

## Supporting Information

### Formal [4 + 2] Cycloaddition of Donor–Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans

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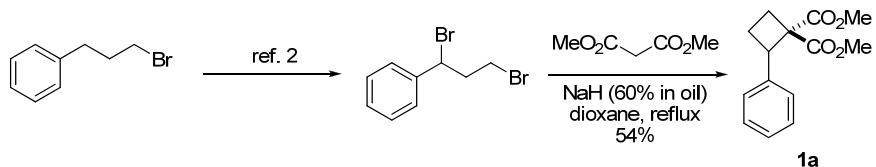
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**Methods.** Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (<sup>1</sup>H NMR and <sup>13</sup>C NMR) were recorded on a Bruker model DRX 400 or 500 (<sup>1</sup>H NMR at 400 MHz or 500 MHz and <sup>13</sup>C NMR at 100 or 125 MHz) spectrometer with solvent resonance as the internal standard (<sup>1</sup>H NMR: CDCl<sub>3</sub> at 7.26 ppm, DMSO-d<sub>6</sub> at 2.54 ppm, and C<sub>6</sub>D<sub>6</sub> at 7.15 ppm; <sup>13</sup>C NMR: CDCl<sub>3</sub> at 77.0 ppm, DMSO-d<sub>6</sub> at 40.45 ppm, and C<sub>6</sub>D<sub>6</sub> at 128.6 ppm). <sup>1</sup>H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, dtd = doublet of triplet of doublet, t = triplet, bt = broad triplet, td = triplet of doublet, q = quartet, qd = quartet of doublet, qn = quintet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with a Chiradex B-DM column (30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250 °C) with helium gas as carrier. Supercritical fluid chromatography was performed on a Berger SFC system equipped with a Chiralpack WO column (modifier = 2.0% MeOH, flow = 2.0 mL/min, pressure = 200 bar, detector = UV, 210 nm, temperature = 40 °C). Optical rotations were measured using a 2.0 mL cell with a 1.0 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Elemental analysis was performed by Atlantic Microlab, Inc. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies Silica G 0.20 mm silica gel plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution, or aqueous ceric ammonium molybdate solution followed by heating. Flash chromatography was performed using Silia-P flash silica gel (40-63 µm) purchased from Silicycle. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

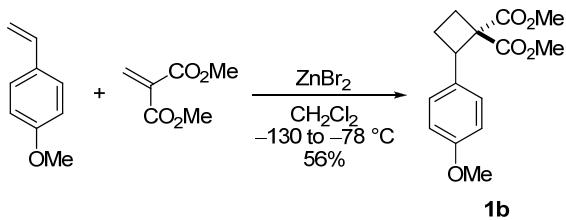
**Materials.** Tetrahydrofuran, toluene, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. 1,4-Dioxane was distilled from a sodium/benzophenone ketyl under N<sub>2</sub> and stored in a Schlenk flask. 1,2-Dichloroethane was purified by distillation from calcium hydride under N<sub>2</sub> prior to use. Benzaldehyde, *p*-anisaldehyde, 4-methylbenzaldehyde, 2-chlorobenzaldehyde, 2-fluorobenzaldehyde, and *trans*-cinnamaldehyde were purified by the following procedure: The neat aldehydes were washed sequentially with a 1 M sodium hydroxide solution and a saturated aqueous sodium bicarbonate solution, dried with magnesium sulfate, and distilled under reduced pressure. 4-Chlorobenzaldehyde was sublimed under reduced pressure. Isobutyraldehyde, cyclohexanecarboxaldehyde, and hexanal were dried over CaSO<sub>4</sub> and distilled under N<sub>2</sub> prior to use. Dimethyl 2,2-methylidene malonate was prepared according to the method of De Keyser<sup>1</sup> and was stored at -30 °C. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

**Preparation of dimethyl 2-phenylcyclobutane-1,1-dicarboxylate (1a):**



Under  $\text{N}_2$ , a flame dried 500-mL 2-neck round-bottomed flask containing a magnetic stir bar was charged with (1,3-dibromopropyl)benzene<sup>2</sup> (13.95 g, 50.2 mmol, 1.0 equiv), dimethyl malonate (7.3 g, 55.3 mmol, 1.1 equiv), and 161 mL anhydrous 1,4-dioxane. The flask was affixed with a reflux condenser and the solution was heated to reflux. Sodium hydride (2.06 g (60% in mineral oil), 51.7 mmol, 1.03 equiv) was added in small portions over approximately 10 minutes. The reaction was allowed to reflux for 1 h, at which point additional sodium hydride [2.06 g (60% in mineral oil), 51.7 mmol, 1.03 equiv] was added in an analogous manner. The reaction was heated at reflux for an additional 12 h, at which point it was slowly cooled to room temperature. The resulting heterogeneous mixture was filtered through celite. The filter cake was washed with copious  $\text{Et}_2\text{O}$  and the filtrate was concentrated. Flash chromatography (2.5 – 3.3 – 5.0%  $\text{EtOAc}/\text{hexanes}$ ) provided **1a** (6.67 g, 26.87 mmol, 54% yield) as a slightly yellow clear oil. Unreacted (1,3-dibromopropyl)benzene was also recovered (2.5 g, 8.99 mmol, 18%). Analytical data for **1a**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3030, 3000, 2952, 1732, 1496, 1435, 1275, 1201, 1107, 791, 699; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.28 (m, 4H), 7.22 – 7.18 (m, 1H), 4.37 (t,  $J$  = 9.2 Hz, 1H), 3.77 (s, 3H), 3.23 (s, 3H), 2.28 (qd,  $J$  = 9.2, 2.4 Hz, 1H), 2.17 (qd,  $J$  = 8.8, 2.0 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.0, 169.6, 139.1, 128.0, 127.5, 126.9, 59.7, 52.4, 51.7, 45.1, 25.6, 20.7; **TLC** (10%  $\text{EtOAc}/\text{hexanes}$ )  $R_f$  0.31; **Anal.** Calcd. for  $\text{C}_{14}\text{H}_{16}\text{O}_4$ : C, 67.73; H, 6.50. Found: C, 67.45; H, 6.60.

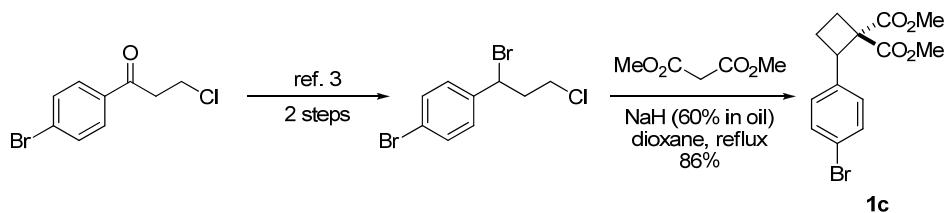
**Preparation of dimethyl 2-(4-methoxyphenyl)cyclobutane-1,1-dicarboxylate (1b):**



In an inert atmosphere glove box, a 100-mL round-bottomed flask was charged with  $\text{ZnBr}_2$  (1.32 g, 5.9 mmol, 1.0 equiv), a magnetic stir bar, and was fitted with a rubber septum. A scintillation vial was charged with dimethyl 2,2-methylidene malonate<sup>1</sup> (DMM, 0.85 g, 5.9 mmol, 1.0 equiv) and fitted with a rubber septum. Both vessels were removed from the glove box and placed under  $\text{N}_2$ . Outside of the glove box, a flame scintillation vial under  $\text{N}_2$  was charged with 1-methoxy-4-vinylbenzene (0.933 g, 0.933 mL, 6.9 mmol, 1.2 equiv). All vials were charged with  $\text{CH}_2\text{Cl}_2$  (13.5 mL, 40.5 mL total). The flask containing  $\text{ZnBr}_2$  was cooled to  $-130$  °C in a pentane/liquid  $\text{N}_2$  bath. To the  $\text{ZnBr}_2$  was added DMM followed by 1-methoxy-4-vinylbenzene (both added via canula over approximately 5 min). The reaction was warmed to  $-78$  °C in an isopropanol/dry ice bath and was allowed to stir for 1 h. A solution of pyridine (1.82 g, 1.85 mL, 23.1 mmol, 4.3 equiv) in  $\text{CH}_2\text{Cl}_2$  (13.0 mL) pre-cooled to  $-78$  °C was added to the reaction via syringe. The reaction was allowed to warm to room temperature, washed with saturated aq.

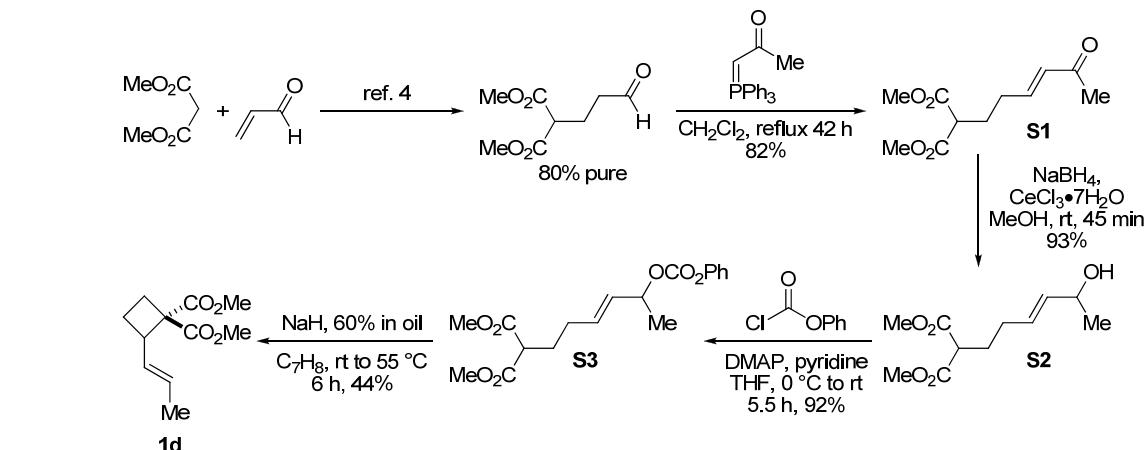
$\text{Na}_2\text{EDTA}$  (2 x 60 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Flash chromatography (7.5% EtOAc/hexanes) afforded **1b** (0.926 g, 3.33 mmol, 56% yield) as a white solid. Analytical data for **1b**: **mp** 55–56  $^{\circ}\text{C}$ ; **IR** (thin film,  $\text{cm}^{-1}$ ) 3000, 2952, 2839, 1732, 1612, 1515, 1435, 1275, 1253, 1107, 1037, 835;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (d,  $J$  = 8.4 Hz, 2H), 6.82 (d,  $J$  = 8.4 Hz, 2H), 4.30 (t,  $J$  = 9.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.27 (s, 3H), 2.71 – 2.65 (m, 1H), 2.57 (qn,  $J$  = 10.0 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.18 – 2.11 (m, 1H);  **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.1, 169.8, 158.6, 131.3, 128.7, 113.4, 59.8, 55.2, 52.4, 51.8, 44.7, 25.5, 21.0; **TLC** (15% EtOAc/hexanes)  $R_f$  0.18; **Anal.** Calcd. for  $\text{C}_{15}\text{H}_{18}\text{O}_5$ : C, 64.74; H, 6.52. Found: C, 64.90; H, 6.58.

**Preparation of dimethyl 2-(4-bromophenyl)cyclobutane-1,1-dicarboxylate (**1c**):**



Dimethyl 2-(4-bromophenyl)cyclobutane-1,1-dicarboxylate (**1c**) was prepared from 1-bromo-4-(1-bromo-3-chloropropyl)benzene<sup>3</sup> (1.13 g, 2.6 mmol, 1.0 equiv), dimethyl malonate (0.530 g, 0.458 mL, 4.01 mmol, 1.1 equiv), sodium hydride [0.36 g (60% in oil), 9.0 mmol], and 1,4-dioxane (14 mL) in an analogous manner to the synthesis of **1a**. The product was purified by flash chromatography (10% EtOAc/hexanes) to afford **1c** (1.01 g, 3.10 mmol, 86% yield) as a slightly yellow oil. Analytical data for **1c**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3000, 2952, 1732, 1489, 1435, 1281, 1201, 1107, 1073, 1011, 831;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (d,  $J$  = 8.3 Hz, 2H), 7.16 (d,  $J$  = 8.3 Hz, 2H), 4.29 (t,  $J$  = 9.6 Hz, 1H), 3.77 (s, 3H), 3.29 (s, 3H), 2.75 – 2.62 (m, 1H), 2.62 – 2.48 (m, 1H), 2.28 (dd,  $J$  = 20.1, 9.1 Hz, 1H), 2.22 – 2.10 (m, 1H);  **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.9, 169.5, 138.2, 131.1, 129.3, 120.9, 59.8, 59.5, 52.5, 52.0, 44.6, 25.7, 20.7; **TLC** (10% EtOAc/hexanes)  $R_f$  0.18; **Anal.** Calcd. for  $\text{C}_{14}\text{H}_{15}\text{O}_4$ : C, 51.40; H, 4.62. Found: C, 51.58; H, 4.54.

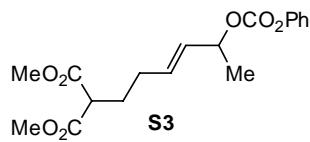
**Preparation of (*E*)-dimethyl 2-(prop-1-enyl)cyclobutane-1,1-dicarboxylate (**1d**):**



**(*E*)-Dimethyl 2-(5-oxohex-3-enyl)malonate (**S1**):** A 250-mL round-bottomed flask containing a magnetic stir bar was charged with dimethyl 2-(3-oxopropyl)malonate<sup>4</sup> (9.9 g, 52.6 mmol, 1.0 equiv, 80% pure), 1-(triphenylphosphoranylidene)-2-propanone, and CH<sub>2</sub>Cl<sub>2</sub> (111 mL). The flask was affixed with a reflux condenser and was heated to reflux for 42 h. The reaction was allowed to cool to room temperature and was concentrated *in vacuo*. The resulting residue was suspended in 30% EtOAc/hexanes and stirred for 2 h and was filtered through celite and concentrated. Flash chromatography (40% EtOAc/hexanes) afforded (*E*)-dimethyl 2-(5-oxohex-3-enyl)malonate (**S1**) (7.84 g, 82% yield based on 80% pure starting material) as a clear colorless oil. Analytical data for **S1**: **IR** (thin film, cm<sup>-1</sup>) 3006, 2956, 1735, 1675, 1437, 1361, 1157, 980; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.71 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 3.72 (s, 6H), 3.36 (t, *J* = 7.6 Hz, 1H), 2.28 – 2.23 (m, 2H), 2.22 (s, 3H), 2.06 (q, *J* = 8.0 Hz, 2H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 198.1, 169.3, 145.5, 132.1, 52.5, 50.8, 29.8, 27.0, 26.9; **TLC** (40% EtOAc/hexanes) *R*<sub>f</sub> 0.28; **Anal.** Calcd. for C<sub>11</sub>H<sub>16</sub>O<sub>5</sub>: C, 57.88; H, 7.07. Found: C, 57.73; H, 7.04.

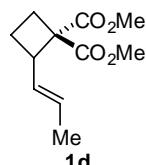
**(*E*)-Dimethyl 2-(5-hydroxyhex-3-enyl)malonate (**S2**):** A 250-mL round-bottomed flask containing a magnetic stir bar was charged with CeCl<sub>3</sub>•7H<sub>2</sub>O (1.75 g, 35.19 mmol, 1.75 equiv) and MeOH (50 mL). The suspension was stirred vigorously until homogeneous (approximately 5 min), at which point (*E*)-dimethyl 2-(5-oxohex-3-enyl)malonate (**S1**) (4.59 g, 20.01 mmol, 1.0 equiv) in MeOH (50 mL) was added. The resulting solution was stirred for 5 min and NaBH<sub>4</sub> (0.837 g, 22.12 mmol, 1.1 equiv) was added in 10 portions over 15 min. The reaction mixture was allowed to stir for 1.5 h and was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and poured into a 2 M aq. HCl solution (150 mL). The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 75 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with 2 M aq. HCl (75 mL), brine (75 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The product was purified by flash chromatography (20% EtOAc/hexanes) to afford (*E*)-dimethyl 2-(5-hydroxyhex-3-enyl)malonate (**S2**) (4.28 g, 18.59 mmol, 93%) as a clear colorless oil. Analytical data for **S2**: **IR** (thin film, cm<sup>-1</sup>) 3421, 2957, 1734, 1438, 1287, 1245, 1158, 1062, 971; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.62 – 5.41 (m, 2H), 4.29 – 4.13 (m, 1H), 3.70 (s, 6H), 3.34 (t, *J* = 7.2 Hz, 1H), 2.03 (dt, *J* = 9.9, 3.8 Hz,

2H), 1.99 – 1.91 (m, 2H), 1.88 (s, 1H), 1.20 (d,  $J$  = 6.4 Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 135.9, 128.3, 68.4, 52.3, 50.9, 29.6, 28.1, 23.3; **TLC** (40% EtOAc/hexanes)  $R_f$  0.19; **Anal.** Calcd. for  $\text{C}_{11}\text{H}_{18}\text{O}_5$ : C, 57.38; H, 7.88. Found: C, 57.35; H, 7.85.



**(E)-Dimethyl 2-(5-(phenoxy carboxyloxy)hex-3-enyl)malonate (S3):**

A flame-dried 250-mL round-bottomed flask was charged with a solution of (E)-dimethyl 2-(5-hydroxyhex-3-enyl)malonate (**S2**) (4.18 g, 18.15 mmol, 1.0 equiv) in tetrahydrofuran (74 mL). The flask was purged with  $\text{N}_2$  and cooled to 0 °C in an ice-water bath. 4-Dimethylaminopyridine (0.22 g, 1.82 mmol, 0.10 equiv) was added in one portion followed by dropwise addition of pyridine (3.59 g, 3.66 mL, 45.38 mmol, 2.5 equiv) via syringe over 10 min. Phenyl chloroformate (5.68 g, 4.55 mL, 36.31 mmol, 2.0 equiv) was added via syringe over 10 min. The reaction was allowed to stir for 30 min at 0 °C and was then warmed to room temperature and was stirred for an additional 4.5 h. The reaction was cooled to 0 °C and quenched with 2 M aq. HCl (75 mL). The organic layer was separated and the aqueous layer extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL). The combined organic extracts were washed with 2 M aq. HCl (2 x 75 mL), 2 M aq. NaOH (2 x 75 mL), dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to afford pure (E)-dimethyl 2-(5-(phenoxy carboxyloxy)hex-3-enyl)malonate (**S3**) (5.88 g, 16.79 mmol, 92%) as a clear colorless oil. Analytical data for **S3**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2954, 1756, 1496, 1437m 1250, 1210, 1154, 1044, 970, 780, 688;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (td,  $J$  = 7.7, 1.8 Hz, 2H), 7.25 – 7.19 (m, 1H), 7.17 (dd,  $J$  = 8.6, 1.0 Hz, 2H), 5.76 (dt,  $J$  = 13.6, 6.6 Hz, 1H), 5.56 (dd,  $J$  = 15.5, 7.1 Hz, 1H), 5.23 (qn,  $J$  = 6.5 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.38 (t,  $J$  = 7.3 Hz, 1H), 2.10 (dd,  $J$  = 14.5, 6.7 Hz, 2H), 2.00 (dt,  $J$  = 7.4, 4.4 Hz, 2H), 1.42 (d,  $J$  = 6.5 Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.5, 152.9, 151.2, 132.4, 130.1, 129.3, 125.8, 121.0, 75.9, 52.3, 50.8, 29.6, 27.8, 29.6, 27.8, 20.2; **TLC** (20% EtOAc/hexanes)  $R_f$  0.21; **Anal.** Calcd. for  $\text{C}_{18}\text{H}_{22}\text{O}_7$ : C, 61.71; H, 6.33. Found: C, 61.79; H, 6.45.

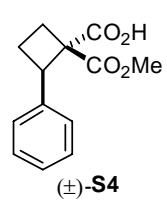
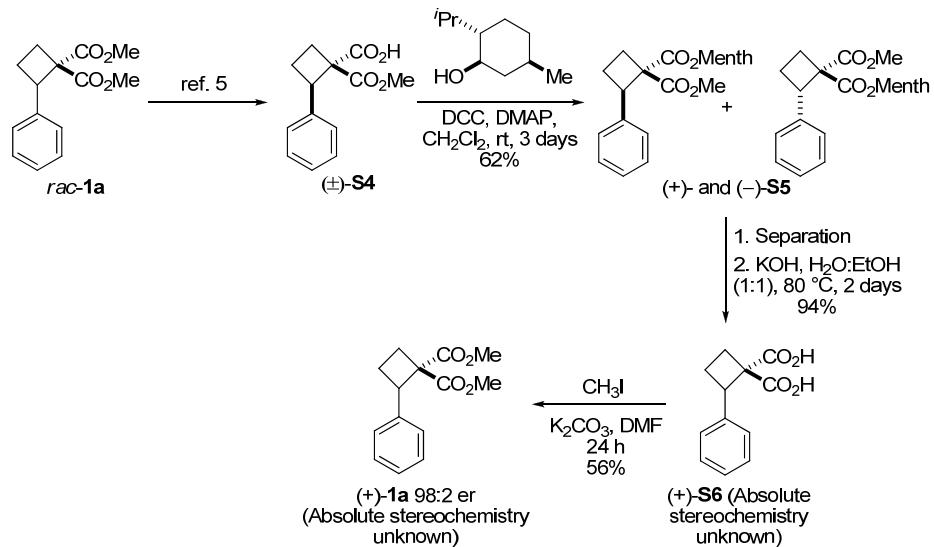


**(E)-Dimethyl 2-(prop-1-enyl)cyclobutane-1,1-dicarboxylate (1d):** A flame-dried 100 mL round-bottomed flask containing a magnetic stir bar was charged with sodium hydride (0.285 g (60% in oil), 7.13 mmol, 2.0 equiv) under  $\text{N}_2$ . The sodium hydride was washed with hexanes to remove the oil and was suspended in  $\text{C}_7\text{H}_8$  (7.0 mL). To this suspension was added a solution of (E)-dimethyl 2-(5-(phenoxy carboxyloxy)hex-3-enyl)malonate (**S3**) (1.25 g, 3.57 mmol, 1.0 equiv) in  $\text{C}_7\text{H}_8$  (10 mL) via canula over 20 min followed by a  $\text{C}_7\text{H}_8$  wash (4 mL). The reaction was stirred at room temperature for 30 min and then warmed to 55 °C for an additional 5 h. The reaction was then cooled to room temperature and poured into 50 mL  $\text{H}_2\text{O}$ . The organic layer was separated and the aqueous layer extracted with  $\text{Et}_2\text{O}$  (3 x 25 mL). The combined organic layers were washed with 2 M aq. NaOH (2 x 25 mL), dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*.

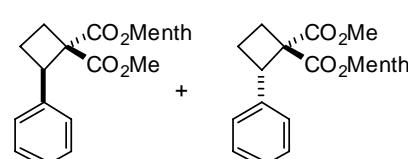
Purification by flash chromatography (7.5% EtOAc/hexanes afforded **1d** (0.33 g, 1.55 mmol, 44% yield) as a volatile clear colorless oil. (Note: While analyzing the flash column fractions using thin layer chromatography, it is necessary to elute the TLC plate twice in 7.5% EtOAc/hexanes to visualize an undesired impurity). Analytical data for **S3**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2998, 2953, 1733, 1436, 1275, 1256, 1201, 1115, 970;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.60 – 5.49 (m, 1H), 5.44 (dd,  $J$  = 15.8, 6.6 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.60 (dd,  $J$  = 16.0, 8.1 Hz, 1H), 2.61 – 2.55 (m, 1H), 2.21 – 2.10 (m, 1H), 2.10 – 1.95 (m, 2H), 1.65 (d,  $J$  = 6.2 Hz, 3H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.0, 170.2, 129.5, 127.6, 58.2, 52.3, 52.0, 43.2, 25.7, 22.1,

17.8; **TLC** (7.5% EtOAc/hexanes)  $R_f$  0.16; **LRMS** (ESI) Calcd. for  $C_{11}H_{16}O_4+Na$ : 235.1, Found: 235.1.

**Preparation of (+)-dimethyl 2-phenylcyclobutane-1,1-dicarboxylate ((+)-1a):**



**(±)-1-(Methoxycarbonyl)-2-phenylcyclobutanecarboxylic acid (S4):** This compound was prepared from *rac*-1a according to the protocol reported by Burger and Coyne<sup>5</sup> and was of sufficient purity for subsequent transformations. Analytical data for S4: **mp** 139–141 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3005, 2952, 1743, 1706, 1496, 1419, 1287, 1204, 1122, 943, 792, 700; **1H NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.30 (m, 4H), 7.25–7.22 (m, 1H), 4.37 (t,  $J = 9.5$  Hz, 1H), 3.32 (s, 3H), 2.76–2.64 (m, 2H), 2.48–2.42 (m, 1H), 2.24–2.19 (m, 1H); **13C NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  177.2, 169.8, 138.6, 128.1, 127.4, 127.1, 59.5, 52.1, 45.6, 25.5, 20.6; **LRMS** (ESI) Calcd. for  $C_{13}H_{14}O_4+Na$ : 257.1, Found: 257.1.

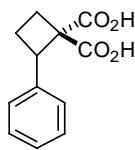


Note: absolute configuration of the (+)- and (-)-S5 isomers is unknown

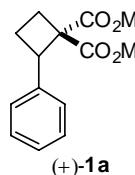
**(+)- and (-)-1-Methyl 2-phenylcyclobutane-1,1-dicarboxylate (S5):** A 100-mL round-bottomed flask was charged with (±)-(methoxycarbonyl)-2-phenylcyclobutanecarboxylic acid (S4) (0.900 g, 3.84 mmol, 1.0 equiv), dicyclohexylcarbodiimide (1.02 g, 4.95 mmol, 1.3 equiv), 4-dimethylaminopyridine (0.469 g, 3.84 mmol, 1.0 equiv), and  $\text{CH}_2\text{Cl}_2$  (20 mL). The resulting solution was

allowed to stir for 30 min, at which time finely ground (–)-menthol (0.650 g, 4.27 mmol, 1.10 equiv) was added in one portion. The flask was sealed with a polypropylene stopper and was allowed to stir for 3 days. The reaction was filtered through celite and the filtrate was washed with saturated aq.  $\text{NH}_4\text{Cl}$  (2 x 20 mL),  $\text{H}_2\text{O}$  (2 x 20 mL), and brine (1 x 20 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Partial separation of the isomers was achieved by flash chromatography (30–60%  $\text{CH}_2\text{Cl}_2$ /hexanes) to afford (–)-1-methyl 2-phenylcyclobutane-1,1-dicarboxylate (0.200 g, 0.537 mmol), (+)-1-methyl 2-phenylcyclobutane-1,1-dicarboxylate (0.174 g, 0.467 mmol), and a mixture of the two isomers (0.560 g, 1.503 mmol), all present as clear slightly yellow oils (total combined yield: 0.934 g, 2.504 mmol, 65%). Analytical data for

(*-*)-**S5**:  $[\alpha]_D^{29} = -115.2$  ( $c = 0.440$ ,  $\text{CHCl}_3$ ); **IR** (thin film,  $\text{cm}^{-1}$ ) 2953, 2871, 1726, 1435, 1198, 1182, 1109, 1037, 956, 757, 698;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.26 (m, 4H), 7.24 – 7.16 (m, 1H), 4.70 (td,  $J = 10.9, 4.3$  Hz, 1H), 4.36 (t,  $J = 8.7$  Hz, 1H), 3.20 (s, 3H), 2.72 (t,  $J = 8.8$  Hz, 1H), 2.58 (dd,  $J = 17.6, 10.5$  Hz, 1H), 2.27 – 2.12 (m, 2H), 2.07 (d,  $J = 11.5$  Hz, 1H), 1.86 – 1.74 (m, 1H), 1.74 – 1.62 (m, 2H), 1.57 – 1.45 (m, 1H), 1.43 – 1.32 (m, 1H), 1.13 – 0.79 (m, 3H), 0.93 (d,  $J = 6.5$  Hz, 3H), 0.84 (d,  $J = 7.1$  Hz, 3H) 0.72 (d,  $J = 6.9$  Hz, 3H);  **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 169.9, 139.3, 128.0, 127.7, 126.8, 75.4, 59.9, 51.4, 47.0, 45.0, 40.5, 34.3, 31.4, 25.9, 25.7, 23.3, 22.0, 20.7, 20.7, 16.0; **TLC** (60%  $\text{CH}_2\text{Cl}_2$ /hexanes)  $R_f$  0.39; **LRMS** (ESI) Calcd. for  $\text{C}_{23}\text{H}_{32}\text{O}_4\text{Na}$ : 395.2, Found: 395.2. Analytical data for (*+*)-**S5**:  $[\alpha]_D^{29} = + 24.9$  ( $c = 0.400$ ,  $\text{CHCl}_3$ ); **IR** (thin film,  $\text{cm}^{-1}$ ) 2953, 2871, 1726, 1456, 1435, 1271, 1199, 1109, 1037, 957, 757;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 – 7.22 (m, 4H), 7.20 (t,  $J = 6.5$  Hz, 1H), 4.75 (td,  $J = 10.9, 4.3$  Hz, 1H), 4.35 (t,  $J = 9.4$  Hz, 1H), 3.23 (s, 3H), 2.75 – 2.55 (m, 2H), 2.31 – 2.11 (m, 2H), 2.02 (d,  $J = 11.9$  Hz, 1H), 1.91 (dq,  $J = 6.6, 4.3$  Hz, 1H), 1.69 (d,  $J = 11.4$  Hz, 2H), 1.58 – 1.47 (m, 1H), 1.40 (dd,  $J = 23.8, 12.4$  Hz, 1H), 1.08 (dd,  $J = 23.0, 12.7$  Hz, 1H), 1.00 – 0.83 (m, 9H), 0.79 (d,  $J = 6.9$  Hz, 3H);  **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 170.0, 139.2, 127.9, 127.6, 126.8, 75.2, 60.1, 51.6, 47.0, 45.1, 40.3, 34.2, 31.4, 26.1, 25.6, 23.4, 22.0, 20.7, 20.6, 16.1; **TLC** (60%  $\text{CH}_2\text{Cl}_2$ /hexanes)  $R_f$  0.35; **LRMS** (ESI) Calcd. for  $\text{C}_{23}\text{H}_{32}\text{O}_4\text{Na}$ : 395.2, Found: 395.2.



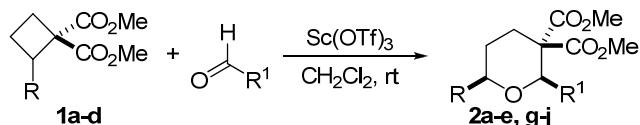
(*+*)-**S6** (**+**-2-**Phenylcyclobutane-1,1-dicarboxylic acid (S6)**): Potassium hydroxide pellets (0.203 g, 3.62 mmol, 9.0 equiv) were dissolved in  $\text{H}_2\text{O}$  (3.25 mL) and diluted with  $\text{EtOH}$  (3.25 mL). This KOH solution was added to a 25-mL round-bottomed flask containing a magnetic stir bar and (*+*)-methyl 2-phenylcyclobutane-1,1-dicarboxylate (**S5**) (0.150 g, 0.403 mmol, 1.0 equiv). The flask was affixed with a reflux condenser and the reaction was heated at reflux for 2 d at which point the reaction was cooled to room temperature and the majority of the ethanol was removed by rotary evaporation. The resulting solution was diluted with  $\text{H}_2\text{O}$  (20 mL) and washed with  $\text{Et}_2\text{O}$  (4 x 20 mL). The aqueous solution was brought to  $\text{pH} = 1$  by addition of concentrated HCl. The acidic solution was extracted with  $\text{Et}_2\text{O}$  (4 x 15 mL) and the combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated to afford pure (*+*)-2-phenylcyclobutane-1,1-dicarboxylic acid (**S6**) (0.083 g, 0.381 mmol, 94%) as a white powder. Analytical data for (*+*)-**S6**:  $[\alpha]_D^{27} = + 65.5$  ( $c = 0.300$ ,  $\text{CHCl}_3$ ); **mp** 125–128 °C (dec.); **IR** (thin film,  $\text{cm}^{-1}$ ) 2953, 2688, 2573, 1699, 1419, 1290, 1222, 1116, 928, 785, 697;  **$^1\text{H NMR}$**  (400 MHz, DMSO)  $\delta$  12.56 (bs, 2H), 7.31 – 7.28 (m, 4H), 7.22 – 7.17 (m, 1H), 4.18 (t,  $J = 9.6$  Hz, 1H), 2.50 – 2.40 (m, 2H), 2.25 – 2.19 (m, 1H), 2.12 – 2.06 (m, 1H);  **$^{13}\text{C NMR}$**  (100 MHz, DMSO)  $\delta$  174.0, 171.7, 140.9, 128.7, 128.4, 127.3, 60.0, 45.1, 26.4, 21.4; **LRMS** (ESI) Calcd. for  $\text{C}_{12}\text{H}_{12}\text{O}_4\text{Na}$ : 243.1, Found: 243.1.



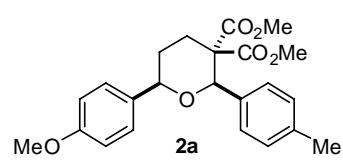
(*+*)-**1a** (**+**-**Dimethyl 2-phenylcyclobutane-1,1-dicarboxylate (1a)**): A flame-dried 1-dram vial containing a magnetic stir bar was charged with (*+*)-2-phenylcyclobutane-1,1-dicarboxylic acid (**S6**) (0.083 g, 0.381 mmol, 1.0 equiv), potassium carbonate (0.208 g, 0.151 mmol, 4.0 equiv), and *N,N*-dimethylformamide (1.75 mL). The resulting suspension was stirred for 30 min and then iodomethane (0.321 g, 0.141 mL, 2.26 mmol, 6.0 equiv) was added in one portion. The reaction was allowed to stir for 24 h and was then poured into a separatory funnel containing  $\text{H}_2\text{O}$  (10 mL). The resulting solution was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL). The combined organic extracts were washed with  $\text{H}_2\text{O}$  (3 x 15 mL) and 50% saturated aq.  $\text{NaCl}$  solution (15 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The product was purified by flash

chromatography (10% EtOAc/hexanes) to afford (+)-**1a** (0.052 g, 0.209 mmol, 56%) as a slightly yellow clear oil in 98:2 er as determined by GC analysis (Chiradex B-DM column, 30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250 °C).  $[\alpha]_D^{27} = +93.9$  ( $c = 0.360$ , CHCl<sub>3</sub>).

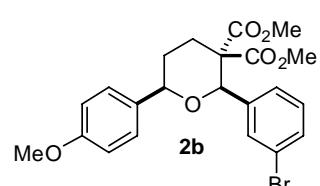
**General Procedure A for the Sc(OTf)<sub>3</sub>-catalyzed [4 + 2] cycloaddition of cyclobutanes **1a-d** with aryl aldehydes to afford tetrahydropyrans **2a-e, g-j**:**



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with Sc(OTf)<sub>3</sub> (0.02 equiv). To this vial was added a solution of the cyclobutane (1.0 equiv) and aldehyde (3.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> ([**1**]<sub>0</sub> = 0.25 M). The vial was sealed with a PTFE-lined screw cap, removed from the glove box, and allowed to stir. Upon disappearance of the cyclobutane as indicated by TLC analysis (with 25% EtOAc/hexanes or CH<sub>2</sub>Cl<sub>2</sub> as the mobile phase), the reaction was filtered through a 1-inch Monstr-Pette plug of silica with CH<sub>2</sub>Cl<sub>2</sub> (12 mL) and concentrated. The resulting tetrahydropyrans **2a-e, g-j** were purified by flash chromatography using the indicated solvent system.

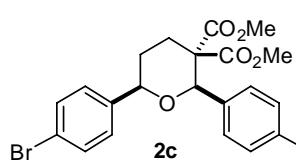


**Dimethyl 6-(4-methoxyphenyl)-2-p-tolyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2a):** The title compound was prepared according to General Procedure A using **1b** (0.090 g, 0.322 mmol, 1.0 equiv), 4-methylbenzaldehyde (0.116 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 15 min, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2a** (0.120 g, 0.301 mmol, 93% yield) as colorless crystals in 96:4 dr. Analytical data for **2a**: mp 126–127 °C; **IR** (thin film, cm<sup>-1</sup>) 3003, 2952, 2839, 1728, 1515, 1435, 1250, 1083, 1035, 826; **1H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.34 (d,  $J$  = 8.0 Hz, 4H), 7.10 (d,  $J$  = 7.7 Hz, 2H), 6.88 (d,  $J$  = 8.4 Hz, 2H), 5.11 (s, 1H), 4.62 (d,  $J$  = 10.0 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.58 (s, 3H), 2.68 (d,  $J$  = 13.3 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.32 (s, 3H), 2.09 (dq,  $J$  = 13.6, 3.8 Hz, 1H), 1.91 (d,  $J$  = 12.0 Hz, 1H); **13C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.3, 169.2, 159.0, 137.0, 136.5, 134.7, 127.9, 127.3, 127.1, 113.7, 82.4, 80.3, 58.6, 55.2, 52.3, 51.5, 32.8, 29.9, 21.1; **TLC** (15% EtOAc/hexanes)  $R_f$  0.16; **Anal.** Calcd. for C<sub>23</sub>H<sub>26</sub>O<sub>6</sub>: C, 69.33; H, 6.58. Found: C, 69.10; H, 6.61.

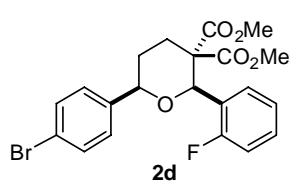


**Dimethyl 6-(4-methoxyphenyl)-2-(3-bromophenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2b):** The title compound was prepared according to General Procedure A using **1b** (0.090 g, 0.322 mmol, 1.0 equiv), 3-bromobenzaldehyde (0.179 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 15 min, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2b** (0.118 g, 0.255 mmol, 79% yield) as a clear colorless oil in 97:3 dr.

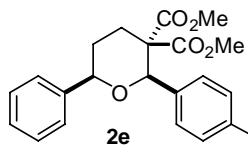
Analytical data for **2b**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3002, 2952, 2838, 1730, 1614, 1515, 1434, 1250, 1082, 1035, 829, 776;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (s, 1H), 7.43 – 7.29 (m, 4H), 7.15 (t,  $J$  = 7.9 Hz, 1H), 6.90 (d,  $J$  = 8.6 Hz, 2H), 5.11 (s, 1H), 4.61 (dd,  $J$  = 11.5, 2.2 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.58 (s, 3H), 2.69 (dt,  $J$  = 13.2, 3.1 Hz, 1H), 2.30 (td,  $J$  = 13.3, 4.2 Hz, 1H), 2.20 – 2.04 (m, 1H), 1.96 – 1.85 (m, 1H);  **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 168.8, 159.2, 141.8, 134.2, 130.6, 130.5, 128.7, 127.1, 126.2, 121.3, 113.8, 81.6, 80.5, 58.5, 55.2, 52.4, 51.6, 32.7, 29.7; **TLC** (15% EtOAc/hexanes)  $R_f$  0.13; **LRMS** (ESI) Calcd. for  $\text{C}_{22}\text{H}_{23}\text{BrO}_6\text{Na}$ : 485.1, Found: 485.1.



**Dimethyl 6-(4-bromophenyl)-2-(4-(trifluoromethyl)phenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2c):** The title compound was prepared according to General Procedure A using **1c** (0.105 g, 0.322 mmol, 1.0 equiv), 4-trifluoromethylbenzaldehyde (0.168 g, 0.967 mmol, 3.0 equiv),  $\text{Sc}(\text{OTf})_3$  (0.0032 g, 0.0064 mmol, 0.02 equiv) and  $\text{CH}_2\text{Cl}_2$  (1.28 mL). After stirring for 15 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2c** (0.146 g, 0.291 mmol, 90% yield) as a yellow powder in 98:2 dr. Analytical data for **2c**: **mp** 107–109 °C; **IR** (thin film,  $\text{cm}^{-1}$ ) 3003 2954, 2858, 1731, 1436, 1327, 1166, 1122, 1068, 1011, 856, 815;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (q,  $J$  = 8.5 Hz, 4H), 7.48 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 8.3 Hz, 2H), 5.20 (s, 1H), 4.64 (dd,  $J$  = 11.4, 2.3 Hz, 1H), 3.70 (s, 3H), 3.54 (s, 3H), 2.71 (dt,  $J$  = 13.3, 3.1 Hz, 1H), 2.31 (td,  $J$  = 13.3, 4.4 Hz, 1H), 2.08 (ddd,  $J$  = 16.8, 13.4, 4.0 Hz, 1H), 2.00 – 1.88 (m, 1H);  **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 168.6, 143.3, 140.8, 131.5, 129.7 (q,  $J$  = 32.0 Hz), 127.8, 127.5, 124.2 (d,  $J$  = 270.0 Hz), 125.6 – 122.7 (m), 121.5, 81.7, 80.0, 58.3, 52.6, 51.7, 32.5, 29.7; **TLC** (15% EtOAc/hexanes)  $R_f$  0.23; **Anal.** Calcd. for  $\text{C}_{22}\text{H}_{20}\text{BrF}_3\text{O}_5$ : C, 52.71; H, 4.02. Found: C, 52.78; H, 4.05.

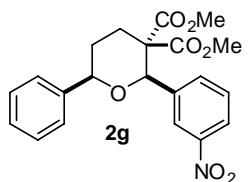


**Dimethyl 6-(4-bromophenyl)-2-(2-fluorophenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2d):** The title compound was prepared according to General Procedure A using **1c** (0.105 g, 0.322 mmol, 1.0 equiv), 2-fluorobenzaldehyde (0.120 g, 0.967 mmol, 3.0 equiv),  $\text{Sc}(\text{OTf})_3$  (0.0032 g, 0.0064 mmol, 0.02 equiv) and  $\text{CH}_2\text{Cl}_2$  (1.28 mL). After stirring for 16.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **2d** (0.136 g, 0.301 mmol, 94% yield) as a clear colorless oil in 99:1 dr. Analytical data for **2d**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2953, 2857, 1735, 1490, 1274, 1255, 1086, 1011, 764;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (t,  $J$  = 7.0 Hz, 1H), 7.47 (d,  $J$  = 8.3 Hz, 2H), 7.38 – 7.21 (m, 3H), 7.17 (t,  $J$  = 7.4 Hz, 1H), 7.02 – 6.88 (m, 1H), 5.17 (s, 1H), 4.62 (dd,  $J$  = 11.2, 2.0 Hz, 1H), 3.66 (s, 6H), 2.65 (dd,  $J$  = 10.6, 3.1 Hz, 1H), 2.52 (td,  $J$  = 13.7, 4.0 Hz, 1H), 1.95 (dd,  $J$  = 13.6, 2.9 Hz, 1H), 1.82 (ddd,  $J$  = 25.6, 13.8, 3.9 Hz, 1H);  **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 168.7, 161.0, 158.6, 141.1, 131.4, 131.1 (d,  $J$  = 3.7 Hz), 129.3 (d,  $J$  = 8.7 Hz), 127.5, 125.8 (d,  $J$  = 12.6 Hz), 123.3 (d,  $J$  = 3.1 Hz), 121.4, 114.2, 113.9, 80.2, 76.8, 57.7, 52.5, 51.8, 32.1, 30.3; **TLC** (20% EtOAc/hexanes)  $R_f$  0.24; **LRMS** (ESI) Calcd. for  $\text{C}_{21}\text{H}_{20}\text{BrFO}_5\text{Na}$ : 473.1, Found: 473.0.



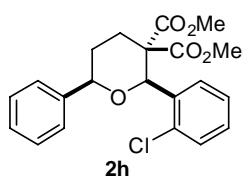
**Dimethyl 6-phenyl-2-(4-(trifluoromethyl)phenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2e):** The title compound was prepared according to General Procedure A using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), 4-trifluoromethylbenzaldehyde (0.168 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL).

After stirring for 4.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2e** (0.126 g, 0.298 mmol, 92% yield) as a clear colorless oil in 99:1 dr. Analytical data for **2e**: **IR** (thin film, cm<sup>-1</sup>) 2954, 2858, 1731, 1436, 1327, 1166, 1121, 1068, 1019, 856; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.34 (m, 4H), 7.34 – 7.27 (m, 1H), 5.22 (s, 1H), 4.70 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.71 (s, 3H), 3.56 (s, 3H), 2.73 (dt, *J* = 13.4, 3.2 Hz, 1H), 2.35 (td, *J* = 13.4, 4.4 Hz, 1H), 2.21 – 2.06 (m, 1H), 2.03 – 1.93 (m, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.1, 168.7, 143.6, 141.9, 129.7 (q, *J* = 32.3 Hz), 128.4, 127.9, 127.7, 125.8, 124.3 (q, *J* = 271.5 Hz), 124.15 (q, *J* = 4.0 Hz), 81.7, 80.8, 58.6, 52.5, 51.6, 32.7, 29.8; **TLC** (15% EtOAc/hexanes) *R<sub>f</sub>* 0.15; **Anal.** Calcd. for C<sub>22</sub>H<sub>21</sub>F<sub>3</sub>O<sub>5</sub>: C, 62.56; H, 5.01. Found: C, 62.81; H, 5.12.



**Dimethyl 2-(3-nitrophenyl)-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2g):** The title compound was prepared according to General Procedure A using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), 3-nitrobenzaldehyde (0.146 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 6.0 h, the reaction was complete as determined by TLC analysis.

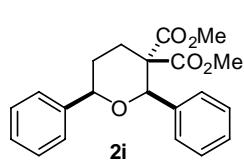
The reaction was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **2g** (0.116 g, 0.290 mmol, 90% yield) as yellow crystals in 98:2 dr. Analytical data for **2g**: **mp** 122–123 °C; **IR** (thin film, cm<sup>-1</sup>) 3032, 2953, 2860, 1731, 1530, 1349, 1275, 1256, 1092, 1069, 806, 699; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.30 (s, 1H), 8.17 – 8.08 (m, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.44 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 5.24 (s, 1H), 4.71 (dd, *J* = 11.5, 2.7 Hz, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 2.78 – 2.70 (m, 1H), 2.36 (td, *J* = 13.4, 4.5 Hz, 1H), 2.17 – 2.05 (m, 1H), 1.99 (ddt, *J* = 13.9, 4.5, 2.8 Hz, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.0, 168.6, 147.7, 141.6 (two overlapping resonances), 133.8, 128.5, 128.1, 127.8, 125.8, 122.6, 122.5, 81.4, 81.1, 58.6, 52.7, 51.9, 32.6, 29.9; **TLC** (20% EtOAc/hexanes) *R<sub>f</sub>* 0.19; **Anal.** Calcd. for C<sub>21</sub>H<sub>21</sub>NO<sub>7</sub>: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.08; H, 5.30; N, 3.51.



**Dimethyl 2-(4-chlorophenyl)-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2h):** The title compound was prepared according to General Procedure A using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), 2-chlorobenzaldehyde (0.136 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 7.0 h, the reaction was complete as determined by TLC analysis.

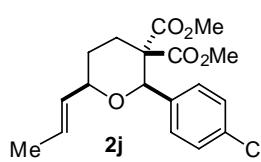
The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2h** (0.122 g, 0.314 mmol, 97% yield) as a white solid in 92:8 dr. Analytical data for **2h**: **mp** 90–92 °C; **IR** (thin film, cm<sup>-1</sup>) 3031, 2952, 2856, 1735, 1437, 1276, 1254, 1166, 1092, 1032, 759, 701; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.14 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.38 – 7.24 (m, 5H), 7.23 – 7.17 (m, 1H), 5.31 (s, 1H), 4.69 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.68 (s, 3H), 3.63 (s, 3H) 2.65 – 2.55 (m, 2H), 1.99 (ddd, *J* = 13.9, 6.6, 3.5 Hz, 1H), 1.82 (dtd, *J* = 14.0, 11.5, 6.1 Hz,

1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 169.5, 168.8, 142.2, 136.4, 133.2, 131.8, 128.9, 128.3, 128.2, 127.6, 126.1, 125.8, 81.0, 78.9, 57.5, 52.7, 51.9, 32.4, 30.6; **TLC** (15% EtOAc/hexanes) R<sub>f</sub> 0.21; **Anal.** Calcd. for C<sub>21</sub>H<sub>21</sub>ClO<sub>5</sub>: C, 64.87; H, 5.44. Found: C, 65.15; H, 5.49.



**Dimethyl 2,6-diphenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2i):**

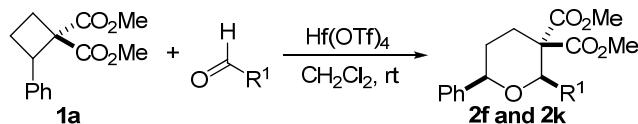
The title compound was prepared according to General Procedure A using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), benzaldehyde (0.103 g, 0.967 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0032 g, 0.0064 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). After stirring for 6.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2i** (0.111 g, 0.313 mmol, 97% yield) as a white waxy solid in 96:4 dr. Analytical data for **2i**: **IR** (thin film, cm<sup>-1</sup>) 3032, 2952, 2857, 1729, 1452, 1435, 1257, 1091, 1068, 700; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.48 (d, *J* = 7.3 Hz, 2H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.33 – 7.20 (m, 4H), 5.17 (s, 1H), 4.69 (dd, *J* = 11.4, 2.2 Hz, 1H), 3.69 (s, 3H), 3.56 (s, 3H), 2.77 – 2.62 (m, 1H), 2.34 (td, *J* = 13.3, 4.3 Hz, 1H), 2.12 (ddd, *J* = 17.0, 13.5, 4.0 Hz, 1H), 2.01 – 1.89 (m, 1H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.3, 142.3, 139.5, 128.3, 127.5, 127.4, 127.2, 125.8, 82.3, 80.7, 58.6, 52.4, 51.5, 32.8, 30.0; **TLC** (15% EtOAc/hexanes) R<sub>f</sub> 0.18; **Anal.** Calcd. for C<sub>21</sub>H<sub>22</sub>O<sub>5</sub>: C, 71.17; H, 6.26. Found: C, 71.16; H, 6.32.



**Dimethyl 2-(4-chlorophenyl)-6-((E)-prop-1-enyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2j):**

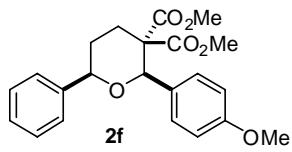
The title compound was prepared according to General Procedure A using **1d** (0.040 g, 0.188 mmol, 1.0 equiv), 4-chlorobenzaldehyde (0.079 g, 0.564 mmol, 3.0 equiv), Sc(OTf)<sub>3</sub> (0.0018 g, 0.0037 mmol, 0.02 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (0.75 mL). After stirring for 6.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (60% CH<sub>2</sub>Cl<sub>2</sub>/hexanes) to afford **2j** (0.047 g, 0.133 mmol, 70% yield) as a clear colorless oil in 94:6 dr. Analytical data for **2j**: **IR** (thin film, cm<sup>-1</sup>) 2953, 2360, 2342, 1731, 1492, 1436, 1090, 1014, 846, 808; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 5.74 (dq, *J* = 12.9, 6.3 Hz, 1H), 5.55 (dd, *J* = 15.4, 6.1 Hz, 1H), 4.96 (s, 1H), 4.16 – 3.97 (m, 1H), 3.65 (s, 3H), 3.53 (s, 3H), 2.68 – 2.50 (m, 1H), 2.14 (td, *J* = 13.4, 4.4 Hz, 1H), 1.95 – 1.79 (m, 1H), 1.70 – 1.65 (m, 1H), 1.69 (d, *J* = 6.4 Hz, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.3, 168.9, 138.2, 133.2, 131.3, 128.9, 127.4, 127.3, 81.4, 79.4, 58.5, 52.4, 51.6, 32.3, 28.0, 17.7; **TLC** (60% CH<sub>2</sub>Cl<sub>2</sub>/hexanes) R<sub>f</sub> 0.28; **Anal.** Calcd. for C<sub>18</sub>H<sub>21</sub>ClO<sub>5</sub>: C, 61.28; H, 6.00. Found: C, 61.51; H, 6.04.

**General Procedure B for the Hf(OTf)<sub>4</sub>-catalyzed [4 + 2] cycloaddition of cyclobutane **1a** with 4-methoxybenzaldehyde and cinnamaldehyde to afford tetrahydropyrans **2f** and **2k**:**

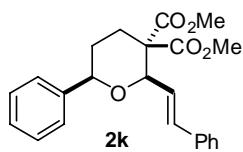


In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with Hf(OTf)<sub>4</sub> (0.0050 g, 0.0064 mmol, 0.02 equiv). To this vial was added a solution of cyclobutane **1a** (0.080 g, 0.322 mmol, 1.0 equiv) and the aldehyde (0.967 mmol, 3.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1.28 mL). The vial was sealed with a PTFE-lined screw cap, removed from the glove box, and

allowed to stir. After disappearance of the cyclobutane was confirmed by TLC analysis, the reaction was filtered through a 1-inch Monstr-Pette plug of silica with  $\text{CH}_2\text{Cl}_2$  (12 mL) and concentrated. The resulting tetrahydropyran products were purified by flash chromatography using the indicated solvent system.

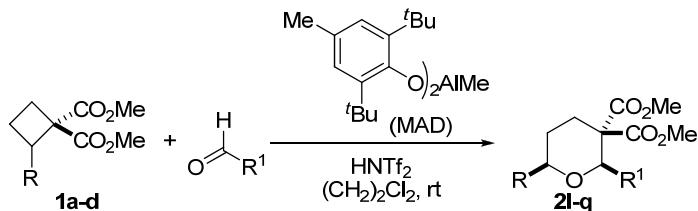


**Dimethyl 2-(4-methoxyphenyl)-6-phenyltetrahydropyran-3,3-dicarboxylate (2f):** The title compound was prepared according to General Procedure B using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), 4-methoxybenzaldehyde (0.132 g, 0.967 mmol, 3.0 equiv),  $\text{Hf}(\text{OTf})_4$  (0.0050 g, 0.0064 mmol, 0.02 equiv) and  $\text{CH}_2\text{Cl}_2$  (1.28 mL). After stirring for 11 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (80 – 90 – 100%  $\text{CH}_2\text{Cl}_2$ /hexanes gradient) to afford **2f** (0.084 g, 0.219 mmol, 68% yield) as a clear colorless oil in 96:4 dr. Analytical data for **2f**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2952, 2930, 1851, 1729, 1613, 1514, 1453, 1435, 1250, 1177, 1069, 1033, 700; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (dd,  $J$  = 7.6, 6.1 Hz, 4H), 7.35 (t,  $J$  = 7.4 Hz, 2H), 7.31 – 7.23 (m, 1H), 6.84 (d,  $J$  = 8.8 Hz, 2H), 5.11 (s, 1H), 4.67 (dd,  $J$  = 11.4, 2.4 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.59 (s, 3H), 2.76 – 2.58 (m, 1H), 2.32 (td,  $J$  = 13.3, 4.3 Hz, 1H), 2.19 – 2.02 (m, 1H), 2.02 – 1.88 (m, 1H); **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 169.2, 159.0, 142.4, 131.7, 128.6, 128.2, 127.5, 125.8, 112.7, 82.1, 80.7, 58.6, 55.1, 52.3, 51.6, 32.7, 30.0; **TLC** (80%  $\text{CH}_2\text{Cl}_2$ /hexanes)  $R_f$  0.18; **Anal.** Calcd. for  $\text{C}_{22}\text{H}_{24}\text{O}_6$ : C, 68.74; H, 6.29. Found: C, 69.00; H, 6.28.

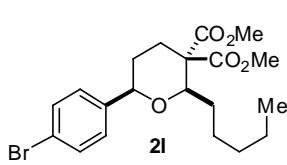


**Dimethyl 6-phenyl-2-styryldihydro-2H-pyran-3,3(4H)-dicarboxylate (2k):** The title compound was prepared according to General Procedure B using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), *trans*-cinnamaldehyde (0.128 g, 0.967 mmol, 3.0 equiv),  $\text{Hf}(\text{OTf})_4$  (0.0050 g, 0.0064 mmol, 0.02 equiv) and  $\text{CH}_2\text{Cl}_2$  (1.28 mL). After stirring for 22 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2k** (0.095 g, 0.264 mmol, 82% yield) as a clear colorless oil in 79:21 dr. Analytical data for **2k**: **IR** (thin film,  $\text{cm}^{-1}$ ) 3030, 2953, 1732, 1451, 1435, 1236, 1171, 1066, 1026, 696; **<sup>1</sup>H NMR** (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.41 (d,  $J$  = 7.4 Hz, 2H), 7.31 (d,  $J$  = 7.3 Hz, 2H), 7.19 (t,  $J$  = 7.5 Hz, 2H), 7.12 – 6.97 (m, 5H), 6.86 (d,  $J$  = 16.1 Hz, 1H), 4.73 (d,  $J$  = 5.7 Hz, 1H), 4.32 (dd,  $J$  = 11.6, 2.2 Hz, 1H), 3.36 (s, 3H), 3.25 (s, 3H), 2.71 – 2.58 (m, 1H), 2.15 (ddd,  $J$  = 25.2, 13.4, 4.0 Hz, 1H), 1.95 (td,  $J$  = 13.3, 4.2 Hz, 1H), 1.62 – 1.50 (m, 1H); **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 169.2, 142.0, 137.1, 131.3, 128.4, 128.3, 127.6, 127.4, 127.4, 126.6, 125.9, 82.2, 80.4, 58.1, 52.5, 52.1, 32.0, 29.9; **TLC** (15% EtOAc/hexanes)  $R_f$  0.23; **Anal.** Calcd. for  $\text{C}_{22}\text{H}_{24}\text{O}_6$ : C, 72.61; H, 6.36. Found: C, 72.67; H, 6.44.

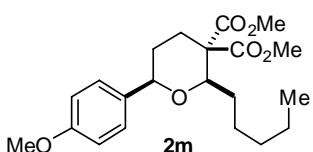
**General Procedure C for the MADNTf<sub>2</sub>-catalyzed [4 + 2] cycloaddition of cyclobutanes **1a-d** with alkyl aldehydes to afford tetrahydropyrans **2l-q**:**



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxy)<sup>6</sup> (MAD, 0.07 equiv), HNTf<sub>2</sub> (0.05 equiv) and (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub> (0.180 mL). The resulting solution was stirred until the evolution of methane gas ceases, approximately 5 min. To this vial is added a solution of the cyclobutane (0.322 mmol, 1.0 equiv) and aldehyde (0.967 mmol, 3.0 equiv) in (CH<sub>2</sub>)<sub>2</sub>Cl<sub>2</sub> (1.00 mL). The vial was sealed with a PTFE-lined screw cap, removed from the glove box, and stirred. Upon disappearance of the cyclobutane as indicated by TLC analysis (with 25% EtOAc/hexanes or CH<sub>2</sub>Cl<sub>2</sub> as the mobile phase), the reaction was filtered through a 1-inch Monstr-Pette plug of silica with CH<sub>2</sub>Cl<sub>2</sub> (12 mL) and concentrated. The resulting tetrahydropyrans **2l-q** were purified by flash chromatography using the indicated solvent system.

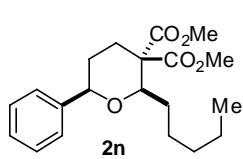


**Dimethyl 6-(4-bromophenyl)-2-pentyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**2l**):** The title compound was prepared according to General Procedure C using **1c** (0.105 g, 0.322 mmol, 1.0 equiv), hexanal (0.097 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045 g, 0.0161 mmol, 0.05 equiv), and 1,2-dichloroethane (1.28 mL). After stirring for 20 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (10% EtOAc/hexanes) to afford **2l** (0.116 g, 0.271 mmol, 84% yield) as a clear colorless oil in 87:13 dr. Analytical data for **2l**: **IR** (thin film, cm<sup>-1</sup>) 2953, 2928, 2859, 1732, 1489, 1435, 1255, 1233, 1083, 1011, 804; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.44 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 4.48 – 4.34 (m, 1H), 3.84 (dd, *J* = 9.7, 1.3 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.66 – 2.53 (m, 1H), 2.08 – 1.89 (m, 2H), 1.89 – 1.75 (m, 2H), 1.75 – 1.62 (m, 1H), 1.62 – 1.48 (m, 1H), 1.40 – 1.19 (m, 5H), 0.87 (bt, *J* = 5.9 Hz, 3H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.5, 169.6, 141.4, 131.3, 127.6, 121.2, 82.1, 79.5, 56.6, 52.4, 52.0, 32.5, 32.4, 31.6, 29.7, 26.9, 22.5, 14.0; **TLC** (10% EtOAc/hexanes) *R<sub>f</sub>* 0.23; **Anal.** Calcd. For C<sub>20</sub>H<sub>27</sub>BrO<sub>5</sub>: C, 56.21; H, 6.37. Found: C, 56.51; H, 6.47.



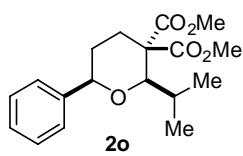
**Dimethyl 6-(4-methoxyphenyl)-2-pentyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**2m**):** Note: This reaction was run at 0 °C. The title compound was prepared according to General Procedure C using **1b** (0.090 g, 0.322 mmol, 1.0 equiv), hexanal (0.097 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045 g, 0.0161 mmol, 0.05 equiv), and 1,2-dichloroethane (1.28 mL). After stirring for 3.5 h at 0 °C, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2m** (0.081 g, 0.214 mmol, 66% yield) as a clear colorless oil in 78:22 dr. Analytical data for **2m**: **IR** (thin film, cm<sup>-1</sup>) 2954, 2930,

2858, 1731, 1614, 1515, 1436, 1249, 1175, 1081, 1034, 825; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (d,  $J$  = 8.5 Hz, 2H), 6.86 (d,  $J$  = 8.6 Hz, 2H), 4.48 – 4.34 (m, 1H), 3.90 – 3.82 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 2.67 – 2.51 (m, 1H), 2.11 – 1.94 (m, 2H), 1.92 – 1.75 (m, 2H), 1.73 – 1.48 (m, 2H), 1.29 (m,  $J$  = 3.1 Hz, 5H), 0.87 (bs, 3H); **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.7, 169.7, 159.1, 134.6, 127.2, 113.7, 82.2, 79.9, 56.9, 55.3, 52.3, 51.9, 32.6, 31.6, 29.4, 27.0, 22.6, 14.0; **TLC** (15% EtOAc/hexanes)  $R_f$  0.22; **Anal.** Calcd. For  $\text{C}_{21}\text{H}_{30}\text{O}_6$ : C, 66.65; H, 7.99. Found: C, 66.81; H, 8.02.



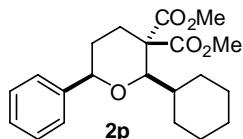
**Dimethyl 2-pentyl-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2n):** The title compound was prepared according to General Procedure C

using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), hexanal (0.097 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045 g, 0.0161 mmol, 0.05 equiv), and 1,2-dichloroethane (1.28 mL). After stirring for 6.0 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (10% EtOAc/hexanes) to afford **2n** (0.103 g, 0.296 mmol, 92% yield) as a clear colorless oil in 85:15 dr. Analytical data for **2n**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2954, 2929, 2859, 1732, 1452, 1435, 1256, 1092, 1068, 698; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 – 7.30 (m, 4H), 7.28 (dd,  $J$  = 7.7, 4.5 Hz, 1H), 4.55 – 4.37 (m, 1H), 3.87 (d,  $J$  = 9.0 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.73 – 2.52 (m, 1H), 2.14 – 1.95 (m, 2H), 1.95 – 1.77 (m, 2H), 1.77 – 1.49 (m, 2H), 1.30 (d,  $J$  = 3.4 Hz, 5H), 0.88 (bs, 3H); **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.6, 169.7, 142.4, 128.2, 127.4, 125.9, 82.2, 80.2, 56.8, 52.4, 51.9, 32.6, 31.6, 29.7, 26.9, 22.6, 14.0; **TLC** (10% EtOAc/hexanes)  $R_f$  0.25; **Anal.** Calcd. For  $\text{C}_{20}\text{H}_{28}\text{O}_5$ : C, 68.94; H, 8.10. Found: C, 69.17; H, 8.06.

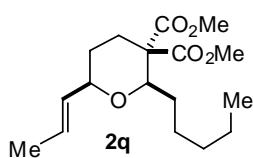


**Dimethyl 2-isopropyl-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2o):** The title compound was prepared according to General Procedure C

using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), isobutyraldehyde (0.070 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045 g, 0.0161 mmol, 0.05 equiv), and 1,2-dichloroethane (1.28 mL). After stirring for 22.0 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (7.5% EtOAc/hexanes) to afford **2o** (0.091 g, 0.284 mmol, 88% yield) as a clear colorless oil in 91:9 dr. Analytical data for **2o**: **IR** (thin film,  $\text{cm}^{-1}$ ) 2953, 2871, 1731, 1450, 1435, 1254, 1092, 1068, 1013, 698; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 4.48 (dd,  $J$  = 10.9, 3.1 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.72 – 3.66 (m, 1H), 2.62 (dt,  $J$  = 12.8, 3.1 Hz, 1H), 2.51 – 2.28 (m, 1H), 2.07 (td,  $J$  = 12.8, 4.8 Hz, 1H), 2.01 – 1.80 (m, 2H), 1.01 (d,  $J$  = 6.6 Hz, 3H), 0.95 (d,  $J$  = 6.9 Hz, 3H); **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2, 169.7, 142.6, 128.2, 127.3, 125.7, 86.9, 80.1, 56.2, 52.3, 52.0, 33.6, 31.7, 29.7, 20.2, 19.8; **TLC** (7.5% EtOAc/hexanes)  $R_f$  0.16; **Anal.** Calcd. For  $\text{C}_{18}\text{H}_{24}\text{O}_5$ : C, 67.48; H, 7.55. Found: C, 67.44; H, 7.67.

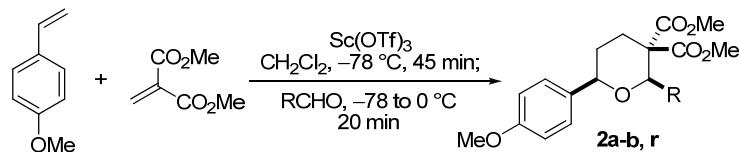


**Dimethyl 2-cyclohexyl-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2p):** The title compound was prepared according to General Procedure C using **1a** (0.080 g, 0.322 mmol, 1.0 equiv), cyclohexanecarboxaldehyde (0.108 g, 0.967 mmol, 3.0 equiv), MAD (0.011 g, 0.023 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0045 g, 0.0161 mmol, 0.05 equiv), and 1,2-dichloroethane (1.28 mL). After stirring for 24.0 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (10% EtOAc/hexanes) to afford **2p** (0.109 g, 0.302 mmol, 94% yield) as a clear colorless oil in 96:4 dr. Analytical data for **2p**: **IR** (thin film, cm<sup>-1</sup>) 2927, 2852, 1730, 1450, 1435, 1093, 1068, 1029, 1009; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 4.45 (dd, *J* = 10.7, 3.0 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.72 – 3.61 (m, 1H), 2.69 – 2.51 (m, 1H), 2.05 (td, *J* = 12.6, 4.8 Hz, 3H), 1.99 – 1.80 (m, 2H), 1.76 – 1.53 (m, 4H), 1.35 – 1.09 (m, 3H), 1.09 – 0.91 (m, 2H); **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 172.3, 169.7, 142.6, 128.2, 127.3, 125.7, 86.2, 80.2, 56.1, 52.3, 52.0, 41.6, 33.7, 30.4, 30.1, 29.8, 26.8, 26.6, 26.3; **TLC** (10% EtOAc/hexanes) *R*<sub>f</sub> 0.32; **Anal.** Calcd. For C<sub>18</sub>H<sub>24</sub>O<sub>5</sub>: C, 69.98; H, 7.83. Found: C, 69.80; H, 7.99.



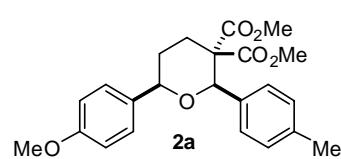
**Dimethyl 2-pentyl-6-((E)-prop-1-enyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2q):** **Dimethyl 2-cyclohexyl-6-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2p):** The title compound was prepared according to General Procedure C using **1d** (0.040 g, 0.188 mmol, 1.0 equiv), hexanal (0.056 g, 0.564 mmol, 3.0 equiv), MAD (0.0063 g, 0.013 mmol, 0.07 equiv), HNTf<sub>2</sub> (0.0027 g, 0.0094 mmol, 0.05 equiv), and 1,2-dichloroethane (0.75 mL). After stirring for 3.5 h, the reaction was complete as determined by TLC analysis. The reaction was worked up and purified by flash chromatography (10% EtOAc/hexanes) to afford **2q** (0.050 g, 0.156 mmol, 85% yield) as a clear colorless oil in 77:23 dr containing an inseparable cyclobutane decomposition product (16%, by mass). Corrected yield: 0.042 g, 0.134 mmol, 72%. Analytically pure material was obtained by HPLC purification. Analytical data for **2q**: **IR** (thin film, cm<sup>-1</sup>) 2955, 2929, 2858, 1733, 1436, 1256, 1230, 1085, 1068, 1016, 966; **<sup>1</sup>H NMR** (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ 5.68 – 5.56 (m, 1H), 5.52 (dd, *J* = 15.6, 4.6 Hz, 1H), 4.00 – 3.83 (m, 1H), 3.74 (d, *J* = 6.4 Hz, 1H), 3.38 (s, 3H), 3.27 (s, 3H), 2.71 – 2.52 (m, 1H), 2.17 (td, *J* = 14.5, 9.8, 4.9 Hz, 1H), 2.10 – 1.93 (m, 2H), 1.92 – 1.70 (m, 2H), 1.54 (m, 1H), 1.48 (d, *J* = 6.0 Hz, 3H), 1.44 – 1.20 (m, 5H), 0.86 (t, *J* = 7.0 Hz, 3H); **<sup>13</sup>C NMR** (100 MHz, C<sub>6</sub>D<sub>6</sub>) δ 172.4, 170.2, 133.4, 126.6, 82.8, 79.7, 57.7, 52.4, 52.1, 33.9, 33.3, 32.7, 29.4, 28.2, 23.6, 18.3, 14.8; **TLC** (10% EtOAc/hexanes) *R*<sub>f</sub> 0.27; **LRMS** (ESI) Calcd. For C<sub>17</sub>H<sub>28</sub>O<sub>5</sub>+Na: 335.2, Found: 335.2.

**General Procedure D for the Sc(OTf)<sub>3</sub>-catalyzed [[2 + 2] + 2] cycloaddition of 1-methoxy-4-vinylbenzene, dimethyl 2,2-methylidene malonate, and aldehydes to afford tetrahydropyrans 2a-b, r:**

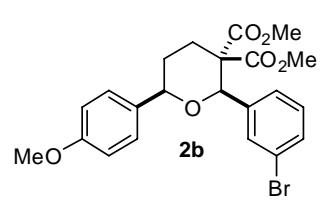


In an inert atmosphere glove box, a 1-dram shell vial containing a magnetic stir bar was charged with Sc(OTf)<sub>3</sub> (0.0171 g, 0.0347 mmol, 0.10 equiv). A second shell vial was charged with dimethyl 2,2-methylidene malonate<sup>1</sup> (DMM, 0.50 g, 0.347 mmol, 1.0 equiv) and fitted with a

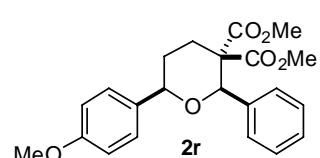
rubber septum. Both vessels were removed from the glove box and placed under N<sub>2</sub>. The Sc(OTf)<sub>3</sub> was suspended in CH<sub>2</sub>Cl<sub>2</sub> (0.25 mL) and cooled to -78 °C in an isopropanol/dry ice bath. The DMM was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) and 1-methoxy-4-vinylbenzene (0.061 g, 0.061 mL, 1.3 equiv) was added via syringe. The resulting solution was drawn into a syringe and added to the Sc(OTf)<sub>3</sub> by syringe pump over 45 min. When the disappearance of DMM was confirmed by TLC (using 20% EtOAc/hexanes, approx 5-10 min), the aldehyde (1.04 mmol, 3.0 equiv) was added neat via syringe. The reaction was held at -78 °C for 20 min and was then warmed to 0 °C for an additional 20 min at which point disappearance of **1b** can be observed by TLC (20% EtOAc/hexanes). The reaction was filtered through a 1-inch Monstr-Pette plug of silica with CH<sub>2</sub>Cl<sub>2</sub> (12 mL) and concentrated. The resulting tetrahydropyrans **2a-b, r** were purified by flash chromatography using the indicated solvent system.



**Dimethyl 6-(4-methoxyphenyl)-2-p-tolylidihydro-2H-pyran-3,3(4H)-dicarboxylate (2a):** The title compound was prepared according to General Procedure D using Sc(OTf)<sub>3</sub> (0.0171 g, 0.0347 mmol, 0.10 equiv), DMM (0.50 g, 0.347 mmol, 1.0 equiv), 1-methoxy-4-vinylbenzene (0.061 g, 0.061 mL, 1.3 equiv), 4-methylbenzaldehyde (0.125 g, 0.124 mL, 1.04 mmol, 3.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (2.25 mL). After work up and purification by flash chromatography (15% EtOAc/hexanes), **2a** (0.096 g, 0.241 mmol, 69% yield) was afforded as colorless crystals in 99:1 dr.

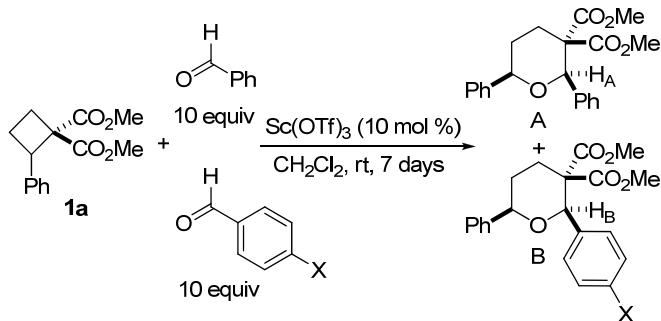


**Dimethyl 6-(4-methoxyphenyl)-2-(3-bromophenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (2b):** The title compound was prepared according to General Procedure D using Sc(OTf)<sub>3</sub> (0.0171 g, 0.0347 mmol, 0.10 equiv), DMM (0.50 g, 0.347 mmol, 1.0 equiv), 1-methoxy-4-vinylbenzene (0.061 g, 0.061 mL, 1.3 equiv), 3-bromobenzaldehyde (0.192 g, 0.122 mL, 1.04 mmol, 3.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (2.25 mL). After work up and purification by flash chromatography (15% EtOAc/hexanes), **2b** (0.076 g, 0.164 mmol, 47% yield) was afforded as a clear colorless oil in 97:3 dr.



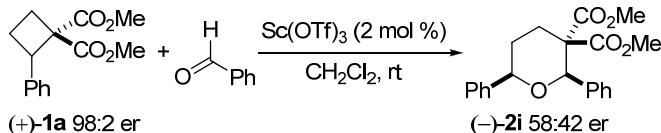
**Dimethyl 6-(4-methoxyphenyl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (2r):** The title compound was prepared according to General Procedure D using Sc(OTf)<sub>3</sub> (0.0171 g, 0.0347 mmol, 0.10 equiv), DMM (0.50 g, 0.347 mmol, 1.0 equiv), 1-methoxy-4-vinylbenzene (0.061 g, 0.061 mL, 1.3 equiv), benzaldehyde (0.110 g, 0.105 mL, 1.04 mmol, 3.0 equiv), and CH<sub>2</sub>Cl<sub>2</sub> (2.25 mL). After work up and purification by flash chromatography (20% EtOAc/hexanes), **2r** (0.079 g, 0.205 mmol, 59% yield) was afforded as a clear colorless oil in 98:2 dr. Analytical data for **2r**: **IR** (thin film, cm<sup>-1</sup>) 2952, 2838, 1730, 1614, 1515, 1435, 1250, 1176, 1082, 1033, 828, 700; **1H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.48 (d, *J* = 7.5 Hz, 4H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.29 (m, 3H), 7.29 – 7.24 (m, 2H), 5.18 (s, 1H), 4.66 (m, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.57 (s, 3H), 2.72 – 2.70 (m, 1H), 2.34 (dt, *J* = 13.5, 4.5 Hz, 1H), 2.18 – 2.10 (m, 1H), 1.96 – 1.93 (m, 1H); **13C NMR** (125 MHz, CDCl<sub>3</sub>) δ 171.3, 169.1, 159.0, 139.4, 134.5, 127.5, 127.4, 127.2, 127.1, 113.6, 82.3, 80.3, 58.5, 55.2, 52.4, 51.6, 32.7, 29.9; **TLC** (20% EtOAc/hexanes) *R<sub>f</sub>* 0.23; **LRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>+Na: 407.2, Found: 407.2.

**Procedure for the competition experiment (Equation 3):**



In an inert atmosphere glove box, a 1-dram vial containing a magnetic stir bar was charged with the  $\text{Sc}(\text{OTf})_3$  (0.0079 g, 0.0161 mmol, 0.10 equiv). To this vial was added a solution of cyclobutane **1a** (0.040 g, 0.161 mmol, 1.0 equiv), benzaldehyde (0.171 g, 1.61 mmol, 10 equiv), and 4-X-PhCHO (1.61 mmol, 10 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.640 mL). The vial was sealed with a PTFE-lined screw cap, removed from the box, and allowed to stir. After 7 days, the contents of the vial were passed through a 1-inch Monstr-Pette plug of silica with  $\text{CH}_2\text{Cl}_2$  (12 mL) and concentrated *in vacuo*. The relative abundance of each product was determined by comparison of the  $^1\text{H}$  NMR resonances of  $\text{H}_A$  and  $\text{H}_B$ .

**Cycloaddition of (+)-**1a** with benzaldehyde (Figure 1):**



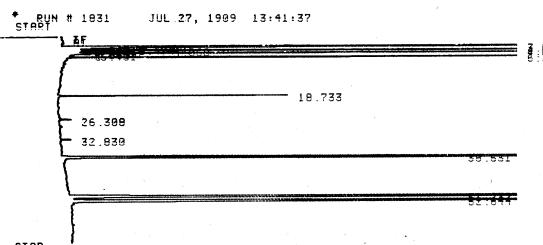
In the glove box, a 1-dram vial containing a magnetic stir bar was charged with  $\text{Sc}(\text{OTf})_3$  (0.001 g, 0.002 mmol, 0.02 equiv) (Vial #1). A solution of cyclobutane (+)-**1a** (0.025 g, 0.101 mmol, 1.0 equiv, 98:2 er), benzaldehyde (0.032 g, 0.302 mmol, 3.0 equiv), hexadecane (approx 0.025 g, GC internal standard) in  $\text{CH}_2\text{Cl}_2$  (0.50 mL) was mixed in a 1-dram vial (Vial #2). A 0.050 mL aliquot was removed ( $t = 0.0$  min) and the remaining contents of Vial #2 were transferred to Vial #1 by pipette, which was then sealed with a PTFE-lined screw cap, removed from the glove box, and allowed to stir. Periodically, 0.050 mL aliquots were removed from the reaction via syringe and quenched with 3.0 M  $\text{NH}_4\text{OH}$  and dried over  $\text{Na}_2\text{SO}_4$ . The er of remaining (+)-**1a** was determined by GC analysis (Chiradex B-DM column, 30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250 °C) and conversion was determined by comparison to the reference sample taken at  $t = 0.0$  min. SFC analysis (Chiralpack, WO, 2.0% MeOH, 2.0 mL/min, 200 bar, 210 nm, 40 °C) was used to determine the er of (-)-**2i**. Analytical data for (-)-**2i**: SFC analysis: er 58:42,  $t_{\text{r-major}}$  6.89 min,  $t_{\text{r-minor}}$  7.59 min;  $[\alpha]_D^{27} = -14.1$  ( $c = 0.100$ ,  $\text{CHCl}_3$ ).

**Table S1:** Stereochemical Analysis of the  $\text{Sc}(\text{OTf})_3$ -Catalyzed Formal [4 + 2] Cycloaddition of (+)-**1a** and Benzaldehyde.

Conversion (%)	0	12	23	32	42	45
(+)- <b>1a</b> er (%)	98	93	88.5	84.5	80.5	79
(-)- <b>2i</b> er (%)	-	59.5	59	58.5	58	58

GC data used to determine conversion and er of (+)-1a using a hexadecane internal standard:

**rac-1a and hexadecane**



Closing signal file M: SIGNAL.BNC  
Starting processed peaks to M: Q8C1F692.PRO  
DIRECTORY FULL

RUN# 1831 JUL 27, 1989 13:41:37

SIGNAL FILE: M: SIGNAL.BNC

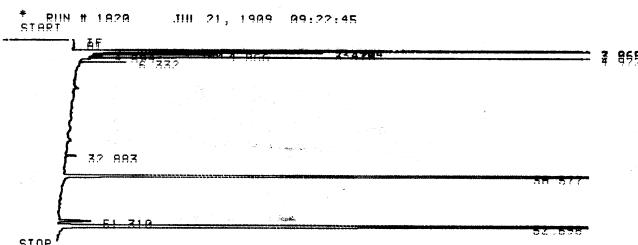
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3.474	2764	TBP	.039	.00264
3.718	1976	TBU	.044	.00198
4.068	26445	BH	.071	.02552
4.212	1827987	SHB	.013	1.74555
4.452	2165	TBP	.059	.00324
4.592	3595	BP	.113	.00377
4.917	37789192	SHB	.073	36.01269
5.401	1818	BP	.027	.00097
6.327	1750484	PB	.058	1.65912
18.733	140129	PU	.147	.13352
26.388	10493	PU	.200	.01991
32.893	12547	I PB	.267	.01196
38.556	4420134	PB	.287	4.21468
51.237	1493539	PU	.490	1.33830
52.776	1407182	UU	.414	1.34170

TOTAL AREA=1.0487E+08  
MUL FACTOR=1.0000E+00

**t = 0.0 min**  
**Conversion: 0%, er: 98:2**



Closing signal file M: SIGNAL.BNC  
Starting processed peaks to M: Q8B9D0E7.PRO  
DIRECTORY FULL

RUN# 1829 JUL 21, 1989 09:22:45

SIGNAL FILE: M: SIGNAL.BNC

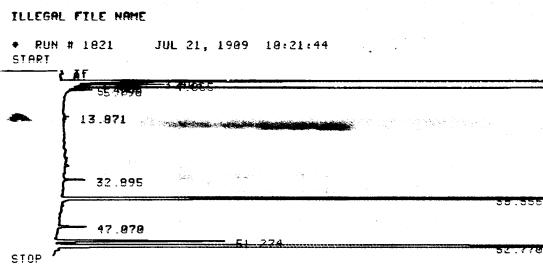
PEAK FILE : M: Q8B9D0E7.PRO

AREAX

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3.479	31059	TUB	.045	.04166
4.066	44369	TBU	.095	.05954
4.594	4574	TUB	.100	.00614
4.972	3734568	SHR	.056	5.01137
6.332	11146	BU	.063	.01496
32.893	11528	PP	.281	.01547
38.577	4018339	PB	.281	5.39131
51.310	49226	BP	.402	.06605
52.698	2256525	PU	.412	3.02794

TOTAL AREA=7.4524E+07  
MUL FACTOR=1.0000E+00

**t = 20 min**  
**Conversion: 12%, er: 93:7**



Closing signal file M: SIGNAL.BNC  
Starting processed peaks to M: Q8B9D0E9.PRO  
DIRECTORY FULL

RUN# 1821 JUL 21, 1989 10:21:44

SIGNAL FILE: M: SIGNAL.BNC

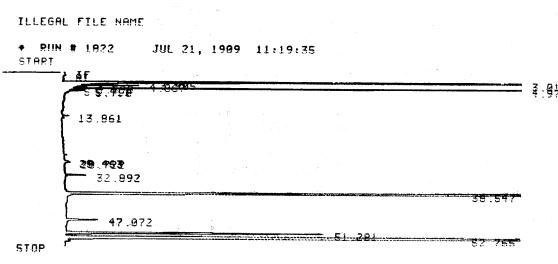
PEAK FILE : M: Q8B9D0E9.PRO

AREAX

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5.798	9433	TPU	.102	.01355
13.871	3969	PU	.155	.00566
32.895	22292	PU	.271	.03225
38.556	7499786	PB	.287	18.05132
47.878	40879	UP	.371	.05915
51.274	262649	BP	.402	.32997
52.778	3527958	PU	.415	5.10330

TOTAL AREA=6.9113E+07  
MUL FACTOR=1.0000E+00

**t = 40 min**  
**Conversion: 23%, er: 88.5:11.5**



Closing signal file M: SIGNAL.BNC  
Starting processed peaks to M: Q8B9E4C9.PRO  
DIRECTORY FULL

RUN# 1822 JUL 21, 1989 11:19:35

SIGNAL FILE: M: SIGNAL.BNC

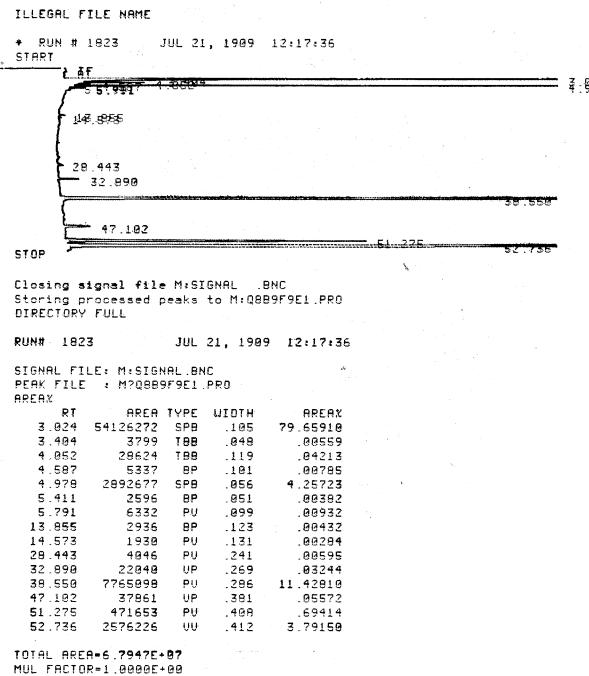
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AREAX

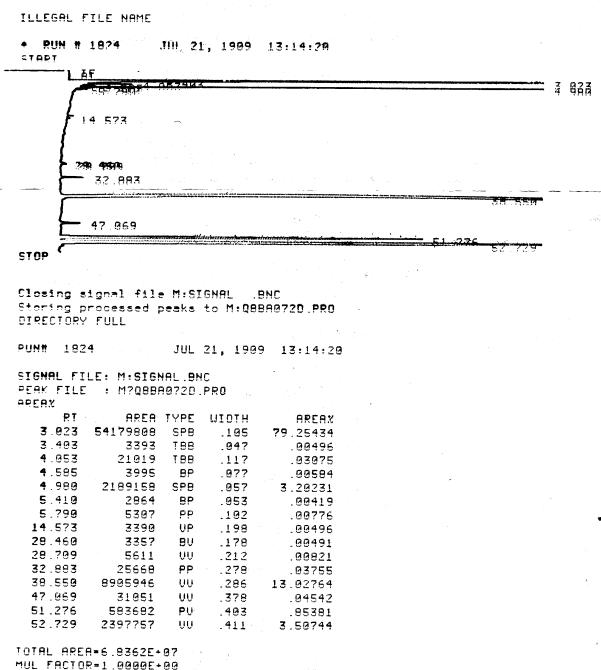
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4.979	2408274	SPB	.057	3.49727
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5.798	7532	PU	.199	.01891
13.861	4963	UU	.142	.00598
20.463	3482	PU	.199	.00594
28.722	4982	UP	.191	.00797
32.892	25297	UU	.290	.03663
38.547	8396243	UB	.285	12.05909
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TOTAL AREA=6.9859E+07  
MUL FACTOR=1.0000E+00

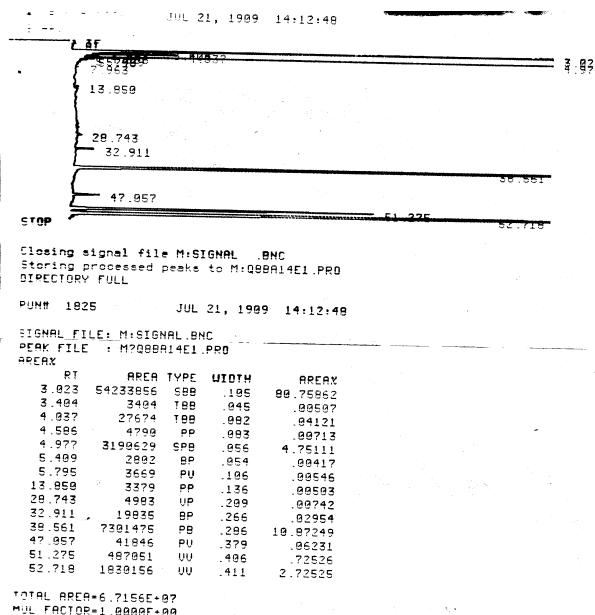
**t = 60 min**  
**Conversion: 32%, er: 84.5:15.5**



**t = 100 min**  
**Conversion: 42%, er: 80.5:19.5**



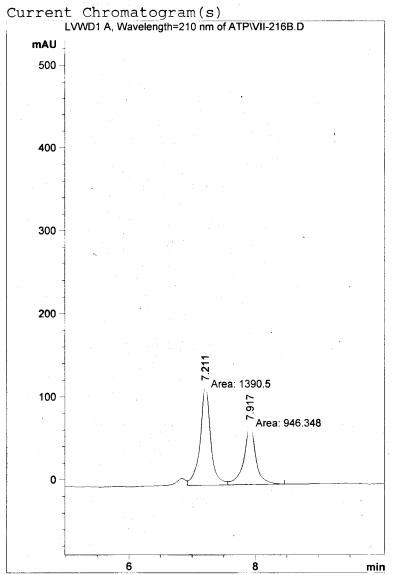
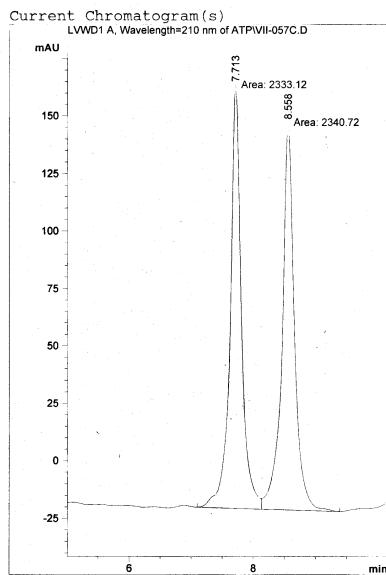
**t = 140 min**  
**Conversion: 45%, er: 79:21**



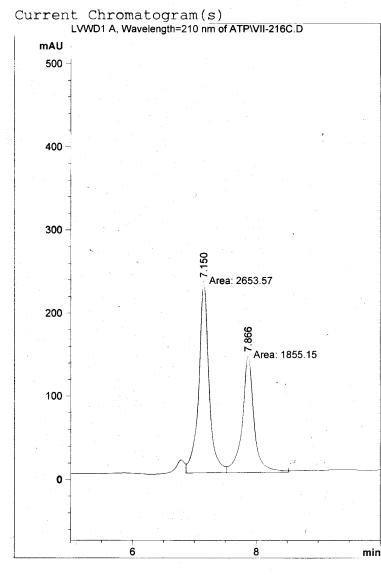
**SFC data used to determine the er of (-)-2i:**

**rac-2i**

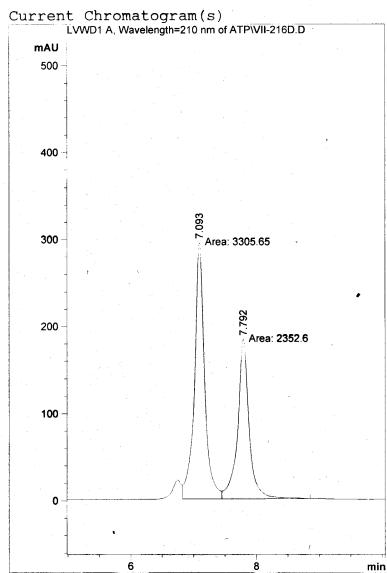
**$t = 20$  min**  
**Conversion: 12%, er: 59.5:40.5**



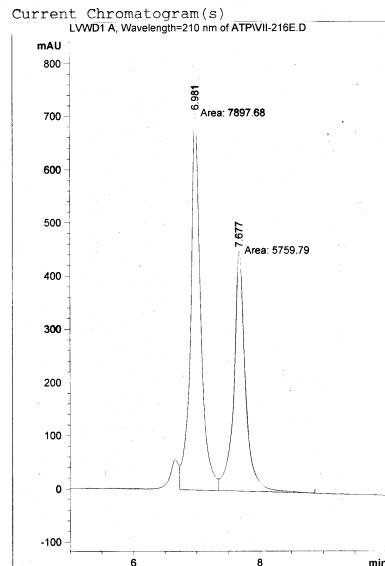
**$t = 40$  min**  
**Conversion: 23%, er: 59:41**



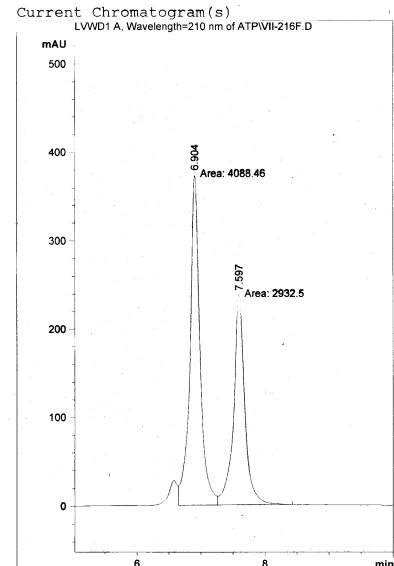
**$t = 60$  min**  
**Conversion: 32%, er: 58.5:41.5**



**$t = 100$  min**  
**Conversion: 42%, er: 58:42**

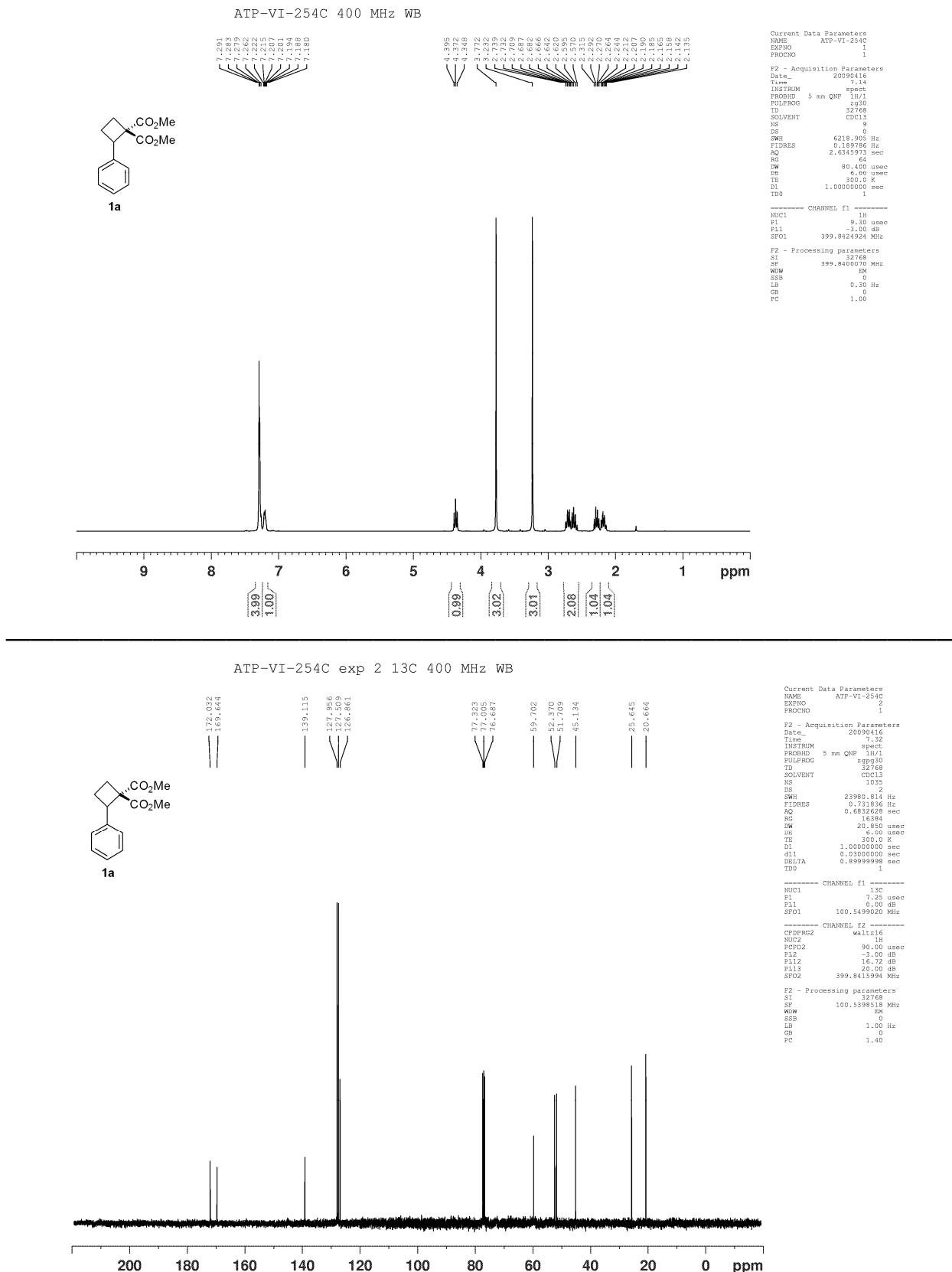


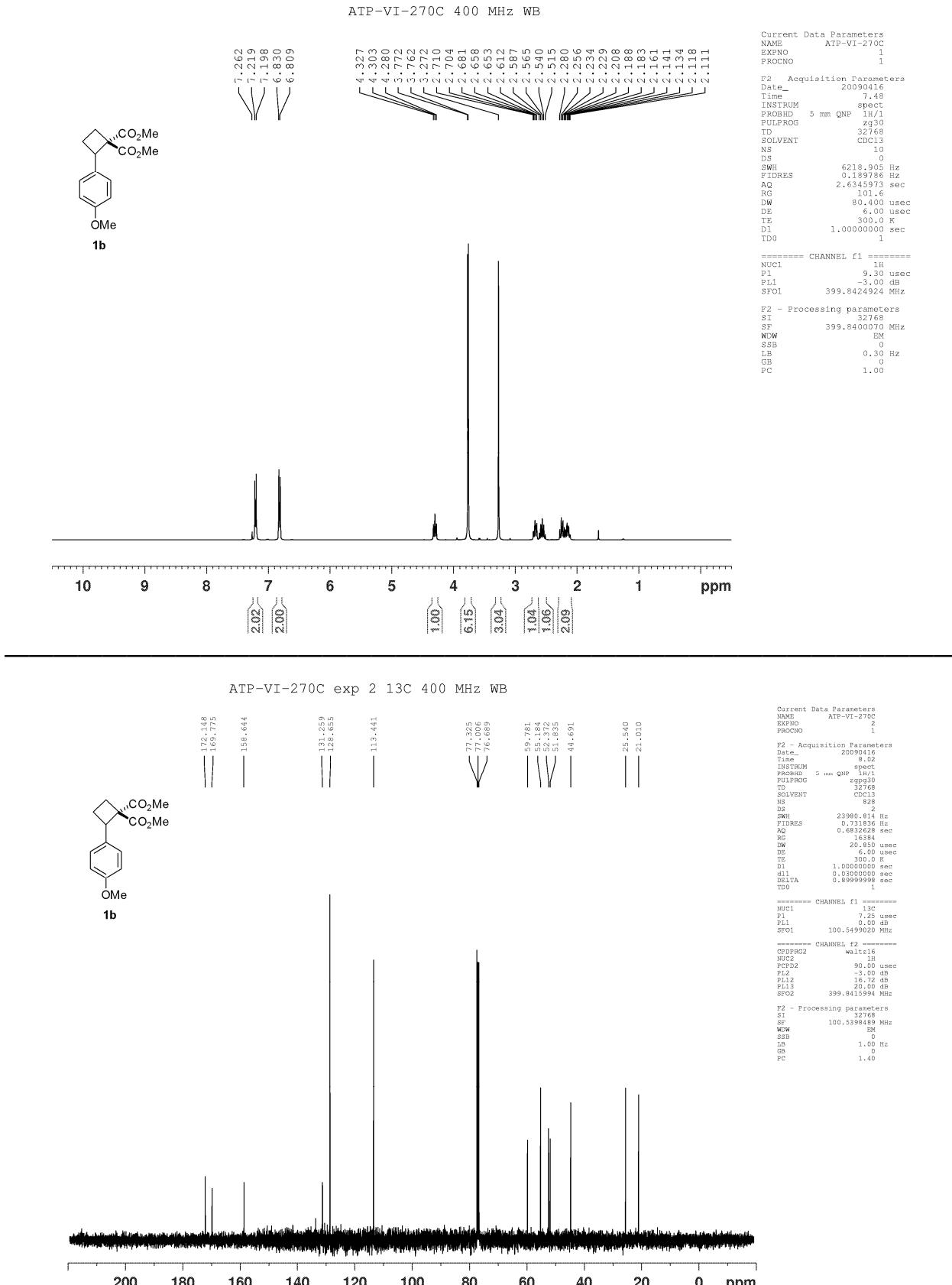
**$t = 140$  min**  
**Conversion: 45%, er: 58:42**



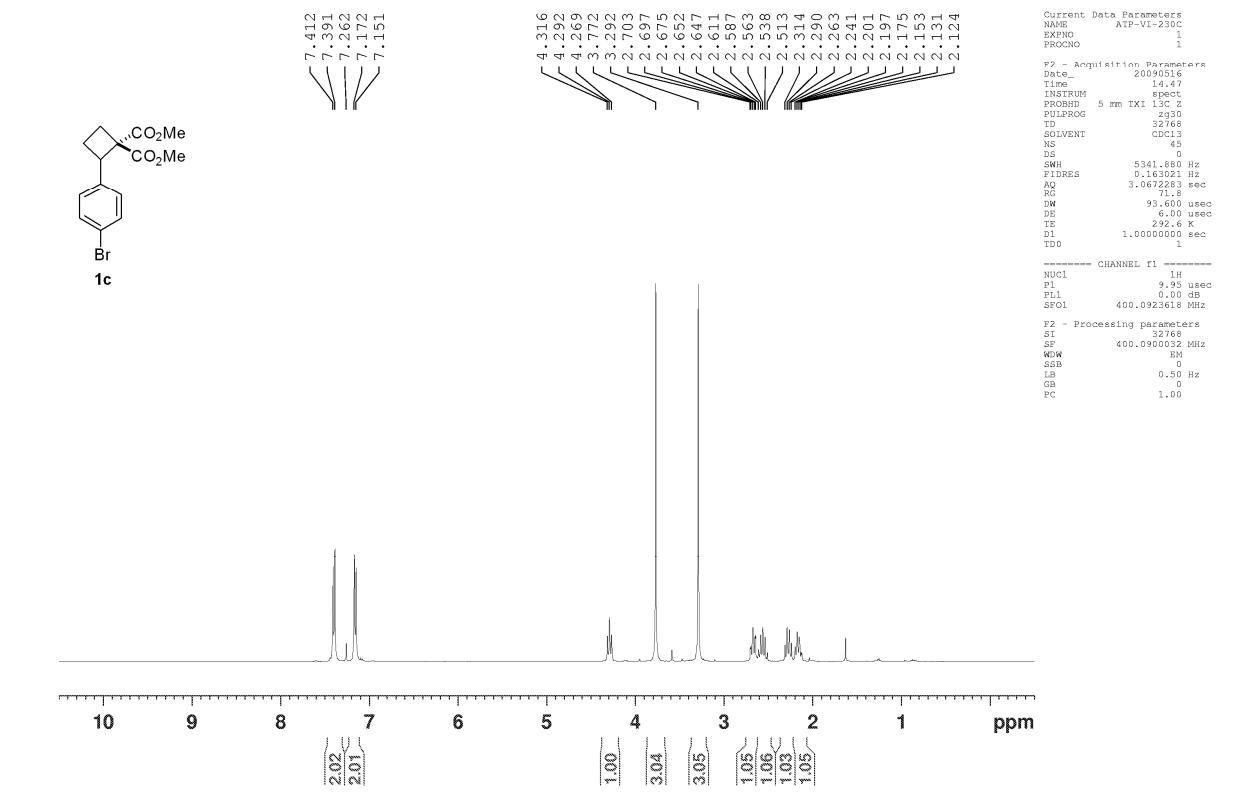
## References:

- (1) De Keyser, J.-L.; De Cock, C. J. C.; Poupaert, J. H.; Dumont, P. *J. Org. Chem.* **1988**, *53*, 4859–4862.
- (2) Corbin, T. F.; Hahn, R. C.; Shechter, H. *Org. Synth.* **1964**, *44* 30–33.
- (3) Varney, M. D.; Romines, W. H., III.; Boritzki, T.; Margosiak, S. A.; Bartlett, C.; Howland, E. *J. J. Heterocyclic Chem.* **1995**, 1493–1498.
- (4) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032–7035.
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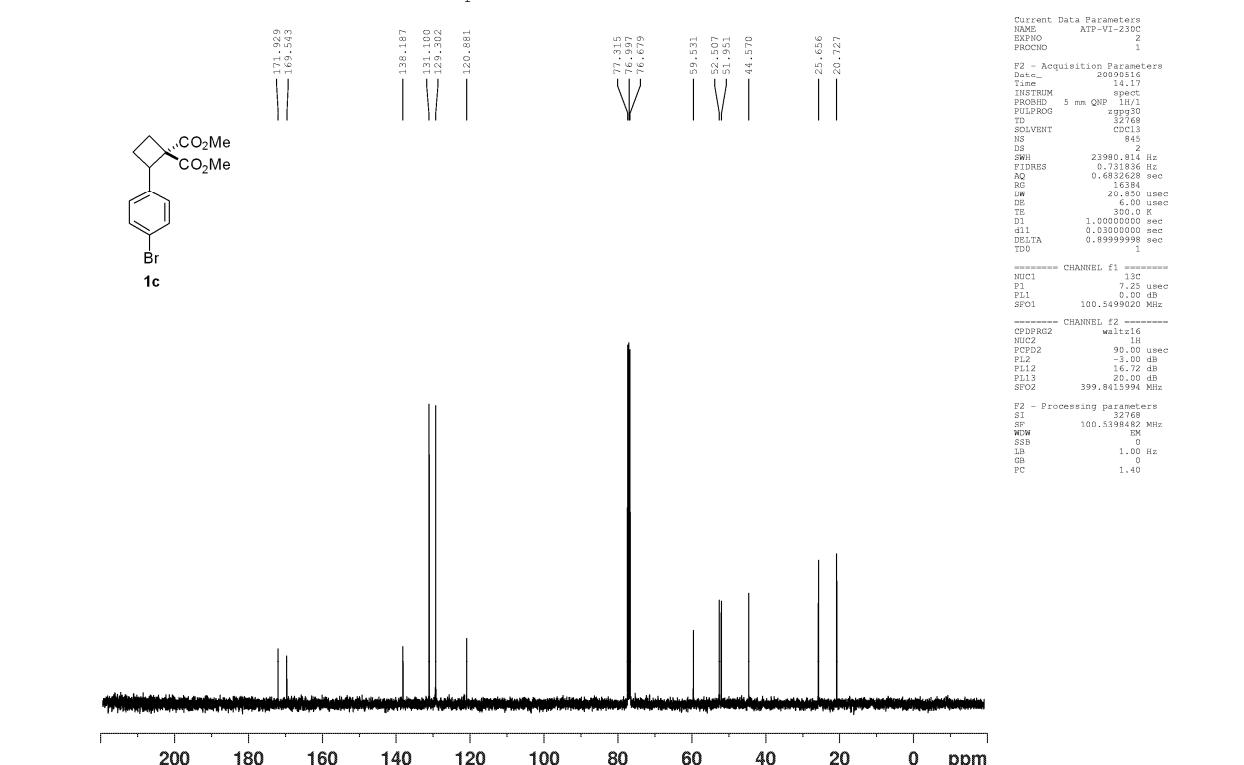


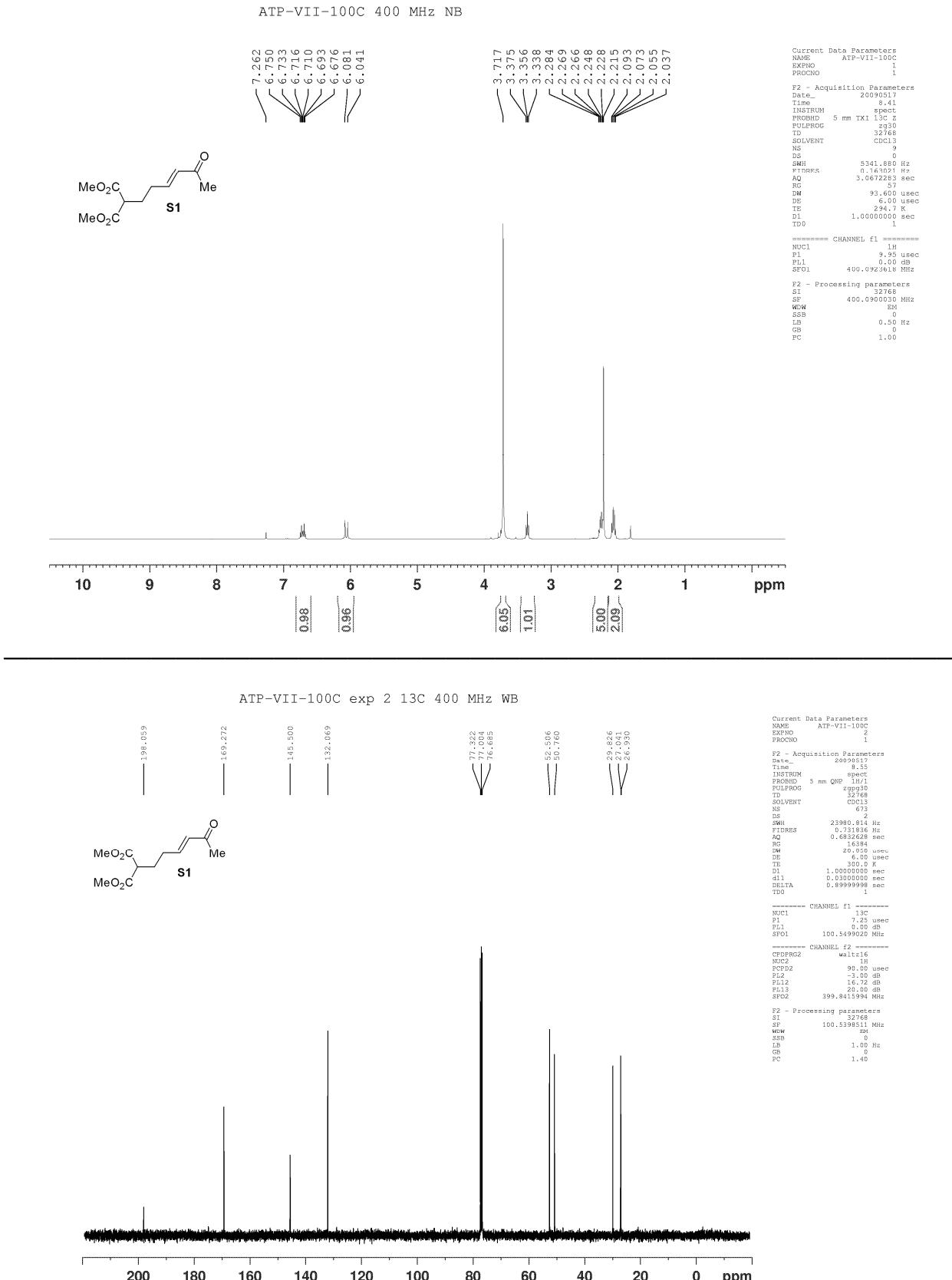


ATP-VI-230C 400 MHz NB

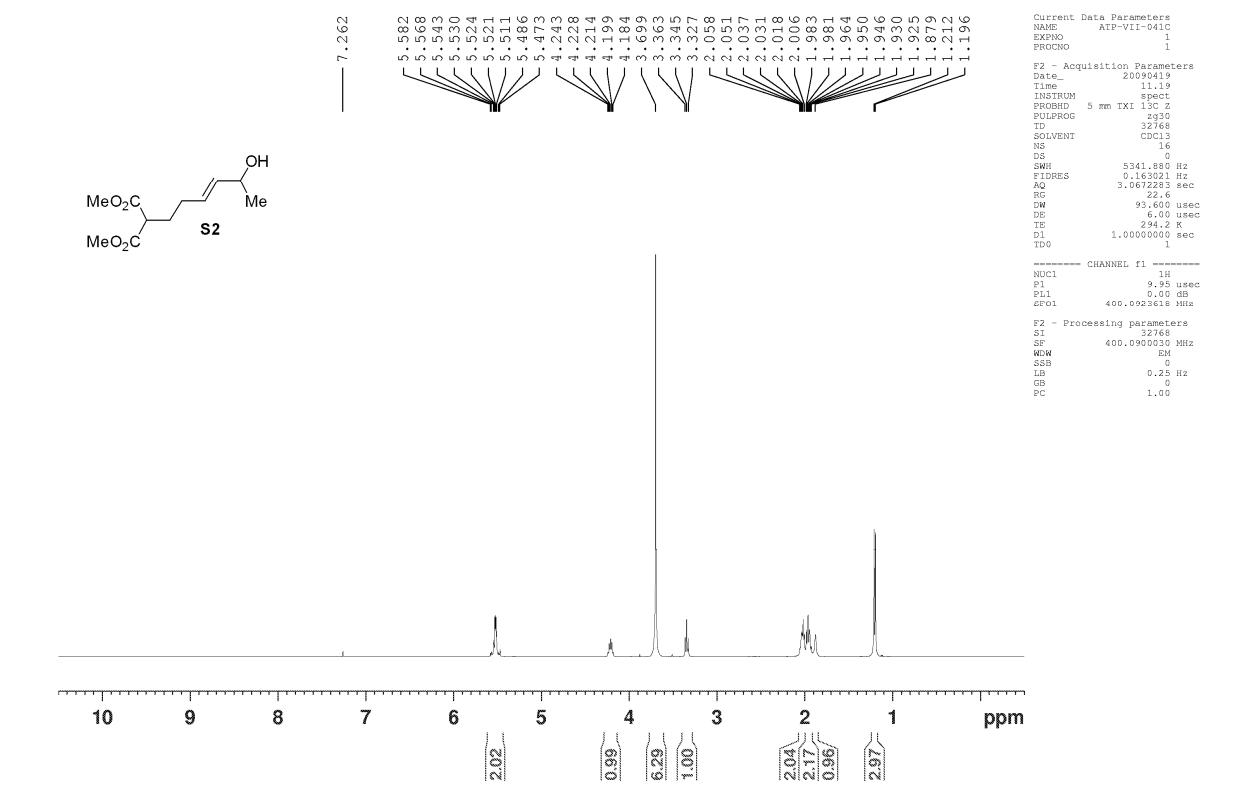


ATP-VI-230C exp 2 13C 400 MHz WB

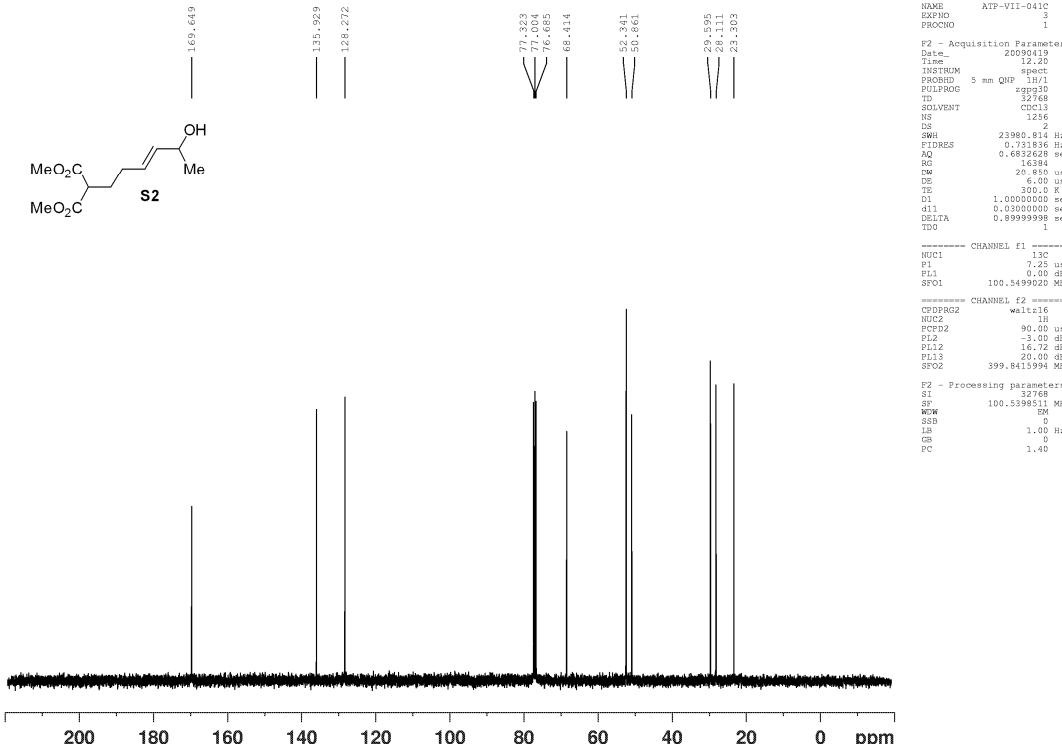


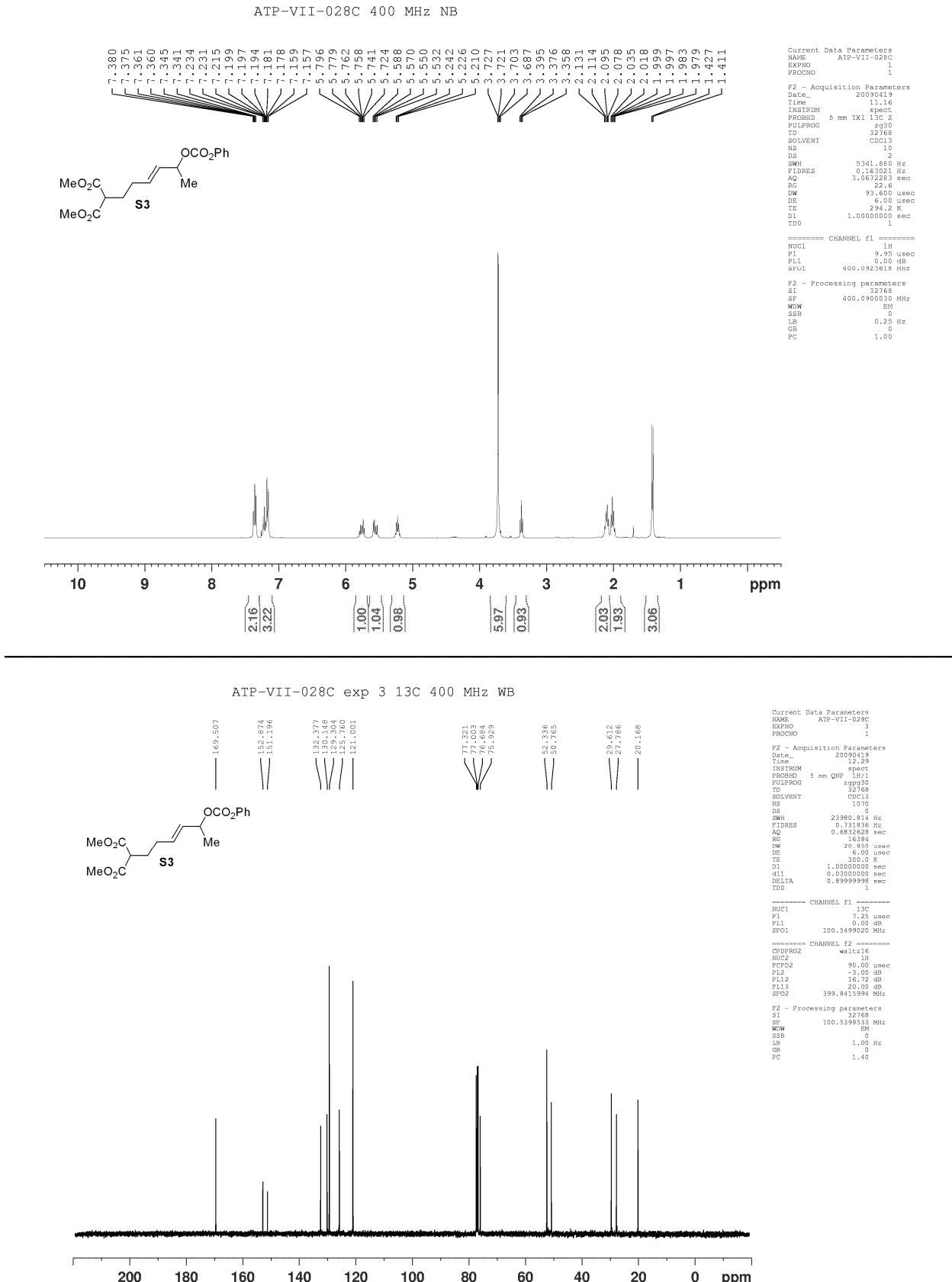


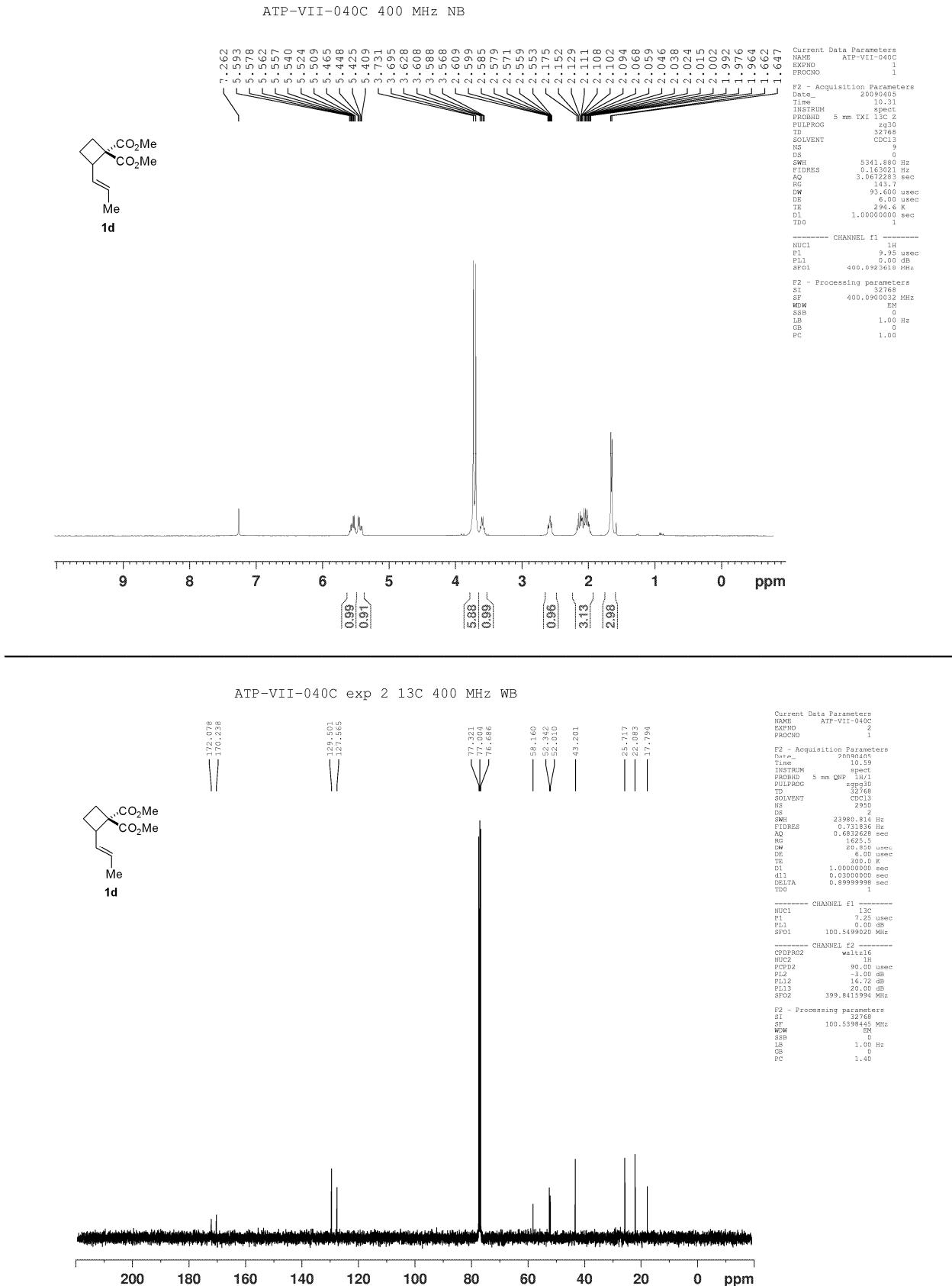
ATP-VII-041C 400 MHz NB

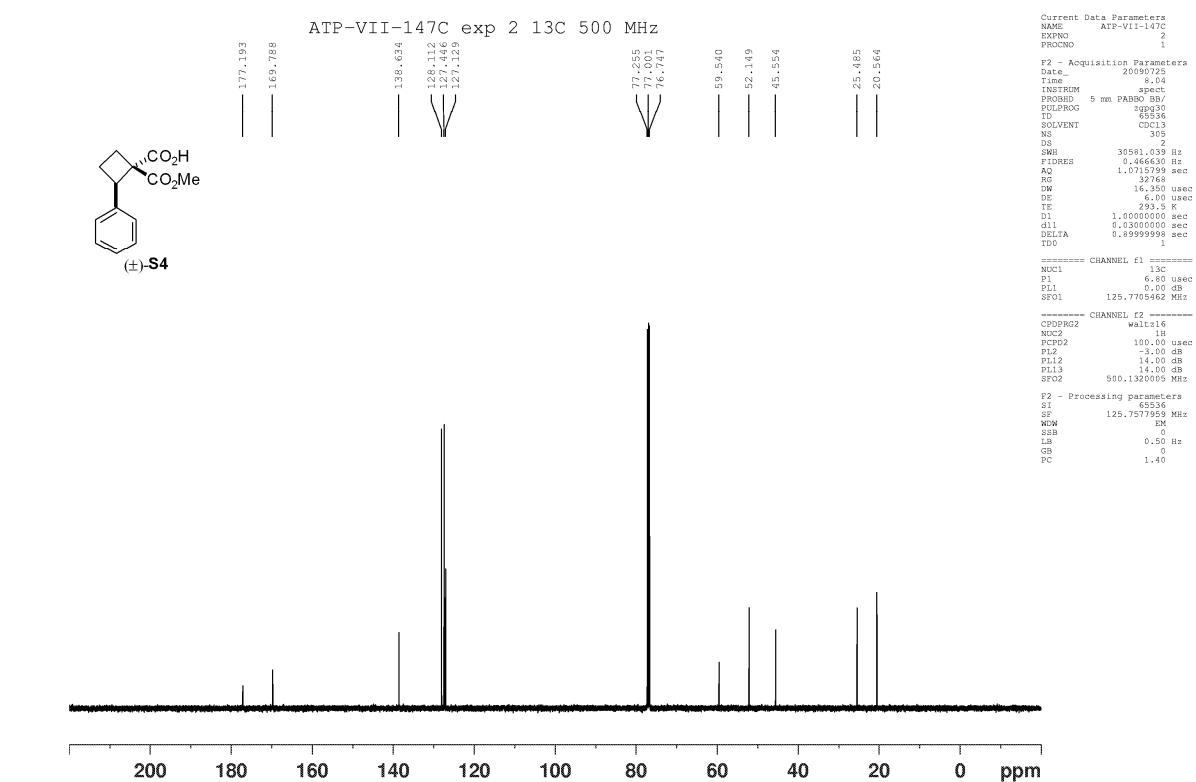
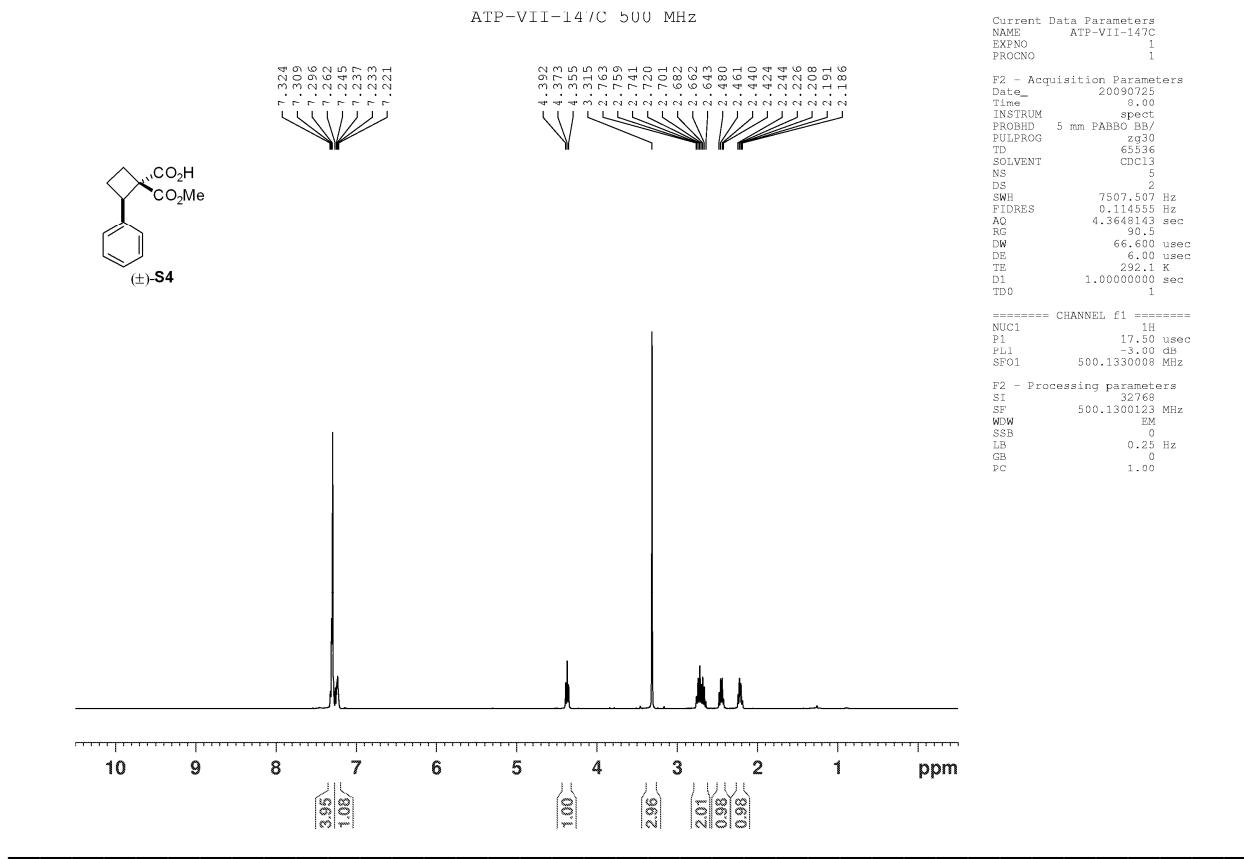


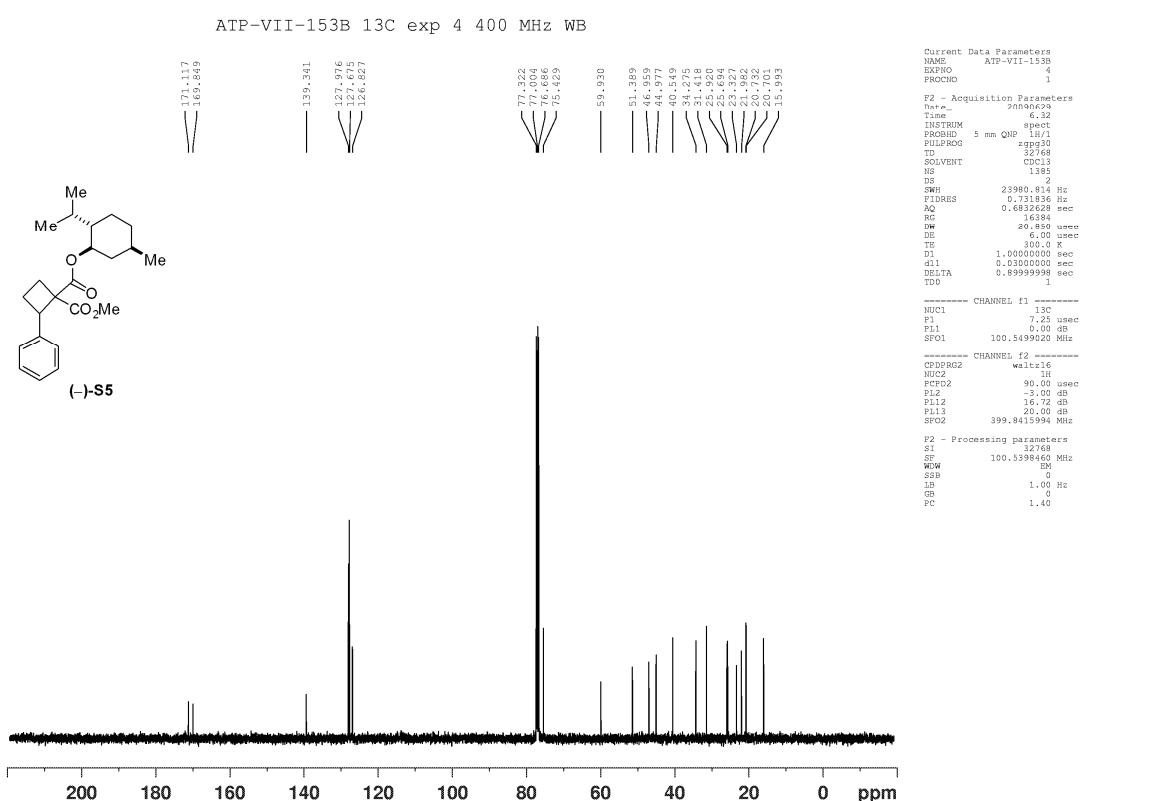
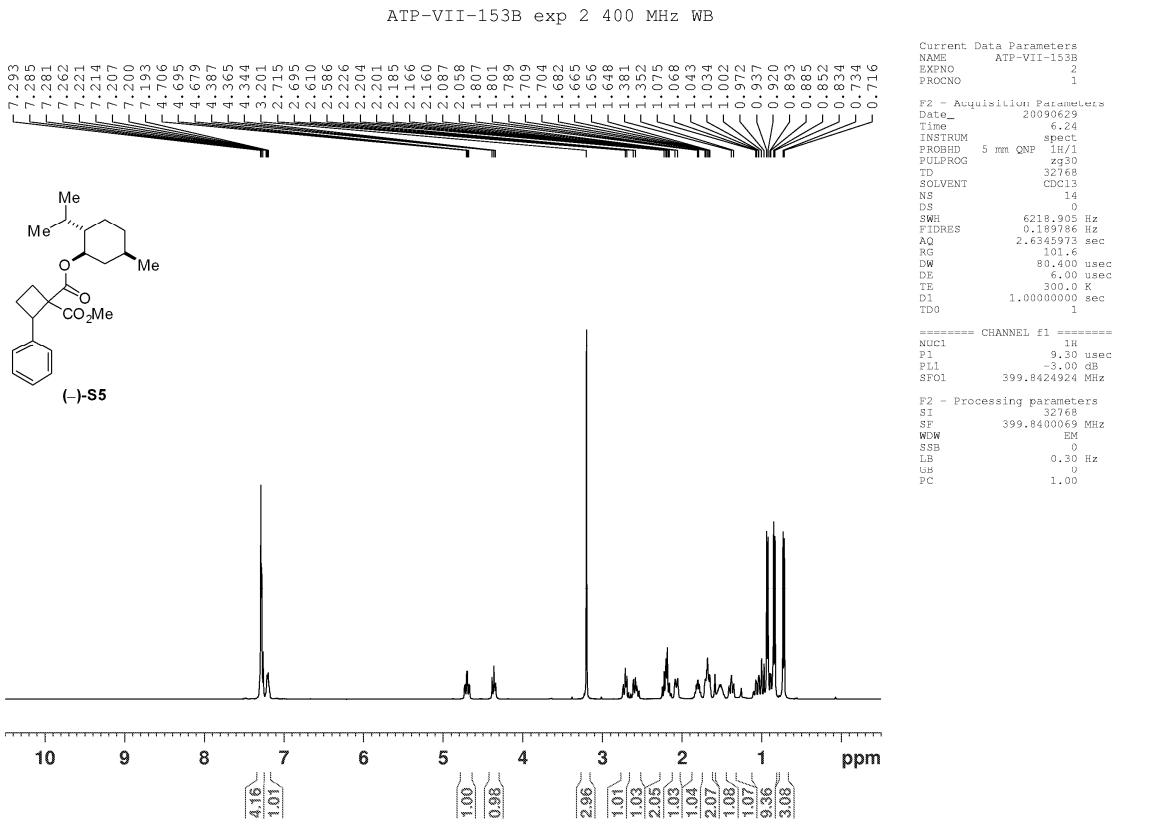
ATP-VII-041C exp 3 13C 400 MHz WB

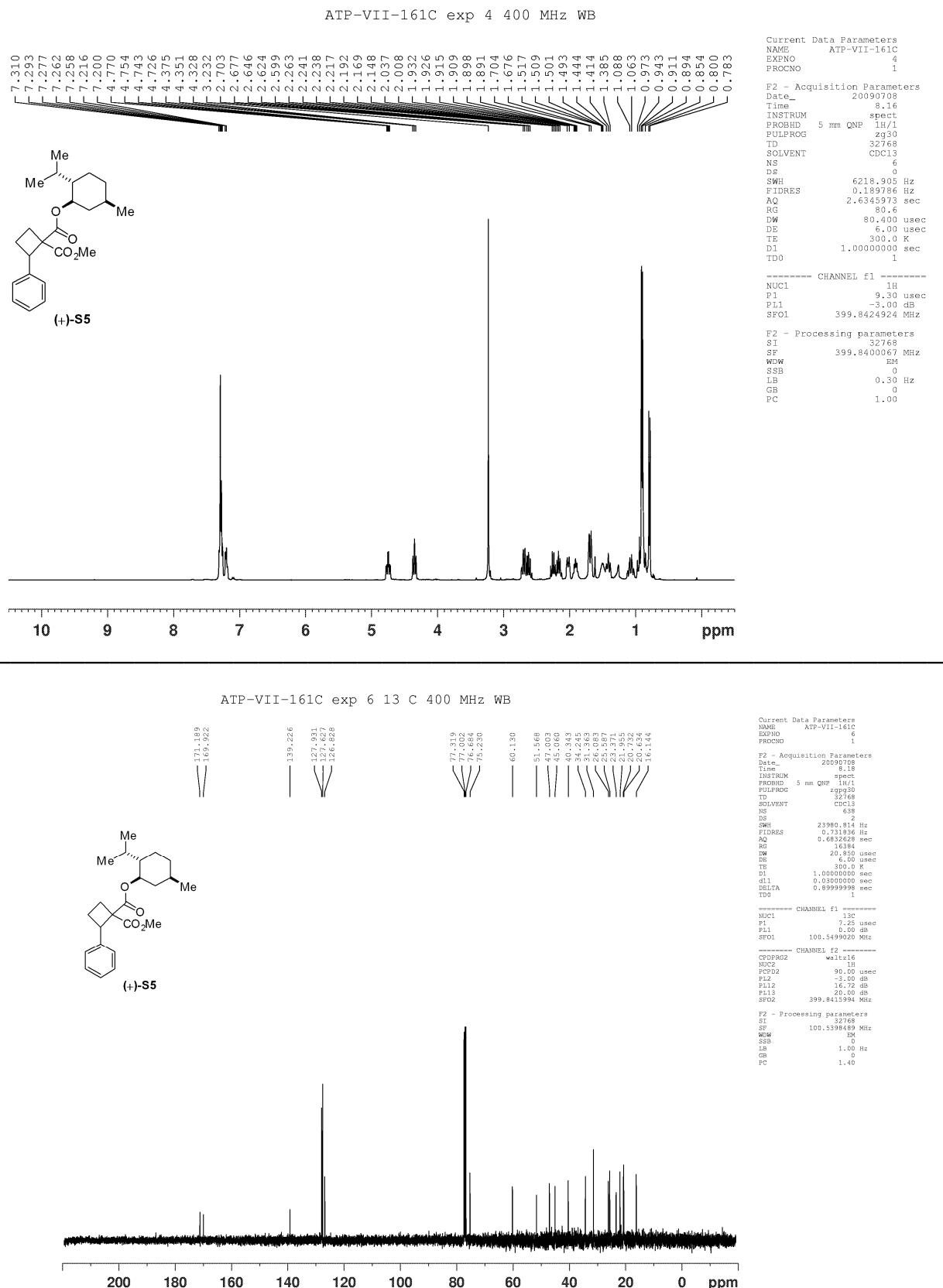


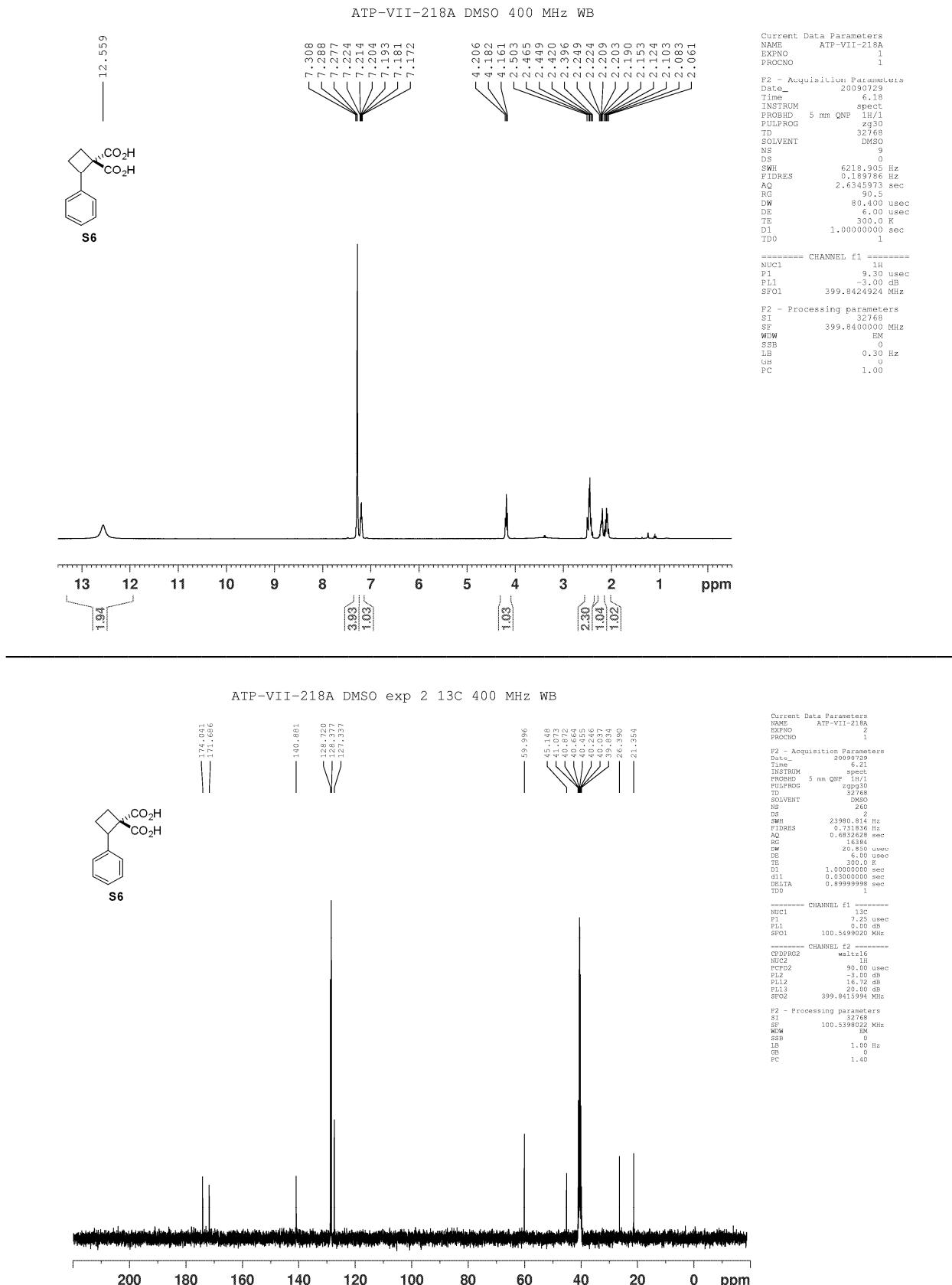




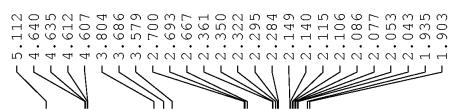
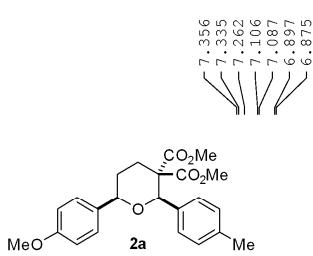








ATP-VII-094C 400 MHz WB

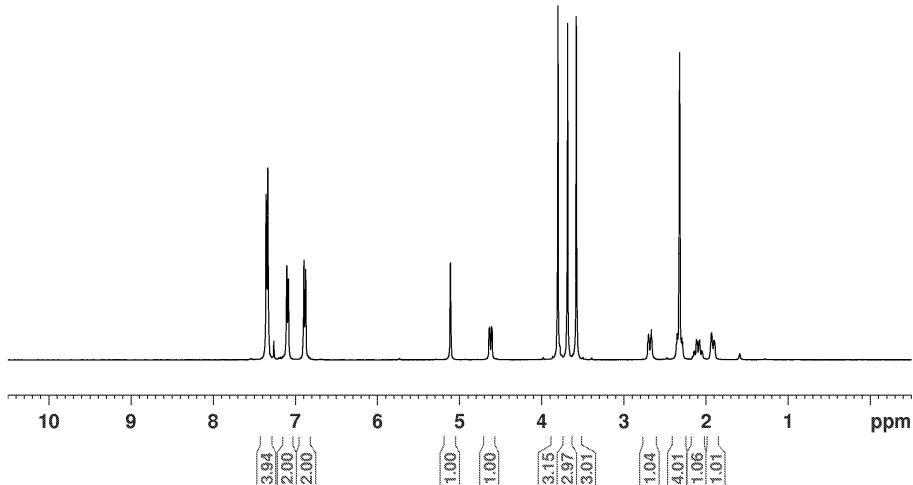


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EXPNO 1  
PROCNO 1

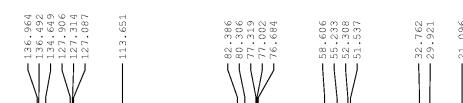
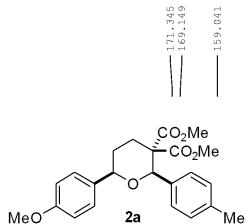
F2 - Acquisition Parameters  
Date 20090427  
Time 7.37  
INSTRUM spect  
PROBHD 5 mm QNP 1H/1  
PULPROG zg30  
TD 32768  
SOLVENT CDCl3  
NS 10  
DS 0  
SWH 6218.905 Hz  
FIDRES 0.1189786 Hz  
AQ 2.6342973 sec  
RG 90  
DW 80.400 usec  
DE 6.00 usec  
TE 300.0 K  
D1 1.0000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 9.30 usec  
PL1 -3.00 dB  
SF01 399.8424924 MHz

F2 - Processing parameters  
SI 32768  
SF 399.8400068 MHz  
WDW EM  
SSB 0  
LB 0.05 Hz  
GB 0  
PC 1.00



ATP-VII-094C exp 3 13C 400 MHz WB



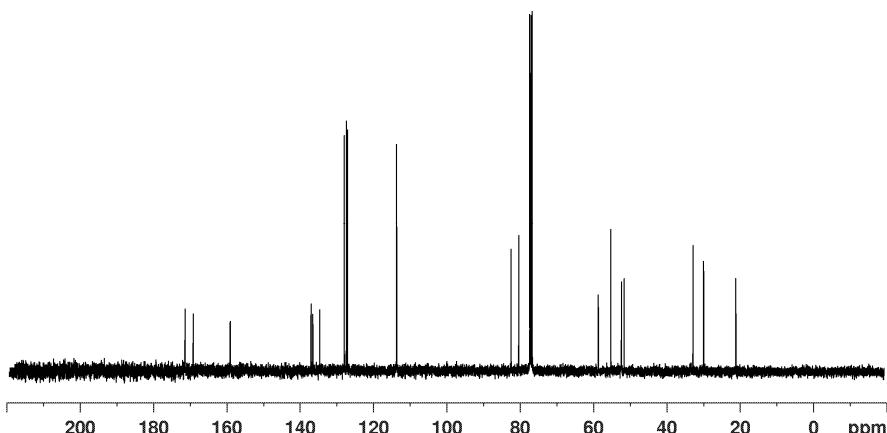
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NAME ATP-VII-094C  
EXPNO 3  
PROCNO 1

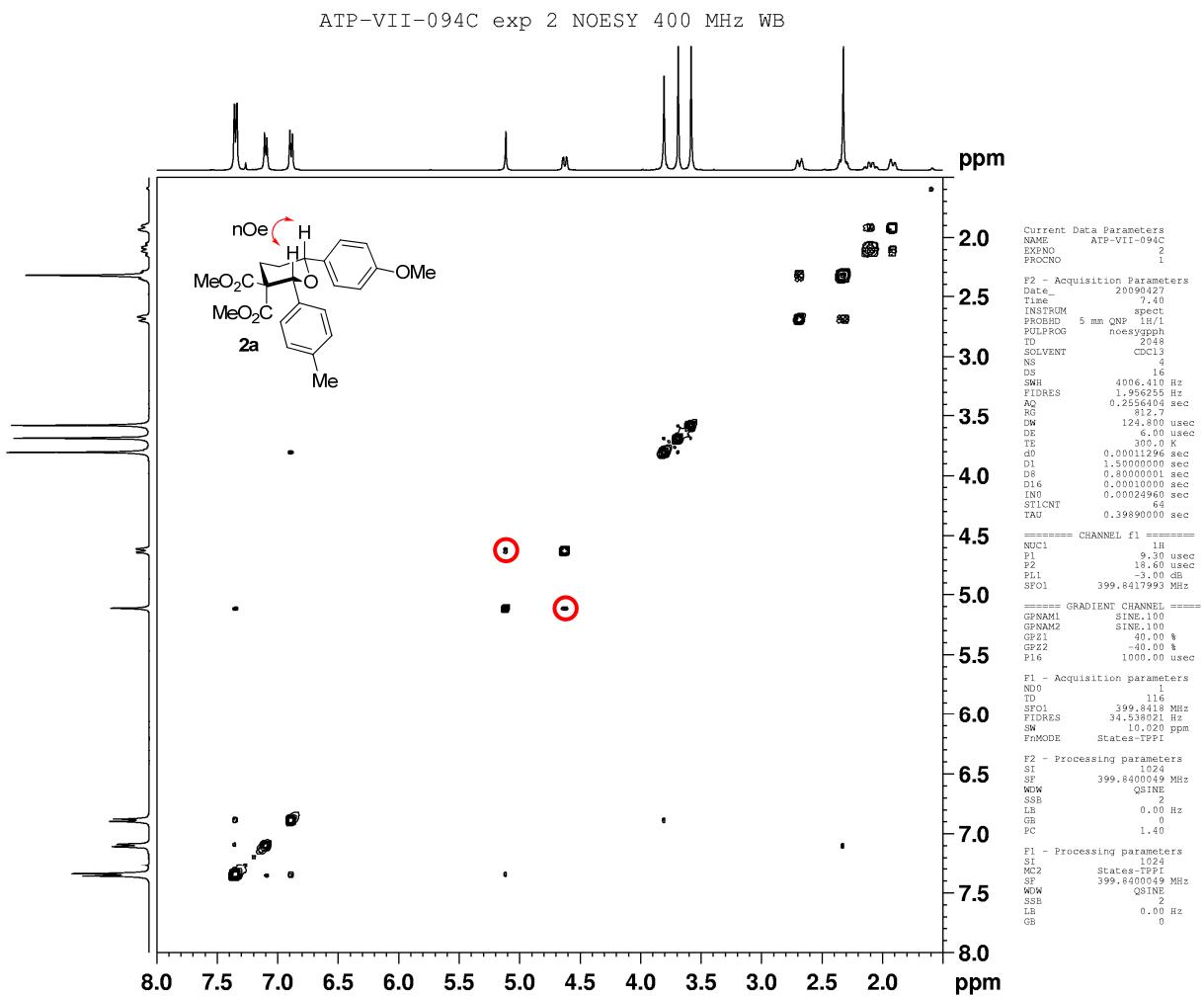
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Time 7.43  
INSTRUM spect  
PROBHD 5 mm QNP 1H/1  
PULPROG zg30  
TD 32768  
SOLVENT CDCl3  
NS 1019  
DS 0  
SWH 23982.814 Hz  
FIDRES 0.731836 Hz  
AQ 0.6832629 sec  
RG 140  
DW 2.00 usec  
DE 6.00 usec  
TE 300.0 K  
D1 1.0000000 sec  
M1 0.0500000 sec  
DELTA 0.8999998 sec  
TD0 1

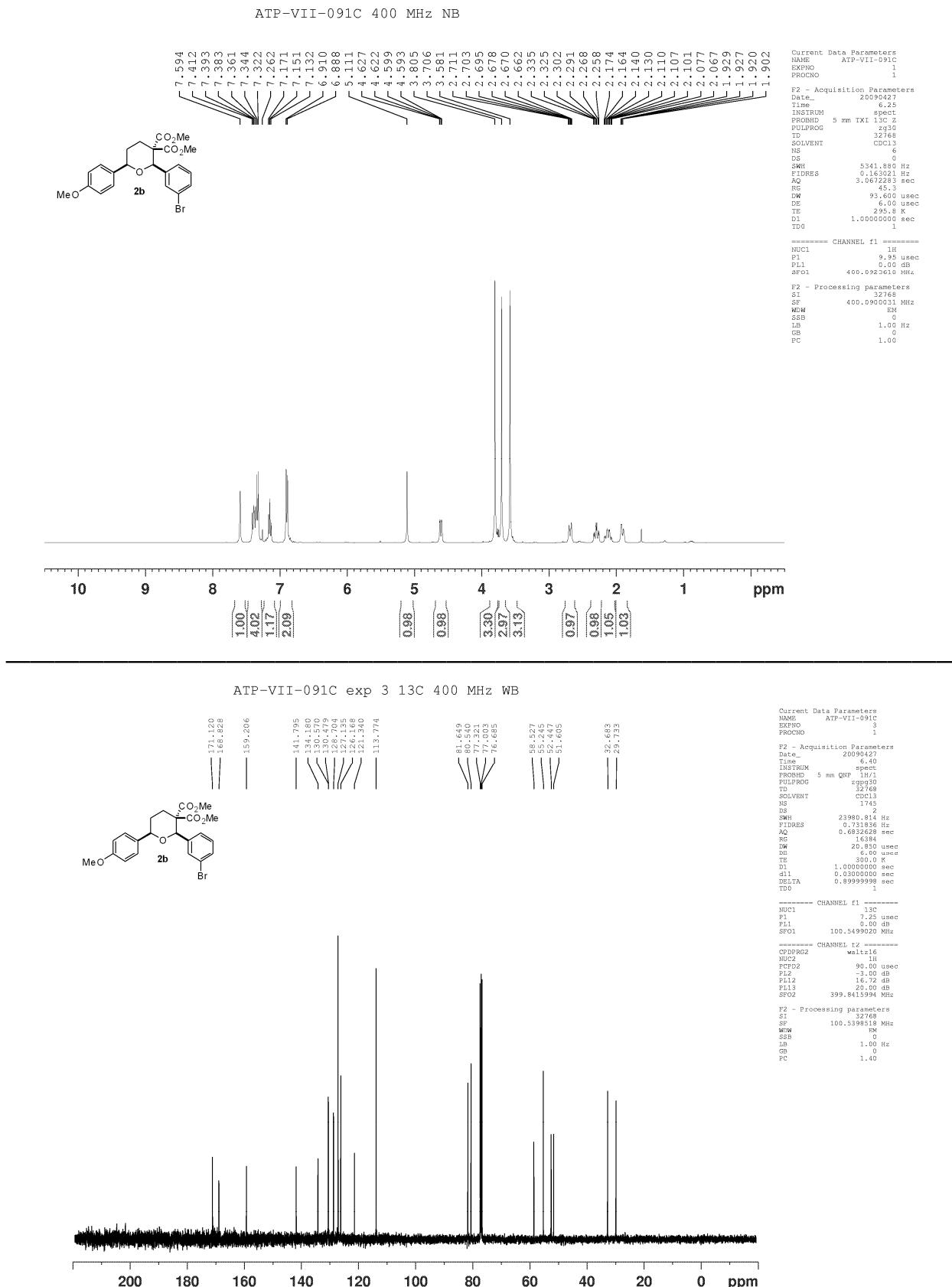
===== CHANNEL f1 =====  
NUC1 13C  
P1 7.35 usec  
PL1 0.00 dB  
SF01 100.5499020 MHz

===== CHANNEL F2 =====  
CP90RG2 waltz16  
NUC2 1H  
PCPD2 90.00 usec  
P2 1.00 dB  
P12 1.00 dB  
PL13 20.00 dB  
SF02 399.8413994 MHz

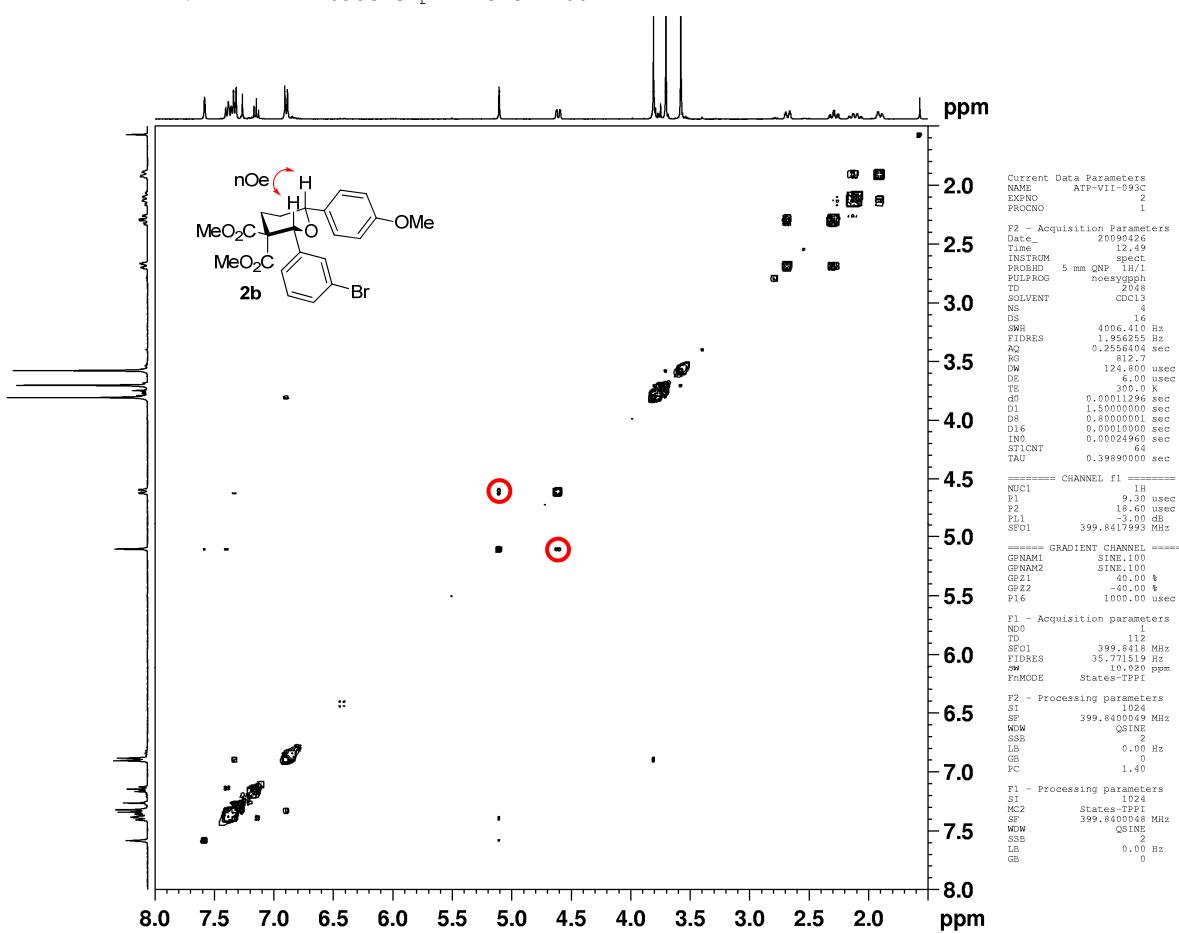
F2 - Processing parameters  
SI 32768  
SF 100.53989318 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



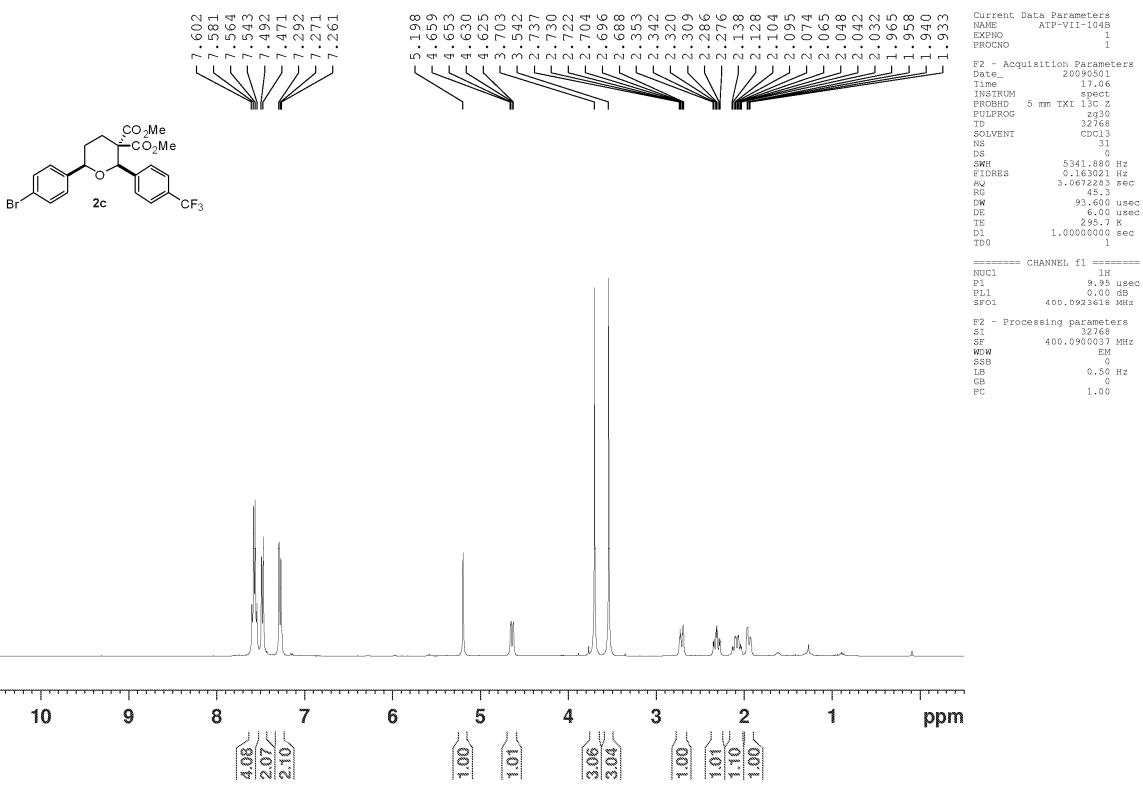




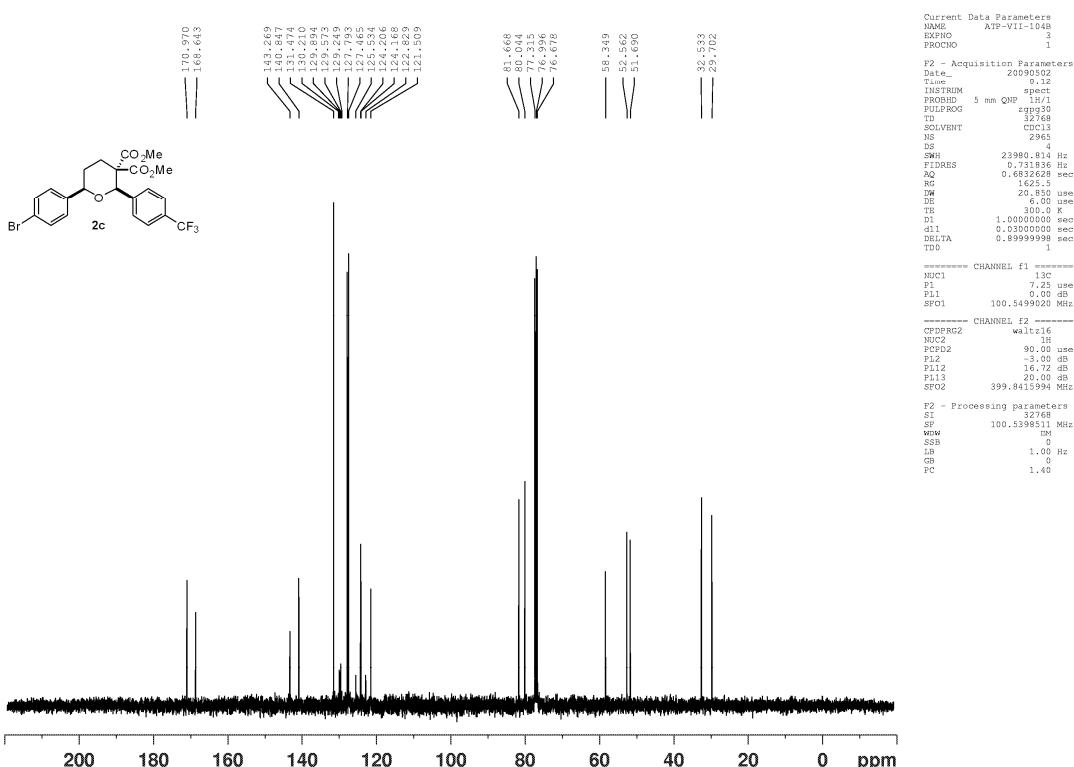
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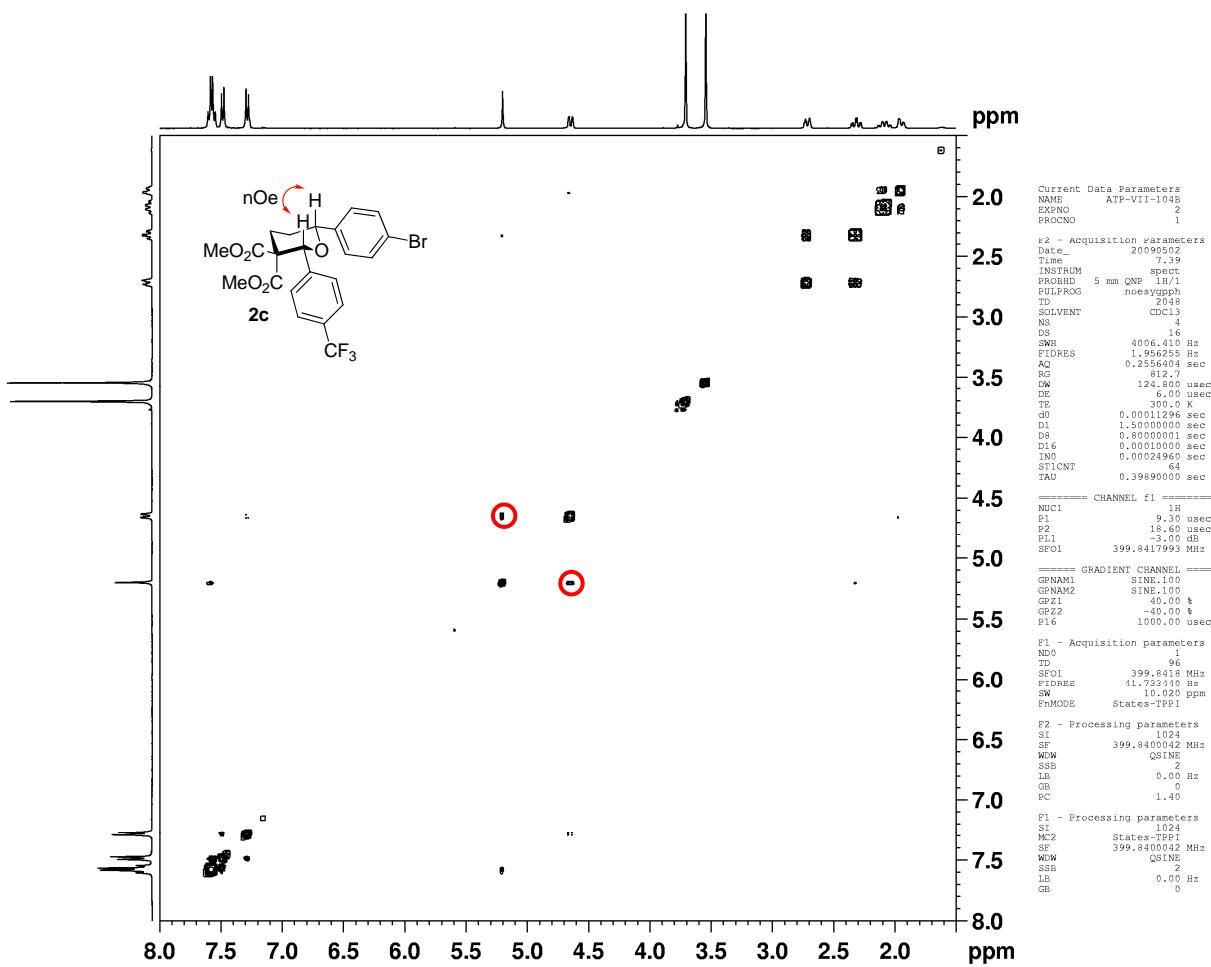
ATP-VII-104B 400 MHz NB



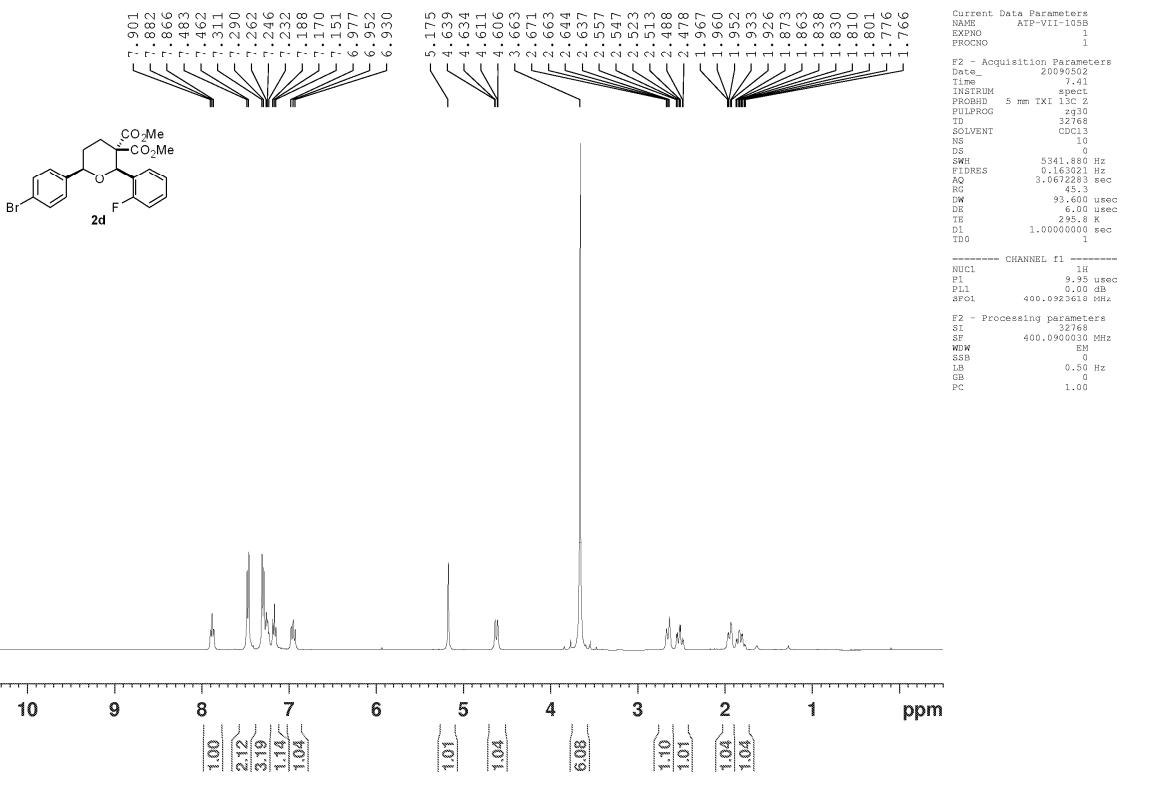
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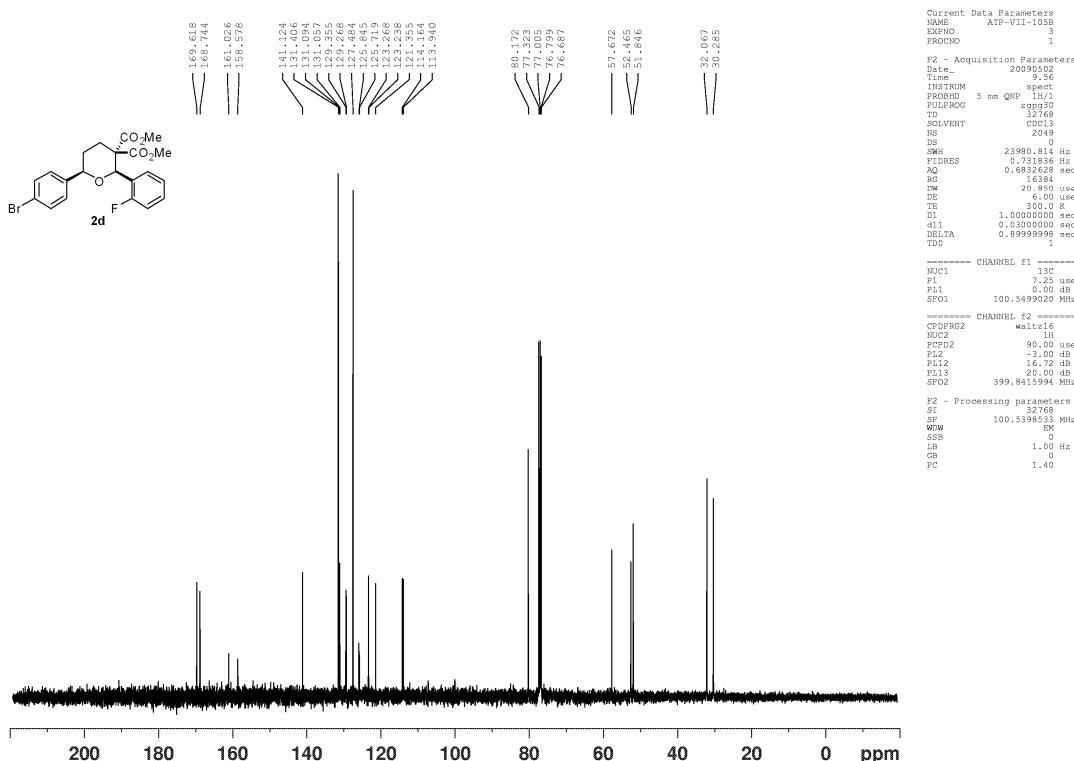
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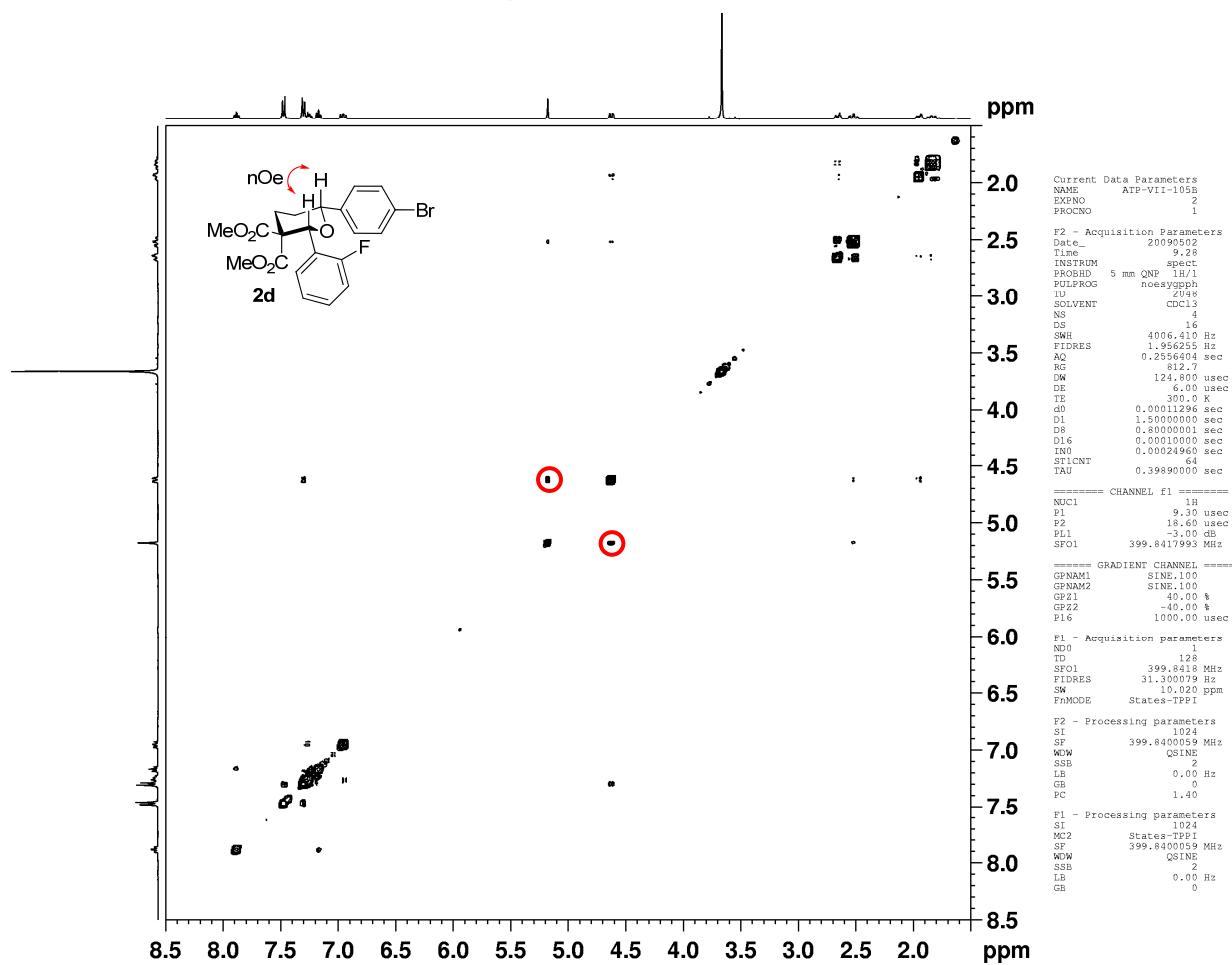
ATP-VII-105B 400 MHz NB

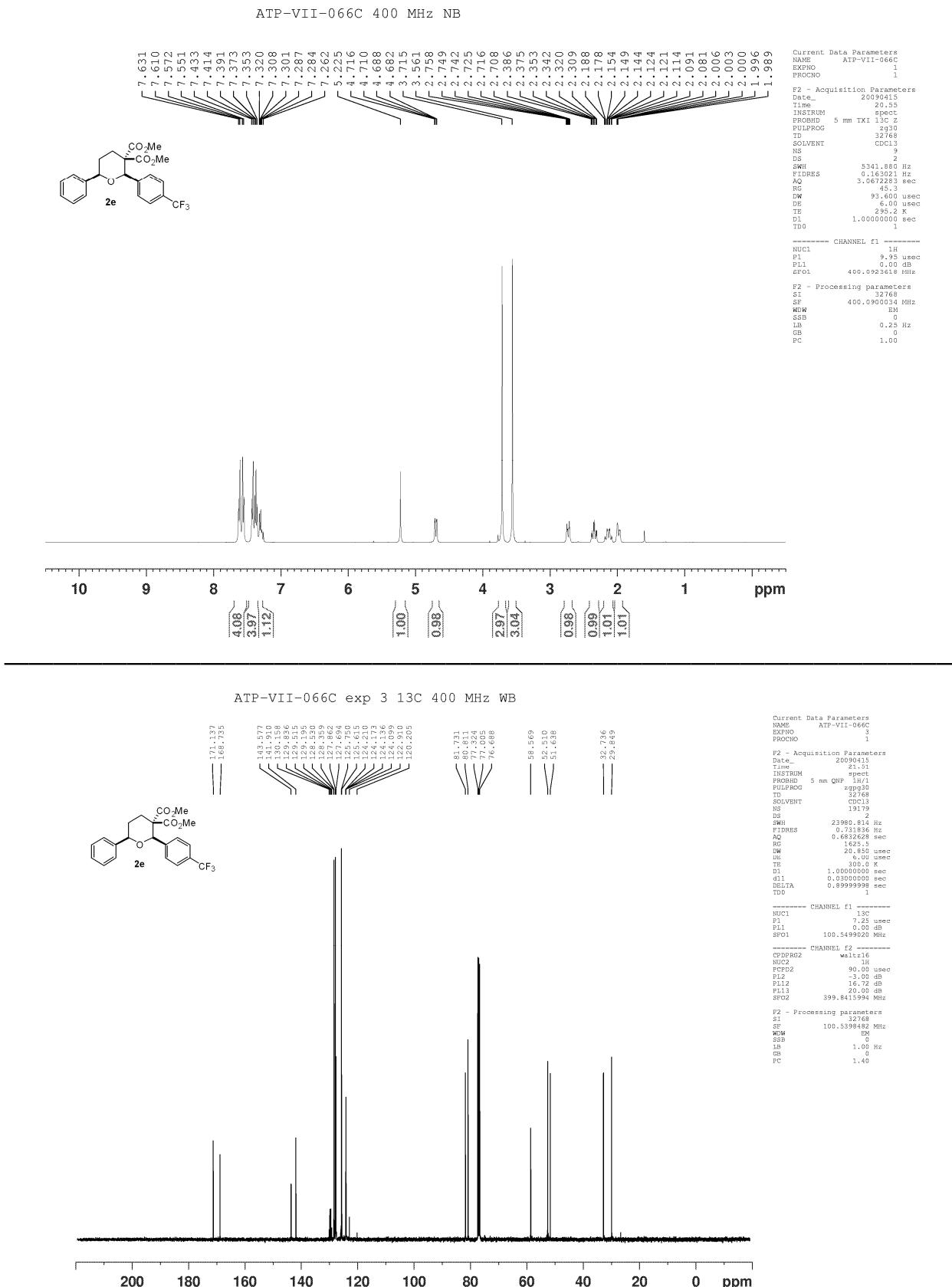


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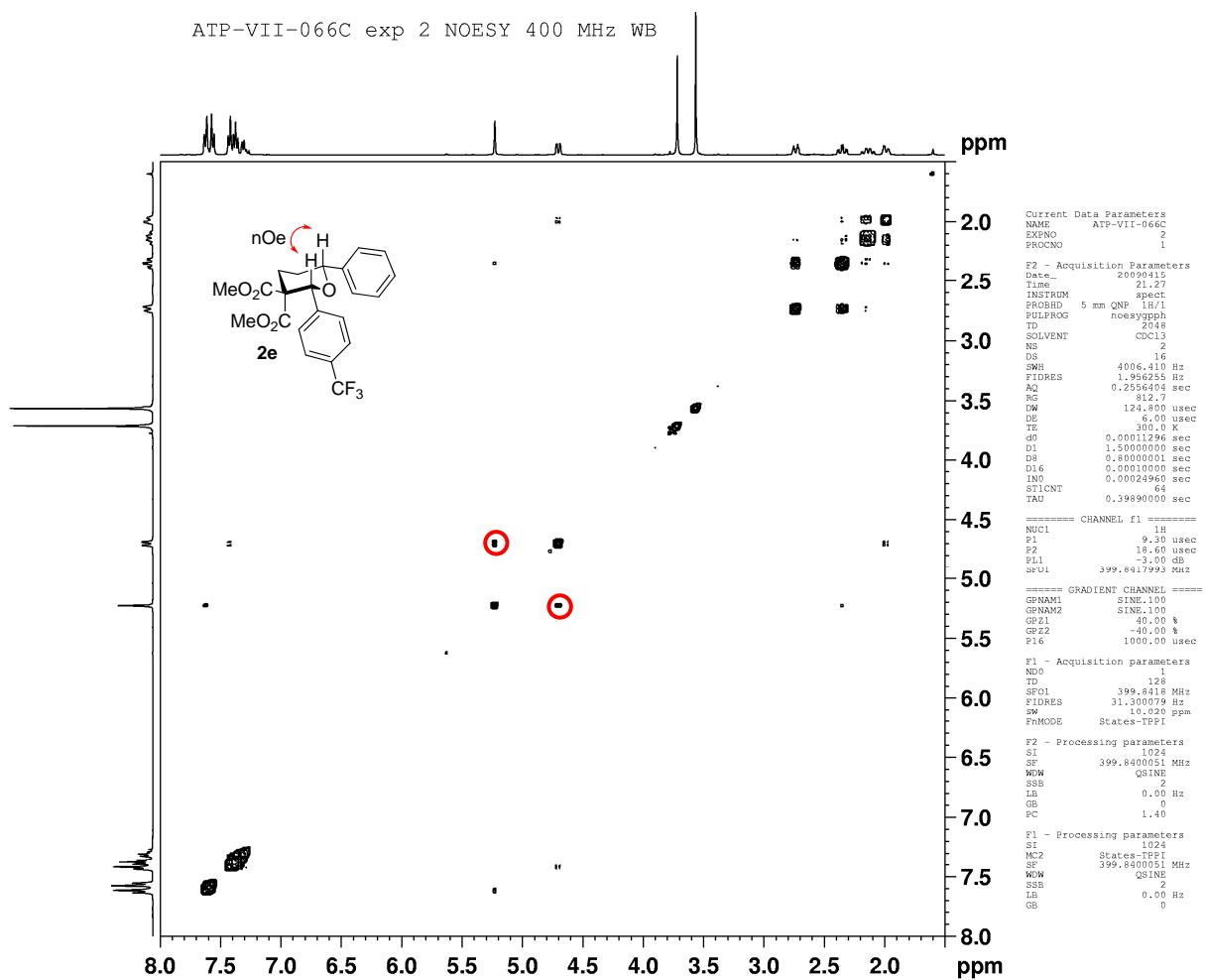


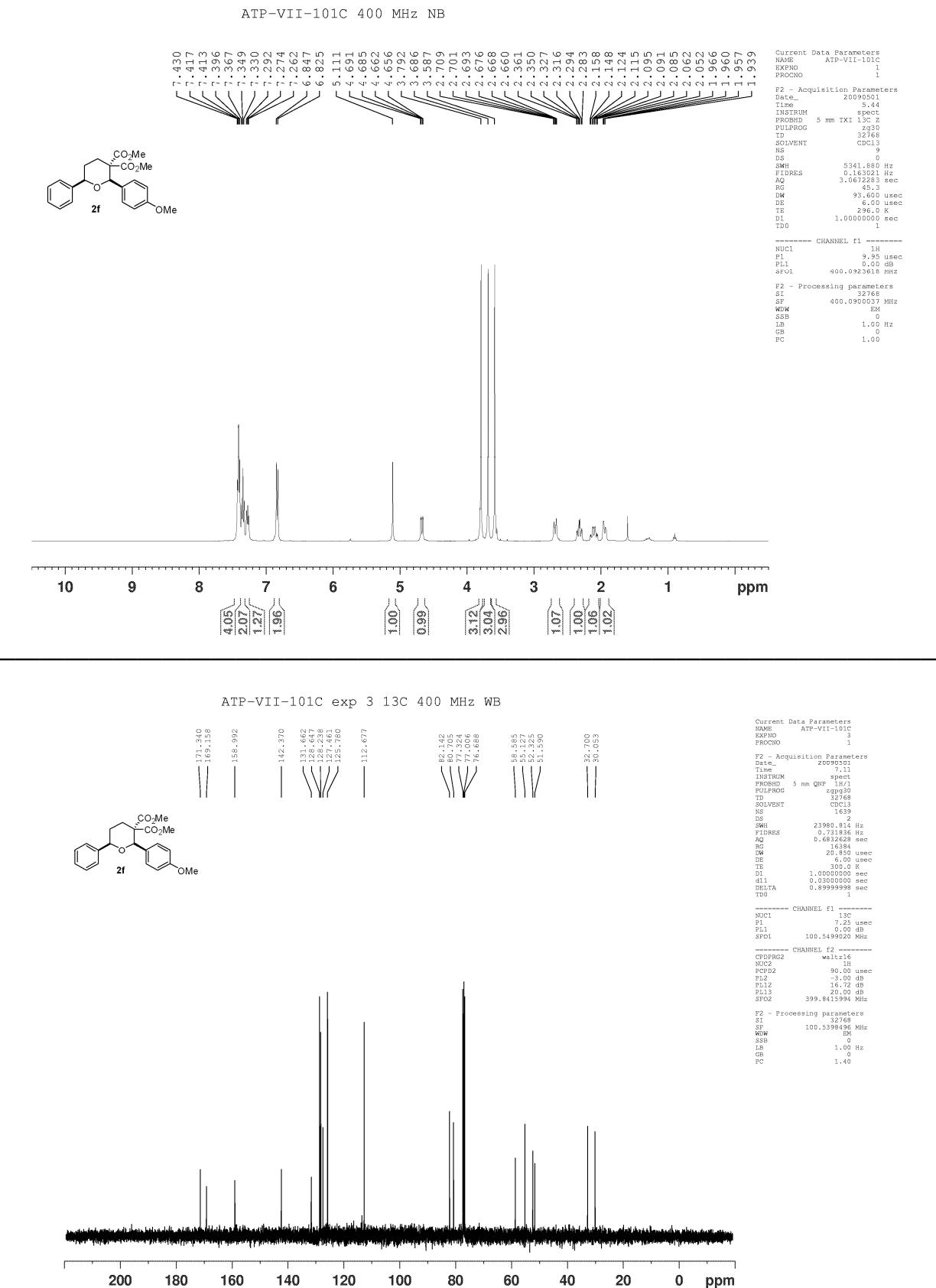
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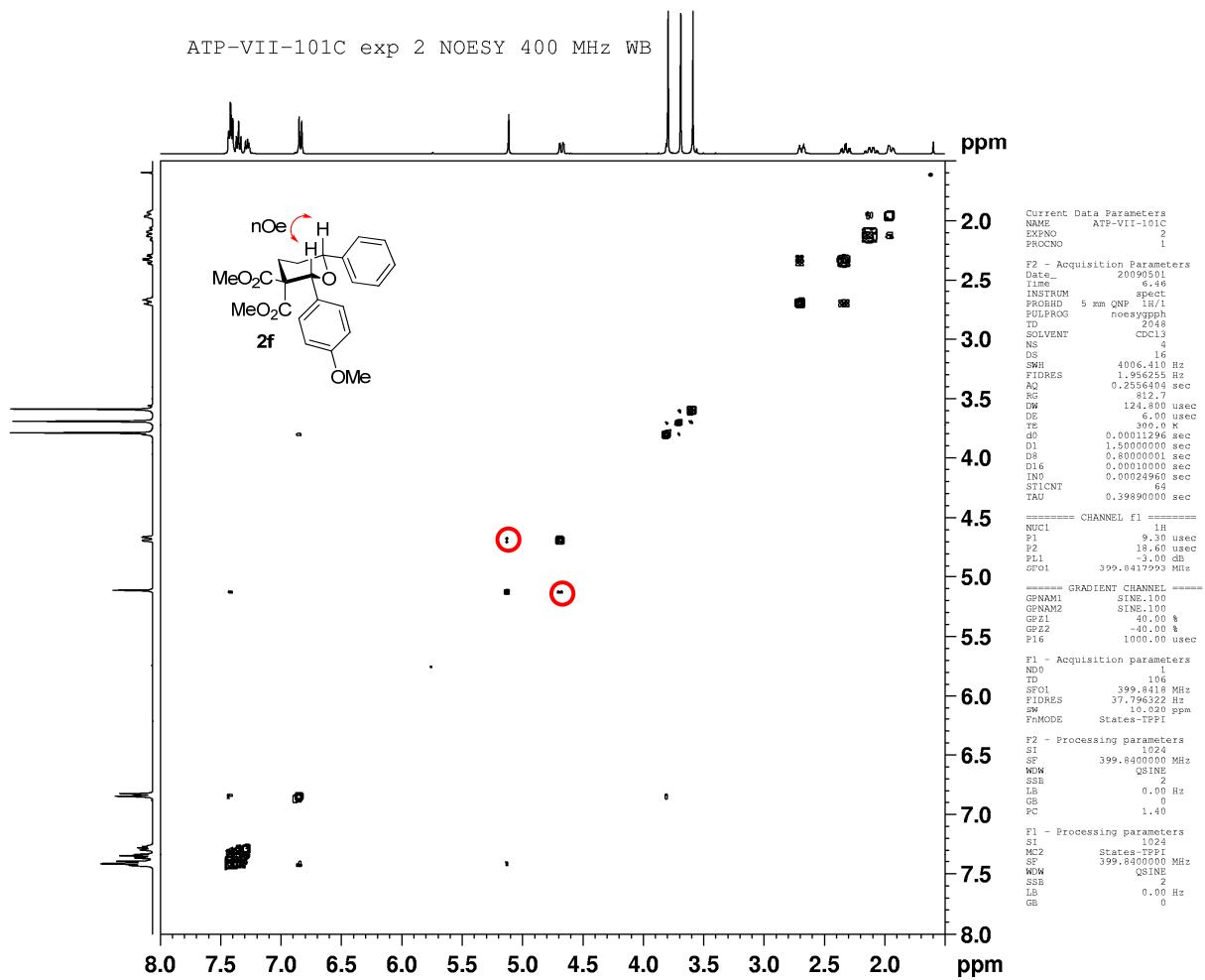




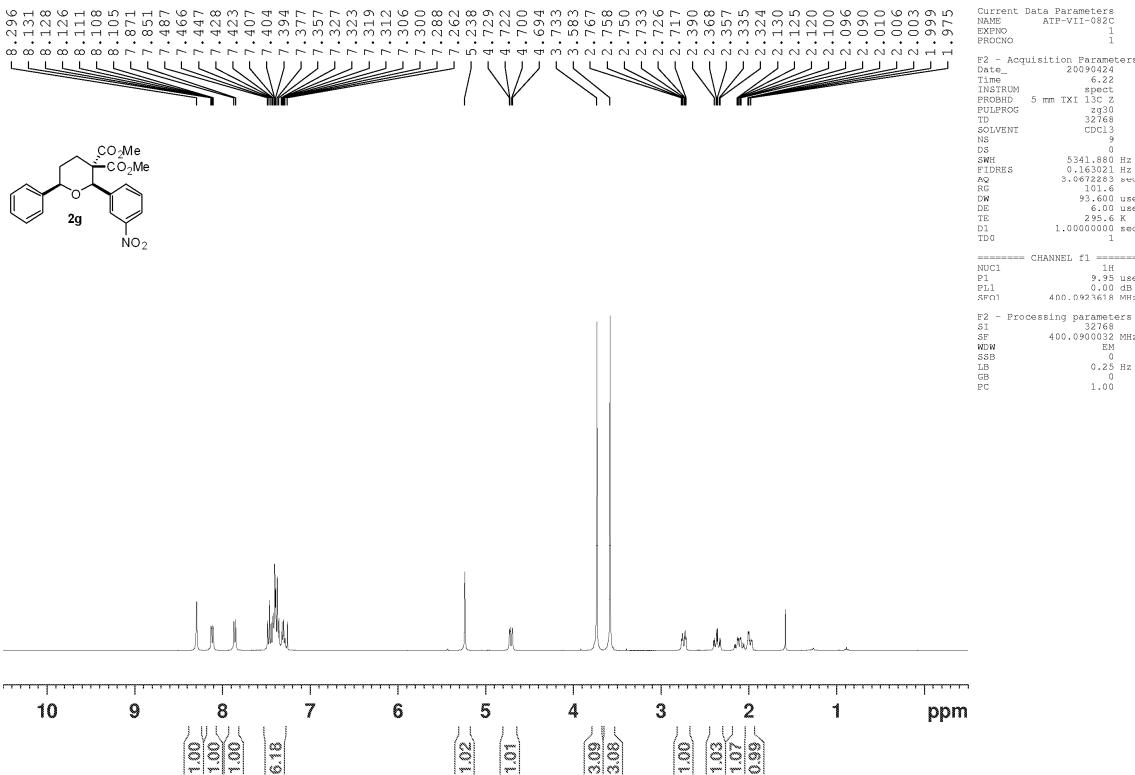
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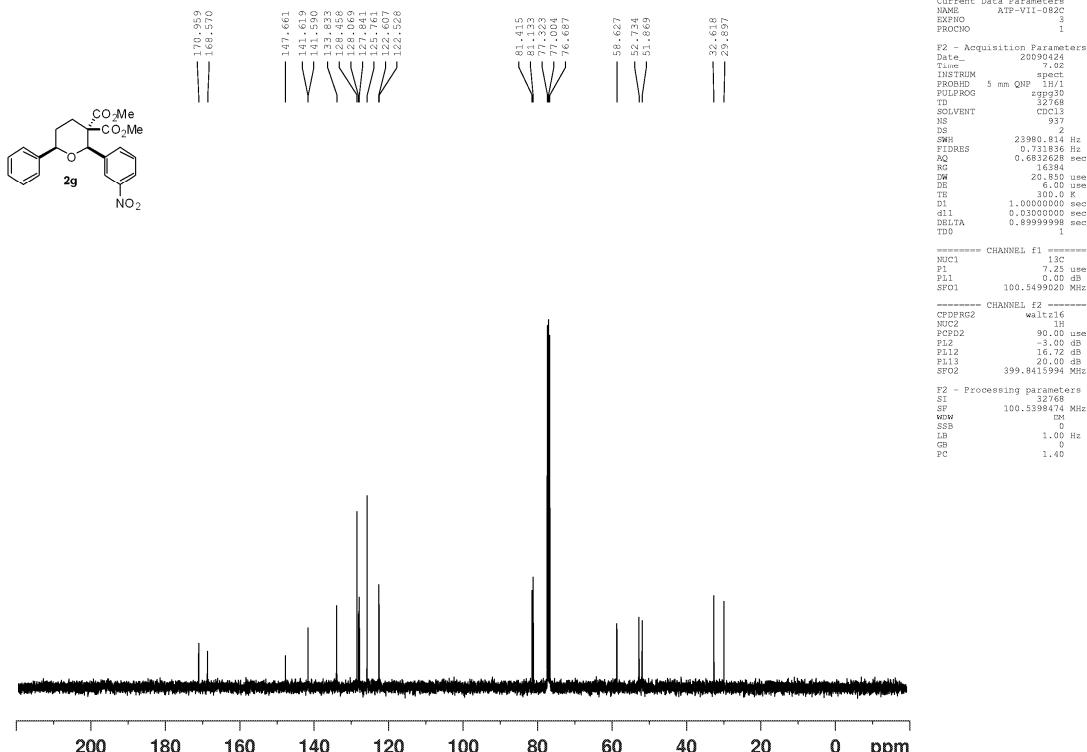




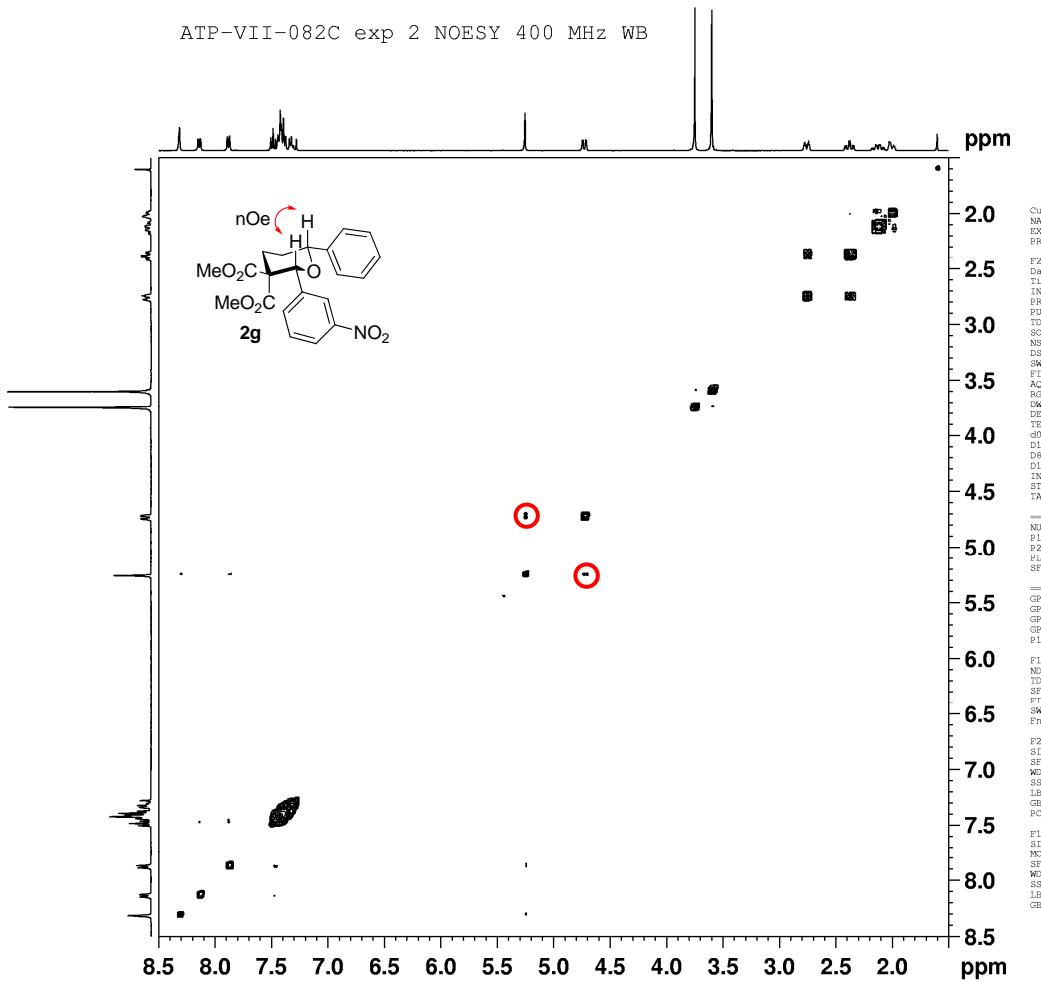
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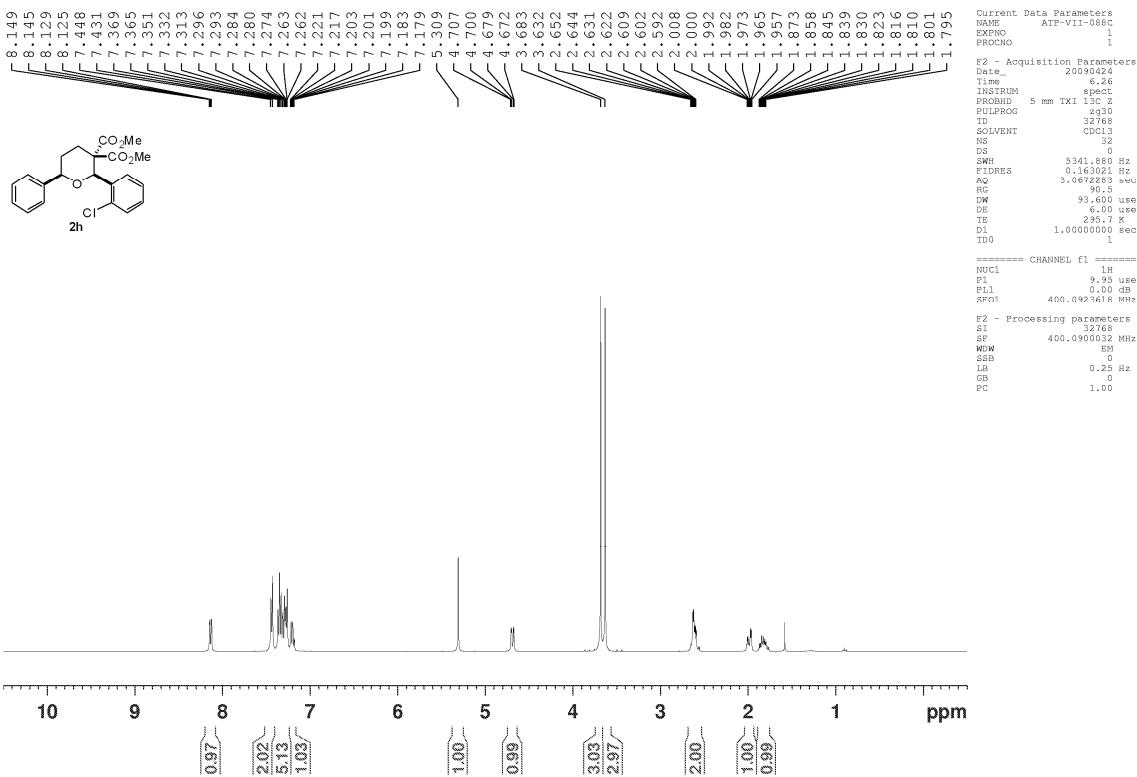
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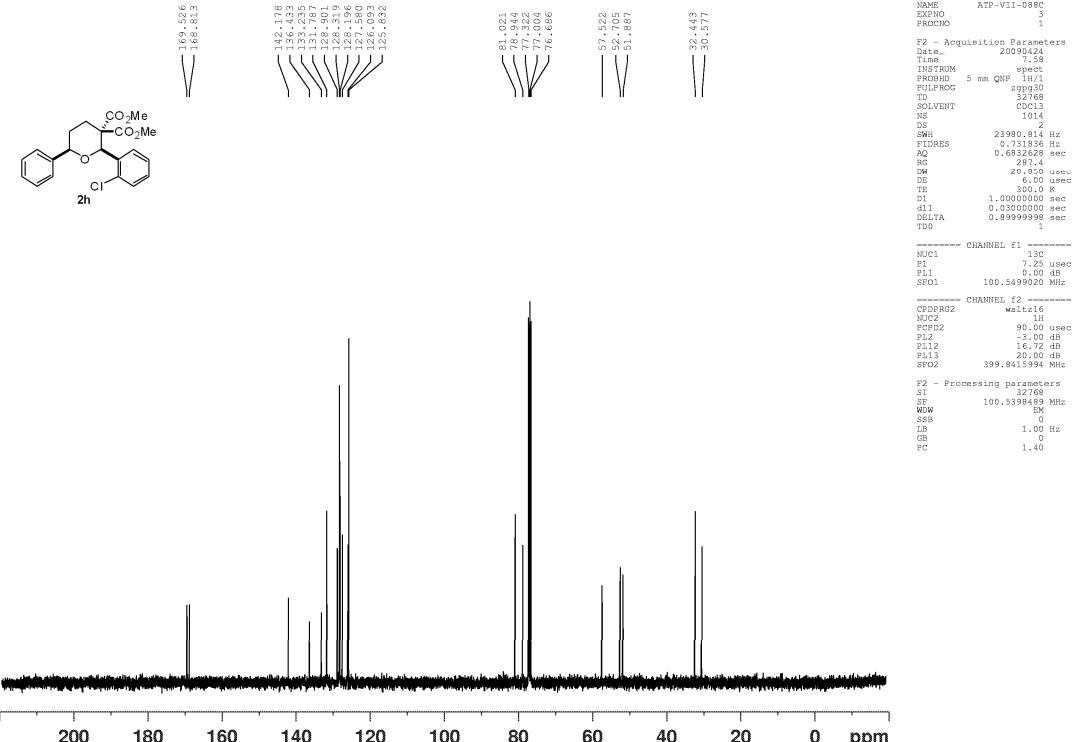
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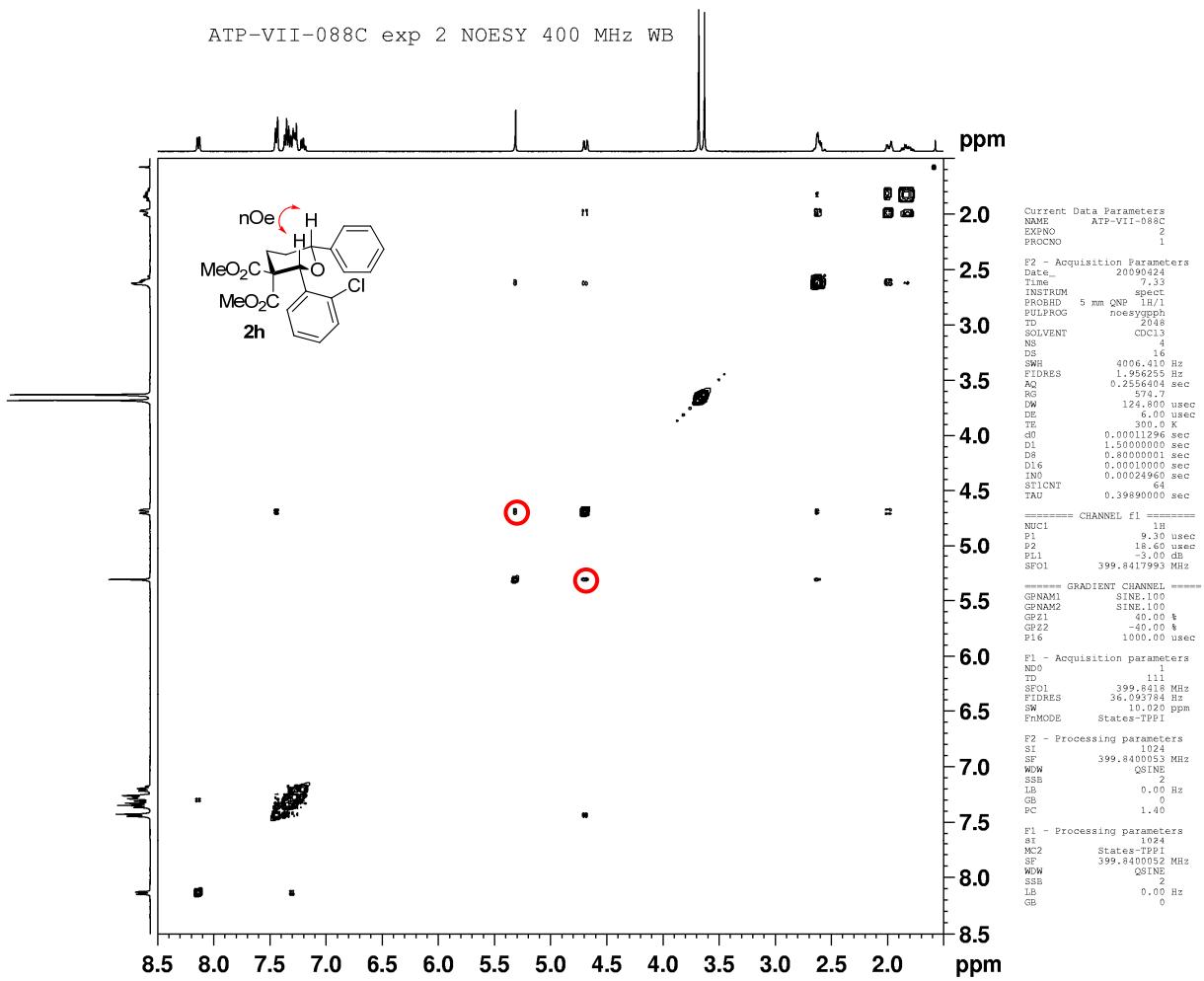


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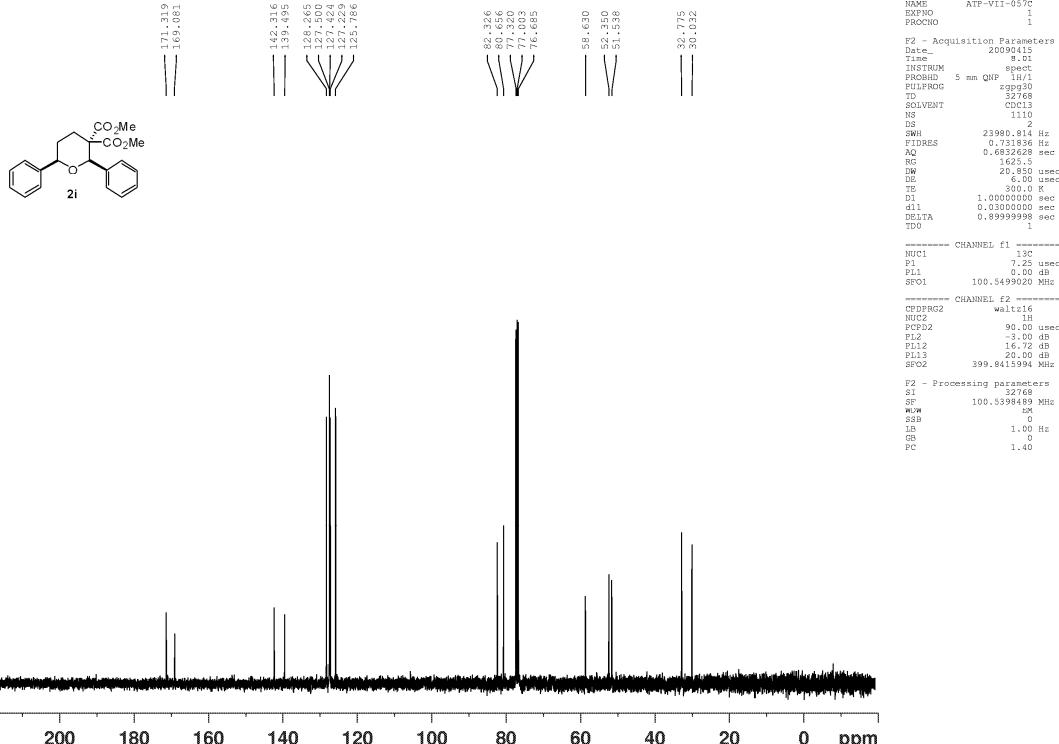
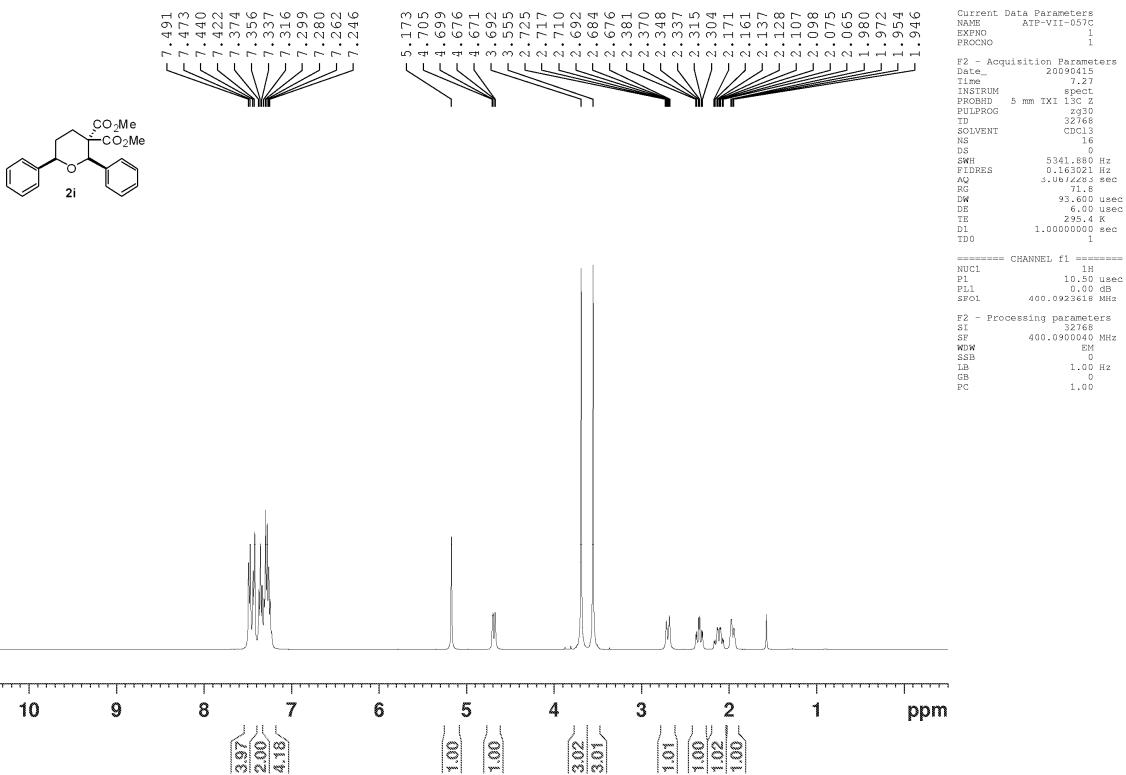


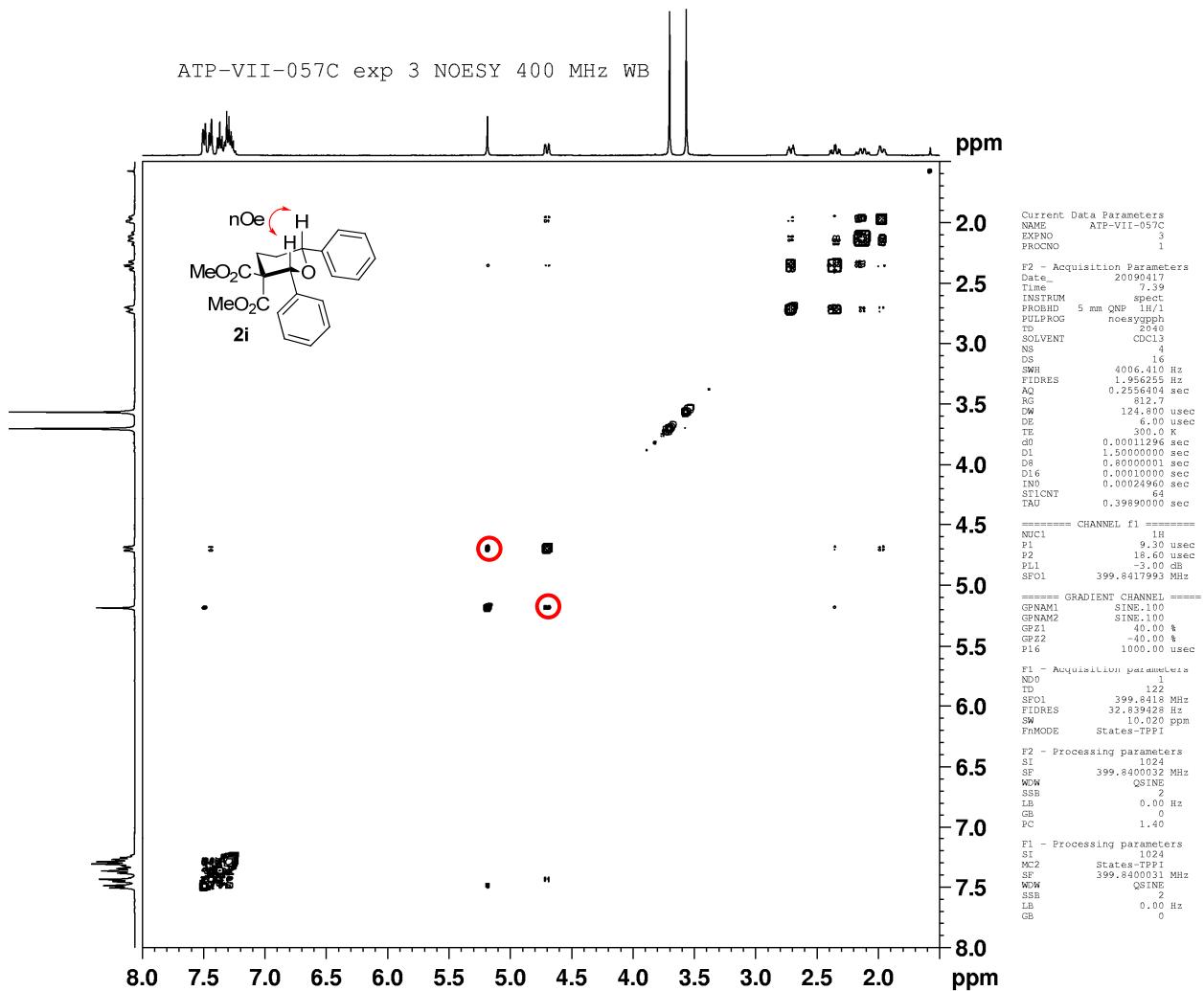
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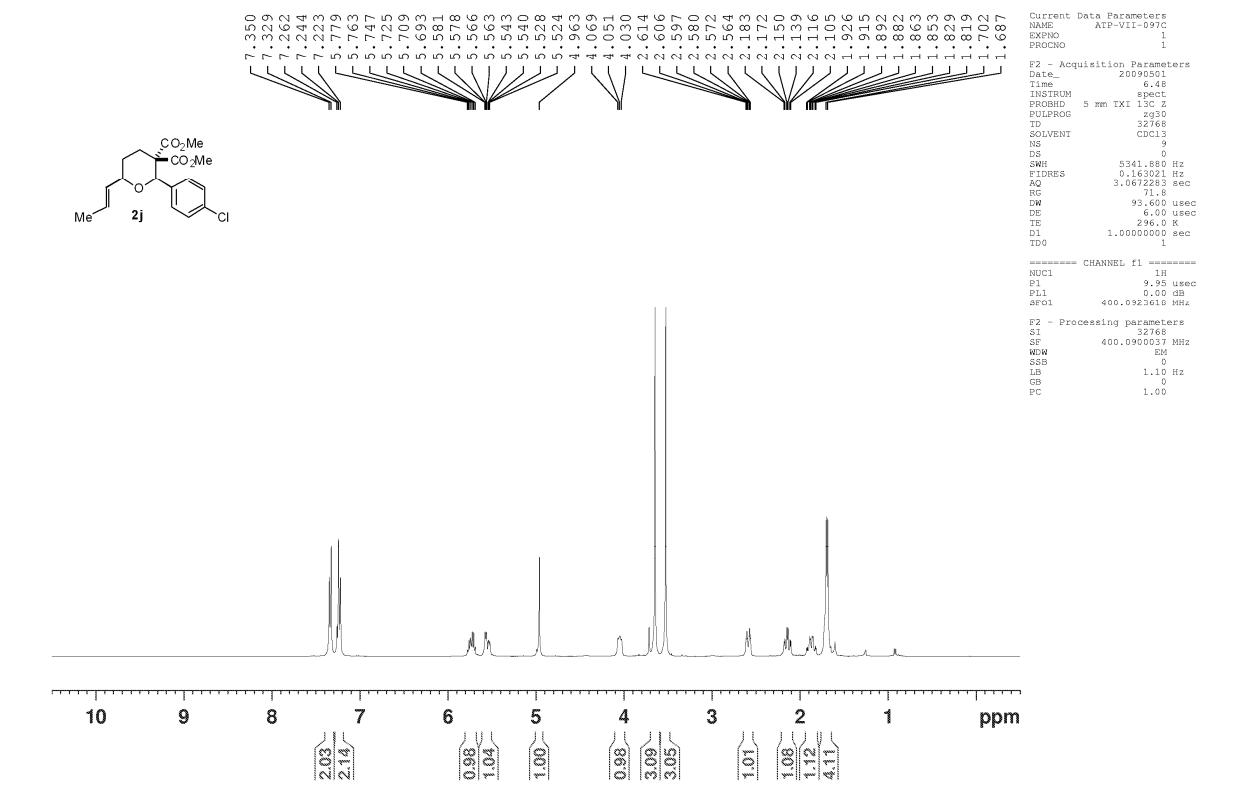


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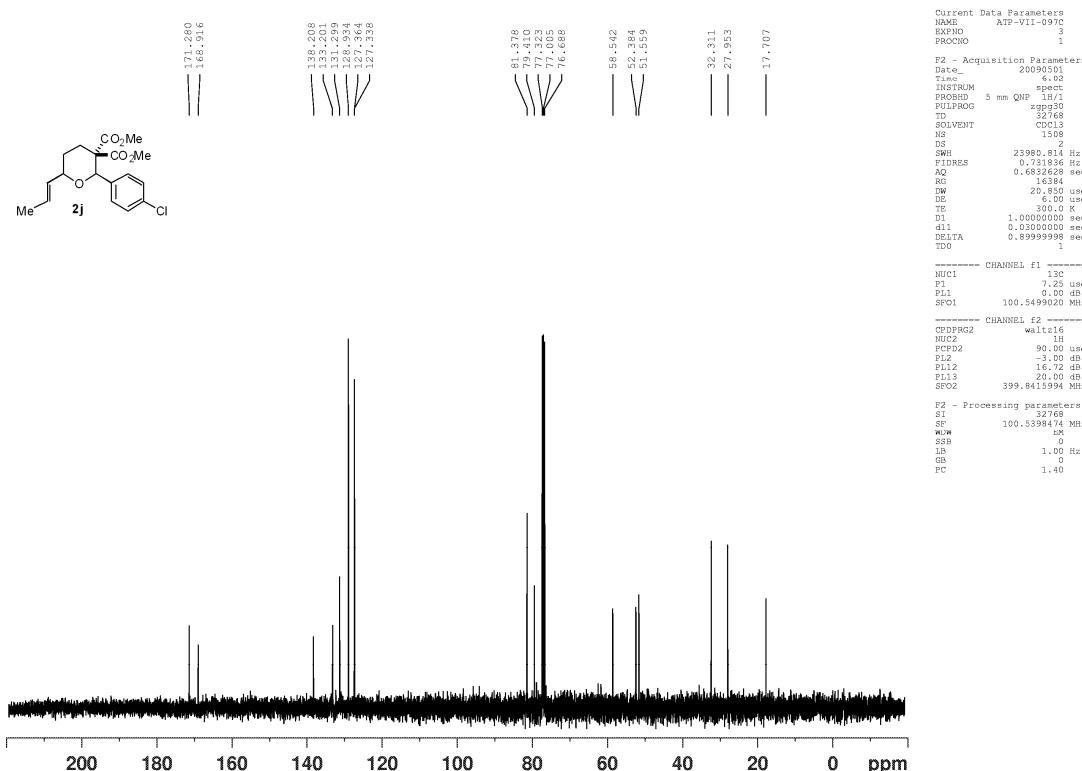




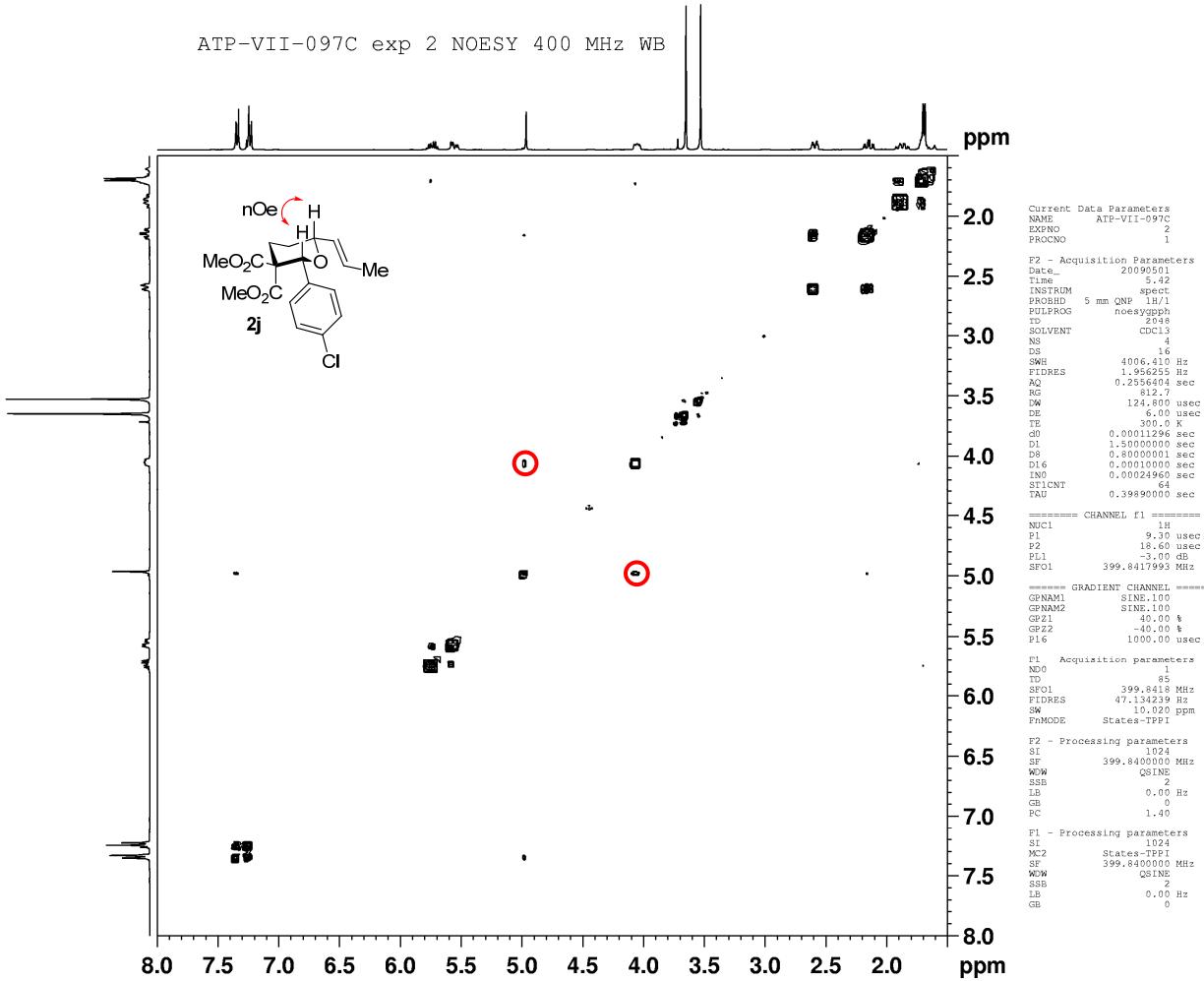
ATP-VII-097C 400 MHz NB

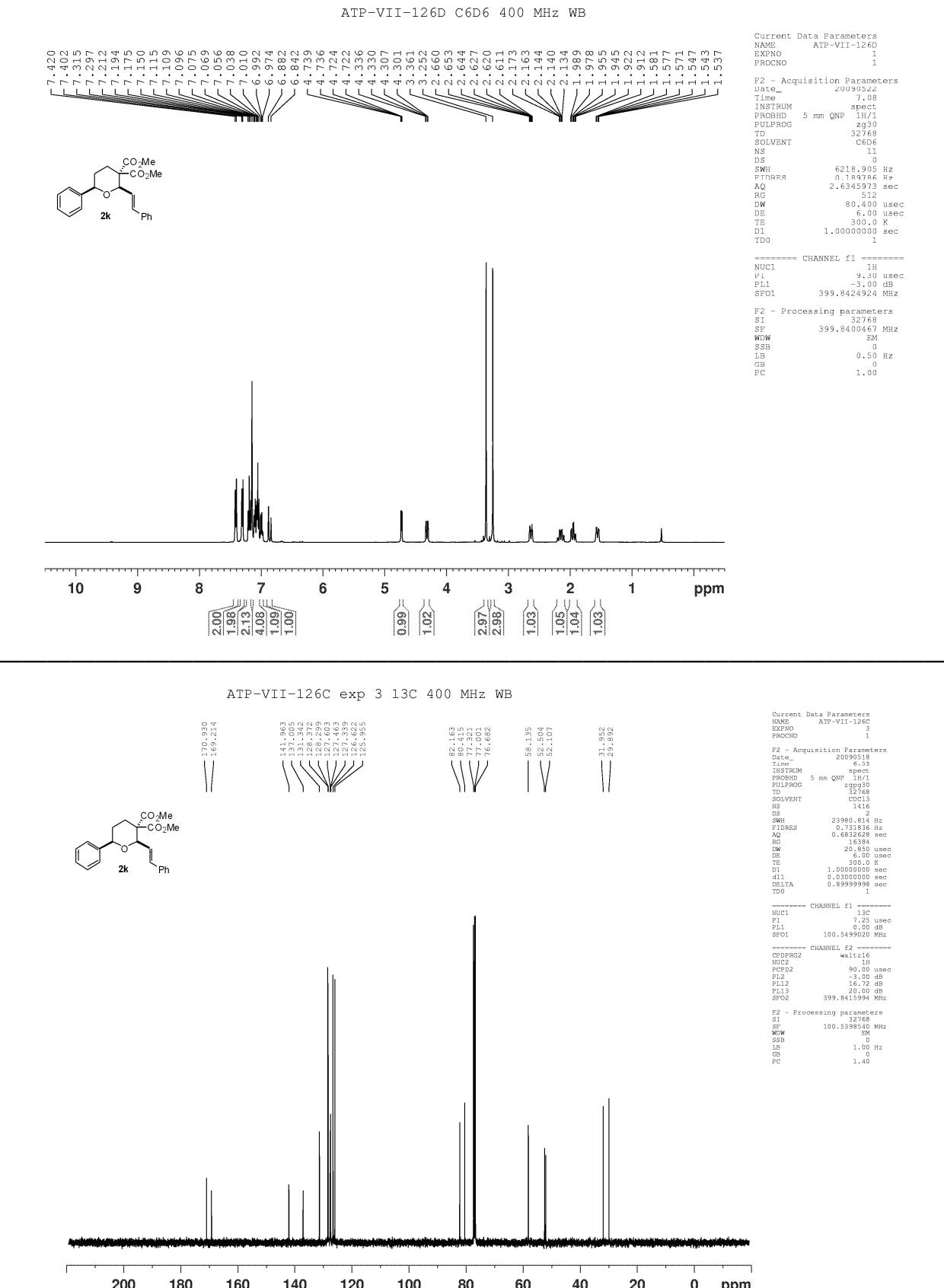


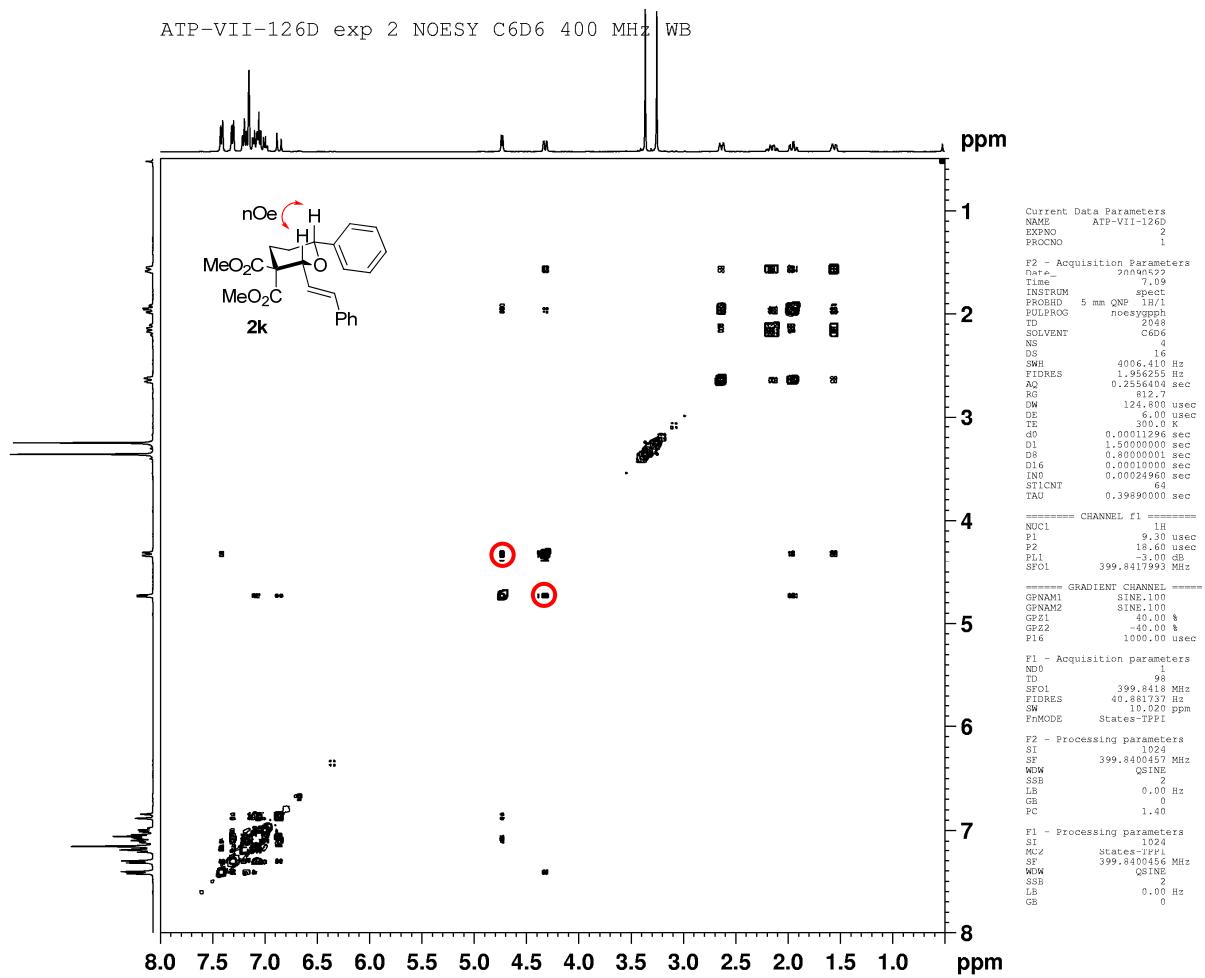
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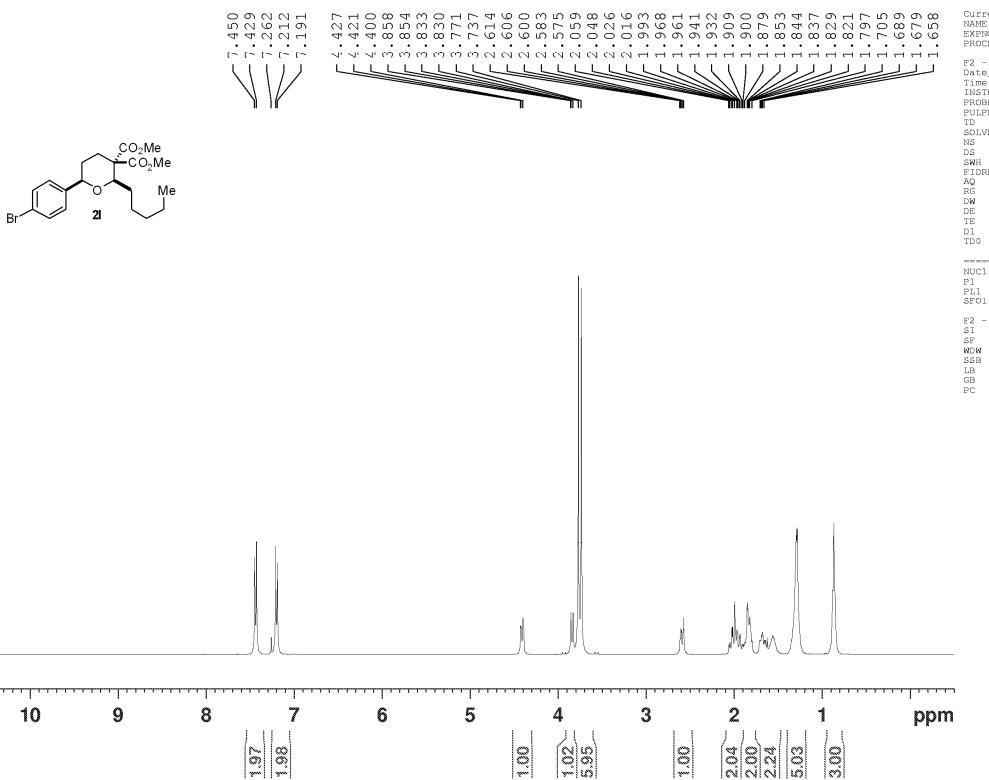
ATP-VII-097C exp 2 NOESY 400 MHz WB



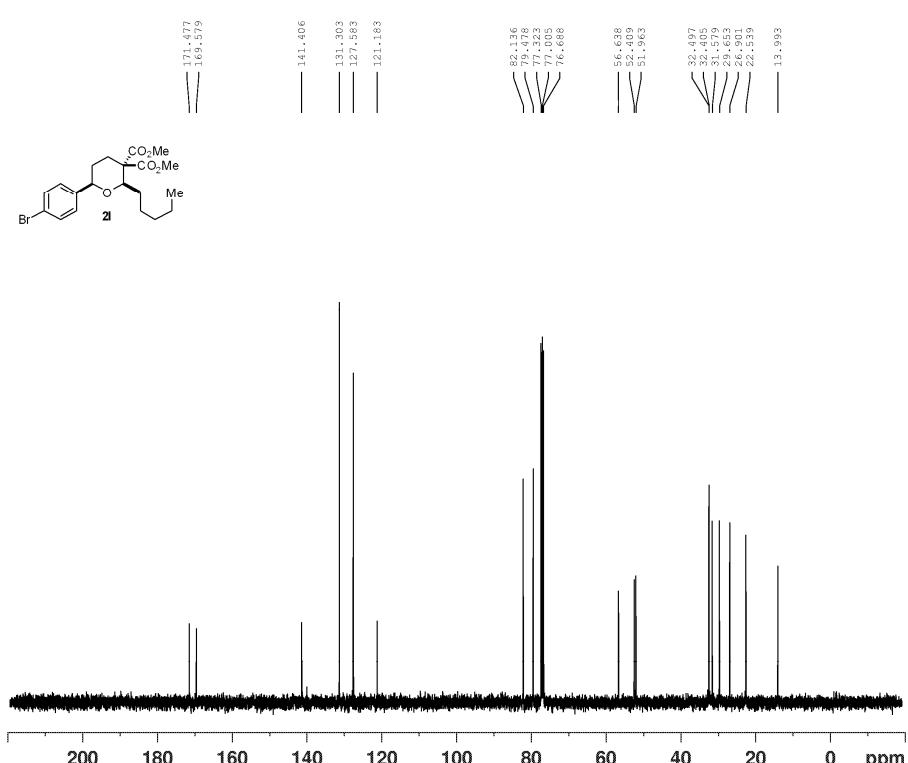




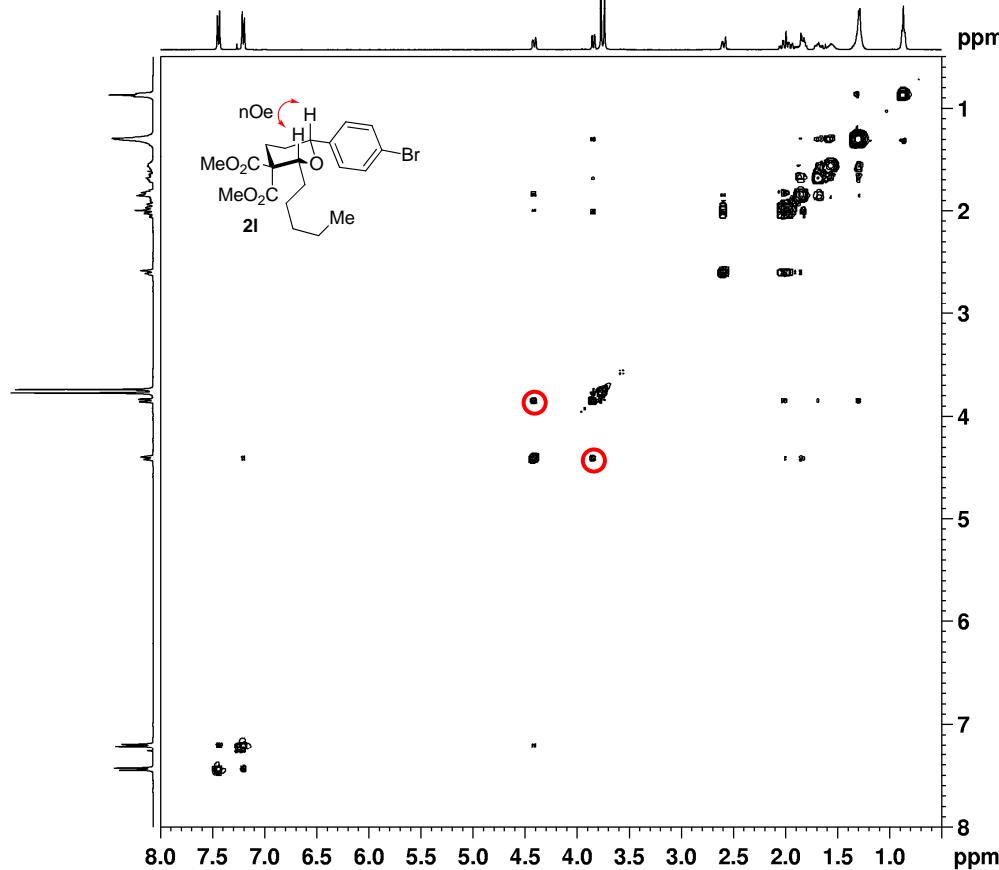
ATP-VII-114D 400 MHz NB

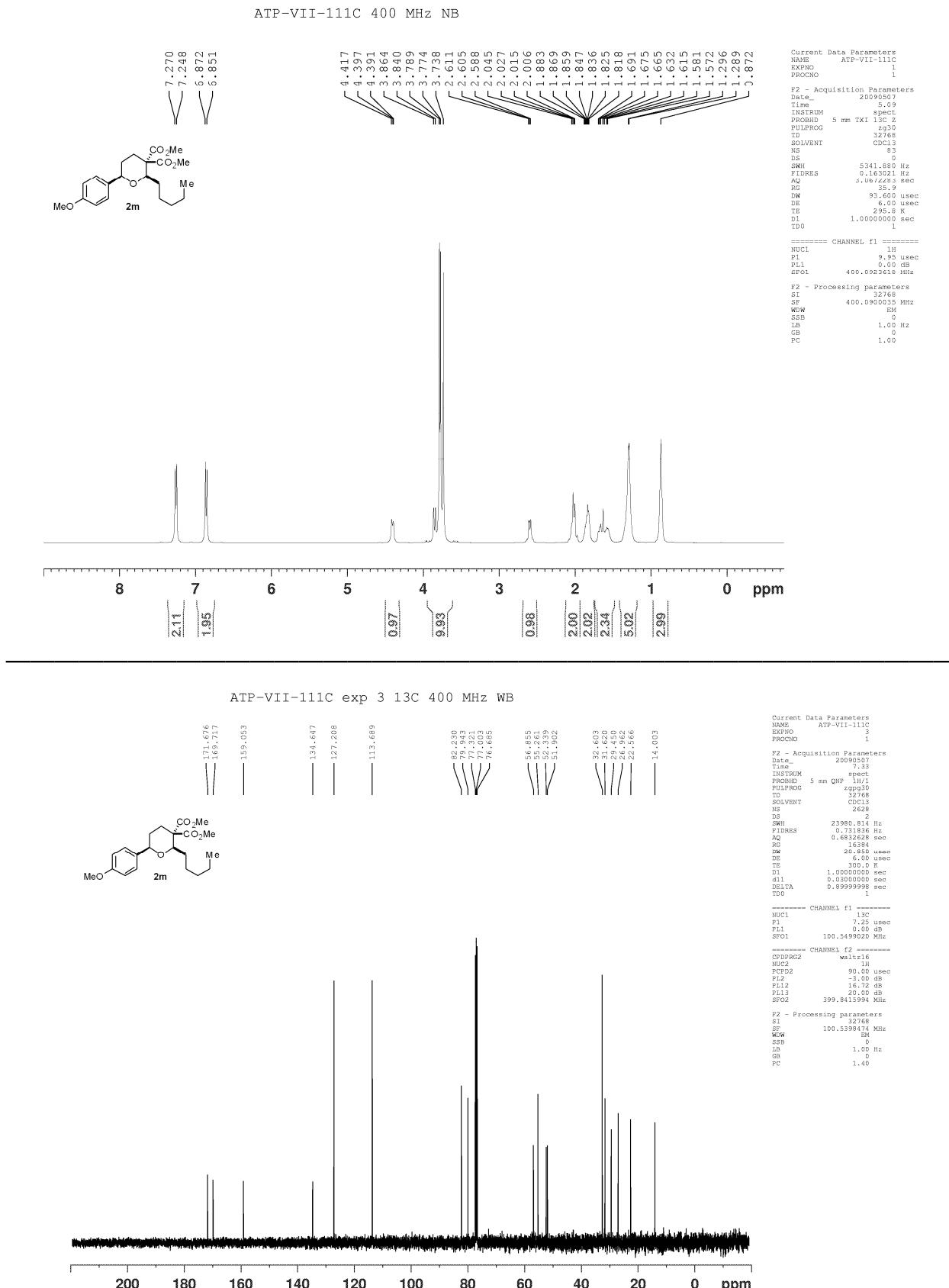


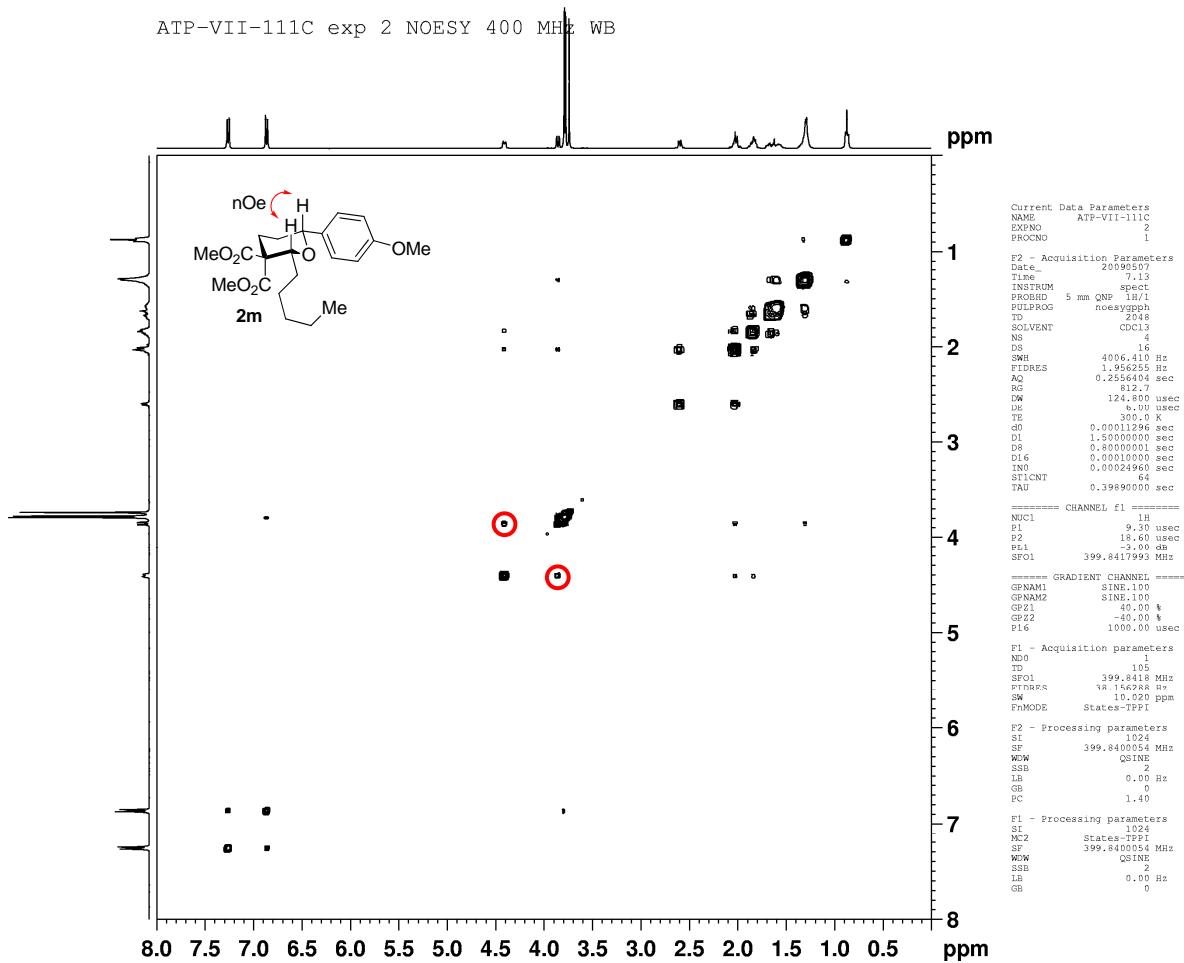
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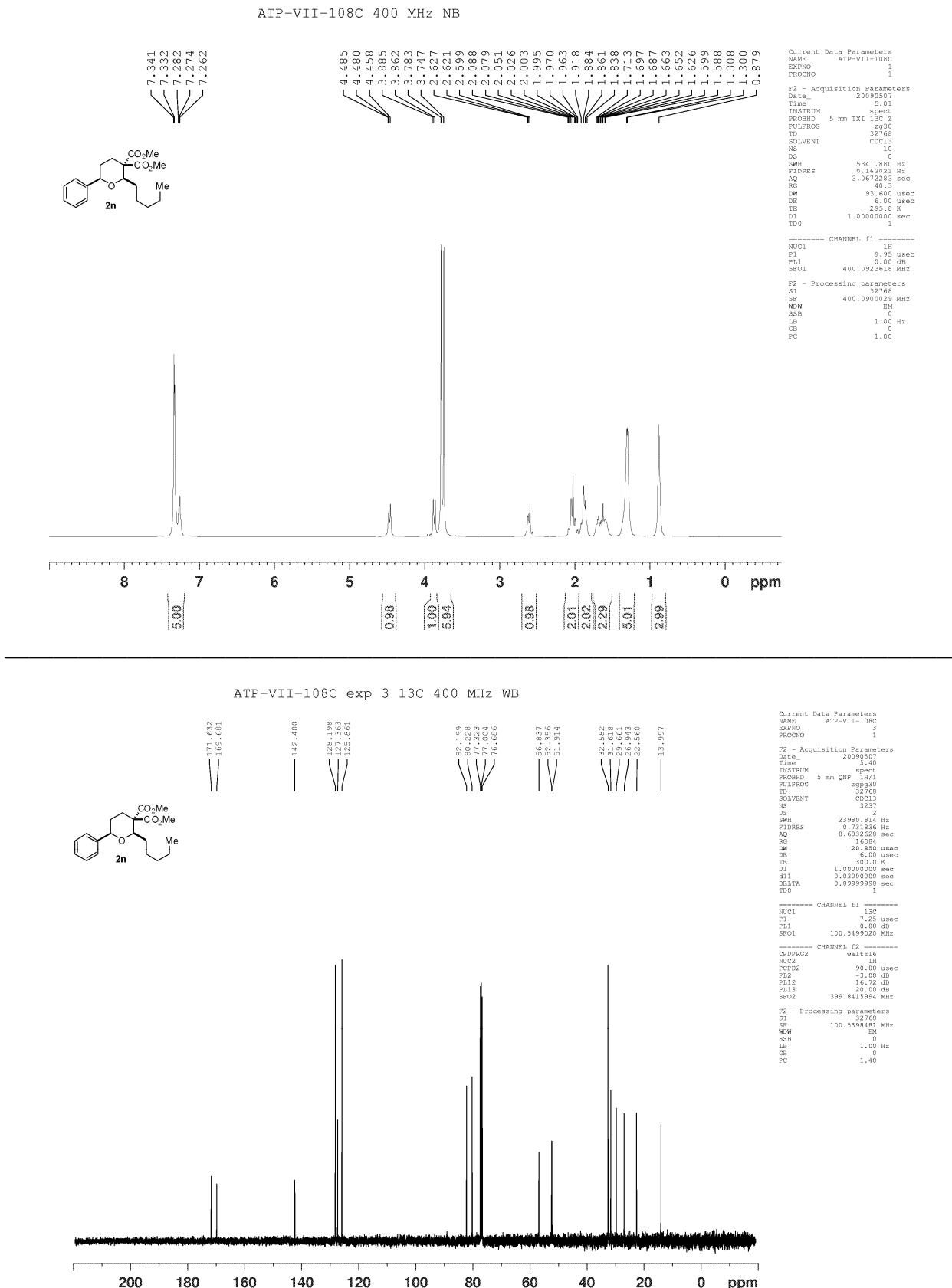


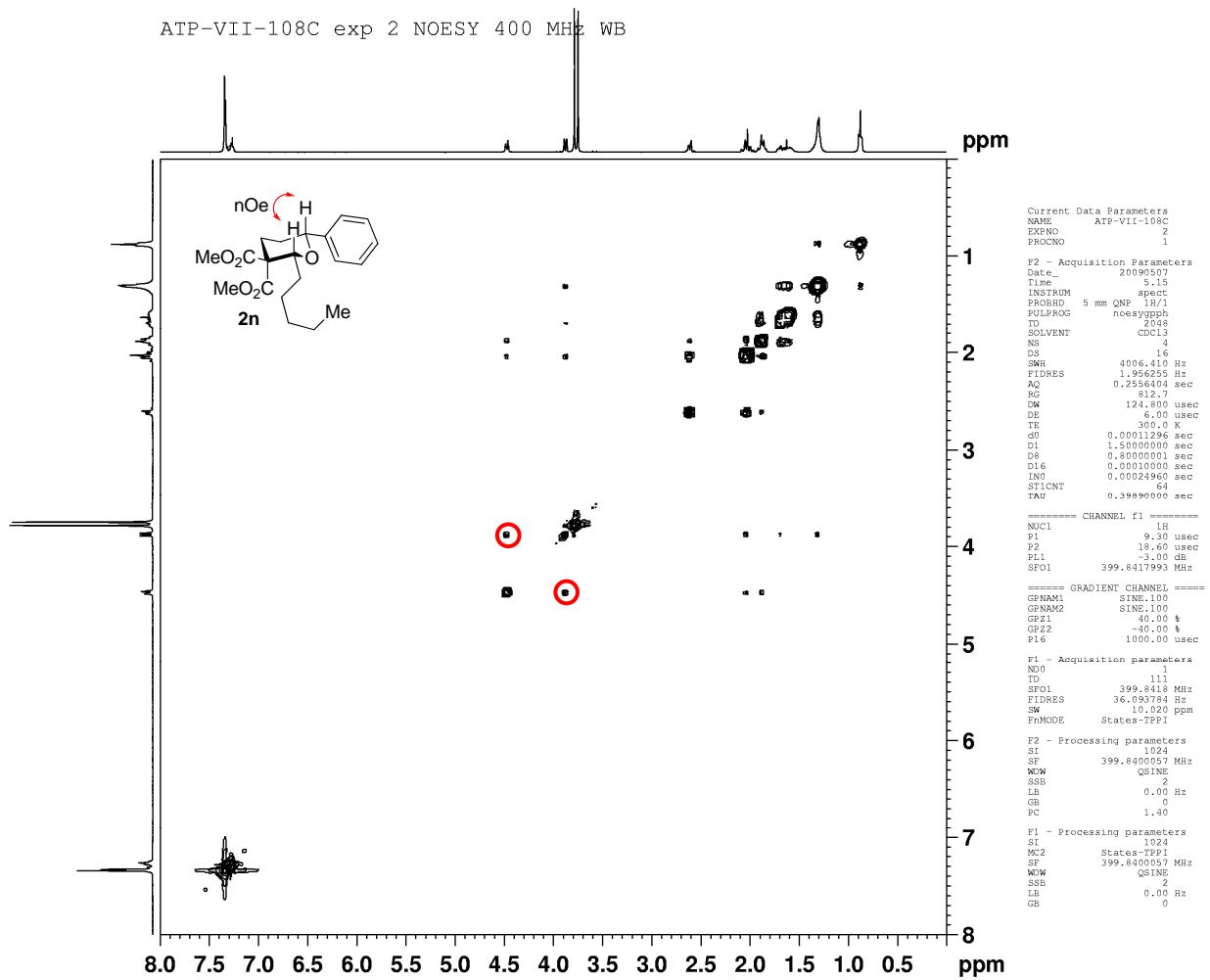
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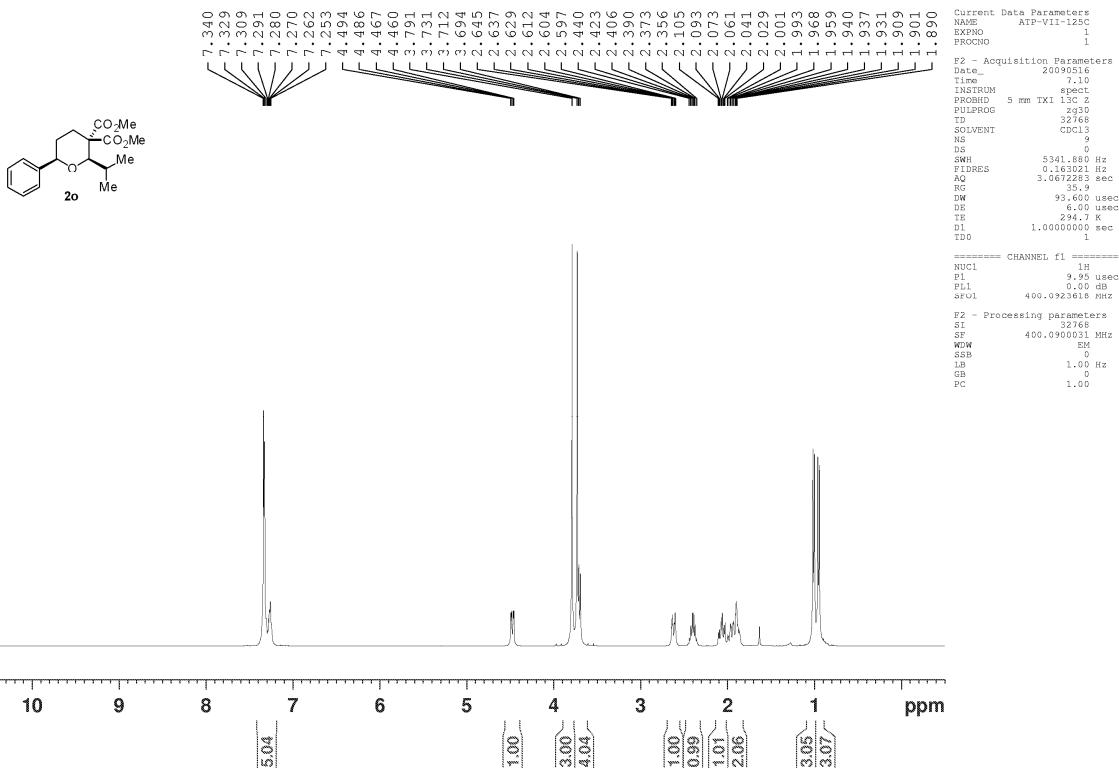




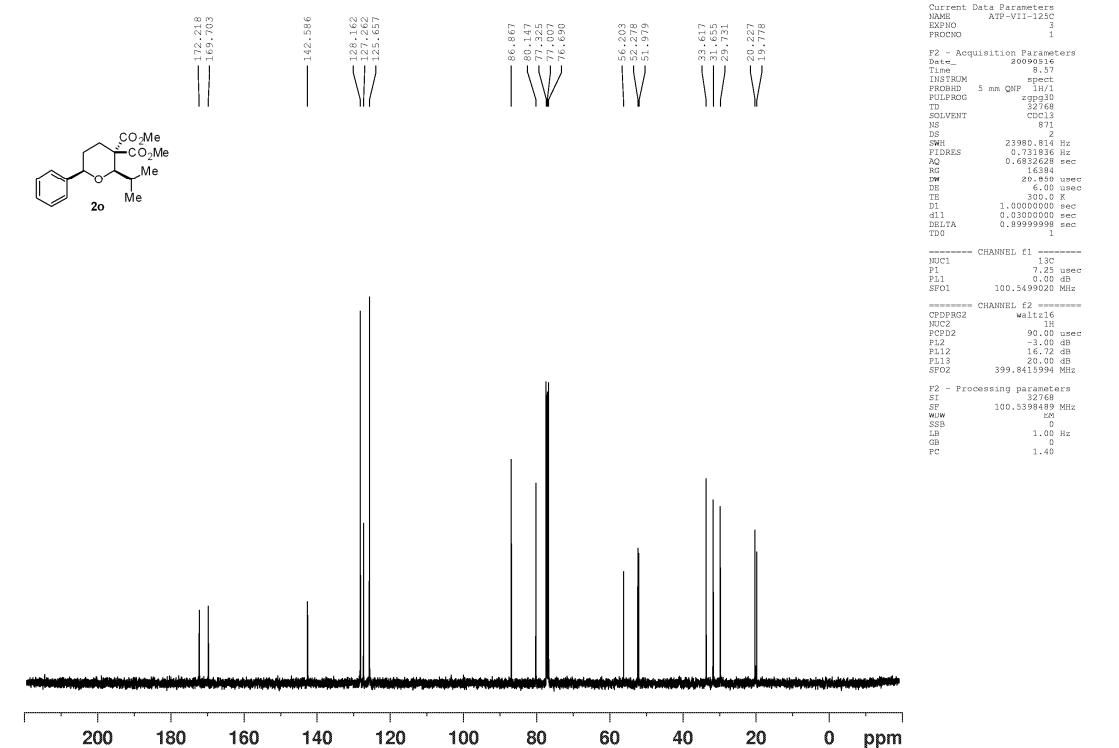


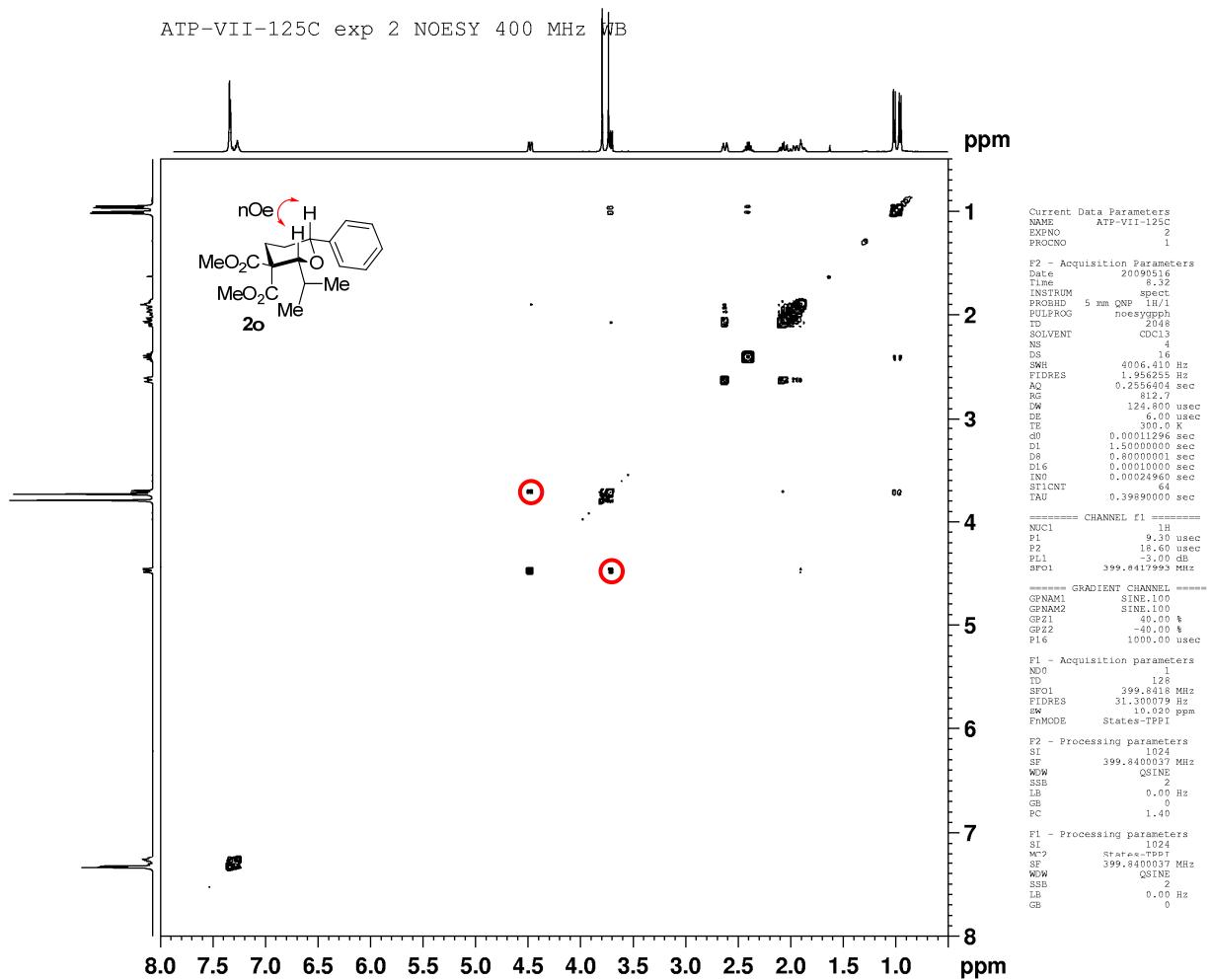


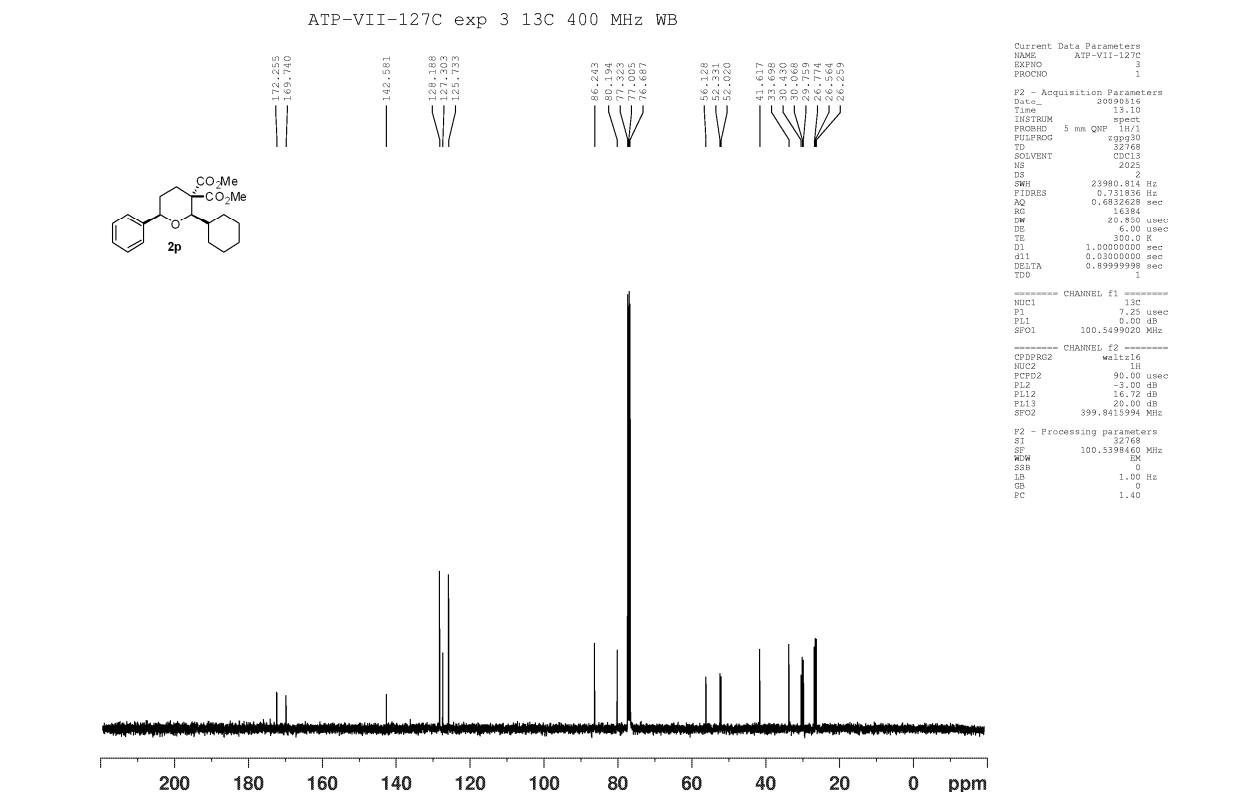
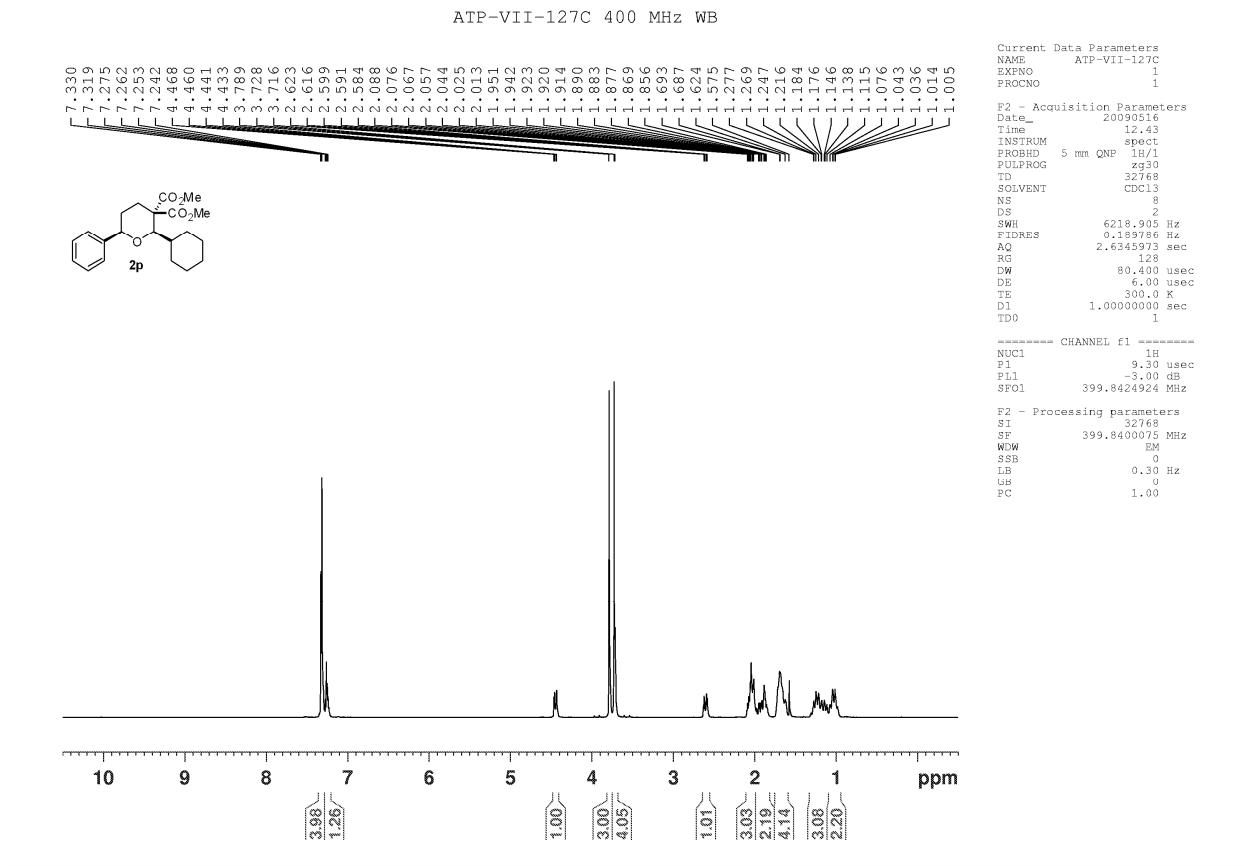
ATP-VII-125C 400 MHz NB

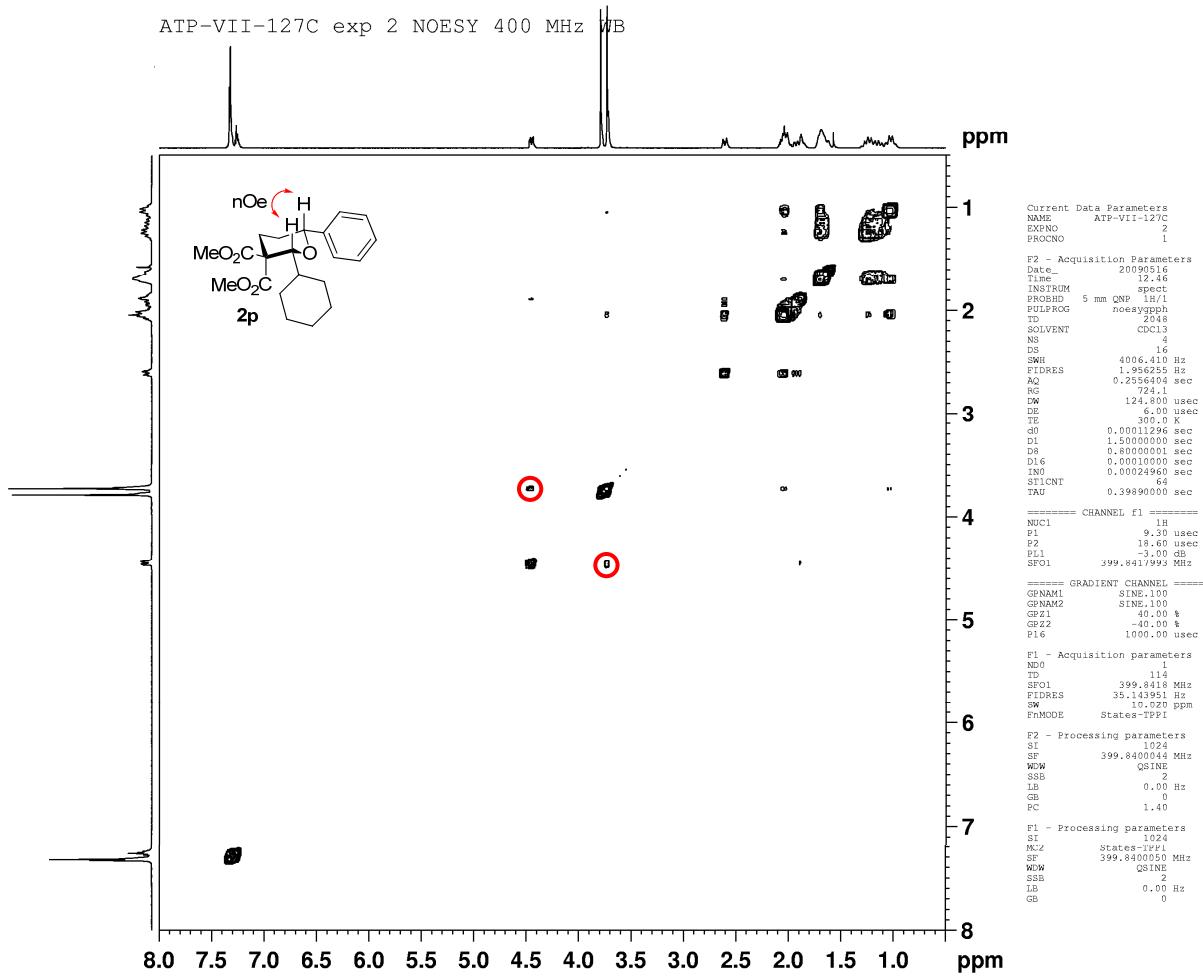


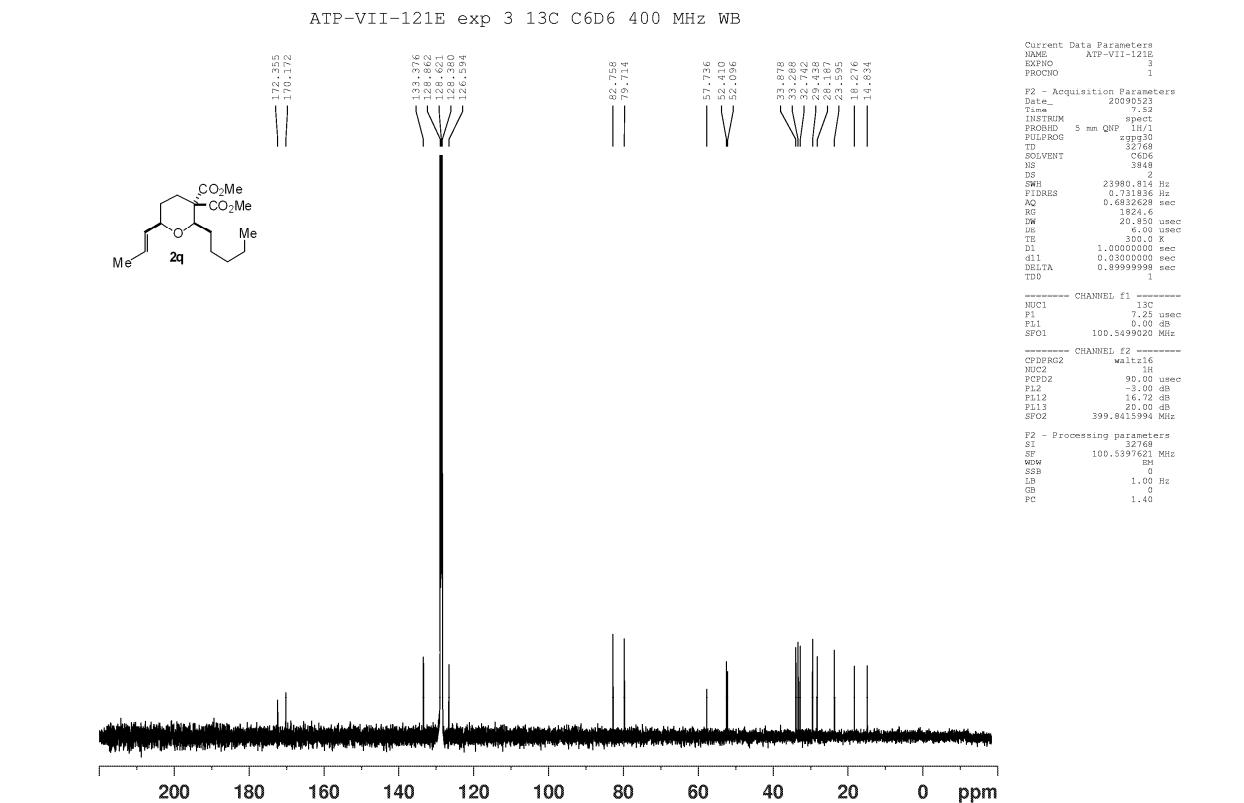
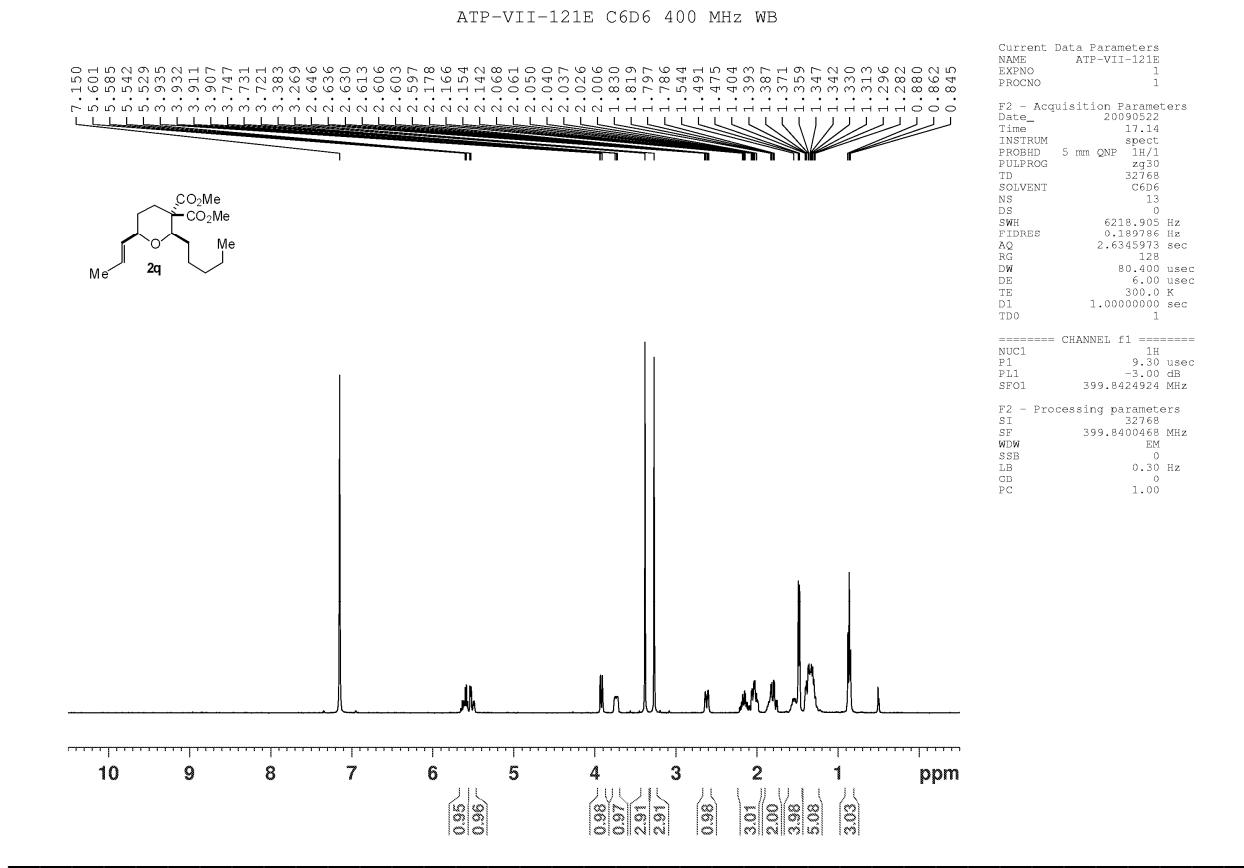
ATP-VII-125C exp 3 13C 400 MHz WB

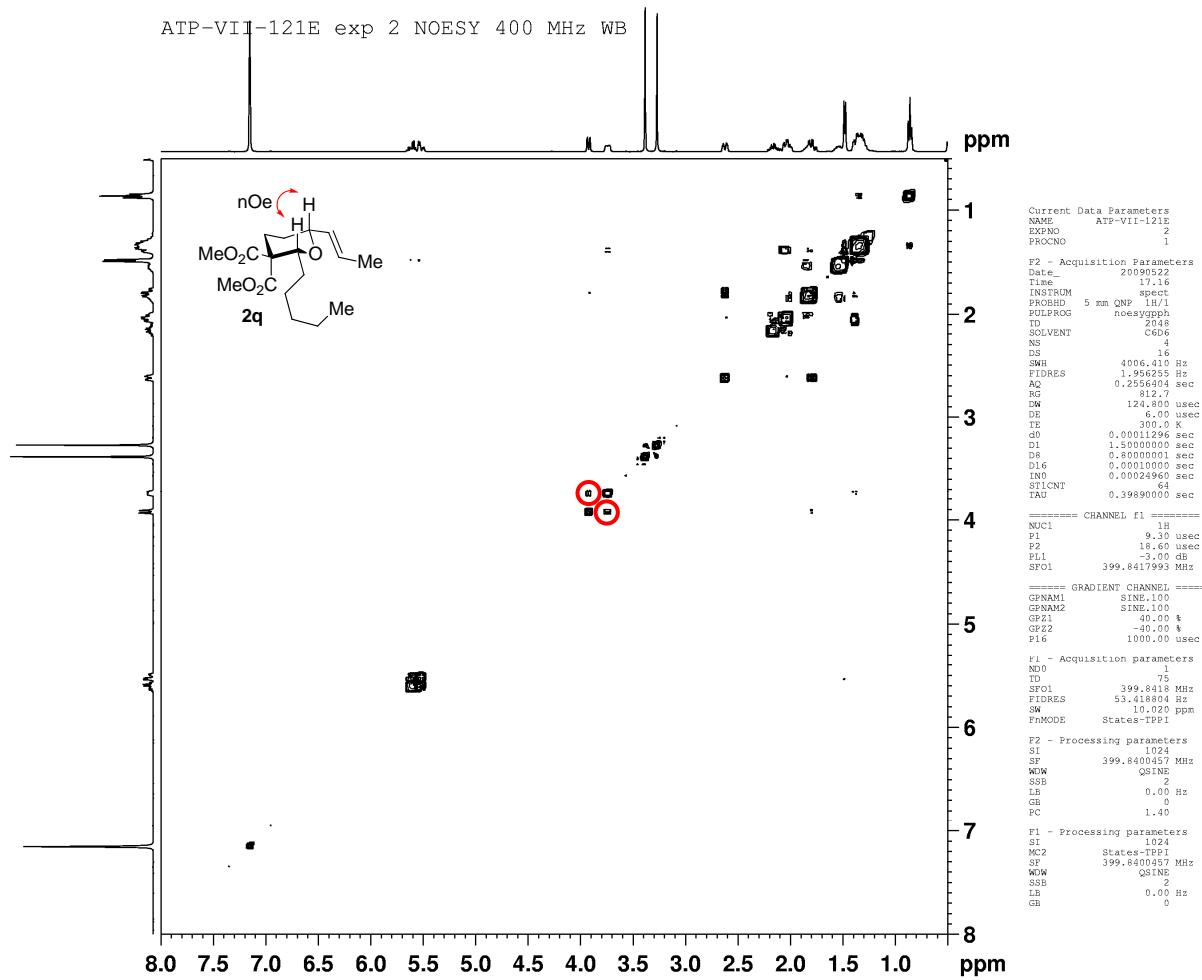


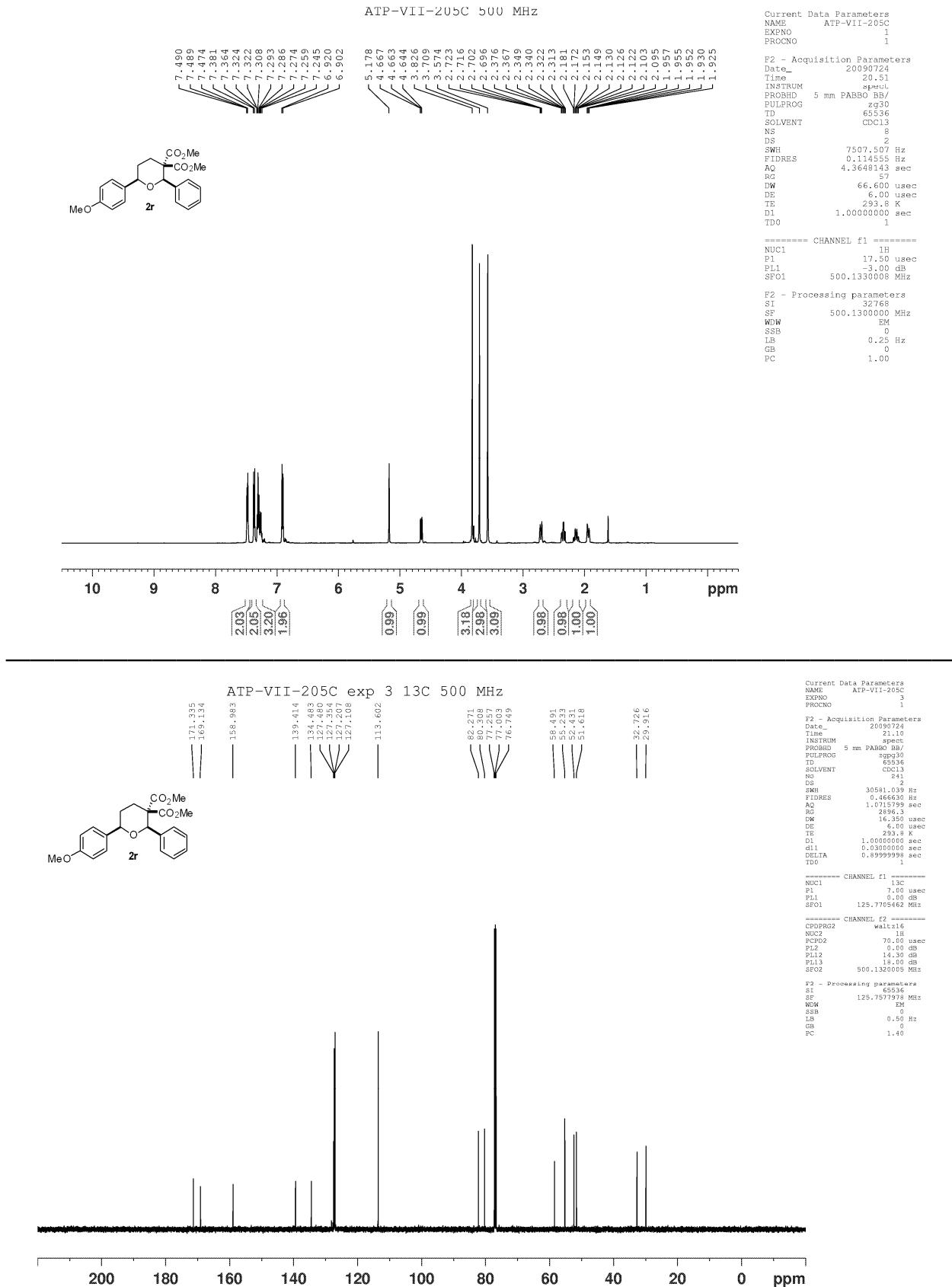












ATP-VII-205C exp 2 NOESY 500 MHz

