Supporting Information (I)

The Total Synthesis of Absinthin

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Part 1. ^{13}C and ^{1}H NMR Spectroscopic Data of Absinthin (PDF)

For comparison, both literature-reported[1] and our ^{13}C and ^{1}H NMR spectroscopic data of absinthin (**1**) were listed in Table S1.

Table S1. A List of ^{13}C and ^{1}H NMR Data for Absinthin

Position	^{13}C (Lit.[1])		^{13}C (Current)		^{1}H (Lit.[1])		^{1}H (Current)	
1, 1’	71.3	57.0	71.3	57.0	2.16	2.29	2.16	2.20
2, 2’	45.6	46.5	45.6	46.6	2.86	2.84	2.83	2.81
3, 3’	122.4	58.8	122.1	58.8	5.50	3.21	5.55	3.20
4, 4’	146.6	135.4	147.3	134.9	--	--	--	--
5, 5’	64.0	147.8	64.0	148.2	--	--	--	--
6, 6’	82.7	81.5	82.6	81.4	4.70	4.60	4.71	4.60
7, 7’	46.3	49.2	46.4	49.3	1.80	1.64	1.78	1.67
8, 8’	27.5	23.6	27.4	23.5	1.80	1.60	1.84	1.76
9, 9’	43.6	42.4	43.6	42.4	1.80	1.60	1.85	1.76
10, 10’	73.9	71.6	74.0	71.9	--	--	--	--
11, 11’	42.2	42.0	42.2	42.0	2.30	2.30	2.27	2.24
12, 12’	179.3	179.8	178.5	178.8	--	--	--	--
13, 13’	13.0	12.1	13.0	12.1	1.25	1.21	1.25	1.20
14, 14’	29.4	32.2	29.3	32.2	1.20	1.31	1.22	1.30
15, 15’	13.6	18.3	13.7	18.3	1.78	1.90	1.78	1.92

Part 2. Experimental Procedures and Analytical Data (PDF)

Experimental Section

General Methods. Melting points are uncorrected. All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. NMR

spectra were recorded in $CDCl_3$ or pyridine-d_5 (^{1}H at 300 MHz and ^{13}C at 75 MHz) using TMS as the internal standard. Analytical samples were obtained by chromatography on silica gel using an EtOAc/hexane mixture as the eluent. Anhydrous solvents and reagents were obtained as follows: dichloromethane was distilled over calcium hydride under N_2; THF, ether and benzene were distilled over sodium benzophenone ketyl under N_2.

***O*-Acetylisophotosantonic lactone (4).** A solution of α-santonin (5.00 g, 21.0 mmol) in glacial AcOH (400 mL) placed in a water-cooled quartz immersion well apparatus (Figure S1) was photolyzed at 16 °C under a nitrogen atmosphere with a high press Hg lamp (150 W) for 7 hours. After the AcOH was evaporated under reduced pressure, the resulting oil was dissolved in hot MeOH (20 mL) and then left in a freezer (–20 °C) overnight. Suction filtration afforded **4** (2.40 g, 38.6%) as a colorless solid: mp 175-178 °C; $[\alpha]^{20}_D$ +46.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H, CH_3), 1.30 (d, *J* = 6.7 Hz, 3H, CH_3), 1.40-1.53 (m, 1H), 1.91 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.03-2.62 (m, 7H), 4.13-4.21 (m, 1H, CH, C1), 4.82 (d, *J* = 10.0 Hz, 1H, CH, C6).

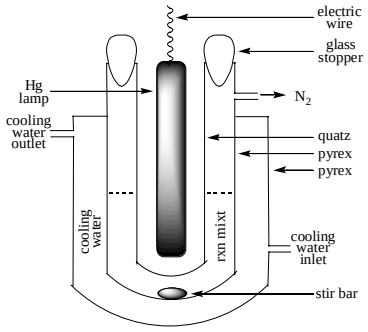

Figure S1. The photochemical reactor used for preparing **4**

Compound 8. To a solution of **4** (1.56 g, 5.09 mmol) in MeOH (45 mL) was added $NaBH_4$ (203 mg, 5.37 mmol) in several portions. The reaction mixture was stirred at room temperature for 30 min and then saturated aqueous $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2/*i*-PrOH (3:1) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give **8** (1.55 g, 99%). For the major isomer (3α-OH): ^{1}H NMR (300 MHz, $CDCl_3$)δ1.17 (s, 3H, CH_3), 1.20 (d, *J* = 7.2 Hz, 3H, CH_3), 1.32-1.44 (m, 1H), 1.49-1.61 (m, 1H), 1.86 (s, 3H, CH_3), 1.91-2.04 (m, 2H), 1.96 (s, 3H, CH_3CO), 2.08-2.27 (m, 2H), 2.30-2.49 (m, 2H), 3.68-3.79 (m, 1H, CH, C1), 4.48-4.57 (m, 1H, CH, C3), 4.66 (d, *J* = 10.8 Hz, 1H, CH, C6).

Compound 9. A solution of **8** (1.18 g, 3.83 mmol) and *o*–nitrophenyl selenocyanate (1.13 g, 4.98 mmol) in dry THF (50 mL) was treated dropwise with tri-*n*-butylphosphine (1.3 mL, 5.22 mmol) at room temperature under nitrogen. After the reaction mixture was stirred for 1 h, the solvent was removed in vacuo. Chromatography of the residue on silica gel using EtOAc/hexane (1:3) gave **9** (1.36 g, 72%) as yellow crystals. For the major isomer: mp (EtOAc) 214-216 °C; $[\alpha]^{20}_D$ -10.2 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.3 Hz, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.35-1.50 (m, 1H), 1.57-1.62 (m, 1H), 1.93 (s, 3H, CH_3), 1.94-2.03 (m, 2H), 2.05 (s, 3H, CH_3CO), 2.16-2.32 (m, 2H), 2.33-2.43 (m, 1H), 2.50-2.63 (m, 1H), 3.87-3.99 (m, 1H, CH, C1), 4.33 (d, *J* = 6.6 Hz, 1H, CH, C3), 4.67 (d, *J* = 10.5 Hz, 1H, CH, C6), 7.31-7.40 (m, 1H, CH), 7.49-7.65 (m, 2H, 2CH), 8.30 (d, *J* = 8.4 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ12.3, 15.5, 19.7, 22.3, 25.3, 34.1, 38.2, 41.2, 49.0, 52.0, 54.2, 81.5, 86.0, 125.6, 126.4, 129.8, 133.4, 134.1,

134.3, 140.4, 147.3, 170.0, 177.7. Anal. Calcd for $C_{23}H_{27}NO_6Se$: C, 56.10; H, 5.53; N, 2.84. Found: C, 56.07; H, 5.10; N, 2.68.

Compound 5. Compound **9** (18 mg, 0.036 mmol) was dissolved in MeOH (4 mL) and treated with a solution of $NaIO_4$ (16 mg, 0.075 mmol) in water (2 mL). The reaction mixture was stirred for 45 min at room temperature, extracted with CH_2Cl_2 (10 mL x 3), washed with brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography of the residue on SiO_2 gave **5** (3.4 mg, 32%, eluted out with EtOAc/hexane, 1:10) as a colorless oil, along with unreacted **9** (9.3 mg, 52%, eluted out with EtOAc/hexane, 1:3). The effective yield of this step was figured out to be 66% if the recovered starting material was taken into account. Compound **5**: $[\alpha]^{20}_D$ -35.5 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23-1.31 (m, 6H, $2CH_3$), 1.40-1.49 (m, 1H), 1.94-2.15 (m, 2H), 2.06 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.23-2.36 (m, 2H), 2.58 (td, 1H, *J* = 13.1, 4.2 Hz), 4.22 (s, 1H, CH, C1), 4.76 (d, *J* = 10.2 Hz, 1H, CH, C6), 6.29 (d, *J* = 5.4 Hz, 1H, CH, C2), 6.36 (d, *J* = 5.4 Hz, 1H, CH, C3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 14.1, 18.7, 22.4, 24.7, 38.7, 41.4, 50.4, 61.1, 80.9, 86.1, 133.2, 135.4, 136.9, 143.9, 170.3, 178.3; Anal. Calad for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.82.

Compound 6. Diene **5** (43.2 mg, 0.149 mmol) was allowed to stand (to undergo automatic dimerization) under an N_2 atmosphere at room temperature for 10 days. The reaction mixture was chromatographed (SiO_2, EtOAc/hexane, 1:10) to give **6** (31 mg, 72%) as colorless crystals along with unreacted diene **5** (10 mg, 23%) as a colorless oil. Compound **6**: mp (EtOAc) 188 ^{o}C (dec.); $[\alpha]^{20}_D$ +18.7 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.21-1.30 (m, 6H, $2CH_3$), 1.32-1.42 (m, 2H), 1.69 (s, 3H, CH_3), 1.77-1.93 (m, 3H), 1.87 (s, 3H, CH_3), 1.93-2.08 (m, 3H), 1.97 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 2.08-2.31 (m, 2H), 2.31-2.45 (m, 1H), 2.45-2.56 (m, 1H), 2.56-2.61 (m, 1H), 2.65-2.75 (m, 1H), 2.85 (s, 1H), 3.19-3.31 (m, 2H), 4.39 (d, *J* = 9.9 Hz, 1H, CH, C6'), 4.46 (d, *J* = 11.1 Hz, 1H, CH, C6), 5.55 (s, 1H, CH, C3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 12.8, 13.4, 17.7, 21.6, 22.4, 22.4, 24.3, 25.6, 27.1, 37.9, 39.6, 41.8, 41.9, 44.5, 46.7, 46.9, 48.9, 54.3, 60.8, 62.6, 69.4, 81.1, 82.4, 86.0, 88.0, 123.9, 134.7, 142.2, 145.1, 170.1, 170.5, 178.0, 178.6; Anal. Calcd for $C_{34}H_{44}O_8$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.62.

Compound 10. A solution of **6** (260 mg, 0.448 mmol) in 10 wt % KOH/MeOH (50 mL) was stirred overnight, acidified with 6M hydrochloric acid to pH 2, and extracted with EtOAc to give a residue, which was purified by column silica gel chromatography using EtOAc/hexane (3:1) to afford **10** (178 mg, 80%) as colorless crystals: mp (EtOAc) 150-152 ^{o}C (dec.); $[\alpha]^{20}_D$ +113.4 (*c* 0.98, MeOH); ^{1}H NMR (300 MHz, pyridine-d_5) δ 1.07 (d, *J* = 6.6 Hz, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.17-1.34 (m, 6H, $2CH_3$), 1.66-2.17 (m, 10H), 1.78 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.22-2.42 (m, 3H), 2.79 (s, 1H), 3.29-3.39 (m, 1H), 3.40-3.50 (m, 1H), 3.67 (s, 1H, 1CH, C3'), 4.53-4.70 (m, 2H, 2CH, C6', C6), 5.68 (s, 1H, 1CH, C3), 5.73-5.92 (br m, 2H, 2OH); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 12.3, 13.0, 14.0, 18.4, 23.1, 25.2, 27.1, 28.2, 42.0, 42.2, 46.0, 46.0, 46.6, 47.3, 47.6, 49.5, 59.6, 60.9, 63.0, 72.2, 74.6, 74.9, 81.9, 83.5, 125.4, 137.0, 142.3, 144.1, 178.6, 178.9; Anal. Calcd for $C_{30}H_{40}O_6 \cdot 2H_2O$: C, 67.64; H, 8.33. Found: C, 67.94; H, 8.27.

Compound 11. To a solution of **10** (209 mg, 0.421 mmol) in dry THF (7 mL) was added Et_3N (1.4 mL, 10 mmol), the mixture was cooled to –78 ^{o}C. A cold (-78 ^{o}C) solution of $SOCl_2$ (0.8 mL, 11 mmol) in anhydrous THF (2 mL) was added dropwise followed by stirring for 7 h. After being poured to cold ether/water, the mixture was thoroughly extracted with EtOAc, washed sequentially with saturated aqueous sodium carbonate solution, water, and brine, and dried over

$MgSO_4$. Filtration and concentration afforded the crude product of the bis(terminal alkene) which used directly without purification.

To a solution of the above bis(terminal alkene) in acetone/H_2O (8:1, 6 mL) were added NMO (50 wt % in water, 0.35 mL, 1.7 mmol) and OsO_4 (4 wt % in H_2O, 0.15 mL, 0.024 mmol). The mixture was stirred for 3 h at room temperature, diluted with saturated aqueous Na_2SO_3 solution (5 mL), and extracted with CH_2Cl_2/*i*-PrOH (3:1). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford the crude product of the tetraol, which was used directly without purification.

The above crude tetraol was dissolved in acetone (5 mL), and a solution of $NaIO_4$ (360 mg, 1.68 mmol) in water (7.5 mL) was added. After being stirred for 2 h at room temperature, the resulting mixture was diluted with saturated aqueous Na_2SO_3 solution (2 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a residue. Purification by column chromatography using EtOAc/hexane (1:3) gave **11** (151 mg, 77.2% from **10**) as colorless crystals: mp 226-228 ^oC (dec.); $[\alpha]^{20}_D$ = +404.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.23-1.38 (m, 6H, $2CH_3$), 1.41-1.60 (m, 2H), 1.74 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.03-2.26 (m, 4H), 2.26-2.64 (m, 6H), 2.65 (s, 1H), 3.03-3.10 (m, 1H), 3.11-3.18 (m, 1H), 3.18-3.25 (m, 1H), 3.59 (d, *J* = 6.3 Hz, 1H, 1CH, C1'), 4.56-4.65 (m, 2H, 2CH, C6', C6), 5.75 (s, 1H, 1CH, C3); ^{13}C NMR (300 MHz, CD_3Cl) δ 12.4, 12.9, 14.1, 16.8, 24.3, 25.0, 42.1, 42.7, 42.8, 42.9, 43.0, 46.3, 46.6, 48.1, 60.5, 60.9, 62.6, 72.4, 79.2, 80.3, 126.3, 132.0, 140.8, 145.9, 177.3, 178.0, 208.2, 210.7; MS (ESI) 465 (M + 1), 482 (M + H_2O); HRMS (ESI) Calcd for $C_{28}H_{32}O_6$ + Na 487.2105, found 487.2091.

(+)-Absinthin (1). To a solution of **11** (58.8 mg, 0.127 mmol) in dry THF (6 mL) was added dropwise a solution of MeLi (0.16 mL, 0.27 mmol, 1.7 M in ether) at –78 ^oC. The resulting reaction mixture was stirred at this temperature for 30 min and quenched with saturated aqueous $NaHCO_3$ solution (2 mL). After being warmed to room temperature, the mixture was extracted with CH_2Cl_2/*i*-PrOH (3:1) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a residue. Purification by column chromatography using EtOAc/hexane (1:5) gave **1** (55.9 mg, 89%) as colorless crystals: mp 165-166 ^oC (dec.); $[\alpha]^{20}_D$ +107.0 (*c* 1.9, $CHCl_3$); $[\alpha]^{20}_D$ +103.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 3H, CH_3), 1.20-1.28 (m, 6H, $2CH_3$), 1.30 (s, 3H, CH_3), 1.43-1.53 (m, 2H, 2OH), 1.53-2.00 (m, 10H), 1.77 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 2.15-2.30 (m, 4H), 2.76-2.88 (m, 2H), 3.18 (d, *J* = 6.6 Hz, 1H, 1CH, C3'), 4.59 (d, *J* = 11.1 Hz, 1H, 1CH, C6'), 4.71 (d, *J* = 10.2 Hz, 1H, 1CH, C6), 5.55 (s, 1H, 1CH, C3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 13.0, 13.7, 18.3, 23.5, 27.4, 29.3, 32.2, 42.0, 42.2, 42.4, 43.6, 45.6, 46.4, 46.6, 49.3, 57.0, 58.8, 64.0, 71.3, 71.9, 74.0, 81.4, 82.6, 122.1, 134.9, 147.3, 148.2, 178.5, 178.8; MS (ESI) 497 (M + 1), 514 (M + H_2O); HRMS (ESI) Calcd for $C_{30}H_{40}O_6$ + Na 519.2720, found 519.2717.

References

1. Beauharie, J.; Fourrey, J. L.; Vuilhorgne, M. *Tetrahedron Lett.* **1980**, *21*, 3191.