Synthesis of Functionalized Diethyl(pyrrrolidin-2-yl)phosphonate and Diethyl(5-oxopyrrolidin-2-yl)phosphonate

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Abstract: Short and efficient syntheses of functionalized (pyrrolidin-2-yl)phosphonate and (5-oxopyrrolidin-2-yl)phosphonate have been developed. The synthetic strategy involved the diastereospecific 1,3-dipolar cycloaddition of N-benzyl-C-(diethoxyphosphoryl)nitrotrone to cis-1,4-dihydroxybut-2-ene and dimethyl maleate, respectively. O,O-Diethyl 3-carbamoyl-4-hydroxy(5-oxopyrrolidin-2-yl)phosphonate was obtained from O,O-diethyl 2-benzyl-4,5-dimethoxyphenyl(isoxazolidin-3-yl)phosphonate by hydrogenation and subsequent treatment with ammonia, whereas transformation of O,O-diethyl 2-benzyl-4,5-dihydroxymethyl(isoxazolidin-3-yl)phosphonate into O,O-diethyl 3-aminomethyl-4-hydroxy(pyrrrolidin-2-yl)phosphonate was accomplished by mesylation followed by hydrogenolysis to undergo intramolecular cyclization and the introduction of amino group via ammonolysis. Stereochemistry of the isoxazolidine cycloadducts, as well as the final functionalized (pyrrolidin-2-yl)- and (5-oxopyrrolidin-2-yl)phosphonates were established based on conformational analyses using vicinal H–H, H–P, and C–P couplings and supported by the observed diagnostic NOESY correlation signals.

Keywords: cycloaddition; isoxazolidines; phosphonates; substituted pyrrolidines

1. Introduction

Pyrrolidine is an important fragment of many natural products [1–4] that can be exemplified by complex structures of swainsonin [5], monocotamine [6], lasiocarpine [7], and senecionine [8]. Pyrrolidine and pyrrolidinone moieties are also present in small biologically active molecules. For example, L-proline 1 and its hydroxylated analogue 2 (Figure 1) are the essential components of collagen, accounting for 30% of its composition and playing key roles in the stability of the collagen [9,10].

On the other hand, pyroglutamic acid 3 (Figure 1) is formed as a result of glutamate dehydrogenation [11]. This is an intermediate substrate involved in the glutathione synthesis [12]. For decades, the basic structure of pyroglutamic acid has been modified and resulted in the syntheses of pharmacologically active compounds such as piracetam 4, oxiracetam 5, nebracetam 6, and its morpholine derivative 7 (Figure 1), which belong to “nootropic drugs” used in treatment of CNS diseases such as epilepsy and depression [13–18].

Hydroxylated pyrrolidine derivatives 8 and 9 (Figure 1) affected brain Glu levels and at the same time they did not exhibit brain and hepatic toxicity. The only disadvantage of these compounds is their inability to overcome the blood-brain interface [19]. Polyhydroxylated derivative of pyrrolidine 10, its enantiomer and 11 (Figure 1) have been obtained as inhibitors of α-glucosidases. Moreover, compound 11 demonstrates superior control of blood glucose levels [20]. On the other hand, antibiotic activity of several pyrrolidine-containing compounds has been observed, including compounds 12 and 13 [21] containing pyrrolidone ring incorporated in bicyclic system, as well as 14 (derivative of equisetin having additional methyl group at C3 in octahydonaphtalenyl moiety) acting on some...
multi-drug resistant bacteria [22] (Figure 1), and their resistance to β-lactamase have been recognized.

Figure 1. Examples of pyrrolidine- and pyrrolidone-containing biologically active compounds.

Over the decades, the importance of phosphonates in medicinal chemistry has been recognized [23–25]. Numerous phosphonates have been reported as analogues of biologically important compounds, including inhibitors of several enzymes, as well as antibacterial, antiviral, and fungicidal agents. Phosphonates have also been applied as mimetics of hydroxy- and amino acids in studies on their mode of action in biochemical transformations [26]. For this reason, phosphoproline 15 (Figure 2) [27] and its functionalized analogues received considerable attention and some of them have been successfully incorporated in biologically active systems such as analogues of dipeptides [28–33]. On the other hand, pyrrolidinone-containing phosphonate 16 (Figure 2), as a mixture of cyclic and non-cyclic form, has been recognized as inhibit NMCA β-lactamase. Moreover, a good activity of the cyclic form in the mixture of 16a and 16b tested against R39 D,D-peptidase has been proved [34].

Figure 2. Phosphoproline 15 and its functionalized analogues 16 and 17.

Several years ago, stereoisomers of analogues of proline as respective diethyl phosphonates 17 (Figure 2) hydroxylated at C4 in pyrrolidine ring have been synthesized in our research group [35]. Herein the syntheses of phosphonates 18 and 19 containing pyrrolidine framework functionalized at C3 and C4 are described (Scheme 1). Since N-substituted
C-phosphorylated nitrones [36] have been successfully applied in the synthesis of various (isoxazolidin-3-yl)phosphonates [36,37] we found them suitable also for the preparation of isoxazolines 20 and 21, which could be then transformed into the designed compounds 18 and 19 or their functionalized analogues. While isoxazolidine cycloadducts obtained from allyl alcohol and C-phosphorylated nitrone have already been successfully transformed into compound 17 (Figure 2) having hydroxy group at C4 in pyrrolidine skeleton [35], the application of 1,4-dihydroxybut-2-ene in 1,3-dipolar cycloaddtion would allow to synthesis pyrrolidine 19 functionalized in both C3 and C4 positions. On the other hand, rearrangement of isoxazolidine 20 to pyrrolidinone 18 would be possible following the strategy demonstrated for several examples of differently functionalized systems [38–41].

![Scheme 1](image1)

Scheme 1. Retrosynthesis of 18 and 19.

2. Results and Discussion

The nitrone 22 was synthesized and fully characterized previously [36]. Cycloaddition of nitrone 22 with dimethyl maleate was then performed and led to the formation of (isoxazolidin-3-yl)phosphonate 20 as a single diastereoisomer in 84% yield after chromatographic purification. Similarly, reaction of nitrone 22 with cis-1,4-dihydroxybut-2-ene gave diastereoisomeric cycloadduct 21 in 70% yield after column chromatography (Scheme 2). In both cases, formation of single diastereoisomeric product (20 or 21) was proved by the analyses of the $^{31}$P and $^1$H NMR spectra of the crude product.

![Scheme 2](image2)

Scheme 2. Reaction and conditions: a. toluene, 60 °C (reaction time: 24 h for the synthesis of 20 and 96 h for the synthesis of 21).

On the other hand, when maleic anhydride was used in the 1,3-dipolar cycloaddition with nitrone 22 isoxazolidine 23 was obtained exclusively in good yield (Scheme 3).

![Scheme 3](image3)

Scheme 3. Reaction and conditions: a. toluene, 24 h, 60 °C, 74%.
Since cis-alkenes were used for cycloadditions (Schemes 2 and 3), the cis relationship between HC4 and HC5 protons in 20 and 21, as well as in 23 can be arbitrarily assigned. To establish a relative configuration of (isoxazolidin-3-yl)phosphonate 18 the detailed conformational analysis was performed based on HCCP [42], HCCP [43,44], and CCCP [45,46] vicinal constants extracted from the $^1$H and $^{13}$C-NMR spectra. The vicinal couplings ($J$(H-C3C4-H)) = 8.0 Hz, $J$(H-C4C5-H)) = 8.3 Hz, $J$(P-CC-C5) = 8.0 Hz, and $J$(P-CN-CO) = 5.5 Hz) indicate the $^{3}E$ conformation of isoxazolinedine ring. In this conformation the pseudoequatorially located diethoxyphosphoryl group at C3 is in trans relationship to both COOMe groups at C4 and C5 positions (Figure 3). On the other hand, to gather evidences for the spatial orientation of substituents in relation to the isoxazolidine moiety in (isoxazolidin-3-yl)phosphonate 21, NOESY experiment was performed. NOE diagnostic signals between HC4 and CH$_2$OP as well as between HC3 and C4-CH$_2$OH protons were noticed (Figure 3), which fully support the trans relationship between the HC3 and HC4 protons.

![Figure 3. The preferred conformation of 20 and the most important NOESY correlation for phosphonate 21 (blue arrows).](image)

Next, transformation of (isoxazolidin-3-yl)phosphonate 20 into (5-oxopyrrolidin-2-yl)phosphonate 24 was performed (Scheme 4). Hydrogenation of the N–O bond together with the removal of benzyl group in isoxazolidine 20 released the free amino group, which subsequently became involved in spontaneous intramolecular cyclization to γ-lactam to produce phosphonate 18 in good yield (75%). When hydrogenation was carried out at a pressure of 15 bar, reaction time was significantly shortened (24 h vs. 5 h); moreover, the application of this procedure allowed to isolate compound 16 in higher yield (94%). Since configurations of all stereogenic centers in isoxazolidine ring (namely at C3, C4, and C5) remain unchanged during this transformation, relative configuration of γ-lactam ring (at C2, C3, and C4, respectively) in 18 can be established unambiguously. 3-Methoxycarbonyl-(5-oxopyrrolidin-2-yl)phosphonate 18 was then successfully transformed into 3-carbamoyl derivative 24 via ammonolysis (56%).

![Scheme 4. Synthesis of γ-lactam 24. Reaction and conditions: a. H$_2$, Pd(OH)$_2$–C, MeOH, rt, 1.01 bar, 24 h, 75% or H$_2$, Pd(OH)$_2$–C, MeOH, rt, 15 bar, 5 h, 94%; b. aq. NH$_3$, MeOH, 17 h, 56%.](image)

In order to support the already established relative stereochemistry of (5-oxopyrrolidin-2-yl)phosphonates 18 and 24, conformational analyses were undertaken. Based on the vicinal couplings found in $^1$H and $^{13}$C-NMR spectra of 18 ($J$(H-C3C4-H)) = 8.8 Hz, $J$(H-C2C3-H)) = 8.8 Hz, $J$(H-C3C2-P) = 17.6 Hz, $J$(P-CC-C4) = 7.8 Hz and $J$(P-CN-CO) = 7.8 Hz) and 24 ($J$(H-C3C4-H)) = 9.1 Hz, $J$(H-C2C3-H)) = 9.0 Hz, $J$(H-C3C2-P) = 18.0 Hz, $J$(P-CC-C4) = 8.7 Hz
and $J(P-CN-CO) = 7.9$ Hz), the preferred $^3E$ conformation of oxopyrrolidine ring was established in both phosphonates 18 and 24. In this conformation all substituents at C2, C3, and C4, namely OH, COR, and P(O)(OEt)$_2$ groups are located equatorially, consequently hydrogen atoms occupy axial positions (Figure 4). Moreover, when NOESY experiments were performed for both phosphonates 18 and 24, NOE diagnostic signals between HC4 and HC2 protons were noticed, which fully support their cis orientations.

![Figure 4. The preferred conformations of 18 and 24 with the most important NOESY correlations (blue arrow).](image)

On the other hand, (isoxazolidin-3-yl)phosphonate 21 was found to be a good substrate for the synthesis of functionalized phosphoproline derivative (Scheme 5). Phosphonate 21 was first mesylated to produce O,O-dimesyl derivative 25, which was then subjected to hydrogenolysis to accomplish cleavage of N–O bond followed by removal of benzyl group together with intramolecular cyclization to form pyrrolidine ring in compound 26 [35]. The resulted crude ammonium mesylate 26 was then neutralized with potassium carbonate in chloroform to give functionalized phosphoproline analogue 27 (38% yield in two steps). Again, when hydrogenation was carried out at 15 bar pressure, the reaction time required for transformation of (isoxazolidin-3-yl)phosphonate 25 into ammonium mesylate 26 was significantly shortened (22 h vs. 6 h), and after neutralization with potassium carbonate phosphoproline analogue 27 was obtained efficiently (70% yield in two steps). Finally, compound 27 was reacted with morpholine to give 28 in 33% yield. Alternatively, mesyl group in 27 was changed to amino function by treatment with sodium azide followed by hydrogenolysis in the presence of Boc$_2$O to produce phosphonate 30 (Scheme 5).

![Scheme 5. Synthesis of functionalized proline analogues 28 and 30. Reaction and conditions: a. MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 2 h, 96%; b. H$_2$, Pd(OH)$_2$–C, MeOH, 1.01 bar, 22 h or H$_2$, Pd(OH)$_2$–C, MeOH, 15 bar, 6 h; c. K$_2$CO$_3$, CHCl$_3$, rt, 3 h, (38% and 70% in two steps: b and c); d. morpholine, neat, rt, 39 h, 33%; e. NaN$_3$, MeOH, 60 °C, 96 h, 43%; f. H$_2$, Pd(OH)$_2$–C, Boc$_2$O, EtOH, rt, 35 h, 69%.](image)
3. Materials and Methods

3.1. General Information

1H-NMR spectra were taken in CDCl$_3$, C$_6$D$_6$ or CD$_3$OD on a Bruker Avance III (600 MHz, Bruker Instruments, Karlsruhe, Germany). For spectra recorded in CDCl$_3$ and C$_6$D$_6$, TMS was used as an internal standard; chemical shifts $\delta$ are given in ppm with respect to TMS and coupling constants $J$ in Hz. 13C-NMR and 31P-NMR spectra were recorded in a 1H-decoupled mode for CDCl$_3$, C$_6$D$_6$ or CD$_3$OD solutions on the Bruker Avance III (600 MHz) spectrometer at 151 and 243 MHz, respectively. IR spectral data were measured on a Bruker Alpha-T FT-IR spectrometer (Bruker Optik GmbH, Ettlingen, Germany). Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Faculty of Pharmacy (Medical University of Lodz) on a Perkin Elmer PE 2400 CHNS analyzer (Perkin-Elmer Corp., Norwalk, CT, USA), and their results were found to be in good agreement (±0.3%) with the calculated values. Experiments at 15 bar pressure were carried out in a Büchi pressure reactor (Büchi AG, Uster, Switzerland).

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh), analytical TLC, Merck TLC plastic sheets silica gel 60 F$_{254}$. TLC plates were developed in chloroform-methanol solvent systems. Visualization of spots was affected with iodine vapors. All solvents were purified by methods described in the literature.

1H$_3$, 13C- and 31P-NMR spectra of all new synthesized compounds are provided in Supplementary Materials.

3.2. General Procedure for the Synthesis of Isoxazolidines 20, 21 and 23

A solution of nitrone 22 (2.0 mmol) and alkene (2.2 mmol) in toluene (4 mL) were stirred at 60 °C for 24 to 96 h (until the disappearance of the nitrone). The reaction mixture was concentrated in vacuo. The crude product was purified by silica gel column.

Dimethyl 2-benzyl-3-(diethoxyphosphoryl)isoxazolidine-4,5-dicarboxylate (20). Compound 20 was prepared from nitrone 22 (2.00 mmol, 0.542 g) and dimethyl maleate (2.20 mmol, 0.276 mL) and purified by column chromatography on a silica gel column with hexane-ethyl acetate (3:2, v/v) and crystallization (chloroform-hexane). Yield: 84% (0.697 g) as a white solid; m.p. = 75–78 °C. IR (KBr, cm$^{-1}$): $\nu_{\text{max}}$ = 2989, 2953, 2908, 1765, 1738, 1442, 1315, 1269, 1221, 1171, 1057, 1026, 984, 743, 707. 1H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.45–7.42 (m, 2H, $H_{Ar}$); 7.34–7.31 (m, 2H, $H_{Ar}$); 7.29–7.27 (m, 1H, $H_{Ar}$); 4.70 (d, $^{3}J_{H_{5}-H_{4}} = 8.3$ Hz, 1H, $HC_{5}$); 4.52 (d, $^{3}J_{H_{5}-H_{4}} = 14.0$ Hz, 1H, $HC_{5}$); 4.28–4.16 (m, 5H, 2 × $CH_{2}$OP; $HC_{4}$); 3.95 (dd, $^{3}J_{H_{4}-P} = 16.3$ Hz, $^{3}J_{H_{3}-H_{4}} = 8.3$ Hz, $^{3}J_{H_{2}-H_{3}} = 8.0$ Hz, 1H, $HC_{4}$); 3.80 (dd, $^{3}J_{H_{3}-H_{4}} = 8.0$ Hz, $^{3}J_{H_{2}-H_{3}} = 2.8$ Hz, 1H, $HC_{3}$); 3.73 (s, 3H, $CH_{3}$O); 3.71 (s, 3H, $CH_{3}$O); 1.35 (t, $^{3}J = 7.0$ Hz, 3H, $CH_{3}$OP); 1.31 (t, $^{3}J = 7.0$ Hz, 3H, $CH_{3}$OP). 13C NMR (151 MHz, CDCl$_3$): $\delta$ = 169.29 (d, $^{3}_{PCCC} = 5.5$ Hz, C(O)C4), 168.88 (C(O)C5), 137.16, 129.10, 128.26, 127.41, 77.39 (d, $^{3}_{PCCC} = 8.0$ Hz, C5), 63.96 (d, $^{3}_{PC} = 169.6$ Hz, C3), 63.93 (d, $^{3}J = 6.5$ Hz, $CH_{2}$N), 62.90 (d, $^{3}J = 5.7$ Hz, COP), 62.88 (d, $^{3}J = 5.7$ Hz, COP), 53.45 (C(O)O), 52.76 (C(O)O), 52.47 (C4), 16.54 (d, $^{3}J = 5.8$ Hz, COP), 16.35 (d, $^{3}J = 5.7$ Hz, COP). 31P NMR (243 MHz, CDCl$_3$): $\delta$ = 19.14. Analysis Calculated for C$_{31}$H$_{26}$NO$_{8}$P: C, 52.05; H, 6.31; N, 3.37; Found: C, 52.05; H, 6.31; N, 3.36.

Diethyl 2-benzyl-3-dihydroxy-isoxazolidinyl-3-phosphonate (21). Compound 21 was prepared from nitrone 22 (2.00 mmol, 0.542 g) and cis-2-butene-1,4-diol (2.20 mmol, 0.194 mL) and purified by column chromatography on a silica gel column with chloroform-methanol (50:1, v/v). Yield: 70% (0.502 g) as a yellowish oil. IR (film, cm$^{-1}$): $\nu_{\text{max}}$ = 3385, 3064, 3032, 1497, 1299, 1050, 1025, 973, 740, 573. 1H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.40–7.38 (m, 2H, $H_{Ar}$); 7.35–7.30 (m, 1H, $H_{Ar}$); 7.30–7.26 (m, 1H, $H_{Ar}$); 4.55 (d, $^{3}J_{H_{5}-H_{4}} = 14.5$ Hz, 1H, $HC_{5}$); 4.32–4.20 (m, 4H, 2 × $CH_{2}$OP; $HC_{4}$); 4.13 (dd, $^{3}J_{H_{4}-H_{3}} = 9.7$ Hz, $^{3}J_{H_{5}-H_{4}} = 5.9$ Hz, $^{3}J_{H_{5}-H_{4}} = 3.5$ Hz, 1H, $HC_{5}$); 3.89 (d, $^{3}J_{H_{3}-H_{4}} = 14.5$ Hz, 1H, $HC_{4}$); 3.86 (dd, $^{3}J_{H_{4}-H_{3}} = 12.5$ Hz, $^{3}J_{H_{5}-H_{4}} = 5.9$ Hz, 1H, $HC_{5}$); 3.76 (dd, $^{3}J_{H_{4}-H_{3}} = 12.5$ Hz, $^{3}J_{H_{5}-H_{4}} = 3.5$ Hz, 1H, $HC_{5}$), 3.78–3.74 (m, 2H, $CH_{2}$C4), 3.10–3.00 (m, 2H, $HC_{4}$, $HC_{5}$), 3.00–2.95 (m, 2H, $HC_{4}$, $HC_{5}$), 2.80–2.75 (m, 2H, $HC_{4}$, $HC_{5}$), 2.00–1.95 (m, 2H, $HC_{4}$, $HC_{5}$), 1.90–1.85 (m, 2H, $HC_{4}$, $HC_{5}$).
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3.3. Preparation of γ-Lactam 18

Procedure A: A solution of isoxazolidine 20 (0.045 g, 0.108 mmol) in methanol (1 mL) was kept under an atmospheric pressure of hydrogen over 20% Pd(OH)2–C (1.4 mg) at room temperature for 24 h. The suspension was filtered through a layer of Celite. The solution was concentrated, and the residue was chromatographed on silica gel column with chloroform-methanol (10:1, v/v).

Procedure B: A solution of isoxazolidine 20 (0.208 g, 0.50 mmol) in methanol (5 mL) was kept in a pressure reactor under 15 bar pressure of hydrogen over 20% Pd(OH)2–C (6.5 mg) at room temperature for 5 h. The suspension was filtered through a layer of Celite. The solution was concentrated, and the residue was chromatographed on a silica gel column with chloroform-methanol (100:1, v/v) to give pure γ-lactam 18 (0.024 g, 0.081 mmol, 75%).

Methyl 2-(diethoxyphosphoryl)-4-hydroxy-5-oxypyrrrolidine-3-carboxylate (18). White solid; m.p. = 120–124 °C. IR (KBr, cm−1): νmax = 3296, 3189, 3126, 2989, 2957, 2925, 2796, 1741, 1713, 1441, 1374, 1178, 1049, 1010, 862, 753. 1H NMR (600 MHz, CDCl3): δ = 7.15 (brs, 1H, NH), 4.54 (d, 3JH3–OH = 7.6 Hz, 1H, OH), 4.46 (dd, 3JH3–H4 = 8.8 Hz, 3JH3–OH = 7.6 Hz, 1H, H4C4), 4.25–4.14 (m, 4H, 2 × CH2OP), 4.07 (dd, 3JH3–H2 = 8.8 Hz, 3JH2–H2 = 3.2 Hz, 1H, H2C2), 3.79 (s, 3H, CH3O), 3.40 (dt, 3JH3–P = 17.6 Hz, 3JH3–H3 = 8.8 Hz, 3JH3–H2 = 8.8 Hz, 1H, H3C3), 1.35 (t, 3JH2–H3 = 7.0 Hz, 3H, CH3CH2OP), 1.32 (t, 3JH2–H3 = 7.0 Hz, 3H, CH3CH2OP). 13C NMR (151 MHz, CDCl3): δ = 174.94 (d, 3JPCNC = 7.8 Hz, C5), 171.35 (d, 3JPCNC = 2.3 Hz, C(O)CH3), 72.89 (d, 3JPCPC = 7.8 Hz, C4), 63.77 (d, 3JH3–P = 7.1 Hz, COP), 63.66 (d, 3JH3–P = 7.1 Hz, COP), 52.82 (CH3O), 49.72 (d, 3JCCP = 4.3 Hz, C3), 48.65 (d, 1JC = 167.1 Hz, CP), 16.41 (d, J = 6.0 Hz, COP), 16.36 (d, J = 6.0 Hz, COP). 31P NMR (243 MHz, CDCl3) δ = 20.63.
Analysis Calculated for C_{19}H_{18}NO_{7}P: C, 40.68; H, 6.15; N, 4.74. Found: C, 40.88; H, 6.23; N, 4.91.

3.4. Ammonolysis of 18

To a solution of γ-lactam 18 (0.030 g, 0.10 mmol) in methanol (0.5 mL), aqueous NH_{3} (25%, 0.4 mL) was added. The homogenous mixture was stirred at room temperature for 17 h. Solvents were removed in vacuo, and the residue was evaporated with anhydrous methanol (3 × 5 mL), chloroform (3 × 5 mL) and chromatographed on silica gel with chloroform-methanol (10:1, v/v) to give pure 24 (0.016 g, 60%).

2-(diethoxyphosphoryl)-4-hydroxy-5-oxopyrrolidine-3-carboxamide (24). White solid; m.p. = 133–135 °C. IR (KBr, cm\(^{-1}\)): \(\nu_{\text{max}} = 3500, 3199, 2986, 1711, 1679, 1231, 1045, 1020.\)

\(^1\)H NMR (600 MHz, CD_{3}OD): \(\delta = 4.40\) (d, \(^3\)J\text{H-H} = 9.0 Hz, 1H, HC4), 4.25–4.20 (m, 4H, 2 × CH_{2}OP), 4.08 (dd, \(^3\)J\text{H-H} = 9.0 Hz, \(^2\)J\text{H-H} = 2.0 Hz, 1H, HC2), 3.18 (dt, \(^3\)J\text{H-H} = 18.0 Hz, \(^3\)J\text{H-H} = 9.0 Hz, 1H, HC3), 1.38 (t, \(^3\)J\text{H-H} = 7.0 Hz, 6H, 2 × CH_{3}CH_{2}OP). \(^13\)C NMR (151 MHz, CD_{3}OD): \(\delta = 174.65\) (d, \(^3\)J\text{PCNC} = 7.9 Hz, C5), 74.11 (d, \(^3\)J\text{PC} = 8.7 Hz, C4), 64.91 (d, \(\delta = 6.7 Hz, COP), 64.82 (d, \(\delta = 6.7 Hz, COP), 51.83 (d, \(\delta = 4.3 Hz, C3), 49.51 (d, \(\delta = 167.4 Hz, CP), 16.74 (d, \(\delta = 5.6 Hz, CCOP), 16.67 (d, \(\delta = 5.4 Hz, CCOP). \(^31\)P NMR (243 MHz, CD_{3}OD) \(\delta = 21.25\). Analysis Calculated for C_{9}H_{17}N_{2}O_{6}P: C, 38.58; H, 6.12; N, 10.00. Found: C, 38.29; H, 6.33; N, 9.92.

3.5. Mesylation of (Isoxazolidin-3-yl)Phosphonate 21

To a solution of isoxazolidine 21 (0.188 g, 0.523 mmol) in methylene chloride (6 mL) triethylamine (1.569 mmol, 0.219 mL) and mesyl chloride (1.569 mmol, 0.122 mL) were added at 0°C. The reaction mixture was stirred at this temperature for 2 h. The residue was washed with water (3 × 3 mL) and dried over MgSO_{4}. The solution was concentrated, and the residue was chromatographed on silica gel column with chloroform to give pure dimesylate 25 (0.250 g, 96%).

Diethyl 2-benzyl-4,5-(dimesyloxymethyl)-3-phosphonate (25). Colourless oil. IR (film, cm\(^{-1}\)): \(\nu_{\text{max}} = 3030, 2986, 2934, 1243, 1177, 1052, 964, 812, 754, 628.\) \(^1\)H NMR (600 MHz, CDCl_{3}): \(\delta = 7.39–7.33\) (m, 4H, A_{4}), 7.31–7.28 (m, 1H, A_{3}), 4.39 (d, \(\delta = 7.0 Hz, H_{A_{2}}\)) = 14.3 Hz, 1H, HA_{2}CPh), 4.46 (dd, \(\delta = 16.6 Hz, 1H, HA_{1}C-C_{4}), 4.40 (dd, \(\delta = 11.6 Hz, 1H, HA_{3}C-C_{4}), 4.43–4.42 (m, 7H, 2 × CH_{2}OP, 16.67 (d, \(\delta = 5.6 Hz, CCOP), 16.67 (d, \(\delta = 5.4 Hz, CCOP). \(^31\)P NMR (151 MHz, CDCl_{3}): \(\delta = 33.00, 31.99, 29.86, 17.11, 16.79, 12.31, 10.45, 10.20.\)

\(^13\)C NMR (151 MHz, CDCl_{3}): \(\delta = 136.22, 129.30, 122.29, 127.65, 75.93 (d, \(\delta = 33.00, 31.99, 29.86, 17.11, 16.79, 12.31, 10.45, 10.20.\)

\(^31\)P NMR (151 MHz, CDCl_{3}): \(\delta = 33.00, 31.99, 29.86, 17.11, 16.79, 12.31, 10.45, 10.20.\)

3.6. The Synthesis of (Pyrrolidin-2-yl)Phosphonate 24 from Dimesylate 25

Procedure A: A solution of dimesylate 25 (0.20 g, 0.39 mmol) in methanol (2.5 mL) was kept under atmospheric pressure of hydrogen over 20% Pd(OH)_{2}-C (3.9 mg) at room temperature for 22 h. The reaction progress was controlled by TLC. The suspension was filtered through a layer of Celite. The solution was concentrated, and the residue was chromatographed on silica gel column with chloroform-methanol (10:1, v/v) to give pure 27 (0.049 g, 38%).
Procedure B: A solution of dimesylate 25 (0.236 g, 0.46 mmol) in methanol (5 mL) was kept in a pressure reactor under 15 bar pressure of hydrogen over 20% Pd(OH)$_2$-C (10 mg) at room temperature for 6 h. The suspension was filtered through a layer of Celite. The solution was concentrated to give ammonium mesylate 26 (2 mg), which was then dissolved in chloroform (10 mL) and anhydrous potassium carbonate (0.127 g, 0.92 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. Then anhydrous MgSO$_4$ was added, and the suspension was filtered through a layer of Celite. The solution was concentrated, and the residue was chromatographed on silica gel column with chloroform-methanol (100:1, v/v) to give pure 27 (0.106 g, 70%).

Diethyl 4-hydroxy-3-mesyloxyaminomethyl(pyrrolidin-2-yl)-phosphonate (27). Colorless oil. IR (film, cm$^{-1}$): $\nu_{max}$ = 3386, 2986, 2875, 1644, 1532, 1222, 1174, 1025, 970, 818. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 4.31 (dd, $J$ = 10.2 Hz, $J$ = 5.6 Hz, 1H, HCH-C3), 4.25–4.15 (m, 6H, HCC, HCH-C3, 2 × CH$_2$OP), 3.26 (dd, $J$$_{H2-P}$ = 7.9 Hz, $J$$_{H2-H3}$ = 5.8 Hz, 1H, HC2), 3.17 (dd, $J$$_{Ha-Hb}$ = 11.5 Hz, $J$$_{H1-H}$ = 5.3 Hz, 1H, HHC5), 3.10 (dd, $J$$_{Ha-Hb}$ = 11.4 Hz, $J$$_{H5-H}$ = 3.0 Hz, 1H, HHC5), 3.06 (s, 3H, CH$_3$), 2.65 (dddd, $J$$_{H-P}$ = 18.5 Hz, $J$$_{H-H-C}$ = 5.8 Hz, $J$$_{H-H-H}$ = 5.8 Hz, $J$$_{H-H-H}$ = 3.0 Hz, 1H, HHC5), 1.36 (t, $J$ = 7.1 Hz, 3H, CH$_2$CH$_2$OP), 1.35 (t, $J$ = 7.1 Hz, 3H, CH$_2$CH$_2$OP). $^1$H NMR (600 MHz, CD$_2$OD): $\delta$ = 4.45 (dd, $J$ = 10.3 Hz, $J$ = 4.3 Hz, 1H, CH$_2$-C3), 4.35 (dd, $J$ = 10.3 Hz, $J$ = 5.2 Hz, 1H, CH$_2$-C3), 4.27–4.20 (m, 4H, 2 × CH$_2$OP), 4.18 (dd, $J$ = 5.9 Hz, $J$ = 5.8 Hz, 1H, HC4), 3.30 (dd, $J$$_{H2-P}$ = 8.9 Hz, $J$$_{H2-H3}$ = 8.8 Hz, 1H, HC2), 3.15 (s, 3H, CH$_3$), 3.06 (dd, $J$$_{Ha-Hb}$ = 11.5 Hz, $J$$_{H1-H}$ = 3.0 Hz, 1H, HHC5), 2.86 (dddd, $J$$_{H-P}$ = 11.5 Hz, $J$$_{H-H-C}$ = 5.7 Hz, $J$$_{H-H-H}$ = 5.7 Hz, 1H, HHC5), 2.47 (dddd, $J$$_{H-P}$ = 18.0 Hz, $J$$_{H-H-C}$ = 8.8 Hz, $J$$_{H-H-H}$ = 5.8 Hz, $J$$_{H-H-H}$ = 5.2 Hz, 1H, HHC5), 1.39 (t, $J$ = 7.1 Hz, 3H, CH$_2$CH$_2$OP), 1.38 (t, $J$ = 7.1 Hz, 3H, CH$_2$CH$_2$OP).

$^{13}$C NMR (151 MHz, CD$_2$OD): $\delta$ = 74.65 (d, $J$$_{PCC}$ = 7.9 Hz, C4), 69.44 (d, $J$$_{PCC}$ = 2.6 Hz, COMs), 64.48 (d, $J$ = 7.1 Hz, COP), 64.21 (d, $J$ = 7.2 Hz, COP), 55.35 (d, $J$$_{PC}$ = 167.5 Hz, C2), 55.09 (d, $J$$_{PC}$ = 8.9 Hz, C5), 50.19 (C3), 37.13 (CH$_3$), 16.80 (d, $J$ = 5.6 Hz, POCC), 16.80 (d, $J$ = 5.7 Hz, POCC). $^{31}$P NMR (243 MHz, CDCl$_3$): $\delta$ = 26.33. Analysis Calculated for C$_{10}$H$_{22}$NO$_7$PS: C, 36.25; H, 6.69; N, 4.23. Found: C, 36.46; H, 6.96; N, 4.20.

3.7. Synthesis of (Pyrrrolidin-2-yl)Phosphonate 28

(Pyrrolidin-2-yl)-phosphonate 27 (0.040 g, 0.12 mmol) with morpholine (1.5 mL) was kept at room temperature for 39 h. After that chloroform (15 mL) was added. The solution was washed with water (2 × 10 mL), dried over MgSO$_4$ and concentrated. The solution was chromatographed on silica gel column with chloroform-methanol (100:1, 50:1, v/v) to give pure 28 (0.014 g, 33%).

Diethyl (4-hydroxy-3-(piperidin-1-ylmethyl)pyrrolidin-2-yl)phosphonate (28). Colourless oil. IR (film, cm$^{-1}$): $\nu_{max}$ = 3442, 2960, 2930, 2859, 2815, 1646, 1446, 1222, 1049, 1027. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 4.30–4.05 (m, 4H, 2 × CH$_2$OP), 4.08–4.05 (br m, 1H, HHC4), 3.75–3.70 (br m, 4H), 3.37 (dd, $J$$_{H2-P}$ = 5.4 Hz, $J$$_{H2-H3}$ = 5.4 Hz, 1H, HC2), 3.27 (dd, $J$$_{Ha-Hb}$ = 10.9 Hz, $J$$_{H1-H}$ = 5.6 Hz, 1H, HHC5), 3.03 (dd, $J$$_{Ha-Hb}$ = 10.9 Hz, $J$$_{H1-H}$ = 4.5 Hz, 1H, HHC5), 2.60–2.45 (m, 7H, HCC, 3 × CH$_2$-C3), 1.38 (t, $J$ = 7.1 Hz, 3H, CH$_2$CH$_2$OP), 1.36 (t, $J$ = 7.1 Hz, 3H, CH$_2$CH$_2$OP). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 77.16 (d, $J$$_{PCC}$ = 5.4 Hz, C4), 66.69 (CH$_2$-O-CH$_2$), 61.11 (d, $J$$_{PCC}$ = 8.8 Hz, CH$_2$N), 63.12 (d, $J$ = 7.4 Hz, COP), 62.37 (d, $J$ = 7.5 Hz, COP), 55.64 (d, $J$$_{PC}$ = 166.1 Hz, C2), 53.75 (2 × CH$_2$N), 53.60 (d, $J$$_{PC}$ = 6.6 Hz, C5), 45.40 (C3), 16.62 (d, $J$ = 5.5 Hz, POCC), 16.54 (d, $J$ = 5.9 Hz, POCC). $^{31}$P NMR (243 MHz, CDCl$_3$): $\delta$ = 28.04. Analysis Calculated for C$_{13}$H$_{27}$N$_2$O$_3$P: C, 48.44; H, 8.44; N, 8.69. Found: C, 48.27; H, 8.48; N, 8.93.

3.8. Synthesis of azide 29

To a solution of mesylate 27 (0.100 g, 0.30 mmol) in methanol (2 mL) sodium azide was added (0.060 g, 0.90 mmol). The reaction mixture was stirred at 60°C for 96 h. The solvent was removed and the residue was chromatographed on silica gel column with chloroform-methanol (100:1, 50:1, v/v) to give pure azide 29 (0.036 g, 43%).
Diethyl (3-(azidomethyl)-4-hydroxyzyxolidine-2-yl)phosphonate (29). Colourless oil. IR (film, cm⁻¹): νmax = 3535, 2985, 2933, 2872, 2103, 1648, 1445, 1354, 1225, 1175, 1026, 970. 

¹H NMR (600 MHz, CDCl₃): δ = 4.26–4.13 (m, 4H, 2 × CH₂OP), 4.11 (dd, 3JH₄-H₅ = 5.2 Hz, 3JH₄-H₃ = 2.5 Hz, 3JH₂-H₃ = 2.5 Hz, 1H, HC₄), 3.45 (dd, 2JH₄-H₃ = 12.2 Hz, 2JH₁-H₃ = 6.7 Hz, 4JH₁-P = 0.9 Hz, 1H, HCHN₃), 3.40 (dd, 2JH₁-H₄ = 12.2 Hz, 2JH₁-H₃ = 6.7 Hz, 1H, HCH₅N₃), 3.23 (dd, 2JH₂-H₁ = 7.2 Hz, 3JH₁-H₂ = 4.8 Hz, 1H, HC₂), 3.17 (dd, 2JH₄-H₂ = 11.3 Hz, 3JH₃-H₄ = 5.2 Hz, 1H, HHC₅), 3.07 (dd, 2JH₃-H₀ = 11.3 Hz, 3JH₅-H₄ = 2.5 Hz, 1H, HHC₅), 2.79 (dd, 2JH₅-H₂ = 7.0 Hz, 3JH₂-H₃ = 6.7 Hz, 3JH₁-H₂ = 4.8 Hz, 3JH₃-H₄ = 2.5 Hz, 1H, HHC₅), 1.36 (t, 3J = 7.1 Hz, 6H, 2 × CH₃CH₂OP). ¹³C NMR (151 MHz, CDCl₃): δ = 75.36 (d, 3JPCCCC = 5.5 Hz, C₄), 63.36 (d, J = 6.9 Hz, COP), 58.24 (d, J = 7.0 Hz, COP), 55.94 (d, JPC = 164.1 Hz, C₂), 56.87 (d, JPCNC = 8.6 Hz, C₅), 52.48 (d, JPCCCC = 10.5 Hz, CH₂N₃), 49.35 (C₃), 16.57 (d, J = 5.5 Hz, POCC), 16.53 (d, J = 5.5 Hz, POCC). ³¹P NMR (243 MHz, CDCl₃): δ = 27.42. Analysis Calculated for C₉H₁₉N₄O₄P: C, 38.85; H, 6.88; N, 20.14. Found: C, 39.03; H, 6.94; N, 20.11.

3.9. Synthesis of (Pyrrolidin-2-yl)Phosphonate 30

A solution of azide 29 (0.036 g, 0.13 mmol) Boc₂O (0.125 g, 0.572 mmol) in ethanol (0.5 mL) was kept under atmospheric pressure of hydrogen over 20% Pd(OH₂)₂C (1.7 mg) at room temperature for 35 h. The suspension was filtered through a layer of Celite. The solution was concentrated, and the residue was chromatographed on silica gel column with chloroform-methanol (100:1, 50:1, 25:1, 10:1) to give pure 27 (0.050 g, 69%).

tert-butyl 3-[(tert-butoxycarbonyl)amino]methyl]-2-(diethoxyphosphoryl)-4-hydroxypyrrolidin-1-carboxylate (30). Colourless oil. IR (film, cm⁻¹): νmax = 3312, 2980, 2933, 1743, 1703, 1519, 1279, 1125, 1028. ¹H NMR (600 MHz, CDCl₃): δ = 5.40–5.00 (br s, 1H, OH), 4.80–4.72 (br m, 1H, HC₄), 4.25–4.15 (br m, 5H, 2 × CH₂OP and HCHN), 4.10–4.00 (br m, 1H, HCHN), 3.48–3.40 (br m, 1H, HCH₅), 3.28–3.20 (br m, 2H, HC₂ and HC₅), 2.85–2.70 (m, 1H, H₃C), 1.50 (s, 9H, (CH₃)₃C), 1.48 (s, 9H, (CH₃)₃C), 1.46 (br s, 9H, (CH₃)₃C), 1.35 (t, J = 7.0 Hz, 6H, 2 × CH₃CH₂OP). ¹³C NMR (151 MHz, CDCl₃): δ = 165.12 (C=O), 153.75 (C=O), 152.98 (C=O), 82.86 (C(CH₃)₃), 80.78 (C(CH₃)₃), 79.37 (C(CH₃)₃), 76.01 (very broad s, C₄, 60%) and 75.13 (very broad s, C₄, 40%), 62.83 (d, J = 7.2 Hz, CH₂OP), 62.53 (br d, J = 7 Hz, CH₂OP), 55.76 (very broad d, J = 167 Hz, C₂, 40%) and 54.75 (very broad d, J = 164 Hz, C₂, 60%), 50.47 (very broad s, C₅, 60%) and 50.11 (very broad s, C₅, 40%), 47.00 (very broad s, CH₂N, 40%) and 45.45 (very broad s, CH₂N, 60%), 42.46 (C₃, 60%) and 41.93 (C₃, 40%), 28.37, 28.26, 27.71, 16.48 (d, J = 5.7 Hz, POCC), 16.43 (very broad s, POCC). ³¹P NMR (243 MHz, CDCl₃): δ = 24.06. Analysis Calculated for C₂₁H₄₅N₂O₄P: C, 52.16; H, 8.21; N, 5.07. Found: C, 52.32; H, 8.14; N, 5.02.

4. Conclusions

The 1,3-dipolar cycloadditions of N-benzyl-C-(diethoxyphosphoryl)nitrone 22 with dimethyl maleate and cis-1,4-dihydroxynbut-2-ene, as well as maleic anhydride proceeded diastereospecifically to give cycloadducts 20, 21 and 23, respectively. Isoxazolidine 20 was smoothly hydrogenated to substituted (5-oxopyrrolidin-2-yl)phosphonate 18 and subsequently transformed into derivative 24 by exchanging of COOMe at C₃ into amido function. For transformation of isoxazolidine 21 into functionalized derivative of (pyrrolidin-2-yl)phosphonate 28, reaction sequence consisted of a standard mesylation of both hydroxy groups, a hydrogenolytic cleavage of the N–O bond, removal of benzyl group followed by spontaneous formation of the pyrrolidine ring by intramolecular SN₂ reaction and finally exchanging the other mesyloxy group to amino function. Since 3-methoxy carbonyl-(5-oxopyrrolidin-2-yl)phosphonate 18 and 3-mesylkoxy methyl(pyrrolidin-2-yl)phosphonate 27 contain reactive groups, i.e., COOMe at C₃ in 18 and MsO at C₃ in 27, studies on their further functionalization based on their reactions with other nucleophiles are underway in our laboratory. The presented methodology could also be adopted for the synthesis of other stereoisomeric isoxazolidines via application of respective trans-alkenes in 1,3-dipolar cycloaddition to C-phosphorylated nitron 22. Moreover, the syntheses elaborated herein pave
the way for new enantiomerically pure functionalized phosphonate analogues of prolines, substituted glutamic acid by application of the N-chiral C-phosphorylated nitrones.

**Supplementary Materials:** Figure S1: $^1$H NMR Spectrum for 20 in CDCl$_3$, Figure S2: $^{13}$C NMR Spectrum for 20 in CDCl$_3$, Figure S3: $^{31}$P NMR Spectrum for 20 in CDCl$_3$, Figure S4: $^1$H NMR Spectrum for 21 in CDCl$_3$, Figure S5: $^{13}$C NMR Spectrum for 21 in CDCl$_3$, Figure S6: $^{13}$C NMR Spectrum for 21 in CDCl$_3$, Figure S7: $^{31}$P NMR Spectrum for 21 in CDCl$_3$, Figure S8: $^{13}$C NMR Spectrum for 21 in CDCl$_3$, Figure S9: $^1$H NMR Spectrum for 23 in CDCl$_3$, Figure S10: $^{13}$C NMR Spectrum for 23 in CDCl$_3$, Figure S11: $^{31}$P NMR Spectrum for 23 in CDCl$_3$, Figure S12: $^1$H NMR Spectrum for 18 in CDCl$_3$, Figure S13: $^{13}$C NMR Spectrum for 18 in CDCl$_3$, Figure S14: $^{31}$P NMR Spectrum for 18 in CDCl$_3$, Figure S15: $^1$H NMR Spectrum for 24 in CD$_2$OD, Figure S16: $^{13}$C NMR Spectrum for 24 in CD$_2$OD, Figure S17: $^{31}$P NMR Spectrum for 24 in CD$_2$OD, Figure S18: $^1$H NMR Spectrum for 25 in CDCl$_3$, Figure S19: $^{13}$C NMR Spectrum for 25 in CDCl$_3$, Figure S20: $^{31}$P NMR Spectrum for 25 in CDCl$_3$, Figure S21: $^1$H NMR Spectrum for 27 in CDCl$_3$, Figure S22: $^{13}$C NMR Spectrum for 27 in CDCl$_3$, Figure S23: $^{31}$P NMR Spectrum for 27 in CDCl$_3$, Figure S24: $^{13}$C NMR Spectrum for 27 in CDCl$_3$, Figure S25: $^1$H NMR Spectrum for 28 in CDCl$_3$, Figure S26: $^{13}$C NMR Spectrum for 28 in CDCl$_3$, Figure S27: $^{31}$P NMR Spectrum for 28 in CDCl$_3$, Figure S28: $^1$H NMR Spectrum for 29 in CDCl$_3$, Figure S29: $^{13}$C NMR Spectrum for 29 in CDCl$_3$, Figure S30: $^{31}$P NMR Spectrum for 29 in CDCl$_3$, Figure S31: $^1$H NMR Spectrum for 30 in CDCl$_3$, Figure S32: $^{13}$C NMR Spectrum for 30 in CDCl$_3$, Figure S33: $^{31}$P NMR Spectrum for 30 in CDCl$_3$.

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