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One-Pot and Catalyst-Free Transformation of N-Protected 1-Amino-1-Ethoxyalkylphosphonates into Bisphosphonic Analogs of Protein and Non-Protein α-Amino Acids

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Abstract: Herein, we describe the development of one-pot transformation of α-ethoxy derivatives of phosphorus analogs of protein and non-protein α-amino acids into biologically important N-protected 1-aminobisphosphonates. The proposed strategy, based on the three-component reaction of 1-(N-acylamino)-1-ethoxyphosphonates with triphenylphosphonium tetrafluoroborate and triethyl phosphite, facilitates good to excellent yields under mild reaction conditions. The course of the reaction was monitored by 31P NMR spectroscopy, allowing the identification of probable intermediate species, thus making it possible to propose a reaction mechanism. In most cases, there is no need to use a catalyst to provide transformation efficiency, which increases its attractiveness both in economic and ecological terms. Furthermore, we demonstrate that the one-pot procedure can be successfully applied for the synthesis of structurally diverse N-protected bisphosphonic analogs of α-amino acids. As shown, the indirect formation of the corresponding phosphonium salt as a reactive intermediate during the conversion of 1-(N-acylamino)-1-ethoxyphosphonate into a 1-aminobisphosphonate derivative is a crucial component of the developed methodology.

Keywords: α-aminobisphosphonates; α-ethoxyphosphonates; phosphonium salts; N-acylimidates; Michaelis–Becker reaction; Michaelis–Arbuzov reaction

1. Introduction

1-(N-Acylamino)alkylene-1,1-bisphosphonates belong to the group of geminal 1-amino-1,1-bisphosphonates (ABPs), and they are characterized by the presence of the P-C(N)-P skeleton. In addition to being synthetic analogs of inorganic pyrophosphate, which is a regulator of calcium metabolism in living organisms, these compounds are considered as structural analogs of α-aminophosphonic acids, which are phosphorus equivalents of α-amino acids [1]. It is known that α-aminophosphonic acids exhibit significant biological activity, including anti-viral, anti-bacterial, anti-inflammatory, and anti-tumor, are potent enzyme inhibitors, and act as herbicides and regulators of plant growth [2–5]. Their functionalization with an additional phosphonyl group results in the formation of 1-amino-1,1-bisphosphonates (Figure 1a), the activity of which is even stronger, due to the presence of a P-C-P backbone, which has a documented affinity for hydroxyapatite and is resistant to enzymatic hydrolysis [6]. The above factors determine the biological properties of ABPs and the wide range of applications associated therewith.
Along with 1-hydroxy-1,1-bisphosphonates, ABPs are a potent inhibitors of bone resorption used in clinical practice in the treatment of diseases such as osteoporosis, Paget’s disease, or hypercalcemia [7,8]. An example of this is cycloheptylaminomethylene-1,1-bisphosphonate, which is a representative of the latest generation of anti-osteoporotic drugs, commercialized as Indacronate [9]. In addition to anti-resorptive activity, ABPs also show other useful properties, including anti-bacterial [10], anti-viral [11], anti-parasitic [12,13], and herbicidal [14], which provides evidence of their continued development as therapeutics and plant protection agents (Figure 1b). Clinical trials have been conducted on the use of ABPs in oncological therapy, especially immunotherapy [15]. Moreover, thanks to their high affinity for hydroxyapatite and the presence of the amino group in the α position, which enables their further structural modification, they have also become of interest for new drug delivery systems to bone tissue. This is achieved by the formation of conjugates with pharmacological agents, such as radioisotopes, anti-inflammatory drugs, proteins, and agents intended for augmentation of systemic bone mass or antibiotics. The conjugates of ABPs with cytostatics appear to be particularly promising, and they are being tested for their potential use in targeted anti-cancer therapies [16,17]. The high affinity for mineralized tissues is also utilized in the synthesis of new diagnostic agents that enable the imaging of bone tissue by MRI or PET, which is an interesting alternative to the currently used scintigraphy [18]. Great potential for application as a contrast agent in MRI imaging is demonstrated by the complex of the BPAMD ligand with gadolinium, containing a fragment of ABP as a “bone-seeking” moiety (Figure 1b) [19]. The chelating properties of some ABPs are also used to remove radioactive metallic toxins from water or blood [20], as well as for the functionalization of the surface of supermagnetic iron oxide nanoparticles (SPION) used in MRI [18].

Due to the important applications of ABPs, the development of a general and efficient method for their synthesis, or the improvement of previous synthetic methods, still attracts much attention. Currently, there is a range of different methods for the preparation of ABPs. However, they are often utilized for the simplest representatives of this group of compounds, i.e., derivatives of ABPs containing only hydrogen and a variously substituted amino group at the central carbon atom. Among the known methods for the synthesis of ABPs, the following should be mentioned: three-component condensation of amines with dialkyl phosphites in the presence of ethyl orthoformate [21–23], Beckmann rearrangement of oximes in the presence of phosphites by using POCl₃ as a promoter [24], prolonged heating of nitriles with excess phosphoric acid in the presence of phosphorus trichloride and anhydrous benzenesulfonic acid [12], bisphosphonylation of amides

Figure 1. (a) Comparison of the structures of α-amino acid, α-aminophosphonic acid and α-aminobisphosphonic acid. (b) Representative examples of α-aminobisphosphonates with medical applications.
using diethyl phosphite in the Tf$_2$O-activated reaction in the presence of 2,6-lutidine as a base [25], double hydrophosphonylation of nitriles with dialkyl phosphites mediated by titanocene/propylene oxide [26], or ZnCl$_2$/Et$_3$N system [20], as well as nickel-catalyzed double hydrophosphonylation of aromatic nitriles with trialkyl phosphites assisted by Et$_3$B as a reaction promoter [27]. Most of these synthetic strategies, especially those using unreactive nitriles, are carried out under harsh reaction conditions and in the presence of catalytic systems or mediators (often hazardous agents). What is more, as the side chains attached to the α carbon have a significant influence on the biological activities [8,28], it seems that the purposeful synthesis of functionalized α-aminobisphosphonate derivatives is of big importance in the search for compounds with a desirable biomedical profile. This is especially true of such models with the substituents at the α-position identical with those characteristic for natural α-amino acids, both protein and non-protein. The development of a general method for the synthesis of ABPs, providing structural diversity of the product and performed under mild, preferably catalyst-free reaction conditions, is thus highly sought after.

Recently, we have focused our efforts on developing a new synthetic procedure that allows access to not only α-aminobisphosphonic acids derivatives but also to their asymmetrical analogs. This allows the scope of applicability to be extended and thus the universality of the proposed method for synthesis of bisphosphorus organic compounds. Because each of the phosphorus groups is introduced separately into the final molecule, it has been found that phosphorus analogs of α-amino acids functionalized with a nucleofugal group at the α position are convenient substrates for this type of transformation. To the best of our knowledge, there are only a few reports on the preparation of tetraethyl 1-(N-acylamino)alkylene-1,1-bisphosphonates in the Michaelis–Arbuzov-type reaction of triethyl phosphate with diethyl 1-(N-acylamino)alkylphosphonates containing a nucleofugal group at the α-position. Despite the presence of the N-acylalino group and the dialkoxyphosphoryl group with an electron-withdrawing inductive effect, this type of functionalization of 1-(N-acylamino)alkylphosphonates is necessary to display the electrophilicity of their α-carbon required for further reaction. Thus, only one example of this type of transformation has been reported in the literature involving diethyl 1-(N-benzoylamino)bromomethylphosphonate synthesized by photochemical bromination of the starting 1-(N-benzoylamino)methylphosphonate with NBS [29]. The subsequent Michaelis–Arbuzov-type reaction of diethyl 1-(N-benzoylamino)bromomethylphosphonate with trimethyl and triethyl phosphites provided the expected 1-(N-benzoylamino)methylene-1,1-bisphosphonates in a yield of 56–90% (Scheme 1).

Other substrates that have been used in this reaction in the presence of Hüning’s base and methyltriphenylphosphonium iodide as catalysts are diethyl 1-(N-acetylamino)-1-triphenylphosphonomiumalkylphosphonate tetrafluoroborates 4, which can be considered as α-functionalized triphenylphosphonium derivatives of 1-(N-acetylamino)alkylphosphonates [30]. The starting phosphonium salts 4 were synthesized here from diethyl 1-aminoalkylphosphonates readily available from N-acyl-α-amino acids [31,32] by initially subjecting them to electrochemical oxidation to introduce the nucleofugal methoxy group into the α-position, which was followed by nucleophilic substitution of the obtained diethyl 1-(N-acetylamino)-1-methoxyalkylphosphonates with triphenylphosphonium tetrafluoroborate (Scheme 1, pathway a). The biggest limitation of this transformation is the electrochemical oxidation step, which was efficiently performed for only two of the simplest models of phosphorus analogs of α-amino acids, namely for the derivative of glycine and alanine, having at the α-position a hydrogen atom or a methyl group, respectively. Attempts to perform this process for the phosphorus analogs of valine and phenylalanine have failed, possibly due to a steric hindrance of the bulky substituent at the α-position.
Scheme 1. Synthetic routes for the synthesis of tetraethyl 1-(N-acylamino)alkylene-1,1-
bisphosphonates from α-functionalized derivatives of phosphorus analogs of α-amino
acids, such as diethyl 1-(N-benzoylamino)bromomethylphosphonate [29] and diethyl
1-(N-acetylamino)-1-triphenylphosphoniumalkylphosphonate tetrafluoroborates 4 obtained
from α-methoxyphosphonates (pathway a) [30] or α-ethoxyphosphonates (pathway b) [33].

To overcome this problem, we looked for a different method of obtaining α-alkoxy
derivatives of diethyl α-aminophosphonates with the result of the development of another
procedure for the preparation of diethyl 1-(N-acylamino)-1-ethoxyalkylphosphonates 3
obtained in a Michaelis–Becker-type reaction of ethyl N-acylimidates 2 with diethyl phosphite
(Scheme 1, pathway b) [33]. This opened up the wider applicability of this method,
since the electrochemical oxidation step required in the previous transformation is omitted
in this case, while the starting N-acylimidates 2 are readily available from the well-known
class of chemical compounds, i.e., ethyl imidate hydrochlorides 1 [34,35]. We then
converted 1-(N-acylamino)-1-ethoxyalkylphosphonates 3 into diethyl 1-(N-acylamino)-1-
triphenylphosphoniumalkylphosphonate tetrafluoroborates 4, whose utility in the synthesis
of tetraethyl 1-(N-acylamino)alkylene-1,1-bisphosphonates 5 has so far been de-
scribed for only three models of α-ethoxy derivatives of diethyl alkylphosphonates 3,
such as phosphorus analogs of glycine, alanine and phenylglycine, which have the amino
group protected with selected acyl groups (acetyl or phenylacetyl). The target tetraethyl
1-(N-acylamino)alkylene-1,1-bisphosphonates 5 were synthesized here in the Michaelis–
Arbuzov-type α-amidoalkylation reaction of triethyl phosphite with the previously ob-
tained phosphonium salts 4 in a double catalytic system in the presence of methyltriph-
henylphosphonium iodide and Hüning’s base.

In a continuation of our efforts to improve the recently developed procedure for the
preparation of organobisphosphorus compounds, and hoping that it has the potential

In our previous works:

- pathway a: 2 examples, 70–75% yield, R^2 = H, Me
  - 1. SiO_2-Pip, MeOH
  - 2. Ph_3P-HBF_4
  - SiO_2-Pip - silica gel-supported piperidine
  - PG - protecting group (Ac)

- pathway b: 3 examples, 43–73% yield, R^1 = Me, CH_2Ph, R^2 = H, Me, Ph
  - 1, SiO_2-Pip, MeOH
  - 2. Ph_3P-HBF_4
  - SiO_2-Pip - silica gel-supported piperidine
  - PG - protecting group (Ac)

This work:

- pathway a: 2 examples, 70–75% yield, R^2 = H, Me
  - 1. SiO_2-Pip, MeOH
  - 2. Ph_3P-HBF_4
  - SiO_2-Pip - silica gel-supported piperidine
  - PG - protecting group (Ac)

- pathway b: 3 examples, 43–73% yield, R^1 = Me, CH_2Ph, R^2 = H, Me, Ph
  - 1. SiO_2-Pip, MeOH
  - 2. Ph_3P-HBF_4
  - SiO_2-Pip - silica gel-supported piperidine
  - PG - protecting group (Ac)

- pathway c: 14 examples, 40–95% yield
  - 1. SiO_2-Pip, MeOH
  - 2. Ph_3P-HBF_4
  - SiO_2-Pip - silica gel-supported piperidine
  - PG - protecting group (Ac)
to become a general method for the synthesis of ABPs, we report an efficient, catalyst-
free one-pot transformation of $\alpha$-ethoxyaminophosphonate derivatives into tetraethyl
1-(N-acylamino)alkylene-1,1-bisphosphonates possessing at the $\alpha$ position a side chain
identical with those characteristic for natural $\alpha$-amino acids, both protein and non-protein
(Scheme 1, pathway c).

2. Results and Discussion

2.1. Optimization of Conditions for the Synthesis of $\alpha$-Ethoxy Derivatives of Phosphorus Analogs
of $\alpha$-Amino Acids

The starting diethyl 1-(N-acylamino)-1-ethoxyalkylphosphonates (Table 1, 3a–n) were
synthesized according to a previously described two-step protocol with some modifications
(Scheme 2) [33]. The general procedure consists of acylation of the imidate hydrochloride
1 with an acyl chloride (Step 1) and the Michaelis–Becker-like addition of diethyl phosphite
to ethyl N-acylimidate 2 (Step 2).

| Entry | Comp. 3 | PG | $R^2$ | Nu (eq.) | Time [days] | Temperature [$^\circ$C] | Yield |
|-------|---------|----|-------|---------|-------------|------------------------|-------|
| 1     | 3a      | Cbz | Me    | 1.2     | 2           | rt                     | 94    |
| 2     | 3b      | Piv | Me    | 1.2     | 3           | rt                     | 74    |
| 3     | 3c      | Cbz | H     | 1.2     | 2           | $-10$                  | 93    |
| 4     | 3d      | Cbz | CH$_2$Ph | 2     | 4           | $-20$                  | 88    |
| 5     | 3e      | Ac  | CH$_2$Ph | 1.2   | 4           | rt                     | 53    |
| 6     | 3f      | Cbz | Et    | 1.2     | 3           | $-5$                   | 82    |
| 7     | 3g      | Cbz | Pr    | 2       | 4           | $-10$                  | 68    |
| 8     | 3h      | Cbz | i-Pr  | 2       | 7           | $-40$                  | 53    |
| 9     | 3i      | Cbz | Bu    | 2       | 4           | $-10$                  | 54    |
| 10    | 3j      | Cbz | i-Bu  | 3       | 7           | $-40$                  | 32    |
| 11    | 3k      | Ac  | i-Bu  | 2       | 7           | $-40$                  | 65    |
| 12    | 3l      | Cbz | CH$_2$OMe | 1.2   | 4           | $-10$                  | 91    |
| 13    | 3m      | Cbz | Ph    | 1.2     | 3           | rt                     | 82    |
| 14    | 3n      | Cbz | 1,4-CH$_2$-C$_6$H$_4$OMe | 3     | 3           | $-25$                  | 70    |

1 Reaction conditions: diethyl N-acylimidate 2 (1 eq.), diethyl phosphite (1.2–3.0 eq.), 18-crown-6 (0.12 eq.), K$_2$CO$_3$
(1.35 eq.), hexane. 2 Isolated yield.

These modifications in the acylation step of ethyl imidate hydrochlorides 1, most often
with benzyl chloroformate, require a different base for this reaction (hitherto, Et$_3$N has
been used in the acylation reaction with acetyl chloride). This change was introduced
following optimization studies to select an appropriate base to improve the efficiency of
acylation, and sometimes even allow it to be carried out, taking into account the key role
of the base environment in this reaction. Since the use of Et$_3$N in the acylation reaction of
ethyl acetimidate hydrochloride 1a with benzyl chloroformate was unsuccessful (Scheme 2,
entry 1), 2,4,6-collidine and (i-Pr)$_2$EtN (Hünig’s base) were used as bases for this reaction.
When the weaker aromatic base such as 2,4,6-collidine was used, the expected reaction took
place with the product being isolated in a moderate yield of 55% (entry 2). Therefore, we
tried to perform the same reaction using Hünig’s base with comparable strength to Et$_3$N
but non-nucleophilic in nature to prevent side reactions. This facilitated a higher yield of
90% for the acylation product (entry 3). The lack of nucleophilic character of Hünig’s base
can be explained by the presence of two sterically extended isopropyl groups. Based on this
successful result, the acylation reactions for all the remaining ethyl imidate hydrochlorides
with benzyl chloroformate were carried out with the use of this base (Scheme 2), except for
the 2-methoxyacetimidate hydrochloride 11 which, in the case of 2,4,6-collidine, proved to
be much more effective (entry 15).
As for the second step of the synthesis of 1-(N-acylamino)-1-ethoxyalkylphosphonates 3, i.e., the nucleophilic addition of diethyl phosphate to ethyl N-acylimidates 2 in the Michaelis–Becker-like reaction, the modification was required to improve its efficiency. For most of the synthesized models, especially those with an amine group protected with a Cbz group, the Michaelis–Arbuzov-type reaction with triethyl phosphite [30]. Therefore, to increase the electrophilicity of this position, it was necessary to convert α-ethoxyphosphonate 3 to the corresponding phosphonium salt 4, which is much more reactive and thus susceptible to subsequent reaction with the nucleophilic triethyl phosphate. To better understand the reaction mechanism for the preparation of diethyl 1-(N-acylamino)-1-triphenylphosphoniumalkylphosphonate tetrafluoroborates 4 from 1-(N-acylamino)-1-ethoxyalkylphosphonates 3, we attempted the synthesis of another model phosphonium salt from the α-ethoxy derivative of the

| Entry | Imidate 2 | R¹ | R² | Base          | Yield ² [%] |
|-------|-----------|----|----|---------------|------------|
| 1     | 2a        | OCH₃Ph | Me | Et₃N         | –          |
| 2     | 2a        | OCH₃Ph | Me | 2,4,6-collidine | 55         |
| 3     | 2a        | OCH₃Ph | Me | (i-Pr)₂EtN   | 90         |
| 4     | 2b        | –Bu  | Me | Et₃N         | 80         |
| 5     | 2c        | OCH₃Ph | H | (i-Pr)₂EtN   | 34         |
| 6     | 2d        | OCH₃Ph | CH₃Ph | (i-Pr)₂EtN | 88         |
| 7     | 2e        | Me    | CH₃Ph | Et₃N     | 85         |
| 8     | 2f        | OCH₃Ph | Et | (i-Pr)₂EtN   | 80         |
| 9     | 2g        | OCH₃Ph | Pr | (i-Pr)₂EtN   | 95         |
| 10    | 2h        | OCH₃Ph | i-Pr | (i-Pr)₂EtN | 79         |
| 11    | 2i        | OCH₃Ph | Bu | (i-Pr)₂EtN   | 91         |
| 12    | 2j        | OCH₃Ph | i-Bu | (i-Pr)₂EtN | 99         |
| 13    | 2k        | Me    | i-Bu | 2,4,6-collidine | 63         |
| 14    | 2k        | Me    | i-Bu | (i-Pr)₂EtN   | 99         |
| 15    | 2l        | OCH₃Ph | CH₃OMe | 2,4,6-collidine | 74         |
| 16    | 2m        | OCH₃Ph | Ph | (i-Pr)₂EtN   | 58         |
| 17    | 2m        | OCH₃Ph | 1,4-CH₂-C₆H₄OMe | (i-Pr)₂EtN | 98         |

1 Reaction conditions: imidate hydrochloride 1 (1 eq.), base (2.2 eq.), acyl chloride (1 eq.), CHCl₃, Ar atmosphere, rt. ² Isolated yield. ³ Hünig’s base (2.1 eq.) was dosed in two equal portions, before and after the addition of benzyl chloroformate (1.25 eq.). ⁴ Toluene was used as a solvent.

Scheme 2. Two-step synthesis of 1-(N-acylamino)-1-ethoxyalkylphosphonates from ethyl imidate hydrochlorides and yields of acylation of ethyl imidate hydrochlorides 1 with acid chlorides in a presence of selected bases.

2.2. Development of an Optimized One-Pot Procedure for the Synthesis of Bisphosphonate Analogs of α-Amino Acids

The electrophilicity of the α-carbon atom of the synthesized α-ethoxyphosphonate derivative 3 is too low to allow its direct transformation into the target bisphosphonate 5 using the Michaelis–Arbuzov-type reaction with triethyl phosphate [30]. Therefore, to increase the electrophilicity of this position, it was necessary to convert α-ethoxyphosphonate 3 to the corresponding phosphonium salt 4, which is much more reactive and thus susceptible to subsequent reaction with the nucleophilic triethyl phosphate.
phosphorus analog of phenylalanine 3d with the intention of isolating and purifying it. For this purpose, triphenylphosphonium tetrafluoroborate was added to α-ethoxyphosphonate in a slight molar deficiency (0.9 eq. to 1 eq. 3d). To our surprise, the $^{31}$P NMR analysis of the reaction mixture taken after 10 and 30 min at room temperature did not confirm the presence of the expected phosphonium salt 4d. Therefore, this synthesis was repeated according to the same procedure, but modifying the reaction conditions by lowering the temperature to $−15 \, ^{\circ}C$. Again, no characteristic signals belonging to the corresponding phosphonium salt were found. Due to the predicted instability of the synthesized diethyl 1-(N-benzylxycarbonylamino)-1-triphenylphosphonium-2-phenylethylphosphonate tetrafluoroborate, it was decided to conduct another experiment at $−40 \, ^{\circ}C$, which was analogous to the described procedure above but with a slight molar excess of triphenylphosphonium tetrafluoroborate (5%). After 40 min of reaction, NMR analysis was performed, which provided very promising results with two clearly visible doublets at 13.9 and 39.8 ppm of the same coupling constant ($J = 12.9 \, Hz$), confirming the presence of the desired phosphonium salt 4d (Figure 2b).

![Figure 2](image_url)

**Figure 2.** (a) $^{31}$P NMR spectrum of the reaction mixture obtained in the synthesis of phosphonium salt 4d carried out with a slight molar deficiency of Ph$_3$P·HBF$_4$ at $−40 \, ^{\circ}C$. (b) $^{31}$P NMR spectrum of the reaction mixture obtained in the synthesis of a phosphonium salt 4d conducted with a slight molar excess of Ph$_3$P·HBF$_4$ at $−40 \, ^{\circ}C$. (c) $^{31}$P NMR spectrum of the reaction mixture obtained in the one-pot synthesis of bisphosphonic derivative 5d performed with the use of Ph$_3$P·HBF$_4$ in a molar excess at room temperature.

In subsequent experiments, the conditions for the synthesis of 4d were modified in order to assess their impact on the reaction course (Figure 2). Initially, it was assumed that in the synthesis of phosphonium salt, the temperature was a determining factor having an influence on the reaction course. This was based on the results of the first experiments, in which two expected doublets at 13.9 and 39.8 ppm were observed only for the reaction carried out at $−40 \, ^{\circ}C$. However, subsequent experiments showed that it is not the temperature but the molar ratio of triphenylphosphonium tetrafluoroborate to...
substrate 3 that is of key importance for obtaining phosphonium salt 4. During a detailed analysis of reaction mixture $^{31}$P NMR spectra, it was observed that in those syntheses in which a slight molar deficiency of $\text{Ph}_3\text{P} \cdot \text{HBF}_4$ was used, the following signals were present in the spectrum, at approximately 18.1 ppm of high intensity together with a weaker signal at −2.8 ppm and broad intense signal at 3.3 ppm corresponding to $\text{Ph}_3\text{P} \cdot \text{HBF}_4$ in the equilibrium (Figure 2a). In contrast, there was a lack of the signal at 18.1 ppm when excess $\text{Ph}_3\text{P} \cdot \text{HBF}_4$ was used, and the equilibrium of the reaction shifted toward an intermediate with the signal at about −2.8 ppm, and phosphonium salt 4d, appearing in the form of two doublets (Figure 2b).

An explanation is presented in Scheme 3, which illustrates the proposed mechanism for the formation of phosphonium salt 4 in an equilibrium reaction via intermediates 6–8. In the first step, $\alpha$-ethoxyphosphonate 3 reacts with triphenylphosphonium tetrafluoro- borate to give salt 6 with a protonated ethoxy group in the $\alpha$ position and liberated triphenylphosphine. When there is a shortage of triphenylphosphonium tetrafluoroborate in relation to reaction substrate, it becomes partially blocked at this stage. Ethanol is cleaved from the resulting salt 6, the iminophosphonate 8 (which is in equilibrium with iminium type cation 7) is formed and $\text{Ph}_3\text{P} \cdot \text{HBF}_4$ is regenerated. This results in an intense $^{31}$P NMR spectrum signal at approximately 18.1 ppm, belonging to the starting compound 3d, along with the broad signal of $\text{Ph}_3\text{P} \cdot \text{HBF}_4$ (3.3 ppm) and intermediate iminophosphonate 8 at about −2.8 ppm (which is consistent with the literature data for this type of imines [36]). Conversely, in the case of an excess of triphenylphosphonium tetrafluoroborate (higher acidity of the reaction mixture), iminium-type cation 7 is formed more readily. Finally, the active electrophilic center of iminium-type cation 7 is attacked by triphenylphosphine and the desired phosphonium salt 4 is formed (Scheme 3).

![Scheme 3](image)

Scheme 3. A plausible mechanism for the formation of diethyl 1-(N-acylamino)-1-triphenylphosphoniumalkylphosphonate tetrafluoro- borate 4 proposed based on the analysis of $^{31}$P NMR spectra (161.9 MHz/CDCl$_3$; ppm) of reaction mixtures obtained in reactions of substrate 3 and $\text{Ph}_3\text{P} \cdot \text{HBF}_4$ used in various molar ratios.

The confirmation of the proposed phosphonium salt 4 formation mechanism is illustrated in the $^{31}$P NMR spectra of the reaction mixture (Figure 2a,b), with signals belonging to $\alpha$-ethoxyphosphonate 3d at approximately 18.1 ppm, $\text{Ph}_3\text{P} \cdot \text{HBF}_4$ at 3.3 ppm, intermediate iminophosphonate 8d at about −2.8 ppm and expected phosphonium salt 4d with the corresponding two doublets at 13.9 and 39.8 ppm. The presence of all these signals on the spectra of the reaction mixtures is evidence that this is an equilibrium reaction, in the course of which the acidity of the environment is of critical importance. On the other hand, reducing the temperature allows an unstable reaction intermediate to be observed in the $^{31}$P NMR spectrum as two intense doublets belonging to the expected phosphonium salt 4d.

On the basis of the postulated mechanism, it was concluded that diethyl 1-(N-benzyloxy carbonylamino)-1-triphenylphosphonium-2-phenylethylphosphonate tetrafluoro-
oroborate 4d, which is a reactive intermediate in this synthetic route, has to be used in situ in the subsequent transformation into α-aminobisphosphonate derivative 5d. Hence, we attempted to transform diethyl 1-(N-acylamino)-1-ethoxyalkylphosphonates 3 into 1-(N-acylamino)alkylene-1,1-bisphosphonates 5 via the corresponding phosphonium salts using a one-pot method (Figure 2c). Our screening tests, described above with the use of the model 3d as substrate, showed that during the synthesis of phosphonium salt 4d, iminophosphonate 8d is spontaneously formed in the equilibrium mixture. From this, we concluded that the addition of Hünig’s base as a catalyst in the synthesis of the bisphosphonates is redundant. Indeed, carrying out the one-pot synthesis of tetraethyl 1-(N-benzyloxycarbonylamino)-2-phenylethylene-1,1-bisphosphonate 5d by dissolving all the reactants, namely substrate 3d, Ph₃P·HBF₄ and triethylphosphite, used in a molar ratio of 1:1.05:1.5, in dichloromethane at 0–5 °C in the presence of methyltriphenylphosphonium iodide as a catalyst (0.25 eq.) and left at this temperature for 45 min, then at room temperature overnight, resulted in the expected product 5d with an estimated yield of 52% (Table 2, entry 1). This success inspired further optimization of the transformation conditions. This included the question of whether the presence of methyltriphenylphosphonium iodide is necessary here, since the function of the dealkylating agent for triethoxyphosphonium salt, obtained as an intermediate in the Michaelis–Arbuzov reaction, could potentially be performed by triphenylphosphine that is present in the reaction mixture [37,38]. The next experiment was therefore carried out in an analogous manner but without the addition of any catalysts, providing an estimate yield of bisphosphonate 5d of 73% (Table 2, entry 2). This result provided unequivocal evidence that the catalyst methyltriphenylphosphonium iodide is not required for this reaction to proceed efficiently, and thus, the reaction takes place in an autocatalytic system. It was also considered whether the dosing of the reactants at a reduced temperature is required and what molar ratio of Ph₃P·HBF₄ to α-ethoxyphosphonate 3d will be the most favorable. Table 2 shows the molar ratios of these reagents used together with the bisphosphonate yields afforded in the given experiments when performed at room temperature. It was found that it is sufficient to use a slight molar excess of Ph₃P·HBF₄ at the level of 5–8% in the synthesis of α-aminobisphosphonate, and that room temperature is optimal for this transformation (entries 3 and 4). The progress of the reaction was monitored by NMR spectroscopy, and finally, it was concluded that 6 h was sufficient time for the substrate to completely react (entry 5). The product was isolated from the reaction mixture by extraction with toluene and subsequent purification of the extract by column chromatography to afford the target bisphosphonate in a yield of 86%.

Table 2. Screening of reaction conditions in the synthesis of bisphosphonate model 5d from α-ethoxyphosphonate 3d by the one-pot method.

| Entry | Molar Ratios | MePh₃P⁺ I⁻ | Temperature [°C] | Time [h] | Yield [%] ¹ |
|-------|--------------|------------|-----------------|---------|-------------|
| 1     | 3d 1 1.06    | +          | 0–5 for 45 min. then rt | 24 | 52         |
| 2     | 3d 1 1.08    | –          | 0–5 for 45 min. then rt | 24 | 73         |
| 3     | 3d 1 1.05    | –          | rt               | 24 | 77         |
| 4     | 3d 1 1.27    | –          | rt               | 24 | 75         |
| 5     | 3d 1 1.06    | –          | rt               | 6  | 86 ²       |

¹ Yield estimated from the ¹H NMR spectrum of the reaction mixture relative to the known mass of the internal standard (diphenyldimethylsilane). ² Isolated yield. + Denotes the addition of MePh₃P⁺ I⁻ as a catalyst. − Denotes that the experiment was performed without the addition of MePh₃P⁺ I⁻.

2.3. Scope of the Reaction

We then studied the scope of the one-pot reaction for the synthesis of various models of bisphosphonic analogs of protein and non-protein α-amino acids 5 according to the previous optimal conditions (Scheme 4).
It was enough to combine all reagents without any catalyst in a chosen solvent and leave it for 5 to 24 h at room temperature to successfully perform the reaction. Subsequent isolation of the obtained product initially by extraction with toluene and then column chromatography provided target compounds in moderate range of 54–62% (entries 3, 7, 8, 17).

These optimized conditions were tested on other α-amino acids, the amino group was protected with an easily removable benzyloxycarbonyl group. For most models, these conditions were well matched, and it was enough to combine all reagents without any catalyst in a chosen solvent and leave it for 5 to 24 h at room temperature to successfully perform the reaction. Subsequent isolation of the obtained product initially by extraction with toluene and then column chromatography provided target compounds with good to excellent yields (72–95%; Cbz-protected amino group). However, in some cases, the use of Ph₃P·HBF₄ in a molar ratio of 1.2 to 1 relative to substrate was required to conduct the reaction under catalyst-free conditions (Scheme 4, entries 1–3, 19).

For the majority of the synthesized bisphosphonic derivatives of α-amino acids, the amino group was protected with an easily removable benzyloxycarbonyl group. However, the tested procedure also worked well for models with the amino group protected with other acyl groups, such as acetyl or pivaloyl, leading to expected product yields in a moderate range of 54–62% (entries 3, 7, 8, 17).

We also tested the influence of the solvent on the yield of ABPs during synthesis, finding a general relationship that acetonitrile is a better solvent for this transformation. How-
ever, for some bisphosphonates, a higher reaction yield was noted with dichloromethane (cf. entries 5, 6 and 20, 21).

For one model, namely the N-Cbz-protected α-ethoxy derivative of phosphorus analog of leucine, the impact of the excess of triethyl phosphate on the efficiency of the synthesis of the corresponding bisphosphonate 5j was also evaluated. We noted that the reaction yield was higher with the use of 1.5 eq. of P(OEt)3 (74%) than for 1.2 eq. of the nucleophile used (62%) (entries 15, 16).

It should be noted that in the case of the bisphosphonic derivative of serine 5l, the final one-pot reaction was successfully carried out only when the Hünig’s base was also used as a catalyst and when the reaction temperature was raised to 70 °C. The selection of such parameters undoubtedly facilitated the transformation of the indirectly formed phosphonium salt 4l into the target product 5l (Figure 3b), which was obtained with a yield of 52% (Scheme 4, entry 18). The course of the reaction at a lower temperature or without the use of a catalyst ended at the stage of phosphonium salt generation, which can be seen in the 31P NMR spectrum of the reaction mixture in the form of two doublets with the same coupling constant, which was accompanied by the very small signal of the desired product 5l (δ = 17.9 ppm) (Figure 3a).

![Figure 3](image_url)

**Figure 3.** (a) 31P NMR spectrum of the reaction mixture obtained from the synthesis of the bisphosphonic derivative of serine 5l without the use of Hünig’s base catalyst at 70 °C. (b) 31P NMR spectrum of the reaction mixture obtained in the synthesis of bisphosphonic derivative of serine 5l performed in the presence of catalytic Hünig’s base at 70 °C.

The functional role of Hünig’s base as a catalyst in the synthesis of a bisphosphonic serine derivative relies on assisting the generation of the corresponding N-acyliminophosphonate 8l from the resulting phosphonium salt 4l during the final Michaelis–Arbuzov-type reaction. This is the rate-determining step of the transformation. For the serine model, due to the presence of an electron-withdrawing methoxymethyl group at the α position, the stabilization of the iminophosphonate 8l is reduced (Scheme 5), so that the reaction equilibrium is strongly shifted toward the phosphonium salt 4l. Hence, the addition of Hünig’s base is necessary to allow the Michaelis–Arbuzov-type reaction to be performed, as it is shown in the postulated mechanism for this transformation (Scheme 5).
Scheme 5. The role of Hünig’s base as a catalyst for the Michaelis–Arbuzow-type reaction in the synthesis of bisphosphonic derivatives of serine 5l (R² = CH₂OMe) and glycine 5c (R² = H) models.

Moreover, in the case of the bisphosphonic derivative of glycine 5c, not only was the Hünig’s base catalyst and an increased temperature (70 °C) required, but the intended one-pot transformation was not achieved. This is likely due to the reversible nature of the transformation being carried out, during which the recovery of the starting α-ethoxyphosphonate 3c in the equilibrium reaction was privileged (Scheme 3), due to the presence of ethanol in the reaction mixture. To overcome this problem, the synthesis of the bisphosphonic derivative 5c was carried out according to a two-step procedure. First, the phosphonium salt 4c was obtained by heating the residue after evaporation of the solvent from a homogeneous mixture, which was prepared by dissolving α-ethoxyphosphonate 3c and triphenylphosphonium tetrafluoroborate at 85 °C under reduced pressure for 5 h. Next, the crude phosphonium salt 4c was subjected to the Michaelis–Arbuzow-type reaction after dissolving in acetonitrile by treatment with triethylphosphite in the presence of Hünig’s base, resulting in a very good yield of the target product 5c (82%) (Scheme 4, entry 4).

Regarding the prospects for the further use of synthesized bisphosphonate models 5, we can carry out structural modifications to increase their application potential in medical chemistry. One future research direction involves the synthesis of conjugates by combining compounds with proven biological activity (e.g., anti-cancer) with α-aminobisphosphonates that can be used as drug carriers. Their functional role in these complexes includes not only the targeted delivery of pharmaceuticals to the bone tissue but also synergistic action with anti-cancer drugs. Minor modifications to the structure of α-aminobisphosphonates will also be of interest. The acylation of α-aminobisphosphonates with the use of appropriate chloroacetyl chlorides will allow the production of building blocks that are useful in the synthesis of ligands, which can be used as potential contrast agents for imaging of bone mineral by MRI after complexing with paramagnetic ions.

3. Materials and Methods
3.1. General Information

Melting points were determined in capillaries in a Stuart Scientific SMP3 melting point apparatus and were uncorrected. ¹H-NMR spectra were acquired on a Varian 400 spectrometer at an operating frequency of 400 MHz using tetramethylsilane (TMS) as the resonance shift standard. ³¹C-NMR spectra were recorded on a Varian 400 at 100 MHz, us-
ing solvent resonance as the internal standard. $^{31}$P-NMR spectra were recorded on a Varian 400 at 161.9 MHz without the resonance shift standard, with respect to H$_3$PO$_4$ as 0 ppm. All chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. IR-spectra were measured on a Nicolet 6700 FT-IR spectrophotometer, Thermo Scientific (attenuated total reflectance method; ATR). The high-resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) using a Waters Corporation Xevo G2 QTOF instrument. The reactions of Michaelis–Becker-like addition of diethyl phosphite to ethyl N-acylimidates were performed at reduced temperatures using Julabo ultra-low refrigerated-circulator F81-ME. For TLC analysis, Merck TLC silica gel 60 F$_{254}$ plates were used. The plates were visualized by UV light (254 nm) and/or dipped in a solution of cerium sulfate and tetrachloride of ammonium heptamolybdate in H$_2$SO$_4$aq and heated. Kieselgel 60 (Merck, 0.040–0.063 mm) was used for column chromatography.

Materials. All solvents and common reagents were obtained from commercial suppliers. Diethyl phosphite and triethyl phosphite were purchased from Acros Organics.

$^1$H, $^{13}$C, $^{31}$P NMR spectrum of all new compounds 3, 4c and 5 are available in Supplementary Materials.

3.2. Substrate Synthesis

Commercially available ethyl acetimidate and ethyl benzimidate hydrochlorides (1a and 1m) were used. Ethyl formimidate hydrochloride 1c was synthesized according to the procedure described by Schmitz and Ohme [39]. The rest of ethyl imidate hydrochlorides 1 were obtained according to the protocol given by Yadav and Babu [40].

General procedure for the synthesis of diethyl 1-(N-acylamino)-1-ethoxyalkylphosphonates 3.

Step 1: N-Acylation reactions of ethyl imidate hydrochlorides 1 were carried out according to the modified procedure described by Kuźnik et al. [33]. The appropriate base (17.6 mmol, 2.2 eq.) was added to a solution of ethyl imidate hydrochloride 1 (8.0 mmol, 1.0 eq.) in dry CH$_2$Cl$_2$ (25 mL) and cooled in an ice bath. Then, acid chloride (8.0 mmol, 1.0 eq.) was added to the reaction mixture dropwise. The ice bath was removed, and the mixture was stirred under argon atmosphere, at room temperature, for 24 h, and the solvent was evaporated under reduced pressure. To separate the product from base hydrochloride, hexane (15 mL) was added to the residue. The precipitate was filtered over celite, and the filtrate was concentrated to give ethyl N-acylimidate 2.

Due to the instability of the ethyl N-(benzyloxy carbonyl)formimidate 2c, N-acylation of ethyl formimidate hydrochloride 1c was carried out in an ice bath, and the reaction time was reduced to 2 h. The obtained compound was immediately used in the next step.

Synthesis of ethyl N-(benzyloxy carbonyl)phenylacetimidate 2d was performed using Büning’s base (2.1 eq.), added in two equal portions, before and after the addition of benzyl chloride (1.25 eq.). N-Acylation of ethyl benzimide hydrochloride 1m was carried out using toluene as a solvent.

**Ethyl N-(benzyloxy carbonyl)acetimidate** (2a). Pale yellow oil; 90% yield (1.592 g). $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.40–7.32 (m, 5H), 5.19 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.05 (s, 3H) 1.28 (t, J = 7.2 Hz, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 167.9, 161.5, 135.9, 128.5, 128.4, 128.3, 68.1, 63.2, 18.4, 13.8. HRMS (ESI) m/z: calcd for C$_{12}$H$_{15}$NO$_2$Na [M + Na]$^+$ 244.0950, found 244.0951.

**Ethyl N-(pivaloyl)acetimidate** (2b) [41]. Pale yellow oil; 80% yield (1.095 g). $^1$H-NMR (400 MHz, CDCl$_3$): δ 4.12 (q, J = 7.0 Hz, 2H), 1.98 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.18 (s, 9H). $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 191.7, 161.3, 62.5, 41.4, 27.1, 18.0, 14.0. HRMS (ESI) m/z: calcd for C$_9$H$_{16}$NO$_2$ [M + H]$^+$ 172.1338, found 172.1343.

**Ethyl N-(benzyloxy carbonyl)formimidate** (2c). Pale yellow oil; 34% yield (565 mg). $^1$H-NMR (400 MHz, CDCl$_3$): δ 8.45 (s, 1H), 7.54–7.28 (m, 5H), 5.12 (s, 2H), 4.34 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 167.1, 161.9, 135.6, 128.5, 128.5, 128.3, 68.4, 64.5, 13.8. HRMS (ESI) m/z: calcd for C$_{11}$H$_{14}$NO$_3$ [M + H]$^+$ 208.0974, found 208.0977.

**Ethyl N-(benzyloxy carbonyl)-2-phenylacetacetimidate** (2d). Pale yellow oil; 88% yield (2.095 g).

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.35–7.19 (m, 10H), 5.13 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.68
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Ethyl N-(acetyl)-2-phenylacetimidate (2e) [42]. Pale yellow oil; 85% yield (1.389 g). 1H-NMR (400 MHz, CDCl3): δ 7.42–7.28 (m, 5H), 5.18 (s, 2H), 4.12 (q, J = 7.2 Hz, 2H), 2.72 (sept, J = 7.0 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.12 (d, J = 6.8 Hz, 6H). 13C-NMR (100 MHz, CDCl3): δ 172.2, 161.2, 136.0, 128.5, 128.4, 128.2, 68.1, 62.9, 32.8, 19.5, 13.7. HRMS (ESI) m/z: calcd for C14H12NO2Na [M + Na]+ 272.1263, found 272.1264.

Ethyl N-(benzoxycarbonyl)-2-methylpropanimidate

Ethyl N-(benzoxycarbonyl)-2-methylpropanimidate (2h). Pale yellow oil; 79% yield (1.580 g).

Ethyl N-(benzoxycarbonyl)-2-methylpropanimidate (2i) [43]. Pale yellow oil; 91% yield (1.912 g). 1H-NMR (400 MHz, CDCl3): δ 7.42–7.29 (m, 5H), 5.18 (s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 1.53 (qu, J = 7.6 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25 (sept, J = 7.2 Hz, 2H), 0.85 (t, J = 7.2 Hz, 3H). 13C-NMR (100 MHz, CDCl3): δ 170.0, 161.4, 135.9, 128.5, 128.3, 68.0, 62.9, 34.4, 19.5, 13.8, 13.6. HRMS (ESI) m/z: calcd for C14H12NO2Na [M + Na]+ 250.1443, found 250.1445.

Ethyl N-(benzoxycarbonyl)-pentanimidate (2j). Yellow oil; 99% yield (2.083 g). 1H-NMR (400 MHz, CDCl3): δ 7.42–7.26 (m, 5H), 5.18 (s, 2H), 4.15 (q, J = 7.0 Hz, 2H), 2.02 (d, J = 7.2 Hz, 2H), 1.97 (sept, J = 6.8 Hz, 1H). 1.28 (t, J = 7.2 Hz, 3H), 0.85 (d, J = 6.8 Hz, 6H). 13C-NMR (100 MHz, CDCl3): δ 169.1, 161.3, 135.9, 128.6, 128.5, 128.4, 68.0, 62.9, 41.1, 26.3, 22.2, 13.9. HRMS (ESI) m/z: calcd for C15H14N2O3Na [M + H]+ 264.1600, found 264.1599.

Ethyl N-(acetyl)-3-methylbutanimidate (2k). Pale yellow oil; 99% yield (1.358 g). 1H-NMR (400 MHz, CDCl3): δ 4.09 (q, J = 7.1 Hz, 2H), 2.20 (d, J = 7.2 Hz, 2H), 2.16 (s, 3H), 2.05 (m, 1H), 1.28 (t, J = 7.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 6H). 13C-NMR (100 MHz, CDCl3): δ 183.4, 162.2, 62.4, 41.0, 26.7, 26.1, 22.3, 13.9. HRMS (ESI) m/z: calcd for C9H16NO2 [M + H]+ 172.1383, found 172.1343.

Ethyl N-(benzoxycarbonyl)-2-methoxyacetimidate (2l). Pale yellow oil; 74% yield (1.481 g).

Ethyl N-(benzoxycarbonyl)-2-methoxyacetimidate (2m). Pale yellow oil; 58% yield (1.316 g). 1H-NMR (400 MHz, CDCl3): δ 7.55–7.50 (m, 5H), 5.12 (s, 2H), 4.34 (q, J = 7.0 Hz, 2H), 3.14 (t, J = 7.0 Hz, 3H).

Ethyl N-(benzoxycarbonyl)-2-(4-methoxyphenyl)acetimidate (2n). Yellow oil; 96% yield (2.519 g).

Ethyl N-(acyl)-2-phenylacetimidate (2o) [42]. Yellow oil; 100% yield (1.404 g). 1H-NMR (400 MHz, CDCl3): δ 7.35–7.23 (m, 5H), 7.11–7.09 (m, 2H), 6.80–6.76 (m, 2H), 5.13 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 3.61 (s, 2H), 1.25 (t, J = 7.2 Hz, 3H). 13C-NMR (100 MHz, CDCl3): δ 168.06, 161.19, 158.62, 135.76, 130.26, 128.57, 128.51, 128.31, 113.90, 68.17, 63.42, 55.20, 37.96, 13.79. HRMS (ESI) m/z: calcd for C15H22NO4 [M + H]+ 328.1549, found 328.1546.
Step 2: Transformation of ethyl N-acylimidates 2 into diethyl 1-(N-acylamino)-1-ethoxyalkylphosphonates 3 was carried out according to the modified protocol given by Kuźniak et al. [33]. Potassium carbonate (4 wt % H2O) (2.7 mmol, 373 mg, 1.35 eq.) and 18-crown-6 (0.24 mmol, 63 mg, 0.12 eq.) were added to the solution of ethyl N-acylimidate 2 (2 mmol, 1 eq.) in hexane (6.4 mL). Then, diethyl phosphate (2.4 mmol, 331 mg, 0.31 mL, 1.2 eq. or 4.0 mmol, 552 mg, 0.51 mL, 2 eq. or 6.0 mmol, 829 mg, 0.77 mL, 3 eq.) was added dropwise. The reaction mixture was stirred vigorously at room or reduced temperature for the appropriate time period (Table 1). Then, K2CO3 was filtered off, and crude product was isolated by washing first with hexane and then with CH2Cl2. The crude product was further purified by column chromatography on silica gel using the mixture of CH2Cl2/MEOH/Et3N (100:1:1) as the eluent.

**Diethyl 1-((N-benzyloxycarbonylamino)-1-ethoxy-2-phenylethylphosphonate (3a).** White solid; 94% yield (338 mg); mp 69.4 to 71.0 °C. 1H-NMR (400 MHz, CDCl3): δ 7.39–7.30 (m, 5H), 5.71 (br d, J = 7.9 Hz, 1H), 5.09 (ABq, J = 12.2 Hz, 2H), 4.24–4.12 (m, 4H)α, 3.67–3.60 (m, 2H), 1.90 (d, J = 15.0 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H) and 1.32 (t, J = 7.2 Hz, 3H)β, 1.17 (t, J = 7.0, 3H). 13C-NMR (100 MHz, CDCl3): δ 154.6 (d, J = 16.4 Hz), 136.2, 128.5, 128.2, 128.1, 84.4 (d, J = 196.8 Hz), 66.7, 63.8 (d, J = 6.9 Hz), 63.4 (d, J = 6.9 Hz), 58.5 (d, J = 8.0 Hz), 18.9, 16.4 (d, J = 5.3 Hz), 15.4. 31P-NMR (162 MHz, CDCl3): δ 18.5. IR (ATR): 3203, 1676, 1519, 1244, 1021, 958 cm−1. HMRS (ESI) m/z: calcd for C15H27NO3P [M + H]+ 360.1578, found 360.1578. Overlapping signals of P(O)(OCH2)2 groups. Overlapping signals of P(O)(OCH2CH2)2 groups.

**Diethyl 1-((N-benzyloxycarbonylamino)-1-ethoxyethylphosphonate (3e).** Colorless oil; 74% yield (230 mg). 1H-NMR (400 MHz, CDCl3): δ 6.41 (br d, J = 7.5 Hz, 1H), 4.26–4.14 (m, 4H)α, 3.67–3.59 (m, 2H), 1.95 (d, J = 15.4 Hz, 3H), 1.35 (t, J = 7.0 Hz, 3H) and 1.34 (t, J = 7.0 Hz, 3H)β, 1.22 (s, 9H), 1.19 (t, J = 7.0 Hz, 3H). 13C-NMR (100 MHz, CDCl3): δ 178.8 (d, J = 9.9 Hz), 84.9 (d, J = 194.5 Hz), 63.9 (d, J = 6.9 Hz), 63.1 (d, J = 6.9 Hz), 58.6 (d, J = 9.5 Hz), 39.9, 27.5, 18.7, 16.5 (d, J = 5.3 Hz), 16.4 (d, J = 5.4 Hz), 15.5. 31P-NMR (162 MHz, CDCl3): δ 19.1. IR (ATR): 3283, 1676, 1519, 1244, 1021, 958 cm−1. HMRS (ESI) m/z: calcd for C15H27NO3P [M + H]+ 310.1783, found 310.1790. Overlapping signals of P(O)(OCH2CH2)2 groups. Overlapping signals of P(O)(OCH2CH2)2 groups.
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1H), 2.04 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H).

13C-NMR (100 MHz, CDCl3): δ 170.3 (d, J = 9.2 Hz), 135.6 (d, J = 4.0 Hz), 131.1, 127.7, 126.6, 87.6 (d, J = 185.9 Hz), 63.4 (d, J = 7.2 Hz), 62.8 (d, J = 7.2 Hz), 59.9 (d, J = 5.3 Hz), 38.9, 24.5, 16.4 (d, J = 6.1 Hz), 16.1 (d, J = 6.1 Hz), 15.2. 31P-NMR (162 MHz, CDCl3): δ 17.9. IR (ATR): 3185, 1670, 1548, 1218, 1029, 962, 749, 696 cm⁻¹. HRMS (ESI) m/z: calc for C16H24NO5P [M + H]+ 344.1627, found 344.1627. a Overlapping signals of CαCH2C6H5 and P(O)(OCH2CH3)2 groups.

Diethyl 1-(N-benzyloxycarbonylamo)-1-ethoxyphosphonate (3f). White solid; 82% yield (306 mg); mp 59.4 to 60.8 °C. 1H-NMR (400 MHz, CDCl3): δ 7.38–7.30 (m, 5H), 5.77 (d, J = 8.0 Hz, 1H), 5.09 (ABq, J = 10.0 Hz, 2H), 4.24–4.11 (m, 4H)⁴, 3.68–3.56 (m, 2H), 2.61 (ddq, J1 = 23.4 Hz, J2 = 15.0 Hz, J3 = 7.5 Hz, 1H), 2.25 (tq, J1 = 14.9 Hz, J2 = 7.5 Hz, 1H), 1.33 (t, J = 7.0 Hz, 3H) and 1.32 (t, J = 7.0 Hz, 3H)⁵. 31P-NMR (100 MHz, CDCl3): δ 154.4 (d, J = 16.1 Hz), 156.2, 128.5, 128.1, 128.0, 127.8 (d, J = 189.7 Hz), 66.7, 63.6, 63.1 (d, J = 7.1 Hz), 58.4 (d, J = 7.2 Hz), 25.2, 16.4 (d, J = 15.3 Hz), 8.5 (d, J = 2.1 Hz). 31P-NMR (162 MHz, CDCl3): δ 19.0. IR (ATR): 3253, 1231, 1024, 773 cm⁻¹. HRMS (ESI) m/z: calc for C17H25NO3P [M + Na]+ 396.1552, found 396.1545. a Overlapping signals of P(O)(OCH2CH3)2 groups. b Overlapping signals of P(O)(OCH2CH3)2 groups.

Diethyl 1-(N-benzyloxycarbonylamo)-1-ethoxybutylphosphonate (3g). Colorless oil; 68% yield (263 mg). 1H-NMR (400 MHz, CDCl3): δ 7.39–7.31 (m, 5H), 5.78 (br d, J = 8.0 Hz, 1H), 5.08 (ABq, J = 12.2 Hz, 2H), 4.23–4.11 (m, 4H)⁴, 3.68–3.55 (m, 2H), 2.61–2.47 (m, 1H), 2.23–2.11 (m, 1H), 1.54–1.44 (m, 2H), 1.33 (t, J = 7.0 Hz, 3H) and 1.32 (t, J = 7.0 Hz, 3H)⁵. 31P-NMR (100 MHz, CDCl3): δ 154.4 (d, J = 16.1 Hz), 136.2, 128.5, 128.1, 128.0, 87.3 (d, J = 189.7 Hz), 66.6, 63.6, 63.1 (d, J = 7.1 Hz), 63.1 (d, J = 7.0 Hz), 58.4 (d, J = 7.4 Hz), 34.4, 17.2 (d, J = 2.0 Hz), 16.4 (d, J = 5.5 Hz), 15.3, 14.4. 31P-NMR (162 MHz, CDCl3): δ 19.0. IR (ATR): 2976, 1737, 1499, 1240, 1019, 969, 742 cm⁻¹. HRMS (ESI) m/z: calc for C18H32NO4P [M + Na]+ 410.1708, found 410.1706. a Overlapping signals of P(O)(OCH2CH3)2 groups. b Overlapping signals of P(O)(OCH2CH3)2 groups.

Diethyl 1-(N-benzyloxycarbonylamo)-1-ethoxy-2-ethylphosphonophosphate (3h). White solid; 53% yield (205 mg); mp 54.2 to 55.5 °C. 1H-NMR (400 MHz, CDCl3): δ 7.37–7.31 (m, 5H), 5.91 (br d, J = 10.8 Hz, 1H), 5.09 (ABq, J = 12.2 Hz, 2H), 4.21–4.12 (m, 4H)⁴, 3.68–3.56 (m, 2H), 3.19 (dsept, J1 = 32.6 Hz, J2 = 7.0 Hz 1H), 1.33 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H). 13C-NMR (100 MHz, CDCl3): δ 154.6 (d, J = 18.2 Hz), 136.3, 128.5, 128.2, 128.1, 90.2 (d, J = 185.8 Hz), 66.7, 63.4 (d, J = 7.2 Hz, 62.9 (d, J = 7.6 Hz), 58.6 (d, J = 6.5 Hz), 31.4, 17.7 (d, J = 3.1 Hz), 17.5, 16.4 (d, J = 5.3 Hz), 15.3, 13.1. 31P-NMR (162 MHz, CDCl3): δ 19.7. IR (ATR): 3218, 1723, 1544, 1239, 1023, 976, 745 cm⁻¹. HRMS (ESI) m/z: calc for C18H32NO4P [M + Na]+ 388.1889, found 388.1890. a Overlapping signals of P(O)(OCH2CH3)2 groups.

Diethyl 1-(N-benzyloxycarbonylamo)-1-ethoxy-3-methylphosphonophosphate (3i). Colorless oil; 32% yield (135.7 mg). 1H-NMR (400 MHz, CDCl3): δ 7.36–7.31 (m, 5H), 5.88 (br d, J = 8.8 Hz, 1H), 5.08 (ABq, J = 12.2 Hz, 2H), 4.25–4.11 (m, 4H)⁴, 3.61 (qd, J = 7.0, 1.0 Hz, 2H), 2.62 (dd, J1 = 26.3 Hz, J2 = 15.0 Hz, J3 = 7.9 Hz, 1H), 2.09–2.03 (m, 1H), 1.96 (dd, J1 = 15.0 Hz, J2 = 9.1 Hz, J3 = 4.3 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H)and 1.32 (t, J = 7.2 Hz, 3H)⁵. 13C-NMR (100 MHz, CDCl3): δ 154.4 (d,
Overlapping signals of P(O)(O)(O) and P(O)(O)CH₂ groups. Overlapping signals of P(O)(O)CH₂ groups.

Diethyl 1-(N-acetylaminol)-1-ethoxy-3-methylbutylphosphonate (3k). White solid; 64% yield (198 mg); mp 58.6 ± 59.7 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.37–7.30 (m, 5H), 5.97 (br d, 2H, 4.26–4.15 (m, 5H)), 3.92 (dd, J₁ = 10.6 Hz, J₂ = 9.3 Hz, 2H), 3.75–3.61 (m, 2H), 3.41 (s, 3H), 1.34 (td, J₁ = 7.2 Hz, J₂ = 0.4 Hz, 3H), and 1.33 (td, J₁ = 7.2 Hz, J₂ = 0.4 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 6.7 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 170.1 (d, J = 12.9 Hz), 88.8 (d, J = 187.3 Hz), 64.1 (d, J = 7.2 Hz, 62.7 (d, J = 7.2 Hz), 59.0 (d, J = 8.0 Hz, 39.7, 24.9, 24.7 (d, J = 3.0 Hz), 24.5, 23.1, 16.43 (d, J = 6.1 Hz) and 16.40 (d, J = 5.3 Hz)b, 15.1. ³¹P-NMR (162 MHz, CDCl₃): δ 19.6. IR (ATR): 3197, 1670, 1541, 1224, 1070, 956, 759 cm⁻¹. HMRS (ESI) m/z: calc for C₁₉H₂₂NO₅P [M + H]⁺ 310.1783, found 310.1776. Overlapping signals of P(O)(O)CH₂ groups. Overlapping signals of P(O)(O)CH₂ groups. Overlapping signals of P(O)(O)CH₂ groups.

Diethyl 1-(N-benzyloxycarbamino)-1-ethoxy-2-methoxyethylphosphonate (3l). White solid; 91% yield (354 mg); mp 60.1 ± 62.1 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.37–7.30 (m, 5H), 5.97 (br d, 2H, 4.26–4.15 (m, 5H)), 3.92 (dd, J₁ = 10.6 Hz, J₂ = 9.3 Hz, 2H), 3.75–3.61 (m, 2H), 3.41 (s, 3H), 1.34 (td, J₁ = 7.2 Hz, J₂ = 0.4 Hz, 3H), and 1.33 (td, J₁ = 7.2 Hz, J₂ = 0.4 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 6.7 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 154.4 (d, J = 14.3 Hz), 136.1, 128.5, 128.2, 128.1, 86.0 (d, J = 188.8 Hz), 72.5, 67.0, 63.6 (d, J = 7.2 Hz), 63.5 (d, J = 6.9 Hz), 59.4, 59.3 (d, J = 6.0 Hz), 16.4 (d, J = 5.7 Hz), 15.4. ³¹P-NMR (162 MHz, CDCl₃): δ 17.9. IR (ATR): 3327, 2985, 2965, 1533, 1245, 1027, 987, 758 cm⁻¹. HMRS (ESI) m/z: calc for C₁₇H₂₃NO₅P [M + Na]⁺ 412.1501, found 412.1494. Overlapping signals of C₆H₅CH₂OMe and P(O)(O)CH₂ groups.

Diethyl 1-(N-benzyloxycarbamino)-1-ethoxy-1-phenylmethylphosphonate (3m). White solid; 82% yield (345 mg); mp 96.6 ± 97.6 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.55–7.52 (m, 2H), 7.35–7.28 (m, 8H), 6.23 (d, J = 10. Hz, 1H), 5.04 (ABq, J = 12.4 Hz, 2H), 4.14–3.67 (m, 6H), 1.26 (t, J = 7.0 Hz, 3H) and 1.25 (td, J₁ = 7.0 Hz, J₂ = 0.8 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H), 1.10 (td, J₁ = 7.0 Hz, J₂ = 0.5 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 159.5, 155.4 (d, J = 14.1 Hz), 138.0, 133.1, 129.5, 129.1, 128.5 (d, J = 3.8 Hz), 114.0, 88.3 (d, J = 187.3 Hz), 67.2, 63.78 (d, J = 7.2 Hz) and 62.73 (d, J = 7.2 Hz), 60.1 (d, J = 4.2 Hz), 55.8, 39.1 (d, J = 5.0 Hz), 15.7 (d, J = 5.7 Hz) and 15.6 (d, J = 5.7 Hz), 14.6. ³¹P-NMR (162 MHz, CD₂CN): δ 17.29. IR (ATR): 3197, 2973, 1720, 1514, 1255, 1019, 972, 738, 697 cm⁻¹. HMRS (ESI) m/z: calc for C₁₉H₂₃NO₅P [M + Na]⁺ 488.1814, found 488.1812. Overlapping signals of P(O)(O)CH₂CH₂OCH₃ groups. Overlapping signals of C₆H₅OCH₃ and C₆H₅CH₂CH₂CH₃ groups.

Synthesis of diethyl 1-(N-benzyloxycarbamino)-1-triphenylphosphonium-methylphosphonate tetrafluoroborate 4c.

Diethyl 1-(N-benzyloxycarbamino)-1-triphenylphosphonium-methylphosphonate tetrafluoroborate 4c was synthesized as previously described by Kuźnik et al. [33]. In...
brief, triphenylphosphonium tetrafluoroborate (1.12 mmol, 392 mg, 1.12 eq.) and diethyl 1-(N-benzyloxycarbonylamino)-1-ethoxymethylphosphonate 3c (1.0 mmol, 649 mg, 1 eq.) were added to a solution of diethyl phosphite (1.5 mmol, 249 mg, 1.5 eq.) and triphenylphosphonium tetrafluoroborate (1.05–1.08 mmol, 368 mg–378 mg, 1.05–1.08 eq.) in dry MeCN or CHCl₃ (4 mL). The mixture was heated at 70 °C for 8 h. The product 5c was isolated and purified in an analogous manner as described in the procedure above.

**Tetraethyl 1-(N-benzyloxycarbonylamino)ethylene-1,1-bisphosphonate (5a).** Colorless crystals; 95% yield (430 mg), mp 47.1 to 48.7 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.36–7.31 (m, 5H), 5.40 (br t, J = 3.4 Hz, 1H), 5.07 (s, 2H), 4.25–4.12 (m, 8H), 1.98 (t, J = 17.0 Hz, 3H), 1.33 (t, J = 7.2 Hz, 6H) and 1.31 (t, J = 7.2 Hz, 6H)b. ¹³C-NMR (100 MHz, CDCl₃): 154.3, 136.3, 128.4, 128.11, 128.09, 66.73, 63.83 (d, J = 3.4 Hz) and 63.80 (d, J = 3.4 Hz) and 63.75 (d, J = 3.4 Hz) and 63.72 (d, J = 3.4 Hz)c, 55.8 (t, J = 146.9 Hz), 16.5–16.3 (m)b, 16.2 (br t, J = 4.1 Hz). ¹³P-NMR (162 MHz, CDCl₃): 19.6. IR (ATR) 3218, 1714, 1537, 1229, 1016, 958, 750. HRMS (ESI) m/z: calcld for C₁₃H₂₃NO₃P₂ [M + H]+ 542.1603, found 542.1610. *Overlapping signals of PPh₃ and NH groups.

**Tetraethyl 1-(N-benzyloxycarbonylamino)ethylene-1,1-bisphosphonate (5b).** Colorless crystals; 62% yield (247 mg), mp 50.8 to 52.3 °C. ¹H-NMR (400 MHz, CDCl₃): δ 6.19 (br t, J = 4.6 Hz, 1H), 4.28–4.19 (m, 8H)c, 2.01 (t, J = 17.0 Hz, 3H), 1.35 (t, J = 7.0 Hz, 12H), 1.20 (s, 9H). ¹³C-NMR (100 MHz, CDCl₃): δ 177.7 (t, J = 5.1 Hz), 63.76 (d, J = 3.4 Hz) and 63.73 (d, J = 3.4 Hz) and 63.67 (d, J = 3.4 Hz) and 63.64 (d, J = 3.4 Hz)d, 56.7 (t, J = 144.9 Hz), 39.8, 27.4, 16.7 (t, J = 4.5 Hz), 16.5–16.4 (m)b. ¹³P-NMR (162 MHz, CDCl₃): 20.0. IR (ATR) 3276, 1677, 1515, 1233, 1016, 945. HRMS (ESI) m/z: calcld for C₁₃H₂₃NO₃P₂ [M + H]+ 402.1811, found 402.1813. *Overlapping signals of P(O)(OCH₂CH₃)₂ groups. *Overlapping signals of P(O)(OC₆H₄CH₃)₂ groups.
Tetraethyl 1-(N-benzyloxy carbonylamino)methylene-1,1-bisphosphonate (5c). Colorless crystals; 82% yield (357 mg), mp 59.8 to 60.7 °C. 1H-NMR (400 MHz, CDCl3): δ 7.36–7.31 (m, 5H), 5.32 (br d, J = 10.4 Hz, 1H), 5.15 (s, 2H), 4.59 (td J1 = 21.9, J2 = 10.4 Hz), 4.25–4.12 (m, 8H), 1.32 (t, J = 7.0 Hz, 6H) and 1.29 (t, J = 7.0 Hz, 6H)b. 13C-NMR (100 MHz, CDCl3): δ 155.5 (t, J = 4.9 Hz), 135.9, 128.5, 128.3, 128.1, 67.6, 63.5, 46.0 (t, J = 146.8 Hz), 16.3–16.2 (m)b. 31P-NMR (162 MHz, CDCl3): 16.3. IR (ATR) 3534, 1717, 1528, 1266, 1019, 977, 736. HRMS (ESI) m/z: calcld for C25H29O7Na2P2 [M + Na]⁺ 460.1266, found 460.1261. a Overlapping signals of P(O)(OCH2CH2)3 groups. b Overlapping signals of P(O)(OCH2CH2)3 groups.

Tetraethyl 1-(N-benzyloxy carbonylamino)ethylene-1,1-bisphosphonate (5d). Colorless crystals; 86% yield (455 mg), mp 60.2 to 61.5 °C. 1H-NMR (400 MHz, CDCl3): δ 7.44–7.34 (m, 5H), 7.26–7.16 (m, 5H), 5.44 (t, J = 12.7 Hz, 1H), 5.18 (s, 2H), 4.30–4.15 (m, 4H), 4.13–4.03 (m, 2H), 3.98–3.88 (m, 2H), 3.58 (dd, J = 15.3, 11.7 Hz, 2H), 1.30 (t, J = 7.2 Hz, 6H), 1.19 (t, J = 7.2 Hz, 6H).13C-NMR (100 MHz, CDCl3) δ 154.9 (t, J = 8.8 Hz), 136.4, 135.3 (t, J = 8.6 Hz), 131.2, 128.49, 128.45, 128.2, 127.7, 126.7, 67.1, 63.9 (d, J = 7.5 Hz), 63.0 (d, J = 7.4 Hz), 61.2 (t, J = 143.1 Hz), 35.5, 16.3 (d, J = 6.3 Hz), 16.2 (d, J = 6.2 Hz). 31P-NMR (162 MHz, CDCl3): 18.8. IR (ATR) 3224, 1711, 1534, 1266, 1022, 963, 752. HRMS (ESI) m/z: calcld for C31H35O7Na2P2 [M + Na]⁺ 550.1736, found 550.1732. a Overlapping signals of P(O)(OCH2CH2)3 groups.
16.40 (d, J = 3.0 Hz) and 16.37 (d, J = 2.9 Hz) and 16.34 (d, J = 3.0 Hz)b.  
31P-NMR (162 MHz, CDCl3): 20.7. IR (ATR) 3433, 1743, 1500, 1244, 1019, 966, 741. HRMS (ESI) m/z: calcd for C20H36NO5P2 [M + H]+ 480.1916, found 480.1917. aOverlapping signals of P(O)(OCH3)2 groups. bOverlapping signals of P(O)(OCH2CH3)2 groups. 

Tetraethyl 1-(N-benzyloxycarbonylamino)pentylene-1,1-bisphosphonate (5i). Colorless crystals; 90% yield (444 mg), mp 56.0 to 57.2 °C. 1H-NMR (400 MHz, CDCl3) δ 7.37–7.29 (m, 5H), 5.47 (br t, J = 8.5 Hz, 1H), 5.08 (s, 2H), 4.26–4.14 (m, 8H)a, 2.38–2.26 (m, 2H), 1.57–1.49 (m, 2H), 1.37–1.25 (m, 2H) and 1.33 (t, J = 7.0 Hz, 6H)b, 1.345 (t, J = 13.6 Hz, 3H), 4.28–4.17 (m, 8H). Overlapping signals of C and P(O)(OCH3)2 groups. 

Tetraethyl 1-(N-benzyloxycarbonylamino)-2-methoxyethylene-1,1-bisphosphonate (15). Colorless crystals; 52% yield (248 mg), oil; 52% yield (248 mg), mp 108.8 to 110.3 °C. 1H-NMR (400 MHz, CDCl3) δ 6.25 (br t, J = 13.0 Hz, 1H), 4.28–4.17 (m, 8H)a, 2.18–2.07 (m, 3H), 2.02 (s, 3H), 1.349 (t, J = 7.0 Hz, 6H) and 1.345 (t, J = 7.0 Hz, 6H)b, 0.96 (d, J = 6.3 Hz, 6H). 13C-NMR (100 MHz, CDCl3) δ: 116.2 (t, J = 6.9 Hz), 63.6 (d, J = 7.3 Hz), 63.1 (d, J = 7.2 Hz), 60.9 (t, J = 143.2 Hz), 38.4 (t, J = 2.6 Hz), 25.4 (t, J = 8.0 Hz), 24.2, 23.9, 16.4 (d, J = 6.0 Hz) and 16.3 (d, J = 6.3 Hz)b. 31P-NMR (162 MHz, CDCl3): 20.9. IR (ATR) 3441, 1682, 1549, 1233, 1026, 971. HRMS (ESI) m/z: calcd for C15H33NO6P2 [M + Na]+ 516.1892, found 516.1891. aOverlapping signals of P(O)(OCH3)2 groups. bOverlapping signals of P(O)(OCH2CH3)2 groups. cOverlapping signals of P(O)(OCH2CH2CH3) and P(O)(OCH2CH2CH2)2 groups. dOverlapping signals of P(O)(OCH3)2 groups.
Tetraethyl 1-(N-benzyloxycarbonylamino)-2-(4-methoxyphenyl)ethylene-1,1-bisphosphonate (5n). Colorless crystals; 74% yield (412 mg), mp 71.7 to 73.5 °C. $^1$H-NMR (400 MHz, CDCl$_3$) δ 7.44–7.34 (m, 5H), 7.14–7.09 (m, 2H), 6.71–6.69 (m, 2H), 5.43 (br t, $J = 12.8$ Hz), 5.17 (s, 2H), 4.29–4.17 (m, 4H), 4.13–4.08 (m, 2H), 4.05–3.91 (m, 2H), 3.75 (s, 3H), 3.52 (dd, $J_1 = 15.3$, $J_2 = 11.8$ Hz, 2H) 1.31 (t, $J = 7.1$ Hz, 6H), 1.21 (t, $J = 7.1$ Hz, 6H).

$^{13}$C-NMR (100 MHz, CDCl$_3$) δ 158.5, 154.9 (t, $J = 8.8$ Hz), 136.3, 132.1, 128.46, 128.45, 128.2, 127.2 (t, $J = 8.6$ Hz), 113.1, 67.0, 63.9 (d, $J = 7.4$ Hz), 63.0 (d, $J = 7.6$ Hz), 61.1 (t, $J = 143.0$ Hz), 55.2, 34.7, 16.3 (d, $J = 6.3$ Hz), 16.2 (d, $J = 6.2$ Hz). $^{31}$P-NMR (162 MHz, CDCl$_3$): 19.0. IR (ATR) 3251, 1715, 1513, 1247, 1028, 953, 774. HRMS (ESI) m/z: calcld for C$_{25}$H$_{37}$NO$_9$NaP$_2$ [M + Na]$^+$ 580.1841, found 580.1839.

4. Conclusions

In conclusion, we developed a simple and efficient methodology for the preparation of N-protected bisphosphonic analogs of protein and non-protein α-amino acids. The optimization of our procedure, consisting of the reaction of 1-(N-acylamino)-1-ethoxyphosphonates 3 with triphenyolphosphonium tetrafluoroborate and triethyl phosphite, highlights the one-pot synthesis conducted in mild conditions. In most cases, there is no need to use any catalyst as it is autocatalytic in nature. Relatively easy access to the starting α-ethoxyphosphonates 3, obtained from ethyl N-acylimidates 2, simple work-up of the reaction mixture and good to excellent yields of the target products 5 are additional advantages of the proposed protocol. The methodology provided constitutes a convenient approach for the synthesis of structurally diverse N-protected 1-aminobisphosphonate derivatives 5 and can be considered a new universal strategy for the construction of bisphosphorus organic compounds containing the P-C(N)-P skeleton.

It is worth emphasizing that the one-pot method reported here proceeds through the indirect transformation of α-ethoxyphosphonates, non-reactive in the Michaelis–Arbuzow-type reaction, into the corresponding phosphonium salts 4 of high reactivity and thus susceptibility to further reaction with phosphorus nucleophiles. This is another confirmation of the synthetic potential of phosphonium salts, which are increasingly gaining in importance. As reactive intermediates, they often enable transformations that are difficult to perform with other methods.

Supplementary Materials: The following can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27113571/s1. Supporting information includes $^1$H, $^{13}$C, $^{31}$P NMR of all new compounds 3, 4c and 5, as well as a tabulated summary of the characteristic $^{13}$C NMR data of these compounds.

Author Contributions: Conceptualization, A.K.; methodology, A.K. and D.K.; formal analysis, A.K., D.K., W.H., K.S. and K.E.; investigation, A.K., D.K., W.H., K.S. and K.E.; writing—original draft preparation, A.K.; writing—review and editing, A.K. and D.K.; visualization, A.K. and D.K.; supervision, A.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of all described compounds are available from the authors.

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