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Synthesis of mono- and di-substituted 2,4,5-trifluorobenzoic acid synthons, key precursors for biologically active 6-fluoroquinolones

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Abstract—In the search for new potent antiparasitical fluoroquinolones, a QSAR analysis by molecular connectivity led to the design of R^5 (Me or Et)/R^8 (MeO, Me or Et)-substituted analogs of the most powerful antibacterial or antiparasitical fluoroquinolones known so far. Unfortunately, the synthetic schemes that were elaborated in literature for 3- and 3,6-di-substituted 2,4,5-trifluorobenzoic acids, the key precursors of the target R^5/R^8-substituted 6-fluoroquinolones, led in our hands to poor yields and/or to inextricable mixtures of derivatives. This led us to reinvestigate the key alkylation steps of the 2,4,5-trifluorophenyl-oxazoline synthons and the subsequent deprotection of their oxazoline into acid with the aim of optimising the syntheses of 3- and 3,6-di-substituted 2,4,5-trifluorobenzoic acids, which constitute the entries to our target derivatives.

1. Introduction

Several quinolones and more particularly fluoroquinolones are widely used as antibacterial and antimycobacterial drugs to treat various infectious diseases.[1–7] A few fluoroquinolones were also shown to display antiparasitical activities against *Toxoplasma gondii* and *Plasmodium falciparum* that are responsible of toxoplasmosis and malaria, respectively. The first quinolone which showed antibacterial activities was nalidixic acid which was isolated in 1962.[8] Since then, more than ten thousands of quinolones have been patented, and the successive chemical modifications improved considerably their potency and spectrum of activity [for reviews, see Refs. 9–20] and parasitical responses.[21–24] Quinolones are bactericidal by interfering with bacterial DNA topoisomerases II (DNA gyrase) and IV, which are enzymes involved in DNA replication, decatenation, recombination and repair.[13,25–27] This inhibition results from formation of a strong ternary complex between the quinolone and the DNA/DNA gyrase duplex, which traps the enzyme on DNA.[9,28,29] There are clues that quinolones act on similar targets located within the apicoplast of the *T. gondii* and *P. falciparum* parasites and through similar pathways, although no definitive evidence has been provided up to now. However, the spread of multidrug-resistant bacterial and *P. falciparum* strains has highlighted the need to develop new antibacterial and antiparasitical drugs.[7,16,30]

The most active quinolones share common features which are (i) a bicyclic quinolone structure or a naphthyridone one (the quinolone carbon atom in position 8 (see Fig. 1a) has been replaced by nitrogen), (ii) an alkyl (ethyl, cyclopropyl, 2-fluoroethyl) or aryl (2,4-difluorophenyl) in position 1 as R^1, (iii) a hydrogen in position 2, (iv) a carboxylic acid in position 3, (v) a carbonyl in position 4, and (vi) a five or six-membered *N*-heterocycle or azabicycle in position 7. Other chemical modifications at any of the 1 to 4 positions have resulted in much less active compounds. These structural features are conserved in fluoroquinolones which contain a fluorine atom in position 6 as R^6. These derivatives are among the most active quinolones which display further a much broader spectrum of activity.[10,15,17] The most often used, relatively safe and well-tolerated quinolones as antibacterials are indeed 6-fluoroquinolones which include norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin (MXFX), and gatifloxacin (GTFX). These two latter derivatives with grepafloxacin (GPFX) and trovafloxacin (TVFX) (GPFX and TVFX were taken off from the market more or less shortly after launch) account for among the most powerful antiparasitical fluoroquinolones known so far (for their chemical structure, see Fig. 1b).[21,22] If a huge number of (fluoro)quinolones differing by the nature of

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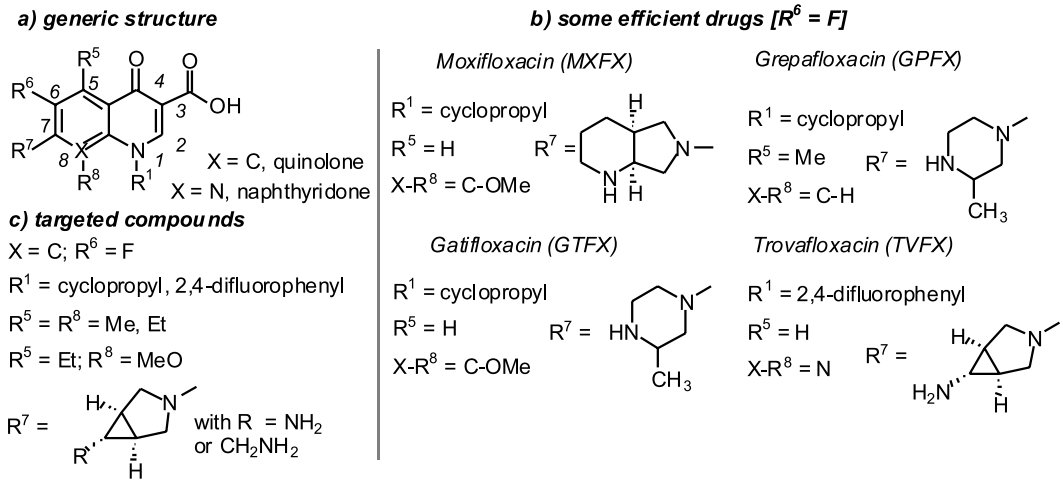


Figure 1. Chemical structure of (a) generic quinolones, (b) selected highly active antibacterial and antiparasitical 6-fluoroquinolones, and (c) our targeted R^5/R^8-substituted 6-fluoroquinolones.

the R^7 substituent were elaborated enabling the establishment of structure/antibacterial,[31] antituberculosis,[32] or antiparasitical relationships,[21,23,24] only a limited number of R^5 or/and R^8 substituted 6-fluoroquinolones are known, probably due to the difficult access to the precursors of these derivatives. Although R^5 or/and R^8-substituted 6-fluoroquinolones have been the focus of intensive search, R^5 or R^8 substitutions are restricted to F, Cl, Br, NH_2, Me, MeO, EtO, MeS, OH, F_2CHO, or CF_3O.[33–39] R^5- and R^8-substituted 6-fluoroquinolones are also scarce and R^5/R^8 substitutions are limited to Me/F, Me/Cl, Me/Me, Me/OMe, Cl/Me, NH_2/F, NH_2/Cl, NH_2/Me, NHMe/Me, NMe_2/Me, NH_2/OMe, NH_2/OEt.[33,34,36,40–42]

In the search for new potent antiparasitical fluoroquinolones, a QSAR analysis by molecular connectivity of a series of quinolones active against *T. gondii* was performed.[21,23] This analysis led to the design of R^5- and R^8-substituted 6-fluoroquinolones which were predicted to display higher or at least comparable biological activities to those of already known fluoroquinolones. Among the virtual computer designed, potentially active derivatives, we selected those presented in Figure 1c. They are R^5-(Me or Et)-substituted analogs of MXFX or GTFX (wherein R^5 is H and R^8 is OMe) or R^5/R^8-substituted analogs of GPFX (wherein R^5 is Me and R^8 is H). Their structure combines also the R^7 substituent found in TVFX. Unfortunately, the synthetic schemes that were elaborated in literature for the access of R^5- and/or R^8-substituted 6-fluoroquinolones starting from the oxazoline synthons **2** or **5** (see retrosynthetic pathway in Fig. 2), when applied for the preparation of the target derivatives shown in Figure 1c, led in our hands to poor yields and/or to inextricable mixtures of derivatives. This led us to reinvestigate the key alkylation steps of position 3 and 6 in the oxazoline synthons **2** and **5**, and the subsequent deprotection of their oxazoline into the acid function with the aim of optimising the syntheses of derivatives **9** and **10** which constitute the entries to our target derivatives shown in Figure 1c.

2. Results and discussion

2.1. Alkylation (Scheme 1A and B)

When oxazoline **2** was reacted with 1 equiv of LDA then with excess methyl iodide, as described in literature,[33] we obtained a 67% conversion of **2** into its 3-Me-derivative **5a**. However, separation of **5a** from the starting material was most difficult to achieve. To avoid this time-consuming separation and to optimise formation of derivative **5a**,**b**, we investigated alkylation of oxazoline **2** using increasing

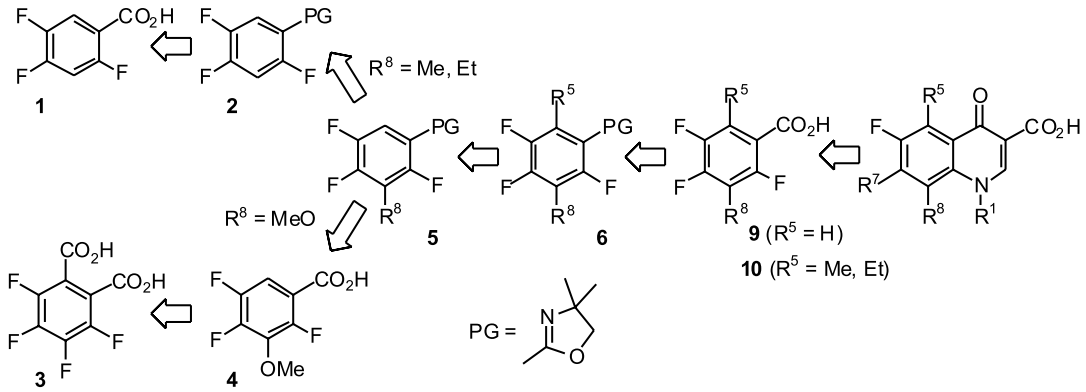
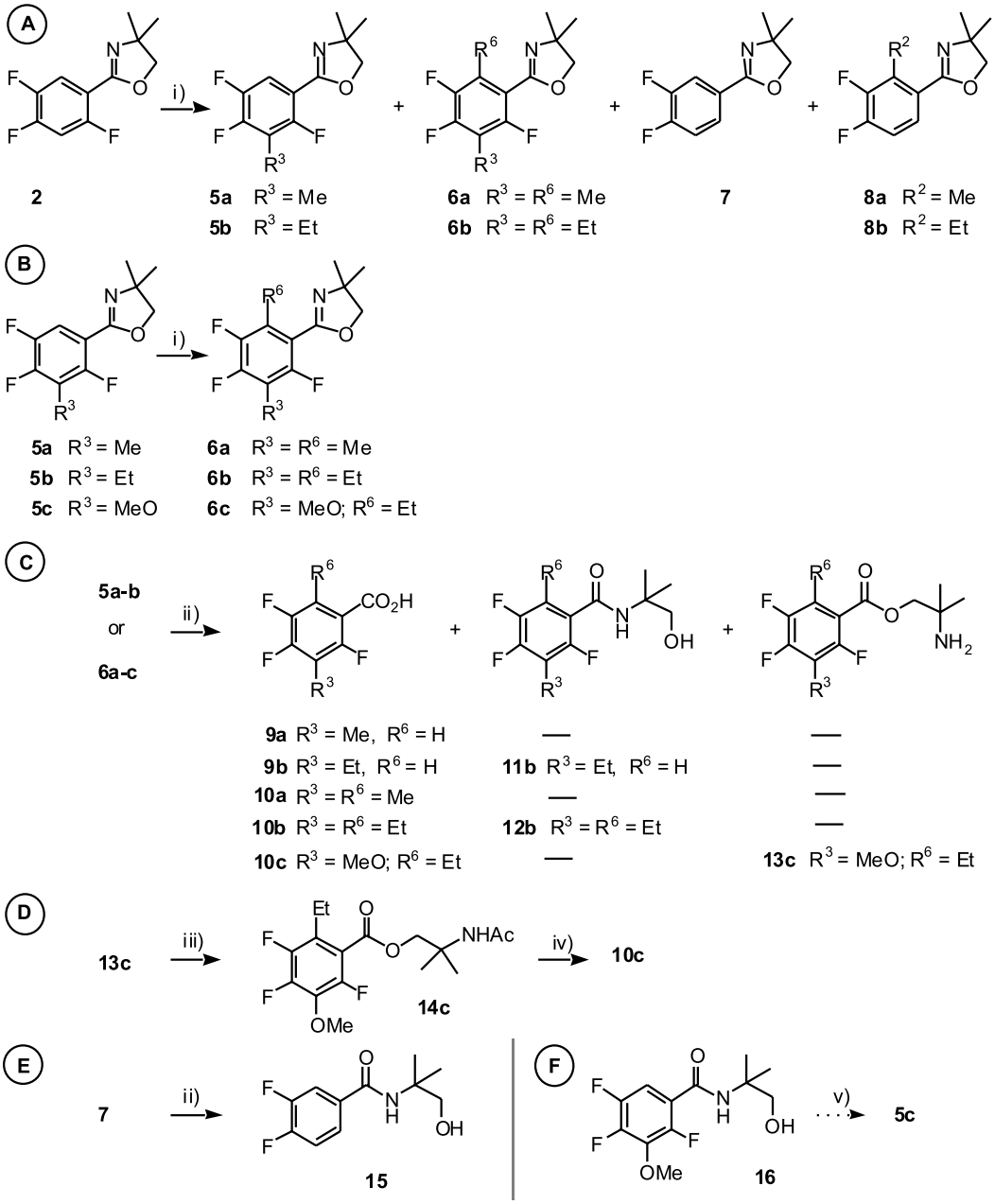


Figure 2. Retrosynthetic pathway to the targeted R^5/R^8-substituted 6-fluoroquinolones.



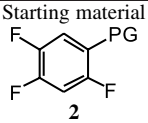
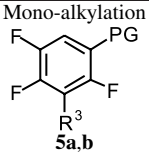
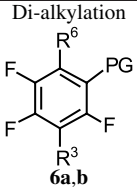
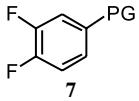
Scheme 1. (A) to (D): synthetic pathway to mono- and di-substituted 2,4,5-trifluorobenzoic acids. (A): alkylation of 2-(2,4,5-trifluorophenyl)-4,4-dimethyl-oxazoline **2**. (B): Alkylation of 2-(3-substituted-2,4,5-trifluorophenyl)-4,4-dimethyl-oxazoline **5a–c**. (C): Acid hydrolysis of the oxazolines **5a**,**b** and **6a–c**. (D): conversion of ester **13c** into acid **10c**. (E): Acid hydrolysis of the oxazoline **7** into amide **15**. (F): Chemical structure of **16**, precursor of **5c**. (i) LDA, THF, −78 °C then RI, −78 °C to rt: (ii) aq HCl (see text and Table 3), reflux; (iii) Ac_2O, pyridine; (iv) aq NaOH, rt; (v) (a) $CHCl_3$, $SOCl_2$, (b) aq NaOH, rt.

amounts of LDA in THF at −78 °C (Scheme 1A)[†] followed by the action of excess methyl or ethyl iodide. Work-up and column chromatography of the crude reaction mixtures led us to show that the reaction issue depended drastically on the LDA:**2** molar ratio. The issues of these reactions with the formation of, among others, the expected R^3-alkylated trifluoro derivatives **5a**,**b**, the R^3- and R^6-dialkylated trifluoro species **6a**,**b**, the difluoro derivative **7** and its alkylated analogs **8a**,**b** (vide infra), and the relative proportions of these derivatives in the crude reaction mixture determined by means of ^{19}F NMR are collected in Table 1.

Our data indicate that much higher conversion levels of **2** into **5a** could be obtained when increasing the amount of LDA equivalents from 1 to 1.7–1.9 (entries 2 and 3). For 1.9 LDA equivalents however, one observes the formation of the 3,6-dimethylated trifluoro species **6a** (16%, entry 3) and traces of by-products among which we could isolate and identify the difluoro derivative **7** and its methylated analogue **8a** (see entry 3). Similar results were obtained when oxazoline **2** was reacted with 2 equiv of LDA, then with excess ethyl iodide, though much lower amounts of 3,6-diethylated trifluoro species **6b** were detected (entry 4).

[†] The R^3 and R^6 groups in the chemical structures shown in Scheme 1 and Tables 1–3 are featuring the R^8 and R^5 substituents in the target 6-fluoroquinolones, respectively.

Table 1. Alkylation on 2-(2,4,5-trifluorophenyl)-4,4-dimethyl-oxazolines by alkyl halides

Entry	RI	LDA:**2** molar ratio	Relative mol%[a]				
			Starting material  **2**	Mono-alkylation  **5a**,**b**	Di-alkylation  **6a**,**b**	 **7**	Other **8a**,**b**
1	MeI	1.05	33	67	0	0	0
2	MeI	1.35–1.72	7–10	90–93	0	0	0
3	MeI	1.90	<1	82	16	<1	<1
4	EtI	2.00	0	96	2	2	0
5	EtI	2.10	0	71	16	5	8[b]
6	EtI	2.65–2.75	0	40–46	17–20	12–16	22–28[c]
7	EtI	7.9	0	0	0	~25[d]	[e]

[a] As determined by ^{19}F NMR of the crude reaction mixture; PG represents the oxazolinyl group.
[b] Compound **8b** and three unidentified compounds.
[c] Compound **8b** and four unidentified compounds.
[d] Major compound.
[e] Complex mixture.

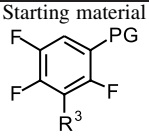
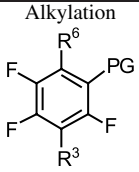
The use of higher amounts of LDA equivalents led to a subsequent decrease of the proportion of mono-alkylated species **5b** but this decrease was not compensated by the formation of the diethylated trifluoro species **6b** (see entries 5–7). These conditions favoured mostly formation of by-products, the major compound in the complex mixture being the difluoro derivative **7** (entry 7).

Our results indicate further that the 3,6-di-alkyl substituted compounds **6a**,**b** are not attainable cleanly and in good yields from **2** using a one-pot reaction. These compounds are best obtained by repeating the alkylation procedure on the isolated 3-alkylated species **5a**,**b** (Scheme 1B). Table 2 presents the results of the alkylation reaction of **5a**,**b** and of their 3-methoxy-analog **5c**. By contrast to the alkylation of the position 3, a large excess of LDA was needed to obtain high conversion levels of alkylation of position 6. Fortunately, the use of such large excesses of LDA did not led to by-products. Complete conversion of the starting material was however not obtained. The lower conversion levels of **5b** and **5c** into **6b** and **6c**, respectively, as compared with those of **5a** into **6a** are most likely related to steric effects of the alkyl iodide. Indeed, the use of the more powerful ethyl trifluoromethanesulfonate-alkylating agent did not improve the conversion levels of **5b** into **6b** (data not shown).

All products were unambiguously and fully characterised by ^{1}H, ^{19}F, and DEPT ^{13}C NMR. That mono-alkylation took place on position 3 was unequivocally attested by comparing the spectra of **5a**,**b** with those of the starting material and with those reported in literature for **5a**.[33,43] Thus, the ^{1}H NMR spectra of **5a**,**b** display the expected pattern for the sole aromatic H-6 proton (triplet of doublet at 7.51 ppm and doublet of doublet of doublet at 7.40 ppm for **5a** and **5b**, respectively, due to characteristic $^{3}J_{H-F}$ and $^{4}J_{H-F}$ couplings), and for the methyl (a triplet at 2.24 ppm due to the two $^{4}J_{H-F}$ couplings) or ethyl group (a triplet at 1.10 ppm and a quadruplet 2.62 ppm), respectively. The ^{13}C resonance of the quaternary aromatic C-3 carbon (at 116.4 and 122.5 ppm for **5a** and **5b**, respectively) adjacent to two fluorine atoms appears as a doublet of doublet with $^{2}J_{C-F}$ coupling constants in the 17–24 Hz range, as expected.[44] The ^{19}F NMR confirms the presence of three fluorine resonances, each being a doublet of doublet due to ^{3}J, ^{4}J and/or $^{5}J_{F-F}$ couplings.

The structure of the 3,6-di-alkylated Me/Me or Et/Et derivatives **6a**,**b** is attested by the absence of aromatic ^{1}H resonances, the presence of the expected patterns of the two alkyl moieties in both their ^{1}H and ^{13}C NMR spectra, and the presence of the characteristic three fluorine resonances in their ^{19}F NMR spectra.

Table 2. Alkylation of 2-(3-substituted-2,4,5-trifluorophenyl)-4,4-dimethyl-oxazolines by alkyl halides

Entry	R^3	RI	LDA:**5a–c** molar ratio	Relative mol%[a]	
				Starting material 	Alkylation 
8	Me	MeI	3.3	16	84
9	Me	MeI	3.6	5	95
10	Et	EtI	7.0	25	75
11–16	MeO	EtI	5.9 to 10.4	23±3	77±3

[a] As determined by ^{19}F NMR of the crude reaction mixture; PG represents the oxazolinyl group.

The difluoro oxazoline by-product **7** obtained in the course of alkylation of compound **2** could be identified and purified after hydrolysis into its benzamide **15** (see Scheme 1E). The presence in its ^{19}F, ^{13}C and ^{1}H NMR spectra of, respectively, (i) two ^{19}F doublets (integrating each for one fluorine) with a high coupling constant (20.6 Hz) characteristic of a $^{3}J_{F-F}$,[44] (ii) two ^{13}C–F doublets of doublet (due to $^{1}J_{C-F}$ of 250–255 Hz and $^{2}J_{C-F}$ of 12–13 Hz), and three aromatic ^{13}C–H resonances (one doublet and two doublets of doublet due to $^{3,4}J_{C-F}$ couplings), and (iii) a ^{1}H pattern in the aromatic region integrating for one proton at 7.18 ppm (H_5) and two protons at 7.50 ppm (H_2 and H_6) supports strongly the proposed structure for **15** and, consequently, for **7**.

Concerning by-products **8a**,**b** which are the methylated/ethylated analogue of **7**, respectively, only **8a** was purified and **8b** was identified by analogy in the mixture. The ^{19}F NMR spectrum of **8a** exhibits the characteristic ^{19}F pattern of the two C–F bonds in ortho ($^{3}J_{F-F}=20.6$ Hz) on the benzene ring measured for **7**. The ^{1}H NMR spectrum of **8a** affirmed the presence of unaffected oxazoline moiety, of only one aromatic methyl substituent in ortho to a F-atom (doublet at 2.52 ppm, $^{4}J_{H-F}=2.9$ Hz) and of two H-aromatic protons. The ortho location of these two protons on the benzene ring (and, consequently, of the methyl moiety on the C-2 position) is further confirmed by the typical high $^{3}J_{H-H}$ coupling constant of 8.7 Hz.

2.2. Oxazoline deprotection (Scheme 1C)

Deprotection of oxazolines **5a**,**b** and **6a–c** into acids **9a**,**b** and **10a–c**, respectively, was accomplished by treatment of the oxazolinyl derivatives with aqueous acidic media as described in literature.[33,45,46] However, the issue of this treatment depended on the presence/absence of a substituent on the C-6 position and on the acidic conditions used, the oxazolinyl moiety being hydrolysed to give the desired acid **9** or **10**, or a mixture of acid **9** or **10** and amide **11** or **12**, or even and unexpectedly the ester **13**. Though quite unusual, hydrolysis of aromatic oxazolines into amides or esters was already reported.[36,45,47] Formation of esters, such as **13c**, was observed only in the case of the methoxy derivative **6c**, its corresponding acid **10c** being obtained indirectly by acetylation of **13c** with acetic anhydride and subsequent alkaline hydrolysis of resulting hydrolysis of resulting **14c** (Scheme 1D).[36]

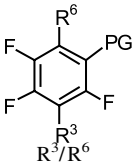
The issue of hydrolysis with the acidic conditions used was more carefully checked in the case of the ethyl-substituted derivatives **5b** and **6b**. As shown in Table 3, hydrolysis of the monoethyl derivative **5b** when performed with 1 N HCl under reflux gave a mixture of acid **9b** and amide **11b**. The acid **9b** was obtained in high yield when **5b** was refluxed in 6 N HCl for 8 h. By contrast, hydrolysis of the diethyl derivative **6b** when performed with 6 N HCl under reflux, even for 14 h, led to the amide **12b** as sole compound. More drastic conditions (12 N HCl) were needed to obtain the acid **10b** from **12b**.

Formation of acid, amide or ester was attested by IR, ^{1}H, ^{19}F, and ^{13}C NMR. The acid structure is confirmed by (i) the presence of a ν(C=O) vibration at 1700–1710 cm^{-1} and a ^{13}C resonance at 162–170 ppm in their IR and ^{13}C spectra, respectively, which are characteristic of a C(O)OH function, and (ii) the absence of the characteristic oxazoline ^{1}H and ^{13}C signals of their respective starting material.

The $C(O)OCH_2C(Me)_2NH_2$ amino-ester sequence in **13c** and the $C(O)NHC(Me)_2CH_2OH$ amido-alcool sequence in **11b** was proven by comparing (i) the ^{1}H and ^{13}C resonances of the OCH_2 group which appears more downfield for **13c** (singlet at 4.06 and 75.2 ppm, respectively) than for **11b** (singlet at 3.60 and 70.0 ppm, respectively), and (ii) the ^{13}C resonance of the quaternary carbon which appears more upfield for **13c** (49.4 ppm) than for **11b** (56.5 ppm), as expected, all values being further in line with literature.[48] Amido-alcool **11b** (and **16** from which **5c** is obtained,[33] Scheme 1F) displays for the NH proton a ^{1}H signal which is likely a doublet (J of 13.9 Hz) owing to space ^{1}H–^{19}F spin–spin interactions with the fluorine in ortho as a result of an intramolecular N–H···F hydrogen bond.[49–52] This is further supported by the fact that the NH proton of **15** (which has no fluorine in *ortho*) appears as a singlet.

It is further noticeable that the amido-alcool **12b** displays ^{1}H and ^{13}C chemical shifts for the CH_2O group of the amido-alcool sequence (at 3.91 and 51.0 ppm, respectively) that differ quite substantially from those measured for the amido-alcool derivatives **11b**, **15**, and **16** (at 3.60–3.70 and 69–71 ppm, respectively), the ^{1}H and ^{13}C chemical shifts for the adjacent $NC(Me)_2$ unit being very similar and in line with literature.[53,54] IR spectrum of **12b** confirmed unambiguously the amide linkage ν(C=O) at 1641 cm^{-1}.

Table 3. Deprotection of the oxazolinyl moiety

Starting compound	Conditions		Products % yield[a]		
	HCl (N)	Time (h)[b]	Acid **9** or **10**	Amide **11** or **12**	Ester **13**
Et/H (**5b**)	1	6	28	36	0
Et/H (**5b**)	6	8	82	2[c]	0
Et/Et (**6b**)	6	14	nd	73	0
MeO/Et (**6c**)	1	6	0	0	98

[a] Purified compound unless otherwise indicated.
[b] Stirring under reflux.
[c] Estimated by ^{19}F NMR.

3. Conclusion

With the aim of optimising the syntheses of 3- and 3,6-disubstituted 2,4,5-trifluorobenzoic acids, which constitute the entries to R^5/R^8-substituted 6-fluoroquinolones, our reinvestigation of the key alkylation steps of the 2,4,5-trifluorophenyl-oxazoline synthons led us to show that monoalkylation was cleanly performed with a high conversion into the 3-substituted 2,4,5-trifluorophenyl-oxazoline when using 1.7–1.9 LDA equivalents. Our results indicated further that the 3,6-dialkyl substituted compounds are best obtained by repeating the alkylation procedure on the isolated 3-mono-alkylated species. Concerning the deprotection of the oxazoline into the acid function, this step required more drastic conditions (12 N HCl, 12 h) than those reported in literature in order to avoid the intermediary formation of amides.

4. Experimental

4.1. Generalities

Alkylation reactions were conducted under an anhydrous nitrogen atmosphere using dry THF and reagents. Anhydrous THF was prepared by standard methods. Column chromatography purifications were carried out on Silica Gel 60 (E. Merck, 70–230 mesh). The purity of all new compounds was checked by thin-layer chromatography (TLC) and NMR. TLC analyses were performed on precoated Silica Gel F254 plates (E. Merck) with detection by UV. Melting points, determined with a Electrothermal model 3100 apparatus, are uncorrected. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Brucker AC 200 spectrometer at 200, 50.3, and 188.3 MHz, respectively. Chemical shifts (δ) are given in ppm relative to the signal indirectly (i) to $CHCl_3$ (δ 7.27) for ^{1}H, (ii) to $CDCl_3$ (δ 77.16) for ^{13}C and (iii) to $CFCl_3$ (δ 0.0) for ^{19}F. Concerning the description of the NMR spectra, the atoms are depicted as C_x, H_y, and F_z according to their standard nomenclature numbering. IR spectra were realized on a Spectrum BX Perkin Elmer FTIR as KBr disk. Electron-spray ionization mass spectra (ESI MS) in positive/negative mode were recorded on a Finnigan MAT TSQ 7000 apparatus equipped with an atmospheric pressure ionization source. The high resolution mass spectrometry analyses were performed by the 'Service Commun de Spectrométrie de Masse', at the Institut de Chimie des Substances Naturelles, Gif sur Yvette, France.

4.1.1. Reagents and starting materials. 2,4,5-Trifluorobenzoic acid **1** and 3,4,5,6-tetrafluoro-phthalic acid **3** were purchased from Lancaster, thionyl chloride from Fluka, and acetic anhydride, 2-amino-2-methyl-propan-1-ol, 2.5 M *n*-BuLi in hexane, diisopropylamine, iodoethane, 2.0 M iodomethane in *tert*-butyl methyl ether, and oxalyl chloride from Aldrich.

2-(2,4,5-Trifluorophenyl)-4,4-dimethyl-oxazoline **2** was synthesized from 2,4,5-trifluoro-benzoic acid **1**, as described in literature.[33] Its NMR data, which were only described succinctly in literature and limited to ^{1}H NMR, are given in detail hereafter: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6H, CH_3), 4.09 (s, 2H, OCH_2), 6.95 (td, 1H, H_3, $^3J_{H-F}$=10.0 Hz, $^4J_{H-F}$=6.4 Hz), 7.72 (ddd, 1H, H_6, $^3J_{H-F}$=10.6 Hz, $^4J_{H-F}$=8.9, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 28.2 (2 CH_3), 68.0 (CMe_2), 79.0 (CH_2O), 106.7 (dd, C_3, $^2J_{C-F}$=28.0, 21.0 Hz), 112.9 (ddd, C_1, $^2J_{C-F}$=12.8 Hz, $^3J_{C-F}$=6.0 Hz, $^4J_{C-F}$=4.2 Hz), 118.9 (d, C_6, $^2J_{C-F}$=22.2 Hz), 146.4 (ddd, C_5, $^1J_{C-F}$=245.9 Hz, $^2J_{C-F}$=12.9 Hz, $^4J_{C-F}$=3.6 Hz), 151.8 (dt, C_4, $^1J_{C-F}$=257.2 Hz, $^2J_{C-F}$=$^3J_{C-F}$=14.6 Hz), 156.7 (dd, C_2, $^1J_{C-F}$=255.6 Hz, $^3J_{C-F}$=8.7 Hz), 157.2 (dt, C=N, $^3J_{C-F}$=6.3 Hz); ^{19}F NMR ($CDCl_3$) δ −109.8 (dd, 1F, F_2, $^5J_{F-F}$=15.8 Hz, $^4J_{F-F}$=7.2 Hz), −128.9 (dd, 1F, F_4, $^3J_{F-F}$=22.0 Hz, $^4J_{F-F}$=7.2 Hz), −142.5 (dd, 1F, F_5, $^3J_{F-F}$=22.0 Hz, $^5J_{F-F}$=15.8 Hz).

2,4,5-Trifluoro-3-methoxy-benzoic acid **4** was prepared from 3,4,5,6-tetrafluoro-phthalic acid **3** according to the procedure described in references.[35,55] This acid **4** was used for the synthesis of compound 2-(2,4,5-trifluoro-3-methoxy-phenyl)-4,4-dimethyl-oxazoline, **5c**, which was performed using the same two-step experimental procedure than that applied for **2**.[33] Briefly, a mixture of 3.28 g (15.9 mmol) of 2,4,5-trifluoro-3-methoxy-benzoic acid **4**, 2.00 mL (22.8 mmol) of oxalyl chloride and 5 drops of DMF was stirred at room temperature for 24 h. The oily material obtained after evaporation under reduced pressure was redissolved in CH_2Cl_2 (20 mL) and added dropwise to 9.0 mL (94.2 mmol) of 2-amino-2-methyl-propan-1-ol in CH_2Cl_2 (15 mL) cooled at 0 °C. The resulting mixture was then stirred at room temperature for 48 h. After filtration, the organic phase was successively washed with water, 5% Na_2CO_3 aq solution, water, then 5% $KHSO_4$ aq solution. After drying over Na_2SO_4 and filtration, the solvent was evaporated affording 4.30 g (15.5 mmol, 97%) of the amido-alcool **16** as an oil [R_f=0.30 (7:3 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H, CH_3), 3.68 (d, 2H, OCH_2, $^3J_{H-H}$=6.1 Hz), 4.04 (d, 3H, OCH_3, $^5J_{H-F}$=0.9 Hz), 4.11 (t, 1H, OH, $^3J_{H-H}$=6.1 Hz), 6.74 (d, 1H, NH, $^5J_{H-F}$=13.1 Hz), 7.55 (ddd, 1H, H_6, $^3J_{H-F}$=10.6 Hz, $^4J_{H-F}$=8.6, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (2 CH_3), 55.9 (CMe_2), 61.7 (t, OCH_3, $^4J_{C-F}$=3.5 Hz), 69.1 (CH_2OH), 110.7 (dd, C_1, $^2J_{C-F}$=21.0 Hz, $^3J_{C-F}$=2.7 Hz), 118.4 (ddd, C_6, $^2J_{C-F}$=13.2 Hz, $^3J_{C-F}$=6.2, 3.7 Hz), 137.6 (ddd, C_3, $^2J_{C-F}$=17.6, 11.3 Hz, $^3J_{C-F}$=2.2 Hz), 145.7 (ddd, C_4, $^1J_{C-F}$=256.0 Hz, $^2J_{C-F}$=15.4 Hz, $^3J_{C-F}$=5.5 Hz), 146.9 (ddd, C_5, $^1J_{C-F}$=247.0 Hz, $^2J_{C-F}$=11.4 Hz, $^4J_{C-F}$=2.9 Hz), 149.6 (dt, C_2, $^1J_{C-F}$=246.0 Hz, $^3J_{C-F}$=$^4J_{C-F}$=3.5 Hz), 161.4 (t, C=O, $^3J_{C-F}$=$^4J_{C-F}$=1.3 Hz); ^{19}F NMR ($CDCl_3$) δ −133.6 (dd, 1F, F_2, $^5J_{F-F}$=13.8 Hz, $^4J_{F-F}$=8.9 Hz), −139.7 (dd, 1F, F_5, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=13.8 Hz), −146.5 (dd, 1F, F_4, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=8.9 Hz)]. The amido-alcohol **16** (4.30 g, 15.5 mmol) in $CHCl_3$ (30 mL) was then reacted with 3.4 mL (47 mmol) of $SOCl_2$ overnight at room temperature. After precipitation with Et_2O and filtration, the solid was dissolved in a NaOH aq solution (pH 8) and extracted with CH_2Cl_2. The organic layer was then dried over Na_2SO_4, filtrated, and evaporated giving 2.56 g (9.9 mmol, 65%) of the oxazoline **5c** as a colorless oil: R_f=0.80 (7:3 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6H, 2 CH_3), 3.92 (t, 3H, OCH_3, $^5J_{H-F}$=1.1 Hz), 3.96 (s, 2H, OCH_2), 7.26 (ddd, 1H, H_6, $^3J_{H-F}$=10.5 Hz, $^4J_{H-F}$=8.5, 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 28.1 (2 CH_3), 62.0 (t, OCH_3, $^4J_{C-F}$=3.5 Hz), 67.9 (CMe_2), 78.8 (CH_2O), 110.6 (dd, C_1, $^2J_{C-F}$=11.0 Hz, $^3J_{C-F}$=2.4 Hz),

112.3 (ddd, C_6, $^2J_{C-F}=11.0$ Hz, $^3J_{C-F}=7.7$, 4.0 Hz), 138.5 (ddd, C_3, $^2J_{C-F}=15.6$, 11.2 Hz, $^3J_{C-F}=2.8$ Hz), 146.0 (ddd, C_4, $^1J_{C-F}=255.4$ Hz, $^2J_{C-F}=15.0$ Hz, $^3J_{C-F}=5.1$ Hz), 146.7 (ddd, C_5, $^1J_{C-F}=245.5$ Hz, $^2J_{C-F}=11.4$ Hz, $^4J_{C-F}=3.6$ Hz), 151.0 (dt, C_2, $^1J_{C-F}=257.6$ Hz, $^3J_{C-F}=^4J_{C-F}=3.3$ Hz), 157.2 (dt, C=N, $^3J_{C-F}=5.9$ Hz, $^4J_{C-F}=^5J_{C-F}=2.4$ Hz); ^{19}F NMR ($CDCl_3$) δ −129.2 (dd, 1F, F_2, $^5J_{F-F}=13.1$ Hz, $^4J_{F-F}=9.6$ Hz), −140.8 (dd, 1F, F_5, $^3J_{F-F}=21.0$ Hz, $^5J_{F-F}=13.1$ Hz), −146.7 (dd, 1F, F_4, $^3J_{F-F}=21.0$ Hz, $^4J_{F-F}=9.6$ Hz).

4.2. Alkylation reaction

4.2.1. General procedure: synthesis of 2-(3-methyl-2,4,5-trifluoro-phenyl)-4,4-dimethyl-oxazoline (5a). A solution of 1.0 mL (7.1 mmol) of diisopropylamine in 8 mL of dry THF cooled at −78 °C was treated dropwise with 3.0 mL of 2.0 M *n*-BuLi (6.0 mmol; 1.72 equiv) in hexane and stirred for 30 min. To this LDA solution was added a solution of 800 mg (3.49 mmol) of **2** in 4 mL of dry THF, and the solution was stirred for 1 h at −78 °C. A 2.0 M iodomethane solution in *tert*-butyl methyl ether (4.8 mL, 9.6 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was treated with water and extracted with ethyl acetate. The organic phase was washed with 5% $KHSO_4$, water, 5% Na_2CO_3. dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (97:3 hexane/ethyl acetate) to give 793 mg (3.26 mmol, 93%) of **5a** as a colorless oil. $R_f=0.40$ (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 6H, $NCCH_3$), 2.24 [t, 3H, CH_3 (R^3)], $^4J_{H-F}=2.1$ Hz), 4.07 (s, 2H, CH_2O), 7.51 (td, 1H, H_6, $^3J_{H-F}=$ $^4J_{H-F}=9.7$, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 7.2 [CH_3 (R^3)], 28.1 ($NCCH_3$), 67.9 (CMe_2), 78.7 (CH_2O), 111.8 (ddd, C_6, $^2J_{C-F}=13.9$ Hz, $^3J_{C-F}=6.6$, 4.0 Hz), 115.1 (ddd, C_1, $^2J_{C-F}=21.2$ Hz, $^3J_{C-F}=3.3$ Hz, $^4J_{C-F}=1.8$ Hz), 116.4 (dd, C_3, $^2J_{C-F}=$ 23.2, 17.4 Hz), 146.2 (ddd, C_5, $^1J_{C-F}=245.2$ Hz, $^2J_{C-F}=13.5$ Hz, $^4J_{C-F}=3.7$ Hz), 150.5 (ddd, C_4, $^1J_{C-F}=$ 252.9 Hz, $^2J_{C-F}=14.3$ Hz, $^3J_{C-F}=8.4$ Hz), 155.3 (ddd, C_2, $^1J_{C-F}=255.0$ Hz, $^3J_{C-F}=6.6$ Hz, $^4J_{C-F}=2.6$ Hz), 157.4 (dt, C=N, $^3J_{C-F}=4.0$ Hz, $^4J_{C-F}=^5J_{C-F}=$ 2.0 Hz); ^{19}F NMR ($CDCl_3$) δ −114.5 (dd, 1F, F_2, $^5J_{F-F}=15.8$ Hz, $^4J_{F-F}=8.9$ Hz), −132.8 (dd, 1F, F_4, $^3J_{F-F}=22.0$ Hz, $^4J_{F-F}=8.9$ Hz), −142.9 (dd, 1F, F_5, $^3J_{F-F}=22.0$ Hz, $^5J_{F-F}=15.8$ Hz).

4.2.2. Synthesis of 2-(3-ethyl-2,4,5-trifluoro-phenyl)-4,4-dimethyl-oxazoline (5b). Compound **5b** was obtained likewise by stirring **2** (301 mg, 1.31 mmol) with LDA prepared in situ (1.05 mL of 2.5 M *n*-BuLi (2.6 mmol) and 0.50 mL (3.6 mmol) of diisopropylamine in 10 mL of dry THF), then adding 0.42 mL (5.3 mmol) of neat iodoethane. Work-up followed by chromatography (97:3 hexane/ethyl acetate) afforded 324 mg (1.26 mmol, 96%) of **5b** as a colorless oil: $R_f=0.55$ (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, CH_3CH_2, $^3J_{H-H}=7.5$ Hz), 1.27 (s, 6H, $NCCH_3$), 2.62 (q, 2H, CH_3CH_2, $^3J_{H-H}=7.5$ Hz), 3.97 (s, 2H, CH_2O), 7.40 (ddd, 1H, H_6, $^3J_{H-F}=10.4$ Hz, $^4J_{H-F}=$ 9.0, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3CH_2), 16.3 (CH_3CH_2), 28.1 ($NCCH_3$), 67.9 (CMe_2), 78.7 (CH_2O), 112.1 (ddd, C_6, $^2J_{C-F}=13.9$ Hz, $^3J_{C-F}=6.6$, 4.4 Hz), 115.3 (ddd, C_1, $^2J_{C-F}=21.2$ Hz, $^3J_{C-F}=3.5$ Hz, $^4J_{C-F}=1.7$ Hz), 122.5 (dd, C_3, $^2J_{C-F}=22.5$, 17.0 Hz), 146.3 (ddd, C_5, $^1J_{C-F}=245.2$ Hz, $^2J_{C-F}=13.9$ Hz, $^4J_{C-F}=3.7$ Hz), 150.3 (ddd, C_4, $^1J_{C-F}=252.9$ Hz, $^2J_{C-F}=14.1$ Hz, $^3J_{C-F}=$ 8.8 Hz), 155.0 (ddd, C_2, $^1J_{C-F}=250.7$ Hz, $^3J_{C-F}=7.0$ Hz, $^4J_{C-F}=2.6$ Hz), 157.5 (dt, C=N, $^3J_{C-F}=6.2$ Hz, $^4J_{C-F}=$ $^5J_{C-F}=1.8$ Hz); ^{19}F NMR ($CDCl_3$) δ −116.7 (dd, 1F, F_2, $^5J_{F-F}=15.8$ Hz, $^4J_{F-F}=8.3$ Hz), −134.9 (dd, 1F, F_4, $^3J_{F-F}=22.0$ Hz, $^4J_{F-F}=8.3$ Hz), −142.6 (dd, 1F, F_5, $^3J_{F-F}=22.0$ Hz, $^5J_{F-F}=15.8$ Hz).

4.2.3. Synthesis of 2-(3,6-dimethyl-2,4,5-trifluoro-phenyl)-4,4-dimethyl-oxazoline (6a). The general alkylation procedure when applied to 322 mg (1.32 mmol) of **5a** in 5 mL of THF, LDA prepared from 2.40 mL of 2.5 M *n*-BuLi (4.8 mmol) with 0.90 mL (6.4 mmol) of diisopropylamine in 5 mL of dry THF, then 6.50 mL (13.0 mmol) of 2 M iodomethane in *tert*-butyl methyl ether, afforded after work-up and column chromatography (97:3 hexane/ethyl acetate) 324 mg (1.26 mmol, 95%) of **6a** as a colorless oil: $R_f=0.60$ (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6H, $NCCH_3$), 2.09 [t, 3H, CH_3 (R^3)], $^4J_{H-F}=1.7$ Hz), 2.20 (d, 3H, CH_3 (R^6), $^4J_{H-F}=$ 2.3 Hz), 4.01 (s, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ 7.0 (td, CH_3 (R^3), $^3J_{C-F}=3.6$ Hz, $^4J_{C-F}=1.8$ Hz), 11.3 (dt, CH_3 (R^6), $^3J_{C-F}=4.4$ Hz, $^4J_{C-F}=2.2$ Hz), 28.2 ($NCCH_3$), 68.1 (CMe_2), 79.0 (CH_2O), 112.6 (dd, C_3, $^2J_{C-F}=23.4$, 17.9 Hz), 113.2 (dt, C_1, $^2J_{C-F}=17.9$ Hz, $^3J_{C-F}=^4J_{C-F}=3.8$ Hz), 124.4 (ddd, C_6, $^2J_{C-F}=16.5$ Hz, $^3J_{C-F}=3.5$, 1.3 Hz), 145.4 (ddd, C_5, $^1J_{C-F}=242.0$ Hz, $^2J_{C-F}=13.4$ Hz, $^4J_{C-F}=$ 3.8 Hz), 149.9 (ddd, C_4, $^1J_{C-F}=250.0$ Hz, $^2J_{C-F}=15.0$ Hz, $^3J_{C-F}=9.7$ Hz), 154.6 (ddd, C_2, $^1J_{C-F}=247.0$ Hz, $^3J_{C-F}=$ 7.9 Hz, $^4J_{C-F}=3.1$ Hz), 157.1 (m, C=N); ^{19}F NMR ($CDCl_3$) δ −120.6 (dd, 1F, F_2, $^5J_{F-F}=15.1$ Hz, $^4J_{F-F}=$ 6.2 Hz), −136.1 (dd, 1F, F_4, $^3J_{F-F}=21.0$ Hz, $^4J_{F-F}=$ 6.2 Hz), −146.0 (dd, 1F, F_5, $^3J_{F-F}=21.0$ Hz, $^5J_{F-F}=$ 15.1 Hz).

4.2.4. Synthesis of 2-(3,6-diethyl-2,4,5-trifluoro-phenyl)-4,4-dimethyl-oxazoline (6b). The general alkylation procedure when applied to LDA prepared in situ from 6.6 mL of 2.5 M *n*-BuLi (16.5 mmol) in hexane, and 3.0 mL (21.7 mmol) of diisopropylamine in 15 mL of dry THF, 605 mg (2.35 mmol) of **5b** in 8 mL of THF, then to 2.0 mL (25.0 mmol) of neat iodoethane afforded after work-up and chromatography (97:3 hexane/ethyl acetate) 513 mg (1.80 mmol, 76%) of compound **6b** as a colorless oil: $R_f=0.60$ (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 6H, CH_3CH_2, $^3J_{H-H}=7.5$ Hz), 1.39 (s, 6H, $NCCH_3$), 2.70 (bq, 4H, 2 CH_2, $^3J_{H-H}=7.5$ Hz), 4.10 (s, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ 13.7 [CH_3CH_2 (R^3)], 14.6 [CH_3CH_2 (R^6)], 16.0 (bd, CH_3CH_2, (R^3), $^3J_{C-F}=1.8$ Hz), 20.0 (bd, CH_3CH_2, (R^6), $^3J_{C-F}=1.8$ Hz), 28.1 ($NCCH_3$), 68.2 (CMe_2), 79.1 (CH_2O), 113.0 (dt, C_1, $^2J_{C-F}=18.3$ Hz, $^3J_{C-F}=^4J_{C-F}=3.8$ Hz), 118.9 (dd, C_3, $^2J_{C-F}=22.7$, 17.6 Hz), 130.7 (dd, C_6, $^2J_{C-F}=15.9$ Hz, $^3J_{C-F}=2.4$ Hz), 145.3 (ddd, C_5, $^1J_{C-F}=242.6$ Hz, $^2J_{C-F}=13.2$ Hz, $^4J_{C-F}=$ 3.7 Hz), 149.7 (ddd, C_4, $^1J_{C-F}=250.3$ Hz, $^2J_{C-F}=14.8$ Hz, $^3J_{C-F}=10.1$ Hz), 154.4 (ddd, C_2, $^1J_{C-F}=247.4$ Hz, $^3J_{C-F}=$ 8.2 Hz, $^4J_{C-F}=3.1$ Hz), 157.0 (d, C=N, $^3J_{C-F}=1.2$ Hz); ^{19}F NMR ($CDCl_3$) δ −122.5 (dd, 1F, F_2, $^5J_{F-F}=15.1$ Hz, $^4J_{F-F}=6.2$ Hz), −138.0 (dd, 1F, F_4, $^3J_{F-F}=21.3$ Hz, $^4J_{F-F}=6.2$ Hz), −148.2 (dd, 1F, F_5, $^3J_{F-F}=21.3$ Hz, $^5J_{F-F}=15.1$ Hz).

4.2.5. Synthesis of 2-(6-ethyl-2,4,5-trifluoro-3-methoxyphenyl)-4,4-dimethyl-oxazoline (6c). The general alkylation procedure when applied to LDA prepared in situ from 35.4 mL of 2.5 M *n*-BuLi (88.5 mmol) with 16.2 mL (116 mmol) of diisopropylamine in 120 mL of dry THF, and **5c** (3.26 g, 12.6 mmol), then to 12.5 mL (156 mmol) of neat iodoethane, gave after work-up and chromatography (95:5 hexane/ethyl acetate) 2.37 g (8.24 mmol, 65%) of **6c** as a colorless oil: R_f=0.50 (85:15 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.10 (q, 3H, CH_3CH$_2$,, $^3J_{H-H}$=7.5 Hz), 1.33 (s, 6H, NCCH$_3$), 2.64 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.1 Hz), 3.91 (s, 3H, OCH$_3$), 4.04 (s, 2H, OCH$_2$); ^{13}C NMR ($CDCl_3$) δ 14.6 (*C*H$_3$CH$_2$), 19.7 (CH$_3$*C*H$_2$), 28.0 (NC*C*H$_3$), 61.9 (OCH$_3$), 68.2 (*C*Me$_2$), 79.1 (CH$_2$O), 113.3 (dt, C$_1$, $^2J_{C-F}$=16.1 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.6 Hz), 126.5 (d, C$_6$, $^2J_{C-F}$=16.1 Hz), 135.5 (ddd, C$_3$, $^2J_{C-F}$=15.6, 11.5 Hz, $^3J_{C-F}$=2.5 Hz), 145.4 (ddd, C$_4$, $^1J_{C-F}$=252.9 Hz, $^2J_{C-F}$=15.7 Hz, $^3J_{C-F}$=6.2 Hz), 145.7 (ddd, C$_5$, $^1J_{C-F}$=243.3 Hz, $^2J_{C-F}$=11.0 Hz, $^4J_{C-F}$=3.7 Hz), 150.0 (dt, C$_2$, $^1J_{C-F}$=249.2 Hz, $^3J_{C-F}$=$^4J_{C-F}$=3.7 Hz), 156.4 (C=N); ^{19}F NMR ($CDCl_3$) δ −134.5 (dd, 1F, F$_2$, $^5J_{F-F}$=12.4 Hz, $^4J_{F-F}$=6.9 Hz), −145.9 (dd, 1F, F$_5$, $^3J_{F-F}$=21.0 Hz, $^5J_{F-F}$=12.7 Hz), −149.3 (dd, 1F, F$_4$, $^3J_{F-F}$=21.0 Hz, $^4J_{F-F}$=6.9 Hz).

4.3. By-products

4.3.1. 4,4-Dimethyl-2-(3,4-difluoro-2-methyl-phenyl)-oxazoline (8a). The title compound was isolated by chromatographic purification (97:3 hexane/AcOEt) of the reaction mixture obtained when the methylation of **2** was performed with 1.9 equiv of LDA: R_f=0.45 (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6H, NCCH$_3$), 2.52 (d, 3H, CH$_3$, $^4J_{H-F}$=2.9 Hz), 4.07 (s, 2H, CH$_2$), 7.00 (q, 1H, H$_5$, $^3J_{H-Fr4e}$∼$^4J_{H-F}$∼$^3J_{H-H}$∼8.7 Hz), 7.51 (ddd, 1H, H$_6$, $^3J_{H-H}$=8.7 Hz, $^4J_{H-F}$=5.2 Hz, $^5J_{H-F}$=2.0 Hz); ^{19}F NMR ($CDCl_3$) δ −134.7 (d, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz), −140.6 (d, 1F, F$_3$, $^3J_{F-F}$=20.6 Hz).

4.3.2. 2-(3,4-Difluoro-phenyl)-4,4-dimethyl-oxazoline (7). The title compound was identified as its deprotected compound 3,4-difluoro-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide **15**. This derivative was isolated after acid hydrolysis (1 N HCl for 6 h) of a mixture containing **5b** and **7** which resulted from the ethylation of **2** with >2 equiv of LDA, and chromatographic purification (silica gel; 9:1 to 3:2 hexane/AcOEt). R_f=0.10 (7:3 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H, NCCH$_3$), 3.65 (s, 2H, CH$_2$O), 6.32 (br s, 1H, NH), 7.18 (m, 1H, H$_5$), 7.50 (m, 2H, H$_2$ and H$_6$); ^{13}C NMR ($CDCl_3$) δ 24.5 (NC*C*H$_3$), 56.6 (*C*Me$_2$), 70.5 (CH$_2$O), 116.9 (dd, C$_2$, $^2J_{C-F}$=18.5 Hz, $^3J_{C-F}$=1.3 Hz), 117.5 (d, C$_5$, $^2J_{C-F}$=17.9 Hz), 123.5 (dd, C$_6$, $^3J_{C-F}$=7.2 Hz, $^4J_{C-F}$=3.9 Hz), 132.1 (t, C$_1$, $^3J_{C-F}$=$^4J_{C-F}$=4.4 Hz), 150.3 (dd, C$_3$, $^1J_{C-F}$=250.5 Hz, $^2J_{C-F}$=13.0 Hz), 152.6 (dd, C$_4$, $^1J_{C-F}$=254.2 Hz, $^2J_{C-F}$=12.6 Hz), 166.2 (C=O); ^{19}F NMR ($CDCl_3$) δ −133.0 (d, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz), −136.5 (d, 1F, F$_3$, $^3J_{F-F}$=20.6 Hz).

4.4. General procedure for the NMR analysis of the crude reaction mixture

The alkylation reaction was performed in the same way as described above for the LDA:**2** and LDA:**5a–c** ratios indicated in Tables 1 and 2, respectively. After hydrolysis and evaporation of the solvent, the residue was extracted with ethyl acetate. The organic phase was washed with water, dried, and concentrated. The residue was then dissolved in $CDCl_3$ for ^{1}H and ^{19}F NMR spectra recording. The ^{19}F chemical shifts of **2**, **5**, **6**, **7** and **8** were used for the identification of the compounds present in the crude mixture and the relative percentages of each of these compounds were calculated by integrating its ^{19}F resonances with respect to the overall integration.

4.5. Hydrolysis of the oxazoline derivatives

4.5.1. Hydrolysis of 5a and synthesis of 3-methyl-2,4,5-trifluoro-benzoic acid (9a). A suspension of compound **5a** (64 mg, 0.24 mmol) in 10 mL 3 N HCl was refluxed for 8 h. The reaction mixture was then extracted with 3×20 mL CH_2Cl_2. The organic phase was extracted with 1 N NaOH (3×20 mL). After acidification of the combined aqueous phases to pH 1 with 6 N HCl, extraction with CH_2Cl_2 (3×30 mL), the organic phase was washed with water until neutrality, dried (Na_2SO_4), filtrated, and concentrated leading to 42 mg (0.22 mmol, 92%) of **9a** as a white solid: R_f=0.60 (84:14:2 CH_2Cl_2/MeOH/$H_2$0, UV); ^{1}H NMR ($CDCl_3$) δ 2.29 (t, 3H, CH$_3$, $^4J_{H-F}$=2.1 Hz), 7.70 (td, 1H, H$_6$, $^3J_{H-F}$=$^4J_{H-F}$=9.5, 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 7.7 (CH$_3$), 113.1 (m, C$_6$), 117.0 (d, C$_1$, $^2J_{C-F}$=20.6 Hz), 117.4 (dd, C$_3$, $^2J_{C-F}$=24.1, 17.2 Hz), 146.5 (ddd, C$_5$, $^1J_{C-F}$=246.7 Hz, $^2J_{C-F}$=13.8 Hz, $^4J_{C-F}$=3.4 Hz), 152.9 (ddd, C$_4$, $^1J_{C-F}$=256.6 Hz, $^2J_{C-F}$=13.8 Hz, $^3J_{C-F}$=8.0 Hz), 157.5 (ddd, C$_2$, $^1J_{C-F}$=259.9 Hz, $^3J_{C-F}$=8.0 Hz, $^4J_{C-F}$=2.3 Hz), 168.1 (C=O); ^{19}F NMR ($CDCl_3$) δ −112.7 (dd, 1F, F$_2$, $^5J_{F-F}$=16.2 Hz, $^4J_{F-F}$=11.7 Hz), −127.5 (dd, 1F, F$_4$, $^3J_{F-F}$=22.0 Hz, $^4J_{F-F}$=11.7 Hz), −141.9 (dd, 1F, F$_5$, $^3J_{F-F}$=22.0 Hz, $^5J_{F-F}$=16.2 Hz); ESI-MS (negative mode): 189.3 $(M-H)^-$ in agreement with the mass calculated for M=$C_8H_5F_3O_2$ (190.02).

4.5.2. Hydrolysis of 5b and synthesis of 3-ethyl-2,4,5-trifluoro-benzoic acid (9b) and 3-ethyl-2,4,5-trifluoro-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide (11b).

4.5.2.1. 3-Ethyl-2,4,5-trifluoro-benzoic acid (9b). A suspension of **5b** (940 mg, 3.66 mmol) in 10 mL of 6 N HCl was stirred under reflux for 8 h. Work-up as described for **9a** led to 645 mg (3.01 mmol, 82%) of acid **9b** as a white solid. ^{19}F NMR of the organic phase resulting from CH_2Cl_2 extraction of the reaction mixture showed the presence of 2% mol of benzamide **11b** (see below) besides acid **9b**. R_f 0.65 (84:14:2 CH_2Cl_2/MeOH/$H_2$0, UV); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, CH$_3$, $^3J_{H-H}$=7.5 Hz), 2.78 (q, 2H, CH$_2$, $^3J_{H-H}$=7.5 Hz), 7.71 (td, 1H, H$_6$, $^3J_{H-F}$=$^4J_{H-F}$=9.4, 6.7 Hz), 11.70 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH$_3$), 16.5 (CH$_2$), 113.3 (ddd, C$_6$, $^2J_{C-F}$=12.1 Hz, $^3J_{C-F}$=5.9, 4.0 Hz), 117.2 (dt, C$_1$, $^2J_{C-F}$=20.5 Hz, $^3J_{C-F}$=$^4J_{C-F}$=2.0 Hz), 123.4 (dd, C$_3$, $^2J_{C-F}$=22.5, 17.0 Hz), 146.6 (ddd, C$_5$, $^1J_{C-F}$=246.6 Hz, $^2J_{C-F}$=13.7 Hz, $^4J_{C-F}$=3.5 Hz), 152.8 (ddd, C$_4$, $^1J_{C-F}$=256.9 Hz, $^2J_{C-F}$=13.9 Hz, $^3J_{C-F}$=9.0 Hz), 157.4 (ddd, C$_2$, $^1J_{C-F}$=260.5 Hz, $^3J_{C-F}$=7.5 Hz, $^4J_{C-F}$=2.4 Hz), 168.8 (C=O); ^{19}F NMR ($CDCl_3$) δ −114.9 (dd, 1F, F$_2$, $^5J_{F-F}$=15.8 Hz, $^4J_{F-F}$=11.7 Hz), −129.4 (dd, 1F, F$_4$, $^3J_{F-F}$=22.0 Hz, $^4J_{F-F}$=11.7 Hz), −141.5 (dd, 1F, F$_5$, $^3J_{F-F}$=22.0 Hz, $^5J_{F-F}$=15.8 Hz).

4.5.2.2. 3-Ethyl-2,4,5-trifluoro-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide (11b). Hydrolysis of **5b** (418 mg, 1.62 mmol) when performed with 1 N HCl during 6 h at reflux and work-up as described above afforded acid **9b** (94 mg, 0.46 mmol, 28%). Evaporation of the organic phase after extraction with 1 N NaOH and chromatography of the residue (9:1 to 3:2 hexane/AcOEt) led to the title compound **11b** (160 mg, 0.58 mmol, 36%) as a colorless liquid: R_f=0.30 (7:3 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 1.35 (s, 6H, NCCH$_3$), 2.68 (q, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz), 3.60 (s, 2H, OCH_2), 4.59 (s, 1H, OH), 6.91 (d, 1H, NH, $^5J_{H-F}$=13.9 Hz), 7.60 (td, 1H, H$_6$, $^3J_{H-F}$=$^4J_{H-F}$=9.4, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8 (*C*H$_3$CH$_2$), 16.4 (CH$_3$*C*H$_2$), 24.3 (NC*C*H$_3$), 56.5 (*C*Me$_2$), 70.0 (CH$_2$OH), 116.1 (ddd, C$_6$, $^2J_{C-F}$=21.0 Hz, $^3J_{C-F}$=3.7, 1.8 Hz), 117.9 (dt, C$_1$, $^2J_{C-F}$=14.3 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.6 Hz), 122.1 (dd, C$_3$, $^2J_{C-F}$=25.8, s17.4 Hz), 147.1 (ddd, C$_5$, $^1J_{C-F}$=246.3 Hz, $^2J_{C-F}$=13.5 Hz, $^4J_{C-F}$=2.9 Hz), 150.6 (ddd, C$_4$, $^1J_{C-F}$=254.0 Hz, $^2J_{C-F}$=14.3 Hz, $^3J_{C-F}$=9.9 Hz), 154.3 (ddd, C$_2$, $^1J_{C-F}$=243.7 Hz, $^3J_{C-F}$=7.0 Hz, $^4J_{C-F}$=2.6 Hz), 162.2 (d, C=O, $^3J_{C-F}$=3.6 Hz); ^{19}F NMR ($CDCl_3$) δ −121.1 (dd, 1F, F$_2$, $^5J_{F-F}$=16.5 Hz, $^4J_{F-F}$=8.9 Hz), −133.8 (dd, 1F, F$_4$, $^3J_{F-F}$=22.0 Hz, $^4J_{F-F}$=8.9 Hz), −141.2 (dd, 1F, F$_5$, $^3J_{F-F}$=22.0 Hz, $^5J_{F-F}$=16.5 Hz).

4.5.2.3. Hydrolysis of 6b into 3,6-diethyl-2,4,5-trifluoro-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide (12b). A suspension of **6b** (270 mg, 0.95 mmol) in 6 mL of 6 N HCl was refluxed for 12 h. The aqueous phase was extracted with CH_2Cl_2. The organic phase was then dried (Na_2SO_4), filtrated, and concentrated leading to 208 mg (0.69 mmol, 73%) of **12b** as a white solid: R_f=0.65 (4:1 hexane/AcOEt, UV); mp=125–127 °C; IR (KBr, cm^{-1}): 3246 (NH), 3060 (OH), 1641 (C=O), 1563 (CNH), 1464 (NH); ^{1}H NMR ($CDCl_3$) δ 1.18 and 1.20 (t, t, 3H, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 1.48 (s, 6H, NCCH$_3$), 2.71 (bq, 4H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz), 3.91 (s, 2H, CH$_2$O), 5.78 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.0 [*C*H$_3$CH$_2$ (R^3)], 15.1 [*C*H$_3$CH$_2$ (R^6)], 16.2 [CH$_3$*C*H$_2$ (R^3)], 20.2 [CH$_3$*C*H$_2$ (R^6)], 25.2 (NC*C*H$_3$), 51.0 (CH$_2$O), 55.3 (*C*Me$_2$), 119.0 (dd, C$_3$, $^2J_{C-F}$=23.2, 17.4 Hz), 121.0 (dt, C$_1$, $^2J_{C-F}$=18.7 Hz, $^3J_{C-F}$=$^4J_{C-F}$=2.9 Hz), 129.3 (dd, C$_6$, $^2J_{C-F}$=15.5 Hz, $^3J_{C-F}$=4.2 Hz), 145.7 (ddd, C$_4$, $^1J_{C-F}$=249.6 Hz, $^2J_{C-F}$=14.8 Hz, $^3J_{C-F}$=10.1 Hz), 149.2 (ddd, C$_5$, $^1J_{C-F}$=243.2 Hz, $^2J_{C-F}$=13.2 Hz, $^4J_{C-F}$=3.7 Hz), 152.6 (ddd, C$_2$, $^1J_{C-F}$=243.0 Hz, $^3J_{C-F}$=8.1 Hz, $^4J_{C-F}$=3.3 Hz), 163.6 (C=O); ^{19}F NMR ($CDCl_3$) δ −125.7 (dd, 1F, F$_2$, $^5J_{F-F}$=15.1 Hz, $^4J_{F-F}$=5.5 Hz), −139.0 (dd, 1F, F$_4$, $^3J_{F-F}$=21.3 Hz, $^4J_{F-F}$=5.5 Hz), −147.7 (dd, 1F, F$_5$, $^3J_{F-F}$=21.3 Hz, $^5J_{H-F}$=15.1 Hz); ESI-MS (positive mode): 303.7 (M)$^+$ in agreement with the mass calculated for M=$C_{15}H_{20}F_3NO_2$ (303.32).

4.5.2.4. Hydrolysis of 12b into 3,6-diethyl-2,4,5-trifluoro-benzoic acid (10b). A suspension of 76 mg (0.25 mmol) of **12b** in 5 mL of 12 N HCl was refluxed for 24 h. The reaction mixture was made basic with 10 N NaOH, then washed with CH_2Cl_2 (recovery of 48 mg of starting material 64%). The aqueous phase acidified with 12 N HCl was extracted with CH_2Cl_2. The organic phase was then washed with water until neutrality, dried (Na_2SO_4), filtrated, concentrated giving 21 mg (0.09 mmol, 36%) of acid **10b** as a white solid: R_f=0.70 (CH_2Cl_2/MeOH/H$_2$0 84/14/2 UV); ^{1}H NMR ($CDCl_3$) δ 1.22 and 1.24 (t, t, 3H, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 2.71 (bq, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz), 2.83 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 [*C*H$_3$CH$_2$ (R^3)], 14.9 [*C*H$_3$CH$_2$ (R^6)], 16.3 [CH$_3$*C*H$_2$ (R^3)], 20.4 [CH$_3$*C*H$_2$ (R^6)], 116.0 (m, C$_1$), 119.6 (dd, C$_3$, $^2J_{C-F}$=22.4, 17.8 Hz), 130.7 (d, C$_6$, $^2J_{C-F}$=16.1 Hz), 145.7 (ddd, C$_5$, $^1J_{C-F}$=242.0 Hz, $^2J_{C-F}$=13.2 Hz, $^4J_{C-F}$=3.5 Hz), 150.5 (dt, C$_4$, $^1J_{C-F}$=253.0 Hz, $^2J_{C-F}$=$^3J_{C-F}$=10.2 Hz), 154.3 (ddd, C$_2$, $^1J_{C-F}$=250.0 Hz, $^3J_{C-F}$=5.7 Hz, $^4J_{C-F}$=2.3 Hz), 169.5 (C=O); ^{19}F NMR ($CDCl_3$) δ −121.3 (dd, 1F, F$_2$, $^5J_{F-F}$=14.4 Hz, $^4J_{F-F}$=7.6 Hz), −135.6 (dd, 1F, F$_4$, $^3J_{F-F}$=21.3 Hz, $^4J_{F-F}$=7.6 Hz), −147.2 (dd, 1F, F$_5$, $^3J_{F-F}$=21.3 Hz, $^5J_{F-F}$=14.4 Hz); ESI-MS (negative mode): 231.40 (M−H)$^-$, 187.07 (M–H–CO$_2$)$^-$ in agreement with the mass calculated for M=$C_{11}H_{11}F_3O_2$ (232.18); high resolution ESI-MS (negative mode): 231.0645 (M−H)$^-$, in agreement with the mass calculated for (M−H)$^-$=$C_{11}H_{10}F_3O_2$ (231.0633).

4.5.2.5. Hydrolysis of 6a into 3,6-dimethyl-2,4,5-trifluoro-benzoic acid (10a). A suspension of **6a** in 12 N HCl was stirred under reflux for 36 h. Work-up as described for **10b** led to **10a** whose NMR data are identical to those reported in literature.[33]

4.5.2.6. Hydrolysis of 6c into (2-amino-2-methyl-propyl) 6-ethyl-2,4,5-trifluoro-3-methoxy-benzoate (13c). A suspension of **6c** (770 mg, 2.68 mmol) in 10 mL of 1 N HCl was stirred under reflux for 6 h. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4), filtrated, and concentrated to give 556 mg (1.63 mmol, 61%) of **13c** (as its HCl salt) as a white solid. The remaining aqueous phase was made basic with NaOH aq solution and was extracted by CH_2Cl_2, which, after work-up, gave another crop of 305 mg (1.0 mmol, 37%) of **13c** as its NH$_2$ form: mp=162–163 °C; IR (KBr, cm^{-1}): 1706 (C=O), 1469 and 1413 (CO); ^{1}H NMR ($CDCl_3$) δ 1.13 (bt, 9H, CH$_3$), 2.65 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.1 Hz), 3.95 (s, 3H, OCH$_3$), 4.06 (s, 2H, OCH$_2$); ^{13}C NMR ($CDCl_3$) δ 14.9 (*C*H$_3$CH$_2$), 19.9 (CH$_3$*C*H$_2$), 27.1 (NC*C*H$_3$), 49.4 (*C*Me$_2$), 62.1 (t, OCH$_3$, $^4J_{C-F}$=3.5 Hz), 75.2 (OCH$_2$), 117.1 (dt, C$_1$, $^2J_{C-F}$=15.7 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.0 Hz), 125.8 (dd, C$_6$, $^2J_{C-F}$=16.1 Hz, $^3J_{C-F}$=2.2 Hz), 135.7 (ddd, C$_3$, $^2J_{C-F}$=15.9, 11.3 Hz, $^3J_{C-F}$=2.4 Hz), 145.7 (ddd, C$_4$, $^1J_{C-F}$=253.9 Hz, $^2J_{C-F}$=15.9 Hz, $^3J_{C-F}$=6.0 Hz), 145.9 (ddd, C$_5$, $^1J_{C-F}$=244.4 Hz, $^2J_{C-F}$=11.0 Hz, $^4J_{C-F}$=3.6 Hz), 149.5 (dt, C$_2$, $^1J_{C-F}$=249.6 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.0 Hz), 163.9 (dd, C=O, $^3J_{C-F}$=2.9 Hz, $^4J_{C-F}$=1.5 Hz); ^{19}F NMR ($CDCl_3$) δ −134.8 (dd, 1F, F$_2$, $^5J_{F-F}$=12.4 Hz, $^4J_{F-F}$=6.9 Hz), −145.1 (dd, 1F, F$_5$, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=12.4 Hz), −148.4 (dd, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=6.9 Hz).

Compound **13c** (as its HCl salt): ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 1.46 (s, 6H, NCCH$_3$), 2.65 (bq, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz), 3.98 (s, 3H, OCH$_3$), 4.37 (s, 2H, OCH$_2$); ^{19}F NMR ($CDCl_3$) δ −133.0 (dd, 1F, F$_2$, $^5J_{F-F}$=12.6 Hz, $^4J_{F-F}$=7.9 Hz), −145.0 (dd, 1F, F$_5$, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=12.4 Hz), −147.4 (dd, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=7.9 Hz).

4.6. Synthesis of 6-ethyl-2,4,5-trifluoro-3-methoxy-benzoic acid (10c)

A mixture of **13c** as its HCl salt (365 mg, 1.07 mmol), pyridine (0.40 mL, 4.90 mmol) in 5 mL of acetic anhydride was stirred at 60 °C for 6 h. After cooling, water was added and the mixture was extracted with Et_2O. The combined organic phases were washed to neutrality, dried (Na_2SO_4), filtrated, and concentrated leading to 335 mg (0.96 mmol, 90%) of 2-acetylamino-2-methylpropyl 6-ethyl-2,4,5-trifluoro-3-methoxy-benzoate **14c** as an oil: R_f=0.65 (1:4 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 1.30 (s, 6H, NCCH$_3$), 1.84 (s, 3H, CH$_3$C=O), 2.59 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.0 Hz), 3.92 (s, 3H, OCH$_3$), 4.43 (s, 2H, OCH$_2$), 6.07 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.0 (*C*H$_3$CH$_2$), 20.7 (CH$_3$*C*H$_2$), 23.8 [*C*H$_3$C(O)], 24.1 (NC*C*H$_3$), 53.1 (*C*Me$_2$), 62.0 (t, OCH$_3$, $^4J_{C-F}$=3.3 Hz), 69.7 (OCH$_2$), 117.0 (dt, C$_1$, $^2J_{C-F}$=15.7 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.1 Hz), 125.6 (dd, C$_6$, $^2J_{C-F}$=16.1 Hz, $^3J_{C-F}$=2.2 Hz), 135.6 (ddd, C$_3$, $^2J_{C-F}$=15.9, 11.4 Hz, $^3J_{C-F}$=2.4 Hz), 145.5 (ddd, C$_4$, $^1J_{C-F}$=254.0 Hz, $^2J_{C-F}$=15.9 Hz, $^3J_{C-F}$=6.2 Hz), 145.8 (ddd, C$_5$, $^1J_{C-F}$=244.1 Hz, $^2J_{C-F}$=10.6 Hz, $^4J_{C-F}$=4.0 Hz), 149.3 (dt, C$_2$, $^1J_{C-F}$=248.5 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.0 Hz), 170.7 (C(O)O), 174.5 (C(O)N); ^{19}F NMR ($CDCl_3$) δ −135.1 (dd, 1F, F$_2$, $^5J_{F-F}$=12.4 Hz, $^4J_{F-F}$=6.9 Hz), −145.1 (dd, 1F, F$_5$, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=12.4 Hz), −148.4 (dd, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=6.9 Hz).

Hydrolysis of **14c** (335 mg, 0.96 mmol) was performed in 5 mL of 1 N NaOH under reflux for 5 h. After cooling, the aqueous phase was made acidic with 12 N HCl and extracted with CH_2Cl_2. After drying over Na_2SO_4, the organic phase was filtrated and concentrated affording 200 mg (0.85 mmol, 89%) of **10c** as a white solid: R_f=0.70 (84:14:2 CH_2Cl_2/MeOH/H_2O, UV); mp=79–80 °C; IR (KBr, cm^{-1}): 1707 (C=O), 1469, 1413, 1244; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 2.81 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.3 Hz), 4.03 (t, 3H, OCH$_3$, $^5J_{H-F}$=1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.9 (*C*H$_3$CH$_2$), 20.1 (CH$_3$*C*H$_2$), 62.3 (t, OCH$_3$, $^4J_{C-F}$=3.5 Hz), 115.9 (dt, C$_1$, $^2J_{C-F}$=14.3 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.1 Hz), 126.7 (dd, C$_6$, $^2J_{C-F}$=16.2 Hz, $^3J_{C-F}$=1.7 Hz), 136.0 (ddd, C$_3$, $^2J_{C-F}$=15.7, 11.3 Hz, $^3J_{C-F}$=2.6 Hz), 146.1 (ddd, C$_5$, $^1J_{C-F}$=244.1 Hz, $^2J_{C-F}$=10.8 Hz, $^4J_{C-F}$=4.0 Hz), 146.4 (ddd, C$_4$, $^1J_{C-F}$=255.1 Hz, $^2J_{C-F}$=15.7 Hz, $^3J_{C-F}$=6.4 Hz), 150.7 (dt, C$_2$, $^1J_{C-F}$=253.6 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.0 Hz), 169.8 (d, C=O, $^3J_{C-F}$=1.5 Hz); ^{19}F NMR ($CDCl_3$) δ −133.2 (dd, 1F, F$_2$, $^5J_{F-F}$=12.4 Hz, $^4J_{F-F}$=8.3 Hz), −144.7 (dd, 1F, F$_5$, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=12.4 Hz), −146.8 (dd, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=8.3 Hz); ESI-MS (negative mode): 233.4 (M−H)$^-$, 189.4 (M−H–CO$_2$)$^-$ in agreement with the mass calculated for M=$C_{10}H_9F_3O_3$ (234.2); high resolution ESI-MS (negative mode): 233.0413 (M−H)$^-$ in agreement with the mass calculated for (M−H)$^-$=$C_{10}H_8F_3O_3$ (233.0426).

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