

## Supporting information

### A Divergent and Concise Total Synthesis of (-)-Lycoposerramine R and (+)-Lycopladine A

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#### Table of Contents:

General Information .....	1
Experimental data .....	2 - 12
Spectra for the synthesized compounds .....	13 - 24

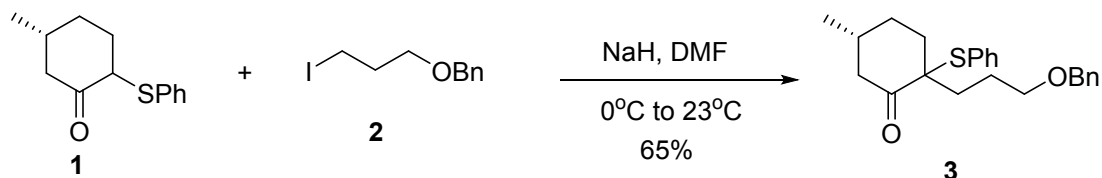
#### General Information

All reactions involving air or moisture sensitive reagents or intermediates were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals purchased commercially were used without further purification. Tetrahydrofuran and toluene were distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. Yields refer to isolated compounds, unless otherwise stated. Reactions were monitored by using thin-layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel plates (60F-254) using Tsingdao silica gel (60, particle size 0.040–0.063 mm). And the silica gel from the same company was also used for flash column chromatography. NMR spectra were recorded on a Brüker AVANCE 400 ( $^1\text{H}$ : 400 MHz,  $^{13}\text{C}$ : 100 MHz) or a Brüker AVANCE 500 ( $^1\text{H}$ : 500 MHz,  $^{13}\text{C}$ : 125 MHz) instrument. Chemical shifts were reported in parts per million (ppm) with respect to the residual solvents  $\text{CDCl}_3$  ( $^1\text{H}$  NMR:  $\delta$  = 7.26;  $^{13}\text{C}$  NMR:  $\delta$  = 77.16) and  $\text{CD}_3\text{OD}$  ( $^1\text{H}$  NMR:  $\delta$  = 3.31;  $^{13}\text{C}$  NMR:  $\delta$  = 49.00). Peak multiplicities were reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet, br = broad signal. Optical rotations were measured on a WZZ-2S automatic polarimeter. High resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

## Experimental data

### Total synthesis of (-)-lycposerramine R(1)

#### Synthesis of compound 3



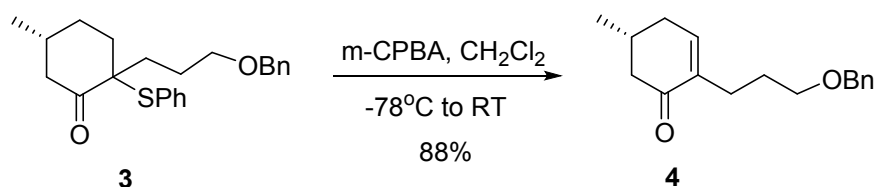
Thioether **1**<sup>1</sup> (20.0 g, 90.8 mmol) was dissolved in DMF (450 mL) and cooled to 0°C. Solid NaH (3.99 g, 60% oil dispersion, 99.9 mmol) was added in portions over a period of five minutes with extensive gas evolution. After 60 minutes the iodo compound **2**<sup>2</sup> (27.6 g, 99.9 mmol) was added neat, dropwise over a period of ten minutes. The cooling bath was removed and the solution was stirred for 1 hour. The reaction mixture was diluted with NH<sub>4</sub>Cl (aq., 1.5 L) and EtOAc (0.75 L). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was purified by using silica gel chromatography (25/1, petroleum ether/EtOAc) to afford a diastereomeric mixture of ketones **3** as a viscous yellow oil (21.7 g, 65%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40 – 7.17 (m, 10H), 4.51 – 4.42 (m, 2H), 3.49 – 3.37 (m, 2H), 3.24 (dd, *J* = 14.2, 5.3 Hz, 0.72H), 3.11 (dd, *J* = 14.2, 12.6 Hz, 0.28H), 2.33 – 2.24 (m, 1H), 2.20 – 1.98 (m, 3H), 1.94 – 1.61 (m, 4H), 1.59 – 1.45 (m, 2H), 1.07 (d, *J* = 5.8 Hz, 0.83H), 0.95 (d, *J* = 7.0 Hz, 2.17H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 208.04, 207.06, 138.59, 136.58, 136.11, 130.62, 130.37, 129.25, 129.09, 128.80, 128.70, 128.31, 128.29, 72.87, 70.52, 70.31, 61.95, 60.15, 45.90, 45.16, 35.60, 34.44, 33.67, 31.96, 31.33, 30.93, 29.74, 28.00, 24.17, 23.99, 22.14, 19.74.

HRMS (ESI) *m/z*: calculated for C<sub>23</sub>H<sub>29</sub>O<sub>2</sub>S [M+H]<sup>+</sup> 369.1888, found 369.1892.

#### Synthesis of compound 4



The diastereomeric mixture of ketones **3** (20.0 g, 54.3 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (360 mL) and placed in a -78°C bath. A solution of *m*-CPBA (11.2 g, 55.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (180 mL) was added over over a period of 1 hour to the solution at -78°C. The cooling bath was removed and the solution was stirred for 10 hours where upon the solution became clear. The reaction mixture was then diluted with NaHSO<sub>3</sub> (10% aq.,

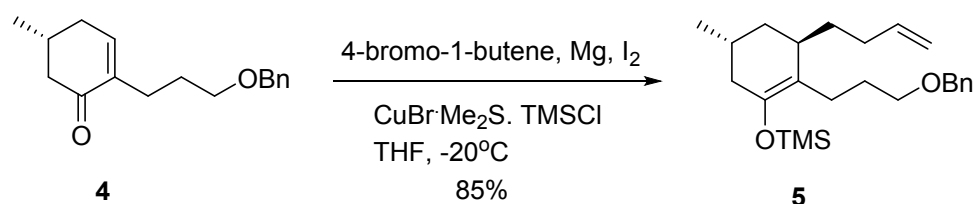
200 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 400 mL). The combined organic extracts were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by using silica gel chromatography (20/1, petroleum ether/EtOAc) to afford enone **4** as a light yellow oil (12.3 g, 88%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.26 (m, 5H), 6.68 – 6.63 (m, 1H), 4.49 (s, 2H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.51 – 2.43 (m, 1H), 2.37 (dt, *J* = 18.3, 4.4 Hz, 1H), 2.27 (t, *J* = 7.6 Hz, 2H), 2.20 – 1.94 (m, 3H), 1.72 (tt, *J* = 13.0, 6.4 Hz, 2H), 1.03 (d, *J* = 6.3 Hz, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 199.58, 144.53, 138.92, 138.63, 128.31, 127.69, 127.47, 72.82, 69.74, 46.67, 34.37, 30.61, 28.54, 26.13, 21.15.

**HRMS** (ESI) *m/z*: calculated for C<sub>17</sub>H<sub>23</sub>O<sub>2</sub> [M+H]<sup>+</sup> 259.1698, found 259.1693.

## Synthesis of compound 5



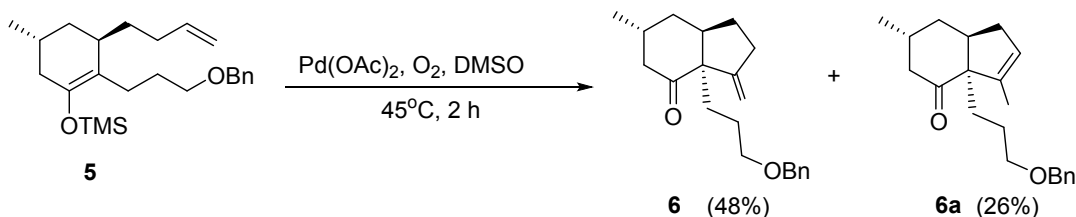
Magnesium turnings (1.2g, 46.5 mmol) were stirred under an argon atmosphere. Iodine crystals (15 mg) were added followed by freshly distilled THF (78 mL). 4-bromo-1-butene (6.3 g, 46.5 mmol) was diluted with anhydrous THF (15 mL), a portion (2 mL) of the above solution was added directly to the THF suspension to start the reaction (heat was required to initiate), then the left over was added dropwise to the above suspension over over a period of 20 mins with heating. After the addition was complete, the mixture was then refluxed for 1.5 h. Copper bromide dimethyl sulfide complex (297 mg, 1.4 mmol) was dissolved in anhydrous THF (45 mL) under an argon atmosphere. The solution was then cooled to –20°C and the Grignard solution was added via syringe over over a period of 5 mins. After 30 mins at –20°C a mixture of **4** (6.0g, 23.2 mmol) and TMSCl (5.1 g, 46.5 mmol) in THF(20 mL) was added (20 mins) and the reaction stirred for 15 min. at –20°C before being warmed up to room temperature. The reaction mixture was then treated with Et<sub>3</sub>N (20 mL) sat. NH<sub>4</sub>Cl (60 mL) solution and the organic layer was separated. The aqueous solution was extracted with EtOAc (3 × 60 mL) and the organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by using silica gel chromatography (100/1, petroleum ether/EtOAc) to afford **5** as a colorless oil (7.6 g, 85%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.25 (m, 5H), 5.90 – 5.70 (m, 1H), 5.05 – 4.91 (m, 2H), 4.51 (s, 2H), 3.46 (t, *J* = 6.7 Hz, 2H), 2.44 – 2.30 (m, 1H), 2.20 – 1.93 (m, 4H), 1.90 – 1.79 (m, 2H), 1.76 (ddd, *J* = 9.0, 6.6, 3.0 Hz, 1H), 1.72 – 1.62 (m, 2H), 1.62 – 1.53 (m, 2H), 1.27 (dtd, *J* = 14.6, 9.9, 5.0 Hz, 1H), 1.16 (td, *J* = 12.4, 5.5 Hz, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.16 (s, 9H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 143.68, 139.12, 138.87, 128.27, 127.54, 127.35, 118.74, 114.25, 72.74 70.77, 38.90, 35.48, 34.51, 32.21, 28.24, 24.81, 24.54, 21.81, 0.80.

**HRMS** (ESI)  $m/z$ : calculated for  $C_{24}H_{39}O_2Si$   $[M+H]^+$  387.2719, found 387.2721.

## Synthesis of compound 6



The silyl enol ether **5** (6.5 g, 16.8 mmol) was dissolved in dry DMSO (170 ml) and stirred under an oxygen atmosphere.  $Pd(OAc)_2$  (377 mg, 1.7 mmol) was added in one portion and resulting the mixture was heated to  $45^\circ C$  and stirred at that temperature for 2h. The reaction was diluted with sat.  $NaHCO_3$  (500 mL) solution and EtOAc (300 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc ( $3 \times 300$  mL). The organic extracts were combined and washed with brine (800 mL), dried over  $Na_2SO_4$ , filtered, and concentrated. The crude product was purified by using silica gel chromatography (25/1, petroleum ether/EtOAc) to afford **6** as a light yellow oil (2.5 g, 48%) in addition to **6a** (1.4 g, 26%).

**For 6:**  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.39 – 7.21 (m, 5H), 5.02 (s, 1H), 4.77 (s, 1H), 4.49 (s, 2H), 3.53 – 3.36 (m, 2H), 2.58 – 2.43 (m, 3H), 2.43 – 2.30 (m, 1H), 2.26 – 2.13 (m, 1H), 2.08 (dd,  $J = 14.7, 7.0$  Hz, 1H), 1.91 – 1.76 (m, 2H), 1.75 – 1.65 (m, 1H), 1.61 – 1.43 (m, 5H), 0.96 (d,  $J = 6.8$  Hz, 3H).

$^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  212.28, 153.50, 138.60, 128.34, 127.63, 127.48, 108.45, 72.86, 70.74, 62.82, 46.09, 42.63, 34.08, 32.08, 30.32, 29.31, 28.74, 25.50, 20.33.

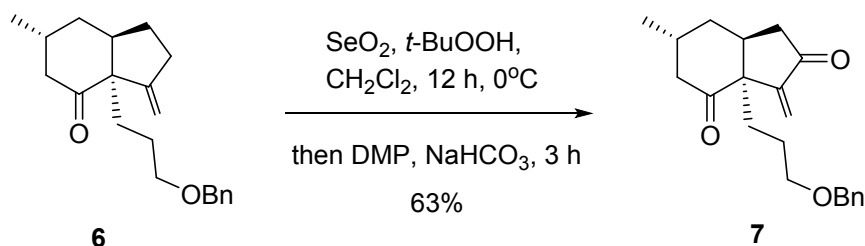
**HRMS** (ESI)  $m/z$ : calculated for  $C_{21}H_{29}O_2$   $[M+H]^+$  313.2168, found 313.2175.

**For 6a:**  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.37 – 7.27 (m, 5H), 5.47 (d,  $J = 36.3$  Hz, 1H), 4.49 (s, 2H), 3.52 – 3.41 (m, 2H), 2.60 – 2.45 (m, 2H), 2.38 (ddd,  $J = 16.2, 5.7, 1.7$  Hz, 1H), 2.19 – 2.01 (m, 2H), 1.91 (dd,  $J = 16.3, 9.7$  Hz, 1H), 1.75 (dd,  $J = 12.1, 9.0$  Hz, 1H), 1.68 – 1.62 (m, 1H), 1.60 (d,  $J = 1.6$  Hz, 3H), 1.59 – 1.56 (m, 2H), 1.48 – 1.38 (m, 2H), 0.95 (d,  $J = 6.6$  Hz, 3H).

$^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  215.22, 141.35, 138.55, 128.33, 127.99, 127.62, 127.49, 72.94, 70.82, 64.85, 47.24, 42.26, 37.60, 36.76, 30.48, 26.76, 24.80, 21.94, 14.06.

**HRMS** (ESI)  $m/z$ : calculated for  $C_{21}H_{29}O_2$   $[M+H]^+$  313.2168, found 313.2153.

## Synthesis of compound 7



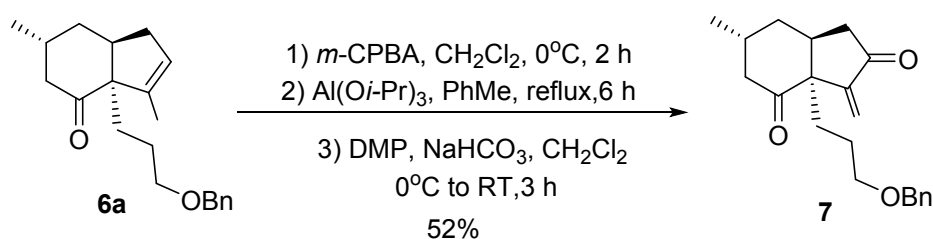
A mixture of *tert*-butyl hydroperoxide (5-6 M solution in anhydrous decane, 2.7 mL, 14.8 mmol), SeO<sub>2</sub> (411 mg, 3.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (24 mL) was stirred at room temperature for 1 h. The reaction was cooled to 0°C and compound **6** (2.3 g, 7.4 mmol) was cannulated into the reaction flask containing CH<sub>2</sub>Cl<sub>2</sub> (12 mL). The reaction mixture was stirred for 12 hours at 0°C before TLC analysis showed full conversion. NaHCO<sub>3</sub> (1.2 g, 14.8 mmol) and Dess-Martin periodinane (3.8 g, 8.9 mmol) were added sequentially at that temperature. The colorless suspension was stirred at room temperature for 3 h before TLC analysis indicated full conversion. A 1:1 mixture of saturated aq. NaHCO<sub>3</sub> and 10% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 mL) was added and the biphasic mixture was stirred vigorously until two clear phases formed. Extraction with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by using silica gel chromatography (10/1, petroleum ether/EtOAc) to afford **7** as a colorless oil (1.5 g, 63%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.27 (m, 5H), 6.21 (s, 1H), 5.28 (s, 1H), 4.49 (s, 2H), 3.49 – 3.43 (m, 2H), 2.72 – 2.69 (m, 1H), 2.58 – 2.46 (m, 2H), 2.18 (dd, *J* = 18.6, 5.5 Hz, 3H), 1.97 (dd, *J* = 18.7, 6.8 Hz, 1H), 1.79 – 1.56 (m, 5H), 1.02 (d, *J* = 5.9 Hz, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 210.18, 204.09, 146.60, 138.39, 128.37, 127.61, 127.59, 120.84, 72.98, 70.16, 59.95, 45.75, 42.21, 36.28, 34.61, 32.63, 28.21, 25.37, 20.56.

HRMS (ESI) *m/z*: calculated for C<sub>21</sub>H<sub>27</sub>O<sub>3</sub> [M+H]<sup>+</sup> 327.1960, found 327.1968.

### Conversion of compound **6a** to **7**



A solution of **6a** (1.2 g, 3.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (28 mL) was cooled to 0°C, and a solution of 85% *m*-CPBA (810 mg, 4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise to the solution at 0°C. The solution was stirred at that temperature for 2 h before a 1:1 mixture of saturated aq. NaHCO<sub>3</sub> and 10% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 mL) was added and the biphasic mixture was stirred vigorously until two clear phases formed. Extraction with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL) and the combined organic extracts were washed with brine (60 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the corresponding crude epoxide, which was immediately dissolved in dry toluene (40 mL), and Al(*Oi*-Pr)<sub>3</sub> (776 mg) was added in one portion. The mixture was refluxed for 6 h before being cooled to room temperature. Saturated aq. NaHCO<sub>3</sub> was added. Extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The

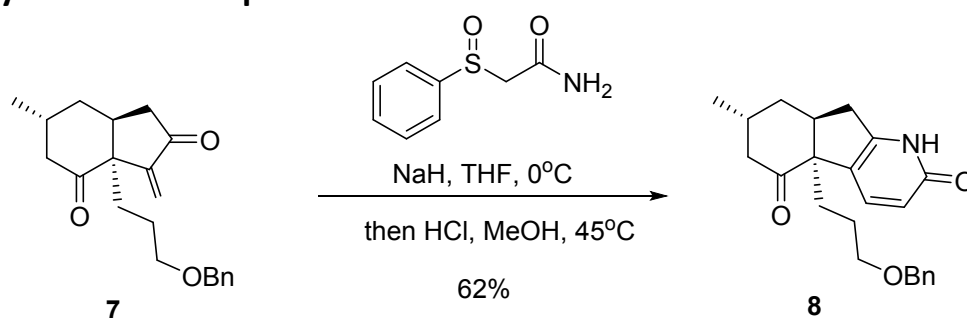
residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL), NaHCO<sub>3</sub> (638 mg, 7.6 mmol) and Dess-Martin periodinane (1.9 g, 4.6 mmol) were added sequentially at that temperature. The colorless suspension was stirred for 3 h before TLC analysis indicated full conversion. A 1:1 mixture of saturated aq. NaHCO<sub>3</sub> and 10% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 mL) was added and the biphasic mixture was stirred vigorously until two clear phases formed. After extraction with EtOAc (3 × 50 mL), the combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by using silica gel chromatography (10/1, petroleum ether/EtOAc) to afford **7** as a colorless oil (643 mg, 52%).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.27 (m, 5H), 6.21 (s, 1H), 5.28 (s, 1H), 4.49 (s, 2H), 3.49 – 3.43 (m, 2H), 2.72 – 2.69 (m, 1H), 2.58 – 2.46 (m, 2H), 2.18 (dd, *J* = 18.6, 5.5 Hz, 3H), 1.97 (dd, *J* = 18.7, 6.8 Hz, 1H), 1.79 – 1.56 (m, 5H), 1.02 (d, *J* = 5.9 Hz, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 210.18, 204.09, 146.60, 138.39, 128.37, 127.61, 127.59, 120.84, 72.98, 70.16, 59.95, 45.75, 42.21, 36.28, 34.61, 32.63, 28.21, 25.37, 20.56.

**HRMS** (ESI) *m/z*: calculated for C<sub>21</sub>H<sub>27</sub>O<sub>3</sub> [M+H]<sup>+</sup> 327.1960, found 327.1968.

## Synthesis of compound **8**



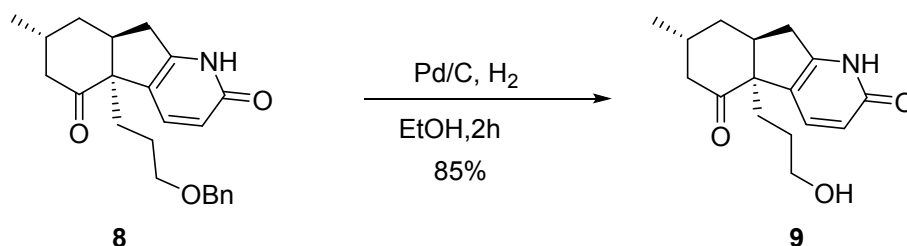
To a stirred solution of **7** (500 mg, 1.5 mmol) and 2-(phenylsulfinyl)acetamide<sup>3</sup> (561 mg, 3.0 mmol) in tetrahydrofuran (15 mL) was added sodium hydride (60% purity, 72 mg, 1.8 mmol) at 0°C. After consumption of the starting material, methanolic hydrogen chloride (5% HCl in methanol, 5 mL) was added to the reaction mixture at 0°C. After being stirred for 18 h at 45°C, the solvent was removed in *vacuo*, and the residue was partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified by using silica gel chromatography (20/1, CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford **8** as a colorless oil (347 mg, 62%).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.40 (d, *J* = 9.2 Hz, 1H), 7.35 – 7.27 (m, 5H), 6.40 (d, *J* = 9.2 Hz, 1H), 4.47 (s, 2H), 3.43 (t, *J* = 6.3 Hz, 2H), 3.03 (dd, *J* = 17.0, 8.7 Hz, 1H), 2.85 (dd, *J* = 5.3, 3.0 Hz, 1H), 2.70 (dd, *J* = 16.9, 7.9 Hz, 1H), 2.41 – 2.31 (m, 1H), 2.04 (t, *J* = 11.1 Hz, 2H), 1.98 – 1.91 (m, 1H), 1.83 – 1.66 (m, 3H), 1.66 – 1.39 (m, 3H), 1.02 (d, *J* = 5.9 Hz, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 213.41, 166.14, 148.40, 139.85, 138.37, 128.38, 127.61, 127.60, 121.08, 117.35, 73.00, 70.15, 60.05, 47.02, 42.01, 35.24, 35.00, 33.45, 27.27, 25.30, 21.82.

**HRMS** (ESI) *m/z*: calculated for C<sub>23</sub>H<sub>28</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 366.2069, found 366.2071.

## Synthesis of compound 9



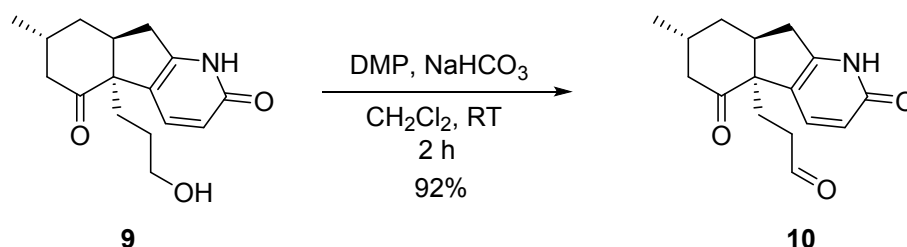
A solution of **8** (200 mg, 0.55 mmol) in 5.5 mL ethanol was degassed by sparging with H<sub>2</sub>. The solution was charged with 220 mg 10% Pd/C. The mixture was stirred at room temperature for 2 h, filtered over celite and concentrated. The crude product was purified by silica gel chromatography (10/1, CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford **9** as a white foam (128 mg, 85%).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.40 (d,  $J$  = 9.2 Hz, 1H), 6.40 (d,  $J$  = 9.2 Hz, 1H), 3.61 (t,  $J$  = 6.3 Hz, 2H), 3.05 (dd,  $J$  = 17.0, 8.7 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.70 (dd,  $J$  = 17.0, 7.8 Hz, 1H), 2.43 – 2.33 (m, 1H), 2.08 – 2.01 (m, 2H), 1.98 – 1.91 (m, 1H), 1.83 – 1.68 (m, 3H), 1.67 – 1.39 (m, 3H), 1.02 (d,  $J$  = 5.9 Hz, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>)  $\delta$  213.43, 166.12, 148.51, 139.77, 121.09, 117.39, 62.67, 60.03, 46.97, 42.02, 35.31, 35.10, 33.08, 28.06, 27.25, 21.79.

**HRMS** (ESI)  $m/z$ : calculated for C<sub>16</sub>H<sub>22</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 276.1600, found 276.1605.

## Synthesis of compound 10



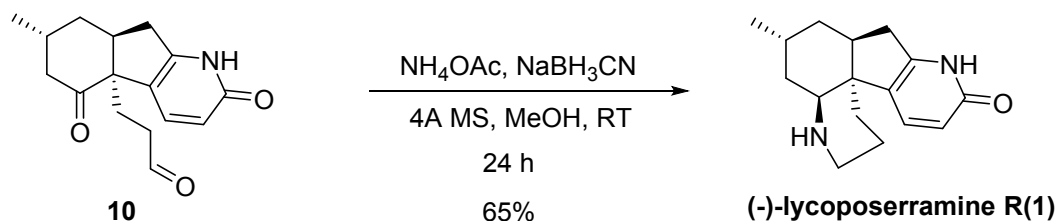
To a solution of **9** (100 mg, 0.36 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.6 mL) was added NaHCO<sub>3</sub> and the Dess-Martin reagent (297 mg, 0.7 mmol) sequentially at room temperature. The resulting mixture was stirred at the same temperature for 2 h and it was then quenched with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5 mL) and sat. aq. NaHCO<sub>3</sub> (5 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL x 3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified by silica gel chromatography (15/1, CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford **10** as a slight yellow oil (91 mg, 92%).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.74 (s, 1H), 7.35 (d,  $J$  = 9.1 Hz, 1H), 6.42 (d,  $J$  = 9.1 Hz, 1H), 3.09 (dd,  $J$  = 15.2, 6.5 Hz, 1H), 2.79 – 2.63 (m, 2H), 2.49 – 2.35 (m, 3H), 2.23 – 2.13 (m, 1H), 2.10 – 1.98 (m, 3H), 1.80 (d,  $J$  = 14.1 Hz, 1H), 1.65 (d,  $J$  = 9.0 Hz, 1H), 1.03 (d,  $J$  = 5.3 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  212.63, 200.55, 166.11, 149.02, 139.34, 120.21, 117.71, 59.57, 46.64, 42.04, 35.38, 35.08, 29.68, 27.94, 27.23, 21.62.

**HRMS** (ESI)  $m/z$ : calculated for C<sub>16</sub>H<sub>20</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 274.1443, found 274.1442.

## Synthesis of (-)-lycoposerramine R(1)



A flame-dried round-bottom flask was charged with ketoaldehyde **10** (25 mg, 0.09 mmol) in MeOH (1.8 mL), followed by addition of  $\text{NH}_4\text{OAc}$  (69 mg, 0.9 mmol), 4A MS (200 mg) and  $\text{NaBH}_3\text{CN}$  (57 mg, 0.9 mmol) respectively. The reaction mixture was stirred at room temperature for 24 h. The reaction was diluted with saturated aq.  $\text{NaHCO}_3$  (10 mL) and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3×8 mL). The combined organic phases were washed with saturated aq.  $\text{NaHCO}_3$  (5 mL), then dried over  $\text{K}_2\text{CO}_3$  and concentrated. The crude product was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2:\text{MeOH}=19:1 + 0.5\%$  aq.  $\text{NH}_3$ ) to afford (-)-lycoposerramine R(1) as a slight yellow gel (15 mg, 65%).  $[\alpha]_{\text{D}}^{25} -26$  (0.2,  $\text{CHCl}_3$ ).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (d,  $J = 9.1$  Hz, 1H), 6.34 (d,  $J = 9.1$  Hz, 1H), 3.20 (dd,  $J = 17.1, 6.9$  Hz, 2H), 2.92 (dd,  $J = 12.1, 4.7$  Hz, 1H), 2.79 (td,  $J = 11.4, 2.7$  Hz, 1H), 2.33 (d,  $J = 16.8$  Hz, 1H), 2.19 (dd,  $J = 13.8, 6.8$  Hz, 1H), 1.81 – 1.72 (m, 1H), 1.69 – 1.65 (m, 1H), 1.59 – 1.39 (m, 5H), 1.28 – 1.16 (m, 2H), 0.96 (d,  $J = 7.0$  Hz, 3H).

**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.06, 150.41, 143.26, 124.43, 114.80, 57.14, 49.32, 47.93, 41.83, 38.10, 36.08, 35.98, 34.71, 25.56, 22.77, 20.55.

**HRMS** (ESI)  $m/z$ : calculated for  $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$  259.1810, found 259.1806.

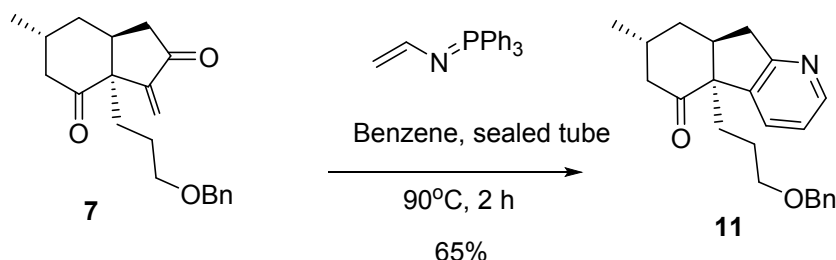


## Comparison of natural<sup>4</sup> and synthetic (-)-LycoposerramineR

$\delta_H$ (ppm)		$\delta_C$ (ppm)	
Natural	Synthetic	Natural	Synthetic
(400 MHz, CDCl <sub>3</sub> )	(400 MHz, CDCl <sub>3</sub> )	(100 MHz, CDCl <sub>3</sub> )	(125 MHz, CDCl <sub>3</sub> )
8.33 (d, 9.2, 1H)	8.32 (d, 9.1, 1H)	165.8	166.06
6.34 (d, 9.2, 1H)	6.34 (d, 9.1, 1H)	150.4	150.41
3.17 – 3.23 (m, 2H)	3.20 (dd, 17.1, 6.9, 2H)	143.3	143.26
2.92 (dd, 12.1, 4.8, 1H)	2.92 (dd, 12.1, 4.7, 1H)	124.5	124.43
2.80 (ddd, 11.6, 3.0, 1H)	2.79 (td, 11.4, 2.7, 1H)	115.0	114.80
2.33 (d, 17.0, 1H)	2.33 (d, 16.8, 1H)	57.1	57.14
2.19 (ddd, 6.9, 6.9, 1H)	2.19 (dd, 13.8, 6.8, 1H)	49.4	49.32
1.72– 1.79 (m, 1H)	1.72 – 1.81 (m, 1H)	47.8	47.93
1.66– 1.69 (m, 1H)	1.65 – 1.69 (m, 1H)	42.0	41.83
1.47– 1.55 (m, 1H)	1.39 – 1.59 (m, 5H)	38.1	38.10
1.42– 1.50 (m, 1H)	from above	36.2	36.08
1.41– 1.59 (m, 2H)	from above	36.0	35.98
1.39– 1.50 (m, 1H)	from above	34.6	34.71
1.20– 1.25 (m, 2H)	1.16 – 1.28 (m, 2H)	25.6	25.56
0.96 (d, 6.9, 3H)	0.96 (d, 7.0, 3H)	22.7	22.77
		20.6	20.55

## Total synthesis of (+)-lycopoladine A(2)

### Synthesis of compound 11



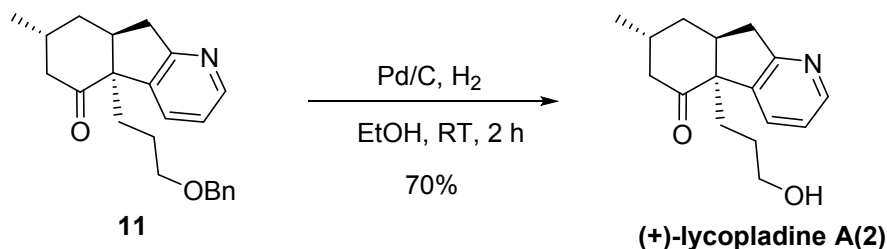
A flame-dried tube was charged with **7** (100 mg, 0.31 mmol) in dry benzene (3 mL) followed by addition of (*N*-Vinylimino)phosphorene<sup>5</sup> (186 mg, 0.62 mmol). The tube then was sealed and heated at 90°C for 2 h before cooled to room temperature. The reaction mixture was then diluted with saturated aq. NaHCO<sub>3</sub> (5 mL) and EtOAc (5 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was purified by silica gel chromatography (2/1, petroleum ether/EtOAc) to afford **11** as a slight yellow oil (69 mg, 65%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.38 (d, *J* = 4.7 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.31 (td, *J* = 14.8, 7.4 Hz, 5H), 7.12 – 7.07 (m, 1H), 4.46 (s, 2H), 3.43 (t, *J* = 6.0 Hz, 2H), 3.16 (dd, *J* = 16.2, 7.8 Hz, 1H), 2.93 – 2.79 (m, 2H), 2.35 (d, *J* = 12.4 Hz, 1H), 2.20 – 1.97 (m, 3H), 1.82 (dd, *J* = 18.0, 8.6 Hz, 2H), 1.75 – 1.57 (m, 2H), 1.47 (m, 1H), 1.04 (d, *J* = 5.7 Hz, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 212.63, 163.44, 148.76, 138.39, 137.72, 133.55, 128.38, 127.60, 121.57, 72.98, 70.22, 61.32, 46.90, 41.47, 38.66, 34.72, 33.38, 27.81, 25.50, 21.60.

HRMS (ESI) *m/z*: calculated for C<sub>23</sub>H<sub>28</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 350.2120, found 350.2106.

### Synthesis of (+)-lycopoladine A(2)



A solution of **11** (50 mg, 0.14 mmol) in 1.5 mL ethanol was degassed by sparging with H<sub>2</sub>. The solution was charged with 100 mg 10% Pd/C. The mixture was stirred at room temperature for 2 h, filtered over celite and concentrated. The crude product was purified by silica gel chromatography (20/1, CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford (+)-lycopoladine A(2) as a white solid (25 mg, 70%). [α]<sub>D</sub><sup>23</sup> + 135 (0.5, MeOH).

**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  8.29 (dd,  $J$  = 5.0, 1.4 Hz, 1H), 7.66 (dd,  $J$  = 7.7, 1.4 Hz, 1H), 7.24 (dd,  $J$  = 7.6, 5.1 Hz, 1H), 3.56 – 3.49 (m, 2H), 3.08 (dd,  $J$  = 16.2, 8.1 Hz, 1H), 3.00 – 2.92 (m, 1H), 2.82 (dd,  $J$  = 16.2, 8.8 Hz, 1H), 2.29 (dd,  $J$  = 12.5, 5.2 Hz, 2H), 2.15 – 2.02 (m, 2H), 1.93 – 1.80 (m, 3H), 1.56 (m, 1H), 1.40 – 1.31 (m, 1H), 1.08 (d,  $J$  = 6.5 Hz, 3H).

**<sup>13</sup>C NMR** (125 MHz, MeOD)  $\delta$  214.70, 164.36, 148.79, 140.03, 136.12, 123.06, 62.85, 62.73, 47.77, 43.49, 38.65, 34.89, 33.45, 29.54, 29.15, 22.02.

**HRMS** (ESI)  $m/z$ : calculated for C<sub>16</sub>H<sub>22</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 260.1651, found 260.1657.

## Comparison of natural<sup>6</sup> and synthetic (+)-lycopoladine A

$\delta_H$ (ppm)		$\delta_C$ (ppm)	
Natural	Synthetic	Natural	Synthetic
(400 MHz, CD <sub>3</sub> OD)	(400 MHz, CD <sub>3</sub> OD)	(100 MHz, CD <sub>3</sub> OD)	(125 MHz, CD <sub>3</sub> OD)
8.30 (dd, 5.0, 1.4, 1H)	8.29 (dd, 5.0, 1.4, 1H)	214.6	214.70
7.67 (dd, 7.7, 1.4, 1H)	7.66 (dd, 7.7, 1.4, 1H)	164.3	164.36
7.24 (dd, 7.6, 5.1, 1H)	7.24 (dd, 7.6, 5.1, 1H)	148.8	148.79
3.53 (m, 2H)	3.56 – 3.49 (m, 2H)	140.0	140.03
3.09 (dd, 16.5, 8.2, 1H)	3.08 (dd, 16.2, 8.1, 1H)	136.1	136.12
2.97 (m, 1H)	3.00 – 2.92 (m, 1H)	123.0	123.06
2.83 (dd, 16.5, 9.1, 1H)	2.82 (dd, 16.2, 8.8, 1H)	62.8	62.85
2.29 (m, 2H)	2.29 (dd, 12.5, 5.2, 2H)	62.7	62.73
2.12 (m, 1H)	2.15 – 2.02 (m, 2H)	47.7	47.77
2.06 (ddd, 13.6, 13.6, 4.6, 1H)	from above	43.5	43.49
1.90 (m, 1H)	1.93 – 1.80 (m, 3H)	38.6	38.65
1.88 (m, 1H)	from above	34.8	34.89
1.83 (m, 1H)	from above	33.4	33.45
1.56 (m, 1H)	1.56 (m, 1H)	29.5	29.54
1.35 (m, 1H)	1.40 – 1.31 (m, 1H)	29.1	29.15
1.08 (d, 6.5, 3H)	1.08 (d, 6.5, 3H)	22.0	22.02

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