Supporting Information for

Asymmetric Total Synthesis of (+)-Ovafolinins A and B

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1. General information

Tetrahydrofuran (THF) and toluene were dried and distilled from sodium and benzophenone. Dichloromethane (CH$_2$Cl$_2$) was dried and distilled from calcium hydride. All commercial reagents and other solvents were used as received without further purification. Reactions were followed with TLC (254 nm silica gel 60-F plates); Visualization was accomplished with UV light. Flash chromatographies were carried out on silica gel 200-300 mesh. All NMR spectra were obtained at ambient temperature using Bruker-AVANCE III-400MHz spectrometer. $^1$H NMR and $^{13}$C NMR spectra were recorded using CDCl$_3$. Spectra were referenced internally to the residual proton resonance in CDCl$_3$ (δ $^1$H = 7.26 ppm, δ $^{13}$C = 77.16 ppm) with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. $^1$H NMR data were recorded as follows: multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, coupling constant in Hz, integration). The known products were characterized by comparing to the corresponding $^1$H-NMR and $^{13}$C-NMR from the literatures. High resolution mass spectrometry (HRMS) data were obtained on a Micro TOF-Q II (hybrid quadrupolar/time-of-flight) API US system by electrospray ionization (ESI) in the positive ion mode using a Bruker instrument. A Beijing Taike XT-4 microscopy melting point apparatus was used to measure the melting points of the compounds. Optical rotations were measured on a Rudolph Research Analytical Autopol II automatic polarimeter.
2. The synthesis of bromide 8

4-(benzyloxy)-3,5-dimethoxybenzaldehyde (11)

![Chemical structure](image)

To a stirred solution of syringaldehyde 10 (10.0 g, 54.9 mmol, 1 eq.) in DMF (50 mL) at room temperature was added K$_2$CO$_3$ (9.1 g, 65.9 mmol, 1.2 eq.) and BnBr (9.8 g, 57.6 mmol, 1.2 eq.). After 36 h, the reaction was quenched with H$_2$O (200 mL) and extracted with Et$_2$O (3 x 100 mL). The combined organic phases were washed with brine (3 x 200 mL) then dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The obtained residue was purified by silica gel flash chromatography (silica gel, EtOAc/petroleum ether, 1:10) to afford 11 (13.7 g, 50.5 mmol, 92% yield) as a white solid.

TLC: $R_f = 0.36$ (silica gel, EtOAc/petroleum ether, 1:5).

Melting Point: 60-61 °C.

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 3.88 (s, 6H), 5.12 (s, 2H), 7.10 (s, 2H), 7.28-7.35 (m, 3H), 7.46 (d, $J = 6.6$ Hz, 2H), 9.84 (s, 1H) ppm.

$^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 56.3, 75.1, 106.7, 182.1, 182.3, 182.5, 131.9, 137.3, 142.4, 154.0, 191.2 ppm.

HRMS (m/z): calculated for C$_{16}$H$_{16}$NaO$_4$ $^{+}$ [M+Na]$^+$: 295.0941, found 295.0943.

2-(benzyloxy)-5-(bromomethyl)-1,3-dimethoxybenzene (8)

![Chemical structure](image)

To a stirred solution of aldehyde 11 (8.00 g, 33.09 mmol, 1 eq.) in MeOH/DCM (2:1, 90 mL) was added NaBH$_4$ (1.25 g, 33.09 mmol, 1 eq.) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The mixture was then quenched with acetone (10 mL) at 0 °C and stirred for 0.5 h. Solvent was removed under reduced pressure. The residue was added ethyl acetate (60 mL) and H$_2$O (100 mL), then it was stirred vigorously for 1 h at room temperature. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 60 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was used directly without further purification.

The crude product was dissolved in DCM (100 mL). PBr$_3$ (7.94 g, 33.09 mmol, 1 eq.) was added at 0 °C. After stirred at 0 °C for 2h, the reaction was poured into ice water (150 mL) and the mixture was extracted with Et$_2$O (3 x 60 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (silica gel,
EtOAc/petroleum ether, 1:10) to afford bromide 8 (8.01 g, 23.82 mmol, 72% yield in 2 steps) as a white solid.

TLC: Rf = 0.54 (silica gel, EtOAc/petroleum ether, 1:5).

Melting Point: 57-58 °C.

1H NMR (400 MHz; CDCl3): δ 3.82 (s, 6H), 4.45 (s, 2H), 4.99 (s, 2H), 6.60 (s, 2H), 7.28-7.36 (m, 3H), 7.47-7.49 (d, J = 7.5 Hz, 2H) ppm.

13C NMR (100 MHz; CDCl3): δ 34.5, 56.2, 75.2, 106.3, 127.0, 128.3, 128.6, 133.4, 137.2, 137.8, 153.6 ppm.


3. The synthesis of phenol 5

4-(benzyloxy)-3,5-dimethoxyphenol (5)

To a stirred solution of aldehyde 11 (4.0 g, 14.7 mmol, 1 eq.) in DCM (100 mL) at 0 °C was added m-CPBA (5.0 g, 29.4 mmol, 2 eq.) and NaHCO3 (3.7 g, 44.1 mmol, 3 eq.). The resulting mixture was allowed warming to room temperature and stirred for 5 h. Solid was filtrated and washed with DCM (100 mL). The combined solvent was removed under reduced pressure. The residue was dissolved in MeOH (40 mL). KOH (2.5 g, 44.1 mmol, 3 eq.) was added. The mixture was stirred for 1 h. Solvent was removed under reduced pressure, water (100 mL) was added. The system was adjusted to pH=2 with 2M HCl and extracted with diethyl ether (3 x 50 mL). The organic extracts were combined, dried over Na2SO4 and solvent removed under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/petroleum ether, 1:3) to give phenol 5 (2.7 g, 10.3 mmol, 70%) as a light yellow solid.

TLC: Rf = 0.50 (silica gel, EtOAc/petroleum ether, 1:1).

Melting Point: 117-118 °C.

1H NMR (400 MHz; CDCl3): δ 3.63 (s, 6H), 4.91 (s, 2H), 5.99 (s, 2H), 7.24-7.32 (m, 3H), 7.45 (d, J = 6.6 Hz, 2H) ppm.

13C NMR (100 MHz; CDCl3): δ 55.9, 75.6, 93.1, 128.0, 128.2, 128.8, 130.0, 137.6, 152.9, 153.9 ppm.

HRMS (m/z): calculated for C15H16NaO4+ [M+Na]+: 283.0941, found 283.0946.

4. The synthesis of hemiacetal 14

(3R,4R)-3-(4-(benzyloxy)-3,5-dimethoxybenzyl)-4-vinyl-dihydrofuran-2(3H)-one (7)
To a stirred solution of (S)-Taniguchi lactone 9 (200 mg, 1.78 mmol, 1 eq.) in THF (10 mL) at −78 °C was slowly added LiHMDS (1.0 M in THF, 2.14 mL, 2.14 mmol, 1.2 eq.). After stirring for 10 min at the same temperature, a solution of bromide 8 (720 mg, 2.14 mmol, 1.2 eq.) in THF (10 mL) was added in 5 min. The reaction mixture was allowed to slowly warm up, stirred for an additional 1 h, then quenched by the addition of a saturated aqueous solution of NH₄Cl (0.25 mL). The organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:5) to afford lactone 7 (468 mg, 1.27 mmol, 71% yield, diastereoselectivity > 95 : 5) as a white solid.

**TLC:** Rₜ = 0.24 (silica gel, EtOAc/petroleum ether, 1:5).

**Melting Point:** 111 °C.

**¹H NMR** (400 MHz; CDCl₃): δ 2.63–2.68 (m, 1H), 2.79-2.89 (m, 1H), 3.99 (ddd, J = 42.1, 14.1, 5.3 Hz, 1H), 3.78 (s, 3H), 3.85 (t, J = 9.5 Hz, 1H), 4.23 (t, J = 8.5 Hz, 1H), 4.99 (s, 2H), 5.09 (d, J = 11.1 Hz, 1H), 5.13 (d, J = 3.8 Hz, 1H), 5.58 (m, ddd, J = 16.9, 9.6, 7.5 Hz, 1H), 6.41 (s, 2H), 7.28-7.35 (m, 3H), 7.48 (d, J = 6.9 Hz, 2H) ppm.

**¹³C NMR** (100 MHz; CDCl₃): δ 33.7, 44.5, 46.6, 56.1, 69.9, 74.9, 106.5, 118.7, 127.8, 128.1, 128.5, 133.2, 135.1, 135.4, 137.8, 153.4, 177.8 ppm.

**HRMS (m/z):** calculated for C₂₂H₂₄NaO₅ [M+Na]⁺: 391.1516, found 391.1505.

[α]⁺₂₅ = -17.2 (c=1.0, CHCl₃).

(2R,3R)-benzyl 2-(4-(benzyloxy)-3,5-dimethoxybenzyl)-3-(benzyloxymethyl)pent-4-enoate (12)

To a solution of 7 (420 mg, 1.14 mmol, 1 eq.) in toluene (7.0 mL) at room temperature was added KOH (320 mg, 5.71 mmol, 5 eq.) and BnBr (976 mg, 5.71 mmol, 5 eq.). Then the flask was put into oil-bath pre-heated at 65 °C. After 7 h, the reaction was quenched with H₂O (20 mL) and extracted with EtOAc (3 x 20 mL). The organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:10) to afford ester 12 (545 mg, 0.89 mmol, 78% yield) as a colorless oil.

**TLC:** Rₜ = 0.41 (silica gel, EtOAc/petroleum ether, 1:5).

**¹H NMR** (400 MHz; CDCl₃): δ 2.69-2.80 (m, 2H), 2.85-2.92 (m, 2H), 3.47 (d, J = 5.9 Hz, 2H), 3.69 (s,
(2R,3R)-2-(4-(benzyloxy)-3,5-dimethoxybenzyl)-3-(benzyloxymethyl)pent-4-en-1-ol (13)

To a stirred solution of ester 12 (1.27 g, 1.78 mmol, 1 eq.) in THF (20 mL) at 0 °C was carefully added LiAlH₄ (128 mg, 2.14 mmol, 1.2 eq.). After stirring for 0.5 h at the same temperature, the reaction mixture was carefully quenched by the addition of H₂O (0.25 mL). Then aq. HCl (1N, 20 mL) and Et₂O (20 mL) were added and the solution was stirred for 0.5 h. The layers were separated and the aqueous phase was extracted with Et₂O (2 x 20 mL). The organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:4 to 1:2) to afford alcohol 13 (1.26 g, 1.76 mmol, 99% yield) as a white solid.

TLC: Rᵣ = 0.37 (silica gel, EtOAc/petroleum ether, 1:2).

Melting Point: 59-60 °C.

¹H NMR (400 MHz; CDCl₃): δ 1.88-1.93 (m, 1H), 2.44-2.58 (m, 3H), 2.70 (dd, J = 13.6, 4.5 Hz, 1H), 3.45 (dd, J = 11.4, 4.8 Hz 1H), 3.53-3.65 (m, 3H), 3.76 (s, 6H), 4.53 (dd, J = 17.2, 11.8, Hz 2H), 4.96 (m, 2H), 5.15-5.27 (m, 2H), 5.79-5.88 (m, 1H), 6.36 (s, 2H), 7.24-7.34 (m, 8H), 7.48 (d, J = 6.9 Hz, 2H) ppm.

¹³C NMR (100 MHz; CDCl₃): δ 35.3, 44.9, 45.4, 56.1, 61.8, 71.9, 73.5, 75.1, 108.0, 117.3, 127.9, 128.2, 128.6, 135.0, 136.1, 137.7, 138.0, 138.2, 153.3 ppm.

HRMS (m/z): calculated for C₂₉H₂₈NaO₅⁺ [M+Na⁺]: 589.2298, found 589.2308. 

[α]₂₅° = +19.4 (c=1.0, CHCl₃).

(3R,4R)-4-(4-(benzyloxy)-3,5-dimethoxybenzyl)-3-(benzyloxymethyl)-tetrahydrofuran-2-ol (14)

To a stirred solution of alcohol 13 (100 mg, 0.22 mmol, 1 eq.) in t-BuOH/H₂O/THF (1:1:1, 6 mL) was added K₂OsO₄·2H₂O (4 mg, 0.01 mmol) and NMO (50% aq. 152 mg, 0.66 mmol, 3 eq.). The resulting mixture was stirred at 35 °C for 2 days. The mixture was quenched with saturated aqueous Na₂SO₃ (4 mL)
and stirred for 1 h. The mixture was extracted with ethyl acetate (3 x 5 mL). The organic layers were combined and washed with aqueous KOH (1 M, 10 mL) then dried over Na$_2$SO$_4$. Solvent was removed under reduced pressure. The crude product was used directly in next step without further purification.

To a stirred solution of crude product in acetone/H$_2$O (3:1, 8 mL) was added NaIO$_4$ (139 mg, 0.66 mmol, 3 eq.) which was then stirred at room temperature for 0.5 h. The mixture was quenched with addition of brine (10 mL) and extracted with Et$_2$O (3 x 10 mL). The organic extracts were combined and dried over Na$_2$SO$_4$. Solvent was removed under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:1) to afford hemiacetal 14 (94 mg, 0.20 mmol, 93% yield in 2 steps) as a colorless oil.

**TLC:** $R_f= 0.41$ (silica gel, EtOAc/petroleum ether, 1:1).

$^1$H NMR (400 MHz; CDCl$_3$ mixture of 2 diastereoisomers, signals of minor indicated by *): $\delta$ 2.39 (dd, $J = 13.6, 10.5$ Hz, 1H), 2.47-2.51 (m, 1H), 2.53-2.56* (m, 1H), 2.63-2.65* (m, 2H), 2.83-2.86* (m, 1H), 2.77 (dd, $J = 13.6, 5.5$ Hz, 1H), 2.87-2.93 (m, 1H), 3.52 (t, $J = 8.6$ Hz, 1H), 3.57-3.59* (m, 1H), 3.61-3.66 (m, 2H), 3.73-3.75* (m, 1H), 3.77 (s, 6H), 3.77* (s, 6H), 3.80-3.88 (m, 1H), 4.01 (t, $J = 7.8$ Hz, 1H), 4.54 (s, 1H), 4.56* (s, 2H), 4.97 (s, 2H), 5.46 (s, 1H), 5.51* (s, 1H), 6.33 (s, 2H), 6.34* (s, 2H), 7.25-7.36 (m, 12H), 7.48 (d, $J = 7.1$ Hz, 3H) ppm.

$^{13}$C NMR (100 MHz; CDCl$_3$ mixture of 2 diastereoisomers, signals of minor indicated by *): $\delta$ 34.0, 35.7*, 40.5*, 40.7, 46.2*, 49.2, 56.2, 66.7*, 67.4, 72.0, 73.5, 73.7*, 75.1, 99.3*, 101.4, 105.6, 105.8, 127.8, 127.9, 128.0, 128.2, 128.6, 135.4, 136.4, 136.9*, 138.0, 138.1, 153.5 ppm.

**HRMS** (m/z): calculated for C$_{28}$H$_{32}$NaO$_6$ $^+ [M+Na]^+$: 487.2091, found 487.2091.

The initially proposed double Friedel-Crafts reaction process between 5 and 14 was checked in DCM with trifluoroacetic acid (TFA 2 eq.), AlCl$_3$ (2 eq.), TiCl$_4$ (2 eq.) and BF$_3$·OEt$_2$, respectively. All experiments lead to complicated system. And no reasonable products were obtained after the column chromatography. As a note, the treatment of 5 and 14 with TFA in hexafluoropropanol (HFIP) gave an unexpected product 18 through an intramolecular Friedel-Crafts reaction/reduction/deprotection process.

![Diagram of reaction](image)

To a stirred solution of hemiacetal 14 (17 mg, 0.037 mmol, 1 eq.) in HFIP (0.5 mL), was added phenol 5 (17 mg, 0.073 mmol, 2 eq.) and TFA (4 mg, 0.073 mmol, 1 eq.). After 10 min at room temperature, the reaction was quenched with aq.NaHCO$_3$ (2 mL) and extracted with EtOAc (3 x 3 mL). The organic phases were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The obtained residue was purified by
flash column chromatography (silica gel, EtOAc/petroleum ether, 1:1) to afford 18 (7 mg, 0.020 mmol, 53% yield) as a colorless oil and phenol 5 (15 mg).

**TLC:** \( R_f = 0.14 \) (silica gel, EtOAc/petroleum ether, 1:1).

**\(^1H\) NMR (400 MHz; CDCl\(_3\)):** \( \delta \) 1.16-1.80 (m, 2H), 2.37 (dd, \( J = 16.6, 9.7 \) Hz, 1H), 2.59 (dd, \( J = 16.1, 9.8 \) Hz, 1H), 2.69 (dd, \( J = 16.1, 3.8 \) Hz, 1H), 2.81 (dd, \( J = 16.6, 4.2 \) Hz, 1H), 2.88 (s, 1H), 2.64-3.70 (m, 2H), 3.80 (s, 3H), 3.84-3.53 (m, 5H), 4.98 (s, 2H), 6.43 (s, 1H), 7.31 (t, \( J = 7.2 \) Hz, 1H), 7.37 (t, \( J = 7.2 \) Hz, 2H), 7.51 (d, \( J = 7.2 \) Hz, 2H) ppm.

**\(^{13}C\) NMR (100 MHz; CDCl\(_3\)):** \( \delta \) 26.4, 32.9, 40.0, 40.4, 56.1, 60.8, 66.2, 66.4, 75.4, 107.6, 122.1, 127.9, 128.3, 128.4, 128.5, 131.2, 132.1, 135.2, 136.4, 138.0, 138.1, 138.4, 151.4, 151.8 ppm.

**HRMS (m/z):** calculated for C\(_{21}\)H\(_{26}\)NaO\(_5\)\(^+\) \([\text{M+Na}]^+\): 381.1672, found 381.1690.

**[\(\alpha\)]\(_{25}^D\) = -36.4 (c=1.0, CHCl\(_3\)).**

5. Total syntheses of (+)-ovafolinin B (2)

2-(benzyloxy)-5-((3R)-2-((4-(benzyloxy)-3,5-dimethoxyphenoxy)methyl)-3-(benzyloxymethyl)pent-4-enyl)-1,3-dimethoxybenzene (15)

![Reaction scheme for the synthesis of 15](image)

To a stirred solution of alcohol 13 (100 mg, 0.32 mmol, 1 eq.) in toluene/Et\(_2\)O (4:1, 5 mL), was added PPh\(_3\) (113 mg, 0.68 mmol, 2 eq.), phenol 5 (112 mg, 0.64 mmol, 2 eq.) and DIAD (87 mg, 0.68 mmol, 2 eq.). The resulting mixture was stirred for 18h at room temperature. Solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/petroleum ether, 1:8) to give ether 15 (143 mg, 20.3 mmol, 94%) as a colorless oil.

**TLC:** \( R_f = 0.55 \) (silica gel, EtOAc/petroleum ether, 1:2).

**\(^1H\) NMR (400 MHz; CDCl\(_3\)):** \( \delta \) 2.28-2.33 (m, 1H), 2.47-2.53 (m, 1H), 2.73-2.79 (m, 1H), 2.83 (dd, \( J = 13.6, 4.5 \) Hz, 1H), 3.58-3.64 (m, 2H), 3.65 (s, 6H), 3.74 (s, 1H), 3.76-3.82 (m, 2H), 5.17-5.24 (m, 2H), 5.87-5.96 (m, 1H), 6.04 (s, 1H), 6.33 (s, 1H), 7.27-7.35 (m, 11H), 7.46-7.48 (m, 4H) ppm.

**\(^{13}C\) NMR (100 MHz; CDCl\(_3\)):** \( \delta \) 34.9, 41.0, 44.7, 60.0, 56.2, 67.0, 71.7, 73.2, 75.1, 75.3, 92.3, 106.2, 117.7, 127.7, 127.8, 127.9, 128.2, 128.4, 128.5, 128.6, 131.2, 135.2, 136.4, 138.0, 138.1, 138.4, 151.4, 155.8 ppm.

**HRMS (m/z):** calculated for C\(_{44}\)H\(_{48}\)NaO\(_8\)\(^+\) \([\text{M+Na}]^+\): 727.3241, found 727.3242.

**[\(\alpha\)]\(_{25}^D\) = +36.6 (c=1.0, CHCl\(_3\)).**

(2R)-3-((4-(benzyloxy)-3,5-dimethoxyphenoxy)methyl)-4-(4-(benzyloxy)-3,5-dimethoxyphenyl)-2-(benzyloxymethyl)butanal (16)
To a stirred solution of olefin 15 (0.95 g, 1.35 mmol, 1 eq.) in t-BuOH/H₂O/THF (1:1:1, 60 mL) was added K₂OsO₄·H₂O (25 mg, 0.07 mmol) and NMO (50% aq. 0.93 g, 4.05 mmol, 3 eq.). The resulting mixture was stirred at 35 °C for 2 days. The mixture was quenched with saturated aqueous Na₂SO₃ (40 mL) and stirred for 1 h. The mixture was extracted with ethyl acetate (3 x 40 mL). The organic layers were combined and washed with aqueous KOH (1 M, 40 mL) and dried over Na₂SO₄. Solvent was removed under reduced pressure. The crude product was used directly in next step without further purification.

To a stirred solution of crude product in acetone/H₂O (3:1, 40 mL) was added NaIO₄ (0.85 g, 4.05 mmol, 3 eq.) and stirred for 1 h at room temperature. The mixture was quenched with addition of brine (20 mL) and extracted with Et₂O (3 x 40 mL). The organic extracts were combined and dried over Na₂SO₄. Solvent was removed under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether, 1:5) to afford aldehyde 14 (734 mg, 1.04 mmol, 77% yield in 2 steps) as a colorless oil.

**TLC**: R f 0.45 (silica gel, EtOAc/petroleum ether, 1:2).

**¹H NMR** (400 MHz; CDCl₃): δ 2.70-2.74 (m, 1H), 2.78-2.84 (m, 3H), 3.68 (s, 6H), 3.76 (s, 6H), 3.83 (d, J = 4.3 Hz, 2H), 3.85-3.92 (m, 2H), 4.52 (s, 2H), 4.92 (s, 2H), 4.96 (s, 2H), 6.05 (s, 2H), 6.36 (s, 2H), 7.27-7.37 (m, 11H), 7.46-7.49 (m, 4H), 9.85 (d, J = 0.9 Hz, 1H) ppm.

**¹³C NMR** (100 MHz; CDCl₃): δ 35.8, 38.6, 53.0, 55.9, 56.1, 66.4, 67.1, 73.5, 75.0, 75.3, 92.0, 106.1, 127.7, 127.8, 127.9, 128.1, 128.5, 128.6, 137.6, 137.7, 153.4, 153.9, 155.3, 203.5 ppm.

**HRMS** (m/z): calculated for C₄₃H₄₆NaO₉⁺ [M+Na]⁺: 729.3034, found 729.3036. [α]D²⁵ = +21.6 (c=1.0, CHCl₃).

(13R,14R)-2,11-bis(benzyloxy)-14-((benzyloxy)methyl)-1,3,10,12-tetramethoxy-6,7,8,13-tetrahydro-7,13-methanodibenzo[b,e]oxonine (3)

To a stirred solution of 16 (26 mg, 0.04 mmol, 1 eq.) in DCM (1 mL) was added TFA (4 mg, 0.68 mmol, 4 eq.). The resulting mixture was stirred for 1 h at room temperature. The mixture was quenched with saturated aqueous NaHCO₃ (3 mL) and extracted with ethyl acetate (3 x 4 mL). The organic layers were combined, dried over Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, EtOAc/petroleum ether=1:10) to afford 3 (22 mg, 0.03 mmol,
87% yield) as a colorless oil.

TLC: R_f = 0.57 (silica gel, EtOAc/petroleum ether, 1:2).

^1^H NMR (400 MHz; CDCl_3): δ 2.35 (d, J = 6.3 Hz, 1H), 2.40 (t, J = 7.6 Hz, 1H), 2.91 (d, J = 17.6 Hz, 1H), 3.10 (dd, J = 17.5, 7.1 Hz, 1H), 3.40 (s, 3H), 3.49 (t, J = 8.8 Hz, 1H), 3.62 (dd, J = 9.2, 7.2 Hz, 1H), 3.70 (s, 3H), 3.78 (s, 3H), 3.86 (d, J = 12.1 Hz, 1H), 3.97 (s, 3H), 4.45 (dd, J = 12.1, 2.6 Hz, 1H), 4.52 (dd, J = 22.7, 11.9 Hz, 2H), 4.64 (s, 1H), 4.86 (d, J = 10.8 Hz, 2H), 4.95 (d, J = 12.6 Hz, 2H), 5.06 (d, J = 10.7 Hz, 2H), 6.27 (s, 1H), 6.42 (s, 1H), 7.23-7.25 (m, 1H), 7.27-7.38 (m, 10H), 7.43 (d, J = 7.0 Hz, 2H), 7.54 (d, J = 4.7 Hz, 2H) ppm.

^13^C NMR (100 MHz; CDCl_3): δ 29.6, 30.6, 33.9, 41.2, 55.8, 55.9, 60.4, 62.1, 72.5, 73.3, 74.9, 75.3, 80.3, 101.8, 106.5, 122.9, 124.4, 127.6, 127.7, 127.9, 128.3, 128.4, 131.2, 137.6, 138.1, 138.6, 139.2, 151.6, 151.9, 152.0, 152.3, 156.4 ppm.

HRMS (m/z): calculated for C_{43}H_{44}NaO_8^+ [M+Na]^+: 711.2928, found 711.2927.

[α]_{D}^{25} = +137.2 (c=1.0, CHCl_3).

(+)-ovafolinin B (2)

A mixture of 3 (311 mg, 0.45 mmol, 1 eq.) and 10% Pd/C (50% wetted, 40 mg) in EtOAc/EtOH (1:2, 15 mL) was evacuated and back-filled with H_2 three times. After stirring for 12 h at room temperature, the mixture was filtered over a pad of Celite and eluted with EtOAc (15 mL). The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, MeOH/DCM, 1:20) to provide (+)-ovafolinin B (187 mg, 0.45 mmol, 99% yield) as a colorless amorphous.

TLC: R_f = 0.24 (silica gel, MeOH/DCM, 1:20).

^1^H NMR (400 MHz; CDCl_3): δ 2.18–2.21 (m, 2H), 2.86 (d, J = 17.4 Hz, 1H), 3.03 (dd, J = 17.4, 6.9 Hz, 1H), 3.39 (s, 3H), 3.59 (dd, J = 10.6, 6.9 Hz, 1H), 3.69 (dd, J = 10.6, 7.9 Hz, 1H), 3.71 (s, 3H), 3.78 (br d, J = 11.4 Hz, 1H), 3.78 (s, 3H), 3.92 (s, 3H), 4.40 (dd, J = 12.0, 2.4 Hz, 1H), 4.58 (br s, 1H), 5.71 (s, 1H), 5.58 (s, 1H), 6.24 (s, 1H), 6.37 (s, 1H) ppm.

^13^C NMR (100 MHz; CDCl_3): δ 29.2, 29.9, 33.9, 43.4, 55.8, 56.0, 59.8, 61.7, 64.8, 80.4, 101.2, 105.5, 122.4, 123.8, 126.2, 134.7, 136.4, 144.6, 145.3, 146.2, 152.9 ppm.

HRMS (m/z): calculated for C_{22}H_{26}NaO_8^+ [M+Na]^+: 441.1520, found 441.1516.

[α]_{D}^{17} = +166.0 (c=0.16, MeOH).

6. Total syntheses of (+)-ovafolinin A (1)

(+)-ovafolinin A (1)
To a solution of (+)-ovafolinin B (2) (20 mg, 0.05 mmol, 1 eq.) in MeCN (2 mL) was added Cu(OAc)$_2$ (113 mg, 0.10 mmol, 2 eq.). The resulting mixture was stirred for 2 h at 65 °C. The mixture was cooled to room temperature and added Na$_2$EDTA (4 mL). After stirring for 0.5 h, the mixture was extracted with ethyl acetate (3 x 4 mL). The organic layers were combined and dried over Na$_2$SO$_4$ then concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (silica gel, MeOH/DCM, 1:40) to afford (+)-ovafolinin A (1) (18.4 mg, 0.04 mmol, 91% yield) as a colorless amorphous.

**TLC:** $R_f = 0.37$ (silica gel, MeOH/DCM, 1:20).

**$^1$H NMR** (400 MHz; CDCl$_3$): $\delta$ 2.31-2.35 (m, 1H), 2.59-2.62 (m, 1H), 3.24 (s, 1H), 3.74 (br d, $J = 8.6$ Hz, 1H), 3.77 (s, 3H), 3.86 (s, 3H), 3.99 (dd, $J = 13.2, 2.82$ Hz, 1H), 4.06 (s, 3H), 4.14 (dd, $J = 8.5, 5.7$ Hz, 1H), 4.50 (d, $J = 2.4$ Hz, 1H), 4.53 (d, $J = 13.4$ Hz, 1H), 4.76 (d, $J = 4.4$ Hz, 1H), 5.47 (s, 1H), 5.49 (s, 1H), 6.26 (s, 1H), 6.53 (s, 1H) ppm.

**$^{13}$C NMR** (100 MHz; CDCl$_3$): $\delta$ 37.5, 39.9, 43.1, 56.0, 56.2, 59.3, 60.7, 69.5, 72.6, 79.2, 100.9, 104.9, 123.0, 124.7, 128.9, 135.2, 138.7, 144.1, 145.1, 145.8, 146.3, 152.1 ppm.

**HRMS** ($m/z$): calculated for C$_{22}$H$_{24}$NaO$_8$ $^+$ [M+Na]$^+$: 439.1363, found 439.1362.  
$[\alpha]_D^{22} = +159.4$ (c=0.36, MeOH).
7. Comparison of $^1$H NMR data of synthetic and natural ovafolinin A and B in CDCl$_3$

![Ovafolinin A (1)](image1)

![Ovafolinin B (2)](image2)

<table>
<thead>
<tr>
<th>H</th>
<th>ovafolin A natural</th>
<th>ovafolin A synthetic</th>
<th>ovafolin B natural</th>
<th>ovafolin B synthetic</th>
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<td>2.24 (1H, *)</td>
<td>2.18-2.21 (1H, m)</td>
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<td>2.22 (1H, *)</td>
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</table>
8. Copies of $^1$H NMR and $^{13}$C NMR Spectra

Copy of $^1$H NMR spectrum of compound 9

Copy of $^{13}$C NMR spectrum of compound 9
Copy of $^1\text{H}$ NMR spectrum of compound 11

Copy of $^{13}\text{C}$ NMR spectrum of compound 11
Copy of $^1$H NMR spectrum of compound 8

Copy of $^{13}$C NMR spectrum of compound 8
Copy of $^1$H NMR spectrum of compound 5

Copy of $^{13}$C NMR spectrum of compound 5
Copy of $^1$H NMR spectrum of compound 7

Copy of $^{13}$C NMR spectrum of compound 7
Copy of $^1$H NMR spectrum of compound 12

Copy of $^{13}$C NMR spectrum of compound 12
Copy of $^1$H NMR spectrum of compound 13

Copy of $^{13}$C NMR spectrum of compound 13
Copy of $^1$H NMR spectrum of compound 14

Copy of $^{13}$C NMR spectrum of compound 14
Copy of $^1$H NMR spectrum of compound 15

Copy of $^{13}$C NMR spectrum of compound 15
Copy of $^1$H NMR spectrum of compound 16 (containing small amount of EtOAc and Et$_2$O)

Copy of $^{13}$C NMR spectrum of compound 16 (containing small amount of EtOAc and Et$_2$O)
Copy of $^1$H NMR spectrum of compound 3 (containing small amount of EtOAc)

Copy of $^{13}$C NMR spectrum of compound 3 (containing small amount of EtOAc)
Copy of $^1$H NMR spectrum of (+)-ovafolinin B (2) (containing small amount of EtOAc and CH$_2$Cl$_2$)

Copy of $^{13}$C NMR spectrum of (+)-ovafolinin B (2) (containing small amount of EtOAc and CH$_2$Cl$_2$)
Copy of $^1$H NMR spectrum of (+)-ovafolinin A (1)

Copy of $^{13}$C NMR spectrum of (+)-ovafolinin A (1)
Copy of $^1$H NMR spectrum of compound 18

Copy of $^{13}$C NMR spectrum of compound 18
Copy of DEPT-135 spectrum of compound 18