Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Fluorine Chemistry 126 (2005) 1487–1492
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

New synthesis of polyfluoroalkyl racemic α-amino acids

L. Delon, P. Laurent, H. Blancou *

Laboratoire Organisation Moléculaire, Evolution et Matériaux Fluorés, UMR CNRS 5073, Université Montpellier II, CC17, Place E. Bataillon, F34095 Montpellier Cedex 05, France

Received 22 June 2005; received in revised form 29 July 2005; accepted 29 July 2005
Available online 4 November 2005

Abstract

We describe here a new synthesis of racemic α-amino acids containing polyfluorinated aliphatic long chain $R_F(CH_2)_3Y$ ($R_F = C_2F_5, C_6F_{13}, C_8F_{17}$) (Y = CH($NH_2$)COOH) based on Sörensen's method. The radical addition of perfluoroalkyl iodides R_FI ($R_F = C_2F_5, C_6F_{13}, C_8F_{17}$) at room temperature to ethyl-2-carbetoxy-2-phthalimido-pent-4-enoate **3** was first initiated by Et_3B/O_2. Then, the reduction of adducts **4a–c** using $Et_3B/O_2/Bu_3SnH$ leads to ethyl-2-carbetoxy-2-phthalimido-5-perfluoroalkyl-pentanoate **5a–c** under mild conditions. Experimental conditions for optimisation of the iodoperfluoroalkylation step using Et_3B/O_2 were studied. Finally, deprotection of **5a–c** gave the desired products **6a–c** in good yields.

Keywords: Fluorinated amino acids; Perfluoroalkyl iodide; Radical initiation; Triethylborane; Tributyltin hydride

1. Introduction

The increased importance of fluorinated compounds in medicine and engineering applications such as artificial blood, antipsychotics, anticancer drugs and insecticides has stimulated the study of fluorine chemistry. Modification of bioactive compounds by the introduction of fluorine and fluoroalkyl groups is an area of current interest [1–4].

Fluorine containing amino acids have found a wide range of applications in enzymology and pharmaceutical, medicinal and agricultural chemistry as a consequence of their utility in biochemical processes and modifying biological activity [5–10]. For example, α-trifluoroalanine is an important compound of this class of fluorinated amino acids [11–13] and it is known to act as a suicide inhibitor for a number of pyridoxal enzymes [14–16]. Whereas the literature is rich in methodologies for the preparation of mono- or di-fluorinated α-amino acids [17–19], few examples of synthetic routes leading to α-amino acids containing highly fluorinated *n*-alkyl chains have been reported [20–25]. We describe here a new and efficient synthesis of these compounds starting from diethyl phthalimidomalonate **2** according to Sörensen's amino acid synthesis pathway [26,27] (Scheme 1).

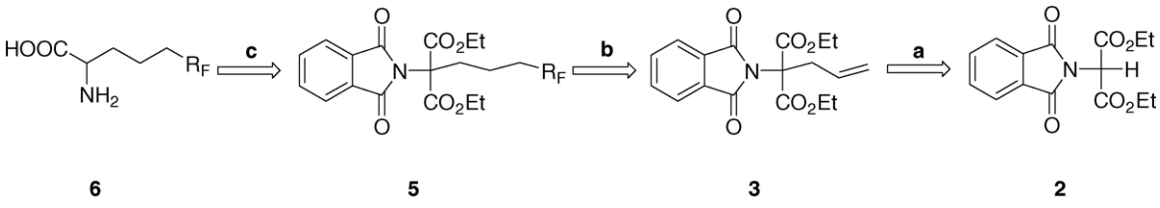
2. Results and discussion

Some years ago we reported on the synthesis of racemic α-amino acids of general formula $R_F(CH_2)_{n-1}Y$ (Y = CH(NH_2)COOH) ($R_F = C_6F_{13}$, C_8F_{17}; $n = 3$ and 10) starting from the corresponding carboxylic acid [28]. A general method to synthesise different carboxylic acids containing a perfluoroalkyl group was thus developed [29]. Because of the inevitable loss of material in this process, it seemed better to introduce the perfluoroalkyl group towards the end of the reaction sequence.

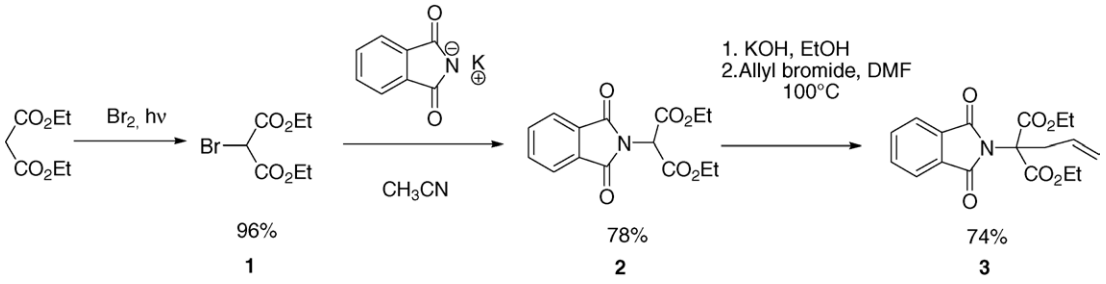
Free radical addition of perfluoroalkyl iodide (R_FI) on unsaturated compounds such as an olefin using a radical initiator is one of the best methods for the introduction of the perfluoroalkyl segment in organic compounds [30,31]. Several chemical sources such as peroxides, azonitriles, redox systems, metals or transition metal complexes, currently used to efficiently generate perfluoroalkyl radicals starting from R_FI, have been reviewed [32,33]. Thus, a large

* Corresponding author. Tel.: +33 4 67 14 39 19; fax: +33 4 67 63 10 46.
E-mail address: hubert.blancou@univ-montp2.fr (H. Blancou).

0022-1139/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2005.07.013



Scheme 1.

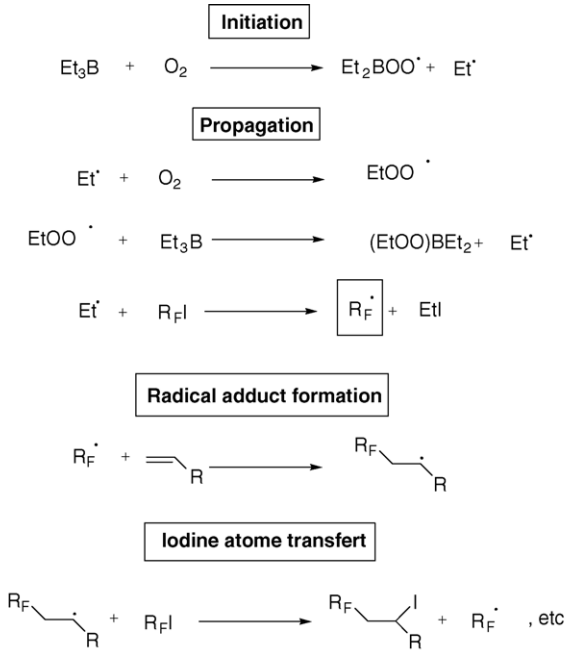


Scheme 2.

variety of unsaturated molecules containing functional groups can undergo iodoperfluoroalkylation involving a radical pathway. In this context, olefinic aminomalonate **3** derived from diethyl phthalimidomalonate **2** appeared to be an attractive precursor since it has a protected α-amino acid group [34]. We were able to prepare **3** in 55% overall yield starting from diethyl malonate (Scheme 2).

The synthesis of protected highly fluorinated α-amino acids **5a–c** was performed by perfluoroalkylation of **3** using R_FI as perfluoroalkyl radical source. In the retrosynthetic pathway described above, step **b** was essential (Scheme 1). Thus, we focused on addition of R_FI to olefin **3** using a radical initiator followed by reduction of adducts **4a–c** with a reducing agent.

We successfully explored triethylborane in this reaction, which is known to give free alkyl radicals upon treatment with oxygen [35]. In fact, Et_3B/O_2 has the advantage over classical initiators of being efficient even at low temperature (−78 °C). Utimoto and Oshima were the first to apply the reaction of triethylborane with oxygen to initiate such radical reactions [36]. Since they revealed shortly afterwards that Et_3B/O_2 induces iodoperfluoroalkylation on unsaturated



Propagation steps occurring in the radical chain addition of R_FI ($F\text{-}(CF_2)_{n-1}$) to an alkene using Et_3B/O_2 as an initiator

Scheme 3.

Table 1
Addition of perfluoroalkyl iodide to **3** using Et_3B/O_2

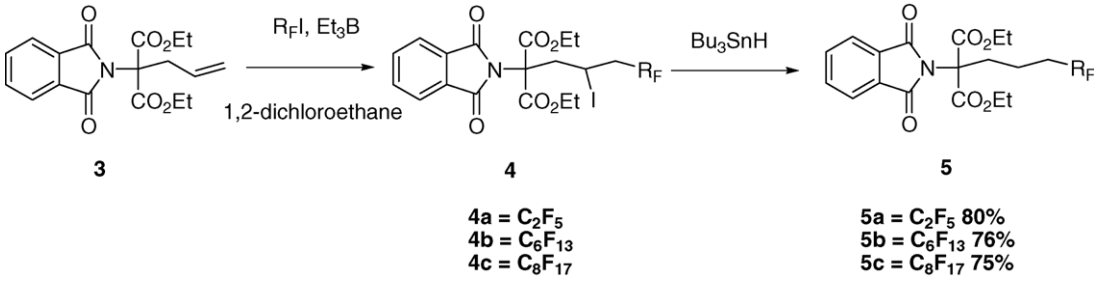
R_F	$[ET_3B]/[R_FI]$	Solvent[a]	Tansformation[b] (%)	[*C*] (mol L^{-1})[a]
C_6F_{13}	0.1 (1 M hexane)	DMF	65	2.9
C_6F_{13}	0.2 (1 M hexane)	DMF	69	2.9
C_6F_{13}	0.1 (1 M THF)	Toluene	72	5.8
C_8F_{17}	0.1 (1 M THF)	Toluene	69	5.8
C_6F_{13}	0.2 (1 M THF)	Toluene	78	5.8
C_8F_{17}	0.2 (1 M THF)	Toluene	75	5.8
C_6F_{13}	0.2 (1 M THF)	THF	63	4.8
C_8F_{17}	0.2 (1 M THF)	THF	60	4.8
C_6F_{13}	0.1 (1 M hexane)	1,2-Dichloroethane	80	2.9
C_8F_{17}	0.1 (1 M hexane)	1,2-Dichloroethane	80	2.9
C_6F_{13}	0.2 (1 M hexane)	1,2-Dichloroethane	95	2.9
C_8F_{17}	0.2 (1 M hexane)	1,2-Dichloroethane	95	2.9
C_2F_5	0.2 (1 M hexane)	1,2-Dichloroethane	90	2.9
C_6F_{13}	0.2 (1 M hexane)	No solvent	100	—
C_8F_{17}	0.2 (1 M hexane)	No solvent	100	—

[a] In a typical experimental procedure, reactions were performed at a given concentration of **3** in solvent with a stoichiometric amount of R_FI. Introduction of Et_3B (1 M solution in hexane or THF) via a syringe at 25 °C under vigorous stirring led to an instantaneous and exothermic reaction.
[b] Conversions were determined by ^1H NMR spectroscopy by the relative integration of the allylic protons signals of compound **3** compared with that of the phthalimide proton signal in the crude product.

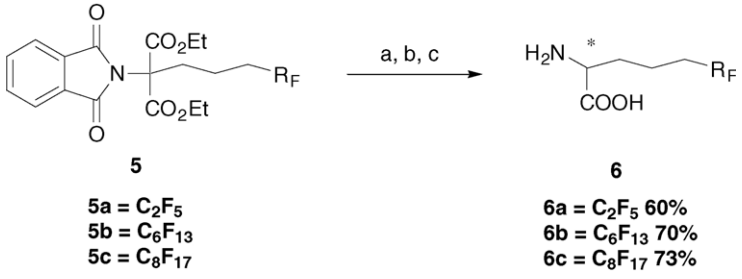
molecules under mild conditions [37], the use of Et_3B/O_2 in the chemistry of perfluoroalkyl radicals was investigated [38–40] even for perfluoroalkylation of olefins containing polymers [41,42]. The proposed mechanism for the radical addition of R_FI on **3** initiated by autoxidation of trietylborane is described in Scheme 3.

In these reactions, the choice of solvent is critical to mediate iodoperfluoroalkylation in high yields. The most ideal solvents are apolar solvents such as hexane or pentane [37–42]. However, in our case, compound **3** showed very poor solubility in such solvents. Consequently, we performed the reaction at room temperature in other organic solvents in which **3** was soluble in order to optimise yields (Table 1).

In this study, 1,2-dichloroethane was a good alternative solvent to hexane or pentane. In other solvents such as DMF, toluene or THF, the reaction was incomplete even after a prolonged time. The $[R_FI]/[Et_3B]$ ratio was also adjusted to



Scheme 4.



Scheme 5.

determinate the minimal initiator level required. We found that 20% molar ratio was necessary to give 95% ($R_F = C_6F_{13}$, C_8F_{17}) and 90% ($R_F = C_2F_5$) transformation under optimal conditions (solvent and concentration). Moreover, it appeared that when the reaction was performed without solvent, this lead to a quantitative addition of non-volatile R_FI ($R_F = C_6F_{13}$, C_8F_{17}) on **3**. Then, the in situ deiodination of adducts **4a–c** in 1,2-dichloroethane using tributyltin hydride was initiated by a residual amount of triethylborane present in media [36], leading to **5a–c** in quantitative yield (observed by ^{19}F NMR spectroscopy of the crude product). KF treatment [36] and recrystallization are however required to obtain **5a–c** in high purity (Scheme 4).

Finally, deprotection of the resulting protected α-amino acids **5a–c**, performed by hydrazinolysis of phthalimide group as described in the classical Gabriel method [43] followed by saponification and then decarboxylation of diester function, gave racemic α-amino acids **6a–c** in good yields (Scheme 5).

3. Conclusion

In summary we have developed a new and efficient method for the synthesis of highly fluorinated racemic α-amino acids starting from diethyl malonate. In this case, Et_3B/O_2 and Bu_3SnH were used to induce perfluoroalkylation of **3** at room temperature. Optimisation of the iodoperfluoroalkylation step was executed in order to obtain adducts **4a–c** in good yields. Thus, we have demonstrated that a wide range of fluorinated chains can be introduced into amino acid side chains.

The method is reproducible and each step proceeds in better that 60% yield with only one chromatographic purification required (step b, Scheme 1, $R_F = C_2F_5$). All the steps in the synthetic pathway can be performed on a multigram scale to produce **6a–c** in large quantities.

4. Experimental

4.1. General experimental procedures

Bromine, diethylmalonate, potassium phthalimide, allyl bromine, triethylborane and tributyltin hydride were purchassed from Aldrich. Different perfluoroalkyl iodides were purchased from Elf Atochem.

The products were characterised by ^1H ^{19}F and ^{13}C NMR spectroscopy, all at room temperature and recorded in $CDCl_3$ and [$(CD_3)_2SO$)] on a Brucker AVANCE 300 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield of the standard (TMS and CCl_3F). Infrared spectra were recorded on a Brucker IFS 25 instrument in the transmitance mode. Frequencies are given in cm^{-1}. Mass spectra were recorded on a Jeol SX 102 spectrometer. Melting points were recorded on a Stuart SMP3 instrument.

4.2. Synthesis of diethyl bromomalonate (*1*)

A mixture of diethylmalonate (480 g, 3 mol) and CCl_4 (450 mL) was placed in a flask equipped with a magnetic stirring bar, reflux condenser and an additional funnel containing Br_2 (498 g, 3 mol). Several millilitres of Br_2 were added to the flask which then irradiated with a Tensor lamp. As the red colour disappeared, more Br_2 was added drop wise to maintain a gentle reflux. After complete addition, the solution was heated at reflux for 1 h, then cooled and diluted with additional CCl_4. The solution was washed with 5% Na_2CO_3 (2 mL × 300 mL), dried over Na_2SO_4 filtered, and distilled over reduced pressure to give **1** (691 g, 96%) as a colorless liquid which is identified with literature [34].

^1H NMR ($CDCl_3$) δ (ppm): 1.32 (t, 6H, $J = 7.2$ Hz); 4.31 (q, 4H, $J = 7.2$ Hz); 4.84 (s, 1H).

^{13}C NMR ($CDCl_3$) δ (ppm): 13.2 (s, $\mathbf{CH_3}CH_2O$); 41.8 (s, Br**CH** ($CO_2Et)_2$); 62.1 ($CH_3\mathbf{CH_2}O$ s); 163.8 (s, $\mathbf{C}O_2Et$).

4.3. Synthesis of diethyl phthalimidomalonate (*2*)

Diethyl bromomalonate (720 g, 3 mol) was added to potassium phthalimide (555 g, 3 mol) in 200 mL of anhydrous MeCN. Reaction was very exothermic and the mixture was stirred at room temperature during 1 h and then 1 h at reflux. After cooling, solvent was distilled under reduced pressure and residual solid was washed with H_2O (1 L) and filtered. Product was dissolved in CH_2Cl_2 (4 L) and washed twice with H_2O (2 L × 0.5 L). Organic layer was dried on Na_2SO_4 and distilled under reduced pressure. The crude product was purified by crystallization from EtOH to give pure product **2** (720 g, 78%) as a white powder.

mp: 78 °C (ref. [34] 75–76 °C). ^1H NMR ($CDCl_3$) δ (ppm): 1.31 (t, 6H, $J = 7.1$ Hz); 4.32 (q, 4H, $J = 7.2$ Hz); 5.49 (s, 1H); 7.76–7.89 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.6 (s, $\mathbf{CH_3}$ CH_2O); 57.7 ($\mathbf{CH}(CO_2Et)_2$); 62.2 (s, $CH_3\mathbf{CH_2}O$); 123.1 (s, $\mathbf{CH}_{Ar}$); 131.0 (s, $\mathbf{CH}_{Ar}$); 133.8 (s, $\mathbf{CH}_{Ar}$); 163.7 (s, C=O); 165.8 (s, C=O). I.R (KBr) ν_{max} (cm^{-1}): 1733 ($\nu_{C=O}$) 2987 (ν_{CH}) 3029 (ν_{CHAr}). MS (FAB+) *m/z*: 306 $(M + H)^+$, 215, 214, 197, 123.

4.4. Synthesis of ethyl-2-carbetoxy-2′-phthalimidopent-4-enoate (*3*)

A solution of KOH (62.5 g, 1.1 mol) in 35 mL of H_2O was completed with EtOH (100 mL) and added to a mixture of diethyl phthalimidomalonate (338 g, 1.1 mol) in EtOH (2 L). A yellow solid was formed instantaneously, filtered, washed with anhydrous ether (3mL × 100 mL) and dried under reduced pressure. Potassium phthalimidomalonate salt (340 g, 1 mol) was obtained, dissolved in anhydrous DMF (340 mL) and allyl bromide (121 g, 1 mol) was added drop wise. The mixture was kept at 100 °C under stirring

during 1 h, then cooled at room temperature and product was isolated by precipitation in H_2O (2 L). A white solid was filtrate, dissolved in Et_2O (1 L), washed with H_2O (100 mL) and dried over Na_2SO_4. The organic layer was then filtered and solvent distilled under reduced pressure to give **3** (280 g, overall yield: 74%) as a white solid.

mp: 62 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.25 (t, 6H, J = 7.1 Hz); 3.15 (d, 2H, J = 7.2 Hz); 4.25 (q, 4H, J = 7.2 Hz); 4.90 (m, 2H); 5.95 (m, 1H); 7.70 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.2 (s, **C**$\mathbf{H_3}$$CH_2O$); 37.2 (s, **C**$\mathbf{H_2}$CH=CH); 62.0 ($CH_3$**C**$\mathbf{H_2}$O s); 67.0 (s, **C**$(CO_2Et)_2$); 119.1 (s, **C**$\mathbf{H_2}$=CH); 122.8 (s, **C**$\mathbf{H}_{Ar}$); 130.8 (s, **C**$\mathbf{H}_{Ar}$), 132.1 (s, CH_2=**C**$\mathbf{H}$); 133.7 (s, **C**$\mathbf{H}_{Ar}$); 165.3 (s, C=O); 166.4 (s, C=O). IR (KBr) ν_{max} (cm^{-1}): 1736 ($\nu_{C=O}$) 2986 (ν_{CH}). MS (FAB−) *m/z*: 345 (M−), 305, 270, 231, 199, 146. HRMS: calculated for $C_{18}H_{19}O_6N$: 345.1212; found: 345.1231.

4.5. Synthesis of ethyl-2-carbetoxy-2-phthalimido-5-perfluoroalkyl-pentanoate (**5a–c**) ($R_F = C_2F_5$, C_6F_{13}, C_8F_{17})

Triethylborane (1.0 M hexane solution, 4.35 mL, 4.35×10^{-3} mol) was added to a solution of **3** (10 g, 3.0×10^{-2} mol) and R_FI (3.0×10^{-2} mol, 7.1 g $R_F = C_2F_5$, 12.9 g $R_F = C_6F_{13}$, 15.8 g $R_F = C_8F_{17}$) in 1,2-dichloroethane (10 mL) at 25 °C. The resultant mixture was stirred at 25 °C during 0.5 h. Bu_3SnH (8.4 g, 7.8 mL, 3.0×10^{-2} mol) was added via a syringe and the mixture was stirred at 25 °C during 2 h. Solvent was distilled under reduce pressure, the crude product was dissolved in Et_2O (60 mL) and KF (6.9 g, 0.12 mol) was added to the solution. The mixture was stirred at room temperature during 24 h and filtered. Solvent was distilled under reduced pressure. **5a** was purified by column chromatography on silica gel (petroleum ether/diethyl ether = 80/20) to give a colorless oil (10.8 g, 80%). **5b** was crystallized from heptane to give pure product (14.6 g, 76%) as a white powder. **5c** was crystallized by precipitation in a petroleum ether–diethyl ether mixture to give pure product (16.6 g, 75%) as a white powder.

5a ($R_F = C_2F_5$): ^{1}H NMR ($CDCl_3$) δ (ppm): 1.21 (t, 6H, J = 7.1 Hz); 1.68 (m, 2H); 1.92–2.10 (m, 2H); 2.49 (m, 2H); 4.25 (q, 4H, J = 7.2 Hz); 7.68–7.81 (m; 4H). ^{19}F NMR ($CDCl_3$) δ (ppm): −85.5 (s, 3F); −118.26 (t, 2F, J = 19.7 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.1 (s, **C**$\mathbf{H_3}$$CH_2O$); 15.0 (s, CH_2**C**$\mathbf{H_2}$$CH_2$); 29.9 (t, **C**$\mathbf{H_2}$$CF_2$, J = 21.9 Hz); 31.9 (s, CH_2**C**$\mathbf{H_2}$–N); 62.1 (s, CH_3**C**$\mathbf{H_2}$O); 66.7 (s, CH_2**C**$(CO_2Et)_2$); 111.8–120.8 (m, **C**$\mathbf{_2}$$F_5$); 123.3 (s, **C**$\mathbf{H}_{Ar}$); 130.7 (s, **C**$\mathbf{H}_{Ar}$); 133.8 (s, **C**$\mathbf{H}_{Ar}$); 165.5 (s, C=O); 166.7 (s, C=O). IR (KBr) ν_{max} (cm^{-1}): 1000–1200 (ν_{CF}) 1725 ($\nu_{C=O}$) 3030 (ν_{CHAr}). MS (FAB+) *m/z*: $(M + H)^+$ (466) 392, 346, 318. HRMS: calculated for $C_{20}H_{21}F_5NO_6$: 466.1289; found: 466.1287.

5b ($R_F = C_6F_{13}$): mp: 96 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.28 (t, 6H, J = 6.9 Hz); 1.74–1.85 (m, 2H); 2.05–2.25(m, 2H); 2.60 (m, 2H); 4.32 (q, 4H, J = 7.2 Hz); 7.74–7.91 (m; 4H). ^{19}F NMR ($CDCl_3$) δ (ppm): −81.1 (t, 3F, J = 11.2 Hz); −114.3 (t, 2F, J = 14.1 Hz); −121.9 (s, 2F); −122.9 (s, 2F); −123.7 (s, 2F); −126.2 (m, 2F). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.7 (s, **C**$\mathbf{H_3}$$CH_2O$); 15.6 (s, CH_2**C**$\mathbf{H_2}$$CH_2$); 30.5–31,0 (t, **C**$\mathbf{H_2}$$CF_2$, J = 22.6 Hz); 32,6 (s, CH_2**C**$\mathbf{H_2}$–N); 62.8 (s, CH_3**C**$\mathbf{H_2}$O); 67.5 (s, CH_2**C**$(CO_2Et)_2$); 110.2–121.9 (m, **C**$\mathbf{_6}$$F_{13}$); 123.5 (s, **C**$\mathbf{H}_{Ar}$); 131.6 (s, **C**$\mathbf{H}_{Ar}$); 134.2 (s, **C**$\mathbf{H}_{Ar}$); 166.1 (s, C=O); 167.4 (s, C=O). IR (KBr) ν_{max} (cm^{-1}): 1000–1200 (ν_{CF}) 1727 ($\nu_{C=O}$) 3024 (ν_{CHAr}). MS (FAB+) *m/z*: $(M + H)^+$ (666) 546, 518. HRMS: calculated for $C_{24}H_{21}F_{13}NO_6$: 666.1161; found: 666.1157

5c ($R_F = C_8F_{17}$): mp: 65 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.20 (t, 6H, J = 7.1 Hz); 1.63–1.77 (m, 2H); 1.95–2.16 (m, 2H); 2.51 (m, 2H); 4.23 (q, 4H, J = 7.1 Hz); 7.64–7.82 (m; 4H). ^{19}F NMR ($CDCl_3$) δ (ppm): −81.0 (t, 3F, J = 11.3 Hz); −114.4 (t, 2F, J = 14.1 Hz); −122.9 (s, 2F), −122.1(s, 4F); −122.9 (s, 2F); −123.7 (s, 2F); −126.3 (s, 2F). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.0 (s, **C**$\mathbf{H_3}$$CH_2O$); 14.9 (s, CH_2**C**$\mathbf{H_2}$$CH_2$); 29.8–30.4 (t, **C**$\mathbf{H_2}$$CF_2$, J = 22.6 Hz); 31.9 (s, CH_2**C**$\mathbf{H_2}$–N); 62.1 (s, CH_3**C**$\mathbf{H_2}$O); 66.7 (s, CH_2**C**$(CO_2Et)_2$); 106.1–122.3 (m, **C**$\mathbf{_8}$$F_{17}$) 122.9 (s, **C**$\mathbf{H}_{Ar}$); 130.7 (s, **C**$\mathbf{H}_{Ar}$); 133.8 (s, **C**$\mathbf{H}_{Ar}$); 165.4 (s, C=O); 166.6 (s, C=O). IR (KBr) ν_{max} (cm^{-1}): 1000–1200 (ν_{CF}) 1724 ($\nu_{C=O}$) 2988 (ν_{CH}) 3103 (ν_{CHAr}). MS (FAB+) *m/z*: $(M + H)^+$ (766) 692, 646, 618. HRMS: calculated for $C_{26}H_{21}F_{17}NO_6$: 766.1097; found: 766.1093.

4.6. Synthesis of 2-amino-5-perfuoroalkyl-pentanoïc acids (**6a–c**) ($R_F = C_2F_5$, C_6F_{13}, C_8F_{17})

Hydrazine hydrate (98%) (0.450 g, 9.6×10^{-3} mol) was added to a solution of **5a–c** (7.5×10^{-3} mol, $R_F = C_2F_5$: 3.5 g, $R_F = C_6F_{13}$: 5 g, $R_F = C_8F_{17}$: 5.7 g) in EtOH (15 mL). The mixture was kept at reflux and stirred during 24 h. Phtalyl hydrazide was filtered and organic layer was distilled under reduced pressure. Resultant product was dissolved in EtOH (20 mL), a solution of KOH (1.05 g, 1.8×10^{-2} mol) in H_2O (3 mL) was added and the mixture kept at reflux under stirring during 5 h. EtOH was then distilled under reduced pressure, HCl aq. 32% (40 mL) was added and the mixture was kept at reflux and stirred during 24 h. HCl solution was distilled under reduced pressure, the remained product was dissolved in H_2O (20 mL) and the mixture was adjusted at pH 6 using KOH solution (0.75 M). Precipitated amino acid was filtered and washed with water (10 mL). Products were crystallized from a H_2O/EtOH mixture to give pure products **6a–c** [**6**(**a**), $R_F = C_2F_5$, 1.25 g (60%); **6**(**b**), $R_F = C_6F_{13}$, 2.5 g (70%); **6**(**c**), $R_F = C_8F_{17}$, 3.16 g (73%)].

6a ($R_F = C_2F_5$) ^{1}H NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): 1.68 (m, 2H); 1.92 (m, 2H); 2.30 (m, 2H); 3.98 (s, 1H); 8.50 (s, 3H). ^{19}F NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): −85.8 (s, 3F); −118.3 (s, 2F). ^{13}C NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): 15.89 (s, CH_2**C**$\mathbf{H_2}$$CH_2$), 28.8 (t, CH_2**C**$\mathbf{H_2}$$CF_2$, J = 21.1 Hz), 29.1 (s, CH_2**C**$\mathbf{H_2}$CH), 51.5 (s, CH_2**C**$\mathbf{H}(NH_2)COOH$), 112.4–120.7 (m, **C**$\mathbf{_2}$$F_5$); 170.8 (s, **C**$O_2H$). MS (FAB+) *m/z*: $(M + H)^+$ (236) 154, 136.

HRMS: calculated for $C_7H_{11}F_5NO_2$: 236.0710; found: 236.0751.

6b ($R_F = C_6F_{13}$) ^{1}H NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): 1.68 (m, 2H); 1.92 (m, 2H); 2.28 (m, 2H); 3.98 (s, 1H); 8.45 (s, 3H). ^{19}F NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): −80.6 (s, 3F); −113.5 (s, 2F); −121.9 (s, 2F); −122.9 (s, 2F); −123.3 (s, 2F); −126.1 (s, 2F). ^{13}C NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): 15.7 (s, $CH_2\mathbf{CH_2}CH_2$); 29.0 (s, $CH_2\mathbf{CH_2}CH$), 29.2 (t, $CF_2\mathbf{CH_2}CH_2$, J = 21.9 Hz); 51.5 (s, $CH_2\mathbf{CH}(NH_2)COOH$); 110.2–122.1 (m, $\mathbf{C_6}F_{13}$); 170.7 (s, **C**OOH). MS (FAB+) *m/z*: $(M + H)^+$ (436) 390. HRMS: calculated for $C_{11}H_{11}F_{13}NO_2$: 436.0582; found: 436.0567.

6c ($R_F = C_8F_{17}$) ^{1}H NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): 1.68 (m, 2H); 1.89 (m, 2H); 2.26 (m, 2H); 3.98 (s, 1H); 8.38 (s, 3H). ^{19}F NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): −80.9 (s, 3F); −113.7 (m, 2F); −121.9 (s, 2F); −122.1 (s, 3F); −122.9 (s, 2F); −123.4 (s, 2F); −126.3 (s, 2F). ^{13}C NMR [$(CD_3)_2SO + CF_3CO_2H$] δ (ppm): 16.3 (s, $CH_2\mathbf{CH_2}CH_2$); 29.5 (s, $CH_2\mathbf{CH_2}CH$), 29.7 (t, $CF_2\mathbf{CH_2}CH_2$, J = 21.9 Hz); 52.0 (s, $CH_2\mathbf{CH}(NH_2)COOH$); 106.8–122.8 (m, $\mathbf{C}_8F_{17}$); 171.3 (s, **C**OOH). MS (FAB+) *m/z*: $(M + H)^+$ (536) 490. HRMS: calculated for $C_{13}H_{11}F_{17}NO_2$: 536.0518; found: 536.0515.

References

[1] J.P. Bégué, D. Bonnet-Delpon, Chimie bioorganique et médicinale du fluor, Savoirs Actuels, EDP Sciences/CNRS, 2005.
[2] F.M.D. Ismail, J. Fluorine Chem. 118 (2002) 27–33.
[3] I. Ojima, J.R. Mc Carthy, J.R. Welch, Biomedical frontiers of fluorine chemistry, ACS Symposium Series, vol. 639, 1996.
[4] R. Filler, Y. Kobayashi, L.M. Yagupolskii, Studies in organic chemistry, in: Organofluorine Compounds in Medicinal Chemistry and Biomedical Application, Elsevier, Amsterdam, 1993, p. 48.
[5] J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, J. Wiley and Sons, New York, 1991.
[6] J.T. Welch, Tetrahedron 43 (1987) 3123–3197.
[7] D. Desmarteau, V. Montanari, US Patent 2001/0046960A1, 29 November 2001.
[8] D.C. Klein, K.L. Kirk, J.L. Weller, J. Oka, A. Parfitt, I.S. Owens, Mol. Pharmacol. 12 (1976) 720–730.
[9] C. Walsh, Tetrahedron 38 (1982) 871–909.
[10] C. Walsh, Adv. Enzymol. 55 (1983) 197–289.
[11] T. Sakai, F. Yan, S. Kashino, K. Uneyama, Tetrahedron 52 (1996) 233–244.
[12] V.A. Soloshonok, V.P. Kukhar, Tetrahedron 53 (1997) 8307–8314.
[13] N. Lebouvier, C. Laroche, F. Huguenot, T. Brigaud, Tetrahedron Letts. 43 (2002) 2827–2830.
[14] J. Kollonitsch, L. Barash, F.M. Kahan, H. Kropp, Nature 243 (1973) 346–347.
[15] W. Faraci, C. Walsh, Biochemistry 28 (1989) 431–437.
[16] E. Wang, C. Walsh, Biochemistry 20 (1981) 7539–7546.
[17] X. Qiu, W. Meng, F. Qing, Tetrahedron 60 (2004) 6711–6745.
[18] M. Mae, H. Amii, K. Uneyama, Tetrahedron Lett. 41 (2000) 7893–7896.
[19] T. Tsushima, K. Kawada, S. Ishihara, N. Ushida, O. Shiratori, J. Higaki, M. Hirata, Tetrahedron 44 (1988) 5375.
[20] N.O. Brace, J. Org. Chem. 32 (1967) 430–434.
[21] K. Uneyama, J. Hao, H. Amii, Tetrahedron Lett. 39 (1998) 4079–4082.
[22] H. Watanabe, Y. Hashizume, K. Uneyama, Tetrahedron Lett. 33 (1992) 4333–4336.
[23] J.G. Riess, C. Blaignon, M. Leblanc, French Patent 1987/2620445.
[24] V.P. Kukhar, J. Fluorine Chem. 69 (1994) 199–205.
[25] V.A. Soloshonok, D.V. Avilov, V.P. Kukhar, L.V. Meervelt, N. Mischenko, Tetrahedron Lett. 38 (1997) 4671–4674.
[26] C.S. Marvel, M. Palmer Stoddard, J. Org. Chem. 3 (1938) 198–203.
[27] D. Cabaret, S.A. Adediran, M.J. Garcia Gonzalez, R.F. Pratt, M. Wakselman, J. Org. Chem. 64 (1999) 713–720.
[28] D. Tra Anh, H. Blancou, A. Commeyras, J. Fluorine Chem. 94 (1999) 57–60.
[29] N. Requirand, H. Blancou, A. Commeyras, Bull. Soc. Chim. Fr. 130 (1993) 798–806.
[30] W.R. Dolbier, Chem. Rev. 96 (1996) 1557–1584.
[31] N.O. Brace, J. Fluorine Chem. 108 (2001) 147–175.
[32] G.G. Furin, Russ. Chem. Rev. 69 (2000) 491–522.
[33] N.O. Brace, J. Fluorine Chem. 93 (1999) 1–25.
[34] K.J. Martinkus, C.H. Tann, S.J. Could, Tetrahedron 39 (1983) 3493–3505.
[35] C. Ollivier, P. Renaud, Chem. Rev. 101 (2001) 3415–3434.
[36] K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, K. Utimoto, Bull. Chem. Soc. Jpn. 62 (1989) 143–147.
[37] Y. Takeyama, Y. Ichinose, K. Oshima, K. Utimoto, Tetrahedron Lett. 30 (1989) 3159–3162.
[38] K. Miura, Y. Takeyama, K. Oshima, K. Utimoto, Bull. Chem. Soc. Jpn. 64 (1991) 1542–1553.
[39] K. Iseki, M. Takahashi, D. Asada, T. Nagai, Y. Kobayaschi, J. Fluorine Chem. 74 (1995) 269–271.
[40] G. Foulard, T. Brigaud, C. Portella, Tetrahedron 52 (1996) 6187–6200.
[41] Y. Ren, T.P. Lodge, M.A. Hillmyer, Macromolecules 34 (2001) 4780–4787.
[42] Y. Ren, T.P. Lodge, M.A. Hillmyer, Macromolecules 35 (2002) 3889–3894.
[43] M.S. Gibson, R.W. Bradshaw, Angew. Chem. Int. Ed. 7 (1968) 919–930.