Journal of Fluorine Chemistry 131 (2010) 1362–1367

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis of novel α-CF_3-trifluoroalanine derivatives containing *N*-(diethoxyphosphoryl)difluoroacetyl group

Romana Pajkert [a], Gerd-Volker Röschenthaler [b,*]

[a] Adam Mickiewicz University, Faculty of Chemistry, Grunwaldzka 6, 60-780 Poznan, Poland
[b] School of Engineering and Science, Jacobs University, Campus Ring 1, D-28759 Bremen, Germany

ARTICLE INFO

Article history:
Received 2 June 2010
Received in revised form 23 September 2010
Accepted 30 September 2010
Available online 7 October 2010

Keywords:
Fluorinated amino acids
Trifluoromethyl group
Acylimines
Aminoalkylation
Regioselectivity
Fluorine NMR

ABSTRACT

An efficient synthesis of biologically interesting α-CF_3-trifluoroalanine derivatives bearing *N*-(diethoxyphosphoryl)difluoroacetyl moiety in good yields has been elaborated. The key substrate, α-TFM-imino ester, prepared from methyl trifluoropyruvate and (diethoxyphosphoryl)difluoroacetamide, followed by dehydration, was subjected to regiospecific reactions with various nucleophiles, including organometallic, π-donor compounds and sodium borohydride. These novel products may find a viable application in the modification of peptides or serve as potential drug candidates.

1. Introduction

Fluorinated α-amino acids, due to their unique properties, have recently received extensive attention in biological and pharmaceutical studies [1]. This is directly connected with specific electronic and structural features of a fluorine atom such as high electronegativity, electron density, steric hindrance or small steric size that can change the acidity or basicity of neighbouring groups and the overall reactivity and stability of a molecule [2]. Moreover, the sensitivity of ^{19}F NMR spectroscopy along with large ^{19}F–^{1}H coupling constant renders fluorine incorporation a particularly powerful tool for investigations of biological processes.

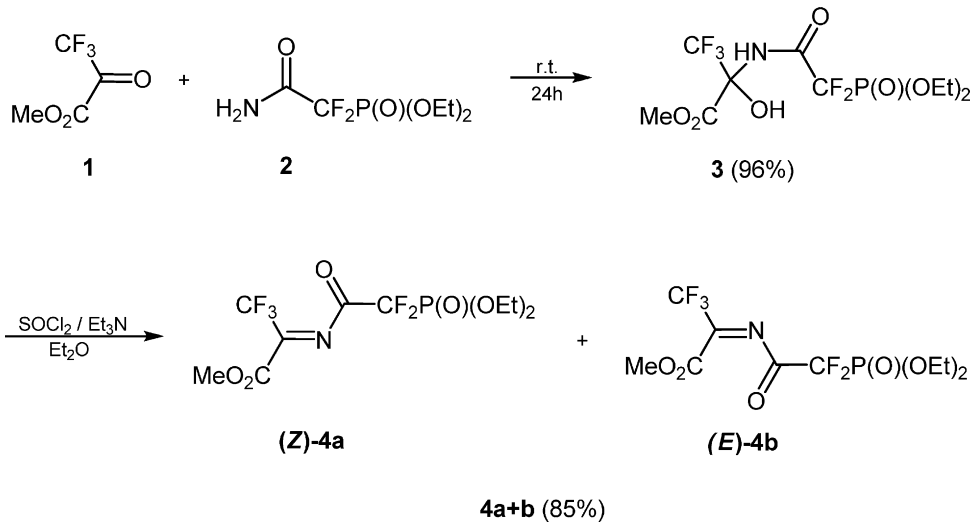
Among others, α-trifluoromethylated amino acid derivatives form a special class of non-natural CF_3-AAs of intensive synthetic activity. Their properties can be generalized as follows. (a) The low toxicity of the trifluoromethyl group combined with its high stability make it an attractive tool for pharmaceutical applications [3]. (b) The introduction of TFM-AAs into peptides exerts relevant polarization effects thus improving metabolic stability [4]. (c) The higher *in vivo* absorption rate in permeability through certain "body barriers" of TFM-modified peptides has been observed [3]. (d) The structural similarity of the CF_3 group to the isopropyl moiety reduces conformational flexibility, decreasing simultaneously the side effect deriving from low binding affinity [5]. (e) The ability of the fluorine atom to act as a weak hydrogen bond acceptor and high electronegativity of the CF_3 group makes the possibility of the creation of new interactions with enzymes or receptor subsites [6]. (f) Some α-TFM-AAs have been considered as irreversible inhibitors of pyridoxal phosphate dependent enzymes as well as various amino acid decarboxylases or transaminases and posses anticancer, antibacterial and antihypertensive properties [7].

Generally, there are two fundamental approaches to obtain α-trifluoromethyl amino acid derivatives. The first concept concerns direct fluorination of non-fluorinated materials and the second one assumes the use of functionalized fluorine-containing building blocks including fluorinated α-imino esters [8]. Although the first approach is more straightforward, the control of regio- and stereoselectivity of conducting processes is usually difficult to achieve. Therefore, the building block strategy has found widespread use in the designing of various non-natural α-CF_3-amino acids with enhanced biological activity.

It should be also noted, that the change of the biological activity could be accomplished not only through the introduction of fluorinated substituent but also towards the concomitant protection of the amino group by different substituents especially those containing phosphonate moiety. In this context, amino acid derivatives bearing *N*-oxalylamino or *N*-phosphonoformyl derivatives have been widely studied due to their high inhibitory activity towards herpetic diseases, AIDS and important metalloenzymes, including MMPs (matrix metalloproteinases) [9]. Although, no examples concerning synthesis and application of *N*-fluorophosphonate amino acid analogues have been already described.

* Corresponding author. Tel.: +49 4212003138.
E-mail address: g.roeschenthaler@jacobs-university.de (G.-V. Röschenthaler).

0022-1139/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2010.09.010



Scheme 1.

For these reasons, we were interested in the synthesis of α-CF_3-amino acid derivatives containing *N*-(diethoxyphosphoryl)difluoroacetyl moiety which could be potentially useful for the design of novel inhibitors of medically important enzymes. As it has been mentioned before, the presence of a trifluoromethyl group significantly changes the overall reactivity and properties of amino acids. However, the additional introduction of a difluoromethylenephosphonate substituent to α-CF_3-amino acid derivative could result in the creation of molecules with modified activity or interactions towards enzymes. Nevertheless, it is well-known that difluoromethylenephosphonates are considered as hydrolytically stable mimics of naturally occurring phosphate esters, which is directly connected with excellent electronic and structural similarity to the phosphate moiety and resulted from the relative resistance of fluorinated phosphonates to metabolic transformations [10].

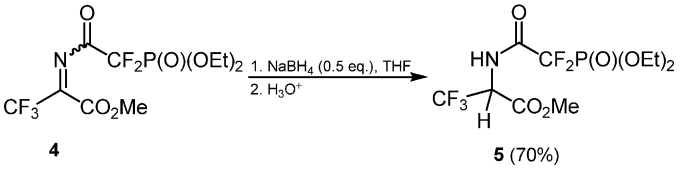
2. Results and discussion

One of the synthetic methodologies for the preparation of α-CF_3-trifluoroalanine analogues bearing *N*-substituent involves the use of appropriate imines derived from the commercially available methyl 3,3,3-trifluoropyruvate (MeTFP) and various amines and amides, followed by the elimination of water under the action of dehydrating agent [8].

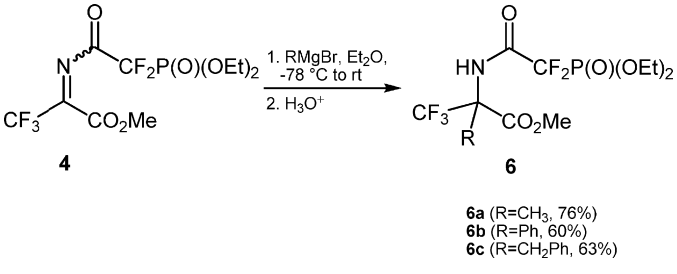
Hence, the novel imine containing *N*-(diethoxyphosphoryl)difluoroacetyl compound **4** was obtained in a two-step procedure by the condensation of MeTFP **1** with (diethoxyphosphoryl)difluoroacetamide **2** at room temperature in the absence of solvent. Further dehydration of the stable hemiamidal **3** using thionyl chloride/triethylamine in anhydrous ether at −20 °C afforded **4** in excellent yield (Scheme 1). As observed, the use of other standard agents such as: trifluoroacetic anhydride/pyridine or quinoline [11,12] gave the desired imine in only 30% yield.

As judged from spectral analysis, compound **4** is distinguished by the high electron deficiency of the azomethine bond and was obtained as a mixture of *E*/*Z*-isomers in a 1:3 ratio, according to the ^{19}F NMR data. Similarly to other acylimines of MeTFP, the extraordinary electrophilicity of the C=N double bond, stemming from the concurrent action of three strong electron-withdrawing groups (CF_3, COOMe and $CF_2P(O)(OEt)_2$), makes compound **4** especially reactive towards various nucleophilic and reducing agents. For this reason, the C=N bond undergoes rapid hydration with stoichiometric amount of water to form hydroxy adduct **3** when exposed on air and hence the usage of dry atmosphere for all manipulation with this compound was mandatory.

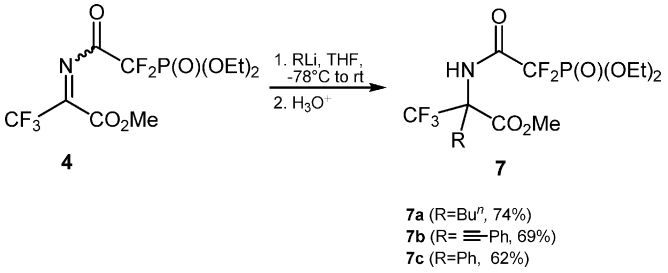
The synthesis of the simplest member of the trifluoroalanine family possessing *N*-(diethoxyphosphoryl)difluoroacetyl function has been accomplished *via* the reduction of C=N double-bond of the acylimine **4** with sodium borohydride. This reaction proceeded smoothly even at room temperature, in anhydrous THF using 0.5 equivalent of $NaBH_4$ giving the desired product **5** in a good yield. As monitored by ^{19}F and ^{31}P NMR, a higher excess of the reducing agent led to the partial decomposition of the difluoromethylenephosphonate moiety and produced compound **5** in only 20% (Scheme 2).



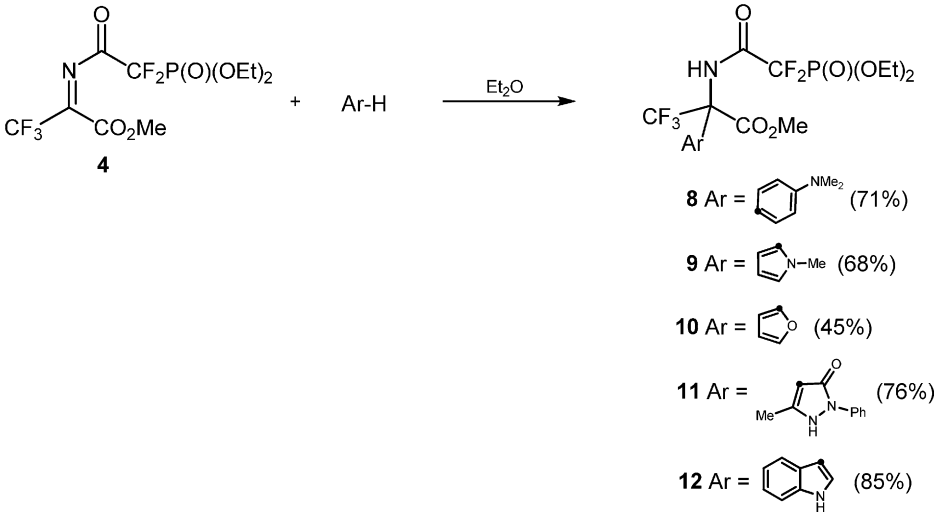
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

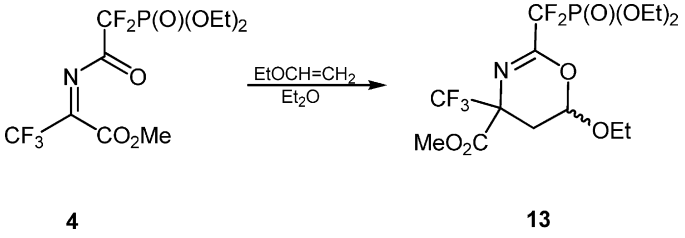
At the same time, other α-CF_3-trifluoroalanine derivatives have been prepared by the treatment of the corresponding Schiff base **4** with various nucleophiles such as: organomagnesium and lithium reagents and π-donor aromatic compounds.

The following alkylation and arylation reactions of acylimine 4 with Grignard reagents (methyl and phenyl magnesium bromide or benzyl magnesium chloride) were found to proceed smoothly at −78 °C in anhydrous diethyl ether, giving rise to appropriate α-CF_3-amino acid derivatives **6a**–**6c** in good yields (60–76%) (Scheme 3).

As expected, the best results were obtained when methyl magnesium bromide was used as a nucleophilic reagent, due to the small size of a methyl group in comparison to phenyl and benzyl substituents.

Under closely related conditions as for organomagnesium reagents, the nucleophilic addition of organolithium compounds to highly electrophilic azomethine C=N bond of imine **4** has regiospecifically occurred, providing to products **7a**–**c** in good yields. It should be however pointed out, that no traces of products of the competing nucleophilic substitution on the phosphonate group were detectable in the crude reaction mixture as it was usually observed in some reactions of organolithium compounds with difluoromethylenephosphonate-containing molecules (Scheme 4) [13].

Our further investigations in the synthesis of trifluoroalanine derivatives has revealed the Friedel-Crafts type electrophilic aminoalkylation of π-rich aromatic and heteroaromatic compounds with α-imino ester **4**, including indole, *N*-methylpyrrole, furan, *N*,*N*-dimethylaniline as well as 1-phenyl-3-methylpyrazol-5-one. This procedure required simple stirring of substrates in dry diethyl ether at room temperature until the ^{19}F NMR analysis show the complete consumption of the starting material **4** (usually 12–48 h) allowing the corresponding α-aryl(heteraryl)-β,β,β-trifluoroalanine derivatives **8**–**12**. In all cases, the *C*-amidoalkylation on aromatic ring occurred regioselectively to the sites of maximal π-electron density as shown in Scheme 5.



Scheme 6.

During the course of our research, we recognized that the acylimine **4** in reaction with non-aromatic unsaturated π-donor compound such as ethyl vinyl ether behaves as 1,3-dipolar azadiene bearing the conjugated C=N–C=O system. Therefore, when reacted with dienophile such as ethyl vinyl ether, the formation of dihydrooxazine **13** occurred as a result of [4+2]-cycloaddition (Scheme 6). As it has been known from the literature [12,14], these reactions usually proceed regiospecifically under mild conditions and give the corresponding dihydrooxazines as mixtures of two diastereoisomers. The formation of a mixture of isomers could be unambiguously explained due to the principles of the Diels–Alder reaction. In this case, the cycloaddition of unsymmetric dienophile to unsymmetric diene undergoes apparently *via* the *endo*- and *exo*-transition states producing dihydrooxazine **13** as a 1:1 mixture of *endo*- and *exo*-isomers.

3. Conclusions

In conclusion, the results presented here offer a convenient and easy route to various interesting α-CF_3-trifluoroalanine derivatives possessing the *N*-(diethoxyphosphoryl)difluoroacetyl moiety in good yields. These new compounds could exhibit potential biological activity or represent a new class of building blocks in the preparation of medicinally important peptides.

4. Experimental

4.1. General remarks

All reactions were carried out under an atmosphere of dry nitrogen. THF was freshly distilled from sodium benzophenone ketyl. All other reagents were distilled or recrystallized, if necessary. Diethyl 2-amino-1,1-difluoro-2-oxoethylphosphonate **2** was prepared according to the procedure described by Blackburn et al. [15]. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM) and TLCs using Merck silica gel 60 F_{254}. Visualization was achieved by UV light or by spraying with $Ce(SO_4)_2$ solution in 5% H_2SO_4. ^1H (200.13 MHz), ^{13}C (50.32 MHz), ^{19}F (188.31 MHz) and ^{31}P NMR (80.99 MHz) have been achieved on a Bruker Avance DPX-200 spectrometer in $CDCl_3$ as a solvent. TMS was the internal standard in ^1H NMR; $CFCl_3$ was used as a reference for

^{19}F NMR and 85% H_3PO_4 in ^{31}P NMR. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. ^{31}P NMR spectra were broadband decoupled from hydrogen nuclei. Mass spectra were recorded on a Varian MAT CH7A instrument at 70 eV. Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected.

4.2. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoro-2-hydroxy propanoate (3)

A mixture of methyl 3,3,3-trifluoropyruvate (11.7 g, 7.6 mL, 0.07 mol) and amide (10 g, 0.05 mol) was stirred at room temperature for 24 h. The excess of MeTFP was removed *in vacuo* and the crude product was washed with CCl_4 to give pure hemiamidal **3**. Yield: 96%, white solid, m.p. 68–70 °C.

^{1}H NMR ($CDCl_3$): δ 8.09 (br.s., N*H*), 5.46 (br.s., O*H*), 4.39 (dq, 5 lines, $^3J_{HH} \sim {}^3J_{HP}$ 7.4 Hz, 4H, OCH_2), 3.95 (s, 3H, OCH_3), 1.38 (t, 6H, $^3J_{HH}$ 6.6 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 165.67 (s, CO_2Me), 162.17 (td, $^2J_{CF}$ 26.0 Hz, $^2J_{CP}$ 18.2 Hz, $COCF_2$), 121.56 (q, $^1J_{CF}$ 279.8 Hz, CF_3), 113.40 (td, $^1J_{CF}$ 272.3 Hz, $^1J_{CP}$ 201.1 Hz, CF_2P), 80.99 (q, $^2J_{CF}$ 33.6 Hz, CCF_3), 66.65 (d, $^2J_{CP}$ 6.5 Hz, OCH_2), 66.53 (d, $^2J_{CP}$ 6.5 Hz, OCH_2), 55.36 (OCH_3), 16.60 (d, $^3J_{CP}$ 5.5 Hz, CH_3); ^{19}F NMR ($CDCl_3$): δ −119.40 (d, 2F, $^2J_{FP}$ 94.8 Hz, CF_2), −81.62 (s, 3F, CF_3); ^{31}P NMR ($CDCl_3$): δ 4.1 (t, $^2J_{PF}$ 94.4 Hz, CF_2P); HRMS Calculated for: $C_{10}H_{15}F_5NO_7P$ (M^+) 387.1944, found: 387.1948.

4.3. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetylimino)-3,3,3-trifluoropropanoate (4)

To a cold (−20 °C) solution of hemiamidal **3** (10 g, 0.026 mol) in anhydrous diethyl ether (120 mL), freshly distilled triethylamine (2.6 g, 3.6 mL, 0.026 mol) was added dropwise, followed by the addition of thionyl chloride (3.1 g, 1.9 mL, 0.026 mol). The resulting mixture was additionally stirred at −20 °C over a period of 3 h and the precipitated pyridinium chloride was filtered off under dry nitrogen. The filtrate was concentrated and distilled in a vacuum to give pure product **4** as a mixture of two isomers.

Yield: 85%, yellow oil, b.p. 110–115 °C (0.2 mmHg).

Minor isomer: ^{1}H NMR ($CDCl_3$): δ 4.36 (dq, 5 lines, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.4 Hz, OCH_2), 4.02 (s, 3H, OCH_3), 1.41 (t, 6H, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 172.20 (td, $^2J_{CF}$ 29.7 Hz, $^2J_{CP}$ 16.1 Hz, $COCF_2$), 155.26 (CO_2Me), 147.62 (q, $^2J_{CF}$ 36.6 Hz, CCF_3), 117.44 (q, $^1J_{CF}$ 279.4 Hz, CF_3), 112.07 (td, $^1J_{CF}$ 274.7 Hz, $^1J_{CP}$ 201.2 Hz, CF_2P), 66.34 (d, $^2J_{CP}$ 6.5 Hz, OCH_2), 55.61 (OCH_3), 16.61 (d, $^3J_{CP}$ 5.5 Hz, CH_3); ^{19}F NMR ($CDCl_3$): δ −118.94 (d, 2F, $^2J_{FP}$ 95.3 Hz, CF_2), −71.22 (s, 3F, CF_3); ^{31}P NMR ($CDCl_3$): δ 2.97 (t, $^2J_{PF}$ 95.5 Hz, CF_2P).

Major isomer: ^{1}H NMR ($CDCl_3$): δ 4.36 (dq, 5 lines, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.4 Hz, OCH_2), 3.95 (s, 3H, OCH_3), 1.41 (t, 6H, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 172.20 (td, $^2J_{CF}$ 29.7 Hz, $^2J_{CP}$ 16.1 Hz, $COCF_2$), 161.36 (CO_2Me), 147.62 (q, $^2J_{CF}$ 36.6 Hz, CCF_3), 116.44 (q, $^1J_{CF}$ 279.4 Hz, CF_3), 112.56 (td, $^1J_{CF}$ 274.7 Hz, $^1J_{CP}$ 201.2 Hz, CF_2P), 66.61 (d, $^2J_{CP}$ 6.5 Hz, OCH_2), 55.64 (OCH_3), 16.61 (d, $^3J_{CP}$ 5.5 Hz, CH_3); ^{19}F NMR ($CDCl_3$): δ −118.94 (d, 2F, $^2J_{FP}$ 95.3 Hz, CF_2), −77.43 (s, 3F, CF_3); ^{31}P NMR ($CDCl_3$): δ 4.17 (t, $^2J_{PF}$ 93.8 Hz, CF_2P); HRMS Calculated for: $C_{10}H_{13}F_5NO_6P$ (M^+) 369.1794, found: 369.1789.

4.4. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoropropanoate (5)

To the solution of imine **4** (660 mg, 1.7 mmol) in dry THF (10 mL) cooled to 0 °C, sodium borohydride (32.16 mg, 0.85 mmol) was added in two portions. The reaction mixture was stirred overnight at room temperature under nitrogen, then carefully quenched with cold 1 M solution of HCl and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. After evaporation of solvents, the crude product was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate).

Yield: 70%, yellowish oil.

^{1}H NMR ($CDCl_3$): δ 7.45 (d, N*H*), 5.32 (q, $^3J_{HF}$ 6.7 Hz, *H*C-CF_3), 4.35 (dq, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 6.7 Hz, OCH_2), 3.91 (s, 3H, OCH_3), 1.40 (t, 6H, $^3J_{HH}$ 6.7 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 164.35 (q, $^3J_{CF}$ 8.5 Hz, CO_2Me), 162.08 (td, $^2J_{CF}$ 25.7 Hz, $^2J_{CP}$ 17.8 Hz, $COCF_2$), 122.40 (q, $^1J_{CF}$ 283.1 Hz, CF_3), 111.96 (td, $^1J_{CF}$ 272.3 Hz, $^1J_{CP}$ 201.6 Hz, CF_2P), 66.35 (d, $^2J_{CP}$ 6.9 Hz, OCH_2), 66.21 (d, $^2J_{CP}$ 7.0 Hz, OCH_2), 54.51 (OCH_3), 54.13 (q, $^2J_{CF}$ 33.2 Hz, CCF_3), 16.67 (d, $^3J_{CP}$ 5.5 Hz, CH_3); ^{19}F NMR ($CDCl_3$): δ −119.07 (d, 2F, $^2J_{FP}$ 95.7 Hz, CF_2), −73.32 (d, 3F, $^3J_{FH}$ 8.2 Hz, CF_3); ^{31}P NMR ($CDCl_3$): δ 4.08 (t, $^2J_{PF}$ 95.2 Hz, CF_2P); HRMS Calculated for: $C_{10}H_{15}F_5NO_6P$ (M^+) 371.1950, found: 371.1954.

4.5. General procedure for the preparation of 6

A solution of the Grignard reagent (3.2 M MeMgBr in THF for **5a**, 1 M PhMgBr in THF for **6b**, 1 M $PhCH_2Cl$ in Et_2O for **5c**; 1 mmol) was added dropwise to a stirred solution of imine **4** (330 mg, 0.9 mmol) in dry ether (10 mL) at −78 °C. After 1 h at that temperature the reaction was allowed to warm up to room temperature and the mixture was quenched with cold 1 M HCl. The organic layer was separated and washed with water. The aqueous layers were extracted with diethyl ether, the organic layers were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate.

4.5.1. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoro-2-methylpropanoate (6a)

Yield: 76%, colourless oil.

^{1}H NMR ($CDCl_3$): δ 7.90 (br.s., N*H*), 4.30 (dq, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.2 Hz, OCH_2), 3.85 (s, 3H, OCH_3), 1.86 (s, 3H, CH_3), 1.40 (t, 6H, $^3J_{HH}$ 6.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 165.40 (CO_2Me), 161.70 (td, $^2J_{CF}$ 25.0 Hz, $^2J_{CP}$ 18.1 Hz, $COCF_2$), 122.00 (q, $^1J_{CF}$ 287.3 Hz, CF_3), 112.80 (td, $^1J_{CF}$ 293.1 Hz, $^1J_{CP}$ 200.9 Hz, CF_2P), 66.45 (d, $^2J_{CP}$ 6.5 Hz, OCH_2), 59.30 (q, $^2J_{CF}$ 30.2 Hz, CCF_3), 54.74 (OCH_3), 16.73 (d, $^3J_{CP}$ 5.5 Hz, CH_3), 16.00 (CH_3); ^{19}F NMR ($CDCl_3$): δ −119.06 (d, 2F, $^2J_{FP}$ 95.7 Hz, CF_2), −77.21 (s, 3F, CF_3); ^{31}P NMR ($CDCl_3$): δ 4.75 (t, $^2J_{PF}$ 95.1 Hz, CF_2P); HRMS Calculated for: $C_{11}H_{17}F_5NO_6P$ (M^+) 385.2216, found: 385.2217.

4.5.2. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoro-2-phenylpropanoate (6b)

Yield: 60%, colourless oil.

^{1}H NMR ($CDCl_3$): δ 8.00 (br.s., N*H*), 7.47 (m, 5H, H_{Ar}), 4.35 (dq, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.2 Hz, OCH_2), 3.89 (s, 3H, OCH_3), 1.40 (t, 6H, $^3J_{HH}$ 6.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 165.92 (CO_2Me), 161.69 (td, $^2J_{CF}$ 25.0 Hz, $^2J_{CP}$ 18.1 Hz, $COCF_2$), 131.29, 129.98, 129.58, 126.88, 122.97 (q, $^1J_{CF}$ 287.3 Hz, CF_3), 113.62 (td, $^1J_{CF}$ 293.1 Hz, $^1J_{CP}$ 200.9 Hz, CF_2P), 66.54 (d, $^2J_{CP}$ 6.5 Hz, OCH_2), 66.48 (d, $^2J_{CP}$ 6.5 Hz, OCH_2), 65.10 (q, $^2J_{CF}$ 29.2 Hz, CCF_3), 54.46 (OCH_3), 16.73 (d, $^3J_{CP}$ 5.5 Hz, CH_3); ^{19}F NMR ($CDCl_3$): δ −118.66 (d, 2F, $^2J_{FP}$ 95.6 Hz, CF_2), −72.12 (s, 3F, CF_3); ^{31}P NMR ($CDCl_3$): δ 4.89 (t, $^2J_{PF}$ 95.1 Hz, CF_2P); HRMS Calculated for: $C_{16}H_{19}F_5NO_6P$ (M^+) 447.2909, found: 447.2911.

4.5.3. Methyl 2-benzyl-2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoro-2-propanoate (6c)

Yield: 63%, yellowish oil.

^{1}H NMR ($CDCl_3$): δ 7.56 (br.s., N*H*), 7.26 (m, 3H, H_{Ar}), 7.12 (m, 2H, H_{Ar}), 4.28 (m, 4H, OCH_2), 4.26 (d, 1H, $^2J_{HaHb}$ 14.0 Hz, CH_2), 4.20 (s, 3H, OCH_3), 3.46 (d, 1H, $^2J_{HbHa}$ 14.0 Hz, CH_2), 1.35 (t, 6H, $^3J_{HH}$ 6.6 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 166.47 (CO_2Me), 159.10 (td, $^2J_{CF}$ 24.8 Hz, $^2J_{CP}$ 17.6 Hz, $COCF_2$), 134.35, 131.37, 127.60, 125.87,

121.39 (q, $^1J_{CF}$ 288.1 Hz, *C*F$_3$), 112.69 (td, $^1J_{CF}$ 293.1 Hz, $^1J_{CP}$ 200.9 Hz, *C*F$_2$P), 66.29 (d, $^2J_{CP}$ 6.5 Hz, O*C*H$_2$), 65.30 (q, $^2J_{CF}$ 31.0 Hz, *C*CF$_3$), 54.60 (O*C*H$_3$), 34.40 (*C*H$_2$), 16.70 (d, $^3J_{CP}$ 5.5 Hz, *C*H$_3$); ^{19}F NMR (CDCl$_3$): δ −118.21 (d, 2F, $^2J_{FP}$ 96.8 Hz, C*F*$_2$), −73.50 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 4.51 (t, $^2J_{PF}$ 96.2 Hz, CF$_2$*P*); HRMS Calculated for: $C_{17}H_{21}F_5NO_6P$ (M^+) 461.3175, found: 461.3179.

4.6. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-2-(trifluoromethyl)hexanoate (7a)

n-BuLi (0.38 mL, 2.5 M solution in hexanes; 0.9 mmol) was added dropwise to a stirred solution of imine **4** (330 mg, 0.9 mmol) in anhydrous ether at −78 °C. After 2 h at −78 °C, the reaction was allowed to warm up to room temperature. The mixture was quenched with cold 1 M HCl, the organic layer was separated and washed with water. The aqueous phases were extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over MgSO$_4$ and the solvents removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1.

Yield: 74%, yellowish oil.

^{1}H NMR (CDCl$_3$): δ 7.56 (br.s., N*H*), 4.34 (dq, 5 lines, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.2 Hz, OC*H*$_2$), 3.92 (s, 3H, OC*H*$_3$), 2.91 (dt, $^2J_{HaHb}$ 10.2 Hz, $^3J_{HaH}$ 3.9 Hz C*H*$_a$H$_b$CH$_2$), 2.26 (dt, $^2J_{HaHb}$ 10.5 Hz, $^3J_{HbH}$ 3.4 Hz, CH$_a$*H*$_b$CH$_2$), 2.13 (s, 3H, C*H*$_3$), 1.40 (t, 6H, $^3J_{HH}$ 7.8 Hz, OCH$_2$C*H*$_3$), 1.32 (m, C*H*$_2$), 1.04 (m, C*H*$_2$), 0.93 (t, 3H, $^3J_{HH}$ 7.8 Hz, C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 167.21 (q, $^3J_{CF}$ 1.51 Hz, *C*O$_2$Me), 160.56 (td, $^2J_{CF}$ 24.6 Hz, $^2J_{CP}$ 17.6 Hz, *C*OCF$_2$), 124.01 (q, $^1J_{CF}$ 287.8 Hz, *C*F$_3$), 111.85 (td, $^1J_{CF}$ 272.7 Hz, $^1J_{CP}$ 200.8 Hz, *C*F$_2$P), 67.48 (q, $^2J_{CF}$ 29.6 Hz, *C*CF$_3$), 66.07 (d, $^2J_{CP}$ 6.5 Hz, OCH$_2$), 66.29 (d, $^2J_{CP}$ 6.5 Hz, OCH$_2$), 54.78 (OCH$_3$), 28.30 (CH$_2$), 25.58 (*C*H$_2$), 22.62 (CH$_2$), 16.69 (d, $^3J_{CP}$ 5.6 Hz, *C*H$_3$), 14.05 (CH$_3$); ^{19}F NMR (CDCl$_3$): δ −118.32 (d, 2F, $^2J_{FP}$ 97.1 Hz, C*F*$_2$), −75.07 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 4.72 (t, $^2J_{PF}$ 96.8 Hz, CF$_2$*P*); HRMS Calculated for: $C_{14}H_{23}F_5NO_6P$ (M^+) 427.3013, found: 427.3015.

4.7. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-4-phenyl-2-(trifluoromethyl)but-3-ynoate (7b)

n-BuLi (0.38 mL, 2.5 M solution in hexanes; 0.9 mmol) was added dropwise to a stirred solution of phenylacetylene (0.09 g, 0.1 mL, 0.9 mmol) in anhydrous ether at −78 °C. Then a solution of imine **4** (330 mg, 0.9 mmol) in 2 mL of dry Et$_2$O was carefully added. After 2 h at −78 °C, the reaction was allowed to warm up to room temperature. The mixture was quenched with cold 1 M HCl, the organic layer was separated and washed with water. The aqueous phases were extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over MgSO$_4$ and the solvents removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1.

Yield: 69%, yellowish oil.

^{1}H NMR (CDCl$_3$): δ 7.66 (br.s., N*H*), 7.52 (m, 2H, H$_{Ar}$), 7.32 (t, 3H, H$_{Ar}$), 4.35 (q, $^3J_{HP}$ 7.2 Hz, OC*H*$_2$), 3.97 (s, 3H, OC*H*$_3$), 1.40 (t, 6H, $^3J_{HH}$ 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 156.76 (*C*O$_2$Me), 155.40 (td, $^2J_{CF}$ 24.8 Hz, $^2J_{CP}$ 17.6 Hz, *C*OCF$_2$), 131.78, 127.98, 127.53, 123.45, 122.44, 122.39 (q, $^1J_{CF}$ 288.1 Hz, *C*F$_3$), 111.69 (td, $^1J_{CF}$ 293.1 Hz, $^1J_{CP}$ 200.9 Hz, *C*F$_2$P), 92.00, 84.48 (q, $^2J_{CF}$ 31.0 Hz, *C*CF$_3$), 66.29 (d, $^2J_{CP}$ 6.5 Hz, OCH$_2$), 53.40 (OCH$_3$), 16.61 (d, $^3J_{CP}$ 5.6 Hz, *C*H$_3$); ^{19}F NMR (CDCl$_3$): δ −118.74 (dd, 2F, $^2J_{FP}$ 95.2 Hz, $^4J_{FH}$ 1.2 Hz, C*F*$_2$), −75.34 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 4.42 (t, $^2J_{PF}$ 95.1 Hz, CF$_2$*P*); HRMS: Calculated for: $C_{18}H_{19}F_5NO_6P$ 471.08702, found: 471.08729.

4.8. General procedure for the reactions with π-donor aromatic compounds (8–10 and 12)

To a cold (0 °C) solution of imine **4** (1.3 mmol) in dry diethyl ether, an equimolar amount of *N*-methylpyrrole, furan or *N*,*N*-dimethylaniline was added. The resulting mixture was warm to room temperature and stirred until ^{19}F NMR analysis indicated the full conversion of imine **4** (usually 12–48 h). The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 3:1).

4.8.1. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-2-(4(dimethylamino)phenyl)-3,3,3-trifluoropropanoate (8)

Yield: 71%, yellow oil.

^{1}H NMR (CDCl$_3$): δ 7.90 (br.s., N*H*), 7.13 (d, 2H, H$_{Ar}$), 6.71 (d, 2H, H$_{Ar}$), 4.35 (dq, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.2 Hz, OC*H*$_2$), 4.00 (s, 3H, OC*H*$_3$), 3.72 (s, 3H, C*H*$_3$), 3.18 (s, 3H, C*H*$_3$), 1.38 (t, 6H, $^3J_{HH}$ 6.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 164.99 (*C*O$_2$Me), 159.45 (td, $^2J_{CF}$ 25.0 Hz, $^2J_{CP}$ 18.1 Hz, *C*OCF$_2$), 149.33, 139.8, 129.00, 122.80 (q, $^1J_{CF}$ 287.3 Hz, *C*F$_3$), 113.62 (td, $^1J_{CF}$ 293.1 Hz, $^1J_{CP}$ 200.9 Hz, *C*F$_2$P), 112.47, 67.10 (q, $^2J_{CF}$ 29.2 Hz, *C*CF$_3$), 66.48 (d, $^2J_{CP}$ 6.5 Hz, OCH$_2$), 54.30 (OCH$_3$), 39.80 (CH$_3$), 16.73 (d, $^3J_{CP}$ 5.5 Hz, CH$_3$); ^{19}F NMR (CDCl$_3$): δ −118.70 (d, 2F, $^2J_{FP}$ 95.7 Hz, C*F*$_2$), −72.16 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 4.61 (t, $^2J_{PF}$ 95.1 Hz, CF$_2$*P*); HRMS Calculated for: $C_{18}H_{24}F_5N_2O_6P$ (M^+) 490.3588, found: 490.3592.

4.8.2. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoro-2-(1-methyl-1H-pyrrol-2-yl)propanoate (9)

Yield: 68%, yellow oil.

^{1}H NMR (CDCl$_3$): δ 7.42 (br.s., N*H*), 6.81 (br.s., H-5), 6.61 (t, 1H, $^3J_{HH}$ 2.6 Hz, H-4), 6.25 (br.s., 1H, H-3), 4.35 (dq, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.8 Hz, OC*H*$_2$), 3.82 (s, 3H, OC*H*$_3$), 3.66 (s, 3H, NC*H*$_3$), 1.41 (t, 6H, $^3J_{HH}$ 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 165.66 (*C*O$_2$Me), 160.40 (td, $^2J_{CF}$ 24.8 Hz, $^2J_{CP}$ 17.6 Hz, *C*OCF$_2$), 123.50 (q, $^1J_{CF}$ 288.1 Hz, *C*F$_3$), 123.19, 121.44, 113.69, 107.56, 112.73 (td, $^1J_{CF}$ 293.1 Hz, $^1J_{CP}$ 200.9 Hz, *C*F$_2$P), 66.34 (d, $^2J_{CP}$ 6.5 Hz, OCH$_2$), 64.41 (q, $^2J_{CF}$ 31.0 Hz, *C*CF$_3$), 53.82 (OCH$_3$), 36.99 (*C*H$_3$), 16.61 (d, $^3J_{CP}$ 5.6 Hz, *C*H$_3$); ^{19}F NMR (CDCl$_3$): δ −118.67 (d, 2F, $^2J_{FP}$ 95.2 Hz, C*F*$_2$), −73.75 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 4.83 (t, $^2J_{PF}$ 95.41 Hz, CF$_2$*P*); HRMS Calculated for: $C_{15}H_{20}F_5N_2O_6P$ (M^+) 450.09823, found 450.09815.

4.8.3. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoro-2-(furan-2-yl)propanoate (10)

Yield: 45%, colourless oil.

^{1}H NMR (CDCl$_3$): δ 7.96 (br.s., N*H*), 7.51 (br.s., 1H, H-5), 6.76 (t, 1H, $^3J_{HH}$ 2.6 Hz, H-4), 6.32 (br.s., 1H, H-3), 4.38 (dq, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.8 Hz, OC*H*$_2$), 3.72 (s, 3H, OC*H*$_3$), 1.40 (t, 6H, $^3J_{HH}$ 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 163.38 (*C*O$_2$Me), 160.20 (td, $^2J_{CF}$ 24.8 Hz, $^2J_{CP}$ 17.7 Hz, *C*OCF$_2$), 134.00, 123.45 (q, $^1J_{CF}$ 288.1 Hz, *C*F$_3$), 123.19, 113.69, 104.74, 112.73 (td, $^1J_{CF}$ 293.1 Hz, $^1J_{CP}$ 200.9 Hz, *C*F$_2$P), 66.34 (d, $^2J_{CP}$ 6.5 Hz, OCH$_2$), 64.41 (q, $^2J_{CF}$ 31.0 Hz, *C*CF$_3$), 53.82 (OCH$_3$), 16.61 (d, $^3J_{CP}$ 5.6 Hz, *C*H$_3$); ^{19}F NMR (CDCl$_3$): δ −118.70 (d, 2F, $^2J_{FP}$ 95.2 Hz, C*F*$_2$), −73.70 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 4.80 (t, $^2J_{PF}$ 95.4 Hz, CF$_2$*P*); HRMS Calculated for: $C_{14}H_{17}F_5NO_7P$ (M^+) 437.1835, found 437.1839.

4.9. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoro-2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)propanoate (11)

A mixture of imine (500 mg, 1.3 mmol) and 1-phenyl-3-methylpyrazol-5-one (225 mg, 1.3 mmol) in dry diethyl ether (10 mL) was stirred overnight at room temperature. The white precipitate was filtered off and washed with diethyl ether to give pure product.

Yield: 76%, white solid, m.p. 82–86 °C.

^{1}H NMR (CDCl$_3$): δ 11.82 (br.s., N*H*), 7.50 (br.s., N*H*), 7.31 (m, 6H, H$_{Ar}$), 4.26 (dq, 5 lines, 4H, $^3J_{HH} \sim {}^3J_{HP}$ 7.2 Hz, OC*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 2.13 (s, 3H, C*H*$_3$), 1.33 (t, 6H, $^3J_{HH}$ 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 165.38 (*C*O$_2$Me), 162.08 (*C*ONPh), 161.10 (td, $^2J_{CF}$

25.0 Hz, $^{2}J_{CP}$ 17.4 Hz, *C*OCF$_2$), 146.53, 134.74, 129.47, 127.49 (C=*C*CH$_3$), 121.70, 121.39 (q, $^{1}J_{CF}$ 288.1 Hz, *C*F$_3$), 111.69 (td, $^{1}J_{CF}$ 293.1 Hz, $^{1}J_{CP}$ 200.9 Hz, *C*F$_2$P), 92.84 (*C*=CCH$_3$), 66.43 (d, $^{2}J_{CP}$ 6.5 Hz, O*C*H$_2$), 66.29 (d, $^{2}J_{CP}$ 6.5 Hz, O*C*H$_2$), 63.15 (q, $^{2}J_{CF}$ 32.5 Hz, *C*CF$_3$), 53.64 (O*C*H$_3$), 16.60 (d, $^{3}J_{CP}$ 5.6 Hz, *C*H$_3$), 11.01 (*C*H$_3$); ^{19}F NMR (CDCl$_3$): δ −118.37 (dd, 2F, $^{2}J_{FP}$ 97.4 Hz, $^{4}J_{FH}$ 1.2 Hz, C*F*$_2$), −76.84 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 3.62 (t, $^{2}J_{PF}$ 96.6 Hz, CF$_2$*P*); HRMS Calculated for: $C_{20}H_{23}F_5N_3O_7P$ (M^+) 543.3784, found: 543.3790.

4.10. Methyl 2-(2-(diethoxyphosphoryl)-2,2-difluoroacetamido)-3,3,3-trifluoro-2-(1H-indol-3-yl)propanoate (12)

Yield: 85%, colourless oil.

^{1}H NMR (CDCl$_3$): δ 12.42 (br.s., N*H*), 7.8 (br.s., N*H*), 7.7 (d, 1H, H$_{Ar}$), 7.5 (d, 1H, H$_{Ar}$), 7.2 (m, 3H, =C*H*), 4.29 (m, 4H, OC*H*$_2$), 3.82 (s, 3H, OC*H*$_3$), 1.33 (t, 6H, $^{3}J_{HH}$ 6.6 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 166.47 (*C*O$_2$Me), 160.40 (td, $^{2}J_{CF}$ 24.8 Hz, $^{2}J_{CP}$ 17.6 Hz, *C*OCF$_2$), 136.65, 125.40 (q, $^{3}J_{CF}$ 10.8 Hz, =*C*H), 124.51, 123.09, 121.39 (q, $^{1}J_{CF}$ 288.1 Hz, *C*F$_3$), 121.08, 119.17, 113.86, 111.69 (td, $^{1}J_{CF}$ 293.1 Hz, $^{1}J_{CP}$ 200.9 Hz, *C*F$_2$P), 109.89, 104.81, 98.99, 66.42 (d, $^{2}J_{CP}$ 6.5 Hz, O*C*H$_2$), 66.29 (d, $^{2}J_{CP}$ 6.5 Hz, O*C*H$_2$), 65.30 (q, $^{2}J_{CF}$ 31.0 Hz, *C*CF$_3$), 54.51 (O*C*H$_3$), 16.61 (d, $^{3}J_{CP}$ 5.58 Hz, *C*H$_3$); ^{19}F NMR (CDCl$_3$): δ −118.41 (d, 2F, $^{2}J_{FP}$ 96.2 Hz, C*F*$_2$), −72.45 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 4.62 (t, $^{2}J_{PF}$ 96.2 Hz, CF$_2$*P*); HRMS Calculated for: $C_{18}H_{20}F_5N_2O_6P$ (M^+) 486.3270, found: 486.3274.

4.11. Methyl 2-((diethoxyphosphoryl)difluoromethyl)-6-ethoxy-4-(trifluoromethyl)-5,6-dihydro-4H-1,3-oxazine-4-carboxylate (13)

To a solution of imine **4** (330 mg, 0.9 mmol) in 5 mL of anhydrous diethyl ether at −20 °C, 0.085 mL (64 mg, 1 mmol) of ethyl vinyl ether was added. The mixture was slowly heated to room temperature and stirred additionally for 1 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 4:1).

Yield: 35%, colourless oil.

^{1}H NMR (CDCl$_3$): δ 4.55 (dd, $^{3}J_{HaH}$ 2.80 Hz, $^{3}J_{HbH}$ 2.80 Hz, C*H*), 4.39 (dq, 5 lines, 4H, $^{3}J_{HH} \sim {}^{3}J_{HP}$ 7.2 Hz, OC*H*$_2$), 3.87 (s, 3H, OC*H*$_3$), 3.72 (dq, 2H, C*H*$_2$), 2.50 (dd, $^{2}J_{HaH}$ 14.2 Hz, $^{3}J_{HaH}$ 3.0 Hz, C*H*$_a$), 3.11 (dd, $^{2}J_{HbHa}$ 14.4 Hz, $^{3}J_{HbHa}$ 9.0 Hz, C*H*$_b$), 1.43 (t, 6H, $^{3}J_{HH}$ 6.60 Hz, OCH$_2$C*H*$_3$), 1.24 and 1.19 (t, 3H, C*H*$_3$); ^{13}C NMR (CDCl$_3$): δ 167.06 (*C*O$_2$Me), 160.78 (td, $^{2}J_{CF}$ 25.1 Hz, $^{2}J_{CP}$ 16.7 Hz, *C*OCF$_2$), 123.93 (q, $^{1}J_{CF}$ 290.6 Hz, *C*F$_3$), 113.05 (td, $^{1}J_{CF}$ 293.1 Hz, $^{1}J_{CP}$ 200.9 Hz, *C*F$_2$P), 100.26, 66.23 and 66.02 (d, $^{2}J_{CP}$ 6.5 Hz, O*C*H$_2$), 64.63, 64.00 (q, $^{2}J_{CF}$ 30.4 Hz, *C*CF$_3$), 54.51 (O*C*H$_3$), 33.74, 16.73 (d, $^{3}J_{CP}$ 5.9 Hz, *C*H$_3$), 15.79 and 15.16 (C*H*$_3$); ^{19}F NMR (CDCl$_3$): δ −118.05 (ABX system $^{2}J_{AX}$ 305.3, $^{2}J_{AB}$ 103.2 Hz, C*F*) and −118.4 (ABX system $^{2}J_{AX}$ 305.3, $^{2}J_{AB}$ 103.2 Hz, C*F*), −74.66 (s, 3F, C*F*$_3$); ^{31}P NMR (CDCl$_3$): δ 4.38 (t, $^{2}J_{PF}$ 96.07 Hz, CF$_2$*P*); HRMS Calculated for: $C_{14}H_{25}F_5NO_7P$ (M^+) 445.3166, found: 445.3170.

Acknowledgements

The Deutsche Forschungsgemeinschaft (Grant RO 362/41-1) is greatly acknowledged for the financial support of this work. We would like also to express our gratitude to Dr. T. Duelcks and D. Kemken (University of Bremen) for recording MS spectra and for the University of Bremen for working facilities.

References

[1] I. Ojima (Ed.), Fluorine in Medicinal Chemistry and Chemical Biology, 1st ed., Blackwell Publishing, 2009.
[2] (a) P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, Viley-VCH, Weinheim, 2004;
(b) D.B. Harper, D. O'Hagan, Nat. Prod. Rep. 11 (1994) 123.
[3] R.E. Banks, J.C. Tatlow, B.E. Smart (Eds.), Organofluorine Chemistry: Principles and Commercial Applications, Plenum Press, New York, 1994.
[4] B. Koksch, N. Sewald, H.-D. Jakubke, K. Burger, in: I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), Biomedical Frontiers of Fluorine Chemistry, ACS Series 639, 1996, pp. 42–58, Washington, DC;
(b) F. Bordusa, C. Dahl, H.-D. Jakubke, K. Burger, B. Koksch, Tetrahedron: Asymmetry 10 (1999) 307;
(c) A. Dal Pozzo, L. Muzi, M. Moroni, R. Rondanin, P. de Castiglione, P. Bravo, M. Zanda, Tetrahedron 54 (1998) 6019;
(d) A. Dal Pozzo, K. Dikovskaya, M. Moroni, M. Fagnoni, R. Vanini, R. Bergonzi, P. de Castiglione, P. Bravo, M. Zanda, J. Chem. Res. (S) (1999) 468.
[5] B. Koksch, N. Sewald, H.-J. Hofmann, K. Burger, H.-D. Jakubke, J. Pept. Sci. 3 (1997) 157.
[6] See for example: L.R. Scolnick, A.M. Clements, J. Liao, L. Crenshaw, M. Hellberg, J. May, T.R. Dean, D.W. Christianson, J. Am. Chem. Soc. 119 (1997) 850.
[7] R. Filler, Y. Kobayashi, L.M. Yagupolskii, Biomedical Aspects of Fluorine Chemistry, Elsevier, Amsterdam, 1993.
[8] For reviews, see:
(a) A. Sutherland, C.L. Willis, Nat. Prod. Rep. 17 (2000) 621;
(b) X.-L. Qiu, W.-D. Meng, F.-L. Qing, Tetrahedron 60 (2004) 6711;
(c) R. Smits, C. Cadicamo, K. Burger, B. Koksch, Chem. Soc. Rev. 37 (2008) 1727;
(d) S. Fustero, J.F. Sanz-Servera, J.L. Acena, M. Sánchez-Rosello, Synlett (2009) 525, and references cited therein.
[9] (a) B. Eriksson, A. Larsson, E. Helgstrand, N.-G. Johanson, B. Öberg, Biochim. Biophys. Acta 67 (1980) 53;
(b) B. Eriksson, B. Öberg, B. Wahren, Biochim. Biophys. Acta 696 (1982) 115;
(c) S.S. Leinbach, J.M. Reno, F.L. Lee, A.F. Isbell, J.A. Boezi, Biochemistry 15 (1976) 426;
(d) C. Crumpacker, Am. J. Med. 92 (Suppl. 2A) (1992) 2A–3S, references cited therein;
(e) P. Chrisp, S. Clissod, Drugs 41 (1991) 102.
[10] V.D. Romanenko, V.P. Kukhar, Chem. Rev. 106 (2006) 3868.
[11] (a) N.S. Osipov, A.S. Golubev, N. Sewald, T. Michel, A.N. Kolomiets, A.V. Fokin, K. Burger, J. Org. Chem. (1996) 7521;
(b) H. Skarpos, D.V. Vorob'eva, S.N. Osipov, I.L. Odinets, E. Breuer, G.-V. Röschenthaler, Org. Biomol. Chem. 4 (2006) 3669.
[12] S.N. Osipov, A.N. Kolomiets, A.V. Fokin, Russ. Chem. Rev. 61 (1992) 798.
[13] A. Henry-dit-Quesnel, L. Toupet, J.-C. Pommelet, T. Lequeux, Org. Biomol. Chem. 1 (2003) 2486.
[14] S.N. Osipov, A.S. Golubiev, N. Sewald, T. Michel, A.F. Kolomiets, A.V. Fokin, K. Burger, J. Org. Chem. (1996) 7521.
[15] G.M. Blackburn, D. Brown, S.J. Martin, J. Chem. Res. (S) 3 (1985) 92.