

## Supporting Information

### Total Synthesis of the Chlorinated Pentacyclic Indole Alkaloid (+)-Ambiguine G

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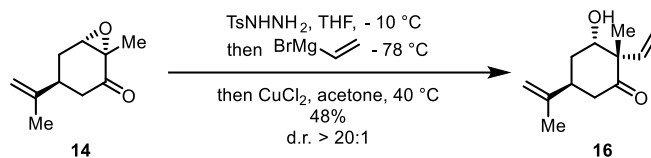
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## I. General Information

Unless stated otherwise, room temperature refers to 22-26 °C. Higher than room temperatures were maintained using pre-heated oil baths. Lower temperatures were maintained using acetone/CO<sub>2</sub>(s) (-78 °C), MeCN/CO<sub>2</sub>(s) (-40 °C) and water/ice (0 °C) baths. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub> or DCM), tetrahydrofuran (THF), and dimethylformamide (DMF) were dried by passage through an activated alumina column purification system (Innovative Technology Inc. Pure Solv™). All commercial reagents and solvents were used as received, except N-bromosuccinimide, (recrystallized from water) and N-chlorosuccinimide (recrystallized from acetic acid).

Thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 Å F254 plates (250 µm) with F-254 fluorescent indicator and visualized by UV fluorescence quenching, ceric ammonium molybdate, or potassium permanganate staining. SiliCycle SiliaFlash P60 silica gel (particle size 40–63 µm) was used for flash chromatography. NMR spectra were measured on Bruker DRX and DMX spectrometers at 500 MHz for <sup>1</sup>H spectra and 126 MHz for <sup>13</sup>C spectra, respectively, and calibrated to either TMS (δ = 0 for <sup>1</sup>H), residual CHCl<sub>3</sub> (δ = 7.26 for <sup>1</sup>H and δ = 77.23 for <sup>13</sup>C), or residual benzene (δ = 7.16 for <sup>1</sup>H and δ = 128.06 for <sup>13</sup>C). Splitting patterns are reported as apparent. Mass spectral data was measured on Agilent technologies 6224 TOF LC/MS. Optical rotations were measured on a Jasco DIP-1000 polarimeter using a 100 mm path-length cell, c = g/100 mL. IR spectra were recorded on a Thermo Scientific Nicolet iS50 FT-IR spectrometer and are reported as frequency of absorption (cm<sup>-1</sup>).

## II. Synthetic Procedures towards Ambiguine G



**Hydroxy ketone 16.** To a 500 mL round bottom flask was added (*S*)-carvone oxide (0.814 g, 4.90 mmol, 1 equiv.) and THF (8.2 mL, 0.6 M). The reaction mixture was then placed in a Cryocooler pre-set at -10 °C. TsNHNH<sub>2</sub> (0.912 g, 4.90 mmol, 1 equiv.) was added in one portion and the resulting colorless solution was stirred at -10 °C for 1.5 days, at which time the reaction turned slightly yellow. The flask was then cooled to -78 °C and another 100 mL of THF was added. The reaction was stirred at this temperature for 5 minutes. Vinylmagnesium bromide (1 M in THF, 22 mL, 22 mmol, 4.5 equiv.) was added slowly into the reaction mixture over 20 minutes. The resulting deep brown solution was stirred at -78 °C for another 1.5 hours, before the addition of 1 M HCl aq. (22 mL). The cooling bath was removed and acetone (100 mL) was added, followed addition of CuCl<sub>2</sub> (0.658 g, 4.90 mmol, 1 equiv.) in one portion. The copper salt soon dissolved upon heating to 40 °C, giving a dark brown solution, which gradually faded into a light brown solution over 1.5 hours. After a total of 2.5 hours at 40 °C (*Note 1*), the reaction was cooled down to room temperature. Most volatiles were removed *in vacuo* and the resulting black aqueous phase was extracted with EtOAc (1 x 50 mL, 3 x 20 mL). The organic layers were combined and washed with 1 M HCl (2 x 40 mL), brine (40 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (15% → 20% EtOAc/hexanes) to afford a mixture of the desired product and other inseparable by products. The mixture was then dissolved in hexane and ran

through a short celite plug to afford the desired product **16** (0.456 g, 48%) as a colorless oil.

*Note 1:* Long reaction time led to significant amounts of byproducts.

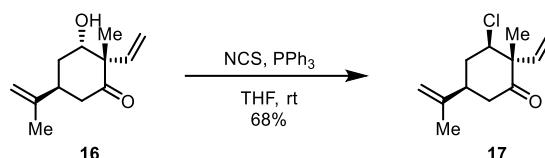
$R_f$  = 0.27 (20% Et<sub>2</sub>O/hexanes), visualized using KMnO<sub>4</sub>

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 6.48 (dd,  $J$  = 18.1, 11.1 Hz, 1H), 5.37 (dd,  $J$  = 11.2, 0.9 Hz, 1H), 5.23 (dd,  $J$  = 18.1, 0.9 Hz, 1H), 4.85-4.81 (m, 1H), 4.77-4.73 (m, 1H), 4.03 (app. t,  $J$  = 5.4 Hz, 1H), 2.87 (dq,  $J$  = 10.2, 5.4, 4.9 Hz, 1H), 2.59 (dd,  $J$  = 14.6, 10.3 Hz, 1H), 2.50 (ddd,  $J$  = 14.6, 5.3, 1.1 Hz, 1H), 2.10-2.03 (m, 2H), 1.97 (s, 1H), 1.78 (app. s, 3H), 1.30 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 211.8, 147.1, 138.5, 116.4, 110.7, 75.8, 56.0, 42.3, 38.6, 32.4, 22.0, 21.2.

**HRMS** (ESI)  $m/z$  calc'd for C<sub>12</sub>H<sub>19</sub>O<sub>2</sub> [M+H]<sup>+</sup> 195.1385, found 195.1380.

$[\alpha]_D^{20}$  = -11.7 ° (c=0.72, CHCl<sub>3</sub>).



**Chloroketone 17.** To a flame-dried 25 mL round bottom flask was added N-chlorosuccinimide (116 mg, 0.87 mmol, 1.05 equiv.), THF (3.2 mL, 0.26 M) and PPh<sub>3</sub> (228 mg, 0.87 mmol, 1.05 equiv.) sequentially. The resulting pink slurry was stirred for 30 minutes at room temperature in the dark. Hydroxy ketone **16** (161 mg, 0.83 mmol, 1 equiv.) in 1.5 mL THF was then added to the reaction mixture, followed by another 1.7 mL of THF. The resulting slurry was stirred at room temperature for 17 hours, at which point the reaction turned into a burgundy solution. The reaction mixture was concentrated *in vacuo*. The resulting black oil was purified by flash chromatography (2% → 4% Et<sub>2</sub>O/hexanes) to afford chloroketone **17** (120 mg, 68%) as a white solid.

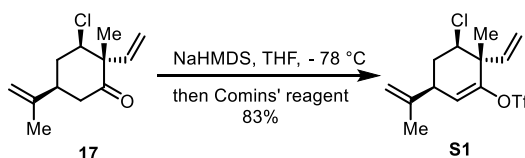
$R_f$  = 0.35 (10% Et<sub>2</sub>O/hexanes), visualized using KMnO<sub>4</sub>

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 5.88 (dd,  $J$  = 17.5, 10.9 Hz, 1H), 5.36 (dd,  $J$  = 10.8, 0.7 Hz, 1H), 5.20 (dd,  $J$  = 17.5, 0.7 Hz, 1H), 4.86-4.81 (m, 1H), 4.78 (app. q,  $J$  = 1.0 Hz, 1H), 4.11 (dd,  $J$  = 12.1, 4.2 Hz, 1H), 2.62 (app. t,  $J$  = 13.9 Hz, 1H), 2.43-2.29 (m, 3H), 2.16 (app. q,  $J$  = 12.2 Hz, 1H), 1.76 (app. s, 3H), 1.39 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 209.7, 145.6, 138.9, 116.8, 111.0, 64.2, 57.2, 42.2, 41.6, 36.8, 20.4, 16.1.

**HRMS** (ESI)  $m/z$  calc'd for C<sub>12</sub>H<sub>18</sub><sup>35</sup>ClO [M+H]<sup>+</sup> 213.1046, found 213.1040.

$[\alpha]_D^{20}$  = +4.5 ° (c=0.13, CHCl<sub>3</sub>).



**Enol triflate S1.** To a flame-dried 100 mL round-bottom flask was added chloroketone **17** (1.18 g, 5.55 mmol, 1 equiv.) and THF (18.5 mL, 0.30 M). The colorless solution was cooled to - 78 °C

followed by the slow addition of NaHMDS (1 M in THF, 6.38 mL, 6.38 mmol, 1.15 equiv.). The yellow solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for 1.5 hour. Comins' reagent (3.27 g, 8.33 mmol, 1.5 equiv.) in THF (7.9 mL) was added dropwise (*Note 1*) and the reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for another 1 hour (*Note 2*), before being quenched with saturated  $\text{NH}_4\text{Cl}$  aq. (20 mL). The reaction was warmed to room temperature, transferred into a separatory funnel containing 10 mL of  $\text{H}_2\text{O}$  and extracted with EtOAc (1 x 30 mL, 2 x 15 mL), washed with saturated  $\text{NH}_4\text{Cl}$  aq. (20 mL), brine (20 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (0%  $\rightarrow$  2% DCM/hexanes) to afford enol triflate **S1** (1.59 g, 83%) as a colorless oil.

*Note 1*: The addition of Comins' reagent needs to be slow to keep the temperature in the flask low to suppress chlorine elimination.

*Note 2*: Extended reaction time led to chlorine elimination.

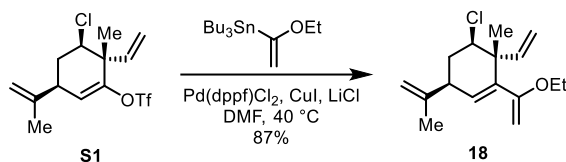
$R_f$  = 0.19 (1% Et<sub>2</sub>O/hexanes), visualized using  $\text{KMnO}_4$

**<sup>1</sup>H NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.74-5.66 (m, 2H), 5.41 (d,  $J$  = 10.7 Hz, 1H), 5.31 (d,  $J$  = 17.3 Hz, 1H), 4.91-4.85 (m, 1H), 4.83 (dt,  $J$  = 1.4, 0.8 Hz, 1H), 4.10 (dd,  $J$  = 12.9, 3.3 Hz, 1H), 3.13 (ddd,  $J$  = 11.0, 6.0, 2.5 Hz, 1H), 2.28 (dddd,  $J$  = 13.3, 6.1, 3.3, 1.0 Hz, 1H), 1.95 (td,  $J$  = 13.1, 10.9 Hz, 1H), 1.75 (dd,  $J$  = 1.5, 0.8 Hz, 3H), 1.39 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.9, 145.3, 138.7, 120.3, 118.9, 118.3 (q,  $J_{19\text{F}-13\text{C}}$  = 319.8 Hz), 112.6, 63.4, 47.3, 42.4, 34.3, 20.2, 17.0.

**HRMS** (ESI)  $m/z$  calc'd for  $\text{C}_{13}\text{H}_{17}^{35}\text{ClF}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  345.0539, found 345.0530.

$[\alpha]_D^{21}$  =  $-51.5^{\circ}$  ( $c$ =0.25,  $\text{CHCl}_3$ ).



**Ethoxy diene 18.** To a flame-dried 100 mL round-bottom flask was added enol triflate **S1** (1.587 g, 4.60 mmol, 1 equiv.) and DMF (bubbled with  $\text{N}_2$  for 45 min before use, 35 mL).  $\text{CuI}$  (88 mg, 0.46 mmol, 0.1 equiv.),  $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$  (376 mg, 0.46 mmol, 0.1 equiv.),  $\text{LiCl}$  (1.034 g, 24.40 mmol, 5.3 equiv.) was added sequentially. Another 11 mL of DMF (bubbled with  $\text{N}_2$  for 45 min before use) was added to make a 0.1 M solution. The reaction flask was purged with Ar for 10 min before the addition of tributyl(1-ethoxyvinyl)tin (1.79 mL, 5.29 mmol, 1.15 equiv.). The dark red solution was then heated to  $40\text{ }^{\circ}\text{C}$ . After 2.5 days at  $40\text{ }^{\circ}\text{C}$ , the brown solution was transferred into a separatory funnel containing  $\text{NH}_3 \cdot \text{H}_2\text{O} : \text{H}_2\text{O}$  1:2 (90 mL), which was extracted with hexanes (1 x 90 mL, 3 x 40 mL). The organic phase was combined and washed with  $\text{NH}_3 \cdot \text{H}_2\text{O} : \text{H}_2\text{O}$  1:2 (3 x 60 mL), brine (60 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (basic alumina, pre-saturated with 10%  $\text{NEt}_3$ /hexanes for 30 minutes, flushed with 10%  $\text{NEt}_3$ /hexanes) to afford the ethoxy diene **18** as a colorless oil (1.068 g, 87%).

$R_f$  = 0.31 (alumina, hexanes), visualized using  $\text{KMnO}_4$

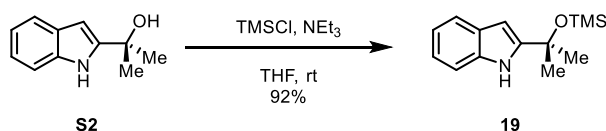
**<sup>1</sup>H NMR** (500 MHz, benzene- $d_6$ ):  $\delta$  5.87 (dd,  $J$  = 2.7, 1.1 Hz, 1H), 5.82 (dd,  $J$  = 17.4, 10.7 Hz, 1H), 5.24-5.15 (m, 2H), 4.73 (dt,  $J$  = 1.8, 0.9 Hz, 1H), 4.69-4.66 (m, 1H), 4.12 (d,  $J$  = 1.7 Hz, 1H),

3.93 (dd,  $J = 12.5, 3.7$  Hz, 1H), 3.85 (d,  $J = 1.6$  Hz, 1H), 3.35 (ddq,  $J = 34.1, 9.4, 7.0$  Hz, 2H), 2.63 (ddd,  $J = 11.0, 6.9, 2.6$  Hz, 1H), 2.08 (dddd,  $J = 13.1, 6.9, 3.7, 1.1$  Hz, 1H), 2.01 (td,  $J = 12.8, 10.9$  Hz, 1H), 1.63 (s, 3H), 1.49 (dt,  $J = 1.8, 0.9$  Hz, 3H), 1.03 (t,  $J = 7.0$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz, benzene- $d_6$ ):  $\delta$  163.7, 147.1, 143.6, 142.8, 129.7, 114.5, 111.4, 84.6, 66.4, 63.1, 45.5, 44.9, 34.8, 20.0, 19.1, 14.5.

HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{16}\text{H}_{24}^{35}\text{ClO}$   $[\text{M}+\text{H}]^+$  267.1516, found 267.1509.

$[\alpha]_D^{20} = -96.5^\circ$  ( $c=0.25$ ,  $\text{CHCl}_3$ ).



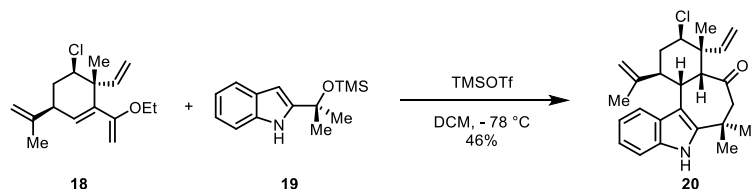
**TMS alcohol 19.** To an oven-dried 100 mL round-bottom flask was added alcohol **S2**<sup>1</sup> (2.856 g, 16.3 mmol, 1 equiv.),  $\text{NEt}_3$  (6.82 mL, 48.9 mmol, 3 equiv.) and THF (16.3 mL, 1 M).  $\text{TMSCl}$  (4.14 mL, 32.6 mmol, 2 equiv.) was added slowly at room temperature. The resulting solution was stirred at room temperature for 2 d before being quenched with saturated  $\text{NaHCO}_3$  aq. (15 mL). The mixture was then transferred into a separatory funnel containing saturated  $\text{NaHCO}_3$  aq. (75 mL) and  $\text{H}_2\text{O}$  (75 mL) and extracted with  $\text{EtOAc}$  (2 x 60 mL 1 x 20 mL). The organic phase was combined and washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (3%→5%  $\text{EtOAc}$ /hexanes) to afford the desired TMS alcohol **19** as an off white solid (3.71 g, 92%).

$R_f = 0.21$  (5%  $\text{EtOAc}$ /hexanes)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.29 (s, 1H), 7.55 (dd,  $J = 7.8, 1.1$  Hz, 1H), 7.36 (dd,  $J = 8.1, 0.9$  Hz, 1H), 7.15 (ddd,  $J = 8.2, 7.1, 1.2$  Hz, 1H), 7.07 (ddd,  $J = 8.0, 7.0, 1.0$  Hz, 1H), 6.23 (dd,  $J = 2.1, 0.9$  Hz, 1H), 1.67 (s, 6H), 0.10 (s, 9H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  146.8, 135.3, 128.6, 121.5, 120.5, 119.7, 110.9, 96.5, 72.3, 31.7, 2.3.

HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{14}\text{H}_{22}\text{NOSi}$   $[\text{M}+\text{H}]^+$  248.1471, found 248.1467.



**Tetracycle 20.** To a flame-dried 50 mL round-bottom flask was added ethoxy diene **18** (534 mg, 2.00 mmol, 2 equiv.), TMS alcohol **19** (248 mg, 1.00 mmol, 1 equiv.) and DCM (10 mL, 0.1 M). The mixture was cooled to  $-78^\circ\text{C}$ , followed by the dropwise addition of  $\text{TMSOTf}$  (redistilled, 190  $\mu\text{L}$ , 2.10 mmol, 1.05 equiv.). The resulting black solution was stirred at  $-78^\circ\text{C}$  for 30 min. The cooling bath was then removed and  $\text{H}_2\text{O}$  (10 mL) was added in one portion. The biphasic solution was stirred rigorously at room temperature for 15 min before the addition of 1 M  $\text{HCl}$  aq. (1.5 mL). The resulting biphasic solution was stirred for another 15 min at the same temperature. The two

phases were separated, and the aqueous phase was washed with DCM (3 x 15 mL). The organic phase was combined, washed with NaHCO<sub>3</sub> aq (25 mL) and brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography twice (1<sup>st</sup> column, 5% → 15% EtOAc/hexanes, 2<sup>nd</sup> column, 2% acetone, 30% DCM, 58% hexanes) to afford the desired product tetracycle **20** as a white solid (182 mg, 46%).

$R_f$  = 0.35 (20% EtOAc/hexanes)

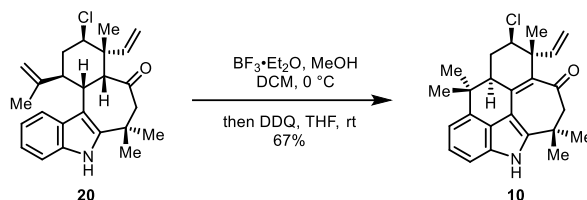
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.96 (s, 1H), 7.53 (d,  $J$  = 8.0 Hz, 1H), 7.29 (d,  $J$  = 8.1 Hz, 1H), 7.15 (ddd,  $J$  = 8.0, 7.0, 1.1 Hz, 1H), 7.05 (ddd,  $J$  = 8.1, 7.0, 1.0 Hz, 1H), 6.23 (dd,  $J$  = 17.7, 11.0 Hz, 1H), 5.44 (dd,  $J$  = 11.9, 4.9 Hz, 1H), 5.102-5.01 (m, 2H), 4.77 (app. s, 1H), 4.57-4.52 (m, 1H), 3.76-3.66 (m, 1H), 3.23 (d,  $J$  = 4.5 Hz, 1H), 2.80 (d,  $J$  = 10.2 Hz, 1H), 2.38 (d,  $J$  = 10.2 Hz, 1H), 2.32-2.24 (m, 2H), 2.20-2.14 (m, 1H), 1.55 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.13 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 211.4, 146.6, 145.7, 140.5, 133.7, 129.7, 121.9, 119.9, 119.1, 113.5, 112.2, 111.7, 110.3, 65.4, 63.6, 59.1, 45.2, 44.9, 38.7, 36.4, 34.4, 29.9, 29.3, 23.4, 19.6.

**IR** (thin film): 3439, 3079, 2964, 2926, 1696, 1490, 1344 cm<sup>-1</sup>

**HRMS** (ESI)  $m/z$  calc'd for C<sub>25</sub>H<sub>31</sub><sup>35</sup>ClNO [M+H]<sup>+</sup> 369.2094, found 369.2094.

$[\alpha]_D^{19}$  = -1.8° (c=0.12, CHCl<sub>3</sub>).



**Enone 19.** To an oven-dried 25 mL round-bottom flask was added tetracycle **20** (58 mg, 0.146 mmol, 1 equiv.) and DCM (2.43 mL, 0.06 M). The mixture was cooled to 0 °C followed by the addition of BF<sub>3</sub>·Et<sub>2</sub>O (72 μL, 0.58 mmol, 4 equiv.), which changed the colorless solution into a dark red solution. MeOH (anhydrous, 6 μL, 0.146 mmol, 1 equiv.) was added and the flask was placed into a Cryocooler pre-set at 0 °C. After being stirred at 0 °C for 4 days, TBAF (1 M in THF, 0.659 mL, 0.659 mmol, 4.5 equiv.) was added and the dark red color became less intense. The reaction mixture was stirred at 0 °C for 15 min before H<sub>2</sub>O (52 μL, 2.92 mmol, 20 equiv.) was added. The reaction mixture was stirred at the same temperature for another 15 min. DDQ (133 mg, 0.58 mmol, 4 equiv.) was added as a solid and the resulting black solution was removed from the 0 °C cooling bath and stirred at room temperature for 2 hours, before it was quenched with 1 M NaOH aq. (5 mL). The aqueous phase was separated and extracted with DCM (4 x 5 mL). The organic phase was combined, washed with 1 M NaOH (2 x 10 mL), brine (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (5%→ 15% EtOAc/hexanes) to afford enone **10** as a yellow solid (39 mg, 67%).

$R_f$  = 0.31 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 8.02(s, 1H), 7.20-7.12 (m, 2H), 7.03 (dd,  $J$  = 6.9, 1.2 Hz, 1H), 5.74 (dd,  $J$  = 17.5, 10.7 Hz, 1H), 5.21 (dd,  $J$  = 10.7, 0.8 Hz, 1H), 5.15 (dd,  $J$  = 17.4, 0.8 Hz, 1H), 4.24 (dd,  $J$  = 12.9, 3.6 Hz, 1H), 3.21 (d,  $J$  = 11.0 Hz, 1H), 2.93 (dd,  $J$  = 11.5, 6.7 Hz, 1H), 2.46 (d,  $J$  = 11.0 Hz, 1H), 2.40 (ddd,  $J$  = 13.1, 6.6, 3.6 Hz, 1H), 2.27 (app. q,  $J$  = 12.6 Hz, 1H), 1.65 (s, 3H),

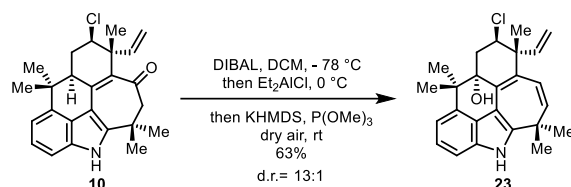
1.54 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 1.04 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  203.9, 144.0, 141.6, 140.1, 138.6, 133.4, 133.0, 125.1, 123.3, 115.6, 113.7, 108.2, 107.1, 67.0, 55.6, 48.3, 45.8, 39.0, 35.9, 30.7, 29.2, 29.0, 25.1, 23.5, 20.1.

HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{25}\text{H}_{39}^{35}\text{ClNO}$   $[\text{M}+\text{H}]^+$  376.1832, found 376.1825.

IR (thin film): 3364, 2966, 1670, 1448, 1466, 1367, 1320, 1176, 756  $\text{cm}^{-1}$

$[\alpha]_D^{19} = +51.3^\circ$  ( $c=0.11$ ,  $\text{CHCl}_3$ ).



**Pentacyclic alcohol 23.** To a flame-dried 25 mL round-bottom flask was added enone **10** (8 mg, 0.0203 mmol, 1 equiv.) and DCM (2.03 mL, 0.01 M). The pale-yellow solution was cooled to -78 °C before the dropwise addition of DIBAL (1 M in PhMe, 81  $\mu\text{L}$ , 0.0812 mmol, 4 equiv.). The resulting orange solution was stirred at -78 °C for 1.5 h before the dropwise addition of HCl (4M in dioxane, 18  $\mu\text{L}$ , 0.0711 mmol, 3.5 equiv.), followed by  $\text{Et}_2\text{AlCl}$  (1 M in hexanes, 20  $\mu\text{L}$ , 0.0203 mmol, 1 equiv.). After 15 min at -78 °C, the dry-ice acetone bath was changed to ice water bath and the reaction was stirred at 0 °C for 10 min, during which time the reaction turned red.  $\text{P}(\text{OMe})_3$  (17  $\mu\text{L}$ , 0.143 mmol, 7 equiv.) was added and the red color faded into yellow. The reaction mixture was then cooled to -78 °C. KHMDS (1 M in THF, 102  $\mu\text{L}$ , 0.102 mmol, 5 equiv.) was added and the cooling bath was removed. Dry air was bubbled through the reaction mixture as it warmed to room temperature. The bubbling continued for a total of 20 min while the reaction was at room temperature before 1 M NaOH (50  $\mu\text{L}$ ) was added. The reaction mixture was stirred at room temperature for another 15 min before the addition of  $\text{MgSO}_4$ . The resulting suspension was stirred for an additional 15 min before filtration. The filtrate was concentrated *in vacuo* and purified by flash chromatography (2%  $\rightarrow$  8% EtOAc/hexanes) to afford a mixture of **23** and its diastereomer as a white solid (5 mg, 63%). The resulting solid was further purified by preparative TLC (4% acetone, 30% DCM, 56% hexanes) to afford **23** (3.7 mg) as a white solid.

$R_f = 0.33$  (20% EtOAc/hexanes)

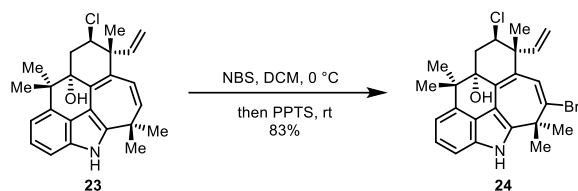
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96 (s, 1H), 7.23-7.19 (m, 2H), 7.09 (dd,  $J = 4.9, 3.0$  Hz, 1H), 5.92 (d,  $J = 11.5$  Hz, 1H), 5.76 (dd,  $J = 17.4, 10.7$  Hz, 1H), 5.41 (d,  $J = 11.5$  Hz, 1H), 5.29 (dd,  $J = 10.7, 1.0$  Hz, 1H), 5.23 (dd,  $J = 17.4, 1.0$  Hz, 1H), 4.51 (dd,  $J = 12.9, 3.8$  Hz, 1H), 2.59 (td,  $J = 13.3, 2.1$  Hz, 1H), 2.46 (dd,  $J = 13.6, 3.8$  Hz, 1H), 2.04 (app. d,  $J = 2.3$  Hz, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.46 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  144.4, 140.9, 137.0, 133.9, 133.0, 132.4, 130.2, 127.7, 123.8, 123.7, 115.7, 115.4, 108.9, 106.8, 78.0, 63.8, 46.8, 45.3, 36.4, 35.6, 28.2, 26.6, 26.2, 18.2, 17.5.

HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{25}\text{H}_{27}^{35}\text{ClNO}$   $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$  376.1832, found 376.1825.

IR (thin film): 3536, 3344, 2969, 1570, 1473, 1458, 1458, 1361, 1308, 1266, 911, 744, 707  $\text{cm}^{-1}$

$[\alpha]_D^{19} = +8.7^\circ$  ( $c=0.17$ ,  $\text{CHCl}_3$ ).



**Bromide 24.** To an oven dried 4 mL vial was added **23** (2.0 mg, 0.0051 mmol, 1 equiv.) and DCM (250  $\mu$ L). The colorless solution was cooled to 0  $^{\circ}$ C. *N*-bromosuccinimide (0.9 mg, 0.0051 mmol, 1 equiv.) was added as a DCM solution (50  $\mu$ L of a stock solution made by dissolving 9 mg of *N*-bromosuccinimide in 500  $\mu$ L DCM). The resulting orange solution was stirred at 0  $^{\circ}$ C for 10 min before the addition of pyridinium *p*-toluenesulfonate (2.6 mg, 0.010 mmol, 2 equiv.) as a DCM solution (100  $\mu$ L of a stock solution made by dissolving 13 mg pyridinium *p*-toluenesulfonate in 500  $\mu$ L DCM). The red solution was stirred at 0  $^{\circ}$ C and then at room temperature. The reaction was stirred at this temperature for 90 minutes before being quenched by NaHCO<sub>3</sub> aq. (500  $\mu$ L). The two phases were separated, and the aqueous phase was extracted with DCM (3 x 1 mL). The organic phase was combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC (40% EtOAc/hexanes) to afford bromide **24** as a yellow solid (1.8 mg, 83%).

$R_f$  = 0.30 (20% EtOAc/hexanes)

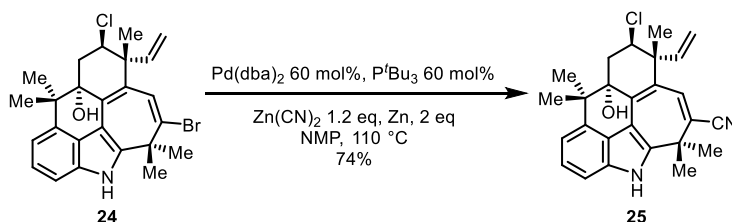
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.03 (s, 1H), 7.26-7.22 (m, 2H), 7.11 (dd,  $J$  = 5.6, 2.2 Hz, 1H), 6.61 (s, 3H), 5.73 (dd,  $J$  = 17.4, 10.6 Hz, 1H), 5.33 (d,  $J$  = 10.6 Hz, 1H), 5.26 (d,  $J$  = 17.4 Hz, 1H), 4.47 (dd,  $J$  = 12.9, 3.7 Hz, 1H), 2.58 (app. t,  $J$  = 13.4 Hz, 1H), 2.45 (dd,  $J$  = 13.7, 3.8 Hz, 1H), 2.01 (s, 1H), 1.90 (s, 3H), 1.60 (s, 3H), 1.47 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$  143.6, 137.3, 137.1, 133.5, 132.9, 131.5, 130.5, 124.5, 123.5, 123.2, 116.1, 115.9, 109.2, 108.0, 77.9, 63.3, 46.8, 45.5, 41.4, 36.3, 28.7, 28.3, 25.0, 18.1, 17.4.

**HRMS** (ESI)  $m/z$  calc'd for C<sub>25</sub>H<sub>26</sub><sup>79</sup>Br<sup>35</sup>ClN [M+H-H<sub>2</sub>O]<sup>+</sup> 4543.0937, found 454.0929.

**IR** (thin film): 3522, 3334, 2966, 1559, 1472, 1457, 1362, 1308, 923, 760 cm<sup>-1</sup>

$[\alpha]_D^{26}$  = +23.0  $^{\circ}$  (c=0.15, CHCl<sub>3</sub>).



**Nitrile 25.** Tri-*tert*-butyl phosphine (12.3 mg) was weighed into an oven-dried 4 mL vial in a glove box. The vial was then capped and taken out of the glove box. *N*-Methylpyrrolidinone (NMP, bubbled with N<sub>2</sub> for 40 minutes before use, 958  $\mu$ L) was added into the vial to make a colorless solution. To different oven-dried 4 mL vial was added Pd(dba)<sub>2</sub> (11.0 mg) and NMP (bubbled with N<sub>2</sub> for 40 minutes before use, 300  $\mu$ L). The dark red solution was purged with N<sub>2</sub> for 3 min, before 300  $\mu$ L of the tri-*tert*-butyl phosphine NMP solution was added. Another 150  $\mu$ L of NMP was added and the mixture was stirred at room temperature for 1 hour.

To an oven-dried 4 mL vial was added bromide **24** (3.0 mg, 0.0063 mmol, 1 equiv.), Zn(CN)<sub>2</sub>



(0.9 mg, 0.0076 mmol, 1.2 equiv.), Zn dust (3.3 mg, 0.0508 mmol, 8 equiv. *Note 1*) and NMP (bubbled with N<sub>2</sub> for 40 minutes before use, 270  $\mu$ L). The vial was purged with N<sub>2</sub> for 3 min. The mixture was heated to 110  $^{\circ}$ C and the pre-prepared Pd(dba)<sub>2</sub>-P'Bu<sub>3</sub> NMP solution (50  $\mu$ L, contained Pd(dba)<sub>2</sub> 0.73 mg, 0.0013 mmol, 0.2 equiv.; P'Bu<sub>3</sub> 0.26 mg, 0.0013 mmol, 0.2 equiv.) was added into the vial containing **24** with rigorous stirring. The resulting clear brown solution was stirred at this temperature for 40 minutes. Another 100  $\mu$ L of the Pd(dba)<sub>2</sub>-P'Bu<sub>3</sub> NMP solution (contained Pd(dba)<sub>2</sub> 1.46 mg, 0.0026 mmol, 0.4 equiv.; P'Bu<sub>3</sub> 0.51 mg, 0.0026 mmol, 0.4 equiv.) was added and the brown solution was stirred at the same temperature for an extra 40 minute. The reaction mixture was then filter through a pad of celite and flashed with EtOAc. The organic phase was washed with H<sub>2</sub>O (3 x 1 mL), brine (1 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude material was purified by prep-TLC (50% EtOAc/hexanes) to afford the desired product nitrile **25** as a yellow solid (2.0 mg, 74%).

*Note 1:* The ratio of Zn dust to Pd(dba)<sub>2</sub> needs to be at least 10 to 1 to ensure reproducible results.

*R<sub>f</sub>* = 0.14 (20% EtOAc/hexanes)

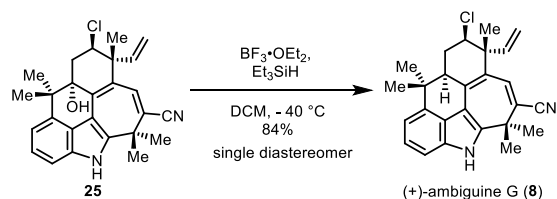
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.17 (s, 3H), 7.30-7.25 (m, 2H), 7.14 (dd, *J* = 5.4, 2.5 Hz, 1H), 6.78 (s, 3H), 5.72 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.35 (d, *J* = 10.6 Hz, 1H), 5.28 (d, *J* = 17.4 Hz, 1H), 4.46 (dd, *J* = 12.9, 3.7 Hz, 1H), 2.60 (t, *J* = 13.3 Hz, 1H), 2.47 (dd, *J* = 13.7, 3.8 Hz, 1H), 2.07 (s, 3H), 1.93 (s, 3H), 1.61 (s, 3H), 1.50 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  143.3, 142.2, 139.7, 136.7, 136.3, 133.1, 132.7, 125.0, 123.1, 119.5, 116.7, 116.6, 111.0, 109.5, 107.6, 78.0, 62.7, 46.7, 45.5, 36.2, 35.7, 28.0, 25.1, 25.0, 18.0, 17.7.

**HRMS** (ESI) *m/z* calc'd for C<sub>26</sub>H<sub>26</sub><sup>35</sup>ClN<sub>2</sub> [M+H-H<sub>2</sub>O]<sup>+</sup> 401.1785, found 401.1777.

**IR** (thin film): 3333, 2972, 2927, 2206, 1559, 1535, 1471, 1363, 1309, 1265, 1078, 1054, 914, 761, 736 cm<sup>-1</sup>

$[\alpha]_D^{19}$  = +82.2  $^{\circ}$  (c=0.13, CHCl<sub>3</sub>).



**(+)-Ambiguine G (8).** To a flame-dried 10 mL round-bottom flask containing nitrile **25** (2.6 mg, 0.0062 mmol, 1 equiv.) was added DCM (478  $\mu$ L, 0.013 M), followed by Et<sub>3</sub>SiH (20  $\mu$ L, 0.124 mmol, 20 equiv.). The resulting yellow solution was cooled to - 40  $^{\circ}$ C. BF<sub>3</sub>·OEt<sub>2</sub> (3.8  $\mu$ L, 0.0310 mmol, 5 equiv.) was added to the reaction mixture slowly as a DCM solution (50  $\mu$ L, made by dissolving 38  $\mu$ L BF<sub>3</sub>·OEt<sub>2</sub> in 462  $\mu$ L DCM), which caused the reaction to turn into a light brown, opaque solution. The reaction was stirred at - 40  $^{\circ}$ C for 30 min and quenched with saturated NaHCO<sub>3</sub> aq. (2 mL) at the same temperature. The resulting mixture was then allowed to warm to rt and extracted with DCM (2 x 2 mL). The organic phase was washed with saturated NaHCO<sub>3</sub> aq. (1 x 2 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by prep-TLC (25% EtOAc/hexanes) to afford (+)-ambiguine G (**8**) as a yellow solid (2.1 mg, single diastereomer, 84%).

$R_f = 0.29$  (20% EtOAc/hexanes)

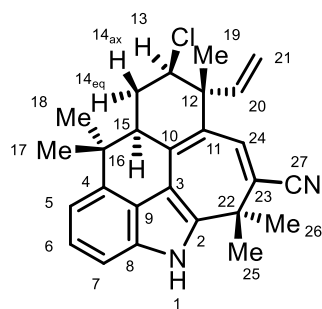
**$^1\text{H}$  NMR** (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.04 (s, 1H), 7.25-7.20 (m, 2H), 7.08 (dd,  $J = 5.5, 2.3$  Hz, 1H), 6.76 (s, 3H), 5.70 (dd,  $J = 17.4, 10.6$  Hz, 1H), 5.32 (d,  $J = 10.6$  Hz, 1H), 5.26 (d,  $J = 17.3$  Hz, 1H), 4.19 (dd,  $J = 12.9, 3.8$  Hz, 1H), 3.18 (dd,  $J = 11.4, 7.4$  Hz, 1H), 2.44 (ddd,  $J = 13.4, 7.4, 3.8$  Hz, 1H), 2.34 (app. q,  $J = 12.6$  Hz, 1H), 1.91 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H).

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  143.9, 142.3, 139.7, 137.5, 135.9, 133.0, 132.5, 124.7, 124.2, 119.9, 116.3, 114.6, 110.3, 109.5, 109.0, 65.5, 48.1, 46.3, 40.3, 35.5, 30.3, 25.1, 24.8, 24.8, 23.4, 18.8.

**HRMS** (ESI)  $m/z$  calc'd for  $\text{C}_{26}\text{H}_{28}^{35}\text{ClN}_2$   $[\text{M}+\text{H}]^+$  403.1941, found 403.1930.

**IR** (thin film): 3343, 2974, 2202, 1653, 1539, 1472, 1457, 1362, 1315  $\text{cm}^{-1}$

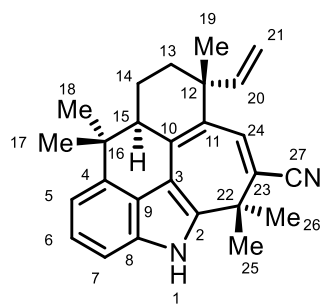
$[\alpha]_D^{20} = +143.2^\circ$  ( $c=0.05$ ,  $\text{CHCl}_3$ ).



(+)-Ambiguine G

**Table S1:** Comparison of the  $^1\text{H}$  NMR data of synthetic ambiguity G with reported data

Position	Synthetic ambiguity G, in $\text{CDCl}_3$ , $\delta_{\text{H}}$ , mult. ( $J$ in Hz)	Reported <sup>2</sup> chemical shift values, in $\text{CDCl}_3$ , $\delta_{\text{H}}$ , mult. ( $J$ in Hz)
N-H	8.04, s	8.06, s
5	7.08, dd (5.5, 2.3)	7.07, dd (8.2, 0.6)
6	7.25-7.20, m, overlapped with H-7	7.24, dd (8.2, 7.5)
7	7.25-7.20, m, overlapped with H-6	7.22, dd (7.5, 0.6)
13	4.19, dd (12.9, 3.8)	4.19, dd (12.7, 3.9)
14 <sub>ax</sub>	2.34, app. q (12.6)	2.34, q (13.3, 12.7, 11.2)
14 <sub>eq</sub>	2.44, ddd (13.4, 7.4, 3.8)	2.44, ddd (13.3, 7.5, 3.9)
15	3.18, dd (11.4, 7.4)	3.18, dd (11.2, 7.5)
17	1.06, s	1.06, s
18	1.56, s	1.56, s
19	1.52, s	1.52, s
20	5.70, dd (17.4, 10.6)	5.71, dd (17.4, 10.8)
21E	5.32, d (10.6)	5.32, d (10.8)
21Z	5.26, d (17.3)	5.26, d (17.4)
24	6.76, s	6.76, s
25	1.91, s	1.91, s
26	1.04, s	1.04, s



(+)-Ambiguine G

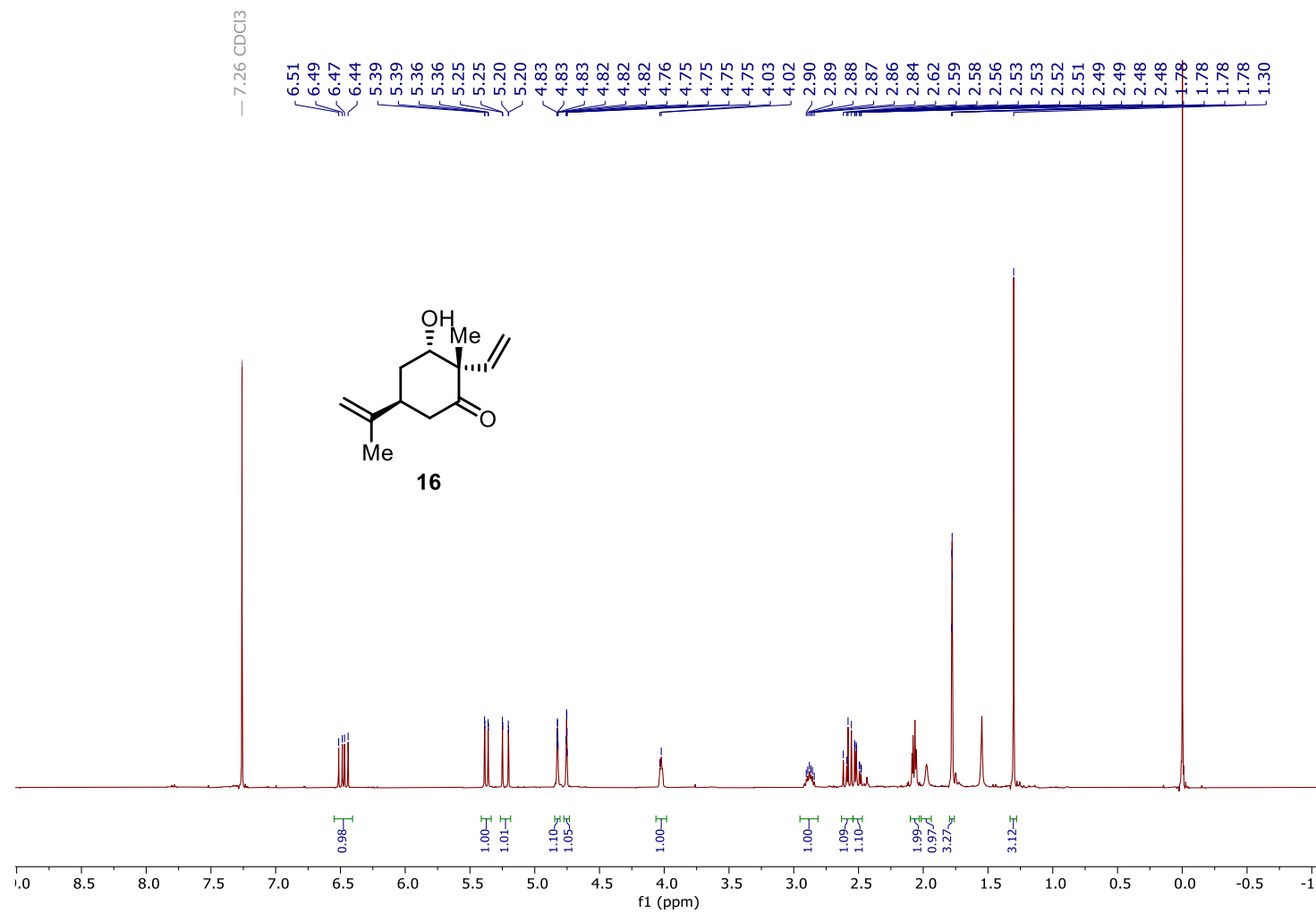
**Table S2:** Comparison of the  $^{13}\text{C}$  NMR data of synthetic ambiguity G with reported data

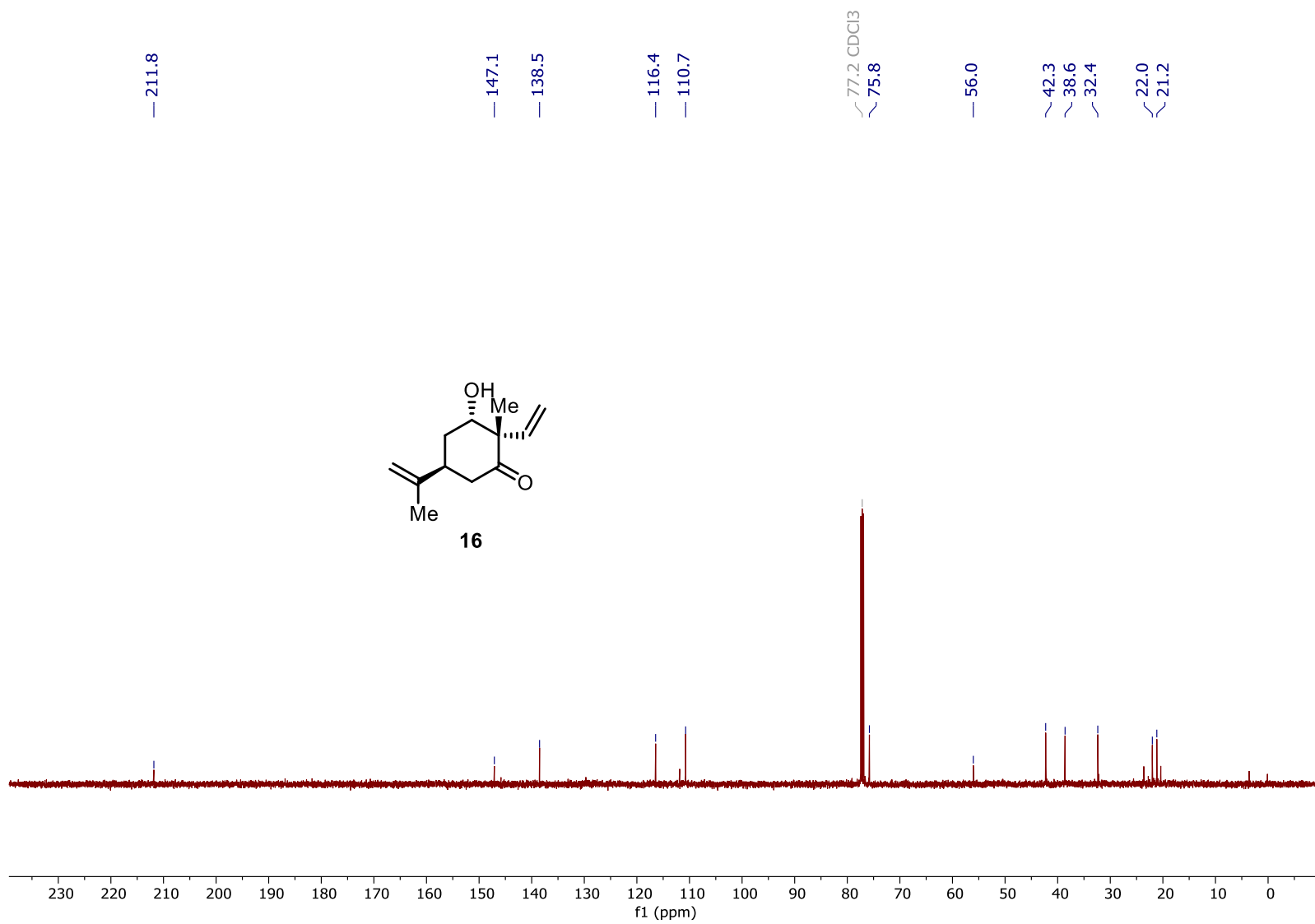
Position	Synthetic ambiguity G (CS1), in $\text{CDCl}_3$ , $\delta_{\text{C}}$ (ppm)	Reported <sup>2</sup> chemical shift values (CS2), in $\text{CDCl}_3$ , $\delta_{\text{C}}$ (ppm)	$\Delta\delta$ (CS1-CS2, ppm)
2	137.5	137.4	0.1
3	110.3	110.1	0.2
4	139.7	139.5	0.2
5	114.6	114.4	0.2
6	124.2	124.1	0.1
7	109.0	108.8	0.2
8	133.0	132.9	0.1
9	124.7	124.5	0.2
10	135.9	135.7	0.2
11	132.5	132.3	0.2
12	46.3	46.2	0.1
13	65.5	65.3	0.2
14	30.3	30.1	0.2
15	48.1	47.9	0.2
16	40.3	40.1	0.2
17	24.8	24.7	0.1
18	23.4	23.2	0.2
19	18.8	18.6	0.2
20	143.9	143.8	0.1
21	116.3	116.1	0.2
22	35.5	35.3	0.2
23	109.5	109.3	0.2
24	142.3	142.1	0.2
25	24.8	24.6	0.2
26	25.1	24.9	0.2
27	119.9	119.7	0.2

### III. References

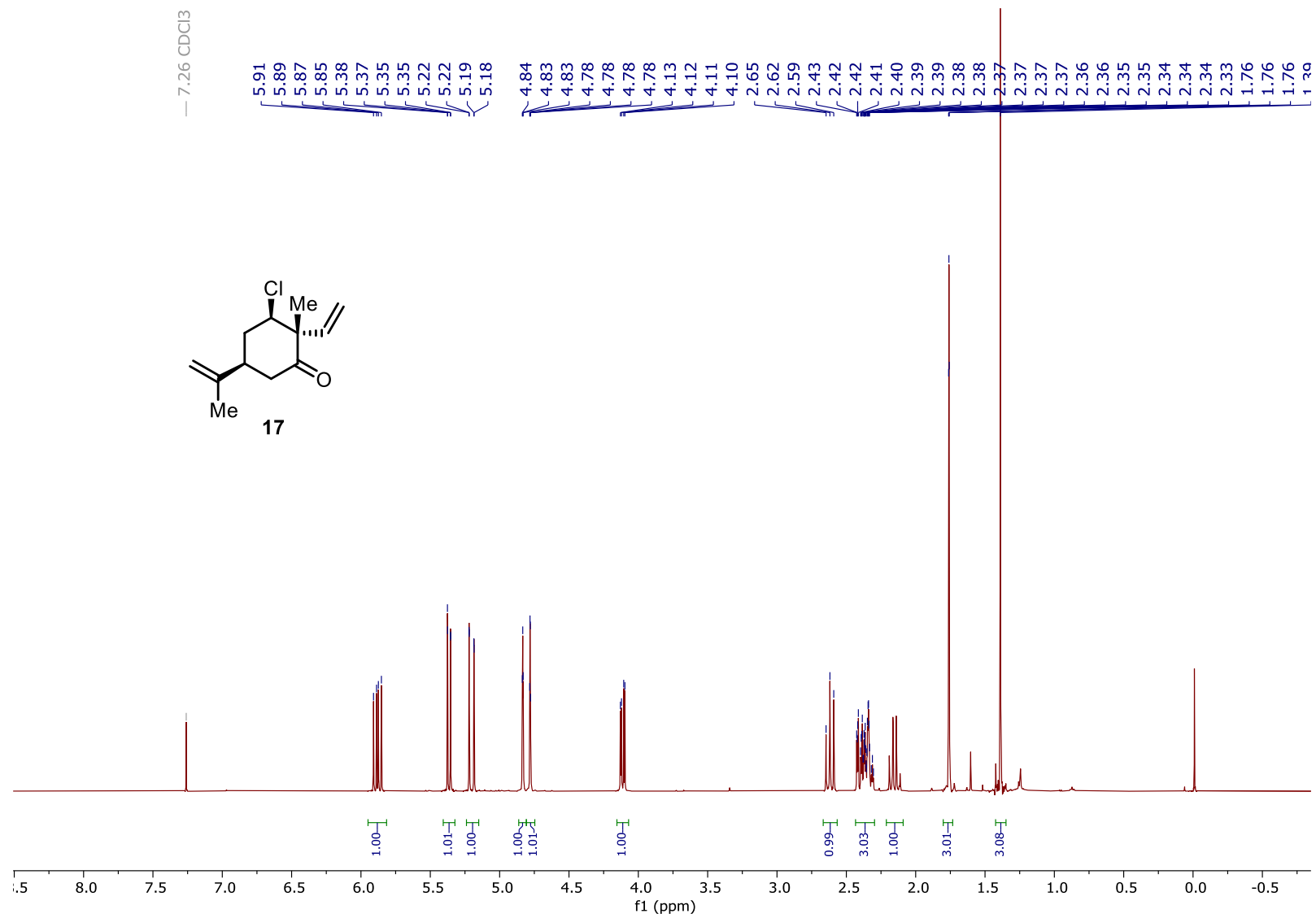
- (1) Xu, J.; Rawal, V. H. Total synthesis of (-)-ambiguine P. *J. Am. Chem. Soc.* **2019**, *141*, 4820-4823.
- (2) Huber, U.; Moore, R. E.; Patterson, G. M. L. Isolation of a nitrile-containing indole alkaloid from the terrestrial blue-green alga *Hapalosiphon delicatulus*. *J. Nat. Prod.* **1998**, *61*, 1304-1306

# IV. NMR Spectra

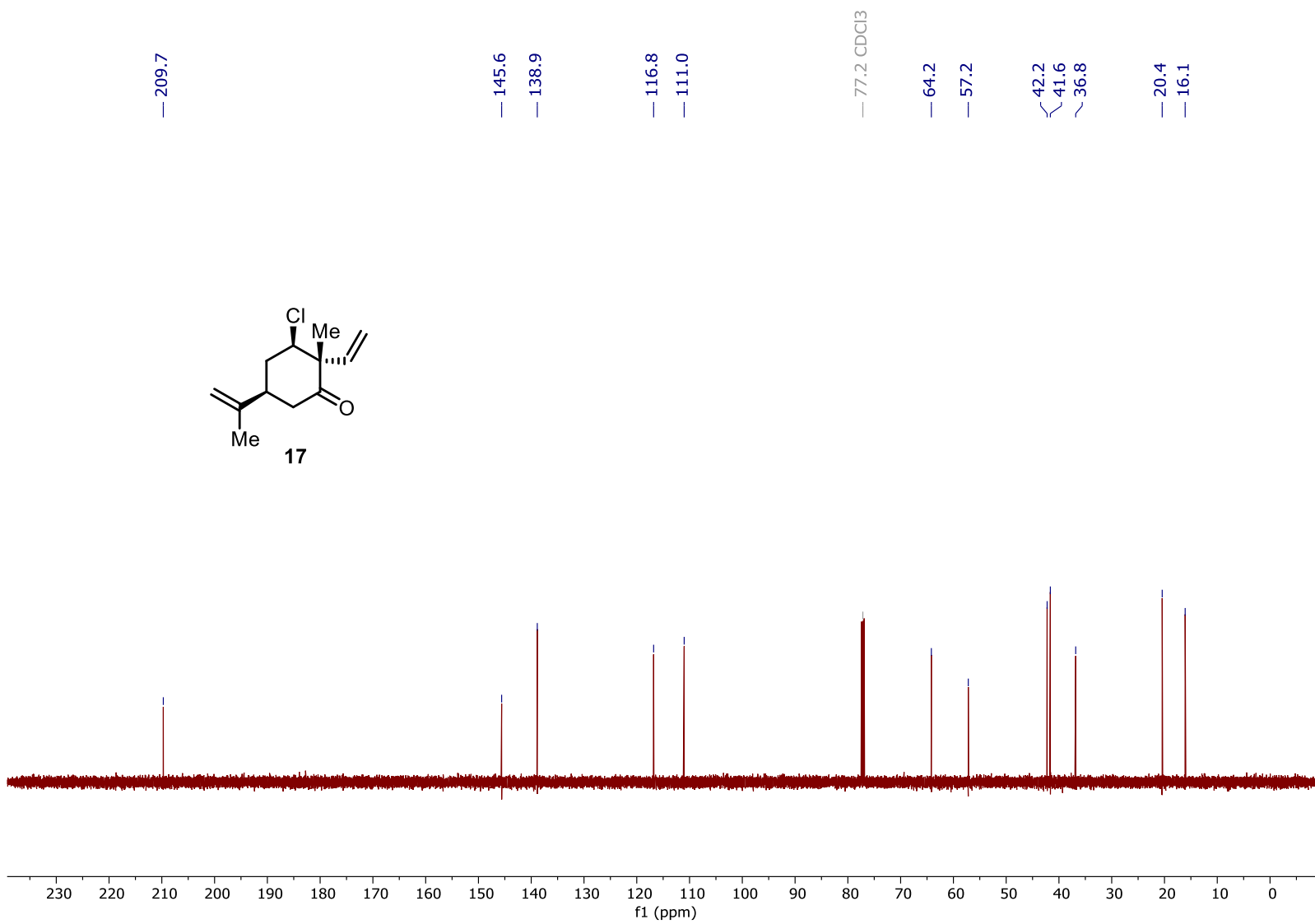
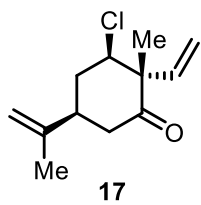


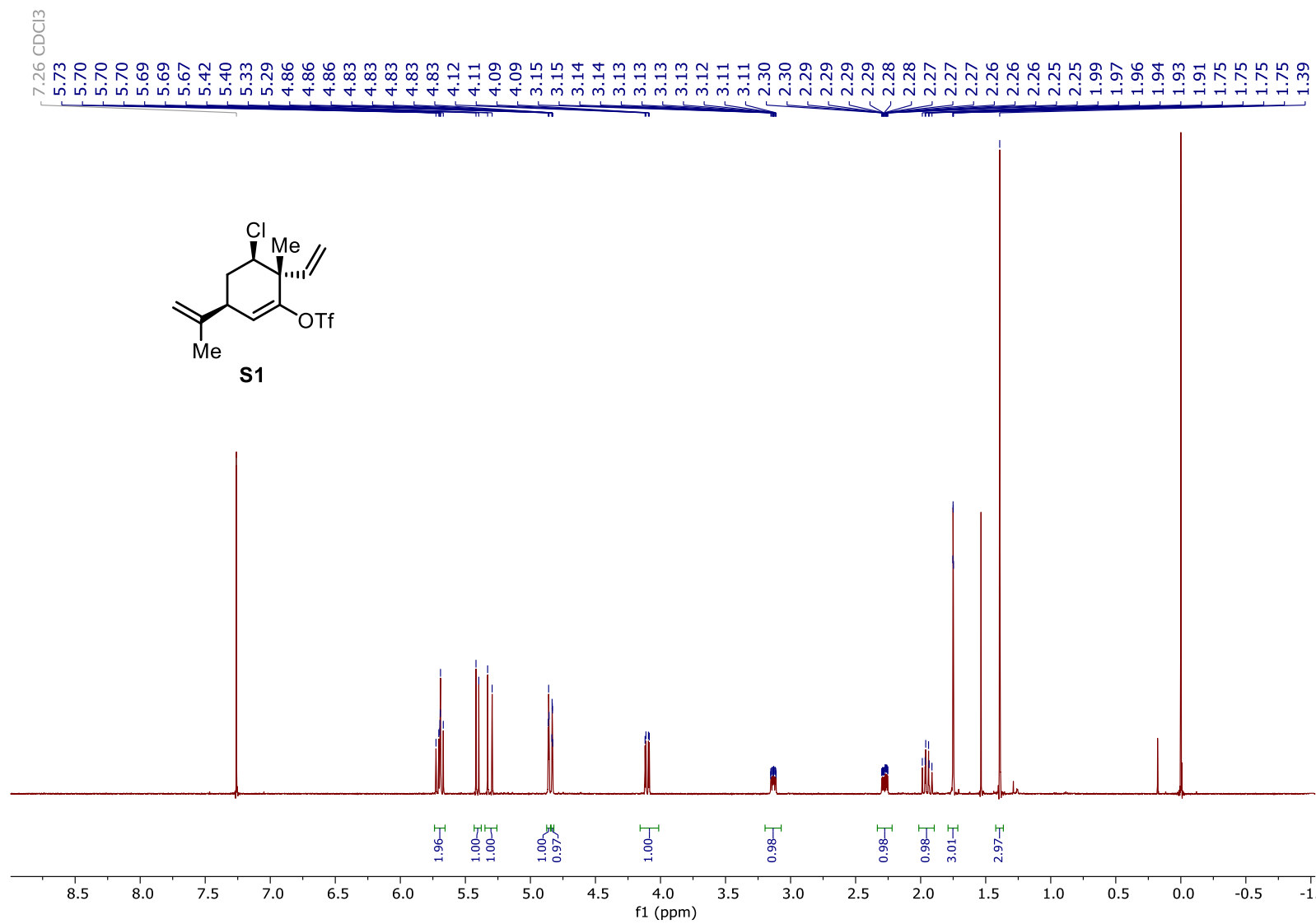


S15

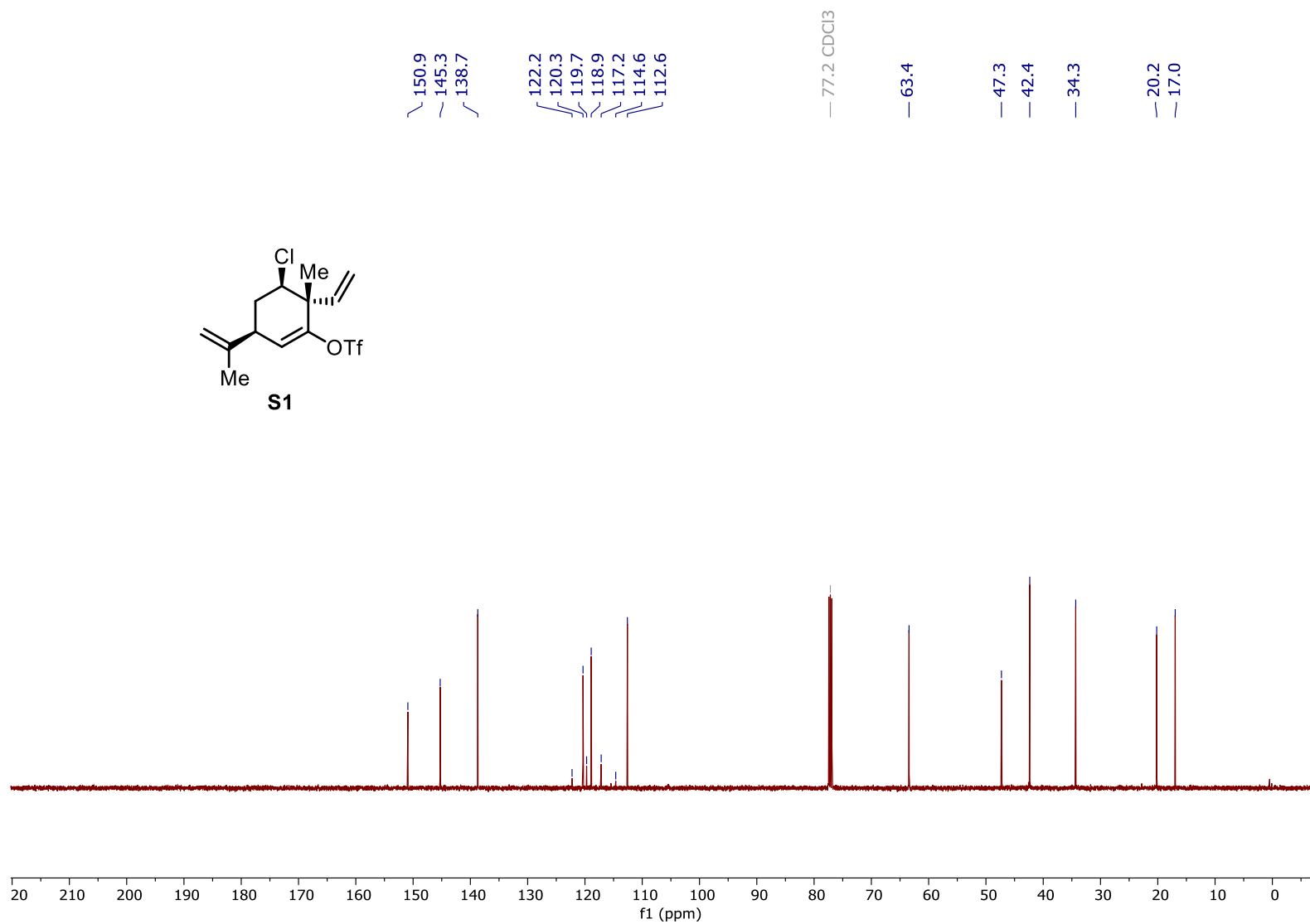
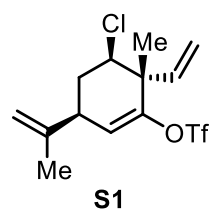


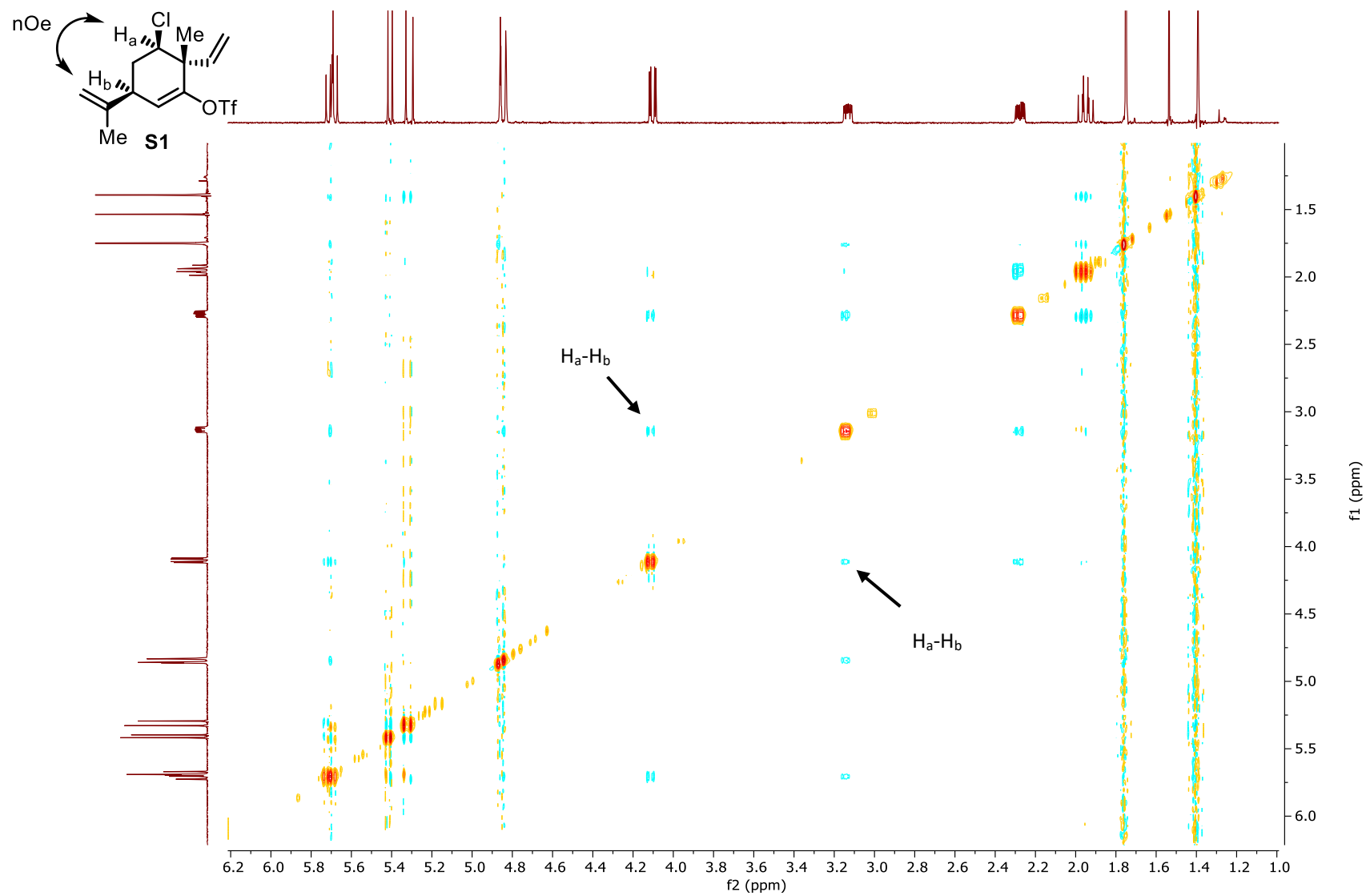


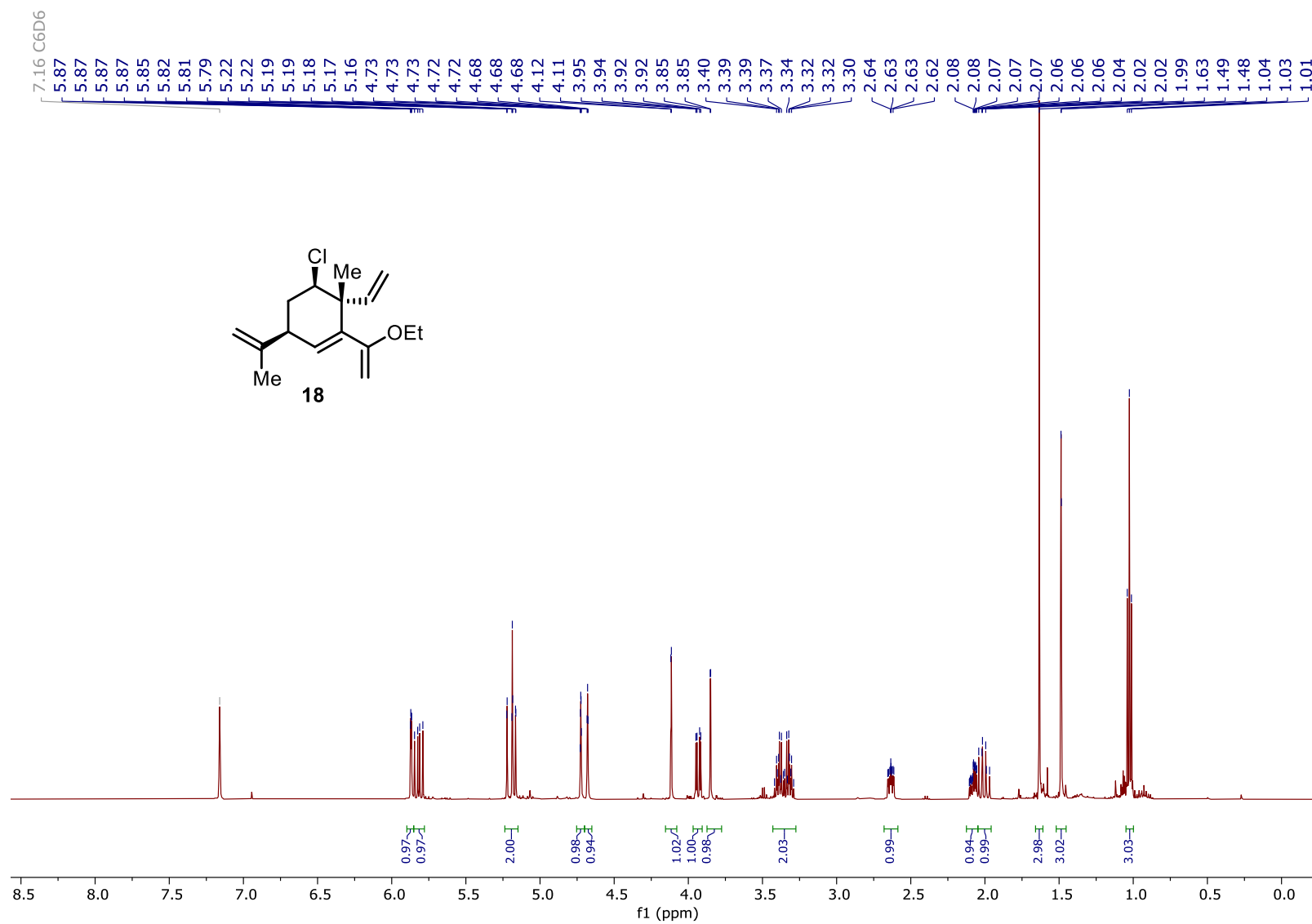




S18







S21

