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Solution and fluorous phase synthesis of β,β-difluorinated 1-amino-1-cyclopentane carboxylic acid derivatives

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ABSTRACT

An efficient protocol for the preparation of β,β-difluorinated 1-amino-1-cyclopentane carboxylic acid derivatives was developed. 2,2-Difluro-4-phenyl-3-butenoic acid **6** was used as substrate for the preparation of the starting vinyl difluoro imino esters **8**. The key steps of this methodology rely on the chemo- and diastereoselective addition of allylzinc bromides over the iminic functionality of **8** and subsequent RCM reaction. This synthetic sequence was successfully applied to fluorous synthesis.

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1. Introduction

α-Amino acids are ubiquitous scaffolds in biologically active compounds. However, when these amino acids are α,α-disubstituted, they are not readily available from the chiral pool. Their medicinal and biological relevance has thus motivated the search for new methodologies to access them [1]. In addition, the incorporation of fluorine atoms into these structures only serves to heighten interest in their preparation since fluorinated amino acids are substructures found in enzyme inhibitors, receptor antagonists, and lipophilicity enhancing agents [2].

Addition of nucleophiles to fluorinated α-imino esters is one of the simplest methods of preparing fluorinated α-amino acids bearing a quaternary carbon center. In contrast to the common strategy involving 1,2-addition of organometallic reagents to aldimines [3], the same reaction with ketimines and imino esters has proven to be much more challenging. Not only are these compounds less electrophilic than their aldimine counterparts, but, in the context of asymmetric catalysis, they are also less able to discriminate between enantiotopic faces because they lack a hydrogen substituent. We have very recently overcome these limitations by making use of phenylglycinol-derived α-imino esters [4]. This allowed us to carry out the addition of allylzinc bromide to allyl difluoroimino esters **1** in a completely chemo- and diastereoselective fashion to afford the corresponding amino ester derivatives as single diastereoisomers. Subsequently, an RCM reaction followed by the removal of the protecting group led to the formation of β,β-difluorinated 1-amino-1-cyclohexanecarboxylic acid **2** in enantiomerically pure form (Scheme 1).

1-Amino-1-cyclopentanecarboxylic acid derivatives are also important substructures in the preparation of conformationally restricted peptidic chains. Indeed, this type of unit has recently been incorporated into the peptidic chain of bradikynin, resulting in new analogues that show reduced antagonistic properties [5]. In the same vein, a similar derivative was included in the structure of peptidomimetics to afford effective inhibitors of cathepsin K [6]. Very recently, 1-amino-1-cyclopentanecarboxylic acid was used as a building block in the preparation of spiroimidazolin-4-ones, which are extremely important in the preparation of antihypertensive drugs [7]. As an extension of the aforementioned methodology, we thus decided to prepare fluorinated analogues of 1-amino-1-cyclopentanecarboxylic acid. In this paper, we report

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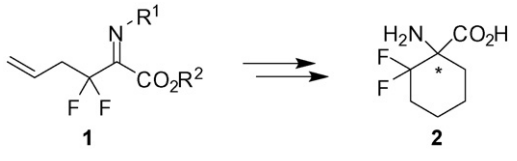
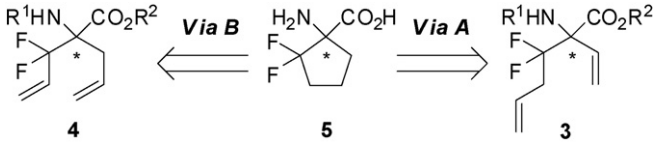
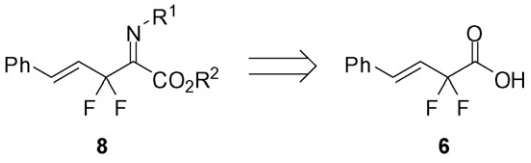


Scheme 1. Previous strategy for the preparation of fluorinated amino acid **2** developed by our group.



Scheme 2. Synthetic strategy for the preparation of **5**.



Scheme 3. Acid **6** as synthetic precursor of imino esters **8**.

on the preparation of the new fluorinated amino acid **5** in enantiomerically pure form, both in solution and in fluorous phase. Our synthetic strategy, which has previously been employed for the preparation of fluorinated amino acid **2**, relies on an RCM reaction of the adequate dienic precursor **3** or **4** (Scheme 2).

2. Results and discussion

A chemoselective addition of vinylmagnesium bromide to the iminic functionality of α-imino esters **1** should render the desired dienic compound **3** (**Via A**); however, all attempts to perform the addition of vinylmagnesium bromide to compounds **1** were unsuccessful, resulting merely in the recovery of the unaltered starting materials. We thus turned our attention to the second route (**Via B**), which involves the preparation of diallyl derivatives **4**.

In this context, very recently Réglier *et al.* have described the preparation of *Z* and *E* ethyl 4-phenyl-2,2-difluoro-3-butenoates through reaction of ethyl chlorodifluoroacetate with phenyl acetylene or β-bromostyrene, respectively [8]. The procedure consists of the stereocontrolled addition of α,α-difluoroacetate radical ($^{\bullet}CF_2CO_2Et$) to phenyl acetylene or β-bromostyrene. It seemed likely that acid **6**, which results from the hydrolysis of one of those esters and is easily available on a multigram scale, would be a suitable *vinyl difluoro* building block for the preparation of imino esters **8** (Scheme 3). Indeed, acid **6** can be considered a synthetic precursor of fluorinated diallyl amino esters **4** since the RCM would remove the phenyl group as styrene.

Fluorinated acid **6** [8] was thus transformed into the corresponding imidoyl chlorides **7** [9], which were then converted into their imidoyl iodides. These are necessary for performing the alkoxycarbonylation reaction mediated by a palladium complex [10] that affords imino esters **8** (Scheme 4).

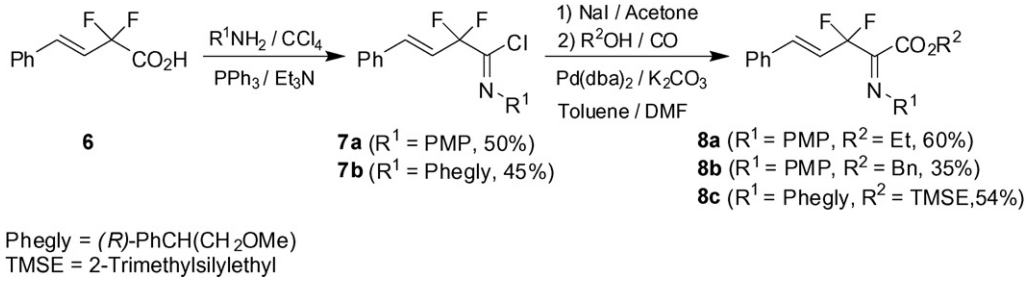
With imino esters **8** in hand, the next step of our synthetic strategy was the chemoselective allylation of the iminic function. The addition of allyl or methallylzinc bromide took place in an efficient and chemoselective manner, affording dienic amino esters **9** in excellent yields (Table 1). It is worth noting that when chiral imino ester **8c** was used, the addition was completely diastereoselective, furnishing dienic systems **9e,f** as single diastereoisomers (Table 1, entries 5, 6). In these cases, an identical stereochemical outcome of the allylzinc bromide addition to phenylglycinol-derived imino esters **1** can be assumed, involving a highly ordered transition state arising from chelation of the imine nitrogen and the oxygen in the chiral auxiliary to the zinc atom [4].

Cyclization was carried out in refluxing dichloromethane in the presence of second generation Grubbs catalyst [Cl_2(IMes)(PCy_3)Ru = CHPh] **11** to afford the desired β,β-difluoro-1-amino-1-cyclopentane carboxylic acid derivatives **10** in moderate to good yields (Table 1).

Deprotection of the amino acid functionality was accomplished in a two-step sequence. The TMSE ester moiety of (−)-**10e** was removed through treatment with TBAF to afford *N*-protected amino acid (−)-**12** in 87% yield. Finally, the cleavage of the methyl ether of phenyl glycinol was achieved by means of hydrogenolysis with palladium hydroxide, which also produced the hydrogenation of the double bond, giving rise to free amino acid (−)-**5** in moderate yield (Scheme 5).

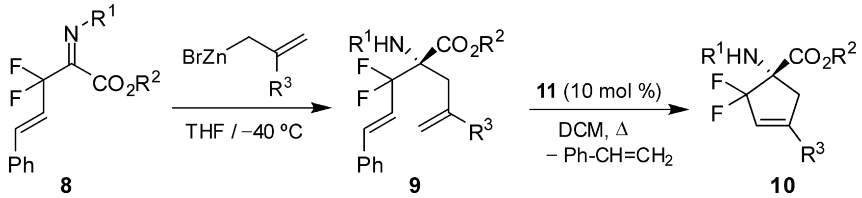
Once we had successfully extended our previously described methodology to the preparation of difluorinated 1-amino-1-cyclopentanecarboxylic acid (−)-**5**, we decided to apply this protocol to fluorous synthesis. One of the greatest benefits of this technique is that it successfully combines solution phase reaction conditions with easy purifications [11]. Recently introduced to organic synthesis by Curran and coworkers, this method is based on the use of perfluoroalkyl chains as phase tags that facilitates the separation process. Our interest in fluorous chemistry prompted us to develop a new fluorous tag, the fluorinated analogue of 2-(trimethylsilyl)ethanol **13** (^{F}TMSE-OH), for the protection of carboxylic acids (Fig. 1). This tag was successfully employed in the synthesis of peptides and modified peptides, and the cleavage was easily achieved under mild conditions through treatment with TBAF [12].

We started by performing the tagging process necessary in fluorous chemistry. The anchoring was carried out through alkoxycarbonylation of the corresponding imidoyl iodide (which



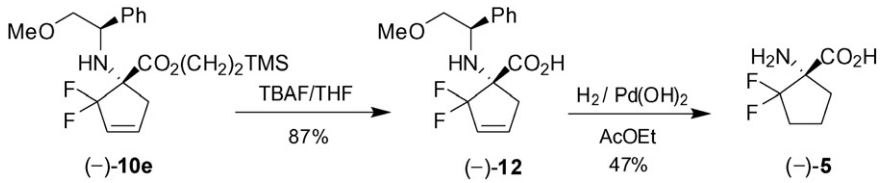
Scheme 4. Preparation of fluorinated α-imino esters **8**.

Table 1
Preparation of fluorinated α-amino acid derivatives **10**



Entry	8	R^1	R^2	R^3	9 (%)	10 (%)
1	**8a**	PMP	Et	H	**9a** (92)	**10a** (80)
2	**8a**	PMP	Et	Me	**9b** (89)	**10b** (65)
3	**8b**	PMP	Bn	H	**9c** (85)	**10c** (86)
4	**8b**	PMP	Bn	Me	**9d** (80)	**10d** (67)[c]
5	**8c**	Phegly[a]	TMSE[b]	H	(*S*)-**9e** (92)	(*S*)-**10e** (88)
6	**8c**	Phegly[a]	TMSE[b]	Me	(*S*)-**9f** (86)	(*S*)-**10f** (55)[d]

[a] Phegly = (*R*)-PhCH(CH_2OMe).
[b] TMSE = trimethylsilylethyl.
[c] Cyclization was performed in toluene.
[d] Cyclization was performed in toluene with second generation Hoveyda-Grubbs catalyst Cl_2(IMes)Ru = CHC_6H_4(O-*i*Pr).



Scheme 5. Release of the amino acid functionality over compound (−)-**10e**.

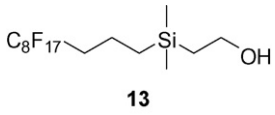
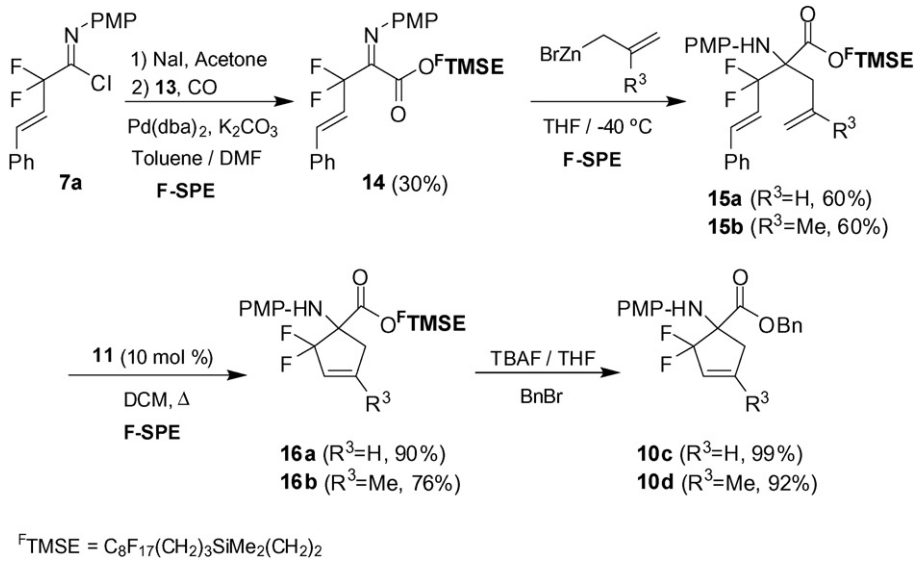


Fig. 1. Fluorous 2-(trimethylsilyl)ethanol **13**: an efficient tag for the protection of carboxylic acids.

results from treating **7a** with NaI) in the presence of fluorous trimethylsilylethanol **13** to furnish fluorous imino ester **14** in moderate yield. Once the fluorous chain had been introduced, the next step was the allylation process, which again occurred in a chemoselective fashion over the iminic functionality. Cyclization through an RCM reaction of the dienic products **15a,b** in the presence of second generation Grubbs catalyst **11** yielded the final amino ester derivatives **16a,b** attached to the fluorous tag. The last step was thus the removal of the tag; this was carried out under very mild conditions in a transesterification protocol involving treatment with TBAF in the presence of an electrophile, *i.e.* benzyl bromide (Scheme 6). It is worth noting that once the fluorous tag had been anchored, the purifications of compounds **14**, **15**, and **16** were easily performed by means of fluorous solid-phase extraction techniques (F-SPE), thus taking advantage of the special properties of fluorous tags.



^{F}TMSE = $C_8F_{17}(CH_2)_3SiMe_2(CH_2)_2$

Scheme 6. Fluorous synthesis of 5-membered ring amino esters **10**.

3. Conclusions

In conclusion, these results prove the versatility and usefulness of our protocol in the preparation of fluorinated 1-amino-1-cycloalkane carboxylic acid derivatives in enantiomerically pure form. The chemoselective addition of allylzinc bromide derivatives over the iminic functionality of imino esters **8** takes place very efficiently, affording a single diastereoisomer when the methyl ether of (*R*)-phenylglycinol is used as a chiral auxiliary. A subsequent RCM reaction furnishes the final five-membered ring amino acid derivatives **10** in moderate to good yields. This methodology has now been successfully adapted to fluorous chemistry, thus enhancing its scope. The incorporation of these units into peptidic sequences is currently underway.

4. Experimental

4.1. General experimental procedures

Reactions were carried out under nitrogen atmosphere unless otherwise indicated. The solvents were purified prior to use: CH_2Cl_2 and CCl_4 were distilled from calcium hydride; hexanes, toluene and THF from sodium. All reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm E. Merck precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). Fluorous solid-phase extractions were performed on Fluoro*Flash*™ silica gel cartridges from *Fluorous Technologies Inc.* Optical rotations were measured on a Jasco P-1020 polarimeter. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a 300 MHz Bruker AC300 spectrometer and 400 MHz Bruker Avance. Chemical shifts are given in ppm (δ), and are referenced to the residual proton resonances of the solvents or to fluorotrichloromethane in the ^{19}F NMR experiments. Coupling constants (*J*) are given in Hertz (Hz). High-resolution mass spectra were carried out on a VGmAutospec (VG Analytical, Micromass Instruments) by the Universidad de Valencia Mass Spectrometry Service. Compound **6** was previously described [8].

4.2. Preparation of fluorinated imidoyl chlorides 7

4.2.1. (1Z,3E)-2,2-Difluoro-N-(4-methoxyphenyl)-4-phenylbut-3-enimidoyl chloride (7a)

By means of the general procedure previously described [9], **7a** was obtained from **6** (1.50 g) as a yellow oil (1.22 g) in 50% yield after flash chromatography with hexanes:diethyl ether (20:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.51 (dt, J_{HH} = 16.2 Hz, J_{HF} = 11.1 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 7.16 (dt, J_1 = 6.5 Hz, J_2 = 3.6 Hz, 2H), 7.37–7.42 (m, 3H), 7.49–7.52 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.3, 114.0, 114.7 (t, $^1J_{CF}$ = 245.0 Hz), 119.6 ($^2J_{CF}$ = 25.1 Hz), 123.2, 127.4, 128.7, 129.4, 134.3, 135.9 (t, $^3J_{CF}$ = 8.7 Hz), 136.9, 137.2 (t, $^2J_{CF}$ = 38.6 Hz), 158.5. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −97.09 (dd, J_{FHA} = 11.3 Hz, J_{FHB} = 2.3 Hz, 2F). HRMS calc. for $C_{17}H_{14}NOClF_2$: 321.0732, found: 321.0735.

4.2.2. (1Z,3E)-2,2-Difluoro-N-[(R)-2-methoxy-1-phenylethyl]-4-phenylbut-3-enimidoyl chloride (7b)

By means of the general procedure previously described [9], **7b** was obtained from **6** (1.0 g) as a yellow oil (0.79 mg) in 45% yield after flash chromatography with hexanes:ethyl acetate (30:1) as eluent. $[\alpha]_D^{25}$ = −11.83 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 3H), 3.65–3.80 (m, 2H), 5.15–5.20 (m, 1H), 6.45 (dt, J_{HH} = 15.9 Hz, J_{HF} = 10.8 Hz, 1H), 7.10 (d, J_{HH} = 16.2 Hz, 1H), 7.33–7.49 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 59.1, 67.1, 76.9, 114.5 (t, $^1J_{CF}$ = 244.8 Hz), 119.8 (t, $^2J_{CF}$ = 25.4 Hz), 127.3, 127.4, 127.9, 128.6, 128.8, 129.4, 134.4, 136.2 (t, $^3J_{CF}$ = 9.0 Hz), 137.9, 140.2 (t, $^2J_{CF}$ = 37.6 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −95.90 (dd, J_{FF} = 260.4 Hz, J_{FH} = 10.7 Hz, 1F), −96.88 (dd, J_{FF} = 259.5 Hz, J_{FH} = 11.3 Hz, 1F). HRMS calc. for $C_{19}H_{18}NOClF_2$: 349.1045, found: 349.1049.

4.3. Preparation of fluorinated α-imino esters 8 and 14

4.3.1. (2E,4E)-Ethyl 3,3-difluoro-2-(4-methoxyphenylimino)-5-phenylpent-4-enoate (8a)

By means of the general procedure previously described [10], **8a** was obtained from **7a** (236 mg) as an orange oil (126 mg) in 60% yield after flash chromatography with toluene:dichloromethane (20:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 3.80 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 6.54 (dt, J_{HH} = 16.2 Hz, J_{HF} = 11.5 Hz, 1H), 6.86 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 7.13 (dt, J_{HH} = 16.4 Hz, J_{HF} = 2.5 Hz, 1H), 7.36–7.39 (m, 3H), 7.49–7.52 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 55.4, 62.1, 114.1, 116.1 (t, $^1J_{CF}$ = 242.6 Hz), 120.2 (t, $^2J_{CF}$ = 25.2 Hz), 121.6, 127.4, 128.7, 129.3, 134.5, 135.7 (t, $^3J_{CF}$ = 9.2 Hz), 140.4, 155.4 (t, $^2J_{CF}$ = 35.1 Hz), 158.5, 162.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.23 (dd, J_{FH1} = 11.5 Hz, J_{FH2} = 2.5 Hz, 2F). HRMS calc. for $C_{20}H_{20}F_2NO_3$: 360.1411, found: 360.1403.

4.3.2. (2E,4E)-Benzyl 3,3-difluoro-2-(4-methoxyphenylimino)-5-phenylpent-4-enoate (8b)

By means of the general procedure previously described [10], **8b** was obtained from **7a** (314 mg) as an orange oil (107 mg) in 35% yield after flash chromatography with toluene:dichloromethane (40:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.18 (s, 2H), 6.55 (dt, J_{HH} = 16.2 Hz, J_{HF} = 11.5 Hz, 1H), 6.75 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 7.10–7.17 (m, 1H), 7.29–7.50 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.3, 67.6, 114.1, 116.1 (t, $^1J_{CF}$ = 243.0 Hz), 120.1 (t, $^2J_{CF}$ = 25.2 Hz), 121.6, 127.4, 128.5, 128.5, 128.6, 128.7, 129.3, 134.0, 134.5, 135.8 (t, $^3J_{CF}$ = 9.1 Hz), 140.2, 154.9 (t, $^2J_{CF}$ = 35.6 Hz), 158.5, 162.1. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.00 (dd, J_{FH1} = 11.5 Hz, J_{FH2} = 2.5 Hz, 2F). HRMS calc. for $C_{25}H_{21}NO_3F_2$: 421.1489, found: 421.1487.

4.3.3. (2E,4E)-2-(Trimethylsilyl)ethyl 3,3-difluoro-2-[(R)-2-methoxy-1-phenylethylimino]-5-phenylpent-4-enoate (8c)

By means of the general procedure previously described [10], **8c** was obtained from **7b** (610 mg) as a yellow oil (344 mg) in 54% yield after flash chromatography with toluene:dichloromethane (30:1) as eluent. $[\alpha]_D^{25}$ = +0.34 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.04–1.09 (m, 2H), 3.33 (s, 3H), 3.67 (d, J = 6.4 Hz, 2H), 4.34–4.41 (m, 2H), 4.95 (d, J = 5.7 Hz, 1H), 6.46 (dt, J_{HH} = 16.2 Hz, J_{HF} = 10.7 Hz, 1H), 7.06 (dt, J_{HH} = 16.2 Hz, J_{HF} = 2.7 Hz, 1H), 7.30–7.43 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −1.6, 17.4, 59.0, 64.6, 67.3, 77.0, 116.2 (t, $^1J_{CF}$ = 242.2 Hz), 120.8 (t, $^2J_{CF}$ = 25.9 Hz), 127.2, 127.3, 127.8, 128.5, 128.7, 129.1, 134.8, 135.8 (t, $^3J_{CF}$ = 9.5 Hz), 138.9, 157.2 (t, $^2J_{CF}$ = 34.4 Hz), 161.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −96.13 (ddd, J_{FF} = 268.6 Hz, J_{FH1} = 10.7 Hz, J_{FH2} = 2.5 Hz, 1F), −97.14 (ddd, J_{FF} = 268.6 Hz, J_{FH1} = 10.4 Hz, J_{FH2} = 2.8 Hz, 1F). HRMS calc. for $C_{25}H_{31}SiNO_3F_2$: 459.2051, found: 459.2050.

4.3.4. (2E,4E)-2-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl)-dimethylsily])ethyl 3,3-difluoro-2-(4-methoxyphenylimino)-5-phenylpent-4-enoate (14)

By means of the general procedure previously described [10], **14** was obtained from **8a** (1.05 g) as a yellow oil (645 mg) in 30%

yield after fluorous solid-phase extraction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.52–0.57 (m, 2H), 0.83–0.89 (m, 2H), 1.50–1.61 (m, 2H), 1.97–2.15 (m, 2H), 3.79 (s, 3H), 4.18–4.24 (m, 2H), 6.54 (dt, J_{HH} = 16.2 Hz, J_{HF} = 11.5 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 7.12 (dt, J_{HH} = 16.2 Hz, J_{HF} = 2.4 Hz, 1H), 7.34–7.41 (m, 3H), 7.48–7.51 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −3.8, 14.6, 14.9, 15.5, 34.3 (t, $^2J_{CF}$ = 22.1 Hz), 55.2, 64.2, 114.2, 116.2 (t, $^1J_{CF}$ = 242.6 Hz), 120.3 (t, $^2J_{CF}$ = 25.2 Hz), 121.8, 127.4, 128.7, 129.3, 134.6, 135.7 (t, $^3J_{CF}$ = 9.1 Hz), 140.4, 155.5 (t, $^2J_{CF}$ = 35.6 Hz), 158.6, 162.6 (the signals from the C_8F_{17} group were obscured due to their low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.39 (t, J = 9.9 Hz, 3F), −98.18 (dd, J_{FH1} = 11.6 Hz, J_{FH2} = 2.5 Hz, 2F), −115.09 (br s, 2F), −122.54 (br s, 6F), −122.54 (br s, 2F), −123.35 (br s, 2F), −124.26 (br s, 2F), −126.74 (br s, 2F). HRMS calc. for $C_{33}H_{31}SiNO_3F_{19}$: 878.1770, found: 878.1768.

4.4. Preparation of the fluorinated dialkylated α-amino esters 9 and 15

4.4.1. (E)-Ethyl 2-allyl-3,3-difluoro-2-(4-methoxyphenylamino)-5-phenylpent-4-enoate (9a)

By means of the general procedure previously described [4], **9a** was obtained from **8a** (35 mg) as a colorless oil (37 mg) in 92% yield after flash chromatography with hexane:ethyl acetate (20:1) as eluent, previously deactivated with a solution of *n*-hexane/Et_3N 2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 2.93 (dd, J_1 = 14.8 Hz, J_2 = 8.1 Hz, 1H), 3.10 (dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H), 3.76 (s, 3H), 4.23–4.31 (m, 2H), 4.70 (br s, 1H), 5.00 (d, J = 11.4 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 5.43–5.57 (m, 2H), 6.36 (ddd, J_{HH} = 16.2 Hz, J_{HF1} = 12.9 Hz, J_{HF2} = 11.2 Hz, 1H), 6.77 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.94 (dt, J_{HH} = 16.2 Hz, J_{HF} = 2.4 Hz, 1H), 7.33–7.39 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 33.0, 55.5, 62.5, 70.3 (t, $^2J_{CF}$ = 26.7 Hz), 114.3, 119.3, 120.6 (t, ^2JCF = 24.7 Hz), 120.6 (t, $^1J_{CF}$ = 249.5 Hz), 120.9 (d, $^5J_{CF}$ = 2.3 Hz), 127.2, 128.7, 129.0, 131.5, 134.5, 135.1 (t, $^3J_{CF}$ = 9.5 Hz), 137.6, 154.0, 170.5. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −101.57 (ddd, J_{FF} = 241.1 Hz, J_{FH1} = 11.1 Hz, J_{FH2} = 2.5 Hz, 1F), −103.14 (dd, J_{FF} = 240.9 Hz, J_{FH} = 12.9 Hz, 1F). HRMS calc. for $C_{23}H_{25}NO_3F_2$: 401.1802, found: 401.1820.

4.4.2. (E)-Ethyl 3,3-difluoro-2-(4-methoxyphenylamino)-2-(2-methylallyl)-5-phenylpent-4-enoate (9b)

By means of the general procedure previously described [4], **9b** was obtained from **8a** (35 mg) as a colorless oil (36 mg) in 89% yield after flash chromatography with hexane:ethyl acetate (20:1) as eluent, previously deactivated with a solution of *n*-hexane/Et_3N 2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3H), 1.53 (br s, 3H), 2.90 (dd, J_1 = 28.2 Hz, J_2 = 16.2 Hz, 2H), 3.65 (s, 3H), 4.12–4.23 (m, 2H), 4.66 (br s, 1H), 4.69 (br s, 2H), 6.18 (dt, J_{HH} = 16.1 Hz, J_{HF} = 12.0 Hz, 1H), 6.66 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.80 (dt, J_{HH} = 16.2 Hz, J_{HF} = 2.4 Hz, 1H), 7.22–7.26 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 24.5, 34.9, 55.5, 62.5, 69.7 (t, $^2J_{CF}$ = 26.3 Hz), 114.2, 120.2, 120.6 (t, $^2J_{CF}$ = 25.2 Hz), 120.9 (t, $^1J_{CF}$ = 255.7 Hz), 127.2, 128.7, 129.0, 134.7, 135.0 (t, $^3J_{CF}$ = 9.3 Hz), 138.1, 139.8, 153.5, 170.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −101.06 (ddd, J_{FF} = 240.0 Hz, J_{FH1} = 11.7 Hz, J_{FH2} = 2.4 Hz, 1F), −102.00 (ddd, J_{FF} = 240.1 Hz, J_{FH1} = 12.3 Hz, J_{FH2} = 1.8 Hz, 1F). HRMS calc. for $C_{24}H_{27}NO_3F_2$: 415.1959, found: 415.1960.

4.4.3. (E)-Benzyl 2-allyl-3,3-difluoro-2-(4-methoxyphenylamino)-5-phenylpent-4-enoate (9c)

By means of the general procedure previously described [4], **9c** was obtained from **8b** (40 mg) as a colorless oil (37 mg) in 85% yield after flash chromatography with hexane:diethyl ether (20:1) as eluent, previously deactivated with a solution of *n*-hexane/Et_3N 2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (dd, J_1 = 15.2 Hz, J_2 = 7.9 Hz, 1H), 3.01 (dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H), 3.66 (s, 3H), 4.58 (br s, 1H), 4.85 (d, J = 17.7 Hz, 1H), 4.87 (d, J = 10.5 Hz, 1H), 5.08 (d, J = 12 Hz, 1H), 5.19 (d, J = 12 Hz, 1H), 5.33–5.47 (m, 1H), 6.17 (dt, J_{HH} = 16.2 Hz, J_{HF} = 12.6 Hz, 1H), 6.66 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 6.73–6.79 (m, 3H), 7.17–7.23 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.2, 55.5, 68.3, 70.5 (t, $^2J_{CF}$ = 26.8 Hz), 114.3, 119.4, 120.4 (t, $^2J_{CF}$ = 24.8 Hz), 120.6 (t, $^1J_{CF}$ = 253.8 Hz), 120.9, 127.2, 128.5, 128.6, 128.6, 129.0, 131.4, 134.6, 134.7, 135.3 (t, $^3J_{CF}$ = 9.4 Hz), 137.6, 154.1, 170.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −101.42 (ddd, J_{FF} = 241.3 Hz, J_{FH1} = 11.5 Hz, J_{FH2} = 2.3 Hz, 1F), −102.63 (dd, J_{FF} = 241.4 Hz, J_{FH} = 12.6 Hz, 1F). HRMS calc. for $C_{28}H_{27}NO_3F_2$: 463.1959, found: 463.1957.

4.4.4. (E)-Benzyl 3,3-difluoro-2-(4-methoxyphenylamino)-2-(2-methylallyl)-5-phenylpent-4-enoate (9d)

By means of the general procedure previously described [4], **9d** was obtained from **8b** (38 mg) as a colorless oil (34 mg) in 80% yield after flash chromatography with hexane:diethyl ether (20:1) as eluent, previously deactivated with a solution of *n*-hexane/Et_3N 2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 3H), 2.90 (dd, J_1 = 24.6 Hz, J_2 = 16.2 Hz, 2H), 3.65 (s, 3H), 4.64 (br s, 1H), 4.68 (br s, 2H), 5.06 (d, J = 12.1 Hz, 1H), 5.20 (d, J = 12.1 Hz, 1H), 6.08 (dt, J_{HH} = 16.1 Hz, J_{HF} = 12.1 Hz, 1H), 6.65 (d, J = 9.1 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.67–6.74 (m, 1H), 7.11–7.15 (m, 2H), 7.19–7.22 (m, 3H), 7.26 (s, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.0, 35.1, 55.5, 68.2, 70.0 (t, $^2J_{CF}$ = 26.3 Hz), 114.2, 114.4, 120.3 (t, $^5J_{CF}$ = 2.5 Hz), 120.4 (t, $^2J_{CF}$ = 24.8 Hz), 120.9 (t, $^1J_{CF}$ = 255.2 Hz), 127.2, 128.5, 128.5, 128.6, 129.0, 134.6, 135.1 (t, $^3J_{CF}$ = 8.8 Hz), 137.9, 139.8, 153.6, 170.6. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −101.17 (d, J_{FH} = 2.1 Hz, 1F), −101.21 (d, J_{FH} = 2.1 Hz, 1F). HRMS calc. for $C_{29}H_{29}NO_3F_2$: 477.2115, found: 477.2112.

4.4.5. (S,E)-2-(Trimethylsilyl)ethyl 2-allyl-3,3-difluoro-2-[(R)-2-methoxy-1-phenylethylamino]-5-phenylpent-4-enoate [(S)-9e]

By means of the general procedure previously described [4], (*S*)-**9e** was obtained from **8c** (150 mg) as a colorless oil (152 mg) in 92% yield after flash chromatography with hexane:ethyl acetate (20:1) as eluent, previously deactivated with a solution of *n*-hexane/Et_3N 2%. $[\alpha]_D^{25}$ = −4.53 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.87–0.93 (m, 2H), 2.46 (dd, J_1 = 14.7 Hz, J_2 = 6.3 Hz, 1H), 2.68 (dd, J_1 = 14.7 Hz, J_2 = 7.5 Hz, 1H), 2.93 (s, 1H), 3.33 (s, 3H), 3.44–3.55 (m, 2H), 3.97–4.12 (m, 2H), 4.32 (br s, 1H), 4.89 (d, J = 7.8 Hz, 1H), 4.91 (d, J = 18.3 Hz, 1H), 5.48–5.61 (m, 1H), 6.44 (dt, J_{HH} = 15.9 Hz, J_{HF} = 12.3 Hz, 1H), 6.88 (dt, J_{HH} = 15.9 Hz, J_{HF} = 2.4 Hz, 1H), 7.23–7.36 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −1.7, 17.2, 34.6, 56.5, 58.9, 63.9, 69.8 (t, $^2J_{CF}$ = 24.7 Hz), 77.9, 118.2, 121.2 (t, $^2J_{CF}$ = 24.1 Hz), 121.5 (t, $^1J_{CF}$ = 255.0 Hz), 127.1, 127.2, 127.7, 128.1, 128.6, 128.8, 132.6, 134.6 (t, $^3J_{CF}$ = 9.6 Hz), 135.0, 142.7, 170.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −98.87 (dd, J_{FF} = 247.9 Hz, J_{FH} = 12.7 Hz, 1F), −101.86 (J_{FF} = 246.8 Hz, J_{FH} = 11.9 Hz, 1F). HRMS calc. for $C_{29}H_{40}SiNO_3F_2$: 502.2589, found: 502.2573.

4.4.6. (S,E)-2-(Trimethylsilyl)ethyl 3,3-difluoro-2-((R)-2-methoxy-1-phenylethylamino)-2-(2-methylallyl)-5-phenylpent-4-enoate [(S)-9f]

By means of the general procedure previously described [4], (*S*)-**9f** was obtained from **8c** (30 mg) as a colorless oil (29 mg) in 86% yield after flash chromatography with hexane:ethyl acetate (30:1) as eluent, previously deactivated with a solution of *n*-hexane/Et_3N 2%. $[\alpha]_D^{25}$ = −68.35 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.97 (t, J = 8.7 Hz, 2H), 1.48 (s, 3H), 2.25 (d, J = 15.6 Hz, 1H), 2.65 (d, J = 15.6 Hz, 1H), 2.87 (br s, 1H), 3.29 (s, 3H), 3.54 (d, J = 6 Hz, 2H), 4.08–4.25 (m, 2H), 4.36 (d, J = 4.2 Hz, 1H), 4.75 (s, 2H), 6.15–6.29 (m, 1H), 6.77 (dt, J_1 = 16.2 Hz, J_2 = 2.1 Hz, 2H), 7.22–7.32 (m,

10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −1.6, 17.2, 23.7, 38.4, 56.7, 58.9, 69.0 (t, $^2J_{CF}$ = 24.6 Hz), 78.2, 114.3, 121.5 (t, $^2J_{CF}$ = 24.0 Hz), 121.9 (t, $^1J_{CF}$ = 257.0 Hz), 126.8, 127.2, 127.8, 127.9, 128.5, 128.7, 134.3 (t, $^3J_{CF}$ = 9.7 Hz), 135.1, 139.9, 143.4, 171.6. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −96.69 (dd, J_{FF} = 248.2 Hz, J_{FH} = 11.4 Hz, 1F), −102.36 (dd, J_{FF} = 248.5 Hz, J_{FH} = 13.0 Hz, 1F). HRMS calc. for $C_{29}H_{40}SiNO_3F_2$: 516.2745, found: 516.2755.

4.4.7. (E)-2-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl) dimethylsilyl]ethyl 2-allyl-3,3-difluoro-2-(4-methoxyphenylamino)-5-phenylpent-4-enoate (15a)

By means of the general procedure previously described [4], **15a** was obtained from **14** (100 mg) as a colorless oil (65 mg) in 60% yield after fluorous solid-phase extraction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.57–0.62 (m, 2H), 1.03–1.06 (m, 2H), 1.53–1.64 (m, 2H), 1.99–2.16 (m, 2H), 2.92 (dd, J_1 = 15.0 Hz, J_2 = 8.1 Hz, 1H), 3.09 (dd, J_1 = 15.0 Hz, J_2 = 6.0 Hz, 1H), 3.75 (s, 3H), 4.20–4.34 (m, 2H), 4.68 (s, 1H), 4.99 (d, J = 11.9 Hz, 2H), 5.43–5.56 (m, 1H), 6.35 (ddd, J_{HH} = 16.2 Hz, J_{HF1} = 12.9 Hz, J_{HF2} = 11.1 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 6.92 (dt, J_{HH} = 16.2 Hz, J_{HF} = 2.4 Hz, 1H), 7.31–7.39 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −3.6, 14.7, 15.0, 15.9, 33.1, 34.4 (t, $^2J_{CF}$ = 22.3 Hz), 55.5, 64.7, 70.2 (t, $^2J_{CF}$ = 26.5 Hz), 114.3, 119.3, 120.6 (t, $^2J_{CF}$ = 24.7 Hz), 120.9, 127.2, 128.7, 129.1, 131.6, 134.7, 135.1 (t, $^3J_{CF}$ = 10.9 Hz), 137.8, 154.0, 170.6 (the signals from the CF_2 and C_8F_{17} groups were obscured due to their low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.42 (t, J = 9.9 Hz, 3F), −101.61 (ddd, J_{FF} = 240.9 Hz, J_{FH1} = 11.0 Hz, J_{FH2} = 2.3 Hz, 1F), −103.29 (dd, J_{FF} = 240.9 Hz, J_{FH} = 12.7 Hz, 1F), −115.09 (t, J = 14.4 Hz, 2F), −122.57 (br s, 6F), −123.57 (br s, 2F), −124.28 (br s, 2F), −126.77–(−126.82) (m, 2F). HRMS calc. for $C_{36}H_{36}SiNO_3F_{19}$: 920.2239, found: 920.2226.

4.4.8. (E)-2-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl) dimethylsilyl] ethyl 3,3-difluoro-2-(4-methoxyphenylamino)-2-(2-methylallyl)-5-phenylpent-4-enoate (15b)

By means of the general procedure previously described [4], **15b** was obtained from **14** (100 mg) as a colorless oil (66 mg) in 60% yield after fluorous solid-phase extraction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.57–0.63 (m, 2H), 1.01–1.06 (m, 2H), 1.54–1.65 (m, 2H), 1.62 (s, 3H), 1.99–2.14 (m, 2H), 2.98 (dd, J_1 = 26.7 Hz, J_2 = 16.5 Hz, 2H), 3.75 (s, 3H), 4.19–4.36 (m, 2H), 4.76 (d, J = 9.7, 3H), 6.27 (dt, J_{HH} = 16.1 Hz, J_{FH} = 12.0 Hz, 1H), 6.75 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 6.89 (dt, J_{HH} = 16.2 Hz, J_{HF} = 2.4 Hz, 1H), 7.33 (s, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −3.6, 15.0, 15.7, 24.1, 34.4 (t, $^2J_{CF}$ = 27.9 Hz), 34.9, 55.5, 64.6, 69.7 (t, $^2J_{CF}$ = 27.9 Hz), 114.2, 120.2, 120.6 (t, $^2J_{CF}$ = 28.5 Hz), 127.2, 128.7, 129.1, 134.7, 135.0 (t, $^3J_{CF}$ = 9.6 Hz), 138.1, 139.8, 153.6, 170.9 (the signals from the CF_2 and C_8F_{17} groups were obscured due to their low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.44 (t, J = 9.9 Hz, 3F), −101.22 (ddd, J_{FF} = 239.8 Hz, J_{FH1} = 11.7 Hz, J_{FH2} = 2.3 Hz, 1F), −102.19 (dd, J_{FF} = 240.0 Hz, J_{FH} = 12.3 Hz, 1F), −115.09 (br s, 2F), −122.57 (br s, 6F), −123.38 (br s, 2F), −124.29 (br s, 2F), −126.78 (br s, 2F). FAB-MS (m/z): 934 ($M+1^+$, 4), 850 (7), 780 (42), 752 (100).

4.5. Preparation of the fluorinated cyclic dialkylated α-amino esters 10 and 16

4.5.1. Ethyl 2,2-difluoro-1-(4-methoxyphenylamino)cyclopent-3-enecarboxylate (10a)

By means of the general procedure previously described [4], **10a** was obtained from **9a** (64 mg) as a brown oil (38 mg) in 80% yield after flash chromatography with hexane:ethyl acetate (20:1) as eluent, previously deactivated with a solution of n-hexane/Et_3N 2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3H), 2.84 (ddd, J_1 = 17.6 Hz, J_2 = 8.4 Hz, J_3 = 2.4 Hz, 1H), 3.55–3.66 (m, 1H), 3.67 (s, 3H), 4.15–4.25 (m, 2H), 4.58 (br s, 1H), 5.84 (dt, J_1 = 6.0 Hz, J_2 = 2.1 Hz, 1H), 6.42 (dd, J_1 = 5.9 Hz, J_2 = 2.3 Hz, 1H), 6.55 (dd, J_1 = 6.6 Hz, J_2 = 2.4 Hz, 2H), 6.76 (dd, J_1 = 6.6 HZ, J_2 = 2.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4, 40.2, 56.0, 62.6, 69.8, 115.1, 116.9, 124.7 (t, $^2J_{CF}$ = 25.9 Hz), 142.1 (t, $^3J_{CF}$ = 11.7 Hz), 138.6, 153.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −90.72 (ddd, J_{FF} = 256.8 Hz, J_{FH1} = 8.4 Hz, J_{FH2} = 3.9 Hz, 1F), −105.59 (dd, J_{FF} = 256.8 Hz, J_{FH} = 6.6 Hz). HRMS calc. for $C_{15}H_{17}NO_3F_2$: 297.1176, found: 297.1163.

4.5.2. Ethyl 2,2-difluoro-1-(4-methoxyphenylamino)-4-methylcyclopent-3-enecarboxylate (10b)

By means of the general procedure previously described [4], **10b** was obtained from **9b** (33 mg) as a brown oil (16 mg) in 65% yield after flash chromatography with hexane:ethyl acetate (20:1) as eluent, previously deactivated with a solution of n-hexane/Et_3N 2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3H), 1.88 (br s, 3H), 2.70 (d, J = 17.2 Hz, 1H), 3.53 (d, J = 17.2 Hz, 1H), 3.74 (s, 3H), 4.13–4.24 (m, 2H), 4.60 (br s, 1H), 5.52 (d, J = 1.6 Hz, 1H), 6.54 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 17.3, 43.7, 55.6, 62.0, 70.3 (dd, $^2J_{CF1}$ = 28.1 Hz, $^2J_{CF2}$ = 16.4 Hz), 114.7, 116.4, 118.7 (dd, $^2J_{CF1}$ = 28.6 Hz, $^2J_{CF2}$ = 25.7 Hz), 130.2 (dd, $^1J_{CF1}$ = 255.6, $^1J_{CF2}$ = 244.6 Hz), 138.3, 153.2, 170.6. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −88.13 (d, J_{FF} = 253.6 Hz, 1F), −103.10 (d, J_{FF} = 253.3 Hz, 1F). HRMS calc. for $C_{16}H_{19}NO_3F_2$: 311.1333, found: 311.1339.

4.5.3. Benzyl 2,2-difluoro-1-(4-methoxyphenylamino) cyclopent-3-enecarboxylate (10c)

By means of the general procedure previously described [4], **10c** was obtained from **9c** (35 mg) as a brown oil (23 mg) in 86% yield after flash chromatography with hexane:ethyl acetate (20:1) as eluent, previously deactivated with a solution of n-hexane/Et_3N 2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72–2.83 (m, 1H), 3.50–3.59 (m, 1H), 3.66 (s, 3H), 4.53 (d, J = 4.1 Hz, 1H), 5.07 (dd, J_1 = 15.2 Hz, J_2 = 12.2 Hz, 2H), 5.77 (dt, J_1 = 6.0 Hz, J_2 = 2.2 Hz, 1H), 6.34 (dd, J_1 = 6.0 Hz, J_2 = 2.3 Hz, 1H), 6.43 (dd, J_1 = 6.6 Hz, J_2 = 2.2 Hz, 2H), 6.63 (dd, J_1 = 6.8 Hz, J_2 = 2.2 Hz, 2H), 7.01–7.04 (m, 2H), 7.17–7.19 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 39.9, 55.6, 67.7, 69.5 (t, $^2J_{CF1}$ = 28.2 Hz, $^2J_{CF2}$ = 16.1 Hz), 114.7, 116.4, 124.2, 128.1, 130.0 (dd, $^1J_{CF1}$ = 259.3 Hz, $^1J_{CF2}$ = 247.8 Hz), 133.4, 135.1, 141.6 (t, $^3J_{CF}$ = 11.5 Hz), 153.3, 170.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −89.80 (ddd, J_{FF} = 256.7 Hz, J_{FH1} = 8.6 Hz, J_{FH2} = 3.4 Hz), −105.26 (dtd, J_{FF} = 256.7 Hz, J_{FH1} = 4.3 Hz, J_{FH2} = 2.6 Hz). HRMS calc. for $C_{20}H_{19}NO_3F_2$: 359.1333, found: 359.1337.

4.5.4. Benzyl 2,2-difluoro-1-(4-methoxyphenylamino)-4-methylcyclopent-3-enecarboxylate (10d)

By means of the general procedure previously described [4], **10d** was obtained from **9d** (35 mg) as a brown oil (22 mg) in 67% yield after flash chromatography with hexane:ethyl acetate (20:1) as eluent, previously deactivated with a solution of n-hexane/Et_3N 2%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (br s, 3H), 2.64 (dd, J_1 = 17.1 Hz, J_2 = 7.8 Hz, 1H), 3.48 (d, J = 16.8 Hz, 1H), 3.67 (s, 3H), 4.56 (d, J = 4.5 Hz, 1H), 5.06 (dd, J_1 = 14.7 Hz, J_2 = 12.3 Hz, 2H), 5.45 (s, 1H), 6.43 (d, J = 9.0 Hz, 2H), 6.64 (d, J = 9.0 Hz, 2H), 7.02 (dd, J_1 = 6.5 Hz, J_2 = 3.0 Hz, 2H), 7.18 (dd, J_1 = 5.3 Hz, J_2 = 1.6 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.3, 43.8, 55.6, 67.7, 70.4 (dd, $^2J_{CF1}$ = 28.3 Hz, $^2J_{CF2}$ = 16.4 Hz), 114.7, 116.3, 118.7 (dd, $^2J_{CF1}$ = 28.8 Hz, $^2J_{CF2}$ = 25.7 Hz), 128.1, 128.3, 130.2 (dd, $^1J_{CF1}$ = 257.4 Hz, $^1J_{CF2}$ = 246.2 Hz), 135.2, 138.3, 153.2, 170.6. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −87.92 (d, J_{FF} = 253.4 Hz, 1F), −103.48 (d, J_{FF} = 253.4 Hz, 1F). HRMS calc. for $C_{20}H_{19}NO_3F_2$: 373.1489, found: 373.1489.

*4.5.5. (S)-2-(Trimethylsilyl)ethyl 2,2-difluoro-1-((R)-2-methoxy-1-phenylethylamino) cyclopent-3-enecarboxylate [(S)-**10e**]*

By means of the general procedure previously described [4], (*S*)-**10e** was obtained from (*S*)-**9e** (110 mg) as a brown oil (76 mg) in 88% yield after flash chromatography with hexane:ethyl acetate (20:1) as eluent, previously deactivated with a solution of *n*-hexane/Et_3N 2%. $[\alpha]_D^{25} = -58.6$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.75 (ddd, $J_1 = 13.7$ Hz, $J_2 = 11.4$ Hz, $J_3 = 5.6$ Hz, 1H), 0.86 (ddd, $J_1 = 13.7$ Hz, $J_2 = 11.6$ Hz, $J_3 = 6.1$ Hz, 1H), 2.43–2.53 (m, 1H), 2.94 (br s, 1H), 3.11–3.22 (m, 1H), 3.32 (s, 3H), 3.36 (dd, $J_1 = 9.8$ Hz, $J_2 = 5.3$ Hz, 1H), 3.45 (dd, $J_1 = 9.8$ Hz, $J_2 = 7.9$ Hz, 1H), 3.77 (td, $J_1 = 11.2$ Hz, $J_2 = 11.1$ Hz, $J_3 = 5.6$ Hz, 1H), 3.88 (br s, 1H), 4.05 (td, $J_1 = 11.1$ Hz, $J_2 = 11.1$ Hz, $J_3 = 6.1$ Hz, 1H), 5.83 (dt, $J_1 = 6.1$ Hz, $J_2 = 2.0$ Hz, 1H), 6.23 (dd, $J_1 = 5.8$ Hz, $J_2 = 2.7$ Hz, 1H), 7.24–7.30 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −1.6, 16.7, 37.1, 57.8, 58.9, 63.9, 71.1 (dd, $^2J_{CF1} = 27.0$ Hz, $^2J_{CF2} = 18.4$ Hz), 125.0 (dd, $^2J_{CF1} = 29.1$ Hz, $^2J_{CF2} = 24.5$ Hz), 127.4, 127.5, 128.3, 129.2 (dd, $^1J_{CF1} = 257.8$ Hz, $^1J_{CF2} = 247.7$ Hz), 141.1 (t, $^3J_{CF} = 11.8$ Hz), 142.0, 170.1. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −91.32 (ddd, $J_{FF} = 258.1$ Hz, $J_{FH1} = 7.1$ Hz, $J_{FH2} = 4.8$ Hz, 1F), −108.40 (dd, $J_{FF} = 257.8$ Hz, $J_{FH} = 2.5$ Hz, 1F). HRMS calc. for $C_{20}H_{30}SiNO_3F_2$: 398.1963, found: 398.1943.

*4.5.6. (S)-2-(Trimethylsilyl)ethyl 2,2-difluoro-1-((R)-2-methoxy-1-phenylethylamino)-4-methylcyclopent-3-enecarboxylate [(S)-**10f**]*

By means of the general procedure previously described [4], (*S*)-**10f** was obtained from (*S*)-**9f** (59 mg) as a brown oil (26 mg) in 55% yield after flash chromatography with hexane: ethyl acetate (20:1) as eluent, previously deactivated with a solution of *n*-hexane/Et_3N 2%. $[\alpha]_D^{25} = -68.85$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ −0.06 (s, 9H), 0.67–0.88 (m, 2H), 1.57 (br s, 3H), 2.20 (dd, $J_1 = 17.4$ Hz, $J_2 = 6.9$ Hz, 1H), 3.01 (d, $J = 22.8$ Hz, 2H), 3.23–3.39 (m, 2H), 3.26 (s, 3H), 3.74–3.87 (m, 2H), 4.02 (td, $J_1 = 11.0$ Hz, $J_2 = 6.2$ Hz, 1H), 5.43 (br s, 1H), 7.19–7.23 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −1.6, 16.8, 17.2, 40.9, 57.8, 58.8, 63.9, 72.1 (dd, $^2J_{CF1} = 26.9$ Hz, $^2J_{CF2} = 18.8$ Hz), 77.9, 119.5 (dd, $^2J_{CF1} = 29.1$ Hz, $^2J_{CF2} = 24.2$ Hz), 127.5, 128.3, 129.6 (dd, $^1J_{CF1} = 256.3$ Hz, $^1J_{CF2} = 247.0$ Hz), 142.1, 152.7 (t, $^3J_{CF} = 11.8$ Hz), 170.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −88.79 (ddd, $J_{FF} = 254.4$ Hz, $J_{FH1} = 11.6$ Hz, $J_{FH2} = 5.4$ Hz, 1F), −106.58 (d, $J_{FF} = 254.4$ Hz, 1F). HRMS calc. for $C_{21}H_{32}SiNO_3F_2$: 412.2119, found: 412.2104.

*4.5.7. 2-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl) dimethylsilyl]ethyl 2,2-difluoro-1-(4-methoxyphenylamino)cyclopent-3-enecarboxylate (**16a**)*

By means of the general procedure previously described [4], **16a** was obtained from **15a** (60 mg) as a brown oil (48 mg) in 90% yield after fluorous solid-phase extraction. ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.52–0.58 (m, 2H), 0.88–0.95 (m, 2H), 1.51–1.62 (m, 2H), 1.97–2.14 (m, 2H), 2.78–2.88 (m, 1H), 3.55–3.66 (m, 1H), 3.73 (s, 3H), 4.12–4.31 (m, 2H), 4.57 (d, $J = 4.3$ Hz, 1H), 5.84 (dt, $J_{HH} = 6.0$ Hz, $J_{HF} = 2.1$ Hz, 1H), 6.40–6.44 (m, 1H), 6.54 (d, $J = 8.9$ Hz, 2H), 6.76 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −3.6, 14.7 (t, $^3J_{CF} = 4.0$ Hz), 15.0, 15.5, 34.4 (t, $^2J_{CF} = 22.0$ Hz), 39.7, 55.5, 64.2, 69.3 (dd, $^2J_{CF1} = 28.2$ Hz, $^2J_{CF2} = 16.7$ Hz), 114.7, 116.4, 124.2 (dd, $^2J_{CF1} = 28.8$ Hz, $^2J_{CF2} = 25.7$ Hz), 138.1, 141.7, 153.3, 170.6 (the signals from the CF_2 and C_8F_{17} groups were obscured due to their low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.42 (t, $J = 10.0$ Hz, 3F), −90.41 (ddd, $J_{FF} = 256.8$ Hz, $J_{FH1} = 8.4$ Hz, $J_{FH2} = 3.9$ Hz, 1F), −105.42 (d, $J_{FF} = 256.8$ Hz, 1F), −115.10 (br s, 2F), −122.57 (br s, 6F), −123.38 (br s, 2F), −124.29 (br s, 2F), −126.77 (br s, 2F). HRMS calc. for $C_{28}H_{29}SiNO_3F_{19}$: 816.1569, found: 816.1561.

*4.5.8. 2-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl) dimethylsilyl]ethyl 2,2-difluoro-1-(4-methoxyphenylamino)-4-methylcyclopent-3-enecarboxylate (**16b**)*

By means of the general procedure previously described [4], **16b** was obtained from **15b** (38 mg) as a brown oil (26 mg) in 76% yield after fluorous solid-phase extraction. ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.51–0.57 (m, 2H), 0.88–0.94 (m, 2H), 1.55 (s, 3H), 1.86–1.89 (m, 3H), 1.96–2.14 (m, 2H), 2.64–2.73 (m, 1H), 3.53 (d, $J = 17.0$ Hz, 1H), 3.73 (s, 3H), 4.10–4.30 (m, 2H), 4.59 (d, $J = 4.5$ Hz, 1H), 5.52 (d, $J = 1.5$ Hz, 1H), 6.52 (d, $J = 8.9$ Hz, 2H), 6.75 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −3.6, 15.0, 15.5, 17.3, 34.4 (t, $^2J_{CF} = 21.8$ Hz), 43.7, 55.6, 64.1, 70.2 (dd, $^2J_{CF1} = 28.3$ Hz, $^2J_{CF2} = 16.5$ Hz), 99.5, 114.7, 116.3, 118.7 (dd, $^2J_{CF1} = 28.7$ Hz, $^2J_{CF2} = 25.6$ Hz), 138.2, 153.2, 170.8 (the signals from the CF_2 and C_8F_{17} groups were obscured due to their low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −81.39 (t, $J = 10.0$ Hz, 3F), −88.17 (d, $J_{FF} = 253.4$ Hz, 1F), −103.20 (d, $J_{FF} = 253.4$ Hz, 1F), −115.09 (br s, 2F), −122.56 (br s, 6F), −123.37 (br s, 2F), −124.28 (br s, 2F), −126.75 (br s, 2F). HRMS calc. for $C_{29}H_{31}SiNO_3F_{19}$: 830.1725, found: 830.1729.

4.6. Release of the amino acid functionality

*4.6.1. (S)-2,2-Difluoro-1-[(R)-2-methoxy-1-phenylethylamino] cyclopent-3-enecarboxylic acid [(−)-**12**]*

By means of the general procedure previously described [4], (−)-**12** was obtained from (*S*)-**10e** (100 mg) as a brown oil (65 mg) in 87% yield after flash chromatography with hexane:ethyl acetate (3:1) with 2% AcOH as eluent. $[\alpha]_D^{25} = -68.85$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 2.50 (d, $J = 17.3$, 1H), 2.95 (d, $J = 17.3$ Hz, 1H), 3.33 (s, 3H), 3.39 (dd, $J_1 = 9.9$ Hz, $J_2 = 4.3$ Hz, 1H), 3.51 (dd, $J_1 = 9.9$ Hz, $J_2 = 4.3$ Hz, 1H), 4.00 (dd, $J_1 = 8.8$ Hz, $J_2 = 4.3$ Hz, 1H), 5.81 (d, $J = 6.2$ Hz, 1H), 6.24 (d, $J = 6.1$ Hz, 1H), 7.05 (br s, 1H), 7.25–7.27 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 36.6, 58.6, 58.8, 71.1 (dd, $^2J_{CF1} = 25.2$ Hz, $^2J_{CF2} = 19.5$ Hz), 76.6, 124.8 (t, $^2J_{CF} = 26.6$ Hz), 127.5, 128.2, 128.6, 129.2 (dd, $^1J_{CF1} = 254.6$ Hz, $^2J_{CF2} = 251.4$ Hz), 139.4, 141.7 (t, $^3J_{CF} = 11.7$ Hz), 171.9. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −95.70 (d, $J_{FF} = 255.7$ Hz, 1F), −100.12 (d, $J_{FF} = 255.7$ Hz, 1F). HRMS calc. for $C_{15}H_{17}NO_3F_2$: 298.1255, found: 298.1256.

*4.6.2. (S)-1-Amino-2,2-difluorocyclopentanecarboxylic acid [(−)-**5**]*

By means of the general procedure previously described [4], (−)-**5** was obtained from (−)-**12** (38 mg) as white solid (10 mg) in 47% yield after filtration and washing with dichloromethane and diethyl ether. $[\alpha]_D^{25} = -6.57$ (*c* 1.0, H_2O). ^1H NMR (400 MHz, DMSO-d_6) δ 1.67–1.85 (m, 4H), 2.08–2.21 (m, 1H), 2.33–2.45 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.0, 32.9, 65.6, 128.2, 169.5. ^{19}F NMR (282.4 MHz, DMSO-d_6) δ −111.80–(−114.08) (m, 1F), −119-10 (d, $J = 228.5$ Hz, 1F).

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