**Supporting Information**

# Rh(I)-Catalyzed [(3+2)+1] Cycloaddition of 1-Yne/Ene-Vinylcyclopropanes and CO: Homologous Pauson-Khand Reaction and Total Synthesis of (±)-α-Agarofuran

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## 1. General

Air and moisture sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry argon. Similarly sensitive liquids and solutions were transferred via syringe. Reactions were stirred using Teflon-coated magnetic stir bars. Elevated temperatures were maintained using Thermostat-controlled silicone oil baths. Organic solutions were concentrated using a Büchi rotary evaporator with a desktop vacuum pump. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium and benzophenone prior to use. Dichloromethane was distilled from $CaH_2$ prior to use. Dichloroethane was distilled from $P_2O_5$ prior to use. Synthetic reagents were purchased from Acros, Aldrich, and Alfa Aesar and used without further purification, unless otherwise indicated. Analytical TLC was performed with 0.25 mm silica gel G plates with a 254 nm fluorescent indicator. The TLC plates were visualized by ultraviolet light and treatment with phosphomolybdic acid stain followed by gentle heating. Purification of products was accomplished by flash chromatography on silica gel and the purified compounds showed a single spot by analytical TLC.

NMR spectra were measured on Varian Mercury 200 ($^1$H at 200 MHz, $^{13}$C at 50 MHz), Varian Mercury Plus 300 ($^1$H at 300 MHz, $^{13}$C at 75 MHz), Bruker ARX 400 ($^1$H at 400 MHz, $^{13}$C at 100 MHz), and Bruker AVANCE 600 ($^1$H at 600 MHz, $^{13}$C at 150 MHz) nuclear magnetic resonance spectrometers. Data for $^1$H-NMR spectra are reported as follows: chemical shift (ppm, referenced to TMS; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dm = doublet of multiplet, ddd = doublet of doublet of doublets, tdd = triplet of doublet of doublets, m = multiplet), coupling constant (Hz), and integration. Data for $^{13}$C-NMR are reported in terms of chemical shift (ppm) relative to residual solvent peak ($CDCl_3$: 77.0 ppm). 1D nOe experiments were conducted on a Bruker AVANCE 600 nuclear magnetic resonance spectrometer. Infrared spectra were recorded on Mettler-Toledo ReactIR iC10 system with an SiComp probe and are reported in wavenumbers ($cm^{-1}$). High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer (ESI). Elemental analysis was performed on a Elementar Vario MICRO CUBE instrument.

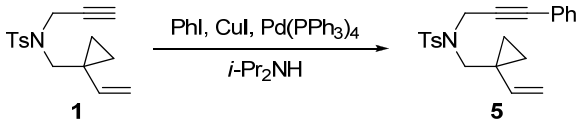
Abbreviations:
DCE = 1,2-dichloroethane
DCM = dichloromethane
DEAD = diethyl azodicarboxylate
DIBAL-H = diisobutylaluminum hydride
dppp = 1,3-bis(diphenylphosphino)propane
EA = ethyl acetate
LDA = lithium diisopropylamide
nOe = nuclear Overhauser effect
PCC = pyridinium chlorochromate
PE = petroleum ether
TBAF = tetrabutylammonium fluoride
TBS = *tert*-butyldimethylsilyl
THF = tetrahydrofuran
TLC = thin layer chromatography

## 2. Experimental Procedures and Characterization Data

### 2.1 Synthesis of Substrates

Substrates **1**, **3**, **7**, and **15** were synthesized according to published methods.[1] Experimental procedures for the synthesis of substrates **5**, **9**, **11**, **13**, and **17** are given below.

**1-Yne-VCP (5)**

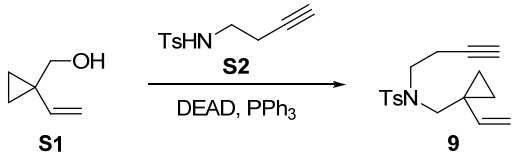



**1** **5**

**1** to **5**: To a stirred solution of 1-yne-VCP **1** (116 mg, 0.40 mmol), $Pd(PPh_3)_4$ (4.6 mg, 4.0 μmol), and CuI (1.5 mg, 7.9 μmol) in anhydrous THF (2 mL) was added iodobenzene (90 mg, 0.44 mmol) and diisopropylamine (121 mg, 1.2 mmol) under argon at room temperature. After stirred for 15 minutes, the reaction mixture was filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (eluted with PE/EA 20:1) to afford 1-yne-VCP **5** (69 mg, 47%).

**5**: White solid, m.p. 110-112 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.75-0.76 (m, 4H), 2.32 (s, 3H), 3.30 (s, 2H), 4.44 (s, 2H), 5.00 (dd, $J$ = 1.0 and 10.6 Hz, 1H), 5.16 (dd, $J$ = 1.0 and 17.5 Hz, 1H), 5.85 (dd, $J$ = 10.6 and 17.5 Hz, 1H), 6.90-7.01 (m, 2H), 7.20-7.29 (m, 5H), 7.75 (d, $J$ = 8.2 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 12.9, 19.7, 21.4, 36.5, 51.7, 81.7, 86.0, 112.4, 122.1, 127.8, 128.1, 128.3, 129.4, 131.4, 135.8, 140.0, 143.3. IR (neat): $\nu$ 2924, 1356, 1166, 1095 cm$^{-1}$. HRMS (ESI) calcd for $C_{22}H_{23}NNaO_2S$ (M+Na): 388.1342. Found: 388.1335.

**1-Yne-VCP (9)**




**S1** **9**

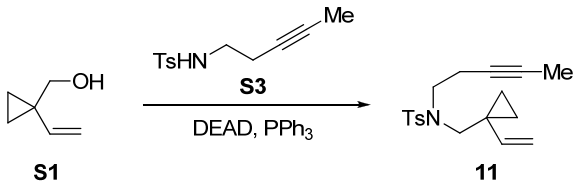
**S1** to **9**: To a stirred solution of alcohol **S1**[1] (116 mg, 1.18 mmol), tosylamide **S2**[2] (218 mg, 0.98 mmol), and $PPh_3$ (522 mg, 1.99 mmol) in anhydrous THF (10 mL) was added DEAD (340 mg, 1.99 mmol) at 0 ºC. The mixture was then stirred for 73 h at room temperature. The mixture was concentrated and filtered through a pad of silica gel (eluted with PE/EA 10:1). The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 20:1) to afford 1-yne-VCP **9** (153 mg, 51%).

**9**: White solid, m.p. 73-74 ºC. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.64-0.67 (m, 2H), 0.75-0.77 (m, 2H), 1.96 (t, $J$ = 2.6 Hz, 1H), 2.42 (s, 3H), 2.49-2.54 (m, 2H), 3.23 (s, 2H), 3.31 (t, $J$ = 8.0 Hz, 2H), 4.95 (dd, $J$ = 1.0 and 10.7 Hz, 1H), 5.01 (dd, $J$ = 1.0 and 17.2 Hz, 1H), 5.85 (dd, $J$ = 10.7 and 17.2 Hz, 1H), 7.30 (d, $J$ = 8.0 Hz, 2H), 7.69 (d, $J$ = 8.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.3, 19.3, 21.1, 21.5, 47.0, 55.4, 69.9, 81.2, 112.6, 127.1, 129.7, 136.6, 140.1, 143.3. IR (neat): $\nu$ 3296, 2931, 1341, 1158 cm$^{-1}$. HRMS (ESI) calcd for $C_{17}H_{22}NO_2S$ (M+H):

(1) Jiao, L.; Lin, M.; Yu, Z.-X. *Chem. Commun.* **2010**, *46*, 1059.
(2) Short, K. M.; Kevin, M.; Ziegler, C. B. Jr. *Tetrahedron Lett.* **1995**, *36*, 355.

304.1366. Found: 304.1362.

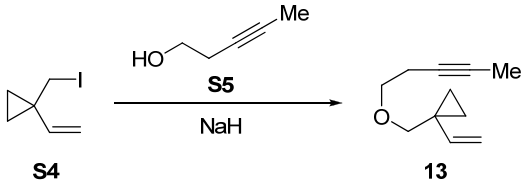
**1-Yne-VCP (11)**




**S1** to **11**: Following the procedure for the preparation of **9** from **S1**, the alcohol **S1** (129 mg, 1.31 mmol) and tosylamide **S3**[3] (247 mg, 1.04 mmol) were converted to 1-yne-VCP **11** (137 mg, 41%).

**11**: Colorless oil. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.64-0.67 (m, 2H), 0.73-0.76 (m, 2H), 1.73 (t, $J$ = 2.4 Hz, 3H), 2.41 (s, 3H), 2.39-2.45 (m, 2H), 3.23 (s, 2H), 3.27 (app. t, $J$ = 8.0 Hz, 2H), 4.93 (dd, $J$ = 0.9 and 10.6 Hz, 1H), 5.00 (dd, $J$ = 0.9 and 17.3 Hz, 1H), 5.86 (dd, $J$ = 10.6 and 17.3 Hz, 1H), 7.29 (d, $J$ = 8.8 Hz, 2H), 7.68 (d, $J$ = 8.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 3.4, 13.1, 19.3, 21.0, 21.4, 47.4, 55.1, 75.8, 77.3, 112.4, 127.1, 129.6, 136.8, 140.1, 143.1. IR (neat): $\nu$ 2924, 1602, 1497, 1345, 1162 cm$^{-1}$. HRMS (ESI) calcd for $C_{18}H_{23}NNaO_2S$ (M+Na): 340.1342. Found: 340.1343.

**1-Yne-VCP (13)**

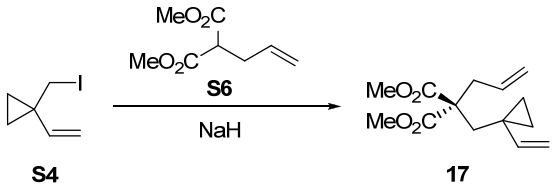



**S4** to **13**: To a suspension of NaH (70% in mineral oil, 70 mg, 2.0 mmol) in anhydrous DMF (4 mL) at 0 °C was added alcohol **S5** (170 mg, 2.0 mmol). The reaction mixture was stirred for 10 min and iodide **S4** (208 mg, 1.0 mmol) was added. The resulting mixture was further stirred for 24 h at room temperature. Water was added to quench the reaction, and the mixture was extracted with ether. The combined organic phase was dried over $MgSO_4$ and concentrated. The crude mixture was purified by flash column chromatography (eluted with PE/EA 100:1) to afford 1-yne-VCP **13** (89 mg, 54%).

**13**: Colorless oil. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.66-0.68 (m, 2H), 0.70-0.74 (m, 2H), 1.77 (t, $J$ = 2.6 Hz, 3H), 2.41 (tq, $J$ = 7.3 and 2.6 Hz, 2H), 3.46 (s, 2H), 3.53 (t, $J$ = 7.3 Hz, 2H), 4.96 (dd, $J$ = 1.5 and 10.8 Hz, 1H), 5.09 (dd, $J$ = 1.5 and 17.6 Hz, 1H), 5.64 (dd, $J$ = 10.8 and 17.6 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 3.5, 12.6, 20.0, 22.4, 69.4, 75.8, 75.9, 76.6, 111.4, 141.6. IR (neat): $\nu$ 2928, 2872, 1639, 1445, 1199 cm$^{-1}$. HRMS (ESI) calcd for $C_{11}H_{16}NaO$ (M+Na): 187.1093. Found: 187.1095.

(3) Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731.

**1-Ene-VCP (17)**




To a suspension of NaH (70% in mineral oil, 45 mg, 1.3 mmol) in anhydrous DMF (2 mL) was added diester **S6** (258 mg, 1.5 mmol) at 0 °C under argon. After stirred for 10 min, iodide **S4** (208 mg, 1.0 mmol) was added and the reaction mixture was further stirred for 75 min at 25 °C. Water was added to quench the reaction, and the mixture was extracted with $CH_2Cl_2$. The combined organic phase was washed with water, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash column chromatography (eluted with PE/EA 50:1) to afford 1-ene-VCP **17** (164 mg, 65%).

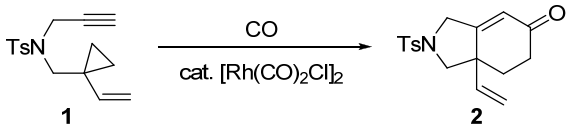
**17**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.52-0.54 (m, 2H), 0.62-0.65 (m, 2H), 2.12 (s, 2H), 2.79 (dt, $J$ = 7.3 and 1.1 Hz, 2H), 3.68 (s, 6H), 4.81-4.86 (m, 2H), 5.06-5.11 (m, 2H), 5.67 (ddt, $J$ = 10.0, 17.0, and 7.3 Hz, 1H), 5.95 (dd, $J$ = 10.0 and 17.5 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.4, 20.1, 37.4, 40.0, 52.1, 58.1, 112.0, 118.7, 133.1, 141.4, 171.6. IR (neat): $\nu$ 2961, 1743, 1643, 1445, 1199 cm$^{-1}$. HRMS (ESI) calcd for $C_{14}H_{20}NaO_4$ (M+Na): 275.1254. Found: 275.1253.

## 2.2 Experimental Details for the Rh(I)-Catalyzed [(3+2)+1] Cycloaddition

**General procedure for the two-component [(3+2)+1] cycloaddition reaction**: A solution of 1-yne/ene-VCP substrate and $[Rh(CO)_2Cl]_2$ (19.5 mg per mmol substrate, 5 mol %) in anhydrous toluene (20 mL per mmol) was degassed by bubbling $CO/N_2$ (balloon pressured mixed gas of CO and $N_2$, 1:4 V/V) for 5 min. Then the reaction mixture was immersed in a hot oil bath and stirred under the above atmosphere. When TLC indicated the disappearance of the starting material, the reaction mixture was cooled to room temperature and concentrated. The crude mixture was submitted to flash column chromatography on silica gel to afford the corresponding [(3+2)+1] cycloadduct.

### Experimental Data for the [(3+2)+1] Cycloadducts

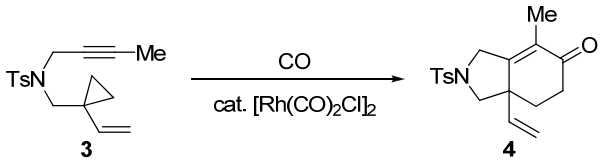
#### Cycloadduct (2)




Following the general procedure, 1-yne-VCP **1** (26.4 mg, 0.091 mmol) was converted to cycloadduct **2** (23.5 mg, 81%). Substrate concentration: 0.05 M, temperature: 80 ºC, reaction time: 1.5 h.

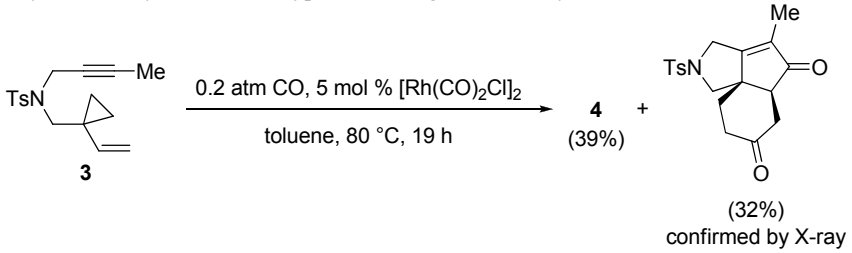
**2**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.86 (dt, $J$ = 4.4 and 13.2 Hz, 1H), 2.03 (ddd, $J$ = 2.2, 5.0, and 12.8 Hz, 1H), 2.31 (dm, $J$ = 17.6 Hz, 1H), 2.38 (dd, $J$ = 4.9 and 13.8 Hz, 1H), 2.44 (s, 3H), 2.91 (d, $J$ = 9.3 Hz, 1H), 3.77 (d, $J$ = 9.3 Hz, 1H), 3.86 (dd, $J$ = 1.6 and 16.8 Hz, 1H), 4.25 (dd, J = 2.2 and 16.8 Hz, 1H), 4.98 (d, $J$ = 17.4 Hz, 1H), 5.17 (d, $J$ = 10.1 Hz, 1H), 5.71 (dd, $J$ = 10.1 and 17.4 Hz, 1H), 5.95 (m, 1H), 7.34 (d, $J$ = 8.0 Hz, 2H), 7.70 (d, $J$ = 8.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.4, 30.8, 32.8, 49.2, 50.6, 59.4, 117.4, 123.4, 127.5, 129.7, 133.0, 137.2, 143.9, 162.5, 197.6. IR (neat): $\nu$ 2939, 1680, 1352, 1170, 1095 cm$^{-1}$. HRMS (ESI) calcd for $C_{17}H_{19}NNaO_3S$ (M+Na): 340.0978. Found: 340.0978.

#### Cycloadduct (4)




This cycloadduct was produced according to the general procedure for the [(3+2)+1] reaction, except that 1 atm CO was used instead.[4] Following this procedure, 1-ene-VCP substrate **3** (14.3 mg, 0.047 mmol) was

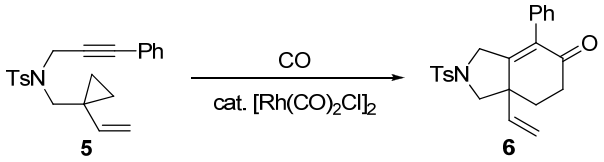
(4) Identical reaction using 0.2 atm CO was less efficient: from 1-yne-VCP **3** (31.0 mg, 0.102 mmol), only 39% yield of **4** (13.3 mg) was obtained, together with a high-polar byproduct (11.7 mg, 32%, see scheme below). Under 1 atm CO, cycloadduct **4** was obtained in a dramatically increased yield, and the byproduct was generated only in trace amount.



converted to the [(3+2)+1] cycloadduct **4** (13.3 mg, 85%). Substrate concentration: 0.05 M, conditions: 80 ºC, reaction time: 7 h.

**4**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.70 (t, $J$ = 1.3 Hz, 3H), 1.85 (dt, $J$ = 4.9 and 13.5 Hz, 1H), 1.99 (ddd, $J$ = 2.2, 4.9, and 12.9 Hz, 1H), 2.33 (ddd, $J$ = 2.2, 4.8, and 17.7 Hz, 1H), 2.43 (ddd, $J$ = 4.8, 13.7, and 17.7 Hz, 1H), 2.45 (s, 3H), 2.86 (d, $J$ = 9.3 Hz, 1H), 3.74 (d, $J$ = 9.3 Hz, 1H), 3.86 (d, $J$ = 16.3 Hz, 1H), 4.16 (dq, $J$ = 16.3 and 1.3 Hz, 1H), 4.92 (d, $J$ = 17.3 Hz, 1H), 5.15 (d, $J$ = 10.6 Hz, 1H), 5.72 (dd, $J$ = 10.6 and 17.3 Hz, 1H), 7.35 (d, $J$ = 8.0 Hz, 2H), 7.72 (d, $J$ = 8.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 11.3, 21.5, 30.8, 32.9, 49.4, 50.1, 59.8, 117.3, 127.6, 129.8, 129.9, 133.2, 138.1, 143.9, 155.9, 197.3. IR (neat): $\nu$ 2924, 2853, 1669, 1348, 1166 cm$^{-1}$. HRMS (ESI) calcd for $C_{18}H_{22}NO_3S$ (M+H): 332.1315. Found: 332.1311.

**Cycloadduct (6)**

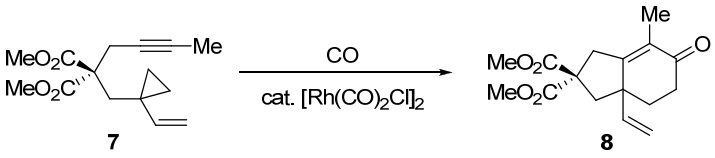



**5** **6**

Following the general procedure, 1-yne-VCP **5** (19.3 mg, 0.053 mmol) was converted to cycloadduct **6** (18.4 mg, 89%). Substrate concentration: 0.05 M, temperature: 80 ºC, reaction time: 1 h.

**6**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.00 (dt, $J$ = 4.9 and 13.2 Hz, 1H), 2.09 (ddd, $J$ = 2.5, 5.3, and 13.2 Hz, 1H), 2.43 (s, 3H), 2.48 (ddd, $J$ = 2.5, 5.0, and 17.7 Hz, 1H), 2.58 (ddd, $J$ = 5.1, 13.6, and 17.7 Hz, 1H), 2.98 (d, $J$ = 9.5 Hz, 1H), 3.68 (d, $J$ = 17.8 Hz, 1H), 3.79 (d, $J$ = 9.5 Hz, 1H), 4.28 (d, $J$ = 17.8 Hz, 1H), 5.13 (d, $J$ 17.2 Hz, 1H), 5.24 ($J$ = 10.1 Hz, 1H), 5.79 (dd, $J$ = 10.1 and 17.2 Hz, 1H), 7.02-7.04 (m, 2H), 7.30 (d, $J$ = 7.8 Hz, 2H), 7.34-7.39 (m, 3H), 7.63 (d, $J$ = 7.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.5, 30.6, 33.3, 49.4, 50.7, 59.6, 117.5, 127.5, 128.26, 128.33, 129.1, 129.7, 133.2, 133.6, 135.8, 138.1, 143.8, 157.7, 195.9. IR (neat): $\nu$ 2935, 1676, 1348, 1166, 1099 cm$^{-1}$. HRMS (ESI) calcd for $C_{23}H_{24}NO_3S$ (M+H): 394.1471. Found: 394.1465.

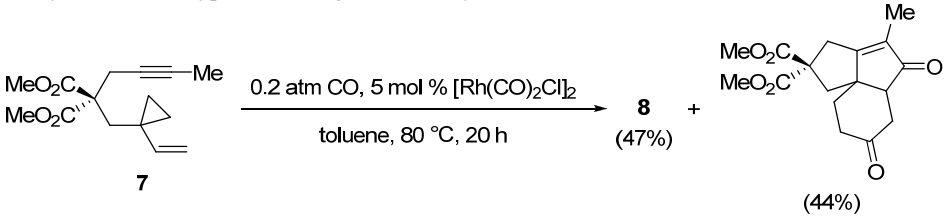
**Cycloadduct (8)**




**7** **8**

This cycloadduct was produced according to the general procedure for the [(3+2)+1] reaction, except that 1 atm CO was used instead.[5] Following this procedure, 1-yne-VCP **7** (18.7 mg, 0.070 mmol) was converted to cycloadduct **8** (12.5 mg, 60%), together with unidentified high-polar byproducts. Substrate concentration: 0.05

(5) The reaction under 0.2 atm CO was proved less efficient: from 1-yne-VCP **7** (37.7 mg, 0.143 mmol), only 47% yield of **8** (19.2 mg) was obtained, together with a high-polar byproduct (20.1 mg, 44%, see scheme below). Under 1 atm CO, cycloadduct **8** was obtained in increased yield, and the byproduct was generated only in trace amount.

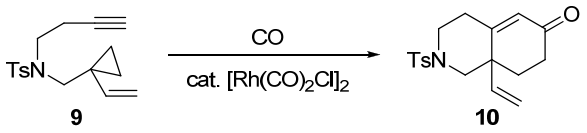



**7**

M, conditions: 80 ºC, reaction time: 3 h.

**8**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.79 (s, 3H), 1.94 (dt, $J$ = 4.8 and 12.8 Hz, 1H), 2.03 (ddd, $J$ = 2.3, 4.8, and 13.0 Hz, 1H), 2.22 (d, $J$ = 12.8 Hz, 1H), 2.30 (ddd, $J$ = 2.7, 5.0 and 17.7 Hz, 1H), 2.40 (ddd, $J$= 5.0, 13.8, and 17.8 Hz, 1H), 2.80 (d, $J$ = 13.0 Hz, 1H), 3.08 (d, $J$ = 20.0 Hz, 1H), 3.49 (dquentet, $J$ = 20.0 and 1.3 Hz, 1H), 3.71 (s, 3H), 3.75 (s, 3H), 4.81 (d, $J$ = 17.8 Hz, 1H), 5.10 (d, $J$ = 10.7 Hz, 1H), 5.62 (dd, $J$ = 10.7 and 17.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 11.2, 33.1, 33.8, 38.4, 46.9, 50.6, 52.9, 53.2, 58.2, 116.6, 130.0, 139.8, 161.0, 171.2, 172.1, 198.4. IR (neat): $\nu$ 2961, 2868, 1739, 1672, 1441 cm$^{-1}$. HRMS (ESI) calcd for $C_{16}H_{21}O_5$ (M+H): 293.1384. Found: 293.1387.

**Cycloadduct (10)**

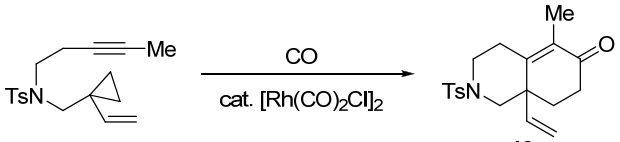


**9** **10**

Following the general procedure for [(3+2)+1] reaction, 1-yne-VCP **9** (33.5 mg, 0.11 mmol) was converted to cycloadduct **10** (33.5 mg, 92%). Substrate concentration: 0.05 M, temperature: 70 ºC, reaction time: 2 h.

**10**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.70-1.82 (m, 2H), 2.16 (d, $J$ = 11.6 Hz, 1H), 2.26-2.38 (m, 3H), 2.43 (s, 3H), 2.46 (ddd, $J$ = 6.3, 13.8, and 16.8 Hz, 1H), 2.80 (dddd, $J$ = 2.2, 6.7, 12.9, and 14.6 Hz, 1H), 3.85-3.92 (m, 2H), 5.04 (d, $J$ = 17.6 Hz, 1H), 5.37 (d, $J$ = 10.6 Hz, 1H), 5.82 (dd, $J$ = 10.6 and 17.6 Hz, 1H), 5.94 (d, $J$ = 2.4 Hz, 1H), 7.34 (d, $J$ = 7.9 Hz, 2H), 7.64 (d, $J$ = 7.9 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.5, 31.3, 31.6, 32.8, 44.0, 46.4, 57.0, 118.0, 127.5, 127.9, 129.8, 133.0, 138.4, 143.8, 159.5, 198.4. IR (neat): $\nu$ 2864, 1672, 1348, 1170 cm$^{-1}$. HRMS (ESI) calcd for $C_{18}H_{22}NO_3S$ (M+H): 332.1315. Found: 332.1310.

**Cycloadduct (12)**

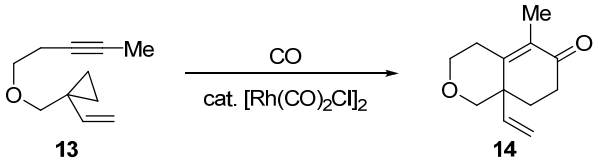


**11** **12**

Following the general procedure for [(3+2)+1] reaction, 1-yne-VCP **11** (21.5 mg, 0.068 mmol) was converted to cycloadduct **12** (18.3 mg, 78%). Substrate concentration: 0.05 M, temperature: 80 ºC, reaction time: 12 h.

**12**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.70-1.74 (m, 2H), 1.78 (d, $J$ = 1.3 Hz, 3H), 2.15 (d, $J$ = 11.7 Hz, 1H), 2.30-2.34 (m, 1H), 2.35-2.37 (m, 1H), 2.43 (s, 3H), 2.45-2.50 (m, 1H), 2.52-2.60 (m, 1H), 2.69 (ddd, $J$ = 2.7, 3.5, and 15.5 Hz, 1H), 3.78 (dd, $J$ = 2.5 and 11.5 Hz, 1H), 3.87 (ddt, $J$ = 5.8, 11.1, and 2.2 Hz, 1H), 4.95 (dd, $J$ = 0.9 and 17.3 Hz, 1H), 5.34 (d, $J$ = 10.6 Hz, 1H), 5.79 (dd, $J$ = 10.6 and 17.3 Hz, 1H), 7.33 (d, $J$ = 8.5 Hz, 2H), 7.65 (d, $J$ = 8.5 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 10.7, 21.5, 27.1, 31.2, 32.7, 44.3, 46.0, 57.2, 117.8, 127.6, 129.7, 132.8, 132.9, 139.3, 143.8, 151.9, 198.1. IR (neat): $\nu$ 2931, 2864, 1672, 1348, 1166 cm$^{-1}$. HRMS (ESI) calcd for $C_{19}H_{24}NO_3S$ (M+H): 346.1471. Found: 346.1465.

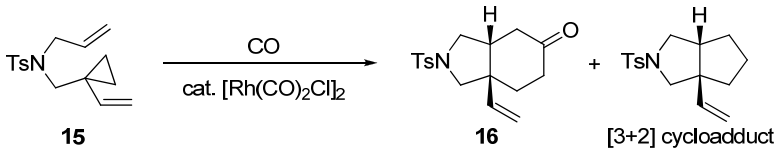
**Cycloadduct (14)**




Following the general procedure for [(3+2)+1] reaction, 1-yne-VCP **13** (25.8 mg, 0.16 mmol) was converted to cycloadduct **14** (20.6 mg, 68%). Substrate concentration: 0.05 M, temperature: 80 ºC, reaction time: 5 h.

**14**: Colorless oil. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.62 (ddd, $J$ =2.8, 5.2, and 13.2 Hz, 1H), 1.73 (dt, $J$ = 4.6 and 13.2 Hz, 1H), 1.84 (s, 3H), 2.37 (ddd, $J$ = 3.0, 4.4, and 16.9 Hz, 1H), 2.49 (ddd, $J$ =5.2, 14.5, and 16.9 Hz, 1H), 2.54-2.59 (m, 2H), 3.26 (d, $J$ = 11.3 Hz, 1H), 3.49 (dt, $J$ = 4.2 and 11.2 Hz, 1H), 3.93 (d, $J$ = 11.3 Hz, 1H), 4.11-4.16 (m, 1H), 4.98 (d, $J$ = 17.4 Hz, 1H), 5.33 (d, $J$ = 10.6 Hz, 1H), 5.80 (dd, $J$ = 10.6 and 17.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$. 10.5, 28.2, 29.1, 32.5, 44.6, 68.1, 78.3, 117.4, 132.0, 140.2, 153.5, 198.5. IR (neat): $\nu$ 2928, 1672, 1117 cm$^{-1}$. HRMS (ESI) calcd for $C_{12}H_{16}NaO_2$ (M+Na): 215.1043. Found: 215.1043.

**Cycloadduct (16)**




This cycloadduct was produced according to the general procedure for the [(3+2)+1] reaction, except that anhydrous 1,4-dioxane was employed as the solvent. Following this procedure, 1-ene-VCP substrate **15** (32.7 mg, 0.112 mmol) was converted to the [(3+2)+1] cycloadduct **16** (18.0 mg, 50%), together with minor amount of [3+2] cycloadduct (6.2 mg, 19%).[1] Substrate concentration: 0.03 M, temperature: 80 ºC, reaction time: 168 h.

**16**: Colorless oil. $^{1}$H NMR (600 MHz, $CDCl_3$): $\delta$ 1.61-1.70 (m, 1H), 1.90 (dm, $J$ = 14.3 Hz, 1H), 2.14-2.22 (m, 2H), 2.34 (dt, $J$ = 6.2 and 14.0 Hz, 1H), 2.41 (dd, $J$ = 6.2 and 15.3 Hz, 1H), 2.44 (s, 3H), 2.51-2.56 (m, 1H), 3.00 (t, $J$ = 9.8 Hz, 1H), 3.19 (d, $J$ = 9.8 Hz, 1H), 3.29 (d, $J$ = 9.8 Hz, 1H), 3.53 (dd, $J$ = 8.1 and 10.1 Hz, 1H), 5.20 (d, $J$ = 17.3 Hz, 1H), 5.28 (d, $J$ = 10.6 Hz, 1H), 5.80 (dd, $J$ = 10.6 and 17.3 Hz, 1H), 7.33 (d, $J$ = 8.5 Hz, 2H), 7.70 (d, $J$ = 8.5 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.5, 29.6, 36.9, 39.0, 43.7, 45.1, 51.2, 58.0, 116.0, 127.3, 129.8, 133.8, 139.4, 143.7, 209.3. IR (neat): $\nu$ 2946, 1717, 1602, 1494, 1345, 1162 cm$^{-1}$. HRMS (ESI) calcd for $C_{17}H_{21}NNaO_3S$ (M+Na): 342.1134. Found: 342.1129.

The nOe correlation between the olefinic proton and the bridge C-H in cycloadduct **16** indicates a *cis* relationship of the vinyl group and the bridge hydrogen atom (Figure S1).

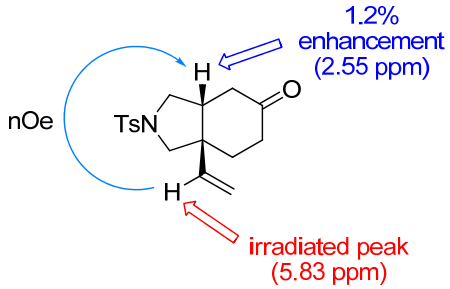
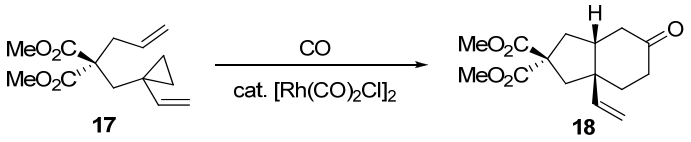



***Figure S1.*** 1D nOe analysis of cycloadduct **16** (the 1D nOe spectrum is on page S28).

**Cycloadduct (18)**

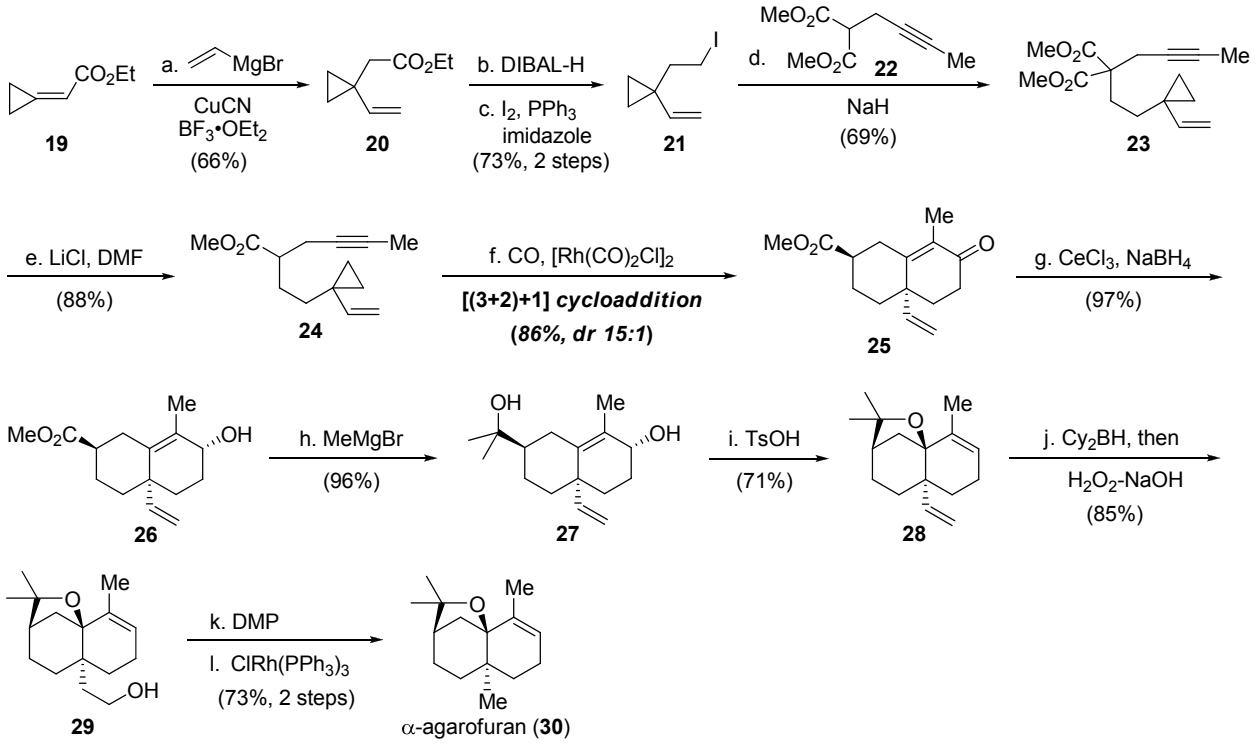



This cycloadduct was produced according to the general procedure for the [(3+2)+1] reaction, except that anhydrous 1,4-dioxane was employed as the solvent. Following this procedure, 1-ene-VCP substrate **17** (29.7 mg, 0.118 mmol) was converted to the [(3+2)+1] cycloadduct **18** (23.2 mg, 70%). Substrate concentration: 0.05 M, temperature: 80 ºC, reaction time: 18 h. The cycloaddduct contains minor amount of inseparable impurities, but compound **18** was a single diastereomer as indicated by NMR. The ring-fusion stereochemistry was assigned by analogy to cycloadduct **16**.

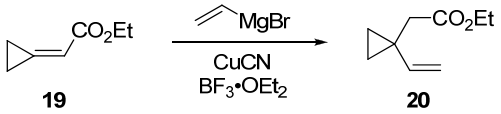
**18**: Colorless oil. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.85-2.02 (m, 3H), 2.20 (dm, $J$ = 14.7 Hz, 1H), 2.27 (d, $J$ = 14.2 Hz, 1H), 2.29 (dt, $J$ = 14.9 and 2.1 Hz, 1H), 2.38 (dd, $J$ = 6.4 and 13.1 Hz, 1H), 2.45 (d, $J$ = 14.2 Hz, 1H), 2.51 (dd, $J$ = 6.0 and 14.9 Hz, 1H), 2.55-2.63 (m, 2H), 3.721 (s, 3H), 3.724 (s, 3H), 5.22 (d, $J$ = 17.7 Hz, 1H), 5.24 (d, $J$ = 10.7 Hz, 1H), 5.93 (dd, $J$ = 10.7 and 17.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 31.2, 37.5, 39.2, 40.6, 44.8, 46.1, 46.2, 52.9, 57.6, 114.0, 143.0, 172.5, 172.7, 211.3. IR (neat): $\nu$ 2954, 1736, 1438, 1263, 1345, 1199, 1062 cm$^{-1}$. HRMS (ESI) calcd for $C_{15}H_{20}NaO_5$ (M+Na): 303.1203. Found: 303.1202.

## 2.3 Synthesis of α-Agarofuran

**Complete synthetic route:**




**Vinylcyclopropane Ester (20)**

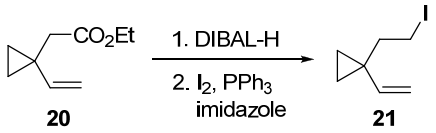



**19** to **20**: To a flame dried flask was added freshly distilled THF (60 mL) and vinylmagnesium bromide (0.7 M in THF, 90 mL, 63.0 mmol). The solution was cooled to -78 ºC and powdered CuCN (6.01 g, 67.1 mmol) was added in one portion under argon. After stirred for 15 min at -78 ºC, neat $BF_3{\cdot}OEt_2$ (4.61 g, 32.5 mmol) was added dropwise. After 5 min, a solution of ester **19**[6] (3.63 g, 32.4 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred at -78 ºC for 2 h. Water (60 mL) was added to quench the reaction and the resulting mixture was allowed to warm to room temperature. After ether extraction, the combined organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with pentane/ether 20:1) to afford vinyl ester **20** (3.28 g, 66%).

**20**: Colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.70-0.80 (m, 4H), 1.26 (t, $J$ = 7.1 Hz, 3H), 2.42 (s, 2H), 4.14 (q, $J$ = 7.1 Hz, 2H), 4.92 (dd, $J$ = 0.8 and 10.7 Hz, 1H), 4.96 (dd, $J$ = 0.8 and 17.4 Hz, 1H), 5.54 (dd, $J$ = 10.7 and 17.4 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 14.1, 14.2, 19.7, 40.6, 60.2, 110.8, 143.0, 172.1.

(6) Henderson, J. R.; Parvez, M.; Keay, B. A. *Org. Lett.* **2007**, *9*, 5167.

**Vinylcyclopropane Iodide (21)**




**20** to **21**: To a solution of vinylcyclopropane ester **20** (2.94 g, 19.1 mmol) in $CH_2Cl_2$ (40 mL) was added DIBAL-H (1 M in hexane, 57 mL, 57 mmol) dropwise at 0 ºC. The reaction mixture was stirred for 30 min then water (10 mL) was added to quench the reaction. Saturated aqueous solution of potassium sodium tartrate was added and the resulting mixture was stirred overnight. The organic layer was separated and the aqueous phase was extrated with $CH_2Cl_2$. The combined organic phase was dried over $MgSO_4$ and concentrated. The crude product was filtered through a pad of silica gel (eluted with pentane/ether 5:1) to afford crude alcohol (1.82 g, 85%), which was used in the next step without further purification. To a solution of the above crude alcohol, $PPh_3$ (6.42 g, 24.5 mmol), and imidazole (2.24 g, 32.9 mmol) in anhydrous $CH_2Cl_2$ (70 mL) was added iodine (6.81 g, 26.8 mmol) in small portions at 0 ºC. The resulting solution was refluxed for 2.5 h and then cooled. The reaction mixture was washed with aqueous $Na_2S_2O_3$ solution and dried over $MgSO_4$. The dried solution was concentrated and pentane was added. The resulting mixture was filtered to remove $Ph_3PO$, and the filtrate was concentrated to give the crude product. Flash column chromatography on silica gel (eluted with pentane/ether 50:1) gave vinylcyclopropane iodide **21** (3.11 g, 73% for 2 steps).

**21**: Colorless oil. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.61-0.64 (m, 4H), 2.03 (app. t, $J$ = 8.0 Hz, 2H), 3.19 (app. t, $J$ = 8.0 Hz, 2H), 4.95 (dd, $J$ = 1.3 and 17.2 Hz, 1H), 4.97 (dd, $J$ = 1.1 and 11.0 Hz, 1H), 5.54 (dd, $J$ = 11.0 and 17.2 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 2.1, 13.7, 24.4, 41.1, 111.8, 141.8.

**1-Yne-VCP (23)**


**21** to **23**: To a suspension of NaH (70% in mineral oil, 209 mg, 6.1 mmol) in DMF (8 mL) was added a solution of diester **22** (1.06 g, 5.8 mmol) in DMF (10 mL) at 0 ºC. After stirred for 5 min, a solution of vinyl iodide **21** (1.08 g, 4.9 mmol) in DMF (10 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred for 73 h. Then water (50 mL) was added to quench the reaction. The resulting mixture was extracted with ether and the combined organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/AE 50:1 to 10:1) to afford 1-yne-VCP **23** (933 mg, 69%).

**23**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.54-0.56 (m, 2H), 0.59-0.61 (m, 2H), 1.26-1.31 (m, 2H), 1.76 (t, $J$ = 2.7 Hz, 3H), 2.14-2.18 (m, 2H), 2.75 (q, $J$ = 2.5 Hz, 2H), 3.73 (s, 6H), 4.92 (dd, $J$ = 1.3 and 10.6 Hz, 1H), 4.97 (dd, $J$ =1.3 and 17.3 Hz, 1H), 5.49 (dd, $J$ = 10.6 and 17.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 3.4, 14.4, 22.1, 23.2, 29.5, 30.0, 52.6, 56.9, 73.3, 78.8, 110.8, 143.2, 171.0. IR (neat): $\nu$ 2961, 1742, 1438, 1207 cm$^{-1}$. HRMS (ESI) calcd for $C_{16}H_{22}NaO_4$ (M+Na): 301.1410. Found: 301.1404.

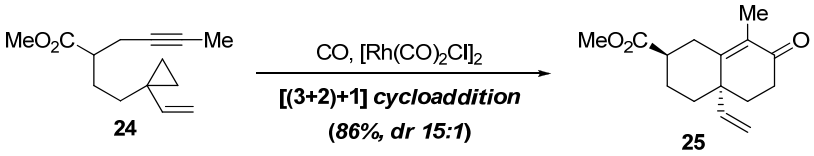
**1-Yne-VCP (24)**


23 24

**23** to **24**: A solution of 1-yne-VCP **23** (932 mg, 3.3 mmol) and anhydrous LiCl (480 mg, 11.3 mmol) in DMF (17 mL) was bubbled argon for 5 min. The reaction mixture was heated at 150 ºC for 2.5 h under argon. The reaction mixture was cooled to room temperature and water (100 mL) was added. The mixture was extracted with ether, and the combined organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/AE 50:1 to 20:1) to afford 1-yne-VCP **24** (653 mg, 88%).

**24**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.54-0.58 (m, 4H), 1.35 (ddd, $J$ = 5.9, 10.8, and 13.8 Hz, 1H), 1.43 (ddd, $J$ = 5.9, 10.3, and 13.8 Hz, 1H), 1.72-1.79 (m, 2H), 1.76 (t, $J$ = 2.5 Hz, 3H), 2.33 (ddq, $J$ = 6.9, 16.3, and 2.5 Hz, 1H), 2.43 (ddq, $J$ = 6.9, 16.3, and 2.5 Hz, 1H), 2.51 (ddd, $J$ = 5.9, 7.4, and 14.8 Hz, 1H), 3.69 (s, 3H), 4.90 (dd, $J$ = 1.0 and 10.5 Hz, 1H), 4.92 (dd, $J$ = 1.0 and 17.5 Hz, 1H), 5.53 (dd, $J$ = 10.5 and 17.5 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 3.5, 14.1, 14.2, 21.5, 22.3, 28.7, 33.2, 44.9, 51.7, 76.0, 77.3, 110.9, 143.4, 175.3. IR (neat): $\nu$ 2920, 2858, 1743, 1468, 1378, 1166, 1099 cm$^{-1}$. HRMS (ESI) calcd for $C_{14}H_{20}NaO_2$ (M+Na): 243.1356. Found: 243.1351.

**Cycloadduct (25)**

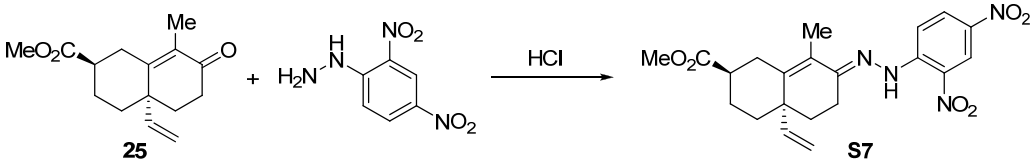



24 25

Following the general procedure for [(3+2)+1] reaction, 1-yne-VCP **24** (301 mg, 1.30 mmol) was converted to cycloadduct **25** (294 mg, 86%). Substrate concentration: 0.05 M, temperature: 80 ºC, reaction time: 46 h.

**25**: Colorless oil. $^1$H NMR (400 MHz, $C_6D_6$): $\delta$ 1.17 (ddd, $J$ = 3.1, 5.1, and 13.3 Hz, 1H), 1.25-1.28 (m, 1H), 1.33-1.37 (m, 1H), 1.39-1.41 (m, 1H), 1.45 (ddd, $J$ = 3.4, 4.9, and 9.7 Hz, 1H), 1.82-1.90 (m, 2H), 2.10 (d, $J$ = 1.3 Hz, 3H), 2.19 (ddd, $J$ = 3.0, 4.9, and 16.4 Hz, 1H), 2.29 (ddd, $J$ = 4.9, 14.6, and 16.4 Hz, 1H), 2.38-2.41 (m, 1H), 2.88 (dt, $J$ = 15.3 and 2.2 Hz, 1H), 3.27 (s, 3H), 4.54 (dd, $J$ = 1.3 and 17.7 Hz, 1H), 4.92 (dd, $J$ = 1.3 and 10.6 Hz, 1H), 5.12 (dd, $J$ = 10.6 and 17.7 Hz, 1H). $^{13}$C NMR (100 MHz, $C_6D_6$): $\delta$ 11.0, 23.5, 28.8, 33.5, 35.0, 37.4, 40.6, 43.9, 51.1, 116.5, 133.5, 141.9, 153.6, 173.9, 197.0. IR (neat): $\nu$ 2924, 2861, 1739, 1672, 1192 cm$^{-1}$. HRMS (ESI) calcd for $C_{15}H_{20}NaO_3$ (M+Na): 271.1305. Found: 271.1302.

The [(3+2)+1] cycloadduct **25** was converted to its 2,4-dinitrophenylhydrazone derivative **S7**, whose structure was determined by X-ray single-crystal diffraction analysis.




25 S7

**25** to **S7**: To a solution of compound **25** (27.3 mg, 0.12 mmol) and 2,4-dinitrophenylhydrazine (55 mg, 0.28 mmol) in ethanol (1 mL) was added a drop of concentrated HCl. The reaction mixture was heated to 60 ºC in an oil bath for 1 h and then cooled to room temperature. The solvent was evaporated and the crude product was

purified by flash column chromatography on silica gel (eluted with PE/EA 5:1) to afford 2,4-dinitrophenyl-hydrazone **S7** (42.2 mg, 90%). Recrystallization in $CH_2Cl_2$/EtOAc gave single crystals suitable for X-ray diffraction analysis.

**S7:** Red crystals, m.p. 155-157 ºC. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.52 (dt, $J$ = 3.9 and 13.6 Hz, 1H), 1.65-1.78 (m, 3H), 1.82 (ddt, $J$ = 3.8, 5.0, and 13.6 Hz, 1H), 2.02-2.07 (m, 1H), 2.15 (s, 3H), 2.25-2.36 (m, 2H), 2.62 (ddd, $J$ = 2.7, 4.4, and 16.3 Hz, 1H), 2.86-2.91 (m, 1H), 3.20 (dm, $J$ = 15.4 Hz, 1H), 3.70 (s, 3H), 4.82 (dd, $J$ = 1.3 and 17.4 Hz, 1H), 5.22 (dd, $J$ = 1.3 and 10.2 Hz, 1H), 5.60 (dd, $J$ = 10.2 and 17.4 Hz, 1H), 8.01 (d, $J$ = 9.4 Hz, 1H), 8.32 (dd, $J$ = 2.6 and 9.4 Hz, 1H), 9.13 (d, $J$ = 2.6 Hz, 1H), 11.23 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 12.5, 20.8, 23.3, 28.4, 33.6, 36.7, 40.3, 43.2, 51.7, 116.6, 116.8, 123.6, 129.3, 129.8, 130.0, 137.7, 142.0, 145.0, 145.2, 155.1, 175.0. MS (ESI): *m/z* 429 (M+H). Calcd for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65; N, 13.08. Found: C, 58.97; H, 5.63; N, 13.14.

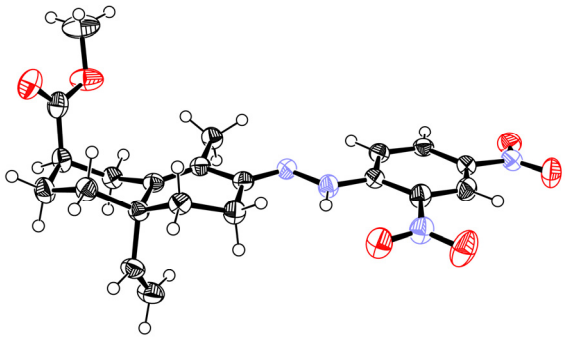
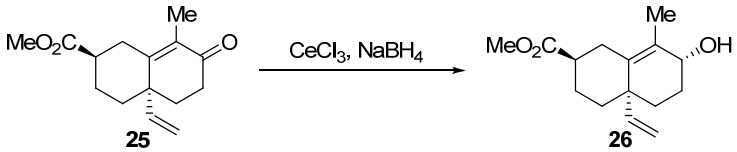


***Figure S2.*** ORTEP figure of compound **S7**. Ellipsoids are drawn at 50% probability.

**Allylic alcohol (26)**




**25** **26**

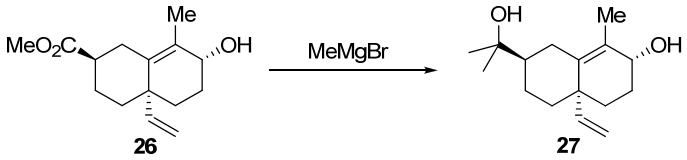
A solution of cycloadduct **25** (584 mg, 2.4 mmol) and $CeCl_3 \cdot 7H_2O$ (2.25 g, 6.0 mmol) in methanol (15 mL) was cooled to –45 °C in a dry ice-acetonitrile bath. To the stirred solution was added powdered $NaBH_4$ (177 mg, 4.7 mmol) in one batch and the resulting mixture was stirred for 30 min. Acetone (2 mL) and brine (30 mL) was added to quench the reaction, and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate and the combined organic phase was dried over $MgSO_4$ and evaporated. The crude mixture was purified by flash column chromatography on silica gel (eluted with PE/EA 10:1 to 3:1) to afford allylic alcohol **26** (571 mg, 97%).

**26**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.31-1.54 (m, 5 H), 1.60 (dt, $J$ = 13.7 and 3.2 Hz, 1H), 1.71 (ddt, $J$ = 3.8, 4.8, and 13.8 Hz, 1H), 1.77-1.85 (m, 1H), 1.84 (s, 3H), 1.97 (dm, $J$ = 13.8 Hz, 1H), 2.11 (ddm, $J$ = 5.5 and 14.6 Hz, 1H), 2.70-2.75 (m, 1H), 2.94 (dt, $J$ = 14.5 and 2.3 Hz, 1H), 3.66 (s, 3H), 4.06 (t, $J$ = 7.0 Hz, 1H), 4.89 (dd, $J$ = 1.6 and 17.5 Hz, 1H), 5.20 (dd, $J$ = 1.5 and 10.4 Hz, 1H), 5.59 (dd, $J$ = 10.4 and 17.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.5, 23.6, 27.3, 27.8, 34.5, 37.4, 40.8, 43.3, 51.4, 71.4, 116.1, 132.1, 132.5, 144.9, 175.2. IR (neat): $\nu$ 3360, 2935, 1728, 1456, 1203, 1032 cm$^{-1}$. HRMS (ESI) calcd for $C_{15}H_{22}NaO_3$ (M+Na): 273.1461. Found: 273.1464.

The stereochemistry of allylic alcohol **26** was assigned based on the chemical shift and coupling constants of

the carbinol proton in similar bicyclic systems. For a quasi-equatorial (3α) alcohol, NMR spectrum shows this proton as a triplet at ca. 4.0 ppm ($J$ = 6-7 Hz); while for a quasi-axial (3β) alcohol, the proton appears at ca. 3.8 ppm as a broadened singlet peak.[7,8]

**Bicyclic diol (27)**

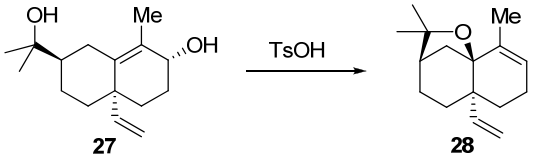



**26** **27**

To a stirred solution of allylic alcohol **26** (557 mg, 2.2 mmol) in anhydrous THF (10 mL) was added MeMgBr (1 M in THF, 11.0 mL, 11.0 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4.5 h. Methanol (5 mL) was added to quench the reaction, and then saturated aqueous $NH_4Cl$ solution was added. The resulting mixture was extracted with ether, and the combined organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 5:1 to 2:1) to afford bicyclic diol **27** (532 mg, 96%).

**27**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.18 (s, 3H), 1.22 (s, 3H), 1.38-1.46 (m, 4H), 1.49-1.69 (m, 5H), 1.76-1.79 (m, 1H), 1.83 (s, 3H), 1.84-1.91 (m, 1H), 2.21 (dd, $J$ = 6.1 and 15.7 Hz, 1H), 2.42 (dd, $J$ = 6.3 and 15.7 Hz, 1H), 4.02 (t, $J$ = 7.8 Hz, 1H), 4.90 (dd, $J$ = 1.5 and 17.5 Hz, 1H), 5.16 (dd, $J$ = 1.7 and 10.4 Hz, 1H), 5.70 (dd, $J$ = 10.4 and 17.5 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 14.9, 22.0, 26.5, 27.3, 28.4, 29.0, 34.8, 36.0, 42.6, 42.8, 71.4, 73.8, 115.3, 131.0, 135.1, 145.9. IR (neat): $\nu$ 3371, 2942, 1710, 1639, 1386, 1143 cm$^{-1}$. HRMS (ESI) calcd for $C_{16}H_{26}NaO_2$ (M+Na): 276.1825. Found: 273.1827.

**Tricyclic diene (28)**



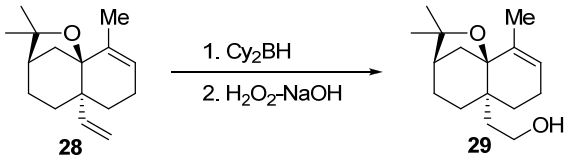

**27** **28**

To a stirred solution of bicyclic diol **27** (340 mg, 1.4 mmol) in toluene (14 mL) at 0 °C was added TsOH•$H_2O$ (14.4 mg, 0.076 mmol, 5 mol % to **27**). After stirred for 1.5 h at 0 °C, the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether, and the combined organic phase was dried over $MgSO_4$ and evaporated. The crude mixture was purified by flash column chromatography on silica gel (eluted with PE/EA 50:1) to afford tricyclic diene **28** (224 mg, 71%).

**28**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.17 (dd, $J$ = 4.5 and 11.9 Hz, 1H), 1.24 (s, 3H), 1.39 (s, 3H), 1.57-1.67 (m, 2H), 1.68-1.82 (m, 7H), 1.88-2.02 (m, 3H), 2.26 (dd, $J$ = 4.7 and 11.9 Hz, 1H), 5.07 (dd, $J$ = 1.4 and 11.0 Hz, 1H), 5.14 (dd, $J$ = 1.5 and 17.8 Hz, 1H), 5.69 (s, 1H), 5.85 (dd, $J$ = 11.0 and 17.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 19.0, 22.7, 22.9, 24.6, 30.08, 30.11, 33.0, 33.8, 44.2, 45.0, 81.5, 83.9, 112.7, 128.3, 132.6, 143.2. IR (neat): $\nu$ 2935, 2242, 1654, 1471, 1371, 1140 cm$^{-1}$. HRMS (ESI) calcd for $C_{16}H_{24}NaO$ (M+Na): 255.1719. Found: 255.1718.

(7) Huffman, J. W.; Desai, R. C. *J. Org. Chem.* **1982**, *47*, 3254.
(8) Stoltz and co-workers reported the Luche reduction of a similar bicyclic enone compound in the total synthesis of (+)-carissone, resulting in the same stereochemical outcome, see: Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289.

**Tricyclic enol (29)**

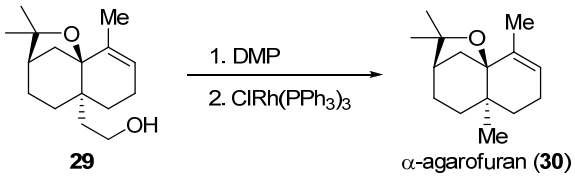



28 29

Borane-dimethyl sulfide complex (2 M in THF, 1.9 mL, 3.8 mmol) was added to a flask containing 10 mL anhydrous THF and the solution was cooled to 0 °C. Cyclohexene (670 mg, 8.0 mmol) was added dropwise under stirring. The reaction mixture was stirred for 15 min at 0 °C, and then for 1 h at 25 °C. The resulting white suspension contains $Cy_2BH$ with a concentration of ca 0.3 M. To a stirred solution of tricyclic diene **29** (22.5 mg, 0.097 mmol) in anhydrous THF (0.5 mL) was added the above prepared suspension of $Cy_2BH$ (0.7 mL, 0.21 mmol) at room temperature. After stirred for 4 h at room temperature, the reaction mixture was cooled to 0 °C and aqueous NaOH solution (1 M, 1.0 mL, 1.0 mmol) and then $H_2O_2$ (30% aqueous solution, 0.4 mL) was added dropwise. The resulting mixture was stirred for 2 h under room temperature and then extracted with ether. The combined extract was dried over $MgSO_4$ and concentrated. The crude mixture was purified by flash column chromatography on silica gel (eluted with PE/EA 20:1 to 5:1) to afford tricyclic enol **29** (20.5 mg, 85%).

**29**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.15 (dm, $J$ = 13.8 Hz, 1H), 1.24 (s, 3H), 1.35 (br s, 1H), 1.37 (s, 3H), 1.49-1.76 (m, 11H), 1.92-1.97 (m, 3H), 2.24 (dd, $J$ = 4.3 and 12.3 Hz, 1H), 3.67-3.74 (m, 2H), 5.67 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 19.3, 22.7, 22.9, 24.5, 28.2, 30.1, 30.4, 32.2, 35.1, 38.9, 43.6, 61.2, 80.9, 85.0, 127.7, 132.4. IR (neat): $\nu$ 3393, 2935, 1672, 1460, 1143, 1054 cm$^{-1}$. HRMS (ESI) calcd for $C_{16}H_{26}NaO_2$ (M+Na):273.1825. Found: 273.1827.

**α-Agarofuran (30)**



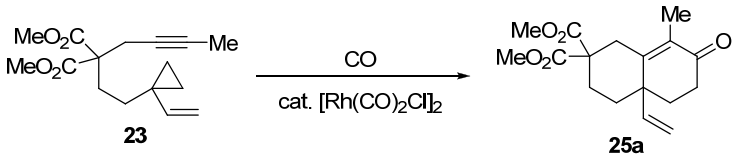

29 α-agarofuran (**30**)

To a stirred solution of tricyclic enol **29** (22.1 mg, 0.088 mmol) in $CH_2Cl_2$ (1 mL) was added powdered $NaHCO_3$ (22.2 mg, 0.26 mmol) and Dess-Martin periodinane (57.3 mg, 0.14 mmol). The reaction mixture was stirred for 30 min at room temperature and then directly subjected to flash column chromatography on silica gel (eluted with PE/AE 10:1) to afford the crude aldehyde (19.7 mg, 90%), which was used in the next step without further purification. To a solution of the above crude aldehyde in dry toluene (1 mL) was added Winkinson's catalyst (111 mg, 0.12 mmol), and the resulting suspension was heated in an 120 °C oil bath to reflux under argon for 4 h. The reaction mixture was cooled to room temperature and filtered through a pad of silica gel (eluted with PE/AE 10:1). The filtrate was evaporated and crude mixture was purified by flash column chromatography on silica gel (eluted with PE/EA 5:1) to afford α-agarofuran **30** (14.2 mg, 73% for 2 steps).

α-agarofuran **30**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.91 (s, 3H), 1.06 (dd, $J$ = 5.3 and 12.4 Hz, 1H), 1.17-1.21 (m, 1H), 1.24 (s, 3H), 1.37 (s, 3H), 1.63-1.78 (m, 5 H), 1.70 (s, 3H), 1.89-2.06 (m, 3H), 2.22 (dd, $J$ = 4.8 and 12.4 Hz, 1H), 5.62 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 19.0, 21.9, 22.5, 22.8, 24.5, 30.2, 32.4, 32.9, 34.4, 37.0, 44.3, 80.9, 84.9, 127.3, 132.6. IR (neat): $\nu$ 1684, 1464, 1386, 1371, 1147, 1095, 1076, 1009, 879, 838 cm$^{-1}$. HRMS (ESI) calcd for $C_{15}H_{24}NaO$ (M+Na):243.1719. Found: 243.1721. The spectroscopic data is

identical to that previously reported.[9]

**Cycloadduct (25a)**



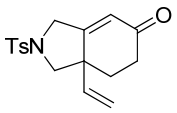

**23** **25a**

Following the general procedure for [(3+2)+1] reaction, 1-yne-VCP **23** (29.4 mg, 0.106 mmol) was converted to cycloadduct **25a** (6.8 mg, 21%), together with the recovered yne-VCP **23** (18.7 mg, 64%). Substrate concentration: 0.05 M, conditions: 80 ºC for 17.5 h and then 90 ºC for 29.5 h.

**25a**: Colorless oil. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.50 (dt, $J$ = 3.6 and 14.2 Hz, 1H), 1.72 (ddd, $J$ = 3.1, 5.3, and 13.2 Hz, 1H), 1.80-1.86 (m, 2H), 1.94 (d, $J$ = 1.8 Hz, 3H), 1.99 (dt, $J$ = 3.5 and 14.0 Hz, 1H), 2.25-2.32 (m, 2H), 2.36-2.45 (m, 2H), 3.38 (dd, $J$ = 2.3 and 15.1 Hz, 1H), 3.72 (s, 3H), 3.74 (s, 3H), 4.87 (dd, $J$ = 0.9 and 17.3 Hz, 1H), 5.30 (dd, $J$ = 0.9 and 10.5 Hz, 1H), 5.59 (dd, $J$ = 10.5 and 17.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 10.8, 27.3, 32.7, 33.2, 34.7, 37.3, 43.4, 52.6, 52.9, 56.5, 117.5, 134.2, 140.9, 153.0, 170.8, 171.8, 198.9. IR (neat): $\nu$ 2928, 2857, 1743, 1669, 1460, 1255 cm$^{-1}$. HRMS (ESI) calcd for $C_{17}H_{23}O_5$ (M+H): 307.1540. Found: 307.1539.

(9) Nakanishi, T.; Yamagata, E.; Yoneda, K.; Nagashima, T.; Kawasaki, I.; Yoshida, T.; Mori, H.; Miura, I. *Phytochem.* **1984**, *23*, 2066.

## 3. $^{1}H$ and $^{13}C$-NMR Spectra for New Compounds

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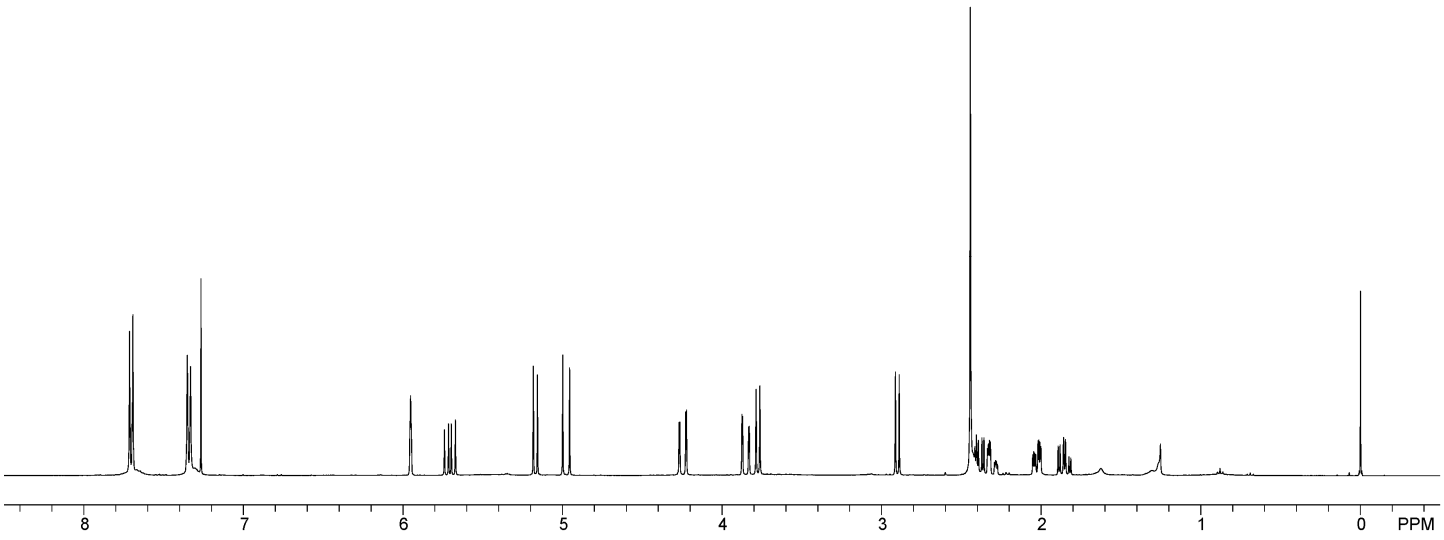


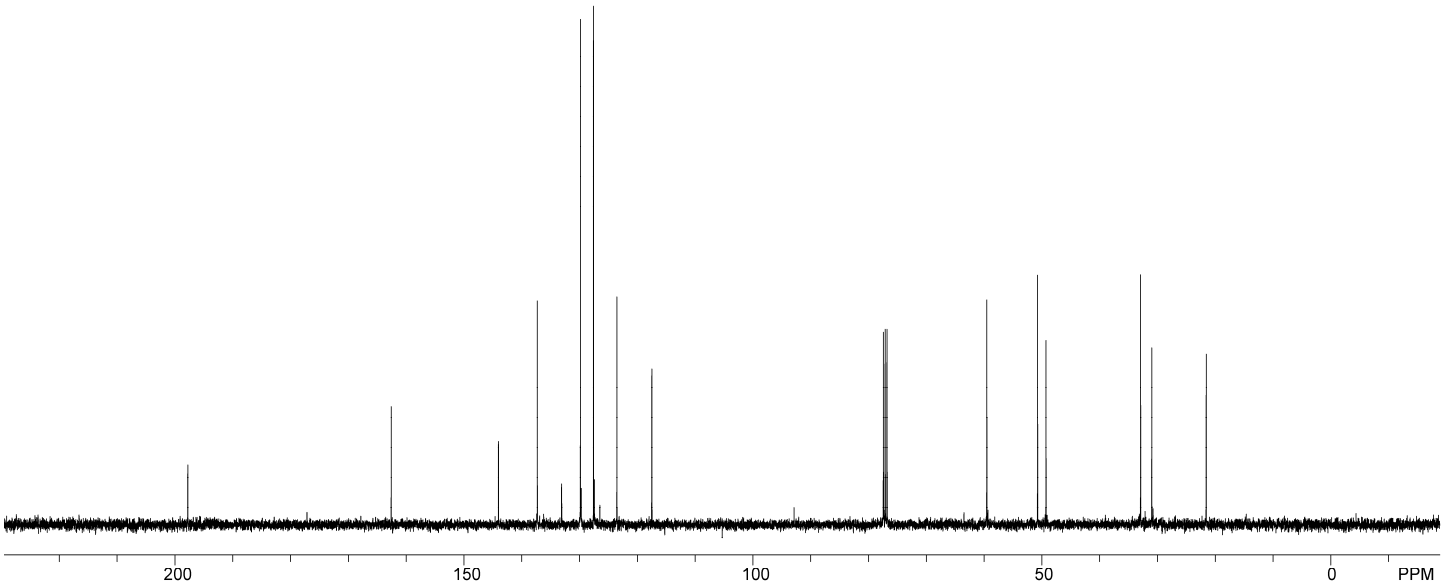

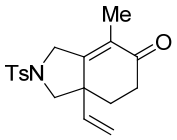


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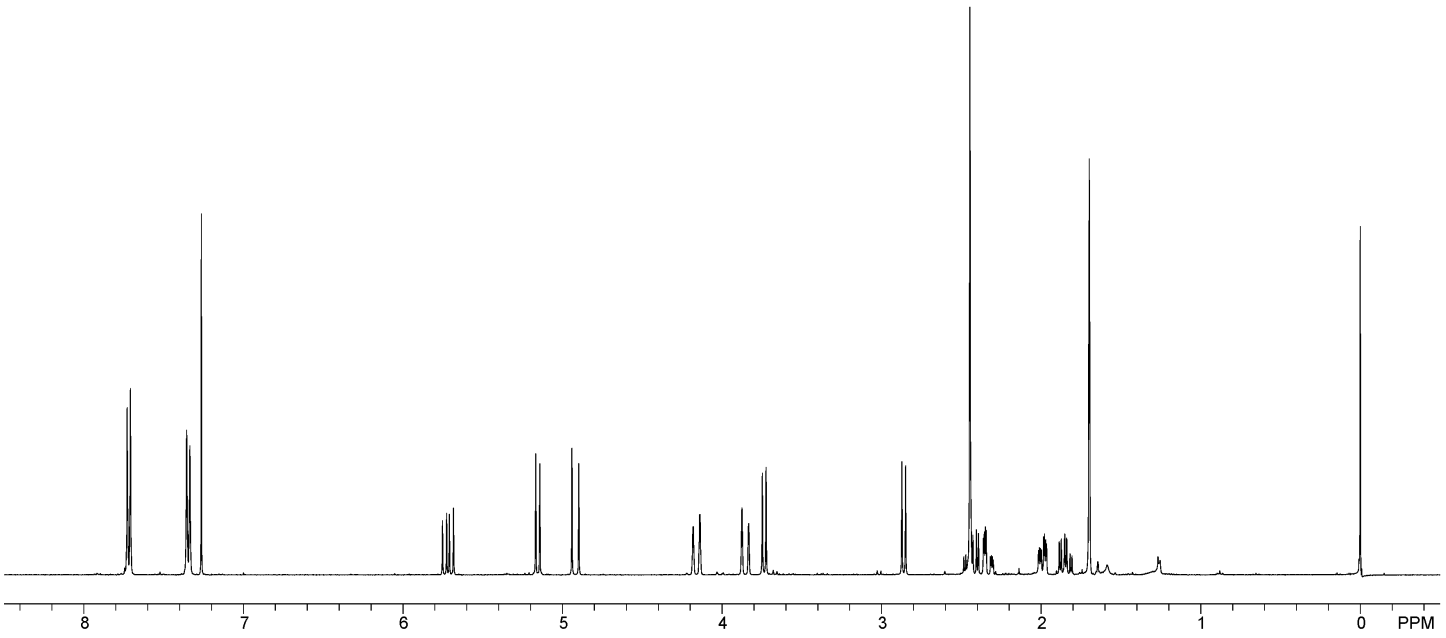


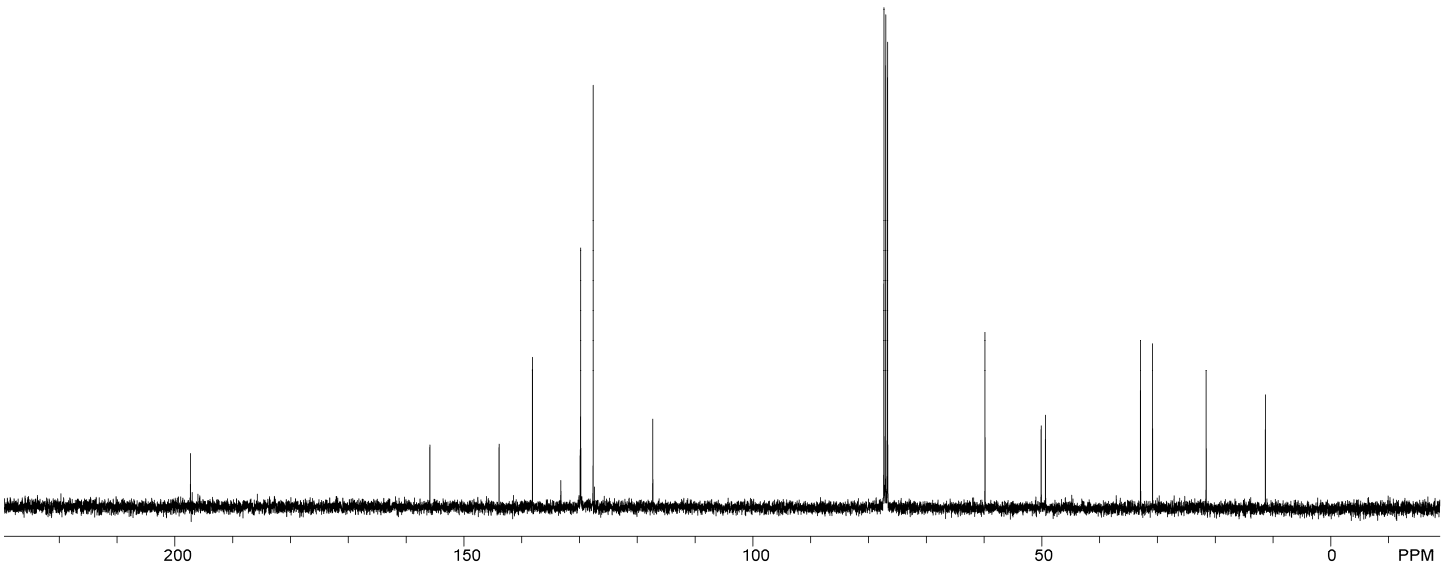

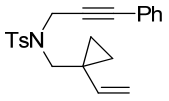


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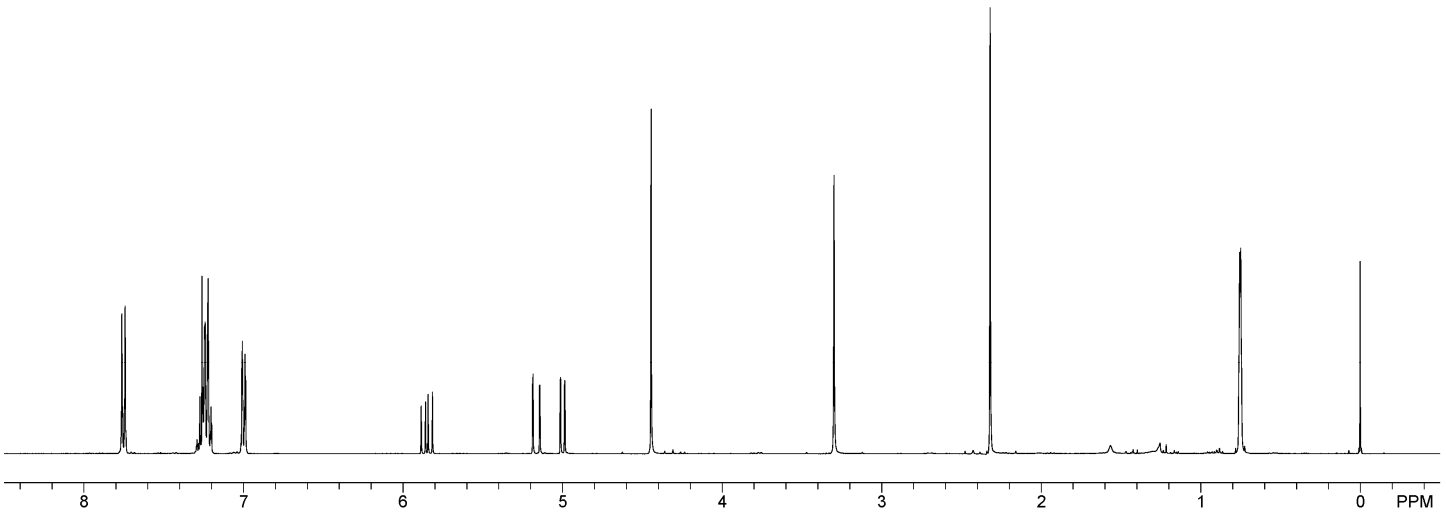


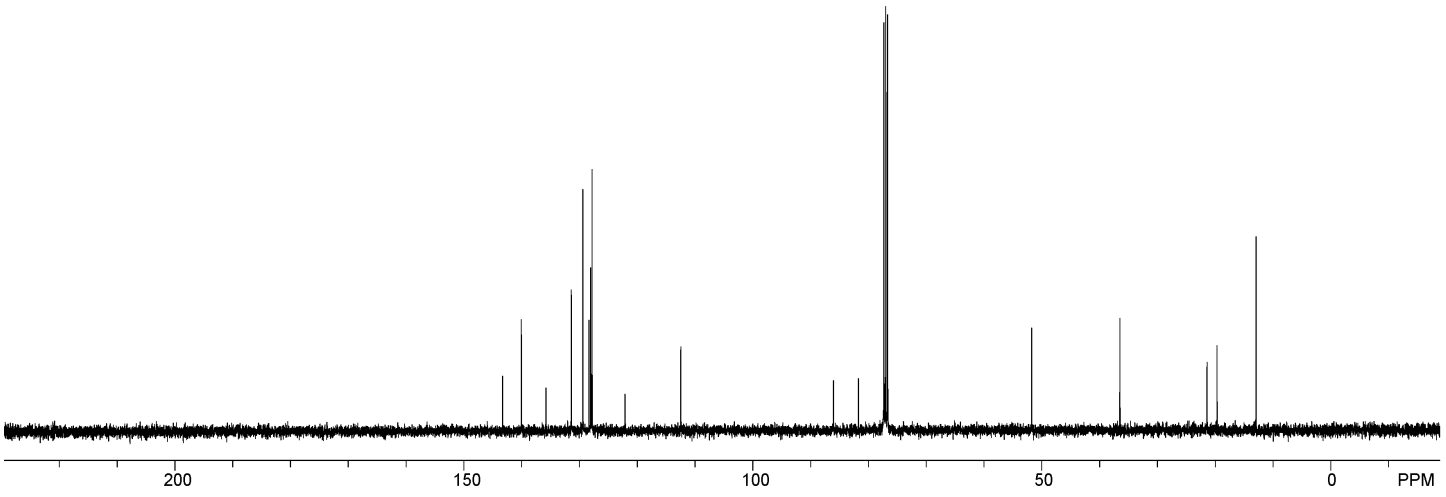

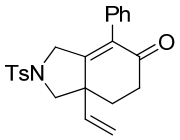


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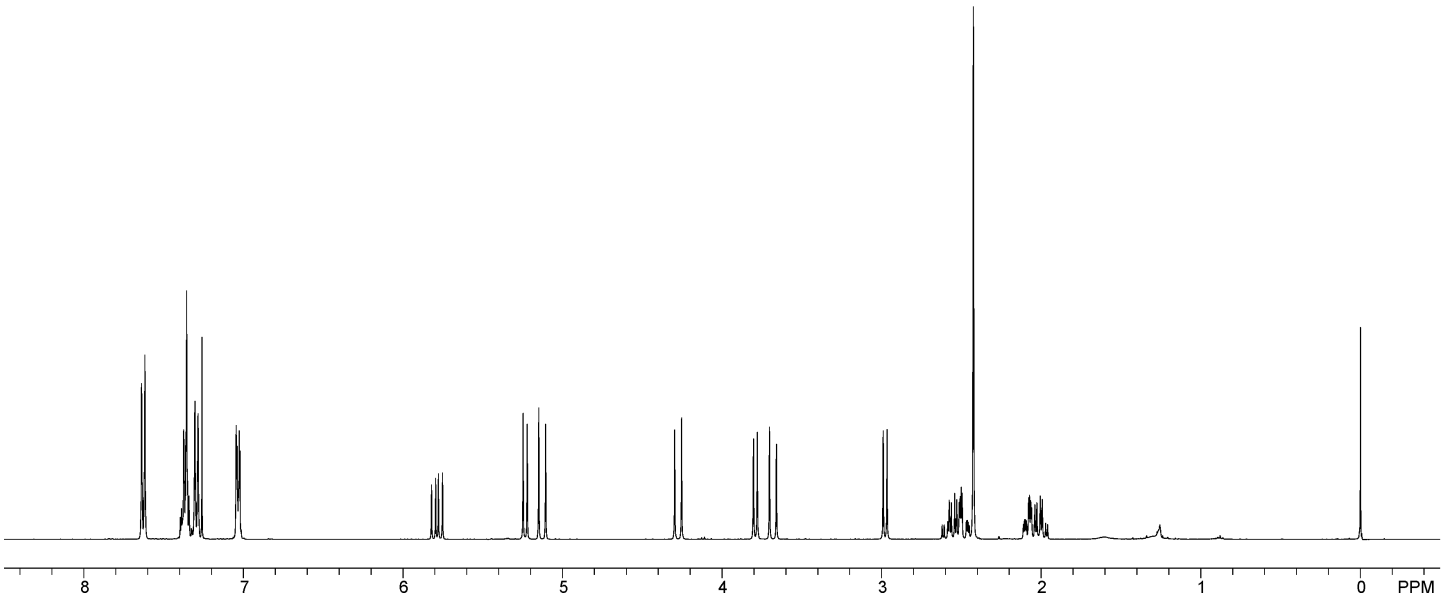


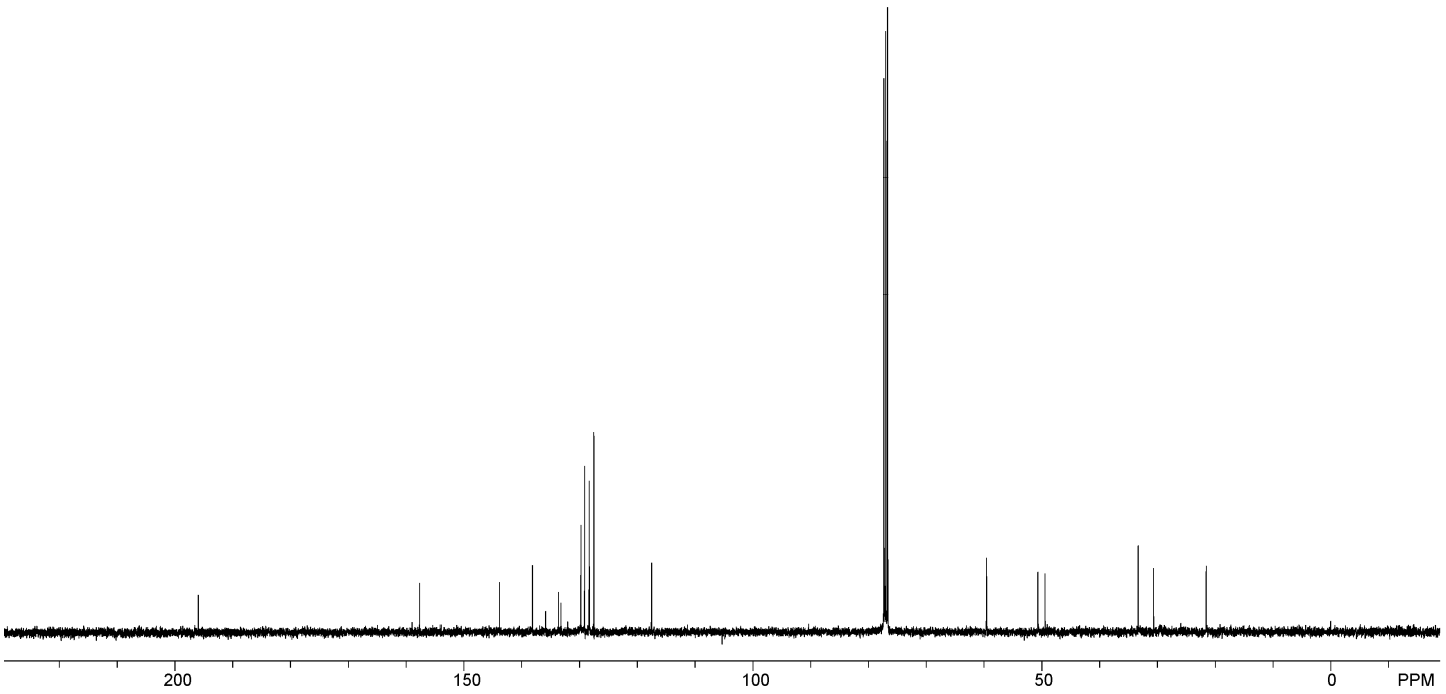

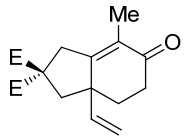


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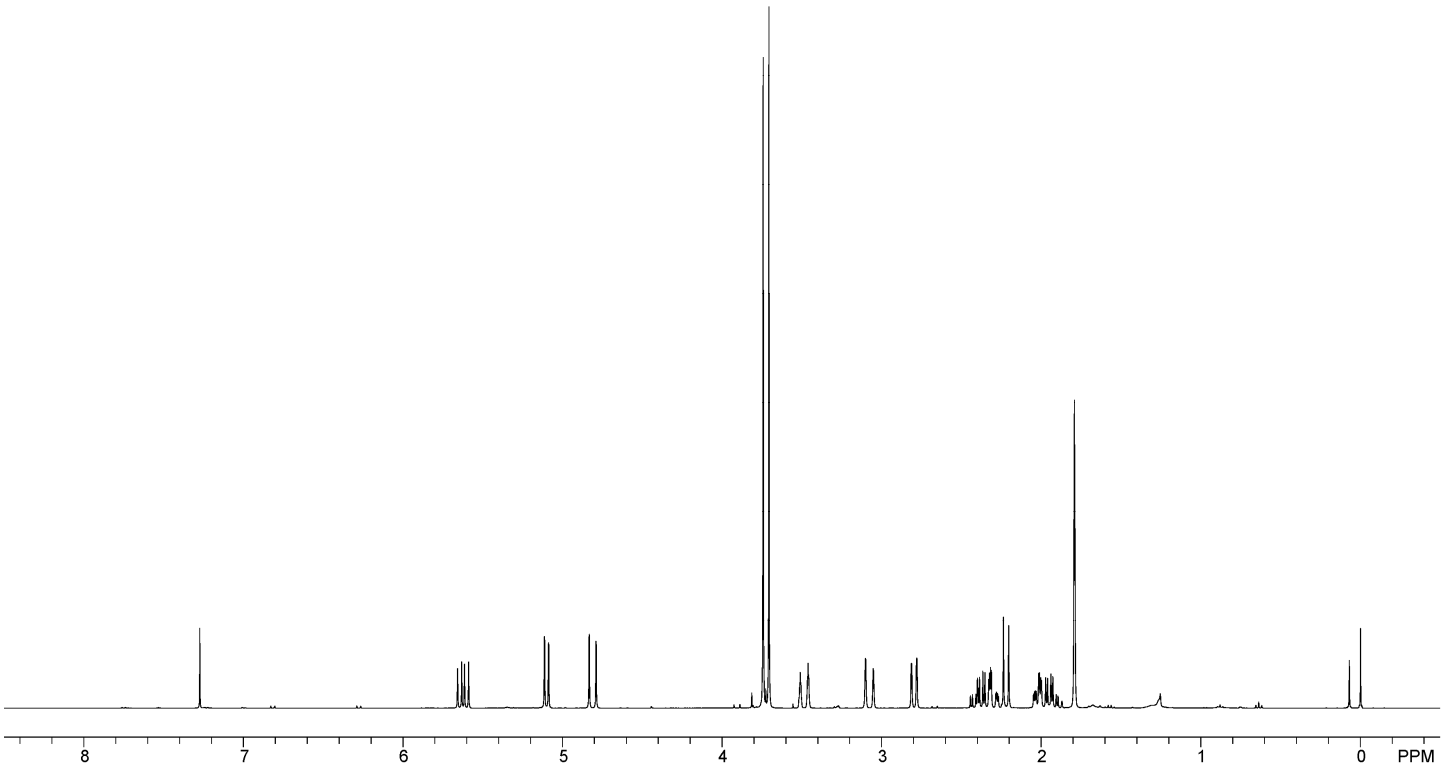


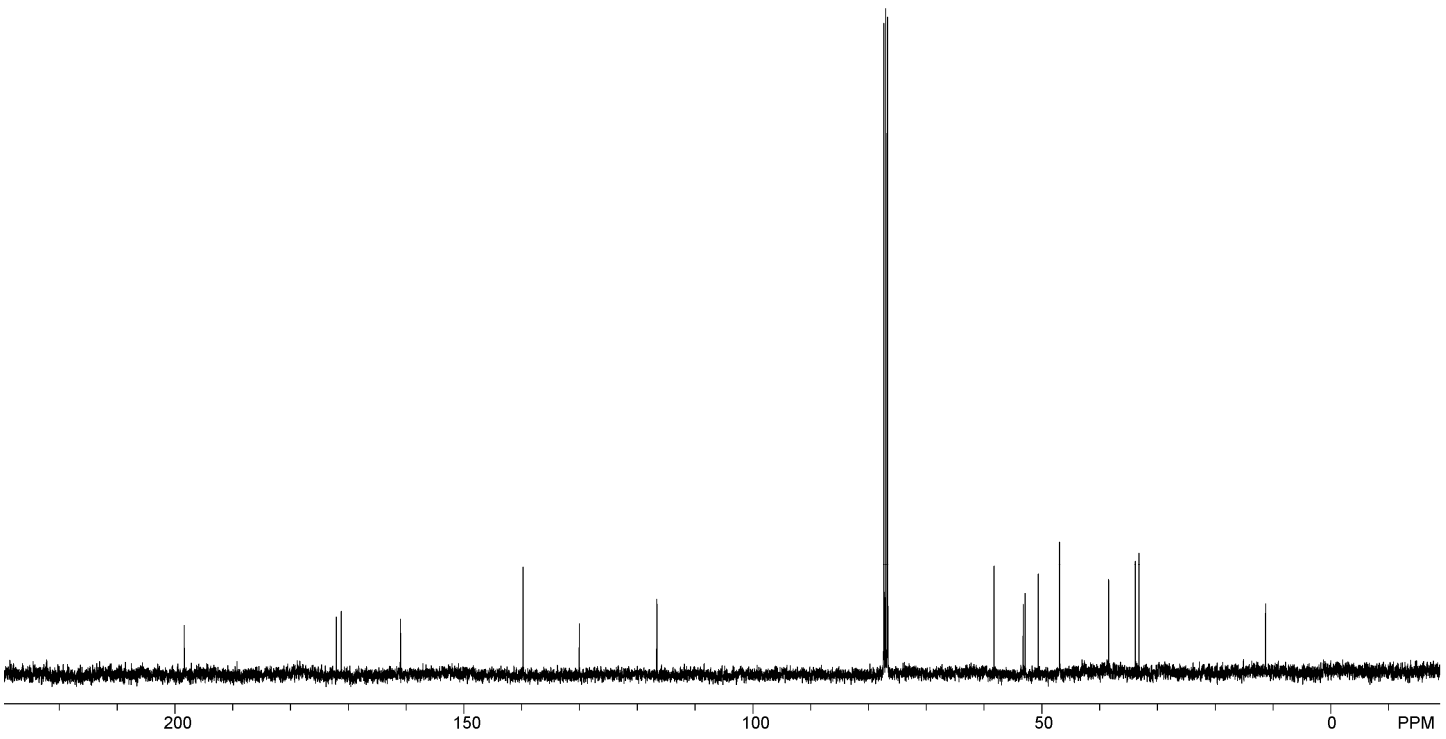

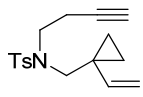


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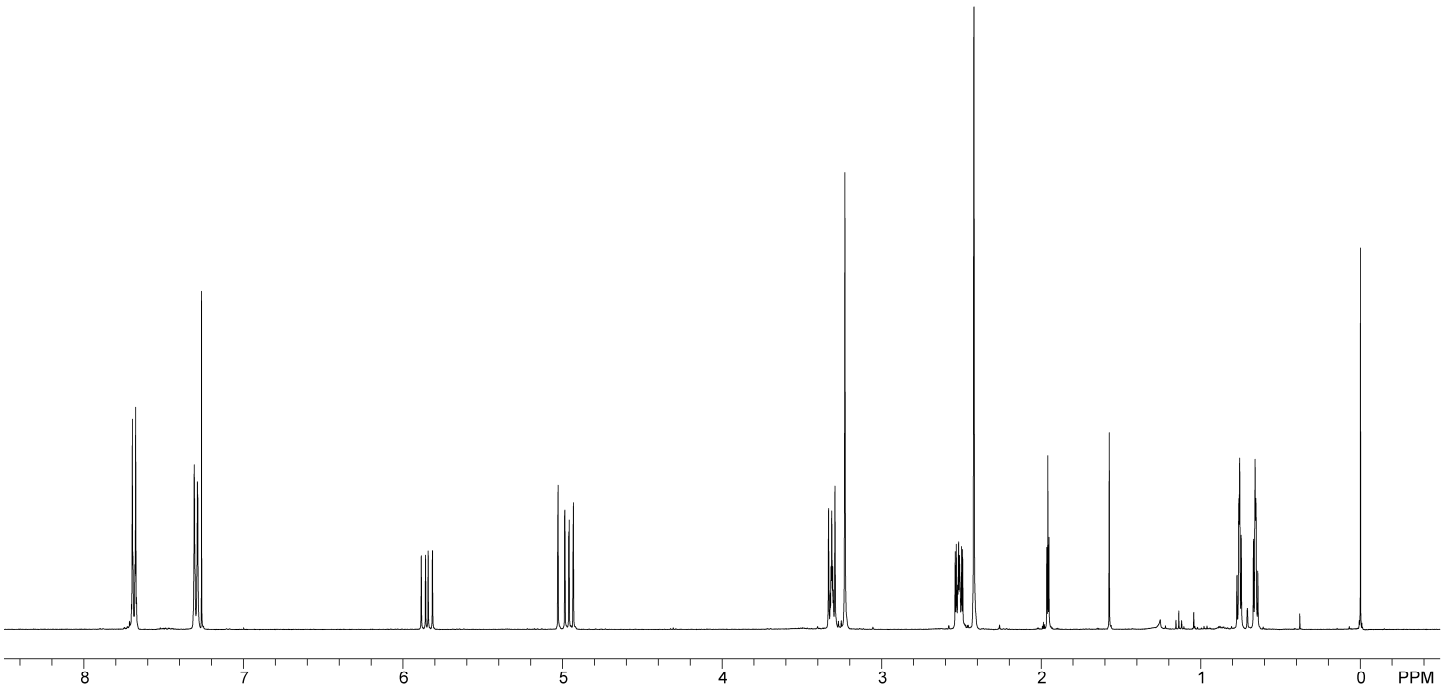


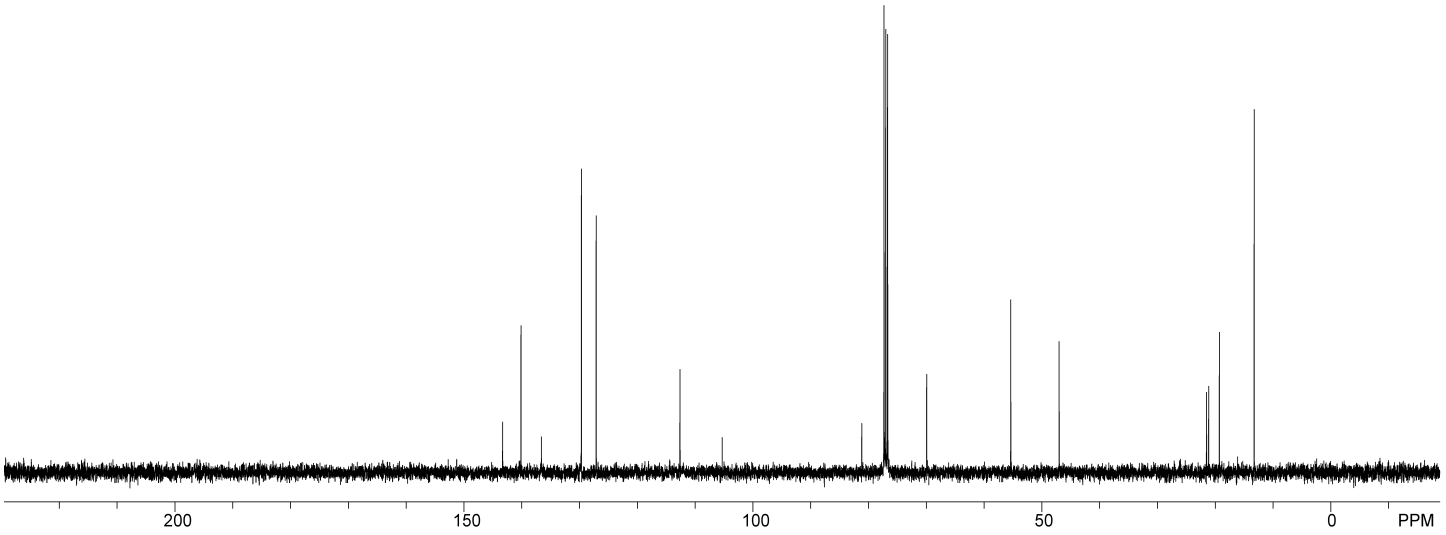

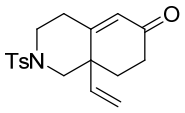


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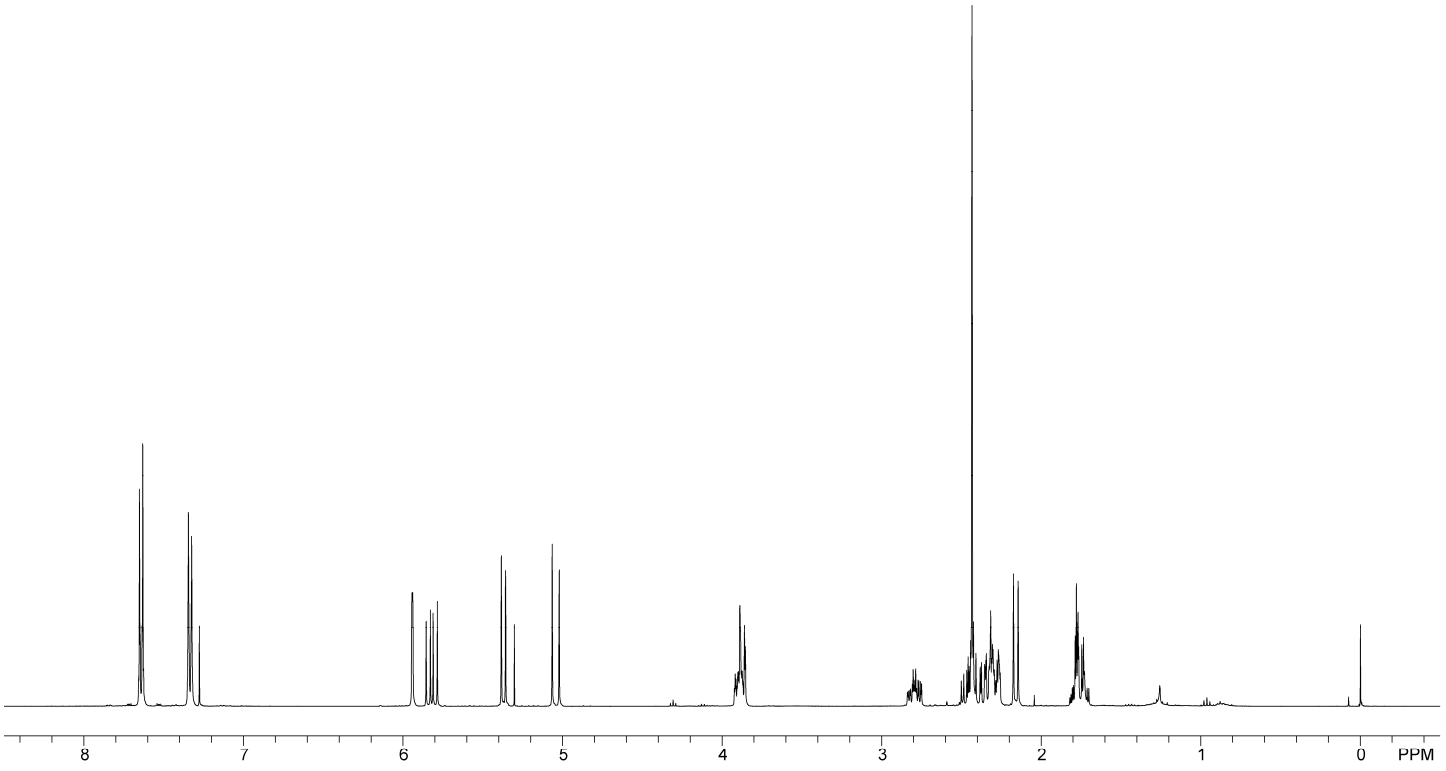


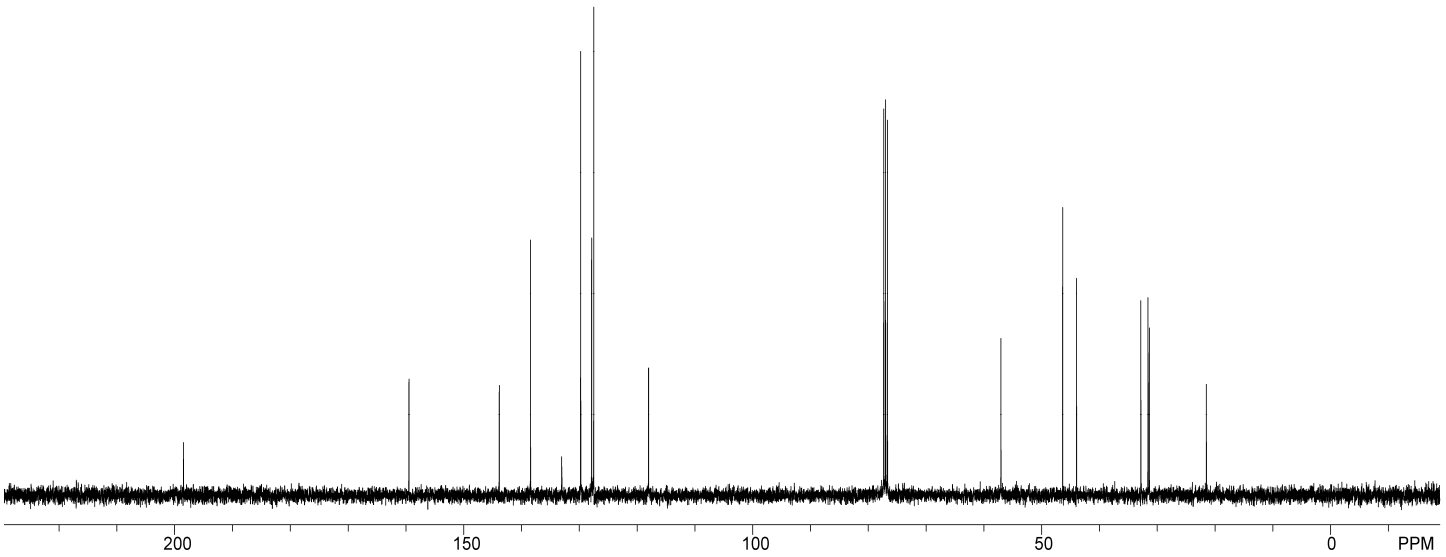

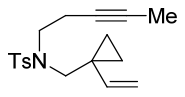


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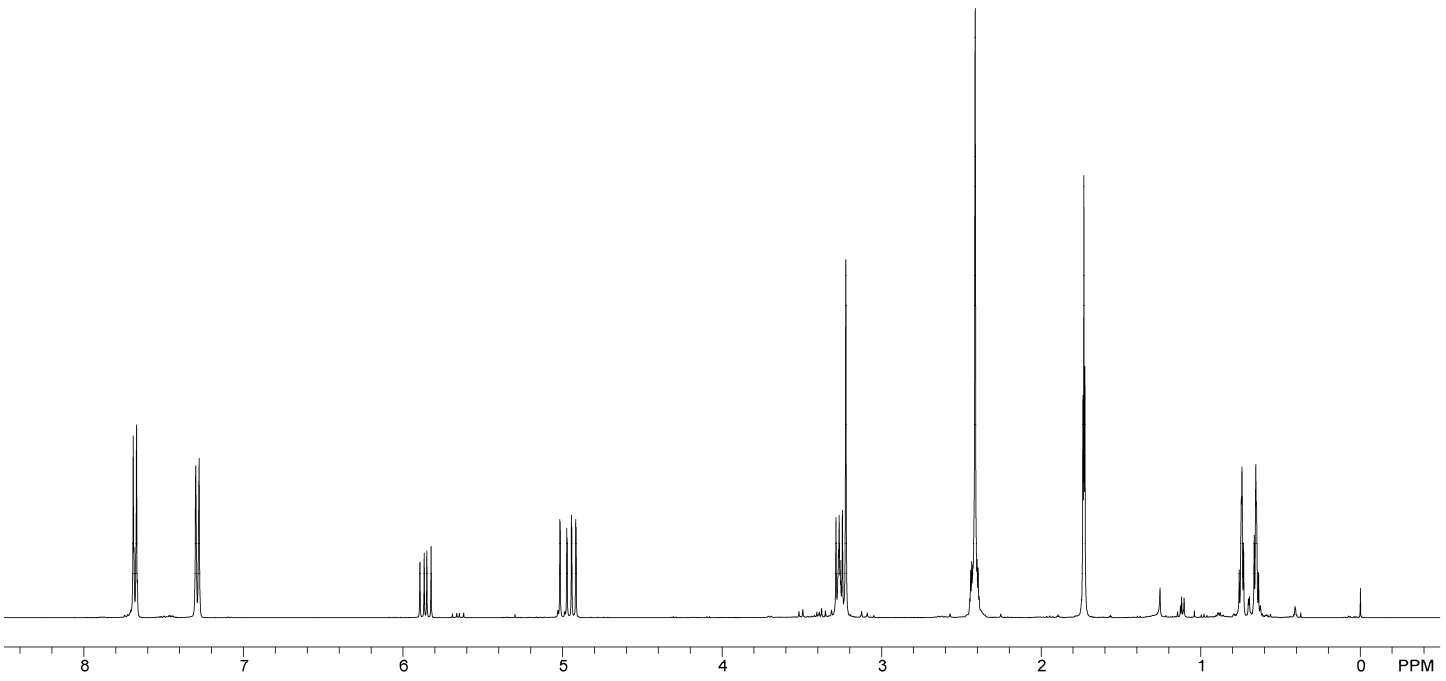


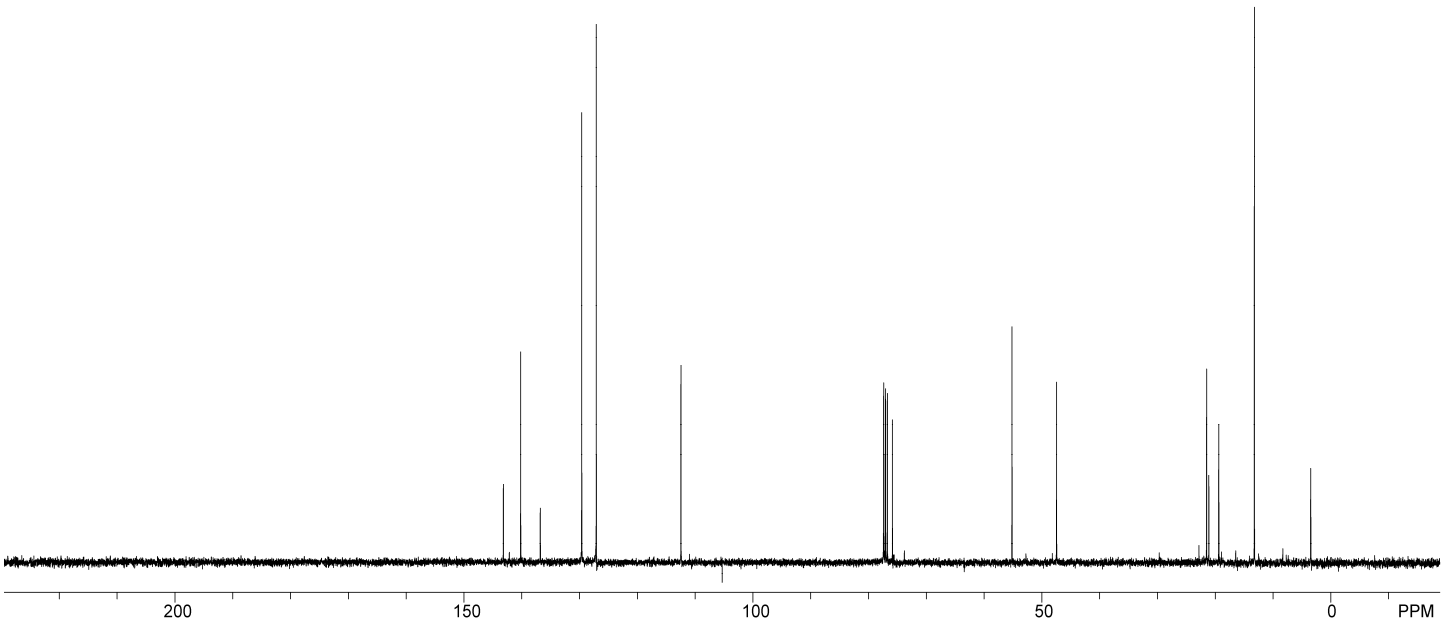

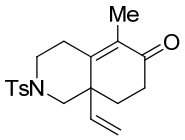


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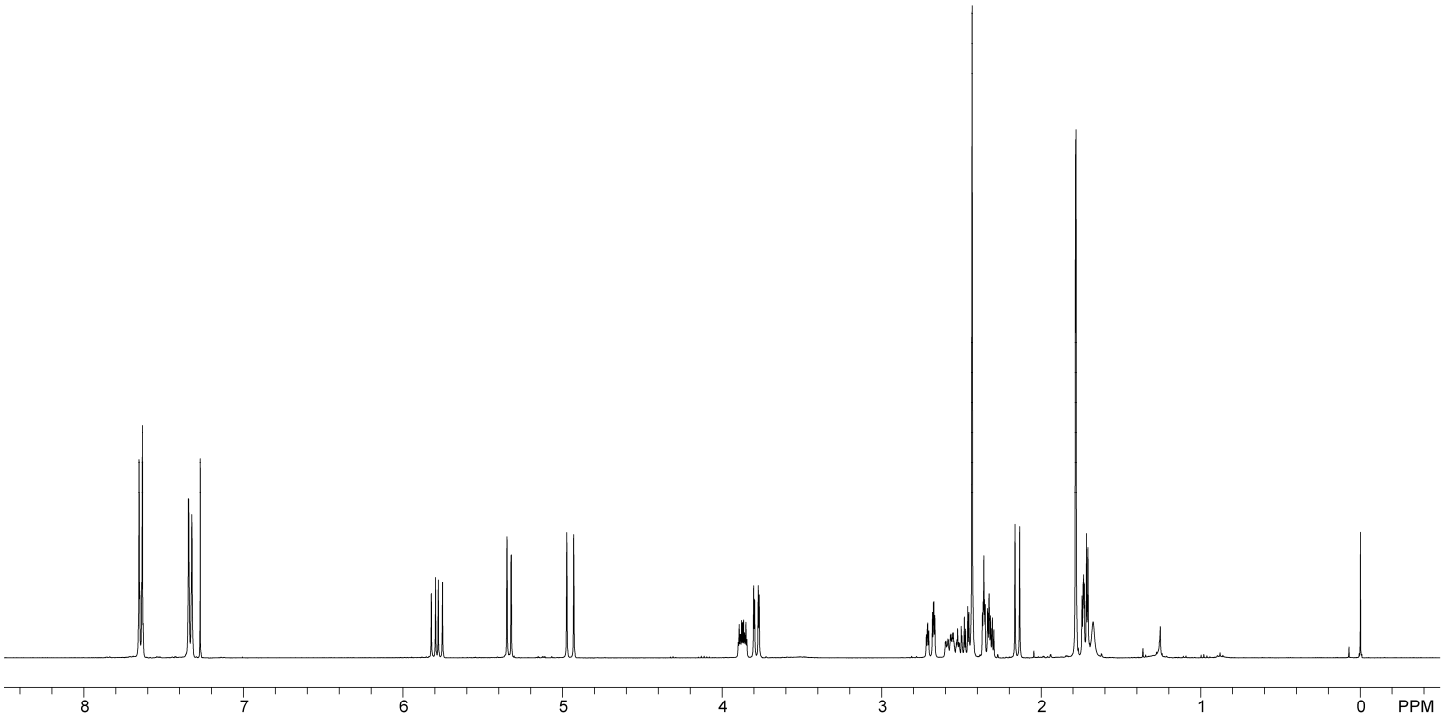


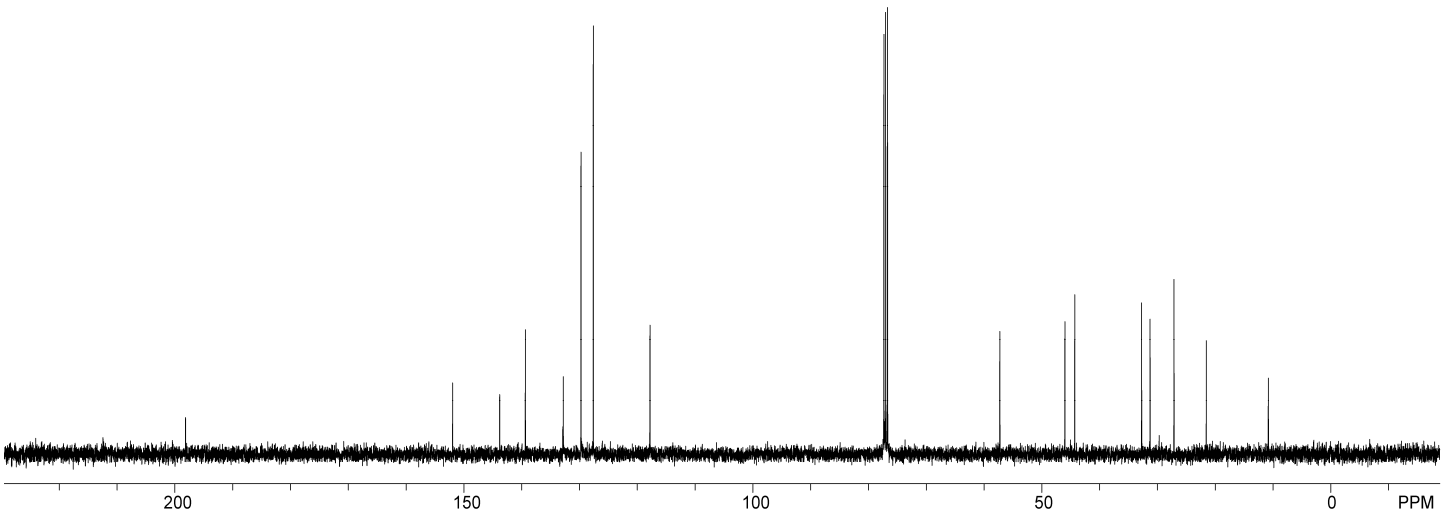

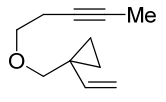


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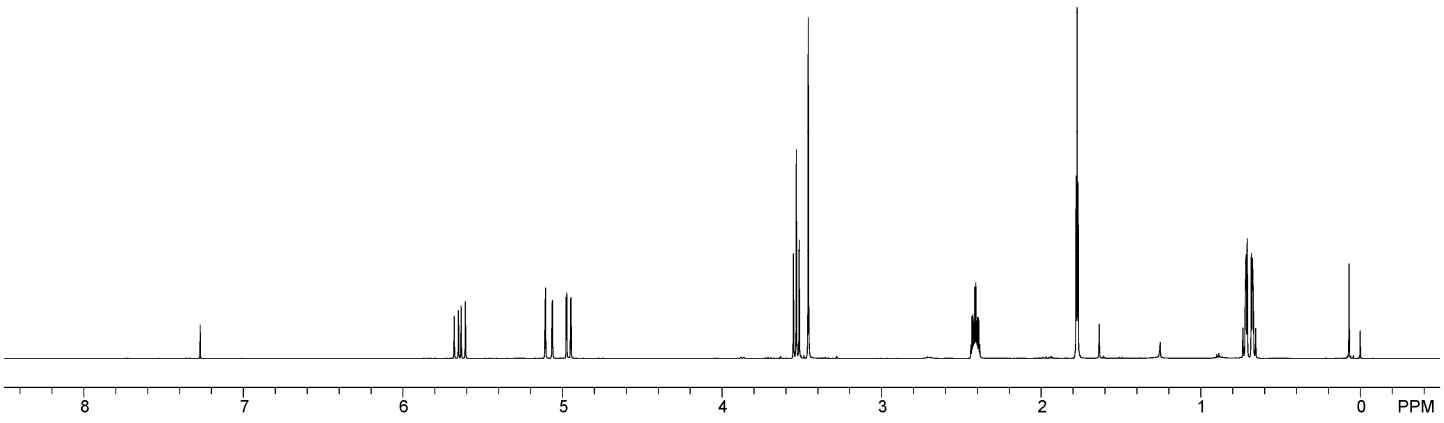


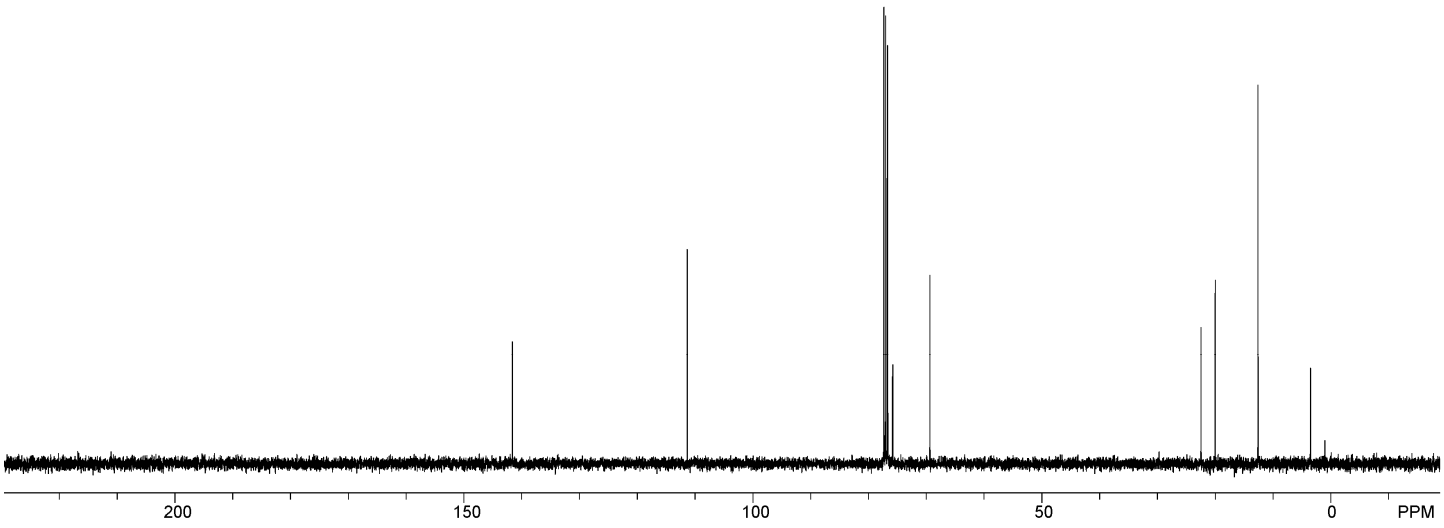

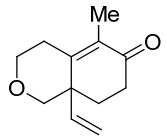


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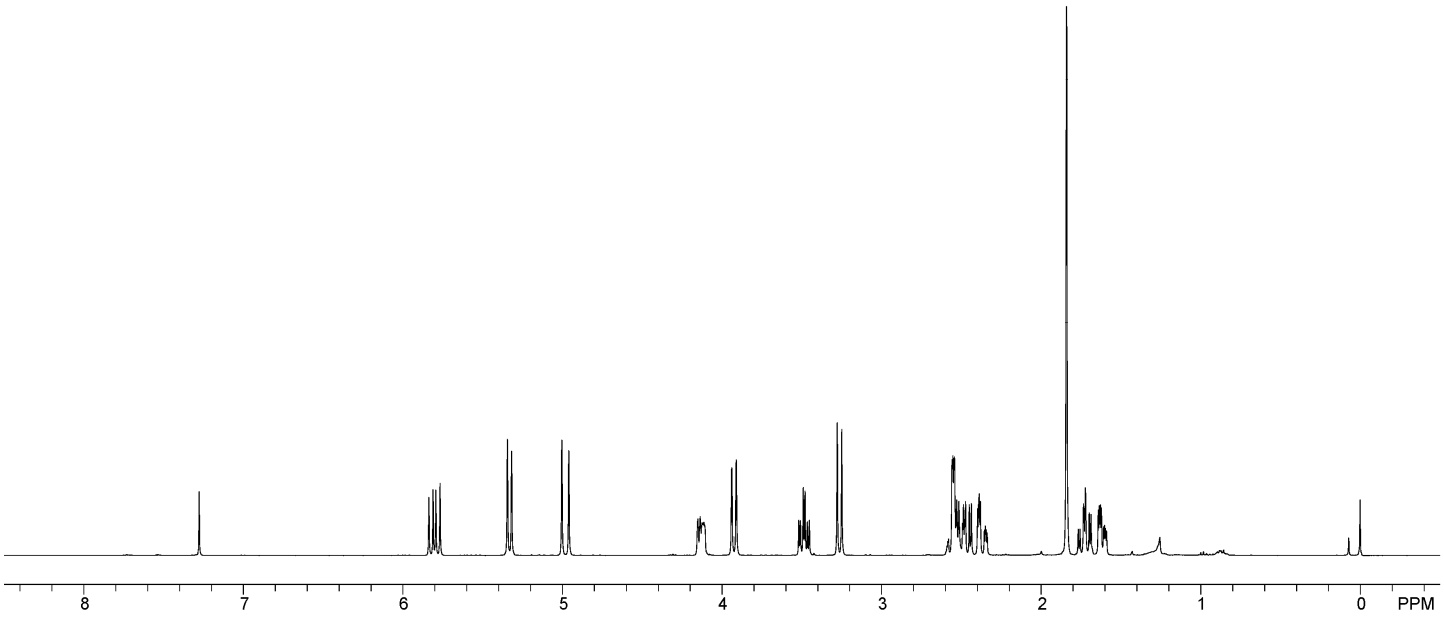


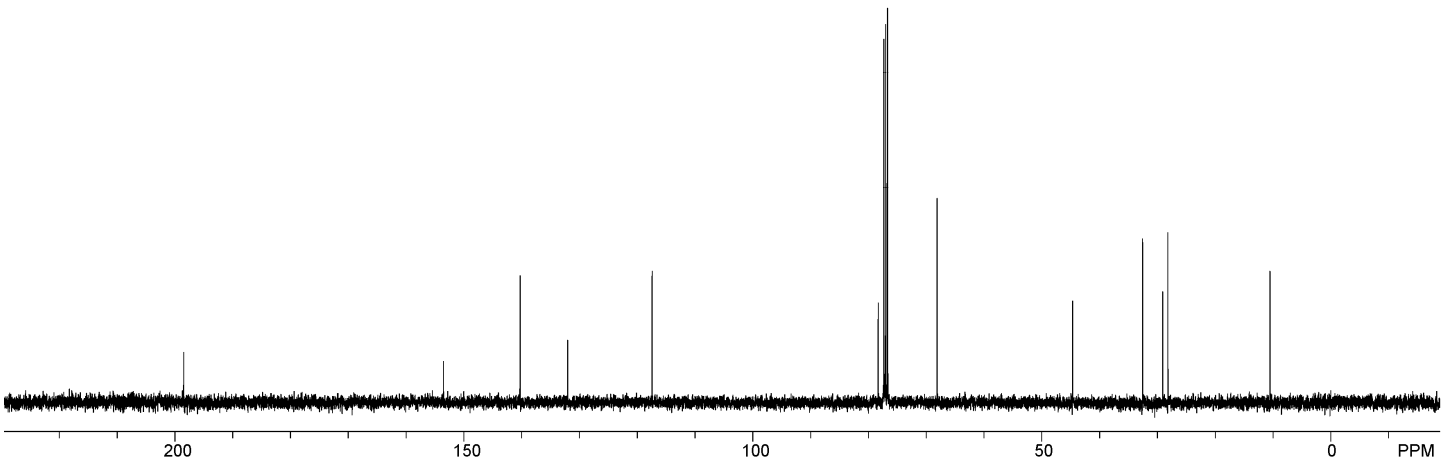

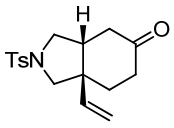


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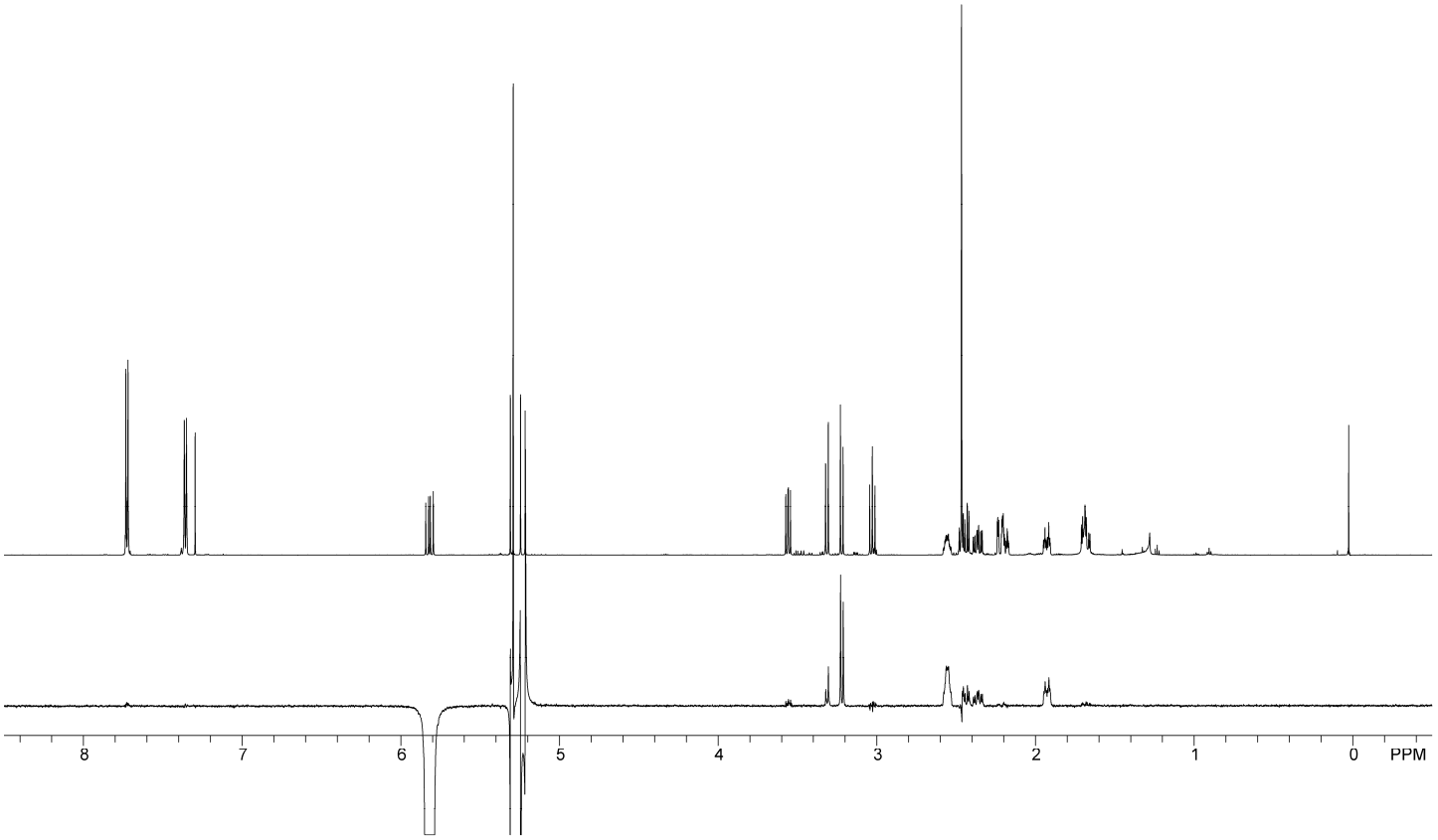
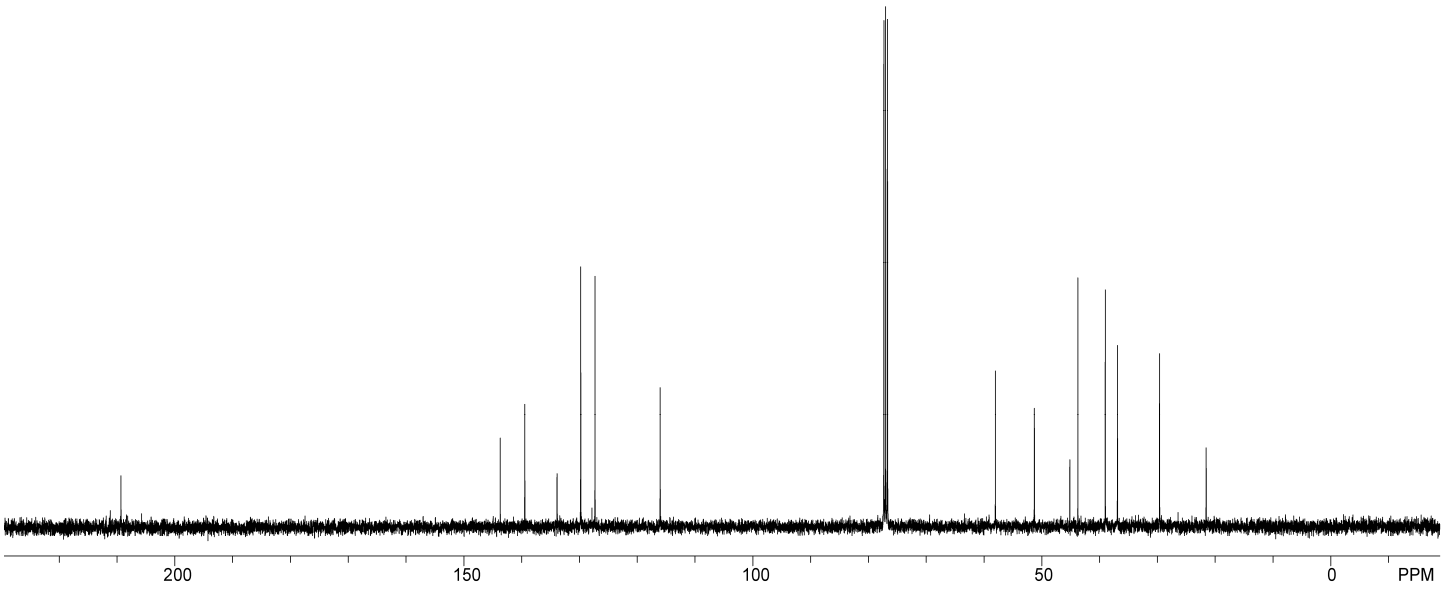
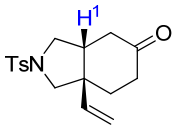


**HSQC Spectra for Cycloadduct 16**

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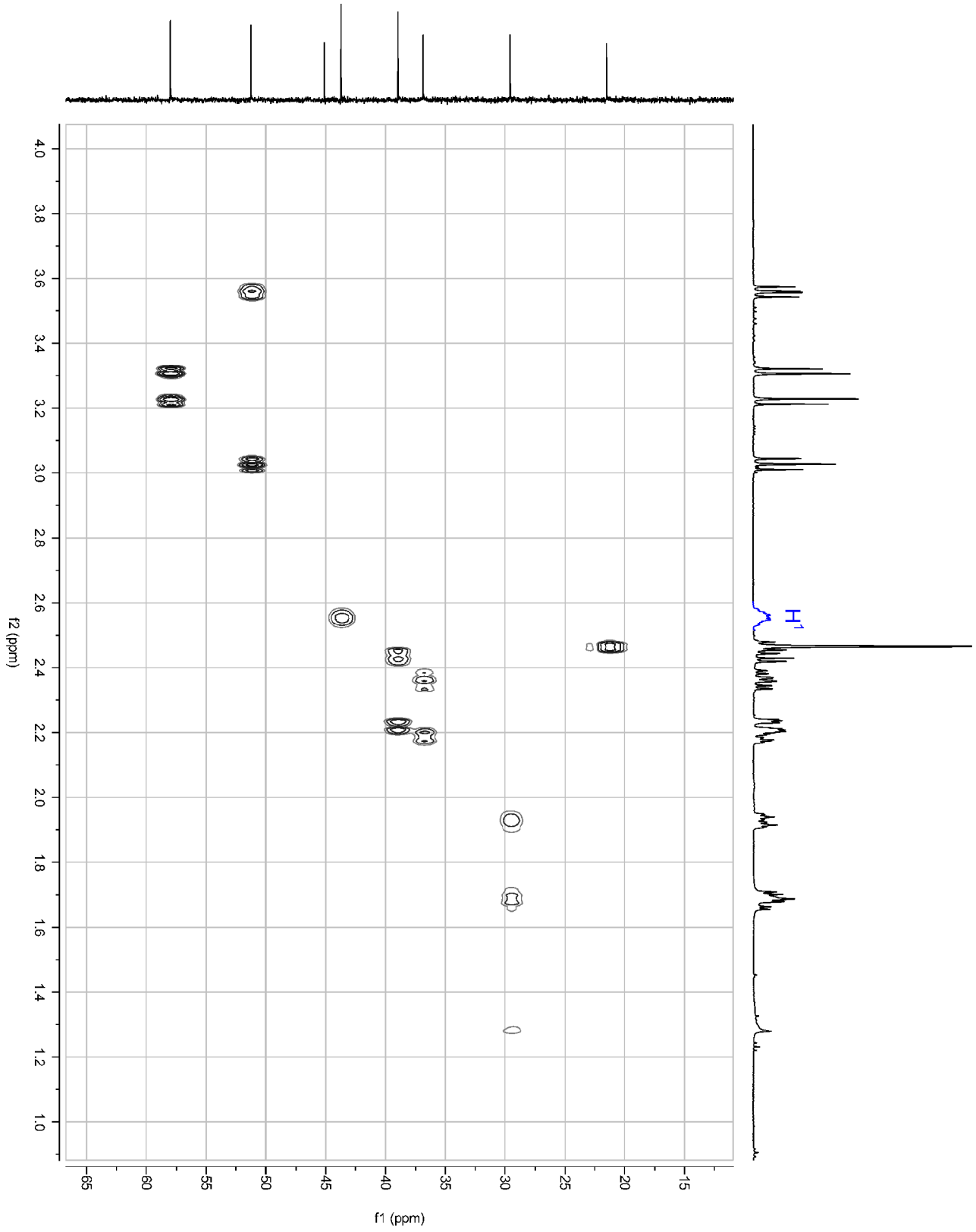

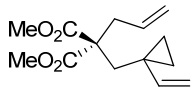


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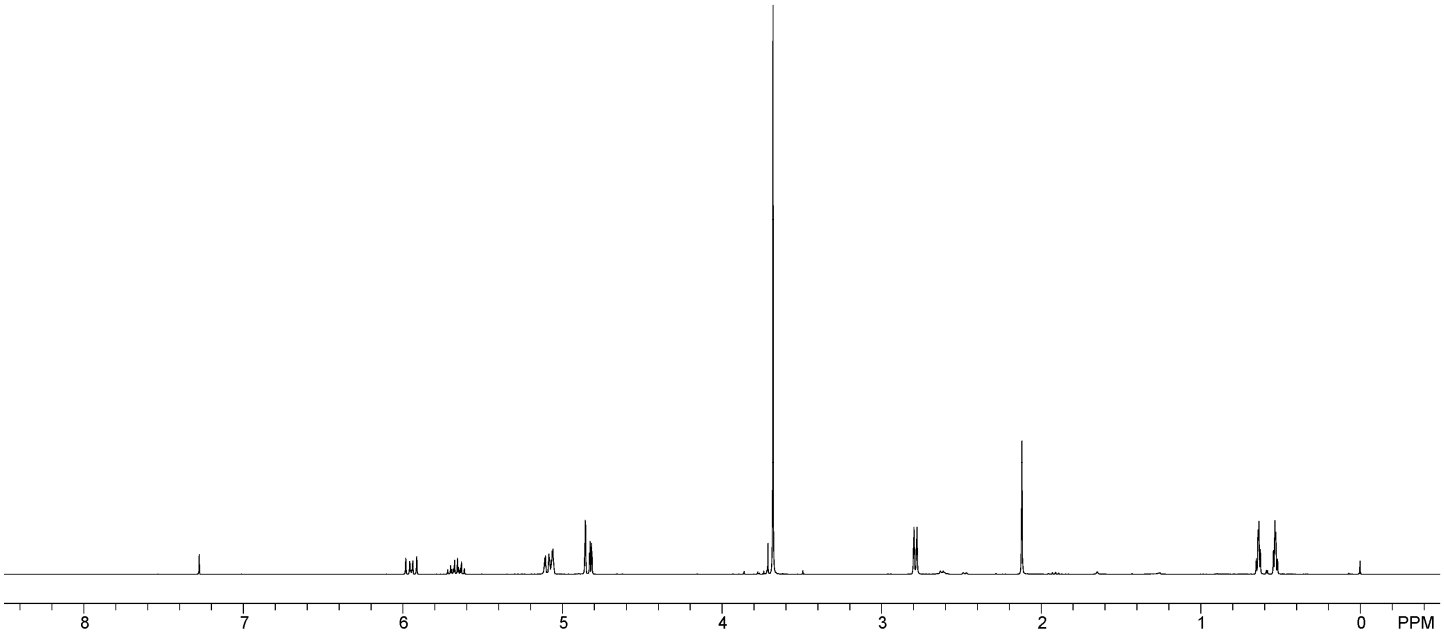


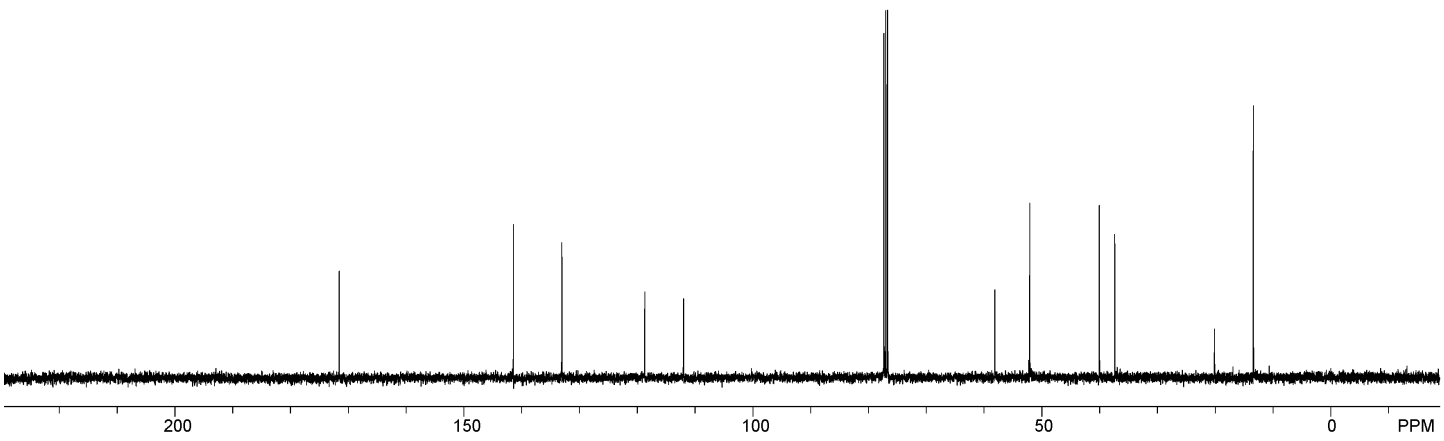

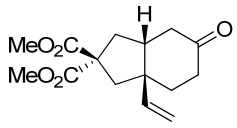


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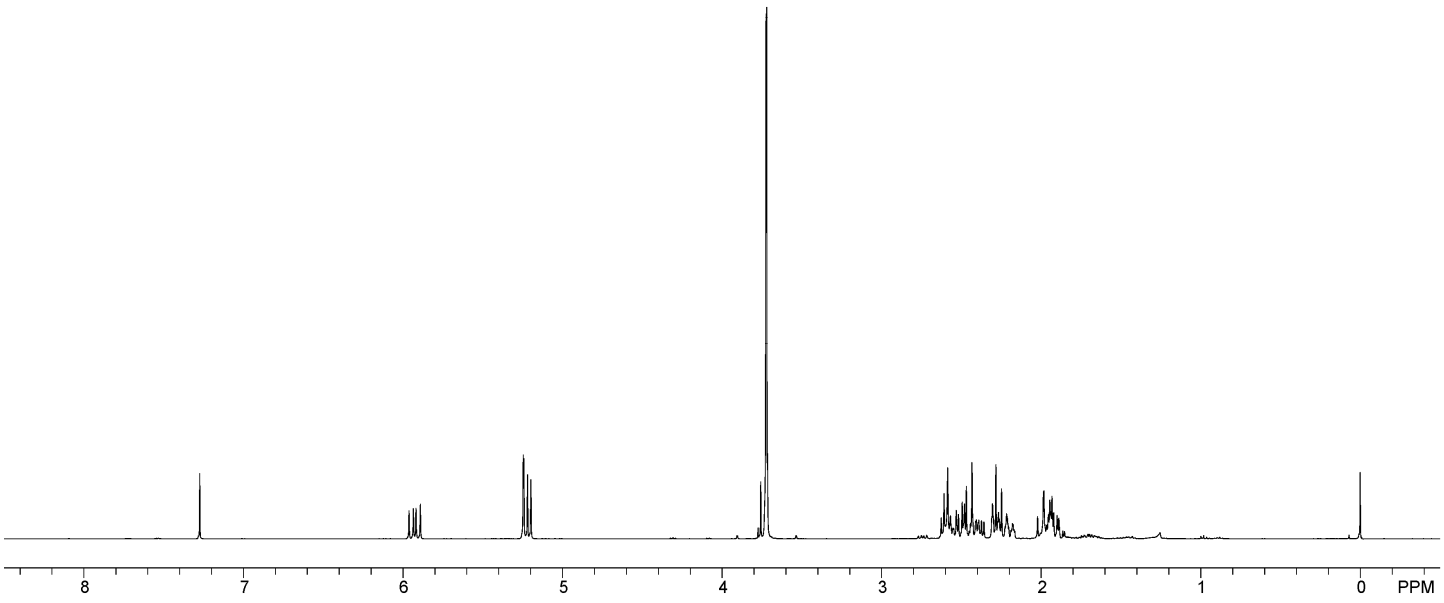


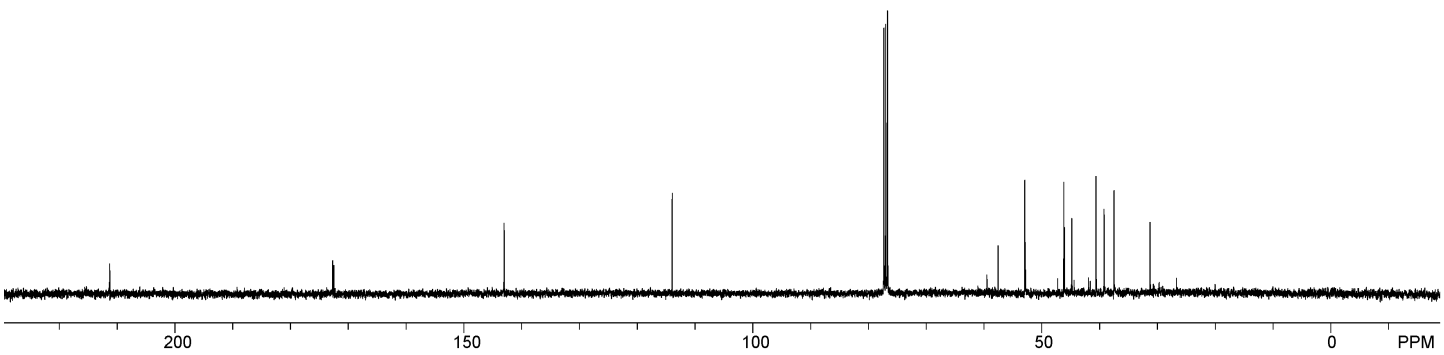

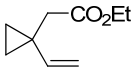


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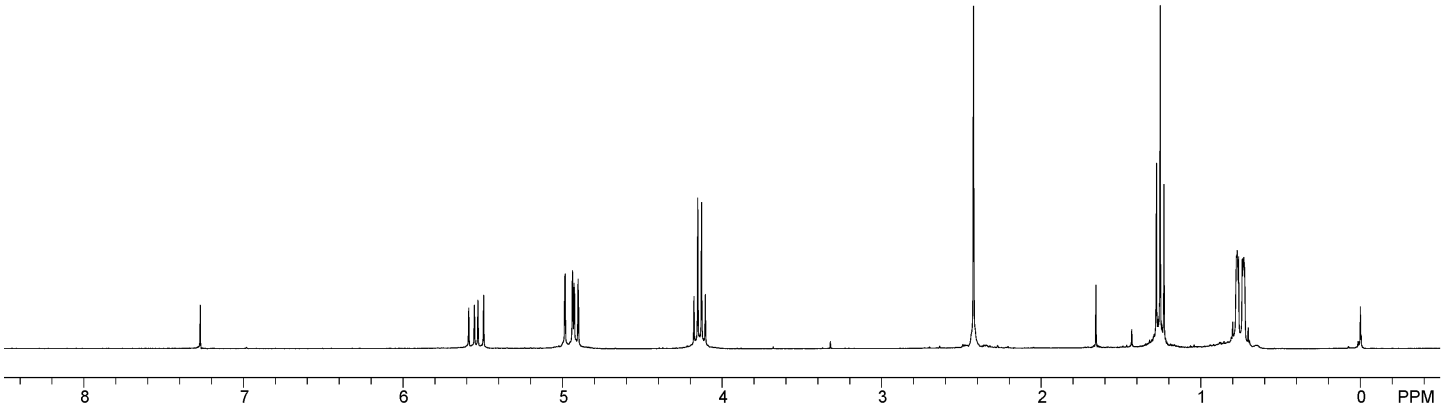


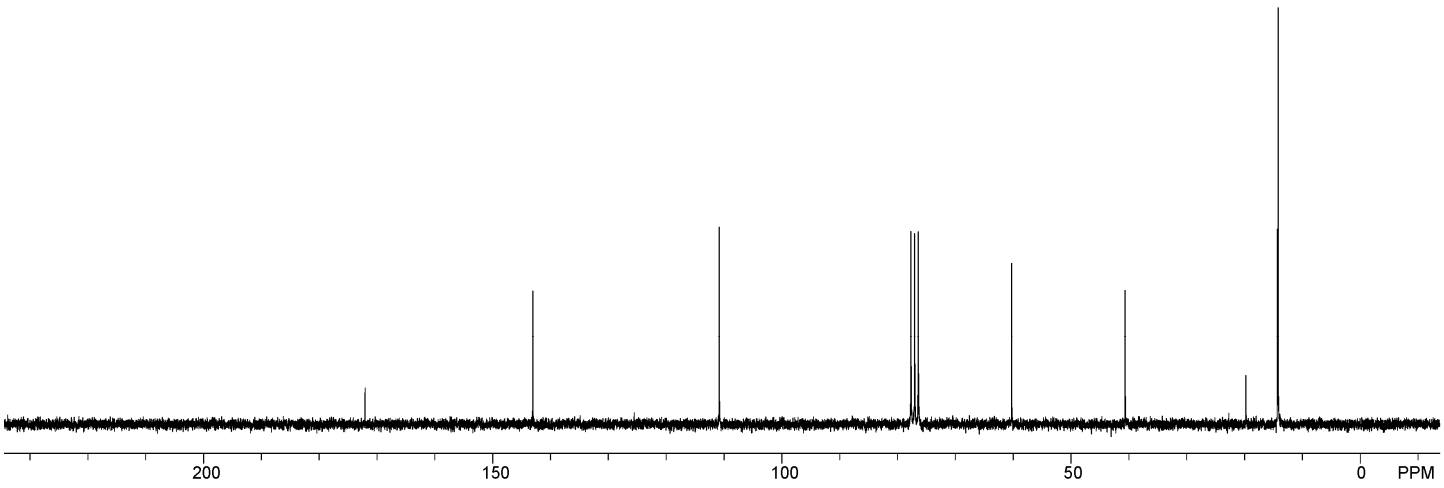

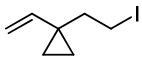

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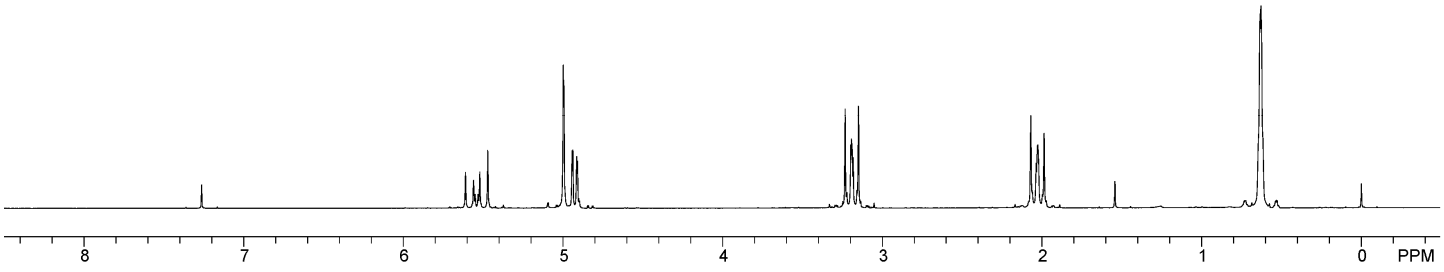


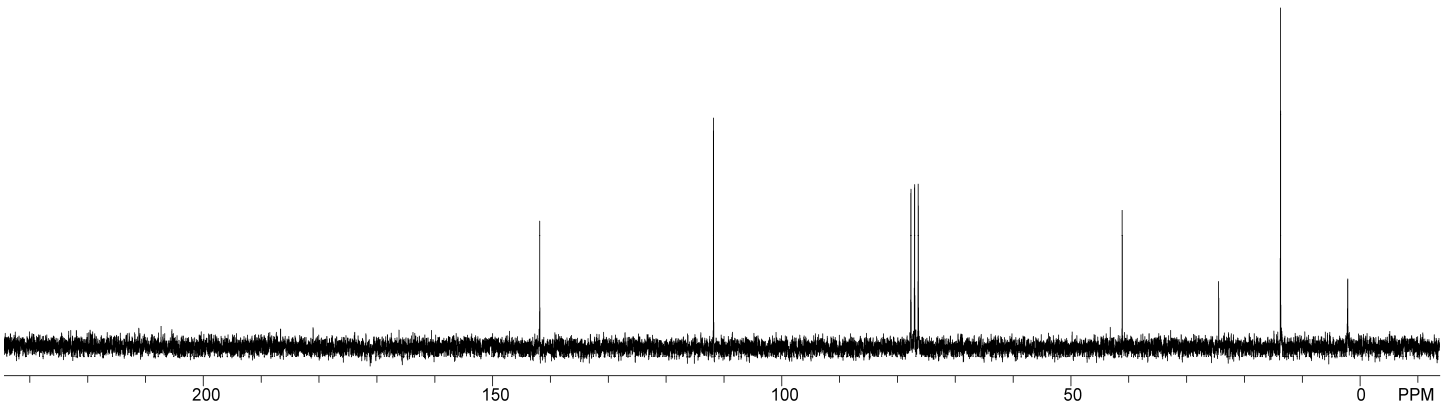

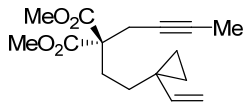


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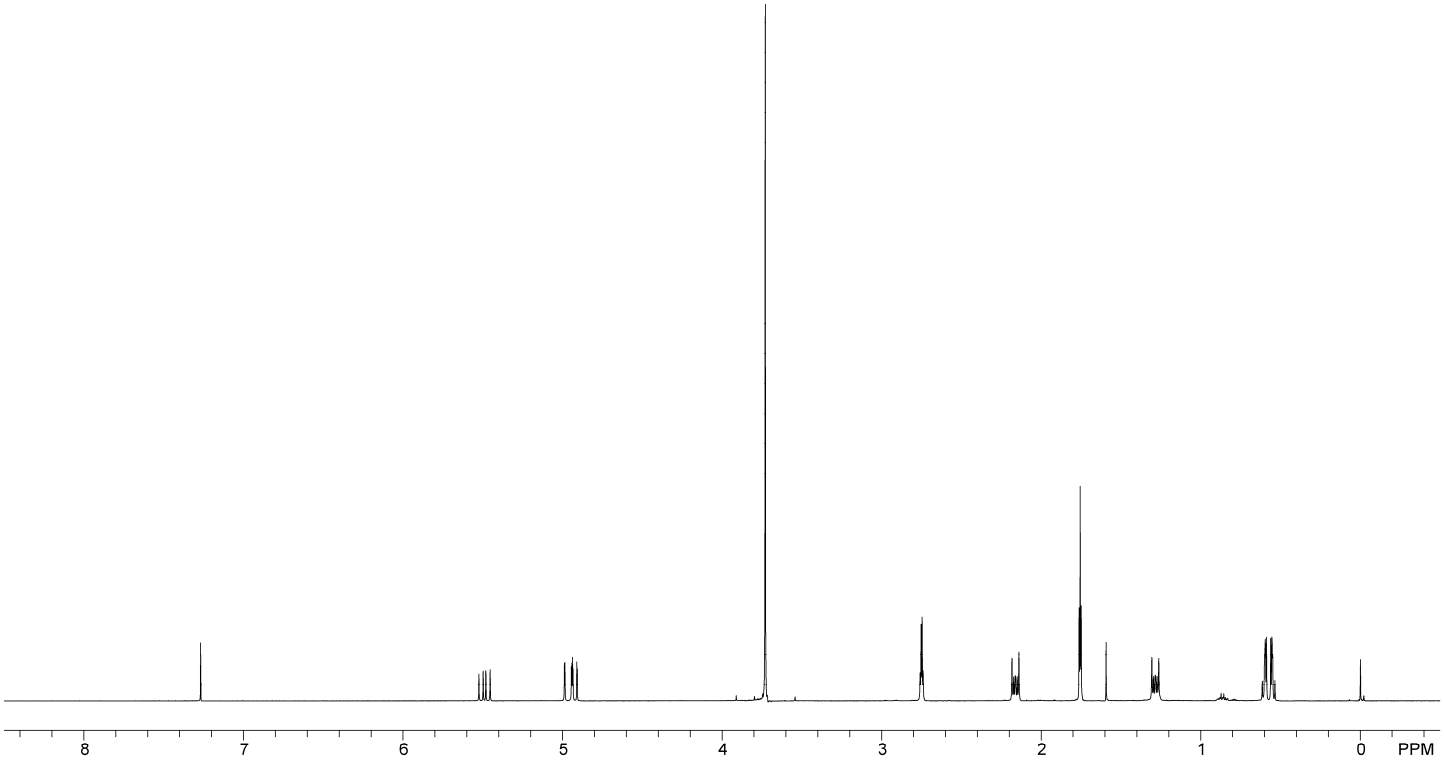


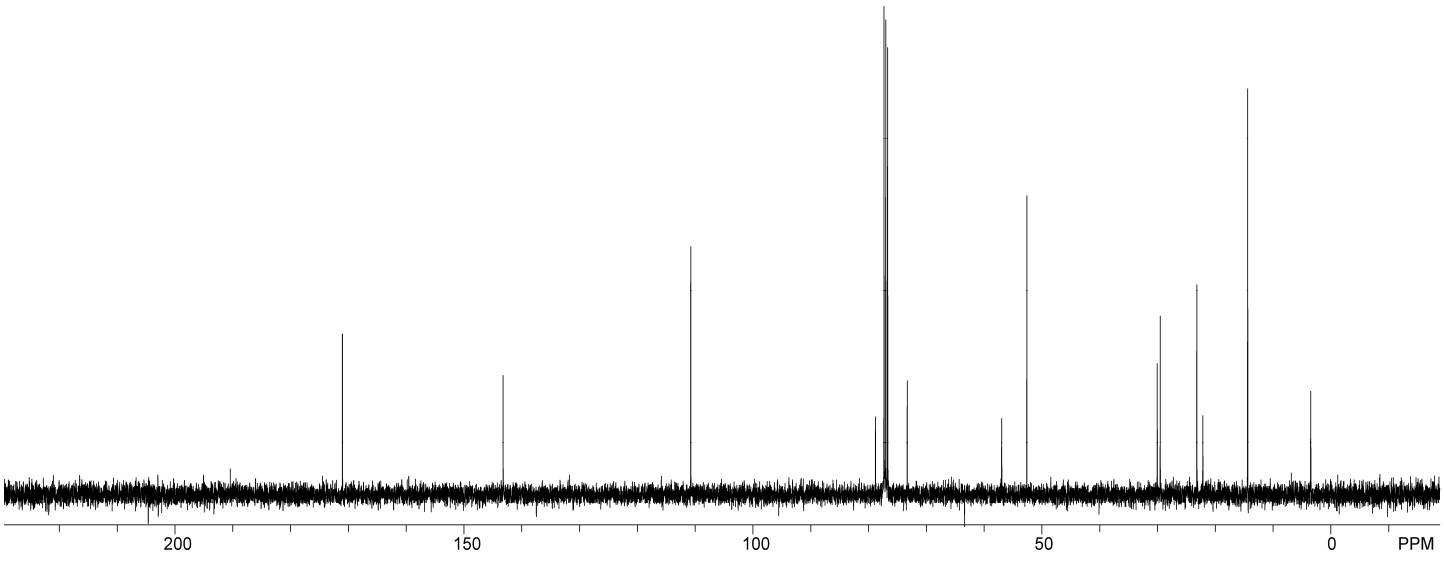

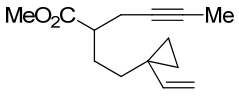


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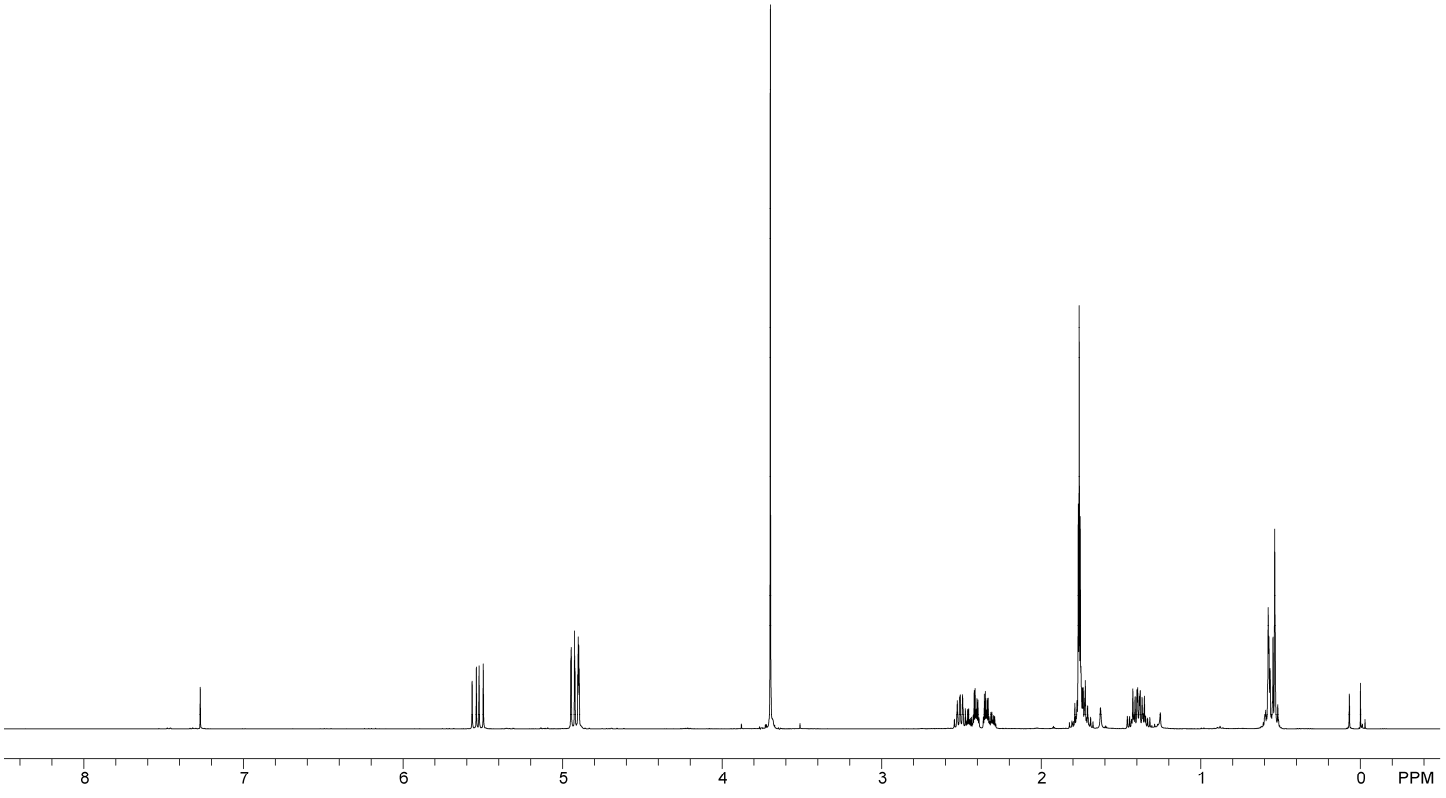


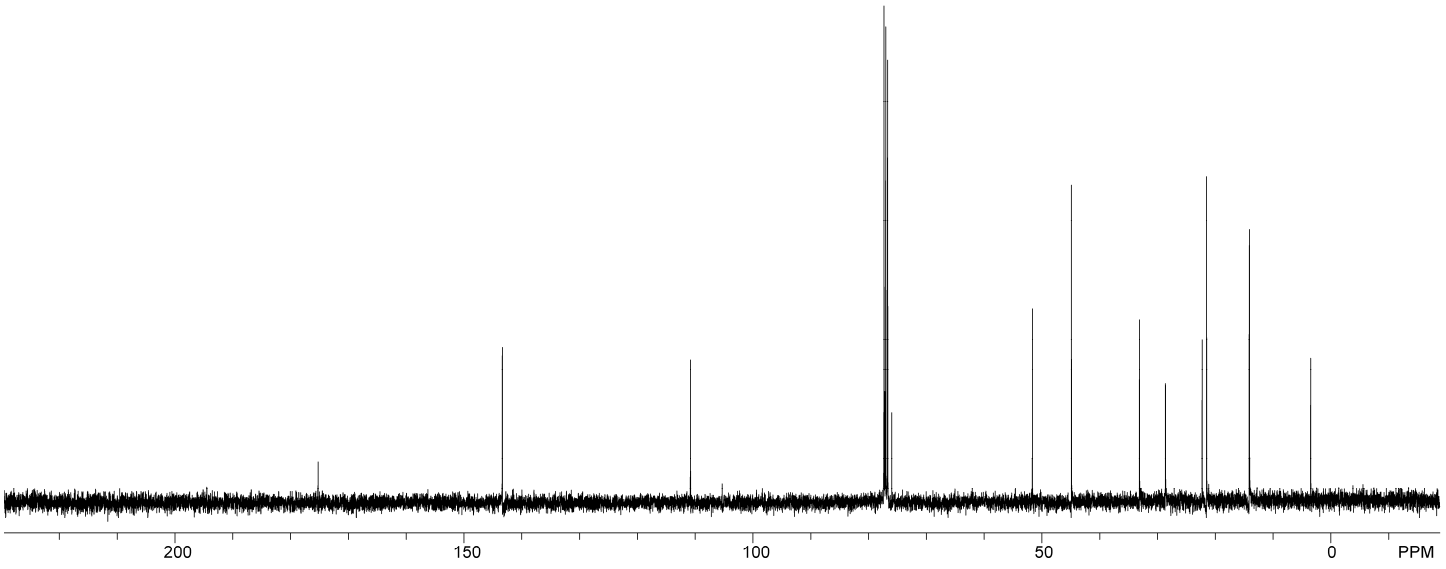

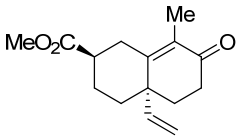


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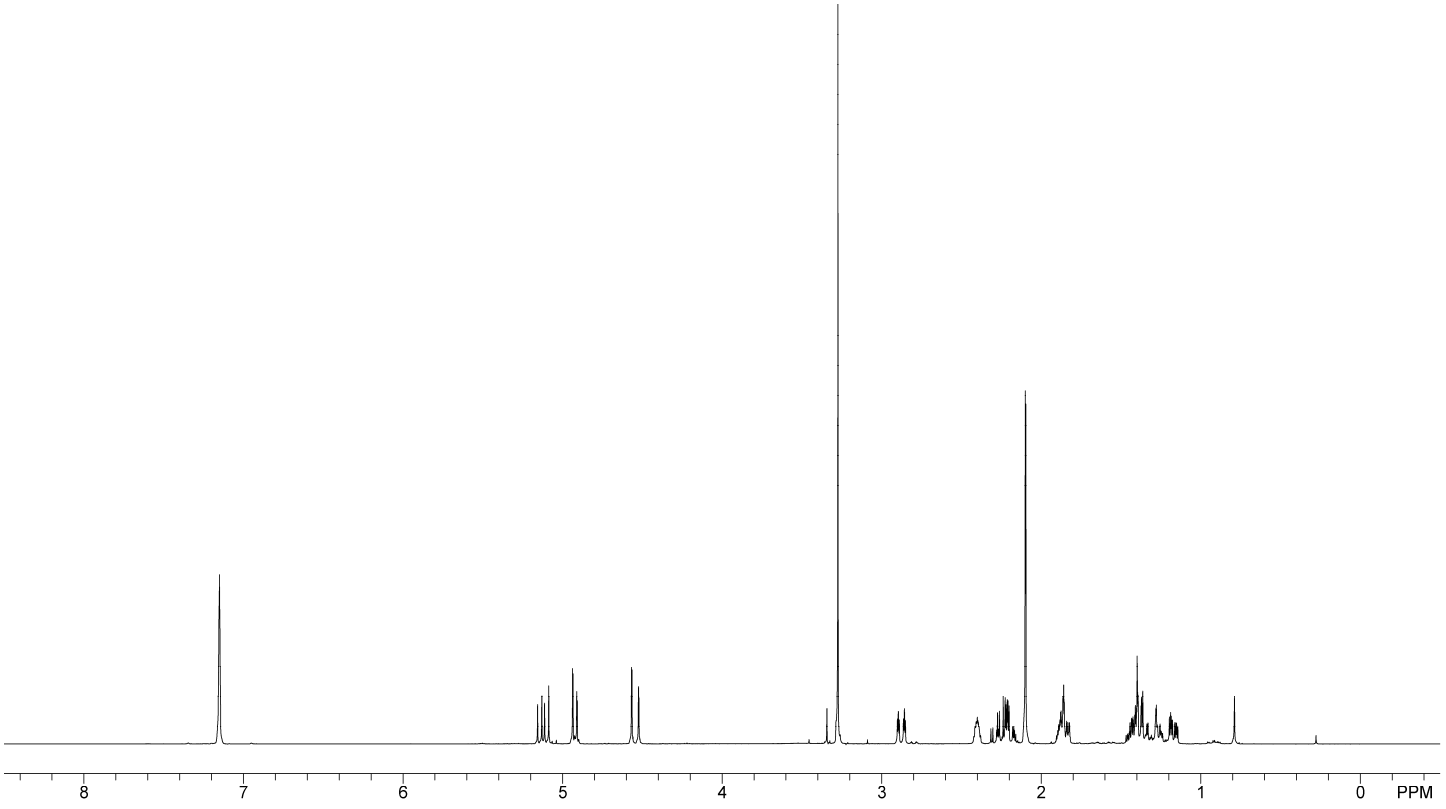


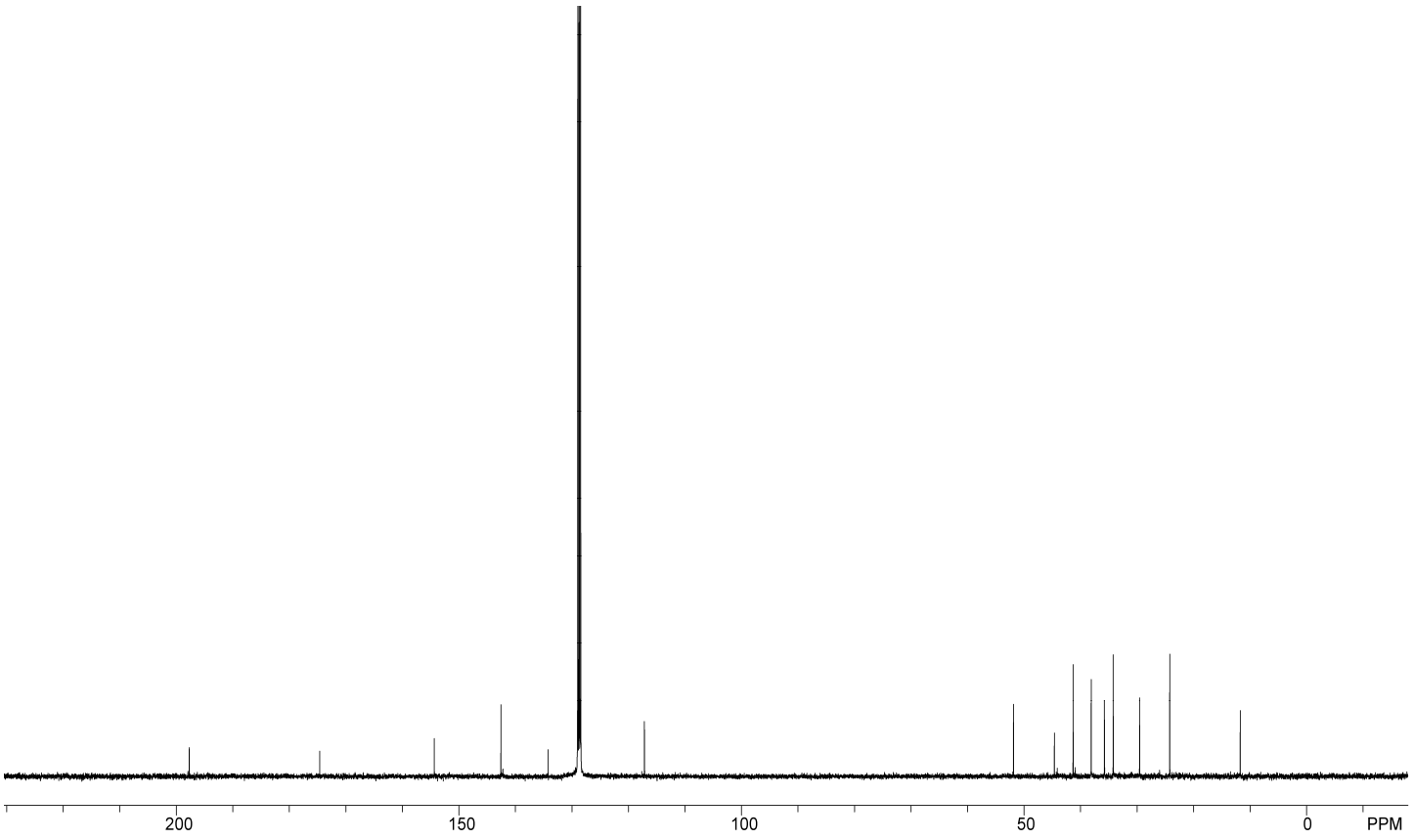

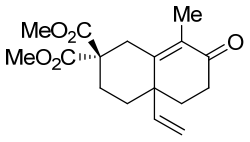


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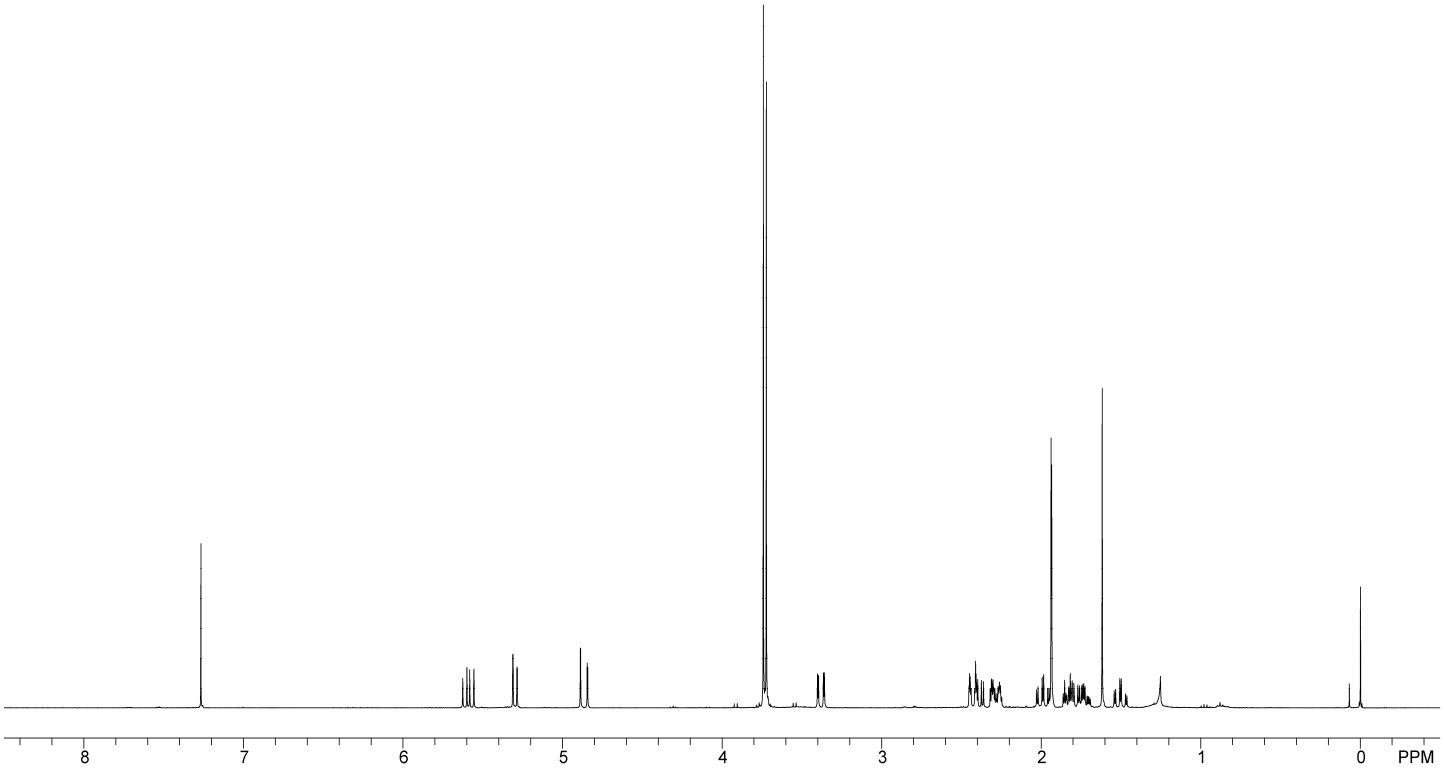


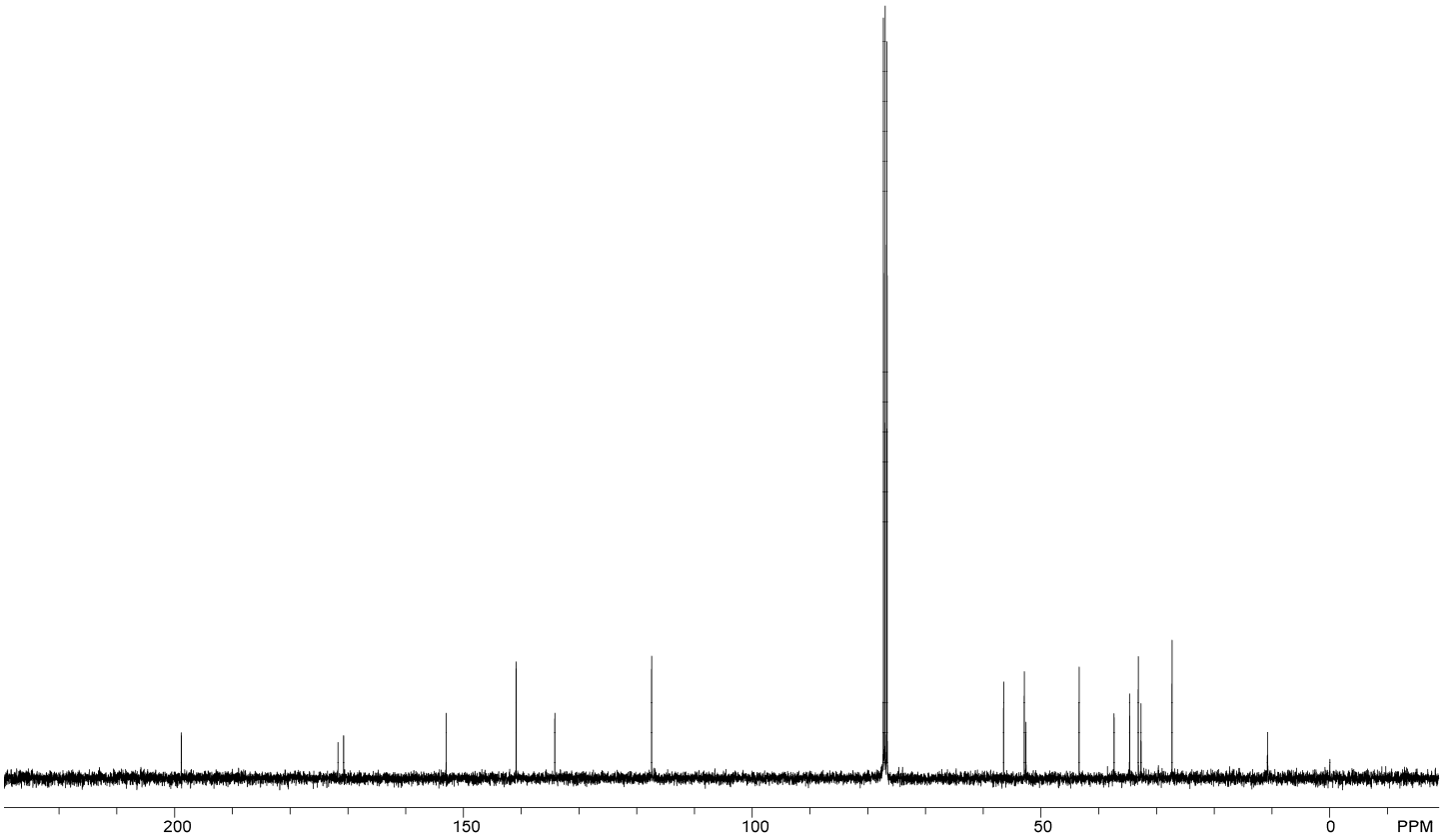

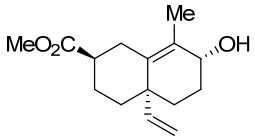


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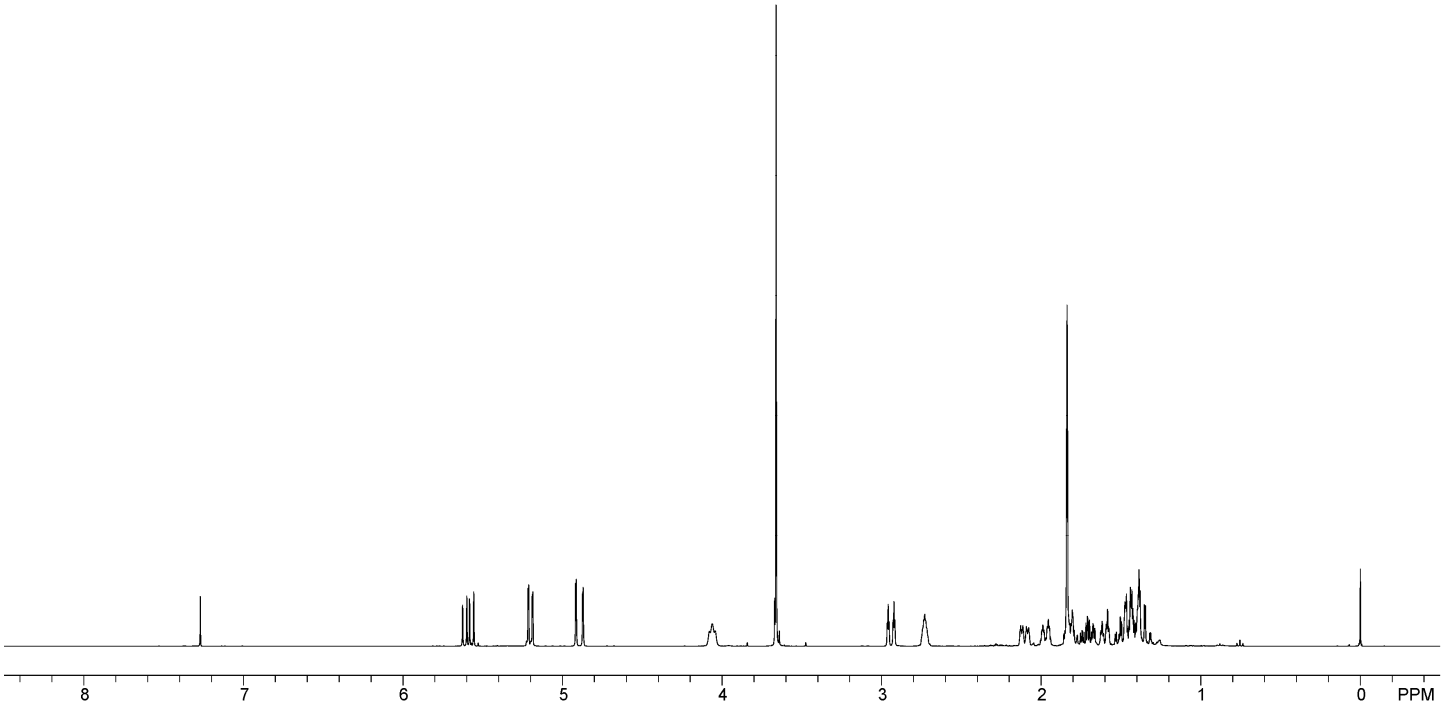


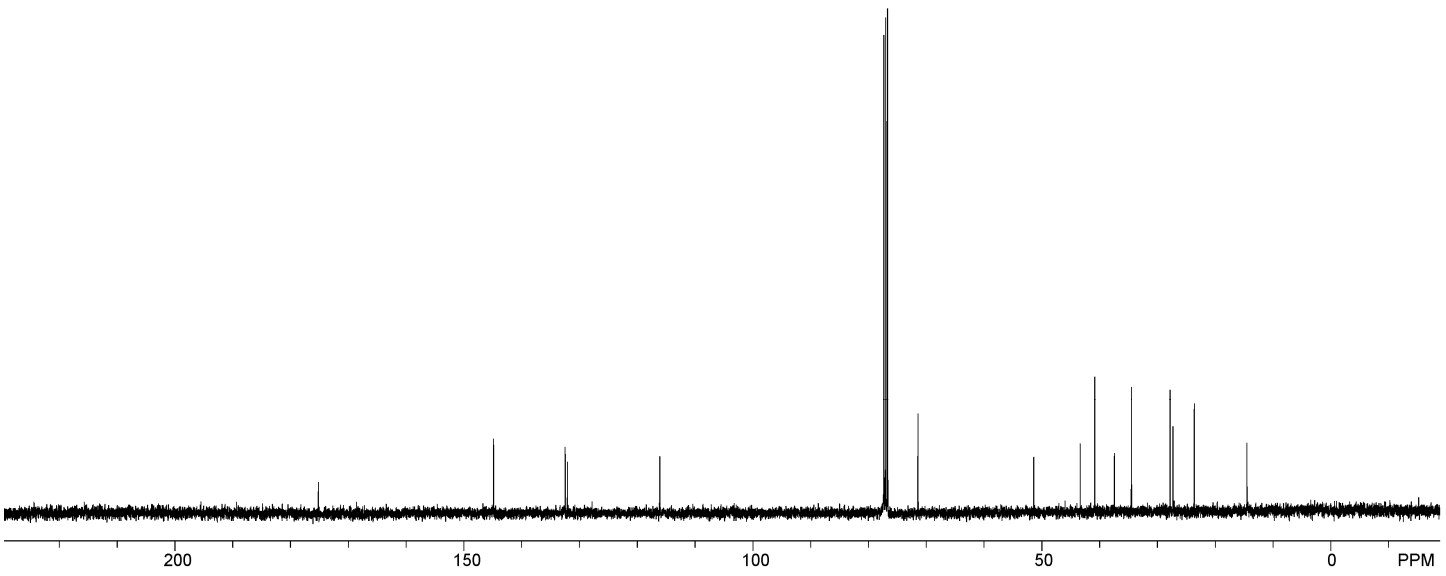

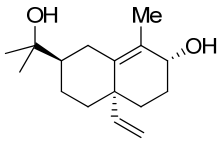


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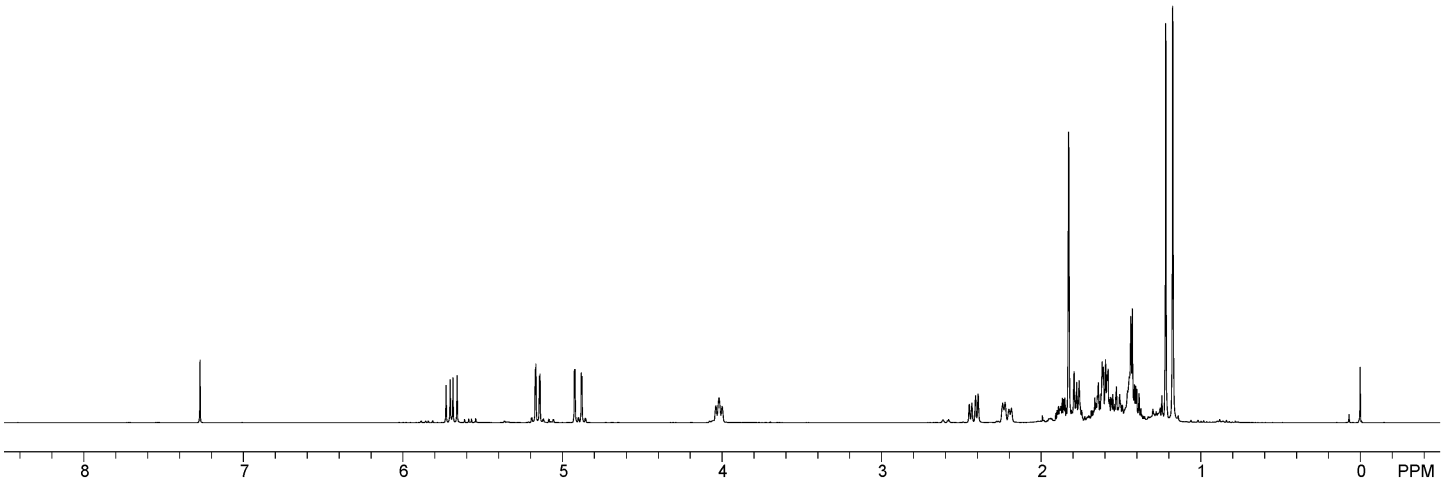


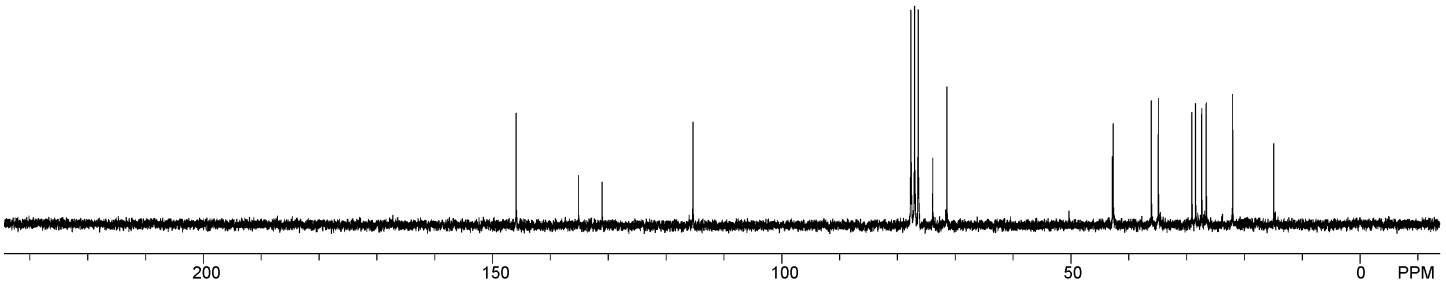

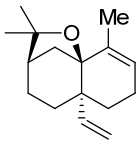


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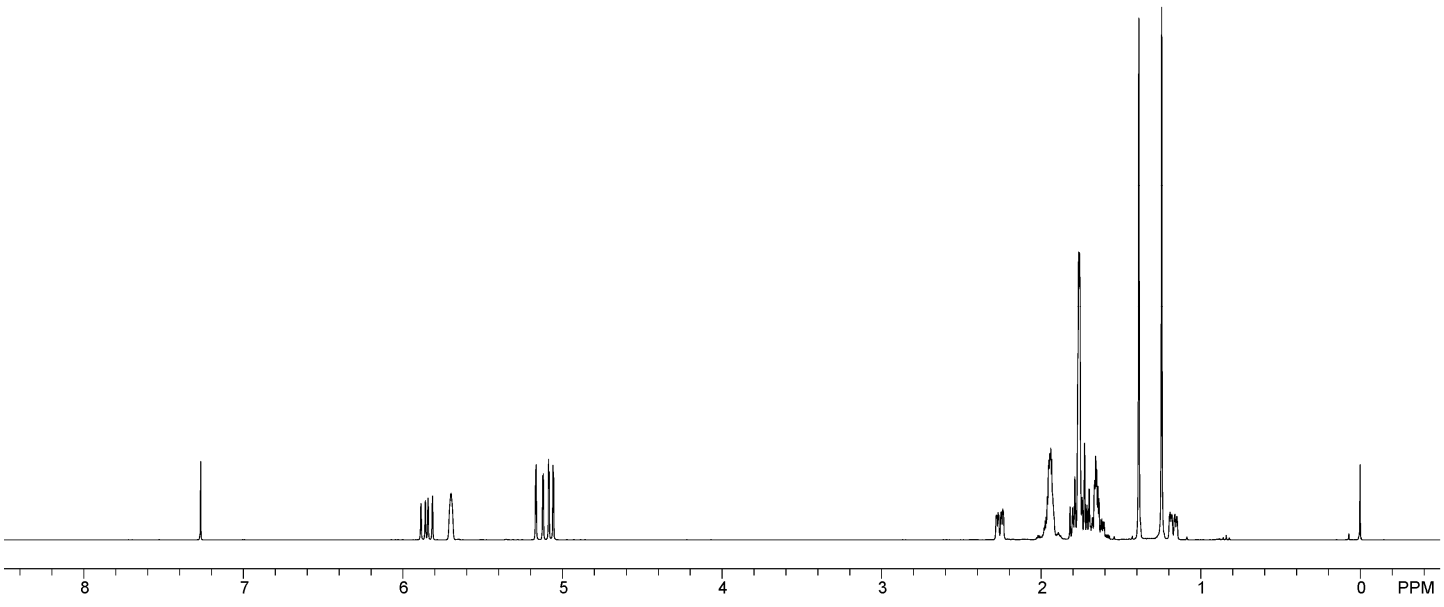


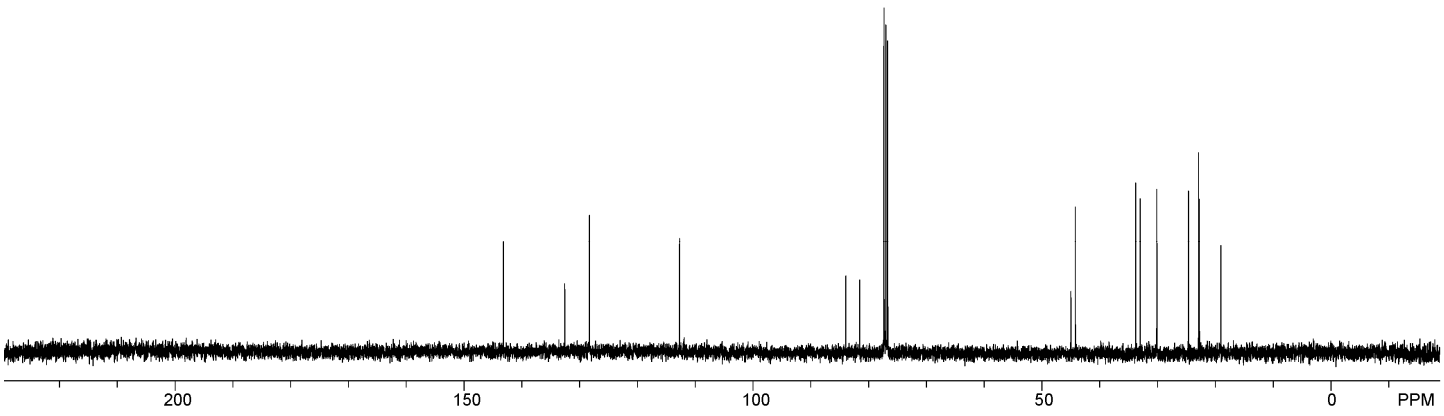

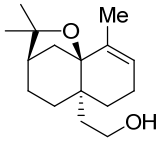


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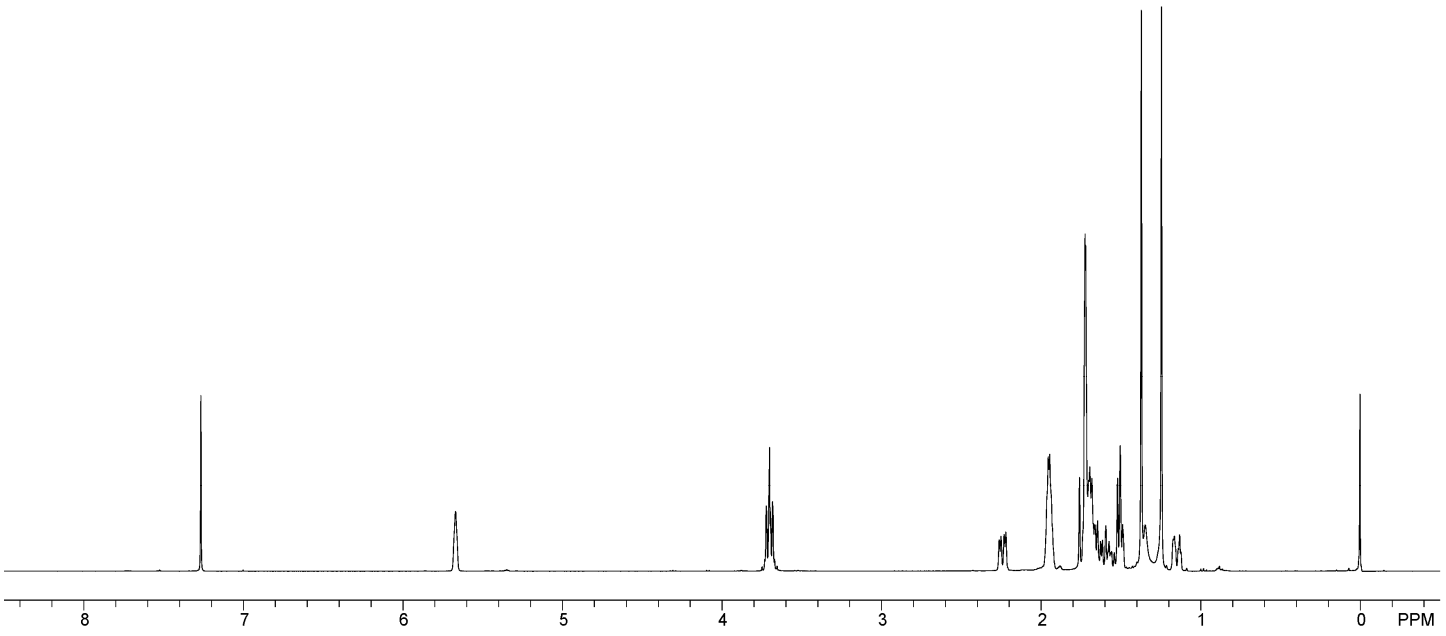
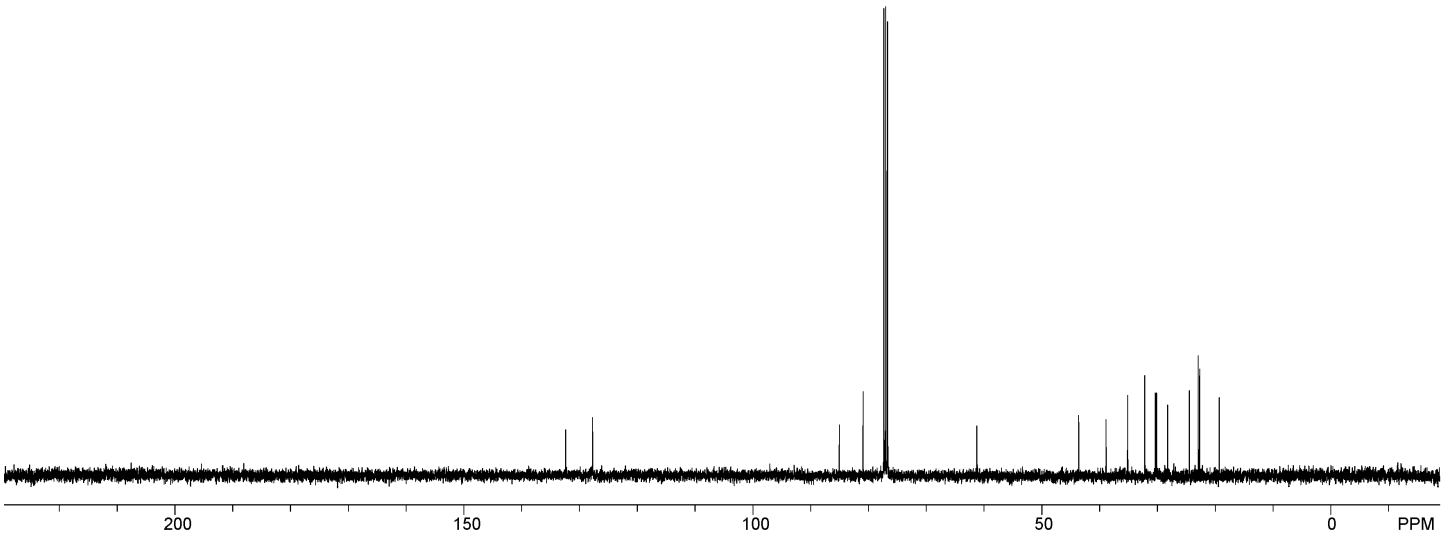
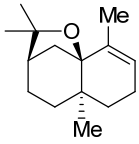
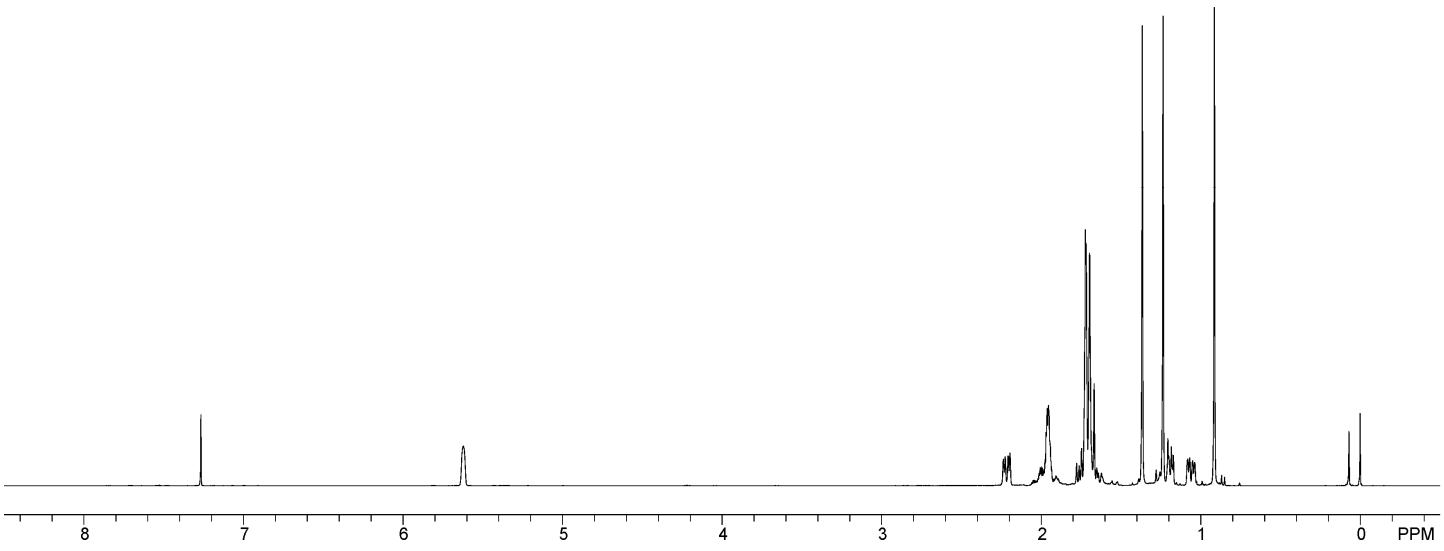
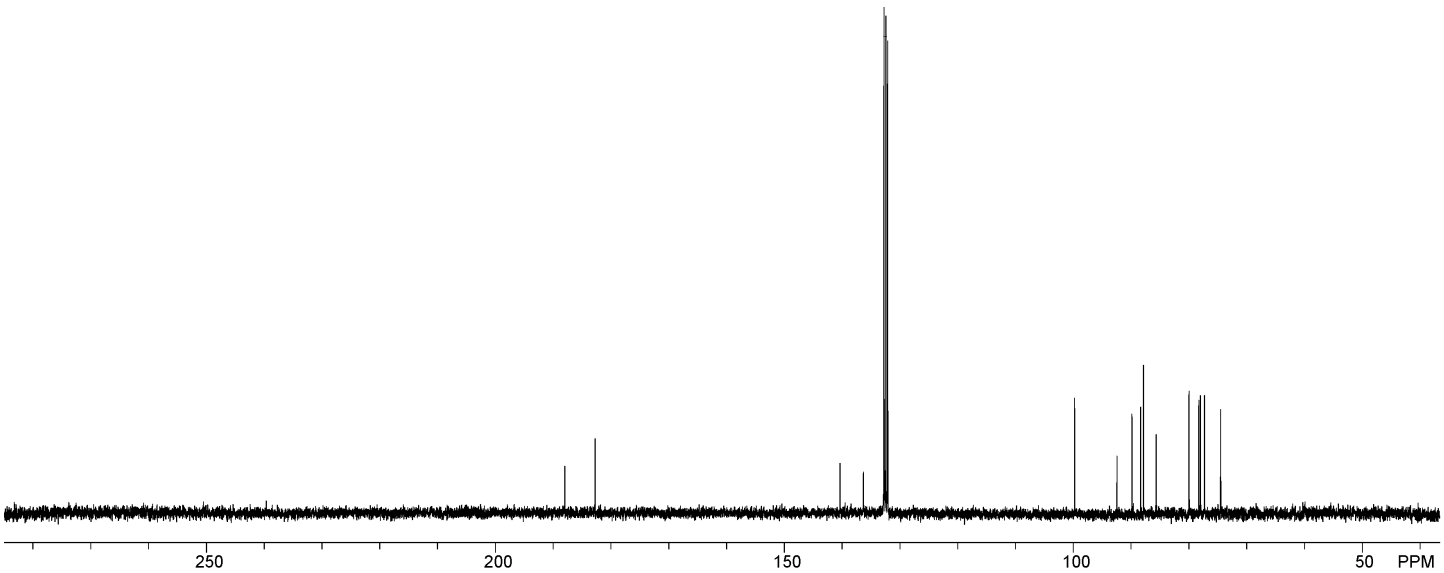


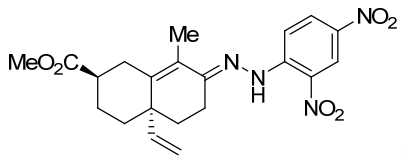






**30** (α-agarofuran)






**S7**