Asymmetric Synthesis of (S)-Tylophorine and (S)-Cryptopleurine via one-pot Curtius Rearrangement and Friedel-Crafts Reaction tandem Sequence

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General information All chemicals were analytical grade and anhydrous solvents were prepared by standard methods before use. $^1$H NMR and $^{13}$C NMR spectra were obtained by using a Bruker AV400 spectrometer and CDCl$_3$ or DMSO-$d_6$ as solvent. Melting points are uncorrected. High-resolution mass spectra (HRMS) were obtained with a FTICR-MS (Ionspec 7.0T) spectrometer. Optical rotations were measured with an Autopol IV auto digital polarimeter (Rudolph Research Analytical).

(R)-3-(5-(benzyloxy)pentanoyl)-4-isopropyl oxazolidin-2-one (9a). To a solution of (R)-4-isopropyl oxazolidin-2-one (1.0 g, 7.7 mmol) in THF (30 mL) was added n-BuLi (3.2 mL, 7.8 mmol, 2.4 M in THF) dropwise at -78 °C under an atmosphere of Ar. The mixture was stirred at this temperature for 30 min to give lithio-oxazolidinone solution. In another flask, 5-(benzyloxy)pentanoic acid (1.6 g, 7.7 mmol) and triethylamine (1.5 mL, 10.7 mmol) were mixed together in THF (150 mL) at 0 °C, to which pivaloyl chloride (1.5 mL, 10.7 mmol) was added slowly. After stirring at this temperature for 30 min, the lithio-oxazolidinone solution was added to this freshly formed mixed anhydride, and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with saturated aqueous ammonium chloride and extracted with EtOAc (20 mL × 3). The combined organic layer was successively washed with saturated aqueous NaHCO$_3$ (30 mL), saturated aqueous ammonium chloride (30 mL) and brine (30 mL), and then dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give compound 9a (1.6 g, 67%) as a colourless oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.32 (dd, $J = 15.6, 13.2$ Hz, 5H), 4.50 (s, 2H), 4.45–4.38 (m, 1H), 4.27–4.16 (m, 2H), 3.51 (t, $J$
= 6.4 Hz, 2H), 3.06–2.86 (m, 2H), 2.42–2.31 (m, 1H), 1.82–1.73 (m, 2H), 1.73–1.65 (m, 2H), 0.91 (d, \(J = 7.2\) Hz, 3H), 0.86 (d, \(J = 7.2\) Hz, 3H);\(^{13}\)C NMR(100 MHz, CDCl\(_3\)) \(\delta 172.9, 153.9, 138.4, 128.2, 127.4, 127.3, 72.7, 69.8, 63.2, 58.2, 35.0, 28.9, 28.2, 21.0, 17.7, 14.5\); HRMS (MALDI) calcd for C\(_{18}\)H\(_{25}\)NO\(_4\)Na [M+Na\(^+\)] 342.1681, found 342.1684.

(R)-3-((S)-5-(benzyloxy)-2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)pentanoyl)-4-isopropyloxazolidin-2-one (11a). To a solution of compound 9a (1.2 g, 3.8 mmol) in THF (50 mL) was added NaHMDS (4.4 mL, 4.4 mmol, 1 M in THF) via a syringe dropwise at -78 \(^\circ\)C under an atmosphere of Ar. One hour later, 2,3,6,7-tetramethoxyphenanthryl bromide(1.0 g, 2.5 mmol in THF (100 mL)) was added slowly via a syringe. The reaction mixture was stirred at this temperature overnight and then quenched with aqueous saturated ammonium chloride. After separation, the aqueous layer was extracted with EtOAc (100 mL \(\times 3\)). The combined organic phase was washed with brine (100 mL \(\times 2\)), dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound 11a (0.9 g, 60%) as a white solid: mp 65–67 \(^\circ\)C; \([\alpha]^{26}_D\) -7.4 (c 0.14, CHCl\(_3\)).\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.81\) (s, 1H), 7.75 (s, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.33–7.26 (m, 3H), 7.25–7.22 (m, 2H), 7.14 (s, 1H), 4.66–4.57 (m, 1H), 4.41 (t, \(J = 2.2\) Hz, 2H), 4.42–4.40 (m, 1H), 4.14–4.09 (m, 9H), 4.08–4.03 (m, 1H), 4.01 (s, 3H), 3.56 (dd, \(J = 13.6, 8.4\) Hz, 1H), 3.46–3.35 (m, 2H), 3.16 (dd, \(J = 13.6, 7.6\) Hz, 1H), 2.10–1.99 (m, 1H), 1.95–1.84 (m, 1H), 1.69–1.60 (m, 3H), 1.59–1.50 (m, 1H), 0.75 (d, \(J = 7.2\) Hz, 3H), 0.27 (d, \(J = 6.8\) Hz, 3H).\(^{13}\)C NMR (100 MHz,
CDCl$_3$) $\delta$ 176.2, 153.6, 149.0, 148.9, 148.8, 148.7, 138.4, 130.5, 128.3, 127.6, 127.5, 126.2, 125.9, 125.5, 124.9, 123.9, 107.9, 105.2, 103.3, 102.7, 72.9, 70.1, 58.4, 56.2, 56.1, 56.0, 55.9, 42.6, 36.7, 28.8, 28.3, 27.6, 17.9, 13.8; HRMS (MALDI) calcd for C$_{37}$H$_{43}$NO$_8$ [M]$^+$ 629.2983, found 629.2974.

(S)-5-(benzyloxy)-2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)pentanoic acid (8a). A solution of 11a (0.47 g, 0.75 mmol) in THF/H$_2$O (3/1, 20 mL) was added 30% H$_2$O$_2$ (3.3 mL) within 5 min, then LiOH (0.21g, 5.0 mmol) was added. The reaction mixture was stirred at room temperature for 3 hours and then quenched with aqueous saturated sodium sulfite in ice-bath, and then stirred at this temperature for another 0.5 h. The aqueous layer was extracted with CH$_2$Cl$_2$ (20 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound 8a (0.35 g, 85%) as a white solid: mp 132–134 °C; [α]$^D_{26} +12$ (c 0.12, CHCl$_3$).$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.25 (s, 1H), 8.10 (s, 1H), 8.04 (s, 1H), 7.51 (s, 1H), 7.47 (s, 1H), 7.36-7.25 (m, 6H), 4.47–4.39 (m, 2H), 4.09 (s, 3H), 4.07 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.46 (t, $J = 6.0$ Hz, 2H), 3.36 (dd, $J = 14.0$, 7.6 Hz, 1H), 3.17 (dd, $J = 14.0$, 6.0 Hz, 1H), 2.85–2.75 (m, 1H), 1.81–1.59 (m, 4H);$^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 176.5, 148.9, 148.7, 148.6, 148.3, 138.6, 130.9, 128.1, 127.3, 127.2, 125.7, 124.6, 124.5, 123.4, 108.1, 104.8, 104.4, 103.7, 71.7, 69.3, 55.9, 55.8, 55.4, 55.2, 45.5, 35.9, 28.8, 27.2; HRMS (MALDI) calcd for C$_{31}$H$_{34}$O$_7$ [M]$^+$ 518.2299, found 518.2295.

(S)-3-(3-(benzyloxy)propyl)-6,7,10,11-tetramethoxy-3,4-
dihydrodibenzo[f,h]isoquinolin-1(2H)-one (13a). A solution of 8a (0.4 g, 0.77 mmol) in toluene (30 mL) was added triethylamine (0.5 mL, 3.6 mmol) and diphenylazidophosphate (DPPA) (0.5 mL, 2.3 mmol), and the mixture was stirred for 3 hours in ice-bath. Then the mixture was added BF$_3$Et$_2$O (0.22 mL, 2.3 mmol), stirred another 1 hour at room temperature, and then quenched with aqueous saturated ammonium chloride. The toluene was evaporated in vacuo, and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound 13a (0.22 g, 56%) as a white solid: mp 162–164 °C. [α]$_D$ +102.6 (c 0.3, CHCl$_3$). $^1$H NMR (400 MHz, MeOD) δ 8.75 (s, 1H), 7.79 (d, $J$ = 2.4 Hz, 2H), 7.31 (s, 1H), 7.25–7.15 (m, 5H), 4.46 (s, 2H), 4.04 (s, 3H), 4.02 (s, 3H), 3.94 (s, 6H), 3.62 (br, 1H), 3.52 (d, $J$ = 5.6 Hz, 2H), 3.37–3.31 (m, 1H), 2.95 (dd, $J$ = 16.0, 9.6 Hz, 1H), 1.80–1.75 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.9, 150.7, 149.1, 148.9, 148.8, 138.2, 134.5, 128.4, 127.7, 127.0, 124.5, 124.2, 123.3, 120.6, 108.1, 104.9, 103.2, 102.4, 73.2, 69.7, 56.0, 55.9, 55.8, 49.8, 32.4, 31.9, 26.0; HRMS (ESI) calcd for C$_{31}$H$_{33}$NO$_6$ [M+H]$^+$ 516.2381, found 516.2383.

(S)-3-(3-hydroxypropyl)-6,7,10,11-tetramethoxy-3,4-
dihydrodibenzo[f,h]isoquinolin-1(2H)-one (14a). To a solution of 13a (0.22 g, 0.43 mmol) in glacial acetic acid was added 10% Pd-C (0.02 g), and then the reaction mixture was stirred under an atmosphere of H$_2$. The reaction mixture was stirred at room temperature overnight and then quenched with aqueous saturated sodium...
bicarbonate. The aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound 14a (0.15 g, 83%) as a white solid: mp 196–198 °C. [α]° 26 +83.3 (c 0.12, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.95 (s, 1H), 7.76 (s, 1H), 7.75 (s, 1H), 7.25 (s, 1H), 7.23 (s, 1H), 4.13 (s, 3H), 4.12 (s, 3H), 4.08 (s, 3H), 4.00 (s, 3H), 3.80–3.67 (m, 3H), 3.32 (dd, J = 15.6, 3.6 Hz, 1H), 2.99 (dd, J = 15.6, 11.6 Hz, 1H), 2.66 (br, 1H), 1.95–1.85 (m, 2H), 1.82–1.75 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.1, 150.6, 149.1, 148.9, 148.8, 134.7, 127.0, 124.5, 124.1, 123.2, 120.5, 108.0, 104.9, 103.1, 102.5, 62.2, 56.1, 56.0, 55.9, 55.8, 49.9, 32.6, 31.4, 28.5; HRMS (MALDI) calcd for C₃₂H₂₈NO₆ [M+H]+ 426.1911, found 426.1905.

(S)-3-(6,7,10,11-tetramethoxy-1-oxo-1,2,3,4-tetrahydrodibenzo[f,h]isoquinolin-3-yl)propyl methanesulfonate (7a). To a solution of 14a (16.2 mg, 0.04 mmol) in CH₂Cl₂ (10 mL) was added triethylamine (10.5 µL), the reaction mixture was stirred 10 minutes and then MsCl (5.9 µL) was added. After stirring for 1 hour, the reaction was quenched with aqueous saturated ammonium chloride and concentrated in vacuo. The aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound 7a (14.9 mg, 78%) as a white solid: mp 126–128 °C. [α]° 26 +44.8 (c 0.13, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.96 (s, 1H), 7.82 (s, 1H), 7.78 (s, 1H), 7.32 (s, 1H), 6.45 (s, 1H), 4.35–4.20 (m, 2H), 4.15 (s, 3H), 4.13 (s, 3H), 4.07 (s, 6H), 3.81 (br,
1H), 3.46 (d, J = 15.6 Hz, 1H), 3.19–3.07 (m, 1H), 3.01 (s, 3H), 1.97–1.92 (m, 2H), 1.92–1.82 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 167.7, 150.7, 149.1, 149.0, 148.8, 134.2, 127.1, 124.5, 124.1, 123.2, 120.4, 108.0, 104.9, 103.2, 102.5, 69.3, 56.1, 56.0, 55.94, 55.91, 49.4, 37.4, 32.2, 30.9, 25.6; HRMS (MALDI) calcd for C29H30NO8S [M+H]+ 504.1687, found 504.1680.

*(S*)-2,3,6,7-tetramethoxy-12,13,13a,14-tetrahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinolin-9(11H)-one (6a). To a solution of 7a (0.19 g, 0.38 mmol) in THF (20 mL) was added NaH (16.2 mg, 0.67 mmol), and then the reaction mixture was heated at reflux for 3 hours. After cooling to room temperature, the reaction was quenched with aqueous ammonium chloride, and then concentrated in vacuo. The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over Na2SO4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound 6a (0.14 g, 93%) as a white solid: mp 287–289 °C; [α]D +150 (c 0.13, CHCl3), 1H NMR (400 MHz, CDCl3) δ 9.02 (s, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.27 (s, 1H), 4.15 (d, J = 12.2 Hz, 3H), 4.11 (s, 3H), 4.09 (s, 3H), 4.04 (s, 3H), 3.93–3.76 (m, 3H), 3.54 (dd, J = 15.4, 3.6 Hz, 1H), 2.90 (t, J = 14.4 Hz, 1H), 2.46–2.38 (m, 1H), 2.17 (s, 1H), 1.95 (d, J = 12.6 Hz, 2H), 13C NMR (100 MHz, CDCl3) δ 164.7, 150.3, 148.9, 148.8, 148.7, 133.3, 126.7, 124.4, 124.3, 123.2, 122.5, 108.0, 104.8, 103.1, 102.3, 56.0, 55.9, 55.9, 55.2, 45.4, 33.9, 32.6, 23.6; HRMS (MALDI) calcd for C24H26NO5 [M+H]+ 408.1805, found 408.1805.

*(S*)-tylophorine. To a solution of 6a (11.6 mg, 0.03 mmol) in THF (20 mL) was
added LiAlH$_4$ (2.2 mg, 0.05 mmol), and then the reaction mixture was heated at reflux for 3 hours. After cooling to room temperature, the reaction was quenched with aqueous ammonium chloride, and then concentrated in vacuo. The aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give (S)-tylophorine (10.5 mg, 94%) as a white solid: mp 281–283 °C; (lit.$^{1a}$ mp 280-283 °C, lit.$^{1b}$ mp 282-284 °C); $\delta$ +82.0 (c 0.5, CHCl$_3$), (lit.$^{1c}$ $\delta$ +78.9 (c 0.5, CHCl$_3$)). Chiral HPLC analysis (Chiral AD-H, n-heptane/isopropyl alcohol/ triethylamine 70:30:0.1, 1.0 mL/min, 10.805 min (S isomer), 14.481 min (R isomer)), enantiomeric excess 94%;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (s, 2H), 7.31 (s, 1H), 7.16 (s, 1H), 4.63 (d, $J$ = 14.7 Hz, 1H), 4.12 (s, 6H), 4.06 (s, 6H), 3.68 (d, $J$ = 14.6 Hz, 1H), 3.48 (t, $J$ = 8.1 Hz, 1H), 3.37 (d, $J$ = 16.1 Hz, 1H), 2.97–2.86(m, 1H), 2.48 (d, $J$ = 8.8 Hz, 2H), 2.25 (d, $J$ = 5.6 Hz, 1H), 2.04 (d, $J$ = 7.5 Hz, 1H), 1.94 (s, 1H), 1.79 (d, $J$ = 9.7 Hz, 1H);$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.7, 148.5, 148.4, 126.3, 126.1, 125.9, 124.4, 123.6, 123.4, 104.0, 103.4, 103.3, 103.1, 60.2, 56.1, 55.9, 55.8, 55.2, 54.0, 33.8, 31.3, 21.6; HRMS (ESI) calcd for C$_{24}$H$_{28}$NO$_4$ [M+H]$^+$ 394.2018, found 394.2015.

(R)-3-(6-(Benzylxoy)hexanoyl)-4-isopropyloxazolidin-2-one (9b). The synthetic procedure was similar with that of compound 9a, and was obtained as a light yellow oil (5.8 g, 99%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37–7.27 (m, 5H), 4.50 (s, 2H), 4.47–4.35 (m, 1H), 4.31–4.15 (m, 2H), 3.48 (t, $J$ = 6.5 Hz, 2H), 3.07–2.93 (m, 1H), 2.93–2.80 (m, 1H), 2.45–2.28 (m, 1H), 1.72–1.62 (m, 4H), 1.50–1.41 (m, 2H), 0.91 (d,
$J = 7.0 \text{ Hz, } 3\text{H}), 0.87 (d, J = 6.9 \text{ Hz, } 3\text{H});$ $^{13}\text{C NMR (100 MHz, CDCl}_3) \delta 173.2, 154.0, 128.3, 127.6, 127.5, 72.8, 70.1, 63.3, 58.3, 35.4, 29.5, 28.4, 25.7, 24.2, 17.9, 14.6.$

(R)-3-((S)-5-(Benzyloxy)-2-((3,6,7-trimethoxyphenanthren-9-yl)methyl)pentanoyl)-4-isopropyl-oxazolidin-2-one (11b). The synthetic procedure was similar with that of compound 11a, and was obtained as a colourless oil (1.0 g, 63%); $[\alpha]^{26}_D^{26} -4.6 (c 0.5, \text{CHCl}_3);$ $^1\text{H NMR (400 MHz, CDCl}_3) \delta 7.76 (s, 1\text{H}), 7.79 (s, 1\text{H}), 7.68 (d, J = 8.8 \text{ Hz, 1H}), 7.54 (s, 1\text{H}), 7.44 (s, 1\text{H}), 7.36–7.19 (m, 5\text{H}), 7.14 (dd, J = 8.4, 1.6 \text{ Hz, 1H}), 4.67–4.51 (m, 1\text{H}), 4.42 (s, 2\text{H}), 4.39–4.30 (m, 1\text{H}), 4.20–4.03 (m, 7\text{H}), 4.03–3.91 (m, 4\text{H}), 3.51 (dd, J = 12.8, 8.8 \text{ Hz, 1H}), 3.39 (t, J = 6.0 \text{ Hz, 2H}), 3.15 (dd, J = 13.6, 6.8 \text{ Hz, 1H}), 2.07–1.91 (m, 1\text{H}), 1.91–1.75 (m, 1\text{H}), 1.63–1.35 (m, 5\text{H}), 0.70 (d, J = 7.2 \text{ Hz, 3H}), 0.19 (d, J = 6.8 \text{ Hz, 3H});$ $^{13}\text{C NMR (100 MHz, CDCl}_3) \delta 176.2, 157.9, 153.5, 149.4, 148.6, 138.6, 130.5, 129.8, 129.7, 128.3, 127.6, 127.5, 126.6, 126.3, 125.9, 124.6, 115.3, 105.1, 103.7, 103.6, 72.8, 70.0, 62.7, 58.4, 56.2, 55.9, 55.5, 42.7, 36.6, 32.1, 29.7, 28.2, 24.1, 17.8, 13.7; HRMS (ESI) calcd for C$_{37}$H$_{47}$N$_2$O$_7$ [M+NH$_4^+$]$^+$ 631.3378, found 631.3381.

(S)-5-(Benzyloxy)-2-((3,6,7-trimethoxyphenanthren-9-yl)methyl) hexanoic acid (8b). The synthetic procedure was similar with that of compound 8a, and was obtained as a white solid (0.65 g, 81%): mp 81–83 °C; $[\alpha]^{26}_D^{26} +7.6 (c 1.0, \text{CHCl}_3);$ $^1\text{H NMR (400 MHz, CDCl}_3) \delta 7.93 (s, 1\text{H}), 7.84 (s, 1\text{H}), 7.73 (d, J = 8.8 \text{ Hz, 1H}), 7.46 (s, 1\text{H}), 7.42 (s, 1\text{H}), 7.35–7.20 (m, 5\text{H}), 7.17 (dd, J = 8.8, 2.4 \text{ Hz, 1H}), 4.42 (s, 2\text{H}), 4.11 (s, 3\text{H}), 4.04 (s, 3\text{H}), 4.01 (s, 3\text{H}), 3.51 (dd, J = 14.4, 6.4 \text{ Hz, 1H}), 3.39 (t, J = 6.4 \text{ Hz, 2H}), 3.08 (dd, J = 14.0, 7.2 \text{ Hz, 1H}), 2.94–2.90 (m, 1\text{H}), 1.84–1.79 (m, 1\text{H}), 1.69–
1.54 (m, 3H), 1.53–1.46 (m, 1H), 1.45–4.35 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$
180.0, 158.0, 149.4, 148.7, 138.4, 130.5, 129.8, 128.3, 127.6, 127.5, 126.3, 125.8,
125.7, 124.9, 115.4, 104.5, 104.0, 103.9, 72.8, 69.9, 56.0, 55.9, 55.6, 45.4, 36.4, 31.6,
29.5, 24.2; HRMS (ESI) calcd for C$_{31}$H$_{38}$NO$_6$ [M+NH$_4$]$^+$ 520.2694, found 520.2687.

(S)-3-(4-(Benzyloxy)butyl)-6,7,10-trimethoxy-3,4-dihydrodibenzo[f,h]isoquinolin-1(2H)-one (13b).

The synthetic procedure was similar with that of compound 13a, and was obtained as a white solid (0.25 g, 50%): mp 106–108 °C; $[\alpha]_D^{26}$ +140 (c 0.54, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.30 (d, $J = 9.6$ Hz, 1H), 7.85 (s, 1H), 7.82 (d, $J = 2.8$ Hz, 1H), 7.33–7.26 (m, 6H), 7.24 (d, $J = 2.8$ Hz, 1H), 6.78 (s, 1H), 4.49 (s, 2H), 4.10 (s, 3H), 4.03 (s, 3H), 4.00 (s, 3H), 3.79–3.64 (m, 1H), 3.51 (t, $J = 6.0$ Hz, 2H), 3.30 (dd, $J = 15.6$, 4.0 Hz, 1H), 2.96 (dd, $J = 16.0$, 10.8 Hz, 1H), 1.75–1.55 (m, 6H), $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.6, 157.7, 150.3, 149.5, 138.4, 134.1, 130.9, 129.5, 128.4, 127.7, 126.7, 124.3, 123.3, 121.5, 115.3, 104.9, 104.1, 103.7, 73.0, 69.9, 56.0, 55.9, 55.4, 49.8, 34.7, 32.3, 29.6, 22.5; HRMS (ESI) calcd for C$_{31}$H$_{34}$NO$_5$ [M+H]$^+$ 500.2431, found 500.2436.

(S)-3-(4-Hydroxybutyl)-6,7,10-trimethoxy-3,4-dihydrodibenzo[f,h]isoquinolin-1(2H)-one (14b).

The synthetic procedure was similar with that of compound 14a, and was obtained as a white solid (80.0 mg, 80%): mp 96–99 °C; $[\alpha]_D^{26}$ +188.0 (c 0.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.28 (d, $J = 9.6$ Hz, 1H), 7.92 (s, 1H), 7.87 (d, $J = 2.4$ Hz, 1H), 7.34 (s, 1H), 7.29 (d, $J = 2.4$ Hz, 1H), 6.46 (s, 1H), 4.13 (d, $J = 11.2$ Hz, 3H), 4.07 (s, 3H), 4.02 (s, 3H), 3.81–3.75 (m, 1H), 3.72(t, $J = 5.2$ Hz, 2H), 3.39 (dd, $J = 15.6$, 4.0 Hz, 1H), 3.04 (dd, $J = 16.0$, 11.2 Hz, 1H), 1.84–1.74 (m, 2H), 1.74–
1.60 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.6, 157.8, 150.5, 149.6, 134.0, 131.0, 129.5, 126.8, 124.3, 123.3, 121.5, 115.3, 104.9, 104.3, 103.8, 62.3, 56.0, 56.0, 55.5, 49.8, 34.6, 32.4, 32.3, 21.9; HRMS (ESI) calcd for C$_{24}$H$_{28}$NO$_5$[M+H]$^+$ 410.1962, found 410.1960.

(S)-4-(6,7,10-Trimethoxy-1-oxo-1,2,3,4-tetrahydrodibenzo[f,h]isoquinolin-3-yl)butyl methanesulfonate (7b). The synthetic procedure was similar with that of compound 7a, and was obtained as a white solid (81.0 mg, 83%): mp 119–121 °C; [$\alpha$]$_D$ +127.8 ($c$ 0.56, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.30 (d, $J = 9.6$ Hz, 1H), 7.93 (s, 1H), 7.88 (d, $J = 2.4$ Hz, 1H), 7.35 (s, 1H), 7.29 (dd, $J = 9.6$, 2.4 Hz, 1H), 6.18 (s, 1H), 4.28 (t, $J = 6.0$ Hz, 2H), 4.13 (s, 3H), 4.08 (s, 3H), 4.02 (s, 3H), 3.78 (br, 1H), 3.41 (dd, $J = 16.0$, 4.4 Hz, 1H), 3.06 (dd, $J = 15.6$, 10.4, 1H), 3.01 (s, 3H), 1.86–1.77 (m, 4H), 1.71–1.65 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.4, 157.7, 150.4, 149.6, 133.8, 130.9, 129.4, 126.7, 124.3, 123.3, 121.5, 115.3, 104.9, 104.2, 103.7, 69.4, 56.0, 55.5, 49.6, 37.3, 34.2, 32.2, 28.9, 21.7; HRMS (ESI) calcd for C$_{25}$H$_{30}$NO$_7$S[M+H]$^+$ 488.1732, found 488.1739.

(S)-2,3,6-Trimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-9-one (6b). The synthetic procedure was similar with that of compound 6a, and was obtained as a white solid (58.5 mg, 90%): mp 200–202 °C; [$\alpha$]$_D$ +246.2 ($c$ 0.57, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.58 (d, $J = 9.2$ Hz, 1H), 7.90 (s, 1H), 7.86 (d, $J = 2.4$ Hz, 1H), 7.32 (s, 1H), 7.24 (dd, $J = 9.6$, 2.8 Hz, 1H), 4.74 (d, $J = 13.6$ Hz, 1H), 4.13 (s, 3H), 4.07 (s, 3H), 4.02 (s, 3H), 3.61–3.57 (m, 1H), 3.41 (dd, $J = 16.4$, 4.8 Hz, 1H), 3.00 (dd, $J = 16.4$, 11.2 Hz, 1H), 2.93–2.85 (m, 1H), 2.04 (d, $J = 10.4$ Hz,
1H), 1.91 (d, J = 9.6 Hz, 2H), 1.72–1.58 (m, 2H), 1.57–1.39 (m, 1H), 13C NMR (100 MHz, CDCl3) δ167.2, 157.5, 150.3, 149.5, 132.7, 131.1, 130.1, 126.6, 124.1, 123.8, 121.2, 115.0, 104.6, 104.3, 103.7, 56.0, 55.9, 55.5, 52.6, 42.5, 33.0, 32.9, 24.7, 22.9; HRMS (ESI) calcd for C24H26NO4[M+H]+ 392.1856, found 392.1860.

(S)-Cryptopleurine. The synthetic procedure was similar with that of compound (S)-tylophorine, and was obtained as a white solid (26.0 mg, 94%): mp 194–196 °C (lit.2 m.p. 191–192 °C); [α]26 +86.3 (c 0.40, CHCl3) (lit.3 [α]23 +106 (c 1, CHCl3)), ee>98%; Chiral HPLC analysis (Chiral AD-H, n-heptane/isopropyl alcohol/triethylamine70:30:0.1, 1 mL/min, 23.128 min (S isomer), 20.807 min (R isomer)) enantiomeric excess 98%; 1H NMR (400 MHz, CDCl3) δ 7.89 (s, 1H), 7.88 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.24 (s, 1H), 7.19 (dd, J = 9.0, 2.2 Hz, 1H), 4.43 (d, J = 15.6 Hz, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 4.01 (s, 3H), 3.61 (d, J = 15.6 Hz, 1H), 3.26 (d, J = 11.2 Hz, 1H), 3.07 (d, J = 10.2 Hz, 1H), 2.90–2.83 (m, 1H), 2.36–2.26 (m, 2H), 2.03 (d, J = 13.2 Hz, 1H), 1.88 (d, J = 12.4 Hz, 1H), 1.80–1.75 (m, 1H), 1.61–1.36 (m, 3H); 13C NMR (100MHz, CDCl3) δ 157.3, 149.2, 148.2, 130.0, 126.4, 125.6, 124.4, 124.0, 123.6, 123.3, 114.7, 104.6, 103.7, 57.5, 56.2, 56.1, 55.9, 55.8, 55.5, 34.7, 33.8, 25.9, 24.3; HRMS (ESI) calcd for C24H28NO3[M+H]+ 378.2069, found 378.2070.

References:

$^1$H NMR of compound 9a (400 MHz, CDCl$_3$)

$^1$H NMR of compound 11a (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound **11a** (100 MHz, CDCl$_3$)

$^1$H NMR of compound **8a** (400 MHz, DMSO-$d_6$)
$^{13}$C NMR of compound 8a (100 MHz, DMSO-$d_6$)

$^1$H NMR of 12a (400 MHz, CDCl$_3$)
$^{13}$C NMR of 12a (100 MHz, CDCl$_3$)

$^1$H NMR of compound 13a (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 13a (100 MHz, CDCl$_3$)

$^1$H NMR of compound 14a (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 14a (100 MHz, CDCl$_3$)

$^1$H NMR of compound 7a (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound $7a (100 \text{ MHz, CDCl}_3)$

$^1$H NMR of compound $6a (400 \text{ MHz, CDCl}_3)$
$^{13}$C NMR of compound 6a (100 MHz, CDCl$_3$)

$^1$H NMR of compound (S)-Tylophorine (400 MHz, CDCl$_3$)
$^{13}$C NMR of (S)-Tylophorine (100 MHz, CDCl$_3$)

$^1$H NMR of compound 9b (400 MHz, CDCl$_3$)
$^1$H NMR of compound 11b (400 MHz, CDCl$_3$)
\textbf{13C NMR of compound 11b (100 MHz, CDCl$_3$)}

\textbf{1H NMR of compound 8b(400 MHz, CDCl$_3$)}
$^{13}$C NMR of compound 8b (100 MHz, CDCl$_3$)

$^1$H NMR of compound 13b (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 13b (100 MHz, CDCl$_3$)

$^1$H NMR of compound 14b (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 14b (100 MHz, CDCl$_3$)

$^1$H NMR of compound 7b (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 7b (100 MHz, CDCl$_3$)

$^1$H NMR of compound 6b (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 6b (100 MHz, CDCl$_3$)

$^1$H NMR of (S)-Cryptopleurine (400 MHz, CDCl$_3$)
$^{13}$C NMR of (S)-Cryptopleurine (100 MHz, CDCl$_3$)
HPLC for racemic tylophorine and (S)-tylophorine

Conditions:

wave length: 254 nm

flow rate: 1.0 mL/ min

mobile phase: i-PrOH(0.1% Et$_3$N):hexane = 25:75

pressure: 53 bar

HPLC for racemic tylophorine

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HPLC for racemic Cryptopleurine and (S)-Cryptopleurine

Conditions:

wave length: 254 nm

flow rate: 1.0 mL/min

mobile phase: i-PrOH(0.1% Et$_3$N):hexane = 25:75

pressure: 62 bar

HPLC for racemic Cryptopleurine

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HPLC for (S)-Cryptopleurine

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