Diastereoselective Synthesis of Fluorinated, Seven-membered β -Amino Acid Derivatives *via* Ring-Closing Metathesis

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Supporting Information

General procedure for the preparation of the fluorinated imidoyl chlorides 5.

A 200 mL two-necked flask equipped with a septum cap, a condenser, and a Teflon-coated magnetic stir bar was filled with Ph₃P (132 mmol), Et₃N (53 mmol), CCl₄ (220 mmol), and 2,2-difluoro-4-pentenoic acid (44 mmol). After the solution was stirred for *ca.* 10 min (ice bath), the corresponding amine (53 mmol) dissolved in CCl₄ (220 mmol) was added. The mixture was then refluxed under constant stirring (3 h). Solvents were removed under reduced pressure, and the residue was diluted with hexane and filtered. The filtrate was concentrated under reduced pressure, and the residue was distilled to afford compounds **5** as yellow oils.

N1-(4-Methoxyphenyl)-1-chloro-2,2-difluoro-4-penten-1-imine (5a). (80%) B.p. 79-81 °C (2·10⁻² Torr); ¹H NMR (400 MHz, CDCl₃) δ 3.05-3.87 (m, 2H), 3.72 (s, 3H), 5.19-5.26 (m, 2H), 5.71-5.88 (m, 1H), 6.83 (d, *J* = 9.0, 2H), 7.04 (d, *J* = 9.0, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 39.5 (t, ²*J*_{CF} = 24.1), 55.4 (q), 114.1 (d), 117.1 (t, ¹*J*_{CF} = 245.0), 121.4 (t), 123.1 (d), 127.9 (t, ³*J*_{CF} = 5.0), 136.9 (t, ²*J*_{CF} = 33.0), 158.6 (s); ¹⁹F NMR (376.5 MHz, CDCl₃) δ -98.60 (t, *J*_{FH} = 16.0, 2F); HRMS calc. for (M⁺) C₁₂H₁₂ClF₂NO, 259.0575, found 259.0580.

[†] X-ray analysis.

N1-(2-Methoxyphenyl)-1-chloro-2,2-difluoro-4-penten-1-imine (5b). (82%) B.p. 70-73 °C ($2 \cdot 10^{-2}$ Torr); ^1H NMR (300 MHz, CDCl_3) δ 2.94-3.07 (m, 2H), 3.73 (s, 3H), 5.22-5.29 (m, 2H), 5.78-5.91 (m, 1H), 6.76-6.92 (m, 3H), 7.09-7.17 (m, 1H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 39.6 (t, $^2J_{\text{CF}} = 24.1$), 55.6 (q), 111.6 (d), 116.9 (t, $^1J_{\text{CF}} = 247.8$), 120.1 (d), 120.5 (d), 121.5 (t), 127.0 (d), 127.7 (t, $^3J_{\text{CF}} = 5.2$), 134.4 (s), 141.5 (t, $^2J_{\text{CF}} = 36.2$), 149.1 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -99.02 (t, $J_{\text{FH}} = 15.5$, 2F); HRMS calc. for (M^+) $\text{C}_{12}\text{H}_{12}\text{ClF}_2\text{NO}$, 259.0575, found 259.0580.

N1-(4-Fluorophenyl)-1-chloro-2,2-difluoro-4-penten-1-imine (5c). (50%) B.p. 74-77 °C ($2 \cdot 10^{-1}$ Torr); ^1H NMR (300 MHz, CDCl_3) δ 2.90-3.03 (m, 2H), 5.21-5.27 (m, 2H), 5.72-5.86 (m, 1H), 6.92-7.04 (m, 4H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 39.5 (t, $^2J_{\text{CF}} = 24.1$), 115.9 (d, $^2J_{\text{CF}} = 23.0$), 117.0 (t, $^1J_{\text{CF}} = 247.8$), 121.7 (t), 122.4 (d, $^3J_{\text{CF}} = 8.6$), 127.6 (t, $^3J_{\text{CF}} = 5.2$), 139.7 (t, $^2J_{\text{CF}} = 38.0$), 140.5 (d, $^4J_{\text{CF}} = 2.9$), 161.1 ($^1J_{\text{CF}} = 246.1$); ^{19}F NMR (282.4 MHz, CDCl_3) δ -99.05 (t, $J_{\text{FH}} = 15.5$, 2F); HRMS calc. for (M^+) $\text{C}_{11}\text{H}_9\text{ClF}_3\text{N}$, 247.0376, found 247.0384.

General Procedure for the Synthesis of β -Fluoroalkyl β -Imino Esters (4).

n-Butyllithium (2.5 M in hexane, 12.6 mmol) was added dropwise to a stirred solution of diisopropylamine (12.6 mmol) in THF (10 mL) at -30 °C. After the reaction mixture was stirred for 30 min, the solution was cooled to -40 °C and alkenyl ester **6** (6.3 mmol) in THF (15 mL) was added dropwise. The resulting mixture was stirred at -40 °C for 30 min and then at -20 °C for 1 hour after which time it was cooled to -78 °C. A solution of the corresponding imidoyle chloride **5** (6.3 mmol) in THF (15 mL) was then slowly added. The reaction mixture was monitored by means of TLC analysis, and after the total disappearance of the starting material, the solvents were removed under reduced pressure. The reaction mixture was quenched with saturated NH_4Cl aq, the phases were separated, and the aqueous layer was extracted with methylene chloride (3x25 mL). The combined organic layers were dried over anhydrous sodium sulfate. Filtration and evaporation furnished the crude products **4**, which were purified as indicated.

Ethyl 2-allyl-4,4-difluoro-3-(4-methoxyphenylimine)-6-heptenoate (4a). Flash chromatography [*n*-hexane-EtOAc (7:1)] on silica gel ($R_f=0.50$) gave a yellow oil (85%): ^1H NMR (300 MHz, CDCl_3) δ 1.21 (t, $J = 7.1$, 3H), 2.42-2.52 (m, 1H), 2.66-2.74 (m, 1H), 2.88-3.02 (m, 2H), 3.71-3.74 (m, 4H), 4.04-4.16 (m, 2H), 4.92-4.99 (m, 2H), 5.16-5.21 (m, 2H), 5.40-5.51 (m, 1H), 5.73-5.87 (m, 1H), 6.65 (dd, $J_1 = 6.8$, $J_2 = 1.3$, 2H), 6.81 (dd, $J_1 = 6.8$, $J_2 = 1.2$, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 14.1 (q), 32.3 (t), 39.9 (t, $^2J_{\text{CF}} = 23.6$), 45.6 (d), 55.4 (q), 61.4 (t), 114.2 (d), 117.8

(t), 119.8 (d), 120.6 (t), 120.8 (t, $^1J_{\text{CF}} = 246.7$), 128.8 (dd, $^3J_{\text{ICF}} = 5.8$, $^3J_{\text{2CF}} = 3.5$), 134.5 (d), 141.3 (s), 156.7 (s), 162.6 (dd, $^2J_{\text{ICF}} = 33.9$, $^2J_{\text{2CF}} = 26.4$), 169.2 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -91.99 (dt, $J_{\text{FF}} = 290.3$, $J_{\text{FH}} = 16.4$, 1F), -102.93 (dt, $J_{\text{FF}} = 288.0$, $J_{\text{FH}} = 21.0$, 1F); HRMS calc. for (M^+) $\text{C}_{19}\text{H}_{23}\text{F}_2\text{NO}_3$, 351.1655, found 351.1646.

Ethyl 2-allyl-4,4-difluoro-3-(2-methoxyphenylimine)-6-heptenoate (4b). Flash chromatography [*n*-hexane-EtOAc (9:1)] on silica gel ($R_f=0.50$) gave a yellow oil (80%): ^1H NMR (300 MHz, CDCl_3) δ 1.17 (t, $J = 7.0$, 3H), 2.36-2.46 (m, 1H), 2.65-2.75 (m, 1H), 2.91-3.06 (m, 2H), 3.47 (t, $J = 7.1$, 1H), 3.67 (s, 3H), 4.00-4.09 (m, 2H), 4.84-4.93 (m, 2H), 5.13-5.21 (m, 2H), 5.49-5.62 (m, 1H), 5.76-5.90 (m, 1H), 6.63 (dd, $J_1 = 7.5$, $J_2 = 1.7$, 1H), 6.79-6.86 (m, 2H), 6.98-7.04 (m, 1H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 13.9 (q), 32.0 (t), 39.8 (t, $^2J_{\text{CF}} = 24.7$), 46.5 (d), 55.1 (q), 61.1 (t), 111.2 (d), 116.7 (t), 119.2 (d), 120.4 (d), 120.5 (t), 120.7 (t, $^1J_{\text{CF}} = 245.5$), 125.5 (d), 128.8 (dd, $^3J_{\text{ICF}} = 5.8$, $^3J_{\text{2CF}} = 4.0$), 135.0 (d), 137.0 (s), 148.3 (s), 163.9 (dd, $^2J_{\text{ICF}} = 33.9$, $^2J_{\text{2CF}} = 27.6$), 169.0 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -92.71 (dt, $J_{\text{FF}} = 272.2$, $J_{\text{FH}} = 15.5$, 1F), -102.09 (dt, $J_{\text{FF}} = 271.2$, $J_{\text{FH}} = 19.6$, 1F); HRMS calc. for (M^+) $\text{C}_{19}\text{H}_{23}\text{F}_2\text{NO}_3$, 351.1646, found 351.1652.

Ethyl 2-allyl-4,4-difluoro-3-(4-fluorophenylimine)-6-heptenoate (4c). Flash chromatography [*n*-hexane-EtOAc (10:1)] on silica gel ($R_f=0.40$) gave a yellow oil (82%): ^1H NMR (300 MHz, CDCl_3) δ 1.21 (t, $J = 7.2$, 3H), 2.43-2.53 (m, 1H), 2.66-3.01 (m, 3H), 3.60 (dd, $J_1 = 9.6$, $J_2 = 5.5$, 1H), 4.11 (dq, $J_1 = 7.2$, $J_2 = 2.1$, 2H), 4.90-5.02 (m, 2H), 5.15-5.21 (m, 2H), 5.39-5.53 (m, 1H), 5.70-5.85 (m, 1H), 6.63-6.99 (m, 4H); ^{13}C NMR (75.5 MHz, CDCl_3) Imino Z form: δ 14.0 (q), 32.1 (t), 39.7 (dd, $^2J_{\text{ICF}} = 25.3$, $^2J_{\text{2CF}} = 23.6$), 45.9 (d), 61.5 (t), 115.8 (d, $^2J_{\text{CF}} = 22.4$), 117.4 (t, $^1J_{\text{CF}} = 223.7$), 117.8 (t), 119.9 (d, $^3J_{\text{CF}} = 8.1$), 120.7 (t), 128.6 (dd, $^3J_{\text{ICF}} = 6.3$, $^3J_{\text{2CF}} = 3.5$), 134.2 (d), 160.0 (d, $^1J_{\text{CF}} = 243.2$), 163.3 (dd, $^2J_{\text{ICF}} = 34.5$, $^2J_{\text{2CF}} = 26.5$), 168.8 (s). Enamino Z form: 14.1 (q), 36.0 (t), 40.0 (t, $^2J_{\text{CF}} = 24.1$), 41.8 (d), 60.6 (t), 115.5 (d, $^2J_{\text{CF}} = 23.0$), 118.0 (t), 119.8 (d, $^3J_{\text{CF}} = 8.1$), 120.7 (t), 128.8 (t, $^3J_{\text{CF}} = 4.6$), 134.9 (d), 114.1 (t, $^3J_{\text{CF}} = 2.3$), 159.7 (d, $^1J_{\text{CF}} = 243.2$), 171.0 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ Imino Z form: -91.94 (dt, $J_{\text{FF}} = 271.1$, $J_{\text{FH}} = 15.4$, 1F), -103.11 (dt, $J_{\text{FF}} = 271.1$, $J_{\text{FH}} = 20.1$, 1F), -119.49 a -119.58 (m, 1F). Enamino Z form: -94.08 (dt, $J_{\text{FF}} = 279.6$, $J_{\text{FH}} = 15.5$, 1F), -100.04 (dt, $J_{\text{FF}} = 276.8$, $J_{\text{FH}} = 19.0$, 1F), -120.22 a -120.31 (m, 1F); HRMS calc. for (M^+) $\text{C}_{18}\text{H}_{20}\text{F}_3\text{NO}_2$, 339.1446, found 339.1447.

Benzyl 2-allyl-4,4-difluoro-3-(4-methoxyphenylimine)-6-heptenoate (4d). Flash chromatography [*n*-hexane-EtOAc (10:1)] on silica gel ($R_f=0.50$) gave a yellow oil (76%): ^1H NMR

(300 MHz, CDCl₃) δ 2.45-2.67 (m, 1H), 2.89-3.03 (m, 3H), 3.68-3.78 (m, 4H), 4.91-5.11 (m, 6H), 5.39-5.53 (m, 1H), 5.61-5.72 (m, 1H), 6.57 (d, J = 8.9, 2H), 6.75 (d, J = 8.9, 2H), 7.27 (s, 5H); ¹³C NMR (75.5 MHz, CDCl₃) Imino Z form: δ 32.2 (t), 39.6 (dd, $^1J_{\text{ICF}}$ = 25.3, $^2J_{\text{2CF}}$ = 23.6), 39.5 (t, $^2J_{\text{CF}}$ = 24.1), 45.6 (d), 55.3 (q), 67.2 (t), 114.0 (d), 114.2 (d), 117.8 (t), 119.7 (d), 120.5 (t), 120.8 (dd, $^1J_{\text{ICF}}$ = 247.2, $^1J_{\text{2CF}}$ = 244.4), 123.1 (d), 128.4 (d), 128.5 (d), 134.3 (d), 135.2 (s), 141.1 (s), 156.8 (s), 162.3 (dd, $^2J_{\text{ICF}}$ = 34.5, $^2J_{\text{2CF}}$ = 26.5), 169.0 (s). Enamino Z form: 39.5 (t, $^2J_{\text{CF}}$ = 24.1), 53.4 (q); ¹⁹F NMR (282.4 MHz, CDCl₃) δ -91.71 (ddd, J_{FF} = 272.2, J_{1FH} = 19.6, J_{2FH} = 10.3, 1F), -103.25 (ddd, J_{FF} = 272.2, J_{1FH} = 21.6, J_{2FH} = 17.5, 1F); HRMS calc. for (M⁺) C₂₄H₂₅F₂NO₃, 413.1803, found 413.1804.

General Procedure for the Ring-Closing Metathesis Reaction.

A solution of compound **4** in dry methylene chloride (10⁻² M) was added *via* syringe to a stirred solution of ruthenium alkylidene catalyst **1** or **2** (see Table 2 in the main text) (15 mol %) in dry methylene chloride. The flask was fitted with a condenser and refluxed under argon. Upon completion of the reaction as determined by means of TLC, the solvents were removed under reduced pressure and the crude reaction mixture was purified through flash column chromatography.

(±)-Ethyl 6,6-difluoro-7-(4-methoxyphenylimine)-3-cyclohepten-1-carboxylate (9a).

Flash chromatography [*n*-hexane-EtOAc (10:1)] on silica gel (R_f =0.30) gave a brown oil (75%): ¹H NMR (300 MHz, CDCl₃) Imino Z form: δ 1.19 (t, J = 7.2, 3H), 2.22-2.28 (m, 1H), 2.65-2.97 (m, 3H), 3.72 (s, 3H), 3.85-3.87 (m, 1H), 4.06-4.11 (m, 2H), 5.55-5.58 (m, 1H), 5.79-5.83 (m, 1H), 6.67 (d, J = 8.9, 2H), 6.81 (d, J = 8.9, 2H). Enamino Z form: 9.13 (brs, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.9 (q), 26.2 (t), 37.0 (t, $^2J_{\text{CF}}$ = 28.2), 45.6 (d), 55.4 (q), 61.8 (t), 114.3 (d), 118.8 (t, $^1J_{\text{CF}}$ = 243.2), 119.8 (d), 123.3 (dd, $^3J_{\text{ICF}}$ = 7.5, $^3J_{\text{2CF}}$ = 4.6), 128.5 (d), 141.3 (s), 156.7 (s), 162.7 (dd, $^2J_{\text{ICF}}$ = 28.2, $^2J_{\text{2CF}}$ = 19.0), 169.2 (s); ¹⁹F NMR (282.4 MHz, CDCl₃) δ Imino Z form: -95.21 (ddd, J_{FF} = 248.5, J_{1FH} = 16.5, J_{2FH} = 8.3, 1F), -98.17 (ddd, J_{FF} = 247.4, J_{1FH} = 24.7, J_{2FH} = 9.3, 1F). Enamino Z form: -90.52 (t, J_{FH} = 15.4, 2F); HRMS calc. for (M⁺) C₁₇H₁₉F₂NO₃, 323.1333, found 323.1325.

(±)-Ethyl 6,6-difluoro-7-(2-methoxyphenylimine)-3-cyclohepten-1-carboxylate (9b).

Flash chromatography [*n*-hexane-EtOAc (10:1)] on silica gel (R_f =0.45) gave a brown oil (90%): ¹H NMR (300 MHz, CDCl₃) Imino Z form: δ 1.15 (t, J = 7.2, 3H), 2.23-2.32 (m, 1H), 2.59-3.02 (m,

3H), 3.65-3.67 (m, 1H), 3.69 (s, 3H), 3.98-4.07 (m, 2H), 5.54-5.61 (m, 1H), 5.82-5.89 (m, 1H), 6.69-7.05 (m, 4H). Enamino Z form: 7.81 (brs, 1H); ^{13}C NMR (75.5 MHz, CDCl_3) Imino Z form: δ 13.8 (q), 25.8 (t), 36.6 (t, $^2J_{\text{CF}} = 27.6$), 46.3 (d), 55.4 (q), 61.4 (t), 111.4 (d), 119.6 (t, $^1J_{\text{CF}} = 235.2$), 119.7 (d), 120.8 (d), 122.6 (dd, $^3J_{\text{ICF}} = 8.1$, $^3J_{2\text{CF}} = 4.6$), 125.3 (d), 128.8 (d), 137.0 (s), 147.7 (s), 163.7 (dd, $^2J_{\text{ICF}} = 28.2$, $^2J_{2\text{CF}} = 19.0$), 169.0 (s). Enamino Z form: 35.7 (t, $^2J_{\text{CF}} = 27.6$), 55.5 (q), 60.7 (t), 110.5 (d), 118.5 (dd, $^3J_{\text{ICF}} = 9.2$, $^3J_{2\text{CF}} = 6.9$), 120.4 (d), 121.9 (t, $^3J_{\text{CF}} = 6.3$), 122.3 (d), 128.6 (d), 132.5 (s), 145.3 (t, $^2J_{\text{CF}} = 25.3$), 149.9 (s), 168.9 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ Imino Z form: -95.77 (ddd, $J_{\text{FF}} = 247.4$, $J_{\text{IFH}} = 16.5$, $J_{2\text{FH}} = 7.2$, 1F), -98.80 (ddd, $J_{\text{FF}} = 247.9$, $J_{\text{IFH}} = 25.8$, $J_{2\text{FH}} = 8.3$, 1F). Enamino Z form: -93.82 (t, $J_{\text{FH}} = 14.4$, 2F); HRMS calc. for (M^+) $\text{C}_{17}\text{H}_{19}\text{F}_2\text{NO}_3$, 323.1333, found 323.1325.

(±)-Ethyl 6,6-difluoro-7-(4-fluorophenylimine)-3-cyclohepten-1-carboxylate (9c). Flash chromatography [*n*-hexane-EtOAc (10:1)] on silica gel ($R_f=0.45$) gave a yellow oil (60%): ^1H NMR (300 MHz, CDCl_3) Imino Z form: δ 1.19 (t, $J = 7.2$, 3H), 2.22-2.33 (m, 1H), 2.65-3.05 (m, 3H), 3.76-3.81 (m, 1H), 4.09 (dq, $J_1 = 7.2$, $J_2 = 1.2$, 2H), 5.56-5.60 (m, 1H), 5.78-5.86 (m, 1H), 6.65-6.99 (m, 4H). Enamino Z form: 8.86 (brs, 1H); ^{13}C NMR (75.5 MHz, CDCl_3) Imino Z form: δ 14.0 (q), 26.1 (t), 37.1 (t, $^2J_{\text{CF}} = 27.6$), 45.9 (d), 61.8 (t), 116.0 (d, $^2J_{\text{CF}} = 22.4$), 119.9 (d, $^3J_{\text{CF}} = 8.1$), 128.4 (d), 123.5 (t, $^3J_{\text{CF}} = 8.1$), 144.2 (s), 160.0 (d, $^1J_{\text{CF}} = 243.2$), 163.4 (dd, $^2J_{\text{ICF}} = 27.6$, $^2J_{2\text{CF}} = 19.0$), 168.9 (s). Enamino Z form: 25.0 (t), 36.6 (t, $^2J_{2\text{CF}} = 28.2$), 60.8 (t), 115.4 (d, $^2J_{\text{CF}} = 22.4$), 118.8 (d, $^3J_{\text{CF}} = 6.3$), 128.8 (d), 123.4 (t, $^3J_{\text{CF}} = 8.1$); ^{19}F NMR (282.4 MHz, CDCl_3) δ Imino Z form: -95.40 (ddd, $J_{\text{FF}} = 248.5$, $J_{\text{IFH}} = 16.5$, $J_{2\text{FH}} = 9.3$, 1F), -98.12 (ddd, $J_{\text{FF}} = 247.4$, $J_{\text{IFH}} = 25.0$, $J_{2\text{FH}} = 10.3$, 1F), -119.59 a -119.68 (m, 1F). Enamino Z form: -90.89 (t, $J_{\text{FH}} = 15.5$, 2F), -120.10 a -120.19 (m, 1F); HRMS calc. for (M^+) $\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_2$, 311.1133, found 311.1144.

(±)-Benzyl 6,6-difluoro-7-(4-methoxyphenylimine)-3-cyclohepten-1-carboxylate (9d). Flash chromatography [*n*-hexane-EtOAc (8:1)] on silica gel ($R_f=0.40$) gave a yellow oil (65%): ^1H NMR (300 MHz, CDCl_3) δ 2.23-2.32 (m, 1H), 2.64-3.00 (m, 2H), 3.67 (s, 3H), 3.87-3.92 (m, 1H), 5.04 (dd, $J_1 = 18.5$, $J_2 = 12.2$, 2H), 5.51-5.56 (m, 1H), 5.73-5.81 (m, 1H), 6.57 (d, $J = 8.9$, 2H), 6.70 (d, $J = 8.9$, 2H), 7.25-7.26 (m, 5H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 26.2 (t), 37.0 (t, $^2J_{\text{CF}} = 28.2$), 45.7 (d), 55.3 (q), 67.3 (t), 114.3 (d), 118.8 (dd, $^1J_{\text{ICF}} = 250.1$, $^2J_{2\text{CF}} = 243.8$), 119.7 (d), 123.4 (dd, $^3J_{\text{ICF}} = 8.1$, $^3J_{2\text{CF}} = 5.2$), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 135.1 (s), 141.1 (s), 156.7 (s), 162.4 (dd, $^2J_{\text{ICF}} = 28.2$, $^2J_{2\text{CF}} = 19.0$), 169.1 (s); ^{19}F NMR (282.4 MHz, CDCl_3) Imino Z form: δ -94.51 (ddd, $J_{\text{FF}} = 248.5$, $J_{\text{IFH}} = 16.5$, $J_{2\text{FH}} = 9.3$, 1F), -98.00 (ddd, $J_{\text{FF}} = 248.5$, $J_{\text{IFH}} = 25.8$, $J_{2\text{FH}} =$

10.3, 1F). Enamino Z form: -90.06 (t, $J_{\text{FH}} = 15.4$, 2F); HRMS calc. for (M^+) $\text{C}_{22}\text{H}_{21}\text{F}_2\text{NO}_3$, 385.1490, found 385.1503.

General procedure for the reduction of β -iminoesters 4 and 9. Synthesis of β -aminoesters 7 and 8.

Trifluoroacetic acid was added to a stirred solution of the β -iminoester **4** or **9** (1 mmol) in dry THF (15 mL) at 0 °C until pH 4 was reached, upon which sodium cyanoborohydride was added slowly (3.0 mmol). Stirring was continued until no more starting material was detected (TLC). The reaction mixture was then quenched with NH_4Cl aq., the phases were separated, and the aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over sodium sulfate. Filtration and evaporation furnished the crude products **7** (from **4**) or **8** (from **9**), which were then purified as indicated below.

***cis*-($\pm$)-Ethyl 6,6-Difluoro-7-(4-methoxyaniline)-3-ciclohepten-1-carboxilate (*cis*-**8a**).**

Flash chromatography [*n*-hexane-EtOAc (5:1)] on silica gel ($R_f=0.40$) gave a white solid (90%): m.p. 108-110 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.95 (t, $J = 7.1$, 3H), 2.42-2.61 (m, 3H), 2.81-3.00 (m, 2H), 3.66 (s, 3H), 3.87 (dq, $J_1 = 7.1$, $J_2 = 3.6$, 2H), 4.31-4.35 (m, 1H), 5.49-5.56 (m, 1H), 5.78-5.85 (m, 1H), 6.64 (d, $J = 9.4$, 2H), 6.68 (d, $J = 9.4$, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 14.3 (q), 24.0 (t), 33.0 (t, $^2J_{\text{CF}} = 28.2$), 43.8 (d), 56.1 (q), 61.6 (t), 61.6 (t, $^2J_{\text{CF}} = 25.3$), 115.0 (d), 116.3 (d), 122.7 (t, $^1J_{\text{CF}} = 246.1$), 123.5 (dd, $^3J_{\text{ICF}} = 10.9$, $^3J_{2\text{CF}} = 3.5$), 130.7 (d), 141.6 (s), 153.4 (s), 172.6 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -96.03 (dt, $J_{\text{FF}} = 245.4$, $J_{\text{FH}} = 14.4$, 1F), -99.05 (ddt, $J_{\text{FF}} = 245.4$, $J_{1\text{FH}} = 31.0$, $J_{2\text{FH}} = 6.2$, 1F); HRMS calc. for (M^+) $\text{C}_{17}\text{H}_{21}\text{F}_2\text{NO}_3$, 325.1490, found 325.1481.

X-Ray crystal structure of compound *cis*-8a****

Colorless prism of 0.66 x 0.40 x 0.33 mm size, monoclinic, $\text{C}2/c$, $a = 16.8027(2)$, $b = 10.6195(1)$, $c = 19.6975(2)$ Å, $\beta = 106.934(1)$, $V = 3362.3(1)$ Å³, $Z = 8$, $D_c = 1.285$ gcm⁻³, $\theta_{\text{max}} = 26.4^\circ$, diffractometer Kappa CCD, Mo $\text{K}\alpha$ ($\lambda = 0.71073$ Å), ω -scan, $T = 293(2)$ K, 6608 reflections collected of which 3438 were independent ($R_{\text{int}} = 0.019$), direct primary solution and refinement on F^2 (SHELXL-97, G.M. Sheldrick, University of Göttingen, 1997), 214 refined parameters, free NH, other hydrogen atoms riding, the Et group is disordered over two sites, $R1[I > 2\sigma(I)] = 0.0507$, $wR2$ (all data) = 0.1697.

Crystal packing of compound *cis*-8a

The crystal packing from the X-ray diffraction data of compound **8a** has been studied. In the crystal, two symmetry related N-H $\cdots$ O=C hydrogen bonds form a dimer with a HN $\cdots$ C=O torsion angle of 47.6° (see figure 1a, table 1). The crystal packing of the dimmers involves weak C-H $\cdots$ F and C-H $\cdots$ O hydrogen bonds (see structure *b* in Figure 3 and Table 4 below).

Figure 3. Crystal packing of compound *cis*-8a. a) Dimers formed through N(1)-H(1) $\cdots$ O(1)ⁱ hydrogen bonds. b) A view showing C(5)-H(5) $\cdots$ F(1)ⁱⁱ, C(17)-H(17A) $\cdots$ F(2)ⁱⁱⁱ, C(16)-H(16) $\cdots$ F(1)^{iv} and C(1)-H(1) $\cdots$ O(3)^v weak hydrogen bonds.

Table 4. Hydrogen bonds for *cis*-8a (Å and °).

D-H $\cdots$ A	d(D $\cdots$ A)	d(H $\cdots$ A)	<(DHA)
N(1)-H(1N) $\cdots$ O(1) ⁱ	3.150(2)	2.235(15)	172.5(17)
C(5)-H(5) $\cdots$ F(1) ⁱⁱ	3.322(2)	2.57	138.5
C(17)-H(17A) $\cdots$ F(2) ⁱⁱⁱ	3.325(2)	2.47	147.7
C(16)-H(16) $\cdots$ F(1) ^{iv}	3.394(2)	2.57	148.2
C(1)-H(1) $\cdots$ O(3) ^v	3.334(2)	2.52	139.9

Symmetry transformations used to generate equivalent atoms: i: -x + 1/2, -y + 1/2, -z + 1; ii: -x + 1/2, y + 1/2, -z + 1/2, iii: -x, y-1, -z + 1/2, iv: -x, y, -z + 1/2 and v: x, y + 1, z.

***cis*-(±)-Ethyl 6,6-Difluoro-7-(2-methoxyaniline)-3-ciclohepten-1-carboxilate (*cis*-8b).**

Flash chromatography [*n*-hexane-EtOAc (5:1)] on silica gel ($R_f=0.40$) gave a white solid (88%): m.p. 55-57 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.94 (t, $J = 7.0$, 3H), 2.46-3.01 (m, 5H), 3.76 (s, 3H), 3.86 (q, $J = 7.1$, 2H), 4.52 (brs, 1H), 4.64-4.67 (m, 1H), 5.49-5.58 (m, 1H), 5.80-5.89 (m, 1H), 6.59-6.79 (m, 4H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 13.7 (q), 23.4 (t), 32.3 (dd, $^2J_{\text{ICF}} = 28.8$, $^2J_{2\text{CF}} = 27.0$), 43.4 (d), 55.7 (q), 59.2 (dd, $^2J_{\text{ICF}} = 32.8$, $^2J_{2\text{CF}} = 25.9$), 61.1 (t), 109.8 (d), 111.6 (d), 117.8 (d), 121.1 (d), 122.4 (t, $^1J_{\text{CF}} = 246.7$), 123.1 (dd, $^3J_{\text{ICF}} = 12.1$, $^3J_{2\text{CF}} = 2.3$), 130.4 (d), 136.8 (s), 146.9 (s), 171.9 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -95.16 (dt, $J_{\text{FF}} = 245.4$, $J_{\text{FH}} = 13.4$, 1F), -100.27 (ddt, $J_{\text{FF}} = 244.3$, $J_{\text{IFH}} = 33.0$, $J_{2\text{FH}} = 5.1$, 1F); HRMS calc. for (M^+) $\text{C}_{17}\text{H}_{21}\text{F}_2\text{NO}_3$, 325.1490, found 325.1485.

***cis*-(±)-Ethyl 6,6-Difluoro-7-(4-fluoroaniline)-3-ciclohepten-1-carboxilate (*cis*-8c).**

Flash chromatography [*n*-hexane-EtOAc (5:1)] on silica gel ($R_f=0.40$) gave a white solid (80%): m.p. 95-96 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.94 (t, $J = 7.2$, 3H), 2.41-3.01 (m, 5H), 3.88 (m, 3H), 4.32-4.35 (m, 1H), 5.50-5.58 (m, 1H), 5.79-5.87 (m, 1H), 6.62 (d, $J = 9.0$, 2H), 6.81 (d, $J = 9.0$, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 13.8 (q), 23.6 (t), 32.6 (t, $^2J_{\text{CF}} = 27.0$), 43.4 (dd, $^3J_{\text{ICF}} = 6.3$, $^3J_{2\text{CF}} = 1.7$), 61.2 (t), 115.4 (dd, $^3J_{\text{ICF}} = 7.5$, $^3J_{2\text{CF}} = 1.7$), 115.6 (d, $^2J_{\text{CF}} = 22.4$), 122.2 (t, $^1J_{\text{CF}} = 246.1$), 123.1 (dd, $^2J_{\text{ICF}} = 10.9$, $^2J_{2\text{CF}} = 3.5$), 130.3 (d), 143.4 (s), 156.5 (d, $^1J_{\text{CF}} = 236.9$), 172.0 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -96.24 (dt, $J_{\text{FF}} = 246.4$, $J_{\text{FH}} = 14.4$, 1F), -98.91 (ddt, $J_{\text{FF}} = 245.4$, $J_{\text{IFH}} = 31.0$, $J_{2\text{FH}} = 5.1$, 1F), -126.70 (m, 1F); HRMS calc. for (M^+) $\text{C}_{16}\text{H}_{18}\text{F}_3\text{NO}_2$, 313.1290, found 313.1281.

***cis*-(±)-Benzyl 6,6-Difluoro-7-(4-methoxyaniline)-3-ciclohepten-1-carboxilate (*cis*-8d).**

Flash chromatography [*n*-hexane-EtOAc (5:1)] on silica gel ($R_f=0.40$) gave a white solid (72%): m.p. 72-74 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.44-3.06 (m, 5H), 3.66 (s, 3H), 3.70 (m, 1H), 4.27-4.37 (m, 1H), 4.74 (d, $J = 12.1$, 1H), 4.86 (d, $J = 12.1$, 1H), 5.46-5.54 (m, 1H), 5.75-5.84 (m, 1H), 6.59 (d, $J = 9.2$, 2H), 6.65 (d, $J = 9.2$, 2H), 7.02-7.28 (m, 5H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 23.6 (t), 32.6 (t, $J = 27.0$), 43.4 (dd, $^3J_{\text{ICF}} = 6.3$, $^3J_{2\text{CF}} = 1.7$), 55.6 (q), 61.1 (dd, $^2J_{\text{ICF}} = 32.2$, $^2J_{2\text{CF}} = 25.3$), 67.1 (t), 114.6 (d), 115.9 (d), 120.3 (d), 122.2 (t, $^1J_{\text{CF}} = 246.3$), 123.1 (dd, $^3J_{\text{ICF}} = 10.9$, $^3J_{2\text{CF}} = 3.5$), 127.9 (d), 128.3 (d), 128.4 (d), 130.2 (d), 131.5 (d), 135.1 (s), 141.0 (s), 153.0 (s), 172.1 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -95.97 (dt, $J_{\text{FF}} = 245.4$, $J_{\text{FH}} = 15.5$, 1F), -98.63 (ddt, $J_{\text{FF}} = 245.8$, $J_{\text{IFH}} = 29.9$, $J_{2\text{FH}} = 6.2$, 1F); HRMS calc. for (M^+) $\text{C}_{22}\text{H}_{23}\text{F}_2\text{NO}_3$, 387.1646, found 387.1649.

***trans*-(±)-Ethyl 6,6-Difluoro-7-(4-methoxyaniline)-3-ciclohepten-1-carboxilate (*trans*-8a).** Flash chromatography [*n*-hexane-EtOAc (7:1)] on silica gel (R_f =0.30) gave a white solid (25%): m.p. 83-85 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.08 (t, J = 7.2, 3H), 2.32-2.72 (m, 5H), 3.66 (s, 3H), 3.94-4.05 (m, 3H), 5.56-5.65 (m, 1H), 5.86-5.94 (m, 1H), 6.61 (d, J = 9.2, 2H), 6.68 (d, J = 9.2, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 14.1 (q), 27.6 (t), 34.1 (t, $^2J_{\text{CF}}$ = 27.1), 47.5 (d), 55.6 (q), 61.0 (t), 63.4 (t, $^2J_{\text{CF}}$ = 23.6), 114.6 (d), 115.5 (d), 121.8 (t, $^1J_{\text{CF}}$ = 244.4), 123.4 (dd, $^3J_{1\text{CF}}$ = 11.5, $^3J_{2\text{CF}}$ = 1.7), 131.3 (d), 141.5 (s), 152.7 (s), 173.0 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -91.35 (m, J_{FF} = 248.5, 1F), -112.58 (m, J_{FF} = 246.2, 1F); HRMS calc. for (M^+) $\text{C}_{17}\text{H}_{21}\text{F}_2\text{NO}_3$, 325.1490, found 325.1481.

***anti*-(±)-Ethyl 2-allyl-4,4-difluoro-3-(4-methoxyaniline)-6-heptenoate (*anti*-7a).** Flash chromatography [*n*-hexane-EtOAc (12:1)] on silica gel (R_f =0.40) gave a yellow oil (33%, 70% *syn*+*anti*): ^1H NMR (300 MHz, CDCl_3) δ 0.84 (d, J = 6.4, 1H), 1.18 (t, J = 7.1, 3H), 1.98-3.17 (m, 5H), 3.66 (s, 3H), 4.02-4.15 (m, 3H), 4.81-5.17 (m, 4H), 5.50-5.81 (m, 2H), 6.55 (d, J = 9.0, 2H), 6.69 (d, J = 9.0, 2H); ^{19}F NMR decoupling (282.4 MHz, CDCl_3) δ -104.10 (d, J_{FF} = 247.4, 1F), -107.78 (d, J_{FF} = 247.4, 1F); HRMS calc. for (M^+) $\text{C}_{19}\text{H}_{25}\text{F}_2\text{NO}_3$, 353.1803, found 353.1816.

***syn*-(±)-Ethyl 2-allyl-4,4-difluoro-3-(4-methoxyaniline)-6-heptenoate (*syn*-7a).** Flash chromatography [*n*-hexane-EtOAc (12:1)] on silica gel (R_f =0.30) gave a yellow oil (37%, 70% *syn*+*anti*): ^1H NMR (300 MHz, CDCl_3) δ 1.16 (t, J = 7.1, 3H), 2.23-2.80 (m, 5H), 3.49 (d, J = 11.3, 1H), 3.68 (s, 3H), 3.97-4.11 (m, 3H), 4.92-5.14 (m, 4H), 5.59-5.75 (m, 2H), 6.53 (d, J = 9.0, 2H), 6.71 (d, J = 9.0, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 14.1 (q), 30.9 (d), 33.4 (t), 39.2 (dd, $^2J_{1\text{CF}}$ = 25.9, $^2J_{2\text{CF}}$ = 24.2), 45.5 (d), 55.7 (q), 58.1 (dd, $^2J_{1\text{CF}}$ = 28.2, $^2J_{2\text{CF}}$ = 23.0), 60.7 (t), 114.6 (d), 114.9 (d), 117.1 (t), 121.0 (t), 124.1 (dd, $^1J_{1\text{CF}}$ = 250.7, $^2J_{2\text{CF}}$ = 247.2), 128.7 (dd, $^3J_{1\text{CF}}$ = 8.1, $^3J_{2\text{CF}}$ = 2.9), 135.1 (d), 140.5 (s), 152.6 (s), 173.4 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -102.78 (dt, J_{FF} = 249.5, J_{FH} = 20.6, 1F), -110.62 (m, J_{FF} = 249.5, 1F); HRMS calc. for (M^+) $\text{C}_{19}\text{H}_{25}\text{F}_2\text{NO}_3$, 353.1803, found 353.1816.

Synthesis of *cis*-(±)-Ethyl 3,3-difluoro-2-(4-methoxyaniline)-1-cycloheptanecarboxilate (*cis*-11a). Palladium on active carbon (10%) was added to a stirred solution of compound *cis*-8a (1 mmol) in MeOH (15 mL) at room temperature. The flask was then put under vacuum and subsequently filled with hydrogen. The resulting mixture was stirred until the starting material

could no longer be detected (TLC). The reaction mixture was then filtered through Celite® and the solvents were removed to yield the crude product *cis*-**11a**, which was purified by means of flash chromatography [*n*-hexane-EtOAc (7:1)] on silica gel (R_f =0.35). This afforded a yellow solid (99% yield): m.p. 70-71 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.00 (t, J = 7.1), 1.18-1.23 (m, 1H), 1.61-1.67 (m, 4H), 1.84-1.90 (m, 2H), 2.00-2.14 (m, 2H), 2.88-2.94 (m, 1H), 3.66 (s, 3H), 3.91 (dq, J_1 = 7.1, J_2 = 1.9, 2H), 4.14-4.21 (m, 1H), 6.62 (d, J = 9.1, 2H), 6.68 (d, J = 9.1, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 13.9 (q), 20.4 (dd, $^3J_{\text{ICF}}$ = 10.4, $^3J_{2\text{CF}}$ = 2.9), 25.2 (t), 33.8 (t, $^2J_{\text{CF}}$ = 25.3), 43.5 (t, $^3J_{\text{CF}}$ = 5.2), 55.6 (q), 60.9 (t), 61.6 (dd, $^2J_{\text{ICF}}$ = 31.6, $^2J_{2\text{CF}}$ = 25.3), 114.6 (d), 115.8 (d), 125.3 (t, $^1J_{\text{CF}}$ = 246.1), 141.2 (s), 152.9 (s), 172.9 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -92.16 (dq, J_{FF} = 246.4, J_{FH} = 11.4, 1F), -93.70 (m, J_{FF} = 247.0, 1F); HRMS calc. for (M^+) $\text{C}_{17}\text{H}_{23}\text{F}_2\text{NO}_3$, 327.1646, found 327.1646.

Synthesis of *cis*-(±)-Ethyl 7-amino-6,6-difluoro-3-cycloheptene-1-carboxylate (*cis*-**10a**).

A solution of ammonium cerium nitrate (8.5 mmol) in water (15 mL) was added slowly to a stirred solution of compound *cis*-**8a** (2.8 mmol) in acetonitrile (30 mL) at 0 °C. After 2 hours, a solution of NaHCO_3 5% was added until pH 6 was reached. Then sodium sulfite was added until the mixture became a brown suspension. The mixture was then extracted with ethyl acetate (4x30 mL) and the organic phases were mixed and dried over anhydrous sodium sulfate. The mixture was subsequently filtered and the solvents were removed under vacuum, to afford the crude product *cis*-**10a**, which was purified through flash column chromatography [*n*-hexane-EtOAc (3:1)] on silica gel (R_f =0.5). This gave a yellow oil (95% yield): ^1H NMR (300 MHz, CDCl_3) δ 1.21 (t, J = 7.1, 3H), 1.47 (br s, 2H), 2.19-2.27 (m, 1H), 2.33-2.48 (m, 1H), 2.61-2.71 (m, 1H), 2.80-2.84 (m, 1H), 2.95-3.13 (m, 1H), 3.71-3.76 (m, 1H), 4.11 (q, J = 7.1, 2H), 5.42-5.50 (m, 1H), 5.78-5.85 (m, 1H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 14.1 (q), 22.7 (t), 31.5 (dd, $^2J_{\text{ICF}}$ = 28.2, $^2J_{2\text{CF}}$ = 26.5), 43.4 (d), 56.7 (t, $^2J_{\text{CF}}$ = 27.0), 60.9 (t), 122.8 (dd, $^3J_{\text{ICF}}$ = 12.6, $^3J_{2\text{CF}}$ = 2.3), 131.4 (d), 173.4 (s); ^{19}F NMR (282.4 MHz, CDCl_3) δ -96.70 (dt, J_{FF} = 248.5, J_{FH} = 13.4, 1F), -102.58 (ddt, J_{FF} = 248.5, J_{IFH} = 34.0, $J_{2\text{FH}}$ = 5.2, 1F); HRMS calc. for (M^+) $\text{C}_{10}\text{H}_{15}\text{F}_2\text{NO}_2$, 219.1066, found 219.1071.