Supporting Information

Studies on Asymmetric Total Synthesis of (–)-β-Hydrastine by Chiral Epoxide Ring-Opening Cascade Cyclization Strategy

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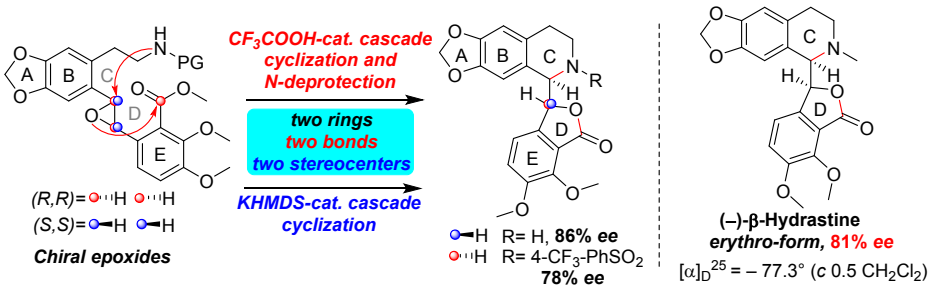


Table of Contents

1. General Information

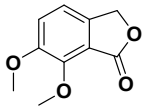
All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise indicated. Tetrahydrofuran (THF) was freshly distilled over sodium metal under a N_2 atmosphere prior to each use. All reactions were monitored by thin layer chromatography (TLC) (250 μm thickness, F-254 indicator) and visualized by UV irradiation. Volatile solvents were removed under reduced pressure using a rotary evaporator. Flash column chromatography was performed over silica gel (200 - 300 mesh) purchased from Yantai Jiangyou Co., China.

Proton nuclear magnetic resonance (^{1}H NMR, 400 MHz and 600 MHz) and carbon nuclear magnetic resonance (^{13}C NMR, 100 MHz and 150 MHz) spectra were recorded in $CDCl_3$, DMSO-d_6 on a Bruker ARX-600 NMR or Bruker ARX-400 NMR spectrometer with TMS as an internal standard. Chemical shifts are reported in parts per million (δ ppm) with respect to the residual solvent signal. Peak multiplicities are reported as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, m = multiplet. High resolution accurate mass spectrometry determinations (HRMS) were obtained on a Bruker Micromass Time of Flight mass spectrometer equipped with an electrospray ionization (ESI) detector. Melting points were determined with Buchi melting point B-540 and are uncorrected. Optical rotation was determined at room temperature with an MCP-200 polarimeter (Anton-Paar), sodium lamp and are reported as follows: $[a]_{\lambda}^{T\ ^{\circ}C}$ concentration (c = g / 100 mL, solvent).

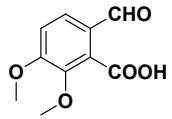
The enantiomeric excess (*ee*) was determined by HPLC using a Shimadzu LC 20A series instrument equipped with UV detector. The HPLC analysis data was reported in relative area % and was not adjusted to weight %. The used chiral HPLC columns were as follows: CHIRALPAK® IH (0.46 cm I.D. ×15 cm L ×5 μm)，CHIRALPAK® IF (0.46 cm I.D. ×15 cm L ×5 μm).

2. Experimental Procedures

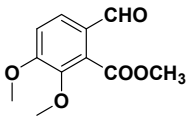
The Synthesis of Substituted Styrene 6



6,7-Dimethoxyisobenzofuran-1(3H)-one (10). To a solution of 2,3-dimethoxybenzoic acid (**8**, 8.0 g, 43.96 mmol, 1.0 equiv.) in dibromomethane (CH_2Br_2, 96 mL) were added $Pd(OAc)_2$ (0.49 g, 0.05 mmol) and K_2HPO_4 (19.1 g, 109.89 mmol, 2.5 equiv.). After being stirring at 96 ºC for 8.0 h, the reaction mixture was cooled to room temperature and filtrated. The filtrate was washed with sat. NaCl, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield crude. The crude product was purified by column chromatography on silica gel, eluting with petroleum ether/EtOAc = 10:1 - 2:1 to yield **10** as a white solid. Yield: 66% (5.6 g). Mp: 92.8 - 96.0 ºC. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.48 (d, J = 8.2 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 5.26 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.61, 152.46, 148.58, 139.47, 119.64, 118.05, 116.51, 68.51, 62.39, 56.96. HRMS (ESI$^+$): m/z calcd. for $C_{10}H_{11}O_4$ $[M+H]^+$ = 195.0657, found 195.0642.

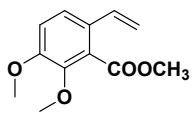


6-Formyl-2,3-dimethoxybenzoic acid (11). 6.22 g (30.0 mmol, 1.0 equiv.) 6,7-dimethoxyisobenzo furan-1(3*H*)-one (**10**), 6.27 g (35.0 mmol, 1.16 equiv.) NBS and 0.47 g AIBN (0.53 g, 3.0 mmol, 0.1 equiv.) were dissolved in CCl_4 (108 mL). After being heating to reflux for 4.0 h, the reaction mixture was cooled to room temperature and filtrated. The filtrate was concentrated under reduced pressure. To the residue was added 10% aq. KOH (60 mL) and heated to 40 ºC for 4.0 h. After cooling the mixture to room temperature and following washing the aqueous solution with CH_2Cl_2 (2 × 20 mL), the pH is adjusted to 1.0 - 2.0 with 2 N HCl. After stirring for 1.0 h at 5 ºC, the precipitate was filtered to give the crude product **11**. Yield: 75% (4.72 g). The product was used without purification in the next step. Mp: 143.6 – 145.3 ºC.



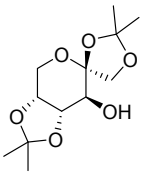
Methyl 6-formyl-2,3-dimethoxybenzoate (12). To a solution of 6-formyl-2,3-dimethoxybenzoic acid **(11)** (8.12 g, 38.67 mmol, 1.0 equiv.) in anhydrous MeOH (93 mL) were added $SOCl_2$ (7.0 mL, 96.67 mmol, 2.5 equiv.) at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min and then for additional 4.0 h at room temperature. After concentrating the mixture under reduced pressure, the residue was then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel, eluting with petroleum ether/EtOAc = 8:1 – 6:1 to yield **12** as a white solid. Yield: 87% (7.54 g). Mp: 78.5 – 80.1 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.91, 166.91, 157.84, 146.41, 129.48, 129.18, 126.69, 112.40, 61.77,

56.19, 52.78. HRMS (ESI$^+$): *m/z* calcd. for $C_{11}H_{13}O_5$ $[M+H]^+$ = 225.0763, found 225.0757; calcd. for $C_{10}H_9O_4$ $[M - OCH_3]^+$ = 193.0501, found 193.0501.

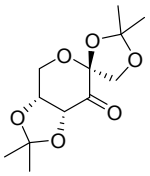


Methyl 2,3-dimethoxy-6-vinylbenzoate (6). To a cooled (0 ºC), rapidly stirred suspension of methyltriphenylphosphonium iodide (14.66 g, 35.36 mmol, 2.0 equiv.) in THF (80 mL) was added KHMDS (26.5 mL of 1.0 M solution in THF, 26.52 mmol, 1.5 equiv.). The resulting bright yellow mixture was allowed to warm to room temperature and was maintained at room temperature for 0.5 h, at which time it was recooled to 0 ºC and methyl 6-formyl-2,3-dimethoxybenzoate **(12)** (3.96 g, 17.68 mmol,1.0 equiv.) was added in four portions. The resulting mixture was allowed to warm to room temperature with stirring, and after 0.5 h the reaction was quenched with H_2O, then the mixture was concentrated *in vacuo* and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography, eluting with petroleum ether/EtOAc = 10:1 – 8:1 to yield **6** as a colorless oil. Yield: 76% (3.03 g). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.60 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.61 (dd, *J* = 17.4, 0.8 Hz, 1H), 5.22 (dd, *J* = 11.0, 0.8 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.97, 152.09, 145.87, 132.94, 129.39, 128.28, 121.43, 115.11, 113.78, 61.54, 56.03, 52.37. HRMS (ESI$^+$): *m/z* calcd. for $C_{12}H_{15}O_4$ $[M+H]^+$ = 223.0970, found 223.0970; calcd. for $C_{11}H_{11}O_3$ $[M - OCH_3]^+$ = 191.0708, found 191.0712.

The Synthesis of (*R,R*)-Catalyst 13

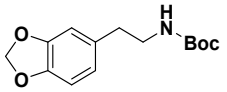


1,2:4,5-Di-*O*-isopropylidene-D-psicopyranose (*14*). To the D-fructose (30.0 g, 166.7 mmol) in acetone (600 mL) was added concentrated H_2SO_4 (1.0 mL, 16.7 mmol) under N_2 after cooling to 0 ºC. The resulting reaction mixture was stirred overnight at 25 ºC. After neutralizing with 10% NaOH/H_2O, the reaction mixture was concentrated to a solid, which was then dissolved in CH_2Cl_2 (300 mL). The resulting solution was washed with water (3 × 150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a white solid. After recrystallization in *n*-hexane - CH_2Cl_2 (4:1, v/v), alcohol **14** (23.7 g) was obtained as white needles. Yield: 54.6%; Mp：118.2 – 120.5 °C, $[\alpha]_D^{25}$ = – 153.3° (c 1.0, acetone); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 4.21 (dd, *J* = 5.8, 2.9 Hz, 1H), 4.18 (d, *J* = 8.8 Hz, 1H), 4.14 (d, *J* = 6.9 Hz, 1H), 4.12 (dd, *J* = 13.3, 2.9 Hz, 1H), 4.01 (d, *J* = 13.3 Hz, 1H), 3.99 (d, *J* = 8.8 Hz, 1H), 3.67 (d, *J* = 6.9 Hz, 1H), 1.77 (brs, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H). ^{1}H NMR data were in agreement with the described ones.[1] MS (ESI$^+$): *m/z* $[M+H]^+$ =261.2.

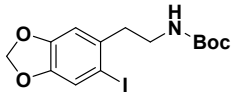


1,2:4,5-Di-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose (*13*). Compound **14** (6.53 g, 25.1 mmol), Et_3BzNCl (290 mg, 1.3 mmol), $NaIO_4$ (8.06 g, 37.8 mmol), and K_2CO_3 (530 mg, 3.8 mmol) were vigorously stirred in a mixture of 25 mL of $CHCl_3$ and 25 mL of H_2O. $RuCl_3$ monohydrate (290 mg, 1.3 mmol) were added, and the reaction mixture was heated at 70 °C. 2-Propanol (10 mL) was added after 2 h, and the suspension was further stirred for 2 h. The reaction mixture was filtered through a Celite pad, and this material was washed with CH_2Cl_2 (2 × 20 mL). This solution was mixed with the filtrate, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with saturated Na_2SO_3 (130 mL), brine (100 mL), and water (100 mL). The white solid was obtained after drying and evaporating the solvents. Purification of the crude product by flash chromatography, eluting with *n*-hexane - CH_2Cl_2 (4:1, v/v) to yield **13** as a white acicular solid. Yield: 59.5% (3.87 g). Mp：97.5 – 99.9 °C, $[\alpha]_D^{25}$ = – 124.09° (c 1.0, acetone); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.73 (d, J = 5.6 Hz, 1H), 4.61 (d, J = 9.5 Hz, 1H), 4.55 (ddd, J = 5.6, 2.2, 1.0 Hz, 1H), 4.39 (dd, J = 13.5, 2.2 Hz, 1H), 4.12 (d, J = 13.5, 1H), 4.00 (d, J = 9.5 Hz, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.40 (s, 6H). The ^{1}H NMR data obtained are consistent with those reported in the literature.[1] ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.94, 113.83, 110.65, 104.14, 77.93, 75.89, 70.02, 60.10, 27.16, 26.52, 26.06, 26.02. The ^{13}C NMR data obtained are consistent with those reported in the literature.[2] MS (ESI^+): *m/z* $[M+Na]^+$ =281.2.

The Synthesis of (–)-β-Hydrastine

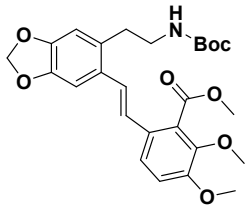


tert-Butyl (2-(benzo[d][1,3]dioxol-5-yl)ethyl)carbamate (7). NEt_3 (4.0 mL, 30.0 mmol, 1.5 equiv.) and di-*tert*-butyl dicarbonate $[(Boc)_2O]$ (6.54 g, 30.0 mmol, 1.5 equiv.) were added to a solution of 2-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-amine **(9)** (3.30 g, 20.0 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) at 0 ºC. After stirring for 3.0 h at room temperature, the reaction was quenched by addition of brine at 0 ºC. The mixture was then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with a 10% aq. citric acid solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by stirring with petroleum ether and the solid was filtrated to give *N*-Boc carbamate **7** as a white solid. Yield: 97% (5.16 g). The product was used without further purification in the next step.



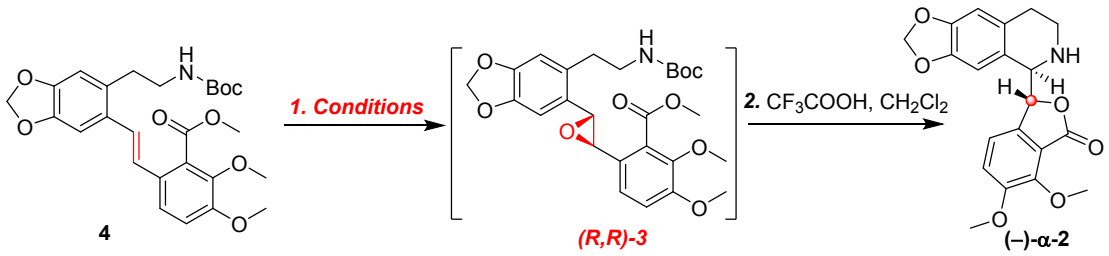
tert-Butyl (2-(6-iodobenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (5). The *N*-Boc-protected amine **7** (5.16 g, 19.47 mmol, 1.0 equiv.) was suspended together with silver trifluoroacetate (4.4 g, 20.0

mmol, 1.02 equiv.) in CH_2Cl_2 (200 mL). After the mixture was cooled to - 10 ºC, iodine (4.94 g, 19.47 mmol, 1.0 equiv.) was added slowly to maintain the temperature < - 5 ºC. After being stirred for 10 min, the mixture was filtrated over Celite, the solution was washed with a saturated aqueous solution of sodium thiosulfate until decolorization and then washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **5** as a white solid. Yield: 84% over two steps (6.37 g). The product was used without further purification in the next step. Mp: 86.7 – 88.6 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.74 (s, 1H), 5.95 (s, 2H), 4.58 (s, 1H), 3.34 – 3.28 (m, 2H), 2.85 (t, *J* = 6.9 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.84, 148.55, 147.16, 134.93, 118.68, 109.88, 101.59, 87.93, 79.29, 77.25, 77.04, 76.83, 40.67, 28.44. HRMS (ESI$^+$): m/z calcd. for $C_{28}H_{37}I_2N_2O_{10}$ $[2M+H]^+$ = 783.0639, found 783.0677.



Methyl (E)-6-(2-(6-(2-((tert-butoxycarbonyl)amino)ethyl) benzo[d][1,3]dioxol-5-yl)vinyl)-2,3-dimethoxybenzoate (4). A solution of methyl 2,3-dimethoxy-6-vinylbenzoate **(6)** (1.95 g, 8.78 mmol, 1.0 equiv.), *tert*-butyl (2-(6-iodobenzo[*d*][1,3] dioxol-5-yl)ethyl)carbamate **(5)** (3.6 g, 9.22 mmol, 1.05 equiv.), silver acetate (1.61 g, 9.66 mmol, 1.1 equiv.), and palladium acetate (0.2 g, 0.88 mmol, 0.1 equiv.) in acetic acid (25 mL) was heated at 117 ºC for 1.5 h under Ar atmosphere. The resulting dark reaction mixture was poured into water (250 mL), and then extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography, eluting with petroleum ether/EtOAc = 10:1 – 5:1 to yield **4** as a light yellow oil. Yield: 76% (3.22 g). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.65 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 15.9 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.10 (s, 1H), 6.95 (t, *J* = 5.5 Hz, 1H), 6.76 (s, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 5.99 (s, 1H), 3.88 (s, 1H), 3.86 (s, 2H), 3.74 (s, 2H), 3.08 – 3.01 (m, 1H), 2.76 (t, *J* = 7.5 Hz, 1H), 1.37 (s, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.81, 156.11, 151.88, 147.46, 146.84, 145.55, 132.06, 129.46, 128.48, 127.77, 126.82, 124.17, 122.26, 114.77, 110.50, 105.13, 101.44, 78.09, 61.40, 56.50, 52.84, 46.00, 33.42, 28.72. HRMS (ESI$^+$): *m/z* calcd. for $C_{26}H_{32}NO_8$ $[M+H]^+$ = 486.2128, found 486.2101.

Table S1. Optimization of Asymmetric Epoxidation of (*E*)-Stilbene 4 for the Acid-Catalyzed Cascade Cyclization



Entry[a]	Conditions	Yeild[b] (%)	ee[c] (%)
1	Ketone **13** (3.0 equiv.), Oxone (5.6 equiv.), $NaHCO_3$ (18.9 equiv.), CH_3CN-CH_2Cl_2-H_2O (v/vv=1:4:5), 0 ℃, 48 h	ND	–
2	Ketone **13** (3.0 equiv.), Oxone (5.0 equiv.), $NaHCO_3$ (15.5 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-aq.Na_2EDTA (4×10^{-4} M) (v/v=1.5:1), 0 ℃, 2.0 h	ND	–
3	Ketone **13** (5.0 equiv.), Oxone (5.0 equiv.), $NaHCO_3$ (15.5 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-aq.Na_2EDTA (4×10^{-4} M) (v/v=1.5:1), 0 ℃, 2.0 h	ND	–
4	Ketone **13** (0.3 equiv.), Oxone (2.02 equiv.), K_2CO_3 4.04 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-DMM-buffer[d] (pH=7.0) (v/v/v=1:2:1), 0 ℃, 24 h	ND	–
5	Ketone **13** (0.3 equiv.), Oxone (1.38 equiv.), K_2CO_3 (5.8 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-DMM-buffer[e] (v/v/v=1:2:2), 0 ℃, 1.5 h	ND	–
6	Ketone **13** (1.6 equiv.), Oxone (1.6 equiv.), K_2CO_3 (6.74 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-DMM-buffer[e] (v/v/v=1:2:2), 0 ℃, 1.5 h	ND	–
7	Ketone **13** (2.0 equiv.), Oxone (1.6 equiv.), K_2CO_3 (6.74 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-DMM-buffer[e] (v/v/v=1:2:2), 0 ℃, 1.5 h	ND	–
8	Ketone **13** (3.0 equiv.), Oxone (1.6 equiv.), K_2CO_3 (6.74 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-DMM-buffer[e] (v/v/v=1:2:2), 0 ℃, 1.5 h	ND	–
9	Ketone **13** (3.0 equiv.), Oxone (1.6 equiv.), K_2CO_3 (6.74 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-DMM-buffer[e] (v/v/v=1:2:2), -10 ℃, 2 h	trace[f]	–
10	Ketone **13** (1.6 equiv.), Oxone (1.6 equiv.), K_2CO_3 (6.74 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-DMM-buffer[e] (v/v/v=1:2:2), -10 ℃, 2 h	trace[f]	–
11	Ketone **13** (1.6 equiv.), Oxone (1.38 equiv.), K_2CO_3 (5.8 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-DMM-buffer[e] (v/v/v=1:2:2), -10 ℃, 2 h	trace[f]	–
12[g]	Ketone **13** (0.3 equiv.), Oxone (1.38 equiv.), K_2CO_3 (5.8 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-buffer[e] (v/v=3:2), 0 ℃ to rt, 24 h	trace[f]	–
13	Ketone **13** (3.0 equiv.), Oxone (1.38 equiv.), K_2CO_3 (5.8 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-bufer[e] (v/v=3:2), 0 ℃ to rt, 24 h	trace[h]	–
14[i]	**Ketone 13 (3.0 equiv.), Oxone (4.6 equiv.), K_2CO_3 (18.6 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-buffer[e] (v/v=3:2, 25 mL), 0 ℃ 4.5 h**	**42**	**86**
15[i]	Ketone **13** (1.0 equiv.), Oxone (4.6 equiv.), K_2CO_3 (18.6 equiv.), Bu_4NHSO_4 (5 mol %), CH_3CN-buffer[e] (v/v=3:2, 25 mL), 0 ℃ 8 h	24	79
16[j]	Ketone **13** (3.0 equiv.), 30% H_2O_2 (30 equiv.), CH_3CN-buffer[k](v/v=2:1), 0 ℃ 36 h	25	58
17[j]	Ketone **13** (3.0 equiv.), 30% H_2O_2 (30 equiv.), CH_3CN-EtOH-CH_2Cl_2, (v/v/v=1:1:2), buffer[l], 0 ℃ 36 h	40	71

[a]Substrate **4** (0.1 mmol). [b]Isolated yield of **(–)-α-2**. [c]The enantiomeric excess was determined by chiral HPLC (Chiralpak IH). [d]Buffer: 0.05 M aq.Na_2HPO_4-0.05 M aq.KH_2PO_4, pH=7.0. [e]Buffer: 0.05 M $Na_2B_4O_7$•10 H_2O of aqueous Na_2EDTA (4×10^{-4} M) solution. [f]Most of the starting material was recovered. [g]Substrate **4** (1 mmol). [h]Most of the epoxide ***(R,R)-3*** was decomposed. [i]Substrate **4** (0.3 mmol). [j] Substrate **4** (0.4 mmol). [k]Buffer: 1.0 M K_2CO_3 in 4×10^{-4} M of EDTA. [l]Buffer: 2.0 M K_2CO_3 in 4×10^{-4} M of EDTA.

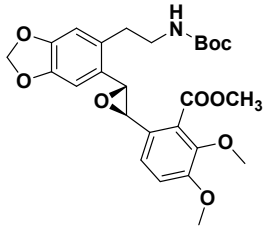
General Experimental Procedure for studies summarized in Tables S1 (entries 1-15) and focused on optimizing the formation of [(R,R)-3].

To a three-neck round-bottom flask were added the mixed solvent (entry 1) or the mixed solvent

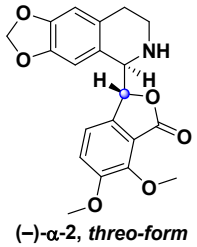
and buffer (entries 2-15), compound **4** (0.1 mmol, 1.0 equiv.), tetrabutylammonium hydrogen sulfate (15 mg). The reaction mixture was cooled to 0 ℃ or −10 ℃. Then, the solid Oxone, $NaHCO_3$, ketone **13** were added in portions (entry 1) or a solution of Oxone in aqueous Na_2(EDTA) (4×10^{-4} M), a solution of K_2CO_3 in water and a solution of ketone **13** in acetonitrile were added in dropwise through three separate addition funnels. The reaction was stirred for the corresponding reaction time, and monitored by TLC. The crude product **(*R,R*)-3** was directly used for the following acid-catalyzed cascade cyclization. The results were analyzed by chiral HPLC (Chiralpak IH).

General Experimental Procedure for studies summarized in Tables S1 (entries 16-17) and focused on optimizing the formation of [(R,R)-3].

To a solution of compound **4** (0.4 mmol, 1.0 equiv.) in the solvent was add the buffer followed by ketone **13** (0.4 mmol, 1.0 equiv.) and 30% H_2O_2 (4.0 equiv.) at 0 ℃. Upon stirring at 0 ℃ for 12 h, additional ketone **13** (0.4 mmol, 1.0 equiv.) and 30% H_2O_2 (4.0 equiv.) were added and the mixture was stirred at 0 ℃ for another12 h. And then ketone **13** (0.4 mmol, 1.0 equiv.) and 30% H_2O_2 (4.0 equiv.) were added in again for stirring the last 12 h. The reaction was then monitored by TLC to follow the reaction to completion, and quenched by addition of aq. $Na_2S_2O_3$. The mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4. The solvent was removed under vacuum to give crude product **(*R,R*)-3**, which was directly used for the next step. The results were analyzed by chiral HPLC (Chiralpak IH).



Methyl 6-((2R,3R)-3-(6-(2-((tert-butoxycarbonyl)amino)-ethyl)benzo[d][1,3]dioxol-5-yl)oxiran-2-yl)-2,3-dimethoxy-benzoate [(R,R)-3]. To a 100 mL three-neck round-bottom flask were added buffer (0.05 M $Na_2B_4O_7$•$10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA), 10 mL), acetonitrile (15 mL), compound **4** (120 mg, 0.3 mmol, 1.0 equiv.), tetrabutylammonium hydrogen sulfate (15 mg). The reaction mixture was cooled with an ice bath. A solution of Oxone (0.85 g, 1.38 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 6.5 mL), a solution of K_2CO_3 (0.8 g, 5.8 mmol) in water (6.5 mL) and a solution of ketone 13 (0.23 g, 0.9 mmol) in acetonitrile (3.0 mL) were added dropwise through three separate addition funnels over a period of 4.5 h. The reaction was then monitored by TLC to follow the reaction to completion, and quenched by addition of water (20 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL), washed with brine (3×20 mL), dried over Na_2SO_4. The solvent was removed under vacuum to give crude product **(*R,R*)-3** (≈ 150 mg, ≈ 0.3 mmol, > 95% crude yield), which was directly used for the next step.

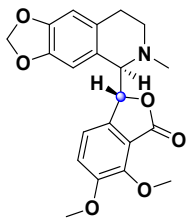


(–)-α-2, *threo-form*

(–)-α-N-demethyl Hydrastine [***(–)-α-2, threo-form***]. To a stirred solution of the above epoxide

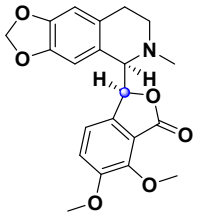
(*R,R*)-3 (≈ 0.3 mmol) in CH_2Cl_2 (30 mL) at 0 ºC was added CF_3CO_2H (0.55 mL, 7.5 mmol, 30 equiv.). Upon stirring at 0 ºC for 3.0 h (the epoxide was consumed as judged by TLC), Additional CF_3CO_2H (2.2 mL, 120.0 mmol, 4 × 30 equiv.) was added to the reaction mixture at 0 ºC. After stirring for additional 3.0 h at room temperature, the reaction mixture was concentrated and redissolved in CH_2Cl_2 (20 mL) and water (10 mL). The mixture was adjusted to pH = 8.0 – 9.0 with ammonium hydroxide and then extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine (20 mL × 3) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give crude product **(–)-α-2** (≈ 110 mg, > 99% crude yield), which was directly used for the next step.

For the analysis, small amounts of the crude **(*R,R*)-3** (50 mg, 0.1 mmol) were converted to **(–)-α-2** in above conditions and purified by preparative thin layer chromatography (PTLC, CH_2Cl_2/MeOH= 100:1) to give **(–)-α-2** (15.4 mg) as a light yellow solid. Yield: 42.1% for two steps, **86% *ee*** (Chiralpak IH column, *n*-Hexane/Ethanol/Diethylamine = 40:60:0.1, 220 nm, 0.8 mL/min, 35 ºC, t_{major} = 5.537 min, t_{minor} = 7.569 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.2 Hz, 1H), 7.12 (dd, J = 8.2, 0.6 Hz, 1H), 6.71 (s, 1H), 6.56 (s, 1H), 5.90 (dd, J = 6.7, 1.4 Hz, 2H), 5.69 (d, J = 2.9 Hz, 1H), 5.35 (t, J = 4.6 Hz, 1H), 4.42 (d, J = 3.0 Hz, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 3.20 (dt, J = 12.0, 5.2 Hz, 1H), 2.90 (ddd, J = 12.2, 7.9, 4.6 Hz, 1H), 2.83 – 2.66 (m, 1H), 2.60 (dt, J = 15.9, 5.0 Hz, 1H). HRMS (ESI$^+$): *m/z* calcd. for $C_{20}H_{20}NO_6$ $[M+H]^+$ = 370.1291, found 370.1277.



(–)-α-Hydrastine (*threo-form)*

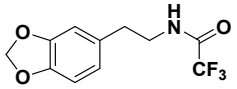
***(–)-α-Hydrastine* (*threo-form*).** To a stirred solution of the above crude product **(–)-α-2** (≈ 0.3 mmol, 1.0 equiv.) in HCOOH (2.5 mL) was added 37% HCHO (1.5 mL). After the reaction mixture was heated to reflux and stirred for 30 min (detected by TLC), the reaction mixture was concentrated and the resulting residue was stirred with water (≈ 10 mL) and CH_2Cl_2 (20 mL), adjusted to pH = 9.0 – 10.0 with ammonium hydroxide, and then extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine (20 mL × 3) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give crude product **Hydrastine**, which was purified by preparative thin layer chromatography (silica gel), eluting with CH_2Cl_2/MeOH=100:1 to give **(–)-α-Hydrastine [*threo-form*]** (28.0 mg) as a white solid. Yield: 29.6% over three steps from compound **4**. Mp: 153.2 – 155.0 ºC, $[\alpha]_D^{25}$ = – 123.5° (c 0.5, CH_2Cl_2) (lit[1] = 162.0 – 163.5 ºC， $[\alpha]_D^{25}$ = – 141°)；^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, J = 8.2 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.64 (s, 1H), 6.37 (s, 1H), 5.83 (d, J = 1.0 Hz, 1H), 5.78 (s, 1H), 5.55 (d, J = 2.8 Hz, 1H), 4.01 (d, J = 2.3 Hz, 1H), 3.98 (s, 3H), 3.84 (s, 3H), 3.16 – 3.00 (m, 1H), 2.85 – 2.65 (m, 1H), 2.56 (s, 3H), 2.53 (d, J = 9.9 Hz, 1H), 2.46 (d, J = 15.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.89, 152.24, 147.67, 146.25, 145.78, 140.94, 129.81, 125.10, 119.24, 118.22, 117.99, 108.14, 107.38, 100.74, 80.89, 66.22, 62.30, 56.72, 51.26, 44.93, 29.14. HRMS (ESI$^+$): *m/z* calcd. for $C_{21}H_{22}NO_6$ $[M+H]^+$ = 384.1447, found 384.1435.



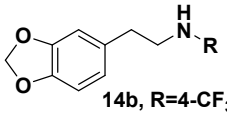
(–)-β-Hydrastine, *erythro-form*

(–)-α-Hydrastine epimerized to (–)-β-Hydrastine. To a stirred solution of the above **(–)-α-Hydrastine** (110 mg, 0.3 mmol, 1.0 equiv.) in MeOH (16 mL) was added MeOK (1.33 g, 18.9 mmol, 65.8 equiv.). After the reaction mixture was stirred at room temperature for 22 h (detected by TLC), the reaction mixture was diluted with water (5.0 mL) and concentrated, the resulting residue was adjusted to pH = 2.0 with 2 N HCl at 0 ºC, then stirred at room temperature for 30 min. The aqueous layer was adjusted to pH = 9.0 with ammonium hydroxide and then extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give crude product **(–)-β-Hydrastine**, which was purified by column chromatography (silica gel), eluting with petroleum ether/EtOAc = 2:1 (0.15% Et_3N) to give **(–)-β-Hydrastine** (71.0 mg) as a light yellow solid. Yield: 64.5%, **81% *ee*** (Chiralpak IF column, *n*-Hexane/Ethanol/Diethylamine = 30:70:0.1, 220 nm, 1.0 mL/min, 35 ºC, t_{major} = 5.868 min, t_{minor} = 7.317 min). Mp: 125.4 – 128.2 ºC， $[\alpha]_D^{25}$ = – 77.3° (c 0.5, CH_2Cl_2) (lit[1] M.p. 132 ºC, $[\alpha]_D^{25}$ = – 68°). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, J = 8.2 Hz, 1H), 6.58 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 6.36 (s, 1H), 5.91 (dd, J = 4.6, 1.4 Hz, 2H), 5.51 (d, J = 2.4 Hz, 1H), 4.06 (s, 3H), 4.00 (d, J = 3.7 Hz, 1H), 3.89 (s, 3H), 2.92 (t, J = 13.1 Hz, 1H), 2.68 – 2.57 (m, 2H), 2.56 (s, 3H), 2.35 – 2.25 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.69, 152.54, 148.01, 146.78, 145.78, 140.70, 130.24, 124.46, 119.64, 118.61, 117.63, 108.54, 107.77, 100.87, 82.86, 66.11, 62.33, 56.81, 48.96, 44.74, 26.54. HRMS (ESI$^+$): *m/z* calcd. for $C_{21}H_{22}NO_6$ $[M+H]^+$ = 384.1447, found 384.1433.

The Syntheses of (*E*)-stilbenes 16a-c

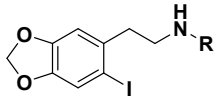


***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-2,2,2-trifluoroacetamide (14a).** NEt_3 (6.0 mL, 45.0 mmol, 2.2 equiv.) was added to a solution of 2-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-amine **(9)** (3.30 g, 20.0 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL). After cooling the mixture to - 20 ºC, trifluoroacetic anhydride (3.1 mL, 22.0 mmol,1.1 equiv.) was dropped slowly. After that, the reaction mixture was stirred at - 20 ºC for 1.0 and then at room temperature for 3.5 h. After the reaction was complete, the reaction was quenched by addition of water at 0 ºC and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water, a 10% aq. citric acid solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by stirring with petroleum ether and the solid was filtrated to give **14a** as a white solid. Yield: 95% (4.96 g). The product was used without further purification in the next step.



14b, R=4-CF_3-PhSO_2
14c, R=MeSO_2

Referring the general procedures for the preparation of ***7****, N-protected* ***14b*** *and* ***14c*** *were smoothly synthesized. The crude product* ***14b*** *and* ***14c*** *were used without further purification in the next step.*



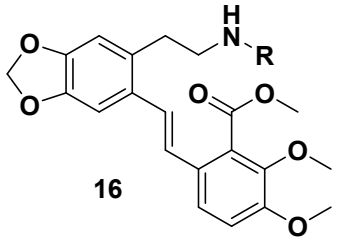
15

The general procedures for the preparation of ***15a, 15b*** *and* ***15c*** *were as same as those of the preparation of* ***5****.*

2,2,2-Trifluoro-N-(2-(6-iodobenzo[d][1,3]dioxol-5-yl)ethyl)acetamide (15a): White solid, yield: 82.3% over two steps; Mp: 129.6 – 132.8 ºC; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.25 (s, 1H), 6.72 (s, 1H), 6.34 (s, 1H), 5.98 (s, 2H), 3.58 (q, J = 6.8 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H). MS (ESI$^+$): *m/z* $[M+Na]^+$ = 409.9.

N-(2-(6-iodobenzo[d][1,3]dioxol-5-yl)ethyl)-4-(trifluoromethyl)benzenesulfonamide (15b): White solid, yield: 88.0% over two steps; Mp: 121.0 – 122.8 ºC; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.94 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.15 (s, 1H), 6.63 (s, 1H), 5.94 (s, 2H), 4.64 (t, J = 6.1 Hz, 1H), 3.24 (q, J = 6.9 Hz, 2H), 2.85 (t, J = 7.0 Hz, 2H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 148.67, 147.55, 143.58, 134.46, 134.24, 133.20, 127.56, 126.61 – 126.11 (m), 122.33, 118.84, 109.92, 101.77, 87.85, 43.16, 40.43. HRMS (ESI$^+$): *m/z* calcd. for $C_{16}H_{12}F_3INO_4S$ $[M-H]^-$ = 497.9489, found 497.9513.

N-(2-(6-iodobenzo[d][1,3]dioxol-5-yl)ethyl)methanesulfonamide (15c): White solid, yield: 79.0% over two steps; Mp: 132.8 – 134.4 ºC; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.78 (s, 1H), 5.97 (s, 2H), 4.35 (s, 1H), 3.35 (dd, J = 13.6, 6.8 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H), 2.91 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 148.75, 147.60, 133.57, 118.88, 110.12, 101.79, 87.89, 43.19, 41.03, 40.54. HRMS (ESI$^-$): *m/z* calcd. for $C_{10}H_{11}INO_4S$ $[M-H]^-$ = 367.9459, found 367.9464.



16

The general procedures for the preparation of ***16a, 16b*** *and* ***16c*** *were as same as those of the preparation of* ***4****.*

Methyl (E)-2,3-dimethoxy-6-(2-(6-(2-(2,2,2-trifluoroacetamido)ethyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzoate (16a): light yellow oil, yield: 67.5%; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 7.61 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 15.8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.11 (s, 1H), 6.79 (s, 1H), 6.69 (d, J = 15.9 Hz, 1H), 6.01 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.74 (s, 3H), 3.30 (m, 2H), 2.91 – 2.85 (m, 2H). ^{13}C-NMR (151 MHz, $CDCl_3$) δ 168.43, 157.33 (d, J = 36.9 Hz), 152.04, 147.60, 147.23, 146.13, 130.17, 129.36, 128.09, 127.86, 126.30, 125.98, 122.10, 116.76, 114.44 (d, J = 126.1 Hz),

109.90, 106.03, 101.26, 61.53, 56.05, 52.52, 40.96, 32.59. MS (ESI^+): *m/z* $[M+Na]^+$ = 504.3.

Methyl (E)-2,3-dimethoxy-6-(2-(6-(2-((4-(trifluoromethyl)phenyl)sulfonamido)ethyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzoate (16b): light yellow oil, yield: 75.0%; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 15.9 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.94 (s, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.55 (s, 1H), 5.97 – 5.93 (m, 2H), 4.75 (t, J = 6.2 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.13 (dd, J = 13.9, 6.9 Hz, 2H), 2.89 (t, J = 7.3 Hz, 2H). ^{13}C-NMR (150 MHz, DMSO-d_6) δ 167.79, 152.00, 147.44, 146.99, 145.57, 144.74, 132.60, 130.99, 129.50, 128.49, 127.77, 127.60, 126.77 (d, J = 3.6 Hz), 126.57, 124.68, 122.10, 114.89, 110.67, 105.33, 101.51, 61.37, 56.51, 52.82, 44.16, 33.33. HRMS (ESI^+): *m/z* calcd. for $C_{28}H_{26}F_3NO_8SNa$ $[M+Na]^+$ = 616.1229, found 616.1230.

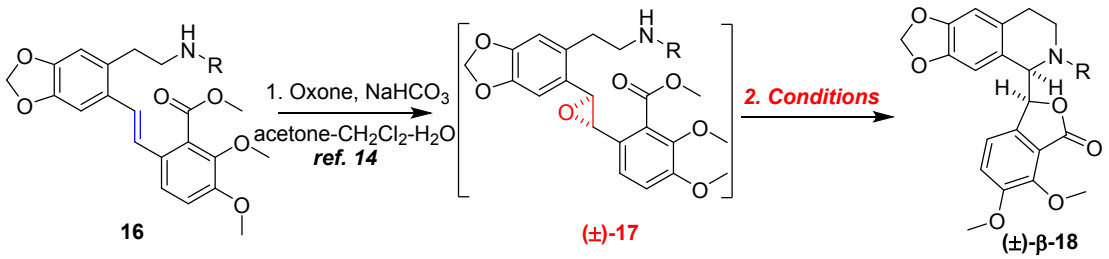
Methyl (E)-2,3-dimethoxy-6-(2-(6-(2-(methylsulfonamido)ethyl)benzo[d][1,3]dioxol-5-yl)vinyl) benzoate (16c): light yellow oil, yield: 73.0%; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 15.9 Hz, 1H), 7.02 (s, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.75 (d, J = 15.8 Hz, 1H), 6.67 (s, 1H), 5.96 (s, 2H), 4.38 (t, J = 6.7 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.29 (dd, J = 13.6, 7.0 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.87 (s, 3H). ^{13}C-NMR (150 MHz, DMSO-d_6) δ 167.81, 151.95, 147.52, 147.00, 145.55, 131.48, 129.56, 128.48, 127.66, 126.69, 124.59, 122.19, 114.91, 110.70, 105.29, 101.52, 61.40, 56.51, 52.87, 44.21, 33.83. HRMS (ESI^+): *m/z* calcd. for $C_{22}H_{25}NO_8SNa$ $[M+Na]^+$ = 486.1199, found 486.1188.

General procedures for the preparation of racemic model substrates [(±)-17] for the base-catalyzed cascade cyclization. To the stirred mixture of compound **16** (0.1 mmol, 1.0 equiv), $NaHCO_3$ (1.89 mmol, 18.9 equiv), H_2O (2.5 mL), CH_2Cl_2 (2.0 mL), and acetone (0.5 mL) was added Oxone (0.56 mmol, 5.6 equiv) at 0 ºC in portions. The reaction was then monitored by TLC to follow the reaction to completion, quenched with water (3.0 mL), and extracted with CH_2Cl_2 (5 mL×3). The combined organic layer was then washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give crude product **(±)-17**, which was directly used for the next step. *During the isolation process, we found that the epoxides **[(±)-17]** were prone to decomposition. To address this issue, a two-step procedure was developed in which the epoxidation and cascade cyclizations were performed sequentially with only one isolation operation at the end (**Table S2**).*

General Experimental Procedure for studies summarized in Tables S2 and focused on optimizing the formation of [(±)-β-18].

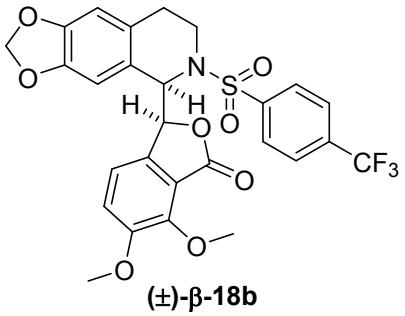
To a flame dried, N_2 flushed three-neck round-bottom flask, a stir bar and the starting substrate **16** (0.1 mmol) was placed and dissolved in the solvent (2.0 mL) at 0 ºC. Then the base was added in dropwise (or in portion). The reaction was stirred for 12 h (unless noted otherwise) at the corresponding reaction temperature.

Table S2. Optimization of Racemic Model Substrates [(±)-17] for the Base-Catalyzed Cascade Cyclization



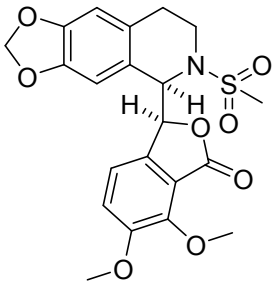
Entry[a]	17	Base (equiv.)	Solvent	Temp. (ºC)	T (h)	Yield[b] (%)
1	**17a**	60% NaH (2.5)	1,4-Dioxane	0 - 65	12	–[c]
2	**17a**	KHMDS (1.2)	1,4-Dioxane	0 - 65	12	ND[d]
3	**17a**	KHMDS (1.2)	1,4-Dioxane	0 - 84	12	□–[c]
4	**17a**	KHMDS (1.2)	dry THF	0 - 65	12	ND[d]
5	**17a**	KHMDS (1.2)	dry THF	0 - rt	12	ND[d]
6	**17a**	LDA (1.2)	dry THF	0 - 65	12	□–[c]
7	**17a**	*n*-BuLi (1.2)	dry THF	–78 - rt	12	□–[c]
8	**17b**	KHMDS (1.2)	dry THF	0 - 65	12	11
9	**17b**	KHMDS (1.5)	1,4-Dioxane	0 - 65	12	10
10	**17b**	**KHMDS (1.5)**	**dry THF**	**0 - 65**	**5.0**	**30**
11	**17c**	KHMDS (1.5)	dry THF	0 - 65	12	ND[d]
12	**17c**	NaHMDS (1.5)	dry THF	0 - 65	12	ND[d]
13	**17c**	KHMDS (1.5)	1,4-Dioxane	0 - 84	12	□–[c]
14	**17c**	60% NaH (2.5)	1,4-Dioxane	0 - 65	12	15
15	**17c**	60% NaH (2.5)	1,4-Dioxane	0 - 65	24	10
16	**17c**	60% NaH (2.5)	1,4-Dioxane	0 - 60	12	16
17	**17c**	60% NaH (1.5)	1,4-Dioxane	0 - 60	5.0	19

[a]The substrate **16** (0.1 mmol) was dissolved in solvent and then the base was added in dropwise. [b]Isolated yield of **(±)-β-18** in two steps. [c]Most of the epoxide **(±)-17** was decomposed. [d]The **(±)-β-18** was not detected by TLC and the epoxide **(±)-17** was recovered. NaHMDS = Sodium bis(trimethylsilyl)amide. KHMDS = Potassium bis(trimethylsilyl)amide. LDA = Lithium diisopropylamide.



(±)-β-6,7-dimethoxy-3-(6-((4-(trifluoromethyl)phenyl)sulfonyl)-5,6,7,8-tetrahydro-[1,3]dioxolo [4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one. To a flame dried, N_2 flushed three-neck round-

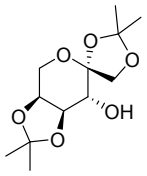
bottom flask, a stir bar and the starting substrate **17b** (0.21 g, 0.4 mmol, 1.0 equiv.) was placed and dissolved in dry THF (5.0 mL) at 0 ºC. Then the 1.0 M KHMDS (0.6 mL, 0.6 mmol, 1.5 equiv.) was slowly added in dropwise. The reaction mixture was then warmed to 65 ºC and stirred for 5 h. After quenching the reaction by saturated ammonium chloride, the reaction mixture was concentrated and the resulting residue was stirred with water (≈ 10 mL) and CH_2Cl_2 (20 mL), adjusted to pH = 2.0 with 1 N HCl and stirred for 30 min. Then the mixture was adjusted to pH = 9.0 – 10.0 with ammonium hydroxide, and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was washed with brine (15 mL × 3) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give crude product **(±)-β-18b**, which was purified by the flash chromatography (silica gel), eluting with petroleum ether/EtOAc =4:1, to give **(±)-β-18b** (60 mg) as a white solid. Yield: 29.9% over two steps. Mp: 154.3 – 156.4 ºC; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.44 (s, 1H), 5.90 (s, 1H), 5.85 (d, J = 1.5 Hz, 1H), 5.83 (d, J = 1.5 Hz, 1H), 5.74 (d, J = 3.0 Hz, 1H), 5.34 (d, J = 2.8 Hz, 1H), 4.00 – 3.96 (m, 3H), 3.93 (s, 3H), 3.62 – 3.56 (m, 1H), 3.49 (ddd, J = 13.3, 9.5, 5.1 Hz, 1H), 2.76 (dt, J = 16.3, 4.8 Hz, 1H), 2.55 (ddd, J = 16.1, 9.4, 6.2 Hz, 1H). HRMS (ESI$^+$): *m/z* calcd. for $C_{27}H_{22}F_3NO_8SNa$ $[M+Na]^+$ = 600.0916, found 600.0912.



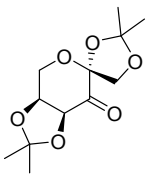
(±)-β-18c

6,7-dimethoxy-3-(6-(methylsulfonyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one. To a flame dried, N_2 flushed three-neck round-bottom flask, a stir bar and the starting substrate **17c** (0.17 g, 0.4 mmol, 1.0 equiv.) was placed and dissolved in dry 1,4-dioxane (10.0 mL) at 0 ºC. Then the 60% NaH (24 mg，0.6 mmol, 1.5 equiv.) was slowly added in protion. The reaction mixture was then warmed to 60 ºC and stirred for 5 h. After quenching the reaction by saturated ammonium chloride, the reaction mixture was concentrated and the resulting residue was stirred with water (≈ 10 mL) and CH_2Cl_2 (20 mL), adjusted to pH = 2.0 with 1 N HCl and stirred for 30 min. Then the mixture was adjusted to pH = 9.0 – 10.0 with ammonium hydroxide, and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was washed with brine (15 mL × 3) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give crude product **(±)-β-18c**, which was purified by the flash chromatography (silica gel), eluting with petroleum ether/EtOAc =4:1, to give **(±)-β-18c** (30 mg) as a white solid. Yield: 19.2% over two steps. Mp: 190.8 – 196.5 ºC; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.15 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.61 (s, 1H), 6.23 (s, 1H), 5.91 (s, 2H), 5.72 (d, J = 3.4 Hz, 1H), 5.34 (d, J = 3.4 Hz, 1H), 4.04 (s, 3H), 3.90 (s, 3H), 3.68 (ddd, J = 13.3, 5.6, 3.4 Hz, 1H), 3.00 – 2.94 (m, 1H), 2.93 (s, 3H), 2.87 (ddd, J = 16.5, 10.6, 6.0 Hz, 1H), 2.69 (dt, J = 16.3, 3.8 Hz, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 167.16, 153.08, 148.51, 147.57, 146.21, 139.02, 128.63, 121.82, 119.03, 118.61, 117.57, 109.22, 106.80, 101.19, 82.30, 62.39, 57.99, 56.78, 40.69, 40.03, 27.74. HRMS (ESI$^+$): *m/z* calcd. for $C_{21}H_{21}NO_8SNa$ $[M+Na]^+$ = 470.0886, found 470.0880.

The Synthesis of (*S,S*)-Catalyst *ent*-13

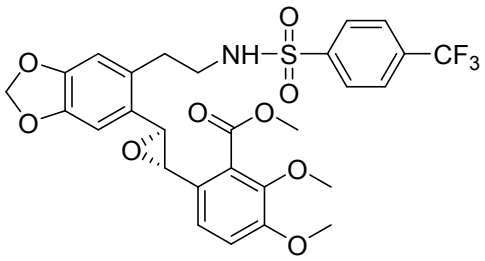


1,2:4,5-Di-*O*-isopropylidene-L-psicopyranose (*ent-14*). To the L-fructose (2.2 g, 12.2 mmol) in acetone (100 mL) was added concentrated H_2SO_4 (70 μL, 1.2 mmol) under N_2 after cooling to 0 ºC. The resulting reaction mixture was stirred overnight at 25 ºC. After neutralizing with 10% NaOH/H_2O, the reaction mixture was concentrated to a solid, which was then dissolved in CH_2Cl_2 (50 mL). The resulting solution was washed with water (25 mL) and brine (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a white solid. After recrystallization in *n*-hexane - CH_2Cl_2 (4:1, v/v), alcohol ***ent-14*** (1.71 g) was obtained as white needles. Yield: 54.8%; Mp: 116.4 – 117.8 °C, $[\alpha]_D^{25}$ = + 141.08° (c 0.314, acetone) [lit[3] M.p. 115 – 116 °C, $[\alpha]_D^{25}$ = □ 142.4° (c 1.05, $CHCl_3$)]; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.22 (dd, J = 5.8, 2.1 Hz, 1H), 4.19 (d, J = 8.8 Hz, 1H), 4.15 – 4.10 (m, 2H), 4.01 (d, J = 13.4 Hz, 1H), 3.99 (d, J = 8.8 Hz, 1H), 3.67 (d, J = 6.9 Hz, 1H), 1.94 (brs, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 111.84, 109.44, 104.50, 77.30, 73.31, 72.34, 70.43, 60.75, 27.94, 26.45, 26.24, 25.95； HRMS (ESI$^+$): *m/z* calcd for $C_{12}H_{20}O_6Na$ $[M+Na]^+$ = 283.1158, found 283.1158.



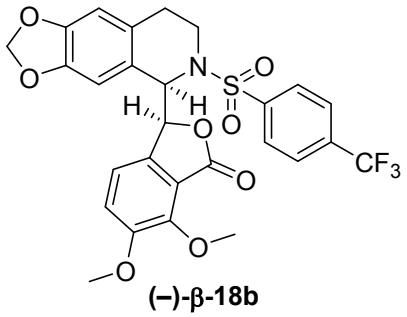
1,2:4,5-Di-*O*-isopropylidene-L-erythro-2,3-hexodiuro-2,6-pyranose (*ent-13*). Compound ***ent-14*** (8.93 g, 34.4 mmol), Et_3BzNCl (0.78 g, 3.4 mmol), $NaIO_4$ (11.02 g, 51.5 mmol), and K_2CO_3 (0.71 g， 5.2 mmol) were vigorously stirred in a mixture of 35 mL of $CHCl_3$ and 35 mL of H_2O. $RuCl_3$ monohydrate (0.77 g, 3.4 mmol) were added, and the reaction mixture was heated at 70 °C. 2-Propanol (12 mL) was added after 2 h, and the suspension was further stirred for 2 h. The reaction mixture was filtered through a Celite pad, and this material was washed with CH_2Cl_2 (3 × 20 mL). This solution was mixed with the filtrate, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with saturated Na_2SO_3 (130 mL), brine (100 mL), and water (100 mL). The white solid was obtained after drying and evaporating the solvents. Purification of the crude product by flash chromatography, eluting with *n*-hexane - CH_2Cl_2 (4:1, v/v) to yield **ent-13** as a white acicular solid. Yield: 57.5% (5.1 g). Mp: 98.1 – 100.0 °C, $[\alpha]_D^{25}$ = + 113.7° (c 1.0, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.73 (d, J = 5.6 Hz, 1H), 4.61 (d, J = 9.5 Hz, 1H), 4.57 – 4.53 (m, 1H), 4.39 (dd, J = 13.5, 2.1 Hz, 1H), 4.12 (d, J = 13.5 Hz, 1H), 4.00 (d, J = 9.5 Hz, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.40 (s, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 196.94, 113.82, 110.64, 104.13, 77.93,75.88, 70.01, 60.09, 27.15, 26.52, 26.06, 26.01. MS (ESI$^+$): *m/z* $[M+Na]^+$ = 280.8.

The Synthesis of the Phthalide Tetrahydroisoquinoline Core of (–)-β-Hydrastine in Method B



(*S,S*)-17b

methyl 2,3-dimethoxy-6-((2S,3S)-3-(6-(2-((4-(trifluoromethyl)phenyl)sulfonamido)ethyl)benzo[d][1,3]dioxol-5-yl)oxiran-2-yl)benzoate [(S,S)-17b]. To a 100 mL three-neck round-bottom flask were added buffer (0.05 M $Na_2B_4O_7$•$10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA), 10 mL), acetonitrile (15 mL), compound **16b** (150 mg，0.3 mmol, 1.0 equiv.), tetrabutylammonium hydrogen sulfate (15 mg). The reaction mixture was cooled with an ice bath. A solution of Oxone (0.85 g, 1.38 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 6.5 mL), a solution of K_2CO_3 (0.8 g, 5.8 mmol) in water (6.5 mL) and a solution of ketone ***ent*-13** (0.23 g, 0.9 mmol) in acetonitrile (3.0 mL) were added dropwise through three separate addition funnels over a period of 4.5 h. The reaction was then monitored by TLC to follow the reaction to completion, and quenched by addition of water (20 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL), washed with brine (3×20 mL), dried over Na_2SO_4. The solvent was removed under vacuum to give crude product **(*S,S*)-17b**, which was directly used for the next step.

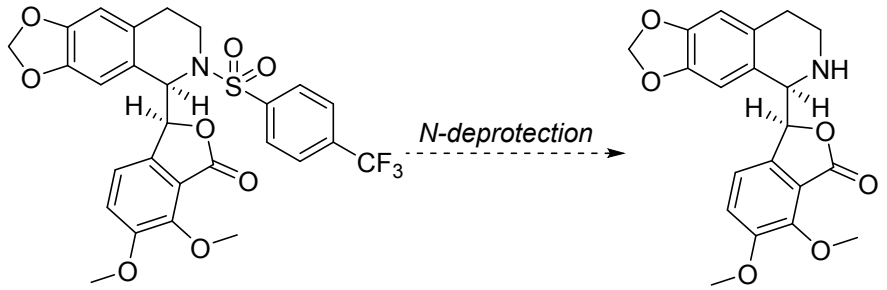


(–)-β-18b

(S)-6,7-dimethoxy-3-((R)-6-((4-(trifluoromethyl)phenyl)sulfonyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3H)-one. To a flame dried, N_2 flushed three-neck round-bottom flask, a stir bar and the starting substrate **17b** (≈0.3 mmol, 1.0 equiv.) was placed and dissolved in dry THF (5.0 mL) at 0 ºC. Then the 1.0 M KHMDS (0.45 mL, 0.45 mmol, 1.5 equiv.) was slowly added in dropwise. The reaction mixture was then warmed to 65 ºC and stirred for 5 h. After quenching the reaction by saturated ammonium chloride, the reaction mixture was concentrated and the resulting residue was stirred with water (≈ 10 mL) and CH_2Cl_2 (20 mL), adjusted to pH = 2.0 with 1 N HCl and stirred for 30 min. Then the mixture was adjusted to pH = 9.0 – 10.0 with ammonium hydroxide, and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was washed with brine (15 mL × 3) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give crude product **(–)-β-18b**, which was purified by the flash chromatography (silica gel), eluting with petroleum ether/EtOAc =4:1, to give **(–)-β-18b** (12 mg) as a white solid. Yield: 8.3% (29.5% brsm) over two steps, **78% *ee*** (Chiralpak IA column, *n*-

Hexane/Ethanol/Diethylamine = 70:30:0.1, 254 nm, 1.0 mL/min, 35 ºC, t_{major} = 3.694 min, t_{minor} = 8.726 min). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.44 (s, 1H), 5.90 (s, 1H), 5.84 (dd, J = 13.1, 1.3 Hz, 2H), 5.74 (d, J = 2.8 Hz, 1H), 5.34 (d, J = 2.9 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.67 – 3.55 (m, 1H), 3.55 – 3.44 (m, 1H), 2.76 (dt, J = 16.4, 4.8 Hz, 1H), 2.56 (ddd, J = 15.7, 9.1, 6.2 Hz, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.76, 153.10, 148.59, 147.56, 145.81, 143.13, 139.10, 134.49 (d, J = 33.1 Hz), 127.67, 126.26 (dd, J = 7.3, 3.3 Hz), 126.26 (dd, J = 7.3, 3.3 Hz), 123.13 (d, J = 273.4 Hz), 121.20, 119.11, 118.47, 117.26, 108.87, 106.91, 101.11, 83.16, 62.41, 59.46, 56.82, 41.10, 27.02； HRMS (ESI$^+$): *m/z* calcd. for $C_{27}H_{22}F_3NO_8SNa$ $[M+Na]^+$ = 600.0916, found 600.0907.

Table S3. Attempts to the Optimization of the Reaction Conditions for *N*-Deprotection of **(–)-β-18b**

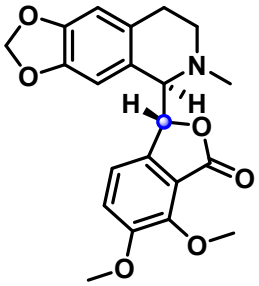


Entry[a]	Conditions	Yield[b] (%)
1	Mg, MeOH, Sonication, rt, 1.0 h	ND[c]
2	Mg, NH_4Cl, MeOH, THF, Sonication, 3.0 h, rt	ND[c]
3	SmI_2, THF, 0 ºC – rt, 12 h	ND[c]
4	Na naphthalide, THF, 2 h, –78 ºC	ND[c]

[a]The substrate **(–)-β-18b** (15 mg). [b]Isolated yield of **(–)-β-2**. [c]The **(–)-β-2**was not detected by TLC and the substrate **(–)-β-18b** was decomposed.

3. Natural Product Spectra Comparisons

(–)-α-Hydrastine ^{1}H NMR spectra comparison:

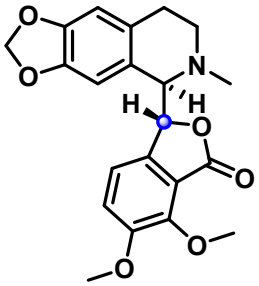


(–)-α-Hydrastine
threo-form

Lit[4] data [(±)-α-Hydrastine, 270 MHz]	**Our synthetic data (600 MHz, $CDCl_3$)**	**Δδ (ppm)**
7.04, 7.29 (AB type, *J* = 8.3 Hz, each 1H)	7.27 (d, *J* = 8.2 Hz, 1H)	0.02
	7.04 (d, *J* = 8.2 Hz, 1H)	0
6.65 (s, 1H)	6.64 (s, 1H)	0.01
6.37 (s, 1H)	6.37 (s, 1H)	0
5.78, 5.83 (each d, *J* = 1.3 Hz, each 1H)	5.83 (d, *J* = 1.0 Hz, 1H)	0
	5.78 (d, *J* = 1.0 Hz, 1H)	0
5.54 (d, *J* = 3.3 Hz, 1H)	5.55 (d, *J* = 2.8 Hz, 1H)	0.01
4.00, (d, *J* = 3.3 Hz, 1H)	4.01 (d, *J* = 2.3 Hz, 1H)	0.01
3.98 (s, 3H)	3.98 (s, 3H)	0
3.84 (s, 3H)	3.84 (s, 3H)	0
3.00-3.10 (m, 1H)	3.0-3.16 (m, 1H)	-[a]
2.40-2.80 (m, 3H)	2.85 – 2.65 (m, 1H)	-[a]
	2.53 (d, *J* = 9.9 Hz, 1H)	-[a]
	2.46 (d, *J* = 15.6 Hz, 1H)	-[a]
2.55 (s, 3H)	2.56 (s, 3H)	0.01

[a]*These three resonances did not perfectly match with the reported values.[4] We believe this difference might be due to the better resolution obtainedby acquiring our ^{1}H NMR spectrum on a 600 MHz NMR instrument.*

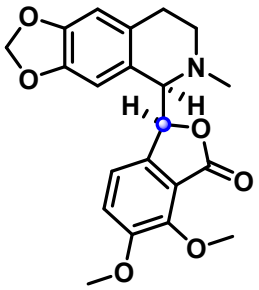
(–)-α-Hydrastine ^{13}C NMR spectra comparison:



(–)-α-Hydrastine
threo-form

Lit[5] data	**Our synthetic data (150 MHz, $CDCl_3$)**	**Δδ (ppm)**
168.0	167.89	0.11
152.3	152.24	0.06
147.6	147.67	0.07
146.3	146.25	0.05
145.8	145.78	0.02
141.1	140.94	0.06
130.0	129.81	0.19
125.3	125.10	0.20
119.3	119.24	0.06
118.4	118.22	0.18
118.1	117.99	0.11
108.2	108.14	0.06
107.4	107.38	0.02
100.7	100.74	0.04
81.8	80.89	0.09
66.2	66.22	0.02
62.2	62.30	0.10
56.7	56.72	0.02
51.3	51.26	0.04
44.9	44.93	0.03
29.2	29.14	0.06

(-)-β-Hydrastine ^{1}H NMR spectra comparison:

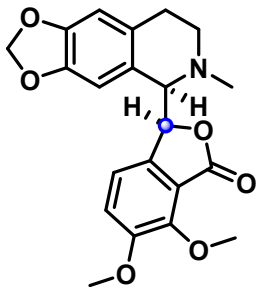


(–)-β-Hydrastine
erythro-form

Lit[5] data (270 MHz)	**Our synthetic data (600 MHz, $CDCl_3$)**	***Δδ* (ppm)**
7.08 (1H)	7.08 (d, *J* = 8.3 Hz, 1H)	0
6.52 (1H)	6.54 (d, *J* = 8.2 Hz, 1H)	0.02
6.58 (s, 1H)	6.58 (s, 1H)	0
6.40 (s, 1H)	6.36 (s, 1H)	0.04
5.91 (s, 2H)	5.91 (dd, 2H)	-[a]
5.48 (d, 1H)	5.51 (d, 1H)	0.03
4.06 (s, 3H)	4.06 (s, 3H)	0
3.98 (d, 1H)	4.00 (d, *J* = 3.7 Hz, 1H)	0.02
3.89 (s, 3H)	3.89 (s, 3H)	0
2.85-2.94 (m, 1H)	2.92 (t, 1H)	-[a]
2.42-2.65 (m, 2H)	2.68-2.57 (m, 2H)	0
2.55 (s, 3H)	2.56 (s, 3H)	0.01
2.22-2.32 (m, 1H)	2.35 – 2.25 (m, 1H)	0

[a]These two resonances did not perfectly match with the reported values.[5] We believe this difference might be due to the better resolution obtainedby acquiring our ^{1}H NMR spectrum on a 600 MHz NMR instrument.

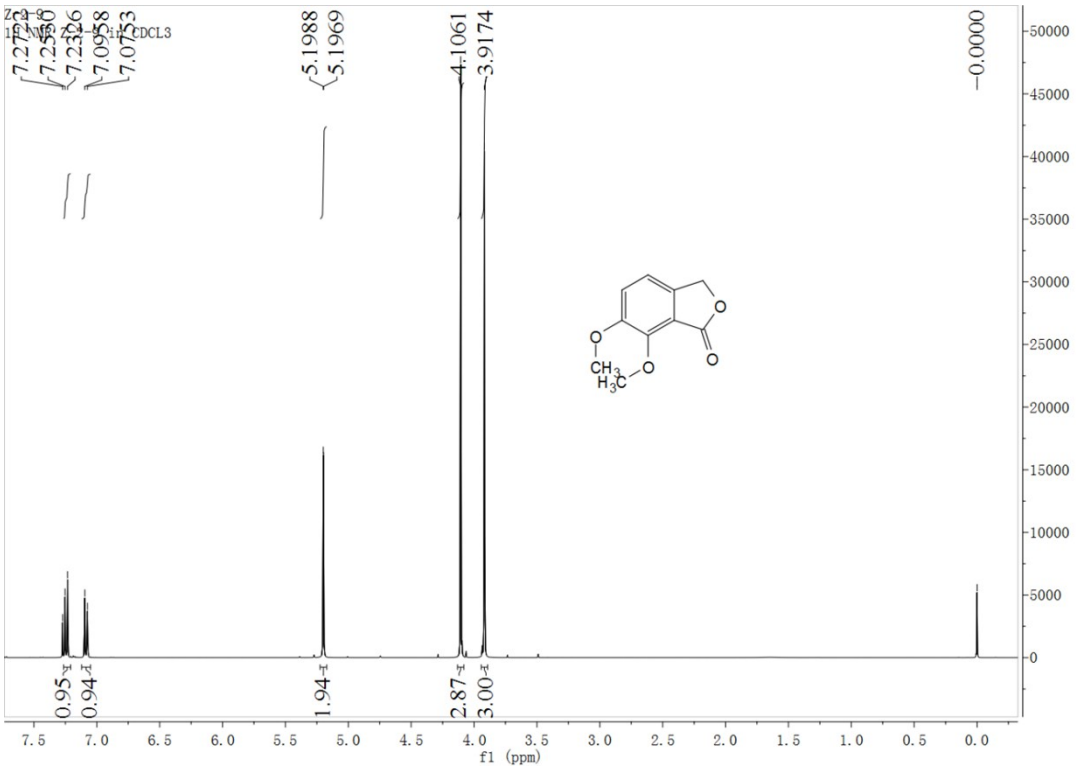
(-)-β-Hydrastine ^{13}C NMR spectra comparison:



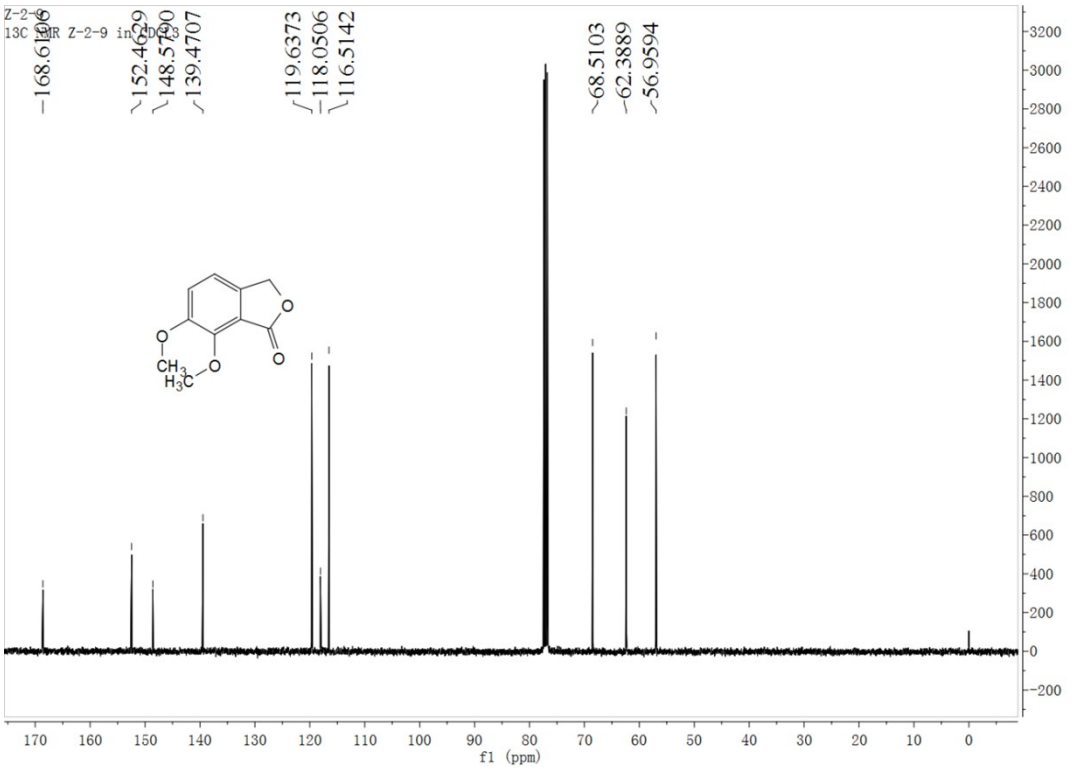
(–)-β-Hydrastine
erythro-form

Lit[5] data	**Our synthetic data (150 MHz, $CDCl_3$)**	***Δδ* (ppm)**
167.0	167.69	0.69
152.6	152.54	0.06
147.5	148.01	0.51
146.3	146.78	0.48
145.4	145.78	0.38
140.4	140.70	0.30
130.0	130.24	0.24
124.5	124.46	0.04
119.4	119.64	0.24
118.5	118.61	0.11
117.3	117.63	0.33
108.1	108.54	0.44
107.3	107.77	0.47
100.4	100.87	0.47
82.7	82.86	0.16
66.0	66.11	0.11
62.0	62.33	0.33
56.7	56.81	0.11
49.0	48.96	0.04
44.7	44.74	0.04
26.7	26.54	0.16

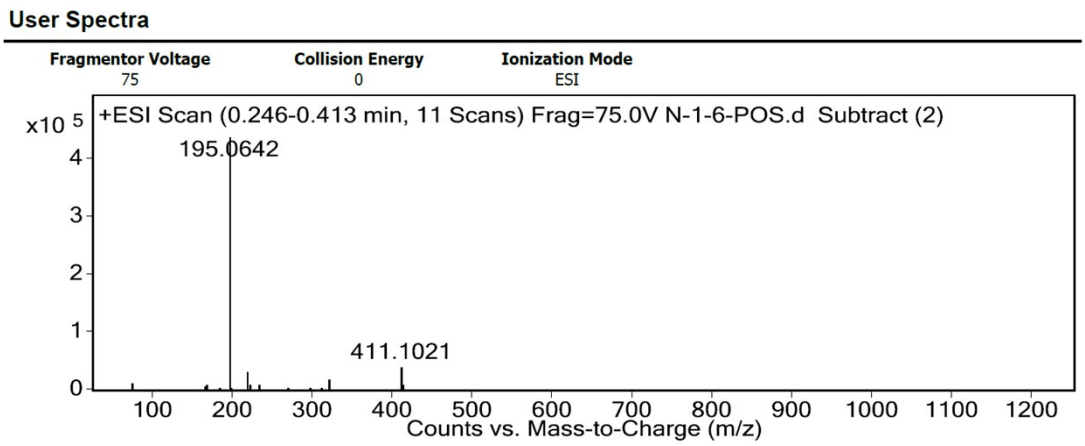
4. Copies of ^{1}H and ^{13}C-NMR Spectra, HRMS (or MS) and HPLC Spectra



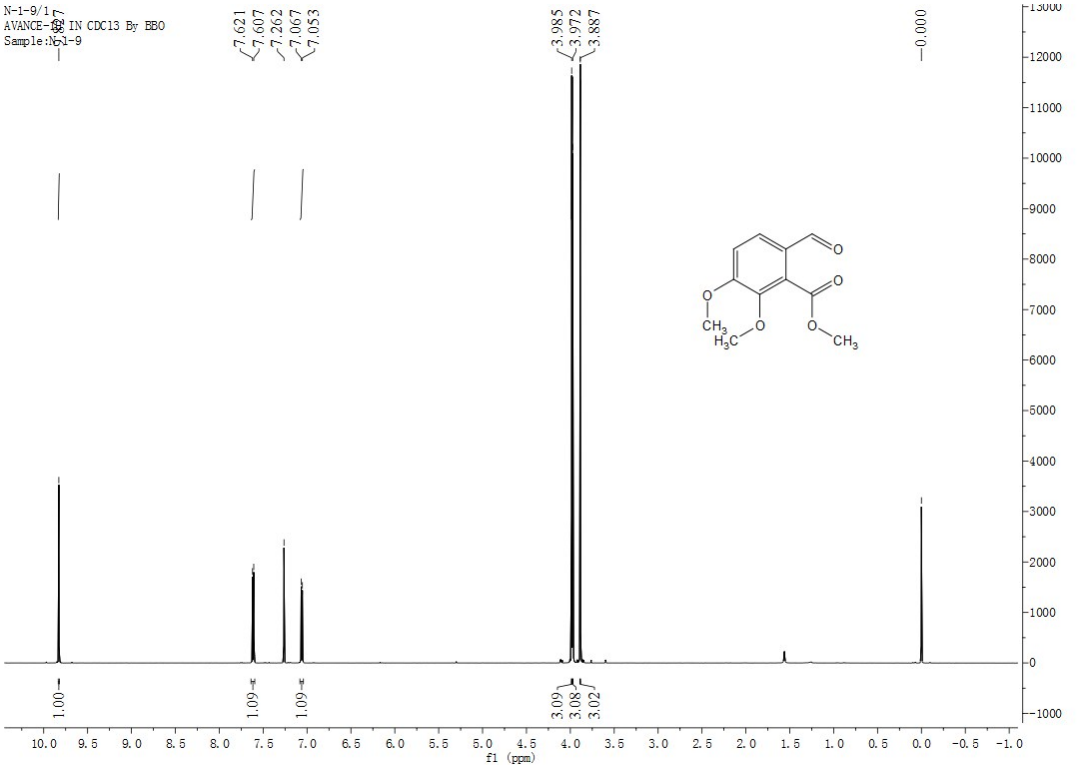
^{1}H NMR (600 MHz, DMSO-d_6) spectrum for compound 10



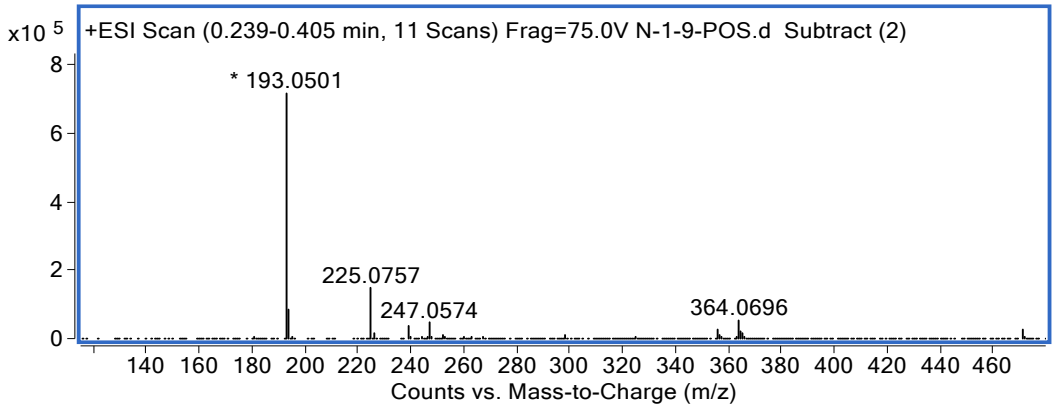
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for compound 10



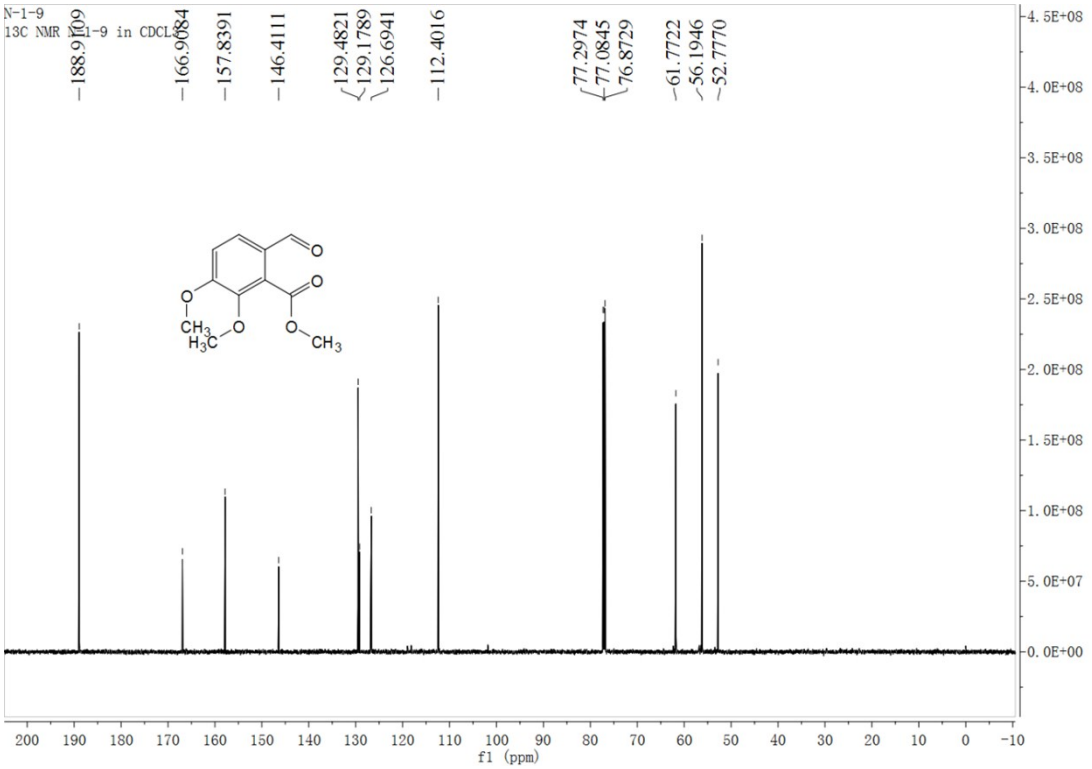
HRMS for compound 10



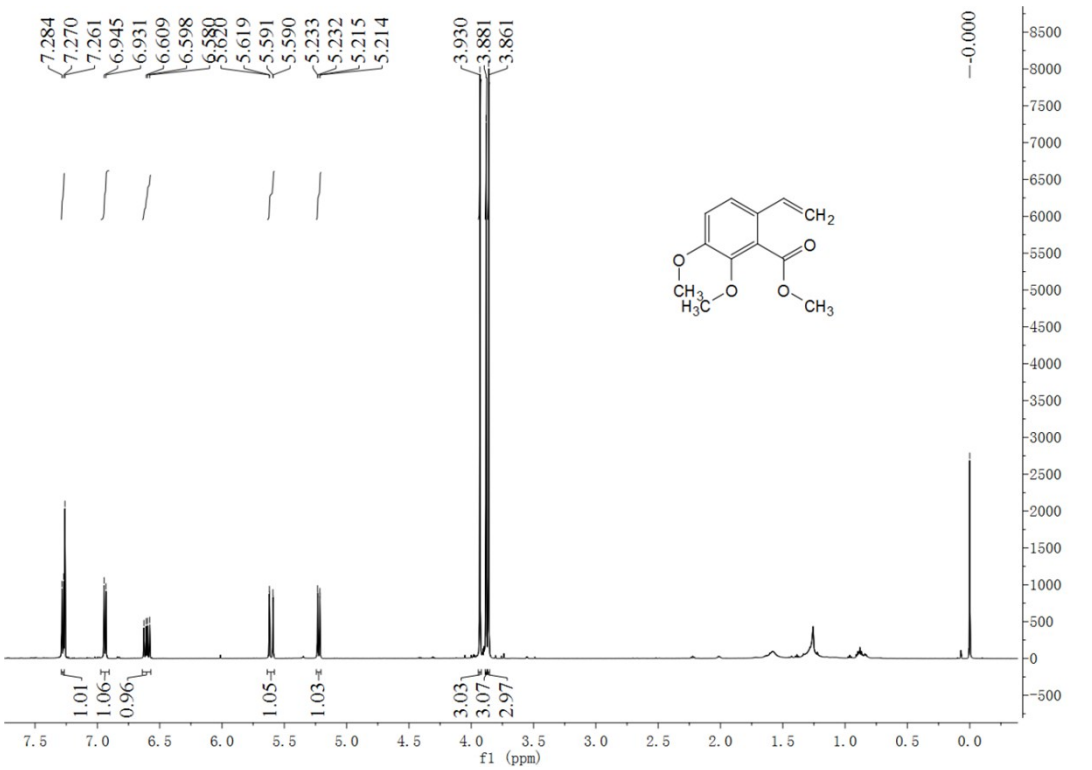
^{1}H NMR (600 MHz, $CDCl_3$) spectrum for compound 12



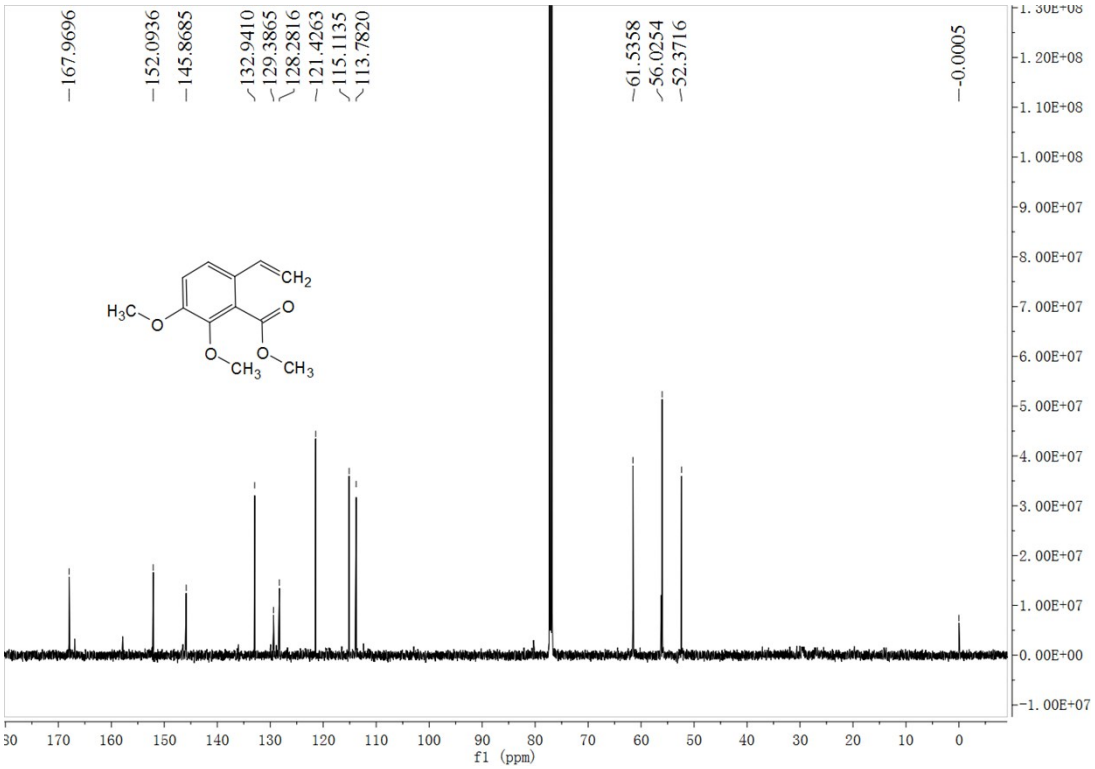
HRMS for compound 12



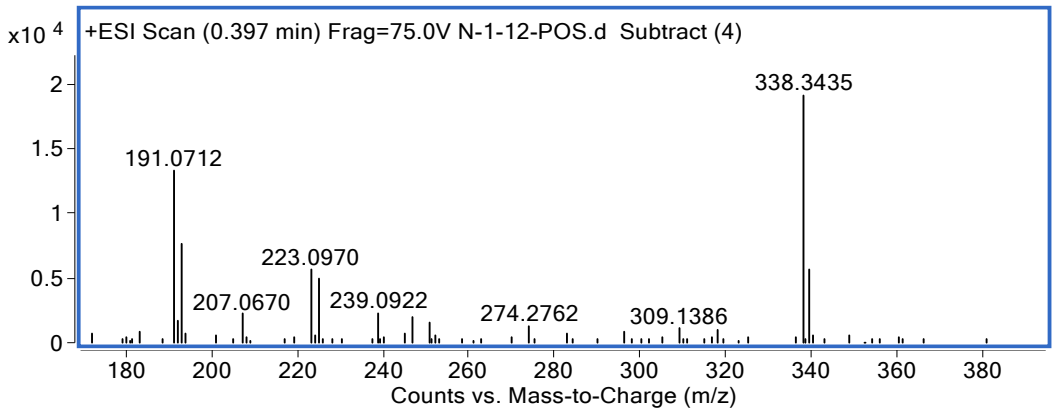
^{13}C NMR (150 MHz, $CDCl_3$) spectrum for compound 12



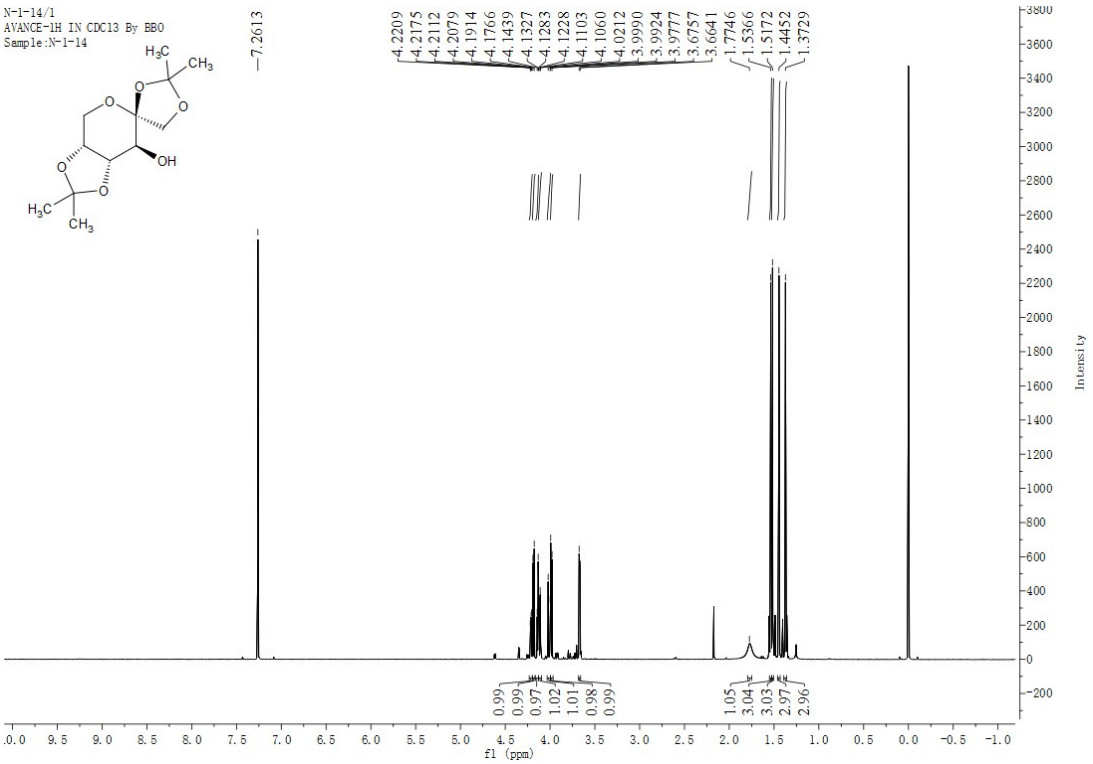
^{1}H NMR (600 MHz, $CDCl_3$) spectrum for compound 6



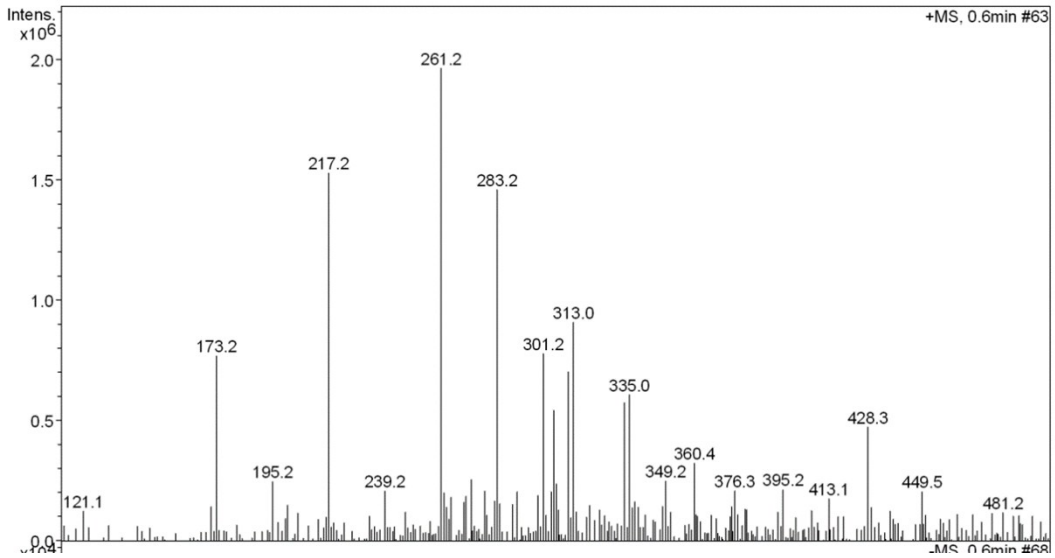
^{13}C NMR (150 MHz, $CDCl_3$) spectrum for compound 6



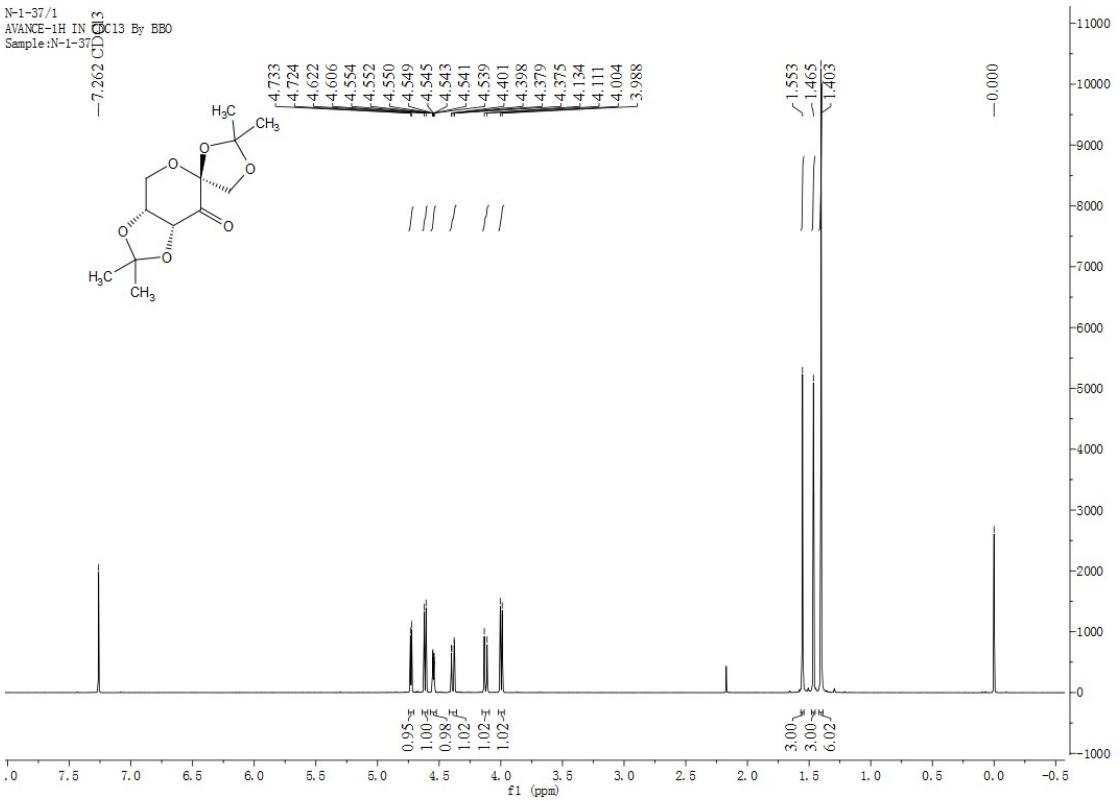
HRMS for compound 6



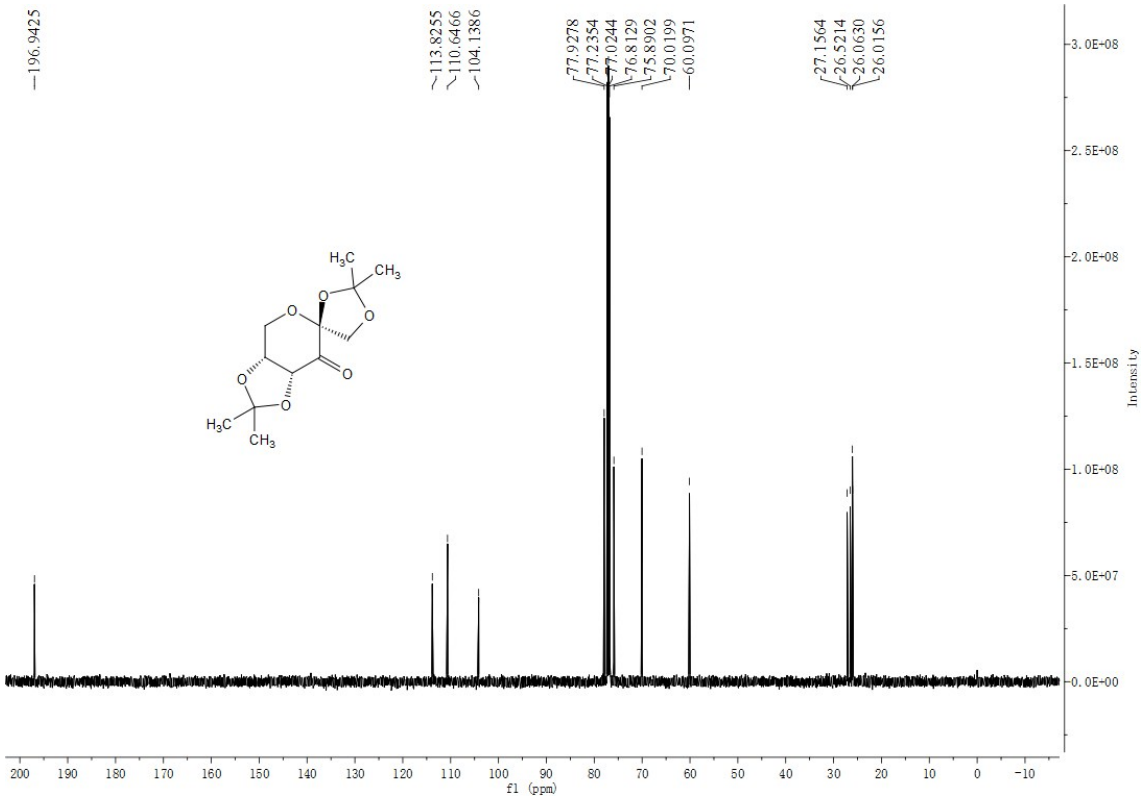
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for 14



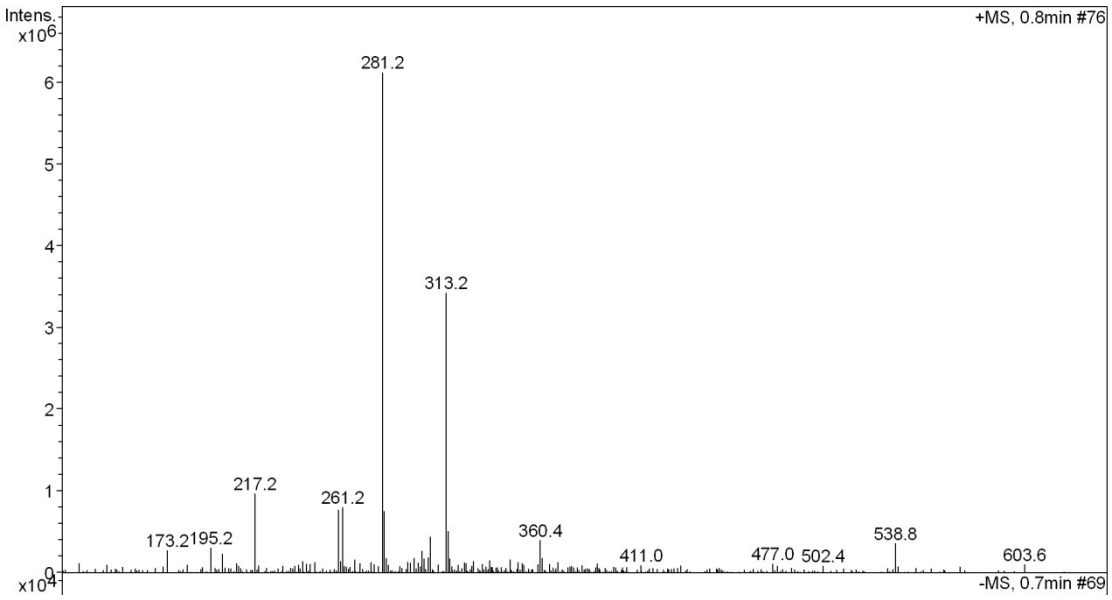
MS for 14



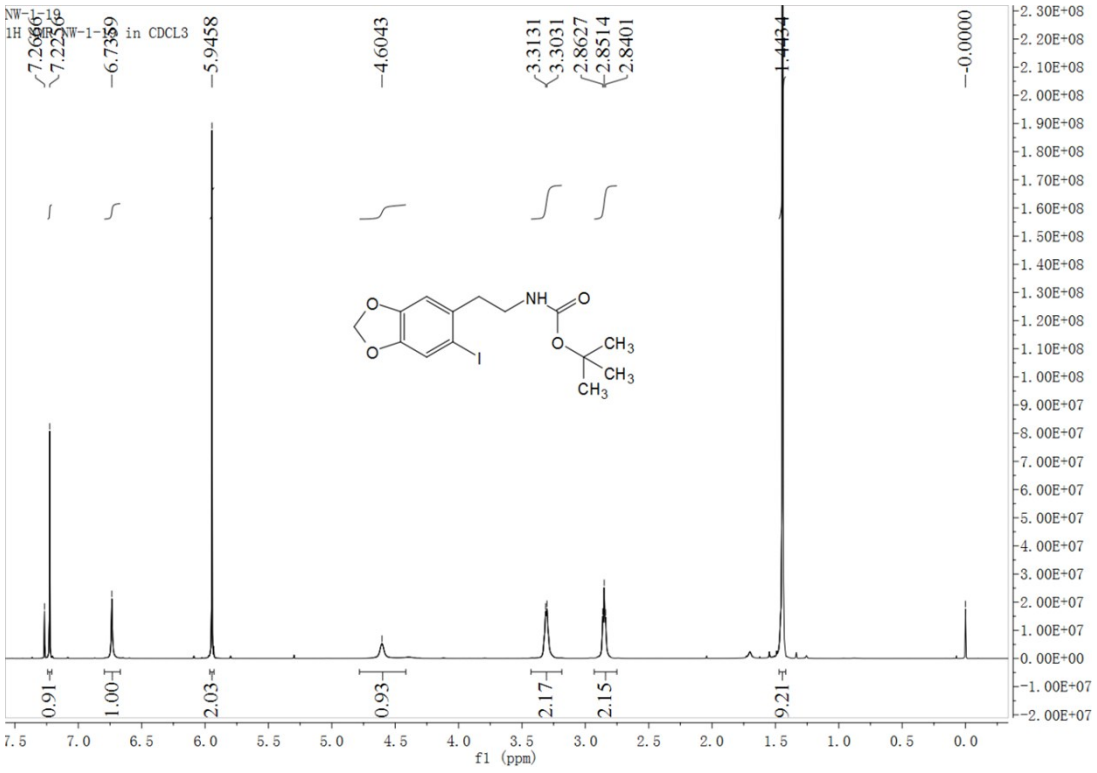
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for 13



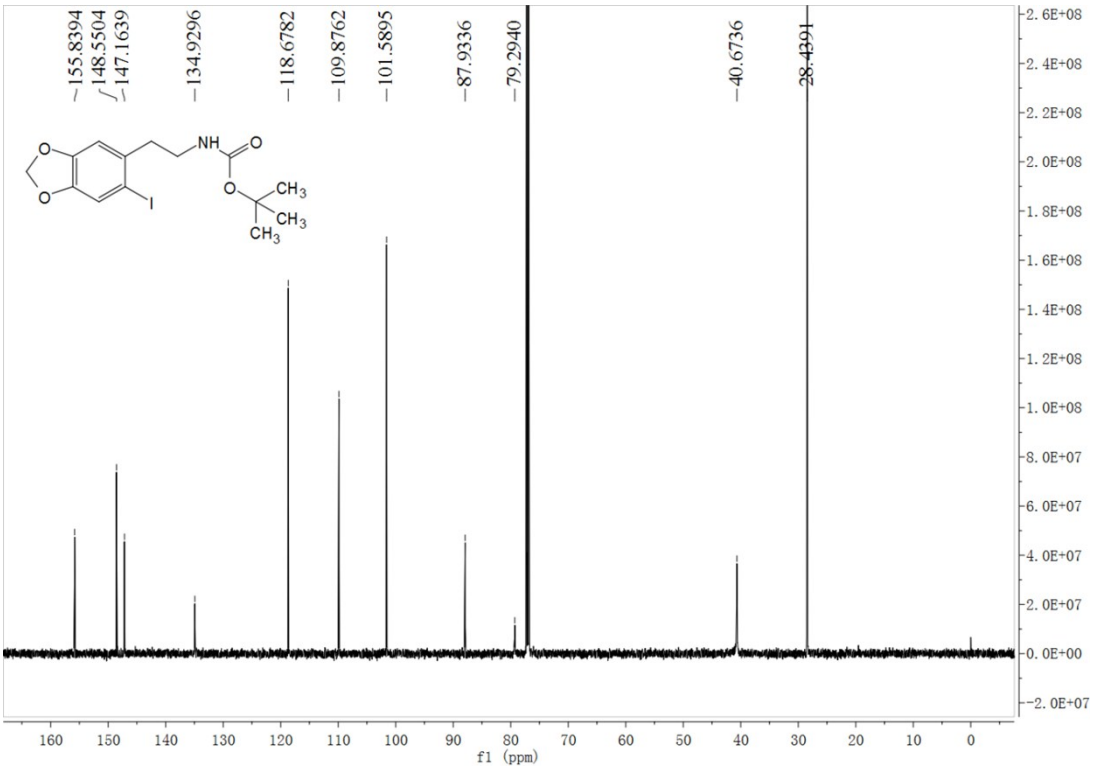
^{13}C-NMR (150 MHz, $CDCl_3$) spectrum for 13



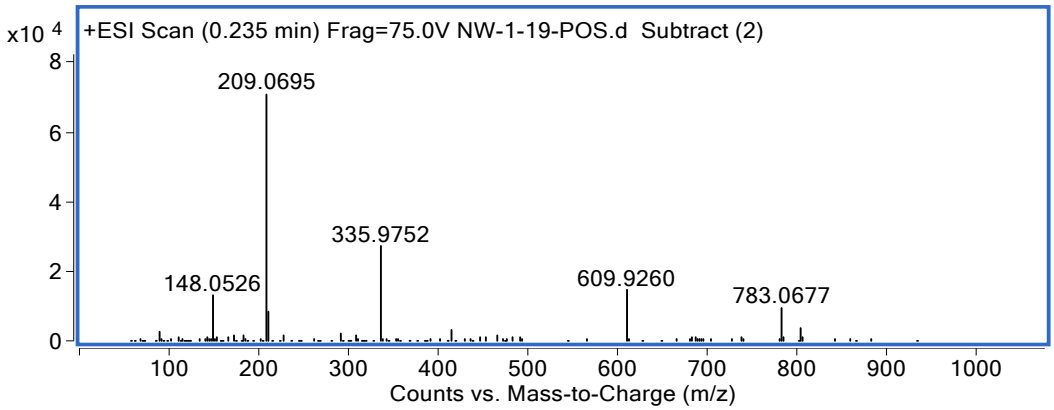
MS for 13



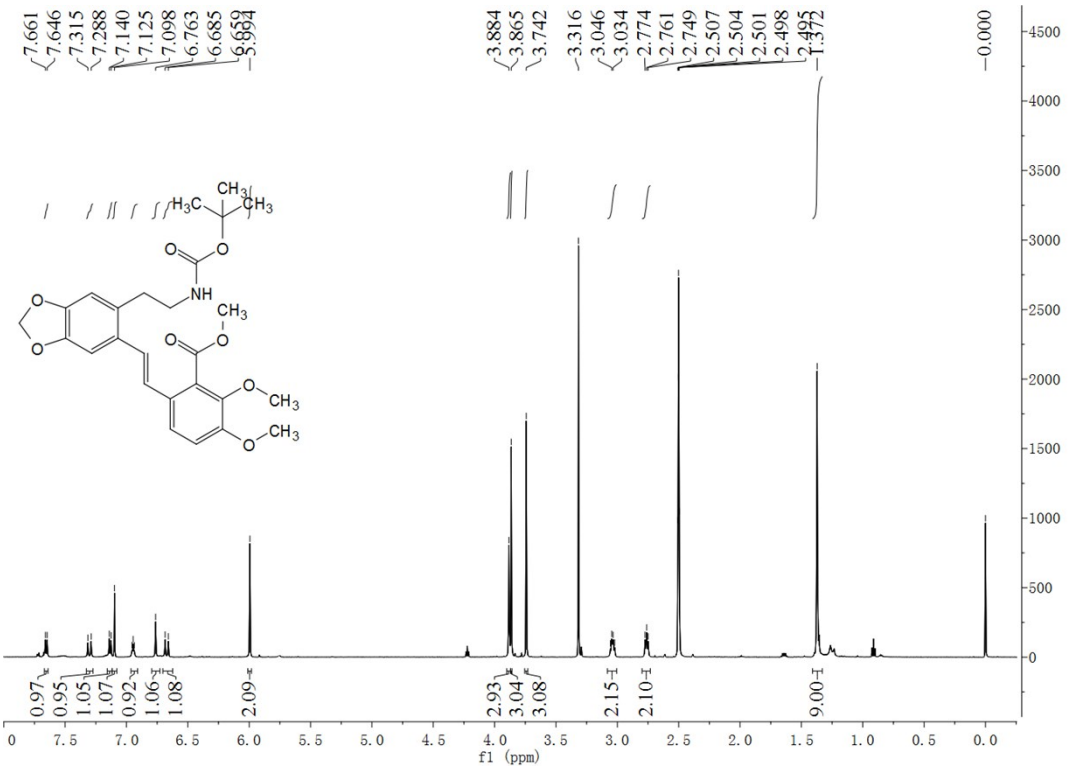
^{1}H NMR (600 MHz, $CDCl_3$) spectrum for compound 5



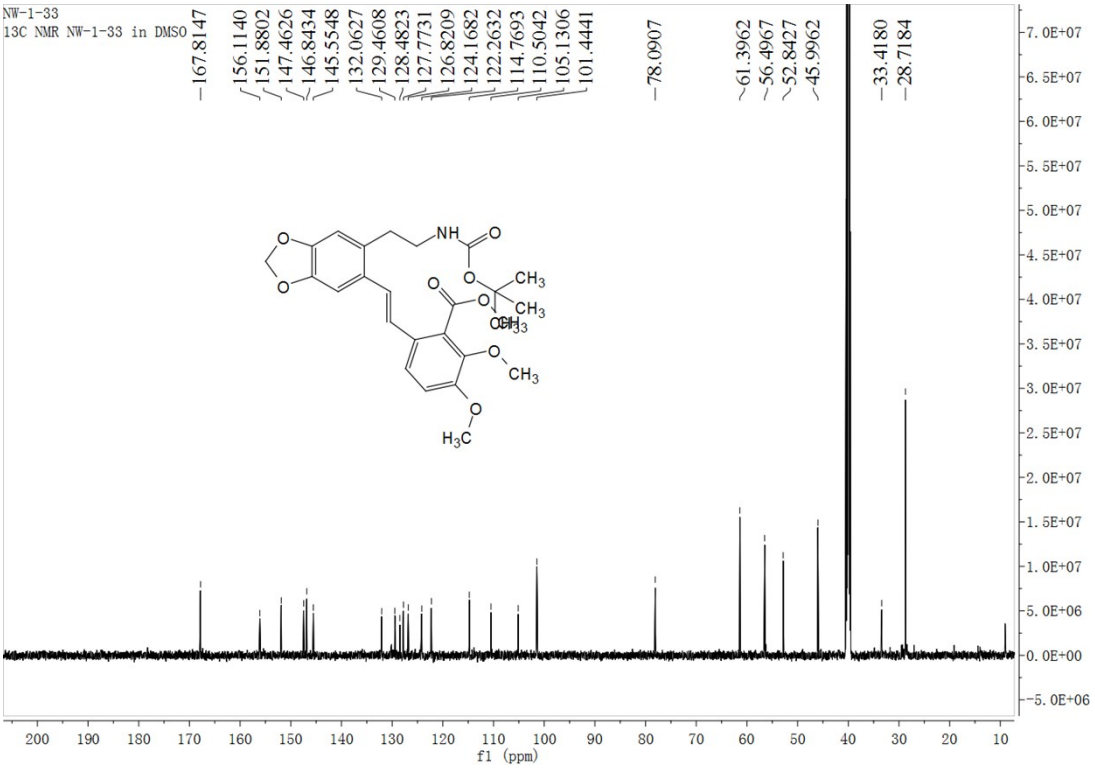
^{13}C NMR (150 MHz, $CDCl_3$) spectrum for compound 5



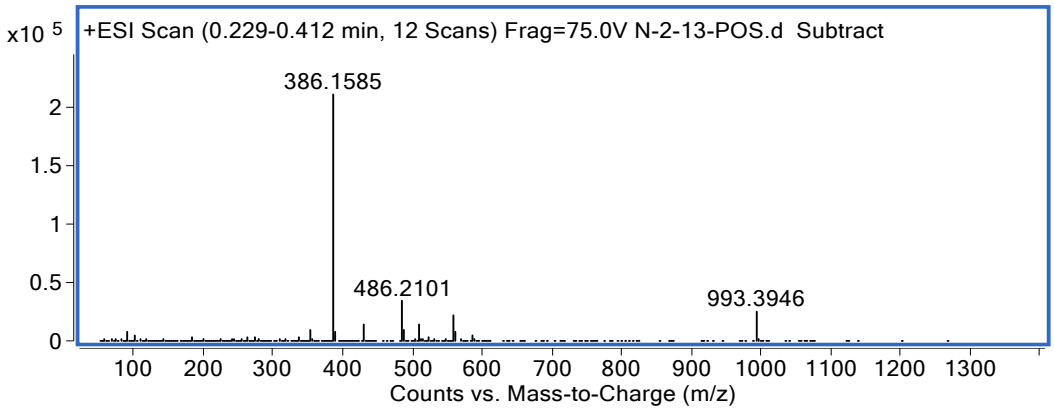
HRMS for compound 5



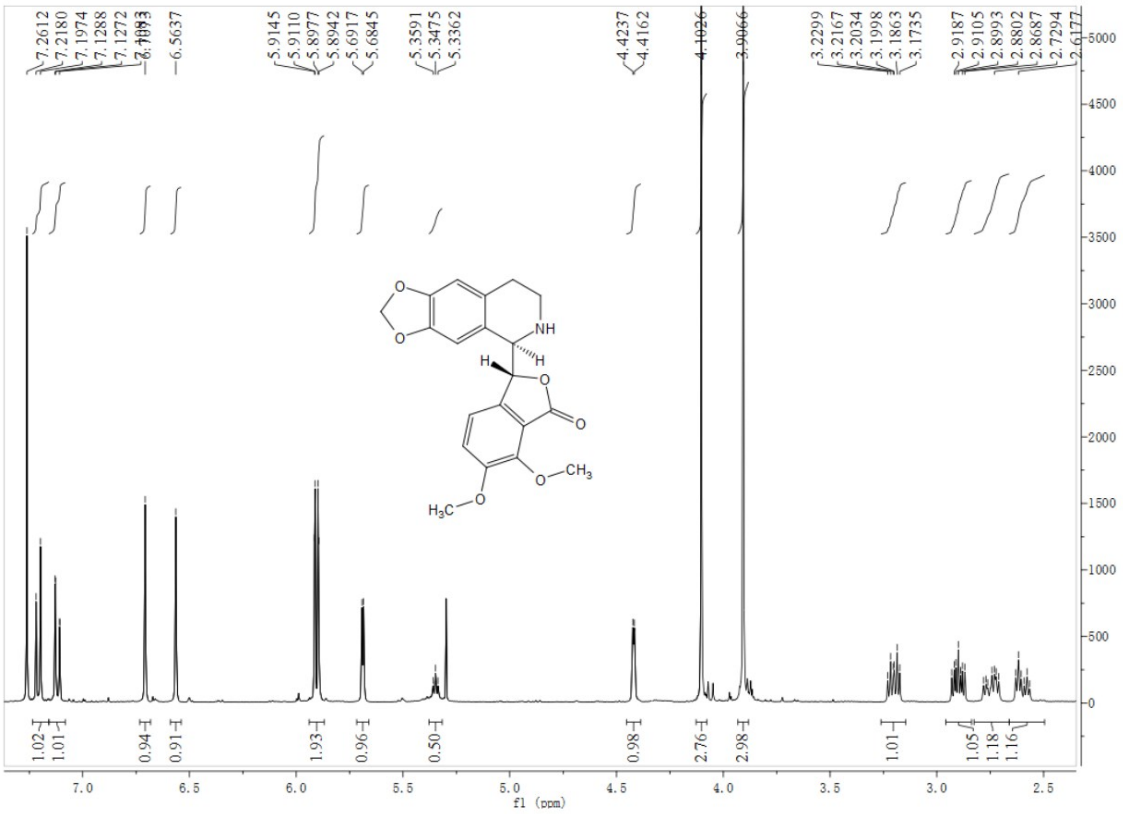
^{1}H NMR (600 MHz, DMSO-d_6) spectrum for compound 4



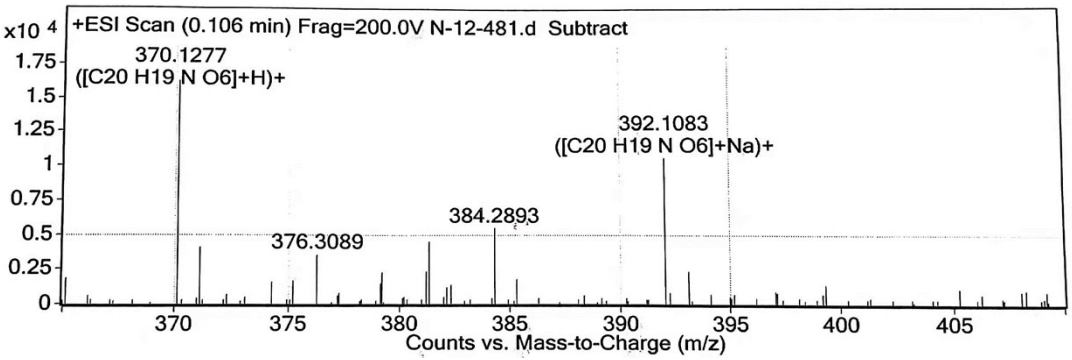
^{13}C NMR (150 MHz, DMSO-d_6) spectrum for compound 4



HRMS for compound 4



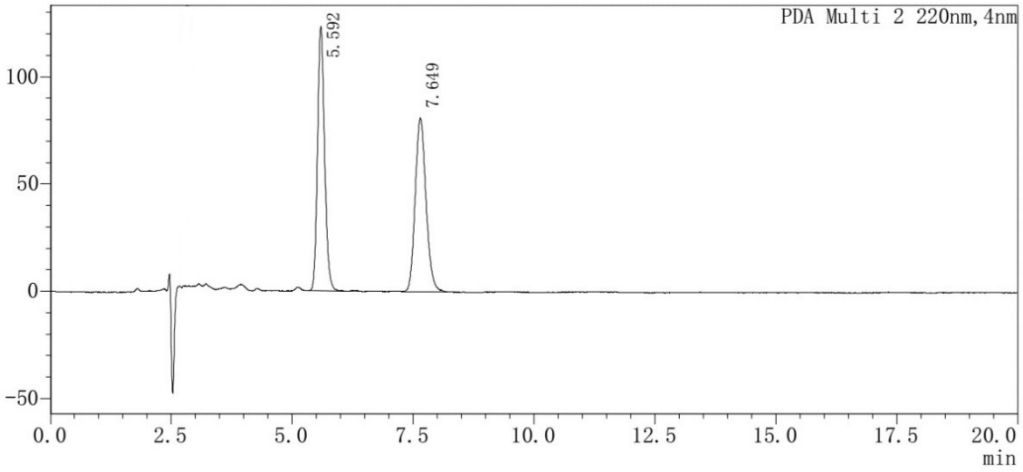
^{1}H-NMR (400 MHz, $CDCl_3$) spectrum for (−)-α-2



HRMS for (−)-α-2

Chiral HPLC spectrum for (–)-α-2

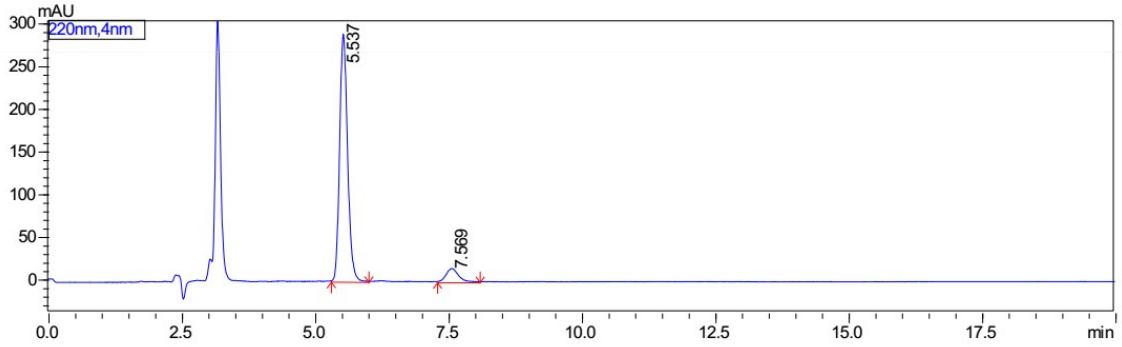
Column	:	CHIRALPAK® IH(IH00CD-VK018)
Column size	:	0.46 cm I.D. ×15 cm L ×5 μm
Injection	:	4 μl
Mobile phase	:	n-Hexane/ Ethanol / Diethylamine = 40/ 60/ 0.1 (v/v/v)
Flow rate	:	0.8 ml/min
Wave length	:	UV 220 nm
Temperature	:	35℃
Sample solution	:	X mg/ml in EtOH30% MeOH30% Hexane40%(荡洗)
HPLC equipment	:	Shimadzu LC 20A QA&QC-HPLC-12



<Column Performance Report>

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.592	1265119	50.055	6855	1.164	--
2	7.649	1262355	49.945	5560	1.152	6.046

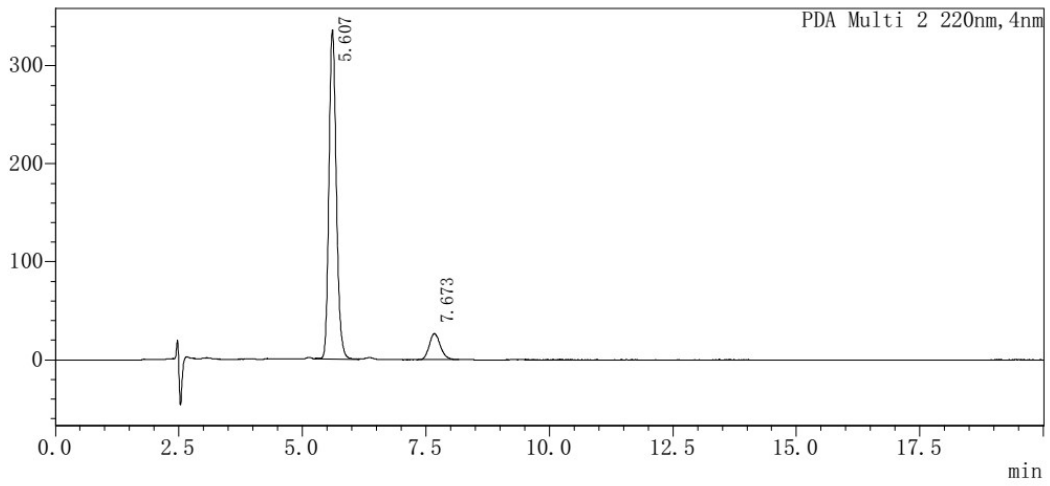
***Rac*-[(±)-α-2]**



<Column Performance Report>

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.537	2977655	92.719	6665	1.183	--
2	7.569	233812	7.281	5629	1.159	6.021

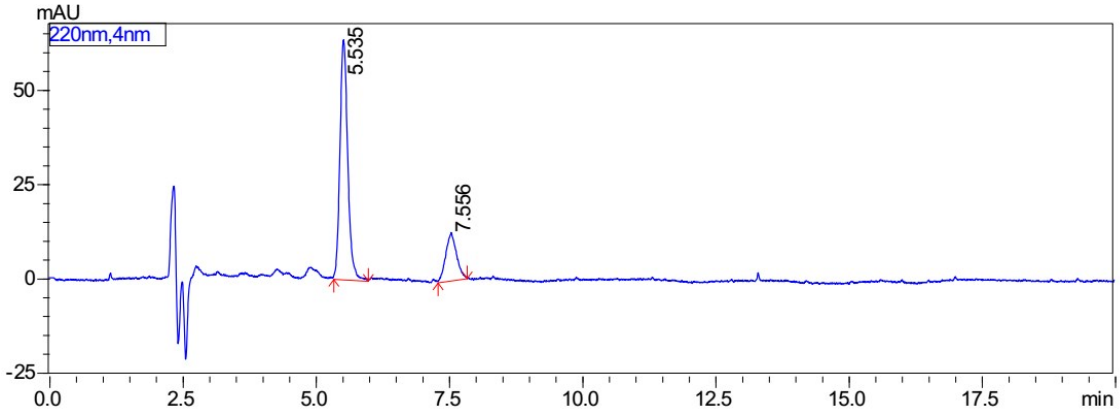
Table S1 entry 14 [(–)-α-2]



<Column Performance Report>

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.607	3462326	89.236	6872	1.173	--
2	7.673	417645	10.764	5632	1.179	6.080

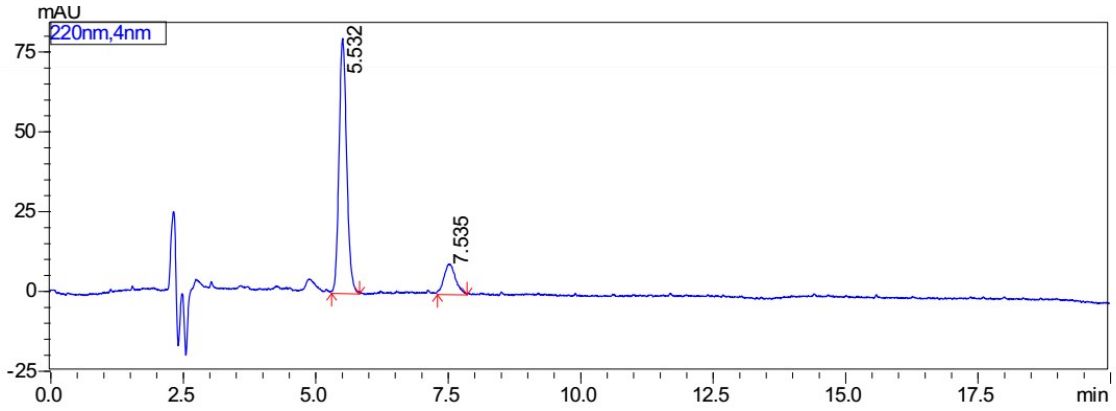
Table S1 entry 15



<Column Performance Report>

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.535	636685	79.076	7073	1.212	--
2	7.556	168471	20.924	6113	1.070	6.219

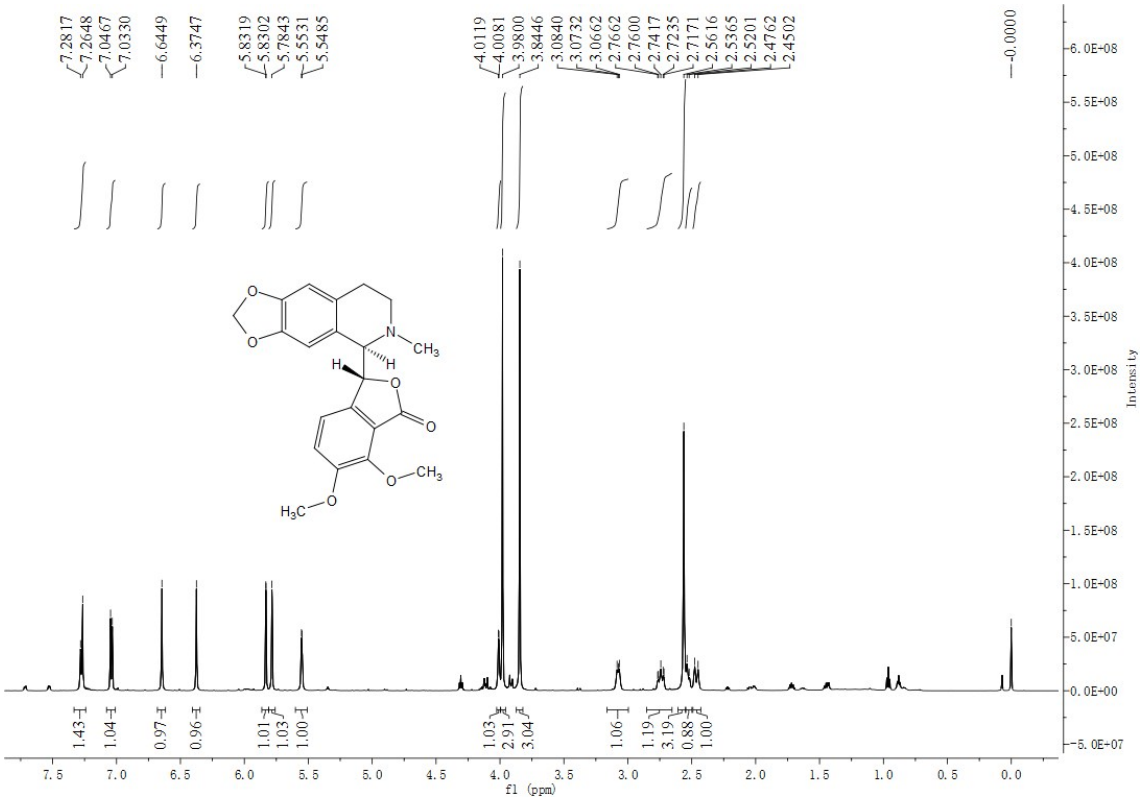
Table S1 entry 16



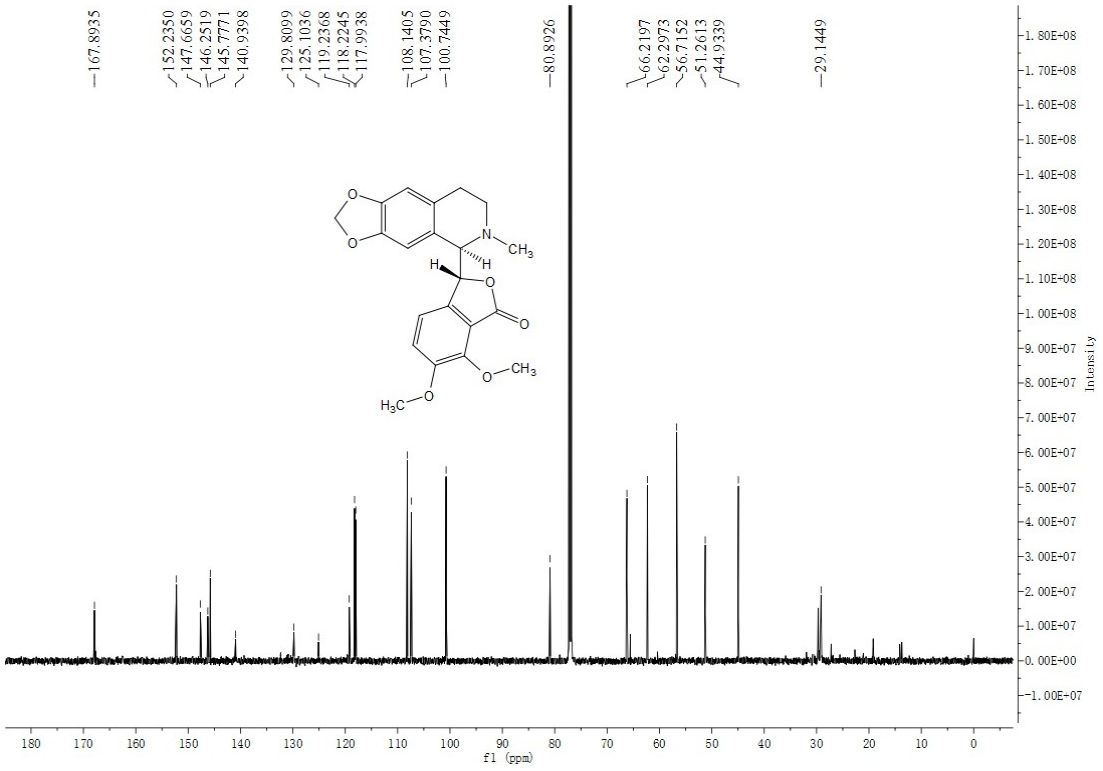
<Column Performance Report>

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.532	793531	85.309	7064	1.147	--
2	7.535	136650	14.691	6000	1.131	6.138

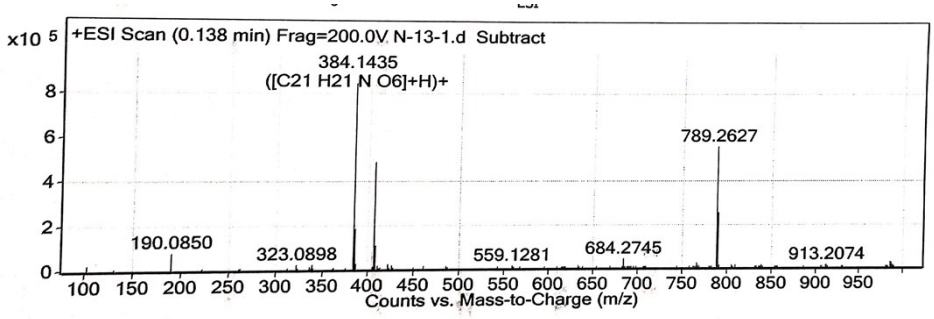
Table S1 entry 17



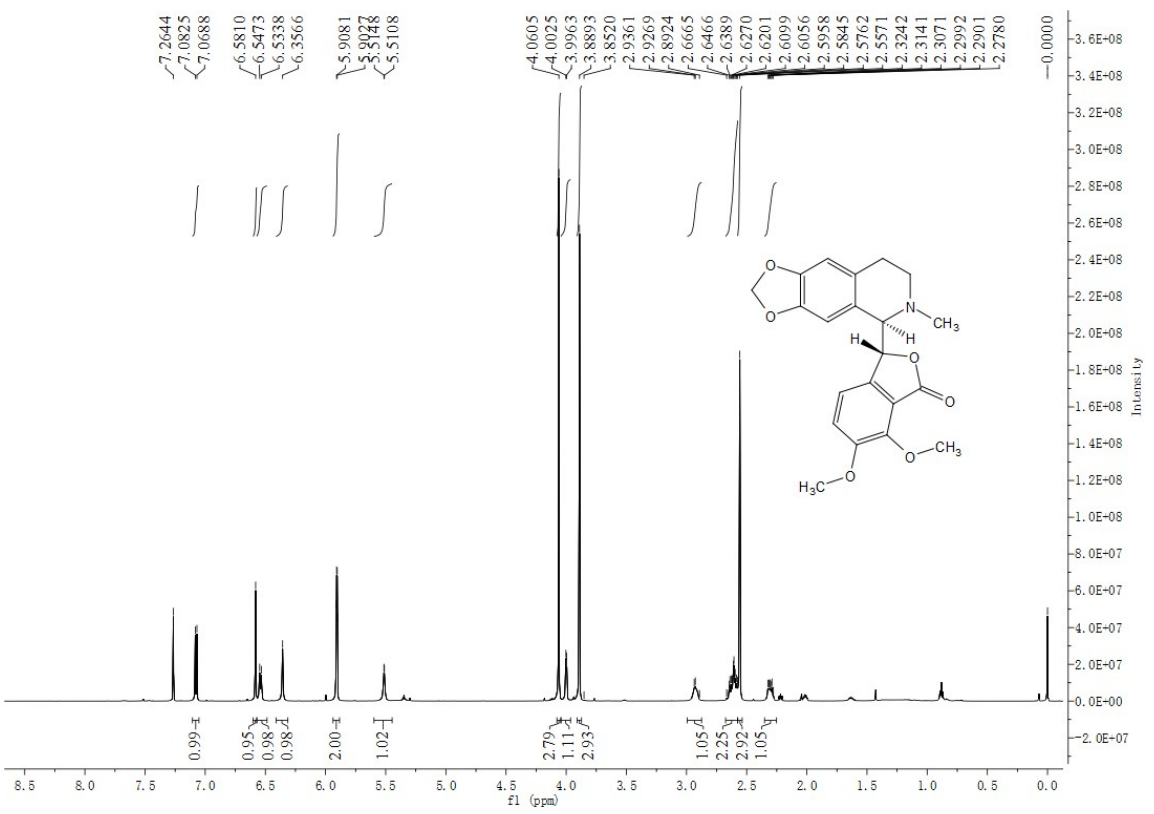
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for (−)-α-Hydrastine



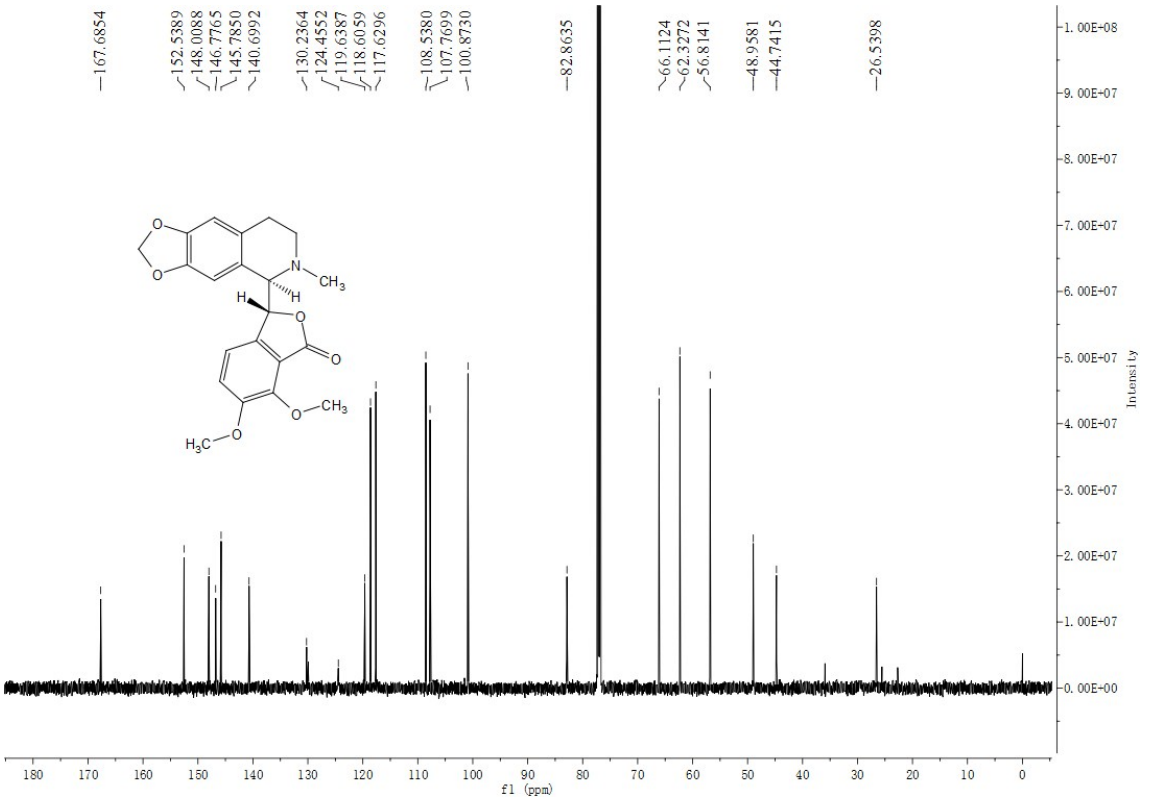
^{13}C-NMR (150 MHz, $CDCl_3$) spectrum for (−)-α-Hydrastine



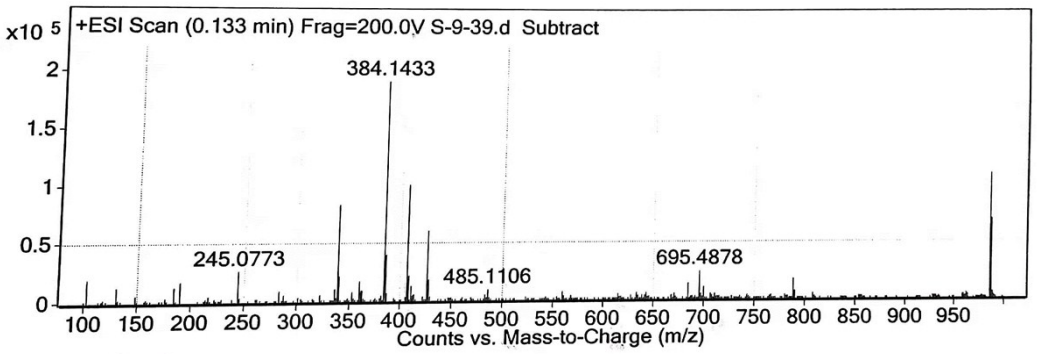
HRMS for (−)-α-Hydrastine



^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for (−)-β-Hydrastine



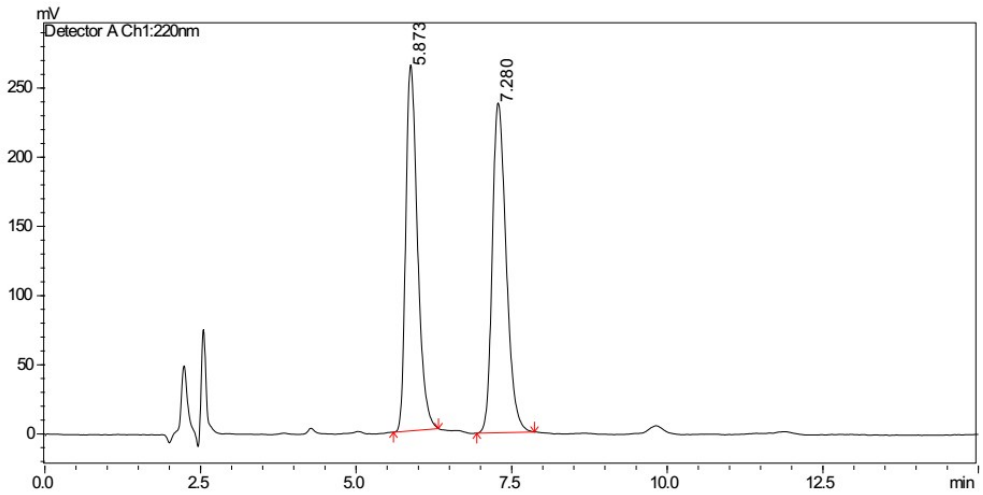
^{13}C-NMR (150 MHz, $CDCl_3$) spectrum for (−)-β-Hydrastine



HRMS for (–)-β-Hydrastine

Chiral HPLC spectrum for (–)-β-Hydrastine

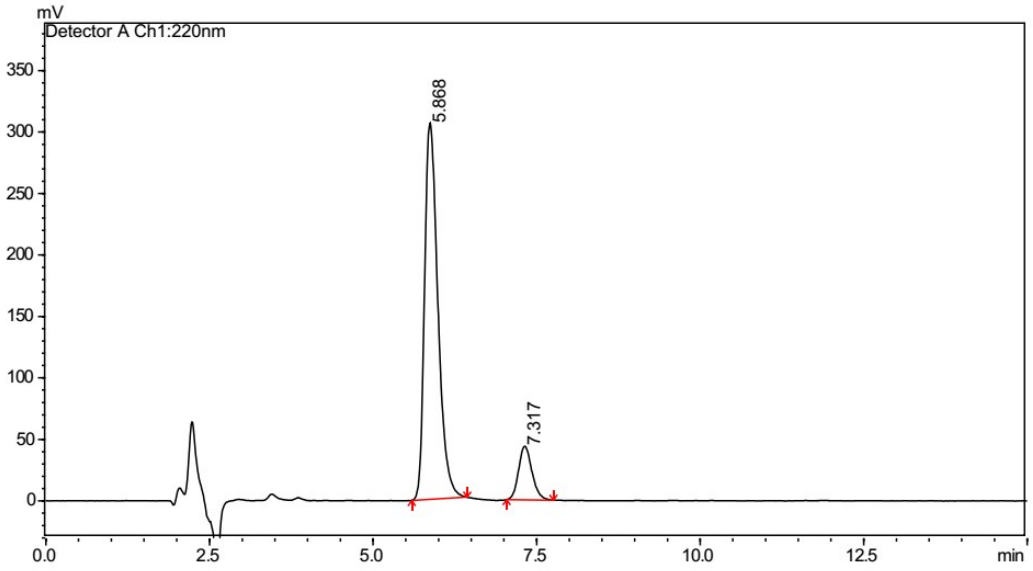
Column	:	CHIRALPAK® IF
Column size	:	0.46 cm I.D. ×15 cm L ×5 μm
Injection	:	10μl
Mobile phase	:	n-Hexane/ Ethanol/Diethylamine=70/30/0.1 (v/v/v)
Flow rate	:	1.0 ml/min
Wave length	:	UV 220 nm
Temperature	:	35℃
Sample solution	:	1.0mg/mL inDCM10% EtOH 20% n-Hexane 70%
HPLC equipment	:	Shimadzu LC 20A QA&QC-HPLC-10



<Column Performance Report>

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.873	3474236	48.3197	4648.293	1.418	--
2	7.280	3715874	51.6803	5091.448	1.322	3.738

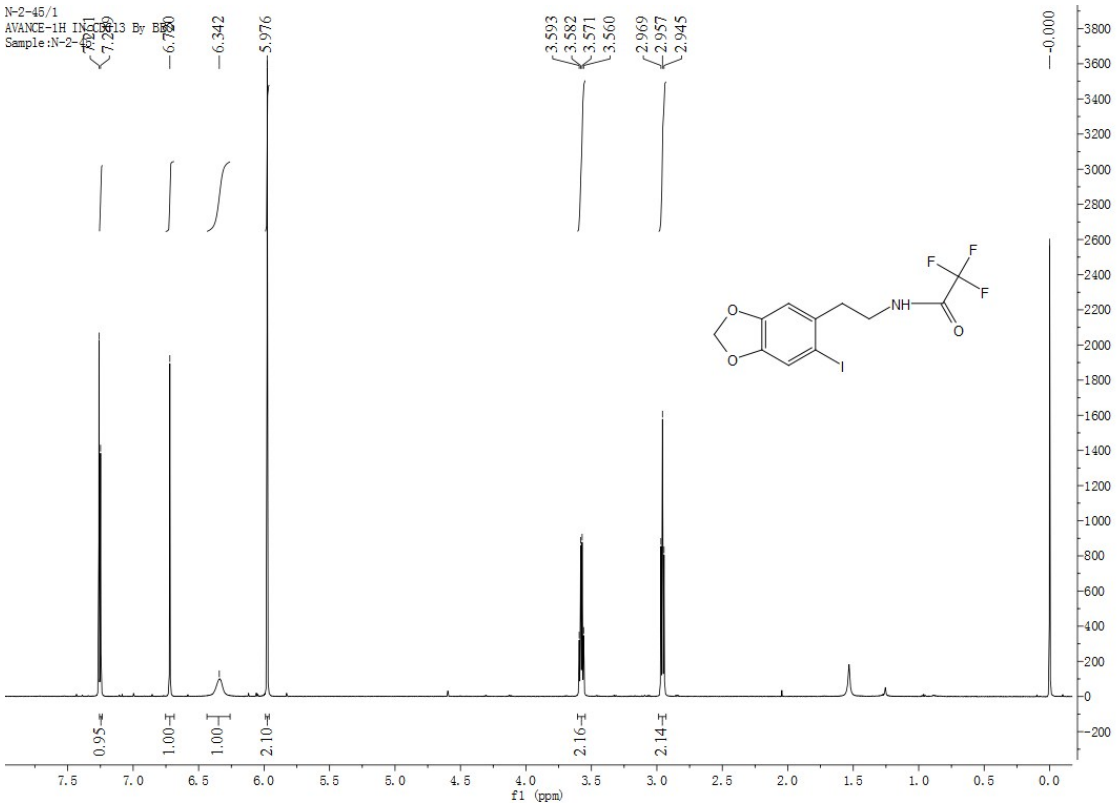
***Rac*-β-Hydrastine**



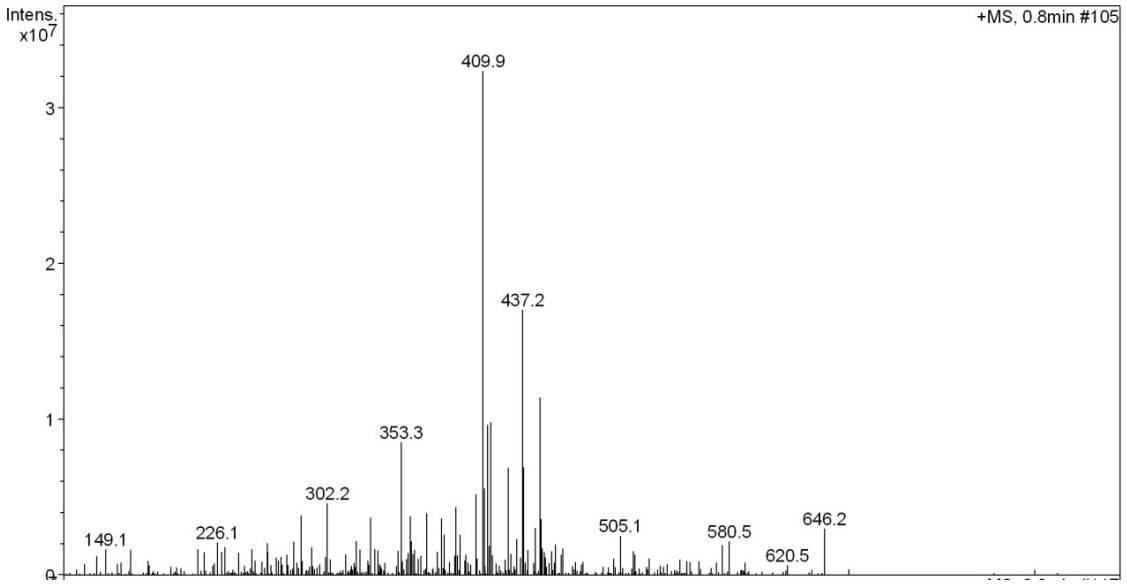
<Column Performance Report>

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	5.868	4347126	90.4651	4047.164	1.452	--
2	7.317	623003	9.5349	6019.769	1.186	3.883

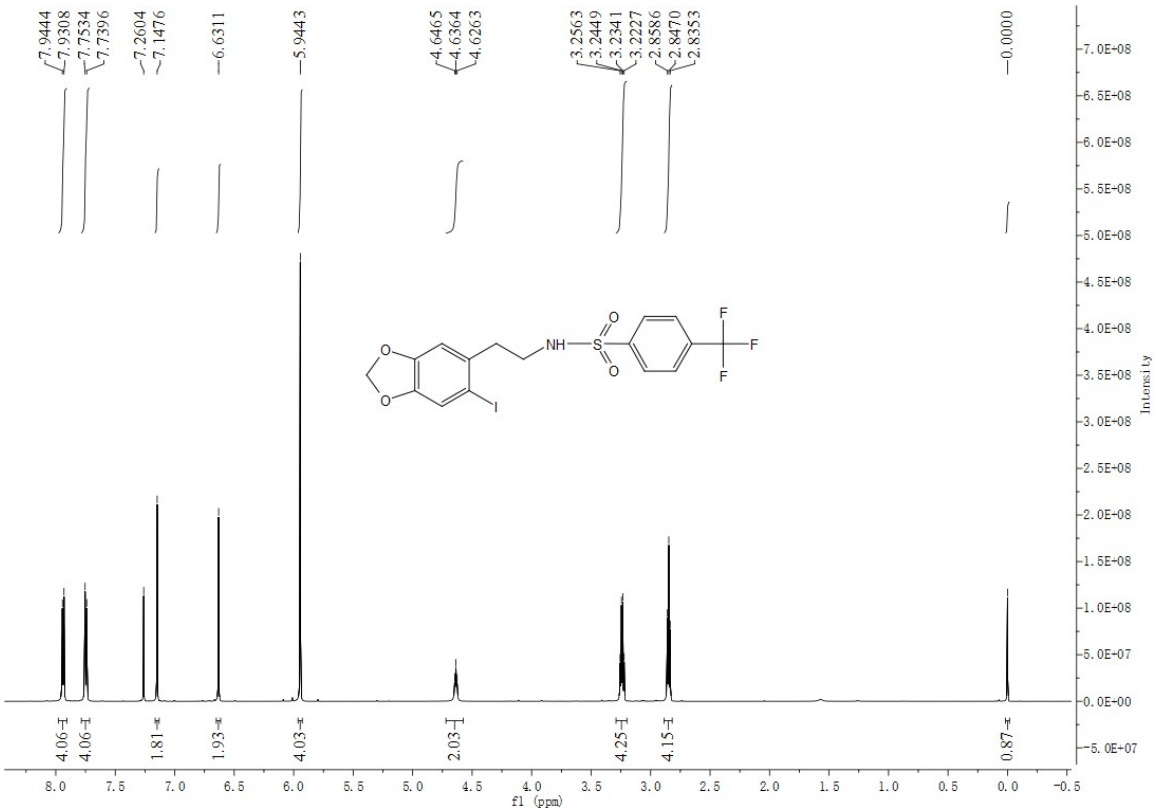
(−)-β-Hydrastine



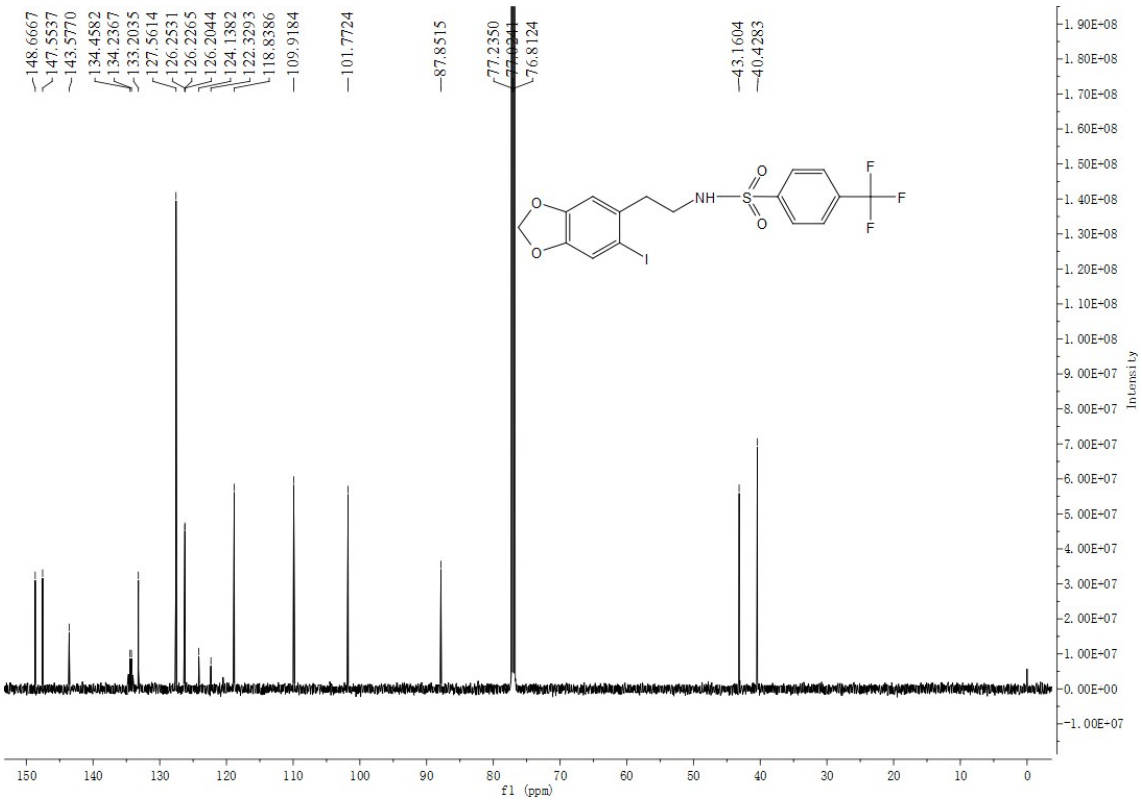
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for 15a



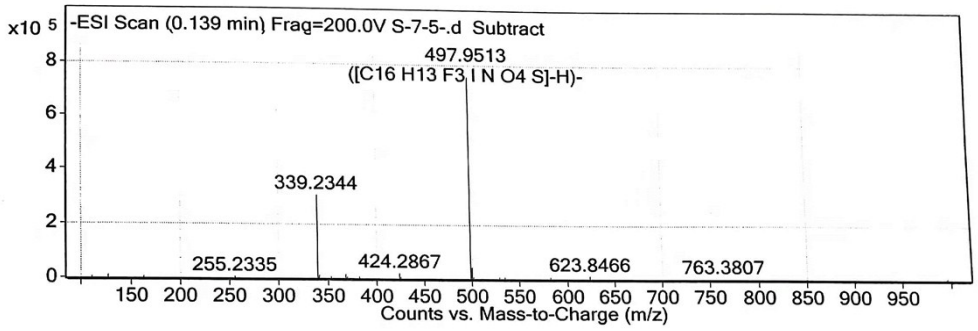
MS for 15a



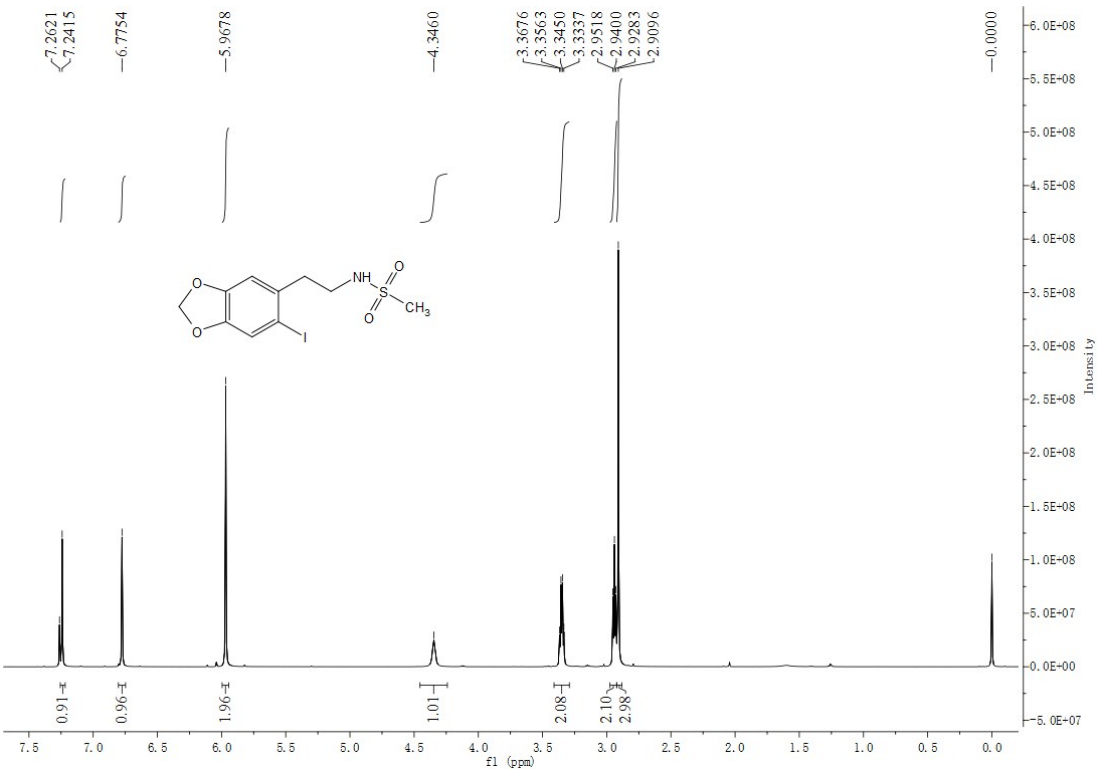
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for 15b



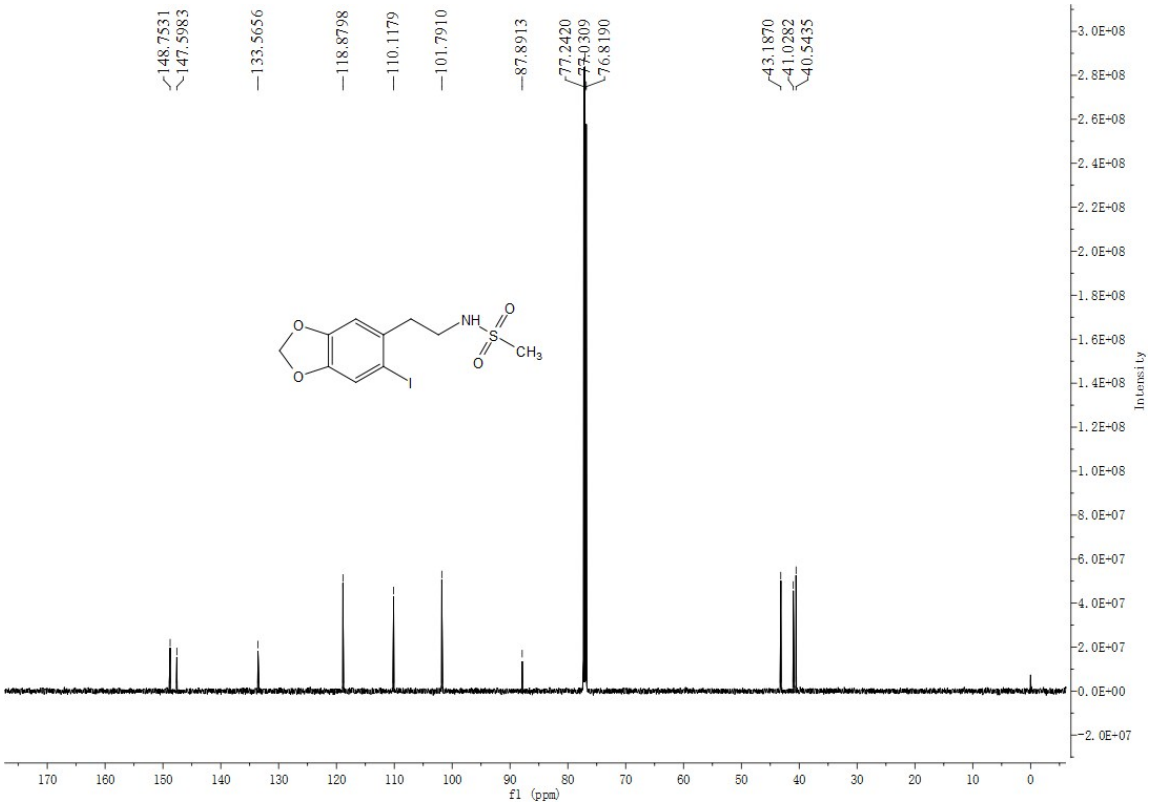
^{13}C-NMR (151 MHz, $CDCl_3$) spectrum for 15b



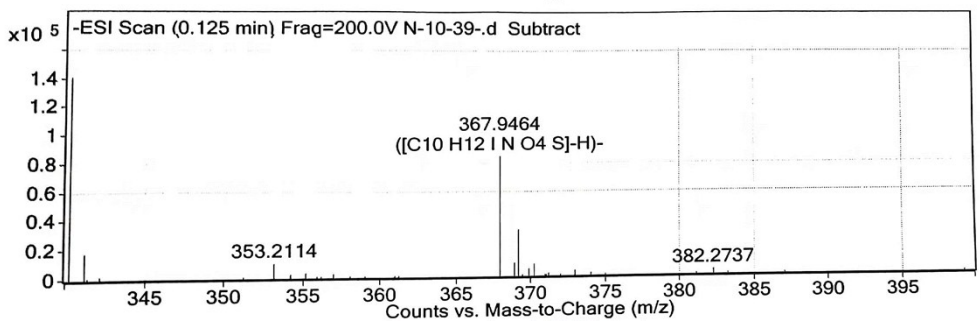
HRMS for 15b



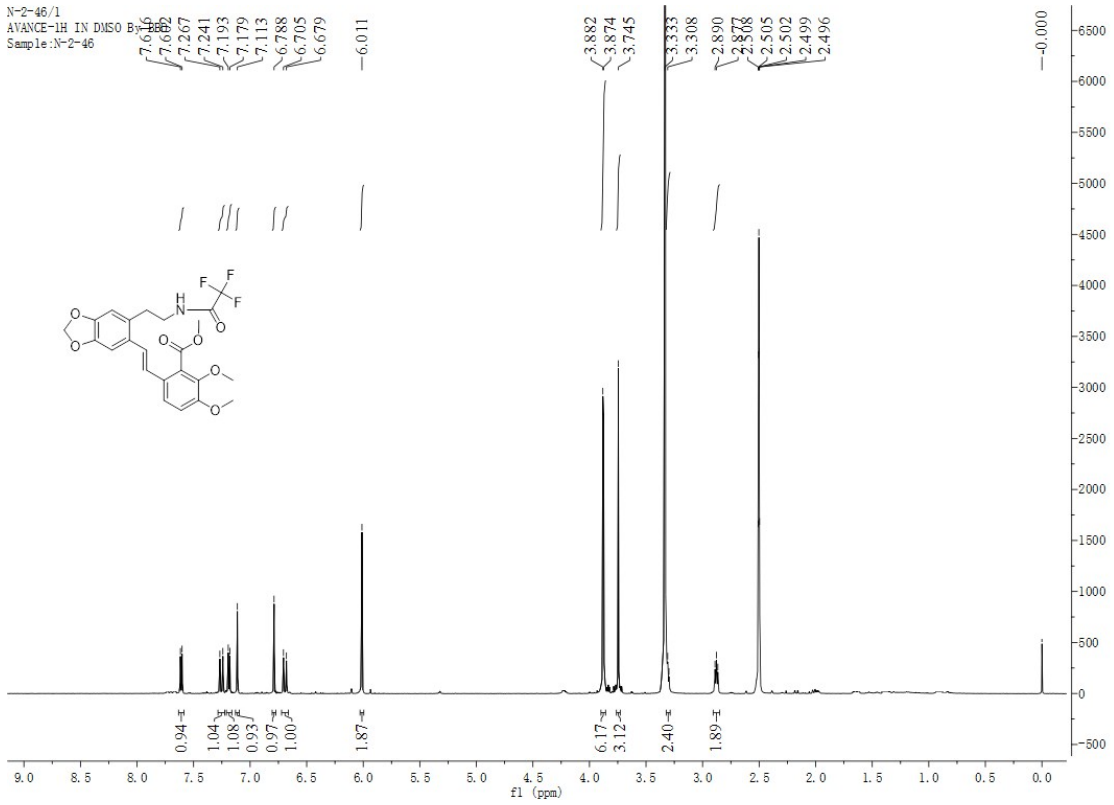
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for15c



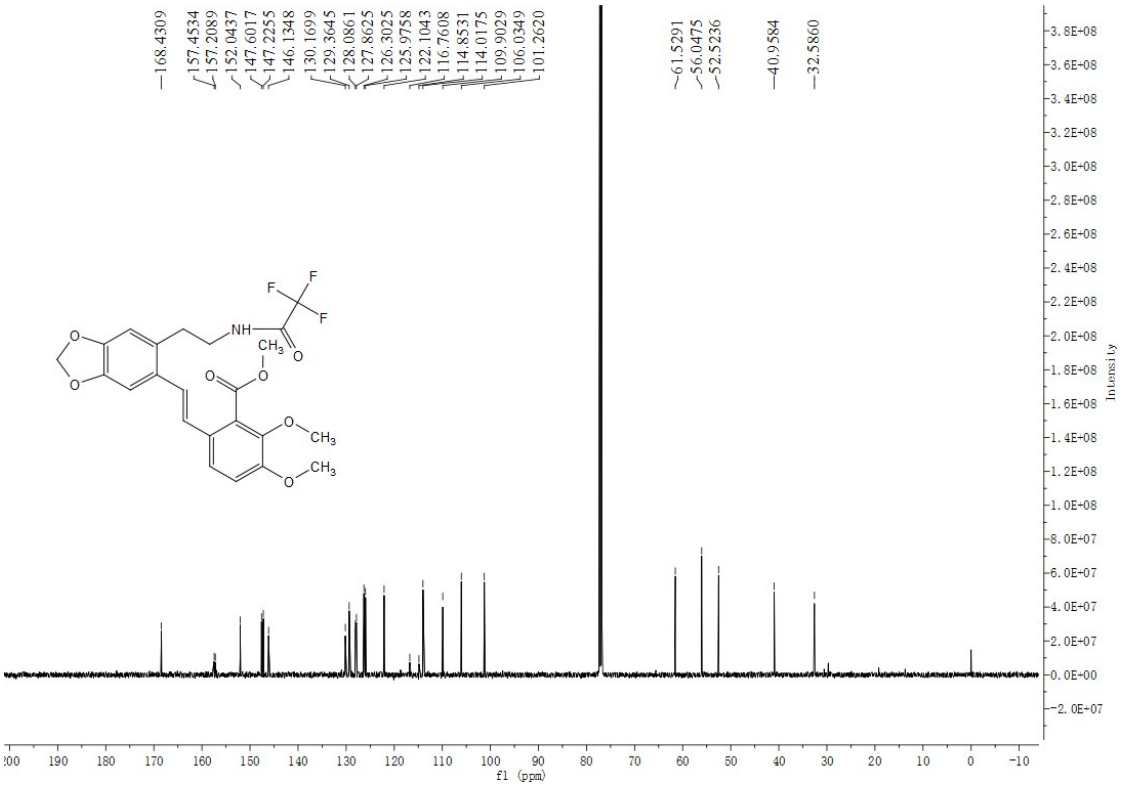
^{13}C-NMR (150 MHz, $CDCl_3$) spectrum for 15c



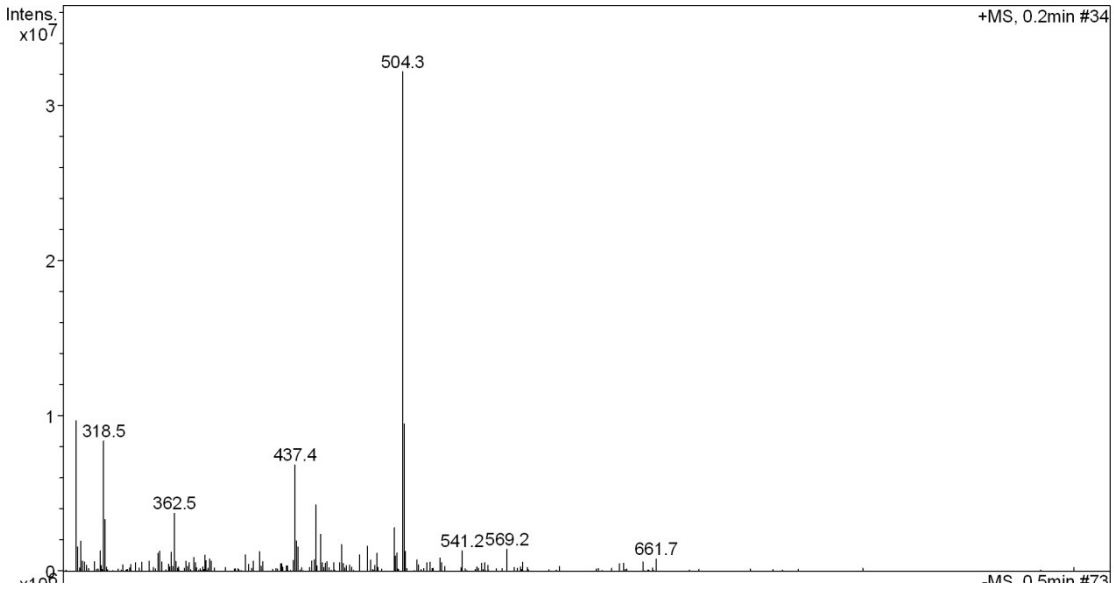
HRMS for 15c



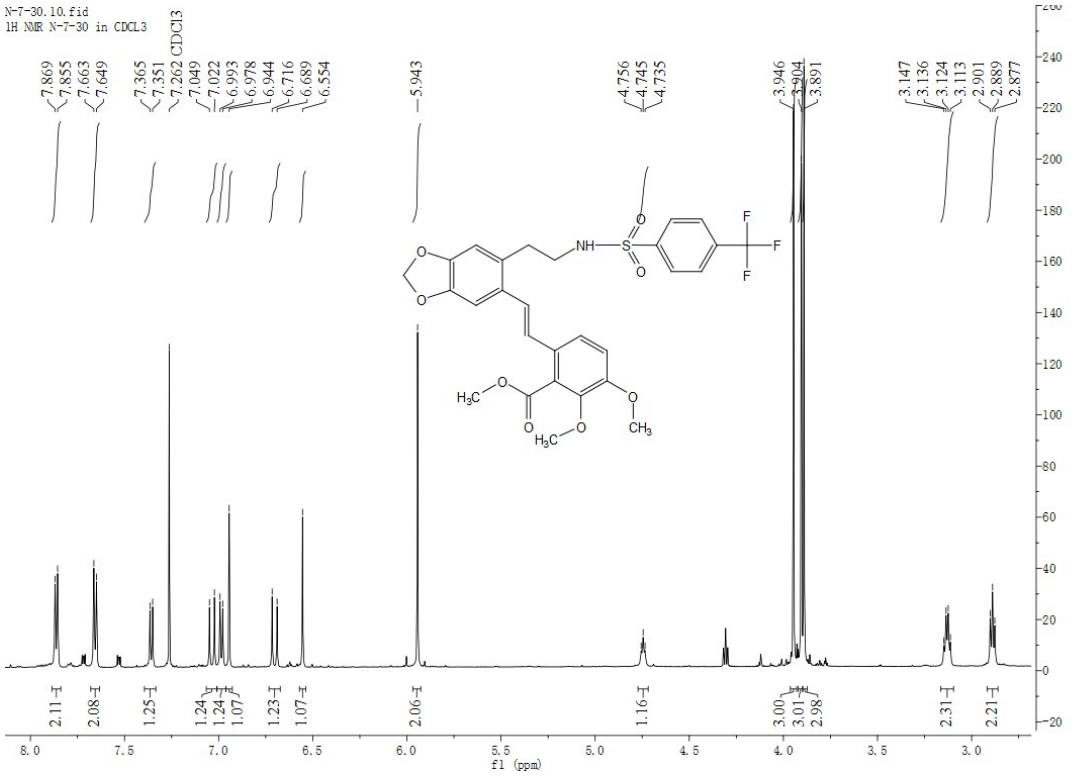
^{1}H-NMR (600 MHz, DMSO-d_6) spectrum for 16a



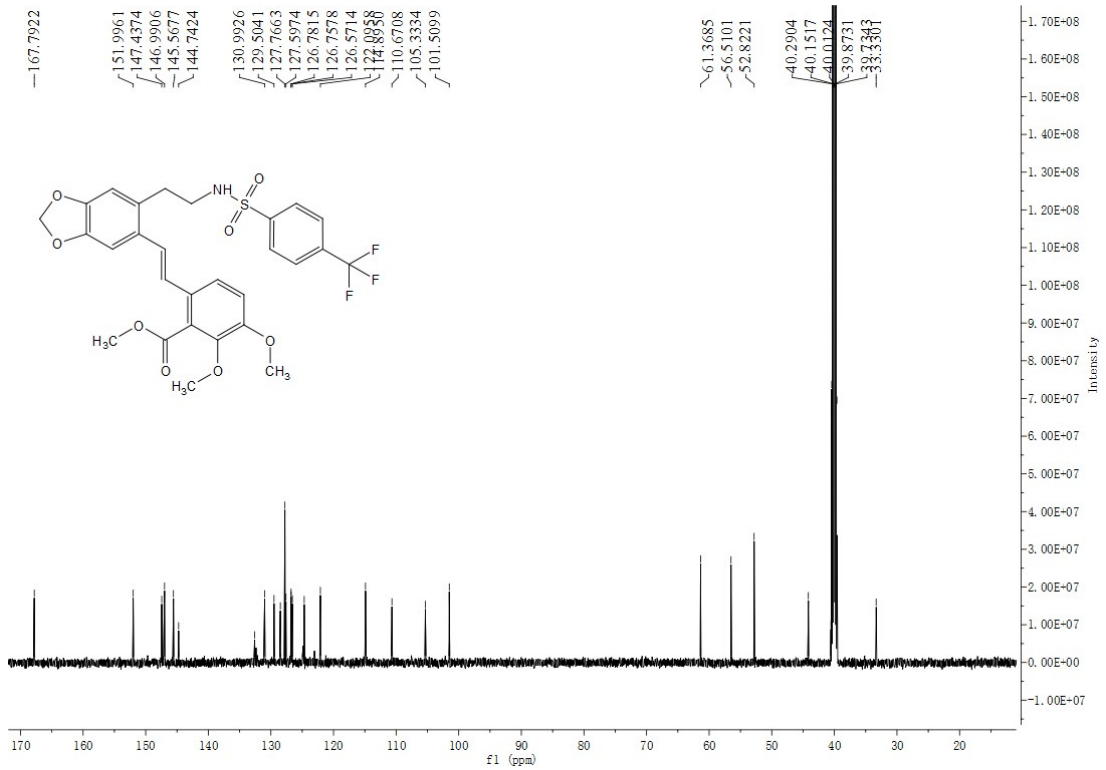
^{13}C-NMR (150 MHz, $CDCl_3$) spectrum for 16a



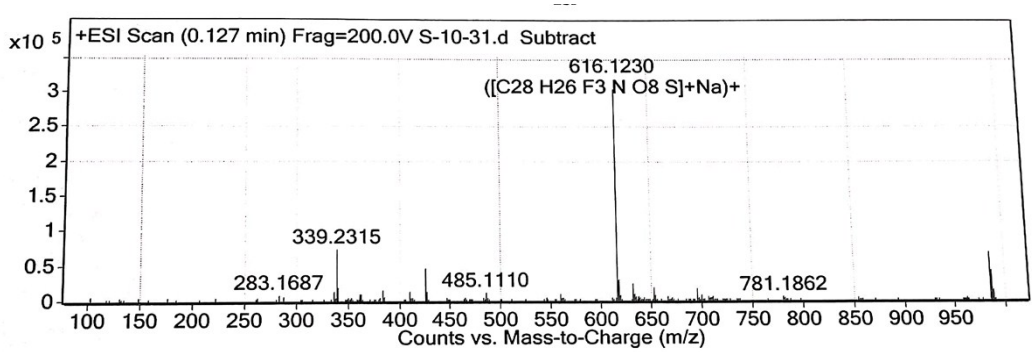
MS for 16a



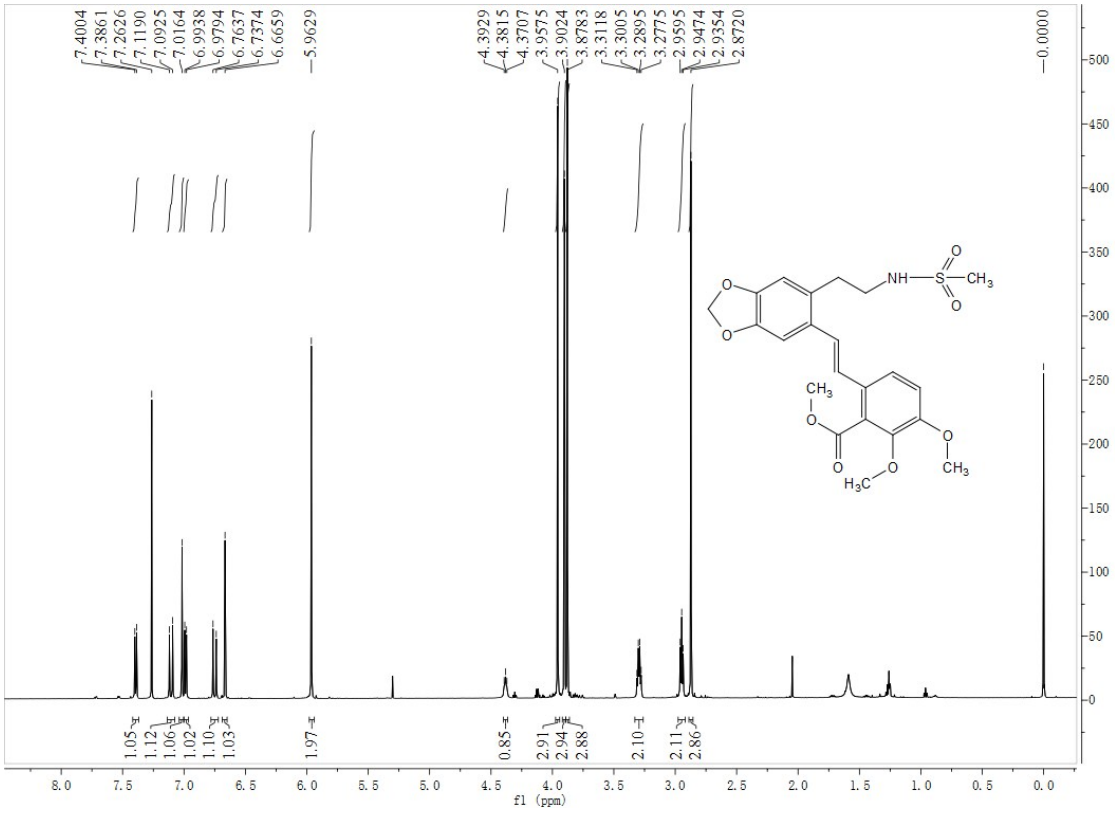
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for 16b



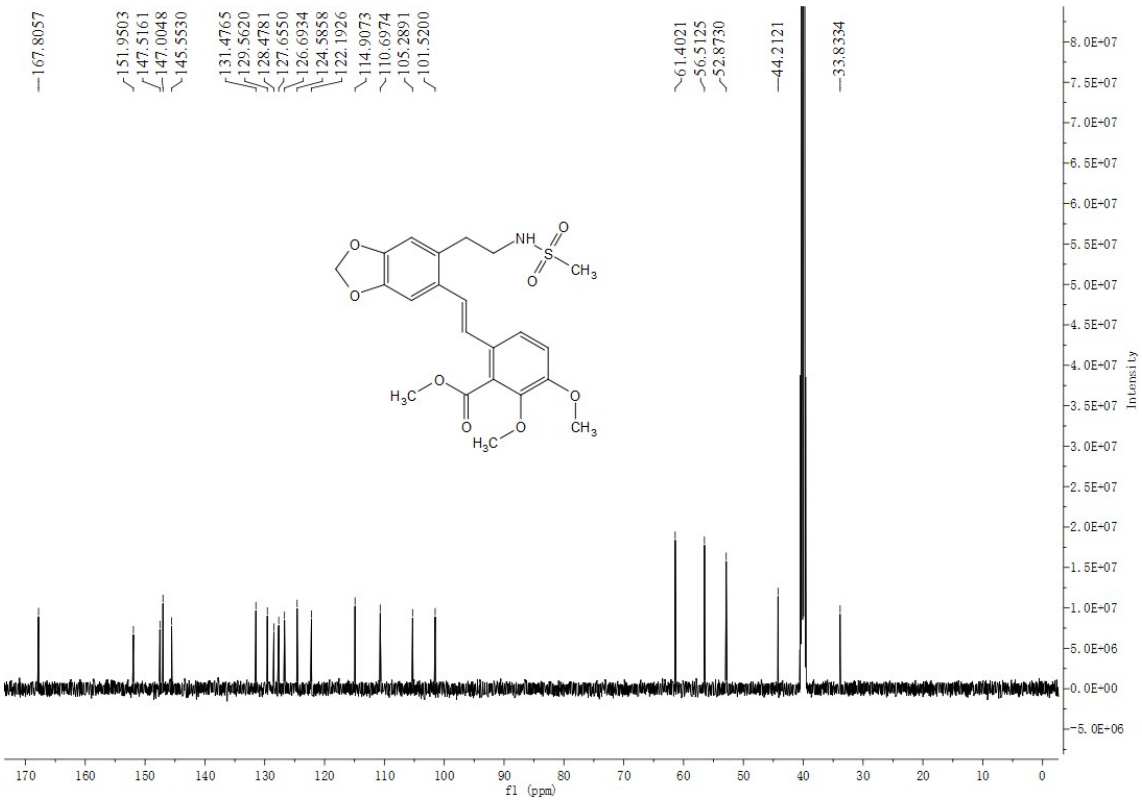
^{13}C-NMR (150 MHz, DMSO-d_6) spectrum for 16b



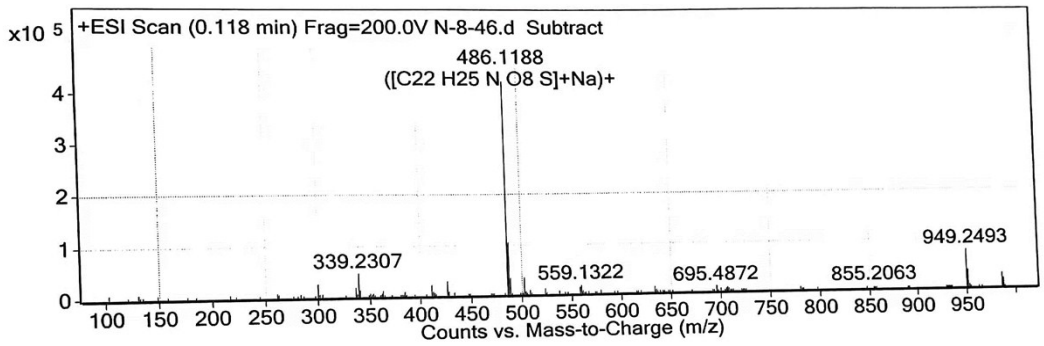
HRMS for 16b



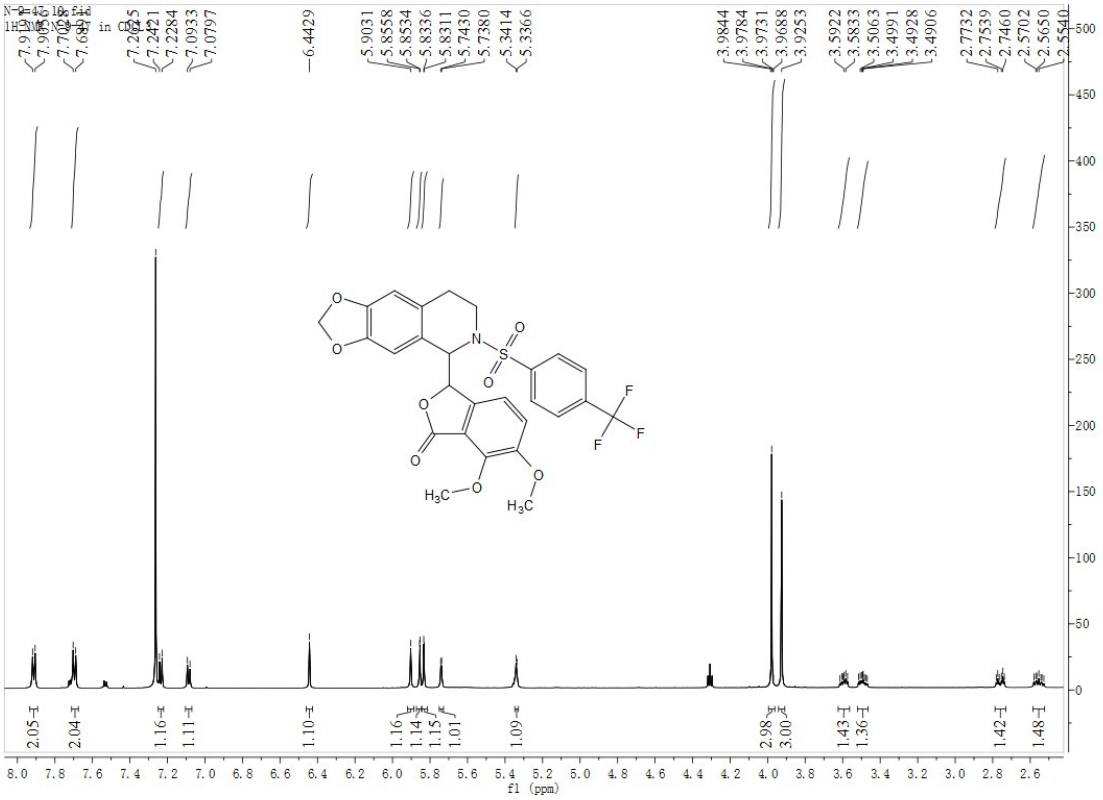
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for 16c



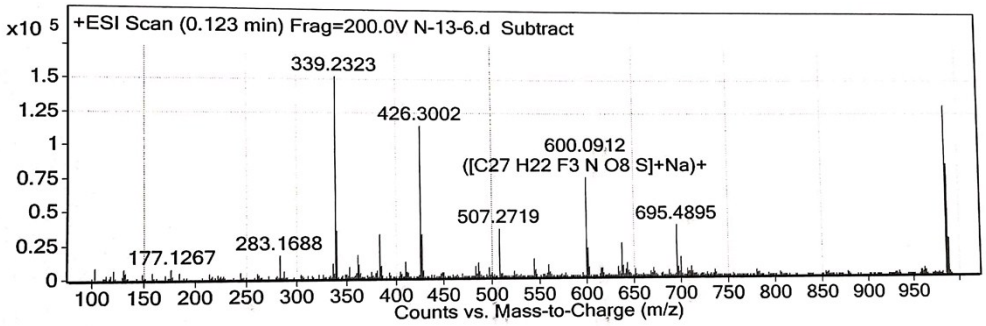
^{13}C-NMR (150 MHz, DMSO-d_6) spectrum for 16c



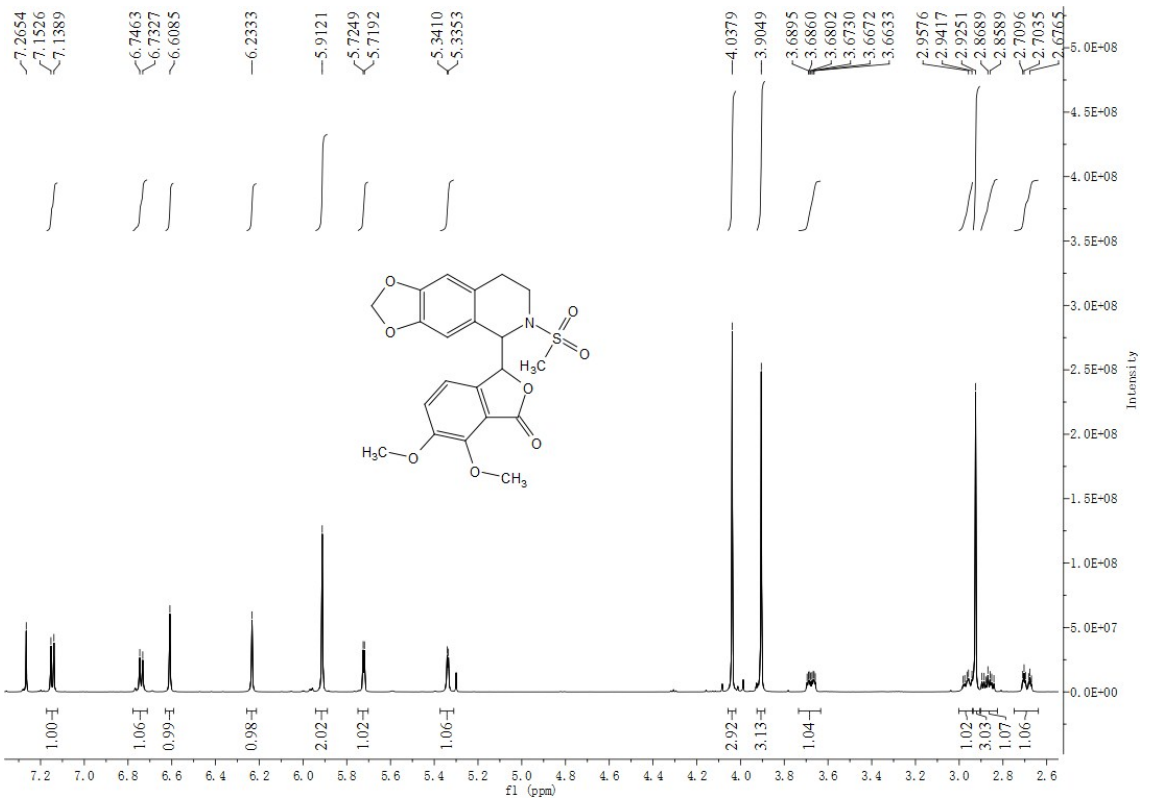
HRMS for 16c



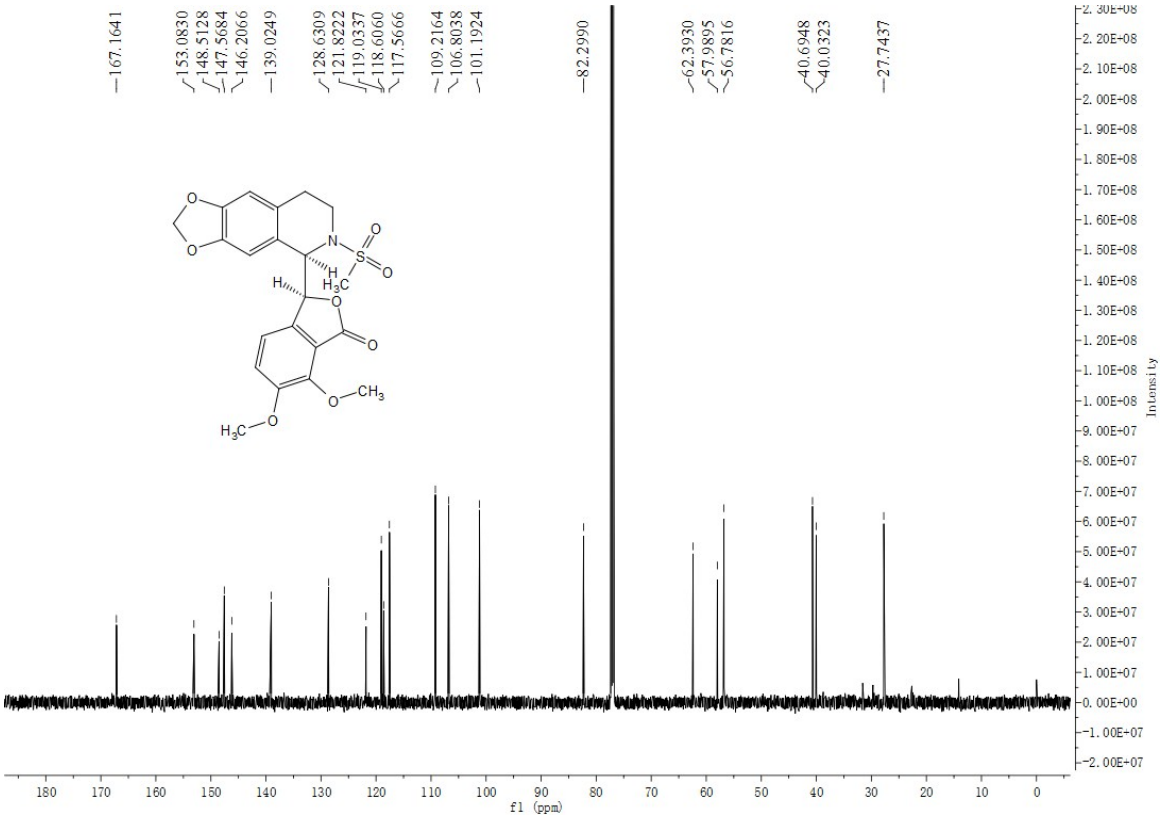
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for (±)-β-18b



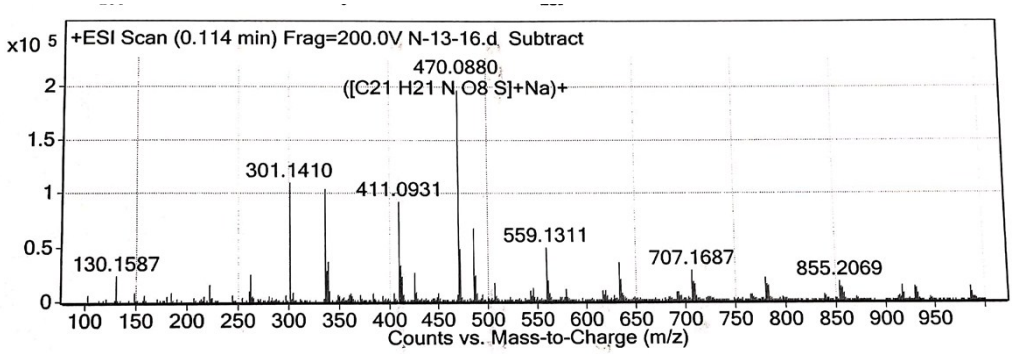
HRMS for (±)-β-18b



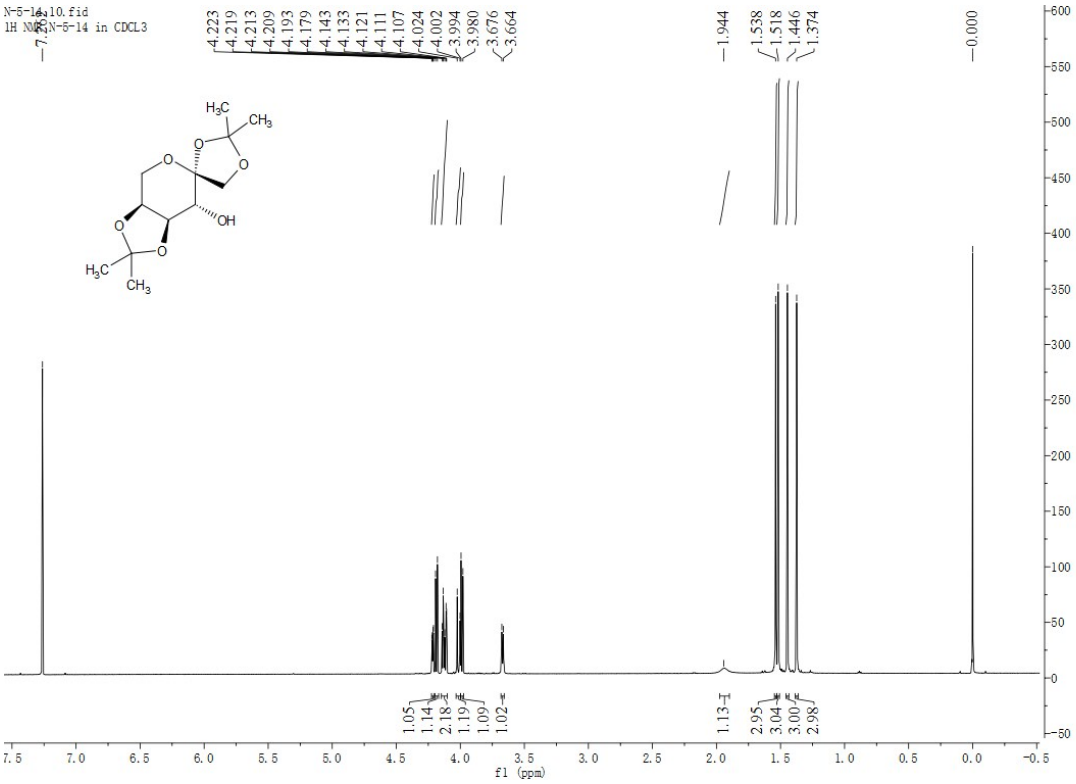
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for (±)-β-18c



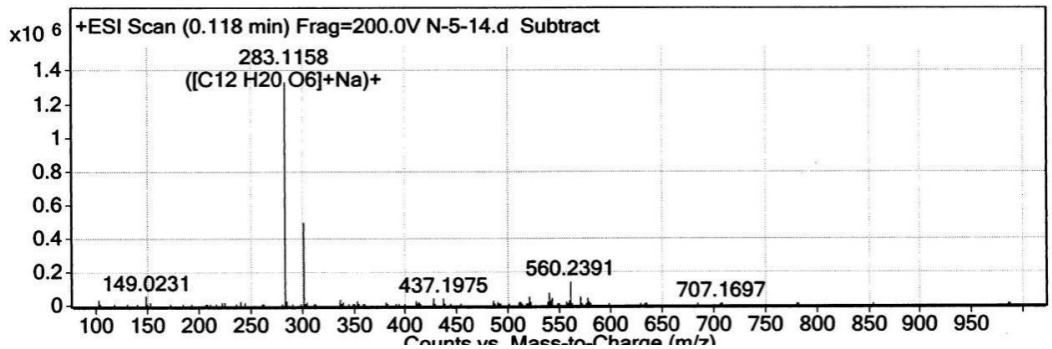
^{13}C-NMR (150 MHz, DMSO-d_6) spectrum for (±)-β-18c



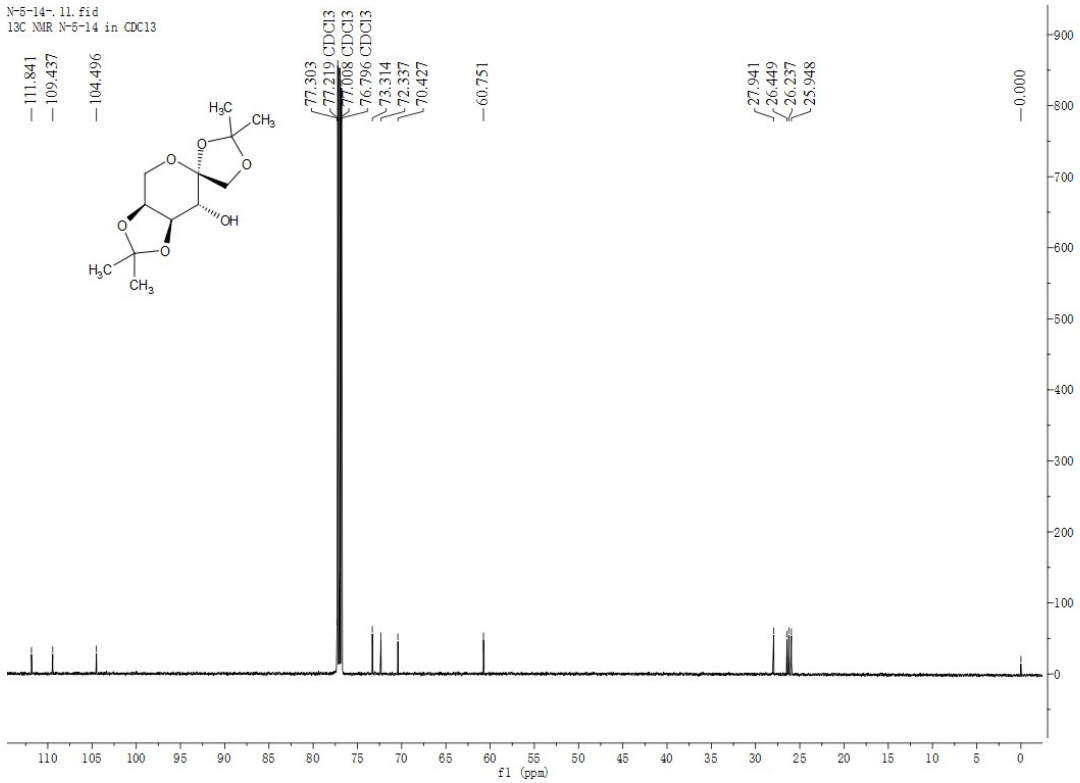
HRMS for (±)-β-18c



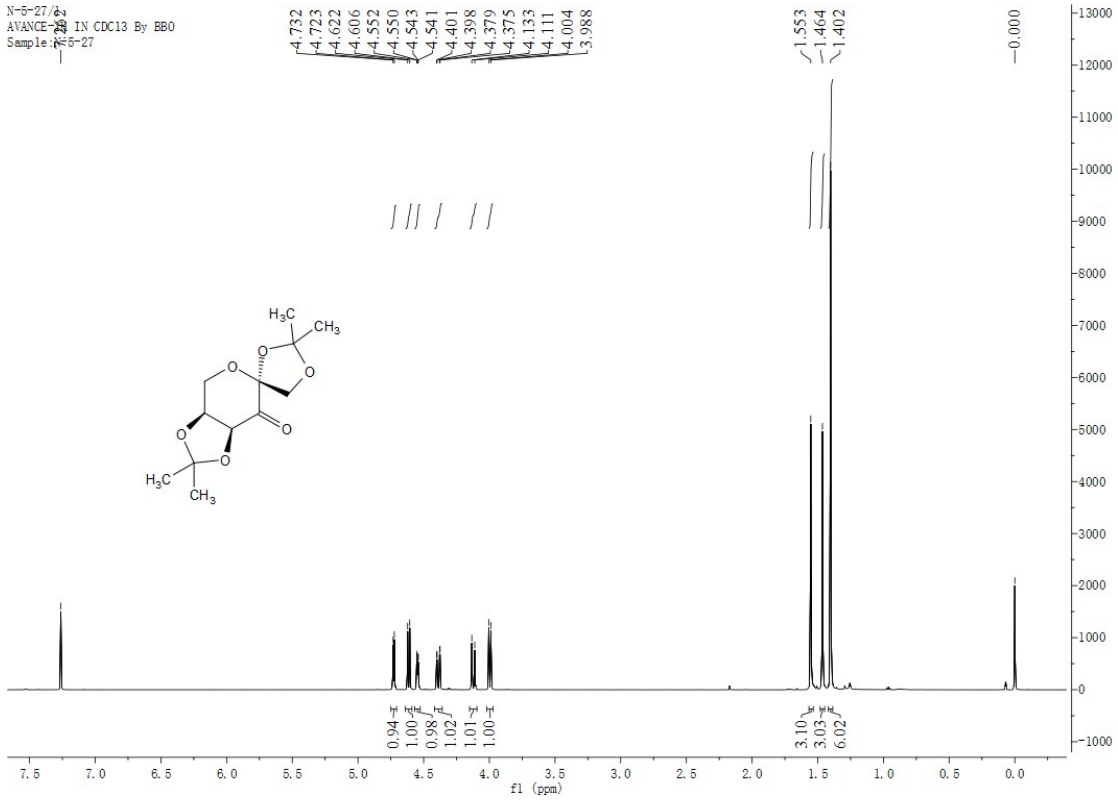
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for *ent*-14



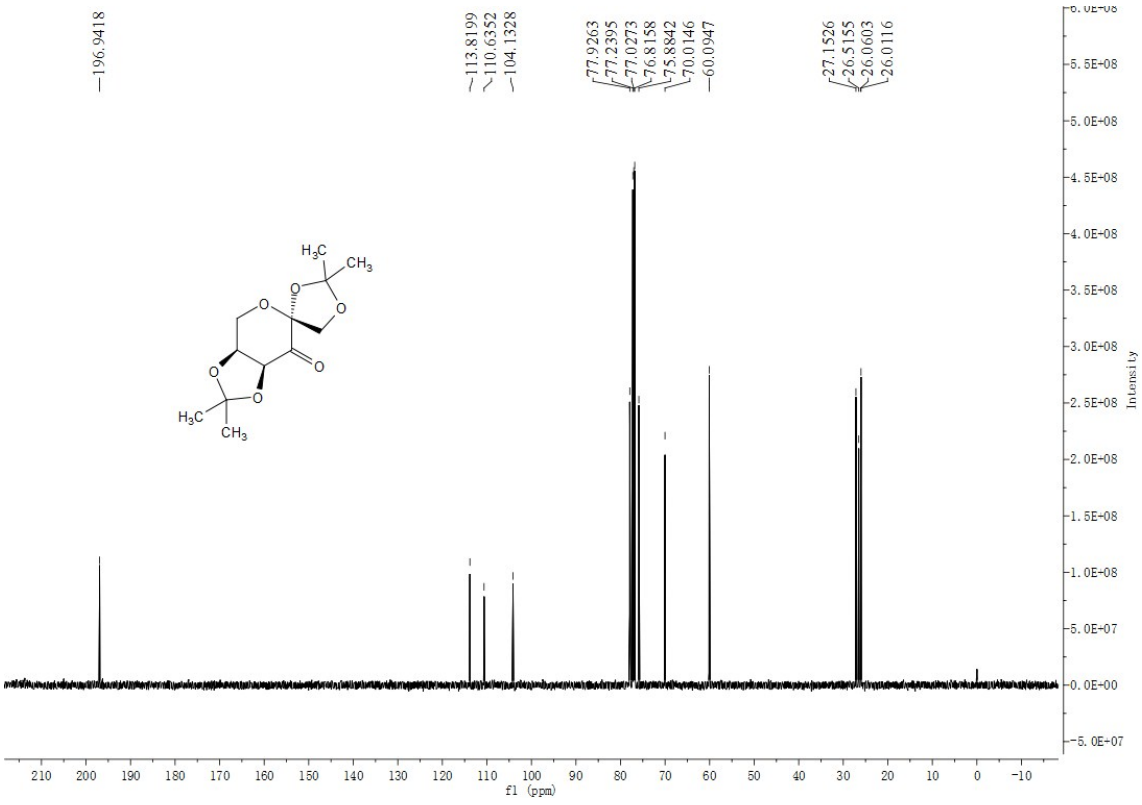
HRMS for *ent*-14



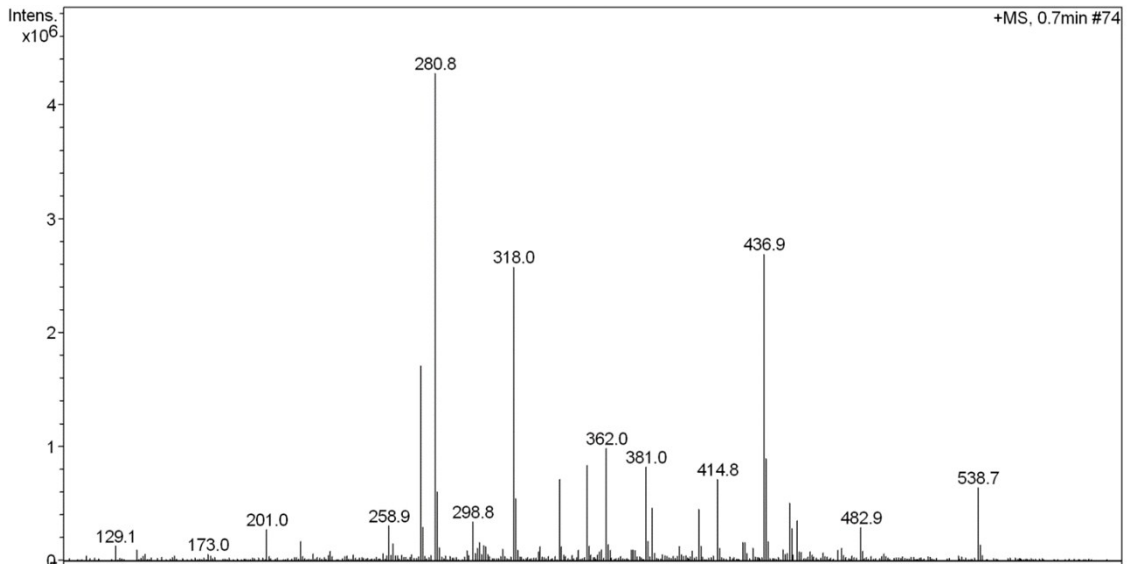
^{13}C-NMR (150 MHz, $CDCl_3$) spectrum for *ent*-14



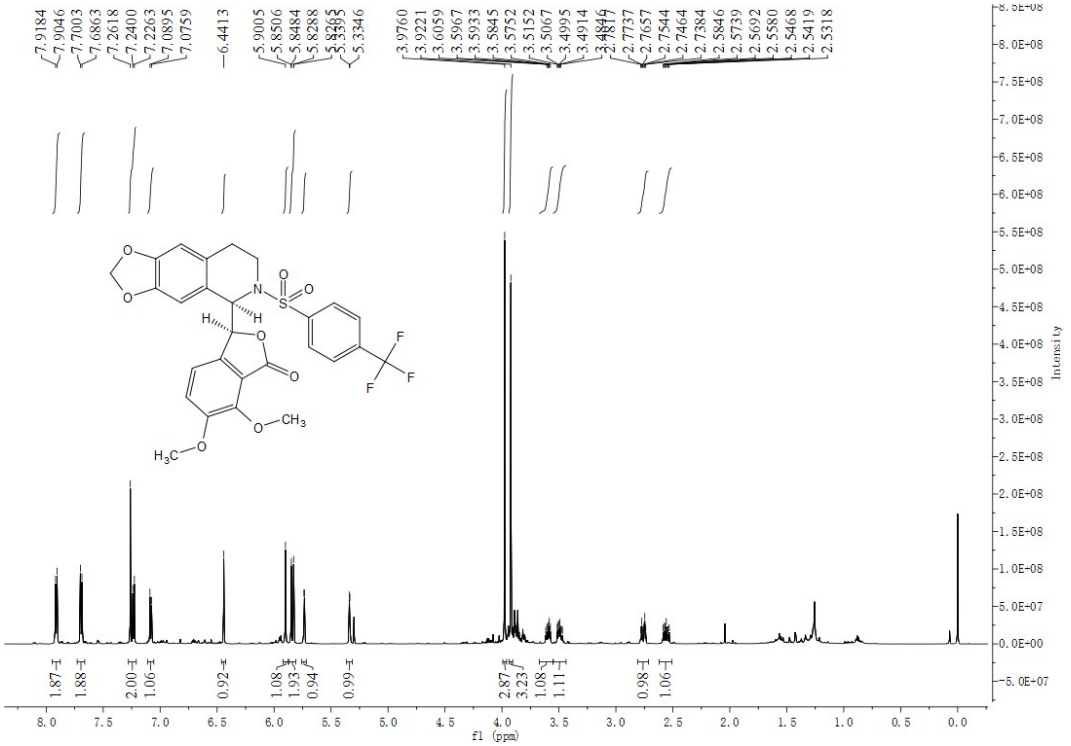
^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for *ent*-13



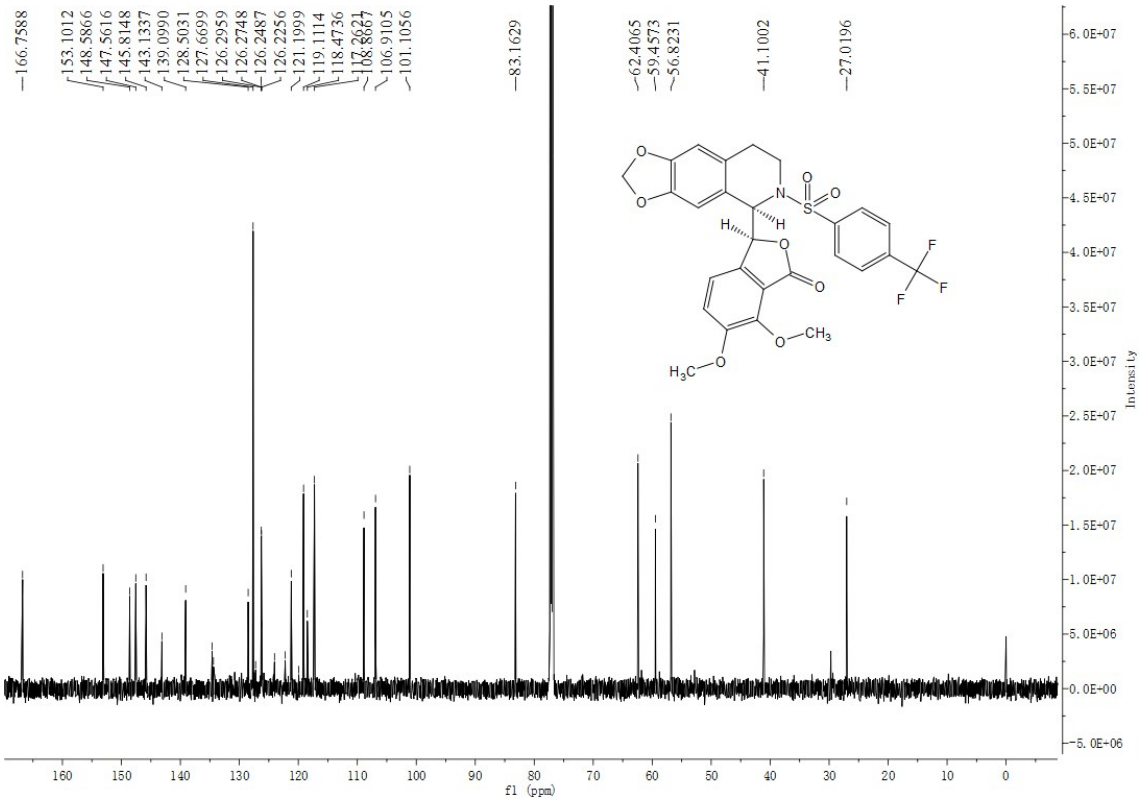
^{13}C-NMR (150 MHz, $CDCl_3$) spectrum for *ent*-13



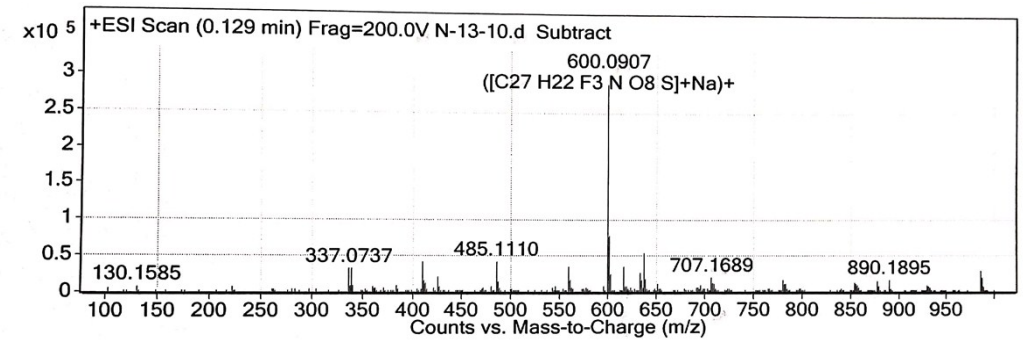
MS for *ent*-13



^{1}H-NMR (600 MHz, $CDCl_3$) spectrum for (−)-β-18b



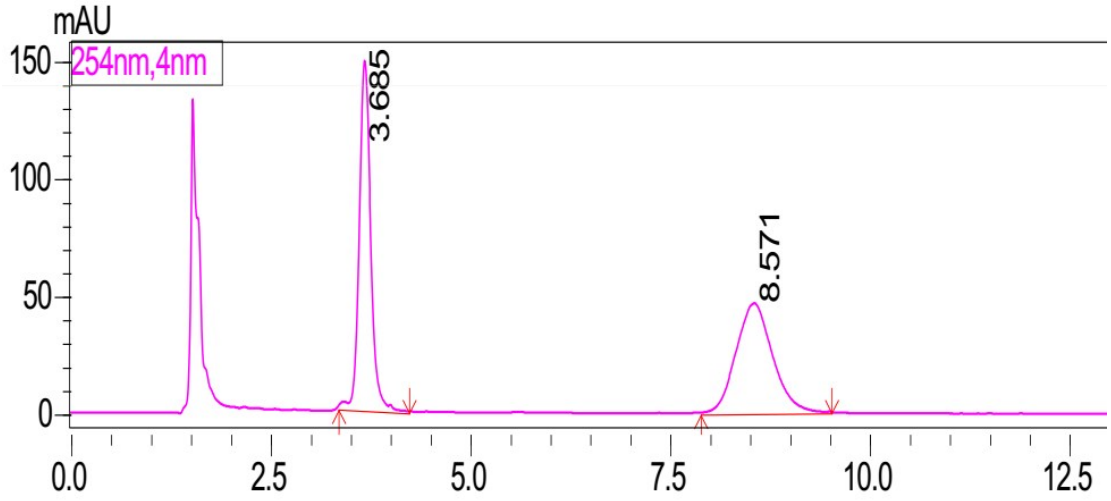
^{13}C-NMR (150 MHz, DMSO-d_6) spectrum for (−)-β-18b



HRMS for (–)-β-18b

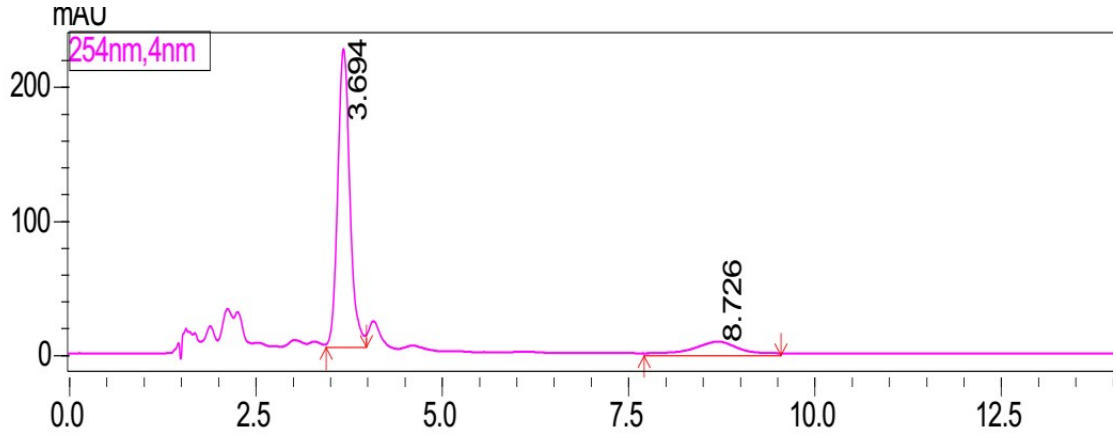
Chiral HPLC spectrum for (–)-β-18b

Column	:	CHIRALPAK® IA	
Column size	:	0.46 cm I.D. ×10 cm L ×5 μm	
Injection	:	10 μl	
Mobile phase	:	Hexane/ Ethanol / Diethylamine = 70/ 30/ 0.1	(v/v/v)
Flow rate	:	1.0 ml/min	
Wave length	:	UV 254 nm	
Temperature	:	35℃	
Sample solution	:	0.8 mg/ml in DCM50% Hexane50%	
HPLC equipment	:	Shimadzu LC 20A QA&QC-HPLC-12	



Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	3.685	1480419	50.587	3365	1.176	--
2	8.571	1446040	49.413	1694	1.085	8.989

***Rac*-18b**



<Column Performance Report>

Peak No.	Time	Area	Area %	Plate number	Tailing	Resolution
1	3.694	2513716	89.196	2540	1.203	--
2	8.726	304469	10.804	1434	0.902	8.284

(–)-β-18b

6. References

(1) (a) Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564-577. (b) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133-2144.

(2) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235; (b) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807.

(3) Wang, B.; Wu, X.-Y.; Wong, O. A.; Nettles, B.; Zhao, M.-X.; Chen, D.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 3986-3989.

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