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Straightforward asymmetric synthesis of Ala-Ψ[CF=CH]-Pro, a proline-containing pseudodipeptide bearing a fluoroolefin as a peptide bond mimic†

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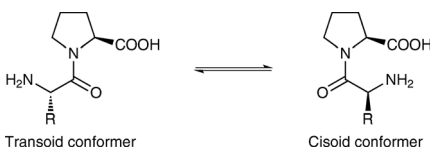
From ethyl-2-oxocyclopentanecarboxylate, we developed an asymmetric synthesis of the fluorinated dipeptide Ala-Ψ[(Z)CF=CH]-Pro analogue of the transoid parent dipeptide. The fluorinated pseudodipeptide could be incorporated into various peptides or proteins for conformational, structural studies and biological activity studies and could also play a relevant role as an enzyme inhibitor.

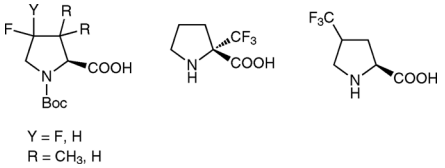
Proline is one of the most studied amino acids due to its unique properties and its numerous implications in biological processes.[1] Proline is the only natural amino-acid with a constrained backbone (secondary cyclic amine) conferring it much higher rigidity than other amino acids. When inserted in a peptide, proline lacks hydrogen on the amide moiety and so can only play a role as a hydrogen bond acceptor. It is well known that the peptide bond is in equilibrium between transoid and cisoid conformations. In dipeptides containing proline residues, the probability to find the *cis* form is very high (0.1 to 0.4) compared to other dipeptides for which this probability is less than 10^{-3}; both *cis* and *trans* forms in the AA-Pro unit (where AA represents any amino acid) are very close energetically, explaining why proline is often implied in turns (Scheme 1). For all these reasons proline is of main interest in peptide chemistry and having an analogue of a single conformer, without any equilibrium, would be a relevant tool for biological and structural studies.

Moreover, the incorporation of one or more fluorine atoms in a molecule often changes significantly its properties (biological, physical, chemical and physiological) compared to a non-fluorinated one.[2] In this context numerous fluorinated prolines bearing one or more fluorine atoms in various positions have been studied to increase the conformational and biochemical stabilities of the amino acid for specific applications like 4-fluoroproline,[3] 4,4-difluoroproline,[3b] 4,4-difluoro-3,3-dimethylproline,[4] 4-trifluoromethylproline,[5] or α-trifluoromethylproline (Scheme 2).[6]

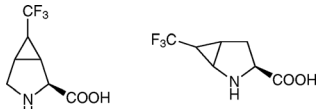


Scheme 1 Cisoid and transoid conformers of dipeptide AA-Pro.

In addition, a fluorine atom can also be used as an efficient tool for structural study by ^{19}F NMR spectroscopy thanks to the high sensitivity of fluorine chemical shifts to its local environment.[7] For example, some fluorinated proline analogues have been developed as ^{19}F-labeled amino acids by Ulrich, Komarov and others for conformational study of peptides (Scheme 3).[8]



Scheme 2 Examples of fluorinated proline analogues.



Scheme 3 ^{19}F-Labeled trifluoromethyl proline analogues.

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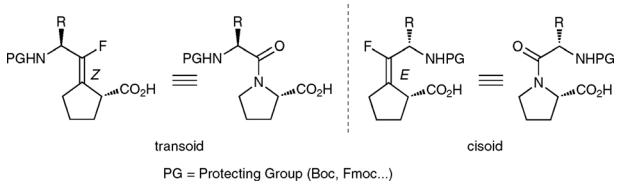
† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C and ^{19}F NMR spectra and a CIF file for compound **(Z)-10**. CCDC 872138. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2nj40891k



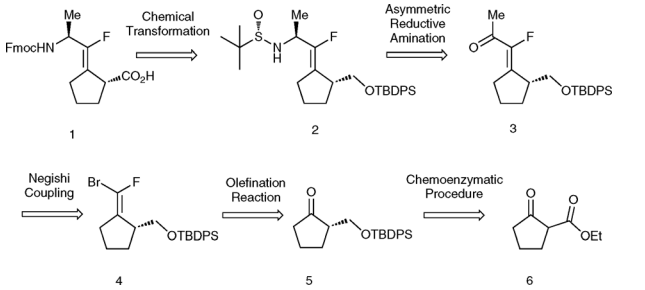
Scheme 4 Dipeptide AA-Ψ[CF=CH]-Pro analogues.

Nevertheless, very few reports have described the fluorinated modification of the peptide bond of the dipeptide unit AA-Pro, essentially due to synthetic difficulties. A goal of our group is the development of new methodologies for the synthesis of fluoropeptidomimetics bearing a fluoroolefin moiety as a peptide bond mimic. Indeed, the fluoroolefin moiety has interesting geometric and electronic similarities with a peptide bond and could be considered as an efficient peptide bond mimic.[9] We wish to develop a new chiral constrained AA-Pro unit in stable transoid or cisoid form, without an equilibrium between these conformers (Scheme 4). Recently, Chang *et al.* synthesized a fluorinated constrained Val-Ψ[(*Z*)CF=CH]-Pro and used it to design new efficient hepatitis C virus NS5A inhibitors.[10]

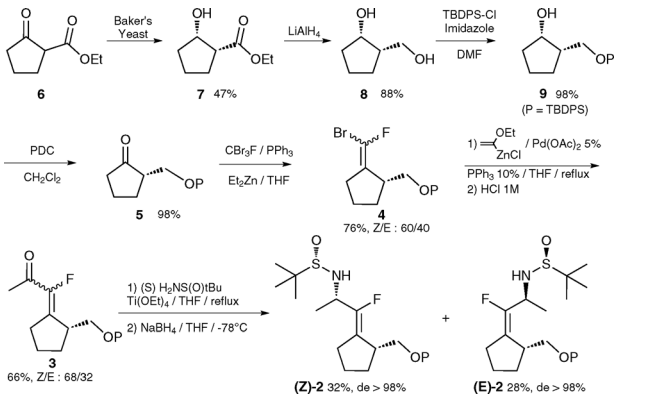
Herein we present the first asymmetric synthesis of Ala-Ψ[(*Z*)CF=C]-Pro **1**. Indeed, besides the fact that this dipeptide unit can be found in numerous peptides and proteins, this compound in the *Z* configuration is well known to be an effective mimic of the native Ala-Pro unit. Moreover, this fluorinated analogue is also very relevant as a pharmaceutical candidate for the treatment of different diseases acting as an enzymatic inhibitor of dipeptidyl peptidase.[11] For this purpose, the Ala-Ψ[(*Z*)CF=C]Pro unit has already been synthesised but not in a straightforward and asymmetric manner. As a matter of fact, Welch *et al.* have generated the fluoroolefin moiety by a Peterson reaction and the racemic mixture of each diastereoisomer of the final dipeptide analogue **1** was obtained after separation by column chromatography.[11f] Augustyns *et al.* have generated the fluoroolefin moiety from a Horner–Wadsworth–Emmons reaction and finally obtained the racemic dipeptide unit **1**.[11b]

Contrary to a previously reported study using the Boc substituent as the protecting group,[11] we decided to introduce the Fmoc protecting group, commonly used in peptide solid phase synthesis, at the *N*-terminal side of the dipeptide. Our retrosynthetic strategy to reach compound **1** begins with the chemical transformation of chiral allylamine **2** obtained by asymmetric reductive amination of α-fluoroketone **3**.[12] Compound **3** could be obtained by a palladium mediated Negishi cross-coupling between α-ethoxyvinylzinc chloride and gem-bromofluoroolefin **4**.[13] This could be effected by olefination reaction of ketone **5**.[14] This chiral ketone **5** could be synthesised by a chemoenzymatic procedure from ethyl-2-oxocyclopentanecarboxylate **6** (Scheme 5).[15]

As depicted in Scheme 6, we started the asymmetric synthesis using the chemoenzymatic procedure described by Buisson and Azerad[15b] to synthesise the chiral ketone **5** in a pure form with an overall yield of 40% in four steps; the first step being the limiting step with 47% yield. Then we proceeded to



Scheme 5 Retrosynthesis of Ala-Ψ[(*Z*)CF=C]Pro **1**.

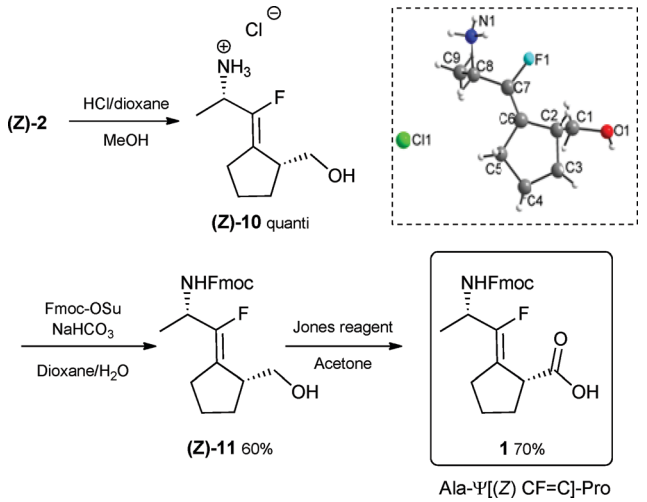


Scheme 6 Asymmetric synthesis of precursor **2**.

an olefination reaction leading to **4** in 76% yield and a 60/40 *Z*/*E* ratio. The Negishi reaction was then carried out from **4** furnishing compound **3** in 66% yield and a slightly improved 68/32 *Z*/*E* ratio. Indeed, partial isomerisation can occur during the hydrolysis step.[13b] The diastereoselective reductive amination of α-fluorenone **3** was performed with (*S*)-*tert*-butanesulfinamide as a chiral auxiliary. Products **2** in both *Z* and *E* configuration were isolated in moderate 32% and 28% yield, respectively, but with a very good diastereomeric ratio of up to 96%. As previously reported in the literature,[12] the attack of the hydride proceeded from the *Re* face of sulfinyl imine allowing the same configuration as that of the native peptide to be obtained. At this stage, it was relatively easy to separate both *Z* and *E* diastereoisomers by column chromatography.

In order to obtain specifically the relevant transoid conformer analogue, the major diastereoisomer **(*Z*)-2** was submitted to subsequent deprotection of *tert*-butane sulfoxide and silyl groups, which afforded product **(*Z*)-10** in quantitative yield. The stereochemistry of this compound **(*Z*)-10** was verified by X-ray analysis which confirmed the reduction process.‡ Then the compound **(*Z*)-10** was subjected to Fmoc protection of the primary amine, which gave the product **(*Z*)-11** in 60% yield.

‡ Crystal data for **(Z)-10**: $C_9H_{17}ClFNO$, M = 209.69, orthorhombic, a = 6.8983(6) Å, α = 90°, b = 12.0634(10) Å, β = 90°, c = 12.5086(10) Å, γ = 90°, U = 1040.93(15) Å^3, T = 293(2) K, space group $P212121$ (no. 19), Z = 48 336 reflections measured, 2137 independent reflections (R_{int} = 0.0174). Final R values = 0.0272 (all data) and $wR(F^2)$ = 0.07 (all data). Flack parameters = 0.03(5). CCDC 872138.



Scheme 7 Access to the fluorinated analogue Ala-Ψ[(*Z*)CF=CH]-Pro **1**.

The final step, Jones oxidation of alcohol to acid, allowed the fluorodipeptide analogue Fmoc-Ala-Ψ[(*Z*)CF=C]-Pro **1** in a pure form with 70% yield to be obtained (Scheme 7).

We described here the first asymmetric synthesis of an Ala-Ψ[(*Z*)CF=C]-Pro unit. This dipeptide could have many applications in structural study of peptide or protein as well as a therapeutic agent such as a DPPIV or DPPII inhibitor. New asymmetric synthetic methodologies are currently under investigation to enlarge the scope of the synthesized dipeptide AA-Pro. Indeed, we recently developed a new methodology based on organometallic addition onto α-fluoroenimines generated from easily accessible α-fluoroacrylate derivatives.[16] This methodology will be applied soon to the proline residue in order to develop an efficient access to a wide range of enantiopure AA-Pro dipeptides both in transoid and cisoid conformations.

Experimental section

General

All organometallic reagents were commercially available and purchased from Aldrich or Acros. Reactions with organometallics were carried out under an argon atmosphere. THF was distilled prior to use from sodium benzophenone ketyl under a nitrogen atmosphere and dichloromethane from CaH_2. TLC was performed on Merck 60F-250 silica gel plates, using UV light as a visualizing agent and an ethanolic solution of phosphomolybdic acid and heat as a developing agent. Flash column chromatography purifications were carried out using silica gel (70–230 mesh). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR ($CFCl_3$ as internal reference) were recorded at 300.13, 75.47 and 282.40 MHz, respectively, on a Bruker DXP 300. Abbreviations used for peak multiplicity are s: singlet, brs: broad singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet. *J* was used to indicate coupling constant in Hertz. 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. Electronic impact (EI – 70 eV), chemical ionization (CI – 200 eV) or high-resolution MS experiments were recorded on a JEOL AX 500 mass spectrometer using a mass resolution of 5000 and with TOF as a mass analyzer for HRMS. Elemental analyses were performed on a CE Instruments EA 110 CHNS-O instrument.

Ethyl-2-(*S*)-hydroxy-(*R*)-cyclopentane carboxylate (7). To a solution of ethyl 2-oxocyclopentanecarboxylate (16 g) in water at room temperature Baker's yeast (20 g) and glucose (8 g) were added portionwise. The mixture was stirred for 4 days and then extracted with Et_2O (3×). The combined organic layers were washed with water and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: cyclohexane/EtOAc: 80/20) to afford the expected keto-alcohol as an orange oil in 47% yield. R_f = 0.40 (cyclohexane/EtOAc: 50/50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.42–4.20 (m, 1H), 4.16 (q, ^3J = 7.2 Hz, 2H), 3.13 (brs, 1H), 2.66 (dt, ^3J = 4.2 Hz, ^3J = 8.9 Hz, 1H), 2.02–1.57 (m, 6H), 1.26 (t, ^3J = 7.1 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.2, 73.8, 60.8, 49.6, 34.1, 26.6, 22.2, 14.4.

(1*S*,2*S*)-2-Methanolhydroxycyclopentane (8). To a suspension of $LiAlH_4$ (2.6 g, 68.2 mmol, 1 equiv.) in dry THF (70 mL) at 0 °C under argon was added dropwise a solution of ethyl-2-(*S*)-hydroxy-(*R*)-cyclopentane carboxylate (10.79 g, 68.2 mmol, 1 equiv.) in THF (200 mL). The mixture was stirred at room temperature overnight and then NaOH aq. (1 M, 23 mL, 0.3 equiv.) was added slowly at −40 °C. The salts were filtered off on $MgSO_4$ and the filter cake was washed with Et_2O (at least 1.6 L). Concentration under reduced pressure furnished quantitatively crude 2-(*S*)-methanol-(*S*)-hydroxycyclopentane as a pale yellow oil, which was pure enough to be used in the next step without purification. R_f = 0.20 (cyclohexane/EtOAc: 80/20). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.30−4.26 (m, 1H), 3.92 (brs, 2H), 3.69−3.62 (m, 2H), 2.01−1.89 (m, 1H), 1.83−1.70 (m, 2H), 1.64−1.45 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 74.5, 62.4, 46.1, 34.9, 25.4, 22.1.

2-(*S*)-(*tert*-Butyldiphenylsilyloxymethyl)-(*S*)-hydroxycyclopentane (9). To a stirred solution of 2-(*S*)-methanol-(*S*)-hydroxycyclopentane (7.73 g, 66.55 mmol, 1 equiv.) in dry DMF (770 mL) was added at 0 °C imidazole (22.65 g, 333 mmol, 5 equiv.), followed by *tert*-butylchlorodiphenylsilane (20.7 mL, 79.86 mmol, 1.2 equiv.). The mixture was allowed to warm to room temperature and stirred overnight. The mixture was shaken with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3×). The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: cyclohexane/EtOAc: 90/10) to afford 2-(*S*)-(*tert*-butyldiphenylsilyloxymethyl)-(*S*)-hydroxycyclopentane as a white solid in 98% yield. R_f = 0.70 (cyclohexane/EtOAc: 80/20). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69−7.67 (m, 4H), 7.42−7.40 (m, 6H), 4.42 (m, 1H), 3.94−3.77 (m, 2H), 2.90 (brs, 1H), 1.81−1.91 (m, 1H), 1.73−1.61 (m, 3H), 1.43−1.35 (m, 2H), 1.06 (s, 9H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 135.6, 133.2, 129.9, 127.7, 75.2, 64.4, 46.1, 34.7, 26.9, 25.5, 22.4, 19.2.

2-(*S*)-(*tert*-Butyldiphenylsilyloxymethyl)cyclopentanone (5). To a mixture of pyridinium dichromate (64 g, 166 mmol, 2.5 equiv.)

and powdered molecular sieves (4 Å, 130 g) in CH_2Cl_2 (500 mL) under argon was added dropwise 2-(*S*)-(*tert*-butyldiphenylsilyloxymethyl)-(*S*)-hydroxycyclopentane (23.6 g, 66.55 mmol, 1 equiv.) in CH_2Cl_2 (200 mL) at room temperature. The mixture was stirred at room temperature for 2 h. After the reaction was completed, controlled by TLC, the mixture was diluted with Et_2O and filtered through silica gel. Evaporation of solvents gave pure 2-(*S*)-(*tert*-butyldiphenyl silyloxymethyl)cyclopentanone as a white solid in 98% yield. R_f = 0.30 (cyclohexane/EtOAc: 95/5). IR (neat, cm^{-1}): ν 3417, 3070, 2956, 2932, 2858, 1741, 1428, 1111, 1080, 750, 505. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68−7.65 (m, 4H), 7.53−7.41 (m, 6H), 3.97 (dd, ^2J = 4.5 Hz, ^3J = 10.2 Hz, 1H), 3.78 (dd, ^2J = 3.4 Hz, ^3J = 10.2 Hz, 1H), 2.30−2.01 (bm, 6H), 1.96−1.71 (m, 1H), 0.94 (s, 9H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 220.2, 135.8, 134.9, 129.8, 127.8, 62.8, 51.0, 39.3, 27.0, 26.6, 21.2, 19.4. MS (EI^+): *m/z* = 199 $[M - 2Ph]^+$. Elemental analysis for $C_{22}H_{28}O_2Si$: calcd: C, 74.95; H, 8.01. Found: C, 74.76; H, 8.14%.

((2-(Bromofluoromethylene) cyclopentyl)-(*R*)-methoxy)-*tert*-butyldiphenylsilane (4). To a solution of triphenylphosphine (28.59 g, 109.01 mmol, 7 equiv.), tribromofluoromethane (10.7 mL, 109.01 mmol, 7 equiv.), and 2-(*S*)-(*tert*-butyldiphenylsilyloxymethyl)-cyclopentanone (5.49 g, 15.57 mmol, 1.0 equiv.) in anhydrous THF (200 mL) was added a solution of diethylzinc (109 mL of a 1 M solution in hexane, 109.01 mmol, 7 equiv.) dropwise *via* a syringe pump over 30 min at room temperature under argon. The mixture was stirred for 1 h and the resulting solution was then quenched with methanol. After 15 min the mixture was concentrated under reduced pressure and the residue then chromatographed on silica gel (eluent: 100% cyclohexane), affording the desired mixture of (*Z*) and (*E*) ((2-(bromofluoromethylene)cyclopentyl)-(*R*)-methoxy)*tert*-butyldiphenylsilane (*Z*/*E*: 60/40) as a pale yellow oil in 76% yield. R_f = 0.70 (cyclohexane/EtOAc: 98/2). IR (neat, neat cm^{-1}): ν 3394, 3071, 2958, 2857, 1682, 1471, 1428, 1111, 1092, 823, 701, 504. ^1H NMR (300 MHz, $CDCl_3$): δ 7.61−7.56 (m, 4H), 7.31−7.24 (m, 6H), 3.64−3.61 (m, 1H), 3.50−3.41 (m, 1H), 3.03−2.95 (m, $0.4H_Z$), 2.72−2.61 (m, $0.6H_E$), 2.42−2.26 (m, $1.1H_E$), 2.24−2.12 (m, $0.9H_Z$), 2.10−1.59 (bm, 4H), 0.97 (s, 9H). ^{19}F NMR (282.5 MHz): δ −74.0 (m, $0.4F_Z$), −77.3 (m, $0.6F_E$). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.9 (d, ^1J = 249 Hz), 136.4, 135.2, 134.4, 131.0, 130.4, 128.7, 128.4, 125.3 (2d, ^2J = 10 Hz), 64.9, 64.2, 46.3, 45.3, 32.8, 31.3, 30.2, 29.8, 27.6, 26.7, 25.3, 24.7, 20.0. MS (EI^+): *m/z* = 447 $[M^+]$. Elemental analysis for $C_{23}H_{28}BrFOSi$: C, 61.74; H, 6.31. Found: C, 61.57; H, 6.42%.

(*Z*) and (*E*) 1-(2-(*R*)-Methoxy-*tert*-butyldiphenylsilane)-cyclopentylidene-1-fluoropropan-2-one (3). To a solution of potassium *tert*-butoxide (3.96 g, 35.26 mmol, 3 equiv.) in anhydrous THF (175 mL) at −78 °C under argon was added ethylvinylether (3.37 mL, 35.26 mmol, 3 equiv.) followed by addition of *n*-BuLi in hexane dropwise (14.1 mL of a 2.5 M solution in hexane, 35.26 mmol, 3 equiv.). The mixture was stirred for 30 min at −78 °C and a solution of dry zinc chloride (9.61 g, 70.53 mmol, 6 equiv.) in THF (280 mL) was added dropwise. After 10 min, the cooling bath was removed and the solution was allowed to warm to room temperature for 30 min. The mixture was then added slowly to a solution of palladium diacetate (132 mg, 0.59 mmol, 0.05 equiv.), triphenylphosphine (308 mg, 1.18 mmol, 0.1 equiv.) and (*Z*) and (*E*) ((2-(bromofluoromethylene)cyclopentyl)-(*R*)-methoxy)-*tert*-butyldiphenylsilane **4** (5.26 g, 11.7 5 mmol, 1 equiv.) in anhydrous THF (115 mL) at 70 °C under argon. The mixture was stirred for 1 h. After the reaction was completed, controlled by monitoring the ^{19}F-NMR signal of the reaction mixture, HCl aq. (1 M, 300 mL) was added and the mixture was stirred for 15 min before being extracted with Et_2O (3×, 300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel (eluent: cyclohexane/EtOAc: 98/2), affording the mixture of (*Z*) and (*E*) 1-(2-(*R*)-methoxy-*tert*-butyldiphenylsilane)-cyclopentylidene-1-fluoropropan-2-one (*Z*/*E*: 68/32) as a yellow oil in 65% yield. R_f = 0.58 and 0.62 (cyclohexane/EtOAc: 95/5). IR (neat, cm^{-1}): ν 3072, 2968, 2930, 1702, 1638, 1477, 1428, 1382, 1277, 1089, 1049, 881, 703, 505. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.60 (m, 4H), 7.43–7.34 (m, 6H), 3.77–3.50 (m, 2.6H), 3.15–3.13 (m, 0.6H), 2.72–2.67 (m, 1H), 2.50–2.44 (m, 1H), 2.21 (2d, ^4J = 5.3 Hz, 3H), 1.97–1.65 (bm, 4H), 1.04 (s, 9H). ^{19}F NMR (282.5 MHz): δ −119.2 (m, $0.4F_E$), −123.6 (m, $0.6F_Z$). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 192.2 (d, ^2J = 41 Hz), 191.7 (d, ^2J = 40 Hz), 148.6 (d, ^1J = 251 Hz), 148.5 (d, ^1J = 251 Hz), 139.3 (d, ^2J = 14 Hz), 138.5 (d, ^2J = 13 Hz), 134.6, 132.6, 128.5, 126.6, 63.3, 62.8, 44.8, 43.3, 30.3, 29.3, 28.7, 27.5, 26.3, 25.8, C15), 23.8, 21.7, 18.2. HRMS: calculated for $C_{25}H_{32}FO_2Si$: 411.2135. Found: 411.2138.

***N*-{(1*R*)-2-[(2*S*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)cyclopentylidene]-2-fluoro-1-methylethyl}-2-methyl-2-propanesulfinamide (2).** A solution of $Ti(OEt)_4$ (2.08 mL, 10.0 mmol, 5 equiv.) and ketone **3** (822.0 mg, 2.0 mmol, 1 equiv.) in dry THF (20 mL) was prepared under argon. Then, (*S*)-*tert*-butanesulfinamide (1.21 g, 10.0 mmol, 5 equiv.) was added and the mixture was heated to reflux for 8 h. The mixture was cooled down to −78 °C and $NaBH_4$ (302.8 mg, 8.0 mmol, 4 equiv.) was added. The mixture was stirred for 7 h at −78 °C and then allowed to warm to room temperature. The resulting solution was poured into an equal volume of brine with rapid stirring. The resulting suspension was filtered through a plug of celite® and the filter cake was washed with EtOAc. The aqueous layer was extracted with EtOAc (2×) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (eluent: PE/EtOAc: 85/15 → 78/22) to afford the first desired (*E*) diastereomer in 28% yield and then the desired (*Z*) diastereomer **2** in 32% yield as colorless oil.

Diastereomer ***(E)*-2.** R_f = 0.19 (PE/EtOAc: 85/15). IR (neat, cm^{-1}): ν 3071, 2958, 1713, 1473, 1428, 1189, 1112, 1086, 702, 505. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.66 (m, 4H), 7.42–7.26 (m, 6H), 3.78–3.51 (m, 3H), 3.20 (d, ^3J = 8.3 Hz, 1H), 2.67–2.63 (m, 1H), 2.35–2.09 (m, 2H), 1.69–1.54 (m, 4H), 1.19 (d, ^3J = 6.7 Hz, 3H), 1.04 (s, 9H). ^{19}F NMR (282.5 MHz): δ −125.1 (dd, ^3J = 27.8 Hz, ^4J = 3.3 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 153.1 (d, ^1J = 249.5 Hz), 135.7, 134.2, 133.8, 129.7, 127.7, 120.2 (d, ^2J = 16.4), 64.9 (d, ^4J = 4.4 Hz), 55.7, 50.9 (d, ^2J = 28.0 Hz), 43.1 (d, ^3J = 4.9 Hz), 29.4, 27.5 (d, ^4J = 3.3 Hz), 27.1, 22.9, 22.4, 19.6, 19.4. MS (EI^+): *m/z* = 516.27 $[M + H^+]$. Elemental analysis for $C_{29}H_{42}FNO_2SSi$:

C, 67.53; H, 8.21; N, 2.72; S, 6.22. Found: C, 67.75; H, 8.43; N, 2.75; 6.25%.

Diastereomer **(*Z*)-2**. R_f = 0.12 (PE/EtOAc: 85/15). IR (neat, cm^{-1}): ν 3069, 2964, 2852, 1710, 1412, 1192, 1108, 1092, 700, 513. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.65 (m, 4H), 7.41–7.37 (m, 6H), 4.24–4.06 (m, 1H), 3.77–3.57 (m, 2H), 3.48 (d, ^3J = 7.14 Hz, 1H), 3.11–3.08 (m, 1H), 2.49–2.22 (m, 2H), 1.90–1.81 (m, 2H), 1.76–1.66 (m, 2H), 1.32 (d, ^3J = 6.8 Hz, 3H), 1.20 (s, 9H), 1.04 (s, 9H). ^{19}F NMR (282.5 MHz): δ −130.4 (d, ^3J = 26.8 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.3 (d, ^1J = 249.0 Hz), 135.7, 133.9, 129.5, 127.6, 121.0 (d, ^2J = 14.8 Hz), 64.6 (d, ^4J = 3.8 Hz), 55.8, 50.8 (d, ^2J = 28.0 Hz), 43.1, 29.4, 28.6 (d, ^4J = 4.6 Hz), 26.8, 24.9, 22.6, 19.3, 19.01. MS (EI^+): *m/z* = 516.27 [M + H^+]. Elemental analysis for $C_{29}H_{42}FNO_2SSi$: C, 67.53; H, 8.21; N, 2.72; S, 6.22. Found: C, 67.60; H, 8.28; N, 2.74; 6.24%.

(*Z*) (2*R*)-1-[(2*S*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)cyclopentylidene]-1-fluoro-2-propanaminium chloride ((*Z*)-10). To a solution of **(*Z*)-2** (213.0 mg, 0.41 mmol, 1 equiv.) in dry MeOH (2 mL) was added 4 M HCl in dioxane (412 μL, 1.65 mmol, 4 equiv.). The mixture was stirred at room temperature for 1h15 and then concentrated under reduced pressure to near dryness. The residue was then washed with Et_2O. The ether-insoluble residue was concentrated under reduced pressure to afford pure amine hydrochloride **(*Z*)-10**. $[\alpha]_D^{20}$ = −39,7 (*c* 0.38, H_2O). IR (neat, cm^{-1}): ν 3405, 3310, 2949, 2876, 1695, 1519, 1450, 1304, 1244, 1046, 1016, 738, 707. ^1H NMR (300 MHz, D_2O): δ 4.28 (dq, ^3J = 27.2 Hz, ^3J = 6.6 Hz, 1H), 3.65–3.60 (m, 1H), 3.48–3.42 (m, 1H), 2.99 (brs, 1H), 2.30–2.28 (m, 2H), 1.76–1.70 (m, 4H), 1.42 (d, ^3J = 6.8 Hz, 3H). ^{19}F NMR (282.5 MHz): δ −132.5 (d, ^3J = 26.9 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.3 (d, ^1J = 245 7 Hz), 129.1 (d, ^2J = 13.2 Hz), 66.1 (d, ^4J = 4.6 Hz), 49.9 (d, ^2J = 28.7 Hz), 46.5, 32.6, 31.5, 27.9, 19.21. Elemental analysis for $C_9H_{17}ClFNO$: C, 51.5; H, 8.17; O, 7.63. Found: C, 51.23; H, 8.04; O, 7.44%.

(*Z*) 9*H*-Fluoren-9-ylmethyl (1*R*)-2-[(2*S*)-2-({[*tert*-butyl(diphenyl)-silyl]oxy}methyl)cyclopentylidene]-2-fluoro-1-methylethylcarbamate ((*Z*)-11). To a solution of amine hydrochloride derivative **(*Z*)-10** (86.034 mg, 0.41 mmol, 1 equiv.) in dioxane (4 mL per mmol of amine hydrochloride) and water (4 mL per mmol of amine hydrochloride) was added $NaHCO_3$ (104.1 mg, 1.24 mmol, 3 equiv.) at 0 °C, followed by Fmoc-OSu (167.2 mg, 0.49 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 HCl (1 N, 8 mL per mmol of amine hydrochloride) and extracted with AcOEt (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 (PE/EtOAc: 88/12 → 75/25), affording **(*Z*)-11** in 60% yield as a colorless gum. $[\alpha]_D^{20}$ = −7,3 (*c* 0.62, $CHCl_3$). R_f = 0.22 (cyclohexane/EtOAc: 50/50). IR (neat, cm^{-1}): ν 3406, 3320, 3065, 2952, 2874, 1702, 1534, 1450, 1247, 1054, 759, 740. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, ^3J = 7.5 Hz, 2H), 7.60 (d, ^3J = 7.2 Hz, 2H), 7.43–7.28 (m, 4H), 5.23 (d, ^3J = 8.5 Hz, 1H), 4.92–4.51 (m, 1H), 4.42–4.38 (m, 2H), 4.21 (t, ^3J = 6.6 Hz, 1H), 3.71–3.66 (m, 1H), 3.51–3.45 (m, 1H), 2.55–2.22 (m, 2H), 2.00 (brs, 1H), 1.81–1.55 (m, 4H), 1.33 (d, ^3J = 6.9 Hz, 3H). ^{19}F NMR (282.5 MHz): δ −130.1 (d, ^3J = 28.9 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 155.6, 152.2 (d, ^1J = 248.1 Hz), 143.9, 141.3, 127.7, 127.1, 125.1, 121.4 (d, ^2J = 15.9 Hz), 120.2, 66.8, 64.1, 47.2, 46.2 (d, ^2J = 27.5 Hz), 43.5, 29.4, 28.2 (d, ^3J = 5.2 Hz), 24.8, 18.5. MS (EI^+): *m/z* = 396 [M + H^+]. Elemental analysis for $C_{24}H_{26}FNO_3$: C, 72.89; H, 6.63; N, 3.54; S. Found: C, 73.15; H, 6.91; N, 3.56%.

(*Z*) (1*S*)-2-((*Z*,2*R*)-2-[{(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-1-fluoropropylidene)cyclopentanecarboxylic acid 1. To a solution of *N*-protected amino alcohol **(*Z*)-11** (110.9 mg, 0.28 mmol, 1 equiv.) in acetone (3 mL per mmol of alcohol) at 0 °C was added Jones reagent (2.74 N, 3 equiv.). The reaction mixture was stirred at 0 °C for 1 h and then quenched with isopropyl alcohol (10 equiv.) and water (13 mL per mmol of alcohol). The mixture was extracted with AcOEt (3×) 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 (PE/EtOAc: 60/40 then 50/50 with 0.1% of acetic acid), affording **1** as a colorless gum in 70% yield. $[\alpha]_D^{20}$ = −44,3 (*c* 0.63, $CHCl_3$). IR (neat, cm^{-1}): ν 3328, 3066, 2960, 1707, 1522, 1450, 1300, 1249, 1057, 759, 740, 621. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, ^3J = 7.5 Hz, 2H), 7.58 (d, ^3J = 7.2 Hz, 2H), 7.41–7.29 (m, 4H), 5.00 (d, ^3J = 8.1 Hz, 1H), 5.00–4.51 (m, 1H), 4.45–4.37 (m, 2H), 4.21 (t, ^3J = 6.8 Hz, 1H), 3.56 (brs, 1H), 2.62–2.42 (m, 2H), 2.10–1.72 (m, 4H), 1.35 (d, ^3J = 6.8 Hz, 3H). ^{19}F NMR (282.5 MHz): δ −125.3 (d, ^3J = 27.8 Hz).). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.2, 156.3, 153.9 (d, ^1J = 251.1 Hz), 144.9, 141.9, 128.4, 127.8, 126.0, 120.7, 119.1 (d, ^2J = 15.4 Hz), 66.9, 47.9, 46.6 (d, ^2J = 26.9 Hz), 45.8 (d, ^3J = 2.2 Hz), 32.2, 28.6 (d, ^3J = 4.4 Hz), 26.3, 17.6. MS (EI^+): *m/z* = 410.0 [M + H^+]. Elemental analysis for $C_{24}H_{24}FNO_4$: C, 70.40; H, 5.91; N, 3.42; S. Found: C, 70.48; H, 6.00; N, 3.45%.

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