Synthetic Procedures

General Procedures. All reactions were performed in oven-dried or flame-dried glassware under a positive pressure of nitrogen unless otherwise noted. Flash column chromatography was performed as described by Still et al. employing SiliaFlash® P60 (230-400 mesh, SiliCycle).[2] Flash column chromatography was conducted on a Biotage Isolera automated chromatography system or manually in a glass column unless otherwise specified. Preparatory and analytical thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} plates (EMD Millipore). TLC plates were visualized by exposure to ultraviolet light (UV) and exposure to an aqueous solution of ceric ammonium molybdate (CAM), *p*-anisaldehyde or ninhydrin followed by heating on a hot plate. Organic solvents were concentrated under reduced pressure on a Büchi rotary evaporator.

Materials. Commercial reagents and solvents were used as received with the following exceptions: tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), *tert*-butyl methyl ether (MTBE), toluene, and *N,N*-dimethylformamide (DMF) were degassed with argon and passed through a solvent purification system (designed by Pure Process Technology) utilizing alumina columns as described by Grubbs et al.[3] *n*-Butyllithium was purchased as a 2.5 M solution in hexanes (Sigma-Aldrich). The molarities of *n*-butyllithium solutions were determined by titration using 1,10-phenanthroline as an indicator (average of three determinations). 4-Bromobenzaldehyde (EMD Millipore, ≥ 98%), *t*-Butyl dimethylphosphonoacetate (TCI, > 95.0%) and 1-Boc-4-piperidone (Sigma-Aldrich, 98%) were used as purchased. $CDCl_3$ (Cambridge Isotope Laboratories) was used with and stored over activated molecular sieves (4Å) prior to use. Deuterated solvents CD_3OD and DMSO-d_6 (Cambridge Isotope Laboratories) were used as purchased. Extraction and chromatography solvents were reagent grade and used without purification (VWR or Fisher Scientific). Celite® 545 (EMD Millipore) was used.

Instrumentation. ^{1}H NMR spectra were recorded with a Varian INOVA-500 spectrometer in parts per million (δ), and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: δ 7.26 ($CHCl_3$), CD_3OD: δ 3.31 (CD_2HOD), DMSO-d_6: δ 2.50 (C_2D_5HSO). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or combinations thereof. ^{13}C NMR spectra were recorded on the Varian INOVA-500 spectrometer in parts per million (δ) and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.00, CD_3OD: δ 49.15, DMSO-d_6: δ 39.51). High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) mass spectroscopy experiments on an Agilent 6210 TOF LC/MS (Harvard FAS Division of Science Small Molecule Mass Spectrometry).

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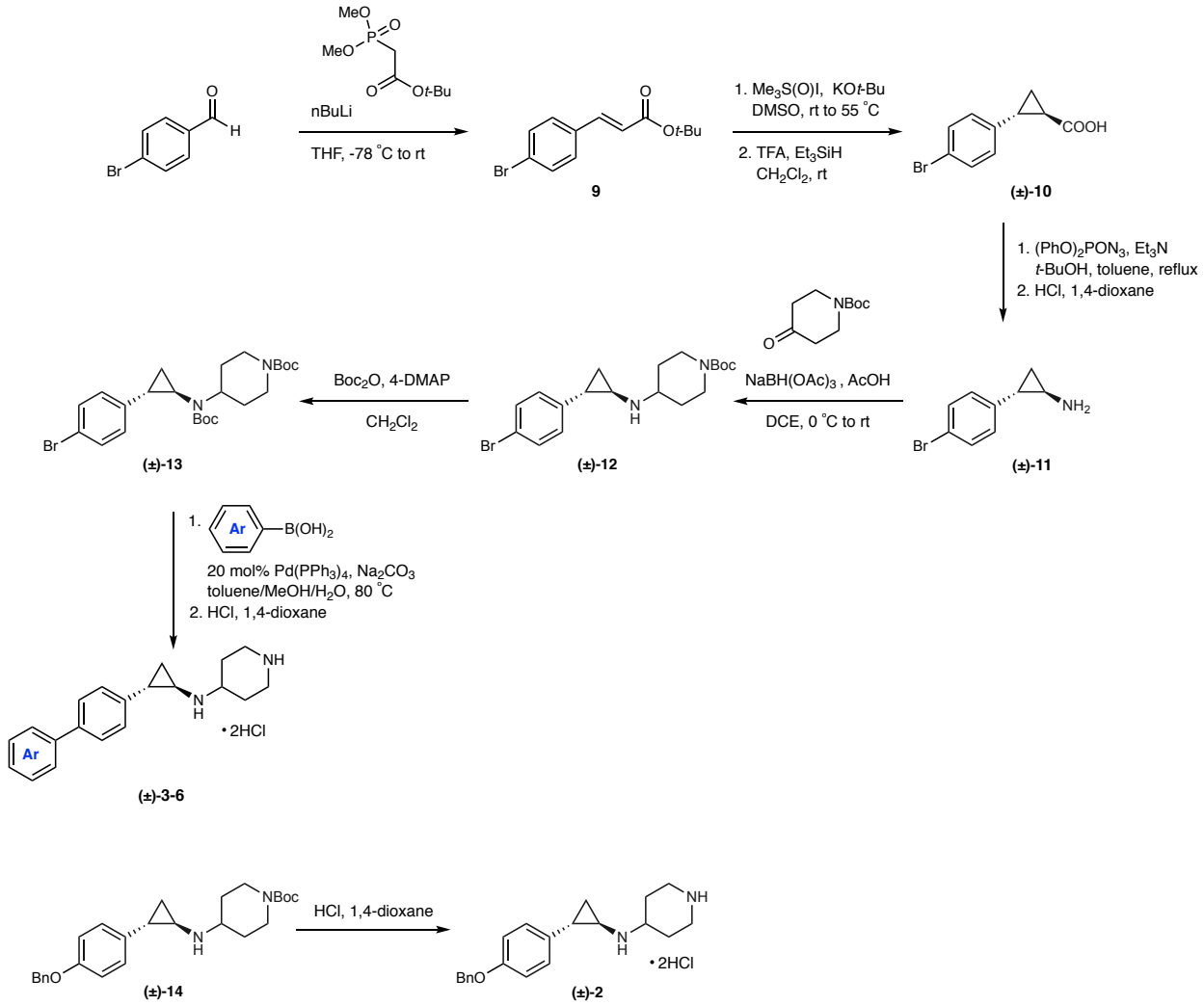
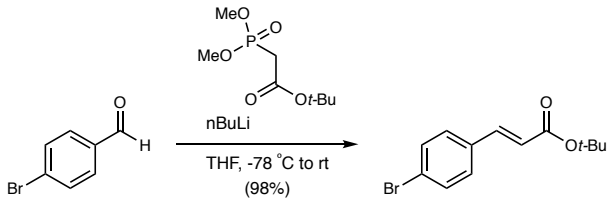
2. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
3. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

Synthetic Scheme towards GSK-LSD1 Analogs: [4]



4. The synthesis and characterization of compound **10** are reported in McCafferty, D. G. et al. *U.S. Pat. Appl. Publ.* **2014**, US 20140343118. Compounds **12**, **14** and **AW1** were previously prepared and characterized in Munoz O. et al. *PCT Int. Appl.* **2013**, WO 2013057320, 258.



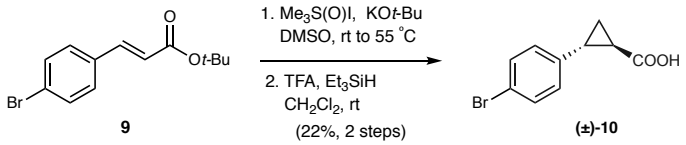
9

General Procedure for tert-butyl (E)-3-(4-bromophenyl)acrylate (9):

According to a literature procedure,[5] *n*-BuLi (1.95 mL, 4.86 mmol, 1.20 equiv, 2.50 M in hexanes) was added dropwise at –78 °C to a stirred solution of *tert*-butyl dimethylphosphonoacetate (0.96 mL, 4.86 mmol, 1.20 equiv) in THF (4.00 mL). After stirring for 30 min at –78 °C, a solution of aldehyde (750 mg, 4.05 mmol, 1.00 equiv) in THF (4.66 mL) was also cooled to –78 °C and transferred via cannula. The resulting solution was stirred at –78 °C for 30 min before being allowed to warm to room temperature and stirred until disappearance of the starting material was observed by TLC analysis. Upon cooling back to -78 °C, the solution was quenched with saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic fractions were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, eluent: 0 to 30% EtOAc/hexanes, v/v) to afford acrylate **9** in high diastereoselectivity (98% yield; >90% *E:Z*).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55–7.48 (m, 3H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 1.53 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 166.00, 142.12, 133.59, 132.05, 129.32, 124.12, 120.91, 80.72, 28.17. **HRMS** (ESI) (*m/z*) calc'd for $C_{13}H_{15}BrO_2$ $[M+H]^+$: 282.0250, 283.0283, 284.0229, 285.0263, 286.0297, 287.0305, 288.0339, 289.0373, 290.0406 found 282.0253, 283.0287, 284.0232, 285.0266.

5. Davies S. G.; Mulvaney A. W.; Russell A. J.; Smith A. D. *Tetrahedron: Asymmetry* **2007**, *18*, 1554–1566.

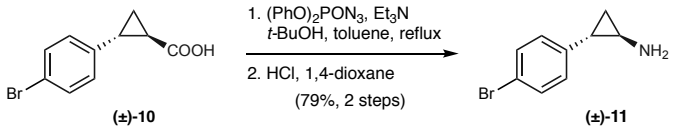


General Procedure for (±)-2-(4-bromophenyl)cyclopropane-1-carboxylic acid (10):

According to a literature procedure,[6] an anhydrous DMSO solution (5.00 mL) of intermediate **9** (1.12 g, 3.97 mmol, 1.00 equiv) was added in one portion to a mixture of $Me_3S(O)I$/KO*t*-Bu (1:1 mixture, 2.18 g/1.11 g, 9.93 mmol, 2.50 equiv) in a round-bottomed flask. The resulting solution was stirred for 30-60 min at 50–60 °C until disappearance of the starting material was observed by TLC analysis. The mixture was then treated with brine (25 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water (2 × 25 mL) and brine (1 × 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, eluent: 0 to 25% EtOAc/hexanes, v/v). The resulting ester was taken up in CH_2Cl_2 (0.90 mL). TFA (895 µL, 11.70 mmol, 13.00 equiv) and triethylsilane (182 µL, 2.25 mmol, 2.50 equiv) were subsequently added according to a modified literature procedure.[6] After stirring for 1.5 to 2 h, TFA was removed by a stream of nitrogen in a well-ventilated hood, and any remaining solvent was removed under reduced pressure. The crude material was passed through a silica plug (silica gel, eluent: 50% EtOAc/hexanes, v/v) to afford *trans*-cyclopropane (±)-**10** as a single diastereomer (22% yield, two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 2.56 (ddd, *J* = 10.4, 6.7, 4.1 Hz, 1H), 1.89 (ddd, *J* = 8.5, 5.2, 4.2 Hz, 1H), 1.68 (dt, *J* = 9.4, 5.0 Hz, 1H), 1.37 (dddd, *J* = 8.5, 6.7, 4.8, 1.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 177.98, 138.53, 131.60, 128.03, 120.45, 26.44, 23.65, 17.40. **HRMS** (ESI) (*m/z*) calc'd for $C_{10}H_9BrO_2$ $[M+H]^+$: 240.9859, 241.9892, 242.9838, 243.9872, 244.9905, 245.9914, 246.9948 found 240.9855, 241.9888, 242.9834, 243.9867, 244.9895, 246.9118.

6. Ciaccio J. A; Aman C. E. *Synthetic Communications* **2006**, *36*, 1333–1341.



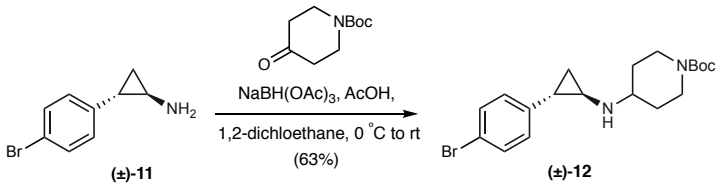
(±)-10 (±)-11

General Procedure for (±)-2-(4-bromophenyl)cyclopropan-1-amine (11):

According to a modified literature procedure,[7] acid **10** (210 mg, 0.87 mmol, 1.00 equiv) was first dissolved in dry toluene (3.35 mL) in a round-bottomed flask. Diphenyl phosphoryl azide (225 µL,1.04 mmol, 1.20 equiv) and triethylamine (243 µL, 1.74 mmol, 2.00 equiv) were added under a nitrogen atmosphere and stirred for 30 min at room temperature. The reaction mixture was then heated and refluxed for 1.5 h before *t*-BuOH (1.01 mL, 0.87 mmol, 1.00 equiv) was added, and the resulting solution was refluxed overnight. The reaction mixture was cooled to room temperature and was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, eluent: 0 to 30% EtOAc/hexanes, v/v) to afford the carbamate intermediate. The obtained carbamate product (0.93 mmol, 1.00 equiv) was taken up in 1,4-dioxane (345 μL) and 4.0 M HCl in 1,4-dioxane was added (690 μL, 2.76 mmol, 4.00 equiv). The reaction mixture was stirred at room temperature until completion as monitored by TLC (4 h) before being concentrated under reduced pressure. The residue was taken up in water (15 mL), diluted with saturated aqueous $NaHCO_3$ solution (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford cyclopropyl amine (±)-**11**, which was used directly in the next step without further purification (79% yield, two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 2.51 (dt, *J* = 7.3, 3.6 Hz, 1H), 1.82 (ddd, *J* = 9.1, 5.7, 3.1 Hz, 1H), 1.06 (ddd, *J* = 9.5, 5.3, 4.3 Hz, 1H), 0.94 (dt, *J* = 7.2, 5.5 Hz, 1H). **HRMS** (ESI) (*m/z*) calc'd for $C_9H_{10}BrN$ $[M+H]^+$: 212.0069, 213.0103, 214.0049, 215.0082, 216.0116, 217.0150, 218.0183, 219.0217 found 212.0065, 213.0099, 214.0044, 215.0077, 216.0110, 217.1428, 218.1461.

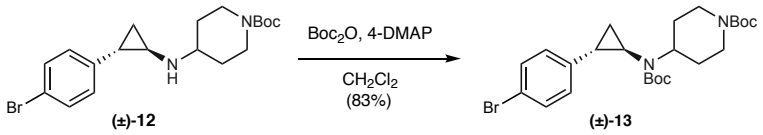
7. Benelkebir H. et al. *Bioorganic & Medicinal Chemistry* **2011**, *19*, 3709–3716.



General Procedure for (±)-tert-butyl 4-((2-(4-bromophenyl)cyclopropyl)amino)-piperidine-1-carboxylate (12):

According to a literature procedure,[4] to a solution of amine **11** (146 mg, 0.69 mmol, 1.00 equiv) in 1,2-dichloroethane (4.60 mL) was added *t*-butyl 4-oxopiperidine-1-carboxylate (165 mg, 0.83 mmol, 1.20 equiv) and acetic acid (39 μL, 0.69 mmol, 1.00 equiv). The solution was cooled to 0 °C and sodium triacetoxy borohydride (263 mg, 1.24 mmol, 1.80 equiv) was slowly added. The reaction was stirred at room temperature overnight. The solvent was then removed under reduced pressure and the crude residue was diluted in water (10 mL) and quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The combined aqueous layers were then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, eluent: 50 to 100% EtOAc/hexanes, v/v) to afford secondary amine (±)-**12** (63% yield).

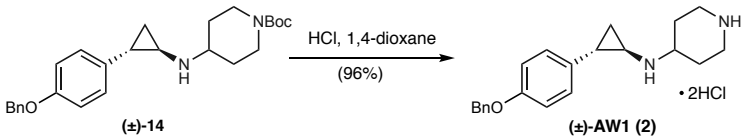
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.31 (m, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.01 (m, 4H), 2.88–2.69 (m, 1H), 2.37–2.22 (m, 1H), 1.94–1.76 (m, 4H), 1.45 (s, 9H), 1.08 (dt, J = 9.6, 4.9 Hz, 1H), 1.01–0.94 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 154.75, 141.18, 131.24, 127.27, 118.98, 79.36, 55.26, 39.75, 32.64, 28.40, 25.17, 17.04. **HRMS** (ESI) (*m/z*) calc'd for $C_{19}H_{27}N_2O_2$ $[M+H]^+$: 395.1329, 396.1362, 397.1308, 398.1342, 399.1375, 400.1409, 401.1418, 402.1451 found 395.1316, 396.1349, 397.1295, 398.1329, 399.1357, 400.1368.



General Procedure for (±)-tert-butyl 4-((2-(4-bromophenyl)cyclopropyl)(tert-butoxycarbonyl)-amino)piperidine-1-carboxylate (13):

To a solution of (±)-**12** (170 mg, 0.43 mmol, 1.00 equiv) in CH_2Cl_2 (4.30 mL) was added Boc_2O (281 mg, 1.29 mmol, 3.00 equiv) and 4-dimethylaminopyridine (4-DMAP, 16 mg, 0.13 mmol, 0.30 equiv). The reaction was stirred at room temperature overnight. The mixture was then concentrated under reduced pressure and purified by column chromatography (silica gel, eluent: 0 to 35% EtOAc/hexanes, v/v) to afford carbamate (±)-**13** (83%).

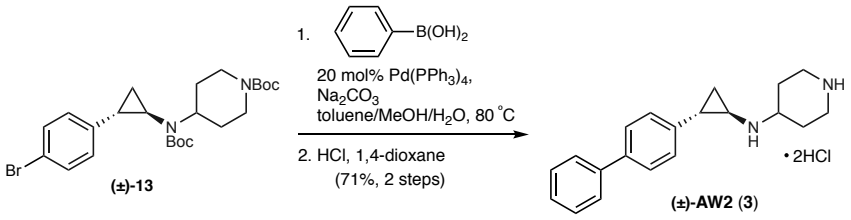
^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.51–7.30 (m, 2H), 6.99 (d, J = 7.9 Hz, 2H), 4.36–4.00 (m, 2H), 3.87 (s, 1H), 2.72 (s, 2H), 2.57 (s, 1H), 2.25 (ddd, J = 10.1, 6.7, 3.6 Hz, 1H), 1.80 (s, 3H), 1.46 (d, J = 5.6 Hz, 18H), 1.36–1.22 (m, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ: 154.54, 150.67, 147.65, 138.61, 131.44, 127.93, 120.15, 84.89, 79.73, 58.39, 37.24, 28.37, 27.38, 16.91. **HRMS** (ESI) (*m/z*) calc'd for $C_{24}H_{35}BrN_2O_4$ $[M+H]^+$: 495.1853, 496.1885, 497.1836, 498.1866, 499.1894 found 495.1846, 496.1883, 497.1826, 498.1862, 499.1895.



(±)-*N*-(2-(4-(benzyloxy)phenyl)cyclopropyl)piperidin-4-amine AW1 (2):

Carbamate intermediate (±)-**14** was synthesized as described for (±)-**12** and the NMR spectra match those reported in the literature.[4] Briefly, carbamate (±)-**14** (42 mg, 0.10 mmol, 1.00 equiv) was dissolved in 1,4-dioxane (50 μL) and treated with 4.0 M HCl solution in 1,4-dioxane (100 μL, 0.40 mmol, 4.00 equiv). The reaction mixture was stirred at room temperature until completion before being concentrated under reduced pressure. The residue was dissolved in water/MeOH (10 mL) and subsequently washed with hexanes/Et_2O (2 × 20 mL, 1:1, v/v). The water/MeOH layer was concentrated under reduced pressure to afford (±)-**AW1•**HCl as a white solid (96% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.08 (d, J = 14.6 Hz, 2H), 9.39 (d, J = 10.7 Hz, 1H), 9.00 (d, J = 10.7 Hz, 1H), 7.43 (d, J = 7.0 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.34–7.29 (m, 1H), 7.15–7.08 (m, 2H), 6.97–6.91 (m, 2H), 5.08 (s, 2H), 3.49 – 3.32 (m, 4H), 2.92 (q, J = 12.5, 11.9 Hz, 2H), 2.83 (p, J = 4.2 Hz, 1H), 2.54 (ddd, J = 10.1, 6.3, 3.5 Hz, 1H), 2.25 (d, J = 13.2 Hz, 2H), 1.93 (dt, J = 12.2, 4.6 Hz, 2H), 1.55 (ddd, J = 10.2, 5.9, 4.2 Hz, 1H), 1.26–1.16 (m, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ: 157.03, 137.11, 130.69, 128.39, 127.75, 127.61, 127.55, 114.81, 69.15, 52.56, 41.23, 34.84, 24.95, 24.84, 19.79, 12.12. **HRMS** (ESI) (*m/z*) calc'd for $C_{21}H_{26}N_2O$ $[M+H]^+$: 323.2118, found 323.2117.

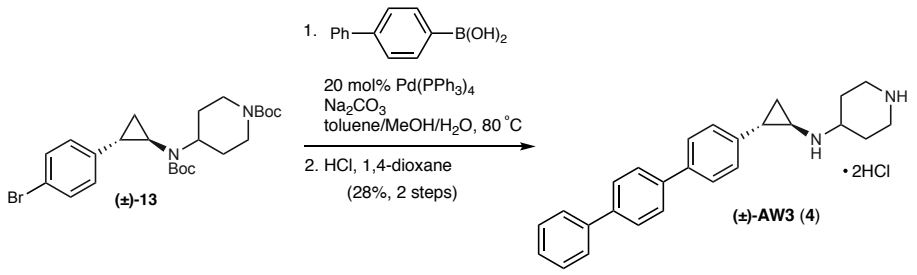


***(±)-N-(2-([1,1'-biphenyl]-4-yl)cyclopropyl)piperidin-4-amine* AW2 (3):**

According to a modified literature procedure,[8] tetrakis(triphenylphosphine)palladium (14 mg, 0.01 mmol, 0.20 equiv), phenylboronic acid (30 mg, 0.24 mmol, 4.00 equiv), and Na_2CO_3 (13 mg, 0.12 mmol, 2.00 equiv) were added to a solution of the aryl bromide (±)-**13** (30 mg, 0.06 mmol, 1.00 equiv) in a degassed mixture of toluene/MeOH/water (540 μL/120 μL/10 μL, 80/18/2, v/v/v) under a nitrogen atmosphere. The reaction mixture was heated to 80 °C for 18 h. After cooling to room temperature, the mixture was diluted with EtOAc, filtered through a plug of celite and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 0 to 35% EtOAc/hexanes, v/v). The intermediate was subsequently dissolved in 1,4-dioxane (21 μL, 2.0 M) and 4.0 M HCl solution in 1,4-dioxane was added (43 μL, 0.17 mmol, 4.00 equiv). The reaction mixture was stirred at room temperature until completion as monitored by TLC and then concentrated under reduced pressure. The residue was dissolved in water/MeOH (5 mL) and subsequently washed with 1:1 hexanes/Et_2O (2 × 10 mL). The water/MeOH layer was concentrated under reduced pressure to afford (±)-**AW2•**HCl as a yellow solid (71% yield, two steps).

^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.05 (d, J = 15.2 Hz, 2H), 9.16 (s, 1H), 8.92 (t, J = 11.3 Hz, 1H), 7.70–7.54 (m, 4H), 7.52–7.39 (m, 2H), 7.40–7.32 (m, 1H), 7.32–7.26 (m, 2H), 3.61–3.47 (m, 3H)[9], 3.09–2.85 (m, 3H), 2.63 (ddd, J = 10.0, 6.3, 3.5 Hz, 1H), 2.31–2.18 (m, 2H), 2.01–1.85 (m, 2H), 1.63 (ddd, J = 10.4, 6.2, 4.5 Hz, 1H), 1.34 (dt, J = 7.8, 6.3 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ: 139.71, 138.39, 137.95, 128.91, 127.33, 126.95, 126.71, 126.47, 52.63, 41.34, 35.11, 25.04, 20.25, 12.69. **HRMS** (ESI) (*m/z*) calc'd for $C_{20}H_{24}N_2$ $[M+H]^+$: 293.2012, found 293.2011.

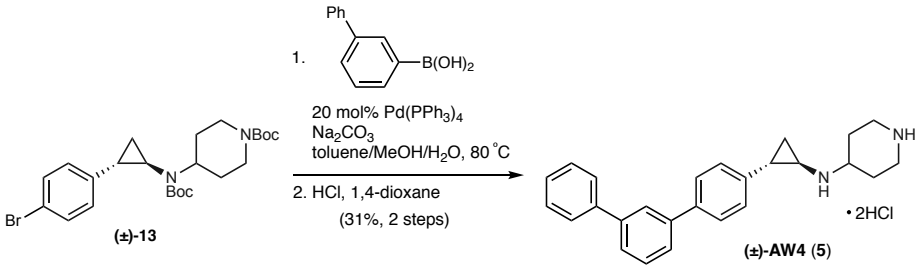
8. Miyamura S. et al. *Organic & Biomolecular Chemistry,* **2016**, *14*, 8576–8585.
9. Protons overlap with residual water peak from DMSO-d_6.



(±)-*N*-(2-([1,1':4',1''-terphenyl]-4-yl)cyclopropyl)piperidin-4-amine AW3 (4):

(±)-**AW3** was prepared according to the general protocol for (±)-**AW2**. (±)-**AW3**•HCl was isolated as a yellow solid (28% yield, two steps).

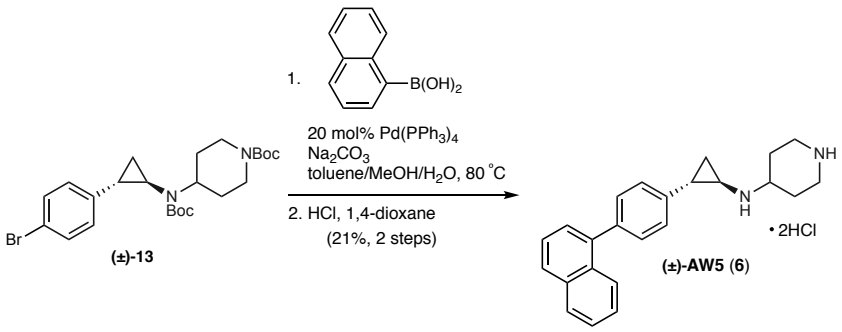
^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.94 (s, 2H), 9.07–8.97 (m, 1H), 8.84 (d, J = 11.5 Hz, 1H), 7.76 (s, 4H), 7.74–7.66 (m, 4H), 7.49 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 3.58–3.43 (m, 3H)[9], 3.03 (td, J = 8.3, 4.1 Hz, 1H), 2.94 (q, J = 12.0 Hz, 2H), 2.62 (ddd, J = 10.4, 6.2, 3.4 Hz, 1H), 2.25 (d, J = 13.3 Hz, 2H), 1.97–1.84 (m, 2H), 1.62 (dt, J = 10.4, 5.5 Hz, 1H), 1.36 (q, J = 6.7 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ: 139.08, 138.66, 138.06, 137.81, 136.66, 128.98, 127.18, 127.16, 126.97, 126.59, 126.53, 52.65, 41.40, 35.13, 24.98, 20.31, 12.25. **HRMS** (ESI) (*m/z*) calc'd for $C_{26}H_{28}N_2$ $[M+H]^+$: 369.2325, found 369.2325.



(±)-*N*-(2-([1,1':3',1''-terphenyl]-4-yl)cyclopropyl)piperidin-4-amine AW4 (5):

(±)-**AW4** was prepared according to the general protocol for (±)-**AW2**. (±)-**AW4**•HCl was isolated as a yellow solid (31% yield, two steps).

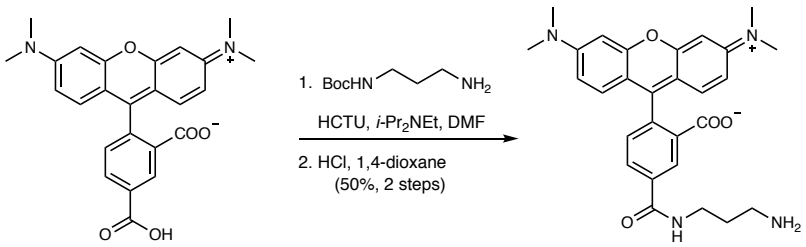
^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.96 (d, J = 11.3 Hz, 2H), 9.04 (d, J = 10.7 Hz, 1H), 8.85 (d, J = 11.2 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 7.73 (dd, J = 18.2, 7.9 Hz, 4H), 7.68–7.60 (m, 2H), 7.55 (t, J = 7.7 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 3.59–3.41 (m, 3H)[9], 3.07–2.88 (m, 3H), 2.63 (ddd, J = 10.1, 6.5, 3.6 Hz, 1H), 2.31–2.20 (m, 2H), 1.98–1.85 (m, 2H), 1.62 (dt, J = 10.5, 5.5 Hz, 1H), 1.36 (q, J = 6.7 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ: 140.94, 140.45, 140.14, 138.38, 138.12, 129.58, 128.94, 127.59, 126.96, 125.82, 125.67, 124.94, 52.67, 41.41, 35.17, 25.09, 20.32, 12.77. **HRMS** (ESI) (*m/z*) calc'd for $C_{26}H_{28}N_2$ $[M+H]^+$: 369.2325, found 369.2323.



(±)-*N*-(2-(4-(naphthalen-1-yl)phenyl)cyclopropyl)piperidin-4-amine AW5 (6):

(±)-**AW5** was prepared according to the general protocol for (±)-**AW2**. (±)-**AW5**•HCl was isolated as a yellow solid (21% yield, two steps).

^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.12 (s, 2H), 9.29 (s, 1H), 8.98 (s, 1H), 8.21 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 7.9, 5.2 Hz, 2H), 7.94 (dd, J = 7.6, 1.7 Hz, 1H), 7.84 (dd, J = 8.6, 1.9 Hz, 1H), 7.81–7.74 (m, 2H), 7.59–7.47 (m, 2H), 7.39–7.29 (m, 2H), 3.57–3.47 (m, 1H), 3.39 (d, J = 8.9 Hz, 2H)[9], 3.05–2.87 (m, 3H), 2.67 (dt, J = 10.2, 4.8 Hz, 1H), 2.32–2.22 (m, 2H), 1.96 (dq, J = 21.8, 10.3, 9.4 Hz, 2H), 1.66 (dt, J = 10.4, 5.5 Hz, 1H), 1.40–1.33 (m, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ: 138.25, 138.10, 137.02, 133.30, 132.16, 128.44, 128.12, 127.46, 127.03, 126.98, 126.39, 126.06, 124.92, 52.62, 41.30, 35.29, 25.07, 20.35, 12.80. **HRMS** (ESI) (*m/z*) calc'd for $C_{24}H_{26}N_2$ $[M+H]^+$: 343.2169, found 343.2169.



15

5-((3-aminopropyl)carbamoyl)-2-(6-(dimethylamino)-3-(dimethyliminio)-3H-xanthen-9-yl)benzoate (15):

According to a modified literature procedure,[10] to a solution of 5(6)-TAMRA (40 mg, 0.09 mmol, 1.00 equiv) in DMF (1.0 mL) was added N-Boc-1,3-propanediamine (16 μL, 0.09 mmol, 1.00 equiv), HCTU (0.09 mmol, 1.10 equiv) and *i*-Pr$_2$NEt (32 μL, 0.19 mmol, 2.00 equiv). The reaction was stirred at room temperature overnight and subsequently concentrated under reduced pressure. The residue was then dissolved in 4.0 M HCl in 1,4-dioxane (180 μL). The reaction mixture was stirred at room temperature until completion as monitored by TLC before being concentrated under reduced pressure. The resultant residue was purified by C18 reverse phase column chromatography using a Büchi C18 40 μm reverse phase 12 g cartridge (eluent: 0 to 100 % water/MeCN with 0.1% TFA, v/v) to afford TAMRA label **15** (56% yield, two steps).

^{1}H NMR (500 MHz, CD_3OD, major isomer reported) δ: 8.80 (d, *J* = 1.8 Hz, 1H), 8.29 (dd, *J* = 31.6, 8.1, 1.8 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.13-6.99 (dd, *J* = 9.5, 5.1 Hz, 6H), 3.50 (t, *J* = 6.7 Hz, 2H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.04 (q, *J* = 7.0 Hz, 2H).

10. The synthesis and characterization of SI-7 is reported in Egloff C. et al. *Chem. Commun.*, **2014**, 50, 10049–10051.

TAMRA Labeled GFI1B Peptide Synthesis and Purification:

GFI1B wt (PRSFLVKSK) and GFI1B F5A (PRSALVKSK) peptides were synthesized by manual fluorenylmethyloxycarbonyl (Fmoc) solid phase peptide synthesis using 2-chlorotrityl chloride resin (AAPPTec) at 65 °C. The resin (112 mg, 0.89 mmol/g) was suspended and allowed to swell in dry CH_2Cl_2 for 1 h. After removing CH_2Cl_2, a solution of Fmoc-Lys (Boc)-OH (70 mg, 0.10 mmol, 1.50 equiv) in 4.0 mL of CH_2Cl_2 and 2,4,6-collidine (10 equiv) was added to the resin and the mixture was agitated for 2 h at room temperature. The unreacted resin was capped with a solution of CH_2Cl_2/MeOH/*i*-Pr_2NEt (17:2:1, 5.0 mL) for 30 min at room temperature followed by washing the resin twice with DMF. Fmoc deprotection was achieved with 5 % piperazine in DMF for 5 min followed by coupling of the amino acid in the presence of 2-(6-Chloro-1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU) and *i*-Pr_2NEt (AA:HCTU:*i*-Pr_2NEt:resin; 3:2.8:6:1) for 7 min. Deprotection of the peptide was achieved by agitation at room temperature in a 1:4 hexafluoroisopropanol/CH_2Cl_2 solution (5.0 mL). The suspension was filtered, and the resin was washed with additional 1:4 hexafluoroisopropanol/CH_2Cl_2 solution (1:4, 5.0 mL), followed by CH_2Cl_2 (2 × 10 mL). The combined filtrates were concentrated under reduced pressure. The identity of the peptide was confirmed by MALDI TOF/ TOF mass spectrometry (Bruker ultrafleXtreme).

HCTU (20.6 mg, 0.05 mmol, 2.00 equiv), hydroxybenzotriazole (7.63 mg, 0.05 mmol, 2.00 equiv), and *i*-Pr_2NEt (21.7 μL, 0.12 mmol, 5.00 equiv) were added sequentially to a solution of peptide (43 mg, 0.02 mmol, 1.00 equiv) in DMF (5.0 mL) at room temperature. After stirring for 30 min, the 5(6)-TAMRA label described above (24 mg, 0.05 mmol, 2.00 equiv) was added and the reaction was stirred for 12 h at room temperature. The reaction mixture was subsequently concentrated under reduced pressure and purified by column chromatography (silica gel, eluent: 18% MeOH, 2% NH_4OH in chloroform, v/v). All fractions containing the desired product were combined and concentrated under reduced pressure. The purified product was subjected to global deprotection by treatment with a solution consisting of 95% trifluoroacetic acid (TFA), 2.5% H_2O and 2.5% triisopropyl silane (TIPS) for 2 h at room temperature. The crude peptides were precipitated with cold MTBE, washed three times with cold MTBE, and dried under nitrogen. The peptides were purified on a preparative reverse phase high performance liquid chromatography system (Agilent) with a C18 column using a linear gradient of solvent A (0.1% TFA in Millipore H_2O) and solvent B (90% CH_3CN, 9.9% H_2O, 0.1% TFA). The identities of the purified peptides were assessed by MALDI-TOF/TOF mass spectrometry. The purity of the peptides was assessed on an Agilent HPLC with an analytical Agilent-C18 column (4.6 mm × 150 mm) using a linear gradient of solvent A and solvent B.

MALDI TOF/TOF MS (*m/z*) calc'd for GFI1B wt (PRSFLVKSK) $[M+H]^+$: 1529.896 found 1530.02. calc'd for GFI1B F5A (PRSALVKSK) $[M+H]^+$: 1453.83 found 1453.87.