Sequential Deconjugative Electrophilic Fluorination/ Cross-Metathesis: Toward synthesis of fluoro analogues of biologically active compounds.

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General Methods and Materials

All reactions were conducted under an argon atmosphere and oven flamed glassware was used. Methylene chloride was distilled over calcium hydride under a nitrogen atmosphere. All other solvents and commercially available reagents were used as received. Reactions were monitored by TLC performed using 0.25 mm E. Merck 5735 Kiegelsel silica gel coated aluminum plates (60F254) using UV radiation (254 nm) as visualizing agent and using solutions of p-anisaldehyde–sulfuric acid–acetic acid in EtOH or KMnO₄–K₂CO₃ in water followed by heating as developing agent. Flash column chromatography was carried out under pressure on Merck silica gel 40-60 mesh. ¹H NMR and ¹³C NMR spectra were recorded at 25 °C on a Brucker Avance 300 MHz (¹H), 282 MHz (¹⁹F) and 75 MHz (¹³C), and calibrated using solvent as internal standard (¹H: CDCl₃ 7.26 ppm; ¹³C CDCl₃ 77.16 ppm). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or a combination of these. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a ZnSe plate (ATR). High resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT95XP and accurate to ± 0.001.

I-Procedure for Dehydroxyfluorination of α-hydroxy-β,γ-unsaturated amide.

A solution of Deoxo-Fluor (1.5 mmol, 1.5 equiv., 50% in THF) was added to a solution of 1 (1 mmol, 1 equiv.) in CH₂Cl₂ (4 mL) at -78 °C placed in a round-bottom flask. After addition the solution was mixed at -78 °C for 1 h and the progress of the reaction was monitored by T.L.C. The reaction was allowed to cool to r.t and was then worked up by adding saturated aqueous NaHCO₃ solution. The product was extracted into CH₂Cl₂ (3 x 10 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude was purified over silica gel to give the fluoroolefin 2.

II-General Procedure for Deconjugative Electrophilic Fluoration of γ-Silyl Butenamides

A solution of allyltrimethylsilane 3a-o (1 equiv.) and Selectfluor (1.5 equiv.) in Acetonitrile (0.2M) was heated to reflux under argon. After completion, reaction was quenched with saturated aqueous NH₄Cl solution and extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was purified over silica gel to give the products 4a-o.

III-Procedure for Cross Metathesis of allylic fluoride.

In a flask, allylic fluoride 4 (0.5 mmol, 1equiv.) was dissolved in dry CH₂Cl₂ (5 ml). Then 1-hexadecene (0.75 mmol, 1.5 equiv.) and 2nd generation Hoveyda-Grubbs catalyst (7 mol%) were added and the reaction mixture was stirred at room temperature for 24 hours. The solution was concentrated under vaccum and the crude was directly purified over silica gel to give the corresponding product fluoroamide 5.

(S,E)-Methyl 2-(4-fluorooctadec-2-enamido)-3-phenylpropanoate (2).
29.4, 24.6, 22.8. \textbf{IR} (neat) \( \nu \) 3317, 2916, 2848, 1738, 1633, 1538 cm\(^{-1}\). \textbf{HRMS} (ESI+): m/z: Calcd for C\(_{28}\)H\(_{45}\)NO\(_3\)F [M+H]: 462.3383, found: 462.3381.

(2S)-methyl 2-(2-fluorobut-3-enamido)-3-phenylpropanoate (4a).

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{MeO}_2\text{C} & \quad \text{F} \\
\text{Ph} & \quad 4a
\end{align*}
\]

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.32-7.20 (m, 3H), 7.16-7.06 (m, 2H), 6.97 (brm, 1H), 6.05-5.80 (m, 1H), 5.49 (d, \( J = 17 \) Hz, 0.5H), 5.43 (d, \( J = 17.4 \) Hz, 0.5H), 5.4-5.3 (brm, 2H+0.5H, CH-F), 5.16 (d, \( J = 4.1 \) Hz, 0.5H, CH-F), 4.93-4.84 (m, 1H), 3.70 and 3.68 (2s, 3H), 3.22-3.04 (m, 2H).

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)): -187.51, -187.95.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 171.1, 171.0, 167.7 (d, \( J_{C-F} = 20.5 \) Hz), 167.5 (d, \( J_{C-F} = 20.5 \) Hz), 135.5, 135.4, 130.9 (d, \( J_{C-F} = 18.5 \) Hz), 130.8 (d, \( J_{C-F} = 18.5 \) Hz), 129.9, 129.1, 128.4, 128.3, 127.0, 126.9, 119.0 (d, \( J_{C-F} = 11.9 \) Hz), 118.6 (d, \( J_{C-F} = 12 \) Hz), 90.3 (d, \( J_{C-F} = 187.2 \) Hz) 52.6, 52.5, 52.2, 52.1 37.4. \textbf{IR} (neat) \( \nu \) 3321, 2953, 1742, 1672, 1524 cm\(^{-1}\). \textbf{HRMS} (ESI+): m/z: Calcd for C\(_{14}\)H\(_{17}\)NO\(_3\)F [M+H]: 266.1192, found: 266.1186.

(S)-Methyl 2-(2-fluorobut-3-enamido)-2-phenylacetate (4b).

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{MeO}_2\text{C} & \quad \text{F} \\
\text{Ph} & \quad 4b
\end{align*}
\]

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.35-7.33 (m, 5H), 6.97 (brm, 1H), 6.10-5.86 (m, 1H), 5.49 (m, 4H), 5.23 (dt, \( J = 5.0, 1.8 \) Hz, 0.5H, CH-F), 5.17 (dt, \( J = 5.0, 1.7 \) Hz, 0.5H, CH-F), 3.70 and 3.69 (2s, 3H).

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)): -187.57, -187.86.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 170.7, 170.6, 167.6 (d, \( J_{C-F} = 20.6 \) Hz), 167.5 (d, \( J_{C-F} = 20.7 \) Hz), 135.9, 135.8, 130.83 (d, \( J_{C-F} = 18.5 \) Hz), 130.8 (d, \( J_{C-F} = 18.5 \) Hz), 129.0, 128.75, 128.7, 127.3, 127.1, 119.3 (d, \( J_{C-F} = 12 \) Hz), 119.1 (d, \( J_{C-F} = 12 \) Hz), 90.6 (d, \( J_{C-F} = 187.2 \) Hz), 90.5 (d, \( J_{C-F} = 187.4 \) Hz), 56.0, 55.9, 52.9, 52.8, 37.4. \textbf{IR} (neat) \( \nu \) 3322, 2955, 1741, 1675, 1514 cm\(^{-1}\). \textbf{HRMS} (ESI+): m/z: Calcd for C\(_{14}\)H\(_{17}\)NO\(_3\)F [M+H]: 252.1036, found: 252.1033.

(2S)-Methyl 2-(2-fluorobut-3-enamido)-4-methylpentanoate (4c).

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{MeO}_2\text{C} & \quad \text{F} \\
\text{Ph} & \quad 4c
\end{align*}
\]

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.73 (brs, 1H), 6.01-5.88 (m, 1H), 5.47 (d, \( J = 17.3 \) Hz, 1H ), 5.36 (m, 0.5H, CH-F), 5.33 (d, \( J = 10.3 \) Hz, 1H), 5.17 (m, 0.5H, CH-F), 4.58 (m, 1H), 3.68 and 3.67 (2s, 3H), 1.63-1.54 (m, 3H), 0.88 (brs, 6H). \(^{19}\)F NMR (282 MHz, CDCl\(_3\)): -187.11, -188.04. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 172.8, 172.7, 168.2 167.9, 131.1 (d, \( J_{C-F} = 18.5 \) Hz), 130.9 (d, \( J_{C-F} = 18.5 \) Hz), 119.4 (d, \( J_{C-F} = 11.9 \) Hz), 118.7 (d, \( J_{C-F} = 11.9 \) Hz), 90.7 (d, \( J_{C-F} = 187.0 \) Hz), 90.6 (d, \( J_{C-F} = 187.4 \) Hz), 52.4, 50.3, 50.2,

(S)-Methyl 2-(2-fluorobut-3-enamido)-3-methylbutanoate (4d).

\[
\text{MeO}_2\text{C} \quad \text{F} \\
\text{HN} \quad \text{O} \\
\text{Me} \quad \text{HN} \quad \text{O} \\
\text{MeO}_2\text{C} \quad \text{F}
\]

\(^1^H\) NMR (300 MHz, CDCl₃) δ 6.76 (brs, 1H), 6.01-5.82 (m, 1H), 5.42 (d, J = 17.3 Hz, 1H), 5.29 (m, 0.5H, CH-F), 5.27 (d, J = 10.5 Hz, 1H), 5.13 (m, 0.5H, CH-F), 4.45 (m, 1H), 3.63 (brs, 3H), 2.12 (m, 1H), 0.86-0.78 (m, 6H). \(^{19}F\) NMR (282 MHz, CDCl₃): -187.53, -188.23. \(^{13}C\) NMR (75 MHz, CDCl₃) δ 171.3, 171.5, 167.96 (d, Jₐₙ₋₉ = 20.2 Hz), 167.92 (d, Jₐₙ₋₉ = 20.3 Hz), 131.2 (d, Jₐₙ₋₉ = 18.6 Hz), 130.9 (d, Jₐₙ₋₉ = 18.6 Hz), 119.0 (d, Jₐₙ₋₉ = 12 Hz), 118.5 (d, Jₐₙ₋₉ = 12 Hz), 90.5 (d, Jₐₙ₋₉ = 187.1 Hz), 56.6, 56.4, 52.1, 52.0, 31.2, 31.1, 18.7, 17.6, 17.5. IR (neat) ν 3321, 2966, 1740, 1678, 1524 cm⁻¹. HRMS (ESI+): m/z: Calcd for C₁₀H₁₇NO₃F [M+H]^+: 218.11192, found: 218.11184.

(2S)-Dimethyl 2-(2-fluorobut-3-enamido)succinate (4e).

\[
\text{MeO}_2\text{C} \quad \text{F} \\
\text{HN} \quad \text{O} \\
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{HN} \quad \text{O} \\
\text{MeO}_2\text{C} \quad \text{F}
\]

\(^1^H\) NMR (300 MHz, CDCl₃) δ 6.27 (d, J = 6.7 Hz, 1H), 5.97-5.79 (m, 1H), 5.43 (d, J = 17.3 Hz, 0.5H), 5.40 (d, J = 17.3 Hz, 0.5H), 5.30-5.25 (m, 1H+0.5H for CH-F), 5.10 (m, 0.5H for CH-F), 4.76 (m, 1H), 3.64 (s, 3H), 3.57 (s, 3H), 2.94-2.68 (m, 2H). \(^{19}F\) NMR (282 MHz, CDCl₃): -187.66, -188.24. \(^{13}C\) NMR (75 MHz, CDCl₃) δ 171.0, 170.9, 170.4, 170.3, 168.02 (d, Jₐₙ₋₉ = 20.7 Hz), 167.99 (d, Jₐₙ₋₉ = 20.7 Hz), 130.9 (d, Jₐₙ₋₉ = 18.6 Hz), 130.8 (d, Jₐₙ₋₉ = 18.6 Hz), 119.3 (d, Jₐₙ₋₉ = 11.9 Hz), 119.0 (d, Jₐₙ₋₉ = 11.9 Hz), 90.4 (d, Jₐₙ₋₉ = 187.0 Hz), 90.3 (d, Jₐₙ₋₉ = 187.2 Hz), 52.7, 51.9, 48.0, 35.7. IR (neat) ν 3356, 2957, 1733, 1679, 1524 cm⁻¹. HRMS (ESI+): m/z: Calcd for C₁₀H₁₅NO₅F [M+H]^+: 248.0934, found: 248.0922.

(2S)-Methyl 3-(tert-butyldiphenylsilyloxy)-2-(2-fluorobut-3-enamido)propanoate (4f).

\[
\text{MeO}_2\text{C} \quad \text{F} \\
\text{HN} \quad \text{O} \\
\text{MeO}_2\text{C} \quad \text{OTBDPS} \\
\text{HN} \quad \text{O} \\
\text{MeO}_2\text{C} \quad \text{F}
\]

\(^1^H\) NMR (300 MHz, CDCl₃) δ 7.64-7.36 (m, 11H), 6.10-5.96 (m, 1H), 6.05-5.80 (m, 1H), 5.58 (d, J = 17 Hz, 1H), 5.42 (d, J = 10.8 Hz, 1H), 5.35 (dt, J = 5.2 and 1.58 Hz, 0.5H, CH-F), 5.35 (dt, J = 5.17 and 1.56 Hz, 0.5H, CH-F), 4.70 (dt, J = 8.2 and 3.02 Hz, 1H), 4.17 (dd, J = 10.3 and 2.8 Hz, 1H), 3.92 (dd, J = 10.2 and 3.1 Hz, 1H), 3.76 (s, 3H), 1.06 (s, 9H). \(^{19}F\) NMR (282 MHz, CDCl₃): -187.2 and -188.5. \(^{13}C\) NMR (75 MHz, CDCl₃) δ 170.2, 167.9 (d, Jₐₙ₋₉ = 20.4 Hz), 135.5, 135.0, 132.7, 130.9 (d, Jₐₙ₋₉ = 18.5 Hz), 130.0, 127.9, 119.5 (d, Jₐₙ₋₉ = 11.9 Hz), 90.7 (d, Jₐₙ₋₉ = 187.4 Hz), 64.0, 53.8, 52.6, 26.7, 19.3. IR
(neat) υ 3440, 2953, 2857, 1748, 1692, 1520 cm⁻¹. HRMS (ESI+): m/z: Calcd for C₂₄H₃₁NO₄FSi [M+H]⁺: 444.0600, found: 444.2000.

2-Fluorobut-3-enamide (4g).

![Structure of 2-Fluorobut-3-enamide (4g)](image)

¹H NMR (300 MHz, CDCl₃) δ 6.80 (brs, 1H), 6.39 (brs, 1H), 6.02 -5.97 (m, 1H), 5.52 (d, J = 17.3 Hz, 1H), 5.39 (d, J = 10.7 Hz, 1H), 5.31 (dt, J = 5.2 and 1.6 Hz, 0.5H, CH-F), 5.17 (dt, J = 5.2 and 1.6 Hz, 0.5H, CH-F). ¹⁹F NMR (282 MHz, CDCl₃): -184.86. ¹³C NMR (75 MHz, CDCl₃) δ 171.6 (d, J₉-F = 21.4 Hz), 130.9 (d, J₉-F = 18.5 Hz), 119.5 (d, J₉-F = 12 Hz), 90.6 (d, J = 187.4 Hz). IR (neat) υ 3398, 3182, 2953, 1728, 1662 cm⁻¹. HRMS (ESI+): m/z: Calcd for C₂₄H₃₁NO₄FSi [M+H]⁺: 444.2006, found: 444.2000.

Ethyl 2-(2-fluorobut-3-enamido)benzoate (4h).

![Structure of Ethyl 2-(2-fluorobut-3-enamido)benzoate (4h)](image)

¹H NMR (300 MHz, CDCl₃) δ 8.71 (dd, J = 8.4 and 0.8 Hz, 1H), 8.07 (dd, J = 8.0 and 1.6 Hz, 1H), 7.55 (td, J = 8.0 and 1.6 Hz, 1H), 7.14 (td, J = 7.6 and 1.1 Hz, 1H), 6.20-6.02 (m, 1H), 5.63 (d, J = 17.2 Hz, 1H), 5.50 (dt, J = 5.0 and 1.7 Hz, 1H), 5.44 (d, J = 10.8 Hz, 1H), 5.33 (dt, J = 5.0 and 1.7 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 1H). ¹⁹F NMR (282 MHz, CDCl₃): -186.6. ¹³C NMR (75 MHz, CDCl₃) δ 167.9, 167.1 (d, J₉-F = 19.2 Hz), 140.2, 134.5, 131.2 (d, J₉-F = 18.9 Hz), 131.0, 123.3, 120.4, 119.1 (d, J₉-F = 12Hz), 116.1, 90.9 (d, J₉-F = 187.0 Hz), 61.6, 14.2. IR (neat) υ 3255, 2993, 1682, 1590, 1518 cm⁻¹. HRMS (ESI+): m/z: Calcd for C₁₃H₁₅NO₃F [M+H]⁺: 252.1025, found: 252.1030.

Ethyl 4-(2-fluorobut-3-enamido)benzoate (4i).

![Structure of Ethyl 4-(2-fluorobut-3-enamido)benzoate (4i)](image)

¹H NMR (300 MHz, CDCl₃) δ 8.23 (brs, 1H, NH), 8.01 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz 1H), 6.15-5.99 (m, 1H), 6.03 (d, J = 17.2 Hz, 1H), 5.49 (dt, J = 5.0 and 1.7 Hz, 1H), 5.45 (d, J = 10.9 Hz, 1H), 5.32 (dt, J = 5.0 and 1.7 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 1H). ¹⁹F NMR (282 MHz, CDCl₃): -185.4. ¹³C NMR (75 MHz, CDCl₃) δ 166.4 (d, J₉-F = 19.2 Hz), 166.1, 140.7, 130.9, 130.6 (d, J₉-F = 18.6 Hz), 126.9, 119.8 (d, J₉-F = 12 Hz), 119.3, 90.9 (d, J₉-F = 189.3 Hz), 61.1, 14.4. IR (neat) υ 3316, 2976, 1716, 1676, 1602, 1537, 1281 cm⁻¹. HRMS (ESI+): m/z: Calcd for C₁₃H₁₅NO₃F [M+H]⁺: 252.1036, found: 252.1032.
2-fluoro-N-((S)-1-phenylethyl)but-3-enamide (4j).

\[ \text{HN} \quad \text{Ph} \quad \text{F} \]

\( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.29-7.26 (m, 5H), 6.57 (brs, 1H), 6.10-5.86 (m, 1H), 5.51-5.09 (m, 4H), 1.49 (d, \( J = 6.5 \) Hz, 1.5 H), 1.47 (d, \( J = 6.0 \) Hz, 1.5 H). \( ^{19}\text{F NMR} \) (282 MHz, CDCl\(_3\)): -187.13, -187.53.

\( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 167.4, 167.1, 142.55, 142.5, 131.3 (d, \( J_{CF} = 18.5 \) Hz), 131.2 (d, \( J_{CF} = 18.5 \) Hz), 128.8, 128.7, 127.6, 126.2, 126.1, 118.9 (d, \( J_{CF} = 12.1 \) Hz), 118.7 (d, \( J_{CF} = 11.9 \) Hz), 90.9 (d, \( J_{CF} = 187.3 \) Hz), 90.8 (d, \( J_{CF} = 187.4 \) Hz), 48.6, 48.5, 21.8, 21.7. \( \text{IR} \) (neat) v 3337, 2991, 1657, 1532 cm\(^{-1}\). \( \text{HRMS} \) (ESI+): m/z: Calcd for C\(_{12}\)H\(_{15}\)NO\(_F\) [M+H]+: 208.1138, found: 208.1128.

\( (4R)\)-3-(2-Fluorobut-3-enoyl)-4-isopropyloxazolidin-2-one (4k).

\[ \text{O} \quad \text{N} \quad \text{F} \]

\( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 6.48 (d, \( J = 5.0 \) Hz, 0.5H, CH-F), 6.32 (d, \( J = 4.9 \) Hz, 0.5H, CH-F), 6.16-5.95 (m, 3H), 5.70 (d, \( J = 16 \) Hz, 0.5H), 5.66 (d, \( J = 16.8 \) Hz, 0.5H), 5.45 (d, \( J = 10.6 \) Hz, 1H), 4.54-4.26 (m, 0.5H), 2.38-2.30 (m, 0.5H), 0.91 (d, \( J = 8.3 \) Hz, 3H), 0.85 (d, \( J = 6.8 \) Hz, 3H).

\( ^{19}\text{F NMR} \) (282 MHz, CDCl\(_3\)): -187.23, -190.32. \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 168.1, 153.6, 153.5, 130.1 (d, \( J = 19.4 \) Hz), 129.9 (d, \( J_{CF} = 19.1\)Hz), 121.5 (d, \( J_{CF} = 11.1 \) Hz), 120.9 (d, \( J_{CF} = 11.1 \) Hz), 87.9 (d, \( J_{CF} = 179.3 \) Hz), 87.7 (d, \( J_{CF} = 180.8 \) Hz), 64.7, 64.3, 28.4, 28.3, 18.0, 17.8, 14.9, 14.6. \( \text{IR} \) (neat) v 2966, 1775, 1716, 1374 cm\(^{-1}\). \( \text{HRMS} \) (ESI+): m/z: Calcd for C\(_{10}\)H\(_{15}\)NO\(_3\)F [M+H]+: 216.1036, found: 216.1029.

\( (4R)-4\text{-Benzyl-3-(2-fluorobut-3-enoyl)}\)oxazolidin-2-one (4l).

\[ \text{Ph} \quad \text{O} \quad \text{N} \quad \text{F} \]

\( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.45-7.26 (m, 5H), 6.48 (dtt, \( J = 6.4, 5.5, 1.1 \) Hz, 0.5H, CH-F), 6.33 (dtt, \( J = 6.5, 5.5, 1.1 \) Hz, 0.5H, CH-F), 6.13-5.99 (m, 1H), 5.77 (d, \( J = 14 \) Hz, 0.5H), 5.74 (d, \( J = 13.5 \) Hz, 0.5H), 5.75-5.72 (m, 0.5H), 5.70-5.67 (m, 0.5H), 5.48 (d, \( J = 10.7 \) Hz, 1H), 4.90-4.69 (m, 1H), 0.97 (d, \( J = 6.6 \) Hz, 1.5H), 0.88 (d, \( J = 6.6 \) Hz, 1.5H), \( ^{19}\text{F NMR} \) (282 MHz, CDCl\(_3\)): -188.55, -188.78. \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 167.7 (d, \( J_{CF} = 12.9 \) Hz), 167.4 (d, \( J_{CF} = 12.9 \) Hz), 152.5, 132.9, 132.7, 129.9 (d, \( J_{CF} = 19.7 \) Hz), 129.8 (d, \( J_{CF} = 19.4 \) Hz), 129.0, 128.8, 125.6, 121.2 (d, \( J_{CF} = 11.2 \) Hz), 120.9 (d, \( J_{CF} = 11.1 \) Hz), 88.0 (d, \( J_{CF} = 180.1 \) Hz), 87.5 (d, \( J_{CF} = 179.9 \) Hz), 79.9, 55.2, 54.5, 14.3. \( \text{IR} \) (neat) v 2986, 1771, 1714, 1343 cm\(^{-1}\). \( \text{HRMS} \) (ESI+): m/z: Calcd for C\(_{14}\)H\(_{15}\)NO\(_3\)F [M+H]+: 264.1036, found: 264.1024.
(S)-Methyl 1-(2-fluorobut-3-enoyl)pyrrolidine-2-carboxylate (4m).

\[
\begin{align*}
\text{H NMR} \ (300 \text{ MHz, CDCl}_3) & \ \delta \ 6.06 - 5.89 (m, 1H), \ 5.56 - 5.29 (m, 3H, CH-F+CH_2=), \ 4.64 - 4.43 (m, 1H), \\
& \ 3.68 (s, 3H), \ 2.13 - 1.90 (m, 4H).
\end{align*}
\]

\[
\begin{align*}
\text{19F NMR} \ (282 \text{ MHz, CDCl}_3): & \ -182.60, \ -183.37, \ -183.58, \ -183.90.
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR} \ (75 \text{ MHz, CDCl}_3) & \ \text{for major dia} \ \delta \ 172.2, \ 166.3 \ (d, \ J_{C-F} = 21.7 \text{ Hz}), \ 130.5 \ (d, \ J_{C-F} = 19.5 \text{ Hz}), \\
& \ 120.2 \ (d, \ J_{C-F} = 11.3 \text{ Hz}), \ 90.8 \ (d, \ J_{C-F} = 183.6 \text{ Hz}), \ 59.5, \ 52.2, \ 46.5, \ 28.3, \ 24.8. \IR \ (\text{neat}) \ \nu \ 2956, \ 1741, \ 1652, \ 1434 \text{ cm}^{-1}.
\end{align*}
\]

HRMS (ESI+): m/z: Calcd for C_{10}H_{15}NO_3F [M+H]^+: 216.1036, found: 216.1029.

(2S)-Methyl 2-((2S)-2-(2-fluorobut-3-enamido)-4-methylpentanamido)-3-phenylpropanoate (4o).

\[
\begin{align*}
\text{H NMR} \ (300 \text{ MHz, CDCl}_3) & \ \delta \ 7.29 - 7.26 (m, 3H), \ 7.10 - 7.08 (m, 2H), \ 6.74 (d, \ J = 9 \text{ Hz}, 1H, NH), \ 6.57 \ (d, \ J = 6 \text{ Hz}, 1H, NH), \ 6.10 - 5.95 \ (m, 1H), \ 5.54 \ (d, \ J = 17 \text{ Hz}, 1H), \ 5.39 \ (d, \ J = 10 \text{ Hz}, 1H), \ 5.25 - 5.12 \ (m, 1H, CH-F), \ 4.88 - 4.82 \ (m, 1H), \ 4.54 - 4.48 \ (m, 1H), \ 3.73 \text{ and 3.72 (2s, 3H), 3.20 - 3.04 (m, 2H), 1.68 - 1.56 (m, 3H), 0.95 - 0.90 (md, 6H).}
\end{align*}
\]

\[
\begin{align*}
\text{19F NMR} \ (282 \text{ MHz, CDCl}_3): & \ -187.24, \ -187.98.
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR} \ (75 \text{ MHz, CDCl}_3) & \ \delta \ 171.7, \ 171.6, \ 171.0, \ 170.9, \ 168.3, \ 168.0, \ 135.7, \ 135.6, \ 167.7, \ 131.0 \ (d, \ J_{C-F} = 18.4 \text{ Hz}), \ 130.9 \ (d, \ J_{C-F} = 18.6 \text{ Hz}), \ 129.3, \ 128.7, \ 128.6, \ 127.2, \ 119.9 \ (d, \ J_{C-F} = 12 \text{ Hz}), \ 119.0 \ (d, \ J_{C-F} = 11.9 \text{ Hz}), \ 90.7 \ (d, \ J_{C-F} = 187.4 \text{ Hz}), \ 90.6 \ (d, \ J_{C-F} = 187.8 \text{ Hz}), \ 53.3, \ 52.4, \ 51.3, \ 41.1, \ 37.9, \ 24.7, \ 22.8, \ 22.2. \IR \ (\text{neat}) \ \nu \ 3264, \ 2960, \ 1742, \ 1647, \ 1546 \text{ cm}^{-1}.
\end{align*}
\]


(S,E)-Methyl 2-(2-fluoroctadec-3-enamido)-3-phenylpropanoate (5a).

\[
\begin{align*}
\text{H NMR} \ (300 \text{ MHz, CDCl}_3) & \ \delta \ 7.34 - 7.29 (m, 3H), \ 7.17 - 7.13 (m, 2H), \ 6.82 \ (m, 1H), \ 6.05 - 5.90 \ (m, 1H), \ 5.66 - 5.46 \ (m, 1H), \ 5.29 \ (d, \ J = 6.7 \text{ Hz}, 0.5H), \ 5.12 \ (d, \ J = 6.7 \text{ Hz}, 0.5H), \ 4.95 \ (m, 1H), \ 3.78 \text{ and 3.76 (2s, 3H), 3.28 - 3.12 (m, 2H), 2.10 \ (m, 1H), 1.41 - 1.34 (m, 24H), 0.93 \ (t, J = 6.2 \text{ Hz}, 3H).}
\end{align*}
\]

\[
\begin{align*}
\text{19F NMR} \ (282 \text{ MHz, CDCl}_3): & \ -178.58, \ -179.36.
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR} \ (75 \text{ MHz, CDCl}_3) & \ \delta \ 171.4, \ 171.3, \ 167.5 \ (d, \ J_{C-F} = 20.4 \text{ Hz}), \ 167.4 \ (d, \ J_{C-F} = 20.5 \text{ Hz}), \ 139.3 \ (d, \ J_{C-F} = 11.2 \text{ Hz}), \ 138.6 \ (d, \ J_{C-F} = 11.2 \text{ Hz}), \ 135.6, \ 135.5, \ 129.3, \ 129.2, \ 128.7, \ 128.6, \ 127.3, \ 127.2, \ 122.7 \ (d, \ J_{C-F} = 18.3 \text{ Hz}), \ 122.6 \ (d, \ J_{C-F} = 18.3 \text{ Hz}), \ 91.1 \ (d, \ J_{C-F} = 183.6 \text{ Hz}), \ 91.0 \ (d, \ J_{C-F} = 184.2 \text{ Hz}), \ 52.8, \ 52.6, \ 52.5, \ 52.4, \ 37.9, \ 32.3, \ 31.9, \ 29.7, \ 29.6, \ 29.5, \ 29.4, \ 29.2, \ 29.1, \ 28.5, \ 22.7, \ 14.2. \IR \ (\text{neat}) \ \nu \ 3292, \ 2916, \ 2850, \ 1738, \ 1661, \ 1545 \text{ cm}^{-1}.
\end{align*}
\]

HRMS (ESI+): m/z: Calcd for C_{28}H_{43}NO_3F [M+H]^+: 462.3383, found: 462.3385.
(2S)-methyl 2-((E)-2-fluoro-octadec-3-enamido)-2-phenylacetate (5b).

![Chemical structure of 5b]

**1H NMR** (300 MHz, CDCl₃) δ 7.36-7.26 (m, 5H+1H NH), 5.99 (m, 1H), 5.67-5.56 (m, 1H), 5.59 (d, J = 7.4 Hz, 1H), 5.31 and 5.15 (dd, J = 17.0, 6.8, 1H), 3.74 (s, 3H), 2.10 (m, 1H), 1.41-1.34 (m, 24H), 0.88 (t, J = 6.2 Hz, 3H). **19F NMR** (282 MHz, CDCl₃): -178.08, -178.33, -179.07, -179.49. **13C NMR** (75 MHz, CDCl₃) δ 170.9, 170.8, 168.4 (d, J_C-F = 21.9 Hz), 168.3 (d, J_C-F = 22.1 Hz), 139.4 (d, J_C-F = 11.2 Hz), 139.1 (d, J_C-F = 11.3 Hz), 136.1, 129.1, 128.8, 127.4, 127.3, 122.6 (d, J_C-F = 18.3 Hz), 122.5 (d, J_C-F = 18.3 Hz), 91.2 (d, J_C-F = 183.5 Hz), 91.1 (d, J_C-F = 183.8 Hz), 56.1, 52.9, 32.4, 32.3, 30.0, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.6, 22.8, 14.2. **IR** (neat) υ 3308, 2915, 2850, 1738, 1659, 1538 cm⁻¹. **HRMS** (ESI⁺): m/z: Calcd for C₂₇H₄₂NO₃FNa [M+Na]⁺: 470.3046, found: 470.3043.

(2S)-methyl 2-((E)-2-fluoro-octadec-3-enamido)-3-methylbutanoate (5d).

![Chemical structure of 5d]

**1H NMR** (300 MHz, CDCl₃) δ 6.77 (m, 1H), 5.99 (m, 1H), 5.58 (m, 1H), 5.22 (m, 1H), 4.56 (m, 1H), 3.74 and 3.73 (s, 3H), 2.20 (m, 1H), 2.07 (m, 2H), 1.47-1.14 (m, 24H), 0.89 (m, 9H). **19F NMR** (282 MHz, CDCl₃): -177.49, -177.48, -178.28, -179.20. **13C NMR** (75 MHz, CDCl₃) δ 171.9, 171.8, 168.9 (d, J_C-F = 21.6 Hz), 168.8 (d, J_C-F = 21.5 Hz), 139.3 (d, J_C-F = 11.3 Hz), 138.7 (d, J_C-F = 11.4 Hz), 123.0 (d, J_C-F = 18.4 Hz), 122.7 (d, J_C-F = 18.3 Hz), 91.24 (d, J_C-F = 183.7 Hz), 91.18 (d, J_C-F = 184.2 Hz), 56.7, 52.2, 32.3, 32.0, 31.5, 31.3, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 28.6, 22.7, 18.9, 17.8, 17.7, 14.2. **IR** (neat) υ 3308, 2918, 2850, 1742, 1669, 1543 cm⁻¹. **HRMS** (ESI⁺): m/z: Calcd for C₂₄H₄₄NO₃FNa [M+Na]⁺: 436.3203, found: 436.3202.

(2S)-dimethyl 2-((E)-2-fluoro-octadec-3-enamido)succinate (5e).

![Chemical structure of 5e]

**1H NMR** (300 MHz, CDCl₃) δ 7.27 (m, 1H), 5.98 (m, 1H), 5.58 (m, 1H), 5.29 and 5.12 (t, J = 6.20 Hz, 1H), 4.87 (dt, J = 8.4 Hz, 4.3 Hz, 1H), 3.77 and 3.76 (s, 3H), 3.70 and 3.69 (s, 3H), 3.06 (dt, J = 17.2 Hz, 4.7 Hz, 1H), 2.85 (dt, J = 17.2 Hz, 4.7 Hz, 1H), 2.08 (m, 2H), 1.45-1.17 (m, 24H), 0.86 (t, J = 7.0 Hz, 3H). **19F NMR** (282 MHz, CDCl₃): -178.52, -178.63, -179.13, -179.79. **13C NMR** (75 MHz, CDCl₃) δ 171.3, 171.2, 170.6, 170.3, 168.9 (d, J_C-F = 22 Hz), 168.8 (d, J_C-F = 22 Hz), 139.6 (d, J_C-F = 11.2 Hz), 139.2 (d, J_C-F = 11.2 Hz), 122.6 (d, J_C-F = 18.3 Hz), 122.5 (d, J_C-F = 18.3 Hz), 91.0 (d, J_C-F = 183.9 Hz), 52.9, 52.2, 48.1, 36.0, 32.3, 32.0, 29.7, 29.6, 29.5, 29.4, 29.2, 28.6, 22.7, 18.9, 14.2. **IR** (neat) υ 3247, 2915, 2849, 1743, 1662, 1543 cm⁻¹. **HRMS** (ESI⁺): m/z: Calcd for C₂₄H₄₂NO₃FNa [M+Na]⁺: 466.2942, found: 466.2945.

(2S)-methyl 3-(tert-butyldiphenylsilyloxy)-2-((E)-2-fluoro-octadec-3-enamido)propanoate (5f).
$^1$H NMR (300 MHz, CDCl$_3$) δ 7.62 (m, 4H), 7.42 (m, 6H), 6.05 (m, 1H), 5.65 (m, 1H), 5.27 and 5.19 (t, $J$ = 7.0 Hz, 48.7 Hz, 1H), 4.71 (m, 1H), 4.16 (m, 1H), 3.91 (m, 1H), 3.78 (s, 3H), 2.12 (m, 2H), 1.50 – 1.21 (m, 24H), 1.06 (s, 9H), 0.90 (t, $J$ = 6.23 Hz, 3H). $^{19}$F NMR (282 MHz, CDCl$_3$): -177.58, -177.79, -178.03, -179.19. $^{13}$C NMR (75 MHz, CDCl$_3$) for major dia δ 170.3, 168.7 (d, $J_{CF}$ = 21.8 Hz), 139.6 (d, $J_{CF}$ = 11.2 Hz), 135.6, 134.9, 132.8, 132.7, 130.0, 127.9, 122.7 (d, $J_{CF}$ = 18.3 Hz), 122.6 (d, $J_{CF}$ = 18.3 Hz), 91.2 (d, $J_{CF}$ = 183.7 Hz), 64.2, 52.8, 52.6, 32.4, 32.0, 29.8, 29.7, 29.5, 29.3, 29.2, 28.6, 26.8, 26.7, 22.8, 19.3, 14.2. IR (neat) υ 3442, 2924, 2854, 1751, 1692, 1518 cm$^{-1}$. HRMS (ESI+): m/z: Calcd for C$_{38}$H$_{58}$NO$_4$FSiNa [M+Na]$^+$: 662.4017, found: 662.4024.

$(E)$-2-fluorooctadec-3-enamide (5g).

$^1$H NMR (300 MHz, CDCl$_3$) δ 6.36 (brs, 1H), 6.03-5.98 (m+brs, 2H), 5.62 (m, 1H), 5.27 and 5.19 (dd, $J$ = 6.8 Hz, 49.1 Hz, 1H), 2.10 (m, 2H), 1.47-1.61 (m, 24H), 0.88 (t, $J$ = 6.4 Hz, 3H). $^{19}$F NMR (282 MHz, CDCl$_3$): -174.74, -176.46. $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.8 (d, $J_{CF}$ = 22.5Hz), 139.4 (d, $J_{CF}$ = 11.2 Hz), 122.6 (d, $J_{CF}$ = 18.2 Hz), 91.1 (d, $J_{CF}$ = 183.8 Hz), 32.3, 32.0, 29.8, 29.7, 29.6, 29.5, 29.3, 28.6, 22.8, 14.2. IR (neat) υ 3381, 3187, 2914, 2847, 1652, 1421 cm$^{-1}$. HRMS (ESI+): m/z: Calcd for C$_{18}$H$_{34}$NOFNa [M+Na]$^+$: 322.2522, found: 322.2519.

$(S)$-methyl-2-((S)-2-((E)-2-fluorooctadec-3-enamido)-4-methylpentanamido)-3-phenylpropanoate (5o).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.27 (m, 3H), 7.09 (m, 2H), 6.64 (m, 1H), 6.45 (d, $J$ = 7.93 Hz, 1H) 6.00 (m, 1H), 5.56 (m, 1H), 5.17 (dd, $J$ = 7.18 Hz, 49.29 Hz, 1H), 4.84 (m, 1H), 4.45 (m, 1H), 3.73 (s, 3H), 3.11 (m, 2H), 2.08 (m, 2H) 1.47 – 1.21 (m, 24H), 1.4 (t, $J$ = 7.2 Hz, 3 H), 0.89 (t, $J$ = 6.80 Hz, 3H). $^{19}$F NMR (282 MHz, CDCl$_3$): -177.50, -177.67, -178.63, -179.45. $^{13}$C NMR (75 MHz, CDCl$_3$) for major dia δ 171.6, 171.1, 168.8 (d, $J_{CF}$ = 22.0 Hz), 139.2 (d, $J_{CF}$ = 11.2 Hz), 135.7, 129.3, 128.5, 127.0, 122.7 (d, $J_{CF}$ = 18.4 Hz), 91.0 (d, $J_{CF}$ = 183.4 Hz), 53.3, 52.2, 51.3, 51.0, 41.2, 40.9, 37.8, 32.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.5, 24.7, 22.8, 22.7, 22.1, 14.1. IR (neat) υ 3278, 2915, 2850, 1752, 1649, 1551 cm$^{-1}$. HRMS (ESI+): m/z: Calcd for C$_{34}$H$_{55}$N$_2$O$_4$FNa [M+Na]$^+$: 597.4044, found: 597.4049.

NMR Spectra Images of Products 2, 4a-o and 5a: