Supporting Information

Enantioselective construction of substituted pyridine and seven-membered carbocyclic skeleton: Biomimetic synthesis of (-)-rupestine D, (-)-guaipyridine, (-)-epiguaipyridine, (-)-cananodine and their stereoisomers

Cun Zhang [a,b], Bianlin Wang [a], Paruke Aibibula [a,b], Jiangyu Zhao [a] and Haji Akber Aisa*[a,b]

[a] *State Key Laboratory Basis of Xinjiang Indigenous Medicinal Plants Resource Utilization, Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, South Beijing Road 40-1, Urumqi, 830011,*
P. R. China;
[b] *university of chinese Academy of sciences, Yuquan Rd 19 A, Beijing, 100049, P. R. China*

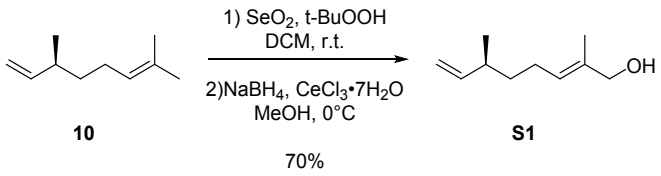
Table of Contexts

1. General Information…….....S2
2. Experimental Procedures and and Characterization Data…… …...S3
3. Comparison of ^{1}H NMR and ^{13}C NMR data of rupestine D (5) and cananodine (3) by table……..…….....S17
4. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra of the synthesized compounds…….....S18
5. Single Crystal X-ray Data…….....S39

1. General Information

All reactions were performed in round-bottomed flasks or test tubes. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Solvent purification was conducted according to Purification of Laboratory Chemicals 2nd edn (Perrin, D. D., Armarego, W. L. F. and Perrin, D. R., Pergamon Press: Oxford, 1980). The solvents for reactions without water and oxygen were degassed in flame-dried glassware via syringe needle under Ar for 30 min. Reactions were monitored by thin layer chromatography (TLC, Silica gel 60 HF_{254}) supplied by Merk KGaA (Germany). Visualization was accomplished with UV light, exposure to iodine, stained with ethanolic solution of phosphomolybdic acid or basic solution of $KMnO_4$. The products were purified by flash column chromatography on silica gel (200 – 300 meshes) from the Shanghai Titan Scientific Ci.,Ltd (China). Melting points were determined on a Buchi M-560. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet 6700 spectrometer. Optical rotation was obtained from Rudolph Research Analytical Autopol IV automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian INOVA-400MHz instruments and calibrated by using residual undeuterated chloroform (δ, ^{1}H NMR = 7.260, ^{13}C NMR = 77.00). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublet, dt = triplet of doublet, t = triplet, q = quartet, m = multiplet, br = broad and coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a UHPLC-Q-orbitrap-MS (Thermo, Bremen, Germany).

2. Experimental Procedures and and Characterization Data

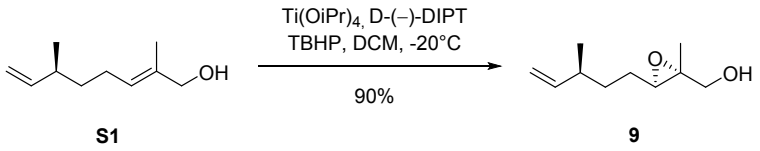


Preparation of S1: (*R*)-(–)-citronellene (41.0 g, 297 mmol, 1 equiv) in 0.6 L of CH_2Cl_2 was added dropwise to a solution of SeO_2 (3.30 g, 49.5 mmol) and TBHP (42.0 g, 70% wt% in water, 326 mmol) at room temperature, Stirring was continued for an additional 30 min at 0 °C after this mixture was stirred at room temperature for 2 h, then, the reaction was quenched by an aqueous sat. $Na_2S_2O_3$ solution. The solution was extracted with MTBE (3×600 mL) and combined organic layers were washed with brine, The organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure.

A magnetically stirred solution of the mixture of the previous step and $CeCl_3 \cdot 7H_2O$ (55.2 g, 148 mmol) in MeOH (200 mL) was cooled to 0 °C and then treated, in portions, with sodium borohydride (5.61 g, 148 mmol) (CAUTION: EVOLUTION OF HYDROGEN GAS). The resulting mixture was stirred at 0 °C for 1 h before being quenched with water (50 mL) and then concentrated under reduced pressure. The residue so-formed was extracted with MTBE (3×100 mL) and combined organic layers were washed with brine, The combined organic phases were dried over Na_2SO_4, then purified by flash chromatography on silicagel (PE/EA, 15:1) to give a colorless liquid product **S1** (32.0 g, 207 mmol 70%).

$[\alpha]_D^{20}$ = +9 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 5.38 – 5.34 (m, 1H), 4.96 – 4.88 (m, 2H), 3.95 (d, *J* = 6.0 Hz, 2H), 2.14 – 2.07 (m, 1H), 2.05 – 1.92 (m, 3H), 1.63 (s, 2H), 1.32 (qd, *J* = 7.2, 1.5 Hz, 2H), 0.97 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.41, 134.59, 126.12, 112.63, 68.75, 37.33, 36.27, 25.24, 20.09, 13.56.
IR(KBr) 3334, 3077, 2961, 2914, 2863, 1639, 1455, 995, 910 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{10}H_{18}O$ $[M + H]^+$ 155.1436, found 155.1428.

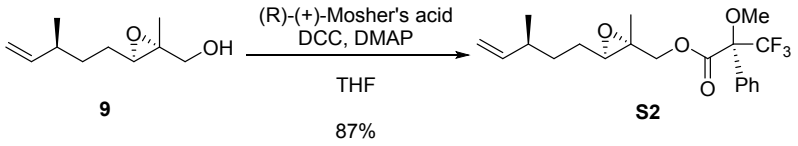


Preparation of 9: To a stirred mixture of $Ti(O^iPr)_4$ (3.39 g, 11.9 mmol), CaH_2 (20 mg), silica gel (20

mg) and 4 Å molecular sieves (20 mg) in 80 mL of dry CH_2Cl_2 was added D-(–)-diisopropyl tartrate (DIPT) (2.78 g, 11.9 mmol) in 80 mL of dry CH_2Cl_2 at –20 ℃ under N_2 and stirred for 10 min. A solution of compound **S1** (15.3 g, 99.3 mmol) in 40 mL of dry CH_2Cl_2 was injected and stirred for another 10 min. Then the mixture was cooled to –50 ℃, 45.8 mL of anhydrous TBHP (2.6 M in toluene,119 mmol) was injected slowly. After addition, the mixture was allowed to warm to –20 ℃, stirred for 2 h and monitored by TLC. The reaction mixture was quenched by 100 mL of 10% aqueous tartaric acid, warmed to room temperature, and stirring was continued until the aqueous layer became clear. The reaction mixture was extracted with ethyl acetate, washed successively with 5% aqueous NaOH, saturated aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel chromatography (PE/EA–6:1) to give epoxide **9** (15.2 g, 89.3 mmol, 90%).

$[\alpha]_D^{20} = +7$ (c 0.10, MeOH);

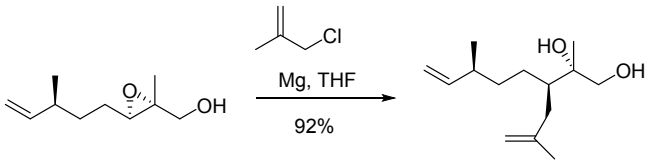
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 5.00 – 4.93 (m, 2H), 3.67 (dd, *J* = 12.2, 4.5 Hz, 1H), 3.57 (dd, *J* = 12.2, 8.5 Hz, 1H), 3.02 (t, *J* = 5.9 Hz, 1H), 2.21 – 2.14 (m, 1H), 1.80 (dd, *J* = 8.5, 4.5 Hz, 1H), 1.60 – 1.48 (m, 3H), 1.42 – 1.38 (m, 1H), 1.27 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 143.99, 113.10, 65.29, 60.91, 60.04, 37.53, 33.01, 25.85, 20.09, 14.22.
IR(KBr) 3393, 2919, 2849, 1644, 1469, 1278, 1103 cm^{-1};
HRMS (ESI): *m/z* calcd. for $C_{10}H_{18}O_2$ $[M + H]^+$ 171.1385, found 171.1376.



Preparation of S2: To a magnetically stirred solution of epoxide **9** (20 mg, 0.117 mmol) in dry THF was added (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (41.2 mg, 0.176 mmol), DCC (36.3 mg, 0.176 mmol) and DMAP (7.2 mg, 0.058 mmol). The resultant mixture was stirred at room temperature for 2 h. The reaction mixture was slowly quenched with aqueous saturated NH_4Cl solution (10 mL), then concentrated under reduced pressure. The residue so-formed was extracted with MTBE (3×20 mL) and combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA–20:1) afforded the product **S2** (39.3 mg, 0.101 mmol, 87%) as a colorless oil. (89% de, determined by ^{1}H NMR analysis of its Mosher ester **S2**).

$[\alpha]_D^{20}$ = +78.66 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 2H), 7.44 – 7.39 (m, 3H), 5.71 – 5.59 (m, 1H), 5.00 – 4.88 (m, 2H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.22 (d, *J* = 11.7 Hz, 1H), 3.55 (s, 3H), 2.87 (dd, *J* = 6.7, 5.3 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.63 – 1.41 (m, 4H), 1.29 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.21, 143.85, 131.96, 129.70, 128.74, 128.46, 127.39, 126.82, 123.22($q_{C\text{-}F}$, *J* = 286 Hz), 113.22, 84.7($q_{C\text{-}F}$, *J* = 28 Hz), 69.75, 61.23, 57.97, 55.44, 37.46, 32.83, 25.73, 20.12, 14.38.
^{19}F NMR (376 MHz, $CDCl_3$) δ -70.44.
IR(KBr) 2933, 2854, 1755, 1666, 1452, 1271, 1168, 721 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{10}H_{18}F_3O_4$ $[M + Na]^+$ 409.1603, found 409.1585.



9 **S3**

Preparation of S3: Magnesium turnings (16.3 g, 670 mmol) and spiked with I_2 (trace) were added to a flame dried three-neck 2 L round-bottom flask assembled with a constant pressure funnel, which had been previously flame dried and allowed to cool under a stream of nitrogen and then, anhydrous THF (200 mL) was added in using syringe. Freshly distilled THF (1 L) mixed with 3-chloro-2-methylpropene (55.1 g, 609 mmol) in the constant pressure funnel were slowly added to the flask and heated to a slight boiling to initiate the reaction. After several minutes, the reaction mixture turned from yellow to turbid gray. After dropping was finished, the reaction was stirred for 3 hours at the room temperature.

To epoxide **9** (20.7 g, 122 mmol) in anhydrous THF (100 mL) at room temperature under N_2 were treated with newly prepared Grignard reagent at 0°C. The resultant mixture was stirred at 0°C for 2 h. The reaction mixture was slowly quenched with aqueous saturated NH_4Cl solution (200 mL), then concentrated under reduced pressure. The residue so-formed was extracted with MTBE (3×200 mL) and combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA– 6:1) afforded the product **S3** (25.3 g, 112 mmol, 92%) as a colorless oil.

$[\alpha]_D^{20}$ = –25 (c 0.10, MeOH);

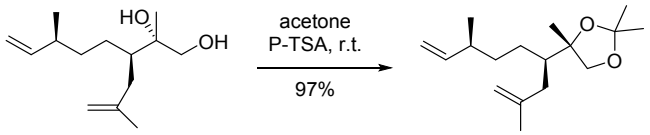
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 4.95 – 4.87 (m, 2H), 4.75 (s, 2H), 3.54 (d, *J* = 11.1 Hz, 1H), 3.38 (d, *J* = 11.1 Hz, 1H), 2.37 (brs, 2H), 2.10 – 2.02 (m, 2H), 1.90 – 1.84 (m,

1H), 1.73 (s, 3H), 1.69 – 1.52 (m, 2H), 1.41 – 1.25 (m, 2H), 1.14 – 1.08 (m, 1H), 1.07 (s, 3H), 0.96 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.58, 144.75, 112.39, 111.68, 75.94, 68.25, 42.68, 39.67, 38.23, 36.17, 27.77, 22.37, 20.07, 19.91.

IR(KBr) 3404, 3074, 2968, 2933, 1645, 1456, 1374, 1042, 994, 909, 888 cm^{-1};

HRMS (ESI): m/z calcd. for $C_{14}H_{26}O_2$ $[M + H]^+$ 227.2011, found 227.2002.



S3 **11**

Preparation of 11: Compound **S3** (51.1 g, 226 mmol) was reacted with acetone (450 mL) in the presence of p-TsOH·H_2O (4.30 g, 22.6 mmol cat.) under a N_2 atmosphere at room temperature over 2 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution (100 mL), then concentrated under reduced pressure. The residue so-formed was extracted with MTBE (3×100 mL) combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA– 20:1) afforded the product **11** (58.3 g, 219 mmol, 97%) as colorless oil.

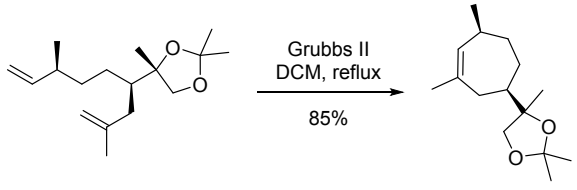
$[\alpha]_D^{20}$ = –21 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (ddd, J = 17.5, 10.3, 7.4 Hz, 1H), 4.95 – 4.87 (m, 2H), 4.73 (d, J = 8.7 Hz, 2H), 3.77 (d, J = 8.5 Hz, 1H), 3.68 (d, J = 8.4 Hz, 1H), 2.03 – 2.10 (m, 1H), 1.97 – 1.84 (m, 2H), 1.72 (s, 3H), 1.70 – 1.66 (m, 1H), 1.64 – 1.50 (m, 1H), 1.40 (s, 3H), 1.38 – 1.25 (m, 5H), 1.21 – 1.13 (m, 4H), 0.96 (d, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.90, 144.39, 112.20, 112.07, 108.59, 84.43, 73.75, 44.28, 40.76, 38.00, 35.56, 28.14, 27.55, 26.89, 22.23, 21.36, 19.85.

IR(KBr) 3075, 2981, 2934, 2864, 1643, 1455, 1377, 1253, 1059, 908, 890 cm^{-1};

HRMS (ESI): m/z calcd. for $C_{17}H_{30}O_2$ $[M + H]^+$ 267.2324, found 267.2314.



11 **7**

Preparation of 7: A solution of diene **11** (6.00 g, 23.0 mmol) in CH_2Cl_2 (1.5 L, 0.015 M) was treated

with Grubbs second generation catalyst (2.40 g, 2.39 mmol), and the reaction mixture was refluxed for 2 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, PE:EA-50:1) afforded the product **7** (4.56 g, 19.2 mmol 85%) as colorless crystals.

*The single crystal of the **A08** was cultivated from a mixture of n-hexane and MTBE.* **X-ray crystallographic data**: see **S37**.

$[\alpha]_D^{20}$ = –48 (c 0.10, MeOH);

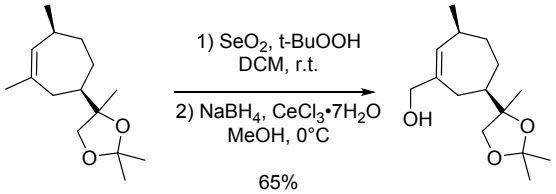
mp 40.5-42.5℃;

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1H), 3.83 (d, *J* = 8.3 Hz, 1H), 3.70 (d, *J* = 8.3 Hz, 1H), 2.33 (s, 1H), 2.17 – 1.98 (m, 2H), 1.93 – 1.79 (m, 1H), 1.77 – 1.71 (m, 1H), 1.68 (s, 3H), 1.58 – 1.63 (m, 2H), 1.52 – 1.42 (m, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H), 0.97 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.15, 131.77, 109.08, 84.17, 73.43, 44.76, 34.57, 33.25, 31.74, 27.41, 27.30, 27.08, 27.04, 23.14, 21.31.

IR(KBr) 2982, 2933, 2856, 1455, 1377, 1368, 1060 cm^{-1};

HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{26}O_2$ $[M + H]^+$ 239.2011, found 239.2001.



7 **S4**

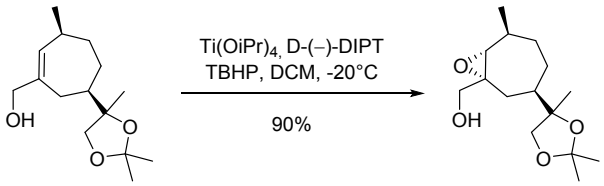
Preparation of S4: Compound **7** (10.0 g, 42.0 mmol) in 100 mL of CH_2Cl_2 was added dropwise to a solution of SeO_2 (466 mg, 4.2mmol) and TBHP (5.13 g, 70% wt% in water, 46.2 mmol) at room temperature, stirring was continued for an additional 30 min at 0 °C, then this mixture was stirred at room temperature for 2 h, the reaction was quenched by an aqueous sat. $Na_2S_2O_3$ solution. The solution was extracted with MTBE (3×150 mL) and combined organic layers were washed with brine, The organic layers were dried over Na_2SO_4, The solvent was evaporated under reduced pressure.

A magnetically stirred solution of the mixture of the previous step and $CeCl_3 \cdot 7H_2O$ (7.82 g, 21 mmol) in MeOH (30 mL) was cooled to 0 °C and then treated, in portions, with sodium borohydride (794 mg, 21 mmol) (CAUTION: EVOLUTION OF HYDROGEN GAS). The resulting mixture was stirred at 0 °C for 1 h before being quenched with water (50 mL) and then concentrated under reduced pressure. The residue so-formed was extracted with MTBE (3×100 mL) and combined organic layers were washed with brine, The combined organic phases were dried over Na_2SO_4, then purified by flash

chromatography on silicagel (PE/EA, 15:1) to give a colorless liquid product **S4** (6.94 g, 27.3 mmol 65%).

$[\alpha]_D^{20}$ = –37 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (s, 1H), 3.92 (d, *J* = 4.4 Hz, 2H), 3.85 (d, *J* = 8.4 Hz, 2H), 3.70 (d, *J* = 8.4 Hz, 2H), 2.38 (s, 1H), 2.17 – 1.80 (m, 4H), 1.71 – 1.44 (m, 4H), 1.39 (s, 3H), 1.37 (s, 3H), 1.20 (s, 3H), 1.00 (d, *J* = 7.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.74, 133.29, 109.10, 84.18, 73.38, 69.46, 45.20, 32.68, 32.03, 29.91, 27.26, 27.11, 27.06, 22.55, 21.13.
IR(KBr) 3425, 2985, 2933, 2867, 1455, 1377, 1250, 1201, 1058 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{26}O_3$ $[M + H]^+$ 255.1960, found 255.1953.



S4 **12**

Preparation of 12: To a stirred mixture of $Ti(O^iPr)_4$ (1.34 g, 4.72 mmol), CaH_2 (10 mg), silica gel (10 mg) and 4 Å molecular sieves (10 mg) in 10 mL of dry CH_2Cl_2 was added D-(–)-diisopropyl tartrate (DIPT) (1.10 g, 4.72 mmol) in 20 mL of dry CH_2Cl_2 at –20 ℃ under N_2 and stirred for 10 min. A solution of compound **S4** (10.0 g, 39.3 mmol) in 30 mL of dry CH_2Cl_2 was injected and stirred for another 10 min. Then the mixture was cooled to –50 ℃, 18.17 mL of anhydrous TBHP (2.6 M in toluene,119 mmol) was injected slowly. After addition, the mixture was allowed to warm to –20 ℃, stirred for 2 h and monitored by TLC. The reaction mixture was quenched by 50 mL of 10% aqueous tartaric acid, warmed to room temperature, and stirring was continued until the aqueous layer became clear. The reaction mixture was extracted with ethyl acetate, washed successively with 5% aqueous NaOH, saturated aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel chromatography (PE/EA–3:1) to give epoxide **12** (9.56 g, 35.4 mmol, 90%).

$[\alpha]_D^{20}$ = +4 (c 0.10, MeOH);

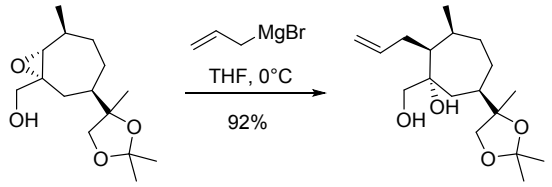
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (d, *J* = 8.3 Hz, 1H), 3.72 (d, *J* = 8.3 Hz, 1H), 3.61 (dd, *J* = 12.1, 5.3 Hz, 1H), 3.51 (dd, *J* = 12.1, 7.6 Hz, 1H), 3.07 (d, *J* = 5.1 Hz, 1H), 2.44 – 2.41 (m, 1H), 1.90 – 1.75

(m, 3H), 1.70 – 1.47 (m, 4H), 1.40 (s, 3H), 1.34 (s, 3H), 1.17 (s, 3H), 1.12 – 1.06 (m, 1H), 1.04 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.17, 83.83, 73.92, 66.66, 63.63, 62.44, 43.26, 31.21, 30.96, 29.96, 27.58, 26.87, 24.53, 21.09, 15.87.

IR(KBr) 3454, 2984, 2933, 2867, 1455, 1378, 1212, 1057 cm^{-1};

HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{26}O_4$ $[M + H]^+$ 271.1909, found 271.1901.



12 **S5**

Preparation of S5: To epoxide **12** (14.0 g, 51.8 mmol) and copper iodide (990 mg, 5.20 mmol) in anhydrous THF (100 mL) at room temperature under N_2 were treated with allylmagnesium bromide (129 mL, 129 mmol 1 M in ether) in THF at 0°C. The resultant mixture was stirred at 0 °C for 2 h. The reaction mixture was slowly quenched with aqueous saturated NH_4Cl solution (20 mL), then concentrated under reduced pressure. The residue so-formed was extracted with MTBE (3×100 mL) and combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA– 1:1) afforded the product **S5** (14.9 g, 47.7 mmol, 92%) as colorless oil.

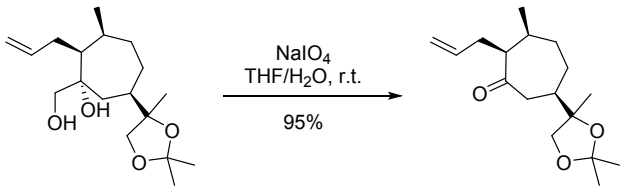
$[\alpha]_D^{20}$ = +37 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dddd, *J* = 17.0, 10.0, 8.1, 5.8 Hz, 1H), 5.07 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.99 (dd, *J* = 10.1, 0.9 Hz, 1H), 3.82 (d, *J* = 8.3 Hz, 1H), 3.69 (d, *J* = 8.3 Hz, 1H), 3.53 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.33 (dd, *J* = 11.1, 6.6 Hz, 1H), 2.42 (dddd, *J* = 10.9, 7.0, 5.6, 1.5 Hz, 1H), 2.27 – 2.16 (m, 1H), 2.13 (s, 1H), 2.04 – 1.94 (m, 2H), 1.90 – 1.82 (m, 2H), 1.65 (s, 1H), 1.63 – 1.48 (m, 2H), 1.45 – 1.41 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.28 – 1.17 (m, 2H), 1.16 (s, 3H), 0.95 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.57, 114.98, 109.07, 84.19, 75.81, 73.81, 69.33, 50.07, 39.28, 38.63, 30.54, 30.33, 28.17, 27.72, 27.49, 27.10, 22.17, 20.77.

IR(KBr) 3435, 2983, 2934, 2869, 1377, 1058, 988, 908 cm^{-1};

HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{32}O_4$ $[M + Na]^+$ 335.2199, found 335.2184.

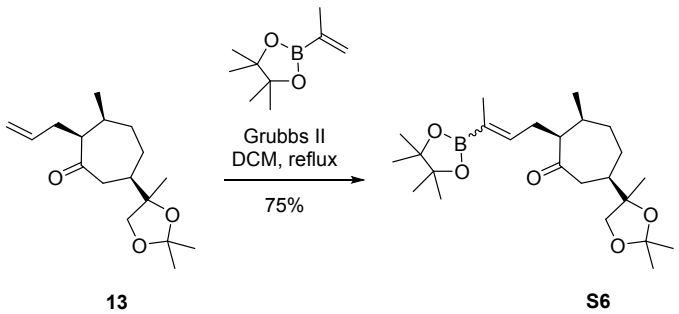


S5 **13**

Preparation of 13: To a solution of **S5** (20.0 g, 64.1 mmol) in 20:1 mixture of THF (100 mL) and water (5 mL) was added $NaIO_4$ (16.5 g, 76.9 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was slowly quenched with aqueous saturated $Na_2S_2O_3$ solution (20 mL). The aqueous layer was back-extracted with MTBE (3×100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA–15:1) afforded the product **13** (17.1 g, 60.9 mmol, 95%) as colorless oil.

$[\alpha]_D^{20}$ = +72 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dddd, *J* = 16.1, 10.0, 8.1, 5.8 Hz, 1H), 5.00 – 4.93 (m, 2H), 3.75 (d, *J* = 8.6 Hz, 1H), 3.62 (d, *J* = 8.6 Hz, 1H), 2.89 (td, *J* = 7.1, 2.3 Hz, 1H), 2.58 – 2.42 (m, 1H), 2.34 (dt, *J* = 17.4, 2.8 Hz, 1H), 2.21 – 1.86 (m, 5H), 1.84 – 1.68 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.24–1.14 (m, 4H), 0.72 (d, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 212.32, 136.70, 116.36, 109.27, 83.42, 72.63, 54.32, 47.16, 43.81, 37.05, 33.68, 33.11, 27.27, 27.08, 24.95, 21.05, 13.65.
IR(KBr) 2983, 1699, 1379, 1058, 993, 912 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{28}O_3$ $[M + Na]^+$ 303.1936, found 303.1921.



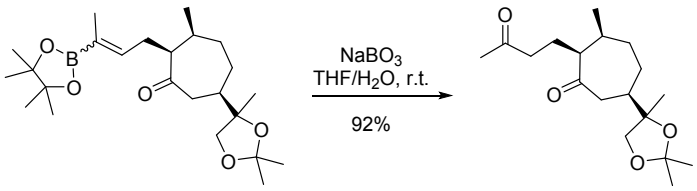
13 **S6**

Preparation of S6: A solution of grubbs second generation catalyst (1.82 g, 2.14 mmol) in 50 mL of anhydrous CH_2Cl_2 was added to a solution of 2-(1-methylethenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.00 g, 53.5 mmol) under a nitrogen atmosphere. The reaction mixture was brought to reflux. A solution of **13** (3.00 g, 10.7 mmol) in 100 mL of CH_2Cl_2 was slowly added 2 h via a syringe pump. The solvent was concentrated under reduced pressure. Purification by flash column

chromatography (silica gel, PE/EA–20:1) afforded the product **S6** (3.38 g, 8.03 mmol, 75%) as colorless oil.

$[\alpha]_D^{20}$ = +41 (c 0.10, MeOH);

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.15 – 6.12 (m, 1H), 3.79 (d, *J* = 8.6 Hz, 1H), 3.65 (d, *J* = 8.5 Hz, 1H), 2.97 (ddd, *J* = 8.1, 6.1, 2.2 Hz, 1H), 2.53 – 2.43 (m, 1H), 2.39 (ddd, *J* = 17.7, 3.8, 2.1 Hz, 1H), 2.25 – 2.20 (m, 1H), 2.18 – 2.13 (m, 1H), 2.09 – 2.00 (m, 2H), 1.95 (dt, *J* = 14.0, 2.8 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.69 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.25 (s, 13H), 1.20 (s, 3H), 0.77 (d, *J* = 7.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 212.57, 143.66, 109.28, 83.46, 83.14, 72.68, 54.22, 47.10, 43.82, 37.08, 33.27, 28.58, 27.34, 27.07, 25.04, 24.81, 24.77, 21.02, 14.09, 13.70.
IR(KBr) 2980, 1698, 1378, 1369, 1146, 1058, 860, 670 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{41}BO_5$ $[M + Na]^+$ 443.2945, found 443.2939.



S6 **14**

Preparation of 14: To a solution of **S6** (1.60 g, 3.81 mmol) in 5:1 mixture of THF (10 mL) and water (2 mL) was added $NaBO_3 \cdot 4H_2O$ (1.75 g, 11.4 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was slowly quenched with aqueous saturated $Na_2S_2O_3$ solution, The aqueous layer was back-extracted with MTBE (3×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA–15:1) afforded the product **14** (1.09 g, 3.50 mmol, 92%) as a pale colorless oil.

$[\alpha]_D^{20}$ = +43 (c 0.10, MeOH);

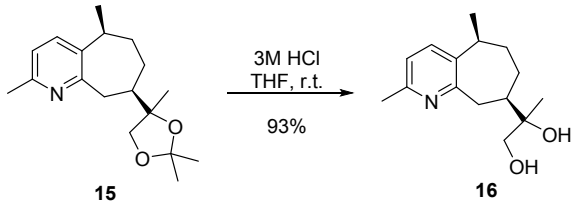
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.79 (d, *J* = 8.6 Hz, 1H), 3.66 (d, *J* = 8.6 Hz, 1H), 2.88 (ddd, *J* = 9.6, 4.4, 2.4 Hz, 1H), 2.45 (ddd, *J* = 17.2, 8.7, 5.9 Hz, 1H), 2.37 (ddd, *J* = 17.7, 4.0, 2.3 Hz, 1H), 2.26 (ddd, *J* = 17.2, 8.5, 6.3 Hz, 1H), 2.17 (dd, *J* = 17.7, 12.3 Hz, 1H), 2.11 (s, 4H), 2.09 – 1.97 (m, 2H), 1.92 (d, *J* = 14.6 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.49 (dddd, *J* = 13.4, 8.7, 6.3, 4.3 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.21 (s, 4H), 0.76 (d, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 212.54, 208.67, 109.32, 83.41, 72.51, 54.01, 47.27, 43.65, 41.78, 36.98, 34.91, 29.86, 27.29, 27.07, 24.89, 24.17, 21.30, 13.97.
IR(KBr) 2932, 2874, 1715, 1698, 1378, 1368, 1057 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{30}O_4$ $[M + Na]^+$ 333.2042, found 333.2035.

14 **15**

Preparation of 15: To a solution of **14** (1.50 g, 4.84 mmol) in EtOH (10 mL) was added $Cu(OAc)_2$ (1.06 g, 5.81 mmol) and NH_4OAc (447 mg, 5.81 mmol). The reaction mixture was stirred for 12 h at room temperature and then filtered over a pad of Celite and concentrated in vacuo. The residue was diluted with water (20 mL) and extracted with MTBE (3×20 mL), and the combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (PE/EA–5:1) to give product **15** as colorless oil (1.19 g, 4.11 mmol, 85%).

$[\alpha]_D^{20}$ = +21 (c 0.10, MeOH);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 4.03 (d, *J* = 8.5 Hz, 1H), 3.85 (d, *J* = 8.5 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.95 – 2.81 (m, 2H), 2.47 (s, 3H), 2.04 (d, *J* = 13.4 Hz, 1H), 1.81 – 1.71 (m, 3H), 1.61 – 1.51 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.29 (d, *J* = 7.3 Hz, 3H), 1.24 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.60, 154.58, 137.15, 136.41, 121.02, 109.13, 84.30, 74.49, 45.39, 41.60, 37.58, 33.41, 27.38, 27.19, 25.26, 23.81, 19.99, 18.29.
IR(KBr) 2932, 2866, 1462, 1377, 1208, 1058 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{27}NO_2$ $[M + H]^+$ 290.2120, found 290.2111.

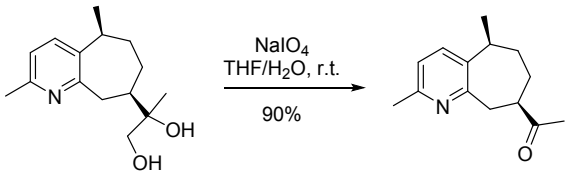


15 **16**

Preparation of 16: To a stirred solution of compound **15** (1.50 g, 5.18 mmol) in THF (5 mL) was added aqueous 3 M HCl (5 mL) at room temperature. After stirring for 6 hours at room temperature. The reaction mixture was slowly quenched with aqueous saturated $NaHCO_3$ solution, then mixture was extracted with MTBE (3×20 mL). The combined organic layer was dried over Na_2SO_4. filtered, and concentrated in vacuo. The residue was purified by silica column chromatography (CH_2Cl_2/MeOH–15:1) to afford product **16** (1.20 g, 4.82mmol, 93%) as a colorless oil.

$[\alpha]_D^{20}$ = +20 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 3.50 (d, *J* = 11.8 Hz, 1H), 3.21 (d, *J* = 11.7 Hz, 1H), 3.17 – 2.97 (m, 3H), 2.47 (s, 3H), 1.95 – 1.78 (m, 2H), 1.74 – 1.61 (m, 1H), 1.55 – 1.41 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.09 (s, 3H), 1.05 – 0.84 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.62, 154.24, 136.24, 134.35, 121.43, 73.50, 65.32, 43.67, 35.39, 34.11, 33.61, 25.09, 23.49, 23.21, 18.74.
IR(KBr) 3400, 2928, 1592, 1463, 1375, 830 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{23}NO_2$ $[M + H]^+$ 250.1807, found 250.1799.

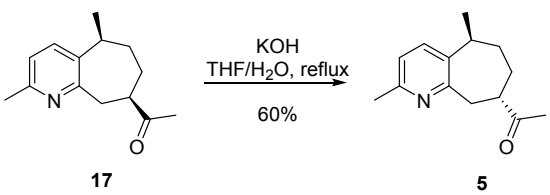


16 **17**

Preparation of 17: To a solution of **16** (1.50 g, 6.02 mmol) in 5:1 mixture of THF (5 mL) and water (1 mL) was added $NaIO_4$ (1.54 g, 7.23 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was slowly quenched with aqueous saturated $Na_2S_2O_3$ solution (20 mL), The aqueous layer was back-extracted with MTBE (3×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA–1:1) afford product **17** (1.18 g, 5.42 mmol, 90%) as a colorless oil.

$[\alpha]_D^{20}$ = –60 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 3.31 (dd, *J* = 14.7, 9.3 Hz, 1H), 3.23 (dd, *J* = 14.7, 3.2 Hz, 1H), 3.02 – 2.94 (m, 1H), 2.68 (tt, *J* = 9.1, 3.3 Hz, 1H), 2.47 (s, 3H), 2.21 (s, 3H), 2.07 – 1.98 (m, 1H), 1.90 – 1.66 (m, 2H), 1.30 (d, *J* = 7.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 210.83, 157.49, 154.66, 137.76, 135.96, 121.25, 49.48, 39.68, 37.43, 32.16, 28.59, 28.15, 23.88, 18.87.
IR(KBr) 2924, 1708, 1463, 1353, 825 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{19}NO$ $[M + H]^+$ 218.1545, found 218.1538.



17 **5**

Preparation of 5: To a solution of **17** (250 mg, 1.15 mmol) in 10:1 mixture of THF (5 mL) and water (0.5 mL) was added KOH (130 mg, 2.30 mmol) at reflux for 3 h. The reaction mixture was slowly quenched with aqueous saturated NH_4Cl solution (10 mL), The aqueous layer was back-extracted with MTBE (3×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA–1:1) afforded the **17** and **5** (238 mg, 1.09 mmol, 95%) as a pale yellow solid.

The mixture was added to 10:1 mixture of n-hexane (1 mL) and MTBE (0.2 mL), then reflux and filter, the solution was volatilized naturally and slowly to obtain crystal **5**. Then, the mixture was cleaned with n-hexane for three times to afford product **5** (150 mg, 0.69 mmol, 60%) as colorless transparent crystal.

$[\alpha]_D^{20}$ = –26 (c 0.10, MeOH);

mp 105.5–107 °C;

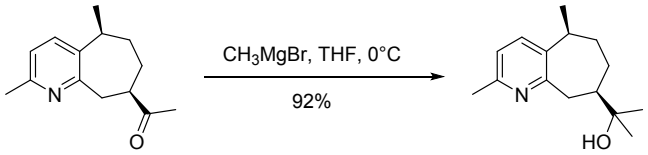
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 3.26 – 3.08 (m, 2H), 3.00 – 2.90 (m, 1H), 2.58 – 2.52 (m, 1H), 2.49 (s, 3H), 2.21 (s, 3H), 2.12 – 2.01 (m, 1H), 1.93 – 1.77 (m, 2H), 1.33 (d, *J* = 7.3 Hz, 3H), 1.30 – 1.21 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.13, 159.19, 154.46, 137.74, 132.39, 121.12, 49.54, 39.62, 35.02, 34.75, 32.99, 28.48, 23.88, 20.33.

IR(KBr) 2916, 1706, 1463, 1357, 826 cm^{-1};

HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{19}NO$ $[M + H]^+$ 218.1545, found 218.1536.

*The single crystal of the **5** was cultivated from a mixture of n-hexane and MTBE.* **X-ray crystallographic data**: see **S39**.



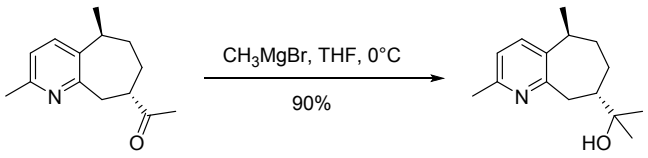
17 **19**

Preparation of 19: To compound **17** (50 mg, 0.23 mmol) in anhydrous THF (2 mL) at room temperature under N_2 were treated with methylmagnesium bromide (1M in ether, 0.69 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 minutes. The reaction mixture was slowly quenched with aqueous saturated NH_4Cl solution (5 mL). The aqueous layer was back-extracted with MTBE (3×10 mL) and combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica

gel, CH_2Cl_2/MeOH–15:1) afforded the product **19** (49 mg, 0.21 mmol, 92%) as a pale colorless oil.

$[\alpha]_D^{20}$ = +3 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 3.24 (dd, *J* = 14.6, 4.5 Hz, 1H), 3.03 – 2.98 (m, 2H), 2.47 (s, 3H), 1.95 – 1.80 (m, 1H), 1.80 – 1.66 (m, 2H), 1.65 – 1.55 (m, 1H), 1.52 – 1.37 (m, 1H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 1.23 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.24, 154.57, 136.87, 135.45, 120.96, 73.73, 47.18, 39.31, 36.33, 33.67, 27.34, 26.82, 26.03, 23.85, 18.60.
IR(KBr) 3400, 2924, 1462, 1376, 826 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{19}NO$ $[M + H]^+$ 234.1858, found 234.1851.

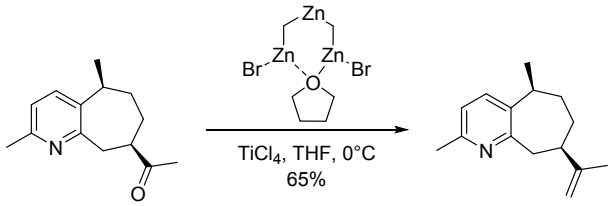


5 **21**

Preparation of 21: To compound **5** (50 mg, 0.23 mmol) in anhydrous THF (2 mL) at room temperature N_2 were treated with methylmagnesium bromide (1M in ether,0.69 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 minutes. The reaction mixture was slowly quenched with aqueous saturated NH_4Cl solution (5 mL), The aqueous layer was back-extracted with MTBE (3×10 mL) and combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH–15:1) afforded the product **21** (49.4 mg, 0.21 mmol, 90%) as a pale colorless oil.

$[\alpha]_D^{20}$ = –26 (c 0.10, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 3.23 (d, *J* = 13.3 Hz, 1H), 2.99 – 2.91 (m, 1H), 2.90 – 2.80 (m, 1H), 2.46 (s, 3H), 2.08 (dt, *J* = 13.3, 2.5 Hz, 1H), 1.88 (d, *J* = 12.9, 4.3 Hz, 1H), 1.64 – 1.50 (m, 1H), 1.40 (t, *J* = 11.0 Hz, 1H), 1.30 (d, 3H), 1.23 (s, 6H), 0.91 – 0.74 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 160.86, 154.00, 137.98, 132.39, 120.64, 73.15, 47.88, 39.29, 36.10, 35.12, 32.71, 27.74, 25.60, 23.63, 20.59.
IR(KBr) 3396, 2920, 1463, 1366, 819 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{19}NO$ $[M + H]^+$ 234.1858, found 234.1852.

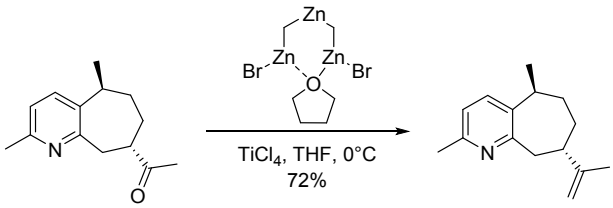


17 **3**

Preparation of 3: To a stirred suspension of Nysted reagent (1.57 g, 20 wt% suspension in THF, ca. 0.69 mmol) was added $TiCl_4$ (87.0 mg, 0.46 mmol) at 0 °C. The resultant mixture was stirred at that temperature for 10 min before a solution of compound **17** (10 mg, 0.046 mmol) in THF (1 mL) was added. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution (5 mL), then concentrated under reduced pressure. The residue so-formed was extracted with MTBE (3×20 mL) combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA–10:1) afforded the product **3** (6.5 mg, 0.03 mmol 65%) as colorless oil.

$[\alpha]_D^{20} = -23$ (c 0.10, MeOH);

^{1}H NMR (400 MHz, Benzene-d_6) δ 6.97 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 4.82 (s, 1H), 4.74 (s, 1H), 3.40 (d, J = 14.3, 1H), 3.26 (dd, J = 14.3, 9.6 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.45 (s, 3H), 2.20 (t, J = 10.0 Hz, 1H), 1.85 – 1.74 (m, 1H), 1.72 (s, 3H), 1.66 – 1.62 (m, 1H), 1.62 – 1.54 (m, 2H), 1.12 (d, J = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, Benzene-d_6) δ 159.66, 155.05, 151.09, 137.37, 135.93, 120.64, 109.16, 44.66, 44.48, 38.09, 33.54, 31.30, 24.12, 20.91, 18.53.
IR(KBr) 3070, 2961, 2922, 2854, 1644, 1590, 1573, 1460, 886,821 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{21}N$ $[M + H]^+$ 216.1752, found 216.1752.



5 **20**

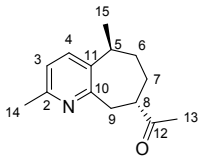
Preparation of 20: To a stirred suspension of Nysted reagent (1.57 g, 20 wt% suspension in THF, ca. 0.69 mmol) was added $TiCl_4$ (87.0 mg, 0.46 mmol) at 0 °C. The resultant mixture was stirred at that temperature for 10 min before a solution of compound **5** (10 mg, 0.046 mmol) in THF (1 mL) was

added. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution (5 mL), then concentrated under reduced pressure. The residue so-formed was extracted with MTBE (3×20 mL) combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, PE/EA–10:1) afforded the product **20** (7.2 mg, 0.033 mmol 72%) as colorless oil.

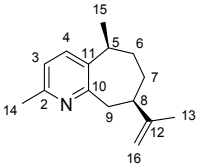
$[\alpha]_D^{20} = -4$ (c 0.10, MeOH);

^{1}H NMR (400 MHz, Benzene-d_6) δ 7.11 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 4.79 (s, 1H), 4.75 (s, 1H), 3.39 (d, J = 13.3 Hz, 1H), 3.05 (dd, J = 13.3, 10.9 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.48 (s, 3H), 2.14 – 2.01 (m, 1H), 1.89 – 1.77 (m, 1H), 1.68 (s, 3H), 1.65 – 1.48 (m, 2H), 1.19 – 1.00 (m, 4H).
^{13}C NMR (100 MHz, Benzene-d_6) δ 161.25, 154.68, 151.30, 137.79, 131.80, 120.55, 109.05, 44.76, 44.72, 37.61, 36.76, 35.34, 24.07, 20.74, 20.64.
IR(KBr) 3070, 2961, 2922, 2854, 1644, 1590, 1573, 1460, 886,821 cm^{-1};
HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{21}N$ $[M + H]^+$ 216.1752, found 216.1752.

3. Comparison of ^{1}H NMR and ^{13}C NMR data of rupestine D (5) and cananodine (3) by table



rupestine D (**5**)



guaipyridine (**3**)

Table 1. ^{1}H NMR comparision

	natural **5** ($CDCl_3$)	synthetic **5** ($CDCl_3$)	natural **3** (Benzene-d_6)	synthetic **3** (Benzene-d_6)
3	7.00 (d, J = 8.0)	6.98 (d, J = 7.8)	6.96 (d, J = 7.7)	6.97 (d, J = 7.6)
4	7.40 (d, J = 8.0)	7.37 (d, J = 7.8)	6.63 (d, J = 7.7)	6.64 (d, J = 7.7)
5	3.04 - 2.94 (m)	3.00 - 2.90 (m)	2.72 - 2.66 (m)	2.75 - 2.65 (m)
6α	1.30 - 1.23 (m)	1.30 - 1.21 (m)	1.59 - 1.55 (m)	1.62 - 1.54 (m)
6β	1.94 - 1.82 (m)	1.93 - 1.77 (m)	1.59 - 1.55 (m)	1.62 - 1.54 (m)
7α	1.94 - 1.82 (m)	1.93 - 1.77 (m)	1.83 - 1.76 (m)	1.85 - 1.74 (m)
7β	2.11 - 2.04 (m)	2.12 - 2.01 (m)	1.64 - 1.60 (m)	1.66 - 1.62 (m)
8	2.60 - 2.54 (m)	2.58 - 2.52 (m)	2.19 (br t, J = 10.0)	2.20 (t, J = 10.0)

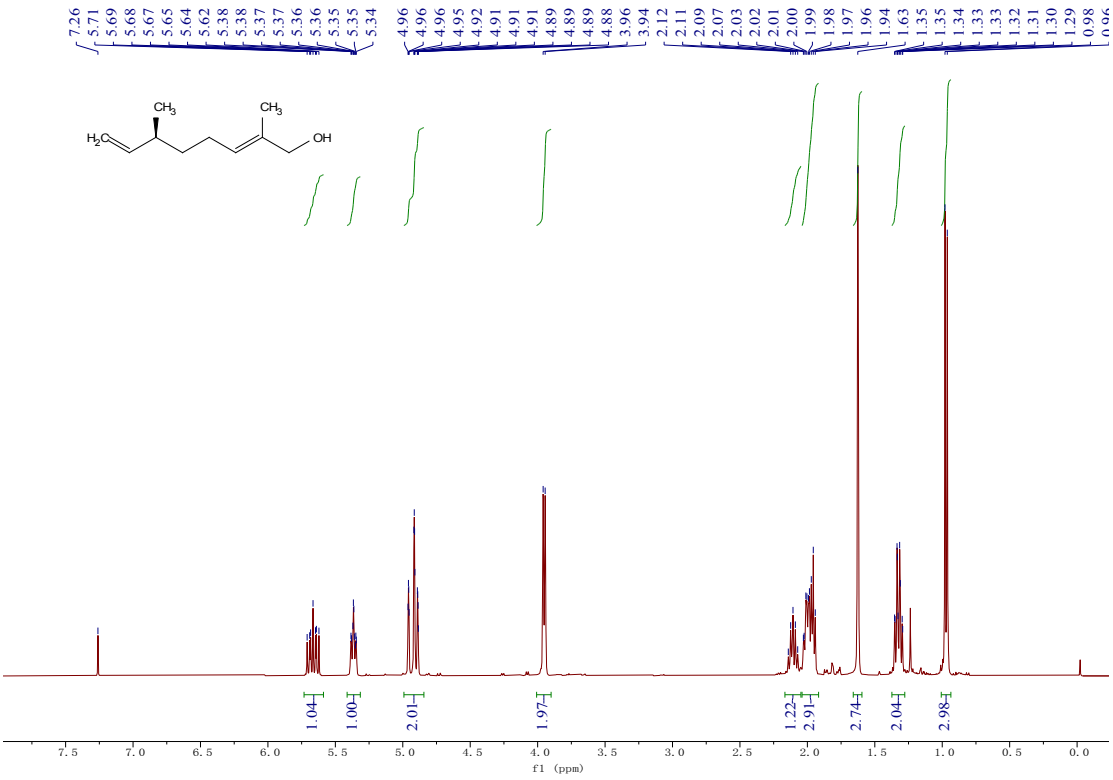
9***α***	3.28 - 3.13 (m)	3.26 - 3.08 (m)	3.41 (br d, J = 14.3)	3.40 (d, J = 14.3)
9***β***	3.28 - 3.13 (m)	3.26 - 3.08 (m)	3.27 (dd, J = 14.3, 9.8)	3.26 (dd, J = 14.3, 9.6)
13	2.23 (s)	2.21 (m)	1.73 (s)	1.72 (s)
14	2.51 (s)	2.49 (m)		
15	1.35 (d, J = 7.2)	1.33 (d, J = 7.3)		
16***α***			4.82 (s)	4.82 (s)
16***β***			4.75 (1H, br s)	4.74 (s)

Table 2. ^{13}C NMR comparision

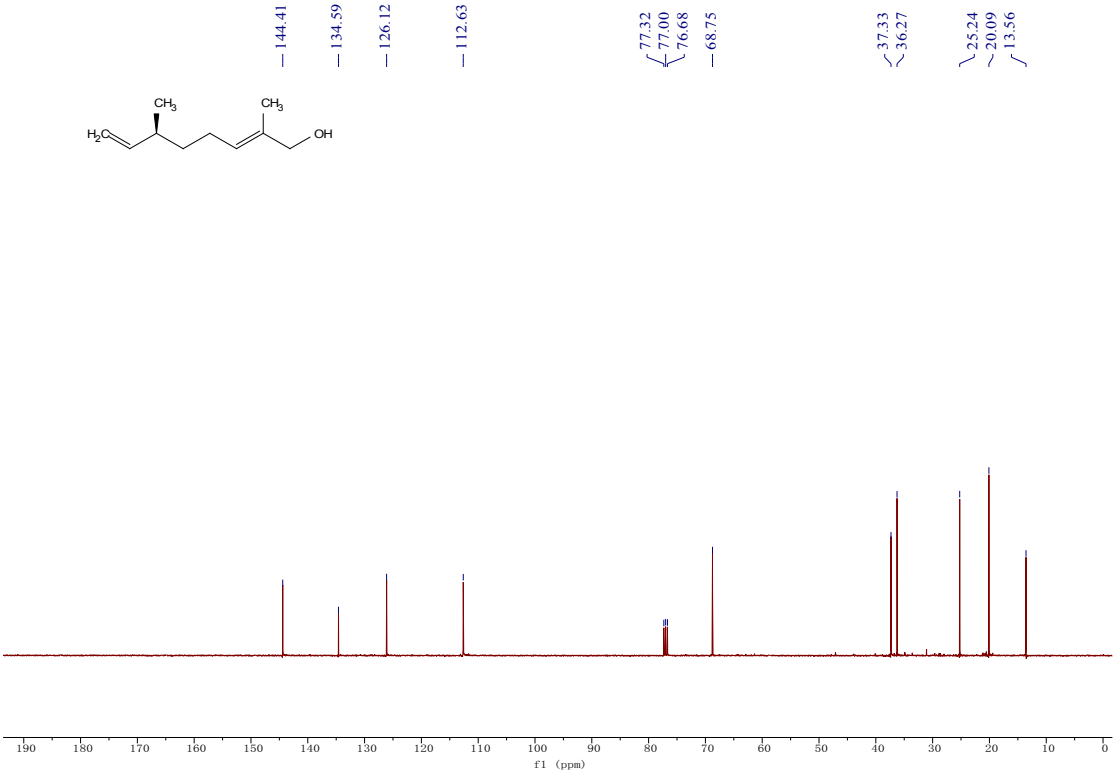
	Rupestine D ($CDCl_3$)	**5** ($CDCl_3$)	Guaipyridine (Benzene-d_6)	**3** (Benzene-d_6)
2	154.36	154.46	154.8	155.05
3	121.24	121.12	120.5	120.64
4	132.60	132.39	135.8	135.93
5	34.76	34.75	37.8	38.09
6	34.96	35.05	33.4	33.54
7	32.92	32.99	31.4	31.30
8	49.47	49.54	44.6	44.66
9	39.43	39.62	44.4	44.48
10	159.05	159.17	159.7	159.66
11	137.90	137.74	137.3	137.37
12	211.07	211.13	150.9	151.09
13	28.49	28.48	20.8	20.91
14	23.71	23.88	24	24.12
15	20.32	20.33	18.4	18.53
16			109	109.16

4. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra of the synthesized compounds

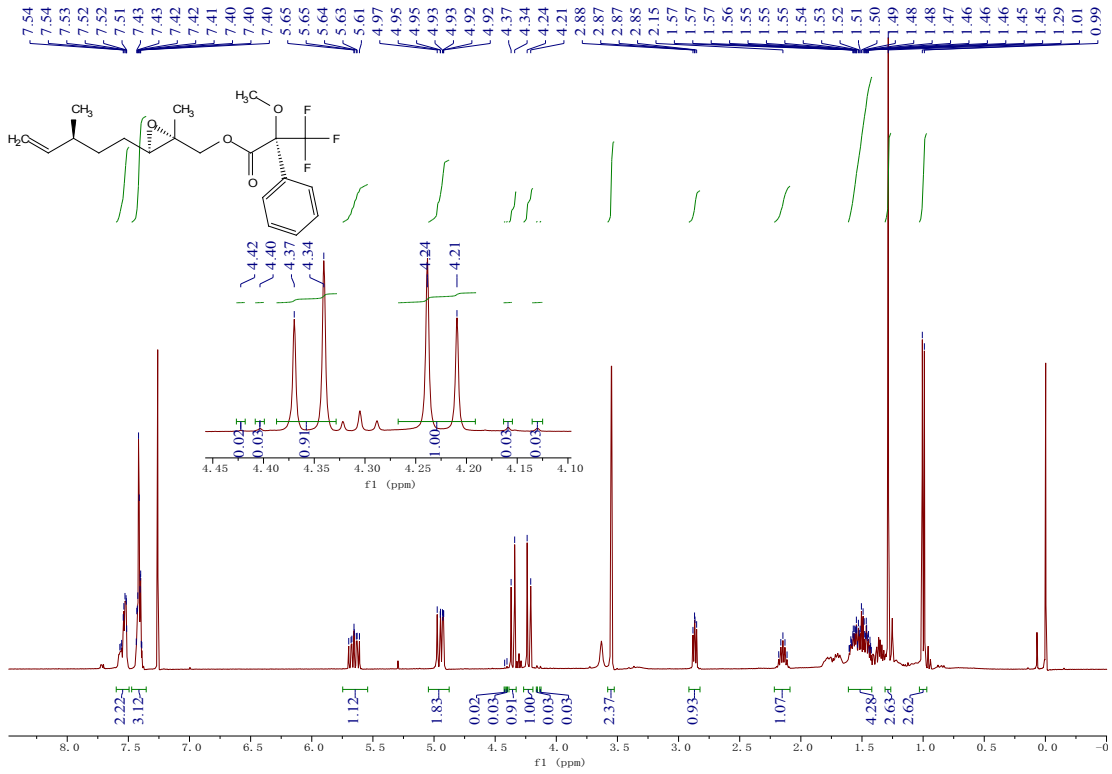
^{1}H NMR spectra of **S1** ($CDCl_3$, 400 MHz)



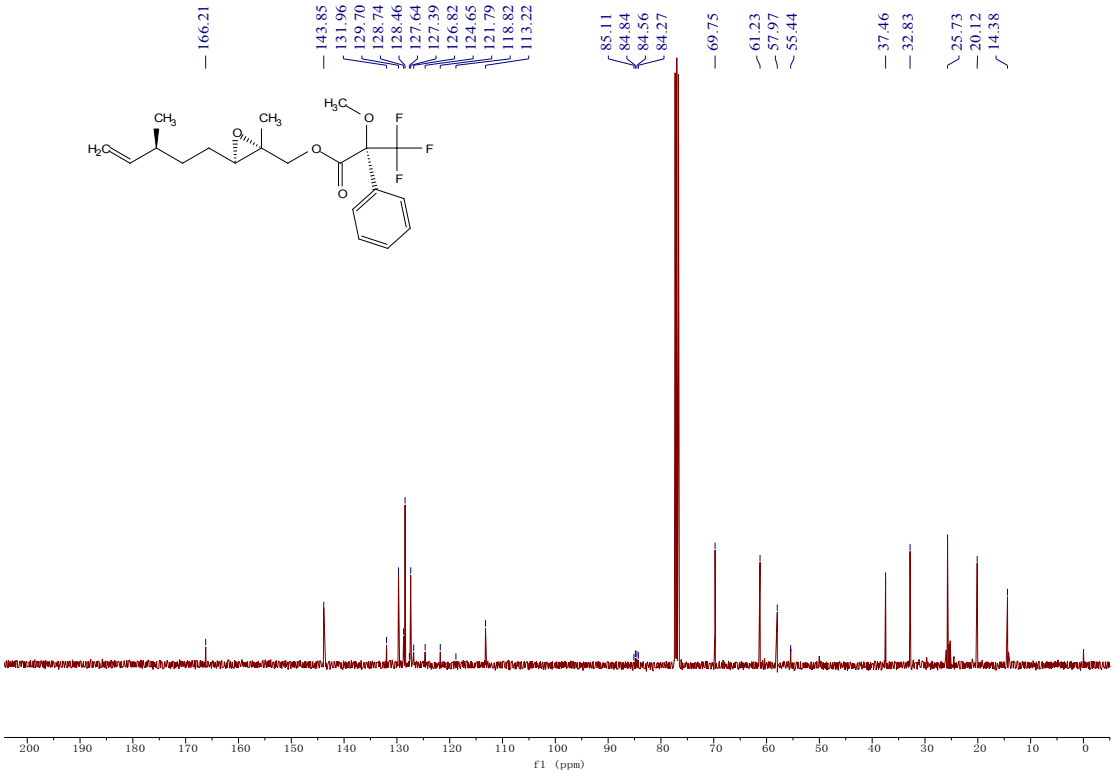
^{13}C NMR spectra of **S1** ($CDCl_3$, 100 MHz)



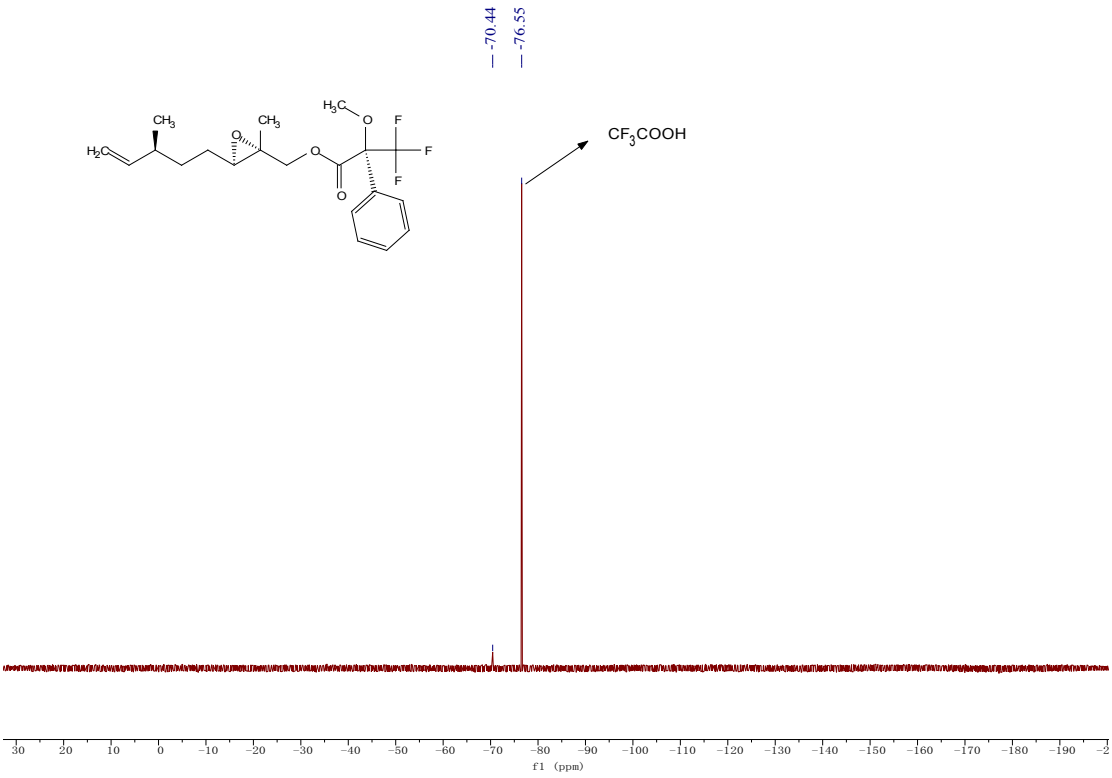
^{1}H NMR spectra of **S2** ($CDCl_3$, 400 MHz)



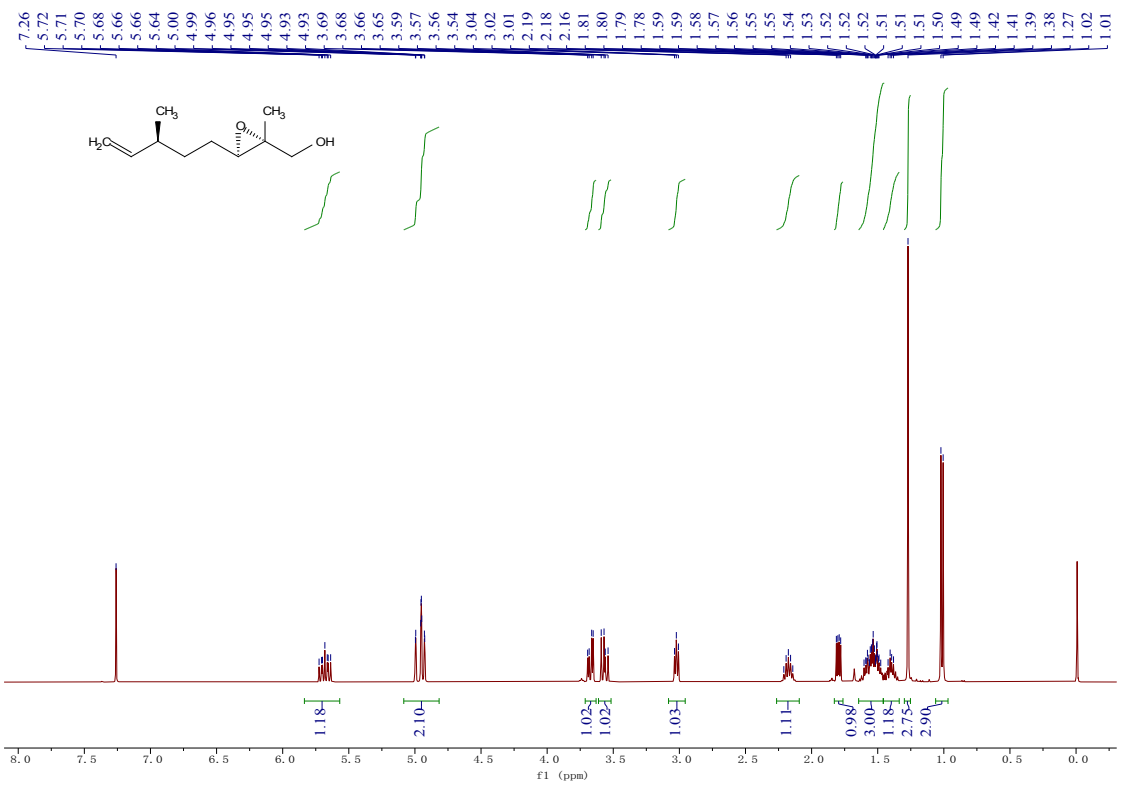
^{13}C NMR spectra of **S2** (CDCl$_3$, 100 MHz)



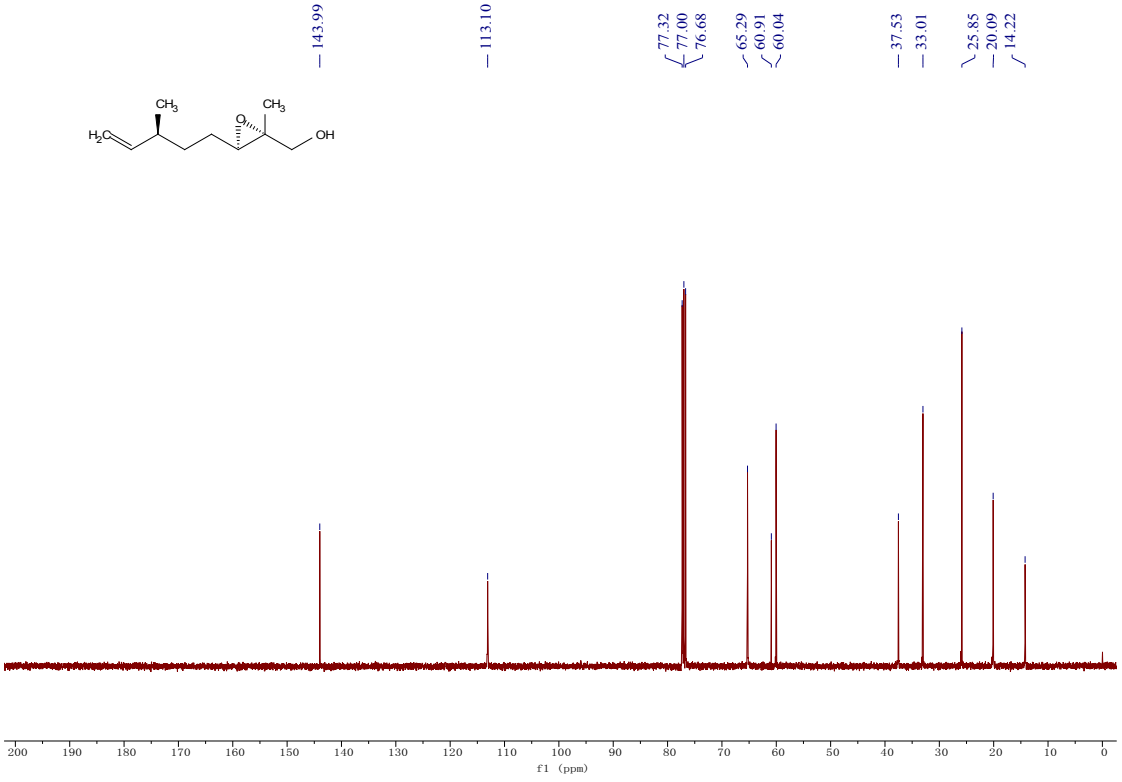
^{19}F NMR spectra of **S2** (CDCl$_3$, 376 MHz)



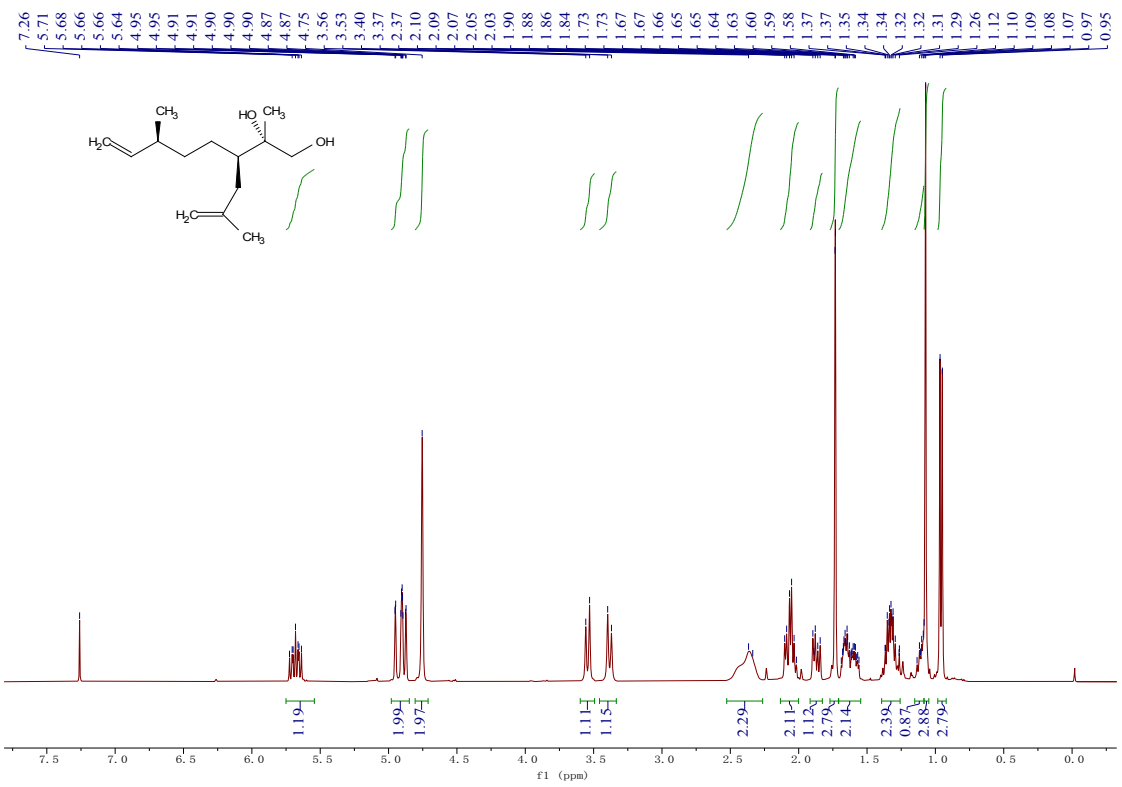
^{1}H NMR spectra of **9** ($CDCl_3$, 400 MHz)



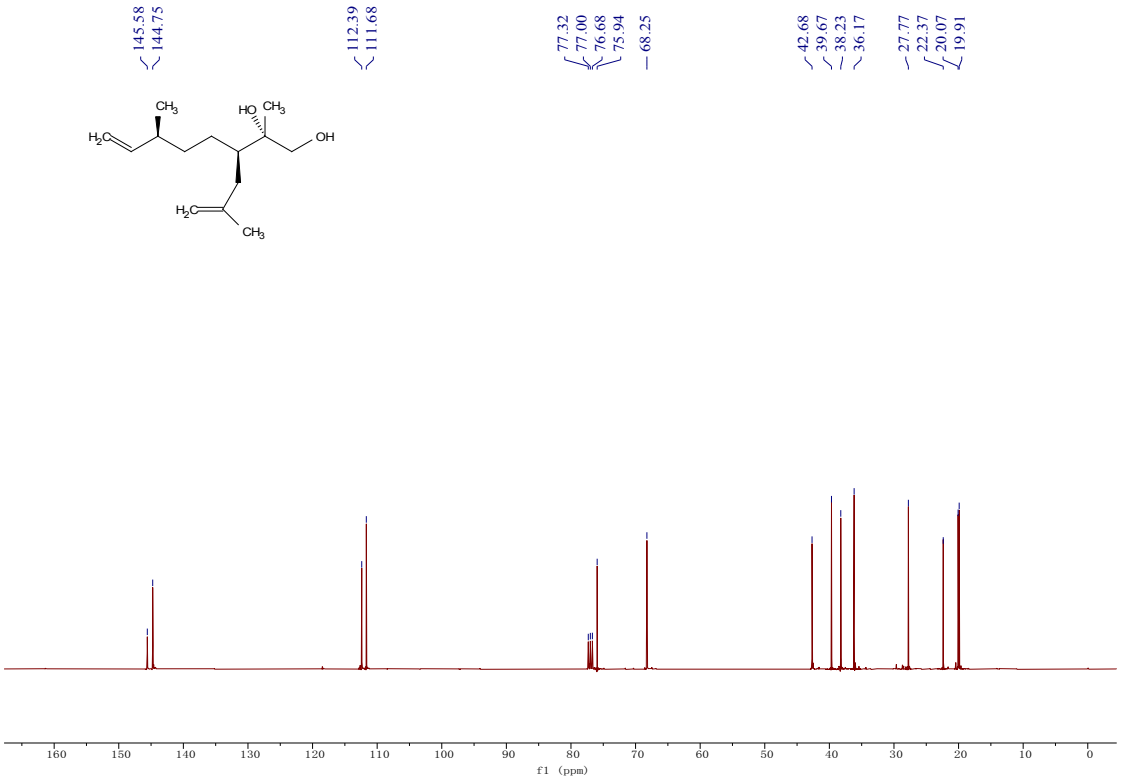
^{13}C NMR spectra of **9** ($CDCl_3$, 100 MHz)



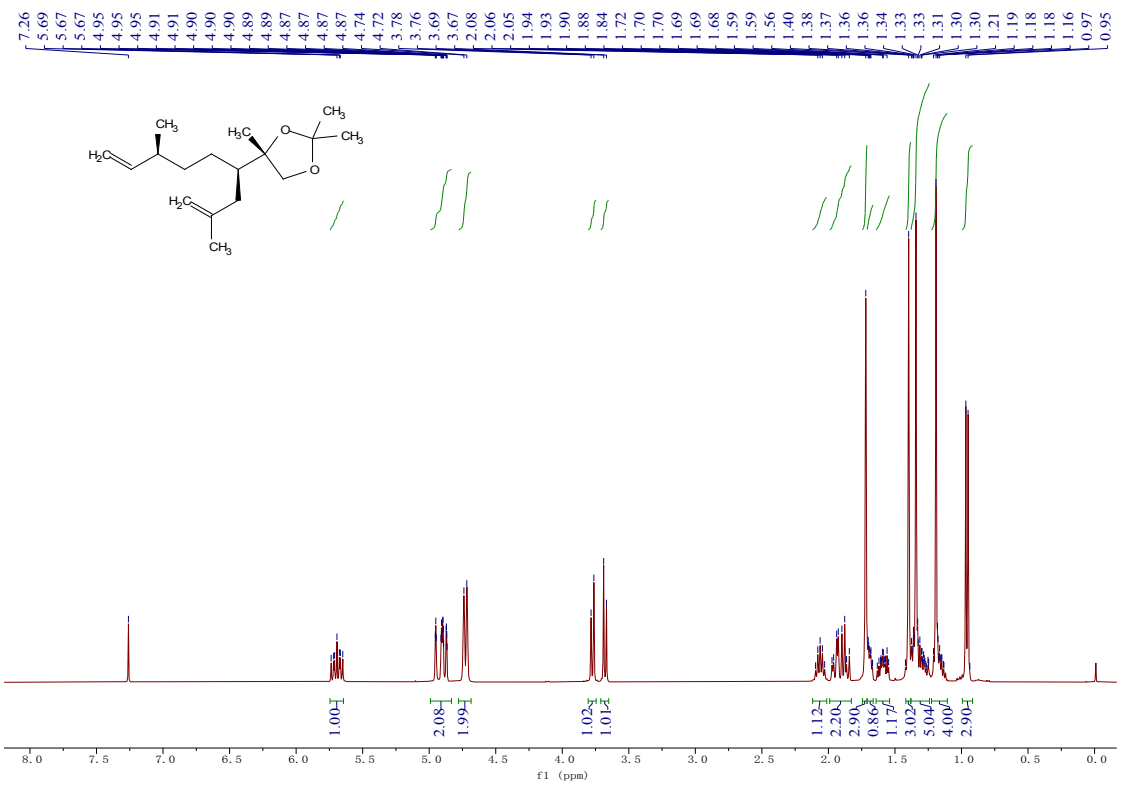
^{1}H NMR spectra of **S3** ($CDCl_3$, 400 MHz)



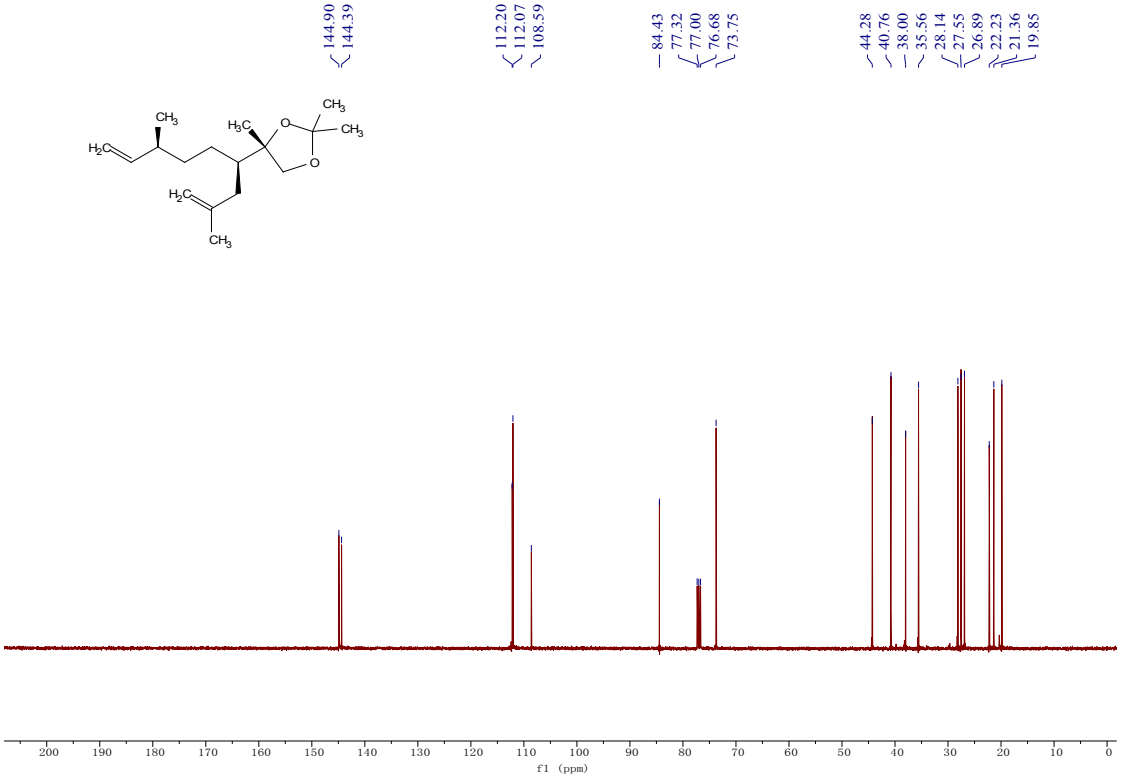
^{13}C NMR spectra of **S3** ($CDCl_3$, 100 MHz)



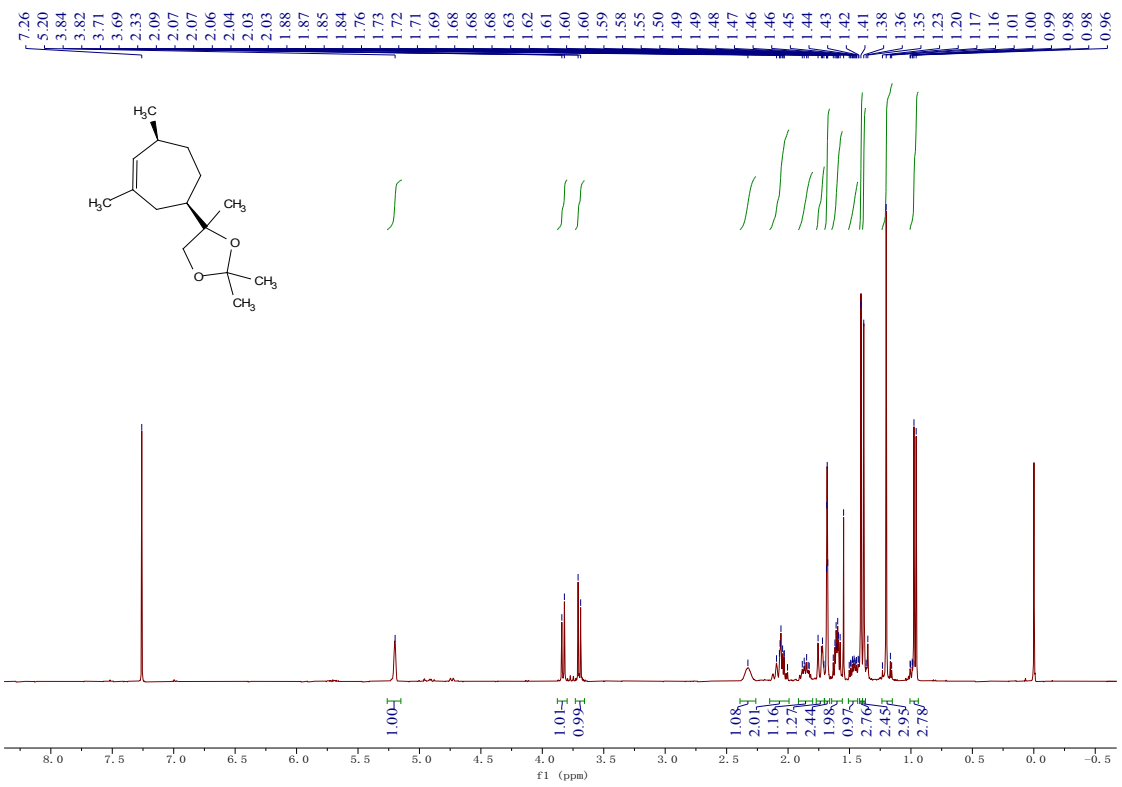
^{1}H NMR spectra of **11** ($CDCl_3$, 400 MHz)



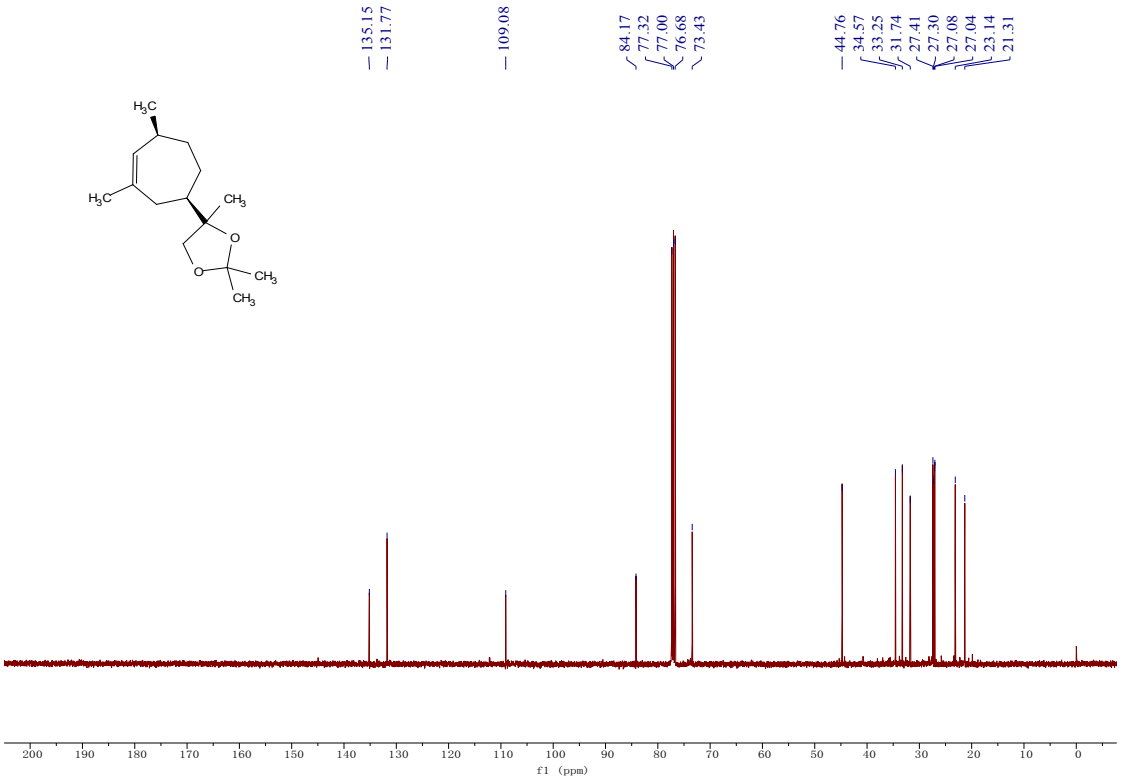
^{13}C NMR spectra of **11** ($CDCl_3$, 100 MHz)



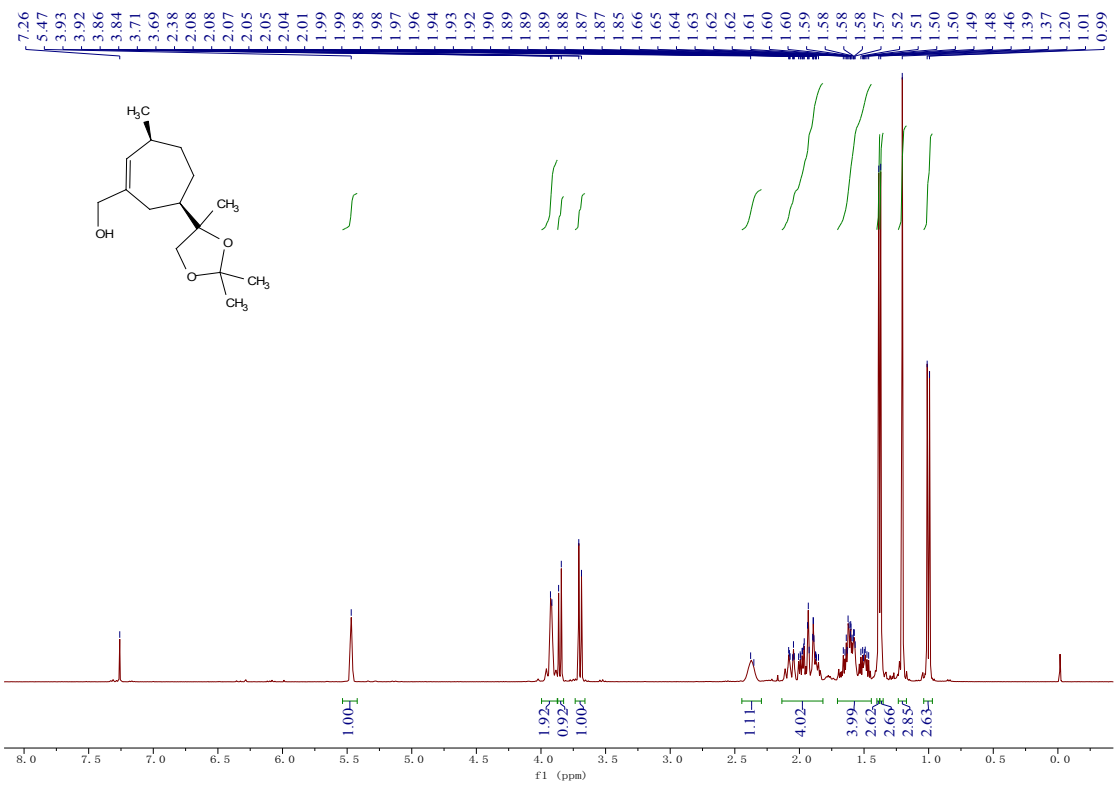
^{1}H NMR spectra of **7** ($CDCl_3$, 400 MHz)



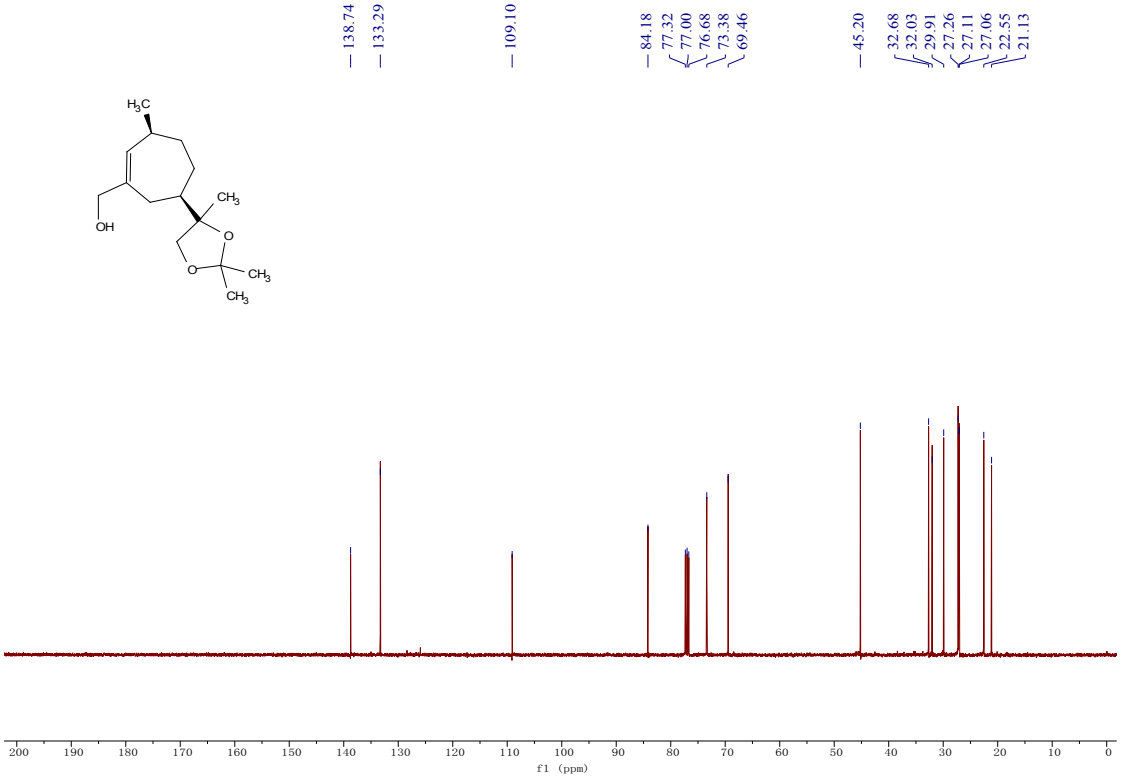
^{13}C NMR spectra of **7** ($CDCl_3$, 100 MHz)



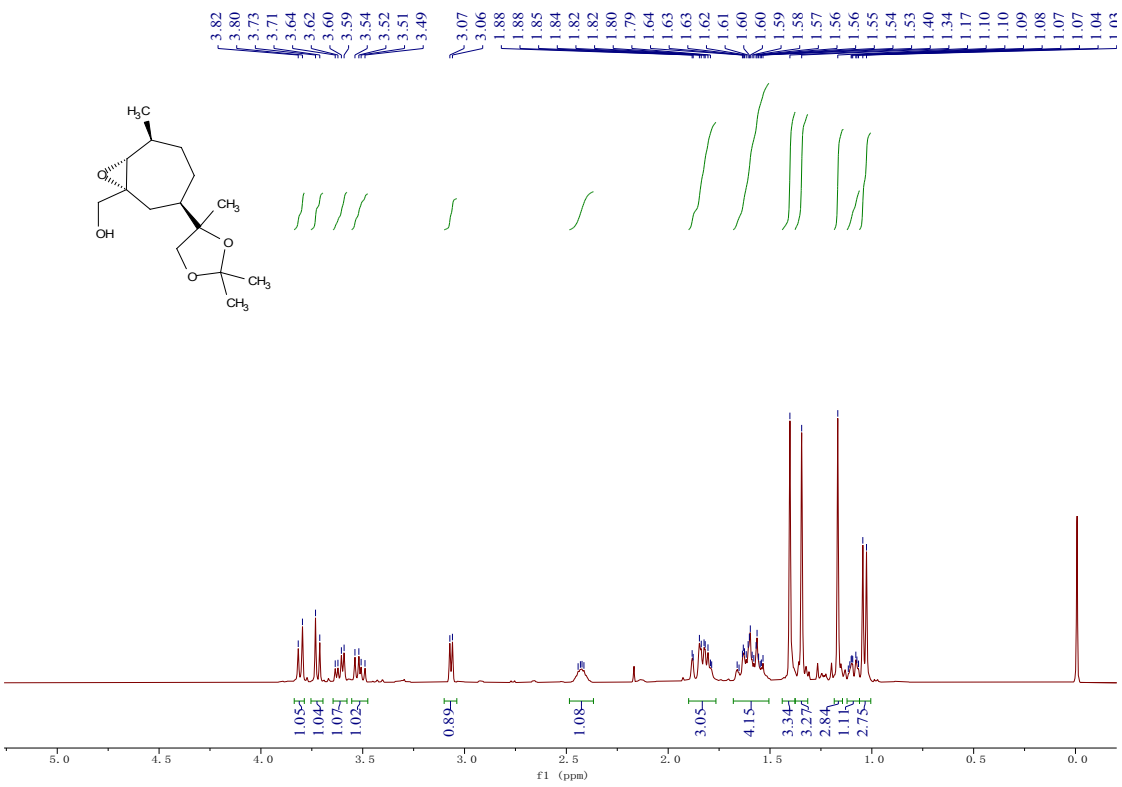
^{1}H NMR spectra of **S4** ($CDCl_3$, 400 MHz)



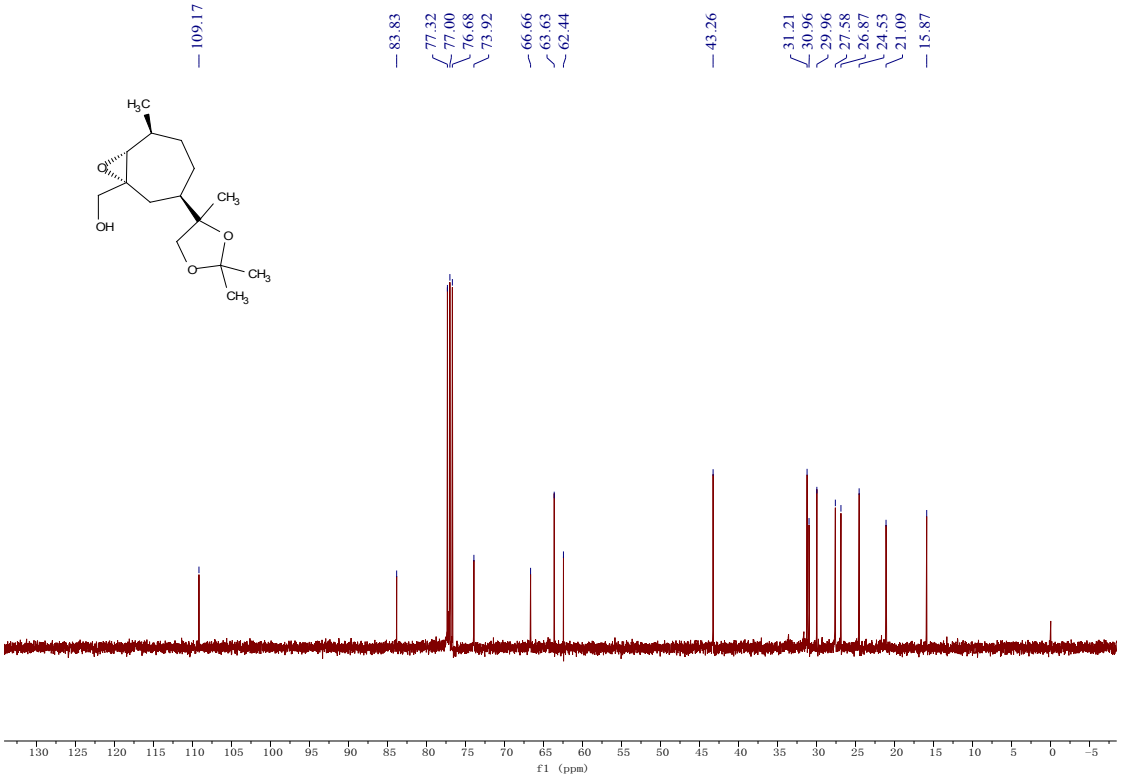
^{13}C NMR spectra of **S4** ($CDCl_3$, 100 MHz)



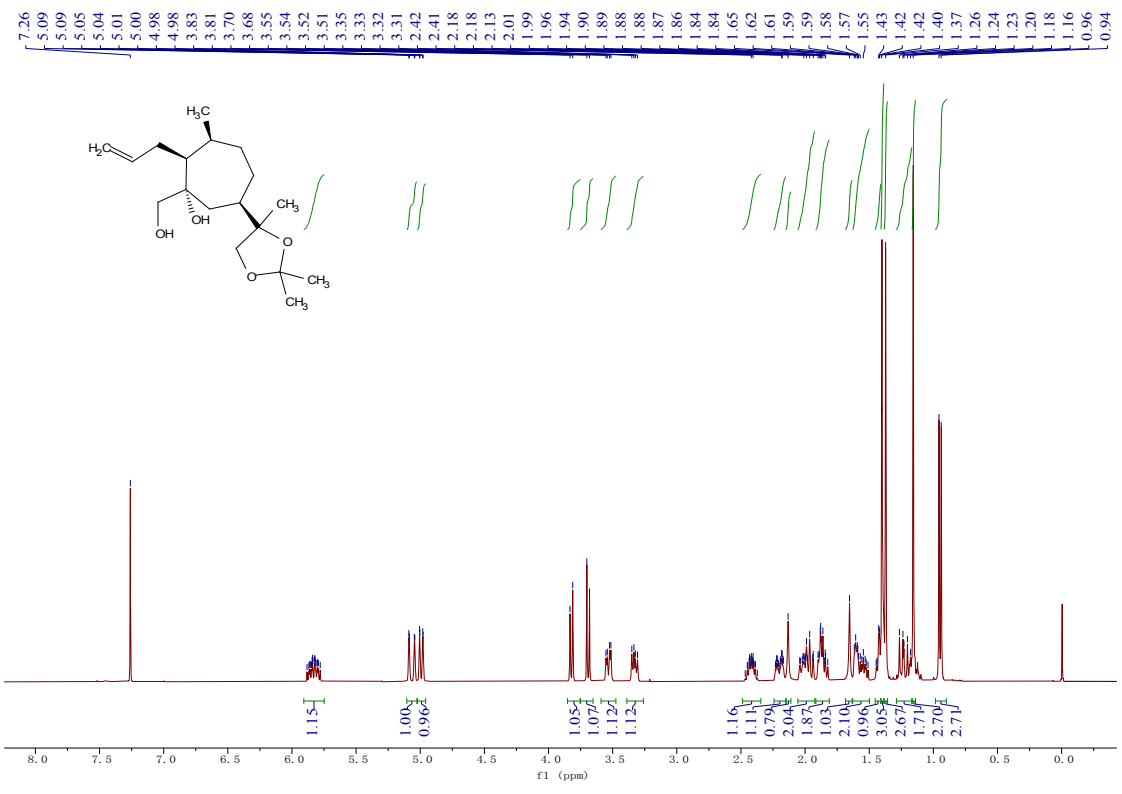
^{1}H NMR spectra of **12** ($CDCl_3$, 400 MHz)



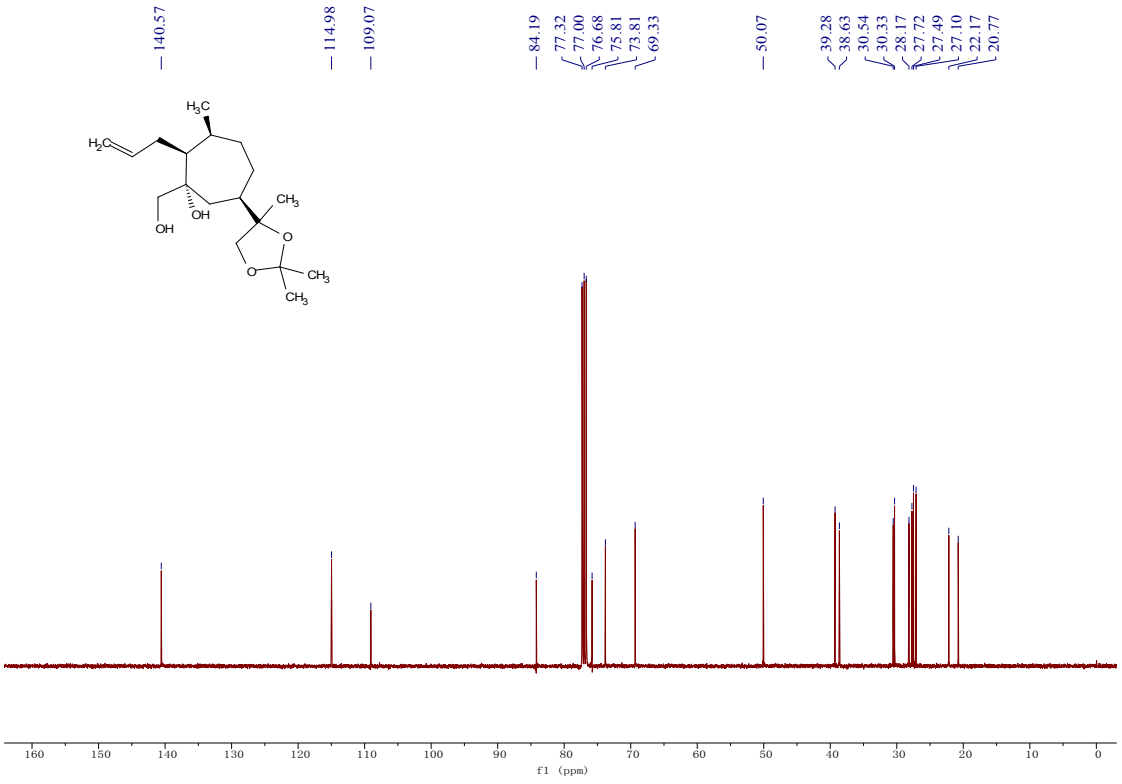
^{13}C NMR spectra of **12** ($CDCl_3$, 100 MHz)



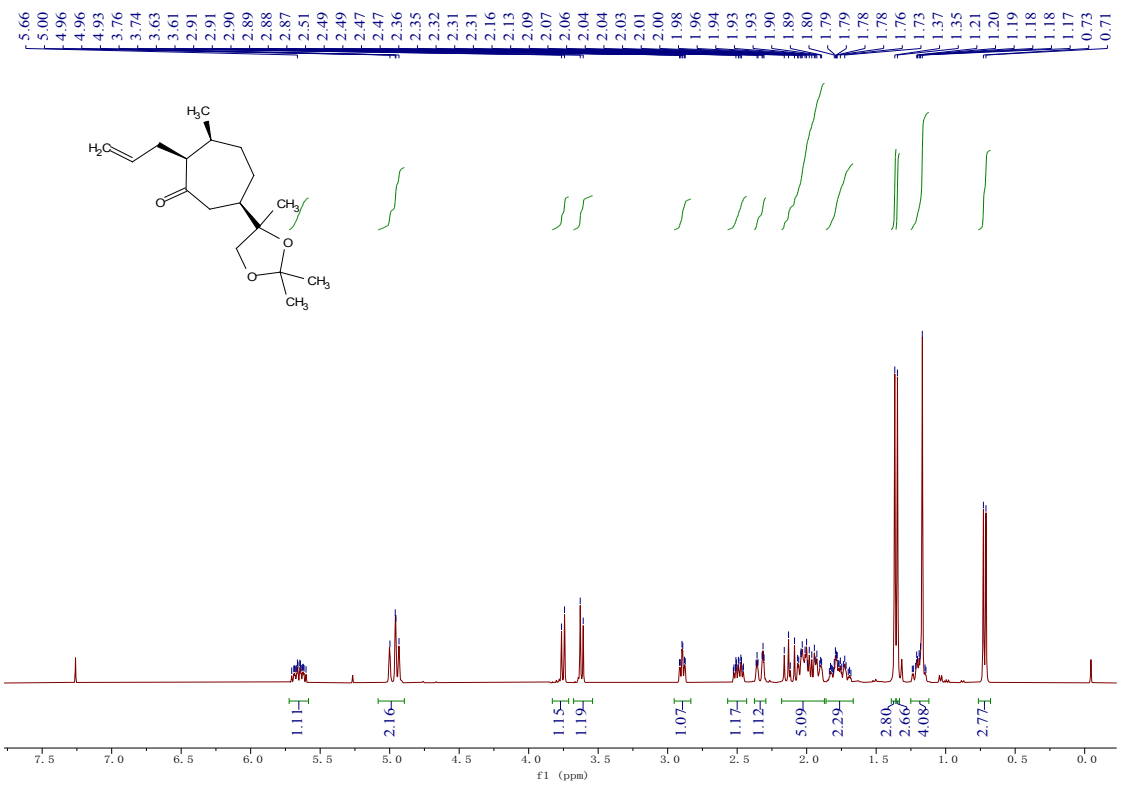
^{1}H NMR spectra of **S5** ($CDCl_3$, 400 MHz)



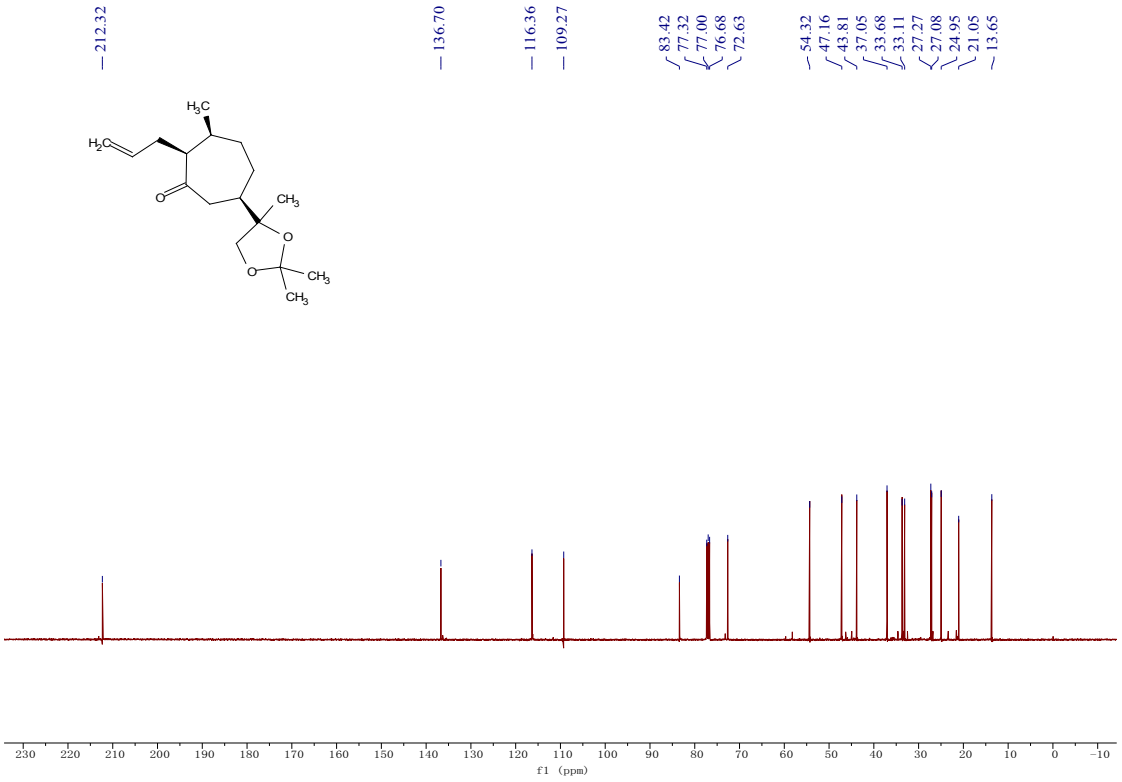
^{13}C NMR spectra of **S5** ($CDCl_3$, 100 MHz)



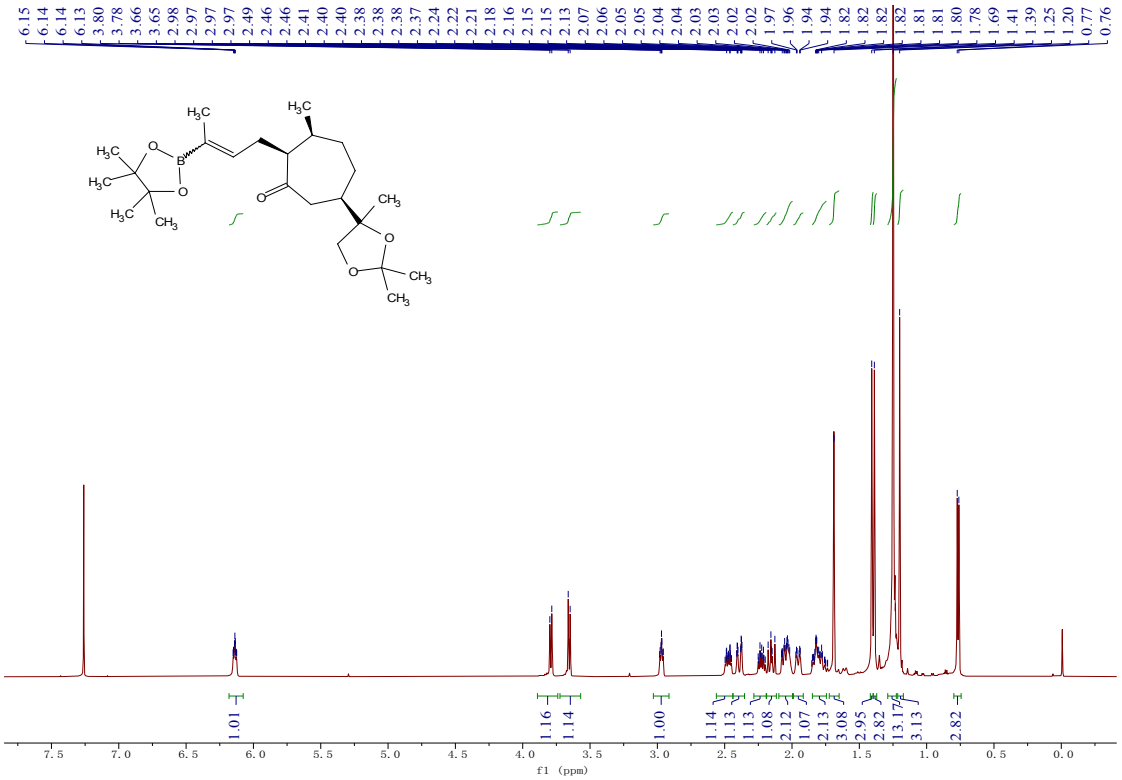
^{1}H NMR spectra of **13** ($CDCl_3$, 400 MHz)



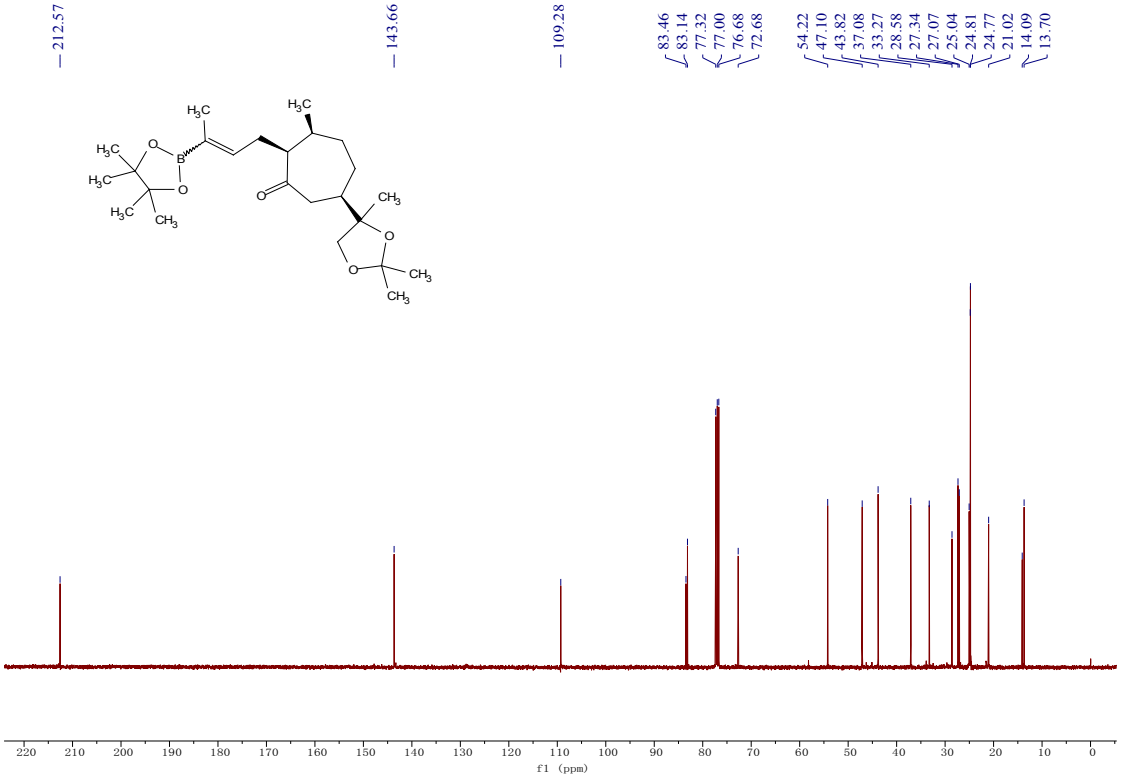
^{13}C NMR spectra of **13** ($CDCl_3$, 100 MHz)



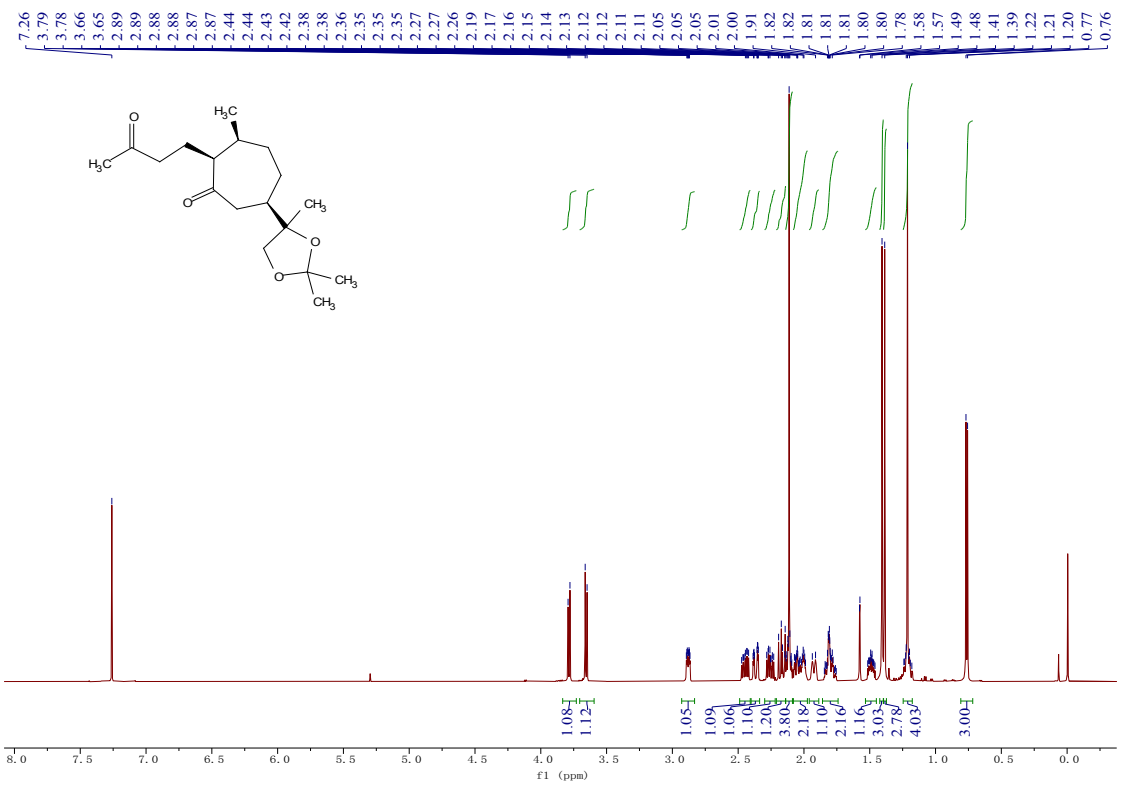
^{1}H NMR spectra of **S6** ($CDCl_3$, 400 MHz)



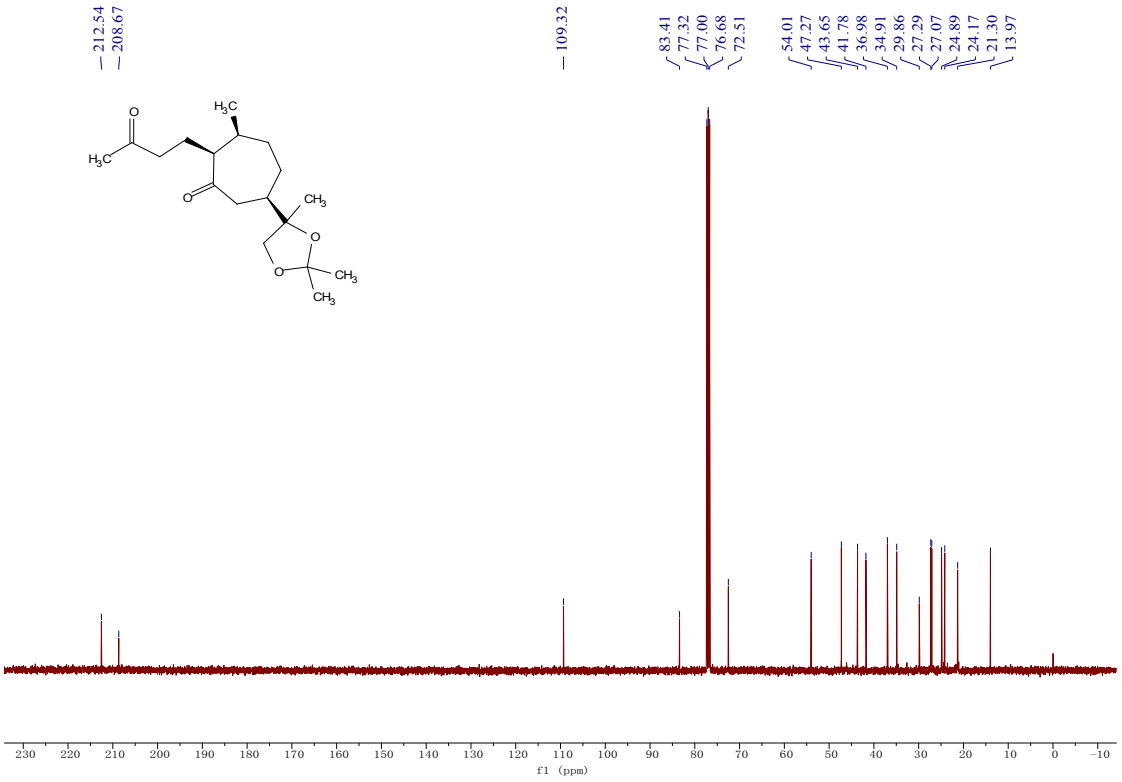
^{13}C NMR spectra of **S6** ($CDCl_3$, 100 MHz)



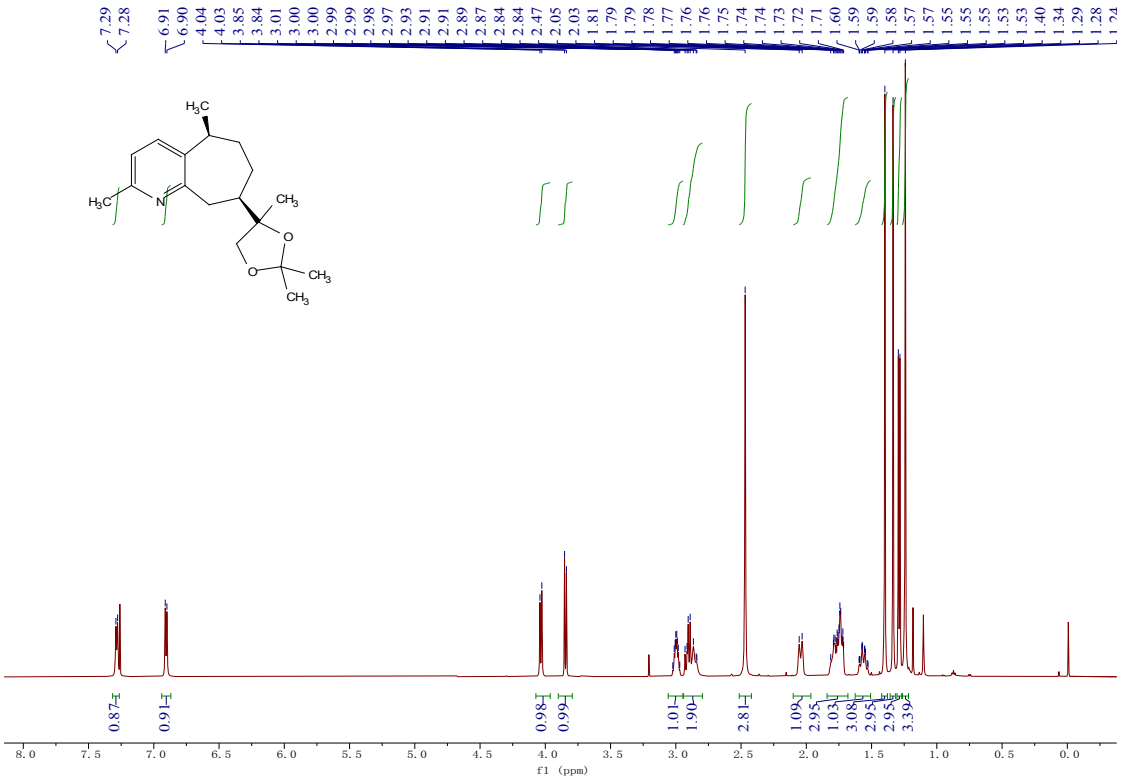
^{1}H NMR spectra of **14** ($CDCl_3$, 400 MHz)



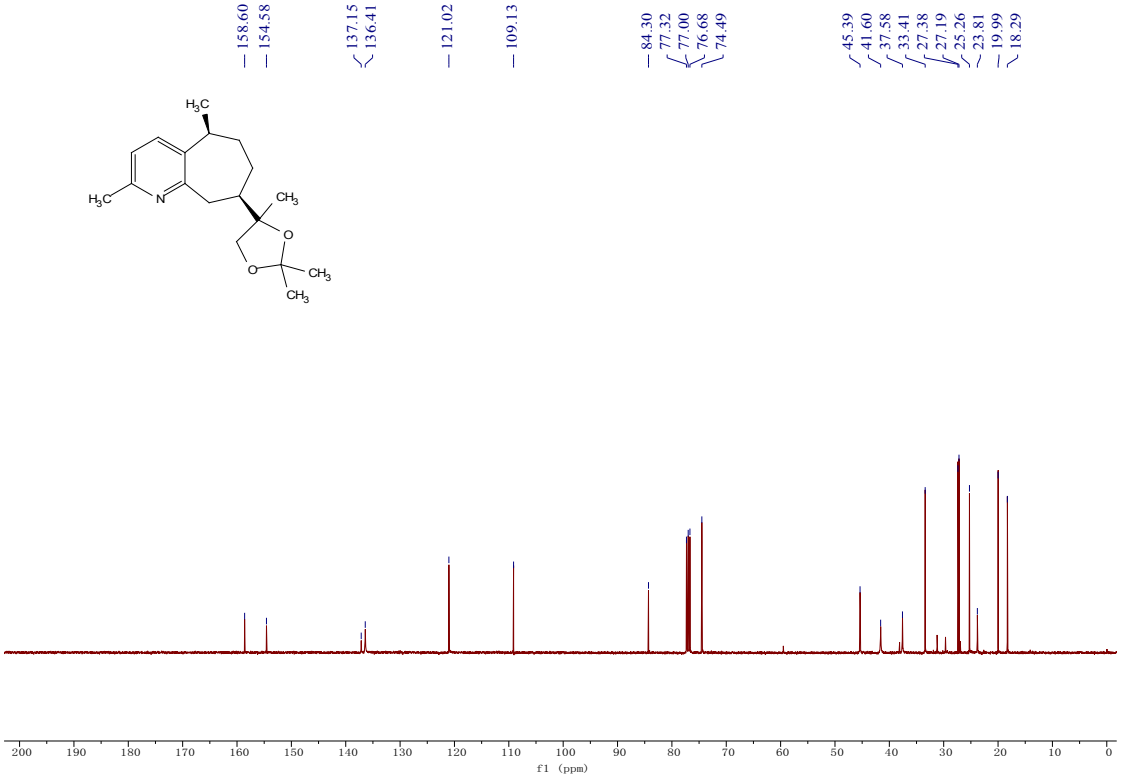
^{13}C NMR spectra of **14** ($CDCl_3$, 100 MHz)



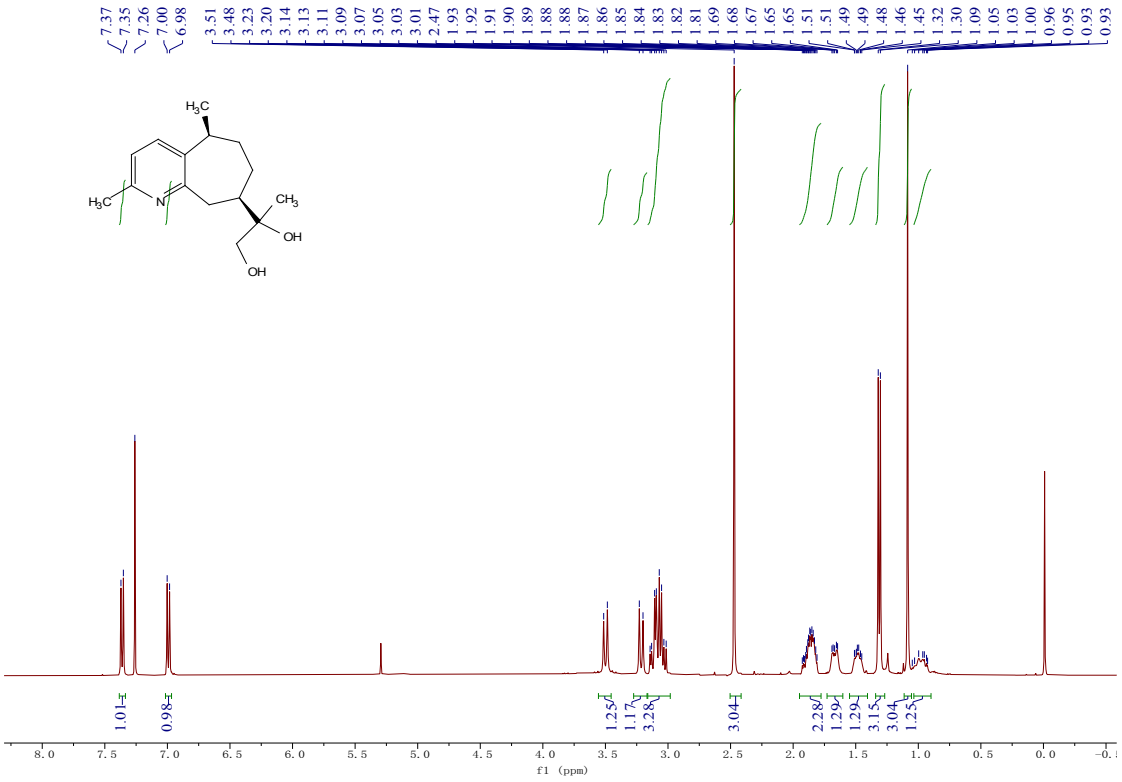
^{1}H NMR spectra of **15** ($CDCl_3$, 400 MHz)



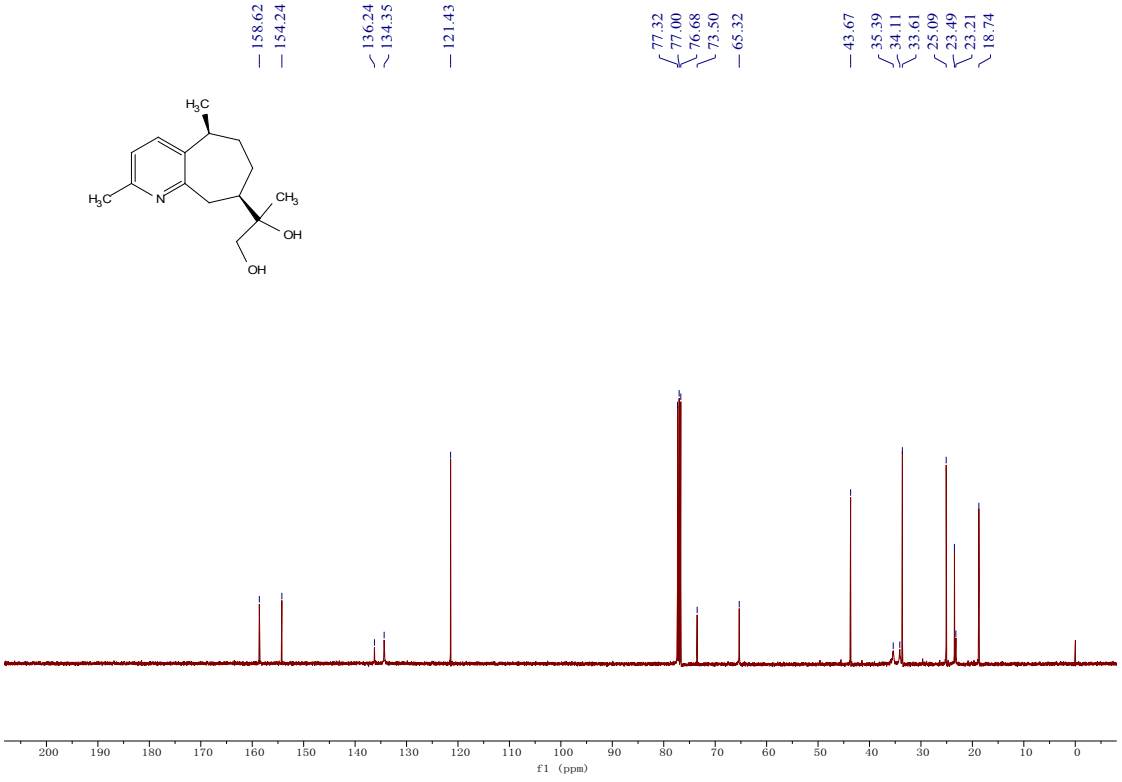
^{13}C NMR spectra of **15** ($CDCl_3$, 100 MHz)



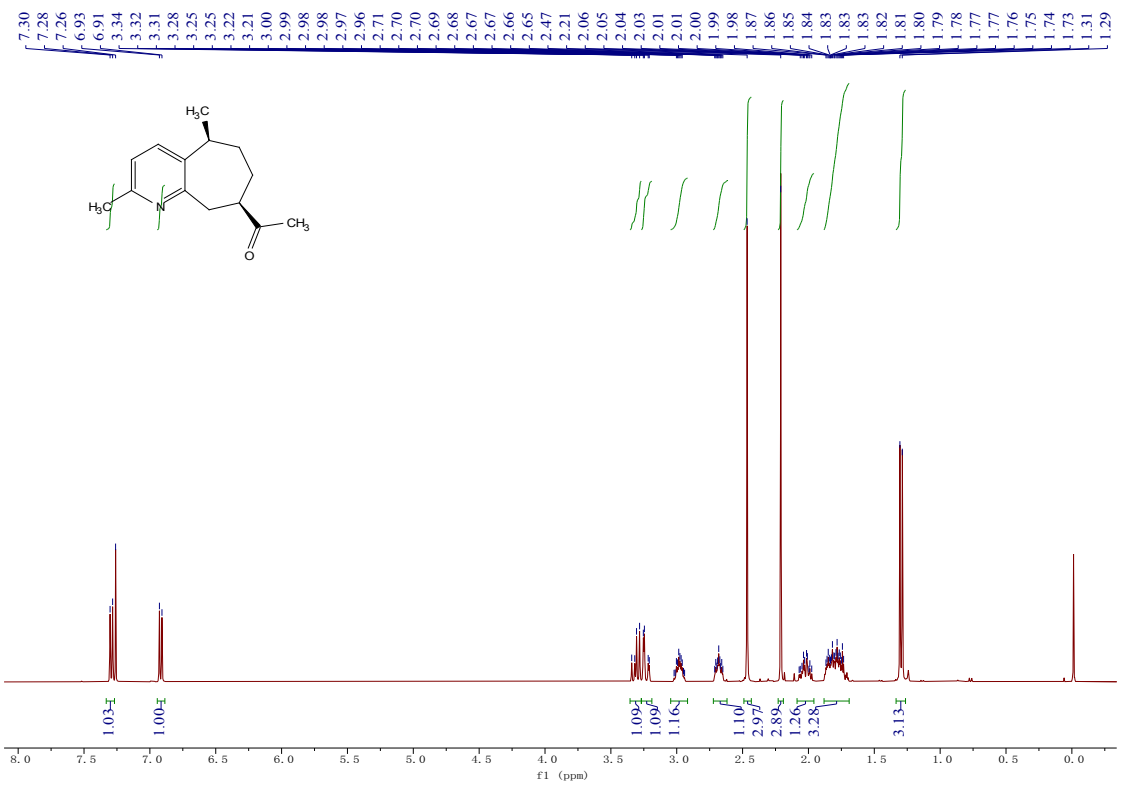
^{1}H NMR spectra of **16** ($CDCl_3$, 400 MHz)



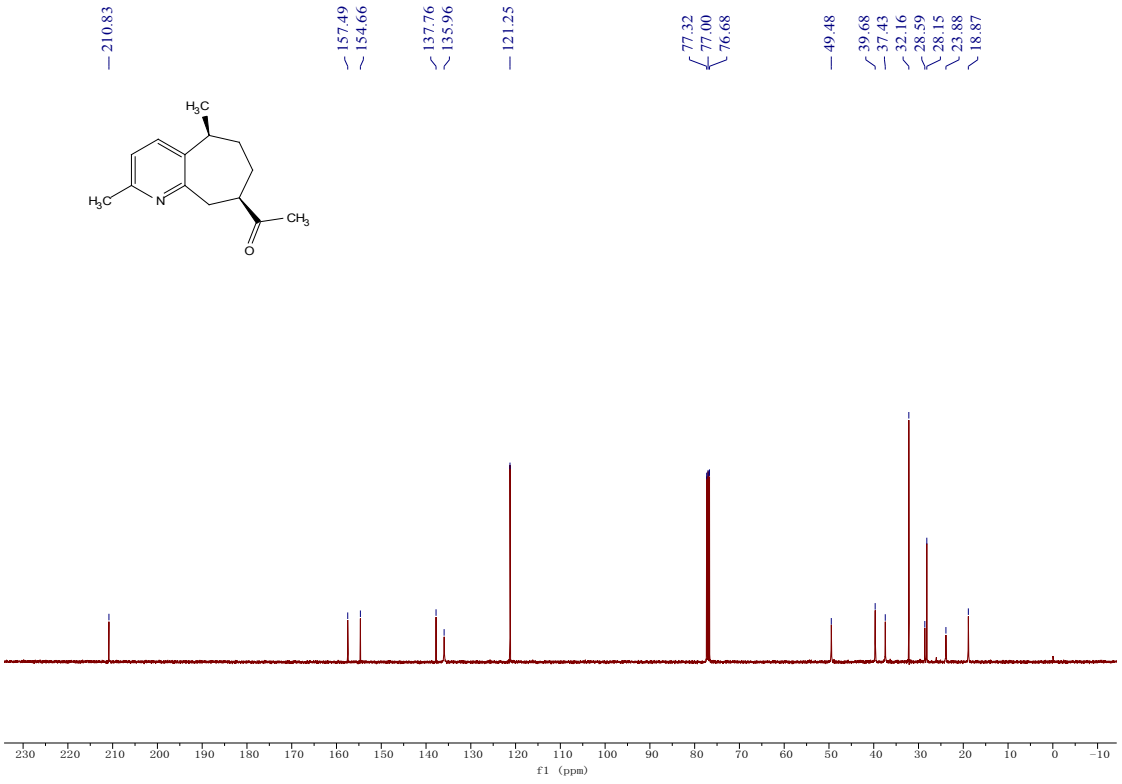
^{13}C NMR spectra of **16** ($CDCl_3$, 100 MHz)



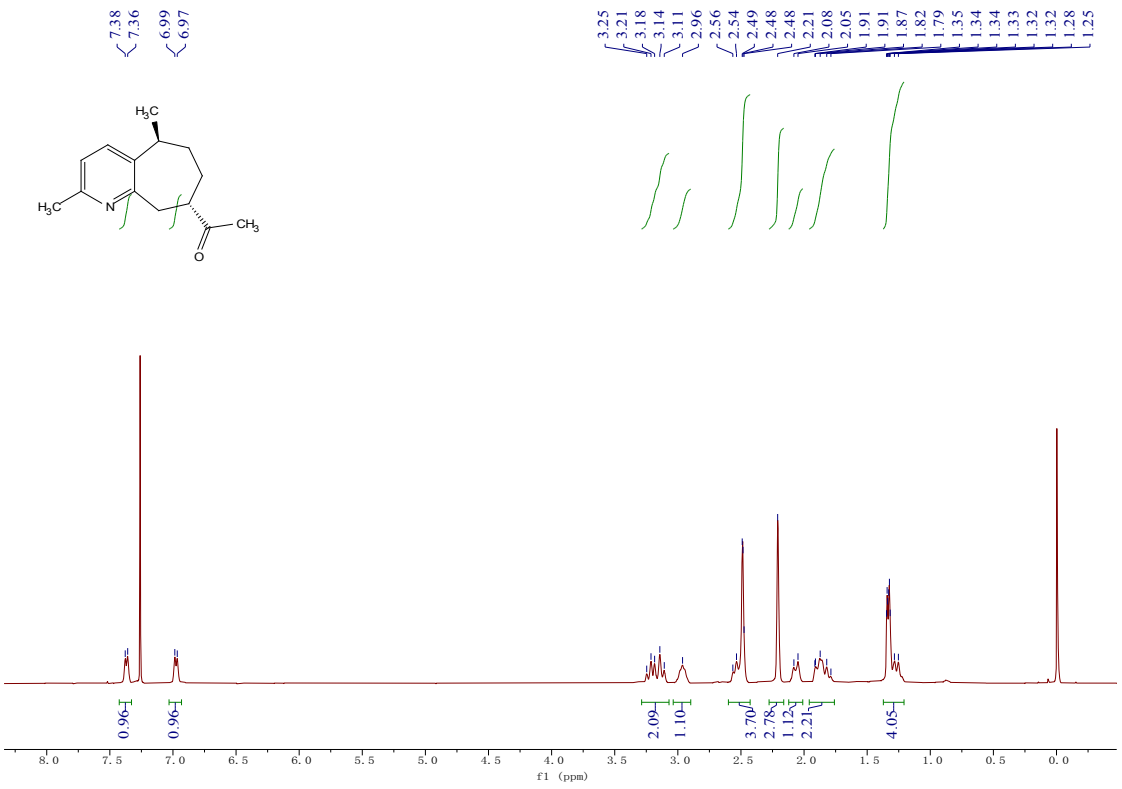
^{1}H NMR spectra of **17** ($CDCl_3$, 400 MHz)



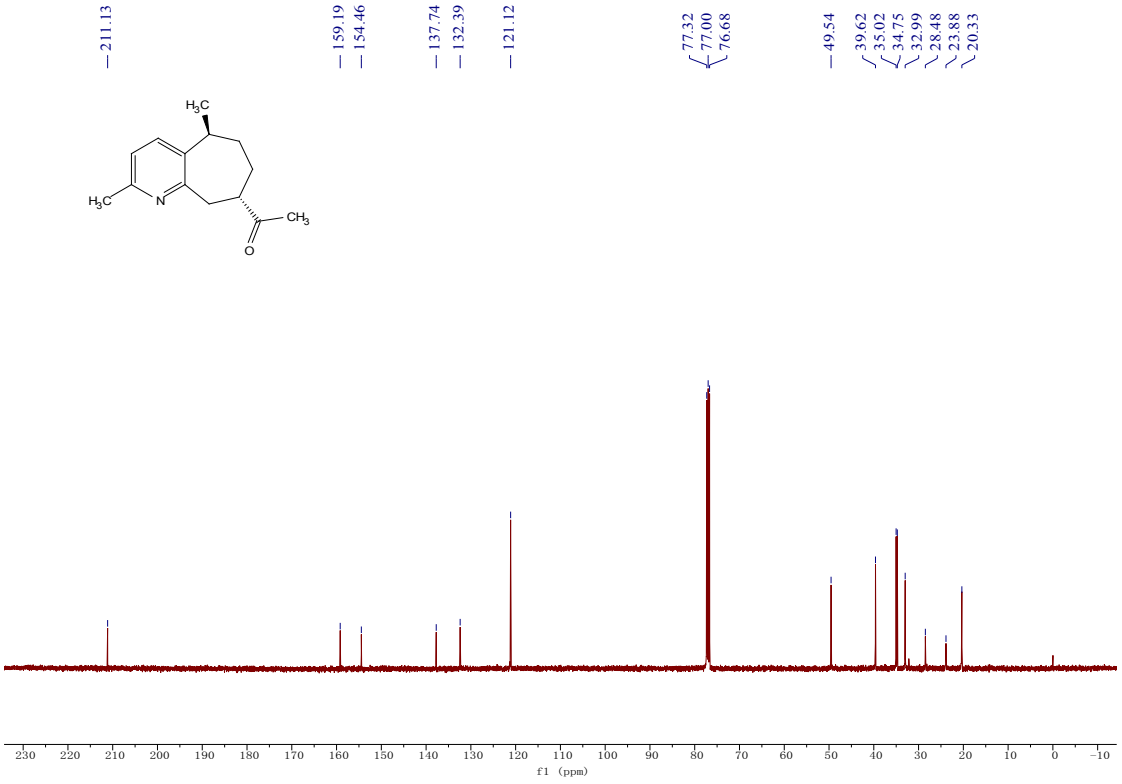
^{13}C NMR spectra of **17** ($CDCl_3$, 100 MHz)



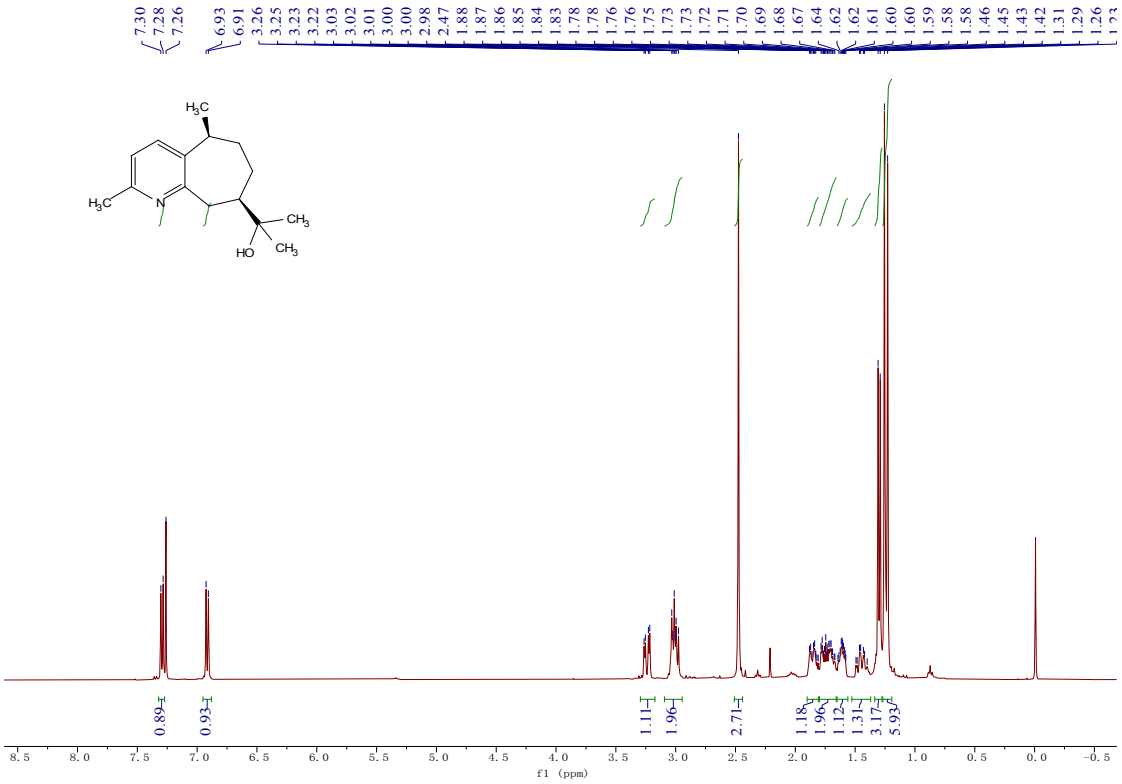
^{1}H NMR spectra of **5** ($CDCl_3$, 400 MHz)



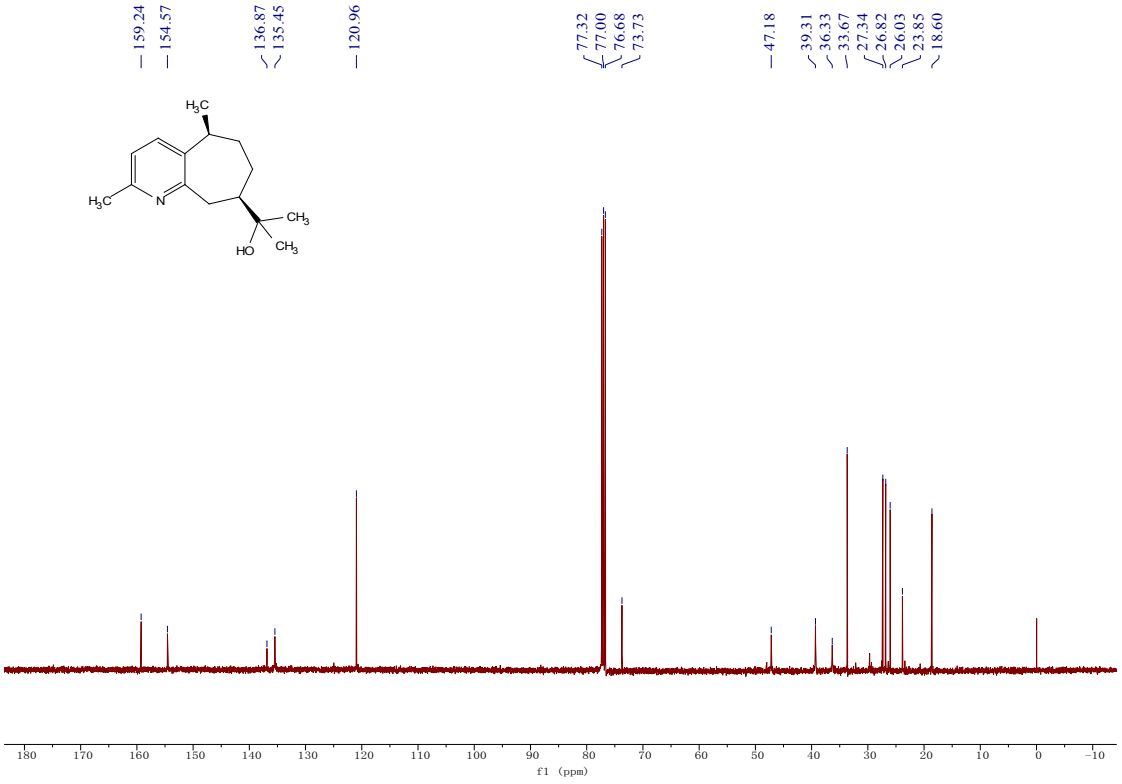
^{13}C NMR spectra of **5** (CDCl$_3$, 100 MHz)



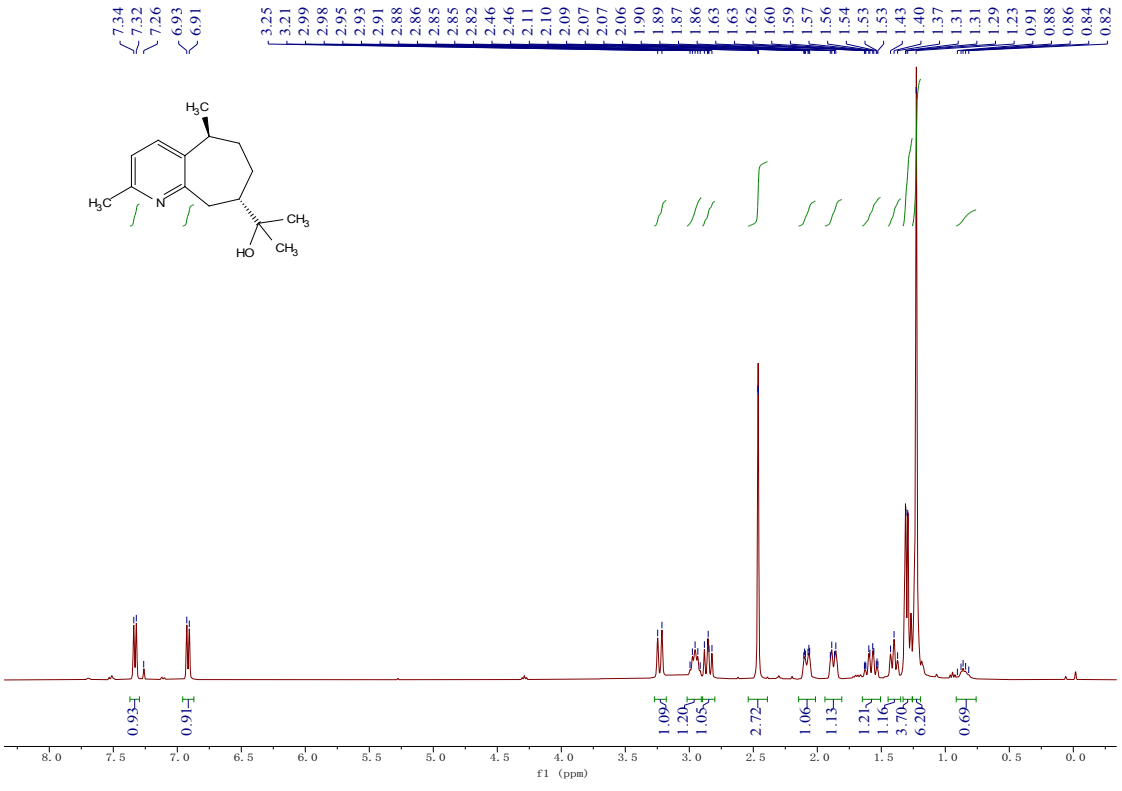
^{1}H NMR spectra of **19** (CDCl$_3$, 400 MHz)



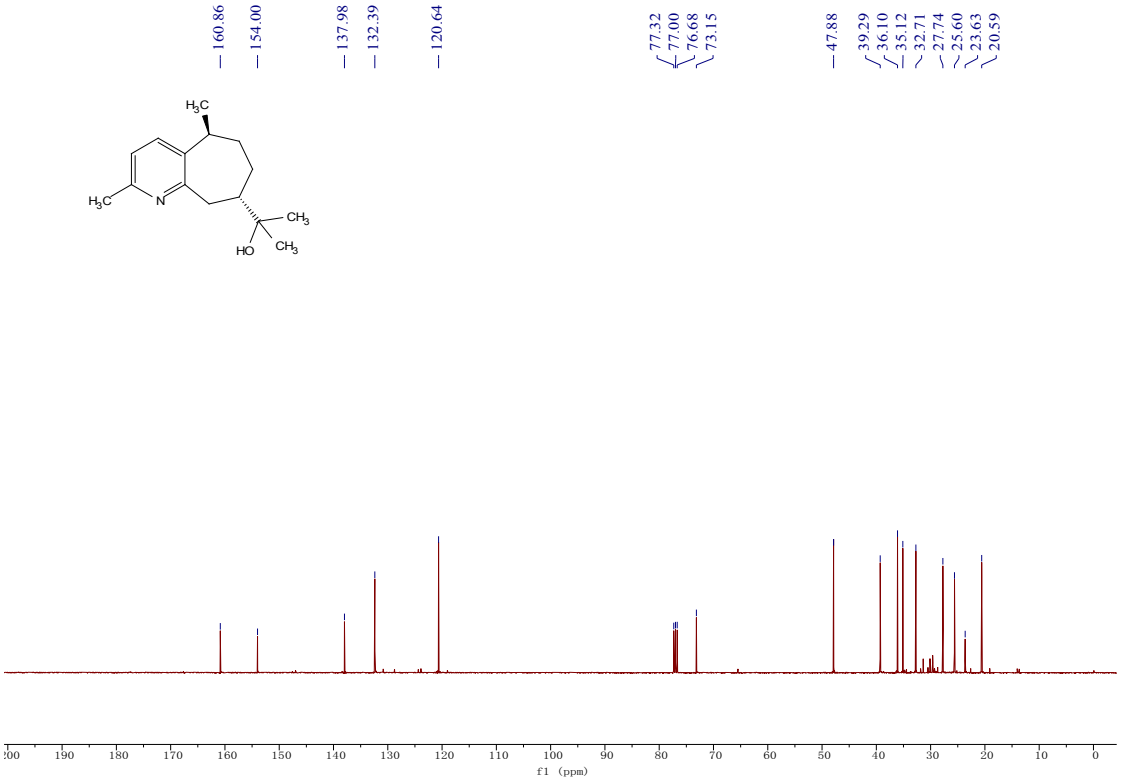
^{13}C NMR spectra of **19** ($CDCl_3$, 100 MHz)



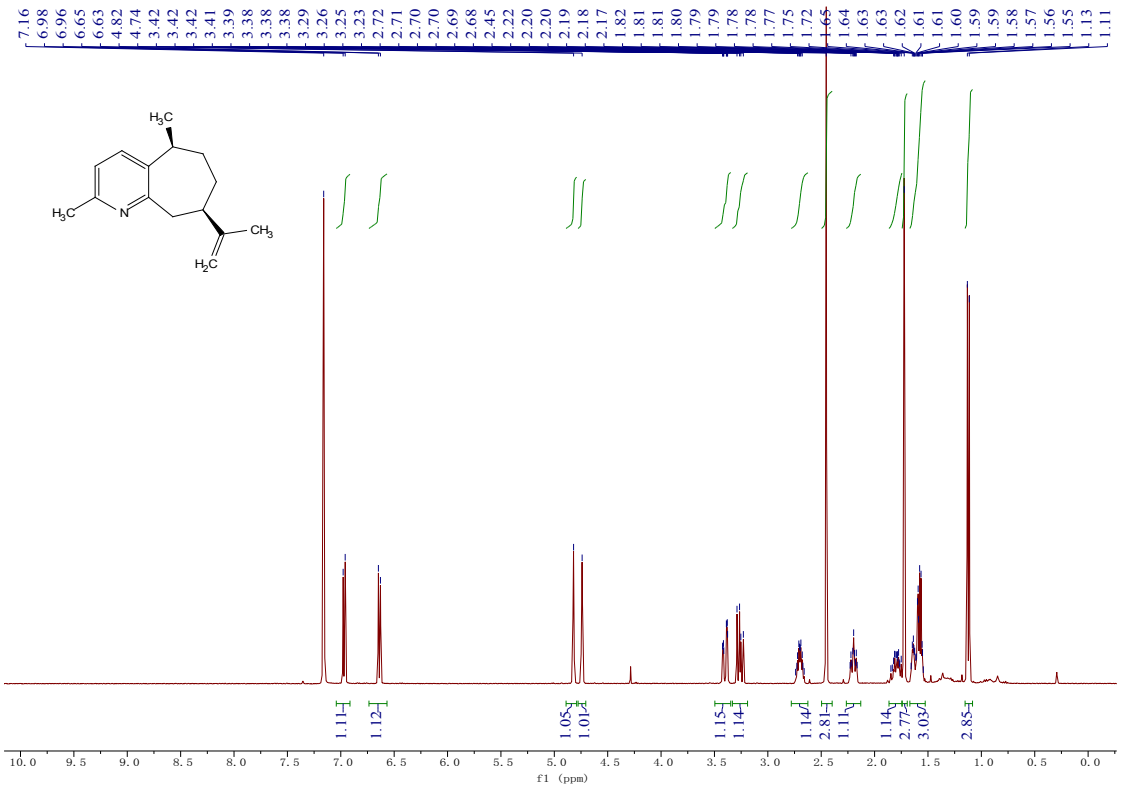
^{1}H NMR spectra of **21** ($CDCl_3$, 400 MHz)



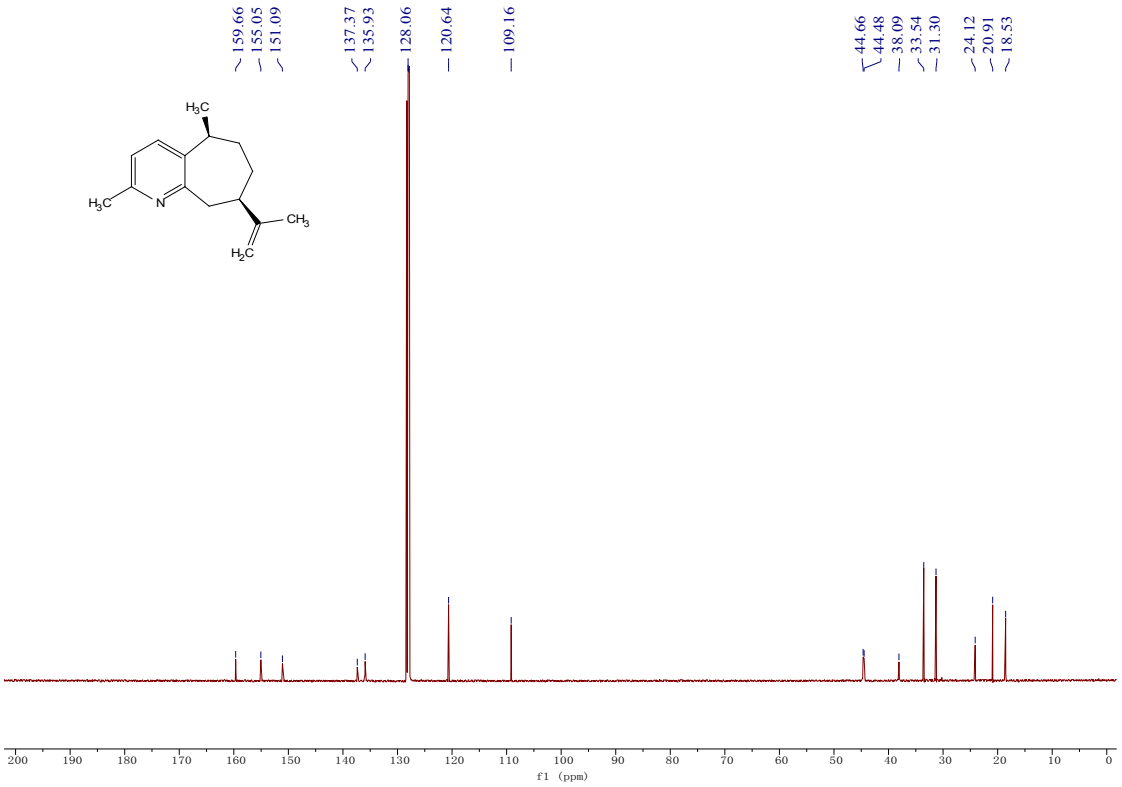
^{13}C NMR spectra of **21** ($CDCl_3$, 100 MHz)



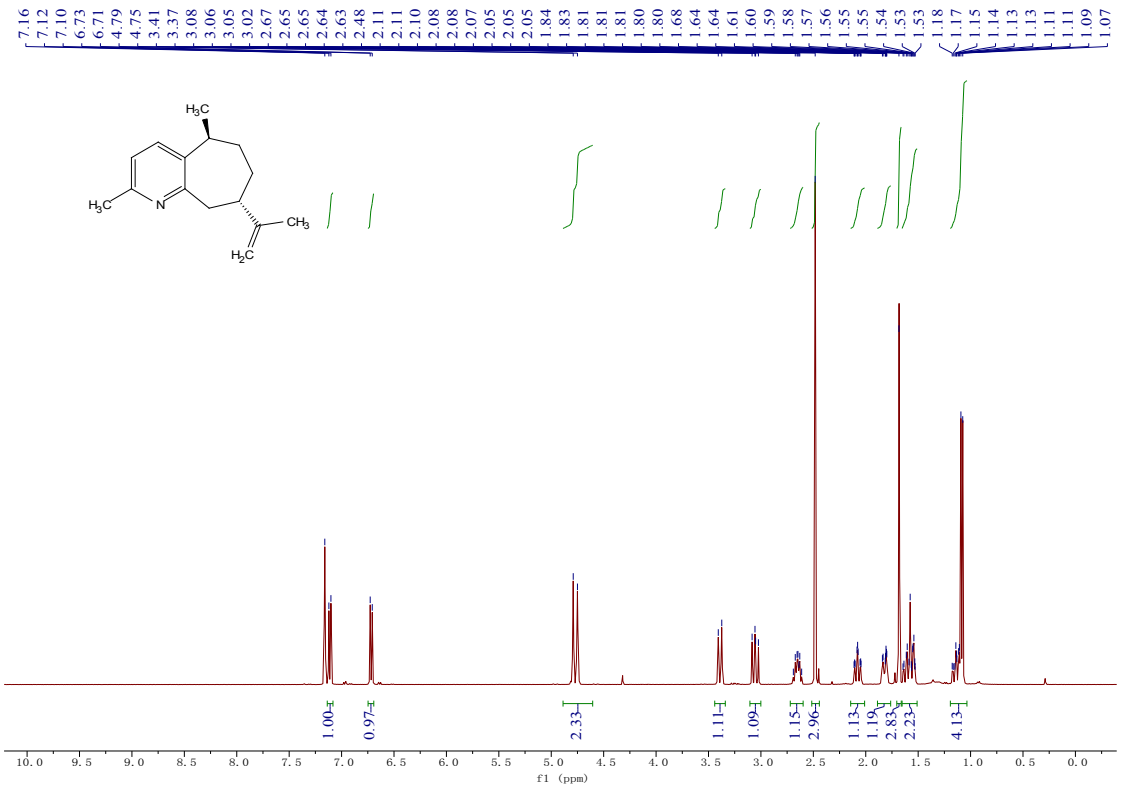
^{1}H NMR spectra of **3** (Benzene-D_6, 400 MHz)



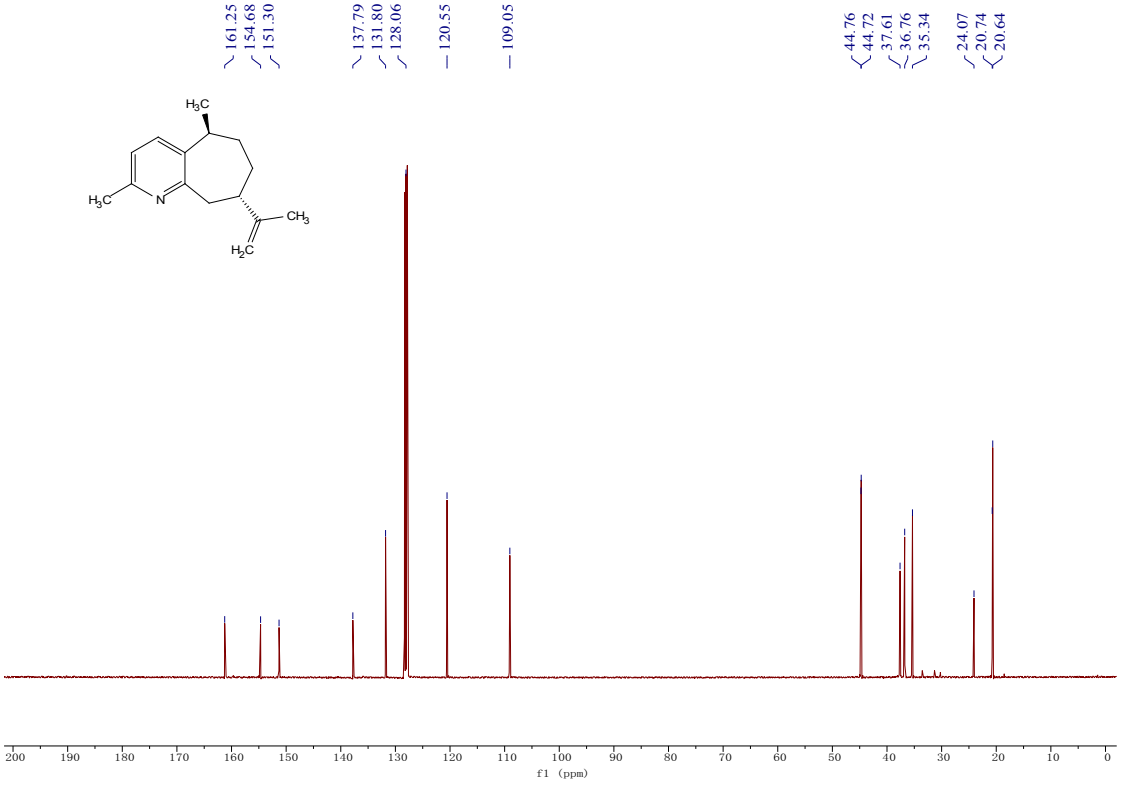
^{13}C NMR spectra of **3** (Benzene-D$_6$, 100 MHz)



^{1}H NMR spectra of **20** (Benzene-D$_6$, 400 MHz)

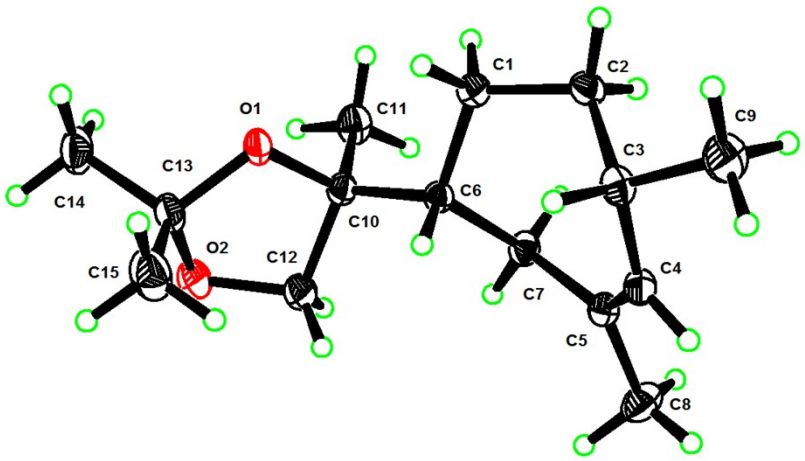


^{13}C NMR spectra of **20** (Benzene-D$_6$, 100 MHz)



5. Single Crystal X-ray Data

5.1 X-ray crystallographic data for 7



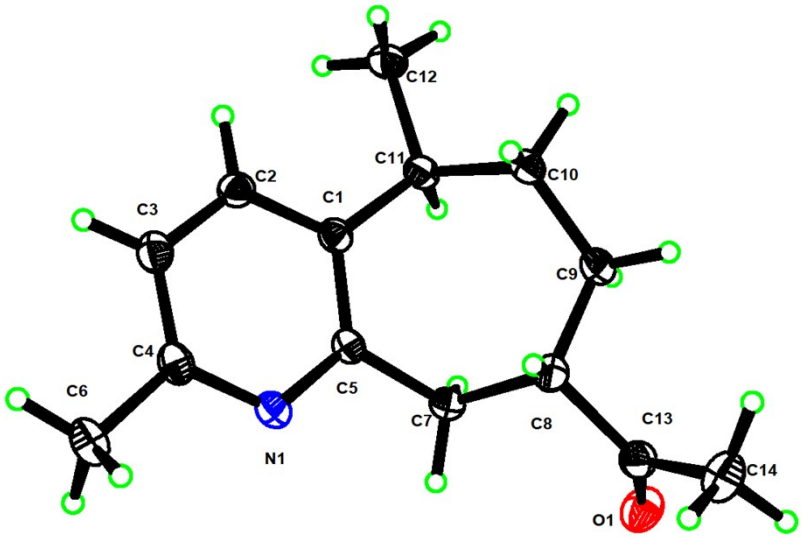
Structure deposited at the Cambridge Crystallographic Data Center (CCDC 2084871)

Crystal data and structure refinement for CCDC 2084871

Identification code	22020929S4S4_0m
Empirical formula	$C_{15}H_{26}O_2$
Formula weight	238.36
Temperature/K	160.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.2068(2)
b/Å	9.6747(3)
c/Å	23.6894(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1422.52(7)
Z	4
ρ_{calc}g/cm^3	1.113
μ/mm^{-1}	0.555
F(000)	528.0
Crystal size/mm^3	0.15 × 0.08 × 0.05
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.464 to 144.952
Index ranges	$-7 \le h \le 7$, $-11 \le k \le 11$, $-29 \le l \le 28$
Reflections collected	11340

Independent reflections	2771 [R_{int} = 0.0347, R_{sigma} = 0.0271]
Data/restraints/parameters	2771/0/159
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0310, wR_2 = 0.0733
Final R indexes [all data]	R_1 = 0.0331, wR_2 = 0.0750
Largest diff. peak/hole / e $Å^{-3}$	0.16/-0.12
Flack parameter	-0.08(9)

5.2 X-ray crystallographic data for 5



Structure deposited at the Cambridge Crystallographic Data Center (CCDC 2084872)

Crystal data and structure refinement for CCDC 2084872

dentification code	cu_220201016_0m
Empirical formula	$C_{14}H_{19}NO$
Formula weight	217.30
Temperature/K	150.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	4.9824(2)
b/Å	11.7685(5)
c/Å	10.6674(5)
α/°	90
β/°	101.617(2)
γ/°	90

Volume/Å^3	612.67(5)
Z	2
ρ_{calc}g/cm^3	1.178
μ/mm^{-1}	0.571
F(000)	236.0
Crystal size/mm^3	0.15 × 0.08 × 0.05
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.462 to 136.432
Index ranges	$-5 \leq h \leq 5$, $-13 \leq k \leq 14$, $-12 \leq l \leq 12$
Reflections collected	10051
Independent reflections	2194 [R_{int} = 0.0486, R_{sigma} = 0.0398]
Data/restraints/parameters	2194/1/148
Goodness-of-fit on F^2	1.073
Final R indexes [I>=2σ (I)]	R_1 = 0.0383, wR_2 = 0.1012
Final R indexes [all data]	R_1 = 0.0395, wR_2 = 0.1025
Largest diff. peak/hole / e Å^{-3}	0.15/-0.19
Flack parameter	-0.01(15)