Total Synthesis of Penicibilaenes via C−C Activation-Enabled Skeleton Deconstruction and Desaturation Relay-Mediated C−H Functionalization

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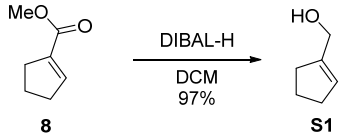
1. General Information

Unless noted otherwise, all solvents were dried by filtration through a Pure-Solv MD-5 Solvent Purification System (Innovative Technology), all reactions were carried out under nitrogen atmosphere, all commercially available substrates were used without further purification. Thin layer chromatography (TLC) analysis was run on silica gel plates purchased from EMD Chemical (silica gel 60, F254). Infrared spectrum was recorded on a Nicolet iS5 FT-IR Spectrometer. Samples were scanned as neat liquids or dissolved in dichloromethane on potassium bromide (KBr) salt plates. Frequencies were reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectra (HRMS) were obtained on an Agilent 6224 TOF-MS spectrometer and were reported for the molecular ion $[M]^+$, $[M+Na]^+$, or $[M+H]^+$. Nuclear magnetic resonance (NMR) spectrum (^1H NMR and ^{13}C NMR) were recorded with a 400 MHz Bruker Avance-III-HD nanobay spectrometer equipped with a BBFO SmartProbe (400 MHz for ^1H, 101 MHz for ^{13}C) or a 500 MHz Bruker Avance-III spectrometer equipped with a ^1H (^{13}C,^{31}P) TXI probe (500 MHz for ^1H, 126 MHz for ^{13}C). For $CDCl_3$ solutions, the chemical shifts were reported as parts per million (ppm) referenced to residual protium or carbon of the solvents: $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ C (77.00 ppm). For actone-D6 solutions, the chemical shifts were reported as parts per million (ppm) referenced to residual protium or carbon of the solvents: acetone-D6 δ H (2.05 ppm) and acetone-D6 δ C (29.84 ppm). Coupling constants were reported in Hertz (Hz). Data for ^1H NMR spectra were reported as following: chemical shift (δ, ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (Hz), and integration.

2. Experimental Procedure and Characterization Data

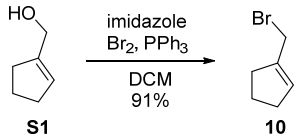
*Synthesis of compound **S1***



Following the literature reported procedure,[1] a flask containing dichloromethane (600 mL) was cooled to −78 °C, then diisobutylaluminum hydride (DIBAL-H, 1M in hexane, 540 mL, 540 mmol) was added at −78 °C. Compound **8** (31.13 g, 247 mmol) was then added slowly to the reaction mixture. After being stirred at −78 °C for 2 h and 0 °C for 30 min, the reaction mixture was quenched with Rochelle salt (sat. in H_2O, 800 mL) and stirred at room temperature overnight. The mixture was extracted with dichloromethane (3 × 300 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give compound **S1** (23.59 g, 97% yield) as a colorless oil.

Spectra matched with literature report.[1]

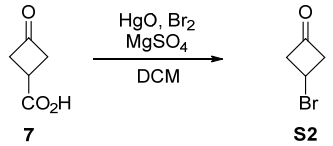
*Synthesis of compound **10***



To a solution of PPh_3 (52 g, 198 mmol) in dichloromethane (800 mL), Br_2 was added (10.2 mL, 198 mmol) dropwise at 0 °C. Adding extra PPh_3 may be necessary at this stage, until the reaction mixture becomes colorless. After this, imidazole (14.6 g, 214 mmol) and compound **S1** (16.2 g, 165 mmol) were added slowly to the reaction mixture at 0 °C. After being stirred at room temperature overnight, the reaction mixture was quenched with Na_2SO_3 (sat. in H_2O, 400 mL) and extracted with dichloromethane (3 × 300 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, pure pentane) to give bromide **10** (24.25 g, 91% yield) as a colorless oil.

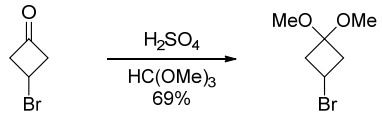
Spectra matched with literature report.[2]

*Synthesis of compound **S2***



Following the literature reported procedure,[3] to a solution of compound **7** (5 g, 44 mmol) in dichloromethane (130 mL), $MgSO_4$ (5.3 g, 44 mmol) and HgO (red, 14.3 g, 66 mmol) were added at room temperature, and the reaction mixture was then heated to reflux. Br_2 (3.4 mL, 66 mmol) in dichloromethane (35 mL) was then added to the reaction mixture dropwise. After refluxing for 2 h, the reaction mixture was cooled to room temperature and filtered through Celite. The solvent was removed under reduced pressure to give crude compound **S2** (6.69 g) as a colorless oil. The crude compound **S2** was directly used in next step without further purification.

*Synthesis of compound **11***

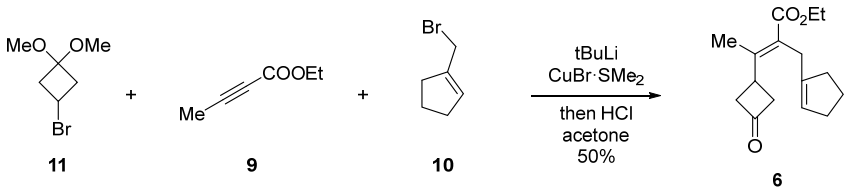


S2 **11**

To a solution of compound **S2** (6.7 g, 44 mmol) in $HC(OMe)_3$ (15 mL, 135 mmol), H_2SO_4 was added (0.47 mL, 8.8 mmol) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was diluted with dichloromethane (100 mL), quenched with 1M HCl (50 mL), and extracted with dichloromethane (3 × 50 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give bromide **11** (5.90 g, 69% yield for 2 steps) as a colorless oil.

$\mathbf{R}_f$ = 0.70 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 – 4.16 (m, 1H), 3.15 (s, 3H), 3.13 (s, 3H), 2.93 – 2.86 (m, 2H), 2.56 – 2.49 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 100.5, 48.9, 48.8, 44.9, 32.9.
IR (KBr) ν_{max} = 2999, 2952, 2832, 1448, 1410, 1276, 1158, 1042, 859, 543 cm^{-1}
HRMS (CI) m/z calcd. for $C_6H_{11}{}^{79}BrO_2^+$ $[M]^+$: 193.9937, found 193.9980; m/z calcd. for $C_6H_{11}{}^{81}BrO_2^+$ $[M]^+$: 195.9917, found 195.9864

*Synthesis of compound **6***

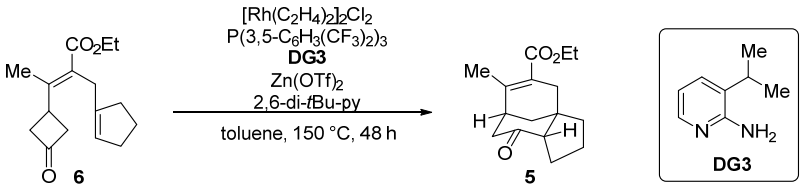


11 **9** **10** **6**

To a solution of compound **11** (3.9 g, 20 mmol) in Et_2O (20 mL), ^{t}BuLi was added (1.7 M in pentane, 25.6 mL, 41 mmol) at −78 °C, and stirred at −78 °C for 1 h. This alkyl lithium solution was added to a separate flask containing $CuBr{\cdot}SMe_2$ (4.1 g, 20 mmol) in tetrahydrofuran (THF, 100 mL) at −78 °C. After stirring at −78 °C for 10 min, compound **9** (2.24 g, 20 mmol) was added to the reaction mixture and stirred at −78 °C for an additional 30 min. Hexamethylphosphoramide (HMPA, 20 mL) and compound **10** (4.3 g, 22 mmol) were then added to the reaction mixture at −78 °C. After stirring at 0 °C for 2 h, the reaction mixture was treated with HCl (2 M in H_2O, 40 mL) and acetone (100 mL). The reaction was then stirred at room temperature overnight and quenched with $NaHCO_3$ (sat. in H_2O, 200 mL) and extracted with ethyl acetate (3 × 100 mL). The organic phase was washed with brine (sat. in H_2O, 3 × 200 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 20:1) to give compound **6** (2.65 g, 50% yield) as a colorless oil.

$\mathbf{R}_f$ = 0.28 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (hept, J = 1.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.61 – 3.51 (m, 1H), 3.20 – 3.07 (m, 6H), 2.27 (tq, J = 7.2, 2.3 Hz, 2H), 2.24 – 2.19 (m, 2H), 2.01 (s, 3H), 1.86 (tt, J = 8.2, 6.7 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0, 169.6, 143.1, 141.7, 128.7, 125.0, 60.4, 51.4, 35.2, 32.3, 31.6, 26.5, 23.4, 15.5, 14.2.
IR (KBr) ν_{max} = 2932, 2846, 1789, 1710, 1446, 1381, 1289, 1214, 1189, 1101, 1064 cm^{-1}
HRMS (ESI) m/z calcd. for $C_{16}H_{23}O_3^+$ $[M+H]^+$: 263.1642, found 263.1610.

*Synthesis of compound **5***



0.05 mmol scale procedure:

A flame dried 4 mL vial was charged with P(3,5-$C_6H_3(CF_3)_2)_3$ (16.8 mg, 0.025 mmol), **DG3** (1.4 mg, 0.01 mmol) and $Zn(OTf)_2$ (18.2 mg, 0.05 mmol) in glove box. After adding a solution of compound **6** (13.1 mg, 0.05 mmol) and $[Rh(C_2H_4)_2Cl]_2$ (1.9 mg, 0.005 mmol) dissolved in toluene (0.5 mL), the vial was sealed and removed from glovebox. The reaction was stirred at 150 °C in a pi-block for 48 h, before being cooled to room temperature. Then the solvent was removed under reduced pressure to give ketone **5** (48% GC yield, 1-methylnaphthalene as internal standard).

Gram-scale procedure:

A flame dried glass pressure vessel was charged with P(3,5-$C_6H_3(CF_3)_2)_3$ (1.07 g, 1.6 mmol), **DG3** (109 mg, 0.8 mmol), $Zn(OTf)_2$ (290 mg, 0.8 mmol) and 2,6-di-*tert*-butylpyridine (380 mg, 2 mmol) in glove box. After adding a solution of compound **6** (1.05 g, 4 mmol) and $[Rh(C_2H_4)_2Cl]_2$ (155 mg, 0.4 mmol) in toluene (40 mL), the vessel was sealed and removed from glovebox. The reaction was then stirred at 150 °C in oil bath for 48 h before being cooled to room temperature. The reaction mixture was quenched with NH_4Cl (sat. in H_2O, 50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate = 20:1 to 10:1) to give compound **5** (0.87 g, combining 2 parallel reactions, 42% yield) as a colorless oil.

$\mathbf{R}_f$ = 0.40 (hexane:ethyl acetate = 2:1)

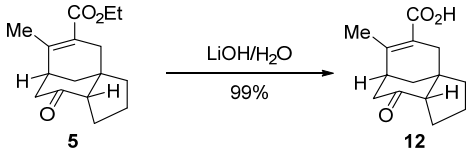
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.1 Hz, 2H), 2.60 (dt, *J* = 4.0, 1.9 Hz, 1H), 2.56 (dd, *J* = 16.0, 5.6 Hz, 1H), 2.46 (dt, *J* = 17.6, 2.1 Hz, 1H), 2.36 (ddt, *J* = 16.0, 3.3, 1.6 Hz, 1H), 2.29 – 2.20 (m, 2H), 2.01 (t, *J* = 2.0 Hz, 3H), 1.98 (dq, *J* = 8.8, 5.2, 4.3 Hz, 1H), 1.91 – 1.80 (m, 3H), 1.78 – 1.72 (m, 1H), 1.64 – 1.59 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.1, 168.1, 147.5, 124.5, 60.2, 59.8, 44.4, 40.6, 40.25, 40.20, 39.7, 32.8, 29.6, 22.3, 20.4, 14.2.

IR (KBr) ν_{max} = 2934, 1708, 1448, 1371, 1238, 1208, 1094, 1056 cm^{-1}

HRMS (ESI) m/z calcd. for $C_{16}H_{23}O_3^+$ $[M+H]^+$: 263.1642, found 263.1643; $C_{16}H_{22}NaO_3^+$ $[M+Na]^+$: 285.1461, found 285.1460.

*Synthesis of compound **12***

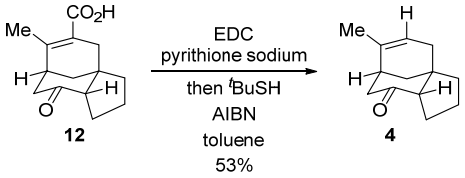


To a solution of compound **5** (320 mg, 1.22 mmol) in tetrahydrofuran (THF, 7.2 mL), $LiOH·H_2O$ (160 mg, 3.7 mmol), water (2.4 mL) and methanol (2.4 mL) were added at room temperature. After stirring at 70 °C overnight, the reaction mixture was extracted with Et_2O (5 mL). The organic phase was discarded and to the aqueous phase 1M HCl was added until pH = 1 and extracted with dichloromethane (3 × 10 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure to give crude compound **12** (283.3 mg, 99% yield) as a white solid. The crude compound **12** was directly used in next step without further purification.

$\mathbf{R}_f$ = 0.42 (pure ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (dq, *J* = 4.0, 1.9 Hz, 1H), 2.59 (dd, *J* = 16.2, 5.7 Hz, 1H), 2.48 (dt, *J* = 17.8, 2.0 Hz, 1H), 2.38 (dq, *J* = 16.1, 2.0 Hz, 1H), 2.31 – 2.23 (m, 2H), 2.10 (t, *J* = 2.0 Hz, 3H), 1.99 (ddt, *J* = 13.2, 8.6, 4.6 Hz, 1H), 1.93 – 1.80 (m, 3H), 1.80 – 1.73 (m, 1H), 1.64 (dd, *J* = 7.5, 5.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0, 173.3, 151.9, 123.4, 59.7, 44.3, 40.8, 40.6, 40.0, 39.7, 32.6, 29.5, 22.3, 20.9.
IR (KBr) ν_{max} = 2932, 2626, 1704, 1629, 1449, 1415, 1273, 917, 732 cm^{-1}
HRMS (ESI) m/z calcd. for $C_{14}H_{19}O_3^+$ $[M+H]^+$: 235.1329, found 263.1330; $C_{14}H_{18}NaO_3^+$ $[M+Na]^+$: 257.1148, found 257.1150.
Melting point: 109.8 – 111.8 °C

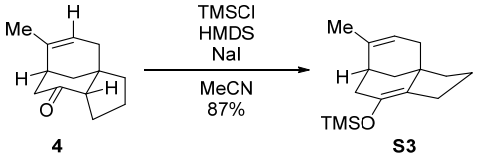
*Synthesis of compound **4***



To a solution of compound **12** (66 mg, 0.28 mmol) in dichloromethane (2.8 mL), pyrithione sodium (51 mg, 0.34 mmol) and *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC, 65 mg, 0.34 mmol) were added at room temperature. After stirring at room temperature for 2 h, the reaction mixture was concentrated under reduced pressure. To the residue, toluene (5.6 mL), 2,2′-azobis(2-methylpropionitrile) (AIBN, 4.6 mg, 0.028 mmol), and ^{t}BuSH (0.32 mL, 2.8 mmol) were added at room temperature. The solution was then bubbled with nitrogen gas for 20 min. Then, after stirring at 75 °C for 1 h, the resulting mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 20:1) to give compound **4** (28.4 mg, 53% yield) as a white solid.

R_f = 0.56 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (dt, *J* = 4.9, 1.9 Hz, 1H), 2.51 (dd, *J* = 15.6, 5.0 Hz, 1H), 2.44 (t, *J* = 3.5 Hz, 1H), 2.33 – 2.24 (m, 2H), 2.20 (t, *J* = 9.6 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.91 – 1.86 (m, 2H), 1.85 – 1.69 (m, 3H), 1.64 (dt, *J* = 2.8, 1.5 Hz, 3H), 1.63 – 1.56 (m, 2H), 1.52 (ddd, *J* = 12.9, 9.9, 8.1 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.3, 136.5, 121.6, 60.5, 44.9, 40.5, 39.6, 39.3, 37.2, 33.5, 29.6, 22.4, 21.5.
IR (KBr) ν_{max} = 2957, 2928, 2828, 1704, 1447, 1327, 1232, 1037, 931, 807 cm^{-1}
HRMS (ESI) m/z calcd. for $C_{13}H_{19}O^+$ $[M+H]^+$: 191.1430, found 191.1430.
Melting point: 45.0 – 46.2 °C

*Synthesis of compound **S3***

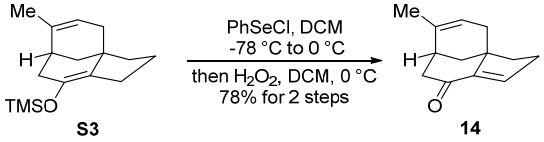


To a solution of compound **4** (50 mg, 0.26 mmol) in acetonitrile (2.6 mL), hexamethyldisilazane (HMDS, 0.22 mL, 1.05 mmol), NaI (157 mg, 1.05 mmol), and chlorotrimethylsilane (TMSCl, 99 μL, 0.78 mmol) were added at room temperature. After stirring at room temperature for 12 h, the reaction mixture was quenched with pH = 7 buffer (aqueous, 5 mL) and extracted with Et_2O (3 × 5 mL). The organic phase was then dried with Na_2SO_4 and concentrated under reduced pressure, then purified by column chromatography (silica gel, hexane:Et_2O = 20:1) to give compound **S3** (59.3 mg, 87% yield) as a colorless oil.

R_f = 0.77 (hexane:ethyl acetate = 10:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (t, *J* = 3.9 Hz, 1H), 2.40 – 2.29 (m, 2H), 2.27 – 2.15 (m, 2H), 1.99 – 1.88 (m, 2H), 1.85 (d, *J* = 17.4 Hz, 1H), 1.79 (dd, *J* = 11.5, 3.9 Hz, 1H), 1.75 – 1.70 (m, 1H), 1.69 – 1.66 (m, 4H), 1.66 – 1.61 (m, 1H), 1.44 – 1.34 (m, 1H), 1.31 – 1.26 (m, 1H), 0.13 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 136.6, 124.3, 120.0, 40.8, 40.6, 37.5, 36.3, 36.2, 34.3, 25.4, 22.0, 21.8, 0.7.
IR (KBr) ν_{max} = 2955, 2913, 1699, 1348, 1251, 1209, 1165, 1004, 873, 842 cm^{-1}
HRMS (ESI) m/z calcd. for $C_{13}H_{17}O^+$ $[M+H]^+$: 189.1274, found 189.1280.

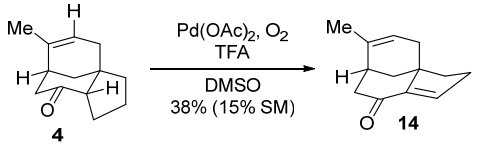
*Synthesis of compound **14***



To a solution of compound **S3** (20 mg, 0.076 mmol) in dichloromethane (1.5 mL), PhSeCl (21 mg, 0.11 mmol) was added at −78 °C. After stirring at −78 °C for 30 min, the reaction mixture was warmed to 0 °C and stirred for 5 min. The reaction was then quenched with $NaHCO_3$ (sat. in H_2O, 2 mL) and extracted with dichloromethane (3 × 2 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was added dichloromethane (1.5 mL) and H_2O_2 (30% in H_2O, 40 μL, 0.38 mmol) at the 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with $Na_2S_2O_3$ (sat. in H_2O, 2 mL) and extracted with dichloromethane (3 × 2 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:Et_2O = 20:1) to give compound **14** (11.2 mg, 78% yield) as a colorless oil.

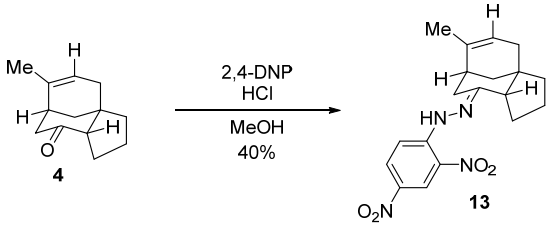
R_f = 0.46 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (t, *J* = 2.9 Hz, 1H), 5.35 – 5.27 (m, 1H), 2.60 – 2.48 (m, 2H), 2.46 (t, *J* = 3.5 Hz, 1H), 2.43 – 2.33 (m, 2H), 2.19 (dt, *J* = 17.5, 3.0 Hz, 1H), 2.10 (dt, *J* = 15.4, 3.1 Hz, 2H), 1.99 – 1.87 (m, 2H), 1.78 – 1.72 (m, 1H), 1.67 (d, *J* = 2.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 149.4, 137.7, 136.5, 120.7, 46.3, 44.2, 41.0, 39.0, 38.1, 36.9, 29.9, 21.5.
IR (KBr) ν_{max} = 2921, 1683, 1612, 1436, 1328, 1261, 1221, 1048, 986, 919 cm^{-1}
HRMS (CI) m/z calcd. for $C_{16}H_{27}OSi^+$ $[M+H]^+$: 263.1826, found 263.1826.

*Synthesis of compound **14** (one step from compound **4**)*



To a solution of compound **4** (49 mg, 0.26 mmol) in dimethyl sulfoxide (DMSO, 1.3 mL), trifluoroacetic acid (TFA, 20 μL, 0.26 mmol) and $Pd(OAc)_2$ (17 mg, 0.077 mmol) were added at room temperature. The solution was then bubbled with O_2 for 20 min. After stirring at 60 °C under O_2 atmosphere for 24 h, the reaction was quenched with $NaHCO_3$ (sat. in H_2O, 3 mL) and extracted with Et_2O (3 × 3 mL). The organic phase was dried with NA_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:Et_2O = 100:1) to give compound **14** (18.4 mg, 38% yield) and compound **4** (7.4 mg, 15% recovery).

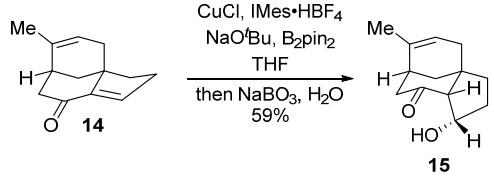
*Synthesis of compound **13***



To a solution of compound **4** (8.1 mg, 0.043 mmol) in methanol (0.5 mL), 2,4-dinitrophenylhydrazine (2,4-DNP, 8.5 mg, 0.043 mmol) and HCl (conc. in H_2O, 2.6 μL, 0.043 mmol) were added at room temperature. After stirring at room temperature overnight, the reaction was quenched with $NaHCO_3$ (sat. in H_2O, 1 mL) and extracted with dichloromethane (3 × 1 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 20:1) to give compound **13** (6.3 mg, 40% yield) as an orange solid.

R_f = 0.61 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.19 (s, 1H), 9.11 (d, *J* = 2.5 Hz, 1H), 8.27 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 5.39 (s, 1H), 2.77 (d, *J* = 15.3 Hz, 1H), 2.48 (t, *J* = 9.2 Hz, 2H), 2.36 – 2.23 (m, 2H), 2.00 – 1.88 (m, 2H), 1.88 – 1.79 (m, 3H), 1.79 – 1.74 (m, 1H), 1.66 (s, 3H), 1.62 – 1.56 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 145.3, 137.4, 135.2, 129.8, 128.7, 123.6, 122.5, 116.5, 54.6, 42.9, 39.8, 38.9, 36.6, 33.4, 31.3, 26.9, 21.74, 21.72.
IR (KBr) ν_{max} = 3321, 2928, 1619, 1591, 1518, 1426, 1336, 1136, 1074, 916, 831, 743 cm^{-1}
HRMS (ESI) m/z calcd. for $C_{19}H_{23}N_4O_4^+$ $[M+H]^+$: 371.1714, found 371.1716.
Melting point: 140.7 – 141.4 °C

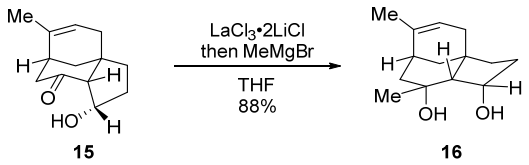
*Synthesis of compound **15***



To a suspension of CuCl (0.5 mg, 0.0054 mmol) in tetrahydrofuran (THF, 0.25 mL), 1,3-Bis(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate (IMes·HBF_4, 2 mg, 0.0054 mmol), and NaO′Bu (1 mg, 0.0108 mmol) were added at room temperature. After stirring at room temperature for 40 min, a solution containing compound **14** (5 mg, 0.027 mmol) and bis(pinacolato)diboron ($B_2(pin)_2$, 9 mg, 0.035 mmol) in tetrahydrofuran (THF, 0.25 mL) was added to the reaction mixture. After stirring at 0 °C for 2 h and room temperature for 1 h, 0.5 mL H_2O and $NaBO_3·4H_2O$ (12.5 mg, 0.081 mmol) were added to the reaction mixture and stirred at room temperature for 3 h. The reaction was then quenched with $Na_2S_2O_3$ (sat. in H_2O, 1 mL) and extracted with ethyl acetate (3 × 2 mL), and the organic phase was dried with NA_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:Et_2O = 4:1) to give compound **15** (3.3 mg, 59% yield) as a colorless oil.

R_f = 0.52 (hexane:ethyl acetate = 2:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (dt, *J* = 5.1, 1.8 Hz, 1H), 4.60 (tt, *J* = 6.3, 3.2 Hz, 1H), 2.49 (dtd, *J* = 16.8, 2.2, 1.3 Hz, 1H), 2.43 (ddq, *J* = 6.1, 4.0, 2.0 Hz, 1H), 2.36 (dd, *J* = 16.9, 5.4 Hz, 1H), 2.27 (d, *J* = 3.6 Hz, 1H), 2.26 – 2.19 (m, 2H), 2.05 – 1.97 (m, 2H), 1.89 – 1.76 (m, 4H), 1.65 (dt, *J* = 2.8, 1.5 Hz, 3H), 1.59 – 1.54 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.7, 137.5, 121.1, 76.1, 64.8, 44.9, 41.7, 41.2, 38.0, 36.0, 35.7, 33.0, 21.5.
IR (KBr) ν_{max} = 3432, 2912, 2828, 1692, 1445, 1330, 1220, 1112, 1039, 808, 564 cm^{-1}
HRMS (ESI): m/z calcd for $C_{13}H_{19}O_2^+$ $[M+H]^+$: 207.1380, found 207.1379.

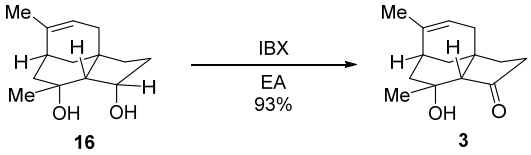
*Synthesis of compound **16***



To a solution of compound **15** (0.234 g, 1.13 mmol) in tetrahydrofuran (THF, 12 mL), $LaCl_3 \cdot LiCl$ (0.5 M in THF, 2.5 mL, 1.25 mmol) was added at 0 °C. After stirring at 0 °C for 1 h, MeMgBr (3M in Et_2O, 0.83 mL, 2.49 mmol) was added to the reaction mixture at 0 °C. After stirring at 0 °C for 30 min, the reaction was quenched with NH_4Cl (sat. in H_2O, 10 mL). HCl (2M in water) was then added to the reaction mixture until all precipitate dissolved, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with $NaHCO_3$ (sat. in H_2O, 30 mL) and brine (sat. in H_2O, 30 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:Et_2O = 4:1) to give compound **16** (0.2202 g, 88% yield) as a white solid.

R_f = 0.36 (hexane:ethyl acetate = 2:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (tt, *J* = 2.8, 1.4 Hz, 1H), 4.63 (td, *J* = 6.6, 3.3 Hz, 1H), 3.02 (d, *J* = 2.4 Hz, 1H), 2.81 (s, 1H), 2.25 (dd, *J* = 6.3, 2.9 Hz, 1H), 2.16 – 2.07 (m, 2H), 2.06 – 1.99 (m, 1H), 1.86 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.75 – 1.69 (m, 3H), 1.67 (q, *J* = 1.9 Hz, 3H), 1.63 (d, *J* = 13.3 Hz, 1H), 1.54 (dd, *J* = 6.5, 1.3 Hz, 1H), 1.48 – 1.42 (m, 1H), 1.38 (s, 3H), 1.36 (dt, *J* = 3.2, 1.4 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 121.1, 76.9, 73.2, 59.4, 41.6, 40.4, 40.3, 39.3, 35.7, 33.2, 33.1, 32.4, 21.9.
IR (KBr) ν_{max} = 3320, 2958, 2929, 2870, 1440, 1370, 1166, 1137, 1094, 1061, 1019, 920, 799 cm^{-1}
HRMS (ESI): m/z calcd for $C_{14}H_{22}NaO_2^+$ $[M+Na]^+$: 245,1512, found 245.1518.
Melting point: 88.3 – 89.6 °C

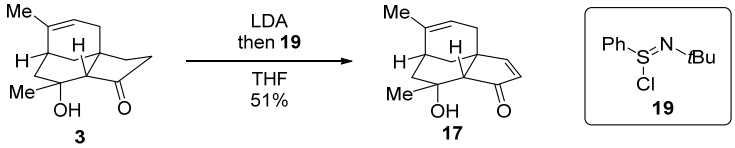
*Synthesis of compound **3***



To a solution of compound **16** (100 mg, 0.45 mmol) in ethyl acetate (9 mL), 2-iodoxybenzoic acid (IBX, 378 mg, 1.35 mmol) was added at room temperature. After stirring at 80 °C for 3 h, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:Et_2O = 4:1) to give compound **3** (92.4 mg, 93% yield) as a white solid.

R_f = 0.40 (hexane:ethyl acetate = 2:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (d, *J* = 1.7 Hz, 1H), 5.37 (ddd, *J* = 4.4, 2.8, 1.5 Hz, 1H), 2.42 – 2.31 (m, 2H), 2.31 – 2.23 (m, 2H), 2.11 – 2.03 (m, 2H), 1.83 – 1.78 (m, 1H), 1.78 – 1.66 (m, 5H), 1.57 (d, *J* = 5.0 Hz, 1H), 1.44 – 1.35 (m, 2H), 1.31 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 222.7, 138.6, 121.6, 71.6, 64.2, 40.03, 39.97, 38.8, 35.8, 35.1, 33.5, 32.9, 30.8, 22.0.
IR (KBr) ν_{max} = 3444, 2922, 2867, 1704, 1439, 1406, 1367, 1154, 1137, 1040, 919, 895, 803 cm^{-1}
HRMS (ESI): m/z calcd for $C_{14}H_{21}O_2^+$ $[M+H]^+$: 221.1536, found 221.1532.
Melting point: 117.6 – 118.7 °C

*Synthesis of compound **17***

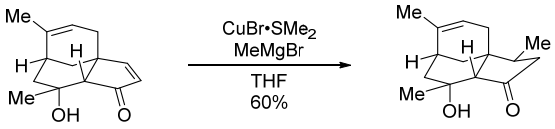


To a solution of diisopropyl amine (7.4 µL, 0.053 mmol) in tetrahydrofuran (THF, 0.1 mL), ^{n}BuLi (2.5 M in THF, 20 µL, 0.051 mmol) was added at 0 °C and stirred for 1 h. This lithium diisopropylamide (LDA) solution was then added to another flask containing compound **3** (5 mg, 0.023 mmol) in tetrahydrofuran (THF, 0.1 mL) at −78 °C. After stirring at −78 °C for 30 min, freshly prepared compound **19** (1M in benzene, 35 µL, 0.035 mmol) was added to the reaction mixture.[4] After stirring at −78 °C for 30 min, the reaction was quenched with NH_4Cl (sat. in H_2O, 1

mL) and extracted with ethyl acetate (3 × 1 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give compound **17** (51% NMR yield) as a white solid.

R_f = 0.41 (hexane:ethyl acetate = 2:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 5.7 Hz, 1H), 6.13 (d, *J* = 5.6 Hz, 1H), 5.31 (dt, *J* = 4.9, 1.7 Hz, 1H), 2.35 – 2.25 (m, 2H), 2.21 (dt, *J* = 11.9, 2.2 Hz, 1H), 1.96 (dd, *J* = 14.9, 9.7 Hz, 1H), 1.92 (s, 1H), 1.69 (dt, *J* = 2.6, 1.5 Hz, 3H), 1.62 – 1.59 (m, 1H), 1.59 – 1.56 (m, 1H), 1.55 (s, 3H), 1.55 – 1.52 (m, 1H), 1.32 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 172.4, 141.0, 132.8, 118.6, 71.8, 59.1, 44.0, 42.4, 39.5, 32.8, 31.0, 28.9, 22.1.
IR (KBr) ν_{max} = 3432, 2961, 2921, 1698, 1675, 1584, 1443, 1384, 1125, 934, 804 cm^{-1}
HRMS (ESI): m/z calcd for $C_{14}H_{19}O_2^+$ $[M+H]^+$: 219.1380, found 219.1374.
Melting point: 146.0 – 146.6 °C

*Synthesis of compound **18***

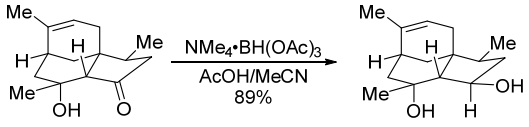


17 **18**

To a solution of compound **17** (4.5 mg, 0.021 mmol) in tetrahydrofuran (THF, 0.4 mL), $CuBr{\cdot}SMe_2$ (8.6 mg, 0.042 mmol) was added at room temperature. The mixture was then cooled to -78 °C and MeMgBr (3 M in Et_2O, 15 μL, 0.044 mmol) was added. After stirring at −78 °C for 1 h and 0 °C for 10 min, the reaction was quenched with NH_4Cl (sat. in H_2O, 1 mL) and extracted with ethyl acetate (3 × 1 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give compound **18** (2.9 mg, 60% yield) as a white solid.

R_f = 0.58 (hexane:ethyl acetate = 2:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (ddq, *J* = 4.3, 3.0, 1.5 Hz, 1H), 5.12 (d, *J* = 1.2 Hz, 1H), 2.61 (dd, *J* = 19.3, 8.3 Hz, 1H), 2.31 – 2.25 (m, 1H), 2.24 (s, 1H), 2.22 (dd, *J* = 5.7, 2.9 Hz, 1H), 2.06 – 1.93 (m, 3H), 1.82 – 1.74 (m, 1H), 1.69 (q, *J* = 1.9 Hz, 3H), 1.66 – 1.62 (m, 1H), 1.45 (dt, *J* = 3.1, 1.4 Hz, 2H), 1.33 (t, *J* = 0.8 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 222.6, 138.5, 121.4, 71.5, 59.8, 44.5, 41.7, 40.7, 37.2, 35.7, 34.9, 30.8, 21.9, 15.7.
IR (KBr) ν_{max} = 3454, 2959, 2924, 1719, 1444, 1409, 1377, 1232, 1197, 1133, 1092, 899 cm^{-1}
HRMS (CI): m/z calcd for $C_{15}H_{23}O_2^+$ $[M+H]^+$: 235.1693, found 235.1690.
Melting point: 85.4 – 86.5 °C

*Synthesis of compound **1***



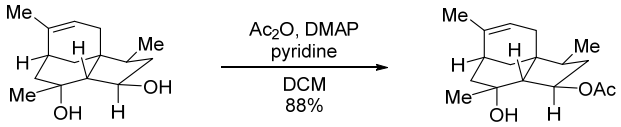
18 Penicibilaene A (**1**)

To a solution of compound **18** (6.7 mg, 0.029 mmol) in acetonitrile (0.3 mL) and acetic acid (0.3 mL), $NMe_4{\cdot}NH(OAc)_3$ (23 mg, 0.086 mmol) was added at room temperature. After stirring at room temperature for 2 h, the reaction was quenched with $NaHCO_3$ (sat. in H_2O, 2 mL) and extracted with ethyl acetate (3 × 2 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 4:1) to give compound **1** (6.0 mg, 89% yield) as a white solid.

R_f = 0.26 (hexane:ethyl acetate = 1:1)

^{1}H NMR (500 MHz, Acetone-D6) δ 5.23 (d, *J* = 4.9 Hz, 1H), 4.45 (p, *J* = 6.9 Hz, 1H), 3.41 (d, *J* = 5.3 Hz, 1H), 3.21 (s, 1H), 2.15 (d, *J* = 8.5 Hz, 1H), 2.10 – 2.04 (m, 3H), 2.04 – 1.97 (m, 2H), 1.93 – 1.86 (m, 1H), 1.90 – 1.83 (m, 2H), 1.78 – 1.70 (m, 1H), 1.73 – 1.65 (m, 2H), 1.63 (d, *J* = 2.0 Hz, 3H), 1.50 (d, *J* = 14.2 Hz, 1H), 1.46 (d, *J* = 6.2 Hz, 1H), 1.38 (td, *J* = 11.8, 8.6 Hz, 1H), 1.30 (ddd, *J* = 11.6, 4.0, 1.4 Hz, 1H), 1.26 (s, 3H), 0.89 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (101 MHz, Acetone-D6) δ 140.9, 120.7, 73.4, 71.3, 61.5, 42.6, 42.54, 42.48, 42.4, 36.0, 35.4, 33.3, 31.4, 22.2, 15.0.
IR (KBr) ν_{max} = 3359, 3300, 2963, 1913, 1443, 1411, 1142, 1113, 1036, 922, 861 cm^{-1}
HRMS (ESI): m/z calcd for $C_{15}H_{25}O_2^+$ $[M+H]^+$: 237.1849, found 237.1842.
Melting point: 159.3 – 160.0 °C

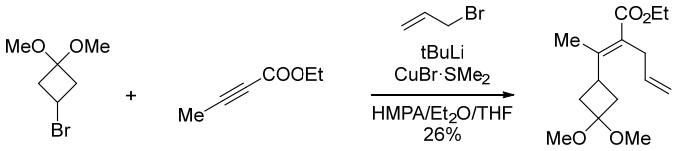
*Synthesis of compound **2***



To a solution of compound **1** (6.0 mg, 0.025 mmol) in dichloromethane (0.5 mL), pyridine (6.1 μL, 0.075 mmol), acetic anhydride (Ac_2O, 4.7 μL, 0.051 mmol), and 4-(dimethylamino)pyridine (DMAP, 0.3 mg, 0.0025 mmol) were added at room temperature. After stirring at room temperature for 24 h, the reaction was quenched with NH_4Cl (sat. in H_2O, 1 mL) and extracted with dichloromethane (3 × 2 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give compound **2** (6.2 mg, 88% yield) as a white solid.

R_f = 0.76 (hexane:ethyl acetate = 1:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (ddd, *J* = 8.7, 7.6, 6.0 Hz, 1H), 5.26 (d, *J* = 4.9 Hz, 1H), 2.31 (ddd, *J* = 12.8, 7.5, 5.8 Hz, 1H), 2.22 (d, *J* = 9.2 Hz, 1H), 2.05 (d, *J* = 17.0 Hz, 1H), 2.00 (s, 3H), 1.83 (dd, *J* = 14.7, 9.1 Hz, 1H), 1.79 – 1.76 (m, 1H), 1.75 – 1.74 (m, 1H), 1.72 (d, *J* = 6.1 Hz, 1H), 1.72 – 1.68 (m, 1H), 1.65 (dt, *J* = 2.7, 1.5 Hz, 3H), 1.53 (dt, *J* = 14.6, 1.3 Hz, 1H), 1.44 (ddd, *J* = 11.8, 3.9, 1.5 Hz, 1H), 1.37 (td, *J* = 12.4, 8.7 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 1H), 0.91 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 140.3, 119.4, 75.5, 71.1, 56.8, 41.8, 41.7, 41.2, 38.3, 34.4, 34.2, 31.9, 30.3, 21.8, 21.4, 13.9.
IR (KBr) ν_{max} = 3505, 2958, 2926, 2886, 1736, 1719, 1458, 1375, 1271, 1245, 1114, 1030, 927, 805 cm^{-1}
HRMS (ESI): m/z calcd for $C_{17}H_{27}O_3^+$ $[M+H]^+$: 279.1955, found 237.1886; $C_{17}H_{26}NaO_3^+$ $[M+Na]^+$: 301.1774, found 301.1768.
Melting point: 122.8 – 123.5 °C

*Synthesis of compound **S4***

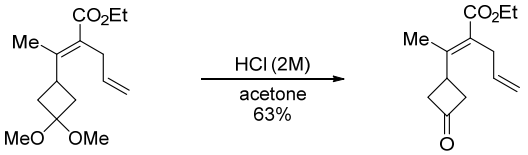


To a solution of compound **11** (195 mg, 1 mmol) in Et_2O (1 mL), ^{t}BuLi (1.6 M in pentane, 1.3 mL, 2.05 mmol) was added at −78 °C and stirred for 1 h. The previously prepared alkyl lithium solution was then added to another flask containing $CuBr{\cdot}SMe_2$ (205 mg, 1 mmol) suspended in tetrahydrofuran (THF, 5 mL) at −78 °C. After stirring at −78 °C for 10 min, compound **9** (112 mg, 1 mmol) was added, and the reaction mixture was stirred at −78 °C for 30 min. Hexamethylphosphoramide (HMPA, 1 mL) and allyl bromide (133 mg, 1.1 mmol) were then added to the reaction mixture at −78 °C. After stirring at 0 °C for 2 h, the reaction mixture was quenched with NH_4Cl (sat. in H_2O, 10 mL) and extracted with ethyl acetate (3 × 5 mL). The organic phase was washed with brine (sat. in H_2O, 10 mL), dried with NA_2SO_4 and concentrated under reduced pressure. The residue was purified by column

chromatography (silica gel, hexane:ethyl acetate = 20:1) to give compound **S4** (70.1 mg, 26% yield) as a colorless oil.

$\mathbf{R}_f$ = 0.50 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.2, 10.1, 6.0 Hz, 1H), 5.04 – 4.94 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.23 – 3.18 (m, 1H), 3.18 (s, 3H), 3.14 (s, 3H), 3.08 – 3.04 (m, 2H), 2.36 – 2.29 (m, 2H), 2.14 – 2.07 (m, 2H), 1.97 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 145.9, 135.7, 126.7, 115.3, 99.9, 60.2, 48.7, 48.4, 36.1, 33.6, 28.4, 16.5, 14.3.
IR (KBr) ν_{max} = 2982, 2949, 1712, 1445, 1274, 1202, 1152, 1043 cm^{-1}
HRMS (ESI): m/z calcd for $C_{15}H_{25}O_4^+$ $[M+H]^+$: 269.1747, found 269.1745.

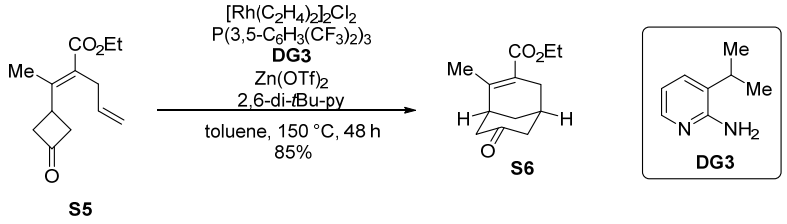
*Synthesis of compound **S5***



To a solution of compound **S4** (70.1 mg, 0.26 mmol) in acetone (5 mL), HCl (2 M in H_2O, 0.25 mL, 0.5 mmol) was added at room temperature. After stirring at room temperature for 12 h, the reaction mixture was quenched with $NaHCO_3$ (sat. in H_2O, 10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was then washed with brine (sat. in H_2O, 20 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate = 20:1) to give compound **S5** (36.4 mg, 63% yield) as a colorless oil.

$\mathbf{R}_f$ = 0.35 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.3, 10.8, 6.0 Hz, 1H), 5.07 – 4.98 (m, 2H), 4.21 (qd, *J* = 7.1, 2.0 Hz, 2H), 3.57 (dd, *J* = 9.3, 7.2 Hz, 1H), 3.23 – 3.08 (m, 6H), 2.02 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8, 169.2, 144.1, 135.3, 127.9, 115.6, 60.5, 51.5, 33.7, 26.5, 15.6, 14.2.
IR (KBr) ν_{max} = 2980, 2932, 1789, 1710, 1446, 1381, 1286, 1207, 1106, 1053 cm^{-1}
HRMS (ESI): m/z calcd for $C_{13}H_{19}O_3^+$ $[M+H]^+$: 223.1329, found 223.1327.

*Synthesis of compound **S6***

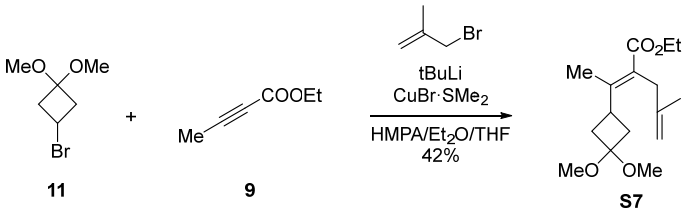


A flame dried 4 mL vial was charged with $P(3,5\text{-}C_6H_3(CF_3)_2)_3$ (13.4 mg, 0.02 mmol), **DG3** (1.4 mg, 0.01 mmol), $Zn(OTf)_2$ (3.6 mg, 0.01 mmol) and 2,6-di-*tert*-butylpyridine (5.6 μL, 0.025 mmol) in glove box. After adding a solution of compound **S5** (11 mg, 0.05 mmol) and $[Rh(C_2H_4)_2Cl]_2$ (1.9 mg, 0.005 mmol) dissolved in toluene (0.5 mL), the vial was sealed and removed from the glove box. The reaction was stirred at 150 °C in a pi-block for 48 h, before it was cooled to room temperature. The reaction mixture was then concentrated under reduced pressure and the residue purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give compound **S6** (9.4 mg, 85% yield) as a colorless oil.

$\mathbf{R}_f$ = 0.31 (hexane:ethyl acetate = 2:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.2 Hz, 2H), 2.65 – 2.49 (m, 4H), 2.47 (d, *J* = 3.8 Hz, 2H), 2.30 (dd, *J* = 16.9, 4.4 Hz, 2H), 2.06 – 2.02 (m, 1H), 2.01 (s, 3H), 1.98 – 1.91 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.1, 168.0, 147.5, 122.9, 60.1, 48.7, 44.6, 38.9, 33.6, 29.7, 29.3, 20.8, 14.2.
IR (KBr) ν_{max} = 2927, 1712, 1639, 1437, 1372, 1238, 1196, 1063 cm^{-1}
HRMS (ESI): m/z calcd for $C_{13}H_{19}O_3^+$ $[M+H]^+$: 223.1329, found 223.1327; $C_{13}H_{18}NaO_3^+$ $[M+Na]^+$: 245.1148, found 245.1144.

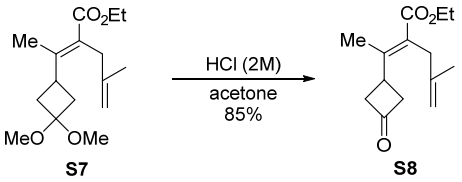
*Synthesis of compound **S7***



To a solution of compound **11** (195 mg, 1 mmol) in Et_2O (1 mL), ^{t}BuLi (1.6 M in pentane, 1.3 mL, 2.05 mmol) was added at −78 °C and stirred at −78 °C for 1 h. To another flask with $CuBr{\cdot}SMe_2$ (205 mg, 1 mmol) suspended in tetrahydrofuran (THF, 5 mL), the previously prepared alkyl lithium solution was then added at −78 °C. After stirring at −78 °C for 10 min, compound **9** (112 mg, 1 mmol) was added to the reaction mixture, which was then stirred at −78 °C for 30 min. Hexamethylphosphoramide (HMPA, 1 mL) and 3-bromo-2-methylpropene (162 mg, 1.2 mmol) were then added to the reaction mixture at −78 °C. After stirring at 0 °C for 2 h, the reaction mixture was quenched with NH_4Cl (sat. in H_2O, 10 mL) and extracted with ethyl acetate (3 × 5 mL). The organic phase was washed with brine (sat. in H_2O, 10 mL), dried with NA_2SO_4, and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate = 20:1) to give compound **S7** (118.6 mg, 42% yield) as a colorless oil.

R_f = 0.47 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (s, 1H), 4.60 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.20 – 3.11 (m, 7H), 3.00 (s, 2H), 2.33 – 2.26 (m, 2H), 2.14 – 2.07 (m, 2H), 1.97 (s, 3H), 1.70 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 145.7, 143.3, 127.1, 110.7, 99.9, 60.1, 48.7, 48.3, 37.3, 36.0, 28.4, 22.7, 16.4, 14.2.
IR (KBr) ν_{max} = 2984, 2948, 1712, 1446, 1274, 1227, 1197, 1151, 1044 cm^{-1}
HRMS (ESI): m/z calcd for $C_{16}H_{27}O_4^+$ $[M+H]^+$: 283.1904, found 283.1902.

*Synthesis of compound **S8***

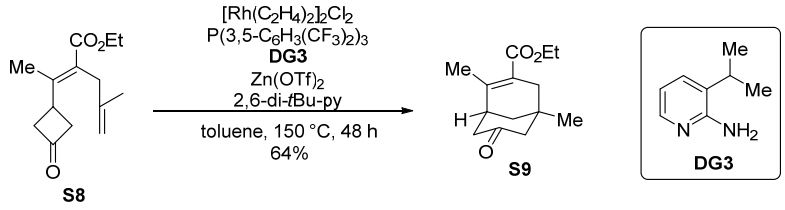


To a solution of compound **S7** (118.6 mg, 0.42 mmol) in acetone (8.5 mL), HCl (2 M in H_2O, 0.4 mL, 0.8 mmol) was added at room temperature. After stirring at room temperature for 12 h, the reaction mixture was quenched with $NaHCO_3$ (sat. in H_2O, 10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with brine (sat. in H_2O, 20 mL) and dried with Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate = 20:1) to give compound **S8** (84.2 mg, 85% yield) as a colorless oil.

R_f = 0.50 (hexane:ethyl acetate = 4:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (s, 1H), 4.63 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.53 (p, *J* = 8.2 Hz, 1H), 3.21 – 3.10 (m, 4H), 3.09 (s, 2H), 2.02 (s, 3H), 1.73 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9, 169.4, 144.1, 143.0, 128.3, 111.0, 60.4, 51.4, 37.5, 26.6, 22.7, 15.5, 14.2.
IR (KBr) ν_{max} = 2980, 2934, 1789, 1710, 1447, 1380, 1292, 1198, 1105, 1069 cm^{-1}

HRMS (ESI): m/z calcd for $C_{14}H_{21}O_3^+$ [M+H]$^+$: 237.1485, found 237.1485.

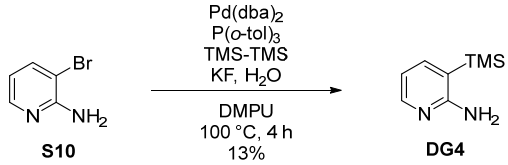
*Synthesis of compound **S9***



A flame dried 4 mL vial was charged with P(3,5-$C_6H_3(CF_3)_2)_3$ (13.4 mg, 0.02 mmol), **DG3** (1.4 mg, 0.01 mmol), $Zn(OTf)_2$ (3.6 mg, 0.01 mmol) and 2,6-di-*tert*-butylpyridine (5.6 µL, 0.025 mmol) in glove box. After adding a solution of compound **S8** (11.8 mg, 0.05 mmol) and $[Rh(C_2H_4)_2Cl]_2$ (1.9 mg, 0.005 mmol) dissolved in toluene (0.5 mL), the vial was sealed and removed from the glove box. The reaction was stirred at 150 °C in a pi-block for 48 h, before being cooled to room temperature. The reaction mixture was then concentrated under reduced pressure and purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give compound **S9** (7.6 mg, 64% yield) as a colorless oil.

R_f = 0.35 (hexane:ethyl acetate = 2:1)
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 3.5 Hz, 1H), 2.46 – 2.42 (m, 2H), 2.31 – 2.21 (m, 2H), 2.20 (s, 2H), 2.01 (t, *J* = 2.0 Hz, 3H), 1.88 – 1.77 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7, 167.8, 147.1, 123.4, 60.1, 55.4, 43.9, 40.7, 40.2, 37.5, 33.9, 31.3, 20.6, 14.2.
IR (KBr) ν_{max} = 2923, 1712, 1638, 1456, 1371, 1241, 1139, 1060 cm^{-1}
HRMS (ESI): m/z calcd for $C_{14}H_{21}O_3^+$ [M+H]$^+$: 237.1485, found 237.1481; $C_{14}H_{20}NaO_3^+$ [M+Na]$^+$: 259.1305, found 259.1301.

*Synthesis of compound **DG4***

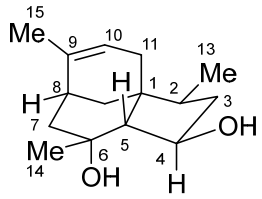


To a solution of compound **S10** (173 mg, 1 mmol) in *N*,*N*'-dimethylpropyleneurea (DMPU, 3.3 mL), bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$, 17 mg, 0.03 mmol), tri(*o*-tolyl)phosphine (P(*o*-tol)$_3$, 27 mg, 0.09 mmol), KF (290 mg, 5 mmol), hexamethyldisilane (244 µL, 1.2 mmol) and H_2O (36 µL, 2 mmol) were added at room temperature. After stirring at 100 °C for 4 h, the reaction mixture was quenched with H_2O (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with brine (sat. in H_2O, 20 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, hexane:ethyl acetate = 4:1) to give compound **DG4** (20.9 mg, 13% yield) as a white solid.

R_f = 0.52 (pure ethyl acetate)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.53 (dd, *J* = 7.1, 2.0 Hz, 1H), 6.64 (dd, *J* = 7.1, 5.0 Hz, 1H), 4.55 (s, 2H), 0.32 (s, 9H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 149.0, 143.9, 116.5, 114.2, -1.4.
IR (KBr) ν_{max} = 3495, 3395, 3308, 3175, 2955, 1607, 1566, 1427, 1252, 873, 839 cm^{-1}
HRMS (ESI): m/z calcd for $C_8H_{15}N_2Si^+$ [M+H]$^+$: 167.0999, found 167.1001.
Melting point: 48.0 – 48.8 °C

3. Comparison of the Spectroscopic Data of the Natural and Synthetic Products

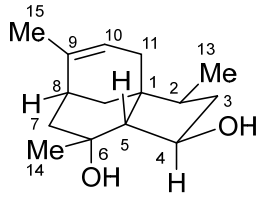
Table S1. Comparison of the ^{1}H-NMR (Acetone-D6) Data of the Synthetic Penicibilaene A (**1**)



Penicibilaene A (**1**)

No.	Wang's isolated natural penicibilaene (**1**)[5] δ ^{1}H [ppm, mult, J (Hz)] 500 MHz	Our synthetic penicibilaene (**1**) δ ^{1}H [ppm, mult, J (Hz)] 500 MHz
2	1.69 (m, 1H)	1.69 (m, 1H)
3α	2.07 (m, 1H)	2.07 (m, 1H)
3β	1.38 (dt,11.7, 8.6, 1H)	1.38 (dt, 11.8, 8.6, 1H)
4	4.45 (m, 1H)	4.45 (p, 6.9, 1H)
5	1.46 (d, 6.2, 1H)	1.46 (d, 6.2, 1H)
7α	1.86 (dd, 12.0, 4.8, 1H)	1.86 (m, 1H)
7β	1.30 (dd, 12.0, 3.9, 1H)	1.30 (ddd, J = 11.6, 4.0, 1.4 Hz, 1H)
8	2.15 (dd, 4.8, 3.9, 1H)	2.15 (d, 8.5, 1H)
10	5.23 (dd, 3.1, 1.5, 1H)	5.23 (d, 4.9 Hz, 1H)
11α	2.01 (d, 16.3, 1H)	2.00 (m, 1H)
11β	1.74 (m, 1H)	1.74 (m, 1H)
12α	1.90 (dd, 14.2, 5.6, 1H)	1.89 (m, 1H)
12β	1.50 (d, 14.2, 1H)	1.50 (d, 14.2, 1H)
13	0.89 (d, 7.1, 3H)	0.88 (d, 7.0, 3H)
14	1.26 (s, 3H)	1.26 (s, 3H)
15	1.63 (br s, 3H)	1.63 (d, 2.0, 3H)
4-OH	3.40 (d, 5.2, 1H)	3.41 (d, 5.3, 1H)
6-OH	3.20 (s, 1H)	3.21 (s, 1H)

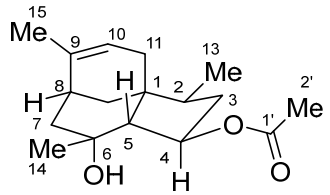
Table S2. Comparison of the ^{13}C-NMR (Acetone-D6) Data of the Synthetic Penicibilaene A (**1**)



Penicibilaene A (**1**)

No.	Wang's isolated natural penicibilaene (**1**)[5] δ ^{13}C [ppm, mult, J (Hz)] 125 MHz	Our synthetic penicibilaene (**1**) δ ^{13}C [ppm, mult, J (Hz)] 101 MHz
1	42.58	42.54
2	42.62	42.60
3	42.5	42.5
4	73.4	73.4
5	61.5	61.5
6	71.3	71.3
7	33.3	33.3
8	36.1	36.0
9	140.9	140.9
10	120.7	120.7
11	35.4	35.4
12	42.4	42.4
13	15.0	15.0
14	31.4	31.4
15	22.2	22.2

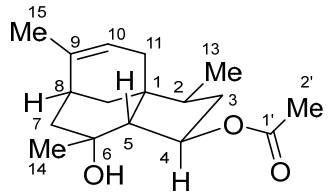
Table S3. Comparison of the ^{1}H-NMR ($CDCl_3$) Data of the Synthetic Penicibilaene B (**2**)



Penicibilaene B (**2**)

No.	Wang's isolated natural penicibilaene (**2**)[5] δ ^{1}H [ppm, mult, J (Hz)] 500 MHz	Our synthetic penicibilaene (**2**) δ ^{1}H [ppm, mult, J (Hz)] 500 MHz
2	1.80 (m, 1H)	1.83 (dd, 14.7, 9.1, 1H)
3α	2.28 (ddd, 12.5, 7.1, 6.6, 1H)	2.31 (ddd, 12.8, 7.5, 5.8, 1H)
3β	1.34 (dt, 12.5, 8.7, 1H)	1.37 (dt, 12.4, 8.7, 1H)
4	5.33 (ddd, 8.7, 6.6, 6.0, 1H)	5.36 (ddd, 8.7, 7.6, 6.0, 1H)
5	1.70 (d, 6.0, 1H)	1.72 (d, 6.1, 1H)
7α	1.78 (dd, 11.9, 6.2, 1H)	1.77 (m, 1H)
7β	1.41 (dd, 11.9, 2.5, 1H)	1.44 (ddd, 11.8, 3.9, 1.5, 1H)
8	2.18 (dd, 6.2, 2.5, 1H)	2.22 (d, 9.2, 1H)
10	5.24 (d, 4.2, 1H)	5.26 (d, 4.9, 1H)
11α	2.02 (d, 16.0, 1H)	2.05 (d, 17.0, 1H)
11β	1.70 (m, 1H)	1.70 (m, 1H)
12α	1.75 (dd, 14.5, 6.3, 1H)	1.75 (m, 1H)
12β	1.50 (d, 14.5, 1H)	1.53 (dt, 14.6, 1.3, 1H)
13	0.88 (d, 6.9, 3H)	0.91 (d, 6.9, 3H)
14	1.13 (s, 3H)	1.15 (s, 3H)
15	1.63 (m, 3H)	1.65 (dt, 2.7, 1.5, 3H)
2'	1.97 (s, 3H)	2.00 (s, 3H)
6-OH		1.13 (s, 1H)

Table S4. Comparison of the ^{1}H-NMR ($CDCl_3$) Data of the Synthetic Penicibilaene B (**2**)

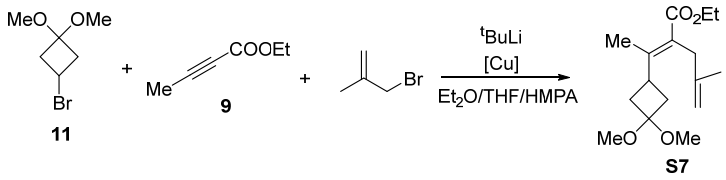


Penicibilaene B (**2**)

No.	Wang's isolated natural penicibilaene (**2**)[5] δ ^{13}C [ppm, mult, J (Hz)] 125 MHz	Our synthetic penicibilaene (**2**) δ ^{13}C [ppm, mult, J (Hz)] 101 MHz
1	41.5	41.2
2	42.1	41.8
3	38.6	38.3
4	75.8	75.5
5	57.1	56.8
6	71.3	71.1
7	32.2	31.9
8	34.7	34.4
9	140.5	140.3
10	119.7	119.4
11	34.4	34.2
12	41.9	41.7
13	14.1	13.9
14	30.5	30.3
15	22.1	21.8
1'	171.1	170.9
2'	21.6	21.4

4. Optimization of Selected Reaction Conditions

Table S5. Optimization of Three-Component Coupling[a]



Entry	[Cu]	Temperature[b]	Yield[c]
1	CuI	–78 °C/–78 °C	trace
2	CuCN	–78 °C/–78 °C	18%[d]
3	CuBr•SMe_2	–78 °C/–78 °C	48%[e]
4	CuBr•SMe_2	0 °C/–78 °C	37%
5	CuBr•SMe_2	–78 °C/0 °C	trace

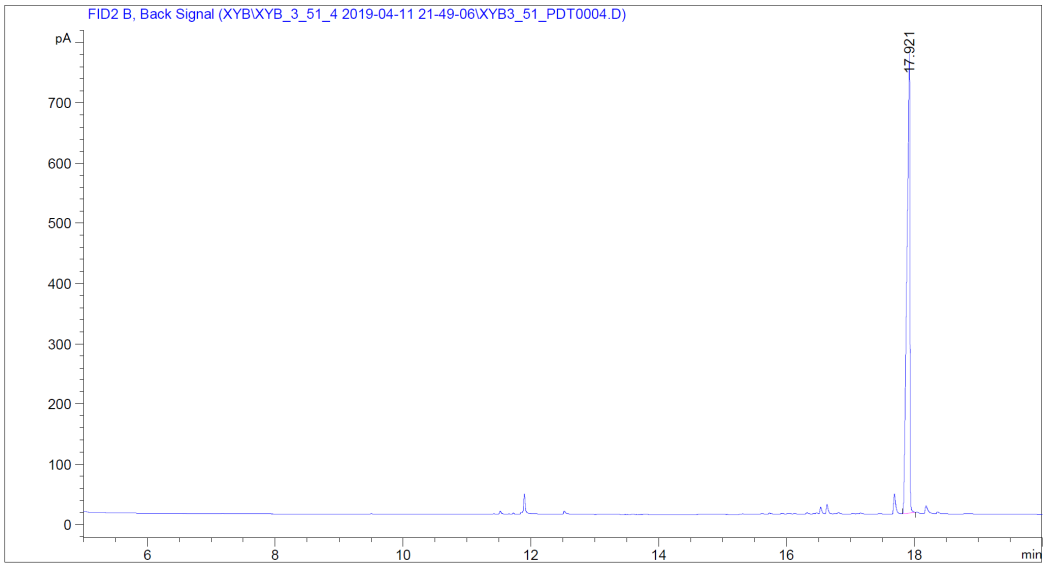
[a]Unless otherwise mentioned, the reaction was run on a 0.26 mmol scale. [b]Temperature for the lithium-bromide exchange step/temperature for the alkyne insertion step. [c]Determined by ^{1}H-NMR using tetrachloroethane as the internal standard. [d]Isolated yield; the reaction was run on a 0.51 mmol scale. [e]Isolated yield.

5. Gas Chromatography Data

GC calibration curve of ketone 5 with 1-methylnaphthalene as the internal standard

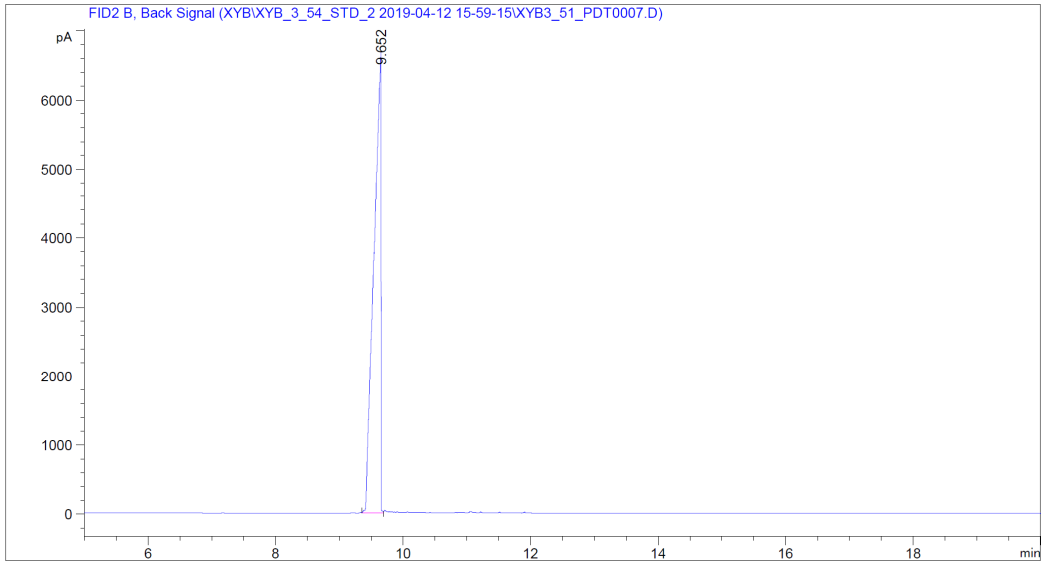
GC Method for ketone **5**: Starting from 50 °C, followed by a temperature increase of 10 °C/min to 280 °C, hold 0 min (total run time: 23 min). Retention time: **5** 17.921 min; 1-methylnaphthalene 9.652 min

GC spectra of compound 5



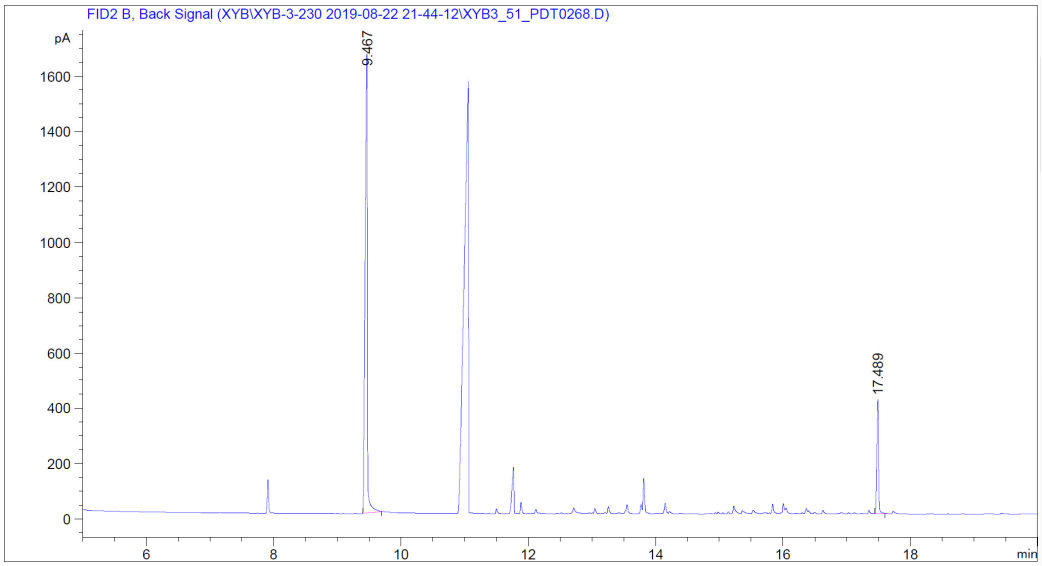
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	17.921	BB	0.0431	2508.40869	763.27112	1.000e2

GC spectra of 1-methylnaphthalene



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	9.652	VV	0.0945	5.04438e4	6563.46289	1.000e2

GC spectra of Table 1, Entry 8



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	9.467	BB	0.0345	4105.78857	1657.66345	84.00989
2	17.489	VB	0.0285	781.47980	413.07098	15.99011

Table S6. GC Data of Compound 5 with 1-Methylnaphthalene as Internal Standard

entry	1-methylnaphthalene		Compound **5**		x	y
	V (μL)	area	m (mg)	area	x = a/a	y = m/V
1	10	6431	1.6 mg	97.4	0.015145	0.16
2	10	8007.6	3.1 mg	308.1	0.038476	0.31
3	10	6699.8	4.7 mg	406.2	0.060629	0.47
4	10	8795.1	6.3 mg	768.9	0.087424	0.63
5	10	6716.5	7.9 mg	778.2	0.115864	0.79

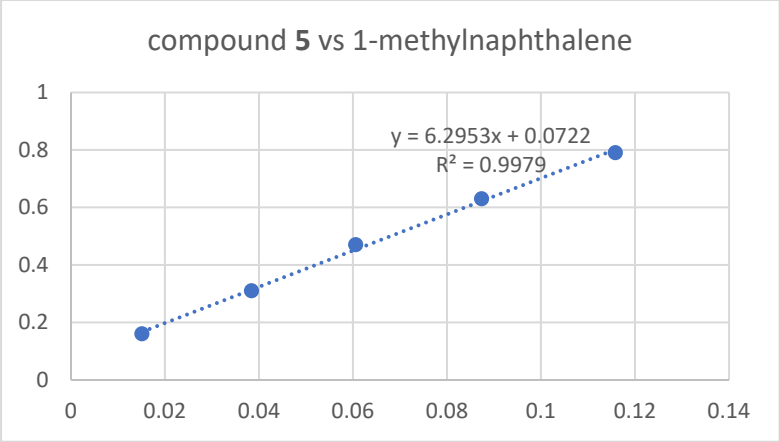


Figure S1. GC calibration Curve of Compound 5 with 1-Methylnathalene as Internal Standard.

GC yield determination for compound 5:

5 μL 1-methylnaphthalene was added as internal standard.

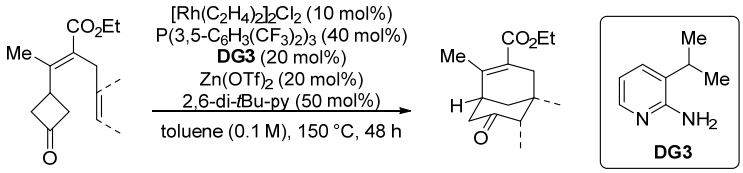
x = (GC area **5**) / (GC area 1-methylnaphthalene) = 781.5 / 4105.8 = 0.1903

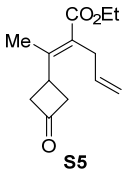
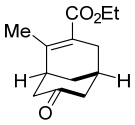
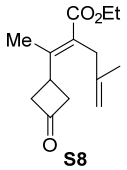
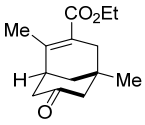
mass of **5** = volume of 1-methylnaphthalene × (6.2953 × 0.1903 + 0.0722) = 6.3 mg

yield of **5** = 6.3 / 13.1 × 100% = 48%

6. Preliminary Result of Substrate Scope

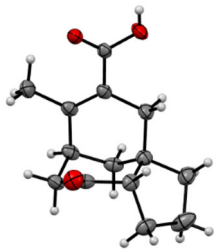
Table S7. Preliminary Result of Substrate Scope of the "Cut-and-Sew" Reaction with α,β-Unsaturated Ester Linker.[a]

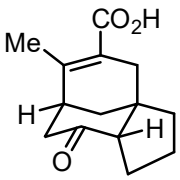


Entry	Substrate	Product	Yield[b]
1	 **S5**	 **S6**	85%
2	 **S8**	 **S9**	64%

[a]Unless otherwise mentioned, the reaction was run on a 0.05 mmol scale. [b]Isolated yield.

7. Crystal Data and Structure Refinement

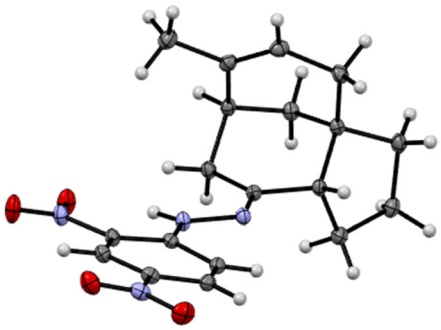


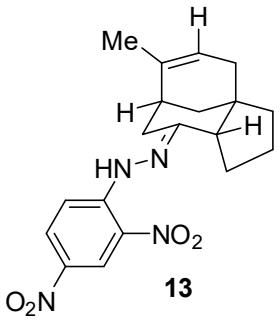


12

CCDC #2078710

Identification code	mo_1019_SHO_YX_0m
Empirical formula	$C_{14}H_{18}O_3$
Formula weight	234.28
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.7164(6)
b/Å	13.8970(8)
c/Å	9.9583(6)
α/°	90
β/°	115.861(2)
γ/°	90
Volume/Å^3	1210.00(13)
Z	4
ρ_{calc}g/cm^3	1.286
μ/mm^{-1}	0.089
F(000)	504.0
Crystal size/mm^3	0.586 × 0.574 × 0.332
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.888 to 48.904
Index ranges	$-11 \le h \le 11$, $-16 \le k \le 16$, $-11 \le l \le 11$
Reflections collected	19941
Independent reflections	2006 [R_{int} = 0.0243, R_{sigma} = 0.0106]
Data/restraints/parameters	2006/0/156
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0356, wR_2 = 0.0930
Final R indexes [all data]	R_1 = 0.0376, wR_2 = 0.0948
Largest diff. peak/hole / e Å^{-3}	0.22/-0.18





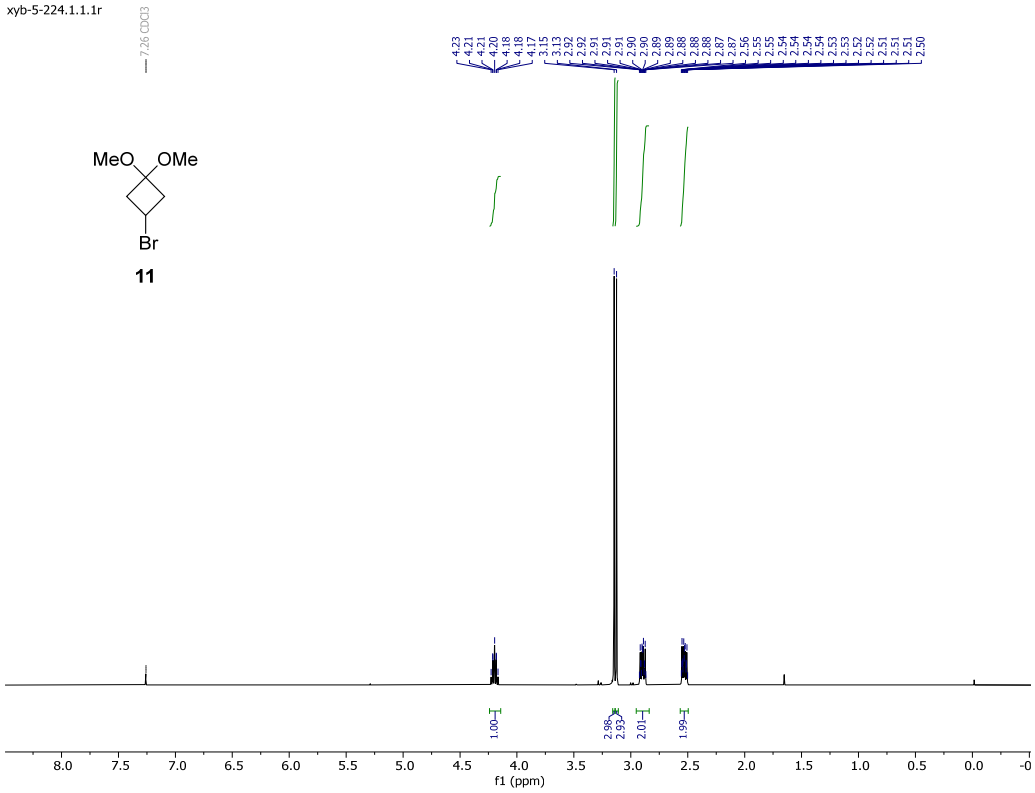
13

CCDC #2078965

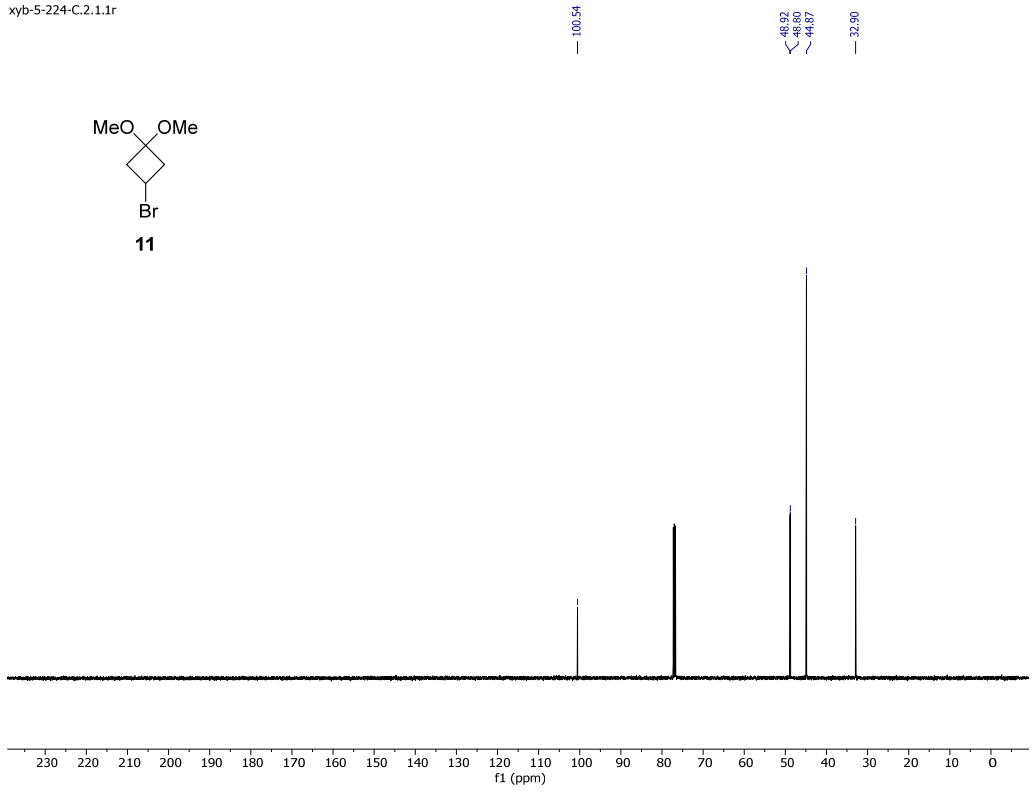
Identification code	xyb-3-286
Empirical formula	$C_{19}H_{22}N_4O_4$
Formula weight	370.40
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	13.5093(13)
b/Å	6.2144(6)
c/Å	20.982(2)
α/°	90
β/°	96.738(2)
γ/°	90
Volume/Å^3	1749.3(3)
Z	4
ρ_{calc}g/cm^3	1.406
μ/mm^{-1}	0.101
F(000)	784.0
Crystal size/mm^3	0.514 × 0.225 × 0.126
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.66 to 61.44
Index ranges	$-19 \le h \le 19$, $-8 \le k \le 8$, $-30 \le l \le 30$
Reflections collected	55097
Independent reflections	5423 [R_{int} = 0.0328, R_{sigma} = 0.0173]
Data/restraints/parameters	5423/0/249
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0401, wR_2 = 0.0995
Final R indexes [all data]	R_1 = 0.0497, wR_2 = 0.1051
Largest diff. peak/hole / e Å^{-3}	0.46/-0.17

8. NMR Spectra

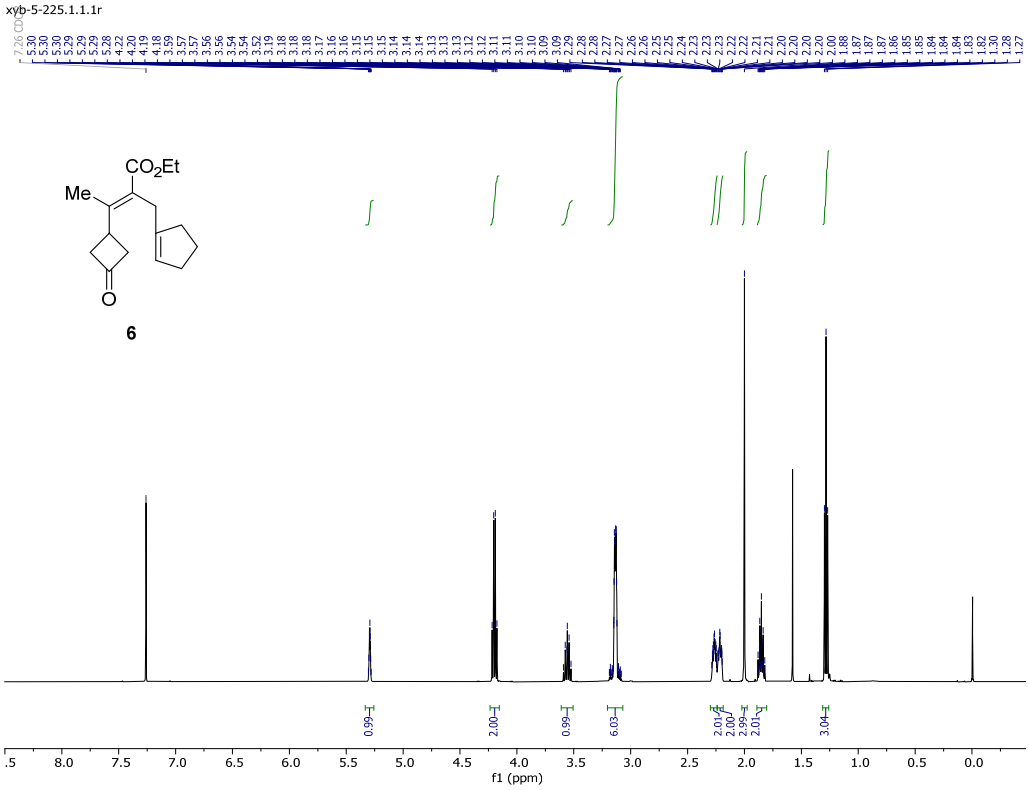
^{1}H-NMR spectrum of **11** in $CDCl_3$, 500 MHz



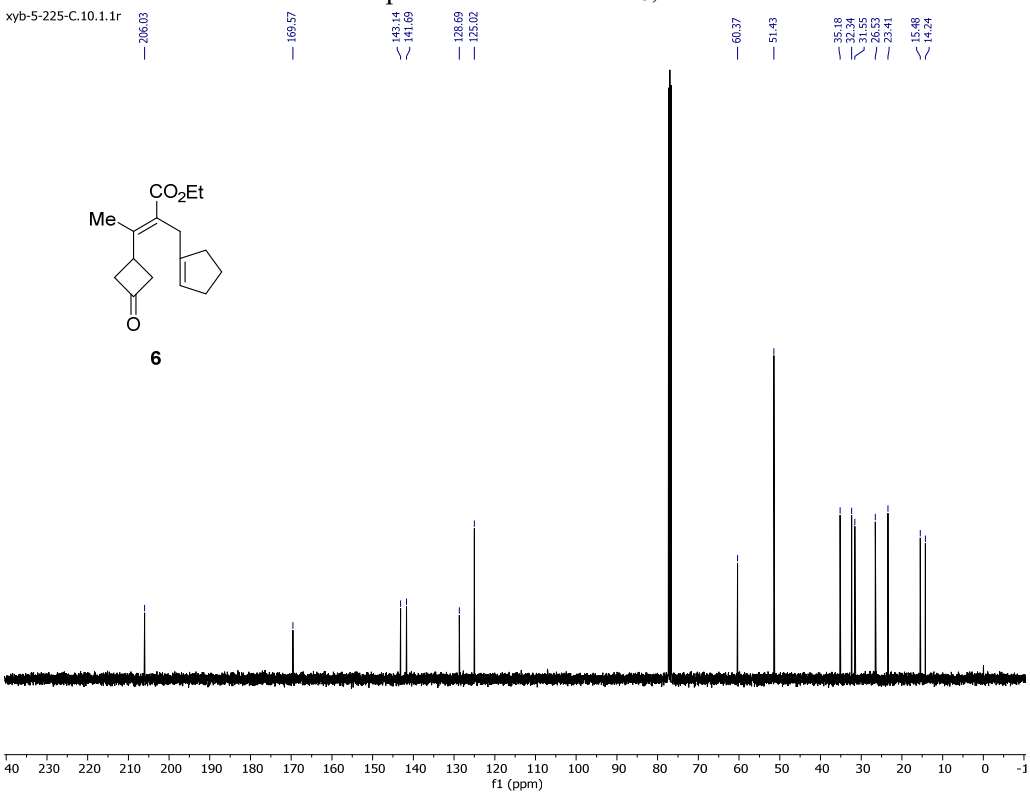
^{13}C-NMR spectrum of **11** in $CDCl_3$, 126 MHz



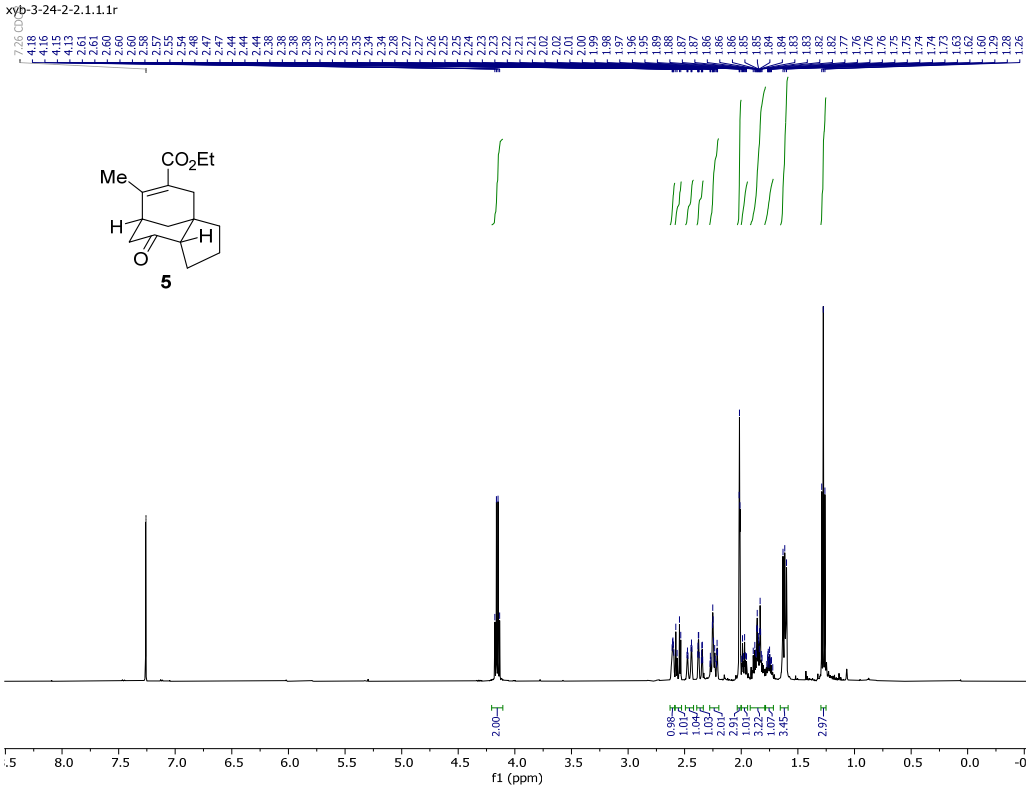
^{1}H-NMR spectrum of **6** in $CDCl_3$, 500 MHz



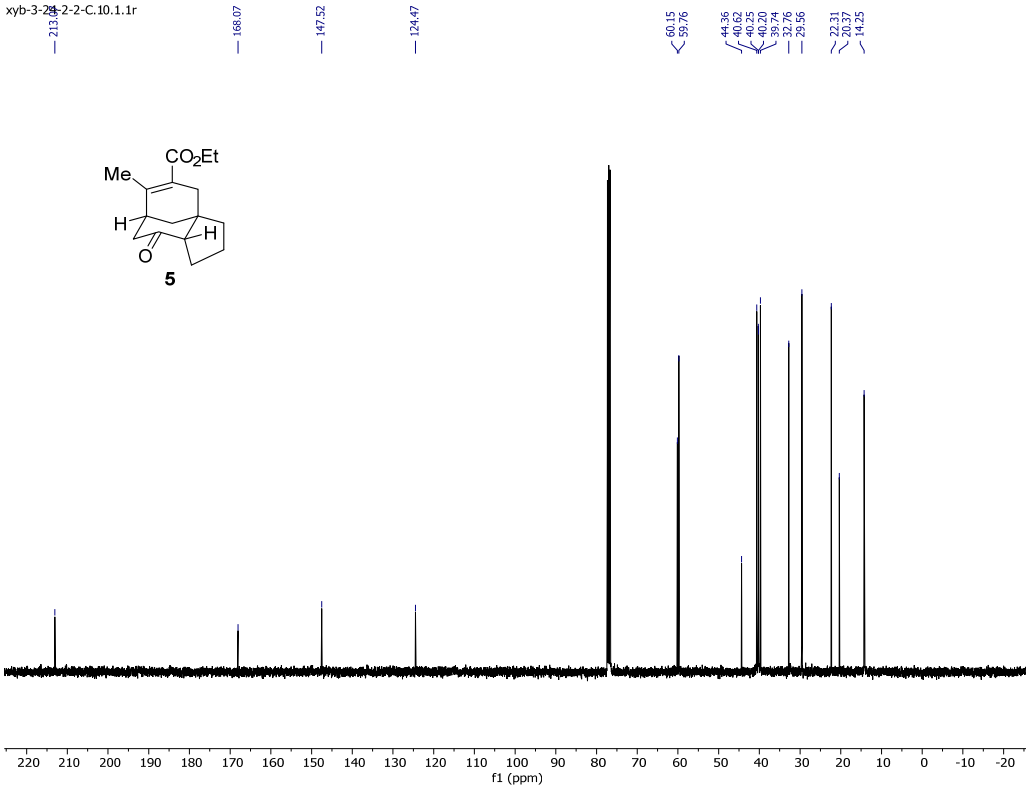
^{13}C-NMR spectrum of **6** in $CDCl_3$, 101 MHz



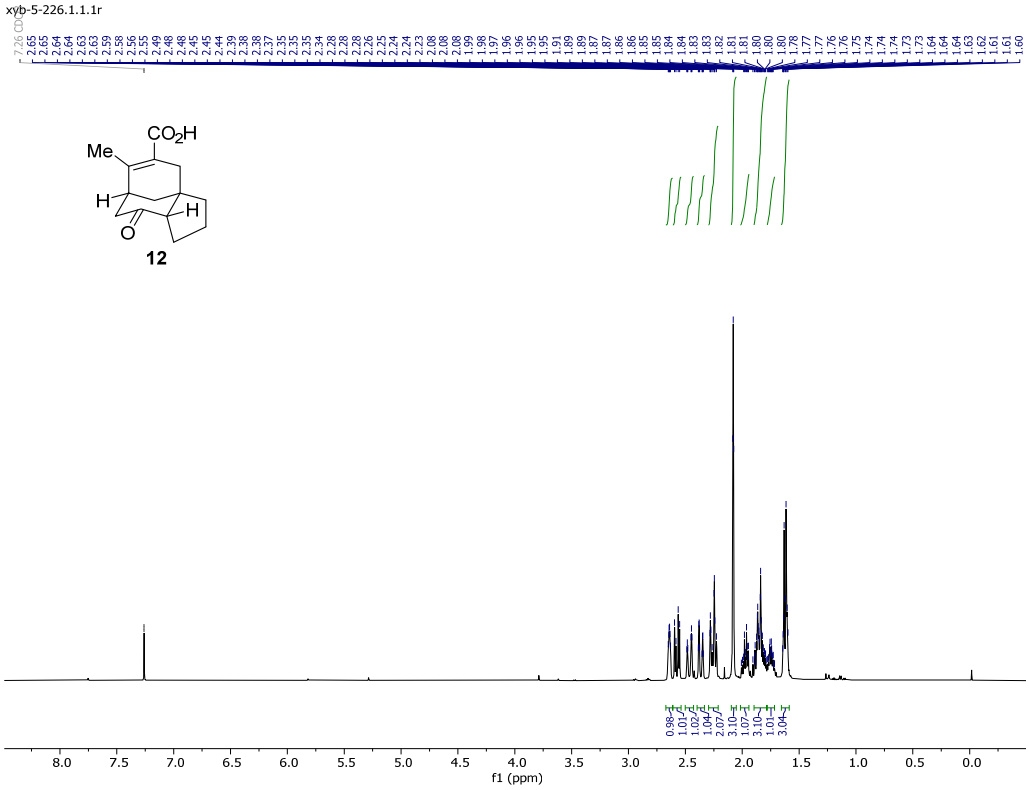
^{1}H-NMR spectrum of **5** in $CDCl_3$, 500 MHz



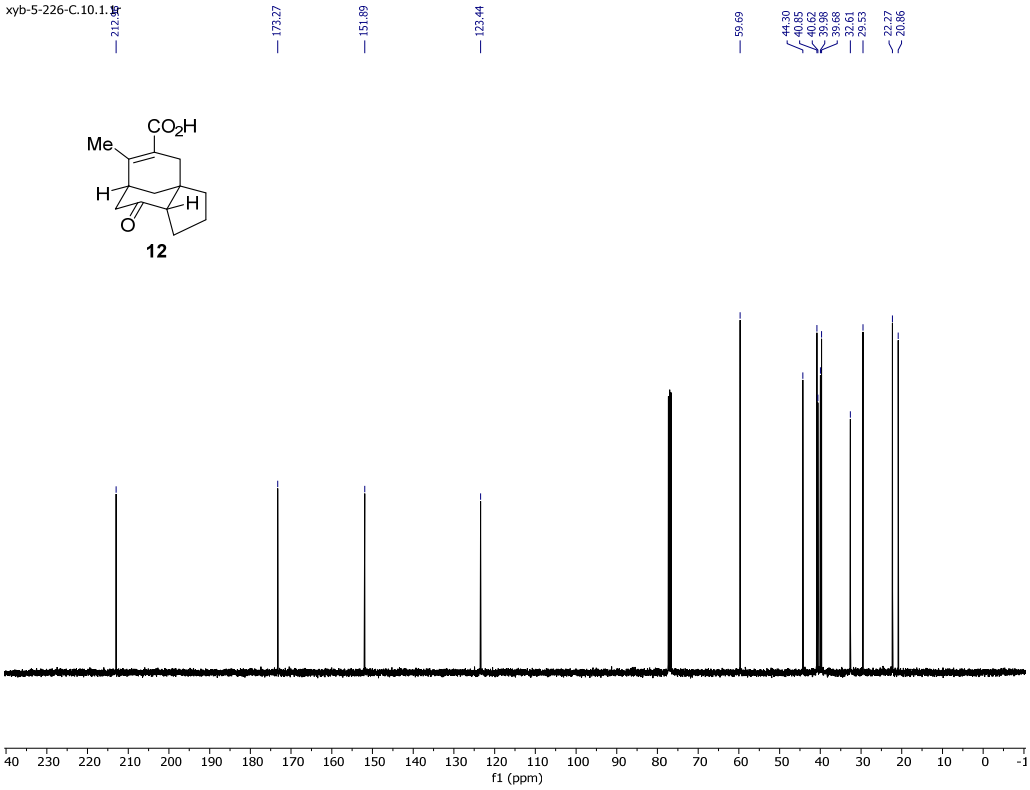
^{13}C-NMR spectrum of **5** in $CDCl_3$, 101 MHz



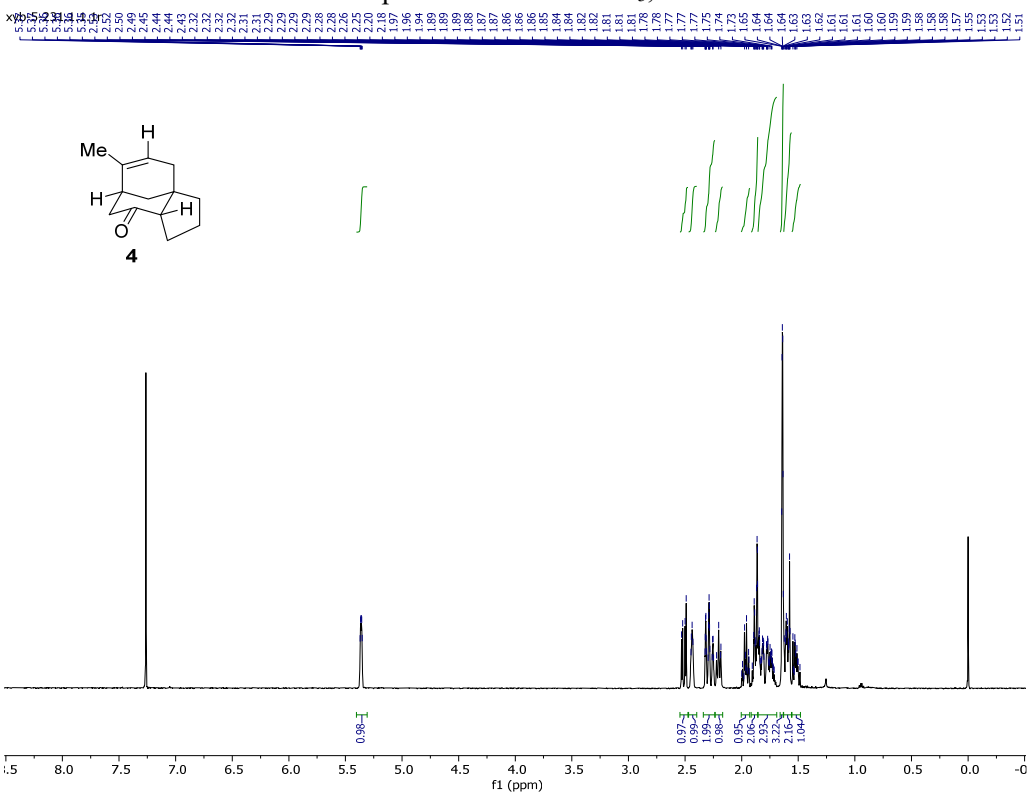
^{1}H-NMR spectrum of **12** in $CDCl_3$, 500 MHz



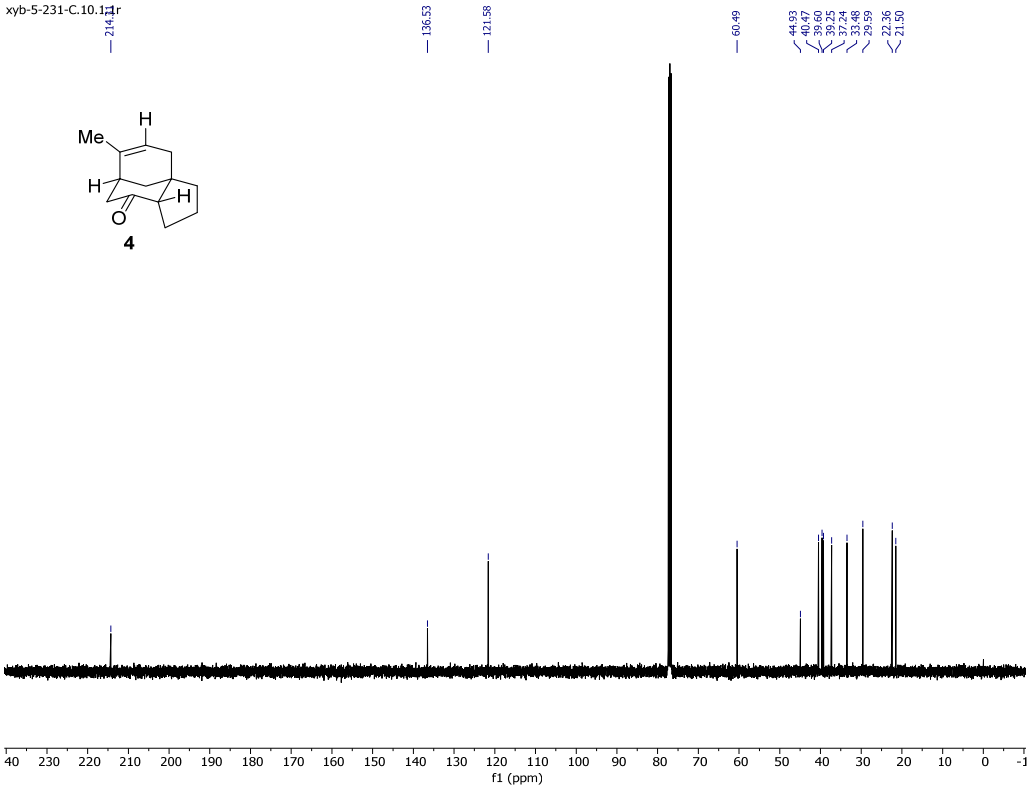
^{13}C-NMR spectrum of **12** in $CDCl_3$, 101 MHz



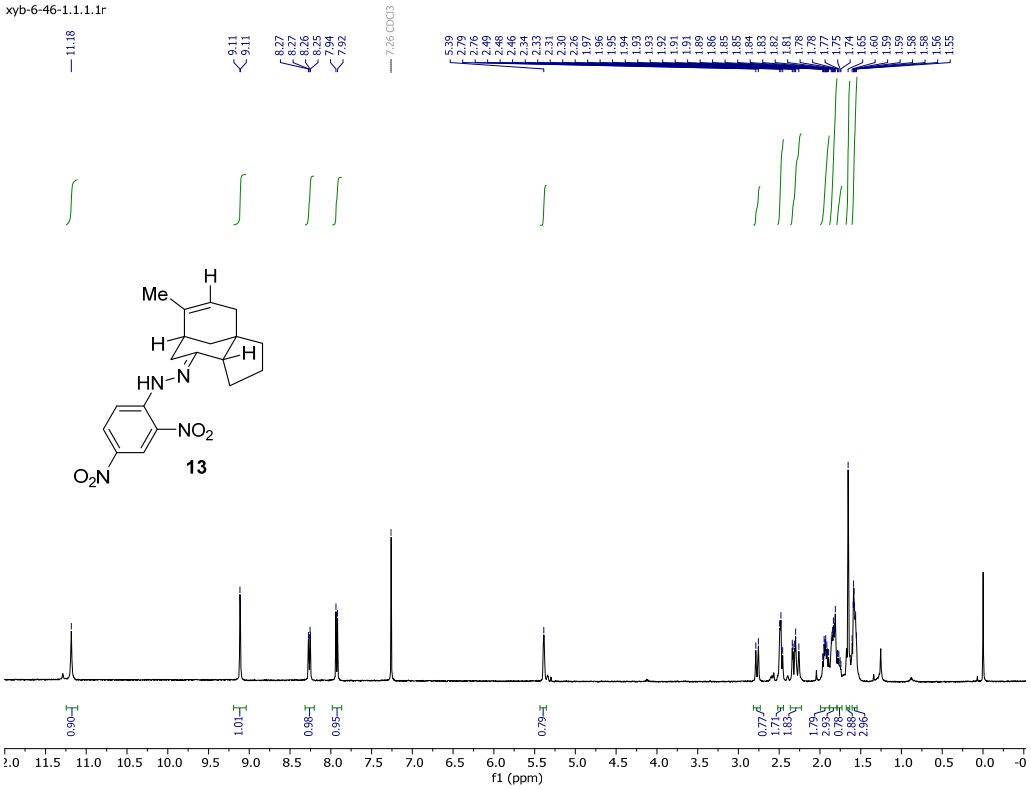
^{1}H-NMR spectrum of **4** in $CDCl_3$, 500 MHz



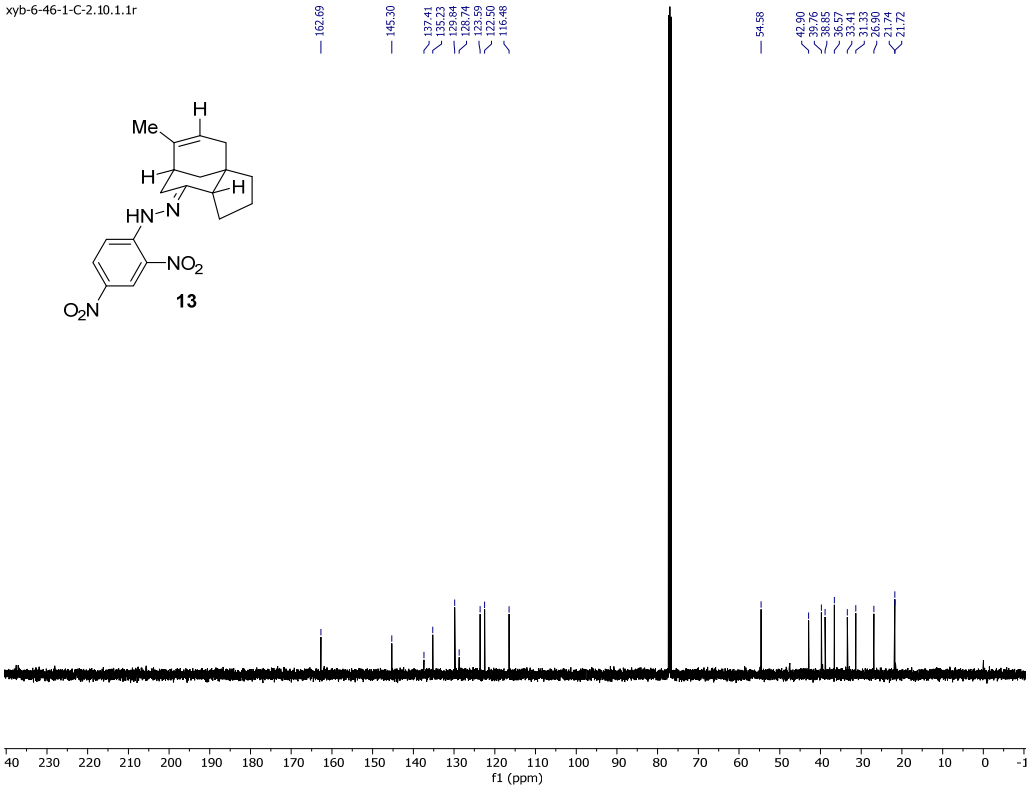
^{13}C-NMR spectrum of **4** in $CDCl_3$, 101 MHz



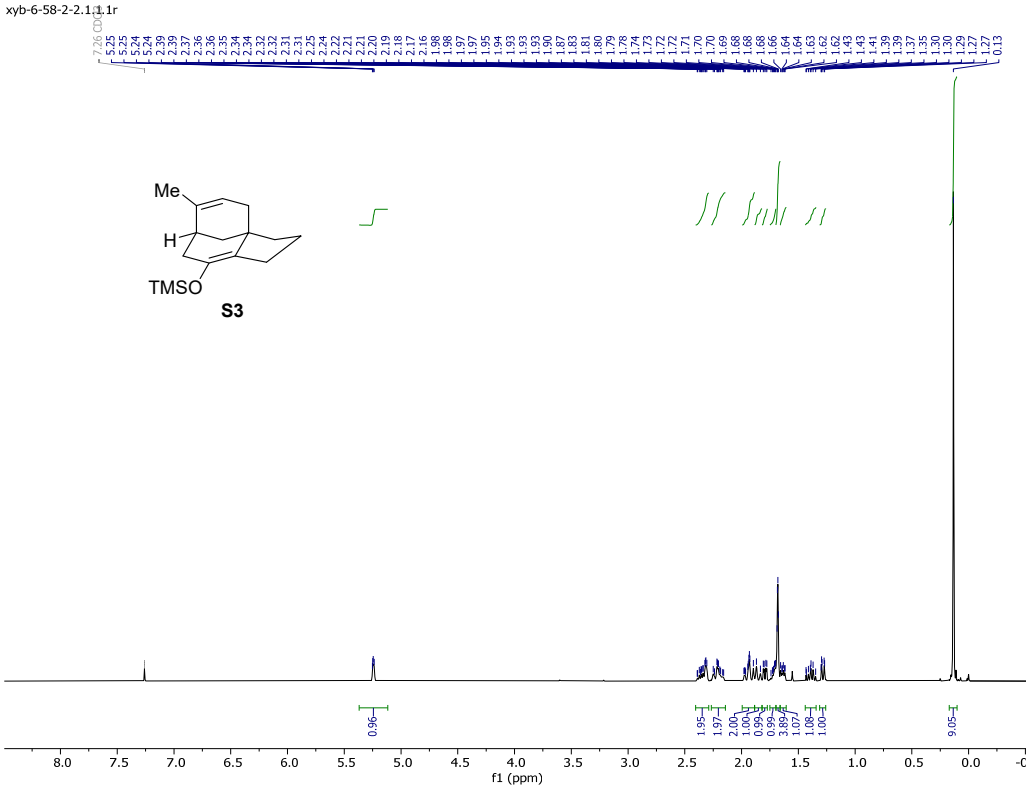
^{1}H-NMR spectrum of **13** in $CDCl_3$, 500 MHz



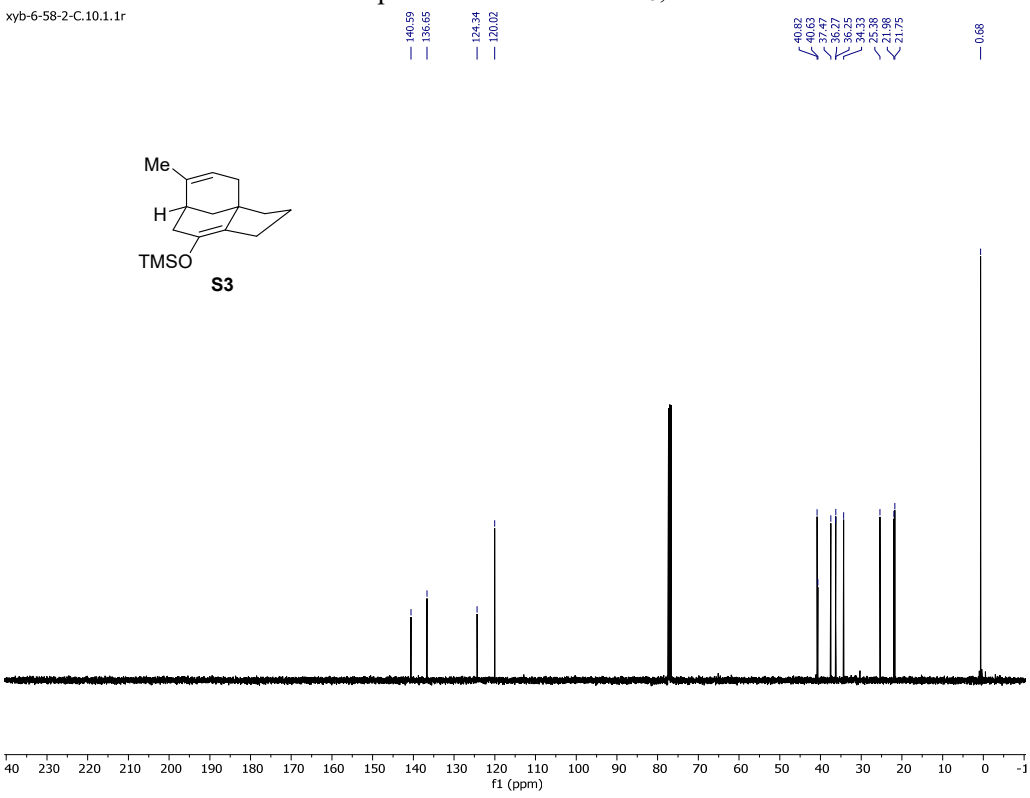
^{13}C-NMR spectrum of **13** in $CDCl_3$, 101 MHz



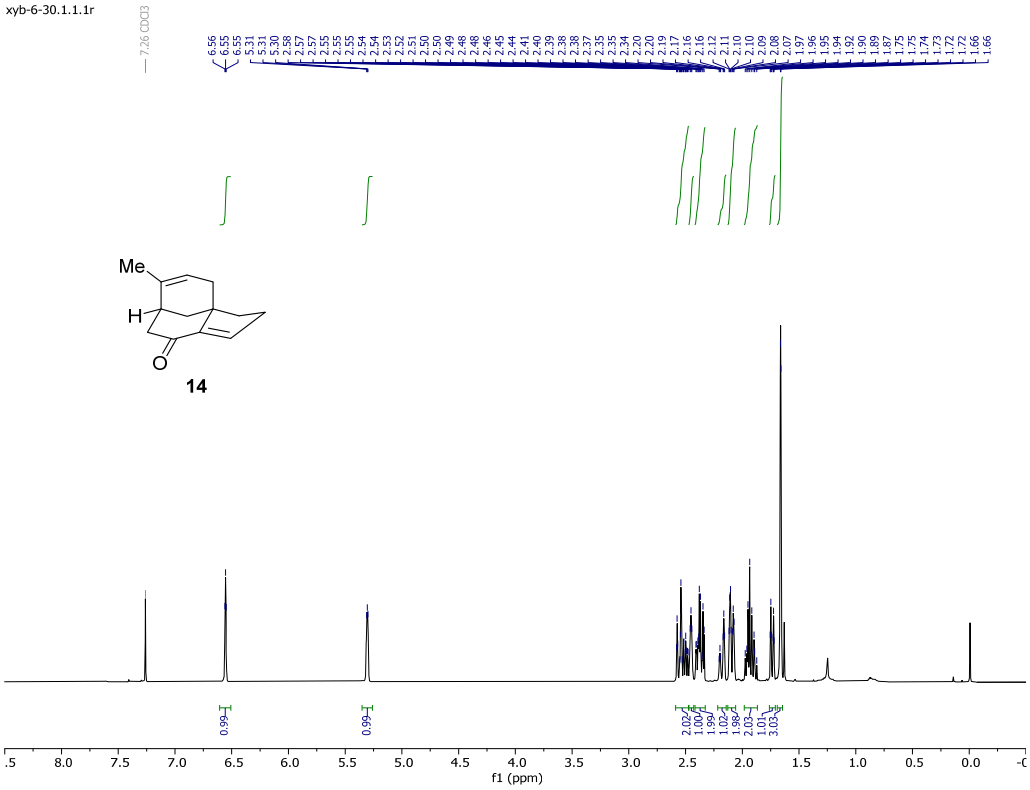
^{1}H-NMR spectrum of **S3** in $CDCl_3$, 500 MHz



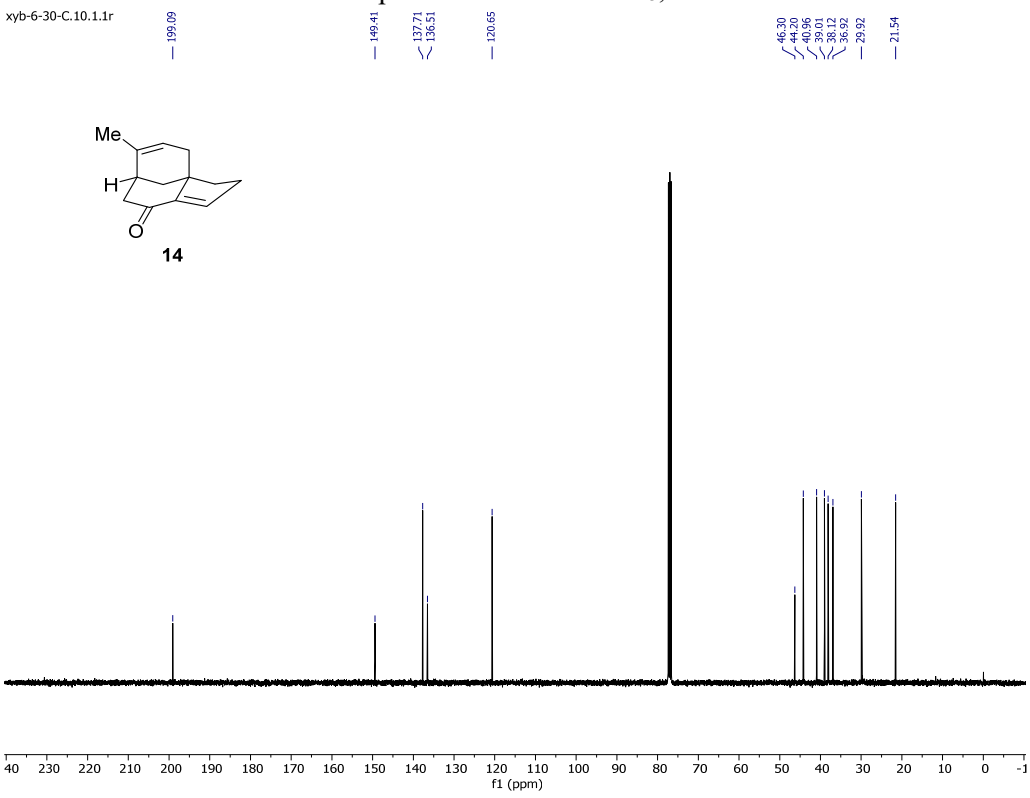
^{13}C-NMR spectrum of **S3** in $CDCl_3$, 101 MHz



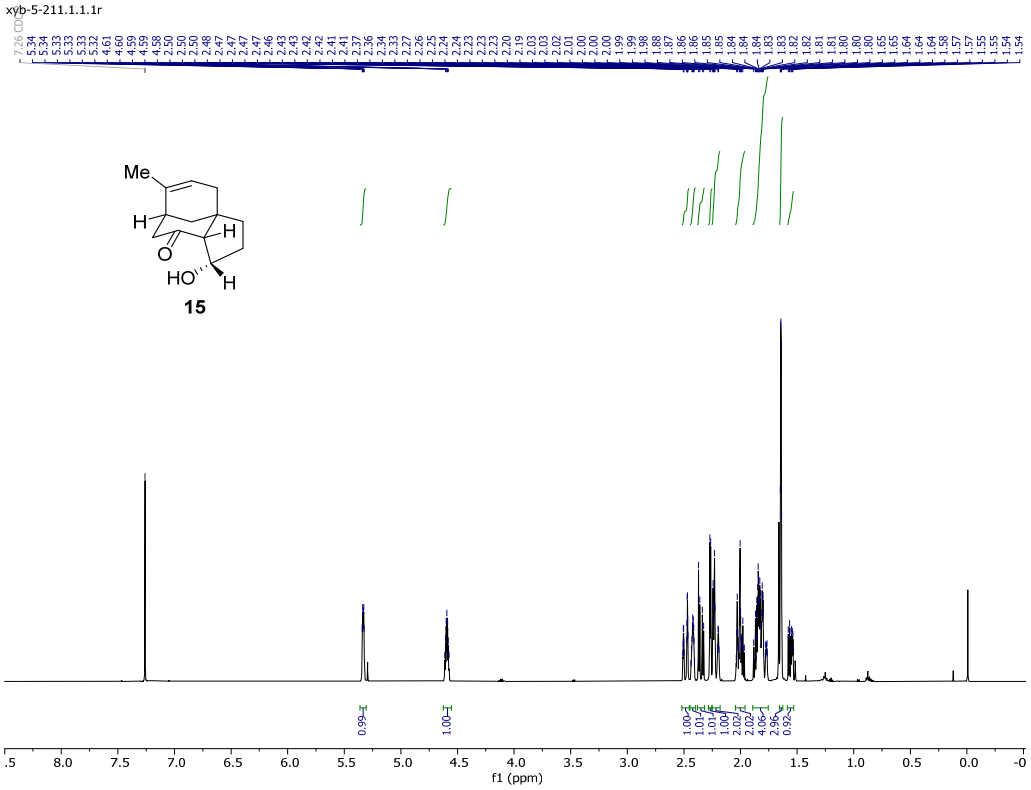
^{1}H-NMR spectrum of **14** in $CDCl_3$, 500 MHz



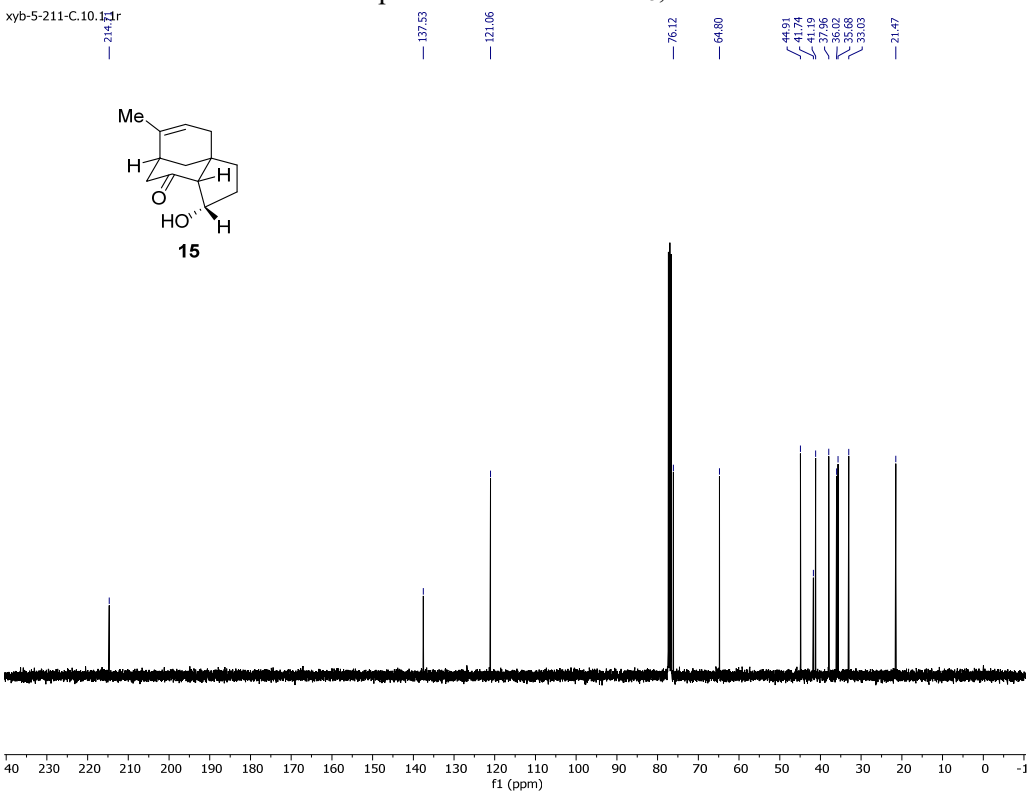
^{13}C-NMR spectrum of **14** in $CDCl_3$, 101 MHz



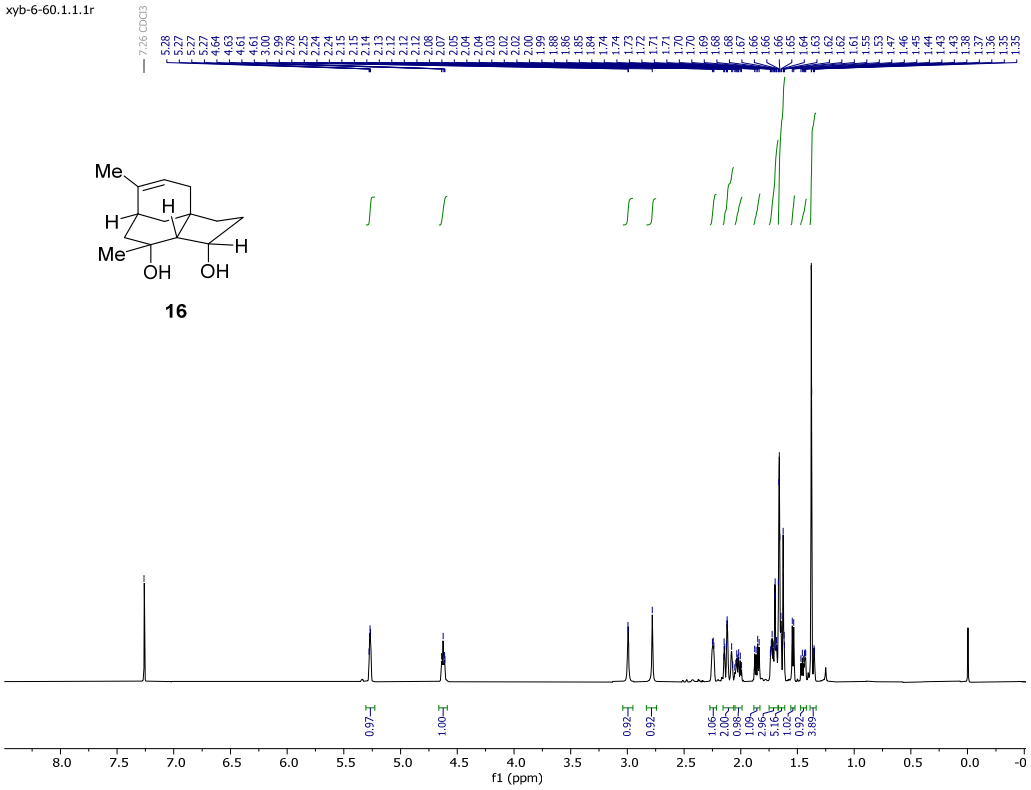
^{1}H-NMR spectrum of **15** in $CDCl_3$, 500 MHz



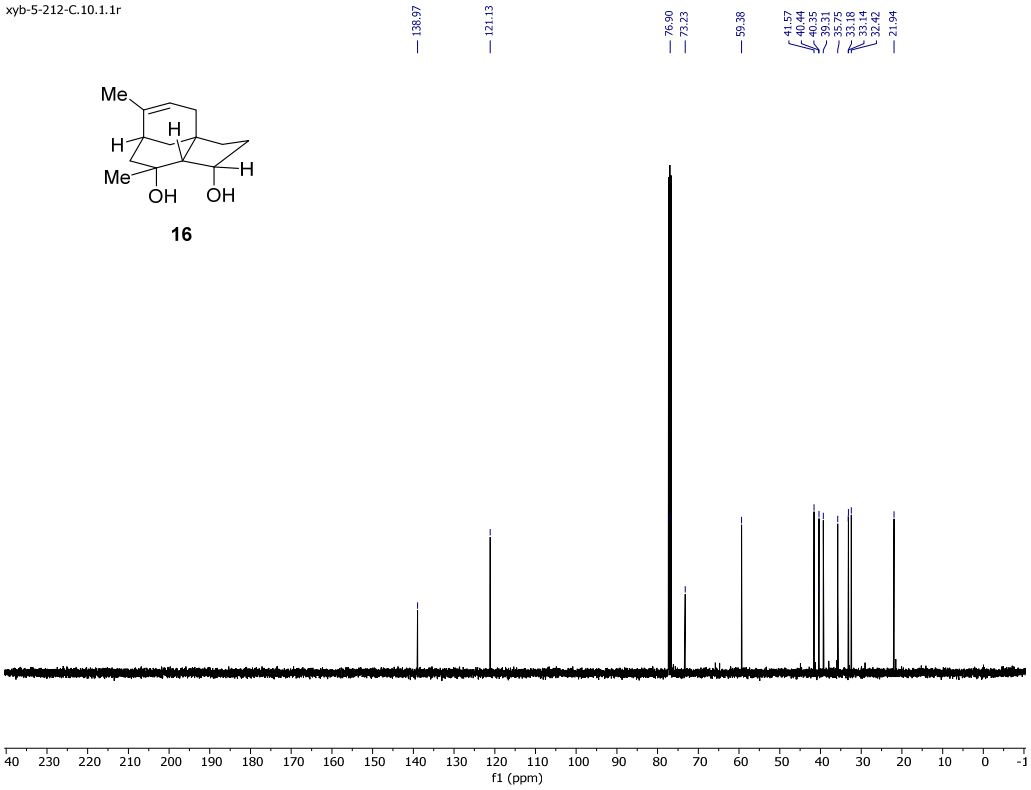
^{13}C-NMR spectrum of **15** in $CDCl_3$, 101 MHz



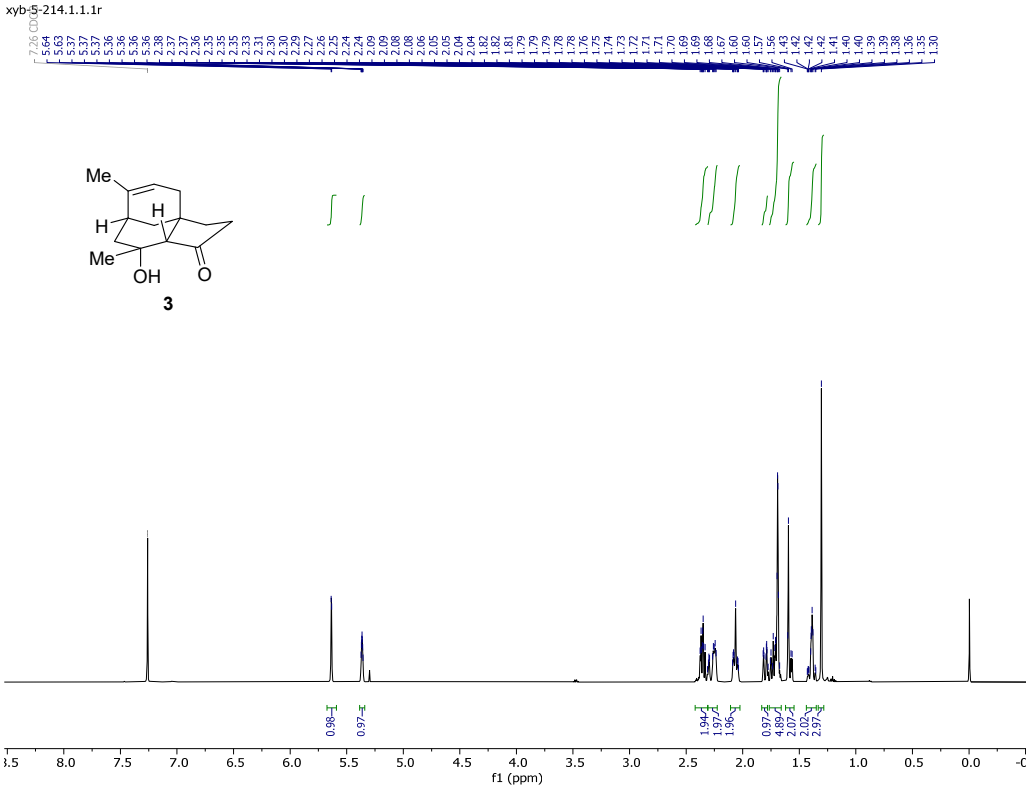
^{1}H-NMR spectrum of **16** in $CDCl_3$, 500 MHz



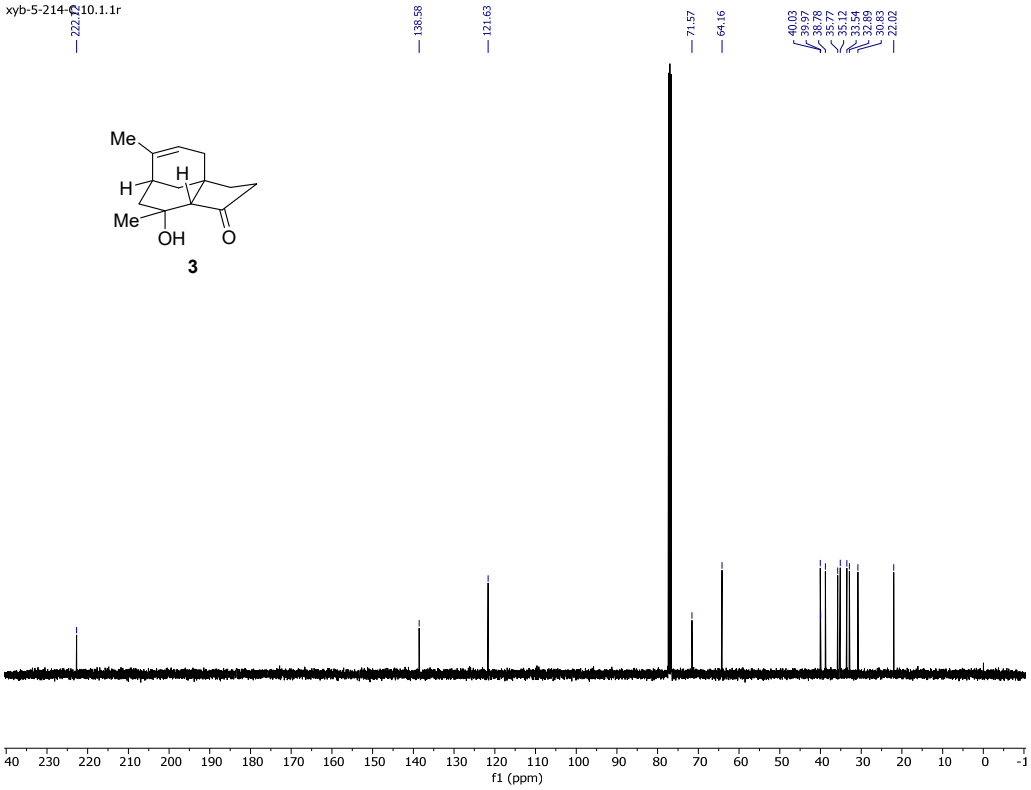
^{13}C-NMR spectrum of **16** in $CDCl_3$, 101 MHz



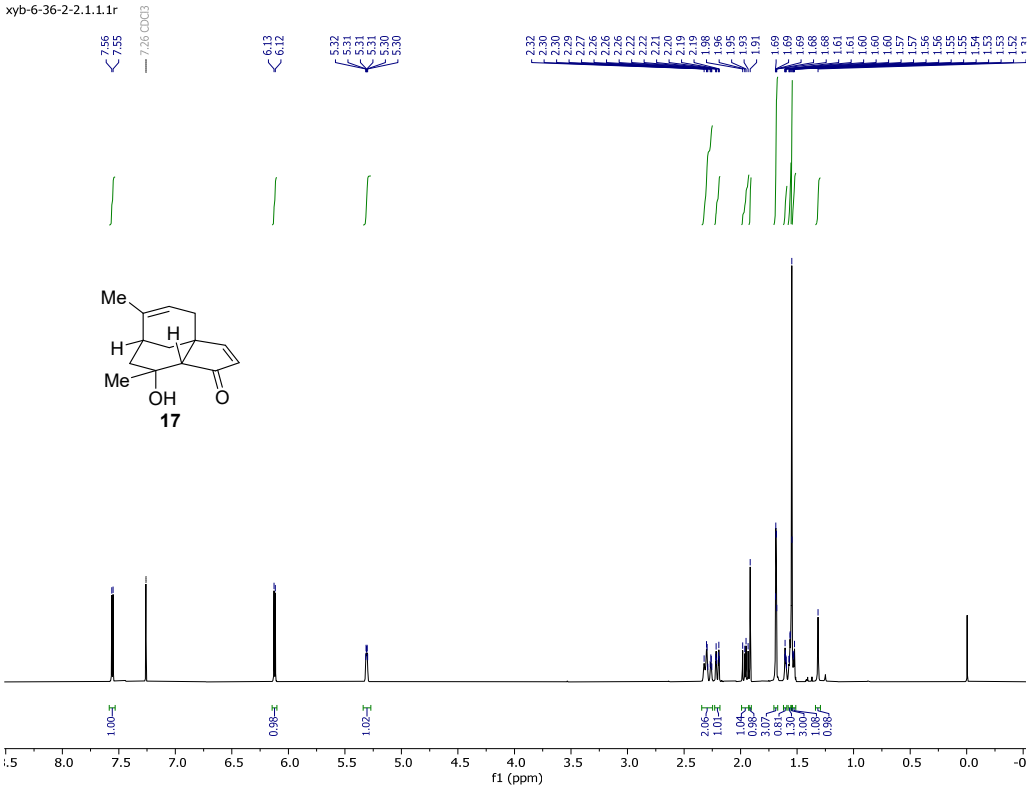
^{1}H-NMR spectrum of **3** in $CDCl_3$, 500 MHz



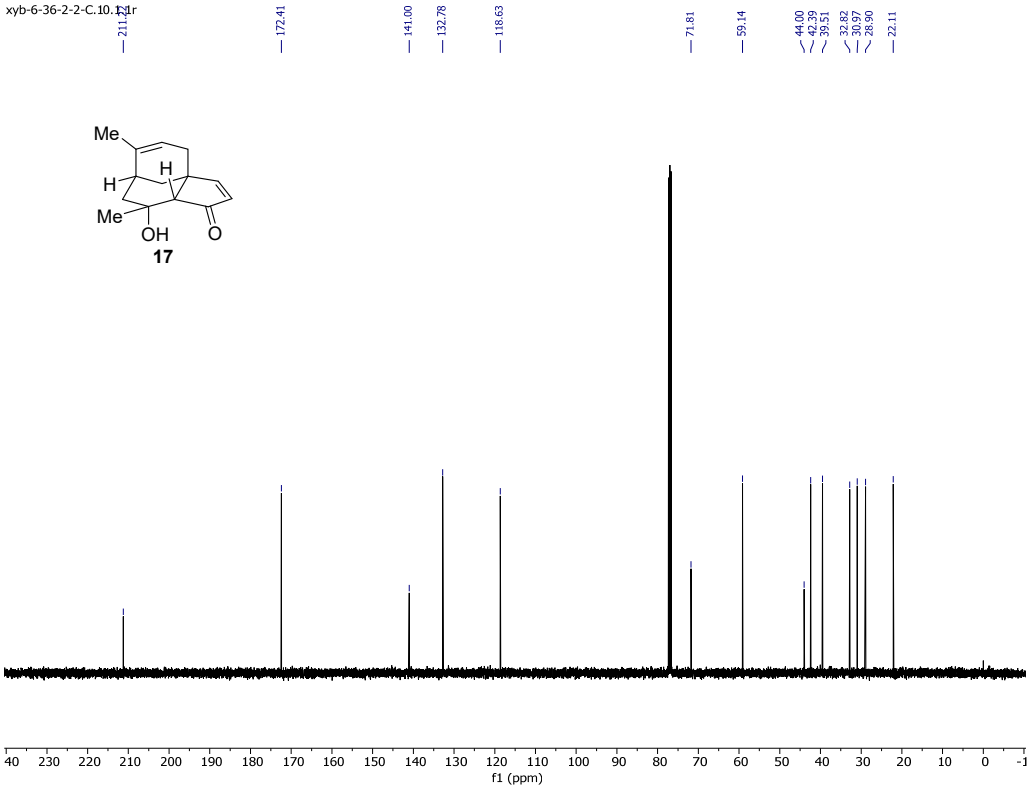
^{13}C-NMR spectrum of **3** in $CDCl_3$, 101 MHz



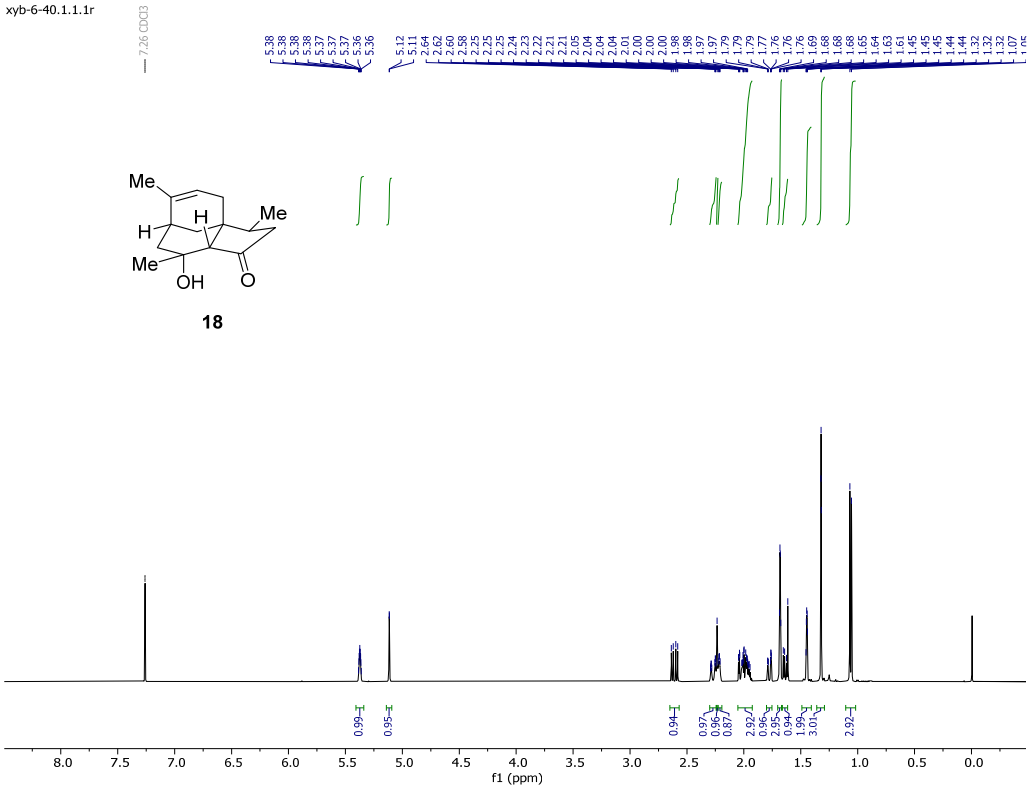
^{1}H-NMR spectrum of **17** in $CDCl_3$, 500 MHz



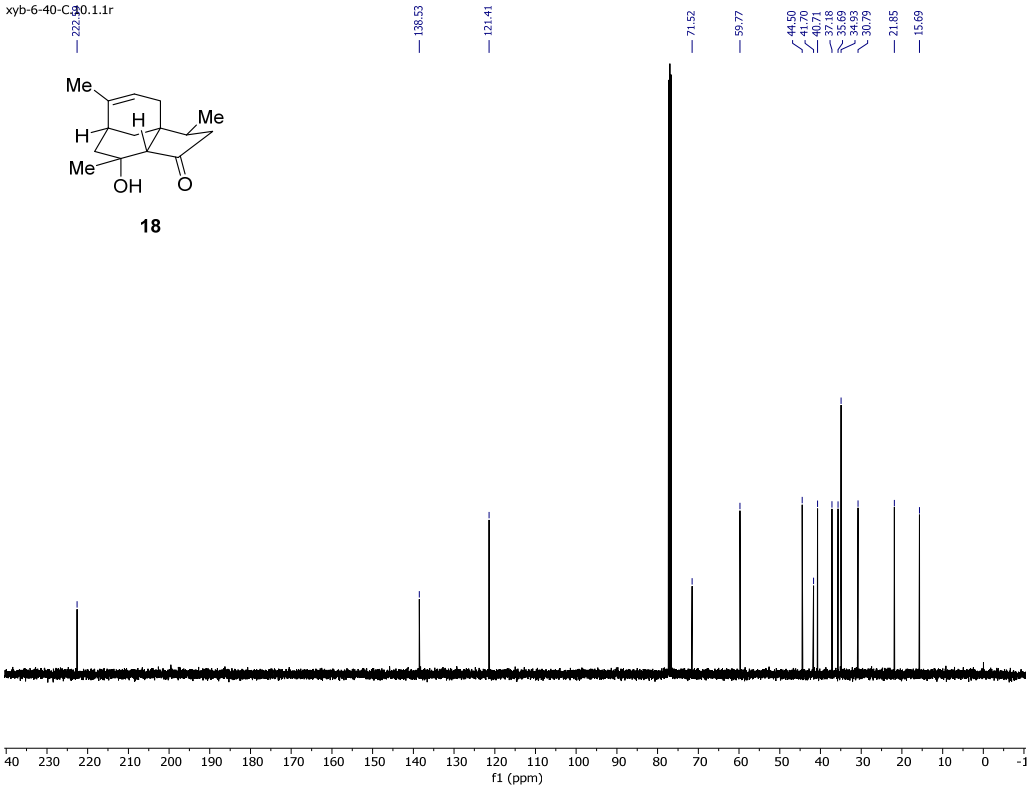
^{13}C-NMR spectrum of **17** in $CDCl_3$, 101 MHz



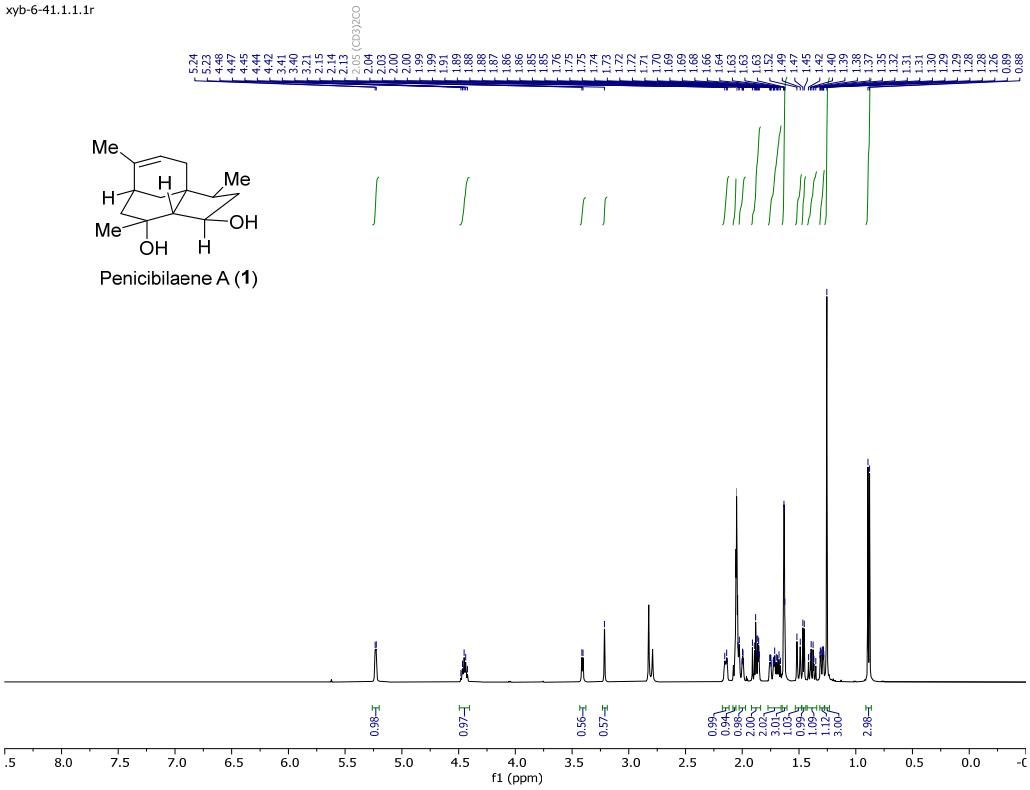
^{1}H-NMR spectrum of **18** in $CDCl_3$, 500 MHz



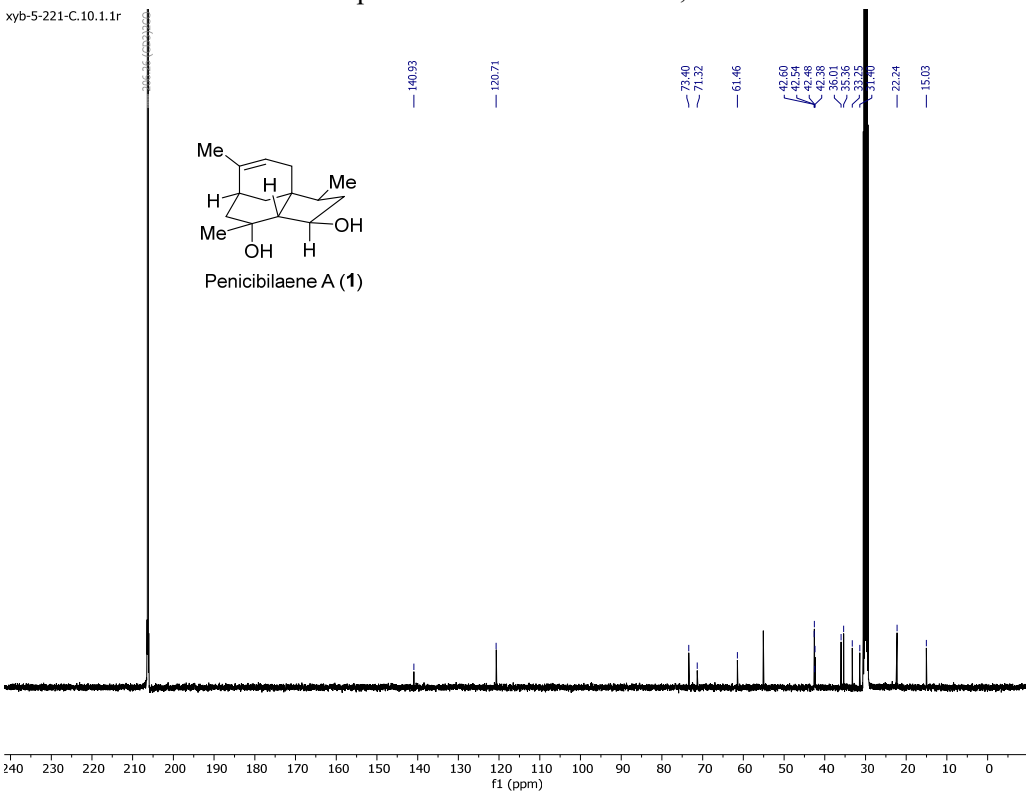
^{13}C-NMR spectrum of **18** in $CDCl_3$, 101 MHz



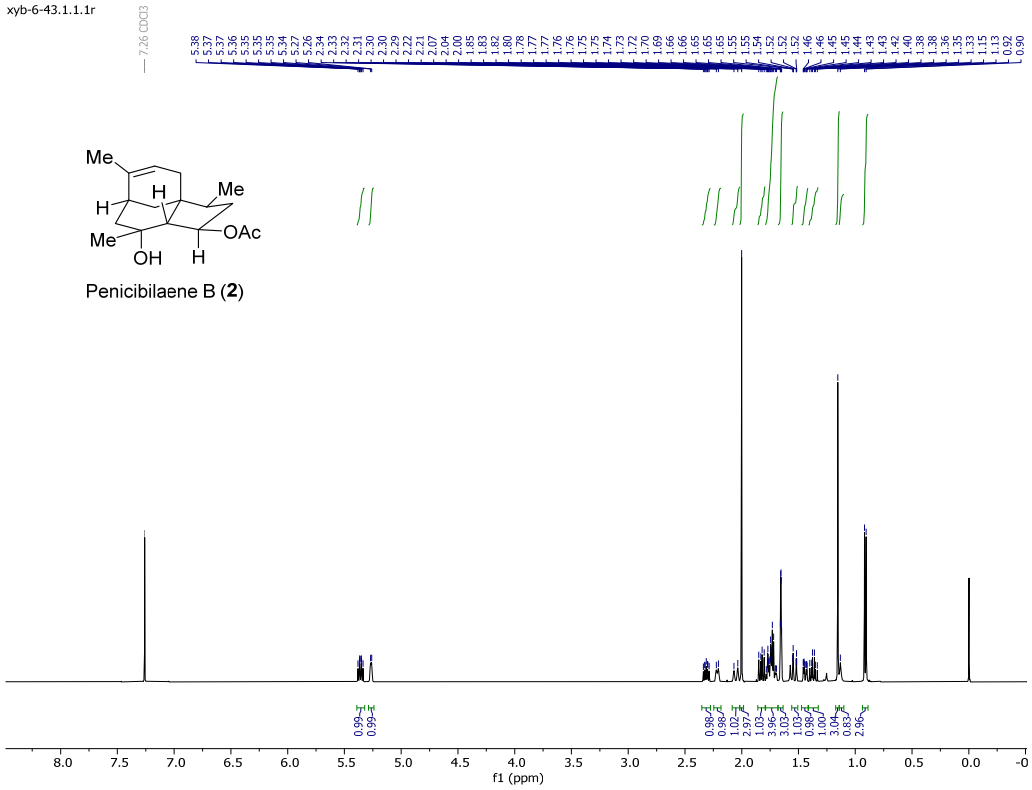
^{1}H-NMR spectrum of **1** in acetone-D6, 500 MHz



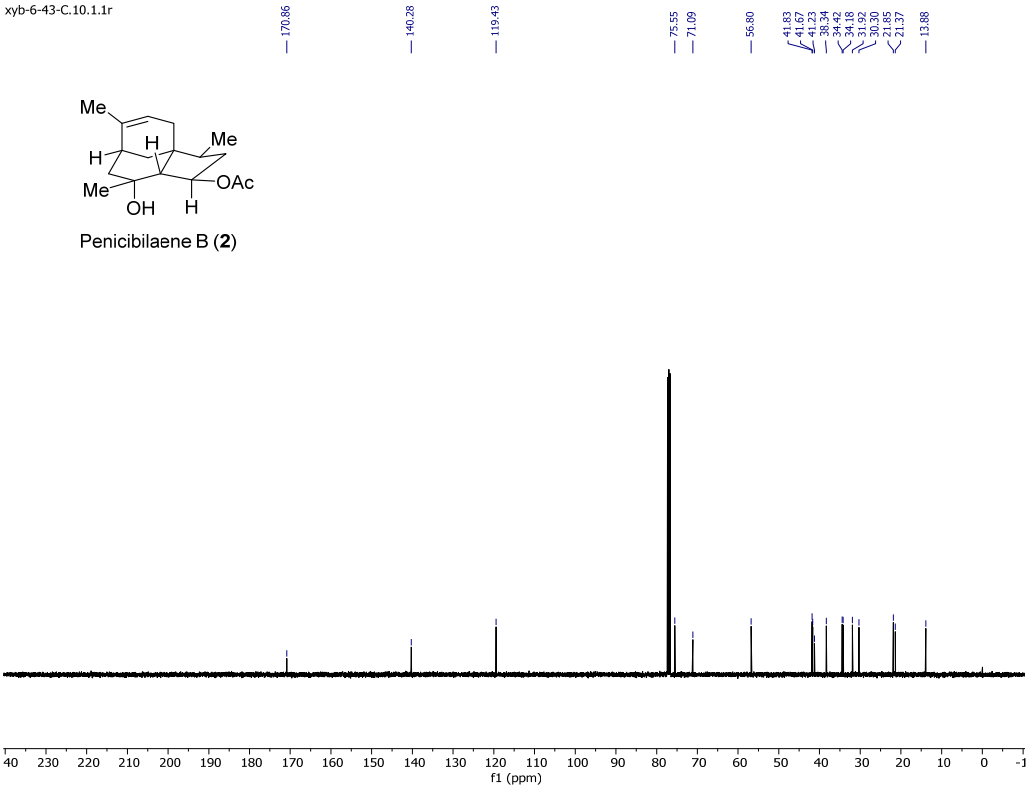
^{13}C-NMR spectrum of **1** in acetone-D6, 101 MHz



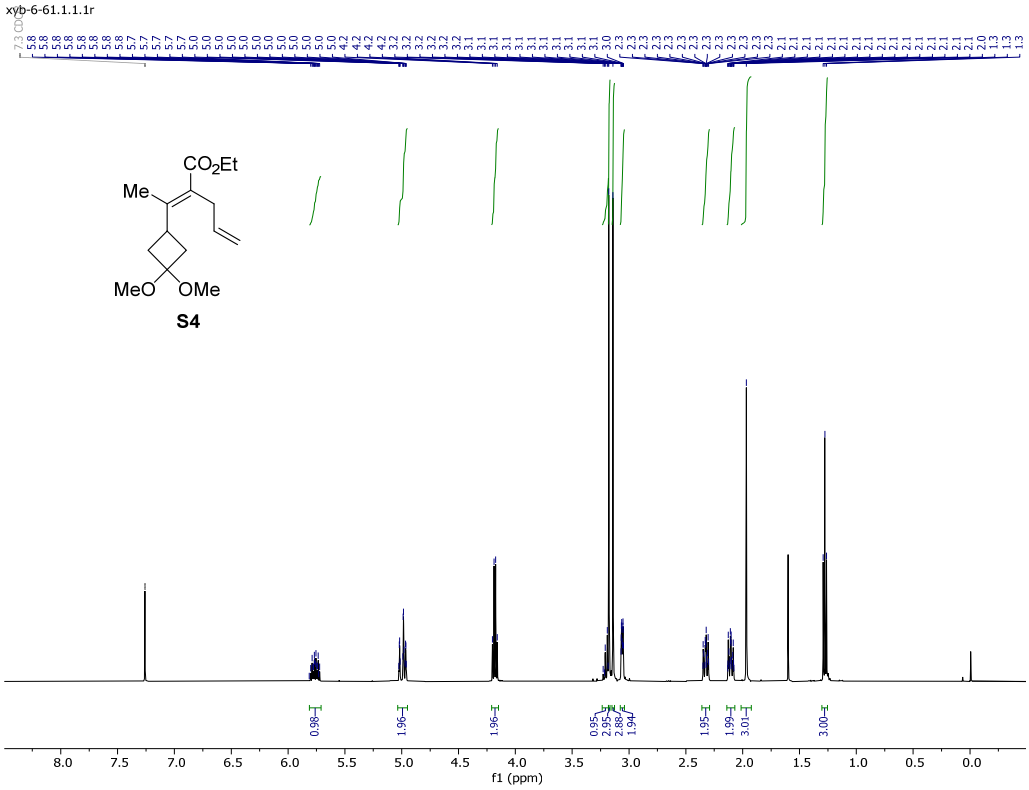
^{1}H-NMR spectrum of **2** in $CDCl_3$, 500 MHz



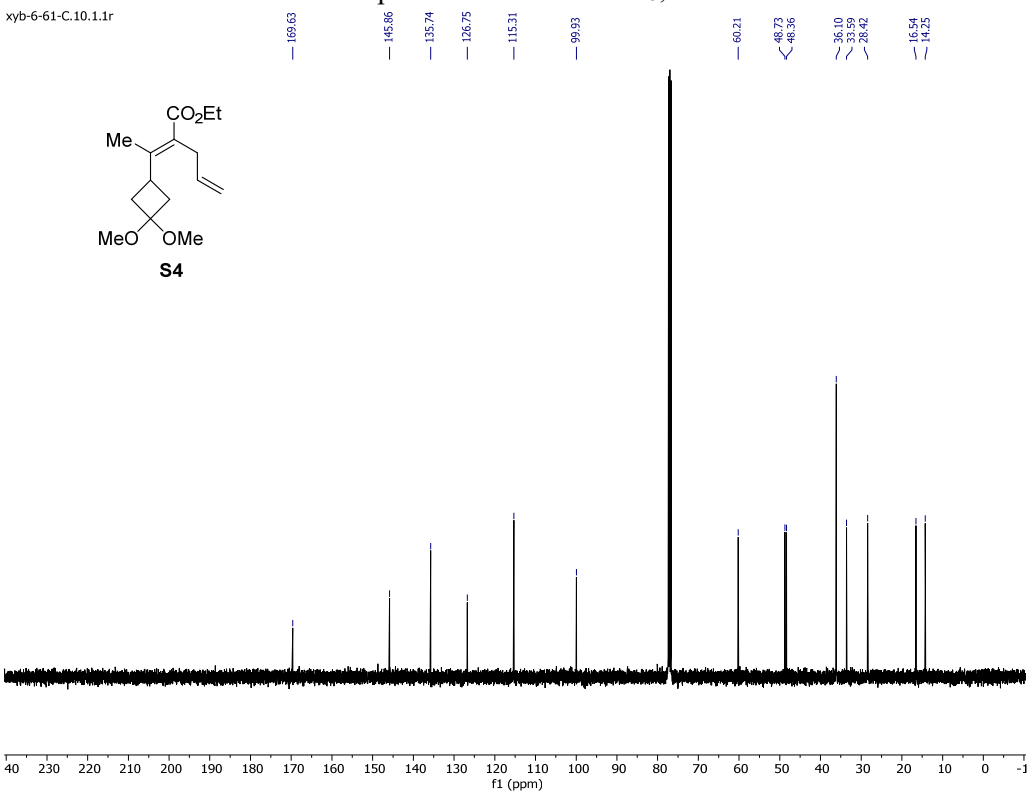
^{13}C-NMR spectrum of **2** in $CDCl_3$, 101 MHz



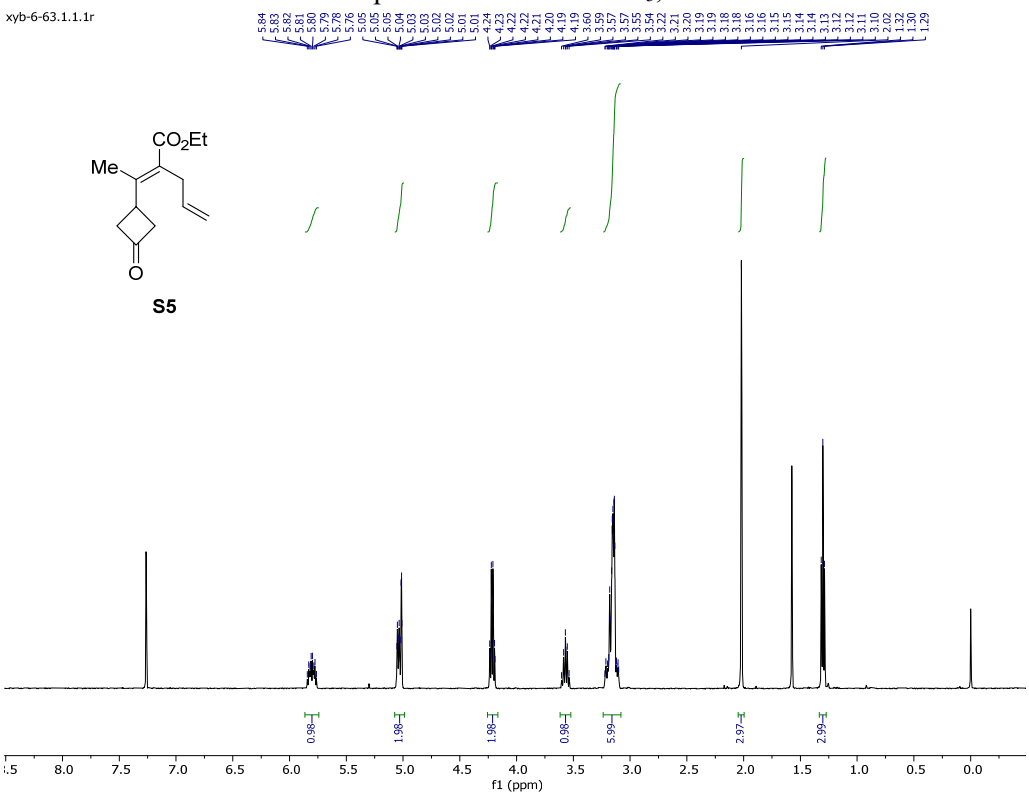
^{1}H-NMR spectrum of **S4** in $CDCl_3$, 500 MHz



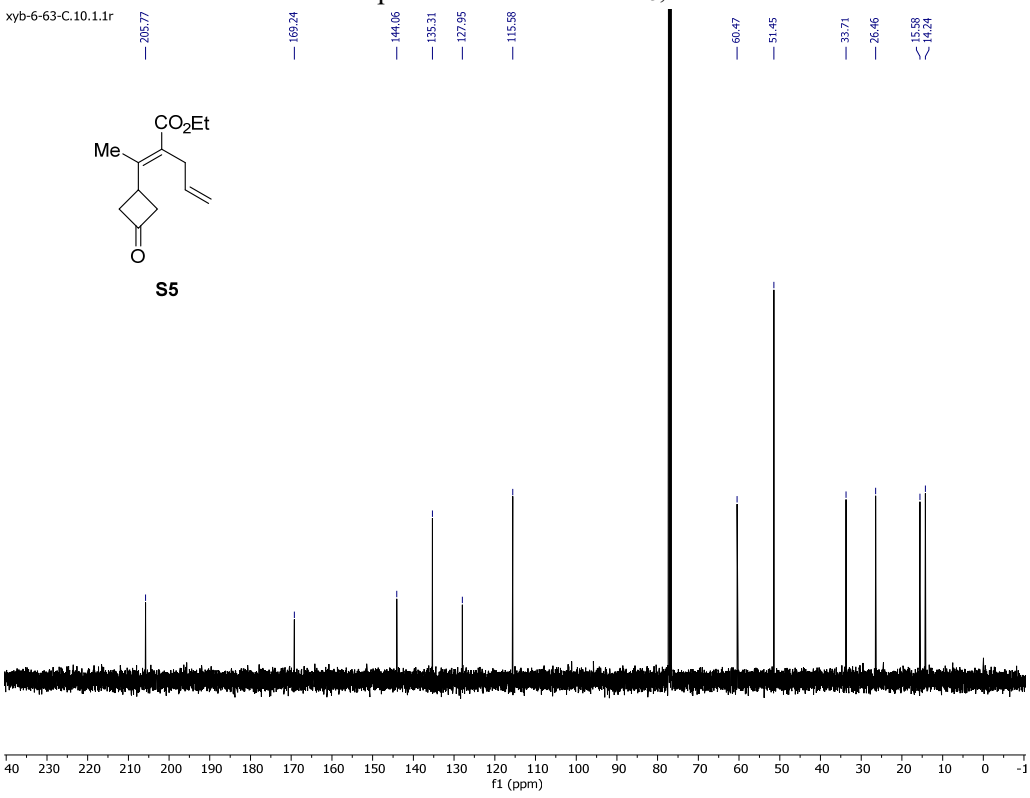
^{13}C-NMR spectrum of **S4** in $CDCl_3$, 101 MHz



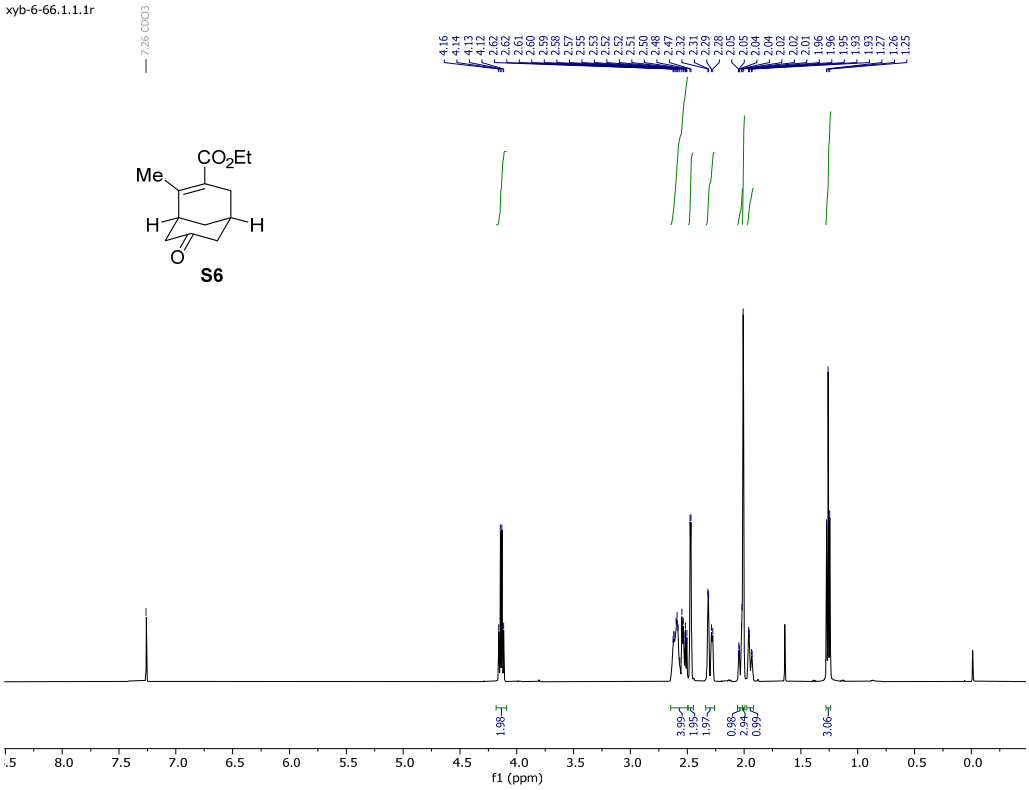
^{1}H-NMR spectrum of **S5** in $CDCl_3$, 500 MHz



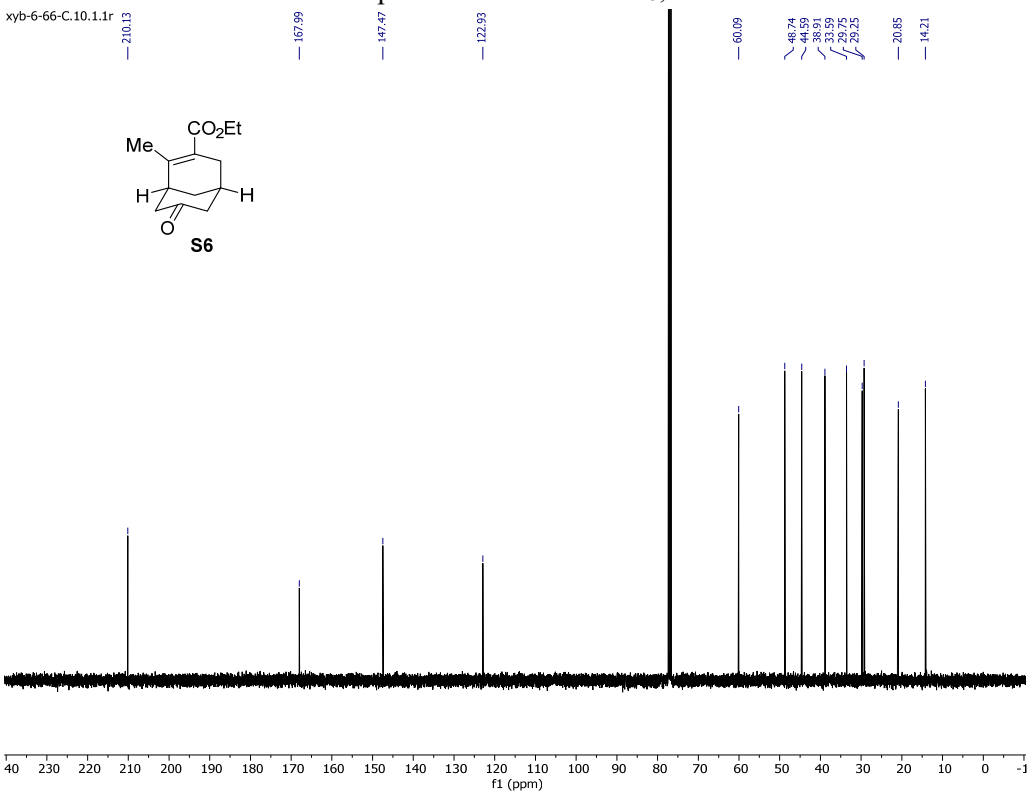
^{13}C-NMR spectrum of **S5** in $CDCl_3$, 101 MHz



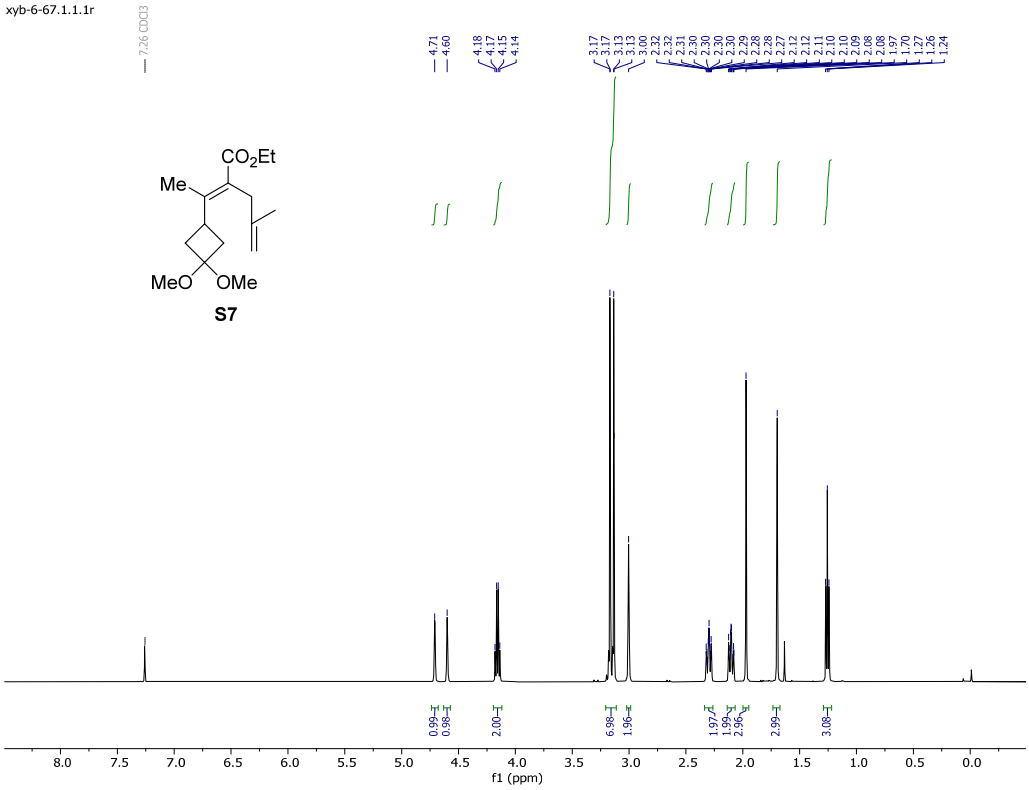
^{1}H-NMR spectrum of **S6** in $CDCl_3$, 500 MHz



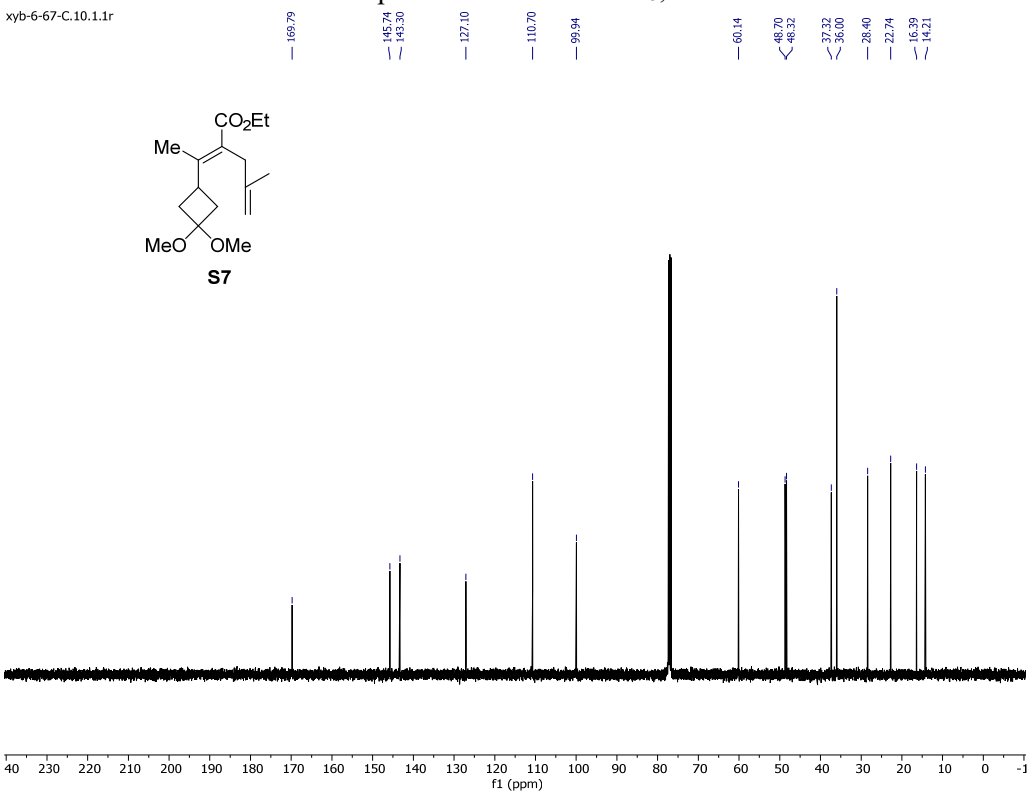
^{13}C-NMR spectrum of **S6** in $CDCl_3$, 101 MHz



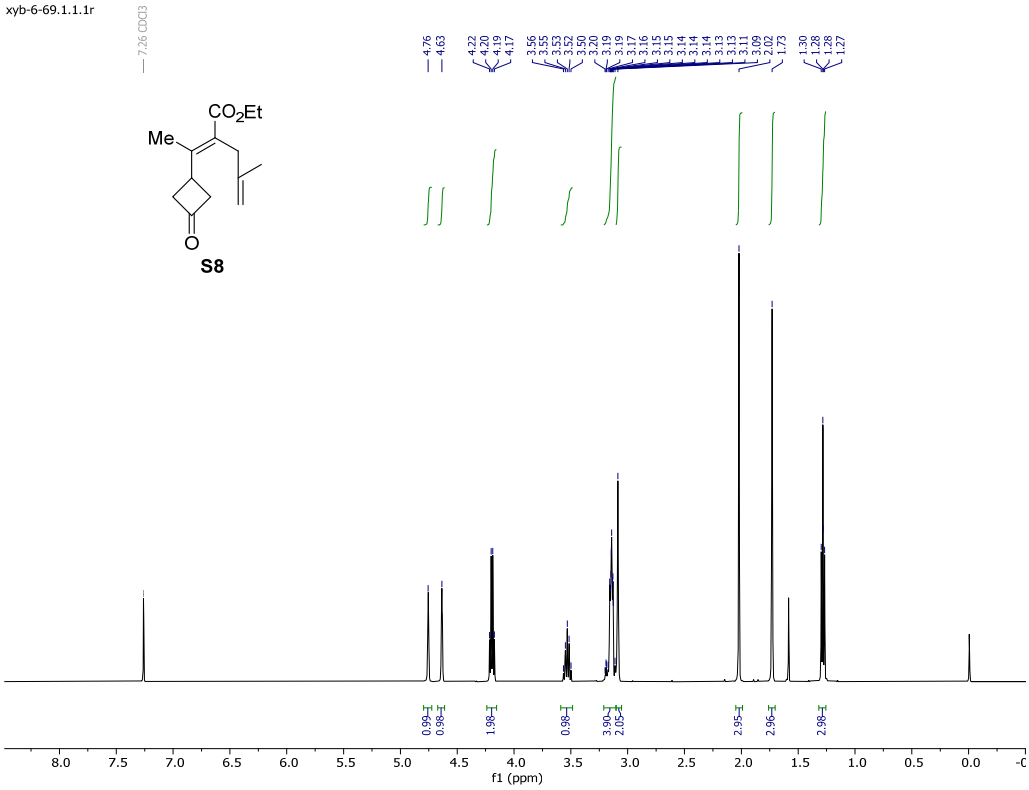
^{1}H-NMR spectrum of **S7** in $CDCl_3$, 500 MHz



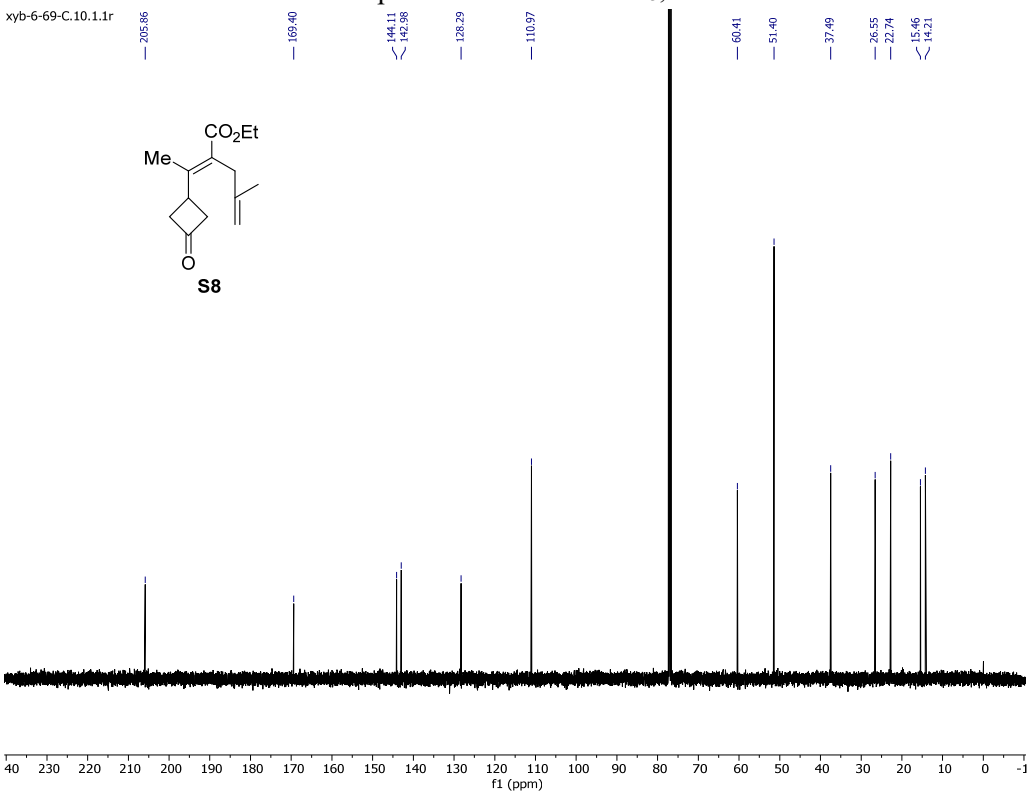
^{13}C-NMR spectrum of **S7** in $CDCl_3$, 101 MHz



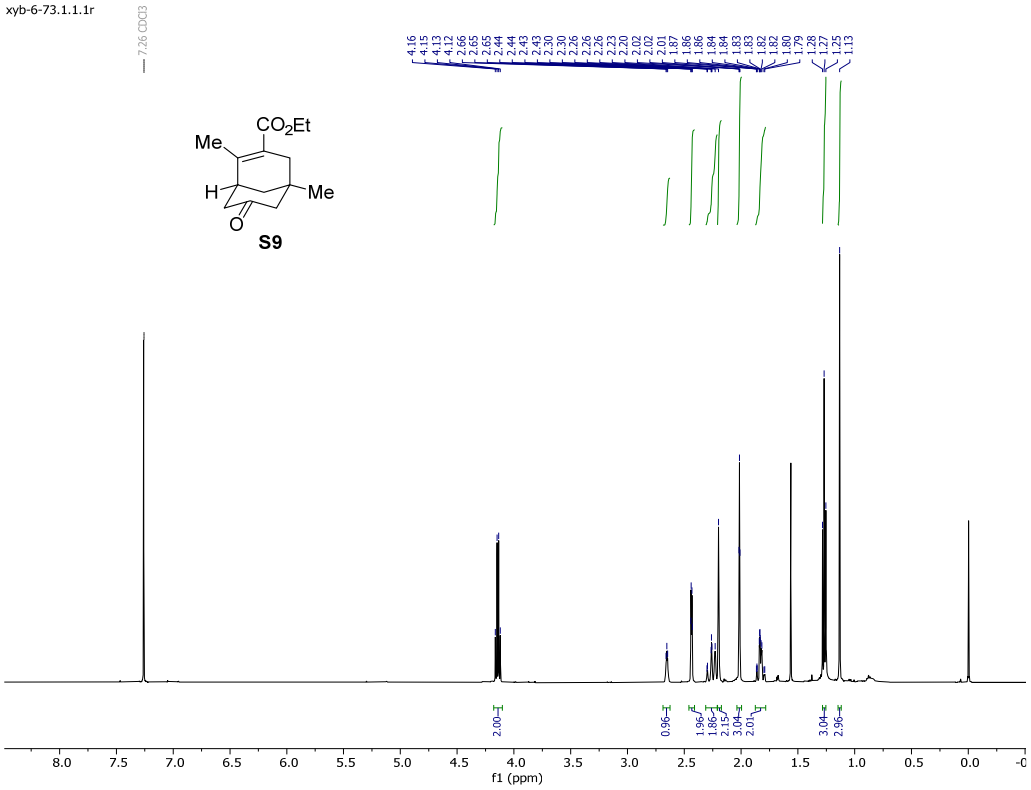
^{1}H-NMR spectrum of **S8** in $CDCl_3$, 500 MHz



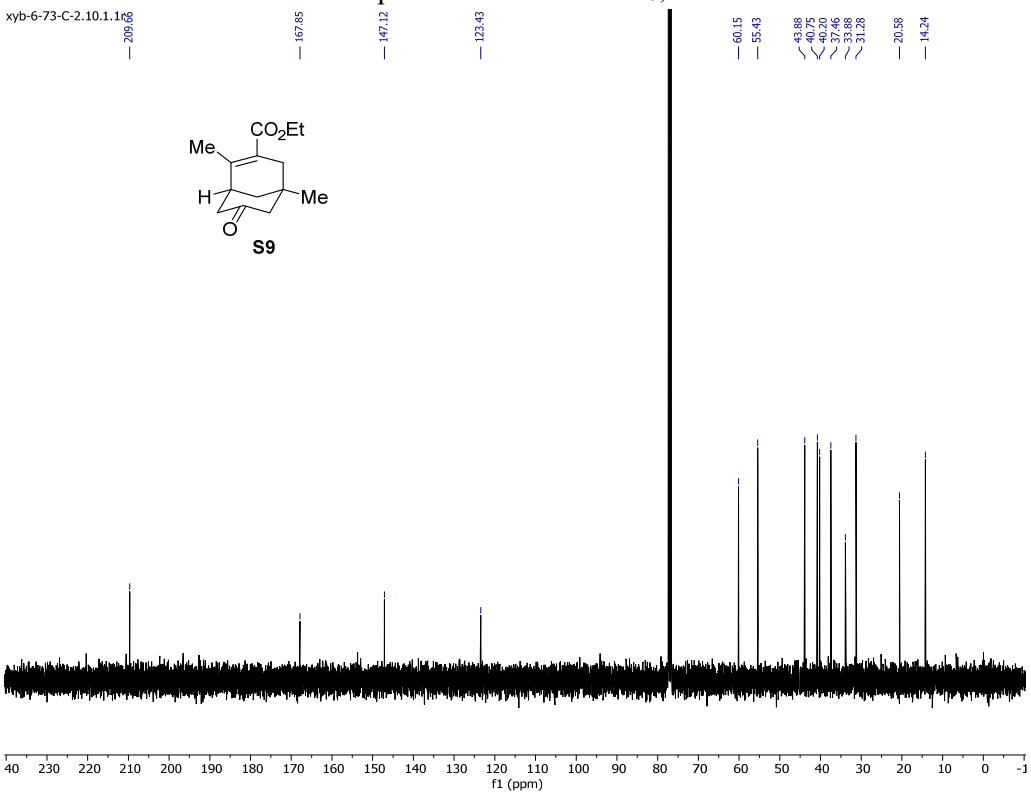
^{13}C-NMR spectrum of **S8** in $CDCl_3$, 101 MHz



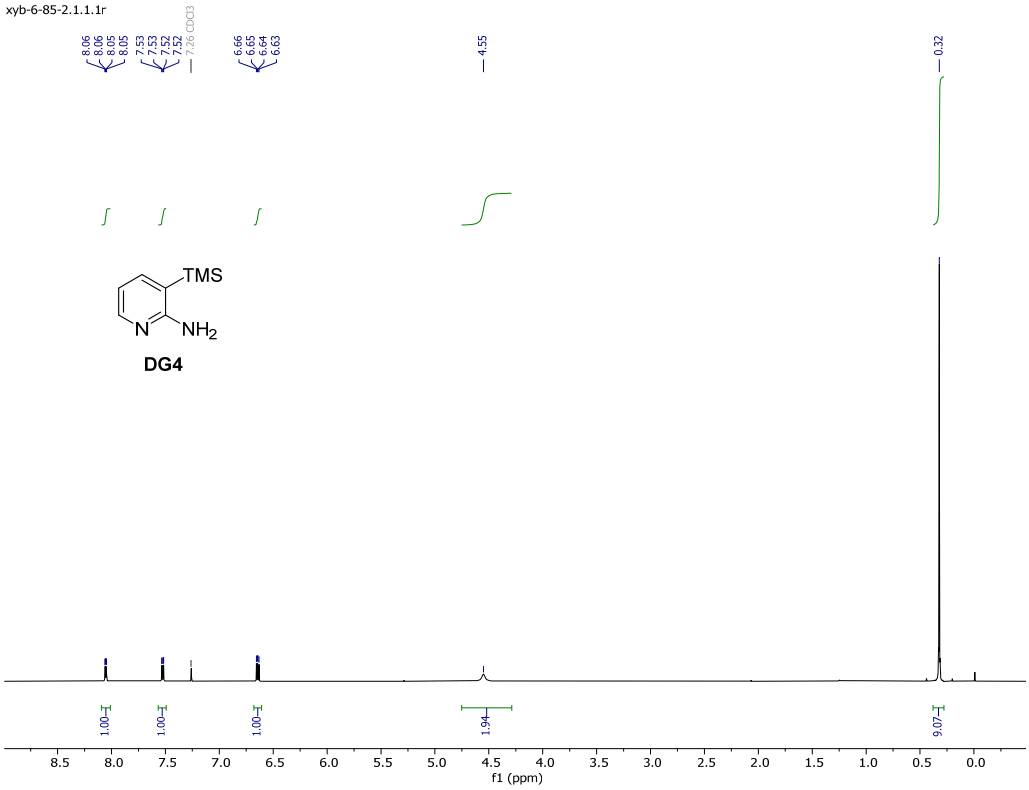
^{1}H-NMR spectrum of **S9** in $CDCl_3$, 500 MHz



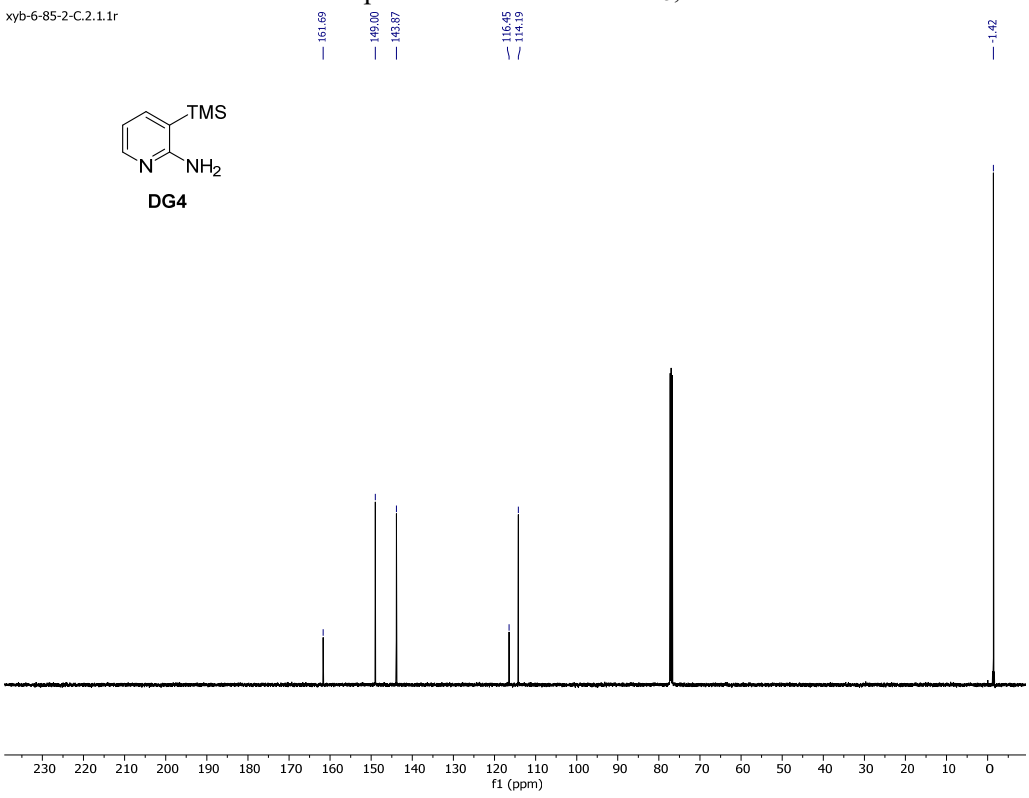
^{13}C-NMR spectrum of **S9** in $CDCl_3$, 101 MHz



^{1}H-NMR spectrum of **DG4** in $CDCl_3$, 500 MHz



^{13}C-NMR spectrum of **DG4** in $CDCl_3$, 101 MHz



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