# **Supplementary Information**

### Synthetic Studies Toward Longeracemine: A SmI<sub>2</sub>-mediated Spirocyclization and Rearrangement Cascade to Construct the 2-Azabicyclo[2.2.1]heptane Framework

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#### I. GENERAL INFORMATION

Unless otherwise stated, all reactions were performed in flame-dried glassware under a nitrogen (N2) atmosphere, and reagents were used as received from the manufacturers. The reactions were monitored and analytical samples purified by normal phase thin-layer chromatography (TLC) using MilliporeSigma glass-backed 60 Å plates (indicator F-254, 250 µM) or by using Sigma Aldrich glass-backed 60 Å reverse phase C-18 fully end-capped plates (fluorescent indicator, 250 µM). Tetrahydrofuran, diethyl ether, benzene, dichloromethane, acetonitrile, dimethylformamide, and toluene were dried using a solvent purification system manufactured by SG Water, USA LLC. Diisopropylamine and N,N-diisopropylamine were dried over CaH<sub>2</sub> and freshly distilled prior to use. Dry air was obtained by slow passage through a 12inch column of CaCl<sub>2</sub>. Reactions involving organometallic reagents were conducted in flame-dried glassware under an argon atmosphere using standard techniques for handling air sensitive reagents,<sup>1</sup> solvents were deoxygenated by bubbling dry argon gas through the neat liquid for 10 min before use, and *n*-butyllithium was titrated immediately prior to use utilizing the method of Watson and Eastham.<sup>2</sup> Manual flash chromatography was performed using the indicated solvent systems with Silicycle SiliaFlash® P60 (230–400 mesh) silica gel as the stationary phase. Automated flash chromatography was performed on a Teledyne RF+UV-Vis MS Comp MPLC using the indicated solvent systems, and Teledyne RediSep® Rf normal phase disposable silica gel columns of the indicated size at the indicated flow rate.

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AvanceTM III 300 MHz, Bruker AscendTM 400 MHz or Bruker AscendTM 600 MHz spectrometer fitted with autosamplers. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) relative to the residual solvent resonance and coupling constants (J) are reported in hertz (Hz). NMR peak pattern abbreviations are as follows: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, dq = doublet of quartets, t = triplet, td = triplet of doublets, tdd = triplet of doublets, q = quartet, td = triplet of doublets, q = quartet, td = triplet of doublets, tdd = triplet of doublets, q = quartet, td = triplet of doublets, td = triplet oqd = quartet of doublets, qdd = quartet of doublet of doublets, qt = quartet of triplets, m = multiplet. Proton spectra recorded in deuterated chloroform are referenced to the residual <sup>1</sup>H signal of CHCl<sub>3</sub> at  $\delta = 7.26$  and are reported relative to TMS at  $\delta = 0.00$ ; carbon spectra are referenced to the central <sup>13</sup>C signal for CDCl<sub>3</sub> at  $\delta = 77.16$  and are reported relative to TMS at  $\delta = 0.00$ . Proton spectra recorded in deuterated dimethylsulfoxide are referenced to the residual <sup>1</sup>H signal of DMSO- $d_5$  at  $\delta = 2.50$  and are reported relative to TMS at  $\delta = 0.00$ ; carbon spectra are referenced to the central <sup>13</sup>C signal for DMSO- $d_6$  at  $\delta = 39.52$  and are reported relative to TMS at  $\delta = 0.00$ . Proton spectra recorded in deuterated acetonitrile are referenced to the residual <sup>1</sup>H signal for acetonitrile- $d_2$  at  $\delta = 1.94$  and are reported relative to TMS at  $\delta = 0.00$ ; carbon spectra are referenced to the central <sup>13</sup>C signals for acetonitrile- $d_3$  at  $\delta = 1.32$  or 118.26, and are reported relative to TMS at  $\delta = 0.00$ . Variable Temperature NMR was performed at the given temperature to allow for the coalescence of rotameric peaks. <sup>13</sup>C NMR peaks reported for inseparable mixtures denote peaks that are differentiable in the observed spectrum. Two-dimensional NMR spectra (HMBC, HSQC, <sup>1</sup>H-<sup>1</sup>H COSY, and <sup>1</sup>H-<sup>1</sup>H NOSEY) when necessary, and all recorded spectra are provided below. Infrared (IR) spectra were recorded on Bruker Platinum-ATR IR spectrometer using a diamond window. High Resolution mass spectra (HRMS) were obtained in the Baylor University Mass Spectrometry Center on a Thermo Scientific LTQ Orbitrap Discovery spectrometer using +ESI or -ESI and reported for the molecular ion  $([M+H]^+)$  and  $[M+Na]^+$  or  $[M-H]^-$  respectively).

<sup>1. (</sup>a) T. L. Rathman, J. A. Schwindeman, Org. Process Res. Dev. 2014, 18, 1192. (b) D. F. Shriver, M. A.

Drezdon, in The Manipulation of Air-Sensitive Compounds, 2nd ed., Wiley, New York, 1986.

<sup>2.</sup> S. C. Watson, J. F. Eastham, J. Organomet. Chem. 1967, 9, 165.

#### **II. EXPERIMENTAL PROCEDURES**

Preparation of Ester 12



Ester 12 was prepared according to the procedure reported by Hodgson and co-workers.<sup>3</sup> To a roundbottomed flask containing a magnetic stir bar and powdered zinc dust (409 mg, 6.25 mmol, 7.3 equiv) was added a 10% aqueous solution of hydrochloric acid (2.5 mL, 6.8 mmol, 8.0 equiv) dropwise to and the reaction mixture stirred for five minutes. At which point, the liquid was decanted and the zinc was washed with acetone (2 x 3 mL) and Et<sub>2</sub>O (3 mL). A suspension of AgOAc (14 mg, 0.0856 mmol, 0.1 equiv) in AcOH (1 mL) was then added with stirring to the digested zinc. After one minute, the supernatant was decanted and the black Zn/Ag couple was washed successively with AcOH (1.5 mL), Et<sub>2</sub>O (4 x 3 mL) and MeOH (3 mL). The moist Zn/Ag was then added to a stirred solution of known bromodiene SI-1<sup>4</sup> (283 mg, 0.856 mmol, 1 equiv) in MeOH (3 mL), and the reaction mixture was stirred for 3 h. The reaction mixture was then filtered through a pad of Celite, extracted with EtOAc (3 x 10 mL), and evaporated *in vacuo*. The residue was purified by silica gel chromatography (40 g SiO<sub>2</sub>, hexanes/EtOAc = 10:1) to afford ester 12 (168 mg, 74% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ , 85 °C)  $\delta$  7.78 (d, J = 2.5 Hz, 1H), 7.18 (dd, *J* = 5.4, 2.5 Hz, 1H), 7.06 (dd, *J* = 5.4, 2.5 Hz, 1H), 5.26 (q, *J* = 2.5 Hz, 1H), 5.21 (bs, 1H), 4.18 (q, J = 7.1 Hz, 2H), 1.36 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 85 °C)  $\delta$  162.2, 154.0, 153.2, 149.4, 143.3, 142.6, 79.6, 67.1, 65.8, 59.8, 27.5, 13.6. FTIR (thin film): 2981, 1710, 1368, 1338, 1318, 1269, 1167, 1081 cm<sup>-1</sup>; **HRMS** (ESI) m/z [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>19</sub>NNaO<sub>4</sub>: 288.1206, found: 288.1206.

NOTE: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in 12.

<sup>3.</sup> D. M. Hodgson, M. L. Jones, C. R. Maxwell, A. R. Cowley, A. L. Thompson, O. Ichihara, I. R. Matthews, *Tetrahedron* **2009**, *65*, 7825–7836.

<sup>4.</sup> C. Zhang, M. L. Trudell, J. Org. Chem. 1996, 61, 7189-7191.

Preparation of Primary Alcohol 16



Primary alcohol 16 was prepared through slight modification of the procedure reported by Hodgson and co-workers for the related sulfone 13.5 Ester 12 (154 mg, 0.581 mmol, 1.0 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (29 mL) and argon gas was bubbled through the solution for 2 h. At which point, 2-iodoethanol (0.18 mL, 2.32 mmol, 4.0 equiv) and Et<sub>3</sub>B (1.0 M in hexane, 0.23 mL, 0.232 mmol, 0.4 equiv) were added via syringe to the degassed solution. To the reaction mixture was added Bu<sub>3</sub>SnH (0.63 mL, 2.32 mmol, 4 equiv) via syringe pump over a period of 1 h, and dry air was injected into the headspace of the reaction mixture, in parallel, at 3 min intervals. After the additions were complete, the reaction mixture was allowed to stir for 3 h, concentrated in vacuo, and purified by silica gel chromatography (40 g SiO<sub>2</sub>, hexanes/EtOAc = 3:1 to 1:1) to afford primary alcohol 16 (44.4 mg, 24% yield) as a colorless oil: <sup>1</sup>H NMR (600 MHz, DMSO- $d_6$ , 27 °C, reported as 1:1 mixture of rotamers)  $\delta$  6.56 – 6.45 (m, 1H), 6.28 – 6.20 (m, 1H), 4.68 (m, 1H), 4.43 (bs, 1H), 4.38 (bs, 1H), 4.09 - 3.89 (m, 2H), 3.49 (apparent q, J = 6.2 Hz, 2H), 2.80 - 2.64 (m, 1H), 1.85–1.75 (m, 1H), 1.68 – 1.50 (m, 2H), 1.35 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H); <sup>13</sup>C NMR (151 MHz, DMSO-d<sub>6</sub>, 27 °C, reported as 1:1 mixture of rotamers) δ 171.4 (2C), 154.7, 154.2, 138.6, 137.3, 133.7, 132.8, 79.4, 79.3, 64.3, 64.0, 61.6, 60.7, 60.1 (2C), 59.5 (2C), 50.2, 49.4, 41.1, 40.0, 37.1, 36.9, 27.8 (2C), 14.0 (2C); FTIR (thin film): 3463, 2977, 1702, 1366, 1277, 1248, 1162, 1095, 1034, 872, 703 cm<sup>-1</sup>; HRMS (ESI) m/z  $[M+Na]^+$  calcd for C<sub>16</sub>H<sub>25</sub>NNaO<sub>5</sub>: 334.1625, found: 334.1628.

*NOTE*: Variable temperature NMR analysis was attempted to achieve coalescence of the rotameric peaks, however, a retro-Diels-Alder reaction of **16** occurred under the VT-NMR conditions to afford **SI-2** and **SI-3** (DMSO- $d_6$ , 85 °C, 1.5 h). See Figure S13 for the monitoring of the retro-Diels-Alder reaction over time.

<sup>5.</sup> D. M. Hodgson, S. Hachisu, and M. D. Andrews, Org. Lett. 2005, 7, 815-817.

Monitoring of Retro Diels-Alder Reaction of 16



SI-2

<sup>1</sup>**H NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 27 °C)  $\delta$  7.23 (t, *J* = 2.2 Hz, 2H), 6.25 (t, *J* = 2.2 Hz, 2H), 1.55 (s, 9H). The spectral data is fully in accord with the literature.<sup>6</sup>

#### SI-3

<sup>1</sup>**H NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 27 °C) δ 6.90 (dt, *J* = 15.8, 7.1 Hz, 1H), 5.88 (dt, *J* = 15.7, 1.6 Hz, 1H), 4.66 (t, *J* = 5.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.51 (td, *J* = 6.3, 5.2 Hz, 2H), 2.33 (qd, *J* = 6.4, 1.6 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>**C NMR** (101 MHz, DMSO-*d*<sub>6</sub>, 27 °C) δ 165.6, 147.2, 122.1, 59.7, 59.4, 35.2, 14.2; **FTIR** (thin film): cm<sup>-1</sup> 3430, 2930, 1699, 1654, 1266, 1161, 1038, 977; **HRMS** (ESI) *m/z* [M+Na]<sup>+</sup> calcd for C<sub>7</sub>H<sub>12</sub>NaO<sub>3</sub>: 167.0684, found: 167.0710. The spectral data is fully in accord with the literature.<sup>7</sup>

<sup>6.</sup> T. Fukuda, Y. Nanjo, M. Fujimoto, K. Yoshida, Y. Natsui, F. Ishibashi, F. Okazaki, H. To, M. Iwao, *Bioorg. Med. Chem.* **2019**, *27*, 265–277.

<sup>7.</sup> K. Heckenbichler, A. Schweiger, L. A. Brandner, A. Binter, M. Toplak, P. Macheroux, K. Gruber, R. Breinbauer *Angew. Chem. Int. Ed.* **2018**, *57*, 7240–7244.

Preparation of Propargyl Alcohol SI-5



Aldehyde **SI-4** was prepared following the general procedure of Njardarson and co-workers.<sup>8</sup> A flask was charged with 4-pentenenitrile **32** (500 mg, 6.16 mmol, 1.0 equiv),  $CH_2Cl_2$  (31 mL) and cooled to – 78 °C in a dry ice/acetone bath. Ozone was bubbled through the –78 °C solution for about 30 minutes, until the reaction turned blue. At which point, nitrogen gas was bubbled through the solution to remove the ozone, then Me<sub>2</sub>S (1.0 mL, 13.6 mmol, 2.2 equiv) was added. The reaction mixture was then gradually allowed to warm to room temperature (23 °C) and stirred for 8 h. The solution was concentrated *in vacuo* to afford **SI-4**,<sup>8</sup> which was used directly for the next step without further purification.

A solution of freshly distilled N,N-diisopropylamine (1.12 mL, 8.01 mmol, 1.3 equiv) in dry THF (40 mL) placed under argon, was cooled to 0 °C and *n*-BuLi (2.40 M in hexane, 3.2 mL, 7.70 mmol, 1.25 equiv) was added via syringe. The mixture was allowed to stir at 0 °C for 15 minutes, then cooled to -78 °C in a dry ice/acetone bath. At which point, freshly prepared acetylene 33<sup>9</sup> (1.61 g, 9.25 mmol, 1.5 equiv) was added dropwise to the reaction mixture. After stirring at -78 °C for 1 h, a solution of crude SI-4 (512 mg, 6.16 mmol, 1.0 equiv) in THF (5 mL) was cooled to -78 °C then added dropwise to the reaction mixture. The reaction mixture was then allowed to stir at -78 °C for 1.5 h, at which point, saturated aqueous NH<sub>4</sub>Cl (25 mL) was added and the mixture was allowed to warm to 23 °C. The mixture was then extracted twice with EtOAc (2 x 25 mL), and the combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (100 g SiO<sub>2</sub>, hexanes/EtOAc= 5:1 to 3:1) to afford SI-5 (769 mg, 48% yield, over 2 steps from SI-5) as colorless oil: <sup>1</sup>H NMR (600 MHz, chloroform-d)  $\delta$  7.39 – 7.24 (m, 5H), 4.51 (s, 2H), 4.42 (bs, 1H), 3.54 (t, J = 6.1 Hz, 2H), 2.63 - 2.40 (m, 3H), 2.33 (td, J = 7.1, 1.9 Hz, 2H), 1.99 - 1.90 (m, 2H), 1.87 – 1.80 (m, 2H); <sup>13</sup>C NMR (151 MHz, chloroform-d) δ 138.3, 128.4, 127.8, 127.7, 119.5, 86.2, 79.7, 73.0, 68.6, 60.5, 33.2, 28.6, 15.6, 13.0; FTIR (thin film): 3414, 2935, 2861, 2248, 1101, 1068, 737, 698  $cm^{-1}$ ; **HRMS** (ESI) m/z [M+Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>19</sub>NNaO<sub>2</sub>: 280.1308, found: 280.1310.

<sup>8.</sup> Q. Yang, C. Draghici, J. T. Njardarson, F. Li, B. R. Smith, P. Das, Org. Biomol. Chem. 2014, 12, 330-344.

<sup>9.</sup> E. D. Slack, C. M. Gabriel, B. H. Lipshutz, Angew. Chem. Int. Ed. 2014, 53, 14051-14054.

Preparation of Ketone 31



To a solution of **SI-5** (769 mg, 2.99 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0 °C, was added NaHCO<sub>3</sub> (753 mg, 8.96 mmol, 3.0 equiv), and Dess-Martin periodinane (1.90 g, 4.48 mmol, 1.5 equiv). The reaction mixture was then allowed to warm to 23 °C and stirred for an additional 1 h. At which point, a solution of saturated, aqueous NaHCO<sub>3</sub> (10 mL) was added followed by a solution of 10% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) and the mixture was extracted twice with EtOAc (2 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (7 g SiO<sub>2</sub>, hexanes/EtOAc= 2:1) to afford **31** (732 mg, 96% yield) as a colorless oil: <sup>1</sup>H NMR (400 MHz, chloroform-*d*)  $\delta$  7.40 – 7.25 (m, 5H), 4.52 (s, 2H), 3.56 (t, *J* = 5.9 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 1.94 – 1.83 (m, 2H);<sup>13</sup>C NMR (101 MHz, chloroform-*d*)  $\delta$  182.6, 138.1, 128.3, 127.6, 118.4, 96.2, 79.9, 72.9, 68.1, 40.2, 27.7, 15.9, 11.4; FTIR (thin film): 2861, 2210, 1673, 1409, 1363, 1167, 1103, 738, 698 cm<sup>-1</sup>; HRMS (ESI) *m/z* [M+Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>17</sub>NNaO<sub>2</sub> 278.1151, found: 278.1153.



To a 0 °C solution of sodium hydride (60% in mineral oil, 37 mg, 0.925 mmol, 1.5 equiv) in DMF (1.8 mL) was added **SI-6** (50 mg, 0.616 mmol, 1.0 equiv). The reaction mixture was allowed to warm to 23 °C and stirred for an additional 30 minutes. At which point, the reaction mixture was cooled to 0°C and benzyl bromide (73  $\mu$ L, 0.616 mmol, 1.0 equiv) was added. The reaction mixture was then allowed to warm to 23 °C and stirred for an additional 4 h. At which point, a solution of saturated, aqueous NH<sub>4</sub>Cl (10 mL) was added and the mixture was extracted twice with hexanes (2 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (10 g SiO<sub>2</sub>, hexanes/EtOAc= 100:1 to 50:1) to afford **35** (80 mg, 75% yield) as a colorless oil; <sup>1</sup>H NMR (400 MHz, chloroform-*d*)  $\delta$  7.40 – 7.20 (m, 3H), 7.14 – 7.09 (m, 2H), 6.58 (d, *J* = 2.5 Hz, 1H), 6.44 (bs, 1H), 6.00 (d, *J* = 2.3 Hz, 1H), 4.99 (s, 2H), 2.10 (s, 3H); <sup>13</sup>C NMR (101 MHz, chloroform-*d*)  $\delta$  138.5, 128.8, 127.7, 127.1, 121.1, 119.3, 119.2, 109.8, 53.3, 12.1; FTIR (thin film): 2921, 1497, 1453, 1329, 1158, 1069, 758, 717, 694 cm<sup>-1</sup>; HRMS (ESI) *m/z* [M+H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>14</sub>N: 172.1121, found: 172.1120.

Preparation of N-Tosyl Bicyclic Esters N-Ts-38 and N-Ts-39



To a flame-dried, 1.5 dram vial containing pyrrole **34**<sup>10</sup> (30 mg, 0.128 mmol, 1.0 equiv) was added ethyl-3-bromopropiolate **37**<sup>11</sup> (42 mg, 0.255 mmol, 2.0 equiv). The reaction mixture was then heated to 90 °C and allowed to stir for 24 h. At which point, the reaction mixture was cooled to 23 °C, concentrated *in vacuo*, and purified by silica gel chromatography (3 g SiO<sub>2</sub>, hexanes/EtOAc= 8:1 to 5:1) to afford an inseparable mixture of bicyclic esters *N-Ts-38* and *N-Ts-39* (11.1 mg, 21% yield, *N-Ts-38* : *N-Ts-39* = 3:1) as colorless oils: <sup>1</sup>H NMR (400 MHz, chloroform-*d*, as a 3:1 mixture of *N-Ts-38* and *N-Ts-39*) *N-Ts-38* δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 6.51 (s, 1 H), 5.34 (t, *J* = 2.6 Hz, 1H), 4.80 (d, *J* = 2.4 Hz, 1H), 4.19 – 3.98 (m, 2H), 2.40 (s, 3H), 1.93 (d, *J* = 1.9 Hz, 3H), 1.25 (td, *J* = 7.1, 1.8 Hz, 3H), *N-Ts-39* δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 6.47 (s, 0.3H), 5.11 (d, *J* = 2.4 Hz, 0.3H), 4.99 (t, *J* = 2.4 Hz, 0.3H), 4.19 – 3.98 (m, 2H), 2.40 (s, 3H), 1.89 (d, *J* = 1.9 Hz, 3H), 1.25 (td, *J* = 7.1, 1.8 Hz, 3H); <sup>13</sup>C NMR (101 MHz, chloroform-*d*, as a 3:1 mixture of *N-Ts-38* and *N-Ts-39*)  $\delta$  161.9, 161.7, 156.8, 154.0, 147.5, 145.0, 144.1, 143.6, 141.6, 135.8, 135.2, 132.5, 130.1, 128.5, 79.0, 77.4, 76.2, 72.8, 70.0, 61.0, 60.9, 21.7, 15.8, 15.7, 14.3; FTIR (thin film): 2981, 1697, 1597, 1346, 1309, 1159, 1091, 814, 702, 583 cm<sup>-1</sup>; HRMS (ESI) *m/z* [M+Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>18</sub><sup>79</sup>BrNNaO<sub>4</sub>S: 434.0032, found: 434.0035.

<sup>10.</sup> P. Folly, Ph.D. Dissertation, University of Fribourg, Fribourg, Switzerland, 2000.

<sup>11.</sup> F. Beltran, I. Fabre, I. Ciofini, L. Miesch, Org. Lett. 2017, 19, 5042-5045.

Preparation of N-Boc Bicyclic Esters N-Boc-38 and N-Boc-39



To a flame-dried, 1.5 dram vial containing pyrrole  $30^{12}$  (100 mg, 0.552 mmol, 1.0 equiv) was added ethyl 3-bromopropiorate  $37^{11}$  (180 mg, 1.10 mmol, 2.0 equiv). The reaction mixture was then heated to 90 °C and allowed to stir for 24 h. At which point, the reaction mixture was cooled to 23 °C, concentrated *in vacuo*, and purified by silica gel chromatography (10 g SiO<sub>2</sub>, hexanes/EtOAc= 40:1 to 30:1) to afford an inseparable mixture of bicyclic esters *N*-Boc-38 and *N*-Boc-39 (108 mg, 55% yield, *N*-Boc-38 : *N*-Boc-39 = 5:1) as yellow oils: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 85 °C, as a 5:1 mixture of *N*-Boc-38 and *N*-Boc-39) *N*-Boc-38:  $\delta$  6.66 – 6.58 (m, 1H), 5.21 (t, *J* = 2.4 Hz, 1H), 4.89 (t, *J* = 2.4 Hz, 1H), 4.28 – 4.14 (m, 2H), 1.98 (d, *J* = 2.0 Hz, 3H), 1.37 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), *N*-Boc-39:  $\delta$  6.66 – 6.58 (m, 1H), 5.03 (d, *J* = 2.4 Hz, 1H), 5.01 (t, *J* = 2.4 Hz, 1H), 4.28 – 4.14 (m, 2H), 1.95 (d, *J* = 2.0 Hz, 3H), 1.37 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 85 °C, as a 5:1 mixture of *N*-Boc-38 and *N*-Boc-39)  $\delta$  161.4, 161.3, 154.5, 153.4, 152.1, 143.6, 143.5, 133.9, 133.9, 131.1, 80.3, 77.9, 77.8, 74.8, 71.8, 68.7, 60.0, 27.3, 27.3, 23.3, 14.7, 14.5, 13.5, 13.5; FTIR (thin film): 2977, 1711, 1596, 1303, 1254, 1204, 1158, 1080, 858, 789 cm<sup>-1</sup>; HRMS (ESI) *m*/z [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>20</sub><sup>79</sup>BrNNaO<sub>4</sub> 380.0468, found: 380.0469.

*NOTE*: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in *N*-Boc-38 and *N*-Boc-39.

<sup>12.</sup> T. Ikawa, A. Takagi, Y. Kurita, K. Saito, K. Azechi, M. Egi, K. Kakiguchi, Y. Kita, S. Akai, *Angew. Chem. Int. Ed.* **2010**, *49*, 5563–5566.

Preparation of Grignard Reagent 40

Fresh Grignard reagent **37** was prepared using the following procedure: To a flame-dried, 100 mL round-bottomed flask containing magnesium turnings (616 mg, 25.3 mmol, 1.2 equiv) cooled to 0 °C in an ice/water bath, was added a 0 °C solution of **SI-7**<sup>13</sup> (4.84 g, 21.1 mmol, 1.0 equiv) and iodine (107.1 mg, 0.422 mmol, 0.02 equiv) in THF (21 mL). The ice/water bath as then removed and the reaction mixture was allowed to warm to 23 °C. The suspension containing **40** was allowed to settle and used for the next step.

Preparation of Benzyl Ethers 41 and SI-8



To a flame-dried flask under argon containing a solution of copper(I) iodide (2.0 g, 10.6 mmol, 1.2 equiv) in dry THF (130 mL) at -78 °C was added a cooled solution (-78 °C) of the freshly prepared Grignard reagent 40 (1.0 M in THF solution, 21 mL, 21.1 mmol, 2.4 equiv). The reaction mixture was allowed to stir at -78 °C for 20 minutes, then warmed to -35 °C and stirred for an additional 15 minutes. At which point a cooled solution (-35 °C) of a mixture of N-Boc-38 and N-Boc-39 (3.15g, 8.79 mmol, 1.0 equiv, N-Boc-38: N-Boc-39 = 5:1) in THF (25 mL) was added. The reaction mixture was then allowed to stir at -35 °C for 1 h. At which point, a solution of saturated, aqueous NH<sub>4</sub>Cl (50 mL) was added and the mixture was allowed to warm to 23 °C and extracted twice with Et<sub>2</sub>O (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (80 g SiO<sub>2</sub>, hexanes/EtOAc= 20:1 to 10:1) to afford an inseparable mixture of 41and SI-8 (3.30 g, 88% yield, 38 : SI-8 = 5:1) as yellow oils: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 85 °C, as a mixture of **38** : **SI-8** = 5:1) **41**: δ 7.40 – 7.22 (m, 5H), 6.55 (bs, 1H), 5.11 (s, 1H), 4.84 (d, J = 2.1 Hz, 1H), 4.47 (s, 2H), 4.22 – 4.05 (m, 2H), 3.52 – 3.42 (m, 2H), 2.84 – 2.76 (m, 2H), 2.84 – 1H), 2.74 - 2.66 (m, 1H), 1.92 (d, J = 2.0 Hz, 3H), 1.83 - 1.70 (m, 2H), 1.35 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H), SI-8:  $\delta$  7.40 – 7.22 (m, 5H), 6.40 (bs, 1H), 4.98 (s, 1H), 4.92 (s, 1H), 4.47 (s, 2H), 4.22 – 4.05 (m, 2H), 3.52 - 3.42 (m, 2H), 2.84 - 2.76 (m, 1H), 2.64 - 2.57 (m, 1H), 1.91 (d, J = 2.0 Hz, 3H), 1.83 - 1.70 (m, 2H), 1.35 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>, 85 °C, as a mixture of 41 : SI-**8** = 5:1) δ 163.3, 163.1, 153.5, 152.0, 139.5, 139.5, 138.3, 138.3, 134.7, 134.7, 131.6, 127.6, 126.9, 126.8, 126.8, 126.7, 79.3, 73.9, 73.9, 71.6, 71.5, 70.5, 68.8, 68.8, 67.1, 67.0, 59.2, 59.2, 27.4, 27.3, 26.0, 25.2, 14.6, 14.6, 13.6; FTIR (thin film): 2977, 1706, 1368, 1333, 1256, 1200, 1167, 1100, 1071 cm<sup>-1</sup>; HRMS (ESI) m/z [M+Na]<sup>+</sup> calcd for C<sub>25</sub>H<sub>33</sub>NNaO<sub>5</sub>: 450.2251, found: 450.2252.

NOTE: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in 38 and SI-8.

<sup>13.</sup> K. J. Frankowski, J. E. Golden, Y. Zeng, Y. Lei, J. Aubé, J. Am. Chem. Soc. 2008, 130, 6018-6024.

Preparation of Alcohols SI-9 and SI-10



To a cooled solution (-78 °C) of a mixture of 41 and SI-8 (1.40 g, 3.27 mmol, 1.0 equiv, 41: SI-8 = 5:1) in THF (17 mL), was added DIBAL-H (1.0 M hexane solution, 10 mL, 10 mmol, 3.0 equiv). The reaction mixture was allowed to stir at -78 °C for 1.5 h, at which point, an aqueous solution of saturated Rochelle salt (25 mL) was added and the mixture was allowed to warm to 23 °C and stirred for 14 h. The mixture was then extracted twice with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (60 g SiO<sub>2</sub>, hexanes/EtOAc= 2:1 to 1:1) to afford an inseparable mixture of **SI-9** and **SI-10** (1.11 g, 88% yield, **SI-9** : **SI-10** = 5:1) as colorless oils: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ , 85 °C, as a mixture of SI-9 : SI-10 = 5:1) SI-9:  $\delta$  7.36 – 7.25 (m, 5H), 6.42 (bs, 1H), 4.86 (s, 1H), 4.58 (d, J = 2.0 Hz, 1H), 4.45 (s, 2H), 4.11 (d, J = 13.6 Hz, 1H), 3.98 (d, J = 13.6 Hz, 1H), 3.44 – 3.37 (m, 2H), 2.36 – 2.20 (m, 3H), 1.89 (d, J = 2.0 Hz, 3H), 1.73 – 1.59 (m, 2H), 1.35 (s, 9H), SI-10: δ 7.36 – 7.25 (m, 5H), 6.34 (s, 1H), 4.74 (s, 1H), 4.67 (s, 1H), 4.45 (s, 2H), 4.11 (d, J = 13.6 Hz, 1H), 3.98 (d, J = 13.6 Hz, 1H), 3.44 - 3.37 (m, 2H), 2.16 - 2.09 (m, 3H), 1.89 (d, J = 2.0 Hz, 3H), 1.73 - 1.59 (m, 2H), 1.35 (s, 9H); <sup>13</sup>C NMR (101 MHz, DMSO- $d_6$ , 85 °C, as a mixture of SI-9 : SI-10 = 5:1)  $\delta$  153.6, 152.5, 148.2, 138.4, 134.4, 127.7, 126.9, 126.9, 126.8, 126.8, 78.5, 78.5, 72.4, 71.6, 71.5, 68.7, 67.8, 55.9, 55.5, 28.0, 27.6, 26.6, 23.1, 23.0, 14.8, 14.7; FTIR (thin film): 3429, 2974, 2930, 2855, 1704, 1685, 1365, 1332, 1254, 1164, 1080, 1012, 736, 697 cm<sup>-1</sup>; **HRMS** (ESI) m/z [M+Na]<sup>+</sup> calcd for C<sub>23</sub>H<sub>31</sub>NNaO<sub>4</sub>: 408.2145, found: 408.2147.

NOTE: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in SI-9 and SI-10.

Preparation of Aldehyde 42



To a cooled solution (0 °C) containing a mixture of **SI-9** and **SI-10** (1.11 g, 2.88 mmol, 1.0 equiv, **SI-9** : **SI-10** = 5:1) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL), was added NaHCO<sub>3</sub> (1.06 g, 12.7 mmol, 4.4 equiv) followed by Dess-Martin periodinane (2.44 g, 5.76 mmol, 2.0 equiv) and the reaction mixture was allowed to stir for 2 h at 0°C. At which point, a solution of saturated aqueous NaHCO<sub>3</sub> (10 mL) followed by a 10% aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) were sequentially added. The mixture was extracted twice with EtOAc (2 x 50 mL), and the combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (60 g SiO<sub>2</sub>, hexanes/EtOAc= 5:1 to 3:1) to afford **42** (788 mg, 71% yield) as a yellow oil: <sup>1</sup>**H NMR** (400 MHz, DMSO-*d*<sub>6</sub>, 85 °C)  $\delta$  9.80 (s, 1H), 7.36 – 7.24 (m, 5H), 6.50 (bs, 1H), 5.18 (bs, 1H), 4.91 (d, *J* = 2.0 Hz, 1H), 4.47 (s, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.90 – 2.70 (m, 2H), 1.92 (d, *J* = 1.9 Hz, 3H), 1.90 – 1.77 (m, 2H), 1.35 (s, 9H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 85 °C)  $\delta$  183.7, 153.5, 152.0, 138.2, 134.6, 127.7, 127.7, 126.9, 126.9, 126.8, 79.5, 73.5, 71.6, 68.3, 64.4, 27.5, 27.3, 24.2, 14.6; **FTIR** (thin film): 2856, 1707, 1651, 1366, 1327, 1254, 1161, 1099, 1079, 736, 698 cm<sup>-1</sup>; **HRMS** (ESI) *m/z* [M+Na]<sup>+</sup> calcd for C<sub>23</sub>H<sub>29</sub>NNaO<sub>4</sub>: 406.1989, found: 406.1989.

NOTE: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in 42.

*NOTE*: Compound 42 decomposes slowly under the variable temperature NMR conditions (DMSO- $d_6$ , 85 °C).

Preparation of Alkyl Bromide SI-12



To a cooled solution (0 °C) of **SI-11<sup>14</sup>** (4.2 g, 21.4 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (22 mL), was added carbon tetrabromide (7.8 g, 23.5 mmol, 1.1 equiv) and triphenylphosphine (6.2 g, 23.5 mmol, 1.1 equiv), and the reaction mixture was allowed to subsequently warm to 23 °C. After stirring at 23 °C for 12 h, the reaction mixture was concentrated *in vacuo*, filtered through short pad of Celite, washing with five portions of Et<sub>2</sub>O (50 mL each), and the resulting filtrate was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (60 g SiO<sub>2</sub>, hexanes/EtOAc= 40:1 to 20:1) to afford **SI-12** (4.9 g, 89% yield) as a colorless oil: <sup>1</sup>H NMR (400 MHz, chloroform-*d*)  $\delta$  7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.81 (s, 3H), 3.58 (t, *J* = 5.9 Hz, 2H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.12 (p, *J* = 6.2 Hz, 2H);<sup>13</sup>C NMR (101 MHz, chloroform-*d*)  $\delta$  159.4, 130.5, 129.4, 114.0, 73.0, 67.6, 55.4, 33.1, 30.9; **FTIR** (thin film): 2858, 1612, 1511, 1362, 1301, 1243, 1172, 1095, 1033, 816 cm<sup>-1</sup>; **HRMS** (ESI) *m/z* [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>15</sub><sup>79</sup>BrNaO<sub>2</sub>: 281.0148, found: 281.0151.

<sup>14.</sup> Y. Hayashi, H. Yamaguchi, M. Toyoshima, K. Okado, T. Toyo, M. Shoji, *Org. Lett.* **2008**, *10*, 1405–1408.

Preparation of Grignard Reagent 43

Fresh Grignard reagent **43** was prepared using the following procedure: To a flame-dried, 100 mL round-bottomed flask, under argon, containing magnesium turnings (377 mg, 15.5 mmol, 1.2 equiv) cooled to 0 °C in an ice/water bath was added a cooled solution (0 °C) of **SI-12** (3.35 g, 12.9 mmol 1.0 equiv) and iodine (65.6 mg, 0.258 mmol, 0.02 equiv) in THF (13 mL). Upon completion of the addition of **SI-12**, the reaction mixture was allowed to warm to 23 °C. The resulting Grignard reagent **43** was decanted from residual magnesium and used directly for the next step.





A flame-dried, 500-mL round-bottomed flask containing a large magnetic stir bar, was charged with cerium(III) chloride heptahydrate (4.81 g, 12.9 mmol, 3.5 equiv) and heated to 140 °C under vacuum (ca. 0.1 Torr) and allowed to stir at 140 °C for 2 h. At which point, the flask was cooled to 23 °C, THF (100 mL) was added, and the suspension was stirred at 23 °C for 16 h. Then the reaction mixture was cooled to -78 °C and freshly prepared Grignard reagent 43 (1.0 M in THF solution, 13 mL, 12.9 mmol, 3.5 equiv) was added at -78 °C. After stirring for 1.5 h, a solution of 42 (1.40 g, 3.65 mmol, 1.0 equiv) in THF (20 mL) was cooled to -78 °C and added to the reaction mixture, which was allowed to stir for an additional 1 h at -78 °C. At which point, a solution of saturated aqueous NH<sub>4</sub>Cl (25 mL) was added to the reaction mixture, and it was then allowed to warm to 23 °C, filtered through short pad of Celite, and the filtrate was extracted five times with EtOAc (5 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (80 g SiO<sub>2</sub>, hexanes/EtOAc= 2:1 to 1:1) to afford 44 (1.46 g, 71% yield, as a 3:2 mixture of diastereomers) as a colorless oils: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 85 °C, as a 3:2 mixture of diastereomers) 7.37 - 7.24 (m, 5H), 7.21 (dd, J = 8.6, 2.4 Hz, 2H), 6.88 (dd, J = 8.6, 1.7 Hz, 2H), 6.38 (bs, 1H),  $[4.92 (t, J = 2.3 \text{ Hz}, 0.6\text{H}), 4.87 (t, J = 2.3 \text{ Hz}, 0.4\text{H}), 1\text{H total}], 4.57 (s, 1\text{H}), 4.45 (s, 2\text{H}), [4.36 (s, 2\text{H}), 14.36 (s, 2\text$ 0.8H), 4.34 (s, 1.2H), 2H total], 4.28 - 4.24 (m, 1H), 3.75 (s, 3H), 3.52 - 3.30 (m, 4H), 2.40 - 2.13 (m, 2H), 1.88 (s, 3H), 1.77 – 1.57 (m, 3H), 1.56 – 1.43 (m, 3H), [1.35 (s, 5.4H), 1.34 (s, 3.6H), 9H total]; <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 85 °C) δ 158.4, 158.4 153.5, 151.3, 151.3, 150.4, 138.4, 138.4, 134.8, 134.8, 130.5, 130.5, 128.4, 128.4, 127.7, 126.9, 126.8, 126.7, 126.7, 113.3, 113.3, 78.5, 78.5, 71.6, 71.5, 71.5, 71.2, 71.2, 71.1, 69.2, 69.0, 68.9, 68.9, 65.2, 65.1, 54.7, 30.8, 28.1, 28.1, 27.6, 27.5, 24.9, 23.3, 23.2, 14.8, 14.7; **FTIR** (thin film): 3453, 2932, 2854, 1703, 1512, 1365, 1339, 1246, 1168, 1092, 1031, 821, 737, 698 cm<sup>-1</sup>; **HRMS** (ESI): m/z [M+Na]<sup>+</sup> calcd for C<sub>34</sub>H<sub>45</sub>NNaO<sub>6</sub>: 586.3139, found: 586.3136.

NOTE: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in 44.

Preparation of TBS Ether SI-13



To a -78 °C solution of 44 (430 mg, 0.830 mmol, 1.0 equiv, 3:2 mixture of diastereomers) in CH<sub>2</sub>Cl<sub>2</sub> (17 mL) was added 2,6-lutidine (0.58 mL, 4.98 mmol, 6.0 equiv), tert-butyldimethylsilyl trifluoromethanesulfonate (0.57 mL, 2.49 mmol, 3.0 equiv), and the reaction mixture was allowed to stir at -78 °C for 50 minutes. At which point, a solution of saturated aqueous NaHCO<sub>3</sub> (25 mL) was added, the mixture was allowed to warm to 23 °C, and then was extracted twice with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in *vacuo*. The resulting residue was purified by silica gel chromatography (30 g SiO<sub>2</sub>, hexanes/EtOAc= 8:1 to 5:1) to afford SI-13 (466 mg, 84% yield, as 3:2 mixture of diastereomers) as colorless oils: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ , 85 °C, as 3:2 mixture of diastereomers)  $\delta$  7.38 – 7.23 (m, 5H), 7.20 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), [6.42 (s, 0.6H), 6.34 (s, 0.4H), 1H total], [4.89 (bs, 0.6H), 4.84 (bs, 0.4H), 1H total], [4.63 (bs, 0.4H), 4.62 (bs, 0.6H), 1H total], 4.45 (s, 2H), 4.45 - 4.41 (m, 1H), [4.35 (s, 0.8H), 4.33 (s, 1.2H), 2H total], 3.74 (s, 3H), 3.49 – 3.32 (m, 4H), 2.39 – 2.27 (m, 1H), 2.25 – 2.14 (m, 1H), 1.87 (d, J = 1.9 Hz, 3H), 1.79 - 1.24 (m, 6H), 1.34 (d, J = 1.6 Hz, 9H), [0.88 (s, 5.4H), 0.85 (s, 3.6H), 9H total], [0.01](s, 1.8H), -0.02 (s, 1.8H), -0.03 (s, 1.2H), -0.13 (s, 1.2H), 6H total]; <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 85 °C, as 3:2 mixture of diastereomers) & 158.4, 158.4, 151.0, 138.4, 138.3, 134.6, 130.4, 130.4, 128.4, 128.4, 127.7, 126.8, 126.8, 126.7, 126.7, 113.3, 113.3, 78.6, 78.4, 71.4, 71.4, 71.2, 71.2, 71.1, 69.0, 68.9, 67.1, 66.9, 66.1, 65.8, 65.8, 54.7, 31.4, 28.0, 27.6, 27.5, 25.3, 25.3, 24.7, 23.3, 17.4, 14.6, -5.3, -5.4, -5.6, -5.6; FTIR (thin film): 2929, 2854, 1704, 1513, 1364, 1340, 1247, 1170, 1079, 1035, 831, 775, 697 cm<sup>-1</sup>; HRMS (ESI) m/z [M+Na]<sup>+</sup> calcd for C<sub>40</sub>H<sub>59</sub>NNaO<sub>6</sub>Si: 700.4004, found: 700.4001.

*NOTE*: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in SI-13.

Preparation of Primary Alcohol SI-14



To a cooled (0 °C) biphasic solution of SI-13 (412.7 mg, 0.618 mmol, 1.0 equiv, as a 3:2 mixture of diastereomers) in CH<sub>2</sub>Cl<sub>2</sub> (26 mL) and pH 7 phosphate buffer (5 mL), was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (561 mg, 2.47 mmol, 4.0 equiv). The reaction mixture was then allowed to stir at 0 °C for 1.5 h. At which point, a saturated aqueous solution of NaHCO<sub>3</sub> (10 mL) was added followed by a 10% aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL), and the mixture was extracted twice with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in *vacuo*. The resulting residue was purified by silica gel chromatography (20 g SiO<sub>2</sub>, hexanes/EtOAc= 5:1 to 2:1) to afford SI-14 (245 mg, 71% yield, as a 3:2 mixture of diastereomers) as yellow oils: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 85 °C, as a 3:2 mixture of diastereomers) δ 7.39 - 7.20 (m, 5H), [6.44 (bs, 0.6H), 6.35 (brs, 0.4H), 1H total], [4.91 (s, 0.6H), 4.84 (s, 0.4H), 1H total], 4.62 (s, 1H), 4.53 - 4.36 (m, 3H), 3.55 -3.31 (m, 4H), 2.40 – 2.14 (m, 2H), 1.88 (bs, 3H), 1.80 – 1.55 (m, 2H), 1.55 – 1.31 (m, 2H), 1.35 (s, 9H), 1.31 – 1.12 (m, 2H), 0.99 – 0.77 (m, 9H), [0.02 (s, 1.8H), -0.01 (s, 1.2H), -0.02 (s, 1.8H), -0.12 (s, 1.2H) 6H total]; <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>, 85 °C, as a 3:2 mixture of diastereomers) δ 151.1, 138.4, 138.4, 127.7, 127.7, 126.9, 126.8, 126.8, 126.7, 78.6, 78.6, 78.4, 78.4, 71.5, 68.9, 68.8, 67.2, 67.1, 60.5, 60.4, 31.3, 28.0, 28.0, 27.6, 27.5, 25.4, 25.3, 25.3, 23.3, 23.3, 17.4, 17.3, 14.7, 14.7, -3.7, -5.2, -5.4, -5.5, -5.6; FTIR (thin film): 3458, 2929, 2855, 1705, 1365, 1252, 1167, 1057, 833, 774, 697 cm<sup>-1</sup>; HRMS (ESI) *m/z*  $[M+Na]^+$  calcd for C<sub>32</sub>H<sub>51</sub>NNaO<sub>5</sub>Si: 580.3429, found: 580.3428.

NOTE: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in SI-14.

*NOTE*: Compound SI-14 decomposes slowly under the variable temperature NMR conditions (DMSO- $d_6$ , 85 °C).

Preparation of Aldehyde 29



To a cooled solution (0 °C) of SI-14 (220.3 mg, 0.395 mmol, 1.0 equiv, as a 3:2 mixture of diastereomers) in CH2Cl2 (4 mL) was added NaHCO3 (146 mg, 1.74 mmol, 4.4 equiv), Dess-Martin periodinane (335 mg, 0.790 mmol, 2.0 equiv), and allowed to stir at 0 °C for 3 h. At which point, a saturated aqueous solution of NaHCO<sub>3</sub> (10 mL) was added followed by a 10% aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL), and the mixture was extracted twice with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (3 g SiO<sub>2</sub>, hexanes/EtOAc= 8:1) to afford **29** (183 mg, 83% yield, as a 3:2 mixture of diastereomers) as colorless oils: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 85 °C, as a 3:2 mixture of diastereomers)  $\delta$  [9.67 (s, 0.4H), 9.63 (s, 0.6H), 1H total], 7.39 – 7.22 (m, 5H), [6.47 (t, J = 2.3 Hz, 0.6H), 6.35 (bs, 0.4H), 1H total], [4.91 (s, 0.6H), 4.85 (s, 0.4H), 1H total], 4.64 (bs, 1H), 4.54 – 4.41 (m, 3H), 3.55 -3.35 (m, 2H), 2.41 - 2.13 (m, 4H), [1.89 (d, J = 2.0 Hz, 1.8H), 1.88 (d, J = 2.0 Hz, 1.2H), 3H total], 1.81-1.57 (m, 3H), 1.57 - 1.38 (m, 1H), [1.36 (s, 3.6H), 1.35 (s, 5.4H), 9H total], [0.88 (s, 5.4H), 0.86 (s, 3.6H), 9H total], [0.02 (s, 1.8H), -0.01 (s, 1.2H), -0.01 (s, 1.8H), -0.12 (s, 1.2H), 6H total]; <sup>13</sup>C NMR (101 MHz. DMSO-d<sub>6</sub>, 85 °C, as a 3:2 mixture of diastereomers) & 201.9, 201.8, 151.1, 138.4, 138.3, 134.5, 127.7, 126.8, 126.8, 78.8, 78.5, 71.5, 68.9, 66.7, 66.3, 66.1, 65.8, 27.9, 27.6, 27.5, 27.2, 25.4, 25.3, 25.3, 23.3, 17.3, 14.7, 14.6, -3.7, -5.3, -5.5, -5.6, -5.7; FTIR (thin film): 2929, 2856, 1706, 1366, 1253, 1166, 1075, 834, 776, 697 cm<sup>-1</sup>; **HRMS** (ESI) m/z [M+Na]<sup>+</sup> calcd for C<sub>32</sub>H<sub>49</sub>NNaO<sub>5</sub>Si: 578.3272, found: 578.3270.

NOTE: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amide in 29.

#### Preparation of Spirocycles 48a and 48b



Fresh SmI<sub>2</sub> reagent (0.05 M in THF) was prepared using the following procedure: To a Schlenk tube equipped with a stir-bar and a reflux condenser was added freshly shaved samarium (328 mg, 2.17 mmol, 1.8 equiv), 1.2-diiodoethane (340 mg, 1.21 mmol, 1.0 equiv), and the flask was immediately covered with aluminum foil due to the light sensitivity of the reagent. Then dry THF (24 mL) was added with stirring, and the reaction mixture was heated to 55 °C, in the dark, for 4 h. At which point the reaction mixture was allowed to cool to 23 °C and settle for at least 10 min prior to use. To a solution of **29** (128 mg, 0.230 mmol, 1.0 equiv, as a 3:2 mixture of diastereomers) in THF (12 mL) was dropwise added the fresh SmI<sub>2</sub> solution (13.8 mL, 0.690 mmol, 3.0 equiv) at 23 °C. After stirring at 23 °C for 1h, air was bubbled into the reaction mixture the reaction color changes from blue to yellow upon quenching of any active radical species. Then a solution of saturated, aqueous NH<sub>4</sub>Cl (10 mL) was added followed by a saturated aqueous solution of Rochelle's salt (10 mL). The suspension was extracted twice with EtOAc (2 x 25 mL) and the combined organic layers were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (10 g SiO<sub>2</sub>, hexanes/EtOAc= 4:1) to afford **48a** (54 mg, 42% yield) as a colorless oil and **48b** (38 mg, 29% yield) as a colorless oil: **48a**: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ , 85 °C)  $\delta$  7.36 – 7.24 (m, 5H), 5.81 (bs, 1H), 4.47 (s, 2H), 4.20 (d, J = 2.6 Hz, 1H), 4.10 – 4.06 (m, 1H), 3.83 (bs, 1H), 3.76 (bs, 1H), 3.44 (td, J = 6.2, 2.2 Hz, 2H), 3.23 (d, J = 9.7 Hz, 1H), 2.52 - 2.52 Hz, 22.49 (m, 1H), 2.16 – 2.08 (m, 1H), 1.99 – 1.92 (m, 1H), 1.89 – 1.72 (m, 2H), 1.81 (d, J = 1.2 Hz, 3H), 1.63 -1.47 (m, 3H), 1.44 - 1.33 (m, 1H), 1.38 (s, 9H), 0.85 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H);  $^{13}$ C NMR (101) MHz, DMSO-*d*<sub>6</sub>, 85 °C) δ 153.9, 149.9, 138.4, 127.6, 126.8, 126.7, 124.6, 77.3, 76.1, 74.7, 71.6, 70.3, 64.2, 59.2, 57.4, 48.7, 32.7, 32.5, 27.9, 25.5, 25.5, 23.8, 17.2, 14.0, -5.1, -5.2; FTIR (thin film): 3462, 2929, 2855, 1692, 1364, 1250, 1175, 1101, 1013, 833, 773, 697 cm<sup>-1</sup>; **HRMS** (ESI) m/z [M+Na]<sup>+</sup> calcd for C<sub>32</sub>H<sub>51</sub>NNaO<sub>5</sub>Si: 580.3429, found: 580.3425; **48b:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 85 °C) δ 7.39 – 7.24 (m, 5H), 5.97 (bs, 1H), 4.48 (s, 2H), 4.35 (d, J = 2.8 Hz, 1H), 3.77 (dd, J = 5.1, 2.8 Hz, 1H), 3.69 (bs, 1H), 3.51 (bs, 1H), 3.47 (t, J = 6.0 Hz, 2H), 3.17 (d, J = 9.8 Hz, 1H), 2.61 (d, J = 9.8 Hz, 1H), 1.93 – 1.66 (m, 3H), 1.80 (d, J = 2.0 Hz, 3H), 1.66 – 1.46 (m, 4H), 1.41 – 1.31 (m, 1H), 1.37 (s, 9H), 0.88 (s, 9H), 0.00 (s, 9 3H), -0.01 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>, 85 °C) δ 154.2, 146.4, 138.4, 128.4, 127.7, 126.9, 126.8, 77.3, 76.5, 76.2, 71.5, 71.2, 69.9, 62.5, 57.6, 48.9, 33.4, 31.9, 27.8, 25.3, 25.2, 22.9, 17.1, 13.7, -4.8, -5.5; FTIR (thin film): 3485, 2929, 2855, 1694, 1364, 1251, 1174, 1083, 833, 773, 697 cm<sup>-1</sup>; HRMS (ESI) m/z [M+Na]<sup>+</sup> calcd for C<sub>32</sub>H<sub>51</sub>NNaO<sub>5</sub>Si: 580.3429, found: 580.3426.

NOTE: NMR spectra were taken at 85 °C due to the rotameric nature of the Boc amides in 48a and 48b.

#### Preparation of Secondary Amine 49



To a cooled solution (0 °C) of **48a** (9.7 mg, 0.0174 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (0.9 mL) was added 2,6-lutidine (20  $\mu$ L, 0.174 mmol, 10.0 equiv) followed by triethylsilyl trifluoromethanesulfonate (20  $\mu$ L, 0.0869 mmol, 5.0 equiv), and the reaction mixture was allowed to stir at 0 °C for 1.5 h, then allowed to warm to 23 °C and stirred for an additional 1 h. At which point, a second portion of 2,6-lutidine (20  $\mu$ L, 0.174 mmol, 10.0 equiv) followed by triethylsilyl trifluoromethanesulfonate (20 µL, 0.0869 mmol, 5.0 equiv) was added at 23 °C, and the reaction mixture was allowed to stir at 23 °C for an additional 3.5 h. Then a solution of saturated aqueous NaHCO<sub>3</sub> (5 mL) was added and the mixture was extracted three times with EtOAc ( $3 \times 10 \text{ mL}$ ). The combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1 g SiO<sub>2</sub>, hexanes/EtOAc= 1:1, and then, CH<sub>2</sub>Cl<sub>2</sub>/MeOH= 10:1) to afford 49 (8.2 mg, 83% yield) as a light brown oil: <sup>1</sup>H NMR (400 MHz, acetonitrile-*d*<sub>3</sub>) δ 7.41 – 7.24 (m, 5H), 7.17 (bs, 1H), 6.73 (bs, 1H), 5.86 (bs, 1H), 4.49 (s, 2H), 4.41 (t, J = 2.8 Hz, 1H), 4.37 (t, J = 8.0 Hz, 1H), 4.03 (t, J = 5.6 Hz, 1H), 3.49 (t, J = 5.9 Hz, 2H), 3.28 (ddd, J = 10.5, 7.3, 2.9 Hz, 1H), 2.65 (ddd, J = 10.5, 6.9, 3.6 Hz, 1H), 2.26 – 2.10 (m, 2H), 1.98 -1.79 (m, 3H), 1.94 (s, 3H), 1.64 -1.50 (m, 2H), 1.39 -1.24 (m, 1H), 0.98 (t, J = 7.9 Hz, 9H), 0.86 (s, 3H), 1.94 (s, 3H), 1.64 -1.50 (m, 2H), 1.39 -1.24 (m, 1H), 0.98 (t, J = 7.9 Hz, 9H), 0.86 (s, 3H), 1.94 (s, 9H), 0.72 (q, J = 7.6 Hz, 6H), 0.01 (s, 3H), 0.00 (s, 3H); <sup>13</sup>C NMR (101 MHz, acetonitrile- $d_3$ )  $\delta$  159.0, 140.0, 129.2, 128.5, 128.4, 122.9, 75.9, 74.5, 73.6, 73.4, 71.4, 68.1, 58.9, 47.3, 32.0, 31.6, 27.2, 26.4, 24.6, 18.5, 15.2, 7.2, 5.4, -4.3, -4.4; FTIR (thin film): 2954, 2879, 2857, 1456, 1361, 1287, 1251, 1161, 1100, 1054, 1029, 837, 777, 733, 637 cm<sup>-1</sup>; **HRMS** (ESI) m/z [M+H]<sup>+</sup> calcd for C<sub>33</sub>H<sub>58</sub>NO<sub>3</sub>Si<sub>2</sub>: 572.3950, found: 572.3945.

## **III. NMR SPECTRA**
































































Figure S31. <sup>1</sup>H NMR (400 MHz, chloroform-*d*) *N*-Tosyl Bicyclic Esters *N*-*Ts*-38 and *N*-*Ts*-39 (-1 – 4.5 ppm inset)



Figure S32. <sup>1</sup>H NMR (400 MHz, chloroform-*d*) *N*-Tosyl Bicyclic Esters *N*-*Ts*-38 and *N*-*Ts*-39 (4.5 – 10 ppm inset)















































































































Figure S88. <sup>1</sup>H NMR (400 MHz, acetonitrile- $d_3$ ) Secondary Amine 49 (-1 – 5 ppm inset)



Figure S89. <sup>1</sup>H NMR (400 MHz, acetonitrile- $d_3$ ) Secondary Amine 49 (5 – 10 ppm inset)









