Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Acid-catalysed intramolecular addition of β-ketoesters to 1,3-dienes

Supporting Information

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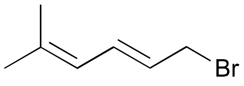
1 General experimental information

Unless otherwise stated, commercially available reagents were used as received. Solvents were dried by distillation under argon from the followings: tetrahydrofuran (THF): sodium/benzophenone; diethyl ether (Et_2O): sodium/benzophenone; toluene (tol): sodium; 1,2-dichloroethane (DCE): calcium hydride; *N,N*-diisopropylethylamine (DIPEA): calcium hydride. Wet toluene or wet DCE was prepared by shaking these solvents with water in a separatory funnel followed by collection of the organic layer. The water content of wet and distilled solvents was routinely checked by Karl-Fischer titration with a Mettler Toledo C20 KF coulometer. Flash chromatography (FC) was performed on 40-63 µm silica gel with mixtures of ethyl acetate (EA) and cyclohexane (Cy) or pentane. TLC plates were visualized by exposure to UV (254 nm) and/or *p*-anisaldehyde staining. NMR spectra were recorded on an AM250, AV300 or AV360 MHz Bruker spectrometers. ^1H NMR chemical shifts were referenced to the residual solvent signal; ^{13}C NMR chemical shifts were referenced to the deuterated solvent signal. Data are represented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J)* in Hz and integration. Infrared spectra were recorded on a FTIR spectrometer (Perkin-Elmer spectrum one, NaCl pellets or Bruker Vertex 70 ATR Pike Germanium) and are reported in cm^{-1}. High-resolution mass spectra were obtained by electrospray ionization with a TOF instrument (MicrOTOFq Bruker or LCT Waters spectrometer) using ESI-TOF (electrospray ionization-time of flight). MS were recorded on DSQ Thermo Fisher instrument by electronic impact

2 Starting materials

2.1 Preparation of the substrate

2.1.1 Preparation of compound SM1



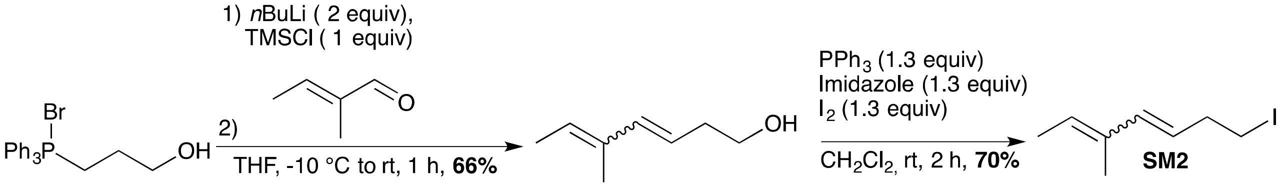
SM1
$C_7H_{11}Br$
MW=175,07

A heat gun-dried 250 mL round bottom flask was charged with $LiAlH_4$ (1.4 g, 37.3 mmol, 1.2 equiv), suspended in Et_2O (30 mL), and cooled to 0 °C. A solution of ethyl (2*E*)-5-methylhexa-2,4-dienoate[1] (4.8 g, 31.1 mmol, 1.0 equiv) in Et_2O (50 mL) was slowly cannulated into the $LiAlH_4$ suspension, and the reaction mixture was allowed to warm to rt. After stirring at rt for 2 h, the reaction was cooled to 0 °C, diluted with Et_2O, and slowly quenched with water (1.4 mL). This biphasic mixture was stirred for 10 min and then 10% aq. NaOH (1.4 mL) was added. The stirring was maintained for 30 min. The mixture was filtered and concentrated *in vacuo* to afford ***(E)-5-methylhexa-2,4-dien-1-ol*** as a colorless oil (3.4 g, 30.2 mmol, 39%). **^1H NMR (250 MHz, $CDCl_3$):** δ 6.45 (ddt, *J* = 15.1, 11.0, 1.5 Hz, 1H), 5.83 (dd, *J* = 10.9, 2.0 Hz, 1H), 5.70 (dt, *J* = 15.1, 6.3 Hz, 1H), 4.17 (dd, *J* = 6.3, 1.5 Hz, 2H), 1.78 (d, *J* = 2.0 Hz, 3H), 1.76 (d, *J* = 2.0 Hz, 3H), 1.46 (br s, 1H).

To a stirred solution of (*E*)-5-methylhexa-2,4-dien-1-ol (1.3 g, 10.3 mmol, 1.0 equiv) in anhydrous Et_2O (20 mL) at 0 °C, under argon, was added PBr_3 (0.39 mL, 4.2 mmol, 0.4 equiv). The reaction mixture was stirred for 2 h, and poured into sat aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (equal volume), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the ***(E)-1-bromo-5-methylhexa-2,4-diene*** **SM1** as a yellow oil (1.5 g, 7.9 mmol, 77%). The crude bromide was used immediately in the synthesis of **9** without further purification. **^1H NMR (250 MHz, $CDCl_3$):** δ 6.56-6.14 (m, 1H), 5.88-5.67 (m, 2H), 4.09 (dd, *J* = 8.1, 1.5 Hz, 2H), 1.80 (d, *J* =

2.0 Hz, 3H), 1.78 (d, *J* = 2.0 Hz, 3H).

2.1.2 Preparation of compound SM2

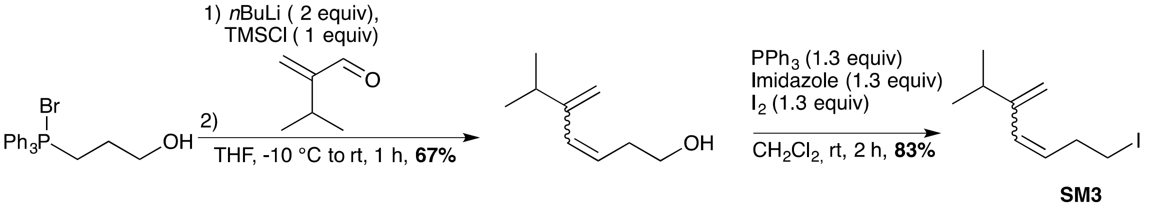


To a solution of triphenylphosphine (37.7 g, 143.9 mmol, 1.0 equiv) in toluene (40 mL) was added 3-bromopropanol (20 g, 143.9 mmol, 1.0 equiv). The mixture was stirred at reflux until a white solid was formed. The solid was filtered, washed with toluene and dried under reduced pressure to afford (3-hydroxypropyl)triphenylphosphonium as a white powder (45 g, 78%). **^{1}H NMR (360 MHz, $CDCl_3$):** δ 7.83-7.65 (m, 15H), 4.13 (br s, 1H), 3.86-3.71 (m, 4H), 1.90-1.78 (m, 2H). Spectral properties were consistent with those previously reported.[2]

To a solution of (3-hydroxypropyl)triphenylphosphonium (12.49 g, 31.1 mmol, 1.0 equiv) in THF (0.34 M) at -10 °C was added *n*BuLi (24.9 mL, 62.2 mmol, 2.0 equiv, 2.5 M in hexane). After 1 h at -10 °C, TMSCl (2.89 mL, 31.1 mmol, 1.0 equiv) was added and the solution was stirred at -10 °C for 30 min. The solution was then cooled to -78 °C, tiglic aldehyde (3.0 mL, 31.1 mmol, 1 equiv) was added slowly and the mixture was stirred for 3 h at rt. The reaction was quenched by addition of citric acid solution (until decoloration of the solution) followed by extraction with Et_2O (3 x equal volume). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by FC (pentane/Et_2O: 80/20) to afford a ***(3E,5E)-5-methylhepta-3,5-dien-1-ol*** as a yellow oil (2.6 g, 20.6 mmol, 66%, mixture of isomers, *E/Z* = 70/30*)*. **^{1}H NMR (360 MHz, $CDCl_3$, major isomer)** δ 6.15 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.54-5.44 (m, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.35 (ddt, *J* = 7.3, 6.4, 1.5 Hz, 2H), 1.74-1.63 (m, 6H). **MS (ESI+):** *m/z* calculated for $C_8H_{15}O$ $(M + H)^+$ 126.10, found 127.06.

To a stirred solution of dry CH_2Cl_2 (0.2 M) at rt was added, in the following order: triphenyl phosphine (7.39 g, 38.09 mmol, 1.3 equiv), imidazole (1.91 g, 38.1 mmol, 1.3 equiv) and bi-sublimed iodine (7.13 g, 38.09 mmol, 1.3 equiv) forming a dark orange solution. The (3*E*,5*E*)-5-methylhepta-3,5-dien-1-ol (2.6 g, 20.6 mmol) from the previous step was added and the solution immediately turned bright yellow. After 2 h the reaction is complete. 150 mL of fridge-cold pentane was added to the solution. After 30 min, triphenylphosphine oxide was filtered over a pad of silica gel and elution with 150 mL of pentane afforded a bright pink solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to gives **SM2** as an orange oil (4.0 g, 17.8 mmol, 70%, mixture of isomers, *E/Z* = 80/20*)*. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ (major isomer) 6.13 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.58-5.38 (m, 2H), 3.16 (t, *J* = 7.4 Hz, 2H), 2.65 (ddt, *J*= 7.4, 6.9, 1.5 Hz, 2H), 1.78-1.64 (m, 6H**). SM2** was used directly in the next step without purification.

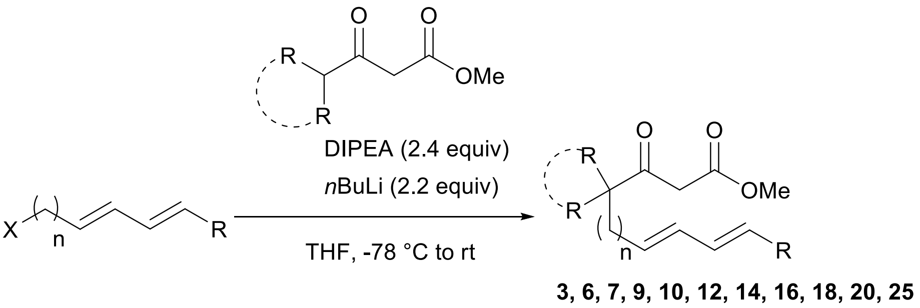
2.1.3 Preparation of compound SM3



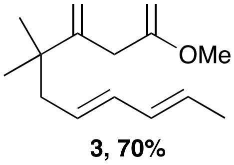
6-Methyl-5-methylenehept-3-en-1-ol was obtained from 3-methyl-2-methylenebutanal[3] (5.0 g, 51.0 mmol) as a yellow oil (4.0 g, 28.5 mmol, 67%, mixture of isomers, *E/Z* = 30/70) in the same way as **SM2**. **^{1}H NMR (360 MHz, $CDCl_3$, major isomer)**: δ 5.99 (dt, *J* = 11.7, 1.6 Hz, 1H), 5.54 (dt, *J* = 11.7, 7.3 Hz, 1H), 4.98 (d, *J* = 2.2 Hz, 1H), 4.79 (d, *J* = 2.2 Hz, 1H), 3.68 (t, *J* = 6.8 Hz, 2H), 2.49 (ddt, *J* = 7.3, 6.8, 1.6 Hz, 2H), 2.31 (sept, *J* = 6.9 Hz, 1H), 1.71 (br s, 1H), 1.02 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 151.2 (C), 132.1 (CH), 128.0 (CH), 110.8 (CH_2), 62.9 (CH_2), 34.7 (CH_2), 32.2 (CH), 21.6 (2 CH_3).

Following the iodation procedure, **SM3** was obtained from *6-methyl-5-methylenehept-3-en-1-ol* (2.0 g, 14.3 mmol) as an orange oil (2.9 g, 11.8 mmol, 83%, mixture of isomers, *E/Z* = 30/70). ^{1}H NMR (250 MHz, $CDCl_3$, major isomer) δ 5.98 (dt, *J* = 11.7, 1.9 Hz, 1H), 5.47 (dt, *J* = 11.7, 7.5 Hz, 1H), 4.99 (d, *J* = 2.2 Hz, 1H), 4.73 (d, *J* = 2.2 Hz, 1H), 3.15 (t, *J* = 7.4 Hz, 2H), 2.78 (ddt, *J* = 7.5, 7.4, 1.9 Hz, 2H), 2.31 (sept, *J* = 6.9 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 6H). **SM3** was used directly in the next step without purification.

2.1.4 General procedure for the synthesis of 1,3-dienyl β-ketoester derivatives



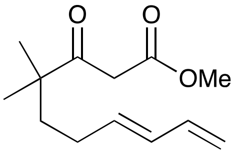
An oven-dried round bottom flask equipped with a stir bar and closed with a septum was evacuated and placed under Ar (balloon). THF (0.25 M) and DIPEA (2.4 equiv) were added (by syringes) and the mixture was cooled at -78 °C for 15 min. *n*BuLi (2.2 equiv, 2.5 M in hexane) was added by syringe and the resulting solution was stirred for 15 min at -78 °C and allowed to warm to 0 °C. After 15 min at 0 °C, the β-ketoester (1.0 equiv) was added by syringe and the resulting solution was stirred for 15 min at 0 °C. The alkylating diene (1.5 equiv) was added by syringe. The reaction was allowed to warm to rt and stirred 14-18 h. Then, the reaction was poured into sat aq NH_4Cl (equal volume) and this solution was extracted with Et_2O (3 x equal volume). The combined organic layers were washed with brine (equal volume), dried over $MgSO_4$, and evaporated. Purification by FC (Cy/EtOAc: 95/5) afforded the desired compound.



3, 70%
$C_{13}H_{20}O_3$
MW= 224,30

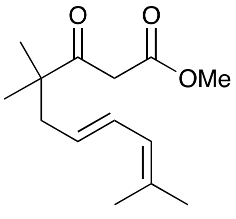
Following the general procedure, the title compound was obtained from (2*E*,4*E*)-l-bromohexa-2,4-diene [4] (5.3 g, 32.9 mmol) and methyl isobutyrylacetate (3.6 mL, 25.3 mmol) as a yellow oil (4 g, 17.8 mmol, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07-5.89 (m, 2H), 5.69-5.28 (m, 2H), 3.71 (s, 3H), 3.51 (s, 2H), 2.24 (d, *J* = 7.2 H, 2H), 1.71 (d, *J* = 6.0 Hz, 3H), 1.12 (s, 6H). **^{13}C NMR (90 MHz, $CDCl_3$):** δ 207.5 (C), 168.2 (C), 134.1 (CH), 131.2 (CH), 128.5 (CH), 125.6 (CH), 52.3 (CH_3), 48.6 (C), 44.4 (CH_2), 42.5 (CH_2), 23.9 (2 CH_3), 18.1 (CH_3). **FT-IR (film):** *v* 3431, 2968, 1748, 1708, 1651, 1620, 1437, 1322, 1285, 1260, 1220, 1149. **HRMS (ESI+):** *m/z* calculated for $C_{13}H_{20}O_3Na$ $(M + Na)^+$ 247.1305, found 247.1302.



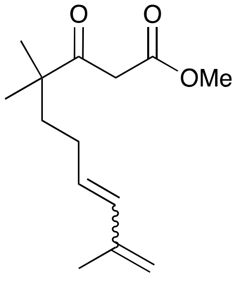
6, 14%
$C_{13}H_{20}O_3$
MW= 224,30

Following the general procedure, the title compound was obtained from (3*E*)-6-iodohexa-1,3-diene[5] (2.1 g, 10.1 mmol) and methyl isobutyrylacetate (1.5 g, 10.1 mmol) as a yellow oil (315 mg, 1.4 mmol, 14%). **^{1}H NMR (250 MHz, CDC1$_3$):** δ 6.32-6.17 (m, 1H), 6.04-5.96 (m, 1H), 5.66- 5.55 (m, 1H), 5.09-4.92 (m, 2H), 3.69 (s, 3H), 3.49 (s, 2H), 1.97-1.94 (m, 2H), 1.62-1.55 (m, 2H), 1.10 (s, 6H). **^{13}C NMR (63 MHz, $CDCl_3$):** (ketone and enol forms) δ 207.5 (C), 184.6 (C), 168.2 (C), 137.3 (CH), 134.1 (CH), 131.0 (CH), 115.4 (CH_2), 87.0 (C), 52.3 (CH_3), 48.1 (2 C), 44.4 (2 CH_2), 39.1 (CH_2), 27.9 (2 CH_2), 24.0 (2 CH_3). **FT-IR (film):** *v* 3433, 2971, 1751, 1707, 1650, 1618, 1437, 1310, 1273, 1218, 1150. **HRMS (ESI+):** *m/z* calculated for $C_{13}H_{20}O_3Na$ $(M + Na)^+$ 247.1310, found 247.1295.



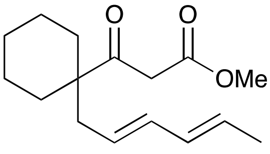
7, 20%
$C_{14}H_{22}O_3$
MW=238,33

Following the general procedure, the title compound was obtained from (4*E*)-6-bromo-2-methylhexa-2,4-diene **SM1** (1.5 g, 8.6 mmol) and methyl isobutyrylacetate (1.0 mL, 7.1 mmol) as a yellow oil (340 mg, 1.4 mmol, 20%). **^{1}H NMR (300 MHz, CDC1$_3$):** δ 6.35-6.15 (m, 1H), 5.84-5.71 (m, 1H), 5.49-5.33 (m, 1H), 3.72 (s, 3H), 3.53 (s, 2H), 2.30 (d, *J* = 7.2 Hz, 2H), 1.74 (d, *J*= 5.5 Hz, 6H), 1.14 (s, 6H). **^{13}C NMR (63 MHz, CDC1$_3$):** δ 207.5 (C), 168.2 (C), 134.5 (C), 130.6 (CH), 134.5 (CH), 124.8 (CH), 52.4 (CH_3), 48.7 (C), 44.6 (CH_2), 42.9 (CH_2), 26.0 (CH_3), 24.0 (2 CH_3), 18.2 (CH_3). **FT-IR (film):** *v* 3438, 2969, 2929, 1750, 1707, 1649, 1437, 1402, 1385, 1365, 1323, 1273, 1223, 1154. **HRMS (ESI+):** *m/z* calculated for $C_{14}H_{22}O_3Na$ $(M + Na)^+$ 261.1461, found 261.1448.



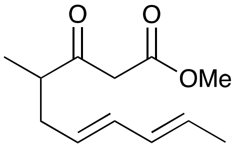
9, 84%
$C_{14}H_{22}O_3$
MW= 238,33

Following the general procedure, the title compound was obtained from 6-iodo-2-methylhexa-1,3-diene[5] (mixture of isomers, *E/Z* = 50/50) and methyl isobutyrylacetate as a bright yellow oil 84%). **^{1}H NMR (300 MHz, $CDCl_3$):** (mixture of isomers, *E/Z* = 50/50, keto and enol forms) δ 12.27 (s, 1H), 12.26 (s, 1H), 6.12 (dd, *J* = 15.6, 1.3 Hz, 1H), 5.82 (dq, *J* = 11.6, 1.3 Hz, 1H), 5.58 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.31 (dt, *J* = 11.8, 7.4 Hz, 1H), 5.04 (s, 1H), 5.03 (s, 1H), 4.95-4.89 (m, 1H), 4.88-4.82 (m, 1H), 4.81-4.78 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.53 (s, 2H), 2.21-2.09 (m, 2H), 2.06-1.95 (m, 2H), 1.82 (d, *J* = 13.0 Hz, 1H), 1.67-1.54 (m, 4H), 1.15 (s, 6H), 1.14 (s, 6H). **^{13}C NMR (90 MHz, $CDCl_3$):** (mixture of isomers, *E/Z* = 50/50, keto and enol forms) δ 207.5 (C), 207.4 (C), 184.6 (C), 168.1 (C), 141.8 (C), 141.5 (C) 133.3 (CH), 132.8 (CH), 131.4 (CH), 131.1 (CH), 130.8 (CH), 130.4 (CH), 130.3 (CH), 129.6 (CH), 115.4 (CH_2), 115.1 (CH_2), 114.7 (CH_2), 114.3 (CH_2), 86.8 (C), 52.2 (CH_3), 51.1 (CH_3), 48.1 (C), 48.0 (C), 44.0 (CH_2), 40.6 (CH_2), 39.9 (CH_2), 39.3 (CH_2), 28.0 (CH_2), 27.8 (CH_2), 25.4 (CH_3), 25.2 (CH_3), 24.0 (CH_3), 23.9 (CH_3), 23.8 (CH_2), 23.2 (CH_3), 18.5 (CH_3). **FT-IR (film):** *v* 3446, 1750, 1707, 1648, 1438, 1304, 1268, 1219, 1155. **HRMS (ESI+):** *m/z* calculated for $C_{14}H_{22}O_3Na$ $(M + Na)^+$ 261.1461, found 261.1452.



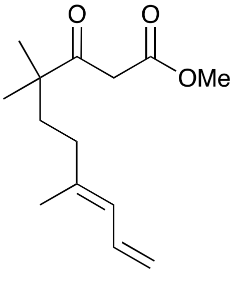
10, 49%
$C_{16}H_{24}O_3$
MW= 264,37

Following the general procedure, the title compound was obtained from (2*E*,4*E*)-l-bromohexa-2,4-diene[4] (2.2 g, 13.8 mmol) and methyl 3-cyclohexyl-3-oxopropanoate[6] (1.7 g, 9.2 mmol) as a yellow oil (1.2 g, 4.5 mmol, 49%). **^{1}H NMR (360 MHz, CDCl$_3$):** (keto and enol forms) δ 6.04-5.91 (m, 2H), 5.67- 5.62 (m, 1H), 5.45-5.27 (m, 1H), 3.72 (s, 3H), 3.51 (s, 2H), 2.24 (d, *J* = 7.2 Hz, 2H), 1.97-1.89 (m, 2H), 1.72 (d, *J*= 6.0 Hz, 3H), 1.64-1.26 (m, 8H). **^{13}C NMR (90 MHz, CDCl$_3$): (**keto form) δ 207.0 (C), 168.2 (C), 134.0 (CH), 131.1 (CH), 128.5 (CH), 124.7 (CH), 53.0 (C), 52.2 (CH_3), 44.4 (CH_2), 41.4 (CH_2), 32.7 (2 CH_2), 25.7 (CH_2), 22.6 (2 CH_2), 18.0 (CH_3). **FT-IR (film):** *v* 3439, 2933, 2855, 1751, 1704, 1648, 1616, 1437, 1297, 1260, 1229, 1145. **HRMS (ESI+):** *m/z* calculated for $C_{16}H_{24}O_3Na$ $(M + Na)^+$ 287.1607, found 287.1607.



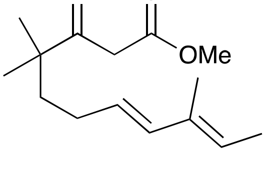
12, 17%
$C_{12}H_{18}O_3$
MWeight= 210,27

Following the general procedure, the title compound was obtained from (2*E*,4*E*)-1-bromohexa-2,4-diene[4] (3.0 g, 19.0 mmol) and methyl 3-oxovalerate (2.0 ml, 15.8 mmol) as a yellow oil (550 mg, 2.6 mmol, 17%). **^{1}H NMR (300 MHz, CDCl$_3$):** (keto and enol forms) δ 6.10-5.92 (m, 2H), 5.69-5.35 (m, 2H), 3.72 (s, 3H), 3.48 (s, 2H), 2.77-2.06 (m, 3H), 1.72 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H).**^{13}C NMR (90 MHz, CDCl$_3$):** δ 205.8 (C), 167.7 (C), 133.2 (CH), 131.2 (CH), 128.4 (CH), 127.4 (CH), 52.4 (CH_3), 47.9 (CH_2), 46.8 (CH), 35.7 (CH_2), 18.2 (CH_3), 15.8 (CH_3). **FT-IR (film):** *v* 3429, 2915, 1645, 1463, 1365, 1275. **HRMS (ESI+):** *m/z* calculated for $C_{12}H_{19}O_3$ $(M + H)^+$ 210.13, found 211.1471.



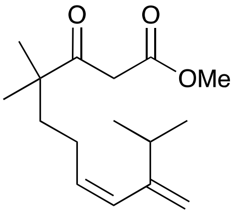
14, 26%
$C_{14}H_{22}O_3$
MW= 238,33

Following the general procedure, the title compound was obtained from (3*E*)-6-iodo-4-methylhexa-1,3-diene[5] (1.0 g, 4.5 mmol) and methyl isobutyrylacetate (0.58 mL, 4.1 mmol) as a bright yellow oil (250 mg, 1.0 mmol, 26%). **^{1}H NMR (250 MHz, CDCl$_3$):** (keto and enol forms) δ6.61-6.46 (m, 1H), 5.82 (d, *J* = 11.1 Hz, 1H), 5.12-4.96 (m, 2H), 3.72 (s, 3H), 3.52 (s, 2H), 2.04-1.88 (m, 2H), 1.74 (s, 3H), 1.67-1.60 (m, 2H), 1.15 (s, 6H). **^{13}C NMR (63 MHz, CDCl$_3$):** (keto and enol forms) δ207.4 (C), 184.6 (C), 173.5 (C), 168.1 (C), 138.8 (2 C), 133.2 (CH), 132.7 (CH), 125.8 (CH), 125.5 (CH), 115.1 (CH_2), 114.7 (CH_2), 52.2 (CH_3), 51.1 (CH_3), 48.1 (2 C), 44.4 (2 CH_2), 38.1 (2 CH_2), 34.7 (2 CH_2), 25.5 (2 CH_3), 24.0 (2 CH_3) 16.7 (2 CH_3). **MS:** *m/z* calculated for $C_{14}H_{26}NO_3$ $(M + NH_4)^+$ 256.2, found 256.2.



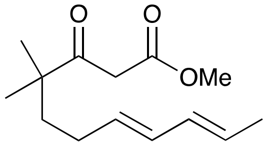
16, 70%
$C_{15}H_{24}O_3$
MW= 252,35

Following the general procedure, the title compound was obtained from (2*E*,4*E*)-7-iodo-3-methylhepta-2,4-diene **SM2** (3.0 g, 12.7 mmol) and methyl isobutyrylacetate (1.2 mL, 8.5 mmol) as a bright oil (1.5 g, 5.9 mmol, 70%). **^{1}H NMR (250 MHz, CDCl$_3$):** (mixture of isomers, *E/Z* = 80/20; keto and enol forms) δ6.07-6.01 (m, 1H), 5.49-5.43 (m, 2H), 3.70 (s, 3H), 3.53 (s, 2H), 2.00-1.95 (m, 2H), 1.76-1.56 (m, 8H), 1.12 (s, 6H). **^{13}C NMR (63 MHz, CDCl$_3$):** (mixture of isomers, *E/Z* = 80/20, keto and enol forms) δ207.6 (C), 184.9 (C), 168.2 (C), 135.4 (2 CH), 134.9 (2 C), 126.0 (2 CH), 125.1 (2 CH), 86.9 (C), 52.3 (CH_3), 51.2 (CH_3), 48.2 (2 C), 44.1 (2 CH_2), 39.8 (2 CH_2), 28.2 (2 CH_2), 24.1 (4 CH_3), 13.7 (2 CH_3) 12.1 (2 CH_3). **FT-IR (film):** *v* 3435, 2970, 1751, 1707, 1651, 1622, 1437, 1323, 1274, 1217, 1154. **MS:** *m/z* calculated for $C_{15}H_{28}NO_3$ $(M + NH_4)^+$ 270.2, found 270.3.



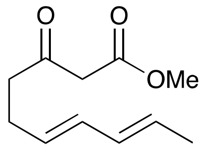
18, 48%
$C_{16}H_{26}O_3$
MW= 266,38

Following the general procedure, the title compound was obtained from **SM3** (3.0 g, 12.0 mmol) and methyl 4-methyl-3-oxopentanoate (1.3 ml, 9.2 mmol) as a yellow oil (1.2 g, 4.4 mmol, 48%). **^{1}H NMR (360 MHz, $CDCl_3$):** (mixture of isomers, *E/Z* = 30/70, keto and enol forms) δ 5.83 (dt, *J* = 11.5, 1.7 Hz, 1H), 5.45 (dt, *J* = 11.5, 7.1 Hz, 1H), 4.95 (d, *J* = 2.2 Hz, 1H), 4.71 (d, *J* = 2.2 Hz, 1H), 3.72 (s, 3H), 3.52 (s, 2H), 2.34-2.22 (m, 1H), 2.14-2.03 (m, 1H) 1.61-1.54 (m, 1H), 1.14 (s, 6H), 1.00 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (75 MHz, $CDCl_3$):** (mixture of isomers, *E/Z* = 30/70, keto and enol forms) δ 207.6 (C), 168.2 (C), 151.3 (C), 131.4 (CH), 129.8 (CH), 110.4 (CH_2), 52.3 (CH_3), 48.3 (C), 44.1 (CH_2), 40.1 (CH_2), 34.7 (CH), 24.0 (2 CH_3), 23.9 (CH_2), 21.6 (2 CH_3). **FT-IR (film):** *v* 3432, 1750, 1658, 1645, 1625, 1458, 1440, 1256, 1218. **HRMS (ESI+):** *m/z* calculated for $C_{16}H_{26}O_3Na$ $(M + Na)^+$ 289.1774, found 289.1776.



20, 65%
$C_{14}H_{22}O_3$
MW= 238,33

Following the general procedure, the title compound was obtained from (2*E*,4*E*)-7-iodohepta-2,4-diene[5] (3.0 g, 13.5 mmol) and methyl isobutyrylacetate (1.3 mL, 9.0 mmol) as a yellow oil (1.4 g, 5.9 mmol, 65%). **^{1}H NMR (250 MHz, $CDCl_3$):** (mixture of isomers, *E/Z* = 70/30, keto and enol forms) δ 6.34-6.18 (m, 1H), 6.84-6.05 (m, 1H), 5.76-5.58 (m, 1H), 5.30-5.12 (m, 1H), 3.73 (s, 3H), 3.54 (s, 2H), 2.12-1.87 (m, 2H), 1.81-1.68 (m, 2H), 1.64-1.51 (m, 2H), 1.16 (s, 6H). **^{13}C NMR (63 MHz, $CDCl_3$):** (mixture of isomers, *E/Z* = 70/30, keto and enol forms) δ207.7 (C), 184.8 (C), 173.6 (C), 168.3 (C), 131.5 (CH), 130.9 (CH), 130.8 (CH), 130.0 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 127.7 (CH), 126.9 (CH), 126.7 (CH), 87.0 (C), 52.4 (CH_3), 51.3 (CH_3), 48.3 (C), 48.2 (C), 44.2 (CH_2), 39.8 (CH_2), 39.5 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 25.6 (2 CH_3), 24.1 (2 CH_3), 23.2 (CH_2), 23.1 (CH_2), 18.4 (CH_3), 18.1 (CH_3). **FT-IR (film):** *v* 3407, 1750, 1702, 1646, 1625, 1438, 1276, 1219, 1148. **HRMS (ESI+):** *m/z* calculated for $C_{14}H_{22}O_3Na$ $(M + Na)^+$ 261.1461, found 261.1467.



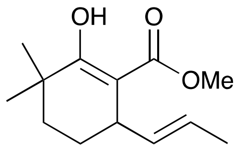
25, 62%
$C_{11}H_{16}O_3$
MW= 196.25

To a solution of methyl acetoacetate (1.2 mL, 11.1 mmol, 1 equiv) in THF (0.7 M) at -10 °C was slowly added NaH (0.532, 1.2 equiv, 60% in mineral oil). The solution was stirred for 15 min at -10 °C until decoloration of the solution. *n*BuLi (5.32 mL, 1.2 equiv, 2.5 M in hexane) was then added dropwise and the solution was stirred 15 min at -10 °C. The (3*E*)-6-iodohexa-1,3-diene (3.0 g, 14.4 mmol, 1.3 equiv) was added rapidly. The mixture was stirred 30 min at -10 °C, warmed to rt and stirred overnight. The reaction was quenched by addition of aq sat NH_4Cl (equal volume) followed by extraction with Et_2O (3 x equal volume). The combined organic layers were washed with brine (equal volume) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by FC (Cy/EtOAc: 95/5) to afford the desired compound as a bright oil (1.35 g, 6.9 mmol, 62%). **^{1}H NMR (300 MHz, $CDCl_3$):** δ6.28 (ddd, *J* = 17.0, 10.3, 9.7 Hz, 1H), 6.04 (ddt, *J* = 15.3, 10.3, 1.5 Hz, 1H), 5.62 (dt, *J* = 15.3, 7.3 Hz, 1H), 5.09 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.97 (dd, *J* = 9.7, 1.5 Hz, 1H), 3.72 (s, 3H), 3.43 (s, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 2.9 (tdd, *J* = 7.3, 7.2, 1.5 Hz, 2H), 1.70 (tt, *J* = 7.3, 7.2 Hz, 2H). **^{13}C NMR (90 MHz, $CDCl_3$):** δ 202.5 (C), 167.7 (C), 137.1 (CH), 133.9 (CH), 132.0 (CH), 115.5 (CH_2), 52.5 (CH_3), 49.2 (CH_2), 42.3 (CH_2), 31.7 (CH_2), 22.8 (CH_2). **FT-IR (film):** *v* 3451, 1752, 1717, 1646, 1628, 1438, 1316, 1242. **HRMS (ESI+):** *m/z* calculated for $C_{11}H_{16}O_3Na$ $(M + Na)^+$ 219.0992, found 219.0992.

3 Catalytic reactions

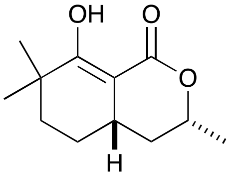
3.1 Catalyst screening (Table 1)

In air, **5** (50 mg, 0.22 mmol) and cat were charged in a 10 mL tube equipped with a Teflon-coated magnetic stir bar. Then, (wet) solvent (0.15 M), TfOH or Brønsted acid (0-5 mol%) were introduced and the tube was sealed with a plastic stopper. The reaction tube was immersed and stirred in a preheated oil bath at the indicated temperature during the indicated time. The reaction mixture was cooled to rt and quenched with a saturated solution of $NaHCO_3$ (5 mL). The organic layer was extracted with Et_2O, washed with brine, dried over $MgSO_4$ and evaporated to afford the crude product. Purification by FC (Cy/EtOAc, 90/10) affords the corresponding product.



4
$C_{13}H_{20}O_3$
MW= 224,30

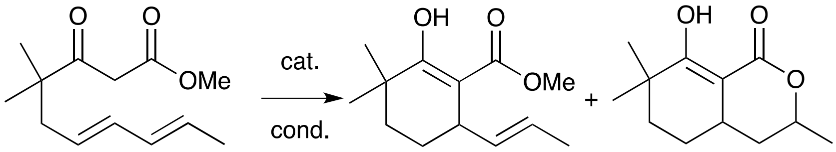
Entry 13, Table 1: following the general procedure, the reaction performed with Tf_2NH (5 mol%) during 24 h at 110 °C afforded, after purification by FC, the product **4** as a yellow oil (49 mg, 0.21 mmol, 99%). **^{1}H NMR (360 MHz, $CDCl_3$):** δ 12.60 (s, 1H, -O*H*), 5.53-5.38 (m, 1H), 5.30-5.19 (m, 1H), 3.70 (s, 3H), 3.18 (br s, 1H), 1.79-1.61 (m, 6H), 1.51-1.42 (m, 1H), 1.17 (s, 3H), 1.16 (s, 3H). **^{13}C NMR (90 MHz, $CDCl_3$):** δ 210.1 (C=0), 207.1 (C=0), 179.4 (C-OH), 170.4 (C-OH), 134.5 (C), 132.2 (CH), 126.5 (CH), 124.7 (C), 59.7 (CH), 52.0 (CH_2), 51.5 (CH_2), 45.2 (CH_2), 44.7 (CH_2), 39.1 (CH), 35.9 (C), 35.5 (C), 33.4 (C), 31.1 27.5 (CH_3), 27.2 (CH), 27.0 (CH_3), 25.2 (CH_3), 24.9 (CH_3), 18.1 (CH_3). **HRMS (ESI+):** *m/z* calculated for $C_{13}H_{20}O_3Na$ $(M + Na)^+$ 247.1305, found 247.1303.



5
$C_{12}H_{18}O_3$
MW= 210,27

Entry 14, Table 1: following the general procedure, the reaction performed with $Bi(OTf)_3$ (5 mol%)/TfOH (5 mol%) during 24 h at 110 °C afforded, after purification by FC, the two diastereomers of **5** as a pale yellow oil (35.8 mg, 0.17 mmol, 76%). **^{1}H NMR (360 MHz, $CDCl_3$):** (major diastereomer) δ13.59 (s, 1H, -O*H*), 4.45 (qdd, *J* = 11.4, 6.4, 2.4 Hz, 1H), 1.91 (ddd, *J* = 13.4, 3.9, 2.4 Hz, HI), 1.71 (ddd, *J* = 12.5, 7.3, 3.8 Hz, 1H), 1.64-1.56 (m, 2H), 1.33-1.28 (m, 1H), 1.28-1.23 (m, 1H), 1.37 (d, 3H, *J* = 6.4 Hz), 1.21, (s, 3H), 1.20 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** (major diastereomer) δ 181.3 (C-OH), 177.7 (COOMe), 95.3 (C), 76.6 (CH), 37.9 (CH_2), 37.6 (CH_2), 36.6 (C), 34.3 (CH), 27.7 (CH_3), 27.6 (CH_3), 26.8 (CH_2), 21.9 (CH_3). **FT-IR (film):** *v* 3018, 2968, 1750, 1708, 1620, 1437, 1322, 12220, 1149. **HRMS (ESI+):** *m/z* calculated for $C_{12}H_{18}O_3Na$ $(M + Na)^+$ 233.1148, found 233.1148. The relative stereochemistry of the product was determined by 2D NOESY and was confirmed by X-ray diffraction.

3.2 Optimisation studies for the intramolecular tandem hydroalkylation /hydroalkoxylation of the 1,3 dienyl β-keto ester 3 (related to Table 1)



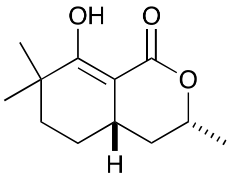
3 **4** **5**

Entry[a]	cat.	solvent	conditions	**6**/**7**[b]	% Yield of **7**
1	Bi(OTf)$_3$ (5 mol%)	**EtOH**	80 °C, 24 h	NR[d]	-
2	Bi(OTf)$_3$ (5 mol%)	**wet MeNO$_2$**	80 °C, 24 h	100/-	-
3	Bi(OTf)$_3$ (5 mol%)	wet tol[c]	80 °C, 24 h	100/0	80[e]
4	Bi(OTf)$_3$ **(10 mol%)**	wet tol	80 °C, 24 h	55/45	30
5	**In(OTf)$_3$** (5 mol%)	wet tol	80 °C, 24 h	100/0	70[e]
6	In(OTf)$_3$ **(10 mol%)**	wet tol	80 °C, 24 h	86/14	10
7	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	wet tol	80 °C, **5 h**	79/21	19
8	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	wet tol	80 °C, **24 h**	35/65	39
9	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	wet tol	80 °C, **48 h**	23/77	38
10	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	wet tol	80 °C, **60 h**	0/100	67
11	TfOH (5 mol%)	wet tol	80 °C, 60 h	21/79	41
12	Bi(OTf)$_3$ (5 mol%) / **Tf$_2$NH** (5 mol%)	wet tol	80 °C, 5 h	86/14	5
13	Bi(OTf)$_3$ (5 mol%) / Tf$_2$NH (5 mol%)	wet tol	80 °C, **24 h**	57/43	18
14	Bi(OTf)$_3$ (5 mol%) / Tf$_2$NH (5 mol%)	wet tol	80 °C, **48 h**	40/60	47
15	Bi(OTf)$_3$ (5 mol%) / Tf$_2$NH (5 mol%)	wet tol	80 °C, **60 h**	38/62	58
16	Tf$_2$NH (5 mol%)	wet tol	80 °C, 60 h	100/0	99[e]
17	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	wet tol	**rt**, 24 h	NR	-
18	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	wet tol	**50 °C**, 24 h	85/15	13
19	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	wet tol	110 °C, 24 h	0/100	76
20	Bi(OTf)$_3$ (5 mol%)	wet tol	110 °C, 24 h	29/71	40
21	TfOH (5 mol%)	wet tol	110 °C, 24 h	0/100	65
22	Bi(OTf)$_3$ **(1 mol%)** / TfOH (5 mol%)	wet tol	110 °C, 24 h	38/62	44
23	Bi(OTf)$_3$ (5 mol%) / TfOH **(1 mol%)**	wet tol	110 °C, 24 h	21/79	52
24	Bi(OTf)$_3$ **(3 mol%)** / TfOH **(3 mol%)**	wet tol	110 °C, 24 h	8/92	71
25	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	tol + **1 equiv H$_2$O**	110 °C, 24 h	0/100	43
26	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	tol + **10 equiv H$_2$O**	110 °C, 24 h	0/100	11
27	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	tol + **100 equiv H$_2$O**	110 °C, 24 h	CM	-
28	Bi(OTf)$_3$ (5 mol%) / TfOH (5 mol%)	tol + **0.15 equiv MgSO$_4$.7H$_2$O**	110 °C, 24 h	0/100	64

[a] Reactions set up in air using 0.22 mmol of **5** in 10 mL sealed tubes; [b] Ratio determined by ^{1}H NMR; [c] Water content: < 290 ppm (Karl Fischer titration); [d] Abbreviations: NR = no reaction, CM = complex mixture; [e] % yield of **6**

3.3 Scope studies of Bi(OTf)$_3$/TfOH-catalysed intramolecular addition of β-ketoesters to 1,3-dienes (Table 2 and Scheme 5)

General procedure: in air, Bi(OTf)$_3$ (5 mol%) and wet toluene (0.15 M) were charged in a 10 mL tube equipped with a Teflon-coated magnetic stir bar. Then, the substrate (50 mg, 1 equiv) and TfOH (5 mol%) were added and the tube was sealed with a plastic stopper. The reaction tube was immersed and stirred in a preheated oil bath at the indicated temperature during the indicated time. Then, the reaction mixture was cooled to rt and quenched with a saturated solution of NaHCO$_3$ (5 mL). The organic layer was extracted with Et$_2$O, washed with brine, dried over MgSO$_4$ and evaporated to afford the crude product. Purification by FC (Cy/EtOAc, 90/10) affords the corresponding product.

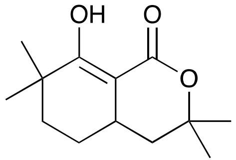


5

$C_{12}H_{18}O_3$

MW= 210,27

Entry 2, Table 2: the general procedure was followed with **3** (50 mg, 0.22 mmol) during 24 h at 110 °C to afford the two diastereomers of **5** as a pale yellow oil (25.3 mg, 0.12, 54%, dr = 82/18).



8

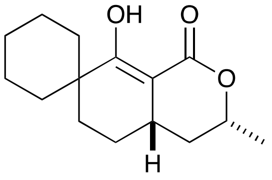
$C_{13}H_{20}O_3$

MW= 224,30

Entry 3, Table 2: the general procedure was followed with **7** (50 mg, 0.21 mmol) during 9 h at 50 °C to afford the desired product **8** as a pale yellow oil (27.1 mg, 0.12 mmol, 58%).

Entry 4, Table 2: the general procedure was followed with **9** (50 mg, 0.21 mmol) during 5 h at 80 °C to afford the desired product **8** as a pale yellow oil (39.5 mg, 0.18 mmol, 84%).

^{1}H NMR (300 MHz, CDCl$_3$): δ 13.76 (s, 1H, -OH), 2.57 (dddd, J = 13.0, 11.1, 3.9, 3.6 Hz, 1H), 1.79 (dd, J = 13.4, 3.9 Hz, 1H), 1.68-1.60 (m, 3H), 1.48-1.42 (m, 1H), 1.39 (d, J = 10.2 Hz, 6H), 1.33-1.25 (m, 1H), 1.20, (s, 6H). **^{13}C NMR (90 MHz, CDCl$_3$):** δ 181.4 (C-OH), 172.2 (COOMe), 94.4 (C), 81.9 (C), 41.2 (CH2), 37.6 (CH_2), 36.5 (C), 30.3 (CH), 27.5 (2 CH_3), 26.7 (CH_2), 26.6 (2 CH_3). FT-IR (film): *v* 3434, 1627, 1455, 1394, 1372, 1306, 1203, 1127. **HRMS (ESI+):** ***m/z*** calculated for $C_{13}H_{20}O_3Na$ (M + Na)$^+$ 247.1305, found 247.1296.

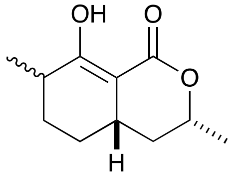


11

$C_{15}H_{22}O_3$

MW= 250,34

Entry 5, Table 2: the general procedure was followed with **10** (50 mg, 0.19 mmol) during 12 h at 110 °C to afford the desired product **11** as a pale yellow oil (25.2 mg, 0.10 mmol, 53%). **^{1}H NMR (360 MHz, CDCl$_3$):** δ 13.80 (s, 1H, -O*H*), 4.45 (qdd, *J* =11.3, 6.0, 2.4 Hz, 1H), 2.52-2.40 (m, 1H), 2.28-2.19 (m, 1H), 2.09-1.98 (m, 1H), 1.95-1.87 (m, 1H), 1.82-1.41 (m, 8H), 1.36 (d, 3H, *J* = 6.4 Hz), 1.32-1.11 (m, 4H). **^{13}C NMR (91 MHz, CDCl$_3$):** δ 181.7 (C-OH), 172.7 (COOMe), 95.9 (C), 76.7 (CH), 40.1 (C), 37.8 (CH_2), 35.8 (CH_2), 33.8 (CH), 31.8 (CH_2), 30.2 (CH_2), 26.4 (CH_2), 25.6 (CH_2), 21.9 (CH_3), 21.3 (CH_2), 21.0 (CH_2). **FT-IR (film):** *v* 3431, 2928, 2859, 1634, 1599, 1449, 1396, 1269, 1241, 1226, 1202, 1167, 1115. **HRMS (ESI+):** ***m/z*** calculated for $C_{15}H_{23}O_3$ (M + H)$^+$ 251.1642, found 251.1633.

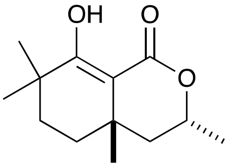


13

$C_{11}H_{16}O_3$

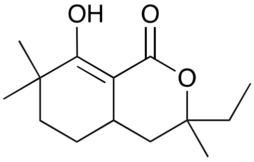
MW= 190,25

Entry 6, Table 2: the general procedure was followed with **12** (50 mg, 0.24 mmol) during 24 h at 110 °C to afford the desired product **13** as as a yellow solid (14.1 mg, 0.07 mmol, 31%). **^{1}H NMR (360 MHz, CDCl$_3$):** (mixture of diastereomers) δ 13.52 (s, 1H), 13.31 (s, 1H), 4.44 (m, 2H), 2.53-2.35 (m, 4H), 2.02-1.77 (m, 8H), 1.37 (d, *J* = 6.4 Hz, 6H,), 1,34-1,26 (m, 4H), 1.21-0.91 (m, 6H). **^{13}C NMR (90 MHz, CDCl$_3$):** (mixture of diastereomers) δ 178.3 (C-OH), 178.1 (C-OH), 172.2 (COOMe), 172.0 (COOMe), 96.2 (C), 76.5 (CH), 74.8 (CH), 37.6 (CH_2), 37.5 (CH_2), 34.7 (CH), 33.5 (CH), 32.7 (CH), 30.8 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 25.4 (CH_2), 21.8 (CH_3), 21.7 (CH_3), 19.6 (CH_3), 18.1 (CH_3). **FT-IR (film):** *v* 3431, 1638, 1454, 1402, 1303, 1236, 1150, 1114. **HRMS (ESI+): m/z** calculated for $C_{11}H_{16}O_3Na$ (M + Na)$^+$ 219.0992, found 219.0986.



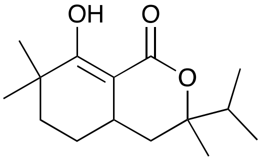
15
$C_{13}H_{20}O_3$
MW= 224,30

Entry 7, Table 2: the general procedure was followed with **14** (50 mg, 0.21 mmol) during 24 h at 80 °C to afford the desired product **15** as a pale yellow oil (31.7 mg, 0.14 mmol, 67%). **^{1}H NMR (250 MHz, $CDCl_3$):** δ 13.50 (s, 1H, -OH), 4.78-4.74 (m, 1H), 1.93-1.92 (m, 1H), 1.75 (dd, J = 13.3, 3.2 Hz, 1H), 1.57-1.45 (m, 4H), 1.40 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 3.2 Hz, 6H), 1.15 (s, 3H). **^{13}C NMR (91 MHz, $CDCl_3$):** δ 180.0 (C-OH), 172.0 (COOMe), 98.9 (C), 73.4 (CH), 45.0 (CH_2), 36.2 (C), 33.6 (CH_2), 33.3 (CH_2), 32.1 (C), 27.6 (CH_3), 27.5 (CH_3), 26.3 (CH_3), 22.1 (CH_3). **FT-IR (film):** *v* 3433, 2967, 2933, 1737, 1706, 1634, 1456, 1394, 1296, 1262, 1240, 1178, 1137. **MS:** ***m/z*** calculated for $C_{13}H_{21}O_3$ $(M + H)^+$ 225.1, found 225.1.



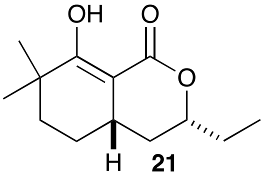
17
$C_{14}H_{22}O_3$
MW= 238,33

Entry 8, Table 2: the general procedure was followed with **16** (50 mg, 0.20 mmol) during 24 h at 80 °C to afford two diastereomers of **17** (33.4 mg, 0.14 mmol, 71%, dr = 50/50) as a pale yellow oil. **^{1}H NMR (250 MHz, $CDCl_3$):** (mixture of diastereomers) δ 13.77 (s, 1H, -O*H)*, 2.63-2.44 (m, 1H), 1.85-1.71 (m, 1H), 1.69-1.59 (m, 6H), 1.45 (d, *J* = 13.0 Hz, 1H), 1.35-1.25 (m, 3H), 1.19 (s, 6H), 0.97 (q, *J* = 7.5 Hz, 3H). **^{13}C NMR (63 MHz, $CDCl_3$):** (mixture of diastereomers) δ 172.4 (COOMe), 94.9 (C), 94.7 (C), 83.7 (C), 83.4 (C), 39.2 (CH_2), 38.7 (CH_2), 37.8 (2 CH_2), 36.7 (2 C), 35.8 (CH_2), 31.9 (CH_2), 30.3 (CH), 30.1 (CH), 27.7 (4 CH_3), 27.0 (2 CH_2), 26.7 (CH_3), 24.8 (CH_3), 8.5 (CH_3), 7.9 (CH_3). **FT-IR (film):** *v* 3429, 2975, 2933, 1633, 1455, 1393, 1281, 1236, 1200, 1151, 1129. **HRMS (ESI+):** ***m/z*** calculated for $C_{14}H_{22}O_3Na$ $(M + Na)^+$ 261.1467, found 261.1658.



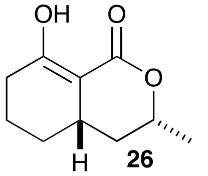
19
$C_{15}H_{24}O_3$
MW= 252,35

Entry 9, Table 2: the general procedure was followed with **18** (50 mg, 0.19 mmol) during 24 h at 50 °C to afford two diastereomers of **19** (20.0 mg, 0.08 mmol, 42%, dr = 50/50) as a yellow solid. **^{1}H NMR (360 MHz, $CDCl_3$):** (mixture of diastereomers) δ 13.76 (s, 1H, -O*H*), 2.62-2.50 (m, 1H), 1.89 (sept, *J* = 6.9 Hz, 1H), 1.72 (dd, *J* = 12.7, 3.6 Hz, 1H), 1.68-1.60 (m, 4H), 1.41-1.34 (m, 1H), 1.31 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H**). ^{13}C NMR (90 MHz, $CDCl_3$):** (mixture of diastereomers) δ 181.3 (C-OH), 172.6 (COOMe), 95.0 (C), 85.9 (C), 38.7 (CH), 37.8 (CH_2), 36.7 (C), 35.9 (CH_2), 30.1 (CH), 27.8 (CH_3), 27.7 (CH_3), 27.1 (CH_2), 22.7 (CH_3), 17.2 (CH_3), 17.0 (CH_3). **FT-IR (film):** *v* 3428, 1631, 1451, 1392, 1300, 1282, 1199. **HRMS (ESI+):** *m/z* calculated for $C_{15}H_{25}O_3$ $(M)^+$ 253.1800, found 253.1798.



21
$C_{13}H_{20}O_3$
MW= 224,30

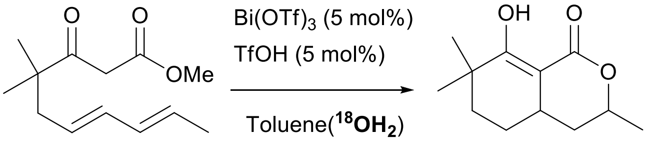
Entry 10, Table 2: the general procedure was followed with **20** (50 mg, 0.21 mmol) during 24 h at 110 °C to afford two diastereomers of **21** (24.7 mg, 0.11 mmol, 52%, dr = 90/10) as a pale yellow oil. **^{1}H NMR (250 MHz, $CDCl_3$):** (major diastereomer) δ 13.60 (s, 1H, -O*H),* 4.25 (qdd, *J* = 11.6, 6.1, 2.3 Hz, 1H), 2.63-2.44 (m, 1H), 1.85-1.71 (m, 1H), 1.69-1.59 (m, 4H), 1.35-1.25 (m, 3H), 1.19 (s, 6H), 1.01 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (63 MHz, $CDCl_3$):** (major diastereomer) δ 180.1 (C-OH), 172.5 (COOMe), 95.4 (C), 81.5 (CH), 37.4 (CH_2), 36.4 (C), 35.2 (CH_2), 34.0 (CH), 28.7 (CH_2), 27.6 (CH_3), 27.4 (CH_3), 26.7 (CH_2), 9.2 (CH_3). **FT-IR (film):** *v* 2944, 2928, 1740, 1634, 1602, 1455, 1399, 1278, 1232, 1209, 1162. **HRMS (ESI+):** ***m/z*** calculated for $C_{13}H_{20}O_3$ $(M + Na)^+$ 247.1305, found 247.1301.



26
$C_{10}H_{14}O_3$
MW= 182,22

Scheme 5: the general procedure was followed with **25** (50 mg, 0.25 mmol) during 24 h at 110 °C to afford two diastereomers of **26** (22 mg, 0.11 mmol, 44%, dr = 85/15) as a pale yellow oil. **^{1}H NMR (250 MHz, CDCl$_3$):** (major diastereomer) δ 13.25 (s, 1H, -O*H*), 4.45 (qdd, *J* = 11.5, 6.3, 2.3 Hz, 1H), 2.59-2.44 (m, 1H), 2.41-2.33 (m, 2H), 1.98-1.83 (m, 2H), 1.75-1.58 (m, 2H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.26-1.06 (m, 2H). **^{13}C NMR (63 MHz, CDCl$_3$):** δ 174.9 (C-OH), 172.3 (COOMe), 96.9 (C), 76.7 (CH), 37.7 (CH$_2$), 33.1 (CH), 29.7 (CH$_2$), 29.2 (CH$_2$), 21.9 (CH$_3$), 21.1 (CH$_2$). **FT-IR (film):** *ν* 1641, 1449, 1413, 1302, 1272, 1250 1235, 1172, 1105. **HRMS (ESI+):** ***m/z*** calculated for $C_{10}H_{14}O_3Na$ (M + Na) 205.0840, found 205.0835.

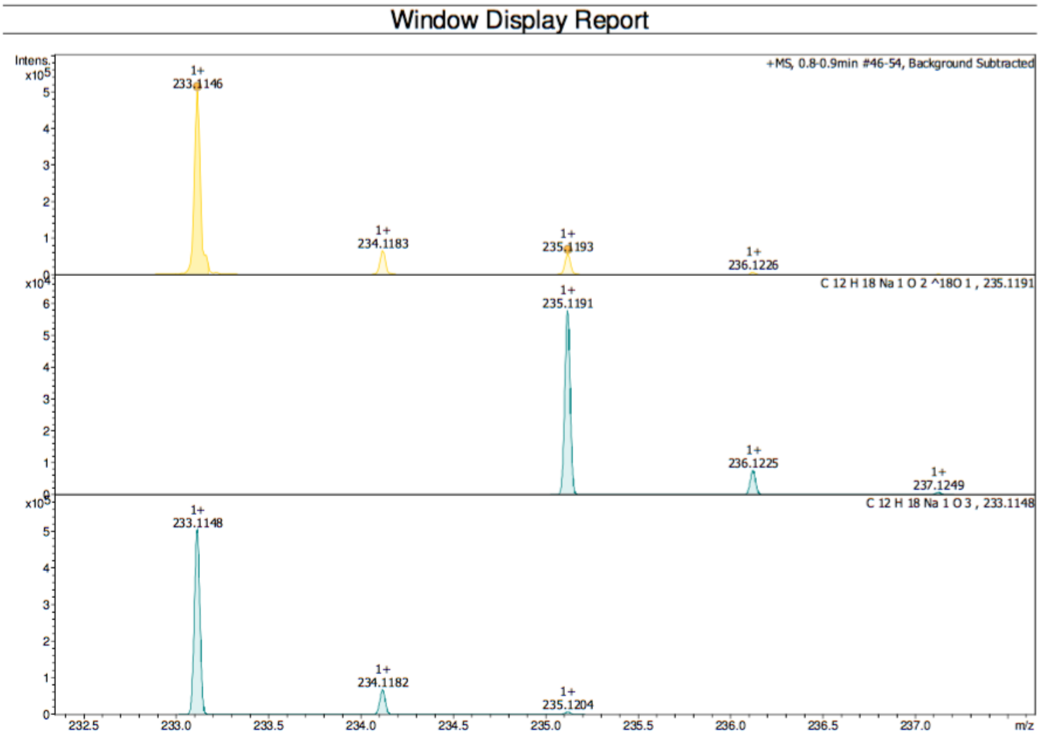
4 ^{18}O Labeling experiment



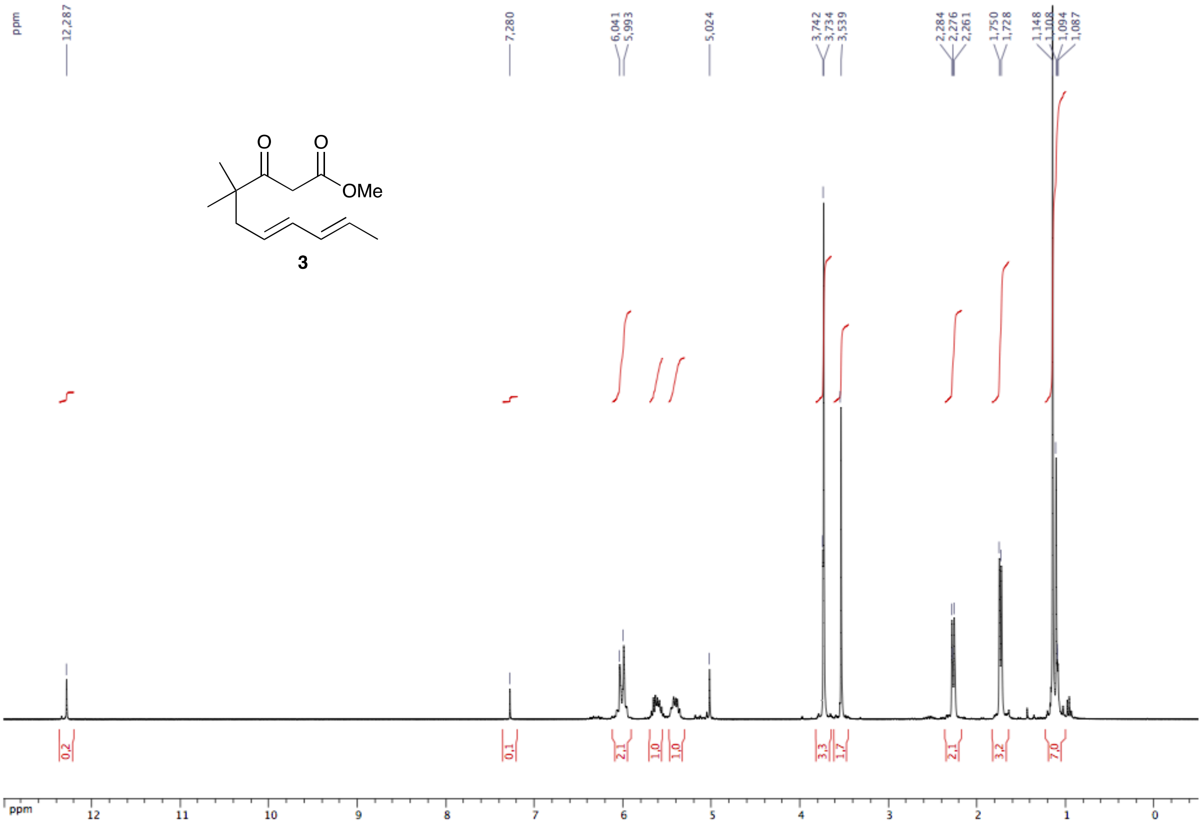
3

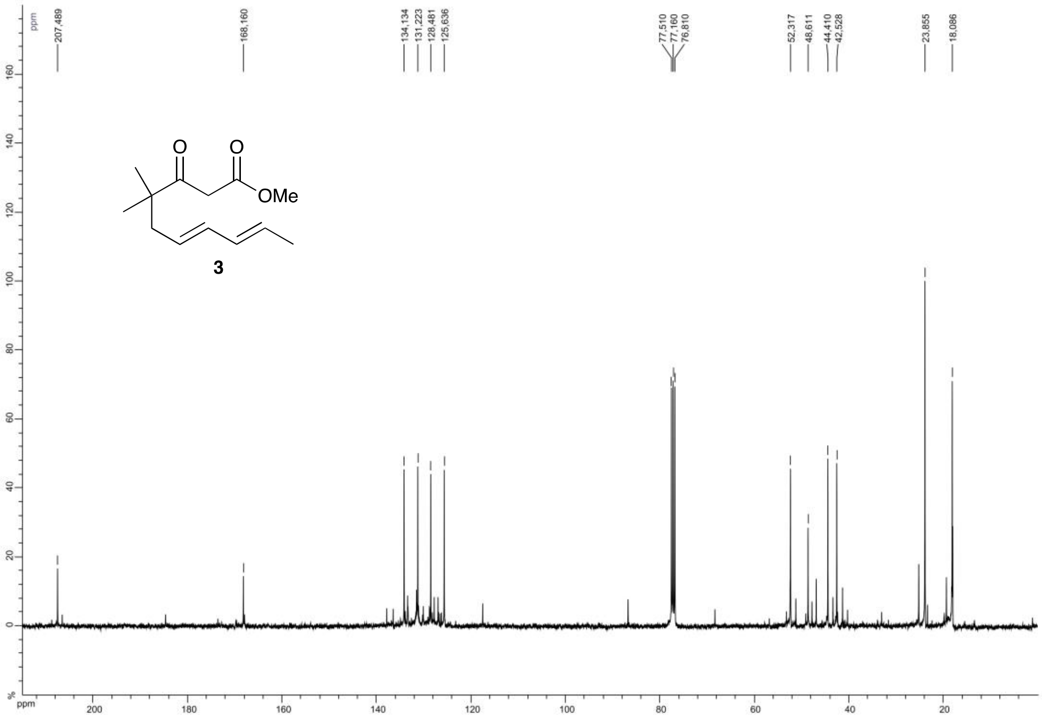
^{16}O-**5**/^{18}O-**5** (90/10)

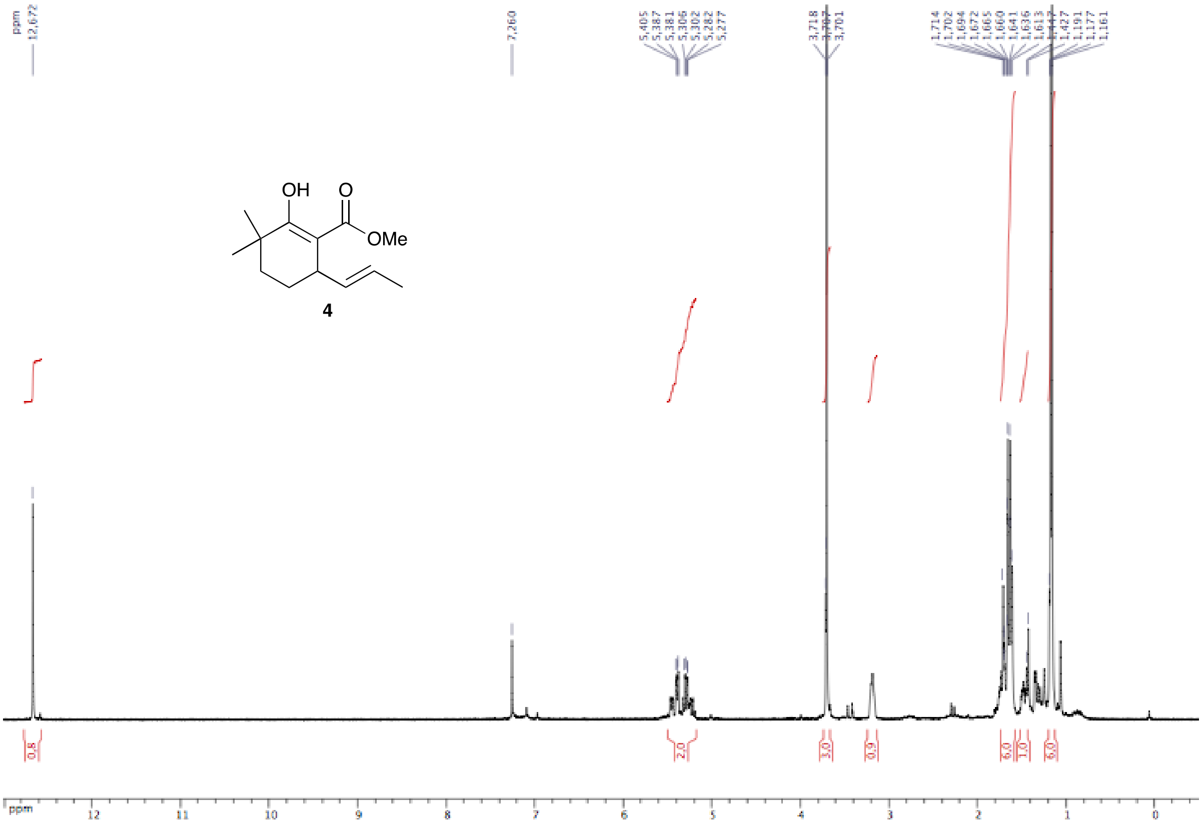
Scheme 7: the general procedure was followed with **3** in wet toluene (humidified with ^{18}OH$_2$) during 8 h at 110 °C. After purification, the ^{1}H NMR spectral data were consistent with the values observed for **5**. HRMS *m/z* (% relative intensity, ion): 233.1148 (90%, $C_{12}H_{18}Na_1O_3$, **^{16}O-5**), 235.1193 (10%, $C_{12}H_{18}Na_1O_2{}^{18}O_1$, **^{18}O-5**). The percentage of ^{18}O in synthetic **^{18}O-5** was therefore calculated to be 10%.



5 Copies of ^{1}H and ^{13}C NMR spectra



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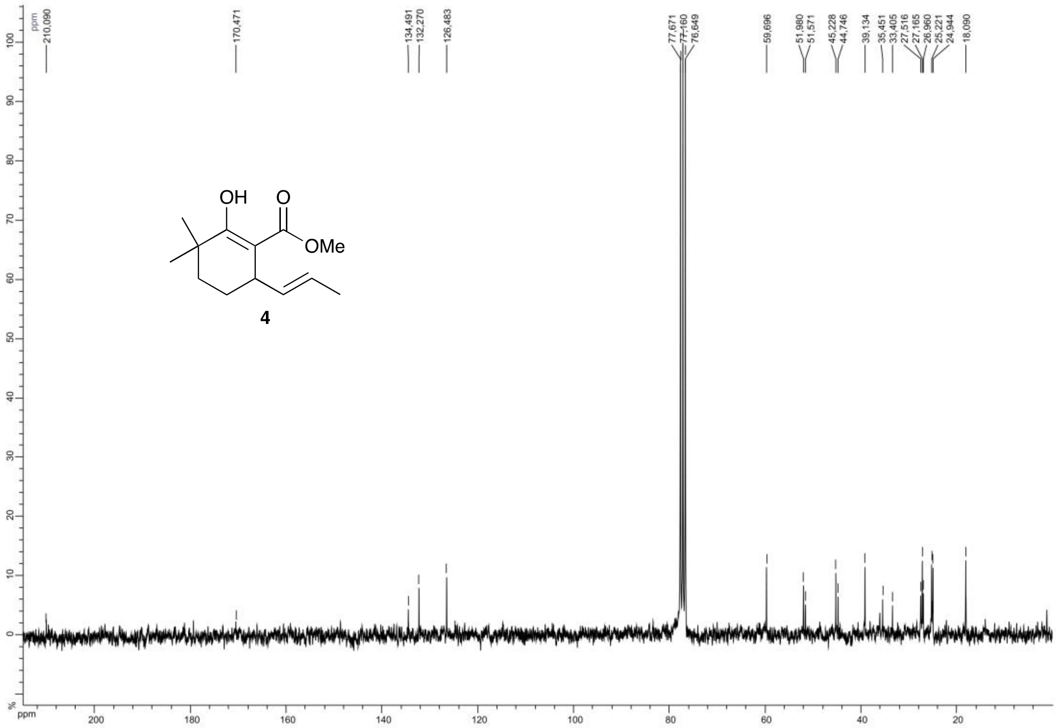
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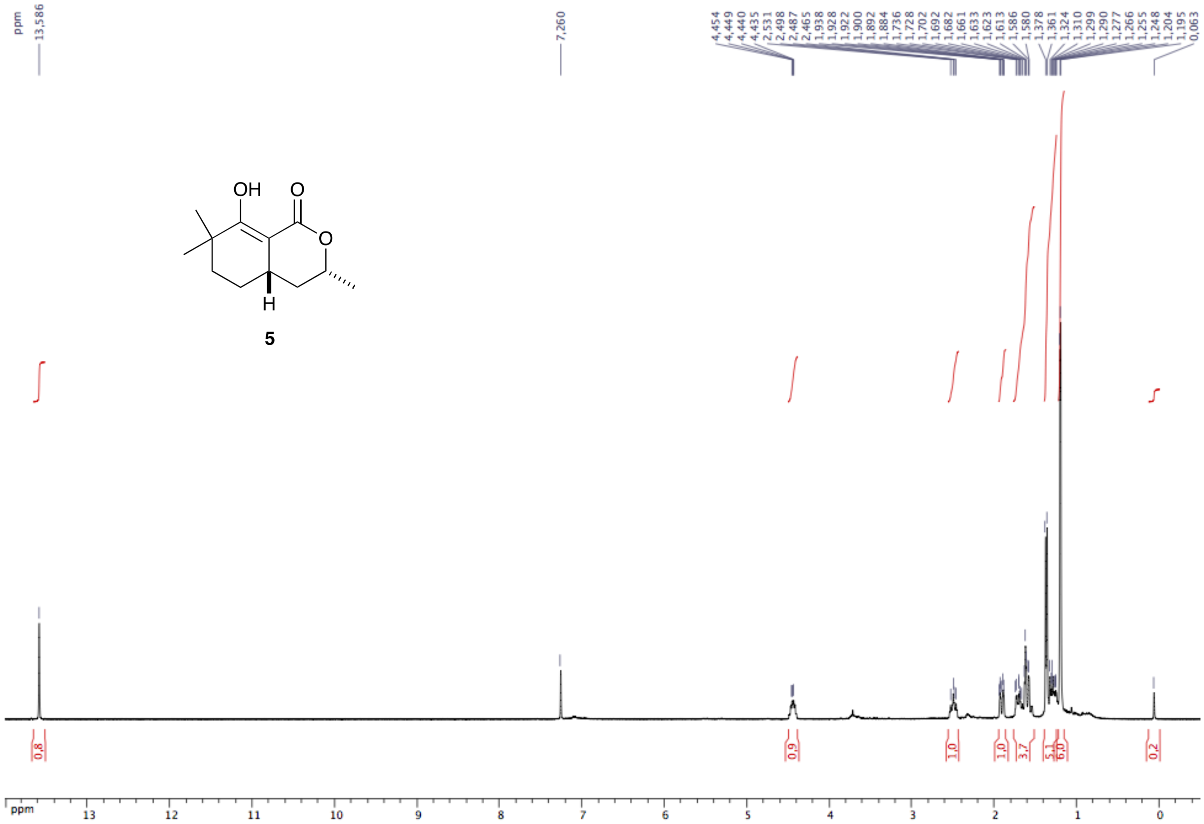
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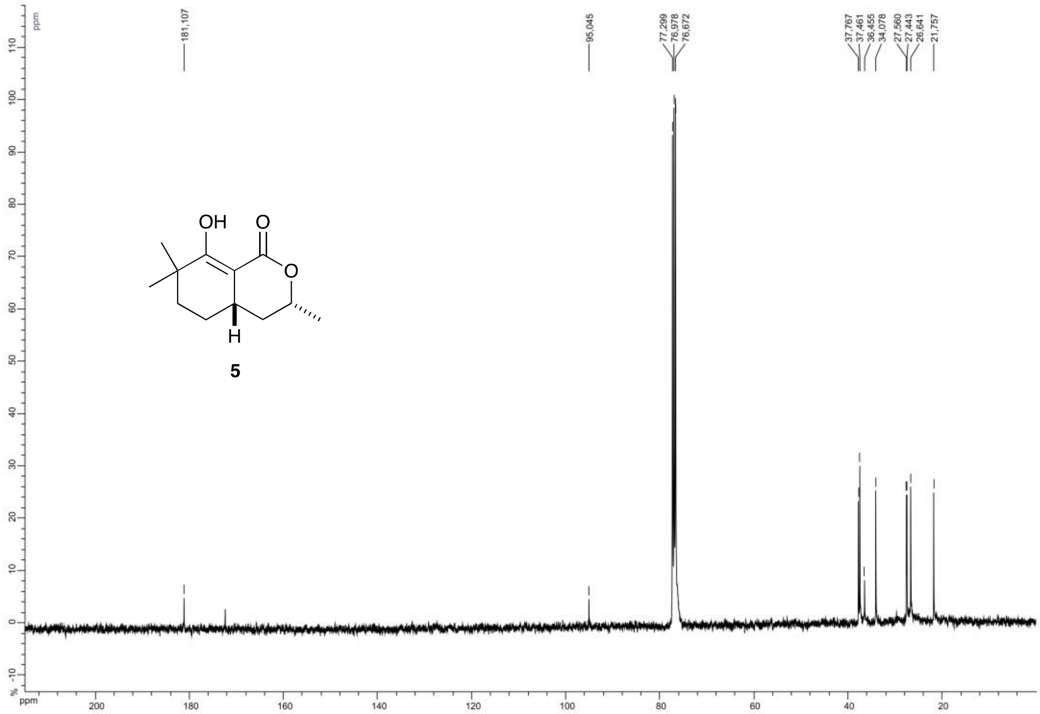
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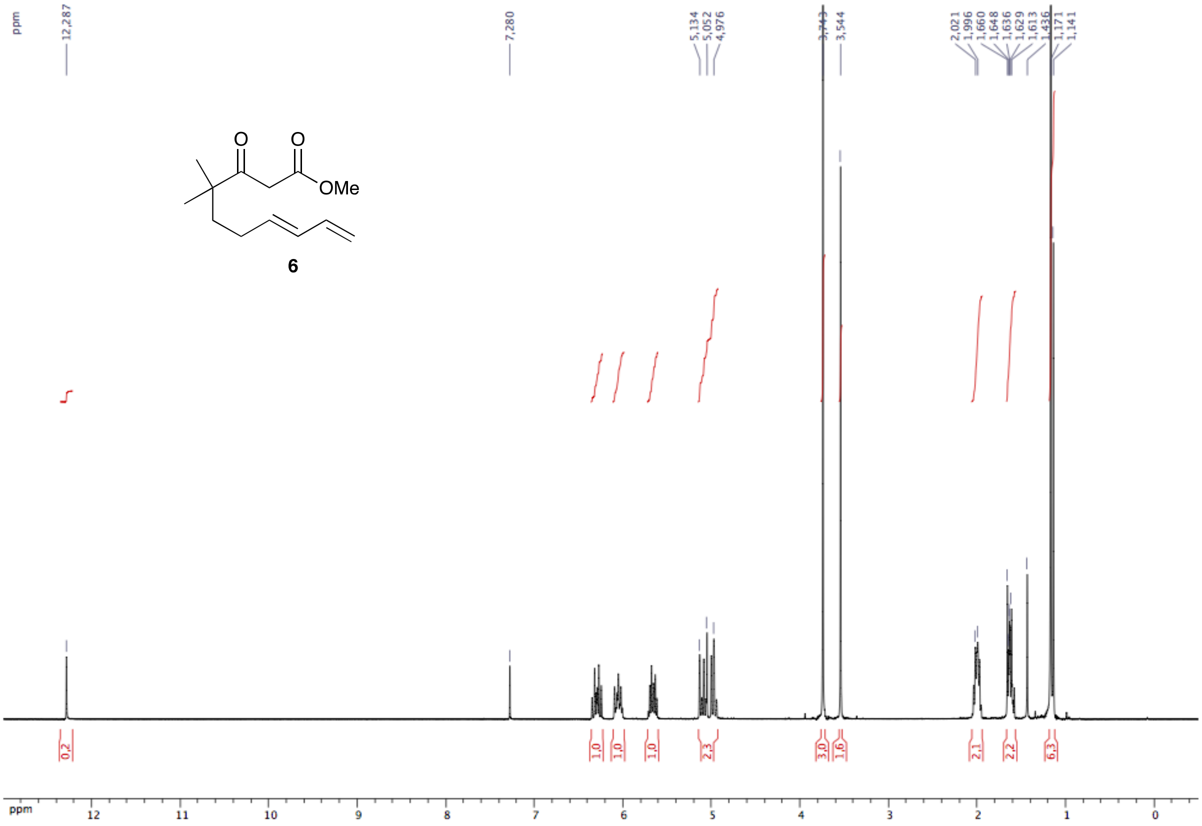
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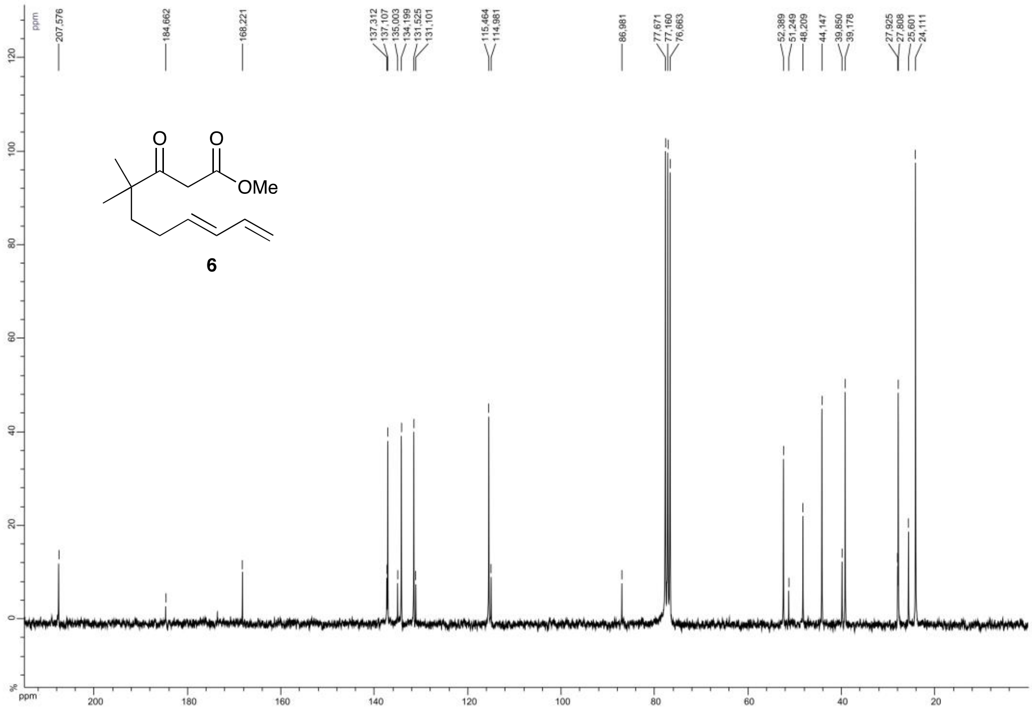
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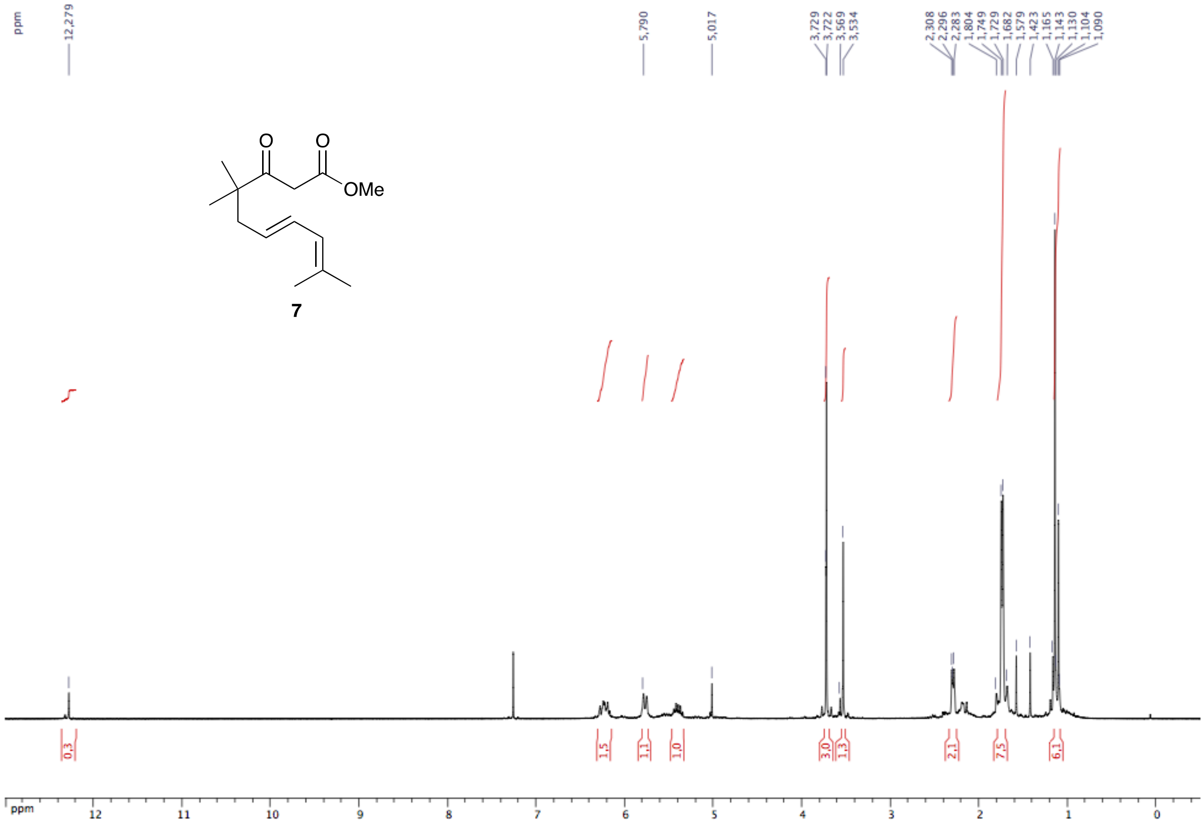
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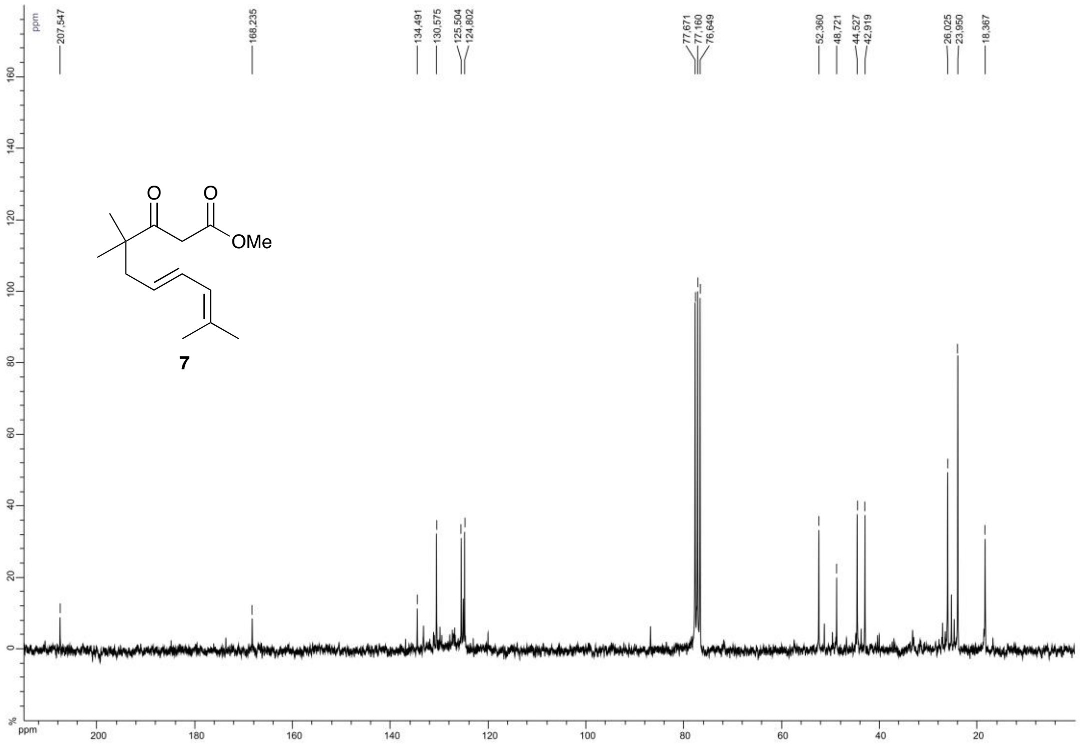
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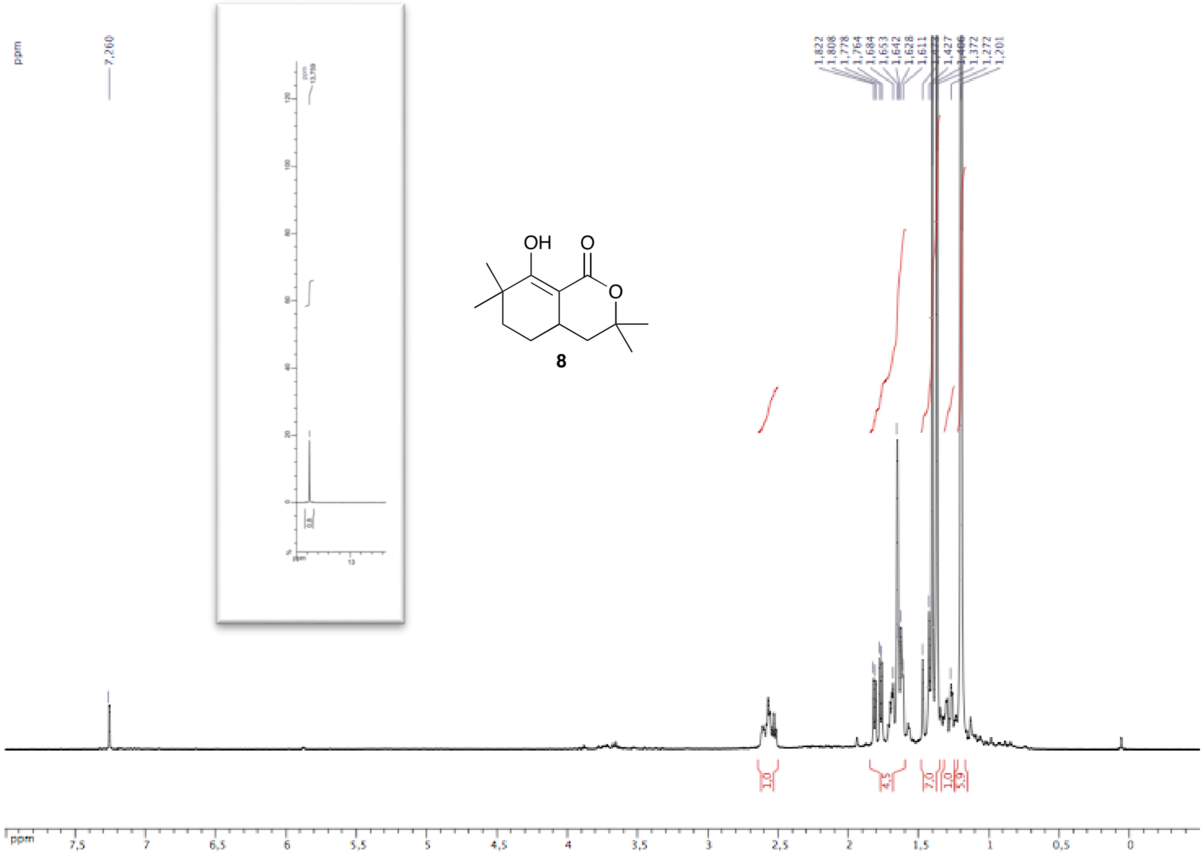
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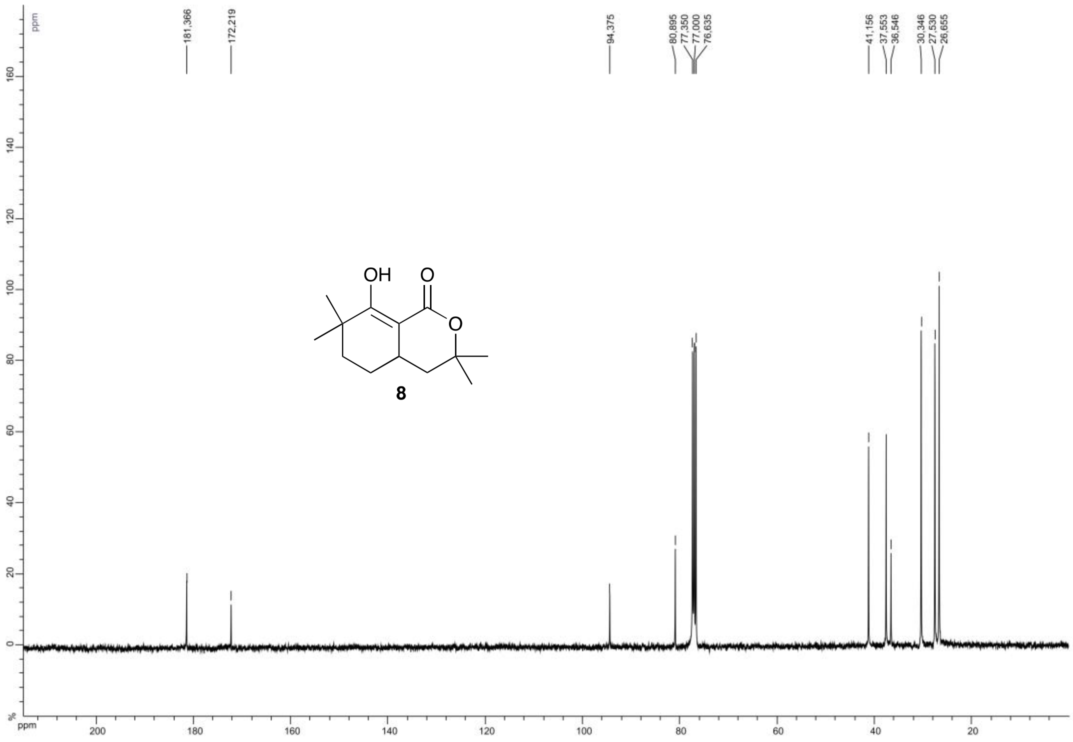
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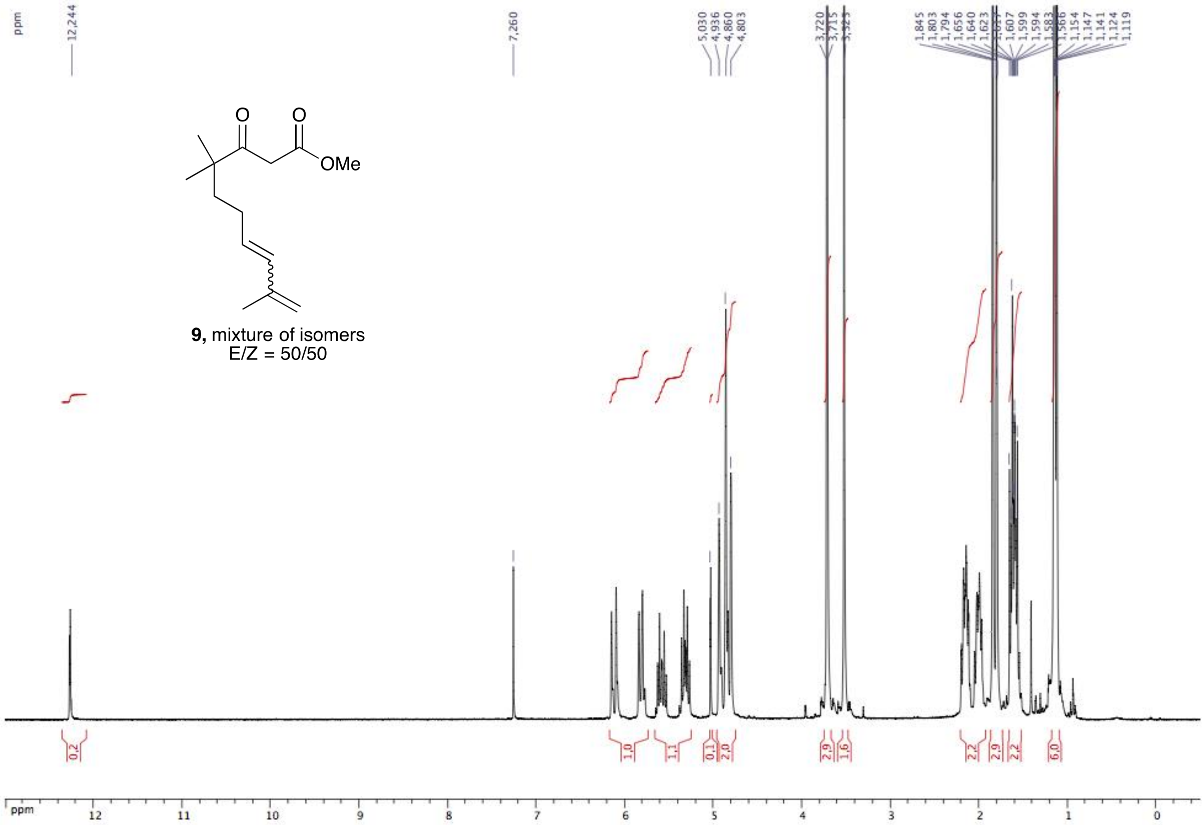
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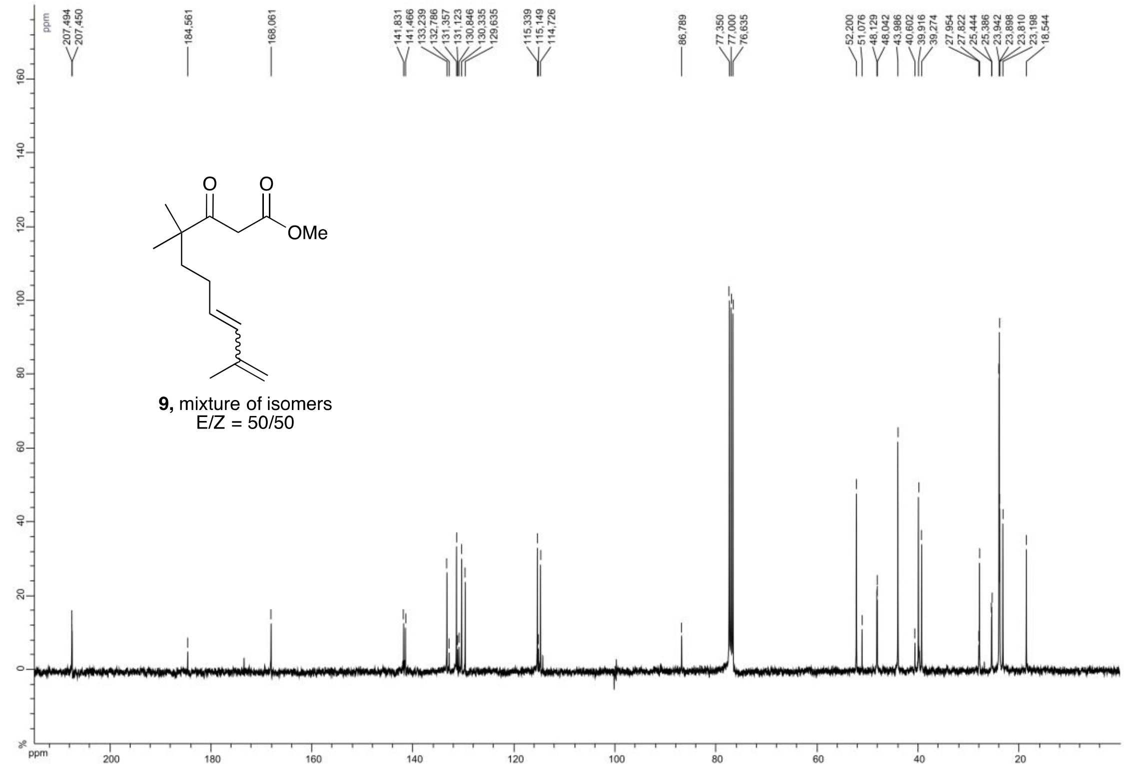
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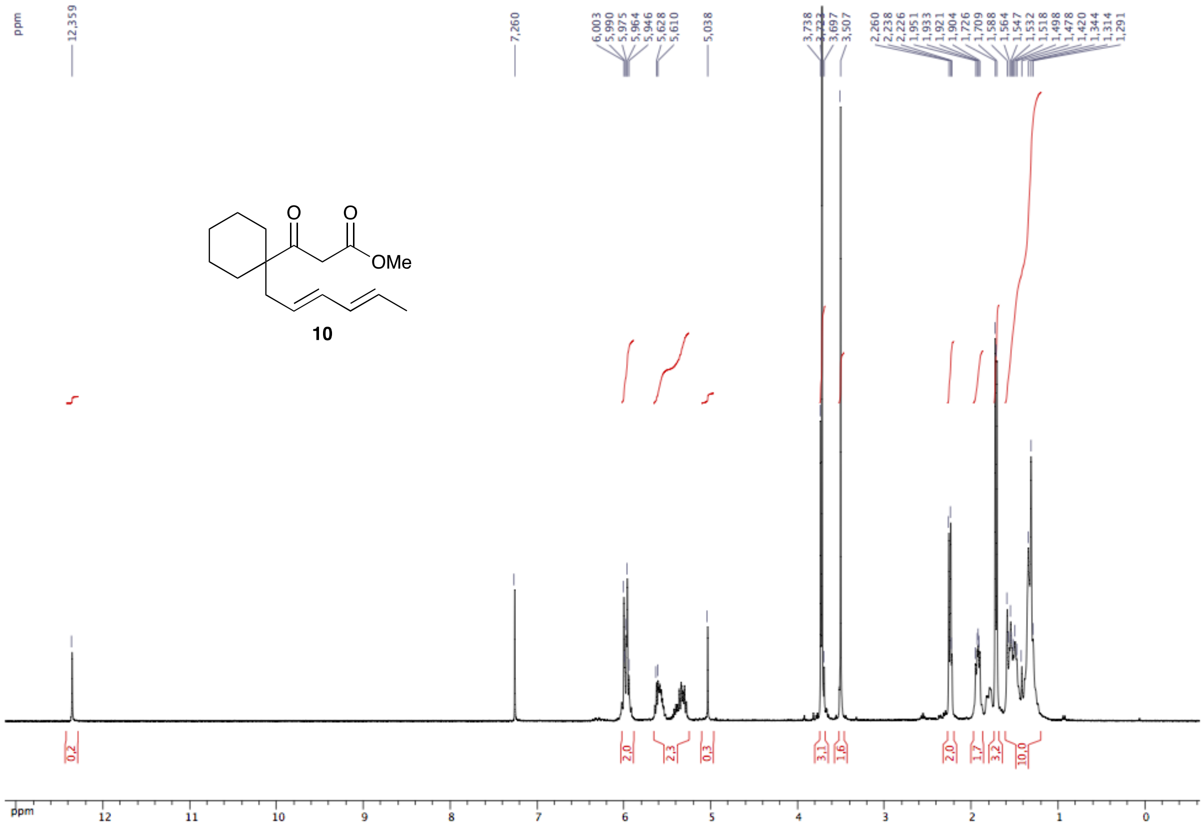
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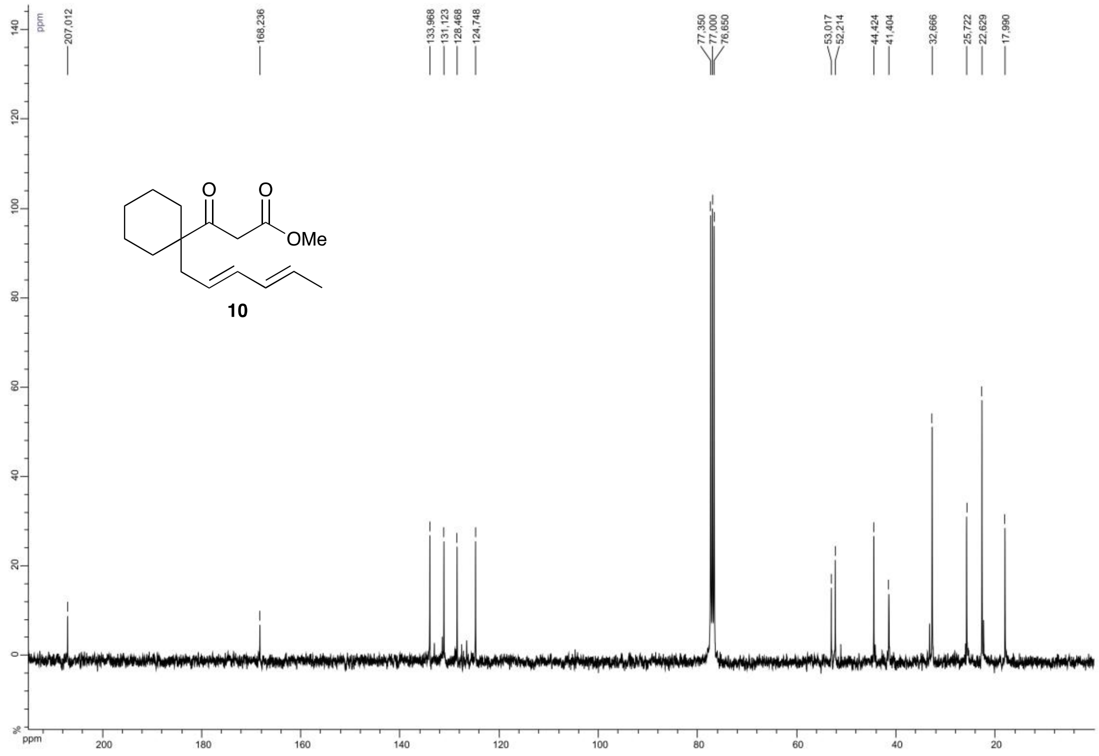
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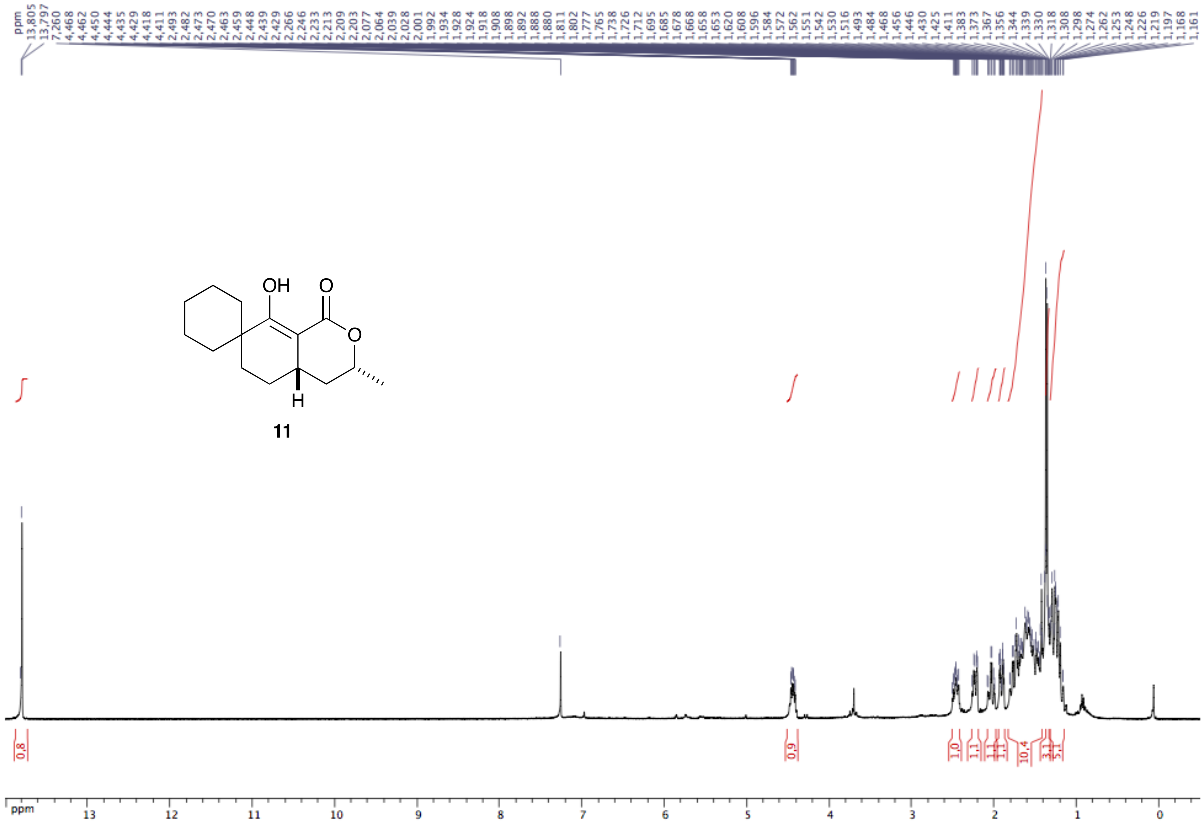
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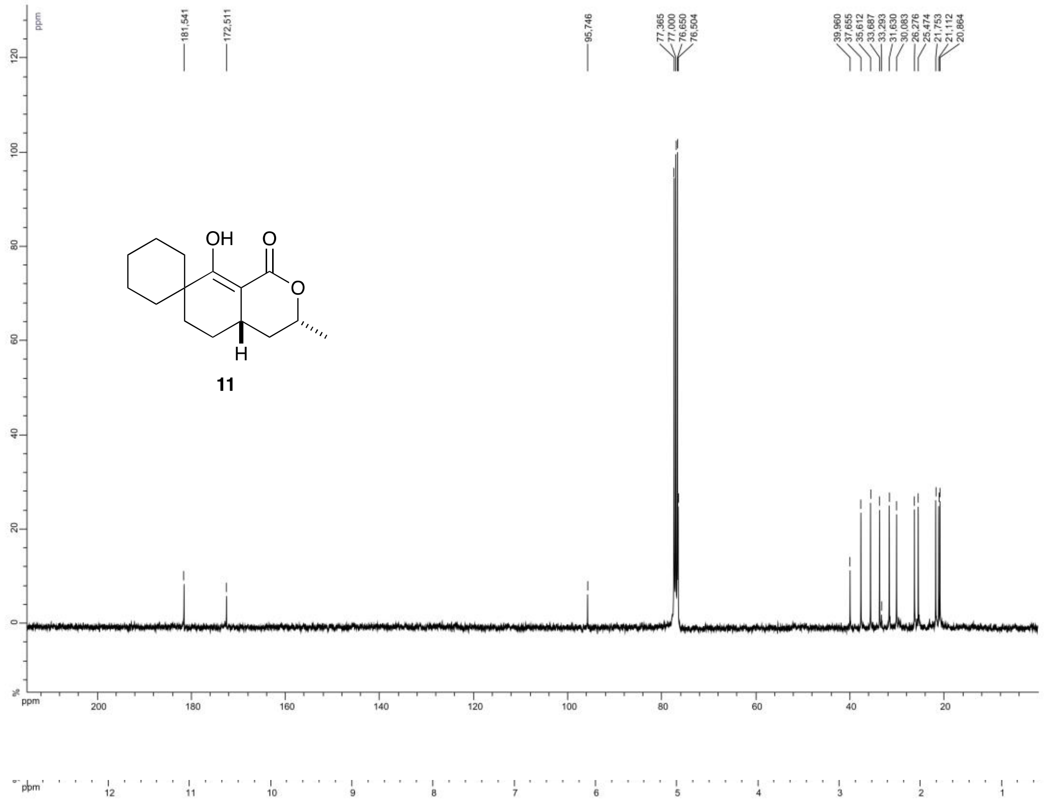
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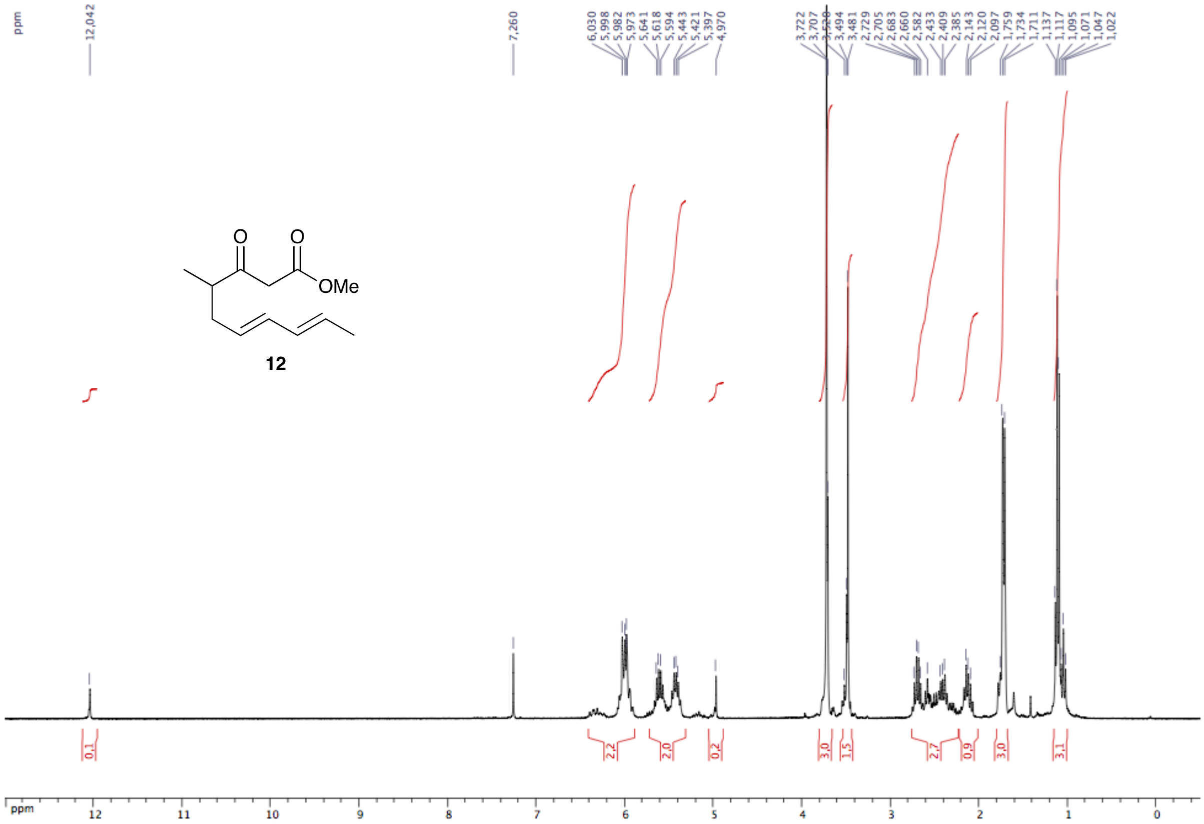
120
100
80
60
40
20
ppm
12
11
10
9
8
7
6
5
4
3
2
1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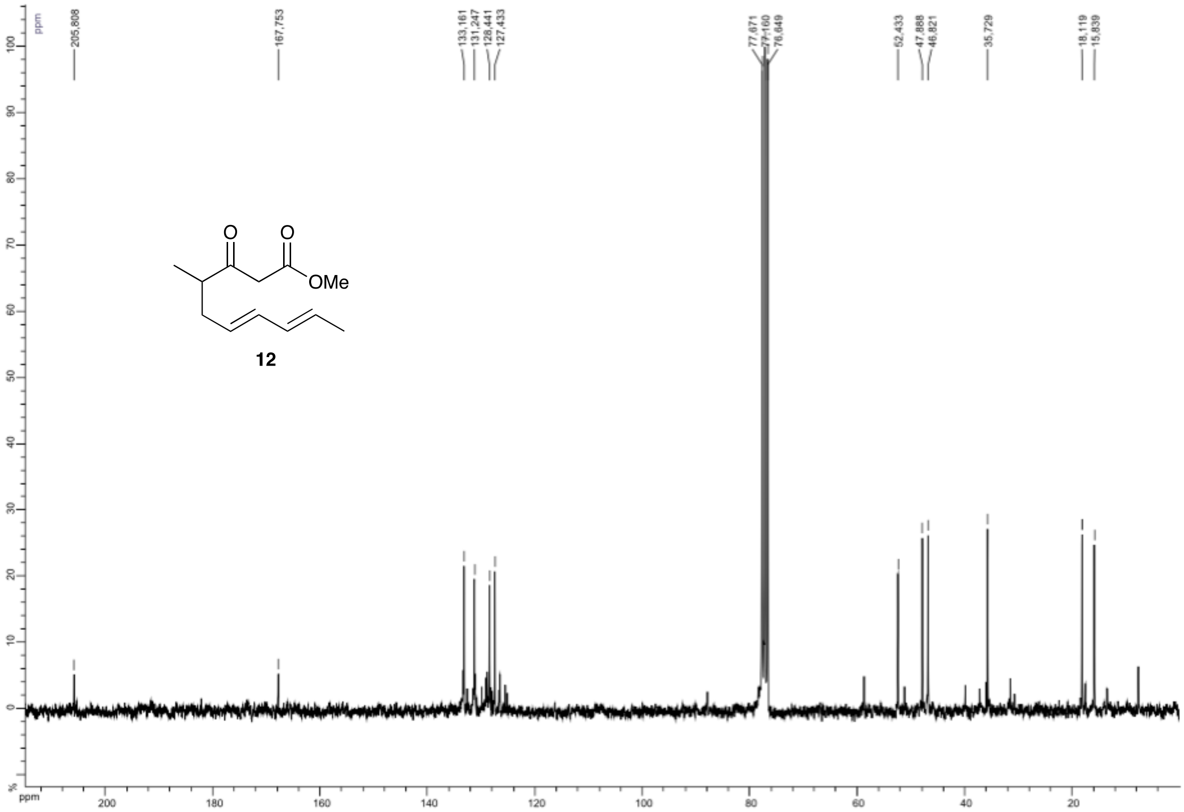
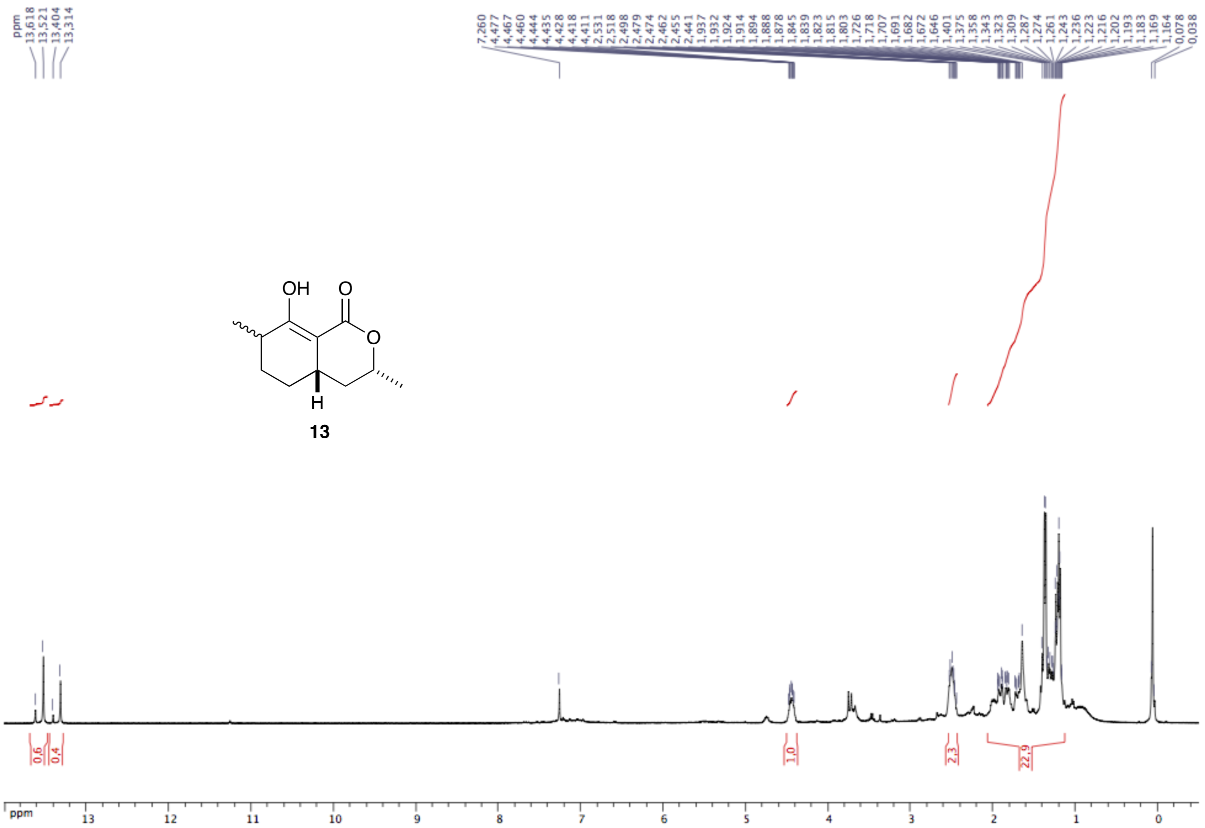
6,030
5,998
5,982
5,973
5,641
5,618
5,594
5,443
5,421
5,397
4,970
3,722
3,707
3,528
3,494
3,481
2,729
2,705
2,683
2,660
2,582
2,433
2,409
2,385
2,143
2,120
2,097
1,759
1,734
1,711
1,137
1,117
1,095
1,071
1,047
1,022
O
O
OMe
12
0,1
2,2
2,0
0,2
3,0
1,5
2,7
0,9
3,0
3,1
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0


ppm
205,808
167,753
133,161
131,247
128,441
127,433
77,671
77,160
76,649
52,433
47,888
46,821
35,729
18,119
15,839
O
O
OMe
12
100
90
80
70
60
50
40
30
20
10
0
%
ppm
200
180
160
140
120
100
80
60
40
20


ppm
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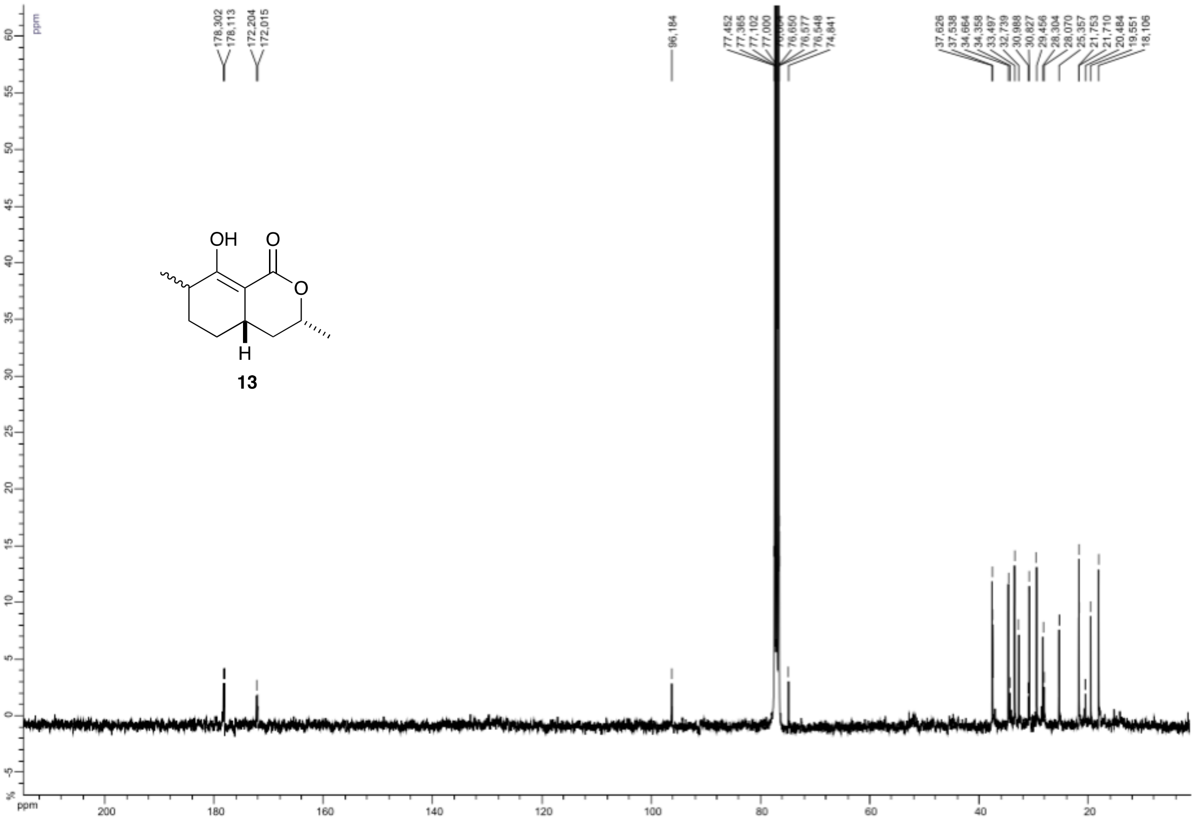
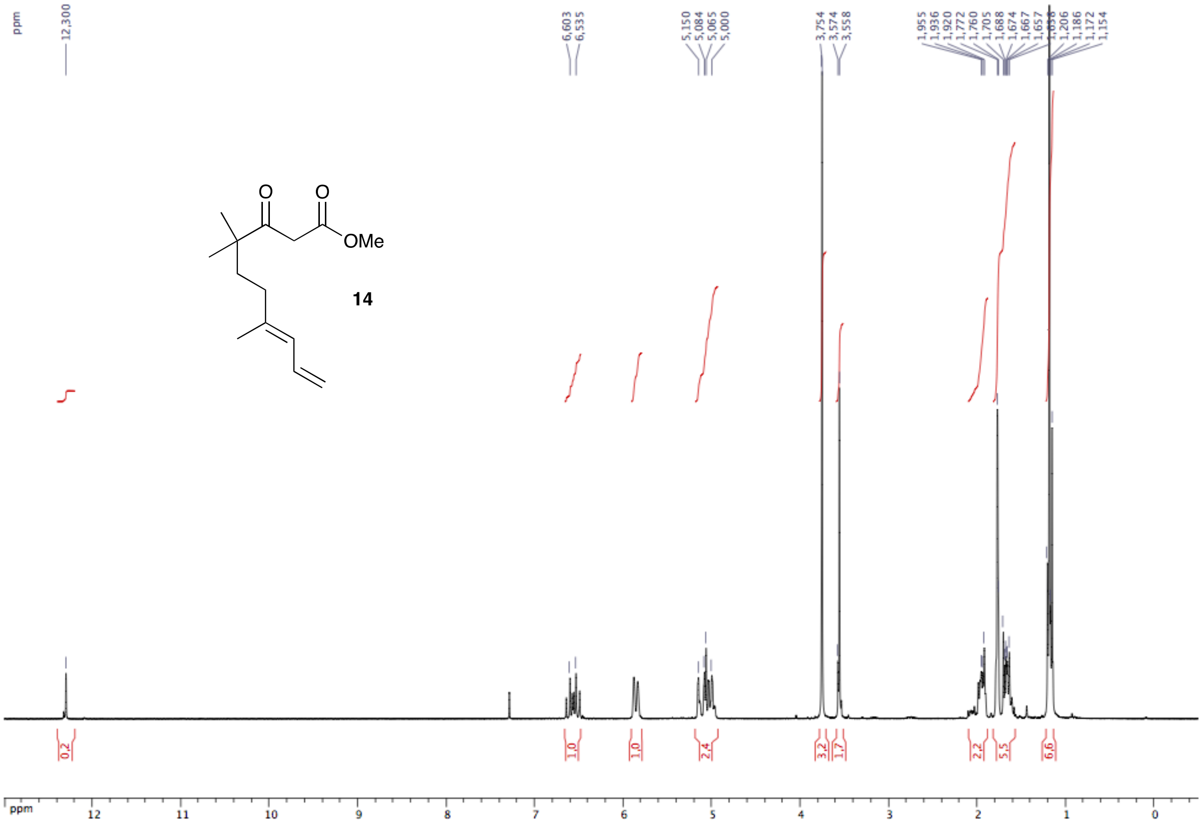
13,404
13,314
7,260
4,477
4,467
4,460
4,444
4,435
4,428
4,418
4,411
2,531
2,518
2,498
2,479
2,474
2,462
2,455
2,441
1,937
1,932
1,924
1,914
1,894
1,888
1,878
1,845
1,839
1,823
1,815
1,803
1,726
1,718
1,707
1,691
1,682
1,672
1,646
1,401
1,375
1,358
1,343
1,323
1,309
1,287
1,274
1,261
1,243
1,236
1,223
1,216
1,202
1,193
1,183
1,169
1,164
0,078
0,038
OH
O
O
H
13
0,6
0,4
1,0
2,3
22,9
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0


ppm
178,302
178,113
172,204
172,015
96,184
77,452
77,365
77,102
77,000
76,650
76,577
76,548
74,841
37,626
37,538
34,664
34,358
33,497
32,739
30,988
30,827
29,456
28,304
28,070
25,357
21,753
21,710
20,484
19,551
18,106
OH
O
O
H
13
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
%
ppm
200
180
160
140
120
100
80
60
40
20


ppm
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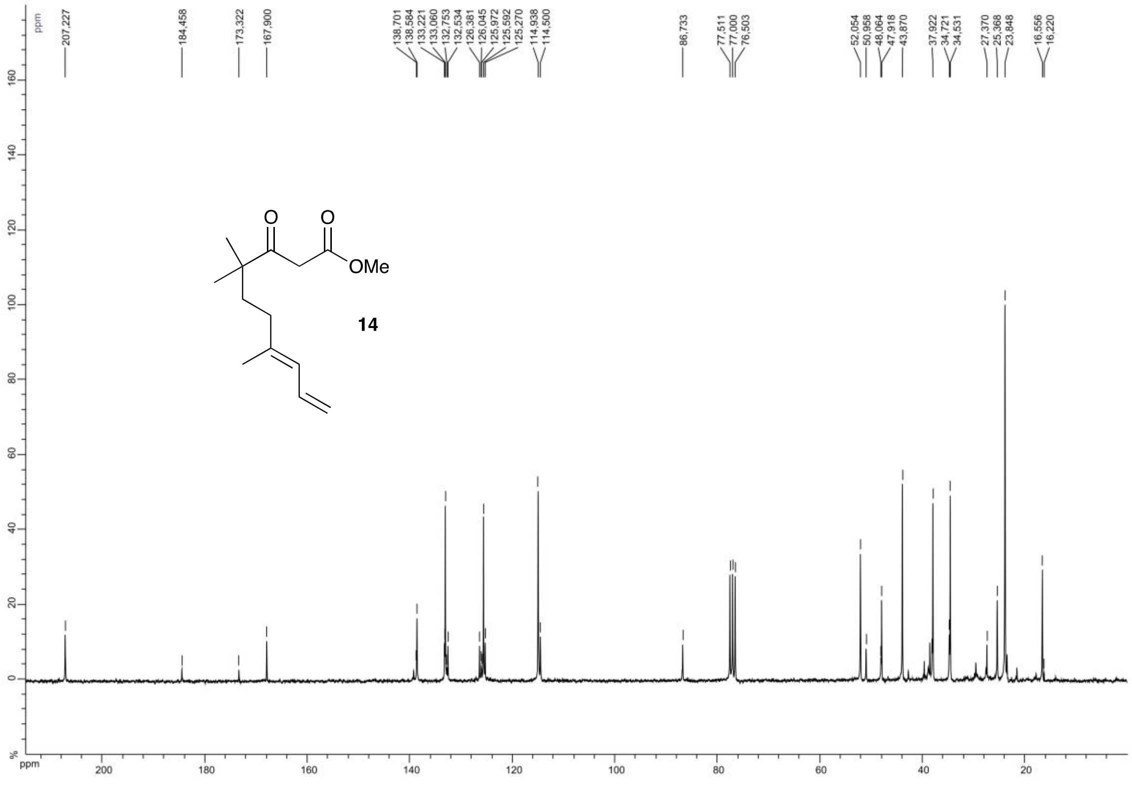
6,535
5,150
5,084
5,065
5,000
3,754
3,574
3,558
1,955
1,936
1,920
1,772
1,760
1,705
1,688
1,674
1,667
1,657
1,636
1,206
1,186
1,172
1,154
O
O
OMe
14
0,2
1,0
1,0
2,4
3,2
1,7
2,2
5,5
6,6
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0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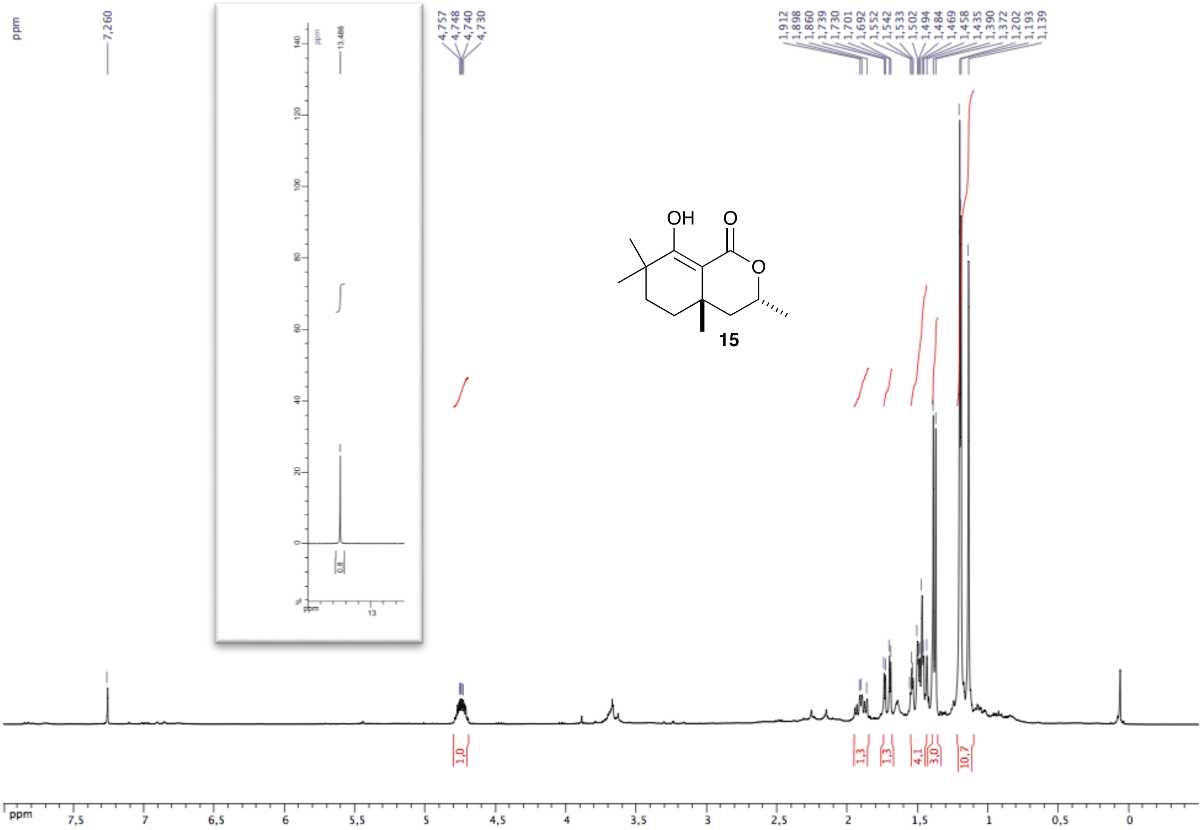
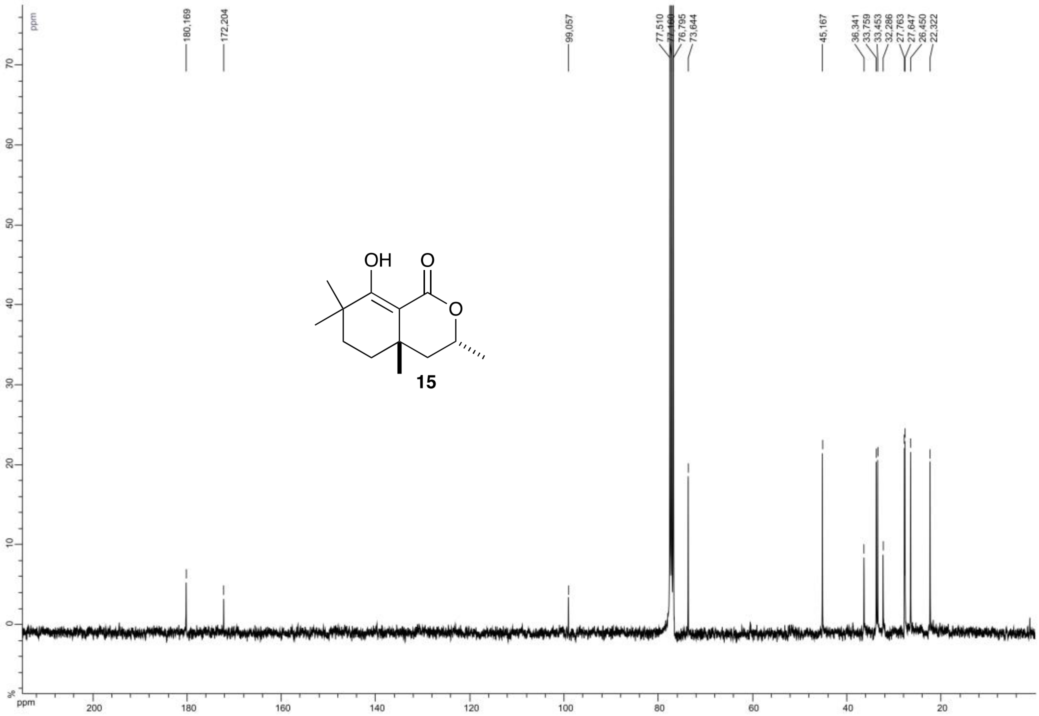
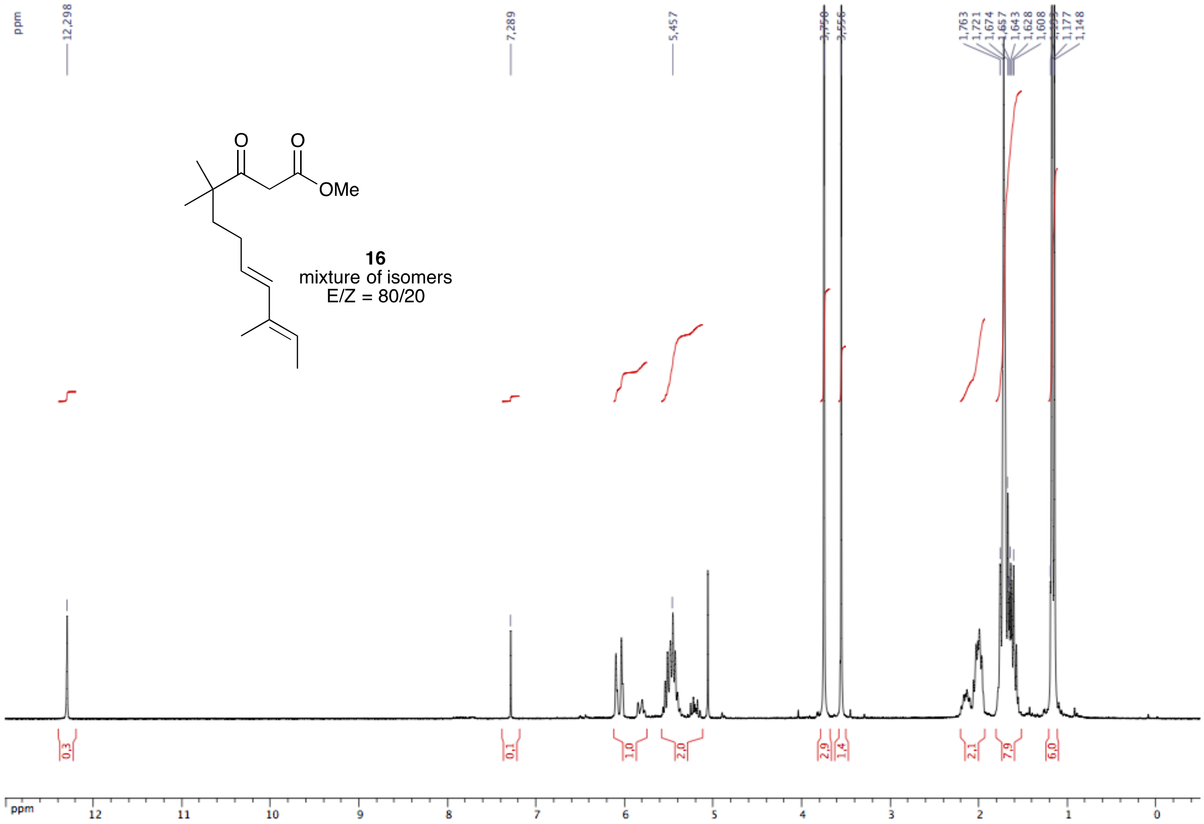
173,322
167,900
138,701
138,584
133,221
133,060
132,753
132,534
126,381
126,045
125,972
125,592
125,270
114,938
114,500
86,733
77,511
77,000
76,503
52,054
50,958
48,064
47,918
43,870
37,922
34,721
34,531
27,370
25,368
23,848
16,556
16,220
160
140
120
100
80
60
40
20
0
%
O
O
OMe
14
ppm
200
180
160
140
120
100
80
60
40
20

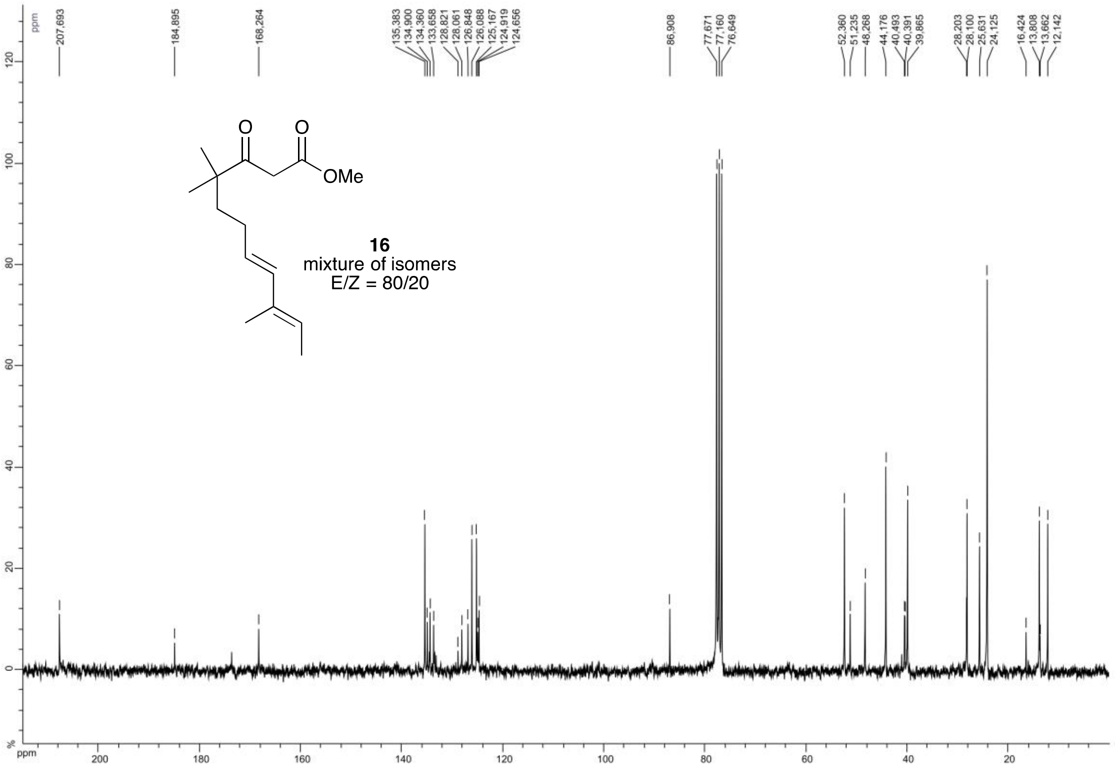

15

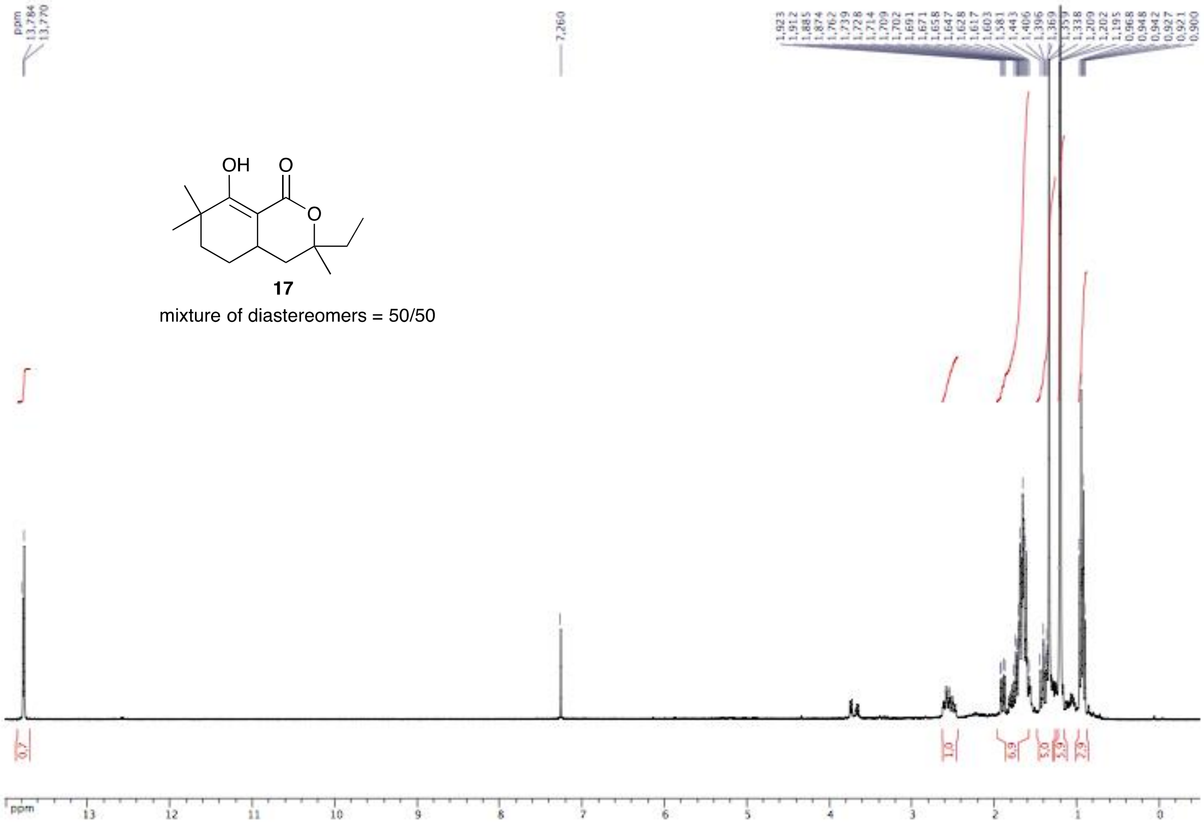
OH
O
O
ppm
7,260
4,757
4,748
4,740
4,730
1,912
1,898
1,860
1,739
1,730
1,701
1,692
1,552
1,542
1,533
1,502
1,494
1,484
1,469
1,458
1,435
1,390
1,372
1,202
1,193
1,139
13,486
0,8
1,0
1,3
1,3
4,1
3,0
10,7
ppm 7,5 7 6,5 6 5,5 5 4,5 4 3,5 3 2,5 2 1,5 1 0,5 0


15

OH
O
O
ppm
180,169
172,204
99,057
77,510
77,160
76,795
73,644
45,167
36,341
33,759
33,453
32,286
27,763
27,647
26,450
22,322
70 60 50 40 30 20 10 0 %
ppm 200 180 160 140 120 100 80 60 40 20

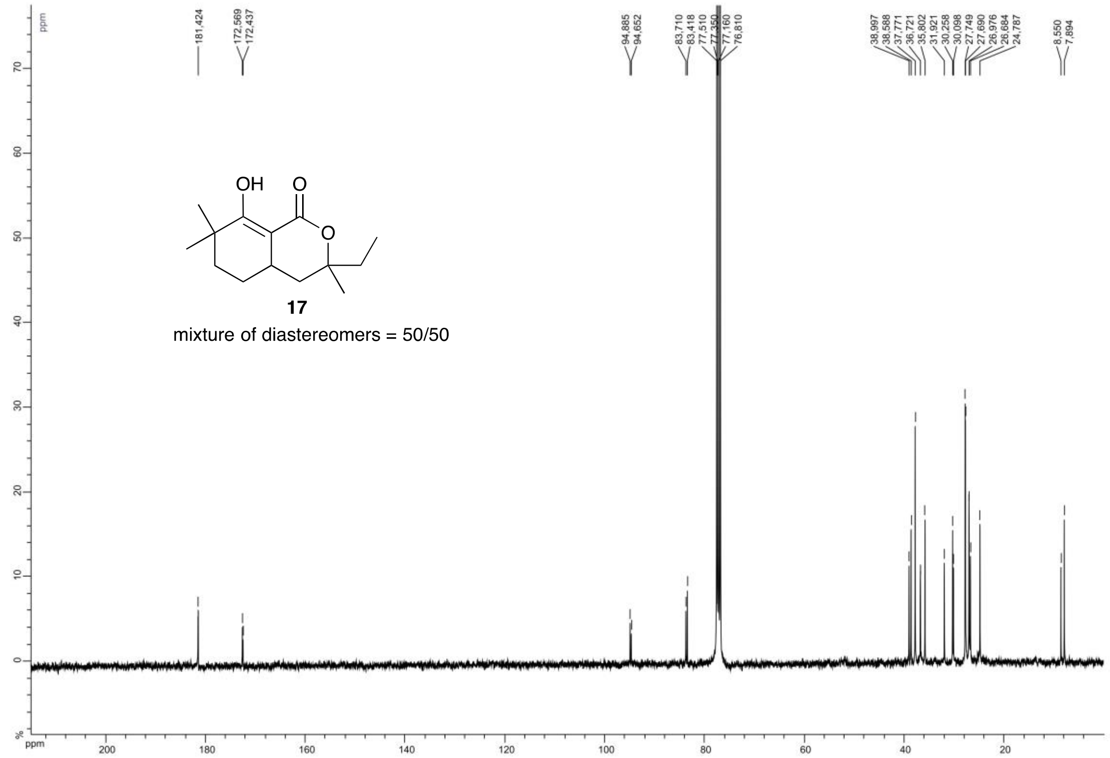

ppm
12,298
7,289
5,457
3,758
3,556
1,763
1,721
1,674
1,657
1,643
1,628
1,608
1,177
1,148
O
O
OMe
16
mixture of isomers
E/Z = 80/20
0,3
0,1
1,0
2,0
2,9
1,4
2,1
7,9
6,0
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0


ppm
207,693
184,895
168,264
135,383
134,900
134,360
133,658
128,821
128,061
126,848
126,088
125,167
124,919
124,656
86,908
77,671
77,160
76,649
52,360
51,235
48,268
44,176
40,493
40,391
39,865
28,203
28,100
25,631
24,125
16,424
13,808
13,662
12,142
O
O
OMe
16
mixture of isomers
E/Z = 80/20
120
100
80
60
40
20
0
%
ppm
200
180
160
140
120
100
80
60
40
20



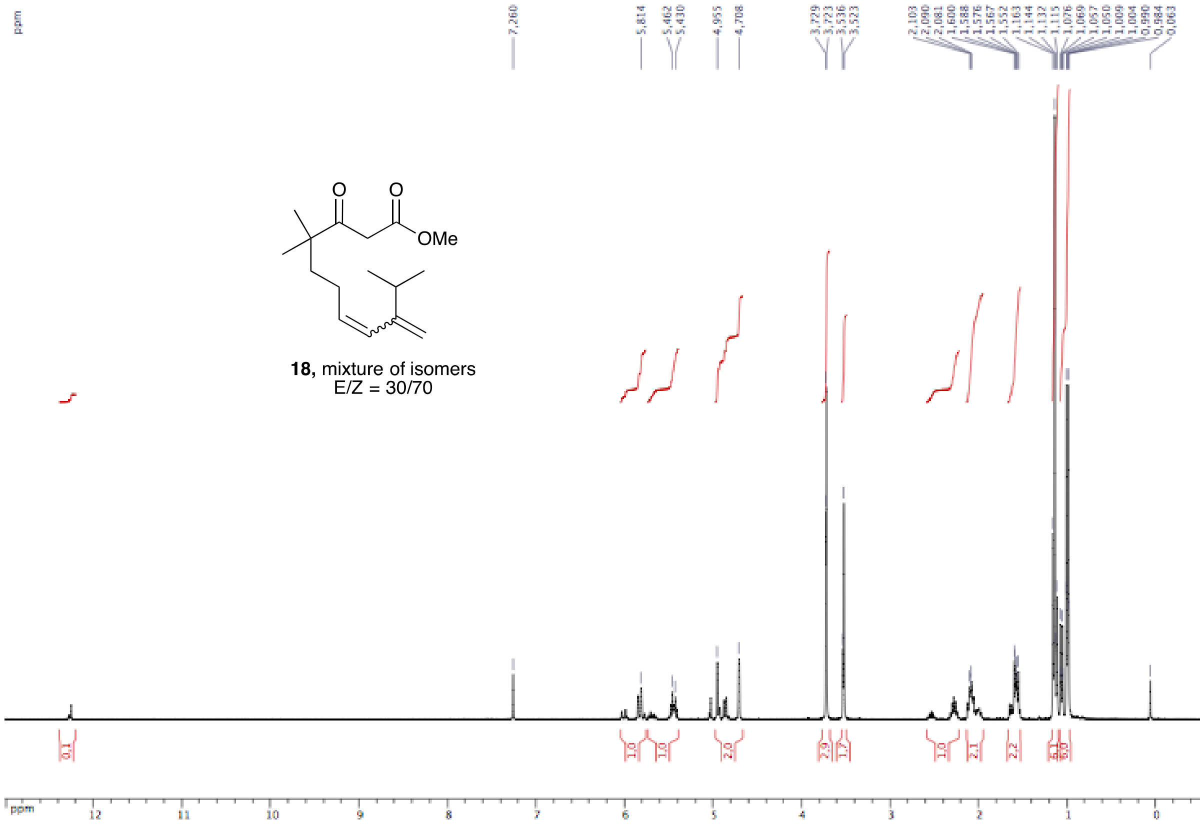
17

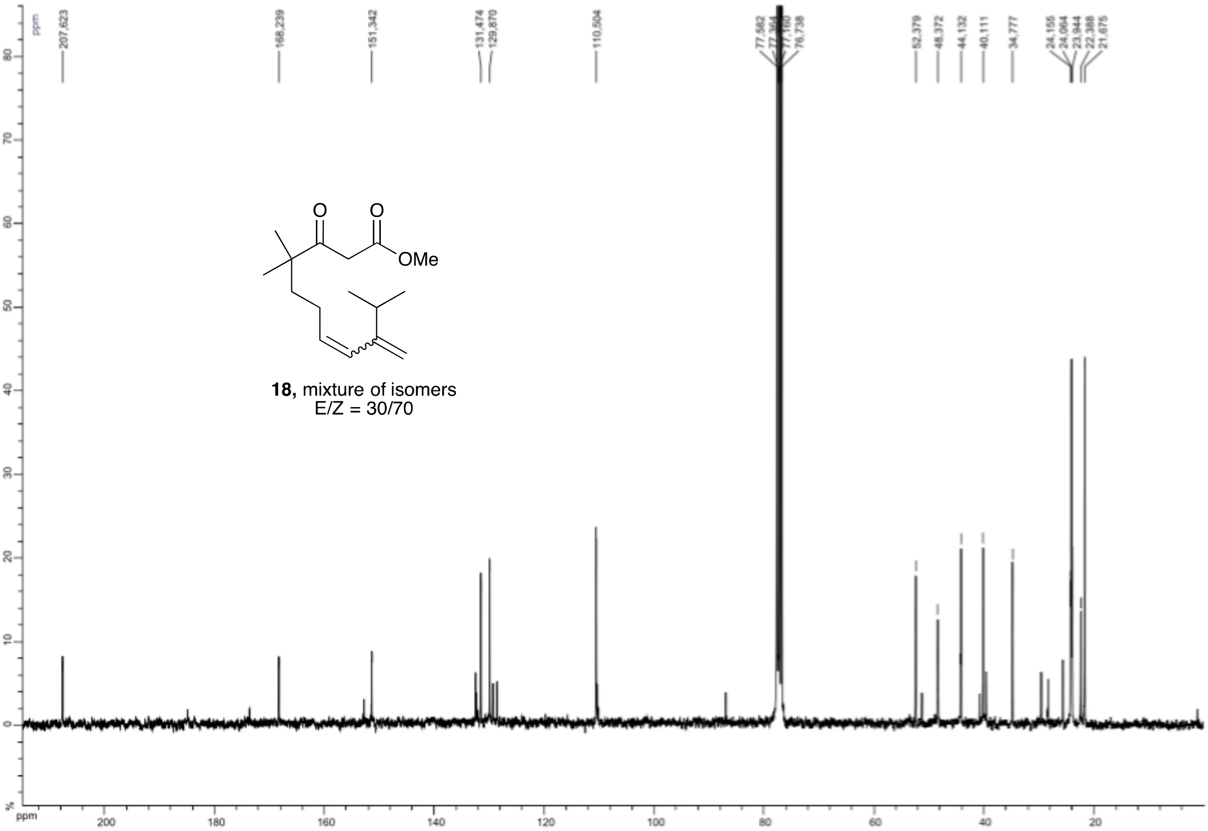
mixture of diastereomers = 50/50

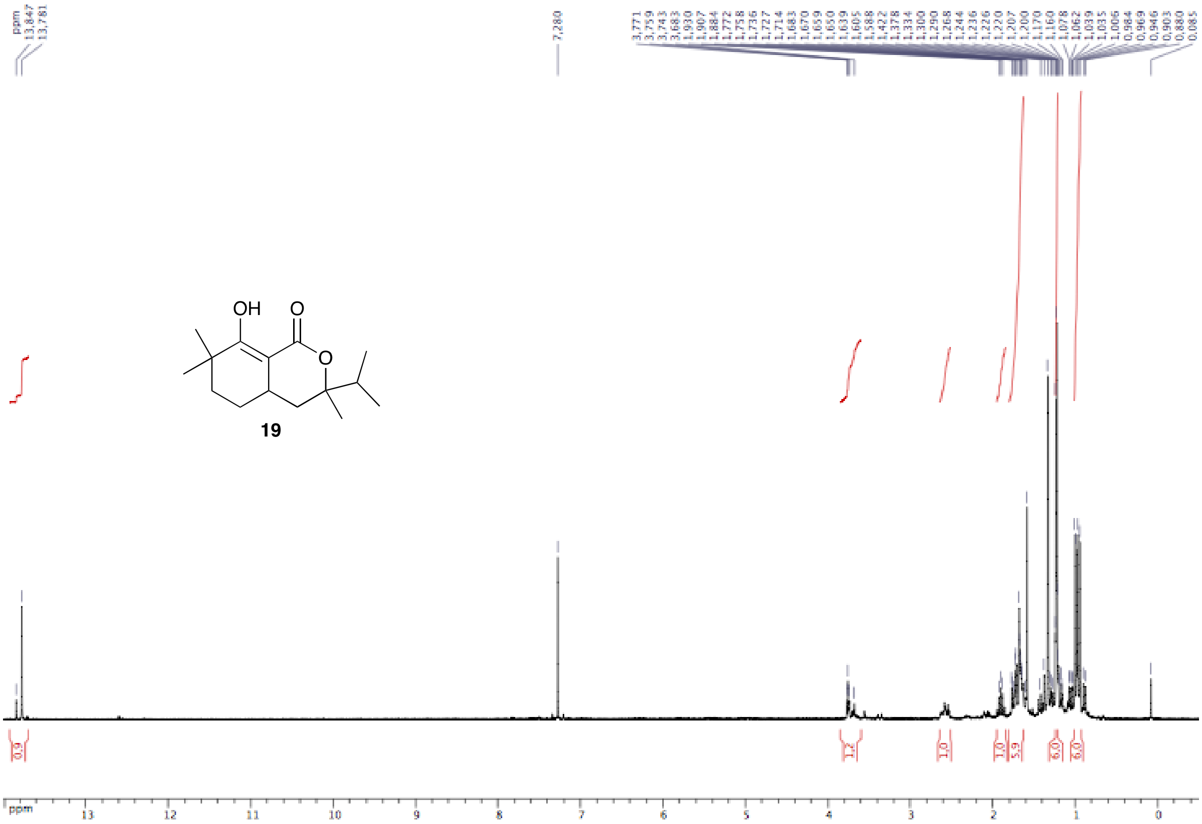


17

mixture of diastereomers = 50/50


18, mixture of isomers
E/Z = 30/70


18, mixture of isomers
E/Z = 30/70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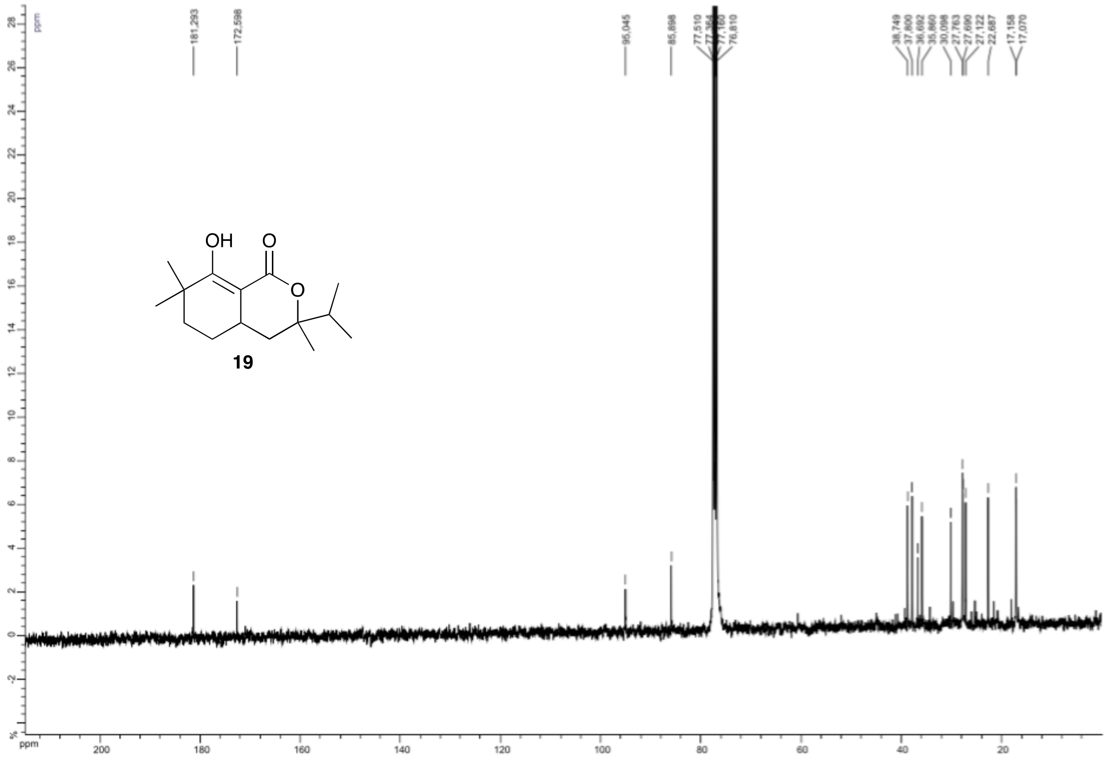
3,771
3,759
3,743
3,683
1,930
1,907
1,884
1,772
1,758
1,736
1,727
1,714
1,683
1,670
1,659
1,650
1,639
1,605
1,588
1,422
1,378
1,334
1,300
1,290
1,268
1,244
1,236
1,226
1,220
1,207
1,200
1,170
1,160
1,078
1,062
1,039
1,035
1,006
0,984
0,969
0,946
0,903
0,880
0,085
OH
O
O
19
0,9
1,2
1,0
1,0
5,9
6,0
6,0
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0


ppm
181,293
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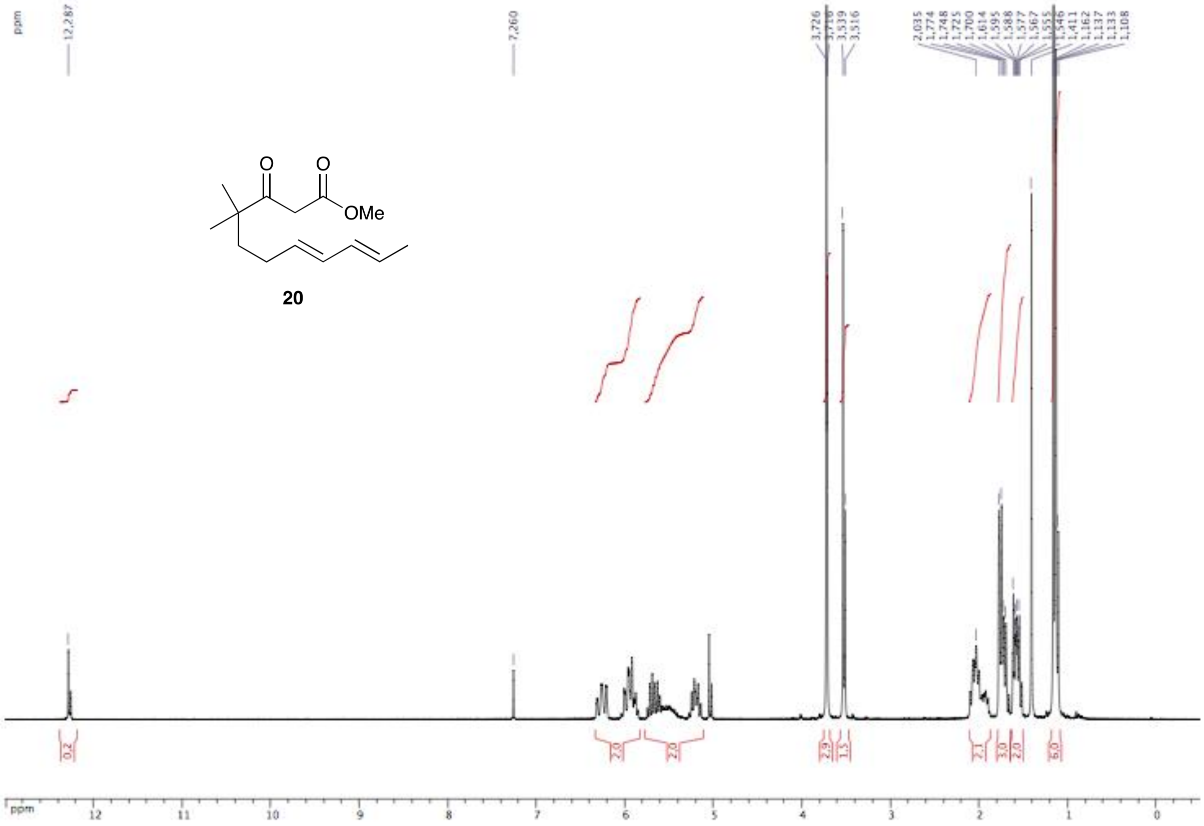
95,045
85,898
77,510
77,364
77,160
76,810
38,749
37,800
36,692
35,860
30,098
27,763
27,690
27,122
22,687
17,158
17,070
OH
O
O
19
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
%
ppm
200
180
160
140
120
100
80
60
40
20


ppm
12,287
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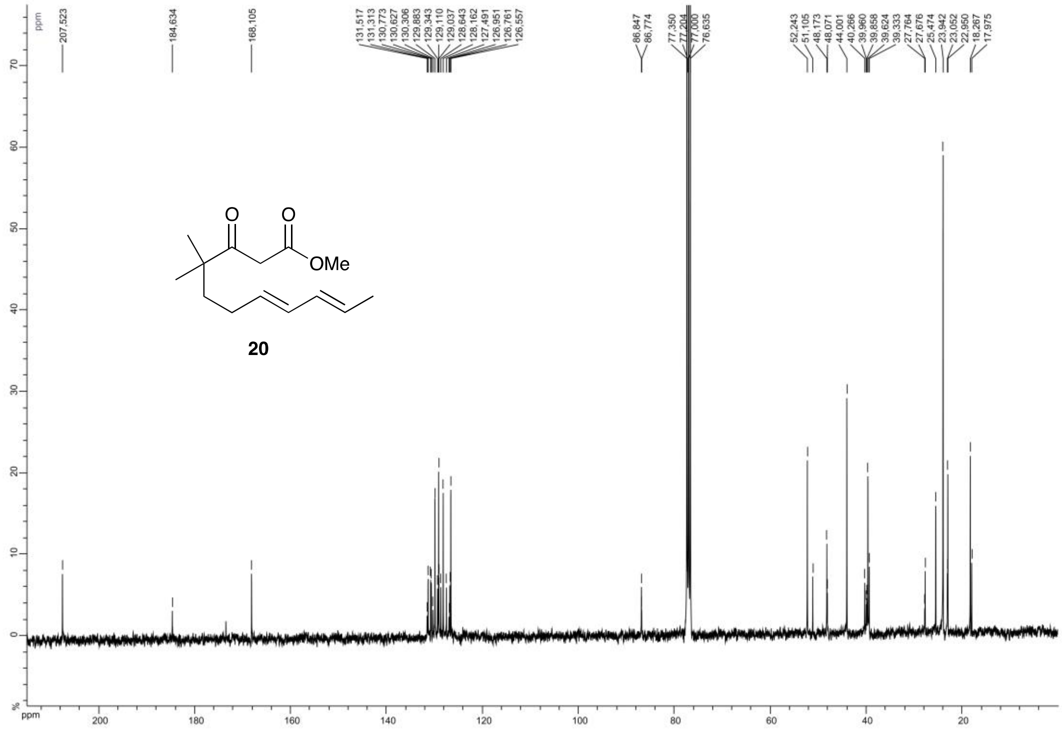
3,726
3,716
3,539
3,516
2,035
1,774
1,748
1,725
1,700
1,614
1,595
1,588
1,577
1,567
1,555
1,546
1,411
1,162
1,137
1,133
1,108
O
O
OMe
20
0.2
2.0
2.0
2.9
1.5
2.1
3.0
2.0
6.0
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0


ppm
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131,313
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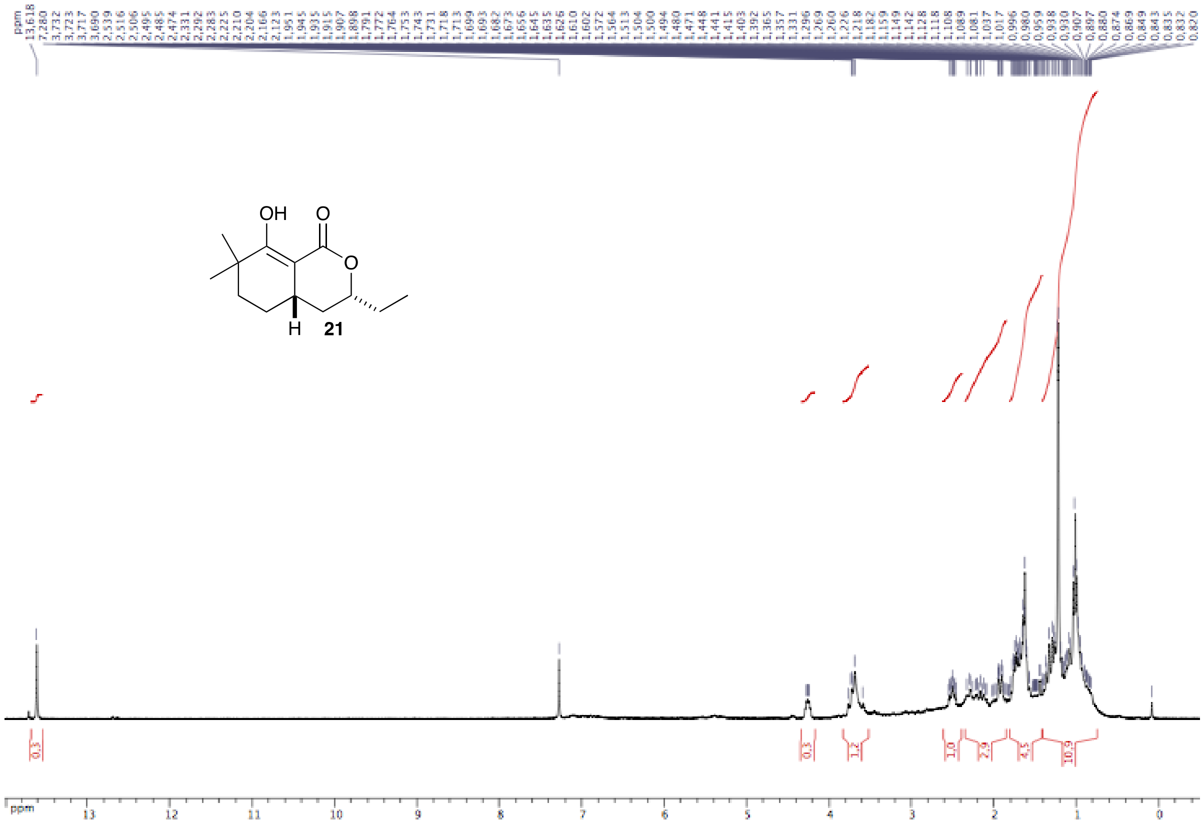
130,627
130,306
129,883
129,343
129,110
129,037
128,643
128,162
127,491
126,951
126,761
126,557
86,847
86,774
77,350
77,204
77,000
76,635
52,243
51,105
48,173
48,071
44,001
40,266
39,960
39,858
39,624
39,333
27,764
27,676
25,474
23,942
23,052
22,950
18,267
17,975
O
O
OMe
20
70
60
50
40
30
20
10
0
%
ppm
200
180
160
140
120
100
80
60
40
20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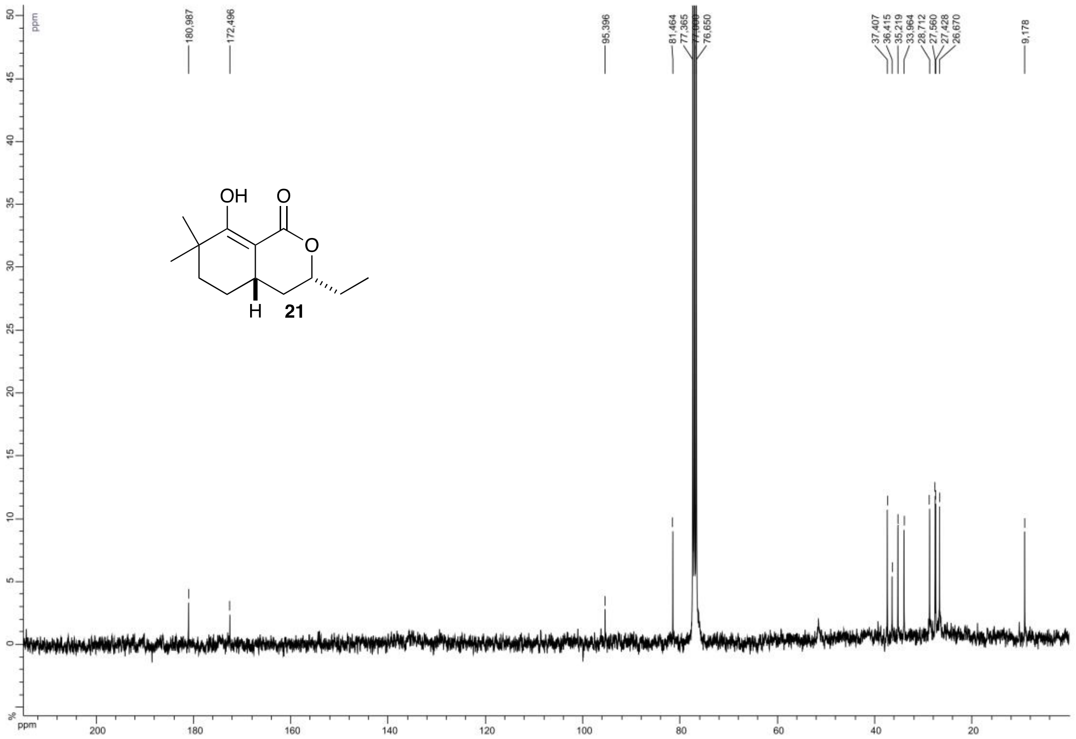
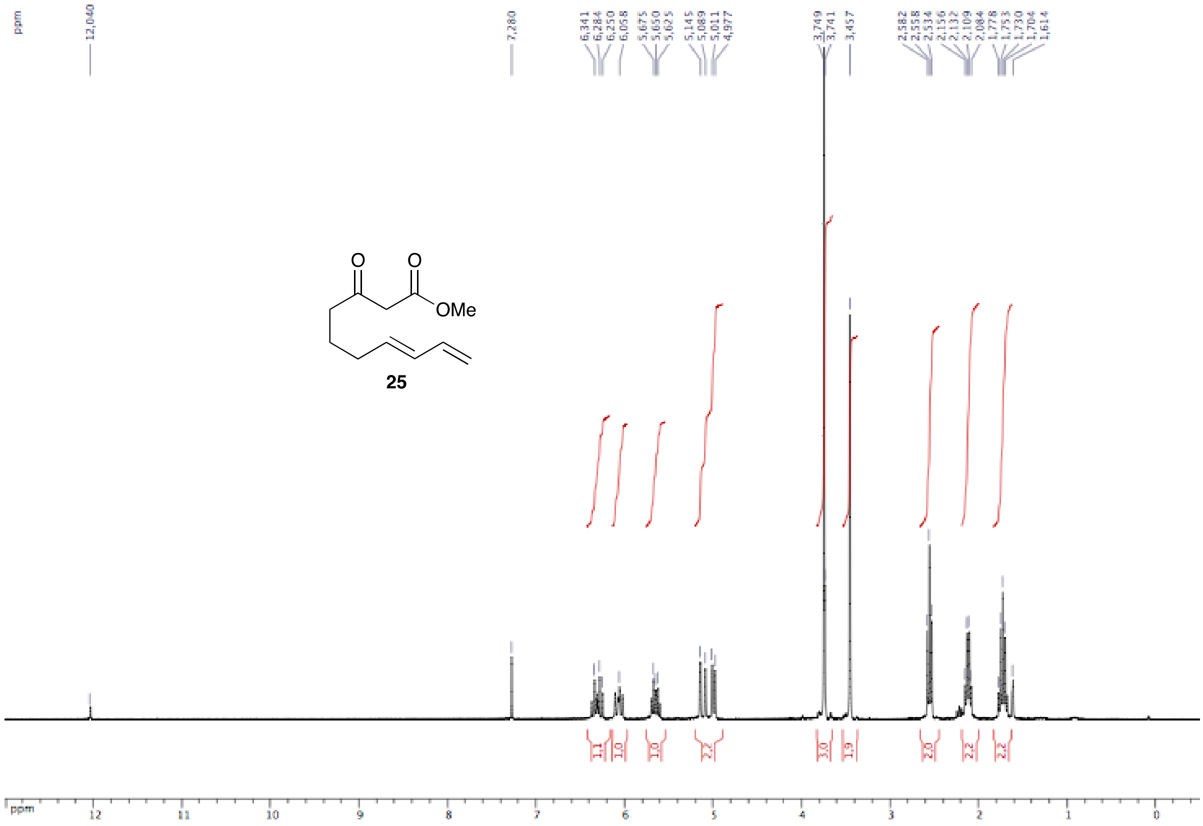
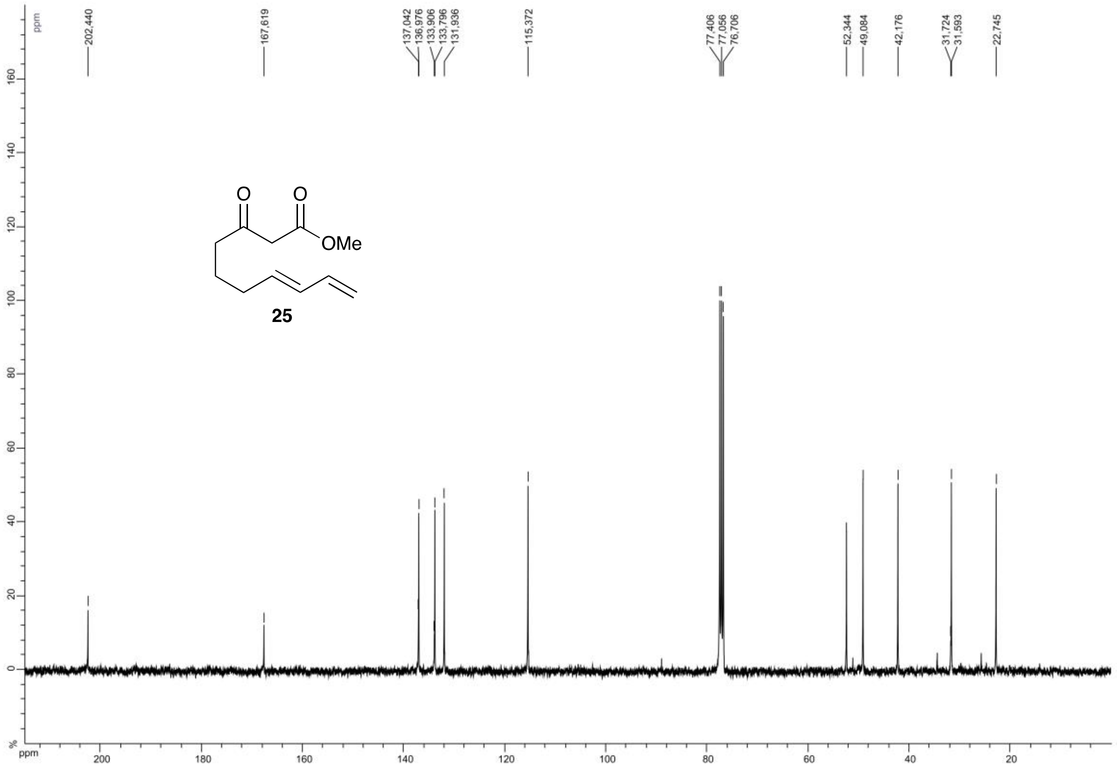
3,732
3,723
3,717
3,690
2,539
2,516
2,506
2,495
2,485
2,474
2,331
2,292
2,283
2,225
2,210
2,204
2,166
2,123
1,951
1,945
1,935
1,915
1,907
1,898
1,791
1,772
1,764
1,753
1,743
1,731
1,718
1,713
1,699
1,693
1,682
1,673
1,656
1,645
1,635
1,626
1,610
1,602
1,572
1,564
1,513
1,504
1,500
1,494
1,480
1,471
1,448
1,441
1,415
1,403
1,392
1,365
1,357
1,331
1,296
1,269
1,260
1,226
1,218
1,182
1,159
1,149
1,142
1,128
1,118
1,108
1,089
1,081
1,037
1,017
0,996
0,980
0,959
0,938
0,930
0,907
0,897
0,880
0,874
0,869
0,849
0,843
0,835
0,832
0,820
OH
O
O
H
21
0,3
0,3
1,2
1,0
2,9
4,5
10,9
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0


ppm
180,987
172,496
95,396
81,464
77,365
77,000
76,650
37,407
36,415
35,219
33,964
28,712
27,560
27,428
26,670
9,178
50
45
40
35
30
25
20
15
10
5
0
%
OH
O
O
H
21
ppm
200
180
160
140
120
100
80
60
40
20



ppm
12,040
7,280
6,341
6,284
6,250
6,058
5,675
5,650
5,625
5,145
5,089
5,011
4,977
3,749
3,741
3,457
2,582
2,558
2,534
2,156
2,132
2,109
2,084
1,778
1,753
1,730
1,704
1,614
O
O
OMe
25
1,1
1,0
1,0
2,2
3,0
1,9
2,0
2,2
2,2
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0



ppm
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137,042
136,976
133,906
133,796
131,936
115,372
77,406
77,056
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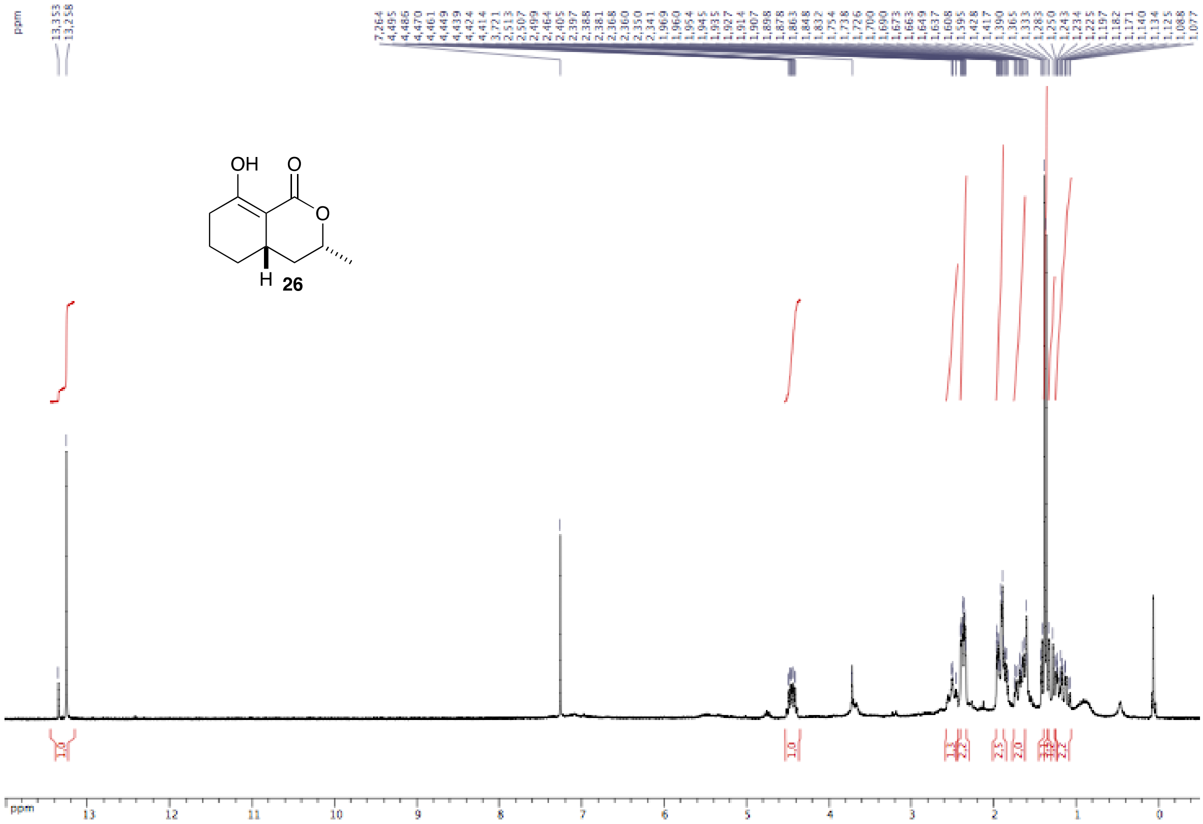
49,084
42,176
31,724
31,593
22,745
O
O
OMe
25
160
140
120
100
80
60
40
20
0
%
ppm
200
180
160
140
120
100
80
60
40
20


ppm
13.353
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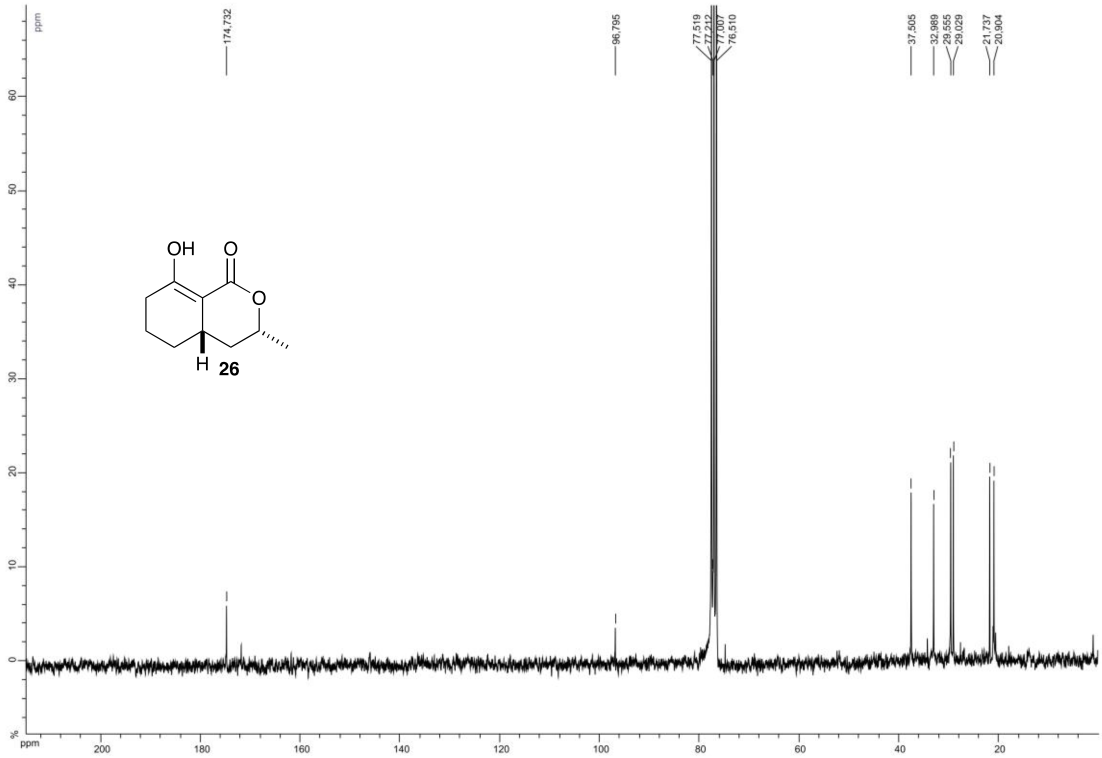
7.264
4.495
4.485
4.470
4.461
4.449
4.439
4.424
4.414
3.721
2.513
2.507
2.499
2.464
2.405
2.397
2.388
2.381
2.368
2.360
2.350
2.341
1.969
1.960
1.954
1.945
1.935
1.927
1.914
1.907
1.898
1.878
1.863
1.848
1.832
1.754
1.738
1.726
1.700
1.690
1.673
1.663
1.649
1.637
1.608
1.595
1.428
1.417
1.390
1.365
1.333
1.283
1.250
1.243
1.234
1.225
1.197
1.182
1.171
1.140
1.134
1.125
1.088
1.077
OH
O
O
H
26
1.0
1.0
2.5
2.0
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0


ppm
174.732
96.795
77.519
77.212
77.007
76.510
37.505
32.989
29.555
29.029
21.737
20.904
OH
O
O
H
26
60
50
40
30
20
10
0
%
ppm
200
180
160
140
120
100
80
60
40
20

6 X-ray diffraction study of compound 5 and 17

X-ray diffraction data for compounds **5** ant **17** were collected by using a Kappa X8 APPEX II Bruker diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation. Crystal was mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flashfrozen in a nitrogen-gas stream at 100 K. The temperature of the crystal was maintained at the selected value (100K) by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97[1] and refined against F^2 by full-matrix least-squares techniques using SHELXL-2014[2] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.[3]

The crystal data collection and refinement parameters are given in Table S1.

CDC 1001233 and 1497250 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure.

1) Sheldrick, G. M. SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany, **1997**.
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Table S1. Crystallographic data and structure refinement details for compounds **5** and **17**.

Compound	**5**	**17**
Empirical Formula	$C_{12} H_{18} O_3$	$C_{14} H_{22} O_3$
M_r	210.26	238.31
Crystal size, mm^3	0.11 x 0.06 x 0.01	0.21 x 0.06 x0.02
Crystal system	triclinic	triclinic
Space group	*P -1*	*P -1*
a, Å	7.3024(6)	5.704(2)
b, Å	8.6519(8)	6.297(3)
c, Å	8.9513(6)	18.887(9)
α, °	77.266(2)	93.901(11)
β, °	86.338(2)	95.455(10)
γ, °	88.215(2)	106.130(10)
Cell volume, $Å^3$	550.42(8)	645.6(5)
Z	2	2
T, K	100(1)	100(1)
Radiation type; wavelength Å	MoKα; 0.71073	MoKα; 0.71073
F_{000}	228	260
μ, mm^{-1}	0.090	0.084
θ range, °	2.337 - 30.490	2.177 - 30.517
Reflection collected	5 638	9 528
Reflections unique	2 395	3 599
R_{int}	0.0237	0.0750
GOF	1.010	0.989
Refl. obs. ($I>2\sigma(I)$)	1 751	1 969
Parameters	784	159
wR_2 (all data)	0.1137	0.2402
R value ($I>2\sigma(I)$)	0.0429	0.0788
Largest diff. peak and hole ($e^-.Å^{-3}$)	-0.213 ; 0.314	-0.393 ; 0.585

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