JOC The Journal of Organic Chemistry

Article

Fluorous L-Carbidopa Precursors: Highly Enantioselective Synthesis and Computational Prediction of Bioactivity

Albert Granados, Anna Del Olmo López, Francesca Peccati, Thierry Billard, Mariona Sodupe, and Adelina Vallribera

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02685 • Publication Date (Web): 04 Dec 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Fluorous L-Carbidopa Precursors: Highly Enantioselective Synthesis and Computational Prediction of Bioactivity

Albert Granados,[†] Anna del Olmo, Francesca Peccati,[†] Thierry Billard,[‡] Mariona Sodupe[†,*] and Adelina Vallribera[†,*]

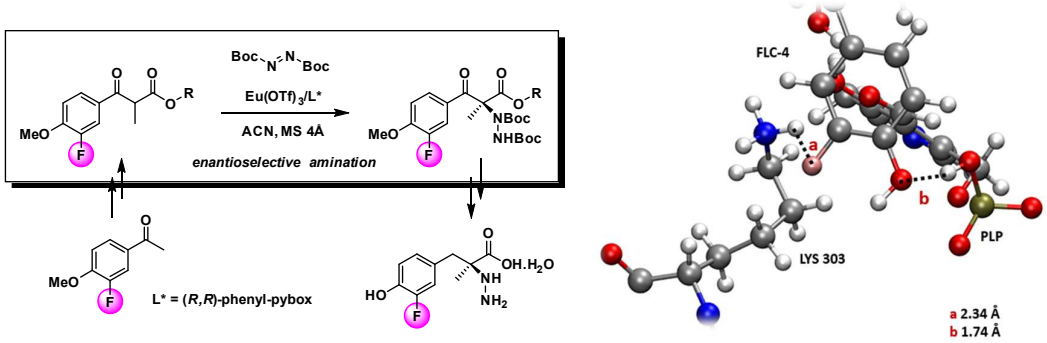
Department of Chemistry, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Barcelona (Spain).

[†]Centro de Innovación en Química Avanzada (ORFEO-CINQA).

[‡]Institute of Chemistry and Biochemistry (ICBMS-UMR CNRS 5246), Université Claude Bernard-Lyon 1, 43 Bd du 11 novembre 1918, Bat. Raulin, 69622 Villeurbanne Cedex (France)

*E-mails: adelina.vallribera@uab.cat, mariona.sodupe@uab.cat

Abstract. New fluorous enantiopure (*S*)-α-aminated β-keto esters were prepared through a highly enantioselective electrophilic α-amination step in the presence of europium triflate and (*R,R*)-phenyl-pybox. These compounds are precursors of fluorinated analogues of L-Carbidopa, which is known to inhibit DOPA decarboxylase (DDC), a key protein in Parkinson's disease. Fluorination provides better stability for biological applications, which could possibly lead to better DDC inhibitors than L-Carbidopa itself. Induced fit docking computational simulations performed on the newly structures interacting with DDC highlight that for an efficient binding at the DDC site at least one hydroxyl substituent must be present at the aromatic ring of the L-Carbidopa analogues, and point out that the presence of fluorine can further concur to fix the position of the ligand in the active site.



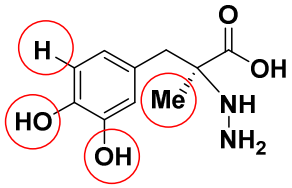
Parkinson's disease is a chronic and progressive neurological disorder whose origin is linked to the degeneration of dopamine-producing cells in the brain.[1] DOPA decarboxylase (DDC), which is abundant in the nervous system and kidney, is responsible for the synthesis of dopamine via decarboxylation of L-DOPA. Dopamine itself is not able to cross the blood-brain barrier and thus cannot be used as a drug in the treatment of Parkinson's disease. Moreover, when administered L-DOPA is rapidly converted to dopamine in the blood stream and only a small percentage will reach the nervous system. By adding DDC inhibitors, the most common among which is L-Carbidopa, greater amounts of L-DOPA reach the brain, with a substantial increase of dopamine in nerve cells.[2] At the same time, dopamine side effects related to a high concentration in the blood stream are diminished. The inhibitor is covalently linked to DDC by forming a hydrazone derivative of the cofactor.[3]

Since the preparation of fludrocortisone, one of the earliest synthetic fluorinated drugs,[4] fluorine substitution in medicinal compounds is commonly used to improve metabolic stability, bioavailability and protein-ligand interactions.[5] The incorporation of a fluorine atom(s) or fluorinated group(s) often provides molecules with quite unique properties. It is estimated that 30% of the leading 30 blockbuster drugs by sales contains fluorine.[6] This element is generally incorporated into the organic drug during the optimization studies. Almost every new drug discovery and development program explores fluorine-containing drug candidates.

A factor limiting the clinical use of many pharmaceuticals is their excessively rapid metabolic degradation. The key to many of these degradation processes is oxidative metabolism by the cytochrome P450 family. The strategic incorporation of fluorine(s) into metabolism site(s) has been widely used to prevent this deactivation.[7] Cytohrome P450 oxidation is easier for electron-rich π systems such as aromatic moieties. Introduction of a fluorine substituent avoids oxidation of the C_{ar}-F site and can also induce electronic effects on its neighbors, decreasing the pK_a value and the Lewis basicity and retarding its oxidation. For instance, it can increase the acidity of an alcohol group, which in turn will promote a better binding to the enzyme binding site.[8]

In the present study fluorine(s) or fluorine-containing groups are incorporated into the synthetic precursors of L-Carbidopa, which could be transformed to fluorous L-Carbidopa

derivatives by previously described chemistry. We envisioned different fluorination positions (Figure 1) as a tool to block undesired metabolic pathways. We were also concerned about whether the presence of hydroxylic groups on the aromatic moiety is essential for binding to DDC and thus for yielding the desired biologic activity. Therefore, some of the fluorous L-Carbidopa analogues will be computationally studied to assess how fluorination can tune their affinity for the DDC target. Further biochemistry binding experiments of these compounds with DDC, which are not the objective of this manuscript, could confirm the theoretical hypothesis.



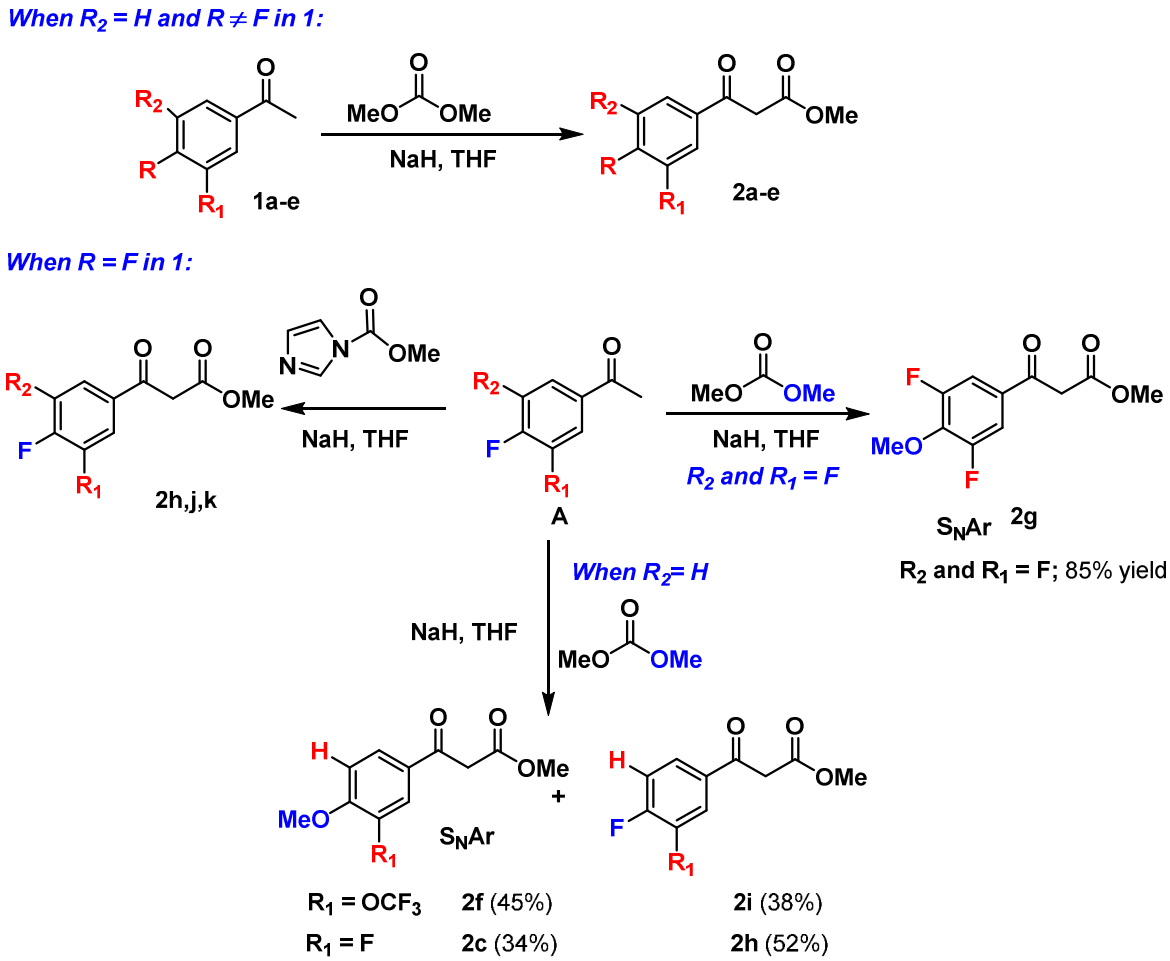
L-Carbidopa

Figure 1. L-Carbidopa formula indicating the positions where fluorine atoms or groups will be introduced.

We have previously described a straightforward methodology for the synthesis of L-Carbidopa (seven steps, 50% overall yield and 98% *ee*) through a key enantioselective α-amination step,[9] which will be used in this work to synthesize enantiopure fluorous L-Carbidopa precursors.

We first selected a series of fluorous commercially available acetophenones **1** to prepare the corresponding β-keto esters **2**. Using dimethylcarbonate and 2 equiv of NaH as a base, the desired products **2a,**[10] **2b,**[11] **2c**[11] and **2d-e** were obtained in excellent yields (92-97%, Scheme 1 and Table 1). However, for 4-fluoro acetophenones **A** (Scheme 1, R = F) possessing an electron withdrawing group in *orto* to the C_{ar}-F, as F and $-OCF_3$,[12] we observed a partial S_NAr reaction on the C_{ar}- F to form C_{ar}-OMe in the same conditions. Indeed, the nucleophilic addition-elimination reaction of the sodium enolate of **1** with dimethylcarbonate involves methoxide as a leaving group which partially reacts as nucleophile at the C_{ar}-F, producing the introduction of the OMe substituent. Thus, mixtures of 4-fluoro (**2i** and **2h**) and 4-methoxy (**2f**[13] and **2c**) β-ketoesters were obtained (Scheme 1). Additionally, for C_{ar}-F possessing electron withdrawing groups in both *orto* positions, as for example for the 3,4,5-trifluoroacetophenone, **A(1k)**, the

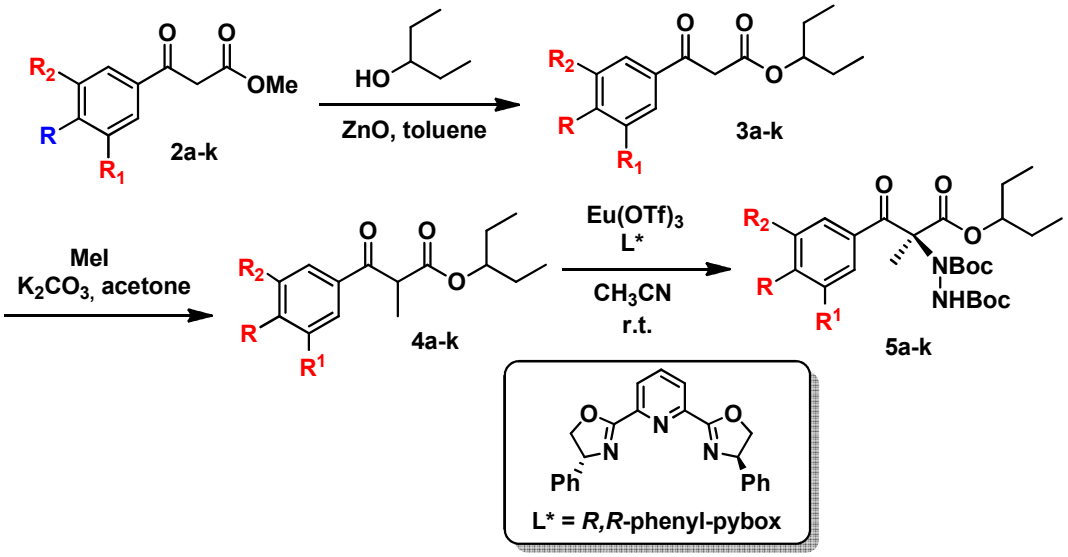
S_NAr reaction of methoxide at the C_{ar}-F is synthetically useful to selectively obtain the substitution product **2g** (85% yield, Scheme 1, Table 1). The solution to avoid fluoride loss was found in using methyl 1H-imidazole-1-carboxylate in the presence of 1.5 equiv of NaH. The corresponding β-keto esters **2h, 2j and 2k** were afforded in yields between 80-96% (Scheme 1, Table 1).



Scheme 1. Different methodologies used in the preparation of β-keto esters **2.**

Our previous experience suggested that a β-keto ester substrate bearing an OR group bulkier than methoxy might be necessary to achieve efficient enantioinduction, and secondary 3-pentyl group fulfills these requirements.[14] Therefore transesterification of **2a-k** with 3-pentanol was accomplished using catalytic amounts of ZnO in refluxing toluene rendering **3a-k** in excellent yields (80-99% yield, Scheme 2, Table 1).[15] Subsequent alkylation under classical conditions

using methyl iodide and potassium carbonate in anhydrous acetone afforded the α-methyl β-keto esters **4a-k** (52-96% yield, Scheme 2, Table 1).



Scheme 2. Synthesis of fluorous (*S*)-α-aminated β-keto esters **5a-k.**

Table 1. Yields of reactions indicated in Scheme 1.

R_2	R	R_1	Yield 2a-k	Yield 3a-k	Yield 4-k
H	CF_3	H	92% (2a)	85% (3a)	85% (4a)
H	OCF_3	H	93% (2b)	85% (3b)	81% (4b)
H	OCH_3	F	92% (2c)	89% (3c)	89% (4c)
H	OCH_3	CF_3	95% (2d)	92% (3d)	90% (4d)
H	OCH_3	OCH_3	97% (2e)[a]	99% (3e)[a]	96% (4e)[a]
H	OCH_3	OCF_3	45% (2f)[b]	95% (3f)	81% (4f)
F	OCH_3	F	85% (2g)	85% (3g)	89% (4g)
H	F	F	96% (2h)	80% (3h)	92% (4h)
H	F	OCF_3	38% (2i)[b]	92% (3i)	86% (4i)

H	**F**	**CF_3**	**80% (2j)**	**88% (3j)**	**88% (4j)**
F	**F**	**F**	**84% (2k)**	**82% (3k)**	**89% (4k)**

[a] Previously prepared, see ref. 9;[b] Reaction of 3-trifluoromethoxy-4-fluorobenzophenone with dimethylcarbonate and NaH as base gave 45% of **2f** and 38% of **2i**.

Substrates **4a-k** underwent enantioselective electrophilic α-amination in *S* configuration with di-*tert*-butyl azodicarboxylate[16] using a $Eu(OTf)_3$/L* mixture as a catalyst. A solution of $Eu(OTf)_3$ (0.017 mmol) and (*R,R*)-phenyl-pybox (0.023 mmol) in dry acetonitrile (1.5 mL) was stirred overnight in the presence of 4Å molecular sieves under argon atmosphere at room temperature. Then, the β-keto ester (0.184 mmol) and the electrophile (0.298 mmol) were sequentially added. We have previously reported that in those cases the best choice for the pybox ligand was (*R,R*)-diphenylpybox,[14b] however using fluorous substrates, the simpler and commercially available (*R,R*)-phenyl-pybox employed at room temperature gave excellent chemical yields (70-87%) and excellent *ee*'s (90-100%). The presence of the phenyl substituents in the pybox ligand is essential for a good enantioselection, probably due to π stacking interactions between the aromatic moiety of the substrate **4** (Scheme 3) and the aromatic ring of the phenylpybox (using (*R,R*)-isopropylpybox only a moderate 63% was obtained in the same conditions for **5e**). In addition, the enantiomeric excesses were much greater (90-99%) with electron withdrawing groups as substituents in the aromatic positions (**5a-d, f-k** in Figure 2) than those obtained for the aromatic electronic rich derivatives (80% *ee* for **5e** in Figure 2) in the same conditions.

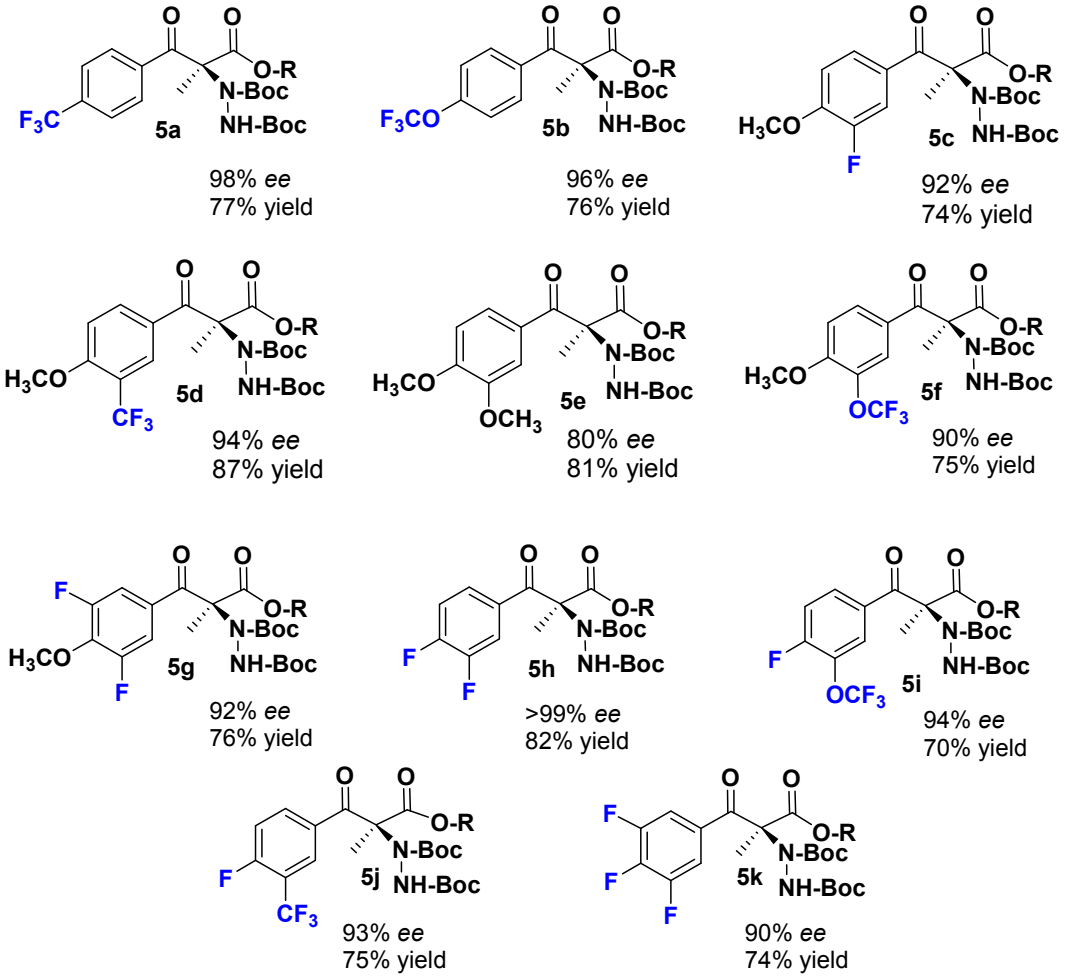


Figure 2. Structures, yields and *ee*'s of the α-amination step (Scheme 2) for compounds **5.**

The mechanism of this type of reaction has been proposed previously.[14a,17] There is enough evidence in the literature to propose the formation of the intermediate corresponding to the coordination of pybox ligand, β-keto ester and azo reactive to the europium atom in the disposition shown in Figure 3. One of the phenyl ring on the oxazoline unit can attain a conformation to present a suitable distance so as to provide stabilizing π interactions. This is possible when the right-side phenyl is parallel to the aryl ring of **4**. In this pausible intermediate (Figure 3) the bulkiness of the ester in **4** is also responsible of the coordination of the ketoester with this functional group ortogonal to the left-side phenyl. The C-N formation step is the

chiral-determining step. Formation of a six-membererd ring transition state has been proposed by other authors.[17]

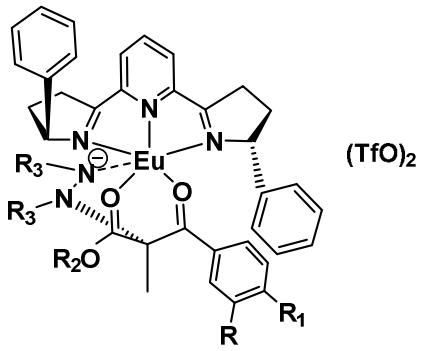
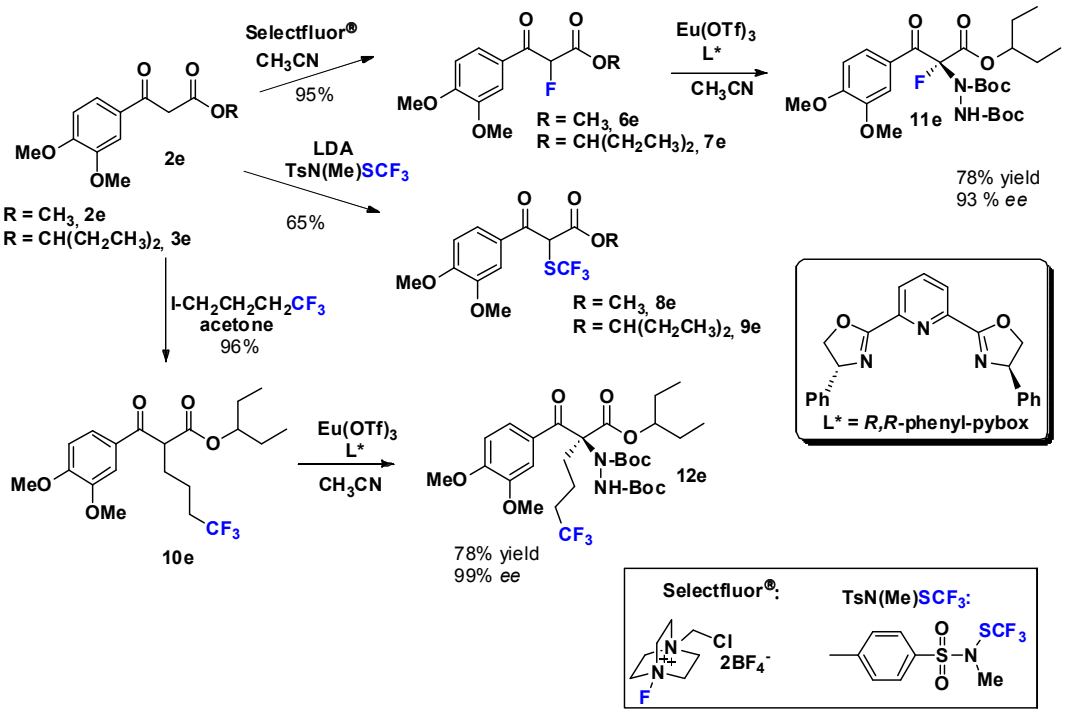


Figure 3. Schematic representation of a plausible intermediate of the enantioselective α-amination reaction

Precursors **5** (except non fluorous 5e) could be easily converted to fluorous L-Carbidopa analogues following a chemistry well established and previously published by our group.[9]

Other fluorous derivatives were also prepared. Monofluorination of β-keto esters **2e** and **3e** with Selectfluor®[18] in acetonitrile gave compounds **6e** and **7e** with excellent 95% yield in both cases. The amination step was carried out using di-*tert*-butyl azodicarboxylate, $Eu(OTf)_3$ and commercially available (*R,R*)-phenyl-pybox at room temperature, obtaining **11e** in a high yield and excellent 93% *ee* (Scheme 3). Other fluorinated groups, such as $–SCF_3$,[19] could also be introduced in the intercarbonylic position, although they are too bulky for the following amination process. The introduction of $–CF_3$ was discarded since in the amination conditions HF will be lost. Thus, we thought to intercalate at least one methylene group. However, commercially available I-CH_2CF_3 and I-$CH_2CH_2CF_3$ underwent acid elimination in the alkylation step basic conditions. Using trifluoroiodobutane (Scheme 3) a 96% yield of **10e** was obtained and the enantioselective amination step was accomplished with a 99% of *ee* (78% yield).



Scheme 3. Introduction of fluorine and fluorous groups in the intercarbonylic position and subsequent α-amination step.

The assignment of the absolute configuration of compounds **5** and **12e** as *S* was based on the comparison of the circular dichroism (CD) (all compounds show a positive Cotton Effect), and the position of the major peak on the chiral HPLC spectrum with previously described analogues prepared in our laboratories.[9,14c] In the case of **11e,** due to the presence of F in the intercarbonylic chiral carbon, the asymmetric induction is obtained in the same sense although the resulting product is the (*R*) enantiomer.

Additionally, induced fit docking simulations were performed to assess how fluorination of the L-Carbidopa scaffold can modify its affinity for the DDC receptor. To do so, some of the fluorinated analogues of L-Carbidopa (Figure 5) were tested using the PELE suite[20,21] (see SI for further details), which provides an efficient tool for the prediction of binding poses of ligand/receptor complexes. The L-Carbidopa/DDC complex was derived from the structure reported in PDB file 1JS3. DDC is a dimer, with two equivalent binding sites for Carbidopa,

which, as already mentioned, forms a hydrazone intermediate with the pyridoxal 5'-phosphate (PLP) cofactor. The docking method was first tested on this complex, by cleaving the Carbidopa-PLP covalent bond and submitting an unconstrained binding site search simulation for the same L-Carbidopa on the receptor. Satisfactorily, the ligand is docked in the crystallographic binding site with the correct conformation, with the aldehyde group of PLP correctly oriented to start the reaction with the hydrazine group of L-Carbidopa (Figure 4a).

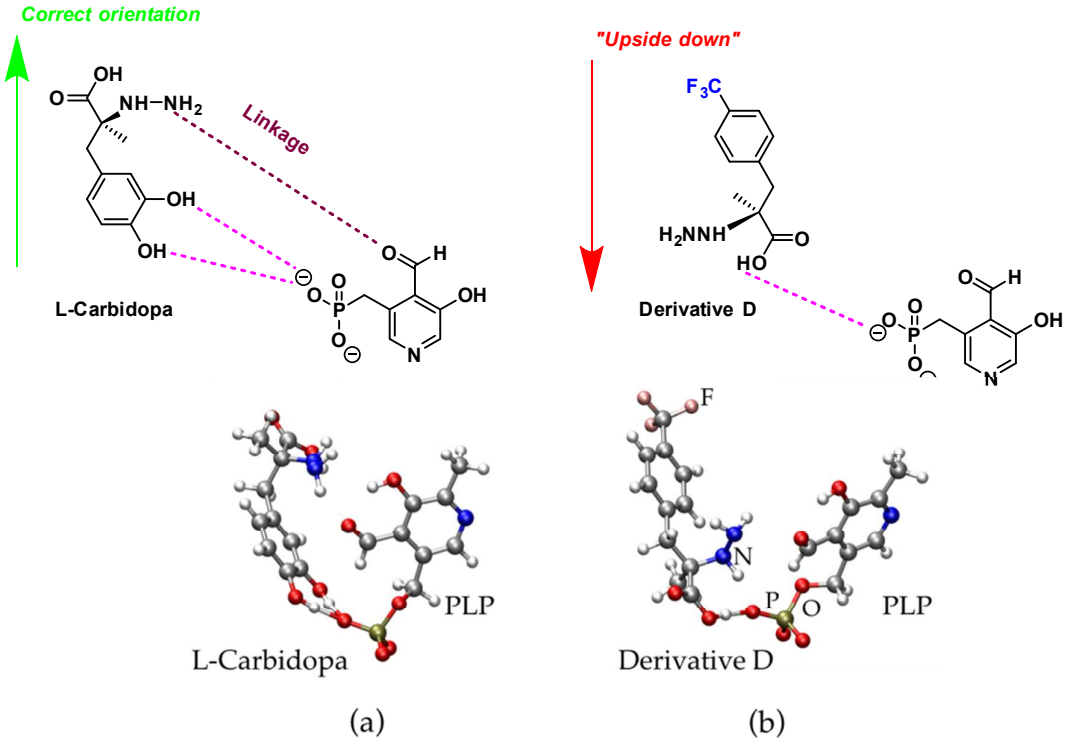


Figure 4. Relative orientation of the ligand and PLP cofactor for L-Carbidopa and a fluorinated derivative from induced fit docking simulations.

Overall, eight fluorinated analogues of L-Carbidopa were tested (Figure 5) and results highlighted that one aromatic hydroxyl group is fundamental to guarantee the correct orientation of the ligand in the binding site of the receptor (for a full description of the results see the SI).

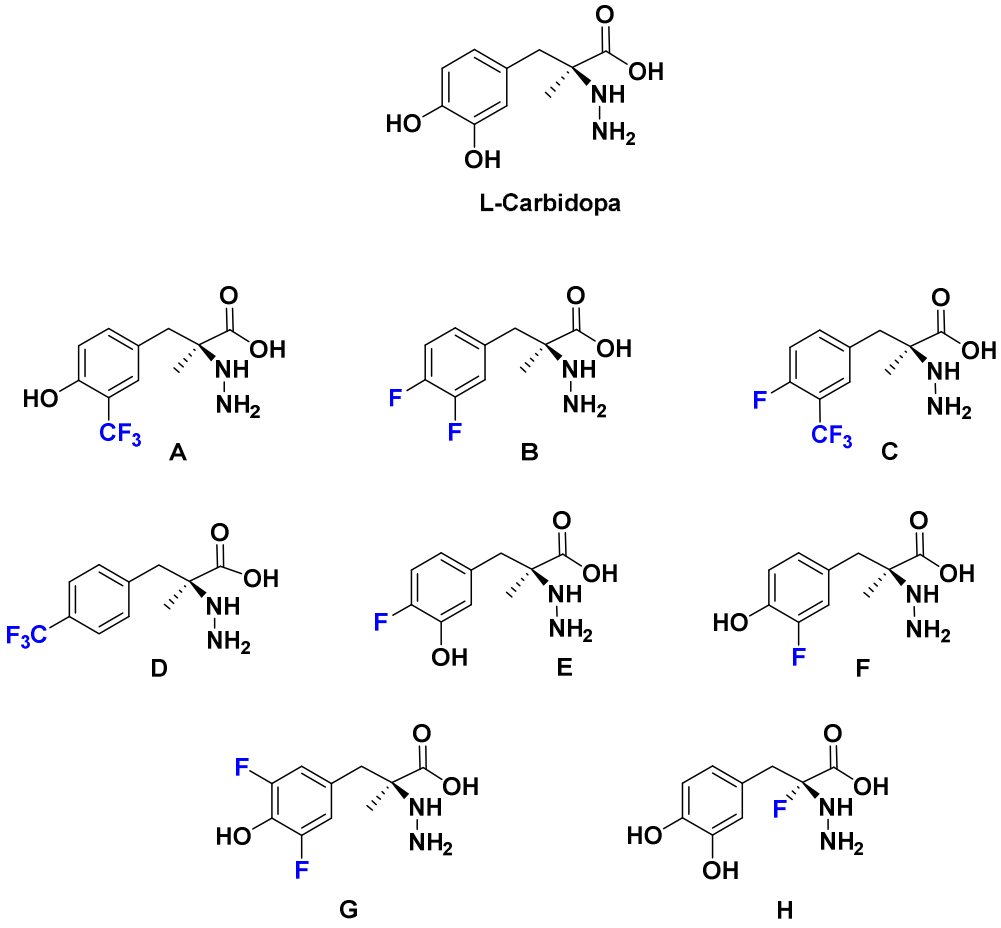


Figure 5. The eight fluorinated analogues of L-Carbidopa tested as DDC ligands.

As reported in Figure 4a, the hydroxyl groups form strong hydrogen bonds (1.48 Å) with the phosphate group of PLP. If at least one of the two hydroxyl groups is preserved, our simulations show that the molecule enters the active site of DDC in a suitable orientation. If, conversely, the ligand does not present a hydroxyl group, then these hydrogen bonds cannot be formed. In such cases, molecules that are not forbidden to enter the binding pocket by sterical factors will assume an "upside down" conformation (Figure 4b), in which the carboxyl group of the ligand is involved in interaction with the phosphate. Thus, according to these calculations, a hydrogen bond donor has to be maintained on the aromatic ring for the ligand to act as an inhibitor for DDC.

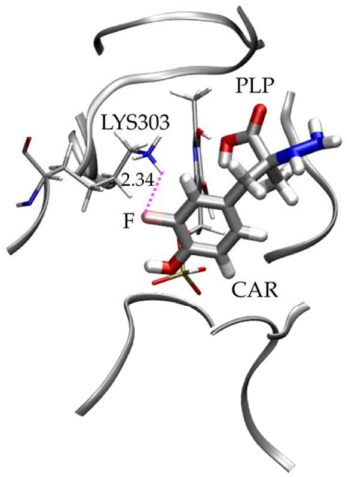


Figure 6. Positioning of fluorinated analogue **F** of L-Carbidopa in the active site of DDC, with indication of an electrostatic interaction with a positively charged residue, LYS303. Distance in Å.

Figure 6 reports the binding pose of derivative **F** in the active site of DDC. This molecule presents a fluorine atom and a hydroxyl group on the aromatic ring. While the oxygen of the hydroxyl group acts as hydrogen bond acceptor (distance 1.74 Å), maintaining the molecule in the correct orientation in the site, the fluorine atom, which bears a negative partial charge, is involved in an electrostatic interaction with a nearby positively charged lysine residue. This suggests that fluorination may result in the formation of stabilizing interactions that further concur to fixing the position of the ligand in the active site of DDC.

In this work we present the preparation of (*S*)-fluorous precursors of L-Carbidopa through a highly enantioselective α-amination key step of a series of acyclic β-keto esters possessing different fluorous substituents at the arene ring or in the intercarbonilic position, with excellent chemical yields (70-87%) and enantiomeric excesses (90-99%). We found that neither using diphenyl-pybox as chiral ligand nor working at low temperature is essential. The advantage of this finding is that the simple commercially available phenyl-pybox (both enantiomers are commercial giving access to both **(*S*)** and **(*R*)-5** enantiomers) can be used, and that reactions can be performed at room temperature. They could be transformed to fluorous L-Carbidopa

derivatives following previously known chemistry. Some of the fluorous L-Carbidopa analogues were then studied to assess how fluorination tunes their affinity for the DDC target. We conclude that the presence of at least one hydroxyl group on the arene moiety of L-Carbidopa scaffold is crucial to maintain the molecule in the correct orientation for inhibition of the DDC binding site. Additionally, fluorine atoms may be involved in electrostatic interactions with positively charged residues of DDC, indicating that fluorination can concur in stabilizing the inhibitor-receptor complex. Further binding experiments with DDC should be performed to confirm this hypothesis.

Experimental Section

General Information. GLC chromatographies were performed on a capilar column (5% biphenyl and 95 % dimethylpolysiloxane) of 15 m x 0.25 mm with stationary phase diameter of 0.25 μm. Column chromatographies were performed on silica gel (230-400 mesh). IR spectra were determined either by transmission or by Attenuated Total Reflectance mode (ATR). Enantiomeric excesses were determined, unless otherwise stated, by HPLC using a chiral column Chiracel Daicel-AD-H**.** NMR spectra were recorded operating at 250MHz, 360MHz and 400 MHz. Optical rotations are reported as follows: $[\alpha]_D^{rt}$ (c in g per 100 mL, solvent). ^{13}C-NMR spectra were registered at 62.5, 91 and 101 MHz,. Elemental analyses are the average of two determinations. HRMS were recorded by a Bruker micrOTOF-QII Mass Spectrometer (fly-time analyzer) through positive electrospray ionization.

General procedure for the preparation of fluorous β-keto esters 2. In a 250 mL round bottom flash 2 eq. of sodium hydride, 25 mL THF and 2 eq. of dimethyl carbonate (1.5 equiv. when using methyl 1H-imidazole-1-carboxylate) are disposed. The second step consists on preparing a solution of the acetophenone derivative (1 eq.) in THF, that solution is added dropwise to the first solution by using an addition funnel. Once the addition is finished, the mixture is warmed to reflux until TLC analyses shows that starting material has been totally consumed. When the reaction is finished, the reaction is neutralized with HCl 1M and the solution is brought to pH acidic, then extractions with dichloromethane are carried out. The organic fractions are dried with sodium sulfate and solvent is removed under vacuum. The reaction crude is purified with silica gel column chromatography using hexane:AcOEt (4:1) as eluent obtaining the desired methyl β-keto esters.

Methyl 3-(3-trifluoromethyl-4-methoxyphenyl)-3-oxopropanoate, 2d. yellowish solid; Mp. 43-45ºC; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): keto (85%) - enol (15%) mixture, 3.72 (s, 3H), 3.77 (s, 0.13H), 3.95 (s, 5H), 5.58 (s, 0.7H), 7.01 (d, *J* = 9.1 Hz, 0.16H), 7.05 (d, *J* = 9.1 Hz, 1H), 7.88 (dd, *J* = 1.9 Hz, *J* = 9.1 Hz, 0.15H), 7.94 (s ap, 0.15H), 8.09 (dd, *J* = 2.0 Hz, *J* = 9.1 Hz, 1H), 8.14 (s ap, 1H), 12.54 (s, 0.14H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -63.2 (s, 0.5F), -63.4 (s, 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 91 MHz) δ (ppm): 45.3, 51.4, 52.5, 56.1, 56.3, 86.3, 111.8, 111.9, 119.0 (q, *J* = 31.8 Hz), 122.9 (q, *J* = 273.9 Hz), 125.2, 128.1 (q, *J* = 20.1 Hz), 131.2, 134.4, 159.7, 161.5, 167.7, 169.8, 173.5, 190.1; IR (ATR) ν (cm^{-1}): 2976, 1728, 1684; HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{12}F_3O_4$ 277.0682; found 277.0679. Isolated yield: 240 mg (95%) from 200 mg of **1d**.

Methyl 3-((3-trifluoromethoxy-4-fluoro)phenyl)-3-oxopropanoate, 2i. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): keto (75%) - enol (25%) mixture, 3.78 (s, 3H), 3.83 (s, 1H), 4.00 (s, 2H), 5.65 (s, 0.35H), 7.29 (t, *J* = 8.9 Hz, 1H), 7.35 (t, *J* = 8.9 Hz, 0.3H), 7.73 (m, 0.67H), 7.93 (m, 2H), 12.54 (s, 0.36H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -58.8 (m, 3.9F), -119.3 (q, *J* = 4.5 Hz, 1F), -123.9 (q, *J* = 4.5 Hz, 0.36F);^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 45.5, 51.6, 52.6, 87.8, 117.5 (d, *J* = 19.4 Hz), 117.8 (d, *J* = 19.4 Hz), 120.3 (q, *J* = 260.0 Hz), 121.8, 124.3, 126.1 (d, *J* = 7.8 Hz), 129.1 (d, *J* = 7.8 Hz), 132.9 (d, *J* = 3.3 Hz), 156.2 (d, *J* = 258.3 Hz), 157.9 (d, *J* = 258.3 Hz), 167.2, 168.6, 173.1, 188.5; IR (ATR) ν (cm^{-1}): 2968, 1735, 1685,; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{11}H_8F_4O_4Na$ 303.0251; found 303.0244; Isolated yield: 105 mg (38%) from 220 mg of **1i**.

Methyl 3-((3-trifluoromethyl-4-fluoro)phenyl)-3-oxopropanoate, 2j. Oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): keto (70%) - enol (30%) mixture, 3.75 (s, 3H), 3.80 (s, 1.2H, $OC\underline{H}_3$), 4.01 (s, 2H), 5.65 (s, 0.75H), 7.25 (t, *J* = 9.3 Hz, 0.4H), 7.32 (t, *J* = 9.2 Hz, 1H), 7.90 – 7.97 (m, 0.4H), 8.01 (dd, *J* = 6.6 Hz, *J* = 1.8 Hz, 0.4H), 8.13 – 8.20 (m, 1H), 8.32 (dd, *J* = 6.6 Hz, *J* = 1.8 Hz, 1H), 12.54 (s, 0.4H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -62.2 (d, *J* = 12.6 Hz, 1.2F), -62.3 (d, *J* = 12.6 Hz, 3F), -106.2 (q, *J* = 12.6 Hz, 1F), -110.7 (q, *J* = 12.6 Hz, 0.35F); ^{13}C NMR [^{1}H] ($CDCl_3$, 90 MHz) δ (ppm): 45.4, 51.6, 52.6, 87.9, 117.3 (d, *J* = 21.4 Hz), 117.6 (d, *J* = 21.4 Hz), 121.9 (q, *J* = 273.9 Hz), 122.1 (q, *J* = 273.9 Hz), 125.2 (m), 128.2 (m), 129.8 (d, *J* = 3.7 Hz), 131.6 (d, *J* = 9.1 Hz), 132.3 (d, *J* = 3.7), 134.60 (d, *J* = 9.5 Hz), 161.2 (d, *J* = 267.3 Hz), 162.8 (d, *J* = 267.3 Hz), 167.3, 168.5, 173.2, 189.8; IR (ATR) ν (cm^{-1}): 2958, 1739, 1681; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{11}H_8F_4O_3Na$ 287.0302; found 287.0299; Isolated yield: 307 mg (80%) from 300 mg of **1j**.

Methyl 3-(3,4,5-trifluorophenyl)-3-oxopropanoate, 2k. Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): keto (60%) - enol (40%) mixture , 3.78 (s, 3H), 3.83 (s, 2.3Hl), 3.96 (s, 2H), 5.63 (s, 0.75H), 7.42 (dd, 1.42H, *J* = 7.7 Hz, *J* = 6.5 Hz, enol, 2H), 7.62 (dd, *J* = 7.7 Hz, *J* = 6.5 Hz,

2H), 12.50 (s, 0.7H);^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -131.9 (d, , J = 20.1 Hz, 0.75F), -133.4 (d, , J = 20.1 Hz, 2F), -151.2 (t, J = 20.1 Hz, 0.4F) -155.8 (t, J = 20.1 Hz, 1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 64 MHz) δ (ppm): 45.4, 51.7, 52.8, 61.4, 88.3, 110.5 (dd, J = 6.7 Hz, J = 15.7 Hz), 112.2 (dd, J = 6.7 Hz, J = 15.7 Hz), 129.4 (t, J = 6.3 Hz), 141.1, 125.2, 128.1 (q, J = 20.1 Hz), 131.2, 134.4, 159.7, 154.5 (d, J = 252.8 Hz), 167.1, 167.8, 173.0, 188.9; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{10}H_7F_3O_3Na$ 255.0239; found 255.0233; Isolated yield: 270 mg (84%) from 240 mg of **1k**.

General procedure for transesterification reactions. Preparation of compounds 3. In a 100 mL round bottom flash, 1.50 mmol of the methoxy β-keto ester were dissolved in 2 mL of toluene. Then, 10 equivalents of 3-pentanol and 25 mg (0.20 eq.) of ZnO were added. The system was carried out to reflux temperature; a distillation system is required in order to isolate the methanol formed during the reaction. Upon reaction completion the solution is filtered off through Celite® and the solvent is removed under reduced pressure. The reaction crude is purified with silica gel column chromatography using hexane:AcOEt (4:1) as eluent obtaining the desired 3-pentanyl β-keto esters.

3-Pentanyl 3-(4-(trifluoromethyl)phenyl)-3-oxopropanoate, 3a. Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): keto (67%) - enol (33%) mixture, 0.85 (t, J = 7.5 Hz, 6H), 0.94 (t, J = 7.5 Hz, 3H), 1.47 – 1.61 (m, 4H), 1.61 – 1.70 (m, 2H), 3.83 (s, 2.3H), 4.03 (s, 2H), 4.83 (quint, J = 6.1 Hz, 1H), 4.93 (quint, J = 6.1 Hz, 0.5H), 5.74 (s, 0.5H), 7.67 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 8.2 Hz, 2H), 12.69 (s, 0.5H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -63.0 (s, 1.6F), -63.3 (s, 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 64 MHz) δ (ppm): 9.4, 9.5, 26.2, 26.5, 46.4, 77.2, 78.5, 89.2, 123.5 (q, J = 272.8 Hz), 123.8 (q, J = 272.8 Hz), 125.4 (q, J = 3.8 Hz), 125.8 (q, J = 3.8 Hz), 126.3, 128.8, 132.6 (q, J = 32.7 Hz), 134.9 (q, J = 32.7 Hz), 136.9, 138.7, 166.8, 169.3, 172.9, 191.7; IR (ATR) ν (cm^{-1}): 1735, 1694; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{17}F_3O_3Na$ 325.1022; found 325.102; Isolated yield: 210 mg (85%) from 200 mg of **2a**.

3-Pentanyl 3-(4-(trifluoromethoxy)phenyl)-3-oxopropanoate, 3b. Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): keto (67%) - enol (33%) mixture, 0.85 (t, J = 7.5 Hz), 0.94 (t, J = 7.5 Hz, 3H), 1.47 – 1.61 (m, 4H), 1.61 – 1.70 (m, 2H), 3.83 (s, 2.3H), 4.03 (s, 2H), 4.83 (quint, J = 6.1 Hz, 1H), 4.93 (quint, J = 6.1 Hz, 0.5H), 5.74 (s, 0.5H), 7.67 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 8.07 (d, J = 8.2 Hz, 2H), 12.69 (s, 0.5H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -63.0 (s, 1.6F), -63.3 (s, 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 64 MHz) δ (ppm): 9.4, 9.5, 26.2, 26.5, 46.4, 77.2, 78.5, 89.2, 123.5 (q, J = 272.8 Hz), 123.8 (q, J = 272.8 Hz), 125.4 (q, J = 3.8 Hz), 125.8 (q, J = 3.8 Hz), 126.3, 128.8, 132.6 (q, J = 32.7 Hz), 134.9 (q, J = 32.7 Hz), 136.9, 138.7, 166.8, 169.3, 172.9, 191.7; IR (ATR) ν (cm^{-1}): 2971, 1735, 1694; HR-MS (ESI)

m/z: $[M+Na]^+$ Calcd for $C_{15}H_{17}F_3O_4Na$ 341.0971; found 341.0974; Isolated yield: 260 mg (85%) from 250 mg of **2b**.

3-Pentanyl 3-(3-fluoro-4-methoxyphenyl)-3-oxopropanoate, 3c. Oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): keto (89%) - enol (11%) mixture, 0.83 (t, *J* = 7.5 Hz), 0.91 (t, *J* = 7.5 Hz, 0.7H), 1.47 – 1.63 (m, 4.66 H), 3.92 (s, 2H), 3.94 (s, 3H), 4.80 (quint, *J* = 7.2 Hz), 4.88 (quint, *J* = 7.2 Hz, 0.12H), 5.56 (s, 0.12H), 6.99 (t, *J* = 8.3 Hz, 0.16H), 7.06 (t, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 10.8 Hz, *J* = 3.6 Hz, 0.12H), 7.54 (dd, *J* = 10.8 Hz, *J* = 3.6 Hz, 0.12H), 7.68 (dd, *J* = 10.8 Hz, *J* = 3.6 Hz, 1H), 7.73 (s ap, 1H), 12.69 (s, 0.12H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -133.8 (s, 1F), -63.5 (s, 0.1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 91 MHz) δ (ppm): 9.4, 9.4, 26.3, 26.5, 46.1, 56.2, 56.3, 86.8, 112.4 (d, *J* = 1.6 Hz), 112.8 (d, *J* = 1.6 Hz), 113.8 (d, *J* = 20.1 Hz), 116.0 (d, *J* = 20.1 Hz), 122.5 (d, *J* = 3.2 Hz), 126.1 (d, *J* = 3.2 Hz), 129.3 (d, *J* = 5.4 Hz), 152.0 (d, *J* = 249.3 Hz), 152.4 (d, *J* = 11.0 Hz), 167.8, 170.1, 173.5, 190.1; IR (ATR) ν (cm^{-1}): 2973, 1726, 1685; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}FO_4Na$ 305.1160; found 305.115; Isolated yield: 280 mg (89%) from 250 mg of **2c**.

3-Pentanyl 3-(3-trifluoromethyl-4-methoxyphenyl)-3-oxopropanoate, 3d. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): keto (90%) - enol (10%) mixture, 0.86 (t, *J* = 7.5 Hz, 6H), 0.94 (t, *J* = 7.5 Hz, 0.80H), 1.55 – 1.72 (m, 4.5H), 3.97 (s, 0.4H), 3.98 (s, 3H), 4.00 (s, 0.3H), 4.83 (quint, *J* = 6.2 Hz, 1H), 4.91 (quint, *J* = 6.2 Hz, 0.11H), 5.64 (s, 0.12H), 7.05 (d, *J* = 9.1 Hz, 0.09H), 7.09 (d, *J* = 9.1 Hz, 1H), 7.95 (dd, *J* = 1.9 Hz, *J* = 9.1 Hz, 0.13H), 8.00 (d, *J* = 2.0 Hz, 0.13H), 8.16 (dd, *J* = 2.0 Hz, *J* = 9.1 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 12.76 (s, 0.10H);^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -62.78 (s, 0.12F), -63.01 (s, 1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.4, 9.5, 26.2, 26.5, 46.0, 56.1, 56.3, 78.3, 85.9, 111.7, 111.8, 119.0 (q, *J* = 31.2 Hz), 122.9 (q, *J* = 272.6 Hz), 125.1, 125.5, 128.1 (q, *J* = 5.0 Hz), 131.2, 134.4, 161.4, 167.0, 169.6, 173.1, 190.2; IR (ATR) ν (cm^{-1}): 2976, 1728, 1610; Elemental analysis Calcd $C_{16}H_{19}F_3O_4$ C: 57.83%, H: 5.76%. Found C: 58.20%, H: 5.91%; Isolated yield: 222 mg (92%) from 200 mg of **2d**.

3-Pentanyl 3-(3-trifluoromethoxy-4-methoxyphenyl)-3-oxopropanoate, 3f. Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): keto (70%) - enol (30%) mixture, 0.81 (t, *J* = 7.4 Hz, 6H), 0.89 (t, *J* = 7.4 Hz, 2.5H), 1.48 – 1.62 (m, 5.7H), 3.97 (s, 5H), 4.77 (quint, *J* = 7.4 Hz), 4.87 (quint, *J* = 7.3 Hz, 0.5H), 5.63 (s, 0.34H), 6.98 (d, *J* = 8.6 Hz, 0.4H), 7.02 (d, *J* = 8.6 Hz, 1H), 7.62 (s, 0.4H), 7.67 (dd, *J* = 8.6 Hz, *J* = 2.1 Hz, 0.4H), 7.83 (s, 1H), 7.87 (dd, *J* = 8.6 Hz, *J* = 2.1 Hz, 1H) 12.72 (s, 0.4H);^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -58.9 (s, 1.3F), -59.0 (s, 3F);^{13}C NMR [^{1}H] ($CDCl_3$, 91 MHz) δ (ppm): 9.3, 9.5, 26.2, 26.5, 46.0, 56.0, 56.2, 76.9, 78.3, 86.9, 112.2 (d, *J* = 19.3 Hz), 112.5 (d, *J* = 19.3 Hz), 120.5 (q, *J* = 259.8 Hz), 120.7, 123.1, 125.9, 126.2, 129.1, 129.3, 137.8, 137.9, 154.3, 156.4, 167.1 169.5, 173.2, 190.1; IR (ATR) ν (cm^{-1}):

2972, 1731, 1683; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{19}F_3O_5Na$ 371.1077; found 371.1079; Isolated yield: 262 mg (95%) from 220 mg of **2f**.

3-Pentanyl 3-(3,5-difluoro-4-methoxyphenyl)-3-oxopropanoate, 3g. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): keto (80%) - enol (20%) mixture, 0.86 (t, *J* = 7.5 Hz, $6H_3$), 0.93 (t, *J* = 7.5 Hz, 2.1H), 1.60 (m, 5H), 3.92 (s, 2H), 4.07 (t, *J* = 4.0 Hz), 4.12 (t, *J* = 4.0 Hz, 3H), 4.83 (quint, *J* = 6.7 Hz, 1H), 4.90 (quint, *J* = 6.7 Hz, 0.3H), 5.64 (s, 0.3H), 7.34 (d, *J* = 9.7 Hz, 0.3H), 7.53 (d, *J* = 9.7 Hz, 2H), 12.64 (s, 0.3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -126.9 (s, 2F), -127.8 (s, 0.5F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 9.4, 26.2, 26.4, 45.8, 61.5 (q, *J* = 4.0 Hz), 77.0, 78.4, 88.0, 110.0 (dd, *J* = 17.4 Hz, *J* = 7.5 Hz), 112.8 (dd, *J* = 17.4 Hz, *J* = 7.5 Hz), 127.9 (t, *J* = 6.3 Hz), 129.8 (t, *J* = 6.3 Hz), 138.6 (t, *J* = 13.2 Hz), 141.1 (t, *J* = 13.2 Hz), 156.7 (dd, *J* = 250.2 Hz, *J* = 5.9 Hz), 155.1 (dd, *J* = 250.2 Hz, *J* = 5.9 Hz), 166.7, 168.3, 172.8, 188.9 (t, *J* = 2.2 Hz); IR (ATR) ν (cm^{-1}): 2970, 1732, 1694; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{18}F_2O_4Na$ 323.1063; found 323.1065; Isolated yield: 261 mg (85%) from 250 mg of **2g**.

3-Pentanyl 3-(3,4-difluorophenyl)-3-oxopropanoate, 3h. Oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): keto (70%) - enol (30%) mixture, 0.85 (t, *J* = 7.4 Hz, 6H), 0.93 (t, *J* = 7.4 Hz, 2.67H), 1.55 (m, 4H), 1.65 (m, 1.50H), 3.96 (s, 2H), 4.82 (quint, *J* = 7.4 Hz, 1H), 4.92 (quint, *J* = 7.4 Hz, 0.30H), 5.62 (s, 0.24H), 7.27 (m, 1H), 7.62 (m, 0.7H), 7.82 (m, 2H), 12.69 (s, 0.26H,); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -129.0 (d, *J* = 20.9 Hz, 1F), -133.7 (d, *J* = 21.1 Hz, 0.3F, enol), -137.0 (d, *J* = 20.9 Hz, 1F), -137.2 (d, *J* = 21.1 Hz, 0.3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.4, 9.6, 26.3, 26.5, 46.2, 78.6, 88.2, 115.8 (d, *J* = 19.3 Hz), 118.2 (m), 122.5 (dd, *J* = 7.6 Hz, *J* = 3.6 Hz), 126.07 (dd, *J* = 7.6 Hz, *J* = 3.6 Hz), 133.7 (dd, *J* = 7.6 Hz, *J* = 3.7 Hz), 150.9 (dd, *J* = 251.5 Hz, *J* = 18.4 Hz), 154.4 (dd, *J* = 253.5 Hz, *J* = 18.1 Hz), 166.2, 173.4, 190.5; IR (ATR) ν (cm^{-1}): 2973, 2943, 1737, 1695; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{16}F_2O_3Na$ 293.0960; found 293.0955; Isolated yield: 201 mg (80%) from 200 mg of **2h**.

3-Pentanyl 3-(3-trifluoromethoxy-4-fluorophenyl)-3-oxopropanoate, 3i. Oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): keto (67%) - enol (33%) mixture, 0.83 (t, *J* = 7.4 Hz, 6H), 0.92 (t, *J* = 7.4 Hz, 3H), 1.51 – 1.58 (m, 4H), 1.59 – 1.66 (m, 2H), 3.97 (s, 2H), 4.81 (quint, *J* = 7.4 Hz, 1H), 4.91 (quint, *J* = 7.3 Hz, 0.5H), 5.63 (s, 0.5H), 7.24 (t, *J* = 8.6 Hz, 0.5H), 7.31 (t, *J* = 8.6 Hz, 1H), 7.72 (m, 1H), 7.94 (m, 2H), 12.72 (s, 0.5H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -59.36 (d, *J* = 7.8 Hz, 1F), -59.42 (d, *J* = 6.5 Hz, 3F), -120.25 (q, *J* = 5.5 Hz, 1F), -124.83 (q, *J* = 5.5 Hz, 0.5F); ^{13}C NMR [^{1}H] ($CDCl_3$, 91 MHz) δ (ppm): 9.3, 9.5, 26.2, 26.5, 46.2, 77.2, 78.6, 80.8, 117.4 (d, *J* = 19.3 Hz), 117.7 (d, *J* = 19.3 Hz), 121.8, 124.3, 126.1 (d, *J* = 8.5 Hz), 129.1 (d, *J* = 8.5 Hz), 130.8 (d, *J* = 3.8 Hz), 133.2 (d, *J* = 3.8 Hz), 136.5 (dq, *J* = 19.2 Hz, *J* = 2.8 Hz), 136.8 (dq, *J* = 19.2 Hz, *J* = 2.8 Hz), 156.1 (d, *J* = 258.4 Hz), 157.7 (d, *J* = 258.4 Hz), 166.7, 168.4,

172.9, 189.9; IR (ATR) ν (cm^{-1}): 2991, 2960, 1739, 1681; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{16}F_4O_4Na$ 359.0877; found 359.0884; Isolated yield: 275 mg (92%) from 230 mg of **2i**.

3-Pentanyl 3-(3-trifluoromethyl-4-fluorophenyl)-3-oxopropanoate, 3j. Oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): keto (71%) - enol (29%) mixture, 0.86 (t, *J* = 7.5 Hz, 6H), 0.94 (t, *J* = 7.5 Hz, 2.5H), 1.51 – 1.74 (m, 6.4H), 4.01 (s, 2H), 4.83 (quint, *J* = 6.2 Hz, 1H), 4.93 (quint, *J* = 6.2 Hz, 0.4H), 5.68 (s, 0.4H), 7.27 (t, *J* = 9.2 Hz, 0.4H), 7.34 (t, *J* = 9.1 Hz, 1H), 7.95 – 8.01 (m, 0.4H), 8.04 (d, *J* = 6.7 Hz, 0.4H), 8.18 – 8.22 (m, 1H), 8.26 (d, *J* = 6.7 Hz, 1H), 12.75 (s, 0.40H);^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -61.67 (d, 1.3F, *J* = 12.6 Hz), -61.82 (d, *J* = 12.5 Hz, 3F), -105.74 (q, *J* = 12.5 Hz, 1F), -110.45 (q, *J* = 12.6 Hz, 0.4F); ^{13}C NMR [^1H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 9.5, 26.2, 26.4, 46.1, 77.3, 78.6, 88.5, 117.2, 117.6, 119.1 (dd, *J* = 13.2 Hz, *J* = 33.6 Hz), 121.9 (q, *J* = 272.7 Hz), 122.1 (q, *J* = 272.7 Hz), 125.1, 130.0 (d, *J* = 3.8 Hz), 131.5 (d, *J* = 9.1 Hz), 132.4 (d, *J* = 3.7 Hz), 134.5 (d, *J* = 9.8 Hz), 161.1 (d, *J* = 262.2 Hz), 162.7 (d, *J* = 265.2 Hz), 166.6, 168.3, 172.8, 189.9; IR (ATR) ν (cm^{-1}): 2993, 2958, 1739, 1681; Elemental analysis Calcd for $C_{16}H_{19}F_3O_4$ C: 57.83%, H: 5.76%. Found C: 58.20%, H: 5.91%; Isolated yield: 215 mg (88%) from 200 mg of **2j**.

3-Pentanyl 3-(3,4,5-trifluorophenyl)-3-oxopropanoate, 3k. Oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): keto (67%) - enol (33%) mixture, 0.87 (t, *J* = 7.4 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.57 (m, 4H), 1.65 (m, 2H), 3.95 (s, 2H), 4.83 (m, 1H), 4.92 (m, 0.5H), 7.44 (m, 1H), 7.63 (m, 2H), 12.68 (s, 0.5H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -131.7 (d, *J* = 19.9 Hz, 2F), -133.2 (d, *J* = 19.9 Hz, 1F), -151.2 (t, *J* = 19.9 Hz) -155.7 (t, *J* = 19.9 Hz, 0.5F); ^{13}C NMR [^1H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 9.5, 26.2, 26.4, 46.0, 77.4, 78.4, 88.9, 110.4 (dd, *J* = 16.6 Hz, *J* = 6.4 Hz), 113.1 (dd, *J* = 16.6 Hz, *J* = 6.4 Hz), 129.6 (m, Ar<u>C</u>), 131.6, 143.4, 151.2, 166.4, 167.5, 172.7, 189.0; IR (ATR) ν (cm^{-1}): 3018, 2962, 2921, 1755, 1628, 1517, 1450, 1217, 1174, 1043; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{15}F_3O_3Na$ 311.0865; found 311.0866; Isolated yield: 255 mg (82%) from 250 mg of **2k**.

General procedure for the alkylation reactions. Preparation of compounds 4 and 10e. In a 10 ml round-bottom flash provided with a reflux condenser 1.25 mmol of β-ketoester is dissolved in 3 ml of dry acetone. After solution of starting material 1.38 mmol of K_2CO_3 and 1.82 mmol of the corresponding iodide are added. The system is maintained at 40ºC with stirring up to 24 hours. After reaction completion (TLC) the solution is filtered, the crude is extracted with CH_2Cl_2 and washed with HCl 1M. Organic phase is dried with sodium sulphate and purified with column chromatography using mixtures of hexane:AcOEt (7:3) as eluent.

3-Pentanyl 3-(4-trifluoromethylphenyl)-2-methyl-3-oxopropanoate, 4a. Oil; ^1H NMR (360 MHz, $CDCl_3$) δ (ppm): 0.70 (t, *J* = 7.4 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H), 1.45 (m, 7H), 4.37 (q, *J* = 7.0 Hz, 1H), 4.71 (quint, *J* = 6.2 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 8.10 (d, *J* = 8.3 Hz,

2H);^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -63.1 (s, 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 91 MHz) δ (ppm): 9.1, 9.2, 13.4, 26.1, 49.0, 78.2, 123.4 (q, *J* = 272.7 Hz), 125.6 (q, *J* = 3.7 Hz), 128.8, 134.5 (q, *J* = 32.8 Hz), 138.8, 170.2, 194.7; IR (ATR) ν (cm^{-1}): 2973, 1736, 1697; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{19}F_3O_3Na$ 339.1179; found 339.1176; Isolated yield: 160 mg (85%) from 180 mg of **3a**.

3-Pentanyl 3-(4-trifluoromethoxyphenyl)-2-methyl-3-oxopropanoate, 4b. Oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): 0.66 (t, *J* = 7.4 Hz, 3H), 0.75 (t, *J* = 7.4 Hz, 3H), 1.43 (m, 7H), 4.33 (q, *J* = 7.0 Hz, 1H), 4.72 (quint, *J* = 6.2 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 8.4 Hz, 2H);^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -58.1 (s, 3F);^{13}C NMR [^{1}H] ($CDCl_3$, 91 MHz) δ (ppm): 9.1, 9.3, 13.4, 26.2, 48.8, 78.1, 120.2 (q, *J* = 258.8 Hz), 120.4, 130.5, 134.3, 152.7 (q, *J* = 1.8 Hz), 170.5, 194.1. IR (ATR) ν (cm^{-1}): 2976, 1740, 1680; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{19}F_3O_4Na$ 355.1128; found 355.1124; Isolated yield: 143 mg (81%) from 160 mg of **3b**.

3-Pentanyl 3-((3-fluoro-4-methoxy)phenyl)-2-methyl-3-oxopropanoate, 4c. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.72 (t, *J* = 7.5 Hz, 3H), 0.79 (t, *J* = 7.5 Hz, 3H), 1.48 (m, 7H), 3.94 (s, 3H), 4.29 (q, *J* = 7.0 Hz, 1H), 4.73 (quint, 1H, *J* = 7.5 Hz), 7.00 (t, *J* = 8.3 Hz, 1H), 7.73 (dd, *J* = 2.2 Hz, *J* = 10.9 Hz, 1H), 7.78 (ddd, *J* = 1.0 Hz, *J* = 2.2 Hz, *J* = 10.9 Hz, 1H);^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -134.4 (s, 1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.2, 9.3, 13.6, 26.1, 26.1, 48.4, 56.2, 77,9, 112.3 (d, *J* = 1.6 Hz), 116.1 (d, *J* = 20.1 Hz), 125.9 (d, *J* = 3.2 Hz), 129.2 (d, *J* = 5.4 Hz), 151.9 (d, *J* = 248.5 Hz), 152.1 (d, *J* = 11.0 Hz), 170.6, 193.3; IR (ATR) ν (cm^{-1}): 2974, 2941, 1728, 1688; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{21}FO_4Na$ 319.1316; found 319.1303; Isolated yield: 185 mg (89%) from 200 mg of **3c**.

3-Pentanyl 3-((3-trifluoromethyl-4-methoxy)phenyl)-2-methyl-3-oxopropanoate, 4d. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.75 (t, *J* = 6.3 Hz, 3H), 0.79 (t, *J* = 6.3 Hz, 3H), 1.42 – 1.57 (m, 7H), 3.99 (s, 3H), 4.35 (q, *J* = 7.0 Hz, 1H), 4.83 (quint, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 8.19 (dd, *J* = 2.0 Hz, *J* = 8.7 Hz, 1H), 8.25 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -63.42 (s, 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 9.4, 13.6, 26.2, 48.4, 56.3, 78.2, 111.7, 119.0 (q, *J* = 31.0 Hz), 123.0 (q, *J* = 273.4 Hz), 128.2 (q, *J* = 5.1 Hz), 128.3, 134.3, 161.2, 170.5, 193.3; IR (ATR) ν (cm^{-1}): 2972, 2948, 1723, 1618; Elemental analysis calculated for $C_{16}H_{19}F_3O_4$ C: 57.83%, H: 5.76%. Found C: 58.20%, H: 5.91%; Isolated yield: 187 mg (90%) from 200 mg of **3d**.

3-Pentanyl 3-((3-trifluoromethoxy-4-methoxy)phenyl)-2-methyl-3-oxopropanoate, 4f. Oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): 0.70 (t, *J* = 7.4 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 3H), 1.47 (m, 7H), 3.95 (s, 3H), 4.29 (q, *J* = 7.0 Hz, 1H), 4.73 (quint, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 7.90 (s, 1H), 7.95 (dd, *J* = 8.6 Hz, *J* = 2.1 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -58.82 (s, 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 91 MHz) δ (ppm): 9.2, 9.3, 16.6, 26.2, 26.2, 48.5, 56.3,

78.1, 112.1, 120.5 (q, J = 260.5 Hz), 123.4, 129.1 (d, J = 8.5 Hz), 129.2, 137.9 (d, J = 2 Hz), 156.2, 170.6, 193.1; IR (ATR) ν (cm^{-1}): 2978, 2932, 1736, 1688; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{21}F_3O_5Na$ 385.1239; found 385.1232; Isolated yield: 150 mg (81%) from 180 mg of **3f**.

3-Pentanyl 3-((3,5-difluoro-4-methoxy)phenyl)-2-methyl-3-oxopropanoate, 4g. Oil; ^1H NMR (360 MHz, $CDCl_3$) δ (ppm): 0.75 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H), 1.51 (m, 7H), 3.95 (s, 3H), 4.11 (q, J = 4.0 Hz, 1H), 4.76 (quint, J = 6.7 Hz, 1H), 7.56 (d, J = 9.5 Hz, 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -127.1 (s, 2F); ^{13}C NMR [^1H] ($CDCl_3$, 91 MHz) δ (ppm): 9.3, 9.4, 13.6, 26.2, 48.5, 61.6, 78.3, 112.9 (dd, J = 16.4 Hz, J = 7.9 Hz), 129.9 (t, J = 6.7 Hz), 140.9 (t, J = 13.3 Hz), 154.8 (dd, J = 250.0 Hz, J = 5.7 Hz), 170.3, 192.5 (t, J = 2.0 Hz); IR (ATR) ν (cm^{-1}): 2970, 1732, 1694; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{20}F_2O_4Na$ 337.1222; found 337.122; Isolated yield: 140 mg (89%) from 150 mg of **3g**.

3-Pentanyl 3-(3,4-difluorophenyl)-2-methyl-3-oxopropanoate, 4h. Oil; ^1H NMR (360 MHz, $CDCl_3$) δ (ppm): 0.72 (t, J = 7.4 Hz, 3H), 0.80 (t, J = 7.4 Hz, 3H), 1.49 (m, 7H), 4.29 (q, J = 7.0 Hz, 1H), 4.75 (quint, J = 7.4 Hz, 1H), 7.26 (dd, J = 21.0 Hz, J = 8.6 Hz, 1H), 7.82 (m, 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -129.5 (d, J = 21.0 Hz, 1F), -136.1 (d, J = 21.0 Hz, 1F); ^{13}C NMR [^1H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 9.4, 13.5, 26.1, 26.2, 48.8, 78.3, 117.6 (d, J = 117.6 Hz), 117.9 (dd, J = 18.1 Hz, J = 1.4 Hz), 125.6 (dd, J = 7.4 Hz, J = 4.0 Hz), 133.2 (t, J = 4.0 Hz), 150.5 (dd, J = 251.3 Hz, J = 13.0 Hz), 153.8 (dd, J = 251.3 Hz, J = 13.0 Hz), 170.3, 193.1; IR (ATR) ν (cm^{-1}): 2973, 1735, 1693; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{18}F_2O_3Na$ 307.1116; found 307.1114; Isolated yield: 183 mg (92%) from 190 mg of **3h**.

3-Pentanyl 3-((3-trifluoromethoxy-4-fluoro)phenyl)-2-methyl-3-oxopropanoate, 4i. Oil; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 0.72 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H), 1.49 (m, 7H), 4.31 (q, J = 7.0 Hz, 1H), 4.76 (quint, J = 6.2 Hz, 1H), 7.34 (t, J = 9.1 Hz, 1H), 7.98 (m, 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -59.3 (d, J = 4.8 Hz, 3F), -120.6 (q, J = 4.8 Hz, 1F); ^{13}C NMR [^1H] ($CDCl_3$, 101 MHz) δ (ppm): 9.1, 9.3, 13.4, 26.1, 26.1, 48.8, 78.3, 117.6 (d, J = 19.4 Hz), 120.3 (q, J = 263.4 Hz), 124.4, 128.9 (d, J = 8.4 Hz), 133.1 (d, J = 3.6 Hz), 136.7 (dq, J = 12.9 J = 2.2 Hz), 157.6 (d, J = 261.8 Hz), 170.1, 192.8; IR (ATR) ν (cm^{-1}): 2999, 2985, 1745, 1686; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{18}F_4O_4Na$ 373.1033; found 373.1041; Isolated yield: 135 mg (86%) from 150 mg of **3i**.

3-Pentanyl 3-((3-trifluoromethyl-4-fluoro)phenyl)-2-methyl-3-oxopropanoate, 4j. Oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.75 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H), 1.51 (m, 7H), 4.36 (q, J = 7.0 Hz, 1H), 4.77 (quint, 7.2 Hz, 1H), 7.33 (t, J = 9.2 Hz), 8.24 (ddd, J = 9.2 Hz, J = 6.7 Hz, J = 2.3 Hz, 1H), 8.30 (dd, J = 6.7 Hz, J = 2.3 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -61.8 (d, J = 12.6 Hz, 3F), -106.3 (q, J = 12.6 Hz, 1F); ^{13}C NMR [^1H] ($CDCl_3$,

101 MHz) δ (ppm): 9.1, 9.3, 13.4, 26.1, 26.1, 48.8, 78.3, 117.5 (d, *J* = 19.4 Hz), 120.3 (q, *J* = 260.0 Hz), 124.4, 128.9 (d, *J* = 8.4 Hz), 133.1 (d, *J* = 3.7 Hz), 136.7, 157.6 (d, *J* = 261.8 Hz), 170.1, 192.8; IR (ATR) ν (cm^{-1}): 2993, 2958, 1739, 1681; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{18}F_4O_3Na$ 357.1090 found 357.1091; Isolated yield: 180 mg (88%) from 200 mg of **3j**.

3-Pentanyl 3-((3,4,5-trifluoro)phenyl)-2-methyl-3-oxopropanoate, 4k. Oil; ^1H NMR (360 MHz, $CDCl_3$) δ (ppm): 0.74 (t, *J* = 7.5 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H), 1.44 – 1.50 (m, 7H), 4.25 (q, *J* = 7.0 Hz, 1H), 5.75 (quint, 7.2 Hz, 1H), 7.66 (dd, *J* = 7.7 Hz, *J* = 6.7 Hz, 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -132.3 (d, *J* = 20.1 Hz, 2F), -152.0 (t, *J* = 20.1 Hz, 1F); ^{13}C NMR [^1H] ($CDCl_3$, 63 MHz) δ (ppm): 9.2, 9.3, 13.4, 26.2, 48.7, 78.4, 113.1, 131.7 (d, *J* = 4.4 Hz), 143.3 (dt, *J* = 260.7 Hz, *J* = 15.5 Hz), 151.2 (ddd, *J* = 253.1 Hz, *J* = 10.3 Hz, *J* = 3.3 Hz), 170.0, 192.1; IR (ATR) ν (cm^{-1}): 2994, 2962, 1751, 1621; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{17}F_3O_3Na$ 325.1022; found 325.1019; Isolated yield: 176 mg (89%) from 190 mg of **3k**.

3-Pentanyl 3-(3,4-dimethoxybenzoyl)-6,6,6-trifluorohexanoate, 10e. Oil; ^1H NMR (360 MHz, $CDCl_3$) δ (ppm): 0.68 (t, *J* = 7.4 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H), 1.43 (m, 4H), 1.59 (quint *J* = 7.4 Hz, 2H), 2.08 (m, 4H, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 4.24 (t, *J* = 7.1 Hz, 1H), 4.70 (quint, *J* = 6.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -66.9 (s, 3F); ^{13}C NMR [^1H] ($CDCl_3$, 91 MHz) δ (ppm): 9.3, 9.3, 20.1 (q, *J* = 2.9 Hz), 26.1, 26.2, 27.9, 33.6 (q, *J* = 28.7 Hz), 53.9, 55.9, 56.0, 78.1, 110.0, 110.5, 123.3, 126.9 (q, *J* = 276.4 Hz), 129.3, 149.1, 153.7, 169.6, 192.7; IR (ATR) ν (cm^{-1}): 2970, 1965, 1730, 1675, 1585, 1514, 1418, 1257, 1134, 1023; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{27}F_3O_5Na$ 427.1703; found 427.1702; Isolated yield: 422 mg (96%) from 320 mg of **3k**.

General procedure for α-fluorination with Selectfluor®. In a 25 mL round bottom flask with a magnetic stirrer 3.15 mmol of Selectfluor® are dissolved in 10 mL of acetonitrile. Then, 2.1 mmol of the desired β-keto ester are disposed into the system. The reaction is warmed up to 50ºC during 24 hours. The reaction completion is followed by TLC. Once there are no evidences of the presence of the starting material, the crude is poured into 25 mL of methyl *tert*-buthyl ether. After filtration, the organics are removed in a vacuum system and the crude residue is purified by flash silica gel chromatography using mixture of hexane:AcOEt (4:1) obtaining the desired α-fluoro β-keto ester.

Methyl 3-(3,4-dimethoxyphenyl)-2-fluoro-3-oxopropanoate, 6e. White solid; Mp. 59-60ºC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): keto (95%) - enol (5%) mixture, 3.75 (s, 0.15H), 3.83 (s, 3H), 3.90 (s, 0.15H), 3.93 (s, 3H), 3.96 (s, 3H), 5.85 (d, *J* = 49.5 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.74 (dd, *J* = 2.1 Hz, *J* = 8.6 Hz, 1H); ^{19}F NMR (235 MHz,

$CDCl_3$) δ (ppm): -188.8 (d, *J* = 49.5 Hz, 1F); ^{13}C NMR [^1H] ($CDCl_3$, 101 MHz) δ (ppm): 53.3, 56.1, 56.3, 90.1 (d, *J* = 197.3 Hz), 110.3, 111.2 (d, *J* = 2.3 Hz), 125.1 (d, *J* = 5.4 Hz), 126.4 (d, *J* = 2.3), 149.4, 154.7, 165.4 (d, *J* = 23.2 Hz), 187.7 (d, *J* = 20.1 Hz); IR (ATR) ν (cm^{-1}): 2965, 1742, 1681; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{13}FO_5Na$ 279.0639; found 279.0631; Isolated yield: 504 mg (95%) from 500 mg of **2e**.

3-Pentanyl 3-(3,4-dimethoxyphenyl)-2-fluoro-3-oxopropanoate, 7e. Oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): keto (92%) - enol (8%) mixture, 0.70 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H), 1.62 (abs. compl., 4H), 3.93 (s, 3H), 3.96 (s, 3H), 4.89 (quint, *J* = 6.2 Hz, 1H), 5.82 (d, *J* = 48.9 Hz, 1H), 6.91 (d, *J* = 8,6 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.74 (dd, *J* = 1.9 Hz, *J* = 8.6Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -188.3 (d, *J* = 48.8 Hz, 1F); ^{13}C NMR [^1H] ($CDCl_3$, 101 MHz) δ (ppm): 9.4, 9.6, 26.4, 26.5, 56.2, 56.3, 80.1, 89.7 (d, *J* = 200.3 Hz), 110.3, 111.2 (d, *J* = 2.1 Hz), 125.0 (d, *J* = 4.6 Hz), 126.6 (d, *J* = 2.1), 149.4, 154.6 165.4 (d, *J* = 23.2 Hz), 188.1 (d, *J* = 20.1 Hz); IR (ATR) ν (cm^{-1}): 2969, 1749, 1679; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{21}FO_5Na$ 335.1265; found 335.1267; Isolated yield: 510 mg (95%) from 500 mg of **3e**.

General procedure for the introduction of the trifluoromethylthio group in the α-position. **A** dry and nitrogen-flushed-10mL tube equipped with a magnetic stirrer and a septum is charged with the desired β-keto ester (0.38 mmol) and $TsNMeSCF_3$ (1.2 equiv.). The tube was evacuated and refilled with nitrogen three times, and then dry 0.5 mL of THF is added. Under a gentle argon atmosphere, the reaction mixture was cooled to 0°C, and LDA 2M (0.2equiv.) solution (in THF/heptanes/ethylbenzene) was added dropwise via a syringe. The conversion was checked by TLC until the starting material disappeared. The reaction is quenched with distilled water after completion. Reaction is warmed at room temperature and 5 mL of Et_2O were added. The organic layer is washed with aqueous HCl 0.5M solution, $NaHCO_3$ saturated solution, NaCl 1M solution, and then the organics are dried over $NaSO_4$. After filtration, the solvent was removed and the crude was purified by flash chromatography with hexane:AcOEt (7:3) to give the desired product.

Methyl 3-(3,4-dimethoxyphenyl)-2-trifluoromethylthio-3-oxopropanoate, 8e. Oil; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): keto (57%) - enol (43%) mixture, 3.70 (s, 3H), 3.82 (s, 0.7H), 3.83 (s, 0.7H), 3.84 (s, 3H), 3.88 (s, 3H), 5.61, 6.84 (d, *J* = 8.5 Hz, 0.3H), 6.87 (d, *J* = 8.5 Hz, 0.3H), 7.19 (d, *J* = 1.9 Hz, 0.3H), 7.27 (dd, *J* = 1.9 Hz, *J* = 8.5Hz, 0.3H), 7.46 (d, *J* = 1.9 Hz, 1H), 7.61 (dd, *J* = 2.1 Hz, *J* = 8.6Hz, 1H), 14.49 (s, 0.23H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -40.8 (s, 3F), -45.4 (s, 0.9F); ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm): 52.8, 53.7, 54.5, 55.7, 55.7, 55.8, 55.9, 110.0, 110.2, 110.7, 112.2, 123.1, 124.2, 127.6, 129.1 (q, *J* = 312.1 Hz, S$\underline{C}F_3$), 130.0 (q, *J* = 312.1 Hz), 148.0, 149.3, 151.5, 154.7, 166.6, 173.7, 183.5, 186.53; IR (ATR): 2970, 1735,

1675; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{13}F_3O_5SNa$ 361.0333; found 361.0335; Isolated yield: 180 mg (65%) from 200 mg of **2e**.

3-Pentanyl 3-(3,4-dimethoxyphenyl)-2-trifluoromethylthio-3-oxopropanoate, 9e. Oil; ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): keto (57%) - enol (43%) mixture, 0.69 (t, *J* = 7.5 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 1.5H), 1.51 (m, 4H), 1.69 (m, 1H), 3.90 (s, 0.6H), 3.92 (s, 3H), 3.96 (s, 3H), 4.77 (quint, *J* = 6.2 Hz, 1H), 4.97 (quint, *J* = 6.2 Hz, 0.2H), 5.59 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 0.3H), 6.91 (d, *J* = 8.5 Hz, 0.3H), 7.26 (d, *J* = 1.9 Hz, 0.2H), 7.34 (dd, *J* = 1.9 Hz, *J* = 8.5Hz, 0.3H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.70 (dd, *J* = 2.1 Hz, *J* = 8.5Hz, 1H), 14.81 (s, 0.2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -40.6 (s, 3F), -44.8 (s, 0.6F); ^{13}C NMR ($CDCl_3$, 91 MHz) δ (ppm): 9.1, 9.2, 9.4, 26.0, 26.1, 26.2, 55.4, 55.8, 56.0, 56.2, 79.6, 80.4, 110.0, 110.2, 110.8, 112.3 , 123.1, 124.3, 127.6, 129.3 (q, *J* = 312.1 Hz,), 130.0 (q, *J* = 312.1 Hz), 148.1, 149.4, 151.3, 154.7, 166.1, 173.3, 183.5, 186.9; IR (ATR): 2970, 2939, 1675, 1585; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{21}F_3O_5SNa$ 417.0957; found 417.0965; Isolated yield: 132 mg (66%) from 150 mg of **3e**.

General procedure for the enantioselective α-amination reactions. A solution of $Eu(OTf)_3$ (0.017 mmol) and Ph-*pybox* (0.023 mmol) in dry acetonitrile (1.5 mL) was stirred overnight in the presence of 4Å molecular sieves under argon atmosphere at room temperature. Then, the β-ketoester (0.184 mmol) and the electrophile (0.298 mmol) were sequentially added. The mixture was stirred for the time indicated in the tables (TLC monitoring), and the product was chromatographed through a silica gel column with hexane:AcOEt (4:1) as eluent.

(*S*)-di-*tert*-butyl-(2-methyl-1,3-dioxo-1-(pentan-3-yloxy)-3-(4-(trifluoromethyl)phenyl) propan-2-yl)hydrazine-1,2-dicarboxylate, 5a. White solid, Mp. 42-44ºC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 – 1.82 (complex abs., 31H), 4.92 (broad s, 1H,), 6.20 (s, 1H), 7.31 (broad s, 2H), 8.60 (broad s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -63.1 (s, 3F); ^{13}C NMR [^1H] ($CDCl_3$, 101 MHz) δ (ppm): 9.4, 9.5, 26.2, 26.3 – 28.1, 79.6, 81.6, 116.5, 119.0, 119.8, 121.6, 124.1, 131.3, 1542.1, 155.6, 169.2, 189.4, 190.2; IR (ATR) ν (cm^{-1}): 3284, 2980, 2915, 1746, 1710, 1685, 1670, 1602; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{37}F_3N_2O_7Na$ 569.2445; found 569.2453; $[\alpha]_D^{20}$ = 91.4 (c = 0.009, CH_3CN), 98% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 15.81 min and $t_r(R)$ = 19.12 min with hexane:isopropanol (98:2); Isolated yield: 133 mg (77%) from 100 mg of **4a**.

(*S*)-di-*tert*-Butyl-1-(2-methyl-1,3-dioxo-1-(pentan-3-yloxy)-3-(4-(trifluoromethoxy)phenyl) propan-2-yl)hydrazine-1,2-dicarboxylate, 5b. White solid, Mp. 60-62ºC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 – 1.82 (complex abs., 31H), 4.92 (broad s, 1H), 6.20 (s, 1H), 7.29 (broad s, 2H), 8.60 (broad s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -57.6 (s, 3F); ^{13}C NMR [^1H]

($CDCl_3$, 101 MHz) δ (ppm): 9.4, 9.5, 26.2, 26.3 – 28.1, 79.6, 81.6, 116.5, 119.0, 119.8, 121.6, 124.1, 131.3, 1542.1, 155.6, 169.2, 189.4, 190.2.IR (ATR) ν (cm^{-1}): 3284, 2980, 2915, 1746, 1710, 1685, 1670, 1602; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{37}F_3N_2O_8Na$ 585.2394; found 585.2394; $[\alpha]_D^{20}$ = 105.7 (c = 0.013, CH_3CN), 96% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, t_r(*S*) = 9.41 min and t_r(*R*) = 16.75 min with hexane:isopropanol (99.5:0.5); Isolated yield: 101 mg (76%) from 80 mg of **4b**.

(*S*)-di-*tert*-Butyl-1-(1-(3-fluoro-4-methoxyphenyl)-2-methyl-1,3-dioxo-3-(pentan-3-yloxy) propan-2-yl)hydrazine-1,2-dicarboxylate, 5c. White solid, Mp. 44-45ºC; ^{1}H NMR (400 MHz, 55ºC, $CDCl_3$) δ (ppm): 0.93 (t, 3H, *J* = 7.5 Hz), 1.00 (t, 3H, *J* = 7.5 Hz), 1.27 – 1.55 (complex, abs., 18H), 1.67 (m, 4H), 1.81 (s, 3H), 3.94 (s, 3H), 4.89 (broad s, 1H), 6.15 (s, 1H), 7.00 (d, 1H, *J* = 7.3 Hz), 8.17 (s, 1H), 8.43 (s, 1H); ^{19}F NMR (376 MHz, 55ºC, $CDCl_3$) δ (ppm): -135.5 (s, 1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 26.2, 26.3, 27.5, 28.1, 56.1, 79.4, 81.5, 112.4, 117.2, 126.8, 128.1, 151.3, 155.5, 156.1, 169.3, 190.1.IR (ATR) ν (cm^{-1}): 3234, 2974, 2936, 1737, 1704, 1696, 1686, 1611; Elemental analysis Calcd for $C_{26}H_{39}FN_2O_8$: C: 59.30%, H: 7.46%, N: 5.32%. Experimental: C: 59.47%, H: 7.54%, N: 5.16%; $[\alpha]_D^{20}$ = 115.4 (c = 0.013, CH_3CN), 92% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, t_r(*S*) = 13.80 min and t_r(*R*) = 21.04 min with hexane:isopropanol (95:5); Isolated yield: 111 mg (74%) from 85 mg of **4c**.

(*S*)-di-*tert*-Butyl-1-(1-(4-methoxy-3-(trifluoromethyl)phenyl)-2-methyl-1,3-dioxo-3-(pentan -3-yloxy)propan-2-yl)hydrazine-1,2-dicarboxylate, 5d White solid, Mp. 33-35ºC; ^{1}H NMR (400 MHz, 55ºC, $CDCl_3$) δ (ppm): 0.96 (complex abs., 6 H), 1.29 – 1.54 (complex abs., 18H), 1.68 (m, 4H), 1.82 (s, 3H) 3.97 (s, 3H), 4.89 (broad s, 1H), 6.21 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 8.56 (s, 1H), 8.93 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -62.5 (s, 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.4, 9.6, 20.2, 26.1, 26.2, 27.4 – 28.0, 56.1, 79.5, 81.6 – 85.3, 111.2, 118.8, 123.2, 129.2, 134.9, 135.9, 155.8, 156.6, 160.4, 160.2, 169.4, 189.0, 190.0; IR (ATR) ν (cm^{-1}): 3297, 2980, 2938, 1739, 1716, 1689, 1610, 1607; HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{40}F_3N_2O_8$ 577.2731; found 577.2739; $[\alpha]_D^{20}$ = 94.3 (c = 0.010, CH_3CN), 94% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, t_r(*S*) = 16.89 min and t_r(*R*) = 22.92 min with hexane:isopropanol (98:2); Isolated yield: 115 mg (87%) from 80 mg of **4d**.

(*S*)-di-*tert*-Butyl-1-(1-(4-methoxy-3-(trifluoromethoxy)phenyl)-2-methyl-1,3-dioxo-3-(pentan-3-yloxy)propan-2-yl)hydrazine-1,2-dicarboxylate, 5f. White solid, Mp. 63-64ºC; ^{1}H NMR (400 MHz, 55ºC, $CDCl_3$) δ (ppm): 0.97 (complex abs., 6 H), 1.26 – 1.71 (complex abs., 18H), 1.68 (m, 4H), 1.83 (s, 3H) 3.96 (s, 3H), 4.91 (broad s, 1H), 6.19 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 8.37 (s, 1H), 8.73 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -58.4 (s, 3F); ^{13}C

NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 20.7, 26.2, 26.3, 27.5 – 28.1, 56.0, 79.5, 81.4, 111.9, 119.34, 121.9, 124.6, 127.9, 130.2, 137.8, 155.4, 155.5, 156.13, 169.2, 160.2, 169.4, 189.3. IR (ATR) ν (cm^{-1}): 3294, 2981, 2922, 1715, 1709, 1679, 1622, 1615; HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{40}F_3N_2O_9$ 593.2680; found 593.2682; $[\alpha]_D^{20}$ = 81.4 (c = 0.010, CH_3CN), 90% ee (absolute configuration *S*). HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 14.00 min and $t_r(R)$ = 21.40 min with hexane:isopropanol (98:2); Isolated yield: 103 mg (75%) from 85 mg of **4f**.

(*S*)-di-*tert*-Butyl-1-(1-(3,5-difluoro-4-methoxyphenyl)-2-methyl-1,3-dioxo-3-(pentan-3-yloxy)propan-2-yl)hydrazine-1,2-dicarboxylate, 5g. White solid, Mp. 42-43ºC; ^{1}H NMR (400 MHz, 55ºC, $CDCl_3$) δ (ppm): 0.96 (complex abs., 6 H), 1.32 – 1.56 (complex abs., 18H), 1.66 (m, 4H), 1.80 (s, 3H) 4.09 (s, 3H), 4.89 (broad s, 1H), 6.16 (s, 1H), 8.16 (s, 2H); ^{19}F NMR (376 MHz, 55ºC, $CDCl_3$) δ (ppm): -127.8 (s, 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 9.4, 20.4, 26.2, 26.3, 27.6 – 28.1, 61.3, 79.6, 81.7, 113.7, 128.9, 140.1, 153.3, 153.3, 153.4, 155.6, 155.7, 155.8, 159.2, 169.0, 188.3.IR (ATR) ν (cm^{-1}): 3291, 2981, 2922, 1745, 1725, 1682, 1664, 1621; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{38}F_2N_2O_8Na$ 567.2488; found 567.2493; $[\alpha]_D^{20}$ = 101.1 (c = 0.011, CH_3CN), 92% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 10.03 min and $t_r(R)$ = 15.45 min with hexane:isopropanol (98:2); Isolated yield: 132 mg (76%) from 100 mg of **4g**.

(*S*)-di-*tert*-Butyl-1-(1-(3,4-difluorophenyl)-2-methyl-1,3-dioxo-3-(pentan-3-yloxy)propan-2-yl)hydrazine-1,2-dicarboxylate, 5h. White solid, Mp. 35-37ºC; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): 0.91 – 1.98 (abs. complex, 32 H), 4.89 (bs, 1H), 6.23 (s, 1H), 7.23 (bs, 1H), 8.13 – 8.62 (complex abs., 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -131.3 (d, *J* = 297.6 Hz, 1F), -137.17 (d, *J* = 150.7 Hz, 1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.6, 20.5, 26.2, 26.3, 27.4 – 28.2, 78.3, 81.6 – 85.3, 117.6, 117.0, 118.8, 131.8, 148.6, 155.7, 169.2, 188.6, 188.9, 189.7. IR (ATR) ν (cm^{-1}): 3286, 2988, 2925, 1745, 1715, 1700, 1682, 1669, 1618; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{36}F_2N_2O_7Na$ 537.2383; found 537.2389; $[\alpha]_D^{20}$ = 91.7 (c = 0.009, CH_3CN), >99% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 16.05 min and $t_r(R)$ = 20.67 min with hexane:isopropanol (95:5); Isolated yield: 88 mg (82%) from 60 mg of **4h**.

(*S*)-di-*tert*-butyl-1-(1-(4-fluoro-3-(trifluoromethoxy)phenyl)-2-methyl-1,3-dioxo-3-(pentan-3-yloxy)propan-2-yl)hydrazine-1,2-dicarboxylate, 5i. White solid, Mp. 51-54ºC; ^{1}H NMR (400 MHz, 55ºC, $CDCl_3$) δ (ppm): 0.96 (complex abs., 6 H), 1.30 – 1.56 (complex abs., 18H), 1.68 (m, 4H), 1.83 (s, 3H), 4.91 (bs, 1H), 6.21 (s, 1H), 7.29 (s, 1H), 8.56 (complex abs., 2H);^{19}F NMR (376 MHz, 55ºC, $CDCl_3$) δ (ppm): -58.8 (complex abs., 3F), -121.7 (complex abs., 1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 26.2, 26.3, 27.5 – 28.0, 79.7, 80.7, 81.7, 116.7,

121.7, 125.7, 135.9, 136.3, 155.5, 159.5, 161.7, 168.9, 183.7; IR (ATR) ν (cm^{-1}): 3286, 2988, 2925, 1745, 1725, 1702, 1690, 1679, 1615; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{36}F_4N_2O_8Na$ 603.2320; found 603.2300; $[\alpha]_D^{20}$ = 79.4 (c = 0.010, CH_3CN), 94% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 17.85 min and $t_r(R)$ = 22.94 min with hexane:isopropanol (99:1); Isolated yield: 85 mg (70%) from 70 mg of **4i**.

(*S*)-di-*tert*-Butyl-1-(1-(4-fluoro-3-(trifluoromethyl)phenyl)-2-methyl-1,3-dioxo-3-(pentan-3-yloxy)propan-2-yl)hydrazine-1,2-dicarboxylate, 5j. White solid, Mp. 39-41ºC; ^{1}H NMR (400 MHz, 55ºC, $CDCl_3$) δ (ppm): 0.93 - 1.80 (complex abs., 31H), 4.92 (bs, 1H), 6.25 (s, 1H), 7.37 (s, 1H), 8.97 (complex abs., 2H); ^{19}F NMR (376 MHz, 55ºC, $CDCl_3$) δ (ppm): -61.4 (complex abs., 3F), -108.6 (complex abs., 1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.4, 9.6, 19.9, 26.1, 26.3, 27.5 – 29.6, 79.7, 81.7, 83.4, 116.7, 118.7, 120.8, 123.6, 129.2, 131.2, 135.3, 155.8, 156.7, 160.6, 163.2, 169.0, 188.4, 189.6.IR (ATR) ν (cm^{-1}): 3295, 2980, 2915, 1749, 1724, 1702, 1690, 1679, 1615; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{36}F_4N_2O_7Na$ 587.2351; found 587.2365; $[\alpha]_D^{20}$ = 107.7 (c = 0.010, CH_3CN), 93% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 16.51 min and $t_r(R)$ = 20.65 min with hexane:isopropanol (99:1); Isolated yield: 110 mg (75%) from 90 mg of **4j**.

(*S*)-di-*tert*-Butyl-1-(1-(3,4,5-trifluorophenyl)-2-methyl-1,3-dioxo-3-(pentan-3-yloxy) propan-2-yl)hydrazine-1,2-dicarboxylate, 5k. White solid, Mp. 37-39ºC; ^{1}H NMR (400 MHz, 55ºC, $CDCl_3$) δ (ppm): 0.98 (complex abs., 6 H), 1.40 – 1.78 (complex abs., 25H), 4.91 (broad s, 1H), 6.24 (s, 1H), 7.98 – 8.50 (complex abs., 2H); ^{19}F NMR (376 MHz, 55ºC, $CDCl_3$) δ (ppm): -133.0 (complex abs., 2F), -153.7 (complex abs., 1F); ^{13}C NMR [^{1}H] ($CDCl_3$, 91 MHz) δ (ppm): 9.3, 9.6, 20.0, 20.9, 26.1, 27.6 – 28.1, 79.8, 81.8, 83.6, 113.8, 114.0, 114.6, 126.7, 130.3, 141.1, 144.0, 144.2, 149.4, 149,5, 152.3, 155.5, 187.5, 188.8. IR (ATR) ν (cm^{-1}): 3286, 2988, 2925, 1745, 1715, 1700, 1682, 1669, 1618; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{35}F_3N_2O_7Na$ 555.2289; found 555.2298. $[\alpha]_D^{20}$ = 126.7 (c = 0.009, CH_3CN), 90% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 15.21 min and $t_r(R)$ = 19.65 min with hexane:isopropanol (98:2); Isolated yield: 110 mg (74%) from 80 mg of **4k**.

(*R*)-di-*tert*-Butyl-1-(1-(3,4-dimethoxyphenyl)-2-fluoro-1,3-dioxo-3-(3-pentanyl-3-oxyl) propan-2-yl)hydrazine-1,2-dicarboxylate, 11e. White solid, Mp. 37-39ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.79 (abs. compl., 6H), 1.30-1.46 (abs. compl., 22H), 3.34 (s, 3H), 3.80 (s, 3H), 4.77 (abs. compl., 1H), 6.38 (s, 1H), 6.55 (d, *J* = 8.6 Hz, 1H), 8.08 (s, 1H), 8.26 (s, 1H);^{19}F NMR (DMSO, 100.6 MHz) δ (ppm): -122.1 (s, 1F); ^{13}C NMR (DMSO, 100.6 MHz) δ (ppm): 8.3, 8.6, 25.0, 25.2, 26.9-27.7, 55.5, 55.7, 78.5, 78.8, 79.8, 110.8, 125.0, 126.2, 148.1, 153.5,

154.6, 155.2, 159.6, 186.1; IR (ATR) ν (cm^{-1}): 3313, 2975, 2937, 2882, 1736, 1691, 1594, 1584; HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{39}FN_2O_9Na$ 565.2532; found 565.2528; $[\alpha]_D^{20}$ = 99.3 (c = 0.012, CH_3CN), 94% ee (absolute configuration *R*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 19.03 min and $t_r(R)$ = 37.29 min with hexane:isopropanol (95:5); Isolated yield: 132 mg (78%) from 100 mg of **7e**.

(*S*)-di-*tert*-Butyl-1-(2-(3,4-dimethoxybenzoyl)-6,6,6-trifluoro-1-oxo-1-(pentan-3-yloxy) hexan-2-yl)hydrazine-1,2-dicarboxylate, 12e. White solid, Mp. 78-80ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 – 1.70 (complex abs., 31H), 1.94 (m, 4H), 2.30 (m, 2H), 3.94 (bs, 6H), 4.91 (bs, 1H), 6.15 (s, 1H), 6.91 (bs, 1H), 7.99-8.38 (complex abs., 2H, ArH);^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -61.4 (complex abs., 3F); ^{13}C NMR [^{1}H] ($CDCl_3$, 101 MHz) δ (ppm): 9.3, 9.5, 9.6, 17.6, 26.0, 26.1, 26.2, 26.3 – 29.6, 33.6, 33.9, 34.2,55.9, 56.1, 78.3, 79.5, 81.5, 81.7, 84.9, 110.1, 111.1, 111.4, 122.9, 123.8, 125.3, 128.1, 148.6, 152.9, 155.6, 155.8, 169.4, 188.8, 189.7; IR (ATR) ν (cm^{-1}): 3300, 2982, 2925, 1744, 1715, 1701, 1690, 1679, 1600. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $C_{30}H_{46}F_3N_2O_9$ 635.3150; found 635.3164; $[\alpha]_D^{20}$ = 99.3 (c = 0.008, CH_3CN), 99% ee (absolute configuration *S*); HPLC separation: Daicel AD-H, a racemic mixture shows two peaks, $t_r(S)$ = 10.40 min and $t_r(R)$ = 18.95 min with hexane:isopropanol (95:5); Isolated yield: 98 mg (78%) from 80 mg of **10e**.

Acknowledgements

We are thankful for financial support form Spain's MICINN (CTQ2014-53662-P, CTQ2014-59544-P) and MEC (CTQ2014-51912-REDC, CTQ2016-81797-REDC) and DURSI-Generalitat de Catalunya (2014SGR-1105, 2014SGR-482).

Supporting Information

Copies of the ^{1}H, ^{13}C and ^{19}F NMR are reported. IR, HRMS spectra, the HPLC chromatograms and the details of experiment procedures are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) a) Damier, P.; Hirsch, E. C.; Agid, Y.; Graybiel, A. M. *Brain*, **1999**, *122*, 1437-1438; b) Zanforlin, E. Zagotto, G. Ribaudo, G. *ACS Chem. Neurosci.,* **2017**, *8*, 2356-2368; c) Ellis, J. *M*.; Fell, M. *J. Bioorg. Med. Chem. Lett.* **2017***, 27,* 4247-4255.

(2) (a) Hayek, J. *Schweizerische Medizinische Wochenschrift*, **1977**, *107*, 474-479. (b) Delea, T. E.; Thomas, S. K.; Hagiwara, M. *CNS Drugs* **2011**, *25*, 53-66.

(3) a) Burkhard, P.; Dominici, P.; Borri-Voltattori, C.; Jansonius, J. N.; Malashkevick, V. N. *Nat. Struct. Mol. Biol.* **2001**, *8*, 963-967.b) Bertoldi, M. *Archiv. Biochem. Biophys.* **2014**, *546*, 1-7.

(4) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455-1456.

(5) a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330; b) O'Hagan *J. Fluorine Chem.* **2010**, *131*, 1071-1081; c) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832-2842; d) Samart, B. E. *J. Fluorine Chem*. **2001**, *109*, 3-11.

(6) a) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303-319; b) Ismail F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27-33; c) Müller, K; faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881-1886.

(7) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443-470.

(8) Fluorine in Medicinal Chemistry and Chemistry Biology, Wiley-Blackwell, **2009**.

(9) Pericas, A.; Shafir, A.; Vallribera, A. *Org. Lett.* **2013**, *15*,1448-1451. Highligted in *Synfacts 2013*, 700.

(10) Yang, P.; Xu, H.; Zhou, S. *Angew Chem. Int. Ed.* **2014**, *53*, 12210-12213.

(11) Kalish, V.; Brookfield, F. A.; Courtney, S. M.; Frost, L. M.; Toscano, J. P.; Guthrier, D. A.; North, C. L. PCT. Int. Appl. 2015183939 A1.

(12) Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* **2002**, *8*, 799-804.

(13) Qi, H.; Choi, S.; Dakka, A.; Karp, G. M.; Narasimhan, J.; Naryshkin, N.; Turpoff, A. A.; Weetall, E. Welch, M. L.; Woll. M. G. PCT Int. Appl. (2013), WO 2013119916 A2 20130815.

(14) a) Comelles, J.; Pericas, A.; Moreno-Mañas, M.; Vallribera, A.; Drudis-Solé, G.; Lledos, A.; Roglans, A.; Gracía-Granda, S.; Roces-Fernández, L. *J. Org. Chem.* **2007**, *72*, 2077-2087; b) Pericas, A.; Jiménez, R.; Granados, A.; Shafir, A. ; Vallribera, A.; Roglans, A.; Molins, E. *ChemistrySelect* **2016**, *1*, 4305-4312.

(15) Pericas, A.; Shafir, A.; Vallribera, A. *Tetrahedron* **2008**, *64*, 9258-9263. Highlighted in *Synfacts*, **2009**, 81.

(16) Genet, J. –P.; Greck, C.; D. Lavergne B. in *Modern Amination Methods*, (Eds.: A. Ricci), Wiley-VCH, Weinheim, **2000**, pp. 65-102.

(17) Yu, Y.; Shen, W.; Zhang, J.; he, R. Li, M. *J. Mol. Model* **2008**, *14*, 237-247

(18) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vicent, S. P. M; Wong, C.-H. *Angew. Chem. Int. Ed.* **2005**, *44*, 192-212.

(19) a) Alazet, S.; Zimmer, L. Billard, T. *Chem Eur. J.* **2014**, *20*, 8589-8593. b) Milandou, L. J. C. B.; Carreyre, H.; Alazet, S.; Greco, G.; Martin-Mingoit, A.; Loumpangou, C. N.; Ouamba, J.-M.; Billard, T.; Thibaudeau, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 169-172.

(20) Madadkar-Sobhani, A.; Guallar, V. *Nucleic Acids Res.* **2013**, *41*, 322-328.

(21) Borrelli, K. W.;Vitalis, A.; Alcantara, R.; Guallar, V. J. *Chem. Theory Comput.,* **2005**, *1*, 1304-1311.