

Supporting Information for

Unified Total Synthesis of Five Gelsedine-type Alkaloids: (–)-Gelsenicine, (–)-Gelsedine, (–)-Gelsedilam, (–)-14-Hydroxygelsenicine, and (–)-14,15-Dihydroxygelsenicine

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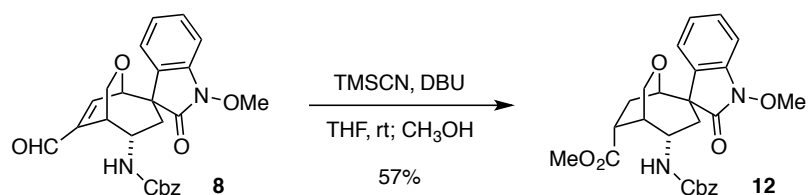
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General. All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Dehydrated tetrahydrofuran, dichloromethane and toluene were purchased from Kanto Chemicals Co., and were used after passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Dehydrated methanol, ethanol, pyridine and acetonitrile were purchased from Wako Pure Chemical Industries, Ltd. and stored over activated MS3A*. All other reagents were commercially available and used without further purification. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60F₂₅₄. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40-100 µm) purchased from Kanto Chemical Co., Inc. Preparative thin layer chromatography (PTLC) separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F₂₅₄. ¹H and ¹³C NMR were recorded on a JEOL ECS-400 spectrometer. All ¹H NMR spectra are reported in units, parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are indicated in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All ¹³C NMR spectra are reported in ppm relative to the central line of the triplet for CDCl₃ at 77.0 ppm. Infrared spectra (IR) were recorded on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrophotometer, and are reported in wavenumbers (cm⁻¹). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-T100LP AccuTOF LC-plus in positive electrospray ionization (ESI) method using PEG or sodium trifluoroacetate as the internal standard. Optical rotations were measured on a JASCO P-2200 Digital Polarimeter at room temperature, using the sodium D line. Melting points, determined on a Yanaco Micro Melting Point Apparatus, are uncorrected.

* Molecular sieves were “activated” in the following manner: A round-bottom flask containing molecular sieves was heated in a regular microwave for 1.5-2.0 minute and the flask was immediately evacuated. When cooled to room temperature, the flask was backfilled with argon. The above procedure was repeated three times.

Methyl (1*R*,2*S*,4*S*,5*S*,9*R*)-4-(((benzyloxy)carbonyl)amino)-1'-methoxy-2'-oxo-7-oxaspiro[bicyclo[3.2.2]nonane-2,3'-indoline]-9-carboxylate (12)



A 10-mL, screw cap glass test tube equipped with a magnetic stir bar was charged with **8** (5.1 mg, 0.011 mmol) and THF (300 μ L). The solution was added TMSCN (14.2 μ L, 0.114 mmol) and DBU (13.6 μ L, 0.0909 mmol) at room temperature and stirred at the same temperature for 30 min. The reaction mixture was added CH₃OH (46 μ L, 1.14 mmol) and the stirring was continued for additional 30 min. The reaction was quenched with sat. NaHCO₃ aq (1 mL) and the resulting mixture was partitioned between EtOAc (1 mL) and water (1 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (1 mL) three times. The combined organic phase was dried over MgSO₄ (ca. 1 g), filtered and concentrated *in vacuo* to give the mixture of the diastereomers (**12**:15-*epi*-**12** = 2.6:1). The residue was purified by preparative thin layer chromatography (*n*-hexane/EtOAc = 1/1) to afford **10** (3.1 mg, 6.5 μ mol, 57%) as white foam. [TH03065, TH05208]

R_f = 0.35 (*n*-hexane/EtOAc = 1/1, UV, Ce-PMA);

$[\alpha]_D^{23}$ -94.7 (c = 0.72, CHCl₃);

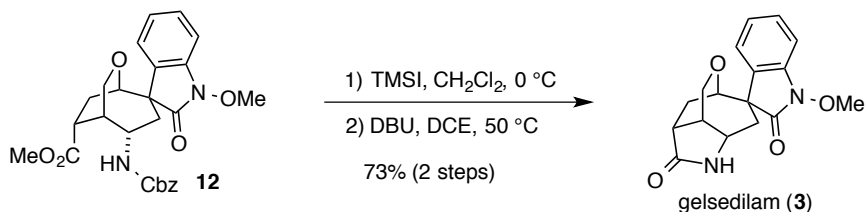
IR (film, cm⁻¹) 2944, 1717, 1507, 1232;

¹H NMR (CDCl₃, 400 MHz) δ 7.50 (d, J = 7.6 Hz, 1H), 7.40–7.27 (m, 6H), 7.12 (dd, J = 7.6, 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.22 (d, J = 8.7 Hz, 1H), 5.09 (d, J = 12.4 Hz, 1H), 5.02 (d, J = 12.4 Hz, 1H), 4.48 (ddd, J = 12.8, 8.7, 4.6 Hz, 1H), 4.13 (dd, J = 10.1, 2.1 Hz, 1H), 3.98 (s, 3H), 3.91 (dd, J = 10.1, 2.4 Hz, 1H), 3.78 (s, 3H), 3.67 (d, J = 6.4 Hz, 1H), 3.17 (dd, J = 15.6, 5.0 Hz, 1H), 2.98 (ddd, J = 12.8, 5.0, 5.0 Hz, 1H), 2.70 (br, 1H), 2.37 (ddd, J = 15.6, 12.8, 6.4 Hz, 1H), 2.13 (dd, J = 13.7, 12.8 Hz, 1H), 1.73 (dd, J = 13.7, 4.6 Hz, 1H);

¹³C NMR (CDCl₃, 100 MHz) δ 175.6 (C), 172.0 (C), 155.4 (C), 138.7 (C), 136.6 (C), 128.5 (CH), 128.4 (CH), 128.03 (C), 128.03 (CH), 127.9 (CH), 126.9 (CH), 123.3 (CH), 107.2 (CH), 71.2 (CH), 69.3 (CH₂), 66.5 (CH₂), 63.4 (CH₃), 53.3 (C), 53.0 (CH), 52.5 (CH₃), 40.2 (CH), 37.3 (CH), 34.5 (CH₂), 23.3 (CH₂);

HRMS (ESI) calcd for C₂₆H₂₈N₂NaO₇ ([M+Na]⁺) 503.1794, found 503.1776.

Gelsedilam (3)



A 10-mL, screw cap glass test tube equipped with a magnetic stir bar was charged with **12** (2.1 mg, 4.4 μ mol) and CH₂Cl₂ (300 μ L). The clear solution was stirred at 0 °C for 5 min, then freshly prepared trimethylsilyl iodide¹ (1.0 M solution in CH₂Cl₂, 43.7 μ L, 0.0437 mmol) was added and warmed to room temperature. After 20 min at room temperature, the reaction mixture was added NH₃ in CH₃OH (7.0 M solution, 6.2 μ L, 0.044 mmol) and the solution was concentrated *in vacuo*. The residue was dissolved in 1,2-dichloroethane (300 μ L), then DBU (9.8 μ L, 0.066 mmol) was added at room temperature. The solution was warmed to 50 °C and stirring was continued for 90 min. The reaction was quenched with sat. NH₄Cl aq (1 mL) and extracted with CHCl₃/CH₃OH = 9/1 (1 mL). The organic phase was collected and the aqueous phase was extracted with CHCl₃/CH₃OH = 9/1 (1 mL) three times. The combined organic phase was dried over MgSO₄ (ca. 1 g), filtered and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (CHCl₃/CH₃OH = 9/1) to afford gelsedilam (**3**) (1.0 mg, 3.2 μ mol, 73%) as white foam. [TH03050, TH05241, TH05242]

R_f = 0.40 (CHCl₃/CH₃OH = 9/1, UV, Ce-PMA);

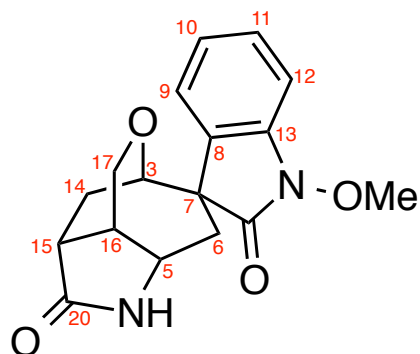
[α]_D²² -148 (*c* = 0.40, CHCl₃);

IR (film, cm⁻¹) 3319, 2925, 1716, 1681, 1616, 1465, 1043;

¹H NMR (CDCl₃, 400 MHz) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.28 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H), 7.09 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 5.68 (brs, 1H), 4.24 (brd, *J* = 2.3 Hz, 2H), 4.12 (m, 1H), 3.96 (s, 3H), 3.80 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.86 (brt, *J* = 8.2 Hz, 1H), 2.65 (dd, *J* = 10.5, 8.2 Hz, 1H), 2.52 (brd, *J* = 15.3 Hz, 1H), 2.34 (dd, *J* = 15.6, 4.1 Hz, 1H), 2.33 (ddd, *J* = 15.3, 10.5, 5.0 Hz, 1H), 2.02 (dd, *J* = 15.6, 2.3 Hz, 1H);

¹³C NMR (CDCl₃, 100 MHz) δ 180.0, 171.6, 138.4, 131.4, 128.2, 124.3, 123.3, 106.9, 74.8, 63.4, 62.0, 56.6, 55.8, 36.6, 36.4, 35.7, 27.0;

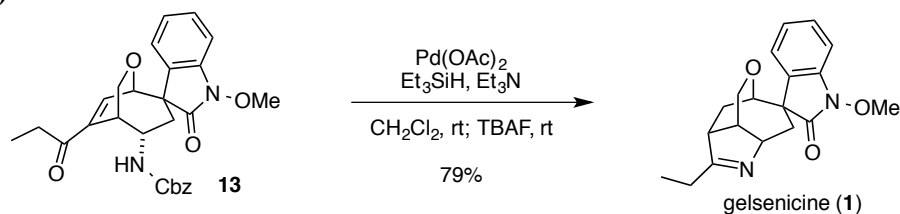
HRMS (ESI) calcd for C₁₇H₁₈N₂NaO₄ ([M+Na]⁺) 337.1164, found 337.1163.



¹H and ¹³C NMR Data for Gelsedilam (**3**)

	Reference (Natural)		This Synthesis	
	δ_{H} (400 Hz) ²	δ_{C} (125 Hz) ²	δ_{H} (400 Hz)	δ_{C} (100 Hz)
2		171.6		171.6
3	3.80 (dd, J = 4.8, 2.0 Hz, 1H)	74.8	3.80 (dd, J = 5.0, 1.4 Hz, 1H)	74.8
5	4.12 (m, 1H)	56.5	4.12 (m, 1H)	56.6
6	2.35 (dd, J = 15.6, 3.9 Hz, 1H) 2.03 (dd, J = 15.6, 2.4 Hz, 1H)	36.6	2.34 (dd, J = 15.6, 4.1 Hz, 1H) 2.02 (dd, J = 15.6, 2.3 Hz, 1H)	36.4
7		55.8		55.8
8		131.3		131.4
9	7.48 (d, J = 7.6 Hz, 1H)	124.4	7.48 (d, J = 7.8 Hz, 1H)	124.3
10	7.08 (t, J = 7.6 Hz, 1H)	123.4	7.09 (ddd, J = 7.8, 7.8, 1.4 Hz, 1H)	123.3
11	7.28 (t, J = 7.6 Hz, 1H)	128.4	7.28 (ddd, J = 7.8, 7.8, 1.4 Hz, 1H)	128.2
12	6.91 (d, J = 7.6 Hz, 1H)	107.0	6.92 (d, J = 7.8 Hz, 1H)	106.9
13		138.4		138.4
14	2.53 (brd, J = 15.4 Hz, 1H) 2.31 (m, 1H)	27.1	2.52 (brd, J = 15.3 Hz, 1H) 2.33 (ddd, J = 15.3, 10.5, 5.0 Hz, 1H)	27.0
15	2.65 (dd, J = 9.0, 8.2 Hz, 1H)	36.7	2.65 (dd, J = 10.5, 8.2 Hz, 1H)	36.6
16	2.86 (brt, J = 8.2 Hz, 1H)	35.6	2.86 (brt, J = 8.2 Hz, 1H)	35.7
17	4.24 (m, 2H)	62.0	4.24 (brd, J = 2.3 Hz, 2H)	62.0
20		179.8		180.0
<i>N</i> _a -OMe	3.95 (s, 3H)	63.6	3.96 (s, 3H)	63.4
<i>N</i> _b -H	5.77 (brs, 1H)		5.68 (brs, 1H)	

Gelsenicine (1)



A 10-mL, screw cap glass test tube equipped with a magnetic stir bar was charged with **13** (4.6 mg, 9.7 μmol), $\text{Pd}(\text{OAc})_2$ (2.2 mg, 9.7 μmol), Et_3N (4.0 μL , 0.029 mmol), and CH_2Cl_2 (300 μL). The clear solution was stirred at room temperature for 5 min, then Et_3SiH (15.4 μL , 0.0965 mmol) was added. After stirring for 30 min at the same temperature, the reaction mixture was added TBAF (1.0 M solution in THF, 9.7 μL , 9.7 μmol) and stirring was continued for additional 30 min at room temperature. The reaction was quenched with sat. NaHCO_3 aq (1 mL) and extracted with $\text{CHCl}_3/\text{CH}_3\text{OH} = 9/1$ (1 mL). The organic phase was collected and the aqueous phase was extracted with $\text{CHCl}_3/\text{CH}_3\text{OH} = 9/1$ (1 mL) three times. The combined organic phase was dried over MgSO_4 (ca. 1 g), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH} = 100/1$ to 25/1) to afford gelsenicine (**1**) (2.5 mg, 7.7 μmol , 79%) as white solid. [TH03066, TH05226]

$R_f = 0.37$ ($\text{CHCl}_3/\text{CH}_3\text{OH} = 9/1$, UV, Ce-PMA);

Mp 167.5–169.5 $^\circ\text{C}$;

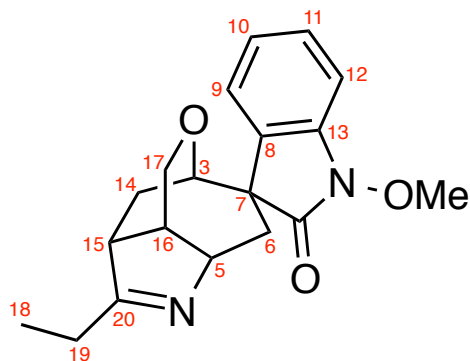
$[\alpha]_D^{23} -147$ ($c = 0.45$, CHCl_3);

IR (film, cm^{-1}) 2965, 1726, 1465;

^1H NMR (CDCl_3 , 400 MHz) δ 7.54 (d, $J = 7.3$ Hz, 1H), 7.26 (ddd, $J = 7.8, 7.8, 1.4$ Hz, 1H), 7.07 (ddd, $J = 7.8, 7.3, 0.9$ Hz, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 4.41 (m, 1H), 4.30 (dd, $J = 11.0, 2.8$ Hz, 1H), 4.27 (dd, $J = 11.0, 1.8$ Hz, 1H), 3.95 (s, 3H), 3.73 (dd, $J = 4.4, 1.8$ Hz, 1H), 2.86 (dd, $J = 9.2, 9.2$ Hz, 1H), 2.72 (dq, $J = 17.4, 7.3$ Hz, 1H), 2.57 (m, 1H), 2.40 (dq, $J = 17.4, 7.3$ Hz, 1H), 2.40 (dd, $J = 15.6, 4.6$ Hz, 1H), 2.37 (dd, $J = 15.2, 1.8$ Hz, 1H), 2.29 (dd, $J = 15.6, 2.3$ Hz, 1H), 2.14 (ddd, $J = 15.2, 9.6, 4.4$ Hz, 1H), 1.29 (t, $J = 7.3$ Hz, 3H);

^{13}C NMR (CDCl_3 , 100 MHz) δ 184.3, 171.2, 138.0, 132.2, 128.0, 124.6, 123.3, 106.5, 74.9, 72.5, 63.3, 62.1, 55.8, 42.5, 39.8, 37.7, 27.0, 25.6, 10.0;

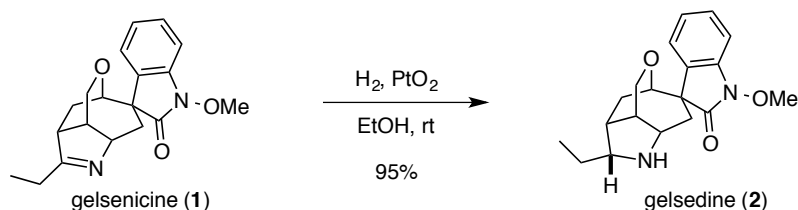
HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{NaO}_3$ ($[\text{M}+\text{Na}]^+$) 349.1528, found 349.1534.



¹H and ¹³C NMR Data for Gelsenicine (**1**)

	Reference (Semisynthesis)		This Synthesis	
	δ_{H} (500 Hz) ³	δ_{C} (125 Hz) ⁴	δ_{H} (400 Hz)	δ_{C} (100 Hz)
2		171.2		171.2
3	3.74 (dd, $J = 4.7, 2.0$ Hz, 1H)	74.8	3.73 (dd, $J = 4.4, 1.8$ Hz, 1H)	74.9
5	4.40 (m, 1H)	72.5	4.41 (m, 1H)	72.5
6	2.40 (dd, $J = 15.6, 5.0$ Hz, 1H)	37.7	2.40 (dd, $J = 15.6, 4.6$ Hz, 1H)	37.7
	2.29 (dd, $J = 15.6, 2.2$ Hz, 1H)		2.29 (dd, $J = 15.6, 2.3$ Hz, 1H)	
7		55.8		55.8
8		132.2		132.2
9	7.53 (d, $J = 7.0$ Hz, 1H)	124.6	7.54 (d, $J = 7.3$ Hz, 1H)	124.6
10	7.07 (td, $J = 7.6, 1.0$ Hz, 1H)	123.3	7.07 (ddd, $J = 7.8, 7.3, 0.9$ Hz, 1H)	123.3
11	7.25 (td, $J = 7.5, 1.3$ Hz, 1H)	128.0	7.26 (ddd, $J = 7.8, 7.8, 1.4$ Hz, 1H)	128.0
12	6.87 (d, $J = 7.9$ Hz, 1H)	106.5	6.88 (d, $J = 7.8$ Hz, 1H)	106.5
13		138.0		138.0
14	2.39 (dd, $J = 14.9, 2.2$ Hz, 1H)	27.0	2.37 (dd, $J = 15.2, 1.8$ Hz, 1H)	27.0
	2.13 (ddd, $J = 14.9, 10.3, 4.6$ Hz, 1H)		2.14 (ddd, $J = 15.2, 9.6, 4.4$ Hz, 1H)	
15	2.86 (t, $J = 9.3$ Hz, 1H)	42.5	2.86 (dd, $J = 9.2, 9.2$ Hz, 1H)	42.5
16	2.57 (m, 1H)	39.8	2.57 (m, 1H)	39.8
17	4.30 (dd, $J = 11.0, 3.9$ Hz, 1H)	62.1	4.30 (dd, $J = 11.0, 2.8$ Hz, 1H)	62.1
	4.27 (dd, $J = 11.0, 1.7$ Hz, 1H)		4.27 (dd, $J = 11.0, 1.8$ Hz, 1H)	
18	1.29 (t, $J = 7.3$ Hz, 3H)	10.0	1.29 (t, $J = 7.3$ Hz, 3H)	10.0
19	2.71 (dq, $J = 17.1, 7.3$ Hz, 1H)	25.6	2.72 (dq, $J = 17.4, 7.3$ Hz, 1H)	25.6
	2.41 (dq, $J = 17.1, 7.3$ Hz, 1H)		2.40 (dq, $J = 17.4, 7.3$ Hz, 1H)	
20		184.2		184.3
<i>N</i> _a -OMe	3.95 (s, 3H)	63.3	3.95 (s, 3H)	63.3

Gelsedine (2)



A 10-mL, glass test tube with ground joint equipped with a three way cock and a magnetic stir bar was charged with gelsenicine (**1**) (4.5 mg, 0.014 mmol) and platinum oxide (3.2 mg, 0.014 mmol) in EtOH (300 μ L). The suspension was stirred under H₂ atmosphere (balloon, 1 atm) at room temperature. After 7 h, the resulting solution was filtered through Celite and washed with EtOAc (5 mL), concentrated *in vacuo* to afford the crude product. The residue was purified with preparative thin layer chromatography (CHCl₃/CH₃OH = 3/1) to afford gelsedine (**2**) (4.3 mg, 0.013 mmol, 95%) as a white film. [TH03068]

R_f = 0.08 (CHCl₃/CH₃OH = 9/1, UV, Ce-PMA);

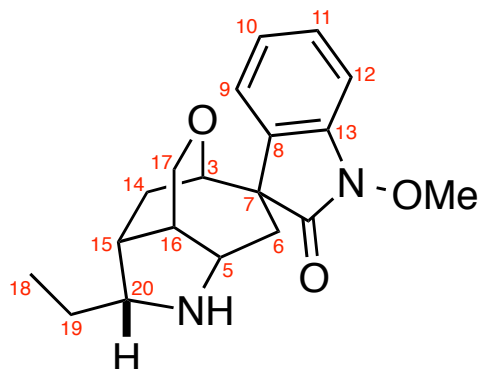
[α]_D²³ -124 (*c* = 0.29, CHCl₃);

IR (film, cm⁻¹) 3308, 2925, 1706, 1617, 1464, 1436, 1323, 1220, 1042;

¹H NMR (CDCl₃, 400 MHz) δ 7.40 (d, *J* = 7.4 Hz, 1H), 7.29 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.12 (dd, *J* = 7.7, 7.4 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 4.33 (dd, *J* = 11.0, 4.1 Hz, 1H), 4.25 (d, *J* = 11.0 Hz, 1H), 4.00 (s, 3H), 3.73 (m, 1H), 3.50 (d, *J* = 6.9 Hz, 1H), 2.99 (m, 1H), 2.49 (m, 1H), 2.20 (m, 1H), 2.17 (m, 1H), 2.13 (dd, *J* = 16.0, 3.7 Hz, 1H), 2.02 (dd, *J* = 16.0, 2.8 Hz, 1H), 1.92 (ddd, *J* = 16.0, 11.4, 6.9 Hz, 1H), 1.83 (m, 1H), 1.75 (m, 1H), 1.01 (t, *J* = 7.4 Hz, 3H);

¹³C NMR (CDCl₃, 100 MHz) δ 174.5, 137.9, 131.6, 128.2, 125.3, 123.7, 107.1, 74.5, 65.4, 63.8, 63.4, 59.6, 57.3, 41.6, 34.5, 33.7, 21.4, 21.2, 12.0;

HRMS (ESI) calcd for C₁₉H₂₂N₂NaO₃ ([M+Na]⁺) 329.1865, found 329.1871.

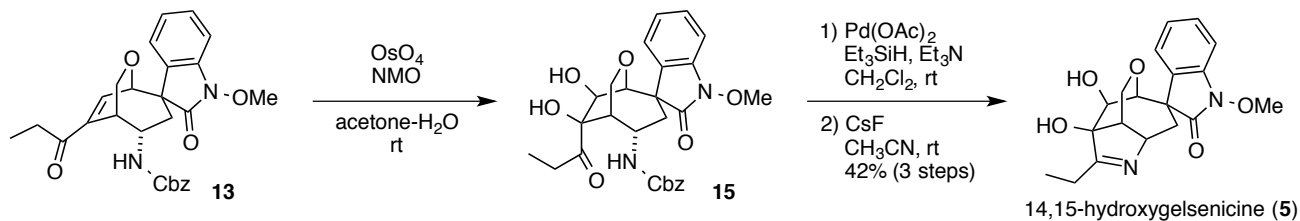


¹H and ¹³C NMR Data for Gelsedine (**2**)

	Reference (Semisynthesis)		This Synthesis	
	δ_{H} (500 Hz) ³	δ_{C} (125 Hz) ³	δ_{H} (400 Hz)	δ_{C} (100 Hz)
2		174.4		174.5
3	3.68 (d, $J = 7.1$ Hz, 1H)	74.5	3.50 (d, $J = 6.9$ Hz, 1H)	74.5
5	3.68 (m, 1H)	59.7	3.73 (m, 1H)	59.6
6	2.12 (dd, $J = 15.8, 3.6$ Hz, 1H)	33.8	2.13 (dd, $J = 16.0, 3.7$ Hz, 1H)	33.7
	2.02 (dd, $J = 15.8, 3.0$ Hz, 1H)		2.02 (dd, $J = 16.0, 2.8$ Hz, 1H)	
7		57.3		57.3
8		131.7		131.6
9	7.40 (dd, $J = 7.7, 0.7$ Hz, 1H)	125.3	7.40 (d, $J = 7.4$ Hz, 1H)	125.3
10	7.13 (td, $J = 7.6, 1.0$ Hz, 1H)	123.6	7.12 (dd, $J = 7.7, 7.4$ Hz, 1H)	123.7
11	7.29 (td, $J = 7.7, 1.2$ Hz, 1H)	128.1	7.29 (dd, $J = 7.7, 7.7$ Hz, 1H)	128.2
12	6.95 (brd, $J = 7.7$ Hz, 1H)	107.1	6.95 (d, $J = 7.7$ Hz, 1H)	107.1
13		137.9		137.9
14	2.19 (dd, $J = 15.4, 4.1$ Hz, 1H)	21.2 [†]	2.20 (m, 1H)	21.2
	1.91 (ddd, $J = 15.1, 10.3, 7.1$ Hz, 1H)		1.92 (ddd, $J = 16.0, 11.4, 6.9$ Hz, 1H)	
15	2.16 (m, 1H)	34.6	2.17 (m, 1H)	23.5
16	2.48 (m, 1H)	41.7	2.49 (m, 1H)	41.6
17	4.34 (dd, $J = 10.7, 4.1$ Hz, 1H)	63.8	4.33 (dd, $J = 11.0, 4.1$ Hz, 1H)	63.8
	4.26 (d, $J = 10.8$ Hz, 1H)		4.25 (d, $J = 11.0$ Hz, 1H)	
18	1.01 (t, $J = 7.5$ Hz, 3H)	12.0	1.01 (t, $J = 7.4$ Hz, 3H)	12.0
19	1.83 (m, 1H)	21.4 [†]	1.83 (m, 1H)	21.4
	1.71 (m, 1H)		1.75 (m, 1H)	
20	2.96 (m, 1H)	65.5	2.99 (m, 1H)	65.4
<i>N</i> _a -OMe	4.00 (s, 3H)	63.3	4.00 (s, 3H)	63.4

[†]Assignments may be interchanged.

14,15-Dihydroxygelsenicine (5)



A 10-mL, screw cap glass test tube equipped with a magnetic stir bar was charged with **13** (10.7 mg, 0.0225 mmol), acetone (250 μL), and water (150 μL). The clear solution was stirred at room temperature, then OsO_4 (0.04 M solution in *t*-BuOH, 56.1 μL , 2.25 μmol) and *N*-methylmorpholine *N*-oxide (13.2 mg, 0.113 mmol) was sequentially added. After stirring for 30 min at the same temperature, the reaction mixture was added sat. $\text{Na}_2\text{S}_2\text{O}_3$ aq (1 mL), sat. NaHCO_3 aq (1 mL), and EtOAc (1 mL). After phases were partitioned, organic phase was collected and the aqueous phase was extracted with $\text{CHCl}_3/\text{CH}_3\text{OH} = 9/1$ (1 mL) three times. The combined organic phase was dried over MgSO_4 (ca. 1 g), filtered and concentrated *in vacuo* to give the crude **15**. A 10-mL, screw cap glass test tube equipped with a magnetic stir bar was charged with the residue, $\text{Pd}(\text{OAc})_2$ (5.0 mg, 0.022 mmol), Et_3N (9.4 μL , 0.067 mmol), and CH_2Cl_2 (300 μL). The clear solution was stirred at room temperature and Et_3SiH (35.9 μL , 0.225 mmol) was added. After stirring for 10 min at the same temperature, the reaction was quenched with sat. NaHCO_3 aq (1 mL) and extracted with EtOAc (1 mL). The organic phase was collected and the aqueous phase was extracted with $\text{CHCl}_3/\text{CH}_3\text{OH} = 9/1$ (1 mL) five times. The combined organic phase was dried over MgSO_4 (ca. 1 g), filtered and concentrated *in vacuo*. A 10-mL, screw cap glass test tube equipped with a magnetic stir bar was charged with the residue and CH_3CN (300 μL). The solution was stirred at room temperature for 5 min, and cesium fluoride (6.8 mg, 0.045 mmol) was added. After stirring for 10 min at the same temperature, the reaction was quenched with sat. NH_4Cl aq (1 mL) and extracted with $\text{CHCl}_3/\text{CH}_3\text{OH} = 9/1$ (1 mL). The organic phase was collected and the aqueous phase was extracted with $\text{CHCl}_3/\text{MeOH} = 9/1$ (500 μL) ten times. The combined organic phase was dried over MgSO_4 (ca. 1 g), filtered and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography ($\text{CHCl}_3/\text{CH}_3\text{OH} = 3/1$) to afford 14,15-dihydroxygelsenicine (**5**) (3.4 mg, 9.5 μmol , 42% for 3 steps) as pale yellow foam. [TH05236, TH05238, TH05239]

$R_f = 0.36$ ($\text{CHCl}_3/\text{CH}_3\text{OH} = 9/1$, UV, Ce-PMA);

$[\alpha]_D^{23} -99.4$ ($c = 0.17$, CHCl_3);

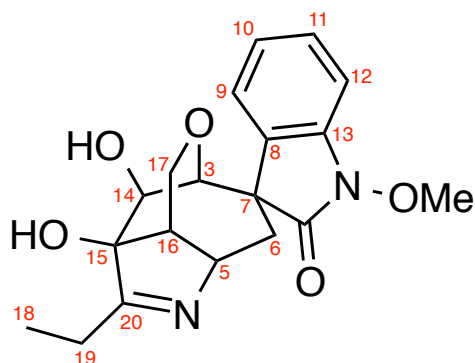
IR (film, cm^{-1}); 2920, 2360, 2340, 1718, 1651, 1617, 1466, 1321;

^1H NMR (CDCl_3 , 400 MHz) δ 7.50 (d, $J = 7.8$ Hz, 1H), 7.30 (ddd, $J = 7.8, 7.8, 0.9$ Hz, 1H), 7.11 (ddd, $J = 7.8, 7.8, 0.9$ Hz, 1H), 6.91 (d, $J = 7.8$ Hz, 1H), 4.47 (m, 1H), 4.33 (m, 1H), 4.32 (dd, $J = 11.0, 3.7$ Hz, 1H), 4.26 (d, $J = 11.0$ Hz, 1H), 3.94 (s, 3H), 3.85 (d, $J = 2.3$ Hz, 1H), 2.58 (m, 2H), 2.40 (dd, $J = 15.6, 4.1$ Hz, 1H), 2.40 (m, 1H), 2.34 (dd, $J = 15.6, 2.3$ Hz, 1H), 1.32 (t, $J = 7.3$ Hz,

3H);

^{13}C NMR (CDCl_3 , 100 MHz) δ 183.7, 170.6, 138.1, 131.3, 128.6, 124.6, 123.7, 107.0, 78.9, 77.2, 69.4, 66.4, 63.5, 60.6, 53.5, 46.3, 36.1, 21.9, 9.6;

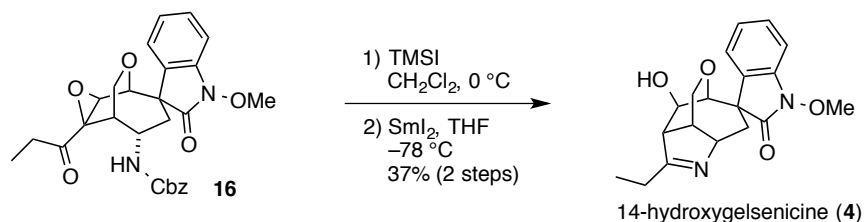
HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{NaO}_5$ ($[\text{M}+\text{Na}]^+$) 381.1426, found 381.1426.



^1H and ^{13}C NMR Data for 14,15-Dihydroxygelsenicine (**5**)

	Reference (Natural)		This Synthesis	
	δ_{H} (500 Hz) ⁵	δ_{C} (125 Hz) ⁵	δ_{H} (400 Hz)	δ_{C} (100 Hz)
2		170.6		170.6
3	3.82 (d, $J = 2.1$ Hz, 1H)	77.2	3.85 (d, $J = 2.3$ Hz, 1H)	77.2
5	4.44 (m, 1H)	69.2	4.47 (m, 1H)	69.4
6	2.38 (dd, $J = 15.6, 4.6$ Hz, 1H) 2.28 (dd, $J = 15.6, 2.4$ Hz, 1H)	36.1	2.40 (dd, $J = 15.6, 4.1$ Hz, 1H) 2.34 (dd, $J = 15.6, 2.3$ Hz, 1H)	36.1
7		53.6		53.5
8		131.3		131.3
9	7.49 (d, $J = 7.6$ Hz, 1H)	124.6	7.50 (d, $J = 7.8$ Hz, 1H)	124.6
10	7.08 (td, $J = 7.6, 0.9$ Hz, 1H)	123.6	7.11 (ddd, $J = 7.8, 7.8, 0.9$ Hz, 1H)	123.7
11	7.28 (td, $J = 7.6, 0.9$ Hz, 1H)	128.5	7.30 (ddd, $J = 7.8, 7.8, 0.9$ Hz, 1H)	128.6
12	6.88 (d, $J = 7.6$ Hz, 1H)	106.9	6.91 (d, $J = 7.8$ Hz, 1H)	107.0
13		138.0		138.1
14	4.31 (d, $J = 2.1$ Hz, 1H)	66.0	4.33 (m, 1H)	66.4
15		78.8		78.9
16	2.38 (overlapped)	46.3	2.40 (m, 1H)	46.3
17	4.31 (dd, $J = 11.0, 3.5$ Hz, 1H) 4.22 (brd, $J = 11.0$ Hz, 1H)	60.5	4.32 (dd, $J = 11.0, 3.7$ Hz, 1H) 4.26 (d, $J = 11.0$ Hz, 1H)	60.6
18	1.28 (t, $J = 7.3$ Hz, 3H)	9.6	1.32 (t, $J = 7.3$ Hz, 3H)	9.6
19	2.54 (m, 2H)	22.0	2.58 (m, 2H)	21.9
20		184.0		183.7
N_{a} -OMe	3.91 (s, 3H)	63.4	3.94 (s, 3H)	63.5

14-Hydroxygelsenicine (4)



A 10-mL, screw cap glass test tube equipped with a magnetic stir bar was charged with **16** (10.2 mg, 0.0213 mmol) and CH_2Cl_2 (250 μL). The clear solution was stirred at 0 $^\circ\text{C}$ for 5 min and freshly prepared trimethylsilyl iodide¹ (1 M solution in CH_2Cl_2 , 85 μL , 0.085 mmol) was added. After stirring for 1.5 h at 0 $^\circ\text{C}$, the reaction mixture was quenched with sat. NaHCO_3 aq (15 μL) and sat. NaHSO_3 aq (15 μL). The mixture was acidified with 3 N HCl aq (100 μL) to pH = 2. The mixture was extracted with *n*-hexane/ EtOAc = 3/1 (2 mL) and the organic phase was discarded. The aqueous phase was then basified with 5 N NaOH aq (65 μL) to pH = 8, and extracted with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ = 5/1 (1 mL) seven times. The combined organic extract was dried over MgSO_4 (ca. 1 g), filtered and concentrated *in vacuo* to give the crude amine. A 10-mL, glass test tube with ground joint equipped with a three way cock and a magnetic stir bar was charged with the residue and THF (500 μL). The clear solution was stirred at -78°C for 10 min and samarium iodide (0.1 M solution in THF, 530 μL , 0.0530 mmol) was added. After stirring for 10 min at -78°C , CH_3OH (100 μL) was added. Stirring was continued for additional 10 min, then the reaction was quenched with opening the flask and addition of brine (1 mL). The reaction mixture was extracted with EtOAc (1 mL). The organic phase was collected and the aqueous phase was extracted with $\text{CHCl}_3/\text{CH}_3\text{OH}$ = 9/1 (1 mL) three times. The combined organic phase was dried over MgSO_4 (ca. 1 g), filtered and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography ($\text{EtOAc}/\text{CH}_3\text{OH}$ = 9/1) to afford 14-hydroxygelsenicine (**4**) (2.7 mg, 7.9 μmol , 37% for 2 steps) as a colorless oil. [TH03057, TH03060]

R_f = 0.43 ($\text{CHCl}_3/\text{CH}_3\text{OH}$ = 9/1, UV, Ce-PMA);

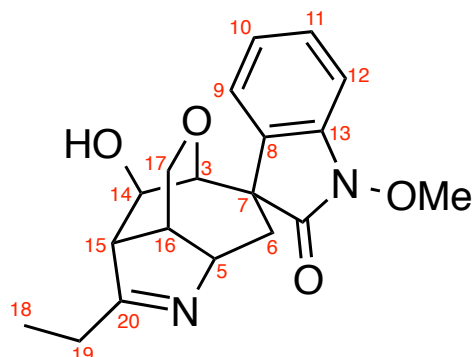
$[\alpha]_D^{23}$ -143 (c = 0.21, CHCl_3);

IR (neat, cm^{-1}) 3273, 2935, 2916, 1718, 1646, 1616, 1465, 1040;

^1H NMR (CDCl_3 , 400 MHz) δ 7.52 (d, J = 7.6 Hz, 1H), 7.28 (dd, J = 7.6, 7.6 Hz, 1H), 7.09 (dd, J = 7.6, 7.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 4.46 (m, 1H), 4.45 (dd, J = 11.0, 3.2 Hz, 1H), 4.42 (m, 1H), 4.34 (d, J = 11.0 Hz, 1H), 3.95 (s, 3H), 3.69 (s, 1H), 2.90 (d, J = 8.2 Hz, 1H), 2.78 (dq, J = 17.0, 7.3 Hz, 1H), 2.61 (ddd, J = 8.2, 8.2, 3.2 Hz, 1H), 2.50 (dq, J = 17.0, 7.3 Hz, 1H), 2.43 (dd, J = 15.6, 4.6 Hz, 1H), 2.32 (dd, J = 15.6, 2.3 Hz, 1H), 1.31 (t, J = 7.3 Hz, 3H);

^{13}C NMR (CDCl_3 , 100 MHz) δ 181.1, 170.9, 138.0, 131.6, 128.3, 124.6, 123.6, 106.8, 79.2, 71.9, 66.5, 63.4, 61.8, 53.7, 52.2, 38.3, 37.5, 26.0, 10.0;

HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{NaO}_4$ ($[\text{M}+\text{Na}]^+$) 365.1477, found 365.1472.



¹H and ¹³C NMR Data for 14-Hydroxygelsenicine (4)

	Reference (Natural)		This Synthesis	
	δ_{H} (500 Hz) ⁶	δ_{C} (125 Hz) ⁶	δ_{H} (400 Hz)	δ_{C} (100 Hz)
2		170.9		170.9
3	3.68 (brs, 1H)	79.2	3.69 (s, 1H)	79.2
5	4.41 (m, 1H)	71.9	4.42 (m, 1H)	71.9
6	2.42 (dd, $J = 15.6, 4.6$ Hz, 1H)	37.5	2.43 (dd, $J = 15.6, 4.6$ Hz, 1H)	37.5
	2.31 (dd, $J = 15.6, 2.1$ Hz, 1H)		2.32 (dd, $J = 15.6, 2.3$ Hz, 1H)	
7		53.7		53.7
8		131.6		131.6
9	7.51 (d, $J = 7.6$ Hz, 1H)	124.6	7.52 (d, $J = 7.6$ Hz, 1H)	124.6
10	7.09 (brt, $J = 7.6$ Hz, 1H)	123.5	7.09 (dd, $J = 7.6, 7.6$ Hz, 1H)	123.6
11	7.27 (brt, $J = 7.6$ Hz, 1H)	128.3	7.28 (dd, $J = 7.6, 7.6$ Hz, 1H)	128.3
12	6.89 (d, $J = 7.6$ Hz, 1H)	106.8	6.89 (d, $J = 7.6$ Hz, 1H)	106.8
13		138.0		138.0
14	4.44 (overlapped)	66.4	4.46 (m, 1H)	66.5
15	2.89 (d, $J = 8.5$ Hz, 1H)	52.2	2.90 (d, $J = 8.2$ Hz, 1H)	52.2
16	2.59 (td, $J = 8.5, 3.3$ Hz, 1H)	38.3	2.61 (ddd, $J = 8.2, 8.2, 3.2$ Hz, 1H)	38.3
17	4.44 (overlapped)	61.8	4.45 (dd, $J = 11.0, 3.2$ Hz, 1H)	61.8
	4.33 (d, $J = 11.0$ Hz, 1H)		4.34 (d, $J = 11.0$ Hz, 1H)	
18	1.30 (t, $J = 7.3$ Hz, 3H)	10.0	1.31 (t, $J = 7.3$ Hz, 3H)	10.0
19	2.77 (dq, $J = 17.1, 7.3$ Hz, 1H)	26.0	2.78 (dq, $J = 17.0, 7.3$ Hz, 1H)	26.0
	2.49 (dq, $J = 17.1, 7.3$ Hz, 1H)		2.50 (dq, $J = 17.0, 7.3$ Hz, 1H)	
20		181.1		181.1
<i>N</i> _a -OMe	3.94 (s, 3H)	63.4	3.95 (s, 3H)	63.4

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