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Synthesis of functionalized α-CF_3-α-aminophosphonates *via* Cu(I)-catalyzed 1,3-dipolar cycloaddition

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ABSTRACT

A convenient method for the preparation of α-CF_3-α-aminophosphonates bearing alkynyl group at the α-carbon atom has been described. New alkynylphosphonates have been further utilized in the synthesis of functionalized triazole-containing α-CF_3-α-aminophosphonates *via* copper-catalyzed (3+2)-cycloaddition to different organic azides.

1. Introduction

During the past three decades α-(fluoromethyl)-substituted α-amino acids, which can function as highly selective inhibitors of pyridoxal phosphate dependent enzymes [1], have been attracting considerable interest as potent low-molecular bioregulators and as building blocks for the modification of bioactive peptides [2].

Since α-aminophosphonate derivatives are structural mimics of α-amino acids, some of these compounds exhibit very high potency in inhibiting the enzymes that are involved in the metabolism of the corresponding amino acids. These compounds have already been found to act as antibacterial agents, neuroactive compounds, anticancer drugs, and pesticides, with some of them already being commercialized [3]. For example, Strater and Lipscomb have reported several L-leucine-phosphonic acid derivatives that are among the most potent low-molecular inhibitors of leucine aminopeptidase [4]. The altered activity of such an enzyme has been associated with HIV infections and several pathological disorders including cancer and cataracts [5].

At the same time, introduction of the fluorine containing group in a biomolecule may change the "normal" route of its interaction with a biological target or the direction of binding. Therefore, such approach is very popular in construction of new biologically active molecules. However, in contrast to the rather well developed aminophosphonic and aminophosphinic acids area, only limited representatives of fluorine containing α-aminophosphonates are currently known [6–13]. Thus, the synthesis of new fluorinated α-aminophosphonates as potential drug candidates is of current interest.

On the other hand, 1,2,3-triazole derivatives have displayed an ample range of application in pharmaceutical and material sciences [14]. Since Meldal and Sharpless developed Cu(I)-catalyzed 1,3-dipolar Huisgen cycloaddition reaction of azides with alkynes [15], the so called "click chemistry" has received growing interest in the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles [16]. The formation of triazoles in this reaction has represented definitive advances: reliable, effective, benign in reaction conditions, and high tolerance to many functional groups. Using this approach, a wide range of compounds with an inert triazole heterocycle could be prepared being of interest in medicinal chemistry and material science [17].

Recently, we have elaborated effective synthetic approaches giving the possibility for facile, rapid, and cheap access to a wide range of novel nitrogen-bisphosphonates [18a], phosphonocarboxylates [18b], triazole-substituted phosphonates [18c], and CF_3-azahistidine analogous [18d] based on "click" methodology. Herein, we present a convenient synthetic pathway to novel functionalized α-CF_3-α-aminophosphonates comprising triazole

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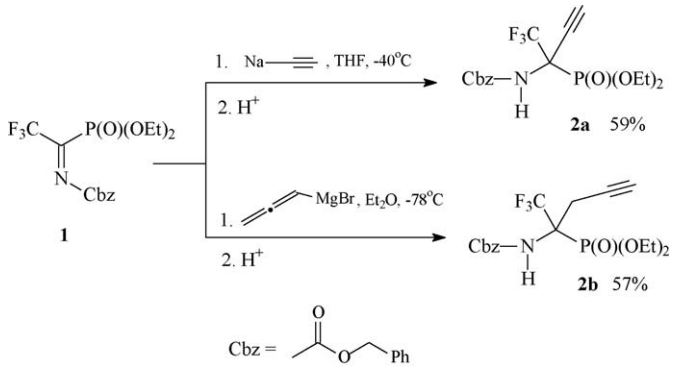
moiety as a linker connecting fluorinated α-aminophosphonate with different functionalities (Fig. 1).

2. Results and discussions

The synthesis of the starting α-alkynyl-α-CF_3-α-aminophosphonates **2a**, **2b** was accomplished *via* the addition of sodium acetylide or Grignard reagent generated from propargyl bromide, to the electrophilic imine **1**. These reactions proceeded in anhydrous diethyl ether or tetrahydrofuran under mild conditions to give the corresponding aminophosphonates in good yields (Scheme 1).

Even though some fluorinated α-alkyl(allyl)-substituted α-aminophosphonates were previously described using the similar methodology [13a,19,20], to the best of our knowledge the derivatives bearing α-alkynyl group were not described previously.

In a standard procedure for regioselective Cu(I)-catalyzed alkyne–azide coupling, the catalyst can be either directly introduced as a Cu(I) salt or generated *in situ* by reduction of Cu(II) salts



Scheme 1.

[15], usually in organoaqueous systems. For the synthesis of the triazolyl-phosphonates **3a**–**h** from ethynyl- or propargyl-substituted phosphonates **2a**,**b**, the procedure involving *in situ* generation of Cu(I) moiety from $CuSO_4$ pentahydrate and sodium

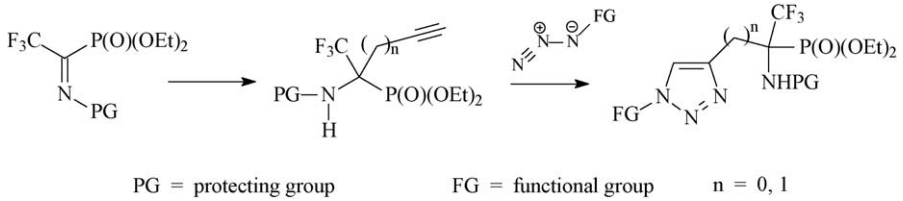
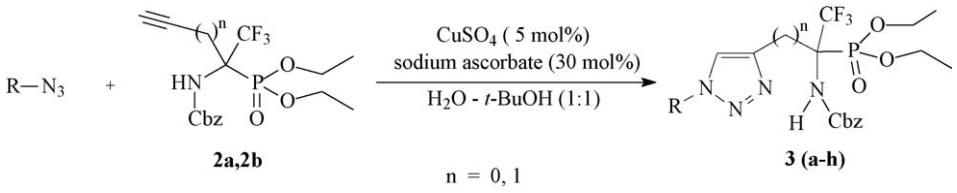
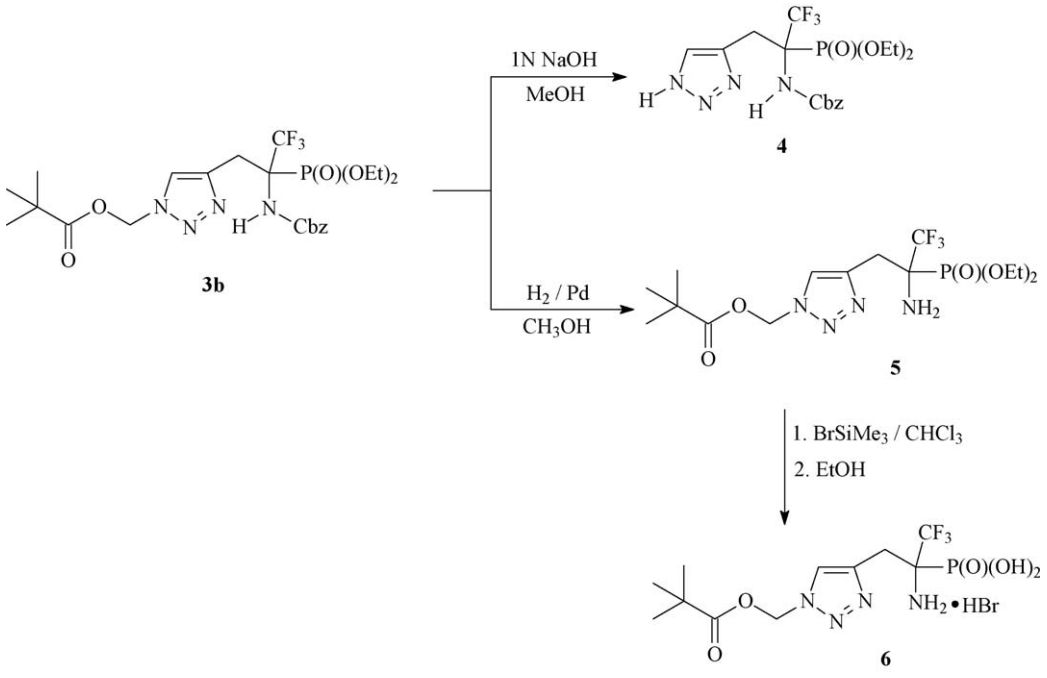


Fig. 1.



Scheme 2.

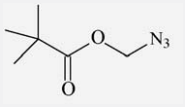
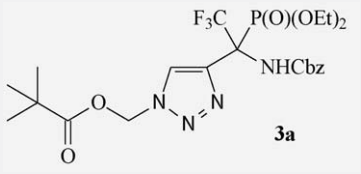
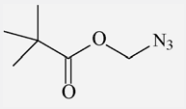
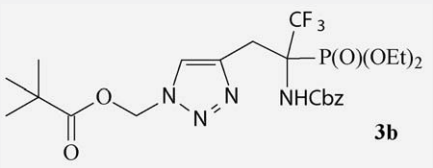
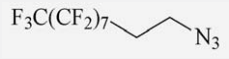
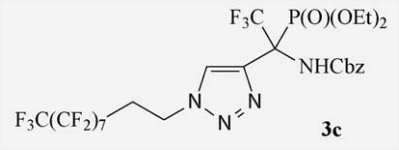
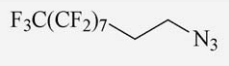
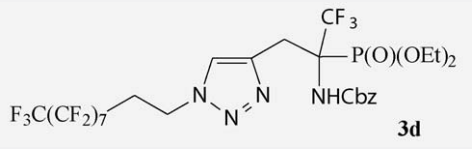
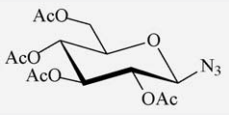
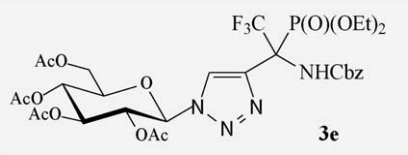
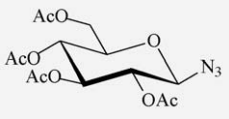
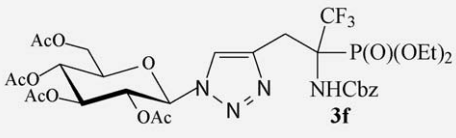
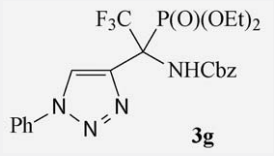
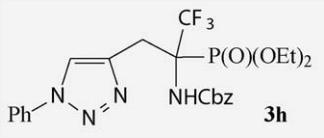


Scheme 3.

ascorbate in a mixture of *tert*-butanol/water in a ratio of 1:1 was the method of choice (Scheme 2).

Thus, acetylene **2a** easily reacted with pivaloylmethyl- and heptadeca-fluoro-decyl azides at room temperature to afford 3,5-disubstituted triazoles **3a** and **3c** in good yields over 8 h (entries 1 and 3, Table 1). The reaction of **2a** with sugar azide (entry 5, Table 1) required more prolonged reaction time (*ca.* 12 h) at the same temperature to yield the corresponding product **3e**. However, in the case of phenyl azide, the best yield of triazole **3g** (52% as determined by the ^{19}F NMR, 38% - isolated) was achieved under

Table 1
Triazole-containing α-CF_3-α-aminophosphonates[a].

Entry	RN_3	Product	Yield[b] (%)
1		 **3a**	89
2		 **3b**	68
3		 **3c**	92
4		 **3d**	72
5		 **3e**	78
6		 **3f**	65
7	PhN_3	 **3g**	38
8	PhN_3	 **3h**	73

[a] Conditions: acetylene (1.0 mmol), azide (1.0 mmol), $CuSO_4$ (5 mol%), sodium ascorbate (30 mol%), H_2O–*tert*-BuOH (1:1), 8–12 h.
[b] Yield after column chromatography.

stirring of reaction mixture at 20 °C for 48 h. The variation of reaction conditions (excess of phenyl azide and temperature) did not affect the yield of the product.

In contrast to ethynylphosphonate **2a**, the cycloaddition of propargyl-containing aminophosphonate **2b** to organic azides proceeded only at 80 °C in the same mixture solvent and lead to completion for 2 h in all cases to afford the corresponding triazoles **3b**, **3d**, **3f**, and **3h**. Such difference in reactivity is apparently connected with electronic factors (alkynes bearing electron-withdrawing groups adjacent to the triple bond usually are more reactive in addition reactions [21]) or with the possible formation of thermordynamically stable six-membered intermediate copper complexe *via* metal coordination on triple and P=O bonds in **2b**. Indeed, the copper coordination on triple bond is well described in Ref. [8g] while phosphoryl compounds are also inclined to form strong copper complexes [22].

Functionalized triazoles **3** derived from propargylphosphonates **2b** can be regarded as phosphoryl analogous of azahistidine—important histidine surrogate [23]. For efficient use of such compounds in peptide synthesis, an easy access to orthogonally protected derivatives is strongly required. To demonstrate a possibility of selective removing of protecting groups *N*-pivaloylmethyl derivative **3b** was selected as the most suitable precursor. Therefore, we have found that the pivaloylmethyl group can be selectively removed under basic conditions for 45 min at room temperature in methanol to afford NH-triazole **4** in good yield. Classical Pd-catalyzed hydrogenation in methanol was successfully applied for deprotection of amino function of **3b**. Final acidolysis of phosphonate group accomplished by the treatment of triazole **5** with trimethylsilylbromide in chloroform followed by hydrolysis of the intermediate silyl ester, yielded the free aminophosphonic acid **6** as HBr salt (Scheme 3).

3. Conclusion

A convenient method for the preparation of new α-CF_3-α-aminophosphonates bearing alkynyl group at the α-carbon atom has been developed. New alkynylphosphonates **2a**, **2b** have been further used in the synthesis of functionalized triazole-containing α-CF_3-α-aminophosphonates *via* copper-catalyzed (3+2)-cycloaddition to different organic azides. To demonstrate a potential of compounds **3** for the possible application in peptide chemistry, the efficient procedures for selective removing of protective groups were also elaborated.

4. Experimental

4.1. General methods

All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. Reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light or spraying by $Ce(SO_4)_2$, solution in 5% H_2SO_4. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). NMR spectra were obtained on a Bruker AV-300 spectrometer operating at 300 MHz, respectively (TMS) for ^1H; 282 MHz for ^{19}F (CF_3COOH); 121 MHz for ^{31}P (H_3PO_4).

4.1.1. Diethyl[(1-{[(benzyloxy)carbonyl]amino}-1-trifluoromethyl)prop-2-yne-1-yl] phosphonate (2a)

Sodium acetylide (18% slurry in xylene; 11.0 mmol) was added dropwise to a stirred solution of imine **1** [20b] (10.0 mmol) in dry THF (25 mL) at −40 °C. After 8 h at −40 °C the reaction mixture was allowed to warm to r.t. within 2 h. The reaction was quenched with saturated solution of NH_4Cl and extracted with Et_2O (2× 25 mL). The combined organic layer was washed with brine (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (acetone–hexane). Yield: 59% (solid), m.p. 99–100 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.44 (m, 6H, $2CH_3$), 2.88 (br.s, 1H, –C≡CH), 4.38 (m, 4H, $2OCH_2$), 5.19 (d_{AB}, 1H, CH_2, J_{AB} = 12.0 Hz), 5.23 (d_{AB}, 1H, CH_2, J_{AB} = 12.0 Hz), 5.65 (d, 1H, NH, $^3J_{H-P}$ = 9.0 Hz), 7.43 (br.s, 5H, Ph). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 5.45. ^{31}P NMR ($CDCl_3$, 121 MHz): δ 14.62. Anal. Calcd for $C_{16}H_{19}F_3NO_5P$: C, 48.86; H, 4.87; N, 3.56. Found: C, 48.94; H, 4.81; N, 3.60.

4.1.2. Diethyl[(1-{[(benzyloxy)carbonyl]amino}-1-trifluoromethyl)but-3-yne-1-yl] phosphonate (2b)

Allenylmagnesiumbromide (solution in Et_2O, 22.0 mmol) was added dropwise to a stirred solution of an imine **1** [20b] (10.0 mmol) in dry Et_2O (25 mL) at −78 °C. After 3 h at −78 °C the reaction mixture was allowed to warm to r.t. within 2 h. The reaction was quenched with saturated solution of NH_4Cl and extracted with Et_2O (2× 25 mL). The combined organic layer was washed with brine (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (acetone–hexane). Yield: 57% (solid), m.p., 88–89 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.42 (t, 6H, $2CH_3$, $^3J_{H-H}$ = 7.1 Hz), 2.13 (s, 1H, –C≡CH), 3.31 and 3.46 (t, 1H and 1H, CH_2, $^3J_{H-H}$ = 14.6 Hz), 4.32 (m, 4H, $2OCH_2$), 5.17 (m, 2H, CH_2,), 5.96 (d, 1H, NH, $^3J_{H-P}$ = 9.3 Hz), 7.40 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 6.70 (d, $^3J_{F-P}$ = 4.1 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 15.42 (d, $^3J_{P-F}$ = 4.1 Hz).

4.2. General procedure for the synthesis of triazoles 3a–h

To a solution of the corresponding acetylene **2a**, **2b** (1.0 mmol) in the mixture of *t*-BuOH-H_2O (3 ml) was added a solution of corresponding azide (1.0 mmol) in the mixture of *t*-BuOH-H_2O (2 ml), sodium ascorbate (0.3 mmol) and 0.5 M copper sulfate pentahydrate (0.05 mmol). The reaction mixture was stirred at room temperature for about 8–12 h (in the case of **2b** at 80 °C, 2 h) until the completion of the reaction monitored by TLC. After evaporation of the solvent under reduced pressure, water was added to a residue and the aqueous layer was extracted twice with ethyl acetate (20 ml). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using EtOAc-hexane as an eluent.

4.2.1. {4-[2-{[(Benzyloxy)carbonyl]amino}-2-(diethoxyphosphoryl)-3,3,3-trifluoropropyl]-1H-1,2,3-triazole-1-yl} pivalate (3a)

Yield: 89% (solid), m.p. 87–88 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (s, 9H, $3CH_3$), 1.29 (m, 6H, $2CH_3$), 4.17 (m, 4H, $2OCH_2$), 5.10 (m, 2H, CH_2), 6.25 (s, 2H, OCH_2), 6.43 (d, 1H, NH, $^3J_{H-P}$ = 8.0 Hz), 7.37 (br.s, 5H, Ph), 8.02 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 6.44. ^{31}P NMR ($CDCl_3$, 121 MHz): δ 13.55 (d, $^3J_{P-H}$ = 7.21 Hz). Anal. Calcd for $C_{22}H_{30}F_3N_4O_7P$: C, 48.03; H, 5.45; N, 10.19. Found: C, 48.09; H, 5.44; N, 10.11.

4.2.2. {4-[2-{[(Benzyloxy)carbonyl]amino}-2-(diethoxyphosphoryl)-3,3,3-trifluoropropyl]-1H-1,2,3-triazole-1-yl}methyl pivalate (3b)

Yield: 68% (solid), m.p. 83–84 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22 (s, 9H, $3CH_3$), 1.33 (q, 6H, $2CH_3$, $^3J_{H-H}$ = 7.3 Hz), 3.81 (m, 2H, CH_2), 4.20 (m, 4H, $2OCH_2$), 5.19 (s, 2H, OCH_2), 5.98 (d, 1H, NH, $^3J_{H-P}$ = 8.9 Hz), 6.18 (d_{AB}, 1H, CH_2, J_{AB} = 10.7 Hz), 6.23 (d_{AB}, 1H, CH_2, J_{AB} = 10.7 Hz), 7.42 (m, 5H, Ph), 7.68 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 8.23 (d, $^3J_{F-P}$ = 3.4 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 15.62 (d, $^3J_{P-F}$ = 3.1 Hz). Anal. Calcd for

$C_{23}H_{32}F_3N_4O_7P$: C, 48.96; H, 5.67; N, 9.93. Found: C, 48.81; H, 5.59; N, 9.85.

4.2.3. Diethyl{1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[(1-(heptadeca-fluoro-decyl)-1H-1,2,3-triazole-4-yl)]ethyl}phosphonate (3c)

Yield: 85% (solid), m.p. 85–86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (m, 6H, $2CH_3$), 2.85 (m, 2H, CH_2), 4.18 (m, 4H, $2OCH_2$), 4.69 (t, 2H, CH_2, $^3J_{H-H}$ = 6.0 Hz), 5.16 (d_{AB}, 1H, CH_2, J_{AB} = 12.0 Hz), 5.07 (d_{AB}, 1H, CH_2, J_{AB} = 12.0 Hz), 6.46 (d, 1H, NH, $^3J_{H-P}$ = 8.0 Hz), 7.37 (s, 5H, Ph), 7.86 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −50.76 (br.s, 2F, CF_2), −48.01 (br.s, 2F, CF_2), −47.36 (br.s, 2F, CF_2), −46.53 (br.s, 6F, $3CF_2$), −38.83 (m, 2F, CF_2), −5.39 (s, 3F, CF_3), 6.52 (s, 3F, CF_3). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 13.70. Anal. Calcd for $C_{26}H_{23}F_{20}N_4O_5P$: C, 35.40; H, 2.61; N, 6.35. Found: C, 35.28; H, 2.45; N, 6.30.

4.2.4. Diethyl{1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[(1-(heptadeca-fluoro-decyl)-1H-1,2,3-triazole-4-yl)methyl]ethyl} phosphonate (3d)

Yield: 92% (oil). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, 3H, CH_3, $^3J_{H-H}$ = 7.1 Hz), 1.35 (t, 3H, CH_3, $^3J_{H-H}$ = 7.1 Hz), 2.79 (m, 2H, CH_2), 3.83 (m, 2H, CH_2), 4.19 (m, 4H, $2OCH_2$), 4.57 (t, 2H, CH_2, $^3J_{H-H}$ = 7.5 Hz), 5.14 (d_{AB}, 1H, CH_2, J_{AB} = 12.0 Hz), 5.22 (d_{AB}, 1H, CH_2, J_{AB} = 12.0 Hz), 5.94 (d, 1H, NH, $^3J_{H-P}$ = 8.5 Hz), 7.34 (s, 1H, CH-triazole), 7.42 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −48.46 (m, 2F, CF_2), −45.78 (br.s, 2F, CF_2), −45.07 (br.s, 2F, CF_2), −44.01 (br.s, 6F, $3CF_2$), −36.50 (t, 2F, CF_2, $^3J_{F-F}$ = 13.4 Hz), −3.09 (t, 3F, CF_3, $^3J_{F-F}$ = 10.1 Hz), 7.94 (s, 3F, CF_3). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 15.62. Anal. Calcd for $C_{27}H_{25}F_{20}N_4O_5P$: C, 36.19; H, 2.79; N, 6.25. Found: C, 36.35; H, 2.73; N, 6.21.

4.2.5. Diethyl{1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[(1-(2,3,4,6-tetra-O-acetyl-β-D-glucopiranozyl)-1H-1,2,3-triazole-4-yl)]ethyl}phosphonate (3e)

Yield: 78% (cristal in oil), mixture of diastereomers 1:1. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (br.s, 6H, $2CH_3$), 1.86 (s, 3H, CH_3), 2.07 (t, 9H, $3CH_3$, $^3J_{H-H}$ = 6.0 Hz), 4.18 (m, 7H, $2OCH_2$, CH_2, CH), 5.11 (m, 2H, CH_2), 5.30 (m, 2H, CH, CH), 5.45 (m, 1H, CH), 5.88 (d, 1H, NH, $^3J_{H-P}$ = 10.0 Hz), 6.39 (t, 1H, CH, $^3J_{H-H}$ = 10.0 Hz), 7.35 (s, 5H, Ph), 8.09 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 6.14 and 6.64. ^{31}P NMR ($CDCl_3$, 121 MHz): δ 13.42. Anal. Calcd for $C_{30}H_{38}F_3N_4O_{14}P$: C, 47.00; H, 5.00; N, 7.31. Found: C, 47.43; H, 5.00; N, 6.92.

4.2.6. Diethyl{1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[(1-(2,3,4,6-tetra-O-acetyl-β-D-glucopiranozyl)-1H-1,2,3-triazole-4-yl)methyl]ethyl}phosphonate (3f)

Yield: 65% (solid), m.p. 61–67 °C, mixture of diastereomers 1:1. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 and 1.34 (t, 6H, $2CH_3$, $^3J_{H-H}$ = 7.1 Hz), 1.88 (s, 6H, $2CH_3$), 2.06 (d, 9H, $3CH_3$, $^3J_{H-H}$ = 3.2 Hz), 2.13 (d, 9H, $3CH_3$, $^3J_{H-H}$ = 3.9 Hz), 3.86 (m, 4H, $2CH_2$), 4.09 (m, 14H, $4OCH_2$, $2CH_2$, 2CH), 5.26 (m, 6H, $2CH_2$, 2CH), 5.44 (m, 4H, 2CH, 2CH), 5.83 (m, 3H, 2CH, NH), 5.96 (d, 1H, NH, $^3J_{H-P}$ = 8.2 Hz), 7.45 (m, 10H, Ph), 7.59 and 7.70 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 8.08 (d, $^3J_{F-P}$ = 3.0 Hz), 8.33 (d, $^3J_{F-P}$ = 3.1 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 15.51 (t, $^3J_{P-F}$ = 4.0 Hz). Anal. Calcd for $C_{31}H_{40}F_3N_4O_{14}P$: C, 47.72; H, 5.13; N, 7.18. Found: C, 47.38; H, 5.08; N, 7.00.

4.2.7. Diethyl{1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[(1-phenyl-1H-1,2,3-triazole-4-yl)]ethyl}phosphonate (3g)

Yield: 38% (oil). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (m, 6H, $2CH_3$), 4.16 (m, 4H, $2OCH_2$), 5.09 (d_{AB}, 1H, CH_2, J_{AB} = 12.0 Hz), 5.17 (d_{AB}, 1H, CH_2, J_{AB} = 12.0 Hz), 6.53 (d, 1H, NH, $^3J_{H-P}$ = 8.0 Hz), 7.36 (br.s, 5H, Ph), 7.51 (m, 3H, Ph), 7.76 (d, 2H, Ph, $^3J_{H-H}$ = 8.0 Hz), 8.23 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 6.72. ^{31}P NMR ($CDCl_3$, 121 MHz): δ 13.76. Anal. Calcd for $C_{22}H_{24}F_3N_4O_5P$: C, 51.57; H, 4.72; N, 10.93. Found: C, 52.26; H, 4.78; N, 10.57.

4.2.8. Diethyl{1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-[(1-phenyl-1H-1,2,3-triazole-4-yl)methyl]ethyl}phosphonate (3h)

Yield: 73% (oil). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21 (t, 3H, CH_3, $^3J_{H-H}$ = 7.2 Hz), 1,26 (t, 3H, CH_3, $^3J_{H-H}$ = 7.2 Hz), 3.84 (m, 2H, CH_2), 4.16 (m, 4H, $2OCH_2$), 5.09 (d_{AB}, 1H, CH_2, J_{AB} = 9.1 Hz), 5.16 (d_{AB}, 1H, CH_2, J_{AB} = 9.1 Hz), 5.96 (d, 1H, NH, $^3J_{H-P}$ = 8.6 Hz), 7.30 (m, 6H, Ph), 7.47 (t, 2H, Ph, $^3J_{H-H}$ = 7.8 Hz), 7.59 (d, 2H, Ph, $^3J_{H-H}$ = 7.0 Hz), 7.81 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 15.51 (d, $^3J_{F-P}$ = 3.4 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 8.04 (d, $^3J_{P-F}$ = 3.4 Hz). Anal. Calcd for $C_{23}H_{26}F_3N_4O_5P$: C, 52.50; H, 4.94; N, 10.64. Found: C, 52.55; H, 5.31; N, 10.48.

4.2.9. Diethyl[1-{[(benzyloxy)carbonyl]amino}-2,2,2-trifluoro-1-(1H-1,2,3-triazole-4-yl methyl)ethyl]phosphonate (4)

To a solution of **3b** (0.2 mmol) in MeOH (3.6 ml), was added NaOH (1M aq solution, 3.6 ml). The reaction mixture was stirred at r.t. for 45 min and subsequently neutralized with 1N HCl (5 ml), diluted with H_2O (20 ml), and was extracted with ethyl acetate (3× 15 ml). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using acetone-hexane as an eluent. Yield: 75%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (q, 6H, $2CH_3$, $^3J_{H-H}$ = 8.1 Hz), 3.70 (m, 2H, CH_2), 4.15 (m, 2H, OCH_2), 5.12 (m, 2H, CH_2), 5.67 (br.s, 1H, CH-triazole), 6.08 (d, 1H, NH, $^3J_{H-H}$ = 10.0 Hz), 7.35 (br.s, 5H, Ph), 7.58 (br.s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 7.37, 8.23 (d, $^3J_{F-P}$ = 3.4 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 15.52 (d, $^3J_{P-F}$ = 2.9 Hz).

4.2.10. {4-[2-Amino-2-(diethoxyphosphoryl)-3,3,3-trifluoropropyl]-1H-1,2,3-triazole-1-yl}methyl pivalate (5)

To a solution of Cbz-protected aminophosphonate **3b** (1.6 mmol) in methanol (20 ml) 10% Pd/C (5 mol%) was added and slow stream of hydrogen was bubbled at room temperature. When TLC indicated no starting material (about 3 h), mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using acetone–hexane as an eluent. Yield: 80% (oil). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (s, 9H, $3CH_3$), 1,35 (q, 6H, $2CH_3$, $^3J_{H-H}$ = 6.5 Hz), 2.07 (br.s, 1H, NH), 3.39 (d, 2H, CH_2, $^3J_{H-H}$ = 10.7 Hz), 4.28 (m, 4H, $2OCH_2$), 6.21 (d, 1H, CH_2, J_{AB} = 10.6 Hz), 6.25 (d, 1H, CH_2, J_{AB} = 10.6 Hz), 7.77 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 5.57 (d, $^3J_{F-P}$ = 4.2 Hz). ^{31}P NMR ($CDCl_3$, 121 MHz): δ 18.23. Anal. Calcd for $C_{15}H_{26}F_3N_4O_5P$: C, 41.86; H, 6.09; N, 13.02. Found: C, 41.84; H, 5.91; N, 12.94.

4.2.11. {1-Amino-1-[(1-{[(2,2-dimethylpropanoyl)oxy]methyl}-1H-1,2,3-triazole-4-yl)methyl]-2,2,2-trifluoroethyl}phosphonic acid hydrobromide (6)

To a solution of aminophosphonate **5** (0.20 mmol) in dry chloroform (5 ml) was added $SiMe_3Br$ (0.80 mmol). The reaction mixture was kept at room temperature 72 h. Then, the volatiles were evaporated under reduced pressure. The residue was dissolved in ethanol (10 ml) and after 20 min at room temperature the solvent was evaporated under reduced pressure. This manipulation was repeated three times, then the residue was treated with ether to afford a solid product. Yield: 85% (solid), m.p. 58–60 °C. ^{1}H NMR (D_2O, 300 MHz): δ 1.05 (s, 9H, $3CH_3$), 3.48 (m, 2H, CH_2), 6.23 (s, 2H, CH_2),8.01 (s, 1H, CH-triazole). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 7.25. ^{31}P NMR ($CDCl_3$, 121 MHz): δ 4.28. Anal. Calcd for $C_{11}H_{19}F_3N_4O_5PBr$: C, 29.03; H, 4.29; N, 12.31. Found: C, 29.61; H, 4.59; N, 11.84.

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