Supporting Information

A de novo synthetic access route to 1,2,3,4-tetrahydroisoquinoline derivatives

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Experimental

General procedure for dihydroxylation of indene and substituted indene derivatives

To a stirred solution of indene and substituted indene derivatives (18 mmol) 0.3 mL of 2% OsO₄ solution in t-BuOH and NMO (1.2 equiv) in acetone/H₂O (30 mL/3 mL) were added and the resulting mixture was stirred for 3 h at room temperature. Workup included treatment with saturated aqueous Na₂SO₃ solution (20 mL) and extraction with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude product was purified by means of column chromatography on silica gel (n-hexane/EtOAc).

General procedure for the synthesis of fluorine-containing N-heterocyclic derivatives by oxidative ring cleavage followed by ring closure with reductive amination

NaIO₄ (1.5 equiv) was added to a stirred solution of dihydroxy compounds (4 mmol) in THF/H₂O (25 mL/2 mL). After stirring for 1 h at 20 °C under Ar atmosphere, H₂O was added until the dissolution of the precipitate (40 mL). The mixture was then extracted with CH₂Cl₂ (3 x 20 mL) and the combined extract was dried over Na₂SO₄. The crude dialdehyde product was immediately used for reductive ring closing without purification. Fluorinated and polyfluorinated amines (1 equiv) and NaHCO₃ (2 equiv) were added to the solution of the corresponding diformyl intermediates in EtOH (20 mL) and the mixture was stirred at 20 °C for 10 min. After the addition of NaCNBH₃ (1 equiv) and AcOH (2 drops), stirring was...
continued for another 4 h at 20 °C. The reaction mixture was diluted with H2O (20 mL) and extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (n-hexane/EtOAc).

(1R*,2S*)-2,3-Dihydro-1H-indene-1,2-diol (2)

White solid; yield: 75% (1.93 g); mp 83-85 °C; Rf = 0.34 (n-hexane/EtOAc 2:1); 1H NMR (400 MHz, DMSO): δ = 2.73-2.80 (m, 1 H, H-3), 2.88-2.97 (m, 1 H, H-3), 4.23-4.29 (m, 1 H, H-2), 4.52 (d, J = 4.64 Hz, 1 H, OH), 4.78 (t, J = 5.72 Hz, 1 H, H-1), 4.94 (d, J = 6.6 Hz, 1 H, OH), 7.16-7.33 (m, 4 H, Ar-H); 13C NMR (100 MHz, DMSO): δ = 39.1, 73.7, 75.8, 125.6, 125.6, 127.1, 128.5, 141.4, 144.8; Anal. Calcd for C9H10O2: C, 71.98; H, 6.71; O, 21.31; found: C, 71.97; H, 6.70; O, 21.30.

2-(2,2-Difluoroethyl)-1,2,3,4-tetrahydroisoquinoline (3)

Brown oil; yield: 31% (247.3 mg); Rf = 0.17 (n-hexane/EtOAc 20:1); 1H NMR (400 MHz, DMSO): δ = 2.77-2.84 (m, 4 H, H-3, H-4) 2.83-2.95 (td, 2 H, CH2CHF2, 1J = 15.6 Hz, 2J = 4.3 Hz), 3.71 (s, 2 H, H-1), 6.02-6.39 (tt, 1 H, CHF2, 1J = 55.8 Hz, 2J = 4.3 Hz), 6.98-7.18 (m, 4 H, Ar-H); 13C NMR (100 MHz, DMSO): δ = 29.2, 51.8, 56.6, 59.5 and 59.8 and 60.02 (t, 2JCF = 28 Hz, CCHF2), 114.5 and 116.9 and 119.3 (t, 1JCF = 237.5 Hz, CHF2), 126.4, 126.9, 127.1, 129.3, 134.6, 135.3; 19F NMR (376 MHz, DMSO): δ = -115.2. MS: (ESI) m/z = 198.2 (M+1); Anal. Calcd for C11H13F2N: C, 66.99; H, 6.64; F, 19.27; N, 7.10; found: C, 66.96; H, 6.63; F, 19.26; N, 7.10.

2-(2,2,2-Trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (4)

Brown oil; yield: 20% (170.8 mg); Rf = 0.24 (n-hexane/EtOAc 20:1); 1H NMR (400 MHz, DMSO): δ = 2.78-2.84 (m, 2 H, H-3), 2.88-2.94 (m, 2 H, H-4), 3.28-3.38 (m, 2 H, CH2CF3), 3.80 (s, 2 H, H-1), 7.00-7.16 (m, 4 H, Ar-H); 13C NMR (100 MHz, DMSO): δ = 29.2, 51.8,
56.2, 57.0 and 57.3 and 57.6 and 57.9 (q, $^2J_{CF} = 29.31$ Hz, CCF$_3$), 123.4 and 125.6 and 128.4 and 131.1 (q, $^1J_{CF} = 268.0$ Hz, CF$_3$), 126.5, 127.0, 127.2, 129.4, 134.5, 135.1; $^{19}$F NMR (376 MHz, DMSO): $\delta = -68.1$ (t, $J = 10.2$); MS: (ESI) m/z = 216.2 (M+1); Anal. Calcd for C$_{11}$H$_{12}$F$_3$N: C, 61.39; H, 5.62; F, 26.48; N, 6.51; found: C, 61.37; H, 5.61; F, 26.47; N, 6.50.

2-(2-Fluoroethyl)-1,2,3,4-tetrahydroisoquinoline (5)

Yellow oil; yield: 76% (546.3 mg); R$_f$ = 0.33 (n-hexane/acetone 4:1); $^1$H NMR (400 MHz, DMSO): $\delta = 2.69$-2.85 (m, 6 H, H-3, H-4, CH$_2$CH$_2$F), 3.63 (s, 2 H, H-1), 4.51-4.71 (dt, 2 H, CH$_2$F, $^1J = 47.9$ Hz, $^2J = 4.9$ Hz), 6.98-7.14 (m, 4 H, Ar-H); $^{13}$C NMR (100 MHz, DMSO): $\delta =$ 29.5, 51.6, 56.4, 58.1 and 58.3 (d, $^2J_{CF} = 19.5$ Hz, CCH$_2$F), 82.1 and 83.7 (d, $^1J_{CF} = 163.4$ Hz, CH$_2$F), 126.3, 126.8, 127.2, 129.3, 134.8, 135.6; $^{19}$F NMR (376 MHz, DMSO): (tt, $J = 47.7$, $J = 28.1$; MS: (ESI) m/z = 180.2 (M+1); Anal. Calcd for C$_{11}$H$_{14}$FN: C, 73.71; H, 7.87; F, 10.60; N, 7.81 found: C, 73.69; H, 7.86; F, 10.59; N, 7.80.

2-(1,1,1-Trifluoropropan-2-yl)-1,2,3,4-tetrahydroisoquinoline (6)

Colorless oil; yield: 34% (312 mg); R$_f$ = 0.22 (n-hexane-EtOAc 10:1); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.32$ (d, 3 H, CH$_3$), 2.78-3.06 (m, 4 H, H-3, H-4), 3.29-3.46 (m, 1 H, N-CH), 3.83-4.03 (dd, 2 H, H-1, $^1J = 46$ Hz, $^2J = 16$ Hz), 6.96-7.16 (m, 4 H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 10.7, 30.5, 47.5, 52.2, 60.4 and 60.7 and 60.9 and 61.2 (q, $^2J_{CF} = 26.3$ Hz, CCF$_3$), 126.1, 126.5, 126.8, 129.0, 129.3, 134.8, 135.4; $^{19}$F NMR (376 MHz, DMSO): $\delta = -71.3$; MS: (ESI) m/z = 229.11 (M+1); Anal. Calcd for C$_{12}$H$_{14}$F$_3$N: C, 62.87; H, 6.16; F, 24.86; N, 6.11, found: C, 62.85; H, 6.15; F, 24.85; N, 6.10.

2-(2,2,3,3,4,4,5,5,5-Nonafluoropentyl)-1,2,3,4-tetrahydroisoquinoline (7)

Yellow oil; yield: 24% (351 mg); R$_f$ = 0.24 (n-hexane); $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 2.88-2.95 (m, 2 H, H-3), 2.96-3.04 (m, 2 H, H-4), 3.23 (t, 2 H, N-CH$_2$, $J = 15.8$ Hz), 3.89 (s, 2 H, H-1), 6.98-7.19 (m, 4 H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 29.1, 52.3, 56.7 and 56.9 and
57.1 (t, $^2J_{C,F}$ = 22 Hz, C(CF$_3$)$_3$), 57.0, 107.9-120.9 (m, 4 C, (CF$_2$)$_3$CF$_3$), 126.2, 126.8, 126.9, 129.2, 134.2, 134.5; $^{19}$F NMR (100 MHz, DMSO): $\delta$ = -81.0, -115.8, -124.1, -126.1. MS: (ESI) m/z = 725.6 (2M+1); Anal. Calcd for C$_{14}$H$_{12}$F$_9$N: C, 46.04; H, 3.31; F, 46.81; N, 3.83; found: C, 46.03; H, 3.30; F, 46.80; N, 3.82.

$\text{CF}_2\text{CF}_2\text{CF}_3$

2-(2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoroheptyl)-1,2,3,4-tetrahydroisoquinoline (8)
Colorless crystals; yield: 53% (992 mg); mp 29-31 °C; $R_f$ = 0.43 (n-hexane/EtOAc 10:1); $^1$H NMR (400MHz, CDCl$_3$): $\delta$ = 2.86-2.94 (m, 2 H, H-3), 2.94-3.03 (m, 2 H, H-4), 3.22 (t, $^2J_{C,F}$ = 16.0 Hz), 3.89 (s, 2 H, H-1), 6.96-7.17 (m, 4 H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 29.1, 52.3, 56.8 and 56.9 and 57.2 (t, $^2J_{C,F}$ = 22 Hz, C(CF$_2$)$_3$), 57.0, 107.8-121.5 (m, 6 C, (CF$_2$)$_3$CF$_3$), 126.2, 126.8, 126.9, 129.2, 134.3, 134.5; $^{19}$F NMR (376 MHz, DMSO): $\delta$ = -78.6, -113.3, -119.6, -120.5, -120.9, -123.8; MS: (ESI) m/z = 466.3 (M+1); Anal. Calcd for C$_{16}$H$_{12}$F$_{13}$N: C, 41.30; H, 2.60; F, 53.08; N, 3.01; found: C, 41.29; H, 2.58; F, 53.06; N, 3.00.

$\text{CF}_2\text{CF}_2\text{CF}_3$

2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-Heptadecafluorodecyl)-1,2,3,4-tetrahydroisoquinoline (9)
Yellow solid; yield: 28% (655 mg); mp 26-28 °C; $R_f$ = 0.24 (n-hexane-EtOAc 10:1); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.33-2.53 (m, 2 H, N-CH$_2$-CH$_2$), 2.76-2.96 (m, 6 H, N-CH$_2$, H-3, H-4), 3.69 (s, 2 H, H-1), 6.99-7.18 (m, 4 H, Ar-H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 29.2, 29.3 and 29.5 and 29.7 (t, $^2J_{C,F}$ = 21 Hz, C(CF$_2$)$_3$), 49.4, 51.0, 56.1, 106.6-122.4 (m, 8 C, (CF$_2$)$_3$CF$_3$), 125.9, 126.5, 126.6, 128.8, 134.0, 134.2; $^{19}$F NMR (376 MHz, DMSO): $\delta$ = -80.9 (t, $J$ = 10.0 Hz), -113.9, -121.6, -121.9, -122.6, -123.4, -126.1; MS: (ESI) m/z = 580.4 (M+1); Anal. Calcd for C$_{19}$H$_{14}$F$_{17}$N: C, 39.39; H, 2.44; F, 55.75; N, 2.42; found: C, 39.38; H, 2.43; F, 55.74; N, 2.41.

(1$^R$,2$^S$)-4-Bromo-2,3-dihydro-1$^H$-indene-1,2-diol (11)
White solid; yield: 68% (400 mg); mp 96-101 °C; Rf = 0.33 (n-hexane/EtOAc 1:1); \( ^1\)H NMR (400 MHz, DMSO): \( \delta = 2.84-2.93 \) (m, 1 H, H-3), 2.97-3.07 (m, 1 H, H-3), 4.13-4.23 (m, 1 H, H-2), 4.70 (t, \( J = 5.52 \) Hz, 1 H, H-1), 4.88 (d, \( J = 6.6 \) Hz, 1 H, OH), 4.91 (d, \( J = 5.7 \) Hz, 1 H, OH), 7.14-7.38 (m, 3 H, Ar-H) ppm; \( ^13\)C NMR (100 MHz, DMSO): \( \delta = 39.5, 72.6, 75.2, 121.3, 125.0, 130.7, 131.2, 143.7, 144.7 \); Anal. Calcd for C\(_9\)H\(_9\)BrO\(_2\): C, 47.19; H, 3.96; Br, 34.88; O, 13.97; found: C, 47.18; H, 3.95; Br, 34.86; O, 13.96.

5-Bromo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (12)

Yellow oil; yield: 53% (274 mg); Rf = 0.29 (n-hexane); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 2.84-3.06 \) (m, 4 H, H-3, H-4), 3.11-3.26 (m, 2 H, CH\(_2\)CF\(_3\)), 3.86 (s, 2 H, H-1), 6.94-7.45 (m, 3 H, Ar-H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 30.2, 51.9, 56.4, 57.6 \) and 57.9 and 58.2 and 58.5 (q, \( ^2\)J\(_{CF} = 30 \) Hz, CCF\(_3\)), 125.8; 121.7 and 124.5 and 127.3 and 130.1 (q, \( ^1\)J\(_{CF} = 279.8 \) Hz, CF\(_3\)), 126.1, 127.6, 130.9, 134.1, 136.9; \(^19\)F NMR (376 MHz, DMSO): \( \delta = -69.2 \) (t, \( J = 9.3 \) Hz); MS: (ESI) m/z = 294.11 (M+1); Anal. Calcd for C\(_{11}\)H\(_{11}\)BrF\(_3\)N: C, 44.92; H, 3.77; Br, 27.17; F, 19.38; N, 4.76; found: C, 44.90; H, 3.76; Br, 27.17; F, 19.37; N, 4.76.

5-Bromo-2-(2,2-difluoroethyl)-1,2,3,4-tetrahydroisoquinoline (13)

Brown oil; yield: 55% (80 mg); Rf = 0.56 (n-hexane/EtOAc 4:1); \(^1\)H NMR (500 MHz, DMSO): \( \delta = 2.84-2.98 \) (m, 6 H, H-3, H-4, CH\(_2\)CHF\(_2\)), 3.78 (s, 2 H, H-1), 5.84-6.10 (tt, 1 H, CHF\(_2\)), \( ^1\)J = 55.8 Hz, \( ^2\)J = 4.2 Hz), 6.95-7.43 (m, 3 H, Ar-H); \(^13\)C NMR (126 MHz, DMSO): \( \delta = 29.8, 51.8, 56.4, 59.0 \) and 59.2 and 59.4 (t, \( ^2\)J\(_{CF} =25.4 \) Hz, CCHF\(_2\)), 113.9 and 115.8 and 117.7 (t, \( ^1\)J\(_{CF} = 243.8 \) Hz, CHF\(_2\)), 125.3, 125.7, 127.2, 130.5, 133.6, 136.4; \(^19\)F NMR (471 MHz, DMSO): \( \delta = -118.3 \) (dt, \( J = 55.9 \) Hz, \( J = 14.8 \) Hz); MS: (ESI) m/z = 276.3 (M+1); Anal. Calcd for C\(_{11}\)H\(_{12}\)BrF\(_2\)N: C, 47.85; H, 4.38; Br, 28.94; F, 13.76; N, 5.07; found: C, 47.83; H, 4.37; Br, 28.93; F, 13.75; N, 5.06.
(1R*,2S*)-2-Methyl-2,3-dihydro-1H-indene-1,2-diol (15)

White solid; yield: 75% (470 mg); mp 81-86 °C; Rf = 0.17 (n-hexane/EtOAc 2:1); 1H NMR (400 MHz, DMSO): δ = 1.31 (s, 3 H, CH₃), 2.97-3.07 (m, 2 H, H-3), 4.14 (s, 1 H, H-1), 4.54 (d, J = 6.8 Hz, 1 H, OH), 5.11 (d, J = 7.0 Hz, 1 H, OH), 7.11-7.30 (m, 4 H, Ar-H); 13C NMR (100 MHz, DMSO): δ = 26.3, 45.2, 79.6, 80.5, 125.4, 125.5, 127.0, 128.2, 141.5, 145.5; Anal. Calcd for C₁₀H₁₂O₂: C, 73.15; H, 7.37; O, 19.49; found C, 73.13; H, 7.36; O, 19.48.

3-Methyl-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (16)

Yellow oil; yield: 33% (219 mg); Rf = 0.56 (n-hexane-EtOAc 10:1); 1H NMR (400 MHz, CDCl₃): δ = 1.15 (d, 3 H, CH₃, J = 6.6 Hz), 2.51-2.60 (m, 1 H, H-3), 2.89 -3.29 (m, 4 H, H-4, CH₂CF₃), 3.92 and 3.96 and 4.00 and 4.05 (dd, 2 H, H-1, 1J = 35 Hz, 2J = 15 Hz), 6.99-7.19 (m, 4 H, Ar-H); 13C NMR (100 MHz, CDCl₃): δ = 17.3, 34.4, 52.4 and 52.7 and 53.0 and 53.3 (q, 2JC,F = 31.3 Hz, CCF₃), 53.7, 54.1, 123.0 and 124.9 and 127.7 and 130.5 (q, 1JC,F = 278 Hz, CF₃), 126.3, 126.9, 127.0, 129.5, 133.8, 134.1; 19F NMR (376 MHz, DMSO): δ = -70.2 (t, J = 9.5 Hz); MS: (ESI) m/z = 230.6 (M+1); Anal. Calcd for C₁₂H₁₄F₃N: C, 62.87; H, 6.16; F, 24.86; N, 6.11, found: C, 62.85; H, 6.15; F, 24.85; N, 6.10.

2-Ethyl-1,2,3,4-tetrahydroisoquinoline (17)

Yellow oil; yield: 59% (253 mg); Rf = 0.51 (n-hexane-EtOAc 1:1); 1H NMR (500 MHz, CDCl₃): δ = 1.33 (t, 3 H, CH₃, J = 7.3 Hz), 2.98-3.06 (m, 4 H, H-3, H-4), 3.29-3.39 (m, 2 H, CH₂CH₃), 4.00 and 4.04 and 4.24 and 4.28 (dd, 2 H, H-1, 1J = 119.6 Hz, 2J = 15.9 Hz), 7.04-7.29 (m, 4 H, Ar-H); 13C NMR (126 MHz, CDCl₃): δ = 9.2, 23.7, 51.3, 52.9, 58.9, 127.0, 127.3, 127.9, 128.7, 130.5 ppm. MS: (ESI) m/z = 201.2 (M+40); Anal. Calcd for C₁₁H₁₅N: C, 81.94; H, 9.38; N, 8.69, found: C, 81.93; H, 9.37; N, 8.68.

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2-Butyl-1,2,3,4-tetrahydroisoquinoline (18)\(^{10}\)
Yellow oil; yield: 23% (118 mg); \(R_f = 0.25\) (\(n\)-hexane-EtOAc 4:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 0.95\) (t, 3 H, CH\(_3\), \(J = 7.4\) Hz), 1.33-1.43 (m, 2 H, \(CH_2\)CH\(_3\)), 1.53-1.65 (m, 2 H, \(CH_2\)CH\(_2\)CH\(_3\)), 2.51 (t, 2 H, NCH\(_2\), \(J = 7.6\) Hz), 2.74 (t, 2 H, H-3, \(J = 5.9\) Hz), 2.91 (t, 2 H, H-4, \(J = 6.2\) Hz), 3.63 (s, 2 H, H-1), 6.99-7.14 (m, 4 H, Ar-H); MS: (ESI) \(m/z = 190.4\) (M+1); Anal. Calcd for C\(_{13}\)H\(_{19}\)N: C, 82.48; H, 10.12; N, 7.40, found: C, 82.46; H, 10.11; N, 7.39.

\[\text{\includegraphics[width=0.5\textwidth]{2-butyl-tetrahydroisoquinoline}}\]

2-Benzyl-1,2,3,4-tetrahydroisoquinoline (19)\(^{11}\)
Yellow solid; yield: 69% (294 mg); mp 96-100 °C; \(R_f = 0.40\) (\(n\)-hexane-EtOAc 6:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 2.75\) (t, 2 H, H-3, \(J = 7.4\) Hz), 2.90 (t, 2 H, H-4, \(J = 7.6\) Hz), 3.63 (s, 2 H, H-1), 3.69 (s, 2 H, \(CH_2\)-Ph), 6.95-7.42 (m, 9 H, Ar-H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta:\) 29.1, 50.6, 56.1, 62.8, 125.5, 126.1, 126.6, 127.1, 128.3, 128.7, 129.1, 134.4, 134.9, 138.4; MS: (ESI) \(m/z = 224.1\) (M+1); Anal. Calcd for C\(_{16}\)H\(_{17}\)N: C, 86.05; H, 7.67; N, 6.27, found: C, 86.03; H, 7.66; N, 6.26.
NMR spectra of the synthetized compounds
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