Electronic Supplementary Information (ESI)

Enantioselective Synthesis and Absolute Configuration Determination of Hydroxywilfordic Acid as a Key Esterifying Subunit of Sesquiterpene Pyridine Alkaloids

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**General information:**

Most of reagents were purchased from Sigma-Aldrich, Alfa-Aesar and TCI, which were used without further purification unless otherwise noted. Natural product was purchased from Angene International Limited. Jacobsen’s (R,R)-thiourea catalyst (CAS# 860994-52-1) was purchased from Shanghai Heat-biochem Co., Ltd. THF was distilled from sodium. All manipulations of oxygen- and moisture-sensitive materials were conducted with a standard Schlenk technique. “Concentrated” refers to the removal of volatile solvents via distillation using a rotary evaporator. “Dried” refers to drying over anhydrous magnesium sulfate, followed by gravity filtration to remove the drying agent. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with the indicated solvents. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel plates (Merck) and visualization was accomplished with UV light (254 and 365 nm) and/or an aqueous alkaline KMnO4 solution followed by heating. Proton and carbon nuclear magnetic resonance spectra (1H NMR and 13C NMR) were recorded on JEOL JNMEX400 (400 MHz, 1H NMR, CDCl3 at 7.24 ppm; 13C NMR, CDCl3 at 77.00 ppm) and Bruker 600 (600 MHz, 1H NMR, CDCl3 at 7.26 ppm; 13C NMR, CDCl3 at 77.16 ppm) spectrometer with Me4Si or solvent resonance as the internal standard. 1H NMR data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet and/or multiple resonances), coupling constant (J) in hertz (Hz) and integration. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700. Enantiomeric excess values were determined by chiral HPLC on a Agilent 1100 serials and Gilson 321 HPLC system using three chiral columns : Chiralpak AD, IG and IA. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700.

**Synthetic procedures:**

**Methyl 2-(3-hydroxybut-1-yn-1-yl)nicotinate (6)**

![Chemical structure of methyl 2-(3-hydroxybut-1-yn-1-yl)nicotinate (6)](image)

To a solution of 5 (540 mg, 2.8 mmol), but-3-yn-2-ol (235 mg, 3.3 mmol), CuI (11 mg, 0.06 mmol) and PdCl2(PPh3)2 (196 mg, 0.28 mmol) in anhydrous MeCN (15 mL), trimethylamine (100 µL) was added under an atmosphere of N2. After stirring in 90 °C overnight, the reaction mixture was cooled to room temperature, diluted with EtOAc, and the organic phase was washed with water and brine, dried over MgSO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1:1) to afford 6 (351 mg, 63%). 1H NMR (400 MHz, CDCl3) δ 8.59 (dd, J = 4.8, 1.8 Hz, 1H), 8.10 (dd, J = 8.0, 1.8 Hz, 1H), 7.21 (dd, J = 8.0, 4.8 Hz, 1H), 4.77 – 4.74 (m, 1H), 4.50 – 4.49 (m, 1H), 3.82 (s, 3H), 1.49 (d, J = 6.6 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 165.2, 152.1, 142.0, 138.0, 128.1, 122.2, 97.0, 81.6, 58.0, 52.3, 23.6.
1st step: To a solution of 6 (1.1 g, 5 mmol) and 10% Pd/C (100 mg) in anhydrous MeOH (10 mL) was placed under an atmosphere of hydrogen. After stirring for 1 h, the reaction mixture was diluted with EtOAc, filtered through short pad of silica gel and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc : n-hexane = 1 : 2) to afford 6s as a yellow oil (933 mg, 85%). 1H NMR (400 MHz, CDCl3) δ 8.59 (dd, J = 4.8, 1.8 Hz, 1H), 8.14 (dd, J = 7.9, 1.8 Hz, 1H), 7.19 (dd, J = 7.9, 4.8 Hz, 1H), 3.89 (s, 3H), 3.76 – 3.70 (m, 2H), 3.29 – 3.24 (s, 3H), 1.98 – 1.89 (m, 1H), 1.86 – 1.77 (m, 1H), 1.17 (d, J = 6.2 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 167.0, 162.9, 151.6, 138.7, 125.5, 121.0, 66.9, 52.4, 38.3, 32.8, 23.1.

2nd step: To a solution of 6s (1.43 g, 6.14 mmol) in CH3CN (15 mL), TPAP (108 mg, 0.3 mmol), 4-methylmorpholine-N-oxide (1.4 g, 12.3 mmol) and molecular sieve (700 mg, 4A, power, 2.5 µm) was added at 0 ℃. After stirred overnight at room temperature, the reaction mixture was diluted with EtOAc, and the organic phase was washed with water and brine, dried over MgSO4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexanes = 1: 1) to afford 4a (800 mg, 57%, recovery yield 80%). 1H NMR (400MHz, CDCl3) δ 8.56 (dd, J = 4.8, 1.7 Hz, 1H), 8.12 (dd, J = 7.9, 1.8 Hz, 1H), 7.16 (dd, J = 7.9, 4.8 Hz, 1H), 3.88 (s, 3H), 3.41 (t, J = 7.2 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.18 (d, 3H). 13C NMR (100MHz, CDCl3) δ 208.2, 166.8, 161.3, 151.6, 138.3, 125.4, 120.9, 52.3, 41.6, 30.7, 30.0.

(E)-4-(Tributylstannyl)but-3-en-2-ol

PdCl2(Cy3P)2 (369 mg, 0.5 mmol) and but-3-yn-2-ol (3.5 g, 50 mmol) were added to toluene (50 mL). Bu3SnH (17.5 g, 60 mmol) diluted in toluene (50 mL) was added dropwise via a dropping funnel at 0 ℃. After stirring overnight at room temperature, the reaction mixture was concentrated and purified by silica gel chromatography (EtOAc : n-hexane = 1 : 5) to afford (E)-4-(tributylstannyl)but-3-en-2-ol (10.3 g, 57%). 1H NMR (600MHz, CDCl3) δ 6.15 – 5.99 (m, 2H), 4.26 – 4.21 (m, 1H), 1.80 (s, 1H), 1.49 – 1.46 (m, 6H), 1.32 – 1.26 (m, 6H), 1.25 (d, J = 6.4 Hz, 3H), 0.89 – 0.86 (m, 15H). 13C NMR (150MHz, CDCl3) δ 152.2, 126.5, 71.4, 29.2, 27.4, 23.2, 13.8, 9.5.

Methyl (E)-2-(3-hydroxybut-1-en-1-yl)nicotinate (7)
To a solution of 5 (914 mg, 5.35 mmol) in toluene (15 mL) was added 4-(tributylstannyl)but-3-en-2-ol (2.32 g, 6.42 mmol) and Pd(PPh₃)₄ (309 mg, 0.27 mmol) at 0°C. The reaction mixture was stirred at ambient temperature for 10 min and then heated to reflux for 3 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc, and the organic phase was washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc : n-hexane = 1 : 1) to afford the 7 as a pale yellow oil (774 mg, 69%). ¹H NMR (400 MHz, CDCl₃) δ 8.67 (dd, J = 4.9, 1.8 Hz, 1H), 8.23 (dd, J = 7.9, 1.8 Hz, 1H), 7.27 (dd, J = 8.0, 4.8 Hz, 1H), 7.16 (dd, J = 11.9, 1.2 Hz, 1H), 6.10 (dd, J = 11.9, 6.9 Hz, 1H), 5.88 (s, 1H), 4.52 – 4.45 (m, 1H), 3.91 (s, 3H), 1.35 (d, J = 6.5 Hz, 3H). ¹³C NMR (100MHz, CDCl3). δ 166.8, 154.9, 152.0, 141.8, 138.5, 125.7, 121.6, 68.4, 52.4, 23.1.

**Methyl (E)-2-(3-oxobut-1-en-1-yl)nicotinate (4b)**

To a solution of 7 (1.20 g, 5.89 mmol) in anhydrous CH₂Cl₂(17mL) was added MnO₂(6.10 g, 2.94 mmol) in at room temperature. The resultant solution was stirred at ambient temperature for 2 h and then filtered through short pad of celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc : n-hexane = 1 : 2) to afford 4b as a white powder. (1.12 g, 91%). ¹H NMR (600 MHz, CDCl₃) δ 8.72 (dd, J = 4.6, 1.7 Hz, 1H), 8.39 (d, J = 15.7 Hz, 1H), 8.23 (dd, J = 8.0, 1.8 Hz, 1H), 7.34 (dd, J = 8.0, 4.6 Hz, 1H), 7.29 (d, J = 15.7 Hz, 1H), 3.94 (s, 3H), 2.41 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 199.0, 166.3, 153.2, 152.5, 139.2, 138.8, 133.2, 126.2, 123.8, 52.9, 28.0.

**Methyl (E)-2-(3-oxobut-1-en-1-yl)nicotinate (4b)**

A solution of methyl 2-bromonicotinate 5 (250 mg, 1.15 mmol), but-3-yn-2-ol (93 µL, 1.2 mmol), PdCl₂(PPh₃)₂ (20 mg, 5% mmol), and Cul (2 mg, 0.01 mmol) in TEA (800 µL, 5.6 mmol) and 1.5 mL THF under nitrogen was magnetically stirred in a heavy-walled vial at the microwave at 150°C for 30 min. After cooling to room temperature,
aqueous work-up and extraction with EtOAc, and the organic phase was washed with water and brine, dried over MgSO4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc : n-hexane = 1 : 2) to afford 4b (35 mg, 15%) and 6 (92 mg, 39%).

**Methyl 2-(3-cyano-3-((trimethylsilyl)oxy)butyl)nicotinate (3a)**

![Chemical structure of 3a](image)

To a solution of 4a (910 mg, 4.39 mmol) in anhydrous CHCl3 (5 mL) was added a liquid of DBU (68 mg, 0.44 mmol) and Trimethylsilyl cyanide (521 mg, 5.26 mmol) in room temperature. After stirring for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc : n-hexane = 1 : 5 to 1 : 1) afforded 3a as a pale yellow liquid. (1.24 g, 93% yield).

\[
{^1}H \text{ NMR (400MHz, CDCl}_3) \delta 8.63 - 8.62 (m, 1H), 8.17 - 8.15 (m, 1H), 7.23 - 7.21 (m, 1H), 3.92 (s, 3H), 3.36 - 3.31 (m, 2H), 2.21 - 2.18 (m, 2H), 1.65 (s, 3H), 0.24 (s, 9H).
\]

\[
{^{13}}C \text{ NMR (400MHz, CDCl}_3) \delta 166.9, 161.2, 151.9, 138.7, 125.7, 121.9, 121.2, 69.3, 52.4, 42.5, 32.0, 28.9, 1.3.
\]

**Methyl 2-(3-cyano-3-((trimethylsilyl)oxy)butyl)nicotinate ((S)-3a and (R)-3a)**

![Chemical structure of 3a](image)

To a solution of 4a (183 mg, 0.88 mmol) in anhydrous CH2Cl2 (2 mL) at -78°C was added Jacobsen amide-thiourea catalyst (36 mg, 0.08 mmol), 2,2,2-trifluoroethanol (100 µL), trimethylsilyl cyanide (263 mg, 2.65 mmol) and the resulting solution was stirred 2 days. The reaction was warmed to room temperature, and concentrated under reduced pressure. The product was purified by silica gel chromatography (EtOAc: n-Hexanes = 1:2) to afford 3a (230 mg, 83%).

**Methyl (E)-2-(3-cyano-3-((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (using DBU)**

![Chemical structure of 3a](image)

To a solution of methyl 2-(3-oxobutenyl) nicotinate (910 mg, 4.4 mmol) in anhydrous CH2Cl2 (2 mL) was added a liquid of DBU (68 mg, 0.44 mmol) and trimethylsilyl cyanide (521 mg, 5.3 mmol) in room temperature. After stirring for 1 h at room temperature the residue was purified by silica gel column chromatography (EtOAc : n-hexane = 1 : 2) afforded cyanide as a pale yellow watery liquid. (1.26 g, 93% yield).
Methyl (E)-2-(3-cyano-3-((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (3b) (using (R,R)-thiourea catalyst)

To a solution of 4b (327 mg, 1.6 mmol) in anhydrous CH₂Cl₂ (10 mL) at -78°C was added Jacobsen amide-thiourea catalyst (33 mg, 0.08 mmol), 2,2,2-trifluoroethanol (450 µL), trimethylsilyl cyanide (0.42 mL, 3.2 mmol) and the resulting solution was stirred 4 days. The reaction was warmed to room temperature, and concentrated under reduced pressure. The product was purified by silica gel chromatography (EtOAc: n-Hexanes = 1:2) to afford (S)-3b (345 mg, 90%, ee% = 94%). ¹H NMR (400MHz, CDCl₃) δ 8.70 – 8.69 (m, 1H), 8.20 (dd, J = 8.23, 2.0 Hz, 1H), 7.83 (d, J = 15.6 Hz, 1H), 7.29 – 7.27 (m, 1H), 6.8 (d, J = 15.1 Hz, 1H), 3.96 (s, 3H), 1.78 (s, 3H), 0.26 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 153.2, 152.1, 138.7, 136.7, 127.8, 124.9, 122.4, 120.5, 69.7, 52.5, 30.5, 1.2.

Methyl (E)-2-(3-cyano-3-((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (using (DHQ)₂AQN)

To a solution of 4b (169 mg, 0.82 mmol) in anhydrous CHCl₃ (1 mL) was added catalyst (70 mg, 0.08 mmol) and trimethylsilyl cyanide (245 mg, 2.47 mmol) at -40°C. After stirring for 48 h, the reaction was warmed to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc : n-hexane = 1 : 2 ) afforded cyanide as a pale yellow watery liquid. (201 mg, 80%).

Methyl (E)-2-(3-cyano-3-((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (using (DHQ)₂PHAL)

To a solution of 4b (155 mg, 0.76 mmol) in anhydrous CHCl₃ (1 mL) was added catalyst (59 mg, 0.08 mmol) and trimethylsilyl cyanide (225 mg, 2.27 mmol) at -40°C. After stirring for 48 h, the reaction was warmed to room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc : n-hexane = 1 : 2 ) afforded cyanide as a pale yellow watery liquid. (189 mg, 80%).

Methyl (E)-2-(3-cyano-3-((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (using Feng’s phenylglycinate)

To a solution of Feng’s phenylglycinate (7 mg, 0.04 mmol) in anhydrous THF (0.5 mL) was added and trimethylsilyl cyanide (26 mg, 0.26 mmol) at -20°C. The mixture was stirred 1 hour at 30°C. 4b (27 mg, 0.13 mmol) and iPrOH (50 µL) in THF (1 mL) was added to the mixture at -45°C. After stirring for 72 h, the reaction was warmed to room temperature, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc : n-hexane = 1 : 2 ) afforded cyanide as a pale yellow watery liquid. (28 mg, 70%).

Ethyl (E)-2-(3-cyano-3-((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (3d)
To a solution of ethyl (E)-2-(3-oxobut-1-en-1-yl)nicotinate (1g, 4.56 mmol) in anhydrous CH2Cl2 (10 mL) at -80°C was added Jacobsen (R,R)-amide-thiourea catalyst (190 mg, 0.49 mmol), 2,2,2-trifluoroethanol (375 µL), trimethylsilyl cyanide (1.25 mL, 10 mmol) and the resulting solution was stirred 4 days. The product was purified by silica gel chromatography (EtOAc: Hexanes = 1:2) to afford ethyl (E)-2-(3-cyano-3-((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (1.14g, 79% yield and >99% recovery yield, ee% = 91%). 1H NMR (600 MHz, CDCl3) δ 8.68 (dd, J = 4.7, 1.8 Hz, 1H), 8.20 (dd, J = 7.9, 1.8 Hz, 1H), 7.82 (d, J = 15.2 Hz, 1H), 7.27 (dd, J = 7.9, 4.7 Hz, 1H), 6.97 (d, J = 15.2 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 1.78 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H), 0.25 (s, 9H).

13C NMR (150 MHz, CDCl3) δ 166.4, 153.2, 152.1, 139.0, 136.8, 128.0, 125.6, 122.6, 120.7, 70.0, 62.0, 30.8, 14.4, 1.5. HRMS (FAB+): calcd for C16H23N2O3Si (M+H)+: 319.1478; found: 319.1481.

Ethyl 2-(3-oxobutyl)nicotinate (4c)

A solution of ethyl (E)-2-(3-oxobut-1-en-1-yl)nicotinate (510 mg, 2.33 mmol) and 10% Pd/C (45 mg) in anhydrous MeOH (3 mL) was placed under an atmosphere of hydrogen. After stirring for 1h, the reaction mixture was diluted with EtOAc, filtered through short pad of celite and concentrated in vacuum. The residue was purified by silica gel column chromatography (EtOAc : n-Hexane = 1:2) to afford ethyl 2-(3-oxobutyl)nicotinate (453 mg, 88%). 1H NMR (600 MHz, CDCl3) δ 8.58 (dd, J = 4.6, 1.4 Hz, 1H), 8.15 (dd, J = 7.8, 1.5 Hz, 1H), 7.18 (dd, J = 7.8, 4.8 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.43 (t, J = 7.2 Hz, 2H), 2.92 (t, J = 7.2 Hz, 2H), 2.20 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). 13C NMR (150 MHz, CDCl3) δ 208.3, 166.6, 161.3, 151.7, 138.5, 125.9, 121.1, 61.5, 41.9, 30.9, 30.1, 14.3. HRMS (FAB+): calcd for C12H16NO3 (M+H)+: 222.1130; found: 222.1131.

Ethyl 2-(3-cyano-3-((trimethylsilyl)oxy)butyl)nicotinate (3c)

To a solution of ethyl ethyl 2-(3-oxobutyl)nicotinate (197 mg, 0.89 mmol) in anhydrous CH2Cl2 (5 mL) at -80°C was added Jacobsen amide-thiourea catalyst (34 mg, 0.09 mmol), 2,2,2-trifluoroethanol (67 µL), trimethylsilyl cyanide (223 µL, 1.8 mmol) and the resulting solution was stirred 4 days. The product was purified by silica gel
chromatography (EtOAc: Hexanes = 1:2) to afford ethyl 2-(3-cyano-3-((trimethylsilyl)oxy)butyl)nicotinate (82.3 mg, 28.4%, recovery yield 91%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.63 (dd, $J$ = 4.8, 1.8 Hz, 1H), 8.16 (dd, $J$ = 7.9, 1.8 Hz, 1H), 7.22 (dd, $J$ = 7.9, 4.8 Hz, 1H), 4.40 (q, $J$ = 7.1 Hz, 2H), 3.41 – 3.31 (m, 2H), 2.24 – 2.18 (m, 2H), 1.66 (s, 3H), 1.40 (t, $J$ = 7.1 Hz, 3H), 0.24 (s, 9H).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 166.6, 161.2, 151.8, 138.7, 126.2, 122.1, 121.3, 69.5, 61.7, 31.9, 29.1, 14.4, 1.4. HRMS (FAB$^+$) m/z: calcd for C$_{16}$H$_{25}$N$_2$O$_3$Si (M+H)$^+$: 321.1634; found: 321.1633.

Methyl 2-(3-hydroxy-4-methoxy-3-methyl-4-oxobutyl)nicotinate (2)

To a solution of 3a (100 mg, 0.33 mmol) in MeOH (3 mL) at 0°C was added c-HCl (0.5 mL) and the resulting solution was stirred at room temperature overnight then heated at 60°C for 1 day to afford crude acid salt. The resulting crude solution was sufficiently concentrated in vacuo. This suspension was immediately dissolved in MeOH (5 mL) and added dropwise diazomethyl trimethylsiane (1 mL, 2.0 M solution in diethyl ether) at 0°C. The reaction mixture was stirred for 1 h at room temperature and the resulting mixture was extracted in ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by column chromatograwphy on silica gel (EtOAc : n-hexane = 1 : 1) to afford 2 as a yellow oil. (42.2 mg, 2 step, 46%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.62 (dd, $J$ = 4.8, 1.8 Hz, 1H), 8.17 (dd, $J$ = 7.9, 1.8 Hz, 1H), 7.22 (dd, $J$ = 7.9, 4.8 Hz, 1H), 4.48 (s, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 3.30 - 3.21 (m, 2H), 2.32 - 2.27 (m, 1H), 2.13 - 2.08 (m, 1H), 1.47 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.5, 166.9, 162.4, 151.7, 138.9, 125.7, 121.2, 74.7, 52.7, 52.6, 39.1, 31.3, 26.3. HRMS (FAB$^+$) m/z: calcd for C$_{13}$H$_{18}$NO$_5$ (M+H)$^+$, 268.1185; found: 268.1188.

Methyl (E)-2-(3-hydroxy-4-methoxy-3-methyl-4-oxobut-1-en-1-yl)nicotinate ((S)-9)

To a solution of (S)-3b (224 mg, 0.7 mmol) in MeOH (3 mL) room temperature was added c-HCl (0.5 mL) and the resulting solution was stirred overnight at 60°C. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was dissolved in MeOH (0.5 mL) and diazomethyl trimethylsiane (5 mL, 2.0 M solution in diethyl ether) was added into the methanol solution. The resulting solution was stirred at room temperature. After 2 days, the reaction mixture was quenched with NaHCO$_3$ and ethyl acetate and the organic phase was washed with water and brine, dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc: Hexanes = 1:2) to afford (S)-9 (134 mg, 67%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.68 (dd, $J$ = 4.7, 1.7 Hz, 1H), 8.15 (dd, $J$ = 7.9, 1.8 Hz, 1H), 7.73 (d, $J$ = 15.2 Hz, 1H), 7.23 (dd, $J$ = 4.7, 1.7 Hz, 1H).
= 7.9, 4.7 Hz, 1H), 7.16 (d, J = 15.2 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.52 (s, 1H), 1.63 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 175.9, 166.9, 154.4, 152.1, 138.8, 138.7, 126.5, 124.8, 122.0, 75.1, 53.5, 52.7, 26.4. (S)-9 : [α]D20 = +16.5 (c 0.12, MeOH). HRMS (FAB+) m/z: calcd for C13H16NO5 (M+H)+, 266.1028; found: 266.1031.

Methyl 2-(3-hydroxy-4-methoxy-3-methyl-4-oxobutyl)nicotinate ((S)-2)

A solution of (S)-9 (10 mg, 0.04mmol) and 10% Pd/C (10 mg) in anhydrous MeOH (1 mL) was placed under an atmosphere of hydrogen. After stirring for 1h, the reaction mixture was diluted with EtOAc, filtered through short pad of celtie and concentrated in vacuum. The residue was purified by silica gel column chromatography (EtOAc : n-Hexane = 1:2) to afford (S)-2 (10 mg, >99%). (S)-2 : [α]D20 = +16.0 (c 1.6, MeOH). ee% = 93.3%.

(S)-2-(3-Carboxy-3-hydroxybutyl)nicotinic acid ((S)-1)

To a solution of (S)-2 (15 mg, 0.06 mmol) in MeOH/H2O (1 mL/1 mL) was added LiOH monohydrate (7 mg, 0.18 mmol). After stirring overnight at room temperature, reaction was quenched with 1N HCl solution, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH2Cl2: MeOH = 1: 1) to afford (S)-1 (white solid, 13.2 mg, 98.5%). 1H NMR (600 MHz, CD3OD) δ 8.34 (s, 1H), 7.85 (d, J = 6.9 Hz, 1H), 7.29 – 7.14 (m, 1H), 3.18 (s, 1H), 3.08 (s, 1H), 2.30 (s, 1H), 2.02 (s, 1H), 1.41 (s, 3H).13C NMR (150 MHz, CD3OD) δ 175.7, 160.2, 148.7, 137.6, 122.3, 64.3, 41.16, 31.64, 26.86. (S)-2-1 : [α]D20 = 20.41 (c 1.47, H2O). HRMS (ESI-TOF) m/z: calcd for C11H12NO5 (M-H)-, 238.0721; found: 238.0702. (The reported optical rotation of hydroxywilfordic acid (1) from Tripterygium wilfordii Hook.: [α]D24 = -24.1 (H2O)) [1]

Methyl 2-(3-hydroxy-4-methoxy-3-methyl-4-oxobutyl)nicotinate (R-2)

Wilfortrine
To a solution of sodium (5.6 mg, 0.24 mmol) in MeOH (1 mL) at 0°C was added solution of wilfortrine (10 mg, 0.011 mmol). After stirring 1 hour at room temperature, reaction was quenched with saturated NaHCO₃ solution, diluted with ethyl acetate and the organic phase was washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc: Hexanes = 1: 1) to afford methyl 2-(3-hydroxy-4-methoxy-3-methyl-4-oxobutyl)nicotinate (2.8 mg, 92%). 1H NMR (600 MHz, CDCl₃) δ 8.63 (dd, J = 4.8, 1.8 Hz, 1H), 8.17 (dd, J = 7.9, 1.8 Hz, 1H), 7.22 (dd, J = 7.9, 4.8 Hz, 1H), 4.48 (s, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 3.31 – 3.21 (m, 2H), 2.31 (ddd, J = 14.0, 8.5, 6.8 Hz, 1H), 2.14 – 2.08 (m, 1H), 1.48 (s, 3H).

13C NMR (150 MHz, CDCl₃) δ 172.5, 170.7, 170.2, 170.0, 169.7, 169.1, 168.2, 165.2, 161.1, 152.4, 148.9, 144.5, 137.9, 125.7, 120.7, 118.3, 109.8, 94.3, 84.9, 77.96, 76.8, 73.7, 73.1, 70.8, 69.9, 69.9, 69.0, 68.8, 60.6, 52.1, 51.3, 38.5, 31.5, 28.3, 22.8, 21.7, 21.3, 21.2, 20.6, 20.6, 18.0. HRMS (ESI-TOF) m/z: calcd for C₄₁H₄₈NO₂₀(M+H)+, 874.2764; found: 874.3102.
Table S1. The NMR comparison of natural product wilfortrine between the reported and our purchased compounds.

<table>
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<th>position</th>
<th>$^1$H-NMR of the reported compound</th>
<th>$^1$H-NMR of our purchased compound</th>
<th>$^{13}$C-NMR the reported compound</th>
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</tbody>
</table>

a. Phytochemistry 1995, 39, 1219-1222
The preparation of two monoacids:

\[ \text{NCO}_2 \text{HCO}_2 \text{H} \text{OH} \text{c-HCl} \text{MeOH} \text{reflux} \]

\[ \text{NCO}_2 \text{HCO}_2 \text{MeOH} \text{OH} \]

\[ \text{H}_2, \text{Pd/C} \text{MeOH} \]

\[ \text{NCO}_2 \text{H} \text{CO}_2 \text{Me} \text{OH} \]

\[ \text{TMSCHN}_2 \text{MeOH} \]

\[ \text{H}_2, \text{Pd/C} \text{MeOH} \]

\[ \text{2-}(3\text{-Hydroxy-4-methoxy-3-methyl-4-oxobutyl})\text{nicotinic acid (Supp-1)} \] and \[2\text{-hydroxy-4-(3-(methoxycarbonyl)pyridin-2-yl)-2-methylbutanoic acid (Supp-2)}\]

To a solution of \( 2 \) (80 mg, 0.3 mmol) in MeOH/H\(_2\)O (1 mL/1 mL) at room temperature was added LiOH monohydrate (40 mg, 1 mmol) and the resulting solution was stirred 2 h at ambient temperature. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH : CH\(_2\)Cl\(_2\) = 1:2) to afford Supp-1 and Supp-2 (1 : 1.9, calculated by proton integral of \(^1\text{H-NMR}\)).

(\(E\))-2-(3-Hydroxy-4-methoxy-3-methyl-4-oxobut-1-en-1-yl)nicotinic acid (Supp-3)

To a solution of \( 3\text{d} \) (450 mg, 1.4 mmol) in MeOH (3 mL) room temperature was added c-HCl (0.5 mL) and the resulting solution was stirred overnight at 60\(^\circ\)C. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was dissolved in MeOH (3 mL) and diazomethyl trimethylsiane (2 mL, 2.0 M solution in diethyl ether) was added into the methanol solution. The resulting solution was stirred at room temperature. After 1 day, the reaction mixture was quenched with NaHCO\(_3\) and ethyl acetate and the organic phase was washed with water and brine, dried over MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc: Hexanes = 1: 2) to afford \( 9 \) (124 mg, 33%), then washed the silica gel with MeOH, filtered and concentrated under reduced pressure to get crude Supp-4 (92 mg, 26%).

2-(3-Hydroxy-4-methoxy-3-methyl-4-oxobutyl)nicotinic acid (Supp-1)

A solution of Supp-3 (85 mg, 0.34 mmol) and 10\% Pd/C (10 mg) in anhydrous MeOH (1 mL) was placed under an atmosphere of hydrogen. After stirring for 1 h, the reaction mixture was diluted with EtOAc, filtered through short pad of Celite and concentrated in vacuum. The residue was purified by silica gel column chromatography (MeOH : CH\(_2\)Cl\(_2\) = 1:2) to afford Supp-1 (66.8 mg, 78%).\(^1\text{H NMR (600 MHz, MeOD) } \delta \) 8.48 (dd, \( J = 4.9, 1.7 \text{ Hz, 1H} \)), 8.12 (dd, \( J = 7.8, 1.7 \text{ Hz, 1H} \)), 7.31 (dd, \( J = 7.8, 4.9 \text{ Hz, 1H} \)), 3.69 (s, 3H), 3.22 (ddd, \( J = 13.0, 10.7, 5.3 \text{ Hz, 1H} \)), 3.15 (ddd, \( J = 13.1, 10.6, 6.0 \text{ Hz, 1H} \)), 2.26 – 2.16 (m, 1H), 2.05 (ddd, \( J = 13.7, 10.5, 5.3 \text{ Hz, 1H} \)), 1.43 (s, 3H). \(^{13}\text{C NMR (150 MHz, MeOD)} \delta \) 178.0, 161.3, 150.5, 139.6, 122.7, 75.7, 52.8, 41.2, 31.6, 26.2.
Copies of $^1$H- and $^{13}$C-NMR spectra

methyl 2-(3-hydroxybut-1-yn-1-yl)nicotinate (6)

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
methyl 2-(3-hydroxybutyl)benzoate (6s)

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
methyl 2-(3-oxobutylnicotinate (4a)

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
(E)-4-(tributylstannyl)but-3-en-2-ol

$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
methyl (E)-2-(3-hydroxybut-1-en-1-yl)nicotinate (7)

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
methyl (E)-2-(3-oxobut-1-en-1-yl)nicotinate (4b)

$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
methyl 2-(3-cyano-3-((trimethylsilyl)oxy)butyl)nicotinate (3a)

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
methyl (E)-2-(3-cyano-3-((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (3b)

\[ ^1H \text{NMR (400 MHz, CDCl}_3) \]

\[ ^{13}C \text{NMR (100 MHz, CDCl}_3) \]
methyl 2-(3-hydroxy-4-methoxy-3-methyl-4-oxobutyl)nicotinate (2)

$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
methyl \((E)-2\)-(3-hydroxy-4-methoxy-3-methyl-4-oxobut-1-en-1-yl)nicotinate (S-9)

\(^1\)H NMR (600 MHz, CDCl\(_3\))

\(^{13}\)C NMR (150 MHz, CDCl\(_3\))
ethyl (E)-2-(3-cyano-3-(((trimethylsilyl)oxy)but-1-en-1-yl)nicotinate (3d)

$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
ethyl 2-(3-oxobutyl)nicotinate (4c)

$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
ethyl 2-(3-cyano-3-((trimethylsilyl)oxy)butyl)nicotinate (3c)

$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
methyl 2-(3-hydroxy-4-methoxy-3-methyl-4-oxobutyl)nicotinate (\textit{R}-2)

$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
(S)-2-(3-carboxy-3-hydroxybutyl)nicotinic acid (S)-1

$^1$H NMR (600 MHz, CD$_3$OD)

$^{13}$C NMR (150 MHz, CD$_3$OD)
Wilfortrine

$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
2-(3-hydroxy-4-methoxy-3-methyl-4-oxobutyl)nicotinic acid (Supp-1)

$^1$H NMR (600 MHz, MeOD)

$^{13}$C NMR (150 MHz, MeOD)
Supp-1 and Supp-2

$^1$H NMR (600 MHz, MeOD)
Determine absolute configuration using ECD analysis

1) Geometry optimization and ECD calculation of (S)-2 and (R)-2 enantiomers

Density functional theory (DFT) calculations were performed using a hybrid functional (Becke 3-parameter (Exchange), Lee, Yang, and Parr with both local and non-local correlation, B3LYP) [2,3] with well-accepted basis set: 6-311+G(d,p). All calculations were performed at the default temperature and pressure (298.15 K and 1.00 atm). All Calculations were performed using Gaussian 09 [4] and the results were visualized with the Gauss View, Gabedit [5] and GaussSum [6] computer programs. Vibrational frequency calculations were used to confirm that the optimized structures were true minimum on the potential energy surface, as characterized by the absence of imaginary vibrational frequencies. The ECD calculation were calculated with TD-DFT (time-dependent density functional theory) using the same level of theory and basis sets. The number of excited states per molecule was 30. Solvent effects were taken into account by using the polarizable continuum model (PCM, MeOH). The ECD spectra were generated by the GaussSum computer programs using a Gaussian band shape with 0.3 eV exponential half-width from dipole-length dipolar and rotational strengths.

2) Circular dichroism spectroscopy

Circular dichroism (CD) measurements were carried out using a ChirascanTM – Circular Dichroism Spectrometer (AppliedPhotophysics, United Kingdom) at 25°C. Compounds were dissolved in MeOH (0.5 mg/mL). The CD spectra were obtained using a cell with a 0.1 cm path length.

3) Experimental and calculated ECD spectrums of (S)-2 and (R)-2 enantiomers

To determine absolute stereochemistry (S and R) of two compounds (S)-2 which was synthesized through Jacobsen catalyst cyanosilylation and (R)-2 which was prepared from methanolysis of naturally occurring wilfortrine, comparing the experimental ECD spectrum with the calculated ECD spectrum. The calculated ECD spectrum of (R)-isomer showed good agreement with the experimental spectrum of compound (R)-2 in methanol. And the calculated ECD spectrum of (S)-isomer matched with the experimental spectrum of the enantiomers of compound (R)-2, too.
Fig. S1 Experimental ECD spectra of synthetic 2 and naturally derived 2.

Fig. S2 calculated ECD spectra of (S)-2 and (R)-2.
Fig. S3 Experimental and calculated ECD spectra of synthetic (S)-2 and naturally derived (R)-2.
References:


