Supporting Information

Construction of the Core Skeleton for Spiroaspertrione A by a Diels–Alder Reaction of Masked *o*-Benzoquinone

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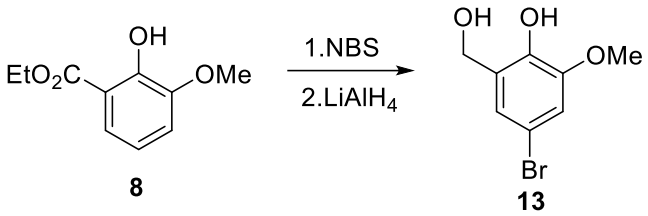
General Experimental

Unless otherwise stated, all reactions were conducted in flame-dried glassware and carried out under a air atmosphere. All reagents were obtained from commercial sources and used as received without further purification. Oxygen and/or moisture sensitive solids and liquids were transferred appropriately. Concentration of solutions in vacuo was accomplished using a rotary evaporator fitted with a water aspirator. Residual solvents were removed under high vacuum (0.1-0.2 mm Hg). Flash column chromatography was performed using the indicated solvents on E. Qingdao silica gel 60 (200 – 300 mesh ASTM). TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2 mm). Compounds were visualized with UV light, iodine, *p*-anisaldehyde stain, ceric ammonium molybdate stain, or phosphomolybdic acid in EtOH. ^{1}H NMR spectra were recorded on Bruker Avance 400 MHz or Avance 500 MHz spectrometers. Chemical shifts were reported in parts per million (ppm), relative to either a tetramethylsilane (TMS) internal standard or the signals due to the solvent. Coupling constants (*J*) are reported in Hertz (Hz) for corresponding solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm), CD_3OD δ_H (3.31 ppm) and DMSO-d_6 δ_H (2.50 ppm). ^{13}C NMR spectra were recorded using a 101 MHz or 126 MHz spectrometer for corresponding solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δ_C (77.16 ppm), CD_3OD δ_C (49.00 ppm) and DMSO-d_6 δ_C (39.52 ppm). High resolution mass spectra were measured on ABI Q-star Elite.

Experimental Procedures

Synthesis of phenol 12



8 **13**

To a suspension of compound **8** (9.10 g, 50 mmol) in AcOH (50 mL) was added *N*-Bromosuccinimide (9.08 g, 51 mmol) at room temperature. The mixture was stirred at room temperature overnight. Upon completion, the clear solution was concentrated under reduced pressure, and the residue was dissolved in EtOAc (100 mL), The solution was washed sequentially with warm water (100 mL x 3) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue can be used directly in the next step without further purification.

To a vigorously stirring solution of above crude product in THF (100 mL) was added $LiAlH_4$ (1.0 M in THF, 60 mL, 60 mmol) dropwise at 0 °C over 30 min. After being stirred at room temperature overnight, the reaction was quenched carefully with 2.0 N aq. HCl (100 mL), and the mixture was extracted with EtOAc (100 mL x 3). The combined organic phases were washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 3:1) to provide **13** (9.98 g, 86%) as a white amorphous powder. Analytical data according to literature.[1]

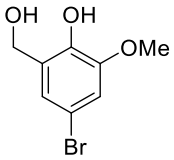
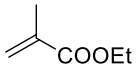
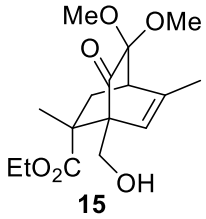
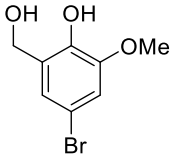
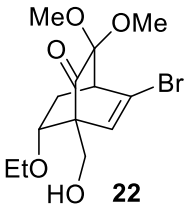
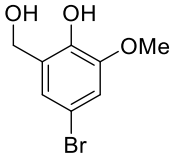
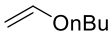
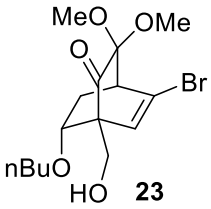
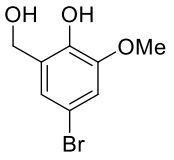
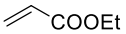
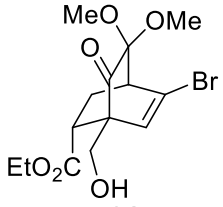
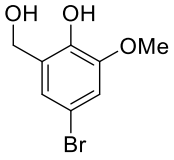
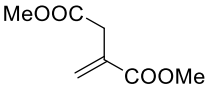
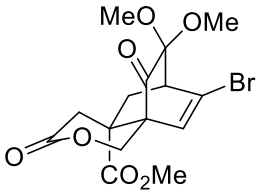
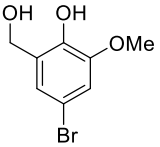
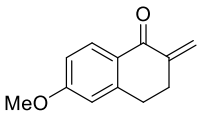
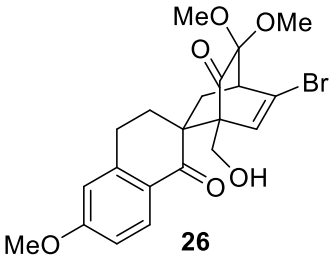
TLC: R_f = 0.45 (silica gel, hexanes/EtOAc = 1:1).

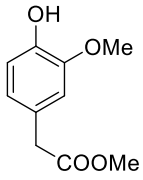
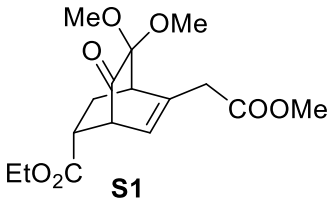
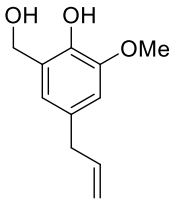
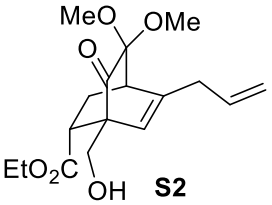
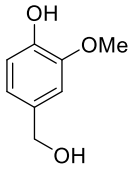
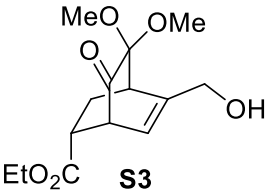
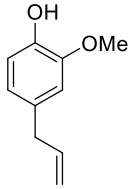
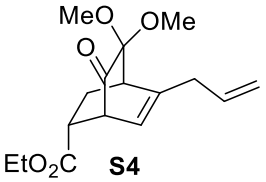
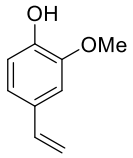
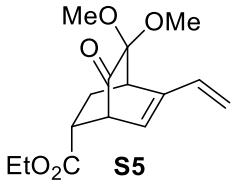
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.02 (d, J = 2.2 Hz, 1H), 6.94 (d, J = 2.2 Hz, 1H), 4.70 (s, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.2, 142.8, 127.9, 123.3, 113.7, 111.4, 61.1, 56.4.

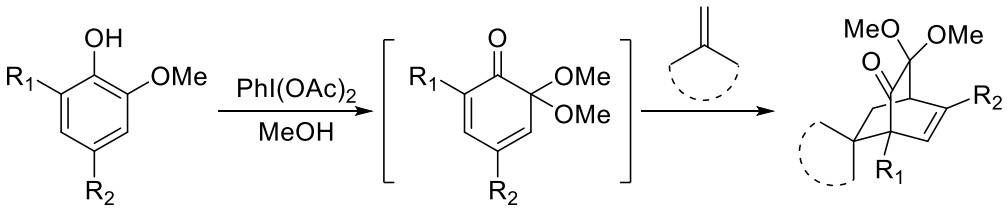
HRMS (ESI) m/z: calculated for $C_8H_9BrNaO_3^+$ $[M + Na]^+$: 255.9633, found 255.9632.

Substrate screening for the Diels–Alder reaction of masked *o*-benzoquinone

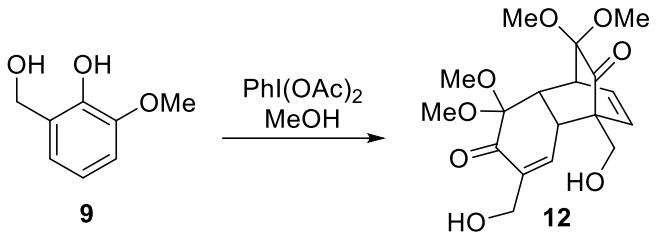
Entry	Phenols	Dienophiles	Products	Yields
1			 **15**	90%
2			 **22**	77%
3			 **23**	84%
4			 **24**	87%
5			 **25**	72%
6			 **26**	65%

7			 **S1**	63%
8			 **S2**	58%
9			 **S3**	53%
10			 **S4**	66%
11			 **S5**	40%

General procedure of the Diels–Alder reaction of masked *o*-benzoquinone



To a solution of $PhI(OAc)_2$ (354 mg, 1.1 mmol) in MeOH (5 mL) was added a mixed solution of phenol (1.0 mmol) and the dienophile (5-20 mmol) in MeOH (5 mL) dropwise via syringe pump over 6 hours. Following the addition, the mixture was stirred at room temperature until the intermediate *o*-benzoquinone was completely consumed. The solution was directly concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel to afford cycloadduct.



9 **12**

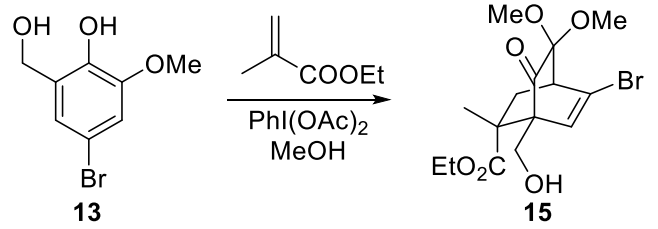
To a solution of compound **9** (154 mg, 1.0 mmol) in MeOH (10 mL) was added $PhI(OAc)_2$ (354 mg, 1.1 mmol) in one portion at room temperature. The mixture was stirred at room temperature until consumption of the intermediate *o*-benzoquinone was complete. The solution was directly concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 1:1) to provide compound **12** (294 mg, 80%) as a light yellow oil.

TLC: R_f = 0.15 (silica gel, hexanes/EtOAc = 1:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.56 (d, *J* = 4.2 Hz, 1H), 6.29 (dd, *J* = 8.2, 6.6 Hz, 1H), 5.57 – 5.53 (m, 1H), 4.35 – 4.25 (m, 2H), 4.15 (d, *J* = 12.3 Hz, 1H), 3.76 (d, *J* = 12.3 Hz, 1H), 3.54 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.47 (s, 3H), 3.41 (s, 3H), 3.29 (dd, *J* = 8.3, 1.6 Hz, 1H), 3.24 (s, 3H), 3.13 (dt, *J* = 6.6, 1.6 Hz, 1H), 3.10 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 205.6, 195.0, 140.3, 139.8, 132.6, 129.5, 98.7, 95.1, 61.0, 60.4, 59.3, 50.6, 50.3, 49.7, 49.0, 39.8, 39.5, 37.7.

HRMS (ESI) m/z: calculated for $C_{18}H_{24}NaO_8^+$ $[M + Na]^+$: 391.1365, found 391.1367.



13 **15**

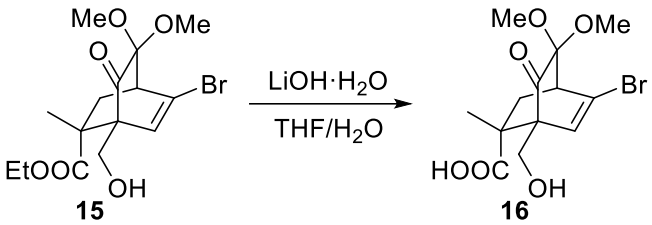
Following the general procedure with compound **13** (232 mg, 1.0 mmol) and ethyl methacrylate (2.49 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 8:1) yielded the compound **15** (340 mg, 90%) as a colorless oil.

TLC: R_f = 0.40 (silica gel, hexanes/EtOAc = 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.40 (d, *J* = 2.4 Hz, 1H), 4.20 (d, *J* = 12.2 Hz, 1H), 4.14 (qd, *J* = 7.2, 1.9 Hz, 2H), 3.73 (d, *J* = 12.2 Hz, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 3.31 – 3.27 (m, 1H), 2.46 (dd, *J* = 13.7, 3.4 Hz, 1H), 1.94 (dd, *J* = 13.6, 2.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 202.0, 174.3, 128.7, 122.8, 94.1, 63.1, 61.5, 59.7, 50.8, 49.9, 48.9, 47.3, 36.6, 22.0, 14.0.

HRMS (ESI) m/z: calculated for $C_{15}H_{21}BrNaO_6^+$ $[M + Na]^+$: 409.0426, found 409.0425.



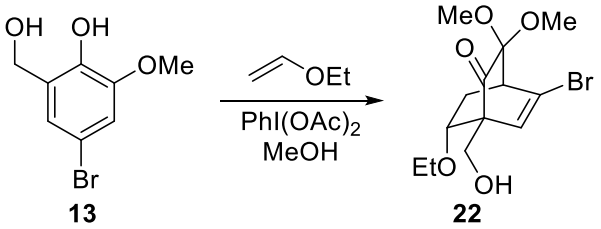
To a solution of compound **15** (189 mg, 0.5 mmol) in THF (3 mL) and H_2O (1 mL) was added $LiOH{\cdot}H_2O$ (63.0 mg, 1.5 mmol) in one portion at 0 °C. After stirred at room temperature for 8 h, the reaction mixture was concentrated in *vacuo*. The residue was dissolved in Et_2O (5 mL) and then acidified to pH 3.0 with 1.0 N aq. HCl at 0 °C. The organic phase was separated and the aqueous phase was extracted with Et_2O (5 mL x 3). The combined organic phases were washed sequentially with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to provide compound **16** (167 mg, 96%) as a white amorphous powder without further purification.

TLC: R_f = 0.30 (silica gel, DCM/MeOH = 20:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.43 (d, *J* = 2.4 Hz, 1H), 4.22 (d, *J* = 12.1 Hz, 1H), 3.88 (d, *J* = 12.1 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.31 (q, *J* = 2.9 Hz, 1H), 2.49 (dd, *J* = 13.7, 3.4 Hz, 1H), 2.00 (dd, *J* = 13.7, 2.7 Hz, 1H), 1.29 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 201.6, 179.7, 128.5, 123.2, 94.1, 62.7, 59.5, 50.8, 50.0, 48.8, 47.1, 36.8, 22.0.

HRMS (ESI) m/z: calculated for $C_{13}H_{17}BrNaO_6^+$ $[M + Na]^+$: 382.0113, found 382.0115.



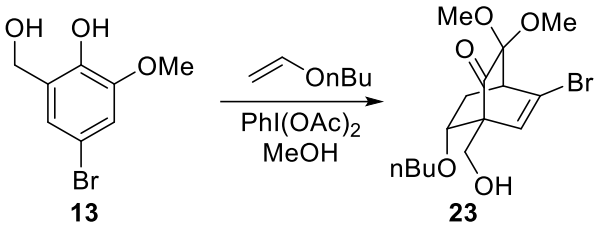
Following the general procedure with compound **13** (232 mg, 1.0 mmol) and ethyl vinyl ether (1.91 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 15:1) yielded the compound **22** (258 mg, 77%) as a pale yellow oil.

TLC: R_f = 0.55 (silica gel, hexanes/EtOAc = 3:1).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.18 (dd, *J* = 2.3, 1.1 Hz, 1H), 4.06 – 3.97 (m, 2H), 3.94 (ddd, *J* = 8.0, 3.8, 1.1 Hz, 1H), 3.60 (dq, *J* = 9.3, 7.0 Hz, 1H), 3.45 – 3.41 (m, 1H), 3.39 (s, 3H), 3.32 (s, 3H), 3.26 (td, *J* = 3.1, 2.1 Hz, 1H), 2.50 (ddd, *J* = 13.5, 8.0, 3.1 Hz, 1H), 1.67 (dt, *J* = 13.5, 3.4 Hz, 1H), 1.26 (s, 2H), 1.19 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 201.0, 125.7, 123.7, 94.2, 75.5, 65.1, 62.1, 60.9, 50.9, 50.1, 48.1, 31.4, 15.3.

HRMS (ESI) m/z: calculated for $C_{13}H_{19}BrNaO_5^+$ $[M + Na]^+$: 357.0319, found 357.0320.



13 **23**

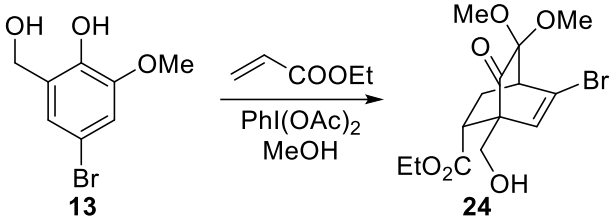
Following the general procedure with compound **13** (232 mg, 1.0 mmol) and n-butyl vinyl ether (2.58 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 20:1) yielded the compound **23** (305 mg, 84%) as a pale yellow oil.

TLC: R_f = 0.45 (silica gel, hexanes/EtOAc = 10:1).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.18 (dd, *J* = 2.4, 1.0 Hz, 1H), 4.05 – 3.97 (m, 2H), 3.92 (ddd, *J* = 8.0, 3.8, 1.1 Hz, 1H), 3.53 (dt, *J* = 9.3, 6.4 Hz, 1H), 3.39 (s, 3H), 3.31 (s, 3H), 3.26 (td, *J* = 3.1, 2.3 Hz, 1H), 2.49 (ddd, *J* = 13.5, 8.0, 3.1 Hz, 1H), 1.65 (dt, *J* = 13.4, 3.4 Hz, 1H), 1.56 – 1.48 (m, 2H), 1.38 – 1.30 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 201.0, 125.7, 123.7, 94.2, 75.7, 69.4, 62.1, 60.9, 50.9, 50.1, 48.1, 31.8, 31.2, 19.3, 13.8.

HRMS (ESI) m/z: calculated for $C_{15}H_{23}BrNaO_5^+$ [M + Na] $^+$: 385.0627, found 385.0628.



13 **24**

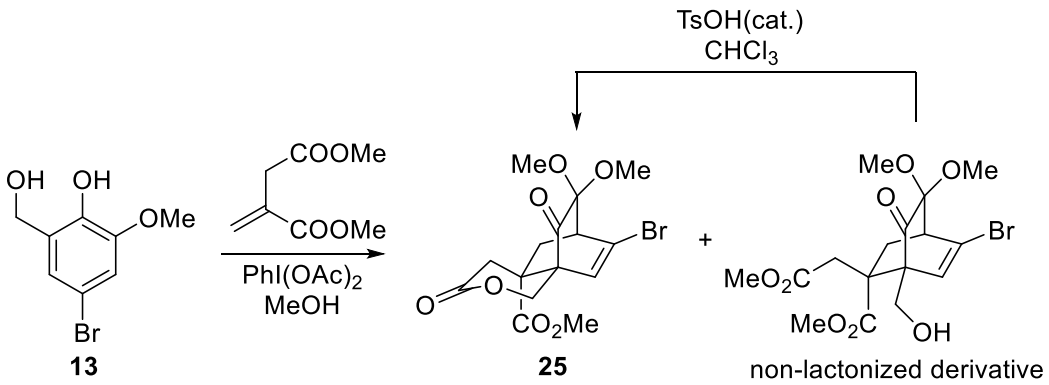
Following the general procedure with compound **13** (232 mg, 1.0 mmol) and ethyl acrylate (2.17 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 8:1) yielded the compound **24** (317 mg, 87%) as a pale yellow oil.

TLC: R_f = 0.35 (silica gel, hexanes/EtOAc = 3:1).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.16 (dd, *J* = 2.3, 0.9 Hz, 1H), 4.16 (t, *J* = 7.1 Hz, 2H), 3.94 (s, 2H), 3.42 (s, 3H), 3.37 (s, 3H), 3.01 (ddd, *J* = 10.0, 6.4, 0.8 Hz, 1H), 2.46 (ddd, *J* = 13.1, 9.9, 3.1 Hz, 2H), 1.91 (ddd, *J* = 13.1, 6.4, 2.8 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 200.9, 172.229, 126.3, 123.9, 94.1, 61.3, 60.8, 58.5, 50.8, 50.3, 49.0, 39.7, 27.9, 14.2.

HRMS (ESI) m/z: calculated for $C_{14}H_{19}BrNaO_6^+$ [M + Na] $^+$: 385.0262, found 385.0260.



13 **25** non-lactonized derivative

Following the general procedure with compound **13** (232 mg, 1.0 mmol) and dimethyl itaconate (0.79 g, 5 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 5:1) afforded an inseparable mixture of compound **25** and its non-lactonized derivative. (3:1 ratio by NMR integration)

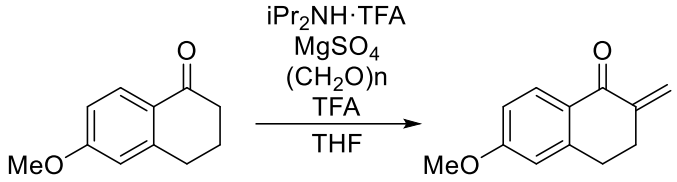
The mixture of compound **25** and non-lactonized derivative was dissolved in chloroform (20 mL), and a catalytic amount of TsOH was added. After stirring at room temperature for 5 hours, the solution can be directly concentrated in *vacuo* to provide compound **25** as a off-white powder in sufficient purity (280 mg, 72%).

TLC: R_f = 0.38 (silica gel, hexanes/EtOAc = 3:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.98 (d, *J* = 2.2 Hz, 1H), 4.97 (d, *J* = 11.6 Hz, 1H), 4.24 (d, *J* = 11.6 Hz, 1H), 3.79 (s, 3H), 3.46 (s, 3H), 3.39 (s, 3H), 3.13 (d, *J* = 18.0 Hz, 1H), 2.49 (dd, *J* = 13.9, 3.6 Hz, 1H), 2.37 (d, *J* = 17.9 Hz, 1H), 2.03 (dd, *J* = 13.9, 2.5 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.1, 172.7, 166.8, 125.7, 124.6, 93.7, 65.7, 55.8, 53.5, 51.0, 50.2, 49.2, 46.6, 38.7, 33.0.

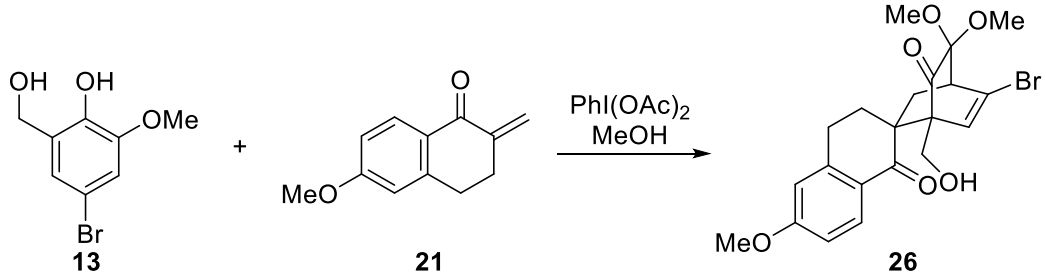
HRMS (ESI) m/z: calculated for $C_{15}H_{17}BrNaO_7^+$ [M + Na] $^+$: 411.0055, found 411.0055.



21

To a solution of 6-methoxy-1-tetralone (880 mg, 5.0 mmol) in THF (20 mL) was added paraformaldehyde (1.2 g, 40 mmol), iPr_2NH • TFA (2.15 g, 10 mmol), magnesium sulfate (600 mg, 5.0 mmol) and trifluoroacetic acid (0.76 mL, 10 mmol) in sequence at room temperature. The mixture was stirred at reflux for 36 h. Upon completion, The reaction mixture was cooled down and the solvent was removed in *vacuo*. The residue was suspended in MeOH (10 mL) and filtered. The filter cake was washed with MeOH (5 mL x 2) to afford the 0.25 M solution of compound **21** in MeOH which can be directly used in the next step without further identification and purification.

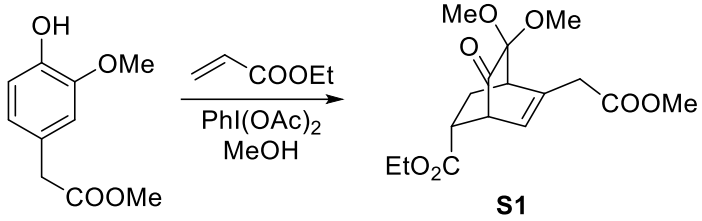
(*This compound is prone to undergo oxa-Diels-Alder reaction and dimerize in concentrated solution. Therefore, it is recommended to use it freshly prepared or store it as a dilute solution at -20°C.*)



13 **21** **26**

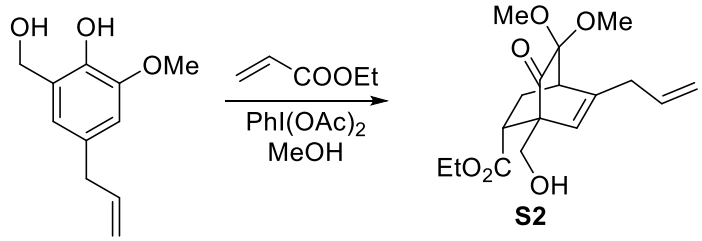
Following the general procedure with compound **13** (232 mg, 1.0 mmol) and compound **21** (0.25 M solution in MeOH, 20 mL, 5 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 8:1) yielded the compound **26** (294 mg, 65%) as a white amorphous powder.

TLC: R_f = 0.42 (silica gel, hexanes/EtOAc = 3:1).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 4.22 (d, *J* = 11.8 Hz, 1H), 3.86 (s, 3H), 3.82 (d, *J* = 11.7 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.29 (q, *J* = 2.9 Hz, 1H), 3.18 (ddd, *J* = 17.6, 12.7, 5.0 Hz, 1H), 2.87 (ddd, *J* = 17.6, 5.1, 2.3 Hz, 1H), 2.46 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.35 – 2.23 (m, 2H), 1.82 (dq, *J* = 13.3, 2.1 Hz, 2H).
^{13}C NMR (101 MHz, Chloroform-d) δ 202.4, 195.8, 163.8, 145.0, 131.2, 130.8, 124.8, 119.4, 113.7, 112.2, 94.2, 63.7, 59.5, 55.5, 51.1, 50.8, 50.0, 48.6, 31.6, 30.3, 26.2.
HRMS (ESI) m/z: calculated for $C_{21}H_{23}BrNaO_6^+$ [M + Na] $^+$: 473.0576, found 473.0575.



S1

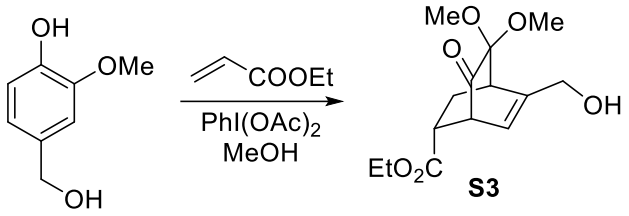
Following the general procedure with methyl 4-hydroxy-3-methoxyphenylacetate[2] (196 mg, 1.0 mmol) and ethyl acrylate (1.65 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 8:1) yielded the compound **S1** (205 mg, 63%) as a yellow oil.
TLC: R_f = 0.55 (silica gel, hexanes/EtOAc = 5:1).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.95 – 5.91 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 3.49 (dd, *J* = 6.4, 2.1 Hz, 1H), 3.33 (d, *J* = 1.5 Hz, 3H), 3.32 (s, 3H), 3.26 (d, *J* = 1.4 Hz, 2H), 3.17 (q, *J* = 2.7 Hz, 1H), 3.02 (ddd, *J* = 10.2, 5.7, 2.1 Hz, 1H), 2.25 (ddd, *J* = 13.1, 10.1, 2.9 Hz, 1H), 1.94 (ddd, *J* = 13.3, 6.0, 3.0 Hz, 1H), 1.27 – 1.23 (m, 4H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 201.4, 172.8, 170.8, 141.7, 121.7, 94.0, 61.1, 51.9, 50.9, 50.0, 49.6, 42.4, 40.7, 39.5, 24.2, 14.2.
HRMS (ESI) m/z: calculated for $C_{16}H_{22}NaO_7^+$ [M + Na] $^+$: 349.1263, found 349.1265.



S2

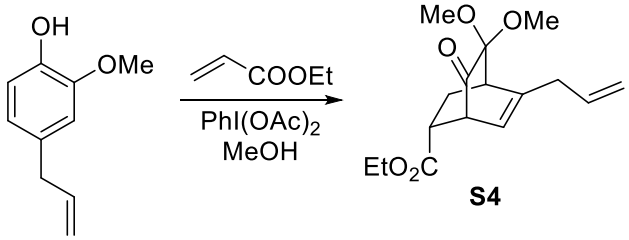
Following the general procedure with 4-allyl-2-(hydroxymethyl)-6-methoxyphenol[3] (194 mg, 1.0 mmol) and ethyl acrylate (1.65 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 8:1) yielded the compound **S2** (188 mg, 58%) as a yellow oil.
TLC: R_f = 0.45 (silica gel, hexanes/EtOAc = 5:1).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.82 (dddd, *J* = 17.2, 10.0, 7.4, 6.4 Hz, 1H), 5.56 (q, *J* = 1.5 Hz, 1H), 5.18 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.15 – 5.11 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.92 (q, *J* = 12.1 Hz, 2H), 3.35 (s, 3H), 3.33 (s, 3H), 3.07 – 2.92 (m, 4H), 2.36 (ddd, *J* = 12.9, 9.9, 3.0 Hz, 1H), 1.62 (ddd, *J* = 12.9, 6.5, 2.8 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 202.7, 172.9, 146.9, 134.2, 119.0, 117.7, 94.3, 61.3, 61.0, 55.7, 50.5, 50.0, 42.0, 39.8, 39.7, 27.5, 14.2.
HRMS (ESI) m/z: calculated for $C_{17}H_{24}NaO_6^+$ [M + Na] $^+$: 347.1468, found 347.1469.



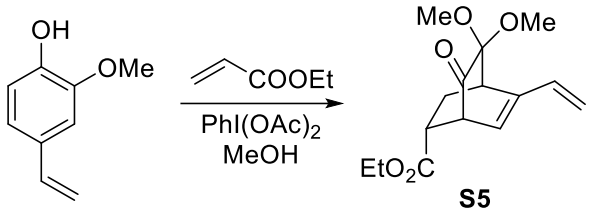
S3

Following the general procedure with vanillyl alcohol (154 mg, 1.0 mmol) and ethyl acrylate (1.65 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 6:1) yielded the compound **S3** (151 mg, 53%) as a yellow oil.
TLC: R_f = 0.32 (silica gel, hexanes/EtOAc = 3:1).
^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.98 (dd, *J* = 6.3, 1.7 Hz, 1H), 4.20 (t, *J* = 1.6 Hz, 2H), 4.14 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.52 (dd, *J* = 6.4, 2.1 Hz, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.22 (q, *J* = 2.7 Hz, 1H), 3.06 (ddd, *J* = 10.1, 5.8, 2.1 Hz, 1H), 2.24 (ddd, *J* = 13.1, 10.1, 2.8 Hz, 1H), 1.81 (ddd, *J* = 13.4, 5.8, 3.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, Chloroform-*d*) δ 201.1, 172.9, 148.1, 118.9, 93.9, 63.8, 61.3, 51.0, 49.7, 49.6, 39.9, 39.4, 29.7, 23.9, 14.1.
HRMS (ESI) m/z: calculated for $C_{14}H_{20}NaO_6^+$ [M + Na] $^+$: 307.1158, found 307.1156.



S4

Following the general procedure with eugenol (164 mg, 1.0 mmol) and ethyl acrylate (1.65 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 30:1) yielded the compound **S4** (194 mg, 66%) as a pale yellow oil.
TLC: R_f = 0.42 (silica gel, hexanes/EtOAc = 15:1).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.83 – 5.73 (m, 1H), 5.72 (dd, *J* = 6.3, 1.9 Hz, 1H), 5.17 – 5.08 (m, 2H), 4.12 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.46 (dd, *J* = 6.4, 2.0 Hz, 1H), 3.33 (s, 3H), 3.31 (s, 3H), 3.02 – 2.88 (m, 4H), 2.20 (ddd, *J* = 13.0, 10.0, 2.9 Hz, 1H), 1.73 (ddd, *J* = 13.3, 6.0, 3.0 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 201.2, 172.9, 147.8, 134.3, 117.8, 117.5, 94.1, 61.0, 50.5, 50.0, 49.8, 42.0, 39.6, 39.3, 24.3, 14.2.
HRMS (ESI) m/z: calculated for $C_{16}H_{22}NaO_5^+$ [M + Na] $^+$: 317.1362, found 317.1363.



S5

Following the general procedure with 4-hydroxy-3-methoxystyrene (150 mg, 1.0 mmol) and ethyl acrylate (1.65 mL, 20 mmol), purification by flash column chromatography on silica gel (hexanes/EtOAc = 30:1) yielded the compound **S5** (112 mg, 40%) as a colorless oil.

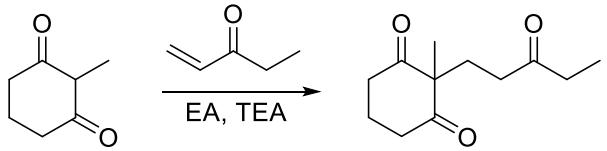
TLC: R_f = 0.35 (silica gel, hexanes/EtOAc = 15:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.41 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.00 (dd, *J* = 6.5, 2.0 Hz, 1H), 5.43 (d, *J* = 17.5 Hz, 1H), 5.18 (d, *J* = 10.7 Hz, 1H), 4.12 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.56 (dd, *J* = 6.5, 1.9 Hz, 1H), 3.51 (q, *J* = 2.7 Hz, 1H), 3.37 (s, 3H), 3.33 (s, 3H), 3.07 (ddd, *J* = 10.1, 6.2, 1.9 Hz, 1H), 2.35 (ddd, *J* = 13.2, 10.1, 3.1 Hz, 1H), 1.72 (ddd, *J* = 13.2, 6.2, 2.8 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.2, 172.8, 145.6, 134.1, 122.6, 114.0, 93.9, 61.1, 50.7, 50.4, 50.1, 39.7, 37.4, 24.7, 14.2.

HRMS (ESI) m/z: calculated for $C_{15}H_{20}NaO_5^+$ [M + Na] $^+$: 303.1208, found 303.1208.

Synthesis of compound 5



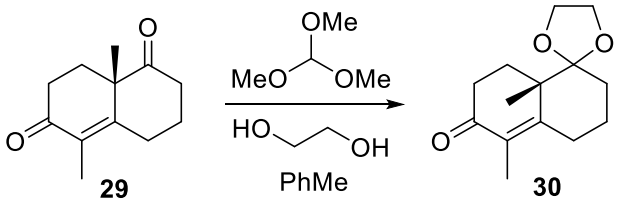
27 **7**

To a suspension of compound **27** (6.3 g, 50.0 mmol) in EA (50 mL) was added ethyl vinyl ketone (5.47 mL, 55.0 mmol) and Et_3N (8.17 mL, 60.0 mmol) sequentially at room temperaure. After stirred at 70 °C overnight, the reaction mixture was directly concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 3:1) to provide compound **7** (10.40 g, 99%) as an light yellow oil. Analytical data according to literature[4].

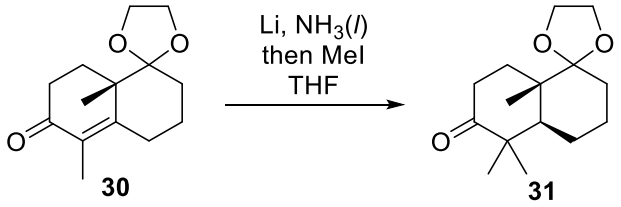
7 **29**

To a solution of compound **7** (10.3 g, 49.0 mmol) in DMF (100 mL) was added *L*-Phenylalanine (8.09 g, 49.0 mmol) and *L*-CSA (5.68 g, 24.5 mmol) sequentially at room temperaure. The suspension was stirred at rt for 7 hours, then heated to 30 °C and stirred for 24 hours. The temperature of the oil bath was increased by 10 °C each day until the reaction had been stirring at 60 °C for 24 hours (totally in 6 days). After cooled to room temperature,

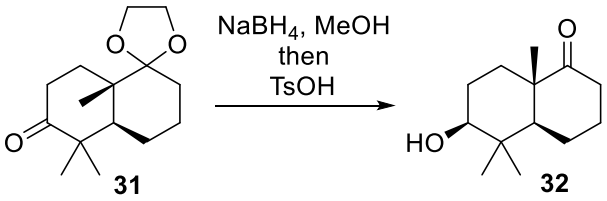
the reaction mixture was quenched with aq. sat $NaHCO_3$ solution (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 3:1) to provide compound **29** (7.8 g, 83%, 95% ee) as a pale-yellow oil. Analytical data according to literature[5].



To a solution of compound **29** (9.21 g, 48.0 mmol) in PhMe (150 mL) was added ethylene glycol (10.70 mL, 192.0 mmol), trimethoxymethane (5.77 mL, 52.8 mmol), *D*-CSA (5.57 g, 24.0 mmol) sequentially at room temperaure. After stirred at room temperature for 12 h, the reaction mixture was quenched with aq. sat $NaHCO_3$ solution (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 3:1) to provide compound **30** (10.20 g, 90%) as a white solid. Analytical data according to literature[4].

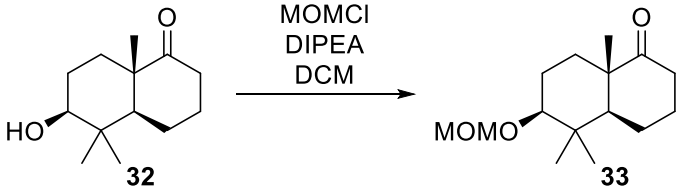


Lithium (1.5 g, 215.0 mmol) was added to liquid ammonia (400 mL) at -78 °C and stirred until the solid was completely dissolved. To this solution compound **30** (10.15 g, 43.0 mmol) in THF (200 mL) was added dropwise over a period of 30 min and it was allowed to stir for 1 h. After addition of MeI (26.8 mL, 430 mmol) in THF (100 mL), the reaction mixture was stirred another 1 h at -78 °C. The cooling bath was removed and the ammonia was allowed to evaporate overnight. The residue was diluted with aq. sat NH_4Cl solution (250 mL) and extracted with Et_2O (3 x 150 mL). The combined organic layers were washed sequentially with water (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 3:1) to provide compound **31** (8.67g, 80%) as a yellow solid. Analytical data according to literature[4].



To a solution of compound **31** (8.45 g, 33.5 mmol) in MeOH (60 mL) was added $NaBH_4$ (1.91 g, 50.3 mmol) over a period of 30 min and it was allowed to stir for 1 h at 0 °C. The reaction mixture was quenched carefully with 2.0 N aq. HCl (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue can be used directly in the next step without further purification.

To a solution of above crude product in acetone/H_2O (v/v = 1/1, 100 mL) was added TsOH (11.2 g, 67.0 mmol) in one portion at room temperature. After being stirred at room temperature overnight, the reaction was quenched with sat. aq. $NaHCO_3$ (100 mL), and the mixture was extracted with EtOAc (100 mL x 3). The combined organic phases were washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 5:1) to provide compound **32** (6.26 g, 89%) as a white solid. Analytical data according to literature[4].



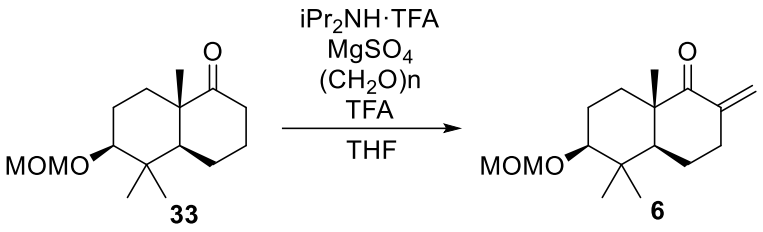
To a solution of compound **32** (6.12 g, 29.1 mmol) in DCM (120 mL) was added DIPEA (15.2 mL, 87.3 mmol) and MOMCl (4.4 mL, 58.2 mmol) sequentially at room temperaure and it was allowed to stir overnight at 40 °C. The reaction mixture was quenched with 1.0 N aq. HCl (100 mL) and extracted with DCM (3 x 50 mL). The combined organic phases were washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 20:1) to provide compound **33** (7.02 g, 95%) as a colorless viscous oil.

TLC: R_f = 0.55 (silica gel, hexanes/EtOAc = 10:1).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.74 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.38 (s, 3H), 3.06 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.57 (td, *J* = 13.9, 7.0 Hz, 1H), 2.19 (ddt, *J* = 14.1, 5.0, 1.8 Hz, 1H), 2.12 – 2.04 (m, 1H), 1.89 – 1.83 (m, 1H), 1.78 – 1.74 (m, 1H), 1.73 – 1.67 (m, 1H), 1.67 – 1.46 (m, 5H), 1.15 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H).

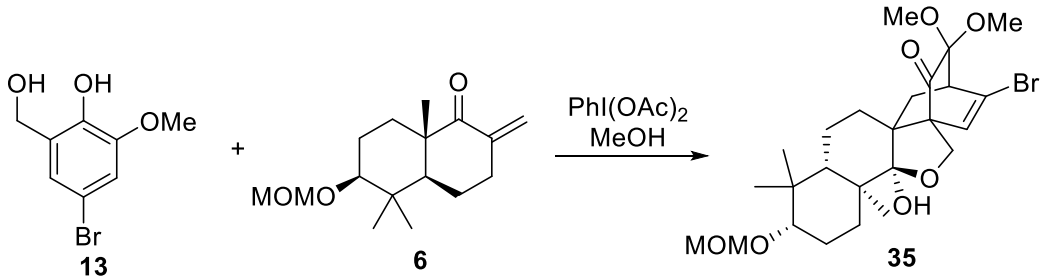
^{13}C NMR (101 MHz, Chloroform-*d*) δ 215.2, 96.0, 84.2, 55.6, 52.9, 48.5, 39.5, 37.5, 31.1, 28.0, 26.2, 23.7, 20.7, 18.6, 16.7.

HRMS (ESI) m/z: calculated for $C_{15}H_{26}NaO_3^+$ $[M + Na]^+$: 277.1780, found 277.1781.



To a solution of compound **33** (254 mg, 1.0 mmol) in THF (4 mL) was added paraformaldehyde (240 mg, 8 mmol), iPr_2NH • TFA (430 mg, 2 mmol), magnesium sulfate (120 mg, 1.0 mmol) and trifluoroacetic acid (0.15 mL, 2.0 mmol) in sequence at room temperature. The mixture was stirred at reflux for 36 h. Upon completion, The reaction mixture was cooled down and the solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and filtered. The filter cake was washed with MeOH (1 mL x 2) to afford the 0.25 M solution of compound **6** in MeOH which can be directly used in the next step without further identification and purification.

(*This compound is prone to undergo oxa-Diels-Alder reaction and dimerize in concentrated solution. Therefore, it is recommended to use it freshly prepared or store it as a dilute solution at -20°C.*)



Phenol **13** (232 mg, 1 mmol) and BHT (22 mg, 0.1 mmol) were dissolved directly in the freshly prepared methanolic solution of compound **6** (4 mL, 0.25 M). This combined solution was added dropwise via syringe over 6 h to a solution of $PhI(OAc)_2$ in MeOH (5 mL) maintained at 40 °C. The mixture was stirred at 40 °C until the intermediate *o*-benzoquinone was completely consumed. The solution was directly concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 8:1) to provide compound **35** (201 mg, 38%) as a white amorphous powder.

TLC: R_f = 0.52 (silica gel, hexanes/EtOAc = 3:1).

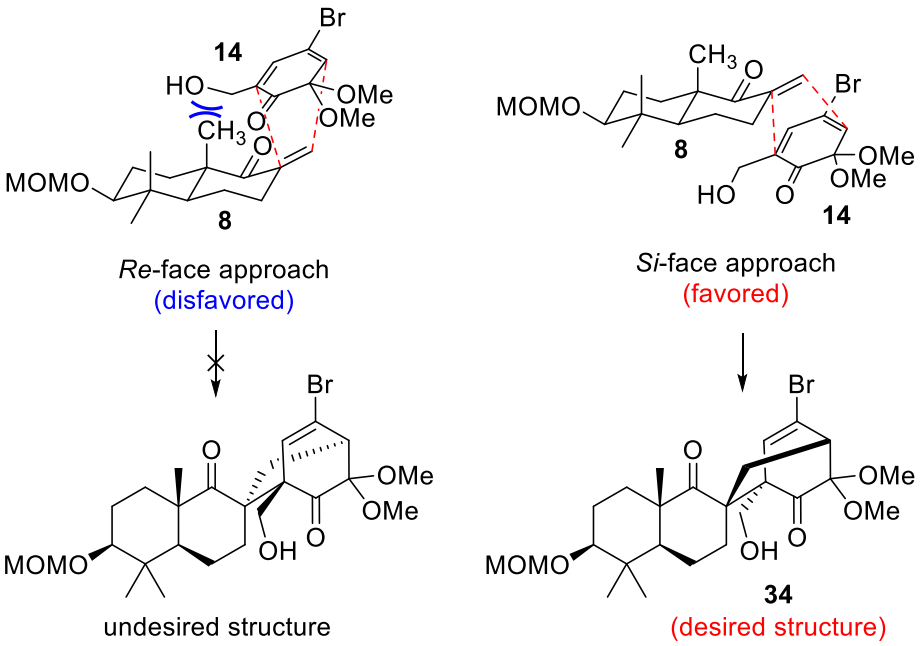
^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.13 (d, *J* = 2.4 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.41 (d, *J* = 9.5 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 1H), 3.82 (d, *J* = 9.5 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 3.39 (s, 3H), 3.32 (dt, *J* = 3.7, 2.3 Hz, 1H), 3.14 (dd, *J* = 11.6, 4.3 Hz, 1H), 2.15 (d, *J* = 1.4 Hz, 1H), 2.06 (s, 1H), 2.03 – 2.00 (m, 1H), 1.98 (d, *J* = 3.7 Hz, 1H), 1.81 (dt, *J* = 13.1, 3.6 Hz, 2H), 1.70 (td, *J* = 13.1, 3.5 Hz, 2H), 1.46 – 1.44 (m, 1H), 1.30 – 1.26 (m, 4H), 1.20 (s, 1H), 1.02 (d, *J* = 3.7 Hz, 3H), 0.99 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 196.5, 131.7, 121.3, 107.6, 96.1, 95.4, 84.4, 67.2, 66.7, 55.6, 51.7, 51.3, 50.6, 50.0, 47.1, 42.3, 38.1, 33.0, 31.3, 29.2, 28.4, 23.5, 18.4, 16.5, 15.7.

HRMS (ESI) m/z: calculated for $C_{25}H_{37}BrNaO_7^+$ $[M + Na]^+$: 553.1695, found 553.1697.

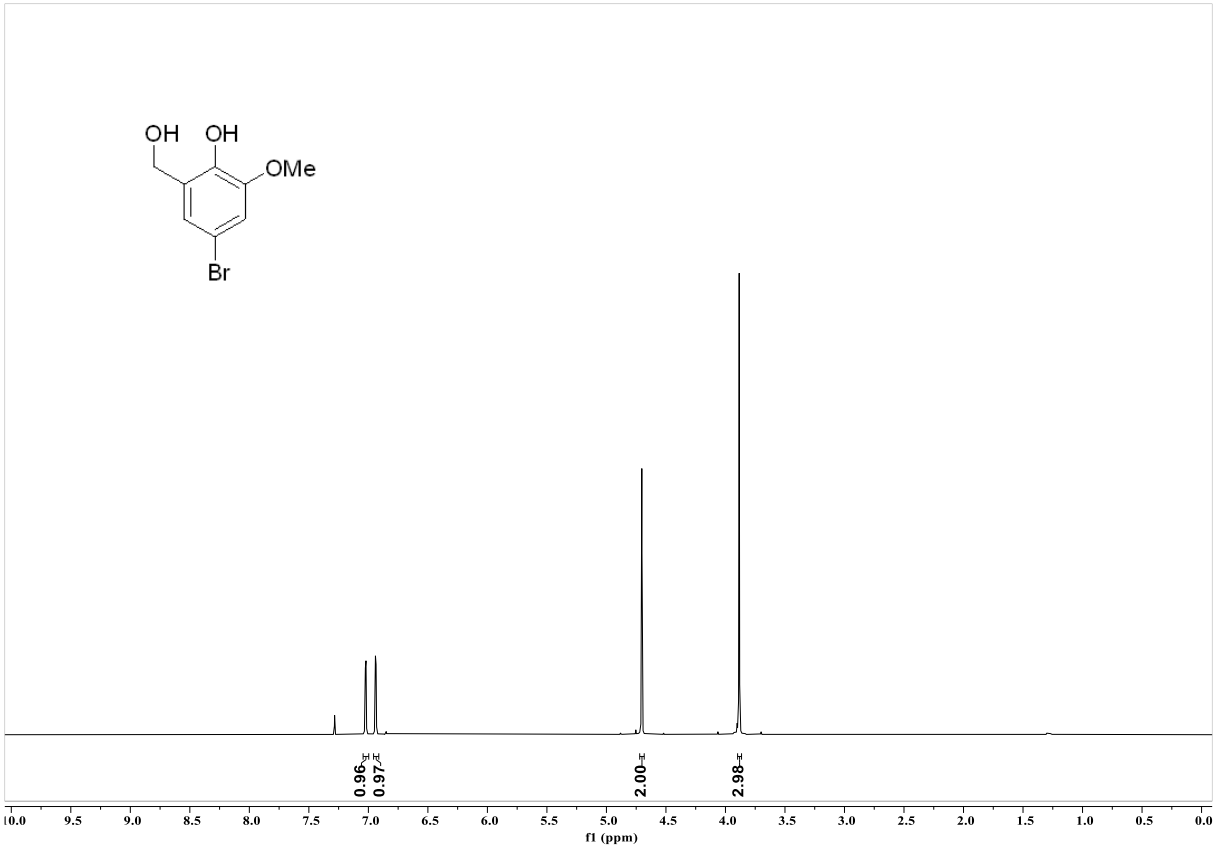
Facial-selectivity Analysis for the Diels-Alder Reaction of Compounds 8 and 14

The Diels-Alder reaction between masked *o*-benzoquinone **14** and enone **8** proceeded undoubtedly with both *endo*-selectivity and *ortho*-regioselectivity.[6, 7] As illustrated below, the facial selectivity was governed by the substrate itself. While **14** could approach **8** from either the *Re*- or *Si*-face, the *Re*-face approach was sterically hindered by repulsion between a methyl group and the masked *o*-benzoquinone **14**, disfavoring this pathway. In contrast, the unhindered *Si*-face approach was favored, leading to the desired product **34**.

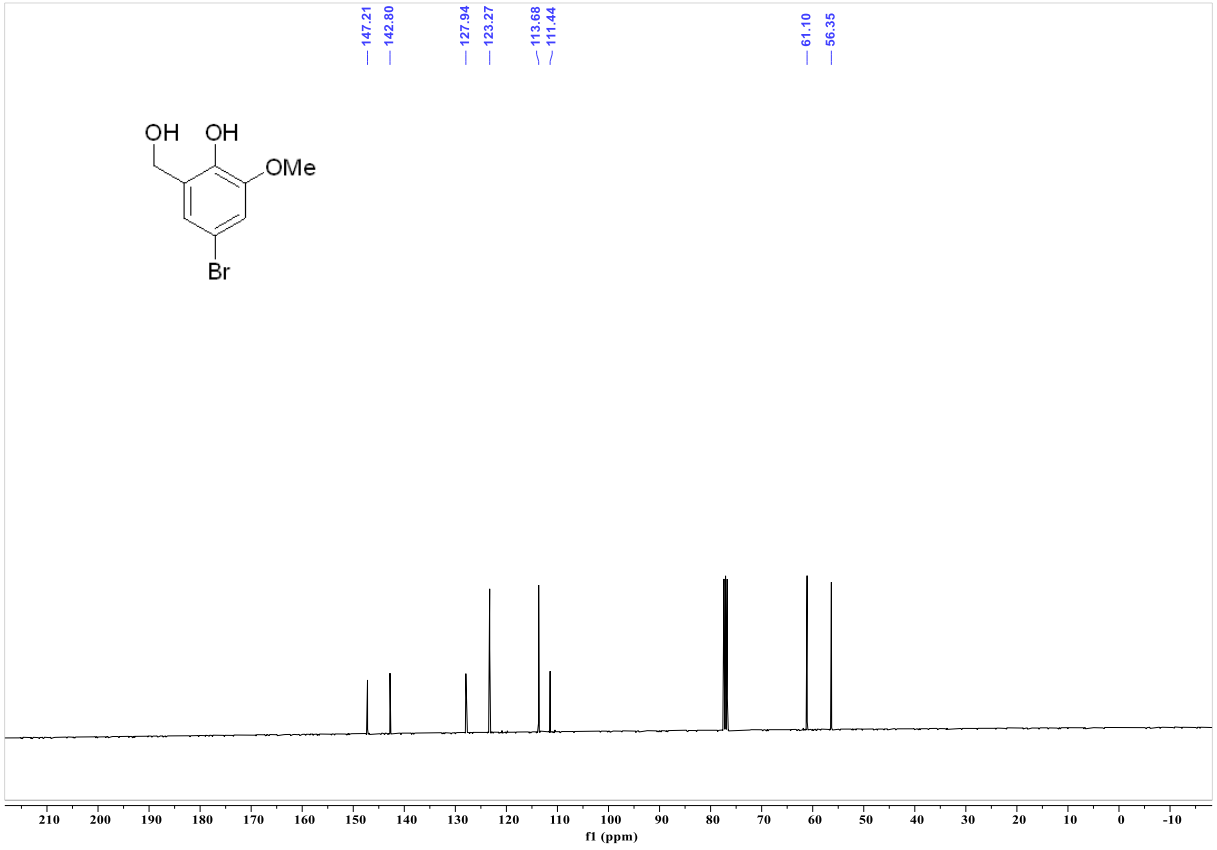


NMR spectra

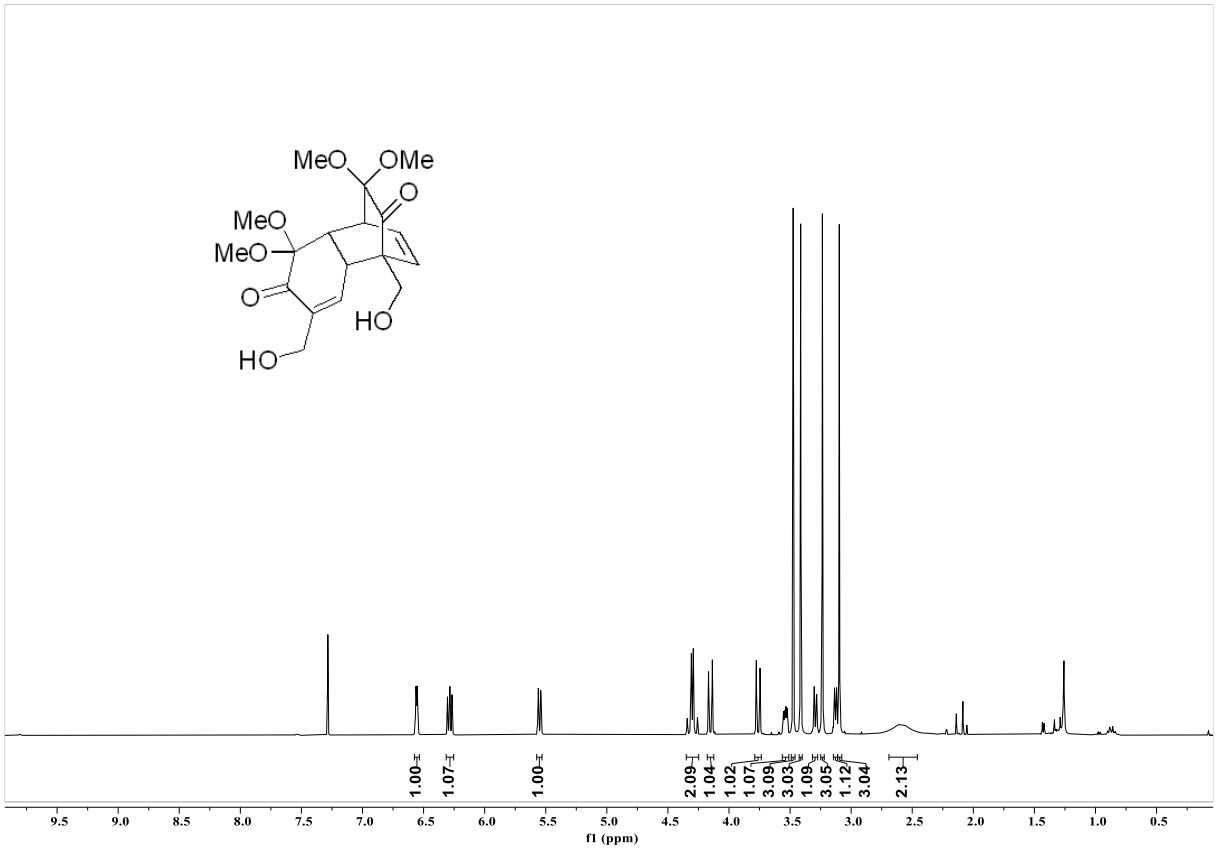
Compound 13 ^{1}H NMR ($CDCl_3$, 400MHz)



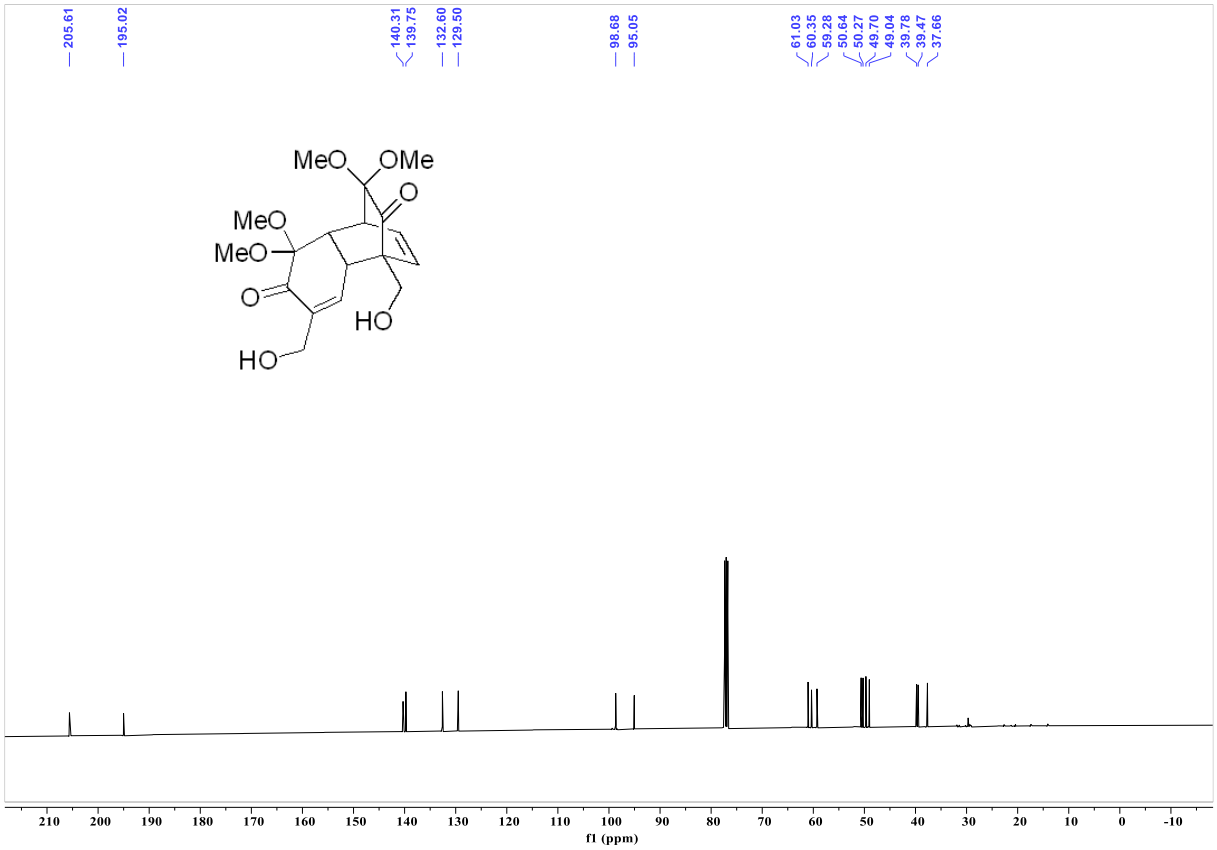
Compound 13 ^{13}C NMR ($CDCl_3$, 100MHz)



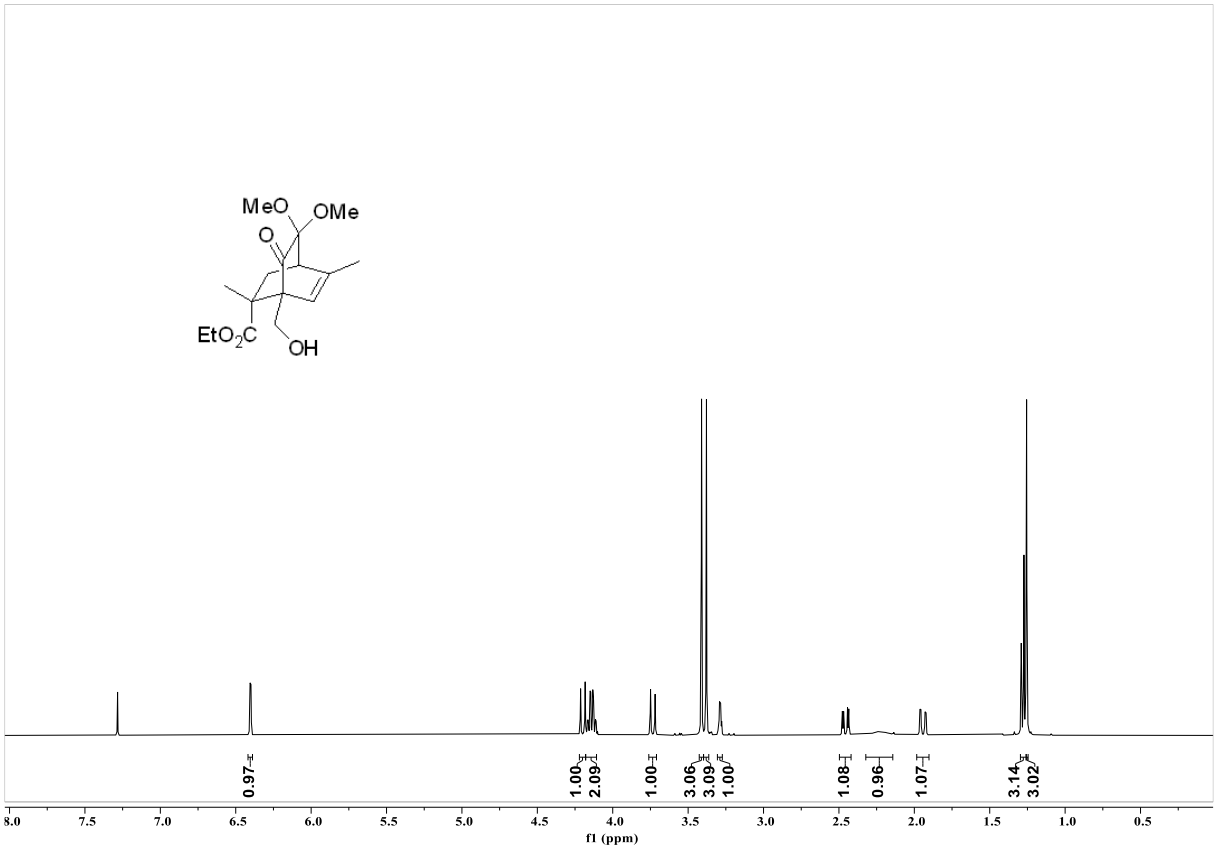
Compound 12 ^{1}H NMR ($CDCl_3$, 400MHz)



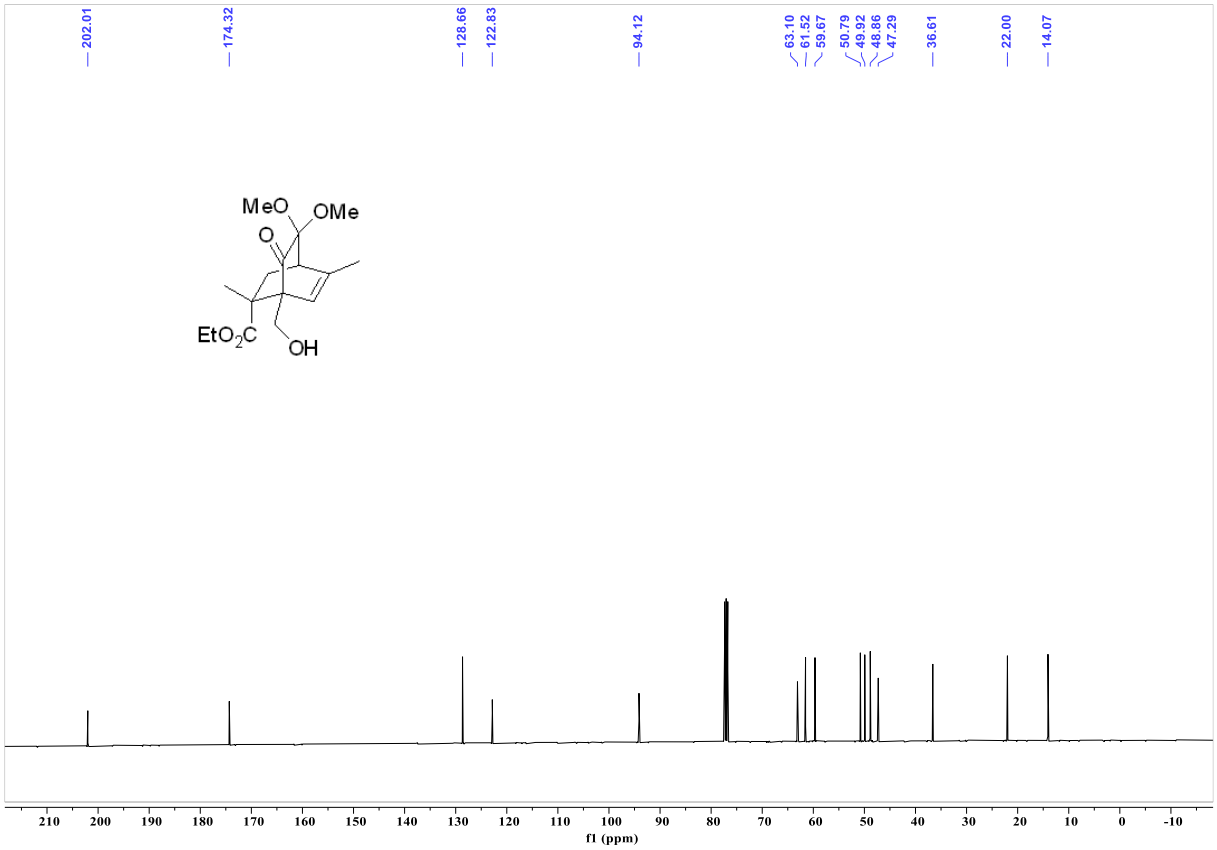
Compound 12 ^{13}C NMR ($CDCl_3$, 100MHz)



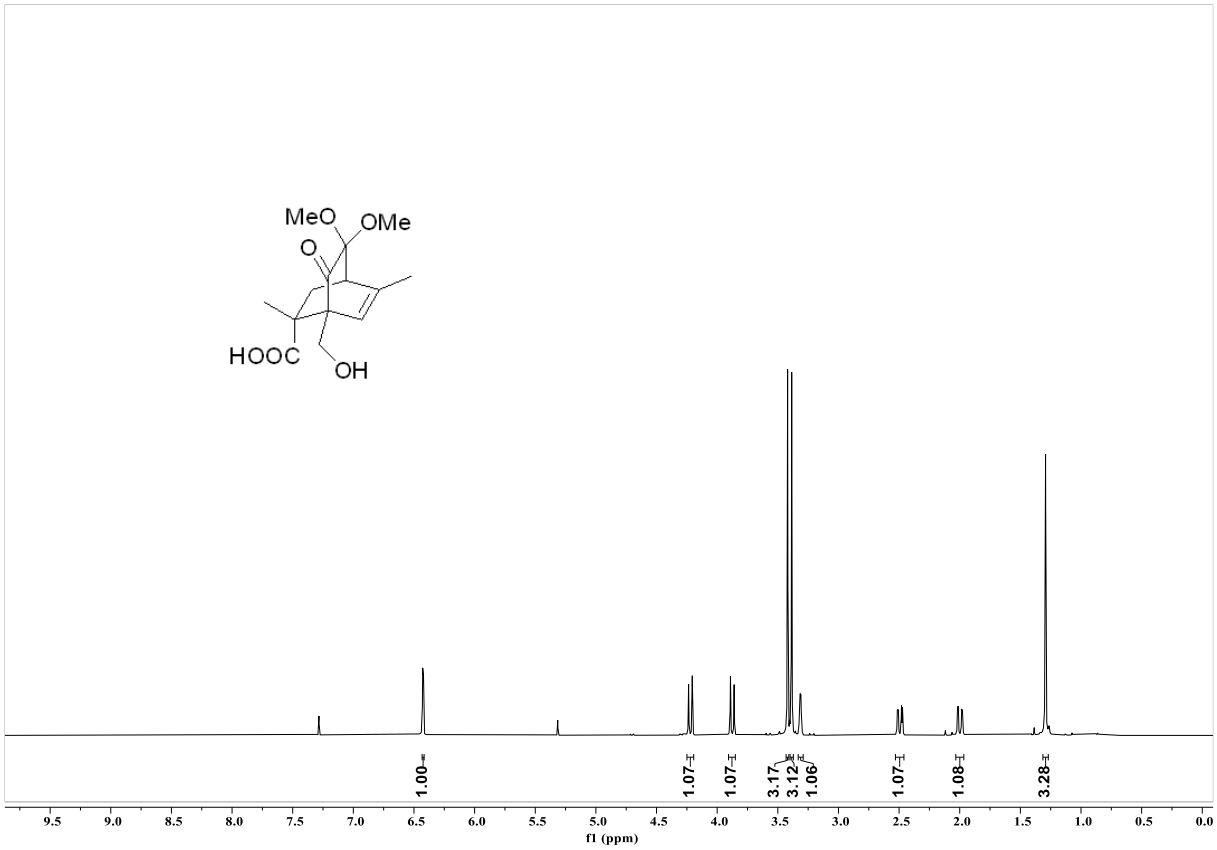
Compound 15 ^{1}H NMR ($CDCl_3$, 400MHz)



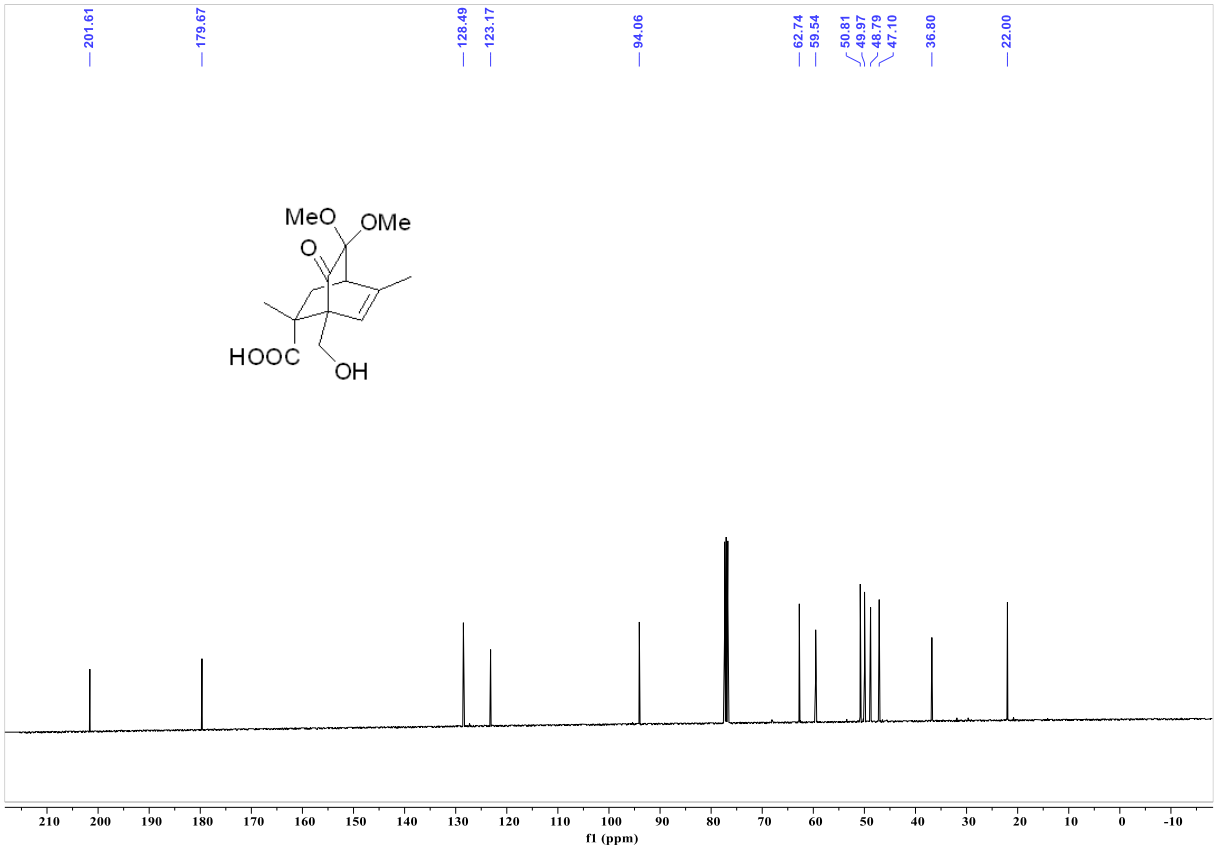
Compound 15 ^{13}C NMR ($CDCl_3$, 100MHz)



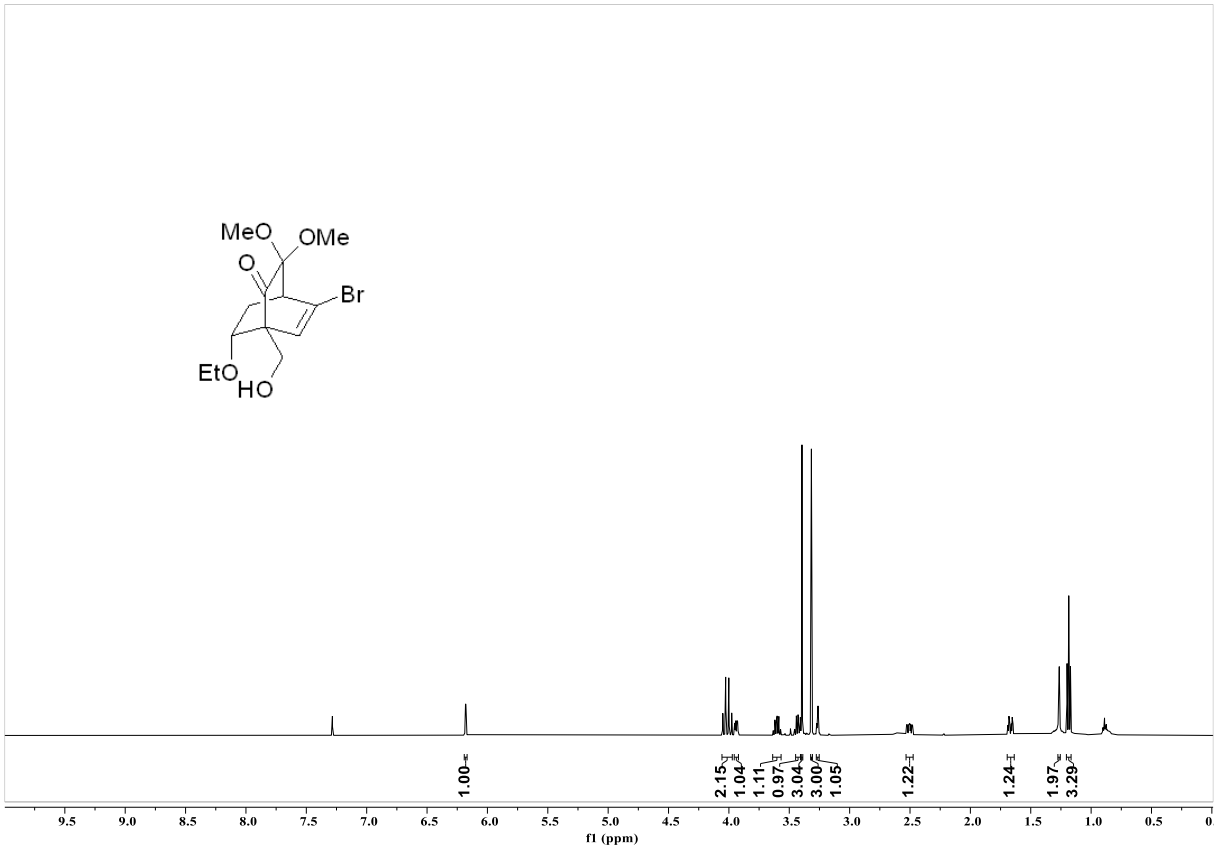
Compound 16 ^{1}H NMR ($CDCl_3$, 400MHz)



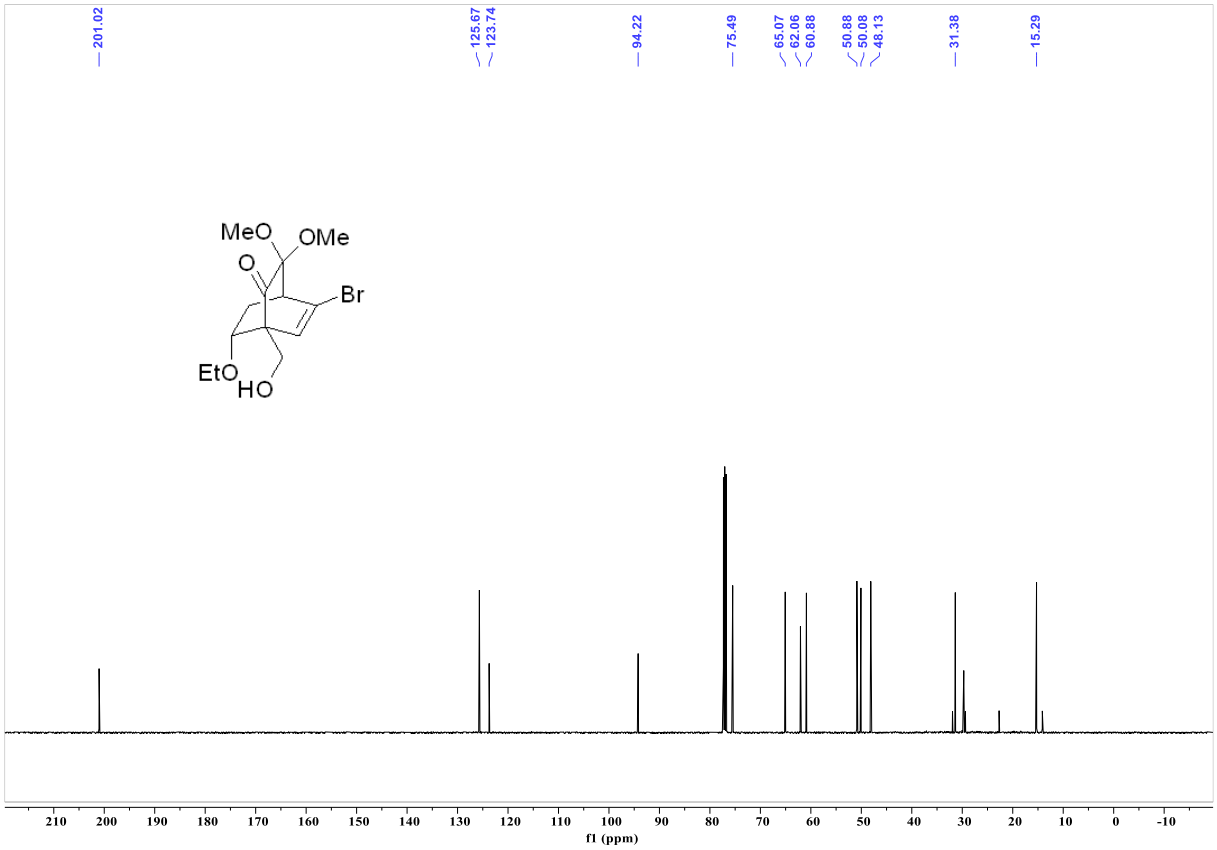
Compound 16 ^{13}C NMR ($CDCl_3$, 100MHz)



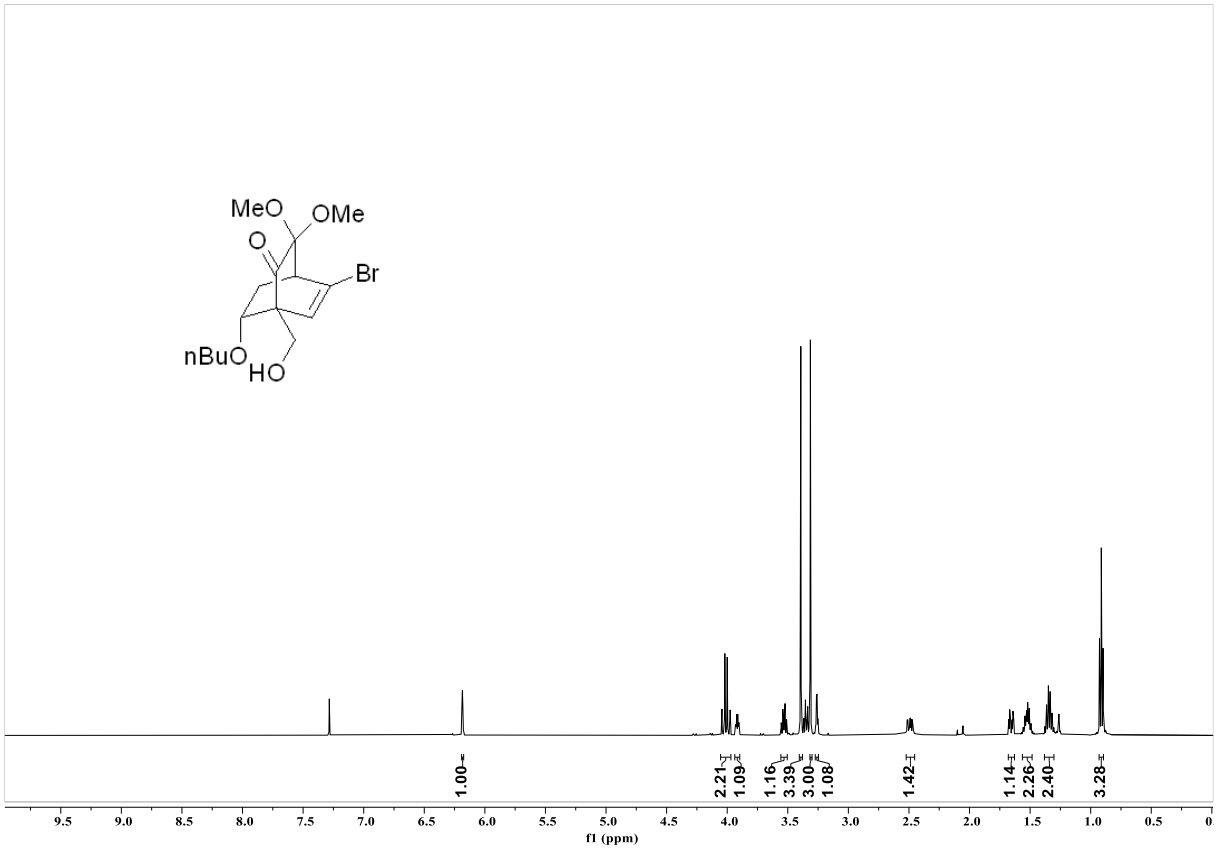
Compound 22 ^{1}H NMR ($CDCl_3$, 500MHz)



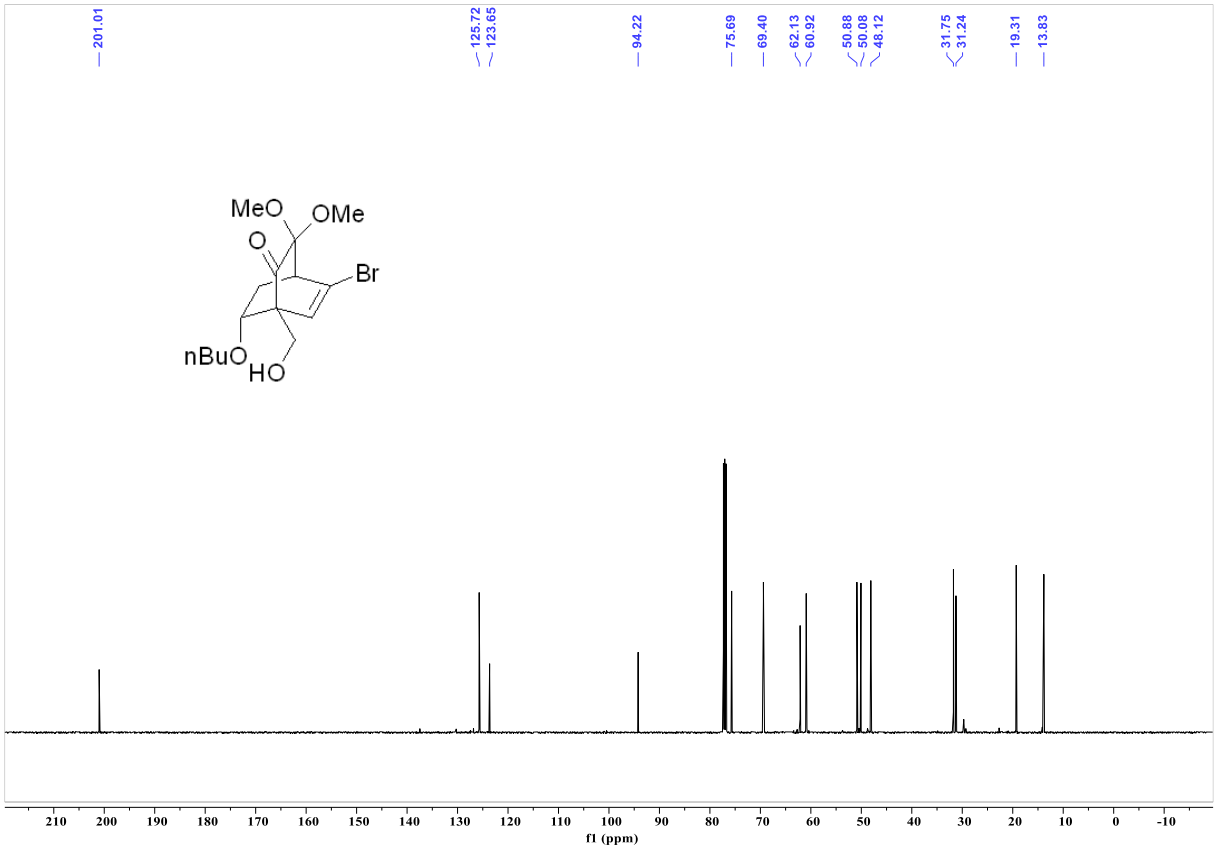
Compound 22 ^{13}C NMR ($CDCl_3$, 125MHz)



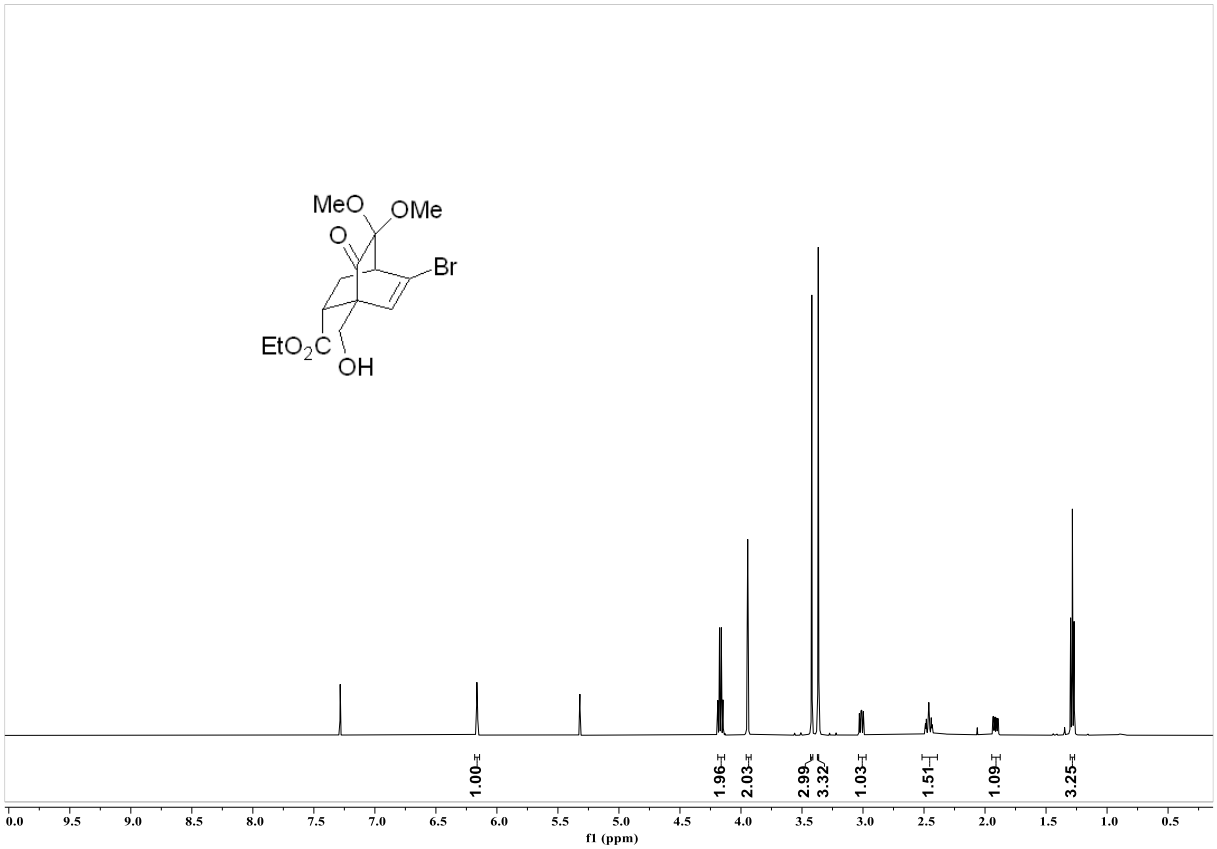
Compound 23 ^{1}H NMR ($CDCl_3$, 500MHz)



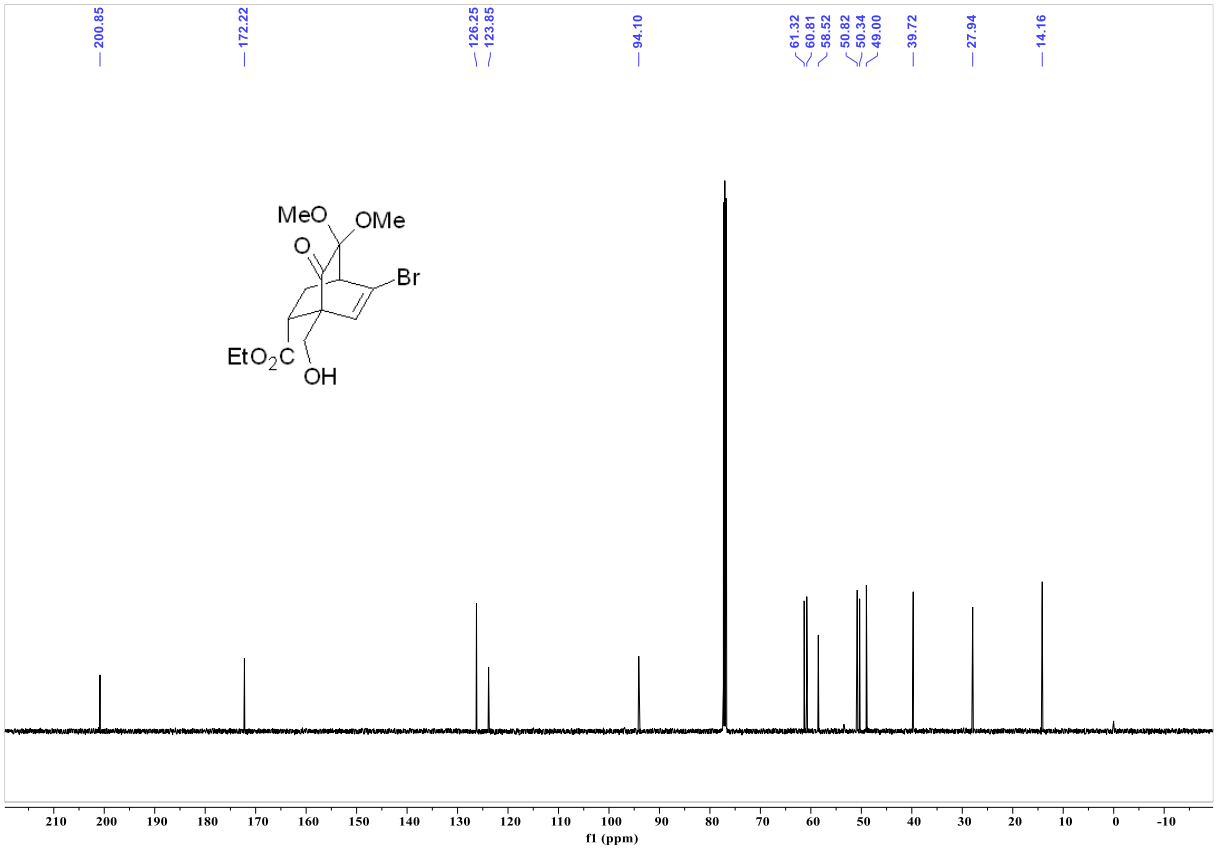
Compound 23 ^{13}C NMR ($CDCl_3$, 125MHz)



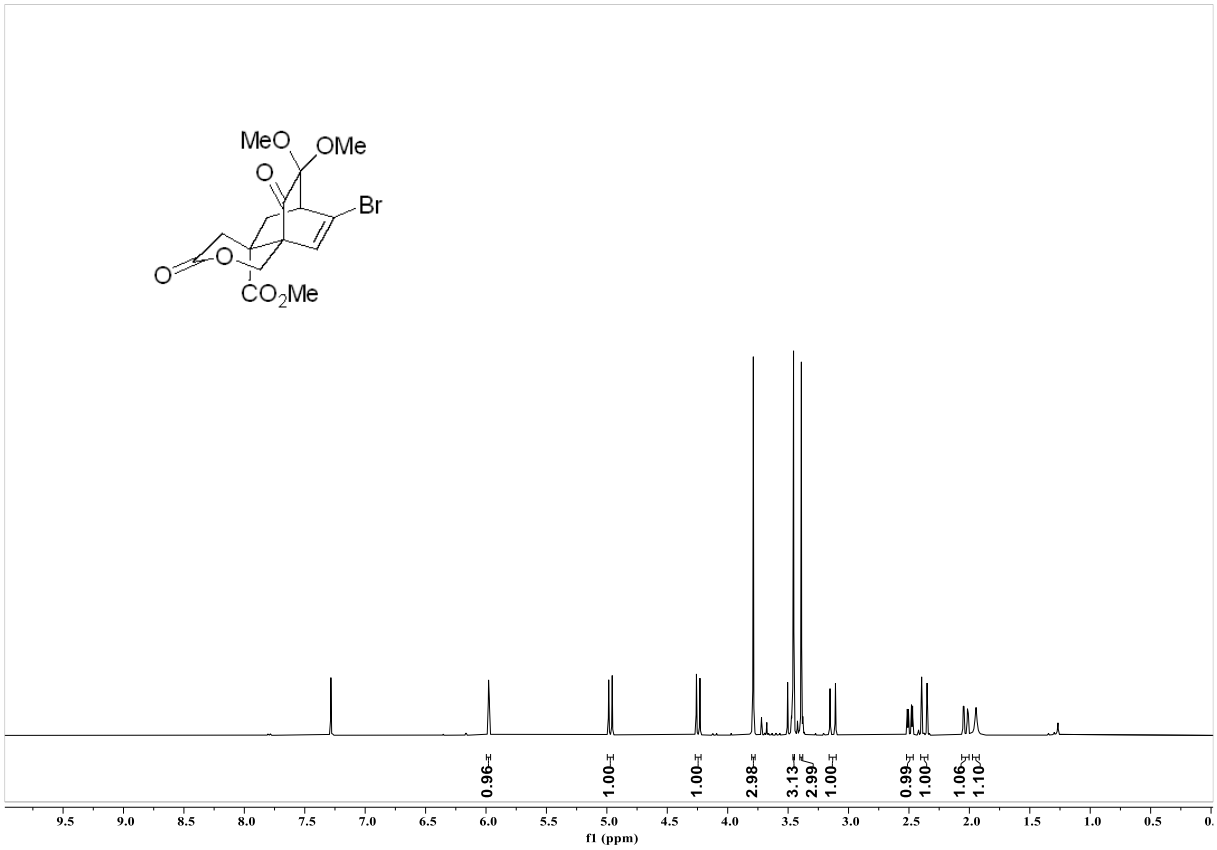
Compound 24 ^{1}H NMR ($CDCl_3$, 500MHz)



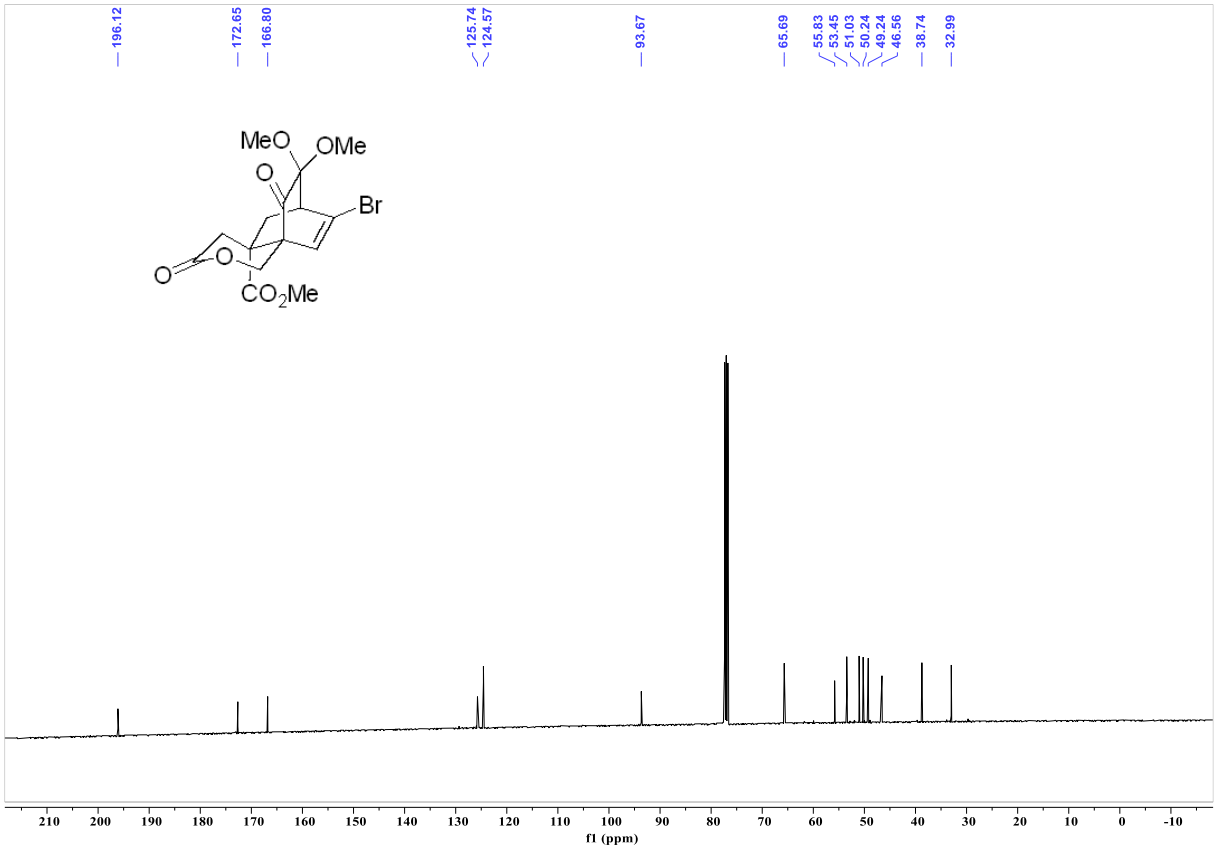
Compound 24 ^{13}C NMR ($CDCl_3$, 125MHz)



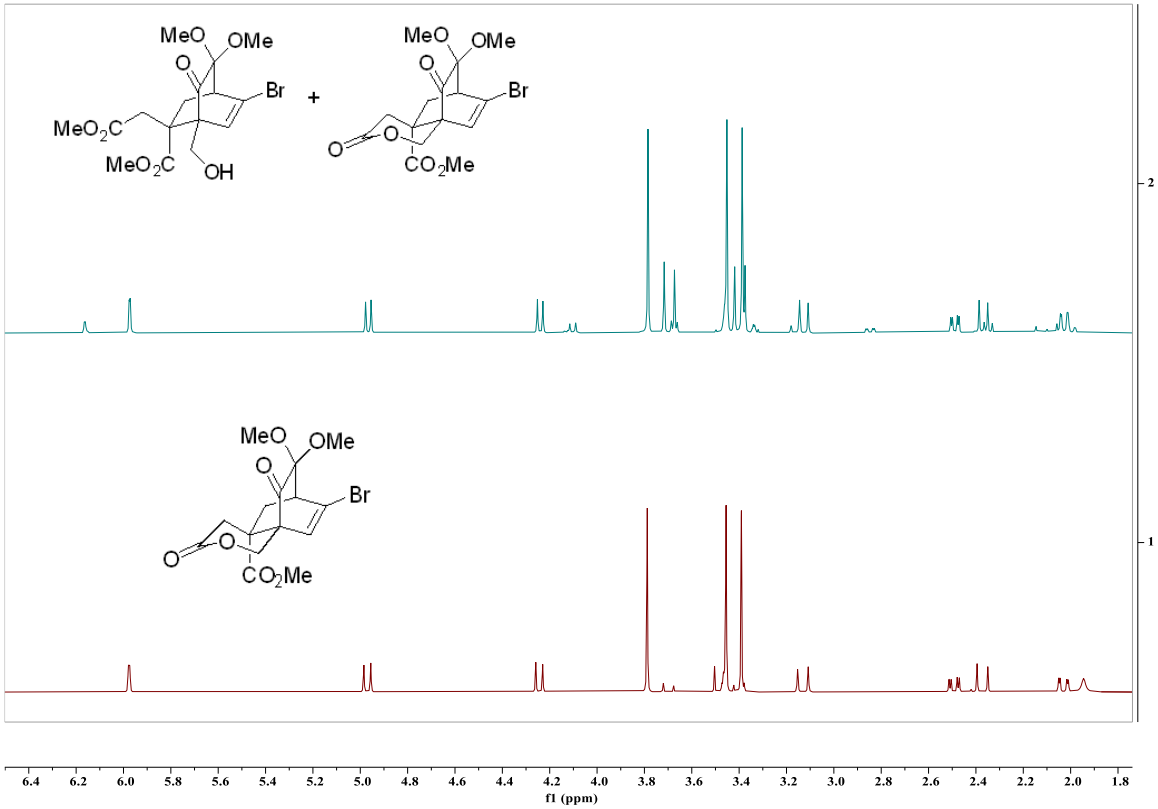
Compound 25 ^{1}H NMR ($CDCl_3$, 400MHz)



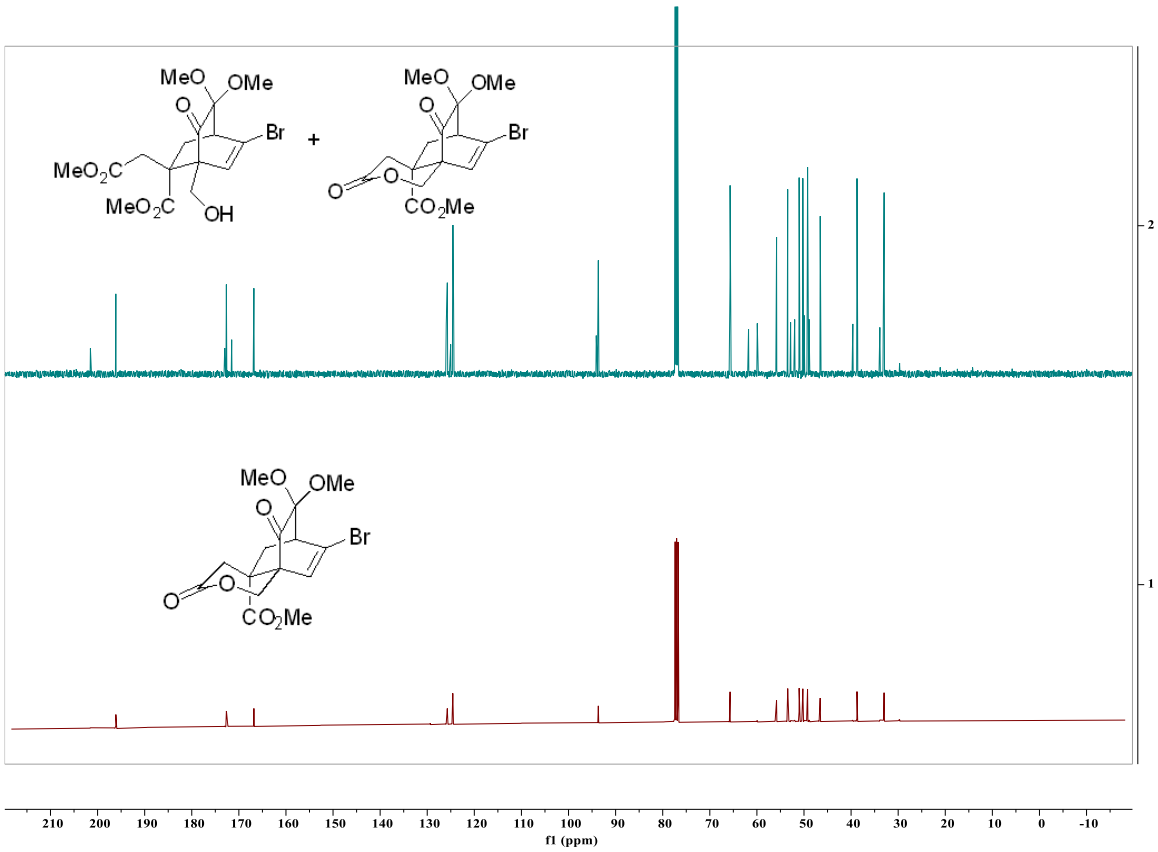
Compound 25 ^{13}C NMR ($CDCl_3$, 100MHz)



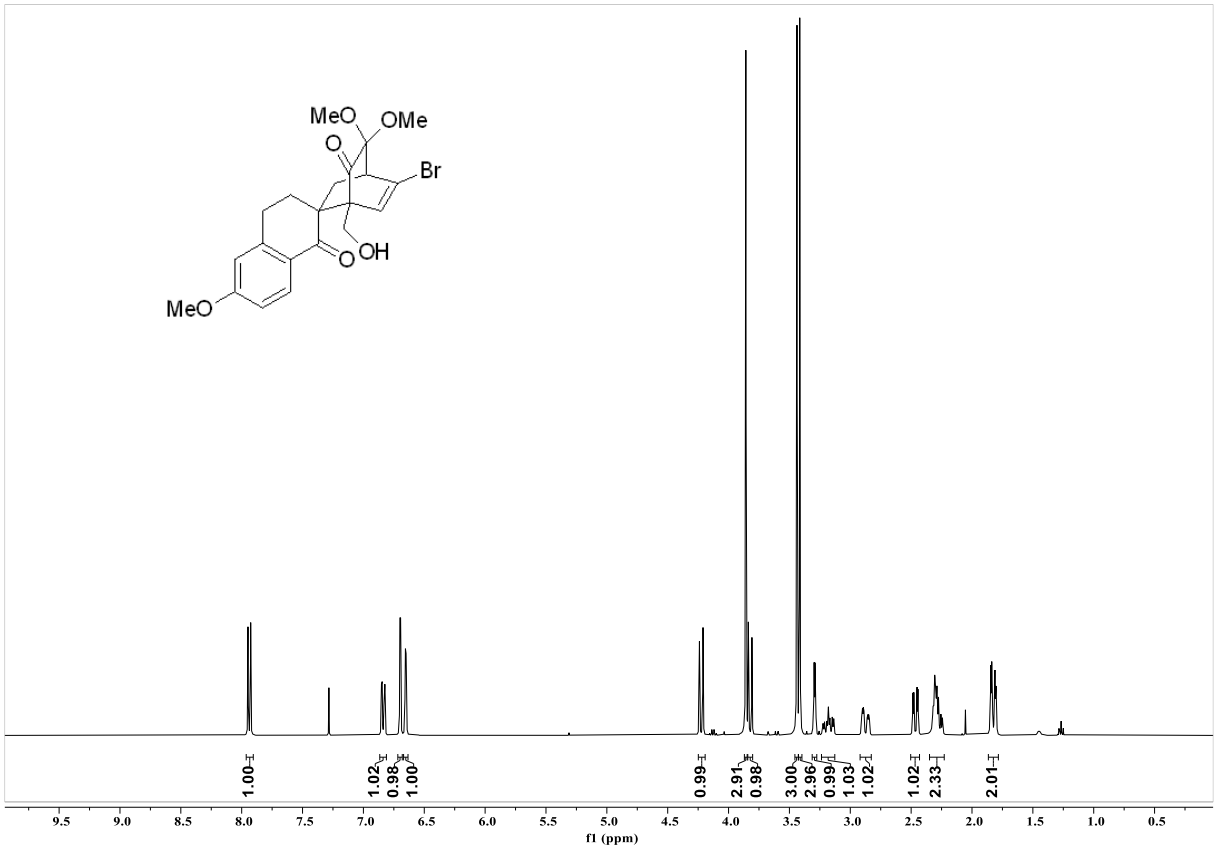
Compound 25 and its non-lactonized derivative ^{1}H NMR ($CDCl_3$, 400MHz)



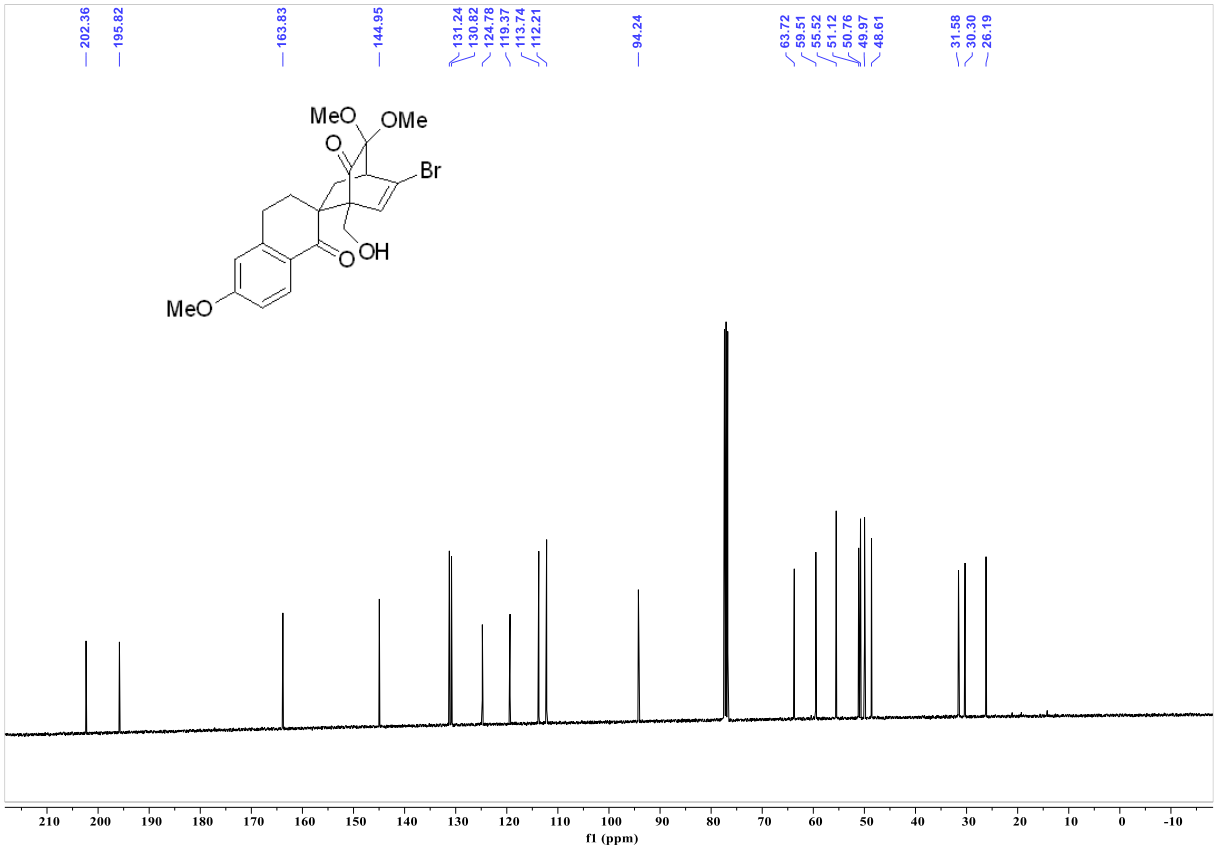
Compound 25 and its non-lactonized derivative ^{13}C NMR ($CDCl_3$, 100MHz)



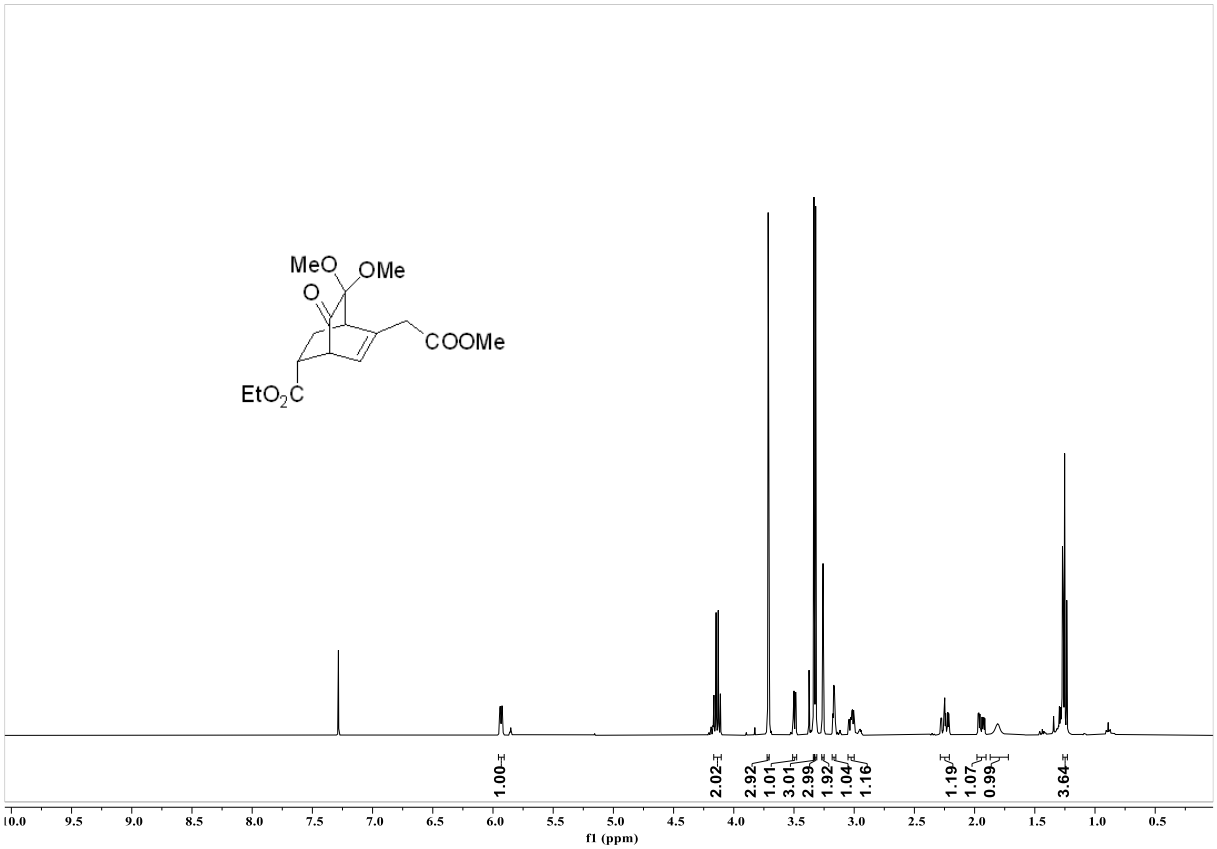
Compound 26 ^{1}H NMR ($CDCl_3$, 400MHz)



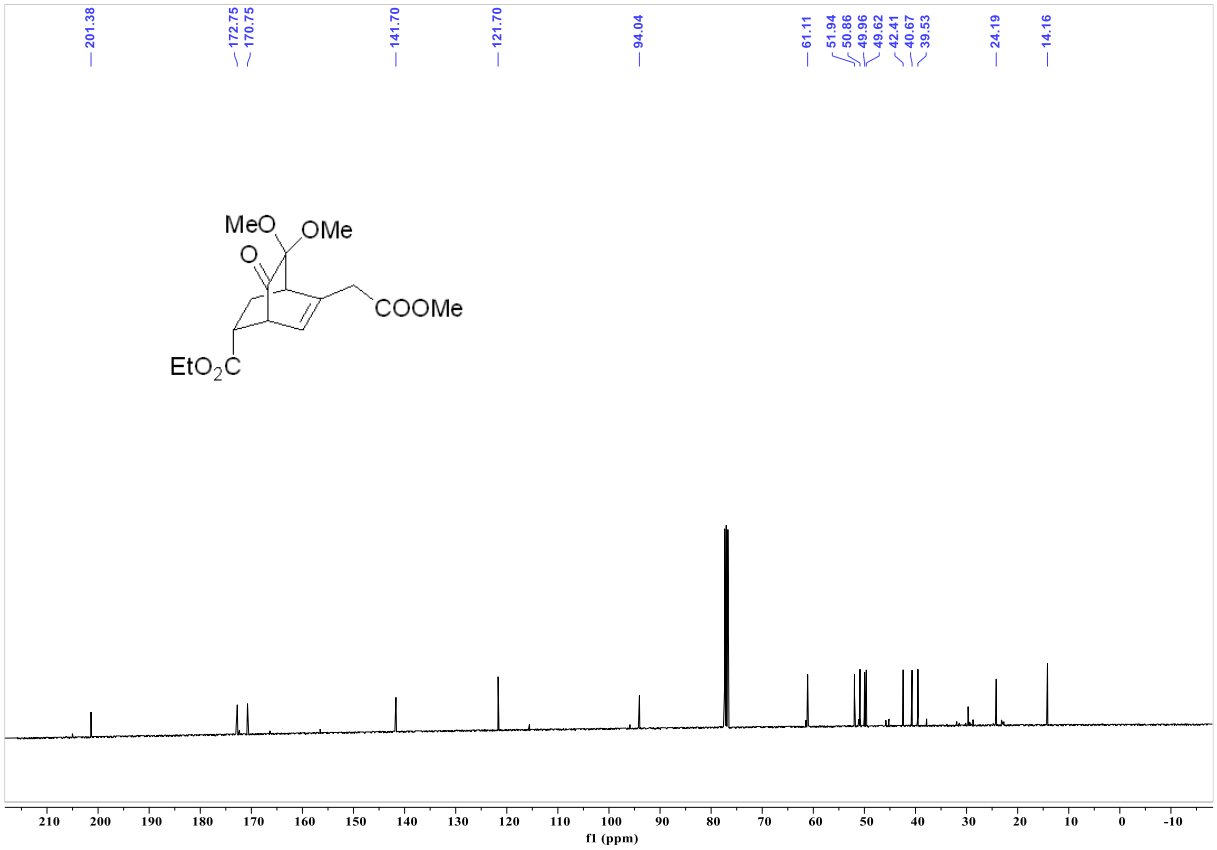
Compound 26 ^{13}C NMR ($CDCl_3$, 100MHz)



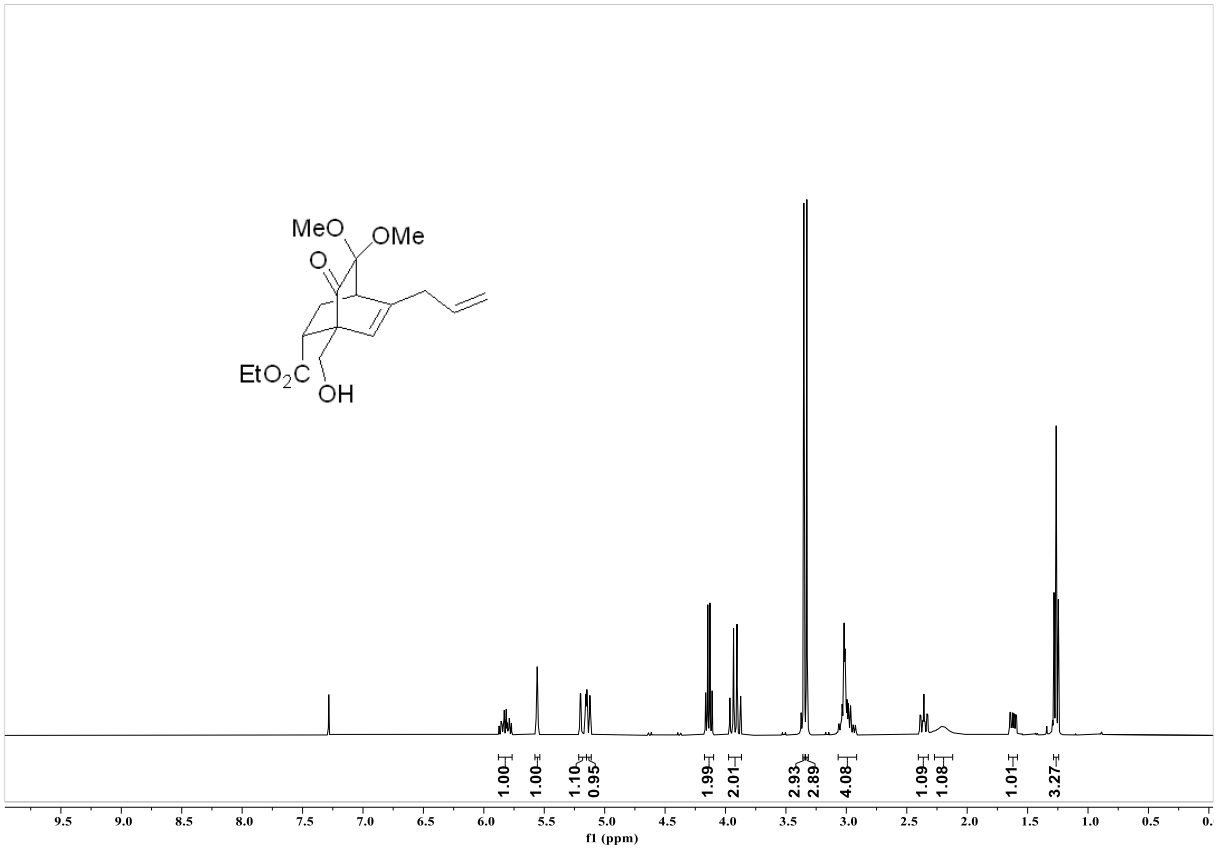
Compound S1 ^{1}H NMR ($CDCl_3$, 400MHz)



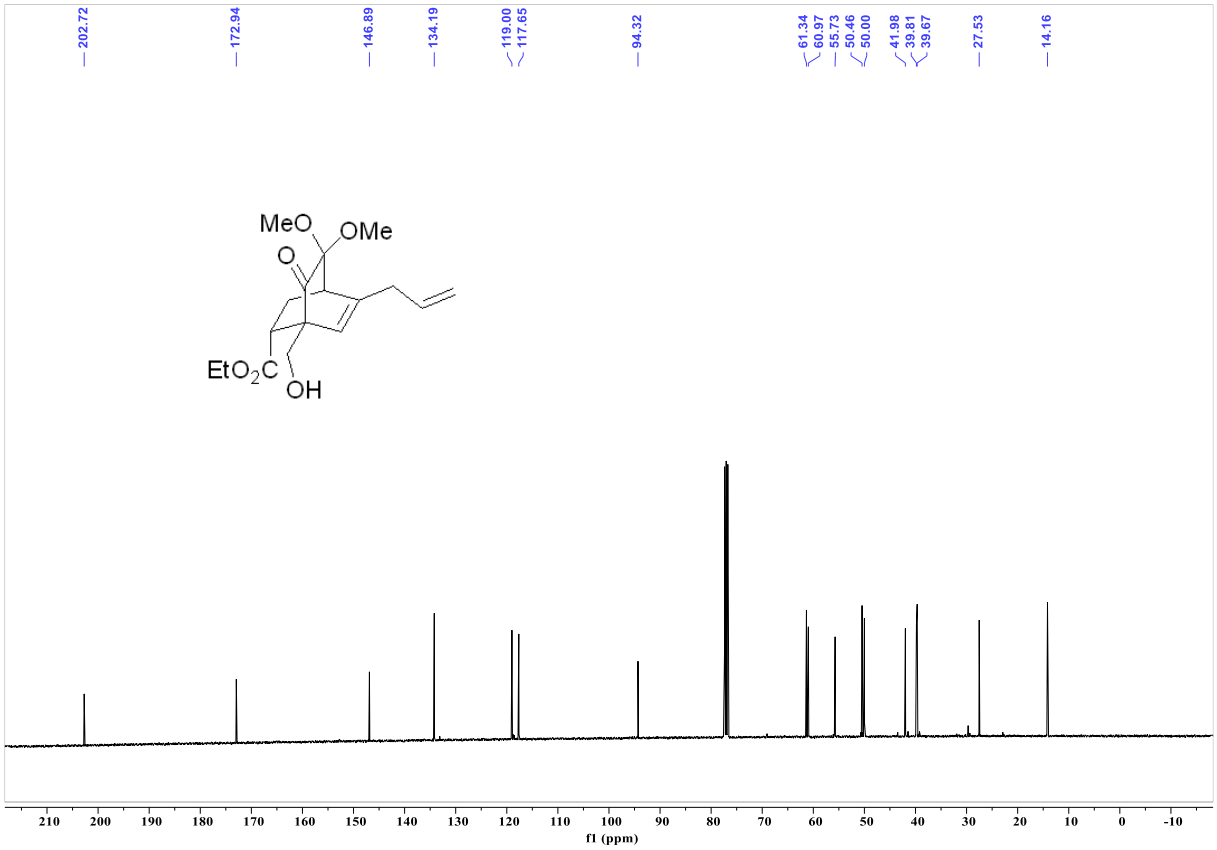
Compound S1 ^{13}C NMR ($CDCl_3$, 100MHz)



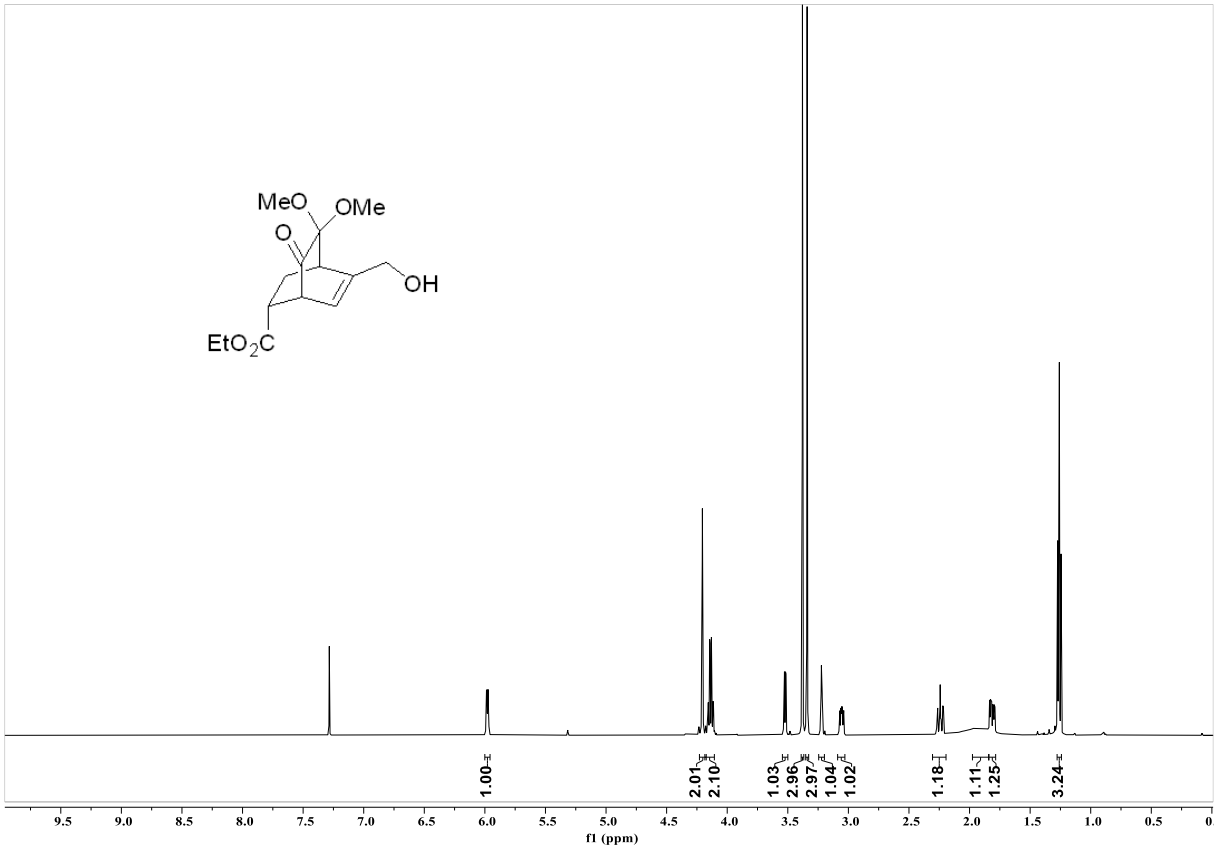
Compound S2 ^{1}H NMR ($CDCl_3$, 400MHz)



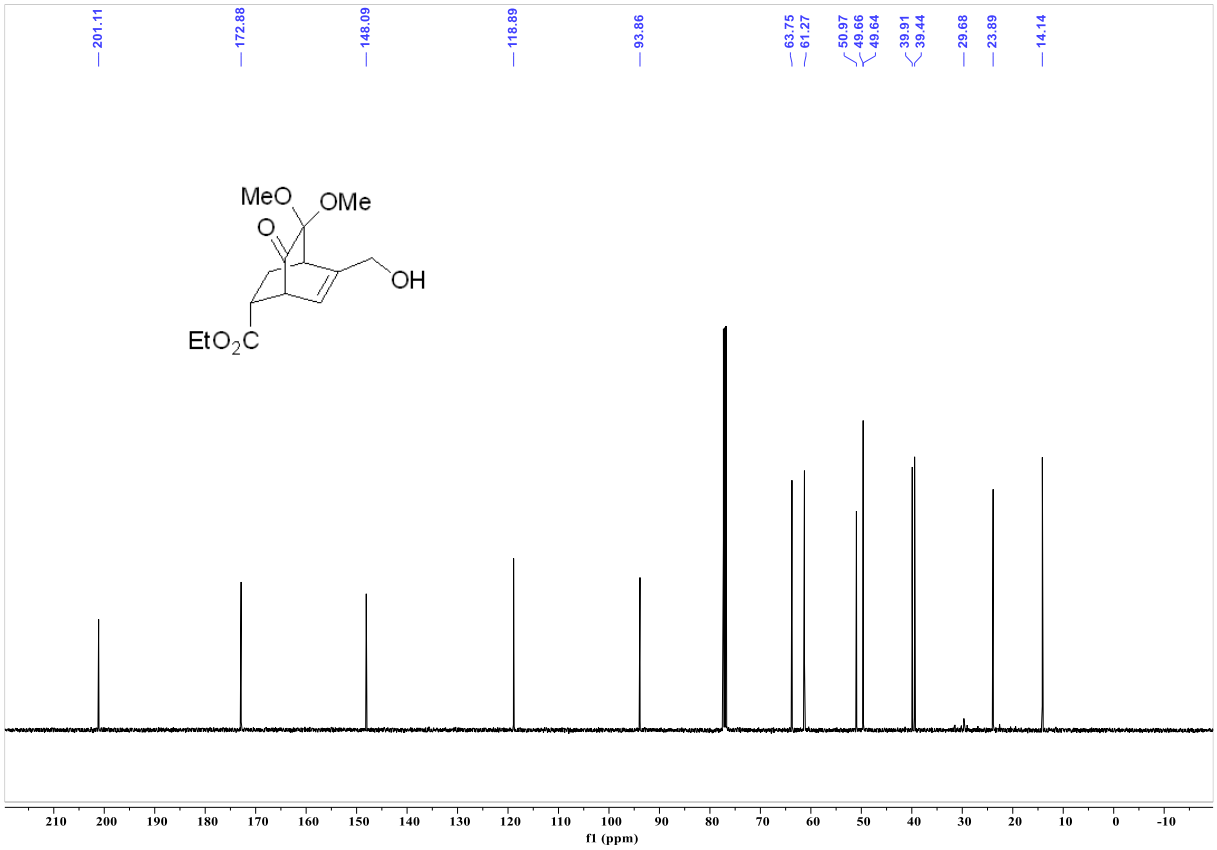
Compound S2 ^{13}C NMR ($CDCl_3$, 100MHz)



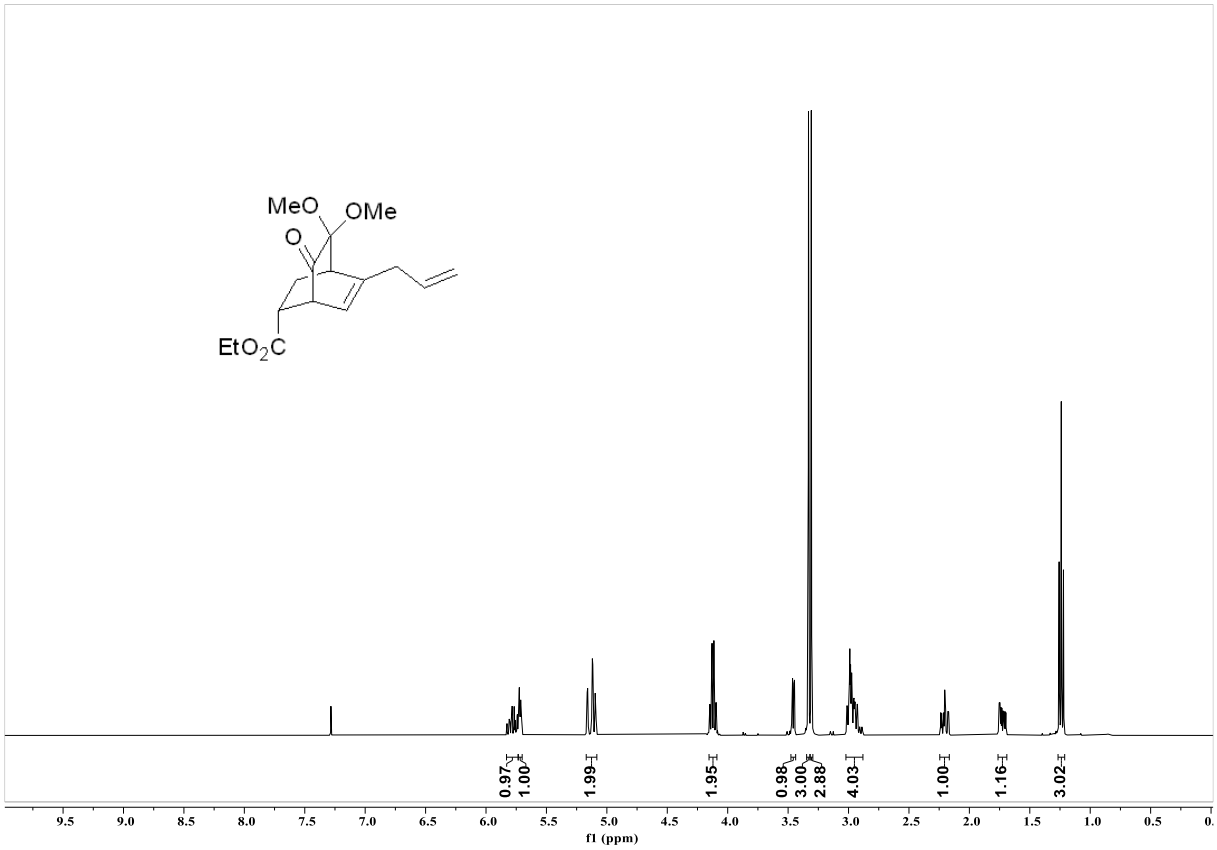
Compound S3 ^{1}H NMR ($CDCl_3$, 500MHz)



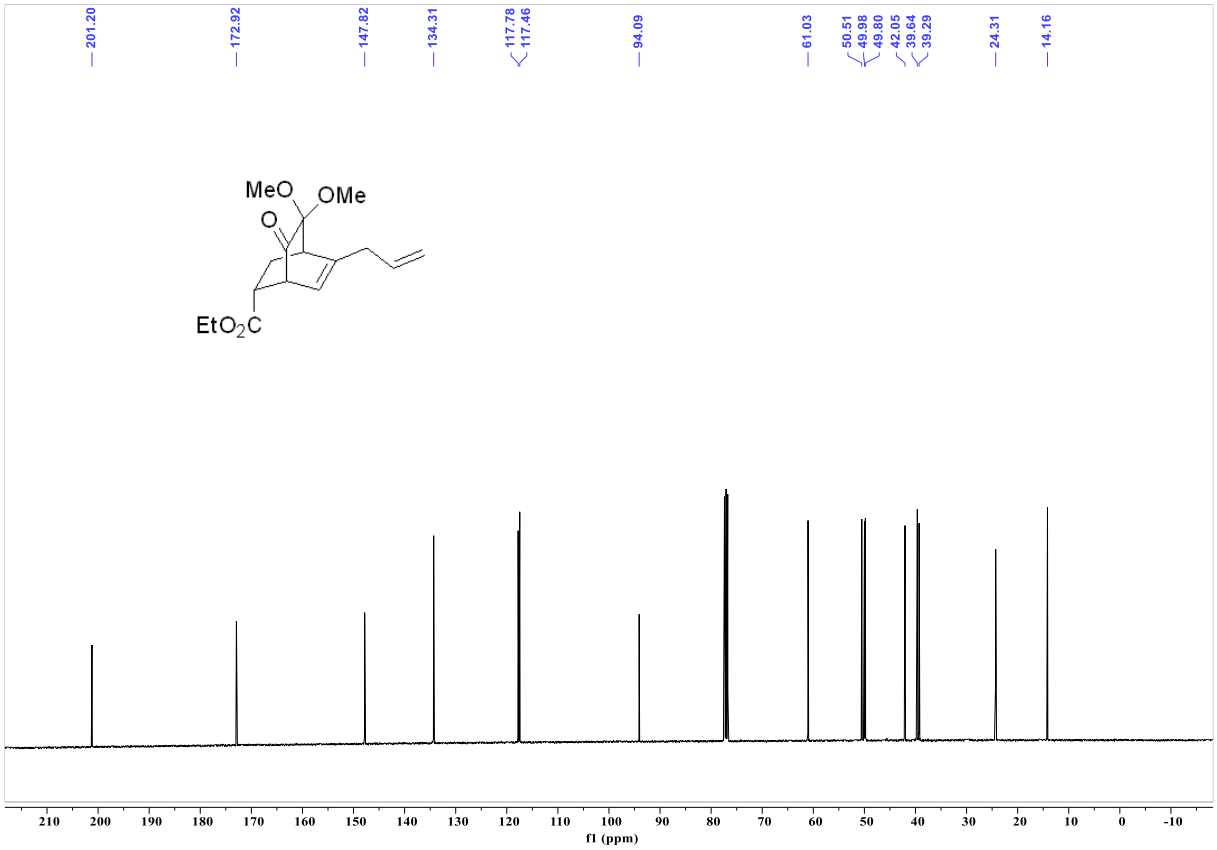
Compound S3 ^{13}C NMR ($CDCl_3$, 125MHz)



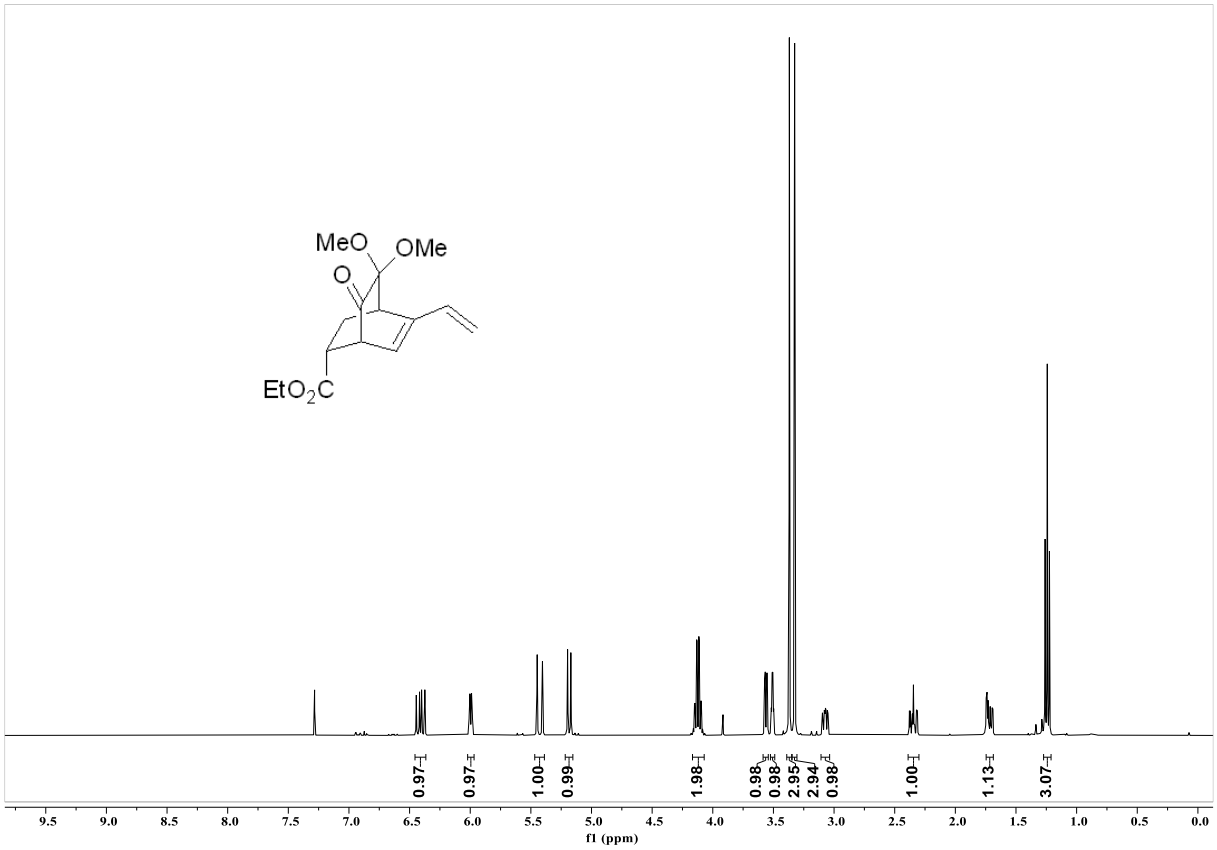
Compound S4 ^{1}H NMR ($CDCl_3$, 400MHz)



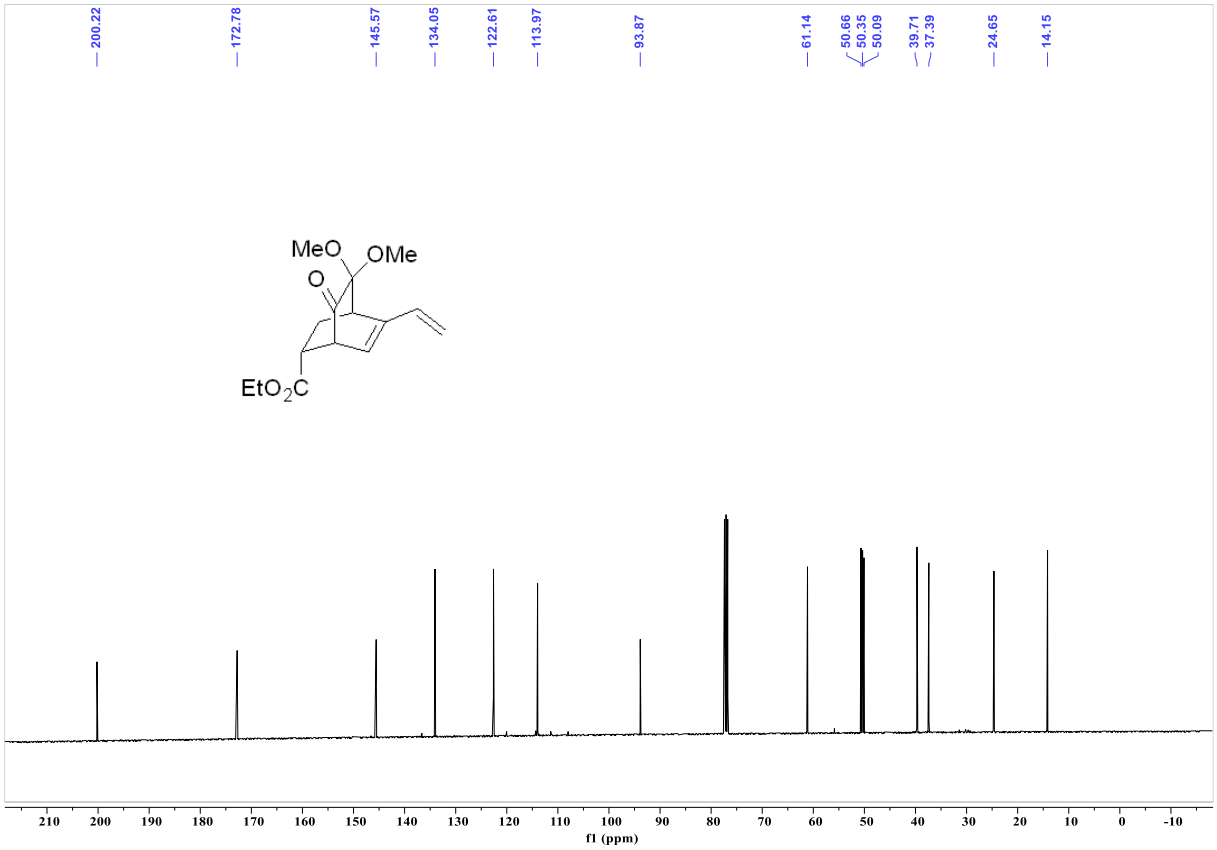
Compound S4 ^{13}C NMR ($CDCl_3$, 100MHz)



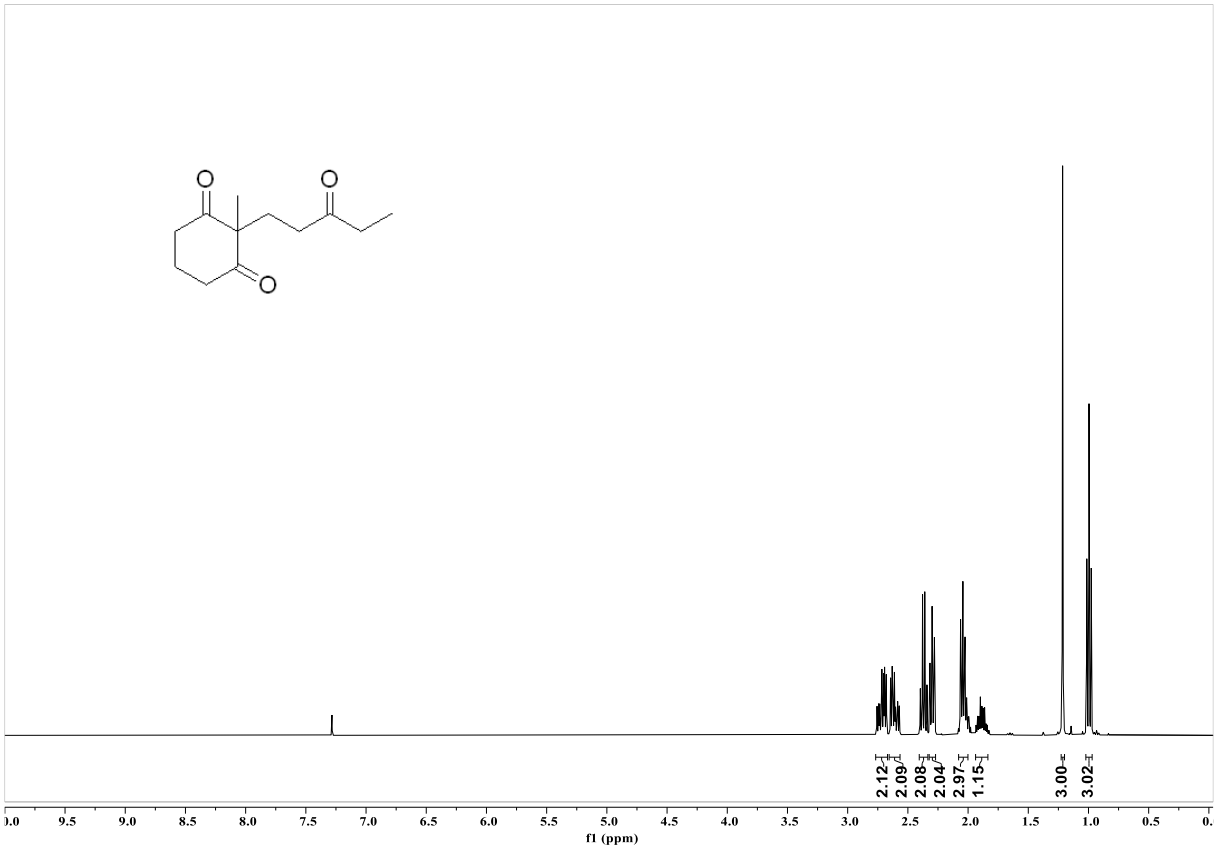
Compound S5 ^{1}H NMR ($CDCl_3$, 400MHz)



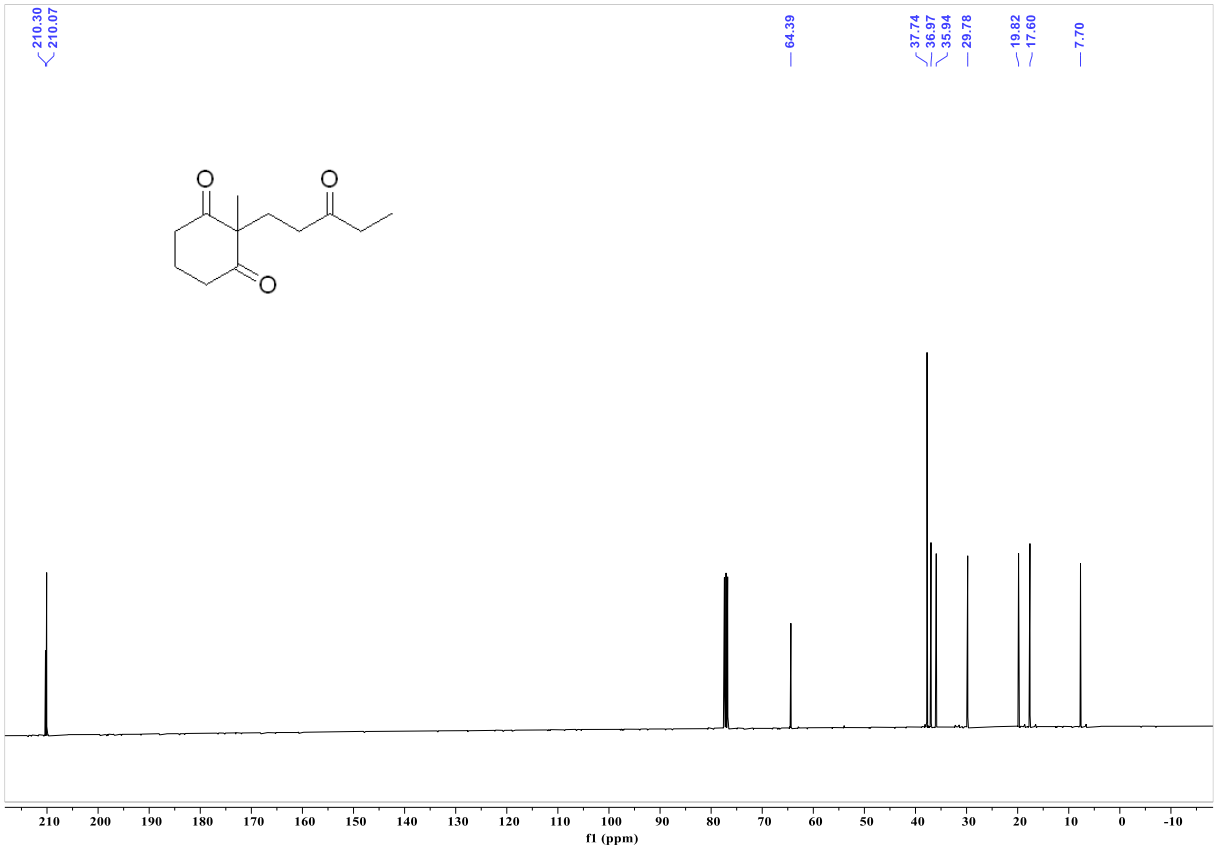
Compound S5 ^{13}C NMR ($CDCl_3$, 100MHz)



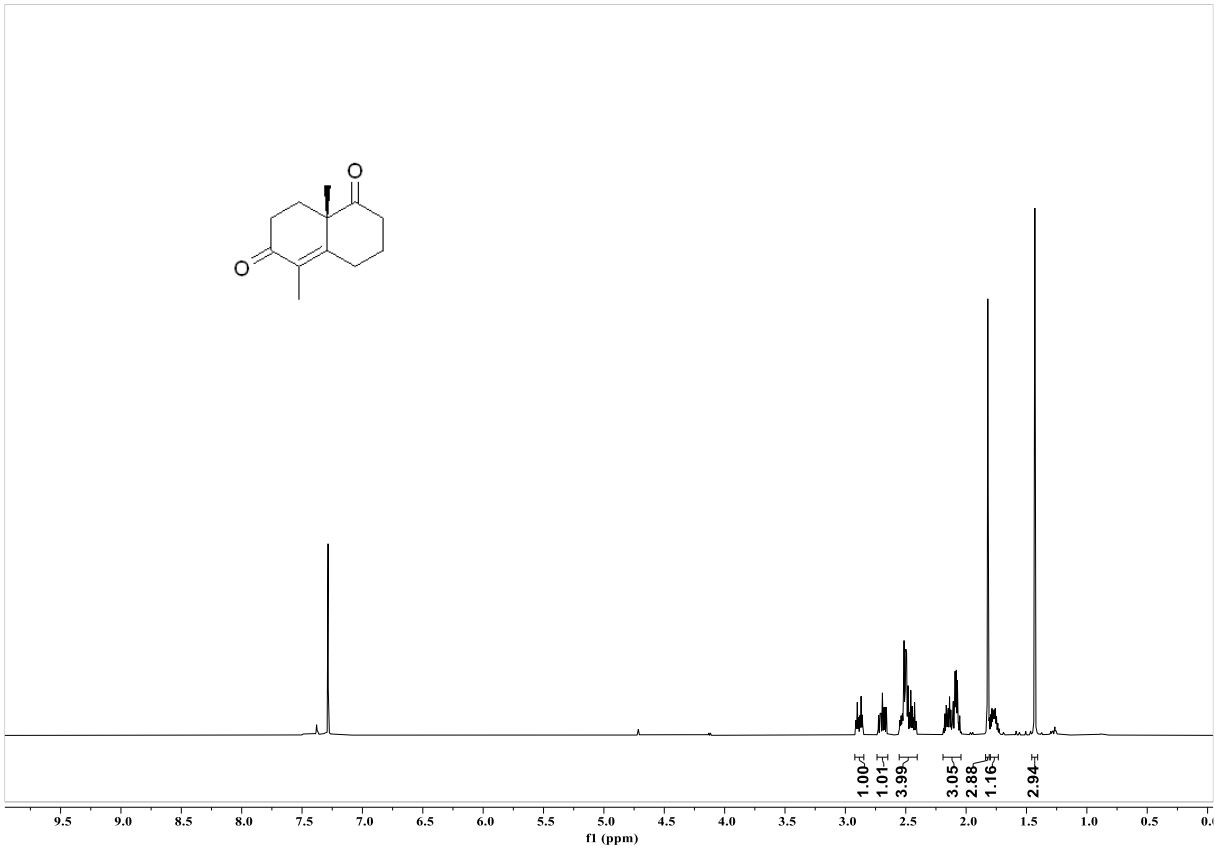
Compound 7 ^{1}H NMR ($CDCl_3$, 500MHz)



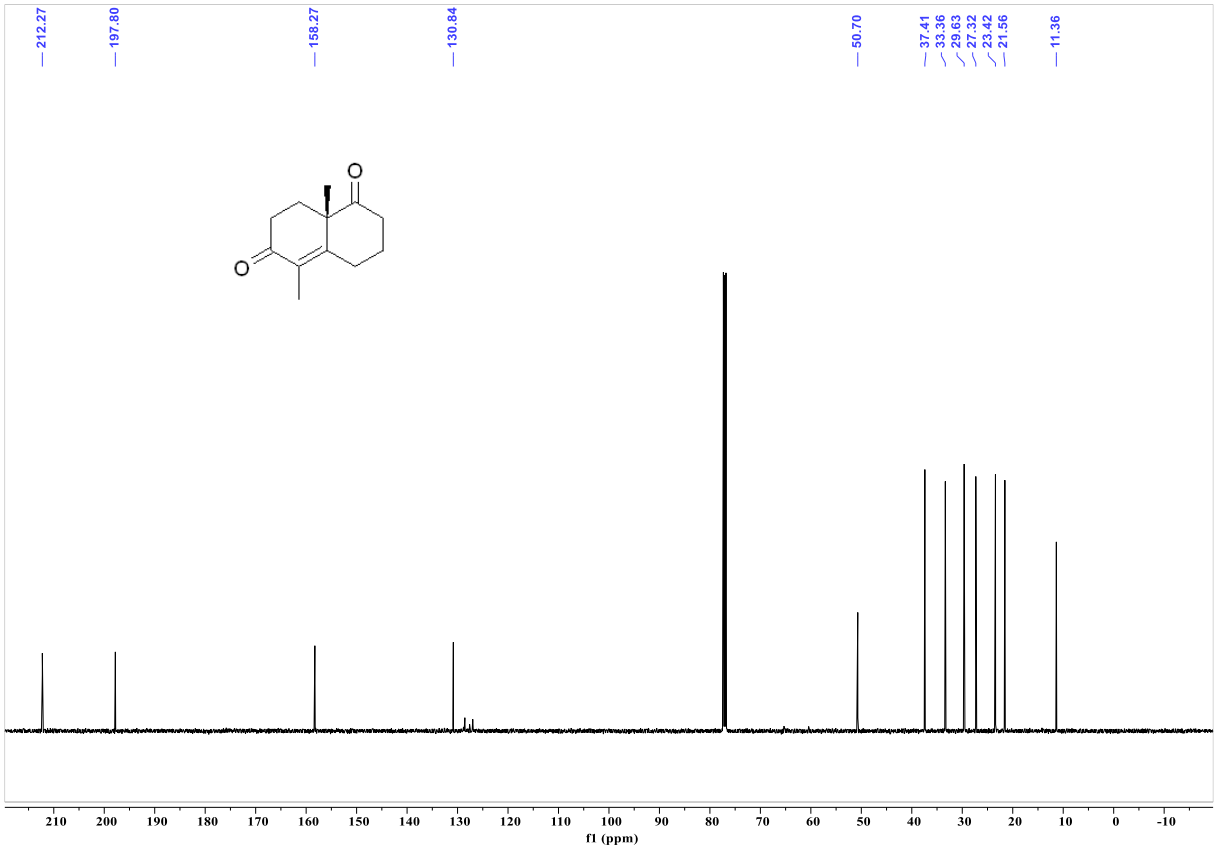
Compound 7 ^{13}C NMR ($CDCl_3$, 125MHz)



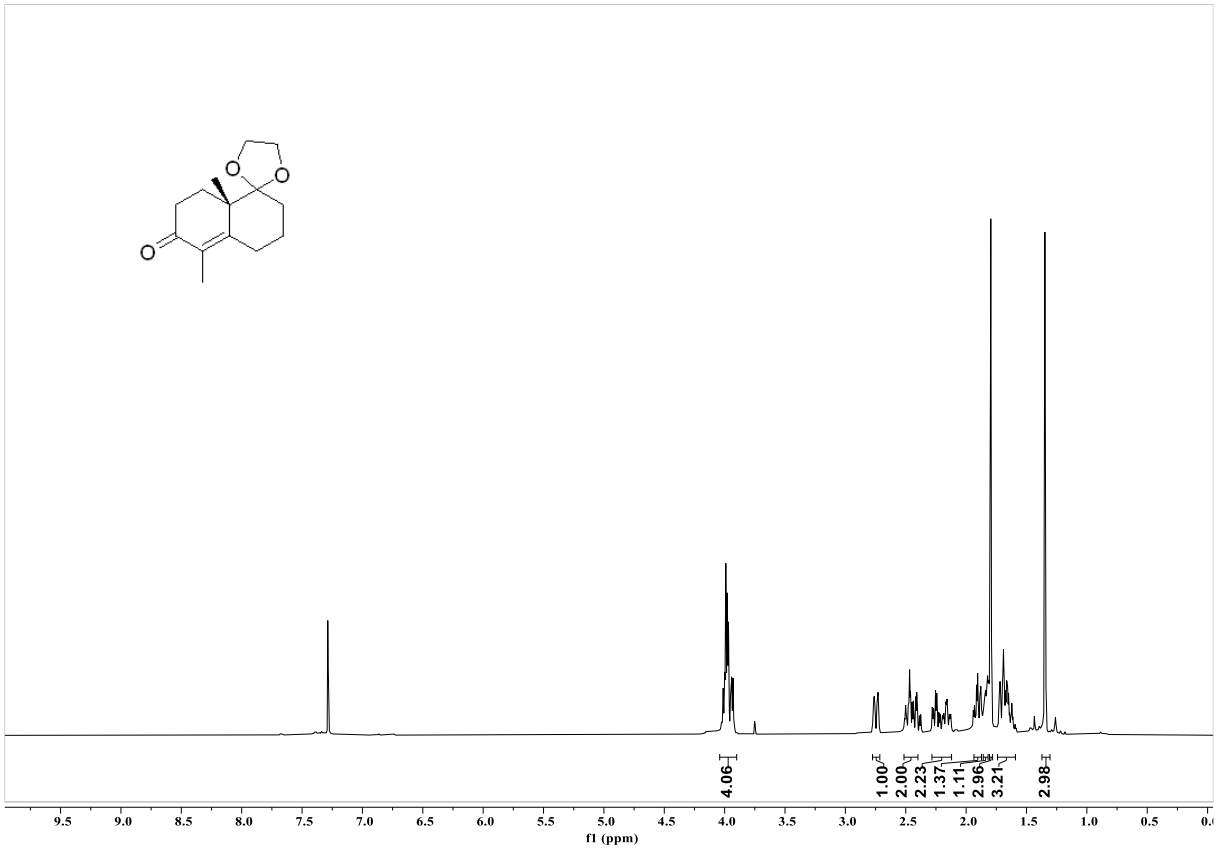
Compound 29 ^{1}H NMR ($CDCl_3$, 500MHz)



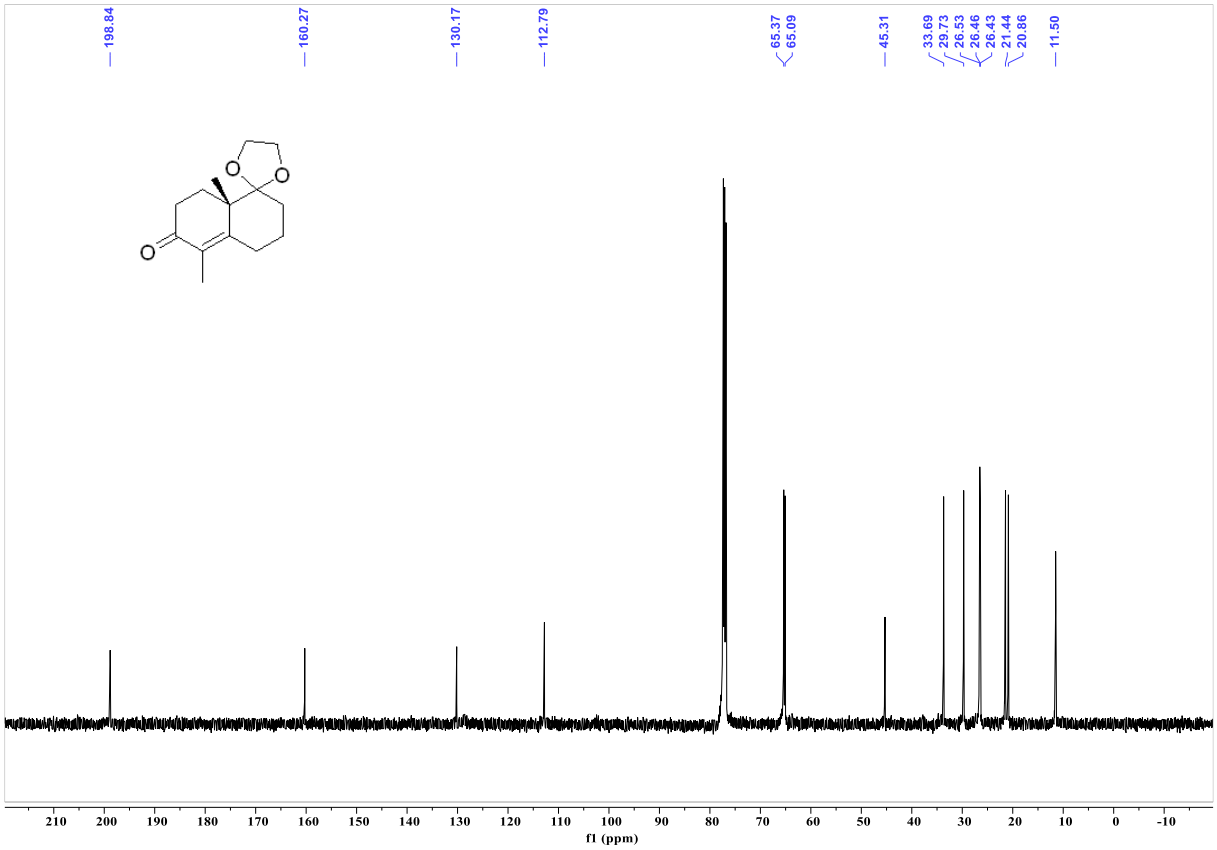
Compound 29 ^{13}C NMR ($CDCl_3$, 125MHz)



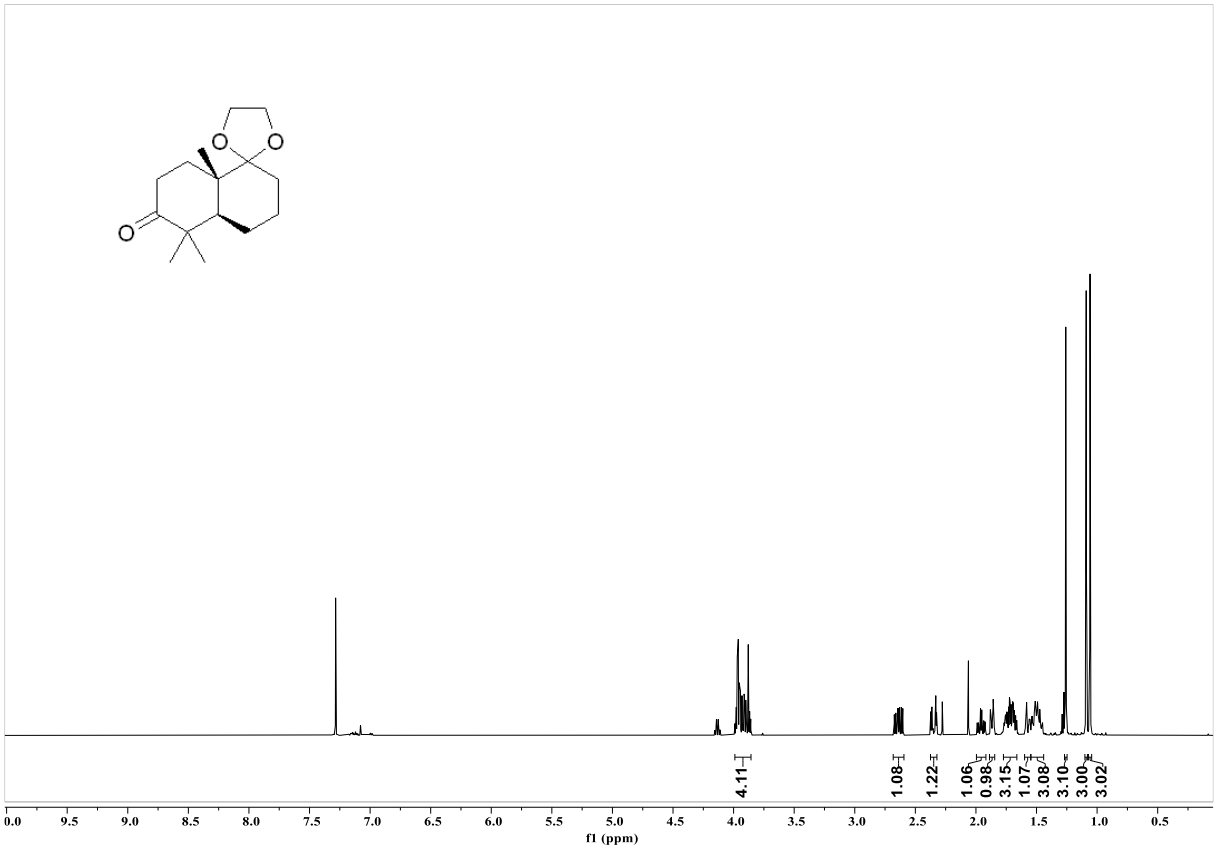
Compound 30 ^{1}H NMR ($CDCl_3$, 500MHz)



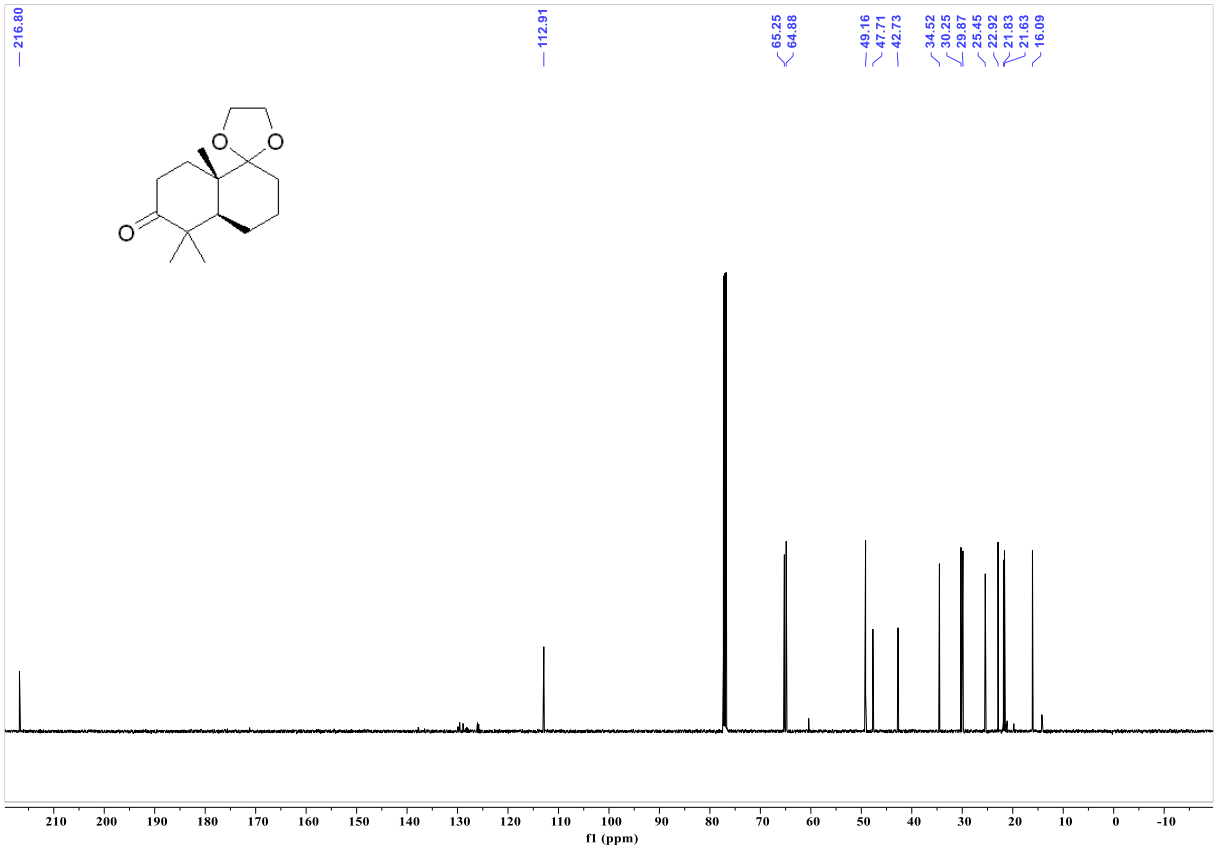
Compound 30 ^{13}C NMR ($CDCl_3$, 125MHz)



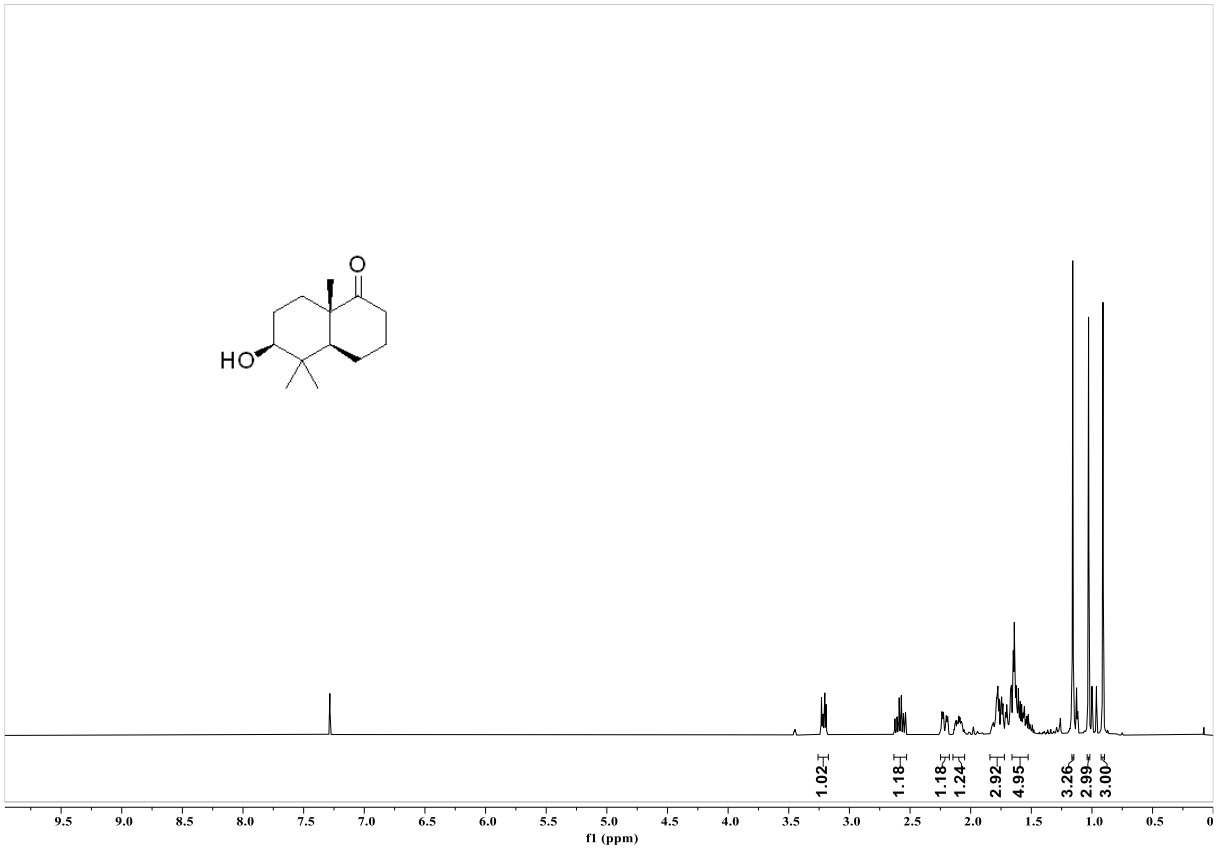
Compound 31 ^{1}H NMR ($CDCl_3$, 500MHz)



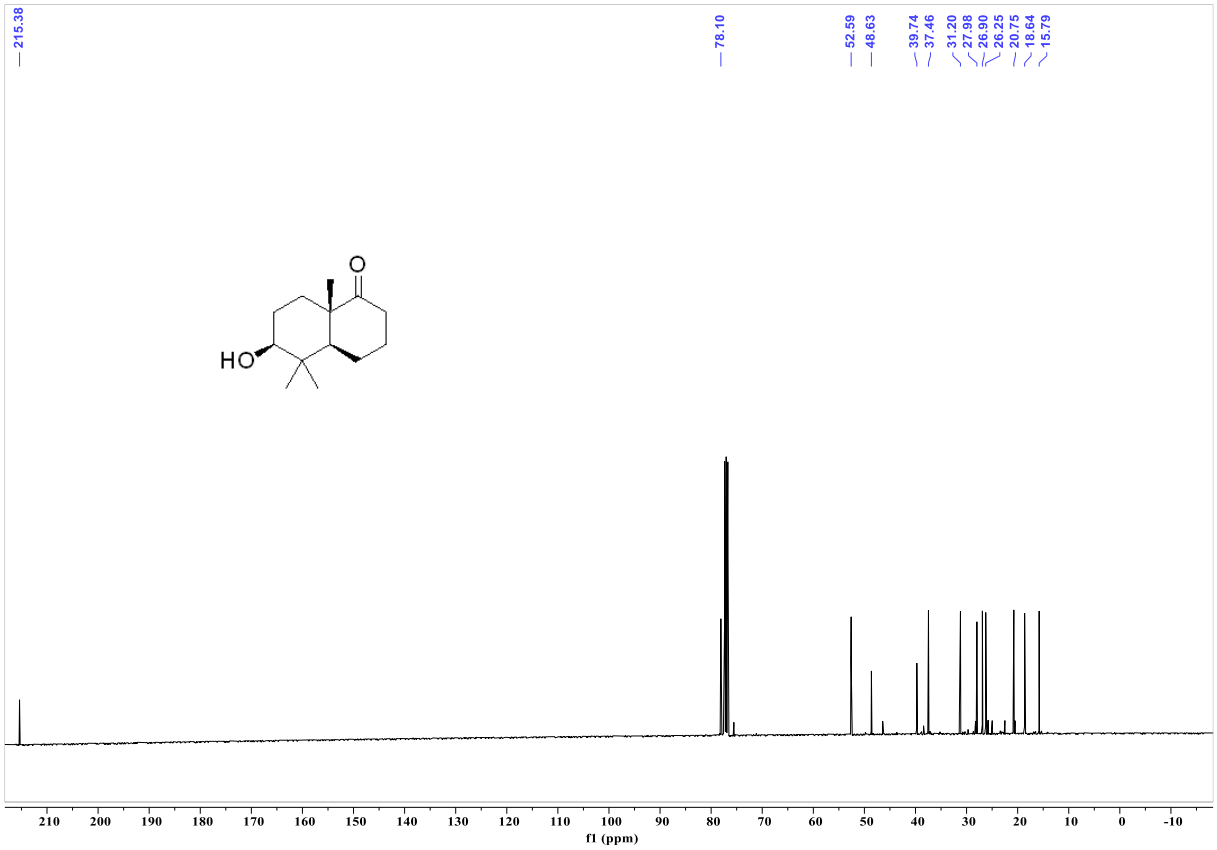
Compound 31 ^{13}C NMR ($CDCl_3$, 125MHz)



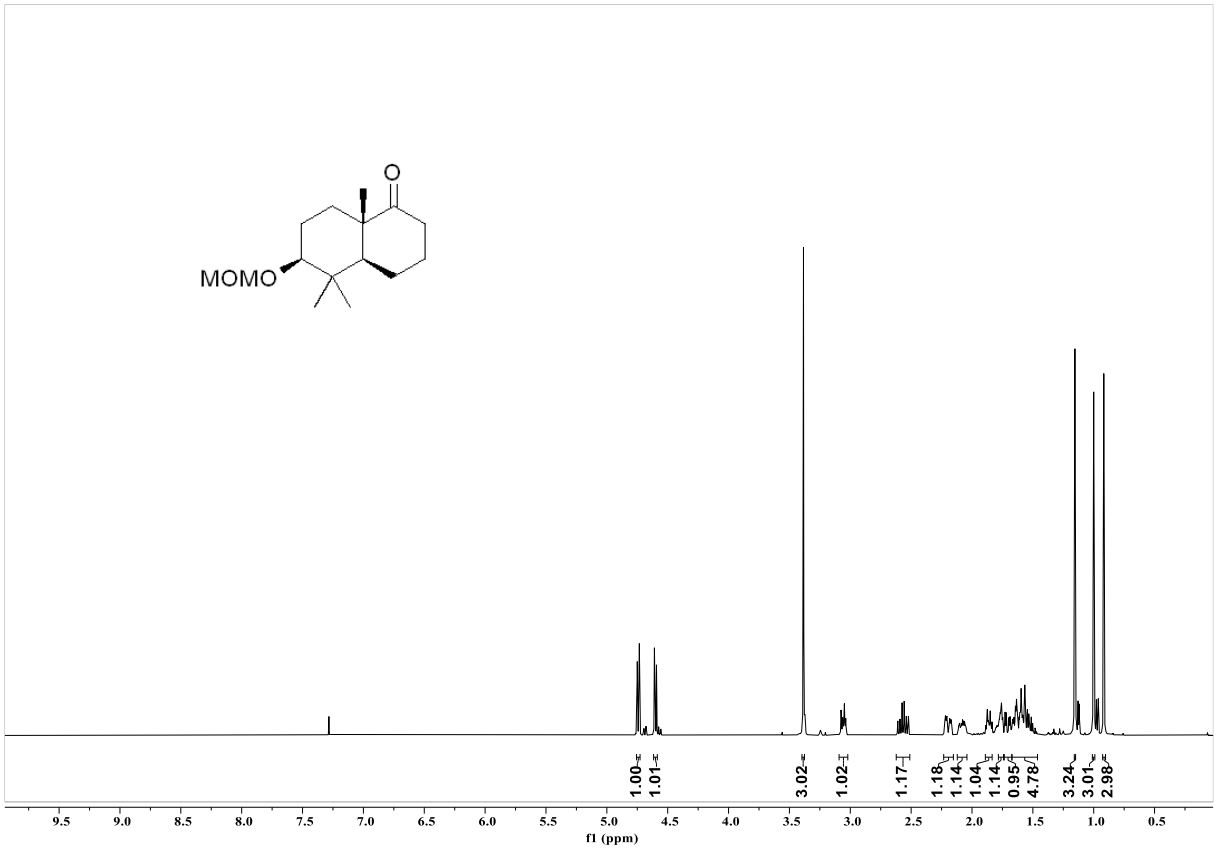
Compound 32 ^{1}H NMR ($CDCl_3$, 500MHz)



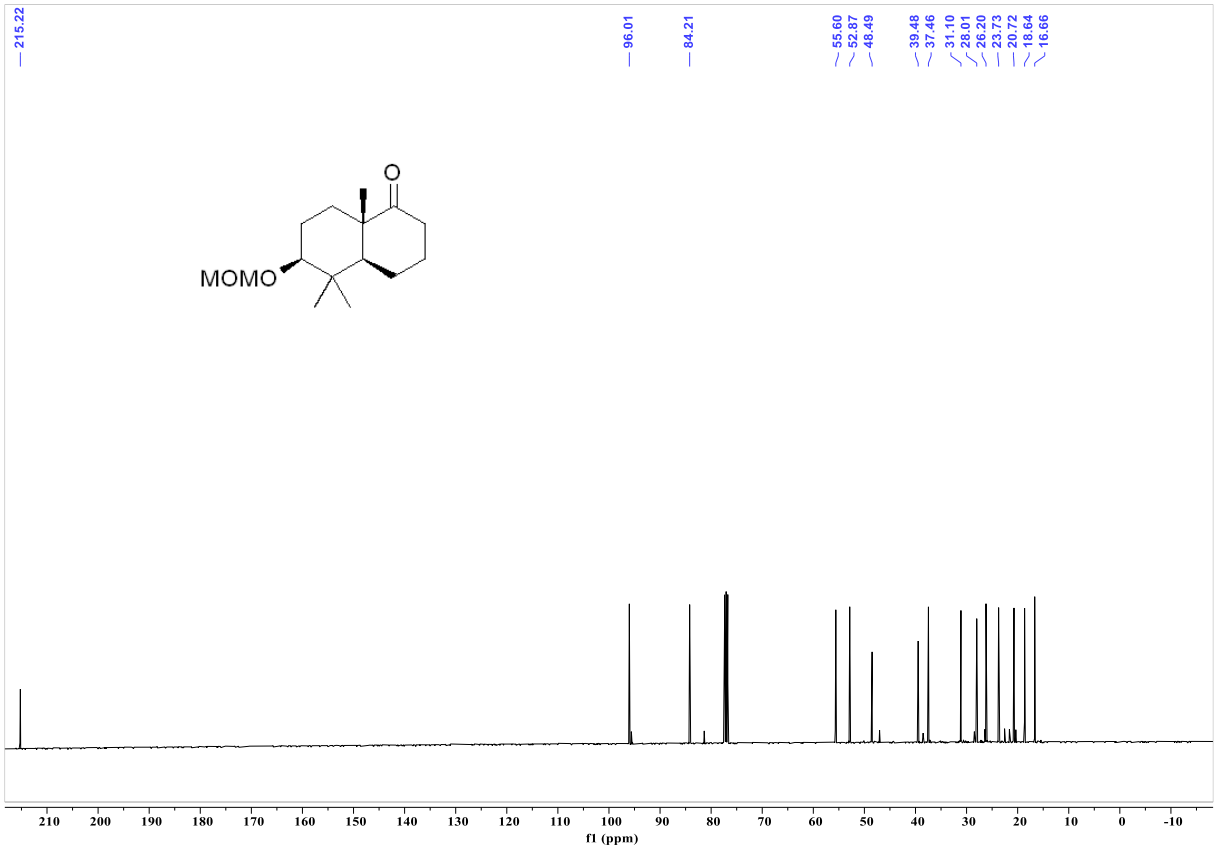
Compound 32 ^{13}C NMR ($CDCl_3$, 125MHz)



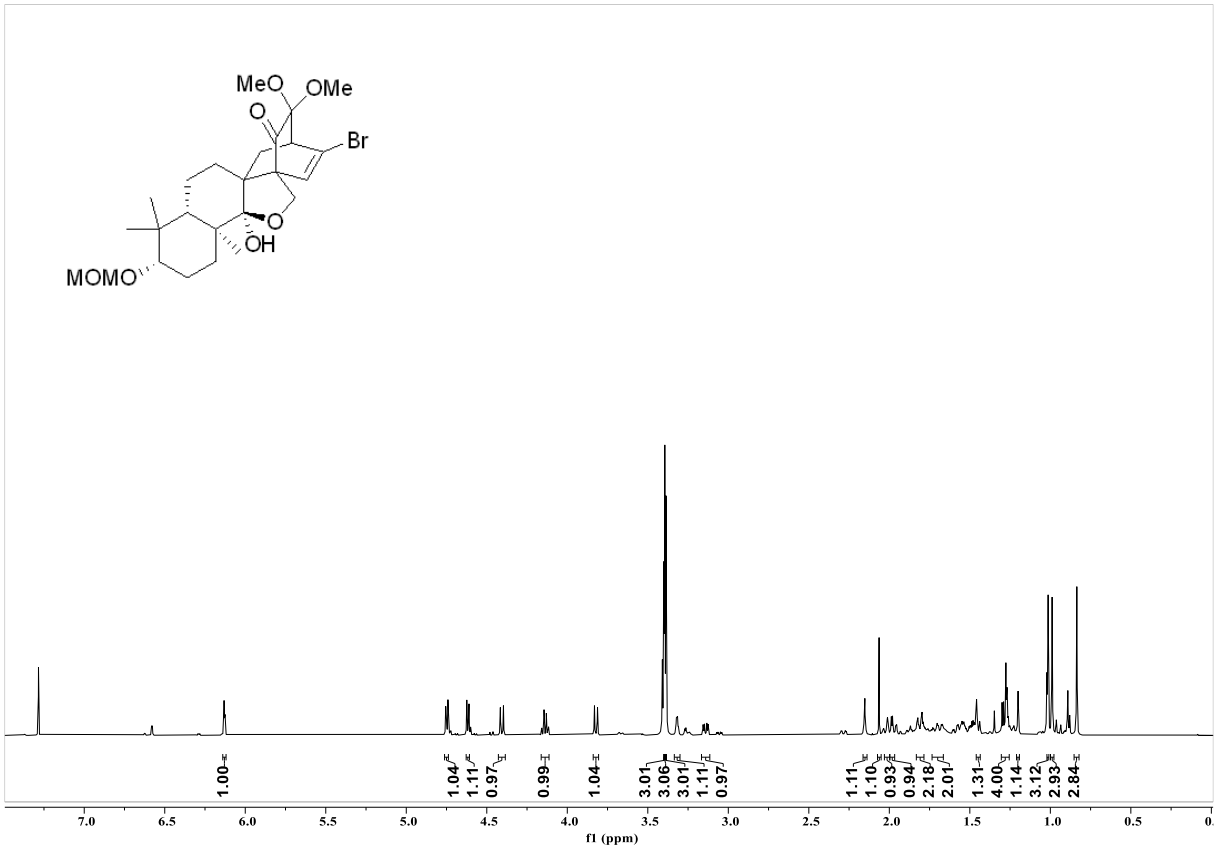
Compound 33 ^{1}H NMR ($CDCl_3$, 500MHz)



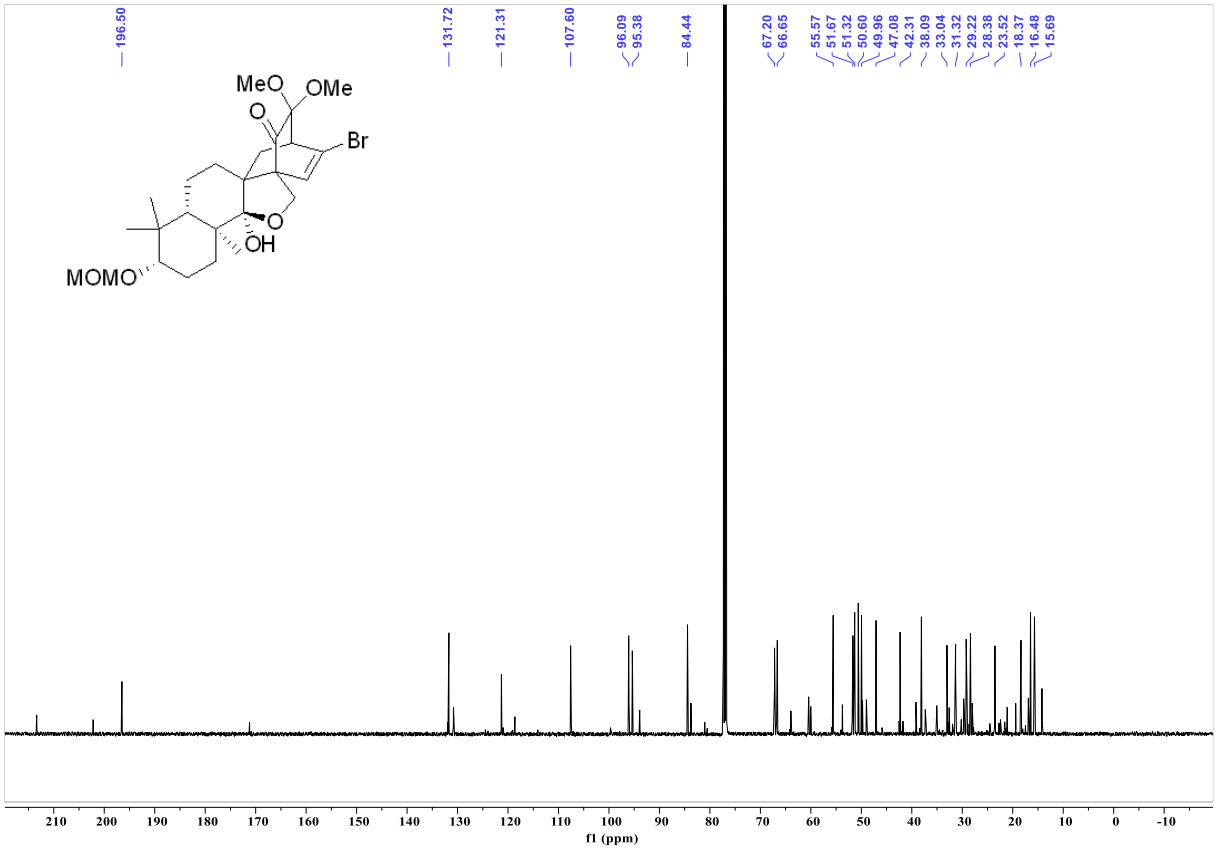
Compound 33 ^{13}C NMR ($CDCl_3$, 125MHz)



Compound 35 ^{1}H NMR ($CDCl_3$, 400MHz)

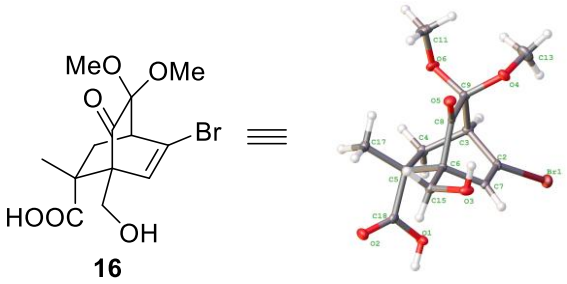


Compound 35 ^{13}C NMR ($CDCl_3$, 100MHz)



X-Ray Crystallographic Data

To grow the crystals used to collect the X-ray data for compound **16**, the following method was used: the 50 mg sample was dissolved with 3 mL petroleum ether and 1 mL DCM in a small vial, which was kept aside at 6 ℃ to obtain crystals.



16 **CCDC 2479348**

Table 1 Crystal data and structure refinement for compound 16.	
Identification code	Compound **16**
Empirical formula	$C_{13}H_{17}BrO_6$
Formula weight	349.17
Temperature/K	100
Crystal system	monoclinic
Space group	P21/n
a/Å	11.8147(4)
b/Å	7.0188(2)
c/Å	18.3836(6)
α /°	90
β /°	108.4120(10)
γ /°	90
Volume/Å3	1446.42(8)
Z	4
ρ calcg/cm3	1.603
μ /mm-1	2.864
F(000)	712.0
Crystal size/mm3	0.12 × 0.06 × 0.05
Radiation	MoK α (λ = 0.71073)
2Θ range for data collection/°	6.258 to 52.784
Index ranges	-14 ⩽ h ⩽ 14, -8 ⩽ k ⩽ 8, -22 ⩽ l ⩽ 22
Reflections collected	15323
Independent reflections	2950 [Rint = 0.0758, Rsigma = 0.0536]
Data/restraints/parameters	2950/0/186
Goodness-of-fit on F2	0.997
Final R indexes [I>=2 σ (I)]	R1 = 0.0346, wR2 = 0.0853
Final R indexes [all data]	R1 = 0.0437, wR2 = 0.0929
Largest diff. peak/hole / e Å-3	0.61/-0.52

To grow the crystals used to collect the X-ray data for compound **26**, the following method was used: the 50 mg sample was dissolved with 3 mL petroleum ether and 1 mL ethyl acetate in a small vial, which was kept aside at 6 ℃ to obtain crystals.

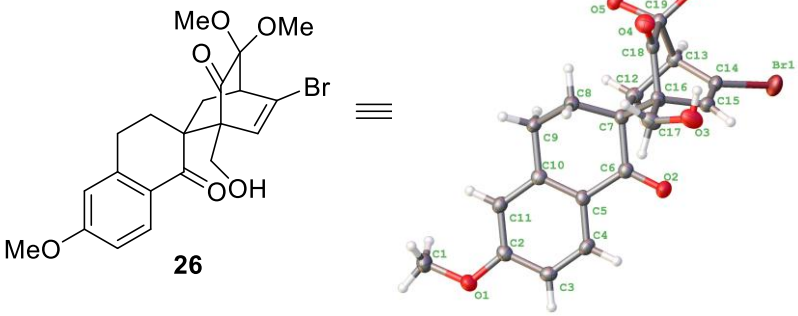


Table 2 Crystal data and structure refinement for compound 26.	
Identification code	Compound **26**
Empirical formula	$C_{21}H_{23}BrO_6$
Formula weight	451.30
Temperature/K	170
Crystal system	monoclinic
Space group	C2/c
a/Å	17.7182(6)
b/Å	7.8021(2)
c/Å	27.5266(9)
α/°	90
β/°	92.8400(10)
γ/°	90
Volume/Å3	3800.6(2)
Z	8
ρcalcg/cm3	1.577
μ/mm-1	2.200
F(000)	1856.0
Crystal size/mm3	0.12 × 0.06 × 0.04
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.604 to 52.784
Index ranges	-22 ≤ h ≤ 21, -9 ≤ k ≤ 8, -34 ≤ l ≤ 34
Reflections collected	21459
Independent reflections	3882 [Rint = 0.0651, Rsigma = 0.0468]
Data/restraints/parameters	3882/0/257
Goodness-of-fit on F2	1.032
Final R indexes [I>=2σ (I)]	R1 = 0.0361, wR2 = 0.0860

Final R indexes [all data]	R1 = 0.0495, wR2 = 0.0931
Largest diff. peak/hole / e Å-3	0.53/-0.54

To grow the crystals used to collect the X-ray data for compound **35**, the following method was used: the 10 mg sample was dissolved with 3 mL petroleum ether and 1 mL chloroform in a small vial, which was kept aside at 6 ℃ to obtain crystals.

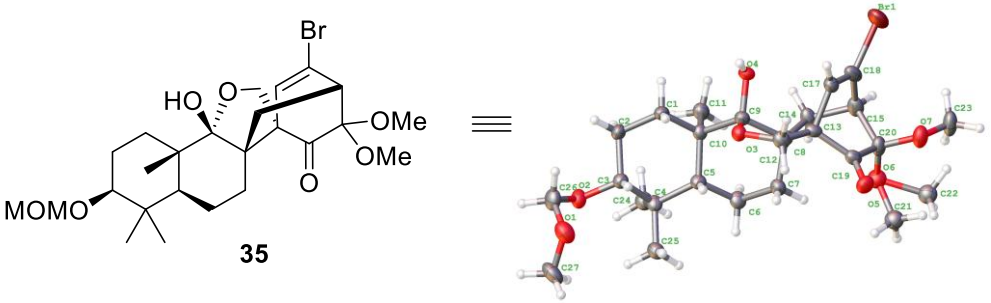


Table 3 Crystal data and structure refinement for compound 35.	
Identification code	Compound **35**
Empirical formula	$C_{25}H_{37}BrO_7$
Formula weight	529.45
Temperature/K	100
Crystal system	monoclinic
Space group	P21/c
a/Å	13.1148(9)
b/Å	13.4534(6)
c/Å	13.5662(5)
α/°	90
β/°	93.033(4)
γ/°	90
Volume/Å3	2390.2(2)
Z	4
ρcalcg/cm3	1.471
μ/mm-1	2.711
F(000)	1112.0
Crystal size/mm3	0.14 × 0.12 × 0.1
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	6.75 to 150.006
Index ranges	-16 ≤ h ≤ 16, -16 ≤ k ≤ 15, -13 ≤ l ≤ 16
Reflections collected	14227
Independent reflections	4697 [Rint = 0.0611, Rsigma = 0.0595]
Data/restraints/parameters	4697/18/310
Goodness-of-fit on F2	1.138

Final R indexes [I>=2σ (I)]	R1 = 0.1044, wR2 = 0.2507
Final R indexes [all data]	R1 = 0.1209, wR2 = 0.2607
Largest diff. peak/hole / e Å-3	1.65/-0.67

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