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DAST mediated preparation of β-fluoro-α-aminophosphonates

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ABSTRACT

Herein, we report a new and convenient method for the synthesis of β-fluoro-α-aminophosphonates starting from naturally occurring L-amino acids. A key step in the synthetic protocol involves nucleophilic fluorination of *N*,*N*-dibenzylated-β-amino alcohols with diethylaminosulfur trifluoride (DAST).

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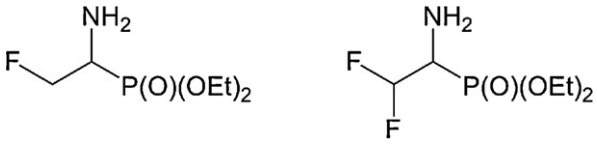
1. Introduction

Organophosphorus compounds are important substrates in biochemical processes. They are potent bioactive molecules used as agrochemicals and pharmaceuticals, as well as effective enzyme inhibitors [1]. It is also known, that the introduction of fluorine atom(s) into organic molecules may change their chemical, physical and biological properties [2]. These fundamental observations are the conceptual base for studies on new organophosphorus–fluorine containing compounds. For example, it has been shown that fluorinated aminophosphonates are useful inhibitors of many enzymes [3]. Cytotoxic and antibacterial activities has been reported for some of the fluorine-containing aminophosphonates [4]. To the best of our knowledge, there are only a few examples of synthesis of β-fluorinated α-aminoalkylphosphonates, which have been found to be an inhibitor of alanine racemase (Scheme 1) [5].



Scheme 1.

Nucleophilic fluorination is one of the common methods of introduction of a fluorine atom into organic compounds [6]. It should be noted that fluorine-containing reagents are usually poor nucleophiles. Fluoride itself is the smallest anion which can form strong hydrogen bonds, however, its solvation can dramatically decrease its nucleophilicity by the formation of stable solvation shells [2]. One of the most common procedures to introduce fluorine atom to phosphonate system is the replacement of hydroxyl group with fluorine. The common and quite useful reagent (stable and commercially available) which can be used is DAST (diethylaminosulfur trifluoride) [7]. However, mechanism of fluorination with DAST in case of α-hydroxyphosphonates depends of the phosphonate system [8].

In this paper we would like to report, neighbouring group participation during DAST-mediated fluorination of series of simple β-amino-α-hydroxyphosphonates. We believe, this is the first example of direct access to various β-fluoro-α-aminophosphonates.

2. Results and discussion

Our synthetic strategy was to synthesize series of *N*-protected α-hydroxyphosphonates (Scheme 2) and next, modify the molecule via introduction a fluorine atom into this system. As starting material a series of simple alkyl and aryl α-amino acids had been chosen. At first α-amino acids **1a–e** (**1a-** Glycine, **1b-** L-Alanine, **1c-** L-Leucine, **1d-** L-Phenylalanine, **1e-** D-Phenylglycine) were transformed into *N*,*N*-dibenzylamino alcohols **2a–e** in two step procedure with good yields. First benzylation with BnBr in presence of K_2CO_3 in water at 80 °C and next reduction of obtained

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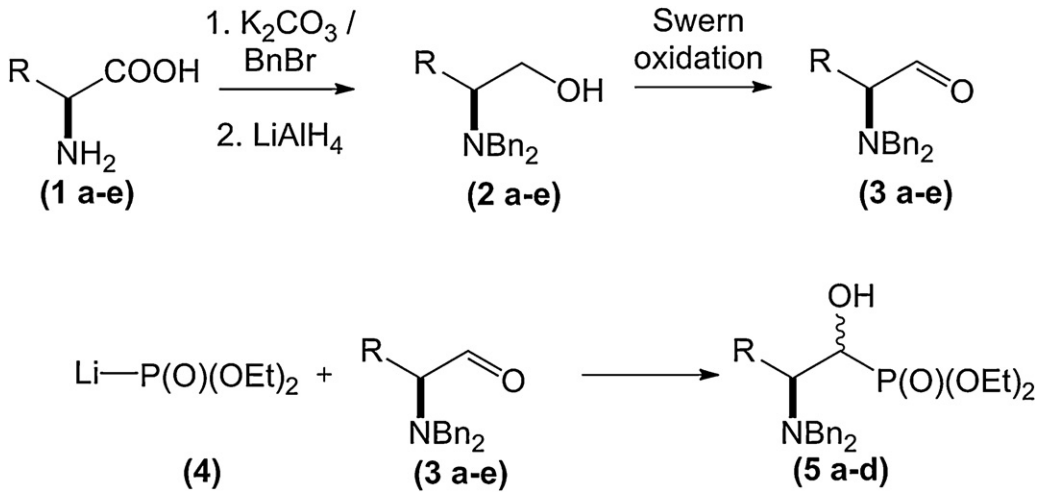
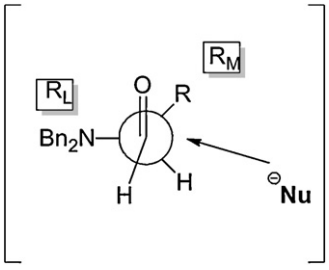


Scheme 2.

esters by $LiAlH_4$ in Et_2O at room temperature yielded aminoalcohols **2a–e** [9]. Conversion of compounds **2a–e** to corresponding aldehydes **3a–e** was carried out using the Swern oxidation under standard conditions in CH_2Cl_2 at −78 °C (oxalyl chloride, DMSO, Et_3N).

Aldehydes **3a–e** after extraction and evaporation of solvents were sufficiently pure to allow to be used directly to introduce C–P bond in Pudovik reaction [10]. Lithium diethyl phosphite **4** was generated in situ from diethyl phosphate/LiHMDS and added to a solution of aldehydes **3a–e** in dry THF at −30 °C. After purification a mixture of chromatographically inseparable diastereoisomers of β-amino-α-hydroxyphosphonates **5a–d** has been obtained in modest yield.

Diastereoselectivity (Table 1) of this reaction can be explained by the Felkin–Ahn model (Scheme 3), and was determined after analysis of the ^{31}P NMR spectra. The absolute configuration at carbon C1 of compounds **5a–d** was deduced from the known stereochemical outcome of the nucleophilic additions to 2-(*N*,*N*-dibenzyloamino)aldehydes [9].



Scheme 3.

In the case of compound **5c** we obtained, almost quantitatively the anti diastereoisomer as it was anticipated. Unfortunately, the Pudovik reaction failed for **5e** derivative. Prepared β-amino-α-hydroxyphosphonates were then treated with DAST in CH_2Cl_2 at −78 °C (Scheme 4).

Table 1
Pudovik reaction.

Compound	R	d.r.	Yield %
5a	H	–	52
5b	Me	80:20	48
5c	*i*-Pr	90:10	44
5d	Bn	85:15	50

^{19}F NNR analysis of the crude products showed, that apart from β-fluorides **6b-d**, we have found α-fluorinated derivatives as impurities which can be removed by the column chromatography. We would suggest that the mechanism of this nucleophilic fluorination, after the activation of hydroxyl group, involves formation of an aziridinium ion as the key step of the synthesis (Scheme 5). A similar mechanism has been recently proposed by O'Hagan et al. during fluorination of *N*,*N*-dibenzyl-β-amino alcohols with Deoxo-Fluor® or DAST [11]. Dolence and Roylance in their work also showed opening aziridinium ring by a fluoride-ion [12].

Diastereoselectivity of this reaction was determined on the bases of the ^{31}P NMR as well as ^{19}F NMR spectra. $^{31}P\{/H\}$ NMR analysis showed different P–F coupling constants between each of diatereoisomer: **6b** $^3J_{P-F}$ = 19.5 Hz, $^3J_{P-F}$ = 7.9 Hz, for compound **6c** $^3J_{P-F}$ = 14.7 Hz, $^3J_{P-F}$ = 9.6 Hz and for **6d** $^3J_{P-F}$ = 15.5 Hz, $^3J_{P-F}$ = 9.4 Hz which can be easily understood by the Karplus dihedral angle relationship (Table 2) [13].

In the case of fluorination of compound **5a** using identical protocol unexpectedly has been observed different regiochemistry. From the complex reaction mixture we were able to isolated major product the α-fluoride **6a**, $^{31}P\{/H\}$ NMR showed large P–F coupling constants $^2J_{P-F}$ = 84.7 Hz, $^2J_{P-F}$ = 76.5 Hz, what unambiguously indicates the fluorine atom is placed at α-position to the phosphorous. Regiochemistry of this reaction might be the consequence of lower stability of the aziridinium ion.

In conclusion we have demonstrated simple procedure to obtain a few β-fluoro-α-aminophosphonates. Those compounds can be used as convenient precursors for the new class of building blocks in the preparation of medicinally important analogs.

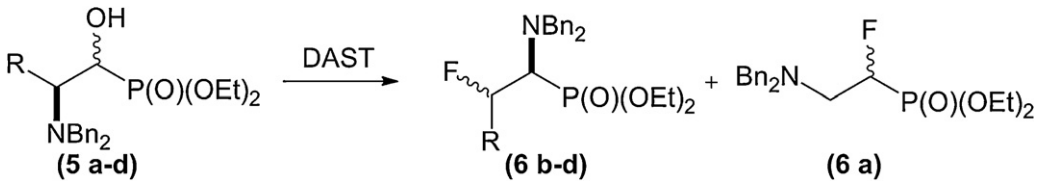
3. Experimental

3.1. General methods

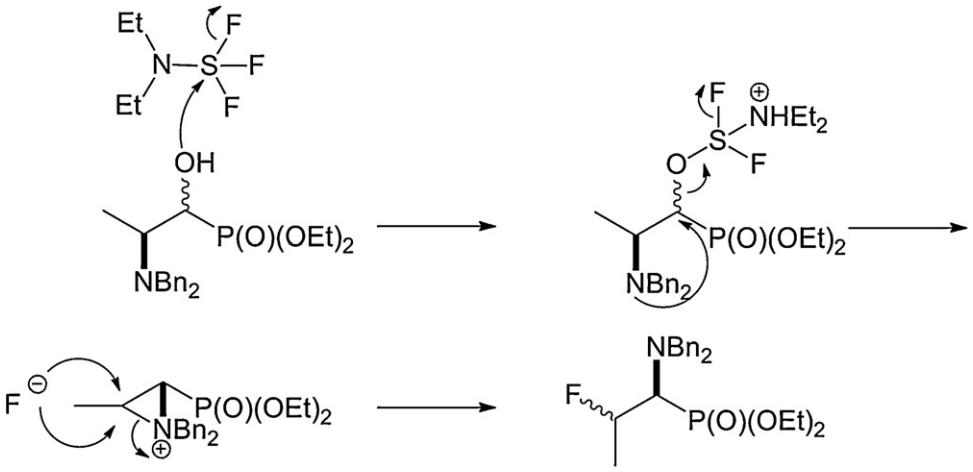
^1H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were performed on Varian GEMINI 300 (300 MHz) and Varian 400

Table 2
DAST-mediated fluorination.

Compound	R	d.r.	Yield %
6b	Me	80:20	55
6c	*i*-Pr	90:10	41
6d	Bn	85:15	60



Scheme 4.



Scheme 5.

(400 MHz) spectrometers. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard ($\delta = 77.0$). Chemical shifts of ^{19}F NMR were expressed in parts per million upfiled from $CFCl_3$ as an internal standard ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{31}P NMR were expressed in parts per million downfield from 85% H_3PO_4 as an external standard ($\delta = 0$) in $CDCl_3$. ^{1}H, ^{13}C NMR chemical shifts are reported for the major diastereoisomer only. Low-resolution and high resolution mass spectra were recorded by electron impact (MS-EI) techniques using AMD-402 spectrometer. Reagent grade chemicals were used. Solvents were dried by refluxing with sodium metal-benzophenone (THF), with $CaCl_2$ (CH_2Cl_2), NaH (Et_2O) and distilled under argon atmosphere. All moisture sensitive reactions were carried out under argon atmosphere using oven-dried glassware. Reaction temperatures below 0 °C were performed using a cooling bath (liquid N_2/hexane or CO_2/isopropanol). TLC was performed on Merck Kieselgel 60-F254 with EtOAc/hexane as developing systems, and products were detected by inspection under UV light (254 nm) and with a solution of potassium permanganate. Merck Kieselgel 60 (230–400 mesh) was used for column chromatography. DAST was obtained from Aldrich.

3.2. General procedures

3.2.1. Benzylation

Amino acids **1a**–**e** (5.6 mmol, 1 equiv.) were added to a solution of potassium carbonate (12.35 mmol, 2.2 equiv.) in H_2O (20 mL) at room temperature. After 15 min benzyl bromide (22.45 mmol, 4 equiv.) was added, and suspension was heated to 80 °C. After 18 h mixture was cooled to room temperature and products were extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with 25 mL of saturated solution of NaCl, dried over $MgSO_4$, filtered and concentrated. The crude products were purified using flash chromatography (hexane/ethyl acetate 85:15, v/v). This methodology provided benzyl 2-(dibenzylamino) derivatives as a colorless oil.

3.2.2. Reduction

Benzyl 2-(dibenzylamino) derivatives (3.92 mmol, 1 equiv.) were added to a stirred suspension of lithium aluminum hydride (11.75 mmol, 3 equiv.) in Et_2O (15 ml) under argon atmosphere at 0 °C. After 15 min cooling bath was removed and mixtures were stirred overnight and cooled again to 0 °C. Mixtures has been worked-up by careful dropwise addition of 0.5 mL of H_2O, 1 mL of 15% KOH and 1.5 mL of H_2O. Aluminum salts were removed by filtration, and the filtrates were concentrated under reduced pressure. Crude products were purified by flash chromatography (hexane/ethyl acetate 70:30, v/v).

2a: Colorless oil ^{1}H NMR (403 MHz, $CDCl_3$) $\delta = 7.39–7.14$ (m, 10 H, Ar), 3.61 (s, 2H, Bn), 3.58–3.54 (t, $J = 5{,}30$ Hz 2H, $CH_2\underline{H_2}OH$), 2.67–2.63 (t, $J = 5.40$ Hz, 2H, $C\underline{H_2}H_2OH$). The NMR data were in good agreement with the reported data from an alternative synthesis [14].

2b: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.43–7.17$ (m, 10 H, Ar), 3.82 (d, $J = 13.3$ Hz, 2H, $NC\underline{H_a}H_bPh$), 3.51–3.35 (m, 1H, $CHC\underline{H_a}H_bOH$), 3.35 (d, $J = 13.3$ Hz, 2H, $NCH_a\underline{H_b}Ph$), 3.38–3.28 (m, 1H, $CHCH_a\underline{H_b}OH$), 3.22–3.08 (s, 1H, OH) 3.05–2.91 (m, 1H, $C\underline{H}CH_2OH$), 0.98 (d, $J = 6.7$ Hz, 3H, CH_3). The NMR data were in good agreement with the reported data from an alternative synthesis [15].

2c: Colorless oil ^{1}H NMR (403 MHz, $CDCl_3$) $\delta = 7.42–7.16$ (m, 10H, Ar), 3.80 (d, $J = 13.3$ Hz, 2H, $NC\underline{H_a}H_bPh$), 3.51–3.40 (m, 2H, $C\underline{H_2}OH$), 3.36 (d, $J = 13.3$ Hz, 2H, $NCH_a\underline{H_b}Ph$), 3.23 (s, 1H, OH), 2.84 (tq, $J = 10.2$, 5.0, 2.6 Hz, 1H, $(CH_3)_2C\underline{H}$), 1.56–1.46 (m, 1H, $C\underline{H}CH_2OH$), 1.21–1.12 (m, 2H, $(CH_3)_2CHC\underline{H_2}$), 0.92 (d, $J = 6.1$ Hz, 3H, CH_3), 0.85 (d, $J = 6.0$ Hz, 3H, CH_3). The NMR data were in good agreement with the reported data from an alternative synthesis [15].

2d: White solid NMR (300 MHz, $CDCl_3$) $\delta = 7.49–7.03$ (m, 15H, Ar), 3.93 (d, $J = 13.3$ Hz, 2H, $NC\underline{H_a}H_bPh$), 3.50 (dd, $J = 16.5$, 6.1 Hz, 1H, $C\underline{H_a}H_bOH$), 3.49 (d, $J = 13.3$, 2H, $NCH_a\underline{H_b}Ph$), 3.35 (s, 1H, OH), 3.20–2.96 (m, 3H, $CH_a\underline{H_b}OH$, $C\underline{H}CH_2OH$, $CHCH_a\underline{H_b}Ph$), 2.43 (dd,

J = 12.9, 9.4 Hz, 1H, CHC$\underline{H}_a$H$_b$Ph). The NMR data were in good agreement with the reported data from an alternative synthesis [16].

3.2.3. Oxidation

DMSO (3.92 mmol, 2 equiv.) was added dropwise to a stirred solution of oxalyl chloride (2.35 mmol, 1.2 equiv.) in CH_2Cl_2 (15 mL) under argon at −78 °C and the reaction mixture was stirred for 5 min. Then a solution of 2-(dibenzylamino)alcohols **2a–d** (1.96 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) were added. After 30 min of stirring at −78 °C triethylamine (7.8 mmol, 4 equiv.) was added, and mixtures were allowed to warm to room temperature over 30 min. The reaction mixtures were then diluted with H_2O (30 mL) and CH_2Cl_2 (30 mL) and the layers were separated. The organic layers were washed with 1% HCl (10 mL), H_2O (10 mL), 5% $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting crude 2-(dibenzylamino)aldehydes **3a–d** were used without additional purification.

3.2.4. Pudovik reaction

Lithium bis-(trimethylsilyl)amide was prepared by addition of *n*-BuLi (3 mmol, 1.3 equiv., 2 M in pentane) to a stirred solution of bis(trimethylsilyl)amine (2.3 mmol, 1.3 equiv.) in THF (1 mL) under an atmosphere of argon at 0 °C. The solution was stirred for additional 30 min. Reaction mixture was then added dropwise to a stirred solution of diethyl phosphite (2.3 mmol, 1.3 equiv.) in THF (2 mL) under an atmosphere of argon at −78 °C. After 10 min the solution was allowed to warm to room temperature over 45 min and then cooled to −30 °C. 2-(dibenzylamino)aldehydes **3a–d** (1.74 mmol, 1 equiv.) in THF (1 mL) were added dropwise into the solution. After addition, reaction mixtures were slowly allowed to warm to room temperature and stirred overnight, quenched by addition of saturated solution of NH_4Cl (10 mL). Crude products were extracted to AcOEt (3 × 10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified using flash chromatography (chloroform/methanol 100:1, v/v).

5a: Colorless oil ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41–7.22 (m, 10H, Ar), 4.17–3.94 (m, 6H, 2x OC$\underline{H}_2$CH$_3$, C$\underline{H}_2$NBn$_2$), 3.85 (d, J = 13.2 Hz, 2H, NC$\underline{H}_a$H$_b$Ph), 3.48 (d, J = 13.4 Hz, 2H, NCH$_a\underline{H}_b$Ph), 3.01–2.76 (m, 1H, C$\underline{H}$CH$_2$NBn$_2$), 1.28–1.22 (td, J = 7.05, 0.5 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.18 (td, J = 7.1, 0.5 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.07, 128.87, 128.23, 127.00, 70.42 (d, $^2J_{C-P}$ = 160.3 Hz), 63.06 (d, $^3J_{C-P}$ = 7.1 Hz), 62.78 (d, $^3J_{C-P}$ = 7.3 Hz), 57.83, 53.22 (d, $^3J_{C-P}$ = 4.0 Hz), 16.19 (d, $^4J_{C-P}$ = 2.2 Hz), 16.12 (d, $^4J_{C-P}$ = 1.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ = 23.43 (s); MS m/z: 378 $[M+H]^+$.

5b: Yellow solid ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.44–7.12 (m, 10H, Ar), 4.20 (dd, J = 9.7, 2.5 Hz, 1H, C$\underline{H}$OH), 4.16–3.91 (m, 4H, OC$\underline{H}_2$CH$_3$), 3.78 (d, J = 14.0 Hz, 2H, NC$\underline{H}_a$H$_b$Ph), 3.63 (d, J = 13.9 Hz, 2H, NCH$_a\underline{H}_b$Ph), 3.24 (dqd, J = 13.9, 7.0, 2.8 Hz, 1H, CH$_3$C$\underline{H}$NBn$_2$), 2.88 (s, 1H, OH) 1.25 (dd, J = 14.8, 7.3 Hz, 6H, C$\underline{H}_3$CHNBn$_2$, OCH$_2$C$\underline{H}_3$), 1.19 (t, J = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.12, 128.66, 128.07, 126.71, 69.40 (d, $^2J_{C-P}$ = 155.0 Hz), 62.45 (d, $^3J_{C-P}$ = 10.4 Hz), 62.36 (d, $^3J_{C-P}$ = 10.4 Hz), 54.32, 52.97 (d, $^3J_{C-P}$ = 6.8 Hz), 16.35, 16.27, 9.75. ^{31}P NMR (163 MHz, $CDCl_3$) major diastereoisomer δ = 23.86 (s), minor diastereoisomer δ = 23.12 (s); MS m/z: 392 $[M+H]^+$.

5c: Colorless oil ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.42–7.12 (m, 10H, Ar), 4.39 (dd, J = 11.5, 6.4 Hz, 1H, C$\underline{H}$OH), 4.25–3.99 (m, 4H, OC$\underline{H}_2$CH$_3$), 3.88 (d, J = 13.7 Hz, 2H, NC$\underline{H}_a$H$_b$Ph), 3.49 (d, J = 13.7 Hz, 2H, NCH$_a\underline{H}_b$Ph), 3.11 (dddd, J = 12.0, 10.1, 4.0, 1.9 Hz, 1H, (CH$_3$)$_2$CHCH$_2$C$\underline{H}$), 2.82 (m, J = 6.9, 3.9 Hz, 1H, (CH$_3$)$_2$C$\underline{H}$CH$_2$CH), 1.91 (tdd, J = 13.2, 6.8, 3.4 Hz, 1H, (CH$_3$)$_2$CHC$\underline{H}_a$H$_b$CH), 1.74 (ddd, J = 14.1, 10.1, 4.0 Hz, 1H, (CH$_3$)$_2$CHCH$_a\underline{H}_b$CH), 1.32 (t, J = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.25 (t, J = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 0.90 (d, J = 6.8 Hz, 3H, CH$_3$), 0.51 (d, J = 6.5 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.02, 129.15, 128.03, 126.80, 65.94 (d, $^2J_{C-P}$ = 153.5 Hz), 62.44 (d, $^3J_{C-P}$ = 7.2 Hz), 54.97 (d, $^3J_{C-P}$ = 6.3 Hz), 54.26, 52.99, 34.93, 23.98, 23.86, 21.15, 16.47 (d, $^4J_{C-P}$ = 5.2 Hz), 16.40 (d, $^4J_{C-P}$ = 5.4 Hz). ^{31}P NMR (163 MHz, $CDCl_3$) major diastereoisomer δ = 24.32 (s), minor diastereoisomer δ = 23.64 (s); MS m/z: 420 $[M+H]^+$.

5d: White solid ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.47–7.03 (m, 15H, Ar), 4.35 (ddd, J = 10.4, 7.2, 1.8 Hz, 1H, C$\underline{H}$OH), 4.22–3.95 (m, 4H, OC$\underline{H}_2$CH$_3$), 3.88 (d, J = 14.2 Hz, 2H, NC$\underline{H}_a$H$_b$Ph), 3.58 (d, J = 14.1 Hz, 2H, NCH$_a\underline{H}_b$Ph), 3.42–3.33 (m, 1H, PhCH$_2$C$\underline{H}$), 3.24 (dd, J = 7.2, 3.9 Hz, 1H, PhC$\underline{H}_a$CH$_b$), 3.09 (dd, J = 7.2, 4.8 Hz, 1H, PhCH$_a$C$\underline{H}_b$), 1.30–1.20 (m, 6H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.27, 139.52, 129.65, 128.55, 127.88, 127.82, 126.52, 125.66, 65.64 (d, $^2J_{C-P}$ = 154.1 Hz), 62.90 (d, $^3J_{C-P}$ = 7.1 Hz), 62.24 (d, $^3J_{C-P}$ = 7.4 Hz), 59.29 (d, $^4J_{C-P}$ = 6.2 Hz), 54.01, 32.23, 16.40, 16.33. ^{31}P NMR (163 MHz, $CDCl_3$) major diastereoisomer δ = 24.23 (s), minor diastereoisomer δ = 23.42 (s); MS m/z: 468 $[M+H]^+$.

3.2.5. Fluorination

To a stirred solution of DAST (1.05 mmol, 1.5 equiv.) in 3 mL of CH_2Cl_2 under an atmosphere of argon at −78 °C a solutions of **5a–d** compounds (1 mmol, 1 equiv.) in 0.5 mL of CH_2Cl_2 were added. The mixtures were stirred at −78 °C for 1 h, followed by 1 h at room temperature. Solutions were poured into a stirred mixture of saturated $NaHCO_3$ and ice chips, extracted to CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified using flash chromatography (hexane/ethyl acetate 50:50, v/v).

6a: Yellow oil ^{19}F NMR (379 MHz, $CDCl_3$) δ = −201.20 (dd, J = 84.8, 44.8 Hz). ^{31}P NMR (163 MHz, $CDCl_3$) δ = 15.02 (d, J = 84.7 Hz).

6b: Pale yellow oil ^{1}H NMR (403 MHz, $CDCl_3$) δ 7.43–7.16 (m, 10H, Ar), 5.11–4.89 (m, 1H, CH$_3$C$\underline{H}$F), 4.24–3.86 (m, 8H, OC$\underline{H}_2$CH$_3$, NC$\underline{H}_2$Ph), 3.12–3.01 (m, 1H, CH$_3$CHFC$\underline{H}$), 1.44–1.30 (m, 6H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.98, 129.08, 128.23, 127.15, 89.14 (dd, J = 169.3, 3.4 Hz, C–F), 61.51 (dd, J = 7.2, 2.1 Hz), 61.35 (dd, J = 7.1, 0.9 Hz), 60.39 (dd, J = 134.9, 24.7 Hz, C–P), 55.65 (d, J = 1.2 Hz), 55.63 (d, J = 1.0 Hz), 19.87 (dd, J = 22.9, 7.2 Hz), 16.52 (d, J = 3.3 Hz), 16.46 (d, J = 3.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) minor diastereoisomer δ = −176.55 to −177.20 (m, 1F), major diastereoisomer −177.81 to −178.41 (m, 1F). ^{31}P NMR (163 MHz, $CDCl_3$) minor diastereoisomer δ = 25.98 (d, $^3J_{P-F}$ = 19.5 Hz), major diastereoisomer 25.56 (d, $^3J_{P-F}$ = 7.9 Hz). HRMS (EI) Calcd. for $C_{21}H_{29}FNO_3P$ $[M]^+$: 393.18690; Found: 393.18579.

6c: Pale yellow oil ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.45–7.11 (m, 10H, Ar), 4.99–4.77 (m, 1H, *i*-PrC$\underline{H}$F), 4.25–3.92 (m, 4H, OC$\underline{H}_2$CH$_3$), 3.98 (d, J = 13.5 Hz, 2H, NC$\underline{H}_a$H$_b$Ph), 3.88 (d, J = 13.6 Hz, NCH$_a\underline{H}_b$Ph), 3.10 (ddd, J = 18.0, 14.4, 6.6 Hz, 1H *i*-PrCHFCH), 1.73–1.62 (m, 1H, (CH$_3$)$_2$C$\underline{H}$), 1.57 (ddd, J = 14.5, 8.8, 2.8 Hz, 1H, (CH$_3$)$_2$CHC$\underline{H}_a$H$_b$), 1.46 (ddd, J = 9.7, 8.2, 5.2 Hz, 1H, (CH$_3$)$_2$CHCH$_a\underline{H}_b$), 1.38 (t, J = 6.2 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.34 (t, J = 6.2 Hz, 3H, OCH$_2$C$\underline{H}_3$), 0.90 (d, J = 6.5 Hz, 3H, C$\underline{H}_3$), 0.88 (d, J = 6.6 Hz, 3H, C$\underline{H}_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.10, 129.20, 128.25, 127.20, 91.32 (dd, J = 171.5, 1.8 Hz, C–F), 61.57 (dd, J = 7.1, 2.3 Hz), 61.39 (dd, J = 7.3, 0.7 Hz), 59.76 (dd, J = 136.0, 24.5 Hz, C–P), 55.75 (d, J = 0.8 Hz), 55.72 (d, J = 0.6 Hz), 42.30 (dd, J = 20.6, 5.8 Hz), 24.53 (dd, J = 2.6, 1.8 Hz), 23.29, 21.80, 16.63 (d, J = 6.0 Hz), 16.55 (d, J = 5.7 Hz). ^{19}F NMR (379 MHz, $CDCl_3$) δ = −184.92 to −185.54 (m, 1F). ^{31}P NMR (121 MHz, $CDCl_3$) minor diastereoisomer δ = 26.48 (d, $^3J_{P-F}$ = 14.7 Hz), major diastereoisomer δ = 25.65 (d, $^3J_{P-F}$ = 9.6 Hz). HRMS (EI) Calcd. for $C_{24}H_{35}FNO_3P$ $[M]^+$: 435.23388; Found: 435.23266.

6d: Pale yellow oil ^{1}H NMR (403 MHz, $CDCl_3$) δ = 7.51–6.91 (m, 15H, Ar), 5.13–4.91 (m, 1H, PhCH$_2$C$\underline{H}$F), 4.24–3.92 (m, 4H, OC$\underline{H}_2$CH$_3$), 4.04 (d, J = 13.4 Hz, 2H, NC$\underline{H}_a$H$_b$Ph), 3.76 (d,

J = 13.5 Hz, 2H, NCH_aH_bPh), 3.34 (ddd, J = 30.6, 14.3, 4.8 Hz, 1H, $PhCH_aCH_b$), 3.21 (ddd, J = 19.4, 18.0, 5.8 Hz, 1H, $PhCH_aCH_b$), 2.79 (ddd, J = 16.2, 14.4, 8.4 Hz, 1H, $PhCH_2CHFCH$), 1.34 (t, J = 6.4 Hz, 3H, OCH_2CH_3), 1.31 (t, J = 6.4 Hz, 3H, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.91, 137.03 (dd, J = 4.6, 1.3 Hz), 129.35, 129.14, 128.51, 128.23, 127.13, 126.60, 92.70 (dd, J = 176.0, 1.8 Hz, C–F), 61.64 (dd, J = 7.0, 1.0 Hz), 61.50 (dd, J = 7.1, 1.8 Hz), 58.51 (dd, J = 140.8, 24.1 Hz, C–P), 55.69 (d, J = 1.1 Hz), 55.65 (d, J = 1.0 Hz), 39.54 (dd, J = 21.6, 5.3 Hz), 16.53 (d, J = 6.1 Hz), 16.46 (d, J = 6.2 Hz). ^{19}F NMR (379 MHz, $CDCl_3$) δ = major diastereoisomer −182.14 to −182.61 (m, 1F), minor diastereoisomer −184.97 −185.51 (m, 1F). ^{31}P NMR (121 MHz, $CDCl_3$) minor diastereoisomer δ = 25.75 (d, $^3J_{P-F}$ = 15.5 Hz), major diastereoisomer 24.50 (d, $^3J_{P-F}$ = 9.4 Hz). HRMS (EI) Calcd. for $C_{27}H_{33}FNO_3P$ $[M]^+$: 469.21820; Found: 469.21699.

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