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Pyrrolidine and oxazolidine ring transformations in proline and serine derivatives of α-hydroxyphosphonates induced by deoxyfluorinating reagents†

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Transformations of α-hydroxyphosphonates derived from proline or serine by treatment with different deoxyfluorinating reagents (DAST, Deoxofluor, PyFluor) are reported. Depending on the applied reagent, as well as the protecting group used (*N*-Cbz, *N*-Boc, *N*-Bn) different types of products are observed. The reaction of *N*-Cbz or *N*-Boc prolinols with DAST or Deoxofluor due to aziridinium intermediate participation gave fluorinated amino phosphonates such as piperidine and pyrrolidine derivatives and/or oxazolidine-2-ones. Similarly, the analogous reaction of *N*-Cbz or *N*-Boc protected serinol yielded oxazolidine-2-ones or its fluorinated analogues. As the second type of product formed by DAST-induced reaction of serine derivatives, aziridines were obtained. Only in the case of deoxyfluorination of *N*-benzyl prolinols were both diastereoisomers of β-fluoropiperidine-α-phosphonates formed, while the reaction of protected *N*-benzyl serinols gave fluorinated oxazolidines. Moreover, application of PyFluor gave sulfonate derivatives.

Introduction

The replacement of the carboxylic groups in amino acids by the phosphonate moiety or related functions resulted in the formation of α- and β-amino phosphonic acid derivatives. Between them, the aminoalkylphosphonate esters are frequently synthesized due to their wide spectrum of biological properties applied in medicine as well as in agriculture.[1] Moreover, amino phosphonates represent models of the tetrahedral transition states in activated complexes formed during the hydrolysis of natural peptides[2] and were proved to be suitable substrates for some enzymes inhibitions.[1a,b] As a representative example, dipeptides containing phosphonated proline analogue have been found as specific irreversible inhibitors of dipeptidyl peptidase IV (DPP IV).[3] On the other hand, a phosphonic acid analogue of serine as a visualization agent in rat kidney and skeletal bones has been applied.[4] The biomedical application of amino phosphonates makes them attractive targets in organic synthesis. Thus, organophosphorus analogues of almost all proteinogenic amino acids have been already obtained. Among them, the preparation of phosphoproline,[5] phosphohomoproline[6] or synthesis of phosphonic acid analogues of serine have been reported.[7] Moreover, since the observation, that group of α-monofluoroalkylaminophosphonates could be applied as a nonhydrolysable isopolar surrogate of naturally occurring phosphates (where C–O–P bridge was replaced by C–CHF–P linkages),[8] several syntheses of some monofluorinated alkylphosphonic acid analogues have been reported.[9] The introduction of the fluorine atom in organic compounds has a deep electronic and steric impact, affecting interactions between fluorine-containing inhibitors and target enzymes.[10] This effect is especially noticeable in a group of fluorinated amino phosphonates.[11] Thus, monofluoro- and difluoro phosphoserine analogues as potent inhibitors of alanine racemase have been reported.[11a] Moreover, dipeptides containing β-fluorinated phosphoproline have been designed as a phosphonate-based transition-state analogue of inhibitors of proline selective serine dipeptidases.[11b]

One of the common strategy in the synthesis of monofluorinated amino phosphonates has involved nucleophilic fluorination of the hydroxyl group in hydroxyphosphonates and as the most common reagents (diethylamino)sulfur trifluoride (DAST),[12] DeoxoFluor[13] and PyFluor[14] were used. Generally, the mechanism of deoxyfluorination with DAST involves the attack of the hydroxyl group of alcohol substrate to the electrophilic deoxyfluorinating agent (with a generation of activated alcohol $-OSF_2NEt_2$ along with fluoride ion).

The latter then displaces of leaving group to produce the corresponding alkyl fluoride. However, β-aminoalcohols such as prolinol derivatives the reaction is frequently going through

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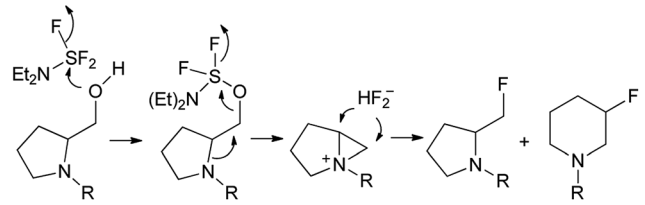
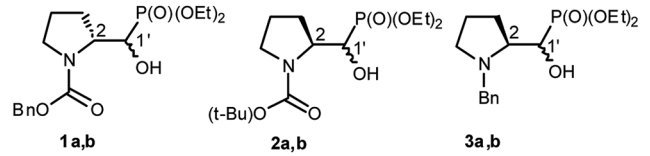
† Electronic supplementary information (ESI) available: Experimental details, compounds characterization, ^{1}H, ^{13}C, ^{31}P and 2D NMR spectra of compounds. See DOI: 10.1039/c8ra05186k



Scheme 1 Deoxyfluorination of prolinol with DAST.



Scheme 2 Structures of starting α-hydroxyphosphonates proline derivatives **1**–**3a,b**.

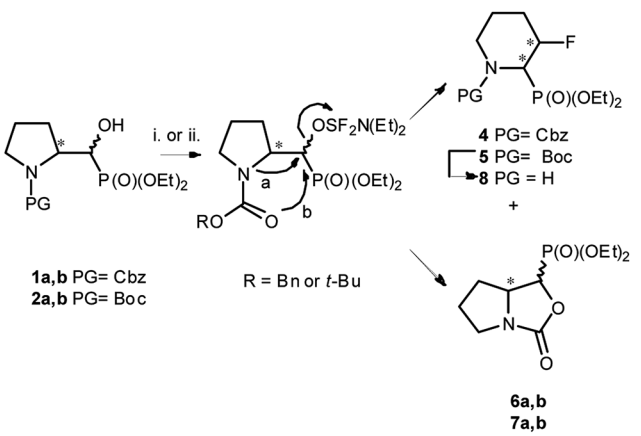
aziridinium intermediate due to neighbouring group participation leading to ring opening by fluoride ion, resulting in restoration or ring expansion in some cases (Scheme 1).[15] In case of phosphonates, depending on the structure and applied reagent, the fluorination proceeds with different regioselectivity. Thus, fluorination with DAST of α-hydroxy-β-aminoalkylphosphonates originated from aliphatic amino acids as well as phenylalanine gave β-fluoro-α-aminoalkylphosphonates as major isomers.[16] For comparison, the application of PyFluor and DBU in the same systems resulted in the formation of mainly α-fluoro-β-aminoalkylphosphonates.[17] On the other hand, the reactions of proline derived α-hydroxyphosphonates with DAST led to the corresponding α-fluoroalkylphosphonates[11b] while the fluorination of β-hydroxy-γ-aminoalkylphosphonates gave the appropriate β-fluoroalkylphosphonates.[11c] Other approaches yielding α-fluoro-β-aminoalkylphosphonates involved electrophilic fluorination of β-ketophosphonates and next enamine formation[18] or addition of anion species $[C(TMS)FP(O)(OEt)_2]^-$ to appropriate iminium salt.[8a] Moreover, applications of suitable methylphosphonate carbanions in the synthesis of α-fluoro-γ-amino phosphonates[11c,19] or γ-monofluoro-β-aminoalkylphosphonates[20] were reported.

Our recent studies revealed that nucleophilic fluorination of α-hydroxyphosphonates derived from *O*-isopropylidene glyceraldehyde with DAST has led to oxirane formation due to the substitution of DAST-derived leaving group by hydroxyl group from the adjacent stereogenic centre.[21] By contrast, stereoselective deoxyfluorination of hydroxyphosphonates derived from an *O*-isopropylidenepentofuranose gave major fluoride possessing D-*glu* configuration. Moreover, we found that fluorination of tertiary alcohols derived from di-*O*-isopropylidenehexofuranose and 1,2-*O*-isopropylidenepentofuranose have been stereo controlled by the neighbouring bottom-face 1,2-*O*-isopropylidene group oxygen atom leading preferentially to one diastereoisomer of allylic, phenylacetylene, styryl, and benzylic fluorides.[22] Herein, we present our studies evaluating different substrates scope for deoxyfluorination reaction with an emphasis on neighbouring group participation resulting transformation of phosphonate amino acids analogues.

Results and discussion

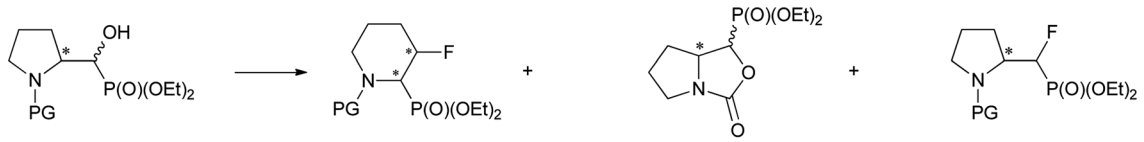
We started with α-hydroxyphosphonates derivatives of proline and serine possessing *N*-carboxybenzyl, *N*-*tert*-butoxycarbonyl, and *N*-benzyl as protecting groups. Thus the nucleophilic fluorination of prolinols such as **1a,b** (Cbz), **2a,b** (Boc) and **3a,b** (Bn) prepared according to known procedures (see Experimental section) were performed. Predominantly diastereoisomers (2*R*,1′*S*)-**1a** and (2*S*,1′*R*) -**2a,3a** were applied, while minor diastereoisomers possess (2*R*,1′*R*)-**1b** and (2*S*,1′*S*)-**2b,3b** configurations, respectively (Scheme 2). Treatment of α-hydroxyphosphonates **1a,b** or **2a,b** with DAST gave mainly two type of phosphonates **4**–**7** (^{31}P NMR)(Scheme 3).

Primary experiments indicated that compounds **4** and **5**, as well as non-fluorinated **6a** or **7a**, arose from major **1a** (2*R*,1′*S*) or **2a** (2*S*,1′*R*) diastereoisomers while from **1b** (2*R*,1′*R*) or **2b** (2*S*,1′*S*) only bicyclic **6b** or **7b** were formed (Table 1). Stereochemistry of the fluorination of **1a** (or **2a**) is a consequence of the transformation of α-hydroxyl moiety into good leaving group ($-OSF_2N(Et)_2$) and its substitution by electron pair of pyrrolidine nitrogen atom (S_N2, pathway a Scheme 3) yielding aziridinium ion, analogously to the intermediate formed during fluorination of proline derivatives (Scheme 1). A subsequent attack of fluoride ion as HF_2^-(second S_N2 reaction) gave preferentially β-fluoro-α-phosphonate piperidine **4** or **5**. Ring expansion during deoxyfluorination of prolinols with DAST has been already reported.[15] Moreover, rearrangement of optically active prolinols by treatment with DAST afforded only one optically active diastereoisomer of piperidines.[15] Also, Kaźmierczak *et al.* reported fluorination of α-hydroxyphosphonate analogues of amino acids such as phenylalanine or valine leading to α-amino-β-fluoroalkylphosphonates *via* aziridinium ion.[16] In our case, two signals of main fluorinated product **4** or **5** [appearing as a mixture of rotamers (1.1 : 1, r.r.),



Scheme 3 Reaction of **1**–**2a,b** with DAST (Table 1) (**4** 43% and **6a,b** 45%; **5** 38% and **7a,b** 53%); or DeoxoFluor (CH_2Cl_2, RT, 24 h)(**4** 38% and **6a,b** 43%; **5** 30% and **7a,b** 48%); and deprotection of **5** (**8** 73%); [configurations of stereogenic centres in the text].

Table 1 Fluorination of **1a,b** or **2a,b** with different fluorinating agents[a]

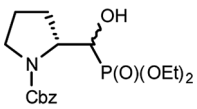
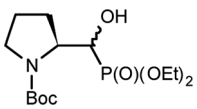


1a,b PG= Cbz
2a,b PG= Boc

4 PG= Cbz
5 PG= Boc

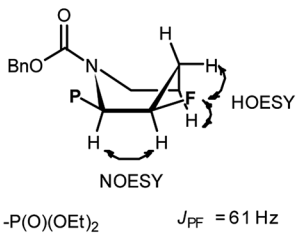
6a,b
7a,b

9 PG= Cbz
10 PG= Boc

Substrate	d.r.	Cond.	Reagent	Products ratio[b] (isolated yield%) **4** or **5**	**6a** : **6b** or **7a** ; **7b**	**9** or **10**
 **1a:1b**	22.8 : 1	i	DAST	11 (43)	9.5 : 1 (45)	2 (8)
	22.8 : 1	ii	DAST	10 (41)	9.2 : 1 (45)	2.6 (7)
	2.6 : 1	iii	DAST	5.3 (36)	6.8 : 5.1 (56)	1 (—)
	1 : 1.4	i	DAST	1 (10)	1 : 2.9 (40)	—
	20 : 1	iv	DeoxoFluor	8.8 (38)	9.1 : 1 (43)	2 (traces)
 **2a:2b**	2.7 : 1	iii	DAST	1.3 (23)	1.4 : 1 (44)	Traces
	3.8 : 1	iii	DAST	1.8 (38)	2.0 : 1 (53)	Traces
	36 : 1	iv	DeoxoFluor	16 (30)	23 : 1 (48)	Traces

[a] (i) −78 °C → 0 °C (1.5 h); (ii) 0 °C → 40 °C (1 h); (iii) −78 °C, 3 h, RT (1 h); (iv) RT (24 h). [b] Ratio of products in crude reaction mixture, ^{31}P NMR.

due to presence of *N*-Cbz or *N*-Boc protecting group, isolated yields 43% and 38%, respectively] were located in ^{19}F NMR at *δ*: −180/179 ppm (as m), in the area habitually occupied by signal of secondary alkyl fluoride.[23] Moreover, coupling constants values $^{2}J_{H2P}$ 21 Hz, $^{2}J_{H3F}$ 46 Hz, $^{3}J_{H2F}$ 19 Hz as well as the location of signals for *C*HF at *δ*: 85 ppm ($^{2}J_{CF}$ 179 Hz), *C*HP at *c.a. δ*: 53 ppm ($^{2}J_{CP}$ 150 Hz, $^{3}J_{CF}$ 22 Hz) in ^{13}C NMR spectra indicated piperidine ring formation with the vicinal arrangement of fluorine substituent and phosphonate moiety. To compare, in case of fluorocyclohexane the values of coupling constants $^{3}J_{HF}$ equal 44 Hz (for *anti*) or $^{3}J_{HF}$ 10 Hz for *gauche* conformations were reported.[23] In our case, we have observed the extremely high value of coupling constants ($^{3}J_{FP}$ 62/63 Hz). Usually, the $^{3}J_{PF}$ coupling constants range from *c.a.* 0 Hz to 9 Hz as observed for two stereoisomers of diethyl 2-fluorocyclohexyl phosphonate.[24] On the other hand, in case of *N*,*N*-dibenzyl-α-amino-β-fluoroalkylphosphonates the values of *J* for conformations *gauche* ($^{3}J_{PF}$ 8–10 Hz) and *anti* ($^{3}J_{PF}$ 15–19 Hz) were reported.[16] In our case the most probably, the high value of coupling constants is due to the attempted arrangement of C–F and C–P bonds with equatorially situated fluorine and phosphonate substituents[25] in the ring. Thus, piperidine existed as slightly twisted boat conformation forced the most probably by bulky *N*-protecting group vicinal to phosphonate moiety (compound **4**, Scheme 4). Stereochemistry of **4** as (2*R*,3*R*) was confirmed by further ^{19}F–^{1}H HOESY experiments showing NOEs between fluorine atom and protons: H-4 and H-5; as well as NOEs between H-2 (C*H*P) and H-3 (C*H*F) (^{1}H–^{1}H NOESY) and indicated the additional participation of protecting group (*N*-Boc) in



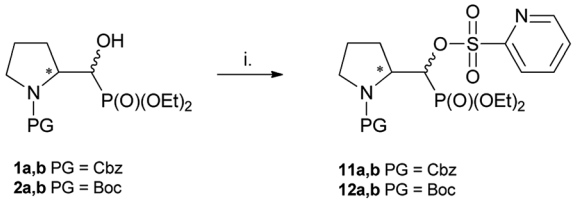
Scheme 4 The slightly twisted boat conformation of **4** with observed correlations and values of coupling constants.

product formation. Also in β-fluoroethylamide C–F and CN(CO) bonds prefer to adopt the *gauche* conformation.[26] To confirm the influence of bulky *N*-Cbz or *N*-Boc groups on a conformation of **4–5**, deprotection of **5** (TFA) was carried out to give compound **8** (yield 73%). Thus, piperidine **8** shows $^{3}J_{FP}$ 5/6 Hz (^{19}F, ^{31}P NMR) indicating the less strained arrangement of fluorine substituent and phosphonate moiety in piperidine ring.

The second main type of products – phosphonates **6a,b** or its enantiomers **7a,b** possess oxazolidine-2-one fragments and have been formed as a result of substitution of DAST derived leaving group in **1–2a,b** by carbonyl electron pair from *N*-Cbz (*N*-Boc) moieties (pathway b, Scheme 3), analogously to the reaction *N*-Boc protected β-aminoalcohol with DAST.[27] Configuration at stereogenic centers in *C*HP of both diastereoisomers of **6** or **7** was reversed compared to appropriate diastereoisomer of starting **1–2a,b**. Thus, the structure of major and minor diastereoisomers of non-fluorinated oxazolidine-2-ones **6a,b** arising from **1a,b** were determined on the base of the NMR spectra and NOESY

experiments and were determined as the *trans* **6a** for major and *cis* **6b** for minor isomers, and respectively their enantiomers *trans* **7a** and *cis* **7b** if starting material was **2a,b**. The stereochemical assignment of *trans*/*cis* oxazolidinones was applied already for determination of stereochemistry in L-phenylalaninal derived hydroxyphosphonates, serving as suitable substrates for aspartyl protease renin inhibitors.[28] Moreover, careful inspection of ^{19}F NMR spectra led to observation of other fluorinated products **9** or **10** visible as traces at δ: −226/227 ppm with two-bond H–F coupling constants value being about $^{2}J_{FH}$ 47 Hz and $^{2}J_{FP}$ 77 ± 2 Hz, analogically to β-amino-α-fluoroalkylphosphonates.[16] Compound **9** was formed solely from **1a** as a second regioisomer of aziridinium ring opening the most probably (pathway a, Schemes 3 and 1). Analogically, compound **10** derived from **2a**. The resulting ratio of products of the reaction of **1a,b** as well as **2a,b** with various fluorinating agents (crude, ^{31}P NMR), with reaction conditions are presented below (Table 1). The presented experiments indicated, that in both cases from **1a,b** as well as from **2a,b** three analogous type of compounds were formed and in different temperatures ranges similar ratio of products was observed (DCM, 4 equiv. of DAST). We have determined that compounds **4** and **5**, as well as **6a** or **7a**, were formed from **1a** or **2a** while from **1b** or **2b** only bicyclic **6b** or **7b** were produced. Compound **9** arising from major diastereoisomer of **1a** was visible as traces in ^{31}P NMR while in the reaction carried out at a higher temperature slightly higher contribution of fluoride **9** was detected. On the other hand, the reactions of **1a,b** or **2a,b** (with a different ratio of stereoisomers) carried out with Deoxofluor (RT, 24 h) gave the same products **4–7**, **9–10** with a parallel ratio to reaction with DAST. Moreover, the reactions of **1a,b** (3.3 : 1, d.r.) or **2a,b** (37 : 1, d.r.) with PyFluor (DBU, toluene, RT, 5 d) gave alkylphosphoryl pyridine-2-sulfonates **11a,b** or **12a,b** (3 : 1 or 74 : 1, d.r.) with yields 78% and 74%, respectively (Scheme 5). Thus, the reaction of **1a,b** with PyFluor gave **11a,b** as a mixture of two appropriate diastereoisomers without any configuration changes analogically to starting materials. The positions of signals in ^{31}P NMR were shifted toward higher field (δ_P 15.1/14.7 ppm for **11a** or δ_P 15.4/15.5 ppm for **12a**), comparing with α-hydroxyphosphonates **1–2a,b**. The formation of sulfonates instead of fluorides was also already reported.[29] Also, Kaźmierczak *et al.* reported the sulfonates formation during fluorination of α-hydroxyphosphonate analogues of amino acids such as phenylalanine possessing phthaloyl protecting group.[17]

On the base of the results described for prolinols **1–2a,b** we next examined the fluorination of diastereoisomeric mixture of **3a,b** having benzyl as *N*-protecting group (Table 2).

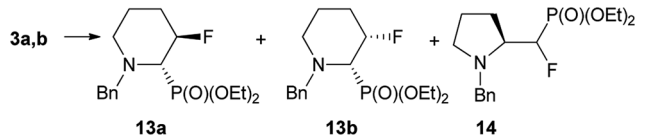


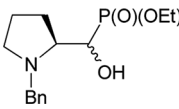
1a,b PG = Cbz
2a,b PG = Boc

11a,b PG = Cbz
12a,b PG = Boc

Scheme 5 Reaction of **1–2a,b** with PyFluor (PyFluor, DBU, MePh, RT, 5d; **11a,b** 78%, **12a,b** 74%).

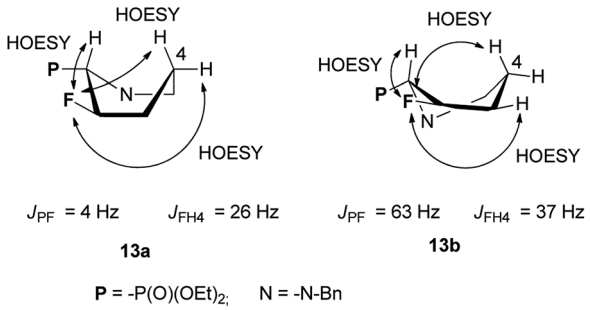
Table 2 Fluorination of **3a,b** with different fluorinating agents[a]



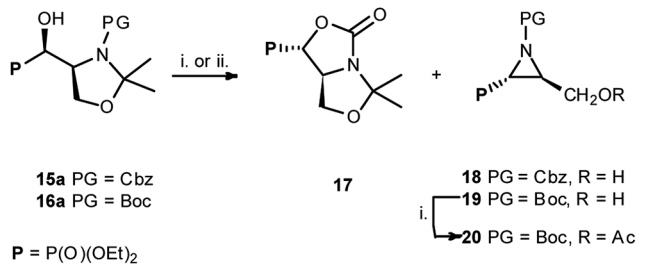
Substrate **3a : 3b**	d.r.	Cond.	**13a**	**13b**	**14**	Yields [%][b] (d.r.)
	1.1 : 1	i	3.2	1	—	59 (3.2 : 1)
	2.1 : 1	ii[c]	9.8	1	—	49 (11.2 : 1)
	2.1 : 1	iii	34	1	—	48 (20 : 1)
	2.1 : 1	iv	5.7	1	—	58 (6.3 : 1)
	1.9 : 1	v[d]	2.2	—	1	19 (—)

[a] (i) DAST, 0 °C → 45 °C (1 h); (ii) DAST, −78 °C (1 h) → 45 °C (0.75 h); (iii) DAST, −78 °C (1 h) → 45 °C (0.75 h), RT (3 h); (iv) Deoxofluor, RT (24 h); (v) PyFluor, DBU, MePh, RT, 5 d. [b] Isolated yields (^{31}P NMR). [c] 27% unreacted **3b**. [d] 44% unreacted **3b**.

When the reaction of **3a,b** (2.1 : 1 d.r.) with DAST was set up at −78 °C, next was carried out at 45 °C for 0.75 h we observed mainly transformation of **3a** into fluorinated product **13a**. In addition, while both isomers **3a** and **3b** were consumed, ratio **13a : 13b** was not corresponding to starting d.r. ratio, presumably due to the presence of other product, not isolated (δ_P: 10 ppm, in the crude reaction mixture). On the other hand, the reaction condition −78 °C (1 h) → 45 °C for 1 h followed by treatment at RT for 3 h gave two fluorinated phosphonates **13a,b** without by-product (^{31}P NMR) with the isolated yield 59%. The separate experiment indicated that compound **13b** is formed from **3b**, and for its formation the higher temperature (45 °C, 0.75 h) was necessary. To compare, the reaction of **3a,b** with Deoxofluor gave **13a,b** with lower diastereoselectivity comparing to reaction with DAST. Surprisingly, the down-field shifted two sets of signals corresponded to compounds **13a** and **13b** and located around δ: −146 ppm ($^{3}J_{FP}$ 3 Hz) and at δ: −145 ppm ($^{3}J_{FP}$ 64 Hz) in ^{19}F NMR indicated that **13a** and **13b** have different structures comparing piperidines **4** and **5**. Nevertheless, the careful analysis of ^{13}C NMR indicated characteristic signals and coupling constants values for C-3 at δ: 96 ppm ($^{1}J_{CF}$ 180 Hz), C-2 at δ: 65 ppm ($^{1}J_{CP}$ 125/150 Hz, $^{2}J_{CF}$ 26/22 Hz) confirming that both compounds are diastereoisomers. On the base of ^{19}F–^{1}H HOESY and NOESY experiments, the arrangement of substituents in **13a** was determined (Scheme 6). Thus, NOE's between fluorine atom and protons: H-2 as well as H-4 (not shown) and H-5 indicated boat conformation and C–P and C–F in a gauche arrangement, additionally confirmed by the value of $^{3}J_{H4F}$ 26 Hz indicating coupling of fluorine with equatorial H-4 (*syn*-periplanar). While compound **13a** had $^{3}J_{FP}$ 4 Hz, analogically to less strained **8**, in case of compound **13b** we have observed analogous vicinal coupling constants as piperidines **4** and **5** ($^{3}J_{FP}$ 63 Hz) suggesting eclipsed conformation, with dihedral angle value *c.a.* 0° between C–P and C–F bond (equatorials). Additionally, ^{19}F–^{1}H HOESY experiments showing NOEs between a fluorine atom and protons: H-2, H-4 and H-5, analogically to compound **4**. These observations allow us to



Scheme 6 The conformations of **13a** and **13b** with observed $^{19}F-^{1}H$ NOEs correlations and some values of coupling constants.



Scheme 7 Reaction of **15–16a** with DAST (i) or DeoxoFluor (ii) from **15a**: DAST: **17** 32% and **18a** 17%; from **16a** (Table 3), and preparation of **20** ((i) Ac_2O, K_2CO_3, AcOEt, **20** 82%).

propose configuration (2*S*,3*R*) for **13a** and (2*S*,3*S*) for piperidine **13b** with *trans*- and *cis*-arrangements of fluorine and phosphonate group in a six-member ring.[25] Analogous reaction of **3a,b** with PyFluor (DBU, toluene) led to **13a** in addition to β-amino-α-fluoroalkylphosphonates **14** (2.2 : 1, crude **13a : 14** ratio). Moreover, remaining diastereoisomer **3b** stayed intact in the reaction mixture, while reaction at a higher temperature (45 °C, 0.75 h) led to decomposition of starting materials. These results are contrary to the reaction of β-amino-α-hydroxyalkylphosphonates with PyFluor where mainly α-fluoroalkylphosphonates were formed,[17] although the amount of the second regioisomer in our case was higher compared to the analogous reaction of **3a,b** with DAST.

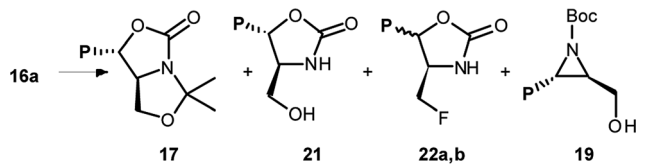
Taking into account the neighbouring groups participation in deoxyfluorination of α-hydroxyphosphonate proline derivatives, we have decided to investigate similar reaction on serine derivatives having *N*-Cbz, *N*-Boc, and *N*-Bn protecting groups. Thus, the reaction with DAST [−78 °C (3 h) → RT (16 h)] carried on **15a,b** or **16a,b** [99 : 1 d.r., (4*S*,1′*R*, : 4*R*,1′*S*)] gave two type of products: bicyclic **17** and aziridines **18** with yields 32% and 17% (or **17** and **19** with yields 40% and 56%, respectively) (Scheme 7).

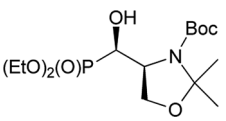
Similarly, to the formation of **6a,b**, bicyclic oxazolidine-2-one **17** arose by the attack of carbamate C=O electron pair (from Cbz or Boc) on leaving group (–$OSF_2N(Et)_2$) coming from the reaction of an alcohol moiety with DAST (Scheme 7). On the base of NMR analysis, we were able to assign stereochemistry of compound **17**. Thus, diagnostic signals located at δ_H 4.38 ppm (dd, *J* 6 Hz, C*H*P) and at δ_H 4.54 ppm (ddt, *J* 15, 7, 6 Hz, C*H*CHP) indicated (1*S*,7a*S*) diastereoisomer of **17**, and additional NOESY experiments confirmed that both protons are on the opposite side of oxazolidinone ring. Moreover, coupling constants value $^{3}J_{PH}$ 15 Hz in case of **17** corresponded to dihedral-angle dependence in phosphonates.[30] Similar value $^{3}J_{PH}$ 11 Hz was also reported by De La Cruz *et al.* and confirmed *trans* oxazolidine-2-one formation.[31] Second isolated type of products, aziridines **18** or **19** were formed by attack of electrons from neighbouring nitrogen atom (*N*-Boc, Cbz) on hydroxyl derived leaving group (-$OSF_2N(Et)_2$), as in case of first step of **4** and **5** formation (pathway a, Scheme 3), with subsequent removal of *N*,*O*-isopropylidene protecting group. These assumptions were confirmed by NMR spectroscopy, as well as the transformation of **19**, to known acetyl derivatives **20** [32] additionally proving configuration (2*S*,3*S*) of compound **19**. Moreover, aziridine **19** existed as a mixture of two rotamers that could be separated by the chromatography techniques.

The formation of aziridine from aziridinium ion by DAST treatment is contrary to known ring-expansion reactions observed for hydroxyphosphonate derivatives of prolinal **1a,b–3a,b**. However, treatment of hydroxy diazepan-2-ones[33] or indolizine[34] derivatives with DAST followed by the nitrogen participation yielded ring contractions as well. On the other hand, application of DAST or Deoxofluor with **16a** under varied conditions gave aziridine **19** and phosphonates **17** and/or **21**, **22a,b** respectively (Table 3).

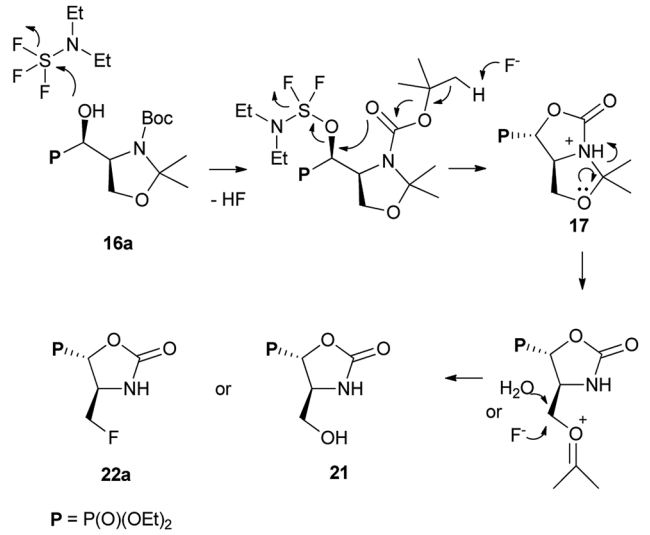
Surprisingly, when the temperature of the reaction mixture was increased (0 °C → RT, 0.75 h) as a major product oxazolidine-2-one **21** (after workup, isolated yield 38%), with a minor aziridine **19**, were obtained. Moreover, extended reaction time at RT [0 °C (0.5 h) → RT (16 h)] gave fluoride **22a** (isolated yield 37%). Analogous treatment of **16a** with DeoxoFluor gave the same results as with DAST. The structure and stereochemistry of compound **21** were assumed to be analogous to **17**, since only *N*,*O*-isopropylidene protecting group was

Table 3 Fluorination of **16a** with DAST or Deoxofluor in varied reaction conditions[a]

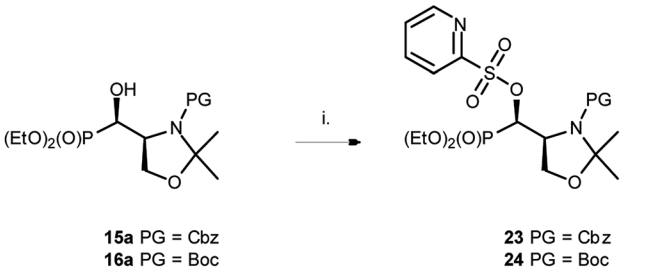


Substrate **16a**	Cond.	Ratio (isolated yield%) **17**	**21**	**22a,b**	**19**
	i	2.1 (40)	—	—	1 (33)
	ii	1.8 (38)	1 (25)	—	1.2 (10)
	iii	1 (4)	9.4 (38)	—	1.9 (8)
	iv	—	1 (—)	16 (20 : 1)	3 (5)
	v	1.6 (34)	—	—	1 (18)

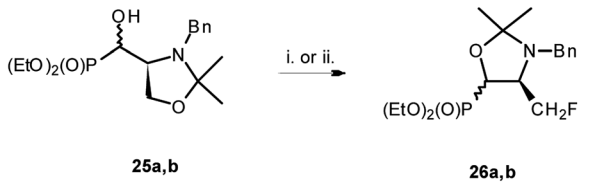
[a] (i) DAST, −78 °C (3 h) → RT (16 h); (ii) DAST, −78 °C → 0 °C (1 h); (iii) DAST, 0 °C → RT (0.5 h); (iv) DAST, −78 °C (3 h) → 0 °C (0.5 h) → RT (16 h); (v) Deoxofluor, RT (30 h).



Scheme 8 The mechanism of DAST-induced transformation of **16a** leading to **21** or **22a**.



Scheme 9 Reaction of **15–16a** with PyFluor. (i) PyFluor, DBU, MePh, RT, 5d; **23a** 60%, **24a** (47%).



Scheme 10 Reaction of **25a,b** with DAST or PyFluor. (i) DAST, RT 0.5 h (**26a** 58%); (ii) PyFluor, DBU, MePh, RT, 5d; **26a** (37%).

removed. Thus *trans*-oxazolidinone ring geometry was confirmed by NMR spectra analysis ($^3J_{HP}$ 18 Hz) indicating (4*S*,5*S*)-**21** configurations. On the base of these observations, we propose the mechanism of DAST-induced transformation of **16a** yielding **21** or **22a** (Scheme 8).

In the beginning, we observed the formation of bicyclic oxazolidine-2-one **17**. Subsequent removal of *N*,*O*-isopropylidene protecting group gave after workup hydroxymethyl derivative **21** or due to the attack of fluoride "HF_2^-" (extended reaction time) led to fluorinated phosphonate oxazolidine-2-one **22a**. Similar DAST-mediated removal of *O*-isopropylidene group has been reported for deoxyfluorination of α-hydroxyphosphonate derivatives of glyceraldehyde yielding fosfomycin analogue.[21] On the other hand, during the reaction of **16a** with DAST, we have observed the **22b** formation, which epimerized during reaction and purification on silica gel to give exclusively **22a** (NMR). The presence of fluoride in exocyclic methyl group is confirmed by the high-field chemical shift of CH_2F signal at $\delta_F \sim -230/-235$ ppm (td, *J* 47, 19/22 Hz). The configurations of **22a** as (4*S*,5*S*) has been confirmed by 2D NMR experiments. Thus, ^{19}F–^1H HOESY experiment showed NOEs between a fluorine atom and geminal protons in CH_2F as well as with H-4 (C*H*P) while no NOEs between H-4 and H-5 has been detected (^1H–^1H NOESY) and proved *trans* arrangement of protons in oxazolidine-2-one ring. Moreover, the reaction of **15a** with DAST at RT yielded **21** and **22a**. Analogously, the deprotection/deoxyfluorination were applied in case of synthesis of *N*-protected L-fluoroalanine. Thus, the desired compound has been obtained by a desilylation/deoxofluorination reaction of oxazolidinone analogue of L-serine using XtalFluor-E in the presence of triethylamine trihydrofluoride.[35]

At the same time, the reaction performed on **15a** as well as on **16a** with PyFluor gave sulfonates **23** or **24** with 60% and 47% isolated yields (Scheme 9), similarly to the reaction of **1–2a,b** with PyFluor leading to compounds **11–12a,b**.

To compare, the reaction of **25a,b** [12.5 : 1 or 3.4 : 1, d.r., (4*S*,1′*R* : 4*R*,1′*S*)]) with DAST at RT (0.5 h) or at 0 °C (2 h) → RT (2 h) gave compound **26a** with a traces of **26b**, while conditions starting from −78 °C (3 h) → 0 °C (1 h) led to the compound **26a** only (as two rotamers in ratio 98 : 2, 58% of yield). Moreover, the reaction of **25a,b** (3.4 : 1) with PyFluor (PyFluor (2.4 eq.), DBU (4 eq.), MePh, RT, 5 d) gave only **26a** (37%) (Scheme 10). The mechanism of the formation of **26a** relied on the attack of fluoride during removal of *O*-isopropylidene protection (as depicted on Scheme 8) followed by substitution of leaving group ($-OSF_2N(Et)_2$) by oxygen atom derived from just created carbonyl group. While ^1H, ^{13}C and ^{19}F NMR spectra of **26a** are similar to **22a** and indicated *trans* arrangement of protons in oxazolidine-2-one ring,[28] as well as presence of CH_2F group, the chemical shifts of signals in ^{31}P NMR are distinctively different from **22a** (δ_P 15.7) but fit to structure of oxazolidine ring in **26a** (δ_P 21.6).[30] Additionally, NOESY experiments indicating correlations between C*H*P–C*H*HF, while other relationship for C*H*N and CH*H*F as well as NOE between a fluorine atom and C*H*N (^1H–^1H NOESY, ^1H–^{19}F HOESY) confirmed the structure of **26a** as *trans* oxazolidine.

Conclusions

In summary, we have discussed the DAST/DeoxoFluor induced transformation of proline or serine derived hydroxyphosphonates having -Cbz, -Boc and -Bn moieties as *N*- protecting groups. It seems that diastereoselective course of deoxyfluorination depends on the participation of the neighbouring group and applied reagent. Thus, the reaction of *N*-Cbz or *N*-Boc prolinols **1–2a** with DAST or Deoxofluor, through aziridinium intermediate and ring opening gave fluorinated piperidine phosphonates **4** or **5** and minors pyrrolidine fluorides **9** or **10**, respectively. In addition, due to the participation

of *N*-protecting group oxazolidine-2-ones **6–7a** were formed. Analogically DAST/DeoxoFluor treatment of the second diastereoisomer of **1–2b** led only to oxazolidine-2-ones **6–7b**. Similarly, the reaction of *N*-Cbz or *N*-Boc protected serinols **15,16a** with DAST or Deoxyfluor yielded analogous oxazolidine-2-one **17** transforming during workup to **21** or by fluorination to **22a,b**, as presented in proposed mechanism. As a second path of the reaction, aziridines **18** and **19** were isolated as the ring contraction products. Only in case of deoxyfluorination of *N*-benzyl prolinols **3a,b** both diastereoisomers of β-fluoropiperidine-α-phosphonates **13a,b** were formed, while the reaction of protected *N*-benzyl serinol **25a,b** gave fluorinated oxazolidines **26a,b**. Moreover, application of PyFluor in the reactions with **1–2a,b** and **15–16a,b** gave sulfonates **11–12a,b** and **23–24**. These studies gave an example of the synthesis of valuable building blocks for the asymmetric synthesis of peptide analogues as well as versatile substrates in the synthesis of biologically active species since amino phosphonates mimic naturally occurring α-amino acids.

Experimental part

General information

^{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 in $CDCl_3$ solution. All 2D 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 ($\delta = 0$) in $CDCl_3$ or $CDCl_3$ ($\delta = 7.26$). Chemical shifts of ^{13}C NMR were expressed in parts per million downfield and upfield from $CDCl_3$ as an internal standard ($\delta = 77.16$). Chemical shifts of ^{19}F NMR were expressed in parts per million upfield from $CFCl_3$ as an internal standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{31}P NMR were expressed in parts per million in $CDCl_3$. All d.r. ratios were evaluated on the basis of ^{31}P NMR in crude reaction mixture. High-resolution mass spectra were recorded by electron spray (MS-ESI) techniques using QToF Impact HD Bruker spectrometer. Reagent grade chemicals were used and solvents were dried by refluxing with sodium metal (toluene), with CaH_2 (DCM) and distilled under an argon atmosphere. All moisture sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Reaction temperatures below 0 °C were performed using a cooling bath (liquid N_2/*i*-PrOH). TLC was performed on Merck Kieselgel 60-F_{254} with EtOAc/hexane, EtOAc//EtOAc/*i*-PrOH/H_2O (4 : 1 : 2, upper layer; SSE) or $CHCl_3$/MeOH 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. DAST was supplied by Sigma Aldrich or Apollo Scientific. All remaining starting materials were supplied by Sigma Aldrich. Substrates have to be well dried prior to use. Compounds **1a,b**, **3a,b**, **15a,b**, **25a,b**;[36] **2a,b**;[6c] **16a,b**[37] were prepared as described.

1. Procedures for the reactions with fluorinating agents

1.1. Procedure A. Reactions of α-hydroxyphosphonates with DAST. To a solution of DAST (4 eq.) in dry CH_2Cl_2 (7 mL) in a cooling bath (liquid N_2/*i*-PrOH, or ice), α-hydroxyphosphonates (1 eq.) in dry CH_2Cl_2 (3 mL) was added slowly and a reaction mixture was kept accordingly to notes below. Then the reaction mixture was diluted with water (5 mL), extracted with CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered and concentrated. The products were isolated using column chromatography ($CHCl_3$/MeOH or EtOAc/hexane).

1.2. Procedure B. Reactions of α-hydroxyphosphonates with DeoxoFluor. To a solution of α-hydroxyphosphonates (1 eq.) in dry CH_2Cl_2 (5 mL), DeoxoFluor (2 eq.) was added and reaction mixture was stirred at room temperature for 24 h under ambient atmosphere. Then the reaction mixture was diluted with water (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, and filtered. Removal of solvent at reduced pressure gave a residue, which was then purified using column chromatography ($CHCl_3$/MeOH or EtOAc/hexane).

1.3. Procedure C. Reactions of α-hydroxyphosphonate with PyFluor. To a solution of α-hydroxyphosphonates (1 eq.) in dry CH_2Cl_2 (5 mL), PyFluor (2.4 eq.) and DBU (4 eq.) was added and reaction mixture was stirred at room temperature for 4 days under ambient atmosphere (monitored by TLC). After reaction was completed, the solvent was removed at reduced pressure, and the products were isolated using column chromatography ($CHCl_3$/MeOH).

Note A1: treatment of **1a : 1b** (22.8 : 1 d.r.) according to procedure A [−78 °C → 0 °C (1.5 h)] gave **4** as a mixture with **9** (60 mg, 43% and 8%, respectively, 5.8 : 1) and **6a,6b** (38 mg, 45%, 9.5 : 1 d.r.).

Note A2: treatment of **1a : 1b** (2.7 : 1 d.r.) according to procedure A [−78 °C (3 h); RT (1 h)] gave **4** (43 mg, 36%) and **6a,6b** (47 mg, 56%, 1.86 : 1 d.r.).

Note A3: treatment of **2a : 2b** (3.8 : 1 d.r.) according to procedure A [−78 °C (3 h); RT (1 h)] gave **5** (60 mg, 38%) and **7a,7b** (65 mg, 53%, 1.9 : 1 d.r.).

Note A4: treatment of **3a : 3b** (1.1 : 1 d.r.) according to procedure A [0 °C → 45 °C (1 h)] gave **13a,b** in few fractions containing different ratio of diastereoisomers (125 mg, 59%, 6.2 : 1 d.r.).

Note A5: treatment of **15a** according to procedure A [0 °C (0.5 h); RT (18 h)] gave **17** (33 mg, 32%) and **18** (21 mg, 17%).

Note A6: treatment of **16a** according to procedure A [−78 °C (3 h); RT (16 h)] gave **17** (18 mg, 40%) and **19** (27 mg, 33%).

Note A7: treatment of **16a** according to procedure A [0 °C → RT (0.5 h)] gave **17** (5 mg, 4%), **19** (12 mg, 8%) and **21** (41 mg, 38%).

Note A8: treatment of **16a** according to procedure A [−78 °C (3 h) → 0 °C (0.5 h); RT (16 h)]; gave **19** (9 mg, 5%) and **22a,b** (59 mg, 37%).

Note A9: treatment of **25a,b** (3.4 : 1 d.r.) according to procedure A (RT, 0.5 h) gave compounds **26a** (19 mg, 58%).

Note B1: treatment of **3a : 3b** (2.1 : 1 d.r.) according to procedure B gave compounds **13a,b** (48 mg, 5.7 : 1, d.r., 74%).

Note C1: treatment of **1a,b** (3.3 : 1 d.r.) according to procedure C, gave **11a,b** (72 mg, 3 : 1, 78%)

Note C2: treatment of **1a,b** (24 : 1:1 d.r.) according to procedure C, gave **11a,b** (36 mg, 18 : 1, 69%)

Note C3: treatment of **2a,b** (37 : 1 d.r.) according to procedure C, gave **12a,b** (42 mg, 74 : 1 d.r., 74%)

Note C4: treatment of **3a : 3b** (1.9 : 1 d.r.) according to procedure C gave compounds **13a** (10 mg, 19%)

Note C5: treatment of **15a** according to procedure C gave compounds **23** (31 mg, 60%).

Note C6: treatment of **16a** according to procedure C gave compounds **24** (32 mg, 47%).

Note C7: treatment of **25a,b** (3.4 : 1 d.r.) according to procedure C gave compounds **26a** (24 mg, 37%).

*(2R,3R)-benzyl 2-(diethoxyphosphoryl)-3-fluoropiperidine-1-carboxylate (**4**).* Isolated with a yield 36% (Note A2) or with 43% as a mixture with **9** (Note A1) as slightly yellow oil, mixture of two rotamers (1.1 : 1). Major rotamer had: ^{1}H NMR (400 MHz) δ = 7.39–7.33 (m, 4H, Ph), 7.33–7.30 (m, 1H, Ph), 5.21 (d, J = 12.3 Hz, 1H, C*H*HPh), 5.12 (d, J = 12.3 Hz, 1H, CH*H*Ph), 5.03 (dd, J = 21.3, 19.4 Hz, 1H, C*H*P), 5.02 (dd, J = 46.6, 12.2 Hz, 1H, C*H*F), 4.17–4.10 (m, 3H, NC*H*H, OCH_2CH$_3$), 4.09–3.99 (m, 2H, OCH_2CH$_3$), 3.37 (td, J = 13.2, 2.6 Hz, 1H, NCH*H*), 2.07–2.02 (m, 2H, CH_2CHF), 1.91–1.76 (m, 1H, NCH$_2$C*H*H), 1.57–1.48 (m, 1H, NCH$_2$CH*H*), 1.32 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.24 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz) δ = 155.37 (d, J = 3.0 Hz, *C*=O), 136.45, 128.50, 128.11, 127.96 (4 × s, Ph), 85.45 (dd, J = 178.9, 19.9 Hz, *C*HF), 67.72 (s, *C*H$_2$Ph), 63.06 (d, J = 7.3 Hz, OCH_2CH$_3$), 62.48 (d, J = 6.8 Hz, OCH_2CH$_3$), 53.23 (dd, J = 150.2, 22.5 Hz, *C*HP), 41.21 (s, NCH_2), 26.36 (d, J = 6.0 Hz, *C*H$_2$CHF), 19.00 (s, NCH$_2$CH_2), 16.36 (d, J = 5.6 Hz, OCH$_2$CH_3), 16.34 (d, J = 6.0 Hz, OCH$_2$CH_3). ^{19}F NMR (377 MHz) δ = −179.55 to −180.05 (m). ^{31}P {/^{1}H} NMR (162 MHz) δ = 19.24 (d, J = 61.7 Hz). Minor rotamer had: ^{1}H NMR (400 MHz) δ = 7.39–7.31 (m, 4H, Ph), 7.33–7.30 (m, 1H, Ph), 5.20 (d, J = 12.3 Hz, 1H, C*H*HPh), 5.12 (d, J = 12.3 Hz, 1H, CH*H*Ph), 5.09 (dd, J = 44.8, 17.7 Hz, 1H, C*H*F), 4.86 (dd, J = 21.0, 18.8 Hz, 1H, C*H*P), 4.26 (d, J = 13.6 Hz, 1H, NC*H*H), 4.17–4.10 (m, 2H, OCH_2CH$_3$), 4.09–3.99 (m, 2H, OCH_2CH$_3$), 3.26 (td, J = 13.3, 2.7 Hz, 1H, NCH*H*), 2.21–2.12 (m, 1H, C*H*HCHF), 2.11–2.07 (m, 1H, *CH*HCHF), 1.91–1.76 (m, 1H, NCH$_2$C*H*H), 1.57–1.48 (m, 1H, NCH$_2$CH*H*), 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.22 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz) δ = 155.73 (d, J = 3.8 Hz, *C*=O), 136.32, 128.48, 128.11, 127.98 (4 × s, Ph), 85.31 (dd, J = 179.0, 20.2 Hz, *C*HF), 67.70 (s, *C*H$_2$Ph), 63.01 (d, J = 7.1 Hz, OCH_2CH$_3$), 62.34 (d, J = 7.1 Hz, OCH_2CH$_3$), 54.11 (dd, J = 150.4, 22.3 Hz, *C*HP), 40.85 (s, NCH_2), 26.15 (d, J = 5.9 Hz, *C*H$_2$CHF), 18.82 (s, NCH$_2$CH_2), 16.44 (d, J = 5.7 Hz, OCH$_2$CH_3), 16.36 (d, J = 5.6 Hz, OCH$_2$CH_3). ^{19}F NMR (377 MHz) δ = −178.86 to −179.39 (m). ^{31}P {/^{1}H} NMR (162 MHz) δ = 18.96 (d, J = 62.0 Hz). HRMS (ESI) calcd for $C_{17}H_{25}FNNaO_5P^+$ ([M + Na]$^+$): 396.1347, found: 396.1361.

*(2S,3S)-tert-butyl 2-(diethoxyphosphoryl)-3-fluoropiperidine-1-carboxylate (**5**).* Isolated with a yield 38% (Note A3), as slightly yellow oil, mixture of two rotamers (1.1 : 1).

Major rotamer had: ^{1}H NMR (400 MHz) δ = 5.07 (br d, J = 42.0 Hz, 1H, C*H*F), 5.00 (dd, J = 21.5, 18.1 Hz, 1H, C*H*P), 4.24–4.09 (m, 4H, 2 × OCH_2CH$_3$), 4.04 (br d, J = 13.6 Hz, 1H, NC*H*H), 3.30 (td, J = 13.3, 3.0 Hz, 1H, NCH*H*), 2.16 (tdd, J = 13.6, 4.7, 2.3 Hz, 1H, C*H*HCHF), 2.08–2.02 (m, 1H, CH*H*CHF), 1.87–1.75 (m, 1H, NCH$_2$C*H*H), 1.53–1.50 (m, 1H, NCH$_2$CH*H*), 1.48 (s, 9H, C(CH_3)$_3$), 1.34 (t, J = 6.1 Hz, 3H, OCH$_2$CH_3), 1.32 (t, J = 6.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz) δ = 154.63 (d, J = 2.9 Hz, *C*=O), 85.56 (dd, J = 178.8, 2.2 Hz, *C*HF), 80.58 (s, *C*(CH$_3$)$_3$), 62.31 (d, J = 6.8 Hz, OCH_2CH$_3$), 62.17 (d, J = 7.1 Hz, OCH_2CH$_3$), 52.35 (dd, J = 149.7, 22.5 Hz, *C*HP), 41.28 (s, NCH_2), 28.30 (s, C(CH_3)$_3$), 26.31 (d, J = 21.4 Hz, *C*H$_2$CHF), 19.03 (s, NCH$_2$CH_2), 16.42 (d, J = 5.9 Hz, OCH$_2$CH_3), 16.31 (d, J = 6.2 Hz, OCH$_2$CH_3). ^{19}F {/^{1}H} NMR (376 MHz) δ = −179.53 (d, J = 63.3 Hz). ^{19}F NMR (376 MHz) δ = −179.25 to −179.78 (m). ^{31}P {/^{1}H} NMR (162 MHz) δ = 19.78 (d, J = 62.9 Hz). Minor rotamer: ^{1}H NMR (400 MHz) δ = 4.99 (br d, J = 42.5 Hz, 1H, C*H*F), 4.80 (dd, J = 24.0, 20.4 Hz, 1H, C*H*P), 4.23–4.21 (m, 1H, NC*H*H), 4.24–4.09 (m, 4H, 2 × OCH_2CH$_3$), 3.15 (td, J = 13.3, 2.9 Hz, 1H, NCH*H*), 2.08–2.02 (m, 2H, CH_2CHF), 1.87–1.75 (m, 1H, NCH$_2$C*H*H), 1.53–1.50 (m, 1H, NCH$_2$CH*H*), 1.48 (s, 9H, C(CH_3)$_3$), 1.36 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.33 (t, J = 6.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz) δ = 154.83 (d, J = 3.5 Hz, *C*=O), 85.35 (dd, J = 178.8, 2.4 Hz, *C*HF), 80.36 (s, *C*(CH$_3$)$_3$), 62.92 (d, J = 7.1 Hz, OCH_2CH$_3$), 62.85 (d, J = 7.1 Hz, OCH_2CH$_3$), 54.35 (dd, J = 150.1, 22.5 Hz, *C*HP), 39.96 (s, NCH_2), 28.27 (s, C(CH_3)$_3$), 26.39 (d, J = 21.6 Hz, *C*H$_2$CHF), 18.85 (s, NCH$_2$CH_2), 16.55 (d, J = 5.6 Hz, OCH$_2$CH_3), 16.42 (d, J = 5.9 Hz, OCH$_2$CH_3). ^{19}F {/^{1}H} NMR (376 MHz) δ = −179.99 (d, J = 63.0 Hz). ^{19}F NMR (376 MHz) δ = −179.74 to −180.25 (m). ^{31}P {/^{1}H} NMR (162 MHz) δ = 19.70 (d, J = 63.1 Hz). HRMS (ESI) calcd for $C_{14}H_{27}FNNaO_5P^+$ ([M + Na]$^+$): 362.1503, found: 362.1511.

*Diethyl ((1R,7aR)-3-oxohexahydropyrrolo[1,2-c]oxazol-1-yl) phosphonate and diethyl ((1S,7aR)-3-oxohexahydropyrrolo[1,2-c]oxazol-1-yl)phosphonate (**6a,6b**) and diethyl ((1S,7aS)-3-oxohexahydropyrrolo[1,2-c]oxazol-1-yl)phosphonate and diethyl ((1R,7aS)-3-oxohexahydropyrrolo[1,2-c]oxazol-1-yl)phosphonate(**7a,7b**).* Isolated with a yield 45% (9.5 : 1 d.r., Note A1) or 56% (1.86 : 1 d.r., Note A2) or 53% (1.9 : 1 d.r., Note A3) as a transparent oil, mixture of two diastereoisomers.

Major diastereoisomer **6a**/**7a** had: ^{1}H NMR (400 MHz) δ = 4.44 (d, J = 4.4 Hz, 1H, C*H*P), 4.27–4.20 (m, 4H, 2 × OCH_2CH$_3$), 4.10 (tdd, J = 11.3, 6.2, 2.7 Hz, 1H, C*H*CHP), 3.66–3.54 (m, 1H, NC*H*H), 3.25–3.16 (m, 1H, NCH*H*), 2.21–2.13 (m, 1H, C*H*HCH), 2.15–2.06 (m, 1H, NCH$_2$C*H*H), 2.02–1.92 (m, 1H, NCH$_2$CH*H*), 1.59–1.48 (m, 1H, CH*H*CH), 1.39–1.33 (m, 6H, 2 × OCH$_2$CH_3). ^{13}C NMR (101 MHz) δ = 159.82 (d, J = 3.9 Hz, *C*=O), 73.80 (d, J = 173.6 Hz, *C*HP), 63.95 (d, J = 6.9 Hz, OCH_2CH$_3$), 63.47 (d, J = 6.7 Hz, OCH_2CH$_3$), 60.30 (s, *C*HCHP), 45.80 (s, NCH_2), 31.49 (d, J = 11.0 Hz, *C*H$_2$CH), 25.51 (s, NCH$_2$CH_2), 16.48 (d, J = 5.4 Hz, 2 × OCH$_2$CH_3). ^{31}P {/^{1}H} NMR (162 MHz) δ = 16.49 (s). Minor diastereoisomer **6b**/**7b** had: ^{1}H NMR (400 MHz) δ = 4.80 (ddd, J = 8.3, 3.6, 2.1 Hz, 1H, C*H*P), 4.27–4.20 (m, 4H, 2 × OCH_2CH$_3$), 4.09–3.99 (m, 1H, C*H*CHP), 3.66–3.54 (m, 1H, NC*H*H), 3.25–3.16 (m, 1H, NCH*H*), 2.15–2.06 (m, 1H, NCH$_2$C*H*H), 2.02–1.92 (m, 2H, CH_2CH), 1.95–1.86 (m, 1H, NCH$_2$CH*H*), 1.39–1.33 (m, 6H, 2 × OCH$_2$CH_3). ^{13}C NMR (101 MHz) δ = 160.17 (d, J = 9.3 Hz, *C*=O), 70.62 (d, J = 172.3 Hz, *C*HP), 63.83 (d, J = 7.0 Hz, OCH_2CH$_3$), 63.15 (d, J = 6.8 Hz, OCH_2CH$_3$), 61.01 (s, *C*HCHP), 45.61 (s, NCH_2), 26.91 (d, J = 5.7 Hz, *C*H$_2$CH), 25.70 (s, NCH$_2$CH_2), 16.44 (br d, J = 5.4 Hz, 2 × OCH$_2$CH_3). ^{31}P {/^{1}H} NMR (162 MHz) δ =

14.56 (s). HRMS (ESI) calcd for $C_{10}H_{18}NNaO_5P^+$ ([M + Na]$^+$): 286.0815, found: 286.0829.

*(2R)-benzyl 2-((diethoxyphosphoryl)fluoromethyl)pyrrolidine-1-carboxylate**9**.* Isolated with a yield 8% as a mixture with **4** (Note A1); slightly yellow oil, a mixture of two rotamers 1.46 : 1. Major rotamer had: ^{19}F NMR (565 MHz) $\delta = -226.78$ (ddd, $J = 78.6$, 46.9, 39.8 Hz). ^{31}P {/^{1}H} NMR (243 MHz) $\delta = 15.71$ (d, $J = 76.5$ Hz). Minor rotamer had: ^{19}F NMR (565 MHz) $\delta = -225.83$ (ddd, $J = 75.1$, 47.1, 33.8 Hz). ^{31}P {/^{1}H} NMR (243 MHz) $\delta = 15.36$ (d, $J = 75.7$ Hz).

*(2S)-tert-butyl 2-((diethoxyphosphoryl)fluoromethyl)pyrrolidine-1-carboxylate (**10**).* Observed in a crude reaction mixture as two rotamers 1.08 : 1. Major rotamer had: ^{19}F NMR (565 MHz) $\delta = -226.96$ (ddd, $J = 79.1$, 47.0, 34.2 Hz). ^{31}P {/^{1}H} NMR (243 MHz) $\delta = 16.14$ (d, $J = 77.6$ Hz). Minor rotamer had: ^{19}F NMR (565 MHz) $\delta = -226.08$ (ddd, $J = 79.9$, 47.2, 34.4 Hz). ^{31}P {/^{1}H} NMR (243 MHz) $\delta = 15.94$ (d, $J = 77.5$ Hz).

*Benzyl (R)-2-((S)-(diethoxyphosphoryl)((pyridin-2-ylsulfonyl)oxy) methyl)pyrrolidine-1-carboxylate (**11a**) and benzyl (R)-2-((R)-(diethoxyphosphoryl)((pyridin-2-ylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (**11b**).* Isolated with yield 78% (3 : 1, d.r., Note C1), or 69% (18 : 1 d.r.; Note C2) as a transparent oil, mixture of two diastereoisomers. Major diastereoisomer **11a** exist as a mixture of two rotamers (1.1 : 1). Major diastereoisomer **11a** (major rotamer) had: ^{1}H NMR (600 MHz) $\delta = 8.68$ (d, $J = 4.0$ Hz, 1H, Ar), 7.92 (d, $J = 7.9$ Hz, 1H, Ar), 7.74 (m, 1H, Ar), 7.47 (br d, $J = 7.6$ Hz, 1H, Ph), 7.44 (dd, $J = 7.6$, 4.8 Hz, 1H, Ar), 7.41–7.33 (m, 3H, Ph), 7.35–7.29 (m, 1H, Ph), 5.77 (dd, $J = 11.9$, 1.7 Hz, 1H, C*H*P), 5.14–5.08 (m, 2H, OCH_2Ph), 4.24 (dd, $J = 9.1$, 4.8 Hz, 1H, C*H*CHP), 4.18–4.06 (m, 4H, 2 × OCH_2CH$_3$), 3.28 (q, $J = 7.7$ Hz, 1H, NC*H*H), 2.96 (ddd, $J = 10.4$, 7.5, 5.5 Hz, 1H, NCH*H*), 2.34–2.22 (m, 1H, C*H*HCH), 2.07–1.97 (m, 1H, CH*H*CH), 1,97–1.87 (m, 1H, NCH$_2$C*H*H), 1.78–1.66 (m, 1H, NCH$_2$CH*H*), 1.33–1.26 (m, 3H, OCH$_2$CH_3), 1.23 (t, $J = 7.0$ Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz) $\delta = 154.92$ (s, *C*═O), 154.20 (s, Ar), 150.38 (s, Ar), 138.06, 136.75, 128.63, 127.96 (4 × s, Ph), 127.68 (s, Ar), 123.36 (s, Ar), 77.51 (d, $J = 159.1$ Hz, *C*HP), 66.86 (s, OCH_2Ph), 63.81 (d, $J = 6.9$ Hz, OCH_2CH$_3$), 63.47 (d, $J = 6.6$ Hz, OCH_2CH$_3$), 57.99 (d, $J = 10.2$ Hz, *C*HCHP), 46.59 (s, NCH_2), 26.04 (s, *C*H$_2$CH), 24.53 (s, NCH$_2$CH_2), 16.50 (d, $J = 5.6$ Hz, 2 × OCH$_2$CH_3)·^{31}P {/^{1}H} NMR (243 MHz) $\delta = 15.15$ (s). Minor rotamer **11a**: ^{1}H NMR (600 MHz) $\delta = 8.72$ (d, $J = 4.4$ Hz, 1H, Ar), 7.86 (m, 1H, Ar), 7.74 (d, $J = 7.8$ Hz, 1H, Ar), 7.54 (dd, $J = 7.7$, 4.7 Hz, 1H, Ar), 7.47 (br d, $J = 7.6$ Hz, 1H, Ph), 7.41–7.33 (m, 3H, Ph), 7.35–7.29 (m, 1H, Ph), 5.58 (dd, $J = 12.1$, 1.7 Hz, 1H, C*H*P), 5.21 (d, $J = 12.1$ Hz, 1H, OCH_2Ph), 5.14–5.08 (m, 1H, OCH_2Ph), 4.20–4.15 (m, 1H, C*H*CHP), 4.18–4.06 (m, 2H, OCH_2CH$_3$), 4.06–3.95 (m, 2H, OCH_2CH$_3$), 3.19 (dt, $J = 10.8$, 7.4 Hz, 1H, NC*H*H), 2.49 (ddd, $J = 10.7$, 7.4, 5.6 Hz, 1H, NCH*H*), 2.34–2.22 (m, 1H, C*H*HCH), 2.07–1.97 (m, 1H, CH*H*CH), 1.78–1.66 (m, 1H, NCH$_2$C*H*H), 1.64–1.57 (m, 1H, NCH$_2$CH*H*), 1.33–1.26 (m, 6H, 2 × OCH$_2$CH_3). ^{13}C NMR (101 MHz) $\delta = 154.45$ (s, *C*═O), 154.36, 150.67, 138.38 (3 × s, Ar), 136.41, 128.66, 128.11, 127.76 (4 × s, Ph), 123.03 (s, Ar), 76.44 (d, $J = 160.9$ Hz, *C*HP), 67.56 (s, OCH_2Ph), 64.12 (d, $J = 7.2$ Hz, OCH_2CH$_3$), 63.32 (d, $J = 6.4$ Hz, OCH_2CH$_3$), 57.13 (d, $J = 10.7$ Hz, *C*HCHP), 47.02 (s, NCH_2), 27.13 (s, *C*H$_2$CH), 23.88 (s, NCH$_2$CH_2), 16.43–16.29 (m, 2 × OCH$_2$CH_3). ^{31}P {/^{1}H} NMR (243 MHz) $\delta = 14.72$ (s). HRMS (ESI) calcd for $C_{22}H_{29}KN_2O_8PS$+ ([M + K]$^+$): 551.1014, found: 551.1022.

Minor diastereoisomer **11b** exist as a mixture of two rotamers (1 : 1). Both rotamers **11b** had: ^{1}H NMR (600 MHz) $\delta = 8.72$–8.69 (m, 1H, Ar), 8.68–8.65 (m, 1H, Ar), 8.05 (d, $J = 7.9$ Hz, 1H, Ar), 7.88–7.79 (m, 2H, Ar), 7.76 (d, $J = 8.0$ Hz, 1H, Ar), 7.55–7.51 (m, 1H, Ph), 7.49 (dd, $J = 7.6$, 4.6 Hz, 1H, Ar), 7.46–7.40 (m, 1H, Ph), 7.40 (d, $J = 7.4$ Hz, 1H, Ar), 7.38–7.33 (m, 2H, Ph), 7.33–7.28 (m, 6H, Ph), 5.34 (t, $J = 8.8$ Hz, 1H, C*H*P), 5.14–5.11 (m, 1H, C*H*P), 5.14–5.11 (m, 1H, OCH_2Ph), 5.12–5.04 (m, 1H, OCH_2Ph), 5.00–4.97 (m, 2H, OCH_2Ph), 4.40–4.29 (m, 2H, 2 × C*H*CHP), 4.19–3.95 (m, 8H, 4 × OCH_2CH$_3$), 3.50–3.41 (m, 2H, NCH_2), 3.40–3.34 (m, 1H, NC*H*H), 3.30–3.22 (m, 1H, NCH*H*), 2.35–2.30 (m, 2H, CH_2CH), 2.06–1.97 (m, 1H, CH_2CH), 1.95–1.87 (m, 2H, NCH$_2$CH_2), 1.82–1.76 (m, 1H, NCH$_2$CH_2), 1.33–1.24 (m, 9H, OCH$_2$CH_3), 1.24–1.17 (m, 3H, OCH$_2$CH_3). ^{13}C NMR (151 MHz) $\delta = 155.24$ (s, *C*═O), 154.69 (s, *C*═O), 154.65, 154.51, 150.40, 150.25, 138.26, 138.20 (6 × s, Ar), 136.68, 136.43, 128.66, 128.48, 128.42, 128.19, 128.06, 127.98 (8 × s, Ph), 127.84 (s, Ar), 127.81 (s, Ar), 123.55 (s, Ar), 123.14 (s, Ar), 76.62 (d, $J = 160.4$ Hz, *C*HP), 76.19 (d, $J = 161.6$ Hz, *C*HP), 67.23 (s, OCH_2Ph), 66.86 (s, OCH_2Ph), 64.01 (d, $J = 6.3$ Hz, 2 × OCH_2CH$_3$), 63.27–63.10 (m, 2 × OCH_2CH$_3$), 57.33 (d, $J = 3.5$ Hz, *C*HCHP), 56.54 (d, $J = 5.1$ Hz, *C*HCHP), 47.04 (s, NCH_2), 46.83 (s, NCH_2), 28.13 (s, *C*H$_2$CH), 27.20 (s, *C*H$_2$CH), 23.69 (s, NCH$_2$CH_2), 22.91 (s, NCH$_2$CH_2), 16.40 (d, $J = 6.3$ Hz, 2 × OCH$_2$CH_3), 16.29 (d, $J = 6.0$ Hz, 2 × OCH$_2$CH_3). ^{31}P {/^{1}H} NMR (243 MHz) $\delta = 15.44$ (s), 15.36 (s).

*tert-butyl (S)-2-((R)-(diethoxyphosphoryl)((pyridin-2ylsulfonyl)oxy) methyl)pyrrolidine-1-carboxylate (**12a**) and tert-butyl (S)-2-((S)-(diethoxyphosphoryl)((pyridin-2-ylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (**12b**).* Isolated with a yield 74% (74 : 1 d.r., Note C3) as a slightly yellow oil. Major diastereoisomer **12a** exist as a mixture of two rotamers (1.7 : 1). Major diastereoisomer **12a** (major rotamer) had: ^{1}H NMR (400 MHz) $\delta = 8.77$–8.70 (m, 1H, Ar), 7.98–7.87 (m, 2H, Ar), 7.57–7.51 (m, 1H, Ar), 5.63 (dd, $J = 12.3$, 1.6 Hz, 1H, C*H*P), 4.27–4.12 (m, 4H, 2 × OCH_2CH$_3$), 4.12–4.06 (m, 1H, C*H*CHP), 3.05 (q, $J = 7.9$ Hz, 1H, NC*H*H), 2.30–2.15 (m, 2H, NCH*H*, CH*H*CH), 2.04–1.87 (m, 1H, CH*H*CH), 1.72–1.52 (m, 2H, NCH$_2$CH_2), 1.52 (br s, 9H, C(CH_3)$_3$), 1.39–1.29 (m, 6H, 2 × OCH$_2$CH_3). ^{13}C NMR (101 MHz) $\delta = 154.58$ (s, *C*═O), 153.69 (s, Ar), 150.64 (s, Ar), 138.38 (s, Ar), 127.67 (s, Ar), 122.96 (s, Ar), 80.49 (s, *C*(CH$_3$)$_3$), 78.06 (d, $J = 140.2$ Hz, *C*HP), 64.12 (d, $J = 7.3$ Hz, OCH_2CH$_3$), 63.14 (d, $J = 6.6$ Hz, OCH_2CH$_3$), 57.14 (d, $J = 11.0$ Hz, *C*HCHP), 46.25 (s, NCH_2), 28.52 (s, C(CH_3)$_3$), 27.01 (s, *C*H$_2$CH), 23.83 (s, NCH$_2$CH_2), 16.46 (d, $J = 5.9$ Hz, 2 × OCH$_2$CH_3). ^{31}P {/^{1}H} NMR (162 MHz) $\delta = 15.38$ (s). Minor rotamer **12a** had: ^{1}H NMR (400 MHz) $\delta = 8.77$–8.70 (m, 1H, Ar), 8.01 (d, $J = 7.9$ Hz, 1H, Ar), 7.98–7.87 (m, 1H, Ar), 7.57–7.51 (m, 1H, Ar), 5.75 (d, $J = 11.7$ Hz, 1H, C*H*P), 4.27–4.12 (m, 1H, C*H*CHP), 4.12–4.06 (m, 2H, OCH_2CH$_3$), 4.06–3.97 (m, 2H, OCH_2CH$_3$), 3.29–3.17 (m, 1H, NC*H*H), 3.05 (q, $J = 7.9$ Hz, 1H, NCH*H*), 2.30–2.15 (m, 1H, C*H*HCH), 2.04–1.87 (m, 3H, CH*H*CH, NCH$_2$CH_2), 1.47 (br s, 9H, C(CH_3)$_3$), 1.27 (br t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3), 1.23 (br t, $J = 6.8$ Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101

MHz) δ = 154.76 (s, *C*=O), 153.69 (s, Ar), 150.30 (s, Ar), 138.05 (s, Ar), 127.63 (s, Ar), 123.40 (s, Ar), 79.79 (s, $C(CH_3)_3$), 76.64 (d, J = 144.5 Hz, *C*HP), 63.42 (d, J = 6.9 Hz, OCH_2CH_3), 63.37 (d, J = 5.6 Hz, OCH_2CH_3), 57.38 (d, J = 9.9 Hz, *C*HCHP), 46.75 (s, NCH_2), 28.63 (s, $C(CH_3)_3$), 26.04 (s, CH_2CH), 24.50 (s, NCH_2CH_2), 16.57 (d, J = 5.8 Hz, 2 × OCH_2CH_3). $^{31}P\{^1H\}$ NMR (162 MHz) δ = 15.55 (s). Minor diastereoisomer **12b** was present in crude reaction mixture as a mixture of two rotamers 3.9 : 1. Major rotamer had: $^{31}P\{^1H\}$ NMR (243 MHz) δ = 15.98 (s). Minor rotamer had: $^{31}P\{^1H\}$ NMR (243 MHz) δ = 15.89 (s). HRMS (ESI) calcd for $C_{19}H_{32}N_2O_8PS^+$ ($[M + H]^+$): 479.1611, found: 479.1606.

*Diethyl ((2S,3R)-1-benzyl-3-fluoropiperidin-2-yl)phosphonate (**13a**) and diethyl ((2S,3S)-1-benzyl-3-fluoropiperidin-2-yl) phosphonate (**13b**).* Isolated with a yield 59% (6.2 : 1 d.r., Note A4) or 74% (5.7 : 1, d.r., Note B1) or 30% (99 : 1, d.r., Note C4), as slightly yellow oil, mixture of two diastereoisomers. Major diastereoisomer **13a** had: ^1H NMR (600 MHz) δ = 7.42–7.37 (m, 3H, Ph), 7.32–7.27 (m, 2H, Ph), 4.15–4.07 (m, 4H, 2 × OCH_2CH_3), 4.06 (dd, J = 14.4, 4.8 Hz, 1H, NC*H*HPh), 3.89 (d, J = 14.0 Hz, 1H, NCH*H*Ph), 3.34 (t, J = 14.5 Hz, 1H, C*H*HCHF), 3.30 (d, J = 9.0 Hz, 1H, CHP), 3.26 (ddd, J = 26.1, 14.2, 2.0 Hz, 1H, C*H*HCHF), 2.97–2.92 (m, 1H, NC*H*H), 2.62 (br dd, J = 12.1, 3.5 Hz, 1H, NC*H*H), 2.56–2.48 (m, 1H, NCH_2CHH), 1.75 (br d, J = 13.0 Hz, 1H, NCH_2CHH), 1.31 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.26 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz) δ = 139.90, 128.46, 128.25, 127.14 (4 × s, Ph), 95.87 (dd, J = 177.6, 3.1 Hz, *C*HF), 64.40 (dd, J = 125.5, 25.9 Hz, *C*HP), 61.79 (dd, J = 7.3, 4.1 Hz, OCH_2CH_3) 60.78 (d, J = 7.2 Hz, OCH_2CH_3), 60.22 (m, CH_2Ph), 45.86 (d, J = 3.2 Hz, NCH_2), 43.28 (dd, J = 21.8, 10.0 Hz, CH_2CHF), 30.20 (d, J = 20.5 Hz, NCH_2CH_2), 16.64 (d, J = 5.8 Hz, OCH_2CH_3), 16.54 (d, J = 5.7 Hz, OCH_2CH_3). ^{19}F NMR (565 MHz) δ = −146.12 (br dt, J = 27.4, 14.2 Hz). $^{19}F\{^1H\}$ NMR (565 MHz) δ = −146.11 (d, J = 3.7 Hz). $^{31}P\{^1H\}$ NMR (243 MHz) δ = 26.96 (d, J = 4.1 Hz).

Minor diastereoisomer **13b** had: ^1H NMR (600 MHz) δ = 7.37–7.32 (m, 3H, Ph), 7.31–7.29 (m, 2H, Ph), 4.27–4.23 (m, 1H, OC*H*HCH$_3$), 4.22–4.18 (m, 1H, OC*H*HCH$_3$), 4.18–4.07 (m, 4H, OCH_2CH_3, NCH_2Ph) 3.43 (dd, J = 21.9, 13.5 Hz, 1H, C*H*P), 3.19 (d, J = 14.6 Hz, 1H, NC*H*H), 3.16 (d, J = 13.1 Hz, 1H, C*H*HCHF), 3.09 (dd, J = 37.3, 14.2 Hz, 1H, CH*H*CHF), 2.69 (br d, J = 13.5 Hz, 1H, NCH*H*), 2.08 (dtd, J = 43.5, 13.6, 4.8 Hz, 1H, NCH_2CHH), 1.92–1.86 (m, 1H, NCH_2CHH), 1.38 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.32 (t, J = 7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz) δ = 135.63, 128.96, 128.27, 128.01 (4 × s, Ph), 95.95 (dd, J = 180.3, 26.3 Hz, *C*HF), 65.36 (dd, J = 146.2, 21.4 Hz, *C*HP), 63.12 (d, J = 7.2 Hz, OCH_2CH_3), 61.25 (d, J = 7.7 Hz, OCH_2CH_3), 60.56 (dd, J = 12.0, 3.6 Hz, CH_2Ph), 46.02 (s, NCH_2), 44.34 (d, J = 20.8 Hz, CH_2CHF), 29.74 (d, J = 22.4 Hz, NCH_2CH_2), 16.75 (d, J = 6.2 Hz, OCH_2CH_3), 16.47 (d, J = 6.2 Hz, OCH_2CH_3). ^{19}F NMR (565 MHz) δ = −144.73 to −145.09 (m). $^{31}P\{^1H\}$ (243 MHz) δ = 23.22 (d, J = 63.4 Hz). HRMS (ESI) calcd for $C_{16}H_{26}FNO_3P^+$ ($[M + H]^+$): 330.1629, found: 330.1626, major peak: $C_{23}H_{32}FNO_3P^+$ ($[M + Bn]^+$): 420.2098, found: 420.2095.

*Diethyl (((S)-1-benzylpyrrolidin-2-yl)fluoromethyl)phosphonate (**14**).* Observed in a crude reaction mixture. Diagnostic signals: ^{19}F NMR (565 MHz) δ = −207.63 (dd, J = 81.6, 44.8 Hz). $^{31}P\{^1H\}$ (243 MHz) δ = 16.51 (d, J = 82.0 Hz).

*Diethyl (1S,7aS)-5,5-dimethyl-3-oxotetrahydro-1H-oxazolo[3,4-c]oxazol-1-ylphosphonate (**17**).* Isolated with a yield 32% (Note A5) or 40% (Note A6) as a slightly yellow oil. Compound **17** had: ^1H NMR (400 MHz) δ = 4.54 (ddt, J = 15.3, 7.3, 6.2 Hz, 1H, C*H*P), 4.38 (dd, J = 6.2, 1.5 Hz, 1H, C*H*CHP), 4.30–4.21 (m, 4H, 2 × OCH_2CH_3), 4.18 (dd, J = 8.6, 6.2 Hz, 1H, OC*H*H), 3.67 (dd, J = 8.6, 7.4 Hz, 1H, OCH*H*), 1.72 (s, 3H, C(CH_3)), 1.45 (s, 3H, C(CH_3)), 1.37 (t, J = 7.0 Hz, 6H, 2 × OCH_2CH_3). ^{13}C NMR (101 MHz) δ = 155.91 (d, J = 6.4 Hz, *C*=O), 95.45 (s, $C(CH_3)_2$), 71.82 (d, J = 176.3 Hz, *C*HP), 68.73 (d, J = 10.6 Hz, OCH_2), 64.29 (d, J = 6.9 Hz, OCH_2CH_3), 63.81 (d, J = 6.7 Hz, OCH_2CH_3), 59.56 (s, *C*HCHP), 27.48 (s, C(*C*H$_3$)), 23.35 (s, C(*C*H$_3$)), 16.64 (d, J = 5.3 Hz, OCH_2CH_3), 16.59 (d, J = 5.7 Hz, OCH_2CH_3). $^{31}P\{^1H\}$ NMR (162 MHz) δ = 15.70 (s). HRMS (ESI) calcd for $C_{11}H_{20}NNaO_6P^+$ ($[M + Na]^+$): 316.0920, found: 316.0929.

*(2S,3S)-benzyl 2-(diethoxyphosphoryl)-3-(hydroxymethyl)aziridine-1-carboxylate (**18**).* Isolated with a yield 17% (Note A5) as a slightly yellow oil. Major rotamer had: ^1H NMR (400 MHz) δ = 7.43–7.34 (m, 5H, Ph), 5.21 (d, J = 12.1 Hz, 1H, C*H*HPh), 5.17 (d, J = 12.1 Hz, 1H, CH*H*Ph), 4.24–4.10 (m, 5H, 2 × OCH_2CH_3, OC*H*H), 3.73 (dd, J = 13.0, 4.1 Hz, 1H, OCH*H*), 3.04 (dtd, J = 7.7, 4.0, 2.3 Hz, 1H, *C*HCP), 2.76–2.70 (m, 1H, C*H*P), 1.36–1.30 (m, 6H, 2 × OCH_2CH_3). ^{13}C NMR (151 MHz) δ = 160.98 (d, J = 7.1 Hz, *C*=O), 135.42, 128.77, 128.73, 128.59 (4 × s, Ph), 68.99 (s, CH_2Ph), 63.41 (d, J = 6.2 Hz, OCH_2CH_3), 62.92 (d, J = 6.1 Hz, OCH_2CH_3), 59.24 (s, OCH_2), 41.84 (d, J = 3.2 Hz, *C*HCP), 31.84 (d, J = 201.2 Hz, *C*HP), 16.55 (d, J = 6.6 Hz, OCH_2CH_3), 16.48 (d, J = 6.8 Hz, OCH_2CH_3). ^{31}P NMR $\{^1H\}$ NMR (162 MHz) δ = 18.43 (s). Minor rotamer (traces) had: $^{31}P\{^1H\}$ NMR (162 MHz) δ = 19.2 (s). HRMS (ESI) calcd for $C_{15}H_{23}NO_6P^+$ ($[M + H]^+$): 344.1258, found: 344.1252.

*(2S,3S)-tert-butyl 2-(diethoxyphosphoryl)-3-(hydroxymethyl) aziridine-1-carboxylate (**19**).* Isolated with a yield 56% (Note A6) or 24% (Note A7) or 5% (Note A8) as a transparent oil. Major rotamer had: ^1H NMR (400 MHz) δ = 4.21–4.14 (m, 4H, 2 × OCH_2CH_3), 4.08 (br d, J = 12.8 Hz, 1H, OC*H*H), 3.67 (dd, J = 12.9, 5.0 Hz, 1H, OCH*H*), 2.96 (dddd, J = 7.5, 5.0, 3.5, 2.6 Hz, 1H, C*H*CHP), 2.60 (dd, J = 18.7, 3.6 Hz, 1H, C*H*P), 1.47 (s, 9H, C(CH_3)$_3$), 1.35 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.34 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (75 MHz) δ = 159.79 (d, J = 6.9 Hz, *C*=O), 82.61 (s, $C(CH_3)_3$), 63.29 (d, J = 6.4 Hz, OCH_2CH_3), 62.81 (d, J = 6.0 Hz, OCH_2CH_3), 60.16 (s, OCH_2), 41.78 (d, J = 3.3 Hz, *C*HCHP), 31.94 (d, J = 201.4 Hz, *C*HP), 28.00 (s, C(CH_3)$_3$), 16.54 (br d, J = 6.2 Hz, 2 × OCH_2CH_3). $^{31}P\{^1H\}$ NMR (162 MHz) δ = 18.89 (s). Minor rotamer had: ^1H NMR (400 MHz) δ = 4.23–4.14 (m, 4H, 2 × OCH_2CH_3), 4.14–4.09 (m, 1H, OC*H*H), 3.64 (dt, J = 12.6, 4.8 Hz, 1H, OCH*H*), 2.98 (dddd, J = 7.6, 5.7, 3.6, 2.4 Hz, 1H, C*H*CHP), 2.60 (dd, J = 18.4, 3.6 Hz, 1H, C*H*P), 2.30 (t, J = 6.7 Hz, 1H, O*H*), 1.48 (s, 9H, C(CH_3)$_3$), 1.36 (t, J = 7.1 Hz, 6H, 2 × OCH_2CH_3). ^{13}C NMR (101 MHz) δ = 159.88 (d, J = 6.9 Hz, *C*=O), 82.77 (s, $C(CH_3)_3$), 63.32 (d, J = 6.4 Hz, OCH_2CH_3), 62.81 (d, J = 6.2 Hz, OCH_2CH_3), 60.58 (d, J = 2.0 Hz, OCH_2), 41.70 (d, J = 3.3 Hz, *C*HCHP), 32.11 (d, J = 201.9 Hz, *C*HP), 28.03 (s, C(CH_3)$_3$),

16.58 (d, J = 6.1 Hz, OCH_2CH_3), 16.57 (d, J = 6.1 Hz, OCH_2CH_3). ^{31}P {/^1H} NMR (162 MHz) δ = 18.74 (s). HRMS (ESI) calcd for $C_{12}H_{24}NNaO_6P$+ ([M + Na]$^+$): 332.1233, found: 332.1240.

*Diethyl ((4S,5S)-4-(hydroxymethyl)-2-oxooxazolidin-5-yl) phosphonate (**21**).* Isolated with a yield 38% (Note A7) as slightly pink oil. Compound **21** had: ^1H NMR (400 MHz) δ = 7.12 (br s, 1H, N*H*), 4.63 (d, J = 5.8 Hz, 1H, C*H*P), 4.25–4.16 (m, 4H, 2 × OCH_2CH_3), 4.11 (ddt, J = 18.4, 5.8, 3.7 Hz, 1H, C*H*CHP), 3.71 (dd, J = 12.0, 3.2 Hz, 1H, OC*H*H), 3.54 (dd, J = 12.0, 4.3 Hz, 1H, OCH*H*), 1.34 (t, J = 7.0 Hz, 6H, 2 × OCH_2CH_3). ^{13}C NMR (101 MHz) δ = 159.00 (d, J = 4.4 Hz, *C*═O), 71.74 (d, J = 173.3 Hz, *C*HP), 64.34 (d, J = 6.9 Hz, OCH_2CH_3), 63.86 (d, J = 6.9 Hz, OCH_2CH_3), 63.04 (d, J = 10.2 Hz, OCH_2), 55.35 (s, *C*HCHP), 16.55 (d, J = 5.0 Hz, OCH_2CH_3), 16.47 (d, J = 5.0 Hz, OCH_2CH_3). ^{31}P{/^1H} NMR (121 MHz) δ = 17.82 (s). HRMS (ESI) calcd for $C_8H_{16}NNaO_6P^+$ ([M + Na]$^+$): 278.0564, found: 278.0564.

*Diethyl ((4S,5S)-4-(fluoromethyl)-2-oxooxazolidin-5-yl)phosphonate (**22a**) and diethyl ((4S,5R)-4-(fluoromethyl)-2-oxooxazolidin-5-yl) phosphonate (**22b**).* Isolated with a yield 37% (Note A8) as transparent oil, a mixture of two invertomers 12.6 : 1. Major invertomer had: ^1H NMR (600 MHz) δ = 6.39 (s, 1H, N*H*), 4.51 (d, J = 6.1 Hz, 1H, C*H*P), 4.50 (ddd, J = 47.1, 10.1, 3.4 Hz, 1H, C*H*HF), 4.40 (ddd, J = 46.6, 9.7, 4.7 Hz, 1H, *CHHF*), 4.29–4.26 (m, 1H, C*H*CHP), 4.26–4.21 (m, 4H, 2 × OCH_2CH_3), 1.37 (t, J = 7.1 Hz, 6H, 2 × OCH_2CH_3). ^{13}C NMR (151 MHz) δ = 157.82 (d, J = 4.7 Hz, *C*═O), 82.82 (dd, J = 176.6, 10.2 Hz, *C*H_2F), 70.85 (dd, J = 174.6, 6.1 Hz, *C*HP), 64.44 (d, J = 7.0 Hz, OCH_2CH_3), 63.92 (d, J = 6.8 Hz, OCH_2CH_3), 53.44 (d, J = 20.7 Hz, N*C*H), 16.59 (d, J = 5.7 Hz, OCH_2CH_3), 16.54 (d, J = 5.9 Hz, OCH_2CH_3). ^{19}F NMR (565 MHz) δ = −230.26 (td, J = 46.6, 18.6 Hz). ^{31}P {/^1H} NMR (243 MHz) δ = 15.70 (s). Minor invertomer had: ^{19}F NMR (565 MHz) δ = −230.66 (td, J = 46.8, 19.2 Hz). ^{31}P {/^1H} NMR (243 MHz) δ = 15.88 (s). HRMS (ESI) calcd for $C_8H_{15}FNNaO_5P^+$ ([M + Na]$^+$): 278.0564, found: 278.0576. Compound **22b**, epimerized during reaction or purification on silica gel yielding **22a**. Major invertomer had: ^{31}P NMR (162 MHz) δ = 15.87 (d, J = 1.2 Hz). ^{19}F NMR (377 MHz) δ = −235.11 (tdd, J = 46.1, 22.8, 1.3 Hz). Minor invertomer had: ^{31}P NMR (162 MHz) δ = 16.84 (s). ^{19}F NMR (377 MHz) δ = −233.90 (td, J = 46.8, 22.6 Hz).

*Benzyl (S)-4-((R)-(diethoxyphosphoryl)((pyridin-2-ylsulfonyl)oxy) methyl)-2,2-dimethyloxazolidine-3-carboxylate (**23**).* Isolated with a yield 60% (Note C5) as a slightly yellow oil, mixture of two rotamers (1.5 : 1). Major rotamer had: ^1H NMR (400 MHz) δ = 8.71 (br d, J = 4.6 Hz, 1H, Ar), 7.95 (d, J = 7.8 Hz, 1H, Ar), 7.94–7.85 (m, 1H, Ar), 7.56–7.49 (m, 2H, Ar), 7.43–7.34 (m, 3H, Ph), 7.36–7.31 (m, 1H, Ph), 5.73 (dd, J = 11.0, 1.5 Hz, 1H, C*H*P), 5.33–5.10 (m, 2H, OCH_2Ph), 4.33–4.28 (m, 1H, C*H*CHP), 4.28–4.25 (m, 1H, OC*H*H), 4.16–4.02 (m, 1H, OCH*H*), 4.16–4.02 (m, 2H, OCH_2CH_3), 3.95–3.88 (m, 2H, OCH_2CH_3), 1.47 (s, 3H, C(CH_3)$_2$), 1.22 (s, 3H, C(CH_3)$_2$), 1.19 (t, J = 7.1 Hz, OCH_2CH_3), 1.18 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz) δ = 154.84 (s, *C*═O), 152.27 (s, Ar), 150.58 (s, Ar), 138.13 (s, Ar), 136.12 (s, Ph), 128.91 (s, Ph), 128.70 (s, Ph), 128.37 (s, Ph), 128.36 (s, Ph), 128.28 (s, Ph), 127.81 (s, Ar), 123.40 (s, Ar), 95.13 (s, *C*(CH_3)$_2$), 75.37 (d, J = 159.0 Hz, *C*HP), 67.69 (s, OCH_2Ph), 63.75–63.53 (m, OCH_2CH_3), 63.44 (d, J = 6.6 Hz, OCH_2CH_3), 63.64 (s, OCH_2), 56.78 (d, J = 10.7 Hz, *C*HCHP), 24.73 (s, C(CH_3)$_2$), 23.70 (s, C(CH_3)$_2$), 16.43 (d, J = 5.6 Hz, OCH_2CH_3), 16.32 (d, J = 5.8 Hz, OCH_2CH_3). ^{31}P {/^1H} NMR (162 MHz) δ = 15.08 (s). Minor rotamer had: ^1H NMR (400 MHz) δ = 8.71 (br d, J = 4.6 Hz, 1H, Ar), 8.03 (d, J = 7.9 Hz, 1H, Ar), 7.94–7.85 (m, 1H, Ar), 7.56–7.49 (m, 2H, Ar), 7.43–7.34 (m, 3H, Ph), 7.36–7.31 (m, 1H, Ph), 5.88 (dd, J = 11.1, 1.6 Hz, 1H, C*H*P), 5.33–5.10 (m, 2H, OCH_2Ph), 4.41–4.36 (m, 1H, C*H*CHP), 4.33–4.28 (m, 1H, OC*H*H), 4.16–4.02 (m, 1H, OCH*H*), 4.16–4.02 (m, 4H, 2 × OCH_2CH_3), 1.49 (s, 3H, C(CH_3)$_2$), 1.44 (s, 3H, C(CH_3)$_2$), 1.33–1.22 (m, 6H, 2 × OCH_2CH_3). ^{13}C NMR (151 MHz) δ = 154.65 (s, *C*═O), 153.51 (s, Ar), 150.29 (s, Ar), 138.05 (s, Ar), 136.15 (s, Ph), 128.91 (s, Ph), 128.70 (s, Ph), 128.37 (s, Ph), 128.30 (s, Ph), 128.27 (s, Ph), 128.16 (s, Ar), 123.70 (s, Ar), 94.67 (s, *C*(CH_3)$_2$), 74.05 (d, J = 161.5 Hz, *C*HP), 67.59 (s, OCH_2Ph), 63.89 (d, J = 6.9 Hz, OCH_2CH_3), 63.75–63.53 (m, OCH_2CH_3), 63.01 (s, OCH_2), 58.02 (d, J = 10.0 Hz, *C*HCHP), 25.93 (s, C(CH_3)$_2$), 25.43 (s, C(CH_3)$_2$), 16.46 (d, J = 5.7 Hz, OCH_2CH_3), 16.33 (d, J = 5.7 Hz, OCH_2CH_3). ^{31}P {/^1H} NMR (162 MHz) δ = 15.36 (s). HRMS (ESI) calcd for $C_{23}H_{31}N_2NaO_9PS^+$ ([M + Na]$^+$): 565.1380, found: 565.1394.

*tert-Butyl (S)-4-((R)-(diethoxyphosphoryl)((pyridin-2-ylsulfonyl) oxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (**24**).* Isolated with a yield 47% (Note C7) as a transparent oil, mixture of two rotamers (1 : 1). Both rotamers had: ^1H NMR (400 MHz) δ = 8.74 (br t, J = 4.8 Hz, 2H, Ar), 8.05 (dd, J = 7.5, 4.5 Hz, 2H, Ar), 7.92 (t, J = 7.8 Hz, 2H, Ar), 7.57–7.51 (m, 2H, Ar), 5.82 (dd, J = 11.0, 1.6 Hz, 1H, C*H*P), 5.77 (d, J = 11.1 Hz, 1H, C*H*P), 4.35–4.30 (m, 1H, C*H*CHP), 4.28–4.23 (m, 3H, 2 × OC*H*H, C*H*CHP), 4.22–3.94 (m, 10H, 2 × OCH*H*, 4 × OCH_2CH_3), 4.11–4.03 (m, 4H, 2 × OCH_2CH_3), 1.58 (s, 12H, 4 × CH_3), 1.53 (s, 9H, 3 × CH_3), 1.47 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.33 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.30 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.30–1.22 (m, 3H, OCH_2CH_3), 1.25 (s, 3H, CH_3), 1.22 (t, J = 7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR (101 MHz) δ = 155.05 (s, *C*═O), 154.81 (s, *C*═O), 152.75 (s, Ar), 151.77 (s, Ar), 150.48 (s, Ar), 150.23 (s, Ar), 138.09 (s, Ar), 137.98 (s, Ar), 127.78 (s, Ar), 127.75 (s, Ar), 123.73 (s, Ar), 123.34 (s, Ar), 94.69 (s, *C*(CH_3)$_2$), 94.33 (s, *C*(CH_3)$_2$), 81.07 (s, *C*(CH_3)$_3$), 81.02 (s, *C*(CH_3)$_3$), 75.93 (d, J = 161.2 Hz, *C*HP), 74.29 (d, J = 161.4 Hz, *C*HP), 63.84 (d, J = 7.4 Hz, OCH_2CH_3), 63.61 (d, J = 6.7 Hz, OCH_2CH_3), 63.54–63.23 (m, 2 × OCH_2CH_3), 63.35 (s, OCH_2), 62.82 (s, OCH_2), 57.61 (d, J = 10.2 Hz, *C*HCHP), 56.98 (d, J = 10.9 Hz, *C*HCHP), 29.83 (s, CH_3), 28.55 (s, 9 × CH_3), 16.48 (d, J = 5.6 Hz, 4 × OCH_2CH_3). ^{31}P NMR (162 MHz) δ = 15.86 (s), 15.62 (s). HRMS (ESI) calcd for $C_{20}H_{34}N_2O_9PS^+$ ([M + H]$^+$): 509.1717, found: 509.1711.

*Diethyl ((4S,5S)-3-benzyl-4-(fluoromethyl)-2,2-dimethyloxazolidin-5-yl)phosphonate (**26a**) and diethyl ((4S,5R)-3-benzyl-4-(fluoromethyl)-2,2-dimethyloxazolidin-5-yl)phosphonate (**26b**).* Isolated with a yield 58% (Note A9) as transparent oil. Major diastereoisomer **26a** (major invertomer) had: ^1H NMR (400 MHz) δ = 7.40–7.37 (m, 2H, Ph), 7.33–7.28 (m, 2H, Ph), 7.26–7.21 (m, 1H, Ph), 4.25 (dd, J = 47.2, 4.0 Hz, 1H, C*H*HF), 4.23 (d, J = 47.4, 4.0 Hz, 1H, CH*H*F), 4.29–4.14 (m, 4H, 2 × OCH_2CH_3), 4.14 (dd, J = 8.7, 2.3 Hz, 1H, C*H*P), 3.94 (d, J = 14.6 Hz, 1H, C*H*HPh), 3.74 (d, J = 14.6 Hz, 1H, CH*H*Ph), 3.62–3.46 (m, 1H, C*H*CHP), 1.40 (s, 3H, CH_3), 1.40–

1.30 (m, 6H, 2 × OCH_2CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (101 MHz) δ = 139.88, 128.41, 128.20, 127.24 (4 × s, Ph), 98.68 (d, J = 6.6 Hz, $C(CH_3)_2$), 82.05 (dd, J = 174.6, 4.4 Hz, CH_2F), 71.09 (dd, J = 172.9, 6.1 Hz, CHP), 64.18 (dd, J = 19.7, 3.5 Hz, NCH), 63.17 (d, J = 6.8 Hz, OCH_2CH_3), 62.76 (d, J = 6.9 Hz, OCH_2CH_3), 52.95 (CH_2Ph), 28.17 (s, CH_3), 22.84 (s, CH_3), 16.62 (d, J = 5.7 Hz, 2 × OCH_2CH_3). ^{19}F NMR (376 MHz) δ = −227.50 (td, J = 47.5, 22.2 Hz). ^{31}P {/^{1}H} NMR (162 MHz) δ = 21.56 (s). Minor invertomer **26a** (observed in a crude reaction mixture) had: ^{19}F NMR (376 MHz) δ = −227.50 (td, J = 47.5, 22.2 Hz). ^{31}P {/^{1}H} NMR (162 MHz) δ = 21.56 (s). Minor diastereoisomer **26b** was observed in a crude reaction mixture. Major inwertomer had: ^{19}F NMR (565 MHz) δ = −230.84 (td, J = 47.1, 27.4 Hz). ^{31}P NMR (243 MHz) δ = 18.90 (s). Minor invertomer had: ^{19}F NMR (565 MHz) δ = −229.67 (td, J = 47.3, 28.1 Hz). ^{31}P {/^{1}H} NMR (162 MHz) δ = 20.09 (s). HRMS (ESI) calcd for $C_{17}H_{27}FNNaO_4P^+$ ([M + Na]$^+$): 382.1557, found: 382.1554.

2. Procedure for *N*-Boc deprotection. Preparation of diethyl (2*S*,3*S*)-3-fluoropiperidin-2-ylphosphonate (8). Treatment of **5** with trifluoroacetic acid (0 °C, 3 h) gave after evaporating and column chromatography ($CHCl_3$/MeOH, 95 : 5) compound **8** as transparent oil (32 mg, 73%): ^{1}H NMR (600 MHz) δ = 4.62 (dqd, J = 48.0, 8.3, 4.4 Hz, 1H, CHF), 4.17 ("pd", J = 7.1, 2.2 Hz, 4H, 2 × OCH_2CH_3), 3.02 (dt, J = 11.7, 3.5 Hz, 1H, NCHH), 2.97 (ddd, J = 10.4, 8.5, 5.4 Hz, 1H, CHP), 2.50 (t, J = 11.2 Hz, 1H, NCHH), 2.26–2.18 (m, 1H, CHHCHF), 1.99 (br s, 1H, NH), 1.74 (tt, J = 7.0, 3.9 Hz, 1H, NCH_2CHH), 1.60–1.48 (m, 2H, CHHCHF, NCH_2-CHH), 1.33 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.32 (t, J = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (151 MHz) δ = 88.28 (dd, J = 177.3, 3.7 Hz, CHF), 62.76 (d, J = 6.7 Hz, OCH_2CH_3), 62.59 (d, J = 6.7 Hz, OCH_2CH_3), 58.09 (dd, J = 156.6, 23.2 Hz, CHP), 45.62 (d, J = 13.8 Hz, NCH_2), 31.12 (dd, J = 19.0, 11.0 Hz, CH_2CHF), 24.12 (d, J = 9.3 Hz, NCH_2CH_2), 16.58 (d, J = 5.7 Hz, 2 × OCH_2CH_3). ^{19}F NMR (565 MHz) δ = −176.49 to −176.61 (m). ^{31}P {/^{1}H} NMR (243 MHz) δ = 23.79 (d, J = 6.0 Hz). HRMS (ESI) calcd for $C_9H_{20}FNO_3P^+$ ([M + H]$^+$): 240.1159, found: 240.1148.

3. Procedure for preparation of diethyl (2*S*,3*S*)-3-acetoxymethyl-1-(*tert*-butoxycarbonyl) aziridin-2-yl-2-phosphonate (20). Reaction of **19** (56 mg, 0.18 mmol) with Ac_2O (86 μL, 92 mg, 0.9 mmol) and K_2CO_3 (50 mg, 0.36 mmol) in anhydrous ethyl acetate (RT, 2 d) gave compound **20** as a transparent oil with a yield 82% (52 mg) as a rotamers mixture (1.1 : 1). Major rotamer had: ^{1}H NMR (400 MHz) δ = 4.31 (dd, J = 12.1, 4.3 Hz, 1H, OCHH), 4.23–4.09 (m, 5H, OCHH, 2 × OCH_2CH_3), 3.18–3.12 (m, 1H, CHCHP), 2.62 (dd, J = 18.4, 3.2 Hz, 1H, CHP), 2.18 (s, 3H, CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 1.33 (t, J = 7.1 Hz, 6H, 2 × OCH_2CH_3). ^{13}C NMR (101 MHz) δ = 179.19 (d, J = 6.0 Hz, C═O), 152.90 (s, C═O), 83.06 (s, $C(CH_3)_3$), 64.63 (s, OCH_2), 62.90 (d, J = 6.2 Hz, OCH_2CH_3), 62.78 (d, J = 6.0 Hz, OCH_2CH_3), 38.14 (d, J = 2.6 Hz, CHCHP), 32.97 (d, J = 195.6 Hz, CHP), 27.78 (s, $C(CH_3)_3$), 23.80 (s, CH_3), 16.56 (d, J = 5.6 Hz, OCH_2CH_3), 16.52 (d, J = 6.1 Hz, OCH_2CH_3). ^{31}P {/^{1}H} NMR (162 MHz) δ = 18.33 (s). Minor rotamer had: ^{1}H NMR (400 MHz) δ = 4.27 (dd, J = 4.3, 0.9 Hz, 2H, OCH_2), 4.23–4.09 (m, 4H, 2 × OCH_2CH_3), 3.03 (dq, J = 7.9, 4.1 Hz, 1H, CHCHP), 2.54 (dd, J = 17.8, 3.5 Hz, 1H, CHP), 2.04 (s, 3H, CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.34 (t, J = 6.7 Hz, 6H, 2 × OCH_2CH_3). ^{13}C NMR (101 MHz) δ = 170.19 (s, C═O), 158.50 (d, J = 7.6 Hz, C═O), 82.47 (s, $C(CH_3)_3$), 63.48 (d, J = 6.3 Hz, OCH_2CH_3), 63.32 (d, J = 6.2 Hz, OCH_2CH_3), 61.57 (s, OCH_2), 38.37 (d, J = 2.7 Hz, CHCHP), 32.79 (d, J = 197.8 Hz, CHP), 27.97 (s, $C(CH_3)_3$), 20.82 (s, CH_3), 16.56 (d, J = 5.6 Hz, OCH_2CH_3), 16.52 (d, J = 6.1 Hz, OCH_2CH_3). ^{31}P {/^{1}H} NMR (162 MHz) δ = 18.63 (s).

Conflicts of interest

There are no conflicts to declare.

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