

## Supporting Information

To accompany

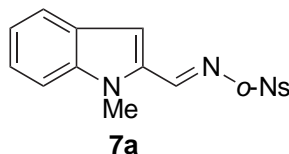
### **An Application of the Phosphine-Catalyzed [4 + 2] Annulation in Indole Alkaloid Synthesis: Formal Syntheses of (±)-Alstonerine and (±)-Macroline**

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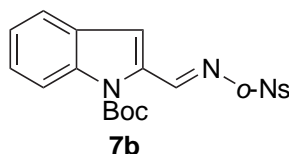
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#### **Experimental Section**

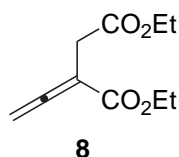
General experimental details: All reactions were carried out under an atmosphere of Ar or N<sub>2</sub> unless otherwise specified. Anhydrous solvents were distilled immediately prior to use: tetrahydrofuran (THF) and diethyl ether (Et<sub>2</sub>O) from sodium/benzophenone ketyl, dichloromethane, benzene, and acetonitrile from calcium hydride, and methanol from magnesium turnings. Most of the reactants were azeotroped with benzene or toluene prior to use. FT-IR spectra were obtained on a Perkin–Elmer paragon 1600 FT-IR. High resolution EI mass spectra were recorded by rapid thermal vaporization of samples deposited on desorption ionization filament that was directly inserted into the electron ionization (EI, 70 eV, 200°C) source of a triple sector high resolution instrument (VG/Micromass Autospec) tuned to 8,000 static resolution (M/DM, 10% valley) using perfluorinated kerosene (formula weight 705, Lancaster Synthesis, Inc., NH) as internal calibrant. Magnet and voltage scans were used over wide and narrow m/z ranges, respectively. Data were analyzed using instrument-supplied software. NMR spectra were obtained on Bruker Avance 500 or Avance 300 spectrometers and calibrated to the residual solvent peak. Coupling constants are listed in hertz. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, br = broad signal, app = apparent. X-ray crystallographic data were collected using a Bruker SMART CCD (charge coupled device) based diffractometer equipped with LT-2 low-temperature apparatus operating at 213K.



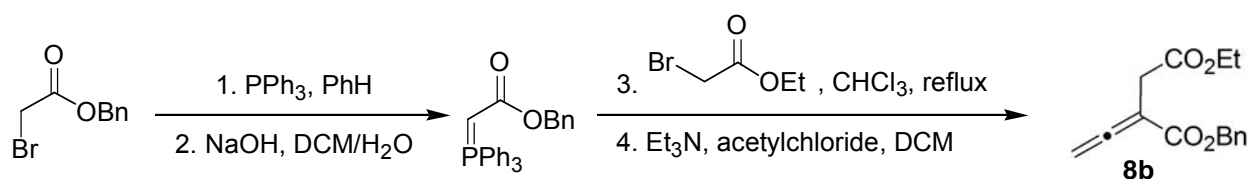
**Imine 7a.** To a suspension of *N*-methyl indole-2-carboxaldehyde (11.7 g, 73.5 mmol), 2-nitrobenzenesulfonamide (14.9 g, 73.5 mmol), and triethylamine (30.8 mL, 220 mmol) in dichloromethane (300 mL) at 0 °C was added titanium(IV) chloride (36.8 mL, 1 M solution in dichloromethane) over 1 h via syringe pump. After 12 h at rt, the solid was filtered through a pad of celite. The mother liquor was concentrated under reduced pressure. The crude mixture was dissolved in dichloromethane (250 mL) and placed in freezer at –20 °C for 12 h. The triethylammonium chloride solid was filtered through celite and the mother liquor was concentrated under reduced pressure. The crude product was crystallized from ethyl acetate and hexane to provide the imine **7a** as a light yellow crystal (19.9 g, 79% yield): mp 162–163 °C; IR (neat, cm<sup>–1</sup>) 1579, 1541, 1471, 1357, 1327, 1314, 1160, 1119, 821; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.00 (s, 1H), 8.35–8.37 (m, 1H), 7.76–7.80 (m, 3H), 7.71 (d, *J* = 8.17 Hz, 1H), 7.43–7.46 (m, 2H), 7.38 (d, *J* = 8.41 Hz, 1H), 7.17 (t, *J* = 7.54 Hz, 1H), 4.09 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 162.6, 148.3, 142.8, 134.2, 132.3, 132.2, 131.4, 131.2, 128.3, 126.8, 124.5, 123.4, 121.6, 121.3, 110.4, 32.2; HRMS (EI) calculated for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S [M]<sup>+</sup>: 343.0627, found: 343.0631.



**Imine 7b.** Compound **7b** was prepared in a manner analogous to **7a** by condensing *N*-Boc indole-2-carboxaldehyde with 2-nitrobenzenesulfonamide to provide imine **7b** (88%) as a light yellow solid: mp 132–134 °C; IR (neat, cm<sup>–1</sup>) 2981, 1739, 1568, 1529, 1358, 1331, 1182, 1120, 819, 754, 591; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.82 (s, 1H), 8.37–8.40 (m, 1H), 8.26 (d, *J* = 8.66 Hz, 1H), 7.76–7.81 (m, 4H), 7.64 (d, *J* = 7.93 Hz, 1H), 7.50 (t, *J* = 7.91, 1H), 7.29 (t, *J* = 7.68, 1H), 1.74 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 166.1, 149.3, 148.4, 139.7, 134.4, 133.1, 132.4, 131.9, 131.7, 129.1, 127.6, 124.6, 124.1, 123.1, 119.1, 116.2, 86.5, 28.0; HRMS (MALDI) calculated for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>6</sub>SNa [M+Na]<sup>+</sup>: 452.0887, found: 452.0860.

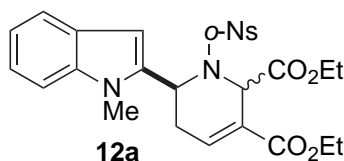


**Allenolate 8.** To a stirred solution of (carbethoxymethylene)triphenylphosphorane (69.6 g, 0.200 mol) in chloroform (300 mL) was added ethyl bromoacetate (90.2 g, 0.540 mol) at rt. The reaction mixture was refluxed for 29 h. The solvent was evaporated under reduced pressure. To the resulting phosphonium salt was added dichloromethane (300 mL) and triethylamine (61 mL, 0.440 mol). After stirring for 1 h, acetyl chloride (14.2 mL, 0.200 mol) was added dropwise over 1 h. After 2 h, the reaction mixture was filtered through a short silica gel column and washed with dichloromethane several times. The combined filtrate was concentrated and the residue was distilled to provide allenolate **8** (28.9 g, 73%) as a colorless oil: bp 0.5 mmHg (92–94 °C); IR (neat,  $\text{cm}^{-1}$ ) 3066, 2984, 1971, 1942, 1739, 1712, 1368, 1264, 1263;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.94 (s, 2H), 3.89 (q,  $J = 7.1$  Hz, 2H), 3.84 (q,  $J = 7.1$  Hz, 2H), 2.93 (s, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H), 0.95 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  214.0, 169.6, 165.6, 94.1, 78.9, 60.7, 60.3, 34.3, 13.7, 13.66; HRMS (EI) calculated for  $\text{C}_{10}\text{H}_{14}\text{O}_4$   $[\text{M}]^+$ : 198.0892, found: 198.0889.

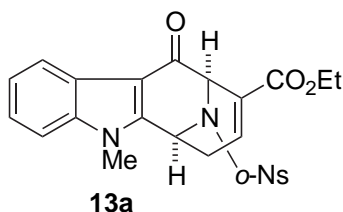


**Allenolate 8b.** To a stirred solution of triphenylphosphine (86.6 g, 0.330 mol) in benzene (400 mL) was added dropwise a solution of benzyl bromoacetate (76.3 g, 0.330 mol) in benzene (200 mL) over 2 h. The reaction was allowed to stir for 12 h. The solid phosphonium bromide product was filtered and washed with benzene and hexane to provide a white solid. The crude solid was dissolved in dichloromethane (300 mL) and sodium hydroxide (13.2 g, 0.330 mol) in water (100 mL) was added over 1 h. After 1 h, the layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 X 50 mL). The combined organics were dried over  $\text{MgSO}_4$  and concentrated to an oil. The crude product was recrystallized from benzene/petroleum ether to provide [(benzyloxycarbonyl)methylene]triphenylphosphorane as a light yellow prism (127.9 g, 95% for two steps). To a solution of the phosphorane (97 g, 0.236

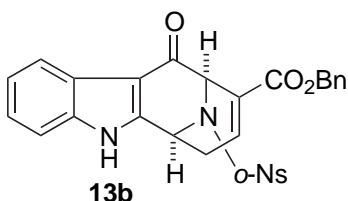
mol) in chloroform (500 mL) was added ethyl bromoacetate (107 g, 0.238 mol). After 13 h of reflux, the solvent was removed under reduced pressure. The crude product was dissolved in dichloromethane (500 mL) and treated with triethylamine (47.8 g, 0.472 mol). The mixture was stirred for 2 h and acetyl chloride (18.5 g, 0.236 mol) was then added dropwise over 1 h via syringe pump. The reaction mixture was allowed to stir for an additional 2 h. The triphenylphosphine oxide was filtered through a short silica column and the solid was washed with dichloromethane. The crude product was purified by silica gel flash column chromatography to afford the allenolate **8b** (32.4 g, 53%) as a colorless oil: IR (neat,  $\text{cm}^{-1}$ ) 2985, 1970, 1939, 1737, 1713, 1263, 1178, 1100, 1029;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21–7.30 (m, 5H), 5.21 (t,  $J = 2.16$  Hz, 2H), 5.18 (s, 2H), 4.11 (q,  $J = 7.15$  Hz, 2H), 3.26 (t,  $J = 2.16$  Hz, 2H), 1.20 (t,  $J = 7.15$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  214.8, 170.4, 166.1, 135.9, 128.5, 128.1, 127.9, 94.5, 79.7, 66.8, 60.9, 34.8, 14.1; HRMS (MALDI) calculated for  $\text{C}_{15}\text{H}_{16}\text{O}_4\text{Na}$   $[\text{M}+\text{Na}]^+$ : 283.0946, found: 283.0941.



**Tetrahydropyridine 12a.** To a stirred solution of imine **7a** (6.80 g, 20 mmol) and  $\text{PBU}_3$  (1.80 mL, 7.2 mmol) in dichloromethane (100 mL) was added allenolate **8** (4.76 g, 24 mmol) dropwise over 2 min. After 2 h, the reaction mixture was concentrated and purified by flash chromatography (silica gel, 1:3 ethyl acetate/hexane) to afford tetrahydropyridine **12a** (8.35 g, 73%) as a 3:1 diastereoisomeric mixture. Recrystallization from ethyl acetate/hexane provided a *cis* diastereoisomer (major) as a pale yellow crystal: mp 180–182  $^\circ\text{C}$ ; IR (neat,  $\text{cm}^{-1}$ ) 2982, 1736, 1718, 1545, 1469, 1371, 1292, 1259, 1172;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (dd,  $J = 7.95$ , 1.25 Hz, 1H), 7.72 (td,  $J = 7.70$ , 1.34 Hz, 1H), 7.65 (td,  $J = 7.70$ , 1.27 Hz, 1H), 7.56 (dd,  $J = 7.95$ , 1.20 Hz, 1H), 7.46 (d,  $J = 7.83$ , 1H), 7.28 (d,  $J = 8.11$ , 1H), 7.20 (td,  $J = 7.75$ , 1.05 Hz, 1H), 7.04–7.01 (m, 2H) 6.32 (s, 1H), 5.66 (d,  $J = 7.23$  Hz, 1H), 5.64 (s, 1H), 4.26 (q,  $J = 7.13$ , 2H), 3.83 (s, 3H), 3.00 (ddq,  $J = 45.62$ , 10.70, 7.16 Hz, 2H), 2.84 (dd,  $J = 20.16$ , 5.12 Hz, 1H), 2.72 (ddt,  $J = 20.16$ , 7.25, 2.48 Hz, 1H), 1.30 (t,  $J = 7.13$  Hz, 3H), 0.76 (t,  $J = 7.16$ , 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.8, 164.7, 148.2, 138.0, 135.4, 134.2, 133.5, 132.5, 131.6, 130.4, 127.4, 126.1, 123.8, 122.5, 120.5, 119.5, 109.1, 103.8, 61.6, 61.0, 53.1, 46.8, 29.9, 27.2, 14.1, 13.2; HRMS (MALDI) calculated for  $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_8\text{SNa}$   $[\text{M}+\text{Na}]^+$ : 564.1411, found: 564.1406.

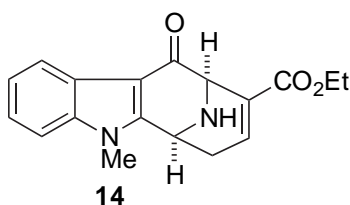


**Bridged Tetracycline 13a.** To a solution of tetrahydropyridine **12a** (3.00 g, 5.54 mmol) in ethyl acetate (115 mL) at 0 °C was added concentrated hydrochloric acid (115 mL) over 2 h. After 48 h, the resulting mixture was diluted with water (200 mL) and extracted with ethyl acetate (5 X 200 mL). The combined organics were washed with water (100 mL), saturated aqueous NaHCO<sub>3</sub> (3 X 100 mL) and brine (100 mL), and dried over MgSO<sub>4</sub>. After removal of solvents, the crude product was purified by flash column chromatography (silica gel, 3:7 ethyl acetate/hexane) to afford the bridged tetracycline **13a** (2.47 g, 90%). Recrystallization from THF/Et<sub>2</sub>O provided a white prism: mp 202–216 °C; IR (neat, cm<sup>-1</sup>) 1714, 1668, 1544, 1479, 1371, 1270, 1172, 765; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.99 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 15 Hz, 1H), 7.27 (d, *J* = 13.0 Hz, 1H), 7.20 (t, *J* = 7.1, 7.8 Hz, 1H), 7.13 (t, *J* = 7.4, 7.1 Hz, 1H), 6.90 (s, 1H), 5.72 (d, *J* = 6.4 Hz, 1H), 5.34 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 3.26 (dd, *J* = 18.9, 5.2 Hz, 1H), 2.49 (dd, *J* = 19.0, 4.2 Hz, 1H), 1.27 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 186.5, 163.3, 147.8, 147.2, 137.2, 135.4, 134.1, 132.2, 131.5, 130.9, 128.9, 123.9, 123.9, 123.7, 122.9, 121.1, 109.8, 107.2, 61.2, 58.1, 46.4, 30.3, 30.2, 14.1; HRMS (MALDI) calculated for C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub>SNa [M+Na]<sup>+</sup>: 518.0992, found: 518.1009.

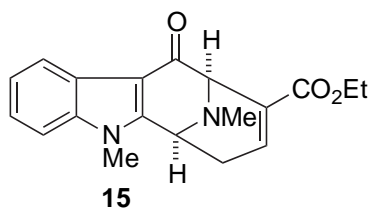


**Bridged Tetracycline 13b.** Compound **12b** was prepared in a manner analogous to **12a** by utilizing the **7b** with allenolate **8b** to afford tetrahydropyridine **12b** as a 1:1 diastereoisomeric mixture (84%), which was carried directly into the next step as the *trans* isomer undergoes isomerization. Compound **13b** was prepared in a manner analogous to **13a** by using **12b** to provide a single diastereoisomeric bridged tetracycline **13b** (78%). Recrystallization from THF/Et<sub>2</sub>O gave a white crystal: mp 209–210 °C; IR (neat, cm<sup>-1</sup>) 3322, 2964, 1709, 1657, 1543,

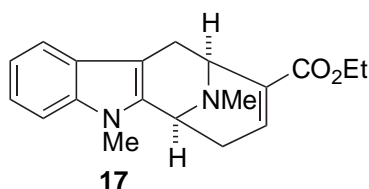
1468, 1455, 1367, 1266, 1168, 1089, 1063, 1050, 759;  $^1\text{H}$  NMR (500 MHz, Acetone- $d_6$ )  $\delta$  11.1 (br s, 1H), 8.02–8.05 (m, 1H), 7.83–7.90 (m, 1H), 7.68–7.80 (m, 3H), 7.40–7.50 (m, 3H), 7.32–7.38 (m, 2H), 7.26–7.32 (m, 1H), 7.17–7.23 (m, 1H), 7.12–7.23 (m, 1H), 6.97 (dd,  $J$  = 4.70, 2.74 Hz, 1H), 5.77 (d,  $J$  = 6.81 Hz, 1H), 5.37 (s, 1H), 5.17–5.27 (m, 2H), 3.20–3.27 (m, 1H), 2.73 (dd,  $J$  = 20.0, 4.83 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  186.5, 163.0, 148.4, 148.2, 147.5, 137.2, 136.1, 136.0, 134.7, 132.2, 131.5, 130.4, 128.3, 127.9, 127.8, 124.3, 124.0, 123.5, 122.3, 120.5, 112.1, 107.0, 66.3, 58.1, 47.5, 30.8; HRMS (MALDI) calculated for  $\text{C}_{28}\text{H}_{21}\text{N}_3\text{O}_7\text{SNa}$   $[\text{M}+\text{Na}]^+$ : 566.0992, found: 566.0997.



**Secondary Amine 14.** To a stirred solution of the bridged tetracycle **13a** (800 mg, 1.64 mmol), and benzenethiol (0.166 mL, 1.64 mmol) in DMF (1 mL) was added anhydrous  $\text{K}_2\text{CO}_3$  (670 mg, 4.84 mmol). After 12 h, the crude mixture was purified by flash column chromatography (silica gel, 10:1 dichloromethane/methanol) to provide **14** with residual DMF after removal of the solvents. The product was dissolved in ethyl acetate (150 mL) and washed with saturated aqueous ammonium chloride (5 X 10 mL). Combined organics were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford the secondary amine **14** as a solid (500 mg, 99%): mp 179–180  $^\circ\text{C}$ ; IR (neat,  $\text{cm}^{-1}$ ) 3301, 3052, 2774, 1712, 1654, 1520;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86–7.89 (m, 1H), 7.03–7.11 (m, 3H), 6.69 (dd,  $J$  = 4.6, 2.4 Hz, 1H), 4.26 (s, 1H), 4.22 (d,  $J$  = 6.5 Hz, 1H), 4.05 (q,  $J$  = 7.1 Hz, 2H), 3.31 (s, 3H), 3.19 (br s, 1H), 2.92 (dd,  $J$  = 19.4, 12.7 Hz, 1H), 2.07 (dd,  $J$  = 19.4, 4.9 Hz, 1H), 1.13 (t,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  193.1, 164.3, 151.9, 136.8, 135.3, 130.1, 124.1, 122.8, 122.3, 120.6, 109.4, 106.7, 60.4, 57.1, 43.6, 29.5, 29.0, 14.0; HRMS (MALDI) calculated for  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3\text{Na}$   $[\text{M}+\text{Na}]^+$ : 333.1210, found: 333.1213.

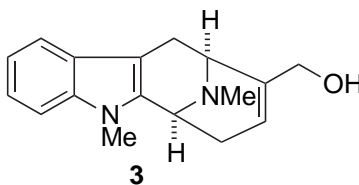


**Tertiary Amine 15.** To the secondary amine **14** (1.60 g, 5.16 mmol) at 0 °C was added aqueous formic acid (0.70 mL, 87% formic acid in water) and aqueous formaldehyde (440 uL, 35% formaldehyde in water). The reaction mixture was warm to rt and then heated to 70 °C for 12 h. The resulting mixture was diluted with ethyl acetate (160 mL) and water (70 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (5 X 50 mL) followed by dichloromethane (5 X 50 mL). The ethyl acetate solutions were combined, washed with water (50 mL), saturated aqueous NaHCO<sub>3</sub> (50 mL), and brine (50 mL). The dichloromethane solutions were combined, washed with water (50 mL), saturated aqueous NaHCO<sub>3</sub> (50 mL), and brine (50 mL). The dichloromethane was combined with the ethyl acetate solutions, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10:1 ethyl acetate/hexane) to provide the tertiary amine **15** (1.64 g, 99%) as a solid: mp 184–186 °C; IR (neat, cm<sup>-1</sup>) 3052, 2974, 2933, 1707, 1658, 1474, 1258, 1131, 1078, 1029, 743; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.11 (dd, *J* = 6.3, 2.2 Hz, 1H), 7.20–7.31 (m, 3H), 6.86 (dd, *J* = 4.8, 2.5 Hz, 1H), 4.25 (d, *J* = 6.3 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.20 (s, 1H), 3.69 (s, 3H), 3.11 (ddt, *J* = 19.3, 6.7, 2.1 Hz, 1H), 2.58 (s, 3H), 2.32 (dd, *J* = 19.3, 4.9 Hz, 1H), 1.27 (t, *J* = 7.0, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 191.7, 164.4, 147.9, 137.4, 134.6, 130.2, 124.2, 123.1, 122.6, 121.5, 109.3, 107.1, 64.3, 60.7, 50.9, 41.5, 29.9, 29.1, 14.1; HRMS (MALDI) calculated for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>Na [M+Na]<sup>+</sup>: 347.1366, found: 347.1367.



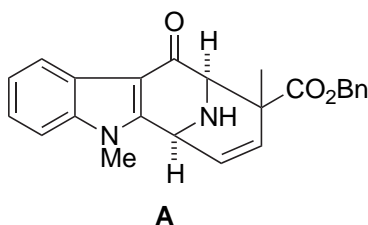
**Tetracycle 17.** To a solution of the tertiary amine **15** (20 mg, 0.034 mmol) in 1,2-dichloroethane (1 mL) was added ZnI<sub>2</sub> (48.9 mg, 0.153 mmol) followed by NaCNBH<sub>3</sub> (45.6 mg, 0.714 mmol). After 10 h at 83 °C, the reaction mixture was allowed to cool and the solids were filtered through a pad of celite. The crude mixture was concentrated and was taken up with ethanol. The solution

was heated to reflux for 10 h, at which point the solvent was removed and the crude mixture was purified by flash column chromatography to afford tetracycle **17** (13.7 mg, 73%) as a thin film. IR (neat,  $\text{cm}^{-1}$ ) 2924, 2850, 1706, 1469, 1413, 1378, 1282, 1251, 1135, 1088, 1036, 741;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (d,  $J = 7.56$  Hz, 1H), 7.28 (d,  $J = 7.56$  Hz, 1H), 7.18 (t,  $J = 7.56$  Hz, 1H), 7.08 (t,  $J = 7.56$  Hz, 1H), 6.95 (dd,  $J = 4.96, 1.85$  Hz, 1H), 4.15–4.22 (m, 2H), 4.15–4.15 (m, 2H), 3.66 (s, 3H), 3.18 (dd,  $J = 16.4, 5.99$  Hz, 1H), 2.98 (dd,  $J = 18.7, 5.29$  Hz, 1H), 2.75 (d,  $J = 16.4$  Hz, 1H), 2.54 (s, 3H), 2.25 (dd,  $J = 18.8, 5.51$  Hz, 1H), 1.27 (t,  $J = 7.10$ , 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.4, 137.0, 135.5, 133.9, 132.3, 126.8, 121.2, 118.9, 118.2, 108.6, 104.6, 60.3, 50.3, 40.4, 30.8, 29.6, 29.2, 22.1, 14.1; HRMS (MALDI) calculated for  $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 311.1760, found: 311.1750.



**Allylic Alcohol 3.** To a solution of tetracycle **17** (13.0 mg, 0.0419 mmol) in toluene (3 mL) at  $-73$   $^{\circ}\text{C}$  was added a solution of DIBAL-H (1 M in toluene, 0.168 mL, 0.168 mmol). After 1 h, the reaction solution was quenched with ethyl acetate (1 mL), followed by saturated sodium potassium tartrate (3 mL). After 2 h of stirring, the aqueous layer was extracted with ethyl acetate (3 X 10 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude product was purified by flash column chromatography to provide allylic alcohol **3** (10.4 mg, 92%) as a white solid: mp  $184$ – $185$   $^{\circ}\text{C}$ ; IR (neat,  $\text{cm}^{-1}$ ) 3357, 3052, 2915, 1469, 1421, 1377, 1377, 1107, 1072, 1010, 1036, 738;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (d,  $J = 7.76$  Hz, 1H), 7.28 (d,  $J = 8.14$  Hz, 1H), 7.16–7.20 (m, 1H), 7.07–7.11 (m, 1H), 5.59 (d,  $J = 4.11$  Hz, 1H), 4.01–4.13 (m, 3H), 3.77 (d,  $J = 5.74$  Hz, 1H), 3.64 (s, 3H), 3.09 (dd,  $J = 16.07, 5.89$  Hz, 1H), 2.87 (dd,  $J = 17.35, 5.12$  Hz, 1H), 2.70 (d,  $J = 16.07$  Hz, 1H), 2.50 (s, 3H), 2.09 (dd,  $J = 17.53, 4.73$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  139.8, 136.9, 134.2, 126.8, 120.9, 119.6, 118.8, 118.0, 108.6, 104.4, 65.0, 53.2, 50.8, 40.2, 30.5, 29.2, 20.7; HRMS (MALDI) calculated for  $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 269.1654, found 269.1652.





**C16-Methylated tetracycline A.** To a solution of **13b** (690 mg, 1.27 mmol) in DMF (1 mL) was added benzenethiol (0.131 mL, 1.27 mmol) followed by  $K_2CO_3$  (527 mg, 3.81 mmol). After 18 h, the solids were filter through a pad of celite and washed with dichloromethane. Solvents were removed under reduced pressure and purified by flash column chromatography (silica gel, 17:1 dichloromethane/methanol) to provide the secondary amine as a yellow solid. To a slurry solution of NaH (60 mg, 2.5 mmol) in THF (10 mL) was added the secondary amine above (400 mg, 1.1 mmol) in DMF (0.5 mL), followed by methyl iodide (0.150 mL, 2.4 mmol). After 4 h, the reaction was quenched with water and solvents were removed under reduced pressure. The crude mixture was purified by silica gel flash column chromatography to provide compound **A** (370 mg, 86%) as a light yellow solid:  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.08–8.11 (m, 1H), 7.05–7.25 (m, 8H), 5.93 (dd,  $J$  = 9.97, 5.41 Hz, 1H), 5.74 (d,  $J$  = 9.97, 1H), 5.01 (m, 2H), 4.40 (d,  $J$  = 5.41 Hz, 1H), 3.65 (s, 1H), 3.53 (s, 3H), 2.94 (bs, 1H), 1.69 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  191.2, 173.0, 156.9, 136.8, 135.7, 130.6, 128.1, 128.0, 127.7, 124.9, 124.6, 122.9, 122.8, 121.5, 109.5, 108.1, 66.9, 65.5, 45.7, 45.6, 30.0, 25.4; MS (EI)  $m/e$  (rel. intensity) 386.2 ( $M^+$ , 50), 295.1 (23), 278.1 (21), 251.1 (100), 206.1 (23), 158.1 (15).