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The fluoroalkene motif as a surrogate of the amide bond: syntheses of AA-Ψ[(*Z*) and (*E*)-CF=CH]-Pro pseudodipeptides and an Enalapril analogue

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ABSTRACT

This work describes the optimization process for the synthesis of pseudodipeptides featuring a proline bound to another amino acid through a fluoroalkene moiety that act as an amide bond surrogate. The synthetic methodology is extended to non-peptidic molecules as demonstrated in the design and synthesis of an Enalapril analogue.

1. Introduction

Of the proteinogenic amino acids, proline is unique owing to its secondary amine function and a saturated ring causing a constrained ϕ dihedral angle. As a consequence, proline confers to protein structures a higher conformational rigidity compared to other amino acids.[1–3] In return, proline lacks hydrogen on its nitrogen atom, meaning it can only play a role as a hydrogen bond acceptor. Peptide bonds adopt the *trans* isomer conformation (>99.9%) while the *cis* AA-Pro peptide bonds range from 10 to 40% (AA stands for any amino acid). Indeed, in the case of AA-Pro, the two isomers are nearly equal energetically because of similar steric hindrance with the neighboring substituents. These properties impact the secondary structure of proline-containing peptides through α-helices and β-sheets. Nevertheless, *cis-trans* isomerization still exists and a complete freeze of a conformation would be highly desirable to define the direction of a peptide chain. In this context, we have developed synthetic routes to pseudodipeptides featuring a fluoroalkene motif as an amide bond replacement.[4,5] Noteworthy, we have access to both *E* and *Z* diastereoisomers and we control the configuration of the newly created stereogenic carbons at C- and N-terminals of the pseudodipeptides. The fluoroalkene moiety possesses steric and electronic similarities with the amide bond, allowing the use of the fluoroalkene as an effective peptide bond mimic.

Moreover, the fluoroalkene is more stable than a simple alkene because isomerization and conjugation with an acid moiety is disfavored by the fluorine atom. Compounds that contain fluoroalkene motifs are also more resistant to enzymatic degradation compared to the peptidic bond.[5] Pseudodipeptides that feature a fluoroalkene moiety and a proline are rare in the literature. This motif (Fig. 1) was constructed by Welch et al. via a Peterson fluoroolefination reaction.[6] Augustyns et al. generated the fluoroolefin moiety by a Horner–Wadsworth–Emmons reaction,[7] as also reported by Chang et al. in the synthesis of the dipeptide Val-Ψ[(*Z*)-CF=CH]-Pro for the design of an efficient hepatitis C virus NS5A inhibitor.[8] Our group reported the synthesis of the dipeptide Ala-Ψ[CF=CH]-Pro with enhanced *E*:*Z* ratio as well as excellent diastereoselectivity.[9] However, a drawback of our synthetic sequence was the way we introduced the *R* chain at the N-terminal side through a Negishi reaction somehow limited the variety of substituents. We

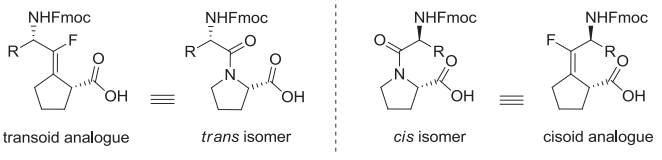

Fig. 1. AA-Pro isomers and fluorinated pseudodipeptide Fmoc-AA-Ψ[(*Z*) and (*E*)-CF=C]Pro analogues.

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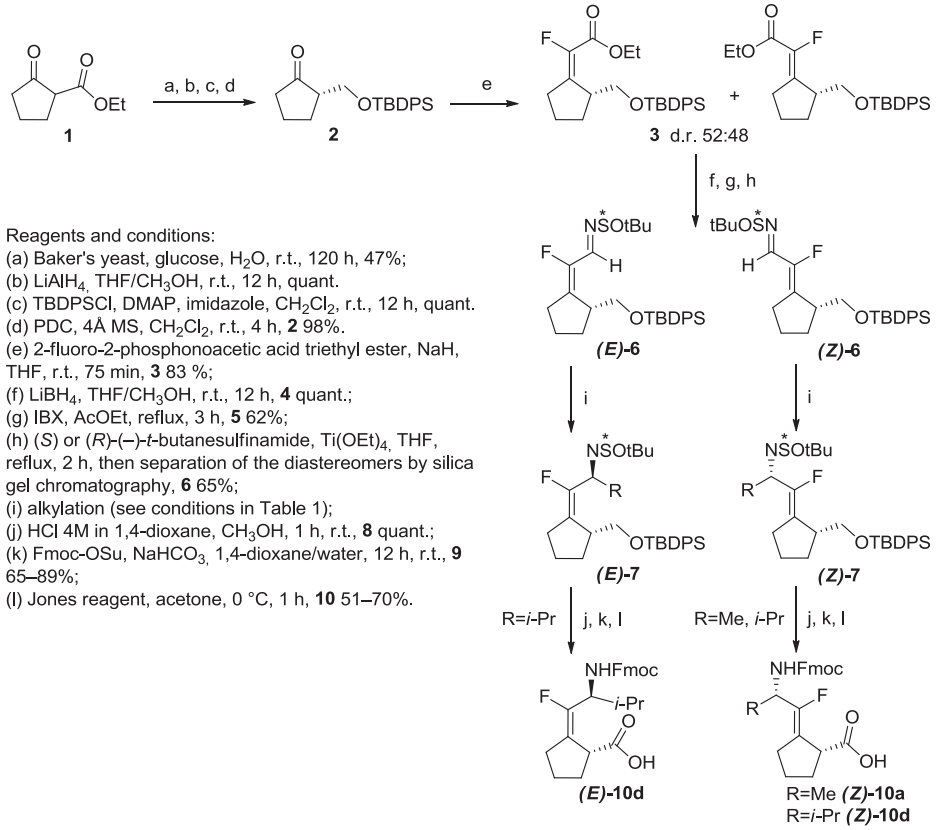
now report an improved synthetic sequence that allows for a wide range of AA-Ψ[(*Z*) and (*E*)-CF=CH]-Pro pseudodipeptides. To further illustrate the generality of the method in the construction of non-peptidic molecules, we prepared an Enalapril analogue as potential inhibitor of angiotensin-converting enzyme.

2. Results and discussion

The synthetic sequence toward the target AA-Ψ[CF=C]-Pro is presented in Scheme 1. Compounds (*E*)-**10** and (*Z*)-**10** were Fmoc protected at the N-terminal side of the dipeptide for direct use in solid phase peptide synthesis. The sequence began with the asymmetric installation of the stereogenic center at the C-terminal side by a microorganism-driven dynamic kinetic resolution of the β-ketoester ethyl 2-oxocyclopentanecarboxylate **1** as described by Buisson and Azerad (step a).[10] The major *cis* (1*R*,2*S*)-β-hydroxy ester was obtained optically enriched (ee>95%) after separation by flash chromatography (*cis*/*trans* ratio>9:1). Next, the ester moiety was reduced (step b), the primary alcohol protected by a bulky silyl group (step c), and the secondary alcohol oxidized (step d) to give **2**. At this stage, the fluoroolefination was investigated to install the peptide bond mimic. Unfortunately, the laboratory conditions established for the synthesis of α-fluoro-α,β-unsaturated esters (α-fluoroacrylates) from aldehydes or ketones with ethyl-dibromofluoroacetate in presence of triphenylphosphine and diethylzinc in dry THF failed in this case.[11] Fortunately, a Horner–Wadsworth–Emmons reaction was successful with ketone **2** and triethyl 2-fluoro-2-phosphonoacetate, affording a nearly enantiopure diastereomeric mixture of compounds **3** (step e).[12] These esters **3** were reduced into the corresponding allylic alcohols **4** (step f), which were next submitted to the oxidation using IBX (step g) in good yields and without epimerization. The intermediate aldehydes **5** were then reacted with either (*R*) or (*S*)-(−) *tert*-butanesulfinamides for the straightforward preparation of β-fluoroenimines **6** according to the well-established Ellman's procedure (step h). The separation of the diastereomers of **3** and **4** was difficult; however, the separation by chromatography was easier for β-fluoroenimines **6**. All the next steps could thus be realized on each pure diastereoisomers. The relative configurations of the α,β-unsaturated imine compounds **6** were easily determined by NOESY NMR experiments. With the key intermediate fluoroenimines **6** in hand, we added organometallic species (Grignard reagents or zincate complexes) (step i), in order to get a diastereocontrol towards *S* configuration of the newly created stereogenic centers at the N-terminal side (as in the native peptide) (Table 1). Indeed, as previously reported in the literature,[13,14] the efficiency of the organometallic addition depends of the *R* group added to the chiral imine and a reversal of the main diastereoisomer could be obtained depending on the choice of the organometallic species. That is why we proceeded with two methods because the stereoselectivity can be planned by the choice of the appropriate couple organometallic species/chiral auxiliaries. So in order to get the *S* configuration of the chiral center at the N-terminal side, we used (*R*)-*tert*-butanesulfinamide with Grignard reagents and (*S*)-*tert*-butanesulfinamide with zincate complexes.

In a first series of experiments, we conducted 1,2-additions of Grignard reagents to imines **6** (R_S) bearing the (*R*)-*tert*-butylsulfinamide auxiliary,[15] *E* and *Z* diastereomers, independently (Table 1, entries 1–4). Precursors of pseudopeptides Ala-Ψ[(*Z*) and (*E*)-CF=CH]-Pro **7a** were obtained in moderate yields and good diastereoselectivities (Table 1, entries 1, 2) whereas only Ser-Ψ[(*Z*)-CF=CH]-Pro (*Z*)-**7b** could be obtained (Table 1, entry 4). The synthesis of the pseudodipeptide Ser-Ψ[CF=C]-Pro was achieved by the addition of a magnesium carbenoid prepared in situ from the corresponding iodomethyl carboxylate with *i*-PrMgCl in THF/1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (5:1) at



Scheme 1. Synthesis of AA-Ψ[CF=C]Pro pseudodipeptides.

Table 1
Diastereoselective additions of Grignard[a] and organozincate reagents[b]

Entry	Substrate	RM	Product	Target mimic	Yield (%)[c]	d.r.[d]
1	(*E*)-**6** (R_S)	MeMgBr	(*E*)-**7a**	Ala-Pro	59	91:9
2	(*Z*)-**6** (R_S)	MeMgBr	(*Z*)-**7a**	Ala-Pro	73	88:12
3	(*E*)-**6** (R_S)	pivOCH$_2$MgCl	(*E*)-**7b**	Ser-Pro	0	—
4	(*Z*)-**6** (R_S)	pivOCH$_2$MgCl	(*Z*)-**7b**	Ser-Pro	39	33:67
5	(*E*)-**6** (S_S)	*i*-BuMgBr+ZnMe$_2$	(*E*)-**7c**	Leu-Pro	45	92:8
6	(*Z*)-**6** (S_S)	*i*-BuMgBr+ZnMe$_2$	(*Z*)-**7c**	Leu-Pro	84	99:1
7	(*E*)-**6** (S_S)	*i*-PrMgCl+ZnMe$_2$	(*E*)-**7d**	Val-Pro	90	96:4
8	(*Z*)-**6** (S_S)	*i*-PrMgCl+ZnMe$_2$	(*Z*)-**7d**	Val-Pro	66	92:8
9	(*E*)-**6** (S_S)	PhCH$_2$MgCl+ZnMe$_2$	(*E*)-**7e**	Phe-Pro	44	95:5
10	(*Z*)-**6** (S_S)	PhCH$_2$MgCl+ZnMe$_2$	(*Z*)-**7e**	Phe-Pro	54	93:7
11	(*E*)-**6** (S_S)	vinylMgBr+ZnMe$_2$	(*E*)-**7f**	Thr-Pro[e]	39	65:35
12	(*Z*)-**6** (S_S)	vinylMgBr+ZnMe$_2$	(*Z*)-**7f**	Thr-Pro[e]	52	85:15

[a] Reaction conditions: Methyl Grignard reagent (3 equiv), toluene, 0 °C or iodomethylpivalate, *i*-PrMgCl, −78 °C, THF/DMPU (5:1), −78 to −50 °C.
[b] Reaction conditions: Grignard reagent (1.5 equiv)+ZnMe$_2$ (1.72 equiv), THF, −78 °C.
[c] Yield of silica gel chromatographed analytically pure compounds.
[d] Diastereomeric ratios were determined by ^{19}F NMR of the crude reaction mixtures.
[e] After hydration of the vinyl function.

−78 °C.[16] Separation of diastereomers by silica gel chromatography provided enantiopure intermediates **7a** and **7b** for use in the next synthetic steps.

Under these conditions that combine the (*R*)-*tert*-butylsulfinamide auxiliary and the use of a Grignard reagent, as previously observed,[13] we obtained the desired stereogenic center of (*S*) configuration at the N-terminal side of **7a**, identical to the configuration of the corresponding natural dipeptide. The absolute configuration of the new stereogenic center was ascribed by X-ray crystallography of compound (*E*)-**9a** (Fig. 2).[9,17] In the case of compound **7b** featuring a methylpivalate moiety, the presence of the chelating carboxyl group clearly modifies the transition-state intermediate and is responsible for the reversal of diastereo selection.

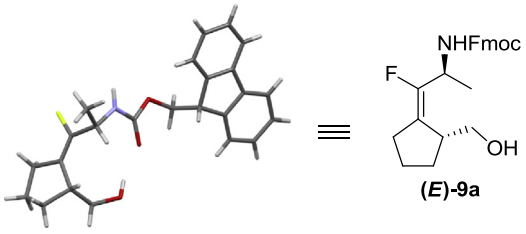


Fig. 2. X-ray structure of Fmoc-Ala-Ψ[(*E*)-CF=CH]-Pro **9a**.

The zincate complexes were generated from the Grignard in presence of dimethylzinc and were reacted with the imines **6** at low temperature in THF.[14,18] The formed triorganozincate species proved to be more reactive than Grignard species and less prone to the β-hydride-transfer side-reaction.[19–21] Reaction yields are moderate to high and, in most cases, the diastereomeric ratios were excellent except for the addition of the vinylzincate which only led to moderate d.r. values (Table 1, entries 5–12). The synthetic sequence was continued with **7a** and **7d** by removal of the chiral auxiliary and concomitant deprotection of the primary alcohol under these acid conditions (step j), affording aminoalcohol **8**. The next step was the Fmoc protection of the primary amine (step k) to get *N*-protected aminoalcohol **9**. Finally, oxidation of the primary alcohol function into a carboxylic acid[22] allowed to get the target pseudodipeptides **10** (step l). This last functional group interconversion was carried out with Jones reagent to prepare both (*E*) and (*Z*) diastereoisomers of Val-Ψ[CF=CH]-Pro **10d**; however, we could only obtain the Ala-Ψ[(*Z*)-CF=CH]-Pro **10a**, its (*E*) isomer giving a messy reaction.[23]

We have enlarged the scope of the asymmetric synthesis of various AA-Ψ[(*Z*) and (*E*)-CF=CH]-Pro pseudodipeptides. These dipeptides are ready-to-use for solid-phase peptide synthesis and could have applications in structural study of peptides or protein as well as therapeutic agents. In addition, our synthetic methodology was extended to non-peptidic molecules as demonstrated in the design and synthesis of an Enalapril analogue (Fig. 3).[24]

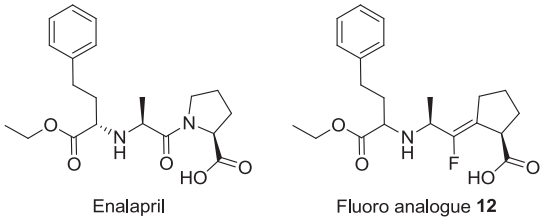
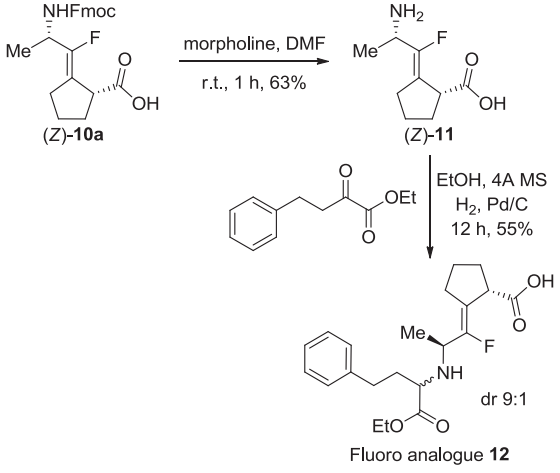


Fig. 3. Structure of Enalapril and fluoro analogue **12**.

Enalapril is an angiotensin-converting-enzyme inhibitor (or ACE inhibitor) that is prescribed to reduce hypertension or to prevent (or treat) heart failure.[25] Some analogues of Enalapril have been designed and synthesized. For example, Tinney et al. reported a series of modified peptides in which various isosteric moieties (O, S, SO, SO$_2$) have been substituted for the amino group and in which the proline residue has been replaced with various hydrophobic amino acids.[26] Greenlee et al. described analogues in which the carbonyl of the scissile peptide bond was replaced by a CHCO$_2$H group; these inhibitors had inhibitory potency equal to that of the parent compound.[27] Bhagwat et al. synthesized dual inhibitors of ACE and neutral endopeptidase (NEP) by incorporating a thiorphan unit at the β-position of the proline ring of Enalapril.[28] In order to synthesize a fluoro analogue of Enalapril featuring the fluoroolefin moiety in place of the amide bond between the Ala and Pro AAs, we started from (*Z*)-**10a**, which was first deprotected to give (*Z*)-**11** and then directly submitted without purification to a reductive amination with ethyl 2-oxo-4-phenylbutanoate in the presence of hydrogen and palladium on carbon. Compound **12** was obtained as a 9:1 mixture of diastereoisomers that were separated by preparative HPLC (Scheme 2).



Scheme 2. Synthesis of **12**, a fluoro analogue of Enalapril.

3. Conclusion

We have described an optimized process toward the synthesis of AA-Ψ[(*Z*) and (*E*)-CF=CH]-Pro pseudodipeptides featuring a fluoroalkene moiety that act as an amide bond surrogate. The new route starting from α-fluoroacrylates is amenable to wider

structural modifications compared to our previous synthetic sequence. Overall, we could control the two stereogenic centers at the C- and N-terminals with a definite geometry of the fluoroalkene. The methodology was extended to a non-peptidic molecule as demonstrated in the design and synthesis of an Enalapril analogue.

4. Experimental section

4.1. General information

Experiments involving organometallics were carried out 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-dry ice bath. All commercial solvents were distilled before use: THF was distilled over sodium and benzophenone under nitrogen atmosphere, toluene over sodium and DCM over CaH_2. TLC were performed on Merck 60F-250 silica gel plates, using UV light as a visualizing agent and ethanolic solution of phosphomolybdic acid and heat as developing agents. Flash column chromatography purifications were carried out using silica gel columns (particle size: 0.040–0.063 mm or 0.063–0.20 mm) or automatically on an SP1 Biotage. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR ($CFCl_3$ as internal reference) were recorded at 300, 75.4, and 282.5 MHz, respectively on a Bruker DXP 300. COSY and NOESY experiments were recorded at 300 MHz on a Bruker DXP 300. Abbreviations used for peak multiplicity are s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet. *J* was used to indicate coupling constants in Hertz. Optical rotations were measured on a Perkin–Elmer 341 polarimeter (λ=589 nm, 20 °C, concentrations used in cg.mL^{-1}). IR spectra were recorded on a Perkin–Elmer 500 FT-IR spectrometer. Absorption bands are reported in cm^{-1}. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Bruker-Esquire mass spectrometer. Elemental analyses were performed on a CE Instruments EA 110 CHNS–O. Compound **2** was synthesized according to reported experimental procedure.[9]

4.2. (*R*)-Ethyl-2-(2-((*tert*-butyldiphenylsilyloxy)methyl)*cyclo*pentylidene)-2-fluoroacetate (3)

To a stirred suspension of sodium hydride (144 mg, 6 mmol, 1.5 equiv) in freshly distilled THF (43 mL) at −30 °C was added dropwise ethyl(diethylphosphono)(fluoro)acetate (1.2 mL, 6 mmol, 1.5 equiv). The yellowish suspension was then stirred for 30 min until hydrogen evolution stopped. A solution of **2** (1.41 g, 4 mmol, 1 equiv) in 10 mL of distilled THF was added dropwise. The cooling bath was removed and the mixture was stirred for an additional 1.5 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentred under reduced pressure. The crude mixture was purified by chromatography on silica gel (cyclohexane/EtOAc: 94/6) to afford a 52:48 mixture of (*Z*) and (*E*) isomers as a colorless oil (1.46 g, 83%). $Rf_{(E)}$=0.54, $Rf_{(Z)}$=0.50 (cyclohexane/EtOAc: 94/06). IR (neat): ν 3470, 2944, 1732, 1372, 1297, 1092, 704, 506 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75–7.63 (m, 4H), 7.44–7.35 (m, 6H), 4.31–4.24 (q, 1H$_{(Z)}$, ^3J=6.9 Hz), 4.20–4.13 (dq, 1H$_{(E)}$, ^3J=7.2 Hz), 3.84–3.70 (m, 1H$_{(E)}$), 3.62–3.47 (m, 1.5H), 3.25–3.17 (m, 0.5H$_{(Z)}$), 2.74–2.67 (m, 1H$_{(Z)}$), 2.57–2.51 (m, 1H$_{(E)}$), 2.22–2.13 (m, 0.5H$_{(E)}$), 2.06–1.96 (m, 0.5H$_{(Z)}$), 1.86–1.66 (m, 3H), 1.31–1.35 (t, 1.5H$_{(Z)}$, ^3J=6.0 Hz), 1.26–1.22 (t, 1.5H$_{(E)}$, ^3J=6.0 Hz), 1.06 (m, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −122.9 (*E*), -127.4 (*Z*) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 161.0 (d, C$_{(E)}$, ^2J=34.7 Hz), 160.4 (d, C$_{(Z)}$, ^2J=34.7 Hz), 142.5 (d, C$_{(E)}$, ^1J=247.3 Hz), 142.4 (d, C$_{(Z)}$, ^1J=248.1 Hz), 141.4 (d, C$_{(E)}$, ^2J=46.7 Hz), 141.2 (d, C$_{(Z)}$, ^2J=46.0 Hz), 135.4 (CH), 133.4 (CH), 129.5 (CH), 127.5 (CH), 64.5 (CH$_{2(E)}$), 63.7 (CH$_{2(Z)}$), 60.7 (CH$_2$), 45.7 (CH$_{(E)}$), 44.3 (CH$_{(Z)}$), 31.0 (CH$_{2(E)}$), 30.2 (CH$_{2(E)}$), 29.7 (CH$_{2(E)}$), 28.6 (CH$_{2(Z)}$), 26.7 (CH$_3$), 24.6 (CH$_{2(E)}$), 22.7 (CH$_{2(Z)}$), 19.1 (C), 14.0 (CH$_3$) ppm MS (ESI$^+$): [M+H]$^+$=441.07. Elemental analysis for $C_{26}H_{33}FOSi$: calcd: C: 70.87; H: 7.55. Found: C: 70.82; H: 7.69.

4.3. (*R*)-2-(2-((*tert*-butyldiphenylsilyloxy)methyl)cyclopentylidene)-2-fluoroethanol (4)

To a mixture of diastereomers **(*Z*)-3** and **(*E*)-3**: 52/48 (288 mg, 0.65 mmol, 1 equiv) in dry THF (11 mL) at 0 °C was added $LiBH_4$ (100 mg, 4.55 mmol, 7 equiv). The reaction mixture was stirred for 20 min at 0 °C and overnight at room temperature. The reaction mixture was quenched carefully with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentred under reduced pressure. The crude mixture was purified by chromatography on silica gel (cyclohexane/EtOAc: 94/6) to afford **(*E*)-4** as a colorless oil (115.8 mg, 45%) and **(*Z*)-4** as a colorless oil (104.4 mg, 40%).

(*E*)-4: Rf=0.52 (cyclohexane/EtOAc: 9/1). IR (neat): ν 3407, 3065, 2958, 2925, 2846, 1717, 1427, 1390, 1251, 1111, 1080, 1007, 915, 823, 734, 703, 611 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.63 (m, 4H), 7.47–7.37 (m, 6H), 4.14–3.94 (m, 2H), 3.51–3.45 (m, 1H), 3.39–3.34 (m, 1H), 2.91 (m, 1H), 2.47–2.23 (m, 2H), 1.76–1.49 (m, 5H), 1.06 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −115.0 (t, ^3J=19.8 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.3 (d, C, ^1J=245.6 Hz), 135.6 (CH), 133.2 (CH), 129.8 (CH), 127.8 (CH), 122.9 (d, C, ^2J=16.3 Hz), 66.3 (CH$_2$), 59.4 (d, CH$_2$, ^2J=32.4 Hz), 42.69 (d, CH, ^3J=4.9 Hz), 29.7 (CH$_2$), 28.6 (CH$_3$), 27.0 (C), 23.2 (CH$_2$), 19.2 (CH$_2$) ppm MS (ESI$^+$): [2M+Na]$^+$=818.67. Elemental analysis for $C_{24}H_{31}FNO_2Si$: calcd: C: 72.32; H: 7.84. Found: C: 72.25; H: 7.90. $[\alpha]_D^{20}$=−26.4 (c 0.50, $CHCl_3$).

(*Z*)-4: Rf=0.42 (cyclohexane/EtOAc: 9/1). IR (neat): ν 3362, 3071, 2953, 2930, 2863, 2358, 1712, 1471, 1427, 1393, 1248, 1142, 1116, 1013, 935, 820, 740, 703, 614, 620 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.66 (m, 4H), 7.43–7.36 (m, 6H), 4.12 (dd, 2H, ^2J=3.0 Hz, ^3J=24.0 Hz), 3.85–3.80 (m, 1H), 3.57–3.51 (m, 1H), 3.07 (m, 1H), 2.29–2.24 (m, 2H), 1.96–1.60 (m, 5H, OH), 1.06 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −120.2 (t, ^3J=19.8 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.3 (d, C, ^1J=245.6 Hz), 135.6 (CH), 133.9 (CH), 129.8 (CH), 127.8 (CH), 123.2 (d, C, ^2J=14.8 Hz), 64.5 (CH$_2$), 59.6 (d, CH$_2$, ^2J=30.5 Hz), 43.2 (CH), 29.7 (CH$_2$), 28.5 (CH$_3$), 27.0 (C), 24.8 (CH$_2$), 19.2 (CH$_2$) ppm MS (ESI$^+$): [2M+Na]$^+$=818.67. Elemental analysis for $C_{24}H_{31}FNO_2Si$: calcd: C: 72.32; H: 7.84. Found: C: 71.97; H: 7.75. $[\alpha]_D^{20}$=−25.7 (c 0.75, $CHCl_3$).

4.4. (*R*)-2-(2-((*tert*-butyldiphenylsilyloxy)methyl)cyclopentylidene)-2-fluoroacetaldehyde (5)

To a diastereomeric mixture of **(*Z*)-4** and **(*E*)-4** (61 mg, 0.14 mmol, 1 equiv) in dry EtOAc (2 mL) was added IBX (118 mg, 0.42 mmol, 3 equiv). The reaction mixture was heated at reflux for 3 h, filtered through a pad of Celite and then concentrated under reduced pressure to afford a mixture of diastereomeric aldehydes as a yellow oil (34 mg, 62%). $Rf_{(E)}$=0.43, $Rf_{(Z)}$=0.28 (cyclohexane/EtOAc: 94/6). IR (neat): ν 3069, 2954, 2937, 2856, 1691, 1478, 1426, 1266, 1111, 1076, 1001, 817, 697, 605 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.49 (d, 0.42H$_{(Z)}$, ^3J=18.0 Hz), 9.38 (d, 0.58H$_{(E)}$, ^3J=18.0 Hz), 7.70–7.60 (m, 4H), 7.47–7.37 (m, 6H), 3.84–3.70 (m, 1H), 3.64–3.42 (m, 1H), 3.38–3.36 (m, 0.58H$_{(E)}$), 3.25–3.21 (m, 0.42H$_{(Z)}$), 2.85–2.66 (m, 1H), 2.61–2.56 (m, 1H), 2.00–1.59 (m, 4H), 1.03 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ (*E*): −129.2 (d, ^3J=16.9 Hz), (*Z*): −133.2 (d, ^3J=14.1 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 182.5 (d, CHO$_{(E)}$, ^2J=7.7 Hz), 182.2 (d, CHO$_{(Z)}$, ^2J=3.6 Hz), 151.0 (d, C$_{(E)}$, ^1J=249.0 Hz), 149.8 (d, C$_{(Z)}$, ^1J=247.5 Hz) 147.3 (C$_{(E)}$), 147.1 (C$_{(Z)}$), 135.5 (CH), 133.3 (C$_{(Z)}$), 132.8 (C$_{(E)}$), 129.8 (CH), 127.8

(CH), 65.5 (d, $CH_{2(E)}$, ^4J=3.8 Hz), 63.8 (d, $CH_{2(Z)}$, ^4J=4.4 Hz), 45.6 ($CH_{(Z)}$), 42.7 ($CH_{(E)}$), 29.5 ($C_{(E)}$), 28.3 ($C_{(Z)}$), 26.8 (CH_3), 25.1 (CH_2), 22.3 (CH_2), 19.2 (CH_2) ppm MS (ESI^+): $[M+H]^+$=397.20; $[M+Na]^+$=419.27. Elemental analysis for $C_{24}H_{29}FO_2Si$: calcd: C: 72.69; H: 7.37. Found: C: 72.98; H: 7.24. $[\alpha]_D^{20}$=−57.3 (c 0.36, $CHCl_3$).

4.5. *N*-(2-((*R*)-2-((*tert*-butyldiphenylsilyloxy)methyl)*cyclo*-pentylidene)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (6 (R_S))

To a diastereomeric mixture of aldehyde **(*E*)-5** and **(*Z*)-5** (1.92 g, 4.84 mmol, 1 equiv) in dry THF (77 mL) were added $Ti(OEt)_4$ (2.54 mL, 12.10 mmol, 2.5 equiv) and (*R*)-*tert*-butanesulfinamide (1.47 g, 12.10 mmol, 2.5 equiv). The reaction mixture was heated at reflux for 2 h and once cooled, poured into an equal volume of brine with rapid stirring. The resulting suspension was filtered through a pad of Celite and the filter cake was washed with EtOAc. The brine layer was extracted with EtOAc. The combined organic portions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (cyclohexane/EtOAc: 8/2) to afford **(*E*)-6 (R_S)** as a yellow oil (873 mg, 36%) and **(*Z*)-6 (R_S)** as a yellow oil (1.05 g, 43%).

(*E*)-6 (R_S): Rf=0.57 (cyclohexane/EtOAc: 8/2). IR (neat): ν 3395, 3070, 2957, 2930, 2856, 1581, 1472, 1428, 1078, 1107, 856, 821, 699, 606, 502, 488 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, 1H, ^3J=21.0 Hz), 7.68–7.63 (m, 4H), 7.42–7.37 (m, 6H), 3.63–3.58 (m, 1H), 3.51–3.46 (m, 1H), 3.35–3.31 (m, 1H), 2.63–2.53 (m, 2H), 1.83–1.57 (m, 4H), 1.24 (s, 9H), 1.05 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −122.3 (d, ^3J=19.8 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.9 (d, C, ^2J=21.1 Hz), 149.6 (d, C, ^1J=243.5 Hz), 142.0 (d, C, ^2J=15.1 Hz), 135.4 (CH), 132.7 (CH), 129.5 (CH), 127.6 (CH), 65.4 (d, CH_2, ^4J=3.8 Hz), 43.0 (CH), 29.2 (CH_2), 28.6 (CH_2), 26.7 (CH_3), 22.6 (CH_2), 22.7 (CH_3), 22.3 (C), 18.8 (C) ppm MS (ESI^+): $[M+H]^+$=500.00. Elemental analysis for $C_{28}H_{38}FNO_2SSi$: calcd: C: 67.29; H: 7.66. Found: C: 67.25; H: 7.62. $[\alpha]_D^{20}$=−187.7 (c 1.48, $CHCl_3$).

(*Z*)-6 (R_S): Rf=0.43 (cyclohexane/EtOAc: 8/2). IR (neat): ν 3071, 2958, 2930, 2857, 1578, 1473, 1428, 1164, 1105, 1083, 818, 739, 700, 613, 503, 488 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, 1H, ^3J=21 Hz), 7.68–7.63 (m, 4H), 7.46–7.35 (m, 6H), 3.84–3.72 (m, 2H), 3.26–3.23 (m, 1H), 2.69–2.62 (m, 2H), 1.97–1.87 (m, 4H), 1.23 (s, 9H), 1.04 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −126.2 (d, ^3J=19.8 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.6 (d, C, ^2J=22.6 Hz), 148.8 (d, C, ^1J=243.5 Hz), 142.2 (d, C, ^2J=13.6 Hz), 135.4 (CH), 132.7 (CH), 129.5 (CH), 127.5 (CH), 64.0 (d, CH_2, ^4J=4.5 Hz), 57.6 (CH_2), 45.0 (CH), 28.9 (CH_2), 26.6 (CH_3), 24.8 (CH_2), 22.3 (CH_3), 22.3 (C), 19.1 (C) ppm MS (ESI^+): $[M+Na]^+$=522.20. Elemental analysis for $C_{28}H_{38}FNO_2SSi$: calcd: C: 67.29; H: 7.66. Found: C: 67.32; H: 7.69. $[\alpha]_D^{20}$=−153.3 (c 1.14, $CHCl_3$).

4.6. *N*-(2-((*S*)-2-((*tert*-butyldiphenylsilyloxy)methyl)*cyclo*-pentylidene)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (6 (S_S))

To a diastereomeric mixture of aldehyde **(*E*)-5** and **(*Z*)-5** (251 mg, 0.63 mmol, 1 equiv) in dry THF (10 mL) were added $Ti(OEt)_4$ (0.33 mL, 1.58 mmol, 2.5 equiv) and (*S*)-*tert*-butanesulfinamide (192 mg, 1.58 mmol, 2.5 equiv). The reaction mixture was heated at reflux for 2 h and once cooled, poured into an equal volume of brine with rapid stirring. The resulting suspension was filtered through a pad of Celite and the filter cake was washed with EtOAc. The brine layer was extracted with EtOAc. The combined organic portions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (cyclohexane/EtOAc: 8/2) to afford **(*E*)-6 (S_S)** (118.3 mg, 37%) and **(*Z*)-6 (S_S)** (84.9 mg, 27%) both as a yellow oil.

(*E*)-6 (S_S): Rf=0.68 (cyclohexane/EtOAc: 8/2). IR (neat): ν 2857, 1579, 1472, 1427, 1359, 1105, 1084, 1005, 998, 821, 738, 700, 689, 613 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, 1H, ^3J=21 Hz), 7.75–7.72 (m, 4H), 7.45–7.37 (m, 6H), 3.62–3.59 (m, 1H), 3.53–3.47 (m, 1H), 3.30 (m, 1H), 2.62–2.58 (m, 2H), 1.83–1.63 (m, 4H), 1.15 (s, 9H), 1.09 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −122.0 (d, ^3J=22.6 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.4 (d, C, ^2J=23.4 Hz), 149.1 (d, C, ^1J=243.5 Hz), 142.6 (d, C, ^2J=15.1 Hz), 134.8 (CH), 133.1 (CH), 129.5 (CH), 127.7 (CH), 65.9 (d, CH_2, ^4J=3.8 Hz), 43.4 (d, CH, ^3J=3.0 Hz), 29.2 (d, CH_2, ^4J=1.5 Hz), 26.8 (C), 26.3 (CH_3), 22.8 (CH_2), 22.7 (CH_3), 21.5 (C), 19.0 (CH_2) ppm MS (ESI^+): $[M+H]^+$=500.13; $[M+Na]^+$=522.20. Elemental analysis for $C_{28}H_{38}FNO_2SSi$: calcd: C: 67.29; H: 7.66. Found: C: 67.25; H: 7.62. $[\alpha]_D^{20}$=+50.0 (c 0.50, $CHCl_3$).

(*Z*)-6 (S_S): Rf=0.53 (cyclohexane/EtOAc: 8/2). IR (neat): ν 2958, 2930, 2857, 1661, 1578, 1472, 1427, 1362, 1278, 1106, 1083, 998, 821, 739, 700, 613, 503, 487 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, 1H, ^3J=18.0 Hz), 7.67–7.62 (m, 4H), 7.44–7.40 (m, 6H), 3.89–3.85 (m, 1H), 3.71–3.65 (m, 1H), 3.24–3.23 (m, 1H), 2.69–2.59 (m, 2H), 2.05–1.70 (m, 4H), 1.23 (s, 9H), 1.05 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −125.4 (d, ^3J=19.8 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.7 (d, C, ^2J=22.6 Hz),148.9 (d, C, ^1J=243.5 Hz), 142.2 (d, C, ^2J=13.6 Hz), 135.5 (CH), 133.4 (CH), 129.6 (CH), 127.6 (CH), 64.0 (d, CH2, ^4J=4.5 Hz), 45.3 (CH), 29.7 (CH_3), 29.5 (CH_2), 26.8 (C), 24.9 (CH_2), 22.1 (CH_3), 22.0 (C), 19.7 (CH_2) ppm MS (ESI^+): $[M+H]^+$=500.00. Elemental analysis for $C_{28}H_{38}FNO_2SSi$: calcd: C: 67.29; H: 7.66. Found: C: 67.24; H: 7.67. $[\alpha]_D^{20}$=+47.0 (c 0.50, $CHCl_3$).

4.7. General procedure for the diastereocontrolled addition of Grignard reagents to (*R*) or (*S*)-chiral *N*-(*tert*-butanesulfinyl)-α-fluoroenimines 6

To a solution of β-fluoroenimine **6** (1 equiv) in anhydrous toluene (0.02 M) at 0 °C under argon was slowly added the Grignard reagent (3 equiv). The reaction mixture was stirred until the reaction was completed as determined by TLC and then quenched with a saturated aqueous solution of NH_4Cl. The solution was warmed to room temperature and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was checked by ^{19}F NMR to determine the diastereomeric ratio (d.r.) and purified by chromatography on silica gel.

4.7.1. N-((S, E)-1-((R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluoropropan-2-yl)-2-methylpropane-2-sulfinamide ((E)-7a). Yellow oil. Rf=0.36 (cyclohexane/EtOAc: 7/3). IR (neat): ν 3070, 2931, 2859, 1428, 1365, 1106, 1072, 823, 737, 701, 611 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.66 (m, 4H), 7.45–7.35 (m, 6H), 3.81–3.62 (m, 1H), 3.60–3.48 (m, 1H), 3.39–3.32 (m, 1H), 3.15 (d, 1H, ^3J=8.7 Hz), 2.73–2.69 (m, 1H), 2.27–2.16 (m, 2H), 1.72–1.52 (m, 4H), 1.35 (d, 3H, ^3J=6.6 Hz), 1.03 (s, 9H), 0.92 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −125.3 (d, ^3J=28.8 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.9 (d, C, ^1J=248.3 Hz), 135.6 (CH), 133.7 (CH), 129.8 (CH), 127.7 (CH), 119.4 (d, C, ^2J=16.4 Hz), 64.5 (d, CH_2, ^4J=4.7 Hz), 55.7 (C), 52.1 (d, CH, ^2J=27.3 Hz), 42.9 (d, CH, ^3J=14.2 Hz), 29.3 (CH_2), 27.2 (d, CH_2, ^4J=3.2 Hz), 26.8 (CH_3), 22.8 (CH_2), 22.5 (CH_3), 20.9 (CH_3), 19.9 (C) ppm MS (ESI^+): $[M+H]^+$=516.00; $[M+Na]^+$=538.27. $[\alpha]_D^{20}$=−7.3 (c 0.60, $CHCl_3$).

4.7.2. N-((S, Z)-1-((R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluoropropan-2-yl)-2-methylpropane-2-sulfinamide ((Z)-7a). Yellow oil. Rf=0.32 (cyclohexane/EtOAc: 7/3). IR (neat): ν

3068, 2962, 2927, 2861, 1711, 1468, 1433, 1367, 1246, 1165, 1104, 1048, 820, 740, 694, 507, 400 cm^{-1}. 1H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 4H), 7.44–7.35 (m, 6H), 4.23–4.09 (m, 1H), 3.85–3.80 (m, 1H), 3.53–3.46 (m, 1H), 3.28 (d, 1H, ^3J=5.1 Hz), 3.03–3.02 (m, 1H), 2.37–2.19 (m, 2H), 1.93–1.82 (m, 4H), 1.32 (d, 3H, ^3J=6.9 Hz), 1.03 (s, 9H), 0.92 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −127.9 (d, ^3J=28.3 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.1 (d, C, ^1J=250.0 Hz), 135.6 (CH), 133.8 (CH), 129.5 (CH), 127.5 (CH), 122.1 (d, C, ^2J=14.4 Hz), 64.5 (d, CH_2, ^4J=3.6 Hz), 55.6 (C), 50.2 (d, CH, ^2J=27.1 Hz), 43.1 (CH_2), 29.6 (d, CH_2, ^3J=19.7 Hz), 28.6 (d, CH_2, ^4J=5.0 Hz), 26.9 (CH_3), 24.9 (CH_2), 22.4 (CH_3), 19.6 (CH_3), 19.3 (C) ppm MS (ESI$^+$): $[M+H]^+$=516.00; $[M+Na]^+$=538.33. Elemental analysis for $C_{29}H_{42}FNO_2SSi$: calcd: C: 67.53; H: 8.21. Found: C: 67.21; H: 8.20. $[\alpha]_D^{20}$=−0.30 (c 0.50, $CHCl_3$).

4.7.3. (2R, Z)-3-(R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-2-(1,1-dimethylethylsulfinamido)-3-fluoropropylpivalate ***((Z)-7b)****.* Colorless oil. Rf=0.55 (cyclohexane/EtOAc: 7/3). IR (neat): ν 2958, 2859, 1732, 1468, 1425, 1365, 1149, 1106, 1074, 822, 738, 700, 614 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.58 (m, 4H), 7.36–7.28 (m, 6H), 4.30–4.14 (m, 1H), 4.06–4.05 (m, 2H), 3.81–3.76 (m, 1H), 3.42–3.36 (m, 2H), 2.96 (m, 1H), 2.36–2.12 (m, 2H), 1.88–1.55 (m, 4H), 1.10 (s, 9H), 1.09 (s, 9H), 0.98 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −127.1 (d, ^3J=25.4 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 178.1 (C), 149.2 (d, C, ^1J=248.1 Hz), 135.6 (CH), 133.9 (CH), 129.5 (CH), 127.6 (CH), 123.9 (d, C, ^2J=13.6 Hz), 63.9 (d, CH_2, ^4J=24.1 Hz), 56.3 (C), 53.5 (d, CH, ^2J=27.1 Hz), 50.9 (CH_2), 43.8 (CH), 38.7 (C), 29.6 (CH_2), 28.4 (CH_2), 27.1 (CH_3), 26.9 (CH_3), 24.3 (CH_2), 22.5 (CH_3), 19.3 (C) ppm MS (ESI$^+$): $[M+Na]^+$=638.40. Elemental analysis for $C_{34}H_{50}FNO_4SSi$: calcd: C: 66.30; H: 8.18; N: 2.27; S: 5.21. Found: C: 66.29; H: 8.02; N: 2.01; S: 4.85. $[\alpha]_D^{20}$=−47.4 (c 1.00, $CHCl_3$).

4.8. General procedure for the diastereocontrolled addition of organozincate reagents to (*S*) or (*R*)-chiral *N*-(*tert*-butanesulfinyl)-α-fluoroenimines 6

To a solution of Grignard reagent (1.5 equiv) in dry THF (0.02 M) was added under argon at room temperature Me_2Zn (1.72 equiv) and the mixture was stirred for 15 min. The resulting organozincate solution was then transferred dropwise with a syringe to a solution of a β-fluoroenimine **(*Z*)-6** or **(*E*)-6** in dry THF under argon at −78 °C. The reaction mixture was stirred until the reaction was completed as determined by TLC then quenched with a saturated aqueous solution of NH_4Cl. The solution was warmed to room temperature and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was checked by ^{19}F NMR to determine the diastereomeric ratio (d.r.) and purified by chromatography on silica gel.

4.8.1. N-((S, E)-1-((R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluoro-4-methylpentan-2-yl)-2-methylpropane-2-sulfinamide ***((E)-7c)****.* Colorless oil. Rf=0.39 (cyclohexane/EtOAc: 7/3). IR (neat): ν 2930, 2860, 1478, 1429, 1358, 1107, 1070, 1007, 998, 823, 738, 700, 690 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.68 (m, 4H), 7.46–7.37 (m, 6H), 3.81–3.76 (m, 1H), 3.65–3.62 (m, 1H), 3.57–3.49 (m, 1H), 3.13 (d, 1H, ^3J=9.0 Hz), 2.68–2.66 (m, 1H), 2.34–2.27 (m, 2H), 2.19–2.12 (m, 2H), 1.71–1.54 (m, 4H), 1.49 (d, 1H, ^3J=6.0 Hz), 1.10 (s, 9H), 1.06 (s, 9H), 0.88 (d, 6H, ^3J=6.0 Hz) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −124.1 (d, ^3J=31.1 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.3 (d, C, ^1J=248.1 Hz), 135.6 (CH), 133.8 (CH), 129.6 (CH), 127.7 (CH), 121.1 (d, C, ^2J=16.6 Hz), 64.6 (d, CH_2, ^4J=4.5 Hz), 55.9 (C), 54.2 (d, C, ^2J=21.1 Hz), 43.3 (d, CH, ^3J=5.3 Hz), 42.6 (CH_2), 29.3 (CH_2), 27.2 (CH_2), 27.0 (CH_3), 24.8 (CH), 22.7 (CH_2), 22.4 (CH_3), 22.3 (CH_3), 19.9 (C) ppm MS (ESI$^+$): $[M+Na]^+$=580.27. Elemental analysis for $C_{32}H_{48}FNO_2SSi$: calcd: C: 68.89; H: 8.67; N: 2.51; S: 5.75 Found: C: 68.47; H: 8.54; N: 2.04; S: 5.06. $[\alpha]_D^{20}$=+36.1. (c 0.69, $CHCl_3$).

4.8.2. N-((S, Z)-1-((R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluoro-4-methylpentan-2-yl)-2-methylpropane-2-sulfinamide ***((Z)-7c)****.* Colorless oil. Rf=0.50 (cyclohexane/EtOAc: 7/3). IR (neat): ν 2956, 2931, 2858, 1468, 1429, 1365, 1107, 1072, 1007, 823, 739, 700, 612 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.57 (m, 4H), 7.32–7.30 (m, 6H), 4.06–3.83 (m, 1H), 3.67–3.62 (m, 1H), 3.57–3.50 (m, 1H), 3.32 (d, 1H, ^3J=9.0 Hz), 2.98–3.02 (m, 1H), 2.46–2.36 (m, 1H), 2.19–2.14 (m, 1H), 1.80–1.38 (m, 6H), 1.19–1.13 (m, 10H), 0.96 (s, 9H), 0.81–0.76 (m, 6H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −130.6 (d, ^3J=28.2 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.3 (d, C, ^1J=248.8 Hz), 135.6 (CH), 133.8 (CH), 129.5 (CH), 127.6 (CH), 121.0 (d, C, ^2J=15.1 Hz), 64.6 (d, CH_2, ^4J=3.8 Hz), 50.8 (d, CH, ^2J=27.9 Hz), 43.2 (d, CH, ^3J=3.0 Hz), 42.2 (CH), 29.3 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 28.6 (CH_3), 24.9 (CH_2), 22.5 (CH_3), 22.4 (C), 19.3 (CH_3), 19.0 (C) ppm MS (ESI$^+$): $[M+Na]^+$=580.27. Elemental analysis for $C_{32}H_{48}FNO_2SSi$: calcd: C: 68.89; H: 8.67; N: 2.51; S: 5.75. Found: C: 68.77; H: 8.81; N: 2.54; S: 5.31. $[\alpha]_D^{20}$=+38.9 (c 0.9, $CHCl_3$).

4.8.3. N-((S, E)-1-(R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluoro-3-methylbutan-2-yl)-2-methylpropane-2-sulfinamide ***((E)-7d)****.* Colorless oil. Rf=0.37 (cyclohexane/EtOAc: 8/2). IR (neat): ν 2957, 2929, 1472, 1427, 1111, 1073, 998, 822, 739, 700, 612 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.60 (m, 4H), 7.41–7.35 (m, 6H), 3.89–3.84 (m, 1H), 3.56–3.49 (m, 1H), 3.28 (d, NH, ^3J=9.0 Hz), 3.18–3.10 (m, 1H), 2.69–2.60 (m, 1H), 2.36–2.23 (m, 2H), 2.19–2.11 (m, 1H), 1.76–1.55 (m, 4H), 1.07 (s, 9H), 1.05 (s, 9H), 0.91 (d, 3H, ^3J=6.0 Hz), 0.80 (d, 3H, ^3J=6.0 Hz) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −122.4 (d, ^3J=30.7 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.3 (d, C, ^1J=247.3 Hz), 135.6 (CH), 133.2 (CH), 133.9 (CH), 127.8 (CH), 121.6 (d, C, ^2J=16.6 Hz), 64.3 (d, CH_2, ^4J=4.5 Hz), 62.2 (d, CH, ^2J=27.1 Hz), 56.2 (CH_3), 43.3 (d, CH, ^3J=5.3 Hz), 32.0 (CH_2), 29.8 (CH_2), 29.3 (CH), 27.1 (CH_3), 26.5 (C), 26.7 (CH_2), 22.5 (CH_3), 19.4 (CH_3) ppm MS (ESI$^+$): $[M+H]^+$=544.85; $[M+Na]^+$=566.40. Elemental analysis for $C_{31}H_{46}FNO_2SSi$: calcd: C: 68.46; H: 8.53; N: 2.58; S: 5.90 Found: C: 68.24; H:8.47; N: 2.57; S: 5.44. $[\alpha]_D^{20}$=+35.5 (c 0.55, $CHCl_3$).

4.8.4. N-((S, Z)-1-(R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluoro-3-methylbutan-2-yl)-2-methylpropane-2-sulfinamide ***((Z)-7d)****.* Colorless oil. Rf=0.50 (cyclohexane/EtOAc: 7/3). IR (neat): ν 2957, 1740, 1428, 1105, 1076, 1008, 822, 739, 700, 613, 503, 489, 444, 427 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.65 (m, 4H), 7.41–7.35 (m, 6H), 3.80–3.76 (m, 1H), 3.62–3.56 (m, 1H), 3.51–3.48 (m, 1H), 3.49–3.47 (m, 1H), 3.15–3.12 (m, 1H), 2.50–2.40 (m, 2H), 2.27–2.19 (m, 1H), 1.73–1.64 (m, 4H), 1.22 (s, 9H), 1.04 (s, 9H), 0.98 (d, 3H, ^3J=6.0 Hz), 0.86 (d, 3H, ^3J=6.0 Hz) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −127.5 (d, ^3J=27.8 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.1 (d, C, ^1J=247.2 Hz), 135.6 (CH), 133.2 (CH), 129.8 (CH), 127.8 (CH), 122.1 (d, C, ^2J=14.8 Hz), 64.6 (d, CH_2, ^4J=3.6 Hz), 62.4 (d, CH, ^2J=26.5 Hz), 56.4 (C), 43.5 (d, CH, ^3J=19.1 Hz), 31.2 (CH_2), 29.6 (CH_2), 28.8 (CH), 26.8 (CH_3), 24.8 (CH_2), 22.9 (CH_3), 22.6 (C), 19.3 (CH_3) ppm MS (ESI$^+$): $[M+H]^+$=544.20; $[M+Na]^+$=566.27. Elemental analysis for $C_{31}H_{46}FNO_2SSi$: calcd: C: 68.46; H: 8.53; N: 2.58; S: 5.90 Found: C: 68.31; H: 8.46; N: 1.93; S: 5.42. $[\alpha]_D^{20}$=+39.0 (c 0.50, $CHCl_3$).

4.8.5. N-((S, E)-1-((R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluoro-3-phenylpropan-2-yl)-2-methylpropane-2-sulfinamide ***((E)-7e)****.* Colorless oil. Rf=0.36 (cyclohexane/EtOAc: 7/3). IR (neat): ν 2956, 2930, 2858, 1472, 1427, 1107, 1064, 822, 739, 700, 612, 503 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.55 (m, 4H),

7.35–7.25 (m, 7H), 7.18–7.13 (m, 3H), 7.02–6.99 (m, 1H), 3.79–3.71 (m, 1H), 3.65–3.60 (m, 1H), 3.37–3.29 (m, 1H), 3.23 (d, 1H, ^3J=9.0 Hz), 2.86–2.71 (m, 2H), 2.23–2.17 (m, 1H), 2.12–2.02 (m, 2H), 1.57–1.36 (m, 4H), 0.98 (s, 9H), 0.94 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −124.5 (dd, ^3J=31.1 Hz, ^4J=2.8 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.1 (d, C, ^1J=247.3 Hz), 137.0 (C), 135.6 (CH), 134.0 (C, ^4J=8.2 Hz), 129.5 (CH), 129.3 (CH), 128.1 (CH), 127.6 (CH), 126.5 (CH), 122.4 (d, C, ^2J=14.3 Hz), 64.2 (d, CH_2, ^4J=3.8 Hz), 57.3 (d, CH, ^2J=26.4 Hz), 56.1 (CH), 39.8 (CH_2), 29.7 (C), 29.1 (CH_2), 28.0 (CH_2), 26.8 (CH_3), 24.1 (CH_2), 22.5 (CH_3), 22.3 (C) ppm MS (ESI$^+$): $[M+Na]^+$=614.33. Elemental analysis for $C_{35}H_{46}FNO_2SSi$: calcd: C: 71.02; H: 7.83; N: 2.37; S: 5.42. Found: C: 70.68; H: 7.90; N: 2.35; S: 5.39. $[\alpha]_D^{20}$=+20.36 (c 0.83, $CHCl_3$).

*4.8.6. N-((S, Z)-1-((R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluoro-3-phenylpropan-2-yl)-2-methylpropane-2-sulfinamide (**(Z)-7e**).* Colorless oil. Rf=0.46 (cyclohexane/EtOAc: 7/3). IR (neat): ν 2957, 2930, 2855, 1472, 1428, 1386, 1365, 1236, 1106, 1069, 822, 739, 699, 612 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.66 (m, 4H), 7.44–7.38 (m, 7H), 7.03–7.01 (m, 4H), 4.19–4.00 (m, 1H), 3.70–3.69 (m, 1H), 3.55–3.52 (m, 1H), 3.07 (d, 1H, ^3J=9.0 Hz), 2.95–2.91 (m, 1H), 2.82–2.74 (m, 1H), 2.25–2.14 (m, 1H), 1.80–1.38 (m, 6H), 1.16 (s, 9H), 1.06 (s, 9H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −129.6 (d, ^3J=28.2 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.5 (d, C, ^1J=248.1 Hz), 137.2 (C), 135.6 (CH), 134.2 (C), 129.6 (CH), 129.4 (CH), 128.2 (CH), 127.6 (CH), 126.6 (CH), 122.5 (d, C, ^2J=15.8 Hz), 64.5 (d, CH_2, ^4J=5.3 Hz), 57.6 (d, CH, ^2J=27.1 Hz), 42.3 (d, CH, ^3J=4.5 Hz), 40.1 (CH_2), 29.0 (CH_2), 27.0 (CH_3), 26.9 (C), 22.7 (CH_2), 22.4 (C), 22.3 (CH_3), 19.3 (CH_2) ppm MS (ESI$^+$): $[M+H]^+$=592.13. Elemental analysis for $C_{35}H_{46}FNO_2SSi$: calcd: C: 71.02; H: 7.83; N: 2.37; S: 5.42. Found: C: 70.91; H: 8.06; N: 2.22; S: 4.91. $[\alpha]_D^{20}$=+44.0 (c 0.60, $CHCl_3$).

*4.8.7. N-((S, E)-1-((R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluorobut-3-en-2-yl)-2-methylpropane-2-sulfinamide (**(E)-7f**).* Colorless oil. Rf=0.50 (cyclohexane/EtOAc: 7/3). IR (neat): ν 2962, 2932, 2860, 1468, 1429, 1105, 1074, 998, 822, 739, 700, 689, 612 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.67 (m, 4H), 7.45–7.36 (m, 6H), 5.81–5.70 (m, 1H), 5.23–5.17 (m, 2H), 4.25–4.12 (m, 1H), 3.80–3.75 (m, 1H), 3.57–3.50 (m, 1H), 3.31–3.28 (d, 1H, ^3J=9.0 Hz), 2.75–2.71 (m, 1H), 2.38–2.30 (m, 2H), 1.68–1.56 (m, 4H), 1.10 (br s, 18H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −121.8 (d, ^3J=31.1 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.6 (d, C, ^1J=248.8 Hz), 135.7 (CH), 134.9 (C), 133.9 (d, CH, ^3J=87.7 Hz), 129.7 (CH), 127.7 (CH), 122.2 (d, C, ^2J=16.6 Hz), 117.3 (CH), 64.8 (CH_2), 57.3 (d, CH, ^2J=26.4 Hz), 55.9 (C), 43.1 (CH), 29.3 (CH_2), 28.4 (CH_2), 27.0 (CH_3), 22.8 (CH_2), 22.4 (CH_3), 19.3 (C) ppm MS (ESI$^+$): $[M+Na]^+$=550.27. Elemental analysis for $C_{30}H_{42}FNO_2SSi$: calcd: C: 68.27; H: 8.02; N: 2.65; S: 6.08. Found: C: 68.35; H: 7.99; N: 2.62; S: 5.95. $[\alpha]_D^{20}$=+35.8 (c 0.59, $CHCl_3$).

*4.8.8. N-((S, Z)-1-((R)-2-((tert-butyldiphenylsilyloxy)methyl)-cyclopentylidene)-1-fluorobut-3-en-2-yl)-2-methylpropane-2-sulfinamide (**(Z)-7f**).* Colorless oil. Rf=0.32 (cyclohexane/EtOAc: 7/3). IR (neat): ν 2930, 2855, 1665, 1463, 1428, 1365, 1244, 1106, 1080, 998, 822, 740, 701, 609 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.67 (m, 4H), 7.45–7.36 (m, 6H), 5.81–5.70 (m, 1H), 5.23–5.17 (m, 2H), 4.25–4.12 (m, 1H), 3.80–3.75 (m, 1H), 3.57–3.50 (m, 1H), 3.31–3.28 (d, 1H, ^3J=9.0 Hz), 2.76–2.71 (m, 1H), 2.38–2.30 (m, 2H), 1.70–1.53 (m, 4H), 1.10 (br s, 18H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −127.2 (d, ^3J=25.4 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.0 (d, C, ^1J=249.6 Hz), 135.6 (CH), 134.6 (d, CH, ^3J=56.5 Hz), 133.8 (C), 129.5 (CH), 127.6 (CH), 122.7 (d, C, ^2J=7.2 Hz), 117.7 (CH), 64.6 (CH_2), 57.3 (d, CH, ^2J=26.4 Hz), 56.1 (C), 43.3 (CH), 29.4 (CH_2), 28.6 (CH_2), 26.8 (CH_3), 24.9 (CH_2), 22.6 (CH_3), 19.3 (C) ppm MS (ESI$^+$): $[M+Na]^+$=550.20. Elemental analysis for $C_{30}H_{42}FNO_2SSi$: calcd: C: 68.27; H: 8.02; N: 2.65; S: 6.08. Found: C: 68.10; H: 7.97; N: 2.62; S: 5.99. $[\alpha]_D^{20}$=+24.4 (c 0.80, $CHCl_3$).

4.9. Synthesis of Ala-Ψ[CF=CH]-Pro (*Z*)-10a

*4.9.1. (S, Z)-1-fluoro-1-(R)-2-(hydromethyl)cyclopentylidene)-propan-2-aminium chloride (**(Z)-8a**).* To a solution of **(Z)-7a** (323 mg, 0.63 mmol, 1 equiv) in 2.50 mL of dry CH_3OH was added 4 M HCl in 1,4-dioxane (4 equiv). The mixture was stirred at room temperature for 75 min and then concentrated under reduced pressure to dryness. The residue was then washed with Et_2O. The ether-unsoluble residue was concentrated under reduced pressure to afford pure **(Z)-8** as a white solid (132 mg, quantitative). The product was used without further purification in the next step: IR (neat): ν 3310, 2949, 2876, 1695, 1519, 1450, 1244, 1047, 1017, 738, 707 cm^{-1}. ^{1}H NMR (300 MHz, D_2O): δ 4.24 (dq, 1H, ^3J=27.0 Hz, ^3J=6.6 Hz), 3.64–3.59 (m, 1H), 3.49–3.43 (m, 1H), 2.97 (bs, 1H), 2.29–2.25 (m, 2H), 1.79–1.55 (m, 4H), 1.39 (d, 3H, ^3J=9.0 Hz) ppm ^{19}F NMR (282.5 MHz, D_2O): δ −132.1 (d, ^3J=27.1 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.3 (d, C, ^1J=245.0 Hz), 129.1 (d, C, ^2J=12.1 Hz), 66.1 (d, CH_2, ^4J=4.5 Hz), 49.9 (d, CH, ^2J=28.6 Hz), 46.5 (CH), 32.3 (CH_2), 31.5 (CH_2), 27.9 (CH_2), 19.2 (CH_3) ppm Elemental analysis for $C_9H_{17}ClFNO$: C: 51.50; H: 8.17; O: 7.63. Found: C: 51.23; H: 8.04; O: 7.44. $[\alpha]_D^{20}$=−39.7 (c 0.38, H_2O).

*4.9.2. (9H-fluoren-9-yl)methyl (S, Z)-1-fluoro-1-((R)-2-(hydroxymethyl)cyclopentylidene)propan-2-ylcarbamate (**(Z)-9a**).* To a solution of **(Z)-8a** (160 mg, 0.770 mmol, 1 equiv) in 1,4-dioxane (3 mL) and water (3 mL) was added $NaHCO_3$ (195 mg, 2.320 mmol, 3 equiv) at 0 °C, followed by Fmoc-OSu (260 mg, 0.770 mmol, 1 equiv). The reaction mixture was stirred at 0 °C for 2 h and at room temperature overnight. The mixture was then poured into ice cold 1N HCl (6.16 mL) and extracted with EtOAc (×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (cyclohexane/EtOAc: 98/2 to 75/25) to afford **(Z)-9a** (252.6 mg, 83%): Rf=0.70 (cyclohexane/EtOAc: 1/1). IR (neat): ν 3306, 2945, 2872, 1695, 1508, 1449, 1243, 1051, 1022, 755, 738, 621 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H), 7.61 (d, 2H), 7.45–7.29 (m, 4H), 5.21 (d, 1H, ^3J=6.0 Hz), 4.90–4.52 (m, 1H), 4.42–4.38 (m, 2H), 4.20 (t, 1H, ^3J=7.0 Hz), 3.69 (m, 1H), 3.51–3.45 (m, 1H), 2.80 (m, 1H), 2.40 (m, 2H), 2.00 (br s, 1H), 1.64 (m, 4H), 1.33 (d, 3H, ^3J=6.0 Hz) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −129.5 (d, ^3J=28.2 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 155.6 (C), 152.0 (d, C, ^1J=247.3 Hz), 143.9 (C), 141.3 (C), 127.7 (CH), 127.1 (CH), 125.1 (CH), 121.4 (d, C, ^1J=15.9 Hz), 120.2 (CH), 66.8 (CH_2), 64.1 (CH_2), 47.2 (CH), 46.2 (d, CH, ^2J=27.5 Hz), 43.5 (CH), 29.4 (CH_2), 28.2 (d, CH_2, ^3J=5.2 Hz), 24.8 (CH_2), 18.5 (CH_3) ppm MS (ESI$^+$): $[M+H]^+$=396; $[M+Na]^+$=418.2. Elemental analysis for $C_{24}H_{26}FNO_3$: C: 72.89; H: 6.63; N: 3.54. Found: C: 72.56; H: 6.61; N: 3.37. $[\alpha]_D^{20}$=−7.3 (c 0.62, $CHCl_3$).

*4.9.3. (R, Z)-2-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl-amino)-1-fluoropropylidene)-cyclopentanecarboxylic acid (**(Z)-10a**).* To a solution of **(Z)-9a** (159 mg, 0.403 mmol, 1 equiv) in acetone (1.2 mL) at 0 °C was added Jones'reagent (2.74 N, 5 equiv). The reaction mixture was stirred at 0 °C for 1 h and then quenched with isopropyl alcohol (308 μL, 4.03 mmol, 10 equiv) and water (5.2 mL, 13 mL/mmol of alcohol). The mixture was extracted with EtOAc and the combined organic layers were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (cyclohexane/EtOAc: 60/40 with 0.1% of acetic acid) affording the carboxylic acid as a colorless gum. The crude product was then purified by preparative HPLC with acetonitrile/formic acid: 45/55 to afford **(Z)-10a** as a colorless gum (115.4 mg, 70%). Rf=0.34 (cyclohexane/EtOAc: 6/4). IR (neat): ν

3328, 3066, 2960, 1707, 1522, 1450, 1300, 1249, 1057, 759, 740, 621 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (m, 2H), 7.58 (m, 2H), 7.41–7.29 (m, 4H), 5.00 (d, 1H, ^3J=8.1 Hz), 5.00–4.51 (m, 1H), 4.45–4.37 (m, 2H), 4.21 (t, 1H, ^3J=6.8 Hz), 3.56 (m, 1H), 2.62–2.42 (m, 2H), 2.10–1.72 (m, 5H), 1.35 (d, 3H, ^3J=6.8 Hz) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −125.3 (d, ^3J=27.8 Hz) ppm ^{13}C NMR (75.4 MHz, $(CD_3)_2CO$): δ 175.2 (C), 156.4 (C), 154.0 (d, C, ^1J=251.8 Hz), 144.9 (C), 142.1 (CH), 128.6 (C), 128.0 (CH), 126.1 (CH), 120.8 (CH), 119.3 (d, C, ^2J=15.1 Hz), 67.0 (CH_2), 47.9 (CH), 46.8 (d, CH, ^2J=27.1 Hz), 46.0 (d, CH, ^3J=2.3 Hz), 32.4 (CH_2), 28.7 (d, CH_2, ^3J=28.7), 26.4 (CH_2), 17.8 (CH_3) ppm MS (ESI$^+$): $[M+H]^+$=410; $[M+Na]^+$=432.2. Elemental analysis for $C_{24}H_{24}FNO_4$: C: 70.40; H: 5.91; N: 3.42. Found: C: 70.48; H: 6.00; N: 3.45. $[\alpha]_D^{20}$=−44.3 (c 0.63, $CHCl_3$).

4.10. Synthesis of Val-Ψ[CF=CH]-Pro (*Z*)-10d and (*E*)-10d

*4.10.1. (S, E)-1-fluoro-1-((R)-2-(hydroxymethyl)-cyclopent-ylidene)-3-methylbutan-2-aminium chloride ((**E**)-8d).* To a solution of **(*E*)-7d** (326 mg, 0.6 mmol, 1 equiv) in dry MeOH (3.2 mL) was added 4 M HCl in 1,4-dioxane (0.6 mL, 2.4 mmol, 4 equiv). The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure to dryness to afford pure **(E)-8d** as a white powder (144 mg, quantitative). The product was used without further purification in the next step: IR (neat): ν 3470, 3380, 3324, 3155, 2952, 2873, 1718, 1606, 1532, 1476, 1391, 1369, 1166, 1053, 1025, 991, 817, 732, 682, 552, 535 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 3.92 (dd, 1H, ^3J=30.0 Hz, ^3J=9.0 Hz), 3.60–3.54 (m, 1H), 3.36 (m, 1H), 2.88–2.80 (m, 1H), 2.53–2.40 (m, 2H), 2.21–2.07 (m, 1H), 1.85–1.59 (m, 4H), 1.09 (d, 3H, ^3J=6.0 Hz), 1.00 (d, 3H, ^3J=9.0 Hz) ppm ^{19}F NMR (282.5 MHz, CD_3OD): δ −123.2 (d, ^3J=28.2 Hz) ppm ^{13}C NMR (75.4 MHz, CD_3OD): δ 149.3 (d, C, ^1J=245.8 Hz), 129.5 (d, C, ^2J=14.3 Hz), 65.2 (d, CH_2, ^4J=3.0 Hz), 58.2 (d, CH, ^2J=27.9 Hz), 44.3 (d, CH, ^3J=4.5 Hz), 30.6 (CH), 30.2 (CH_2), 28.0 (CH_2), 24.6 (CH_2), 19.5 (CH_3). MS ESI$^+$ (TOF): $[(M\text{-}Cl^-)+H^+]$=202.16. HRMS (ESI)$^+$ calculated for $[M+H]^+$ $C_{11}H_{21}NOF$: 202.1604, Found: 202.1607. $[\alpha]_D^{20}$=−9.60 (c 0.27, CH_3OH).

*4.10.2. (S, Z)-1-fluoro-1-((R)-2-(hydroxymethyl)-cyclopent-ylidene)-3-methylbutan-2-aminium chloride ((**Z**)-8d).* To a solution of **(*Z*)-7d** (201 mg, 0.37 mmol, 1 equiv) in dry MeOH (2 mL) was added 4 M HCl in 1,4-dioxane (0.37 mL, 1.48 mmol, 2 equiv). The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure to dryness to afford **(*Z*)-8d** as a white powder (90 mg, quantitative). The product was used without further purification in the next step: IR (neat): ν 3403, 3290, 2946, 2841, 2620, 1622, 1525, 1380, 1177, 1022, 694, 542, 483, 433 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 3.85–3.70 (m, 2H), 3.38 (m, 1H), 3.06 (m, 1H), 2.48–2.24 (m, 2H), 2.15 (m, 1H), 1.82–1.69 (m, 4H), 1.09 (d, 3H, ^3J=6.0 Hz), 1.01 (d, 3H, ^3J=6.0 Hz). ^{19}F NMR (282.5 MHz, CD_3OD): δ −126.8 (d, ^3J=31.1 Hz). ^{13}C NMR (75.4 MHz, CD_3OD): δ 148.3 (d, C, ^1J=246.6 Hz), 128.2 (d, C, ^2J=12.8 Hz), 63.8 (CH_2), 57.3 (d, CH, ^2J=25.6 Hz), 45.2 (CH), 31.1 (CH), 30.4 (CH_2), 29.8 (CH_2), 25.8 (CH_2), 19.6 (CH_3), 19.2 (CH_3). MS ESI$^+$ (TOF): $[(M\text{-}Cl^-)+H^+]$=202.16. HRMS (ESI)$^+$ calculated for $[M+H]^+$ $C_{11}H_{21}NOF$: 202.1604, Found: 202.1607. $[\alpha]_D^{20}$=−26.0 (c 0.25, CH_3OH).

*4.10.3. (9H-fluoren-9-yl)methyl (S, E)-1-fluoro-1-((R)-2-(hydroxymethyl)cyclopentylidene)-3-methylbutan-2-ylcarbamate ((**E**)-9d).* To a solution of **(*E*)-8d** (123 mg, 0.341 mmol, 1 equiv) in 1,4-dioxane (1.4 mL) and water (1.4 mL) was added $NaHCO_3$ (86 mg, 1.023 mmol, 3 equiv) at 0 °C, followed by Fmoc-OSu (115 mg, 0.341 mmol, 1 equiv). The mixture was stirred at 0 °C for 2 h and at room temperature overnight. The mixture was then poured into ice cold HCl (1 N, 2.8 mL) and extracted with EtOAc (×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH: 100/0 to 90/10) to afford **(*E*)-9d** as a white foam (115 mg, 79%): IR (neat): ν 3059, 2958, 2868, 1670, 1512, 1450, 1269, 1219, 1022, 738, 654, 621, 542, 426 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, 2H, ^3J=9.0 Hz), 7.59 (d, 2H, ^3J=9.0 Hz), 7.45–7.31 (m, 4H), 5.01 (d, 1H, NH, ^3J=9.6 Hz), 4.50–4.17 (m, 4H), 3.58 (d, 2H, ^3J=9.0 Hz), 2.83 (m, 1H), 2.54–2.31 (m, 2H), 1.93–1.81 (m, 1H), 1.78–1.63 (m, 4H), 1.03 (d, 3H, ^3J=9.0 Hz), 0.98 (d, 3H, ^3J=6.0 Hz). ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −121.5 (d, ^3J=28.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 156.4 (C), 150.0 (d, C, ^1J=245.8 Hz), 143.7 (C_{Ar}), 141.2 (C_{Ar}), 127.6 (C_{Ar}), 127.0 (C_{Ar}), 125.0 (C_{Ar}), 123.1 (d, C, ^2J=16.6 Hz), 119.9 (C_{Ar}), 66.9 (CH_2), 65.1 (CH_2), 56.8 (d, CH, ^2J=26.4 Hz), 47.1 (CH), 43.4 (d, CH, ^3J=5.3 Hz), 30.9 (CH), 30.6 (CH_2), 26.69 (d, CH_2, ^3J=3.8 Hz), 23.4 (CH_2), 19.3 (CH_3), 19.0 (CH_3). MS ESI$^+$: $[M+H]^+$=423.93; $[2M+Na]^+$=869.00. Anal. Calcd for $C_{26}H_{30}FNO_3$: C: 73.73; H: 7.14; N: 3.31; Found: C: 73.40; H: 7.07; N: 3.45. $[\alpha]_D^{20}$=−13.3 (c 0.55, $CHCl_3$).

*4.10.4. (9H-fluoren-9-yl)methyl (S, Z)-1-fluoro-1-((R)-2-(hydroxymethyl)cyclopentylidene)-3-methylbutan-2-ylcarbamate ((**Z**)-9d).* To a solution of **(*Z*)-8d** (82 mg, 0.23 mmol, 1 equiv) in 1,4-dioxane (1 mL) and water (1 mL) was added $NaHCO_3$ (57.4 mg, 0.684 mmol, 3 equiv) at 0 °C, followed by Fmoc-OSu (76.9 mg, 0.228 mmol, 1 equiv). The mixture was stirred at 0 °C for 2 h and at room temperature overnight. The mixture was then poured into ice cold HCl (1N, 1.6 mL) and extracted with EtOAc (×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH: 90/10) to afford **(*Z*)-9d** as a yellow oil (92 mg, 95%): IR (neat): ν 3070, 2958, 2868, 1791, 1740, 1700, 1515, 1450, 1259, 1216, 1022, 758, 737, 621, 540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, 2H, ^3J=6.0 Hz), 7.60 (d, 2H, ^3J=9.0 Hz), 7.44–7.30 (m, 4H), 5.02 (d, 1H, NH, ^3J=9.0 Hz), 4.52–4.33 (m, 2H), 4.23 (t, 1H, ^3J=9.0 Hz), 4.20–4.07 (m, 1H), 3.74–3.51 (m, 2H), 3.03 (m, 1H), 2.57–2.23 (m, 2H), 1.91–1.81 (m, 1H), 1.79–1.63 (m, 4H), 1.00 (d, 3H, ^3J=6.0 Hz), 0.96 (d, 3H, ^3J=6.0 Hz). ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −126.8 (d, ^3J=28.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 155.9 (C), 150.6 (d, C, ^1J=246.6 Hz), 143.7 (C_{Ar}), 142.3 (C_{Ar}), 127.6 (C_{Ar}), 126.9 (C_{Ar}), 125.0 (C_{Ar}), 121.6 (d, C, ^2J=14.3 Hz), 120.0 (C_{Ar}), 66.5 (CH_2), 64.0 (CH_2), 56.4 (d, CH, ^2J=24.9 Hz), 47.1 (CH), 43.5 (CH), 30.6 (CH), 29.3 (CH_2), 28.4 (d, CH_2, ^3J=5.3 Hz), 24.7 (CH_2), 19.2 (CH_3), 19.1 (CH_3). MS (ESI$^+$): $[M+H^+]$= 424.00; $[M+H_2O]$=440.87. Anal. Calcd for $C_{26}H_{30}FNO_3$: C: 73.73; H: 7.14; N: 3.31; Found: C: 73.35; H: 7.05; N: 3.25. $[\alpha]_D^{20}$=−9.5 (c 0.65, $CHCl_3$).

*4.10.5. (R, Z)-2-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl-amino)-1-fluoro-3-methylbutylidene) cyclopentanecarboxylic acid ((**Z**)-10d).* To a solution of **(*Z*)-9d** (96 mg, 0.227 mmol, 1 equiv) in acetone (0.7 mL) at 0 °C was added Jones'reagent (2.74 N, 5 equiv). The reaction mixture was stirred at 0 °C for 1 h and then quenched with isopropyl alcohol (174 μL, 2.27 mmol, 10 equiv) and water (3 mL, 13 mL/mmol of alcohol). The mixture was extracted with EtOAc and the combined organic layers were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (100% dichloromethane) to afford a mixture of diastereoisomers (80/20) as a colorless gum (53.0 mg, 53%). After this purification, the two diastereoisomers were not separated. Rf=0.22 (100% CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD): δ 7.74 (d, 2H, ^3J=9.0 Hz), 7.60 (d, 2H, ^3J=6.0 Hz), 7.36–7.22 (m, 4H), 4.37–4.23 (m, 2H), 4.12 (t, 1H, ^3J=6.0 Hz), 4.01 (d, 1H, ^3J=9.0 Hz), 3.46–3.42 (m, 1H), 3.03 (t, 2H, ^3J=3.0 Hz), 2.62–2.51 (m, 2H), 2.05–1.60 (m, 3H), 0.95 (d, 6H, ^3J=6.0 Hz) ppm ^{19}F NMR (282.5 MHz, CD_3OD): δ −121.6 (d, ^3J=29.6 Hz), −121.5 (d, ^3J=30.7 Hz) ppm ^{13}C NMR (75.4 MHz, CD_3OD): δ 178.3 (C), 158.6 (C),

153.3 (d, C, ^1J=250.3 Hz), 145.4 (C_{Ar}), 142.7 (C_{Ar}), 129.2 (C_{Ar}), 128.9 (C_{Ar}), 128.2 (C_{Ar}), 126.3 (C_{Ar}), 121.6 (d, C, ^2J=15.8 Hz), 121.0 (C_{Ar}), 67.9 (CH_2), 58.3 (d, CH, ^2J=25.6 Hz), 46.9 (d, CH, ^3J=2.3 Hz), 33.0 (CH), 31.4 (CH_2), 29.7 (CH_2), 27.0 (CH_2), 20.2 (CH_3), 19.8 (CH_3) ppm MS ESI$^+$ (TOF): $[M+NH_4]^+$=455.23; $[M+Na]^+$=460.19; $[M+K]^+$=476.16.; $[M+H]^+$=438.21. HRMS (ESI): calcd for $[M+H]^+$ $C_{26}H_{29}FNO_4$: 438.2081 found: 438.2093.

*4.10.6. (R, E)-2-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl-amino)-1-fluoro-3-methylbutylidene)cyclopentanecarboxylic acid (**(E)-10d**).* To a solution of **(*E*)-9d** (103 mg, 0.245 mmol, 1 equiv) in acetone (3 mL/mmol of alcohol) at 0 °C was added Jones reagent (2.74 N, 5 equiv). The reaction mixture was stirred at 0 °C for 1 h and then quenched with isopropyl alcohol (187 μL, 2.45 mmol, 10 equiv) and water (3.2 mL, 13 mL/mmol of alcohol). The mixture was extracted with EtOAc and the combined organic layers were washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (100% dichloromethane) affording the carboxylic acid as a colorless gum (54.6 mg, 51%). After this purification, the two diastereoisomeres (88:12) were not separated. Rf=0.26 (100% CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 2H, ^3J=7 Hz), 7.56 (d, 2H, ^3J=6.0 Hz), 7.39–7.25 (m, 4H), 5.21 (m, 1H), 4.44–4.17 (m, 3H), 3.40–3.37 (m, 1H), 2.41 (m, 2H), 2.06–1.61 (m, 5H), 0.90 (m, 6H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −115.6 (m), −119.0 (d, ^3J=28.6 Hz) ppm ^{13}C NMR (75.4 MHz, CD_3OD): δ 153.9 (d, C, ^1J=249.6 Hz), 145.5 (d, C, ^2J=21.1 Hz), 142.7 (CH), 128.9 (CH), 128.3 (CH), 126.5 (CH), 121.0 (CH), 68.3 (CH_2), 57.9 (d, CH, ^2J=26.4 Hz), 32.3 (CH), 28.9 (CH_2), 25.9 (CH_2), 19.7 (CH_3) ppm MS ESI$^+$ (TOF): $[M+NH_4]^+$=455.23; $[M+Na]^+$=460.19; $[M+K]^+$=476.16; $[M+H]^+$=438.21. HRMS (ESI): calcd for $[M+H]^+$ $C_{26}H_{29}FNO_4$: 438.2081 found: 438.2086.

4.11. Synthesis of an Enalapril analogue

4.11.1. (1R, Z)-2-((2S)-2-(1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)-1-fluoropropylidene)-cyclopentanecarboxylic acid (12). Fmoc-Ala-Ψ[CF=C]-Pro **(*Z*)-10a** (0.211 mmol, 1 equiv) in DMF (2.7 mL) and morpholine (1.6 equiv) were stirred for 1 h at room temperature. The crude mixture was then concentrated under reduced pressure and filtered on silica gel (dichloromethane/CH_3OH: 8/2+0.1% of acetic acid). The resulting Ala-Ψ[(Z)CF=C]-Pro **(*Z*)-11** was pure enough to be engaged in the reductive amination with ethyl 2-oxo-4-phenylbutanoate (2.3 equiv) in 2 mL of absolute ethanol, 0.22 g of molecular sieves 4 Å, and a catalytic amount of 10% Pd/C (0.22 equiv). The mixture was placed under H_2 atmosphere for 12 h at room temperature. Then, the reaction mixture was filtered through Celite and the filtrate concentrated under reduced pressure to give a pale yellow oil, which was purified by chromatography on silica gel (dichloromethane/CH_3OH: 8/2+0.1% of acetic acid). The resulting mixture was purified by preparative HPLC (MeOH/0.005M ammonium acetate: 45/55) to afford the fluorinated analogue of Enalapril **12** (28.0 mg, 0.074 mmol, 35%). Rf=0.14 (CH_2Cl_2/CH_3OH: 8/2+0.1% acetic acid). IR (neat): ν 2927, 1705, 1625, 1568, 1454, 1357, 1211, 1170, 1096, 862, 748, 699, 633, 577, 493 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.09 (m, 5H), 5.85 (bs, 1H), 4.11 (q, 2H, ^3J=9.0 Hz), 3.48–3.36 (m, 2H), 3.14 (t, 1H, ^3J=6.0 Hz), 2.62 (m, 2H), 2.22–2.09 (m, 2H), 1.92–1.75 (m, 4H), 1.50 (m, 2H), 1.22–1.18 (m, 6H) ppm ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −124.4 (d, ^3J=28.2 Hz) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.2 (C), 152.9 (d, C, ^1J=254.1 Hz), 141.1 (C), 128.5 (CH), 128.3 (CH), 125.9 (CH), 119.8 (d, C, ^2J=16.6 Hz), 60.8 (CH_2), 58.1 (CH), 51.1 (CH), 50.8 (CH), 35.0 (CH_2), 31.9 (CH_2), 31.5 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 18.3 (CH_3), 14.3 (CH_3) ppm MS (ESI$^+$): $[M+H]^+$=378.07. Elemental analysis for $C_{21}H_{28}FNO_4$: calcd: C: 66.82; H: 7.48; N: 3.71 Found: C: 66.90; H: 7.52; N: 3.82. $[\alpha]_D^{20}$=−35.7 (c 0.14, $CHCl_3$).

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