Supporting Information

for

Selectively fluorinated cyclohexane building blocks: Derivatives of carbonylated all-cis-3-phenyl-1,2,4,5-tetrafluorocyclohexane

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1. General experimental

All reactions were carried out in oven-dried glassware under argon. Petrol refers to the petroleum ether fraction 40–60 °C. All chemicals were used as supplied. All NMR spectra were recorded using a Bruker Avance III 500, Bruker Avance II 400 or Bruker Avance 300 spectrometers. The deuterated solvent was used as an internal deuterium lock. $^{13}$C NMR spectra were recorded using the UDEFT pulse sequence and broadband proton decoupling at either 75, 100 or 126 MHz. $^{19}$F NMR spectra were recorded at 282, 376 or 470 MHz. All chemical shifts, $\delta$, are stated in units of parts per million (ppm), relative to a standard, for $^1$H NMR and $^{13}$C NMR the reference point is TMS ($\delta_H$ and $\delta_C$: 0.00 ppm). For $^{19}$F NMR the external reference used is CCl$_3$F ($\delta_F$: 0.00 ppm). Melting points were determined using a Griffin MPA350 or an Electrothermal 9100 melting point apparatus and are uncorrected. High and low resolution mass spectra were obtained by atmospheric pressure chemical ionisation (APCI), electrospray ionization (ESI) and electron ionisation (EI). ESI-MS spectra were recorded on a Waters Micromass LCT spectrometer in positive mode or negative mode. EI-MS spectra were recorded on a Thermo Excalibur Orbitrap spectrometer. Values are reported as a ratio of mass to charge ($m/z$) in Daltons.
Experimental

Ethyl 3-(all cis-2,3,5,6-tetrafluorocyclohexyl)benzoate (9), ethyl 4-(all cis-2,3,5,6-tetrafluorocyclohexyl)benzoate (10)
Pd(OAc)$_2$ (7 mg, 1 mol %) was added to a solution of aryl iodide 6/7 (100 mg, 0.279 mmol), triphenylphosphine (14 mg, 2 mol %) and Et$_3$N (0.07 mL, 0.56 mmol) in ethanol (5 mL) in a flame dried round flask. The flask was evacuated and fixed with a balloon containing carbon monoxide. The reaction was heated under refluxed for 16 h and then brine (10 mL) was added and the mixture extracted into ethyl acetate (2 $\times$ 30 mL). The organic layer was dried (Na$_2$SO$_4$), filtered and evaporated and the product was purified over silica gel eluting with diethyl ether/petrol (1:1) to afford 9 (13 mg 15%) as a colourless solid (mp. 171-172 °C) and 10 (36 mg 42%) as a colourless solid (mp. 188-189 °C).

Ethyl 3-(all cis-2,3,5,6-tetrafluorocyclohexyl)benzoate (9)
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ H 8.06 - 8.02 (2H, m, CH-2, CH-6), 7.81 (1H, dt, J 7.6, 1.4 Hz CH-4), 7.48 (1H, td, J 7.8, 0.4 Hz CH-5), 5.14 - 4.90 (2H, m, CHF-2'), 4.80 - 4.50 (2H, m, CHF-3'), 4.39 (2H, q, J 7.1 Hz, CH$_2$CH$_3$) 2.81 - 2.48 (3H, m, CH-1, CH$_2$H$_3$-4), 1.40 (3H, t J 7.2 Hz, CH$_2$CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ C 166.2 (s, C=O), 135.8 (s, CH-1), 133.3 (t, J 3.6 Hz CH-3), 130.9 (s, 1C, CH-2), 130.2 (s, 1C, CH-4), 129.3 (s, 1C, CH-6), 129.1 (s, 1C, CH-5), 89.7 - 88.0 (m, CHF-2'), 88.1 - 86.2 (m, CHF-3'), 61.1 (s, CH$_2$CH$_3$), 44.1 - 43.7 (m, CH-1'), 27.1 (tt, J 22.0, 2.6 Hz, CH$_2$-4'), 14.3 (s, CH$_2$CH$_3$); $^{19}$F($^1$H) NMR (282 MHz, CDCl$_3$) $\delta$ F -190.8 (2F, dd, J 7.8, 5.1 Hz, CHF-2'), -210.3 (2F, dd, J 7.8, 5.0 Hz, CHF-3'); HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for C$_{15}$H$_{16}$F$_4$NaO$_2$$^+$: 327.0984, found 327.0795.

Ethyl 4-(all cis-2,3,5,6-tetrafluorocyclohexyl)benzoate (10)
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ H 8.05 (2H, d, J 8.4 Hz, CH-3,), 7.56 (2H, d, J 8.2 Hz, CH-2), 5.13 - 4.90 (2H, m, CHF-2'), 4.80 - 4.66 (2H, m, CHF-3'), 4.39 (2H, q, J 7.2 Hz, CH$_2$CH$_3$) 2.86 - 2.43 (3H, m, CH-1, CH$_2$H$_3$-4), 1.39 (3H, t, J 7.2 Hz, CH$_2$CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ C 166.2 (s, C=O), 140.3 (s, CH-1), 130.3 (s, CH-4), 130.1 (s, 2C, CH-2), 129.2 (t, 2C, J 2.7 Hz, CH-3), 89.5 - 87.5 (m, CHF-2'), 88.0 - 86.05 (m, CHF-3'), 61.1 (s, CH$_2$CH$_3$), 44.2 - 43.7 (m, CH-1'), 27.1 (tt, J 22.3, 2.7 Hz, CH$_2$-4'), 14.3 (s, CH$_2$CH$_3$); $^{19}$F($^1$H) NMR (282 MHz, CDCl$_3$) $\delta$ F -190.7 (2F, dd, J 8.1, 5.1 Hz, CHF-2'), -210.1 (2F, dd, J 7.6, 5.1 Hz, CHF-3'); HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for C$_{15}$H$_{16}$F$_4$NaO$_2$$^+$: 327.0984, found 327.0795.

Ethyl 2-(all cis-2,3,5,6-tetrafluorocyclohex-1-yl)benzoate (8)
The same procedure used for as 9 and 10 was carried our using 5 (100 mg, 0.279 mmol). This generated 8 (74 mg, 88%) as a colourless solid, mp. 160–161 °C.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 8.07 - 8.03 (2H, m, CH-3, CH-6), 7.58 (1H, dt, J 1.43, 7.6 Hz, CH-5), 7.42 (1H, dt, J 1.2, 7.8 Hz, CH-4), 5.14 - 4.92 (2H, m, CHF-2'), 4.85 - 4.55 (2H, m, CHF-3'), 4.33 (2H, q, J 7.2 Hz, CH$_2$CH$_3$), 4.06 (1H, tt, J 1.1, 38.0 Hz, CH-1'), 2.85 - 2.67 (1H, m, CH$_3$H$_{13}$B-4'), 2.54 - 2.44 (1H, m, CH$_3$H$_{15}$B-4'), 1.39 (3H, t J 7.2 Hz, CH$_2$CH$_3$); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$C 167.6 (s, C=O), 138.1 (s, CH-1), 132.9 (s, 2C, CH-3), 131.3 (t, J 6.5 Hz CH-2), 131.1 (s, 1C, CH-6), 128.3 (s, 1C, CH-5), 127.4 (s, 1C, CH-4), 90.4 - 88.8 (m, CHF-2'), 88.0 - 86.2 (m, CHF-3'), 61.3 (s, CH$_2$CH$_3$), 38.4-38.1 (m, CH-1'), 27.4 (tt, J 22.2, 2.6 Hz, CH$_2$-4'), 14.2 (s, CH$_2$CH$_3$); $^{19}$F$^{[1]}$H NMR (282 MHz, CDCl$_3$) $\delta$F $-$189.5 (2F, dd, J 7.8, 5.2 Hz, CHF-2'), $-$209.7 (2F, dd, J 7.9, 5.2 Hz, CHF-3'); HRMS (ESI$^+$) m/z [M+Na]$^+$ calcd for C$_{13}$H$_{15}$F$_4$NaO$_2^+$: 327.0984, found 327.0973.

2-(All cis-2,3,5,6-tetrafluorocyclohex-1-yl)benzoic acid (11)

A solution of ethyl benzoate 8 (60 mg, 0.148 mmol) in a mixture of TFA and water, (9:1, 3 mL), was heated at 100 °C for 24 h. The reaction was cooled to ambient temperature and then diluted with water (10 mL). The mixture was washed with ethyl acetate (2 × 20 mL) and the organics were collected, dried (MgSO$_4$) and evaporated. The product was purified over silica gel eluting with ethyl acetate/petrol (2:1) containing acetic acid (1%). This afforded benzoic acid 11 (51 mg, 94%) as colourless solid. Mp. 244–245 °C.

$^1$H NMR (500 MHz, CD$_2$COCD$_3$) $\delta$H 8.09 (1H, dd, J 1.5, 8.0 Hz, CH-6), 8.04 (1H, d, J 8.0 Hz, CH-3), 7.65 (1H, td, J 1.37, 7.6 Hz, CH-5), 7.50 (1H, td, J 1.0, 7.6 Hz, CH-4), 5.20 - 5.07 (2H, m, CHF-2'), 5.06 - 4.90 (2H, m, CHF-3'), 4.17 (1H, tt, J 1.5, 38.8 Hz, CH-1'), 2.63 - 2.55 (1H, m, CH$_3$H$_{13}$B-4'), 2.54 - 2.48 (1H, m, CH$_3$H$_{15}$B-4'); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$C 168.2 (s, C=O), 138.8 (s, CH-1), 132.3 (s, 2C, CH-3), 131.1 (t, J 6.4 Hz CH-2), 131.0 (s, 1C, CH-6), 129.3 (s, 1C, CH-5), 127.6 (s, 1C, CH-4) 91.0 - 89.2 (m, CHF-2'), 87.8 - 86.4 (m, CHF-3'), 38.5 (m, CH-1'), 27.3 (tt, J 22.0, 2.8 Hz, CH$_2$-4'); $^{19}$F$^{[1]}$H NMR (470 MHz, CD$_3$COCD$_3$) $\delta$F $-$190.5 (2F, dd, J 7.6, 5.2 Hz, CHF-2'), $-$210.9 (2F, dd, J 7.2, 5.1 Hz, CHF-3'); HRMS (ESI$^+$) m/z [M-H]$^-$ calcd for C$_{13}$H$_{11}$F$_4$O$_2$: 275.0773, found 275.0701.

3-(All cis-2,3,5,6-tetrafluorocyclohexyl)benzoic acid (12)

Following the procedure described for the preparation of 11, ester 9 (60 mg, 0.148 mmol) afforded carboxylic acid 12 (48 mg, 89%) as colourless solid, mp. 271–272 °C.

$^1$H NMR (400 MHz, CD$_2$COCD$_3$) $\delta$H 8.26 (1H, bs, CH-2), 8.03 (1H, dt, J 7.7, 1.3 Hz CH-6), 7.85 (1H, d, J 7.7 Hz, CH-4), 7.48 (1H, t, J 7.6 Hz, CH-5), 5.29 - 5.10 (2H, m, CHF-2'), 5.06 - 4.91 (2H, m, CHF-3'), 3.33 (1H, t, J 38.5 Hz, CH-1), 2.63 - 2.47 (2H, m, CH$_3$H$_{13}$B-4'); $^{13}$C NMR (100.6 MHz, CD$_3$COCD$_3$) $\delta$C 166.5 (s, C=O), 137.6 (s, CH-1), 133.8 (t, J 2.7 Hz CH-3), 130.8 (s, 1C, CH-2), 130.6 (s, 1C, CH-4), 128.7 (s, 1C, CH-6), 128.6 (s, 1C, CH-5), 90.8 -
88.6 (m, CHF-2’), 88.2 - 86.0 (m, CHF-3’), 43.0 - 42.6 (m, CH-1’), 27.0 (tt, J 22.0, 2.8 Hz, CH₂-4’); \(^{19}\text{F}\{^1\text{H}\} \text{NMR}\) (376.6 MHz, CD₃COCD₃) \(δ_f\) –191.4 (2F, dd, J 7.0 4.8 Hz, CHF-2’), –211.0 (2F, dd, J 8.0, 5.6 Hz, CHF-3’); HRMS (ESI) \(m/z\) [M-H] calcd for C₁₃H₁₁F₄O₂: 275.0773, found 275.0701.

4-(All cis-2,3,5,6-tetrafluorocyclohexyl)benzoic acid (13)

Following the same procedure for the preparation of 11, ester 10 (60 mg, 0.148 mmol) afforded 13 (49 mg, 90%) as colourless solid, mp. 269–270 °C. \(^1\text{H}\) NMR (400 MHz, CD₃COCD₃) \(δ_h\) 8.06 (2H, d, J 8.6 Hz, CH-3’), 7.71 (2H, d, J 8.0, CH-2’), 5.30 - 5.12 (2H, m, CHF-2’), 5.10 - 4.90 (2H, m, CHF-3’), 3.34 (1H, tt, J 38.2, 1.8 Hz, CH-1), 2.63 - 2.46 (2H, m, CH₃H₂-4’); \(^{13}\text{C}\) NMR (125 MHz, CD₃COCD₃) \(δ_c\) 166.5 (s, C=O), 142.1 (s, CH-1), 129.6 (s, CH-4), 129.6 (s, 2C, CH-2), 129.4 (t, 2C, J 2.7 Hz, CH-3), 90.4 - 88.6 (m, CHF-2’), 87.9 - 86.2 (m, CHF-3’), 43.1 - 42.7 (m, CH-1’), 27.0 (tt, J 22.0, 2.8 Hz, CH₂-4’); \(^{19}\text{F}\{^1\text{H}\} \text{NMR}\) (370 MHz, CD₃COCD₃) \(δ_f\) –191.43 (2F, dd, J 7.1, 4.6 Hz, CHF-2’), –210.8 (2F, dd, J 8.2, 5.6 Hz, CHF-3’); HRMS (ESI) \(m/z\) [M-H] calcd for C₁₃H₁₁F₄O₂: 275.0773, found 275.0701.

3-(All cis-2,3,5,6-tetrafluorocyclohex-1-yl)benzaldehyde (14), 4-(all cis-2,3,5,6-tetrafluorocyclohex-1-yl)benzaldehyde (15)

A flame-dried flask was charged with a solution of aryl iodides 6/7 (1.3 g, 3.63 mmol) and Pd(PPh₃)₄ (210 mg, 4.0 mol %) in THF (4 mL). The flask was evacuated and fixed with a balloon containing carbon monoxide and the reaction was heated at 50 °C. A solution of tributyl tin hydride (1.16 g, 4.0 mmol) in dry THF (10 mL) was added dropwise by syringe over 3 h. Upon completion of the addition, the reaction was dilute by NaHCO₃ (20 mL) and the product extracted into diethyl ether. The organics were dried (Na₂SO₄), filtered and the solvent removed. Purification over silica gel, eluting with petrol/ethyl acetate/diethyl ether, (7:2.5:0.5 respectively), afforded benzaldehyde 14 (167 mg, 17%) and 15 (492 mg, 52%) as colorless solids.

3-(All cis-2,3,5,6-tetrafluorocyclohex-1-yl)benzaldehyde (14).

M.p. 182-183 °C, \(^1\text{H}\) NMR (400 MHz, CDCl₃) \(δ_h\) 10.02 (1H, s, CHO), 7.97 (1H, bs, CH-2), 7.87 (1H, dt, J 7.7, 1.4 Hz, CH-6), 7.81 (1H, d, J 7.8 Hz, CH-4), 7.57 (1H, t, J 7.6 Hz, CH-5), 5.14 - 4.92 (2H, m, CHF-2’), 4.82 - 4.54 (2H, m, CHF-3’), 2.88 - 2.62 (2H, m, CH-1, CH₃H₂-4’), 2.56 – 2.45 (1H, m, CH₃H₂-4’); \(^{13}\text{C}\) NMR (125.7 MHz, CDCl₃) \(δ_c\) 192.1 (s, C=O), 136.8 (s, CH-1), 136.7 (t, J 2.6 Hz, CH-3), 135.4 (s, 1C, CH-2), 130.3 (s, 1C, CH-4), 129.7 (s, 1C, CH-6), 129.5 (s, 1C, CH-5), 89.7 - 87.9 (m, CHF-2’), 87.7 - 85.9 (m, CHF-3’), 43.9 - 43.6 (m, CH-1’), 27.0 (tt, J 22.0, 2.6 Hz, CH₂-4’); \(^{19}\text{F}\{^1\text{H}\} \text{NMR}\) (282.3 MHz, CDCl₃) \(δ_f\) –190.4 (2F, dd,
ethyl acetate (1:1) afford ESI+ m/z [M+MeOH+Na]+ calcd for C14H16F4NaO2+: 315.0984, found 315.0975.

4-(All cis-2,3,5,6-tetrafluorocyclohex-1-yl)benzaldehyde (15)
Mp. 218-220 °C. 1H NMR (400 MHz, CDCl3) δH 10.04 (1H, s, CHO), 7.91 (2H, d, J 8.4 Hz, CH-3), 7.68 (2H, d, J 8.0 Hz, CH-2), 5.11 - 4.95 (2H, m, CHF-2’), 4.77 - 4.54 (2H, m, CHF-3’), 2.85 - 2.46 (3H, m, CH-1, CH3H2-4); 13C NMR (100.6 MHz, CDCl3) δC 191.7 (s, C=O), 142.0 (s, CH-1), 136.1 (s, CH-4), 130.1 (s, 2C, CH-2), 130.0 (t, 2C, J 2.3 Hz, CH-3), 89.5 - 87.4 (m, CHF-2’), 87.7 - 85.7 (m, CHF-3’), 44.4 - 44.1 (m, CH-1’), 27.1 (tt, J 22.1, 2.7 Hz, CH2-4’); 19F{1H} NMR (376.6 MHz, CDCl3) δF ~190.2 (2F, dd, J 7.4, 5.1 Hz, CHF-2’), ~209.5 (2F, dd, J 7.8, 5.4 Hz, CHF-3’); HRMS (ESI+) m/z [M+MeOH+Na]+ calcd for C14H16F4NaO2+: 315.0984, found 315.0974.

1,2-Bis(4-(all-cis-2,3,5,6-tetrafluorocyclohexyl)phenyl)ethane (17)
A solution of TiCl4 in DCM (1.0 M) (0.45 mL, 0.45 mmol) was added dropwise to a suspension of Zn (30 mg, 0.46 mmol) in anhydrous THF (2 mL) at 0 °C. The resulting mixture was heated at reflux for 1 h. After cooling to 0 °C, a solution of aldehyde 15 (40 mg, 0.15 mmol) in anhydrous THF (2 mL) was added, and the reaction was heated at reflux for 16 h. The reaction was then poured into a mixture of a saturated NaHCO3 (5 mL) solution and DCM (5 mL) and was stirred for 3 h. After filtration through a Celite pad, and washing with hot chloroform, the layers were separated. The aqueous layer was extracted into ethyl acetate and the combined extracts were dried (Na2SO4), filtered and the solvent removed. The product was taken up in ethyl acetate (10 mL) and was directly hydrogenated by addition of Pd/C catalyst (5 mg) and stirred under an atmosphere of hydrogen. The reaction was stirred for 16 h at 20 °C and was then filtered through a Celite pad and the solvent evaporated. Purification over silica gel eluting with petrol/ethyl acetate (1:1) afford dihydrostilbene 17 (29 mg, 76% over 2 steps) as a colourless solid.
Mp. 158-159 °C. 1H NMR (500 MHz, CD3COCD3) δH 7.48 (4H, d, J 8.0 Hz, CH-3), 7.30 (4H, d, J 8.2, CH-2), 5.19 - 5.06 (4H, m, CHF-2’), 5.05 - 4.89 (4H, m, CHF-3’), 3.16 (2H, t, J 38.8 Hz, CH-1), 2.96 (4H, s, 2PhCH2), 2.61 - 2.46 (4H, m, CH3H6-4); 13C NMR (125.6 MHz, CD3COCD3) δC 141.1 (s, 2C, CH-1), 134.6 (s, 2C, CH-4), 129.2 (s, 4C, CH-2), 128.4 (s, 4C, J 2.3 Hz, CH-3), 90.8 - 89.1 (m, CHF-2’), 88.1 - 86.3 (m, CHF-3’), 42.8 - 42.5 (m, CH-1’), 37.1 (s, 2C, CH2), 27.1 (tt, J 21.8, 2.7 Hz, CH2-4’); 19F{1H} NMR (470.3 MHz, CD3COCD3) δF ~191.3 (4F, d, J 7.5, Hz, CHF-2’), ~210.8 (4F, dd, J 7.7, 5.6 Hz, CHF-3’); HRMS (ESI+) m/z [M+K]+ calcd for C26H26F8K+: 529.1599, found 529.1743.
1-(All-cis-2,3,5,6-tetrafluorocyclohexyl)-4-vinylbenzene (18)

A solution of TiCl₄ in DCM (1.0 M) (2.2 mL, 2.2 mmol) was added to a suspension of zinc dust (88 mg, 1.4 mmol), and diiodomethane (121 mg, 0.45 mmol) in dry THF (2 mL) at 0 °C. An instantaneous reaction occurred which evolved heat and underwent a colour change to dark brown. After 15 min, a solution of aldehyde 15 (40 mg, 0.15 mmol) in THF (2 mL) was added dropwise and the resulting mixture was stirred at 25 °C for 12 h. The reaction was diluted with diethyl ether, poured into 1 M hydrochloric acid (10 mL) and was then extracted into diethyl ether. The separated organic layers were washed with brine (2 x 20 mL), dried (Na₂SO₄), and the solvent removed. The product was purified over silica gel eluting with petrol/ethanol acetate (2:1) to give styrene 18 as colourless solid (31 mg, 79%).

Mp. 154-155 °C . ¹H NMR (500 MHz, CDCl₃) δ_H 7.44 (2H, d, J 8.4 Hz, CH-2), 7.42 (2H, d, J 8.0, CH-3), 6.72 (1H, dd, J 17.6 10.8 Hz, CH=CH₃), 5.77 (1H, d, J 17.5 Hz, CH=CH₃), 5.28 (1H, d, J 10.8 Hz, CH=CH₃), 5.07 - 4.92 (2H, m, CHF-2), 4.73 - 4.53 (2H, m, CHF-3), 2.86 - 2.72 (1H, m, CH₃H₁=1), 2.60 (1H, t, J 37.2 Hz, CH-4), 2.50 - 2.45 (1H, m, CH₃H₂=1);

¹³C NMR (125.7 MHz, CDCl₃) δ_C 137.4 (s, CH-1), 136.1 (s, CH=CH₂), 135.0 (m, CH-4), 129.4 (s, 2C, CH-2), 126.6 (s, 2C, CH-3), 114.5 ((s, CH=CH₂), 89.8 - 88.1 (m, CHF-2’), 87.7 - 86.2 (m, CHF-3’), 43.9 (m, CH-1’), 27.1 (tt, J 22.0, 2.9 Hz, CH₃=4’); ¹⁹F(¹H) NMR (470.4 MHz, CDCl₃) δ_F -190.2 (2F, dd, J 8.0, 5.8 Hz, CHF-2’), -209.7 (2F, dd, J 7.7, 5.8 Hz, CHF-3’); HRMS (ESI*) m/z [M+Na]⁺ calcd for C₁₅H₁₄F₄NaO⁺: 553.2064, found 553.3893.

(4-(All-cis-2,3,5,6-tetrafluorocyclohexyl)phenyl)methanol (19)

NaBH₄ (88 mg, 2.3 mmol) was added to a solution of benzaldehyde 15 (400 mg, 1.53 mmol) in dry THF (10 mL). The reaction was stirred at ambient temperature for 1 h, and was quenched by the addition of solid NH₄Cl (150 mg) followed by water (10 mL). The product was extracted into ethyl acetate (2 x 30 mL), washed with brine and dried (Na₂SO₄). The solvent was removed under reduced pressure and the product purified over silica gel, eluting with petrol/ethyl acetate (1:1) to give benzyl alcohol 19 as a colourless solid (398 mg, 98%).

Mp. 184-185 °C . ¹H NMR (500 MHz, CD₃COCD₃) δ_H 7.52 (2H, d, J 8.0 Hz, CH-3), 7.38 (2H, d, J 8.2 Hz, CH-2), 5.22 - 5.05 (2H, m, CHF-2’), 5.05 - 4.89 (2H, m, CHF-3’), 4.65 (2H, d, J 6.0 Hz, PhCH₂), 4.21 (1H, t, J 5.8 Hz, OH), 3.18 (1H, t, J 38.8 Hz, CH-1), 2.62 - 2.43 (2H, m, CH₃H₂=4’); ¹³C NMR (125.6 MHz, CD₃COCD₃) δ_C 141.8 (s, CH-1), 135.5 (s, CH-4), 129.0 (s, 2C, CH-2), 126.6 (s, 1C, CH-3), 90.8 - 89.0 (m, CHF-2’), 88.1 - 86.3 (m, CHF-3’), 63.4 (s, 1C, PhCH₂), 42.9 - 42.5 (m, CH-1’), 27.1 (tt, J 22.1, 3.0 Hz, CH₃=4’); ¹⁹F(¹H) NMR (470 MHz, CD₃COCD₃) δ_F -191.3 (2F, dd, J 7.5, 5.6 Hz, CHF-2’), -210.8 (2F, dd, J 7.6, 5.6 Hz, CHF-3’); HRMS (ESI*) m/z [M+Na]⁺ calcd for C₁₅H₁₄F₄NaO⁺: 285.0878, found 285.0870.
(3-(All-cis-2,3,5,6-tetrafluorocyclohexyl)phenyl)methanol (28)

Following the same procedure for the reduction of 15, treatment of benzaldehyde 14 (260 mg, 1.0 mmol) afforded benzyl alcohol 28 as colourless solid (258 mg, 98%) mp. 159–160 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) H 7.48 (1H, bs, CH-2), 7.44-7.35 (3H, m, CH-4, CH-5, CH-6), 5.07 - 4.96 (2H, m, CHF-2'), 4.72 (2H, s, PhCH\(_2\)), 4.70 - 4.58 (2H, m, CHF-3'), 2.81 - 2.72 (1H, m, CH\(_2\)H\(_3\)-4), 2.62 (1H, t, J 37.0 Hz, CH-1), 2.51 - 2.44 (1H, m, CH\(_2\)H\(_3\)-4), 1.63 (1H, bs, PhCH\(_2\)OH); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) C 141.5 (s, CH-1), 135.9 (s, CH-3), 129.1 (s, 1C, CH-2), 128.5 (s, 1C, CH-4), 127.7 (s, 1C, CH-6), 126.7 (s, 1C, CH-5), 89.9 - 88.1 (m, CHF-2'), 87.9 - 86.1 (m, CHF-3'), 65.1 (s, PhCH\(_2\)), 44.1 - 43.8 (m, CH-1'), 27.1 (tt, J 22.2, 2.8 Hz, CH\(_2\)-4'); \(^1\)F\(^{1}\)H NMR (470.3 MHz, CDCl\(_3\)) \(\delta\) F -190.2 (2F, dd, J 7.5, 4.5 Hz, CHF-2'), -209.6 (2F, dd, J 7.7, 4.3 Hz, CHF-3'); HRMS (ESI\(^{+}\)) m/z [M+Na\(^{+}\)] calcd for C\(_{13}\)H\(_4\)F\(_4\)NaO\(^{+}\): 285.0878, found 285.0871.

1-(Chloromethyl)-4-(all-cis-2,3,5,6-tetrafluorocyclohexyl)benzene (23)

Mesylchloride (0.007 mL, 0.091 mmol) was added dropwise to a stirred solution of p-benzyl alcohol 19 (20 mg, 0.076 mmol) in dry DCM (2 mL) and trimethylamine (0.02 mL, 0.152 mmol) at -78 °C. The reaction was stirred for 16 h at -78 °C and was then warmed to ambient temperature, when DCM (10 mL) was added. The organics layers were washed with dilute HCl (5 mL) and then saturated NaHCO\(_3\) (10 mL) and then dried (Na\(_2\)SO\(_4\)). After filtration through a Celite pad the organic solvent was evaporated under reduced pressure to afford 23 as colourless solid (18 mg, 85%).

Mp. 171-172 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) H 7.48 (2H, d, J 8.1 Hz, CH-2), 7.40 (2H, d, J 8.2, CH-3), 5.11 - 4.88 (2H, m, CHF-2'), 4.79 - 4.60 (4H, m, PhCH\(_2\), CHF-3'), 2.85 - 2.42 (3H, m, CH-1,CH\(_2\)H\(_3\)-4); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) C 137.4 (s, CH-1), 135.8 (s, CH-4), 129.6 (s, 2C, CH-2), 129.0 (s, 1C, CH-3), 90.2 - 88.0 (m, 2C, CHF-2'), 87.7 - 85.5 (m, 2C, CHF-3'), 45.6 (s, 1C, PhCH\(_2\)), 44.0 - 43.4 (m, 1C, CH-1'), 27.1 (tt, 1C, J 22.2, 2.7 Hz, CH\(_2\)-4'); \(^1\)F\(^{1}\)H NMR (282 MHz, CDCl\(_3\)) \(\delta\) F -190.2 (2F, dd, J 8.7, 5.2 Hz, CHF-2'), -209.7 (2F, dd, J 7.6, 5.2 Hz, CHF-3'); HRMS (ESI\(^{+}\)) m/z [M+H-HCl\(^{+}\)] calcd for C\(_{13}\)H\(_4\)ClF\(_4\): 245.0953, found 245.0943.

1-(Iodomethyl)-4-(all-cis-2,3,5,6-tetrafluorocyclohexyl)benzene (20)

An aqueous solution of HI (57%) (0.58 mL) was added dropwise to a solution of p-benzyl alcohol 19 (120 mg, 0.45 mmol) in chloroform (5 mL). The mixture was allowed to stir at room temperature for 30 h, and then the excess of iodine was destroyed by adding Na\(_2\)SO\(_3\) solution. The product was extracted into chloroform (2 x 30 mL), and the organics were combined and washed with saturated NaHCO\(_3\) solution and then dried (Na\(_2\)SO\(_4\)). Filtration and then removal of the organic solvent under reduced pressure gave benzyl iodide 20 as
The product was used directly without further purification (163 mg, 95%). Mp. 188–189 °C. 

**1H NMR (300 MHz, CDCl₃)** δH 7.40 (4H, bs, CH-3, CH-2), 5.09 - 4.87 (2H, m, CHF-2'), 4.78 - 4.47 (2H, m, CHF-3'), 4.45 (2H, s, PhCH₂), 2.83 - 2.42 (3H, m, CH₂₂H₂₄-4); 

**13C NMR (125.75 MHz, CDCl₃)** δC 139.2 (s, CH-1), 135.2 (s, CH-4), 129.7 (s, 2C, CH-2), 129.1 (s, 1C, CH-3), 89.7 - 87.7 (m, 2C, CHF-2'), 88.2 - 86.2 (m, 2C, CHF-3'), 43.9 - 43.5 (m, 1C, CH-1'), 27.1 (tt, 1C, J 22.1, 2.7 Hz, CH₂₂-4'). 4.8 (s, 1C, PhCH₂); 

**19F{¹H NMR (282 MHz, CDCl₃)** δF -190.2 (2F, dd, J 7.7, 5.1 Hz, CHF-2'), -209.7 (2F, dd, J 7.8, 5.1 Hz, CHF-3'); HRMS (ESI⁺) m/z [M+H-HI⁺]⁺ calcd for C₁₃H₁₄F₄N₃⁺: 245.0953 found.

1-(Iodomethyl)-3-(all-cis-2,3,5,6-tetrafluorocyclohexyl)benzene (29) 

Iodination of 28 (60 mg, 0.23 mmol) followed the procedure used for 19 to afford benzyl iodide 29 (79 mg, 94%) as colourless white solid.

Mp. 172-173 °C; 

**1H NMR (500 MHz, CDCl₃)** δH 7.48 (1H, bs, CH-2), 7.38 (2H, d, J 7.5 Hz, CH-4, CH-6), 7.32 (1H, d, J 7.5 Hz, CH-5), 5.05 - 4.95 (2H, m, CHF-2'), 4.72 - 4.54 (2H, m, CHF-3'), 4.46 (2H, s, PhCH₂), 2.80 - 2.71 (1H, m, CH₂₂H₂₄-4), 2.60 (1H, t, J 38.1 Hz CH-1), 2.51 - 2.45 (1H, m, CH₂₂H₂₄-4); 

**13C NMR (125.7 MHz, CDCl₃)** δC 139.9 (s, CH-1), 136.2 (s, CH-3), 129.5 (s, 1C, CH-2), 129.3 (s, 1C, CH-4), 128.8 (s, 1C, CH-6), 128.5 (s, 1C, CH-5), 89.7 - 88.0 (m, CHF-2'), 87.8 - 86.1 (m, CHF-3'), 43.9 - 43.6 (m, CH-1'), 27.1 (tt, J 22.2, 2.7 Hz, CH₂₂-4'), 5.1 (s, PhCH₂); 

**19F{¹H NMR (470.3 MHz, CDCl₃)** δF -190.2 (2F, dd, J 7.5, 5.6 Hz, CHF-2'), -209.6 (2F, dd, J 7.7, 5.7 Hz, CHF-3'); HRMS (ESI⁺) [M+H-HI⁺]⁺ calcd for C₁₃H₁₄F₄N₃⁺: 245.0953.

1-(Azidomethyl)-4-(all-cis-2,3,5,6-tetrafluorocyclohexyl)benzene (21) 

Tetrabutylammonium azide (80 mg, 0.28 mmol) was added to a solution of benzyl iodide 20 (70 mg, 0.188 mmol) in acetonewater (4:1, 3 mL). The mixture was stirred at 20 °C for 3 h, and was then diluted with water (10 mL). The product was extracted into ethyl acetate (3 × 10 mL) and the organics were combined and dried (Na₂SO₄) and the solvent removed under reduced pressure. The product was purified over silica gel, eluting with petrol/ethyl acetate (2:1), to afford benzyl azide 21 as colourless solid (51 mg, 94%).

Mp. 149-150 °C; 

**1H NMR (300 MHz, CDCl₃)** δH 7.51 (2H, d, J 8.1 Hz, CH-2), 7.34 (2H, d, J 8.2, CH-3), 5.11 - 4.89 (2H, m, CHF-2'), 4.78 - 4.49 (2H, m, CHF-3'), 4.35 (2H, bs, PhCH₂), 2.84 - 2.42 (3H, m, CH₂₂H₂₄-4); 

**13C NMR (125.75 MHz, CDCl₃)** δC 135.6 (s, CH-1), 135.4 (s, CH-4), 129.7 (s, 2C, CH-2), 128.6 (s, 1C, CH-3), 89.8 - 87.7 (m, 2C, CHF-2'), 88.2 - 86.1 (m, 2C, CHF-3'), 54.3 (s, 1C, PhCH₂), 43.9 - 43.5 (m, 1C, CH-1'), 27.1 (tt, 1C, J 22.2, 2.7 Hz, CH₂₂-4'); 

**19F{¹H NMR (282 MHz, CDCl₃)** δF -190.2 (2F, dd, J 7.7, 5.2 Hz, CHF-2'), -209.7 (2F, dd, J 7.8, 5.2 Hz, CHF-3'); HRMS (ESI⁺) m/z [M+H-N₂⁺]⁺ calcd for C₁₃H₁₄F₄N₃⁺: 260.1141, found 260.1055.
1-(Azidomethyl)-3-(all-cis-2,3,5,6-tetrafluorocyclohexyl)benzene (30)

m-Benzyl iodide 29 (60 mg, 0.16 mmol) was treated following the procedure for the preparation 21 above to afford m-benzyl azide 28 as colourless solid (42 mg, 91%). Mp. 145-146 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.47 - 7.39 (3H, m, CH-2, CH-4, CH-6), 7.32 (1H, d, J 7.4 Hz, CH-5), 5.08 - 4.94 (2H, m, CHF-2'), 4.73 - 4.54 (2H, m, CHF-3'), 4.37 (2H, s, PhCH$_2$), 2.82 - 2.73 (1H, m, CH$_2$H$_2$-4), 2.63 (1H, t, J 36.8 Hz CH-1), 2.51 - 2.46 (1H, m, CH$_2$H$_3$-4); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$C 136.2 (s, CH-1), 136.1 (s, CH-3), 129.4 (s, 1C, CH-2), 129.1 (s, 1C, CH-4), 129.0 (s, 1C, CH-6), 127.9 (s, 1C, CH-5), 89.8 - 88.1 (m, CHF-2'), 87.9 - 86.1 (m, CHF-3'), 54.6 (s, PhCH$_2$), 44.1 - 43.8 (m, CH-1'), 27.1 (tt, J 22.0, 2.6 Hz, CH$_2$-4'); $^{19}$F($^1$H) NMR (470.3 MHz, CDCl$_3$) $\delta$F = -190.2 (2F, dd, J 7.5, 4.5 Hz, CHF-2'), -209.6 (2F, dd, J 7.7, 4.3 Hz, CHF-3'); HRMS (ESI$^+$) m/z [M+H-N$_2$]$^+$ calcd for C$_{13}$H$_{14}$F$_4$N$_3$+: 260.1141, found 260.1058.

(4-(All-cis-2,3,5,6-tetrafluorocyclohexyl)phenyl)methanamine hydrochloride (27)

A solution of Ph$_3$P (93 mg, 0.35 mmol) in a THF:H$_2$O (10:1, 3 mL) mixture, was added directly to azide 21 (50 mg, 0.174 mmol) and the reaction was followed by TLC. The solvent was then removed under reduced pressure and the residue dissolved in CH$_2$Cl$_2$ (10 mL) and then 1 M HCl (10 mL) was added. The reaction mixture was left to stir for 1 h, and was then washed with CH$_2$Cl$_2$, and the acidic aqueous layer was collected. The solvent was removed under reduced pressure to afford benzyl amine hydrochloride 25 (38 mg, 74%) as a colourless solid.

Mp. 296-298 ºC. $^1$H NMR (500 MHz, d$_6$-DMSO) $\delta$H 8.49 (3H, bs, NH$_3$Cl), 7.51 (4H, bs, CH-2, CH-3), 5.23 - 5.05 (2H, m, CHF-2'), 5.05 - 4.85 (2H, m, CHF-3'), 4.01 (2H, bd, J 3.5 Hz PhCH$_2$), 3.24 (1H, t, J 39.4 Hz, CH-1), 2.46 - 2.28 (2H, m, CH-1,CH$_2$H$_2$-4); $^{13}$C NMR (125.75 MHz, d$_6$-DMSO) $\delta$C 137.5 (s, CH-1), 133.5 (s, CH-4), 129.5 (s, 2C, CH-2), 129.5 (s, 1C, CH-3), 90.8 - 89.3 (m, 2C, CHF-2'), 88.0 - 86.6 (m, 2C, CHF-3'), 45.7 (s, 1C, PhCH$_2$), 42.2 - 41.8 (m, 1C, CH-1'), 27.3 (t, 1C, J 21.7 Hz, CH$_2$-4'); $^{19}$F($^1$H) NMR (282 MHz, d$_6$-DMSO) $\delta$F = -192.4 (2F, dd, J 7.8, 5.3 Hz, CHF-2'), -211.5 (2F, dd, J 7.7, 5.2 Hz, CHF-3'); HRMS (ESI$^+$) m/z [M+H-HCl]$^+$ calcd for C$_{13}$H$_{17}$ClF$_4$N$: 262.1141, found 262.1204.

Methyl (S)-2-(( tert-butoxycarbonyl)amino)pent-4-ynoate (24)

Thionyl chloride (0.5 mL, 6.5 mmol) was added dropwise over 5 min to dry MeOH (5 mL) at 0 ºC and the solution was stirred for 10 min before propargyl-L-glycine was added (200 mg, 1.77 mmol) in one portion. The reaction was stirred for 16 h at 20 ºC. The solvent and the excess thionyl chloride were then removed under reduced pressure to give an oily residue. The residue was dissolved in MeCN (5 mL), and then Et$_3$N (0.271 mL, 1.9 mmol) and di-tert-
butyl pyrocarbonate (423 mg, 1.9 mmol) were added and the reaction was stirred for 2 h at ambient temperature. The solvent was then evaporated and the resulting residue suspended in 1 M NaHSO₄ (10 mL). The product was extracted into CH₂Cl₂ (3 × 20 mL) and the combined extracts were washed with saturated NaHCO₃ (5 mL) and dried (Na₂SO₄). The solution was filtered through a Celite pad and was evaporated under reduced pressure to afford the product which was purified over silica gel eluting with (ethyl acetate/petrol) (9:1) to give 27 as a colourless oil (308 mg, 81%).

**¹H NMR** (300 MHz, CDCl₃) δ 5.35 (2H, d, J 7.2 Hz, NHBoc), 4.51 – 4.45 (1H, m, CHNHBoc), 3.77 (3H, s, COOCH₃), 2.73 (2H, m, HCCCH₂), 2.04 (1H, s, HCCCH₂), 1.45 (9H, bs, (CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃) δC 171.1, 155.1, 71.6, 60.4, 52.6, 51.9, 28.3, 22.8, 14.2.

**Methyl(S)-2-((tert-butoxycarbonyl)amino)-4-(1-(3-(all-cis-2,3,5,6-tetrafluorocyclohexyl) benzyl)-1H-1,2,3-triazol-4-yl)propanoate (25)**

A suspension of Cu(OAc)₂ (20 mol %) and sodium ascorbate (40 mol %) in H₂O (2 mL) was added to a solution of azide 21 (55 mg, 0.19 mmol), and propargyl-L-glycine 24 (41.0 mg, 0.19 mmol) in tert-butanol (4 mL), and the reaction was stirred for 16 h at 20 °C. Water (10 mL) was added and the product was extracted into ethyl acetate (3 × 30 mL). The combined extracts were washed with aqueous NaHCO₃ followed by brine and then dried (Na₂SO₄). The solvent was removed and the product purified over silica gel eluting with ethyl acetate/petrol (5:1) to afford the protected amino acid 25 as a white solid (71 mg, 72%).

Mp 176 – 178 °C. [α]D -20.56.0 (c= 1 × 10⁻³, DMSO); **¹H NMR** (300 MHz, CDCl₃) δH 7.48 (2H, d, J 8.2 Hz, CH-2, 7.30 (1H, bs, H-triazol), 7.23 (2H, d, J 8.1, CH-3), 5.49 (3H, s, PhCH₂, NHBoc), 5.07 - 4.85 (2H, m, CHF-2'), 4.78 - 4.47 (3H, m, CHF-3', CHNHBoc), 3.67 (3H, s, COOCH₃), 3.21 (2H, d, J 5.2 Hz, triazol-CH₂), 2.82 - 2.37 (3H, m, CH-1, CH₃H₆-4), 1.40 (9H, bs, (CH₃)₃ of Boc); **¹³C NMR** (100.6 MHz, CDCl₃) δC 172.0 (s1C, COOMe), 155.4 (s1C, NHCOO), 143.5 (s1C, CN=N of triazol),136.2 (s, CH-1), 134.7 (s, CH-4), 130.0 (s, 2C, CH-2), 128.35 (s, 1C, CH-3), 122.1 (s,1C, CH-triazol), 89.9 - 87.7 (m, 2C, CHF-2'), 88.0 - 85.8 (m, 2C, CHF-3'), 53.6 (s, 1C, PhCH₂), 53.0 (s1C, CHNHBoc), 52.4 (s1C, COOCH₃), 43.4 - 43.5 (m, 1C, CH-1'), 30.9 (s, 1C, C(CH₃)₃), 28.4 (s, 1C, triazol-CH₂), 28.2 (s, 3C, C(CH₃)₃), 27.1 (tt, 1C, J 22.2, 2.2 Hz, CH₂-4'); **¹⁹F [¹H] NMR** (282 MHz, CDCl₃) δF -190.3 (2F, dd, J 7.6, 5.0 Hz, CHF-2'), -209.7 (2F, dd, J 7.8, 5.2 Hz, CHF-3'); HRMS (ESI⁺) m/z [M+Na]⁺ calcd for C₂₅H₃₀F₄N₄NaO₄+: 537.2101, found 537.2085.
Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(1-(3-(all-cis-2,3,5,6-tetrafluorocyclohexyl)benzyl)-1H-1,2,3-triazol-4-yl)propanoate (31)

Triazole 31 (58 mg, 81%) was prepared as colourless solid following the procedure used above for 25, and using m-benzylazide 30 (40 mg, 0.14 mmol).

Mp.130 – 131 °C. [α]D20 -96.0 (c = 5 × 10⁻⁴, DMSO); ¹H NMR (400 MHz, CDCl₃) δH 7.50 (1H, d, J 7.6 Hz, CH-2), 7.38 (1H, t, J 7.6, CH-5), 7.31 (1H, s, H-triazol), 7.20 (2H, d, J 7.7, CH-4, CH-6), 5.51 (3H, s, PhCH₂, NHBOC), 5.05 - 4.89 (2H, m, CHF-2'), 4.73 - 4.50 (3H, m, CHF-3', CHNHBoc), 3.66 (3H, s, COOCH₃), 3.20 (2H, d, J 5.3 Hz, triazol-CH₂), 2.82 - 2.37 (3H, m, CH-1, CH₃H₂-4), 1.40 (9H, bs, (CH₃)₃ of Boc); ¹³C NMR (125.7 MHz, CDCl₃) δC 172.0 (s,1C, COOMe), 155.4 (s,1C, NHCOO), 143.5 (s,1C, CN=N of triazol), 136.8 (s, CH-1), 135.4 (s, CH-3), 129.6 (s, 2C, CH-2, CH-4), 128.4 (s, 1C, CH-2), 127.3 (s, 1C, CH-5), 122.1 (s,1C, CH-triazol), 89.7 - 88.1 (m, 2C, CHF-2'), 87.6 - 86.1 (m, 2C, CHF-3'), 53.8 (s, 1C, PhCH₂), 53.0 (s,1C, CHNHBoc), 52.4 (s,1C, COOCH₃), 43.9 - 43.5 (m, 1C, CH-1'), 29.7 (s, 1C, C(CH₃)₃), 28.4 (s, 1C, triazol-CH₂), 28.2 (s, 3C, C(CH₃)₃), 27.1 (tt, 1C, J 22.1, 2.4 Hz, CH₂-4'); ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δF -190.3 (2F, t, J 8.4, Hz, CHF-2'), -209.7 (2F, dd, J 9.0, 5.4 Hz, CHF-3'); HRMS (ESI⁺) m/z [M+Na]⁺ calcd for C₂₄H₂₆F₃NaNO₇⁺: 537.2101, found 537.2081.

(S)-2-Amino-3-(1-(4-(all-cis-2,3,5,6-tetrafluorocyclohexyl)benzyl)-1H-1,2,3-triazol-4-yl)propanoic acid hydrochloride (26)

A solution of 25 (60 mg, 0.116 mmol) in a mixture of HCl 6 M/1,4-dioxane (1:1, 6 mL) was stirred at 80 °C for 48 h, until TLC (ethyl acetate:petrol; 2:1), indicated consumption of all starting material. The reaction was then diluted with water (10 mL) and the product extracted into ethyl acetate (2 × 15 mL). The organics layers were washed with water (20 mL) and the aqueous was collected and evaporated to afford 26 (49 mg, 96%) as a colourless hydrochloride salt.

Mp. Decomposed at 290-292 °C. [α]D20 - 44.0 (c = 1 × 10⁻³, DMSO); ¹H NMR (500 MHz, d₆-DMSO) δH 8.44 (3H, bs, NH₃Cl), 8.06 (1H, s, H-triazol), 7.48 (2H, d, J 8.0 Hz, CH-2), 7.31 (2H, d, J 8.0, CH-3), 5.59 (2H, s, PhCH₂), 5.19 - 5.04 (2H, m, CHF-2'), 5.03 - 4.85 (2H, m, CHF-3'), 4.22 (1H, bs, CHNHBoc), 3.25-3.12 (3H, m, triazol-CH₂, CH-1), 2.46 - 2.29 (2H, m, CH₃H₂-4); ¹³C NMR (125.7 MHz, d₆-DMSO) δC 170.5 (s,1C, COOH), 141.3 (s,1C, CN=N of triazol),137.2 (s, CH-1), 135.5 (s, CH-4), 129.6 (s, 2C, CH-2), 128.4 (s, 1C, CH-3), 124.5 (s,1C, CH-triazol), 90.8 - 89.1 (m, 2C, CHF-2'), 88.1 - 86.6 (m, 2C, CHF-3'), 52.8 (s, 1C, PhCH₂), 52.0 (s,1C, CHNHBoc), 42.9 - 41.7 (m, 1C, CH-1'), 27.3 (tt, 1C, J 21.0, 3.2 Hz, CH₂-4'), 26.5 (s, 1C, triazol-CH₂); ¹⁹F{¹H} NMR (282 MHz, d₆-DMSO) δF -189.4 (2F, dd, J 7.6, 5.6 Hz, CHF-2'), -209.8 (2F, dd, J 7.5, 5.6 Hz, CHF-3'); HRMS (ESI⁺) m/z [M+H-HCl]⁺ calcd for C₁₈H₁₁₂F₄ClN₃O₇⁺: 401.1601, found 401.1589.
(S)-2-Amino-3-(1-(3-(all-cis-2,3,5,6-tetrafluorocyclohexyl)benzyl)-1H-1,2,3-triazol-4-yl)propanoic acid hydrochloride (32)

Hydrochloride salt 32 (32 mg, 94%) was prepared following the procedure for the preparation of 26 starting from 31 (40 mg, 0.07 mmol) to afford the free amino acid. Mp. Decomposed at 226 ºC. 

\([\alpha]_D^{20} -78.0 \text{ (c= 5 \times 10}^{-4}, \text{ DMSO).}\)

\(^1H\) NMR (500 MHz, d$_6$-DMSO) \(\delta_H^{8.51 - 8.46 \text{ (3H, bd, NH$_3$), 8.08 (1H, d, J 4.0 Hz, H-triazol),}} \)

7.30 (2H, m, CH-2, CH-6), 7.38 (1H, t, J 7.6, CH-5), 7.23 (1H, d, J 7.7, CH-4), 5.60 (2H, s, PhCH$_2$), 5.19 - 5.05 (2H, m, CHF-2'), 5.04 - 4.86 (2H, m, CHF-3'), 4.22 - 4.18 (1H, m, CHNH$_3$), 3.32 (3H, m, CH-1, triazol-CH$_2$), 2.45 - 2.30 (2H, m, CH$_3$H$_6$-4); \(^{13}C\) NMR (100.6 MHz, d$_6$-DMSO) \(\delta_C^{170.4 \text{ (s,1C, COOH), 141.3 \text{ (s,1C, CN=N of triazol),137.9 \text{ (s, CH-1),}} \)

136.5 (s, CH-3), 129.3 (s, 2C, CH-2), 129.0 (s, 1C, CH-4), 128.9 (s, 1C, CH-5), 127.3 (s, 1C, CH-6), 124.5 (s,1C, CH-triazol), 90.9 - 88.9 (m, 2C, CHF-2'), 88.4 - 86.4 (m, 2C, CHF-3'), 53.2 (s, 1C, PhCH$_2$), 52.0 (s,1C, CHNH$_3$), 42.4 - 41.9 (m, 1C, CH-1'), 31.1 (s, 1C, triazol-CH$_2$), 27.3 (t, 1C, J 21.3 Hz, CH$_2$-4'); \(^{19}F\{'^1H\} NMR (470 MHz, d$_6$-DMSO) \(\delta_F^{–189.5 \text{ (2F, dd, J 7.6, 5.6 Hz, CHF-2′), –209.6 \text{ (2F, dd, J 7.6, 5.6 Hz, CHF-3′); HRMS (ESI\(^+\)) m/z [M+H-HCl]\(^+\) \)

calcd for C$_{18}$H$_{22}$F$_4$ClN$_{4}$O$_2$: 401.1601, found 401.1580.
$^1$H NMR of 8 (CDCl$_3$)

$^{19}$F{$^1$H} NMR of 8 (CDCl$_3$)

$^{13}$C NMR of 8 (CDCl$_3$)
$^1$H NMR of 9 (CDCl$_3$)

1st fraction carb 1:1

$^{19}$F {$^1$H} NMR of 9 (CDCl$_3$)

13C NMR of 9 (CDCl$_3$)

13C observe with 1H decoupling - UDEFT
first fract carbon meta
$^1$H NMR of 10 (CDCl$_3$)

$^{19}$F($^1$H) NMR of 10 (CDCl$_3$)

$^{13}$C NMR of 10 (CDCl$_3$)
$^1$H NMR of 11 (CD$_3$COCD$_3$)

$^{19}$F{$^1$H} NMR of 11 (CD$_3$COCD$_3$)

$^{13}$C NMR of 11 (CD$_3$COCD$_3$)
\( ^1H \text{NMR of 12 (CD}_3\text{COCD}_3) \)

\( ^19\text{F} \{^1H\} \text{NMR of 12 (CD}_3\text{COCD}_3 \)

\( ^{13}\text{C} \text{NMR of 12 (CD}_3\text{COCD}_3) \)
$^{1}H$ NMR of 13 (CD$_3$COCD$_3$)

$^{19}F^{(1}H)\) NMR of 13 (CD$_3$COCD$_3$)

$^{13}C$ NMR of 13 (CD$_3$COCD$_3$)
$^1$H NMR of 14 (CDCl$_3$)

$^{19}$F$^{1}$H NMR of 14 (CDCl$_3$)

$^{13}$C NMR of 14 (CDCl$_3$)
$^1$H NMR of 15 (CDCl$_3$)

$^{19}$F$^1$H NMR of 15 (CDCl$_3$)

$^{13}$C NMR of 15 (CDCl$_3$)
\(^1H\) NMR of 17 (CD\(_3\)COCD\(_3\))

\(^{19}\text{F}\{^1\text{H}\}\) NMR of 17 (CD\(_3\)COCD\(_3\))

\(^{13}\text{C}\) NMR of 17 (CD\(_3\)COCD\(_3\))
$^1$H NMR of 18 (CDCl$_3$)

$^{19}$F{$^1$H} NMR of 18 (CDCl$_3$)

$^{13}$C NMR of 18 (CDCl$_3$)
$^1$H NMR of 19 (CD$_3$COCD$_3$)

$^{19}$F{$^1$H} NMR of 19 (CD$_3$COCD$_3$)

$^{13}$C NMR of 19 (CD$_3$COCD$_3$)
\[ \text{H NMR of 20 (CDCl}_3\text{)} \]

\[ \text{F}\{\text{H} \}\text{ NMR of 20 (CDCl}_3\text{)} \]

\[ \text{C NMR of 20 (CDCl}_3\text{)} \]
$^1$H NMR of 21 (CDCl$_3$)

$^{19}$F{$^1$H} NMR of 21 (CDCl$_3$)

$^{13}$C NMR of 21 (CDCl$_3$)
$^1$H NMR of 23 (CDCl$_3$)

$^{19}$F{$^1$H} NMR of 23 (CDCl$_3$)

$^{13}$C NMR of 23 (CDCl$_3$)
$^1$H NMR of 25 (CDCl$_3$)

$^{19}$F{$^1$H} NMR of 25 (CDCl$_3$)

$^{13}$C NMR of 25 (CDCl$_3$)
$\textbf{1}^\text{H} \text{NMR of 26 (}\text{d}_6\text{-DMSO)}$

$\text{ }$

$\textbf{19}^\text{F(1H)} \text{NMR of 26 (}\text{d}_6\text{-DMSO)}$

$\textbf{13}^\text{C} \text{NMR of 26 (}\text{d}_6\text{-DMSO)}$

S29
$^1$H NMR of 27 (d$_6$-DMSO)

1H Observe
Amine HCl

$^{19}$F{$^1$H} NMR of 27 (d$_6$-DMSO)

13C NMR of 27 (d$_6$-DMSO)

13C Observe with 1H decoupling - UDEFT
Amine HCl

S30
$^1$H NMR of 28 (CDCl$_3$)

$^{19}$F{$^1$H} NMR of 28 (CDCl$_3$)

$^{13}$C NMR of 28 (CDCl$_3$)
$^1$H NMR of 30 (CDCl$_3$)

$^{19}$F{$^1$H} NMR of 30 (CDCl$_3$)

$^{13}$C NMR of 30 (CDCl$_3$)
$^1$H NMR of 32 (d$_6$-DMSO)

$^{19}$F$^1$H NMR of 32 (d$_6$-DMSO)

$^{13}$C NMR of 32 (d$_6$-DMSO)