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

Supporting Information

Cyclopropanation using flow-generated diazo compounds

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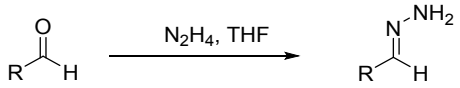
General experimental section. ^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400 DRX-500 Cryo or DRX-600 spectrometer with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C-NMR spectra were recorded on the same spectrometers with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm). All ^{13}C resonances are reported to the nearest 0.1 ppm. DEPT 135, COSY, HMQC, and HMBC experiments were used to aid structural determination and spectral assignment. The multiplicity of ^{1}H signals are indicated as: s = singlet, d = doublet, t = triplet, m = multiplet, br. = broad, or combinations of thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Unless stated otherwise, reagents were obtained from commercial sources and used without purification. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator. Data regarding high resolution mass spectrometry (HRMS) was provided by the Mass Spectrometry Service for the Chemistry Department of the University of Cambridge. All the olefins are commercially available and were used as purchased without further purification. Unless otherwise stated, all the flow reactions were performed using a Uniqsis FlowSyn platform.[1] In-line IR spectroscopy was performed using the Mettler Toledo FlowIR® device.[2]

Preparation of hydrazones:



In a round-bottom flash containing 12 mL of N_2H_4 (1M in THF, 12 mmol), a solution of aldehyde (1M in THF, 10 mmol) was slowly added. The mixture was stirred for 30 min to 2 h (depending on the substrate) at room temperature. The mixture was evaporated under reduced pressure to give the desired hydrazone compound. Hydrazones were used without further purification for the generation of diazo compound.

General procedure for cyclopropanation reaction:

Conditioning phase: A solution of hydrazone (1 mmol, 0.1 M) and Hünig base (2 equiv.) in AcOEt (10 mL) was passed through the column reactor (Omnifit® column[3], 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (0.86 g),[4] at a flow rate of 0.5 mL min^{-1} for 20 min (*phase 1*) and the reactor output was monitored using a Flow-IR® device.[2] The flow was switched to solvent (Hünig base, 0.2 M in AcOEt) for 10 min (*phase 2*). The column was then ready for the generation of the diazo compound.

Generation phase: A solution of hydrazone (2 mmol, 0.1 M) and Hünig's base (2 equiv.) in AcOEt (20 mL) was passed through a conditioned column reactor (Omnifit® column[3], 6.6 mm i.d. × 50 mm length) (*phase 3*) at a flow rate of 0.5 mL min^{-1}. When the FlowIR® showed that the intensity of the diazo peak (region 2050-2100 cm^{-1}, **Figure S1**) was stable,[2] 4 mL of the stream of diazo was combined with 4 mL of solution of olefin (0.05 M in AcOEt, 0.5 mL min^{-1}) at a T-piece and stirred at room temperature in a round-bottom flask for 2h (we observed slight changes in reactivity for the different diazo compounds). The reaction mixture was concentrated under vacuum and purified over silica gel using different gradients of hexane in AcOEt.

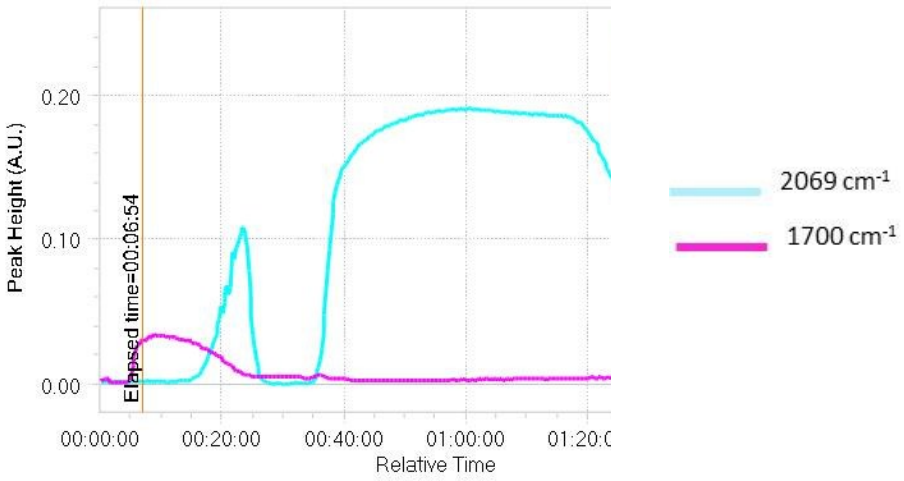


Figure S1. FlowIR® data (peak at 2069 cm^{-1}) for the generation of **2a**.

Synthesis of diols 8a-d

Conditioning phase: vide supra. Generation phase: A solution of hydrazone (2 mmol, 0.1 M) and Hünig's base (2 equiv.) in AcOEt (20 mL) was passed through a conditioned column reactor (Omnifit® column[3], 6.6 mm i.d. × 50 mm length) (*phase 3*) at a flow rate of 0.5 mL min^{-1}. When the FlowIR® showed that the intensity of the diazo peak (region 2050-2100 $cm^{-1,}$ **Figure S1**) was stable,[2] 4 mL of the stream of diazo was combined with 4 mL of the solution of olefin (0.05 M in AcOEt, 0.5 mL min^{-1}) at a T-piece and stirred at room temperature in a round-bottom flask for 2h (we observed slight changes in reactivity for the different diazo compounds). The reaction mixture was concentrated under vacuum and dissolved in 2 mL of dry THF and added dropwise to a solution of $LiAlH_4$, maintained at 0 °C. The reaction mixture was stirred at 0 °C for 1h then quenched with H_2O and extracted with AcOEt. The organic solution was dried over $MgSO_4$, filtered and concentrated to give a crude mixture. The final product was obtained after purification over silica gel (hexane/AcOEt, 1:1 *v*/*v*).

Scale up

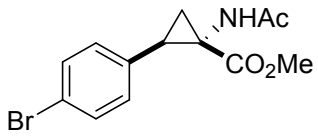
Conditioning phase: A solution of hydrazone (0.1 M) and Hünig base (2 equiv.) in AcOEt (30 mL) was passed through the column reactor (Omnifit® column[3], 6.6 mm i.d. × 100 mm length), packed with activated MnO_2 (3 g),[4] at a flow rate of 0.5 mL min^{-1} for 60 min (*phase 1*) and the reactor output was monitored using a Flow-IR® device.[2] The column was then washed with a standard solution (Hünig's base, 0.2 M in AcOEt) for 20 min (*phase 2*). The column was then ready for the generation of the diazo compound. Generation phase: A solution of hydrazone (0.1 M) and Hünig's base (2 equiv.) in AcOEt (80 mL) was passed through a conditioned column reactor (Omnifit® column[3], 6.6 mm i.d. × 50 mm length) (*phase 3*) at a flow rate of 0.5 mL min^{-1}. When the FlowIR® showed that the intensity of the diazo peak (region 2050-2100 $cm^{-1,}$ **Figure S1**) was stable,[2] the stream of diazo was combined with a solution of olefin (0.05 M in AcOEt, 0.5 mL min^{-1}) at a T-piece and stirred at room temperature in a round-bottom flask for 24h. The reaction mixture was concentrated under vacuum and purified over silica gel using different gradients of hexane in AcOEt.

Telescoped synthesis of 4k

A solution of geraniol (0.2 M in THF, 10 mL) was passed through a column packed with MnO_2 (7 g) at a flow rate of 0.5 mL min^{-1}. The output was delivered to a round-bottom flask containing a solution of hydrazine in THF and MeOH (1.05 equiv, 10 mL 10% v/v MeOH). The reaction mixture was stirred at rt for 2 h and then pumped (1.00 mL min^{-1}) through a column packed with MnO_2 (Omnifit® column[3], 6.6 mm i.d. × 50 mm length, 0.86 g). The reaction stream was combined with a solution of olefin **3a** (0.05 M in AcOEt, 1.00 mL min^{-1}) and the output directly concentrated to give the final product **4k** in 66% yield (as determined by ^{1}H-NMR with internal standard).

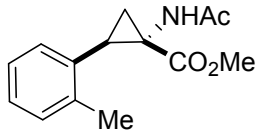
Characterisation data for compounds

(Trans)-methyl 1-acetamido-2-(4-bromophenyl)cyclopropane-1-carboxylate (4a)



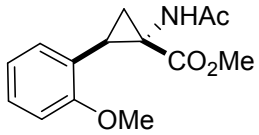
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.92 (s, 1H, NH), 3.34 (s, 3H), 2.75 (t, *J* = 9.1 Hz, 1H), 2.13 (dd, *J* = 8.4, 5.7 Hz, 1H), 2.01 (s, 3H), 1.56 (dd, *J* = 9.6, 5.6 Hz, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.5, 169.9, 134.5, 131.1, 131.1, 121.0, 52.1, 40.4, 34.3, 23.2, 20.6 ppm; **MS:** (ESI+) $C_{13}H_{14}BrNO_3^+$ (M^+) calc.: 312.0235, det.: 312.0251; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3279, 2954, 2327, 1733, 1661, 1530, 1490, 1436, 1371, 1334, 1270, 1209, 1196, 1157, 1073, 1012, 975, 933, 834, 781, 756, 735, 707.

(Trans)-methyl 1-acetamido-2-(o-tolyl)cyclopropane-1-carboxylate (4b)



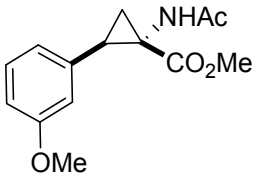
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 4H), 6.99 (s, 1H), 3.41 (s, 3H), 2.77 (t, *J* = 9.0 Hz, 1H), 2.49 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.44 (s, 3H), 2.17 (s, 3H), 1.81 (dd, *J* = 9.6, 5.7 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4 , 170.2, 137.8, 133.6, 129.7, 129.1, 127.3, 125.7, 51.9, 40.9, 33.0, 23.2 , 20.8, 19.7 ppm; **MS:** (ESI+) $C_{14}H_{18}NO_3^+$ (M^+) calc.: 248.1281, det.: 248.1274; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3292, 2953, 1733, 1655, 1531, 1493, 1436, 1372, 1333, 1286, 1226, 1195,1156, 1115, 1031, 977, 932, 880, 825, 789, 757, 731, 701.

(Trans)-methyl 1-acetamido-2-(2-methoxyphenyl)cyclopropane-1-carboxylate (4c)



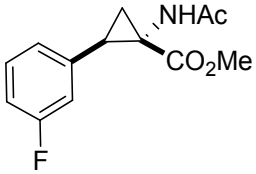
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (td, *J* = 7.7, 1.3 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.45 (s, 1H), 3.80 (s, 3H), 3.30 (s, 3H), 2.58 (t, *J* = 9.1 Hz, 1H), 2.27 (dd, *J* = 8.6, 5.7 Hz, 1H), 2.04 (s, 3H), 1.69 (dd, *J* = 9.5, 5.7 Hz, 1H)ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.2, 170.2, 158.6, 130.1, 128.5, 123.8, 120.3, 109.7, 55.5, 51.8, 40.4, 30.3, 23.3, 20.9 ppm; **MS:** (ESI+) $C_{14}H_{17}NO_4Na^+$ ($M+Na^+$) calc.:286.1055, det.: 286.1052; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3279, 2952, 2839, 1731, 1655, 1603, 1586, 1528, 1496, 1459, 1437, 1372, 1334, 1285, 1246, 1201, 1158, 1117, 1048, 1027, 978, 908, 822, 802, 785, 753, 731.

(Trans)-methyl-1-acetamido-2-(3´-methoxyphenyl)cyclopropane-1-carboxylate (4d)



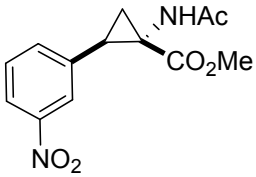
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.1 Hz, 1H), 6.94 – 6.89 (m, 2H), 6.76 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.42 (s, 1H), 3.78 (s, 3H), 3.35 (s, 3H), 2.80 (t, *J* = 9.1 Hz, 1H), 2.22 (dd, *J* = 8.5, 5.6 Hz, 1H), 2.04 (s, 3H), 1.59 (dd, *J* = 9.7, 5.6 Hz, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.2, 170.0 , 159.3, 136.9, 128.9, 121.5, 114.7, 112.8, 55.2, 52.0, 40.6, 34.7, 23.2, 20.6 ppm; **MS:** (ESI+) $C_{14}H_{17}NO_4Na^+$ (M+Na^+) calc.:286.1055, det.: 286.1061; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3279, 2953, 2365, 2343, 1732, 1662, 1604, 1584, 1531, 1490, 1436, 1372, 1334, 1287, 1260, 1199, 1152, 1046, 875,791, 767, 720, 694.

(Trans)-methyl 1-acetamido-2-(3-fluorophenyl)cyclopropane-1-carboxylate (4e)



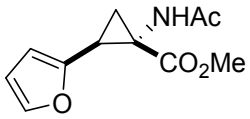
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 14.0, 7.9 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 9.9 Hz, 1H), 6.91 (td, *J* = 8.4, 2.1 Hz, 1H), 6.41 (s, 1H), 3.37 (s, 3H), 2.82 (t, *J* = 9.1 Hz, 1H), 2.19 (dd, *J* = 8.5, 5.7 Hz, 1H), 2.05 (s, 3H), 1.61 (dd, *J* = 9.7, 5.6 Hz, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.4 , 169.9, 163.5, 161.8 , 138.1 (d, *J* = 7.9 Hz), 129.5 (d, *J* = 8.4 Hz), 125.1 (d, *J* = 2.8 Hz), 116.4 (d, *J* = 21.7 Hz), 114.2 (d, *J* = 21.1 Hz), 52.2, 40.6, 34.5 (d, *J* = 2.1 Hz), 23.4, 20.7 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.88 ppm; **MS:** (ESI+) $C_{13}H_{14}NO_3FNa^+$ (M+Na^+) calc.:274.0855, det.: 274.0869; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3279, 3031, 2955, 2372, 2350, 1735, 1663, 1616, 1588, 1531, 1491, 1440, 1373, 1337, 1274, 1249, 1198, 1170, 1144, 1003, 875,792, 722, 689.

(Trans)-methyl-1-acetamido-2-(3-nitrophenyl)cyclopropane-1-carboxylate (4f)



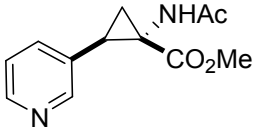
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 6.73 (s, 1H), 3.37 (s, 3H), 2.91 (t, *J* = 9.1 Hz, 1H), 2.21 (dd, *J* = 8.6, 5.7 Hz, 1H), 2.06 (s, 3H), 1.69 (dd, *J* = 9.7, 5.7 Hz, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.7 , 169.7 , 148.0 , 137.9 , 136.1 , 129.0 , 124.3, 122.2 , 52.4, 40.4, 34.6, 23.3, 21.0 ppm; **MS:** (ESI+) $C_{13}H_{14}N_2O_5Na^+$ (M+Na^+) calc.:301.0800, det.: 301.0814; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1})= 3291, 3054, 2959, 2365, 1732, 1664, 1528, 1438, 1349, 1285, 1218, 1197, 1161, 1099, 909, 811, 786, 733, 683.

(Trans)-methyl 1-acetamido-2-(furan-2´-yl)cyclopropane-1-carboxylate (4g)



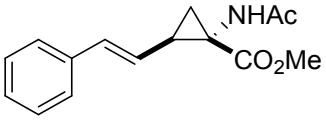
^{1}H NMR (400 MHz, CDCl3) δ 7.29 (s, 1H), 6.36 – 6.26 (m, 2H), 6.17 (d, *J* = 3.2 Hz, 1H), 3.49 (s, 3H), 2.61 (t, *J* = 9.0 Hz, 1H), 2.27 (dd, *J* = 8.1, 5.8 Hz, 1H), 2.02 (s, 3H), 1.71 (dd, *J* = 9.8, 5.8 Hz, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.3, 169.6, 150.0, 142.0, 110.6, 108.6, 52.5, 40.3, 27.0, 23.3, 20.8 ppm; **MS:** (ESI+) $C_{11}H_{14}NO_4Na^+$ ($M+Na^+$) calc.:224.0923, det.:224.0932; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3278, 2954, 1734, 1662, 1529, 1437, 1372, 1333, 1283, 1199, 1163, 1076, 1009, 884, 815, 738.

(Trans)-methyl 1-acetamido-2-(pyridine-3´-yl)cyclopropane-1-carbocylate (4h)



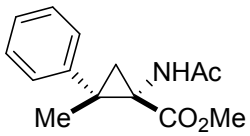
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.49 (d, *J* = 3.9 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.31 (dd, *J* = 7.8, 4.9 Hz, 1H), 6.46 (s, 1H), 3.40 (s, 3H), 2.86 (t, *J* = 9.1 Hz, 1H), 2.23 (dd, *J* = 8.6, 5.8 Hz, 1H), 2.07 (s, 3H), 1.71 (dd, *J* = 9.7, 5.7 Hz, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.5, 169.8, 150.1, 147.7, 137.8, 123.2, 52.4, 40.3, 32.5, 23.4, 20.4 ppm; **MS:** (ESI+) $C_{12}H_{15}N_2O_3^+$ (M^+) calc.:235.1077, det.:235.1073; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3240, 3027, 2160, 1731, 1664, 1534, 1483, 1437, 1372, 1337, 1285, 1197, 1160, 1029, 821, 714.

(Trans)-methyl 1-acetamido-2-(E)-styryl)cyclopropane-1-carboxylate (4i)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 3H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.15 (dd, *J* = 15.9, 9.0 Hz, 3H), 6.13 (s, 1H), 3.71 (s, 3H), 2.28 (dd, *J* = 17.5, 8.9 Hz, 1H), 2.01 (s, 3H), 1.99 (dd, *J* = 8.1, 5.8 Hz, 1H), 1.62 (dd, *J* = 9.4, 5.6 Hz, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.0, 170.8, 137.1, 133.2, 128.7, 127.5, 126.2, 125.5, 52.7, 40.7, 34.1, 24.0, 23.4. **MS:** (ESI+) $C_{15}H_{17}NO_3Na^+$ ($M+Na^+$) calc.:282.1106, det.:282.1116; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3299, 1731, 1664, 1534, 1439, 1335, 1197, 1158, 695.

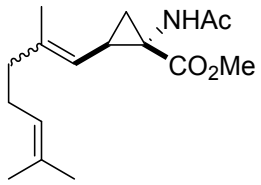
(Trans)-methyl 1-acetamido-2-methyl-2-phenylcyclopropane-1-carboxylate (4j)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 5H), 6.24 (s, 1H), 3.19 (s, 3H), 2.36 (d, *J* = 5.7 Hz, 2H), 2.07 (s, 3H), 1.51 (s, 3H), 1.31 (d, *J* = 5.7 Hz, 2H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.6, 170.9, 142.0, 128.4, 128.4, 126.9,

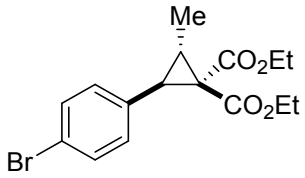
51.9, 43.8, 37.0, 26.3, 24.1, 23.4 ppm ; **MS:** (ESI+) $C_{14}H_{17}NO_3Na^+$ ($M+Na^+$) calc.:270.1106, det.:270.1113; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) =3280, 2989, 1730, 1662, 1604, 1524, 1497, 1436, 1371, 1319, 1263, 1199, 1101, 1085, 1065, 1026, 993, 922, 890, 815, 763, 734, 701.

(Trans)-methyl -1-acetamido-2-(2´,6´-dimethylhepta-1´,5´-dien-1´-yl)cyclopropane-1-carboxylate(4k)



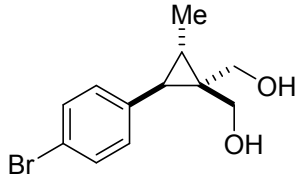
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.45 (s, 1H), 5.08 – 4.97 (m, 2H), 3.65 (s, 3H), 2.17 (dd, *J* = 17.5, 8.5 Hz, 1H), 2.04 – 1.98 (m, 4H), 1.96 (s, 3H), 1.77 (dd, *J* = 8.0, 5.3 Hz, 1H), 1.71 (s, 3H), 1.65 (s, 3H), 1.56 (s, 3H), 1.45 (dd, *J* = 9.6, 5.3 Hz, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.1, 171.1, 140.0, 131.6, 124.0, 119.7, 52.3, 40.5, 39.7, 29.5, 26.6, 25.7, 23.8, 23.2, 17.8, 16.8 ppm; **MS:** (ESI+) $C_{16}H_{25}NO_3Na^+$ ($M+Na^+$) calc.:302.1732, det.:302.1740; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) = 3279, 2914, 2342, 1732, 1663, 1534, 1437, 1374, 1336, 1287, 1196, 1167, 1107, 1027, 869,681.

(Trans)-diethyl 2-(4´-bromophenyl)-3-methylcyclopropane-1,1-dicarboxylate (5a)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 4.33 – 4.19 (m, 2H), 3.94 – 3.82 (m, 2H), 2.96 (d, *J* = 8.0 Hz, 1H), 2.48 (dq, *J* = 8.1, 6.3 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.9, 167.1, 134.5, 131.3, 130.5, 121.2, 61.7, 61.4, 43.5, 36.9, 25.0, 14.4, 14.0, 12.5 ppm; **MS:** (ESI+) $C_{16}H_{19}NO_4BrNa^+$ ($M+Na^+$) calc.:377.0364, det.:377.0364; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) **=** 2982, 2936, 1723, 1492, 1464, 1395, 1369, 1336, 1292, 1260, 1218, 1192, 1142, 1113, 1073, 1026, 1011, 861, 836, 802, 768, 698.

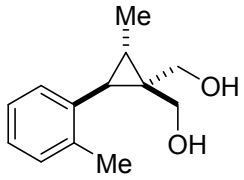
(Trans) 2-(4´-bromophenyl)-3-methylcyclopropane-1,1-diyl)dimethanol (6a)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 3.97 (d, *J* = 11.4 Hz, 1H), 3.82 (d, *J* = 11.4 Hz, 1H), 3.52 (d, *J* = 11.6 Hz, 1H), 3.35 (d, *J* = 11.5 Hz, 1H), 2.28 (s, 2H), 2.28 (s, 2H), 1.87 (d, *J* = 6.0 Hz, 1H), 1.44 – 1.38 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 3H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.3, 131.3, 130.5, 120.1, 66.8,

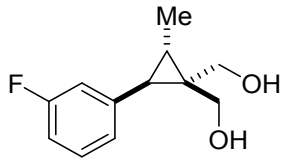
66.1, 34.5, 33.7, 20.7, 13.3. **MS:** (ESI+) $C_{12}H_{15}O_2BrNa^+$ ($M+Na^+$) calc.:293.0148, det.:293.0143 **FT-IR:** film, $\tilde{\nu}$ (cm^{-1})**=** 3351, 2937, 2874, 1491, 1396, 1194, 1071, 1033, 913, 840, 781, 701.

(Trans) 2-methyl-3-(o-tolyl)cyclopropane-1,1-diyl)dimethanol (6b)



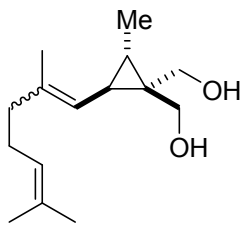
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 – 7.07 (m, 4H), 4.16 (d, *J* = 11.4 Hz, 1H), 3.85 (d, *J* = 11.4 Hz, 1H), 3.43 (d, *J* = 11.5 Hz, 1H), 3.38 (d, *J* = 11.5 Hz, 1H), 2.34 (s, 3H), 2.17 (s, 2H), 1.77 (d, *J* = 6.1 Hz, 1H), 1.52 (p, *J* = 6.2 Hz, 1H), 1.35 (d, *J* = 6.3 Hz, 3H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.1, 136.3, 129.9, 127.7, 126.5, 125.7, 67.2, 66.7, 33.9, 33.2, 20.0, 19.7, 13.5. **MS:** (ESI+) $C_{13}H_{18}O_2Na^+$ ($M+Na^+$) calc.:229.1199, det.:229.1195 **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) **=** 3371, 2924, 2160, 1981, 1458, 1087, 782, 734.

(Trans) 2-(3´-flurophenyl)-3-methylcyclopropane-1´,1´-diyl)dimethanol (6c)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (td, *J* = 7.9, 6.2 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.94 – 6.87 (m, 2H), 4.00 (d, *J* = 11.4 Hz, 1H), 3.84 (d, *J* = 11.4 Hz, 1H), 3.56 (d, *J* = 11.6 Hz, 1H), 3.40 (d, *J* = 11.6 Hz, 1H), 2.04 (s, 2H), 1.93 (d, *J* = 6.0 Hz, 1H), 1.45 (p, *J* = 6.2 Hz, 1H), 1.31 (d, *J* = 6.3 Hz, 3H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.9 (d, *J* = 246.0 Hz), 141.1 (d, *J* = 7.5 Hz), 129.9 (d, *J* = 8.5 Hz), 124.5 (d, *J* = 2.7 Hz), 115.7 (d, *J* = 21.2 Hz), 113.4 (d, *J* = 21.0 Hz), 67.0, 66.3, 34.9, 34.1, 20.9, 13.4 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.33 ppm; **MS:** (ESI+) $C_{12}H_{15}O_2FNa^+$ ($M+Na^+$) calc.:233.0948, det.:233.0944 **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) **=** 3707, 3681, 3666, 3355, 2940, 2982, 2973, 2923, 2053, 1614, 1586, 1490, 1455, 1434, 1346, 1332, 1322, 1271, 1145, 1013, 1013, 869, 789, 756, 693.

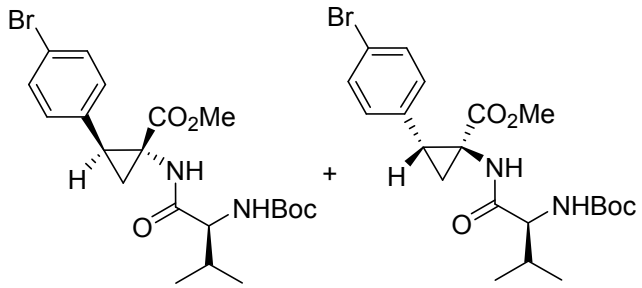
2-(2,6-dimethylhepta-1,5-dien-1-yl)-3-methylcyclopropane-1,1-diyl)dimethanol (6d)



^{1}H NMR (600 MHz, $CDCl_3$) δ 5.10 (s, 1H), 5.05 (tt, *J* = 6.6, 1.3 Hz, 1H), 4.96 (dd, *J* = 8.1, 1.2 Hz, 1H), 3.91 (d, *J* = 11.8 Hz, 1H), 3.89 (d, *J* = 11.8 Hz, 1H), 3.70 (d, *J* = 11.8 Hz, 1H), 3.54 (d, *J* = 11.8 Hz, 1H), 2.01-2.12 (m, 4H), 1.72

(s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.29-1.24 (m, 2H), 1.20 (d, *J* = 6.3 Hz, 3H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.7, 131.9, 124.0, 122.5, 68.1, 66.3, 39.4, 34.6, 28.1, 26.4, 25.7, 25.2, 17.7, 16.6, 13.4 ppm **MS:** (ESI+) $C_{15}H_{26}O_2Na^+$ ($M+Na^+$)= calc.:261.1830, det.:261.1835; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1}) **=** 3676, 3370, 2970, 2922, 1451, 1407, 1394, 1378, 1250, 1076, 1057, 892, 699.

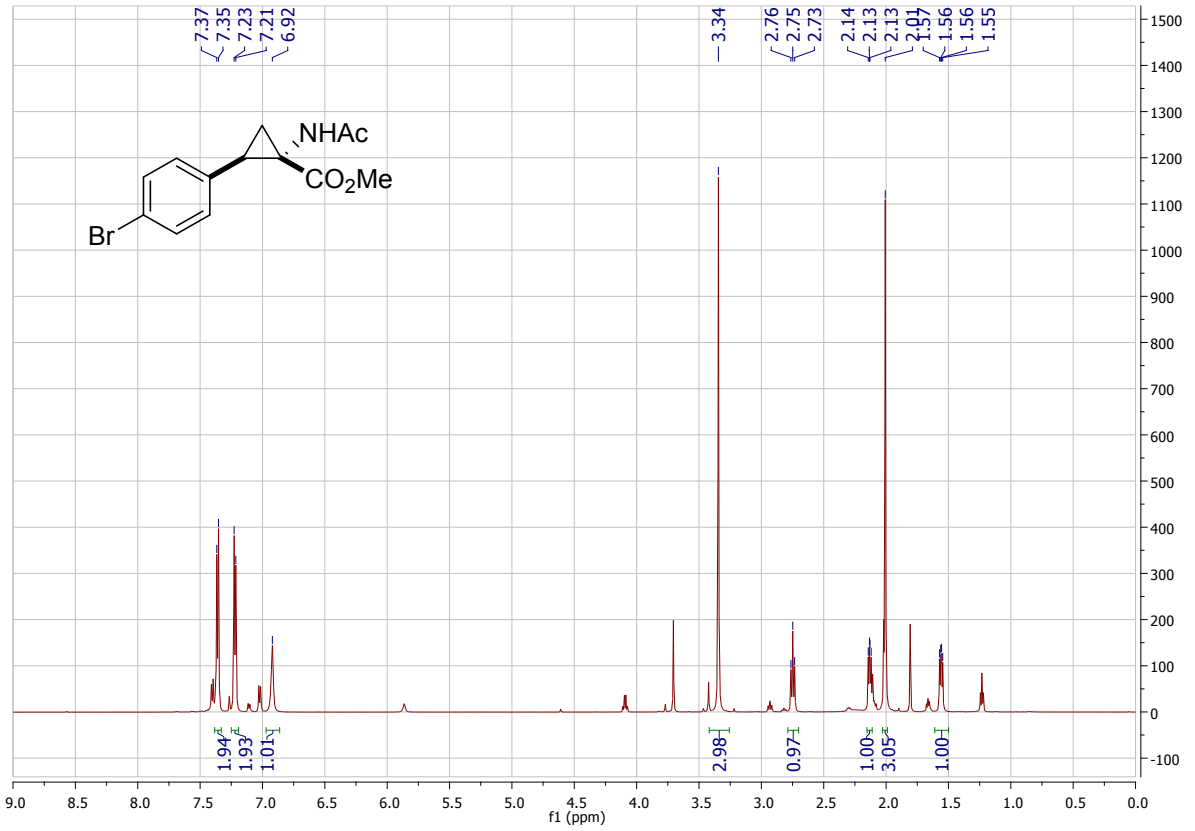
(Trans) 2-(4-bromophenyl)-1-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)cyclopropane-1-carboxylate (6a + 6b) methyl ester (*mixture of diastereoisomers*)

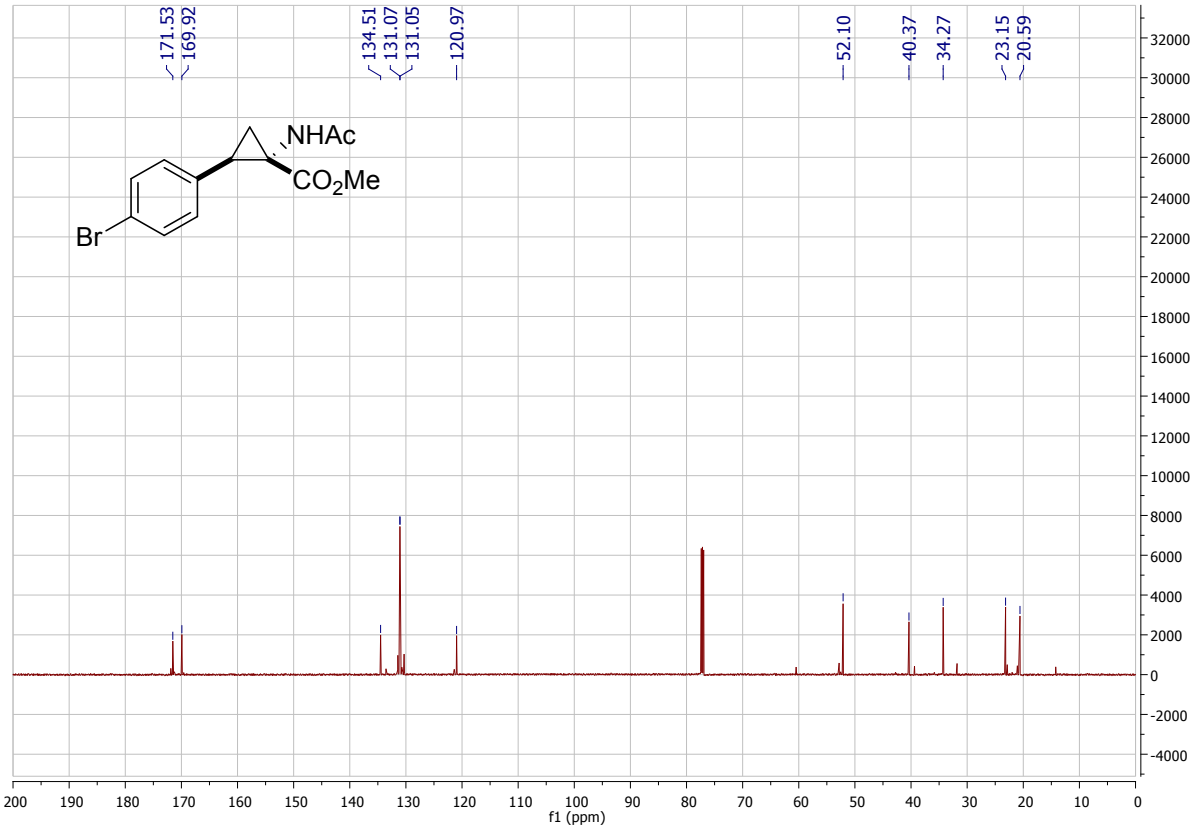


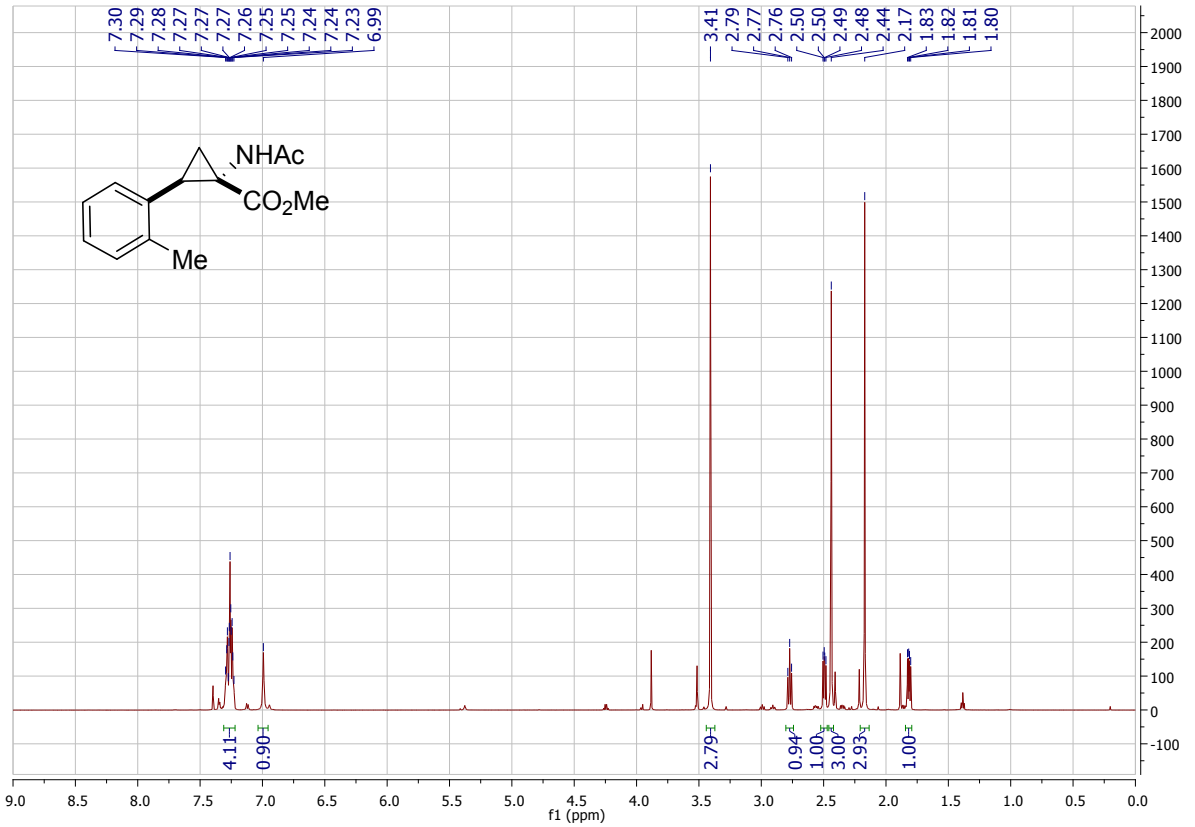
6a **6b**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.31 – 7.26 (m, 2H), 7.06 – 6.97 (m, 1H), 5.24 – 5.03 (m, 1H), 3.98 – 3.91 (m, 1H), 3.37 (d, 3H), 2.83 – 2.72 (m, 1H), 2.28 – 2.11 (m, 2H), 1.63 – 1.53 (m, 1H), 1.48 – 1.42 (m, 9H), 1.08 – 0.93 (m, 6H).ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.8, 169.4, 156.0, 134.3, 134.2, 131.6, 131.4, 131.1, 131.1, 131.1, 130.4, 130.3, 128.6, 121.0, 59.8, 52.7, 52.1, 52.0, 39.9, 39.8, 34.8, 34.6, 31.1, 30.6, 28.3, 20.7, 20.6, 19.3, 19.1, 17.9, 17.7 ppm; **MS:** (ESI+) $C_{21}H_{29}N_2O_5BrNa^+$ ($M+Na^+$) calc.:491.1158, det.:491.1167; **FT-IR:** film, $\tilde{\nu}$ (cm^{-1})**=** 3301, 2965, 1737, 1660, 1524, 1491, 1438, 1391, 1366, 1334, 1297, 1246, 1212, 1158, 1072, 1044, 1012, 910, 881, 833, 795, 733.

^{1}H- and ^{13}C-NMR spectra



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7.27
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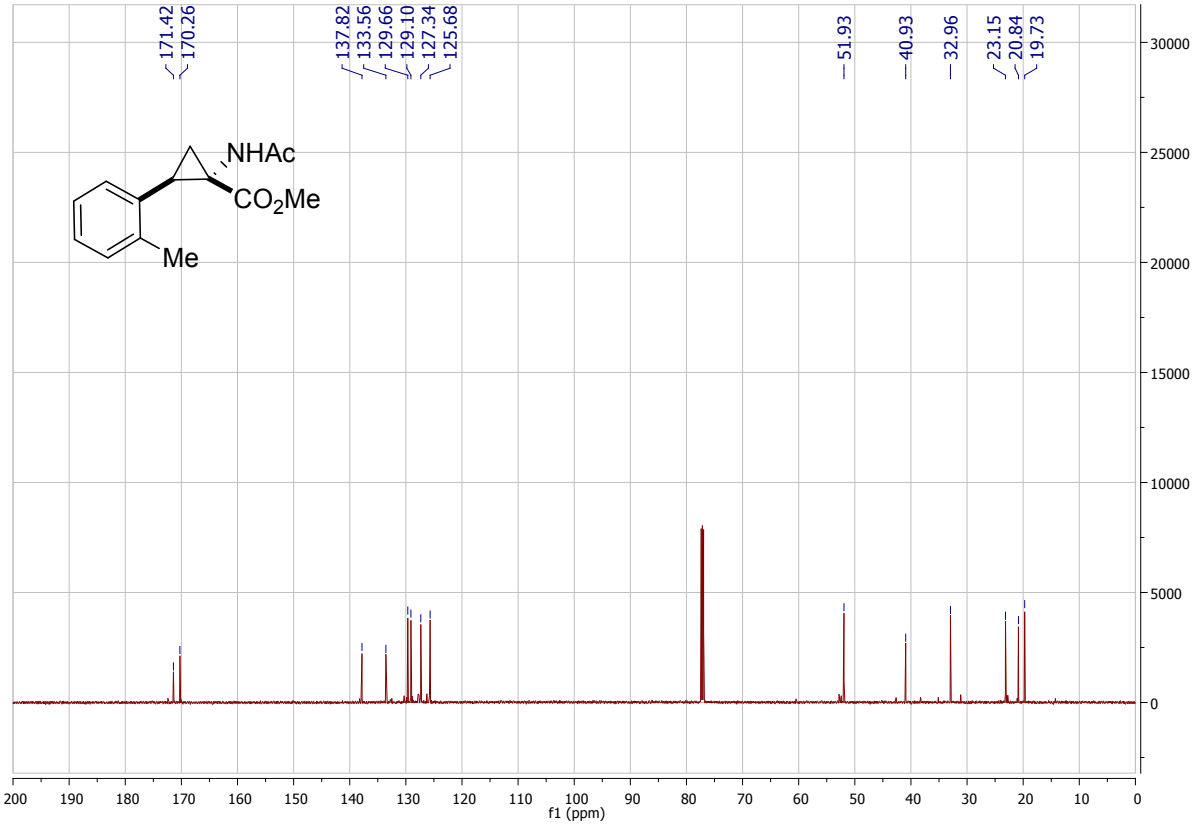
7.27
7.26
7.25
7.25
7.24
7.24
7.23
6.99
3.41
2.79
2.77
2.76
2.50
2.50
2.49
2.48
2.44
2.17
1.83
1.82
1.81
1.80
NHAc
CO2Me
Me
4.11
0.90
2.79
0.94
1.00
3.00
2.93
1.00
f1 (ppm)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129.10
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40.93
32.96
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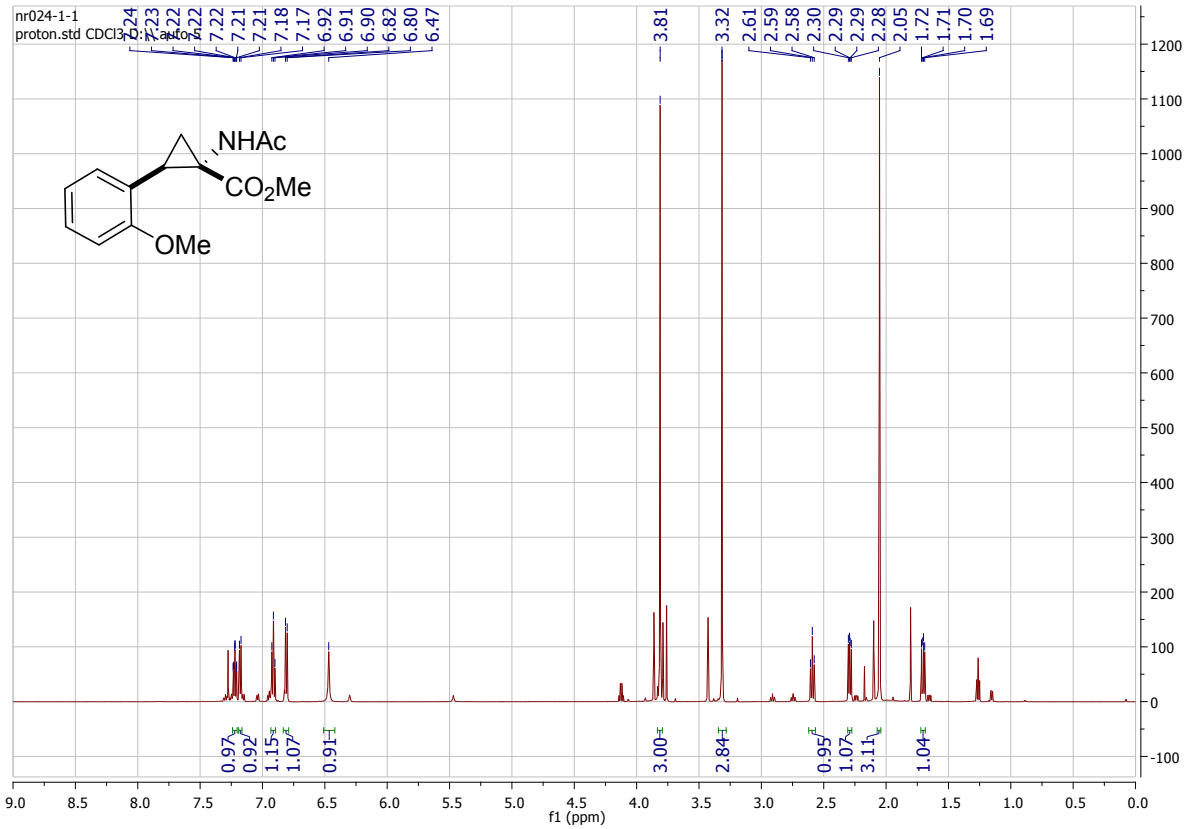
20.84
19.73
NHAc
CO2Me
Me
f1 (ppm)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proton.std CDCl3-D:\ aston-5
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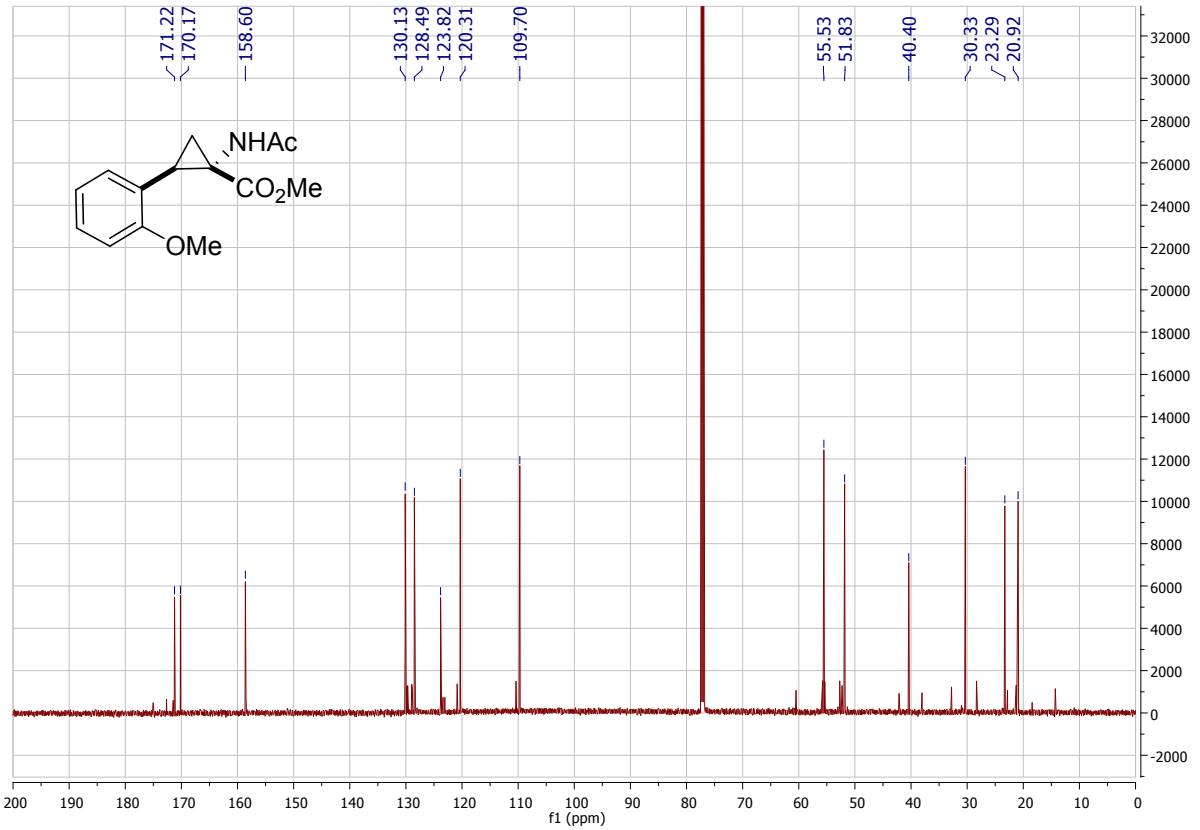
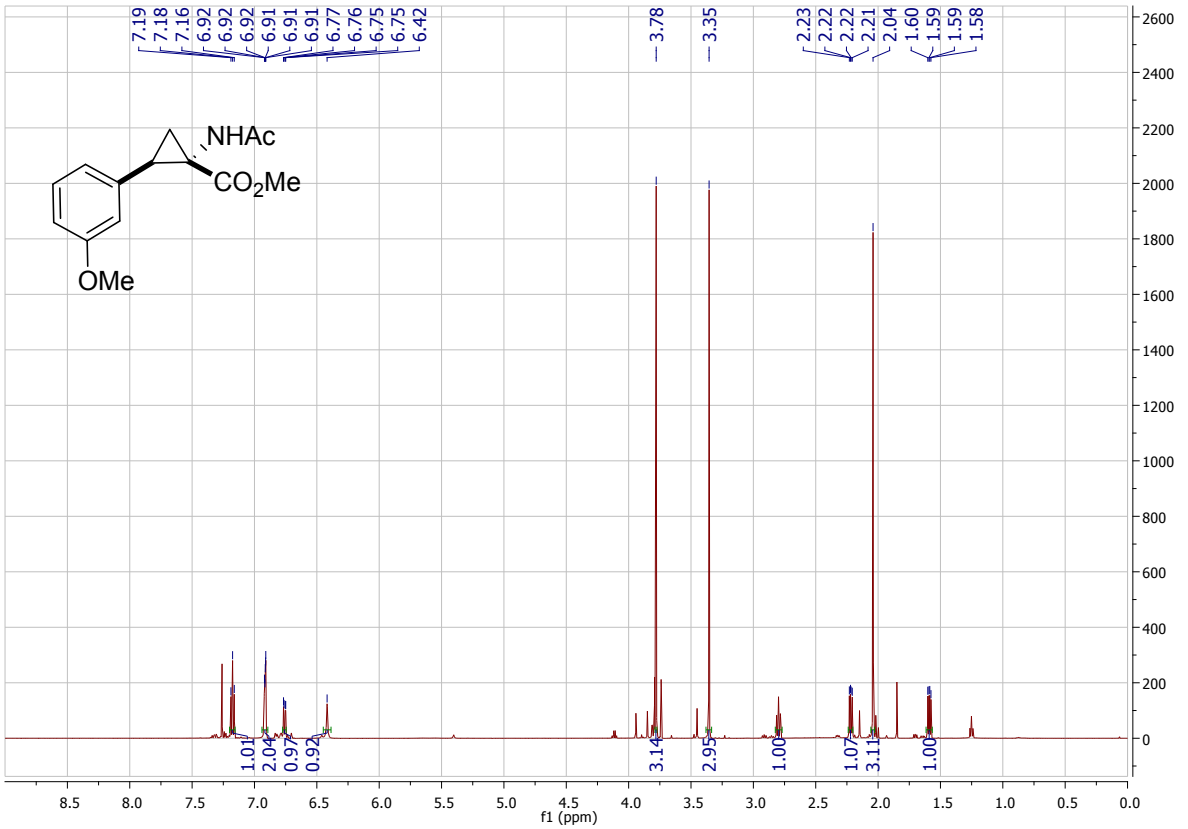
3.81 3.32 2.61 2.59 2.58 2.30 2.29 2.29 2.28 2.05 1.72 1.71 1.70 1.69
NHAc
CO2Me
OMe
0.97 0.92 1.15 1.07 0.91 3.00 2.84 0.95 1.07 3.11 1.04
f1 (ppm)


171.22 170.17 158.60 130.13 128.49 123.82 120.31 109.70 55.53 51.83 40.40 30.33 23.29 20.92
NHAc
CO2Me
OMe
f1 (ppm)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6.92
6.92
6.91
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6.77
6.76
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6.42
3.78
3.35
2.23
2.22
2.22
2.21
2.04
1.60
1.59
1.59
1.58
NHAc
CO2Me
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3.14
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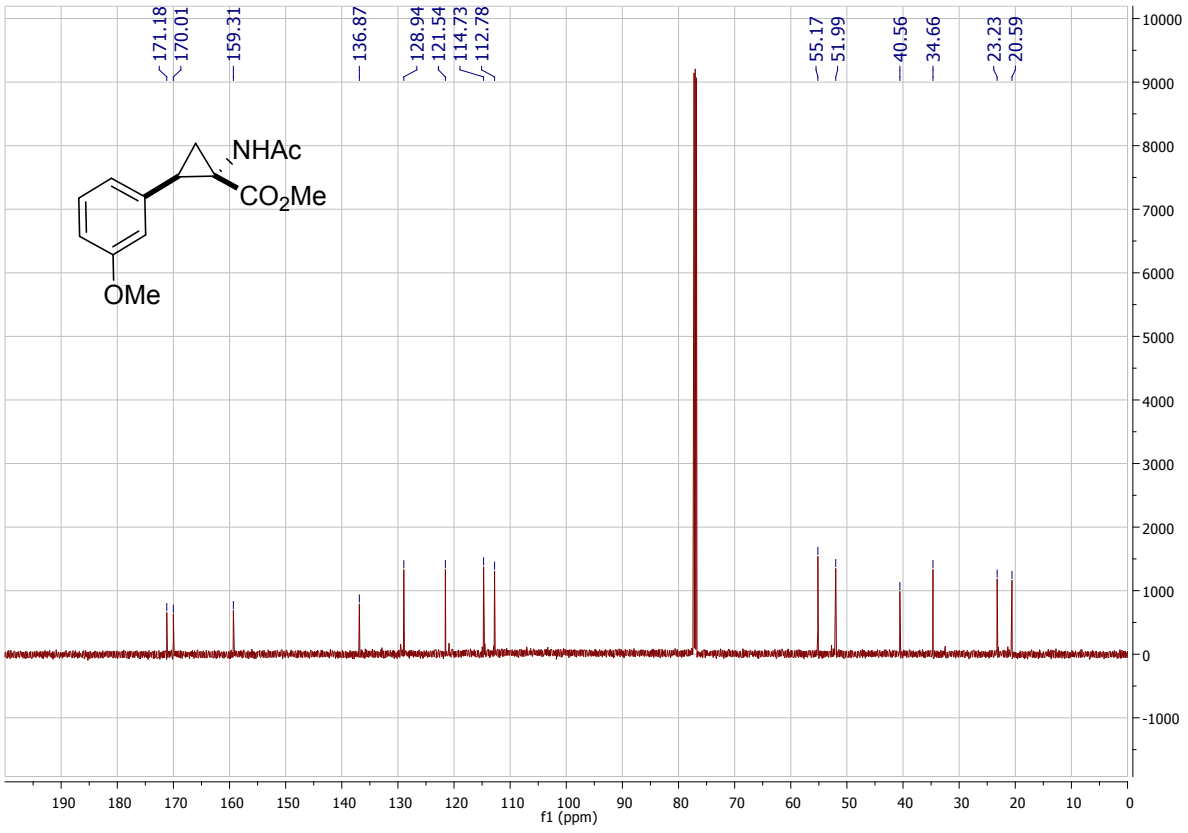
3.11
1.00
f1 (ppm)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20.59
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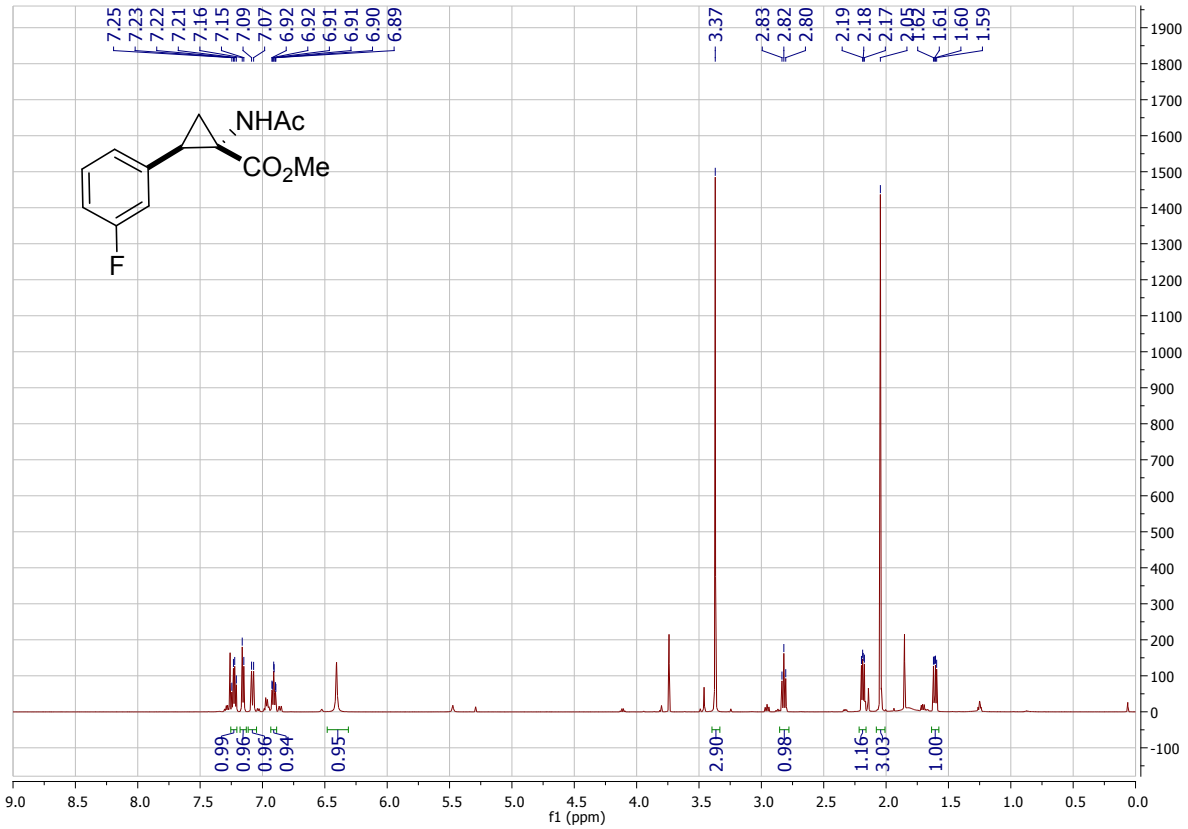
CO2Me
OMe
f1 (ppm)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7.23
7.22
7.21
7.16
7.15
7.09
7.07
6.92
6.92
6.91
6.91
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6.89
3.37
2.83
2.82
2.80
2.19
2.18
2.17
2.05
1.62
1.61
1.60
1.59
NHAc
CO2Me
F
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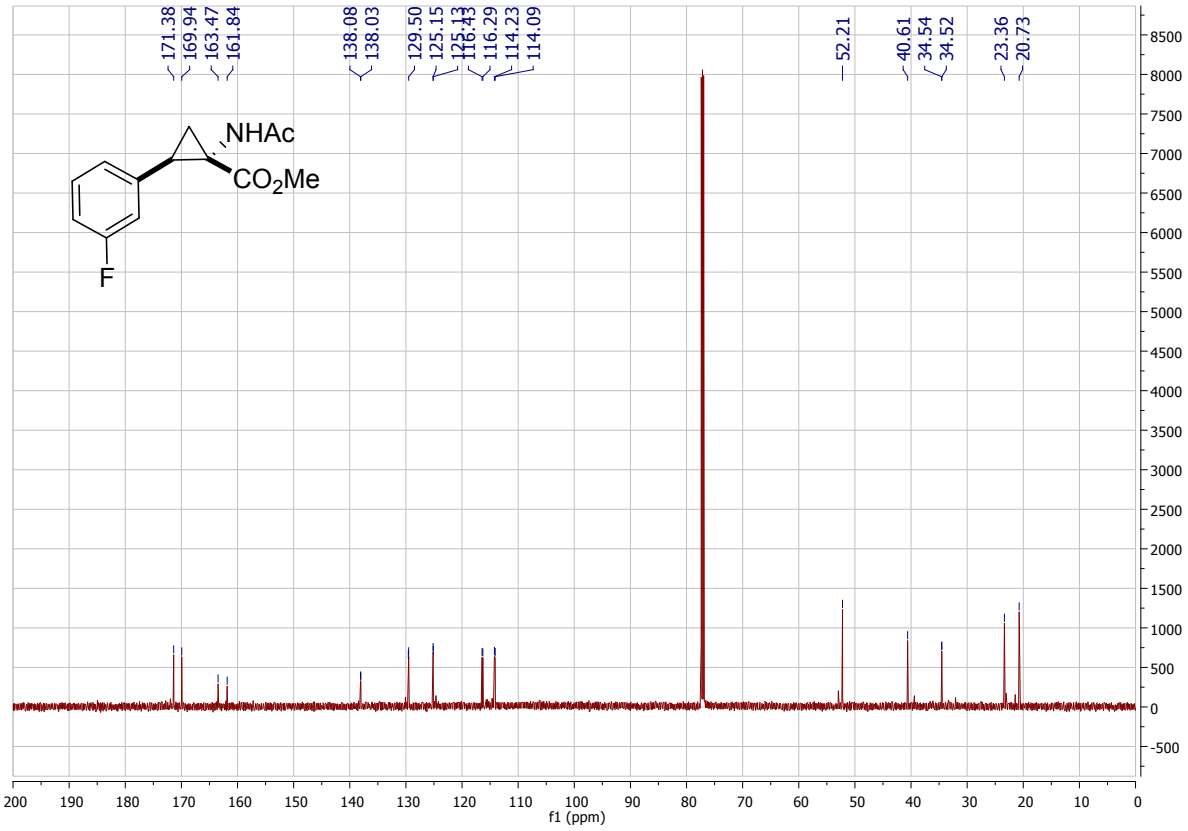
0.96
0.94
0.95
2.90
0.98
1.16
3.03
1.00
f1 (ppm)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125.15
116.29
114.23
114.09
52.21
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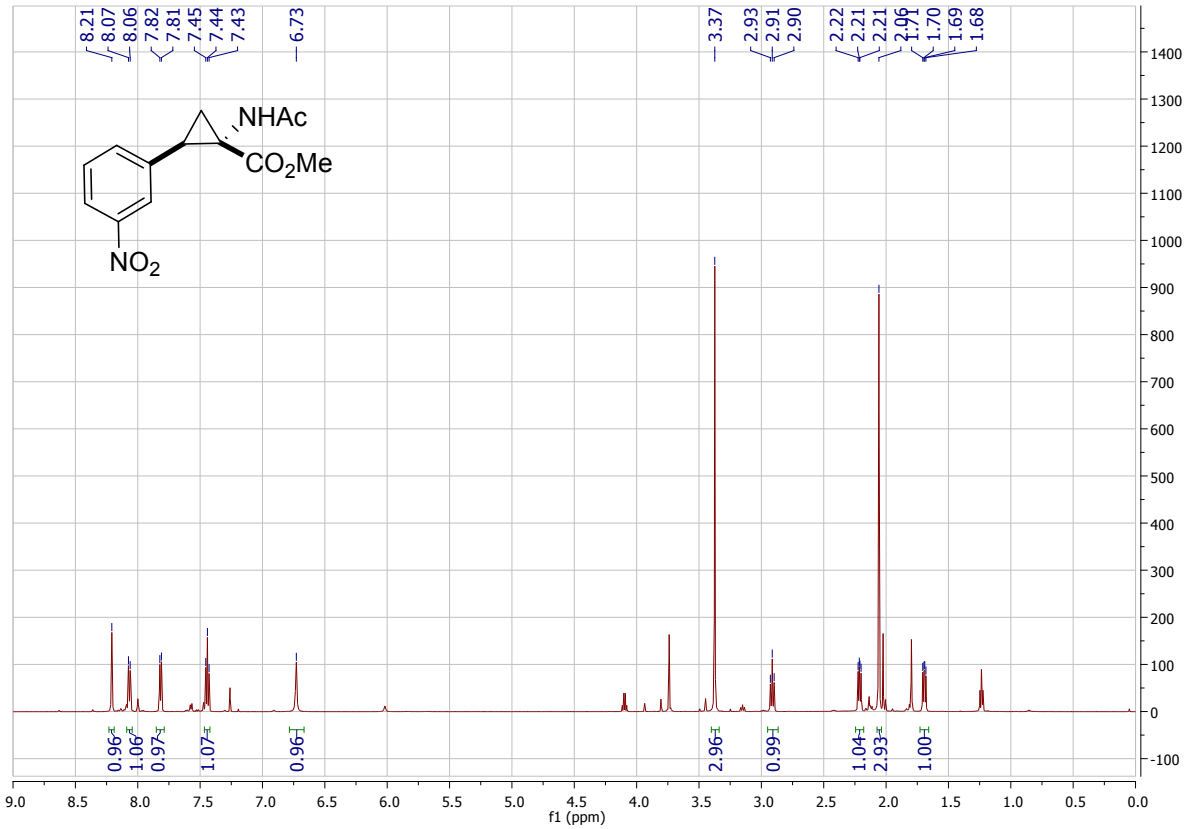
23.36
20.73
NHAc
CO2Me
F
f1 (ppm)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7.44
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3.37
2.93
2.91
2.90
2.22
2.21
2.21
2.06
1.71
1.70
1.69
1.68
NHAc
CO2Me
NO2
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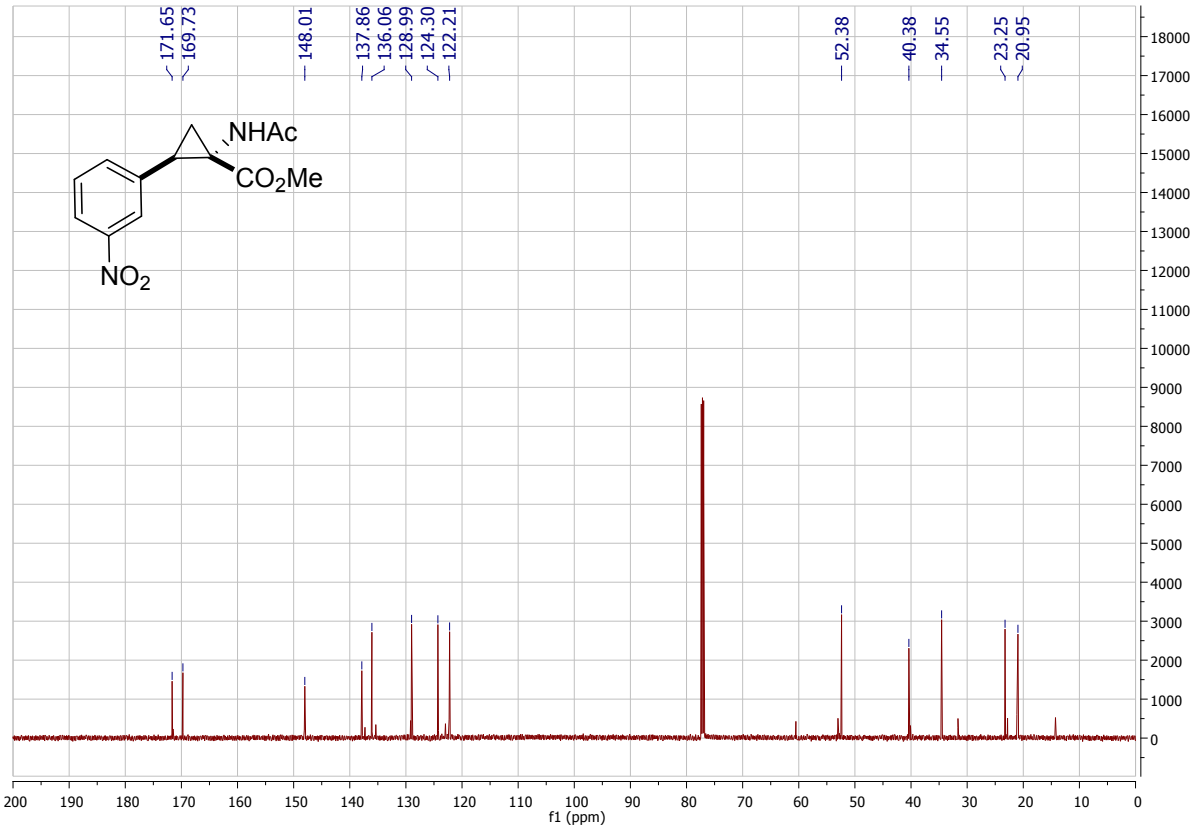
0.97
1.07
0.96
2.96
0.99
1.04
2.93
1.00
f1 (ppm)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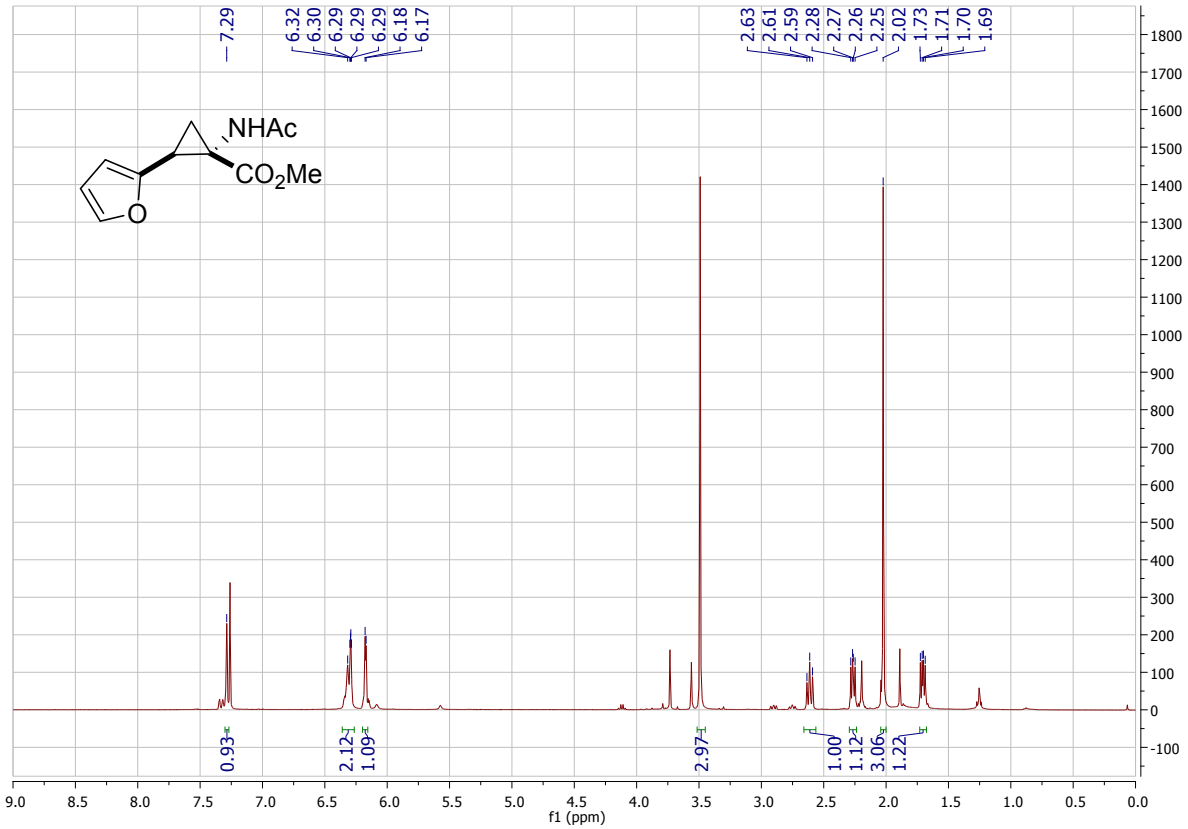
NHAc
CO2Me
NO2
f1 (ppm)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2.27
2.26
2.25
2.02
1.73
1.71
1.70
1.69
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O
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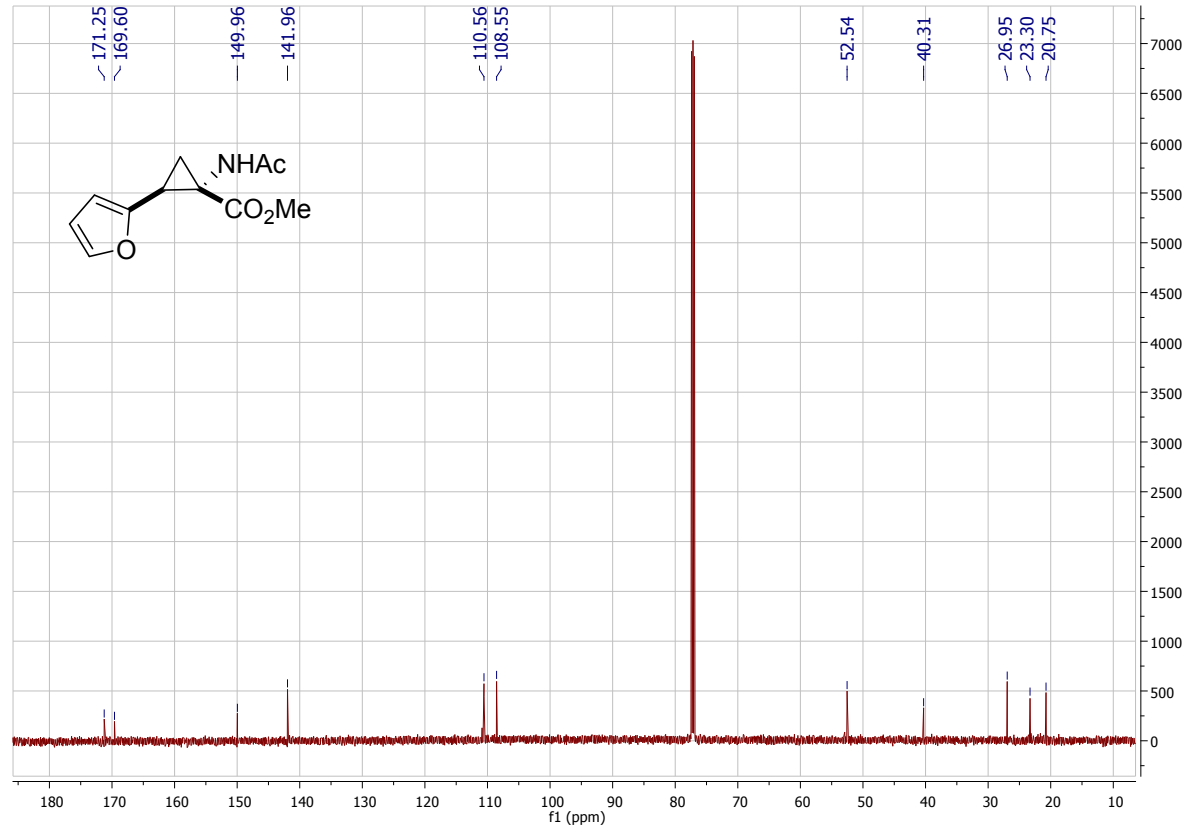
2.12
1.09
2.97
1.00
1.12
3.06
1.22
f1 (ppm)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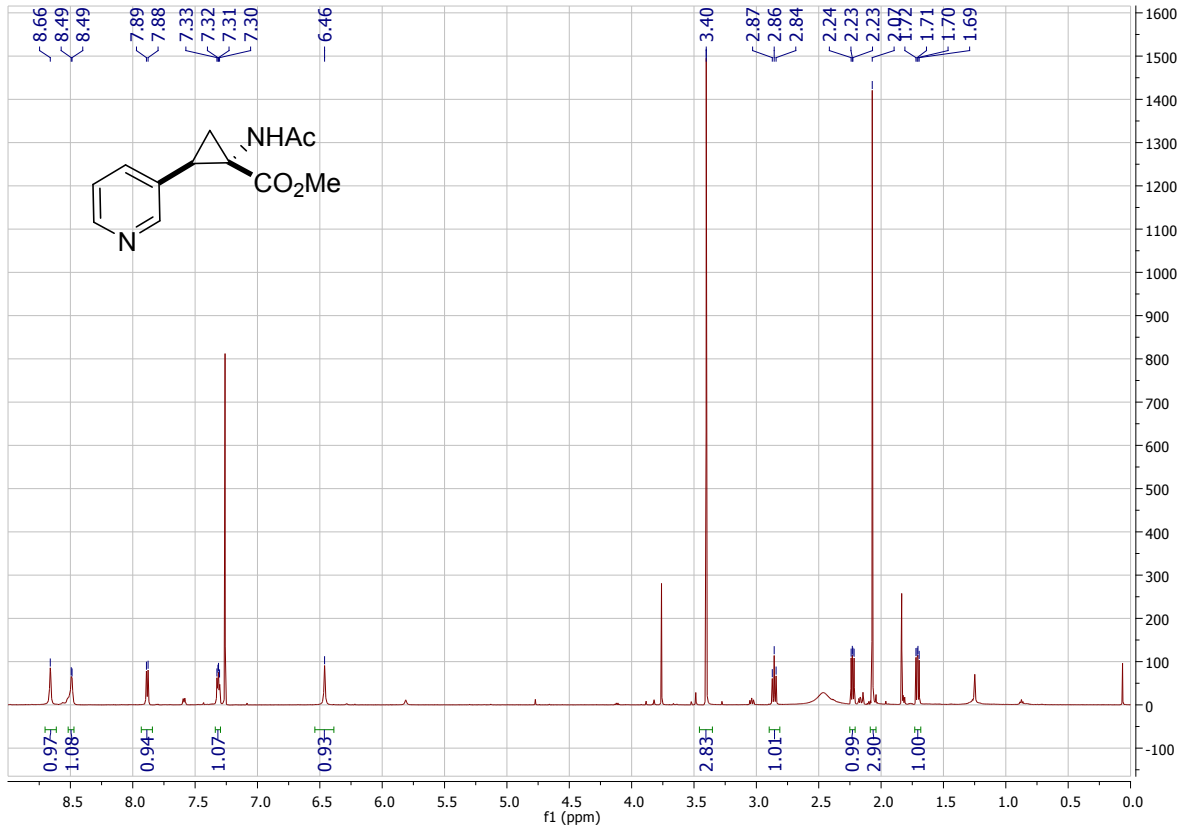
O
f1 (ppm)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2.23
2.23
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1.71
1.70
1.69
NHAc
CO2Me
N
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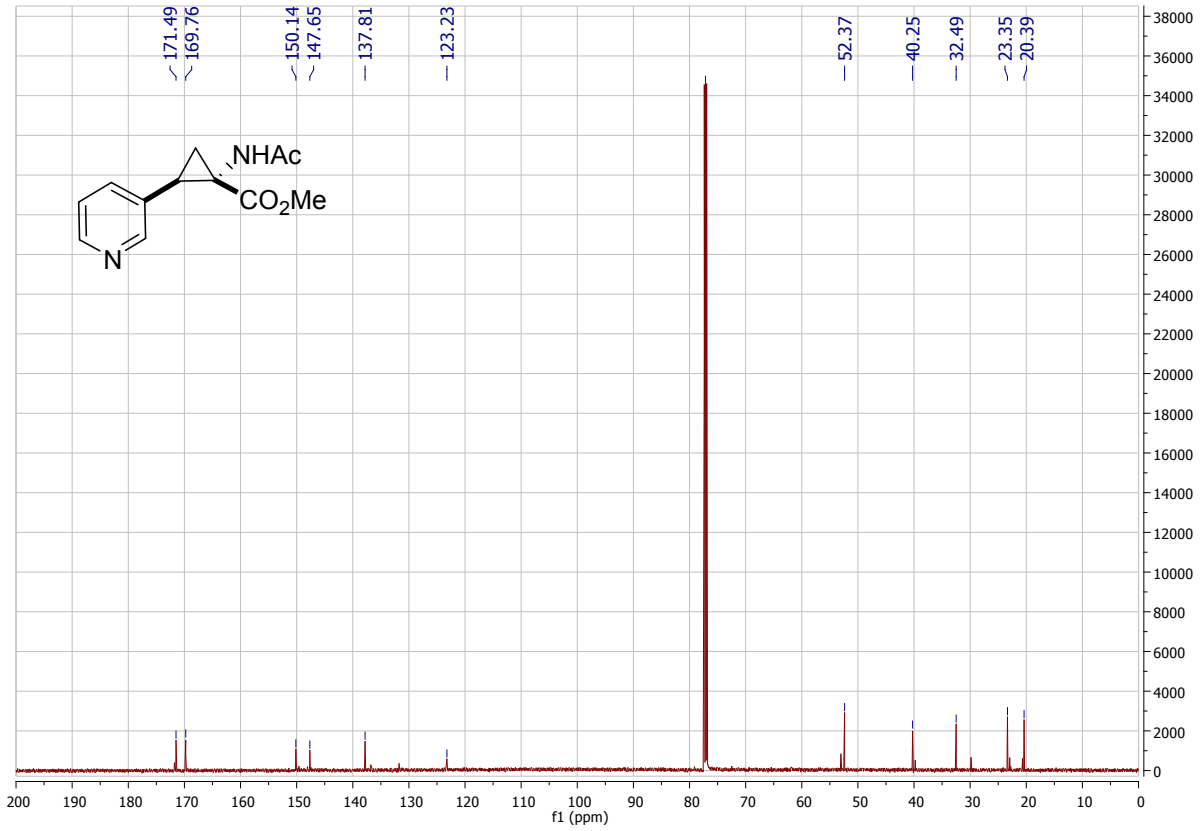
0.94
1.07
0.93
2.83
1.01
0.99
2.90
1.00
f1 (ppm)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NHAc
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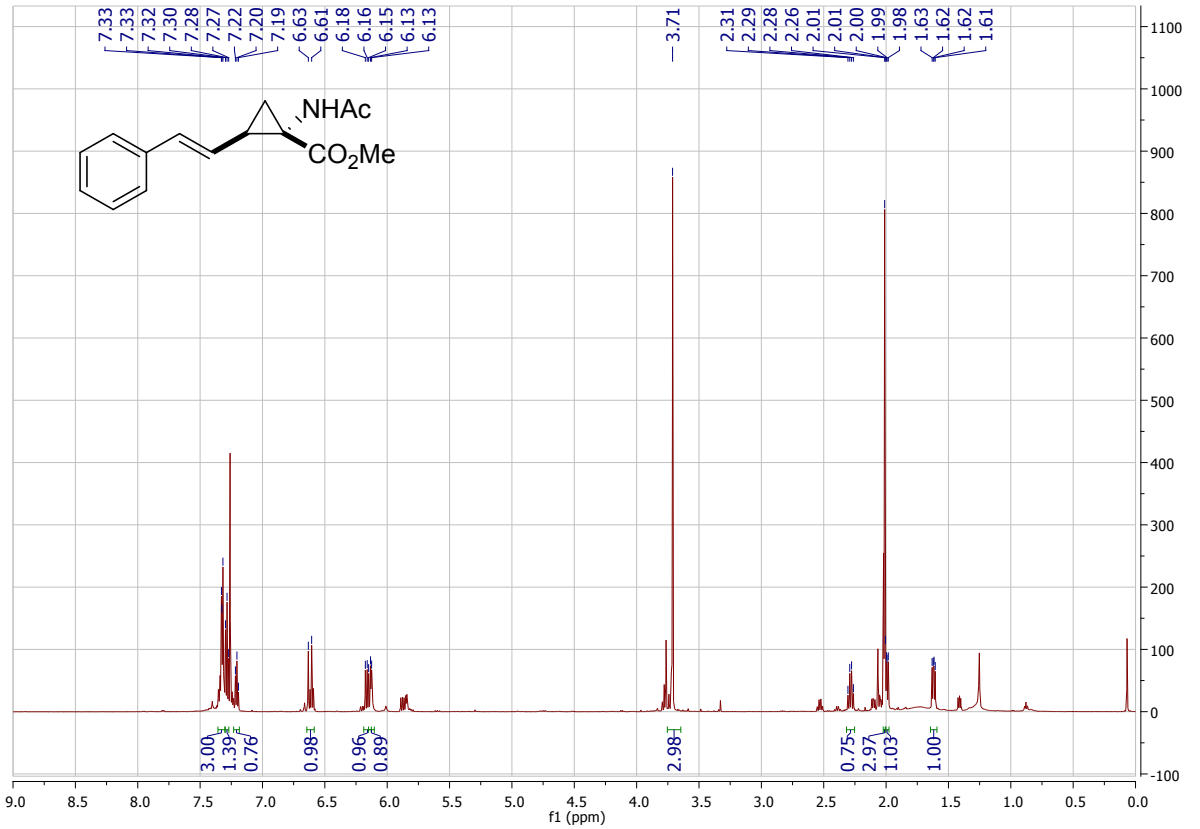
N
f1 (ppm)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6.13
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2.28
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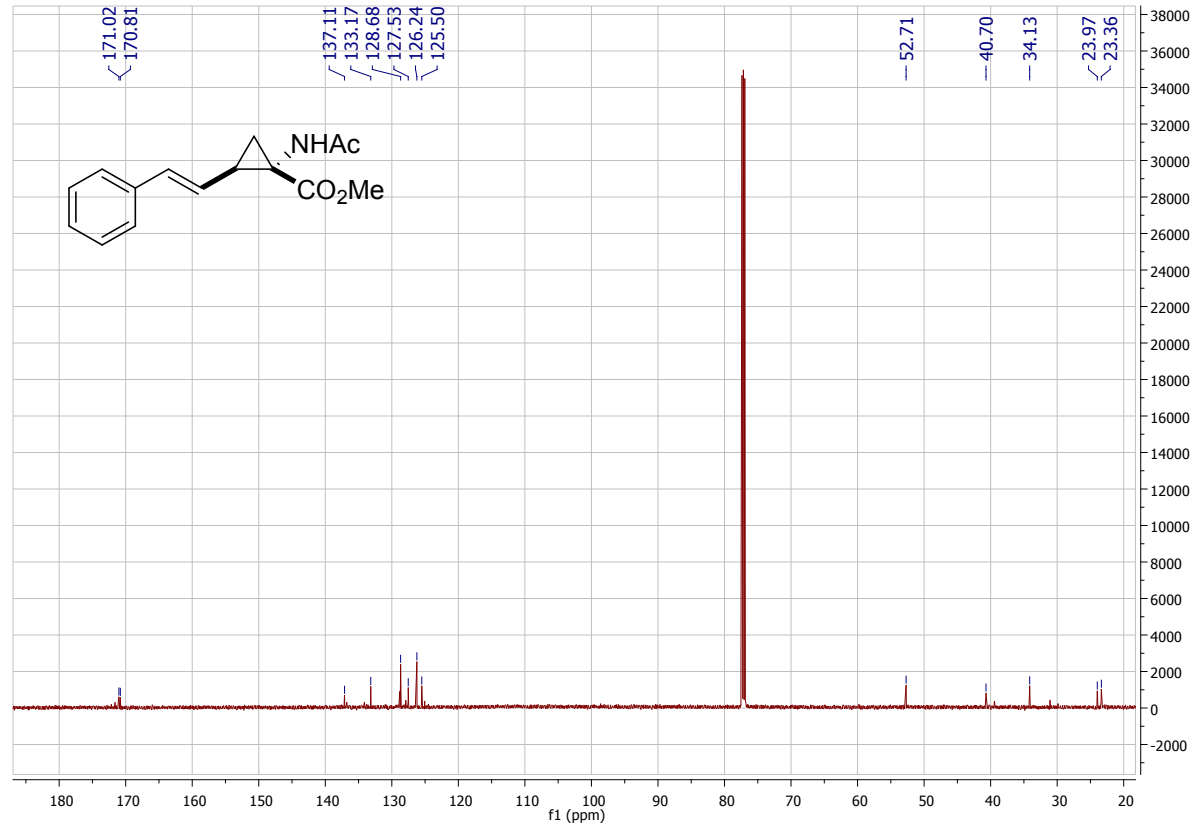
2.00
1.99
1.98
1.63
1.62
1.62
1.61
NHAc
CO2Me
3.00
1.39
0.76
0.98
0.96
0.89
2.98
0.75
2.97
1.03
1.00
f1 (ppm)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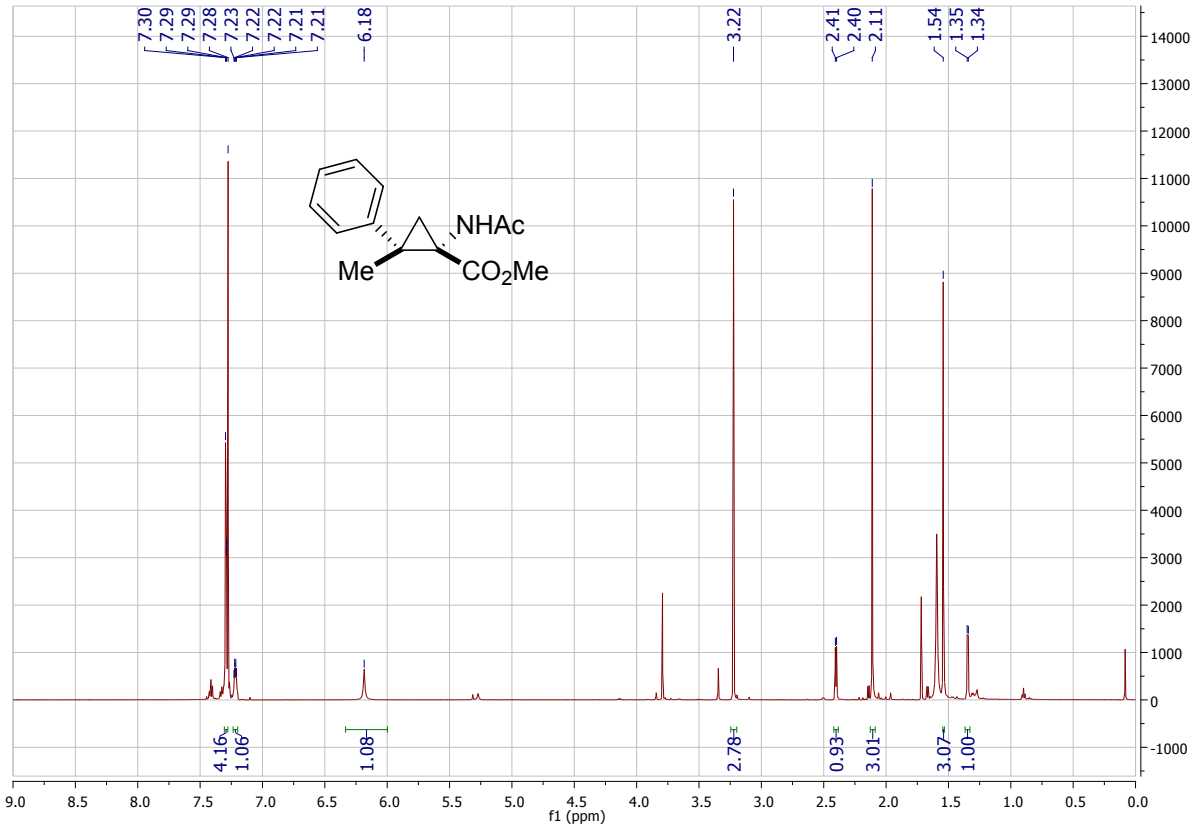
170.81
137.11
133.17
128.68
127.53
126.24
125.50
52.71
40.70
34.13
23.97
23.36
NHAc
CO2Me
f1 (ppm)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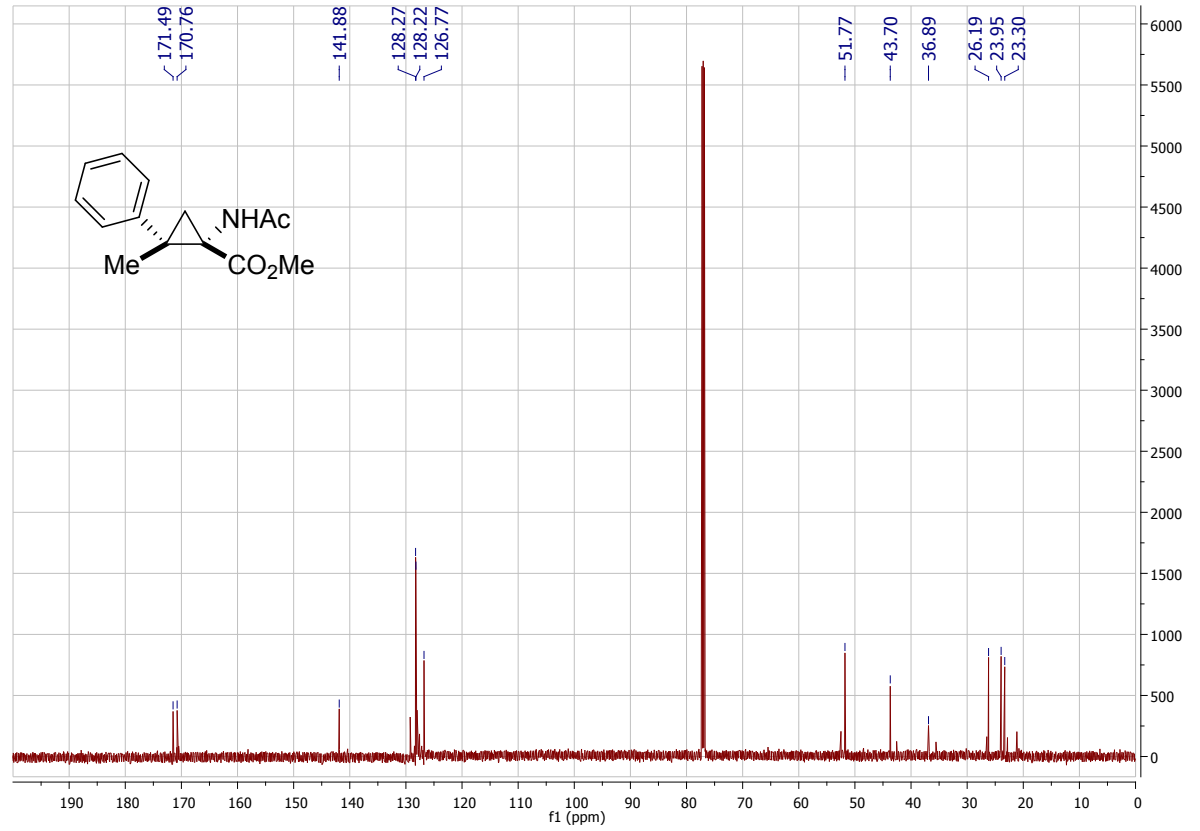
7.29
7.29
7.28
7.23
7.22
7.22
7.21
7.21
6.18
3.22
2.41
2.40
2.11
1.54
1.35
1.34
NHAc
Me
CO2Me
4.16
1.06
1.08
2.78
0.93
3.01
3.07
1.00
f1 (ppm)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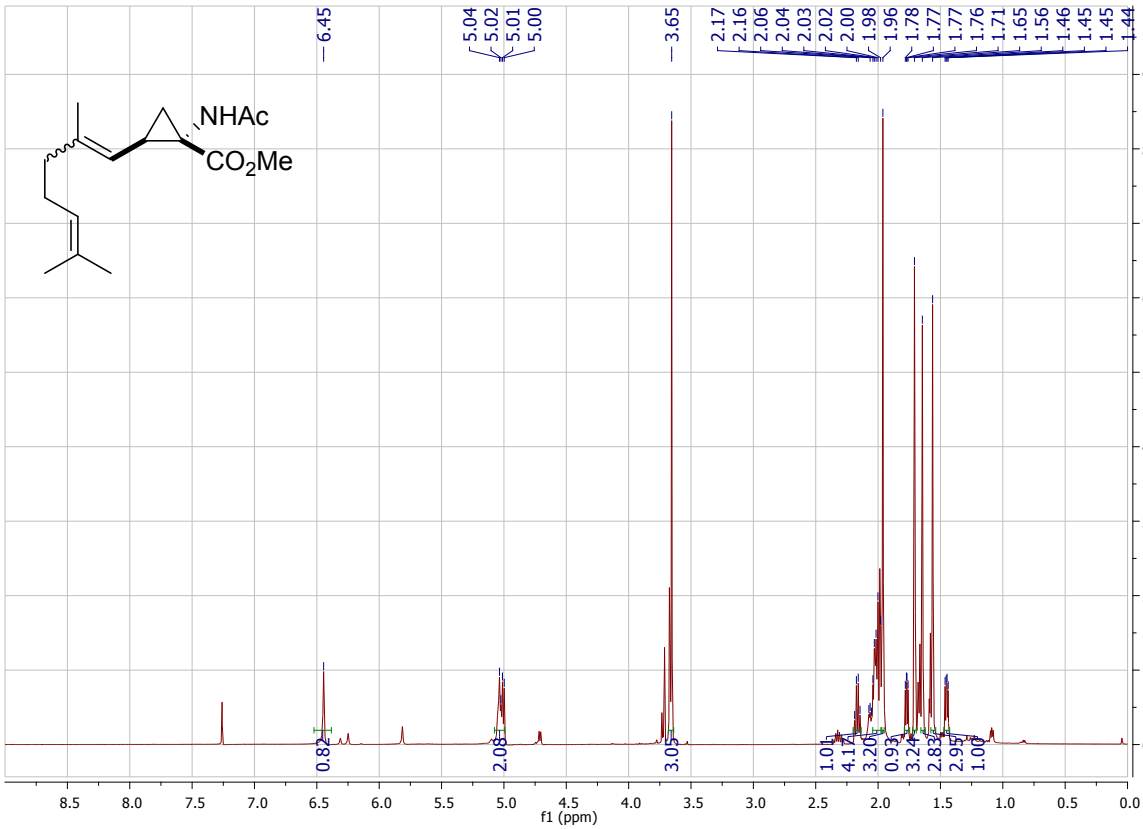
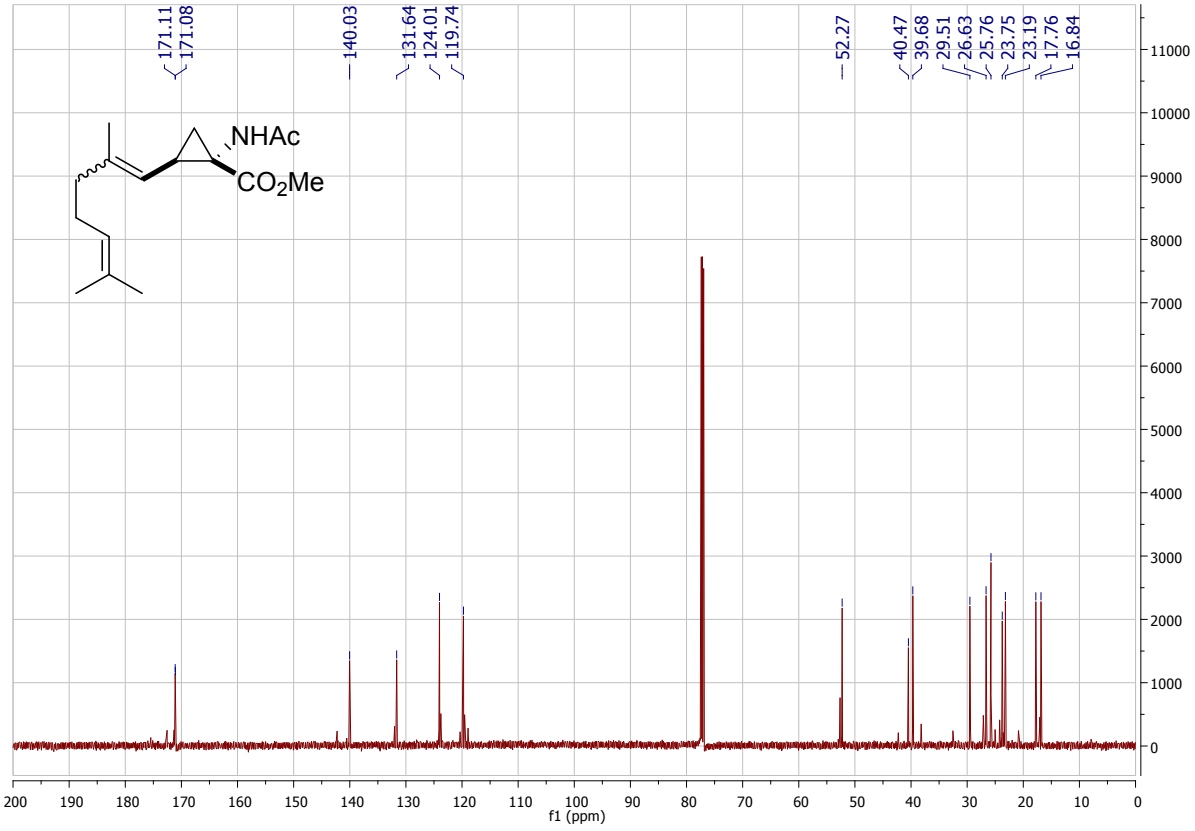
170.76
141.88
128.27
128.22
126.77
51.77
43.70
36.89
26.19
23.95
23.30
NHAc
Me
CO2Me
f1 (ppm)


NHAc
CO2Me
6.45
5.04
5.02
5.01
5.00
3.65
2.17
2.16
2.06
2.04
2.03
2.02
2.00
1.98
1.96
1.78
1.77
1.77
1.76
1.71
1.65
1.56
1.46
1.45
1.45
1.44
0.82
2.08
3.05
1.01
4.12
3.20
0.93
3.24
2.83
2.99
1.08
f1 (ppm)


NHAc
CO2Me
171.11
171.08
140.03
131.64
124.01
119.74
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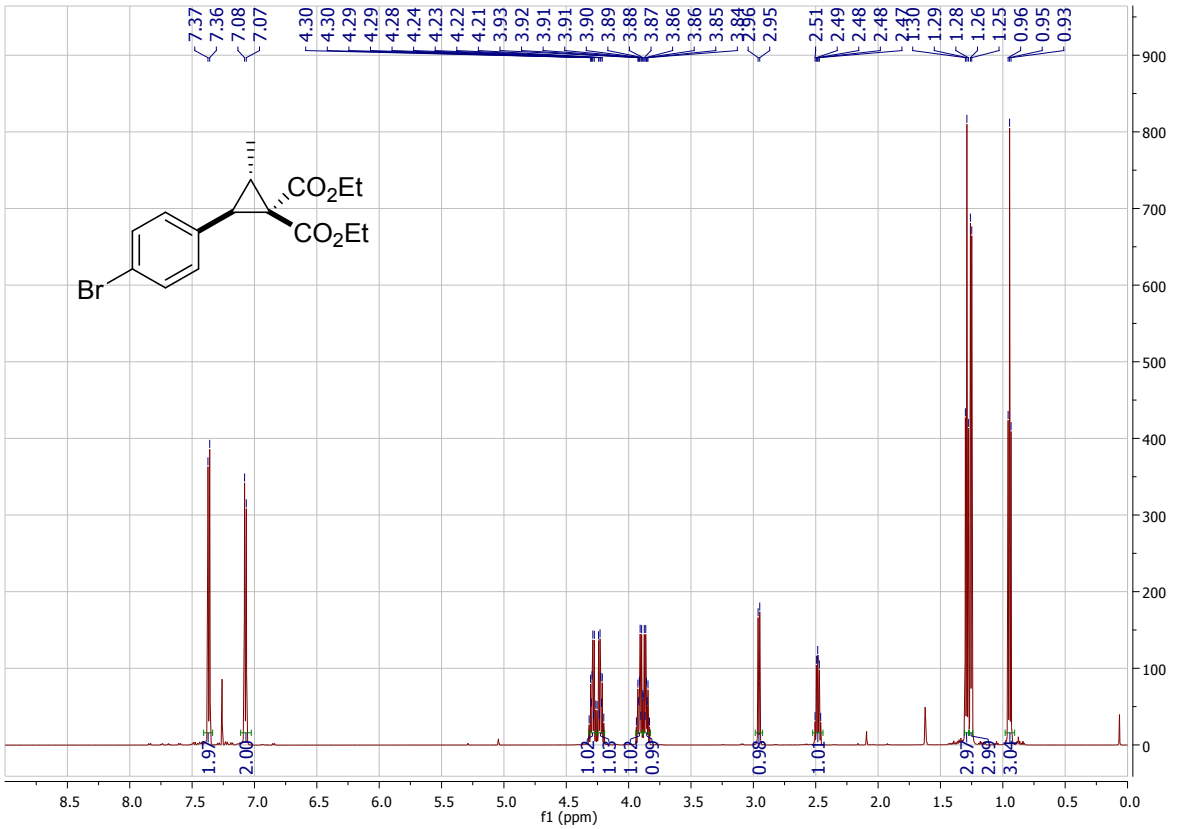
40.47
39.68
29.51
26.63
25.76
23.75
23.19
17.76
16.84
f1 (ppm)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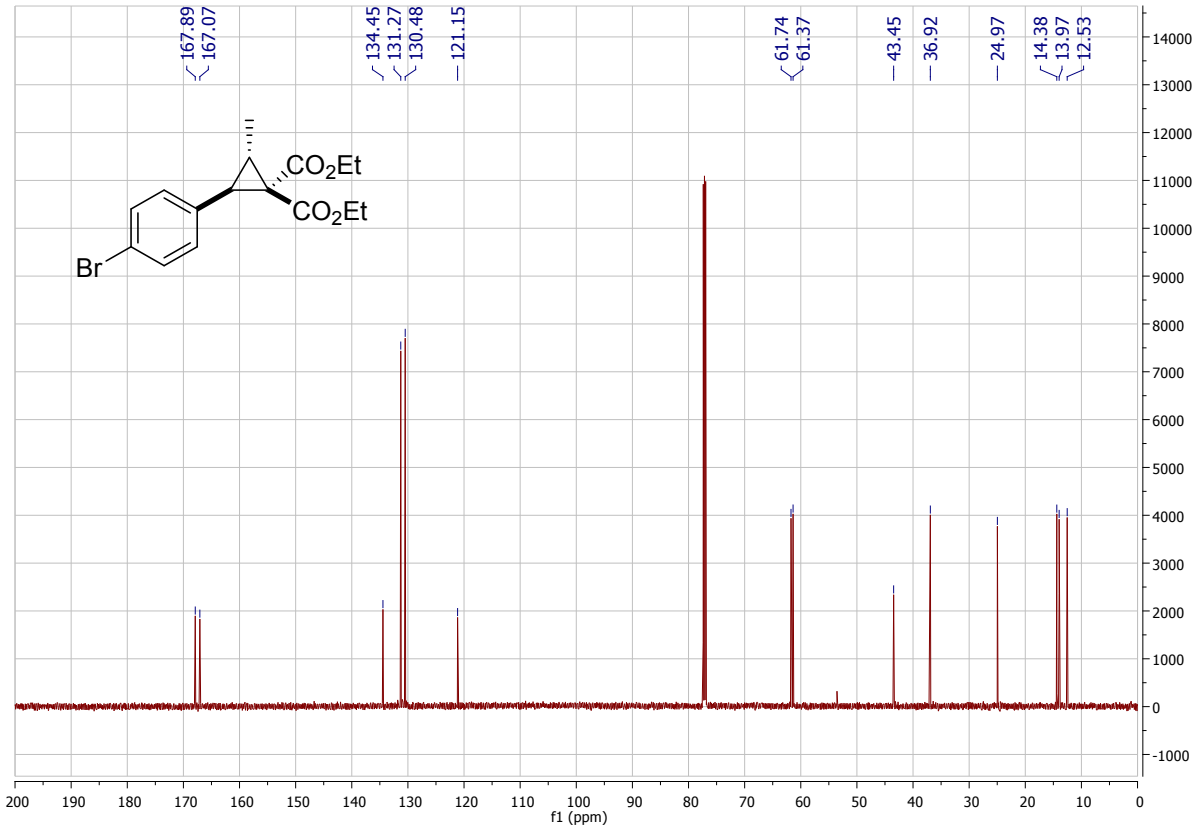
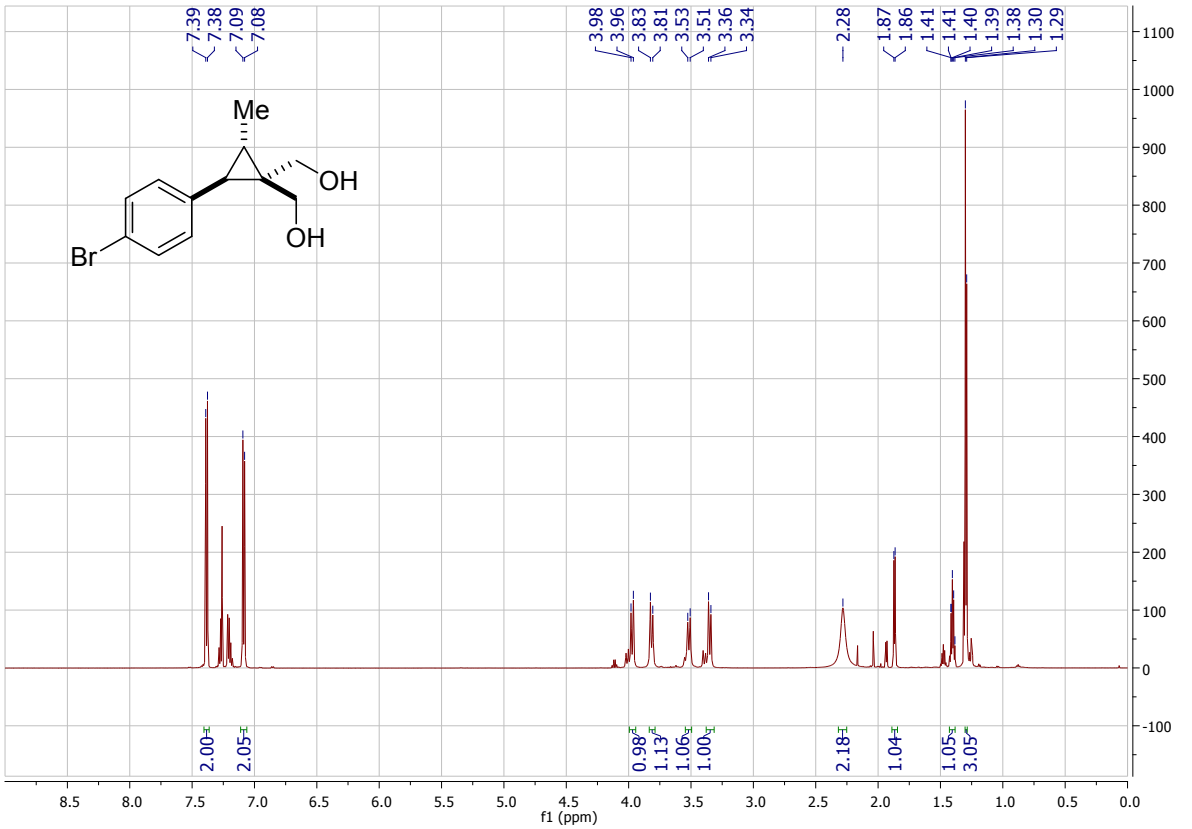
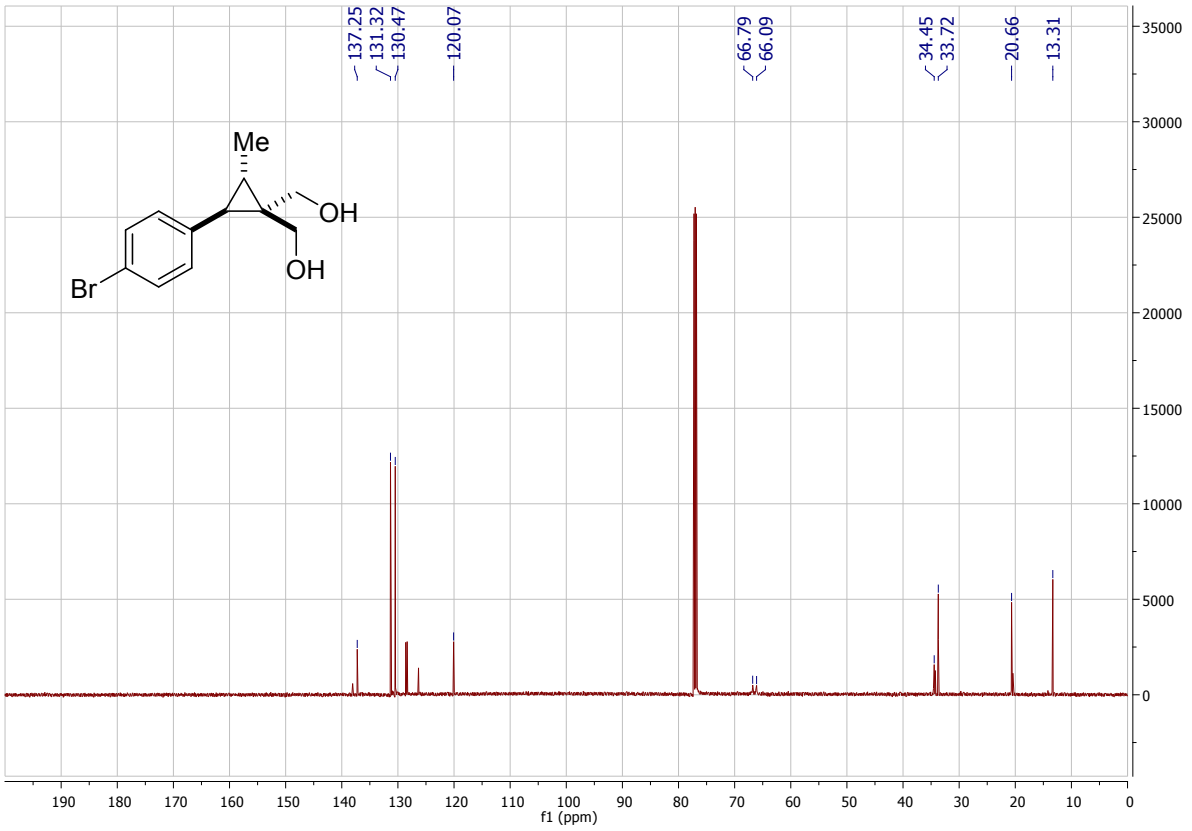
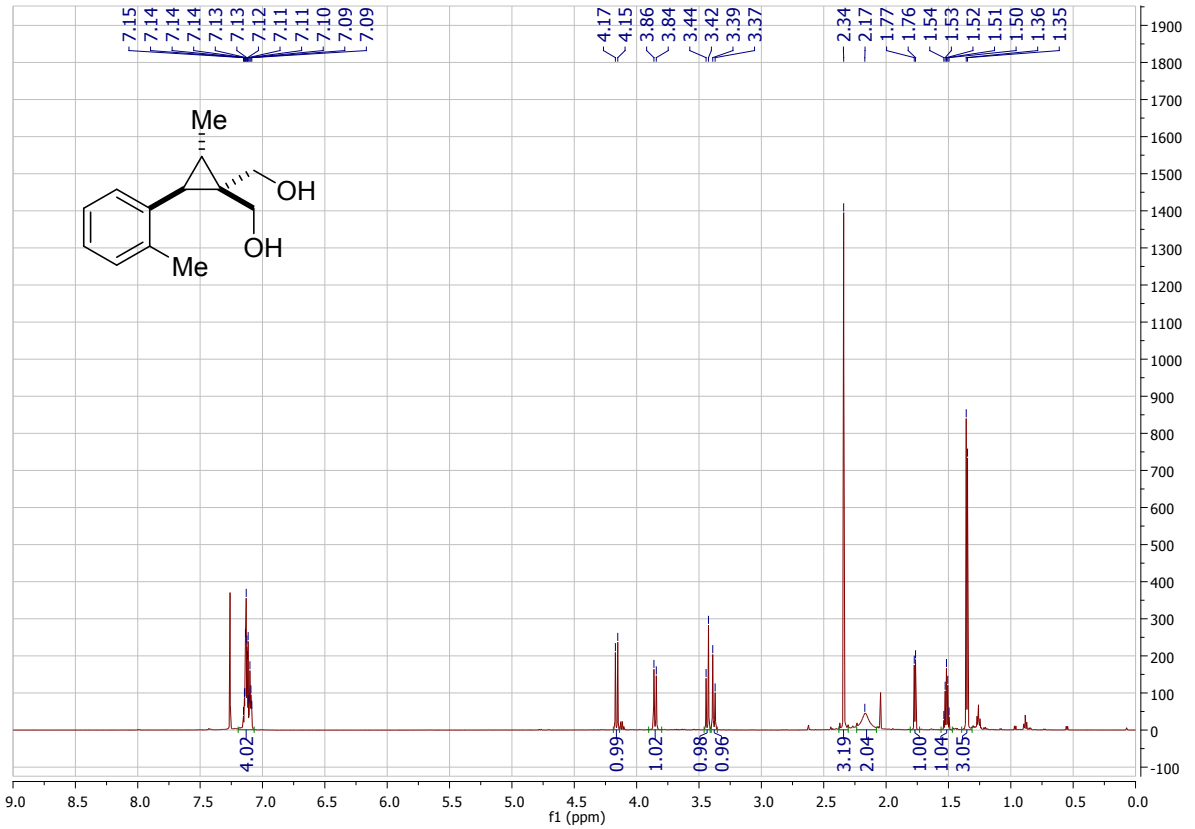
7.36
7.08
7.07
4.30
4.30
4.29
4.29
4.28
4.24
4.23
4.22
4.21
3.93
3.92
3.91
3.91
3.90
3.89
3.88
3.87
3.86
3.86
3.85
3.84
2.95
2.51
2.49
2.48
2.48
2.47
1.30
1.29
1.28
1.26
1.25
0.96
0.95
0.93
CO2Et
CO2Et
Br
1.97
2.00
1.02
1.03
1.02
0.99
0.98
1.01
2.97
2.99
3.04
f1 (ppm)


167.89
167.07
134.45
131.27
130.48
121.15
61.74
61.37
43.45
36.92
24.97
14.38
13.97
12.53
CO2Et
CO2Et
Br
f1 (ppm)


7.39
7.38
7.09
7.08
3.98
3.96
3.83
3.81
3.53
3.51
3.36
3.34
2.28
1.87
1.86
1.41
1.41
1.40
1.39
1.38
1.30
1.29
Me
OH
OH
Br
2.00
2.05
0.98
1.13
1.06
1.00
2.18
1.04
1.05
3.05
f1 (ppm)


137.25
131.32
130.47
120.07
66.79
66.09
34.45
33.72
20.66
13.31
Me
OH
OH
Br
f1 (ppm)


7.15
7.14
7.14
7.14
7.13
7.13
7.12
7.11
7.11
7.10
7.09
7.09
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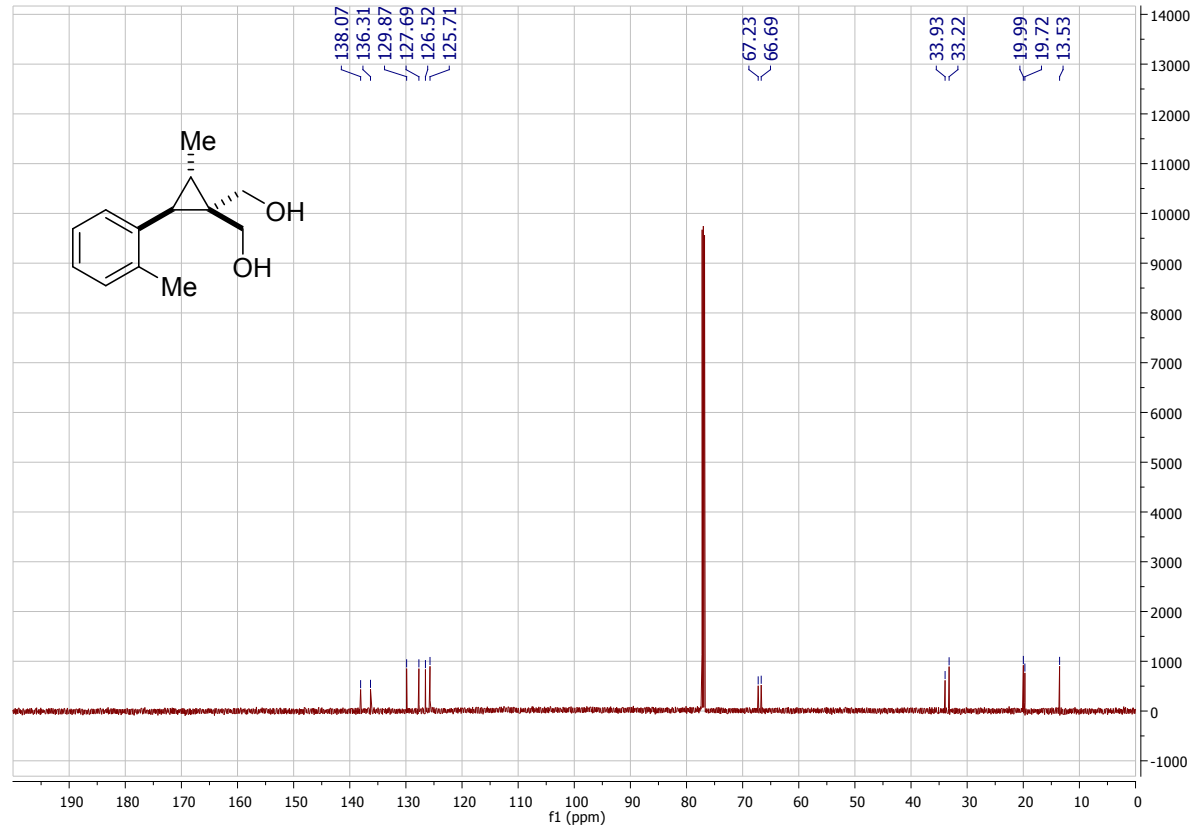
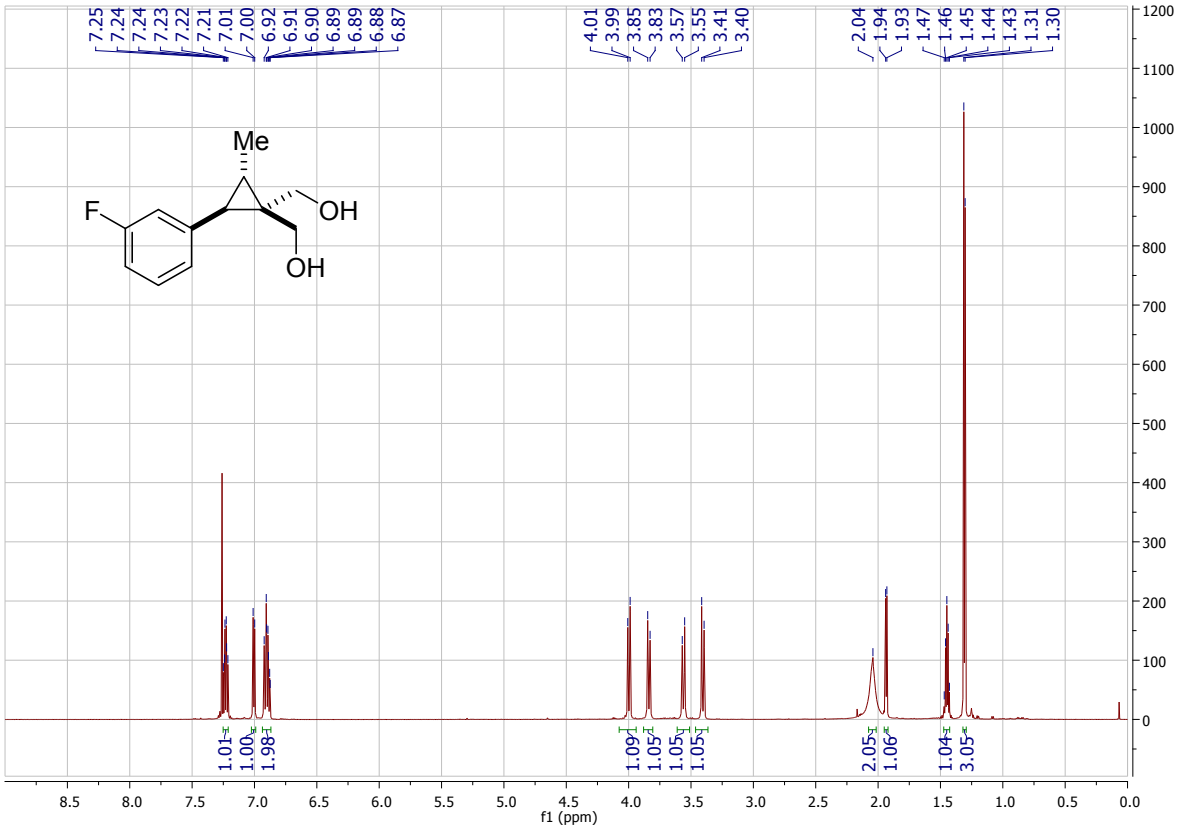
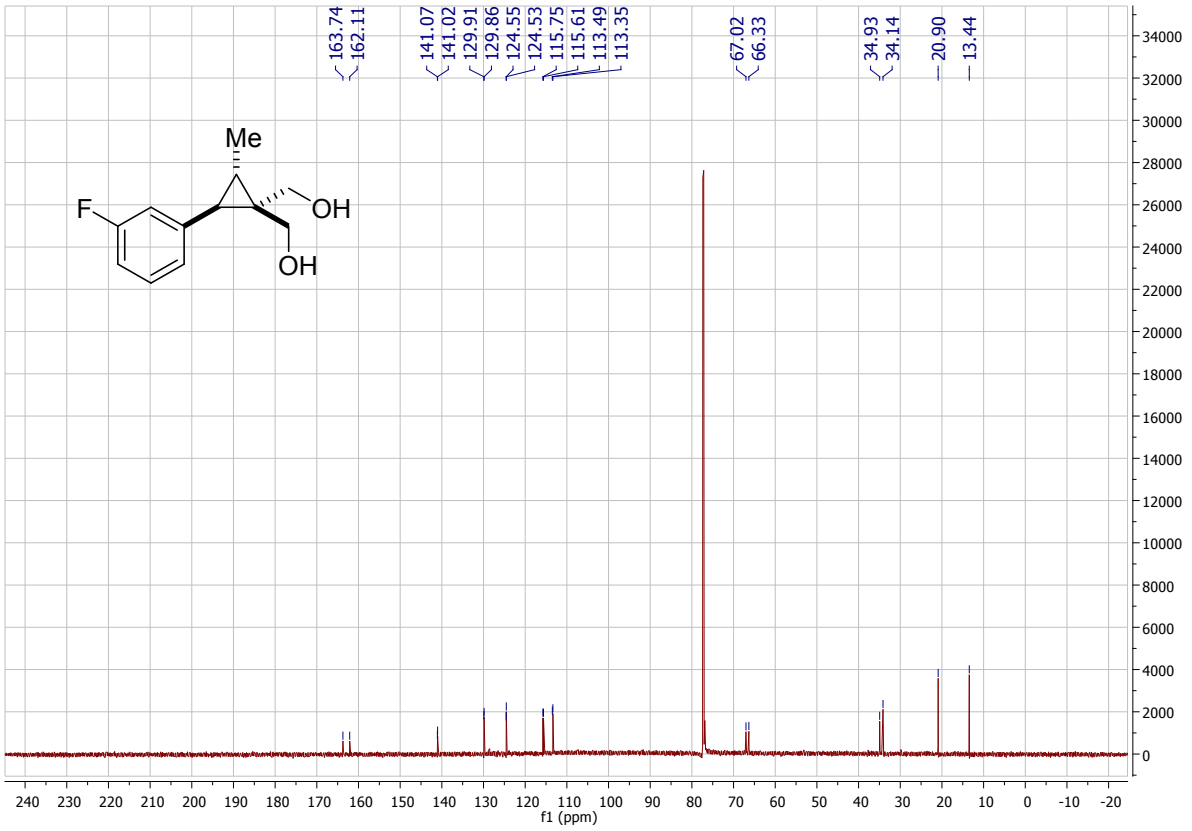
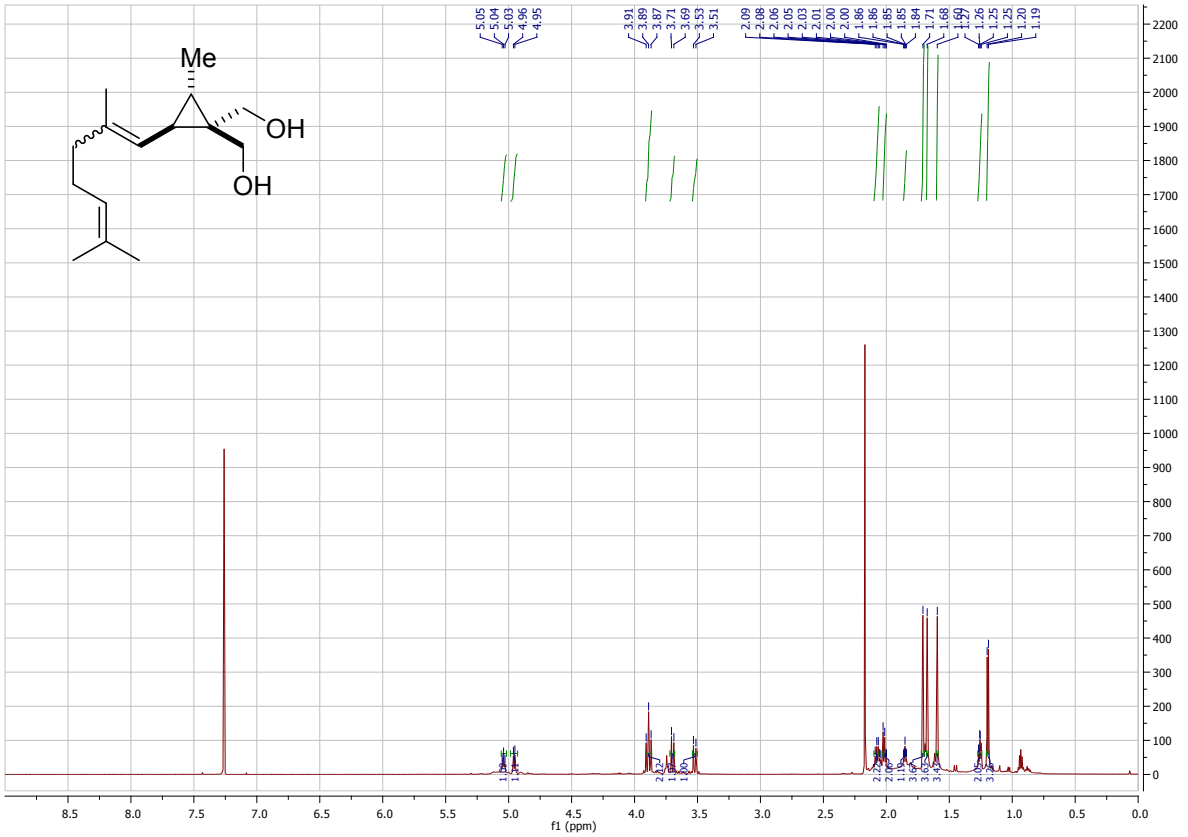
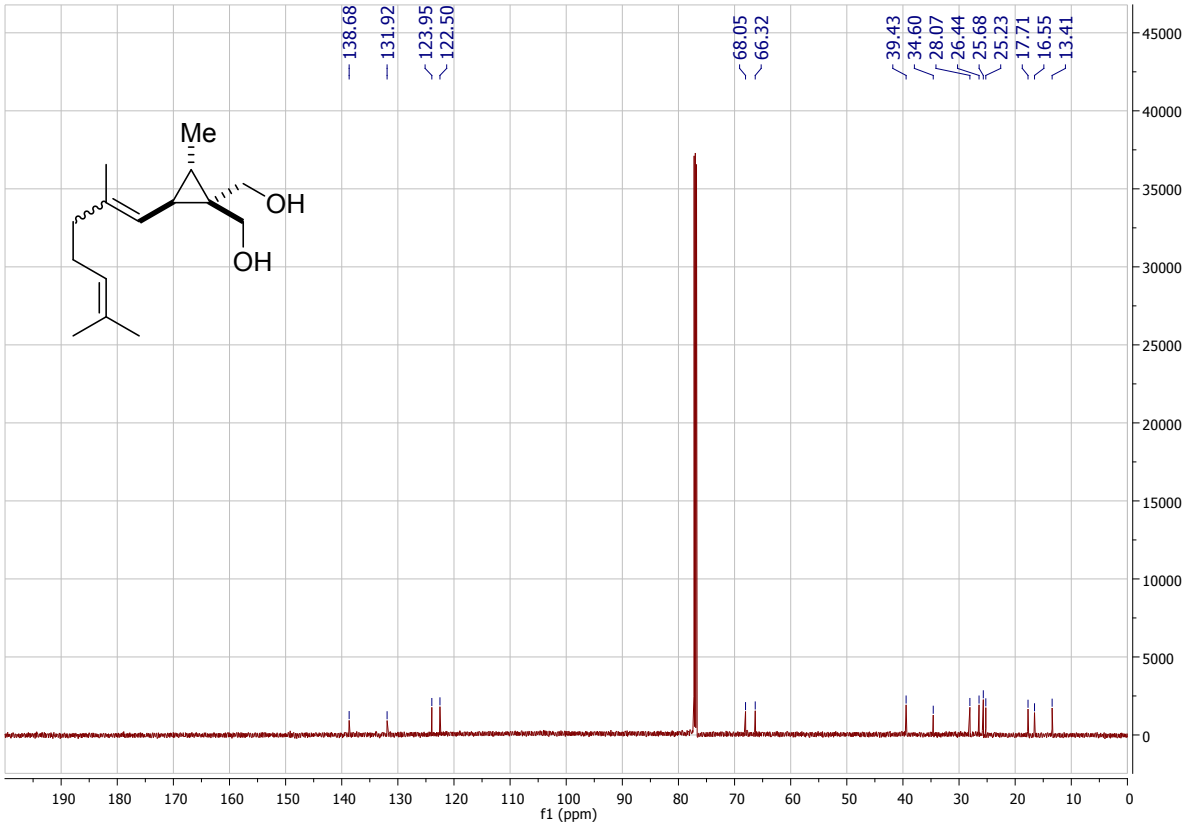
4.15
3.86
3.84
3.44
3.42
3.39
3.37
2.34
2.17
1.77
1.76
1.54
1.53
1.52
1.51
1.50
1.36
1.35
Me
OH
OH
Me
4.02
0.99
1.02
0.98
0.96
3.19
2.04
1.00
1.04
3.05
f1 (ppm)

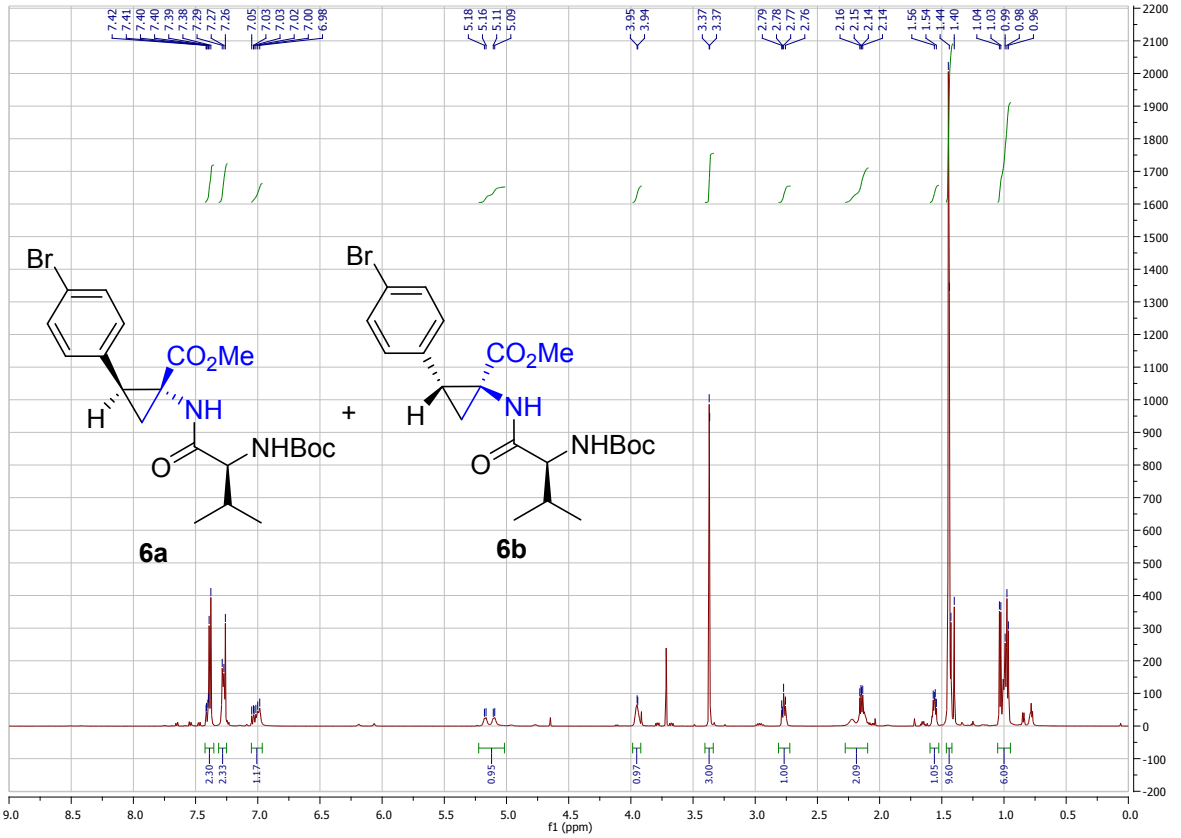

138.07
136.31
129.87
127.69
126.52
125.71
67.23
66.69
33.93
33.22
19.99
19.72
13.53
Me
OH
OH
Me
f1 (ppm)

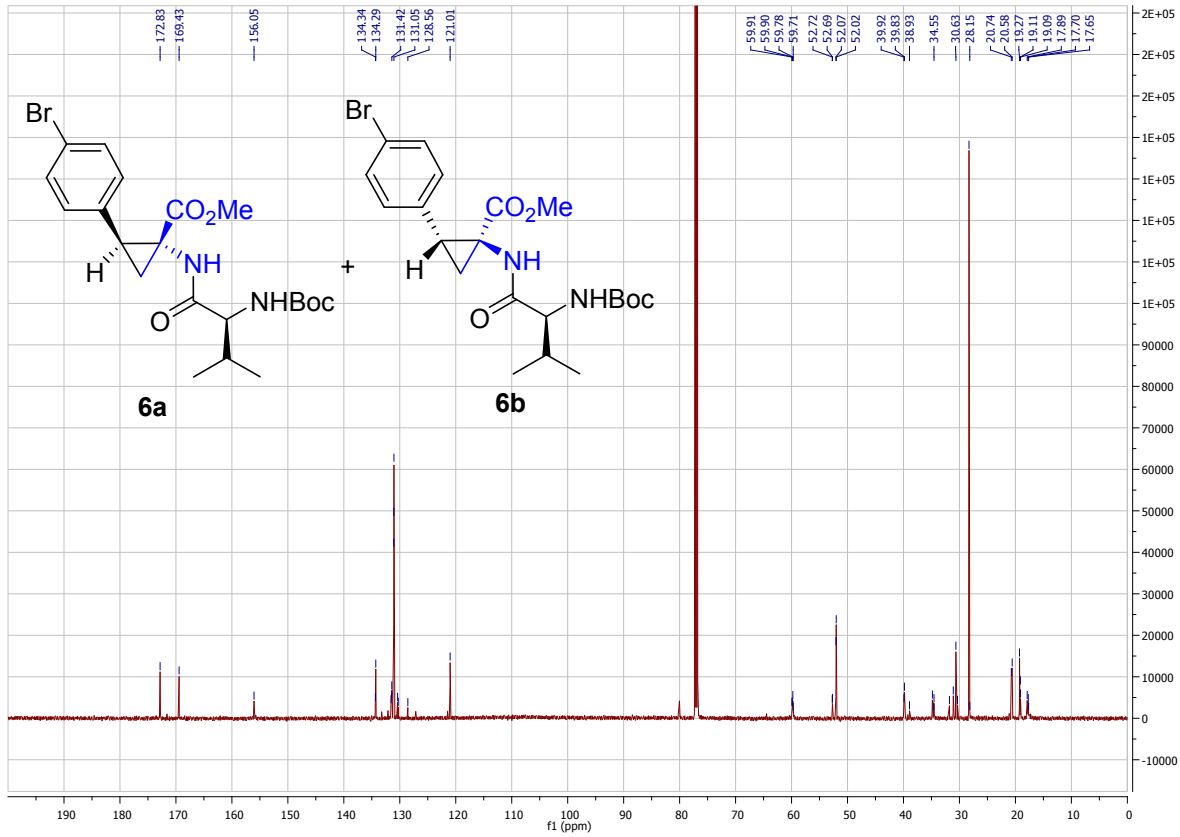

7.25
7.24
7.24
7.23
7.22
7.21
7.01
7.00
6.92
6.91
6.90
6.89
6.89
6.88
6.87
4.01
3.99
3.85
3.83
3.57
3.55
3.41
3.40
2.04
1.94
1.93
1.47
1.46
1.45
1.44
1.43
1.31
1.30
Me
F
OH
OH
1.01
1.00
1.98
1.09
1.05
1.05
1.05
2.05
1.06
1.04
3.05
f1 (ppm)


163.74
162.11
141.07
141.02
129.91
129.86
124.55
124.53
115.75
115.61
113.49
113.35
67.02
66.33
34.93
34.14
20.90
13.44
Me
F
OH
OH
f1 (ppm)


Me
OH
OH
5.05
5.04
5.03
4.96
4.95
3.91
3.89
3.87
3.71
3.69
3.53
3.51
2.09
2.08
2.06
2.05
2.03
2.01
2.00
2.00
1.86
1.86
1.85
1.85
1.84
1.71
1.68
1.60
1.27
1.26
1.25
1.25
1.20
1.19
f1 (ppm)


Me
OH
OH
138.68
131.92
123.95
122.50
68.05
66.32
39.43
34.60
28.07
26.44
25.68
25.23
17.71
16.55
13.41
f1 (ppm)


Br
CO2Me
NH
NHBoc
O
H
+
6a
6b
f1 (ppm)


Br
CO2Me
NH
NHBoc
O
H
+
6a
6b
f1 (ppm)

References

1. For information about the Uniqsis FlowSyn system, see: http://www.uniqsis.com/

2. For information about the Mettler Toledo FlowIR®, see: http://uk.mt.com/gb/en/home/products/L1_AutochemProducts/ReactIR/flow-ir-chemis.html

3. For information about Omnifit® glass columns, see: http://www.omnifit.com/

4. Activated MnO_2 was purchased from Sigma Aldrich (cod. 63548).