Synthesis of fluorophosphonylated acyclic nucleotide analogues *via* copper(I)-catalyzed Huisgen 1-3 dipolar cycloaddition†

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Preparation of several acyclonucleosides containing both a difluoromethylphosphonate group and a triazole moiety is described starting from a difluorophosphonosulfide. The key step of the synthesis involves a copper(I)-catalyzed Huisgen 1-3 dipolar cycloaddition between difluorophosphonylated azides and propargylated nucleobases derived from thymine and 2-amino-6-chloropurine.

Introduction

Conception of new nucleoside and nucleotide analogues plays an important role in medicinal chemistry to develop new drugs targeting diseases caused by viruses such as HIV, HBV and herpes.[1] Consequently, a large number of modifications has been made to both nucleic base and sugar moieties of natural nucleosides.[2] For several decades, particular interest has been devoted to acyclic nucleotides in which the furanose ring of the nucleoside and the phosphate function were respectively replaced by an acyclic chain and a methylene phosphonate group.[3] These chemical changes led to the preparation of many potent marketed antiviral drugs including Adefovir dipivoxil (Hepsera®), Cidofovir (Vistide®) and Tenofovir disoproxil fumarate (Viread®) (Fig. 1).

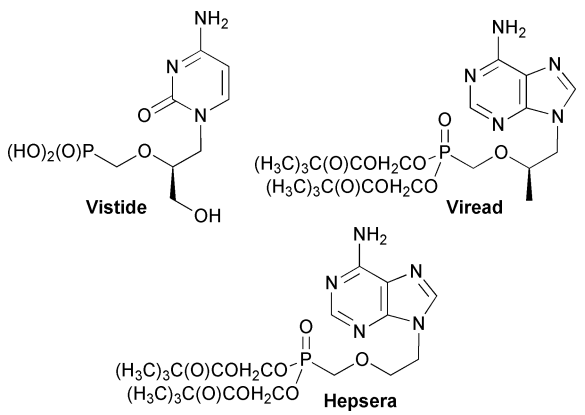

Fig. 1 Acyclonucleotides as antiviral drugs.

Since the pioneering work of Blackburn[4] and Chambers,[5] difluoromethylphosphonates are known to be the best isosteric and isoelectronic phosphate mimics. Thus, many derivatives containing a difluoromethylphosphonate function were studied as potential enzyme inhibitors and as useful probes for elucidation of biochemical processes.[6] In the field of acyclic nucleotides as new drugs for psoriasis and related autoimmune diseases, introduction of a difluoromethylphosphonate group improved their biological activities. For example, fluorinated phosphonate **I** was reported as a Purine Nucleoside Phosphorylase (PNP, EC 2.4.2.1) inhibitor with an increased activity of 5 to 25 fold compared to its non-fluorinated analogue.[7] Additional studies revealed that conformationally constrained analogue **II** containing an aromatic ring also exhibited high PNP inhibitory properties (Fig. 2).[8] Recently, Thymidine Phosphorylase (TP, EC 2.4.2.4), has been identified as playing a crucial role in angiogenesis and represents a potential target in cancer drugs discovery.[9] To date, few multisubstrate inhibitors were described and phosphonate **III** was reported as a good TP inhibitor. However, due to the difficulties to access aliphatic and aromatic difluorophosphonates, no example of specific TPase inhibitors containing a difluoromethylphosphonate function was reported.

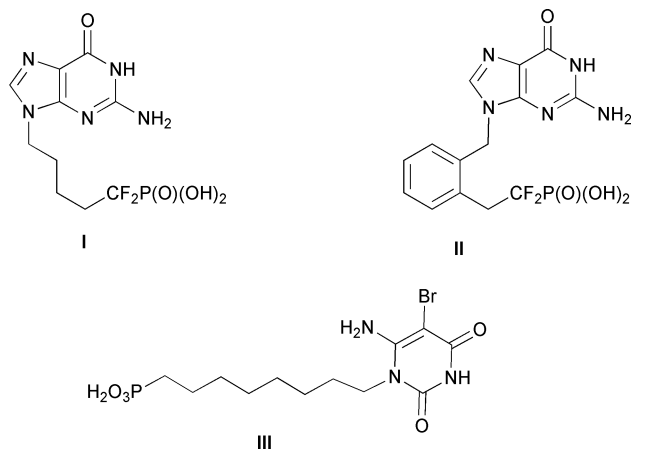

Fig. 2 Phosphonylated acyclic nucleosides as NP inhibitors.

In order to introduce a heterocycle to either substitute the nucleic base or freeze the conformation of an aliphatic spacer, the "click" chemistry appeared as an attractive approach.[10] Triazoles have gained considerable attention in drug discovery,[11] bioconjugation,[12] carbohydrate chemistry,[13] peptidomimetics[14] and PET chemistry.[15] In the field of nucleic acid chemistry, various five-membered triazole nucleosides with pronounced biological activities were developed.[16] However, the replacement of the conventional nucleic base of acyclonucleosides by a triazole moiety

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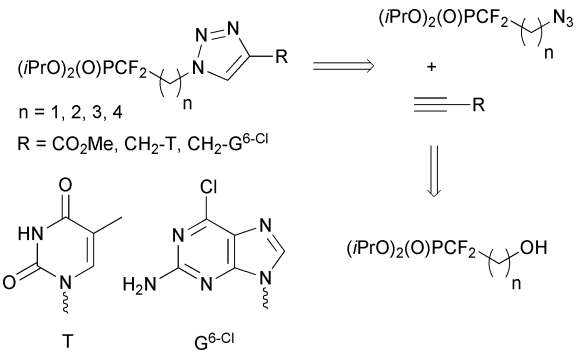
† Electronic supplementary information (ESI) available: Experimental procedure for compounds **2-4**, **6**, **7** and **17**. NMR spectra for all compounds. See DOI: 10.1039/b912724k

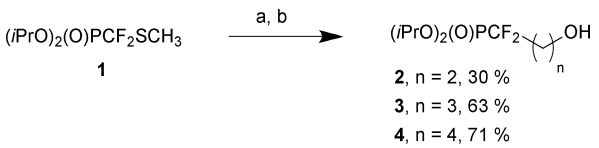
or the introduction of this heterocycle in the backbone of an acyclic nucleoside is less documented,[17] and to the best of our knowledge, none of these modifications has already been mentioned in the case of fluorophosphonylated nucleoside analogues. In this manuscript, we report the synthesis of novel 1,2,3-triazole acyclonucleotides containing a variety of spacers bearing both a difluoromethylphosphonate group and a triazole unit. Depending on the target, this heterocycle is introduced to either mimic a nucleic base or freeze the conformation of the aliphatic chain. The retrosynthetic analysis for these compounds is depicted in Scheme 1. The key step involves a copper(I)-catalyzed Huisgen cycloaddition between azido difluoromethylphosphonates and terminal alkynes.



Scheme 1 Retrosynthetic analysis of 1,2,3-triazole difluorophosphonylated acyclonucleotides.

Results and discussion

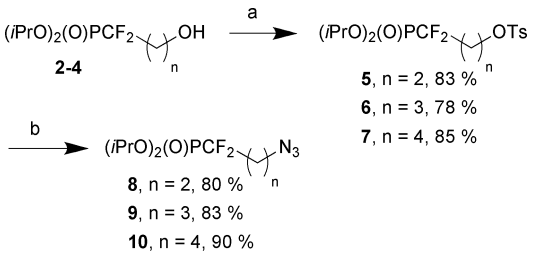
The synthesis of targeted molecules started from hydroxy difluoromethylphosphonates **2-4** easily available from fluorophosphonylated sulfide **1** following our previous procedures (Scheme 2).[18]



Scheme 2 Preparation of difluorophosphonylated hydroxyphosphonates. *Reagents and conditions:* (a) *tert*-BuLi, THF, –78 °C, 5 min; (b) 1,2-cyclic sulfate derived from ethyleneglycol, THF, –78 °C, 15 min to give **2**; trimethylene oxide, $BF_3.Et_2O$, Et_2O, –78 °C, 15 min to give **3**; THF, $BF_3.Et_2O$, –78 °C, 15 min to give **4**.

The phosphonodifluoromethyl lithium was first generated at –78 °C by nucleophilic attack of *tert*-butyllithium onto **1** and then reacted at low temperature with either 1,2-cyclic sulfate derived from ethyleneglycol,[18b] trimethylene oxide or THF,[18a] to produce the corresponding fluorinated hydroxyphosphonates **2-4** in moderate to good yields. Transformation of these compounds into their corresponding azides was then explored (Scheme 3). After activation of the primary hydroxyl function with a tosylate, introduction of the azido group was achieved by reaction with sodium azide in DMF at room temperature. Phosphonodifluoromethyl azides **8-10** were isolated in 80-90% yield.

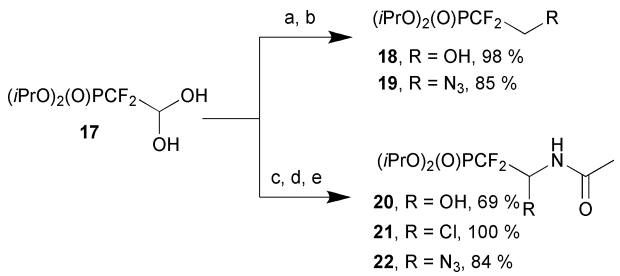
To access constrained 1,2,3-triazoloacyclonucleotides containing different spacer length and the difluoromethylphosphonate function, the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition was tested from fluorophosphonylated azides **8-10** and propargyl thymine (T) or 2-amino-6-chloropurine ($G^{6\text{-Cl}}$) (1.1 equiv).[19] Reactions were conducted in *tert*-BuOH/H_2O (1/1) in the presence of sodium ascorbate (10 mol%) and copper sulfate (5 mol%) at room temperature over 16 h to 24 h. Acyclic nucleotide analogues **11-16** were isolated by flash chromatography in 71-96% yields (Table 1).



Scheme 3 Introduction of the azido group. *Reagents and conditions:* (a) TsCl, NEt_3, CH_2Cl_2, r.t., 24 h; (b) NaN_3, DMF, r.t., 16 h.

Copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reactions did not require any protection of nucleic bases and tolerated the presence of a chlorine atom and/or an amino group on the nucleobase. As expected in the presence of CuI,[20] the 1,4-disubstituted 1,2,3-triazoles were obtained exclusively. The regioisomers were identified by 2D NMR experiments showing a correlation between the C-5 triazole carbon atom and both hydrogen atoms of the methylene group adjacent to the N-1 triazole nitrogen. From propargyl thymine, fluorophosphonylated triazolonucleosides **11**, **13** and **15** containing 2, 3 and 4 carbon atoms in the spacer were isolated in 87-96% yields (Table 1, entries 1, 3, 5). From propargyl 2-amino-6-chloropurine, cycloaddition reactions were also efficient and the corresponding adducts **12**, **14** and **16** were produced in 71-75% yields (Table 1, entries 2, 4, 6).

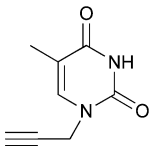
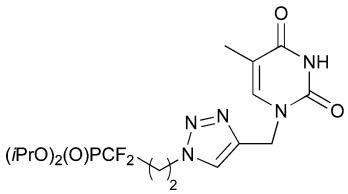
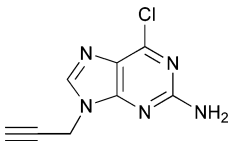
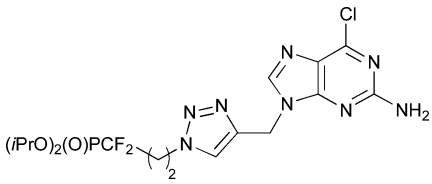
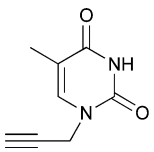
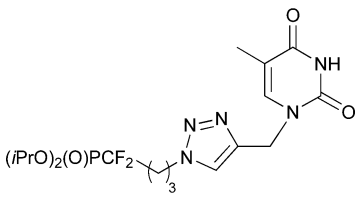
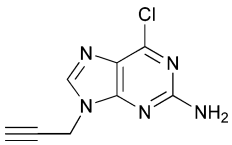
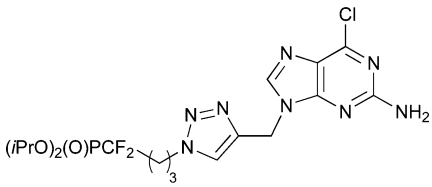
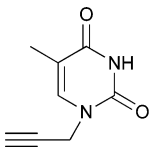
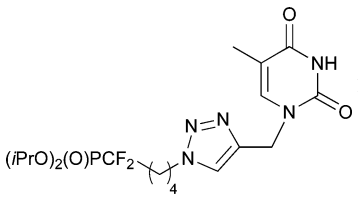
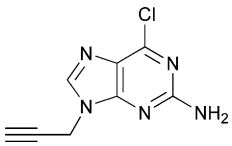
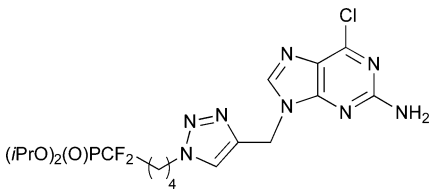
In order to access another series of difluorophosphonylated 1,2,3-triazoloacyclonucleosides containing one carbon atom in the spacer, the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction was next studied from azides **19** and **22**. These azides were synthesized starting from hydrate **17**,[21] easily prepared by addition of the phosphonodifluoromethyl carbanion onto DMF followed by a careful hydrolysis with HCl 3 N (Scheme 4).



Scheme 4 Preparation of azides **19** and **22**. *Reagents and conditions:* (a) $NaBH_4$, EtOH, 0 °C to r.t., 2 h; (b) *1)* Tf_2O, pyridine, CH_2Cl_2, –20 °C, 2 h; *2)* NaN_3, DMF, r.t. 16 h; (c) acetamide, dioxane, reflux 2 h; (d) $SOCl_2$, CH_2Cl_2, r.t. 1 h; (e) NaN_3, DMF, r.t. 16 h.

Reduction of hydrate **17** with $NaBH_4$ at 0 °C afforded the corresponding alcohol **18** in good yield. No reduction of the phosphonate ester moiety was observed. This latter was then

Table 1 Copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition between difluorophosphonylated azides and propargylated nucleobases

Entry	Azide	Alkyne	Time	Product, compound number, yield[a]
1	**8**		24 h	 **11**, 87%
2	**8**		24 h	 **12**, 74%
3	**9**		24 h	 **13**, 96%
4	**9**		18 h	 **14**, 71%
5	**10**		20 h	 **15**, 93%
6	**10**		16 h	 **16**, 75%

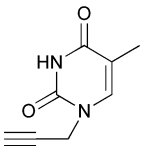
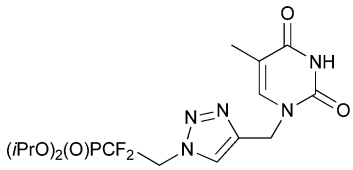
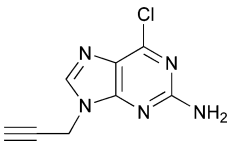
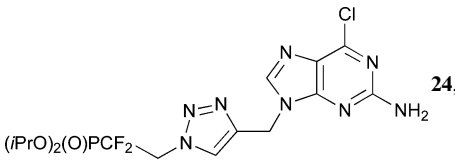
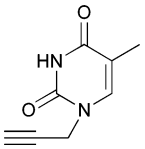
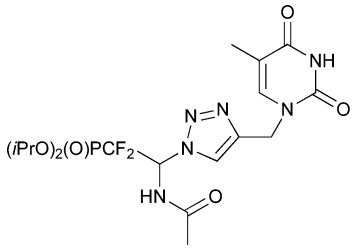
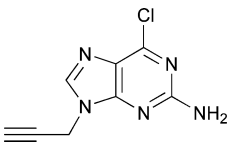
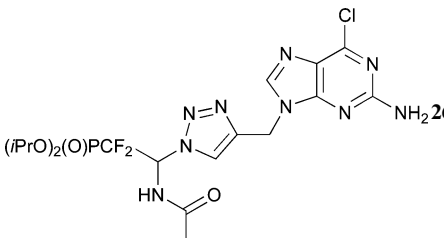
[a] Isolated yields.

transformed into its corresponding tosylate in 89% yield. However, the displacement of the tosylate function with NaN_3 did not occur even under refluxing DMF. The corresponding triflate derivative was prepared and, due to its instability, was directly converted into azide **19** in 85% overall yield.

As reported for the synthesis of trifluoromethylated azide from fluoral hemi-acetal,[22] preparation of **22** was explored from the corresponding aldehyde dihydrate. Difluorophosphonylated hydrate **17** was reacted with acetamide in refluxing dioxane to lead to the protected hemi-aminal **20** in 69% yield. Chlorination of the resulting alcohol was then achieved with thionyl chloride (2 equiv) in dichloromethane in quantitative yield. Compound **21** was directly engaged in the next step without further purification. The azido group was finally introduced at room temperature with sodium azide in DMF. Azide **22** was isolated by flash chromatography in 84% yield.

The 1,3-dipolar cycloaddition reaction was attempted from propargyl thymine and 2-amino-6-chloropurine under the previous experimental conditions (Table 2). In all cases, cycloaddition reactions were faster from propargyl thymine. A total conversion of **19** and **22** was observed after 12 h under stirring at room temperature. The corresponding triazoles **23** and **25** were isolated by flash chromatography in 71 and 62% yields, respectively (Table 2, entries 1, 3). Reactions were also efficient from propargyl 2-amino-6-chloropurine. Difluorophosphonylated triazoles **24** and **26** containing an acetamido group and one carbon atom in the spacer were obtained in good yields (Table 2, entries 2, 4). It is expected that the presence of an acetamido group in **25** and **26** could

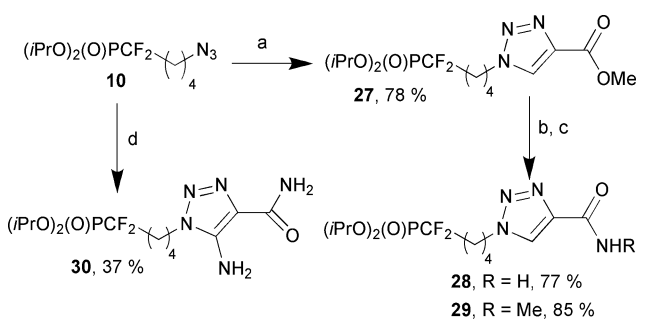
Table 2 Synthesis of difluorophosphonylated 1,2,3-triazole nucleosides containing one carbon atom in the spacer by 1,3-dipolar cycloadditions

Entry	Azide	Alkyne	Time	Product, compound number, yield[a]
1	**19**		12 h	 **23**, 71%
2	**19**		24 h	 **24**, 79%
3	**22**		12 h	 **25**, 62%
4	**22**		24 h	 **26**, 69%

[a] Isolated yields.

play a role in the enzyme binding. Furthermore, this family of difluorophosphonylated triazoles are important building-blocks for the synthesis of modified phosphonopeptides.[22]

Having in hand a large variety of phosphonylated azides the development of difluorophosphonylated acyclic nucleotide analogues in which conventional pyrimidine nucleobases are replaced by functionalized 1,2,3-triazoles was also explored (Scheme 5). Copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction



Scheme 5 Preparation of difluorophosphonylated acyclonucleotides containing a triazole moiety as nucleobase. *Reagents and conditions:* (a) methyl propiolate, CuI, MeCN/H_2O (1/2), r.t., 16 h; (b) MeOH/25% aq. NH_3, r.t., 72 h; (c) MeOH/25% aq. $MeNH_2$, r.t., 72 h; (d) 2-cyanoacetamide, KOH, H_2O/DMF (1/5), r.t., 24 h.

was realized from azide **10** and methyl propiolate following this scheme. Copper(I) iodide (10 mol%) was added to a solution of **10** (1 equiv), methyl propiolate (1 equiv) in MeCN/H_2O (1/2). After stirring overnight at room temperature, the reaction reached completion and triazole **27** was isolated by flash chromatography in 78% yield. In order to mimic the N-1 nitrogen atom and the C-6 carbonyl group present in conventional purine nucleic bases, the ester function of **27** was then converted into the amide.

Difluorophosphonylated 1,2,3-triazole acyclonucleotides **28** and **29** bearing an amide function at position 4 were obtained in good yields by stirring **27** at room temperature for 72 h in ammonia or methyl amine solution (40% in CH_3OH).

Introduction of an amino group onto position 5 of the 1,2,3-triazoles in order to mimic the N-3 nitrogen atom of purine nucleobases was attempted. For that matter, copper(I)-catalyzed 1,3-dipolar cycloaddition with **10** and 2-cyanoacetamide was avoided to prevent the formation of tetrazole derivatives as mentioned in the literature.[23] However, it was shown that the cycloaddition reaction could occur onto the carbon-carbon double bond of a ketenimine instead of the nitrile function when CuI was replaced by a base such as K_2CO_3 or sodium ethoxide.[16p,24] These conditions were applied to the synthesis of **30**. Azide **10** (1 equiv) was added to a solution of 2-cyanoacetamide (1.5 equiv) and potassium hydroxide (1.5 equiv) in H_2O/DMF (1/5). After 24 h of stirring at room temperature, triazole **30** functionalized in

position 5 was isolated by flash chromatography in a modest and non-optimized 37% yield.

Conclusions

In summary, we reported the first synthesis of difluorophosphonylated 1,2,3-triazole acyclonucleotide analogues by a copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction involving functionalized alkynes and difluoromethylphosphonate azides easily prepared in few steps starting from the diisopropyl phosphonodifluoromethyl sulfide **1**. From unprotected propargyl thymine and 2-amino-6-chloropurine, conformational constrained nucleotide analogues containing both a triazole moiety and various spacer length were isolated in good yields.

The copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction was also attempted with highly functionalized secondary difluorophosphonylated azide **22** and led to the preparation of acyclonucleotides **25** and **26** in which a protected amino group was inserted in the spacer. The presence of this could make the binding to the targeted enzyme by additional hydrogen bonding easier.

Finally, introduction of functionalized triazoles onto acyclic nucleotides in order to mimic conventional purine nucleobases was also explored. The copper(I)-catalyzed Huisgen cycloaddition with difluorophosphonylated azide **10** and methyl propiolate followed by amidation reactions afforded 1,4-disubstitued 1,2,3-triazoles **28-29** while the replacement of the copper source by potassium hydroxide in combination with the use of 2-cyanoacetamide resulted in 1,4,5-trisubstituted 1,2,3-triazole **30** formation in moderate to good yields.

Fully deprotected 1,2,3-triazole acyclonucleotides containing the difluoromethylphosphonate group in which the triazole unit is introduced to either substitute the nucleic base or freeze the conformation are currently studied as nucleoside phosphorylase inhibitors and their biological evaluations will be reported in due course.

Experimental

General

All commercially available reagents were bought from Aldrich and used as received. For anhydrous conditions the glassware was dried in the oven at 120 °C and cooled to room temperature under a continuous nitrogen flow. THF, CH_2Cl_2, Et_2O, CH_3CN were dried at a solvent generator from "Innovative Technologies Inc.", which uses an activated alumina column to remove water. BF_3-Et_2O, DMF and NEt_3 were distilled under CaH_2 or 4Å molecular sieves. Flash column chromatography was realized on silica gel 60 (40-63 μm) from Merck with air pressure and were detected by thin layer chromatography, on which the spots were visualized by UV-irradiation and/or $KMnO_4$ solution. NMR spectra were recorded on a 250 MHz or 400 MHz apparatus in deuterated solvent at 25 °C. ^{31}P and ^{19}F NMR spectral lines are with respect to the internal references H_3PO_4 (capillary) and $CFCl_3$. All chemical shifts are reported in δ parts per million (ppm) and coupling constants are in hertz (Hz). High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI or ESI mode. IR spectra were recorded on a Perkin-Elmer ATR IR instrument.

Preparation of tosylate 5

In a 25 mL round bottom flask under N_2 atmosphere were placed the alcohol **2** (0.50 g, 1.92 mmol), tosyl chloride (0.55 g, 2.88 mmol) and anhydrous CH_2Cl_2 (10 cm^3). Triethylamine (0.40 cm^3, 2.88 mmol) was added dropwise and the mixture was stirred 24 h at room temperature. The solution was hydrolyzed with 1 N aqueous HCl solution (2 cm^3) and extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic layers were successively washed with saturated aqueous solutions of $NaHCO_3$ (2 × 2 cm^3) and NaCl (2 × 2 cm^3) and dried over $MgSO_4$. Solvents were evaporated under reduced pressure to leave a yellow oil which was purified by flash column chromatography on silica using ethyl acetate/pentane (6/4) as eluent to give diisopropyl 1,1-difluoro-3-(*p*-toluene-sulfonyl)-propylphosphonate **5** (0.66 g, 83%) as a colourless oil; ν_{max}(ATR)/cm^{-1} 2985, 2937, 2876, 1598, 1454, 1372, 1267, 1192, 1176, 1145, 1095 and 979; δ_H(500 MHz, $CDCl_3$) 1.33 (12 H, dd, *J* 6.2 and 4.2, 2 × (CH_3)$_2$CH), 2.37-2.53 (5 H, m, CH_2CF_2 and CH_3Ph), 4.26 (2 H, t, *J* 7.2, CH_2CH_2), 4.79 (2 H, dsp, *J* 6.3, 2 × $CH(CH_3)_2$), 7.34 (2 H, d, *J* 8.0, H_{ar}) and 7.78 (2 H, d, *J* 6.8, H_{ar}); δ_P(202 MHz, $CDCl_3$) 3.96 (1 P, t, *J* 104.6); δ_F(470 MHz, $CDCl_3$) –112.77 (2 F, td, *J* 18.6 and 104.6); δ_C(126 MHz, $CDCl_3$) 21.3 (s, PhCH_3), 23.9 (2 × d, *J* 4.9, (CH_3)$_2$CH), 24.3 (2 × d, *J* 3.5, (CH_3)$_2$CH), 33.9 (dt, *J* 15.0 and 21.0, CF_2CH_2), 63.2 (dt, *J* 6.2 and 12.5, CH_2O), 74.3 (2 × d, *J* 7.0, 2 × $(CH_3)_2CH$), 118.8 (dt, *J* 218.8 and 260.7, CF_2), 128.2 (2 × s, 2 × C_{ar}), 130.2 (2 × s, 2 × C_{ar}), 132.9 (s, C_{ar}) and 145.37 (s, C_{ar}); *m/z* (ESI) 415.1168 (M + H^+. $C_{16}H_{25}F_2O_6PS$ requires 415.1156), 373 (98%) and 331 (100).

General procedure for the preparation of azides 8-10

In a 25 mL round bottom flask under N_2 atmosphere were placed the tosylate (1.00 mmol), sodium azide (1.10 mmol) and anhydrous DMF (5 cm^3). The mixture was stirred for 16 h at room temperature and the DMF was evaporated. The residue was taken up in Et_2O (15 cm^3) and the aqueous layer was extracted with Et_2O (2 × 15 cm^3). Combined organic layers were washed with water (5 cm^3) and saturated aqueous solution of NaCl (5 cm^3), then dried over $MgSO_4$. Solvents were evaporated under reduced pressure and crude product was purified by flash column chromatography on silica using ethyl acetate/pentane (4/6) as eluent to give the desired azides **8-10** (80-90%) as colourless liquids.

Diisopropyl 3-azido-1,1-difluoropropylphosphonate (8)

(0.27 g, 80%) colourless liquid; ν_{max}(ATR)/cm^{-1} 2983, 2098, 1266 and 980; δ_H(400 MHz, $CDCl_3$) 1.38 (12 H, dd, *J* 6.4 and 3.4, 2× (CH_3)$_2$CH), 2.23-2.48 (2 H, m, CH_2CF_2), 3.57 (2 H, t, *J* 7.3, CH_2N_3) and 4.85 (2 H, dsp, *J* 6.4, 2 × $CH(CH_3)_2$); δ_P(162 MHz, $CDCl_3$) 4.32 (1 P, t, *J* 105.5); δ_F(376 MHz, $CDCl_3$) –112.83 (2 F, td, *J* 19.1 and 105.5); δ_C(101 MHz, $CDCl_3$) 24.0 (2 × d, *J* 4.9, (CH_3)$_2$CH), 24.3 (2 × d, *J* 3.5, (CH_3)$_2$CH), 33.7 (dt, *J* 14.5 and 20.9, CF_2CH_2), 44.1 (dt, *J* 5.8 and 11.6, CH_2N_3), 74.0 (2 × d, *J* 7.0, 2 × $(CH_3)_2CH$) and 119.0 (dt, *J* 218.1 and 260.3, CF_2); *m/z* (ESI) 286.1122 (M + H^+. $C_9H_{18}F_2N_3O_3P$ requires 286.1132), 244 (100%) and 202 (83).

Diisopropyl 4-azido-1,1-difluorobutylphosphonate (9)

(0.29 g, 83%) colourless liquid; ν_{max}(ATR)/cm^{-1} 2984, 2940, 2879, 2096, 1454, 1388, 1378, 1266, 1177, 1144, 1102 and 984; δ_H(250 MHz, $CDCl_3$) 1.38 (12 H, dd, *J* 6.2 and 3.7, 2 × (C*H*$_3$)$_2$CH), 1.75-1.88 (2 H, m, $CH_2CH_2CH_2$), 1.95-2.25 (2 H, m, CH_2CF_2), 3.36 (2 H, t, *J* 6.7, CH_2N_3) and 4.84 (2 H, dsp, *J* 6.3, 2 × C*H*(CH$_3$)$_2$); δ_P(101 MHz, $CDCl_3$) 5.19 (1 P, t, *J* 108.0); δ_F(235 MHz, $CDCl_3$) −112.81 (2 F, td, *J* 19.0 and 108.0); δ_C(63 MHz, $CDCl_3$) 20.9 (dt, *J* 5.0 and 10.1, $CF_2CH_2CH_2$), 23.9 (2 × d, *J* 4.9, (*C*H$_3$)$_2$CH), 24.3 (2 × d, *J* 3.5, (*C*H$_3$)$_2$CH), 31.4 (dt, *J* 14.8 and 21.2, CF_2CH_2), 51.0 (s, CH_2N_3), 73.8 (2 × d, *J* 7.0, 2 × (CH$_3$)$_2$*C*H) and 120.8 (dt, *J* 217.8 and 259.6, CF_2); *m*/*z* (ESI) 300.1288 (M + H$^+$. $C_{10}H_{21}F_2N_3O_3P$ requires 300.1289), 258 (100%), 216 (28) and 188 (63).

Diisopropyl 5-azido-1,1-difluoropentylphosphonate (10)

(0.32 g, 90%) colourless liquid; ν_{max}(ATR)/cm^{-1} 2984, 2939, 2878, 2094, 1456, 1388, 1377, 1266, 1178, 1144, 1103 and 982; δ_H(250 MHz, $CDCl_3$) 1.36 (12 H, dd, *J* 6.2 and 3.6, 2 × (C*H*$_3$)$_2$CH), 1.55-1.70 (4 H, m, $CH_2CH_2CH_2CH_2$), 1.78-2.15 (2 H, m, CH_2CF_2), 3.28 (2 H, t, *J* 6.2, CH_2N_3) and 4.84 (2 H, dsp, *J* 6.3, 2 × C*H*(CH$_3$)$_2$); δ_P(101 MHz, $CDCl_3$) 5.49 (1 P, t, *J* 109.0); δ_F(235 MHz, $CDCl_3$) −113.02 (2 F, td, *J* 20.0 and 109.0); δ_C(63 MHz, $CDCl_3$) 18.3 (dt, *J* 5.0 and 10.1, $CF_2CH_2CH_2$), 23.8 (2 × d, *J* 4.9, (*C*H$_3$)$_2$CH), 24.2 (2 × d, *J* 3.5, (*C*H$_3$)$_2$CH), 28.7 (s, $CH_2CH_2N_3$), 33.5 (dt, *J* 14.5 and 21.1, CF_2CH_2), 51.2 (s, CH_2N_3), 73.7 (2 × d, *J* 7.0, 2 × (CH$_3$)$_2$*C*H) and 120.9 (dt, *J* 217.3 and 259.4, CF_2); *m*/*z* (ESI) 314.1436 (M + H$^+$. $C_{11}H_{22}F_2N_3O_3P$ requires 314.1445), 272 (54%), 244 (10), 230 (9) and 202 (100).

Preparation of alcohol 18

To a solution of difluorophosphonylated hydrate **17** (0.50 g, 1.91 mmol) in absolute ethanol (15 cm^3) was added at 0 °C sodium borohydride (0.14 g, 3.82 mmol). After 10 min, the ice bath was removed and the reaction was stirred at room temperature for 2 h. The mixture was carefully quenched with a saturated aqueous NH_4Cl solution (2 cm^3). Ethanol was removed under reduced pressure and the resulting aqueous layer was extracted with CH_2Cl_2 (3 × 15 cm^3). Combined organic layers were washed with a saturated aqueous NaCl solution (2 × 2 cm^3), dried over $MgSO_4$ and concentrated to give diisopropyl 1,1-difluoro-2-hydroxyethylphosphonate **18** (0.13 g, 98%) as colourless oil; ν_{max}(ATR)/cm^{-1} 3560, 2973, 1236 and 989; δ_H(400 MHz, $CDCl_3$) 1.38 (12 H, dd, *J* 6.1 and 4.1, 2 × (C*H*$_3$)$_2$CH), 3.09 (1 H, br s, OH), 3.95 (2 H, dt, *J* 7.6 and 14.7, C*H*$_2$OH) and 4.85 (2 H, dsp, *J* 6.3, 2 × C*H*(CH$_3$)$_2$); δ_P(162 MHz, $CDCl_3$) 4.54 (1 P, t, *J* 101.7); δ_F(376 MHz, $CDCl_3$) −120.76 (2 F, td, *J* 15.1 and 101.7); δ_C(126 MHz, $CDCl_3$) 24.0 (2 × d, *J* 5.0, (*C*H$_3$)$_2$CH), 24.4 (2 × d, *J* 3.4, (*C*H$_3$)$_2$CH), 63.1 (dt, *J* 16.6 and 25.7, CF_2CH_2), 74.5 (2 × d, *J* 7.1, 2 × (CH$_3$)$_2$*C*H) and 118.1 (dt, *J* 209.3 and 262.9, CF_2); *m*/*z* (ESI) 247.0923 (M + H$^+$. $C_8H_{17}F_2O_4P$ requires 247.0911), 205 (100%) and 163 (33).

Preparation of acetamide 20

To a solution of hydrate **17** (0.22 g, 0.84 mmol) in 1,4-dioxane (3 cm^3) was added acetamide (0.05 g, 0.84 mmol). The mixture was stirred under reflux for 2 h. After solvent evaporation, the crude product was recrystallized from pentane/ethyl acetate to give (diisopropyl) 1,1-difluoro-2-acetamido-2-hydroxyethylphosphonate **20** (0.18 g 69%) as a white solid, mp 129-130 °C; δ_H(400 MHz, $CDCl_3$) 1.38 (12 H, dd, *J* 6.8 and 4.0, 2 × (C*H*$_3$)$_2$CH), 2.04 (3 H, s, CH_3CO), 4.90 (2 H, dsp, *J* 6.0, 2 × C*H*(CH$_3$)$_2$), 5.61-5.85 (1 H, m, $CHCF_2$) and 7.33 (1 H, d, *J* 9.6, NH); δ_P(162 MHz, $CDCl_3$) 4.00 (1 P, dd, *J* 97.2 and 95.6); δ_F(376 MHz, $CDCl_3$) -119.40 (1 F, ddd, *J* 9.4, 95.6 and 304.6) and -121.97 (1 F, ddd, *J* 9.0, 97.2 and 304.6); δ_C(101 MHz, $CDCl_3$) 22.9 (s, *C*H$_3$CO), 23.8 (d, *J* 5.5, *C*H$_3$CH), 23.9 (d, *J* 5.4, *C*H$_3$CH), 24.5 (d, *J* 3.5, *C*H$_3$CH), 24.6 (d, *J* 3.2, *C*H$_3$CH), 73.6 (dt, *J* 14.9 and 28.0, CF_2CH), 74.9 (d, *J* 7.2, (CH$_3$)$_2$*C*H), 75.0 (d, *J* 6.9, (CH$_3$)$_2$*C*H), 116.5 (dt, *J* 205.9 and 270.4, CF_2) and 171.5 (s, C=O); *m*/*z* (ESI) 304.1134 (M + H$^+$. $C_{10}H_{20}F_2NO_5P$ requires 304.1125), 286 (100%) and 244 (12).

Preparation of azide 19

In a 25 mL round bottom flask under N_2 atmosphere were placed the alcohol **18** (0.13 g, 0.53 mmol), pyridine (2 cm^3) and anhydrous CH_2Cl_2 (2 cm^3). Triflic anhydride (0.14 cm^3, 0.79 mmol) was added dropwise at −20 °C and the mixture was stirred for 2 h at this temperature. The solution was poured into cooled saturated aqueous solution of $NaHCO_3$ (2 cm^3). The organic layer was washed a second time with a saturated aqueous solution of $NaHCO_3$ (2 cm^3). The aqueous layers were extracted with CH_2Cl_2 (2 × 15 cm^3). Combined organic layers were washed with a saturated aqueous NaCl solution (2 cm^3), dried over $MgSO_4$ and concentrated to give the triflate intermediate (0.19 g, 95%) as yellow coloured liquid; δ_H(500 MHz, $CDCl_3$) 1.38 (12 H, dd, *J* 6.3 and 3.8, 2 × (C*H*$_3$)$_2$CH), 4.72 (2 H, dt, *J* 2.9 and 14.0, CH_2CF_2) and 4.85 (2 H, dsept, *J* 6.5, 2 × C*H*(CH$_3$)$_2$); δ_P(202 MHz, $CDCl_3$) 1.15 (1 P, t, *J* 95.6); δ_F(470 MHz, $CDCl_3$) −121.08 (2 F, td, *J* 14.0 and 95.6, CF_2) and −74.20 (3 F, s, CF_3); δ_C(63 MHz, $CDCl_3$) 23.5 (2 × d, *J* 5.0, (*C*H$_3$)$_2$CH), 24.0 (2 × d, *J* 3.8, (*C*H$_3$)$_2$CH), 71.3 (dt, *J* 18.7 and 25.4, CF_2CH_2), 75.2 (2 × d, *J* 7.1, 2 × (CH$_3$)$_2$*C*H), 114.4 (dt, *J* 213.0 and 264.8, CF_2) and 118.4 (q, *J* 319.6, CF_3); *m*/*z* (ESI) 379.0394 (M + H$^+$. $C_9H_{16}F_5O_6PS$ requires 379.0404), 337 (95%), 312.9 (14) and 294.9 (20).

In a 25 mL round bottom flask under N_2 atmosphere were placed the obtained triflate (0.50 g, 1.32 mmol), sodium azide (0.09 g, 1.45 mmol) and anhydrous DMF (13 cm^3). The mixture was stirred for 16 h at room temperature and the DMF was evaporated. The residue poured in Et_2O (30 cm^3) and the aqueous layer was extracted with Et_2O (2 × 30 cm^3). Combined organic layers were washed with water (10 cm^3) and saturated solution of NaCl (10 cm^3), dried over $MgSO_4$. Solvents were evaporated under reduced pressure and crude product was purified by flash column chromatography on silica using ethyl acetate/pentane (4/6) as eluent to give diisopropyl 2-azido-1,1-difluoroethylphosphonate **19** (0.30, 85%) as a colourless liquid; ν_{max}(ATR)/cm^{-1} 2986, 2940, 2104, 1389, 1378, 1271, 1180, 1144, 1099, 1074 and 987; δ_H(400 MHz, $CDCl_3$) 1.39 (12 H, dd, *J* 6.2 and 3.9, 2 × (C*H*$_3$)$_2$CH), 3.68 (2 H, dt, *J* 4.7 and 15.8, CH_2CF_2) and 4.88 (2 H, dsp, *J* 6.3, 2 × C*H*(CH$_3$)$_2$); δ_P(162 MHz, $CDCl_3$) 3.02 (1 P, t, *J* 99.9); δ_F(376 MHz, $CDCl_3$) −117.01 (2 F, td, *J* 16.2 and 99.9); δ_C(101 MHz, $CDCl_3$) 24.0 (2 × d, *J* 5.1, (*C*H$_3$)$_2$CH), 24.4 (2 × d, *J* 3.5, (*C*H$_3$)$_2$CH), 52.5 (dt, *J* 18.5 and 23.4, CF_2CH_2), 74.7 (2 × d, *J* 7.0, 2 × (CH$_3$)$_2$*C*H) and 117.9 (dt, *J* 212.8 and 263.4, CF_2); *m*/*z*

(ESI) 272.0984 (M + H^+. $C_8H_{16}F_2N_3O_3P$ requires 272.0976), 230 (100%) and 188 (85).

Preparation of azide 22

To a solution of alcohol **20** (0.20 g, 0.66 mmol) in anhydrous CH_2Cl_2 (5 cm^3) under N_2 atmosphere were added dropwise $SOCl_2$ (0.10 cm^3, 1.32 mmol). The mixture was stirred for 1 h at room temperature and the solvent was evaporated under reduced pressure. The residue was solubilised in DMF (2 cm^3) and sodium azide (0.05 g, 0.73 mmol) was added in one portion. The mixture was stirred for 16 h at room temperature and the DMF was evaporated. The residue was poured in Et_2O (15 cm^3) and the aqueous layer was extracted with Et_2O (2 × 15 cm^3). Combined organic layers were washed with water (5 cm^3) and saturated solution of NaCl (5 cm^3), dried over $MgSO_4$. Solvents were evaporated under reduced pressure and crude product was purified by flash column chromatography on silica using ethyl acetate/pentane (4/6) as eluent to give diisopropyl 2-acetamido-2-azido-1,1-difluoroethylphosphonate **22** (0.22 g, 84%) as a colourless liquid; δ_H(500 MHz, $CDCl_3$) 1.40 (12 H, dd, *J* 6.0 and 3.2, 2 × (CH_3)$_2$CH), 2.09 (3 H, s, CH_3CO), 4.88 (2 H, dsp, *J* 6.5, 2 × C*H*(CH_3)$_2$), 5.79-5.95 (1 H, m, $CHCF_2$) and 7.28 (1 H, d, *J* 9.2, NHCO); δ_P(202 MHz, $CDCl_3$) 2.47 (1 P, dd, *J* 94.9 and *J* 98.3); δ_F(470 MHz, $CDCl_3$) −116.37 (1 F, ddd, *J* 9.4, 98.8 and 305.9) and −118.62 (1 F, ddd, *J* 9.4, 94.1 and 305.9); δ_C(126 MHz, $CDCl_3$) 23.3 (s, CH_3CO), 23.8 (d, *J* 5.5, CH_3CH), 23.9 (d, *J* 5.5, CH_3CH), 24.4 (d, *J* 3.3, CH_3CH), 24.5 (d, *J* 3.2, CH_3CH), 66.7 (dt, *J* 15.3 and 28.3, CF_2CH), 75.4 (d, *J* 7.3, (CH_3)$_2$*C*H), 75.5 (d, *J* 7.3, (CH_3)$_2$*C*H), 115.9 (dt, *J* 207.9 and 266.8, CF_2) and 170.7 (s, C=O); *m/z* (ESI) 329.1205 (M + H^+. $C_{10}H_{19}F_2N_4O_4P$ requires 329.1190), 286 (97%) and 244 (9).

General procedure for the preparation of triazoles 11-16 and 23-26

To a stirred solution of azide (1.00 mmol) in *tert*-BuOH (2.5 cm^3) and water (2.5 cm^3), propargyl nucleobase (1.10 mmol) was added followed by sodium ascorbate (0.10 mmol) and $CuSO_4.5H_2O$ (0.05 mmol). The mixture was stirred for 12-24 h at room temperature. The organic solvent was removed under reduced pressure and the residue was poured in CH_2Cl_2 (10 cm^3) and water (10 cm^3). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 cm^3) and combined organic layers were washed with saturated solution of NaCl (5 cm^3), dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica using CH_2Cl_2/CH_3OH (10/1) as eluent to give the desired triazoles **11-16** and **23-26** (62-96%) as a white solid.

1-[1-(3-Diisopropoxyphosphono-3,3-difluoro-propyl)-1,2,3-triazolo-4-methyl]-thymine (11)

(0.47 g, 79%) white solid, mp 112-113 °C; ν_{max}(ATR)/cm^{-1} 3501, 2984, 1673, 1467, 1377, 1258 and 992; δ_H(400 MHz, $CDCl_3$) 1.38 (12 H, dd, *J* 6.4 and 3.1, 2 × (CH_3)$_2$CH), 1.89 (3 H, d, *J* 1.1, CH_3), 2.60-2.85 (2 H, m, CH_2CF_2), 4.65 (2 H, t, *J* 7.5, CH_2N), 4.87 (2 H, dsp, *J* 6.3, 2 × C*H*(CH_3)$_2$), 4.95 (2 H, s, CH_2NCO), 7.32 (1 H, d, *J* 1.1, CH=CCH_3), 7.79 (1 H, s, CH=CCH_2) and 9.09 (1 H, br s, NH); δ_P(162 MHz, $CDCl_3$) 3.77 (1 P, t, *J* 103.9); δ_F(376 MHz $CDCl_3$) −113.01 (2 F, td, *J* 18.8 and 103.9); δ_C(126 MHz, $CDCl_3$) 12.6 (s, CH_3), 24.0 (2 × d, *J* 4.7, (CH_3)$_2$CH), 24.4 (2 × d, *J* 3.5, (CH_3)$_2$CH), 34.8 (dt, *J* 15.3 and 21.1, CF_2CH_2), 43.1 (s, CH_2NC=O), 43.6 (dt, *J* 6.2 and 12.0, $CF_2CH_2CH_2$), 74.6 (2 × d, *J* 7.1, 2 × (CH_3)$_2$*C*H), 111.6 (s, C_{ar}), 119.1 (dt, *J* 218.0 and 260.5, CF_2), 124.5 (s, C_{ar}), 140.4 (s, C_{ar}), 142.4 (s, C_{ar}), 151.2 (s, C=O) and 164.4 (s, C=O); *m/z* (ESI) 450.1698 (M + H^+. $C_{17}H_{26}F_2N_5O_5P$ requires 450.1718), 408 (84%) and 366 (30).

9-[1-(3-Diisopropoxyphosphono-3,3-difluoro-propyl)-1,2,3-triazolo-4-methyl]-2-amino-6-chloropurine (12)

(0.38 g, 74%) white solid, mp 115-116 °C; ν_{max}(ATR)/cm^{-1} 3460, 3352, 2932, 2854, 1625, 1470, 1272 and 992; δ_H(400 MHz, $CDCl_3$) 1.33 (12 H, dd, *J* 6.7 and 3.2, 2 × (CH_3)$_2$CH), 2.58-2.80 (2 H, m, CH_2CF_2), 4.62 (2 H, t, *J* 7.4, CH_2CH_2N), 4.79 (2 H, dsp, *J* 6.4, 2 × C*H*(CH_3)$_2$), 5.34 (2 H, s, CH_2NC=N), 5.41 (2 H, s, NH_2), 7.69 (1 H, s, CH=CCH_2) and 7.90 (1 H, s, NCH=N); δ_P(162 MHz, $CDCl_3$) 3.63 (1 P, t, *J* 103.6); δ_F(376 MHz, $CDCl_3$) −112.74 (2 F, td, *J* 18.7 and 103.6); δ_C(101 MHz, $CDCl_3$) 24.0 (2 × d, *J* 4.8, (CH_3)$_2$CH), 24.3 (2 × d, *J* 3.7, (CH_3)$_2$CH), 34.9 (dt, *J* 15.3 and 21.2, CF_2CH_2), 38.7 (s, CH_2NC=N), 43.6 (dt, *J* 6.3 and 11.9, $CF_2CH_2CH_2$), 74.6 (2 × d, *J* 7.2, 2 × (CH_3)$_2$*C*H), 121.6 (dt, *J* 217.7 and 260.7, CF_2), 123.8 (s, C_{ar}), 125.3 (s, C_{ar}), 142.3 (s, C_{ar}), 142.4 (s, C_{ar}), 151.6 (s, C_{ar}), 153.7 (s, C_{ar}) and 159.5 (s, C_{ar}); *m/z* (ESI) 493.1436 (M + H^+. $C_{17}H_{24}ClF_2N_8O_3P$ requires 493.1444), 451 (100%), 409 (37), 381 (10), 296 (5), 254 (23), 212 (88), 194 (11) and 159 (36).

1-[1-(4-Diisopropoxyphosphono-4,4-difluoro-butyl)-1,2,3-triazolo-4-methyl]-thymine (13)

(0.30 g, 96%) white solid, mp 119-120 °C; ν_{max}(ATR)/cm^{-1} 3142, 3032, 2979, 2833, 1687, 1652, 1468, 1385, 1278, 1220, 1147, 1104, 1004 and 981; δ_H(250 MHz, $CDCl_3$) 1.34 (12 H, dd, *J* 6.2 and 4.3, 2 × (CH_3)$_2$CH), 1.88 (3 H, d, *J* 1.0, CH_3), 1.89-2.10 (2 H, m, $CH_2CH_2CH_2$), 2.11-2.30 (2 H, m, CH_2CF_2), 4.41 (2 H, t, *J* 7.0, CH_2CH_2N), 4.83 (2 H, dsp, *J* 6.3, 2 × C*H*(CH_3)$_2$), 4.94 (2 H, s, CH_2NCO), 7.33 (1 H, d, *J* 1.2, CH=CCH_3), 7.75 (1 H, s, CH=CCH_2) and 9.31 (1 H, br s, CONHCO); δ_P(101 MHz, $CDCl_3$) 4.72 (1 P, t, *J* 106.6); δ_F(235 MHz, $CDCl_3$) −112.45 (2 F, td, *J* 19.0 and 106.6); δ_C(63 MHz, $CDCl_3$) 12.5 (s, CH_3), 22.3 (dt, *J* 5.0 and 10.0, $CF_2CH_2CH_2$), 23.9 (2 × d, *J* 4.9, (CH_3)$_2$CH), 24.3 (2 × d, *J* 3.5, (CH_3)$_2$CH), 31.3 (dt, *J* 15.2 and 21.4, CF_2CH_2), 43.2 (s, CH_2NC=O), 49.9 (s, CH_2CH_2N), 74.1 (2 × d, *J* 7.1, 2 × (CH_3)$_2$*C*H), 111.5 (s, C_{ar}), 120.5 (dt, *J* 217.6 and 260.0, CF_2), 124.1 (s, C_{ar}), 140.4 (s, C_{ar}), 142.4 (s, C_{ar}), 151.5 (s, C=O) and 164.7 (s, C=O); *m/z* (ESI) 464.1868 (M + H^+. $C_{18}H_{29}F_2N_5O_5P$ requires 464.1874), 422 (100%) and 380 (72).

9-[1-(4-Diisopropoxyphosphono-4,4-difluoro-butyl)-1,2,3-triazolo-4-methyl]-2-amino-6-chloropurine (14)

(0.34 g, 71%) white solid, mp 123-124 °C; ν_{max}(ATR)/cm^{-1} 3465, 3345, 2942, 2856, 1628, 1471, 1276 and 1000; δ_H(250 MHz, $CDCl_3$) 1.25 (12 H, dd, *J* 6.2 and 3.8, 2 × (CH_3)$_2$CH), 1.90-2.07 (2 H, m, CH_2CF_2), 2.08-2.20 (2 H, m, $CH_2CH_2CH_2$), 4.35 (2 H, t, *J* 7.0, CH_2CH_2N), 4.72 (2 H, dsp, *J* 6.3, 2 × C*H*(CH_3)$_2$), 5.51 (2 H, s, CH_2NC=N), 5.60 (2 H, s, NH_2), 7.72 (1 H, s, CH=CCH_2) and 8.31 (1 H, s, NCH=N); δ_P(101 MHz, $CDCl_3$) 4.40 (1 P, t, *J* 106.6); δ_F(235 MHz $CDCl_3$) -112.33 (2 F, td, *J* 19.2 and 106.6); δ_C(63 MHz, $CDCl_3$) 22.3 (dt, *J* 4.9 and 9.5, $CF_2CH_2CH_2$), 23.8

(2 × d, *J* 4.8, (CH$_3$)$_2$CH), 24.2 (2 × d, *J* 3.6, (CH$_3$)$_2$CH), 31.0 (dt, *J* 15.3 and 21.4, CF$_2$$CH_2$), 39.1 (s, CH$_2$NC=N), 49.8 (s, CH$_2$$CH_2$N), 74.0 (2 × d, *J* 7.1, 2 × (CH$_3$)$_2$$C$H), 119.6 (dt, *J* 217.3 and 259.8, CF$_2$), 123.7 (s, C$_{ar}$), 126.3 (s, C$_{ar}$), 129.6 (s, C$_{ar}$), 131.9 (s, C$_{ar}$), 145.4 (s, C$_{ar}$), 151.1 (s, C$_{ar}$) and 156.6 (s, C$_{ar}$); *m*/*z* (ESI) 507.1570 (M + H$^+$. $C_{18}H_{26}ClF_2N_8O_3P$ requires 507.1591), 465 (68%), 423 (27), 395 (9), 310 (55) and 268 (15).

1-[1-(5-Diisopropoxyphosphono-5,5-difluoro-pentyl)-1,2,3-triazolo-4-methyl]-thymine (15)

(0.46 g, 93%) white solid, mp 99-100 °C; ν_{max}(ATR)/cm^{-1} 3143, 3027, 2984, 2935, 2826, 1684, 1651, 1467, 1387, 1271, 1147, 1102 and 978; δ_H(250 MHz, CDCl$_3$) 1.35 (12 H, dd, *J* 6.2 and 3.1, 2 × (CH_3)$_2$CH), 1.48-1.70 (2 H, m, CH$_2$$CH_2CH_2$), 1.88 (3 H, d, *J* 1.1, CH$_3$), 1.89-2.03 (4 H, m, CH$_2$CF$_2$ and CH$_2$CH$_2$N), 4.34 (2 H, t, *J* 7.1, CH$_2$$CH_2$N), 4.82 (2 H, dsp, *J* 6.2, 2 × CH(CH$_3$)$_2$), 4.94 (2 H, s, CH$_2$NCO), 7.33 (1 H, d, *J* 1.1, CH=CCH$_3$), 7.71 (1 H, s, CH=CCH$_2$) and 9.26 (1 H, s, NH); δ_P(162 MHz, CDCl$_3$) 5.21 (1 P, t, *J* 108.0); δ_F(376 MHz CDCl$_3$) -112.90 (2 F, td, *J* 20.0 and 108.0); δ_C(101 MHz, CDCl$_3$) 12.4 (s, CH$_3$), 18.2 (dt, *J* 5.0 and 9.7, CF$_2$CH$_2$$CH_2$), 23.9 (2 × d, *J* 4.8, (CH$_3$)$_2$CH), 24.3 (2 × d, *J* 3.5, (CH$_3$)$_2$CH), 29.9 (s, CH$_2$CH$_2$N), 33.4 (dt, *J* 14.5 and 21.1, CF$_2$$CH_2$), 43.2 (s, CH$_2$NC=O), 50.3 (s, CH$_2$$CH_2$N), 73.8 (2 × d, *J* 7.1, 2 × (CH$_3$)$_2$$C$H), 111.4 (s, C$_{ar}$), 120.5 (dt, *J* 217.4 and 259.5, CF$_2$), 124.2 (s, C$_{ar}$), 140.4 (s, C$_{ar}$), 142.3 (s, C$_{ar}$), 151.5 (s, C=O) and 164.7 (s, C=O); *m*/*z* (ESI) 478.2025 (M + H$^+$. $C_{19}H_{31}F_2N_5O_5P$ requires 478.2031), 436 (100%) and 394.1 (83).

9-[1-(5-Diisopropoxyphosphono-5,5-difluoro-pentyl)-1,2,3-triazolo-4-methyl]-2-amino-6-chloropurine (16)

(0.33 g, 75%) white solid, mp 105-106 °C; ν_{max}(ATR)/cm^{-1} 3470, 3357, 2940, 2852, 1619, 1479, 1270 and 1004; δ_H(400 MHz, CDCl$_3$) 1.29 (12 H, dd, *J* 6.5 and 3.2, 2 × (CH_3)$_2$CH), 1.45-1.64 (2 H, m, CH$_2$$CH_2CH_2$), 1.83-2.10 (4 H, m, CH$_2CF_2$ and CH$_2$CH$_2$N), 4.28 (2 H, t, *J* 7.0, CH$_2$$CH_2$N), 4.76 (2 H, dsp, *J* 6.1, 2 × CH(CH$_3$)$_2$), 5.31 (2 H, s, CH$_2$NC=N), 5.59 (2 H, s, NH$_2$), 7.61 (1 H, s, CH=CCH$_2$) and 7.89 (1 H, br s, NCH=N); δ_P(162 MHz, CDCl$_3$) 4.96 (1 P, t, *J* 107.7); δ_F(376 MHz CDCl$_3$) –112.71 (2 F, td, *J* 19.6 and 107.7); δ_C(101 MHz, CDCl$_3$) 18.2 (dt, *J* 4.8 and 10.2, CF$_2$CH$_2$$CH_2$), 23.9 (2 × d, *J* 4.7, (CH$_3$)$_2$CH), 24.2 (2 × d, *J* 3.5, (CH$_3$)$_2$CH), 29.9 (s, CH$_2$CH$_2$N), 33.2 (dt, *J* 15.6 and 21.8, CF$_2$$CH_2$), 50.2 (s, CH$_2$$CH_2$N), 53.6 (s, CH$_2$NC=N), 73.8 (2 × d, *J* 7.1, 2 × (CH$_3$)$_2$$C$H), 128.0 (dt, *J* 181.9 and 260.0, CF$_2$), 129.7 (s, C$_{ar}$), 142.4 (s, C$_{ar}$), 151.3 (s, C$_{ar}$), 153.3 (s, C$_{ar}$) and 159.6 (s, C$_{ar}$); *m*/*z* (ESI) 521.1906 (M + H$^+$. $C_{19}H_{28}ClF_2N_8O_3P$ requires 521.1896), 479 (65%), 437 (100), 409 (45) and 324 (23).

1-[1-(2-Diisopropoxyphosphono-2,2-difluoro-ethyl)-1,2,3-triazolo-4-methyl]-thymine (23)

(0.34 g, 71%) white solid, mp 138-139 °C; ν_{max}(ATR)/cm^{-1} 3199, 3066, 2988, 2939, 1691, 1676, 1466, 1380, 1310, 1244, 1218, 1180, 1138, 1097, 1060, 1045 and 996; δ_H(250 MHz, CDCl$_3$) 1.31 (12 H, dd, *J* 6.1 and 3.3, 2 × (CH_3)$_2$CH), 1.83 (3 H, d, *J* 1.1, CH$_3$), 4.87 (2 H, dsp, *J* 6.1, 2 × CH(CH$_3$)$_2$), 4.94 (2 H, dt, *J* 2.9 and 15.8, CH$_2$CF$_2$), 4.99 (2 H, s, CH$_2$NCO), 7.32 (1 H, d, *J* 1.1, CH=CCH$_3$), 7.91 (1 H, s, CH=CCH$_2$) and 10.05 (1 H, br s, NH); δ_P(101 MHz, CDCl$_3$) 0.00 (1 P, t, *J* 98.0); δ_F(235 MHz CDCl$_3$) –117.28 (2 F, td, *J* 16.0 and 98.0); δ_C(63 MHz, CDCl$_3$) 12.4 (s, CH$_3$), 23.8 (2 × d, *J* 5.0, (CH$_3$)$_2$CH), 24.2 (2 × d, *J* 3.8, (CH$_3$)$_2$CH), 42.9 (s, CH$_2$NC=O), 51.7 (dt, *J* 15.6 and 22.0, CF$_2$$CH_2$), 75.1 (2 × d, *J* 7.5, 2 × (CH$_3$)$_2$$C$H), 111.4 (s, C$_{ar}$), 115.8 (dt, *J* 214.2 and 264.8, CF$_2$), 125.9 (s, C$_{ar}$), 140.3 (s, C$_{ar}$), 142.7 (s, C$_{ar}$), 151.4 (s, C=O) and 164.7 (s, C=O); *m*/*z* (ESI) 436.1579 (M + H$^+$. $C_{16}H_{25}F_2N_5O_5P$ requires 436.1561), 394 (100%), 352 (47) and 324 (2).

9-[1-(2-Diisopropoxyphosphono-2,2-difluoro-ethyl)-1,2,3-triazolo-4-methyl]-2-amino-6-chloropurine (24)

(0.28 g, 79%) white solid, mp 111-112 °C; ν_{max}(ATR)/cm^{-1} 3451, 3350, 2935, 2847, 1623, 1461, 1265 and 986; δ_H(400 MHz, CDCl$_3$) 1.27 (12 H, dd, *J* 6.3 and 2.9, 2 × (CH_3)$_2$CH), 4.81 (2 H, dsp, *J* 6.2, 2 × CH(CH$_3$)$_2$), 4.92 (2 H, dt, *J* 3.5 and 16.2, CH$_2$CF$_2$), 5.34 (2 H, s, CH$_2$NC=N), 5.57 (2 H, s, NH$_2$), 7.81 (1 H, s, CH=CCH$_2$) and 7.90 (1 H, s, NCH=N); δ_P(202 MHz, CDCl$_3$) 1.84 (1 P, t, *J* 97.4); δ_F(470 MHz CDCl$_3$) –117.02 (2 F, td, *J* 15.6 and 97.4); δ_C(101 MHz, CDCl$_3$) 23.8 (2 × d, *J* 4.8, (CH$_3$)$_2$CH), 24.1 (2 × d, *J* 3.6, (CH$_3$)$_2$CH), 38.6 (s, CH$_2$NC=N), 52.0 (dt, *J* 15.6 and 23.5, CF$_2$$CH_2$), 75.2 (2 × d, *J* 7.1, 2 × (CH$_3$)$_2$$C$H), 115.8 (dt, *J* 214.0 and 264.9, CF$_2$), 125.0 (2 × s, 2 × C$_{ar}$), 142.3 (s, C$_{ar}$), 142.6 (s, C$_{ar}$), 151.4 (s, C$_{ar}$), 153.7 (s, C$_{ar}$) and 159.6 (s, C$_{ar}$); *m*/*z* (ESI) 479.1294 (M + H$^+$. $C_{16}H_{22}ClF_2N_8O_3P$ requires 479.1287), 437 (75%) and 395 (26).

1-[1-(2-Diisopropoxyphosphono-2,2-difluoro-ethyl)-2-acetamido-1,2,3-triazolo-4-methyl]-thymine (25)

(0.18 g, 62%) white solid, mp 121-122 °C; ν_{max}(ATR)/cm^{-1} 3256, 2985, 2115, 1678, 1531, 1377, 1257, 1097 and 991; δ_H(400 MHz, CDCl$_3$) 1.35 (12 H, dd, *J* 6.4 and 2.3, 2 × (CH_3)$_2$CH), 1.89 (3 H, d, *J* 1.2, CH$_3$C=C), 1.99 (3 H, s, CH$_3$CO), 4.49 (2 H, s, CH$_2$NCO), 4.85 (2 H, dsp, *J* 6.4, 2 × CH(CH$_3$)$_2$), 5.74-5.90 (1 H, m, CHCF$_2$), 7.22 (1 H, d, *J* 1.2, CH=CCH$_3$), 7.53 (1 H, s, CH=CCH$_2$), 7.56 (1 H, s, CHNHCO) and 9.80 (1 H, s, CONHCO); δ_P(162 MHz, CDCl$_3$) 2.50 (1 P, dd, *J* 96.9 and 97.5); δ_F(376 MHz CDCl$_3$) –116.31 (1 F, ddd, *J* 8.0, 97.5 and 304.9) and –119.64 (1 F, ddd, *J* 12.8, 96.9 and 304.9); δ_C(101 MHz, CDCl$_3$) 12.7 (s, CH$_3$), 23.3 (s, CH$_3$CO), 23.9 (2 × d, *J* 5.2, (CH$_3$)$_2$CH), 24.4 (2 × d, *J* 3.3, (CH$_3$)$_2$CH), 36.9 (s, CH$_2$NC=O), 66.8 (dt, *J* 15.3 and 27.9, CF$_2$$C$H), 75.4 (2 × d, *J* 7.1, 2 × (CH$_3$)$_2$$C$H), 111.8 (s, C$_{ar}$), 118.4 (dt, *J* 211.7 and 267.2, CF$_2$), 124.5 (s, C$_{ar}$), 138.6 (s, C$_{ar}$), 140.0 (s, C$_{ar}$), 150.7 (s, C$_{ar}$), 164.2 (s, C=O) and 170.7 (s, C=O); *m*/*z* (ESI) 493.1785 (M + H$^+$. $C_{18}H_{27}F_2N_6O_6P$ requires 493.1776), 451 (100%), 286 (94), 244 (9) and 208 (7).

9-[1-(2-Diisopropoxyphosphono-2,2-difluoro-ethyl)-2-acetamido-1,2,3-triazolo-4-methyl]-2-amino-6-chloropurine (26)

(0.33 g, 69%), white solid, mp 126-127 °C; ν_{max}(ATR)/cm^{-1} 3461, 3336, 2929, 2850, 1615, 1468, 1271 and 1000; δ_H(400 MHz, CDCl$_3$) 1.29 (12 H, dd, *J* 6.3 and 2.0, 2 × (CH_3)$_2$CH), 2.06 (3 H, s, CH$_3$C=C), 4.76 (2 H, dsp, *J* 6.3, 2 × CH(CH$_3$)$_2$), 5.37 (2 H, s, CH$_2$NC=N), 5.46 (2 H, s, NH$_2$), 6.83-7.01 (1 H, m, CHCF$_2$), 7.98 (2 H, s, CH=CCH$_2$ and NCH=N) and 8.16 (1 H, s, NH); δ_P(162 MHz, CDCl$_3$) 1.16 (1 P, dd, *J* 97.7 and 93.9); δ_F(376 MHz CDCl$_3$) –116.14 (1 F, ddd, *J* 8.3, 93.9 and 306.1) and –120.63 (1 F, ddd, *J* 14.7, 97.7 and 306.1); δ_C(101 MHz, CDCl$_3$) 23.1 (s, CH$_3$CO), 23.8 (2 × d, *J* 5.2, (CH$_3$)$_2$CH), 24.1 (2 × d, *J* 3.7, (CH$_3$)$_2$CH), 38.6 (s, CH$_2$NC=N), 65.1 (dt, *J* 18.7 and 28.0,

CF_2CH), 75.8 (2 × d, *J* 7.2, 2 × $(CH_3)_2CH$), 115.3 (dt, *J* 211.0 and 270.5, CF_2), 124.3 (s, C_{ar}), 125.2 (s, C_{ar}), 142.0 (s, C_{ar}), 142.5 (s, C_{ar}), 151.6 (s, C_{ar}), 153.8 (s, C_{ar}), 159.6 (s, C_{ar}) and 170.3 (s, C_{ar}); *m/z* (ESI) 536.1497 (M + H^+. $C_{18}H_{25}ClF_2N_9O_4P$ requires 536.1497), 477 (3%), 286 (1) and 251 (100).

Preparation of triazole 27

To a solution of azide **10** (765 mg, 2.45 mmol) in a MeCN/H_2O 1/2 mixture (16 cm^3) was added methyl propiolate (0.220 cm^3, 2.45 mmol) and copper(I) iodide (46.7 mg, 0.245 mmol). The solution was stirred overnight at room temperature. H_2O (2 cm^3) was added and the mixture was extracted with Et_2O (3 × 10 cm^3). Combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica using pentane/ethyl acetate (6/4) as eluent to yield 1-((diisopropyl)-1,1-difluoropentylphosphonyl)-4-methoxycarbonyl-1,2,3-triazole **27** (758 mg, 78%) as a white solid, mp 65-66 °C; ν_{max}(ATR)/cm^{-1} 3123, 2979, 1723, 1541, 1267, 1238, 1222, 1175, 1000 and 976; δ_H(400 MHz, $CDCl_3$) 1.34 (6 H, d, *J* 6.3, $(CH_3)_2CH$), 1.36 (6 H, d, *J* 6.3, $(CH_3)_2CH$), 1.54-1.77 (2 H, m, $CH_2CH_2CH_2$), 1.96-2.21 (4 H, m, CH_2CF_2 and CH_2CH_2N), 3.89 (3 H, s, OCH_3), 4.43 (2 H, t, *J* 7.1, CH_2CH_2N), 4.81 (2 H, dsept, *J* 6.3, 2 × $CH(CH_3)_2$) and 8.09 (1 H, s, CH=C); δ_P(202 MHz, $CDCl_3$) 5.1 (1 P, t, *J* 108.0); δ_F(470 MHz, $CDCl_3$) −112.80 (2 F, td, *J* 20.1 and 108.2); δ_C(101 MHz, $CDCl_3$) 18.2 (dt, *J* 4.9 and 10.0, $CF_2CH_2CH_2$), 23.9 (d, *J* 4.2, $(CH_3)_2CH$), 24.3 (d, *J* 4.0, $(CH_3)_2CH$), 29.9 (s, CH_2CH_2N), 33.3 (dt, *J* 14.3 and 21.2, CF_2CH_2), 50.5 (s, CH_2CH_2N), 52.4 (s, CH_3O), 73.9 (2 × d, *J* 7.1, 2 × $(CH_3)_2CH$), 120.2 (dt, *J* 217.2 and 259.1, CF_2), 127.7 (s, C_{ar}), 140.2 (s, C_{ar}) and 161.3 (s, C=O); *m/z* (ESI) 398.1673 (M + H^+. $C_{15}H_{27}F_2N_3O_5P$ requires 398.1656).

Preparation of amide 28

Compound **27** (260 mg, 0.655 mmol) was stirred in a CH_3OH/25% aqueous NH_3 solution 1/1 (5 cm^3) at room temperature for 72 h. The solvents were removed and the residue was purified by flash column chromatography on silica using CH_2Cl_2/CH_3OH (97/3) as eluent to give 1-((diisopropyl)-1,1-difluoropentylphosphonyl)-4-carbamoyl-1,2,3-triazole **28** (192 mg, 77%) as a white solid, mp 100-101 °C; ν_{max}(ATR)/cm^{-1} 3425, 3194, 3089, 2983, 1651, 1621, 1574, 1466, 1388, 1378, 1268 and 983; δ_H(400 MHz, CD_3OD) 1.35 (6 H, d, *J* 6.1, $(CH_3)_2CH$), 1.36 (6 H, d, *J* 6.1, $(CH_3)_2CH$), 1.42-1.63 (2 H, m, $CH_2CH_2CH_2$), 1.88-2.20 (4 H, m, CH_2CF_2 and CH_2CH_2N), 4.50 (2 H, t, *J* 7.0, CH_2N), 4.72-4.90 (2 H, m, 2 × $(CH_3)_2CH$) and 8.38 (1 H, s, CH=C); δ_P(202 MHz, CD_3OD) 5.10 (1 P, t, *J* 111.2); δ_F(470 MHz, CD_3OD) −113.70 (2 F, td, *J* 20.0 and 111.1); δ_C(101 MHz, CD_3OD) 9.2 (dt, *J* 5.2 and 9.8, $CF_2CH_2CH_2$), 14.5 (d, *J* 4.7, $(CH_3)_2CH$), 14.8 (d, *J* 3.6, $(CH_3)_2CH$), 21.2 (s, CH_2CH_2N), 24.8 (dt, *J* 14.5 and 21.2, CF_2CH_2), 41.6 (s, CH_2CH_2N), 66.2 (2 × d, *J* 7.1, 2 × $(CH_3)_2CH$), 112.5 (dt, *J* 220.1 and 258.3, CF_2), 118.0 (s, C_{ar}), 134.3 (s, C_{ar}) and 155.2 (s, C=O); *m/z* (ESI) 383.1658 (M + H^+. $C_{14}H_{26}F_2N_4O_4P$ requires 383.1660).

Preparation of amide 29

Compound **27** (151 mg, 0.380 mmol) was stirred in a CH_3OH/40% aqueous $MeNH_2$ solution 1/1 (3 cm^3) at room temperature for 72 h. The solvents were removed and the residue was purified by flash column chromatography on silica using CH_2Cl_2/CH_3OH (97/3) as eluent to give 1-((diisopropyl)-1,1-difluoropentylphosphonyl)-4-methyl-carbamoyl-1,2,3-triazole **29** (128 mg, 85%) as a white solid, mp 111-112 °C; ν_{max}(ATR)/cm^{-1} 3342, 3118, 2983, 1654, 1583, 1263, 1011 and 984; δ_H(400 MHz, CD_3OD) 1.35 (6 H, d, *J* 6.3, $(CH_3)_2CH$), 1.37 (6 H, d, *J* 6.3, $(CH_3)_2CH$), 1.50-1.64 (2 H, m, $CH_2CH_2CH_2$), 1.96-2.18 (4 H, m, CF_2CH_2 and CH_2CH_2N), 2.93 (3 H, s, NCH_3), 4.50 (2 H, t, *J* 6.9, CH_2CH_2N), 4.80 (2 H, dsept, *J* 6.3, 2 × $(CH_3)_2CH$), 8.37 (1 H, s, CH=C); δ_P(202 MHz, CD_3OD) 5.40 (1 P, t, *J* 111.2); δ_F(470 MHz CD_3OD) −114.00 (2 F, td, *J* 20.0 and 111.1); δ_C(101 MHz, CD_3OD) 9.1 (dt, *J* 5.0 and 10.1, $CF_2CH_2CH_2$), 14.5 (d, *J* 4.6, $(CH_3)_2CH$), 14.8 (d, *J* 3.8, $(CH_3)_2CH$), 16.6 (s, NCH_3), 21.2 (s, CH_2CH_2N), 24.8 (dt, *J* 14.6 and 21.1, CF_2CH_2), 41.5 (s, CH_2CH_2N), 66.1 (2 × d, *J* 7.1, 2 × $(CH_3)_2CH$), 111.9 (dt, *J* 219.2 and 258.3, CF_2), 117.4 (s, C_{ar}), 134.5 (s, C_{ar}) and 153.5 (s, C=O); *m/z* (ESI) 398.1836 (M + H^+. $C_{15}H_{28}F_2N_4O_4P$ requires 398.1816).

Preparation of triazole 30

Azide **10** (233 mg, 0.744 mmol) in DMF (1 cm^3) was added to a solution of 2-cyanoacetamide (93.7 mg, 1.12 mmol) and KOH (62.5 mg, 1.12 mmol) in H_2O/DMF 1/5 (1.2 cm^3). After 24 h of stirring at room temperature, the reaction mixture was filtered through Celite and the filtrate was evaporated to dryness. The residue was taken up in CH_3OH (10 cm^3) and neutralized with a Dowex 50 resin, filtered and concentrated. The crude product was purified by flash column chromatography on silica using CH_2Cl_2/CH_3OH (90/10) as eluent to give 1-((diisopropyl)-1,1-difluoropentylphosphonyl)-4-carbamoyl-5-amino-1,2,3-triazole **30** (112 mg, 37%) as a white solid, mp 130-131 °C; ν_{max}(ATR)/cm^{-1} 3425, 3193, 3089, 2983, 1651, 1621, 1574, 1466, 1377, 1265, 1180, 1143 and 983; δ_H(400 MHz, CD_3OD) 1.35 (6 H, d, *J* 6.3, $(CH_3)_2CH$), 1.37 (6 H, d, *J* 6.3, $(CH_3)_2CH$), 1.55-1.65 (2 H, m, $CH_2CH_2CH_2$), 1.91 (2 H, quint, *J* 7.0, CF_2CH_2), 2.00-2.17 (2 H, m, CH_2CH_2N), 4.20 (2 H, t, *J* 7.0, CH_2CH_2N), 4.81 (2 H, dsept, *J* 6.3, 2 × $(CH_3)_2CH$) and 4.87 (2 H, s, NH_2); δ_P(202 MHz, CD_3OD) 5.50 (1 P, t, *J* 111.2); δ_F(470 MHz, CD_3OD) −114.00 (2 F, td, *J* 20.0 and 111.1); δ_C(101 MHz, CD_3OD) 19.2 (dt, *J* 5.4 and 10.1, $CF_2CH_2CH_2$), 24.0 (d, *J* 4.6, $(CH_3)_2CH$), 24.4 (d, *J* 3.8, $(CH_3)_2CH$), 29.2 (s, CH_2CH_2N), 34.5 (dt, *J* 14.2 and 21.1, CF_2CH_2), 46.6 (s, CH_2CH_2N), 75.7 (2 × d, *J* 7.1, 2 × $(CH_3)_2CH$), 123.0 (dt, *J* 219.1 and 258.2, CF_2), 146.4 (2 × s, 2 × C_{ar}) and 167.0 (s, C=O); *m/z* (ESI) 398.1771 (M + H^+. $C_{14}H_{27}F_2N_5O_4P$ requires 398.1769).

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