

Application of diethyl ethynylphosphonate to the synthesis of 3-phosphonylated β -lactams via the Kinugasa reaction¹

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

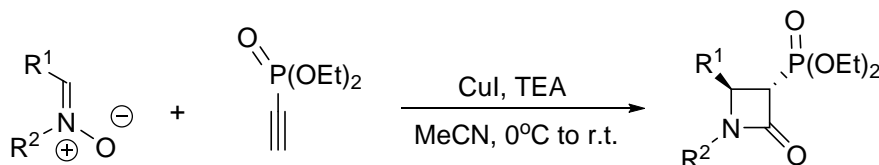
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Abstract

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 spectroscopic analysis.

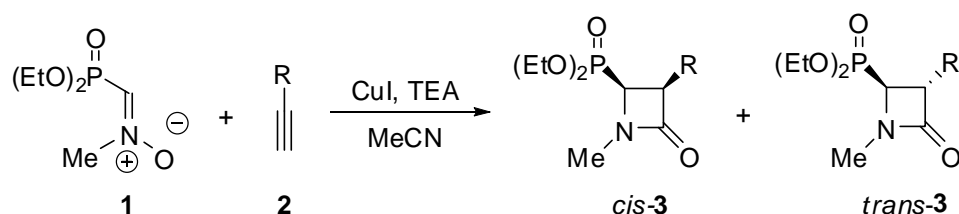


Keywords: β -Lactams, Kinugasa reaction, aldonitrones, ethynylphosphonate, cycloaddition reactions, copper(I) catalysis

Introduction

The importance of modified β -lactams is well documented. They are known not only as important drugs with antimicrobial activity² but also as inhibitors of cholesterol absorption³ and thrombin,⁴ as well as antitumor⁵ and anti-HIV agents.⁶ One of the important modifications comprises the substitution with phosphonyl groups, which are known as bioisosteric functionalities of phosphates.^{7,8} 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,⁹⁻¹¹ including the recently reported Kinugasa approach.¹² In the latter case, the *C*-phosphonylated *N*-methyl nitronone **1** was reacted with mono-substituted acetylenes **2** yielding azetidin-2-ones **3** as mixtures of *cis/trans*-isomers (Scheme 1).



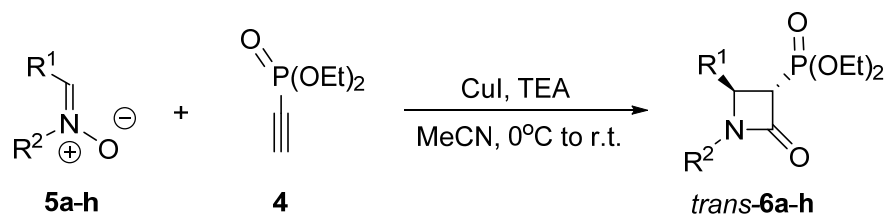
Scheme 1. Kinugasa reaction with a phosphonylated nitronone leading to 4-phosphonylated β -lactams.¹²

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 an *N*-benzylamide,¹⁵ and cyclization of phosphono acet-enamides.¹⁶

3-Phosphonylated β -lactams have never been prepared via Kinugasa reactions starting with diethyl ethynylphosphonate (**4**). Compound **4** has however been used extensively in [3+2]-cycloadditions with organic azides.¹⁷⁻²⁰

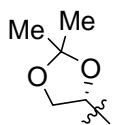
Results and Discussion

In a recent publication we described a new approach to the synthesis of fluorinated β -lactams via Kinugasa reactions with fluorinated nitronones and diverse monosubstituted acetylenes, including methyl propiolate.²¹ In the course of that study, preliminary experiments with diethyl ethynylphosphonate (**4**) were unsuccessful and the formation of a complicated mixture of unidentified products was observed. For that reason, a series of typical nitronones **5a-h**, derived from aryl or alkyl aldehydes, was prepared and subsequently used for reaction with **4**. The first experiment with *N*-benzyl-*C*-phenyl nitronone (**5a**) and **4** was performed in anhydrous acetonitrile, in the presence of CuI and triethylamine (TEA), under an 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). 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-h** with a benzyl, phenyl or methyl group at N(1) were obtained with complete diastereoselectivity and in good yields (Table 1). The type of substituent on the N-atom influences neither the reaction course nor the yield of the formed product.



Scheme 2. Kinugasa reaction with diethyl ethynylphosphonate (**4**) and nitrones **5**.

Table 1. β -Lactams **6** prepared via Kinugasa reaction with diethyl ethynylphosphonate (**4**)

Nitronone 5	R ¹	R ²	β -lactam 6	Yield (%) ^a
a	Ph	PhCH ₂	a	60
b	4-MeOC ₆ H ₄	PhCH ₂	b	61
c	4-F ₃ CC ₆ H ₄	PhCH ₂	c	32
d	4-BrC ₆ H ₄	PhCH ₂	d	56
e	furan-2-yl	PhCH ₂	e	55
f	Ph	Ph	f	56
g	Ph	Me	g	60
h	4-MeC ₆ H ₄	Me	h	62
i	Me(CH ₂) ₄	PhCH ₂	i	26 ^b
j		PhCH ₂	j	58

^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 electron-withdrawing carbonyl and phosphonyl groups. In the case of the previously reported 4-phosphonylated β -lactams, the formation of mixtures in favor of the *trans*-isomers was observed (up to 78:22).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*- β -lactam **6i** was isolated in rather low yield (Figure 1, Table 1). 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 remains unknown.

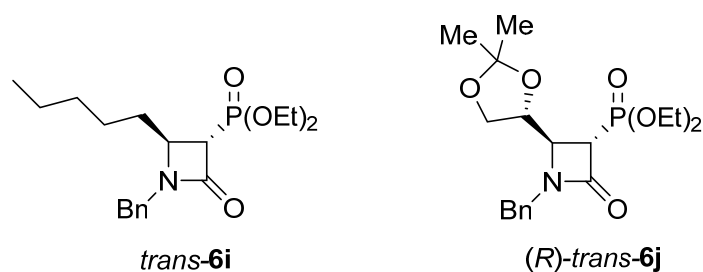


Figure 1. β -Lactams *trans*-**6i** (racemic) and (*R*)-*trans*-**6j** (optically active)

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,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 ¹H-NMR spectra.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 films or KBr pellets; absorptions in cm⁻¹ (w = weak, m = medium, s = strong, vs = very strong). ¹H, ¹³C{¹H}, ³¹P{¹H} and ¹⁹F NMR spectra were measured on a Bruker Avance III instrument (¹H at 600, ¹³C at 150, ³¹P at 234, and ¹⁹F at 565 MHz, respectively) in CDCl₃; chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. The multiplicity of the ¹³C signals was deduced using HMQC and HMBC techniques. ¹H 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.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

In 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 MeCN (2 mL) was introduced, and to the stirred suspension (ice bath), diethyl ethynylphosphonate (**4**, 162 mg, 1.0 mmol) dissolved in dry MeCN (2 mL) was

added. After 5 min a solution of Et₃N (202 mg, 2.0 mmol) in anhydrous and degassed MeCN (3 mL) was added at 0 °C (ice bath) while stirring under the inert atmosphere. After 10 min a solution of a nitron **5a-j** (1.1 mmol) in dry MeCN (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, CH₂Cl₂ (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 EtOAc (up to 100%) as eluent.

Diethyl trans-1-benzyl-2-oxo-4-phenylazetidide-3-phosphonate (6a). Light-yellow oil (224 mg, 60%). IR (ν_{\max} , cm⁻¹): 716m, 971w, 1025m, 1171w, 1260w, 1395w, 1450w, 1759s (C=O), 2854w, 2926w, 2986w. ¹H NMR (600 MHz, CDCl₃): δ 1.22 (3H, t, ³J_{HH} 7.1 Hz, P(O)(OCH₂CH₃)₂), 1.23 (3H, t, ³J_{HH} 7.1 Hz, P(O)(OCH₂CH₃)₂), 3.41 (1H, dd, ³J_{HP} 14.8 Hz, ³J_{HH} 2.1 Hz, CHP(O)(OCH₂CH₃)₂), 4.03–4.11 (4H, m, P(O)(OCH₂CH₃)₂), 3.76, 4.81 (2H, AB system, 2d, ²J_{HH} 15.2 Hz, CH₂Ph), 4.55 (1H, dd, ²J_{HP} 8.6 Hz, ³J_{HH} 2.5 Hz, CHPh), 7.12–7.13 (2H, m, 2CH_{arom}), 7.19–7.25 (5H, m, 5CH_{arom}), 7.26–7.31 (3H, m, 3CH_{arom}). ¹³C NMR (150 MHz, CDCl₃) δ 16.3, 16.4 (2C, 2d, ³J_{CP}(1) 2.7 Hz, ³J_{CP}(2) 2.8 Hz, P(O)(OCH₂CH₃)₂), 45.0 (d, ⁴J_{CP} 1.9 Hz, CH₂Ph), 55.3 (d, ²J_{CP} 2.2 Hz, CHPh), 57.1 (d, ¹J_{CP} 143.3 Hz, CHP(O)(OCH₂CH₃)₂), 62.6, 62.7 (2C, 2d, ²J_{CP}(1) 6.2 Hz, ²J_{CP}(2) 6.4 Hz, P(O)(OCH₂CH₃)₂), 126.4, 127.8, 128.3, 128.7, 128.9, 129.1 (10CH_{arom}), 134.8 (1C_{arom}), 136.3 (d, ³J_{CP} 2.3 Hz, 1C_{arom}), 161.4 (d, ²J_{CP} 6.6 Hz, C=O). ³¹P NMR (243 MHz, CDCl₃) δ 18.60 (s, P(O)(OCH₂CH₃)₂). MS: *m/z* (%) 396.3 (100, [M+Na]⁺). Anal. Calcd for C₂₀H₂₄NO₄P (373.38): C, 64.33; H, 6.48; N, 3.75. Found: C, 64.30; H, 6.44; N, 3.69%.

Diethyl trans-1-benzyl-4-(4-methoxyphenyl)-2-oxoazetidide-3-phosphonate (6b). Light-yellow oil (246 mg, 61%). IR (ν_{\max} , cm⁻¹): 955m, 1032vs, 1167s, 1252vs, 1600s, 1763vs (C=O), 2932w, 2982w. ¹H NMR (600 MHz, CDCl₃): δ 1.31 (3H, t, ³J_{HH} 7.1 Hz, P(O)(OCH₂CH₃)₂), 1.32 (3H, t, ³J_{HH} 7.1 Hz, P(O)(OCH₂CH₃)₂), 3.49 (1H, dd, ³J_{HP} 14.7 Hz, ³J_{HH} 2.3 Hz, CHP(O)(OCH₂CH₃)₂), 3.80, 4.87 (2H, AB system, ²J_{HH} 15.2 Hz, CH₂Ph), 3.83 (3H, s, OCH₃), 4.12–4.23 (4H, m, P(O)(OCH₂CH₃)₂), 4.60 (1H, dd, ³J_{HP} 8.5 Hz, ²J_{HH} 2.5 Hz, CHC₆H₄OCH₃), 7.19–7.22 (4H, m, 4CH_{arom}), 7.38–7.44 (1H, m, 1CH_{arom}), 7.27–7.34 (4H, m, 4CH_{arom}). ¹³C NMR (150 MHz, CDCl₃): δ 16.3, 16.4 (2C, 2d, ³J_{CP}(1) 2.6 Hz, ³J_{CP}(2) 2.7 Hz, P(O)(OCH₂CH₃)₂), 44.8 (d, ⁴J_{CP} 1.8 Hz, CH₂Ph), 55.3 (d, ²J_{CP} 2.8 Hz, CHC₆H₄OCH₃), 57.1 (d, ¹J_{CP} 142.7 Hz, CHP(O)(OCH₂CH₃)₂), 62.5, 62.6 (2C, 2d, ²J_{CP}(1) 6.2 Hz, ²J_{CP}(2) 6.4 Hz, P(O)(OCH₂CH₃)₂), 114.6 (OCH₃), 127.7, 127.8, 128.3, 128.7, 128.9, 129.2, 130.6 (9CH_{arom}), 134.9 (brs, 1C_{arom}), 160.1 (1C_{arom}), 161.1 (1C_{arom}), 162.0 (d, ²J_{CP} 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 C₂₁H₂₆NO₅P (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]azetidide-3-phosphonate (6c). Light-yellow oil (141 mg, 32%). IR (ν_{\max} , cm⁻¹): 960s, 1117s, 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_{HH} 2.2 Hz, CHC₆H₄CF₃), 4.01–4.13 (4H, m, P(O)(OCH₂CH₃)₂), 3.81, 4.81 (2H, AB system, ²J_{HH} 15.2 Hz, CH₂Ph), 4.60 (1H, dd, ³J_{HP} 8.7 Hz, ²J_{HH} 2.6 Hz, CHP(O)(OCH₂CH₃)₂), 7.11–7.13 (2H, m, 2CH_{arom}), 7.20–7.25 (3H, m, 3CH_{arom}), 7.30–7.32 (2H, m, 2CH_{arom}), 7.55–7.56 (2H, m, 2CH_{arom}). 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, CHP(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_{CF} 270.6 Hz, CF₃), 126.1 (q, ³J_{CF} 37.2 Hz, 2 CH_{arom}), 128.0 (1C_{arom}), 126.8, 128.4, 128.8 (5CH_{arom}), 131.2 (q, ²J_{CF} 32.6 Hz, C_{arom}CF₃), 134.4 (1C_{arom}), 140.7 (brs, 1C_{arom}), 161.6 (d, ²J_{CP} 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 C₂₁H₂₆NO₅P (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-oxoazetidide-3-phosphonate (6d). Light-yellow oil (253 mg, 56%). IR (ν_{max}, 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_{HP} 14.8 Hz, ³J_{HH} 2.0 Hz, CHP(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_{HP} 8.7 Hz, ²J_{HH} 2.6 Hz, CHC₆H₄OCH₃), 7.05–7.06 (1H, m, 1CH_{arom}), 7.10–7.12 (2H, m, 2CH_{arom}), 7.19–7.25 (4H, m, 4CH_{arom}), 7.41–7.43 (2H, m, 2CH_{arom}). 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, CHC₆H₄Br), 57.1 (d, ¹J_{CP} 143.5 Hz, CHP(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 (9CH_{arom}), 122.9, 134.5 (2C_{arom}), 135.5 (d, ³J_{CP} 2.4 Hz, 1C_{arom}), 161.7 (d, ²J_{CP} 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 C₂₁H₂₆NO₅P (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-oxoazetidide-3-phosphonate (6e). Light-yellow oil (200 mg, 55%). IR (ν_{max}, cm⁻¹): 701s, 745vs, 970s, 1027vs, 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_{HP} 2.6 Hz, C(4)H), 3.91, 4.74 (2H, AB system, ²J_{HH} 5.3 Hz, CH₂Ph), 4.16–4.24 (4H, m, P(O)(OCH₂CH₃)₂), 4.69 (1H, dd, ³J_{HH} 6.1 Hz, ²J_{HP} 2.6 Hz, CHP(O)(OCH₂CH₃)₂), 6.31–6.32 (1H, m, 1CH_{arom}), 6.34–6.35 (1H, m, 1CH_{arom}), 7.23–7.24 (2H, m, 2CH_{arom}), 7.27–7.30 (1H, m, 1CH_{arom}), 7.32–7.34 (2H, m, 2CH_{arom}), 7.40–7.41 (1H, m, 1CH_{arom}). ¹³C NMR (150 MHz, CDCl₃): δ 16.3, 16.4 (2C, 2d, ³J_{CP}(1) 3.4 Hz, ³J_{CP}(2) 4.0 Hz, P(O)(OCH₂CH₃)₂), 45.2 (d, ⁴J_{CP} 1.5 Hz, CH₂Ph), 48.7 (d, ²J_{CP} 2.1 Hz, C(4)H), 53.5 (d, ¹J_{CP} 144.3 Hz, CHP(O)(OCH₂CH₃)₂), 62.7, 62.8 (2C, 2d, ²J_{CP}(1) 6.2 Hz, ²J_{CP}(2) 6.4 Hz, P(O)(OCH₂CH₃)₂), 110.5, 110.6, 127.7, 128.2, 128.7 (8CH_{arom}), 143.5 (1CH_{arom}), 134.9 (1C_{arom}), 148.6 (d, ³J_{CP} 2.9 Hz, 1C_{arom}), 161.5 (d, ²J_{CP} 6.6 Hz, C=O). ³¹P NMR (243 MHz, CDCl₃): δ 18.44 (s, P(O)(OCH₂CH₃)₂). MS: *m/z* (%) = 386.2 (100, [M+Na]⁺). Anal. Calcd for C₁₈H₂₂NO₅P (363.34): C, 59.50; H, 6.10; N, 3.85. Found: C, 59.53; H, 6.04; N, 3.56%.

Diethyl trans-2-oxo-1,4-diphenylazetidide-3-phosphonate (6f). Pale orange crystals (201 mg, 56%), mp 93–95 °C (CH₂Cl₂/petroleum ether). IR (ν_{max}, cm⁻¹): 690m, 777s, 981s, 1045s, 1149m, 1270s, 1385s, 1505s, 1600m, 1699w, 1746vs (C=O), 2849w, 2963m, 2981m, 3063w. ¹H NMR (600 MHz, CDCl₃): δ 1.18–1.17 (6H, m, P(O)(OCH₂CH₃)₂), 3.47 (1H, dd, ³J_{HP} 15.5 Hz, ³J_{HH} 2.8 Hz, CHP(O)(OCH₂CH₃)₂), 4.09–4.25 (4H, m, P(O)(OCH₂CH₃)₂), 5.15 (1H, dd, ³J_{HP} 9.2 Hz, ²J_{HH} 2.8 Hz, CHPh), 7.26–7.30 (5H, m, 5CH_{arom}), 7.15–7.21 (5H, m, 5CH_{arom}). ¹³C NMR (150 MHz, CDCl₃): δ 16.4 (d, ³J_{CP} 2.7 Hz, P(O)(OCH₂CH₃)₂), 55.9 (d, ²J_{CP} 2.3 Hz, CHPh), 57.3 (d, ¹J_{CP} 143.3 Hz, CHP(O)(OCH₂CH₃)₂), 62.8, 63.2 (2C, 2d, ²J_{CP}(1) 6.5 Hz, ²J_{CP}(2) 6.2 Hz, P(O)(OCH₂CH₃)₂), 117.0, 124.3, 125.9, 128.9, 129.1, 129.3 (10CH_{arom}), 136.6 (d, ³J_{CP} 2.6 Hz, 1C_{arom}), 137.3 (d, ⁴J_{CP} 2.1 Hz, 1C_{arom}), 159.0 (d, ²J_{CP} 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-phenylazetidide-3-phosphonate (6g). Light-yellow oil (178 mg, 60%). IR (ν_{max}, cm⁻¹): 824m, 1028m, 1052s, 1166m, 1252s, 1442m, 1453w, 1761vs (C=O), 2927m, 2984m. ¹H NMR (600 MHz, CDCl₃): δ 1.33 (3H, t, ³J_{HH} 7.0 Hz, P(O)(OCH₂CH₃)₂), 1.38 (3H, t, ³J_{HH} 7.0 Hz, P(O)(OCH₂CH₃)₂), 2.83 (3H, brs, NCH₃), 3.44 (1H, dd, ²J_{HP} 16.5 Hz, ³J_{HH} 1.6 Hz, CHP(O)(OCH₂CH₃)₂), 4.12–4.32 (4H, m, P(O)(OCH₂CH₃)₂), 4.73 (1H, dd, ³J_{HP} 10.9 Hz, ²J_{HH} 2.5 Hz, CHPh), 7.32–7.33 (2H, m, 2CH_{arom}), 7.36–7.39 (1H, m, 1CH_{arom}), 7.41–7.43 (2H, m, 2CH_{arom}). ¹³C NMR (150 MHz, CDCl₃): δ 16.3, 16.4 (2C, 2d, ³J_{CP}(1) 1.9 Hz, ³J_{CP}(2) 1.8 Hz, P(O)(OCH₂CH₃)₂), 27.6 (d,

$^4J_{CP}$ 1.6 Hz, NCH₃), 57.3 (d, $^2J_{CP}$ 2.5 Hz, CHPh), 57.6 (d, $^1J_{CP}$ 143.2 Hz, CHP(O)(OCH₂CH₃)₂), 62.5, 62.9 (2C, 2d, $^2J_{CP}(1)$ 6.1 Hz, $^2J_{CP}(2)$ 6.5 Hz, P(O)(OCH₂CH₃)₂), 126.2, 128.9, 129.2 (5CH_{arom}), 136.5 (d, $^3J_{CP}$ 2.4 Hz, 1C_{arom}), 162.0 (d, $^2J_{CP}$ 6.2 Hz, C=O). ^{31}P NMR (243 MHz, CDCl₃): δ 18.96 (s, P(O)(OCH₂CH₃)₂). MS: m/z (%) 320.2 (100, [M+Na]⁺). Anal. Calcd for C₁₄H₂₀NO₄P (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-oxoazetidine-3-phosphonate (6h). Light-yellow oil (193 mg, 62%). IR (ν_{max} , 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, $^3J_{HH}$ 7.1 Hz, P(O)(OCH₂CH₃)₂), 1.36 (3H, t, $^3J_{HH}$ 7.0 Hz, P(O)(OCH₂CH₃)₂), 2.37 (s, 3H, CH₃C₆H₄), 2.80 (3H, s, NCH₃), 3.41 (1H, dd, $^2J_{HP}$ 16.4 Hz, $^3J_{HH}$ 1.6 Hz, CHP(O)(OCH₂CH₃)₂), 4.10–4.31 (4H, m, P(O)(OCH₂CH₃)₂), 4.68 (1H, dd, $^3J_{HP}$ 10.9 Hz, $^2J_{HH}$ 2.5 Hz, CHC₆H₄CH₃), 7.19–7.22 (4H, m, 4CH_{arom}). ^{13}C NMR (150 MHz, CDCl₃): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}(1)$ 1.9 Hz, $^3J_{CP}(2)$ 1.9 Hz, P(O)(OCH₂CH₃)₂), 27.5 (d, $^4J_{CP}$ 1.6 Hz, NCH₃), 21.1 (CH₃C₆H₄), 54.1 (d, $^2J_{CP}$ 2.8 Hz, CHC₆H₄CH₃), 57.6 (d, $^1J_{CP}$ 137.5 Hz, CHP(O)(OCH₂CH₃)₂), 62.4, 62.9 (2C, 2d, $^2J_{CP}(1)$ 6.0 Hz, $^2J_{CP}(2)$ 6.4 Hz, P(O)(OCH₂CH₃)₂), 126.2, 129.8 (4CH_{arom}), 133.4 (d, $^3J_{CP}$ 2.4 Hz, 1C_{arom}), 138.9 (1C_{arom}), 162.0 (d, $^2J_{CP}$ 6.2 Hz, C=O). ^{31}P NMR (243 MHz, CDCl₃): δ 19.11 (s, P(O)(OCH₂CH₃)₂). MS: m/z (%) 334.3 (100, [M+Na]⁺). Anal. Calcd for C₁₅H₂₂NO₄P (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 (ν_{max} , cm⁻¹): 731s, 1023s, 1241s, 1404m, 1457m, 1757vs (C=O), 2927s, 3053m. 1H NMR (600 MHz, CDCl₃): δ 0.87 (3H, t, $^2J_{HP}$ 15.0 Hz, CH₃), 1.20–1.47 (14H, m, P(O)(OCH₂CH₃)₂, (CH₂)₄), 3.26 (1H, dd, $^2J_{HP}$ 15.0 Hz, $^3J_{HH}$ 2.3 Hz, CHP(O)(OCH₂CH₃)₂), 3.69–3.73 (1H, m, CH(CH₂)₄), 4.12, 4.72, (2H, AB system, $^2J_{HH}$ 15.5 Hz, CH₂Ph), 4.16–4.24 (4H, m, P(O)(OCH₂CH₃)₂), 7.31–7.32 (3H, m, 3CH_{arom}), 7.35–7.38 (2H, m, 2CH_{arom}). ^{13}C NMR (150 MHz, CDCl₃): δ 16.4 (d, $^3J_{CP}$ 6.1 Hz, P(O)(OCH₂CH₃)₂), 32.6 (d, $^3J_{CP}$ 2.6 Hz, CHCH₂), 44.8 (d, $^4J_{CP}$ 1.9 Hz, CH₂Ph), 52.8 (d, $^1J_{CP}$ 145.9 Hz, CHP(O)(OCH₂CH₃)₂), 53.2 (d, $^2J_{CP}$ 2.7 Hz, CH(CH₂)₄), 62.4, 62.6 (2C, 2d, $^2J_{CP}(1)$ 6.3 Hz, $^2J_{CP}(2)$ 6.5 Hz, P(O)(OCH₂CH₃)₂), 127.7, 128.1, 128.7 (5CH_{arom}), 135.4 (1C_{arom}), 161.7 (d, $^2J_{CP}$ 6.6 Hz, C=O). ^{31}P NMR (243 MHz, CDCl₃): δ 20.00 (s, P(O)(OCH₂CH₃)₂). MS: m/z (%) 390.4 (100, [M+Na]⁺).

Diethyl (*R*)-*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 (ν_{max} , 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, $^3J_{HP}$ 14.9 Hz, $^3J_{HH}$ 2.4 Hz, CHP(O)(OCH₂CH₃)₂), 3.58 (1H, dt, $^3J_{HH}(1)$ 6.6 Hz, $^3J_{HH}(2)$ 2.7 Hz, CHOC(CH₃)₂), 3.69 (1H, dd, $^2J_{HH}(1)$ 8.9 Hz, $^3J_{HH}(2)$ 4.9 Hz, CH₂OC(CH₃)₂), 3.93 (1H dd, $^2J_{HH}(1)$ 8.9 Hz, $^3J_{HH}(2)$ 6.9 Hz, CH₂OC(CH₃)₂), 4.55 (1H, dd, $^3J_{HH}$ 6.1 Hz, $^2J_{HP}$ 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, $^2J_{HH}$ 15.2 Hz, CH₂Ph), 7.20–7.21 (1H, m, 1CH_{arom}), 7.26–7.27 (4H, m, 4CH_{arom}). ^{13}C NMR (150 MHz, CDCl₃): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}(1)$ 4.2 Hz, $^3J_{CP}(2)$ 4.2 Hz, P(O)(OCH₂CH₃)₂), 25.0, 26.5 (C(CH₃)₂), 45.8 (d, $^4J_{CP}$ 1.9 Hz, CH₂Ph), 49.3 (d, $^1J_{CP}$ 147.8 Hz, CHP(O)(OCH₂CH₃)₂), 54.3 (d, $^2J_{CP}$ 1.9 Hz, CHCHP(O)(OCH₂CH₃)₂), 62.6, 62.7 (2C, 2d, $^2J_{CP}(1)$ 6.3 Hz, $^2J_{CP}(2)$ 6.4 Hz, P(O)(OCH₂CH₃)₂), 66.0 (CH₂OC(CH₃)₂), 77.5 (d, $^2J_{CP}$ 3.5 Hz, CHCHP(O)(OCH₂CH₃)₂), 110.6 (C(CH₃)₂), 127.7, 128.6, 128.6 (4CH_{arom}), 135.4 (1C_{arom}), 161.1 (d, $^2J_{CP}$ 6.6 Hz, C=O). ^{31}P NMR (243 MHz, CDCl₃): δ 19.06 (s, P(O)(OCH₂CH₃)₂). MS: m/z (%) = 420.3 (100, [M+Na]⁺). Anal. Calcd for C₁₉H₂₈NO₆P (397.40): C, 57.42; H, 7.10; N, 3.52. Found: C, 57.40; H, 7.34; N, 3.33%.

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