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FULL PAPER

Regioselective fluorination of α-hydroxy-β-aminophosphonates by PyFluor

Marcin Kaźmierczak*[a],[b], Maciej Kubicki,[a] and Henryk Koroniak[a]

Abstract: In this paper, we report a simple protocol for the synthesis of α-fluoro-β-aminophosphonates by regioselective fluorination of α-hydroxy-β-aminophosphonates under mild conditions. The fluorination reactions were mediated by PyFluor reagent, and occurred with retention of configuration. As the main reaction products we received a serie of α-fluoro-β-aminophosphonates, which can be used as convenient precursors in the preparation of medicinally important analogues (e.g. dipeptide analogues).

Introduction

The chemistry of fluorinated aminophosphonates is a relatively new area of research, intensively developed over the past three decades.[1] In the eighties of the last century, Blackburn and coworkers along with McKenna and Shen suggested that the introduction of a halogen atom, in particular a fluorine in an alpha position with respect to the phosphorus atom, could result in the formation of mimics of naturally occurring phosphates.[2] Fluorinated phosphonates in relation to their non-fluorinated analogues are characterized by a reduced pKa value. Due to the presence of fluorine atom/s, these derivatives are showing larger dihedral angles in the C–X_2–P system, and the possibility of hydrogen bonds formation (C–F · · · H–X).[3] One should be aware that at the biological level even small changes in such properties often lead to significant changes in the activity of modified molecules, or even they can cause completely different substrate interactions with the receptor. These unique properties associated with fluorinated aminophosphonates make these materials attractive in bioorganic chemistry. Many of them exhibit antineoplastic activities[4], antibacterial[5], antiviral[6], insecticidal[7] and antifungal[8]. Also their derivatives - fluorinated aminophosphonic acids have found use as inhibitors of various enzymes.[9]

Due to the great interest in synthesis of organofluorine compounds, several remarkable reviews about introduction of fluorine atom(s) into organic molecules were published in recent years.[10] One of the most useful methods for introducing a fluorine atom into phosphonate molecules is to use the nucleophilic fluorinating reagents (Figure 1). In practice, the most commonly used procedure is the monofluorination reaction of α-hydroxyphosphonates. In most cases, the reaction occurs with inversion of configuration, however, its mechanism depends on substrate structure.[11] Among of many nucleophilic deoxyfluorinating reagents (diethylamino)sulfur trifluoride (DAST)[12] **1** and bis(2-methoxyethyl)aminosulfur trifluoride (DeoxoFluor)[13] **2** are the most widely used.[14] The only downside of these reagents is fact that they are fuming liquids and are difficult to handle in humid environment due to their violent reaction with water. Recently, (diethylamino)difluorosulfonium tetrafluoroborate (XtalFluor-E)[15] **3**, 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead)[16] **4** and 2-pyridinesulfonyl fluoride (PyFluor)[17] **5** have been introduced as stable and convenient deoxyfluorination reagents.

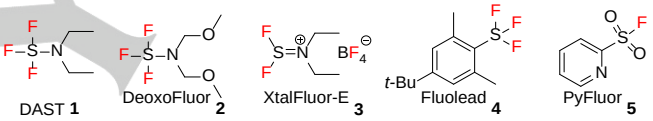
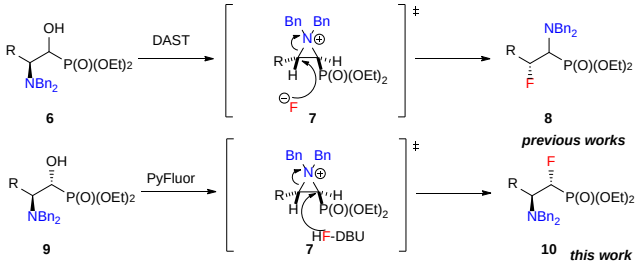


Figure 1. Examples of nucleophilic fluorinating reagents.

The nucleophilic fluorination of β-amino alcohols is a very challenging task. During the fluorination reaction a hydroxyl group from the starting material is converted into a derivative bearing a good leaving group, and the latter can be displaced through an S_Ni mechanism to generate aziridinium ions. These aziridinium ions are opened by F^- either on the less and/or more substituted carbon atom which leads to the formation of rearranged products.[18]

In our previous works we demonstrated DAST mediated preparation of β-fluoro-α-aminophosphonates **8**.[19] The proposed mechanism involved formation of an aziridinium ion **7** as the key step of the synthesis. We report herein a straightforward method of synthesis of new regio- and stereoisomers of **10**, where the R= CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2Ph *(ent.)* (Scheme 1).



Scheme 1. Nucleophilic fluorination of α-hydroxy-β-aminophosphonates.

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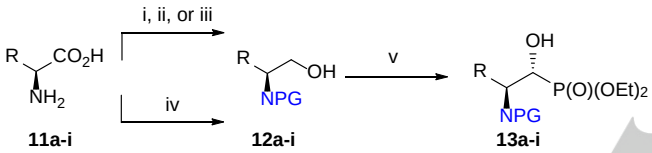
Results and Discussion

The goal of our study was to investigate whether the regioselectivity of the nucleophilic fluorination reaction of α-hydroxy-β-aminophosphonates can be controlled to afford the α-fluoro regioisomers as main products. In order to study the regioselectivity of the nucleophilic fluorination reaction of α-hydroxy-β-aminophosphonates, we examined five nucleophilic fluorinating reagents, as well as the effect of the protecting groups on the nitrogen atom in substrates. Our study required syntheses of α-hydroxy-β-aminophosphonates. The synthetic protocol was initiated from amino acids **11**. Reduction with $LiAlH_4$[20] followed by nitrogen protection using di-*tert*-butyl dicarbonate[21], benzyl chloroformate[22] or phthalic anhydride[23] gave amino alcohols **12a-c**. Compounds **12d-i** were obtained from amino acids using our previously reported procedure.[19a] Amino alcohols **12a-i** were then subjected to the Swern oxidation with oxalyl chloride, DMSO and triethylamine furnished aldehydes which were directly used into introduction of C-P bond with lithium diethyl phosphite in dry THF at -30°C (Scheme 2).[19a]



(a) R= -CH_2Ph, PG= *t*-Boc
(b) R= -CH_2Ph, PG= Cbz
(c) R= -CH_2Ph, PG= Pht
(d) R= -CH_2Ph, PG= Bn_2
(e) R= -CH_2Ph(ent.), PG= Bn_2
(f) R= -CH_3, PG= Bn_2
(g) R= -$CH(CH_3)_2$, PG= Bn_2
(h) R= -$CH_2CH(CH_3)_2$, PG= Bn_2
(i) R= -$CH(CH_3)CH_2CH_3$, PG= Bn_2

Scheme 2. Synthesis of α-hydroxy-β-aminophosphonates. Conditions: i (a) Phenylalanine (1 eq.), $LiAlH_4$ (2 eq.), THF, reflux 12h, (b) aminoalcohol (1 eq.), *t*-Boc_2O (1.1 eq.), H_2O, 35°C, 1h; ii (a) Phenylalanine (1 eq.), $LiAlH_4$ (2 eq.), THF, reflux 12h, (b) aminoalcohol (1 eq.), CbzCl (1.2 eq.), TEA (5 eq.), CH_2Cl_2 0°C → RT, 24h; iii (a) Phenylalanine (1 eq.), $LiAlH_4$ (2 eq.), THF, reflux 12h, (b) aminoalcohol (1 eq.), phthalic anhydride (1 eq.), TEA (0.1 eq.), PhMe, 130°C, 3h Dean -Stark conditions; iv (a) Amino acid (1 eq.), K_2CO_3 (2.2 eq.), BnBr (4 eq.), H_2O, 80°C, 24h, (b) benzyl derivative (1 eq.), $LiAlH_4$ (3 eq), Et_2O, 0°C → RT; v (a) *N*-protected aminoalcohol (1eq.), oxalyl chloride (1.2 eq.), DMSO (2 eq.), CH_2Cl_2, -78°C 30 min., TEA (4 eq.), RT 30min (b) aminoaldehyde (1 eq.), $LiP(O)(OEt)_2$ (1.3 eq.) THF, -30°C → RT.

α-Hydroxy-β-aminophosphonates **13a-i** were obtained as mixtures of two diastereoisomers (Table 1). Diastereoselectivity of this reaction is very well explained in the literature.[24] In order to study the regio- and diastereoselectivity of deoxyfluorination reaction we tried to isolate main diastereoisomers as pure compounds. Stereochemistry of resulting *α*-hydroxyphosphonates **13a-i** was confirmed by NOESY experiments, additionally X-Ray analyses for compounds **13c**, **13d**, **13g** were performed.

Table 1. Synthesis of **13a-i**.

R	PG	Cond.[a]	Product	Yield[b]	d.r.[c]
-CH_2Ph	*t*-Boc	i then v	13a	61	66:34
-CH_2Ph	Cbz	ii then v	13b	52	73:27
-CH_2Ph	Pht	iii then v	13c	72	99:1
-CH_2Ph	Bn_2	iv then v	13d	56	90:10
-CH_2Ph(ent.)[d]	Bn_2	iv then v	13e	50	99:1
-CH_3	Bn_2	iv then v	13f	71	86:14
-$CH(CH_3)_2$	Bn_2	iv then v	13g	38	94:6
-$CH_2CH(CH_3)_2$	Bn_2	iv then v	13h	69	99:1
-$CH(CH_3)CH_2CH_3$	Bn_2	iv then v	13i	34	92:8

[a] Conditions were given in experimental section. [b] Isolated yield of 13a-i from 12a-i. [c] Ratio after isolation based on ^{31}P NMR. [d] Configuration (1*S*,2*R*).

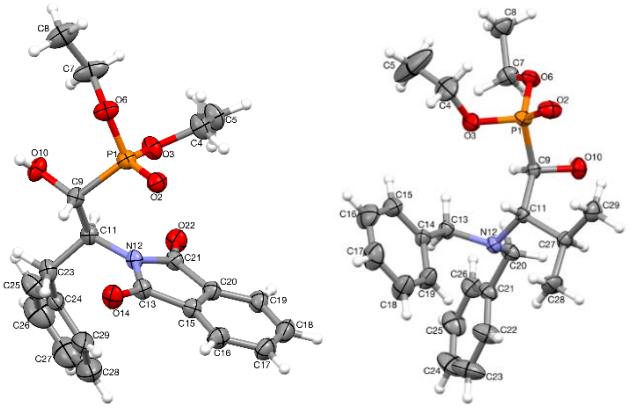


Figure 2. A perspective view of **13c** (left) and **13g** (right) with numbering scheme. Ellipsoids are drawn at the 30% probability level; hydrogen atoms are represented by spheres of arbitrary radii.

Figure 2 shows the perspective views of the molecules. Structural data for **13d** were reported recently.[25] Two of three compounds (**13d** and **13g)** crystallized in the chiral space groups as a single enantiomer (1*R*,2*S*). Compound **13c** in turn crystallized in the centrosymmetric space group $P2_1/c$, so both (1*R*,2*S*) and (1*S*,2*R*) enantiomers were present in the crystals. It should be noted, however, that the conformations of molecules are quite different, as can be seen from the torsion angles (Figure 3, for Table 1 see supplementary information). In the crystal structures intermolecular O-H···O hydrogen bonds (Table 2, see supplementary information) joined molecules into infinite chains, which in turn are connected by means of weaker interactions into three-dimensional structures (for instance, Figure 1, see supplementary information).

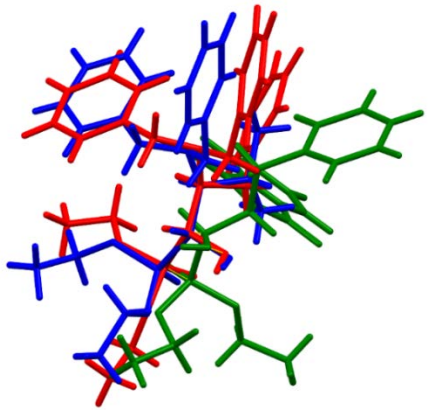
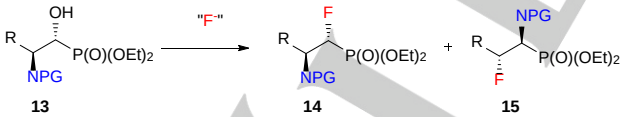


Figure 3. A comparison of conformations of molecules **13c**, **13d** and **13g**, POOOC groups were approximately fitted one onto another.

With series of α-hydroxy-β-aminophosphonates in hand, we selected phenylalanine derivatives **13a-d** with commonly used protecting groups such as *t*-Boc, Cbz, including Pht and Bn_2 as model substrates for number of deoxyfluorination reactions. Five "S-F" reagents were chosen in the current study: DAST **1**, Deoxofluor **2**, XtalFluor-E **3**, Fluolead **4**, PyFluor **5**. Deoxyfluorination reactions were performed using standard protocols, as well as with $SiMe_3$–morpholine additive. It is known that during such transformations basic additives like $SiMe_3$–amines, should enhance the fluoride nucleophilicity, consequently improving stereospecificity of the whole process.[26] These additives are usually combined with DAST **1** or Deoxofluor **2**. Moreover, during the fluorination XtalFluor-E **3** releases tetrafluoroboric acid instead of the DAST-generated HF. It means that XtalFluor-E **3** mediated reaction needs a promoter. 3HF·Et_3N or 2HF·Et_3N are usually used for this purpose. 2HF·Et_3N can be prepared *in situ* from 3HF·Et_3N and Et_3N. This reagent, as a source of fluoride ion, is more nucleophilic and less basic than 3HF·Et_3N itself.[27] On the other hand, Couturier demonstrated that combination of XtalFluor-E **3** with non-nucleophilic strong base, such as DBU, is an alternative protocol avoiding external source of fluoride.[28]



13 **14** **15**

(a) R= -CH_2Ph, PG= *t*-Boc
(b) R= -CH_2Ph, PG= Cbz
(c) R= -CH_2Ph, PG= Pht
(d) R= -CH_2Ph, PG= Bn_2
(h) R= -$CH_2CH(CH_3)_2$, PG= Bn_2

Scheme 3. Optimization of reaction conditions.

At first deoxyfluorination step was conducted on the model substrates **13a-d** (Scheme 3, Table 2). We expected to receive different ratios of resulting α-**14** and β-**15** fluorides. After completion of this step, ^{19}F NMR and ^{31}P NMR spectra of the crude mixture were collected. However, no fluorination took place as evidenced by the absence of signals on ^{19}F NMR when *N*-*t*-Boc-, *N*-Cbz- and *N*-Pht amino alcohols **13a-c** were used. On the other hand, ^{31}P NMR spectra showed that the signals from the substrates **13a-b** disappeared during the reaction and that new ones were formed, probably resulting from the decay of the intermediate - sulfonyl ester. In case of phthalimide derivative **13c** no reaction took place using DAST type reagents - ^{31}P NMR spectra showed only a signal from the substrate. In case of deoxyfluorination **13c** under PyFluor conditions (see supplementary information), the analysis of ^{31}P NMR spectra of the crude reaction mixture showed conversion of the substrate to a new product (δ_P = 15.06 ppm). Such ^{31}P NMR chemical shift is characteristic for α-tosyloxyphosphonates.[29] That data may suggest that formation of a sulfonyl ester occurred, but it has not been replaced by a fluoride ion. Ullervik just reported attempts to PyFluor mediated fluorination of 3,4-isopropylidene protected riboside, where similar sulfonate ester was formed and reaction did not proceed into the fluorinated product.[30]

Table 2. Optimization of reaction conditions.

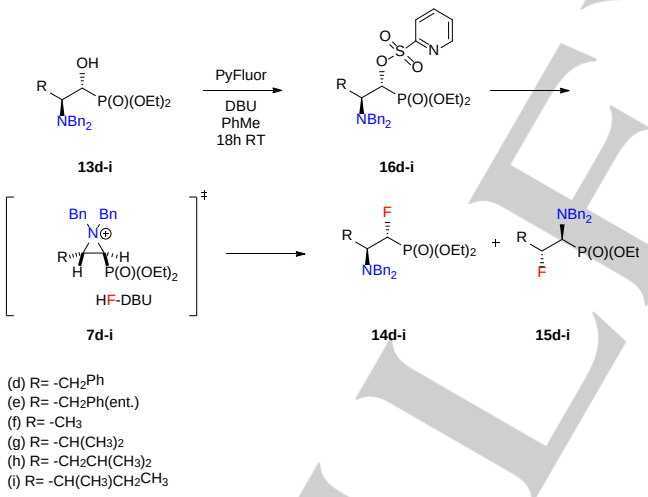
Substrate / reagent	**13a**[j]	**13b**[j]	**13c**[j]	**13d**[j]	**13h**[j]
1[a]	-	-	-	18:82	7:93
1+ TMS-morph.[b]	-	-	-	23:77	14:86
2[c]	-	-	-	10:90	10:90
2+ TMS-morph.[d]	-	-	-	1:99	13:87
3 + 3HF·Et_3N[e]	-	-	-	8:92	11:91
3 + 2HF·Et_3N[f]	-	-	-	9:91	8:92
3 + DBU[g]	-	-	-	13:87	14:86
4[h]	-	-	-	-	-
5[i]	-	-	-	**67:33**	**82:18**

Exact deoxyfluorination conditions were given in experimental section. [a] Alcohol (1 eq.), DAST (1.5 eq.), CH_2Cl_2, -78°C → RT. [b] Alcohol (1 eq.), DAST (3 eq.), TMS-morpholine (3 eq.), CH_2Cl_2, -78°C → RT. [c] Alcohol (1eq.), DeoxoFluor (1.05eq.), CH_2Cl_2, 0°C → RT. [d] Alcohol (1 eq.), DeoxoFluor (3 eq.), TMS-morpholine (3 eq.), CH_2Cl_2, -78°C → RT. [e] Alcohol (1 eq.), XtalFluor-E (1.5 eq.), Et_3N*3HF (2 eq.), CH_2Cl_2, -78°C → RT. [f] Alcohol (1 eq.), XtalFluor-E (1.5 eq.), Et_3N*3HF (2 eq.), Et_3N (1 eq.), CH_2Cl_2, -78°C → RT. [g] Alcohol (1 eq.), XtalFluor-E (1.5 eq.), DBU (1.5 eq.), CH_2Cl_2, -78°C → RT. [h] Alcohol (1 eq.), Fluolead (3 eq.), CH_2Cl_2, 0°C → RT. [i] Alcohol (1 eq.), PyFluor (1.2 eq.), DBU (2 eq.), PhMe, RT. [j] α/β-fluoride crude reaction ratio based on ^{31}P NMR and ^{19}F NMR.

At this stage of our research, only the derivative of dibenzyl *N*-protected phenylalanine **13d** underwent the fluorination reaction. Unfortunately under various deoxyfluorination conditions β-fluoride **15d** was obtained as a major product in most cases. Different regioselectivity of the deoxyfluorination process was only observed when a combination of PyFluor/DBU in toluene at RT was applied. In such conditions α-fluoride **14d** was received as a main product. Encouraged by our results for **13d** derivative, we decided to check the

possibility of controlling the regioselectivity of reaction for substrates bearing several R groups. Leucine derivative **13h** was then subjected to deoxyfluorination under the same conditions. Once again, the application of PyFluor/DBU environment allowed us to receive α-fluoride **14h** as a major regioisomer. Resultant ratios of products in deoxyfluorination reactions of α-hydroxy-β-aminophosphonates **13a-d**, **13h** are summarized in Table 2

We also checked whether the regioselectivity or yield of the deoxyfluorination reaction is dependent on the amount of DBU used. For this purpose, we performed series of experiments on a model alcohol **13d**, increasing the excess of DBU by 0.25 eq (1,25 → 2,75) without changing the other reaction conditions (PyFluor 1,2 eq., PhMe, RT, 24h). During the NMR analysis of the crude mixtures we did not observe any influence of the amount of base on the deoxyfluorination reaction. We then decided to change base from DBU to DMAP, TMP and morpholine, but under standard conditions the reaction failed. It confirms the assumption that during the reaction a Brønsted base is necessary. We would also like to point out that the purity of the solvent does not affect the yield of the process. The same results were obtained carrying out the reaction in toluene distilled directly before the PyFluor- mediated deoxyfluorination and taken directly from the bottle (HPLC grade). Furthermore, from our experience it is not necessary to maintain an inert atmosphere during the reaction.



Scheme 4. Synthesis of **14d-i**.

With this data in hand, we conducted the deoxyfluorination reaction on the other *N*-dibenzyl protected α-hydroxy-β-aminophosphonates (Scheme 4). In each case α-fluoro isomer was a major product (Table 3). Regioselectivity of the last steps ranged from 55:45 for alanine derivative **14f** to 82:18 in case of leucine derivative **14h**. Despite of similar polarity, the final α-**14d-i** and β-fluoro **15d-i** regioisomers could be easily separated by flash column chromatography techniques. Thus, we were able to isolate both regioisomers **14i** and **15i**. β-Fluoride **15i** was not published in our previous reports (see experimental section for NMR data). The stereochemistry of **15i** was confirmed by NMR studies and was in good agreement with our previous work.[19b] α-Fluoro isomers **14d-i** were isolated in moderate to good yields (42–68%).

Table 3. Synthesis of **14d-i**.

R (d.r. of substrate)	Product	α/β[a]	α/β[b]	Yield
-CH_2Ph (d.r.90:10)	d	67:33	99:1	58
-CH_2Ph(ent.)[c] (d.r. 99:1)	e	70:30	99:1	60
-CH_3 (d.r.86:14)	f	55:45	99:1	42
-$CH(CH_3)_2$ (d.r. 94:6)	g	76:24	99:1	61
-$CH_2CH(CH_3)_2$ (d.r. 99:1)	h	82:18	99:1	68
-$CH(CH_3)CH_2CH_3$ (d.r. 92:8)	i	62:38	99:1	51

[a] Crude reaction mixture ratio based on ^{31}P NMR and ^{19}F NMR. [b] Ratio after isolation based on ^{31}P NMR and ^{19}F NMR. [c] Configuration (1*S*,2*R*).

In order to establish the relative configuration of substituents in the synthesized serie of α-fluorides **14d-i**, careful analyses of vicinal coupling constants $^3J_{HH}$, $^3J_{HP}$, $^3J_{HF}$ (Figure 4), as well as ^{1}H-^{1}H, NOESY (Figure 5) and ^{19}F-^{1}H HOESY (Figure 6) interactions were made. The observed vicinal coupling constant between H^1 and H^2 hydrogens were in range from around 2Hz in case of **14f-g**, **14i** to 0 Hz for the rest of α-fluorides **14d-e**, **14h**. This observations lead to conclusion that dihedral angles between H^1 and H^2 hydrogens is around 90°.[31] Moreover, $^3J_{HF}$ values were in range of 29,5-35,1 Hz, which corresponds to dihedral angle around 150° in the H^2CCF system.[32] The proton and fluorine $^3J_{HH,}$, $^3J_{HF}$ values were extremely diagnostic to assign the relative configuration. These data unambiguously revealed the presence of *erythro*-diastereoisomer.[33] Finally, dihedral angle between phosphorous and hydrogen H^2 has to be around 30°, because it corresponds to observed vicinal coupling: 8,1-11 Hz.[34]

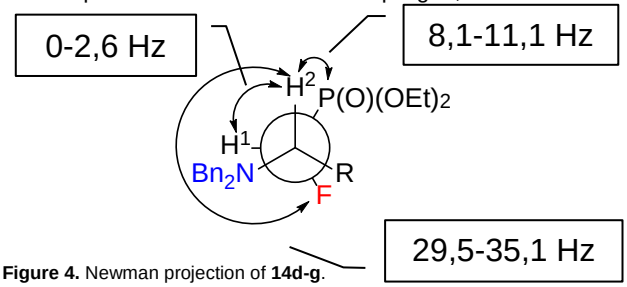


Figure 4. Newman projection of **14d-g**.

Deoxyfluorination of (1*R*,2*S*)-**13d-i** mediated by PyFluor is a reaction with retention of configuration. Moreover, formation of the two regioisomers **14d-i** and **15d-i** clearly indicates that transformation must take place *via* the aziridinium ion. The opening of the three-membered ring, unlike the DAST type mediated reactions, is from the C1 carbon. Similar selective ring-opening of an aziridinium intermediate using PyFluor has

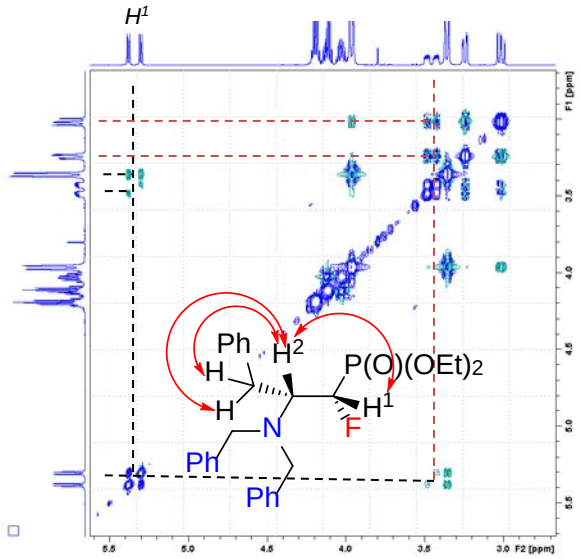


Figure 5. ^{1}H-^{1}H NOESY spectrum of **14d**.

been just reported by Dole.[17b] The different regioselectivity of opening of aziridinium ion during Pyfluor deoxyfluorination of α-hydroxy-β-aminophosphonates **13a-d**, **13h** is influenced by the nature of the nucleophile. Formation of a very reactive amidine hydrogen fluoride is postulated instead of generation HF in case of DAST-type reagents.

In each case (1*R*,2*S*)-**14d-i** α-fluorides were obtained as main diastereoisomers. Further NMR experiments confirmed our assumptions. ^{1}H-^{1}H NOESY spectra of **14d** shows NOEs between H^1 and H^2 protons, which must be located on the same face of the molecule. Figure 6 presents ^{19}F-^{1}H HOESY spectrum of **14d**. This studies also confirmed the presence of (1*R*,2*S*) diastereoisomer, showing strong NOEs between fluorine atom and H^1, as well as all benzylic protons.

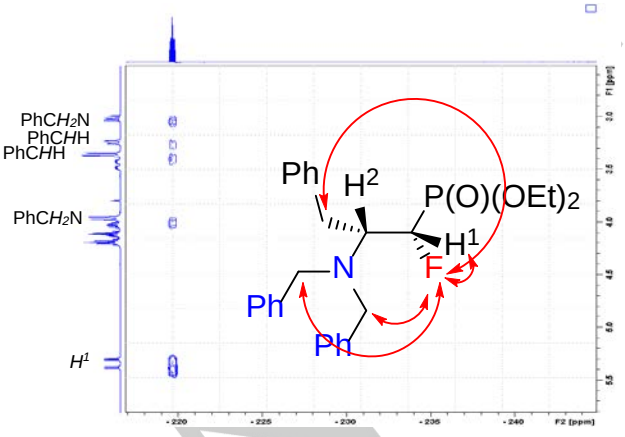


Figure 6. ^{19}F-^{1}H HOESY spectrum of **14d**.

Conclusions

In conclusion, we developed a convenient method for the synthesis of α-fluoro-β-aminophosphonates **14d-i** directly from α-hydroxy-β-aminophosphonates **13d-i** under mild conditions. The reactions were carried out using a new deoxyfluorination reagent-PyFluor, which is a crystalline and more stable alternative to DAST-type reagents. The application of α-fluoro-β-aminophosphonates **14d-i** in synthesis of dipeptide analogues is actively underway in our laboratory research.

Experimental Section

General Methods: ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were performed on Bruker ASCEND 400 (400 MHz), Bruker ASCEND 600 (600 MHz) spectrometers. All 2D and 1D selective NMR spectra were recorded on Bruker ASCEND 600 (600 MHz) spectrometer. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard (δ = 0) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield and upfield from $CDCl_3$ as an internal standard (δ = 77.0). Chemical shifts of ^{19}F NMR were expressed in parts per million upfield from $CFCl_3$ as an internal standard (δ = 0) in $CDCl_3$. Chemical shifts of ^{31}P NMR were expressed in parts per million in $CDCl_3$. High-resolution mass spectra were recorded by electron spray (MS-ESI) techniques using QToF Impact HD Bruker spectrometer. FT-IR spectra were recorded by Attenuated Total Reflectance (ATR) techniques on a FT-IR-4700 Fourier Transform Infrared Spectrometer from JASCO in the range of 650 to 4000 cm^{-1}. Reagent grade chemicals were used. Fluorinating reagents were purchased from Sigma Aldrich or Apollo Scientific. Solvents were dried by refluxing with sodium metal-benzophenone (THF), with CaH_2 (CH_2Cl_2,), with P_2O_5 (PhMe), and distilled under argon atmosphere. All moisture sensitive reactions were carried out under argon atmosphere using ovendried glassware. Reaction temperatures below 0°C were performed using a cooling bath (liquid N_2/hexane). TLC was performed on Merck Kieselgel 60-F254 with EtOAc/hexane and MeOH/$CHCl_3$ as developing systems, and products were detected by inspection under UV light (254 nm) and with a solution of potassium permanganate. Merck Kieselgel 60 (0.063-0.200 μm), Merck Kieselgel 60 (0.040-0.063 μm), Merck Kieselgel 60 (0.015-0.004 μm), were used for column chromatography. X-ray diffraction data were collected at room temperature by the ω-scan technique on Rigaku four-circle diffractometers: (13c) SuperNova (Atlas detector) with mirror-monochromatized CuKα radiation (λ=1.54178Å) and (13g) Xcalibur (Eos detector) with graphite-monochromatized MoKα radiation (λ=0.71073Å. The data were corrected for Lorentz-polarization and absorption effects.[35] Accurate unit-cell parameters were determined by a least-squares fit of 13788 (**13c**), and 6527 (**13g**) reflections of highest intensity, chosen from the whole experiment. The structures were solved with SHELXT [36] and refined with the full-matrix least-squares procedure on F2 by SHELXL-2014/7.[36] All non-hydrogen atoms were refined anisotropically, position of OH hydrogen atom in **13g** was found in difference Fourier map and coordinates of this atom were freely refined; all other hydrogen 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 and hydroxyl groups) times the Ueq value for appropriate non-hydrogen atom. Relevant crystal data are listed in Table 1 (supplementary information), together with refinement details.

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, Nos. CCDC – 1821448 (**13c**), and CCDC - 1821450 (**13g**). 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: www.ccdc.cam.ac.uk.

Experimental Details.

Compounds **12a-i** were prepared according to previously reported procedures. Isolated yield of **12a-i** from **11a-i**: **12a** (94 %), **12b** (75 %), **12c** (85 %), **12d** (89 %), **12e** (89 %), **12f** (80 %), **12g** (72 %), **12h** (75 %), **12i** (80 %). The NMR data were in good agreement.[19-23, 37]

Compounds **13a-i** were prepared according to previously reported procedure. The NMR data for **13a-b**, **13d-h** were in good agreement.[19, 25]

Racemic mixture of diethyl ((1*R*,2*S*)-2-(1,3-dioxoisoindolin-2-yl)-1-hydroxy-3-phenylpropyl)phosphonate (13c): White solid (1160 mg, 72%): 1H NMR (400 MHz, $CDCl_3$) δ = 7.73 (dt, *J* = 7.5, 3.7 Hz, 2H, Ar*H*), 7.65 (dd, *J* = 5.5, 3.1 Hz, 2H, Ar*H*), 7.18 – 7.03 (m, 5H, Ar*H*), 5.07 (dd, *J* = 8.9, 5.0 Hz, 1H, O*H*), 4.84 (dtd, *J* = 11.6, 7.9, 7.5, 3.8 Hz, 1H, C*H*CH_2Ph), 4.80 – 4.70 (m, 1H, C*H*P), 4.25 – 4.10 (m, 2H, OC*H*$_2$$CH_3$), 4.10 – 3.96 (m, 2H, OC*H*$_2$$CH_3$), 3.57 (dd, *J* = 14.1, 3.8 Hz, 1H, C*H*HPh), 3.36 (dd, *J* = 14.1, 11.7 Hz, 1H, CH*H*Ph), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.05 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.92 (s, *C*=O), 137.61 (d, *J* = 1.7 Hz), 133.78, 131.62, 129.00, 128.27, 126.38, 123.09 (7 x Ar), 67.85 (d, *J* = 161.6 Hz, *C*HP), 63.08 (d, *J* = 7.2 Hz, OCH_2CH_3), 62.97 (d, *J* = 7.1 Hz, OCH_2CH_3), 53.19 (d, *J* = 1.6 Hz, *C*HCH$_2$Ph), 34.68 (d, *J* = 10.1 Hz, *C*H$_2$Ph), 16.21 (d, *J* = 5.6 Hz, OCH_2CH_3), 15.93 (d, *J* = 6.3 Hz, OCH_2CH_3). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ = 22.50 (s). HRMS (ESI) calcd for $C_{21}H_{25}NO_6P$ ($[M+H]^+$): 418.1419, found: 418.1412.

Diethyl ((1*R*,2*S*)-2-(dibenzylamino)-1-hydroxy-3-methylpentyl)phosphonate (13i); Colorless oil (634 mg, 32%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 6.7 Hz, 4H, Ar*H*), 7.30 (t, *J* = 7.6 Hz, 4H, Ar*H*), 7.26 – 7.20 (m, 2H, Ar*H*), 4.26 – 4.01 (m, 5H, 2 x OC*H*$_2$$CH_3$, C*H*P), 3.80 (s, 4H, 2 x C*H*$_2$Ph), 3.03 (dd, *J* = 8.3, 3.6 Hz, 1H, O*H*), 2.91 (ddd, *J* = 23.2, 9.5, 4.0 Hz, 1H, C*H*CH(CH$_3$)CH$_2$CH$_3$), 2.16 (dddq, *J* = 12.8, 9.4, 6.4, 3.3 Hz, 1H, C*H*(CH$_3$)CH$_2$CH$_3$), 2.00 (dtt, *J* = 15.0, 7.5, 3.7 Hz, 1H, C*H*HCH$_3$), 1.34 (td, *J* = 7.1, 1.0 Hz, 3H, OCH_2CH_3), 1.30 – 1.24 (m, 4H, OCH_2CH_3, CH*H*CH$_3$), 0.95 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)), 0.91 (t, *J* = 7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 139.64, 129.44, 128.22, 127.05 (4 x s, Ar), 66.63 (d, *J* = 153.4 Hz, *C*HP), 64.12 (d, *J* = 4.0 Hz, *C*HCH(CH$_3$)CH$_2$CH$_3$), 62.52 (d, *J* = 7.1 Hz, OCH_2CH_3), 62.11 (d, *J* = 7.3 Hz, OCH_2CH_3), 55.09 (s, *C*H$_2$Ph), 33.91 (s, C*H*(CH$_3$)CH$_2$CH$_3$), 27.22 (s, *C*HHCH$_3$), 16.75 (s, CH(C*H*$_3$)), 16.43 (d, *J* = 5.9 Hz, OCH_2CH_3), 16.39 (d, *J* = 5.9 Hz, OCH_2CH_3), 11.21 (s, CH_2CH_3). ^{31}P NMR (243 MHz, $CDCl_3$) δ = major diastereoisomer 24.86 (s), minor diastereoisomer 23.44 (s). HRMS (ESI) calcd for $C_{24}H_{37}NO_4P$ ($[M+H]^+$): 434.2460, found: 434.2453.

General procedures for deoxyfluorination.

General procedure for deoxyfluorination of α-hydroxy-β-aminophosphonates **13a-d,h** with DAST,[19a] DeoxoFluor,[38] DAST or DeoxoFluor / TMS-morph,[26a], XtalFluor-E / 3HF·Et$_3$N or 2HF·Et$_3$N or DBU,[28] Fluolead.[16]

PyFluor (1,2 mmol) and DBU (2 mmol) were added to a stirred solution of amino alcohol **13** (1mmol) in 2,5 mL PhMe, under an argon atmosphere. The mixture was stirred at room temperature for 18h. The reaction mixture was then diluted with 20 mL of water and extracted with AcOEt (3 x 15 mL). The organic layers were dried over $MgSO_4$ or Na_2SO_4, filtrated and concentrated under reduced pressure. The crude products were isolated using column chromatography (*n*-hexane/ethyl acetate 10:90, v/v → *n*-hexane/ethyl acetate 40:60, v/v).

Diethyl ((1*R*,2*S*)-2-(dibenzylamino)-1-fluoro-3-phenylpropyl)phosphonate (14d); Colorless oil (272 mg, 58 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.25 (ddt, *J* = 4.6, 3.2, 2.0 Hz, 4H, Ar*H*), 7.14 (dd, *J* = 4.9, 1.8 Hz, 5H, Ar*H*), 7.09 – 7.05 (m, 2H, Ar*H*), 7.00 (dd, *J* = 6.7, 2.9 Hz, 4H, Ar*H*), 5.34 (dd, *J* = 47.2, 8.8 Hz, 1H, C*H*FP), 4.23 – 4.16 (m, 2H, OC*H*$_2$$CH_3$), 4.14 – 4.08 (m, 1H, OC*H*HCH$_3$), 4.06 – 4.00 (m, 1H, OCH*H*CH$_3$), 3.96 (d, *J* = 14.1 Hz, 2H, PhC*H*HN), 3.45 (dddd, *J* = 35.2, 11.4, 5.6, 3.2 Hz, 1H, PhCHHC*H*N), 3.36 (dd, *J* = 14.2, 1.7 Hz, 2H, PhCH*H*N), 3.24 (dd, *J* = 14.7, 3.1 Hz, 1H, PhC*H*HCHN), 3.01 (dd, *J* = 14.7, 11.3 Hz, 1H, PhCH*H*CHN), 1.32 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 139.47, 138.82, 129.66, 128.55, 127.99, 127.88, 126.74, 125.87 (8 x s, Ar), 87.26 (dd, *J* = 186.6, 165.3 Hz, *C*HFP), 63.12 (d, *J* = 6.8 Hz, OCH_2CH_3), 62.71 (d, *J* = 6.9 Hz, OCH_2CH_3), 58.72 (dd, *J* = 18.5, 5.6 Hz, PhCH$_2$*C*H), 53.78 (s, 2 x PhCH_2N), 32.21 (d, *J* = 7.2 Hz, PhCH_2), 16.41 (d, *J* = 5.6 Hz, OCH_2CH_3), 16.34 (d, *J* = 5.6 Hz, OCH_2CH_3). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -220.25 (ddd, *J* = 82.7, 47.2, 35.3 Hz). ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$) δ = -220.24 (d, *J* = 82.2 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$) δ = 17.31 (d, *J* = 82.2 Hz). IR (ATR): 3060.48, 3027.69, 2982.37, 2932.23, 2910.06, 2831.95, 2801.1, 1601.59, 1493.6, 1452.14, 1389.46, 1368.25, 1256.4, 1120.44, 1022.09, 970.98, 742.46, 698.10, 566.00 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{34}FNO_3P$ ($[M+H]^+$): 470.2260, found: 470.2253.

Diethyl ((1*S*,2*R*)-2-(dibenzylamino)-1-fluoro-3-phenylpropyl)phosphonate (14e); Colorless oil (282 mg, 60 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.33 (m, 1H, Ar*H*), 7.26 (m, 2H, Ar*H*), 7.20 – 7.12 (m, 6H, Ar*H*), 7.07 (dd, *J* = 6.5, 2.9 Hz, 2H, Ar*H*), 7.04 – 6.96 (m, 4H, Ar*H*), 5.34 (dd, *J* = 47.2, 8.8 Hz, 1H, C*H*FP), 4.27 – 4.17 (m, 2H, OC*H*$_2$$CH_3$), 4.13 (m, 1H, OC*H*HCH$_3$), 4.04 (m, 1H, OCH*H*CH$_3$), 3.97 (d, *J* = 14.2 Hz, 2H, PhC*H*HN), 3.45 (dddd, *J* = 35.2, 11.4, 5.6, 3.2 Hz, 1H, PhCHHC*H*N), 3.36 (dd, *J* = 14.2, 1.8 Hz, 2H, PhCH*H*N), 3.24 (dd, *J* = 14.7, 3.1 Hz, 1H, PhC*H*HCHN), 3.01 (dd, *J* = 14.7, 11.3 Hz, 1H, PhCH*H*CHN), 1.33 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 139.51, 138.85, 129.69, 128.59, 128.02, 127.91, 126.77, 125.90 (8 x s, Ar), 87.30 (dd, *J* = 186.7, 165.3 Hz, *C*HFP), 63.15 (d, *J* = 6.7 Hz, OCH_2CH_3), 62.75 (d, *J* = 6.7 Hz, OCH_2CH_3), 58.76 (dd, *J* = 18.5, 5.7 Hz, PhCH$_2$*C*H), 53.82 (s, 2 x PhCH_2N), 32.24 (d, *J* = 7.3 Hz, PhCH_2), 16.44 (d, *J* = 5.6 Hz, OCH_2CH_3), 16.38 (d, *J* = 5.5 Hz, OCH_2CH_3). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -220.26 (ddd, *J* = 82.2, 47.2, 35.3 Hz). ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$) δ = -220.25 (d, *J* = 82.2 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$) δ = 17.27 (d, *J* = 83.1 Hz). IR (ATR): 3060.48, 3026.73, 2981.41, 2930.31, 2911.99, 2831.95, 2800.13, 1601.59, 1493.6, 1452.14, 1389.46, 1368.25, 1256.4, 1120.44, 1024.02, 970.98, 743.42, 699.07 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{34}FNO_3P$ ($[M+H]^+$): 470.2260, found: 470.2256.

Diethyl ((1*R*,2*S*)-2-(dibenzylamino)-1-fluoropropyl)phosphonate (14f); Colorless oil (165 mg, 42 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.41 – 7.17 (m, 10H, Ar*H*), 5.14 (ddd, *J* = 47.3, 7.6, 1.5 Hz, 1H, C*H*FP), 4.15 – 4.07 (m, 2H, OC*H*$_2$$CH_3$), 4.07 – 3.88 (m, 2H, OC*H*$_2$$CH_3$), 3.70 (d, *J* = 14.0 Hz, 2H, PhC*H*HN), 3.60 (d, *J* = 14.0 Hz, 2H, PhCH*H*N), 3.36 – 3.24 (m, 1H, CH$_3$C*H*), 1.32 (dd, *J* = 7.1, 1.9 Hz, 3H, C*H*$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.18 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 139.63, 128.59, 128.18, 126.90 (4 x s, Ar), 90.78 (dd, *J* = 185.4, 166.2 Hz, *C*HFP), 63.02 (d, *J* = 6.7 Hz, OCH_2CH_3), 62.49 (d, *J* = 6.7 Hz, OCH_2CH_3), 54.19 (s, PhCH_2), 54.17 (s, PhCH_2), 52.71 (dd, *J* = 19.3, 6.5 Hz, CH$_3$*C*H), 16.34 (d, *J* = 5.6 Hz, OCH_2CH_3), 16.24 (d, *J* = 5.9 Hz, OCH_2CH_3), 9.73 (d, *J* = 7.8 Hz, C*H*$_3$). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -220.51 (ddd, *J* = 81.6, 47.3, 32.6 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -220.51 (d, *J* = 83.1 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$) δ = 16.88 (d, *J* = 82.3 Hz). IR (ATR): 3061.44, 3028.66, 2983.34, 2932.23, 2803.99, 1493.6, 1451.17, 1368.25, 1256.4, 1160.94, 1021.12, 970.02, 742.46, 698.10 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{30}FNO_3P$ ($[M+H]^+$): 394.1947, found: 394.1941.

Diethyl ((1*R*,2*S*)-2-(dibenzylamino)-1-fluoro-3-methylbutyl)phosphonate (14g); Colorless oil (257 mg, 61 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.46 – 7.40 (m, 4H, Ar*H*), 7.33 (t, *J* = 7.6 Hz, 4H, Ar*H*), 7.29 – 7.22 (m, 2H, Ar*H*), 5.32 (ddd, *J* = 46.3, 10.6, 1.9 Hz, 1H, C*H*FP), 4.28 – 4.07 (m, 4H, 2 x O*CH*$_2$CH$_3$), 3.96 (d, *J* = 13.8 Hz, 2H, PhC*H*HN), 3.42 (d, *J* = 13.8 Hz, 2H, PhCH*H*N), 3.00 (dddd, *J* = 32.0, 8.2, 6.2, 1.9 Hz, 1H, $(CH_3)_2$CHC*H*N), 2.35 – 2.19 (m, 1H, $(CH_3)_2$C*H*), 1.38 – 1.35 (m, 3H, OCH$_2$C*H*$_3$), 1.35 – 1.33 (m, 3H, OCH$_2$C*H*$_3$), 1.16 – 1.09 (m, 3H, C*H*$_3$), 0.93 (d, *J* = 6.7 Hz, 3H, C*H*$_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 139.28, 129.12, 128.11, 126.96 (4 x s, Ar), 88.23 (dd, *J* = 189.3, 165.2 Hz, *C*HFP), 63.14 (d, *J* = 6.9 Hz, O*C*H$_2$CH$_3$), 62.50 (d, *J* = 6.7 Hz, O*C*H$_2$CH$_3$), 62.20 (dd, *J* = 18.9, 4.9 Hz, $(CH_3)_2$CH*C*H), 55.17 (s, 2 x Ph*C*H$_2$), 27.81 (d, *J* = 4.9 Hz, $(CH_3)_2$*C*H), 21.36 (d, *J* = 1.6 Hz, *C*H$_3$), 20.74 (d, *J* = 2.5 Hz, *C*H$_3$), 16.45 (d, *J* = 5.5 Hz, OCH$_2$*C*H$_3$), 16.42 (d, *J* = 5.5 Hz, OCH$_2$*C*H$_3$). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -218.93 (ddd, *J* = 79.8, 46.2, 31.9 Hz). ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$) δ = -218.92 (d, *J* = 81.0 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$) δ = 18.29 (d, *J* = 80.7 Hz). IR (ATR): 3061.44, 3029.62, 2958.27, 2930.31, 2801.1, 1601.59, 1492.63, 1451.17, 1366.32, 1259.29, 1160.94, 1097.3, 1024.98, 968.09, 746.317, 700.03 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{34}FNO_3P$ ([M+H]$^+$): 422.2260, found: 422.2253.

Diethyl ((1*R*,2*S*)-2-(dibenzylamino)-1-fluoro-4-methylpentyl)phosphonate (14h); Colorless oil (296 mg, 68 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.42 – 7.14 (m, 10H, Ar*H*), 5.33 (dd, *J* = 47.3, 9.0 Hz, 1H, C*H*FP), 4.22 – 4.14 (m, 2H, OC*H*$_2$CH$_3$), 4.14 – 4.03 (m, 2H, OC*H*$_2$CH$_3$), 3.95 (d, *J* = 13.7 Hz, 2H, PhC*H*HN), 3.31 (dd, *J* = 13.7, 1.7 Hz, 2H, PhCH*H*N), 3.16 (dddd, *J* = 35.9, 11.3, 5.5, 2.6 Hz, 1H, $(CH_3)_2$CHCHHC*H*N), 1.94 (dqd, *J* = 16.2, 6.7, 3.1 Hz, 1H, $(CH_3)_2$C*H*), 1.80 (ddd, *J* = 14.3, 11.1, 2.9 Hz, 1H, $(CH_3)_2$CHC*H*H), 1.43 (ddd, *J* = 14.1, 10.7, 2.7 Hz, 1H, $(CH_3)_2$CHCH*H*), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.91 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 0.42 (d, *J* = 6.5 Hz, 3H, C*H*$_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 139.44, 129.10, 128.07, 126.92 (4 x s, Ar), 87.32 (dd, *J* = 185.6, 165.2 Hz, *C*HFP), 62.89 (d, *J* = 6.7 Hz, O*C*H$_2$CH$_3$), 62.49 (d, *J* = 6.7 Hz, O*C*H$_2$CH$_3$), 54.79 (dd, *J* = 18.9, 5.5 Hz, $(CH_3)_2$CHCH$_2$*C*H), 54.00 (s, 2 x Ph*C*H$_2$), 34.96 (d, *J* = 5.3 Hz, $(CH_3)_2$*C*HCH$_2$), 24.03 (s, *C*H$_3$), 23.77 (s, $(CH_3)_2$*C*H), 20.53 (s, *C*H$_3$), 16.38 ("t", *J* = 5.5 Hz, 2 x OCH$_2$*C*H$_3$). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -221.29 (ddd, *J* = 83.0, 47.3, 35.9 Hz). ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$) δ = -221.29 (d, *J* = 82.9 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$) δ = 17.66 (d, *J* = 83.4 Hz). IR (ATR): 3027.69, 2954.41, 2916.81, 2868.59, 2849.31, 2803.03, 1453.1, 1387.53, 1367.28, 1258.32, 1160.94, 1052.94, 1028.84, 968.09, 747.28, 699.07, 566.97 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{36}FNO_3P$ ([M+H]$^+$): 436.2417, found: 436.2405.

Diethyl ((1*R*,2*S*)-2-(dibenzylamino)-1-fluoro-3-methylpentyl)phosphonate (14i); Colorless oil (222 mg, 51 %): 1H NMR (600 MHz, $CDCl_3$) δ = 7.43 – 7.19 (m, 10H, Ar*H*), 5.30 (ddd, *J* = 46.1, 10.3, 2.6 Hz, 1H, C*H*FP), 4.22 – 4.05 (m, 4H, 2 x OC*H*$_2$CH$_3$), 3.87 (d, *J* = 13.8 Hz, 2H, PhC*H*$_2$), 3.43 (d, *J* = 13.7 Hz, 2H, PhC*H*$_2$), 3.06 (dddd, *J* = 29.5, 9.0, 6.7, 2.6 Hz, 1H, $CH_3CH_2CH(CH_3)$C*H*), 1.97 (dtq, *J* = 13.0, 6.3, 3.3 Hz, 1H, $CH_3CH_2CH(CH_3)$CHC*H*), 1.89 (dtd, *J* = 15.2, 7.6, 3.1 Hz, 1H, CH_3C*H*H), 1.32 (td, *J* = 7.1, 2.7 Hz, 6H, 2 x OCH$_2$C*H*$_3$), 1.26 – 1.16 (m, 1H, CH_3CH*H*), 0.94 (d, *J* = 6.7 Hz, 3H, CH(C*H*$_3$)), 0.77 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 139.20, 129.17, 128.04, 126.91 (4 x s, Ar), 88.28 (dd, *J* = 189.6, 165.1 Hz, *C*HFP), 63.03 (d, *J* = 7.0 Hz, OCH$_2$CH$_3$), 62.43 (d, *J* = 6.7 Hz, OCH$_2$CH$_3$), 61.52 (dd, *J* = 19.2, 4.3 Hz, $CH_3CH_2CH(CH_3)$CH), 54.88 (s, 2 x CH_2Ph, 33.88 (t, *J* = 2.7 Hz, CH_3CH_2*C*H(CH$_3$)), 26.41 (d, *J* = 2.3 Hz, *C*HHCH$_3$), 16.48 (d, *J* = 2.4 Hz, CH(C*H*$_3$)), 16.39 (d, *J* = 1.9 Hz, OCH$_2$*C*H$_3$), 16.35 (d, *J* = 1.9 Hz, OCH$_2$*C*H$_3$), 11.47 (s, CH$_2$*C*H$_3$). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -217.75 (ddd, *J* = 79.6, 46.1, 29.5 Hz). ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$) δ = -217.75 (d, *J* = 79.8 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$) δ = 18.41 (d, *J* = 79.4 Hz). IR (ATR): 3028.66, 2966.95, 2931.27, 2875.34, 2802.06, 1493.6, 1452.14, 1369.21, 1257.36, 1160.94, 1095.37, 1045.23, 1024.02, 963.27, 744.39, 699.07 cm^{-1}.HRMS (ESI) calcd for $C_{24}H_{36}FNO_3P$ ([M+H]$^+$): 436.2417, found: 436.2408.

Diethyl ((1*S*,2*R*)-1-(dibenzylamino)-2-fluoro-3-methylpentyl)phosphonate (15i): Colorless oil (61 mg, 14 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.45 – 7.10 (m, 10H, Ar*H*), 4.69 (dtd, *J* = 46.3, 8.4, 2.7 Hz, 1H, *C*HF), 4.45 – 4.08 (m, 4H, 2 x OC*H*$_2$CH$_3$), 4.02 – 3.85 (m, 4H, 2 x PhC*H*$_2$), 3.28 (dt, *J* = 16.3, 8.4 Hz, 1H, *CH*NP), 1.94 – 1.84 (m, 1H, $CH_3CH_2CH(CH_3)$), 1.41 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.34 (m, 4H, OCH$_2$C*H*$_3$, CH_3C*H*H), 1.23 (dt, *J* = 14.1, 7.4 Hz, 1H, CH_3CH*H*), 0.88 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 0.32 (dd, *J* = 6.9, 1.2 Hz, 3H, CH(C*H*$_3$)). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 139.12, 129.34, 128.28, 127.21 (4 x s, Ar), 93.90 (dd, *J* = 175.3, 1.8 Hz, *C*HF), 61.66 (dd, *J* = 7.2, 3.3 Hz, OCH$_2$CH$_3$), 61.14 (d, *J* = 7.2 Hz, OCH$_2$CH$_3$), 56.53 (dd, *J* = 133.3, 25.7 Hz, *C*HNP), 55.59 (d, *J* = 2.0 Hz, s, 2 x *C*H$_2$Ph), 35.08 (dd, *J* = 19.8, 7.2 Hz, CH_3CH_2*C*H(CH$_3$)), 26.51 (s, CH_3*C*H$_2$), 16.69 (d, *J* = 5.6 Hz, OCH$_2$*C*H$_3$), 16.56 (d, *J* = 5.6 Hz, OCH$_2$*C*H$_3$), 11.67 (s, CH$_2$*C*H$_3$), 11.35 (d, *J* = 7.3 Hz, CH(C*H*$_3$)). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -200.78 (ddt, *J* = 44.6, 30.6, 6.4 Hz). ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$) δ = -200.77 (d, *J* = 4.4 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$) δ = 26.96 (d, *J* = 4.9 Hz). IR (ATR): 3062.41, 3030.59, 2965.02, 2933.2, 2858.95, 1493.6, 1454.06, 1370.18, 1243.86, 1214.93, 1160.94, 1116.58, 1097.3, 1050.05, 1022.09, 955.56, 778.14, 747.28, 699.07 cm^{-1} .HRMS (ESI) calcd for $C_{24}H_{36}FNO_3P$ ([M+H]$^+$): 436.2417, found: 436.2401.

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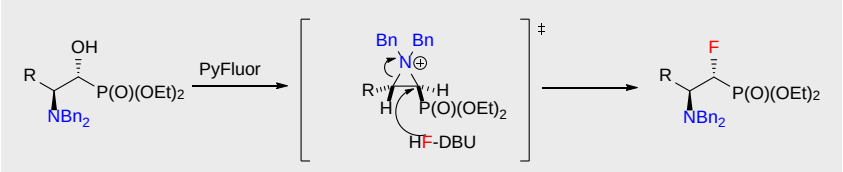

Regioselective fluorination of α-hydroxy-β-aminophosphonates under mild conditions. The fluorination reactions were mediated by PyFluor reagent, and occurred with retention of configuration.

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Marcin Kaźmierczak, Maciej Kubicki, and Henryk Koroniak*

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Regioselective fluorination of α-hydroxy-β-aminophosphonates by PyFluor

*one or two words that highlight the emphasis of the paper or the field of the study