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Preparation and characterization of α-fluorinated-γ-aminophosphonates

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ABSTRACT

Herein we would like to present a synthetic approach to series of α-fluorinated-γ-aminophosphonates, which were prepared by hydrogenolysis of (*E*)-α-fluorovinylphosphonates. The reaction conditions of hydrogenolysis in the presence of palladium on carbon has been optimized. After conversion of aminophosphonates to their oxalte salts, the absolute configuration of the main diastereoisomer has been determined by X-ray analysis. α-Fluorinated-γ-aminophosphonates can be used as convenient precursors (''building blocks'') in the preparation of medicinally important analogues. As an example preparation of dipeptide analogues of α-fluorinated-γ-aminophosphonates was described.

1. Introduction

Aminophosphonates and aminophosphonic acids are important substrates in the study of biochemical processes. They have found a wide range of applications as enzyme inhibitors, agrochemicals and pharmaceuticals in the areas of biological and medicinal chemistry [1]. Due to the unique properties of fluorine atom, such as high electronegativity and electron density, its presence in aminophosphonates moiety can influence chemical reactivity, biological and metabolic stability, chemical bonding ability and solubility [2]. Recently, special interest has been focused on synthesis of fluorinated aminophosphonates due to their promising applications in bioorganic chemistry [3,4]. Many of these compounds exhibit antitumor, antibacterial and antifungal activities [5–9].

The Horner–Wadsworth–Emmons (HWE) olefination reaction of aldehydes or ketones with tetraalkyl fluoromethylenebisphosphonate is one of the synthetic method to get access to α-fluorinated aminophosphonates *via* α-fluorovinylphosphonates [10–15]. Herein we would like to present synthetic approach to series of α-fluorinated-γ-aminophosphonates, as well as their application in the synthesis of dipeptide analogues.

2. Results and discussion

The first step in the synthesis of α-fluorinated-γ-aminophosphonates was a electrophilic fluorination of tetraethyl methylenebisphosphonate with Selectfluor, leading to tetraethyl fluoromethylenebisphosphonate **1**, according to the Prestwich procedure [13]. Carbonyl compounds **2a–f** were prepared from α-amino acids (a-L-alanine, b-L-valine, c-L-leucine, d-L-isoleucine, e-L-phenylalanine, f-D-phenylglycine) in a three step procedure [16]. *N,N*-dibenzylamino aldehydes **2a–f** were then treated with lithiated carbanion generated by addition of *n*-BuLi to tetraethyl fluoromethylenebisphosphonate **1** at −78 °C in dry THF. The HWE olefination afforded (*E*)-α-fluorovinylphosphonates **3a–f** exclusively with good yields. Stereochemistry of compounds **3a–f** was confirmed by spectroscopic analysis [17,18]; *e.g.* **3e** gave a doublet of doublets at −125.74 ppm (dd, $^{2}J_{F-P}$ = 105.4, $^{3}J_{F-H}$ = 40.1 Hz) in ^{19}F NMR spectra. The observed $^{3}J_{F-H}$ = 40.1 Hz coupling constant is consistent to the coupling across the double bond between trans oriented hydrogen and fluorine atoms. Furthermore, analysis of the olefinic proton signal, appearing in the ^{1}H NMR spectra as a doublet of doublets of doublets also confirmed the stereochemistry of the obtained products. For the derivative **3e** this signal occurred at 6.13 ppm (ddd, $^{3}J_{H-F}$ = 40.1, $^{3}J_{H-H}$ = 10.2, $^{3}J_{H-P}$ 8.0 Hz). In this case 8.0 Hz coupling constant corresponds to *Z* relationship between the phosphorous and the olefinic hydrogen atom attached to the double bond (Scheme 1).

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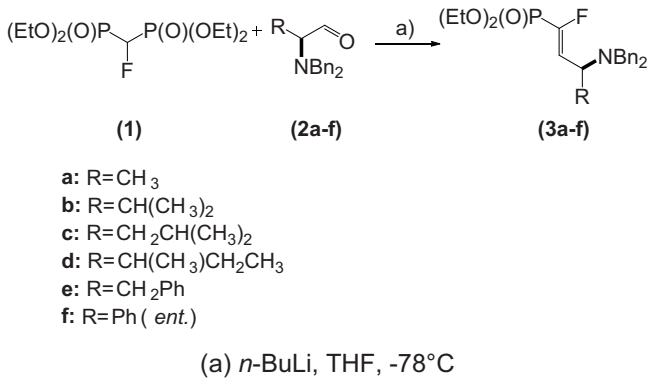
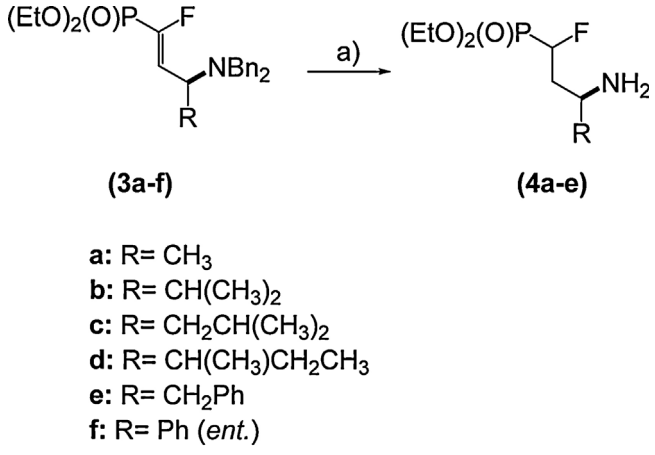


Scheme 1. Synthesis of (*E*)-fluorovinylphosphonates **3a–f**.

The next step in the synthesis was simultaneous hydrogenation of the double bond and removal of benzyl protecting groups (Scheme 2). First, **3a** derivative was chosen as a model substrate to optimize the reaction conditions (solvent, catalyst, catalyst concentration, temperature). The reaction has been carried out under hydrogen atmosphere, in various conditions (Table 1, entry 1–6). Unfortunately, we did not observe formation of the expected products. Next, we have decided to adapt the methodology of hydrogenation proposed by Whittaker, using trifluoroethanol (TFE) as a solvent [19]. Comparing to Whittaker method we increased the amount of the catalyst to 20% (v/v) and extended the reaction time to 3 days (Table 1, entry 7). Under such conditions, other (*E*)-fluorovinylphosphonates were also hydrogenated. After the reaction was completed the catalyst was filtered off and the crude products **4a–e** were purified using flash chromatography. The hydrogenation of diethyl (*R*,*E*)-(3-(dibenzylamino)-1-fluoro-3-phenylprop-1-en-1-yl)phosphonate **3f** resulted in a very complicated mixture of products, which was confirmed by the ^{19}F NMR and $^{31}P\{/^{1}H\}$ NMR analysis. We assume, that this is due to the fact that all phenyl groups of the molecule **3f** are located at the benzylic position on the nitrogen atom and are removed during the hydrogenation reaction.

The aminophosphonates with unprotected amino group **4a–e** were isolated as a mixture of two diastereoisomers, which were characterized by NMR spectroscopy. High diastereoselectivity of the reduction of double bond is due to the fact that hydrogenation takes place mainly from the least hindered face. In Table 2 we present the chemical shifts in ^{19}F and $^{31}P\{/^{1}H\}$ NMR spectra, and the ratio of diastereoisomers present in the mixture. The hydrogenation was also successfully accomplished by Beier approach (Table 1, entry 8), but with lower yield [20].



Scheme 2. Synthesis of α-fluorinated-γ-aminophosphonates **4a–e**.

Table 1
Optimization of reaction conditions for the formation of **4a–e** from **3a–f**.

Entry	Hydrogenation conditions				
	Cat.	v/v (%)	Solvent	Temperature	Time
1	10% Pd/C	5	EtOH	RT	3 days
2	10% $Pd(OH)_2/C$	5	EtOH	RT	3 days
3	20% $Pd(OH)_2/C$	5	EtOH	RT	3 days
4	20% $Pd(OH)_2/C$	5	MeOH	RT	3 days
5	10% Pd/C	5	AcOEt	RT	3 days
6	20% $Pd(OH)_2/C$	5	AcOEt	RT	3 days
7	10% Pd/C	20	TFE	RT	3 days
8	10% Pd/C	20	THF	50 °C	3 h

To determine the absolute configuration of the alpha carbon atom with respect to the fluorine atom of **4a–e**, we decided to convert the amines into their corresponding oxalate salts (Table 3) [21]. The reaction was conducted by addition of the anhydrous oxalic acid in dry solvent to a vigorously mixed solution of amines **4a–e** in a suitable media. For the compounds **4b–e** the reactions were carried out in anhydrous diethyl ether but for amine **4a** – poorly soluble in ether – tetrahydrofuran was used. The precipitation of salts **5a–e** proceeded immediately, however the reaction mixtures were left in a freezer overnight. The next day the oxalates **5a–e** were filtered off to give a white crystalline solid with a quantitative yield.

Unfortunately, the crystals were not suitable for X-ray diffraction studies, moreover we have tried recrystallization of the oxalate salts **5a–e** from acetone and water. Only the recrystallization of **5e** from hot water provided a single crystals suitable for X-ray analysis. The analysis confirmed the structure of the resulting compound **5e**. The crystals of a hydrate turned out to contain only (1*S*,3*S*)-diastereoisomer (Fig. 1)[1], supported by Flack parameter value of 0.024(35). The O1-P1-C31-C32-C33-C34 chain is in all-trans conformation (torsion angles 165°–177°), but phenyl substituent is almost perpendicular to the chain plane, the dihedral angle between these two planes is almost 78°. In the crystal structure the network of relatively strong O–H···O and N–H···O intermolecular hydrogen bonds, involving also water molecules, connect all the components of the crystal into three dimensional structure (Fig. 2).

We assume, on the basis of comparison of the signals intensity in the ^{19}F and $^{31}P\{/^{1}H\}$ NMR spectra of derivatives **4a–e** with those from **5a–e**, that after the hydrogenation reaction in each case the absolute configuration of alpha carbon atom with respect to the fluorine atom is also 1*S* for the main diastereoisomer.

The aminophosphonates **4a–e** also were converted into their dipeptide analogues **6a–e** in reaction with *N*-*tert*-butoxycarbonyl-L-phenylalanine in presence of *N*-hydroxybenzotriazole (HOBt) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) as coupling reagents (Scheme 3) [22]. The above mentioned synthesis of compounds **6a–e** is an example how to incorporate fluorinated aminophosphonate moieties into peptide chain.

In conclusion, we have demonstrated stereoselective synthesis of (*E*)-α-fluorovinylphosphonates. These compounds were converted to α-fluorinated-γ-aminophosphonates. We were able to

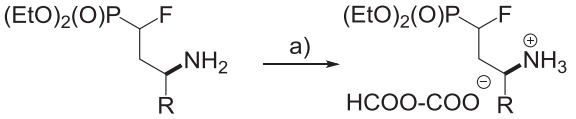
[1] Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, No. CCDC—995090. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk.

Table 2
NMR data and diastereomeric ratio of compounds **4a–e**.

	^{19}F NMR (ppm)	^{31}P{/^{1}H} NMR (ppm)	d.r.	Yield (%)
4a	−208.54 (dddd), −211.22 (dddd)[a]	18.61 (d),[a]17.79 (d)	90:10	87
4b	−206.48 (dddd), −211.88 (dddd)[a]	19.85 (d),[a]18.60 (d)	85:15	72
4c	−206.76 to −207.63 (m), −211.57 (dddd)[a]	18.95 (d),[a]17.97 (d)	80:20	69
4d	−206.08 (dddd), −211.97 (dddd)[a]	19.84 (d),[a]18.56 (d)	80:20	77
4e	−208.87 to − 209.86 (m), −211.48 (dddd)[a]	18.62 (d),[a]17.71 (d)	90:10	82

[a] Signal of the main distereoisomer.

Table 3
Synthesis of oxalate salts **5a–e**.



(4a-e) **(5a-e)**

a: R= CH_3
b: R= $CH(CH_3)_2$
c: R= $CH_2CH(CH_3)_2$
d: R= $CH(CH_3)CH_2CH_3$
e: R= CH_2Ph

(a) $(COOH)_2$, Et_2O or THF

	^{19}F NMR (ppm)	^{31}P{/^{1}H} NMR (ppm)	d.r.
5a	−209.25 (dddd), −210.37 (dddd)[a]	18.41 (d),[a]18.19 (d)	90:10
5b	−209.66 (dddd), −211.88 (dddd)[a]	18.46 (d),[a]17.99 (d)	85:15
5c	−209.51 to −210.22 (m), −210.62 (dddd)[a]	18.38 (d),[a]18.02 (d)	80:20
5d	−209.15 (dddd) −212.16 (dddd)[a]	20.48 (d),[a]19.96 (d)	80:20
5e	−209.78 to −210.36 (m), −210.41 to −211.15 (m)[a]	18.06 (d),[a]17.78 (d)	90:10

[a] Signal of the main distereoisomer.

determine the absolute configuration of the main diastereoisomer by converting them to the oxalate salts. Moreover α-fluorinated-γ-aminophosphonates can be used as convenient precursors for the new class of building blocks in the preparation of medicinally important analogues.

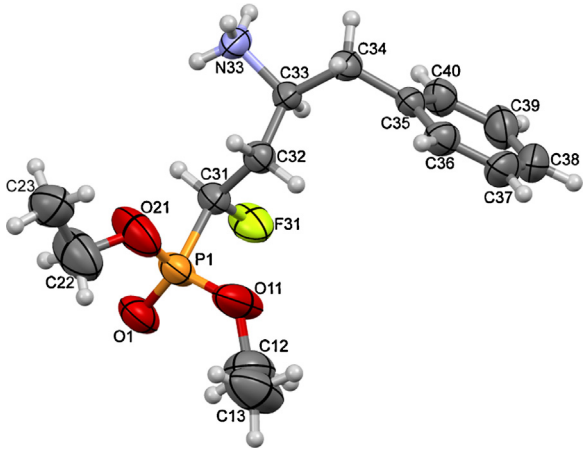


Fig. 1. Molecular structure of compound (1*S*,3*S*)-**5e** (ORTEP image).

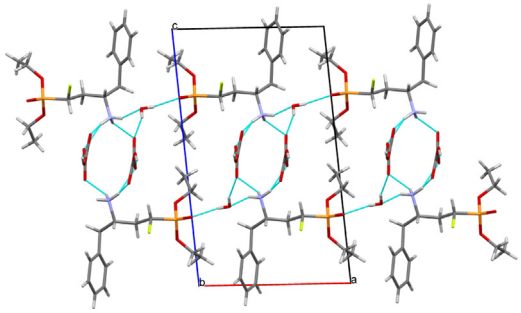
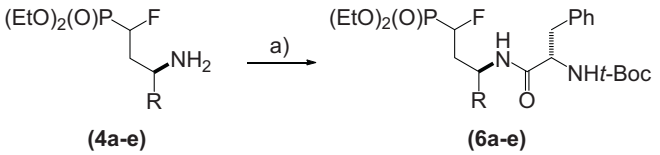


Fig. 2. The fragment of crystal packing as seen approximately along b—direction; thin blue lines denote the hydrogen bonds. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Experimental

3.1. General methods

^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were performed on Varian GEMINI 300 (300 MHz), Varian 400 (400 MHz), Bruker Avance 400 (400 MHz) or Bruker Avance 600 (600 MHz) spectrometers. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard ($\delta = 77.0$). Chemical shifts of ^{19}F NMR were expressed in parts per million upfiled from $CFCl_3$ as an internal standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{31}P NMR were expressed in parts per million downfield from 85% H_3PO_4 as an external standard ($\delta = 0$) in H_2O. ^{1}H, ^{13}C NMR chemical shifts are reported for the major diastereoisomer only. Mass spectra were recorded by electron impact (MS-EI) techniques using AMD-402 or Bruker 320-MS spectrometer. X-ray diffraction data were collected at room temperature by the ω-scan technique on Agilent Technologies four-circle SuperNova (Atlas detector) with mirror-monochromatized Cu *K*α radiation (λ = 1.54178 Å). The data were



(4a-e) **(6a-e)**

a: R= CH_3
b: R= $CH(CH_3)_2$
c: R= $CH_2CH(CH_3)_2$
d: R= $CH(CH_3)CH_2CH_3$
e: R= CH_2Ph

(a) *N-t*-Boc-Phe, DCC, HOBt, DMF, CH_2Cl_2

Scheme 3. Synthesis of dipeptide analogues **6a–e**.

corrected for Lorentz-polarization and absorption effects [23]. Accurate unit-cell parameters were determined by a least-squares fit of 3423 reflections of highest intensity, chosen from the whole experiment. The structures were solved with SIR92 [24] and refined with the full-matrix least-squares procedure on F^2 by SHELXL97 [25]. All non-hydrogen atoms were refined anisotropically, hydrogen atoms involved in strong hydrogen bonds were located in difference Fourier maps and isotropically refined, all other H atoms were placed in the calculated positions, and refined as 'riding model' with the isotropic displacement parameters set at 1.2 (1.5 for methyl groups) times the U_{eq} value for appropriate non-hydrogen atom. Reagent grade chemicals were used Solvents were dried by refluxing with sodium metal-benzophenone (THF), with $CaCl_2$ (CH_2Cl_2), NaH (Et_2O) and distilled under argon atmosphere. All moisture sensitive reactions were carried out under argon atmosphere using oven-dried glassware. Reaction temperatures below 0 °C were performed using a cooling bath (liquid N_2/hexane or CO_2/isopropanol). TLC was performed on Merck Kieselgel 60-F254 with EtOAc/hexane as developing systems, and products were detected by inspection under UV light (254 nm) and with a solution of potassium permanganate. Merck Kieselgel 60 (230–400 mesh) was used for column chromatography. Selectfluor was obtained from Aldrich.

3.2. General procedures

3.2.1. Tetraethyl fluoromethylenebisphosphonate **1**

^{1}H NMR (403 MHz, $CDCl_3$) δ 5.03 (dtd, J = 45.9, 13.6, 0.9 Hz, 1*H*, C<u>H</u>F), 4.36–4.23 (m, 8*H*, 4× O<u>C</u>H$_2$CH$_3$), 1.39 (td, J = 7.0, 0.9 Hz, 12*H*, 4× OCH$_2$C<u>H</u>$_3$). ^{19}F NMR (379 MHz, $CDCl_3$) δ −228.32 (dt, $J_{F-P,H}$ = 63.3, 45.9 Hz, 1F). ^{31}P{/^{1}H} NMR (163 MHz, $CDCl_3$) δ 11.07 (d, J_{P-F} = 63.3 Hz, 2P).

Tetraethyl fluoromethylenebisphosphonate **1** was prepared according to the Prestwich procedure [13].

3.2.2. N,N-*dibenzylamino aldehydes* ***2a–f***

3.2.2.1. N,N-dibenzylamino alcohols were prepared from α-amino acids [16]. The NMR data of all the synthesized *N,N*-dibenzylamino alcohols were in good agreement with the reported data from an alternative synthesis [16,26,27].

*3.2.2.2. N,N-dibenzylamino alcohols were next converted to corresponding N,N-dibenzylamino aldehydes **2a–f** [16].* Carbonyl compounds **2a–f** after extraction and evaporation of solvents, were sufficiently pure to be used directly in the HWE reaction.

3.2.3. Horner–Wadsworth–Emmons reaction

Lithium tetraethyl fluoromethylenebisphosphonate was prepared by addition of *n*-BuLi (3 mmol, 1.3 equiv., 2 M in pentane) to a stirred solution of tetraethyl fluoromethylenebisphosphonate **1** (2.3 mmol, 1.3 equiv.) in THF (1 mL) under an atmosphere of argon at −78 °C. After 10 min *N,N*-dibenzylamino aldehydes **2a–f** (1.74 mmol, 1 equiv.) in THF (1 mL) were added dropwise into the solution. Reaction mixtures were then slowly allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of saturated solution of NH_4Cl (10 mL). Crude products were extracted to AcOEt (3 × 10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified using flash chromatography (*n*-hexane: AcOEt 95:5 → 50:50).

3a: Yield: 73%, pale yellow oil, ^{1}H NMR (403 MHz, $CDCl_3$) δ 7.38–7.20 (m, 10*H*, Ar), 6.05 (ddd, J = 41.0, 9.3, 8.1 Hz, 1*H*, C<u>H</u>CFP), 4.28–4.10 (m, 4*H*, 2× O<u>C</u>H$_2$CH$_3$), 3.89 (dqd, J = 9.0, 6.9, 2.1 Hz, 1*H*, CH$_3$C<u>H</u>NBn$_2$), 3.79 (d, J = 13.8 Hz, 2*H*, O<u>C</u>H$_2$CH$_3$), 3.36 (d, J = 13.8 Hz, 2*H*, O<u>C</u>H$_2$CH$_3$), 1.43 (td, J = 7.1, 0.5 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.36 (td, J = 7.1, 0.6 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.27 (d, J = 6.8 Hz, 3*H*, C<u>H</u>$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.56 (dd, J = 276.4, 232.8 Hz, <u>C</u>FP), 139.61, 128.46, 128.11, 126.84, 125.57 (dd, J = 25.7, 6.3 Hz), 63.06 (d, J = 6.4 Hz), 63.04 (d, J = 4.7 Hz), 53.92, 48.50 (dd, J = 10.3, 1.9 Hz), 18.16, 16.27 (d, J = 6.1 Hz), 16.15 (d, J = 6.2 Hz). ^{19}F NMR (379 MHz, $CDCl_3$) δ −127.02 (dd, J = 105.1, 41.0 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ 4.86 (d, J = 105.1 Hz, 1P).

3b: Yield: 68%, pale yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.19 (m, 10*H*, Ar), 6.00 (ddd, J = 40.9, 10.7, 8.1 Hz, 1*H*, C<u>H</u>CFP), 4.35–4.08 (m, 4*H*, 2× O<u>C</u>H$_2$CH$_3$), 3.86 (d, J = 13.6 Hz, 2H, NC<u>H</u>$_a$H$_b$Ph), 3.26–3.16 (m, 1*H*, C<u>H</u>NBn$_2$), 3.21 (d, J = 13.7 Hz, 2*H*, NCH$_a$<u>H</u>$_b$Ph), 1.87 (qd, J = 13.1, 6.6 Hz, 3*H*, C<u>H</u>(CH$_3$)$_2$), 1.47 (td, J = 7.1, 0.5 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.37 (td, J = 7.1, 0.5 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.08 (d, J = 6.5 Hz, 3*H*, C<u>H</u>$_3$), 0.77 (d, J = 6.6 Hz, 3*H*, C<u>H</u>$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.67 (dd, J = 275.5, 231.2 Hz, <u>C</u>FP), 139.36, 128.64, 128.04, 126.81, 123.57 (dd, J = 25.7, 7.5 Hz), 63.06 (d, J = 5.4 Hz), 62.96 (d, J = 5.3 Hz), 59.51 (d, J = 9.5 Hz), 54.05, 29.10, 20.03, 19.98, 16.30 (d, J = 6.1 Hz), 16.11 (d, J = 6.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ −126.32 (dd, J = 106.8, 40.9 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ 4.88 (d, J = 106.8 Hz, 1P).

3c: Yield: 60%, pale yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.19 (10*H*, Ar), 6.02 (ddd, J = 40.9, 10.1, 8.0 Hz, 1*H*, C<u>H</u>CFP), 4.33–4.09 (m, 4*H*, 2× O<u>C</u>H$_2$CH$_3$), 3.83 (d, J = 13.6 Hz, 2*H*, NC<u>H</u>$_2$Ph), 3.79–3.75 (m, 1*H*, C<u>H</u>NBn$_2$), 3.26 (d, J = 13.6 Hz, 2*H*, NC<u>H</u>$_2$Ph), 1.82–1.59 (m, 2*H*, (CH$_3$)$_2$C<u>H</u>C<u>H</u>$_a$,CH$_b$), 1.46 (td, J = 7.1, 0.5 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.37 (td, J = 7.1, 0.6 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.26 (dt, J = 13.8, 4.9 Hz, 1*H*, (CH$_3$)$_2$CHCH$_a$C<u>H</u>$_b$), 0.79 (d, J = 6.6 Hz, 3*H*, C<u>H</u>$_3$), 0.65 (d, J = 6.5 Hz, 3*H*, C<u>H</u>$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.86 (dd, J = 275.8, 232.1 Hz, <u>C</u>FP), 139.37, 128.59, 127.95, 126.77, 124.36 (dd, J = 25.5, 7.0 Hz), 62.97 (d, J = 3.6 Hz), 62.92 (d, J = 3.7 Hz), 53.91, 50.52 (d, J = 9.7 Hz), 41.67, 24.35, 22.62, 21.85, 16.19 (d, J = 6.1 Hz), 16.04 (d, J = 6.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ −126.87 (dd, J = 106.1, 40.9 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ 4.85 (d, J = 106.2 Hz, 1P).

3d: Yield: 45%, pale yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.19 (m, 10*H*, Ar), 6.02 (ddd, J = 40.9, 10.7, 8.1 Hz, 1*H*, C<u>H</u>CFP), 4.36–4.07 (m, 4*H*, 2× O<u>C</u>H$_2$CH$_3$), 3.85 (d, J = 13.6 Hz, 2*H*, NC<u>H</u>$_a$H$_b$Ph), 3.34 (td, J = 10.8, 1.4 Hz, 1*H*, C<u>H</u>NBn$_2$), 3.21 (dd, J = 13.6, 1.2 Hz, 2*H*, NCH$_a$<u>H</u>$_b$Ph), 2.06–1.98 (m, 1*H*, C<u>H</u>CH$_3$), 1.75–1.60 (m, 1*H*, CH$_3$C<u>H</u>$_a$), 1.47 (dt, J = 7.1, 0.4 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.37 (dt, J = 7.1, 0.5 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.17–1.01 (m, 1*H*, CH$_3$C<u>H</u>$_b$), 0.74 (br. t, J = 7.0 Hz, 6*H*, 2×C<u>H</u>$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.65 (dd, J = 275.4, 231.3 Hz, <u>C</u>FP), 139.40, 128.81), 128.07, 126.86, 123.56 (dd, J = 25.7, 7.5 Hz), 63.06 (d, J = 5.6 Hz), 62.97 (d, J = 5.4 Hz), 57.71 (d, J = 9.5 Hz), 54.21, 35.04, 25.10, 16.33 (d, J = 6.1 Hz), 16.16 (d, J = 6.2 Hz), 15.91, 10.33. ^{19}F NMR (282 MHz, $CDCl_3$) δ −126.57 (dd, J = 107.5, 40.8 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ 4.97 (d, J = 107.5 Hz, 1P).

3e: Yield: 69%, pale yellow oil, ^{1}H NMR (403 MHz, $CDCl_3$) δ 7.33–7.17 (m, 13*H*, Ar), 7.04 (dd, J = 7.7, 1.7 Hz, 2*H*, Ar), 6.13 (ddd, J = 40.1, 10.2, 8.0 Hz, 1*H*, C<u>H</u>CFP), 4.23 (dqd, J = 8.4, 7.1, 1.4 Hz, 2*H*, O<u>C</u>H$_2$CH$_3$), 4.17–4.06 (m, 1*H*, PhCH$_2$C<u>H</u>NBn$_2$), 4.04–3.95 (m, 1*H*, OCH$_a$<u>H</u>$_b$), 3.93 (d, J = 13.8 Hz, 2*H*, NC<u>H</u>$_2$Ph), 3.82 (ddq, J = 10.1, 8.3, 7.1 Hz, 1*H*, O<u>C</u>H$_a$H$_b$), 3.37 (d, J = 13.8 Hz, 2*H*, NC<u>H</u>$_2$Ph), 3.09 (dd, J = 13.7, 7.3 Hz, 1H PhC<u>H</u>$_a$H$_b$), 2.83 (dd, J = 13.7, 8.4 Hz, 1*H*, PhCH$_a$<u>H</u>$_b$), 1.44 (td, J = 7.1, 0.6 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$), 1.24 (td, J = 7.1, 0.7 Hz, 3*H*, OCH$_2$C<u>H</u>$_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.43 (dd, J = 277.9, 229.6 Hz, <u>C</u>FP), 139.27, 138.10, 129.31, 128.55, 128.15, 128.11, 126.93, 126.20, 123.63 (dd, J = 25.8, 6.9 Hz), 63.18 (d, J = 5.4 Hz), 62.97 (d, J = 5.0 Hz), 54.47 (d, J = 10.0 Hz), 54.16, 39.04, 16.31 (d, J = 6.1 Hz), 16.06 (d, J = 6.5 Hz). ^{19}F NMR (379 MHz, $CDCl_3$) δ −125.74 (dd, J = 105.4, 40.1 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ 4.55 (d, J = 105.4 Hz, 1P).

3f: Yield: 64%, pale yellow oil, ^{1}H NMR (403 MHz, $CDCl_3$) δ 7.51–7.18 (m, 15*H*, Ar), 6.42 (ddd, J = 39.6, 10.1, 7.9 Hz, 1*H*, C<u>H</u>CFP), 4.97 (d, J = 10.2 Hz, 1*H*, C<u>H</u>NBn$_2$), 4.33–4.12 (m, 4*H*, 2× O<u>C</u>H$_2$CH$_3$), 3.76 (d, J = 13.6 Hz, 2*H*, NC<u>H</u>$_a$H$_b$Ph), 3.43 (d, J = 13.7 Hz, 2*H*, NCH$_a$<u>H</u>$_b$Ph),

1.45 (td, J = 7.1, 0.4 Hz, 3*H*, $OCH_2C\underline{H}_3$), 1.34 (td, J = 7.1, 0.4 Hz, 3*H*, $OCH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.28 (dd, J = 279.1, 231.7 Hz, $\underline{C}FP$), 139.77 (d, J = 1.6 Hz), 138.96, 128.57, 128.27, 128.13, 127.55, 127.34, 126.94, 121.97 (dd, J = 26.5, 5.4 Hz), 63.16 (d, J = 5.5 Hz), 63.14 (d, J = 5.6 Hz), 56.28 (dd, J = 10.3, 2.9 Hz), 53.78, 16.28 (d, J = 6.1 Hz), 16.10 (d, J = 6.1 Hz). ^{19}F NMR (379 MHz, $CDCl_3$) δ −125.32 (dd, J = 103.9, 39.5 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, $CDCl_3$) δ 4.19 (d, J = 104.1 Hz, 1P).

3.2.4. Hydrogenation reaction

Derivatives **3a–f** (1 equiv.) were dissolved in 5 mL of TFE and then 10% Pd/C (20% v/v) was added. The solutions were stirred under an atmosphere of hydrogen at room temperature for 3 days. After this time the catalyst was filtered off, the solvent was evaporated and the crude products were purified using flash chromatography ($CHCl_3$:MeOH 100:0 → 50:50).

4a: Yield: 87%, colorless oil ^1H NMR (300 MHz, $CDCl_3$) δ 5.05 (dddd, J = 47.2, 11.4, 3.4, 2.3 Hz, 1*H*, C$\underline{H}$FP), 4.28–4.15 (m, 4*H*, 2× $OC\underline{H}_2CH_3$), 3.23–3.12 (m, 1*H*, $NH_2C\underline{H}$), 2.04 (tddd, J = 8.4, 6.0, 5.4, 3.0 Hz, 1*H*, $CHFPC\underline{H}_aH_b$), 1.85–1.65 (m, 1*H*, $CHFPCH_a\underline{H}_b$), 1.64 (s, 2*H*, $N\underline{H}_2$), 1.37 (t, J = 7.1 Hz, 6*H*, 2× $OCH_2C\underline{H}_3$), 1.18 (d, J = 6.5 Hz, 3*H*, $C\underline{H}_3$). ^{19}F NMR (282 MHz, $CDCl_3$) δ minor diastereoisomer −208.54 (dddd, J = 74.4, 47.3, 40.0, 16.6 Hz, 1F), major diastereoisomer −211.22 (dddd, J = 74.6, 47.2, 43.5, 14.8 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 18.61 (d, J = 74.5 Hz, 1P), minor diastereoisomer 17.79 (d, J = 74.4 Hz, 1P).

4b: Yield: 72%, colorless oil ^1H NMR (300 MHz, $CDCl_3$) δ 5.28–5.05 (m, 1*H*, C$\underline{H}$FP), 4.33–4.10 (m, 4*H*, 2× $OC\underline{H}_2CH_3$), 2.82–2.73 (m, 1*H*, $NH_2C\underline{H}$), 2.13–1.92 (m, 1*H*, $CHFPC\underline{H}_aH_b$), 1.73–1.46 (m, 2*H*, $CHFPCH_a\underline{H}_b$, $C\underline{H}(CH_3)_2$), 1.37 (t, J = 7.1 Hz, 6*H*, 2× $OCH_2C\underline{H}_3$), 1.30 (s, 2*H*, $N\underline{H}_2$), 0.93 (d, J = 6.8 Hz, 3H, $C\underline{H}_3$), 0.89 (d, J = 6.8 Hz, 3*H*, $C\underline{H}_3$). ^{19}F NMR (282 MHz, $CDCl_3$) δ minor diastereoisomer −206.48 (dddd, J = 75.1, 46.9, 35.7, 18.3 Hz, 1F), major diastereoisomer −211.88 (dddd, J = 74.8, 46.7, 44.6, 14.2 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 19.85 (d, J = 74.8 Hz, 1P), minor diastereoisomer 18.60 (d, J = 75.3 Hz, 1P).

4c: Yield: 69%, colorless oil ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (dddd, J = 47.1, 11.6, 3.1, 2.3 Hz, 1*H*, C$\underline{H}$FP), 4.28–4.14 (m, 2× $OC\underline{H}_2CH_3$), 3.08–2.97 (m, 1*H*, $NH_2C\underline{H}$), 2.17–1.85 (m, 2*H*, $CHFPC\underline{H}_2$), 1.80–1.50 (m, 5*H*, $(CH_3)_2C\underline{H}C\underline{H}_2$, $N\underline{H}_2$), 1.36 (t, J = 7.1 Hz, 6*H*, 2× $OCH_2C\underline{H}_3$), 0.91 (t, J = 6.6 Hz, 6*H*, $(C\underline{H}_3)_2$). ^{19}F NMR (282 MHz, $CDCl_3$) δ minor diastereoisomer −206.76 to −207.63 (m, 1F), major diastereoisomer −211.57 (dddd, J = 74.6, 46.8, 44.4, 14.6 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 18.95 (d, J = 74.7 Hz, 1P), minor diastereoisomer 17.97 (d, J = 74.9 Hz, 1P).

4d: Yield: 77%, colorless oil ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (ddt, J = 46.9, 11.6, 2.1 Hz, 1*H*, C$\underline{H}$FP), 4.30–4.10 (m, 4*H*, 2× $OC\underline{H}_2CH_3$), 2.87 (dd, J = 11.0, 2.9 Hz, 1*H*, $NH_2C\underline{H}$), 2.13–1.87 (m, 1*H*, $CHFPC\underline{H}_aH_b$, 1*H*, $C\underline{H}CH_3$), 1.72–1.59 (m, 1*H*, $CH_3C\underline{H}_a$), 1.57–1.45 (m, 1*H*, $CHFPCH_a\underline{H}_b$), 1.38 (d, J = 7.1 Hz, 6*H*, 2× $OCH_2C\underline{H}_3$), 1.30 (br.s, $N\underline{H}_2$), 1.21–1.09 (m, 1*H*, $CH_3C\underline{H}_b$), 0.91 (t, J = 7.2 Hz, 3*H*, $C\underline{H}_3$), 0.89 (d, J = 6.7 Hz, 3*H*, $C\underline{H}_3$). ^{19}F NMR (282 MHz, $CDCl_3$) δ minor diastereoisomer −206.08 (dddd, J = 75.7, 47.1, 35.0, 18.4 Hz, 1F), major diastereoisomer −211.97 (dddd, J = 74.9, 46.9, 44.4, 14.3 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 19.84 (d, J = 74.9 Hz, 1P), minor diastereoisomer 18.56 (d, J = 75.4 Hz, 1P).

4e: Yield: 82%, colorless oil ^1H NMR (403 MHz, $CDCl_3$) δ 7.34–7.15 (m, 5*H*, Ar), 5.14 (dddd, J = 47.1, 11.5, 3.0, 2.3 Hz, 1*H*, C$\underline{H}$FP), 4.25–4.14 (m, 4*H*, 2× $OC\underline{H}_2CH_3$), 3.29–3.21 (m, 1*H*, $NH_2C\underline{H}$), 2.86 (dd, J = 13.5, 4.8 Hz, 2*H*, $NC\underline{H}_aH_bPh$), 2.55 (dd, J = 13.5, 8.6 Hz, 2*H*, $NCH_a\underline{H}_bPh$), 2.24–2.09 (m, 1*H*, $CHFPC\underline{H}_aH_b$), 1.83–1.63 (m, 1*H*, $CHFPCH_a\underline{H}_b$), 1.54 (s, 2*H*, $N\underline{H}_2$), 1.37–1.32 (m, 6*H*, 2× $OCH_2C\underline{H}_3$). ^{19}F NMR (379 MHz, $CDCl_3$) δ minor diastereoisomer −208.87 to −209.86 (m, 1F), major diastereoisomer −211.48 (dddd, J = 74,5, 47.8, 44.1, 14.4 Hz). $^{31}P\{/^1H\}$ NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 18.62 (d, J = 74.4 Hz, 1P), minor diastereoisomer 17.71 (d, J = 74.6 Hz, 1P).

3.2.5. Oxalate synthesis

A solution of derivatives **4a–e** (1 equiv.) in anhydrous diethyl ether or tetrahydrofuran were added dropwise to a vigorously stirred solutions of oxalic acid (1 equiv.) in suitable solvent. The mixtures were left overnight in a freezer. The next day, the precipitates were filtered off to give a white solid.

5a: White solid ^1H NMR (403 MHz, D_2O, TMS in $CDCl_{3\ ext}$) δ 5.38–5.19 (m, 1*H*, C$\underline{H}$FP), 4.34–4.24 (m, 4*H*, $OC\underline{H}_2CH_3$), 3.77–3.68 (m, 1*H*, $C\underline{H}NH_3^+$), 2.40–2.15 (m, 2*H*, $CHFPC\underline{H}_2$), 1.41 (d, J = 6.7 Hz, 3*H*, $C\underline{H}_3$), 1.37 (t, J = 7.1 Hz, 6*H*, 2× $OCH_2C\underline{H}_3$). ^{13}C NMR (101 MHz, D_2O, $CDCl_{3\ ext}$) δ 165.64 (s, C(O)), 85.34 (dd, J = 175.8, 173.1 Hz, $\underline{C}PF$), 65.36 (d, J = 7.0 Hz), 65.15 (d, J = 6.8 Hz), 45.00 (d, J = 15.3 Hz), 33.71 (d, J = 19.6 Hz), 17.75, 15.74, 15.69. ^{19}F NMR (121 MHz, D_2O, $CFCl_3$ in $CDCl_{3\ ext}$) δ minor diastereoisomer −209.25 (dddd, J = 76.2, 46.4, 44.3, 14.5 Hz, 1F), major diastereoisomer −210.37 (dddd, J = 64.6, 46.3, 38.7, 18.8 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, D_2O) δ major diastereoisomer 18.41 (d, J = 76.2 Hz, 1P), minor diastereoisomer 18.19 (d, J = 76.3 Hz, 1P).

5b: White solid ^1H NMR (300 MHz, D_2O, TMS in $CDCl_{3\ ext}$) δ 5.43–5.17 (m, 1*H*, C$\underline{H}$FP), 4.41–4.21 (m, 4*H*, $OC\underline{H}_2CH_3$), 3.57–3.36 (m, 1*H*, $C\underline{H}NH_3^+$), 2.50–1.97 (m, 2*H*, $CHFPC\underline{H}_2$), 1.49–1.42 (m, $(CH_3)_2C\underline{H}$), 1.39 (t, J = 7.1 Hz, 6*H*, 2× $OCH_2C\underline{H}_3$), 1.04 (t, J = 7.0 Hz, 6*H*, 2× $C\underline{H}_3$). ^{13}C NMR (75 MHz, D_2O, $CDCl_{3\ ext}$) δ 164.50 (s, C(O)), 85.25 (dd, J = 176.4, 173.0 Hz, $\underline{C}PF$), 65.40 (d, J = 7.1 Hz), 65.20 (d, J = 6.9 Hz), 53.49 (d, J = 12.4 Hz), 29.71, 29.44 (d, J = 19.5 Hz), 17.25, 17.06, 15.79, 15.72. ^{19}F NMR (282 MHz, D_2O, $CFCl_3$ in $CDCl_{3\ ext}$) δ minor diastereoisomer −209.66 (dddd, J = 76.5, 45.2, 39.7, 15.1, 1F), major diastereoisomer −211.88 (dddd, J = 75.7, 45.9, 38.9, 18.0 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, D_2O) δ major diastereoisomer 18.46 (d, J = 76.4 Hz, 1P), minor diastereoisomer 17.99 (d, J = 77.1 Hz, 1P).

5c: White solid ^1H NMR (403 MHz, D_2O, TMS in $CDCl_{3\ ext}$) δ 5.42–5.23 (m, 1*H*, C$\underline{H}$FP), 4.35–4.25 (4*H*, $OC\underline{H}_2CH_3$), 3.76–3.60 (m, 1*H*, $C\underline{H}NH_3^+$), 2.27 (m, 2*H*, $CHFPC\underline{H}_2$), 1.81–1.56 (m, 3*H*, $(CH_3)_2C\underline{H}C\underline{H}_2$), 1.38 (t, J = 7.0 Hz, 6*H*, 2× $OCH_2C\underline{H}_3$), 0.96 (t, J = 6.0 Hz, 6H, $(C\underline{H}_3)_2$). ^{13}C NMR (101 MHz, D_2O, $CDCl_{3\ ext}$) δ 164.34 (s, C(O)), 85.30 (dd, J = 174.7, 173.4 Hz, $\underline{C}PF$), 65.38 (d, J = 6.8 Hz), 65.18 (d, J = 6.8 Hz), 46.89 (d, J = 13.9 Hz), 40.58, 31.97 (d, J = 19.4 Hz), 23.86, 21.51, 21.32, 15.79, 15.74. ^{19}F NMR (282 MHz, D_2O, $CFCl_3$ in $CDCl_{3\ ext}$) δ minor diastereoisomer −209.51 to −210.22 (m, 1F), major diastereoisomer −210.62 (dddd, J = 77.2, 46.0, 41.0, 17.8 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, D_2O) δ major diastereoisomer 18.38 (d, J = 79.7 Hz, 1P), minor diastereoisomer 18.02 (d, J = 76.9 Hz, 1P).

5d: White solid ^1H NMR (300 MHz, D_2O, TMS in $CDCl_{3\ ext}$) δ 5.42–5.11 (m, 1*H*, C$\underline{H}$FP), 4.38–4.20 (m, 4*H*, 2× $OC\underline{H}_2CH_3$), 3.63–3.54 (m, 1*H*, $C\underline{H}NH_3^+$), 2.39–2.03 (m, $CHFPC\underline{H}_aH_b$, 1*H*, $C\underline{H}CH_3$), 1.94–1.78 (m, 1*H*, $CH_3C\underline{H}_a$), 1.53–1.42 (m, $CHFPCH_a\underline{H}_b$), 1.37 (t, J = 7.0 Hz, 6*H*, 2× $OCH_2C\underline{H}_3$), 1.31–1.23 (m, 1*H*, $CH_3C\underline{H}_b$), 1.00–0.95 (t, J = 7.3 Hz, 3*H*, $C\underline{H}_3$), 0.92 (d, J = 7.0 Hz, 3*H*, $C\underline{H}_3$). ^{13}C NMR (101 MHz, D_2O, $CDCl_{3\ ext}$) δ 164.64 (s, C(O)), 85.16 (dd, J = 176.6, 173.0 Hz), 65.36 (d, J = 7.0 Hz), 65.16 (d, J = 6.9 Hz), 51.51 (d, J = 12.8 Hz), 36.40, 28.50 (d, J = 19.6 Hz), 24.80, 15.77, 15.72, 13.02, 10.60. ^{19}F NMR (282 MHz, D_2O, $CFCl_3$ in $CDCl_{3\ ext}$)) δ minor diastereoisomer −209.15 (dddd, J = 76.2, 47.2, 33.5, 14.5, 1F), major diastereoisomer −212.16 (dddd, J = 76.5, 46.1, 37.9, 18.9 Hz, 1F). $^{31}P\{/^1H\}$ NMR (121 MHz, D_2O) δ major diastereoisomer 20.48 (d, J = 77.1 Hz, 1P), minor diastereoisomer 19.96 (d, J = 78.5 Hz, 1P).

5e: White solid ^1H NMR (300 MHz, D_2O, TMS in $CDCl_{3\ ext}$) δ 7.51–7.30 (m, 5*H*, Ar), 5.48–5.21 (m, 1*H*, C$\underline{H}$FP), 4.31–4.16 (m, 4*H*, $OC\underline{H}_2CH_3$), 3.97–3.85 (m, 1*H*, $C\underline{H}NH_3^+$), 3.10 (d, J = 7.3 Hz, 2*H*, $PhC\underline{H}_2$), 2.48–2.08 (m, 2*H*, $CHFPC\underline{H}_2$), 1.41–1.23 (m, 1*H*). ^{13}C NMR (75 MHz, D_2O, $CDCl_{3\ ext}$) δ 165.50 (s, C(O)), 135.15, 129.46, 129.25,

127.78, 85.20 (dd, J = 176.3, 173.2 Hz, CPF), 65.35 (d, J = 7.1 Hz), 65.15 (d, J = 6.9 Hz), 49.77 (d, J = 12.9 Hz), 37.85, 31.37 (d, J = 19.5 Hz), 15.74, 15.67. ^{19}F NMR (282 MHz, D_2O, $CFCl_3$ in $CDCl_3$ ext) δ minor diastereoisomer −209.78 to −210.36 (m, 1F), major diastereoisomer −210.41 to −211.15 (m, 1F). ^{31}P{/^{1}H} NMR (121 MHz, D_2O) δ major diastereoisomer 18.06 (d, J = 76.4 Hz, 1P), minor diastereoisomer 17.78 (d, J = 76.6 Hz, 1P). Crystal data: $(C_{14}H_{24}FNO_3P)^+\cdot(C_2HO_4)^-\cdot H_2O$, M_r = 411.36, monoclinic, $P2_1$, a = 10.3025(4)Å, b = 5.6308(2) Å, c = 17.5579(6) Å, β = 94.938(4)°, V = 1014.78(6) Å^3, Z = 2, d_x = 1.35g cm^{-3}, F(0 0 0) = 436, μ(Cu K_α) = 1.66 cm^{-1}. Agilent SuperNova diffractometer, λ(Cu K_α) = 1.54178 Å, 4277 reflections collected, 2953 unique (R_{int} = 2.03%), final R = 3.98%, wR2 = 10.99%, S = 1.028, $(\Delta\rho)_{max/min}$ in final ΔF map: 0.36/−0.24e Å^{-3}.

3.2.6. Dipeptide synthesis

To a cooled (0 °C) solution of derivatives **4a–e** (1.05 equiv.) in methylene chloride a solution of a blocked *N*-phenylalanine (1 equiv.), HOBt (1.25 equiv.) in a 3:7 CH_2Cl_2/DMF and DCC (1.25 equiv.) were added. Stirring was continued at this temperature for 30 min and then the solutions were stirred for 18 h at room temperature. The DCU was filtered off, and the filtrates were washed with cold solutions of 1 M NaOH, water, 1 M citric acid, water, 1 M $NaHCO_3$, water. The organic extracts were dried over anhydrous $MgSO_4$. Drying agent was filtered off and the solvent was evaporated. The crude products were purified by flash chromatography (*n*-hexane:AcOEt 50:50 → 40:60).

6a: Yield: 84%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.02 (m, 5*H*, Ar), 6.05 (br.d, J = 8.7 Hz, 1*H*, NH), 5.12 (br.d, J = 5.3 Hz, 1*H*, NH), 4.51 (dd, J = 47.1, 10.5 Hz, 1*H*, CHFP), 4.34–3.97 (m, 6*H*, 2× OCH_2CH_3, 2× CHNH), 3.04 (d, J = 7.0 Hz, 2*H*, CH_2Ph), 2.04–1.66 (m, 2*H*, CH_2CHF), 1.43–1.40 (s, 9*H*, $C(CH_3)_3$), 1.36 (t, J = 7.1 Hz, 6*H*, 2× OCH_2CH_3), 1.15 (d, J = 6.7 Hz, 3*H*, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.81, 155.30, 136.61, 129.21, 128.54, 126.86, 85.62 (dd, J = 180.4, 171.4 Hz, CFP), 79.98, 63.27 (d, J = 6.9 Hz), 62.85 (d, J = 6.8 Hz), 55.99, 41.91 (d, J = 15.7 Hz), 38.41, 36.37 (d, J = 19.8 Hz), 28.17, 20.87, 16.41 (d, J = 4.4 Hz), 16.35 (d, J = 4.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ minor diastereoisomer −207.50 to −208.56 (m, 1F), major diastereoisomer −209.23 to −210.11 (m, 1F). ^{19}F{/^{1}H} NMR (377 MHz, $CDCl_3$) δ minor diastereoisomer −207.94 (d, J = 74.8 Hz, 1F), major diastereoisomer −209.59 (d, J = 73.6 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 17.94 (d, J = 73.6 Hz, 1P), minor diastereoisomer 17.30 (d, J = 74.8 Hz, 1P). MS-EI $[M + 1]^+$ = 475 *m*/*z*.

6b: Yield: 70%, white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.11 (m, 5*H*, Ar), 5.91 (d, J = 9.7 Hz, 1*H*, NH), 5.06 (d, J = 8.1 Hz, 1*H*, NH), 4.41–4.29 (m, 1*H*, CHFP), 4.27–4.19 (m, 4*H*, 2× OCH_2CH_3), 4.17–4.05 (m, 4*H*), 4.00–3.91 (m, 1*H*, CHNH), 3.06 (dd, J = 13.6, 7.8 Hz, 1*H*, NCH_aH_bPh), 2.97 (dd, J = 13.5, 6.5 Hz, 1*H*, NCH_aH_bPh), 1.95–1.83 (m, 1*H*, CHFPCH_aH_b), 1.77–1.59 (m, 2*H*, CHFPCH_aH_b, $CH(CH_3)_2$) 1.36 (s, 9*H*, $C(CH_3)_3$), 1.30 (t, J = 7.1 Hz, 6*H*, 2× OCH_2CH_3), 0.79 (t, J = 7.0 Hz, 6*H*, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.24, 155.46, 136.72, 129.20, 128.61, 126.92, 85.44 (dd, J = 180.8, 171.3 Hz, CFP), 80.20, 63.30 (d, J = 6.6 Hz), 62.76 (d, J = 6.8 Hz), 56.29, 49.93 (d, J = 13.7 Hz), 37.72, 33.88, 32.55 (d, J = 20.5 Hz), 28.19, 18.85, 18.82, 16.44 (d, J = 3.6 Hz), 16.36 (d, J = 3.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ minor diastereoisomer −205.75 to −206.42 (m, 1F), major diastereoisomer −210.01 to −211.03 (m, 1F). ^{19}F{/^{1}H} NMR (377 MHz, $CDCl_3$) δ minor diastereoisomer −206.06 (d, J = 77.2 Hz, 1F), major diastereoisomer −210.44 (d, J = 74.1 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 18.67 (d, J = 74.1 Hz, 1P), minor diastereoisomer 18.15 (d, J = 76.8 Hz, 1P). MS-EI $[M]^+$ = 502 *m*/*z*.

6c: Yield: 65%, white solid, ^{1}H NMR (403 MHz, $CDCl_3$) δ 7.33–7.16 (m, 5*H*, Ar), 5.93 (d, J = 9.1 Hz, 1*H*, NH), 5.08 (s, 1*H*, NH), 4.48 (dd, J = 47.3, 10.4 Hz, 1*H*, CHFP), 4.31–4.25 (m, 1*H*, CHNH), 4.24–4.10 (m, 5*H*, 2× OCH_2CH_3, CHNH), 3.08 (dd, J = 13.6, 7.4 Hz, 1*H*, NCH_aH_bPh), 3.02 (dd, J = 13.8, 6.6 Hz, 1*H*, NCH_aH_bPh), 2.11–1.89 (m, 2*H*, CH_2CHF), 1.79–1.51 (m, 3*H*, $(CH_3)_2CHCH_2$), 1.41 (s, 9*H*, $C(CH_3)_3$), 1.35 (t, J = 7.1 Hz, 3*H*, OCH_2CH_3), 1.34 (t, J = 7.1 Hz, 3*H*, OCH_2CH_3), 0.89 (d, J = 6.5 Hz, 3*H*, CH_3), 0.86 (d, J = 6.6 Hz, 3*H*, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.85, 155.36, 136.60, 129.19, 128.55, 126.86, 85.51 (dd, J = 180.3, 171.3 Hz, CFP), 80.06, 63.21 (d, J = 6.8 Hz), 62.73 (d, J = 6.8 Hz), 56.07, 43.80 (d, J = 18.0 Hz), 37.87, 35.62 (d, J = 19.8 Hz), 28.14, 24.58, 22.89, 21.91, 16.40 (d, J = 4.6 Hz), 16.34 (d, J = 5.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ minor diastereoisomer −206.43 to −207.60 (m, 1F), major diastereoisomer −209.31 to −210.67 (m, 1F). ^{19}F{/^{1}H} NMR (377 MHz, $CDCl_3$) δ minor diastereoisomer −207.14 (d, J = 75.7 Hz, 1F), major diastereoisomer −209.96 (d, J = 74.0 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 18.53 (d, J = 74.1 Hz, 1P), minor diastereoisomer 18.23 (d, J = 75.8 Hz, 1P). MS-EI $[M^+]$ = 516 *m*/*z*.

6d: Yield: 58%, white solid, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5*H*, Ar), 5.90 (d, J = 9.6 Hz, 1*H*, NH), 5.05 (br. s, 1*H*, NH), 4.36 (dd, J = 47.7, 9.1 Hz, 1*H*, CHFP), 4.27 (dd, J = 14.8, 7.5 Hz, 1*H*, CHNH), 4.22–4.13 (m, 4*H*, 2× OCH_2CH_3), 4.12–4.06 (m, 1*H*, CHNH), 3.09 (dd, J = 13.6, 8.0 Hz, 1*H*, NCH_aH_bPh), 3.04 (dd, J = 13.7, 6.5 Hz, 1*H*, NCH_aH_bPh), 2.06–1.90 (m, 2*H*, CH_2CHF), 1.72–1.62 (m, 1*H*, $CHCH_3$), 1.57–1.49 (m, 1*H*, $CH_3CH_aH_b$), 1.42 (s, 9*H*, $C(CH_3)_3$), 1.36 (t, J = 7.1 Hz, 6*H*, 2× OCH_2CH_3), 1.10–1.00 (m, 1*H*, $CH_3CH_aH_b$), 0.87 (t, J = 7.3 Hz, 3*H*, $CH_3CH_aH_b$), 0.81 (d, J = 6.8 Hz, 3*H*, CH_3CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.03, 155.48, 136.72, 129.23, 128.66, 126.96, 85.42 (dd, J = 180.9, 171.1 Hz, CFP), 80.22, 63.33 (d, J = 6.9 Hz), 62.77 (d, J = 6.7 Hz), 56.25, 49.00 (d, J = 13.9 Hz), 38.51, 33.88, 31.65 (d, J = 20.6 Hz), 28.21, 24.90, 16.47 (d, J = 4.3 Hz), 16.41 (d, J = 5.4 Hz), 14.78 (d, J = 4.1 Hz), 11.54. ^{19}F NMR (379 MHz, $CDCl_3$) δ minor diastereoisomer −204.80 to −205.76 (m, 1F), major diastereoisomer −209.97 to −211.01 (m, 1F). ^{19}F{/^{1}H} NMR (377 MHz, $CDCl_3$) δ minor diastereoisomer −205.48 (d, J = 76.1 Hz, 1F), major diastereoisomer −210.43 (d, J = 74.1 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 18.69 (d, J = 74.1 Hz, 1P), minor diastereoisomer 18.15 (d, J = 76.8 Hz, 1P). MS-EI $[M^+]$ = 516 *m*/*z*.

6e: Yield: 79%, white solid, ^{1}H NMR (403 MHz, $CDCl_3$) δ 7.35–7.05 (m, 10*H*, Ar), 5.94 (br.d, J = 7.7 Hz, 1*H*, NH), 4.97 (br.s, 1*H*, NH), 4.82–4.62 (m, 1*H*, CHFP), 4.42–4.30 (m, 1*H*, CHNH), 4.29–4.20 (m, 1*H*, CHNH), 4.20–4.08 (m, 4*H*, 2× OCH_2CH_3), 2.99 (d, J = 7.1 Hz, 2*H*, CH_2Ph), 2.84 (dd, J = 13.6, 6.2 Hz, 1*H*, NCH_aH_bPh), 2.75 (dd, J = 13.7, 7.0 Hz, 1*H*, NCH_aH_bPh), 1.87–1.63 (m, 2*H*, CH_2CHF), 1.40 (s, 9*H*, $C(CH_3)_3$), 1.36–1.28 (m, 6*H*, 2× OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.96, 155.23, 136.88, 129.32, 129.20, 128.62, 128.46, 128.32, 126.94, 126.64, 85.33 (dd, J = 180.7, 171.4 Hz, CFP), 80.11, 63.32 (d, J = 6.8 Hz), 62.81 (d, J = 6.8 Hz), 56.14, 46.58 (d, J = 14.8 Hz), 40.71, 38.19, 33.77 (d, J = 20.0 Hz), 28.19, 16.39 (d, J = 2.8 Hz), 16.34 (d, J = 3.0 Hz). ^{19}F NMR (379 MHz, $CDCl_3$) δ minor diastereoisomer −206.12 to −207.02 (m, 1F), major diastereoisomer −209.79 to −210.64 (m, 1F). ^{19}F{/^{1}H} NMR (377 MHz, $CDCl_3$) δ minor diastereoisomer −205.04 (d, J = 72.8 Hz, 1F), major diastereoisomer −210.15 (d, J = 73.4 Hz, 1F). ^{31}P{/^{1}H} NMR (121 MHz, $CDCl_3$) δ major diastereoisomer 18.27 (d, J = 73.7 Hz, 1P), minor diastereoisomer 17.83 (d, J = 75.9 Hz, 1P). MS-EI $[M + 1]^+$ = 551 *m*/*z*.

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