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Synthesis of Fluorinated Cyclopropyl Amino Acid Analogues: Toward the Synthesis of Original Fluorinated Peptidomimetics.

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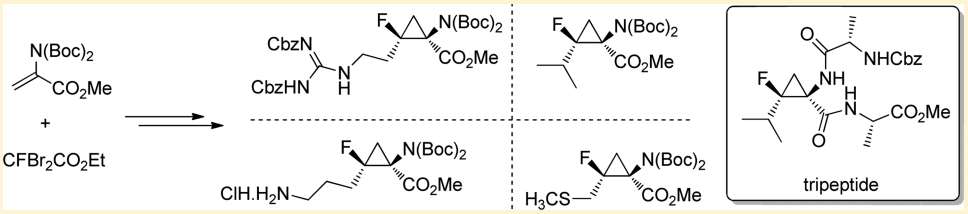
Supporting Information



ABSTRACT: A straightforward, easy, and practical access to various amino acid analogues (methionine, leucine, lysine, and arginine) from a unique fluorinated cyclopropane scaffold is described. Moreover, the synthesis, for the first time, of one tripeptide incorporating a fluorinated cyclopropane amino acid (FCAA) analogue is reported.

INTRODUCTION

Of the numerous emerging fields in organic chemistry, the synthesis of organofluorine compounds has attracted great interest in recent years due to the anomalous physical properties of the fluorine atom as well as restricted synthetic access to these compounds.[1] Indeed, the introduction of one or several fluorine atoms on a compound alters its chemical, physical, and biochemical properties such as solubility, lipophilicity, conformation, metabolic stability, and even intrinsic structure.[2] From a more fundamental point of view, the extraordinary potential of hydrogen or oxygen substitution by fluorine, to modify and/or increase in some cases the pharmacological (in particular metabolic stability) properties of organic molecules, led to the development of original and innovative programs dedicated to new synthetic strategies toward fluorinated biomolecules. In addition to the fluorine atom, the cyclopropane ring has several relevant properties and is present in many natural products and biological molecules.[3] The cyclopropane has a unique structural feature and can be used to constrain the skeleton of a molecule, having an impact in molecule's properties.

Combining the remarkable properties of the fluorine atom to the structural constraint provided by the cyclopropane seemed very useful to lead to fluorinated cyclopropanes as new powerful scaffolds which could be of great interest for many applications in the agrochemical or pharmaceutical domains.[4]

Among this general family, fluorinated cyclopropanes bearing an amino acid moiety can be considered as highly valuable precursors for the synthesis of fluorinated constrained amino acids. This type of amino acid analogues may be incorporated in peptide analogues to imply new highly localized features that may be used in structural and biological studies of bioactive compounds.[5] For example, fluorinated amino acids (trifluoroleucine and trifluoromethionine, in particular) have recently emerged as valuable building blocks for designing hyperstable proteins folds as well as directing highly specific protein−protein interactions.[6] Moreover, the design of small rigid molecules, such as cyclopropane peptidomimetics, that replicate the essential features of oligopeptide secondary structure is a central goal in efforts to identify peptide-like ligands having high affinity for biological targets.[7] The incorporation of cyclopropyl amino acids has already been reported in the literature showing interesting results in terms of biological activity and conformational induction.[7b,d,l,m] To our knowledge, the synthesis of peptidomimetics incorporating within their structure a fluorinated cyclopropyl amino acid analogue has never been reported in the literature. Herein, we report our recent success in tackling this very interesting issue by using a straightforward strategy from a unique fluorinated cyclopropane scaffold (±)-**1**. This latter allowed the synthesis of methionine, leucine, arginine, and lysine analogues which could be further used in peptide synthesis.

RESULTS AND DISCUSSION

In the past decades, many syntheses of highly valuable fluorinated scaffolds from commercially available ethyl dibromofluoroacetate have been developed.[8] Among them, we recently reported a general one-step synthesis of highly functionalized monofluorinated cyclopropanes from electron-deficient alkenes.[9a] Other alternative approaches toward the synthesis of such fluorinated cyclopropanes have been reported. Interestingly, our

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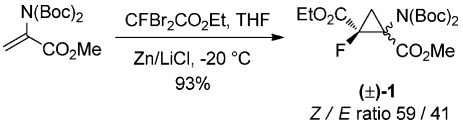
method was successfully applied to the synthesis of the fluorinated amino acid (±)-**1** on a 0.1 mol scale (30 g of Michael acceptor) with 93% yield (Scheme 1).

Scheme 1. Cyclopropanation Process Using Zn/LiCl Combination

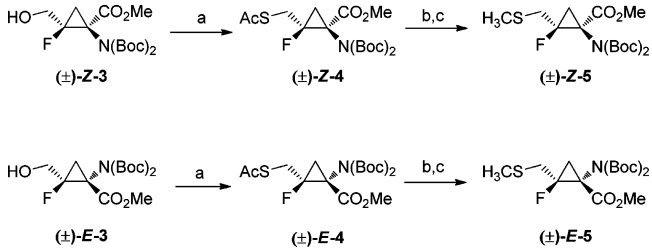


Remarkably, the cyclopropane diester (±)-**1** can be diastereoselectively saponified using lithium hydroxide at 0 °C,[8b,10] thus giving after acid−basic extraction the corresponding *Z* isomer of carboxylic acid (±)-**2** and the *E* isomer of diester **1** as highly enriched diastereisomers. Then, diester (±)-***E*-1** can be saponified regioselectively using lithium hydroxide at room temperature leading to (±)-***E*-2** in 86% yield. In order to build efficiently the lateral chain of the four envisioned amino acid mimics (methionine, leucine, lysine and arginine), the two isomeric alcohols (±)-***E*-3** and (±)-***Z*-3** were synthesized using mixed anhydride formation and subsequent reduction strategy from corresponding substrates (±)-**2** (Scheme 2).

From these two (±)-***Z*-3** and (±)-***E*-3** building blocks, we investigated the synthesis of both isomers of methionine as outlined in Scheme 3. For that purpose, reaction of (±)-***Z*-3** alcohol and thioacetic acid in the presence of triphenylphosphine and diisopropyl azodicarboxylate led to the corresponding thioacetate (±)-***Z*-4** via a Mitsunobu reaction in 83% yield. Subsequent deprotection and in situ methylation afforded the expected (±)-***Z*-5** analogue of methionine.[11] A similar strategy was further applied to (±)-***E*-3** leading in a more moderate overall yield to the corresponding (±)-***E*-5** isomer. For this first amino acid analogue, both isomers of fully protected methionine analogue (±)-***Z*-5** and (±)-***E*-5** were obtained, respectively, in 32% and 19% overall yield from (±)-**1**.

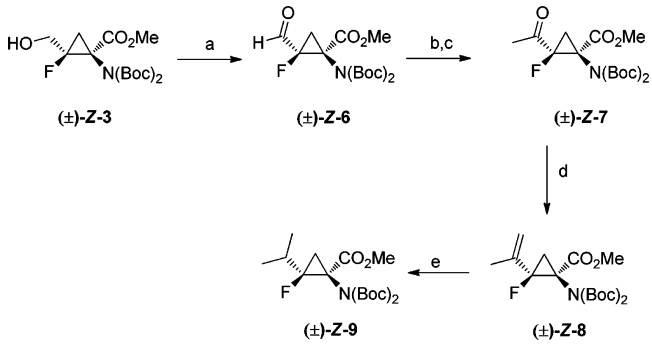
The next goal was to achieve the synthesis of leucine analogue bearing an isopropyl group on the lateral chain. The following sequence was carried out (Scheme 4). Oxidation of primary alcohol (±)-***Z*-3** with IBX in refluxing ethyl acetate afforded the corresponding aldehyde (±)-***Z*-6** in quantitative yield.[12] Treatment with methylmagnesium bromide at low temperature,[13] followed by subsequent oxidation of the corresponding secondary alcohol with IBX, led to the corresponding ketone (±)-***Z*-7** in 55% yield over two steps. Formation of the double bond via a Wittig reaction was achieved using triphenylmethylphosphonium bromide to give alkene (±)-***Z*-8** in 79% yield.

Scheme 3. Synthesis of Racemic Analogues of Methionine (±)-*Z*-5 and (±)-*E*-5[a]



[a]Reagents and conditions: (a) thioacetic acid, DIAD, Ph_3P, THF, 0 °C to rt, 2 h, ((±)-***Z*-4**: 83%, (±)-***E*-4**: 66%); (b) NaOMe, MeOH, 0 °C, 30 min; (c) CH_3I, 0 °C to rt, 90 min, ((±)-***Z*-5**: 74%, (±)-***E*-5**: 61%).

Scheme 4. Synthesis of racemic Analogue of Leucine (±)-*Z*-9[a]

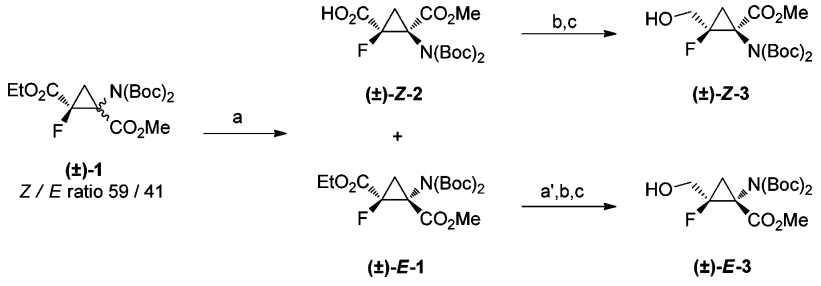


[a]Reagents and conditions: (a) 2-iodoxybenzoic acid, EtOAc, reflux, 5 h, 99%; (b) CH_3MgBr, THF, −10 °C, 30 min, 79%; (c) 2-iodoxybenzoic acid, EtOAc, reflux, 9 h, 69%; (d) Ph_3PCH_3Br, KHMDS, Et_2O, 0 °C to RT, 2 h, 79%; (e) H_2, $(Ph_3P)_3RhCl$, toluene, 20 bar, rt, overnight, 89%.

Finally, hydrogenation of the alkene moiety was achieved using Wilkinson's catalyst[14] under hydrogen pressure leading to the expected target (±)-***Z*-9** (overall yield: 20% from **1**). The stereochemistry of this leucine analogue (±)-***Z*-9** was confirmed by X-ray analysis (Figure 1).[15]

A slightly modified procedure was applied for the synthesis of (±)-***E*-9** from (±)-***E*-2**. Indeed, all attempts to oxidize the secondary alcohol (±)-***E*-3** failed. As an alternative, carboxylic acid (±)-***E*-2** was efficiently converted to the corresponding Weinreb amide which was then treated with methyl lithium at low temperature to generate the expected ketone (±)-***E*-7**. The same final steps (Wittig reaction and hydrogenation using Wilkinson's catalyst) were then applied leading to the expected

Scheme 2. Preparation of Racemic Alcohols (±)-*Z*-3 and (±)-*E*-3[a]



[a]Reagents and conditions: (a) 1 M LiOH, THF/water (10:1), 0 °C, 1 h, 85%; (a′) 1 M LiOH, THF/water (5:2), rt, overnight, 86%; (b) ethyl chloroformate, Et_3N, THF, 10−0 °C, 45 min; (c) $NaBH_4$, MeOH, 0 °C, 1 h, 68% in two steps for (±)-***Z*-3**, 60% in two steps for (±)-***E*-3**.

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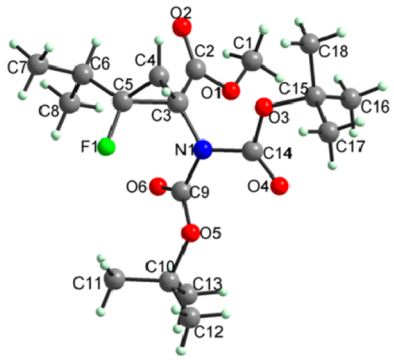
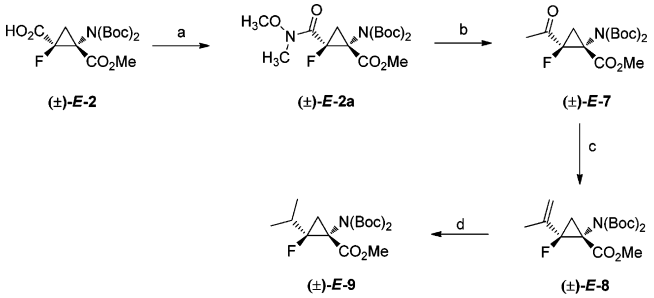


Figure 1. X-ray structure of (1*R*,2*S*)-***Z*-9**.

leucine analogue (±)-***E*-9** (Scheme 5; overall yield: 14% from (±)-**1**).

Scheme 5. Synthesis of Racemic Analogue of Leucine (±)-*E*-9[a]

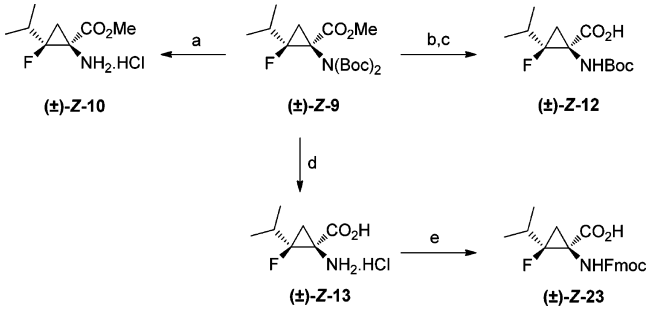


[a]Reagents and conditions: (a) HBTU, DIEA, DMF, 0 °C, 1 h then MeO(Me)NH.HCl, DMF, rt, 16 h, 62%; (b) CH_3Li, −78 °C, 40 min; 57% (c) Ph_3PCH_3Br, KHMDS, Et_2O, 0 °C to rt, 16 h, 65%; (d) H_2, $(Ph_3P)_3RhCl$, toluene, 20 bar, rt, 15 h, 78%.

To demonstrate the high value of our present synthesis, we envisioned carrying out a selective (ester deprotection or carbamate deprotection) and full deprotection of (±)-***Z*-9**. The *N*,*N*-(di-*tert*-butyloxycarbonyl) protection could be removed very efficiently using HCl 4 M in dioxane leading to hydrochloride salt (±)-***Z*-10** in quantitative yield. Attempts to selectively saponify the methyl ester function from (±)-***Z*-9** with lithium hydroxide under reflux did not provide the expected carboxylic derivative. We assumed that this lack of reactivity was probably due to the steric hindrance of the two *N*-*tert*-butyloxycarbonyl groups, impeding the saponification process to occur. Thus, as an alternative approach, treatment of fully protected amino acid (±)-***Z*-9** with ytterbium(III) triflate[16] led to the corresponding mono-*N*-Boc-protected amine compound (±)-***Z*-11** which can be hydrolyzed with lithium hydroxide to give carboxylic acid (±)-***Z*-12**. Both protecting groups of (±)-***Z*-9** were removed simultaneously in acidic conditions (CH_3CO_2H/HCl 12 N) under reflux to generate the fully deprotected fluorocyclopropane analogue of leucine (±)-***Z*-13**. Finally, in order to demonstrate the remarkable potency of the fluorinated cyclopropane amino acid analogues for the synthesis of peptidomimetics and its possible application in peptide solid-phase synthesis using Fmoc strategy, (±)-***Z*-23** was prepared from (±)-***Z*-9** (Scheme 6).

We then turned our attention toward the synthesis of the lateral chain of lysine which was synthesized efficiently following the procedure depicted in Scheme 7. Indeed, Horner–

Scheme 6. Partial and Complete Deprotection Steps for (±)-*Z*-9 and Synthesis of *N*-Fmoc (±)-*Z*-23[a]



[a]Reagents and conditions: (a) HCl 4 N in dioxane, MeOH, rt, 4 h, quant; (b) $Yb(OTf)_3$, CH_3CN, 0 °C to rt, 1 h, 93%; (c) LiOH, MeOH/H_2O, reflux, 4 h, 76%; (d) CH_3CO_2H/HCl 12 N (1:1), reflux, 30 h, 88%; (e) K_2CO_3, Fmoc-OSu, dioxane/water (1/1), 0 °C, 1 h then 40 °C, 3 h, 68%.

Wadsworth–Emmons reaction of (±)-***Z*-6** using diethyl cyanomethylphosphonate was performed giving the corresponding α,β-unsaturated nitrile (±)-***Z*-14** in 70% yield. Catalytic hydrogenation of (±)-***Z*-14** in the presence of PtO_2 (10 bar H_2) afforded the expected scaffold (±)-***Z*-15** in high yield (overall yield: 32% from (±)-**1**).[17] Concerning the *E* analogue, oxidation of the primary alcohol (±)-***E*-3** with IBX afforded (±)-***E*-6**, and a similar procedure was performed for the first step of the sequence leading to α,β-unsaturated nitrile (±)-***E*-14** but in a lower yield (36%) probably because of the cis relationship between the aldehyde and the dicarbamate functions. However, the direct conversion of (±)-***E*-14** to (±)-***E*-15**, using previously reported conditions, did not occur properly. For that purpose, a two-step procedure was developed leading to the expected (±)-***E*-15** in 82% yield (Scheme 7, overall yield: 10% from (±)-**1**).

Finally, we developed the synthesis of the lateral chain of arginine which was obtained efficiently as described in Scheme 8. Treatment of aldehyde (±)-***Z*-6** with nitromethane in the presence of catalytic amount of 1,1,3,3-tetramethylguanidine via the Henry reaction, followed by subsequent crotonisation afforded the corresponding α,β-unsaturated compound (±)-***Z*-16** in 71% yield.[18] The *E* configuration of the alkene bond was assigned from ^1H NMR data. The saturated nitro compound (±)-***Z*-17** was obtained by reduction of (±)-***Z*-16** using sodium borohydride and was then converted to the amine (±)-(±)-***Z*-18** by catalytic hydrogenation.[19] Finally, guanidinylation of (±)-***Z*-20** was achieved in moderate yield using *N*,*N*′-Di-Cbz-*N*″-trifluoromethane sulfonyl guanidine,[20] leading to the expected *Z* *N*-Cbz protected analogue of arginine (±)-***Z*-19**.

Having in hand these four amino acid analogues, we focused on standard peptide-coupling reactions to generate a tripeptide incorporating one fluorinated cyclopropane ((±)-***Z*-9**) as described in Scheme 9. The leucine analog (±)-***Z*-9** was treated with ytterbium(III) triflate to remove efficiently one *N*-*tert*-butyloxycarbonyl group, allowing the subsequent hydrolysis of the methyl ester. The resulting acid (±)-***Z*-12** was coupled with the natural amino-acid H-Ala-OMe in the presence of HATU and DIEA to afford the dipeptide ***Z*-20** as a mixture of diastereoisomers.[21] Subsequent *N*-protecting group removal under standard acidic conditions led to the amine ***Z*-21**. The resulting hydrochloride was coupled with *N*-Cbz protected alanine (HATU/NMM) to afford the final fluorinated cyclopropyl tripeptide ***Z*-22** in very good yield (76%).[22] These two

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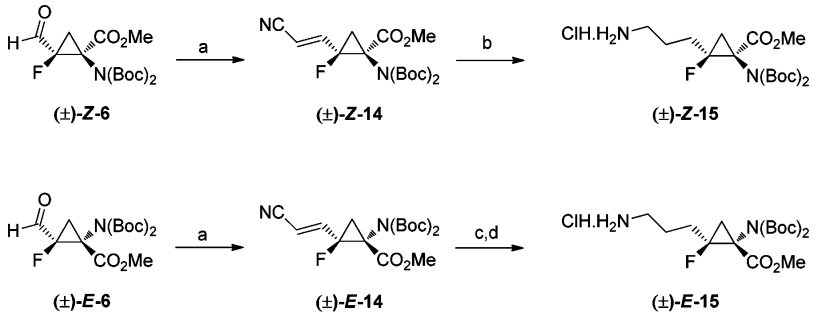
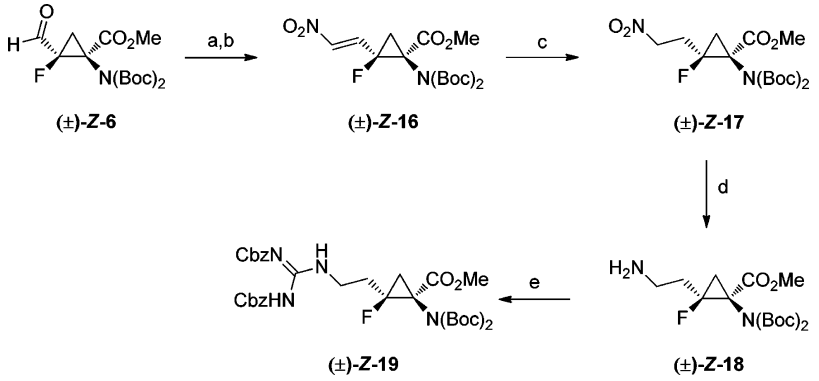
Scheme 7. Synthesis of Racemic Analogues (±)-*Z*-15 and (±)-*E*-15 of Lysine[a]



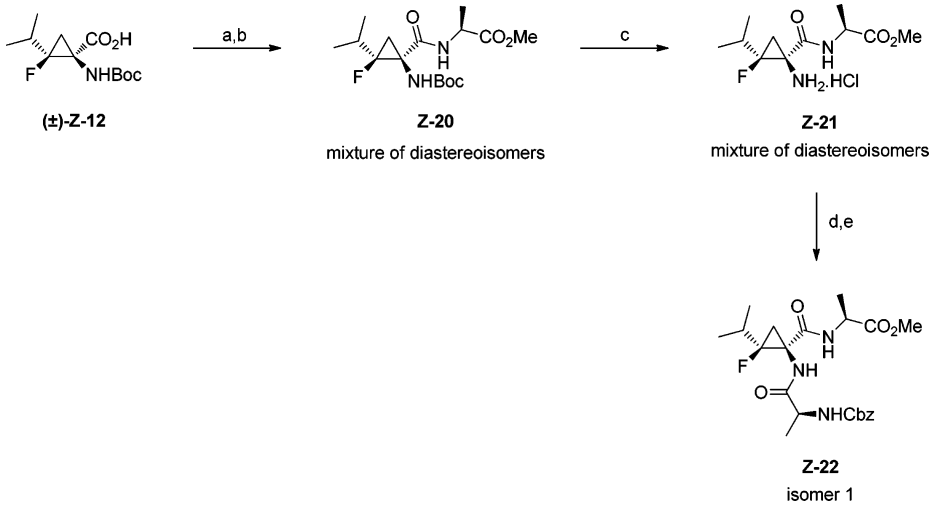
[a]Reagents and conditions: (a) diethyl cyanomethylphosphonate, Et_3N, THF, rt, 16 h, 70% from (±)-*Z*-**6**, 39% from (±)-*E*-**6**; (b) H_2, PtO_2, $CHCl_3$, 10 bar, rt, overnight, 89%. (c) H_2, Pd−C, EtOH, 1 bar, rt, overnight, 94%; (d) H_2, PtO_2, $CHCl_3$, 20 bar, rt, overnight, 87%.

Scheme 8. Synthesis of Racemic *Z*-Analogue of Arginine (±)-*Z*-19[a]



[a]Reagents and conditions: (a) nitromethane, 1,1,3,3-tetramethylguanidine, toluene, 0 °C, 1 h; (b) MsCl, Et_3N, 0 °C to rt, 1 h, 71% in two steps; (c) $NaBH_4$, EtOH, 0 °C to rt, 1 h, 92%; (d) H_2, Pd−C, MeOH, 10 bar, rt, overnight, 86%; (e) *N*,*N*′-di-Cbz-*N*″-trifluoromethanesulfonyl guanidine, Et_3N, CH_2Cl_2, rt, overnight, 24%.

Scheme 9. Synthesis of Fluorinated Cyclopropyl Tripeptide *Z*-22[a]



[a]Reagents and conditions: (a) HATU, DIEA, DMF, 0 °C, 1 h; (b) H-Ala-OMe·HCl, DMAP, DBU, DMF, rt, overnight, 57% in two steps; (c) 4 N HCl in dioxane, MeOH, rt, 4 h, quant; (d) Z-Ala-OH, HATU, NMM, DMF, 0 °C, 1 h; (e) **Z-21**, DMF, rt, overnight, 76% in two steps.

diastereoisomers can be efficiently purified and separated by supercritical fluid chromatography (SFC).[23]

■ CONCLUSION

In conclusion, from a unique fluorinated cyclopropane scaffold, a straightforward, easy, and practical access to new various amino-acid analogues (methionine, leucine, lysine and arginine) was reported. The synthesis, for the first time, of one tripeptide incorporating a fluorinated cyclopropane amino-acid analogue was also described. All these new fluorinated scaffolds can be considered as very useful intermediates for the peptidomimetics building. From these analogues, because of the constrained

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feature of the cyclopropane moiety and the presence of fluorine atom, modified conformations, physical−chemical properties, and/or biological activity can be expected compared to the native peptides. These aspects, as well as the incorporation of these amino acid analogues in more complex structures, are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All reactions were conducted in oven-dried glassware under argon atmosphere. All moisture-sensitive reactants were handled under argon atmosphere. Low temperature experiments were carried out by cooling down the flasks with an acetone bath frozen by dry ice. The flasks were equipped with septum caps. All commercial solvents were distilled prior to use: THF and Et_2O were distilled over sodium/benzophenone under nitrogen atmosphere, CH_2Cl_2 over CaH_2, and toluene over sodium. Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F_{254} plates. Visualization was performed by ultraviolet light and staining with a solution of phosphomolybdic acid. Flash column chromatography was performed using 40−63 μm or 70−200 μm silica gel using compressed air or automated equipment with prepacked silica cartridges. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR were recorded at 300, 75.4, and 282.5 MHz, respectively, on a 300 MHz spectrometer. The following abbreviations were used to explain the multiplicities: s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet, bs: broad singlet, bm: broad multiplet. J was used to indicate coupling constants in hertz (Hz). IR spectra were recorded on a FT-IR spectrometer. Mass spectra were obtained on a quadripole ion trap instrument equipped with an electrospray ionization (ESI) source. High-resolution electrospray mass spectra (HR-ESI MS) were recorded on a QTOF-MS instrument.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-ethoxycarbonyl-2-fluorocyclopropylcarboxylate ((±)-1). Lithium chloride (10.6 mg, 0.25 mol, 2.5 equiv) and zinc (16.4 g, 0.25 mol, 2.5 equiv) were placed into a 1 L round-bottom flask equipped with septum and magnetic stirrer, dried at 170 °C (10^{-1} mbar) for 60 min, and then flushed with argon. Subsequently, 400 mL of freshly distilled THF, 800 μL of DMSO, and 1.6 mL of TMSCl were added, and the mixture was stirred vigorously at 50 °C for 15 min. Then, 10 drops of ethyl dibromofluoroacetate were added, the mixture was immediately cooled to −5 °C, and Boc-ΔAla(N-Boc)-OMe (30.1 g, 1 mmol, 1 equiv) previously dissolved in 50 mL of THF under an argon atmosphere was added. Finally, ethyl dibromofluoroacetate (22 mL, 0.16 mol, 1.6 equiv) was added dropwise over 30 min via a syringe pump, and the resulting mixture was stirred for an additional 10 min at −5 to 0 °C until complete disappearance of starting material (monitored by TLC). Upon completion, the mixture was poured into a mixture of EtOAc (400 mL) and aqueous HCl (0.5 M, 200 mL). Then, the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel to afford (±)-**1** as a pale yellow oil (37.7 g, 93%) as a mixture of Z and E stereoisomers (dr 59:41 by ^{19}F NMR). Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.51. MS (ESI positive mode): m/z 428.20 $[M + Na]^+$, 833.20 $[2M + Na]^+$. IR (neat): 3445, 1799, 1748, 1371, 1278, 1255, 1159, 1122, 1101, 1027, 855, 785 cm^{-1}. Anal. Calcd for $C_{18}H_{28}FNO_8$: C, 53.33; H, 6.96; N, 3.45. Found: C, 52.95; H, 6.64; N, 3.71.

*Major Isomer ((±)-**Z**-**1**).* ^{1}H NMR (300.1 MHz, $CDCl_3$): 4.22 (q, 2H, J_{HH} = 7.1 Hz), 3.66 (s, 3H), 2.55 (dd, 1H, J_{HH} = 9.0 Hz, J_{HF} = 15.9 Hz), 1.84 (dd, 1H, J_{HH} = 8.9 Hz, J_{HF} = 20.7 Hz), 1.42 (2s, 18H), 1.26 (t, 3H, J_{HH} = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 167.7 (J_{CF} = 2.6 Hz), 164.1 (J_{CF} = 25.7 Hz), 151.1, 151.0, 83.4, 81.2 (J_{CF} = 241.8 Hz), 62.3, 52.8, 46.5 (J_{CF} = 10.2 Hz), 28.0, 27.9, 26.5 (J_{CF} = 8.2 Hz), 13.9. ^{19}F NMR (282.4 MHz, $CDCl_3$): −185.5 (dd, J_{FH} = 16.1, 20.9 Hz).

*Minor Isomer ((±)-**E**-**1**).* ^{1}H NMR (300.1 MHz, $CDCl_3$): 4.22 (q, 2H, J_{HH} = 7.2 Hz), 3.76 (s, 3H), 2.77 (dd, 1H, J_{HH} = 8.4 Hz, J_{HF} = 17.7 Hz), 2.04 (dd, 1H, J_{HH} = 8.4 Hz, J_{HF} = 10.8 Hz), 1.46 (2s, 18H), 1.30 (t, 3H, J_{HH} = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 166.2 (J_{CF} = 2.3 Hz), 165.4 (J_{CF} = 25.3 Hz), 151.1, 151.0, 83.4, 83.3, 81.5 (J_{CF} = 248.0 Hz), 62.4, 53.2, 48.2 (J_{CF} = 13.7 Hz), 27.9, 27.7, 26.8 (J_{CF} = 8.9 Hz), 13.9. ^{19}F NMR (282.4 MHz, $CDCl_3$): −195.0 (dd, J_{FH} = 10.7, 17.5 Hz).

2-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-1-fluoro-2-methoxycarbonylcyclopropylmethanoic Acid ((±)-*Z*-2). In a 500 mL, three-necked, round-bottom flask equipped with magnetic stirrer was dissolved (±)-**1** (19.83 g, 48.9 mmol, 1 equiv) in a mixture of THF/water 10:1 (300 mL) and cooled to 0 °C. Subsequently, a molar solution of lithium hydroxide (73 mL, 73 mmol, 1.5 equiv) was added dropwise via a dropping funnel. The solution was stirred at 0 °C until complete consumption of (±)-*Z*-**1** was observed (monitored by ^{19}F NMR). Upon completion, 1 M $KHSO_4$ solution was added until pH 2, and aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were concentrated in vacuo. The oily residue was dissolved in Et_2O, and the desired acid (±)-*Z*-**2** was extracted with 1 M $NaHCO_3$ solution (3 × 50 mL) in its sodium salt form. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford (±)-*E*-**1** (contaminated by 7% (±)-*Z*-**1**) as a yellow oil (7.05 g, 87%). The aqueous layer was acidified to pH 2 by addition of 1 M $KHSO_4$ solution and extracted with Et_2O (4 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford (±)-*Z*-**2** (contaminated by 8% of (±)-*E*-**2**) as a yellow syrup (9.26 g, 85%). Analytical TLC (silica gel 60): (20% cyclohexane in ethyl acetate) R_f = 0.21. ^{1}H NMR (300.1 MHz, $CDCl_3$): 9.52 (bs, 1H), 3.72 (s, 3H, CH_3), 2.63 (dd, 1H, J_{HH} = 9.2 Hz, J_{HF} = 16.9 Hz), 1.95 (dd, 1H, J_{HH} = 9.2 Hz, J_{HF} = 20.8 Hz), 1.48 (2s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 167.9, 166.5 (J_{CF} = 26.4 Hz), 151.4, 151.0, 84.2, 83.7, 80.9 (J_{CF} = 241.4 Hz), 53.2, 46.5 (J_{CF} = 10.0 Hz), 27.8, 27.7, 26.4 (J_{CF} = 8.4 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −183.3 (dd, J_{FH} = 17.0, 21.0 Hz). MS (ESI negative mode): m/z 376.07 $[M - H]^-$. IR (neat): 3500, 2981, 2927, 1748, 1371, 1283, 1156, 1112, 852, 772 cm^{-1}. Anal. Calcd for $C_{16}H_{24}FNO_8$: C, 50.92; H, 6.41; N, 3.71. Found: C, 51.13; H, 6.65; N, 3.76.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-fluoro-2-(hydroxymethyl)cyclopropyl Carboxylate ((±)-3). *General Procedure for the Synthesis of (±)-**Z**- and (±)-**E**-**3**.* In a 250 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-**2** (2.74 g, 7.26 mmol, 1 equiv) in THF (50 mL) and the mixture cooled to −10 °C. Triethylamine (1.08 mL, 7.99 mmol, 1.1 equiv) and ethyl chloroformate (1.11 mL, 11.62 mmol, 1.6 equiv) were added slowly, and the reaction mixture was stirred for 45 min at −10 °C until complete disappearance of starting material (monitored by TLC). The mixture was taken up in Et_2O, stirred for 10 min, and filtered through a pad of Celite, and the filtrate was concentrated in vacuo. After being cooled to −10 °C, the residue was dissolved in MeOH (50 mL), and sodium borohydride (549 mg, 14.52 mmol, 2 equiv) was added portionwise. The reaction mixture was stirred for 1 h at 0 °C until complete disappearance of starting material (monitored by TLC). Upon completion, the mixture was quenched with saturated NH_4Cl solution (40 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (40 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting yellow residue was purified by column chromatography on silica gel to afford the expected product.

*(±)-**Z**-**3**.* Compound (±)-*Z*-**3** was obtained as a yellow oil in 68% yield. Analytical TLC (silica gel 60): (40% ethyl acetate in cyclohexane) R_f = 0.29. ^{1}H NMR (300.1 MHz, $CDCl_3$): 4.27 (ddd, 1H, J_{HH} = 5.7, 12.8 Hz, J_{HF} = 15.6 Hz), 4.08 (ddd, 1H, J_{HH} = 5.4, 12.0 Hz, J_{HF} = 30.6 Hz), 3.75 (s, 3H), 3.02 (t, 1H, J_{HH} = 5.7 Hz), 2.20 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 17.4 Hz), 1.80 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 22.2 Hz), 1.48 (2s, 18H, CH_3-9). ^{13}C NMR (75.4 MHz, $CDCl_3$): 169.8 (J_{CF} = 2.3 Hz), 152.8, 151.8, 86.1 (J_{CF} = 233.2 Hz), 83.6, 83.2, 60.9 (J_{CF} = 23.1 Hz), 52.9, 44.4 (J_{CF} = 9.3 Hz), 27.9, 27.8, 26.8 (J_{CF} = 9.3 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −177.4 (dddd, J_{FH} = 15.8, 17.4, 22.0, 30.5 Hz). MS (ESI positive mode): m/z 385.93 $[M + Na]^+$, 748.93 $[2M + Na]^+$. IR (neat): 3436, 2924, 2854, 1736, 1456, 1370, 1281, 1157, 1121, 1042, 762 cm^{-1}. HRMS (ESI positive mode): calcd for $C_{16}H_{26}FNO_7Na$ 386.1591, found 386.1599.

*(±)-**E**-**3**.* Compound (±)-*E*-**3** was obtained as a white solid in 68% yield. Mp: 66−69 °C. Analytical TLC (silica gel 60): (30% ethyl acetate

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in cyclohexane) R_f = 0.24. ^{1}H NMR (300.1 MHz, $CDCl_3$): 4.08 (dd, 1H, J_{HH} = 11.6 Hz, J_{HF} = 25.0 Hz), 3.78 (s, 3H), 3.68 (ddd, 1H, J_{HH} = 1.7, 13.8 Hz, J_{HF} = 24.2 Hz), 2.50 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 20.4 Hz), 1.52 (s, 9H), 1.45 (s, 9H), 1.11 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 11.1 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 167.6, 154.1, 151.8, 86.3 (J_{CF} = 240.5 Hz), 84.4, 83.8, 62.4 (J_{CF} = 21.2 Hz), 53.0, 47.2 (J_{CF} = 14.9 Hz), 27.9, 27.8, 23.5 (J_{CF} = 9.9 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −191.1 (dddd, J_{FH} = 11.9, 20.3, 24.3, 27.4 Hz). MS (ESI positive mode): m/z 386.07 [M + Na]$^+$, 749.00 [2M + Na]$^+$. IR (neat): 3418, 2930, 2359, 1746, 1435, 1370, 1248, 1157, 1123, 1046, 849, 762 cm^{-1}. Anal. Calcd for $C_{16}H_{26}FNO_7$: C, 52.88; H, 7.21; N, 3.85. Found: C, 52.84; H, 7.38; N, 3.84.

Methionine Analogue. Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-((acetylthio)methyl)-2-fluorocyclopropylcarboxylate ((±)-4). *General Procedure for the Synthesis of (±)-Z- and (±)-E-4.* In a 50 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved triphenylphosphine (1.44 g, 5.49 mmol, 2 equiv) in THF (15 mL) and the mixture cooled to 0 °C. Subsequently, diisopropyl azodicarboxylate (1.08 mL, 5.49 mmol, 2 equiv) was added slowly, and the reaction mixture was stirred for 30 min at 0 °C until a precipitate was observed. Then, (±)-**3** (1 g, 2.75 mmol, 1 equiv) and thioacetic acid (0.394 mL, 5.49 mmol, 2 equiv) were added. The reaction mixture was stirred for 1 h at 0 °C and allowed to warm to room temperature for 1 h until complete disappearance of starting material (monitored by TLC and ^{19}F NMR). The reaction mixture was concentrated in vacuo, taken up in a mixture of Et_2O/cyclohexane (1:1), and stirred for 30 min. The precipitate was filtered off, and the filtrate was concentrated in vacuo to afford an orange oil. The crude product was purified by column chromatography on silica gel to afford the expected product as a yellow oil.

*(±)-**Z-4***. Compound (±)-*Z*-**4** was obtained as a yellow oil in 83% yield. Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.32. ^{1}H NMR (300.1 MHz, $CDCl_3$): 3.89 (dd, 1H, J_{HH} = 14.7 Hz, J_{HF} = 35.4 Hz), 3.79 (s, 3H), 3.56 (ddd, 1H, J_{HH} = 1.6, 13.9 Hz, J_{HF} = 11.9 Hz), 2.41 (s, 3H), 2.11 (dd, 1H, J_{HH} = 8.6 Hz, J_{HF} = 17.5 Hz), 1.72 (ddd, 1H, J_{HH} = 1.5, 8.5 Hz, J_{HF} = 21.0 Hz), 1.51 (d, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 193.9, 169.3 (J_{CF} = 2.5 Hz), 151.4, 151.2, 84.4 (J_{CF} = 225.3 Hz), 83.0, 82.9, 52.8, 46.4 (J_{CF} = 9.3 Hz), 30.2, 29.5 (J_{CF} = 21.5 Hz), 27.8, 27.7, 21.7 (J_{CF} = 7.6 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −172.2 (dddd, J_{FH} = 11.9, 17.5, 20.9, 35.0 Hz). MS (ESI positive mode): m/z 444.20 [M + Na]$^+$, 865.00 [2M + Na]$^+$. IR (neat): 3446, 3110, 2981, 1799, 1731, 1480, 1430, 1366, 1268, 1117, 1022, 966, 919, 854, 790, 729, 622 cm^{-1}. Anal. Calcd for $C_{18}H_{28}FNO_7S$: C, 51.29; H, 6.70; N, 3.32; S, 7.61. Found: C, 51.27; H, 6.71; N, 3.19; S, 7.22.

*(±)-**E-4***. Compound (±)-*E*-**4** was obtained as a yellow oil in 66% yield. Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.36. ^{1}H NMR (300.1 MHz, $CDCl_3$): 3.74 (s, 3H), 3.62 (ddd, 1H, J_{HH} = 2.1, 14.7 Hz, J_{HF} = 9.9 Hz), 3.26 (dd, 1H, J_{HH} = 14.7 Hz, J_{HF} = 36.3 Hz), 2.46 (ddd, 1H, J_{HH} = 2.1, 8.7 Hz, J_{HF} = 19.1 Hz), 2.36 (s, 3H), 1.50 (d, 18H), 1.31 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 11.9 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 194.4, 168.6, 151.8, 151.5, 86.5 (J_{CF} = 238.3 Hz), 83.4, 83.2, 52.8, 48.7 (J_{CF} = 14.0 Hz), 32.2 (J_{CF} = 22.8 Hz), 30.3, 28.2, 28.1, 25.9 (J_{CF} = 9.9 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −182.0 (dddd, J_{FH} = 9.9, 11.3, 18.9, 36.2 Hz). MS (ESI positive mode): m/z 444.07 [M + Na]$^+$, 864.87 [2M + Na]$^+$. IR (neat): 3442, 3090, 2985, 1711, 1702, 1363, 1325, 1249, 1168, 1123, 1025, 858, 618 cm^{-1}. Anal. Calcd for $C_{18}H_{28}FNO_7S$: C, 51.29; H, 6.70; N, 3.32; S, 7.61. Found: C, 51.28; H, 6.69; N, 3.36; S, 7.53.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-fluoro-2-((methylthio)methyl)cyclopropylcarboxylate ((±)-5). *General Procedure for the Synthesis of (±)-Z- and (±)-E-5.* In a 50 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-**4** (500 mg, 1.19 mmol, 1 equiv) in MeOH (10 mL) and the mixture cooled to 0 °C. Subsequently, a freshly prepared solution of NaOMe (161 mg, 2.98 mmol, 2.5 equiv) in MeOH (1 mL) was added dropwise. The reaction mixture was then stirred for 30 min before methyl iodide (185 μL, 2.98 mmol, 2.5 equiv) was added dropwise at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was poured into cold water and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford a yellow oil. The resulting yellow residue was purified by column chromatography on silica gel to give the desired product.

*(±)-**Z-5***. Compound (±)-*Z*-**5** was obtained as a white solid in 74% yield. Mp: 60−62 °C. Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.50. ^{1}H NMR (300.1 MHz, $CDCl_3$): 3.74 (s, 3H), 3.23 (dd, 1H, J_{HH} = 14.9 Hz, J_{HF} = 33.8 Hz), 3.17 (dd, 1H, J_{HH} = 1.5, 14.9 Hz), 2.22 (s, 3H), 2.10 (dd, 1H, J_{HH} = 8.6 Hz, J_{HF} = 18.1 Hz), 1.76 (ddd, 1H, J_{HH} = 1.4, 8.5 Hz, J_{HF} = 21.1 Hz), 1.48 (d, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 169.7 (J_{CF} = 2.2 Hz), 151.7, 151.6, 86.5 (J_{CF} = 232.5 Hz), 83.0, 82.8, 52.8, 46.2 (J_{CF} = 9.5 Hz), 33.5 (J_{CF} = 22.1 Hz), 28.0, 27.9, 27.8 (J_{CF} = 7.9 Hz), 16.6. ^{19}F NMR (282.4 MHz, $CDCl_3$): −170.4 (ddd, J_{FH} = 18.4, 22.0, 33.7 Hz). MS (ESI positive mode): m/z 416.07 [M + Na]$^+$, 809.00 [2M + Na]$^+$. IR (neat): 3105, 2930, 1717, 1335, 1279, 1250, 1155, 1110, 1083, 857, 785, 762, 599 cm^{-1}. Anal. Calcd for $C_{17}H_{28}FNO_6S$: C, 51.89; H, 7.17; N, 3.56; S, 8.15. Found: C, 51.81; H, 7.25; N, 3.57; S, 8.02.

*(±)-**E-5***. Compound (±)-*E*-**5** was obtained as a white solid in 61% yield. Mp: 65−67 °C. Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.39. ^{1}H NMR (300.1 MHz, $CDCl_3$): 3.77 (s, 3H), 3.42 (ddd, 1H, J_{HH} = 2.4, 15.1 Hz, J_{HF} = 11.0 Hz), 2.61 (ddd, 1H, J_{HH} = 2.2, 8.7 Hz, J_{HF} = 19.2 Hz), 2.54 (dd, 1H, J_{HH} = 15.3 Hz, J_{HF} = 36.4 Hz), 2.26 (s, 3H), 1.49 (d, 18H), 1.30 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 12.3 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 167.5, 151.7, 151.5, 88.4 (J_{CF} = 238.6 Hz), 82.9, 82.6, 52.7, 48.8 (J_{CF} = 14.3 Hz), 36.7 (J_{CF} = 23.4 Hz), 27.6, 27.5, 26.1 (J_{CF} = 10.1 Hz), 16.3 (J_{CF} = 2.4 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −179.8 (dddd, J_{FH} = 11.0, 11.9, 19.5, 31.1 Hz). MS (ESI positive mode): m/z 416.13 [M + Na]$^+$. IR (neat): 3111, 2925, 1734, 1367, 1271, 1163, 1129, 1071, 783, 766, 459 cm^{-1}. Anal. Calcd for $C_{17}H_{28}FNO_6S$: C, 51.89; H, 7.17; N, 3.56; S, 8.15. Found: C, 51.85; H, 7.18; N, 3.53; S, 8.06.

Leucine Analogue. Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-fluoro-2-(oxomethyl)cyclopropylcarboxylate ((±)-6). *General Procedure for the Synthesis of (±)-Z- and (±)-E-6.* In a 100 mL round-bottom flask equipped with septum, magnetic stirrer, and reflux condenser under an argon atmosphere were dissolved **3** (1.78 g, 4.90 mmol, 1 equiv) and 2-iodoxybenzoic acid (4.11 g, 14.69 mmol, 3 equiv) in dry EtOAc (50 mL). The resulting suspension was stirred for 5 h under reflux (85 °C) until complete disappearance of starting material (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature and filtered through a pad of Celite, and the filtrate was concentrated in vacuo to afford (±)-**6**. No further purification was needed.

*(±)-**Z-6***. Compound (±)-*Z*-**6** was obtained as a colorless oil in 99% yield. Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.34. ^{1}H NMR (300.1 MHz, $CDCl_3$): 9.90 (d, 1H, J_{HF} = 14.4 Hz), 3.78 (s, 3H), 2.73 (dd, 1H, J_{HH} = 9.1 Hz, J_{HF} = 15.7 Hz), 2.12 (dd, 1H, J_{HH} = 9.3 Hz, J_{HF} = 19.7 Hz), 1.47 (2s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 190.7 (J_{CF} = 17.0 Hz), 168.8 (J_{CF} = 2.6 Hz), 151.0, 150.2, 84.6 (J_{CF} = 242.9 Hz), 83.7, 53.0, 48.3 (J_{CF} = 9.3 Hz), 28.1 (J_{CF} = 7.4 Hz), 27.8, 27.7. ^{19}F NMR (282.4 MHz, $CDCl_3$): −192.9 (ddd, J_{FH} = 14.9, 15.6, 19.7 Hz). MS (ESI positive mode): m/z 383.93 [M + Na]$^+$, 745.00 [2M + Na]$^+$. IR (neat): 3426, 1799, 1736, 1458, 1369, 1276, 1254, 1156, 1121, 829, 784 cm^{-1}. Anal. Calcd for $C_{16}H_{24}FNO_7$: C, 53.18; H, 6.69; N, 3.88. Found: C, 53.19; H, 6.68; N, 3.64.

*(±)-**E-6***. Compound (±)-*E*-**6** was obtained as a white solid in 65% yield. Mp: 75−77 °C. Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.40. ^{1}H NMR (300.1 MHz, $CDCl_3$): 9.57 (d, 1H, J_{HF} = 4.5 Hz), 3.77 (s, 3H), 2.78 (dd, 1H, J_{HH} = 8.5 Hz, J_{HF} = 17.5 Hz), 1.98 (dd, 1H, J_{HH} = 8.6 Hz, J_{HF} = 11.2 Hz), 1.46 (d, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 190.9 (J_{CF} = 35.9 Hz), 167.9, 151.5, 151.3, 86.4 (J_{CF} = 245.7 Hz), 84.1, 83.8, 53.3, 49.0 (J_{CF} = 13.2 Hz), 28.0, 27.9, 25.4 (J_{CF} = 9.2 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −203.2 (ddd, J_{FH} = 4.5, 11.3, 16.7 Hz). MS (ESI positive mode): m/z 383.93 [M + Na]$^+$, 745.00 [2M + Na]$^+$. IR (neat): 3393, 2980, 1737, 1439, 1370, 1253, 1254, 1159, 1123, 850, 773 cm^{-1}. Anal. Calcd for $C_{16}H_{24}FNO_7$: C, 53.18; H, 6.69; N, 3.88. Found: C, 53.20; H, 6.73; N, 3.52.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-(1-hydroxyethyl)-2-fluorocyclopropylcarboxylate. In a 25 mL round-bottom flask equipped with septum and magnetic stirrer under an argon

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atmosphere was dissolved (±)-*Z*-**6** (200 mg, 0.553 mmol, 1 equiv) in THF (6 mL) and the mixture cooled to −20 °C. After the mixture was stirred for 10 min at −20 °C, methylmagnesium bromide 1 M in THF (0.830 mL, 0.830 mmol, 1.5 equiv) was added dropwise. The mixture was stirred for 30 min at −20 °C until complete disappearance of starting material (monitored by ^{19}F NMR). Then, the reaction mixture was quenched by saturated NH_4Cl solution and stirred for 10 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting yellow oil was purified by column chromatography on silica gel to give the desired product (165 mg, 79%) as a colorless oil. Analytical TLC (silica gel 60): (40% ethyl acetate in cyclohexane) R_f = 0.48. ^{1}H NMR (300.1 MHz, $CDCl_3$): 4.20 (ddd, 1H, J_{HH} = 2.9, 6.6 Hz, J_{HF} = 28.1 Hz), 3.75 (s, 3H), 3.63 (d, 1H, J_{HH} = 2.9 Hz), 2.12 (dd, 1H, J_{HH} = 8.6 Hz, J_{HF} = 18.9 Hz), 1.74 (dd, 1H, J_{HH} = 8.6 Hz, J_{HF} = 22.6 Hz), 1.49 (2s, 18H), 1.38 (d, 3H, J_{HH} = 6.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 169.2 (J_{CF} = 2.2 Hz), 153.7, 151.6, 87.3 (J_{CF} = 237.5 Hz), 84.1, 83.2, 65.0 (J_{CF} = 20.5 Hz), 53.0, 45.0 (J_{CF} = 9.1 Hz), 27.8, 27.6, 26.5 (J_{CF} = 9.4 Hz), 17.8 (J_{CF} = 4.1 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −190.5 (ddd, J_{FH} = 18.1, 22.6, 28.4 Hz). MS (ESI positive mode): *m*/*z* 400.07 [M + Na]$^+$, 776.93 [2M + Na]$^+$. IR (neat): 2981, 1733, 1367, 1273, 1248, 1157, 1117, 1053, 868, 852, 836, 785 cm^{-1}. Anal. Calcd for $C_{17}H_{28}FNO_7$: C, 54.10; H, 7.48; N, 3.71. Found: C, 53.93; H, 7.65; N, 3.89.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-acetyl-2-fluorocyclopropylcarboxylate ((±)-*Z*-7). In a 100 mL round-bottom flask equipped with septum, magnetic stirrer, and reflux condenser under an argon atmosphere were dissolved the secondary alcohol (1.31 g, 3.47 mmol, 1 equiv) and 2-iodoxybenzoic acid (2.91 g, 10.41 mmol, 3 equiv) in dry EtOAc (50 mL). The resulting suspension was stirred for 7 h under reflux (85 °C) until complete disappearance of starting material (monitored by ^{19}F NMR). Then, the reaction mixture was cooled to room temperature and filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The resulting crude oil was purified by column chromatography on silica gel to afford (±)-*Z*-**7** as a yellow oil (677 mg, 69%). Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.35. ^{1}H NMR (300.1 MHz, $CDCl_3$): 3.67 (s, 3H), 2.62 (dd, 1H, J_{HH} = 8.8 Hz, J_{HF} = 17.8 Hz), 2.41 (d, 3H, J_{HF} = 3.5 Hz), 1.87 (dd, 1H, J_{HH} = 8.8 Hz, J_{HF} = 20.8 Hz), 1.49 (s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 197.7 (J_{CF} = 27.1 Hz), 167.5 (J_{CF} = 2.6 Hz), 153.4, 153.0, 85.6 (J_{CF} = 244.1 Hz), 83.3, 83.2, 52.9, 47.4 (J_{CF} = 9.9 Hz), 27.6, 27.4, 26.6 (J_{CF} = 1.6 Hz), 24.8 (J_{CF} = 8.1 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −183.9 (tdd, J_{FH} = 3.1, 17.6, 20.6 Hz). MS (ESI positive mode): *m*/*z* 398.07 [M + Na]$^+$, 773.00 [2M + Na]$^+$. IR (neat): 2978, 1733, 1715, 1367, 1272, 1251, 1155, 1115, 1089, 865, 852, 785 cm^{-1}. Anal. Calcd for $C_{17}H_{26}FNO_7$: C, 54.39; H, 6.98; N, 3.73. Found: C, 54.26; H, 7.11; N, 3.86.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-(*N,O*-dimethylhydroxylaminocarbonyl)-2-fluorocyclopropylcarboxylate ((±)-*E*-2a). In a 50 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-*E*-**2** (100 mg, 0.27 mmol, 1 equiv) in anhydrous DMF (4 mL), and the resulting solution was cooled to 0 °C. Subsequently, HBTU (120.6 mg, 0.32 mmol, 1.2 equiv) and DIEA (0.231 mL, 1.33 mmol, 5 equiv) were added, and the reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature for 5 min. Then, a solution of *N,O*-dimethylhydroxylamine hydrochloride (52 mg, 0.53 mmol, 2 equiv) in anhydrous DMF (1.5 mL) was added dropwise, and the resulting orange solution was stirred at room temperature overnight. Upon completion, the reaction mixture was dissolved with EtOAc (10 mL). The organic layer was washed with 1 M $NaHCO_3$ solution (2 × 5 mL), water (5 mL), and brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting crude oil was purified by column chromatography on silica gel to afford (±)-*E*-**2a** as a white solid (70 mg, 62%). Mp: 103−105 °C. Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.46. ^{1}H NMR (300.1 MHz, $CDCl_3$): 3.76 (s, 3H), 3.71 (s, 3H), 3.27 (bs, 3H), 2.56 (dd, 1H, J_{HH} = 8.1 Hz, J_{HF} = 20.0 Hz), 2.28 (bm, 1H), 1.46 (s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 166.5, 152.2, 151.3, 84.2 (J_{CF} = 259.1 Hz), 82.7, 60.7, 53.0, 48.1 (J_{CF} = 13.1 Hz), 27.8, 26.0. ^{19}F NMR (282.4 MHz, $CDCl_3$): −187.2 and −193.2 (bs). MS (ESI positive mode): *m*/*z* 443.13 [M + Na]$^+$, 459.20 [M + K]$^+$, 863.07 [2M + Na]$^+$, 878.87 [2M + K]$^+$. IR (neat): 2983, 1734, 1708, 1655, 1364, 1168, 1125, 1004, 845, 781, 755, 548, 448 cm^{-1}. Anal. Calcd for $C_{18}H_{29}FN_2O_8$: C, 51.42; H, 6.95; N, 6.66. Found: C, 50.98; H, 6.89; N, 6.71.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-acetyl-2-fluorocyclopropylcarboxylate ((±)-*E*-7). In a 50 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-*E*-**2a** (545 mg, 1.30 mmol, 1 equiv) in THF (20 mL). The resulting solution was cooled to −78 °C, and methyllithium 1.5 M in Et_2O (1.73 mL, 2.6 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred for 45 min at −78 °C until complete disappearance of starting material (monitored by TLC). Then the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford (±)-*E*-**7** (278 mg, 57%). Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.33. ^{1}H NMR (300.1 MHz, $CDCl_3$): 3.76 (s, 3H), 2.65 (dd, 1H, J_{HH} = 8.1 Hz, J_{HF} = 17.9 Hz), 2.42 (d, 3H, J_{HF} = 5.2 Hz), 2.05 (dd, 1H, J_{HH} = 8.1 Hz, J_{HF} = 12.0 Hz), 1.46 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 200.0 (J_{CF} = 28.9 Hz), 166.3 (J_{CF} = 1.1 Hz), 152.7, 151.2, 87.1 (J_{CF} = 252.1 Hz), 83.6, 83.2, 53.2, 49.5 (J_{CF} = 13.2 Hz), 27.7, 26.6, 26.3 (J_{CF} = 8.7 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −193.3 (ddd, J_{FH} = 5.3, 11.9, 17.5 Hz). MS (ESI positive mode): *m*/*z* 398.07 [M + Na]$^+$, 773.00 [2M + Na]$^+$. IR (neat): 2984, 1723, 1708, 1366, 1276, 1245, 1216, 1115, 1044, 778, 543 cm^{-1}. Anal. Calcd for $C_{17}H_{26}FNO_7$: C, 54.39; H, 6.98; N, 3.73. Found: C, 54.64; H, 6.95; N, 3.97.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-fluoro-2-(prop-1-en-2-yl)cyclopropylcarboxylate ((±)-8). *General Procedure for the Synthesis of (±)-Z- and (±)-E-8.* In a 100 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was added methyltriphenylphosphonium bromide (1.59 g, 4.46 mmol, 2.5 equiv) in Et_2O (30 mL). The resulting suspension was cooled to 0 °C and the mixture stirred for 10 min. Then potassium bis(trimethylsilyl)amide 0.5 M in toluene (8.92 mL, 4.46 mmol, 2.5 equiv) was added, and the yellow solution was stirred for 10 min at 0 °C. Subsequently, (±)-7 (670 mg, 1.78 mmol, 1 equiv), previously dissolved in Et_2O (10 mL), was added slowly at 0 °C, and the resulting orange solution was allowed to warm to room temperature and stirred for 1 h until complete disappearance of starting material (monitored by TLC and ^{19}F NMR). Then the reaction mixture was quenched with water, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford a brownish oil. The resulting crude oil was purified by column chromatography on silica gel to afford (±)-**8**

(±)-Z-8. Compound (±)-*Z*-**8** was obtained as a white solid in 79% yield. Mp: 79−81 °C. Analytical TLC (silica gel 60): (10% ethyl acetate in cyclohexane) R_f = 0.31. ^{1}H NMR (300.1 MHz, $CDCl_3$): 5.32 (dd, 1H, J_{HH} = J_{gem} = 1.4 Hz, J_{HF} = 4.6 Hz), 5.24 (d, 1H, J_{HH} = J_{gem} = 1.4 Hz), 3.71 (s, 3H), 2.29 (dd, 1H, J_{HH} = 8.3 Hz, J_{HF} = 16.9 Hz), 1.93 (s, 3H), 1.76 (dd, 1H, J_{HH} = 8.3 Hz, J_{HF} = 21.3 Hz), 1.51 (s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 168.9 (J_{CF} = 2.3 Hz), 152.8, 152.2, 136.5 (J_{CF} = 18.5 Hz), 119.4 (J_{CF} = 7.5 Hz), 87.0 (J_{CF} = 228.1 Hz), 83.0, 82.8, 52.5, 46.2 (J_{CF} = 10.9 Hz), 28.0, 27.7, 26.3 (J_{CF} = 9.8 Hz), 19.3. ^{19}F NMR (282.4 MHz, $CDCl_3$): −166.6 (ddd, J_{FH} = 4.5, 16.7, 21.2 Hz). MS (ESI positive mode): *m*/*z* 396.20 [M + Na]$^+$, 769.13 [2M + Na]$^+$. IR (neat): 2980, 1735, 1360, 1269, 1241, 1128, 1092, 916, 876 cm^{-1}. Anal. Calcd for $C_{18}H_{28}FNO_6$: C, 57.90; H, 7.56; N, 3.75. Found: C, 57.89; H, 7.47; N, 3.61.

(±)-E-8. Compound (±)-*E*-**8** was obtained as a white solid in 65% yield. Mp: 75−77 °C. Analytical TLC (silica gel 60): (10% ethyl acetate in cyclohexane) R_f = 0.30. ^{1}H NMR (300.1 MHz, $CDCl_3$): 5.00 (dd, 1H, J_{HH} = J_{gem} = 1.3 Hz, J_{HF} = 2.7 Hz), 4.79 (d, 1H, J_{HH} = J_{gem} = 1.3 Hz), 3.75 (s, 3H), 2.58 (dd, 1H, J_{HH} = 8.9 Hz, J_{HF} = 21.4 Hz), 1.88 (s, 3H), 1.72 (dd, 1H, J_{HH} = 8.9 Hz, J_{HF} = 13.5 Hz), 1.45 (s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 168.0, 151.9, 151.7, 138.2 (J_{CF} = 23.5 Hz), 113.5 (J_{CF} = 8.1 Hz), 86.5 (J_{CF} = 232.8 Hz), 83.0, 82.8, 52.8, 48.6 (J_{CF} = 15.8 Hz), 27.9, 27.8, 25.8 (J_{CF} = 9.7 Hz), 19.7 (J_{CF} = 6.3 Hz). ^{19}F NMR (282.4

MHz, $CDCl_3$): −181.6 (ddd, J_{FH} = 2.3, 13.6, 20.6 Hz). MS (ESI positive mode): m/z 396.07 $[M + Na]^+$, 769.00 $[2M + Na]^+$. IR (neat): 2979, 1744, 1714, 1363, 1243, 1162, 1122, 1062, 904, 851, 835, 749 cm^{-1}. HRMS (ESI positive mode) calcd for $C_{18}H_{28}FNO_6Na$ 396.1798, found 396.1794.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-fluoro-2-isopropylcyclopropylcarboxylate ((±)-9). *General Procedure for the Synthesis of (±)-Z- and (±)-E-9.* A solution of (±)-**8** (207.2 mg, 0.555 mmol, 1 equiv) and tris(triphenylphosphine)rhodium chloride (51.3 mg, 0.055 mmol, 10 mol %) in toluene (20 mL) was stirred under a pressure of hydrogen at 20 bar for 24 h, until complete disappearance of starting material (monitored by TLC). After evaporation of the solvent in vacuo, the resulting orange crude oil was purified by column chromatography on silica gel to afford (±)-**9**.

(±)-Z-9. Compound (±)-*Z*-**9** was obtained as a white solid in 89% yield. Mp: 69−72 °C. Analytical TLC (silica gel 60): (10% ethyl acetate in cyclohexane) R_f = 0.34. ^1H NMR (300.1 MHz, $CDCl_3$): 3.71 (s, 3H), 2.22 (m, 1H), 1.86 (dd, 1H, J_{HH} = 7.8 Hz, J_{HF} = 17.1 Hz), 1.65 (dd, 1H, J_{HH} = 7.8 Hz, J_{HF} = 21.6 Hz), 1.47 (2s, 18H), 1.11 (d, 3H, J_{HH} = 7.2 Hz), 1.02 (d, 3H, J_{HH} = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 170.0 (J_{CF} = 2.3 Hz), 152.8, 152.3, 89.5 (J_{CF} = 237.4 Hz), 82.3, 82.2, 52.5, 45.8 (J_{CF} = 9.6 Hz), 28.6, 28.2 (J_{CF} = 8.8 Hz), 27.9, 27.8, 18.1, 17.3. ^{19}F NMR (282.4 MHz, $CDCl_3$): −189.9 (ddd, J_{FH} = 17.2, 22.0, 33.6 Hz). MS (ESI positive mode): m/z 398.13 $[M + Na]^+$, 772.80 $[2M + Na]^+$. IR (neat): 2890, 1753, 1736, 1726, 1366, 1310, 1292, 1276, 1156, 1112, 1089, 1048, 872, 863 cm^{-1}. Anal. Calcd for $C_{18}H_{30}FNO_6$: C, 57.58; H, 8.05; N, 3.73. Found: C, 57.96; H, 8.32; N, 3.67.

(±)-E-9. Compound (±)-*E*-**9** was obtained as a white solid in 78% yield. Mp: 64−66 °C. Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.38. ^1H NMR (300.1 MHz, $CDCl_3$): 3.74 (s, 3H), 2.38 (dd, 1H, J_{HH} = 8.5 Hz, J_{HF} = 21.2 Hz), 1.85 (m, 1H), 1.49 (s, 18H), 1.18 (d, 3H, J_{HH} = 6.9 Hz), 1.17 (m, 1H), 1.06 (d, 3H, J_{HH} = 6.9 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 168.7, 152.7, 152.6, 89.7 (J_{CF} = 241.1 Hz), 83.2, 52.6, 48.4 (J_{CF} = 15.2 Hz), 30.2 (J_{CF} = 21.4 Hz), 28.0, 25.8 (J_{CF} = 10.4 Hz), 20.0, 17.9 (J_{CF} = 7.6 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −192.1 (ddd, J_{FH} = 14.7, 22.0, 35.6 Hz). MS (ESI positive mode): m/z 398.07 $[M + Na]^+$. IR (neat): 2974, 1745, 1714, 1437, 1355, 1237, 1158, 1122, 1057, 1025, 850, 795, 778, 752 cm^{-1}. Anal. Calcd for $C_{18}H_{30}FNO_6$: C, 57.58; H, 8.05; N, 3.73. Found: C, 57.24; H, 8.02; N, 3.72.

Lysine Analogue. Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)-amino)-2-(2-cyanovinyl)-2-fluorocyclopropylcarboxylate ((±)-14). *General Procedure for the Synthesis of (±)-Z- and (±)-E-14.* In a 100 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-**6** (1.38 g, 3.81 mmol, 1 equiv) in THF (25 mL). Subsequently, diethyl cyanomethylphosphonate (1.23 mL, 7.61 mmol, 2 equiv) and triethylamine (1.07 mL, 7.61 mmol, 2 equiv) were successively added. The resulting suspension was stirred overnight at room temperature until complete disappearance of starting material (monitored by TLC). The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The resulting orange crude oil was purified by column chromatography on silica gel to afford the expected product as a white solid.

(±)-Z-14. Compound (±)-*Z*-**14** was obtained as a white solid in 78% yield. Mp: 105−107 °C. Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.27. ^1H NMR (300.1 MHz, $CDCl_3$): 7.08 (dd, 1H, J_{HH} = J_{trans} = 16.3 Hz, J_{HF} = 23.9 Hz), 5.76 (d, 1H, J_{HH} = J_{trans} = 16.3 Hz), 3.79 (s, 3H), 2.39 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 17.0 Hz), 2.04 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 21.5 Hz), 1.51 (s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 168.7 (J_{CF} = 2.5 Hz), 151.3, 150.9, 145.6 (J_{CF} = 16.1 Hz), 116.4, 100.6 (J_{CF} = 12.6 Hz), 83.8, 83.4, 83.1 (J_{CF} = 237.3 Hz), 53.4, 48.2 (J_{CF} = 9.1 Hz), 29.8 (J_{CF} = 8.5 Hz), 28.2, 28.1. ^{19}F NMR (282.4 MHz, $CDCl_3$): −182.2 (ddd, J_{FH} = 17.2, 21.5, 24.0 Hz). MS (ESI positive mode): m/z 407.07 $[M + Na]^+$, 791.00 $[2M + Na]^+$. IR (neat): 3441, 2981, 2236, 1789, 1737, 1458, 1377, 1276, 1156, 1100, 966, 854, 787 cm^{-1}. Anal. Calcd for $C_{18}H_{25}FN_2O_6$: C, 56.24; H, 6.56; N, 7.29. Found: C, 55.97; H, 6.51; N, 7.32.

(±)-E-14. Compound (±)-*E*-**14** was obtained as a white solid in 39% yield. Mp: 123−125 °C. Analytical TLC (silica gel 60): (20% ethyl acetate in cyclohexane) R_f = 0.23. ^1H NMR (300.1 MHz, $CDCl_3$): 6.40 (dd, 1H, J_{HH} = J_{trans} = 16.2 Hz, J_{HF} = 22.2 Hz), 5.69 (d, 1H, J_{HH} = J_{trans} = 16.2 Hz), 3.78 (s, 3H), 2.79 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 18.9 Hz), 1.57 (dd, 1H, J_{HH} = 9.0 Hz, J_{HF} = 11.1 Hz), 1.48 (2s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 166.4, 151.2, 150.9, 149.1 (J_{CF} = 17.8 Hz), 116.5, 99.7 (J_{CF} = 12.1 Hz), 84.4 (J_{CF} = 242.5 Hz), 84.1, 83.9, 53.2, 49.3 (J_{CF} = 13.0 Hz), 28.1 (J_{CF} = 9.6 Hz), 27.9, 27.8. ^{19}F NMR (282.4 MHz, $CDCl_3$): −191.8 (ddd, J_{FH} = 11.3, 19.2, 22.3 Hz). MS (ESI positive mode): m/z 407.13 $[M + Na]^+$. IR (neat): 3439, 2983, 2243, 1733, 1709, 1364, 1235, 1164, 1127, 979, 966, 844, 776 cm^{-1}. Anal. Calcd for $C_{18}H_{25}FN_2O_6$: C, 56.24; H, 6.56; N, 7.29. Found: C, 56.26; H, 6.52; N, 7.27.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-(2-cyanoethyl)-2-fluorocyclopropylcarboxylate ((±)-E-14a). In a 50 mL round-bottom flask equipped with septum and magnetic stirrer was dissolved (±)-*E*-**14** (72 mg, 0.187 mmol, 1 equiv) in EtOAc (2.5 mL). Subsequently, palladium 10% on dry carbon (19.9 mg, 0.019 mmol, 10 mol %) was added, and the resulting suspension was stirred overnight under an atmospheric pressure of hydrogen at room temperature until complete disappearance of starting material (monitored by TLC). The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to afford the expected product as a white solid (68 mg, 94%). No further purification was needed. Mp: 102−104 °C. Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.40. ^1H NMR (300.1 MHz, $CDCl_3$): 3.73 (s, 3H), 2.64 (m, 2H), 2.51 (m, 2H), 1.82 (m, 1H), 1.49 (s, 9H), 1.47 (s, 9H), 1.29 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 12.3 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 170.7, 152.0, 151.6, 118.7, 85.5 (J_{CF} = 257.6 Hz), 83.6, 83.5, 52.5, 46.7 (J_{CF} = 13.9 Hz), 28.5 (J_{CF} = 21.9 Hz), 28.0, 25.7 (J_{CF} = 10.5 Hz), 13.5. ^{19}F NMR (282.4 MHz, $CDCl_3$): −186.0 (m). MS (ESI positive mode): m/z 409.40 $[M + Na]^+$, 794.87 $[2M + Na]^+$. IR (neat): 2981, 2249, 1739, 1716, 1438, 1368, 1273, 1252, 1220, 1151, 1118, 1100, 956, 853, 784, 760, 462 cm^{-1}. Anal. Calcd for $C_{18}H_{27}FN_2O_6$: C, 55.95; H, 7.04; N, 7.25. Found: C, 55.94; H, 7.09; N, 7.26.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-(3-amino-propyl)-2-fluorocyclopropylcarboxylate Hydrochloride ((±)-15). *General Procedure for the Synthesis of (±)-Z- and (±)-E-1.* A solution of (±)-*Z*-**14** or (±)-*E*-**14a** (0.399 mmol, 1 equiv), chloroform (0.270 mL, 0.399 mmol, 1 equiv), and platinum oxide (13.6 mg, 0.06 mmol, 15 mol %) in EtOH (12 mL) was stirred under a pressure of hydrogen at 20 bar for 24 h until complete disappearance of starting material (monitored by TLC). Upon completion, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to afford (±)-**15**. No further purification was needed.

(±)-Z-15. Compound (±)-*Z*-**15** was obtained as a pale yellow oil in 89% yield. ^1H NMR (300.1 MHz, CD_3OD): 3.73 (s, 3H), 2.98 (m, 2H), 2.03 (m, 2H), 1.69 (m, 2H), 1.51 (s, 18H), 1.46 (m, 2H). ^{13}C NMR (75.4 MHz, CD_3OD): 172.7, 153.6, 87.1 (J_{CF} = 231.3 Hz), 84.8, 59.4, 52.8, 40.7, 30.8, 28.9, 28.8, 26.7 (J_{CF} = 15.6 Hz). ^{19}F NMR (282.4 MHz, CD_3OD): −172.5 (bs). MS (ESI positive mode): m/z 391.13 $[M + H]^+$. IR (neat): 2976, 1744, 1694, 1367, 1279, 1251, 1124, 851, 763, 462 cm^{-1}. HRMS (ESI positive mode): calcd for $C_{18}H_{32}FN_2O_6$ 391.2244, found 391.2245

(±)-E-15. Compound (±)-*E*-**15** was obtained as a colorless oil in 87% yield. ^1H NMR (300.1 MHz, CD_3OD): 3.76 (s, 3H), 3.06 (m, 2H), 2.44 (m, 2H), 2.03 (s, 2H), 1.60−1.48 (m, 20H). ^{13}C NMR (75.4 MHz, CD_3OD): 169.8, 153.4, 153.0, 88.4 (J_{CF} = 237.5 Hz), 84.8, 84.7, 53.3, 40.3, 30.5 (J_{CF} = 21.9 Hz), 28.7, 28.1, 27.0 (J_{CF} = 10.0 Hz), 24.9. ^{19}F NMR (282.4 MHz, CD_3OD): −184.2 (m). MS (ESI positive mode): m/z 391.07 $[M + H]^+$, 780.80 $[2M + H]^+$. IR (neat): 2984, 1739, 1369, 1154, 1105, 851, 787 cm^{-1}. HRMS (ESI positive mode) calcd for $C_{18}H_{32}FN_2O_6$ 391.2244, found 391.2249.

Arginine Analogue. Methyl 1-(*N,N*-(Di-*tert*-butyloxy-carbonyl)amino)-2-(2-nitrovinyl)-2-fluorocyclopropylcarboxy-late ((±)-Z-16). In a 50 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-*Z*-**6** (1 g, 2.77 mmol, 1 equiv) in toluene (12 mL) and the mixture cooled to 0 °C. Subsequently, 1,1,3,3-tetramethylguanidine (35 μL, 0.28 mmol, 10 mol %) and nitromethane (1.49 mL, 27.67 mmol, 10 equiv) were added slowly, and the reaction mixture was stirred for 3 h at 0 °C until complete

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disappearance of starting material (monitored by TLC and ^{19}F NMR). Triethylamine (0.974 mL, 6.93 mmol, 2.5 equiv) and methanesulfonyl chloride (0.322 mL, 4.16 mmol, 1.5 equiv) were added, and the reaction mixture was stirred for 2 h at 0 °C. Upon completion, the reaction mixture was diluted with EtOAc (30 mL) and washed with saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the desired (±)-*Z*-**16** as a white solid (796 mg, 71%). The crude product was directly engaged in the next step. Mp: 106−107 °C. Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.57. ^1H NMR (300.1 MHz, $CDCl_3$): 7.67 (dd, 1H, $J_{HH} = J_{trans}$ = 13.2 Hz, J_{HF} = 26.1 Hz), 7.30 (d, 1H, $J_{HH} = J_{trans}$ = 13.2 Hz), 3.79 (s, 3H), 2.47 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 16.8 Hz), 2.12 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 21.3 Hz), 1.48 (d, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 167.5 (J_{CF} = 2.6 Hz), 150.3, 150.0, 139.1 (J_{CF} = 9.0 Hz), 133.9 (J_{CF} = 14.9 Hz), 82.9, 82.5, 81.2 (J_{CF} = 234.1 Hz), 52.4, 47.2 (J_{CF} = 9.1 Hz), 30.1 (J_{CF} = 9.1 Hz), 29.0, 28.7. ^{19}F NMR (282.4 MHz, $CDCl_3$): −179.1 (ddd, J_{FH} = 16.6, 21.4, 25.9 Hz). MS (ESI positive mode): *m*/*z* 427.07 $[M + Na]^+$, 830.87 $[2M + Na]^+$. IR (neat): 3446, 2981, 2936, 1796, 1732, 1536, 1463, 1435, 1371, 1276, 1256, 1156, 1097, 1119, 972, 854, 784 cm^{-1}. HRMS (ESI positive mode): calcd for $C_{17}H_{25}FN_2O_8Na$ 427.1493, found 427.1485.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-(2-nitroethyl)-2-fluorocyclopropylcarboxylate ((±)-*Z*-17). In a 100 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-*Z*-**16** (780 mg, 1.93 mmol, 1 equiv) in EtOH (40 mL) and the mixture cooled to 0 °C. Sodium borohydride (365 mg, 9.65 mmol, 5 equiv) was added portionwise. After being stirred at room temperature for 1 h, the reaction mixture was evaporated. The resulting residue was dissolved in EtOAc and quenched with saturated NH_4Cl solution (20 mL), and the aqueous layer was extracted by EtOAc (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford (±)-*Z*-**17** as a white solid (720 mg, 92%). Mp: 80−82 °C. Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.33. ^1H NMR (300.1 MHz, $CDCl_3$): 4.65 (m, 2H), 3.77 (s, 3H), 2.91 (m, 2H), 2.03 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 17.9 Hz), 1.79 (dd, 1H, J_{HH} = 8.7 Hz, J_{HF} = 15.7 Hz), 1.51 (2s, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 169.5 (J_{CF} = 2.4 Hz), 152.5, 151.7, 83.3, 83.2, 83.0 (J_{CF} = 232.3 Hz), 71.2, 53.1, 44.5 (J_{CF} = 9.4 Hz), 27.9 (J_{CF} = 8.9 Hz), 27.8, 27.7, 27.4 (J_{CF} = 27.3 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −175.2 (dddd, J_{FH} = 15.5, 17.5, 21.5, 24.6 Hz). MS (ESI positive mode): *m*/*z* 428.93 $[M + Na]^+$. IR (neat): 3441, 2976, 2931, 1740, 1556, 1435, 1368, 1276, 1248, 1159, 1123, 1097, 854, 790 cm^{-1}. HRMS (ESI positive mode): calcd for $C_{17}H_{27}FN_2O_8Na$ 429.1649, found 429.1635.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-(2-aminoethyl)-2-fluorocyclopropylcarboxylate ((±)-*Z*-18). A solution of (±)-*Z*-**17** (272 mg, 0.670 mmol, 1 equiv) and palladium 10% on dry carbon in MeOH (6 mL) was stirred under a pressure of hydrogen at 10 bar for 16 h, until complete disappearance of starting material (monitored by TLC). Upon completion, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to afford the desired product (217 mg, 86%). No further purification was needed. ^1H NMR (300.1 MHz, $CDCl_3$): 4.20 (bs, 2H), 3.75 (s, 3H), 3.07 (m, 2H), 2.53 (m, 2H), 1.99 (dd, 1H, J_{HH} = 8.3 Hz, J_{HF} = 13.1 Hz), 1.67 (dd, 1H, J_{HH} = 7.9 Hz, J_{HF} = 21.8 Hz), 1.48 (d, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 169.5, 153.0, 151.8, 84.8 (J_{CF} = 219.2 Hz), 83.7, 83.2, 53.1, 44.8 (J_{CF} = 9.4 Hz), 37.6, 30.9 (J_{CF} = 19.9 Hz), 28.2, 27.7 (J_{CF} = 9.5 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −172.4 (dddd, J_{FH} = 14.6, 17.4, 22.6, 33.6 Hz). MS (ESI positive mode): *m*/*z* 377.00 $[M + H]^+$. IR (neat): 1699, 1225, 1158, 1105, 1086, 1031, 1011, 846, 782 cm^{-1}. HRMS (ESI positive mode): calcd for $C_{17}H_{30}FN_2O_6$ 377.2088, found 377.2092.

Methyl 1-(*N,N*-(Di-*tert*-butyloxycarbonyl)amino)-2-(2-(2,3-bis((benzyloxy)carbonyl)guanidine)ethyl)-2-fluorocyclopropylcarboxylate ((±)-*Z*-19). In a 10 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved *N,N′*-di-Cbz-*N″*-trifluoromethanesulfonylguanidine (95 mg, 0.213 mmol, 1 equiv) in CH_2Cl_2 (1 mL). Triethylamine (28 μL, 0.213 mmol, 1 equiv) and (±)-*Z*-**18** (80 mg, 0.213 mmol, 1 equiv) were added. The reaction mixture was stirred overnight at room temperature until complete disappearance of starting material (monitored by TLC and ^{19}F NMR). Then, the mixture was quenched with saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (2 × 1 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel to afford (±)-*Z*-**19** as a pale yellow oil (35 mg, 24%). Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.50. ^1H NMR (300.1 MHz, $CDCl_3$): 11.64 (s, 1H), 8.59 (t, 1H, J_{HH} = 5.4 Hz), 7.35−7.18 (10H), 5.08 (s, 2H), 5.05 (s, 2H), 3.63 (m, 2H), 3.57 (s, 3H), 2.33 (dq, 2H, J_{HH} = 5.9 Hz, J_{HF} = 25.4 Hz), 1.92 (dd, 1H, J_{HH} = 8.4 Hz, J_{HF} = 18.2 Hz), 1.59 (dd, 1H, J_{HH} = 8.3 Hz, J_{HF} = 22.1 Hz), 1.42 (d, 18H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 169.6 (J_{CF} = 2.3 Hz), 163.7, 155.7, 153.4, 152.2, 152.0, 136.9, 134.8, 128.8, 128.7, 128.6, 128.5, 128.2, 127.9, 84.8 (J_{CF} = 231.6 Hz), 83.1, 83.0, 68.0, 67.1, 52.7, 44.7 (J_{CF} = 9.3 Hz), 37.5, 28.9 (J_{CF} = 19.8 Hz), 28.1, 28.0, 27.6 (J_{CF} = 9.7 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −172.6 (m). MS (ESI positive mode): *m*/*z* 687.27 $[M + H]^+$, 709.00 $[M + Na]^+$. Anal. Calcd for $C_{34}H_{43}FN_4O_{10}$: C, 59.47; H, 6.31; N, 8.16. Found: C, 59.78; H, 6.38; N, 7.93.

Selective Deprotection and Peptide Coupling. Methyl 1-((*tert*-Butyloxycarbonyl)amino)-2-fluoro-2-isopropylcyclopropylcarboxylate ((±)-*Z*-11). In a 25 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-*Z*-**9** (150 mg, 0.40 mmol, 1 equiv) in CH_3CN (5 mL). The resulting solution was cooled to 0 °C, ytterbium(III) trifluoromethanesulfonate (248 mg, 0.40 mmol, 1 equiv) was added, and the solution was stirred for 1 h at room temperature until complete disappearance of starting material (monitored by TLC). Then, the reaction mixture was dissolved with EtOAc (30 mL), and the organic layer was washed with water (15 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford a pale yellow solid. The resulting crude product was purified by column chromatography on silica gel to afford (±)-*Z*-**11** as a colorless oil (102 mg, 93%). Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.50. ^1H NMR (300.1 MHz, $CDCl_3$): 5.30 and 5.06 (bs, 1H), 3.71, 1.85 (m, 2H), 1.52 (dd, 1H, J_{HH} = 7.8 Hz, J_{HF} = 21.4 Hz), 1.42 (s, 9H), 1.10 (d, 3H, J_{HH} = 6.9 Hz), 0.92 (d, 3H, J_{HH} = 6.9 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 170.2, 155.6, 88.2 (J_{CF} = 236.7 Hz), 80.2, 52.7, 41.4 (J_{CF} = 9.2 Hz), 28.9 (J_{CF} = 20.4 Hz), 28.3, 25.9 (J_{CF} = 7.6 Hz), 17.6 (J_{CF} = 2.1 Hz), 17.3 (J_{CF} = 1.8 Hz). ^{19}F NMR (282.4 MHz, $CDCl_3$): −195.2 (ddd, J_{FH} = 16.1, 21.2, 35.9 Hz), −195.6 (m). MS (ESI positive mode): *m*/*z* 275.73 $[M + H]^+$, 298.20 $[M + Na]^+$. IR (neat): 3255, 2976, 1710, 1360, 1326, 1254, 1200, 1155, 1047, 1027, 857, 706, 642, 442 cm^{-1}. Anal. Calcd for $C_{13}H_{22}FNO_4$: C, 56.71; H, 8.05; N, 5.09. Found: C, 56.66; H, 8.07; N, 5.19.

1-((*tert*-Butyloxycarbonyl)amino)-2-fluoro-2-isopropylcyclopropylcarboxylic Acid ((±)-*Z*-12). In a 25 mL round-bottom flask equipped with septum and magnetic stirrer was dissolved (±)-*Z*-**11** (186 mg, 0.68 mmol, 1 equiv) in a mixture of MeOH/water 2:3 (8.5 mL) and the mixture cooled to 0 °C. Subsequently, lithium hydroxide (81 mg, 3.38 mmol, 5 equiv) was added slowly, and the solution was stirred under reflux until complete disappearance of starting material (monitored by TLC). Upon completion, the reaction mixture was dissolved with EtOAc (10 mL), and 1 M $KHSO_4$ solution was added until pH 2. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford (±)-*Z*-**12** as a white solid (134.1 mg, 76%). No further purification was needed. Mp: 161−163 °C. Analytical TLC (silica gel 60): (50% ethyl acetate in cyclohexane) R_f = 0.17. ^1H NMR (300.1 MHz, CD_3OD): 5.00 (bs, 1H), 2.07 (dq, 1H, J_{HH} = 6.9 Hz, J_{HF} = 33.2 Hz), 1.80 (dd, 1H, J_{HH} = 7.5 Hz, J_{HF} = 15.9 Hz), 1.45 (s, 9H), 1.43 (dd, 1H, J_{HH} = 7.6 Hz, J_{HF} = 20.9 Hz), 1.14 (d, 3H, J_{HH} = 7.0 Hz), 1.04 (d, 3H, J_{HH} = 6.9 Hz). ^{13}C NMR (75.4 MHz, CD_3OD): 176.2, 161.1, 91.9 (J_{CF} = 235.0 Hz), 83.2, 45.0 (J_{CF} = 9.2 Hz), 31.1 (J_{CF} = 20.2 Hz), 29.4, 26.3 (J_{CF} = 8.2 Hz), 18.0 (J_{CF} = 2.3 Hz), 17.8 (J_{CF} = 1.8 Hz). ^{19}F NMR (282.4 MHz, CD_3OD): −191.9

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(ddd, J_{FH} = 16.1, 20.9, 33.9 Hz), −192.5 (ddd, J_{FH} = 16.1, 20.3, 34.7 Hz). MS (ESI positive mode): m/z 259.93 $[M\text{-}H]^-$. IR (neat): 3246, 3089, 2977, 1691, 1646, 1408, 1367, 1165, 1084, 861, 795, 785, 618 cm^{-1}. Anal. Calcd for $C_{12}H_{20}FNO_4$: C, 55.16; H, 7.72; N, 5.36. Found: C, 55.08; H, 7.96; N, 5.51.

Methyl 1-Amino-2-fluoro-2-isopropylcyclopropylcarboxylate Hydrochloride ((±)-*Z*-10). In a 25 mL round-bottom flask equipped with septum and magnetic stirrer was dissolved (±)-*Z*-**9** (700 mg, 1.87 mmol, 1 equiv) in MeOH (5 mL). A solution of HCl 4 M in dioxane (3.5 mL) was added slowly, and the solution was stirred at room temperature until complete disappearance of starting material (monitored by TLC). Then, the reaction mixture was concentrated in vacuo to afford (±)-*Z*-**10** as a pale yellow solid (395 mg, quant.). No further purification was needed. Mp: 192−194 °C. ^{1}H NMR (300.1 MHz, CD_3OD): 3.91 (s, 3H), 2.08 (dq, 1H, J_{HH} = 6.9 Hz, J_{HF} = 34.3 Hz), 1.97 (m, 2H), 1.22 (d, 3H, J_{HH} = 7.0 Hz), 1.07 (d, 3H, J_{HH} = 6.9 Hz). ^{13}C NMR (75.4 MHz, CD_3OD): 167.6, 87.6 (J_{CF} = 235.5 Hz), 54.6, 41.1 (J_{CF} = 9.5 Hz), 29.7 (J_{CF} = 20.1 Hz), 23.2 (J_{CF} = 9.3 Hz), 17.8 (J_{CF} = 1.8 Hz). ^{19}F NMR (282.4 MHz, CD_3OD): −196.6 (m). GCMS: m/z 175 [M − HCl]. IR (neat): 2981, 2879, 2671, 2165, 1995, 1741, 1525, 1339, 1316, 1257, 1197, 1165, 889, 865, 784, 688, 539 cm^{-1}. Anal. Calcd for $C_8H_{15}ClFNO_2$: C, 45.40; H, 7.14; N, 6.62. Found: C, 45.53; H, 7.41; N, 6.60.

1-Amino-2-fluoro-2-isopropylcyclopropylcarboxylic Acid Hydrochloride ((±)-*Z*-13). In a 100 mL round-bottom flask equipped with septum, magnetic stirrer, and reflux condenser was dissolved (±)-*Z*-**9** (366 mg, 0.975 mmol) in a solution of AcOH/HCl 12 N (1:1) (50 mL). The solution was stirred under reflux for 30 h until complete disappearance of starting material (monitored by ^{19}F NMR). Then, the reaction mixture was concentrated in vacuo. The residue was dissolved in 1 M HCl solution, and the aqueous phase was washed with CH_2Cl_2 (10 mL) and Et_2O (10 mL). Subsequently, the aqueous phase was lyophilized to afford (±)-*Z*-**13** as a pale brownish solid (354 mg, 88%). Mp: 204−207 °C. ^{1}H NMR (300.1 MHz, CD_3OD): 5.93 (bs, 2H), 1.98 (bm, 3H), 1.14−1.04 (bm, 6H). ^{13}C NMR (75.4 MHz, CD_3OD): 169.8, 87.8 (J_{CF} = 233.9 Hz), 41.9, 29.9 (J_{CF} = 17.6 Hz), 23.6, 18.2. ^{19}F NMR (282.4 MHz, CD_3OD): −197.1 (bs). MS (ESI negative mode): m/z 160.08 $[M - H - HCl]^-$. IR (neat): 2971, 2878, 1717, 1579, 1488, 1427, 1192, 1136, 1054, 889, 859, 677, 629, 551, 516 cm^{-1}. HRMS (ESI negative mode): calcd for $C_7H_{11}FNO_2$ 160.0774, found 160.0771.

Methyl 2-(1-((*tert*-Butyloxycarbonyl)amino)-2-fluoro-2-isopropylcyclopropylcarboxamido)propanoate (*Z*-20). In a 100 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved (±)-*Z*-**12** (258 mg, 0.99 mmol, 1 equiv) in anhydrous DMF (15 mL), and the resulting solution was cooled to 0 °C. Subsequently, HATU (451 mg, 1.19 mmol, 1.2 equiv) and DIEA (895 μL, 5.14 mmol, 5.2 equiv) were added, and the reaction mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature for 30 min. Then, a solution of alanine methyl ester hydrochloride (579 mg, 4.15 mmol, 4.2 equiv), DBU (621 μL, 4.15 mmol, 4.2 equiv), and DMAP (507 mg, 4.15 mmol, 4.2 equiv) in anhydrous DMF (15 mL) was added dropwise, and the resulting yellow solution was stirred at room temperature overnight. Upon completion, the reaction mixture was dissolved with EtOAc (50 mL). The organic layer was washed with 1 M $NaHCO_3$ solution (3 × 15 mL) and brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting crude oil was purified by column chromatography on silica gel to afford *Z*-**20** (276 mg, 57%) as a mixture of diastereomers (1:1) as a yellowish oil. Analytical TLC (silica gel 60): (30% ethyl acetate in cyclohexane) R_f = 0.36. ^{1}H NMR (300.1 MHz, $CDCl_3$): 7.48, 7.18 (bs, 1H), 5.23, 5.20 (bs, 1H), 4.55 (q, 1H, J_{HH} = 7.2 Hz), 3.73−3.71 (s, 3H), 1.96 (dd, 1H, J_{HH} = 7.7 Hz, J_{HF} = 16.7 Hz), 1.95 (m, 1H), 1.45−1.44 (s, 9H), 1.37 (d, 3H, J_{HH} = 7.2 Hz), 1.28 (dd, 1H, J_{HH} = 7.7 Hz, J_{HF} = 21.8 Hz), 1.10−1.08 (d, 3H, J_{HH} = 7.0 Hz), 0.98−0.96 (d, 3H, J_{HH} = 7.0 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 173.2, 168.3, 168.1, 156.1, 156.0, 88.6 (J_{CF} = 235.2 Hz), 81.2, 52.6, 52.5, 48.6, 48.5, 42.5, 28.5 (J_{CF} = 7.2 Hz), 28.3, 28.2, 27.0, 24.2, 18.7, 18.3, 17.5, 17.4. ^{19}F NMR (282.4 MHz, $CDCl_3$): −194.4 (m), −195.1 (m). MS (ESI positive mode): m/z 369.13 $[M + Na]^+$, 714.80 $[2M + Na]^+$. IR (neat): 3293, 2971, 1755, 1694, 1647, 1507, 1367, 1275, 1249, 1207, 1160, 1059, 1041, 982, 853, 634 cm^{-1}. HRMS (ESI positive mode): calcd for $C_{16}H_{28}FN_2O_5$ 347.1982, found 347.1993.

Methyl 2-(1-Amino-2-fluoro-2-isopropylcyclopropylcarboxamido)propanoate Hydrochloride (*Z*-21). The same procedure as described for the synthesis of (±)-*Z*-**10** was applied to *Z*-**20** to generate *Z*-**21** as a brownish oil in a quantitative yield. ^{1}H NMR (300.1 MHz, CD_3OD): 4.47 (bm, 1H), 3.69 (s, 3H), 3.57 (s, 2H), 2.18 (bm, 1H), 1.79 (bm, 2H), 1.41 (s, 3H), 1.20 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (75.4 MHz, CD_3OD): 173.3, 165.8, 85.8 (J_{CF} = 236.1 Hz), 53.4, 43.8, 42.2, 30.1 (J_{CF} = 19.3 Hz), 20.1 (J_{CF} = 13.1 Hz), 17.8, 17.1, 17.0. ^{19}F NMR (282.4 MHz, CD_3OD): −197.9 (bs). MS (ESI positive mode): m/z 247.11 [M − HCl], 492.80 [2M − HCl]. HRMS (ESI positive mode): calcd for $C_{11}H_{20}FN_2O_3$ 247.1458, found 247.1456.

Methyl 2-(1-(2-(((Benzyloxy)carbonyl)amino)propanamido)-2-fluoro-2-isopropylcyclopropylcarboxamido)propanoate (*Z*-22). In a 10 mL round-bottom flask equipped with septum and magnetic stirrer under an argon atmosphere was dissolved *N*-(benzyloxycarbonyl)-L-alanine (47 mg, 0.21 mmol, 3 equiv) was dissolved in anhydrous DMF (1 mL), and the resulting solution was cooled to 0 °C. Subsequently, HATU (81 mg, 0.21 mmol, 3 equiv) and *N*-methylmorpholine (39 μL, 0.36 mmol, 5 equiv) were added, and the reaction mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature for 30 min. Then, a solution of *Z*-**21** (20 mg, 0.07 mmol, 1 equiv) in anhydrous DMF (0.5 mL) was added dropwise, and the resulting brownish solution was stirred at room temperature overnight. Upon completion, the reaction mixture was dissolved with EtOAc (10 mL). The organic layer was washed with 1 M $NaHCO_3$ solution (2 × 5 mL), water (5 mL), and brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting crude oil was purified by column chromatography on silica gel to afford *Z*-**22** as a mixture of diastereomers (overall yield 76%) which can be easily separated by SFC (CHIRALPAK column IA 250 × 20 mm, mobile phase CO_2 85% MeOH 15%, flow rate 60 mL/min, T = 35 °C, P outlet 100bet, 220 nm). Analytical TLC (silica gel 60): (40% cyclohexane in ethyl acetate) R_f = 0.35. MS (ESI positive mode): m/z 475.27 $[M + Na]^+$. IR (neat): 3269, 3040, 2970, 2880, 1744, 1656, 1624, 1523, 1450, 1317, 1384, 1359, 1072, 1011, 885, 755 cm^{-1}. Anal. Calcd for $C_{22}H_{30}FN_3O_6$: C, 58.53; H, 6.70; N, 9.31. Found: C, 58.87; H, 6.76; N, 9.31.

Diastereoisomer 1. White solid. Mp: 173−175 °C. $[\alpha]^{20}_D$ = −92.8 (0.25, $CHCl_3$). ^{1}H NMR (300.1 MHz, $CDCl_3$): 7.45 (d, 1H, J_{HH} = 7.5 Hz), 7.32 (s, 5H), 6.73 (bs, 1H), 5.29 (d, 1H, J_{HH} = 5.1 Hz), 5.10 (2d, 2H), 4.47 (q, 1H, J_{HH} = 7.2 Hz), 4.05 (q, 1H, J_{HH} = 6.4 Hz), 3.69 (s, 3H), 2.06 (m, 1H), 1.98 (dd, 1H, J_{HH} = 7.8 Hz, J_{HF} = 17.1 Hz), 1.36 (m, 6H), 1.26 (m, 1H), 1.10 (d, 3H, J_{HH} = 7.0 Hz), 1.03 (d, 3H, J_{HH} = 6.9 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 173.8, 173.2, 167.5, 156.4, 135.8, 128.6−128.0, 88.2 (J_{CF} = 234.9 Hz), 67.3, 52.2, 51.1, 48.6, 41.3 (J_{CF} = 8.7 Hz), 28.1 (J_{CF} = 20.1 Hz), 24.2 (J_{CF} = 8.4 Hz), 17.8, 17.0. ^{19}F NMR (282.4 MHz, $CDCl_3$): −194.07 (ddd, J_{FH} = 17.2 Hz, 21.7 Hz, 35.3 Hz).

Diastereoisomer 2. White solid. Mp: 136−139 °C. $[\alpha]^{20}_D$ = +34.4 (0.25, $CHCl_3$). ^{1}H NMR (300.1 MHz, $CDCl_3$): 7.58 (d, 1H, J_{HH} = 6.9 Hz), 7.34 (s, 5H), 6.96 (bs, 1H), 5.40 (d, 1H, J_{HH} = 5.6 Hz), 5.11 (s, 2H), 4.50 (q, 1H, J_{HH} = 7.1 Hz), 4.20 (q, 1H, J_{HH} = 6.7 Hz), 3.70 (s, 3H), 2.00 (m, 1H), 1.93 (dd, 1H, J_{HH} = 7.7 Hz, J_{HF} = 16.7 Hz), 1.41 (t, 6H, J_{HH} = 7.0 Hz), 1.27 (m, 1H), 1.11 (d, 3H, J_{HH} = 7.0 Hz), 1.05 (d, 3H, J_{HH} = 6.9 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): 174.2, 173.2, 167.4, 156.4, 135.9, 128.6−128.1, 87.7 (J_{CF} = 235.9 Hz), 67.2, 52.4, 50.9, 48.6, 41.8 (J_{CF} = 9.0 Hz), 28.4 (J_{CF} = 20.3 Hz), 23.7 (J_{CF} = 9.3 Hz), 17.9, 17.4. ^{19}F NMR (282.4 MHz, $CDCl_3$): −194.09 (m).

1-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-fluoro-2-isopropylcyclopropylcarboxylic Acid ((±)-*Z*-23). In a 10 mL round-bottom flask equipped with septum and magnetic stirrer was dissolved (±)-*Z*-**13** (20 mg, 0.101 mmol, 1 equiv) in dioxane (0.6 mL) and water (0.6 mL), and the resulting solution was cooled to 0 °C. Subsequently, K_2CO_3 (55.8 mg, 0.404 mmol, 4 equiv) was added, followed by 9-fluorenylmethyl succinimidyl carbonate (37.4 mg, 0.111 mmol, 1.1 equiv) previously dissolved in dioxane (0.175 mL). The reaction mixture was stirred at 0 °C for 1 h and at 40 °C for 3 h. Upon completion, the reaction mixture was dissolved with EtOAc (5 mL). The desired acid was extracted with 1 M $NaHCO_3$ solution (2 × 5 mL) in its

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sodium salt form. Then, the combined aqueous layers were acidified to pH 1 by addition of 1 M HCl solution and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford (±)-*Z*-**23** (26.5 mg, 68%) as a white solid. No further purification was needed. Mp: 180−182 °C. Analytical TLC (silica gel 60): (5% methanol in dichloromethane) R_f = 0.19. ^{1}H NMR (300.1 MHz, CD_3OD): 8.01 (bs, 1H), 7.80 (d, 2H, J_{HH} = 8.1 Hz), 7.69 (d, 2H, J_{HH} = 7.4 Hz), 7.35 (dt, 4H, J_{HH} = 7.4 Hz, J_{HH} = 24.7 Hz), 4.28 (m, 3H), 2.17 (dq, 1H, J_{HH} = 7.1 Hz, J_{HF} = 33.3 Hz), 1.84 (dd, 1H, J_{HH} = 7.5 Hz, J_{HF} = 16.0 Hz), 1.52 (dd, 1H, J_{HH} = 7.5 Hz, J_{HF} = 21.2 Hz), 1.18 (d, 3H, J_{HH} = 7.0 Hz), 1.11 (d, 3H, J_{HH} = 6.9 Hz). ^{13}C NMR (75.4 MHz, CD_3OD): 173.6, 159.2, 145.3, 142.6, 128.8, 128.2, 126.4, 120.9, 89.4 (J_{CF} = 235.0 Hz), 68.2, 42.6 (J_{CF} = 9.1 Hz), 30.0 (J_{CF} = 20.5 Hz), 26.4 (J_{CF} = 8.6 Hz), 18.1, 17.9. ^{19}F NMR (282.4 MHz, $CDCl_3$): −193.0 (m). MS (ESI negative mode): *m*/*z* 381.80 $[M - H]^-$, 764.87 $[2M - H]^-$. HRMS (ESI negative mode): calcd for $C_{22}H_{21}FNO_4$ 382.1455, found 382.1451.

■ ASSOCIATED CONTENT

Supporting Information

Copies of spectra for the new compounds; crystallographic information (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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