Propargyl-Substituted Phosphonocarboxylates: Efficient Synthesis and Application to Click Chemistry

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Abstract: An efficient pathway for the selective preparation of monopropargyl-substituted phosphonocarboxylate (PC) has been developed via the addition of sodium acetylenide to ethylidenephosphonate. The reaction works perfectly on multi-gram scales. The synthesis of the corresponding methyl(propargyl)-, trifluoromethyl(propargyl)-, and dipropargyl-substituted derivatives was elaborated based on direct alkylation of either the correspondingly substituted phosphonocarboxylates or methylene phosphonocarboxylate with excess of propargyl bromide. A series of novel potentially biologically active 1,2,3-triazole-containing phosphonocarboxylates were synthesized using copper(I)-catalysed 1,3-dipolar cycloaddition of organic azides with propargyl-substituted phosphonocarboxylates.

Key words: phosphonocarboxylates, ethylidenephosphonate, alkylation, sodium acetylenide, 1,3-dipolar cycloaddition, azides, phosphorylated 1,2,3-triazoles

Bisphosphonates (BPs), being analogues of naturally occurring diphosphates, are the most widely used and effective antiresorptive agents currently available for the treatment of malignant hypercalcemia, tumor-associated bone disease, osteoporosis, and Paget's disease.[1,2] BPs are of interest in the context of cancer and immunotherapy, and they are also effective against parasites responsible for sleeping sickness, Chagas' disease, malaria, leishmaniases, and *T. brucei* infection.[3]

All BPs have high affinity for bone mineral as a consequence of their P–C–P backbone structure, which allows chelation of calcium ions. After successful clinical use of clodronate and etidronate (Figure 1), bisphosphonates containing a basic primary amino-nitrogen atom in a side alkyl chain (as in pamidronate and aledronate), were found to be 10- to 100-fold more potent. Moreover, the third generation of BP drugs, containing a nitrogen atom within a heterocyclic ring[4] (as in risedronate and zoledronate), are up to 10,000-fold more potent than etidronate in some experimental systems.[1] These cyclic nitrogen bisphosphonates (N-BPs) directly and selectively inhibit the activity of osteoclasts – the cells responsible for bone resorption. The detailed inhibitory mechanism of N-BPs is well documented in the literature.[5,6]

Furthermore, it has been found that replacement of one phosphonate group of N-BPs with a carboxylate moiety created a new class of pharmacological agents, namely the phosphonocarboxylates (PCs), that can specifically inhibit bone resorption both *in vitro* and *in vivo* without cytotoxic effect on osteoclasts.[4b]

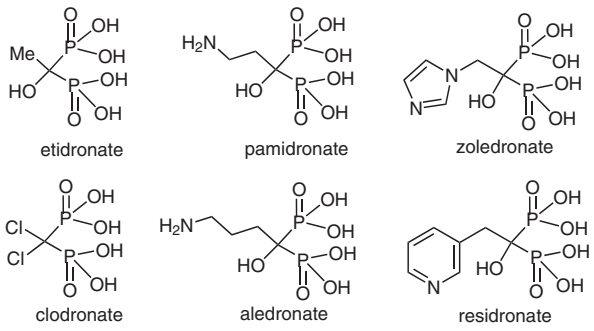

Figure 1 Structures of some bisphosphonates used in clinical studies and medical practice

Phosphonic (phosphinic) acids and phosphoamidates modulating the transition-state analogues or mimics of carboxylic acids might act as inhibitors of hydrolytic enzymes, such as esterases and amidases. Therefore, such compounds may possess antitumor properties [see, for example, a review[7] concerning the application and creation of new phosphorus-based chemotherapeutic drugs, including the phosphorylacetic acid derivatives, such as PALA[8] (*N*-phosphonoacetyl-L-aspartic acid)].

The key features required for high inhibitory potency of the N-BP and N-PC drug families include the structural motif of two geminal phosphonate groups (or a combination of phosphonate and carboxylate moieties respectively), which are responsible for interaction with the molecular target. For maximal potency, the nitrogen atom in the side chain must be a critical distance away from the P–C–P (or P–C–C) chelating group and in a specific spatial configuration. At the same time, the geminal hydroxy group does not influence the ability of these drugs to act at the cellular level. Therefore, the purposeful synthesis of new members of both N-BP and N-PC families, taking into consideration the dependencies mentioned above, is of current interest for further development of more potent drugs.

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Recently,[9] we elaborated an efficient, general synthetic approach giving the possibility for facile, rapid and cheap access to a wide range of novel N-BPs as potent drug candidates based on 'click' methodology, namely copper-catalysed azide–alkyne cycloaddition. The reaction proceeds regioselectively to give the corresponding 4-regioisomers exclusively and the capacity of bidentate phosphorus substrates to form metal-complexes does not influence the selectivity of the process in the presence of the copper(I) salts. The method allows the incorporation of two functionalities into the N-BP molecule simultaneously, as well as the ability to ligate two N-BPs to each another in situ via the one-pot reaction of organic dibromides with propargyl-substituted bisphosphonates, generating both the diazide and copper(I) moiety.

In a continuation of our investigations into biologically active organophosphorus compounds, in this paper we report the possibility of using an approach based on 'click' methodology for the effective synthesis of a wide range of novel 1,2,3-triazole-modified phosphonocarboxylates (N-PCs) as potent drug candidates. It should be mentioned that, despite the great popularity of copper-catalysed azide–alkyne 1,3-dipolar cycloaddition,[10] examples of its application for the synthesis of triazole-substituted phosphonates are limited to a few reports on the cycloaddition of azidoalkylphosphonates to a variety of alkynes,[11] the creation of a single noncompetitive α-2,3-sialyltrasferase inhibitor on a steroid base bearing phosphonate moiety,[12] and the paper mentioned above on bisphosphonate compounds.[9]

In order to construct the desired library of triazole-modified N-PCs, propargyl-substituted phosphonocarboxylates represented suitable starting substrates. According to our data and similar to those reported in the literature,[13] the synthesis of propargyl-substituted phosphonate **2a** based on alkylation of phosphoryl acetic acid ester **1a**[14] by propargyl bromide under phase-transfer catalysis conditions or using classical procedures such as potassium in xylene or deprotonation with sodium hydride (in contrast to a report[15] of a 71% yield of **2a**) is accompanied by substantial amounts of double alkylation (up to 29% of **3**). Moreover, the separation of mono- and dipropargyl substituted phosphonates **2a** and **3** using column chromatography is not effective due to the similar R_f values of these compounds. Therefore, here we want to disclose an efficient synthetic method for the selective preparation of mono-propargyl phosphonate **2a** based on the addition of sodium acetylenide to readily available ethylidenephosphonate **4** (Scheme 1).[16]

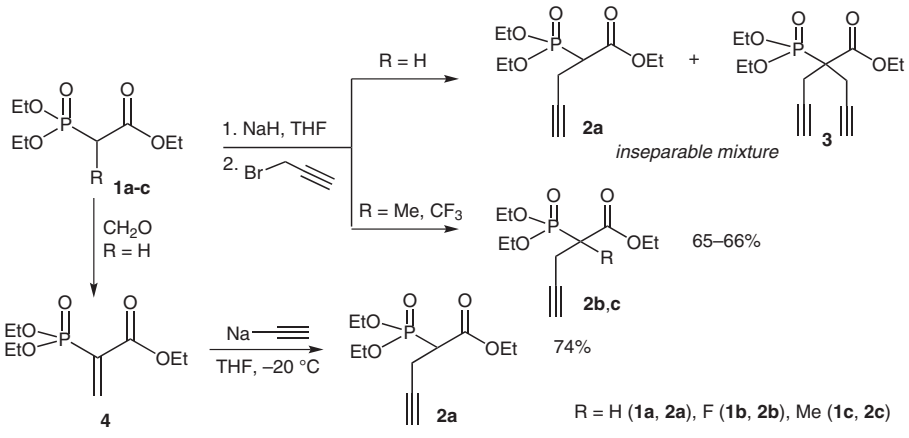
Thus, we have found that the reaction proceeds in anhydrous tetrahydrofuran under mild conditions for several hours to afford the desired monopropargyl product **2a** in high yield. Furthermore, the process can also be realized on multigram scales with excellent results.

In the case of substituted phosphonates **1b** and **1c**, the corresponding monopropargyl derivatives **2b** and **2c**, respectively, were readily obtained via the ordinary procedure under deprotonation with sodium hydride followed by alkylation without any difficulties (Scheme 1).

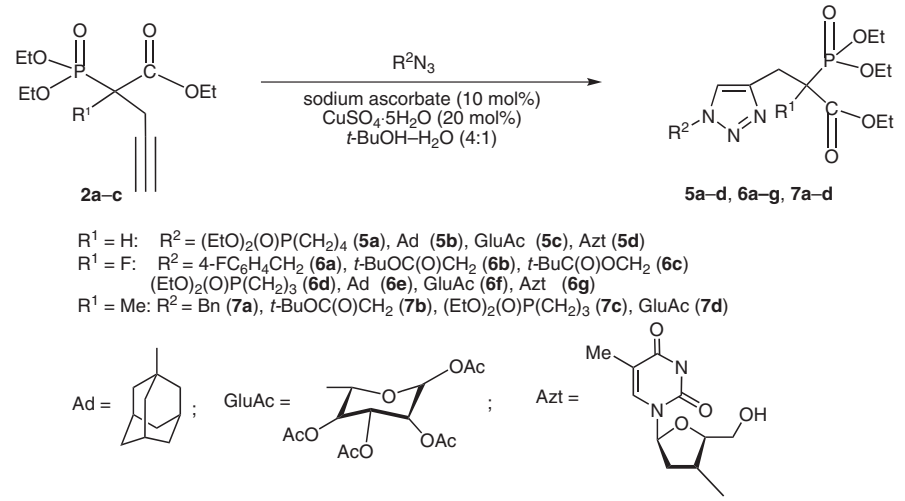
The alkylation of non-substituted phosphonate **1a** by an excess of propargyl bromide (3.5 equiv) under deprotonation with sodium hydride in THF has proven to be a facile route to disubstituted phosphonate **3a**.[17] Thus, having the mono- and dipropargyl-substituted phosphonocarboxylates **2** and **3** in hand, we investigated the possibility of their utilization in [3+2]-cycloaddition with a variety of functionalized organic azides under copper(I) catalysis.[18] To this end, we used the typical procedure previously described by us for regioselective synthesis of the triazole-substituted N-BPs: alkyne–azide coupling was performed in water–alcohol media (t-BuOH–H_2O) and the copper(I) catalyst was generated in situ from copper sulfate and sodium ascorbate (Scheme 2).

1,3-Dipolar Huisgen cycloaddition of propargyl-containing phosphonocarboxylates **2a–c** with a range of available azides was found to proceed smoothly at room temperature (6–8 h) to afford functionalized 1,2,3-triazoles **5a–d**, **6a–g** and **7a–d** in excellent yields (mostly more than 90%) and of high purity after a simple work-up procedure.

Highly functional azides having biologically active residues such as glucose, adamantyl or azidothimidine, and phosphorylated azides, which have recently been efficiently synthesized in ionic liquids by us,[11] are also good



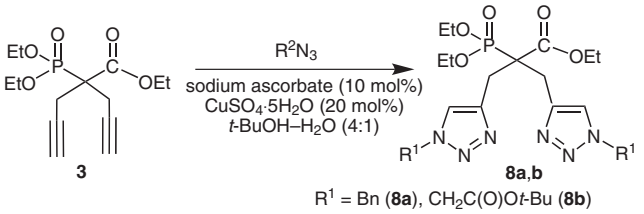
Scheme 1



Scheme 2

partners for propargyl phosphonates **2a–c** in these copper-catalysed reactions.

In a similar manner, copper-catalysed 1,3-dipolar cycloaddition of bispropargyl-substituted phosphonate **3** with azides has been accomplished to afford the corresponding bistriazols **8a** and **8b** in reasonable yields (52–62%; Scheme 3).



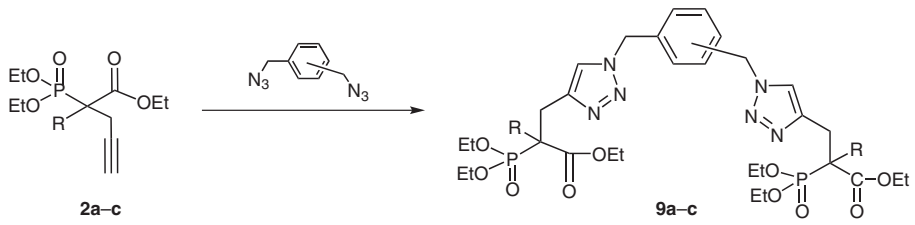
Scheme 3

Conversely, bistriazoles bearing two phosphonocarboxylate moieties could be easily synthesized starting from diazides and phosphonocarboxylates **2a–c** (Scheme 4). Furthermore, in contrast to bistriazoles **8a** and **8b**, this reaction afforded compounds **9a–c** in almost quantitative yields (>94%).

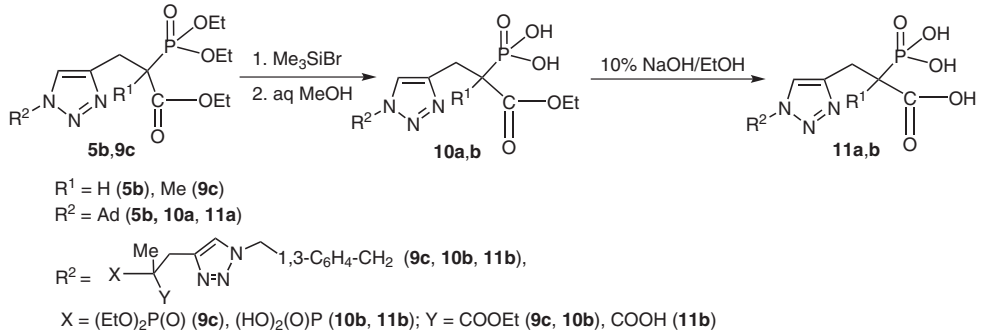
Despite their rather high molecular weight, all of the compounds in this series were obtained as colourless or yellowish oils and only azidotymydine derivative **6g** solidified over time. The structures of the phosphorylated triazoles were unambiguously confirmed by multinuclear NMR and IR spectroscopy along with HRMS and elemental analysis data. In this context it should be mentioned that, according to the NMR data, triazoles **5c**, **6f** and **7d**, bearing the glucose residue, are formed as diastereomeric mixtures in 1:1 ratios. Therefore, these compounds exhibit two singlet signals in the ^{31}P spectra, which are further split into two doublets in the case of fluorine substituted derivative **6f** and the corresponding doubling of signals in the ^{1}H, ^{13}C, and ^{19}F spectra. Unfortunately, we were unable to separate these diastereomers by column chromatography. The corresponding NMR data did not provide any information concerning the formation of diastereomers in the case of triazoles **5g** and **6g**, bearing the Azt-residue.

Compounds **5a**, **6d** and **7c** formed from phosphorylated azides display two signals in the ^{31}P NMR spectra wherein the singlet at ~30 ppm was assigned to the phosphorus nucleus of the side chain, while the upfield-shifted signal which occurred as either a singlet or a doublet depending on the substituent, corresponds to the phosphorus of the phosphonocarboxylate group.

Triazoles of N-PC type can be converted into the corresponding free phosphonic acids via reaction with trimethylbromosilane in chloroform followed by the treatment of the intermediate trimethylsilyl esters with aqueous methanol. Subsequent treatment of the phosphonic acids obtained with sodium hydroxide in ethanol resulted in the free carboxylic acids. The possibility of such total hydro-



Scheme 4 Reaction conditions: sodium ascorbate (10 mol%), $CuSO_4 \cdot 5H_2O$ (20 mol%), *t*-BuOH–H_2O (4:1).



Scheme 5

lysis of all ester groups is illustrated using compounds **5b** and **9c** as representative examples (Scheme 5).

In conclusion, the efficient pathway developed here for selective preparation of mono-propargyl substituted phosphonocarboxylates opens a route to the synthesis of a variety of potentially biologically active phosphonocarboxylates modified by either one or two 1,2,3-triazole rings. The approach gives the possibility for facile, rapid and cheap creation of a library of novel N-PCs as potent drug candidates via the 'click' methodology. Biological tests of the compounds obtained as well as the corresponding free phosphonic acids are under current investigation and will be published elsewhere.

Solvents were freshly distilled from respective drying agents before use. All other reagents were recrystallized or distilled when necessary. Analytical TLCs were performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light or spraying by $Ce(SO_4)_2$ solution in H_2SO_4. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. NMR spectra were obtained on a Bruker DPX-200 spectrometer (^{1}H, 200.13 MHz; ^{31}P, 80.99 MHz; ^{19}F, 188.31 MHz; ^{13}C, 50.32 MHz) and Bruker Avance-300 spectrometer (^{1}H, 300.13 MHz; ^{31}P, 121.49 MHz; ^{13}C, 75.47 MHz) using residual proton signals of deuterated solvent as an internal standard (^{1}H, ^{13}C) relative to TMS and H_3PO_4 (^{31}P) and $CFCl_3$ (^{19}F) as external standards. HRMS were obtained on a Varian MAT CH7A instrument using an EI source operating at 70 eV. IR spectra were recorded in a thin layer or in KBr on a Fourier-spectrometer Magna-IR750 (Nicolet), resolution 2 cm^{-1}, 128 scans. The purities of the crude products were estimated by the ^{1}H and ^{31}P NMR spectra.

The starting α-fluoro-triethylphosphonoacetate (**1b**),[19] triethyl-α-phosphonopropionate(**1c**),[20] ethyl-2-diethylphosphonoacrylate (**4**)[15] and diethoxyphosphoryl substituted azides[18] were obtained according to known procedures. Other reactants were purchased from Aldrich and used without further purification.

Ethyl 2-(Diethoxyphosphoryl)pent-4-ynoate (2a)

To a solution of ethylidenephosphonate **4** (5 g, 21.2 mmol) in anhydrous THF (50 mL) a slurry of fresh sodium acetylenide in xylene (21.2 mmol, 5.65 g of 18% w/w solution) was added dropwise at –15 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight. THF was removed under reduced pressure and Et_2O (50 mL) and 1 N HCl (50 mL) were added. The organic layer was separated and the aqueous phase was extracted into Et_2O (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4. After evaporation of the solvent under reduced pressure the product was purified by column chromatography (hexane–acetone, 10:1) to give the title compound.

Yield: 4.14 g (74%); colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31, 1.34 and 1.35 (3 × t, $^3J_{HH}$ = 6.5 Hz, 9 H, CH_3), 2.02 (br t, $^4J_{HH}$ = 2.0 Hz, 1 H, C≡CH), 2.62–2.97 (m, 2 H, CH and CH_2C≡), 3.16 (part of ABX system, $^2J_{HH}$ = 10.5 Hz, $^3J_{PH}$ = 22.2 Hz, $^4J_{HH}$ = 3.9 Hz, 1 H, CH_2C≡), 4.05–4.23 (m, 4 H, $POCH_2$), 4.23 (q, 2 H, $COCH_2$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.59 (CH_3), 16.80 [d,$^3J_{PC}$ = 5.6 Hz, P(O)OCH_2CH_3], 17.60 (d, $^2J_{PC}$ = 2.5 Hz, PCCH_2), 45.64 (d, $^1J_{PC}$ = 130.3 Hz, PCH), 62.23 (OCH_2), 63.37 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 63.58 (d, $^2J_{PC}$ = 6.5 Hz, $POCH_2$), 70.51 (≡CH), 81.00 (d, $^3J_{PC}$ = 20.6 Hz, C≡CH), 168.25 (d, $^2J_{PC}$ = 5.0 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.36.

HRMS: *m/z* [M^+] calcd for $C_{11}H_{19}O_5P$: 262.09701; found: 262.09800.

Propargyl-Substituted Phosphonates 2b and 2c; General Procedure

A solution of the corresponding phosphonate **1b**,**c** (0.1 mol) in THF (100 mL) was added dropwise to a slurry of NaH (60% in mineral oil, 4.8 g, 0.12 mol) in THF (100 mL) at 0 °C (ice–water bath). The mixture was allowed to warm to r.t., stirred for 30 min at ambient conditions and chilled again to 0 °C. Propargyl bromide (17.9 g, 0.15 mol) was added to this mixture under stirring and after warming to r.t. the mixture was stirred for another 4 h at 20 °C and left overnight under ambient conditions. After removing the THF under reduced pressure, H_2O (100 mL) was added to the residue and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, the filtrate was evaporated, and the residue was distilled under reduced pressure to give the desired compound.

Ethyl 2-(Diethoxyphosphoryl)-2-fluoropent-4-ynoate (2b)

Yield: 66%; yellowish liquid; bp 115–116 °C (1 Torr).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –179.15 (ddd, $^2J_{PF}$ = 81.1 Hz, $^3J_{FH}$ = 12.5 Hz, $^3J_{FH}$ = 34.0 Hz).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.40 (3 overlapping t, 9 H, CH_3), 2.08 (br t, $^4J_{HH}$ = 1.4 Hz, 1 H, C≡CH), 2.90–3.32 (m, 2 H, CH_2C≡), 4.23 (m, $^3J_{HH}$ = 6.0 Hz, 4 H, $POCH_2$), 4.34 (q, $^3J_{HH}$ = 6.0 Hz, 2 H, $COCH_2$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.40 (CH_3), 16.67 [d, $^3J_{PC}$ = 5.6 Hz, P(O)OCH_2CH_3], 25.15 (dd, $^2J_{CF}$ = 21.1 Hz, $^2J_{PC}$ = 3.8 Hz, CH_2C≡C), 63.05 (OCH_2), 64.86 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 65.08 (d, $^2J_{PC}$ = 6.8 Hz, $POCH_2$), 72.65 (≡CH), 76.07 (dd, $^3J_{CF}$ = 17.7 Hz, $^3J_{PC}$ = 3.0 Hz, C≡), 93.80 (dd, $^1J_{CF}$ = 202.3 Hz, $^1J_{PC}$ = 162.0 Hz, PCF), 166.25 (dd, $^2J_{CF}$ = 23.0 Hz, $^2J_{PC}$ = 3.9 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 12.45 (d, $^2J_{PF}$ = 81.1 Hz).

HRMS: *m*/*z* [M$^+$] calcd for $C_{11}H_{18}FO_5P$: 280.08759; found: 280.08830.

Ethyl 2-(Diethoxyphosphoryl)-2-methylpent-4-ynoate (2c)
Yield: 65%; colourless liquid; bp 109–110 °C (1 Torr).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{HH}$ = 6.4 Hz, 3 H, $COCH_2CH_3$), 1.33 (t, $^3J_{HH}$ = 6.8 Hz, 6 H, $POCH_2CH_3$), 1.58 (d, $^3J_{PH}$ = 16.0 Hz, 3 H, CH_3CP), 2.02 (t, $^4J_{HH}$ = 2.0 Hz, 1 H, C≡CH), 2.55 (H_A), and 3.09 (H_B) (ABX-system, $^2J_{HH}$ = 18.0 Hz, $^3J_{PH}$ = 8.0 Hz, $^4J_{HH}$ = 2.0 Hz, 2 H, CH_2C=), 4.05–4.35 (m, 6 H, OCH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.37 (CH_3), 16.72 (d,$^3J_{PC}$ = 4.5 Hz, $POCH_2CH_3$), 17.57 (d, $^2J_{PC}$ = 4.5 Hz, CH_3CP), 24.85 (CH_2C≡C), 47.88 (d, $^1J_{PC}$ = 133.3 Hz, PC), 62.02 ($COCH_2$), 63.22 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 63.75 (d, $^2J_{PC}$ = 8.6 Hz, $POCH_2$), 71.62 (≡CH), 79.42 (d, $^3J_{PC}$ = 9.6 Hz, C≡), 170.40 (d, $^2J_{PC}$ = 3.5 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 25.78.

HRMS: *m*/*z* [M$^+$] calcd for $C_{12}H_{21}O_5P$: 276.11266; found: 276.11353.

Ethyl 2-(Diethoxyphosphoryl)-2-(2-propynyl)pent-4-ynoate (3)
Obtained according to the procedure described for the synthesis of **2b**,**c** except using NaH (2.2 equiv) and propargyl bromide (4.5 equiv).

Yield: 83%; bp 133–135 °C (1 Torr).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, $COCH_2CH_3$), 1.33 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, $POCH_2CH_3$), 2.06 (t, $^4J_{HH}$ = 2.6 Hz, 2 H, C≡CH), 2.98 (d, $^4J_{HH}$ = 2.6 Hz, 2 H, CH_2C=), 3.03–3.07 (m, 2 H, CH_2C=), 4.10–4.30 (m, 6 H, OCH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.23 (CH_3), 16.61 (d, $^3J_{PC}$ = 5.8 Hz, $POCH_2CH_3$), 21.91 (CH_2C≡C), 50.93 (d, $^1J_{PC}$ = 133.6 Hz, PC), 62.29 ($COCH_2$), 63.55 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 71.75 (≡CH), 79.25 (d, $^3J_{PC}$ = 12.3 Hz, C≡), 168.94 (d, $^2J_{PC}$ = 4.5 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.99.

Synthesis of Triazoles; General Procedure
The organic azide (2.0 mmol) and acetylene **2** (2.0 mmol) were suspended in H_2O–*t*-BuOH (1:4, 8 mL) and $CuSO_4{\cdot}5H_2O$ (5 M, 0.1 mmol, 5 mol%) and sodium ascorbate (0.6 mmol) were added. The mixture was stirred at r.t. for 6–8 h, at which time TLC (silica, petroleum ether–acetone) indicated complete conversion. The resulting solution was concentrated under reduced pressure (rotor evaporator) and the residue was dissolved in brine (30 mL) and then extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with aq NH_4OH (5%, 2 × 10 mL), dried over $MgSO_4$, filtered and the solvent was removed under vacuum to give the crude product, which was purified by silica gel column chromatography if required (hexane–acetone, 10:1→1:10).

Ethyl 2-(Diethoxyphosphoryl)-3-{1-[3-(diethoxyphosphoryl)butyl]-1*H*-1,2,3-triazol-4-yl}propanoate (5a)
Yield: 73% (after column chromatography); colorless oil.

IR (thin layer): 1734 (C=O), 1550 (weak, C=C), 1461 (triazole), 1249 (P=O), 1026, 1050 (POC, COC), 964 (triazole) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, $^3J_{HH}$ = 6.0 Hz, 3 H, CH_3), 1.32 and 1.35 (2 × t, $^3J_{HH}$ = 6.0 Hz, 12 H, CH_3CH_2OP), 1.55–1.75 (m, 4 H, $PCCH_2CH_2$), 2.00 (dt, $^3J_{HH}$ = 6.0 Hz, $^3J_{PH}$ = 8.0 Hz, 2 H, PCH_2), 3.15–3.60 (m, 3 H, PCH and CH_2C=C), 4.00–4.25 (m, 10 H, OCH_2), 4.32 (t, $^3J_{HH}$ = 6.0 Hz, 2 H, CH_2N), 7.36 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.24 (CH_3), 16.55 and 16.55 (2 × d, $^3J_{PC}$ = 5.0 Hz, CH_3CH_2OP), 19.78 (d, $^2J_{PC}$ = 5.0 Hz, $PCCH_2$), 23.48 (d, $^2J_{PC}$ = 3.5 Hz, CH_2C=C), 25.03 (d, $^1J_{PC}$ = 141.9 Hz, PCH_2), 30.93 (d, $^3J_{PC}$ = 15.3 Hz, $PCCCH_2$), 45.45 (d, $^1J_{PC}$ = 129.3 Hz, PCH), 49.68 (CH_2N), 61.64 ($COCH_2$), 61.71 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 62.98 (d, $^2J_{PC}$ = 4.5 Hz, $POCH_2$), 63.10 (d, $^2J_{PC}$ = 4.0 Hz, $POCH_2$), 121.99 (=CH), 144.66 (d, $^3J_{PC}$ = 17.1 Hz, *C*=CH), 168.59 (d, $^2J_{PC}$ = 5.0 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.60 (s, 1 P, PCH), 32.15 (s, 1 P, PCH_2).

Anal. Calcd for $C_{19}H_{37}N_3O_8P_2$: C, 45.87; H, 7.50; N, 8.45; P, 12.45. Found: C, 45.97; H, 7.54; N, 8.31; P, 12.18.

Ethyl 3-[1-(1-Adamantyl)-1*H*-1,2,3-triazol-4-yl]-2-(diethoxyphosphoryl)propanoate (5b)
Yield: 95% (crude, 98% purity according to the ^{31}P and ^{1}H NMR data); yellowish oil.

IR (thin layer): 1735 (C=O), 1550 (C=C), 1452 (triazole), 1249 (P=O), 1024, 1052 (POC, COC), 971 (triazole) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3), 1.31 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3CH_2OP), 1.78 (s, 6 H, Adm), 2.20 (s, 9 H, Adm), 3.15–3.60 (m, 3 H, CH and CH_2C=C), 4.05–4.15 (m, 6 H, OCH_2), 7.41 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.52 (CH_3), 16.79 (d, $^3J_{PC}$ = 6.0 Hz, CH_3CH_2OP), 23.64 (CH_2C=C), 29.83, 36.31, 43.38 (Adm), 45.82 (d, $^1J_{PC}$ = 129.3 Hz, PCH), 59.72 (NC_{ipso}), 61.87 (OCH_2), 63.20 (d, $^2J_{PC}$ = 6.0 Hz, $POCH_2$), 63.31 (d, $^2J_{PC}$ = 5.0 Hz, $POCH_2$), 118.50 (=CH), 143.92 (d, $^3J_{PC}$ = 18.1 Hz, *C*=CH), 169.09 (d, $^2J_{PC}$ = 4.5 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.76.

Anal. Calcd for $C_{21}H_{34}N_3O_5P$: C, 57.39; H, 7.80; N, 9.56; P, 7.05. Found: C, 57.24; H, 7.94; N, 9.37; P, 7.04.

Ethyl 2-(Diethoxyphosphoryl)-3-[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]propanoate (5c)
Yield: 95% (crude, 97% purity according to the ^{31}P and ^{1}H NMR data); colourless oil; mixture of two diastereomers in 1:1 ratio.

IR (KBr): 1759 (C=O), 1558 (C=C), 1458 (triazole), 1231 (P=O), 1040, 1050 (POC, COC), 973 (triazole) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.12–1.45 [m, 9 H, $CH_3CH_2OC(O)H$ and CH_3CH_2OP], 1.86, 1.88 [2 × s, 1.5 H and 1.5 H, $CH_3C(O)_{Glu}$], 2.04, 2.07, 2.10 [3 × s, 9 H, $CH_3C(O)_{Glu}$], 3.20–3.60 (m, 3 H, CH_2C=C and PCH), 3.95–4.00 (m, 1 H, *c*-CHO), 4.00–4.05 (m, 1 H, *c*-CHO), 4.10–4.35 (m, 8 H, OCH_2 and CH_2OAc), 5.20–5.25 (m, 1 H, *c*-CHO), 5.38–5.45 (m, 2 H, *c*-CHO), 5.75–5.90 (m, 1 H, *c*-CH), 7.59 and 7.60 (2 × s, 0.5 H and 0.5 H, C=CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.34 (CH_3), 16.70 (d, $^3J_{PC}$ = 5.0 Hz, CH_3), 20.39, 20.44, 20.86, 20.99 (4 × s, CH_3C=O), 23.63 (CH_2C=C), 45.44 and 45.75 (2 × d, $^1J_{PC}$ = 129.5 Hz, PCH), 61.91 (br s, CH_2OAc and OCH_2), 63.27 (br s, $POCH_2$), 68.07, 70.58, 73.00, 75.22 (4 × s, *c*-CHO), 85.85 (*c*-$CH_{Glu}N$), 120.69, 120.52 (2 × s, =CH), 145.67 and 145.63 (2 × d, $^3J_{PC}$ = 17.1 Hz, *C*=CH), 168.51 (d, $^2J_{PC}$ = 7.0 Hz, C=O), 168.63 (d, $^2J_{PC}$ = 5.5 Hz, C=O), 168.97, 169.12, 169.69, 170,21, 170.77 (5 × s, CH_3C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.35.

Anal. Calcd for $C_{25}H_{38}N_3O_{14}P$: C, 47.24; H, 6.03; N, 6:61; P, 4.87. Found: C, 47.17; H, 6.15; N, 6.60; P, 4.73.

Ethyl 3-(1-{3-(Hydroxymethyl)-5-[5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]tetrahydrofuran-2-yl}-1*H*-1,2,3-triazol-4-yl)-2-(diethoxyphosphoryl)propanoate (5d)
Yield: 95% (after column chromatography); colourless oil.

IR (KBr): 3399 (OH), 1735 (C=O), 1695 (C=O), 1554 (weak, C=C), 1473 (triazole), 1273, 1239 (P=O), 1045 and 1023 (POC, COC), 973 (triazole) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3), 1.34 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3CH$_2$OP), 1.90 (s, 3 H, CH_3), 2.80–3.00 (m, 2 H, CH_2CH), 3.20–3.60 (m, 2 H, PCH and CH_{cycl}), 3.65–4.00 (m, 4 H, *c*-CH_2O and CH_2C=C), 3.90–4.05 (m, 2 H, CH_{cycl}), 4.10–4.30 (m, 4 H, $POCH_2$ and $COOCH_2$), 4.30–4.40 (m, 1 H, CH_{cycl}), 5.40–5.50 (m, 1 H, CH_{cycl}), 6.20–6.35 (m, 1 H, CH_{cycl}), 7.59 (s, 1 H, C=CH), 7.64 (s, 1 H, CH_{cycl}), 8.50 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.87 (CH_3), 14.47 (CH_3), 16.77 (d, $^3J_{PC}$ = 6.0 Hz, *C*H_3CH$_2$OP), 23.54 (*C*H_2C=C), 38.34 (*c*-CH_2), 45.40 (d, $^1J_{PC}$ = 129.8 Hz, PCH), 59.66 (CHN), 61.64 (CH_2OH), 62.15 (OCH_2), 63.59 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 85.73 (CHN), 87.31 (*C*HCH$_2$OH), 111.35 (=*C*CH_3), 122.73 (*C*H=C), 137.72 (=CHN), 145.14 (d, $^3J_{PC}$ = 16.6 Hz, *C*=CH), 151.13 (C=O), 164.82 (C=O), 168.85 (d, $^2J_{PC}$ = 4.5 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.59.

Anal. Calcd for $C_{21}H_{32}N_5O_9P{\cdot}2H_2O$: C, 44.60; H, 6.42; N, 12.38; P, 5.48. Found: C, 44.32; H, 6.58; N, 11.59; P, 5.52.

Ethyl 2-(Diethoxyphosphoryl)-2-fluoro-3-[1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]propanoate (6a)
Yield: 83% (after column chromatography); colourless oil.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.19 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, CH_3), 1.36 (br t, $^3J_{HH}$ = 6.8 Hz, 6 H, CH_3), 3.53 (H_A) and 3.77 (H_B) (ABXY system, $^2J_{HH}$ = 15.8 Hz, $^3J_{PH(A)}$ = 12.6 Hz, $^3J_{PH(B)}$ = 4.8 Hz, $^3J_{FH(A)}$ = 12.2 Hz, $^3J_{FH(B)}$ = 39.0 Hz, 2 H, CH_2C=C), 4.10–4.40 (m, 6 H, OCH_2), 5.40 (H_A) and 5.52 (H_B) (AB system, $^2J_{HH}$ = 21.0 Hz, 2 H, CH_2Ar), 7.05 (app t, $^3J_{HH}$ = $^4J_{FH}$ = 8.4 Hz, 2 H, ArH), 7.23 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{FH}$ = 9.8 Hz, 2 H, ArH), 7.41 (s, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.33 (CH_3), 16.80 (d, $^3J_{PC}$ = 5.7 Hz, *C*H_3CH$_2$OP), 31.02 (d, $^2J_{CF}$ = 20.3 Hz, *C*H_2C=C), 63.00 (OCH_2), 64.84 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 65.07 (d, $^2J_{PC}$ = 6.7 Hz, $POCH_2$), 94.89 (dd, $^1J_{PC}$ = 162.9 Hz, $^1J_{CF}$ = 196.9 Hz, PCF), 116.43 (d, $^2J_{CF}$ = 21.8 Hz, *C*HCF$_{Ar}$), 130.27 (d, $^3J_{CF}$ = 8.4 Hz, *C*HCHCF$_{Ar}$), 131.03 (d, $^4J_{CF}$ = 3.1 Hz, C$_{ipso}$), 123.38 (=CH), 140.72 (d, $^3J_{CF}$ = 15.1 Hz, *C*=CH), 163.18 (d, $^1J_{CF}$ = 247.8 Hz, CF_{Ar}), 166.77 (dd, $^2J_{CF}$ = 23.2 Hz, $^2J_{PC}$ = 3.9 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 12.07 (d, $^2J_{PF}$ = 83.0 Hz).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –179.00 (ddd, $^2J_{PF}$ = 83.0 Hz, $^3J_{FH}$ = 12.2 Hz, $^3J_{FH}$ = 38.9 Hz, 1 F, PCF), –113.38 (m, 1 F, C_{Ar}-F).

HRMS: *m*/*z* [M$^+$] calcd for $C_{18}H_{24}F_2N_3O_5P$: 431.14217; found: 431.14112.

Ethyl 3-[1-(2-*tert*-Butoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]-2-(diethoxyphosphoryl)-2-fluoropropanoate (6b)
Yield: 97% (crude, 99% purity according to the ^{31}P and ^1H NMR data); light-yellow oil.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, $^3J_{HH}$ = 6.4 Hz, 3 H, CH_3CH_2O), 1.39 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3CH_2OP), 1.48 (s, 9 H, CH_3 of *t*-Bu), 3.59 (H_A) and 3.83 (H_B) (ABXY system, $^2J_{HH}$ = 16.0 Hz, $^3J_{PH(A)}$ = 8.0 Hz, $^3J_{PH(B)}$ = 6.0 Hz, $^3J_{FH(A)}$ = 13.2 Hz, $^3J_{FH(B)}$ = 39.5 Hz, 2 H, CH_2C=C), 4.20–4.40 (m, 6 H, OCH_2), 4.95 (H_A) and 5.07 (H_B) (AB system, $^2J_{HH}$ = 26.0 Hz, 2 H, CH_2CO), 7.61 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.37 (CH_3), 16.82 (d, $^3J_{PC}$ = 5.5 Hz, *C*H_3CH$_2$OP), 28.33 (CH_3 in *t*-Bu), 31.02 (d, $^2J_{CF}$ = 20.6 Hz, *C*H_2C=C), 51.94 (OC in *t*-Bu), 63.03 (OCH_2), 64.86 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 65.07 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 84.10 (*C*H_2CO), 94.88 (dd, $^1J_{PC}$ = 163.0 Hz, $^1J_{CF}$ = 196.8 Hz, PCF), 124.90 (=CH), 140.42 (d, $^3J_{FC}$ = 15.0 Hz, *C*=CH), 165.56 (C=O), 166.65 (dd, $^2J_{PC}$ = 4.0 Hz, $^2J_{CF}$ = 23.7 Hz, CF*C*=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 12.84 (d, $^2J_{PF}$ = 82.6 Hz).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –179.74 (ddd, $^2J_{PF}$ = 82.7 Hz, $^3J_{FH}$ = 13.2 Hz, $^3J_{FH}$ = 39.5 Hz, C=O).

HRMS: *m*/*z* [M$^+$] calcd for $C_{17}H_{29}FN_3O_7P$: 437.17272; found: 437.17547.

Ethyl 2-(Diethoxyphosphoryl)-1-{[(2,2-dimethyl-1-oxopropoxy)methyl]-1*H*-1,2,3-triazol-4-yl}-2-fluoropropanoate (6c)
Yield: 83% (after column chromatography); light-yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 9 H, CH_3 in *t*-Bu), 1.30 (t, $^3J_{HH}$ = 7.3 Hz, 3 H, CH_3CH_2O), 1.42 and 1.43 (two overlapping t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3CH_2OP), 3.60 (H_A) and 3.84 (H_B) (ABXY system, $^2J_{HH}$ = 15.8 Hz, $^3J_{PH(A)}$ = 8.0 Hz, $^3J_{PH(B)}$ = 4.3 Hz, $^3J_{FH(A)}$ = 11.4 Hz, $^3J_{FH(B)}$ = 39.0 Hz, 2 H, CH_2C=C), 4.37–4.28 (m, 6 H, OCH_2), 6.23 (H_A) and 6.26 (H_B) (AB system, $^2J_{HH}$ = 10.6 Hz, 2 H, NCH_2O), 7.77 (s, 1 H, =CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.68 (CH_3), 16.11 (d, $^3J_{PC}$ = 5.5 Hz, *C*H_3CH$_2$OP), 28.46 (CH_3 in *t*-Bu), 30.14 (d, $^2J_{CF}$ = 19.2 Hz, *C*H_2C=C), 38.43 [C(CH_3)$_3$], 62.27 (OCH_2), 64.15 (d, $^2J_{PC}$ = 7.1 Hz, $POCH_2$), 64.38 (d, $^2J_{PC}$ = 7.1 Hz, $POCH_2$), 94.02 (dd, $^1J_{PC}$ = 162.5 Hz, $^1J_{CF}$ = 197.3 Hz, PCF), 124.18 (=CH), 140.10 (d, $^3J_{FC}$ = 15.4 Hz, *C*=CH), 166.85 (dd, $^2J_{PC}$ = 3.3 Hz, $^2J_{CF}$ = 23.6 Hz, CF-*C*=O),177.25 [C(O)O(*t*-Bu)].

^{31}P NMR (121 MHz, $CDCl_3$): δ = 11.84 (d, $^2J_{PF}$ = 83.1 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –178.63 (ddd, $^2J_{PF}$ = 83.1 Hz, $^3J_{FH}$ = 11.4 Hz, $^3J_{FH}$ = 39.0 Hz).

Anal. Calcd for $C_{17}H_{29}FN_3O_7P$: C, 46.68; H, 6.68; N, 9.61; P, 7.08. Found: C, 46.75; H, 6.74; N, 9.61; P, 7.05.

Ethyl 2-(Diethoxyphosphoryl)-3-{1-[3-(diethoxyphosphoryl)propyl]-1*H*-1,2,3-triazol-4-yl}-2-fluoropropanoate (6d)
Yield: 60% (after column chromatography); colourless oil.

IR (thin layer): 1760, 1742 (C=O), 1550 (w, C=C), 1463 (triazole), 1260, 1236 (P=O), 1200, 1047 and 1025 (POC, COC), 966 (triazole) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, $^3J_{HH}$ = 6.5 Hz, 3 H, CH_3), 1.33 (t, $^3J_{HH}$ = 6.5 Hz, 6 H, CH_3CH$_2$OP), 1.39 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3CH$_2$OP), 1.60–1.77 (m, 2 H, CH_2CH$_2$P), 2.10–2.35 (m, 2 H, CH_2P), 3.55 (H_A) and 3.79 (H_B) (ABXY system, $^2J_{HH}$ = 16.0 Hz, $^3J_{PH(A)}$ = 8.0 Hz, $^3J_{PH(B)}$ = 4.0 Hz, $^3J_{FH(A)}$ = 13.2 Hz, $^3J_{FH(B)}$ = 39.5 Hz, 2 H, CH_2C=C), 4.00–4.45 (2 m, 4 H + 6 H, $POCH_2$ + $COCH_2$), 4.43 (t, $^3J_{HH}$ = 6.5 Hz, 2 H, CH_2N), 7.53 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.14 (CH_3), 16.57 (d, $^3J_{PC}$ = 6.0 Hz, CH_3), 22.44 (d, $^1J_{PC}$ = 142.4 Hz, PCH_2), 23.85 (PC*C*H$_2$), 30.70 (d, $^2J_{CF}$ = 20.6 Hz, *C*H_2C=C), 50.02 (d, $^3J_{PC}$ = 16.1 Hz, CH_2N), 61.87 (d, $^2J_{PC}$ = 6.5 Hz, $POCH_2$), 62.65 (OCH_2), 64.56 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 64.76 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 94.62 (dd, $^1J_{PC}$ = 162.5 Hz, $^1J_{CF}$ = 197.3 Hz), 123.75 (=CH), 139.75 (d, $^3J_{CF}$ = 15.0 Hz, *C*=CH), 166.32 (dd, $^2J_{PC}$ = 4.0 Hz, $^2J_{CF}$ = 23.1 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 31.03 (s, 1 P, PCH_2), 12.77 (d, $^2J_{PF}$ = 82.6 Hz, 1 P, PCF).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –180.17 (ddd, $^2J_{PF}$ = 82.6 Hz, $^3J_{FH}$ = 13.2 Hz, $^3J_{FH}$ = 39.5 Hz).

HRMS: *m*/*z* [M$^+$] calcd for $C_{18}H_{34}FN_3O_8P_2$: 501.18052; found: 501.17839.

Ethyl 3-[1-(1-Adamantyl)-1*H*-1,2,3-triazol-4-yl]-2-(diethoxyphosphoryl)-2-fluoropropanoate (6e)
Yield: 94% (crude, >98% purity according to the ^{31}P and ^1H NMR data); yellowish oil.

IR (thin layer): 1761, 1741 (C=O), 1550 (w, C=C), 1453 (triazole), 1265, 1236 (P=O), 1052, 1037, 1021 (POC, COC), 979 (triazole) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3), 1.38 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3CH_2OP), 1.78 (2 × br s, 6 H and 9 H, Adm), 3.55 (H_A) and 3.81 (H_B) (ABXY system, $^2J_{HH}$ = 16.0 Hz, $^3J_{PH(A)}$ = 8.0 Hz, $^3J_{PH(B)}$ = 4.0 Hz, $^3J_{FH(A)}$ = 11.6 Hz, $^3J_{FH(B)}$ = 39.5 Hz, 2 H, CH_2C=C), 4.15–4.40 (m, 6 H, OCH_2), 7.52 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.40 (CH_3), 16.82 (d, $^3J_{PC}$ = 6.0 Hz, *C*H_3CH_2OP), 29.81, 36.28, 43.32 (Adm), 31.20 (d, $^2J_{CF}$ = 20.1 Hz, CH_2C=C), 59.88 (NC_{ipso}), 62.90 (OCH_2), 64.78 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 65.02 (d, $^2J_{PC}$ = 6.5 Hz, $POCH_2$), 95.09 (dd, $^1J_{PC}$ = 162.5 Hz, $^1J_{CF}$ = 196.8 Hz, PCF), 119.7 (=CH), 139.15 (d, $^3J_{FC}$ = 15.6 Hz, *C*=CH), 166.76 (dd, $^2J_{PC}$ = 4.0 Hz, $^2J_{CF}$ = 23.1 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 12.41 (d, $^2J_{PF}$ = 83.4 Hz).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –179.74 (ddd, $^2J_{PF}$ = 83.4 Hz, $^3J_{FH}$ = 11.3 Hz, $^3J_{FH}$ = 39.4 Hz).

MS (EI): *m*/*z* (%) = 458 (100) $[M + H]^+$, 457 (2) $[M]^+$, 135 (100) [Adm].

Anal. Calcd for $C_{21}H_{33}FN_3O_5P$: C, 55.13; H, 7.27; N, 9.19; P, 6.77. Found: C, 55.04; H, 7.18; N, 9.11; P, 6.59.

Ethyl 2-(Diethoxyphosphoryl)-3-[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]-2-fluoropropanoate (6f)
Yield: 80% (after column chromatography); colourless oil; mixture of two diastereomers in 1:1 ratio.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3), 1.36 and 1.37 (two overlapping t, $^3J_{HH}$ = 7.0 Hz, 6 H, C*H*$_3CH_2OP$), 1.84, 2.00, 2.04, 2.07 (4 × s, 12 H, CH_3C=O), 3.52 (H_A) and 3.77 (H_B) (ABXY system, $^2J_{HH}$ = 16.0 Hz, $^3J_{PH(A)}$ = 8.0 Hz, $^3J_{PH(B)}$ = 6.0 Hz, $^3J_{FH(A)}$ = 11.5 Hz, $^3J_{FH(B)}$ = 38.0 Hz, 2 H, CH_2C=C), 3.90–4.00 (m, 1 H, *c*-CHO), 4.00–4.05 (m, 1 H, *c*-CHO), 4.10–4.35 (m, 8 H, OCH_2 and CH_2OH), 5.15–5.25 (m, 1 H, *c*-CHO), 5.30–5.45 (m, 1 H, *c*-CHO), 5.75–5.85 (m, 1 H, *c*-CH), 7.66 (s, 1 H, C=CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.17 (CH_3), 16.64 (d, $^3J_{PC}$ = 5.5 Hz, CH_3), 20.23, 20.28, 20.73, 20.75, 20.86 (5 × s, *C*H_3C=O), 30.70 (d, $^2J_{CF}$ = 20.6 Hz, *C*H_2C=C), 61.90 (OCH_2), 62.83 and 62.88 (CH_2OH), 64.73 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 64.92 (d, $^2J_{PC}$ = 6.5 Hz, $POCH_2$), 68.07, 70.53, 70.60, 72.99, 75.05 (5 × s, *c*-CHO), 85.66 (s, *c*-CHON), 94.63 (dd, $^1J_{PC}$ = 162.5 Hz, $^1J_{CF}$ = 198.3 Hz), 94.80 (dd, $^1J_{PC}$ = 163.0 Hz, $^1J_{CF}$ = 197.8 Hz), 121.94 and 122.29 (2 × s, =CH), 140.72 (dd, $^3J_{PC}$ = 9.6 Hz, $^3J_{CF}$ = 15.6 Hz, *C*=CH), 166.35 (dd, $^2J_{PC}$ = 3.0 Hz, $^2J_{CF}$ = 23.1 Hz, C=O), 168.93, 169.07, 169.65, 170.14, 170.70 (5 × s, CH_3C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 13.03, 13.00 (2 × d, $^2J_{PF}$ = 82.6 Hz).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –179.90, –180.01 (2 × ddd, $^2J_{PF}$ = 82.6 Hz, $^3J_{FH}$ = 11.3 Hz, $^3J_{FH}$ = 38.0 Hz).

Anal. Calcd for $C_{25}H_{37}FN_3O_{14}P$: C, 45.94; H, 5.71; N, 6.43; P, 4.74. Found: C, 45.84; H, 5.75; N, 6.28; P, 4.67.

Ethyl 3-(1-{3-(Hydroxymethyl)-5-[5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]tetrahydrofuran-2-yl}-1*H*-1,2,3-triazol-4-yl)-2-(diethoxyphosphoryl)-2-fluoropropanoate (6g)
Yield: 91% (crude, 99% purity according to the ^{31}P and ^1H NMR data); mp 125 °C (dec.).

IR (KBr): 3338 (OH), 1745, 1692, 1661 (C=O), 1552 (w, C=C), 1470 (triazole), 1278, 1265 (P=O), 1043, 1015 (POC, COC), 978 (triazole) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, C*H*$_3CH_2OC$), 1.40 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, C*H*$_3CH_2OP$), 1.95 (s, 3 H, CH_3), 2.86 (br, 1 H, OH), 2.90–3.00 (m, 2 H, *c*-C*H*$_2$), 3.35–3.37 (m, 1 H, CH_2C=C), 3.50–3.90 (m, 2 H, C*H*$_2$OH and CH_2C=C), 3.92–4.20 (m, 1 H, CH_2OH), 4.20–4.35 (m, 6 H, $POCH_2$ and $COOCH_2$), 4.35–4.45 (m, 1 H, CH_{cycl}), 5.35–5.45 (m, 1 H, CH_{cycl}), 6.19–6.26 (m, 1 H, CH_{cycl}), 7.44 (s, 1 H, C=CH), 7.64 (s, 1 H, CH_{cycl}), 8.60 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.87 (CH_3), 14.43 (*C*H_3CH_2OC), 16.84 (d, $^3J_{PC}$ = 6.0 Hz, *C*H_3CH_2OP), 30.86 (d, $^2J_{CF}$ = 20.1 Hz, *C*H_2C=C), 38.2 (*c*-CH_2), 59.79 (CHN), 61.72 (CH_2OH), 63.21 (OCH_2), 65.07 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 65.33 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 85.73 (CHN), 87.68 (*C*HCH_2OH), 94.78 (dd, $^1J_{PC}$ = 163.0 Hz, $^1J_{CF}$ = 196.7 Hz, PCF), 111.44 (=*C*CH_3), 123.95 (*C*H=C), 137.84 (=CHN), 140.37 (d, $^3J_{CF}$ = 14.6 Hz, *C*=CH), 151.05 (C=O), 164.68 (C=O), 166.68 (dd, $^2J_{CF}$ = 23.1 Hz, $^2J_{PC}$ = 3.5 Hz).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 13.16 (d, $^2J_{PF}$ = 82.6 Hz).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –179.11 (ddd, $^2J_{PF}$ = 82.6 Hz, $^3J_{FH}$ = 11.3 Hz, $^3J_{FH}$ = 37.6 Hz).

Anal. Calcd for $C_{21}H_{31}FN_5O_9P$: C, 46.07; H, 5.70; N, 12.79. Found: C, 45.88; H, 5.64; N, 12.59.

Ethyl 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-(diethoxyphosphoryl)-2-methylpropanoate (7a)
Yield: 80% (crude, 97% purity according to the ^{31}P and ^1H NMR data); yellowish oil.

IR (thin layer): 1729 (C=O), 1548 (w, C=C), 1498 (triazole), 1266, 1245, 1226 (P=O), 1198, 1049, 1024 (POC, COC), 969 (triazole) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.14 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, C*H*$_3CH_2OC$), 1.30, 1.31 (two overlapping t, $^3J_{HH}$ = 7.0 Hz, 6 H, C*H*$_3CH_2OP$), 1.38 (d, $^3J_{PH}$ = 16.6 Hz, 3 H, CH_3CP), 3.06 (H_A) and 3.55 (H_B) (ABX system, $^2J_{HH}$ = 14.4 Hz, $^3J_{PH}$ = 8.4 Hz, 2 H, CH_2C=), 4.18–4.05 (m, 6 H, OCH_2), 5.45 (s, 2 H, CH_2Ph), 7.40–7.30 and 7.24–7.16 (2 × m, 5 H, Ar), 7.21 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.37 (CH_3), 16,80 (d, $^3J_{PC}$ = 5.7 Hz, CH_3), 17.50 (d, $^2J_{PC}$ = 4.7 Hz, CH_3CP), 30.53 (d, $^2J_{PC}$ = 2.9 Hz, *C*H_2C=C), 49.24 (d, $^1J_{PC}$ = 137.2 Hz, PC), 54.32 (CH_2Ph), 63.25 and 63.53 (2 × d, $^2J_{PC}$ = 7.1 Hz, $POCH_2$), 123.16 (=CH), 128.27 (*o*-C_6H_5), 128.98 (*p*-C_6H_5), 129,39 (*m*-C_6H_5), 135.25 (*ipso*-C_6H_5), 143.57 (d, $^3J_{PC}$ = 17.3 Hz, *C*=CH), 171.24 [d, $^2J_{PC}$ = 3.6 Hz, C(O)].

^{31}P NMR (81 MHz, $CDCl_3$): δ = 26.61.

MS (EI): *m*/*z* (%) = 409 (8) $[M^+]$.

Anal. Calcd for $C_{19}H_{28}N_3O_5P$: C, 55.74; H, 6.89; P, 7.57; N, 10.26. Found: C, 55.86; H, 7.00; N, 10.11; P, 7.60.

Ethyl 3-[1-(2-*tert*-Butoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]-2-(diethoxyphosphoryl)-2-methylpropanoate (7b)
Yield: 65% (after column chromatography); colourless oil.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, C*H*$_3CH_2OC$), 1.35 (t, $^3J_{HH}$ = 6.8 Hz, 6 H, C*H*$_3CH_2OP$), 1.43 (d, $^3J_{PH}$ = 16.0 Hz, 3 H, CH_3CP), 1.47 (s, 9 H, *t*-Bu), 3.14 (H_A) and 3.64 (H_B) (ABX system, $^2J_{HH}$ = 14.0 Hz, $^3J_{PH}$ = 8.0 Hz, 2 H, CH_2C=), 4.17 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, OCH_2), 4.20 (quint, $^3J_{HH}$ = 6.8 Hz, 4 H, $POCH_2$), 5.01 (s, 2 H, CH_2CO), 7.46 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.20 (CH_3), 16.63 (d, $^3J_{PC}$ = 5.5 Hz, CH_3CH_2OP), 17.23 (d, $^2J_{PC}$ = 5.0 Hz, *C*H_3CP), 28.06 (CH_3 in *t*-Bu), 30.25 (d, $^3J_{PC}$ = 2.0 Hz, PC*C*H_2), 48.95 (d, $^1J_{PC}$ = 132.8 Hz, PC), 51.60 (OC in *t*-Bu), 61.77 (OCH_2), 63.07 and 63.37 (2 × d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 83.46 (NCH_2CO), 124.65 (=CH), 142.94 (d, $^3J_{PC}$ = 17.6 Hz, *C*=CH), 165.64 [C(O)^{t}Bu], 170.96 [d, $^2J_{PC}$ = 3.5 Hz, C(O)].

^{31}P NMR (81 MHz, $CDCl_3$): δ = 26.35.

HRMS: *m*/*z* [M$^+$] calcd for $C_{18}H_{32}N_3O_7P$: 433.19779; found: 433.19786.

Ethyl 2-(Diethoxyphosphoryl)-3-{1-[3-(diethoxyphosphoryl)propyl]-1*H*-1,2,3-triazol-4-yl}-2-methylpropanoate (7c)
Yield: 55% (after column chromatography); colourless oil.

IR (thin layer): 1730 (C=O), 1555 (w, C=C), 1463 (triazole), 1240 (P=O), 1197, 1049, 1025 (POC, COC), 966 (triazole) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24–1.38 (m, 15 H, CH_3), 1.41 (d, $^3J_{PH}$ = 16.0 Hz, 3 H, CH_3CP), 1.60–1.80 (m, 2 H, CH_2CH_2P), 2.09–2.30 (m, 2 H, PCH_2), 3.12 (H_A) and 3.64 (H_B) (ABX system, $^2J_{HH}$ = 14.0 Hz, $^3J_{PH}$ = 8.0 Hz, 2 H, CH_2C=), 4.10 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, OCH_2), 4.20 (quint, $^3J_{HH}$ = 6.8 Hz, 8 H, $POCH_2$), 4.41 (t, $^3J_{HH}$ = 7.0 Hz, 2 H, CH_2N), 7.37 (s, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.43 (CH_3), 16.80 (d,$^3J_{PC}$ = 6.0 Hz), 17.49 (d, $^2J_{PC}$ = 4.5 Hz, CH_3CP), 22.79 (d, $^1J_{PC}$ = 143.4 Hz, PCH_2), 24.04 (d, $^2J_{PC}$ = 4.5 Hz, $PCCH_2$), 30.42 (d, $^2J_{PC}$ = 2.5 Hz, CH_2C=C), 49.16 (d, $^1J_{PC}$ = 132.3 Hz, PC), 50.16 (d, $^3J_{PC}$ = 15.0 Hz, CH_2N), 61.95 (OCH_2), 62.12 and 63.50 (2 × d, $^2J_{PC}$ = 6.5 Hz, $POCH_2$), 63.27 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 123.41 (=CH), 143.18 (d, $^3J_{PC}$ = 17.0 Hz, *C*=CH), 171.25 (d, $^2J_{PC}$ = 3.5 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 26.17 (s, 1 P, PCH), 30.87 (s, 1 P, PCH_2).

MS (EI): *m*/*z* (%) = 497 (8) [M]$^+$.

Anal. Calcd for $C_{19}H_{37}N_3O_8P_2$: C, 45.87; H, 7.50; N, 8.45; P, 12.45. Found: C, 45.79; H, 7.57; N, 8.37; P, 12.12.

Ethyl 2-(Diethoxyphosphoryl)-3-[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]-2-methylpropanoate (7d)
Yield: 91% (after column chromatography); colourless oil; mixture of two diastereomers in 1:1 ratio.

IR (KBr): 1759 (C=O), 1556 (w, C=C), 1463 (triazole), 1234 (P=O), 1098, 1041 (POC, COC), 963 (triazole) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22–1.45 (m, 12 H, CH_3CH_2O and $PCCH_3$), 1.84, 1.87, 2.03, 2.07, 2.09, 2.10 (6 × s, 12 H, CH_3C=O), 3.03–3.20 (m, 1 H, CH_2C=C), 3.58–3.71 (m, 1 H, CH_2C=C), 3.95–4.05 (m, 1 H, *c*-CHO), 4.10–4.40 (m, 9 H, OCH_2 and *c*-CHO), 5.15–5.20 (m, 1 H, *c*-CHO), 5.38–5.45 (m, 1 H, *c*-CHO), 5.78–5.90 (m, 1 H, *c*-CH), 7.57 (s, 1 H, C=CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.27 (CH_3), 16.71 (d, $^3J_{PC}$ = 5.0 Hz, $POCH_2CH_3$), 17.11 (d, $^3J_{PC}$ = 5.0 Hz, CH_3CP), 20.22, 20.25, 20.76, 20.87 (4 × s, CH_3C=O), 30.19 (d, $^2J_{PC}$ = 9.1 Hz, CH_2C=C), 48.89 (d, $^1J_{PC}$ = 132.8 Hz, PC), 49.10 (d, $^1J_{PC}$ = 131.8 Hz, PC), 61.85 (CH_2OH and OCH_2), 63.34 ($POCH_2$), 68.09, 70.51, 70.63, 72.87, 75.01 (*c*-CHO), 85.64 (c-OCHN), 121.62 (=CH), 143.59 and 143.94 (2 × d, $^3J_{PC}$ = 10.0 Hz, *C*=CH), 168.97 (d, $^2J_{PC}$ = 8.6 Hz, C=O), 169.65, 170.08, 170.64, 170.88 (4 × s, CH_3C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 26.25, 26.16.

MS (ESI): *m*/*z* = 650 [M + H]$^+$.

Anal. Calcd for $C_{26}H_{40}N_3O_{14}P$: C, 48.07; H, 6.21; N, 6.47; P, 4.77. Found: C, 48.09; H, 6.18; N, 6.37; P, 4.76.

Ethyl 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-2-(diethoxyphosphoryl)propanoate (8a)
Yield: 62% (after column chromatography); colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.13 (t, $^3J_{HH}$ = 6.9 Hz, 6 H, CH_3), 1.16 (t,$^3J_{HH}$ = 7.0 Hz, 3 H, CH_3), 3.30 (s, 2 H, CH_2C=C), 3.37 (d, $^3J_{PH}$ = 2.0 Hz, 2 H, CH_2C=C), 3.95 (q, $^3J_{HH}$ = 7.0 Hz, 4 H, CH_2OP), 4.13 (q, $^3J_{HH}$ = 6.9 Hz, 2 H, CH_2O), 5.41 (s, 4 H, CH_2Ph), 7.05–7.20 (m, 10 H, Ph), 7.60 (s, 2 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.28 (CH_3), 16.64 (d, $^3J_{PC}$ = 6.0 Hz, $POCH_2CH_3$), 28.54 (br s, CH_2C=C), 53.51 (d, $^1J_{PC}$ = 132.8 Hz, PC), 54.10 (CH_2Ph), 62.15 (OCH_2), 63.16 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 124.43 (=CH), 128.21 (*o*-C_{Ph}), 128.77 (*p*-C_{Ph}), 129.26 (*m*-C_{Ph}), 135.55 (*ipso*-C_{Ph}), 143.48 (d, $^3J_{PC}$ = 10.5 Hz, *C*=CH), 170.10 (d, $^2J_{PC}$ = 3.5 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 24.32.

HRMS: *m*/*z* [M$^+$] calcd for $C_{28}H_{35}N_6O_5P$: 566.24066, found: 566.23909.

Ethyl 3-[1-(2-*tert*-Butoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]-2-{[1-(2-*tert*-butoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]methyl}-2-(diethoxyphosphoryl)propanoate (8b)
Yield: 52% (after column chromatography); colourless oil.

IR (KBr): 1750 (C=O), 1549 (w, C=C), 1467 (triazole), 1238 (P=O), 1158, 1052, 1024 (POC, COC), 970 (triazole) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3CH_2OP), 1.29 (t, $^3J_{HH}$ = 7.0 Hz, 3 H, CH_3), 1.46 (s, 18 H, CH_3 in *t*-Bu), 3.40 (s, 2 H, CH_2C=C), 3.44 (d, $^3J_{PH}$ = 4.0 Hz, 2 H, CH_2C=C), 4.00–4.16 (m, 4 H, $POCH_2$), 4.20 (q, $^3J_{HH}$ = 7.0 Hz, 2 H, OCH_2), 4.95 (H_A) and 5.05 (H_B) (AB system, $^2J_{HH}$ = 18.0 Hz, 4 H, CH_2CO), 7.79 (s, 2 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.31 (CH_3), 16.72 (d, $^3J_{PC}$ = 6.0 Hz, $POCH_2CH_3$), 28.29 (CH_3 in *t*-Bu), 51.76 (CO in *t*-Bu), 53.4 (d, $^1J_{PC}$ = 132.8 Hz, PC), 62.26 (OCH_2), 63.40 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 83.75 (CH_2CO), 125.90 (=CH), 143.33 (d, $^3J_{PC}$ = 11.0 Hz, *C*=CH), 165.74 (CH_2CO), 170.39 (d, $^2J_{PC}$ = 4.0 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.54.

Anal. Calcd for $C_{26}H_{43}N_6O_9P$: C, 50.81; H, 7.05; N, 13.67; P, 5.04. Found: C, 50.81; H, 7.07; N, 13.61; P, 4.98.

Diethyl 2,2′-(1,1′-{1,4-Phenylenebismethylenebis[2-diethoxyphosphoryl-3-(1*H*-1,2,3-triazol-4-yl)]})bispropanoate (9a)
Yield: 83% (after column chromatography); colourless oil.

IR (thin layer): 1733 (C=O), 1552 (C=C), 1460 (triazole), 1254 (P=O), 1223, 1048, 1025 (POC, COC), 972 (triazole) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3), 1.33 (t, $^3J_{HH}$ = 7.0 Hz, 12 H, CH_3), 3.15–3.60 (m, 6 H, PCH and CH_2C=C), 4.05–4.25 (m, 12 H, OCH_2), 5.46 (s, 4 H, CH_2Ar), 7.21 (s, 4 H, Ar), 7.29 (s, 2 H, C=CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.29 (CH_3), 16.63 (d, $^3J_{PC}$ = 6.0 Hz, $POCH_2CH_3$), 23.59 (d, $^2J_{PC}$ = 3.0 Hz, CH_2C=C), 45.5 (d, $^1J_{PC}$ = 129.8 Hz, PCH), 53.65 (CH_2Ar), 61.74 (CH_2O), 63.09 (d, $^2J_{PC}$ = 4.0 Hz, $POCH_2$), 63.22 (d, $^2J_{PC}$ = 3.5 Hz, $POCH_2$), 122.24 (=CH), 128.77 ($C_{Ar}H$), 135.80 (*ipso*-C_{Ar}), 145.23 (d, $^3J_{PC}$ = 17.1 Hz, *C*=CH), 168.68 (d, $^2J_{PC}$ = 5.0 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.54.

Anal. Calcd. for $C_{30}H_{46}N_6O_{10}P_2$: C, 50.56; H, 6.51; N, 11.79; P, 8.69. Found: C, 50.68; H, 6.61; N, 11.64; P, 8.42.

Diethyl 2,2′-(1,1′-{1,4-Phenylenebismethylenebis[2-fluoro-2-diethoxyphosphoryl-3-(1*H*-1,2,3-triazol-4-yl)]})bispropanoate (9b)
Yield: 85% (after column chromatography); yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, $^3J_{HH}$ = 7.1 Hz, 6 H, CH_3), 1.33 (t, $^3J_{HH}$ = 7.1 Hz, 12 H, CH_3CH_2OP), 3.48 (H_A) and 3.73 (H_B) (ABXY system, $^2J_{HH}$ = 15.8 Hz, $^3J_{PH(A)}$ = 8.0 Hz, $^3J_{PH(B)}$ = 6.1 Hz, $^3J_{FH(A)}$ = 11.9 Hz, $^3J_{FH(B)}$ = 39.3 Hz, 4 H, CH_2C=C), 4.16–4.26 (m, 12 H, OCH_2), 5.37 (H_A) and 5.48 (H_B) (AB system, $^2J_{HH}$ = 15.1 Hz, 2 H), 7.19 (s, 4 H, ArH), 7.39 (s, 2 H, C=CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.21 (CH_3), 16.68 (d, $^3J_{PC}$ = 6.0 Hz, CH_3CH_2OP), 30.85 (d, $^2J_{CF}$ = 20.0 Hz, CH_2C=C), 53.65

(CH_2Ph), 62.82 (s, OCH_2), 64.91 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 64.70 (d, $^2J_{PC}$ = 7.5 Hz, $POCH_2$), 94.75 (dd, $^1J_{PC}$ = 162.5 Hz, $^1J_{CF}$ = 197.3 Hz, PC), 123.64 (C=*C*H), 128.74 ($C_{Ar}H$), 135.76 (*ipso*-C_{Ar}), 140.34 (d, $^3J_{CF}$ = 15.6 Hz, *C*=CH), 166.48 (dd, $^2J_{CF}$ = 23.0 Hz, $^2J_{PC}$ = 3.5 Hz, C=O).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 11.89 (d, $^2J_{PF}$ = 91.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –178.27 (ddd, $^2J_{PF}$ = 91.7 Hz, $^3J_{FH}$ = 11.9 Hz, $^3J_{FH}$ = 39.3 Hz).

Anal. Calcd for $C_{30}H_{44}F_2N_6O_{10}P_2$: C, 48.14; H, 5.92; N, 11.23; P, 8.27. Found: C, 48.17; H, 5.97; N, 11.27; P, 8.15.

Diethyl 2,2′-(1,1′-{1,3-Phenylenebismethylenebis[2-methyl-2-diethoxyphosphoryl-3-(1*H*-1,2,3-triazol-4-yl)]})bispropanoate (9c)

Yield: 75% (after column chromatography); colourless oil.

IR (thin layer): 1728 (C=O), 1613 (Ar), 1548 (C=C), 1462 (triazole), 1267, 1243 (P=O), 1049, 1023 (POC, COC), 969 (triazole) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3), 1.33 (t, $^3J_{HH}$ = 7.0 Hz, 12 H, C*H*$_3$CH$_2$OP), 1.42 (d, $^3J_{PH}$ = 16.0 Hz, 6 H, CH_3CP), 3.10 (H_A) and 3.59 (H_B) (ABX system, $^2J_{HH}$ = 16.0 Hz, $^3J_{PH(A)}$ = 8.0 Hz, $^3J_{PH(B)}$ = 9.0 Hz, 2 H, CH_2C=C), 4.05–4.25 (m, 16 H, OCH_2), 5.50 (s, 4 H, CH_2Ph), 7.17 (br s, 1 H, ArH), 7.28 (s, 2 H, C=CH), 7.20–7.40 (m, 3 H, ArH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.24 (CH_3), 16.68 (d, $^3J_{PC}$ = 6.0 Hz, *C*H$_3$CH$_2$OP), 17.40 (d, $^2J_{PC}$ = 4.5 Hz, *C*H$_3$CP), 30.38 (*C*H$_2$C=C), 48.97 (d, $^1J_{PC}$ = 132.8 Hz, PC), 53.61 (CH_2Ph), 61.76 (OCH_2), 63.08 (d, $^2J_{PC}$ = 7.0 Hz, $POCH_2$), 123.33 (C=*C*H), 127.36 (ArC-2), 128.01 (ArC-4,6), 129.91 (ArC-5), 136.37 (*ipso*-ArC-1,3), 143.32 (d, $^3J_{PC}$ = 17.0 Hz), 170.98 (d, $^2J_{PC}$ = 3.5 Hz, C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 26.41.

Anal. Calcd for $C_{32}H_{50}N_6O_{10}P_2$: C, 51.89; H, 6.80; N, 11.35; P, 8.36. Found: C, 51.97; H, 6.98; N, 11.21; P, 8.15.

Ethyl (1*H*-1,2,3-Triazol-4-yl)-2-(dihydroxyphosphoryl)propanoates 10a and 10b; General Procedure

A solution of a two-fold excess of TMS-Br (10 mmol) in $CHCl_3$ (2 mL), was added dropwise to a solution of the corresponding phosphonate **5b** (4 mmol) or **9c** (2 mmol) in $CHCl_3$ (2 mL). The reaction mixture was allowed to stir at r.t. for 3 d, then solvent was removed under reduced pressure and the residue was dissolved in 75% MeOH (1 mL). To this solution Et_2O (20 mL) was added and the mixture was kept under ambient conditions overnight. The solvents were decanted and the residue was dried in vacuo to give a white foam.

Ethyl 3-[1-(1-Adamantyl)-1*H*-1,2,3-triazol-4-yl]-2-(dihydroxyphosphoryl)propanoate (10a)

Yield: 84%; white solid; mp 206–207 °C (dec.).

IR (KBr): 2908 (CH), 1725 (C=O), 1453 (triazole), 1240 and 1224 (P=O), 1173, 1161, 1138, 1072 (COC), 978 (triazole) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.10 (t, $^3J_{HH}$ = 7.1 Hz, 3 H, CH_3), 1.76 (s, 6 H, Adm), 2.16 (s, 6 H, Adm), 2.20 (s, 3 H, Adm), 3.00–3.21 (two overlapping m, 1 H and 2 H, CH and CH_2C=C), 4.00–4.07 (q, *J* = 7.1 Hz, 4 H, OCH_2), 7.93 (s, 1 H, =CH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.24 (CH_3), 23.82 (CH*C*H$_2$), 29.11 (CH_{Adm}), 35.57, 42.49 ($CH_{2\text{-}Adm}$), 47.10 (d, $^1J_{PC}$ = 82.5 Hz, PCH), 58.85 (NC_{ipso}), 60.39 (OCH_2), 118.99 (=CH), 144.04 (d, $^3J_{PC}$ = 18.1 Hz, *C*=CH), 169.54 (d, $^2J_{PC}$ = 5.5 Hz, C=O).

^{31}P NMR (121 MHz, DMSO-d_6): δ = 16.15.

Anal. Calcd for $C_{17}H_{26}N_3O_5P$: C, 53.26; H, 6.84; N, 10.96; P, 8.08. Found: C, 52.93; H, 7.01; N, 10.41; P, 7.88.

Diethyl 2,2′-(1,1′-{1,3-Phenylenebismethylenebis[2-methyl-2-dihydroxyphosphoryl-3-(1*H*-1,2,3-triazol-4-yl)]})bispropanoate (10b)

Yield: 78%; white solid; mp 108 °C (dec.).

IR (KBr): 3398–2200 (br, H_2O), 1720 (C=O), 1599 (C=C), 1465 (triazole), 1272, 1222 (P=O), 1145, 1014 (COC), 937 (triazole) cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 0.88, 0.87 (2 × t, $^3J_{HH}$ = 7.0 Hz, 6 H, CH_3), 1.20 (d, $^3J_{PH}$ = 15.4 Hz, 6 H, CH_3CP), 2.88 (H_A) and 3.51 (H_B) (ABX system, $^2J_{HH}$ = 14.5 Hz, $^3J_{PH(A)}$ = 7.1 Hz, $^3J_{PH(B)}$ = 7.7 Hz, 4 H, CH_2C=C), 3.87–3.96 (m, 4 H, OCH_2), 5.46 (AB system, $^2J_{HH}$ = 15.0 Hz, 4 H, CH_2Ph), 7.08 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, ArH), 7.23 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, ArH), 7.24 (s, 1 H, ArH), 7.33 (t, $^3J_{HH}$ = 7.6 Hz, 1 H, ArH), 7.70 and 7.71 (2 × s, 2 H, C=CH).

^{13}C NMR (75 MHz, D_2O): δ = 12.83 (CH_3), 17.40 (d, $^2J_{PC}$ = 4.5 Hz, *C*H$_3$CP), 28.82 (*C*H$_2$C=C), 48.97 (d, $^1J_{PC}$ = 168.3 Hz, PC), 53.83 (CH_2Ph), 62.21 (OCH_2), 125.17 (C=*C*H), 127.36 (ArC-2), 128.38 (ArC-4,6), 129.67 (ArC-5), 134.87 (*ipso*-C-1,3), 142.32 (d, $^3J_{PC}$ = 22.7 Hz, *C*=CH), 172.94 (d, $^2J_{PC}$ = 5.1 Hz, C=O).

^{31}P NMR (121 MHz, DMSO-d_6): δ = 19.93.

Anal. Calcd for $C_{24}H_{34}N_6O_{10}P_2{\cdot}3H_2O$: C, 42.23; H, 5.91; N, 12.31; P, 9.08. Found: C, 42.21; H, 5.97; N, 12.07; P, 8.76.

3-[1-(1-Adamantyl)-1*H*-1,2,3-triazol-4-yl]-2-(dihydroxyphosphoryl)propane Acid (11a)

A solution of NaOH (23 mg, 0.57 mmol) in a mixture of EtOH (2 mL) and H_2O (1 mL) was added to a solution of the phosphonate **10a** (373 mg, 1 mmol) in EtOH (1 mL) at r.t. After stirring over 24 h under ambient conditions, the mix ture was evaporated to dryness, then 1N HCl was added (to pH ~1) and the mixture was washed with $CHCl_3$ (2 × 5 mL). The aqueous phase was evaporated to dryness and MeCN (20 mL) was added to the solid residue. The precipitate (NaCl) was filtered off, washed by MeCN (2 × 5 mL) and the filtrate was evaporated to a volume of ~1 mL. Et_2O (15 mL) was added and the solvents were decanted from the yellowish oil precipitated from the solution and the residue was dried in vacuo to give **11a**.

Yield: 285 mg (80%); white hydroscopic solid; mp 80 °C (dec.).

IR (KBr): 3423, 3140, 2912, 2855, 1725 (C=O), 1598 (C=C), 1453 (triazole), 1215, 1181 (P=O), 1156, 1105, 985, 939 (triazole) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.76 (s, 6 H, Adm), 2.16, 2.20, 2.21 (3 × s, 9 H, Adm), 2.99–3.05 (m, 1 H, CH), 3.12–3.20 (m, 2 H, CH_2C=C), 7.93 (s, 1 H, =CH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.81 (CH-*C*H$_2$), 29.11 (CH_{Adm}), 35.56, 42.50 ($CH_{2\text{-}Adm}$), 46.95 (d, $^1J_{PC}$ = 122.4 Hz, PCH), 58.87 (NC_{ipso}), 118.97 (=CH), 144.38 (d, $^3J_{PC}$ = 18.1 Hz, *C*=CH), 170.78 (d, $^2J_{PC}$ = 4.9 Hz, C=O).

^{31}P NMR (121 MHz, DMSO-d_6): δ = 17.00.

Anal. Calcd for $C_{15}H_{22}N_3O_5P{\cdot}4H_2O$: C, 42.15; H, 7.08; N, 9.83; P, 7.25. Found: C, 42.27; H, 6.83; N, 10.09; P, 6.88.

2,2′-(1,1′-{1,3-Phenylenebismethylenebis[2-methyl-2-dihydroxyphosphoryl-3-(1*H*-1,2,3-triazol-4-yl)]})bispropane Acid (11b)

Obtained according to the above procedure. According to the ^{1}H and ^{13}C NMR data the compound was isolated as a strong solvate with 0.5 EtOH.

Yield: 78%; off-white solid; mp 112 °C (dec.).

^{1}H NMR (300 MHz, D_2O): δ = 1.19 and 1.21 (2 × d, $^3J_{PH}$ = 14.1 Hz, 6 H, CH_3CP), 2.89–2.97 (m, 2 H, CH_2C=C), 3.44–3.57 (m, 1 H, CH_2C=C), 3.82–3.94 (m, 1 H, CH_2C=C), 5.49 (AB system, $^2J_{HH}$ = 15.0 Hz, 2 H, CH_2Ph), 5.51 (s, 2 H, CH_2Ph), 6.99–7.04 (m, 1 H, ArH), 7.18–7.26 (m, 2 H, ArH), 7.34 (t, $^3J_{HH}$ = 7.6 Hz, 1 H,

ArH), 7.70 (d, $^4J_{HH}$ = 6.8 Hz, 1 H, C=CH), 7.84 (d, $^4J_{HH}$ = 4.1 Hz, 1 H, C=CH).

^{31}P NMR (121 MHz, D_2O): δ = 20.27, 19.95 (2 × s, 1:1 ratio).

Anal. Calcd for $C_{20}H_{24}N_6O_{10}P_2 \cdot 0.5EtOH \cdot 2H_2O$: C, 41.12; H, 5.09; N, 13.70; P, 10.10. Found: C, 39.87; H, 4.82; N, 13.56; P, 11.88.

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