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Supporting Information
for

Synthesis of new γ-lactams with gem-difluorinated side chains

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I. General information

NMR spectra were performed on a Bruker AVANCE 300 or Bruker AVANCE 500 (\(^1\)H, 300 MHz or 500 MHz; \(^{13}\)C, 75 MHz or 126 MHz; \(^{19}\)F, 282 MHz or 471 MHz). Solvent peaks were used as reference values with CDCl\(_3\) at 7.26 ppm for \(^1\)H NMR and 77.16 ppm for \(^{13}\)C NMR, with CD\(_3\)CN at 1.94 ppm for \(^1\)H NMR and 1.32 and 118.26 ppm for \(^{13}\)C NMR, with (CD\(_3\))\(_2\)CO at 2.05 ppm for \(^1\)H NMR and 29.84 and 206.26 ppm for \(^{13}\)C NMR, and with C\(_6\)D\(_6\) at 7.16 ppm for \(^1\)H NMR and 128.06 ppm for \(^{13}\)C NMR. Chemical shifts \(\delta\) are given in ppm, and the following abbreviations are used: singlet (s), broad singlet (bs), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), triplet of doublet (td), quadruplet (q), doublet of quadruplet (dq), and multiplet (m). IR spectra were run on a PerkinElmer Spectrum 16 PC spectrometer. High resolution mass spectra were recorded in the Centre Régional de Mesures Physiques de l’Ouest, Rennes (CRMPO), on a Maxis 4G. Melting points were determined with uncertainty of ± 2 °C using a KOFLER BENCH. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F254 Merck plates), and compounds were visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with \(p\)-anisaldehyde/\(\Delta\). Column chromatography was performed using silica gel 60 (40–63 mm, 230–400 mesh). Solvents were used as received from commercial sources. Reagent were purchased from Sigma-Aldrich, Alfa Aesar and Acros. All products reported showed \(^1\)H, \(^{13}\)C, and \(^{19}\)F NMR spectra in agreement with the assigned structures.
II. Experimental procedures and spectral/analytical data

II.A. Synthesis of propargylic alcohols:

II.A.1. Representative procedure: Synthesis of methyl 4-hydroxy-4-phenylbut-2-ynoate (2a):

To a solution of methyl propiolate (3.0 mL, 33.9 mmol, 1.2 equiv) in anhydrous THF (50 mL) cooled at -90°C, was added, dropwise under nitrogen, a 2.5M solution of n-butyllithium (13.5 mL, 1.2 equiv). The reaction mixture was stirred for 30 min at temperature below -80 °C before dropwise addition of benzaldehyde (28.2 mmol) in anhydrous THF (10 mL). After 20 min of stirring at the same temperature, TMSCl (9.0 mL, 2.5 equiv) was added dropwise. The reaction mixture was stirred for additional 1 h at temperature below -80 °C. Then the reaction mixture was allowed to warm to r.t. within 2h. The mixture was then treated with a saturated ammonium chloride solution and extracted with ethyl acetate (3x50mL). The combined organic phases were washed with water, dried over Na$_2$SO$_4$ and concentrated $\text{in vacuo}$. After purification by chromatography on silica gel, the propargylic alcohol $2a$ was obtained as a light yellow oil. 4.84 g (90%).

$R_f = 0.5$ (Cyclohexane / Ethyl Acetate: 7/3). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.53 – 7.47 (m, 2H), 7.43 – 7.31 (m, 3H), 5.55 (s, 1H), 3.78 (s, 3H), 3.00 (bs, 1H, OH). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 153.9, 138.6, 129.0, 129.0, 126.8, 86.8, 77.6, 64.3, 53.1. FT-IR (cm$^{-1}$): 3407, 3064, 3033, 3009, 2954, 2236, 1712, 1493, 1452, 1434, 1245, 1187, 1068, 1001, 942, 918, 841, 749, 696, 665. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{11}$H$_{10}$O$_3$Na) = 213.0522; found: 213.0522 (0 ppm).

II.A.2. Methyl 4-hydroxy-6-phenylhex-2-ynoate (2b):

Starting from 3 g (2.23 mmol) of 3-phenylpropionaldehyde we obtained 3.36 g of $2b$ (69%) as a light yellow oil. Physical data and NMR data are in agreement with literature.$^1$ $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.27 – 6.93 (m, 5H), 4.30 (t, $^3$J$_{H-H}$ = 6.7 Hz, 1H), 3.60 (s, 3H), 3.16 (s, 1H, OH), 2.64 (t, $^3$J$_{H-H}$ = 7.8 Hz, 2H), 1.98 – 1.84 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.1, 140.7, 128.5, 128.5, 126.2, 88.4, 76.3, 61.1, 52.9, 38.2, 31.1.

II.A.3. Methyl 4-(4-chlorophenyl)-4-hydroxybut-2-ynoate (2c):

Starting from 3 g (2.13 mmol) of 4-chlorobenzaldehyde we obtained 3.35 g of 2c (70%) as a light yellow oil; Rf = 0.6 (Cyclohexane / Ethyl Acetate: 7/3). \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.44 – 7.38 (m, 2H), 7.35 – 7.32 (m, 2H), 5.51 (s, 1H), 3.77 (s, 3H), 3.51 – 3.20 (bs, 1H, OH). \(^13\)C NMR (125 MHz, CDCl\(_3\)) δ 154.0, 137.0, 134.8, 129.0, 128.1, 86.4, 77.7, 63.5, 53.2. FT-IR (cm\(^{-1}\)): 3417, 2955, 2238, 1713, 1489, 1434, 1405, 1375, 1245, 1187, 1089, 1074, 1012, 941, 847, 789, 750. HRMS (ESI): calcd. for [M+Na]\(^+\) (C\(_{11}\)H\(_9\)O\(_3\)ClNa) = 247.0132; found: 247.0131 (1 ppm).

II.A.4. Methyl 4-(2-bromophenyl)-4-hydroxybut-2-ynoate (2d):

Starting from 3 g (16.2 mmol) of 2-bromobenzaldehyde we obtained 2.79 g of 2d (64%) as a light yellow oil; Rf = 0.4 (Cyclohexane / Ethyl Acetate: 8/2). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.70 (dd, \(^3\)J\(_{\text{H-H}}\) = 7.8 Hz, \(^4\)J\(_{\text{H-H}}\) = 1.7 Hz, 1H), 7.57 (dd, \(^3\)J\(_{\text{H-H}}\) = 8.0 Hz, \(^4\)J\(_{\text{H-H}}\) = 1.3 Hz, 1H), 7.37 (dd, \(^3\)J\(_{\text{H-H}}\) = 7.6 Hz, \(^4\)J\(_{\text{H-H}}\) = 1.3 Hz, 1H), 7.22 (td, \(^3\)J\(_{\text{H-H}}\) = 7.7, \(^4\)J\(_{\text{H-H}}\) = 1.7 Hz, 1H), 5.89 (d, \(^3\)J\(_{\text{H-H}}\) = 4.9 Hz, 1H), 3.78 (s, 3H), 3.07 (d, \(^3\)J\(_{\text{H-H}}\) = 4.9 Hz, 1H, OH). \(^13\)C NMR (75 MHz, CDCl\(_3\)) δ 153.8, 137.6, 133.2, 130.6, 128.7, 128.2, 122.6, 85.7, 77.5, 63.9, 53.1. FT-IR (cm\(^{-1}\)): 3450, 3064, 2987, 2954, 2901, 2237, 1712, 1696, 1590, 1570, 1469, 1434, 1245, 1187, 1122, 1074, 1048, 1017, 941, 810, 748, 722. HRMS (ESI): calcd. for [M+Na]\(^+\) (C\(_{11}\)H\(_9\)O\(_3\)BrNa) = 290.9627; found: 290.9628 (0 ppm).

II.A.5. Methyl 4-(4-fluorophenyl)-4-hydroxybut-2-ynoate (2e):

Starting from 3 g (24.2 mmol) of 4-fluorobenzaldehyde we obtained 4.07 g of 2e (81%) as a colorless oil; Rf = 0.2 (Cyclohexane / Ethyl Acetate: 8/2). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.53 – 7.44 (m, 2H), 7.12 – 7.03 (m, 2H), 5.55 (d, \(^3\)J\(_{\text{H-H}}\) = 5.9 Hz, 1H), 3.79 (s, 3H), 2.85 (d, \(^3\)J\(_{\text{H-H}}\) = 5.9 Hz, 1H, OH). \(^13\)C NMR (75 MHz, CDCl\(_3\)) δ 163.1 (d, \(^1\)J\(_{\text{C-F}}\) = 247.9 Hz), 153.8, 134.5 (d, \(^4\)J\(_{\text{C-F}}\) = 3.4 Hz), 128.7 (d, \(^3\)J\(_{\text{C-F}}\) = 8.4 Hz), 115.9 (d, \(^2\)J\(_{\text{C-F}}\) = 21.8 Hz), 86.3 (d, \(^6\)J\(_{\text{C-F}}\) = 0.8 Hz), 77.8, 63.7 (d, \(^5\)J\(_{\text{C-F}}\) = 0.8 Hz), 53.1. \(^19\)F \{H\} NMR (282 MHz, CDCl\(_3\)) δ -112.59 (s). \(^19\)F NMR (282 MHz, CDCl\(_3\)) δ -112.54 – -112.65 (m). FT-IR (cm\(^{-1}\)): 3413, 2987, 2957, 2900, 2238, 1712, 1604, 1507, 1435, 1248, 1222, 1187, 1157, 1099, 1073, 1011, 943, 841, 817, 771, 750. HRMS (ESI): calcd. for [M+Na]\(^+\) (C\(_{11}\)H\(_9\)O\(_3\)FNa) = 231.0428; found: 231.0431 (1 ppm).
II.A.6. Methyl 4-hydroxy-4-(4-methoxyphenyl)but-2-ynoate (2f):

Starting from 3 g (22.03 mmol) of anisaldehyde we obtained 3.73 g of 2f (77%) as a light yellow oil; Rf = 0.4 (Cyclohexane / Ethyl Acetate: 7/3). 1H NMR (300 MHz, CDCl3) δ 7.47 – 7.38 (m, 2H), 6.93 – 6.86 (m, 2H), 5.50 (d, 3JHH = 6.1 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.73 (d, 3JHH = 6.1 Hz, 1H, OH). 13C NMR (75 MHz, CDCl3) δ 160.2, 153.9, 130.9, 128.3, 114.3, 112.8, 77.6, 64.0, 55.5, 53.0. FT-IR (cm⁻¹): 3433, 2956, 2902, 2840, 2235, 1711, 1645, 1609, 1592, 1510, 1434, 1241, 1171, 1112, 1071, 1026, 962, 943, 836, 809, 749. HRMS (ESI): calcd. for [M+Na]+ (C12H12O4Na) = 243.0628; found: 243.0631 (1 ppm).

II.A.7. Methyl 4-hydroxy-4-(4-(trifluoromethyl)phenyl)but-2-ynoate (2g):

Starting from 3 g (17.2 mmol) of 4-(trifluoromethyl)benzaldehyde we obtained 3.11 g of 2g (70%) as a yellow oil; Rf = 0.2 (Cyclohexane / Ethyl Acetate: 7/3). 1H NMR (300 MHz, CDCl3) δ 7.67 – 7.60 (m, 4H), 5.63 (d, 3JHH = 4.5 Hz, 1H), 3.79 (s, 1H), 3.27 (d, 3JHH = 4.5 Hz, 1H, OH). 13C NMR (75 MHz, CDCl3) δ 153.8, 142.3 (q, 5JCF = 1.2 Hz), 131.2 (q, 2JCF = 33.1 Hz), 127.0, 125.9 (q, 3JCF = 3.8 Hz), 124.0 (q, 1JCF = 272.2 Hz), 85.8, 78.0, 63.6, 53.2. 19F {H} NMR (282 MHz, CDCl3) δ -62.75 (s). FT - IR (cm⁻¹): 3472, 2960, 2901, 2240, 1720, 1661, 1619, 1582, 1510, 1436, 1412, 1323, 1256, 1167, 1125, 1111, 1064, 1015, 961, 857, 763, 748, 729. HRMS (ESI): calcd. for [M+Na]+ (C12H9O3F3Na) = 281.0396; found: 281.0395 (0 ppm).

II.A.8. Methyl 4-hydroxydodec-2-ynoate (2h):

Starting from 3 g (21.1 mmol) of nonanal we obtained 2.86 g of 2h (60%) as a yellow oil, Rf = 0.5 (Cyclohexane / Ethyl Acetate: 8/2). 1H NMR (300 MHz, CDCl3) δ 4.47 (t, 3JHH = 6.7 Hz, 1H), 3.77 (s, 3H), 1.79 – 1.70 (m, 2H), 1.54 – 1.17 (m, 13H), 0.86 (t, 3JHH = 7.1 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ 154.0, 88.6, 76.3, 62.2, 53.0, 36.9, 31.9, 29.5, 29.3, 29.3, 25.0, 22.8, 14.2. FT-IR (cm⁻¹): 3427, 2953, 2924, 2855, 2236, 1717, 1456, 1434, 1406, 1378, 1334, 1244, 1057, 751. HRMS (ESI): calcd. for [M+Na]+ (C13H22O3Na) = 249.1461; found: 249.1464 (1 ppm).
II.B. Oxidation to propargylic ketones:

II.B.1. Representative procedure: Synthesis of methyl 4-oxo-4-phenylbut-2-ynoate (3a):

To the propargylic alcohol 2a (2 g, 10.5 mmol) in acetone (20 mL) was added dropwise under magnetic stirring at room temperature, a concentrated (5.4 M) solution of Jones reagent until disappearance of the starting material (TLC analysis). After addition of isopropanol (5.0 equiv), the reaction mixture was filtered and the filtrate was extracted with ethyl acetate (3x40mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. After purification by chromatography on silica gel, the propargylic ketone 3a was obtained as a light yellow solid (1.58 g, 80%).

Rᵣ = 0.4 (Cyclohexane / Ethyl Acetate: 8/2). mp= 70 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.14 – 8.08 (m, 2H), 7.70 – 7.63 (m, 1H), 7.55 – 7.47 (m, 2H), 3.89 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 176.2, 152.8, 135.6, 135.3, 129.9, 129.0, 80.2, 80.2, 53.6. FT-IR (cm⁻¹): 2957, 2926, 1707, 1642, 1594, 1581, 1453, 1432, 1318, 1252, 1177, 1063, 1023, 998, 957, 865, 796, 749, 697, 645. HRMS (ESI): calcd. for [M+Na]⁺ (C₁₁H₈O₃Na) = 211.0366; found: 211.0367 (1 ppm).

II.B.2. Methyl 4-oxo-6-phenylhex-2-ynoate (3b):

Starting from 2 g (9.16 mmol) of methyl 4-hydroxy-6-phenylhex-2-ynoate 2b we obtained 1.47 g of 3b (74%) as a light yellow solid. Physical data and NMR data are in agreement with literature.¹ ¹H NMR (300 MHz, CDCl₃) δ 7.24 – 7.03 (m, 5H), 3.72 (s, 3H), 3.01 – 2.70 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 184.8, 152.6, 139.5, 128.6, 128.3, 126.5, 80.7, 78.1, 53.4, 46.7, 29.2.

II.B.3. Methyl 4-(4-chlorophenyl)-4-oxobut-2-ynoate (3c):

Starting from 2 g (8.90 mmol) of methyl 4-(4-chlorophenyl)-4-hydroxybut-2-ynoate 2c we obtained 1.56 g of 3c (79%) as a yellow solid; Rᵣ= 0.6 (Cyclohexane / Ethyl Acetate: 8/2). mp = 54 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, ³J_H-H = 8.0 Hz, 2H), 7.49 (d, ³J_H-H = 8.0 Hz, 2H), 3.89 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 174.9, 152.7, 142.1, 134.1, 131.1, 129.5, 80.5, 79.7, 53.7. FT-IR (cm⁻¹): 2959, 2923, 1715, 1650, 1584, 1437, 1402, 1259, 1171, 1091, 1065, 1010, 956, 867, 849, 743, 676. HRMS (ESI): calcd. for [M+Na]⁺ (C₁₁H₇O₃ClNa) = 244.9976; found: 244.9979 (1 ppm).
II.B.4. Methyl 4-(2-bromophenyl)-4-oxobut-2-ynoate (3d):

Starting from 2 g (7.43 mmol) of methyl 4-(2-bromophenyl)-4-hydroxybut-2-ynoate 2d we obtained 1.67 g of 3d (84%) as a waxy yellow solid; RF = 0.7 (Cyclohexane / Ethyl Acetate: 8/2). 1H NMR (500 MHz, CDCl3) δ 8.04 (dd, J_H-H = 7.7 Hz, J_H-H = 1.8 Hz, 1H), 7.71 (dd, J_H-H = 7.7 Hz, J_H-H = 1.5 Hz, 1H), 7.47 (td, J_H-H = 7.5 Hz, J_H-H = 1.5 Hz, 1H), 7.43 (td, J_H-H = 7.6 Hz, J_H-H = 1.8 Hz, 1H), 3.88 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 175.2, 152.7, 135.5, 135.3, 134.6, 133.9, 127.7, 121.9, 80.9, 80.5, 53.6. FT-IR (cm⁻¹): 3074, 3058, 3016, 2958, 2924.6, 848.2, 1717, 1655, 1580, 1561, 1487, 1463, 1435, 1291, 1245, 1227, 1135, 1071, 1026, 954, 866, 788, 734. HRMS (ESI): calcd. for [M+Na]⁺ (C11H7O3BrNa) = 288.9471; found = 288.9472 (0 ppm).

II.B.5. Methyl 4-(4-fluorophenyl)-4-oxobut-2-ynoate (3e):

Starting from 2 g (9.61 mmol) of methyl 4-(4-fluorophenyl)-4-hydroxybut-2-ynoate 2e we obtained 1.88 g of 3e (95%) as a yellow solid; RF = 0.6 (Cyclohexane / Ethyl Acetate: 8/2). mp = 68 °C. 1H NMR (300 MHz, CDCl3) δ 8.18 – 8.10 (m, 2H), 7.24 – 7.15 (m, 2H), 3.89 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 174.5, 167.2 (d, J_C-F = 258.7 Hz), 152.7, 132.7 (d, J_C-F = 9.9 Hz), 132.2 (d, J_C-F = 2.8 Hz), 116.5 (d, J_C-F = 22.4 Hz), 80.4, 79.8, 53.6. 19F {H} NMR (282 MHz, CDCl3) δ -100.80 (s). FT-IR (cm⁻¹): 3068, 2958, 2930, 2872, 1717, 1649, 1591, 1504, 1433, 1411, 1297, 1242, 1150, 1107, 1061, 1008, 947, 857, 829, 817, 745. HRMS (ESI): calcd. for [M+Na]⁺ (C11H7O3FNa) = 229.0274; found: 229.0274 (0 ppm).

II.B.6. Methyl 4-(4-methoxyphenyl)-4-oxobut-2-ynoate (3f):

Starting from 2 g (9.08 mmol) of methyl 4-hydroxy-4-(4-methoxyphenyl)but-2-ynoate 2f we obtained 1.84 g of 3f (93%) as a colorless solid; RF = 0.3 (Cyclohexane / Ethyl Acetate: 8/2). mp = 71 °C. 1H NMR (300 MHz, CDCl3) δ 8.11 – 8.01 (m, 2H), 7.00 – 6.93 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 174.5, 165.4, 153.0, 132.4, 129.1, 114.3, 80.5, 79.6, 55.8, 53.5. FT-IR (cm⁻¹): 3012, 2982, 2955, 2924, 2847, 1713, 1635, 1585, 1506, 1439, 1334, 1320, 1257, 1157, 1117, 1062, 1015, 956, 870, 842, 744. HRMS (ESI): calcd. for [M+Na]⁺ (C12H10O4Na) = 241.0471; found: 241.0474 (1 ppm).
II.B.7. Methyl 4-oxo-4-(4-(trifluoromethyl)phenyl)but-2-ynoate (3g):

Starting from 2 g (7.75 mmol) of methyl 4-hydroxy-4-(4-(trifluoromethyl)phenyl)but-2-ynoate 2g we obtained 1.57 g of 3g (77%) as a waxy yellow solid; Rf = 0.7 (Cyclohexane / Ethyl Acetate: 8/2). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.25 – 8.19 (m, 2H), 7.81 – 7.75 (m, 2H), 3.90 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.1, 152.5, 138.1 (q, $^3$J$_{C-F}$ = 1.2 Hz), 136.3 (q, $^2$J$_{C-F}$ = 32.9 Hz), 130.2, 126.1 (q, $^3$J$_{C-F}$ = 3.8 Hz), 123.4 (q, $^1$J$_{C-F}$ = 273.0 Hz), 81.1, 79.4, 53.7. $^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ -63.35 (s). FT-IR (cm$^{-1}$): 3016, 2964, 2924, 2850, 1719, 1663, 1615, 1582, 1545, 1435, 1411, 1323, 1285, 1189, 1154, 1111, 1062, 1012, 963, 856, 783, 762, 748, 727, 688. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{12}$H$_7$O$_3$F$_3$Na) = 279.0239; found: 279.0236 (1 ppm).

II.B.8. Methyl 4-oxododec-2-ynoate (3h):

Starting from 2 g (8.83 mmol) of methyl 4-hydroxydodec-2-ynoate 2h we obtained 1.62 g of 3h (82%) as a yellow liquid; Rf = 0.6 (Cyclohexane / Ethyl Acetate: 8/2). $^1$H NMR (300 MHz, CDCl$_3$) δ 3.84 (s, 3H), 2.62 (t, $^3$J$_{H-H}$ = 7.4 Hz, 2H), 1.73 – 1.61 (m, 2H), 1.36 – 1.16 (m, 10H), 0.86 (t, $^3$J$_{H-H}$ = 7.0 Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 186.2, 152.8, 81.1, 77.8, 53.5, 45.4, 31.9, 29.3, 29.1, 28.9, 23.6, 22.7, 14.2. FT-IR (cm$^{-1}$): 2955, 2925, 2856, 1723, 1687, 1456, 1434, 1403, 1377, 1244, 1134, 1098, 990, 891, 747, 723. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{13}$H$_{20}$O$_3$Na) = 247.1305; found: 247.1307 (1 ppm).

II.C. Synthesis of propargylic fluorides:

II.C.1. Representative procedure: Synthesis of methyl 4,4-difluoro-4-phenylbut-2-ynoate (4a):

To the propargylic ketone 3a (1 g, 5.31 mmol) one drop of 95% ethanol and DAST (4.2 mL, 31.8 mmol, 6 equiv) were added. The reaction mixture was stirred at 60 °C for 6 h. After coming back to room temperature and hydrolysis, the reaction mixture was extracted with CH$_2$Cl$_2$ (3x40mL). The organic layers were separated, washed with water (3x20mL), dried over Na$_2$SO$_4$ then filtrated on silica. After purification by chromatography on silica gel, the fluorinated compound 4a was obtained as a yellow oil (0.73 g, 65%).
$R_f = 0.6$ (Cyclohexane / Ethyl Acetate: 8/2). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.71 – 7.59 (m, 2H), 7.56 – 7.41 (m, 3H), 3.84 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.5, 134.5 (t, $^3J_{C-F} = 4.9$ Hz), 111.5 (t, $^1J_{C-F} = 235.1$ Hz), 78.0 (t, $^3J_{C-F} = 5.9$ Hz), 77.4 (t, $^2J_{C-F} = 44.3$ Hz), 53.5. $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -79.61 (s). FT-IR (cm$^{-1}$): 2960, 2852, 1723, 1454, 1436, 1269, 1243, 1193, 1155, 1038, 1017, 970, 766, 748, 693, 652, 610. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{11}$H$_8$O$_2$F$_2$Na) = 233.0385; found: 233.0383 (1 ppm).

II.C.2. Methyl 4,4-difluoro-6-phenylhex-2-ynoate ($4b$):

Starting from 1 g (4.62 mmol) of methyl methyl 4-oxo-6-phenylhex-2-ynoate ($3b$) we obtained 1.00 g of $4b$ (91%) as a yellow oil. Physical data and NMR data are in agreement with literature. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35 – 7.01 (m, 5H), 3.78 (s, 3H), 2.85 – 2.76 (m, 2H), 2.43 – 2.23 (m, 2H). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -86.55 (s).

II.C.3. Methyl 4-(4-chlorophenyl)-4,4-difluorobut-2-ynoate ($4c$):

Starting from 1 g (4.49 mmol) of methyl 4-(4-chlorophenyl)-4-oxobut-2-ynoate ($3c$) we obtained 681 mg of $4c$ (62%) as a yellow oil; $R_f = 0.4$ (Cyclohexane / Ethyl Acetate: 9/1). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.59 (d, $^3J_{H-H} = 8.7$ Hz, 2H), 7.45 (d, $^3J_{H-H} = 8.7$ Hz, 2H), 3.84 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.3, 137.8, 133.0 (t, $^3J_{C-F} = 27.5$ Hz), 129.3, 126.9 (t, $^3J_{C-F} = 4.8$ Hz), 111.1 (t, $^1J_{C-F} = 235.5$ Hz), 78.5 (t, $^3J_{C-F} = 5.8$ Hz), 77.0 (t, $^2J_{C-F} = 44.1$ Hz), 53.6. $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -79.52 (s). FT-IR (cm$^{-1}$): 2958, 2926, 2855, 1725, 1603, 1581, 1492, 1435, 1404, 1269, 1243, 1193, 1158, 1092, 1059, 1031, 1011, 970, 870, 829, 748, 720, 693. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{11}$H$_7$O$_3$F$_2$Na$^{35}$Cl) = 244.99759; found: 244.9979 (1 ppm).

II.C.4. Methyl 4-(2-bromophenyl)-4,4-difluorobut-2-ynoate ($4d$):

Starting from 1 g (3.74 mmol) of methyl 4-(2-bromophenyl)-4-oxobut-2-ynoate ($3d$) we obtained 823 mg of $4d$ (76%) as a yellow oil; $R_f = 0.4$ (Cyclohexane / Ethyl Acetate: 9/1). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.13 – 7.98 (m, 1H), 7.88 – 7.61 (m, 1H), 7.59 – 7.32 (m, 2H), 3.83 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 152.5 (t, $^4J_{C-F} = 2.4$ Hz), 135.0, 133.4 (t, $^2J_{C-F} = 26.5$ Hz), 132.6 (t, $^4J_{C-F} = 1.4$ Hz), 127.6, 127.3 (t, $^3J_{C-F} = 7.9$ Hz), 120.8 (t, $^3J_{C-F} = 3.2$ Hz), 110.3 (t, $^1J_{C-F} = 237.4$ Hz), 77.9 (t,
$^{3}J_{C-F} = 6.1$ Hz), 76.7 (t, $^{2}J_{C-F} = 42.9$ Hz), 53.4. $^{19}$F (H) NMR (471 MHz, CDCl$_3$) $\delta$ -83.00 (s). $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ -83.00 (s). FT-IR (cm$^{-1}$): 2987, 2957, 2901, 1722, 1591, 1573, 1470, 1435, 1282, 1253, 1234, 1193, 1157, 1130, 1059, 1034, 1014, 969, 872, 760, 747, 722. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{11}$H$_7$O$_3$BrNa) = 310.9490; found: 310.9490 (0 ppm).

II.C.5. Methyl 4,4-difluoro-4-(4-fluorophenyl)but-2-ynoate (4e):

Starting from 1 g (4.85 mmol) of methyl 4-(4-fluorophenyl)-4-oxobut-2-ynoate $^{3}e$ we obtained 774 mg of $^{4}e$ (70%) as a yellow oil; R$_f$ = 0.5 (Cyclohexane / Ethyl Acetate: 9/1). $^{1}$H NMR (300 MHz, d$_6$ acetone) $\delta$ 7.86 – 7.78 (m, 2H), 7.42 – 7.33 (m, 2H), 3.86 (s, 3H). $^{13}$C NMR (75 MHz, d$_6$ acetone) $\delta$ 165.4 (dt, $^{1}J_{C-F} = 250.2$ Hz, $^{5}J_{C-F} = 2.0$ Hz), 152.6 (t, $^{4}J_{C-F} = 2.4$ Hz), 131.3 (td, $^{2}J_{C-F} = 27.5, ^{4}J_{C-F} = 3.3$ Hz), 128.8 (dt, $^{3}J_{C-F} = 9.5$ Hz, $^{3}J_{C-F} = 4.9$ Hz), 117.1 (d, $^{5}J_{C-F} = 22.7$ Hz), 112.3 (dd, $^{1}J_{C-F} = 234.0$ Hz), $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -78.42 (d, $^{6}J_{F-F} = 3.4$ Hz), -108.26 (t, $^{6}J_{F-F} = 3.4$ Hz). FT-IR (cm$^{-1}$): 2959, 2927, 2854, 1725, 1605, 1512, 1436, 1305, 1269, 1237, 1193, 1159, 1056, 1028, 971, 838. HRMS (ASAP): calcd. M$^+$ (C$_{11}$H$_7$O$_3$F$_3$) = 228.0393; found: 228.0393 (0 ppm).

II.C.6. Methyl 4,4-difluoro-4-(4-methoxyphenyl)but-2-ynoate (4f):

Starting from 1 g (4.58 mmol) of methyl 4-(4-methoxyphenyl)-4-oxobut-2-ynoate $^{3}f$ we obtained 275 mg of $^{4}f$ (25%) as a yellow oil; R$_f$ = 0.5 (Cyclohexane / Ethyl Acetate: 8/2). $^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.62 – 7.53 (m, 2H), 6.99 – 6.91 (m, 2H), 3.84 (s, 3H), 3.84 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 162.0 (t, $^{5}J_{C-F} = 1.8$ Hz), 152.6 (t, $^{4}J_{C-F} = 2.3$ Hz), 127.1 (t, $^{3}J_{C-F} = 4.8$ Hz), 126.7 (t, $^{2}J_{C-F} = 27.5$ Hz), $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -78.42 (d, $^{6}J_{F-F} = 3.4$ Hz), -108.26 (t, $^{6}J_{F-F} = 3.4$ Hz). FT-IR (cm$^{-1}$): 2959, 2927, 2854, 1725, 1605, 1512, 1436, 1305, 1269, 1237, 1193, 1159, 1056, 1028, 971, 838. HRMS (ESI): calcd. [M+Na]$^+$ (C$_{12}$H$_{10}$O$_3$F$_3$) = 263.0490; found: 263.0488 (1 ppm).

II.C.7. Methyl 4,4-difluoro-4-(4-(trifluoromethyl)phenyl)but-2-ynoate (4g):

Starting from 1 g (3.90 mmol) of methyl 4-oxo-4-(4-(trifluoromethyl)phenyl)but-2-ynoate $^{3}g$ we obtained 857 mg of $^{4}g$ (79%) as a yellow oil; R$_f$ = 0.7 (Cyclohexane / Ethyl Acetate: 8/2). $^{1}$H
NMR (300 MHz, CDCl₃) δ 7.81 – 7.72 (m, 4H), 3.85 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 152.2 (t, ⁴JC-F = 2.4 Hz), 138.0 (tq, ²JC-F = 27.2 Hz, ⁵JC-F = 1.2 Hz), 133.6 (qt, ²JC-F = 32.8 Hz, ⁵JC-F = 1.7 Hz), 126.1 (q, ³JC-F = 3.8 Hz, 2C), 126.1 (t, ³JC-F = 4.9 Hz, 2C), 123.6 (q, ¹JC-F = 272.6 Hz), 110.8 (t, ¹JC-F = 236.4 Hz), 78.8 (t, ³JC-F = 5.9 Hz), 76.6 (t, ²JC-F = 43.6 Hz), 53.6. ¹⁹F NMR (282 MHz, CDCl₃) δ -63.13 (s), -80.81 (s).

FT-IR (cm⁻¹): 2960, 2928, 2857, 1728, 1623, 1437, 1415, 1378, 1324, 1270, 1247, 1167, 1129, 1067, 1035, 1013, 972, 872, 843, 749, 729. HRMS (ASAP): calcd. for [M+H]+ (C₁₂H₈O₂F₅) = 279.0439; found: 279.0439 (0 ppm).

II.C.8. Methyl 4,4-difluorododec-2-ynoate (4h):

Starting from 1 g (4.46 mmol) of methyl 4-oxododec-2-ynoate 3h we obtained 664 mg of 4h (60%) as a yellow oil; Rf = 0.4 (Cyclohexane / Ethyl Acetate: 9/1). ¹H NMR (300 MHz, CDCl₃) δ 3.83 (s, 3H), 2.15 – 1.97 (m, 2H), 1.60 – 1.47 (m, 2H), 1.41 – 1.21 (m, 10H), 0.89 (t, ³JH-H = 6.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 152.6 (t, ⁴JC-F = 2.3 Hz), 114.4 (t, ¹JC-F = 235.5 Hz), 77.7 (t, ²JC-F = 42.6 Hz), 76.3 (t, ³JC-F = 6.5 Hz), 53.4, 38.8 (t, ²JC-F = 24.8 Hz), 31.9, 29.3, 29.2, 29.0, 22.8, 22.5 (t, ³JC-F = 3.5 Hz), 14.2. ¹⁹F {H} NMR (282 MHz, CDCl₃) δ -85.94 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -85.94 (t, ³JH-F = 15.3 Hz). FT-IR (cm⁻¹): 2958, 2928, 2857, 1727, 1459, 1435, 1378, 1314, 1251, 1175, 1125, 1089, 1055, 1012, 984, 938, 748, 644. HRMS (ESI): calcd. for [M+Na]+ (C₁₃H₂₀O₂F₂Na) = 269.1324; found: 269.1327 (1 ppm).

II.D. Synthesis of the alkenes with the gem-difluoroalkyl side chains:

II.D.1. Representative procedure: Synthesis of methyl (Z)-4,4-difluoro-4-phenylbut-2-enoate (5a):

Methyl 4,4-difluoro-4-phenylbut-2-ynoate 4a (0.5 g, 2.38 mmol) was stirred with Lindlar catalyst (10%) in methanol (15 mL) under hydrogen gas. The reaction was monitored by TLC and at the end, the reaction mixture was filtrated on celite, and the product was purified by chromatography to obtain the methyl (Z)-4,4-difluoro-4-phenylbut-2-enoate 5a as a colorless oil (434 mg, 86%).
$R_f = 0.4$ (Cyclohexane / Ethyl Acetate: 8/2). \textsuperscript{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 – 7.59 (m, 2H), 7.46 – 7.41 (m, 3H), 6.22 (dd, $^2J_{H-F} = 25.0$, $^3J_{H-H} = 12.5$ Hz, 1H), 6.13 (dt, $^3J_{H-H} = 12.6$, $^4J_{H-F} = 1.3$ Hz, 1H), 3.69 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.5, 135.9 (t, $^2J_{C-F} = 27.1$ Hz), 134.7 (t, $^2J_{C-F} = 32.3$ Hz), 130.4 (t, $^3J_{C-F} = 1.7$ Hz), 128.6 (s, 2C), 125.5 (t, $^3J_{C-F} = 5.6$ Hz, 2C), 124.9 (t, $^3J_{C-F} = 7.1$ Hz), 118.6 (t, $^1J_{C-F} = 240.5$ Hz), 52.1.

$^{19}$F {H} NMR (471 MHz, CDCl$_3$) δ -88.90 (s).

FT-IR (cm$^{-1}$): 2988, 2955, 2901, 1734, 1663, 1453, 1437, 1393, 1321, 1260, 1242, 1210, 1182, 1143, 1108, 1085, 1042, 991, 906, 824, 767, 696, 549. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{11}$H$_{10}$O$_2$F$_2$Na) = 235.05411; found: 235.0540 (0 ppm); calcd. for [M+K]$^+$ (C$_{11}$H$_{10}$O$_2$F$_2$K) = 251.0280; found: 251.0279 (1 ppm).

II.D.2. Methyl (Z)-4,4-difluoro-6-phenylhex-2-enoate (5b):

Starting from 0.5 g (2.10 mmol) of methyl 4,4-difluoro-6-phenylhex-2-ynoate $4b$ we obtained 327 mg of $5b$ (65%) as a colorless oil; $R_f = 0.3$ (Cyclohexane / Ethyl Acetate: 9/1). \textsuperscript{1}H NMR (500 MHz, CDCl$_3$): 7.32 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 6.10 – 6.00 (m, 2H), 3.77 (s, 3H), 2.87 – 2.81 (m, 2H), 2.54 – 2.41 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.4, 140.5, 136.4 (t, $^2J_{C-F} = 30.9$ Hz), 128.7 (2C), 128.5 (2C), 126.4, 125.3 (t, $^3J_{C-F} = 7.8$ Hz), 120.8 (t, $^1J_{C-F} = 240.7$ Hz), 52.2, 39.0 (t, $^2J_{C-F} = 25.5$ Hz), 28.4 (t, $^3J_{C-F} = 4.4$ Hz). $^{19}$F {H} NMR (471 MHz, CDCl$_3$): -93.80 (s).

FT-IR (cm$^{-1}$): 3778, 3457, 3030, 2952, 2856, 2048, 1738, 1636, 1497, 1439, 1400, 1209, 1167, 1132, 1051, 997, 952, 908, 824, 743, 700, 609, 551. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{13}$H$_{14}$O$_2$F$_2$) = 263.0854; found: 263.0854 (0 ppm).

II.D.3. Methyl (Z)-4-(4-chlorophenyl)-4,4-difluorobut-2-enoate (5c):

Starting from 0.5 g (2.04 mmol) of methyl 4-(4-chlorophenyl)-4,4-difluorobut-2-ynoate $4c$ we obtained 474 mg of $5c$ (94%) as a colorless oil; $R_f = 0.4$ (Cyclohexane / Ethyl Acetate: 9/1). \textsuperscript{1}H NMR (500 MHz, CDCl$_3$) δ 7.57 – 7.53 (m, 2H), 7.43 – 7.37 (m, 2H), 6.20 (dt, $^3J_{H-H} = 12.6$ Hz, $^4J_{H-F} = 11.9$ Hz, 1H), 6.16 (dt, $^3J_{H-H} = 12.6$ Hz, $^4J_{H-F} = 1.1$ Hz, 1H), 3.70 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.3, 136.5 (t, $^5J_{C-F} = 2.0$ Hz), 134.7 (t, $^2J_{C-F} = 32.5$ Hz), 134.5 (t, $^2J_{C-F} = 27.7$ Hz), 128.9 (2C), 127.1 (t, $^3J_{C-F} = 5.5$ Hz, 2C), 125.3 (t, $^3J_{C-F} = 7.2$ Hz), 118.2 (t, $^1J_{C-F} = 240.8$ Hz), 52.2. $^{19}$F {H} NMR (471 MHz, CDCl$_3$) δ -88.48 (s). $^{19}$F NMR (471 MHz, CDCl$_3$) δ -88.48 (d, $^3J_{H-F} = 11.9$ Hz). FT-IR (cm$^{-1}$): 2954, 2928,
2853, 1736, 1664, 1603, 1581, 1492, 1437, 1395, 1258, 1209, 1181, 1144, 1092, 1045, 992, 907, 829, 769. HRMS (ESI): calcd. for [M+Na]+ (C\textsubscript{11}H\textsubscript{9}O\textsubscript{2}F\textsubscript{2}ClNa) = 269.0151; found: 269.0152 (0 ppm).

II.D.4. Methyl (Z)-4-(2-bromophenyl)-4,4-difluorobut-2-enoate (5d):

Starting from 0.5 g (1.73 mmol) of methyl 4-(2-bromophenyl)-4,4-difluorobut-2-ynoate 4d we obtained 176 mg of 5d (35% from 40% conversion) as a colorless oil; R\textsubscript{f} = 0.4 (Cyclohexane / Ethyl Acetate: 9/1). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.82 (ddd, \textsuperscript{3}J\textsubscript{H-H} = 7.9 Hz, \textsuperscript{4}J\textsubscript{H-H} = 1.2 Hz, \textsuperscript{5}J\textsubscript{H-H} = 0.5 Hz, 1H), 7.61 (dd, \textsuperscript{3}J\textsubscript{H-H} = 7.9 Hz, \textsuperscript{4}J\textsubscript{H-H} = 0.9 Hz, 1H), 7.42 (ddd, \textsuperscript{3}J\textsubscript{H-H} = 8.0 Hz, \textsuperscript{3}J\textsubscript{H-H} = 7.4 Hz, \textsuperscript{3}J\textsubscript{H-H} = 1.2Hz, 1H), 7.33 – 7.25 (m, 1H), 6.74 (dt, \textsuperscript{3}J\textsubscript{H-H} = 12.6 Hz, \textsuperscript{3}J\textsubscript{H-F} = 11.7 Hz, 1H), 6.10 (dt, \textsuperscript{3}J\textsubscript{H-H} = 12.6 Hz, \textsuperscript{4}J\textsubscript{H-F} = 1.6 Hz, 1H), 3.59 (s, 3H).
\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 164.5 (t, \textsuperscript{4}J\textsubscript{C-F} = 1.4 Hz), 137.4 (t, \textsuperscript{2}J\textsubscript{C-F} = 32.5 Hz), 136.1 (t, \textsuperscript{2}J\textsubscript{C-F} = 26.6 Hz), 134.2, 131.6 (t, \textsuperscript{4}J\textsubscript{C-F} = 1.7 Hz), 128.6 (t, \textsuperscript{3}J\textsubscript{C-F} = 8.3 Hz), 126.9, 124.8 (t, \textsuperscript{3}J\textsubscript{C-F} = 8.5 Hz), 120.0 (t, \textsuperscript{3}J\textsubscript{C-F} = 4.2 Hz), 117.4 (t, \textsuperscript{1}J\textsubscript{C-F} = 241.7 Hz), 51.9. \textsuperscript{19}F {H} NMR (282 MHz, CDCl\textsubscript{3}) δ -87.30 (s). \textsuperscript{19}F NMR (282 MHz, CDCl\textsubscript{3}) δ -87.30 (d, \textsuperscript{3}J\textsubscript{F-F} = 11.7 Hz). FT-IR (cm\textsuperscript{-1}): 2988, 2953, 2921, 2851, 1734, 1658, 1592, 1572, 1471, 1436, 1395, 1280, 1204, 1147, 1115, 1068, 1032, 1008, 989, 952, 907, 821, 759, 736. HRMS (ESI): calcd. for [M+Na]+ (C\textsubscript{11}H\textsubscript{9}O\textsubscript{2}F\textsubscript{2}BrNa) = 312.9646; found: 312.9647 (0 ppm).

\[ \text{[M+K]}^+ \text{ (C}_{11}\text{H}_9\text{O}_2\text{F}_3\text{BrK}) = 328.9386; \text{ found: 328.9381 (1 ppm)}. \]

II.D.5. Methyl (E)-4,4-difluoro-4-(4-fluorophenyl)but-2-enoate (5e):

Starting from 0.5 g (2.19 mmol) of methyl 4,4-difluoro-4-(4-fluorophenyl)but-2-ynoate 4e we obtained 379 mg of 5e (75%) as a pale yellow oil; R\textsubscript{f} = 0.4 (Cyclohexane / Ethyl Acetate: 9/1). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.64 – 7.56 (m, 2H), 7.16 – 7.07 (m, 2H), 6.28 – 6.10 (m, 2H), 3.70 (s, 3H).
\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 165.4 (t, \textsuperscript{4}J\textsubscript{C-F} = 1.3 Hz), 163.9 (dt, \textsuperscript{1}J\textsubscript{C-F} = 249.9 Hz, \textsuperscript{5}J\textsubscript{C-F} = 2.0 Hz), 134.7 (t, \textsuperscript{2}J\textsubscript{C-F} = 32.5 Hz), 132.0 (t, \textsuperscript{2}J\textsubscript{C-F} = 26.6 Hz), 134.2, 131.6 (t, \textsuperscript{4}J\textsubscript{C-F} = 1.7 Hz), 128.6 (t, \textsuperscript{3}J\textsubscript{C-F} = 8.3 Hz), 126.9, 124.8 (t, \textsuperscript{3}J\textsubscript{C-F} = 8.5 Hz), 120.0 (t, \textsuperscript{3}J\textsubscript{C-F} = 4.2 Hz), 117.4 (t, \textsuperscript{1}J\textsubscript{C-F} = 241.7 Hz), 51.9. \textsuperscript{19}F {H} NMR (282 MHz, CDCl\textsubscript{3}) δ -87.68 (s), -110.40 (t, \textsuperscript{6}J\textsubscript{F-F} = 3.4 Hz). \textsuperscript{19}F NMR (282 MHz, CDCl\textsubscript{3}) δ -87.68 (d, \textsuperscript{3}J\textsubscript{F-H} = 11.1, \textsuperscript{6}J\textsubscript{F-F} = 3.4 Hz), -110.33 to -110.46 (m). FT-IR (cm\textsuperscript{-1}): 2988, 2956, 2901, 1735, 1663, 1606, 1512, 1438, 1393, 1305, 1257, 1231, 1210, 1161, 1143, 1099, 1043, 995, 907, 839, 815, 613, 577, 546. HRMS (ESI): calcd. for [M+Na]+ (C\textsubscript{11}H\textsubscript{9}O\textsubscript{2}F\textsubscript{3}Na) = 253.0447; found: 253.0448 (0 ppm).
II.D.6. Methyl (E)-4,4-difluoro-4-(4-methoxyphenyl)but-2-enoate (5f):

Starting from 0.5 g (2.08 mmol) of methyl 4,4-difluoro-4-(4-methoxyphenyl)but-2-ynoate 4f we obtained 398 mg of 5f (79%) as a colorless oil; Rf = 0.5 (Cyclohexane / Ethyl Acetate: 8/2).

1H NMR (300 MHz, CDCl3) δ 7.57 – 7.50 (m, 2H), 6.97 – 6.90 (m, 2H), 6.26 – 6.07 (m, 2H), 3.82 (s, 3H), 3.69 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 165.6, 161.1 (t, 2J_{C-F} = 32.9 Hz), 134.9 (t, 2J_{C-F} = 32.9 Hz), 128.1 (t, 2J_{C-F} = 27.6 Hz), 127.1 (t, 3J_{C-F} = 5.5 Hz), 124.5 (t, 3J_{C-F} = 7.0 Hz), 118.8 (t, 1J_{C-F} = 239.8 Hz), 113.9, 55.4, 52.1.

19F {H} NMR (282 MHz, CDCl3) δ -87.25 (s). FT-IR (cm⁻¹): 3671, 2956, 2912, 2842, 1735, 1662, 1613, 1586, 1515, 1461, 1437, 1392, 1308, 1249, 1209, 1176, 1142, 1110, 1018, 990, 905, 833, 613, 584, 553. HRMS (ESI): calcd. for [M+Na]^+ (C_{12}H_{12}O_3F_2Na) = 265.0647; found: 265.0649 (1 ppm); [M+K]^+ (C_{12}H_{12}O_3F_2K) = 281.0386; found: 281.0385 (0 ppm).

II.D.7. Methyl (E)-4,4-difluoro-4-(4-(trifluoromethyl)phenyl)but-2-enoate (5g):

Starting from 0.5 g (1.80 mmol) of methyl 4,4-difluoro-4-(4-(trifluoromethyl)phenyl)but-2-ynoate 4g we obtained 403 mg of 5g (80%) as a yellow oil; Rf = 0.7 (Cyclohexane / Ethyl Acetate: 8/2).

1H NMR (500 MHz, CDCl3) δ 7.75 (d, 3J_{H-H} = 8.3 Hz, 2H), 7.71 (d, 3J_{H-H} = 8.4 Hz, 2H), 6.37 – 5.95 (m, 2H), 3.70 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 165.1, 139.6 (t, 2J_{C-F} = 27.1 Hz), 134.5 (t, 2J_{C-F} = 32.2 Hz), 132.5 (q, 2J_{C-F} = 32.6 Hz), 126.2 (t, 3J_{C-F} = 5.5 Hz, 2C), 125.8 (t, 3J_{C-F} = 6.9 Hz), 125.7 (q, 3J_{C-F} = 3.8 Hz, 2C), 123.8 (q, 1J_{C-F} = 272.4 Hz), 118.0 (t, 1J_{C-F} = 241.4 Hz), 52.2. 19F (H) NMR (282 MHz, CDCl3) δ -62.98 (s), -89.23 (d, 3J_{F-H} = 11.2 Hz). FT-IR (cm⁻¹): 3001, 2957, 2920, 1737, 1664, 1623, 1438, 1414, 1395, 1324, 1259, 1214.5, 1168, 1126, 1066, 994, 908, 844, 770, 608. HRMS (ESI): calcd. for [M+Na]^+ (C_{12}H_{9}O_2F_5Na) = 303.0415; found: 303.0414 (0 ppm).

II.D.8. Methyl (E)-4,4-difluorododec-2-enoate (5h):

Starting from 0.5 g (1.80 mmol) of methyl 4,4-difluorododec-2-ynoate 4h we obtained 358 mg of 5h (71%) as a yellow oil; Rf = 0.3 (Cyclohexane / Ethyl Acetate: 9/1).

1H NMR (300 MHz, CDCl3) δ 6.14 – 5.93 (m, 2H), 3.76 (s, 3H), 1.54 – 1.40 (m, 2H), 1.37 – 1.20 (m, 10H), 0.88 (t, 3J_{H-H} = 6.9 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ 165.6 (t, 3J_{C-F} = 1.3 Hz), 136.5 (t, 2J_{C-F} = 31.0 Hz), 124.9 (t, 3J_{C-F} = 7.7 Hz), 121.4 (t, 1J_{C-F} = 240.1 Hz), 52.1, 37.3 (t, 2J_{C-F} = 25.4 Hz), 32.0, 29.5, 29.4, 29.3,
22.8, 22.2 (t, $^3J_{C-F} = 4.0$ Hz), 14.2. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -93.32 (s). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -93.47 to -93.18 (m). FT-IR (cm$^{-1}$): 3671, 3649, 2955, 2926, 2856, 1738, 1664, 1459, 1437, 1400, 1379, 1310, 1206, 1171, 1145, 1096, 1054, 933, 904, 882, 751, 723. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{13}$H$_{22}$O$_2$F$_2$Na) = 271.1480; found: 271.1482 (1 ppm).

II.E. Nitromethane addition on the alkenes with the gem-difluoroalkyl chains:

II.E.1. Representative procedure: Synthesis of methyl 4,4-difluoro-3-(nitromethyl)-4-phenylbutanoate (6a):

To methyl (Z)-4,4-difluoro-4-phenylbut-2-enoate 5a (150 mg, 0.7 mmol) was added nitromethane (75 μl, 1.4 mmol) and potassium carbonate (289 mg, 2.1 mmol) in DMSO (3 ml). The reaction mixture was stirred at room temperature and it was monitored by TLC. At the end concentrated NH$_4$Cl (10 mL) was added and the reaction mixture was extracted with ethyl acetate (3x20mL). The organic layers were separated, washed with water (3x10mL), dried over Na$_2$SO$_4$ and concentrated under vacuum. After purification by chromatography on silica gel, methyl 4,4-difluoro-3-(nitromethyl)-4-phenylbutanoate 6a (174 mg, 90%) was obtained as a yellow oil. R$_f$ = 0.4 (Cyclohexane / Ethyl Acetate: 7/3). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.55 – 7.45 (m, 5H), 4.73 (dd, $^2J_{H-H} = 13.8$ Hz, $^3J_{H-H} = 5.8$ Hz, 1H), 4.53 (dd, $^2J_{H-H} = 13.8$ Hz, $^3J_{H-H} = 6.2$ Hz, 1H), 3.77 – 3.57 (m, 1H), 3.62 (s, 3H), 2.66 (dd, $^2J_{H-H} = 16.9$ Hz, $^3J_{H-H} = 5.2$ Hz, 1H), 2.50 (dd, $^2J_{H-H} = 16.9$, $^3J_{H-H} = 8.2$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.8, 133.9 (t, $^2J_{C-F} = 25.8$ Hz), 131.0, 129.0 (2C), 125.5 (t, $^3J_{C-F} = 6.4$ Hz, 2C), 123.7 (dd, $^1J_{C-F} = 247.4$ Hz), 73.4 (t, $^3J_{C-F} = 3.4$ Hz), 52.3, 42.6 (t, $^2J_{C-F} = 27.1$ Hz), 31.4 (dd, $^3J_{C-F} = 4.2$, 3.0 Hz). $^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ -98.05 (AB system, $^2J_{F-F} = 250.8$ Hz), -104.55 (AB system, $^2J_{F-F} = 250.8$ Hz). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -98.05 (ABX system, dd, $^2J_{F-F} = 250.8$ Hz). FT-IR (cm$^{-1}$): 2956, 2928, 1735, 1556, 1452, 1437, 1379, 1320, 1274, 1231, 1213, 1169, 1132, 1049, 982, 953, 923, 894, 765, 697, 632. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{13}$H$_{13}$NO$_2$F$_2$Na) = 296.0705; found: 296.0706 (0 ppm).
II.E.2. Methyl 4,4-difluoro-3-(nitromethyl)-6-phenylhexanoate (6b):

Starting from 150 mg (0.62 mmol) of methyl 4,4-difluoro-6-phenylhex-2-enoate 5b we obtained 150 mg of 6b (80%) as a yellow oil; Rf = 0.3 (Cyclohexane / Ethyl Acetate: 8/2). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.29 (m, 2H), 7.25 – 7.17 (m, 3H), 4.63 (dd, \(^2\)J\(_{H-H}\) = 14.0 Hz, \(^3\)J\(_{H-H}\) = 5.9 Hz, 1H), 4.43 (dd, \(^2\)J\(_{H-H}\) = 14.0 Hz, \(^3\)J\(_{H-H}\) = 6.1 Hz, 1H), 3.72 (s, 3H), 3.48 – 3.36 (m, 1H), 2.85 (dd, J = 8.0 Hz, 0.4 Hz, 2H), 2.64 (dd, \(^2\)J\(_{H-H}\) = 17.0 Hz, \(^3\)J\(_{H-H}\) = 5.1 Hz, 1H), 2.42 (dd, \(^2\)J\(_{H-H}\) = 17.0 Hz, \(^3\)J\(_{H-H}\) = 8.0 Hz, 1H), 2.26 – 2.12 (m, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.9, 139.9, 128.8, 128.4, 126.6, 123.6 (t, \(^1\)J\(_{C-F}\) = 246.0 Hz), 73.5 (t, \(^3\)J\(_{C-F}\) = 4.7 Hz), 52.4, 40.5 (t, \(^2\)J\(_{C-F}\) = 24.6 Hz), 36.6 (t, \(^2\)J\(_{C-F}\) = 24.5 Hz), 31.4 (t, \(^3\)J\(_{C-F}\) = 4.3 Hz), 27.8 (t, \(^3\)J\(_{C-F}\) = 5.0 Hz). \(^{19}\)F \({\text{H}}\) NMR (471 MHz, CDCl\(_3\)) \(\delta\) -103.12 (A\(_B\) system, \(^2\)J\(_{F-F}\) = 249.7 Hz), -104.86 (A\(_B\) system, \(^2\)J\(_{F-F}\) = 249.7 Hz). FT-IR (cm\(^{-1}\)): 3779, 3453, 2050, 1738, 1635, 1563, 1438, 1383, 1210, 1053, 950, 700, 612. HRMS (ESI): calcd. for [M+Na]\(^+\) (C\(_{14}\)H\(_{17}\)NO\(_4\)F\(_2\)Na) = 324.1018; found: 324.1018 (0 ppm).

II.E.3. Methyl 4-(4-chlorophenyl)-4,4-difluoro-3-(nitromethyl)butanoate (6c):

Starting from 150 mg (0.61 mmol) of methyl 4-(4-chlorophenyl)-4,4-difluorobut-2-enoate 5c we obtained 164 mg of 6c (88%) as a yellow oil; Rf = 0.5 (Cyclohexane / Ethyl Acetate: 7/3). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.52 – 7.30 (m, 4H), 4.72 (dd, \(^2\)J\(_{H-H}\) = 13.9 Hz, \(^3\)J\(_{H-H}\) = 5.9 Hz, 1H), 4.53 (dd, \(^2\)J\(_{H-H}\) = 13.9 Hz, 6.0 Hz, 1H), 3.70 – 3.58 (m, 1H), 3.63 (s, 3H), 2.63 (dd, \(^2\)J\(_{H-H}\) = 17.0 Hz, \(^3\)J\(_{H-H}\) = 5.2 Hz, 1H), 2.50 (dd, \(^2\)J\(_{H-H}\) = 17.0 Hz, \(^3\)J\(_{H-H}\) = 8.2 Hz, 1H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.6, 137.3 (t, \(^5\)J\(_{C-F}\) = 2.2 Hz), 132.4 (t, \(^3\)J\(_{C-F}\) = 26.4 Hz), 129.3, 127.1 (dd, \(^3\)J\(_{C-F}\) = 6.9 Hz, \(^3\)J\(_{C-F}\) = 5.9 Hz), 121.8 (dd, \(^1\)J\(_{C-F}\) = 248.2 Hz, \(^1\)J\(_{C-F}\) = 247.6 Hz), 73.2 (t, \(^3\)J\(_{C-F}\) = 3.5 Hz), 52.4, 42.5 (t, \(^2\)J\(_{C-F}\) = 26.9 Hz), 31.3 (dd, \(^3\)J\(_{C-F}\) = 4.4 Hz, \(^3\)J\(_{C-F}\) = 2.9 Hz). \(^{19}\)F \({\text{H}}\) NMR (471 MHz, CDCl\(_3\)) -97.58 (A\(_B\) system, \(^2\)J\(_{F-F}\) = 252.0 Hz), -104.61 (A\(_B\) system, \(^2\)J\(_{F-F}\) = 252.0 Hz). \(^{19}\)F NMR (471 MHz, CDCl\(_3\)) \(\delta\) -97.58 (A\(_B\)X system, dd, \(^2\)J\(_{F-F}\) = 252.0 Hz, \(^3\)J\(_{F-H}\) = 11.0 Hz), -104.61 (A\(_B\)X system, dd, \(^2\)J\(_{F-F}\) = 252.0 Hz, \(^3\)J\(_{F-H}\) = 17.9 Hz). FT-IR (cm\(^{-1}\)): 2957, 2917, 2850, 1735, 1604, 1556, 1494, 1437, 1403, 1379, 1319, 1274, 1230, 1213, 1167, 1092, 1056, 1017, 982, 951, 895, 830, 718. HRMS (ESI): calcd. for [M+Na]\(^+\) (C\(_{12}\)H\(_{12}\)NO\(_4\)F\(_2\)ClNa) = 330.0315; found: 330.0314 (0 ppm).
II.E.4. Methyl 4-(2-bromophenyl)-4,4-difluoro-3-(nitromethyl)butanoate (6d):

Starting from 150 mg (0.52 mmol) of methyl 4-(2-bromophenyl)-4,4-difluorobut-2-enoate 5d we obtained 143 mg of 6d (79%) as a yellow oil; Rf = 0.3 (Cyclohexane / Ethyl Acetate: 8/2). 1H NMR (500 MHz, CDCl₃) δ 7.69 (d, 3J_H-H = 7.9 Hz, 1H), 7.55 (dd, 3J_H-H = 7.9 Hz, 4J_H-H = 1.5 Hz, 1H), 7.40 (dd, 3J_H-H = 7.9 Hz, 3J_H-H = 7.5 Hz, 1H), 7.33 (dd, 3J_H-H = 7.9 Hz, 3J_H-H = 7.5 Hz, 1H), 4.77 (dd, 2J_H-H = 13.8 Hz, 3J_H-H = 5.7 Hz, 1H), 4.58 (dd, 2J_H-H = 13.8, 3J_H-H = 6.0 Hz, 1H), 4.34 – 4.20 (m, 1H), 3.59 (s, 3H), 2.63 (dd, 2J_H-H = 16.9 Hz, 3J_H-H = 5.5 Hz, 1H), 2.55 (dd, 2J_H-H = 16.9 Hz, 3J_H-H = 8.0 Hz, 1H). 13C NMR (126 MHz, CDCl₃) δ 170.5, 135.4, 132.6 (t, 2JC-F = 25.2 Hz), 132.4, 128.5 (dd, 3JC-F = 10.5 Hz, 3JC-F = 8.6 Hz), 127.6, 121.5 (t, 1JC-F = 249.5 Hz), 120.3 (t, 3JC-F = 3.9 Hz), 73.2 (t, 3JC-F = 3.7 Hz), 52.3, 40.1 (t, 2JC-F = 24.9 Hz), 31.4 (t, 2JC-F = 3.6 Hz). 19F {H} NMR (471 MHz, CDCl₃) δ -98.62 (AB system, 2J_F-F = 254.5 Hz), -102.49 (AB system, 2J_F-F = 254.5 Hz). 19F NMR (471 MHz, CDCl₃) δ -98.62 (ABX system, dd, 2J_F-F = 254.5 Hz, 3J_F-H = -11.1 Hz), -102.49 (ABX system, dd, 2J_F-F = 254.5 Hz, 3J_F-H = 17.7 Hz). FT-IR (cm⁻¹): 2956, 2927, 1735, 1592, 1556, 1472, 1435, 1378, 1283, 1228, 1214, 1164, 1127, 1066, 1048, 1029, 999, 977, 953, 761. HRMS (ESI): calcd. for [M+Na]+ (C₁₂H₁₀NO₃F₂BrNa) = 373.9810; found: 373.9809 (0 ppm).

II.E.5. Methyl 4,4-difluoro-4-(4-fluorophenyl)-3-(nitromethyl)butanoate (6e):

Starting from 150 mg (0.65 mmol) of methyl 4,4-difluoro-4-(4-fluorophenyl)but-2-enoate 5e we obtained 165 mg (87%) as a yellow oil; Rf = 0.3 (Cyclohexane / Ethyl Acetate: 8/2). 1H NMR (300 MHz, CDCl₃) δ 7.54 – 7.44 (m, 2H), 7.20 – 7.10 (m, 2H), 4.72 (dd, 2J_H-H = 13.9 Hz, 3J_H-H = 6.0 Hz, 1H), 4.52 (dd, 2J_H-H = 13.9 Hz, 3J_H-H = 6.0 Hz, 1H), 3.75 – 3.54 (m, 1H), 3.63 (s, 3H), 2.64 (dd, 2J_H-H = 17.0 Hz, 3J_H-H = 5.3 Hz, 1H), 2.49 (dd, 3J_H-H = 16.9 Hz, 3J_H-H = 8.1 Hz, 1H). 13C NMR (75 MHz, CDCl₃) δ 170.6 (d, 4JC-F = 0.5 Hz), 164.1 (dt, 1JC-F = 251.2 Hz, 3JC-F = 2.0 Hz), 130.0 (td, 2JC-F = 26.5, 4JC-F = 3.3 Hz), 127.9 (ddd, 3JC-F = 8.8 Hz, 3JC-F = 6.9 Hz, 3JC-F = 6.0 Hz), 121.8 (t, 1JC-F = 247.7 Hz), 116.2 (d, 2JC-F = 22.1 Hz), 73.3 (t, 3JC-F = 3.5 Hz), 52.4, 42.6 (t, 2JC-F = 27.1 Hz), 31.4 (dd, 3JC-F = 4.4 Hz, 3JC-F = 2.9 Hz). 19F {H} NMR (282 MHz, CDCl₃) δ -97.00 (ABX system, dd, 2J_F-F = 251.8 Hz, 6J_F-F = 3.0 Hz), -103.58 (ABX system, dd, 2J_F-F = 251.8 Hz, 6J_F-F = 2.2 Hz), -109.09 (t, 6J_F-F = 2.7 Hz). 19F NMR (282 MHz, CDCl₃) δ -97.00 (ABXX’ system, ddd, 2J_F-F = 251.8 Hz, 3J_F-H = 11.4 Hz, 6J_F-F = 3.0 Hz), -103.58 (ABXX’ system, ddd, 2J_F-F = 251.8 Hz, 3J_F-H = 17.6 Hz, 6J_F-F = 2.2 Hz), -109.01 to -109.16 (m). FT-IR (cm⁻¹): 2958, 1736, 1609, 1557, 1514, 1437, 1379.9, 1320, 1299.1, 1274.7, 1229.9, 1162.4, S16.
1104, 1054, 985, 952, 895, 840, 603, 567. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{12}$H$_{12}$NO$_4$F$_3$Na) = 314.0611; found: 314.0612 (0 ppm).

II.E.6. Methyl 4,4-difluoro-4-(4-methoxyphenyl)-3-(nitromethyl)butanoate (6f):

Starting from 150 mg (0.62 mmol) of methyl 4,4-difluoro-4-(4-methoxyphenyl)but-2-enoate 5f we obtained 162 mg of 6f (86%) as a yellow oil; R$_f$ = 0.4 (Cyclohexane / Ethyl Acetate: 7/3). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.41 (d, $^3$$J$$_{H-H}$ = 8.9 Hz, 2H), 6.95 (d, $^3$$J$$_{H-H}$ = 8.9 Hz, 2H), 4.71 (dd, $^2$$J$$_{H-H}$ = 13.8 Hz, $^3$$J$$_{H-H}$ = 5.8 Hz, 1H), 4.51 (dd, $^2$$J$$_{H-H}$ = 13.8 Hz, $^3$$J$$_{H-H}$ = 6.2 Hz, 1H), 3.84 (s, 3H), 3.76 – 3.53 (m, 1H, H$_8$), 3.63 (s, 3H), 2.66 (dd, $^2$$J$$_{H-H}$ = 16.9 Hz, $^3$$J$$_{H-H}$ = 5.2 Hz, 1H), 2.48 (dd, $^2$$J$$_{H-H}$ = 16.9 Hz, $^3$$J$$_{H-H}$ = 8.3 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.7, 161.3 (t, $^5$$J$$_{C-F}$ = 1.7 Hz), 126.9 (dd, $^3$$J$$_{C-F}$ = 6.8 Hz, $^3$$J$$_{C-F}$ = 6.0 Hz), 125.8 (t, $^2$$J$$_{C-F}$ = 26.4 Hz), 122.1 (dd, $^1$$J$$_{C-F}$ = 247.6 Hz, $^1$$J$$_{C-F}$ = 247.0 Hz), 114.1, 73.4 (t, $^3$$J$$_{C-F}$ = 3.5 Hz), 55.4, 52.2, 42.6 (t, $^2$$J$$_{C-F}$ = 27.7 Hz), 31.4 (dd, $^3$$J$$_{C-F}$ = 4.2 Hz, $^3$$J$$_{C-F}$ = 2.9 Hz). $^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ -96.83 (AB system, $^2$$J$$_{F-F}$ = 250.0 Hz), -102.84 (AB system, $^2$$J$$_{F-F}$ = 250.0 Hz). FT-IR (cm$^{-1}$): 3671, 2958, 2923, 2846, 1735, 1614, 1557, 1517, 1461, 1437, 1380, 1309, 1253, 1214, 1178, 1118, 1051, 1029, 981, 951, 895, 834, 634, 607, 573. HRMS (ESI): calcd. For [M+K]$^+$ (C$_{13}$H$_{15}$NO$_5$F$_2$K) = 342.0550; found: 342.0550 (0 ppm).

II.E.7. Methyl 4,4-difluoro-3-(nitromethyl)-4-(4-(trifluoromethyl)phenyl)butanoate (6g):

Starting from 150 mg (0.54 mmol) of methyl 4,4-difluoro-4-(4-(trifluoromethyl)-phenyl)but-2-enoate 5f we obtained 155 mg of 6f (85%) as a yellow oil; R$_f$ = 0.3 (Cyclohexane / Ethyl Acetate: 8/2). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.78 – 7.72 (m, 2H), 7.68 – 7.61 (m, 2H), 4.75 (dd, $^2$$J$$_{H-H}$ = 14.0 Hz, $^3$$J$$_{H-H}$ = 6.0 Hz, 1H), 4.55 (dd, $^2$$J$$_{H-H}$ = 13.9 Hz, $^3$$J$$_{H-H}$ = 6.0 Hz, 1H), 3.80 – 3.58 (m, 1H), 3.61 (s, 3H), 2.63 (dd, $^2$$J$$_{H-H}$ = 17.0 Hz, $^3$$J$$_{H-H}$ = 5.4 Hz, 1H), 2.51 (dd, $^2$$J$$_{H-H}$ = 17.0, $^3$$J$$_{H-H}$ = 8.0 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.4, 137.62 (t, $^2$$J$$_{C-F}$ = 26.3 Hz), 133.25 (q, $^2$$J$$_{C-F}$ = 33.0 Hz), 126.3 (t, $^3$$J$$_{C-F}$ = 12.8 Hz), 126.1 (q, $^3$$J$$_{C-F}$ = 3.7 Hz), 123.6 (q, $^1$$J$$_{C-F}$ = 272.5 Hz), 121.5 (t, $^1$$J$$_{C-F}$ = 248.2 Hz), 73.1 (t, $^3$$J$$_{C-F}$ = 3.5 Hz), 52.4, 42.4 (t, $^2$$J$$_{C-F}$ = 26.4 Hz), 31.3 (dd, $^3$$J$$_{C-F}$ = 4.3 Hz, $^3$$J$$_{C-F}$ = 2.9 Hz). $^{19}$F {H} NMR
(282 MHz, CDCl₃) δ -63.10 (s), -97.95 (AB system, ²J_F-F = 253.5 Hz), -105.31 (AB system, ²J_F-F = 253.5 Hz). ¹⁹F NMR (282 MHz, CDCl₃) δ -63.10 (s), -97.95 (AB system, d, ²J_F-F = 253.5 Hz, ³J_F-H = 10.9 Hz), -105.31 (AB system, d, ²J_F-F = 253.5 Hz, ³J_F-H = 18.2 Hz). FT-IR (cm⁻¹): 3671, 2959, 2923, 1737, 1624, 1559, 1524, 1438, 1413, 1380, 1323, 1276, 1233, 1216, 1167, 1127, 1067, 1019, 985, 896, 843. HRMS (ESI): calcd. for [M+Na]⁺ (C₁₃H₁₂NO₄F₅Na) = 364.0578; found: 364.0577 (0 ppm).

II.E.8. Methyl 4,4-difluoro-3-(nitromethyl)dodecanoate (6h):

Starting from 150 mg (0.60 mmol) of methyl-4,4-difluorododec-2-enoate we obtained 131 mg of 6h (70%) as a yellow oil; Rᵣ = 0.3 (Cyclohexane / Ethyl Acetate: 8/2). ¹H NMR (300 MHz, CDCl₃) δ 4.70 (dd, ²J_H-H = 13.9 Hz, ³J_H-H = 5.8 Hz, 1H), 4.50 (dd, ²J_H-H = 13.9 Hz, ³J_H-H = 6.2 Hz, 1H), 3.72 (s, 3H), 3.46 – 3.24 (m, 1H), 2.71 (dd, ²J_H-H = 16.9 Hz, ³J_H-H = 5.1 Hz, 1H), 2.50 (dd, ²J_H-H = 16.9 Hz, ³J_H-H = 8.1 Hz, 1H), 1.95 – 1.75 (m, 2H), 1.55 – 1.40 (m, 2H), 1.39 – 1.17 (m, 10H), 0.88 (t, ³J_H-H = 6.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 124.1 (t, ¹J_C-F = 245.7 Hz), 73.6 (t, ³J_C-F = 4.8 Hz), 52.5, 40.4 (t, ²J_C-F = 24.9 Hz), 34.7 (t, ²J_C-F = 24.6 Hz), 31.9, 31.6 (dd, ³J_C-F = 5.0 Hz, ³J_C-F = 3.8 Hz), 29.4, 29.3, 29.2, 22.8, 21.7 (dd, ³J_C-F = 4.8 Hz, ³J_C-F = 4.2 Hz), 14.2. ¹⁹F NMR {H} (282 MHz, CDCl₃) δ -102.56 (AB system, ²J_F-F = 249.2 Hz), -104.31(AB system, ²J_F-F = 249.2 Hz). FT-IR (cm⁻¹): 2956, 2926, 2856, 1738, 1558, 1460, 1437, 1379, 1328, 1295, 1200, 1176, 1107, 1071, 993, 928. HRMS (ESI): calcd. for [M+Na]⁺ (C₁₄H₂₅NO₄F₂Na) = 332.1644; found: 332.1644 (0 ppm).

II.F. Procedure for the reduction of the nitro group:

II.F.1. Representative procedure: Synthesis of 4-(Difluoro(phenyl)methyl)-pyrrolidin-2-one (7a):

To a stirred solution of methyl 4,4-difluoro-3-(nitromethyl)-4-phenylbutanoate 6a (50 mg, 0.18 mmol) in MeOH (2 mL) was added NiCl₂·6H₂O (85 mg, 0.36 mmol) at room temperature. After stirring for 5 min, NaBH₄ (75 mg, 1.98 mmol) was added in four portions. The reaction mixture was stirred for 30 min at room temperature, then NH₄Cl was added and the reaction mixture was extracted with ethyl acetate (3x5mL). The organic layers were separated, washed with water (3x5mL), dried over Na₂SO₄ and concentrated under vacuum. The 4-
(difluoro(phenyl)methyl)pyrrolidin-2-one 7a was precipitated and washed by diethyl ether to give a colorless solid (31 mg, 80%).

\[ R_f = 0.3 \text{ (DCM / Methanol: 95/5). mp} = 95^\circ \text{C} \]. \( ^1\text{H NMR (300 MHz, CDCl}_3 \) \( \delta \) 7.45 (bs, 5H), 6.55 (s, 1H, NH), 3.2 (dd, 2\( J_{HH} = 9.9 \text{ Hz}, 3\( J_{HH} = 7.0 \text{ Hz}, 1\text{H})), 3.40 (dd, 2\( J_{HH} = 9.9 \text{ Hz}, 3\( J_{HH} = 8.8 \text{ Hz}, 1\text{H})), 3.35 - 3.13 (m, 1\text{H}), 2.51 (dd, 2\( J_{HH} = 17.3 \text{ Hz}, 3\( J_{HH} = 8.1 \text{ Hz}, 1\text{H})), 2.35 (dd, 2\( J_{HH} = 17.3 \text{ Hz}, 3\( J_{HH} = 9.6 \text{ Hz}, 1\text{H})). \( ^{13}\text{C NMR (75 MHz, CDCl}_3 \) \( \delta \) 176.4, 135.4 (t, 2\( J_{CF} = 26.4 \text{ Hz}), 130.5 (t, 5\( J_{CF} = 1.7 \text{ Hz}), 128.9 (2\text{C}), 125.2 (t, 3\( J_{CF} = 6.3 \text{ Hz}, 2\text{C}), 121.9 (t, 1\( J_{CF} = 244.7 \text{ Hz}), 42.5 (t, 2\( J_{CF} = 244.7 \text{ Hz}), 42.0 (t, 3\( J_{CF} = 4.8 \text{ Hz}, 30.8 (t, 3\( J_{CF} = 3.7 \text{ Hz}). \( ^{19}\text{F NMR (282 MHz, CDCl}_3 \) \( \delta \) -103.06 (AB system, 2\( J_{FF} = 248.2 \text{ Hz}), -104.51 (AB system, 2\( J_{FF} = 248.2 \text{ Hz}). \( ^{19}\text{F NMR (282 MHz, CDCl}_3 \) \( \delta \) -103.06 (AB system, 2\( J_{FF} = 248.2 \text{ Hz}, 3\( J_{FH} = 13.3 \text{ Hz}), -104.51 (AB system, 2\( J_{FF} = 248.2 \text{ Hz}, 3\( J_{FH} = 15.4 \text{ Hz}). FT-IR (cm\(^{-1}\)): 3177, 3092, 2984, 2958, 2920, 2852, 1683, 1487, 1453, 1359, 1304, 1273, 1142, 1062, 1041, 991, 795, 763, 702, 686. HRMS (ESI): calcd. for [M+Na\(^+\) (C\(_{11}\)H\(_{11}\)NOF\(_2\)Na) = 234.0701; found: 234.0699 (1 ppm).

II.F.2. 4-(1,1-Difluoro-3-phenylpropyl)pyrrolidin-2-one (7b):

Starting from 50 mg (0.166 mmol) methyl 4,4-difluoro-3-(nitromethyl)-6-phenylhexanoate 6b we obtained 31 mg of 7b (77%) as a colorless solid; \( R_f = 0.3 \text{ (DCM / Methanol: 95/5). mp} = 95^\circ \text{C}. \( ^1\text{H NMR (500 MHz, CDCl}_3 \) \( \delta \) 7.36 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 6.43 (s, 1H, NH), 3.51 – 3.44 (m, 2H), 3.03 – 2.89 (m, 1H), 2.87 – 2.81 (m, 2H), 2.49 – 2.36 (m, 2H), 2.20 – 2.06 (m, 2H). \( ^{13}\text{C NMR (126 MHz, CDCl}_3 \) \( \delta \) 176.4, 140.2, 128.8, 128.4, 126.6, 123.6 (t, 1\( J_{CF} = 243.4 \text{ Hz), 41.8 (t, 3\( J_{CF} = 5.6 \text{ Hz), 40.6 (t, 2\( J_{CF} = 25.9 \text{ Hz), 37.2 (t, 2\( J_{CF} = 25.0 \text{ Hz), 30.7 (dd, 3\( J_{CF} = 3.2, 3\( J_{CF} = 1.6 \text{ Hz), 28.0 (t, 3\( J_{CF} = 4.7 \text{ Hz).} \( ^{19}\text{F NMR (471 MHz, CDCl}_3 \) \( \delta \) -107.17 (AB system, 2\( J_{FF} = 244.7 \text{ Hz), -108.06 (AB system, 2\( J_{FF} = 244.7 \text{ Hz). FT-IR (cm\(^{-1}\)): 3198, 3107, 3086, 3063, 3026, 2966, 292, 2893, 2870, 1664, 1603, 1407, 1454, 1379, 1282, 1197, 1086, 1052, 1036, 930, 905, 741, 698. HRMS (ESI): calcd. for [M+Na\(^+\) (C\(_{13}\)H\(_{15}\)NOF\(_2\)Na) = 262.1014; found: 262.1016 (1 ppm).

II.F.3. 4-((4-Chlorophenyl)difluoromethyl)pyrrolidin-2-one (7c):

Starting from 50 mg (0.163 mmol) of methyl 4-(4-chlorophenyl)-4,4-difluoro-3-(nitromethyl)butanoate 6c we obtained 33 mg of 7c (84%) as a colorless solid; \( R_f = 0.2 \text{ (DCM / Methanol: 95/5). mp} = 113^\circ \text{C}. \( ^1\text{H NMR (300 MHz, CDCl}_3 \) \( \delta \) 7.56 – 7.35 (m, 4H), 6.09 (s, 1H, NH),
3.51 (dd, $^2J_{H-H} = 9.9$ Hz, $^3J_{H-H} = 7.0$ Hz, 1H), 3.42 (dd, $^2J_{H-H} = 9.9$ Hz, $^2J_{H-H} = 9.2$ Hz, 1H), 3.37 – 3.11 (m, 1H), 2.48 (dd, $^2J_{H-H} = 17.4$ Hz, $^3J_{H-H} = 8.0$ Hz, 1H), 2.35 (dd, $^2J_{H-H} = 17.2$ Hz, $^3J_{H-H} = 9.6$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 176.4, 136.8 (t, $^3J_{C-F} = 2.1$ Hz), 133.8 (t, $^3J_{C-F} = 2.70$ Hz), 129.2, 126.72 (t, $^3J_{C-F} = 6.2$ Hz), 121.6 (t, $^1J_{C-F} = 245.0$ Hz), 42.4 (t, $^1J_{C-F} = 28.2$ Hz), 41.9 (t, $^3J_{C-F} = 4.8$ Hz), 30.8 (t, $^3J_{C-F} = 4.4$ Hz). $^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ -102.76 (AB system, $^2J_{F-F} = 249.3$ Hz), -104.42 (AB system, $^3J_{F-F} = 249.3$ Hz). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -102.76 (AB system, $^2J_{F-F} = 249.3$ Hz, $^3J_{F-H} = 13.1$ Hz, -104.42 (AB system, $^2J_{F-F} = 249.3$ Hz, $^3J_{F-H} = 15.8$ Hz). FT-IR (cm$^{-1}$): 3116, 2987, 2969, 2923, 1698, 1604, 1493, 1403, 1265, 1093, 1065, 991. HRMS (ESI): calcd. for [M+Na]+ (C$_{11}$H$_{10}$NOF$_2$ClNa) = 268.0311; found: 268.0310 (0 ppm).

II.F.4. 4-(Difluoro(4-fluorophenyl)methyl)pyrrolidin-2-one (7e):

Starting from 50 mg (0.172 mmol) of methyl 4,4-difluoro-4-(4-fluorophenyl)-3-(nitromethyl)butanoate 6e we obtained 35 mg of 7e (90%) as a colorless solid; $R_f = 0.3$ (DCM / Methanol: 95/5). mp = 128 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.54 – 7.37 (m, 2H), 7.19 – 7.07 (m, 2H), 6.74 (s, 1H, NH), 3.50 (dd, $^2J_{H-H} = 10.1$ Hz, $^3J_{H-H} = 7.0$ Hz, 1H), 3.41 (dd, $^2J_{H-H} = 10.1$ Hz, $^3J_{H-H} = 9.7$ Hz, 1H), 3.32 – 3.10 (m, 1H), 2.48 (dd, $^2J_{H-H} = 17.3$ Hz, $^3J_{H-H} = 8.0$ Hz, 1H), 2.35 (dd, $^2J_{H-H} = 17.3$ Hz, $^3J_{H-H} = 9.7$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 176.3, 163.9 (dt, $^3J_{C-F} = 250.3$ Hz, $^5J_{C-F} = 2.0$ Hz), 131.4 (td, $^2J_{C-F} = 27.1$ Hz, $^4J_{C-F} 3.3$ Hz), 127.4 (dt, $^3J_{C-F} = 8.7$ Hz, $^3J_{C-F} = 6.3$ Hz), 121.7 (t, $^1J_{C-F} = 244.9$ Hz), 116.0 (d, $^1J_{C-F} = 221.1$ Hz), 42.5 (t, $^2J_{C-F} = 28.4$ Hz), 42.0 (t, $^3J_{C-F} = 4.9$ Hz), 30.8 (t, $^3J_{C-F} = 3.7$ Hz). $^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ -101.84 (AB system, $^2J_{F-F} = 249.2$ Hz, $^6J_{F-F} = 2.5$ Hz), -103.71 (AB system, $^2J_{F-F} = 249.2$ Hz, $^6J_{F-F} = 2.5$ Hz), -109.98 (t, $^6J_{C-F} = 2.5$ Hz). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -101.84 (ABXX' system, ddd, $^2J_{F-F} = 249.2$ Hz, $^3J_{F-H} = 12.9$ Hz, $^6J_{F-F} = 2.5$ Hz), -103.71 (ABXX' system, ddd, $^2J_{F-F} = 249.2$ Hz, $^3J_{F-H} = 16.0$ Hz, $^6J_{F-F} = 2.5$ Hz), -109.89 to -110.08 (m). FT-IR (cm$^{-1}$): 3190, 3089, 2922, 1682, 1606, 1512, 1304, 1271, 1219, 1148, 1070, 1043, 994, 844, 841, 797, 598. HRMS (ESI): calcd. for [M+Na]+ (C$_{11}$H$_{10}$NOF$_3$Na) = 252.0607; found: 252.0608 (0 ppm).

II.F.5. 4-(Difluoro(4-methoxyphenyl)methyl)pyrrolidin-2-one (7f):

Starting from 50 mg (0.165 mmol) of methyl 4,4-difluoro-4-(4-methoxyphenyl)-3-(nitromethyl)butanoate 6f we obtained 36 mg of 7f (92%) as a colorless solid; $R_f = 0.2$ (DCM / Methanol: 95/5). mp = 141 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.41 – 7.33 (m, 2H), 6.98 (bs, 1H, NH),
6.96 – 6.89 (m, 1H), 3.82 (s, 3H), 3.47 (dd, 3JH-H = 10.0 Hz, 3JH-H = 7.1 Hz, 1H), 3.38 (t, 3JH-H = 10.0 Hz, 3JH-H = 9.8 Hz, 1H), 3.31 – 3.09 (m, 1H, H8), 2.48 (dd, 3JH-H = 17.3 Hz, 3JH-H = 8.0 Hz, 1H), 2.34 (dd, 3JH-H = 17.3 Hz, 3JH-H = 9.7 Hz, 1H). 13C NMR (75 MHz, CDCl3) δ 176.7, 161.0 (t, 5JC-F = 1.7 Hz), 127.5 (t, 1JC-F = 27.0 Hz), 126.7 (t, 3JC-F = 6.2 Hz), 122.1 (t, 1JC-F = 244.2 Hz), 114.1, 55.45, 42.4 (t, 2JC-F = 28.9 Hz), 42.1 (t, 3JC-F = 4.7 Hz), 30.9 (t, 3JC-F = 3.6 Hz).

19F {H} NMR (282 MHz, CDCl3) δ -101.33 (A/B system, 2JF-F = 247.5 Hz), -102.94 (A/B system, 2JF-F = 247.5 Hz). 19F NMR (282 MHz, CDCl3) δ -63.03 (s), δ -103.38 (A/B system, 2JF-F = 250.5 Hz), -105.32 (A/B system, 2JF-F = 250.5 Hz). 19F NMR (282 MHz, CDCl3) δ -63.03 (s), δ -103.38 (ABX system, 2JF-F = 250.5 Hz, 3JF-H = 13.1 Hz), -105.32 (ABX system, dd, 2JF-F = 247.5 Hz, 3JF-H = 15.4 Hz). FT-IR (cm⁻¹): 3393, 3217, 2987, 2902, 1669, 1516, 1496, 1303, 1178, 1055, 1024, 1006, 993, 837, 822, 581. HRMS (ESI): calcd. for [M+Na]+ (C12H13NO2F2Na) = 302.0546; found: 302.0545 (0 ppm).

II.F.6. 4-(Difluoro(4-(trifluoromethyl)phenyl)methyl)pyrrolidin-2-one (7g):

Starting from 50 mg (0.147 mmol) of methyl 4,4-difluoro-3-(nitromethyl)-4-(4-(trifluoromethyl)phenyl)butanoate 6g we obtained 39 mg of 7g (95%) as a colorless solid; Rf = 0.2 (DCM / Methanol: 95/5). mp = 125 °C. 1H NMR (300 MHz, CD3CN) δ 7.84 – 7.79 (m, 2H), 7.76 – 7.68 (m, 2H), 6.21 (s, 1H), 3.49 – 3.21 (m, 3H), 2.42 – 2.25 (m, 2H). 13C NMR (75 MHz, CD3CN) δ 176.2, 140.2 (tq, 3JC-F = 26.9 Hz, 5JC-F = 1.3 Hz), 132.7 (qt, 3JC-F = 32.5 Hz, 5JC-F = 1.8 Hz), 127.2 (t, 3JC-F = 6.3 Hz), 126.8 (q, 3JC-F = 3.9 Hz), 124.9 (q, 1JC-F = 271.5 Hz), 123.1 (t, 1JC-F = 243.9 Hz), 42.4 (t, 2JC-F = 27.0 Hz), 42.1 (t, 3JC-F = 5.0 Hz), 31.0 (t, 3JC-F = 3.9 Hz). FT-IR (cm⁻¹): 3198, 3107, 2967, 2938, 2902, 1685, 1614, 1516, 1496, 1303, 1249, 1178, 1055, 1024, 1006, 993, 837, 822, 581. HRMS (ESI): calcd. for [M+K]+ (C12H13NO2F2K) = 280.0546; found: 280.0545 (0 ppm).

II.F.7. 4-(1,1-Difluorononyl)pyrrolidin-2-one (7h):

Starting from 50 mg (0.147 mmol) of methyl 4,4-difluoro-3-(nitromethyl)-4-(1,1-difluorononyl)butanoate 6g we obtained 39 mg of 7h (95%) as a colorless solid; Rf = 0.2 (DCM / Methanol: 95/5). mp = 125 °C. 1H NMR (300 MHz, CD3CN) δ 7.84 – 7.79 (m, 2H), 7.76 – 7.68 (m, 2H), 6.21 (s, 1H), 3.49 – 3.21 (m, 3H), 2.42 – 2.25 (m, 2H). 13C NMR (75 MHz, CD3CN) δ 176.2, 140.2 (tq, 3JC-F = 26.9 Hz, 5JC-F = 1.3 Hz), 132.7 (qt, 3JC-F = 32.5 Hz, 5JC-F = 1.8 Hz), 127.2 (t, 3JC-F = 6.3 Hz), 126.8 (q, 3JC-F = 3.9 Hz), 124.9 (q, 1JC-F = 271.5 Hz), 123.1 (t, 1JC-F = 243.9 Hz), 42.4 (t, 2JC-F = 27.0 Hz), 42.1 (t, 3JC-F = 5.0 Hz), 31.0 (t, 3JC-F = 3.9 Hz). FT-IR (cm⁻¹): 3393, 3217, 2987, 2902, 1669, 1624, 1494, 1466, 1413, 1384, 1320, 1283, 1267, 1193, 1173, 1117, 1065, 998, 842, 814, 781, 755, 694, 671, 657, 611. HRMS (ESI): calcd. for [M+Na]+ (C12H13NO2F2Na) = 302.0547; found: 302.0574 (0 ppm).
$^3J_{H-H} = 9.1$ Hz, 2H), 1.91 – 1.68 (m, 2H), 1.58 – 1.39 (m, 2H), 1.26 (s, 10H), 0.86 (d, $^3J_{H-H} = 6.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 176.8, 124.2 (t, $^1J_{C-F} = 242.7$ Hz), 41.9 (t, $^3J_{C-F} = 5.6$ Hz), 40.4 (t, $^2J_{C-F} = 26.2$ Hz), 35.2 (t, $^2J_{C-F} = 25.0$ Hz), 31.9, 30.9, 29.4, 29.4, 29.2, 22.7, 21.9 (t, $^3J_{C-F} = 4.3$ Hz), 14.2.

$^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ δ -106.26 (A B system, $^2J_{F-F} = 244.4$ Hz), -107.69 (A B system, $^2J_{F-F} = 244.4$ Hz). FT-IR (cm$^{-1}$): 3239, 2958, 2919, 2872, 2854, 1682, 1471, 1393, 1276, 1236, 1222, 1199, 1167, 1133, 1055, 966, 923, 761, 723, 667. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{13}$H$_{23}$NOF$_2$Na) = 270.1640; found: 270.1643 (1 ppm).

II.G. Synthesis of the N-Boc protected γ-lactams

II.G.1. Representative procedure: Synthesis of tert-butyl 4-(difluoro(4-fluorophenyl)methyl)-2-oxopyrrolidine-1-carboxylate (8e)

To a stirred solution of gem-difluorinated-γ-lactam 7e (500 mg, 2.18 mmol) in acetonitrile (15 mL) was added at room temperature di-tert-butyl dicarbonate (Boc$_2$O) (620 mg, 2.8 mmol) and DMAP (20 mol %). The reaction mixture was stirred for a further 4 h at room temperature, then concentrated under reduced pressure, and purified by chromatography on silica gel to afford 8e as a colorless solid (620 mg, 86%).

$R_f = 0.5$ (Cyclohexane / Ethyl Acetate: 6/4). mp = 125 °C. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.50 – 7.41 (m, 2H), 7.19 – 7.09 (m, 2H), 3.85 – 3.73 (m, 2H), 3.14 – 2.92 (m, 1H), 2.68 (dd, $^2J_{H-H} = 17.8$ Hz, $^3J_{H-H} = 8.2$ Hz, 1H), 2.56 (dd, $^2J_{H-H} = 17.8$ Hz, $^3J_{H-H} = 9.4$ Hz, 1H), 1.51 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.2, 164.0 (dt, $^1J_{C-F} = 250.8$ Hz, $^5J_{C-F} = 2.0$ Hz), 149.8, 130.9 (td, $^2J_{C-F} = 27.0$ Hz, $^4J_{C-F} = 3.3$ Hz), 127.4 (dt, $^3J_{C-F} = 8.8$ Hz, $^3J_{C-F} = 6.3$ Hz), 121.4 (t, $^1J_{C-F} = 245.4$ Hz), 116.2 (d, $^2J_{C-F} = 22.1$ Hz), 83.6, 45.8 (t, $^3J_{C-F} = 4.7$ Hz), 38.7 (t, $^2J_{C-F} = 28.8$ Hz), 33.4 (t, $^3J_{C-F} = 3.7$ Hz ), 28.1. $^{19}$F (H) NMR (282 MHz, CDCl$_3$) δ δ -102.40 (ABX system, dd, $^2J_{F-F} = 249.7$ Hz, $^6J_{F-F} = 2.0$ Hz), -103.48 (ABX system, dd, $^2J_{F-F} = 249.7$ Hz, $^6J_{F-F} = 2.0$ Hz), -109.67 (t, $^6J_{F-F} = 2.0$ Hz). $^{19}$F NMR (282 MHz, CDCl$_3$) δ δ -102.40 (ABXX' system, ddd, $^2J_{F-F} = 249.7$ Hz, $^3J_{F-H} = 13.1$ Hz, $^6J_{F-F} = 2.0$ Hz), -103.48 (ABXX' system, ddd, $^2J_{F-F} = 249.7$ Hz, $^3J_{F-H} = 13.9$ Hz, $^6J_{F-F} = 2.0$ Hz), -109.59 to -109.76 (m). FT-IR (cm$^{-1}$): 2983, 2927, 1771, 1693, 1607, 1514, 1392, 1367, 1298, 1232, 1202, 1178, 1152, 1104, 1068, 1029, 1014, 987, 835, 775. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{18}$H$_{18}$NO$_3$F$_3$Na) = 352.1131; found: 352.1129 (1 ppm).
II.H.  Alkylation at \( \text{C}_4 \) position of the \( \gamma \)-lactams

II.H.1. Representative procedure: Synthesis of tert-butyl 4-(difluoro(4-fluorophenyl)methyl)-3-methyl-2-oxypyrrolidine-1-carboxylate (9a):

To a solution of protected \( \gamma \)-Lactam 8e (120 mg, 0.36 mmol, 1 equiv) in anhydrous THF (10 mL) cooled at -90°C, was added, dropwise under nitrogen, a 1M solution of Lithium bis(trimethylsilyl)amide (LiHMDS) (380 \( \mu \)L, 1.05 equiv). The mixture was stirred for 30 min at temperature below -80 °C before dropwise addition, of methyl iodide (0.38 mmol, 1.05 equiv). The reaction mixture was stirred for additional 30 min below -80 °C and then allowed to warm to r.t. within 2h. The mixture was then treated with water (10 mL), extracted with ethyl acetate (3x10mL). The combined organic phases were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. After purification by chromatography on silica gel, the alkylated \( \gamma \)-lactam 9a was obtained as a white solid 112 mg (90%).

\( R_f = 0.5 \) (Cyclohexane / Ethyl Acetate: 6/4). mp = 120 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.51 – 7.42 (m, 2H), 7.18 – 7.12 (m, 2H), 3.69 (dd, \( ^2J_{H-H} = 11.3 \) Hz, \( ^3J_{H-H} = 8.6 \) Hz, 1H), 3.61 (dd, \( ^2J_{H-H} = 11.3 \) Hz, \( ^3J_{H-H} = 8.5 \) Hz, 1H), 2.80 – 2.52 (m, 2H), 1.51 (s, 9H), 1.13 (d, \( ^3J_{H-H} = 6.6 \) Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 174.1, 164.0 (dt, \( ^1J_{C-F} = 250.7 \) Hz, \( ^5J_{C-F} = 2.0 \) Hz), 150.0, 131.2 (td, \( ^2J_{C-F} = 27.0 \) Hz, \( ^4J_{C-F} = 3.4 \) Hz), 127.4 (dt, \( ^3J_{C-F} = 8.7 \) Hz, \( ^3J_{C-F} = 6.4 \) Hz), 121.6 (t, \( ^1J_{C-F} = 245.5 \) Hz, 1H), 116.2 (d, \( ^3J_{H-H} = 7.1 \) Hz, 2H), 83.6, 47.0 (t, \( ^2J_{C-F} = 27.9 \) Hz), 44.1 (t, \( ^3J_{C-F} = 5.2 \) Hz), 39.1, 28.1, 15.8. \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) -100.19 (ABX system, dd, \( ^2J_{F-F} = 247.9 \) Hz, \( ^4J_{F-F} = 2.5 \) Hz), -102.43 (ABX system, dd, \( ^2J_{F-F} = 248.0 \) Hz, \( ^6J_{F-F} = 2.5 \) Hz), -110.16 (t, \( ^3J_{F-H} = 2.5 \) Hz). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) -100.19 (ABXX’ system, dddd, \( ^2J_{F-F} = 247.9 \) Hz, \( ^3J_{F-H} = 12.6 \) Hz, \( ^6J_{F-F} = 2.5 \) Hz), -102.43 (ABXX’ system, ddd, \( ^2J_{F-F} = 248.0 \) Hz, \( ^3J_{F-H} = 14.5 \) Hz, \( ^6J_{F-F} = 2.5 \) Hz), -110.10 to -110.21 (m). HRMS (ESI): calcd. for [M+Na]\(^+\)(C\(_{17}\)H\(_{20}\)NO\(_3\)F\(_3\)Na)= 366.1287; found: 366.1289 (0 ppm); calcd. for [M+K]\(^+\)(C\(_{17}\)H\(_{20}\)NO\(_3\)F\(_3\)K)= 382.1027; found: 382.1023 (1 ppm).

The stereochemistry of this molecule has been established through 2D COSY, 2D NOESY (\(^1\)H,\(^1\)H) and 2D HOESY (\(^{19}\)F,\(^1\)H) experiments: see added spectra.
II.H.2. Tert-butyl -3-benzyl-4-(difluoro(4-fluorophenyl)methyl)-2-oxopyrrolidine-1-carboxylate (9b)

Starting from 120 mg (0.364 mmol) protected γ-lactam 8e we obtained 94 mg of 9b (62%) as a colorless solid; Rf = 0.6 (Cyclohexane / Ethyl Acetate: 6/4). mp = 126 °C. 1H NMR (300 MHz, C6D6) δ 7.05 – 6.92 (m, 5H), 6.87 – 6.77 (m, 2H), 6.64 – 6.47 (m, 2H), 3.62 (dd, 2JH-H = 11.5 Hz, 3JH-H = 6.5 Hz, 1H), 3.18 (dd, 2JH-H = 11.5 Hz, 3JH-H = 8.7 Hz, 1H), 2.92 (dd, 2JH-H = 13.4 Hz, 3JH-H = 5.6 Hz, 1H), 2.85 – 2.75 (m, 1H), 2.70 (dd, 2JH-H = 13.4, 3JH-H = 5.2 Hz, 1H), 2.51 – 2.31 (m, 1H), 1.42 (s, 9H).

13C NMR (75 MHz, C6D6) δ 171.8, 163.9 (dt, 1JC-F = 249.6 Hz, 5JF-F = 1.9 Hz), 150.6, 137.7, 131.1 (td, 2JC-F = 27.0 Hz, 4JF-F = 3.2 Hz), 130.0, 128.8, 127.6 (dt, 3JC-F = 8.7 Hz, 1JC-F = 6.3 Hz), 127.0, 122.3 (t, 1JC-F = 245.9 Hz), 115.9 (d, 2JC-F = 22.0 Hz), 82.8, 45.9 (dd, 3JC-F = 2.9 Hz, 3JF-F = 2.5 Hz), 44.1 (t, 3JC-F = 5.0 Hz), 41.7 (t, 2JC-F = 27.5 Hz), 35.3, 28.0, 27.2. 19F {H} NMR (282 MHz, CDCl3) δ -100.07 (A'BX system, dd, 2JF-F = 249.1 Hz, 6JF-F = 2.5 Hz), -109.93 (t, 6JF-F = 2.5 Hz). 19F NMR (282 MHz, CDCl3) δ -100.07 (ABXX' system, ddd, 2JF-F = 249.1 Hz, 3JF-H = 12.8 Hz, 6JF-F = 2.5 Hz), -109.86 to -110.01 (m). FT-IR (cm⁻¹): 3674, 2988, 2972, 2923, 2902, 1749, 1708, 1605, 1513, 1455, 1408, 1393, 1365, 1306, 1280, 1262, 1230, 1151, 1103, 1042, 978, 857, 843, 818, 779, 703. HRMS (ESI): calcd. for [M+Na]+(C23H24NO3F3Na)= 442.1600; found: 442.1600 (0 ppm).

II.H.3. Tert-butyl (3R,4R)-3-allyl-4-(difluoro(4-fluorophenyl)methyl)-2-oxopyrrolidine-1-carboxylate (9c)

Starting from 120 mg (0.364 mmol) protected γ-lactam 8e we obtained 57 mg of 9c (42%) as a colorless solid; Rf = 0.7 (Cyclohexane / Ethyl Acetate: 7/3). mp = 77 °C. 1H NMR (300 MHz, C6D6) δ 6.96 – 6.88 (m, 2H), 6.68 – 6.58 (m, 2H), 5.59 – 5.42 (m, 1H), 4.90 – 4.84 (m, 1H), 4.83 – 4.76 (m, 1H), 3.61 (dd, 2JH-H = 11.4 Hz, 3JH-H = 7.4 Hz, 1H), 3.45 (dd, 2JH-H = 11.4 Hz, 3JH-H = 8.7 Hz, 1H), 2.63 – 2.51 (m, 1H), 2.51 – 2.29 (m, 1H), 2.04 – 1.87 (m, 1H), 1.43 (s, 9H). 13C NMR (75 MHz, C6D6) δ 171.3, 164.0 (dt, 1JC-F = 249.8 Hz, 5JF-F = 1.8 Hz), 150.7, 134.0, 131.4 (td, 2JC-F = 27.1 Hz, 4JC-F = 3.2 Hz), 127.6 (dt, 3JC-F = 8.7 Hz, 1JC-F = 6.4 Hz), 122.1 (t, 1JC-F = 245.8 Hz), 118.8, 115.9 (d, 2JC-F = 22.0 Hz), 82.8, 44.1 (t, 3JC-F = 5.0 Hz), 43.8 (dd, 3JC-F = 3.5 Hz, 1JC-F = 1.7 Hz), 42.1 (t, 1JC-F = 27.7 Hz), 33.7, 28.0. 19F {H} NMR (282 MHz, CDCl3) δ -100.67 (ABX system, dd, 2JF-F = 249.1 Hz, 6JF-F = 2.5 Hz), -109.86 to -110.01 (m).
Hz), -103.56 (ABX system, dd, $^{2}J_{F-F} = 248.7$ Hz, $^{6}J_{F-F} = 2.5$ Hz), -109.66 (t, $^{6}J_{F-F} = 2.5$ Hz). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -100.67 (ABXX’ system, ddd, $^{2}J_{F-F} = 248.7$ Hz, $^{3}J_{F-H} = 12.2$ Hz, $^{6}J_{F-F} = 2.5$ Hz), -103.56 (ABXX’ system, ddd, $^{2}J_{F-F} = 248.7$ Hz, $^{3}J_{F-H} = 14.2$ Hz, $^{6}J_{F-F} = 2.5$ Hz), -109.53 to -109.77 (m).

FT-IR (cm$^{-1}$): 3674, 2986, 2902, 1773, 1693, 1605, 1517, 1403, 1369, 1287, 1260, 1145, 1102, 1051, 1027, 984, 918, 840, 779. HRMS (ESI): calcd. for [M+Na]$^{+}$($C_{19}H_{22}NO_{3}F_{3}$Na)= 392.1444; found: 392.1447 (1 ppm).

II.H.4. Tert-butyl-4-(difluoro(4-fluorophenyl)methyl)-2-oxo-3-(prop-2-yn-1-yl)pyrrolidine-1-carboxylate (9d)

Starting from 120 mg (0.364 mmol) protected γ-lactam 8e we obtained 40 mg of 9d (30%) as a colorless liquid; R$_{f}$ = 0.3 (Cyclohexane / Ethyl Acetate: 8/2). $^{1}$H NMR (300 MHz, CDCl$_3$) δ 7.51 – 7.44 (m, 2H), 7.18 – 7.09 (m, 2H), 3.73 (dd, $^{2}J_{H-H} = 11.2$ Hz, $^{3}J_{H-H} = 9.2$ Hz, 1H), 3.65 (dd, $^{2}J_{H-H} = 11.2$ Hz, $^{3}J_{H-H} = 8.1$ Hz, 1H), 3.35 – 3.08 (m, 1H), 2.87 – 2.73 (m, 2H), 2.23 – 2.11 (m, 1H), 1.98 (t, $^{4}J_{C-F} = 2.6$ Hz, 1H), 1.50 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.5, 164.0 (dt, $^{1}J_{C-F} = 250.9$ Hz, $^{5}J_{C-F} = 2.0$ Hz), 149.7, 130.9 (td, $^{2}J_{C-F} = 26.9$ Hz, $^{4}J_{C-F} = 3.3$ Hz), 127.4 (dt, $^{3}J_{C-F} = 8.7$ Hz, $^{3}J_{C-F} = 6.3$ Hz), 121.5 (t, $^{1}J_{C-F} = 245.5$ Hz), 116.1 (d, $^{2}J_{C-F} = 22.1$ Hz), 83.7, 79.4, 71.8, 44.2 (t, $^{3}J_{C-F} = 5.1$ Hz), 42.7 (t, $^{3}J_{C-F} = 2.6$ Hz), 42.0 (t, $^{2}J_{C-F} = 27.9$ Hz), 28.0, 19.2. $^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ -101.14 (ABX system, dd, $^{2}J_{F-F} = 248.8$ Hz, $^{6}J_{F-F} = 2.6$ Hz), -102.46 (ABX system, dd, $^{2}J_{F-F} = 248.8$ Hz, $^{6}J_{F-F} = 2.6$ Hz), -109.43 (t, $^{6}J_{F-F} = 2.6$ Hz). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -101.44 (ABX system, dd, $^{2}J_{F-F} = 248.8$ Hz, $^{6}J_{F-F} = 2.6$ Hz), -102.46 (ABX system, dd, $^{2}J_{F-F} = 248.8$ Hz, $^{6}J_{F-F} = 2.6$ Hz), -109.43 to -109.53 (m). FT-IR (cm$^{-1}$): 2982, 2921, 1788, 1752, 1717, 1609, 1514, 1393, 1367, 1310, 1290, 1235, 1152, 1083, 1045, 998, 840, 777, 627, 603. HRMS (ESI): calcd. for [M-C$_{4}$H$_{6}$Na]$^{+}$($C_{15}H_{12}NO_{3}F_{3}$Na)= 334.0662; found: 334.0662 (0 ppm).
II.I. Addition of nitroalkanes on the alkenes bearing the gem-difluoroalkyl chains

II.I.1. Representative procedure: Synthesis of methyl-3-(difluoro(4-fluorophenyl)methyl)-4-nitrohexanoate (10e and 11e)

To methyl (Z)-4,4-difluoro-4-phenylbut-2-enoate 5e (200 mg, 0.87 mmol) was added 1-nitropropane (155 μL, 1.7 mmol) and potassium carbonate (360 mg, 2.6 mmol) in DMSO (5 ml). The reaction mixture was stirred at room temperature and it was controlled using TLC. At the end, saturated NH$_4$Cl (5 mL) was added and the reaction mixture was extracted with ethyl acetate (3x10mL). The combined organic layers were washed with water (3x5mL), dried over Na$_2$SO$_4$ and concentrated under vacuum. After purification by chromatography on silica gel, Methyl-3-(difluoro(4-fluorophenyl)methyl)-4-nitrohexanoate 10e and 11e were obtained as a colorless oil 184 mg (66%, 1:1 mixture of 10e / 11e). These diastereoisomers have been separated by chromatography on SiO$_2$.

II.I.2. Methyl-3-(difluoro(4-fluorophenyl)methyl)-4-nitrohexanoate (10e)

Colorless liquid (92 mg, 33%); R$_f$ = 0.4 (Cyclohexane / Ethyl Acetate: 8/2). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.53 – 7.43 (m, 2H), 7.20 – 7.09 (m, 2H), 4.69 (ddd, $^3$J$_{H-H}$ = 11.3 Hz, $^3$J$_{H-H}$ = 5.0 Hz, $^3$J$_{H-H}$ = 3.1 Hz, 1H), 3.70 – 3.53 (m, 1H), 3.57 (s, 3H), 2.69 – 2.50 (m, 2H), 2.12 – 1.74 (m, 2H), 0.96 (t, $^3$J$_{H-H}$ = 7.3 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.8, 164.1 (dt, $^1$J$_{C-F}$ = 251.2 Hz, $^5$J$_{C-F}$ = 2.0 Hz), 130.4 (td, $^2$J$_{C-F}$ = 26.6 Hz, $^4$J$_{C-F}$ = 3.3 Hz), 127.9 (ddd, $^3$J$_{C-F}$ = 8.8 Hz, $^3$J$_{C-F}$ = 6.9 Hz, $^3$J$_{C-F}$ = 6.0 Hz), 122.2 (t, $^1$J$_{C-F}$ = 248.6 Hz), 116.1 (d, $^2$J$_{C-F}$ = 22.1 Hz), 87.6 (t, $^3$J$_{C-F}$ = 2.1 Hz), 52.4, 46.6 (t, $^2$J$_{C-F}$ = 26.1 Hz), 29.7 (dd, $^3$J$_{C-F}$ = 4.3, $^3$J$_{C-F}$ = 3.0 Hz), 23.2 (t, $^4$J$_{C-F}$ = 1.5 Hz), 10.8. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -95.82 (A$^2$B$^2$X system, dd, $^2$J$_{F-F}$ = 251.4 Hz, $^6$J$_{F-F}$ = 3.1 Hz), -101.06 (ABX system, dd, $^2$J$_{F-F}$ = 251.4 Hz, $^6$J$_{F-F}$ = 2.7 Hz). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -95.82 (ABXX system, ddd, $^2$J$_{F-F}$ = 251.4 Hz, $^3$J$_{F-H}$ = 11.5 Hz, $^6$J$_{F-F}$ = 2.7 Hz). FT-IR (cm$^{-1}$): 2954, 1738, 1609, 1554, 1514, 1459, 1438, 1374, 1343, 1314, 1266, 1233, 1196, 1163, 1117, 1104, 1054, 1013, 994, 840, 814. HRMS (ESI): calcd. for [M+Na]$^+$($C_{14}$H$_{16}$NO$_4$F$_3$Na) = 342.0924; found: 342.0925 (0 ppm).
II.I.3.  Methyl-3-(difluoro(4-fluorophenyl)methyl)-4-nitrohexanoate (11e)

Colorless liquid (92 mg, 33%); \( R_t = 0.3 \) (Cyclohexane / Ethyl Acetate: 8/2). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.54 – 7.45 (m, 2H), 7.19 – 7.10 (m, 2H), 4.66 – 4.55 (m, 1H), 3.61 (s, 3H), 3.34 – 3.15 (m, 1H), 2.95 (dd, \(^3\)J\(_{H-H} = 17.9 \) Hz, \(^3\)J\(_{H-H} = 4.0 \) Hz, 1H), 2.69 (dd, \(^2\)J\(_{H-H} = 17.9 \) Hz, \(^3\)J\(_{H-H} = 7.2 \) Hz, 1H), 2.07 (ddq, \(^2\)J\(_{H-H} = 14.5 \) Hz, \(^3\)J\(_{H-H} = 10.3 \) Hz, \(^3\)J\(_{H-H} = 7.3 \) Hz, 1H), 1.75 (dq, \(^2\)J\(_{H-H} = 14.7 \) Hz, \(^3\)J\(_{H-H} = 7.3 \) Hz, \(^3\)J\(_{H-H} = 4.8 \) Hz, 1H), 0.93 (t, \(^3\)J\(_{H-H} = 7.3 \) Hz, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 172.2, 164.1 (dt, \(^1\)J\(_{C-F} = 250.9, \(^3\)J\(_{C-F} = 2.0 \) Hz), 130.5 (td, \(^2\)J\(_{C-F} = 26.6, \(^4\)J\(_{C-F} = 3.3 \) Hz), 128.1 (dt, \(^3\)J\(_{C-F} = 8.8, \(^5\)J\(_{C-F} = 6.4 \) Hz), 122.1 (t, \(^1\)J\(_{C-F} = 248.6 \) Hz), 116.0 (d, \(^2\)J\(_{C-F} = 22.1 \) Hz), 86.7 (dd, \(^3\)J\(_{C-F} = 3.8, \(^5\)J\(_{C-F} = 1.4 \) Hz), 52.4, 46.8 (dd, \(^2\)J\(_{C-F} = 27.3 \) Hz, \(^3\)J\(_{C-F} = 26.3 \) Hz), 28.8 (dd, \(^2\)J\(_{C-F} = 3.4 \) Hz, \(^3\)J\(_{C-F} = 2.9 \) Hz, 10.5. \(^19\)F (H) NMR (282 MHz, CDCl\(_3\)) \( \delta \) -96.86 (ABX system, dd, \(^2\)J\(_{F-F} = 253.7 \) Hz, \(^6\)J\(_{F-F} = 2.5 \) Hz, -101.92 (ABX system, dd, \(^2\)J\(_{F-F} = 253.6 \) Hz, \(^6\)J\(_{F-F} = 1.8 \) Hz), -109.51 (t, \(^6\)J\(_{F-F} = 2.6 \) Hz). \(^19\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) -96.86 (ABXX' system, ddd, \(^2\)J\(_{F-F} = 253.7 \) Hz, \(^3\)J\(_{H-H} = 15.1 \) Hz, \(^5\)J\(_{F-F} = 2.5 \) Hz), -101.92 (ABXX' system, ddd, \(^2\)J\(_{F-F} = 253.6 \) Hz, \(^3\)J\(_{H-H} = 17.3 \) Hz, \(^5\)J\(_{F-F} = 1.8 \) Hz), -109.39 to -109.66 (m). FT-IR (cm\(^{-1}\)): 2973, 2957, 2925, 1739, 1609, 1555, 1514, 1460, 1438, 1413, 1373, 1323, 1299, 1275, 1238, 1196, 1164, 1126, 1104, 1081, 1055, 1005, 841. HRMS (ESI): calcld. for [M+Na]\(^+\)(C\(_{14}H\(_{15}\)NO\(_4\)F\(_2\)Na)= 342.0924; found: 342.0926 (1 ppm).

II.I.4.  4-(Difluoro(4-fluorophenyl)methyl)-5-ethylpyrrolidin-2-one (12e)

Starting from 50 mg (0.364 mmol) of methyl 3-(difluoro(4-fluorophenyl)methyl)-4-nitrohexanoate 10e we obtained 24 mg of 12e (60%) as a colorless waxy solid; \( R_t = 0.5 \) (DCM / Methanol: 95/5). \(^1\)H NMR (300 MHz, CD\(_3\)CN) \( \delta \) 7.65 – 7.54 (m, 2H), 7.28 – 7.18 (m, 2H), 6.53 (bs, 1H), 3.66 (dt, \(^3\)J\(_{H-H} = 7.5 \) Hz, \(^3\)J\(_{H-H} = 4.9 \) Hz, 1H), 3.49 – 3.25 (m, 1H), 2.53 (dd, \(^2\)J\(_{H-H} = 16.1, \(^3\)J\(_{H-H} = 12.0 \) Hz, 1H), 2.07 (dd, \(^2\)J\(_{H-H} = 16.1 \) Hz, \(^3\)J\(_{H-H} = 8.4 \) Hz, 1H), 1.92 – 1.61 (m, 2H), 0.88 (t, \(^3\)J\(_{H-H} = 7.5 \) Hz, 3H). \(^13\)C NMR (75 MHz, CD\(_3\)CN) \( \delta \) 172.6, 164.6 (dt, \(^1\)J\(_{C-F} = 247.5 \) Hz, \(^5\)J\(_{C-F} = 2.1 \) Hz), 133.6 (td, \(^2\)J\(_{C-F} = 26.9 \) Hz, \(^4\)J\(_{C-F} = 3.1 \) Hz), 128.6 (dt, \(^3\)J\(_{C-F} = 8.9 \) Hz, \(^2\)J\(_{C-F} = 6.4 \) Hz), 123.1 (t, \(^{1}\)J\(_{C-F} = 243.9 \) Hz), 116.7 (d, \(^2\)J\(_{C-F} = 22.2 \) Hz), 61.9 (d, \(^3\)J\(_{C-F} = 2.9 \) Hz), 45.3 (t, \(^{2}\)J\(_{C-F} = 27.2 \) Hz), 30.75 (dd, \(^3\)J\(_{C-F} = 5.9 \) Hz, \(^3\)J\(_{C-F} = 1.6 \) Hz), 23.1 (t, \(^{4}\)J\(_{C-F} = 2.1 \) Hz), 10.0 (t, \(^{5}\)J\(_{C-F} = 3.2 \) Hz). \(^19\)F (H) NMR (282 MHz, CDCl\(_3\)) \( \delta \) -98.38 (ABX system, dd, \(^2\)J\(_{F-F} = 249.0 \) Hz, \(^6\)J\(_{F-F} = 2.7 \) Hz), -100.06 (ABX system, dd, \(^2\)J\(_{F-F} = 249.0 \) Hz, \(^6\)J\(_{F-F} = 2.7 \) Hz), -110-19 (t, \(^{6}\)J\(_{F-F} = 2.7 \) Hz). \(^19\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) -98.38 (ABXX' system, ddd, \(^2\)J\(_{F-F} = 249.0 \) Hz, \(^3\)J\(_{F-H} = 20.8 \) Hz, \(^6\)J\(_{F-F} = 2.7 \) Hz), -100.06 (ABXX' system, ddd, \(^2\)J\(_{F-F} = 249.0 \) Hz, \(^3\)J\(_{F-H} = 10.8 \) Hz, \(^6\)J\(_{F-F} = 2.7 \) Hz

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Hz), -110.09 to -110.29 (m). FT-IR (cm⁻¹): 2971, 2926, 1672, 1607, 1515, 1397, 1303, 1260, 1238, 1198, 1048, 1028, 1009, 964, 834, 790, 614. HRMS (ESI): calcd. for [M+Na]+(C₁₃H₁₄NOF₃Na)= 280.0922; found: 280.0923 (0 ppm).

II.I.5. (4S,5R)-4-(Difluoro(4-fluorophenyl)methyl)-5-ethylpyrrolidin-2-one (13e)

Starting from 50 mg (0.364 mmol) methyl 3-(difluoro(4-fluorophenyl)methyl)-4-nitrohexanoate 11e we obtained 26 mg of 13e (64%) as a colorless waxy solid; Rf = 0.39 (DCM / Methanol: 95/5). ¹H NMR (300 MHz, CD₃CN) δ 7.61 – 7.53 (m, 2H), 7.30 – 7.17 (m, 2H), 6.62 (bs, 1H), 3.64 – 3.56 (m, 1H), 3.05 – 2.78 (m, 1H), 2.42 (dd, 2J_H-H = 17.6 Hz, 3J_H-H = 10.0 Hz, 1H), 2.25 (dd, 2J_H-H = 17.6 Hz, 3J_H-H = 5.4 Hz, 1H), 1.51 – 1.28 (m, 2H), 0.79 (t, 3J_H-H = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CD₃CN) δ 175.3, 164.7 (dt, 1J_C-F = 247.6, 5J_C-F = 2.0 Hz), 132.7 (td, 2J_C-F = 27.1 Hz, 4J_C-F = 3.2 Hz), 128.9 (dt, 3J_C-F = 8.9 Hz, 3J_C-F = 6.4 Hz), 123.8 (t, 1J_C-F = 244.1 Hz), 116.6 (d, 2J_C-F = 22.2 Hz), 55.9 (t, 3J_C-F = 3.9 Hz), 47.2 (t, 2J_C-F = 26.9 Hz), 31.3 (t, 3J_C-F = 3.9 Hz), 30.1, 9.8. ¹⁹F {H} NMR (282 MHz, CDCl₃) δ -101.05 (AB system, dd, 2J_F-F = 248.6 Hz, 6J_F-F = 2.3 Hz), -104.11 (AB system, dd, 2J_F-F = 248.6 Hz, 6J_F-F = 2.3 Hz). ¹⁹F NMR (282 MHz, CDCl₃) δ -101.05 (ABX system, dd, 2J_F-F = 248.6 Hz, 6J_F-F = 2.3 Hz), -109.93 (t, 6J_F-F = 2.3 Hz). ¹⁹F NMR (282 MHz, CDCl₃) δ -101.05 (ABXX' system, ddd, 2J_F-F = 248.6 Hz, 3J_F-H = 13.0 Hz, 6J_F-F = 2.3 Hz), -104.11 (ABXX' system, ddd, 2J_F-F = 248.6 Hz, 3J_F-H = 17.3 Hz, 6J_F-F = 2.3 Hz), -109.84 to -110.03 (m). FT-IR (cm⁻¹): 2968, 2935, 2882, 1697, 1609, 1514, 1314, 1273, 1235, 1163, 1042, 1010, 840. HRMS (ESI): calcd. for [M+Na]+(C₁₃H₁₄NOF₃Na)= 280.0920; found: 280.0923 (1 ppm).

The stereochemistry of this molecule has been established through 2D NOESY (¹H,¹H) experiments: see added spectra.

II.I.6. Representative procedure: Synthesis of methyl 3-(difluoro(4-fluorophenyl)methyl)-4-nitro-5-phenylpentanoate (14e) and (15e)

To methyl (Z)-4,4-difluoro-4-phenylbut-2-enoate 5a (200 mg, 0.87 mmol) was added 1-(2-nitroethyl)benzene (262 mg, 1.7 mmol) and potassium carbonate (360 mg, 2.6 mmol) in DMSO (5 ml). The reaction mixture was stirred at room temperature and it was controlled using TLC. At
the end saturated NH₄Cl (5 mL) was added and the reaction mixture was extracted with ethyl acetate (3x10mL). The organic layers were separated, washed with water (3x5mL), dried over Na₂SO₄ and concentrated under vacuum. After purification by chromatography on silica gel, a 1:1 mixture of unseparable diastereoisomers 14e and 15e was obtained as a colorless oil 275 mg (83 % overall yield).

Rᵣ = 0.5 (Cyclohexane / Ethyl Acetate: 8/2). ¹H NMR (300 MHz, CDCl₃) δ 7.57 – 7.49 (m, 2H), 7.45 – 7.37 (m, 2H), 7.34 – 7.04 (m, 14H), 5.04 (dt, ³J_H-H = 10.5 Hz, ³J_H-H = 4.0 Hz, 1H), 4.91 (ddd, ³J_H-H = 8.7, ³J_H-H = 5.9, ³J_H-H = 2.5 Hz, 1H), 3.77 – 3.65 (m, 1H), 3.64 (s, 3H), 3.60 (s, 3H), 3.42 – 3.15 (m, 4H), 3.12 – 2.94 (m, 2H), 2.87 – 2.64 (m, 3H).¹⁹F {H} NMR (282 MHz, CDCl₃) δ -96.35 (ABX system, dd, ²J_F-F = 251.3 Hz, ⁶J_F-F = 2.8 Hz), -96.70 (A'B'X system, dd, ²J_F-F = 253.4 Hz, ⁶J_F-F = 2.7 Hz), -99.83 (A'BX system, dd, ²J_F-F = 251.2 Hz, ⁶J_F-F = 2.4 Hz), -102.00 (A'B'X system, dd, ²J_F-F = 253.3 Hz, ⁶J_F-F = 2.7 Hz), -108.94 (t, ⁶J_F-F = 2.7 Hz), -109.42 (t, ⁶J_F-F = 2.7 Hz). FT-IR (cm⁻¹): 2956, 2922, 1737, 1609, 1555, 1514, 1371, 1275, 1235, 1197, 1162, 1048, 1001, 840, 699. HRMS (ESI): calcd. for [M+Na]+(C₁₉H₁₈NO₄F₃Na)= 404.1080; found: 404.1083 (1 ppm).

II.I.7. 5-Benzyl-4-(difluoro(4-fluorophenyl)methyl)pyrrolidin-2-one (16e)

Starting from 100 mg (0.262 mmol) of the 1:1 mixture of diastereoisomers 14e and 15e we obtained 56 mg of a 1:1 mixture of 16e and 17e (67% overall yield) as a colorless oil. These two diastereoisomers proved to be very difficult to separate but small quantities required for the spectral analyses could be obtained by preparative TLC using (DCM / Methanol: 98/2).

16e: waxy solid, Rᵣ = 0.5 (DCM / Methanol: 95/5). ¹H NMR (300 MHz, CDCl₃) δ 7.61 – 7.51 (m, 2H), 7.37 – 7.08 (m, 7H), 5.43 (bs, 1H), 3.97 – 3.87 (m, 1H), 3.47 – 3.25 (m, 1H), 3.19 – 3.09 (m, 1H), 2.81 – 2.70 (m, 1H), 2.68 (dd, ³J_H-H = 16.7 Hz, ³J_H-H = 11.5 Hz, 1H), 2.23 (dd, ²J_H-H = 16.7 Hz, ³J_H-H = 8.5 Hz, 1H).¹³C NMR (75 MHz, CDCl₃) δ 174.3, 163.9 (dt, ¹J_C-F = 250.8 Hz, ⁵J_C-F = 1.8 Hz), 137.7, 132.3 (td, ²J_C-F = 26.9 Hz, ⁴J_C-F = 3.3 Hz), 129.3, 129.2, 127.3 (dt, ³J_C-F = 8.7 Hz, ³J_C-F = 6.3 Hz), 127.2,
121.7 (t, $^1J_{CF} = 245.7$ Hz), 116.2 (d, $^2J_{CF} = 22.1$ Hz), 56.6, 46.1 (t, $^2J_{CF} = 27.6$ Hz), 38.1 (t, $^3J_{CF} = 3.7$ Hz), 30.2 (t, $^3J_{CF} = 4.1$ Hz). $^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ -97.75 (ABX system, dd, $^2J_{F-F} = 247.2$ Hz, $^6J_{F-F} = 2.7$ Hz), -98.99 (ABX system, dd, $^2J_{F-F} = 248.9$ Hz, $^6J_{F-F} = 2.7$ Hz), -109.78 (t, $^6J_{F-F} = 2.7$ Hz).

FT-IR (cm$^{-1}$): 3199, 3101, 3060, 3028, 2956, 2925, 2854, 1688, 1605, 1512, 1454, 1385, 1298, 1258, 1239, 1188, 1161, 1078, 1053, 1031, 989, 839, 777, 699.

HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{18}$H$_{16}$NOF$_3$Na)= 342.1076; found: 342.1079 (1 ppm).

The stereochemistry of this molecule has been established through 2D NOESY ($^1$H,$^1$H) experiments: see added spectra.

II.I.8. (4S,5R)-5-benzyl-4-(difluoro(4-fluorophenyl)methyl)pyrrolidin-2-one (17e)

17e: waxy solid; $R_f = 0.5$ (DCM / Methanol: 95/5). $^1$H NMR (300 MHz, CD$_3$CN) δ 7.51 – 7.41 (m, 2H), 7.34 – 6.95 (m, 7H), 6.15 (bs, 1H), 3.86 (td, $^3J_{H-H} = 6.4$ Hz, $^3J_{H-H} = 3.5$ Hz, 1H), 3.07 – 2.86 (m, 1H), 2.68 (d, $^3J_{H-H} = 6.4$ Hz, 2H), 2.32 (dd, $^2J_{H-H} = 17.6$ Hz, $^3J_{H-H} = 9.3$ Hz, 1H), 2.24 (dd, $^2J_{H-H} = 17.6$ Hz, $^3J_{H-H} = 5.4$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 174.5, 163.9 (dt, $^1J_{C-F} = 294.8$ Hz, $^5J_{C-F} = 2.1$ Hz), 136.7, 131.4 (td, $^2J_{C-F} = 27.0$ Hz, $^4J_{C-F} = 3.3$ Hz), 129.2, 129.1, 127.5 (dt, $^3J_{C-F} = 8.7$ Hz, $^3J_{C-F} = 6.3$ Hz), 127.3, 121.9 (t, $^1J_{CF} = 231.2$ Hz), 116.1 (d, $^2J_{CF} = 22.1$ Hz), 55.4 (t, $^3J_{CF} = 3.6$ Hz), 47.5 (t, $^2J_{CF} = 27.6$ Hz), 43.2, 30.98 (t, $^3J_{CF} = 3.8$ Hz). $^{19}$F {H} NMR (282 MHz, CDCl$_3$) δ -101.88 (ABX system, dd, $^2J_{F-F} = 247.1$ Hz, $^6J_{F-F} = 2.5$ Hz), -102.97 (ABX system, dd, $^2J_{F-F} = 250.0$ Hz, $^6J_{F-F} = 2.5$ Hz), -109.81 (t, $^6J_{F-F} = 2.5$ Hz). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -101.88 (ABXX’ system, ddd, $^2J_{F-F} = 247.1$ Hz, $^3J_{F-H} = 14.1$ Hz, $^6J_{F-F} = 2.5$ Hz), -102.97 (ABXX’ system, ddd, $^2J_{F-F} = 250.0$ Hz, $^3J_{F-H} = 15.5$ Hz, $^6J_{F-F} = 2.5$ Hz), -109.69 to -109.88 (m). FT-IR (cm$^{-1}$): 3229, 2924, 2853, 1698, 1608, 1514, 1300, 1271, 1235, 1162, 1056, 840. HRMS (ESI): calcd. for [M+Na]$^+$ (C$_{18}$H$_{16}$NOF$_3$Na)= 342.1076; found: 342.1079 (1 ppm).
III. Copies of 

\[ \text{H (CDCl}_3\text{)} \]

and \[ \text{F (CDCl}_3\text{)} \]

NMR spectra of products.
$^{13}C\{^1H\}\text{H} (\text{CDCl}_3, 75 \text{ MHz})$

![Chemical Structure](image)
$^{19}$F (1H) (CDCl$_3$, 282 MHz)
$^{19}F$ (CDCl$_3$, 282 MHz)

$^{19}F$ (CDCl$_3$, 282 MHz)
$^{1}H$ (CDCl$_3$, 300 MHz)

$^{13}C$ ($^{1}H$) (CDCl$_3$, 75 MHz)
19F \{^1H\} (CDCl$_3$, 282 MHz)

19F (CDCl$_3$, 282 MHz)
$^1$H (CDCl$_3$, 500 MHz)

$^{13}$C {$^1$H} (CDCl$_3$, 126 MHz)
$^{19}$F $^1$H (CDCl$_3$, 471 MHz)

4a

$^{19}$F (CDCl$_3$, 471 MHz)
$^1$H (CDCl$_3$, 500 MHz)

$^{13}$C ($^1$H) (CDCl$_3$, 126 MHz)
\[ \text{\textsuperscript{19}F (CDCl}_3, 471 \text{MHz}) \]

\[ \text{\textsuperscript{13}C (CDCl}_3, 471 \text{MHz}) \]
$^{19}$F (1H) (CDCl$_3$, 471 MHz)

4d

$^{19}$F (CDCl$_3$, 471 MHz)

4d
$^{13}C\{\text{H}_1\}(\text{CD})_3\text{CO, 75 MHz})$

$^{	ext{13C}}\{\text{H}_1\}(\text{CD})_3\text{CO, 75 MHz})$

$^1H\{\text{CD})_3\text{CO, 300 MHz)\}$

$^1H\{\text{CD})_3\text{CO, 300 MHz)\}$
$^{19}$F (CDCl$_3$, 282 MHz)

$^{19}$F $^{1}$H (CDCl$_3$, 282 MHz)
$^{19}$F (1H) (CDCl$_3$, 282 MHz)
$^{19}\text{F} \{ 1\text{H} \} (\text{CDCl}_3, 282 \text{ MHz})$

$^{19}\text{F} (\text{CDCl}_3, 282 \text{ MHz})$
$^{19}$F {1H} (CDCl$_3$, 471 MHz)
$^{19}\text{F} \{1\text{H}\} (\text{CDCl}_3, 471\text{MHz})$

$^{19}\text{F} \{1\text{H}\} (\text{CDCl}_3, 471\text{MHz})$
$\delta$ (CDCl$_3$, 282 MHz)

$\delta$ (CDCl$_3$, 282 MHz)
$^{19}$F ($^1$H) (CDCl$_3$, 282 MHz)
$^{19}F$ (CDCl$_3$, 282 MHz)

$^{19}F$ (CDCl$_3$, 282 MHz)
$^{19}$F (1H) (CDCl$_3$, 471 MHz)

$^{19}$F (CDCl$_3$, 471 MHz)
$^{19}$F (1H) (CDCl$_3$, 471 MHz)
$^1\text{H} \ (\text{CDCl}_3, \ 300 \text{ MHz})$

$^{13}\text{C} \ { ^1\text{H} } \ (\text{CDCl}_3, \ 75 \text{ MHz})$
(1H)_{\text{d}} \{ \text{CDCl}_3, 500 \text{ MHz} \}

69

$\text{H}_1 \{ \text{CDCl}_3, 126 \text{ MHz} \}$

69

Chemical shifts and spectral data are shown for the two spectra.
1H (CDCl₃, 282 MHz)

\( \text{S92} \)
$^{19}$F NMR (CDCl$_3$, 282 MHz):

$^{19}$F NMR spectrum shows signals at various chemical shifts.

$^{1}$H NMR (CDCl$_3$, 282 MHz):

$^{1}$H NMR spectrum shows signals at various chemical shifts.

Chemical structure: [Chemical structure image]

Chemical shifts: [List of chemical shifts]

Integration: [Integration values]

Assignments: [Assignment details]

Additional information: [Additional notes]
$^{19}$F \{1H\} (CDCl$_3$, 282 MHz)
$^1$H (CDCl$_3$, 300 MHz)

$^{13}$C ($^1$H) (CDCl$_3$, 75 MHz)
$^{19}F$ (CDCl$_3$, 282 MHz)

$^{79}$

$^{19}F$ (CDCl$_3$, 282 MHz)

$^{79}$
$^{19}$F (CDCl$_3$, 282 MHz)

$^{19}$F (1H) (CDCl$_3$, 282 MHz)
$^1$H (CDCl$_3$, 300 MHz)

$^{13}$C ($^1$H) (CDCl$_3$, 75 MHz)
$^{19}\text{F} \{1\text{H}\} \ (\text{CDCl}_3, \ 282 \text{ MHz})$

$^{19}\text{F} \ (\text{CDCl}_3, \ 282 \text{ MHz})$
$^1$H (CDCl$_3$, 300 MHz)

$^1$H (C$_6$D$_6$, 300 MHz)
S112
$^{19}$F $\{^1$H$\}$ (C$_6$D$_6$, 376 MHz)

$^{19}$F (C$_6$D$_6$, 376 MHz)
2D HOESY \(^{19}\text{F},^{1}\text{H}\) (C\(_6\)D\(_6\), 400 MHz)

2D COSY \(^{1}\text{H},^{1}\text{H}\) (C\(_6\)D\(_6\), 300 MHz)
$^{19}$F {1H} (CDCl$_3$, 282 MHz)

$^{19}$F (CDCl$_3$, 282 MHz)
$^{19}$F {1H} (CDCl₃, 282 MHz)

$^{19}$F (CDCl₃, 282 MHz)
(±) 9d

$^1$H (CDCl$_3$, 300 MHz)

(±) 9d

$^{13}$C $^1$H (CDCl$_3$, 75 MHz)
$^{19}$F $^1$H (CDCl$_3$, 282 MHz)

$^{19}$F (CDCl$_3$, 282 MHz)
$\text{f1 (ppm)}$

$0.0 \; 0.5 \; 1.0 \; 1.5 \; 2.0 \; 2.5 \; 3.0 \; 3.5 \; 4.0 \; 4.5 \; 5.0 \; 5.5 \; 6.0 \; 6.5 \; 7.0 \; 7.5 \; 8.0 \; 8.5 \; 9.0$

$\text{f1 (ppm)}$

$-10 \; 0 \; 10 \; 20 \; 30 \; 40 \; 50 \; 60 \; 70 \; 80 \; 90 \; 100 \; 110 \; 120 \; 130 \; 140 \; 150 \; 160 \; 170 \; 180 \; 190 \; 200 \; 210 \; 220$

$\text{C\{H\}} \quad \text{(CDCl}_3, \; 300 \; \text{MHz})$

$\text{H} \quad \text{(CDCl}_3, \; 300 \; \text{MHz})$

$\text{13C \{H\} \quad \text{(CDCl}_3, \; 75 \; \text{MHz})$
$^{19}\text{F} \{1\text{H}\} (\text{CDCl}_3, 282 \text{ MHz})$

$^{19}\text{F} (\text{CDCl}_3, 282 \text{ MHz})$
2D NOESY ($^1$H, $^1$H) (CD$_3$CN, 400 MHz)

1H (CD$_3$CN, 300 MHz)
$^{13}$C ($^1$H) (CD$_3$CN, 75 MHz)

$^{19}$F ($^1$H) (CDCl$_3$, 282 MHz)
13e

$^{19}$F (CDCl$_3$, 282 MHz)

2D NOESY ($^1$H, $^1$H) (CD$_3$CN, 400 MHz)
$^{13}$C ($^1$H) (CDCl$_3$, 75 MHz)
$^{19}$F ($^1$H) (CDCl$_3$, 282 MHz)

$^{19}$F (CDCl$_3$, 282 MHz)