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Fluoroalkyl substituted (*Z*)-dehydro α-amino ester as a building block for the fluorine-containing cyclopropyl α-amino esters and dihydrooxazole

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ABSTRACT

Multi-functionalized β-trifluoromethyl and β-difluoromethyl substituted (*Z*)-α,β-dehydro α-amino esters have been successfully prepared from *N*-protected fluorinated threonine ester. Applications of this new fluorine-containing building block to the synthesis of biologically important fluorinated cylcopropyl α-amino esters and dihydrooxazole ester have also been reported.

1. Introduction

Development of fluorine-containing building blocks for the introduction of fluorine or a fluorinated moiety into organic molecule is highly advantageous in pharmaceutical and agrochemical researches. The discovery of multi-functionalized fluorine-containing building blocks still represents a great challenge in organic synthesis [1].

Herein, we wish to report a facile and stereoselective route to the preparation of multi-functionalized β-fluoroalkyl (*Z*)-α,β-dehydro amino ester which has been subjected to the pilot study for the synthesis of biologically interested β-fluoroalkyl substituted cyclopropyl α-amino esters and trifluoroethyl substituted dihydrooxazole ester. Preliminary evaluation of this newly excogitated multi-functionalized fluorine-containing building block reveals its potential synthetic value.

2. Results and discussion

The route to the β-fluoroalkyl substituted (*Z*)-α,β-dehydro amino ester (**7** and **9**) was started from fluorinated *syn*-*N*,*N*-dibenzyl threonine ethyl ester **4**, which were stereoselectively synthesized according to the reported procedures for trifluoromethyl substituent (**4a**) [2]. Protection of hydroxyl group of **4a** with Tos group led to the formation of *syn*-**8**, which was further transformed into *N*-dibenzyl protected (*Z*)-α,β-dehydro amino ester (**9**) in excellent yield via a β-elimination of TsOH in the presence of NaH. Other bases which were used for this elimination, such as Et_3N, K_2CO_3 and KOH either provided poor yields or resulted in decomposition of product, and were not suitable for this elimination (Path B, Scheme 1). The exchange of *N*-protection group of **4** from benzyl group to benzoyl group was succeeded through the deprotection of *N*-benzyl group of **4** and followed by addition of benzoyl chloride under basic condition to afford the *N*,*O*-dibenzoyl protected **6** in excellent yields [3]. Subsequential β-elimination of $PhCO_2H$ of **6a** and **6b** by using the bases of *t*-BuOK and DBU resulted in the formations of desired *N*-benzoyl protected trifluoromethyl and difluoromethyl substituted (*Z*)-α,β-dehydro amino ester, respectively (Path A, Scheme 1). *t*-BuOK was once employed as base for accomplishment of β-elimination of both **6a** and **6b**, however, good yield was only observed in the elimination of **6a**. The elimination of difluoromethyl substituent (**6b**) with *t*-BuOK or NaH encountered partial decomposition of **6b** (mainly due to the α-elimination of HF of difluoromethyl group by strong base), and significantly lowered the yield of **7b**.

Other bases were also examined and as a result, DBU was selected as an alternative base to minimize this unexpected side reaction, and the moderate yield of **7b** was obtained under this

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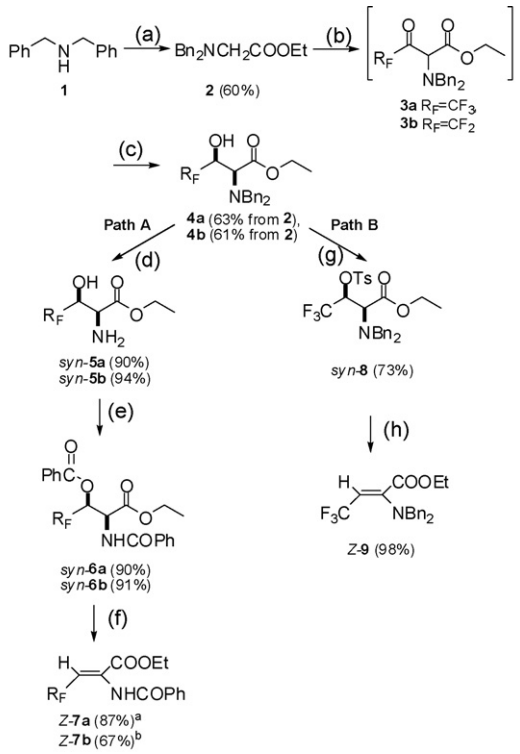


(a) ethyl chloroacetic acetate, ethanol, reflux, overnight; (b) NaH, fluorinated ethyl acetic acetate, THF, reflux, 5h; (c) KBH_4, THF, r.t., over night; (d) H_2, Pd/C, r.t, 3h.; (e) benzoyl chloride, Et_3N, 0°C, 30min; (f) a: ^{t}-BuOK, THF, -18°C, 30min; b: DBU, CH_2Cl_2, -18°C, 1h.; (g) TsCl, pyridine, r.t., 18h. (h) NaH, THF, 0°C, 6h.

Scheme 1. Stereoselective route to fluorinated (*Z*)-α,β-dehydro α-amino esters.

reaction condition. The optimization of β-elimination reaction of **6a** by base was also performed. Results showed that elimination by using organic base, such as *t*-BuOK, DBU, DABCO and Et_3N provided a good yield. Lower reaction temperature was propitious to better stereoselectivity to form *Z* product **7a** (Table 1).

It is known that cyclopropyl α-amino acids are of broad interest as biological probes, enzyme inhibitors, and conformationally constrained analogues of native amino acids [4]. However, the bioactivity and its potential pharmaceutical value of fluoroalkyl substituted cyclopropyl amino acids are less studied due to the lack of efficient way to prepare. This encouraged us to explore the new route to synthesize β-fluoroalkyl substituted cyclopropyl amino acids through the fluorinated building block **9**. However, the initial assignment of cyclopropanation of (*Z*)-α,β-dehydro amino ester **9** with sulfoxonium ylide or diazomethane was failed. The reason for this failure is possibly deduced to the steric hindrances of two

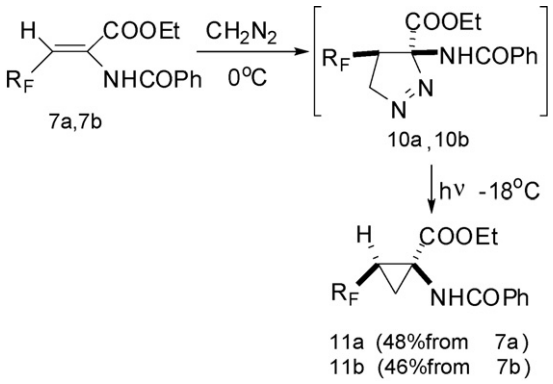
Table 1
Synthesis of trifluoromethyl α,β-dehydroamino esters **7a** by using different bases

Entry	Base	Solvent	Temperature	Time	Yield[a]	*Z*:*E*[b]
1	Pyridine	CH_2Cl_2	RT	24 h	–	–
2	Et_3N	CH_2Cl_2	RT	24 h	78%[c]	1.4:1
3	KOH	CH_2Cl_2	RT	24 h	Trace	–
4	K_2CO_3	CH_2Cl_2	RT	24 h	Trace	–
5	DABCO	CH_2Cl_2	RT	24 h	80%[c]	1.96:1
6	DBU	CH_2Cl_2	RT	1 h	84%[c]	1.41:1
7	DBU	CH_2Cl_2	−18 °C	1 h	70%	Z only
8	NaH	THF	−18 °C	45 min	72%	Z only
9	t-BuOK	THF	−18 °C	30 min	87%	Z only

[a] The yields listed in this table are isolated yields.

[b] The ratio of *Z* and *E* form was determined by ^{19}F NMR.

[c] Total yield for *Z* and *E* product.



Scheme 2. Synthesis of fluorinated cyclopropyl amino esters **11**.

bulky *N*-benzyl groups of **9**. This hypothesis was supported by the successful cyclopropanation of less steric hindered **7** with diazomethane under same reaction condition. During the cyclopropanation process, the pyrazoline intermediate **10** was scheduled to be formed at initial step, the crude **10** (without purification) was then subjected to photolysis by using a 125-W medium-pressure mercury lamp as a photo source and afforded desired *Z*-cylcopropyl α-amino ester **11** in moderate yields (Scheme 2) [5].

The *Z* configuration of **11** was determined by NOE correlations. It was pointed out that the hydrogen linked to nitrogen produced NOE on one of the protons of the methylene group on the ring instead of the proton neighbored to the fluoroalkyl group, which is in agreement with the proposed configuration (Fig. 1). As cycloaddition of diazomethane to a dehydroamino ester followed by nitrogen extrusion has previously been proved to produce the cyclopropane with the same configuration as the starting olefin, therefore, the *Z* geometry of the double bond of **7** was established according to the configuration of cyclopropyl amino esters.

Interesting result was observed while **7a** was treated with sulfoxonium ylide as an alkylidene transfer reagent in DMSO at RT [6]. Reaction did not yield the desired cylcopropyl product **11a**, instead, the dihydrooxazole ester product **12** was formed as only one product (Scheme 3). The X-ray crystallographic analysis confirmed the structure of **12** (Fig. 2) [7].

The yield was not satisfied currently. Preliminary study showed that the reaction which carried out at ambient temperature was quite clean but more than 50% of **7a** remained even with longer reaction time. Increase of reaction temperature to 50 °C could help the consumption of starting materials whereas the reaction became much more complicated. A possible mechanism of its formation was proposed in Scheme 4.

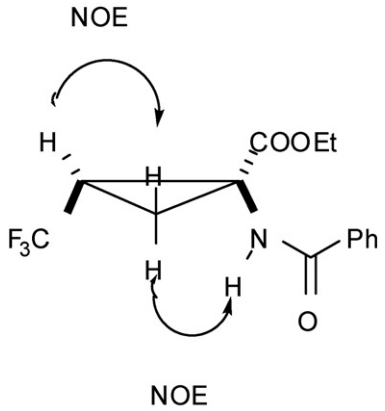
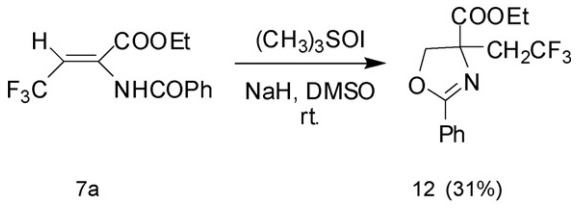


Fig. 1. The NOE correlation of compound **11a**.



Scheme 3. Synthesis of dihydrooxazole ester **12**.

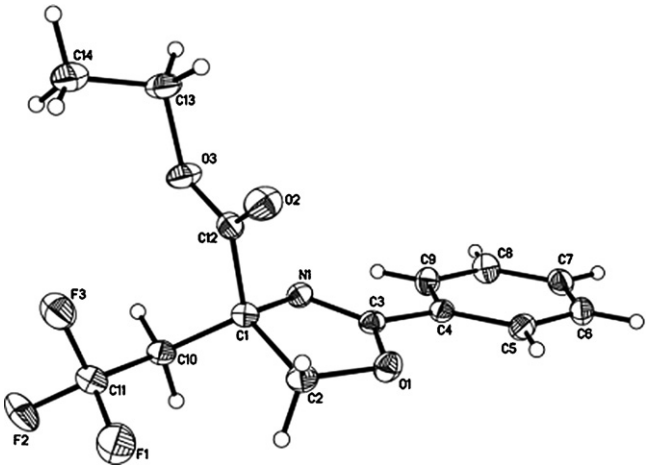
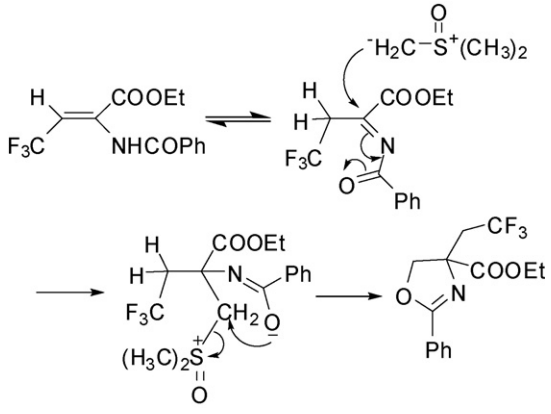


Fig. 2. X-ray crystallography of **12**.



Scheme 4. . Proposed mechanism of the formation of **12**.

It is worth to point out that the β-trifluoromethyl and β-difluoromethyl substituted (*Z*)-α,β-dehydro amino esters **7** and **9** could also be represented as an important precursor of β-trifluoromethyl and β-difluoromethyl substituted α-amino acid through a known reduction process [8]. The dihydrooxazole ester **12** could also be an important precursor of α-fluoroalkyl substituted serines or threonines [9].

3. Conclusions

The multi-functionalized β-trifluoromethyl and β-difluoromethyl substituted (*Z*)-α,β-dehydro amino esters have been successfully prepared as new fluorine-containing building block from *N*-protected fluorinated threonine esters. Preliminary application of this building block to the synthesis of biologically important fluorinated *Z*-cylcopropyl α-amino esters and dihydrooxazole ester were also succeeded. The optimization of reaction conditions is currently under investigation.

4. Experimental

4.1. General procedure for synthesis of fluorinated syn-3-benzamido-4-ethoxy-4-oxobutan-2-yl benzoate (6)

To an ice-chilled mixture of fluorinated *syn*-ethyl 2-amino-3-hydroxybutanoate (**5**) (2.49 mmol) and triethylamine (0.72 mL, 4.98 mmol) in dichloromethane (20 mL) was added benzoyl chloride (0.58 mL, 4.98 mmol) in drop wise. The reaction was completed after about 30 min. The solution was quenched with saturated NH_4Cl (aq) (5 mL), extracted with dichloromethane (3 mL × 15 mL), washed with saturated brine (5 mL). The collected extraction was then dried over anhydrous magnesium sulfate and evaporated to dryness. The crude product was purified by column chromatography.

4.1.1. syn-3-Benzamido-4-ethoxy-1,1,1-trifluoro-4-oxobutan-2-yl benzoate (6a)

6a was obtained as a white solid in 90% yield. mp: 90–92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.31 (t, 3H, J = 7.0 Hz); 4.23–4.29 (m, 2H); 5.57 (dd, 1H, J = 9.0, 2.5 Hz); 6.13 (dq, 1H, J = 6.5, 2.5 Hz); 6.76 (d, 1H, J = 9.0 Hz); 7.46–8.07 (m, 10H). ^{19}F NMR (470 MHz, $CDCl_3$) δ = −74.18 (d, 3F, $^3J_{H-C-C-F}$ = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.13; 51.04; 63.10; 69.59 (q, $^2J_{C-C-F}$ = 32.5 Hz); 122.89 (q, $^1J_{C-F}$ = 280.0 Hz); 127.41; 127.88; 128.90; 128.97; 130.31; 132.35; 133.59; 134.51; 164.28; 167.47; 168.28. IR (KBr) ν = 3294; 3068; 1747; 1642; 1259; 1186; 1144; 712; 692 cm^{-1}.

4.1.2. syn-3-Benzamido-4-ethoxy-1,1-difluoro-4-oxobutan-2-yl benzoate (6b)

6b was obtained as a white solid in 91% yield. mp: 125–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.32 (t, 3H, J = 7.2 Hz); 4.25–4.32 (m, 2 H); 5.36 (dd, 1H, J = 8.5, 2.5 Hz); 5.79–5.85 (m, 1H); 6.14 (td, 1H, J = 54.0, 5.0 Hz); 6.88 (d, 1H, J = 8.5 Hz); 7.45–7.81 (m, 10 H). ^{19}F NMR (470 MHz, $CDCl_3$) δ = −126.75(ddd, 1F, $^2J_{F-C-F}$ = 294.2 Hz, $^2J_{H-C-F}$ = 54.0 Hz, $^3J_{H-C-C-F}$ = 10.3 Hz); −128.89 (ddd, 1F, $^2J_{F-C-F}$ = 294.2 Hz, $^2J_{H-C-F}$ = 54.0 Hz, $^3J_{H-C-C-F}$ = 10.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.02; 51.48 (dd, $^3J_{C-C-C-F}$ = 3.8, $^3J_{C-C-C-F}$ = 3.8 Hz); 62.86; 71.80 (dd, $^2J_{C-C-F}$ = 29.4 Hz, $^2J_{C-C-F}$ = 23.1 Hz); 112.96 (dd, $^1J_{C-F}$ = 245.0 Hz, $^1J_{C-F}$ = 242.5 Hz); 127.26; 128.36; 128.69; 128.76; 130.01; 132.24; 133.27; 134.00; 164.83; 167.63; 168.81. IR (KBr) ν = 3308; 3064; 1740; 1644; 1262; 1142; 1095; 1067; 707; 696 cm^{-1}.

4.2. Procedure for synthesis of (Z)-ethyl 2-benzamido-4,4,4-trifluorobut-2-enoate (7a)

The *syn*-3-benzamido-4-ethoxy-1,1,1-trifluoro-4-oxobutan-2-yl benzoate (**6a**) (300 mg, 0.73 mmol) and potassium *t*-butoxide (165 mg, 1.47 mmol) were dissolved in dry THF (20 mL) under nitrogen. The mixture was stirred at −18 °C (under ice salt bath) for 30 min. The reaction was quenched with saturated brine (5 mL), extracted with dichloromethane (3 mL × 10 mL). The collected extraction was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give a yellow solid. The crude product was recrystallized from ethyl acetate to afford a white solid; yield: 182 mg (87%). mp: 80–82 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.35 (t, 3H, J = 7.2 Hz); 4.35 (q, 2H, J = 7.2 Hz); 6.07 (q, 1H, J = 8.0 Hz), 7.49–7.86 (m, 5H); 7.99 (s, 1H). ^{19}F NMR (470 MHz, $CDCl_3$) δ = −59.44 (d, 3F, $^3J_{H-C-C-F}$ = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.08; 63.01; 111.79 (q, $^2J_{C-C-F}$ = 35.0 Hz); 122.68 (q, $^1J_{C-F}$ = 268.8 Hz); 127.78; 129.07; 132.30; 133.11; 135.25 (q, $^3J_{C-C-C-F}$ = 5.0 Hz); 163.16; 165.74. IR (KBr) ν = 3270; 3087; 1732; 1680; 1654; 1510; 1259; 1189; 1116; 712; 693 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{13}H_{13}F_3NO_3$ $[M+H]^+$: 288.0842. Found: 288.0838.

4.3. Procedure for synthesis of (Z)-ethyl 2-benzamido-4,4,4-trifluorobut-2-enoate (7b)

To a solution of 3-benzamido-4-ethoxy-1,1-difluoro-4-oxobutan-2-yl benzoate (**6b**) (300 mg, 0.77 mmol) in dichloromethane (10 mL) was added DBU (0.23 ml, 1.54 mmol). The mixture was stirred at −18 °C (under ice salt bath) for 1 h and then quenched with saturated NH_4Cl (aq) (3 mL), extracted with dichloromethane (3 mL × 8 mL) and washed with saturated brine (5 mL). The collected dichloromethane extraction was evaporated to dryness under vacuum after dried over anhydrous magnesium sulfate. The crude product was purified by column chromatography to give a white solid; yield: 139 mg (67%). mp: 62–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 1.38 (t, 3H, J = 7.0 Hz); 4.35 (q, 2H, J = 7.0 Hz); 6.49 (td, 1H, J = 10.8, 4.5 Hz); 6.79 (td, 1H, J = 55.0, 4.5 Hz,) ^{19}F NMR (470 MHz, $CDCl_3$) δ = −115.94 (dd, 2F, $^2J_{H-C-F}$ = 55.0 Hz, $^3J_{H-C-C-F}$ = 10.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ=14.12; 63.18; 112.81 (t, $^1J_{C-F}$ = 232.5 Hz); 119.56 (t, $^2J_{C-C-F}$ = 28.8 Hz); 127.63; 129.01; 129.47; 132.84; 133.89; 163.97; 165.48. IR (KBr) ν = 3328, 3067; 1735; 1686; 1661; 1328; 1262; 1159; 1122; 1008; 709; 664 cm^{-1}. HRMS (ESI): m/z calcd for $C_{13}H_{14}F_2NO_3$ $[M+H]^+$: 270.0942. Found: 270.0946.

4.4. Procedure for synthesis of syn-ethyl 2-(dibenzyl-amino)-4,4,4-trifluoro-3-(tosyloxy)butanoate (8)

syn-Ethyl 2-dibenzylamino-4,4,4-trifluoro-3-hydroxybutane (**4a**) (394 mg, 1.03 mmol)and TsCl (197 mg, 1.03 mmol)was dissolved in pyridine (10 mL) and the mixture was stirred at room temperature for 18 h. It was quenched with saturated NH_4Cl (aq) (8 mL), extracted with dichloromethane (3 mL × 10 mL) and washed with saturated brine (5 mL). The collected extraction was evaporated to dryness under vacuum after dried over anhydrous magnesium sulfate and the crude product was purified by column chromatography to afford **8** as a white solid; yield:393 mg (73%). mp: 66–68 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.37 (t, 3H, J = 7.2 Hz); 2.42 (s, 3H); 3.71 (d, 2H, J = 13.5 Hz); 3.87 (d, 1H, J = 5.5 Hz); 4.07 (d, 2H, J = 13.5 Hz); 4.30 (m, 2H); 5.55–5.60 (m, 1H); 7.20–7.74 (m, 14H). ^{19}F NMR (470 MHz, $CDCl_3$) δ = −72.67 (d, 3F, $^3J_{H-C-C-F}$ = 5.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.14; 21.40; 55.78; 59.27; 61.58; 75.37 (q, $^2J_{C-C-F}$ = 31.3 Hz); 122.44 (q, $^1J_{C-F}$ = 281.3 Hz); 127.24; 127.66; 128.23; 129.07; 129.65; 133.50; 138.25; 145.30; 167.82 IR (KBr) ν = 3030; 1734; 1599; 1377; 1182; 1151; 1027; 736; 698 cm^{-1}.

4.5. Procedure for synthesis of ethyl 2-(dibenzylamino)-4,4,4-trifluoro-but-2-enoate (9)

NaH (54 mg, 2.25 mmol, the mineral oil on the surface was washed off with dry THF) was added to a solution of *syn*-ethyl 2-(dibenzylamino)-4,4,4-trifluoro-3-(tosyloxy)butanoate (**8**) (393 mg, 0.75 mmol) in dry THF (15 mL). The mixture was stirred at 0 °C for about 6 h. The reaction was monitored by TLC and quenched with saturated NH_4Cl (aq) (7 mL). The suspension was extracted with ether (3 mL × 10 mL) and washed with saturated brine (5 mL). The collected organic layer was dried over magnesium sulfate and then the solvent was removed in vacuo to give **9** as a white solid; yield: 270 mg (98%). ^{1}H NMR (500 MHz, DMSO) δ = 1.22 (t, 3H, J = 7.0 Hz); 4.17 (s, 4H); 4.21 (q, 2H, J = 7.0 Hz); 5.32 (q, 1H, J = 9.0 Hz); 7.21–7.36 (m, 10H). ^{19}F NMR (470 MHz, DMSO, ppm) δ = −52.83 (d, 3F, $^3J_{H-C-C-F}$ = 9.0 Hz). ^{13}C NMR (125 MHz, DMSO) δ = 13.61; 54.82; 62.12; 98.10 (q, $^2J_{C-C-F}$ = 36.3 Hz); 123.78 (q, $^1J_{C-F}$ = 266.3 Hz); 127.51; 127.96; 128.44; 136.74; 148.33 (q, $^3J_{C-C-C-F}$ = 5.0 Hz); 164.76. IR (KBr) ν = 3031; 1730; 1629; 1448; 1235; 1180; 1099; 737; 698 cm^{-1}. HRMS (ESI): m/z calcd for $C_{20}H_{21}F_3NO_2$ $[M+H]^+$: 364.1524. Found: 364.1527.

4.6. General procedure for the synthesis of fluorinated Z-ethyl 1-benzamido-2-methyl-cyclopropane carboxylate (11)

Excess ethereal solution of diazomethane was distilled into a solution of fluorinated (*Z*)-ethyl 2-benzamido-4,4,4-trifluorobut-2-enoate (**7**) (0.35 mmol) dissolved in ether (10 mL) at 0 °C. The resulting solution was protected from light and stirred for another 3 h. Anhydrous $CaCl_2$ was then added to destroy the excess diazomethane and, after filtration, evaporated under vacuum to give a yellow oil. The pyrazoline obtained was very unstable and was used without further purification. It was then dissolved in toluene (10 mL) and transferred into a quartz glass reactor under nitrogen atmosphere, cooled at −18 °C (under ice salt bath) and irradiated with a 125-W medium-pressure mercury lamp for 3 h. The solvent was removed under vacuum and the crude was purified by column chromatography.

4.6.1. Z-Ethyl 1-benzamido-2-(trifluoromethyl)cyclopropane carboxylate (11a)

11a was obtained as a white solid in 48% yield. mp: 119–21 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.27 (t, 3H, J = 7.2 Hz); 1.88 (t, 1H, J = 7.0 Hz); 2.15 (dd, 1H, J = 9.0 Hz, 7.0 Hz); 2.54–62 (m, 1 H); 4.22 (q, 2H, J = 7.2 Hz); 6.65 (s, 1H); 7.46–.78 (m, 5H). ^{19}F NMR (470 MHz, $CDCl_3$) δ = −61.24 (d, 3F, $^3J_{H-C-C-F}$ = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.20; 19.17; 27.72 (q, $^2J_{C-C-F}$ = 36.3 Hz); 36.60; 62.66; 124.56 (q, $^1J_{C-F}$ = 271.3 Hz); 127.28; 128.89; 132.30; 133.83; 168.79; 169.71. IR (KBr) ν = 3289; 3061; 1734; 1655; 1525; 1275; 1148; 1082; 726; 694 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{16}F_3NO_3$ $[M+H]^+$: 303.1082. Found: 302.1085.

4.6.2. Z-Ethyl 1-benzamido-2-(difluoromethyl)cyclopropane carboxylate (11b)

11b was obtained as a white solid in 46% yield. mp: 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.23 (t, 3H, J = 7.0 Hz); 1.64 (t, 1H, J = 6.5 Hz); 1.95 (t, 1H, J = 6.5 Hz); 2.37–45 (m, 1H); 4.18 (q, 2H, J = 7.0 Hz); 5.81 (td, 1H, J = 56.0, 4.5 Hz); 6.75 (s, 1H); 7.43–78 (m, 5H). ^{19}F NMR (470 MHz, $CDCl_3$) δ = −109.74 (ddd, 1F, $^2J_{F-C-F}$ = 290.5 Hz, $^2J_{H-C-F}$ = 56.0 Hz, $^3J_{H-C-C-F}$ = 8.5 Hz); −116.59 (ddd, 1F, $^2J_{F-C-F}$ = 290.5 Hz, $^2J_{H-C-F}$ = 56.0 Hz, $^3J_{H-C-C-F}$ = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.18; 18.14; 28.43 (t, $^2J_{C-C-F}$ = 29.4 Hz); 36.71 (t, $^3J_{C-C-C-F}$ = 3.8 Hz); 62.29; 115.35 (t, $^1J_{C-F}$ = 237.5 Hz); 127.29; 128.81; 132.27; 133.63; 169.18; 170.40. IR (KBr) ν = 3280; 3031; 1740; 1652; 1524; 1340; 1265; 1187; 1035; 717; 693 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{17}F_2NO_3$ $[M+H]^+$: 285.1177. Found: 285.1180.

4.7. Procedure for synthesis of ethyl 2-phenyl-4-(2,2,2-trifluoroethyl)-4,5-dihydrooxazole-4-carboxylate (12)

Trimethylsulfoxonium iodide (462 mg, 2.1 mmol) was added to a suspension of NaH (60% in mineral oil, 84 mg, 2.1 mmol) in dry DMSO (15 mL), and the mixture was stirred under nitrogen at room temperature for 30 min. A solution of (*Z*)-ethyl 2-benzamido-4,4,4-trifluorobut-2-enoate (**7a**) (200 mg, 0.7 mmol) in DMSO (5 mL) was then added, and the resulting mixture was stirred at room temperature for 3 days. The suspension was quenched with saturated brine (8 mL) and extracted with ether (3 mL × 10 mL). The collected extraction was evaporated to dryness under vacuum after dried over anhydrous magnesium sulfate and the residue was purified by column chromatography to afford compounds **12**; yield: 66 mg (31%); mp: 44–46 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.32 (t, 3H, J = 7.2 Hz); 2.60–2.70 (m, 1H); 3.17–3.27 (m,1H);

4.23–4.37 (m, 2H); 4.46 (d, 1H, J = 9.5 Hz); 5.08 (d, 1H, J = 9.5 Hz); 7.41–7.97 (m, 5H). ^{19}F NMR (470 MHz, $CDCl_3$) δ = −61.21 (t, 3F, $^3J_{H-C-C-F}$ = 10.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.05; 41.21 (q, $^2J_{C-C-F}$ = 27.5 Hz); 62.61; 73.14 (q, $^3J_{C-C-C-F}$ = 2.5 Hz); 74.30; 125.32 (q, $^1J_{C-F}$ = 276.3 Hz); 126.66; 128.64; 128.87; 132.31; 166.12; 170.24. IR (KBr) ν = 2987; 1734; 1635; 1371; 1299; 1259; 1148; 726; 699 cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{15}F_3NO_3$ $[M+H]^+$: 302.1004. Found: 302.1005.

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