**Supporting Information**

**One-pot Double Annulations to Confer Diastereoselective Spirooxindole-pyrrolothiazoles**

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# General information

All solvents were used as received from commercial sources without further purification. 1H NMR and 13C NMR spectra were recorded using Bruker-DRX (400 MHz and 101 MHz, respectively) instruments internally referenced to SiMe4, chloroform, and dimethyl sulfoxide signals. Chemical shifts were reported in parts per million (ppm), Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). LC-MS were performed on Waters UPLC-MS. The mobile phases were MeCN and H2O both containing 0.03% HCO2H. UV detections were conducted at 220 nm, 254 nm and 284 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization).

2. General procedure

**2.1 The cascade synthesis of compound 5**

To a solution of aldehydes 1 (2.2 mmol) and cysteine 2 (1.1 mmol), in 2.0 mL of EtOH was added olefinic oxindoles 4 (1.0 mmol). After being stirred at 90 °C for 9 h. Upon the completion of the reaction as monitored by LCMS, the concentrated reaction mixture was isolated. The products 5 were afforded.

**2.2 The one-pot synthesis of compound 7**

To a solution of aldehydes **1** (1.0 mmol) and cysteine **2** (1.15 mmol), in 3.0 mL of EtOH was added, then stirred at 25°C for 6 h. olefinic oxindoles **4** (1.0 mmol) and aldehydes **6** (1.1 mmol) were added. The solution mixture was stirred at 90 °C for 9 h. Upon the completion of the reaction as monitored by LCMS, the concentrated reaction mixture was isolated. The products **7** were afforded.

**3. Characterization of products**

*Compound* ***5a****:* white solid (70% yield). 1H NMR (400 MHz, CDCl3) *δ* 7.60 – 7.56 (m, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.15 (td, J = 7.7, 1.2 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.03 (dd, J = 7.5, 1.0 Hz, 1H), 6.99 – 6.95 (m, 2H), 6.61 – 6.56 (m, 1H), 5.16 (s, 1H), 4.83 – 4.77 (m, 1H), 4.72 (s, 1H), 3.82 (dq, J = 10.8, 7.1 Hz, 1H), 3.68 – 3.59 (m, 2H), 3.16 – 3.09 (m, 4H), 3.00 (dd, J = 12.3, 1.7 Hz, 1H), 0.68 (t, J = 7.1 Hz, 3H).13C NMR (101 MHz, CDCl3) *δ*174.8, 169.1, 143.7, 140.8, 135.3, 131.3, 133.0, 128.9, 128.9, 128.2, 126.0, 125.2, 122.3, 121.8, 121.2, 107.9, 75.3, 74.7, 67.5, 61.3, 60.7, 56.2, 38.8, 26.4, 13.5. HRMS (ESI-TOF*, m/z*): [M+H]+ calcd. for C29H26Br2N2O3S 641.0109, found: 6411.0113.

*Compound* ***5b****:* off*-*white solid (49% yield). 1H NMR (400 MHz, CDCl3) *δ* 7.49 – 7.45 (m, 1H), 7.36 (dt, J = 1.7, 0.7 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.01 – 6.93 (m, 2H), 6.67 (d, J = 7.8 Hz, 1H), 6.35 – 6.29 (m, 2H), 6.00 (dt, J = 3.3, 0.9 Hz, 1H), 5.96 (dd, J = 3.3, 1.8 Hz, 1H), 5.35 (s, 1H), 4.78 – 4.71 (m, 2H), 3.80 (dd, J = 10.8, 7.1 Hz, 1H), 3.65 (dd, J = 10.8, 7.2 Hz, 1H), 3.54 (d, J = 8.6 Hz, 1H), 3.40 (dd, J = 12.1, 7.3 Hz, 1H), 3.20 (s, 3H), 3.02 (dd, J = 12.1, 1.8 Hz, 1H), 0.70 (t, J = 7.1 Hz, 3H). 13C NMR (101 MHz, CDCl3) *δ* 174.7, 169.0, 153.4, 151.5, 142.3, 142.0, 128.7, 126.5, 125.3, 122.2, 110.1, 109.8, 107.7, 107.5, 107.0, 69.6, 69.2, 67.5, 60.7, 59.8, 56.2, 38.9, 26.6, 13.5. HRMS (ESI-TOF*, m/z*): [M+H]+ calcd. for C25H24N2O5S 465.1484, found: 465.1479.

*Compound* ***5c****:* off*-*white solid (55% yield). 1H NMR (400 MHz, CDCl3) *δ* 8.77 – 8.68 (m, 2H), 8.46 (dd, J = 4.8, 1.5 Hz, 1H), 8.41 (dd, J = 4.8, 1.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 0.7 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.18 (ddd, J = 11.6, 7.9, 4.8 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 6.87 – 6.80 (m, 1H), 5.49 (s, 1H), 5.09 (d, J = 8.6 Hz, 1H), 4.33 (t, J = 7.6 Hz, 1H), 3.92 (d, J = 8.6 Hz, 1H), 3.51 (ddd, J = 7.1, 2.8, 0.7 Hz, 2H), 3.47 – 3.41 (m, 1H), 3.25 (s, 3H), 2.89 (dd, J = 11.6, 7.5 Hz, 1H), 0.61 (t, J = 7.2 Hz, 3H).13C NMR (101 MHz, CDCl3) *δ*174.8, 169.1, 143.7, 140.8, 135.3, 131.3, 133.0, 128.9, 128.9, 128.2, 126.0, 125.2, 122.3, 121.8, 121.2, 107.9, 75.3, 74.7, 67.5, 61.3, 60.7, 56.2, 38.8, 26.4, 13.5.

*Compound* ***5d****:* white solid (61% yield). 1H NMR (400 MHz, CDCl3) *δ* 7.94 – 7.88 (m, 1H), 7.43 (dt, J = 1.8, 0.9 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.09 (tt, J = 7.6, 0.9 Hz, 1H), 6.82 (dq, J = 7.7, 0.8 Hz, 1H), 6.54 (dq, J = 3.3, 0.8 Hz, 1H), 6.42 – 6.37 (m, 1H), 6.20 – 6.13 (m, 2H), 5.52 (s, 1H), 4.63 – 4.59 (m, 1H), 4.17 (d, J = 10.8 Hz, 1H), 3.77 (dd, J = 9.8, 6.7 Hz, 1H), 3.68 (d, J = 0.8 Hz, 1H), 3.61 – 3.50 (m, 2H), 3.47 (d, J = 0.8 Hz, 1H), 3.25 (d, J = 0.9 Hz, 3H), 2.95 (ddd, J = 10.9, 6.7, 0.8 Hz, 1H), 0.66 – 0.60 (m, 3H).13C NMR (101 MHz, CDCl3) *δ* 175.4, 167.5, 155.0, 152.3, 142.9, 142.5, 142.3, 131.3, 128.5, 125.6, 123.0, 110.4, 110.0, 108.7, 107.6, 106.1, 74.6, 67.5, 60.3, 59.2, 56.9, 52.1, 32.8, 26.7, 13.4.

*Compound* ***7a****:* white solid (66% yield). 1H NMR (400 MHz, CDCl3) *δ* 7.67 – 7.62 (m, 1H), 7.24 (s, 1H), 7.21 (dd, J = 7.8, 1.2 Hz, 1H), 7.19 – 7.13 (m, 1H), 7.08 – 7.00 (m, 2H), 6.91 (dd, J = 5.1, 1.2 Hz, 1H), 6.82 – 6.78 (m, 1H), 6.69 – 6.62 (m, 2H), 5.34 (s, 1H), 5.02 (s, 1H), 4.71 – 4.66 (m, 1H), 3.91 (s, 3H), 3.85 – 3.79 (m, 1H), 3.65 (dd, J = 10.8, 7.1 Hz, 1H), 3.57 (d, J = 8.6 Hz, 1H), 3.12 (d, J = 13.2 Hz, 4H), 2.97 (dd, J = 12.1, 1.7 Hz, 1H), 0.69 (t, J = 7.1 Hz, 3H).13C NMR (101 MHz, CDCl3) *δ* 174.7, 169.1, 144.1, 140.1, 137.4, 137.4, 129.0, 126.4, 125.9, 125.9, 125.6, 125.6, 122.2, 119.1, 119.1, 115.3, 115.1, 112.5, 112.4, 107.8, 75.3, 71.5, 66.8, 61.2, 60.7, 56.1, 55.9, 39.0, 26.5, 13.5. HRMS (ESI-TOF*, m/z*): [M+H]+ calcd. for C28H27FN2O4S2 539.1475, found: 539.1477.

*Compound* ***7b****:* white solid (51% yield). 1H NMR (400 MHz, CDCl3) *δ* 7.62 – 7.57 (m, 1H), 7.19 (dd, J = 7.8, 1.3 Hz, 1H), 7.14 – 7.10 (m, 1H), 7.06 – 7.00 (m, 2H), 6.98 – 6.94 (m, 1H), 6.71 – 6.65 (m, 1H), 6.11 (d, J = 3.3 Hz, 1H), 5.97 (dd, J = 3.3, 1.8 Hz, 1H), 5.51 (s, 1H), 4.79 (s, 1H), 4.72 – 4.67 (m, 1H), 3.80 (dd, J = 10.8, 7.1 Hz, 1H), 3.65 (dd, J = 10.8, 7.1 Hz, 1H), 3.53 (d, J = 8.6 Hz, 1H), 3.31 (s, 1H), 3.19 (s, 3H), 3.01 (dd, J = 12.1, 1.7 Hz, 1H), 0.70 (t, J = 7.1 Hz, 3H).13C NMR (101 MHz, CDCl3) *δ* 174.6, 169.0, 151.3, 147.2, 143.9, 142.0, 128.7, 127.2, 126.6, 125.4, 125.3, 125.0, 122.3, 109.9, 107.7, 107.5, 71.9, 68.8, 66.8, 60.7, 59.8, 56.1, 39.4, 26.6, 13.5. HRMS (ESI-TOF*, m/z*): [M+H]+ calcd. for C25H24N2O4S2 481.1256, found: 481.1261.

*Compound* ***7c****:* white solid (43% yield). 1H NMR (400 MHz, CDCl3) *δ* 8.44 (dd, J = 2.3, 0.7 Hz, 1H), 8.26 (dd, J = 4.8, 1.7 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.62 – 7.56 (m, 1H), 7.24 – 7.22 (m, 1H), 7.18 – 7.12 (m, 1H), 7.10 (ddt, J = 3.4, 1.4, 0.7 Hz, 1H), 7.08 – 7.02 (m, 1H), 6.98 – 6.90 (m, 2H), 6.55 (dd, J = 7.8, 1.0 Hz, 1H), 5.32 (d, J = 1.4 Hz, 1H), 4.85 – 4.80 (m, 1H), 4.75 (s, 1H), 3.82 (dd, J = 10.8, 7.1 Hz, 1H), 3.69 – 3.63 (m, 1H), 3.61 (d, J = 8.6 Hz, 1H), 3.34 (dd, J = 12.1, 7.4 Hz, 1H), 3.10 (s, 3H), 3.06 (dd, J = 12.2, 1.7 Hz, 1H), 0.67 (t, J = 7.1 Hz, 3H).13C NMR (101 MHz, CDCl3) *δ* 174.4, 169.0, 149.5, 149.1, 146.6, 143.7, 135.1, 131.7, 129.0, 127.3, 125.7, 125.3, 125.2, 125.1, 122.7, 122.5, 107.8, 72.5, 71.7, 67.1, 61.3, 60.7, 56.2, 39.7, 26.4, 13.5.

*Compound* ***7d****:* white solid (72% yield). 1H NMR (400 MHz, CDCl3) *δ* 7.61 – 7.56 (m, 1H), 7.53 – 7.43 (m, 2H), 7.20 (dd, J = 7.4, 1.5 Hz, 1H), 7.13 (td, J = 7.8, 1.3 Hz, 1H), 7.03 – 6.95 (m, 4H), 6.92 – 6.88 (m, 2H), 6.58 – 6.55 (m, 1H), 5.33 (dd, J = 11.3, 1.8 Hz, 1H), 4.98 – 4.94 (m, 1H), 4.77 (s, 1H), 3.83 (td, J = 7.1, 3.6 Hz, 1H), 3.69 – 3.62 (m, 2H), 3.28 – 3.23 (m, 1H), 3.12 (s, 3H), 3.06 (dd, J = 12.3, 1.7 Hz, 1H), 0.70 (t, J = 7.1 Hz, 3H).13C NMR (101 MHz, CDCl3) *δ* 174.8, 169.2, 144.0, 143.7, 134.9, 133.4, 128.9, 128.8, 128.6, 128.5, 128.0, 126.7, 126.7, 125.9, 125.2, 125.1, 123.7, 123.6, 122.2, 121.8, 115.7, 115.5, 107.8, 107.5, 74.8, 69.9, 69.9, 68.7, 61.4, 60.7, 60.7, 56.2, 56.0, 38.2, 38.1, 26.5, 26.4, 13.5, 13.5.

*Compound* ***7e****:* white solid (66% yield). 1H NMR (400 MHz, CDCl3) *δ* 7.68 – 7.65 (m, 1H), 7.62 – 7.58 (m, 2H), 7.44 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.35 – 7.33 (m, 3H), 7.32 (t, J = 1.2 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.10 (dtd, J = 15.3, 7.6, 1.1 Hz, 2H), 6.85 (dt, J = 7.7, 0.9 Hz, 1H), 5.34 (s, 1H), 4.70 (d, J = 11.1 Hz, 1H), 4.45 (dd, J = 8.0, 2.4 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.60 – 3.49 (m, 2H), 3.25 (s, 3H), 2.61 (dd, J = 12.3, 7.9 Hz, 1H), 2.45 (dd, J = 12.2, 2.5 Hz, 1H), 0.61 (t, J = 7.1 Hz, 3H).13C NMR (101 MHz, CDCl3) *δ* 13C NMR (101 MHz, cdcl3) δ 177.5, 168.0, 144.0, 142.2, 140.9, 139.2, 134.5, 131.7, 131.4, 131.2, 131.1, 130.4, 129.4, 129.3, 129.0, 128.5, 128.4, 126.5, 125.5, 123.7, 123.0, 122.4, 122.2, 121.1, 108.1, 108.0, 74.5, 73.1, 69.4, 60.4, 60.0, 59.2, 52.6, 36.0, 26.8, 13.4.

4. NMR **spectra of products**















 

# 5. Green chemistry metrics analysis

The following formulae were used for calculating Atom Economy (AE), Atom Efficiency (AEf), Carbon Efficiency (CE), Reaction Mass Efficiency (RME), Optimum Efficiency (OE), Mass Productivity (MP), Mass Intensity (MI) and Process Mass Intensity (PMI), E factor, Solvent and Water Intensity (SI and WI) [1-12].























**5.1 Cascade process**

*i. General procedure for the cascade synthesis of compounds* ***5a***



To a solution of 4-bromobenzaldehyde **1a** (2.2 mmol) and cysteine **2** (1.1 mmol), in 2.0 mL of EtOH was added olefinic oxindole **4a** (1.0 mmol). After being stirred at 90 °C for 9 h. Upon the completion of the reaction as monitored by LCMS, the concentrated reaction mixture was isolated on a semi-preparative HPLC with a C18 column. The product **5a** was afforded (70%).

Materials used for metrics calculations: 4-bromobenzaldehyde **1a** (407.0 mg, 2.2 mmol), cysteine **2** (133.3 mg, 1.1 mmol) and olefinic oxindole **4a** (231.3 mg, 1.0 mmol), EtOH (1578 mg, 2 mL), and product **5a** 449.7 mg (0.70 mmol).



















**5.2 Two-step isolated process**

***Step 1: Synthesis of compound 3a***



**Experimental procedures:**

To a solution of 4-bromobenzaldehyde **1a** (1.0 mmol) and in 10.0 mL of EtOH was added cysteine **2a** (1.15 mmol). After being stirred at 25 °C for 6 h. Upon the completion of the reaction as monitored by LC-MS, the reaction solution was slowly cooled down to 5-10 °C, then stirred for 3 h. The product **3a** was collected by filtration, after that, the residual filtrate was isolated on a semi prep-HPLC with C18 column to afford the major product **3a** and combine two purified compound **3a** (86%).

Materials used for metrics calculations: 4-bromobenzaldehyde **1a** (185.0 mg, 1.0 mmol), cysteine **2** (139.3 mg, 1.15 mmol), EtOH (7890 mg, 10 mL) and compound **3a** **247.8** mg (0.86 mmol).

















***Step 2: Synthesis of product 5a***



**Experimental procedures:**

To a solution of 4-bromobenzaldehyde **1a** (1.1 mmol) and intermediate **3a** (1.0 mmol), in 2.0 mL of EtOH was added olefinic oxindole **4a** (1.0 mmol). After being stirred at 90 °C for 9 h. Upon the completion of the reaction as monitored by LC-MS, the concentrated reaction mixture was isolated on a semi-preparative HPLC with a C18 column. The major product **5a** was afforded (73%).

Materials used for metrics calculations: 4-bromobenzaldehyde **1a** (203.5 mg, 1.1 mmol), intermediate **3a** (288.2 mg, 1.0 mmol), olefinic oxindole **4a** (231.3 mg, 1.0 mmol), EtOH (1578 mg, 2 mL) and major product **5a** (469.0 mg, 0.73 mmol).



















**Cumulative metrics for compound 5a:**













**6. References for green metrics**

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