8 Hz, 1H), 5.05−5.25* (m, 4H), 4.05−4.35 (m, 1H), 2.65−3.00 (m, 2H), 2.0−2.35 (m, 2H), 1.45−1.85 (m, 3H), 0.95 (d, J = 6.1 Hz, 3H), 0.93* (d, J = 5.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.80* (d, J = 6.7 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$ + drop of TFA) δ 59.91, 59.17*, 58.81*. Anal. Calcd for $C_{23}H_{30}NO_6P$, %: C, 61.74; H, 6.76; P 6.92. Found: C, 61.39; H, 6.91; P 6.98. HRMS (ESI) calcd for $C_{23}H_{29}NO_6P$ m/z: [M − H]$^-$ 446.1727. Found 446.1706.

*{1-(Benzyloxy)carbonyl)pyrrolidin-2-yl}-(2′-hydroxycarbonyl)-ethylphosphinic Acid (**25a**).* Yield: 0.28 g, 54% (procedure C); pale yellow oil; R_f = 0.2 ($CHCl_3$/EtOH ∼ 95:5). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.80−9.30 (s, broad, 2H), 7.20−7.45 (m, 5H, Ph), 5.11 (AB − system, 2H), 4.05−4.25 (m, 1H), 3.25−3.75 (m, 2H), 1.45−2.90 (m, 8H). ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$) δ 55.08, 54.39*. ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 176.2 (d, J = 12.3 Hz), 156.0, 155.0*, 136.1, 136.0*, 128.5, 128.2, 127.9, 67.7, 67.0*, 55.7 (d, J = 108.1 Hz), 55.6* (d, J = 107.7 Hz), 47.2, 26.4, 26.1*, 25.5, 24.6, 23.0 (d, J = 88.6 Hz), 22.7* (d, J = 92.4 Hz). Anal. Calcd for $C_{15}H_{20}NO_6P$, %: C, 52.79; H, 5.91; N, 4.10. Found: C, 52.54, 52,60; H, 6.12, 6.23; N, 4.00, 3.78.

*{1-(Benzyloxy)carbonyl)pyrrolidin-2-yl}-(2′-ethyloxycarbonyl)-ethylphosphinic Acid (**25b**).* Yield: 0.35 g, 63% (procedure C); pale yellow oil. Physicochemical and spectral data of phosphinic *N*-Cbz-Pro-Gly-OEt **25b** did not differ significantly from those previously published.[15c]

The acid hydrolysis of corresponding N-protected aminophosphinic acids **20**, **21**, and **25** (1 mmol) was carried out by refluxing with 5 mL of 6 N HCl for 7−10 h. The subsequent evaporation of reaction mixture and treatment of residue with propylene oxide in aqueous ethanol made it possible to isolate aminophosphinic acids−pseudodipeptides **22**, **23**, and **26** in the free form.

Characterization of Aminophosphinic Acids 22, 23, and 26. *1-Amino-2-methylpropyl-2′-(hydroxycarbonyl)-ethylphosphinic Acid (**22**).* Yield: 0.16 g, 76%; white solid; mp 184−186 °C. ^{1}H NMR (200 MHz, D_2O) δ 2.80−3.20 (m, 1H), 2.40−2.65 (m, 2H), 2.10−2.30 (m, 1H), 1.75−2.00 (m, 2H), 1.03 (d, J = 7.3 Hz, 3H), 0.99 (d, J = 7.9 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, D_2O) δ 34.73. ^{13}C{^{1}H} NMR (50 MHz, D_2O) δ 177.5 (d, J = 15.0 Hz), 55.7 (d, J = 91.5 Hz), 26.9, 26.8, 24.4 (d, J = 95.9 Hz), 20.1 (d, J = 6.2 Hz), 17.9 (d, J = 5.1 Hz). Anal. Calcd for $C_7H_{16}NO_4P$, %: C, 40.19; H, 7.71; N, 6.70. Found: C, 39.84; H, 7.99; N, 6.55. HRMS (ESI) calcd for $C_7H_{15}NO_4P$ m/z: [M − H]$^-$ 208.0733. Found 208.0730.

*1-Amino-3-methylbutyl-2′-hydroxycarbonyl)-ethylphosphinic Acid (**23**).* Yield: 0.18 g, 81%, white solid; mp 179−181 °C. ^{1}H NMR (200 MHz, D_2O) δ 3.05−3.25 (m, 1H), 2.40−2.60 (m, 2H), 1.70−1.95 (m, 2H), 1.40−1.70 (m, 3H), 0.86 (d, J = 5.9 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{31}P{^{1}H} NMR (81 MHz, D_2O) δ 35.93. ^{13}C{^{1}H} NMR (50 MHz, D_2O) δ 177.2 (d, J = 14.4 Hz), 48.3 (d, J = 92.9 Hz), 36.1, 26.5 (d, J = 3.7 Hz), 24.0 (d, J = 8.9 Hz), 22.6 (d, J = 95.5 Hz), 22.3, 20.0. Anal. Calcd for $C_8H_{18}NO_4P$, %: C, 43.05; H, 8.13; N, 6.28. Found: C, 42. 90; H, 8.33; N, 6.14. HRMS (ESI) calcd for $C_8H_{17}NO_4P$ m/z: [M − H]$^-$ 222.0890. Found 222.0886.

*Pyrrolidin-2-yl)-2′-(hydroxycarbonyl)-ethylphosphinic Acid (**26**).* Yield: 0.13 g, 63%; white solid; mp 186−187 °C. ^{1}H NMR (200 MHz, D_2O) δ 3.35−3.60 (m, 1H), 3.10−3.35 (m, 2H), 2.35−2.65 (m, 2H), 1.60−2.30 (m, 6H). ^{31}P{^{1}H} NMR (81 MHz, D_2O) δ 33.86, 32.32*. ^{13}C{^{1}H} NMR (50 MHz, D_2O) δ 177.2 (d, J = 14.4 Hz), 56.5 (d, J = 92.9 Hz), 47.1 (d, J = 4.8 Hz), 26.7 (d, J = 3.3 Hz), 25.3, 24.1 (d, J = 96.9 Hz), 23.9 (d, J = 7.0 Hz). Anal. Calcd for $C_7H_{14}NO_4P$, %: C, 40.58; H, 6.81; N, 6.76. Found: C, 40.21; H, 6.98; N, 6.51. HRMS (ESI) calcd for $C_7H_{13}NO_4P$ m/z: [M − H]$^-$ 206.0577. Found 206.0572.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02259.

Supporting Information part 1: General experimental procedures; synthesis of the starting compounds; amidoalkylation of phosphonous propionic acid **17a** and its carboxylic esters **17b,c**; general procedures for the synthesis of phosphinic pseudopeptides **20**, **21**, and

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25; NMR ^{31}P spectral study for the amidoalkylation of phosphonous acids **17a−c**, including ^{31}P NMR spectra of reaction mixtures (PDF)

Supporting Information part 2: ^{1}H, ^{13}C, and ^{31}P NMR spectra of starting compounds and pseudopeptides **20−23**, **25**, and **26**; HRMS spectral data and also (PDF)

FAIR data, including the primary NMR FID files, for compounds **20a**, **20b**, **21a**, **21b**, **21c**, **22**, **23**, **25a**, **26** (ZIP)

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Notes

The authors declare no competing financial interest.

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