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FULL PAPER

Deoxyradiofluorination Reaction from β-Hydroxy-α-aminoesters: an Entry to [^{18}F]Fluoroaminoesters under mild conditions

Marine Morlot,[a] Fabienne Gourand,[a] and Cécile Perrio*[a]

Abstract: We report the conversion of β-hydroxy-α-aminoesters derived from serine, α-methylserine or β-phenylserine to the corresponding [^{18}F]fluorinated α or β-aminoesters by deoxyradiofluorination using [^{18}F]fluoride. The method involved the ring opening of an aziridinum intermediate formed *in situ* in the presence of a base after activation of the alcohol function with triflic anhydride. The overall process was carried out at room temperature. Both the efficiency and the regioselectivity of the reaction were found to be dependent on the starting substrates. [^{18}F]Fluoroaminoesters were obtained in radiochemical yields ranging from 10-75%. No improvement was observed for reactions carried out under heating.

Introduction

Modification of organic molecules by introduction of fluorine is known to provide compounds with unique biological properties that could find utility in a variety of fields such as chemical biology, pharmacology, drug discovery and medicinal chemistry for therapeutic and diagnostic developments.[1] In particular, α- and β-aminoacid derivatives bearing a fluorine atom at vicinal aliphatic position have found widespread applications in peptide/protein chemistry and protein recognition, and they represent an important class of 1) enzyme inhibitors, 2) antitumor and antibacterial agents, 3) probes for ^{19}F NMR studies and 4) radiotracers for Positron Emission Tomography after radiolabelling with fluorine-18 such as [^{18}F]NST732 and its regioisomer for apoptosis imaging.[2] As a result, the development of routes to [^{18}F]fluoroaminoacids is demanding. The usual approaches used nucleophilic [^{18}F]fluoride anion in substitution of halides[3] or sulfonates[4] and in ring opening of sulfamidates[5] or aziridines[2k,6]. These reactions required heating conditions and the preparation of precursors may involve a multi-step synthesis. Recently, late-stage manganese salen and decatungstate-catalyzed C-H radiofluorinations were reported but they were restricted to benzylic or branched [^{18}F]fluoroaminoacids.[7]

The deoxyfluorination reaction is a common method to access to aliphatic fluorinated products (Scheme 1).[8,9] Advantages are the use of readily accessible hydroxylated starting materials and the large functional group compatibility. The method has been successfully exploited for the synthesis of a variety of fluoroaminoacids from hydroxyaminoesters.[9] DAST, Deoxo-fluor, XtalFluor, Fluolead, DFI and PhenoFluor are popular reagents to exchange hydroxyl groups for fluorine (Scheme 1). They all usually exhibit high reactivity under mild reaction conditions by converting the alcohol function into an activated leaving group while providing the nucleophilic fluoride source for fluorination. Unfortunately, these polyfluorinated reagents are not suitable for fluorine-18 chemistry due to the inaccessibility of isotopically pure ^{18}F-radiolabelled variants.[10] Recently, PyFluor has been reported as a new monofluorinated reagent efficient for the deoxyfluorination of a broad range of alcohols.[11] Although promising, [^{18}F]PyFluor readily obtained from [^{18}F]fluoride, was found to be relatively weakly reactive in the radiosynthesis of a [^{18}F]fluoroglucose derivative, and optimization and scope studies still are required.

In previous work, we developed the deoxyradiofluorination of ethanolamines for the radiosynthesis of [^{18}F]fluoroethylamines using directly [^{18}F]fluoride (Scheme 1).[12] The reaction involved a three step procedure involving the activation of the aminoalcohol precursor with triflic anhydride, then the *in situ* formation of an aziridinium intermediate by anchimeric assistance of the tertiary amine function, and finally the ring opening by [^{18}F]fluoride. The reaction was found to be efficient at room temperature, confirming the strong electrophilic property of aziridinium. From phenylalaninol substrates (R_3 = Bn), the nucleophilic attack on the aziridinum intermediate occurred preferentially at the quaternary carbon leading to a moderate regioselectivity in favour of the rearranged isomer. These results were in accordance with non-radioactive reactions.

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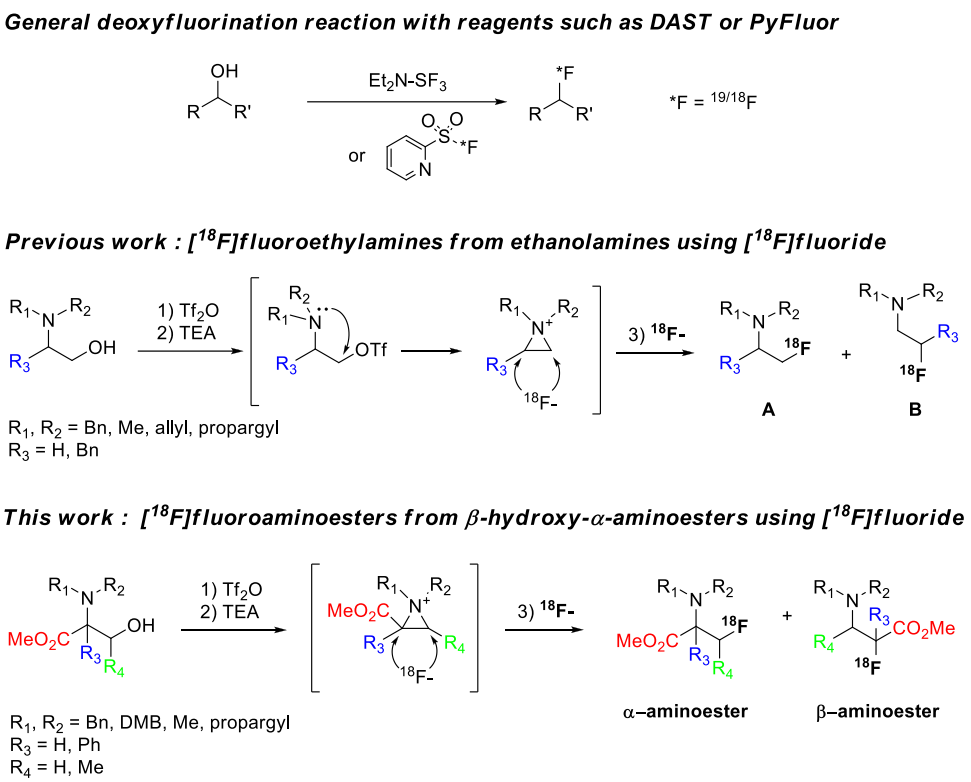


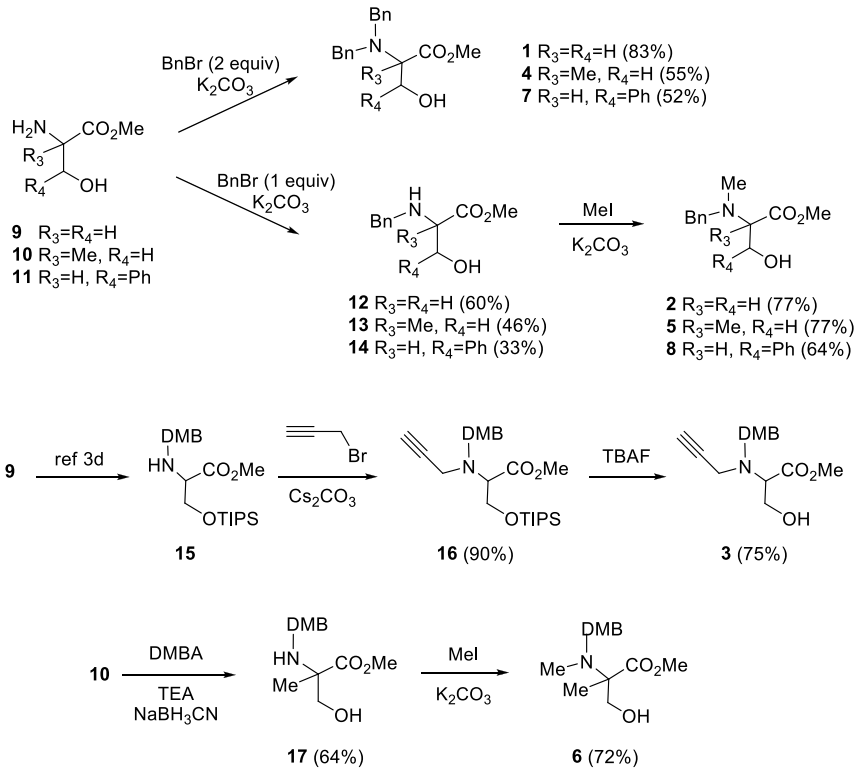
Scheme 1. Deoxy(radio)fluorination reactions

Aziridiniums have been largely proved to be key intermediates in the non-radioactive synthesis of fluoroaminoacids by deoxyfluorination of β-hydroxy-α-aminoesters with reagents such as DAST.[9] Substitution was a major factor that determined the efficiency and the regioselectivity of the ring opening. Fluoro-α-aminoesters were the sole regioisomers obtained from β-phenylserine substrates,[9f] whereas fluoro-β-aminoesters were isolated as the major products starting from serine or methylserine precursors.[9a-e] The aim of this study was to develop a radioactive version of the deoxyfluorination approach to easily access to ^{18}F-fluoroaminoacids. We thus investigated the deoxyradiofluorination reaction of serine esters using [^{18}F]fluoride anion (Scheme 1). For this purpose, it was important to re-visit the reaction under appropriate conditions. We first compared DAST and TBAF in the non-radioactive reaction, then we studied the deoxyradiofluorination and optimized the radiosynthesis conditions. In all cases, we examined the influence of the substituents of both the amine (R_1, R_2) and aziridinium ring (R_3, R_4) on the regioselective formation of the corresponding α- or β-aminoester products.

Results and Discussion

Synthesis of β-hydroxy-α-aminoester precursors 1-8

β-Hydroxy-α-aminoesters **1**-**8** derived from serine (R_3 = H, R_4 = H), α-methylserine (R_3 = Me, R_4 = H) or β-phenylserine (R_3 = H, R_4 = Ph) were chosen as precursors. Their synthesis is depicted in Scheme 2. Methylester of serine compounds **9**-**11** were subject to dibenzylation with benzylbromide (2 equiv) to give the *N*,*N*-dibenzylamine derivatives **1**, **4** and **7** in 83-52% yields.[13] *N*-Monobenzylated analogues **12**-**14** were obtained in 60-33% yields using equimolar amounts of benzyl bromide. Subsequent alkylation with methyl iodide led to *N*-benzyl-*N*-methylamines **2**, **5** and **8** (64-77% yields).[14] The synthesis of *N*-propargyl, *N*-dimethoxybenzyl serine precursor **3** was carried out via the *N*-dimethoxybenzyl-*O*-protected serine ester **15** prepared from serine methylester **9** as previously reported by reductive amination with dimethoxybenzadehyde then protection with triisopropylsilyl (TIPS) group.[3d] Compound **15** was converted to **16** by *N*-alkylation with propargylbromide (90% yield). Deprotection of **16** with TBAF yielded precursor **3** in 75% yield. *N*-Methyl,*N*-dimethoxybenzyl-α-methylserine **6** was obtained according to a two-step synthesis by reductive amination of α-methylserine methylester **10** with dimethoxybenzaldehyde leading to **17** (64% yield), followed by *N*-methylation with methyl iodide (72% yield).

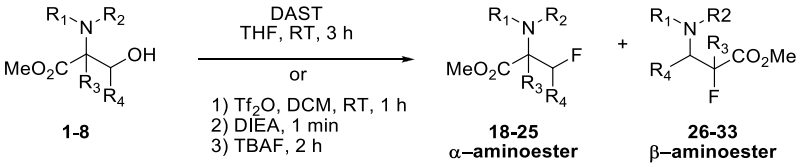


Scheme 2. Syntheses of α-hydroxy-β-aminoester precursors **1**-**8**.

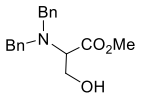
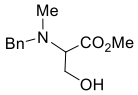
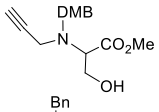
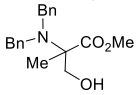
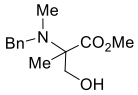
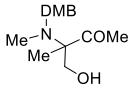
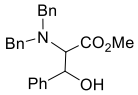
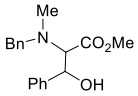
Deoxyfluorination of β-hydroxy-α-aminoesters 1-8 under non-radioactive conditions

Deoxyfluorination of β-hydroxy-α-aminoesters **1**-**8** was first carried out using DAST as reference method. Reactions were performed in THF at room temperature for 3 h. We also performed the deoxyfluorination of **1**-**8** using fluoride anion according to the protocol we previously developed for the deoxyfluorination of ethanolamines.[12] β-Hydroxy-α-aminoesters **1**-**8** were treated with triflic anhydride in CH_2Cl_2 at room temperature for 1 h, then with DIPEA for 1 min and finally with TBAF for 2 h. The results for both DAST and TBAF methods are presented in Table 1. Although no optimization was undertaken, the conversions occured in moderate to high yields. Fluorinations were more efficient with DAST than with TBAF as previously observed for the deoxyfluorination of ethanolamines.[12] However, the differences of yields remained relatively low except for reactions from precursors **3** and **4** (entries 3-4). These results suggested that the *in situ* generation of the intermediate aziridinium may be easier with DAST than in TBAF method. The nature of the nucleophilic fluoride in the two approaches may also have an impact on the fluorination. Globally, no influence of *N*-substituents could be concluded contrary to *C*-substitution. Serine and α-methylserine precursors **1**-**6** displayed a similar behaviour, and led exclusively to fluoro-β-aminoesters **26**-**31** (entries 1-6). These results were consistent with the fluorination of serine esters reported in the literature.[9a-d,15] The nucleophilic attack took place exclusively on the carbon of aziridinium bearing the electron-withdrawing carboxylic function as this atom was the most electropositive.[8i] The methyl in α-position did not have any steric or electronic effect on the overall transformation. Phenylserine substrates **7**-**8** were less reactive than the serine and methylserine analogues **1**-**2** and **4**-**5**; the phenyl group in β significantly inhibited the deoxyfluorination. Moreover, a mixture of fluoro α- and β-aminoesters **24**-**25** and **32**-**33** was obtained (entries 7-8). In these cases, the two carbons of aziridinium ring were both ternary and competitive as electrophile sites. The methylester and phenyl groups were not discriminant toward fluoride. It is noteworthy that Davies *et al* described the fluorination with XtalFluor-E and $Et_3N.3HF$ of the *tert*-butyl ester analogue of substrate **7**.[9f] They obtained the corresponding α-aminoester isomer in 94% yield, revealing a strong director and activating effect of the *tert*-butyl ester function.

Table 1. Deoxyfluorination of **1-8** using DAST or TBAF



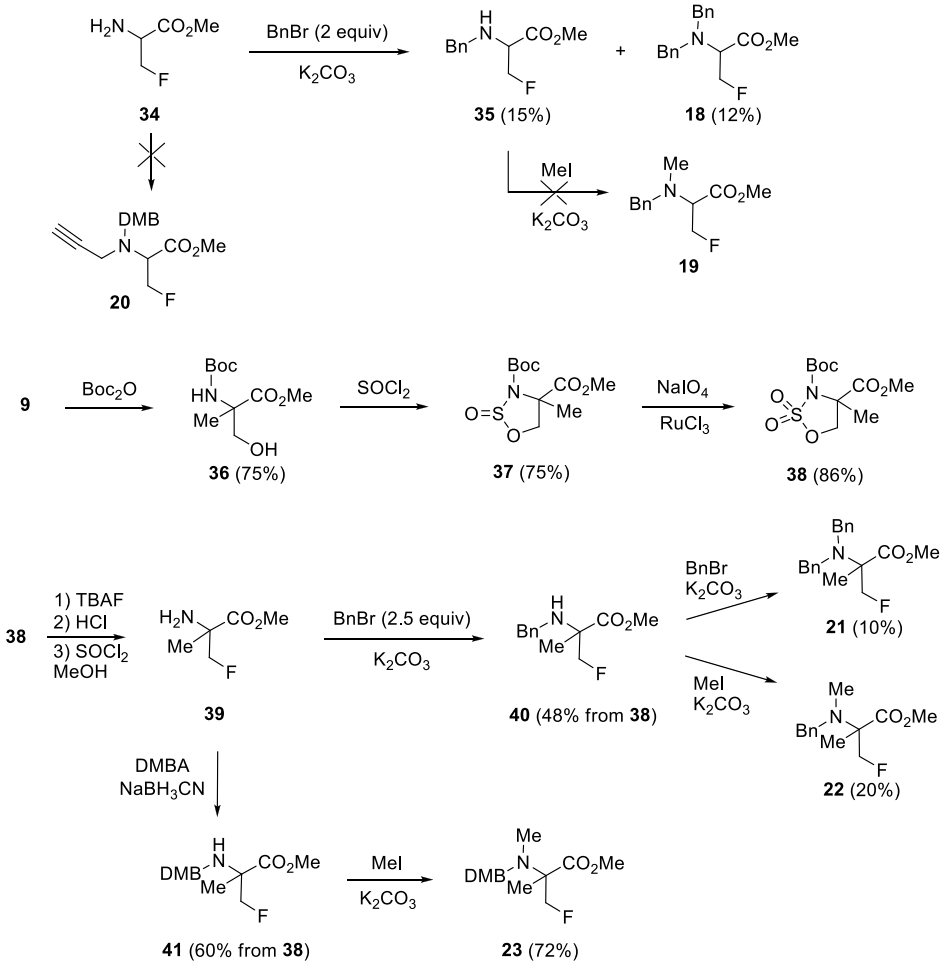
1-8 **18-25** α–aminoester **26-33** β–aminoester

Entry	Substrate		Method	Products		Yield (%)	Ratio
				α	β	(α+β)	(α:β)
1	**1**		DAST TBAF	**18**	**26**	70 60	0:100 0:100
2	**2**		DAST TBAF	**19**	**27**	68 50	0:100 0:100
3	**3**		DAST TBAF	**20**	**28**	85 15	0:100 0:100
4	**4**		DAST TBAF	**21**	**29**	98 50	0:100 0:100
5	**5**		DAST TBAF	**22**	**30**	60 45	0:100 0:100
6	**6**		DAST TBAF	**23**	**31**	56 30	0:100 0:100
7	**7**		DAST TBAF	**24**	**32**	28 14	75:25 80:20
8	**8**		DAST TBAF	**25**	**33**	37 21	50:50 55:45

Synthesis of β-fluorinated α-aminoesters 18-23

Deoxyfluorination of serine and α-methylserine precursors **1**-**6** did not provide the fluorinated α-aminoesters **18**-**23**. However, these compounds **18**-**23** were needed to confirm the identity and the isomeric structure of the radiolabelled products by co-elution in HPLC and we developed alternative syntheses (Scheme 3). The reaction of β-fluoroalanine methyl ester **34** with 2 equiv of benzylbromide led to *N*,*N*-dibenzylfluoroalanine **18** (12% yield) and *N*-monobenzylated analogue **35** (15% yield) that could be separated. All attempts to alkylate **35** with methyl iodide failed and *N*-methyl,*N*-benzylfluoroalanine **19** never could be obtained. We also were unsuccessful in introducing dimethoxybenzyl group by reductive amination from fluoroalanine derivatives in order to prepare *N*-propargylfluoroalanine methyl ester **20**. Fluorinated α-aminoesters **21**-**23** were obtained via the sulfamidate intermediate **38** according to a multistep strategy reported by Yu *et al* for the preparation of *tert*-butyl ester analogues.[5c] Fluorination then deprotection of sulfamidate **38** led to fluoroaminoester **39** which was involved in subsequent transformations without isolation. *N*-Alkylation of **39** with benzylbromide (2.5 equiv) afforded the monobenzyl derivative **40** in 48% yield (calculated from **38**). A second alkylation with benzylbromide or methyliodide gave the *N*-dialkylated aminoesters **21** and **22** in poor yields (10 and 20% respectively).

Fluoroaminoester **39** was efficiently converted to **41** by reductive amination with dimethoxybenzaldehyde. Methylation of **41** to fluoroaminoester **23** occurred in high yield (72%). A similar sulfamidate-based approach for the synthesis of β-fluoroalanine ester **20** failed. The overall syntheses displayed that the presence of the β-fluorine attenuated drastically the nucleophilicity of the amine.[16] However the introduction of the electro-donor DMB group on nitrogen allowed to restore its ability for nucleophilic alkylation.



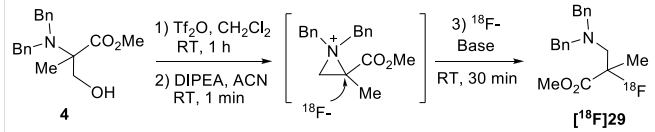
Scheme 3. Syntheses of the β-fluorinated α-aminoesters **18**-**23**.

Deoxyradiofluorination reactions from β-hydroxy-α-aminoester precursors 1-8

The deoxyradiofluorination of α-methylserine methylester **4** was selected as the model reaction for the initial condition screening (Table 2). We first applied the radiolabelling conditions previously defined for the conversion of ethanolamines to [^{18}F]fluoroamines without any modifications.[12] Briefly, the precursor **4** (33 μmol; 10.5 mg) was stirred in the presence of triflic anhydride in dichloromethane (300 μL) for 1 h at room temperature. DIPEA in acetonitrile (200 μL) was added to the crude mixture and allowed to react for 1 min. The resulting solution was transferred onto dry [^{18}F]KF/K_{222}/K_2CO_3 complex prepared according to the classic procedure. The mixture was stirred for 30 min at room temperature and then analysed by both radioTLC and HPLC by comparison with the non-radioactive reference fluoro- α and β-aminoester products **21** and **29**. The radiofluorination of **4** led exclusively to the [^{18}F]fluoro-β-aminoester [^{18}F]**29** (entry 1). The regioselectivity was identical to that observed in non-radioactive chemistry. However, the radiofluorination was unreliable with an incorporation mean about 51% (n = 7) and a deviation about ± 24%. In order to make the radiofluorination reproducible, we

changed the volume of acetonitrile, the nature of [^{18}F]fluoride ([^{18}F]KF/K_{222}/K_2CO_3 and [^{18}F]TBAF obtained with $TBAHCO_3$), the amount of base (K_2CO_3 and $TBAHCO_3$) as well as the quantity of precursor **4**. The treatment of precursor **4** with triflic anhydride was not changed. The use of an increased volume of acetonitrile (up to 1 mL) did not lead to improved and repeatable radiochemical yields (entries 2-4). By increasing the amounts of K_2CO_3 and K_{222}, the radiochemical yields were constant (deviation about 6% only) around 68% (entry 5). The radiochemical yields then fell down drastically when the precursor **4** was taken in low amount (6.6 µmol; 2.1 mg) (entries 6-10). Finally, the replacement of [^{18}F]KF/ K_{222}/K_2CO_3 by [^{18}F]TBAF was detrimental (entries 11-12). This result was different to the previously reported deoxyradiofluorination of β-aminoalcools; in the latter, the reaction was not sensitive to the nature of [^{18}F]fluoride anion.[12] We then selected the following conditions, i.e. precursor **4** (16.5 µmol), triflic anhydride (37 µmol), dichloromethane (300 µL), DIPEA (40 µmol), acetonitrile (700 µL) and [^{18}F]KF prepared using K_2CO_3 (23 µmol) and K_{222} (28 µmol) (entry 8).

Table 2. Optimization of the deoxyradiofluorination reaction.[a]



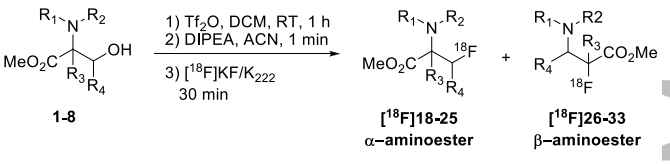
Entry	**4** [µmol]	Base [µmol]		ACN [mL]	RCC [%][b]
1	33	K_2CO_3/K_{222}	15/18	0.2	51±24 (n=6)
2	33	K_2CO_3/K_{222}	15/18	0.5	55±19 (n=3)
3	33	K_2CO_3/K_{222}	15/18	0.7	55±23 (n=9)
4	33	K_2CO_3/K_{222}	15/18	1.0	73±21 (n=3)
5	33	K_2CO_3/K_{222}	23/28	0.7	68±6 (n=4)
6	26.4	K_2CO_3/K_{222}	23/28	0.7	73±8 (n=3)
7	19.8	K_2CO_3/K_{222}	23/28	0.7	67±4 (n=3)
8	16.5	K_2CO_3/K_{222}	23/28	0.7	68±9 (n=3)
9	13.2	K_2CO_3/K_{222}	23/28	0.7	73±8 (n=3)
10	6.6	K_2CO_3/K_{222}	23/28	0.7	18±5 (n=2)
11	16.5	$TBAHCO_3$	23	0.7	49±23 (n=4)
12	16.5	$TBAHCO_3$	23	-[c]	32±2 (n=2)

[a] All radiofluorinations were carried out manually for 30 min at RT. Conditions: Triflic anhydride in CH_2Cl_2 for 1 h then 1 min with DIPEA in ACN then addition to dry [^{18}F]-fluoride at RT. [b] Determined by radioTLC and HPLC (± SEM). [c] In THF (0.7 mL).

The deoxyradiofluoration method was extended to β-hydroxy-α-aminoesters **1**-**8** (Table 3). In the first set of experiments, the radiofluorination step was conducted at room temperature for 30 min. The highest radiochemical yields (32-67%) were obtained starting from serine (entries 1-2) and methylserine (entries 4-5) precursors **1**-**2** and **4**-**5** possessing a dibenzylamine or a benzylmethylamine function. The [^{18}F]fluoro-β-aminoester isomers **[^{18}F]26**-**[^{18}F]27** and **[^{18}F]29**-**[^{18}F]30** were the only radiofluorinated products detected. These results were in accordance with the non-radioactive chemistry. In the case of *N*-dimethoxyphenyl serine and methylserine derivatives **3** and **6**, the formation of the expected [^{18}F]fluoro-β-aminoesters **[^{18}F]28** and **[^{18}F]31** was not observed, and the presence of the α-isomers **[^{18}F]20** and **[^{18}F]23** could not be confirmed (entries 3 and 6). For reminder, the yields for the corresponding non-radioactive reactions were low. The electron-donating effect of the DMB group may decrease the electrophilicity of aziridinum and consequently its reactivity toward fluoride. The radiofluorination of the phenylalanine substrates **7**-**8** was carried out in radiochemical yields that did not exceed 28% and led to mixture of the [^{18}F]fluoro-α- and β-aminoesters as for the non-radioactive version (entries 7-8). However, the α:β ratios were not exactly in the same range.

A second set of assays were realized with the radiofluorination step performed at 90 °C. Heating conditions did not affect the regioselectivity of the reaction. The α:β ratios were similar to those obtained at room temperature. At 90 °C, the radiochemicals yields were not increased except for the *N*-benzyl,*N*-methylmethylserine precursor **5** (entry 5). Thus, temperature did not significantly influence the deoxyradiofluorination.

Table 3. Scope of the deoxyradiofluorniation reaction.[a]



Entry	Precursor	Product α	Product β	T [°C]	RCC [%] α+β[b]	Ratio α:β[c]
1	**1**	[^{18}F]**18**	[^{18}F]**26**	20 90	45±2 55±7	0:100 0:100
2	**2**	[^{18}F]**19**	[^{18}F]**27**	20 90	32±4 39±11	0:100 0:100
3	**3**	[^{18}F]**20**	[^{18}F]**28**	20 90	-[d] -[d]	-[d] -[d]
4	**4**	[^{18}F]**21**	[^{18}F]**29**	20 90	67±3 68±9	0:100 0:100
5	**5**	[^{18}F]**22**	[^{18}F]**30**	20 90	33±7 57±7	0:100 0:100
6	**6**	[^{18}F]**23**	[^{18}F]**31**	20 90	-[d] -[d]	-[d] -[d]
7	**7**	[^{18}F]**24**	[^{18}F]**32**	20 90	17±4 14±3	60:40 62:38
8	**8**	[^{18}F]**25**	[^{18}F]**33**	20 90	28±5 30±1	82:18 83:17

[a] Conditions: Triflic anhydride in CH_2Cl_2 for 1 h then 1 min with DIPEA in ACN then addition to dry [^{18}F]-fluoride at 20 or 90 °C for 30 min. [b] Determined by radioTLC and HPLC (± SEM). [c] Determined by HPLC. [d] Not detected.

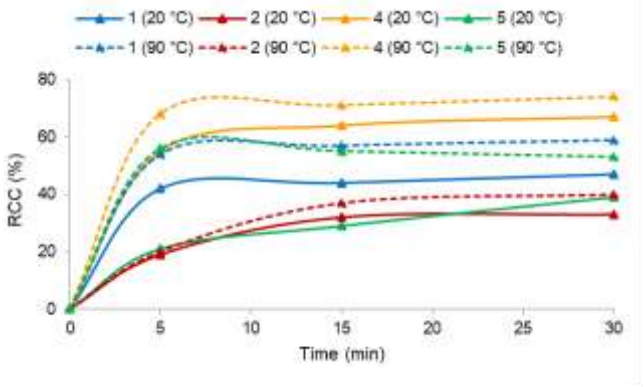


Figure 1. Radiofluorination of serine and methylserine esters **1**-**2** and **4**-**5**.

Finally, we examined the influence of the reaction time under both room temperature and heating conditions in the radiofluorination of reactive serine and methylserine precursors **1**-**2** and **4**-**5** (Figure 1). For all cases and whatever the reaction temperature, the optimum radiochemical yields were reached after 15 min and remained constant until 30 min. The results obtained after 5 min reaction time were slightly below the optimum values, revealing a fast radiofluorination even at room temperature.

Conclusion

We developed the deoxyradiofluorination reaction using [^{18}F]fluoride anion for the radiosynthesis of [^{18}F]fluoroaminoesters from readily prepared stable hydroxyl precursors. The method was efficient and rapid at room temperature from serine and α-methylserine esters bearing a benzylamine function. In addition, the radiofluorination was totally regioselective with the exclusive formation of the [^{18}F]fluoro-β-aminoester products. β-Phenylserine derivatives were less reactive and gave access to a mixture of [^{18}F]fluorinated α and β-aminoester isomers. Although the efficiency of the radiofluorination was dependant on the substrates structures, our results demonstrated the proof of concept of this methodology. The very mild reaction conditions made the approach useful and promising for the radiosynthesis of temperature sensitive and enantiomerically pure aminoacid radiopharmaceuticals. Such developments will be reported in due course.

Experimental Section

Synthetic procedures

General Remarks: All commercially available reagents and solvents were purchased from Sigma-Aldrich, Fluorochem or Apollo Scientific and used without further purification. Thin-layer chromatographies (TLC) were run on precoated aluminum plates of silica gel 60F254, and retention factors (Rf) were established using a UV-lamp at 254 nm. Melting points were determined with an Electrothermal IA900 instrument and are given in °C. IR spectra were recorded on a FT-IR spectrometer and are given in cm^{-1}. ^{1}H, ^{13}C and ^{19}F and ^{11}B NMR spectra were recorded at 400 or 500 MHz (^{1}H), 101 or 126 MHz (^{13}C), 376 or 471 MHz (^{19}F). Samples were dissolved in an appropriate deuterated solvent (CDCl3, MeOD or DMSO). Chemical shifts (δ) are quoted in parts per million (ppm). Coupling constants (J) are given in Hz. Coupling patterns are abbreviated as follows: s (singlet), d (doublet), m (mutiplet), dd (doublet of doublet). High resolution mass spectra (HRMS) were recorded using a Waters Q-TOF micro spectrometer by electrospray ionisation (ESI).

Methyl-2-(dibenzylamino)-3-hydroxypropanoate (1): To serine methylester hydrochloride (500 mg, 3.2 mmol) and K_2CO_3 (1 g, 7.2 mmol) in dry ACN (10 mL) was added benzylbromide (800 µL, 6.5 mmol) under nitrogen atmosphere. After stirring at room temperature for 18 h then filtration, the filtrate was concentrated under vacuum. Purification of the residue by chromatography on silica gel (heptane/EtOAc, 85:15) gave compound **1** as a colorless oil (800 mg, 83%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.38-7.22 (m, 10H), 3.93 (dd, *J* = 10.9, 7.8 Hz, 1H), 3.74 (dd, *J* = 10.9, 5.9 Hz, 1H), 3.87 and 3.59 (AB system, *J* = 13.7 Hz, 4H), 3.79 (s, 3H), 3.49 (dd, *J* = 7.8, 5.9 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 172.0, 139.4, 128.5, 127.9, 126.8, 62.8, 60.6, 54.9, 50.3 ppm. HRMS (ESI): calcd. for $C_{18}H_{22}NO_3$ $[M+H]^+$ 300.1600; found 300.1603.

Methyl-2-(benzylamino)-3-hydroxypropanoate (12): To serine methylester hydrochloride (200 mg, 1.3 mmol) and K_2CO_3 (360 mg, 2.6 mmol) in dry DMF (4 mL) under nitrogen atmosphere was added benzylbromide (155 µL, 1.3 mmol). After stirring at 55 °C for 16 h then dilution with ethyl acetate, the mixture was washed with water (10 mL) then brine (10 mL). The organic phase was separated, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified on silica gel (pentane/EtOAc, 2:1) to give compound **12** as a pale yellow oil (210 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (m, 5H), 3.81 and 3.70 (AB system, *J* = 12.9 Hz), 3.72 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.66 (s, 3H), 3.58 (dd, *J* = 10.9, 6.0 Hz, 1H), 3.37 (dd, *J* = 6.0, 4.4 H, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.8, 138.3, 128.6, 128.5, 127.3, 62.1, 61.7, 52.4, 51.9 ppm. HRMS (ESI): calcd. for $C_{11}H_{16}NO_3$ $[M+H]^+$ 210.1130; found 210.1132.

Methyl-2-(benzylmethylamino)-3-hydroxypropanoate (2): To aminoester **12** (100 mg, 0.45 mmol) and K_2CO_3 (140 mg, 1.0 mmol) in dry DMF (3 mL) under nitrogen atmosphere was added methyliodide (60 µL, 0.97 mmol). After stirring at room temperature for 3 h, then dilution with ethyl acetate, the mixture was washed with water (10 mL) then brine (10 mL). The organic phase was separated, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified on silica gel (pentane/EtOAc, 8:2) to give the product **2** as a pale yellow oil (75 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (m, 5H), 3.83-3.66 (m, 7H), 3.51 (dd, *J* = 9.2, 6.1 Hz, 1H), 2.30 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.9, 138.0, 129.1, 128.6, 127.6, 65.7, 59.2, 58.8, 51.5, 37.4 ppm. HRMS (ESI): calcd. for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1287; found 224.1291.

Methyl-2-((2,4-dimethoxybenzyl)(3-prop-2-yn-1-yl)amino)-3-((triisopropylsilyl)oxy)propanoate (16): To aminoester **15** (1,6 g, 3,8 mmol)[3d] and cesium carbonate (500 mg, 7.4 mmol) in dry ACN (30 mL) was added propargylbromide (700 µL, 3,9 mmol) under nitrogen atmosphere. The reaction mixture was heated to 55 °C for 3 h. After quenching with water (30 mL) then extraction with DCM (3 x 30 mL), the combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. Purification on silica gel (heptane/EtOAc, 94/6) gave compound **16** as a colorless oil (1.6 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (s, 1H), 6.46-6.42 (m, 2H), 4.17-4.02 (m for ABC system, 2H), 3.90 and 3.76 (AB system, *J* = 13.9 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 3.73-3.66 (m, 1H), 3.50 (d, *J* = 1.6 Hz, 2H), 2.22 (t, *J* = 2.3 Hz, 1H), 1.07–1.00 (m, 21H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.1, 160.1, 158.9, 131.2, 119.0, 103.9, 98.5, 80.5, 72.3, 65.9, 63.4, 55.4, 55.4, 51.2, 48.6, 40.5, 17.9, 11.9 ppm. HRMS (ESI): calcd. for $C_{28}H_{50}NO_5Si_2$ $[M+H]^+$ 536.3228; found 536.3238.

Methyl-2-((2,4-dimethoxybenzyl)(prop-2-yn-1-yl)amino)-3-hydroxy-propanoate (3): To TIPS-protected aminoester **16** (1.6 mg, 3.5 mmol) in dry THF (10 mL) was added tetrabutylammonium fluoride (1 M in THF, 12 mL). After stirring at room temperature for 16 h, the solvent was removed under vaccum and the residue was purified on silica gel (heptane/EtOAc, 75/25) to give product **3** as a colorless oil (750 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.1 Hz, 1H), 6.54-6.38 (m, 2H), 4.05 and 3.60 (AB system, *J* = 13.1 Hz, 2H), 3.92-3.82 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.84-3.75 (m, 1H), 3.73 (s, 3H), 3-54-3.35 (m for ABC system, 2H), 2.23 (t, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.4, 160.7, 158.8, 132.0, 118.1, 103.8, 98.9, 79.9, 72.8, 64.5, 59.0, 55.4, 55.3, 51.3, 48.1, 40.1 ppm. HRMS (ESI): calcd. for $[M+H]^+$ $C_{16}H_{21}NO_5$ 308.1498; found 308.1494.

Methyl-2-(dibenzylamino)-3-hydroxy-2-methylpropanoate (4): To a mixture of α-methylserine methyl ester **10**[17] (500 mg, 3.76 mmol) and K_2CO_3 (1 g, 7.25 mmol) in dry ACN (10 mL) was added benzylbromide (1 mL, 8.42 mmol) under nitrogen atmosphere. After stirring at 50 °C for 48 h

then filtration, the filtrate was concentrated under vacuum. Purification of the residue on silica gel (heptane/EtOAc, 9:1) gave compound **4** as a yellow solid (647 mg, 55%). Mp = 106 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.28-7.09 (m, 10H), 3.90 and 3.55 (AB system, *J* = 10.8 Hz, 2H), 3.81 (s, 4H), 3.68 (s, 3H), 1.48 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 174.6, 141.0, 128.2, 127.6, 126.3, 68.6, 66.4, 54.6, 50.6, 17.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{24}NO_3$ $[M+H]^+$ 314.1756; found 314.1760.

Methyl-2-(benzylamino)-3-hydroxy-2-methylpropanoate (13): To aminoester **10**[16] (330 mg, 2.5 mmol) in dry DMF (6 mL) was added under nitrogen atmosphere at room temperature K_2CO_3 (640 mg, 4.6 mmol) then benzylbromide (300 µL, 2.5 mmol). After stirring overnight at 50 °C then quenching with water (20 mL), and extraction with CH_2Cl_2 (3 x 20 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification on silica gel (heptane/EtOAc, 9:1 then 7:3) gave compound **13** as a colorless oil (250 mg, 45%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.44-7.17 (m, 5H), 3.77 (s, 3H), 3.70 (s, 2H), 3.70 and 3.62 (AB system, *J* = 11.0 Hz, 2H), 1.43 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 175, 138, 128.9, 128.7, 127.9, 66.0, 64.4, 52.5, 48.1, 18.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1287; found 224.1288.

Methyl-2-(benzyl(methyl)amino)-3-hydroxy-2-methylpropanoate (5): To a mixture of aminoester **13** (220 mg, 1.0 mmol) and K_2CO_3 (280 mg, 2.0 mmol) in dry DMF (5 mL) was added methyliodide (125 µL, 2.0 mmol) under nitrogen atmosphere. After stirring at room temperature for 3 h, the mixture was quenched with water (20 mL). After extraction with CH_2Cl_2 (3 x 10 mL), the combined organic layers were concentrated under reduced pressure. Purification by chromatography on silica gel (heptane/EtOAc, 75:25) gave compound **5** as a colorless oil (180 mg, 77%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.26-7.19 (m, 5H), 3.78 and 3.67 (AB system, *J* = 11.2 Hz, 2H), 3.72 (s, 3H), 3.65 and 3.58 (AB system, *J* = 13.5 Hz, 2H), 2.20 (s, 3H), 1.43 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 175.0, 138.0, 128.9, 128.7, 127.9, 66.0, 64.4, 52.5, 48.1, 18.9 ppm. HRMS (ESI): calcd. for $C_{13}H_{20}NO_3$ $[M+H]^+$ 238.1443; found 238.1447.

Methyl-2-((2,4-dimethoxybenzyl)amino)-3-hydroxy-2-methylpropanoate (17): To a mixture of aminoester **10** (500 mg, 3.8 mmol) and 2,4-dimethoxybenzaldehyde (650 mg, 3.9 mmol) in dry DMF (10 mL) was added dry triethylamine (560 µL, 4.0 mmol) under nitrogen atmosphere. After stirring at room temperature for 2 h, sodium cyanoborohydride was added in one portion. The reaction mixture was stirred at room temperature overnight then quenched with aqueous $NaHCO_3$ (20 mL). After extraction with CH_2Cl_2 (3 x 10 mL), the combined organic layers were washed with water (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by chromatography on silica gel (heptane/EtOAc, 40:60 then 20:80) gave compound **10** as a yellow oil (685 mg, 64%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.03 (d, *J* = 8.20 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.35 (dd, *J* = 2.3 Hz, 8.2 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.55 (s, 3H), 3.54 and 3.47 (AB system, *J* = 12.0 Hz, 2H), 3.48 (s, 2H) 1.23 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.0, 160.7, 158.8, 130.4, 119.4, 103.9, 97.9, 67.1, 67.0, 54.4, 54.3, 51.1, 42.2, 17.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{22}NO_5$ $[M+H]^+$ 284.1498; found 284.1489.

Methyl-2-((2,4-dimethoxybenzyl)(methyl)amino)-3-hydroxy-2-methylpropanoate (6): To a mixture of **17** (400 mg, 1.4 mmol) and K_2CO_3 (400 mg, 2.9 mmol) in dry DMF (10 mL) was added methyliodide (180 µL, 2.9 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h, then quenched with water (20 mL). After extraction with CH_2Cl_2 (3 x 10 mL), the combined organic layers were concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (heptane/EtOAc, 2:8) gave compound **6** as a yellow oil (300 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8 Hz, 1H), 6,44 (s, 1H) 6.44 (d, *J* = 8 Hz, 1H), 4.02 and 3.81 (AB system, *J* = 11.6 Hz, 2H), 3.77 and 3.60 (AB system, *J* = 11.6 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 2.27 (s, 3H), 1.50 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.3, 160.4, 158.6, 131.9, 119,4, 103.9, 98.8, 64.3, 64.2, 55.4, 55.3, 51.50, 50.64, 34.9, 20.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{24}NO_5$ $[M+H]^+$ 298.1654**;** found 298.1651.

Methyl-2-(benzylamino)-3-hydroxy-3-phenylpropanoate (14): To a mixture of aminoester **11** (300 mg, 1.5 mmol) and K_2CO_3 (470 g, 3.4 mmol) in dry DMF (10 mL) was added benzylbromide (180 µL, 2.5 mmol) under nitrogen atmosphere. After stirring at 50 °C for 20 h, the reaction mixture was quenched with water (20 mL) then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ then concentrated under reduced pressure. Purification by chromatography on silica gel (pentane/EtOAc, 97:3 then 80:20) gave compound **14** as a yellow oil (150 mg, 33%).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24-7.20 (m, 10H), 4.59 (d, *J* = 7.2 MHz, 1H), 3.68 and 3.58 (AB system, *J* = 13.0 Hz, 2H), 3.45 (s, 3H), 3.31 (d, *J* = 7.2 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.5, 140.2, 138.9, 129.0, 128.3, 128.2, 127.4, 126.4, 125.3, 74.3, 67.8, 52.5, 51.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{20}NO_3$ $[M+H]^+$ 286.1443; found 286.1446.

Methyl-2-(dibenzylamino)-3-hydroxy-3-phenylpropanoate (7): To a mixture of aminoester **11** (300 mg, 1.5 mmol) and K_2CO_3 (470 g, 3.4 mmol) in dry DMF (10 mL) was added benzylbromide (360 µL, 3.0 mmol) under nitrogen atmosphere. After stirring at 50 °C for 20 h, the reaction mixture was quenched with water (20 mL) then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ then concentrated under reduced pressure. Purification on silica gel (pentane/EtOAc, 97:3 then 80:20) gave compound **7** as a white solid (293 mg, 52%). Mp = 74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.16 (m, 15H), 4.86 (d, *J* = 10.0 Hz, 1H), 4.06 and 3.37 (AB system, *J* = 13.0 Hz, 4H), 3.55 (s, 3H), 3.34 (d, *J* = 10.0 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.9, 140.4, 137.8, 129.3, 128.9, 128.7, 128.2, 127.7, 127.3, 69.5, 67.6, 54.8, 51.3 ppm. HRMS (ESI): calcd. for $C_{24}H_{26}NO_3$ $[M+H]^+$ 376.1913; found 376.1913.

Methyl-2-(benzyl(methyl)amino)-3-hydroxy-3-phenylpropanoate (8): To a mixture of aminoester **14** (108 mg, 0.38 mmol) and K_2CO_3 (110 mg, 0.81 mmol) in dry DMF (3 mL) was added methyliodide (50 µL, 0.81 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h. After quenching with water (5 mL) then extraction with CH_2Cl_2 (3 x 5 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by chromatography on silica gel (pentane/EtOAc, 97:3) gave compound **8** as a colorless oil (72 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.29 (m, 10H), 4.89 (d, *J* = 10.0 Hz, 1H), 3.91 and 3.64 (AB system, *J* = 13.0 Hz, 2H), 3.60 (s, 3H), 3.38-3.34 (m, 1H) 2.39 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.4, 140.3, 137.8, 129.1, 128.6, 128.3, 128.0, 127.6, 127.3, 72.2, 69.6, 59.6, 51.1, 37.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{22}NO_3$ $[M+H]^+$ 300.1600; found 300.1601.

General procedure for fluorination using DAST. To aminoacid alcohol (0.6 mmol) in dry THF (4 mL) was added DAST (0.7 mmol) under nitrogen atmosphere. The solution was stirred at room temperature for 3 h. After quenching with water then extraction with CH_2Cl_2 (2 x 10 mL), the combined organic layers were concentrated under reduced pressure and the residue was purified by chromatography on silica gel.

General procedure for fluorination using TBAF. To aminoacid alcohol (0.6 mmol) in dry CH_2Cl_2 (4.5 mL) in a conic vial was added a solution of trifluoromethanesulfonic anhydride (1 M in CH_2Cl_2, 0.66 mL) under nitrogen atmosphere. After stirring at room temperature for 1 h, DIPEA (125 µL, 0.72 mmol) then, 1 min later, a solution of TBAF (1 M in THF, 1.2 mL), were added. The reaction mixture was stirred for 2 h at room temperature. After quenching with aqueous NaOH (15%, 5 mL) and extraction with CH_2Cl_2 (2 x 10 mL), the combined organic layers were concentrated under reduced pressure and the residue was purified by chromatography on silica gel.

Methyl-3-(dibenzylamino)-2-fluoropropanoate (26): Compound **26** was obtained from **1** (145 mg, 0.48 mmol) and DAST as a colorless oil (100 mg, 70%) after purification by chromatography on silica gel (heptane/AcOEt, 95/5). Compound **26** was also obtained as a colorless oil (95 mg, 60%) from **1** (160 mg, 0.55 mmol) and TBAF. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.35-7.31 (m, 10H), 5.13-5.00 (m, 1H) 3.87-3.52 (m, 4H), 3.80 (s, 3H), 3.07-3.01 (m, 2H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 171.0 (d, J_{CF} = 21.9 Hz), 133.7, 130.1, 128.9, 128.7, 89.3 (d, J_{CF} = 186.1 Hz), 58.1, 54.2 (d, J_{CF} = 20.1 Hz), 53.4 (d, J_{CF} = 22.8 Hz) ppm. ^{19}F NMR (376.5 MHz, CD_3OD) : δ = -(190.4-190.6) (m) ppm. HRMS (ESI): calcd. for $C_{17}H_{19}FNO_2$ $[M+H]^+$ 288.1400; found 2881403.

Methyl-3-(benzyl(methyl)amino)-2-fluoropropanoate (27): Compound **27** was obtained from **2** (85 mg, 0.38 mmol) and DAST as a colorless oil (59 mg, 68%) after purification by chromatography on silica gel (heptane/AcOEt, 95:5). Compound **27** was also obtained as a colorless oil (42 mg, 50%) from **2** (85 mg, 0.38 mmol) and TBAF. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.19 (m, 5H), 5.07 (ddd, *J* = 49.5, 6.3, 2.6 Hz, 1H), 3.74 (s, 3H), 3.66 and 3.50 (AB system, *J* = 13.2 Hz, 2H), 3.02-2,82 (m, 2H), 2.30 (s, 3H) ppm. ^{13}C NMR (10006 MHz, $CDCl_3$): δ = 69.3 (d, J_{CF} = 24 Hz), 138.2, 129.0, 128.3, 127.3, 89.1 (d, J_{CF} = 185.6 Hz), 62.7 (d, J_{CF} = 1.5 Hz), 57.9 (d, J_{CF} = 19.9 Hz), 52.3, 43.0 (d, J_{CF} = 2.1 Hz) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$) : δ = -(190.6-190.8) (m) ppm. HRMS (ESI): calcd. for $C_{12}H_{17}FNO_2$ $[M+H]^+$ 226.1243; found 226.1248.

Methyl-3-((2,4-dimethoxybenzyl)(prop-2-yn-1-yl)amino)-2-fluoropropanoate (28): Compound **28** was obtained from **3** (95 mg, 0.31 mmol) as a colorless oil (81 mg, 85%) after purification by chromatography on silica gel (heptane/AcOEt, 82:18). Compound **28** was also obtained as a colorless oil (32 mg, 15%) from **3** (160 mg, 0.55 mmol) after purification by chromatography on silica gel (heptane/AcOEt, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.7 Hz, 1H), 6.46-6.44 (m, 2H), 5.19 (ddd, *J* = 49.3, 6.4, 2.7 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.70-3.68

(m, 2H), 3.51-3.37 (m for ABC system, 2H), 3.22-3.00 (m, 2H), 2.25 (t, J = 2.3 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) : δ = 169.1 (d, J_{CF} = 24.6 Hz), 160.3, 158.9, 131.3, 118.5, 103.9, 98.75, 89.4 (d, J_{CF} = 185.6 Hz), 78.9, 73.1, 55.5, 55.4, 54.5 (d, J_{CF} = 20.3 Hz), 52.3, 51.8, 42.9 ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -191.6 (td, J = 26.1, 49.3 Hz) ppm. HRMS (ESI): calcd. for $C_{16}H_{21}FNO_4$ $[M+H]^+$ 310.1455; found 310.1453.

Methyl-3-(dibenzylamino)-2-fluoro-2-methylpropanoate (29): Compound **29** was obtained from **4** (73 mg, 0.23 mmol) and DAST as a colorless oil (72 mg, 98%) after purification by chromatography on silica gel (heptane/AcOEt, 95:5). Compound **29** was also obtained as a colorless oil (48 mg, 50%) from **4** (95 mg, 0.31 mmol) and TBAF. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.20-7.08 (m, 10H), 3.72 and 3.21 (AB system, J = 13.6 Hz, 4H), 3.48 (s, 3H), 2.92-2.63 (m, 2H), 1.28 (d, J = 21.3 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ 174.6 (d, J = 27.0 Hz), 139.0, 128.9, 127.8, 126.7, 97.2 (d, J_{CF} = 183.1 Hz), 59.0, 58.7 (d, J_{CF} = 22.4 Hz), 51.5, 21.0 (d, J_{CF} = 24.4 Hz) ppm. ^{19}F NMR (376.5 MHz, CD_3OD): δ = -155.6 (ddq, J = 31.9, 21.3, 14.9 Hz) ppm. HRMS (ESI): calcd. for $C_{19}H_{23}$ FNO_2 $[M+H]^+$ 316.1713; found 316.1719.

Methyl-3-(benzyl(methyl)amino)-2-fluoro-2-methylpropanoate (30): Compound **30** was obtained from **5** (37 mg, 0.16 mmol) and DAST as a colorless oil (23 mg, 60%) after purification by chromatography on silica gel (heptane/AcOEt, 95:5). Compound **30** was also obtained as a colorless oil (35 mg, 45%) from **5** (75 mg, 0.32 mmol) and TBAF. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29-7.20 (m, 5H), 3.75 (s, 3H), 3.68 and 3.53 (AB system, J = 13.2 Hz, 2H), 3.01-2.70 (m, 2H), 2.25 (s, 3H), 1.52 (d, J = 21.2 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.7 (d, J_{CF} = 27 Hz), 129.1, 128.3, 127.4, 127.3, 96.8 (d, J_{CF} = 187.0 Hz), 62.6 (d, J_{CF} = 22.1 Hz), 52.5, 43.5, 29.7, 21.9 (d, J_{CF} = 24.2 Hz) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -(156.5-156.6) (m) ppm. HRMS (ESI): calcd. for $C_{12}H_{17}$ F NO_2 $[M+H]^+$ 226.1243; found 226.1246.

Methyl-3-((2,4-dimethoxybenzyl)(prop-2-yn-1-yl)amino)-2-fluoro-2-methylpropanoate (31): Compound **31** was obtained from **6** (83 mg, 0.28 mmol) and DAST as a colorless oil (47 mg, 56%) after purification by chromatography on silica gel (heptane/AcOEt, 90:10). Compound **31** was also obtained as a colorless oil (28 mg, 30%) from **6** (97 mg, 0.33 mmol) and TBAF. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.04 (d, J = 8.4 Hz, 1H), 6.39-6.35 (m, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.60 (s, 3H), 3.47 and 3.39 (AB system, J = 13.2 Hz, 2H), 2.95-2.57 (m, 2H), 2.16 (s, 3H), 1.35 (d, J = 20.8 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 172.1 (d, J_{CF} = 27.2 Hz), 160.4, 158.8, 131.3, 118.2, 104.0, 97.7, 96.7 (d, J_{CF} = 184.6 Hz), 62.4 (d, J_{CF} = 19.5 Hz), 55.9 (d, J_{CF} = 2.2 Hz), 54.4, 54.4, 51.5, 42.7 (d, J_{CF} = 3.9 Hz), 20.8 (d, J_{CF} = 24.3 Hz) ppm. ^{19}F NMR (376.5 MHz, CD_3OD): δ = -(157.2 -157.3) (m) ppm. HRMS (ESI): calcd. for $C_{15}H_{22}FNO_4$ $[M+H]^+$ 300.1611; found 300.1612.

Methyl-2-(dibenzylamino)-3-fluoro-3-phenylpropanoate (24): Compound **24** was obtained from **7** (32 mg, 0.09 mmol) and DAST as a colorless oil (6 mg, 20%) after purification by chromatography on silica gel (heptane/AcOEt, 99:1). Compound **24** was also obtained as a colorless oil (4 mg, 7%) from **7** (62 mg, 0.17 mmol) and TBAF. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.16 (m, 15H), 5.96 (dd, J = 7.2, 47.2 Hz), 4.07 and 3.79 (AB system, J = 14.0 Hz, 4H), 3.92-3.84 (m, 1H), 3.67 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.3, 138.1, 135.9, 127.8, 127.4, 127.2, 127.2, 126.0, 125.2 (d, J_{CF} = 7.3 Hz), 91.8 (d, J_{CF} = 179.0 Hz), 64.5 (d, J_{CF} = 22.5 Hz), 54.3, 50.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -186.33 (dd, J = 47.2, 19.4 Hz) ppm. HRMS (ESI): calcd. for $C_{24}H_{25}FNO_2$ $[M+H]^+$ 378.1869; found 378.1872.

Methyl-3-(dibenzylamino)-2-fluoro-3-phenylpropanoate (32): Compound **32** has been obtained as a side product in the synthesis of **24** from **7** and DAST, and isolated after purification by chromatography on silica gel (heptane/AcOEt, 99:1) as a colorless oil (2 mg, 8%). Compound **32** has also been obtained as a side product in the synthesis of **24** from **7** and TBAF, and isolated as a colorless oil (1 mg, 2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32-7.07 (m, 10H), 5.83 (dd, J = 48.5, 5.0 Hz, 1H), 3.97 (dd, J = 22.8, 5.0 Hz, 1H), 3.63 (s, 3H), 3.52 and 3.35 (AB system, J = 13.2 Hz, 2H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.6, 138.8, 135.7, 129.4, 128.7, 128.3, 127.3, 127.1, 126.7 (d, J_{CF} = 6.2 Hz), 89.6 (d, J_{CF} = 191.1 Hz), 67.8 (d, J_{CF} = 22.8 Hz), 56.5, 51.3 ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -198.3 (dd, J = 48.5, 22.8 Hz) ppm. HRMS (ESI): calcd. for $C_{24}H_{25}FNO_2$ $[M+H]^+$ 378.1869; found 378.1871.

Methyl-2-(benzyl(methyl)amino)-3-fluoro-3-phenylpropanoate (25): Compound **25** was obtained from **8** (68 mg, 0.23 mmol) and DAST as a colorless oil (13 mg, 19%) after purification by chromatography on silica gel (heptane/AcOEt, 98:2). Compound **25** was also obtained as a colorless oil (6 mg, 10%) from **8** (62 mg, 0.20 mmol) and TBAF. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.24 (m, 10H) 5.90 (dd, J = 47.4, 8.0 Hz, 1H), 3.97 and 3.77 (AB system, J = 13.2 Hz, 2H), 3.79 (dd, J = 15.8, 8.0 Hz, 1H), 3.61 (s, 3H), 2.51 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.7 (d, J_{CF} = 9.9 Hz), 138.9, 137.0 (d, J_{CF} = 20.5 Hz), 129.9 (d, J_{CF} = 2.2 Hz), 128.8, 128.4, 128.3, 127.1, 126.7 (d, J_{CF} = 6.4 Hz), 92.2 (d, J_{CF} = 178.1 Hz), 70.1 (d, J_{CF} = 24.5 Hz), 59.4, 51.3, 38.7 (d, J_{CF} = 2.1 Hz) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -184.2 (dd, J = 47.4, 15.8 Hz) ppm. HRMS (ESI): calcd. for $C_{18}H_{21}FNO_2$ $[M+H]^+$ 302.1556; found 302.1556.

Methyl-3-(benzyl(methyl)amino)-2-fluoro-3-phenylpropanoate (33): Compound **33** was obtained as a side product in the synthesis of **25** from **8** (68 mg, 0.23 mmol) and DAST, and isolated as a colorless oil (12 mg, 18%) after purification by chromatography on silica gel (heptane/AcOEt, 98:2). Compound **33** was also obtained as a side product in the synthesis of **25** from **72** (62 mg, 0.20 mmol) and TBAF, and isolated as a colorless oil (5 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.12 (m, 15H), 5.38 (dd, J = 49.3, 5.0 Hz, 1H), 3.99 (dd, J = 22.9, 5.0 Hz, 1H), 3.60 (s, 3H), 3.48 and 3.28 (AB system, J = 13.5 Hz, 2H), 2.09 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.3 (d, J_{CF} = 22.9 Hz), 138.8 (d, J_{CF} = 4.2 Hz), 134.2, 129.4, 128.7, 128.3 (d, J_{CF} = 3.5 Hz), 127.1, 89.0 (d, J_{CF} = 191.4 Hz), 68.6 (d, J_{CF} = 21.7 Hz), 59.3, 52.3, 38.6 ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -198 (dd, J = 49.3, 22.9 Hz) ppm. HRMS (ESI): calcd. for $C_{18}H_{21}FNO_2$ $[M+H]^+$ 302.1556; found 302.1555.

Methyl-2-((tert-butoxycarbonyl)amino)-3-hydroxy-2-methylpropanoate (36): To aminoester **9** (2.9 g, 22 mmol) in MeOH/TEA (9/1) (60 mL) was added di-tert-butyl dicarbonate (8.6 g, 39 mmol). After stirring at room temperature overnight, the reaction mixture was concentrated under reduced pressure and purified on silica gel (CH_2Cl_2/MeOH, 97/3) to give compound **36** as a white solid (3.8 g, 75%). Mp = 115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 and 3.76 (AB system, J = 10.8 Hz, 2H), 3.76 (s, 3H), 1.46 (s, 3H), 1.43 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 73.9, 155.4, 80.4, 67.0, 61.0, 52.7, 28.3, 20.8 ppm.

***N-tert*-Butoxycarbonyl-4-methyl-1,2,3-oxathiazolidine-4-carboxylic acid methylester 2-oxide (37):** To aminoester **36** (970 mg, 4.2 mmol) in anhydrous acetonitrile (20 mL) at -40 °C was added dropwide thionyl chloride (780 µL, 10.7 mmol) then dry pyridine (1.7 mL, 21 mmol). After stirring at -40 °C for 30 min, then at room temperature for 30 min, the reaction mixture was washed with water (10 mL), saturated sodium bicarbonate (10 mL), then brine (10 mL). After drying over MgSO4, then concentrating under reduced pressure, the crude product was purified on silica gel (pentane/EtOAc, 85:15) to give compound **37** as pale yellow oil (870 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.16-4.40 (m, 2H), 3.80-3.72 (m, 3H), 1.82-1.38 (m, 12H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 84.5, 79.6, 65.9, 53.4, 28.1, 19.4 ppm. HRMS (ESI): calcd. for $C_{10}H_{17}NO_6SNa$ $[M+Na]^+$ 293.0807; found 293.0805.

***N-tert*-Butoxycarbonyl-4-methyl-1,2,3-oxathiazolidine-4-carboxylic acid methylester 2,2-dioxide (38):** To sulfamidite **37** (850 mg, 3.0 mmol) in acetonitrile cooled at 0 °C(30 mL) was added a catalytic portion of $RuCl_3$ (10 mg, 0.05 mmol) then sodium periodate (650 mg, 3.0 mmol). The reaction mixture was treated with water (30 mL) and stirred at 0 °C for 15 min and then at room temperature overnight. After extraction with ether (2 x 30 mL), the combined organic layers were washed with saturated sodium bicarbonate (40 mL) and brine (40 mL) and dried over $MgSO_4$. The crude mixture was purified on silica gel (pentane/EtOAc, 90:10) to give compound **38** as white solid (775 mg, 86%). Mp = 72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61 and 4.29 (AB system, J = 9.2 Hz, 2H), 3.83 (s, 3H), 1.79 (s, 3H), 1.54 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.3, 147.9, 86.1, 72.8, 65.5, 53.7, 27.9, 20.6 ppm. HRMS (ESI): calcd. for $C_{10}H_{17}NO_7SNa$ $[M+Na]^+$ 318.0623; found 318.0627.

Methyl-2-amino-3-fluoro-2-methylpropanoate (39): To cyclic sulfamidate **38** (125 mg, 0.42 mmol) in anhydrous acetonitrile (4 mL) was added tetrabutylammonium fluoride (1.1 mL of 1.0 M solution in tetrahydrofuran, 1.1 mmol). After stirring at room temperature overnight, the reaction mixture was concentrated under reduced pressure. The residue was treated with 3 N hydrochloric acid in water (8 mL) at 85 °C for 2 h. The reaction mixture was washed ether (3 x 10 mL) and then concentrated under reduced pressure. The crude mixture was dissolved in dry methanol (10 mL) at 0 °C, then thionyl chloride (200 µL, 2.7 mmol) was added dropwise. After refluxing (55 °C) for 48 h, the residue was filtered and the solvent was removed under vacuum to give a mixture of **39** and TBAF as a yellow oil. ^{1}H NMR (400 MHz, CH_3OD): δ = 5.06-4.73 (m, 2H), 3.92 (s, 3H), 1.59 (d, J = 2.0 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, CH_3OD): δ = 174.2, 84.2 (d, J_{CF} = 178.9 Hz), 63.4 (d, J_{CF} = 18.0 Hz), 53.1, 16.7 (d, J_{CF} = 5.6 Hz) ppm. ^{19}F NMR (376.5 MHz, CH_3OD): δ = -(228.2-227.4) (m) ppm. HRMS (ESI): calcd. for $C_5H_{11}FNO_2$ $[M+H]^+$ 136.0774; found 136.0773.

Methyl-2-(benzylamino)-3-fluoro-2-methylpropanoate (40): To a mixture of crude product **39** (0.35 mmol) and K_2CO_3 (115 mg, 0.84 mmol) in anhydrous DMF (3 mL) was added benzylbromide (60 µL, 0.50 mmol) under nitrogen atmosphere. After stirring at 50 °C for 64 h, the mixture was diluted with dichloromethane (15 mL), washed with water (10 mL) then brine (10 mL). After drying over MgSO4 then concentration under vacuum, the crude product was purified by column chromatography

(pentane/EtOAc, 95/5) to give the product **40** as a colorless oil (38 mg, 48% from compound **38**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.14 (m, 5H), 4.52-4.29 (m for ABC system, 2H), 3.68 (s, 3H), 3.61 (s, 2H), 1.29 (d, *J* = 2.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 140.0, 128.6, 128.5, 127.2, 87.1 (d, *J* = 176.5 Hz), 62.5 (d, *J* = 18.0 Hz), 52.3, 48.4, 19.0 (d, *J* = 6.0 Hz) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -225.0 (t, *J* = 47.2 Hz) ppm. HRMS (ESI): calcd. for $C_{12}H_{17}FNO_2$ $[M+H]^+$ 226.1243; found 226.1245.

Methyl-2-(dibenzylamino)-3-fluoro-2-methylpropanoate (21): To a mixture of **40** (90 mg, 0.40 mmol) and K_2CO_3 (120 mg, 0.90 mmol) in dry DMF (3 mL) was added benzylbromide (60 µL, 0.50 mmol) under nitrogen atmosphere. After stirring at 50 °C overnight, the reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$ then concentrated under reduced pressure. Purification on silica gel (pentane/EtOAc, 98:2) gave compound **21** as a colorless oil (12 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.12 (m, 10H), 4.68-4.40 (m for ABC system, 2H), 3.85 (d, *J* = 4.1 Hz, 4H), 3.72 (s, 3H), 1.43 (d, *J* = 2.0 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.3 (d, J_{CF} = 4.4 Hz), 139.9, 128.6, 128.3, 126.7, 86.2 (d, J_{CF} = 175.5 Hz), 67.1 (d, J_{CF} = 18.5 Hz), 52.4, 48.4, 29.7, 19.7 (d, J_{CF} = 5.2 Hz) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -224.1 (t, *J* = 47.6 Hz) ppm. HRMS (ESI): calcd. for $C_{19}H_{23}FNO_2$ $[M+H]^+$ 316.1713; found 316.1719.

Methyl-2-(benzyl(methyl)amino)-3-fluoro-2-methylpropanoate (22): To a mixture of **40** (40 mg, 0.16 mmol) and K_2CO_3 (80 mg, 0.60 mmol) in dry DMF (2.5 mL) was added methyliodide (20 µL, 0.32 mmol) under nitrogen atmosphere. After stirring at room temperature for 3 h, the reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ then concentrated under reduced pressure. Purification of the residue on silica gel (pentane/EtOAc, 99:1) gave compound **22** as a yellow oil (9 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.22 (m, 5H), 4.79-4.55 (m for ABC system, 2H), 3.79 (s, 3H), 3.64 (s, 2H), 2.24 (s, 3H), 1.50 (d, *J* = 2.3 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.0 (d, J_{CF} = 4.3 Hz), 140.0, 128.3, 128.2, 126.9, 85.8 (d, J_{CF} = 165.8 Hz), 66.1 (d, J_{CF} = 18.0 Hz), 56.5 (d, J_{CF} = 1.5 Hz), 51.8, 35.7, 18.6 (d, J_{CF} = 5.2 Hz) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = -225.1 (t, *J* = 47.1 Hz) ppm. HRMS (ESI): calcd. for $C_{13}H_{19}FNO_2$ $[M+H]^+$ 240.1400; found 240.1399.

Methyl-2-((2,4-dimethoxybenzyl)amino)-3-fluoro-2-methylpropanoate (41): To a mixture of **39** (220 mg, 1.6 mmol) and 2,4-dimethoxybenzaldehyde (282 mg, 6.42 mmol) in dry methanol (5 mL), anhydrous triethylamine (230 µL, 1.65 mmol) was added. After stirring at room temperature for 30 min, sodium cyanoborohydride (225 mg, 3.5 mmol) was added in one portion. After stirring at room temperature overnight, dichloromethane (10 mL) was added and the organic layer was washed with sodium bicarbonate solution (3 x 10 mL). After drying over $MgSO_4$, then concentration under vacuum, purification on silica gel (pentane/EtOAc, 9:1) gave product **41** as a pale yellow oil (260 mg, 60%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.27 (d, *J* = 8.8 Hz, 1H), 6.54-6.52 (m, 2H), 4.57 (d, *J* = 47.0 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 3.92-3.78 (m, 2H), 1.51 (d, *J* = 1.5 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 174.3 (d, J_{CF} = 2.5 Hz), 160.2, 158.5, 130.3, 120.4, 103.9, 98.5, 86.9 (d, J_{CF} = 176 Hz), 61.9 (d, J_{CF} = 19.5 Hz), 55.3, 55.2, 52.1, 42.7, 18.9 (d, J_{CF} = 4.7 Hz) ppm. ^{19}F NMR (376.5 MHz, CD_3OD): δ = -225.69 (dt, *J* = 47.0, 1.5 Hz) ppm. HRMS (ESI): calcd. for $C_{14}H_{21}FNO_4$ $[M+H]^+$ 286.1376; found 286.1375.

Methyl-2-((2,4-dimethoxybenzyl)(methyl)amino)-3-fluoro-2-methylpropanoate (23): To a mixture of **41** (135 mg, 0.48 mmol) and K_2CO_3 (145 mg, 1.1 mmol) in dry DMF (5 mL) was added methyliodide (65 µL, 1.1 mmol) under nitrogen atmosphere. After stirring at room temperature for 2 h, the reaction mixture was quenched with water (10 mL) then the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). After drying over $MgSO_4$, then concentration under vacuum, purification of the residue on silica gel (pentane/EtOAc, 97:3) gave compound **23** as a colorless oil (105 mg, 72%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.25 (d, *J* = 8.7 Hz, 1H), 6.47-6.44 (m, 2H), 4.85-4.50 (m for ABC system, 2H), 3.79 (s, 6H), 3.78 (s, 3H), 3.61 and 3.48 (AB system, *J* = 14.4 Hz, 2H), 2.28 (s, 3H), 1.49 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 173.0, 160.0, 158.6, 130.6, 119.9, 103.9, 98.4, 85.9 (d, J_{CF} = 175.2 Hz), 66.1 (d, J_{CF} = 18.9 Hz), 55.4, 55.3, 51.7, 50.2, 35.8, 18.3 (d, J_{CF} = 4.7 Hz) ppm. ^{19}F NMR (376.5 MHz, CD_3OD): δ = -226.3 (t, *J* = 47.1 Hz) ppm. HRMS (ESI): calcd. for $C_{15}H_{22}NO_4FNa$ $[M+Na]^+$ 322.1431; found 3221431.

Methyl-2-(benzylamino)-3-fluoropropanoate (35): To a mixture of **34** (110 mg, 0.93 mmol) and K_2CO_3 (160 mg, 1.1 mmol) in dry acetonitrile (4 mL) was added benzylbromide (111 µL, 0.63 mmol) under nitrogen atmosphere. After stirring at 50 °C overnight, the reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were concentrated under reduced pressure. Purification by chromatography on silica gel (pentane/EtOAc, 99:1 then 95:5) gave compound **35** as a colorless oil (17 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27-7.15 (m, 5H), 4.64-4.44 (m for ABC system, 2H), 3.85 and 3.67 (AB system, *J* = 13.1 Hz, 2H), 3.7 (s, 3H), 3.44 (td, *J* = 26.2, 4.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2 (d, J_{CF} = 5.3 Hz) 139.2, 128.5, 128.3, 127.3, 84.15 (d, J_{CF} = 173.0 Hz), 60.4 (d, J_{CF} = 20.3 Hz), 52.3, 52.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -228.1 (dt, J = 46.9, 26.2 Hz) ppm. HRMS (ESI): calcd for $C_{11}H_{15}FNO_2$ $[M+H]^+$ 212.1087; found 212.1088.

Methyl-2-(dibenzylamino)-3-fluoropropanoate (18): Compound **18** was obtained as a side product in the synthesis of compound **35,** and was isolated as a colorless oil (7 mg, 8%) after purification on silica gel (pentane/EtOAc, 99:1 then 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.21 (m, 10H), 4.81-4.60 (m for ABC system, 2H), 3.90 and 3.75 (AB system, *J* = 13.9 Hz, 4H), 3.81 (s, 3H), 3.76-3.68 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.2, 139.2, 128.7, 127.2, 126.9, 82.3 (d, J_{CF} = 172.2 Hz), 60.9 (d, J_{CF} = 21.4 Hz), 57.9, 51.7 ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$) : δ = -225.4 (dt, J = 46.9, 20.3 Hz) ppm. HRMS (ESI): calcd. for $C_{18}H_{21}FNO_2$ $[M+H]^+$ 302.1556; found 302.1556.

Radiolabelling procedures

General remarks: No-carrier-added (NCA) [^{18}F]-fluoride was produced via the ^{18}O[p,n]^{18}F nuclear reaction by irradiating ^{18}O-enriched water (97%, Eurisotop; 1.8 mL) with a beam of protons (18 MeV; 20–25 µA for 60 min) from a Cyclone 18/9 (IBA) cyclotron at the Cyceron PET Center. [^{18}F]fluoride was delivered to a lead-shielded hot cell in ^{18}O-enriched water by nitrogen gas pressure. Analytical High Performance Liquid Chromatography (HPLC) was carried out by a Waters e2695 (Separations module) coupled with a Waters 2998 (Photodiode Array Detector) and a MIP10 radioactive detector (Nardeux). Semi-preparative HPLC was carried out by a Waters 515 HPLC pump coupled with a Waters 2487 UV detector set up at λ = 254 nm and a MIP10 radioactive detector (Nardeux). Measure of the radioactivity was carried out with a Capintec R15C. QMA cartridges (QMA light, Waters, ABX) were obtained from ABX. Anhydrous high grade solvents (ACN and CH_2Cl_2) purchased from Sigma-Aldrich were used for all radioactive reactions.

Typical procedure for the deoxyradiofluorination reaction: No-carrier-added aqueous cyclotron produced [^{18}F]fluoride (3-5 mCi; 111-185 MBq) was trapped on a quaternary ammonium solid phase extraction cartridge (QMA light, waters, ABX), then was eluted with a ACN/H_2O (3/1, 500 µL) solution containing K_2CO_3 (3.15 mg, 23 µmol) and K_{222} (10.2 mg, 28 µmol). After three azeotropic evaporations with ACN (3 x 500 µL) at 110 °C under a steam of nitrogen, dried [^{18}F]KF/K_{222} complex was cooled to room temperature. In parallel, triflic anhydride (1M solution in CH_2Cl_2, 37 µL, 37 µmol) was added to a solution of the hydroxyaminoester precursor (33 µmol) in CH_2Cl_2 (260 µL). After stirring for 1 h at room temperature, then addition of DIPEA (6-7 µL, 40 µmol) in ACN (200 µL) and stirring for 1 min, the resulting solution was transferred into the vial containing the dried [^{18}F]-KF/K_{222} complex. The final reaction mixture was stirred at RT for 30 min. Activities recovered at the end of the radiosynthesis were in the 1.8-3.2 mCi (66-118 MBq) range. Aliquots (20 µL) were taken off at 5, 10, 15 and 30 min, then diluted in MeOH (0.2 mL) and analyzed by radio-TLC and radio-HPLC for the determination of the RCC and the isomeric ratio respectively.

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Keywords: Deoxyradiofluorination • Aziridinium • Aminoester • Fluorine-18 • Radiochemistry

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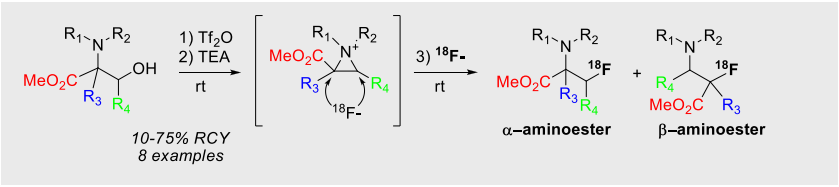

Deoxyradiofluorination of β-hydroxy-α-aminoesters was successfully achieved at room temperature using [^{18}F]fluoride anion. The reaction involved an aziridinium intermediate and yielded the corresponding [^{18}F]fluorinated α or β-aminoesters in good radiochemical yields. Regioselectivity was dependent on the nature of substituents R_1-R_4.

Radiofluorination

*Marine Morlot, Fabienne Gourand and Cécile Perrio**

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Deoxyradiofluorination Reaction from β-Hydroxy-α-aminoesters: an Entry to [^{18}F]Fluoroaminoesters under mild conditions