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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-isopropyloxazolidin-2-one (9a). To a solution of (*R*)-4-isopropyloxazolidin-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_2SO_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 colourlessoil: ^{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, $CDCl_3$) δ172.9, 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 $C_{18}H_{25}NO_4Na$ $[M+Na]^+$ 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 °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 × 3). The combined organic phase was washed with brine (100 mL × 2), dried over Na_2SO_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 °C; $[\alpha]_D^{26}$ -7.4 (*c* 0.14, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 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), 3.45–3.35 (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,

$CDCl_3$) δ 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, 62.8, 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_2O (3/1, 20 mL) was added 30% H_2O_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_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried over Na_2SO_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; $[\alpha]_D^{26}$ +12 (*c* 0.12, $CHCl_3$).^{1}H NMR (400 MHz, DMSO-d_6) δ 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) δ 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 $BF_3{\cdot}Et_2O$ (0.22 mL, 2.3 mmol), stirred another 1 hour at room temperature, and then quenched with aqueous saturated ammonium chloride. Thetoluene 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_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give compound **13a** (0.22g, 56%) as a white solid: mp 162–164 °C. $[\alpha]_D^{26}$ +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, 55.8,55.8, 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 Na_2SO_4, 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. $[\alpha]_D^{26}$ +83.3 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{28}NO_6$ $[M+H]^+$ 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 CH_2Cl_2 (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 CH_2Cl_2 (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over Na_2SO_4, 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. $[\alpha]_D^{26}$ + 44.8 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{29}H_{30}NO_8S$ $[M+H]^+$ 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 Na_2SO_4, 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; $[\alpha]_D^{26}$ +150 (c 0.13, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) 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).^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{26}NO_5$ $[M+H]^+$ 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_2Cl_2 (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over Na_2SO_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);$[\alpha]_D^{26}$ +82.0 (*c* 0.5, $CHCl_3$), (lit.[1c] $[\alpha]_D^{26}$ +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, $CDCl_3$) δ 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, $CDCl_3$) δ 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-(Benzyloxy)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, $CDCl_3$) δ 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 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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-isopropyloxazolidin-2-one (11b). The synthetic procedure was similar with that of compound **11a**, and was obtained as a colourless oil (1.0 g, 63%); $[\alpha]_D^{26}$ −4.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.79 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 7.44 (s, 1H), 7.36–7.19 (m, 5H), 7.14 (dd, J = 8.4, 1.6 Hz, 1H), 4.67–4.51 (m, 1H), 4.42 (s, 2H), 4.39–4.30 (m, 1H), 4.20–4.03 (m, 7H), 4.03–3.91 (m, 4H), 3.51 (dd, J = 12.8, 8.8 Hz, 1H), 3.39 (t, J = 6.0 Hz, 2H), 3.15 (dd, J = 13.6, 6.8 Hz, 1H), 2.07–1.91 (m, 1H), 1.91–1.75 (m, 1H), 1.63–1.35 (m, 5H), 0.70 (d, J = 7.2 Hz, 3H), 0.19 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{37}H_{47}N_2O_7$ $[M+NH_4]^+$ 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; $[\alpha]_D^{26}$ +7.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.84 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 7.35–7.20 (m, 5H), 7.17 (dd, J = 8.8, 2.4 Hz, 1H), 4.42 (s, 2H), 4.11 (s, 3H), 4.04 (s, 3H), 4.01 (s, 3H), 3.51 (dd, J = 14.4, 6.4 Hz, 1H), 3.39 (t, J = 6.4 Hz, 2H), 3.08 (dd, J = 14.0, 7.2 Hz, 1H), 2.94–2.90 (m, 1H), 1.84–1.79 (m, 1H), 1.69–

1.54 (m, 3H), 1.53–1.46 (m, 1H), 1.45–4.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 167.6, 157.7, 150.3, 149.5, 138.4, 134.1, 130.9, 129.5, 128.4, 127.7, 127.6, 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, found500.2436.

(*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, $CDCl_3$) δ 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, $CDCl_3$) δ 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; $[\alpha]_D^{26}$ +127.8 (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$)δ 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 $C_{25}H_{30}NO_7S[M+H]^+$ 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; $[\alpha]_D^{26}$ +246.2 (*c* 0.57, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 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), ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{26}NO_4[M+H]^+$ 392.1856, found 392.1860.

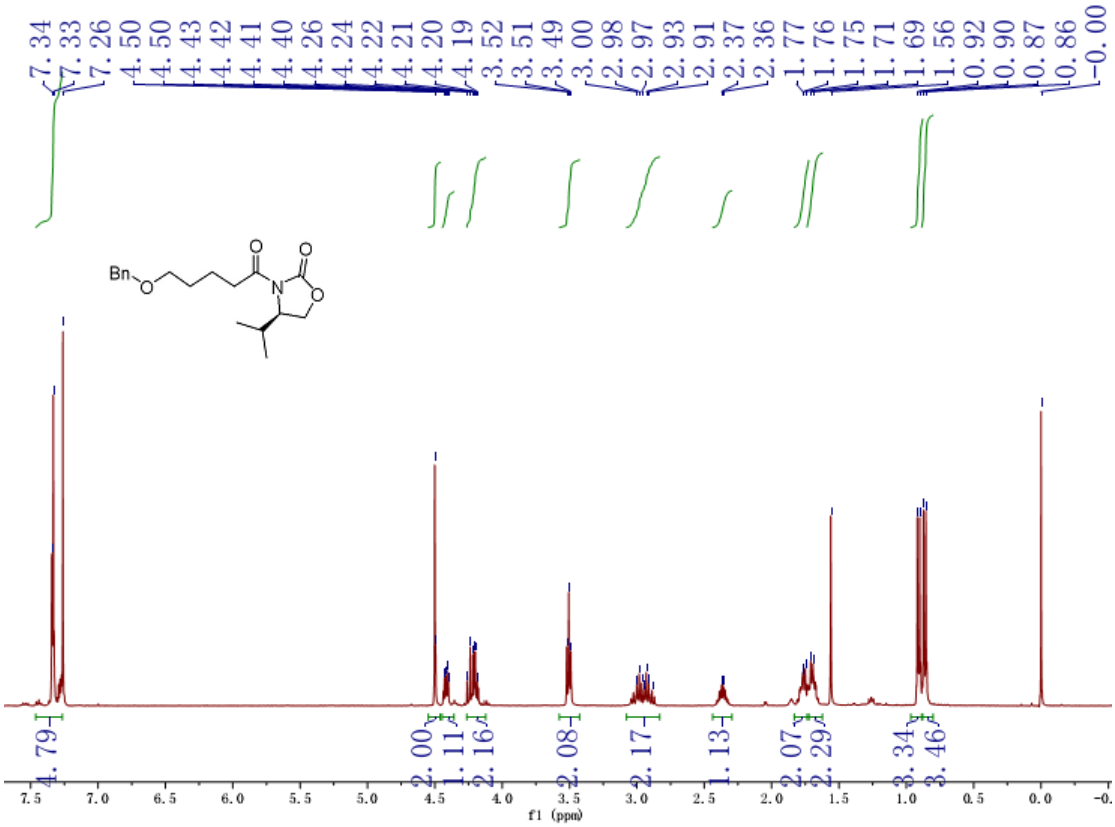
(*S*)-Cryptopleurine. The synthetic procedure was similar with that of compound **(*S*)-tylophorine**, and was obtained as a white solid (26.0 mg, 94%): mp 194–196 °C (lit.[2] m.p. 191–192 °C);$[\alpha]_D^{26}$ +86.3 (*c* 0.40, $CHCl_3$) (lit.[3] $[\alpha]_D^{23}$ +106 (*c* 1, $CHCl_3$)), ee>98%; Chiral 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%; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100MHz, $CDCl_3$) 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 $C_{24}H_{28}NO_3[M+H]^+$ 378.2069, found 378.2070.

References:

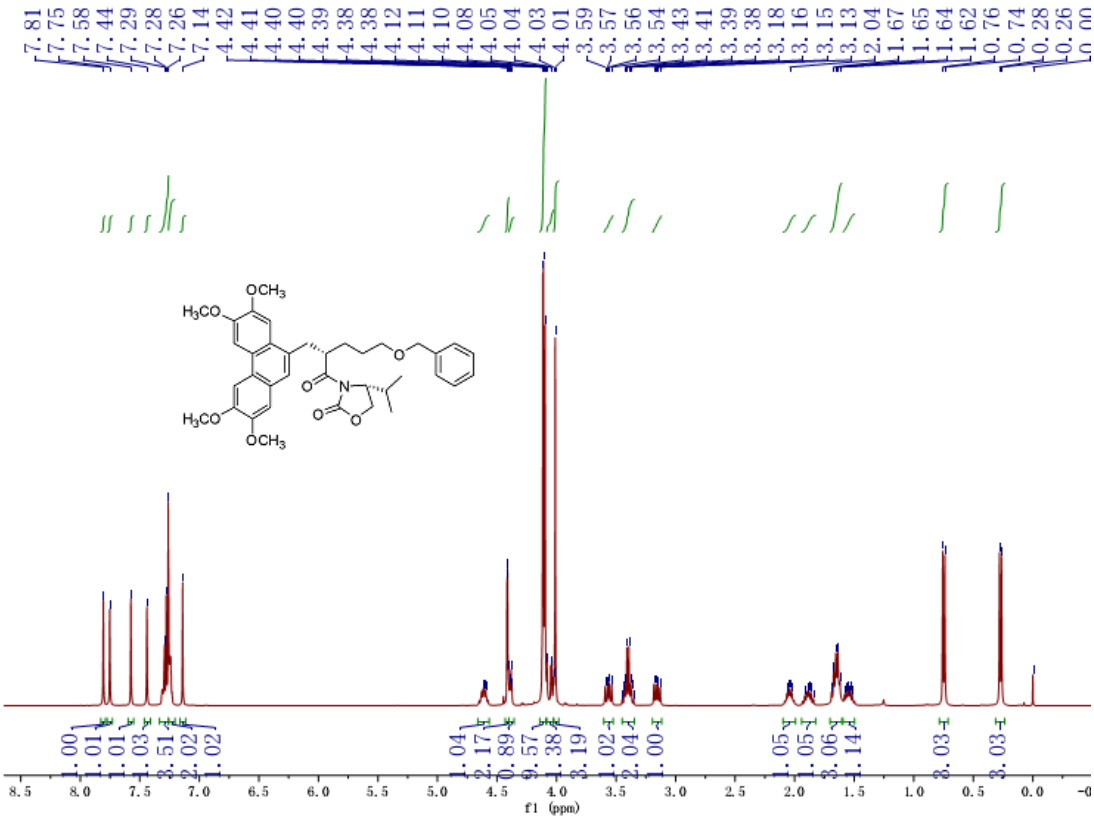
1. (a) Stoye, A.; Opatz, T. *Org. Lett*. **2010**, *12*, 2140–2141. (b) Jin, Z.; Li, S. P.; Wang, Q. M.; Huang, R. Q. *Chin. Chem. Lett.* **2004**, 15, 1164–1166. (c) Georg, G. I.; Niphakis, M. J. *J. Org. Chem*. **2010**, *75*, 6019–6022.
2. Kim, S.; Lee, T.; Lee, E.; Lee, J.; Fan, G. J.; Lee, S. K.; Kim, D. *J. Org. Chem*.

2004, *69*, 3144–3149.

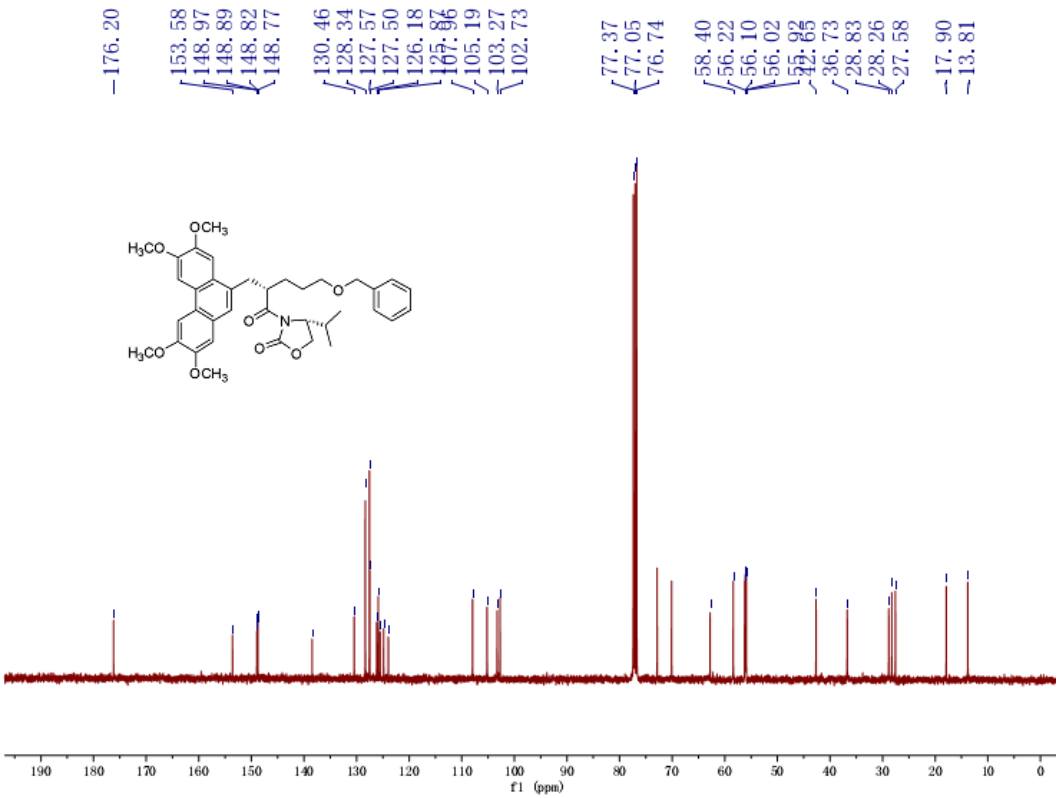
3. Buckley, T. F.; Henry, R. *J. Org. Chem*. **2004**, *48*, 4222–4232.



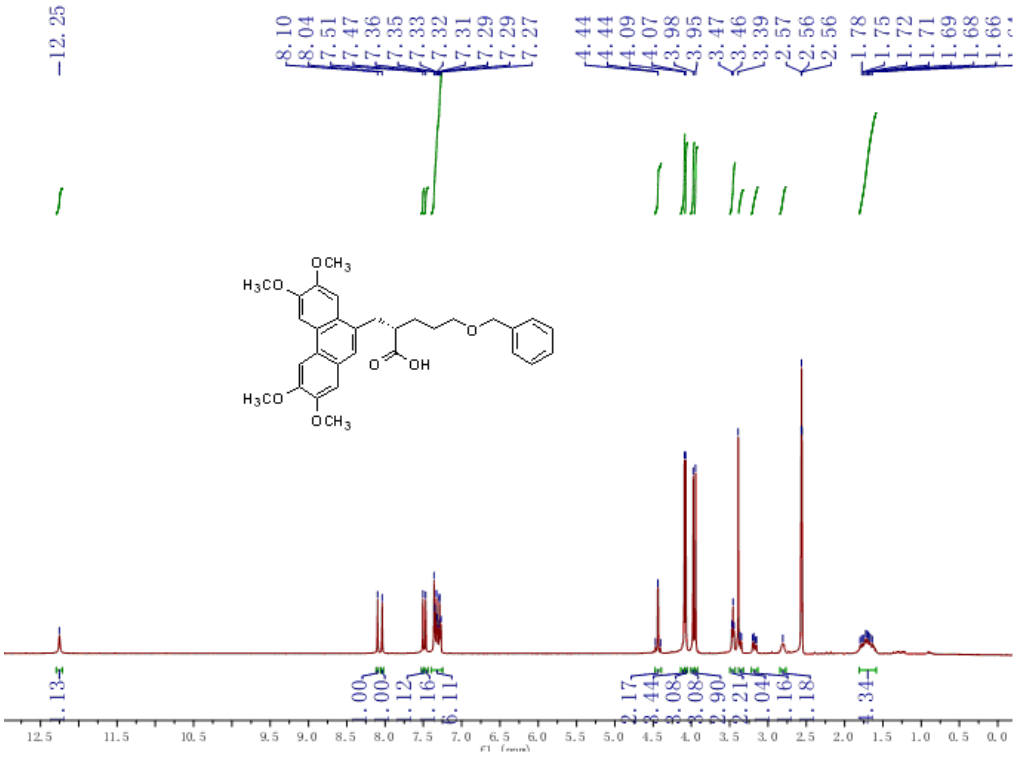
^{1}H NMR of compound **9a** (400 MHz, $CDCl_3$)



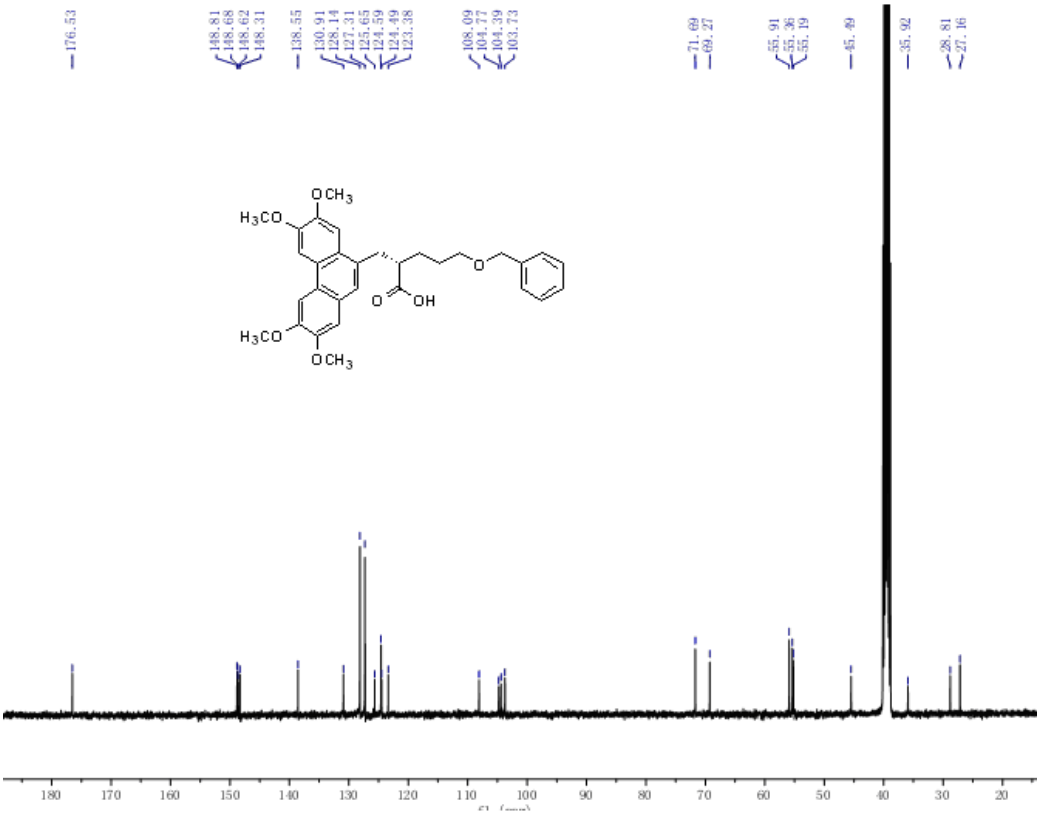
^{1}H NMR of compound **11a** (400 MHz, $CDCl_3$)



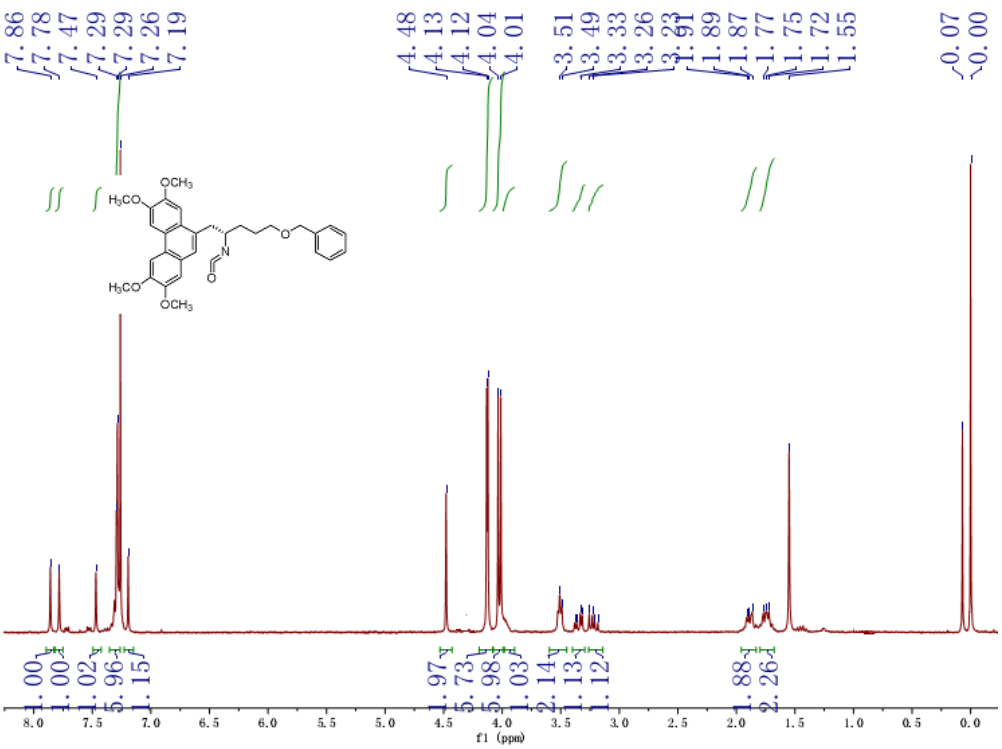
^{13}C NMR of compound **11a** (100 MHz, $CDCl_3$)



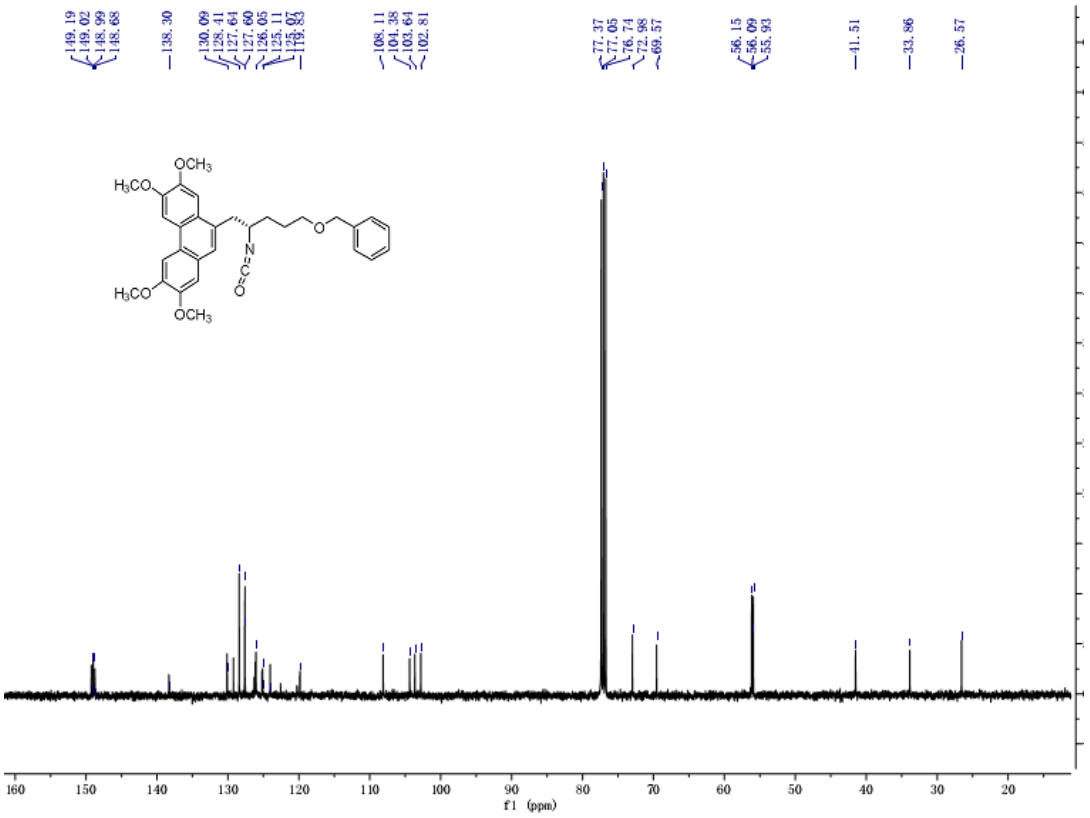
^{1}H NMR of compound **8a** (400 MHz, DMSO-d_6)



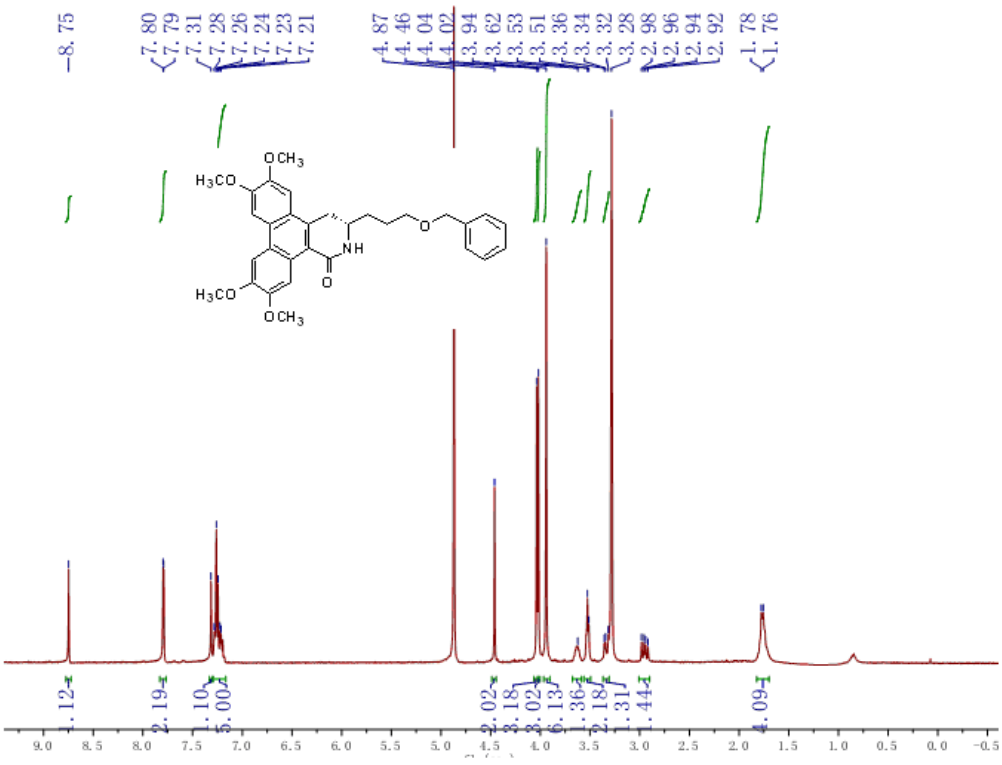
^{13}C NMR of compound **8a** (100 MHz, DMSO-d_6)



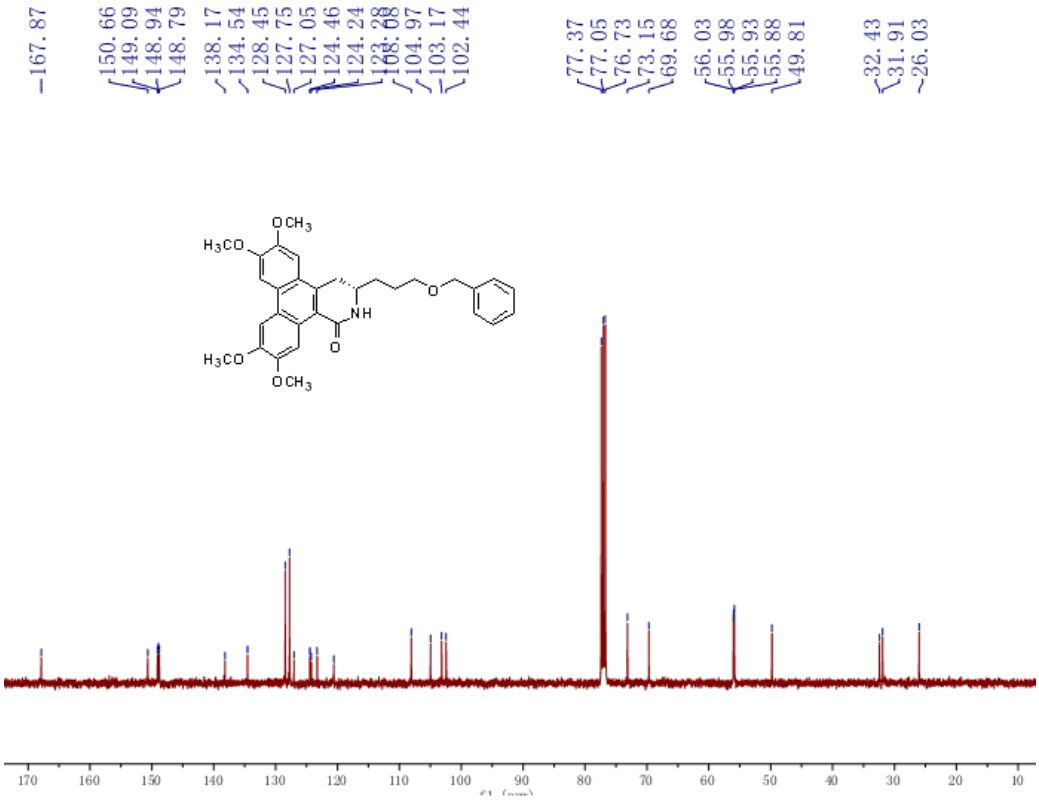
^{1}H NMR of **12a**(400 MHz, $CDCl_3$)



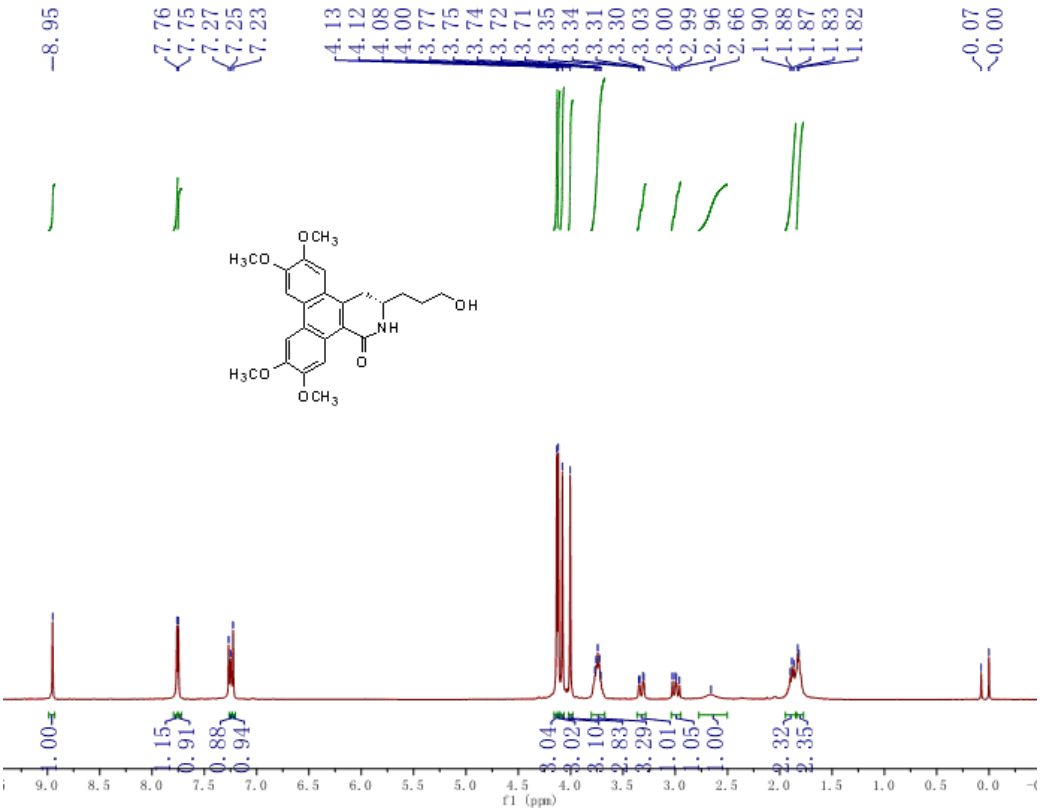
^{13}C NMR of **12a**(100 MHz, $CDCl_3$)



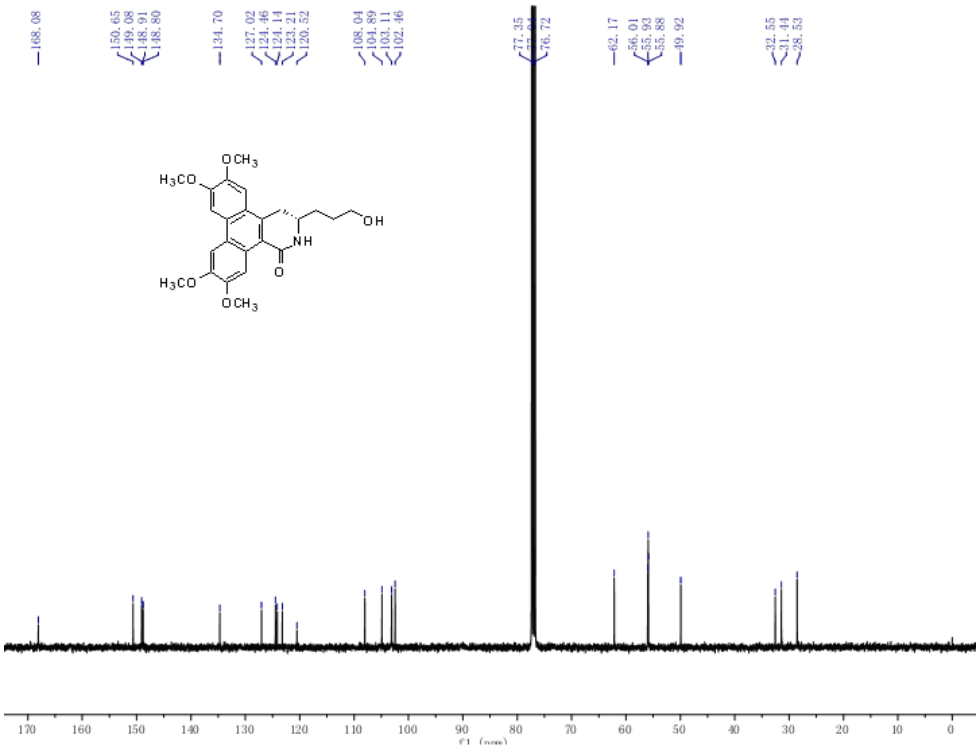
^{1}H NMR of compound **13a**(400 MHz, $CDCl_3$)



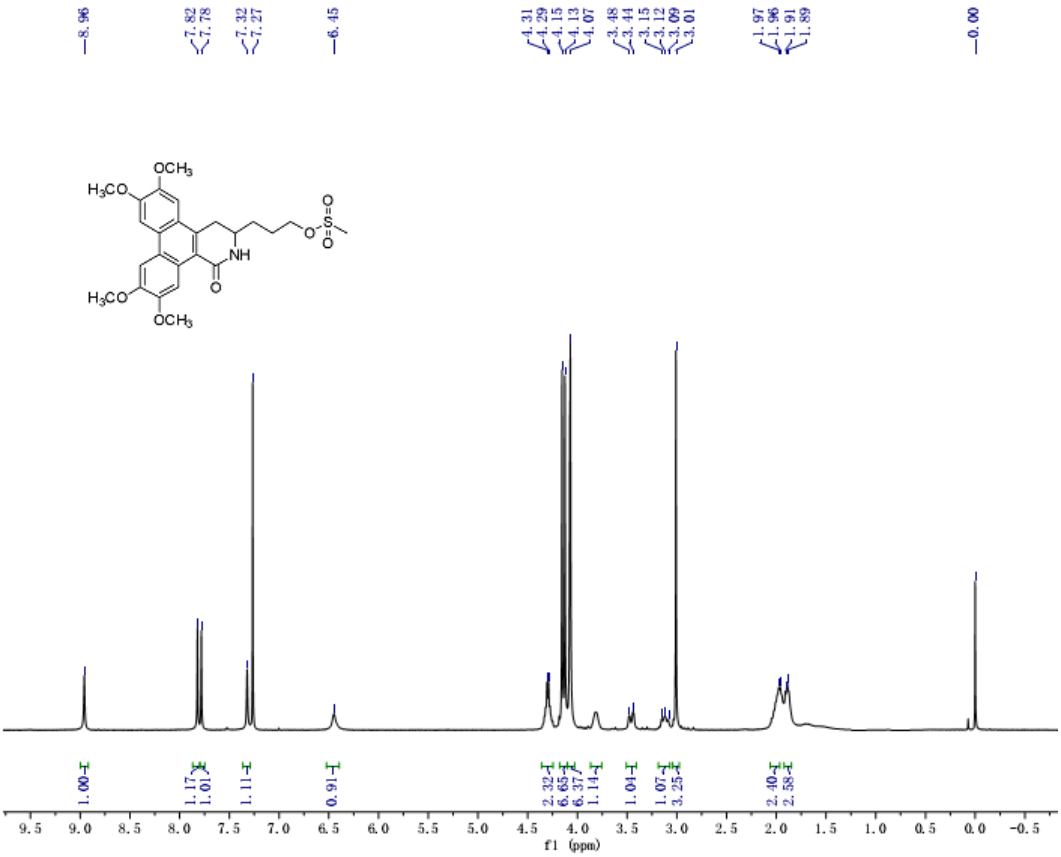
^{13}C NMR of compound **13a**(100 MHz, $CDCl_3$)



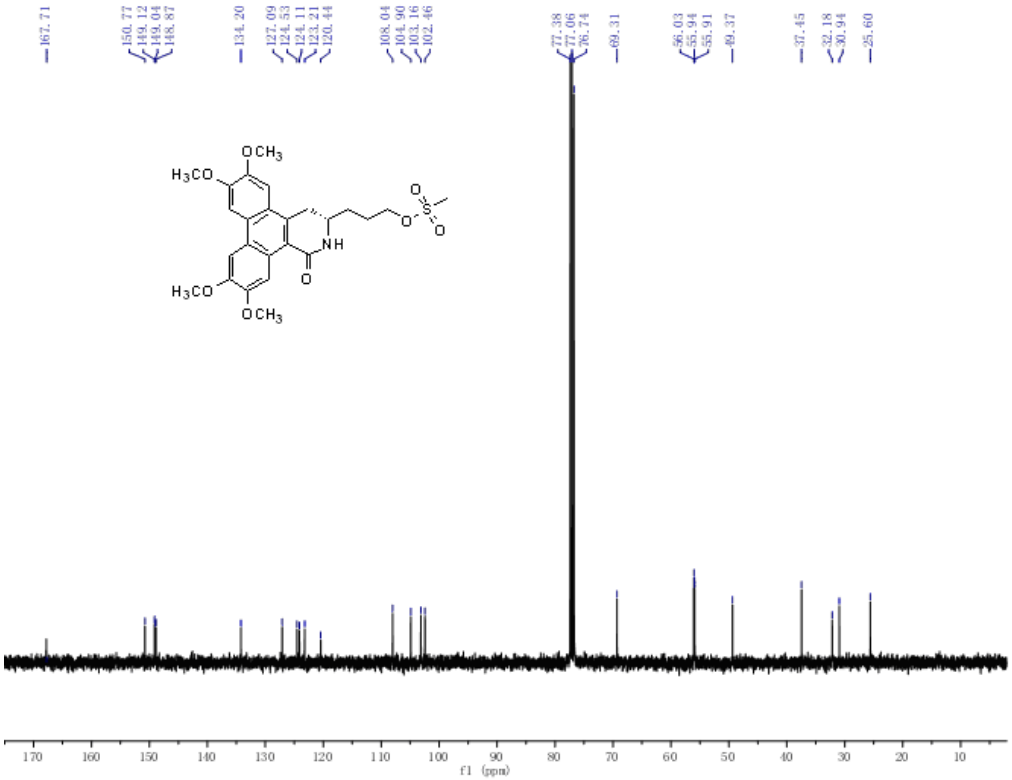
^{1}H NMR of compound **14a**(400 MHz, $CDCl_3$)



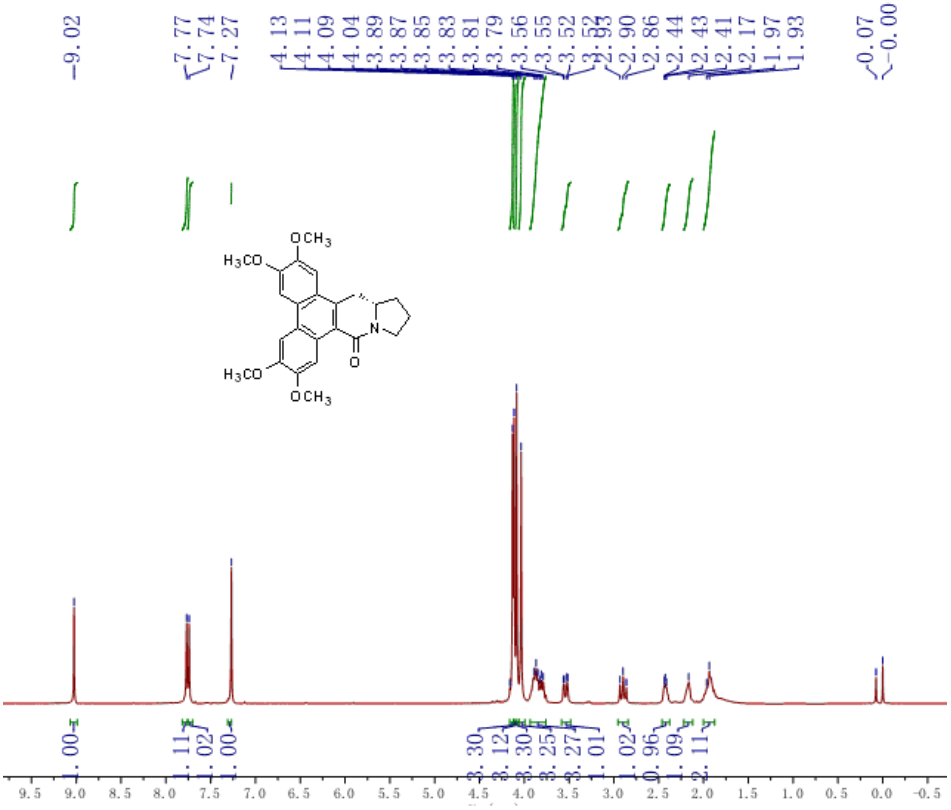
^{13}C NMR of compound **14a**(100 MHz, $CDCl_3$)



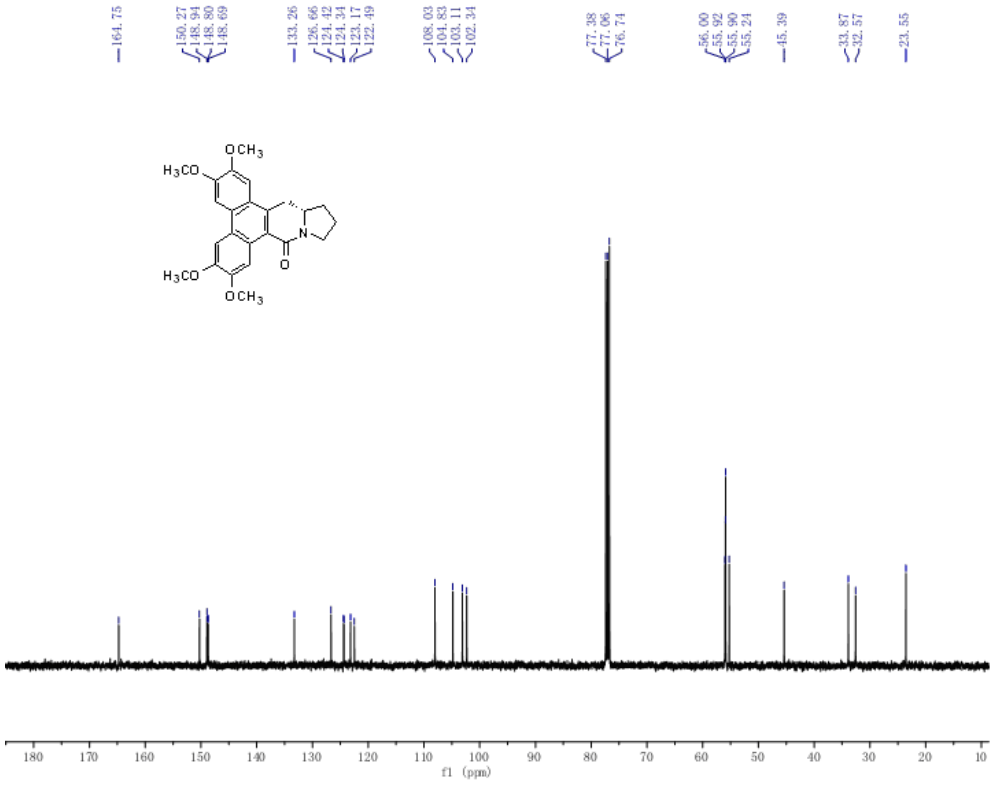
^{1}H NMR of compound **7a**(400 MHz, $CDCl_3$)



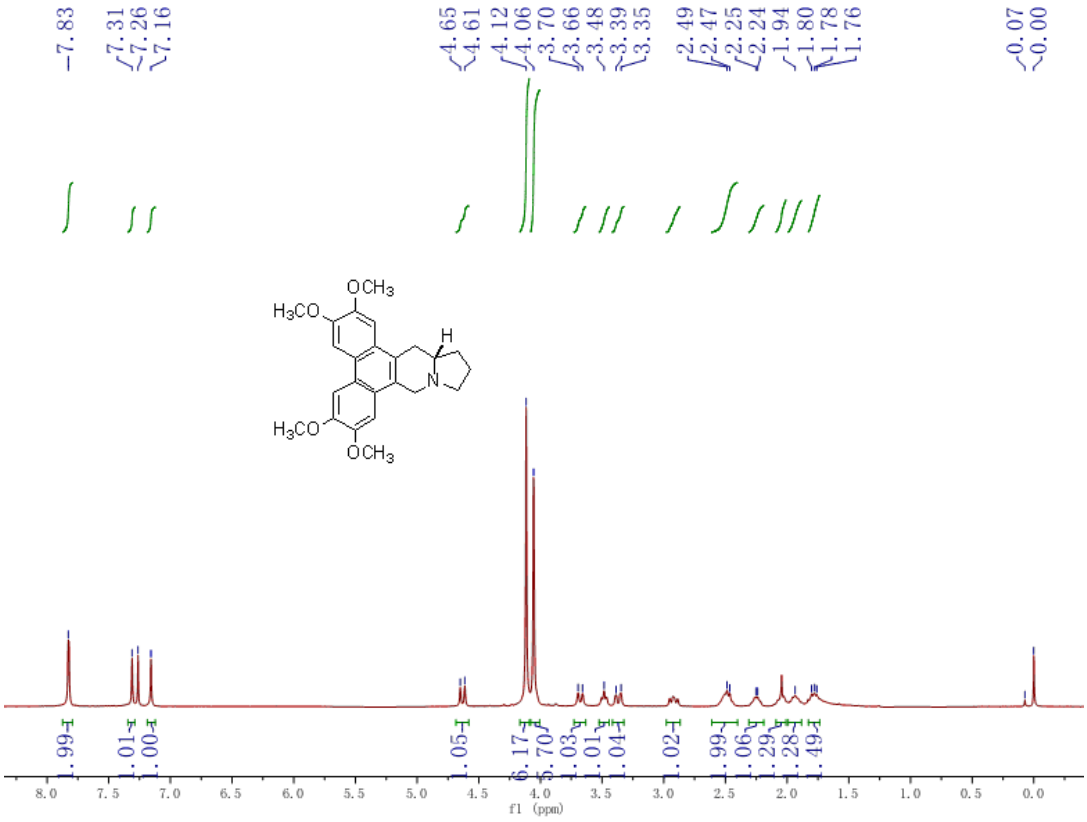
^{13}C NMR of compound **7a**(100 MHz, $CDCl_3$)



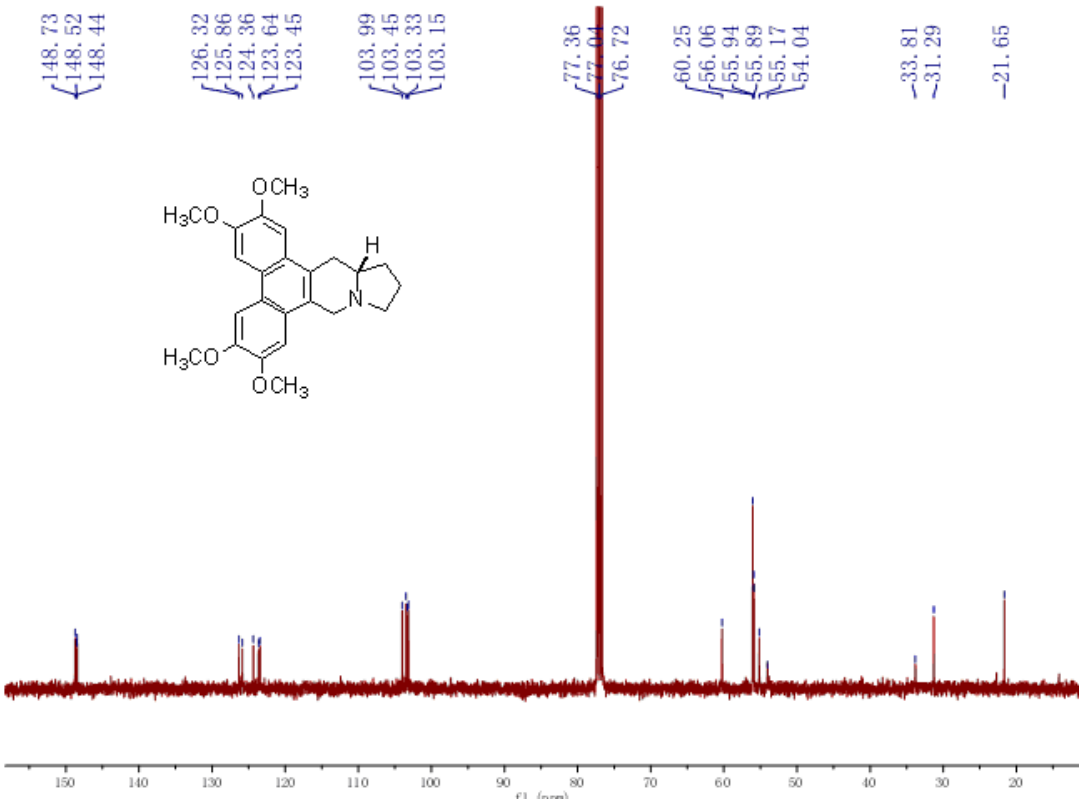
^{1}H NMR of compound **6a**(400 MHz, $CDCl_3$)



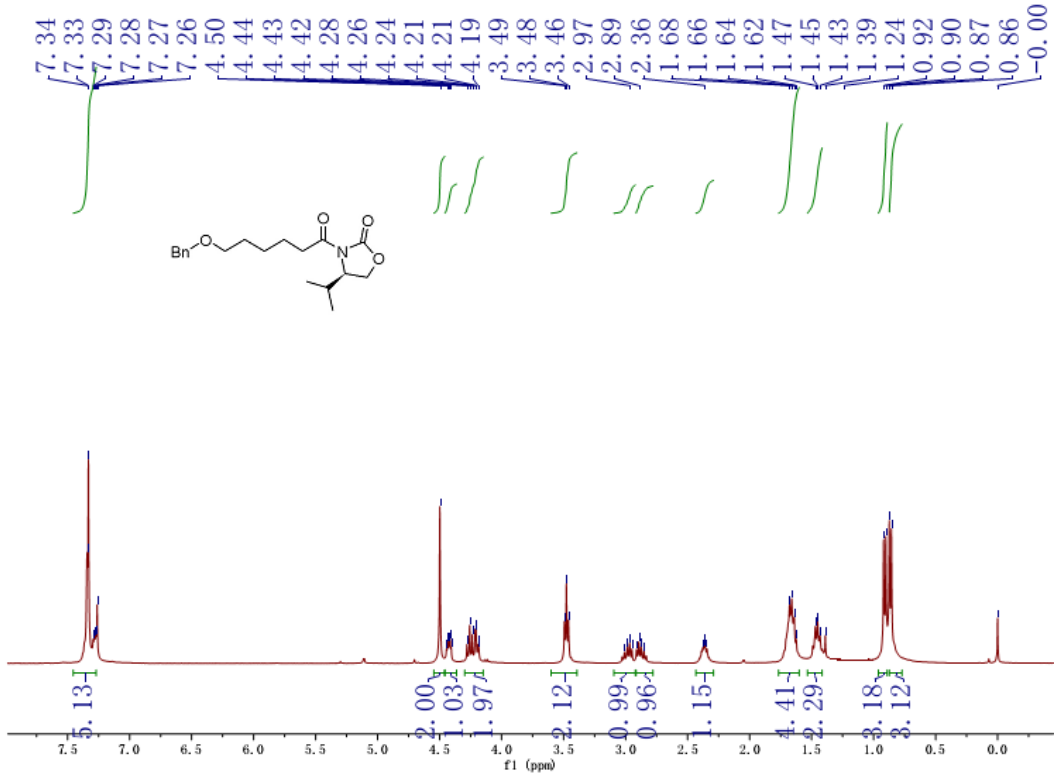
^{13}C NMR of compound **6a**(100 MHz, $CDCl_3$)



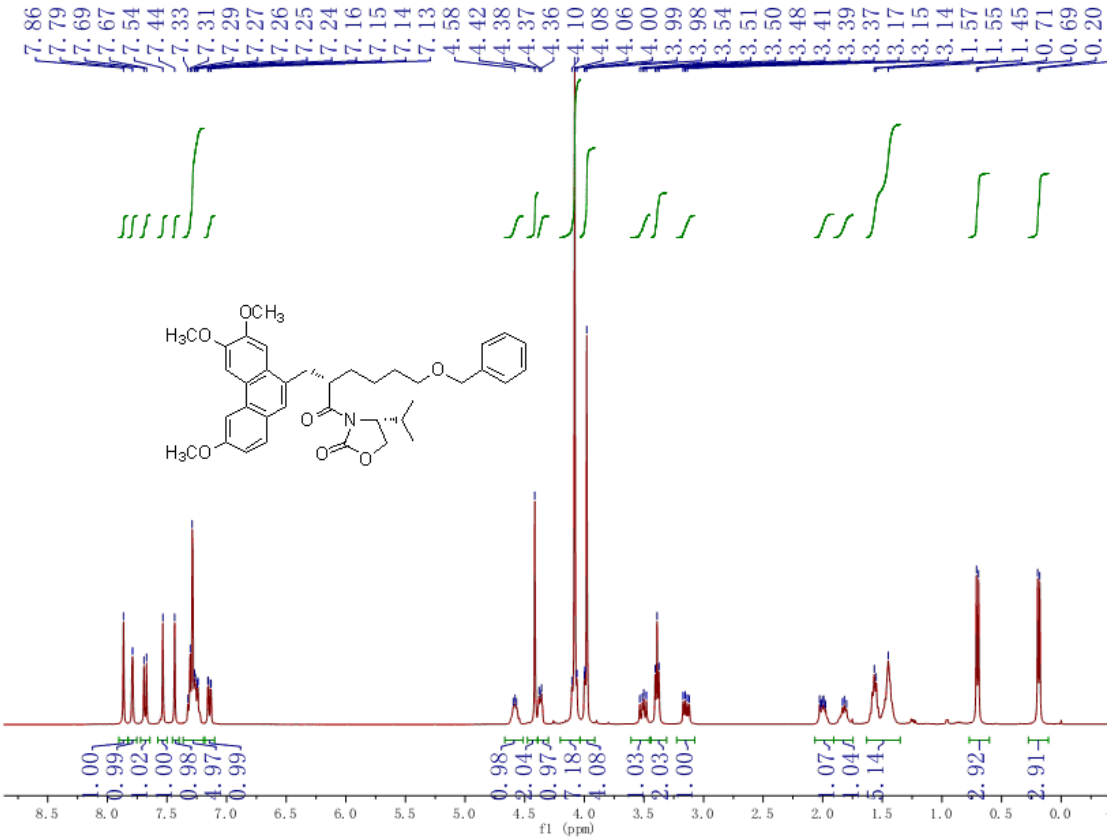
^{1}H NMR of compound **(*S*)-Tylophorine**(400 MHz, $CDCl_3$)



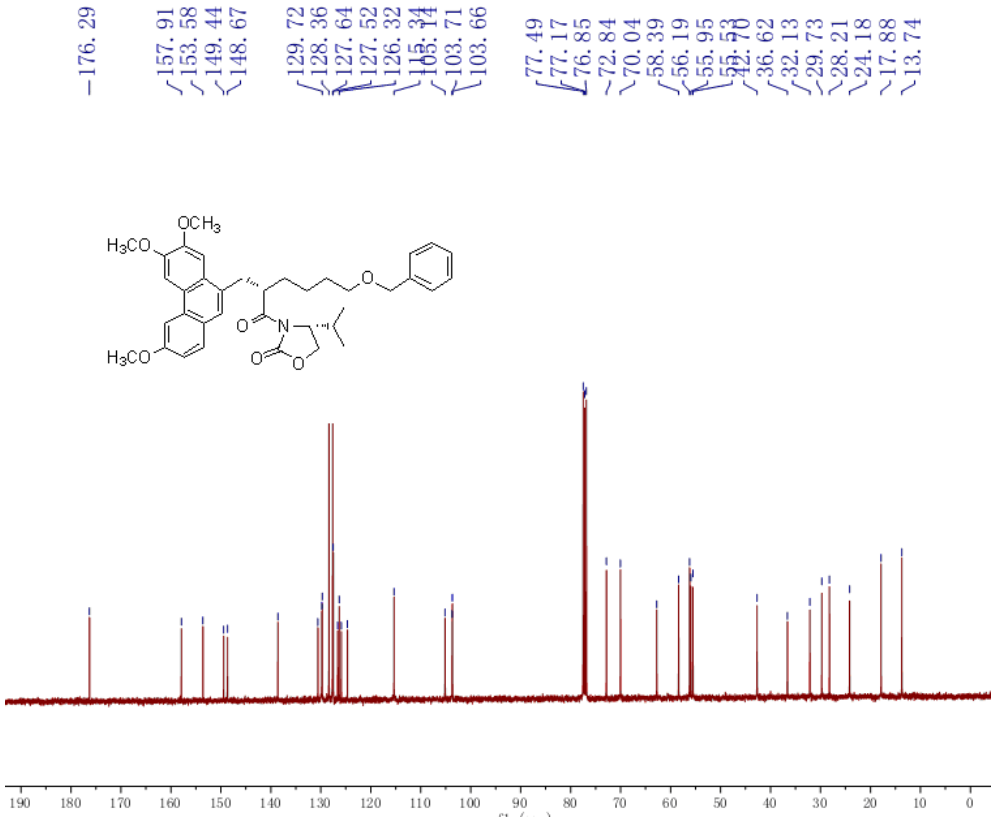
^{13}C NMR of **(*S*)-Tylophorine**(100 MHz, $CDCl_3$)



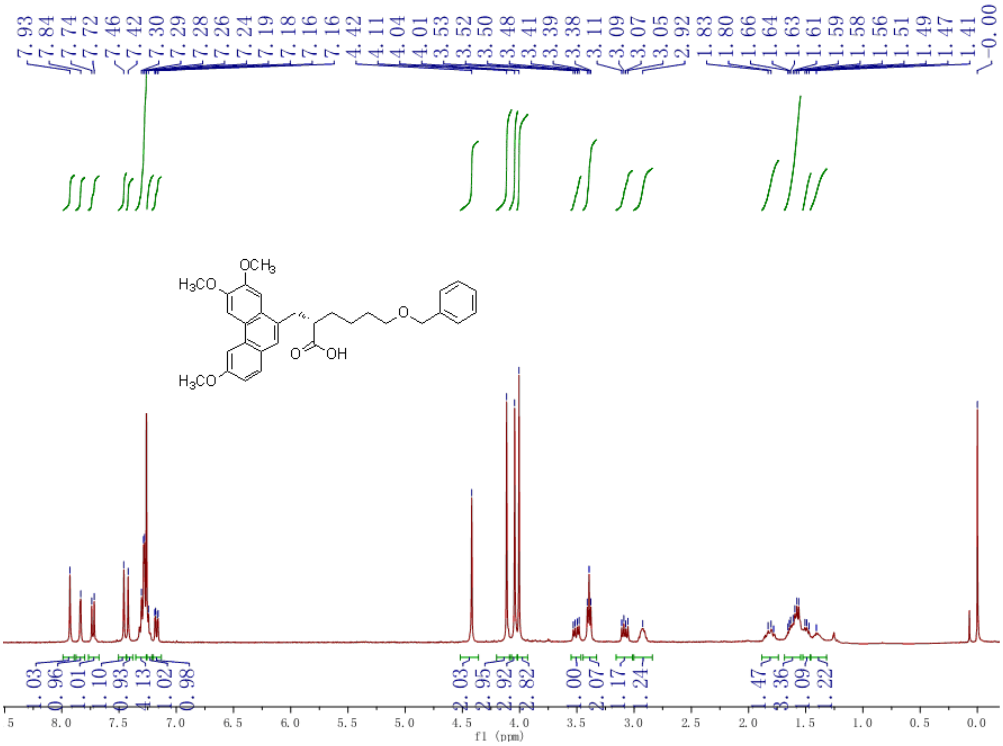
^{1}H NMR of compound **9b**(400 MHz, $CDCl_3$)



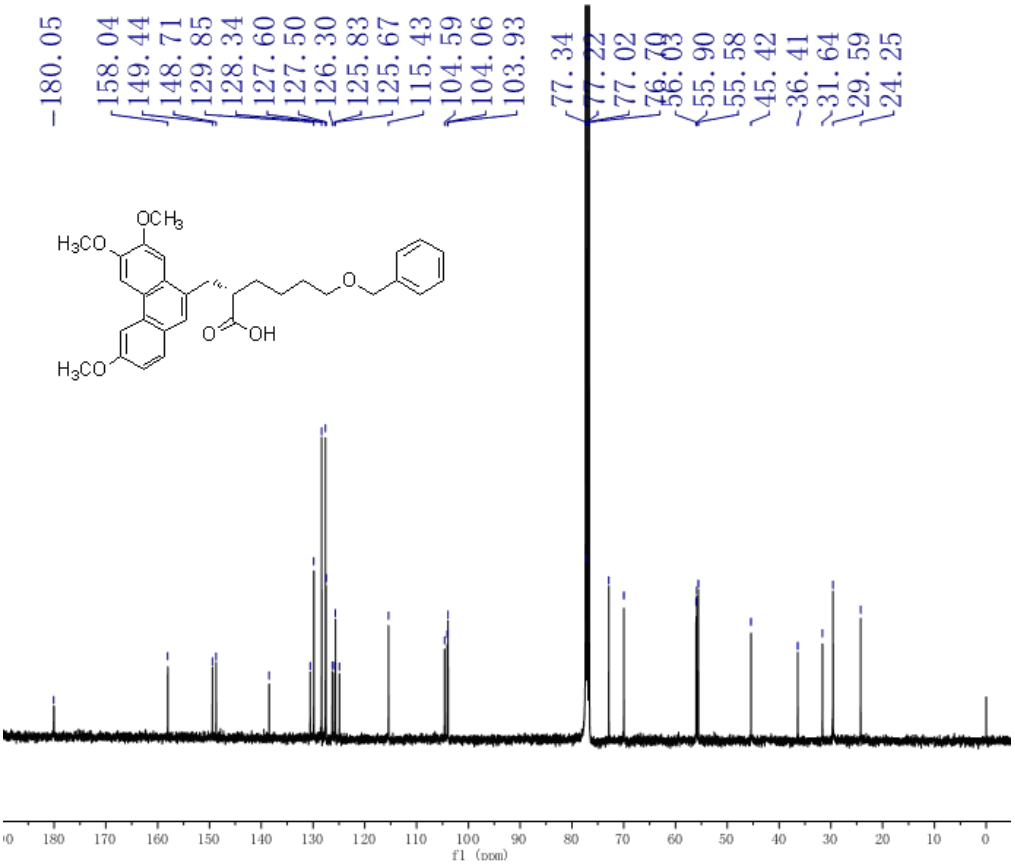
^{1}H NMR of compound **11b**(400 MHz, $CDCl_3$)



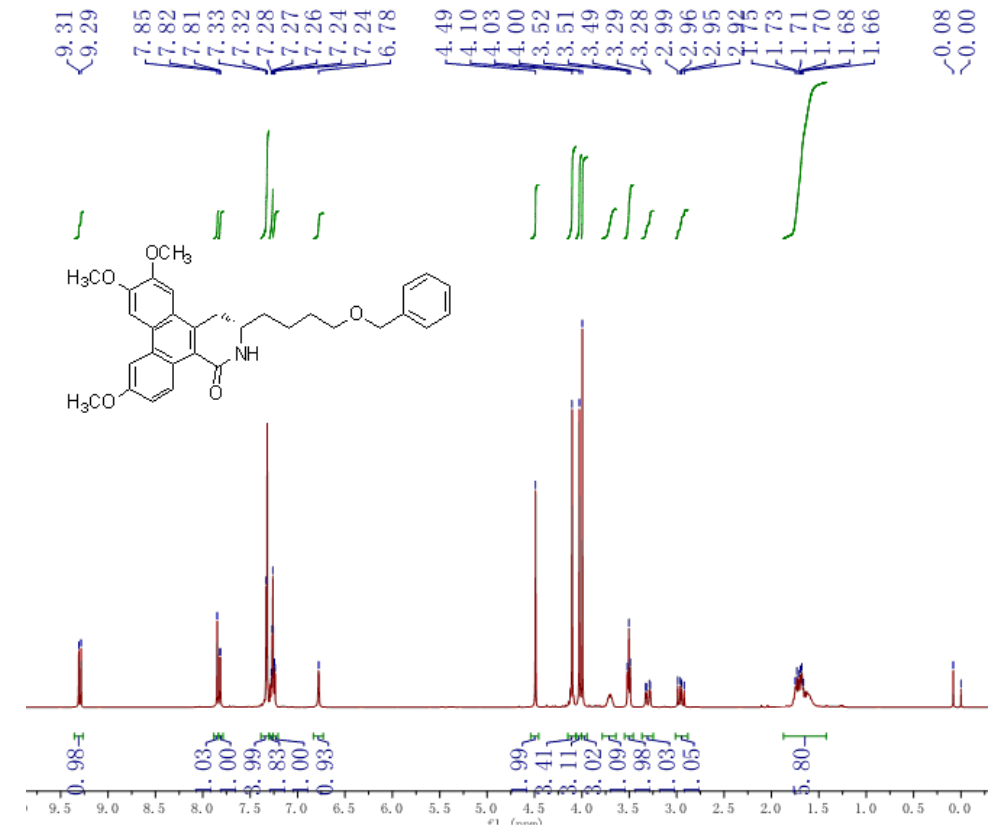
^{13}C NMR of compound **11b** (100 MHz, $CDCl_3$)



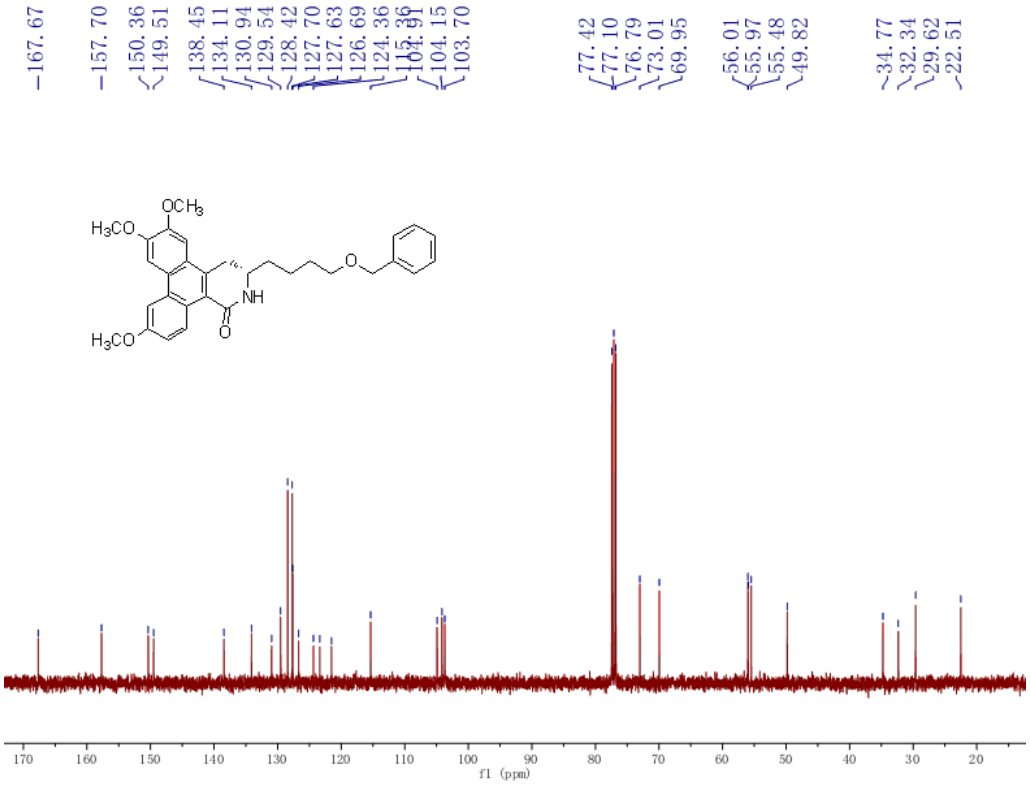
^{1}H NMR of compound **8b**(400 MHz, $CDCl_3$)



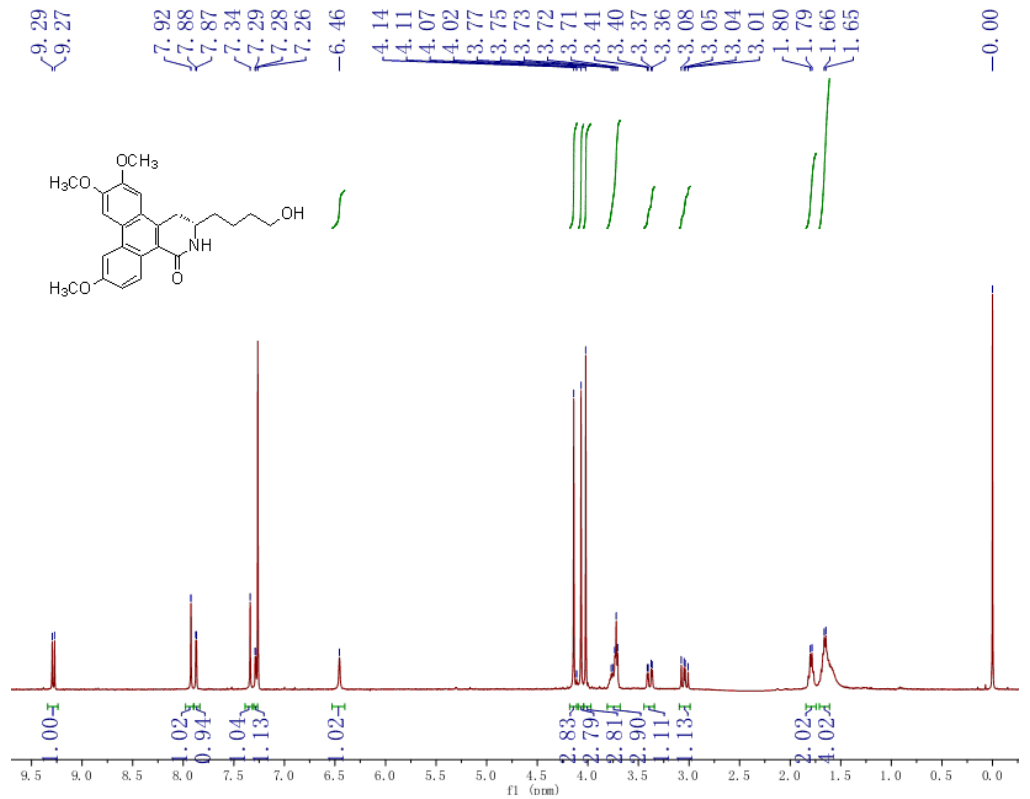
^{13}C NMR of compound **8b**(100 MHz, $CDCl_3$)



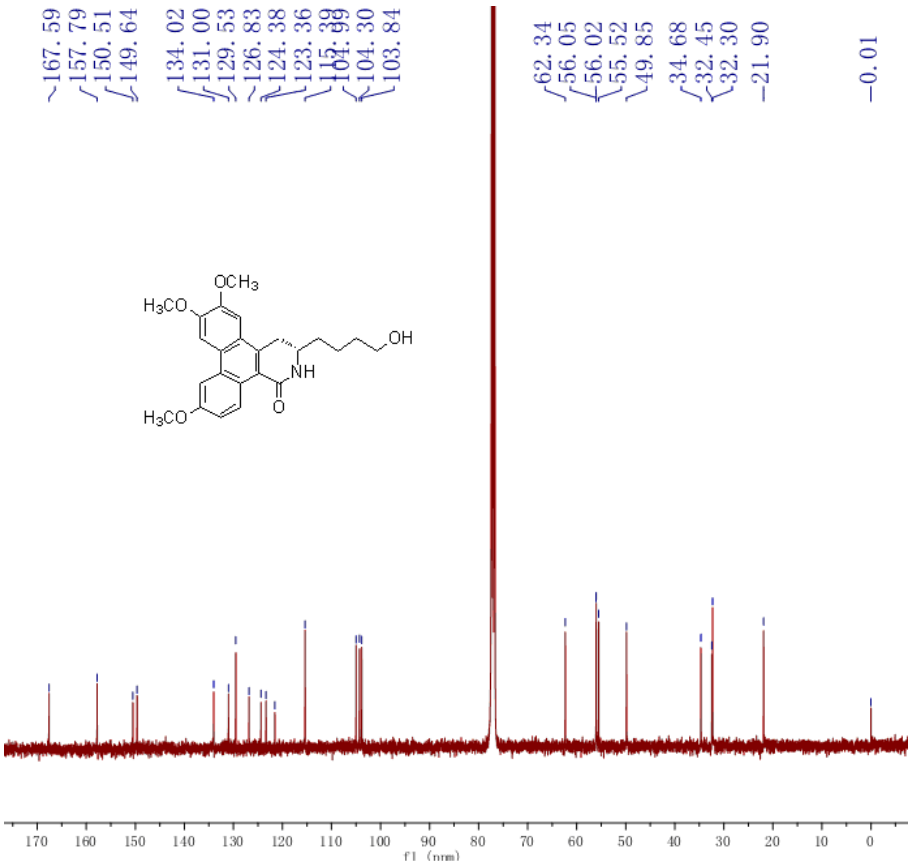
^{1}H NMR of compound **13b**(400 MHz, $CDCl_3$)



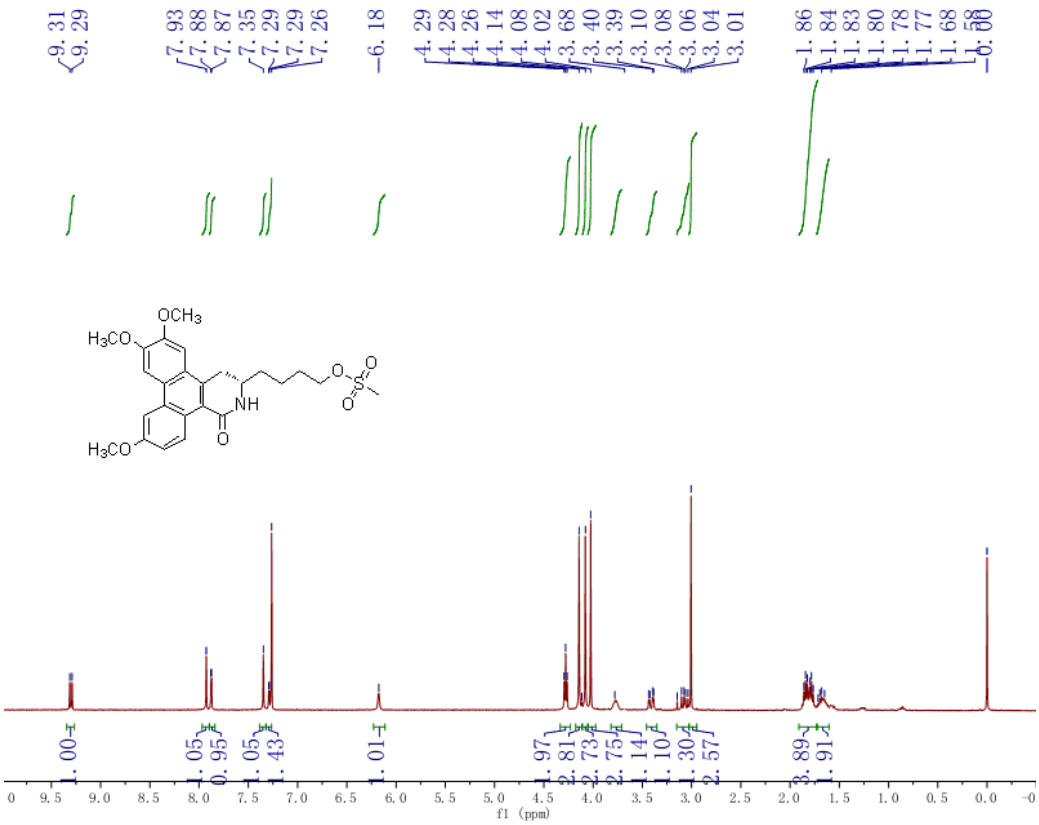
^{13}C NMR of compound **13b**(100 MHz, $CDCl_3$)



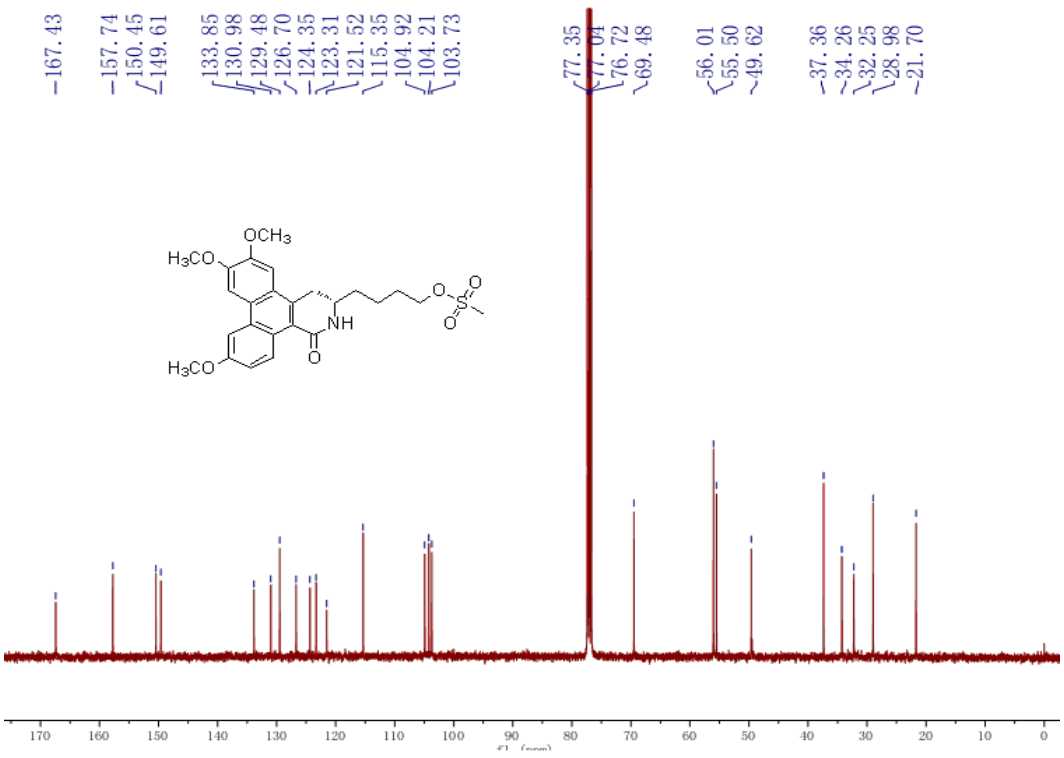
^{1}H NMR of compound **14b**(400 MHz, $CDCl_3$)



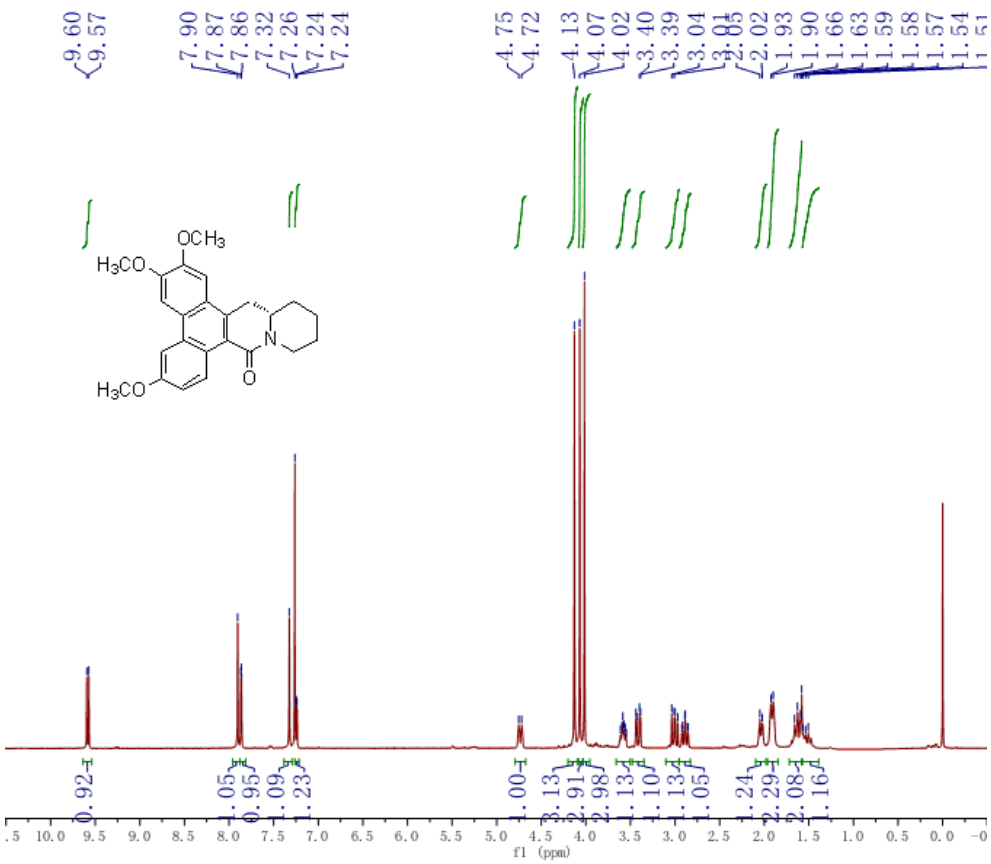
^{13}C NMR of compound **14b**(100 MHz, $CDCl_3$)



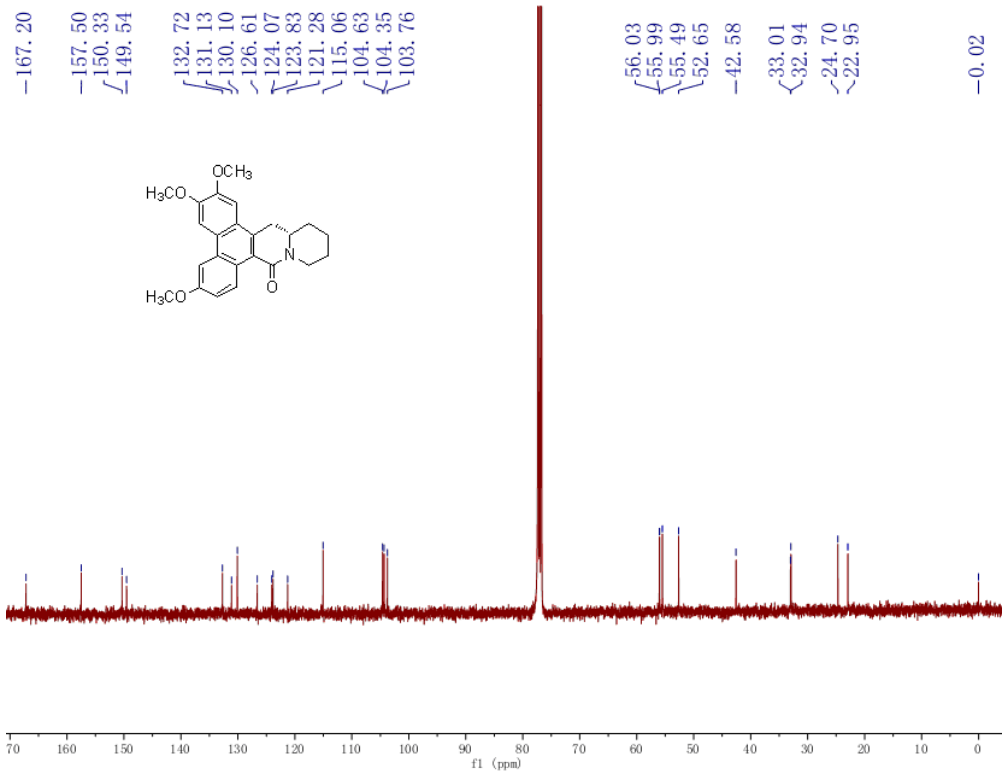
^{1}H NMR of compound **7b**(400 MHz, $CDCl_3$)



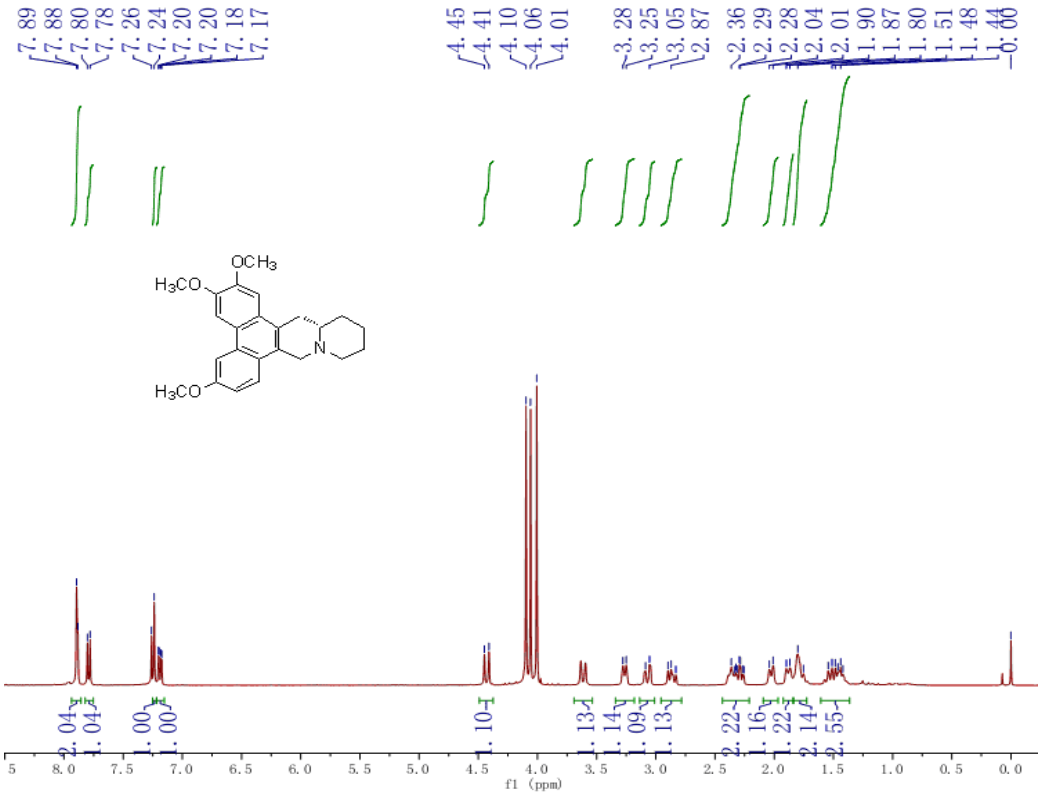
^{13}C NMR of compound **7b**(100 MHz, $CDCl_3$)



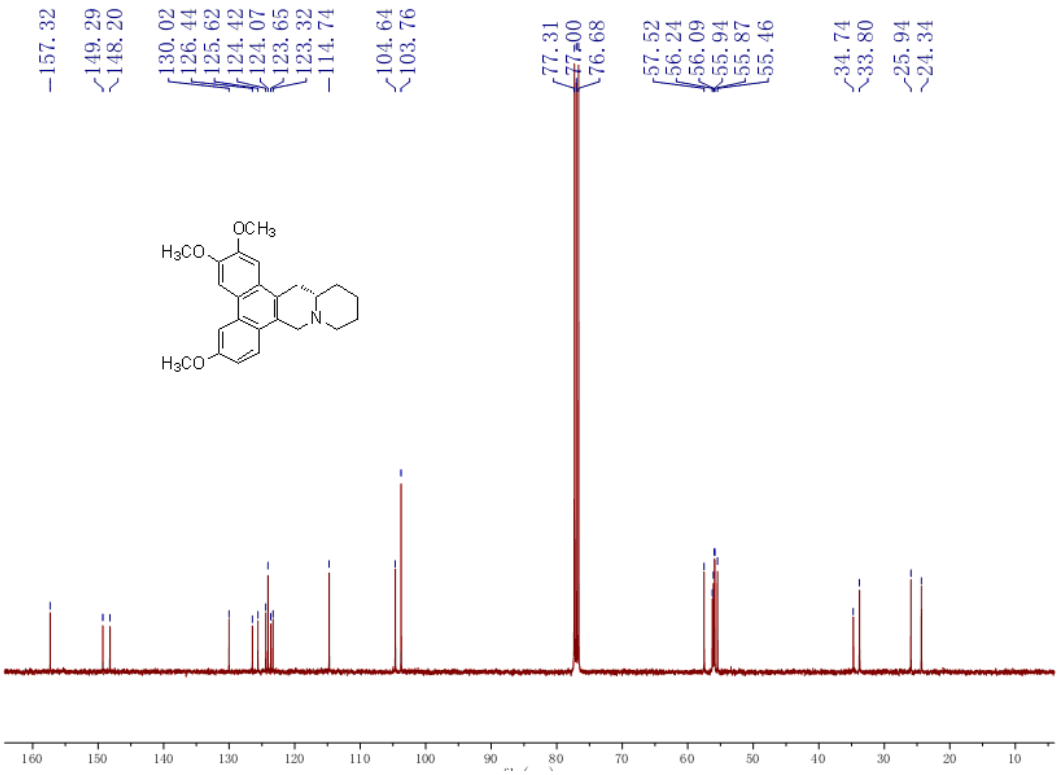
^{1}H NMR of compound **6b**(400 MHz, $CDCl_3$)



^{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:

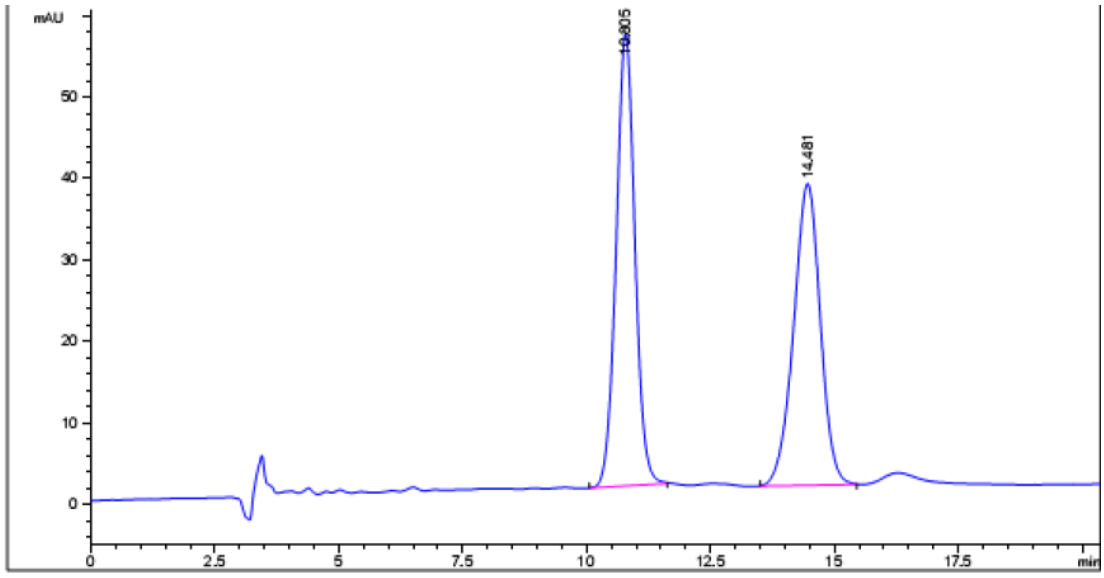
wave length: 254 nm

flow rate: 1.0 mL/ min

mobile phase: i-PrOH(0.1% Et_3N):hexane = 25:75

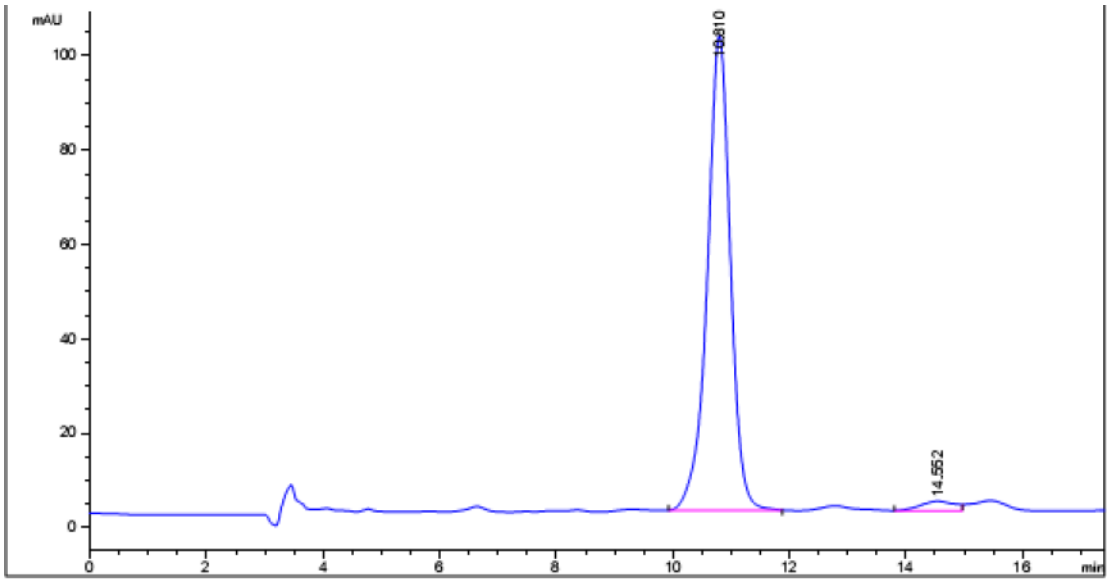
pressure: 53 bar

HPLC for racemic tylophorine



Peaks 峰 #	Retention 保留时间 [min]	Type 类型	Width 峰宽 [min]	Areas 峰面积 mAU *s	Hight 峰高 [mAU]	Areas% 峰面积 %
1	10.805	BB	0.4048	1462.53577	55.53775	51.3129
2	14.481	BB	0.5712	1387.69580	37.02241	48.6871

HPLC for (*S*)- tylophorine



Peaks	Retention	Type	Width	Areas	Hight	Areas%
峰	保留时间	类型	峰宽	峰面积	峰高	峰面积
#	[min]		[min]	mAU *s	[mAU]	%
1	10.810	BB	0.4163	2774.29346	100.60883	97.1474
2	14.552	BV	0.5582	81.46338	2.01223	2.8526

HPLC for racemic Cryptopleurine and (*S*)-Cryptopleurine

Conditions:

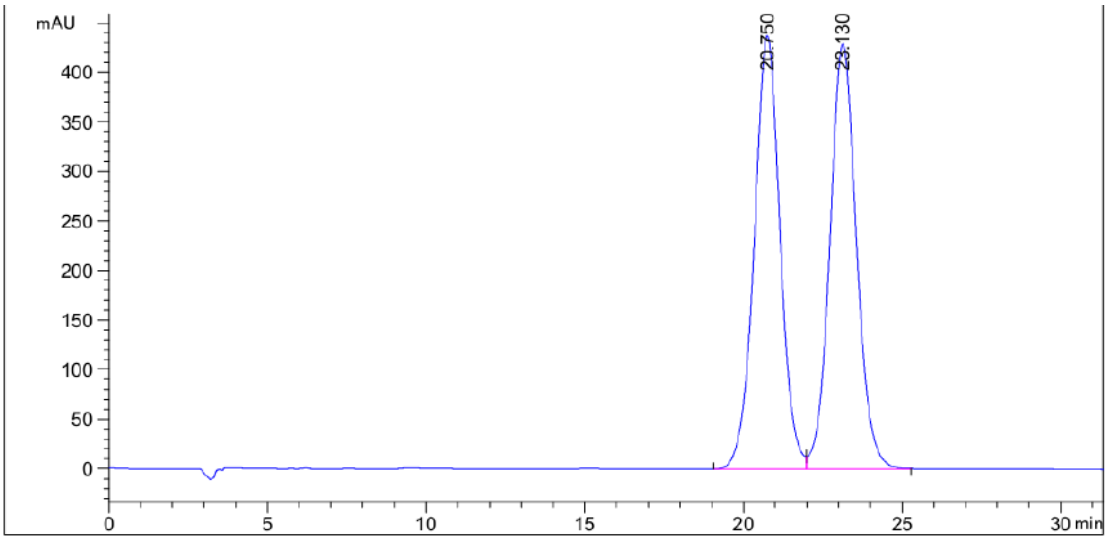
wave length: 254 nm

flow rate: 1.0 mL/ min

mobile phase: i-PrOH(0.1% Et_3N):hexane = 25:75

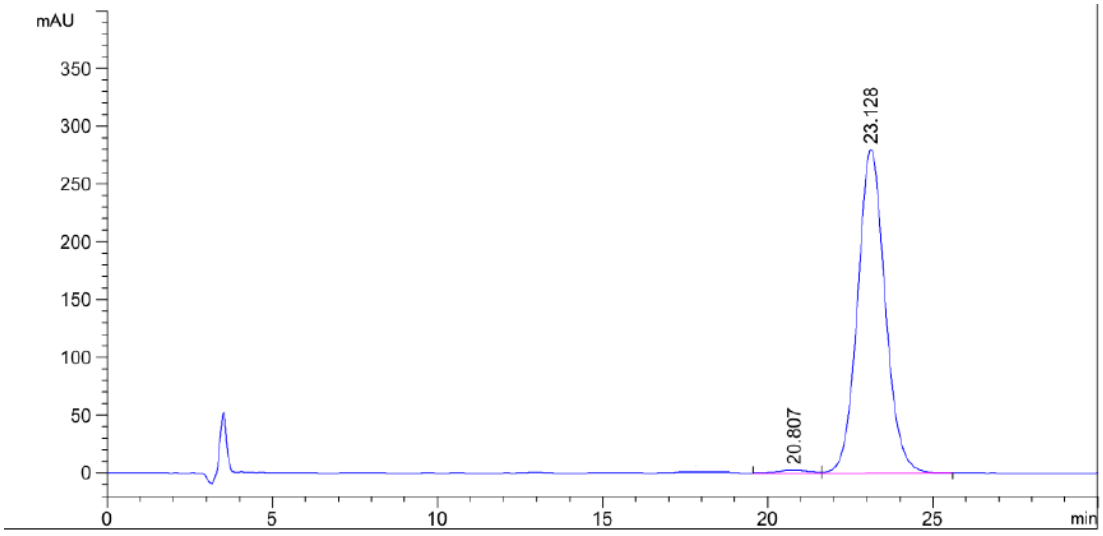
pressure: 62 bar

HPLC for racemic Cryptopleurine



Peaks	Retention	Type	Width	Areas	Hight	Areas%
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 mAU *s	峰高 [mAU]	峰面积 %
1	20.750	BV	0.8669	2.48532e4	437.30865	49.8438
2	23.130	VB	0.8898	2.50090e4	429.00354	50.1562

HPLC for (*S*)-Cryptopleurine



Peaks Retention Type Width Areas Hight Areas%

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 mAU *s	峰高 [mAU]	峰面积 %
1	20.807	BV	0.9385	160.81395	2.43769	0.9802
2	23.128	VB	0.8871	1.62452e4	279.76163	99.0198