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Application of diethyl ethynylphosphonate to the synthesis of 3-phosphonylated β-lactams via the Kinugasa reaction

Marcin K. Kowalski,*, Grzegorz Młoston,*, Emilia Obijalska,* and Heinz Heimgartner

*a Department of Organic and Applied Chemistry, Faculty of Chemistry, University of Łódź, Tamka 12, PL-91-403 Łódź, Poland

b Department of Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

E-mail: gmloston@uni.lodz.pl

Dedicated to Prof. Jacek Młochowski on the occasion of his 80th birthday

Abstract
The easily available diethyl ethynylphosphonate reacts with diverse aldonitrones under Kinugasa reaction conditions at room temperature, providing 3-phosphonylated β-lactams in good yields. In all cases, the reaction led to the trans-isomer exclusively. The trans-configuration was assigned based on 1H-NMR spectroscopy.

Keywords: β-Lactams, Kinugasa reaction, aldonitrones, ethynephosphonate, cycloaddition reactions, copper(I) catalysis

Introduction
The importance of modified β-lactams is well documented. They are known not only as important drugs with antimicrobial activity but also as inhibitors of cholesterol absorptions and thrombin, as well as antitumor and anti-HIV agents. One of the important modifications comprises the substitution with phosphonyl groups, which are known as bioisosteric functionalities of phosphates. The phosphonyl group can be located either at C(3) or C(4) of the β-lactam ring.

There are different methods known for the preparation of 4-phosphonylated β-lactams, including the recently reported Kinugasa approach. In the latter case, the C-phosphonylated N-methyl nitrone 1 reacted with mono-substituted acetylenes yielding azetidin-2-ones as mixtures of cis/trans-isomers (Scheme 1).
Scheme 1. Kinugasa reaction with a phosphonylated nitron to leading to 4-phosphonylated β-lactams.12

The synthesis of 3-phosphonylated β-lactams can be performed using different methods, e.g., [2+2]-cycloaddition of a phosphonylated ketene with an imine (Staudinger reaction),13,14 intramolecular carbene insertion into a CH-bond of a N-benzylamide,15 and cyclization of phosphono acet-enamides.16

The 3-phosphonylated β-lactams have never been prepared via Kinugasa reaction starting with diethyl ethynylphosphonate (4). On the other hand, 4 has extensively been used in [3+2]-cycloadditions with organic azides.17–20

Results and Discussion

In a recent publication we described a new approach to the synthesis of fluorinated β-lactams via Kinugasa reaction with fluorinated nitrones and diverse monosubstituted acetylenes, including methyl propiolate.21 In the course of that study, preliminary experiments with diethyl ethynephosphonate (4) were unsuccessful and the formation of a complicated mixture of unidentified products was observed. For that reason, a series of typical nitrones 5a–h, derived from aryl or alkyl aldehydes, was prepared and subsequently used for the reaction with 4. The first experiment with N-benzyl-C-phenyl nitrone (5a) and 4 was performed in anhydrous acetonitrile, in the presence of CuI and triethylamine (TEA), under argon atmosphere, and after three days the expected diethyl 1-benzyl-2-oxo-4-phenylazetidine-3-phosphonate (6a) was obtained as a yellowish oil in 60% yield (Scheme 2). The 1H-NMR analysis of the crude product revealed the presence of a single product, which was identified as the trans-isomer on the basis of the HC(3)-HC(4) coupling constant of 2.1 Hz.22 Analogously, β-lactams trans-6b–g with a benzyl, phenyl or methyl group at N(1) were obtained with complete diastereoselectivity in good yields (Table 1). The type of substituent on the N-atom influence neither the reaction course nor the yield of the formed product.

Scheme 2. Kinugasa reaction with diethyl ethynephosphonate (4) and nitrones 5
Table 1. $\beta$-Lactams 6 prepared via Kinugasa reaction with diethyl ethynylphosphonate (4)

<table>
<thead>
<tr>
<th>Nitrone 5</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$\beta$-lactam 6</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>PhCH$_2$</td>
<td>a</td>
<td>60</td>
</tr>
<tr>
<td>b</td>
<td>4-MeOC$_6$H$_4$</td>
<td>PhCH$_2$</td>
<td>b</td>
<td>61</td>
</tr>
<tr>
<td>c</td>
<td>4-F$_3$C$_6$H$_4$</td>
<td>PhCH$_2$</td>
<td>c</td>
<td>32</td>
</tr>
<tr>
<td>d</td>
<td>4-BrC$_6$H$_4$</td>
<td>PhCH$_2$</td>
<td>d</td>
<td>56</td>
</tr>
<tr>
<td>e</td>
<td>Furan-2-yl</td>
<td>PhCH$_2$</td>
<td>e</td>
<td>55</td>
</tr>
<tr>
<td>f</td>
<td>Ph</td>
<td>Ph</td>
<td>f</td>
<td>56</td>
</tr>
<tr>
<td>g</td>
<td>Ph</td>
<td>Me</td>
<td>g</td>
<td>60</td>
</tr>
<tr>
<td>h</td>
<td>4-MeC$_6$H$_4$</td>
<td>Me</td>
<td>h</td>
<td>62</td>
</tr>
<tr>
<td>i</td>
<td>Me(CH$_2$)$_4$</td>
<td>PhCH$_2$</td>
<td>i</td>
<td>26$^b$</td>
</tr>
<tr>
<td>j</td>
<td><img src="Image" alt="Structure" /></td>
<td>PhCH$_2$</td>
<td>j</td>
<td>58</td>
</tr>
</tbody>
</table>

$^a$Yield of isolated product  
$^b$Contains ca. 5% of an unknown impurity

In all reactions trans-isomers were isolated exclusively. It seems likely that initially formed cis-products undergo spontaneous isomerization under the basic reaction conditions and the thermodynamically more stable trans-isomers are formed as the final products. This explanation is the more likely as the H-C(3) is expected to show enhanced acidity resulting from the presence of the carbonyl and phosphonyl group. In the case of the reported 4-phosphonylated $\beta$-lactams, the formation of mixtures in favor of the trans-isomers was observed (up to 78:22).\textsuperscript{12}

In order to check the scope of the reaction, two nitrones derived from hexanal and (S)-glyceraldehyde acetonide, respectively, were included in the study of the reaction with 4. In the case of 5i, the trans-$\beta$-lactam 6i was isolated in rather low yield (Figure 1, Table 1).

![Figure 1. $\beta$-Lactams trans-6i (racemic) and (R)-trans-6j (optically active)](Image)
However, again only one isomer was formed in this reaction. The reaction of the enantiopure 5j with 4 gave only one optically active product, trans-6j, isolated in 58% yield. However, the absolute configuration at C(3) and C(4) in this compound is unknown.

Conclusions

The present study shows that 3-phosphonylated β-lactams can be prepared conveniently using easily available diethyl ethynylphosphonate as the acetylenic component in the Kinugasa reaction. In contrast to the alternative method with phosphonylated nitrones leading to 4-phosphonylated analogues,\textsuperscript{12} the reaction occurred with complete diastereoselectivity, and the trans-configurations were established in all cases based on the HC(3),HC(4) coupling constants in the $^1$H-NMR spectra.\textsuperscript{22}

Experimental Section

General
Melting points were determined in capillaries using a Stuart SMP30 apparatus and are uncorrected. IR spectra were recorded with a FT-IR NEXUS spectrophotometer as film or KBr pellets; absorptions in cm$^{-1}$ (w = weak, m = medium, s = strong, vs = very strong). $^1$H,$^{13}$C{$^1$H}, $^{31}$P{$^1$H} and $^{19}$F NMR spectra were measured on a Bruker Avance III instrument ($^1$H at 600, $^{13}$C at 150, $^{31}$P at 234, and $^{19}$F at 565 MHz, respectively) in CDC\textsubscript{3}; chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. The multiplicity of the $^{13}$C signals was deduced using HMQC and HMBC techniques. $^1$H NMR data are presented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, dd=doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, m = multiplet), coupling constant, integration. The mass spectra were recorded on a Finnigan MAT-95 instrument (ESI). Elemental analyses were performed in the Microanalytical Laboratory of the Faculty of Chemistry of the University of Łódź. The applied reagent diethyl ethynylphosphonate (4) was prepared according to a slightly modified protocol described in ref. 25; the modification comprises the desilylation of the final product by using commercial tetrabutylammonium fluoride (TBAF) solution in THF. All nitrones 5a–j were prepared from the corresponding aldehydes and N-hydroxyamines following the standard protocol.\textsuperscript{26} Copper(I) iodide was purchased from Sigma-Aldrich. Anhydrous acetonitrile was purchased from Acros and was degassed before use. Triethylamine (TEA) was purchased from Avantor; it was dried by heating over solid KOH and freshly distilled prior to use.
Reaction of nitrones 5a–j with diethyl ethynylphosphonate (4) – general procedure
To an oven-dried flask equipped with a septum, stirring bar and a balloon filled with argon was placed copper(I) iodide (190 mg, 1.0 mmol). Anhydrous and degassed acetonitrile (2 mL) was introduced, and to the stirred suspension (ice bath), diethyl ethynephosphonate (4, 162 mg, 1.0 mmol) dissolved in dry MeCN (2 mL) was added. After 5 min a solution of triethylamine (202 mg, 2.0 mmol) in anhydrous and degassed MeCN (3 mL) was added at 0 °C (ice bath) while stirring under inert atmosphere. After 10 min a solution of a nitrone 5a–j (1.1 mmol) in dry acetonitrile (3 mL) was added to the suspension of the copper-acetylene complex. After another 10 min, the ice bath was removed and the reaction mixture was left at room temperature for 72 h. After this time, methylene chloride (5 mL) was added and the solvents were removed under reduced pressure. Crude products 6 were purified by flash column chromatography (conditions: Grace Reveleris X2 apparatus with UV-Vis and ELSD detection, using commercially available 12 g or 24 g SiO2 columns, pressure 20 psi, solvent flow rate 25 mL/min) using petroleum ether with increasing amounts of ethyl acetate (up to 100% of AcOEt) as eluent.

**Diethyl trans-1-benzyl-2-oxo-4-phenylazetidine-3-phosphonate (6a):** light-yellow oil (224 mg, 60%). IR (ν<sub>max</sub>, cm<sup>-1</sup>): 716m, 971w, 1025m, 1171w, 1260w, 1395w, 1450w, 1759s (C=O), 2854w, 2926w, 2986w. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 1.22 (3H, t, J<sub>HH</sub> 7.1 Hz, P(O)(OCH<sub>2</sub>CH<sub>3</sub>))<sub>3</sub>, 1.23 (3H, t, J<sub>HH</sub> 7.1 Hz, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 3.41 (1H, dd, J<sub>HP</sub> 14.8 Hz, J<sub>HH</sub> 2.1 Hz, CHP(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 4.03–4.11 (4H, m, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 3.76, 4.81 (2H, AB system, 2d, J<sub>CP</sub> 15.2 Hz, CH<sub>2</sub>Ph), 4.55 (1H, dd, J<sub>HP</sub> 8.6 Hz, J<sub>HH</sub> 2.5 Hz, CHPPh), 7.12–7.13 (2H, m, 2CH<sub>arom</sub>), 7.19–7.25 (5H, m, 5CH<sub>arom</sub>), 7.26–7.31 (3H, m, 3CH<sub>arom</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 16.3, 16.4 (2C), 2d, J<sub>CP</sub> 2.7 Hz, 2.8 Hz, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 45.0 (d, J<sub>CP</sub> 1.9 Hz, CH<sub>2</sub>Ph), 55.3 (d, J<sub>CP</sub> 2.2 Hz, CHPPh), 57.1 (d, J<sub>CP</sub> 143.3 Hz, CHP(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 62.6, 62.7 (2C, 2d, J<sub>CP</sub> 1.8 Hz, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 126.4, 127.8, 128.3, 128.7, 128.9, 129.1 (10CH<sub>arom</sub>), 134.8 (1C<sub>arom</sub>), 136.3 (d, J<sub>CP</sub> 2.3 Hz, 1C<sub>arom</sub>), 161.4 (d, J<sub>CP</sub> 6.6 Hz, C=O). <sup>31</sup>P NMR (243 MHz, CDCl<sub>3</sub>): δ 18.50 (s, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)). MS: m/z (%) 396.3 (100, [M]+[Na]<sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub>P (373.38): C, 64.33; H, 6.44; N, 3.75. Found: C, 64.30; H, 6.44; N, 3.69 %.

**Diethyl trans-1-benzyl-4-(4-methoxyphenyl)-2-oxoazetidine-3-phosphonate (6b):** light-yellow oil (246 mg, 61%). IR (ν<sub>max</sub>, cm<sup>-1</sup>): 955m, 1032w, 1167s, 1252v, 1600s, 1763vs (C=O), 2932w, 2982w. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 1.31 (3H, t, J<sub>HH</sub> 7.1 Hz, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 1.32 (3H, t, J<sub>HH</sub> 7.1 Hz, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 3.49 (1H, dd, J<sub>HP</sub> 14.7 Hz, J<sub>HH</sub> 2.3 Hz, CHP(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 3.80, 4.87 (2H, AB system, J<sub>HH</sub> 15.2 Hz, CH<sub>2</sub>Ph), 3.83 (3H, s, OCH<sub>3</sub>), 4.12–4.23 (4H, m, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 4.60 (1H, dd, J<sub>HP</sub> 8.5 Hz, J<sub>HH</sub> 2.5 Hz, CHC<sub>6</sub>H<sub>4</sub>(OCH<sub>3</sub>)), 7.19–7.22 (4H, m, 4CH<sub>arom</sub>), 7.38–7.44 (1H, m, 1CH<sub>arom</sub>), 7.27–7.34 (4H, m, 4CH<sub>arom</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 16.3, 16.4 (2C, 2d, J<sub>CP</sub> 2.6 Hz, J<sub>CP</sub> 2.7 Hz, P(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 44.8 (d, J<sub>CP</sub> 1.8 Hz, CH<sub>2</sub>Ph), 55.3 (d, J<sub>CP</sub> 2.8 Hz, CHC<sub>6</sub>H<sub>4</sub>(OCH<sub>3</sub>)), 57.1 (d, J<sub>CP</sub> 142.7 Hz, CHP(O)(OCH<sub>2</sub>CH<sub>3</sub>)), 62.5, 62.6 (2C, 2d, J<sub>CP</sub> 1.6 Hz, J<sub>CP</sub> 6.2 Hz, J<sub>CP</sub> 6.4 Hz,
P(O)(OCH₂CH₃)₂, 114.6 (OCH₃), 127.7, 127.8, 128.3, 128.7, 128.9, 129.2, 130.6 (9CHₐrom), 134.9 (brs, 1Cₐrom), 160.1 (1Cₐrom), 161.1 (1Cₐrom), 162.0 (d, 2JₐCP 6.6 Hz, C=O). ³¹P NMR (243 MHz, CDCl₃): δ 18.77 (s, P(O)(OCH₂CH₃)₂). MS: m/z (%) 426.3 (100, [M+Na⁺]). Anal. Calcd for C₂₅H₂₆NO₅P (403.41): C, 62.52; H, 6.50; N, 3.47. Found: C, 62.31; H, 6.33; N, 3.56 %.

**Diethyl trans-1-benzyl-2-oxo-4-[4-(trifluoromethyl)phenyl]azetidine-3-phosphonate (6e):** light-yellow oil (141 mg, 32%). IR (νmax, cm⁻¹): 960s, 1171s, 1170s, 1255s, 1396m, 1600s, 1760vs (C=O), 2930m, 2982m. ¹H NMR (600 MHz, CDCl₃): δ 1.24 (6H, brt, 3J_HH 7.0 Hz, P(O)(OCH₂CH₃)₂), 3.38 (1H, dd, 3J_HH 14.9 Hz, 3J_HHH 2.2 Hz, CHC₆H₄CF₃), 4.01–4.13 (4H, m, P(O)(OCH₂CH₃)₂), 3.81, 4.81 (2H, AB system, 2J_HHH 15.2 Hz, CH₂Ph), 4.60 (1H, dd, 3J_HH 8.7 Hz, 2J_HHH 2.6 Hz, CH₂P(O)(OCH₂CH₃)₂), 7.11–7.13 (2H, m, 2CHₐrom). 7.20–7.25 (3H, m, 3CHₐrom), 7.30–7.32 (2H, m, 2CHₐrom), 7.55–7.56 (2H, m, 2CHₐrom). ¹³C NMR (150 MHz, CDCl₃): δ 16.3, 16.4 (2C, 2d, 3J_Cp(1) 1.8 Hz, 3J_Cp(2) 2.0 Hz, P(O)(OCH₂CH₃)₂), 45.4 (d, 4J_Cp 1.8 Hz, CH₂Ph), 54.7 (d, 2J_Cp 2.0 Hz, CHC₆H₄CF₃), 57.2 (d, 1J_Cp 143.9 Hz, CH₃P(O)(OCH₂CH₃)₂), 62.8, 62.9 (2C, 2d, 2J_Cp(1) 6.2 Hz, 2J_Cp(2) 6.5 Hz, P(O)(OCH₂CH₃)₂), 123.8 (q, 1J_Cp 270.6 Hz, CF₃), 126.1 (q, 3J_Cp 37.2 Hz, 2CH₂), 128.0 (1Cₐrom), 126.8, 128.4, 128.8 (5CHₐrom), 131.2 (q, 2J_C 32.6 Hz, CₐromCF₃), 134.4 (1Cₐrom), 140.7 (brs, 1Cₐrom), 161.6 (d, 2J_C 6.5 Hz, C=O). ³¹P NMR (243 MHz, CDCl₃): δ 18.60 (s, P(O)(OCH₂CH₃)₂). ¹⁹F NMR (565 MHz, CDCl₃): δ –62.78 (s, CF₃). MS: m/z (%) 464.2 (100, [M+Na⁺]). Anal. Calcd for C₂₁H₂₃NO₅P (441.38): C, 57.14; H, 5.25; N, 3.17. Found: C, 57.30; H, 5.41; N, 3.10 %.

**Diethyl trans-1-benzyl-4-(4-bromophenyl)-2-oxazetidine-3-phosphonate (6d):** light-yellow oil (253 mg, 56%). IR (νmax, cm⁻¹): 732w, 884m, 970m, 1027s, 1154m, 1249m, 1394s, 1486m, 1765vs (C=O), 2933m, 3028w. ¹H NMR (600 MHz, CDCl₃): δ 1.22, 1.23 (6H, 2t, 3J_HH(1) 7.0 Hz, 3J_HH(2) 7.1 Hz, P(O)(OCH₂CH₃)₂), 3.36 (1H, dd, 3J_HH 14.8 Hz, 3J_HHH 2.0 Hz, CH₂P(O)(OCH₂CH₃)₂), 4.02–4.12 (4H, m, P(O)(OCH₂CH₃)₂), 3.76, 4.78 (2H, AB system, 2J_HH 15.2 Hz, CH₂Ph), 4.50 (1H, dd, 3J_HH 8.7 Hz, 2J_HHH 2.6 Hz, CH₃C₆H₄OCH₃), 7.05–7.06 (1H, m, 1CHₐrom), 7.10–7.12 (2H, m, 2CHₐrom), 7.19–7.25 (4H, m, 4CHₐrom), 7.41–7.43 (2H, m, 2CHₐrom). ¹³C NMR (150 MHz, CDCl₃): δ 16.3, 16.4 (2C, 2d, 3J_Cp(1) 2.1 Hz, 3J_Cp(2) 2.3 Hz, P(O)(OCH₂CH₃)₂), 45.1 (d, 4J_Cp 1.9 Hz, CH₂Ph), 54.7 (d, 2J_Cp 2.1 Hz, CH₃C₆H₄Br), 57.1 (d, 1J_Cp 143.5 Hz, CH₃P(O)(OCH₂CH₃)₂), 62.7, 62.8 (2d, 2J_Cp(1) 6.2 Hz, 2J_Cp(2) 6.4 Hz, P(O)(OCH₂CH₃)₂), 127.9, 128.1, 128.4, 128.8, 132.4 (9CHₐrom), 122.9, 134.5 (2CHₐrom), 135.5 (d, 3J_Cp 2.4 Hz, 1Cₐrom), 161.7 (d, 2J_C 6.6 Hz, C=O). ³¹P NMR (243 MHz, CDCl₃): δ 18.19 (s, P(O)(OCH₂CH₃)₂). MS: m/z (%) 474.2, 476.2 (100, 65 [M+Na⁺]). Anal. Calcd for C₂₁H₂₅NO₅P (452.28): C, 53.11; H, 5.13; N, 3.10. Found: C, 53.16; H, 5.38; N, 3.32 %.

**Diethyl trans-1-benzyl-4-(furan-2-yl)-2-oxazetidine-3-phosphonate (6e):** light-yellow oil (200 mg, 55%). IR (νmax, cm⁻¹): 701s, 745vs, 970s, 1027v, 1268vs, 1401s, 1774vs (C=O), 2908m, 2984s, 2985w, 3050m. ¹H NMR (600 MHz, CDCl₃): δ 1.33, 1.34 (6H, 2t, 3J_HH(1) 7.0 Hz, 3J_HH(2) 6.9 Hz, P(O)(OCH₂CH₃)₂), 3.87 (1H, dd, 3J_HH 11.8 Hz, 3J_HH 2.6 Hz, C(4)H), 3.91, 4.74 (2H, AB system, 2J_HH 5.3 Hz, CH₂Ph), 4.16–
Diethyl trans-2-oxo-1,4-diphenylazetidine-3-phosphonate (6f). Pale orange crystals (201 mg, 56%), mp 93–95 °C (CH₂Cl₂/petroleum ether). IR (νmax, cm⁻¹): 790, 777s, 981s, 1045s, 1149m, 1270s, 1385s, 1505s, 1600m, 1699w, 1746vs (C=O), 2489w, 2963m, 2981m, 3063w. ¹H NMR (600 MHz, CDCl₃): δ 1.18–1.17 (6H, m, P(O)(OCH₂CH₃)₂), 3.47 (1H, dd, 3JHH 15.5 Hz, 2JHP 2.8 Hz, CHP(O)(OCH₂CH₃)₂), 4.09–4.25 (4H, m, P(O)(OCH₂CH₃)₂), 5.15 (1H, dd, 3JHP 9.2 Hz, 2JHH 2.8 Hz, CHPPh), 7.26–7.30 (5H, m, 5CH₃), 7.15–7.21 (5H, m, 5CH₃). ¹³C NMR (150 MHz, CDCl₃): δ 16.4 (3d, 3JCP 2.7 Hz, P(O)(OCH₂CH₃)₂), 55.9 (d, 2JCP 2.3 Hz, CHPH), 57.3 (d, 1JCP 143.3 Hz, CHP(O)(OCH₂CH₃)₂), 62.8, 63.2 (2C, 2d, 2JCH(1) 6.5 Hz, 2JCP(2) 6.2 Hz, P(O)(OCH₂CH₃)₂), 117.0, 124.3, 125.9, 128.9, 129.1, 129.3 (10CH₃), 136.6 (d, 3JCP 2.6 Hz, 1CH₃), 137.3 (d, 4JCP 2.1 Hz, 1CH₃), 159.0 (d, 2JCP 6.3 Hz, C=O). ³¹P NMR (243 MHz, CDCl₃): δ 17.97 (s, P(O)(OCH₂CH₃)₂). MS: m/z (%) = 382.3 (100, [M⁺Na]+). Anal. Calcd for C₁₉H₂₂NO₄P (359.36): C, 63.50; H, 6.17; N, 3.90. Found C, 63.76; H, 6.10; N, 3.92%.

Diethyl trans-1-methyl-2-oxo-4-phenylazetidine-3-phosphonate (6g): light-yellow oil (178 mg, 60%). IR (νmax, cm⁻¹): 824m, 1028m, 1052s, 1166m, 1252s, 1442m, 1453w, 1761vs (C=O). C=O) 2927m, 2984m. ¹H NMR (600 MHz, CDCl₃): δ 1.33 (3H, t, 3JHH 7.0 Hz, P(O)(OCH₂CH₃)₂), 1.38 (3H, t, 3JHH 7.0 Hz, P(O)(OCH₂CH₃)₂), 2.83 (3H, brs, NCH₃), 3.44 (1H, dd, 2JHH 16.5 Hz, 3JHH 1.6 Hz, CHP(O)(OCH₂CH₃)₂), 4.12–4.32 (4H, m, P(O)(OCH₂CH₃)₂), 4.73 (1H, dd, 3JHP 10.9 Hz, 2JHH 2.5 Hz, CHPPh), 7.32–7.33 (2H, m, 2CH₃), 7.36–7.39 (1H, m, 1CH₃), 7.41–7.43 (2H, m, 2CH₃). ¹³C NMR (150 MHz, CDCl₃): δ 16.3, 16.4 (2C, 2d, 3JCP(1) 1.9 Hz, 3JCP(2) 1.8 Hz, P(O)(OCH₂CH₃)₂), 27.6 (d, 4JCP 1.6 Hz, NCH₃), 57.3 (d, 2JCP 2.5 Hz, CHPPh), 57.6 (d, 1JCP 143.2 Hz, CHP(O)(OCH₂CH₃)₂), 62.5, 62.9 (2C, 2d, 2JCP(1) 6.1 Hz, 2JCP(2) 6.5 Hz, P(O)(OCH₂CH₃)₂), 126.2, 128.9, 129.2 (5CH₃), 136.5 (d, 3JCP 2.4 Hz, 1CH₃), 162.0 (d, 2JCP 6.2 Hz, C=O). ³¹P NMR (243 MHz, CDCl₃): δ 18.96 (s, P(O)(OCH₂CH₃)₂). MS: m/z (%) = 320.2 (100, [M⁺Na]+). Anal. Calcd for C₁₉H₂₀NO₄P (297.29): C, 56.56; H, 6.78; N, 4.71. Found: C, 56.75; H, 7.00; N, 4.43%.

Diethyl trans-1-methyl-4-(4-methylphenyl)-2-oxazetidine-3-phosphonate (6h): light-yellow oil (193 mg, 62%). IR (νmax, cm⁻¹): 973s, 1014m, 1049s, 1160m, 1252s, 1388w, 1442m, 1511w, 1761vs (C=O), 2927m, 2984m. ¹H NMR (600 MHz, CDCl₃):
δ 1.32 (3H, t, 3JHH 7.1 Hz, P(O)(OCH2CH3)2), 1.36 (3H, t, 3JHH 7.0 Hz, P(O)(OCH2CH3)2), 2.37 (s, 3H, CH3C(CH3)2), 2.80 (3H, s, NCH3), 3.41 (1H, dd, 2JHFP 16.4 Hz, 3JHH 1.6 Hz, CHP(O)(OCH2CH3)2), 4.10–4.31 (4H, m, P(O)(OCH2CH3)2), 4.68 (1H, dd, 3JHP 10.9 Hz, 2JHH 2.5 Hz, CHC6H4CH3), 7.19–7.22 (4H, m, 4CHarom).

13C NMR (150 MHz, CDCl3): δ 16.3, 16.4 (2C, 2d, 3JCP(1) 1.9 Hz, 3JCP(2) 1.9 Hz, P(O)(OCH2CH3)2), 27.5 (d, 4JCP 1.6 Hz, NCH3), 21.1 (CH3C(CH3)2), 54.1 (d, 2JCP 2.8 Hz, CHC6H4CH3), 57.6 (d, 1JCP 137.5 Hz, CHP(O)(OCH2CH3)2), 62.4, 62.9 (2C, 2d, 2JCP(1) 6.0 Hz, 2JCP(2) 6.4 Hz, P(O)(OCH2CH3)2), 126.2, 129.8 (4CHarom), 133.4 (d, 3JCP 2.4 Hz, 1Carom), 138.9 (1Carom), 160.2 (d, 2JCP 6.2 Hz, C=O). 31P NMR (243 MHz, CDCl3): δ 19.11 (s, P(O)(OCH2CH3)2). MS: m/z (%) 334.3 (100, [M+Na]+).

Anal. Calcd for C13H22NO4P (311.31): C, 57.87; H, 7.12; N, 4.50. Found: C, 57.65; H, 7.15; N, 4.51 %.

**Diethyl trans-1-benzyl-2-oxo-4-(pent-1-yl)azetidine-3-phosphonate (6i):** pale-yellow oil (96 mg, 26%); could not be obtained in analytically pure form (see Table 1). IR (vmax, cm⁻¹): 731s, 1023s, 1241s, 1404m, 1457m, 1575vs (C=O), 2927s, 3053m.

1H NMR (600 MHz, CDCl3): δ 0.87 (3H, t, 2JHH 15.0 Hz, CH3), 1.20–1.47 (14H, m, P(O)(OCH2CH3)2, (CH2)3), 3.26 (1H, dd, 2JHH 15.0 Hz, 3JHH 2.3 Hz, CHP(O)(OCH2CH3)2), 3.69–3.73 (1H, m, CH(CH2)3), 4.12, 4.72, (2H, AB system, 2JHH 15.5 Hz, CH2Ph), 4.16–4.24 (4H, m, P(O)(OCH2CH3)2), 7.31–7.32 (3H, m, 3CHarom), 7.35–7.38 (2H, m, 2CHarom). 13C NMR (150 MHz, CDCl3): δ 16.4 (d, 3JCP 6.1 Hz, P(O)(OCH2CH3)2), 32.6 (d, 3JCP 2.6 Hz, CH2CH2), 44.8 (d, 4JCP 1.9 Hz, CH2Ph), 52.8 (d, 1JCP 145.9 Hz, CHP(O)(OCH2CH3)2), 53.2 (d, 2JCP 2.7 Hz, CH(CH2)3), 62.4, 62.6 (2C, 2d, 2JCP(1) 6.3 Hz, 2JCP(2) 6.5 Hz, P(O)(OCH2CH3)2), 127.7, 128.1, 128.7 (5CHarom), 135.4 (1CHarom), 161.7 (d, 2JCP 6.6 Hz, C=O). 31P NMR (243 MHz, CDCl3): δ 20.00 (s, P(O)(OCH2CH3)2). MS: m/z (%) 390.4 (100, [M+Na]+)

**Diethyl (S)-trans-1-benzyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoazetidine-3-phosphonate (6j):** pale-yellow oil (230 mg, 58%). [α]D²² = +36.4 (c 1.0 in DCM). IR (vmax, cm⁻¹): 970m, 1028m, 1042m, 1155m, 1257m, 1381w, 1453w, 1763vs (C=O), 2931w, 2985w. 1H NMR (600 MHz, CDCl3): δ 1.19–1.29 (6H, m, P(O)(OCH2CH3)2), 1.25, 1.27 (6H, 2s, 2CH3), 3.20 (1H, dd, 3JHH 14.9 Hz, 2JHH 2.4 Hz, CHP(O)(OCH2CH3)2), 3.58 (1H, dt, 3JHH(1) 1.6 Hz, 3JHH(2) 2.7 Hz, CHOC(CH3)2), 3.69 (1H, dd, 2JHH(1) 8.9 Hz, 3JHH(2) 4.9 Hz, CH2OC(CH3)2), 3.93 (1H dd, 2JHH(1) 8.9 Hz, 3JHH(2) 6.9 Hz, CH2OC(CH3)2), 4.55 (1H, dd, 2JHH 6.1 Hz, 2JHP 2.5 Hz, CHP(O)(OCH2CH3)2), 4.04–4.12 (5H, m, P(O)(OCH2CH3)2), CHP(O)(OCH2CH3)2), 4.12, 4.77 (2H, AB system, 2JHH 15.2 Hz, CH2Ph), 7.20–7.21 (1H, m, 1CHarom), 7.26–7.27 (4H, m, 4CHarom). 13C NMR (150 MHz, CDCl3): δ 16.3, 16.4 (2C, 2d, 3JCP(1) 4.2 Hz, 3JCP(2) 4.2 Hz, P(O)(OCH2CH3)2), 25.0, 26.5 (C(CH3)2), 45.8 (d, 4JCP 1.9 Hz, CH2Ph), 49.3 (d, 1JCP 147.8 Hz, CHP(O)(OCH2CH3)2), 54.3 (d, 2JCP 1.9 Hz, CHCHP(O)(OCH2CH3)2), 62.6, 62.7 (2C, 2d, 2JCP(1) 6.3 Hz, 2JCP(2) 6.4 Hz, P(O)(OCH2CH3)2), 66.0 (CH2OC(CH3)2), 77.5 (d, 2JCP 3.5 Hz, CHCHP(O)(OCH2CH3)2), 110.6 (C(CH3)2), 127.7, 128.6, 128.6 (4CHarom), 135.4 (1CHarom), 161.1 (d, 2JCP 6.6 Hz, C=O). 31P NMR (243 MHz, CDCl3): δ 19.06 (s,
P(O)(OCH$_2$CH$_3$)$_2$). MS: $m/z$ (%) = 420.3 (100, [M+Na$^+$]). Anal. Calcd for C$_{19}$H$_{28}$NO$_6$P (397.40): C, 57.42; H, 7.10; N, 3.52. Found: C, 57.40; H, 7.34; N, 3.33%.

References and Notes

1. Part of the planned Ph.D. thesis of M. K. K., University of Łódź.


