Supporting Information

Formal Total Synthesis of (±)-Hirsutic Acid C Using Tandem Rh(I)-Catalyzed [(5+2)+1] Cycloaddition/Aldol Reaction

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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.

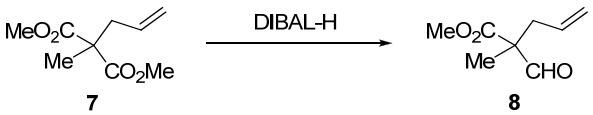
NMR spectra were measured on Varian Mercury Plus 300 (^{1}H at 300 MHz, ^{13}C at 75.5 MHz), Bruker ARX 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), and Bruker AVANCE 600 (^{1}H at 600 MHz, ^{13}C at 150 MHz) nuclear magnetic resonance spectrometers. Data for ^{1}H-NMR spectra are reported as follows: 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 a 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).

Abbreviations:
DIBAL-H = diisobutylaluminum hydride
EA = ethyl acetate
PE = petroleum ether
TBS = *tert*-butyldimethylsilyl
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography

2. Experimental Procedures and Characterization Data

Expermental procedures for the formal total synthesis of (±)-hirsutic acid C

Methyl 2-formyl-2-methylpent-4-enoate (8)

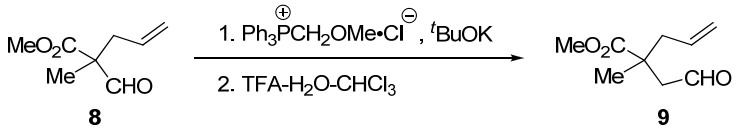


7 **8**

A solution of diester **7** (12.55 g, 67.4 mmol) in anhydrous CH_2Cl_2 (140 mL) was cooled to −78 ºC under argon. To the stirred solution DIBAL-H (140 mL, 1 M in hexane, 140 mmol) was slowly added, maintaining the inner temperature below −70 ºC. Then the reaction mixture was stirred for 30 min. Acetone (10 mL) was added dropwise to quench the reaction, keeping the inner temperature below −60 ºC. Then aqueous HCl (120 mL, 2 M) was added and the reaction mixture was allowed to warm to room temperature. Concentrated aqueous HCl was added until a clear solution formed. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with saturated aqueous potassium sodium tartrate, dried over $MgSO_4$, and concentrated. The crude product was distilled under reduced pressure to afford aldehyde **8** (b.p. 76-84 ºC/10 mmHg, 9.28 g, 88%).

Compound **8**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H), 2.50 (dd, J = 7.4 and 13.8 Hz, 1H), 2.63 (dd, J = 7.4 and 13.8 Hz, 1H), 3.76 (s, 3H), 5.11-5.15 (m, 2H), 5.63-5.73 (m, 1H), 9.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 38.5, 52.4, 57.5, 119.5, 131.7, 172.1, 199.0. IR (neat): ν 2961, 1751, 1728, 1441, 1300, 1240 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{12}NaO_3$ (M+Na): 179.0679. Found: 179.0674.

Methyl 2-methyl-2-(2-oxoethyl)pent-4-enoate (9)



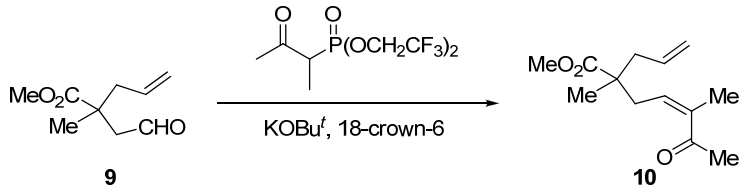
8 **9**

To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (18.57 g, 54.2 mmol) in 80 mL of anhydrous THF was slowly added a solution of KOBu^t (5.83 g, 52.0 mmol) in THF (50 mL) at −40 °C. The resulting cherry-red solution was stirred at −40 °C for 20 min. A solution of aldehyde **8** (3.73 g, 23.9 mmol) in THF (20 mL) was added dropwise, and the resulting mixture was allowed to warm to room temperature during 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL) and the reaction mixture was stirred for 5 min. The reaction mixture was filtrated, and the filtrate was evaporated under reduced pressure. Pentane was added, the resulting mixture was stirred for 1 h, and then filtrated. The filtrate was concentrated and the crude product was dissolved in $CHCl_3$ (50 mL). A solution of TFA-H_2O (20 mL, 1:1) was added dropwise and the resulting reaction mixture was stirred for 40 min. The aqueous phase was separated, and the organic phase was washed successively with water and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 30:1 to 10:1) to afford aldehyde **9** (2.03 g, 50%).

Compound **9**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 2.32-2.43 (m, 2H), 2.52 (dd, J = 1.9

and 17.4 Hz, 1H), 2.81 (d, J = 17.4 Hz, 1H), 3.70 (s, 3H), 5.06-5.13 (m, 2H), 5.70 (ddt, J = 10.4, 17.2, and 7.4 Hz, 1H), 9.74 (t, J = 1.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.5, 43.3, 43.5, 50.7, 52.1, 119.2, 132.6, 176.1, 200.4. IR (neat): ν 2987, 1747, 1728, 1468, 1222 cm^{-1}. HRMS (ESI) calcd for $C_9H_{14}NaO_3$ (M+Na): 193.0835. Found: 193.0830.

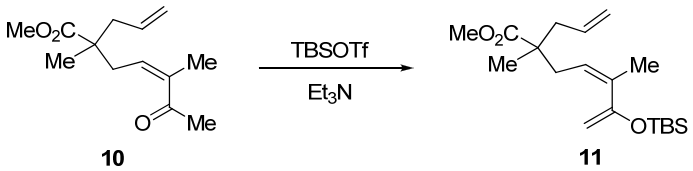
Methyl (*Z*)-2-allyl-2,5-dimethyl-6-oxohept-4-enoate (10)



To a solution of bis(2,2,2-trifluoroethyl) 3-oxobutan-2-ylphosphonate (2.46 g, 77% purity, 5.99 mmol) and 18-crown-6 (1.66 g, 6.28 mmol) in anhydrous THF (50 mL) at −78 °C was added a solution of KOBu^t (679 mg, 6.05 mmol) in THF (20 mL) dropwise under argon. After stirring for 20 min at −78 °C, a solution of aldehyde **9** (852 mg, 5.01 mmol) in THF (20 mL) was added dropwise at −78 °C and the resulting mixture was stirred for another 2 h at −78 °C. The reaction was gradually warmed to room temperature. Saturated NH_4Cl was added and the reaction mixture was extracted with ether twice. The combined organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 30:1 to 10:1) to afford (*Z*)-enone **10** (751 mg, 71%) and a mixture of (*Z*)- and (*E*)-enone **10** (165 mg, 16%, *Z*:*E* = 1:1.4, determined by ^{1}H NMR integration of the enone olefinic proton). The overall yield of (*Z*)- and (*E*)-enone **10** was 87%, *Z*:*E* = 8.6:1.

Compound **10**: Colorless oil. ^{1}H NMR (400 MHz, C_6D_6): δ 1.15 (s, 3H), 1.55-1.56 (m, 3H), 1.83 (s, 3H), 2.13 (dd, J = 7.6 and 13.6 Hz, 1H), 2.39 (dd, J = 7.0 and 13.6 Hz, 1H), 2.67 (ddm, J = 7.7 and 15.4 Hz, 1H), 2.79 (ddm, J = 7.0 and 15.4 Hz, 1H), 3.32 (s, 3H), 4.94-4.98 (m, 2H), 5.54 (tm, J = 7.5 Hz, 1H), 5.66-5.77 (m, 1H). ^{13}C NMR (75.5 MHz, C_6D_6): δ 21.0, 21.6, 29.5, 38.4, 43.6, 46.4, 51.3, 118.2, 133.0, 134.2, 137.9, 176.1, 201.0. IR (neat): ν 2987, 1732, 1695, 1464, 1382 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{20}NaO_3$ (M+Na): 247.1305. Found: 247.1299.

Methyl (*Z*)-2-allyl-6-(*tert*-butyldimethylsilyloxy)-2,5-dimethylhepta-4,6-dienoate (11)

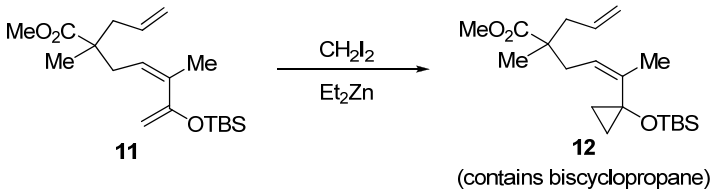


Triethyl amine (1.29 g, 12.8 mmol) and TBSOTf (2.26 g, 8.55 mmol) was sequentially added to a solution of (*Z*)-enone **10** (721 mg, 3.43 mmol) in anhydrous ether (30 mL) at 0 °C. After stirred for 1 h at 0 °C, brine was added and the resulting mixture was extracted by ether. The combined extract was dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 50:1 to 20:1, containing 1% Et_3N) to afford silyl enol ether **11** (1.005 g, 86%).

Compound **11**: Colorless oil. ^{1}H NMR (400 MHz, C_6D_6): δ 0.14 (s, 6H), 0.94 (s, 9H), 1.19 (s, 3H), 1.82-1.83 (m, 3H), 2.17 (dd, J = 8.0 and 13.7 Hz, 1H), 2.45 (dd, J = 6.9 and 13.7 Hz, 1H), 2.61 (ddm, J = 7.8 and 15.0 Hz, 1H), 2.71 (ddm, J = 6.5 and 15.0 Hz, 1H), 3.36 (s, 3H), 4.25 (s, 1H), 4.39 (s, 1H), 4.97-5.02 (m, 2H), 5.33 (tm, J =

7.3 Hz, 1H), 5.71-5.81 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ –4.5, 18.3, 21.7, 22.8, 25.9, 38.7, 43.6, 46.4, 51.2, 94.1, 118.0, 124.8, 134.6, 136.4, 156.8, 176.3. IR (neat): ν 2961, 2868, 1736, 1624, 1464, 1333, 1214 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{34}NaO_3Si$ (M+Na): 361.2169. Found: 361.2168.

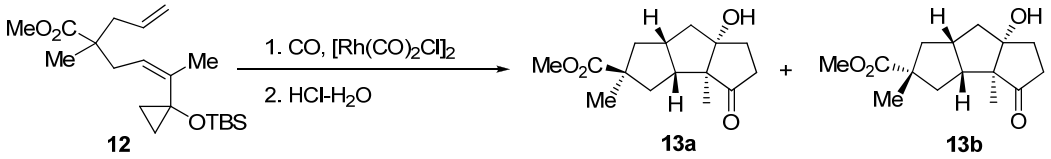
Methyl (*Z*)-2-allyl-5-(1-(tert-butyldimethylsilyloxy)cyclopropyl)-2-methylhex-4-enoate (12)



Diethyl zinc solution (2.9 mL, 1 M in hexane, 2.90 mmol) and CH_2I_2 (845 mg, 3.16 mmol) were sequentially added to a solution of silyl enol ether **11** (880 mg, 2.60 mmol) in anhydrous CH_2Cl_2 (26 mL) at 25 °C. The reaction mixture was stirred for 1.5 h and was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 and the combined organic extract was treated with acetic acid (25 mL) under room temperature for 20 min to hydrolyze the unreacted silyl enol ether. The solution was successively washed with water and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (eluted with PE/EA 100:1 to 30:1) to afford β-ene-VCP **12** (688 mg, contains ca. 28% biscyclopropane, 54%).

Compound **12**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.56-0.65 (m, 2H), 0.82 (s, 9H), 0.83-0.89 (m, 2H), 1.13 (s, 3H), 1.74-1.75 (m, 3H), 2.19 (dd, J = 7.8 and 13.6 Hz, 1H), 2.44 (dd, J = 7.2 and 13.6 Hz, 1H), 2.56-2.59 (m, 2H), 3.66 (s, 3H), 5.03-5.06 (m, 2H), 5.14 (tm, J = 7.1 Hz, 1H), 5.66-5.79 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –3.8, 14.2, 14.3, 17.7, 21.3, 22.4, 25.6, 37.7, 43.6, 46.2, 51.5, 55.8, 117.9, 125.5, 134.2, 137.8, 177.2. IR (neat): ν 2961, 2861, 1739, 1464, 1233 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{36}NaO_3Si$ (M+Na): 375.2326. Found: 375.2323.

1,4-Dimethyl-8-hydroxy-4-methoxycarbonyltricyclo[6.3.0.0^{2,6}]undecan-11-one (13a and 13b)

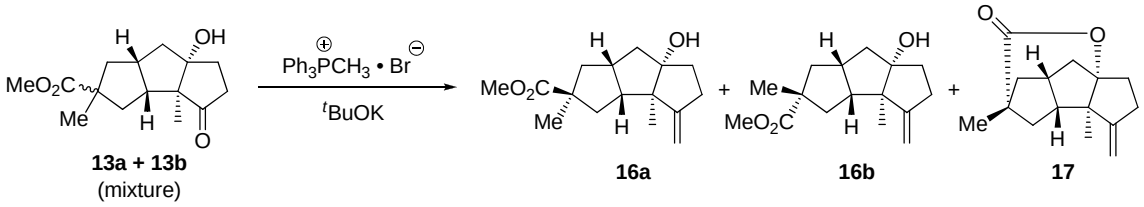


A solution of β-ene-VCP **12** (534 mg, 72% purity, 1.08 mmol) and $[Rh(CO)_2Cl]_2$ (41.5 mg, 107 μmol) in anhydrous dioxane (55 mL) was degassed by bubbling CO/N_2 (1:4 V/V) for 5 min. The solution was heated to 80 °C in an oil bath with stirring under a positive pressure of the mixture gas for 22 h. The solution was cooled to room temperature, and was treated with HCl (5 mL, 1 M in MeOH-H_2O 5:1) under room termperature for 8 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluted

with PE/EA 10:1 to 2:1) to afford tricyclic hydroxyl ketones **13a** and **13b** (150 mg, 52%, **13a**:**13b** = 1:1.5).[1]

Compounds **13a+13b**: Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H, **13a**), 0.99 (s, 3H, **13b**), 1.20 (s, 3H, **13b**), 1.31 (s, 3H, **13a**), 1.52-1.76 (m, 3H, **13a** and **13b**), 1.87-1.96 (m, 3H, **13a** and **13b**), 2.09-2.33 (m, 3H, **13a** and **13b**), 2.45-2.59 (m, 3H, **13a** and **13b**), 2.68-2.75 (m, 1H, **13a**), 2.80-2.88 (m, 1H, **13b**), 3.66 (s, 3H, **13a**), 3.68 (s, 3H, **13b**). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 12.7, 22.5, 24.3, 32.1, 32.1, 35.06, 35.11, 38.0, 39.2, 39.6, 40.3, 44.3, 44.4, 44.6, 45.5, 48.1, 48.5, 50.8, 51.8, 51.8, 52.4, 60.0, 60.3, 88.7, 89.1, 178.0, 178.2, 221.1, 221.4. IR (neat): ν 3475, 2957, 1732, 1464, 1255, 1211 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{22}NaO_4$ (M+Na): 289.1410. Found: 289.1411.

1,4-Dimethyl-8-hydroxy-4-methoxycarbonyl-11-methylenetricyclo[6.3.0.0^{2,6}]undecane (16a and 16b) and 5,8-dimethyl-4-methylene-13-oxa-12-oxotetracyclo[6.3.2.0^{1,5}.0^{6,10}]tridecane (17)

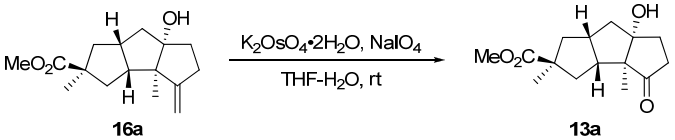


To a solution of KOBu^t (222 mg, 1.98 mmol) in ^{t}BuOH (3 mL) and benzene (12 mL) was added at room temperature under argon methyltriphenylphosphonium bromide (709 mg, 1.98 mmol) in one portion, and the resulting yellow solution was stirred at room temperature for 30 min. A solution of tricyclic hydroxyketone **13** (**13a** + **13b** mixture, **13a**:**13b** = 1:1.5, 176 mg, 0.66 mmol) in dry benzene (3 mL) was added and the reaction mixture was brought to reflux for 1 h in a 100 °C oil bath. The resulting mixture was cooled, concentrated, and filtered through a thin pad of silica gel (eluted with PE/EA 5:1). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (eluted with PE/EA 30:1 to 5:1) to afford tetracyclic compound **17** (14.0 mg, 9%, 15% based on **13b**), tricyclic enol **16a** (52.5 mg, 30%, 75% based on **13a**), and then tricyclic enol **16b** (13.1 mg, 7%, 12% based on **13b**).

Compound **16a**: Colorless oil. R_f = 0.40 (PE/EA = 5:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.32 (s, 3H), 1.29-1.32 (m, 1H), 1.40 (s, 1H), 1.54 (dd, J = 4.9 and 14.0 Hz, 1H), 1.61-1.66 (m, 2H), 1.88 (ddd, J = 4.3, 8.8, and 12.7 Hz, 1H), 1.97 (dd, J = 9.2 and 14.0 Hz, 1H), 2.19 (ddd, J = 1.6, 7.7, and 12.7 Hz, 1H), 2.29-2.36 (m, 1H), 2.42-2.56 (m, 4H), 3.66 (s, 3H), 4.81-4.82 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.9, 25.0, 28.7, 35.9, 40.0, 40.1, 45.0, 45.5, 51.8, 52.3, 53.4, 55.7, 92.0, 105.8, 160.0, 178.6. IR (neat): ν 3527, 2957, 1721, 1468, 1315, 1199 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{25}O_3$ (M+H): 265.1798. Found: 265.1799.

Compound **16b**: Colorless oil. R_f = 0.27 (PE/EA = 5:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.00 (s, 3H), 1.21 (s,

(1) The assignment of the relative configuration of cycloadducts **13a** and **13b** was achieved by oxidation of the stereochemically well-defined compound **16a** and comparison of the product's ^{1}H NMR spectrum with that of **13a** and **13b** mixture. Oxidation of compound **16a** by K_2OsO_4-$NaIO_4$ gave **13a**, indicating that it has identical relative configuration to the natural product.



Procedure for K_2OsO_4-$NaIO_4$ oxidation: To a stirred solution of compound **16a** (4.6 mg, 0.017 mmol) in THF-H_2O (1 mL, 4:1) was added K_2OsO_4·$2H_2O$ (1.0 mg, 0.0027 mmol) and $NaIO_4$ (10.1 mg, 0.047 mmol). The resulting mixture was stirred at room temperature for 9 h. Water was added to quench the reaction, and the reaction mixture was extracted with ether. The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to give crude ketone **13a** (4.5 mg), which gave identical ^{1}H NMR spectra to the minor diastereomer of the **13a** and **13b** mixture.

3H), 1.49 (s, 1H), 1.60-1.70 (m, 3H), 1.83-1.93 (m, 3H), 2.02 (dd, J = 9.2 and 14.3 Hz, 1H), 2.19 (t, J = 12.1 Hz, 1H), 2.31-2.37 (m, 1H), 2.47-2.54 (m, 2H), 2.63 (dt, J = 11.6 and 8.8 Hz, 1H), 3.68 (s, 3H), 4.82-4.84 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.2, 23.3, 29.0, 36.2, 38.7, 39.5, 44.5, 45.1, 50.8, 51.8, 53.1, 55.8, 91.8, 105.6, 160.7, 178.6. IR (neat): ν 3509, 2957, 1724, 1460, 1255 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{24}NaO_3$ (M+Na): 287.1618. Found: 287.1619.

Compound **17**: Colorless crystals, m.p. 125-127 °C. R_f = 0.68 (PE/EA = 5:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.93 (s, 3H), 1.35 (s, 3H), 1.53-1.63 (m, 2H), 1.72-1.77 (m, 2H), 1.95-2.00 (m, 2H), 2.04 (dd, J = 9.3 and 14.8 Hz, 1H), 2.14 (d, J = 13.7 Hz, 1H), 2.32-2.38 (m, 1H), 2.61-2.67 (m, 1H), 2.75-2.79 (m, 1H), 2.86 (t, J = 7.7 Hz, 1H), 4.77-4.78 (m, 1H), 4.82-4.83 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.2, 25.0, 27.1, 28.9, 39.9, 40.4, 44.7, 47.2, 48.7, 51.6, 56.9, 95.0, 105.2, 156.4, 178.3. IR (neat): ν 2972, 1721, 1464, 1117 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{20}NaO_2$ (M+Na): 255.1356. Found: 255.1352.

The structure of tetracyclic lactone **17** was determined by X-ray single crystal analysis (Figure S1). CCDC 779815 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

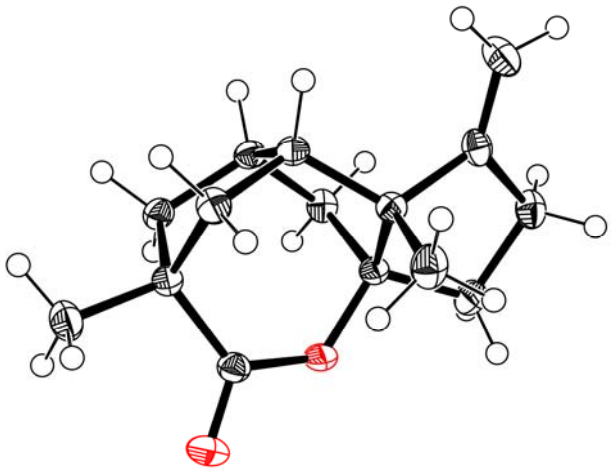
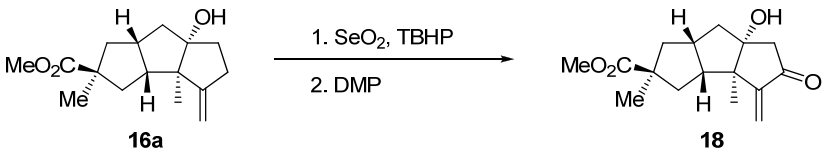


Figure S1. ORTEP figure of compound **17**. Ellipsoids are drawn at 50% probability.

1,4-Dimethyl-8-hydroxy-4-methoxycarbonyl-11-methylenetricyclo[6.3.0.0^{2,6}]undecan-10-one (18)



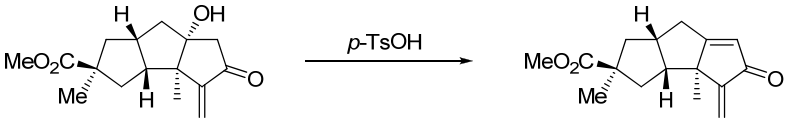
16a **18**

To a stirred solution of tricyclic enol **16a** (20.6 mg, 0.078 mmol) in CH_2Cl_2 (1.5 mL) was sequentially added SeO_2 (5.6 mg, 0.050 mmol) and ^{t}BuOOH (65% aqueous solution, 42 mg, 0.30 mmol). The resulting solution was stirred at room temperature for 2 h. The reaction mixture was poured into water, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. The residue was filtered through a thin pad of silica gel (eluted with PE/EA 2:1 to 1:1) and the filtrate was concentrated. Anhydrous CH_2Cl_2 (1 mL) was added, and then to the resulting solution

was added powdered $NaHCO_3$ (23.0 mg, 0.27 mmol) and Dess-Martin periodinane (57.0 mg, 0.13 mmol). The reaction mixture was stirred under room temperature for 30 min and then directly subjected to flash column chromatography on silica gel (eluted with PE/AE 5:1 to 3:1) to afford the tricyclic hydroxyl enone **18** (17.3 mg, 80% over 2 steps).

Compound **18**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.34 (s, 3H), 1.32-1.36 (m, 1H), 1.67-1.73 (m, 2H), 1.77 (s, 1H), 1.92 (dd, J = 8.4 and 14.1 Hz, 1H), 2.28 (ddd, J = 1.7, 8.0, and 12.7 Hz, 1H), 2.45 (d, J = 18.8 Hz, 1H), 2.48-2.54 (m, 2H), 2.60 (d, J = 18.8 Hz, 1H), 2.59-2.65 (m, 1H), 3.67 (s, 3H), 5.24 (s, 1H), 6.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 24.5, 40.1, 40.2, 45.2, 45.6, 49.4, 51.9, 52.7, 55.0, 86.8, 117.4, 155.0, 178.1, 203.8. IR (neat): ν 3464, 2961, 1732, 1724, 1635, 1464, 1207 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{23}O_4$ (M+H): 279.1591. Found: 279.1589.

1,4-Dimethyl-4-methoxycarbonyl-11-methylenetricyclo[6.3.0.0^{2,6}]undec-8-en-10-one (19)



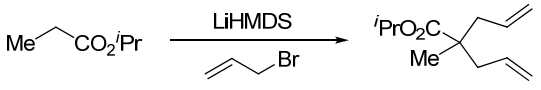
18 **19**

To a solution of tricyclic hydroxy enone **18** (16.6 mg, 0.060 mmol) in benzene (3 mL) was added *p*-TsOH·H_2O (1.0 mg, 0.0053 mmol). The resulting solution was heated to reflux in a 100 °C oil bath under stirring for 1 h and then allowed to cool to room temperature. The reaction mixture was evaporated and the crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 10:1 to 5:1) afforded tricyclic dienone **19** (14.5 mg, 93%).

Compound **19**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.30 (t, J = 12.1 Hz, 1H), 1.38 (s, 3H), 1.57-1.64 (m, 1H), 2.30 (ddd, J = 1.8, 7.3, and 15.2 Hz, 1H), 2.38-2.46 (m, 2H), 2.56 (ddd, J = 0.9, 7.3, and 12.6 Hz, 1H), 2.65-2.76 (m, 1H), 2.80 (dd, J = 8.6 and 14.8 Hz, 1H), 3.66 (s, 3H), 5.17 (s, 1H), 5.89-5.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 24.4, 32.3, 37.0, 44.9, 46.4, 48.2, 51.7, 52.0, 54.9, 113.3, 123.5, 153.7, 177.8, 189.2, 197.5. IR (neat): ν 2972, 1736, 1706, 1624, 1468, 1199 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{20}NaO_3$ (M+Na): 283.1305. Found: 283.1302. The spectroscopic data is identical to that previously reported.[2]

Expermental procedures for the synthesis of 1-ene-VCP 12' and its tandem [(5+2)+1]/aldol reaction

Isopropyl 2-allyl-2-methylpent-4-enoate (S2)



S1 **S2**

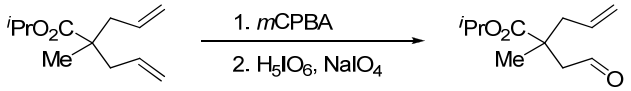
A solution of *n*-BuLi (1.6 M in hexane, 53 mL, 85 mmol) in anhydrous THF (50 mL) was cooled to −10 ºC under argon. To the stirred solution HMDS (14.92 g, 92.4 mmol) was added dropwise, and the resulting mixture was stirred for 10 min. The solution was cooled to −78 ºC, and a solution of ester **S1** (3.65 g, 31.4 mmol) in anhydrous THF (50 mL) was slowly added. After stirred for 30 min, a solution of allyl bromide (12.03 g, 99.4 mmol) in anhydrous THF (50 mL) was added. The reaction mixture was stirred and allowed to warm to room

(2) Banwell, M. G.; Ausin, K. A. B.; Willis, A. C. *Tetrahedron* **2007**, *63*, 6388.

temperature over 16 h. Saturated aqueous NH_4Cl was added to quench the reaction, and the resulting mixture was extracted with CH_2Cl_2. The organic phase was washed sequencially with aqueous 1 M H_2SO_4, saturated $NaHCO_3$, and brine. The organic solution was dried over Na_2SO_4 and concentrated. The crude product was distilled under reduced pressure to afford ester **S2** (b.p. 84-88 ºC/10 mmHg, 3.16 g, 51%).

Compound **S2**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.22 (d, J = 6.4 Hz, 6H), 2.19 (dd, J = 7.6 and 13.3 Hz, 2H), 2.38 (dd, J = 7.1 and 13.3 Hz, 2H), 5.00 (heptet, J = 6.2 Hz, 1H), 5.03-5.08 (m, 4H), 5.67-5.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 21.8, 42.9, 45.5, 67.5, 118.0, 133.9, 175.7. IR (neat): ν 2983, 1724, 1646, 1471, 1378, 1218, 1110 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{20}NaO_2$ (M+Na): 219.1356. Found: 219.1351.

Isopropyl 2-methyl-2-(2-oxoethyl)pent-4-enoate (S3)

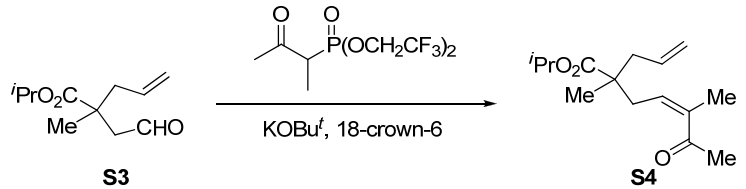


S2 **S3**

To a solution of diene **S2** (1.42 g, 7.23 mmol) in CH_2Cl_2 (15 mL) was added a solution of *m*CPBA (70%, 1.23 g, 4.99 mmol) in CH_2Cl_2 (35 mL). The reaction mixture was stirred for 19.5 h under room temperature. Another batch of *m*CPBA (70%, 0.36 g, 0.15 mmol) was added, and the reaction mixture was further stirred for 45 min. Saturated aqueous $NaHCO_3$ was added to quench the reaction, and the resulting mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated, and the crude product was directly used in the next step. To a stirred solution of the above crude product in THF (30 mL) was successively added a solution of H_5IO_6 (1.65 g, 7.24 mmol) in water (10 mL) and a solution of $NaIO_4$ (1.55 g, 7.25 mmol) in water (10 mL). the resulting mixture was stirred under room temperature for 1 h. Saturated aqueous $NaHCO_3$ was added to quench the reaction, and the resulting mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated, and the crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 50:1 to 3:1) to afforded the unreacted diene **S2** (400 mg, 28%) and aldehyde **S3** (579 mg, 40%).

Compound **S3**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.4 Hz, 3H), 1.27 (s, 3H), 2.34 (dd, J = 7.5 and 13.7 Hz, 1H), 2.40 (dd, J = 7.5 and 13.7 Hz, 1H), 2.48 (dd, J = 2.0 and 17.0 Hz, 1H), 2.78 (d, J = 17.0 Hz, 1H), 5.03 (heptet, J = 6.4 Hz, 1H), 5.06-5.13 (m, 2H), 5.71 (ddt, J = 10.0, 17.1, and 7.5 Hz, 1H), 9.78 (t, J = 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 22.6, 43.3, 43.5, 50.6, 68.2, 119.0, 132.7, 175.0, 200.5. IR (neat): ν 2987, 1721, 1460, 1378, 1218, 1110 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{18}NaO_3$ (M+Na): 221.1148. Found: 221.1143.

Isopropyl (*Z*)-2-allyl-2,5-dimethyl-6-oxohept-4-enoate (S4)

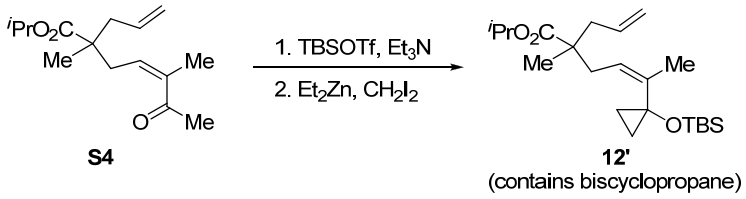


S3 **S4**

To a solution of bis(2,2,2-trifluoroethyl) 3-oxobutan-2-ylphosphonate (1.24 g, 80% purity, 3.14 mmol) and 18-crown-6 (890 mg, 3.37 mmol) in anhydrous THF (30 mL) at −78 °C was added a solution of KOBu^t (360 mg, 3.21 mmol) in THF (10 mL) dropwise under argon. After stirring for 20 min at −78 °C, a solution of aldehyde **S3** (550 mg, 2.81 mmol) in THF (10 mL) was added dropwise at −78 °C and the resulting mixture was stirred for another 2 h at −78 °C. The reaction was gradually warmed to room temperature. Saturated NH_4Cl was added and the reaction mixture was extracted with ether twice. The combined organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 30:1 to 10:1) to afford (*Z*)-enone **S4** (600 mg, 85%) and its (*E*)-isomer (98 mg, 14%). The overall yield of (*Z*)- and (*E*)-enone **S4** was 99%, *Z*:*E* = 6.1:1.

Compound **S4**: Colorless oil. ^{1}H NMR (400 MHz, C_6D_6): δ 0.99 (d, J = 6.3 Hz, 6H), 1.18 (s, 3H), 1.56-1.57 (m, 3H), 1.84 (s, 3H), 2.16 (dd, J = 7.8 and 13.6 Hz, 1H), 2.43 (dd, J = 7.3 and 13.7 Hz, 1H), 2.70 (ddm, J = 7.7 and 15.6 Hz, 1H), 2.83 (ddm, J = 6.8 and 15.6 Hz, 1H), 4.95-5.04 (m, 3H), 5.62 (tm, J = 7.5 Hz, 1H), 5.71-5.85 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 21.1, 21.65, 21.69, 29.5, 38.5, 43.6, 46.0, 67.5, 118.1, 133.4, 134.3, 137.7, 175.2, 200.9. IR (neat): ν 2983, 1724, 1698, 1460, 1378, 1199, 1106 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{24}NaO_3$ (M+Na): 275.1618. Found: 275.1615.

Isopropyl (*Z*)-2-allyl-5-(1-(tert-butyldimethylsilyloxy)cyclopropyl)-2-methylhex-4-enoate (12')

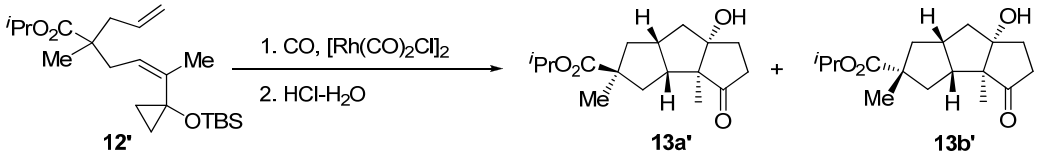


S4 **12'** (contains biscyclopropane)

Triethyl amine (1.0 mL, 7.2 mmol) and TBSOTf (1.07 g, 4.05 mmol) was sequentially added to a solution of (*Z*)-enone **S4** (500 mg, 1.98 mmol) in anhydrous ether (20 mL) at 0 °C. After stirred for 2.5 h at 0 °C, brine was added and the resulting mixture was extracted by ether. The combined extract was dried over Na_2SO_4 and concentrated. The crude product was filtered through a pad of silica gel (eluted with PE/EA 50:1 to 20:1, containing 1% Et_3N) to afford the crude silyl enol ether. Diethyl zinc solution (5.1 mL, 0.57 M in hexane, 2.90 mmol) and CH_2I_2 (648 mg, 2.42 mmol) were sequentially added to a solution of the crude silyl enol ether in anhydrous CH_2Cl_2 (20 mL) at 25 °C. The reaction mixture was stirred for 2 h and was quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 and the organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (eluted with PE/EA 100:1 to 50:1) to afford β-ene-VCP **12'** (565 mg, contains ca. 35% biscyclopropane, 49%).

Compound **12'**: Colorless oil. Due to the inseparable impurities, NMR data is not reported. See page S26 for its ^{1}H and ^{13}C NMR spectra (300 MHz, C_6D_6). IR (neat): ν 2939, 2864, 1732, 1643, 1464, 1378, 1233, 1110 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{41}O_3Si$ (M+H): 381.2820. Found: 381.2822.

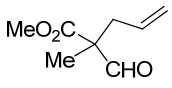
1,4-Dimethyl-8-hydroxy-4-isopropyloxycarbonyltricyclo[6.3.0.0^{2,6}]undecan-11-one (13a' and 13b')



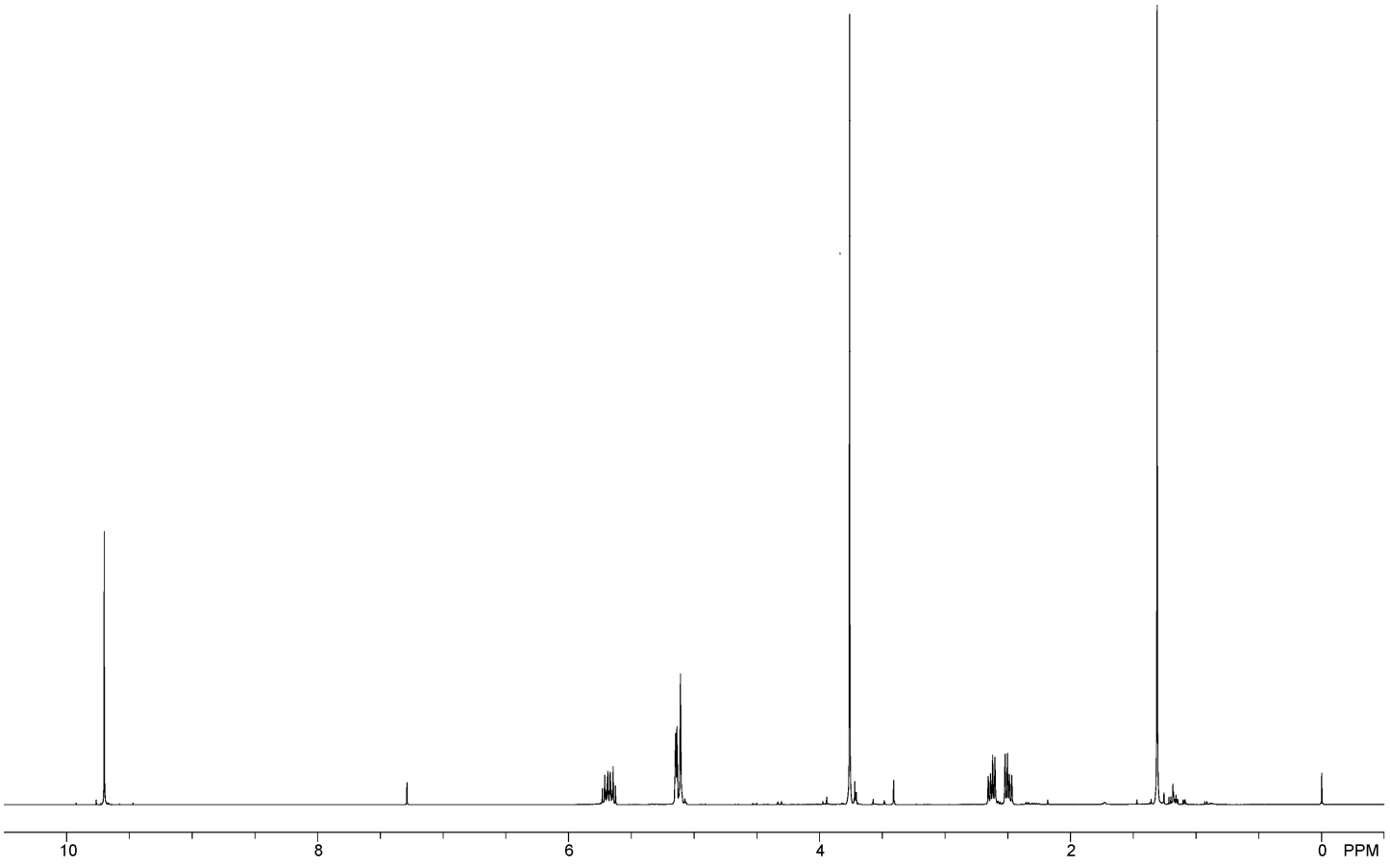
A solution of β-ene-VCP **12'** (135 mg, 65% purity, 0.231 mmol) and $[Rh(CO)_2Cl]_2$ (6.0 mg, 15 μmol) in anhydrous dioxane (8 mL) was degassed by bubbling CO/N_2 (1:4 V/V) for 5 min. The solution was heated to 80 °C in an oil bath with stirring under a positive pressure of the mixture gas for 48 h. The solution was cooled to room temperature, and was treated with HCl (5 drops, 1 M in EtOH-H_2O 5:1) under room termperature for 2 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluted with PE/EA 3:1 to 1:1) to afford tricyclic hydroxyl ketones **13a'** and **13b'** (25.6 mg, 38%, **13a'**:**13b'** = 1:1.3).

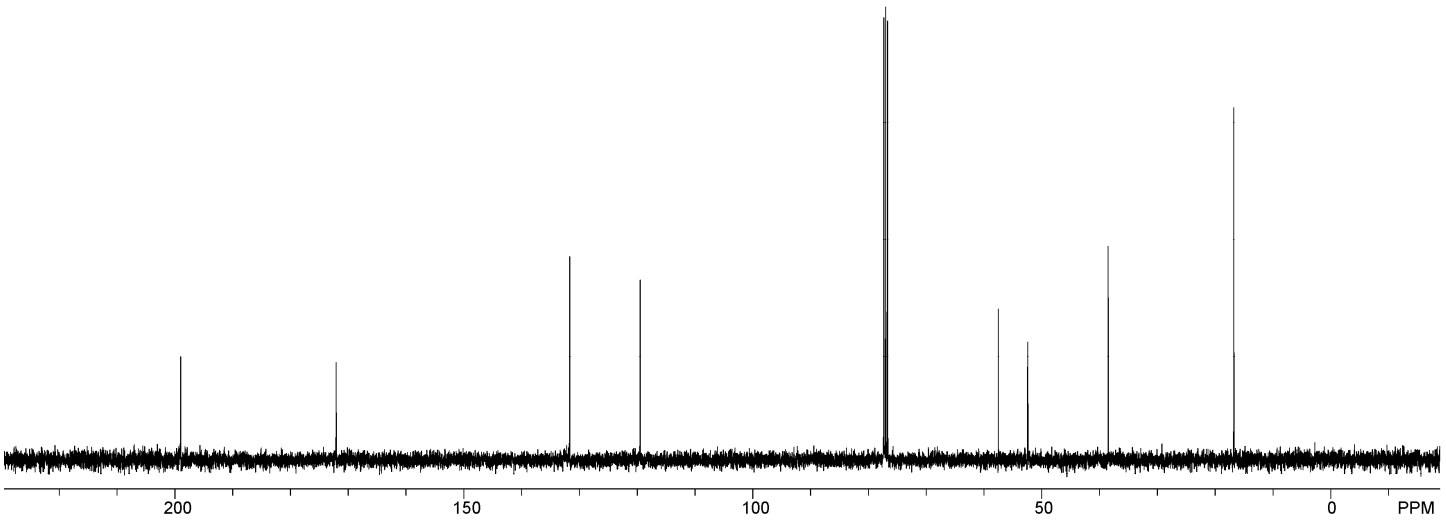
Compounds **13a'+13b'**: Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H, **13a'**), 1.00 (s, 3H, **13b'**), 1.19 (s, 3H, **13b'**), 1.21 (d, J = 5.9 Hz, 3H, **13a'**), 1.22 (d, J = 5.9 Hz, 3H, **13a'**), 1.23 (d, J = 6.4 Hz, 6H, **13b'**), 1.29 (s, 3H, **13a'**), 1.52 (dd, J = 11.5 and 12.8 Hz, 1H, **13a'**), 1.61-1.67 (m, 1H, **13a'** and **13b'**), 1.74 (dd, J = 5.1 and 14.9 Hz, 1H, **13b'**), 1.85-1.99 (m, 3H, **13a'** and **13b'**), 2.08-2.34 (m, 3H, **13a'** and **13b'**), 2.43-2.57 (m, 2H, **13a'** and **13b'**), 2.67-2.74 (m, 1H, **13a'**), 2.78-2.83 (m, 1H, **13b'**), 4.92-5.01 (m, 1H, **13a'** and **13b'**). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.4, 12.8, 21.62, 21.64, 21.7, 22.7, 24.3, 32.1, 32.2, 35.1, 35.2, 37.9, 39.1, 39.7, 40.4, 44.2, 44.4, 44.7, 45.5, 48.3, 48.4, 50.9, 52.5, 60.1, 60.3, 67.46, 67.54, 88.9, 89.3, 176.9, 177.3, 220.9, 221.6. IR (neat): v 3485, 2938, 1721, 1409, 1106 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{17}H_{26}O_4$ (M^+): 294.1831. Found: 294.1828.

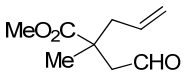
3. ^{1}H and ^{13}C-NMR Spectra for New Compounds



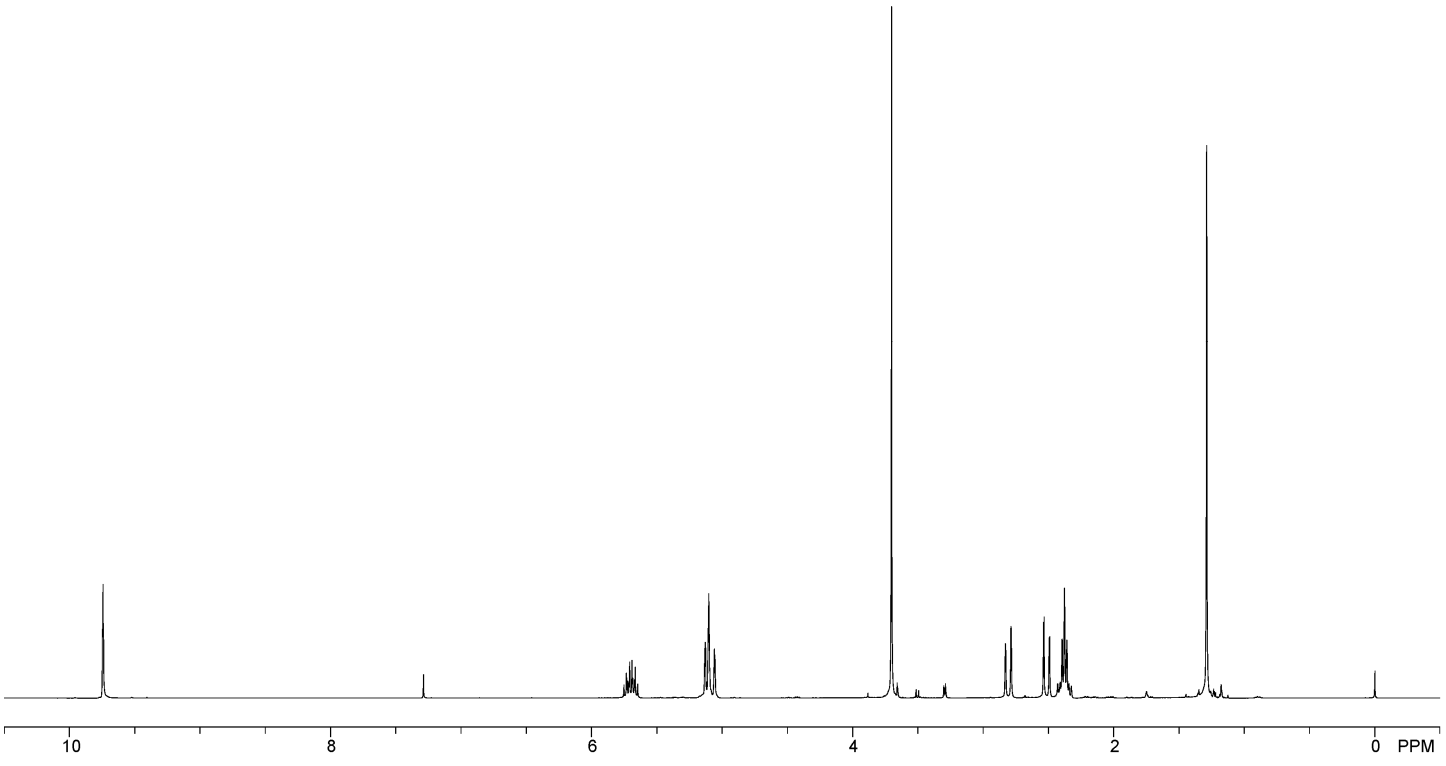
8

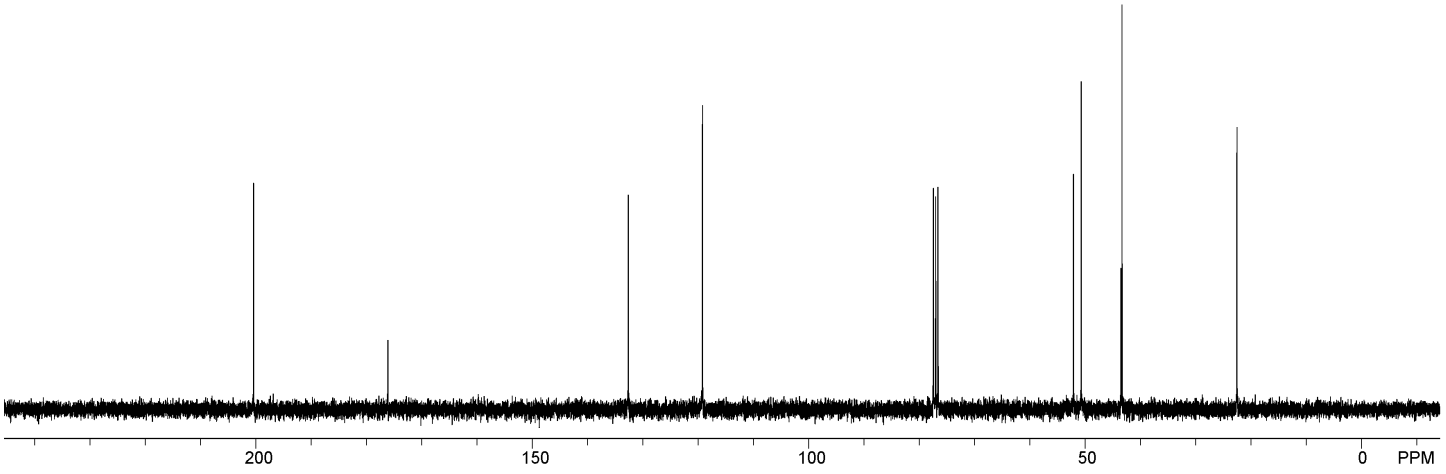


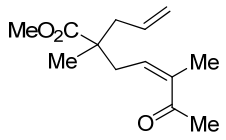




9







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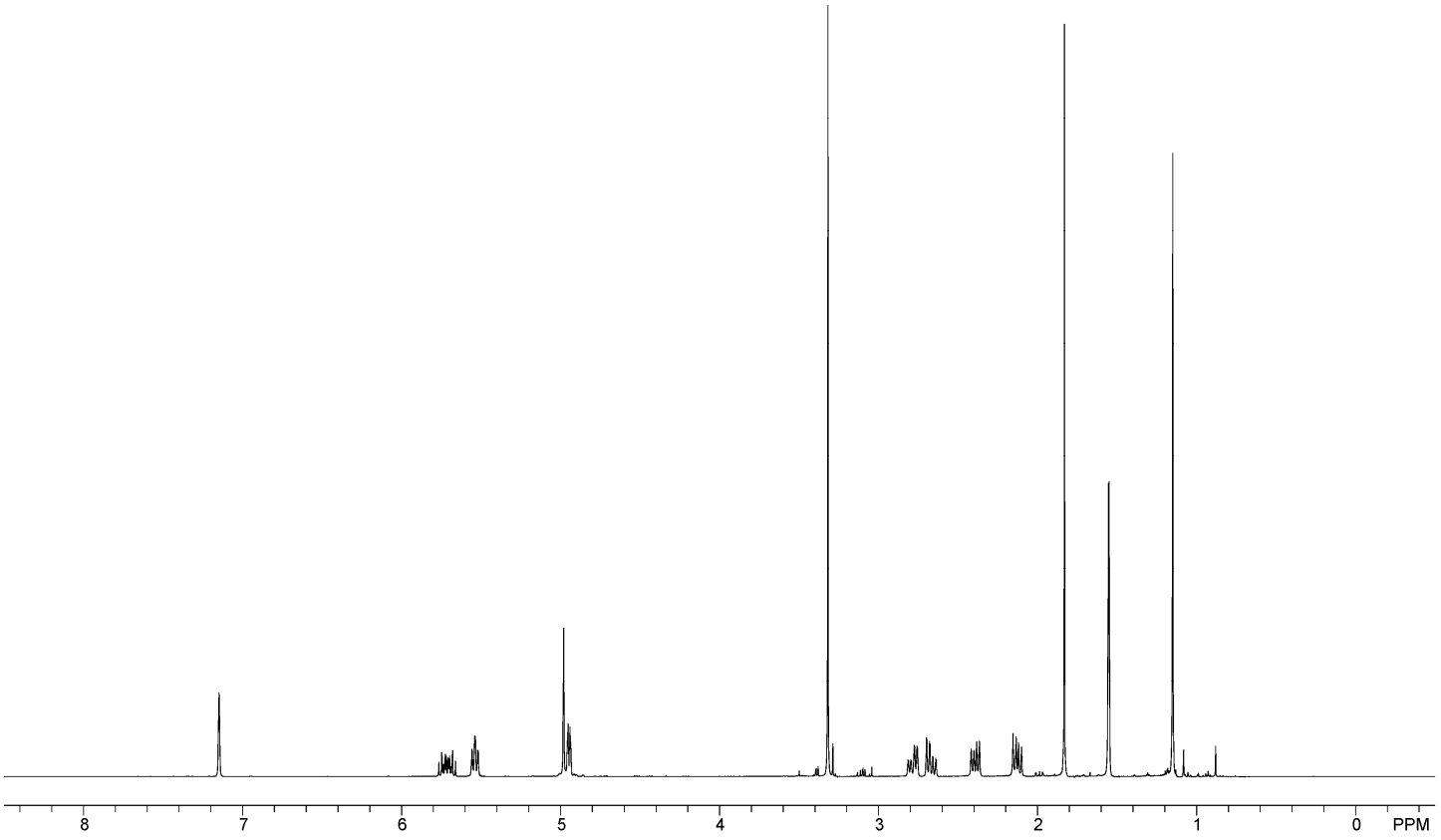

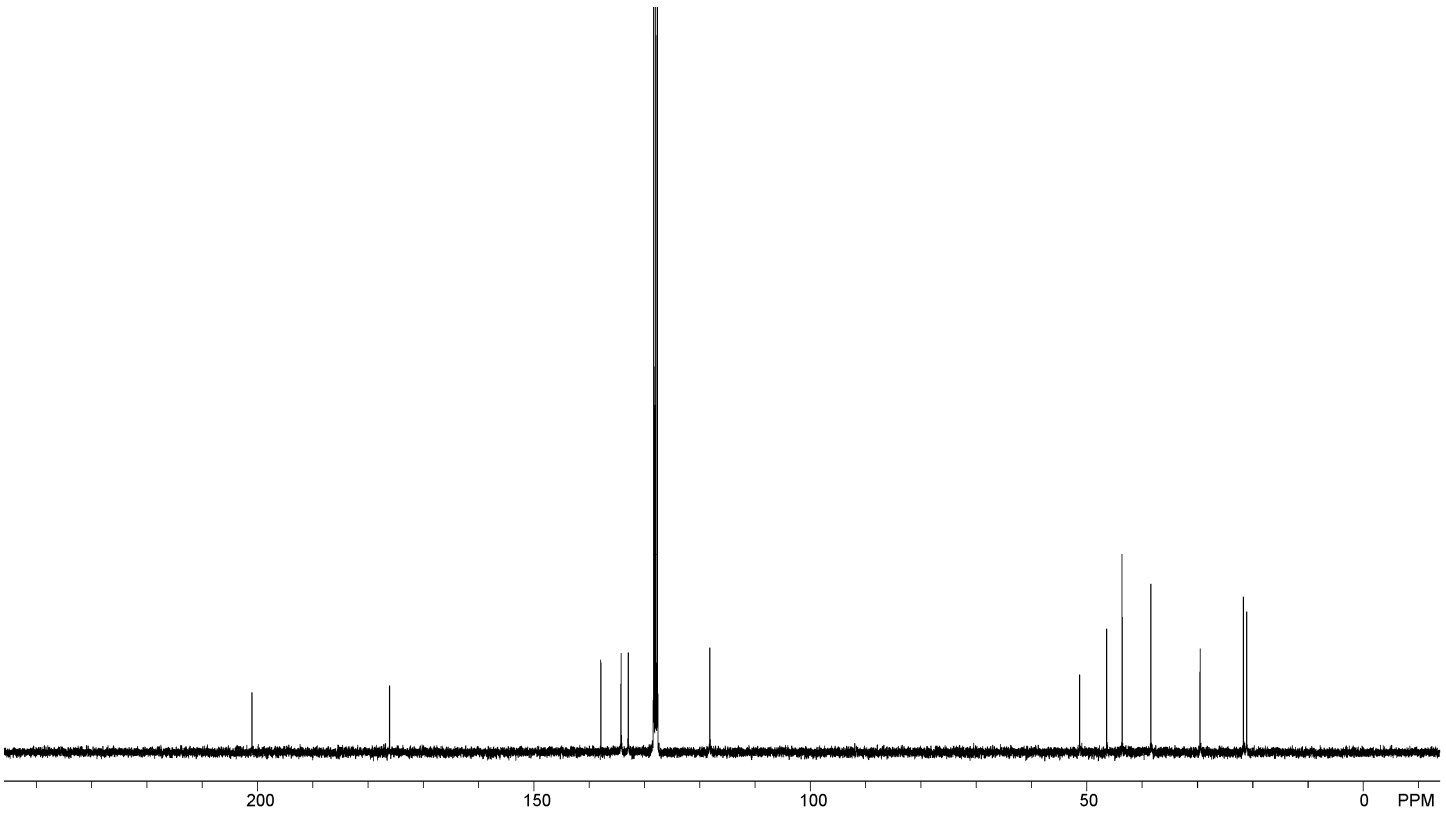

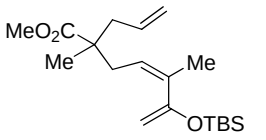

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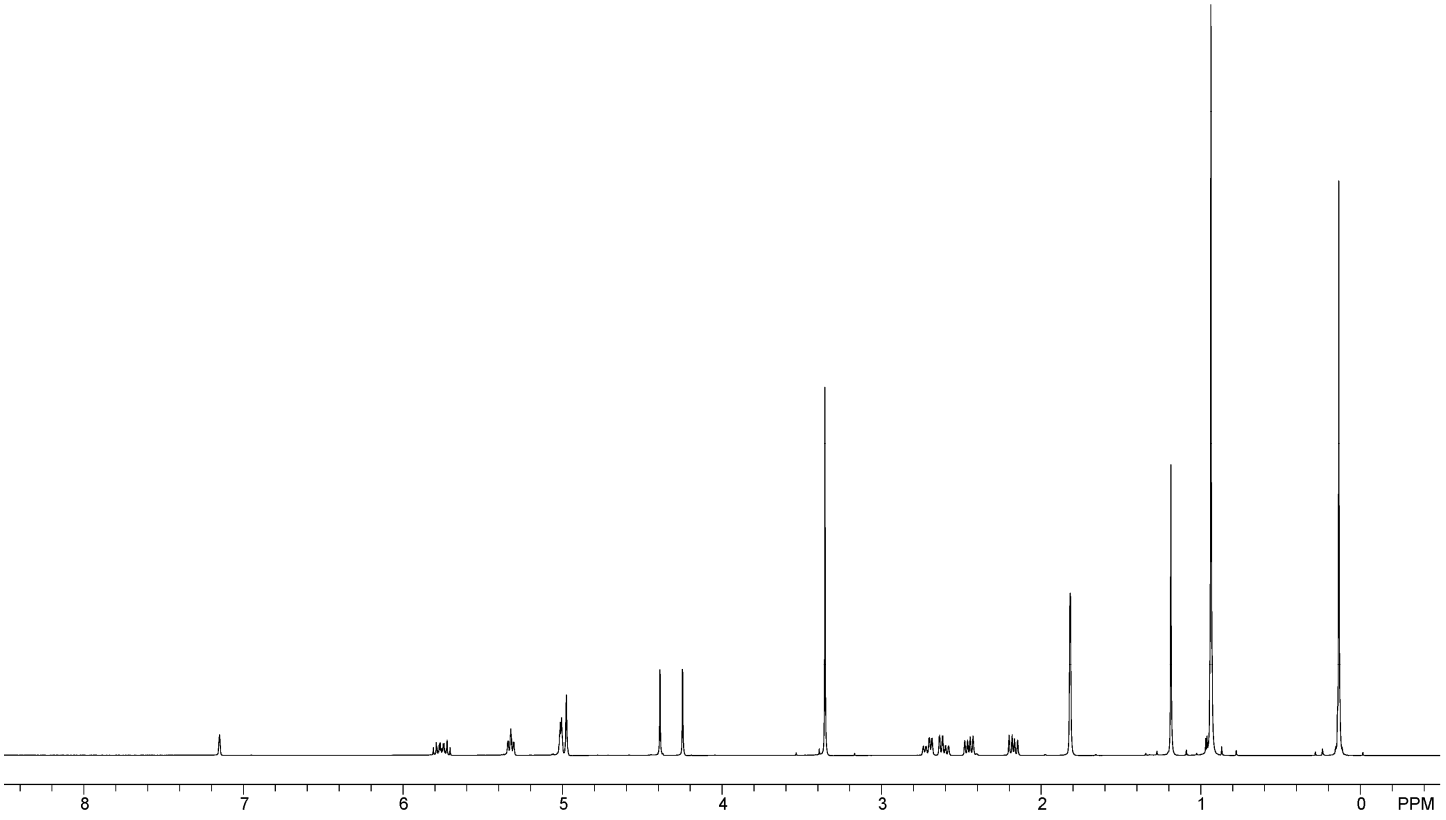
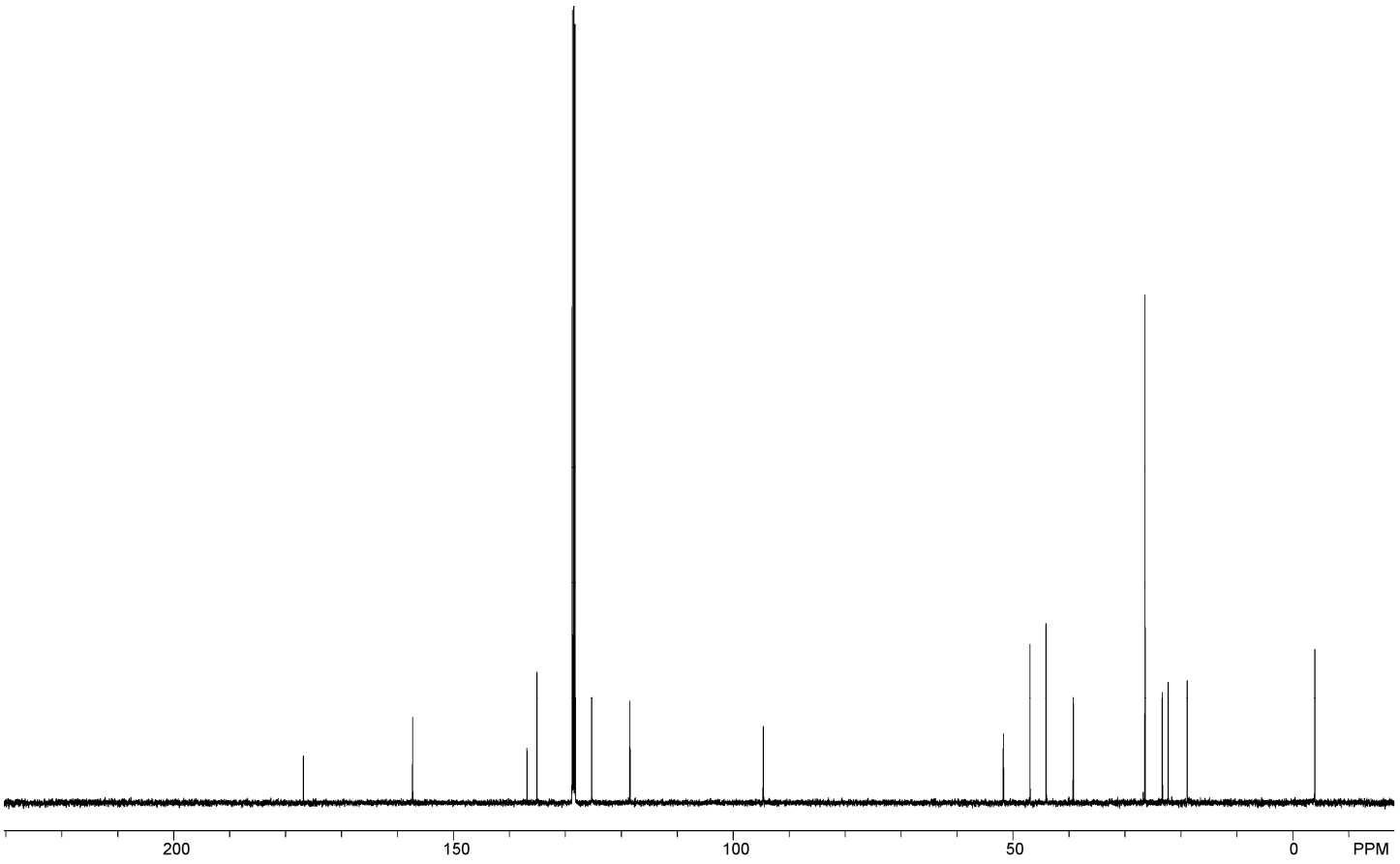
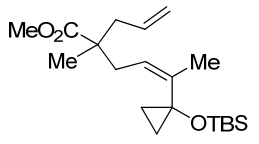
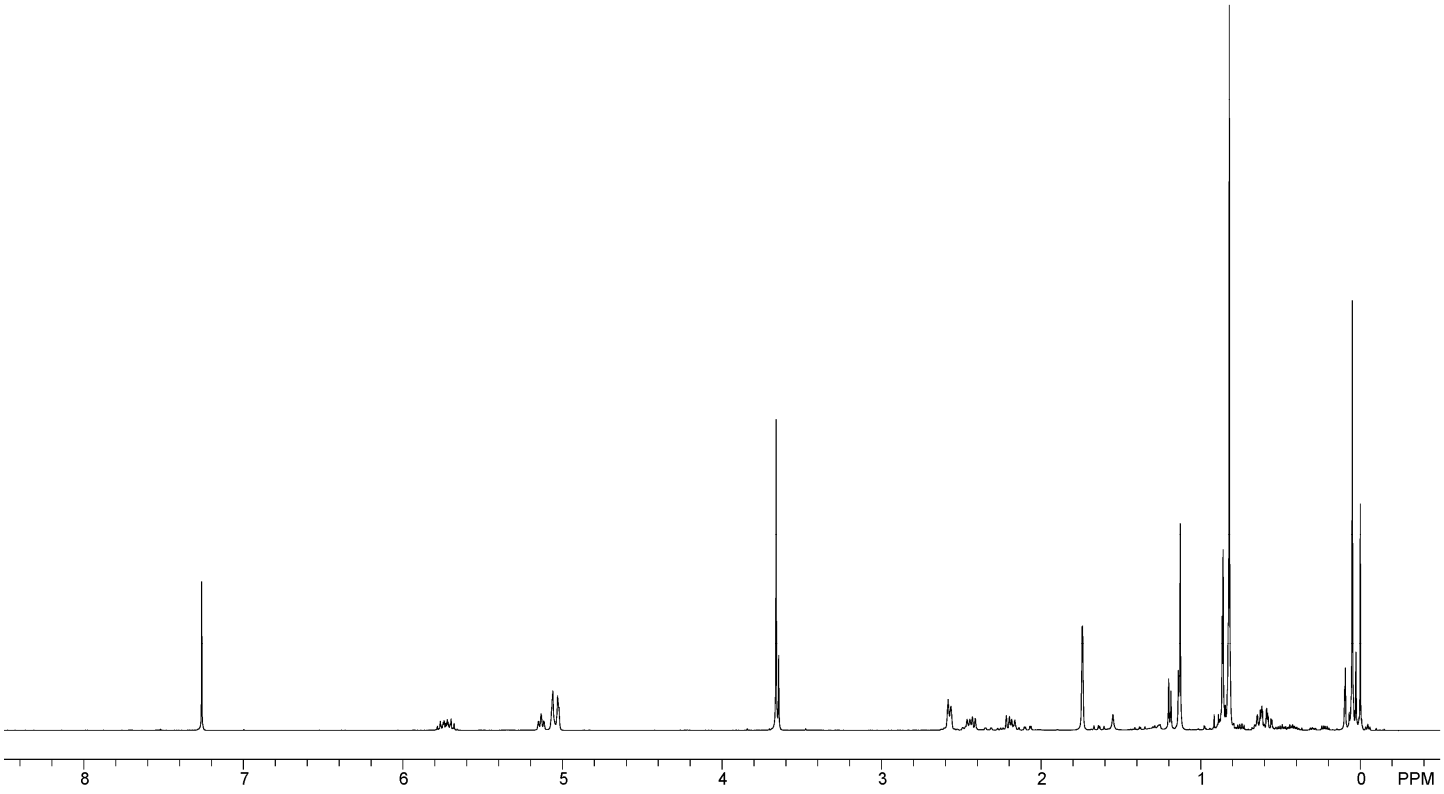
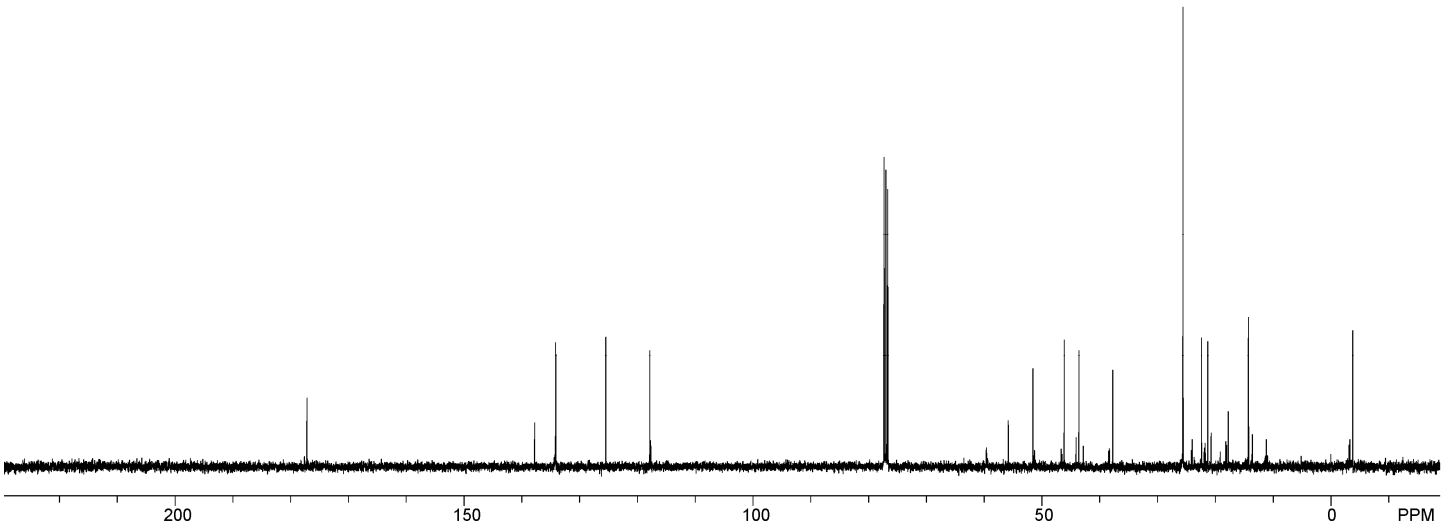


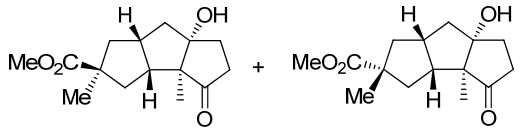




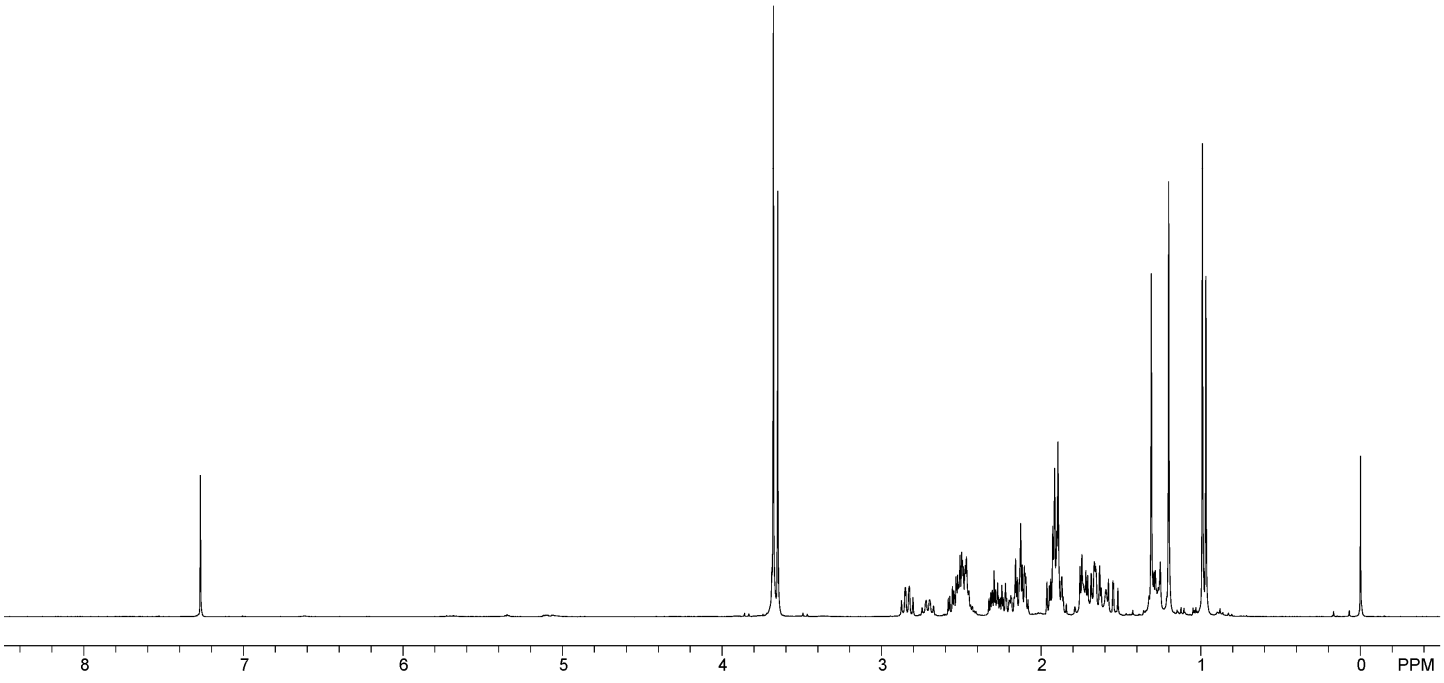
12 (contains unseparable biscyclopropane)

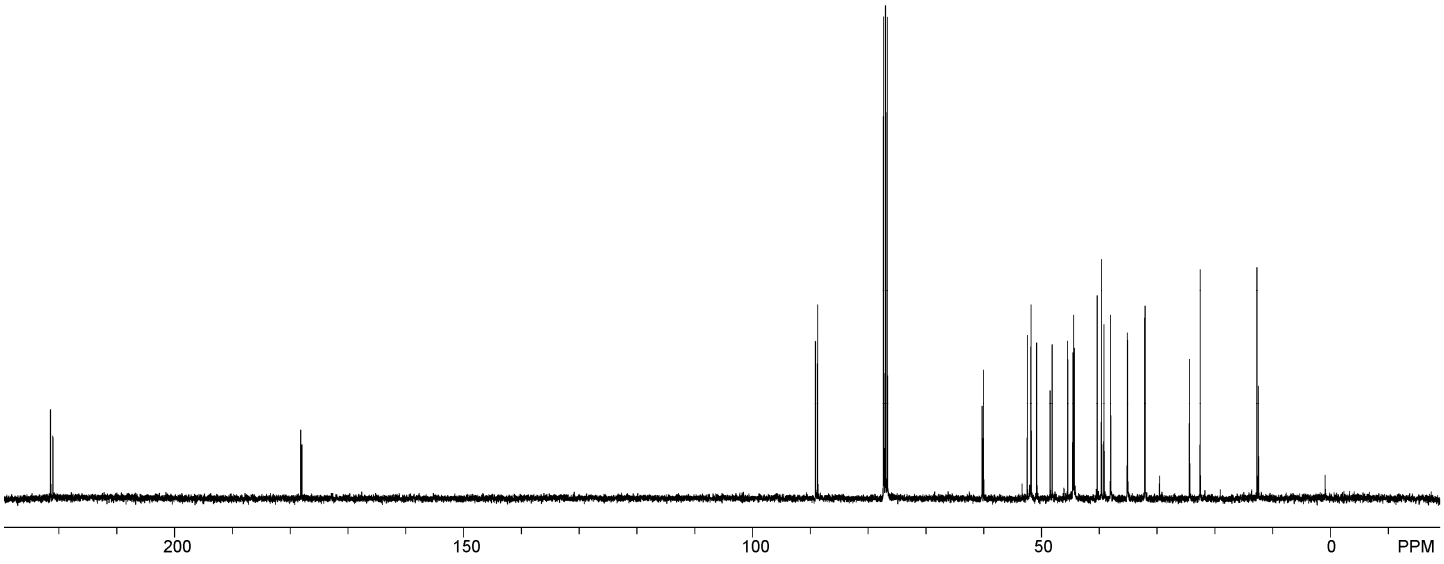


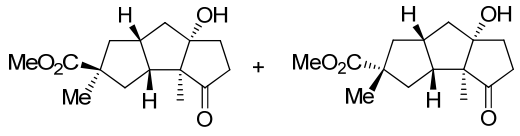




mixture, **13a:13b** = 1:1.5



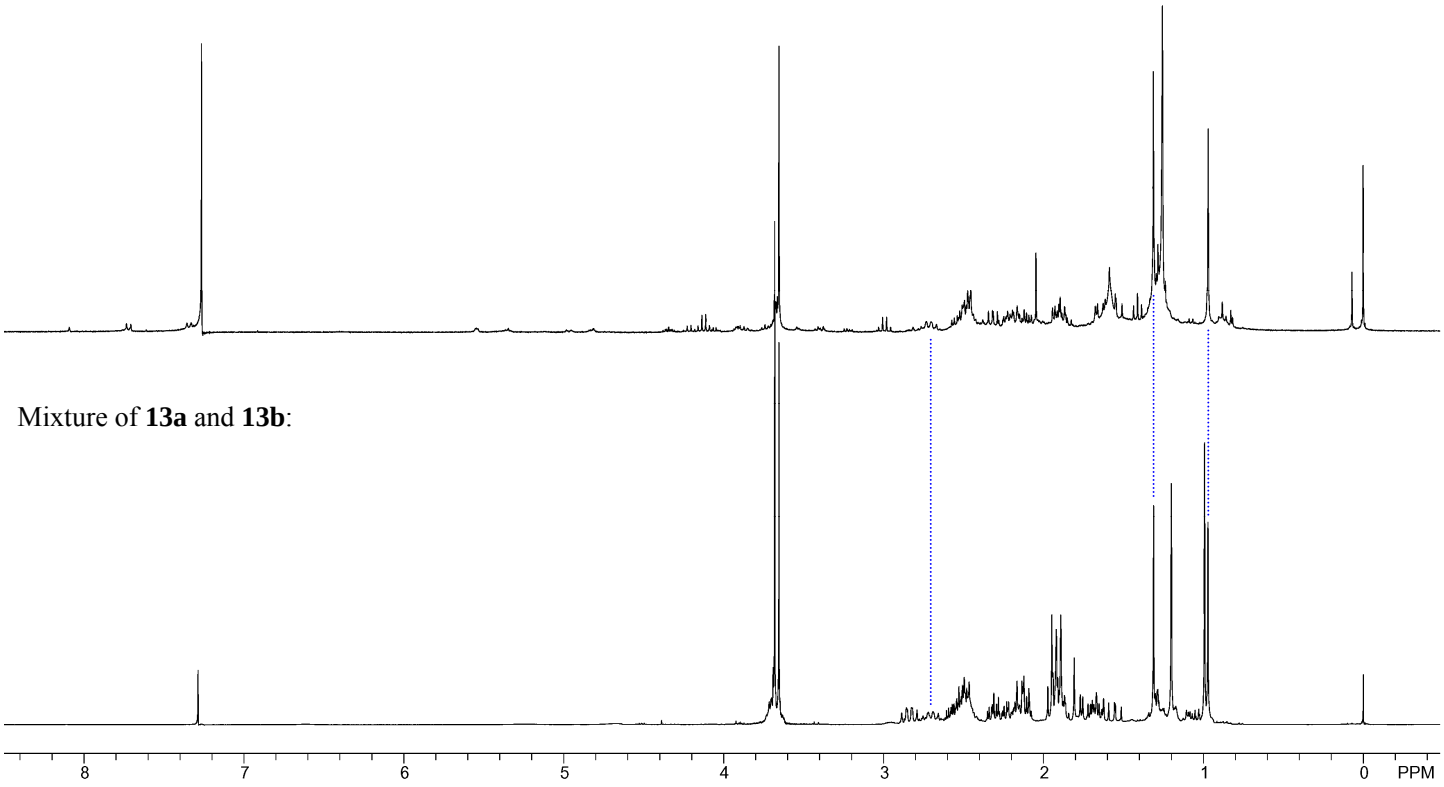




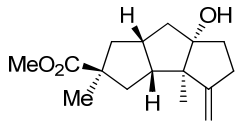
13a + **13b**, assignment for the relative configuration

Crude product **13a** from K_2OsO_4-$NaIO_4$ oxidation of compound **16a**:

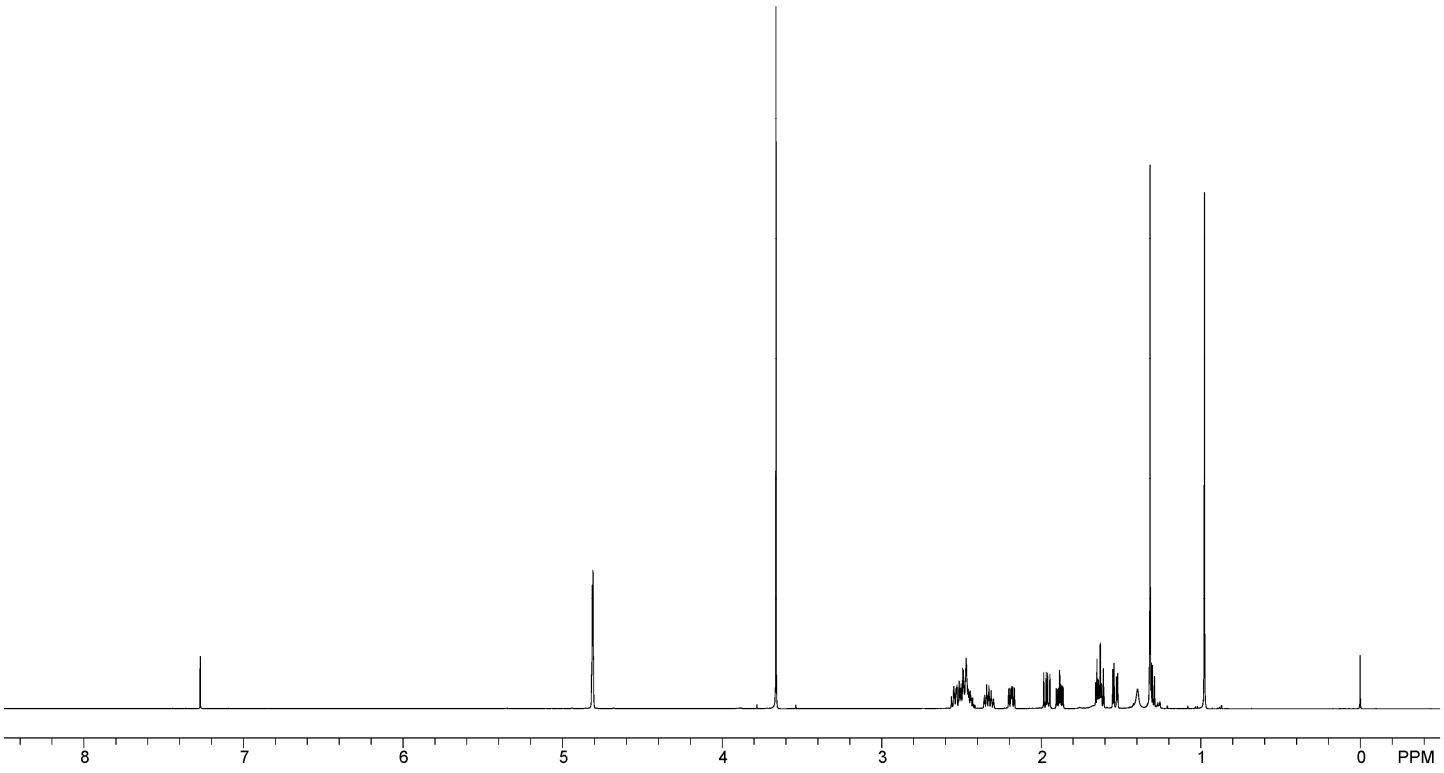
Mixture of **13a** and **13b**:

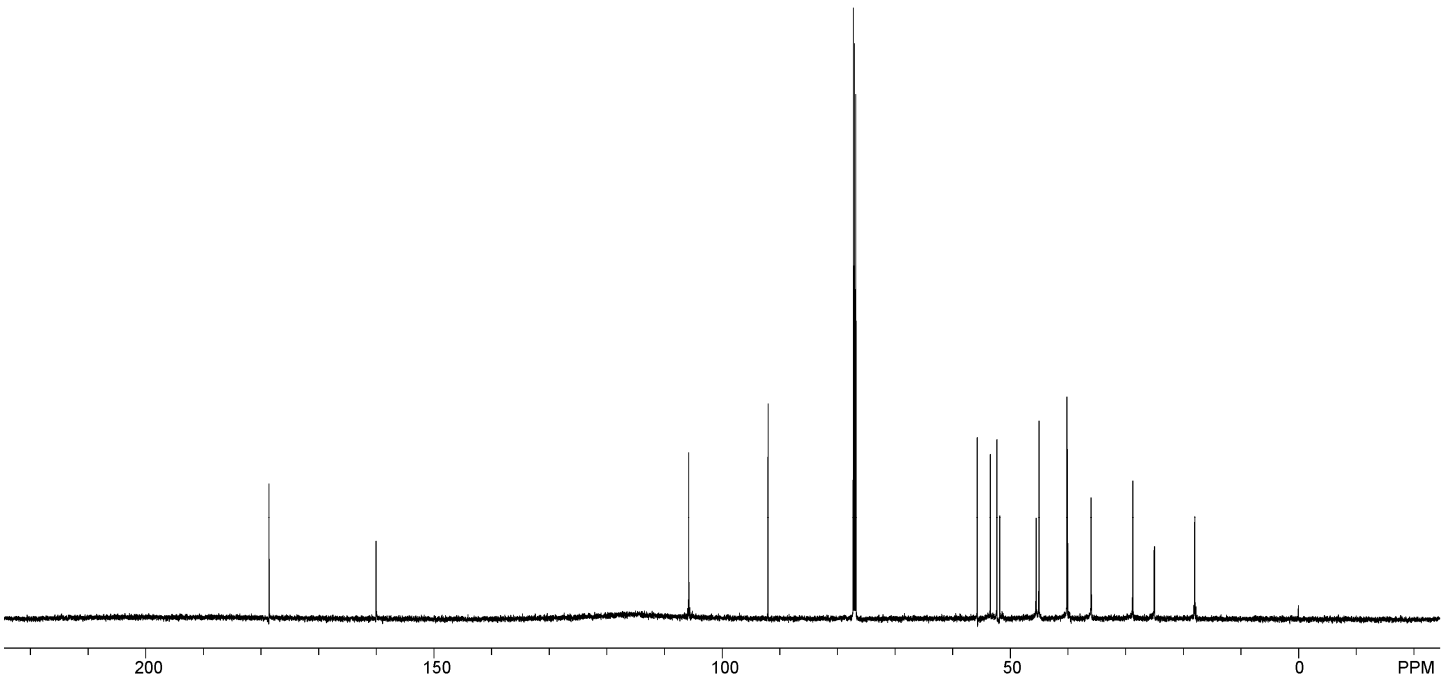


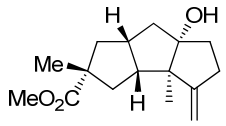
Comparison of the ^{1}H NMR spectrum indicates that the minor isomer **13a** has the correct relative configuration.



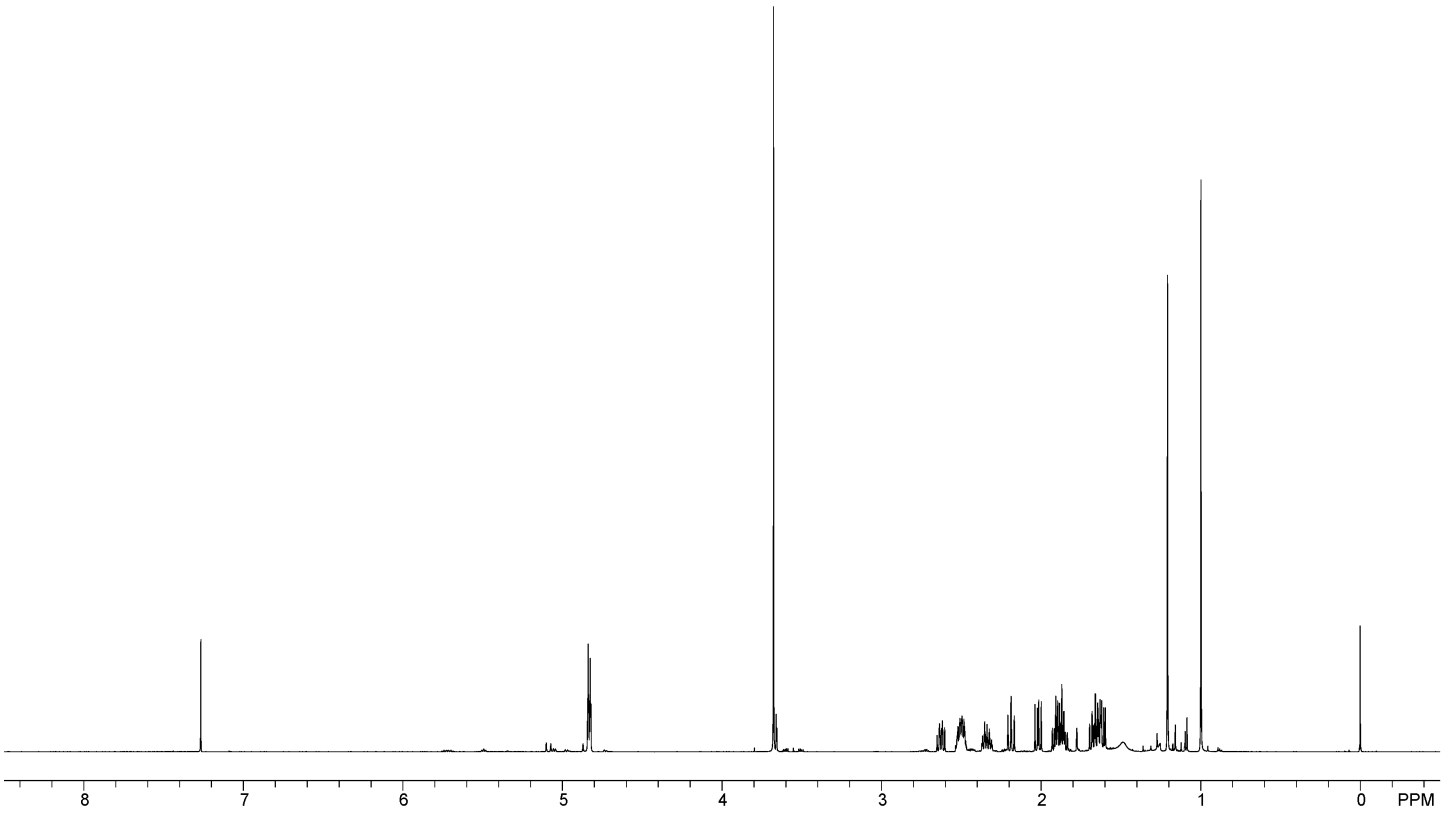
16a

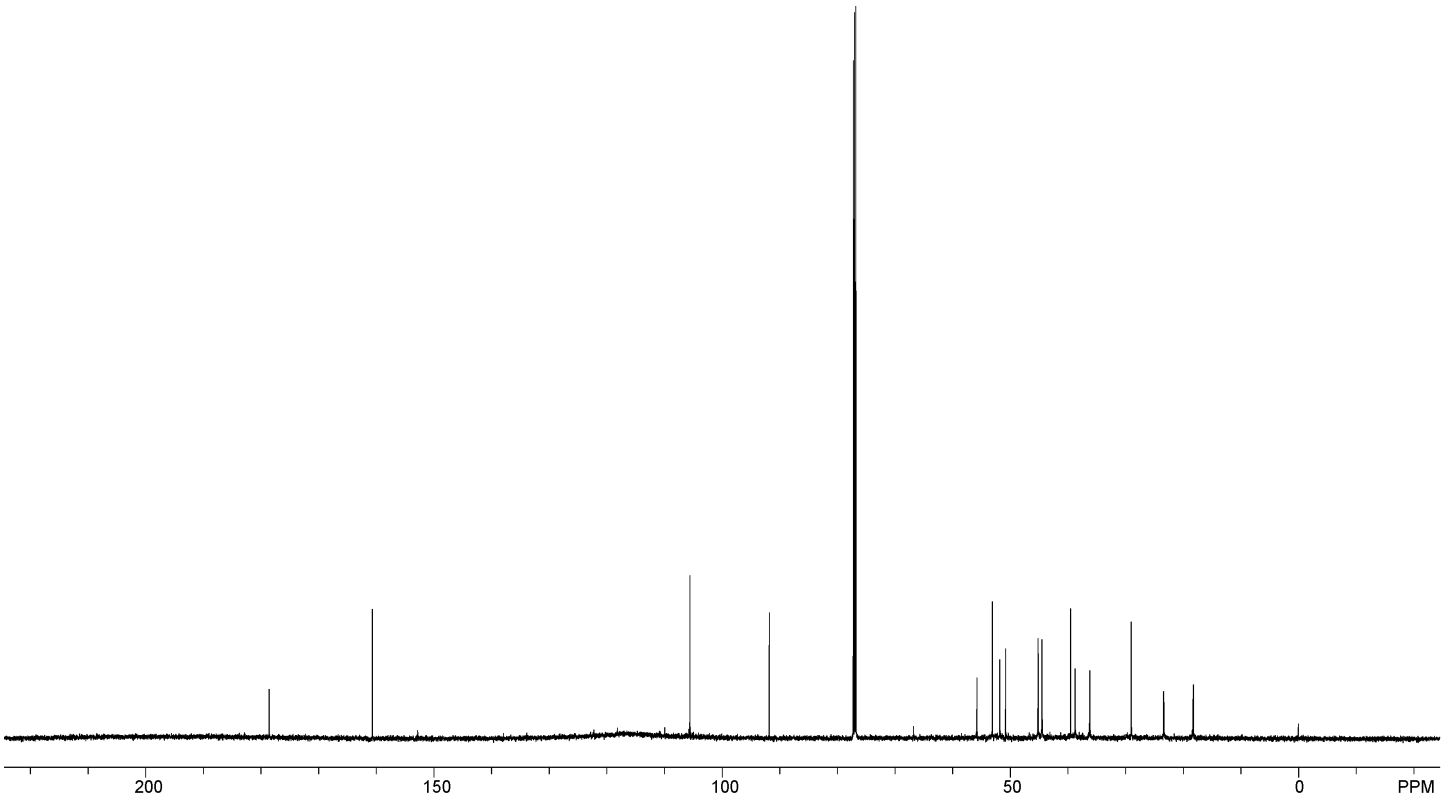


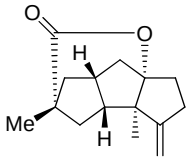




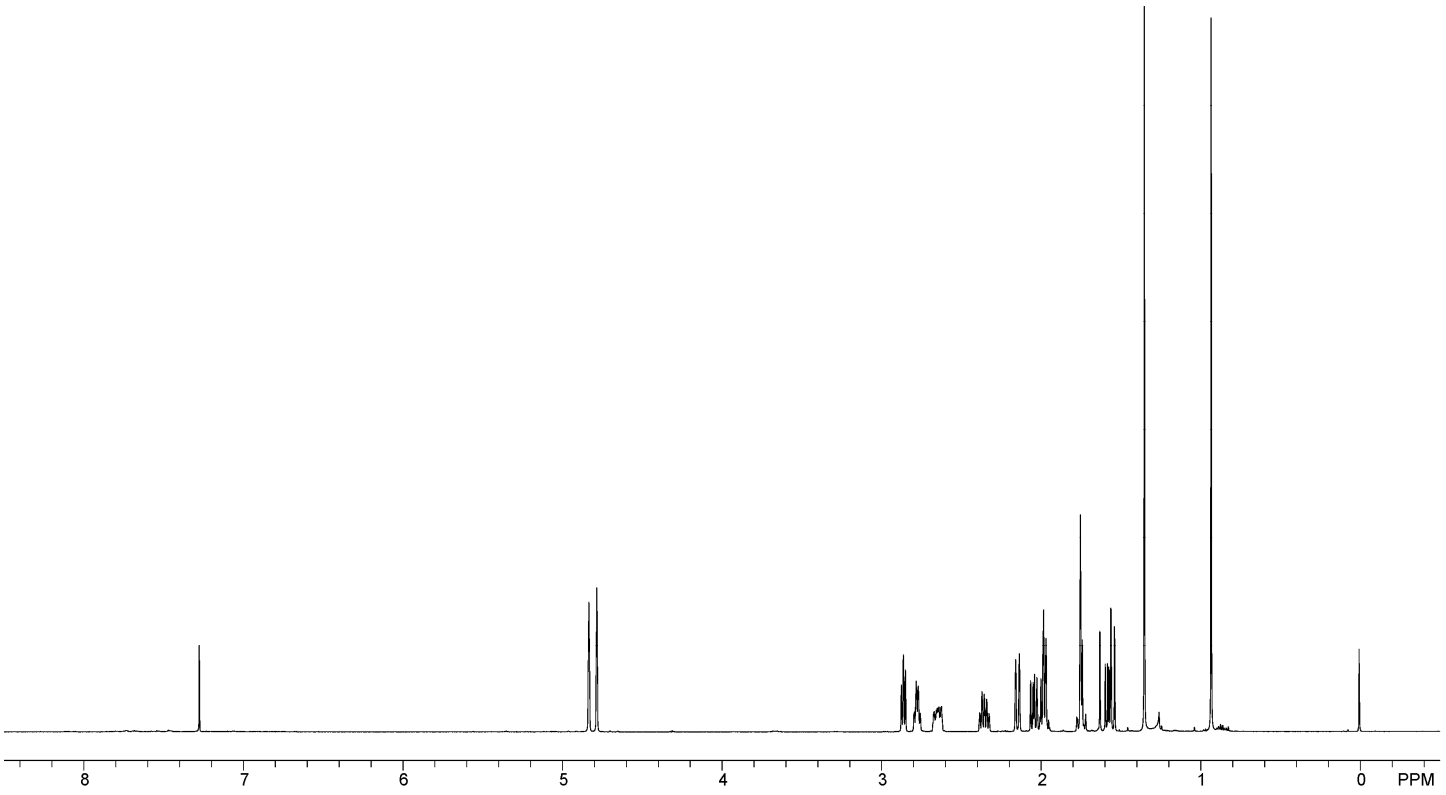
16b

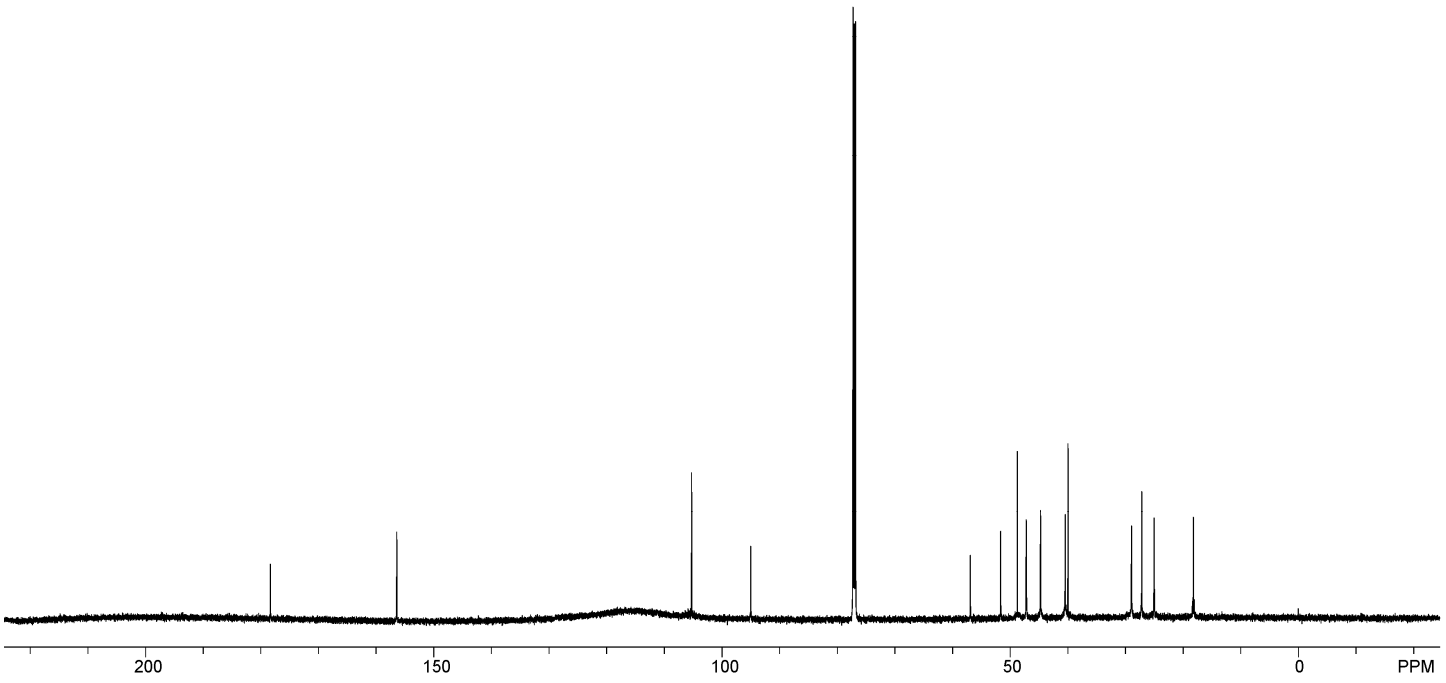


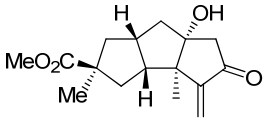




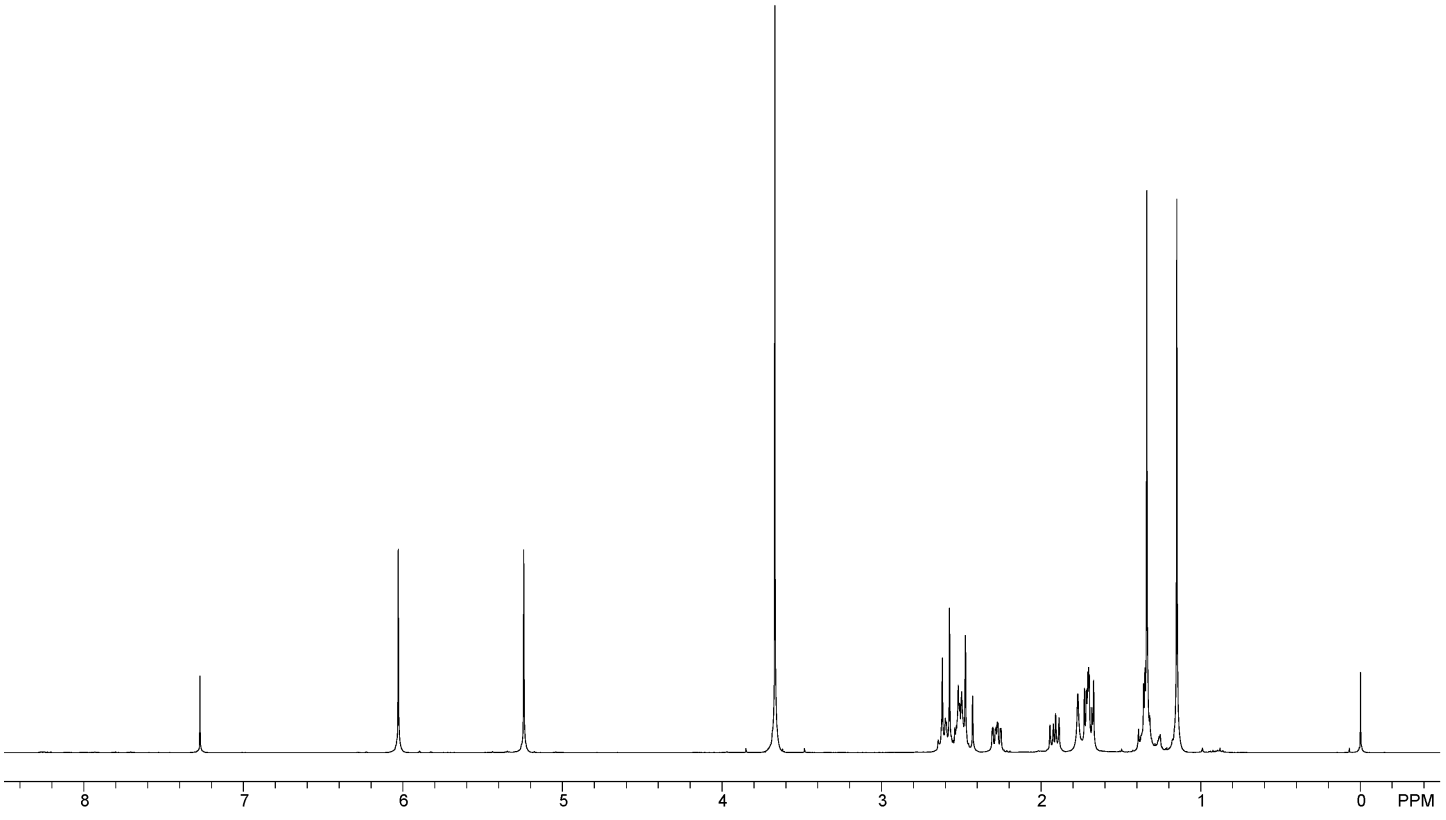
17

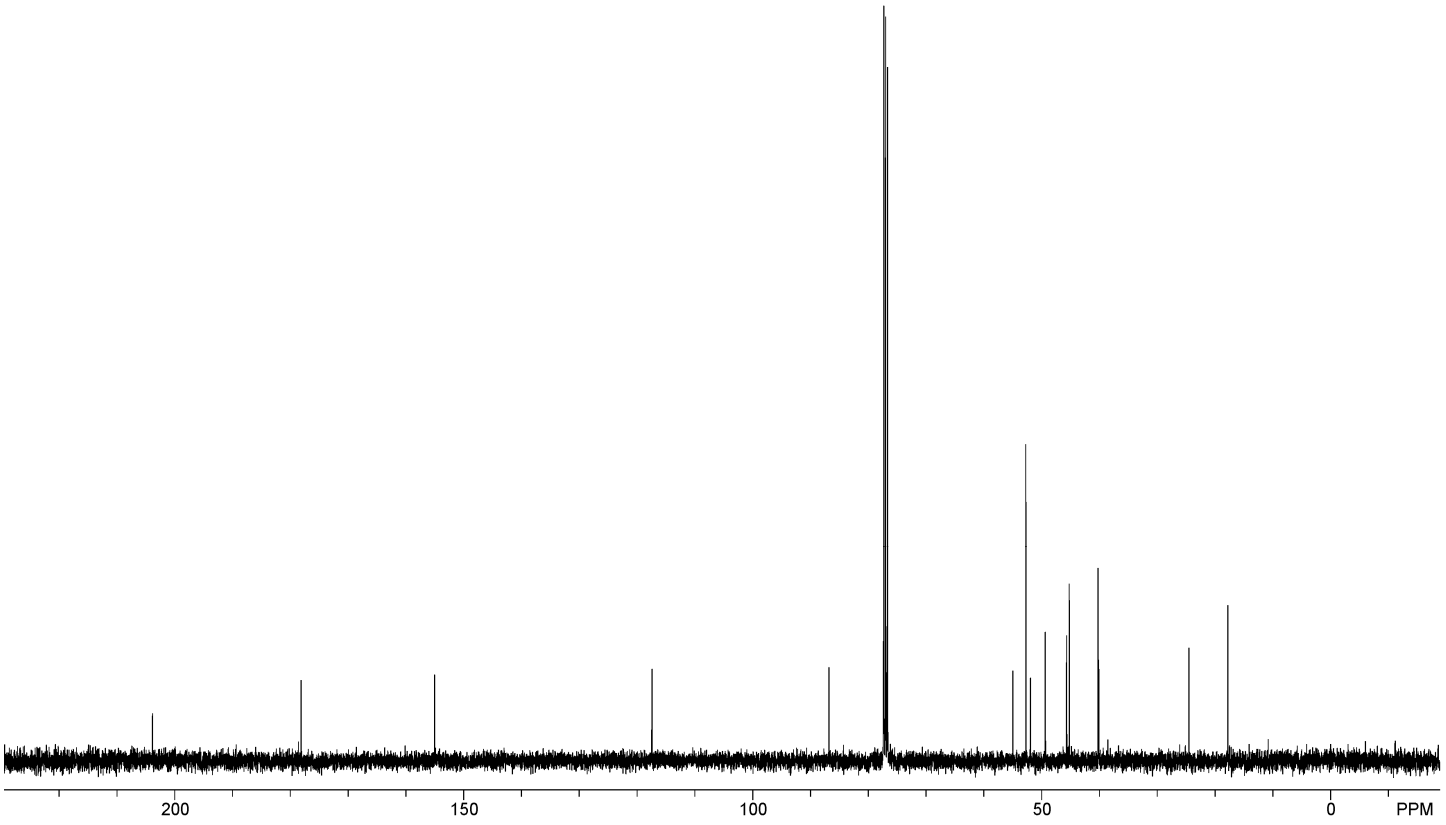


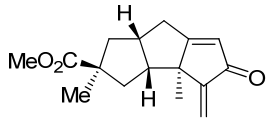




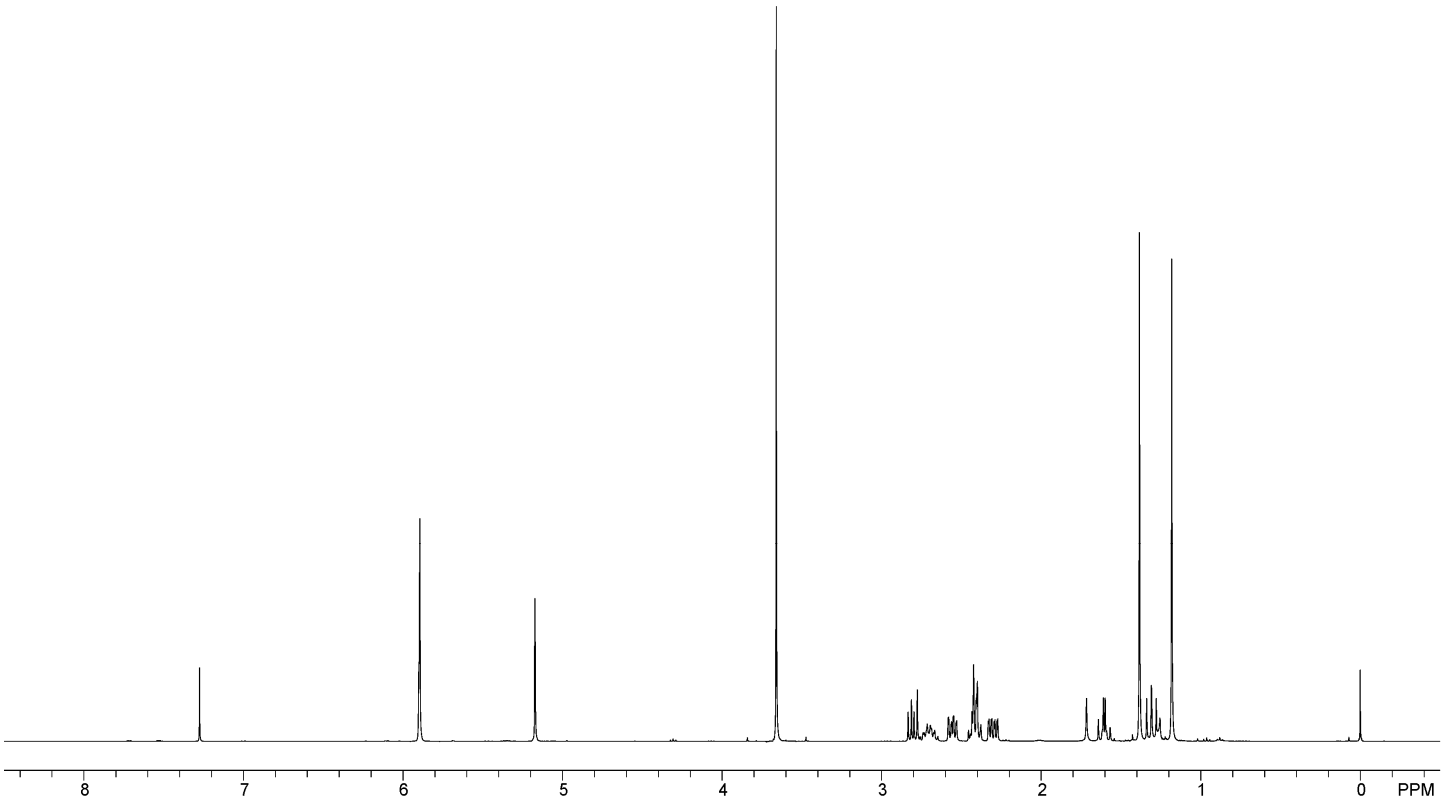
18

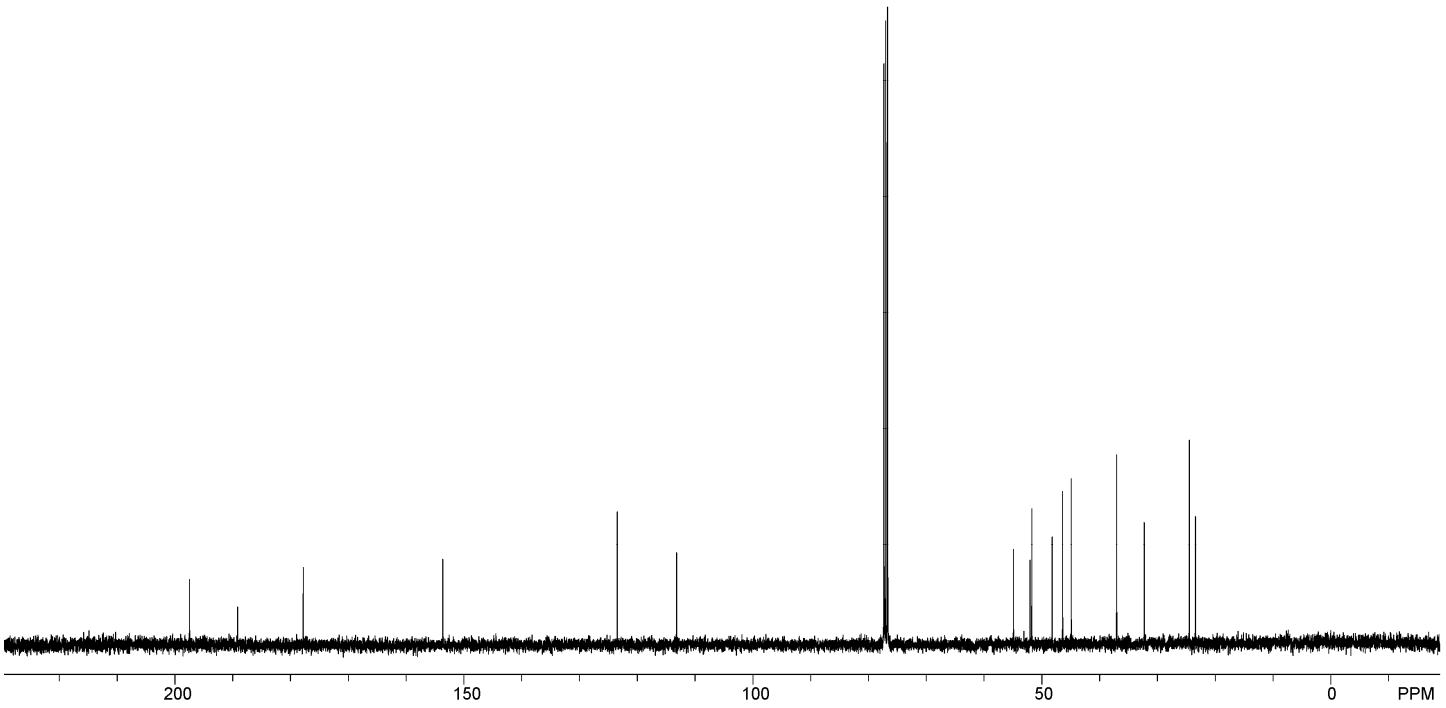


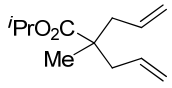




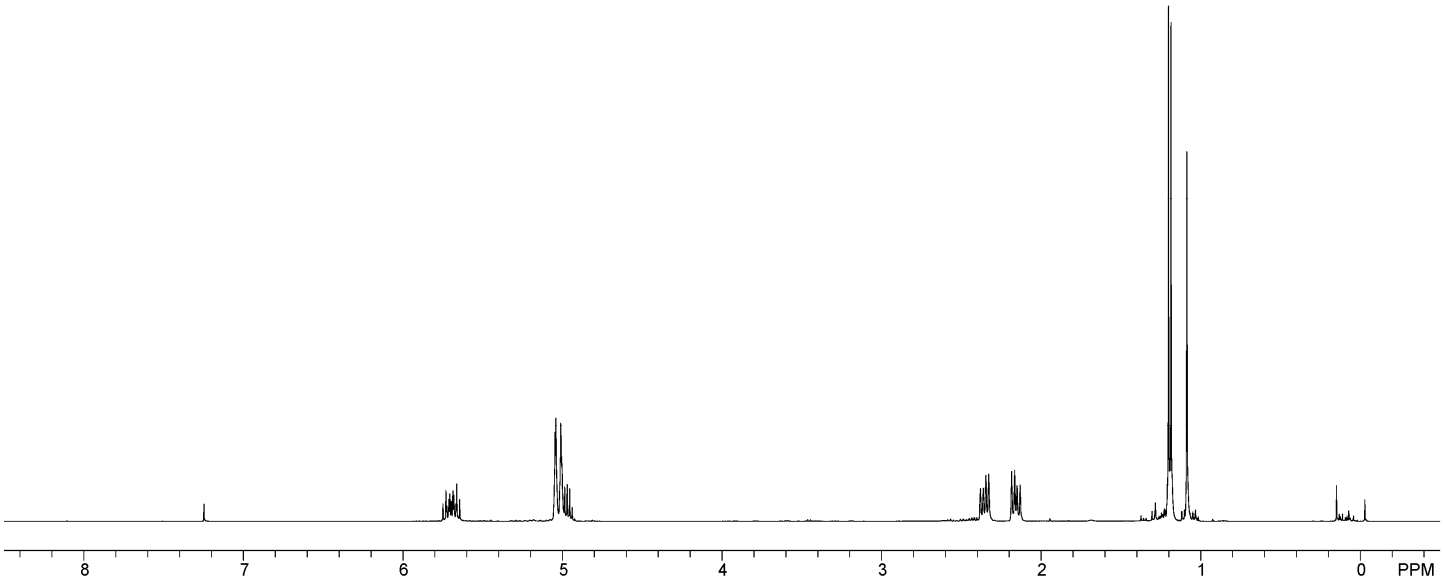
19

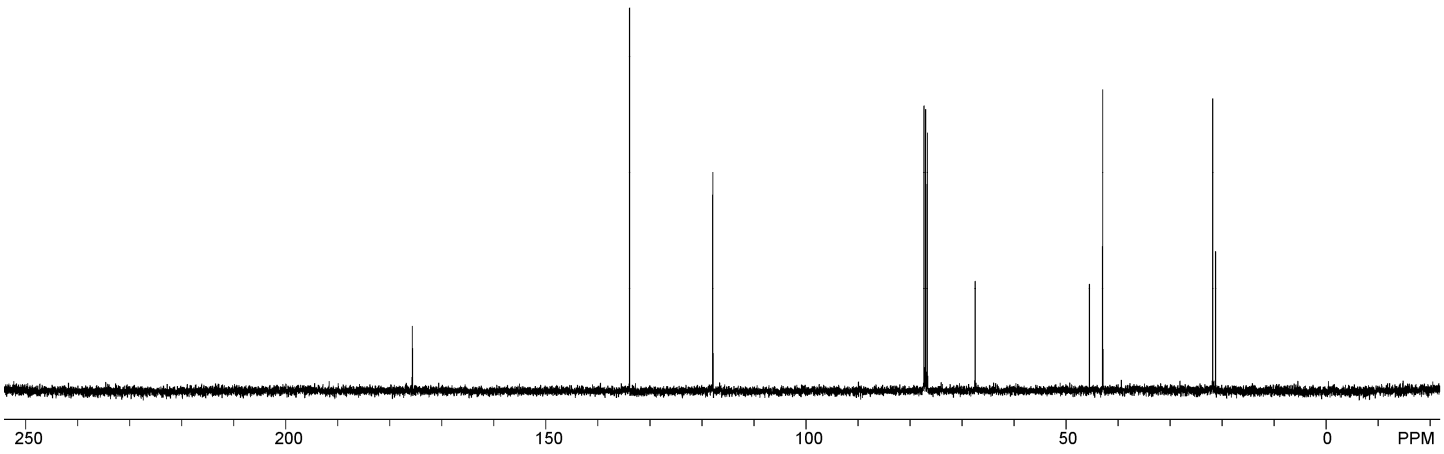


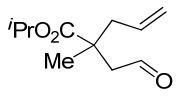




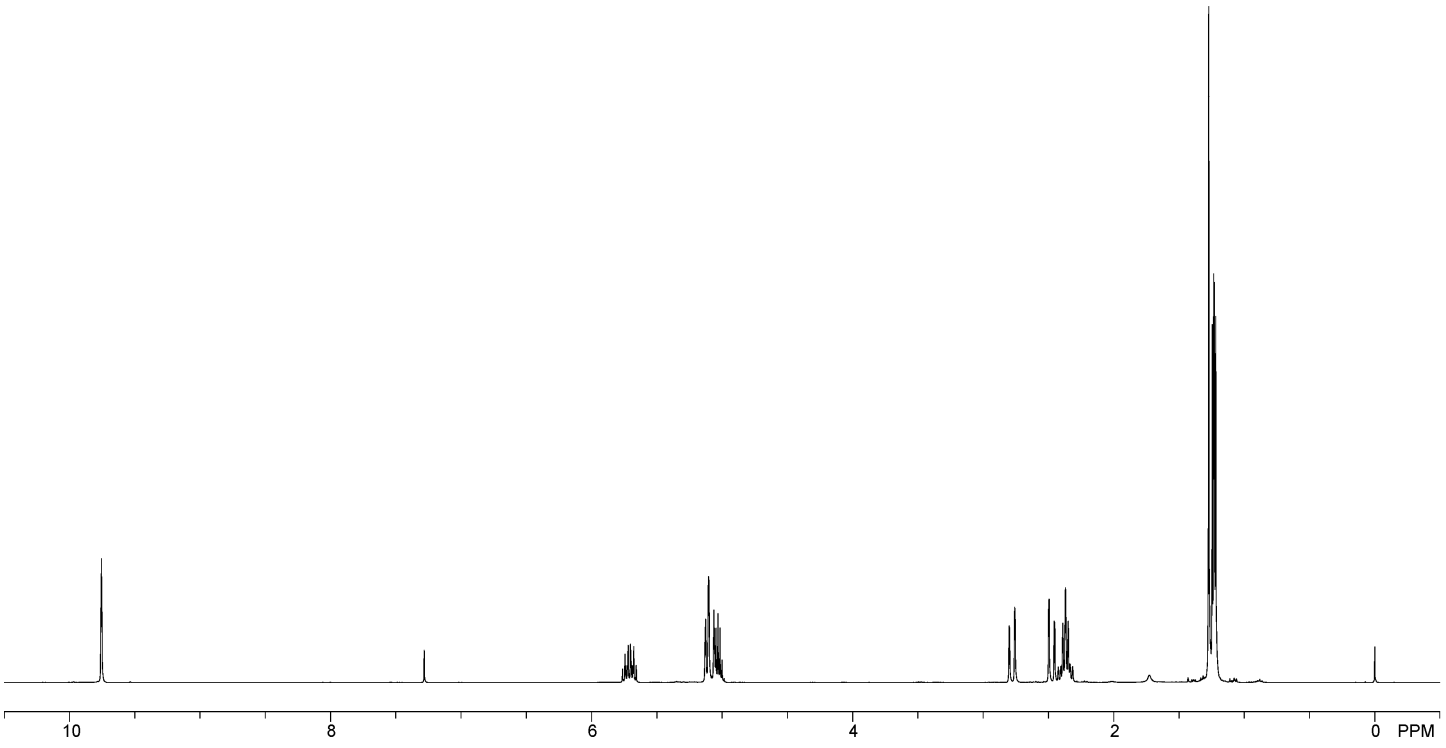
S2

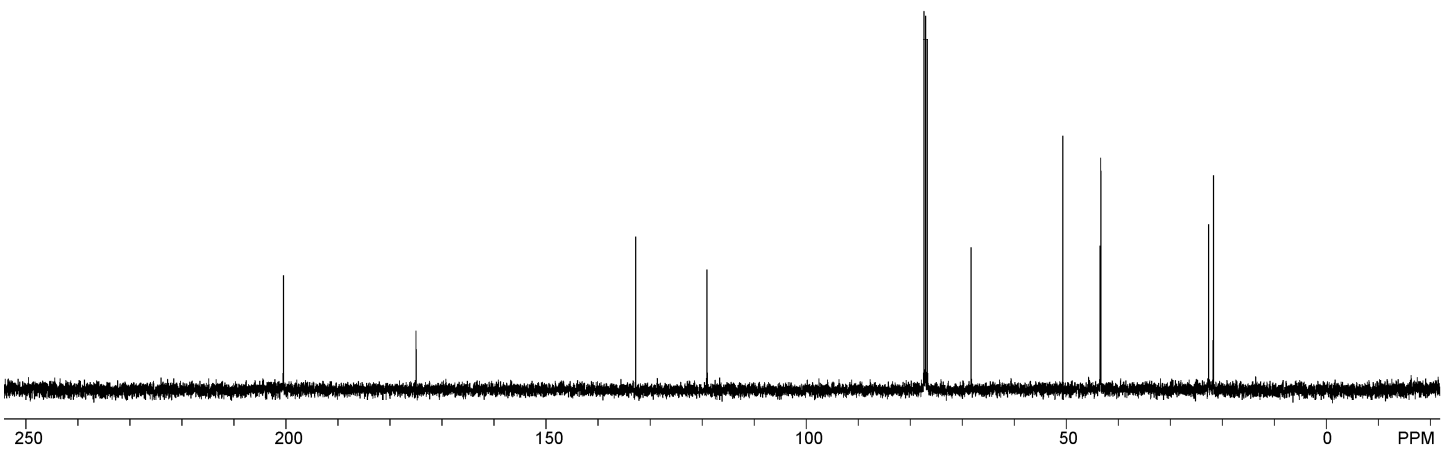


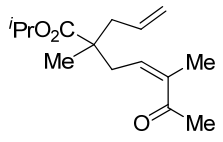




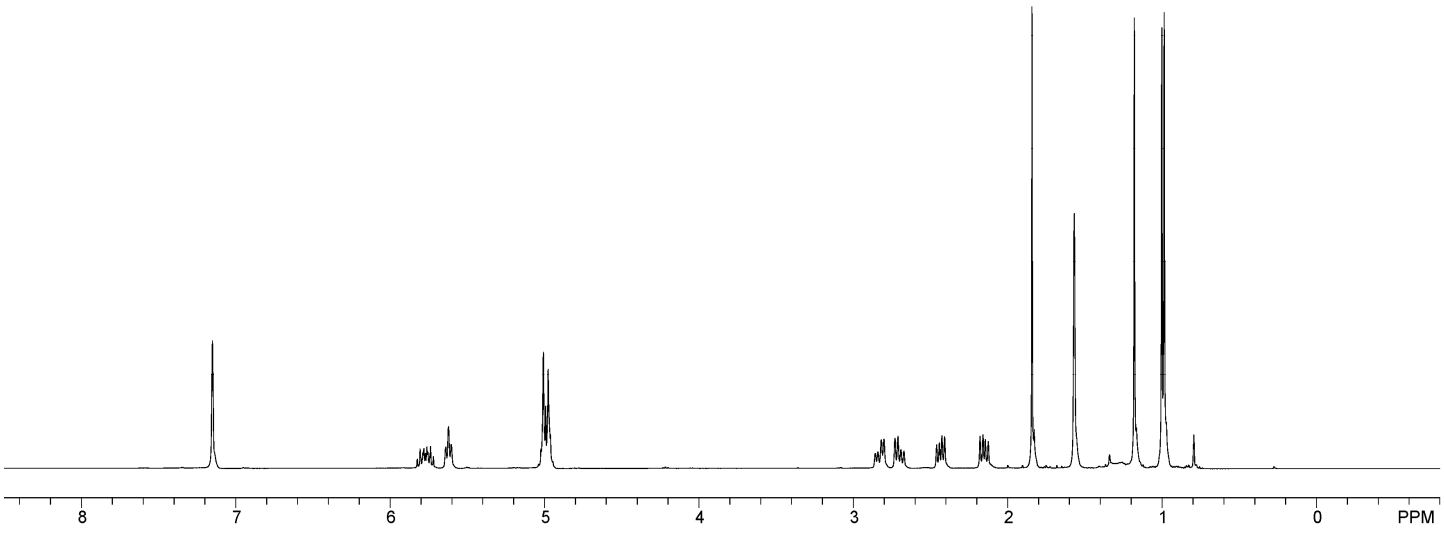
S3

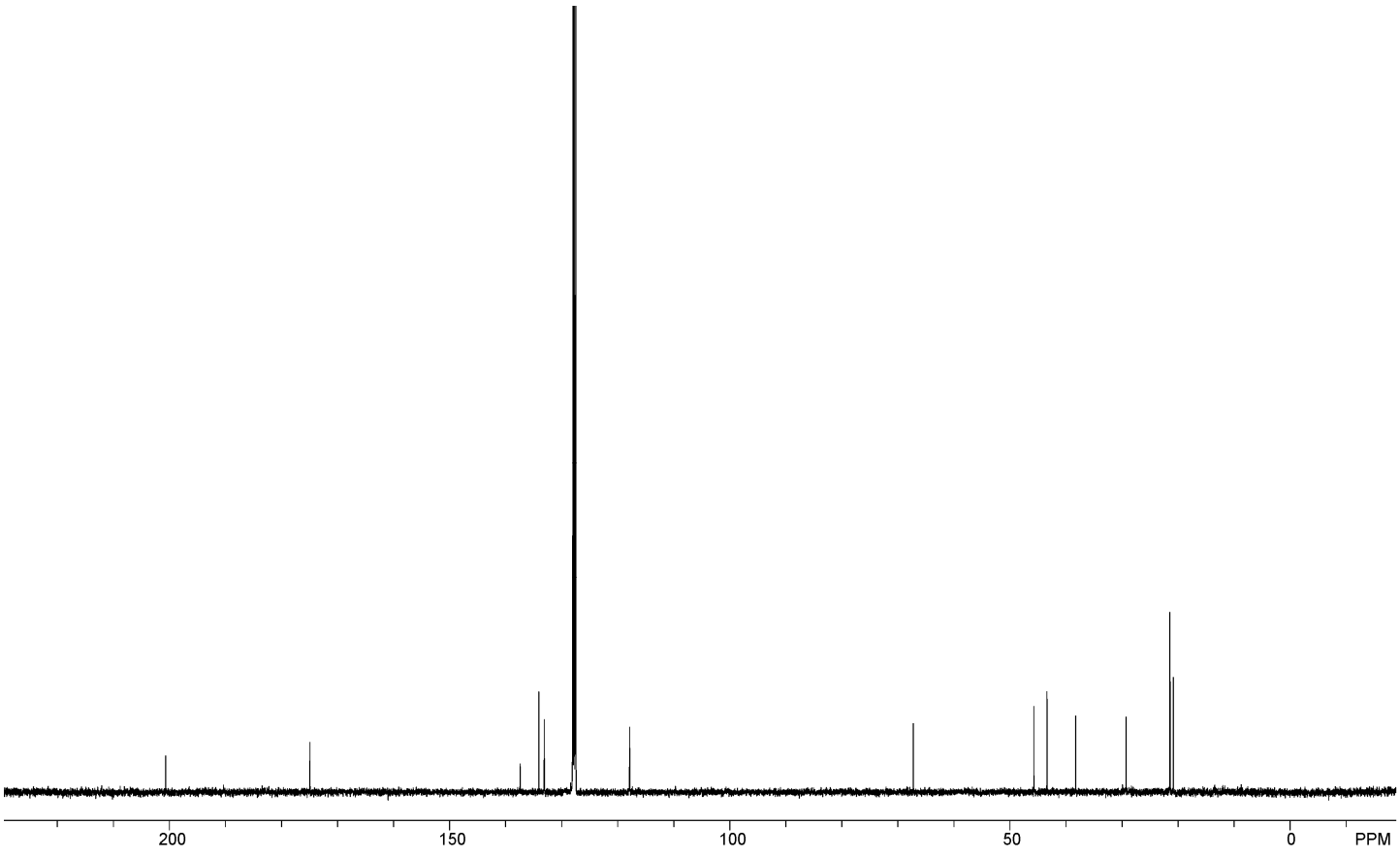


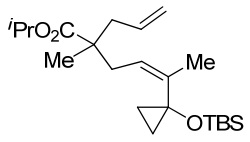




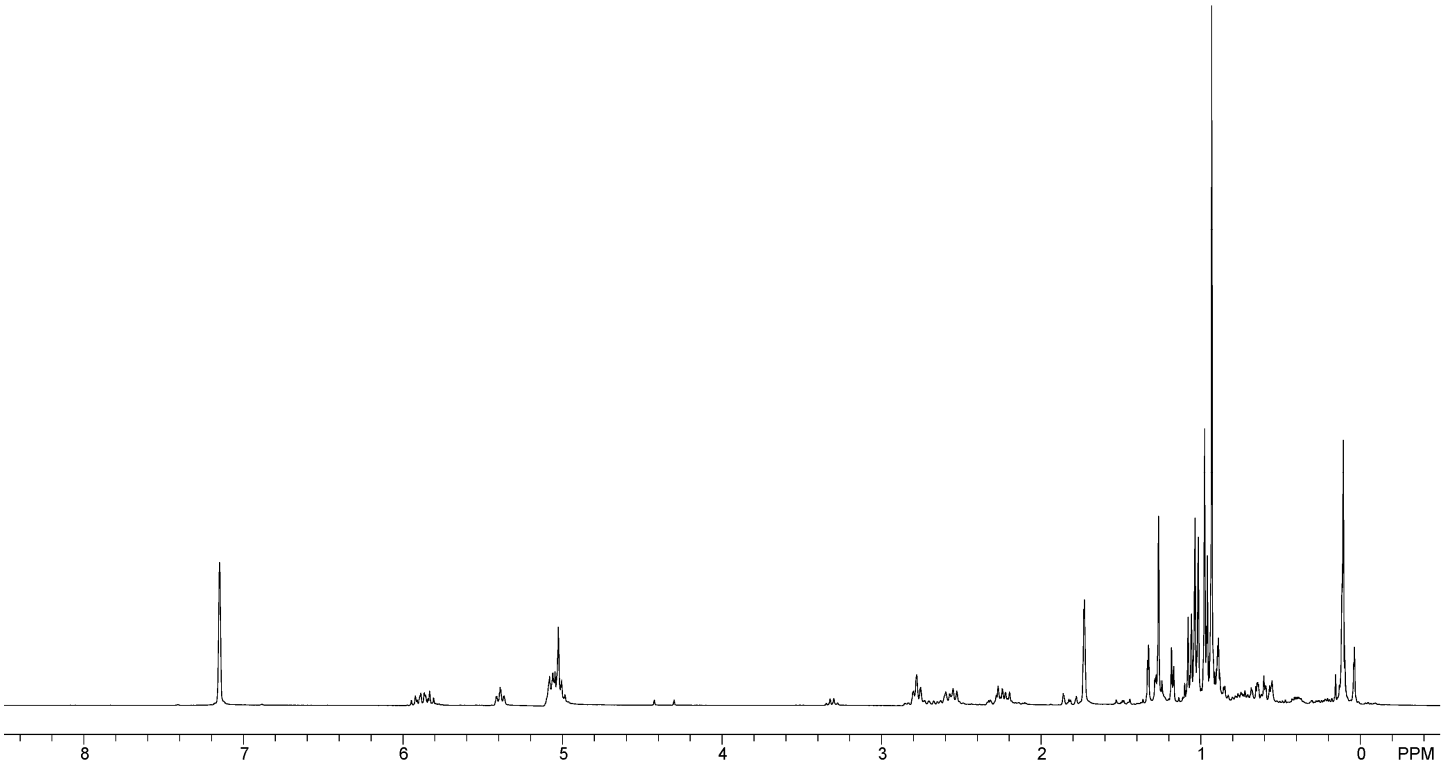
S4

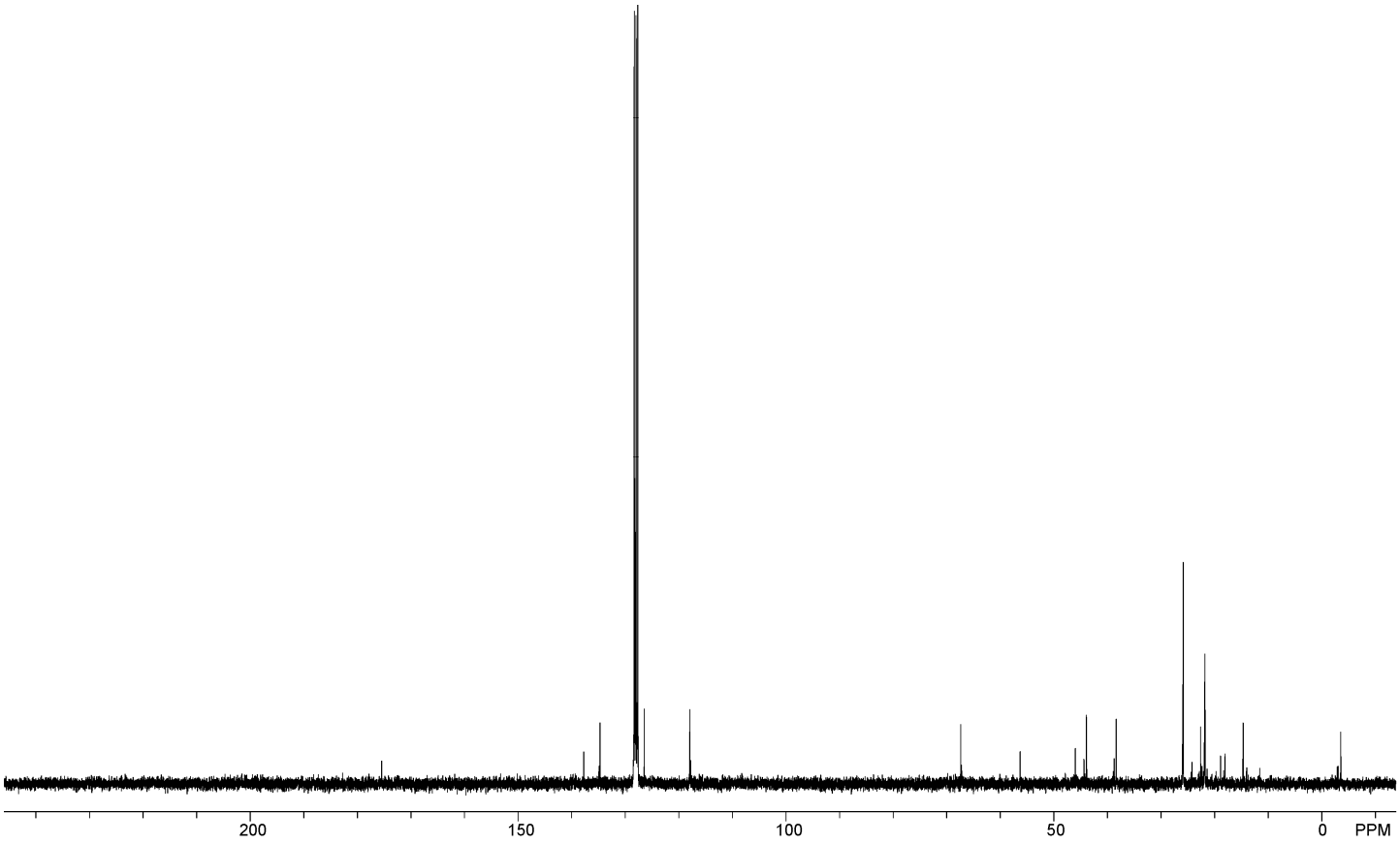


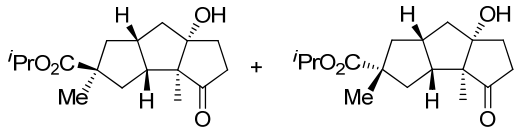




12' (contains inseparable impurities)







mixture, **13a':13b'** = 1:1.3