Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

A unified and straightforward total synthesis of (+)-porantheridine and (-)-6-*epi*-porantheridine

Jiwu Wang [b], Wang Li [a], Lixia Liu [b], Bo Wang [a], Yi Zhou [a], Shuangping Huang [*, b, c], and Xiaoji Wang [*, a, d]

[a] School of Life Science, Jiangxi Science and Technology Normal University, 330013 Nanchang, Jiangxi, P. R. of China.

[b] School of Pharmacy, Jiangxi Science and Technology Normal University, 330013 Nanchang, Jiangxi, P. R. of China

[c] College of Biomedical Engineering, Taiyuan University of Technology, 030024 Taiyuan, Shanxi, P. R. of China

[d] School of Chemical Engineering and Energy Technology, Dongguan University of Technology. 523808 Dongguan, Guangdong, P. R. of China

E-mail: 2012207455@tju.edu.cn

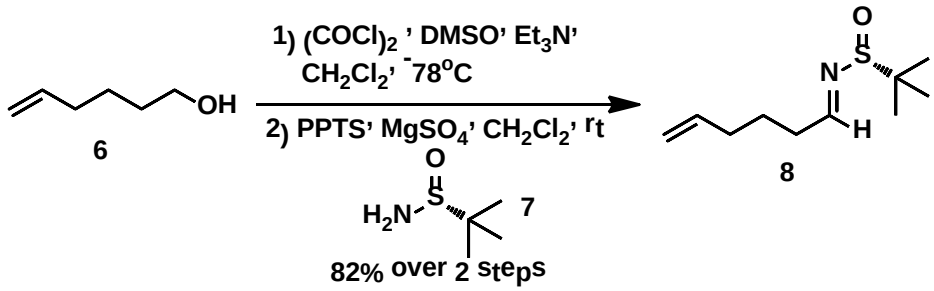
Table of Contents

General Information

All air and water sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially and used without further purification. Anhydrous THF and was distilled from sodium-benzophenone, dichloromethane and N,N-dimethylformamide were distilled from calcium hydride. Yields refer to chromatographically, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60 F-254) that were analyzed by staining with Phosphomolybdic acid (100 mL of 95% EtOH, 10 g Phosphomolybdic acid), fluorescence upon 254 nm irradiation or by staining with Ninhydrin (100 mL Butanol of 1.5 g Ninhydrin and 3 mL of acetic acid) and Dinitrophenylhydrazine (80 mL H_2O, 200 mL of 95% EtOH, 12 g Dinitrophenylhydrazine and 60 mL concentrated sulfuric acid). Silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. IR spectra were obtained using FT-IR Spectrometer. NMR spectra were recorded on a 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublets. High resolution mass spectra were obtained from a MALDI-TOF mass spectrometer.

Synthetic Procedures

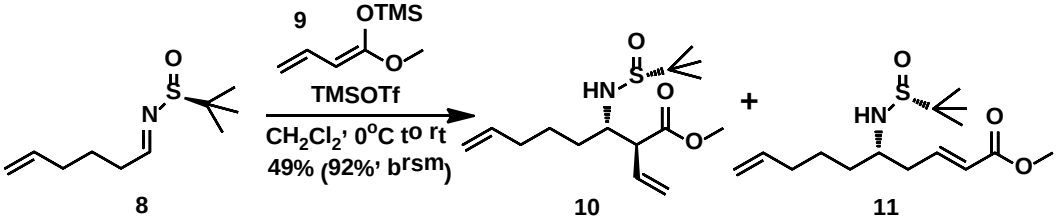
(R,E)-N-(hex-5-en-1-ylidene)-2-methylpropane-2-sulfinamide (8)



A solution of oxalyl chloride (12.7 mL, 149.76 mmol) in CH_2Cl_2 (180 mL) was stirred at -78 ºC for 30 minutes, followed by the dropwise addition of dimethyl sulfoxide (21.3 mL, 299.52 mmol) in CH_2Cl_2 (80 mL) and the resulting mixture was allowed to stirred at the same temperature for another 30 minutes. **6** (10 g, 99.84 mmol) in CH_2Cl_2 (100 mL) was then introduced into the mixture and the latter was allowed to stirred for 30 minutes before triethylamine (80.4 mL, 577.08 mmol) in CH_2Cl_2 (140 mL) was added. After 1 h, the reaction mixture was then diluted with 1M HCl solution and washed with saturated $NaHCO_3$ (2 x 200 mL), followed by 1.0 M $KHSO_4$ (2 x 200 mL). The organic layer was further washed with $NaHCO_3$ (2 x 300 mL) before drying in Na_2SO_4 and evaporated in vacuo. Under nitrogen atmosphere, a suspension of the crude product (9.80 g, 99.84 mmol), (R)-(+)-tert-butylsulfinamide **7** (12.10 g, 99.84 mmol), PPTS (2.51 g, 9.98 mmol), and anhydrous $MgSO_4$ (48 g) in CH_2Cl_2 (192 mL) was stirred for 14 h at room temperature. The mixture was filtered through a pad of Celite and concentrated in vacuo. The residual oil was purified by flash chromatography on silica gel (EtOAc/hexane = 1:5) to produce the desired compound **8** as an oil (18.5 g, 82% yield): $[\alpha]_D^{25}$ = -257.308 (c 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03-4.92 (m, 1H), 4.24-4.17 (m, 2H), 1.75-1.70 (m, 2H), 1.32 (q, *J* = 7.0 Hz, 2H), 0.92 (q, *J* = 7.4 Hz, 2H), 0.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 137.4, 115.3,

77.5, 77.2, 76.9, 56.3, 35.2, 32.9, 24.4, 22.1; IR (neat) 2929, 2864, 1622, 1454, 1365, 1085, 907 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{19}NOSNa$ $[M+Na]^+$ 224.1080, found 224.1081.

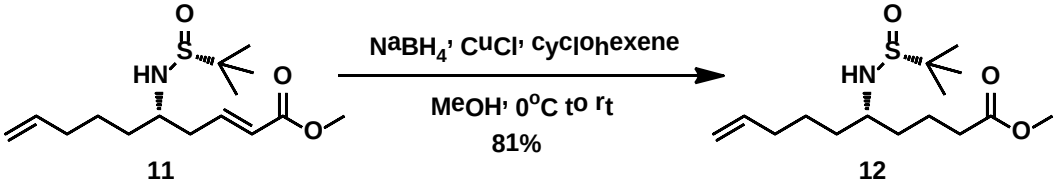
(S,E)-methyl 5-((R)-1,1-dimethylethylsulfinamido)deca-2,9-dienoate (11) [1]



Dienolate **9** (3.0 equiv) was added to a solution of **8** (0.5 g, 2.5 mmol) in CH_2Cl_2 (12 mL) and the solution was cooled to 0 ºC under N_2. TMSOTf (0.54 mL, 3.0 mmol) was added dropwise. After being stirred for 2 h at the same temperature, the reaction was quenched by addition of a saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide an oily residue that was purified by flash chromatography on silica gel (EtOAc/hexane = 1:2) to gave the compounds **11** and **10** (364 mg, 49% yield, 92% brsm yield) as a oil in a 4.3:1. **11**: **[**$\alpha]_D^{25}$ = -80.9 (c 1.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86-6.78 (m, 1H), 5.77 (d, *J* = 15.7 Hz, 1H), 5.71-5.59 (m, 1H), 4.87 (dd, *J* = 20.2, 13.7 Hz, 2H), 3.61 (s, 3H), 3.33-3.27 (m, 1H), 3.07 (d, *J* = 6.0 Hz, 1H), 2.41-2.25 (m, 2H), 1.96 (q, *J* = 7.0 Hz, 2H), 1.51-1.30 (m, 4H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 145.1, 137.9, 123.5, 115.0, 77.5, 77.2, 76.8, 55.8, 55.4, 51.4, 38.2, 35.2, 33.3, 24.9, 22.5; IR (neat) 2944, 2863, 1723, 1653, 1432, 1269, 1048, 910 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{28}NO_3S$ $[M+H]^+$ 302.1784, found 302.1785.

10 : ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.71 (m, 2H), 5.31-5.16 (m, 2H), 4.96 (d, *J* = 22.0, 13.7 Hz, 2H), 3.67 (s, 3H), 3.57 (d, *J* = 10.7 Hz, 1H), 3.22-3.10 (m, 1H), 2.08-1.99 (m, 2H), 1.70-1.43 (m, 4H), 1.18 (t, *J* = 7.1 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 138.1, 133.3, 131.6, 120.4, 119.4, 114.8, 77.5, 77.2, 76.8, 58.8, 58.6, 56.1, 56.0, 54.8, 51.8, 33.7, 33.2, 33.1, 25.0, 24.3, 22.6; IR (neat) 2947, 2859, 1737, 1639, 1437, 1168, 1048, 910 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{28}NO_3S$ $[M+H]^+$ 302.1784, found 302.1784.

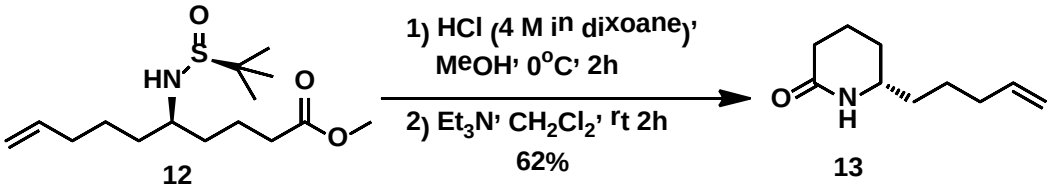
(S)-methyl 5-((R)-1,1-dimethylethylsulfinamido)dec-9-enoate (12)[2]



To a solution of α,β-unsaturated ester **11** (9.15 g, 30.35 mmol), CuCl (6.01 mg, 6.71 mmol) and cyclohexene (24.6 mL, 242.83 mmol) in MeOH (202 mL) at 0 °C was added $NaBH_4$ (11.48 g, 303.54 mmol). The reaction was left at room temperature for 2 h, during which time it turned from green to brown. While still cold, the solvent was removed on the rotary evaporator. The products were partitioned between saturated aqueous NH_4Cl solution (100 mL) and CH_2Cl_2 (100 mL). The organic phase was separated and the aqueous layer was extracted with more CH_2Cl_2 (4 x 100 mL). The organic layers were combined, dried with Na_2SO_4, filtered and concentrated under reduced pressure to provide an oily residue and that was deemed sufficiently purified by flash

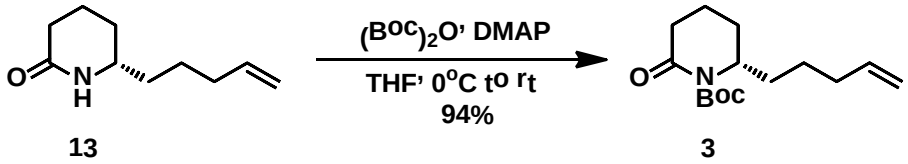
chromatography on silica gel (EtOAc/hexane = 1:2) to produce **12** the colourless oil (7.41 g, 81%): $[\alpha]_D^{25}$ = -34.73 (c 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80-5.70 (m, 1H), 4.94 (d, *J* = 16.9, 15.0 Hz, 2H), 3.63 (s, 3H), 3.21-3.18 (m, 1H), 3.04 (d, *J* = 6.6 Hz, 1H), 2.31 (t, *J* = 7.0 Hz, 2H), 2.04 (d, *J* = 18.6 Hz, 2H), 1.70-1.35 (m, 9H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 138.25, 114.8, 77.5, 77.2, 76.8, 56.3, 55.8, 51.5, 35.7, 34.9, 33.7, 33.5, 24.8, 22.6, 20.7; IR (neat) 2929, 2855, 1742, 1638, 1456, 1364, 1168, 1046, 906 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{29}NO_3SNa$ $[M+Na]^+$ 326.1760, found 326.1754.

(S) -6-(pent-4-en-1-yl)piperidin-2-one (13)[3]



To a stirred solution of **12** (8.15 g, 26.87 mmol) in MeOH (218 mL) was added a 4 M HCl solution in dioxane (67 mL, 268.7 mmol), under a nitrogen atmosphere at 0 °C. After 2 h of stirring at 0 °C, saturated $NaHCO_3$ solution was added and the MeOH was evaporated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was taken up in CH_2Cl_2 (290 mL), and TEA (37.4 mL, 268.7 mmol) was added. The solution was stirred 2 h, and water was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromathy on silica gel (MeOH/CH_2Cl_2 = 1:60) to produce the desired compound **13** as an oil (2.78 g, 62%): $[\alpha]_D^{25}$ = +7.16 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 1H), 5.77-5.67 (m,1H), 4.93 (d, *J* = 16.5, 14.9 Hz, 2H), 3.30 (d, *J* = 4.9 Hz, 1H), 2.33 (d, *J* = 12.8, 9.0 Hz, 1H), 2.26-2.16 (m, 1H), 2.05-1.98 (m, 2H), 1.84 (d, *J* = 9.3 Hz, 2H), 1.66-1.56 (m, 1H), 1.51-1.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 138.1, 115.0, 77.5, 77.2, 76.8, 53.0, 36.3, 33.5, 31.3, 28.2, 24.5, 19.7; IR (neat) 2931, 2853, 1730, 1653, 1404, 1183, 1081, 992, 910 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{18}NO$ $[M+H]^+$ 168.1383, found 168.1383.

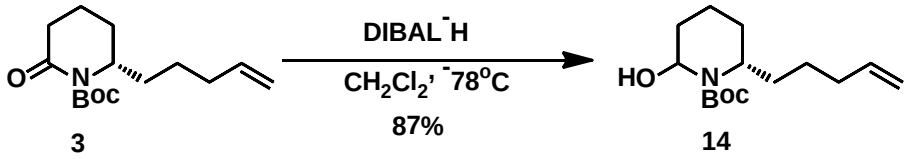
(S)-tert-butyl 2-oxo-6-(pent-4-en-1-yl)piperidine-1-carboxylate (3)



DMAP (1.65 g, 13.52 mmol) was added to a solution of **13** (2.26 g, 13.52 mmol) in THF (65 mL) at room temperature, then cooled to 0 °C, di-tert-butyl dicarbonate (7.77 mL, 33.8 mmol) was added at 0 °C. The reaction mixture was stirred at room was temperature overnight and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography (EtOAc/hexane = 1:8) provided N-protected product **3** as a yellow oil (3.41 g, 94%): $[\alpha]_D^{25}$ = +20.10 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71-5.66 (m, 1H), 4.96-4.88 (m, 2H), 4.16-4.03 (m, 1H), 2.45-2.37 (m, 2H), 2.00 (dd, *J* = 13.9, 7.0 Hz, 2H), 1.91-1.53 (m, 6H),

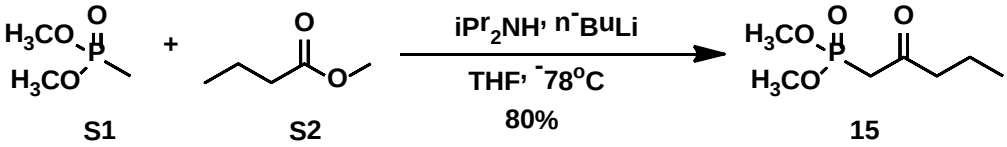
1.45 (s, 9H), 1.40-1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 152.8, 138.1, 114.9, 82.6, 77.5, 77.2, 76.8, 55.5, 34.1, 33.4, 27.9, 25.6, 25.4, 17.0; IR (neat) 2926, 2853, 1715, 1457, 1364, 1286, 1151, 913 cm^{-1}; HRMS (EIS) calcd. for $C_{15}H_{25}NO_3Na$ $[M+Na]^+$ 290.1727, found 290.1726.

(6S)-tert-butyl 2-hydroxy-6-(pent-4-en-1-yl)piperidine-1-carboxylate (14)



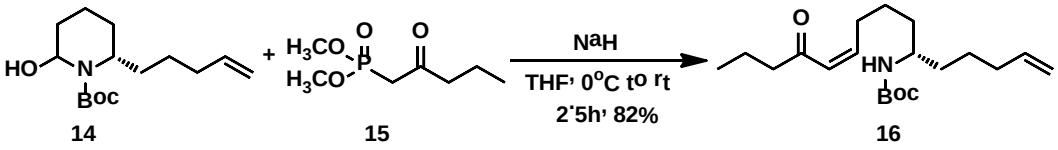
Piperidone **3** (0.7 g, 2.62 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (26 mL) under a N_2 atmosphere and cooled to -78 ºC. diisobutylaluminium hydrogen (4.4 mL, 6.60 mmol, 1.5 M in toluene) was added slowly and reaction mixture was stirred for 0.5 h. The reaction was quenched with MeOH (5 mL) and stirred at -78 ºC for 15 minutes. The quenched reaction was then treated with saturated solution sodium potassium tartrate (10 mL) and vigorously stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The title compound was obtained **14** as a clear oil (0.61 g, 87% yield) after SiO_2 flash chromatography (EtOAc/hexane = 1:10): $[\alpha]_D^{25} = +1.77$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86-5.60 (m, 2H), 4.96 (dd, *J* = 22.5, 13.7 Hz, 2H), 4.04-3.83 (m, 1H), 2.05 (dd, *J* = 14.1, 7.1 Hz, 2H), 1.91-1.79 (m, 2H), 1.75-1.63 (m, 3H), 1.60-1.52 (m, 2H), 1.48-1.39 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 114.6, 80.2, 77.5, 77.2, 76.8, 43.7, 34.2, 33.8, 30.8, 28.5, 27.1, 26.9, 13.3; IR (neat) 3442, 2935, 2859, 1690, 1367, 1174, 1098, 964, 874 cm^{-1}; HRMS (EIS) calcd. for $C_{15}H_{27}NO_3Na$ $[M+Na]^+$ 292.1883, found 292.1883.

dimethyl (2-oxopentyl)phosphonate (15)



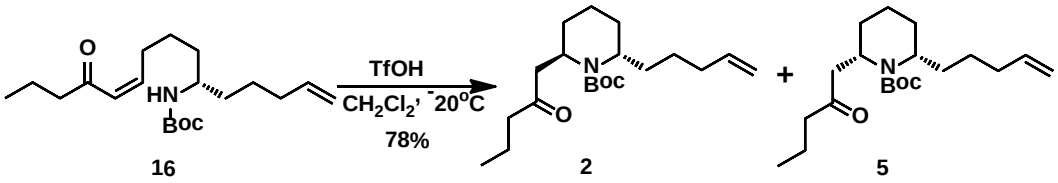
To a stirred solution of diisopropylamine (2.0 equiv) in THF (120 mL) and cooled to 0 ºC, n-BuLi (2.0 equiv) was added slowly to the mixture at 0 ºC. The mixture was cooled to -78 ºC after stirred at 0 ºC for 0.5 h and the Dimethyl methylphosphonate **S1** (10 g, 80.59 mmol, 8.8 mL) was added dropwise at -78 ºC. After 30 min, methyl butyrate **S2** (27.5 mmol, 241.78 mmol, 3.0 equiv) was added and stirred at -78 ºC for 1 h. The mixture was warmed to room temperature and quenched with NH_4Cl. The product was then extracted with EtOAc (3 x 60 mL) and washed with water (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The title compound **15** was obtained as a clear oil (12.52 g, 80% yield) after SiO_2 flash chromatography (EtOAc/hexane = 1:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (d, *J* = 11.2 Hz, 6H), 2.98 (d, *J* = 22.7 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.55-1.42 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 77.5, 77.2, 76.8, 52.3, 52.2, 45.2, 41.1, 39.9, 16.2, 12.8.

(S,Z)-tert-butyl (12-oxopentadeca-1,10-dien-6-yl)carbamate (16)[4]



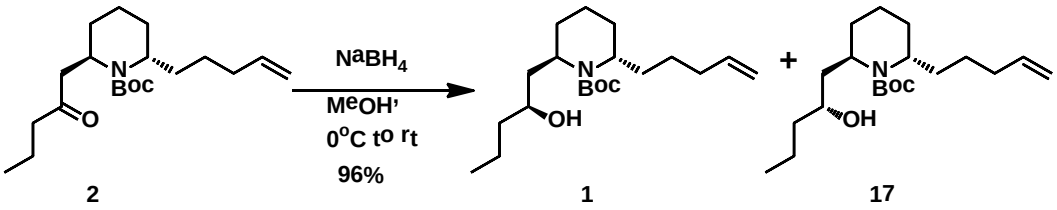
To a flame-dried flask was added anhydrous THF (220 mL) and the flask was purged with N_2. Sodium hydride (0.88 g, 25 mmol, 2.0 equiv, 60% in mineral oil) was added to the flask followed by **15** (4.3 g, 22 mmol, 2.0 equiv) at 0 ºC . The mixture was stirred for 1 h at room temperature. To this solution was added **14** (2.96 g, 10.99 mmol, 1.0 equiv) in THF (30 mL). The reaction was stirred for 2.5 h at room temperature and quenched with saturated NH_4Cl (40 mL). The product was then extracted with EtOAc (3 x 100 mL) and washed with brine (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The title compound **16** was obtained as a colourless oil (3.03 g, 82% yield) after SiO_2 flash chromatography (EtOAc/hexane = 1:9): $[\alpha]_D^{25}$ = +0.6 (c 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75-6.64 (m, 1H), 5.98 (d, *J* = 15.9 Hz, 1H), 5.69-5.63 (m, 1H), 4.85 (dd, *J* = 21.9, 13.7 Hz, 2H), 4.41 (d, *J* = 9.2 Hz, 1H), 3.46 (s, 1H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.18-2.03 (m, 2H), 1.99-1.88 (m, 2H), 1.57-1.45 (m,2H), 1.38 -1.20 (m, 16H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 155.7, 146.6, 138.4, 130.4, 114.5, 78.7, 77.5, 77.2, 76.8, 50.0, 41.9, 35.1, 34.9, 33.4, 32.1, 28.3, 25.1, 24.4, 17.6, 13.7; IR (neat) 2932, 2856, 1695, 1362, 1247, 1171, 992, 907 cm^{-1}; HRMS (EIS) calcd. for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$ 360.2509, found 360.2506.

(2R,6S)-tert-butyl 2-(2-oxopentyl)-6-(pent-4-en-1-yl)piperidine-1-carboxylate (2)[5]



To an oven dried flask equipped with magnetic stir bar was dissolved **16** (182 mg, 0.54 mmol) in dry dichloromethane (0.1 M) under argon atmosphere. The solution was kept at low the temperature (-20 ºC) for 10 minutes before 0.4 mL of TfOH solution (CH_2Cl_2, 0.2 M, 1.0 equiv.) was added . The reaction mixture was stirred for 5 hours until TLC indicated the complete consumption of the starting material and 0.1 mL of triethylamine (1.0 equiv) was added in the reaction mixture before warming up to room temperature. The reaction mixture was then filtered through a pad of celite using diethyl ether to remove the catalyst. The resulting filtrate was condensed in vacuo to provide the crude residue. Purification using flash silica gel chromatography (EtOAc/hexane = 1:9) provided 141 mg (78% yield) of the intramolecular aza-Michael product **2**. The ratio of diastereomers (cis/trans) was 14:86, based on the NMR integration. **2**: $[\alpha]_D^{25}$ = +4.85 (c 1.00, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.86-5.70 (m, 1H), 4.97-4.87 (m, 2H), 4.05 (dd, *J* = 8.7, 4.4 Hz, 1H), 3.83 (d, *J* = 30.0 Hz, 1H), 2.38-2.32 (m, 1H), 2.44-2.36 (m, 2H), 2.01 (dd, *J* = 14.1, 6.9 Hz, 2H), 1.77-1.33 (m, 23H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 155.3, 138.8, 138.6, 114.5, 79.2, 77.5, 77.2, 76.8, 52.6, 47.6, 47.5, 44.90, 33.6, 32.8, 28.5, 26.2, 25.0, 17.2, 15.5, 13.8; IR (neat) 2935, 2867, 1687, 1363, 1171, 1062, 905, 731 cm^{-1}; HRMS (EIS) calcd. for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$ 360.2509, found 360.2510.

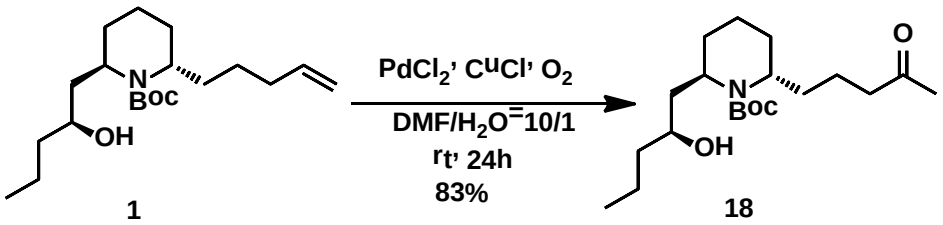
2-((S)-2-hydroxypentyl)-6-(pent-4-en-1-yl)piperidine-1-carboxylate (1)



Sodium borohydride (0.57 g, 15.16 mmol) was added to a solution of **2** (1.42 g, 4.21 mmol) in methanol (21 mL) at 0 ºC, and the mixture was stirred for 0.5 h at room temperature. The resulting mixture was diluted with saturated NH_4Cl (10 mL). and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane = 1:20) to obtain **1** (1.116 g, 78% yield) as a colorless oil and **17** (0.254 g, 18% yield) as a oil. **1**: $[\alpha]_D^{25}$ = +21.05 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.64 (m, 1H), 4.89 (dd, *J* = 21.7, 13.7 Hz, 2H), 3.84-3.82 (m, 1H), 3.60 (dd, *J* = 8.5, 4.3 Hz, 1H), 3.51-3.39 (m, 1H), 1.96 (dd, *J* = 14.0, 7.1 Hz, 2H), 1.76-1.49 (m, 9H), 1.42-1.22 (m, 16H), 0.83 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 138.5, 114.4, 79.5, 77.5, 77.2, 76.8, 69.6, 51.9, 49.3, 43.6, 40.0, 33.7, 33.6, 28.4, 27.6, 26.4, 25.1, 23.7, 18.8, 14.0, 13.6; IR (neat) 3439, 2935, 2870, 1662, 1398, 1362, 1255, 1174, 1072, 907 cm^{-1}; HRMS (EIS) calcd. for $C_{20}H_{37}NO_3Na$ $[M+Na]^+$ 362.2666, found 362.2664.

17: $[\alpha]_D^{25}$ = +22.20 (c 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83-5.73(m, 1H), 5.03-4.88 (m, 2H), 4.16 (dd, *J* = 7.7, 3.6 Hz, 1H), 3.54 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.52-3.42 (m, 1H), 2.04 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.92-1.79 (m, 1H), 1.75-1.56 (m, 7H), 1.47 (d, *J* = 17.3 Hz, 12H), 1.40 -1.30 (m, 5H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.14, 138.7, 114.8, 80.0, 77.5, 76.2, 76.8, 67.2, 52.3, 48.0, 43.8, 39.1, 34.0, 33.8, 28.6, 26.8, 26.2, 22.9, 19.3, 14.2, 13.8; IR (neat) 3450, 2935, 2870, 1659, 1457, 1398,136 4, 1174, 1107, 905, 776 cm^{-1} ; HRMS (EIS) calcd. for $C_{20}H_{37}NO_3Na$ $[M+Na]^+$ 362.2666, found 362.2665.

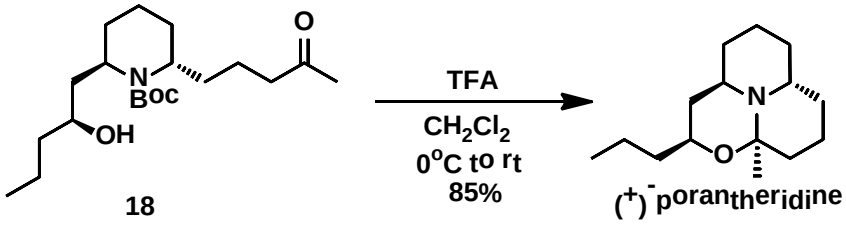
(2R,6R)-tert-butyl2-((S)-2-hydroxypentyl)-6-(4-oxopentyl)piperidine-1-Carboxy-late (18)



A solution of compound **1** (0.85 g, 2.50 mmol) in a 10:1 DMF/H_2O mixture (55 mL) was treated with $PdCl_2$ (177 mg, 1.0 mmol) and CuCl (1.24 g, 12.5 mmol). The reaction mixture was then stirred under O_2 at room temperature for 24 h. The resulting mixture was filtered through Celite, then extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford the crude product which was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) afforded ketone **18** (0.74 g, 83%) : $[\alpha]_D^{25}$ = +21.20 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91-3.88 (brs, 1H), 3.71-3.69 (brs, 1H), 3.58-3.56 (brs, 1H), 2.44-2.43 (m, 2H), 2.13 (s, 3H), 1.80-1.73 (m, 2H), 1.72-1.66 (m, 2H), 1.65-1.33 (m,12H), 1.45 (s, 9H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 155.3, 79.1, 77.5, 77.2, 76.8, 69.0, 51.5, 48.9, 42.9, 39.7, 33.1, 29.4, 28.1, 24.7, 23.6, 20.8, 18.5, 13.7; IR (neat)

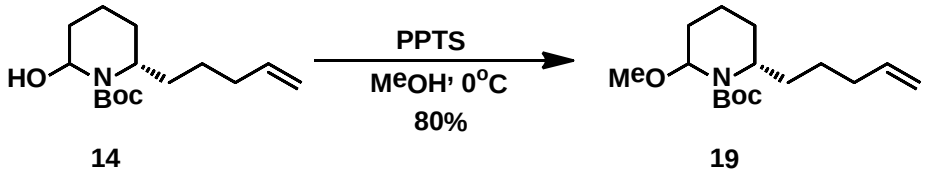
2935, 2870, 1718,1659, 1457, 1364, 1168, 1076, 871, 773 cm^{-1} HRMS (EIS) calcd. for $C_{20}H_{37}NO_4Na$ $[M+Na]^+$ 378.2615, found 378.2616.

(+)-porantheridine



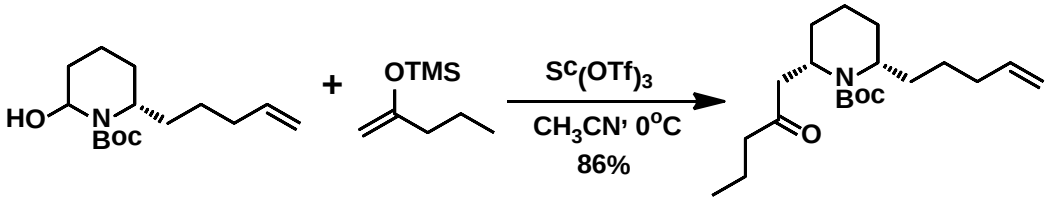
Trifluoroacetic acid (1.24 mL) was added to a solution of compound **18** (62 mg, 0.17 mmol) in CH_2Cl_2 (11 mL) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 2 h. The volatiles were evaporated, and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous lawyer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude product which was purified by flash chromatography ($MeOH/CH_2Cl_2$ = 1:10) to give product **(+)-porantheridine** (35 mg, 85%) as a oil: $[\alpha]_D^{25}$ = +25 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.05-3.85 (m, 1H), 3.64-3.60 (m, 1H), 3.05-2.85 (m, 1H), 1.90-1.52 (m, 5H), 1.49-1.08 (m, 16H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.1, 77.5, 77.2, 76.8, 69.1, 49.3, 48.3, 40.0, 39.2, 34.2, 34.1, 30.8, 27.3, 23.7, 19.8, 19.4, 18.0, 14.3; IR (neat) 2929, 2864, 1628, 1440, 1376, 1255, 1126, 1050, 913, 787, 731 cm^{-1}; HRMS (EIS) calcd. for $C_{15}H_{28}NO$ $[M+H]^+$ 238.2165, found 238.2164.

(6S)-tert-butyl 2-methoxy-6-(pent-4-en-1-yl)piperidine-1-carboxylate (19)



PPTS(0.33 g, 1.3 mmol) was added to the solution of **14** (1.75 g, 6.50 mmol) in MeOH (31 mL) at0 ºC and then stirred for 0.5 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **19** (1.84 g, 80% yield) as a colorless oil.

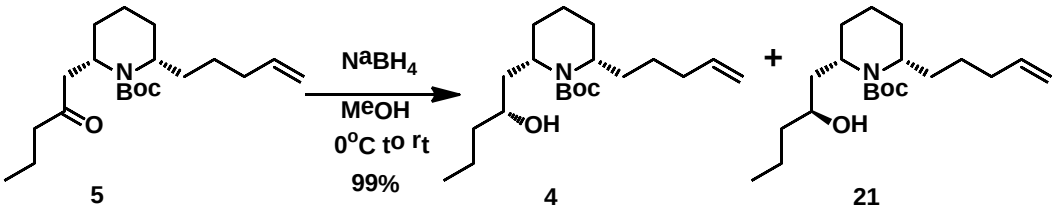
(2S,6S)-tert-butyl 2-(2-oxopentyl)-6-(pent-4-en-1-yl)piperidine-1-carboxylate (5)[6]



To a suspension of $Sc(OTf)_3$ (35 mg, 0.08 mmol) was added a mixture of **19** (0.1 g, 0.35 mmol) and silyl enolate **20** (3.0 equiv, 1.06 mmol) in CH_3CN (1.8 mL) at 0 ºC. The mixture was stirred at 0 ºC for 1 h. Saturated aqueous sodium hydrogen carbonate was then added to quench the reaction,

and aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The product was isolated by silica gel column chromatography to afford product **5** (102 mg, 86% yield): $[\alpha]_D^{25}$ = +32.80 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.71 (m, 1H), 4.98 (dd, *J* = 21.6, 13.7 Hz, 2H), 4.62-4.54 (m, 1H), 4.13-4.01 (m, 1H), 2.72-2.61 (m, 1H), 2.54-2.45 (m, 1H), 2.45-2.37 (m, 2H), 2.07 (dd, *J* = 13.2, 6.4 Hz, 2H), 1.69-1.35 (m, 22H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 155.1, 138.6, 114.6, 79.4, 77.5, 77.2, 76.8, 50.1, 47.4, 46.1, 44.7, 34.0, 38.6, 33.9, 33.4 (m), 28.4, 28.0, 27.3, 26.7, 17.1, 14.0, 13.7; IR (neat) 2932, 2864., 1659, 1401, 1252, 1171, 1098 cm^{-1}; HRMS (EIS) calcd. for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$ 360.2509, found 360.2511.

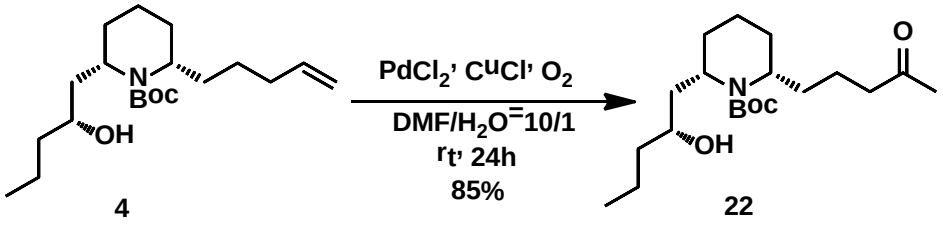
(2S,6S)-tert-butyl2-((R)-2-hydroxypentyl)-6-(pent-4-en-1-yl)piperidine-1-carboxlate (4)



Sodium borohydride (0.51 g, 13.36 mmol) was added to a solution of **5** (1.25 g, 3.71 mmol) in methanol (21 mL) at 0 ºC, and the mixture was stirred for 0.5 h at room temperature. The resulting mixture was diluted with saturated NH_4Cl (10 mL). and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane = 1:20) to obtain **4** (1.025 g, 82% yield) as a colorless oil and **21** (0.213 g, 17% yield) as a oil. **4**: $[\alpha]_D^{25}$ = -23.17 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71-5.54 (m, 1H), 4.82 (dd, *J* = 22.0, 13.7 Hz, 2H), 4.12-4.03 (m, 2H), 3.95-3.85 (m, 1H), 3.40-3.27 (m, 1H), 1.96-1.86 (m, 2H), 1.59 (d, *J* = 9.2 Hz, 1H), 1.51-1.20 (m, 24H), 0.77 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 138.3, 114.4, 79.3, 77.5, 77.2, 76.8, 69.4, 50.2, 47.5, 43.7, 39.9, 33.9, 33.4, 28.2, 27.4, 26.4, 18.7, 13.9; IR (neat) 3436, 2935, 2864, 1659, 1454, 1364, 1325, 1171, 1081, 910 cm^{-1}; HRMS (EIS) calcd. for $C_{20}H_{37}NO_3Na$ $[M+Na]^+$ 362.2666, found 362.2665.

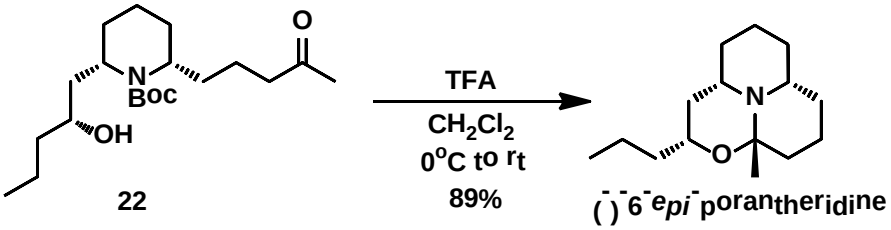
21: $[\alpha]_D^{25}$ = -12.25 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80-5.68 (m, 1H), 4.98 (dd, *J* = 21.6, 13.7 Hz, 2H), 4.74-4.59 (m, 1H), 4.46-4.32 (m, 1H), 4.09-3.99 (m, 1H), 3.46-3.34(m, 1H), 2.02 (q, *J* = 6.3, 5.5 Hz, 2H), 1.82 (t, *J* = 13.0 Hz, 1H), 1.62-1.17 (m, 26H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 138.4, 114.8, 80.2, 77.5, 77.2, 76.8, 67.3, 50.7, 46.3, 43.5, 38.9, 34.4, 33.7, 30.2, 28.5, 27.9, 27.0, 19.2, 14.7, 14.1; IR (neat) 34445, 2932, 2864, 1664,1406, 1171, 1101, 1073 cm^{-1}; HRMS (EIS) calcd. for $C_{20}H_{37}NO_3Na$ $[M+Na]^+$ 362.2666, found 362.2665.

(2S,6R)-tert-butyl2-((R)-2-hydroxypentyl)-6-(4-oxopentyl)piperidine-1-carboxylate (22)



A solution of compound **4** (135 mg, 0.40 mmol) in a 10:1 DMF/H_2O mixture (7.7 mL) was treated with $PdCl_2$ (29 mg, 0.16 mmol) and CuCl (198 mg, 2.0 mmol). The reaction mixture was then stirred under O_2 at room temperature for 24 h. The resulting mixture was filtered through Celite, then extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford the crude product which was purified by column chromatography on silica gel (EtOAc/hexane = 1:2) afforded ketone **22** (121 mg, 85%): $[\alpha]_D^{25}$ = -27.10 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.20-4.08 (m,1H), 4.05-3.86 (m, 1H), 3.52-3.33 (m, 1H), 2.46-2.34 (m, 2H), 2.07 (s, 3H), 1.61-1.30 (m, 25H), 0.86 (t, *J* = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 155.8, 79.7, 77.5, 77.2, 76.8, 69.7, 50.2, 47.7, 43.9, 43.3, 39.9, 34.0, 29.8, 29.6, 28.4, 27.5, 21.3, 18.9, 14.0; IR (neat) 3431, 2935, 2864, 1662, 1409, 1362, 1252, 1171, 1075 cm^{-1}; HRMS (EIS) calcd. for $C_{20}H_{37}NO4Na$ $[M+Na]^+$ 378.2615, found 378.2617.

(-)-6-*epi*-porantheridine



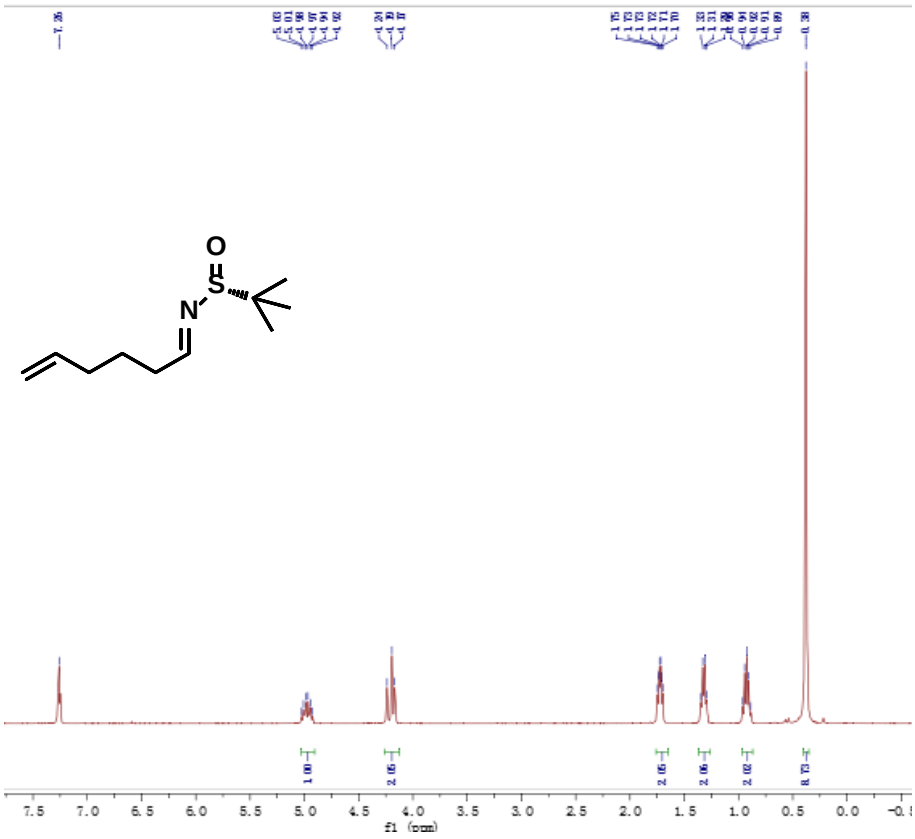
Trifluoroacetic acid (1.2 mL) was added to a solution of compound **22** (58 mg, 0.16 mmol) in CH_2Cl_2 (8 mL) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 2 h. The volatiles were evaporated, and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous lawyer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude product which was purified by flash chromatography (MeOH/CH_2Cl_2 = 1: 10) to give product **(-)-6-*epi*-porantheridine** (34 mg, 89%) as a oil: $[\alpha]_D^{25}$ = +6.0 (c 0.8, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80-3.70 (m, 1H), 2.56-2.39 (m, 1H), 2.15-2.06 (m, 1H), 1.65-1.15 (m, 25H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.2, 77.5, 77.2, 76.8, 67.6, 55.1, 51.7, 39.5, 39.1, 38.5, 34.3, 34.1, 33.7, 23.4, 20.7, 18.3, 14.0, 11.4; IR (neat) 2932, 2864, 1446, 1381, 1238, 1182, 1120, 1084, 731 cm^{-1}; HRMS (EIS) calcd. for $C_{15}H_{28}NO$ $[M+H]^+$ 238.2171, found 238.2165.

References

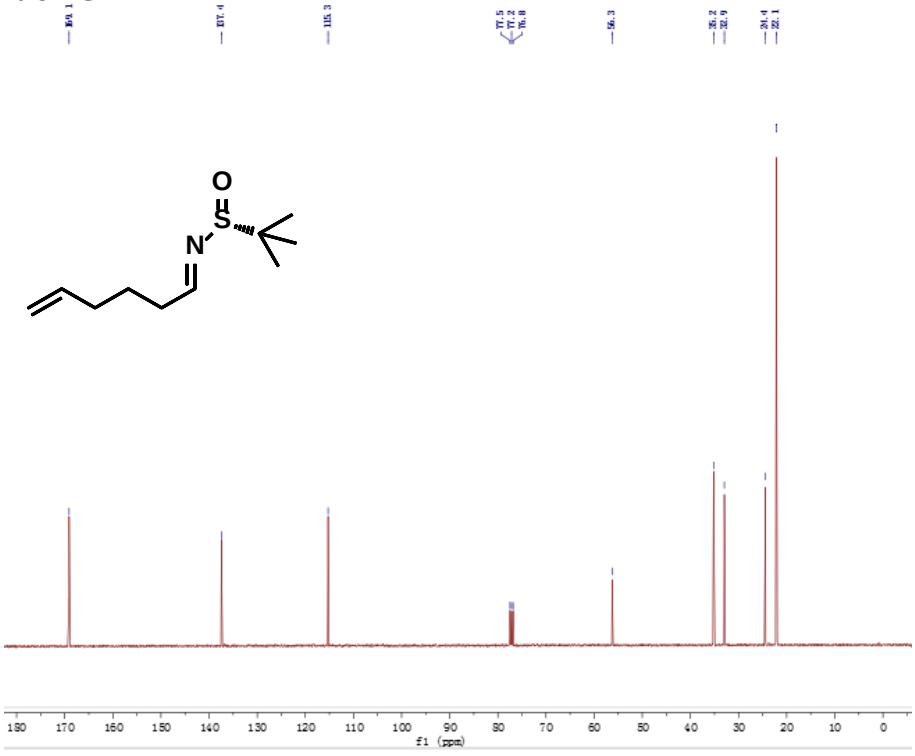
1. Y. L. Liu, J. W. Liu, Y. G. Huang and F.-L. Qing, *Chem. Commun.*, **2013**, *49*, 7492.
2. L. J. Baird, M. S. M. Timmer, P. H. Teesdale-Spittle and J. E. Harvey, *J. Org. Chem.*, **2009**, *74*, 2271.
3. A. Voituriez, F. Ferreira and F. Chemla, *J. Org. Chem.*, **2007**, *72*, 5358.
4. M. J. Niphakis, and G. I. Georg, *Org. Lett.*, **2011**, *13*, 196.
5. C. Zhong, Y.K. Wang, A. W. Hung, S. L. Schreiber and D. W. Young, *Org. Lett.*, **2011**, *13*,5556.
6. O. Okitsu, R. Suzuki and S. Kobayashi, *J. Org. Chem.*, **2001**, *66*, 809.

NMR Spectra

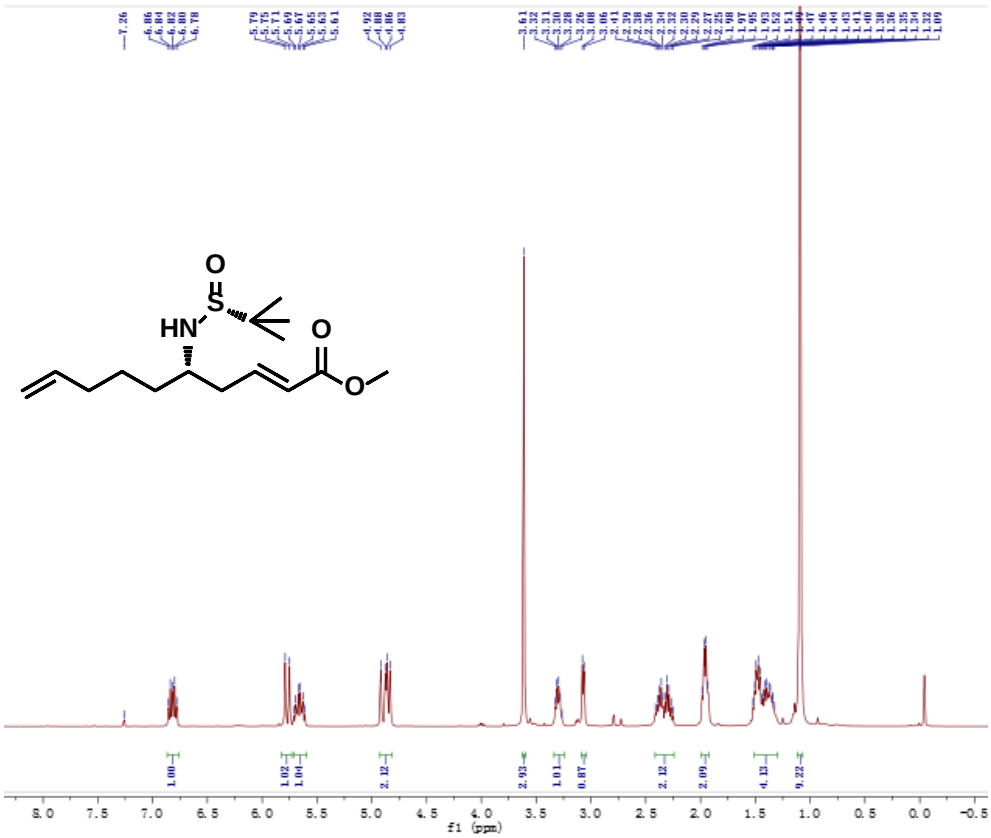
Compound **8**-^{1}H



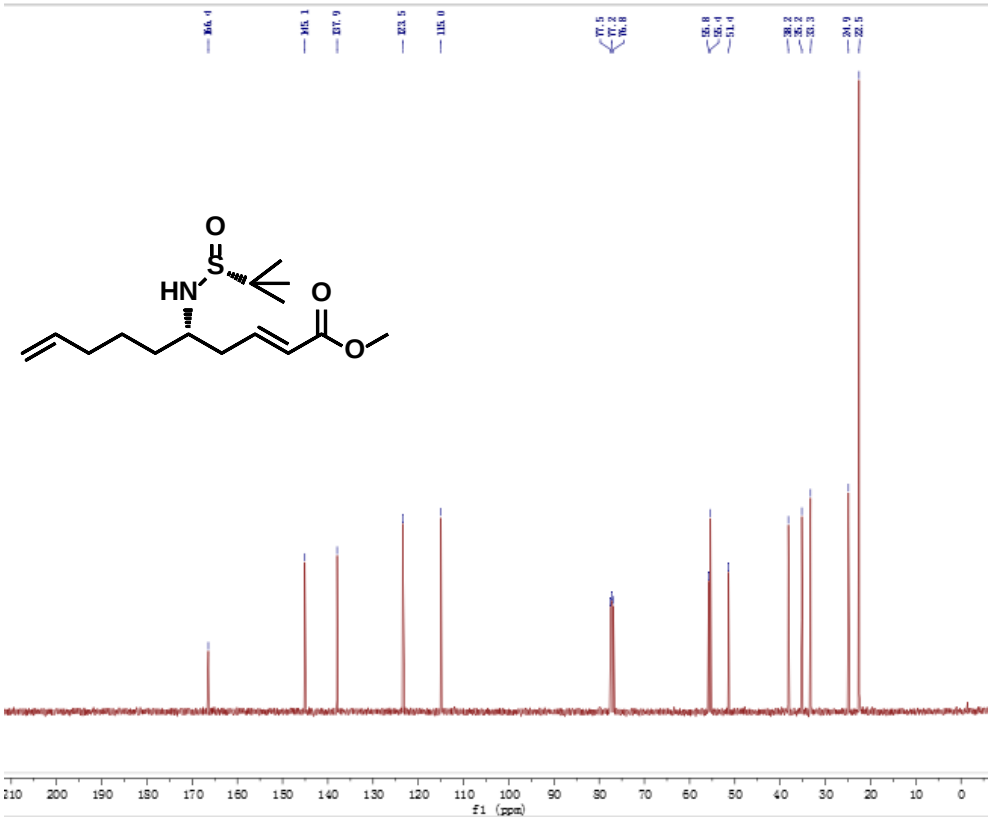
Compound **8**-^{13}C



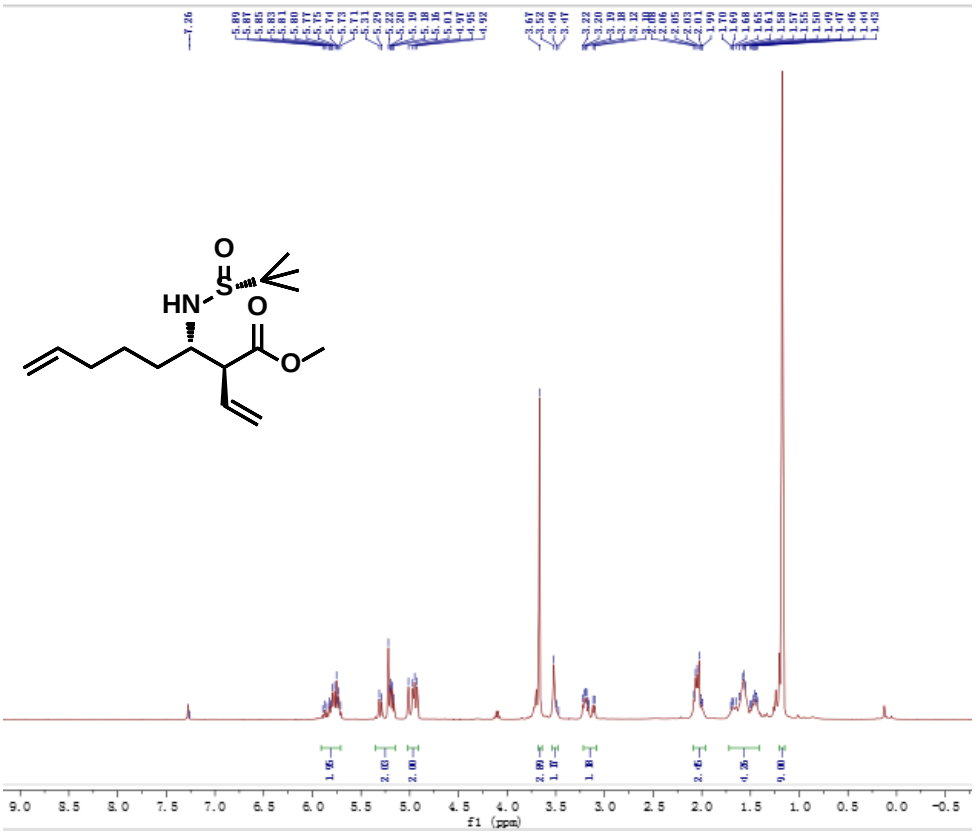
Compound **11**-^{1}H



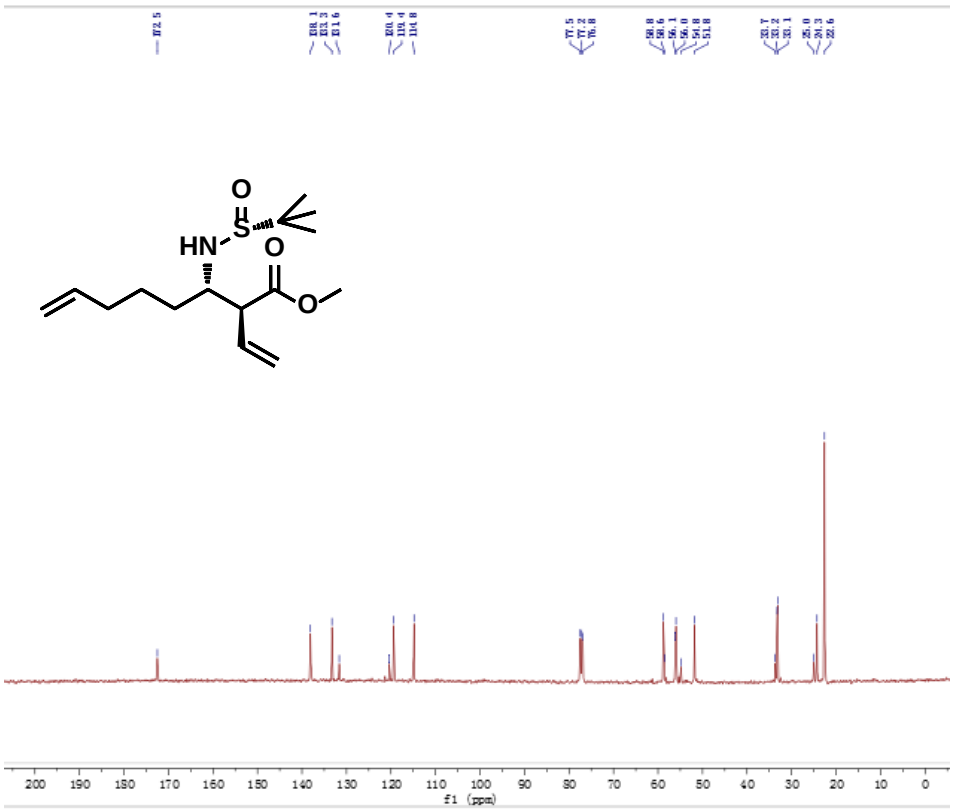
Compound **11**-^{13}C



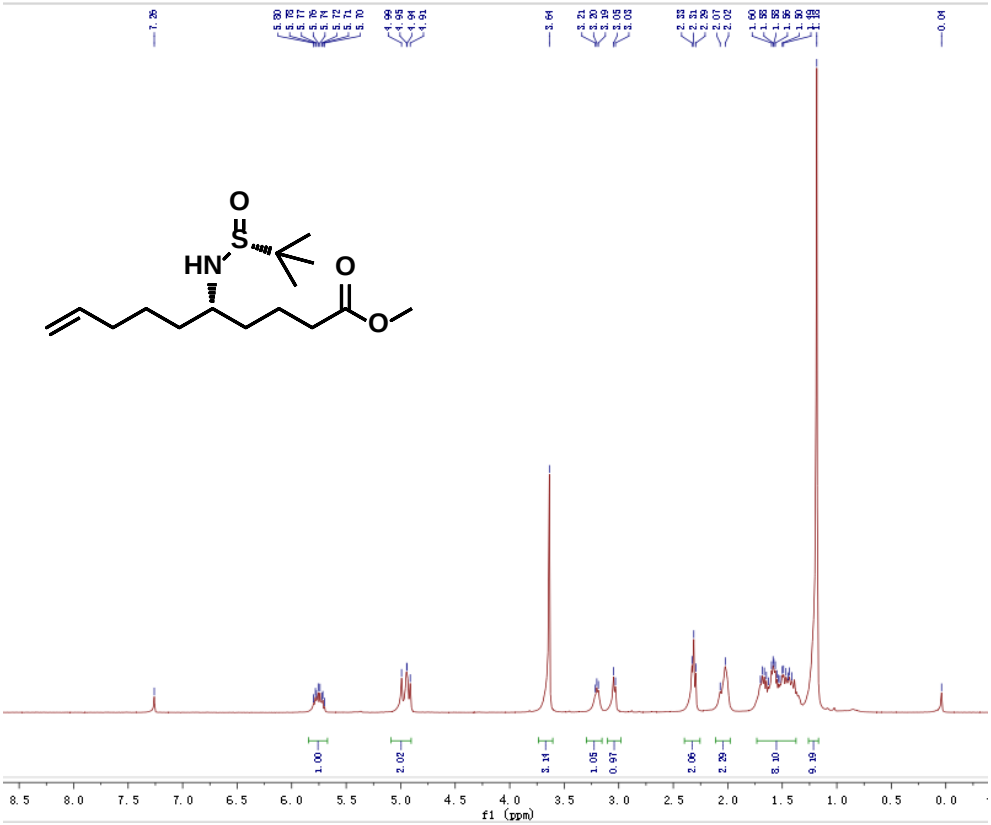
Compound **10**-^{1}H



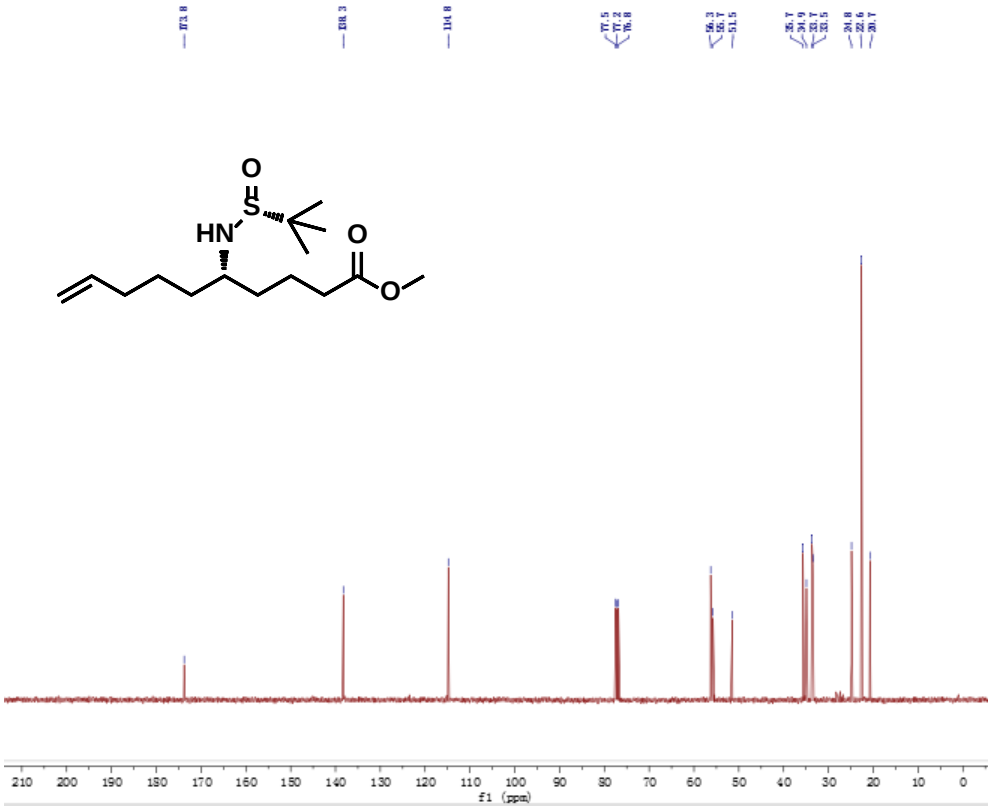
Compound **10**-^{13}C



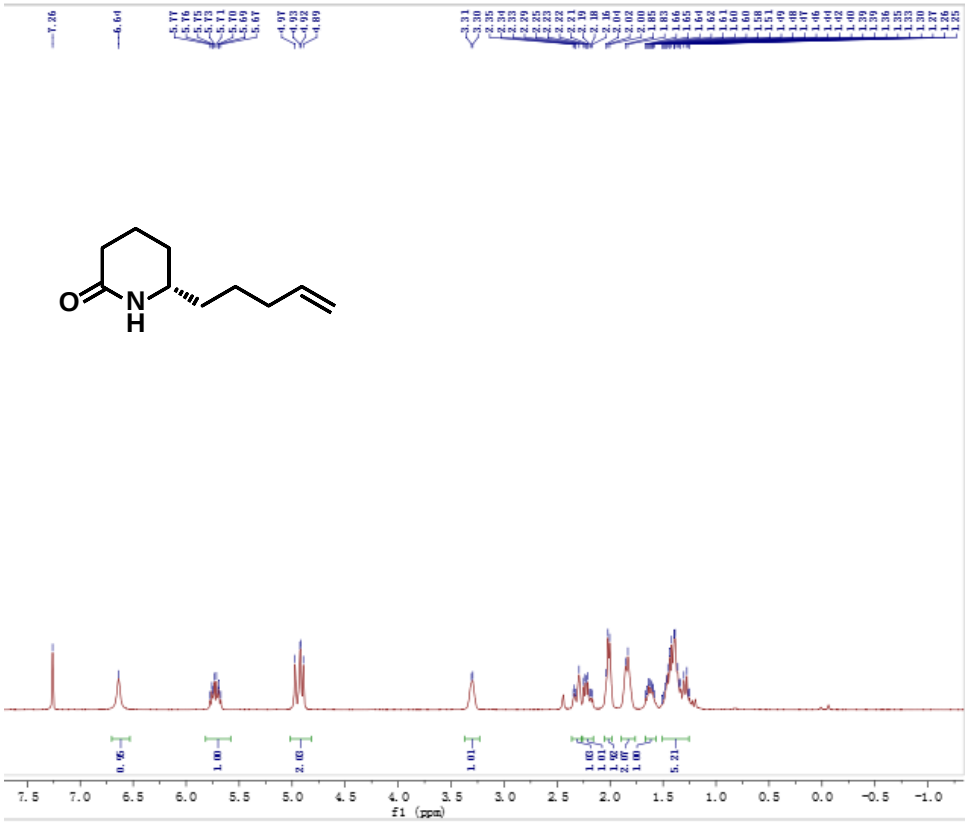
Compound **12**-^{1}H



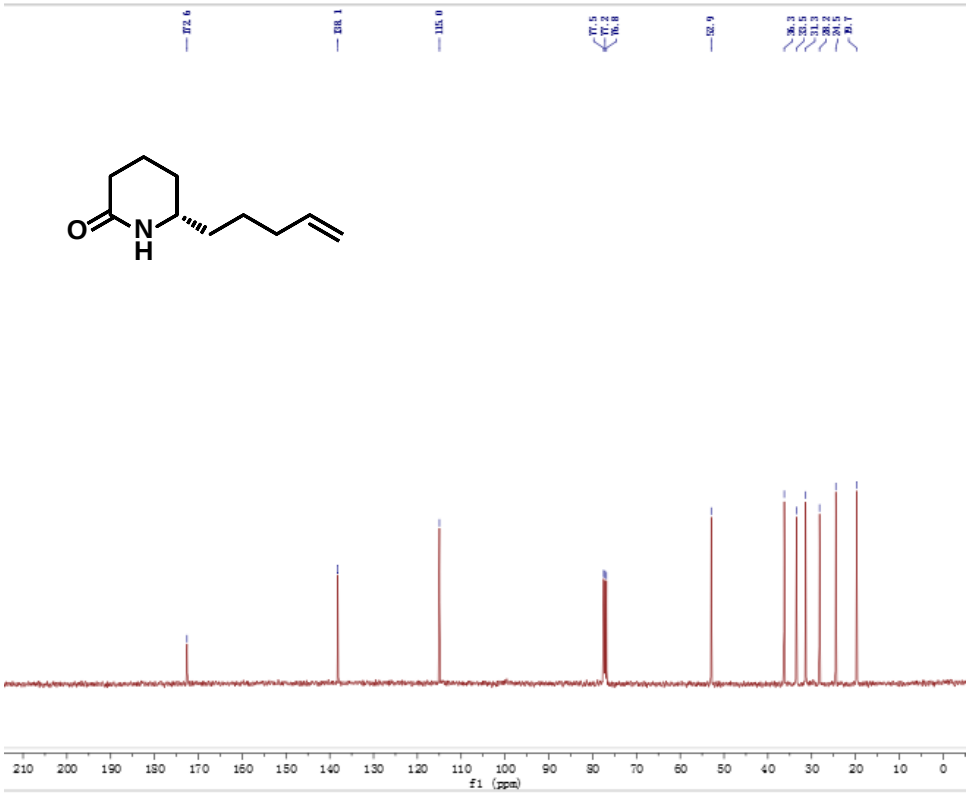
Compound **12**-^{13}C



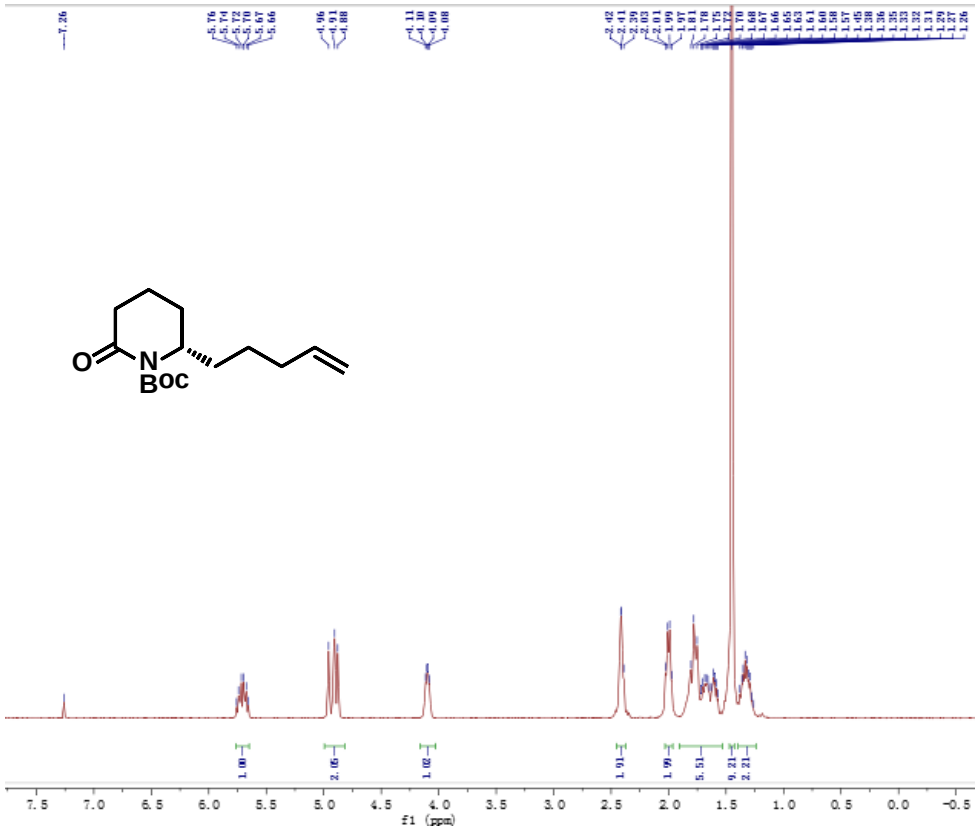
Compound **13**-^{1}H



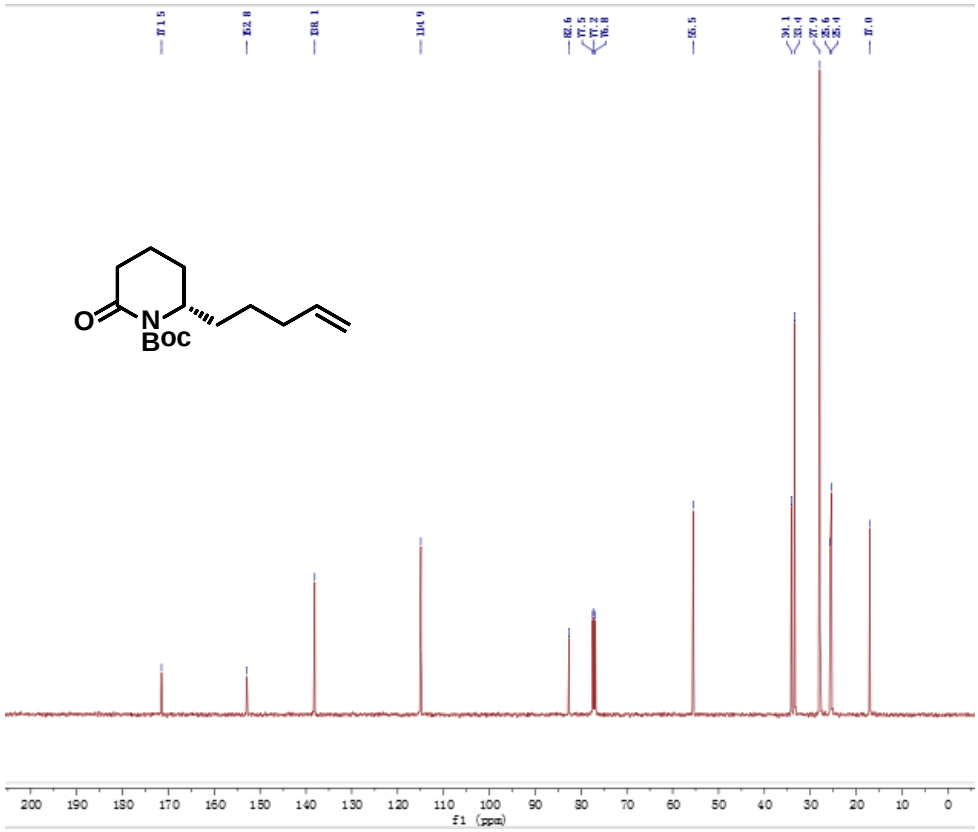
Compound **13**-^{13}C



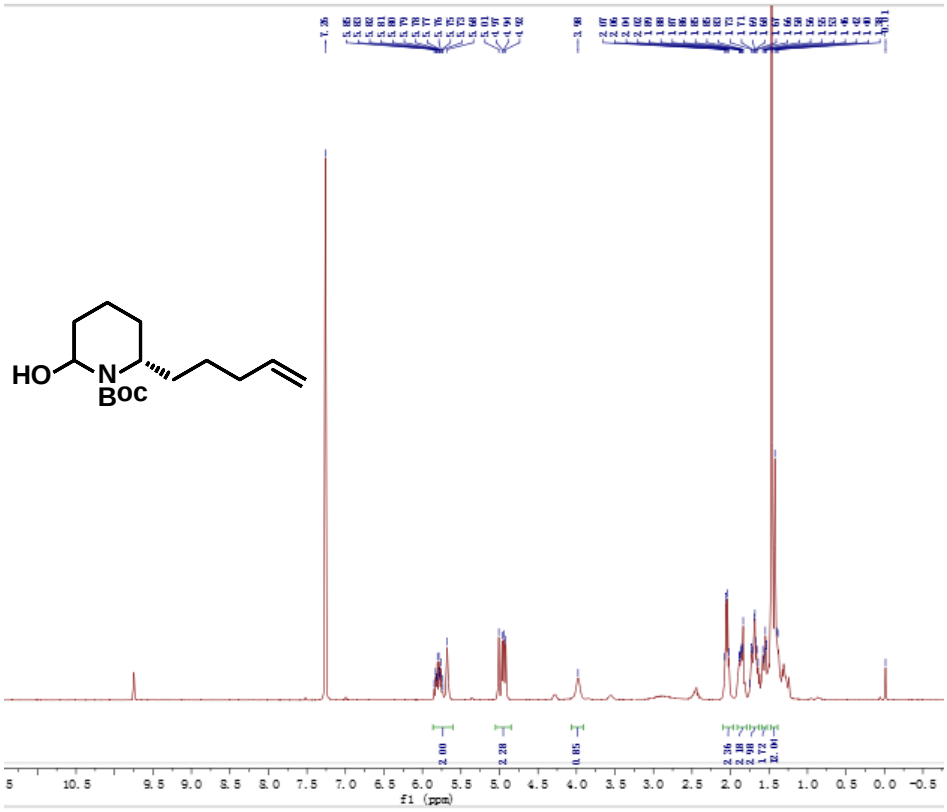
Compound **3**-^{1}H



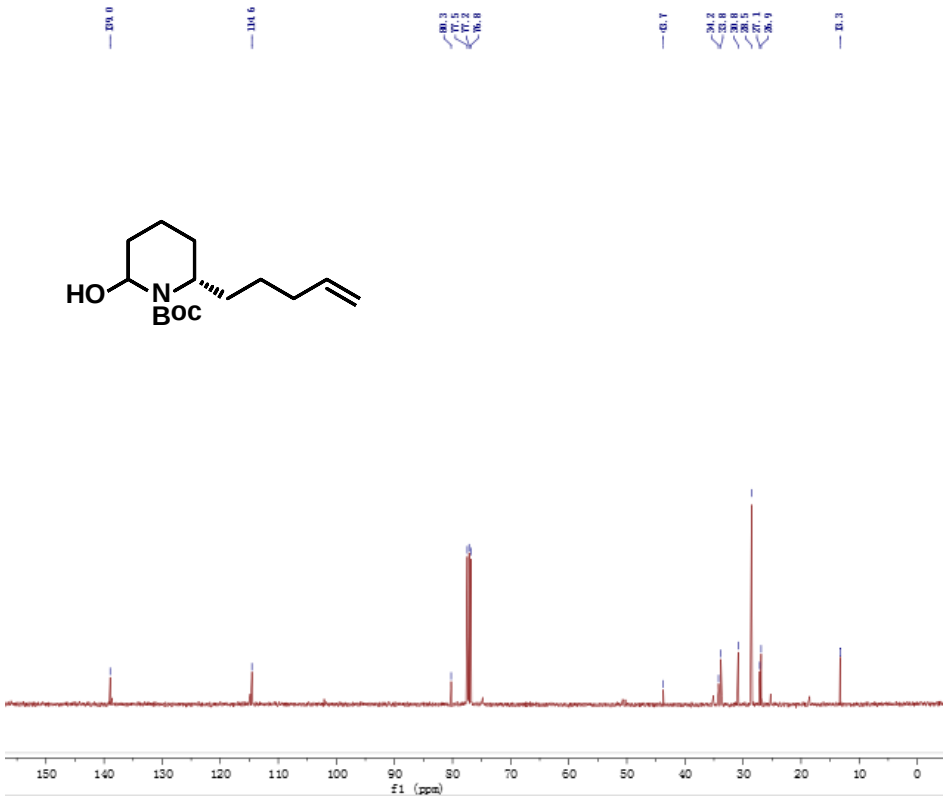
Compound **3**-^{13}C



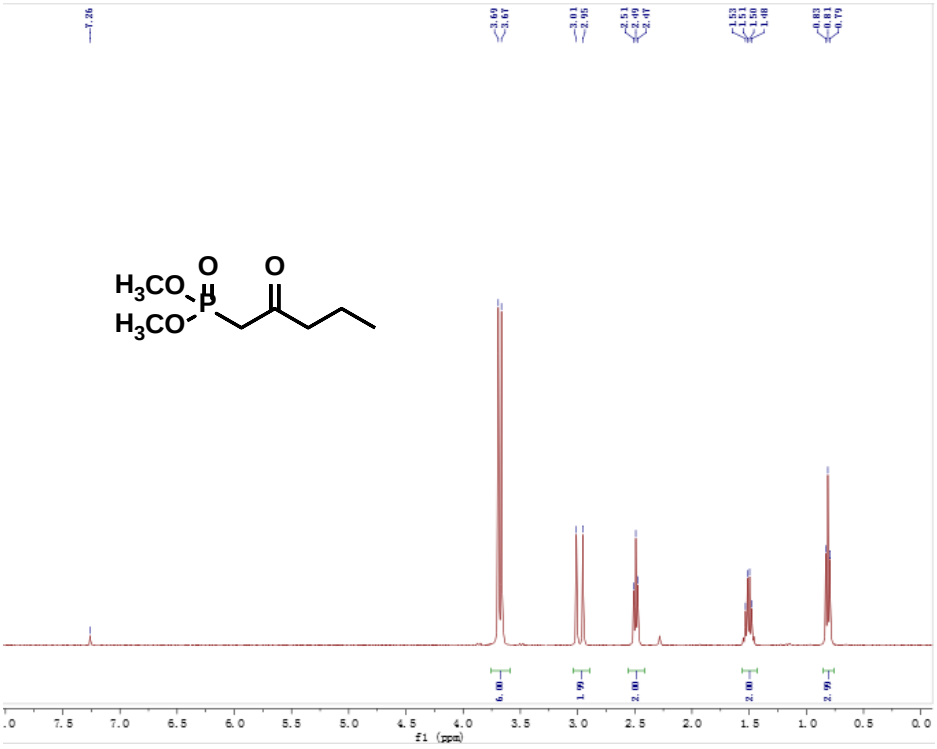
Compound **14**-^{1}H



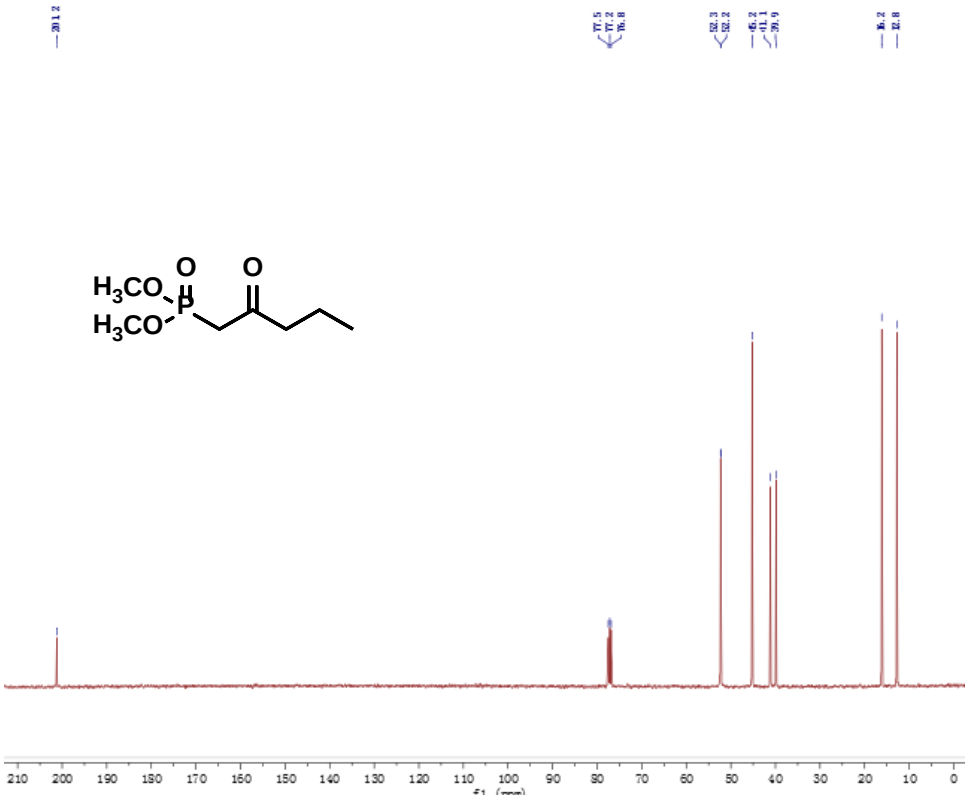
Compound **14**-^{13}C



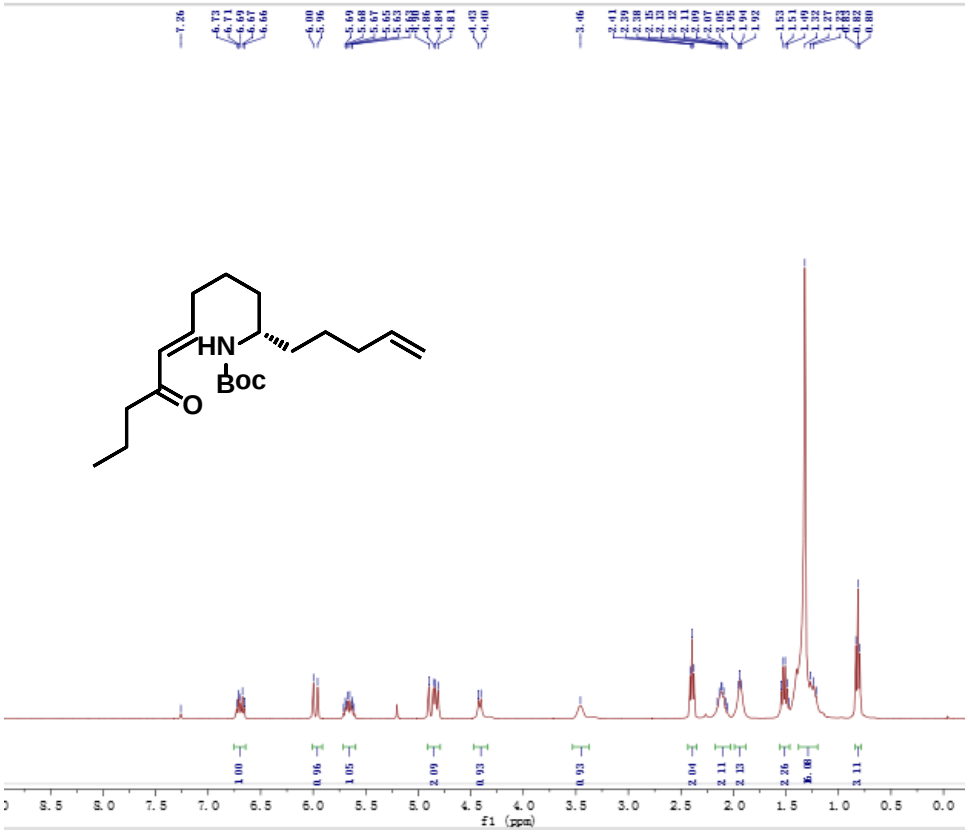
Compound **15**-^{1}H



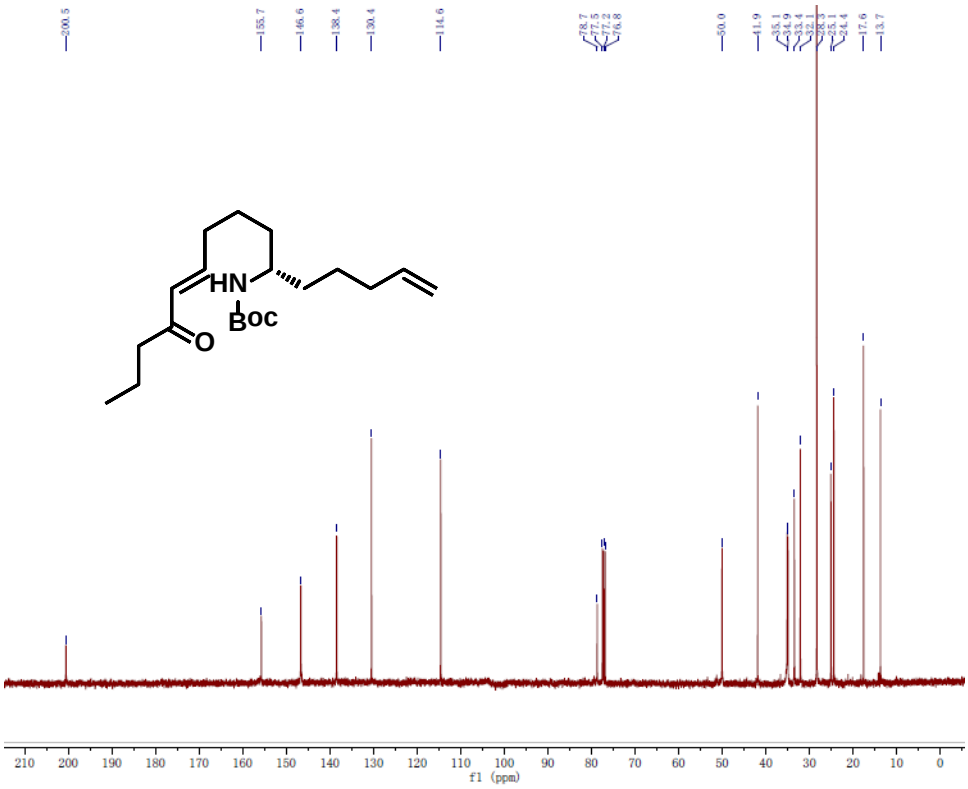
Compound **15**-^{13}C



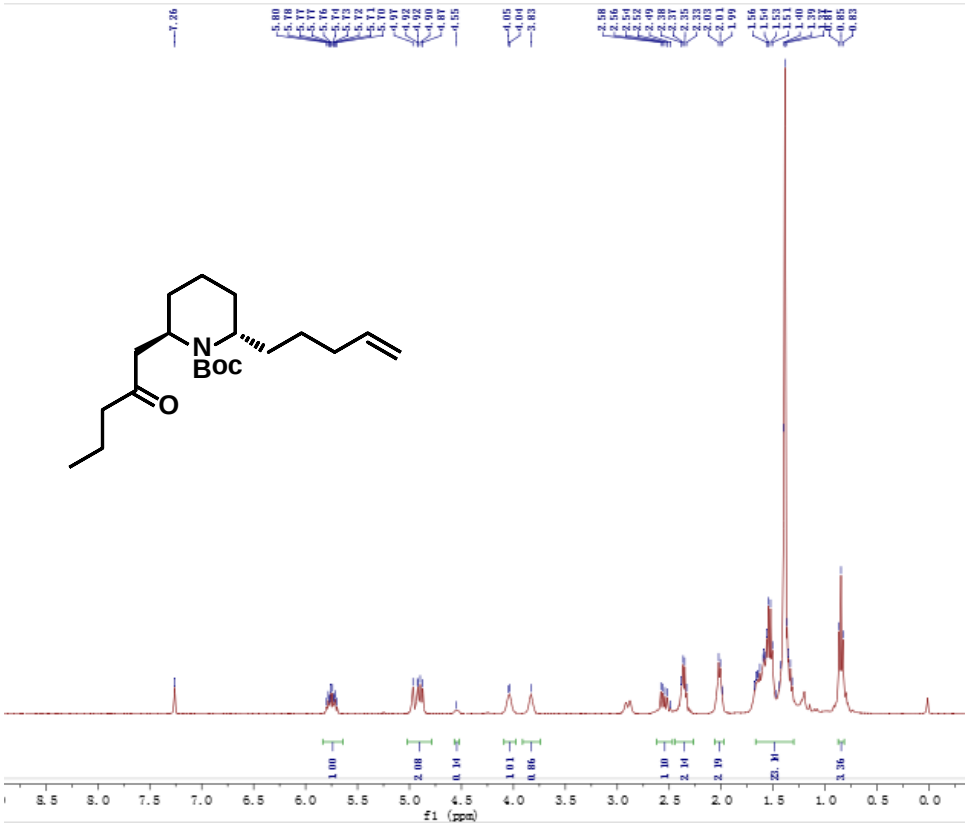
Compound **16**-^{1}H



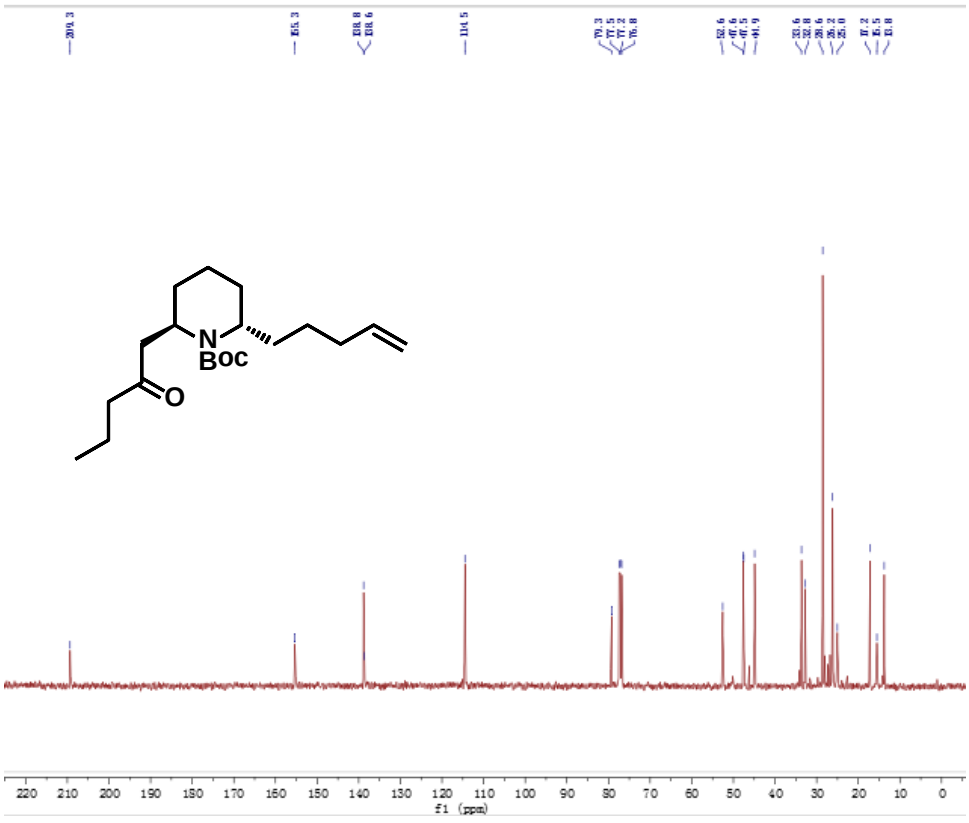
Compound **16**-^{13}C



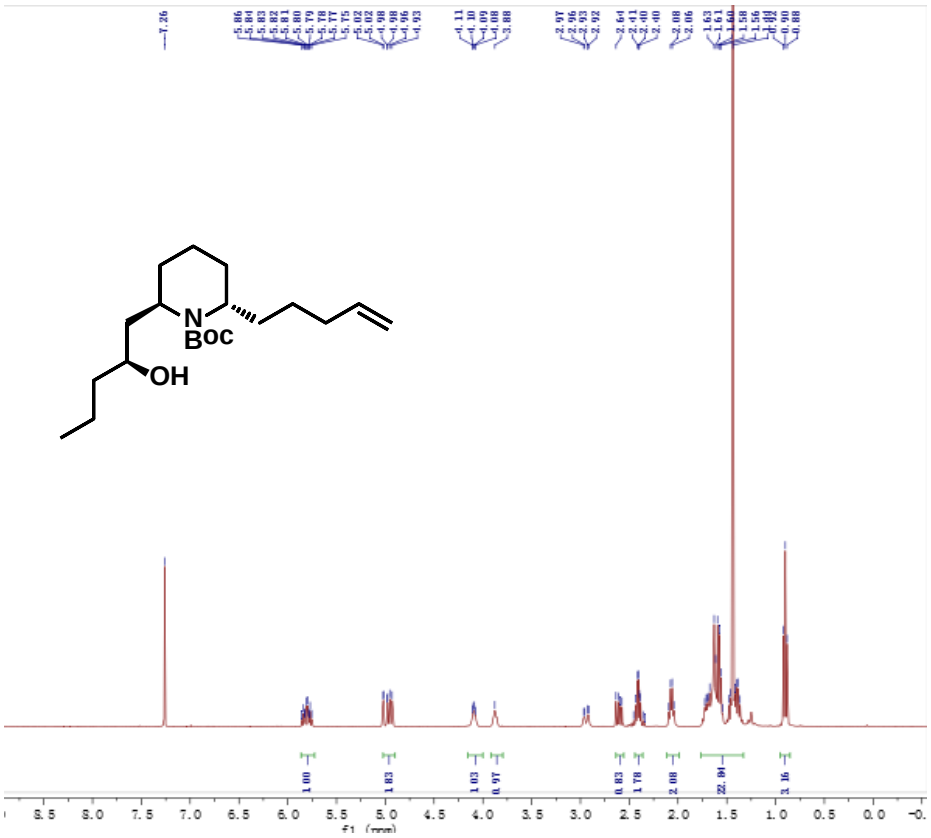
Compound **2**-^{1}H



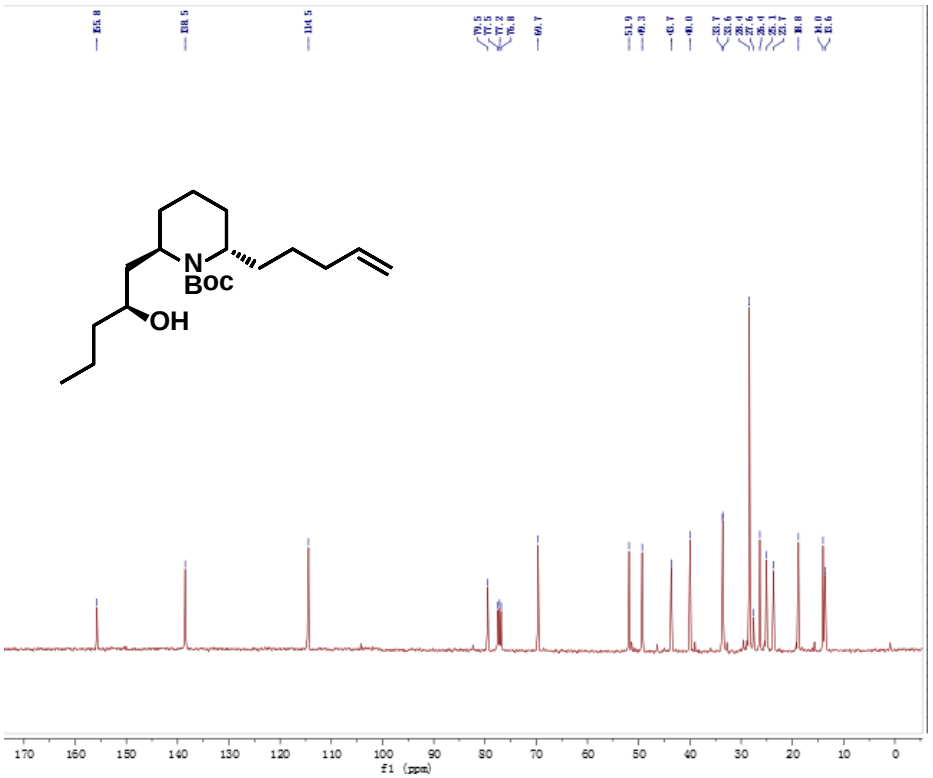
Compound **2**-^{13}C



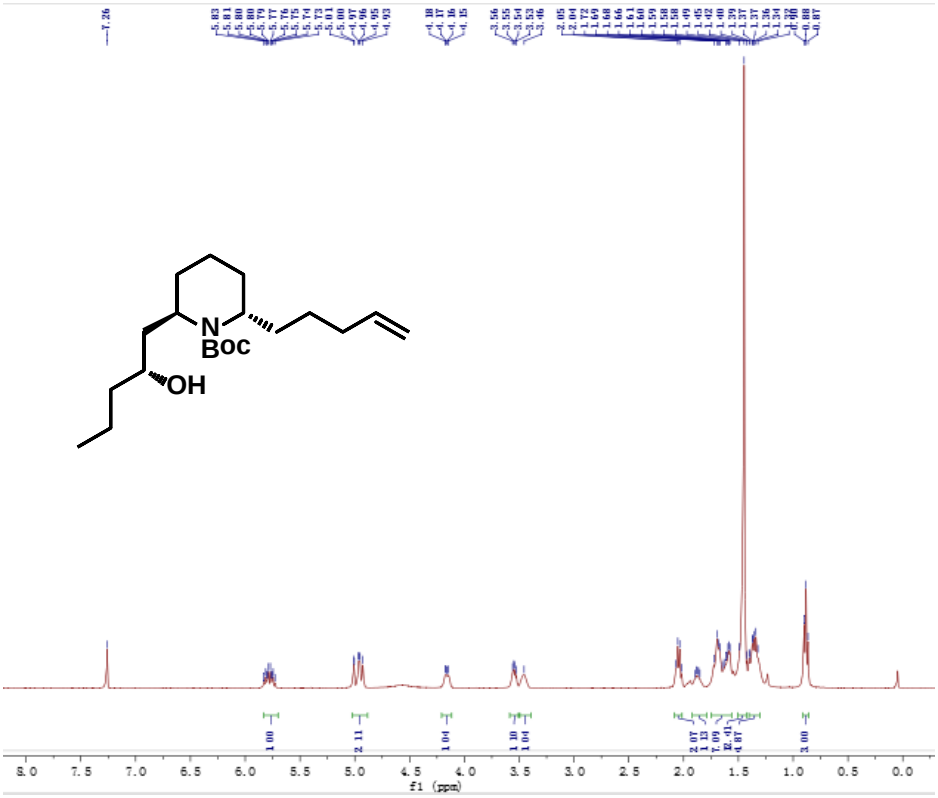
Compound **1**-^{1}H



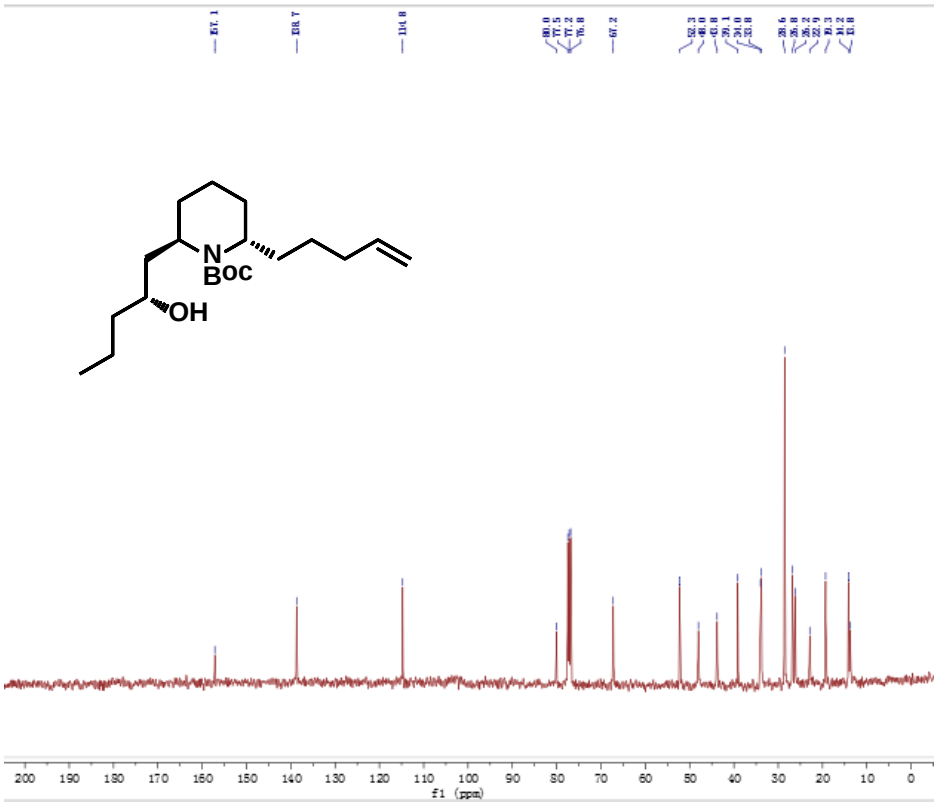
Compound **1**-^{13}C



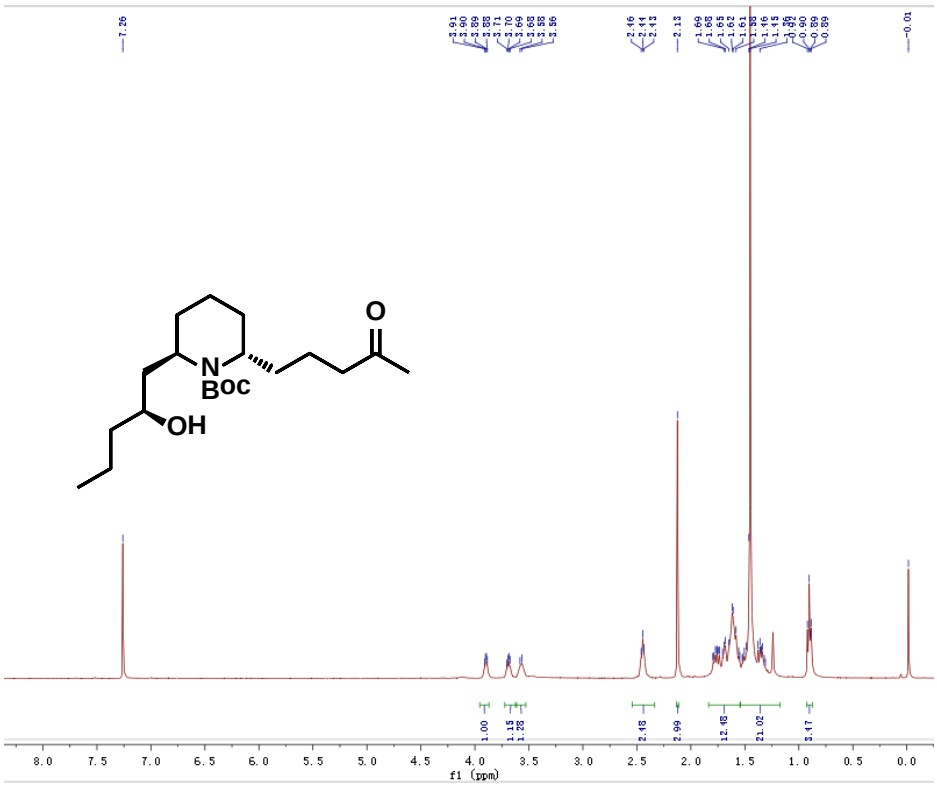
Compound **17**-^{1}H



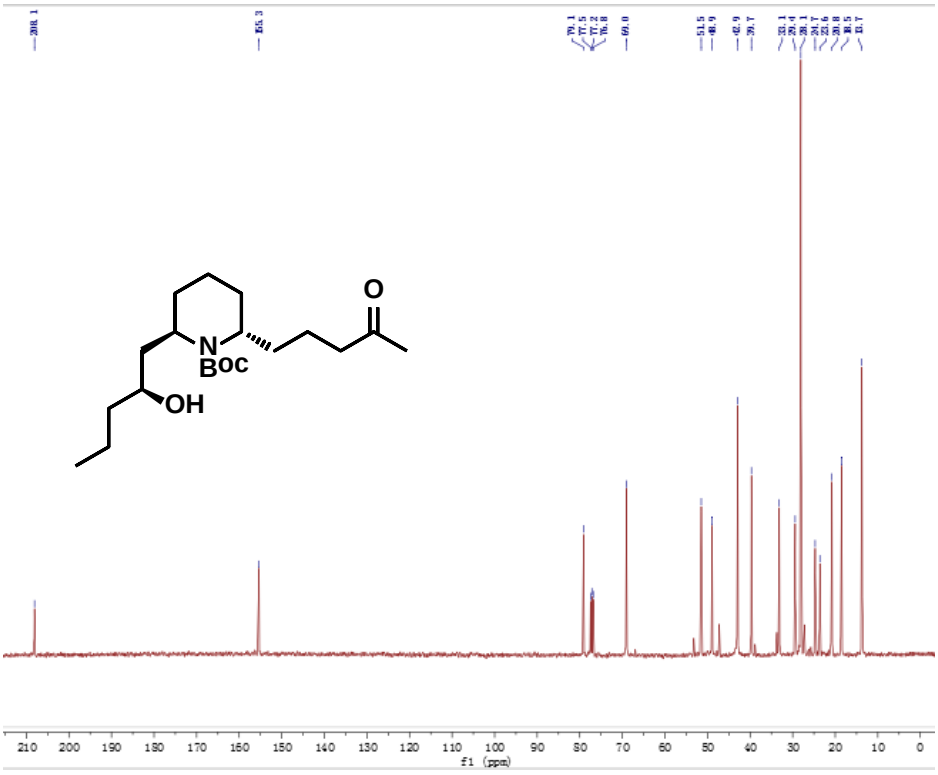
Compound **17**-^{13}C



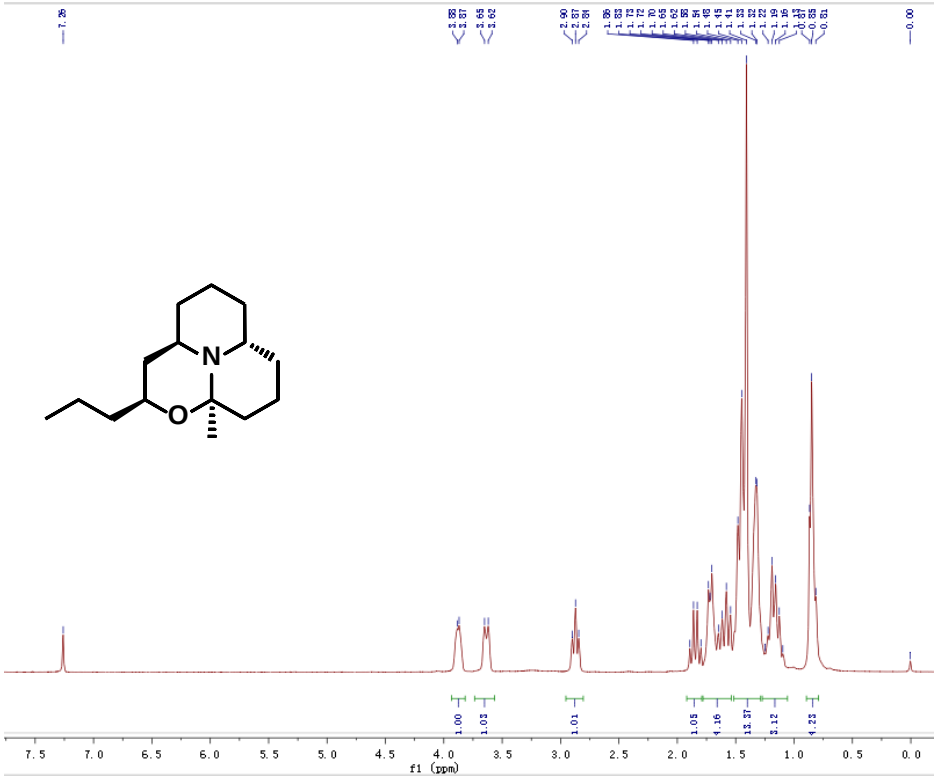
Compound **18**-^{1}H



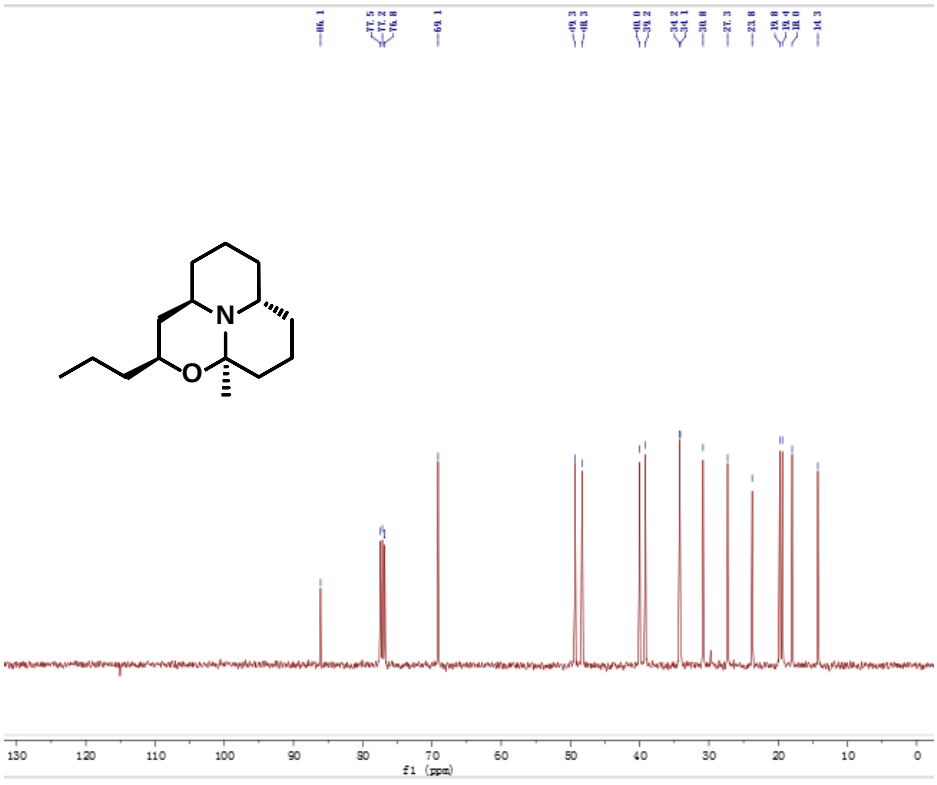
Compound **18**-^{13}C



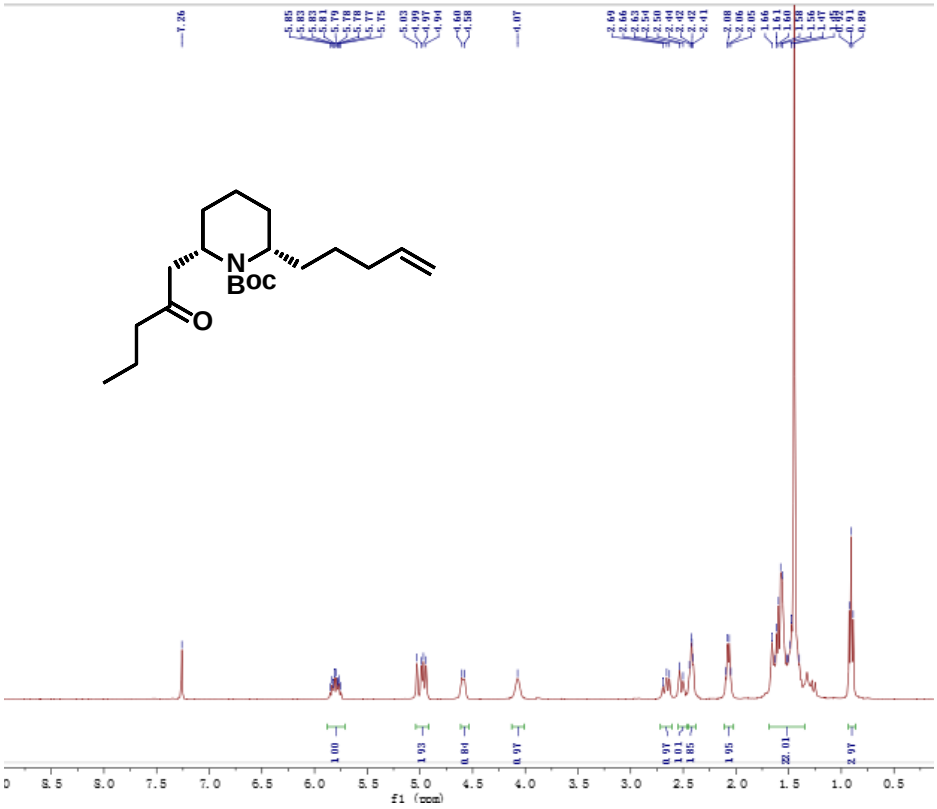
(+)-porantheridine-^{1}H



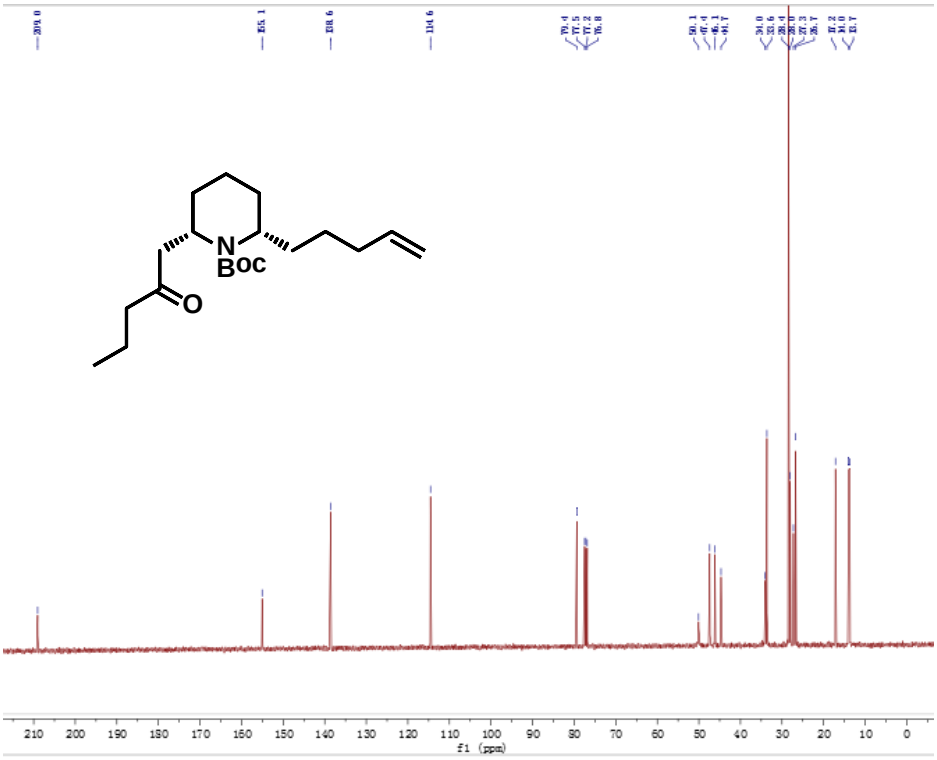
(+)-porantheridine-^{13}C



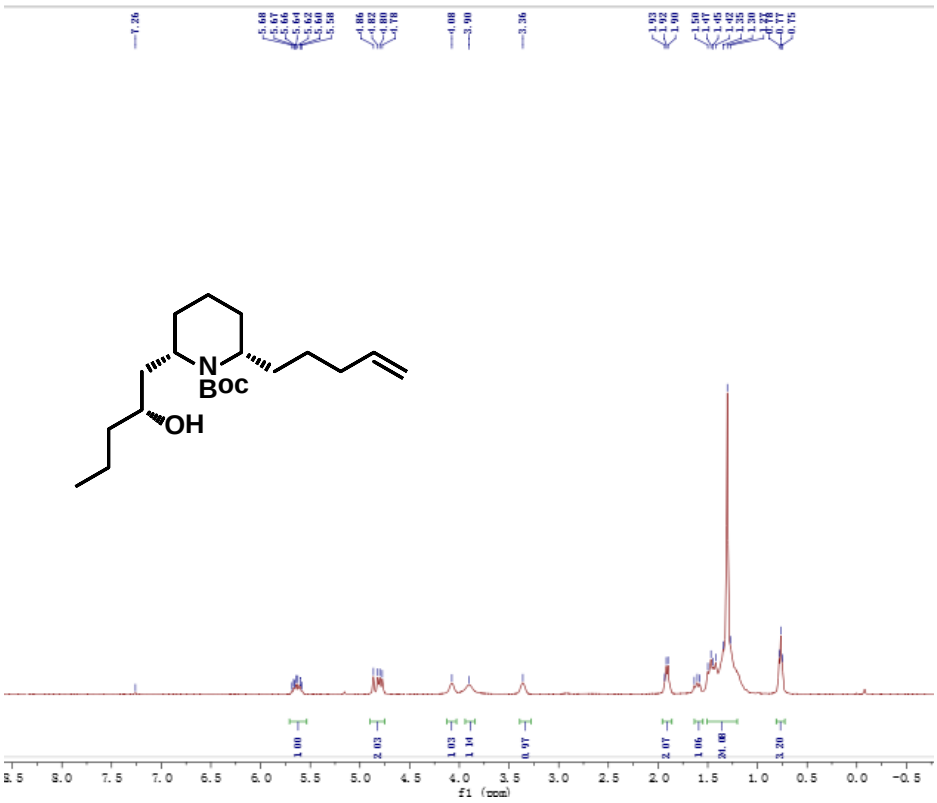
Compound **5**-^{1}H



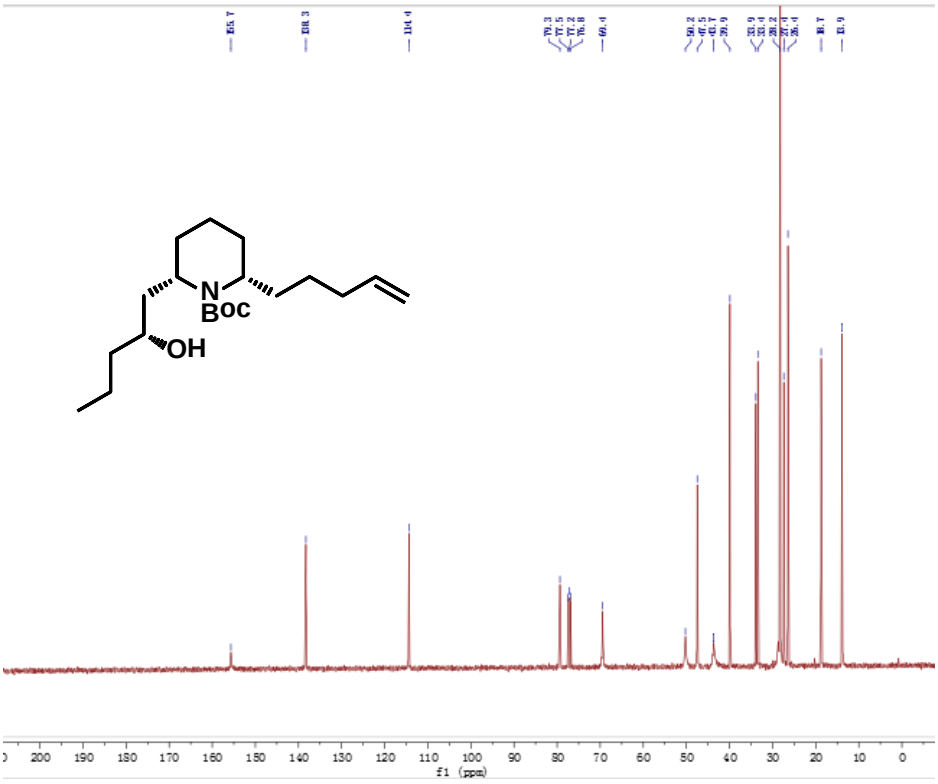
Compound **5**-^{13}C



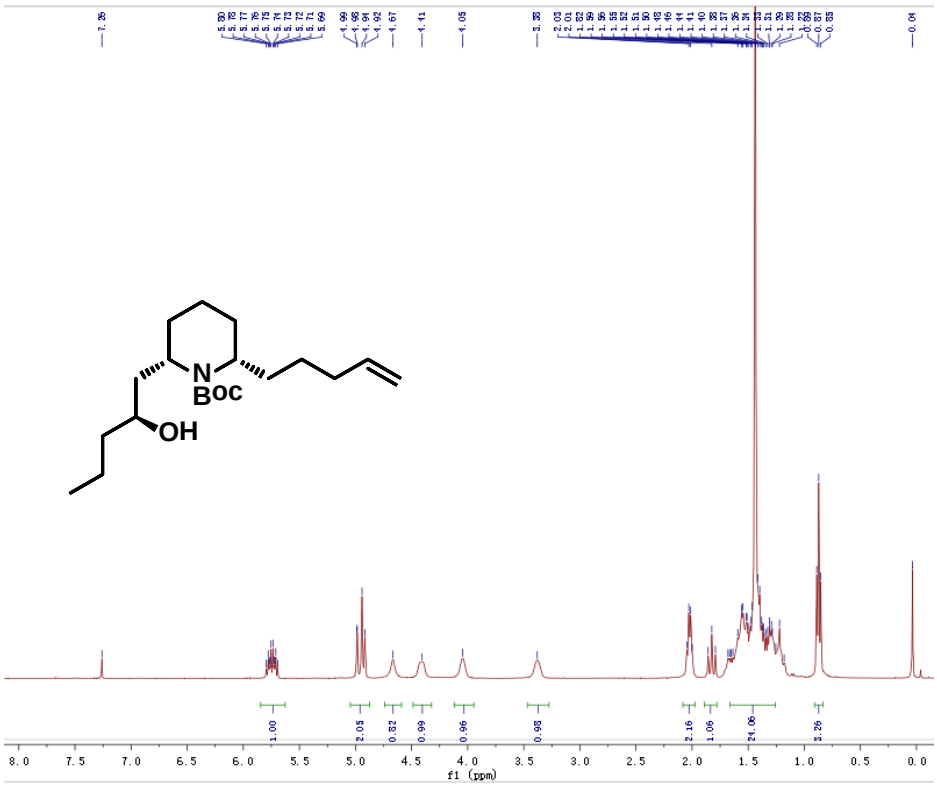
Compound **4**-^{1}H



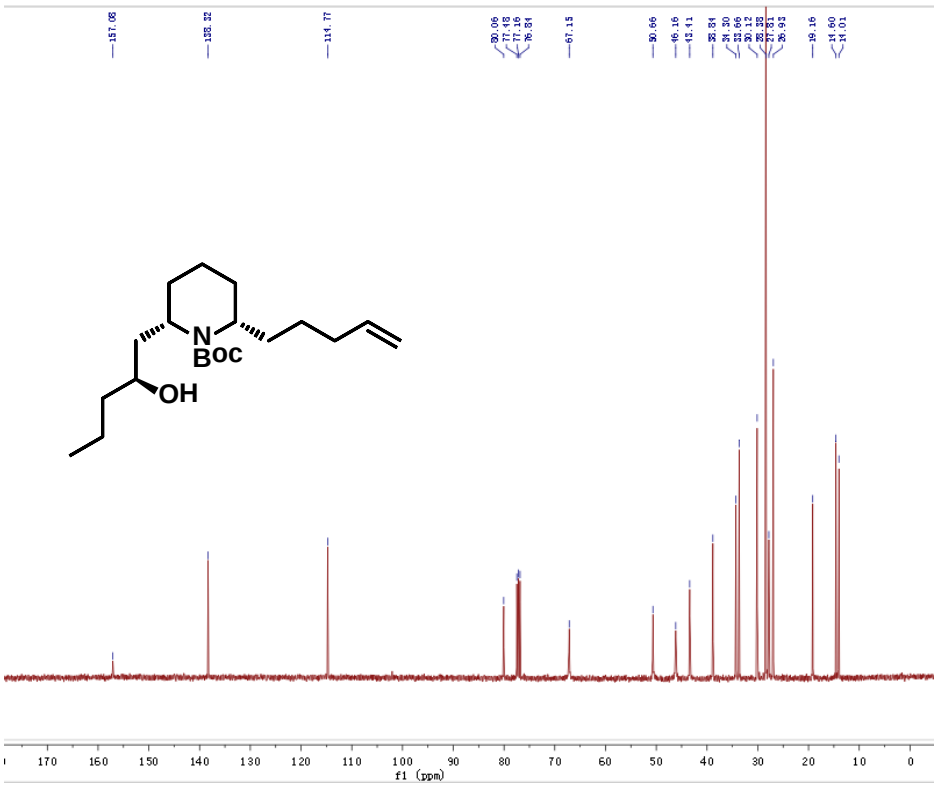
Compound **4**-^{13}C



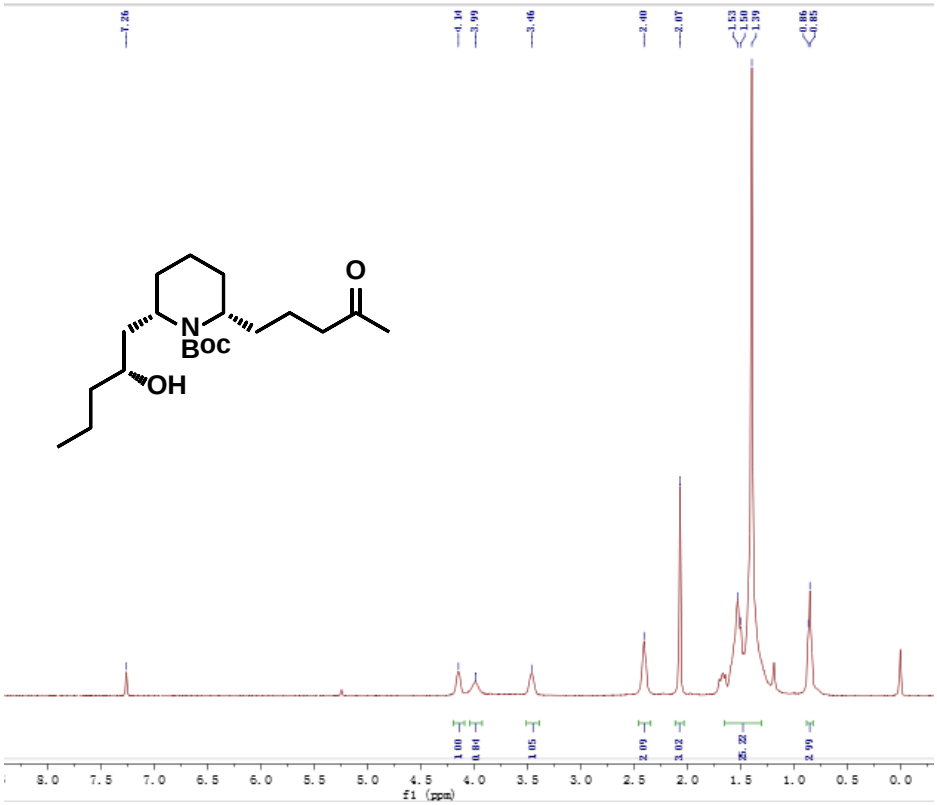
Compound **21**-^{1}H



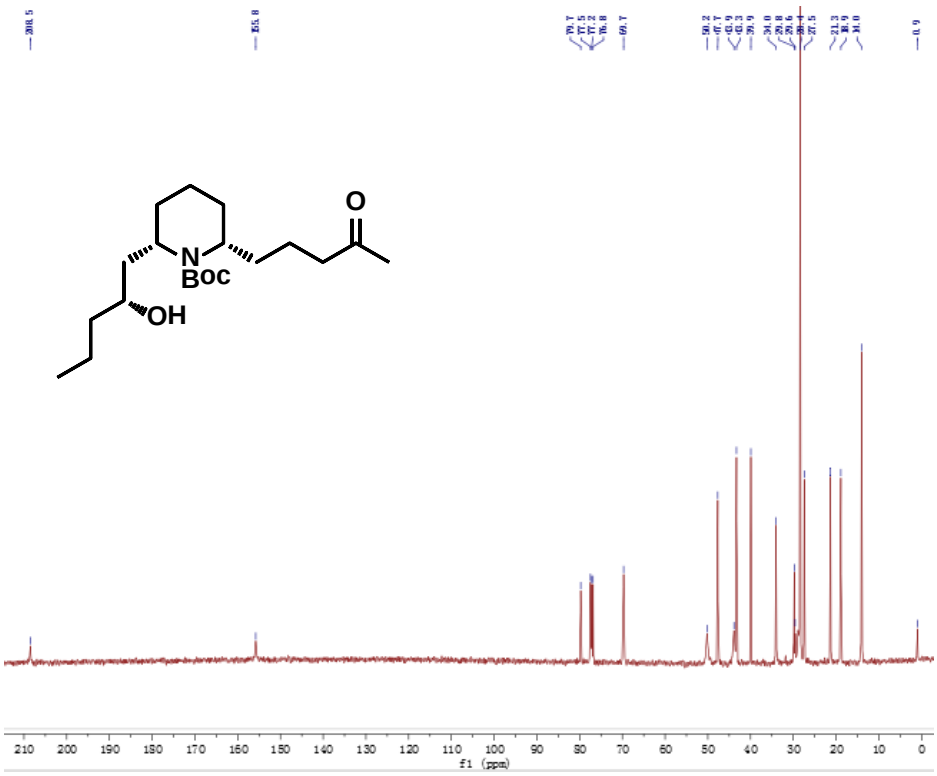
Compound **21**-^{13}C



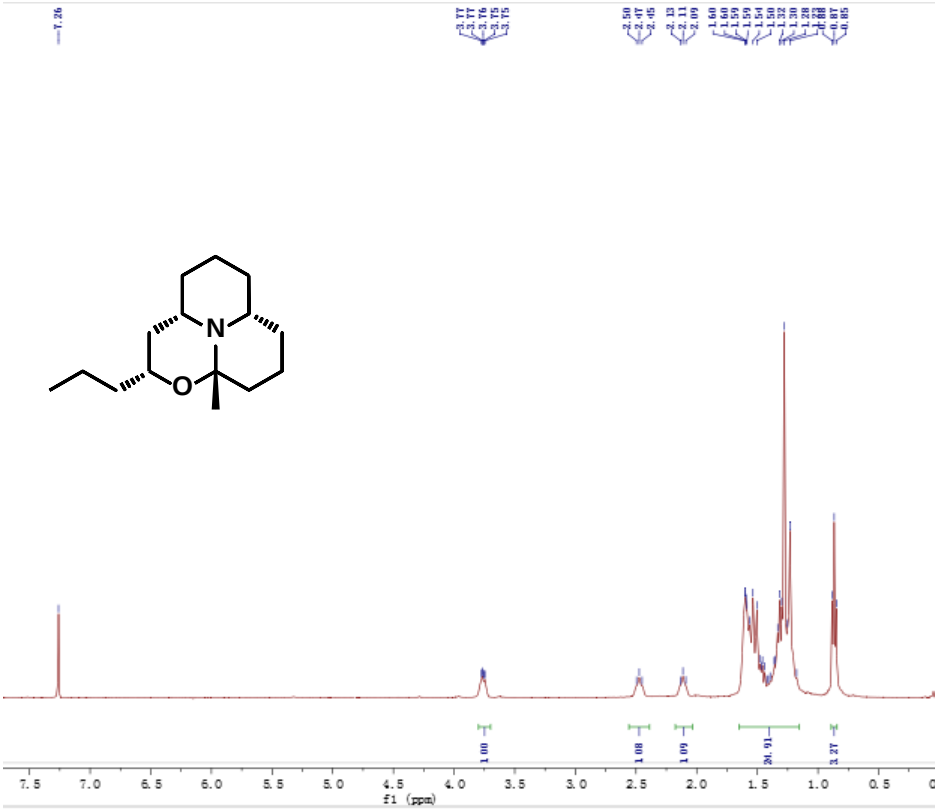
Compound **22**-^{1}H



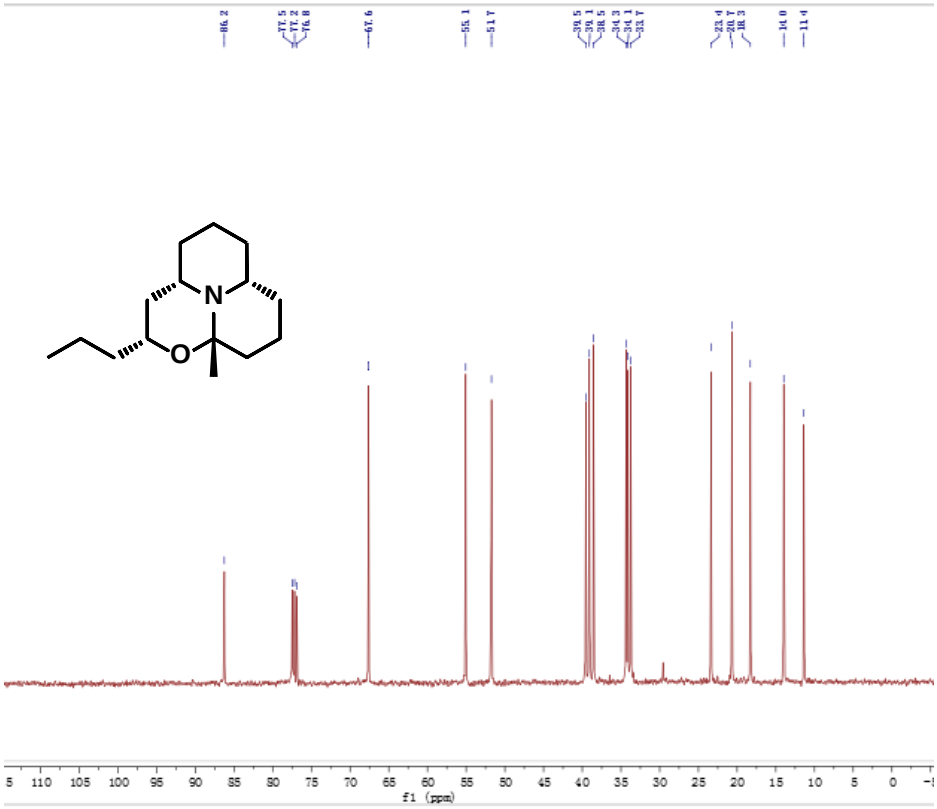
Compound **22**-^{13}C



(-)-6-*epi*-porantheridine-^{1}H

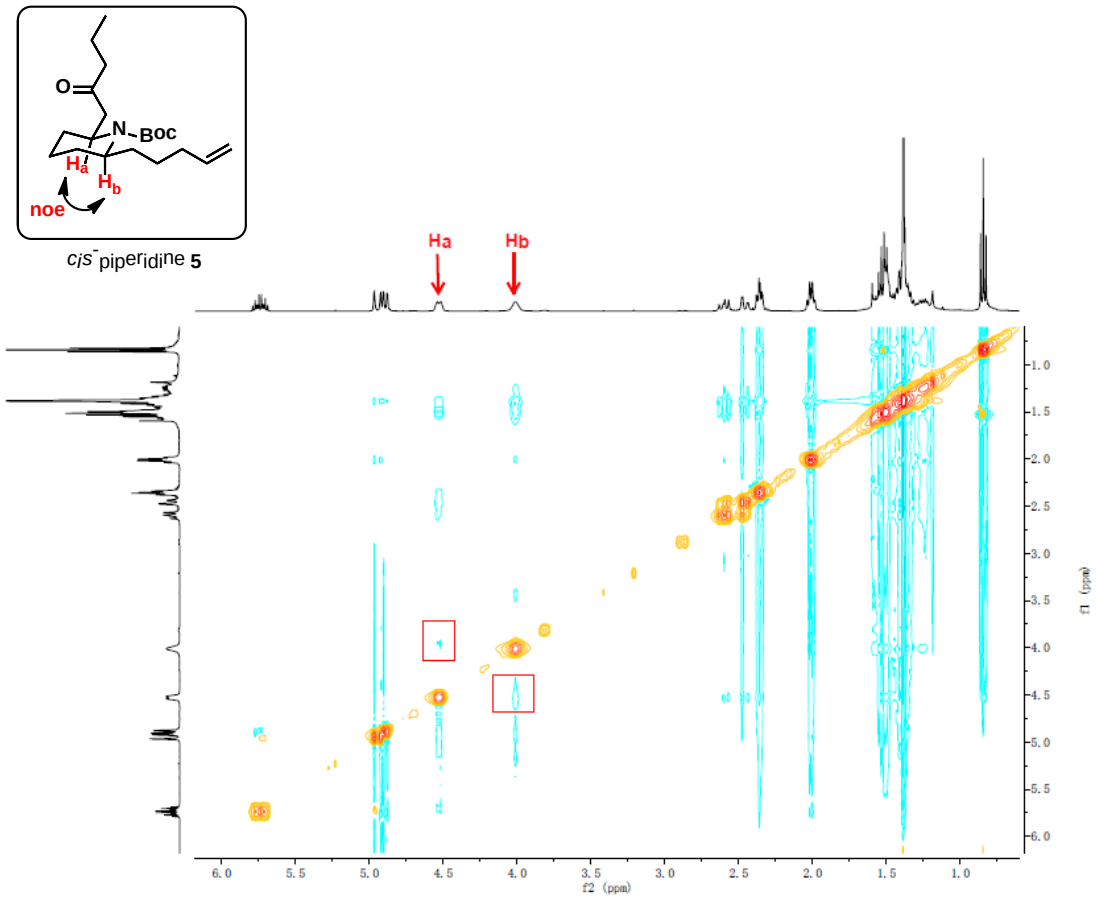


(-)-6-*epi*-porantheridine-^{13}C

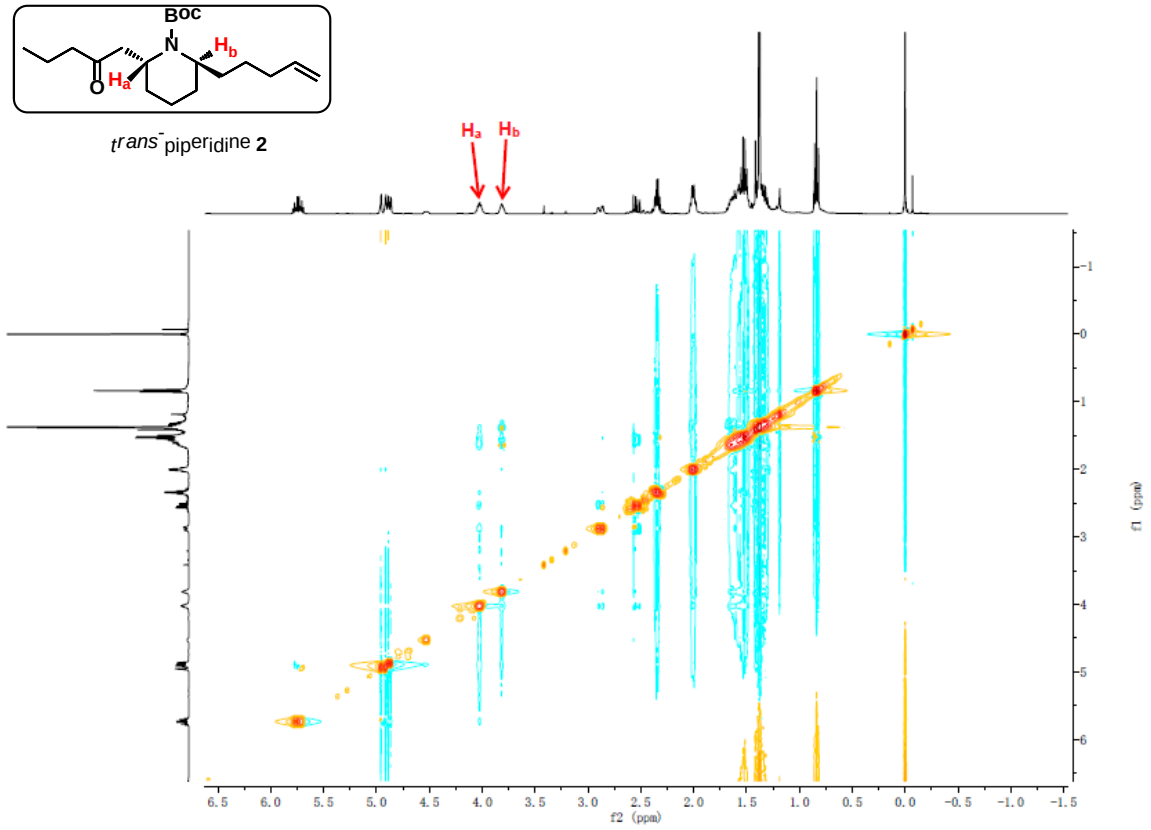


STEREOCHEMICAL ASSIGNMENT OF 2,6-DISUBSTITUTED COMPOUND 2 AND COMPOUND 5

The relative position of the substituents in *cis*-piperidine **5** was established by means of a NOESY experiment which showed an interaction between H_a and H_b, indicating that both display a *cis* relationship. That interaction was not observed in the *trans*-piperidine **2**.



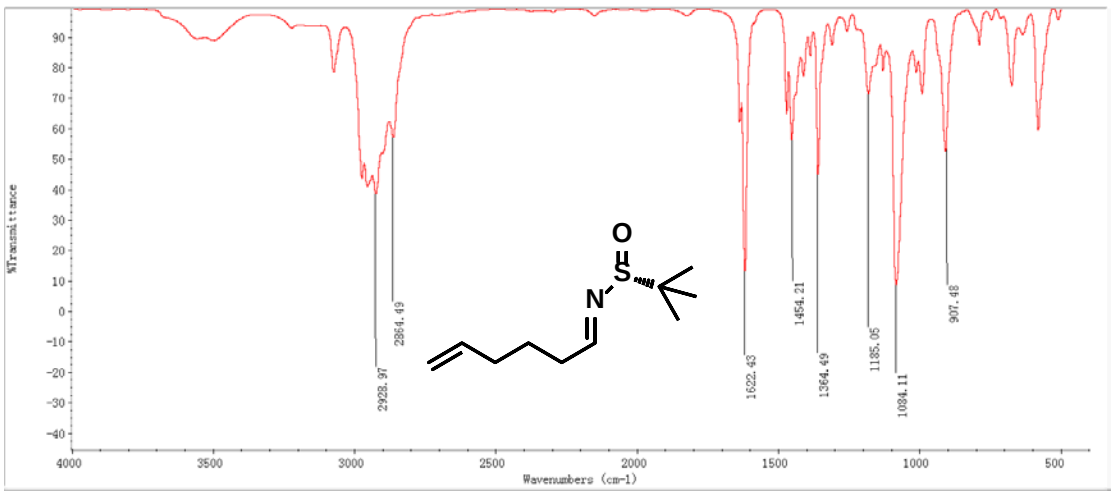
NOESY experiment on *cis*-piperidine **5** ($CDCl_3$, 400 MHz)



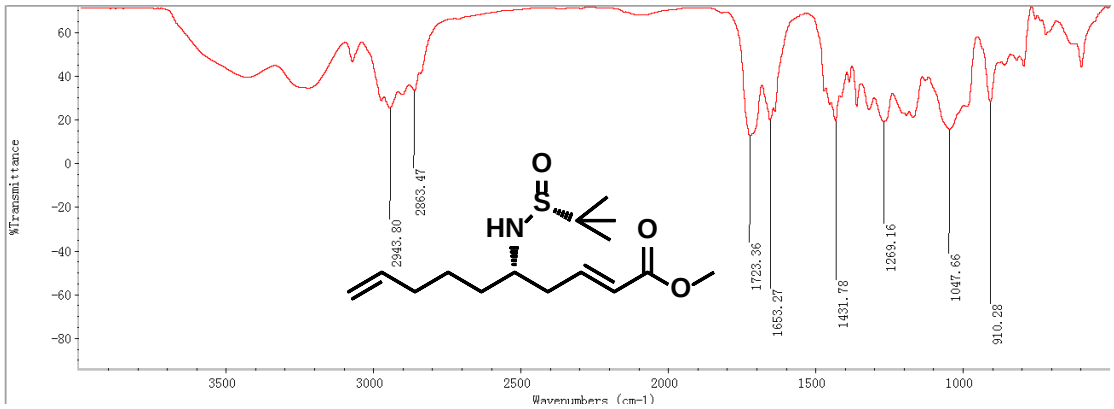
NOESY experiment on *trans*-piperidine **2** ($CDCl_3$, 400 MHz)

IR spectra

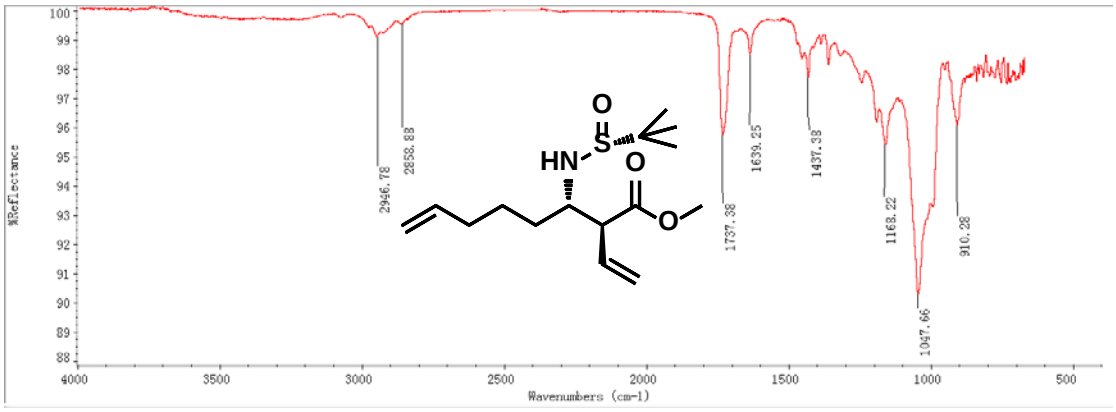
Compound **8**



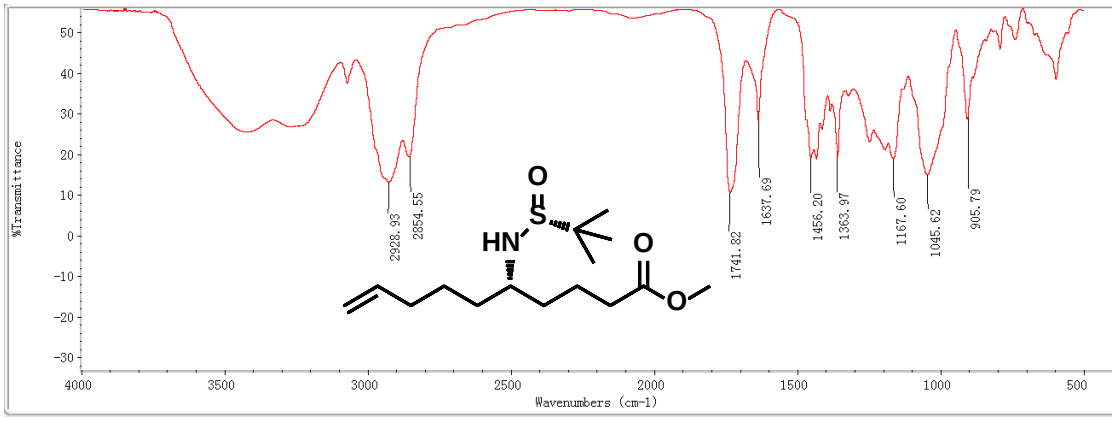
Compound **11**



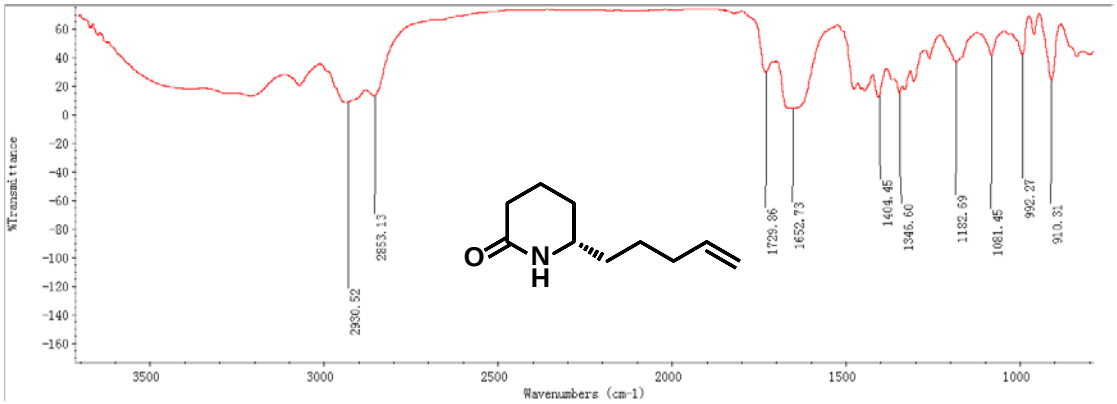
Compound **10**



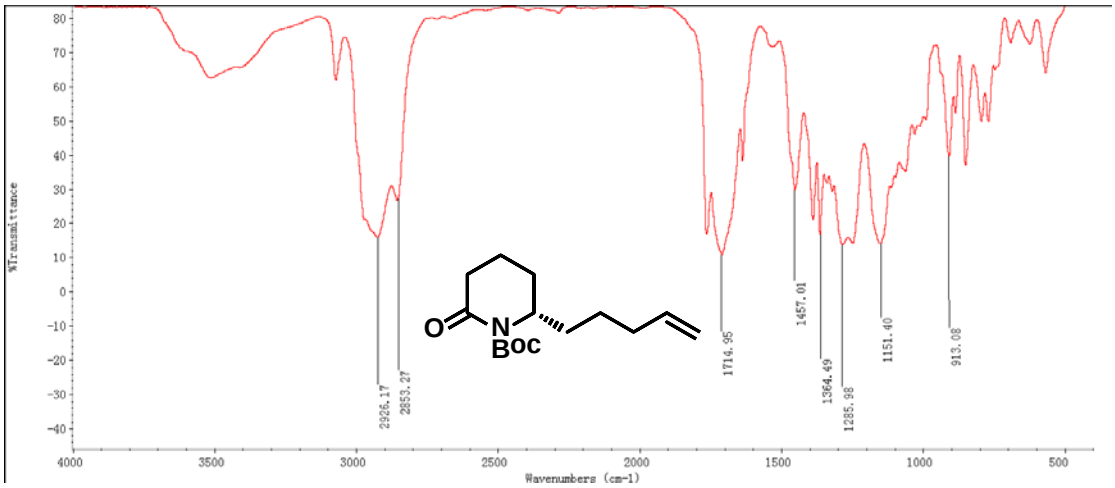
Compound **12**



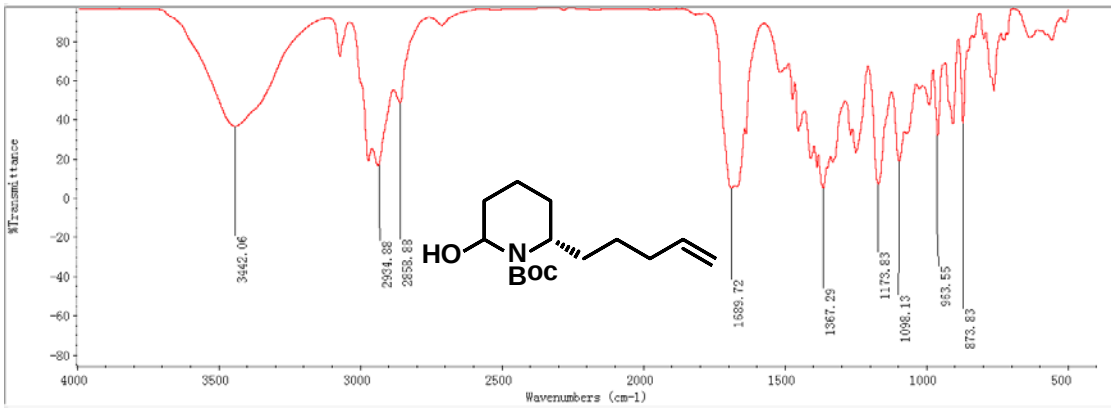
Compound **13**



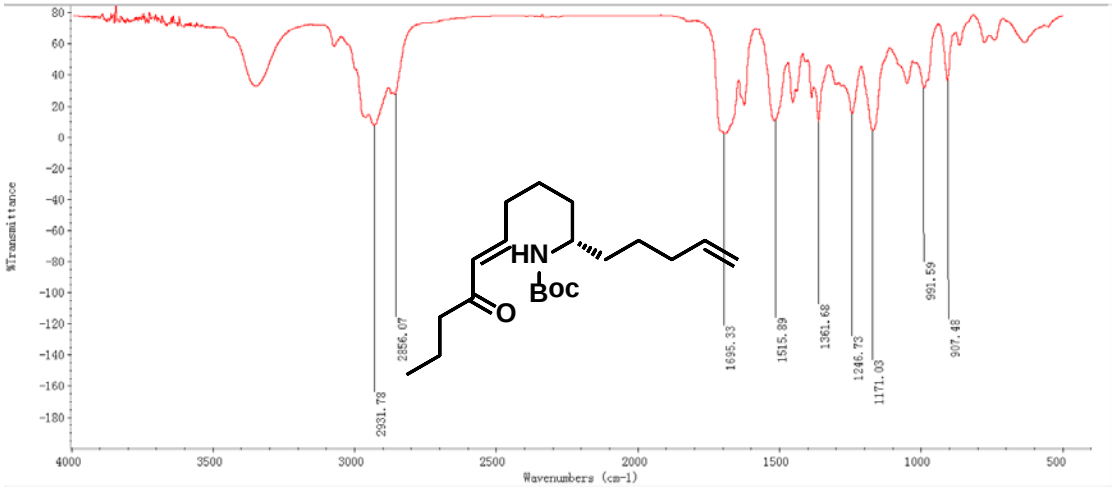
Compound **3**



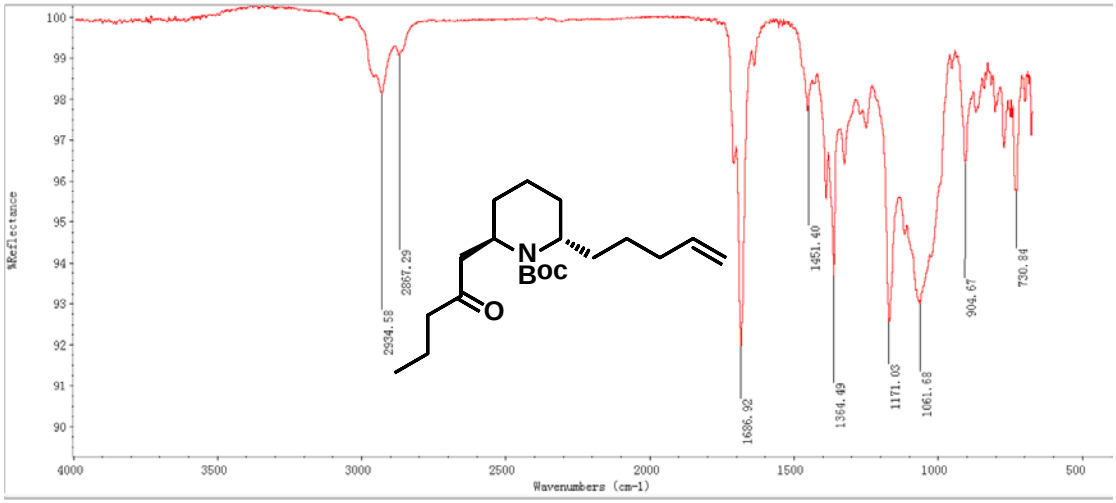
Compound **14**



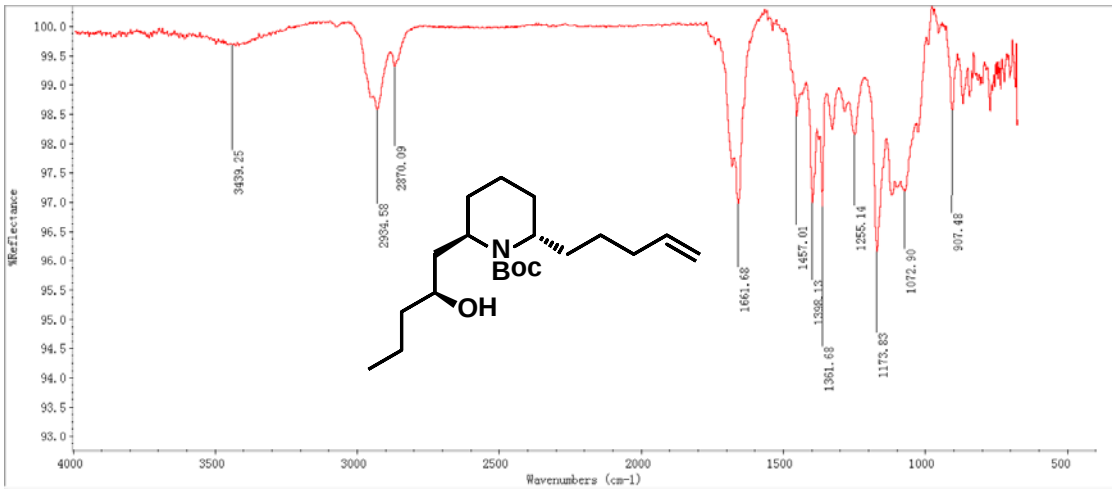
Compound **16**



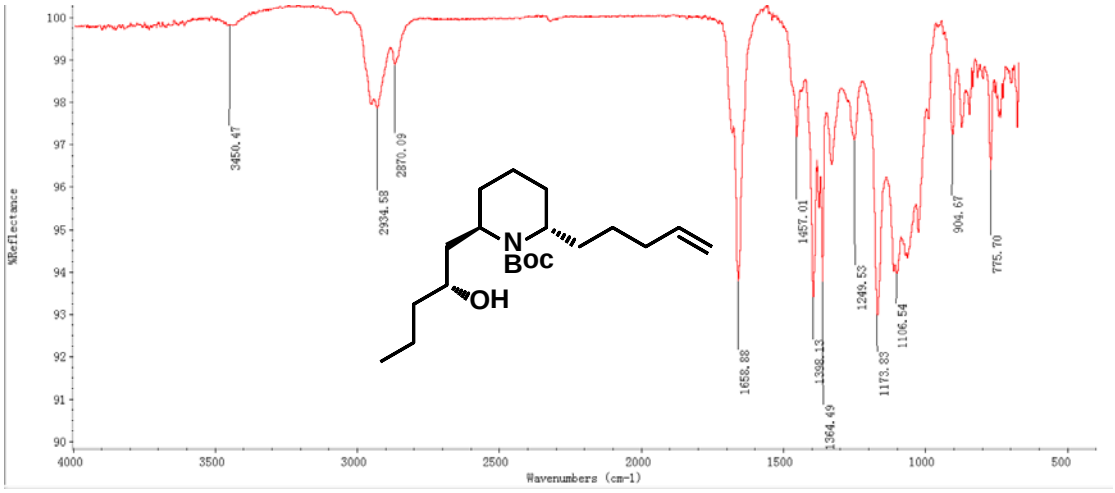
Compound **2**



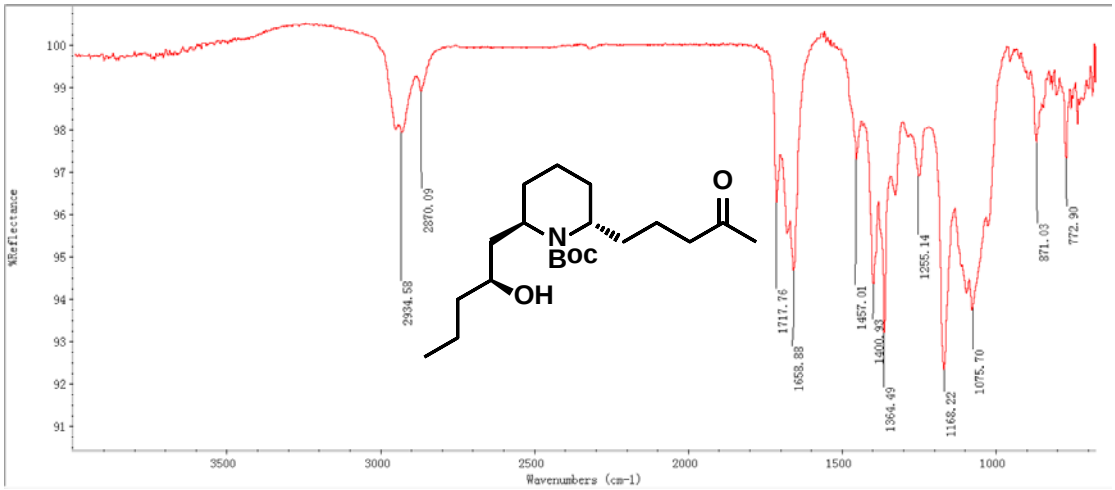
Compound **1**



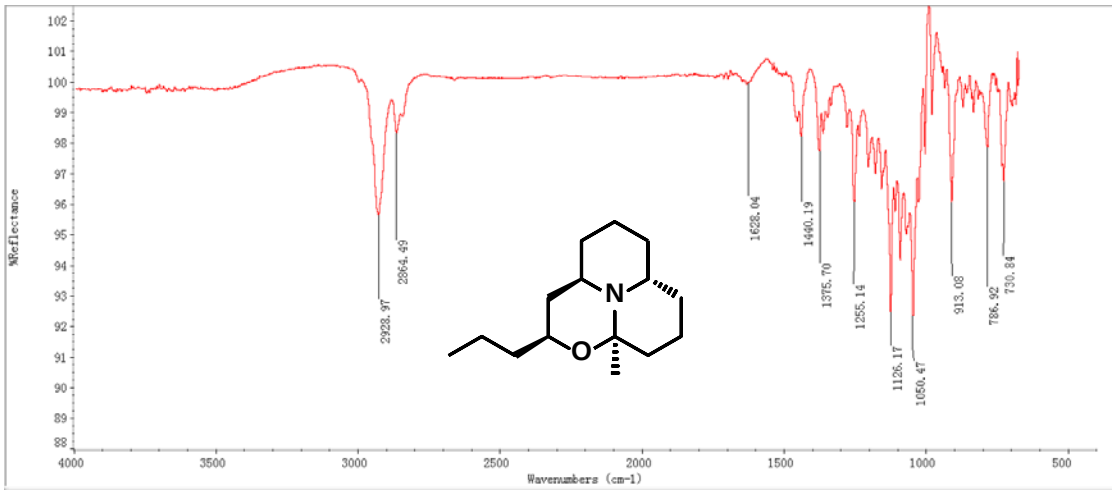
Compound **17**



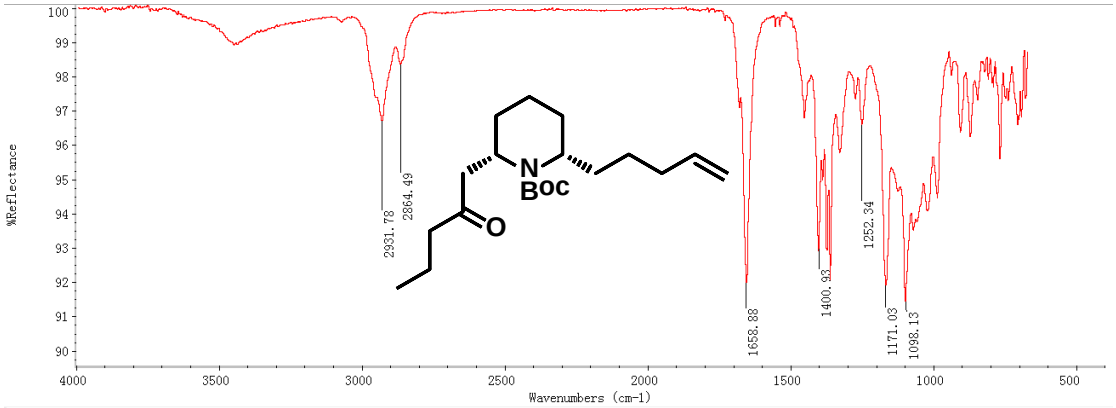
Compound **18**



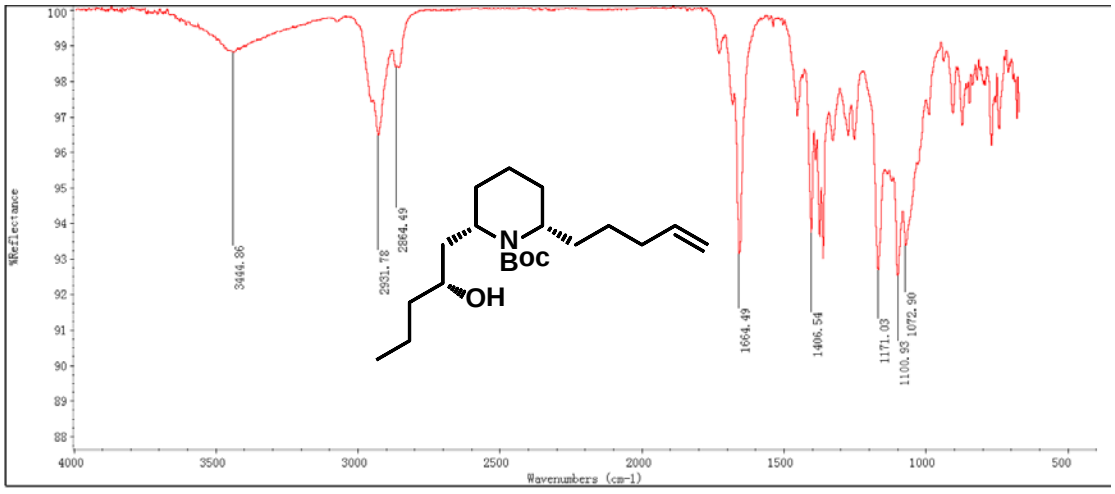
(+)-porantheridine



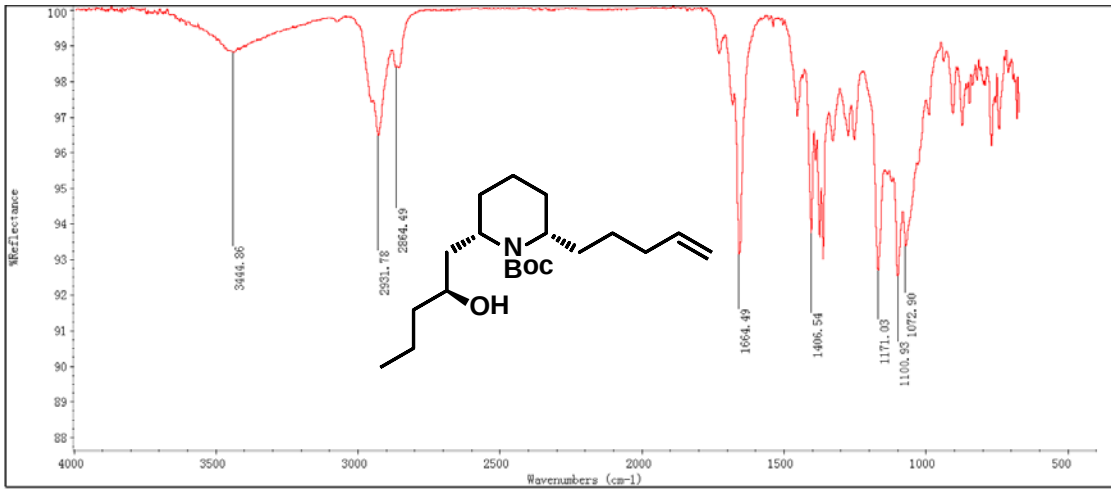
Compound **5**



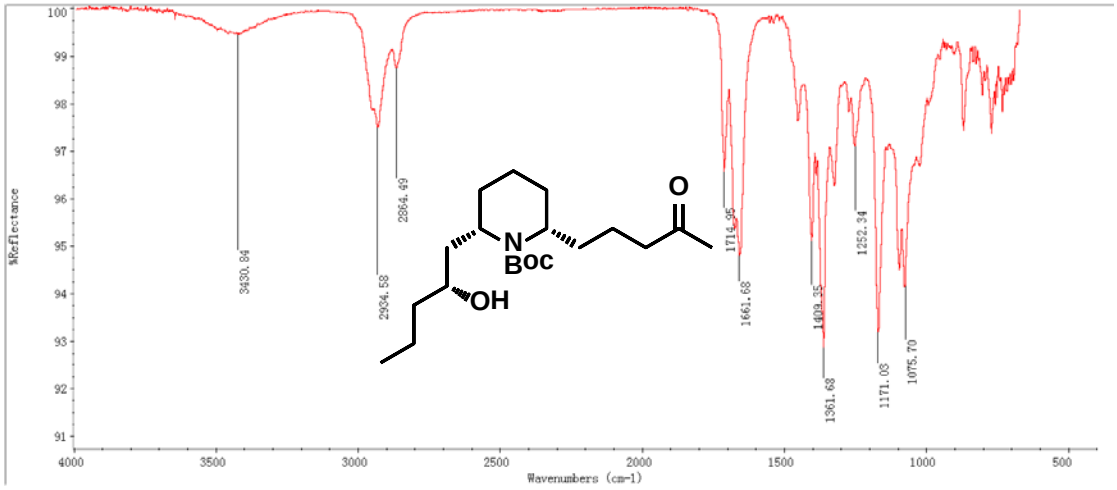
Compound **4**



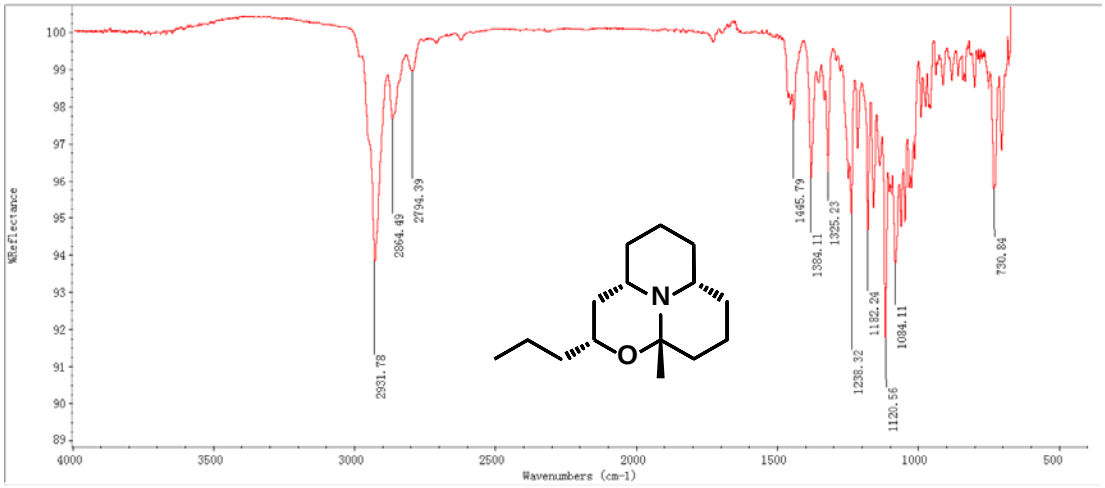
Compound **21**



Compound **22**

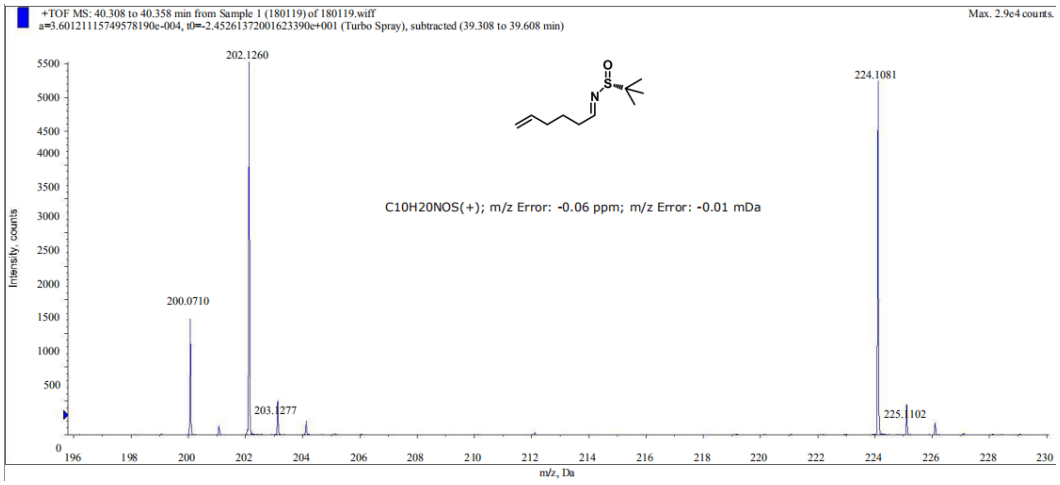


(-)-6-*epi*-porantheridine

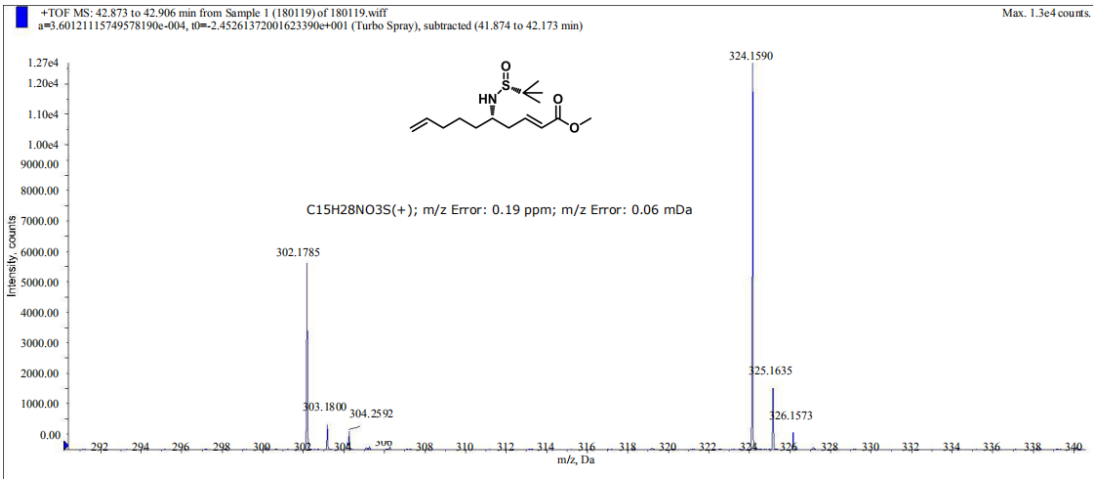


MS spectra:

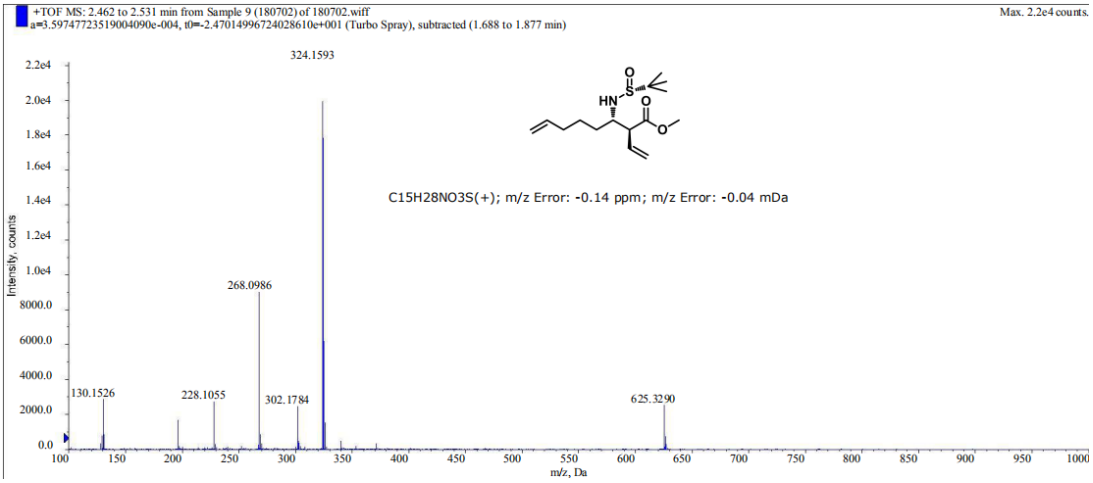
Compound **8**: HRMS (ESI) calcd for $C_{10}H_{19}NOSNa$ $[M+Na]^+$ 224.1080, found 224.1081.



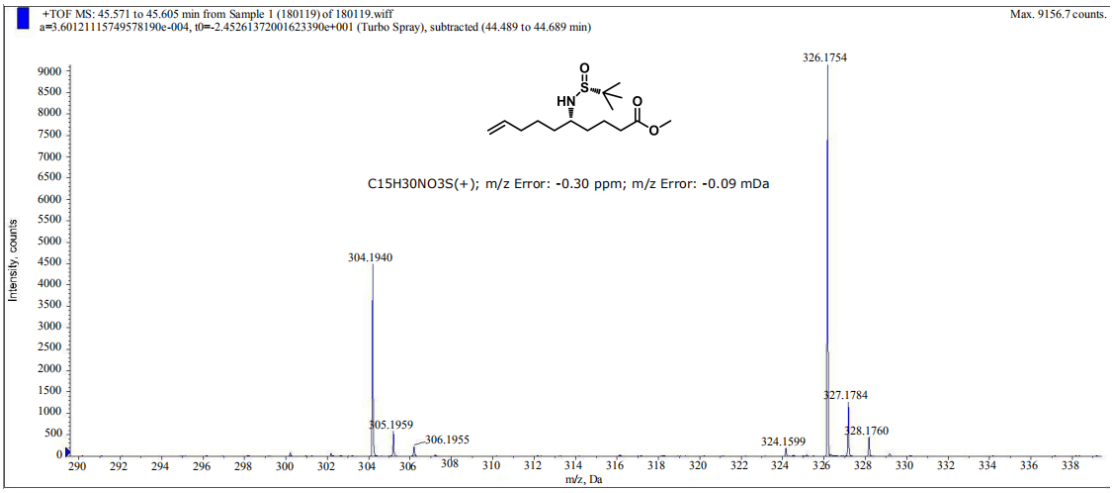
Compound **11**: HRMS (ESI) calcd for $C_{15}H_{28}NO_3S$ $[M+H]^+$ 302.1784, found 302.1785.



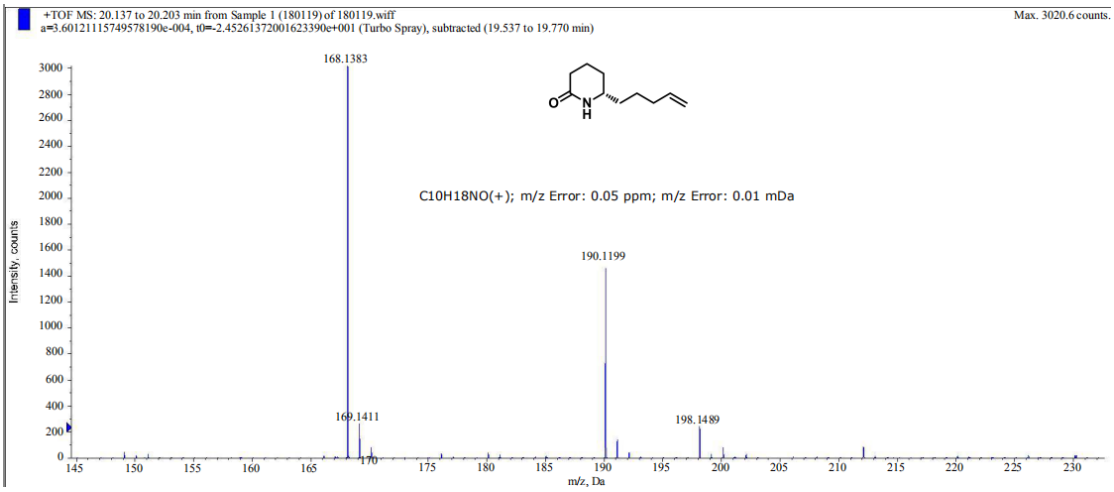
Compound **10**: HRMS (ESI) calcd for $C_{15}H_{27}NO_3SNa$ $[M+H]^+$ 302.1784, found 302.1784.



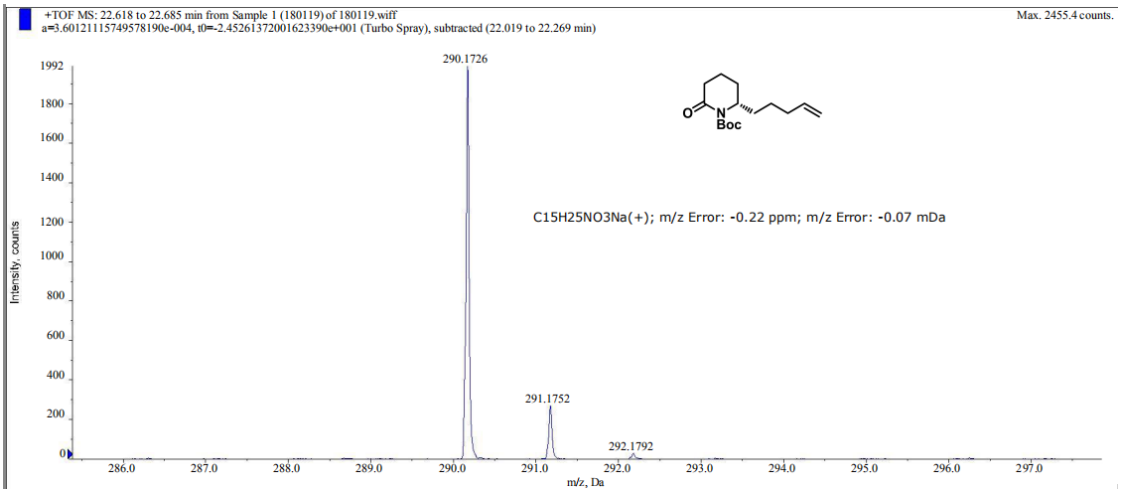
Compound **12**: HRMS (ESI) calcd for$C_{15}H_{29}NO_3SNa$ $[M+Na]^+$ 326.1760, found 326.1754.



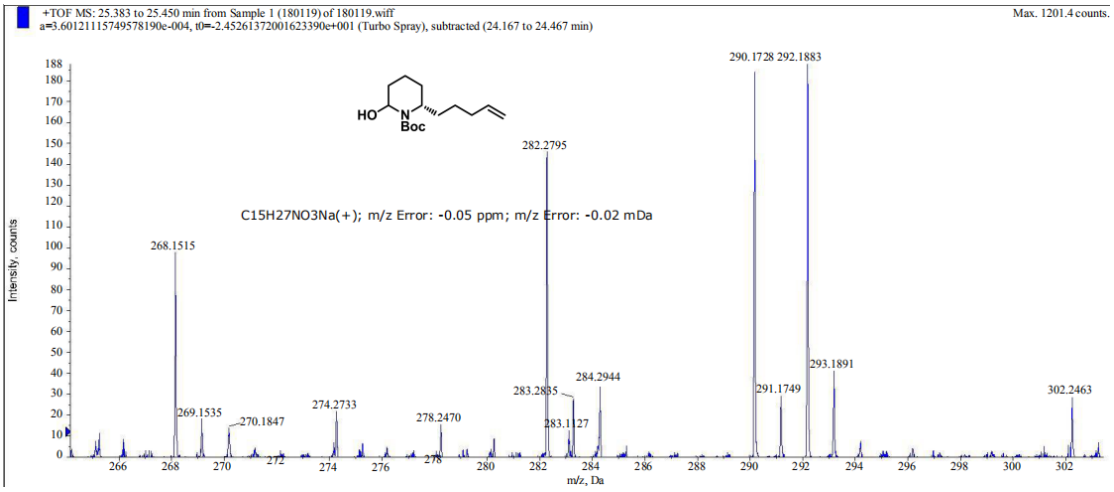
Compound **13**: HRMS (ESI) calcd for $C_{10}H_{18}NO$ $[M+H]^+$ 168.1383, found 168.1383.



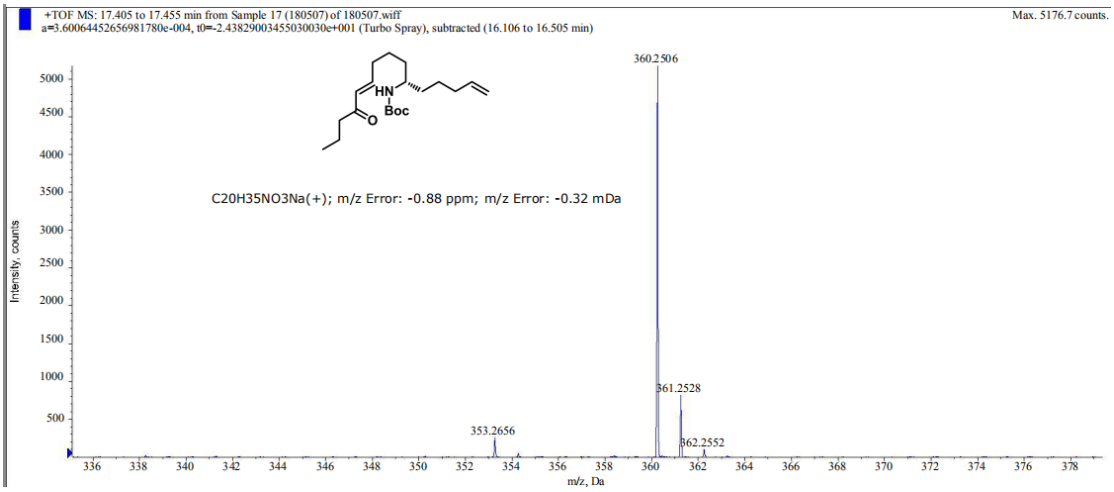
Compound **3**: HRMS (EIS) calcd. for $C_{15}H_{25}NO_3Na$ $[M+Na]^+$ 290.1727, found 290.1726.



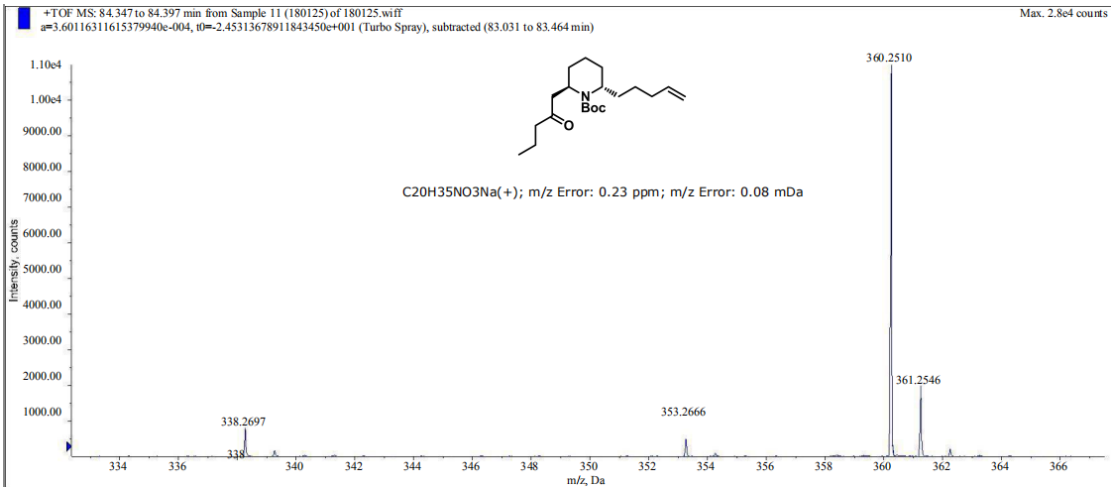
Compound **14**: HRMS (EIS) calcd. for $C_{15}H_{27}NO_3Na$ $[M+Na]^+$ 292.1883, found 292.1883.



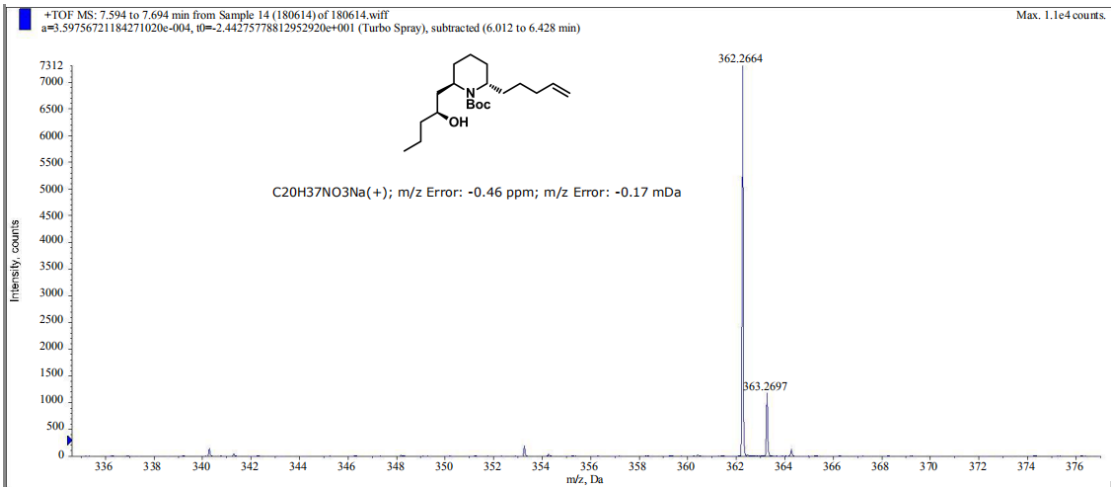
Compound **16**: HRMS (EIS) calcd. for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$ 360.2509, found 360.2506.



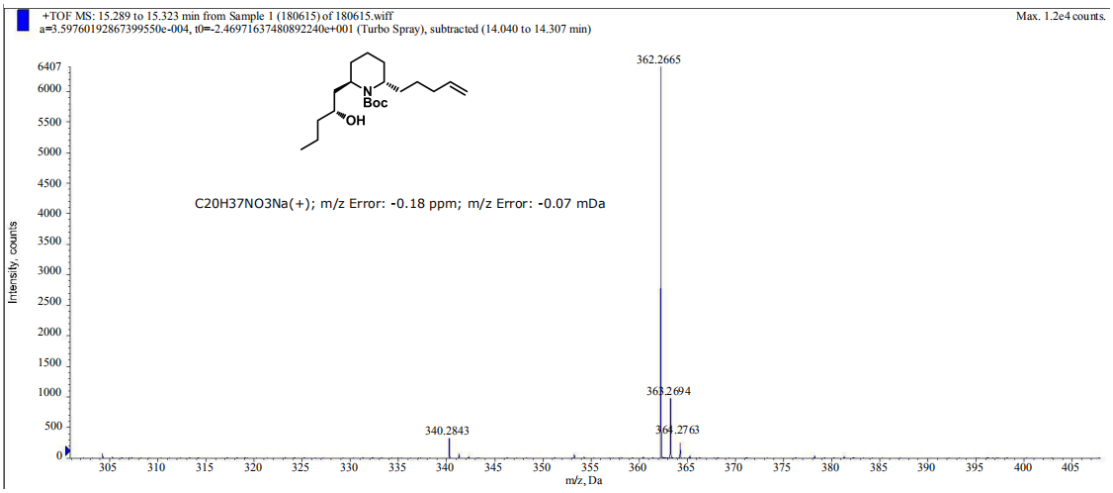
Compound **2**: HRMS (EIS) calcd. for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$ 360.2509, found 360.2510.



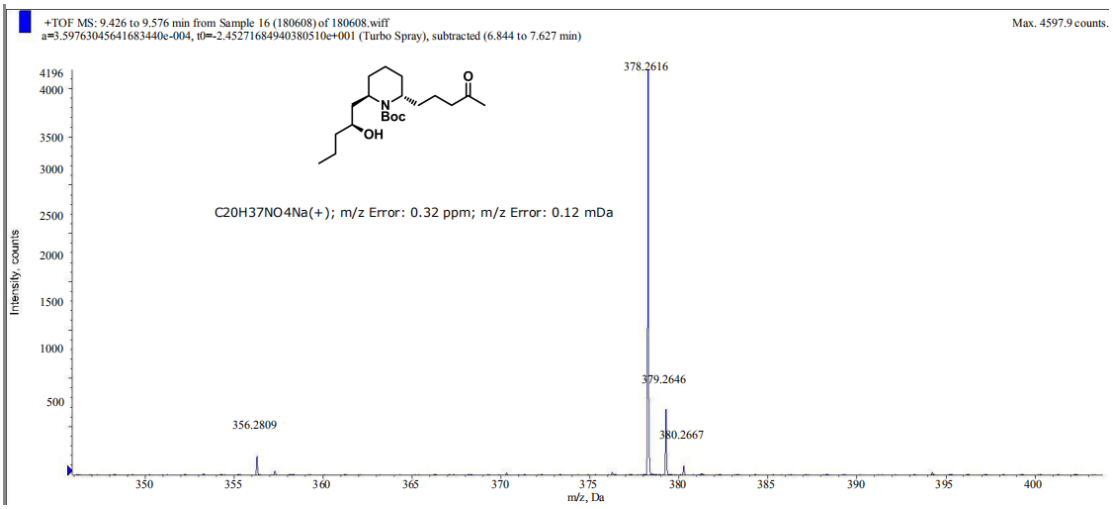
Compound **1**: HRMS (EIS) calcd. for $C_{20}H_{37}NO_3Na$ $[M+Na]^+$ 362.2666, found 362.2664.



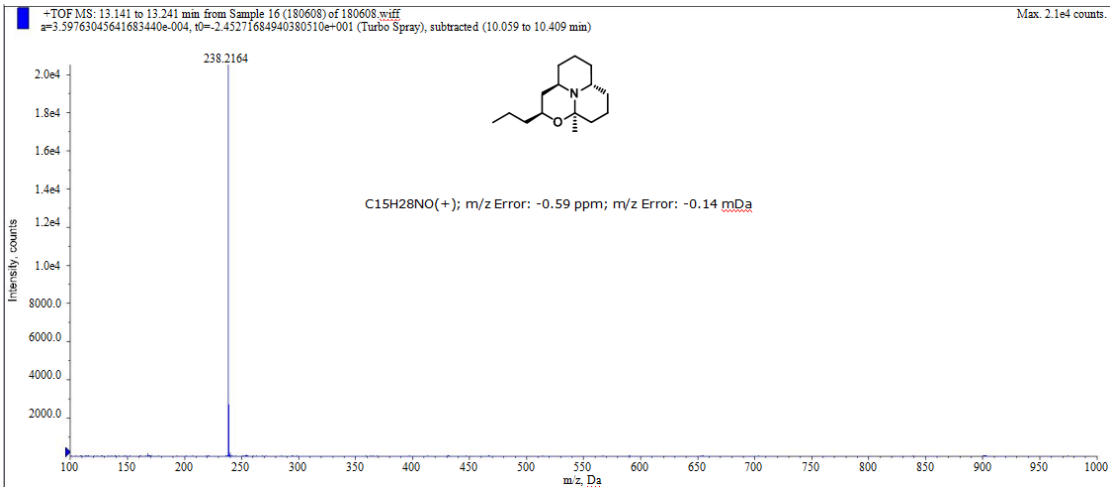
Compound **17**: HRMS (EIS) calcd. for $C_{20}H_{37}NO_3Na$ $[M+Na]^+$ 362.2666, found 362.2665.



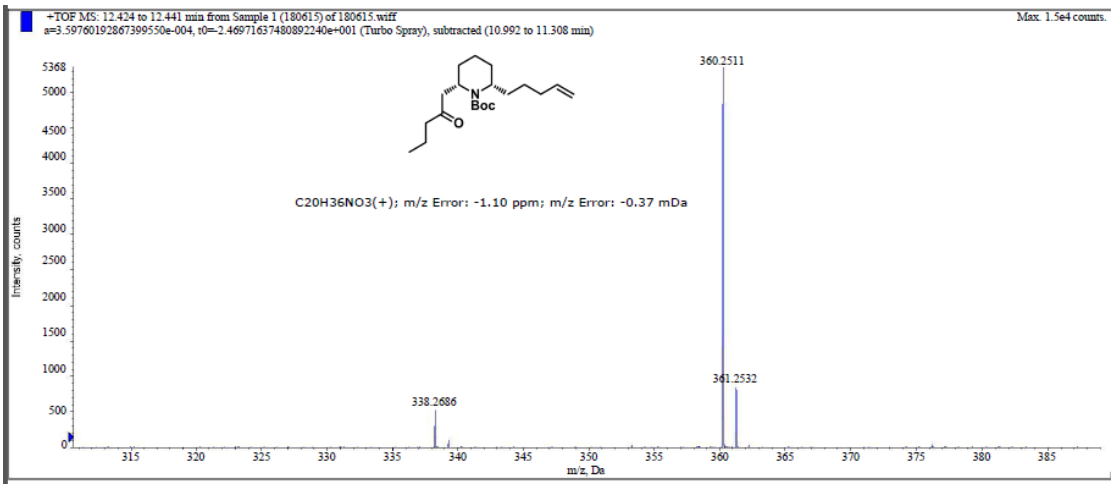
Compound **18**: HRMS (EIS) calcd. for $C_{20}H_{37}NO_4Na$ $[M+Na]^+$ 378.2615, found 378.2616.



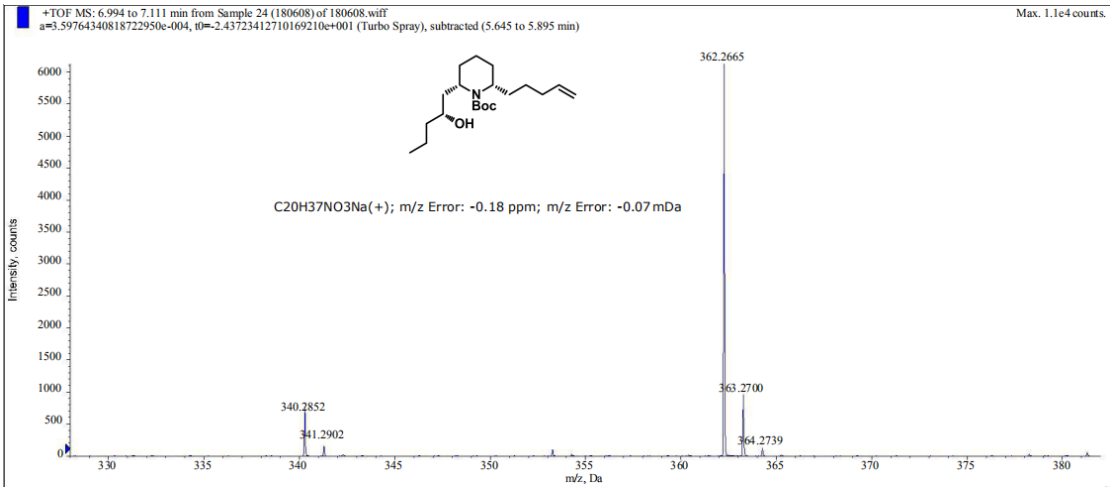
(+)-porantheridine: HRMS (EIS) calcd. for $C_{15}H_{28}NO$ $[M+H]^+$ 238.2165, found 238.2164.



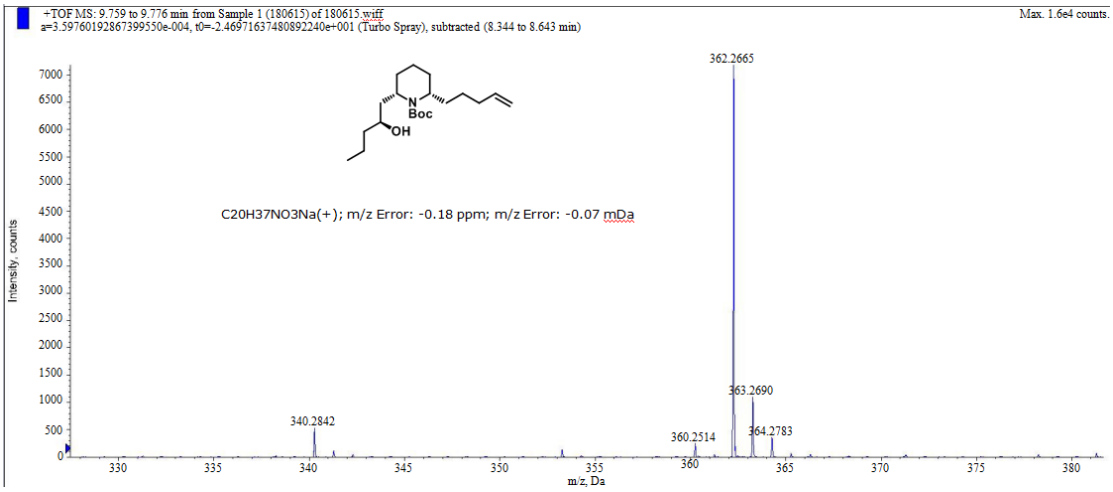
Compound **5**: HRMS (EIS) calcd. for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$ 360.2509, found 360.2511.



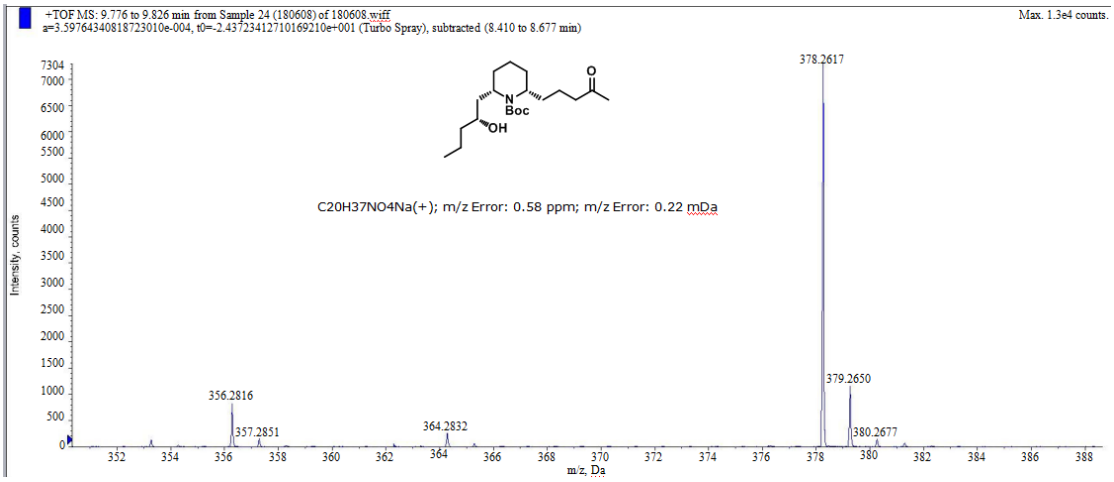
Compound **4**: HRMS (EIS) calcd. for $C_{20}H_{37}NO_3Na$ $[M+Na]^+$ 362.2666, found 362.2665.



Compound **21**: HRMS (EIS) calcd. for $C_{20}H_{37}NO_3Na$ $[M+Na]^+$ 362.2666, found 362.2665.



Compound **22**: HRMS (EIS) calcd. for $C_{20}H_{37}NO_4Na$ $[M+Na]^+$ 378.2615, found 378.2617.



(-)-6-*epi*-porantheridine: HRMS (EIS) calcd. for $C_{15}H_{28}NO$ $[M+H]^+$ 238.2165, found 238.2165.