Synthesis of β,β -Difluorotryptamines

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***tert*-Butyl 3-(2-azido-acetyl)-5-benzyloxy-indole-1-carboxylate (13c).**

***tert*-Butyl 3-(2-azido-1,1-difluoro-ethyl)-5-benzyloxy-indole-1-carboxylate (14c).**

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Supporting Information

Synthetic Procedures

1-Benzenesulfonyl-3-(2-bromo-1-fluoro-ethyl)-1H-indole (6b). To a cooled (0 °C) and stirred solution of indole **5b** (726 mg, 2.57 mmol) dissolved in 30 mL of CH₂Cl₂ was added 0.55 mL (5.13 mmol) of Et₃N·3HF and 0.24 mL of Et₃N. After 15 min, 504 mg (2.83 mmol) of NBS was added in portions. The mixture was allowed to warm to room temperature over 1-2 h and then poured into 100 mL of brine, extracted with CH₂Cl₂ and dried over MgSO₄. After evaporation of solvent, the residue was purified by flash column chromatography (silica gel, EtOAc/Hexane, 9:1) to afford 560 mg (57%) of FBr adduct **6b**. This compound is unstable to storage at room temperature. ¹H NMR: 8.00 (1H, d, 8.4), 7.90 (2H, d, 7.8), 7.68 (1H, d, 2.1), 7.57 (2H, t, 7.8), 7.46 (2H, t, 7.5), 7.37 (1H, t, 7.5), 7.28 (1H, t, 6.8), 5.87 (1H, ddd, 5.4, 6.9, 46.5), 3.69-3.91 (2H, m). HRMS Calcd. For C₁₆H₁₃BrFNO₂S: 380.9834 (Br79), 382.9814 (Br81). Found: 380.9842 (Br79), 382.9818 (Br81).

1-Benzenesulfonyl-3-(1-fluoro-vinyl)-1H-indole (7). To a solution of 550 mg (1.44 mmol) of **6b** in 20 mL of dry DMF was added 596 mg (4.32 mmol) of K₂CO₃. After the resulting mixture was stirred at 80 °C for 6 h it was then evaporated to dryness and partitioned between 50 mL of ether and 50 mL of brine. The organic layer was again

washed with brine, dried over MgSO_4 and evaporated. Separation by silica gel chromatography (EtOAc/Hexane, 9:1) gave 340 mg (78%) of **7** as a white solid.

^1H NMR: 8.03 (1H, d, 8.1), 7.90-7.94 (2H, m), 7.82 (1H, s), 7.74 (1H, d, 7.8), 7.57 (1H, m), 7.46 (2H, t, 7.5), 7.44-7.50 (2H, m), 7.29-7.41 (2H, m), 5.05 (1H, dd, 3.6, 19.8), 4.92 (1H, dd, 3.6, 12.6). ^{19}F NMR: -24.40 (dd, 19.2, 52.2). HRMS Calcd. For $\text{C}_{16}\text{H}_{12}\text{FNO}_2\text{S}$: 301.0573. Found: 301.0576.

1-Benzenesulfonyl-3-(2-bromo-1,1-fluoro-ethyl)-1H-indole (8). Using the procedure as described for the reaction with **5b**, 333 mg (1.2 mmol) of olefin **7** was subjected to bromofluorination with 0.36 mL (2.2 mmol) of $\text{Et}_3\text{N}\cdot 3\text{HF}$ and 214 mg (1.2 mmol) of NBS to give 330 mg (75%) of **8** as an off-white solid. ^1H NMR: 8.00 (1H, d, 9.0), 7.92 (2H, d, 7.5), 7.84 (1H, s), 7.60 (1H, dd, 7.5, 12.6), 7.49 (2H, t, 7.5), 7.39 (1H, t, 7.2), 7.31 (1H, t, 7.8), 3.87 (t, 13.5). ^{19}F NMR: -17.45 (t, 13.5). ^{13}C NMR: 137.83, 135.12, 134.58, 129.73, 127.73, 126.62, 126.04 (t, 8.0), 125.87, 124.34, 120.48, 117.64 (t, 241.2), 116.54 (t, 30.4), 113.97, 33.01 (t, 35.0).

1-Benzenesulfonyl-3-(2-iodo-1,1-fluoro-ethyl)-1H-indole (9). Using a procedure similar to that described for the addition of "FBr" to **5b**, 30 mg (0.1 mmol) of olefin **7** was subjected to iodofluorination with 0.04 mL (0.2 mmol) of $\text{Et}_3\text{N}\cdot 3\text{HF}$ and 0.11 mmol of NIS to afford 41 mg (91%) of **9** as a brown solid. ^1H NMR: 8.00 (1H, d, 9.0), 7.92 (2H, dd, 1.5, 7.5), 7.82 (1H, t, 1.5), 7.60 (1H, dd, 7.5, 12.6), 7.48 (2H, t, 7.5), 7.39 (1H, t, 7.2), 7.30 (1H, t, 7.8), 3.79 (t, 14.7). ^{19}F NMR: -12.63 (t, 14.4). HRMS Calcd. For $\text{C}_{16}\text{H}_{12}\text{F}_2\text{NO}_2\text{I}$: 446.9602. Found: 446.9608.

Characterization Data:

2-Azido-1-(1H-indol-3-yl)-ethanone (12a). ^1H NMR (300 MHz, Acetone- d_6) δ : 8.29 (2H, m), 7.55 (1H, m), 7.28-7.23 (2H, m), 4.50 (2H, s).

***tert*-Butyl 3-(2-azido-acetyl)-indole-1-carboxylate (13a).** ^1H NMR (CDCl_3) δ : 8.35 (1H, d, $J = 9.3$ Hz), 8.25 (1H, s), 8.13 (1H, d, $J = 9.3$ Hz), 7.38-7.42 (2H, m), 4.42 (2H, s), 1.71 (9H, s). ^{13}C NMR (75.46 MHz, CDCl_3) δ : 189.37, 148.98, 135.48, 132.01, 127.23, 126.07, 124.84, 122.61, 117.57, 115.23, 86.06, 55.23, 28.22.

***tert*-Butyl 3-(2-azido-1,1-difluoro-ethyl)-indole-1-carboxylate (14a).** ^1H NMR (CDCl_3) δ : 8.07 (1H, d, $J = 8.4$ Hz), 7.70 (1H, s), 7.53 (1H, d, $J = 8.1$ Hz), 7.26 (1H, t, $J = 7.2$ Hz), 7.18 (1H, t, $J = 7.8$ Hz), 3.73 (2H, t, $J = 12.9$ Hz), 1.58 (9H, s). ^{13}C NMR: 149.25, 135.66, 126.41 (t, 2.6), 125.46 (t, $J = 8.6$ Hz), 123.66, 119.98, 119.56 (t, $J = 241.3$ Hz), 115.73, 114.78 (t, $J = 29.2$ Hz), 85.02, 55.55 (t, $J = 32.1$ Hz), 28.26 (9 C, *t*-Bu). ^{19}F NMR: -20.90 (t, $J = 13.8$). HRMS Calcd. for $\text{C}_{15}\text{H}_{16}\text{F}_2\text{N}_4\text{O}_2$: 322.1241. Found: 322.1242.

***tert*-Butyl 3-(2-amino-1,1-difluoro-ethyl)-indole-1-carboxylate (15a).** ^1H NMR (CDCl_3) δ : 8.18 (1H, d, $J = 8.1$ Hz), 7.77 (1H, s), 7.65 (1H, d, $J = 7.8$ Hz), 7.37 (1H, t, $J = 7.5$ Hz), 7.28 (1H, t, $J = 8.1$ Hz), 3.34 (2H, t, $J = 14.1$ Hz), 1.68 (9H, s). ^{13}C NMR: 149.37 (BOC), 135.72, 126.73 (t, 2.6), 125.28, 124.98 (t, 8.1), 123.48, 121.02 (CF_2 , t, 24.0), 120.20, 115.97 (t, 31.0), 115.64, 84.78, 48.74 (t, 30.4), 28.25 (9C, *t*-Bu). ^{19}F NMR: -25.39 (t, 13.8). HRMS Calcd. for $\text{C}_{15}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_2$: 296.1336. Found: 296.1342.

2-Chloro-1-(5-methoxy-1H-indol-3-yl)-ethanone (11b). ^1H NMR (300 MHz, DMSO- d_6) δ : 12.01 (1H, br s, NH), 8.37 (1H, d, $J = 3.3$ Hz), 7.67 (1H, d, $J = 2.4$ Hz), 7.38 (1H, d, $J = 9.0$ Hz), 6.87 (1H, dd, $J = 8.7$ Hz, 2.4 Hz), 4.84 (2H, s), 3.78 (3H, s). ^{13}C NMR (75 MHz, DMSO- d_6) δ : 186.05 (-C=O), 155.68, 134.85, 131.40, 126.25, 113.48, 113.09, 113.01, 102.86, 55.25 (CH_2Cl), 46.32 (OCH_3).

2-Azido-1-(5-methoxy-1H-indol-3-yl)-ethanone (12b). ^1H NMR (300 MHz, CDCl_3) δ : 11.99 (1H, br s, NH), 8.29 (1H, s), 7.66 (1H, d, $J = 2.4$ Hz), 7.38 (1H, d, $J = 8.7$ Hz), 6.87 (1H, dd, $J = 9.0$ Hz, 2.3 Hz), 4.58 (2H, s), 3.79 (3H, s). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 188.9 (-C=O), 155.7, 134.4, 131.4, 126.0, 113.0, 102.7, 55.2 (CH_2N_3), 53.7 (OCH_3).

***tert*-Butyl 3-(2-azido-acetyl)-5-methoxy-indole-1-carboxylate (13b).** ^1H NMR (300 MHz, CDCl_3) δ : 8.20 (1H, s), 7.99 (1H, d, $J = 9.0$ Hz), 7.86 (1H, d, $J = 2.7$ Hz), 7.01 (1H, dd, $J = 2.7$ Hz, 9.0 Hz), 4.40 (2H, s), 3.89 (3H, s), 1.70 (6H, s). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 189.6 (C=O), 157.6, 149.0 (BOC), 132.2, 132.0, 128.3, 117.3, 116.0, 115.8, 104.2, 86.0, 55.9, 55.1, 28.3 (9C, *t*-Bu). MS (FAB): 330.1344 $\text{C}_{16}\text{H}_{18}\text{O}_4\text{N}_4$.

***tert*-Butyl 3-(2-azido-1,1-difluoro-ethyl)-5-methoxy-indole-1-carboxylate (14b).** ^1H NMR (300 MHz, CDCl_3) δ : 8.06 (1H, d, $J = 9.0$ Hz), 7.77 (1H, s), 7.08 (1H, d, $J = 2.1$ Hz), 7.00 (1H, dd, $J = 9.15$ Hz, 2.7 Hz), 5.29 (1H, s), 3.86 (9H, s), 3.83 (2H, t, $J = 13.2$ Hz), 1.67 (9H, s). ^{13}C NMR (75 MHz, CDCl_3) δ : 156.5, 149.3 (BOC), 130.3, 127.3, 125.9 (t, $J = 8.6$ Hz), 122.9, 119.7, 116.5, 114.5, 102.5, 84.9, 55.9, 55.5, 55.1, 28.3 (9C, *t*-Bu).

***tert*-Butyl 3-(2-amino-1,1-difluoro-ethyl)-5-methoxy-indole-1-carboxylate**

(15b). ^1H NMR (300 MHz, CDCl_3) δ : 8.05 (1H, d, $J = 9.0$ Hz), 7.73 (1H, s), 7.07 (1H, d, $J = 2.4$ Hz), 6.98 (1H, dd, $J = 9.3$ Hz, 2.7 Hz), 5.29 (1H, s), 3.86 (3H, s), 3.33 (2H, t, $J = 14.4$ Hz), 1.66 (9H, s). ^{13}C NMR (75 MHz, CDCl_3) δ : 156.3, 149.3, 130.1, 127.2, 125.4 ($J = 6.56$ Hz), 121.0, (t, $J = 226.0$ Hz), 116.4, 115.6, 114.2, 102.6, 84.6, 55.8, 48.6 (t, $J = 30.3$ Hz), 28.3. ^{19}F NMR (CD_3Cl) δ : -25.43 (t, $J = 15.2$ Hz). HRMS: Calcd. for $\text{C}_{16}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_2$: 326.1442, Found: 326.1455.

***tert*-Butyl 3-(2-acetylamino-1,1-difluoro-ethyl)-5-methoxy-indole-1-**

carboxylate (16). ^1H NMR (300 MHz, CDCl_3) δ : 8.05 (1H, d, $J = 9.3$ Hz), 7.90 (1H, s), 7.15 (1H, d, $J = 2.4$ Hz), 6.98 (1H, dd, $J = 9.0$ Hz, 2.4 Hz), 5.82 (1H, br s), 4.08 (2H, td, $J = 14.4$ Hz, 6.3 Hz), 3.87 (3H, s), 2.04 (3H, s), 1.66 (9H, s). ^{13}C NMR (75 MHz, CDCl_3) δ : 170.4, 156.5, 149.2, 127.3, 125.7 (t, $J = 8.6$ Hz), 122.7, 119.7, 116.4, 114.5, 102.5, 84.8, 55.9, 44.8 (t, $J = 29.8$ Hz), 28.32, 23.45. ^{19}F NMR (282.18 MHz, CD_3Cl) δ : -21.83 (t, 15.2). HRMS m/z (M^+) Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{N}_2\text{F}_2$ 368.1548: Found 368.1554.

5-Methoxy-3-(2-methyl-oxazol-5-yl)-1H-indole (17). ^1H NMR (300 MHz, CDCl_3) 8.43 (bs, 1H, NH), 7.48 (d, 2H, $J = 2.7$ Hz), 7.32 (d, 1H, $J = 9.0$ Hz), 7.24 (d, 1H, $J = 2.4$ Hz), 6.93 (dd, 1H, $J = 2.1$ Hz, 9.4 Hz), 3.90 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) 155.2, 147.6, 131.5, 124.8, 122.4, 120.0, 113.3, 112.4, 106.0, 102.1, 56.1 (OCH_3), 14.2 (CH_3). HRMS Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2$ (MH^+): 229.1979. Found: 229.2233.

(MH⁺). Anal. Calcd for C₁₃H₁₂N₂O₂: C, 68.41; H, 5.38; N, 12.27. Found: C, 68.15; H, 5.35; N, 12.17.

1-(5-Benzyloxy-1H-indol-3-yl)-2-chloro-ethanone (11c). Mp:>218 °C (dec.).

¹H NMR (300 MHz, DMSO-d₆) δ: 12.06 (bs, 1H), 8.37 (d, 1H, *J* = 3.3 Hz), 7.76 (d, 1H, *J* = 2.1 Hz), 7.32-7.49 (m, 6H), 6.95 (dd, 1H, *J* = 8.7 Hz, 2.4 Hz), 5.13 (s, 2H), 4.84 (s, 2H). ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 105.9, 154.6, 137.4, 134.9, 131.5, 128.3, 127.6, 127.5, 126.2, 113.5, 113.4, 113.1, 104.4, 69.6, 46.3. HRMS Calcd for C₁₇H₁₄ClNO₂: 299.0713. Found: 299.0711.

2-Azido-1-(5-benzyloxy-1H-indol-3-yl)-ethanone (12c). ¹H NMR (300 MHz, DMSO-d₆) δ: 12.01 (bs, 1H), 8.29 (d, 1H, *J* = 3.3 Hz), 7.77 (d, 1H, *J* = 2.4 Hz), 7.32-7.50 (m, 6H), 6.95 (dd, 1H, *J* = 8.7 Hz, 2.4 Hz), 5.13 (s, 2H), 4.58 (s, 2H)., ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 188.8, 154.7, 137.4, 134.5, 131.5, 128.4, 127.7, 127.6, 126.0, 113.6, 113.4, 113.1, 104.3, 69.6, 53.8. HRMS Calcd for C₁₇H₁₄N₄O₂: 306.1117. Found: 306.111.

***tert*-Butyl 3-(2-azido-acetyl)-5-benzyloxy-indole-1-carboxylate (13c).** ¹H NMR (300 MHz, CDCl₃) δ: 8.20 (s, 1H), 7.99 (d, 1H, *J* = 9.0 Hz), 7.96 (d, 1H, *J* = 2.7 Hz), 7.32-7.50 (m, 6H), 7.08 (dd, 1H, *J* = 9.15 Hz, 3 Hz), 5.15 (s, 2H), 4.39 (s, 2H), 1.70 (s, 9 Hz)., ¹³C NMR (75.5 MHz, CDCl₃) δ: 189.6, 156.6, 149.0, 137.1, 132.3, 130.2, 128.8, 128.3, 128.2, 127.9, 117.4, 116.4, 116.1, 105.6, 86.1, 70.7, 55.2, 28.3. HRMS Calcd. for C₂₂H₂₂N₄O₄: 406.1641. Found: 406.1651.

***tert*-Butyl ester 3-(2-azido-1,1-difluoro-ethyl)-5-benzyloxy-indole-1-**

carboxylate (14c). ^1H NMR (300 MHz, CDCl_3) δ : 8.05 (d, 1H, $J = 9$ Hz), 7.77 (s, 1H), 7.32-7.49 (m, 6H), 7.16 (s, 1H), 7.06 (dd, 1H, $J = 9.15$ Hz, 2.7 Hz), 5.28 (s, 2H), 5.11 (s, 2H), 3.79 (t, 2H, $J = 13.2$ Hz), 1.67 (s, 9H)., ^{13}C NMR (75.5 MHz, CDCl_3) δ : 155.6, 149.3, 137.1, 130.5, 128.8, 128.2, 127.8, 127.2, 125.9 (t, $J = 8.6$ Hz), 119.6 (t, $J = 241.2$ Hz), 116.5, 115.1, 114.5 (t, $J = 31.0$ Hz), 104.1, 84.9, 70.8, 55.5 (t, $J = 31.5$ Hz), 28.3. ^{19}F NMR (282.18 MHz, CDCl_3) δ : -26.54 (t, $J = 17.2$ Hz). HRMS Calcd. for $\text{C}_{22}\text{H}_{22}\text{F}_2\text{N}_4\text{O}_3$: 428.1660. Found: 428.1660.

***tert*-Butyl 3-(2-amino-1,1-difluoro-ethyl)-5-hydroxy-indole-1-carboxylate**

(15d). ^1H NMR (300 MHz, CDCl_3) δ : 7.99 (d, 1H, $J = 8.7$ Hz), 7.71 (s, 1H), 6.96 (s, 1H), 6.89 (d, 1H, $J = 8.7$ Hz), 3.34 (t, 2H, $J = 14.4$ Hz), 1.65 (s, 9H)., ^{13}C NMR (75.5 MHz, CD_3OD) δ : 155.0, 150.7, 131.13, 129.0, 126.6 (t, $J = 8.0$ Hz), 125.3, 122.2, 119.0, 117.2, 116.7, 116.4, 115.4, 105.9, 85.7, 48.5 (t, $J = 30.4$ Hz), 28.4. ^{19}F NMR (282.18 MHz, CD_3OD) δ : 24.7 (t, $J = 15.2$ Hz).