

*Chemo-, Regio- and Stereoselective Heck
Arylation of Allylated Malonates:
Mechanistic Insights by ESI-MS and
Synthetic Application Toward 5-Arylmethyl-
 γ -lactones*

Caio C. Oliveira,[†] Marcelo V. Marques,[‡] Marla N. Godoi,[‡] Thaís Regiani,[‡] Vanessa G. Santos,[‡] Emerson A. F. dos Santos,[†] Marcos N. Eberlin,[‡] Marcus M. Sá,[‡] Carlos R. D. Correia^{†*}

[†] Instituto de Química, Universidade Estadual de Campinas-UNICAMP, Campinas, SP 13083-970, Brazil

[‡] Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC 88040-900, Brazil

* Laboratório ThoMSon de Espectrometria de Massas, Universidade Estadual de Campinas-UNICAMP, Campinas, SP 13083-970, Brazil

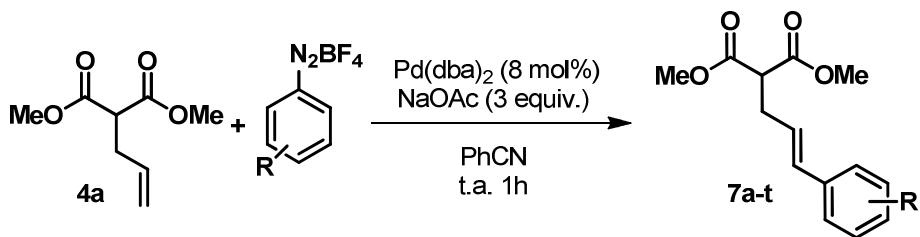
Table of contents

| | |
|---|-----|
| 1. General considerations | S2 |
| 2. General procedure for the Heck-Matsuda reaction | S3 |
| 3. General procedure for the synthesis of 5-arylmethyl- γ -lactones 25 from 7 | S13 |
| 4. Monitoring the Substrate-Directable Heck-Matsuda Reaction by Electrospray Ionization-Mass Spectrometry (ESI-MS). | S18 |
| 5. NMR Spectra | S23 |

General Considerations.

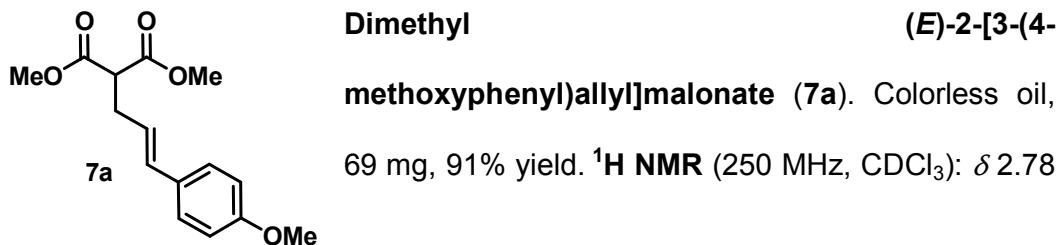
Hydrogen nuclear magnetic resonance spectra (^1H NMR) were obtained at 200 MHz, 250 MHz or 400 MHz. Spectra were recorded in CDCl_3 solutions. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 50 MHz, 62.5 MHz, or 100 MHz. Spectra were recorded in CDCl_3 . Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sx (sextet), dd (double of doublet), ddd (double of double of doublet), dt (double of triplet), appdt (apparent double of triplet), td (triple of doublet), m (multiplet) or brs (broad singlet). IR spectra were recorded using ZnSe for solids and film for liquid samples. ESI-HRMS spectra were recorded on a Q-TOF (ESI-QTOF) equipment. Column chromatography was performed using silica gel (230-400 mesh or 70-230 mesh). Thin layer chromatography (TLC) was performed using silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with phosphomolibdic acid, followed by heating. Microwave-assisted reactions were performed in 10 mL sealed tubes in a monomode microwave CEM-Explorer reactor instrument with infrared temperature monitoring and a non-invasive pressure transducer.

General procedure for the Heck-Matsuda reaction

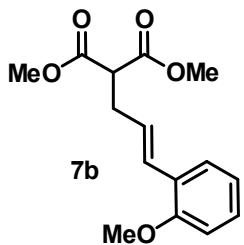


To a round-bottomed flask (or a test tube) were added Pd(dba)₂ (8 mol%, 11.5 mg), sodium acetate (3 equiv, 0.75mmol, 62 mg) and benzonitrile (2.5 mL). To the resulting suspension was then added the olefin **4/21** (1.0 equiv, 0.25 mmol) followed by addition of the arenediazonium tetrafluoroborate (1.0 equiv, 0.30 mmol). The reaction was stirred at room temperature for 1 h. Next, the reaction mixture was loaded directly onto a silica gel column and flash chromatographed using hexanes/ethyl acetate (9:1) as eluent to give the desired Heck adducts as homogeneous materials (single spot on TLC). Except when noted the products were obtained as clean pale yellow or colorless oils.

Notes: a) the physical conditions of the base NaOAc is crucial to attain good yields in the Heck-Matsuda reactions. The NaOAc has limited solubility in benzonitrile, and its use as a fine powder is recommended; b) The Pd(dba)₂ can be replaced by Pd(OAc)₂ using the same reaction conditions, except that an atmosphere of CO (balloon) is required.

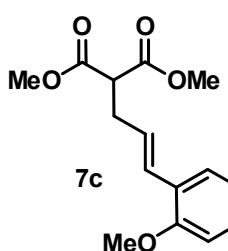


(td, $J= 1.1, 7.4, 2\text{H}$); 3.51 (t, $J= 7.4, 1\text{H}$); 3.74 (s, 6H); 3.79 (s, 3H); 5.99 (dt, $J= 7.3$ and $15.7, 1\text{H}$); 6.42 (d, $J= 15.7, 1\text{H}$); 6.87 (d, $J= 8.7, 2\text{H}$); 7.25 (d, $J= 8.7, 2\text{H}$). **^{13}C NMR** (63.5 MHz, CDCl_3): δ 32.3; 50.8; 52.5; 55.3; 113.7; 123.1; 126.9; 129.9; 132.3; 159.1; 169.3. HRMS calculated for ($\text{C}_{15}\text{H}_{18}\text{O}_5\text{Na}$) 301.1052. Found: 301.1043. The spectroscopic data obtained for this compound were consistent with the data available in the literature: Doucet, H.; Lemhadri, M.; Battace, A.; Zair, T.; Santelli, M. *J. Organomet. Chem.* **2007**, 692, 2270.



Dimethyl (*E*)-2-(3-(2-methoxyphenyl)allyl)malonate

(**7b**). Colorless oil, 72 mg, 95% yield. **^1H NMR** (250 MHz, CDCl_3): δ 2.82 (t, $J= 7.6, 2\text{H}$); 3.54 (t, $J= 7.6, 1\text{H}$); 3.75 (s, 6H); 3.83 (s, 3H); 6.13 (dt, $J= 6.8$ and $15.5, 1\text{H}$); 6.80 (d, $J= 15.5, 1\text{H}$); 6.89 (m, 2H); 7.20 (td, $J= 1.6$ and $7.8, 1\text{H}$); 7.37 (dd, $J= 1.45$ and $7.6, 1\text{H}$) **^{13}C NMR** (100 MHz, CDCl_3): δ 32.7; 52.0; 52.5; 55.4; 110.8; 120.6; 126.0; 126.2; 126.8; 127.8; 128.5; 156.5; 169.4. HRMS calculated for ($\text{C}_{15}\text{H}_{18}\text{O}_5\text{Na}$) 301.1052. Found: 301.1032. The spectroscopic data obtained for this compound were consistent with the data available in the literature: Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, 134, 15331.

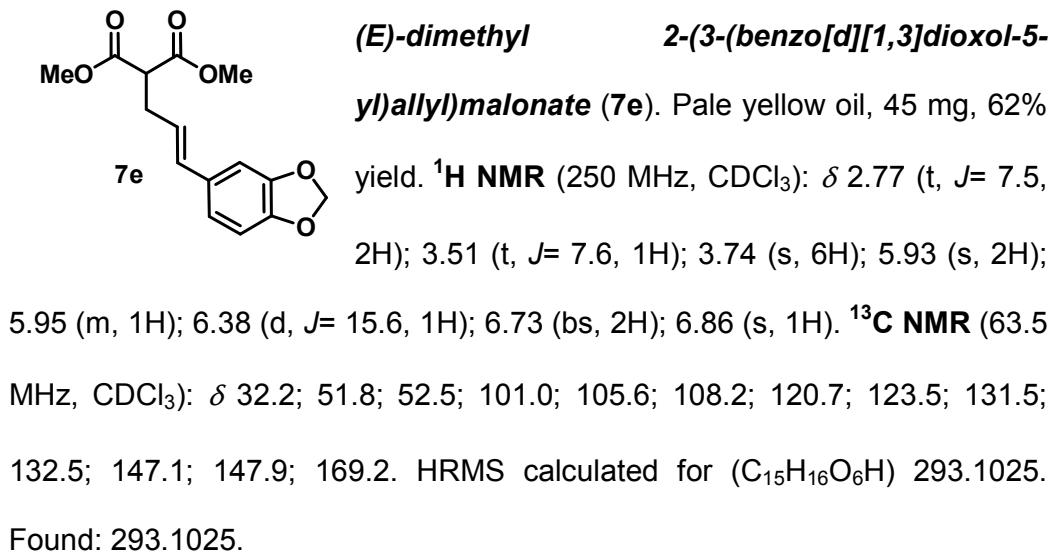
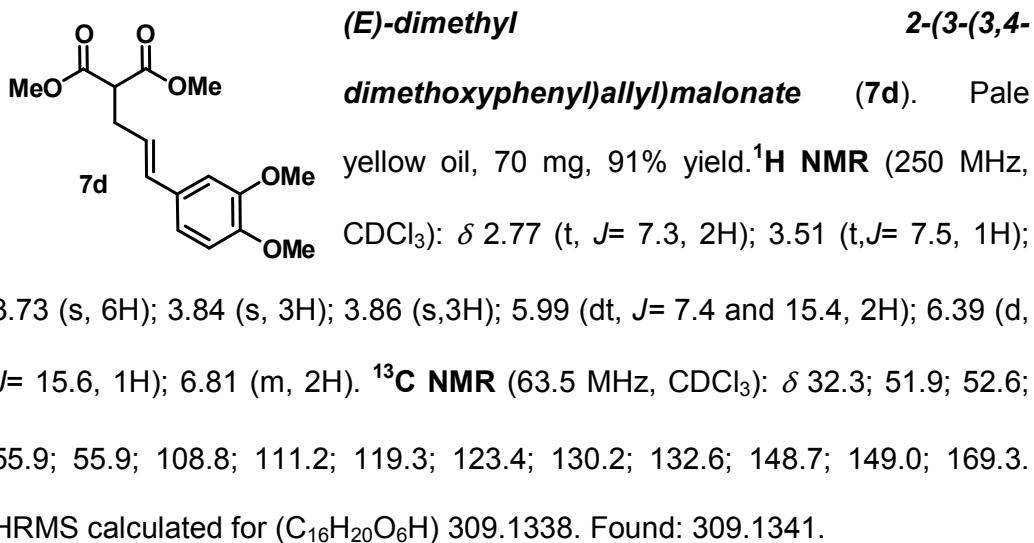


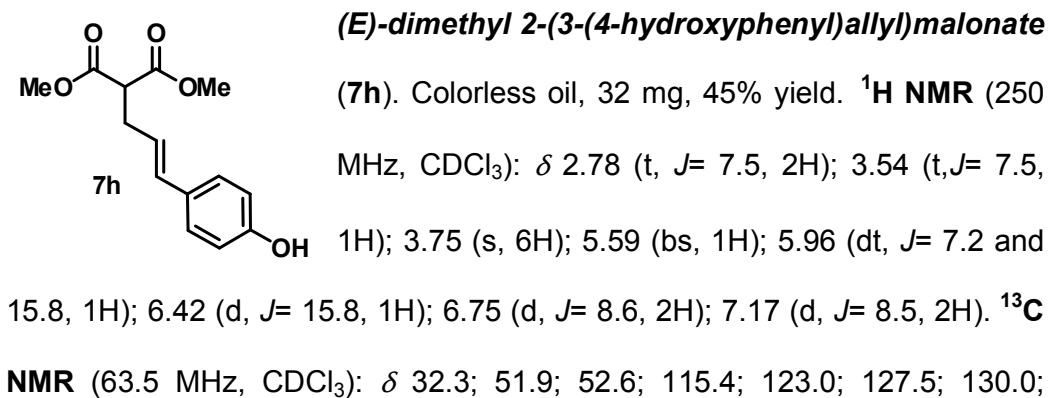
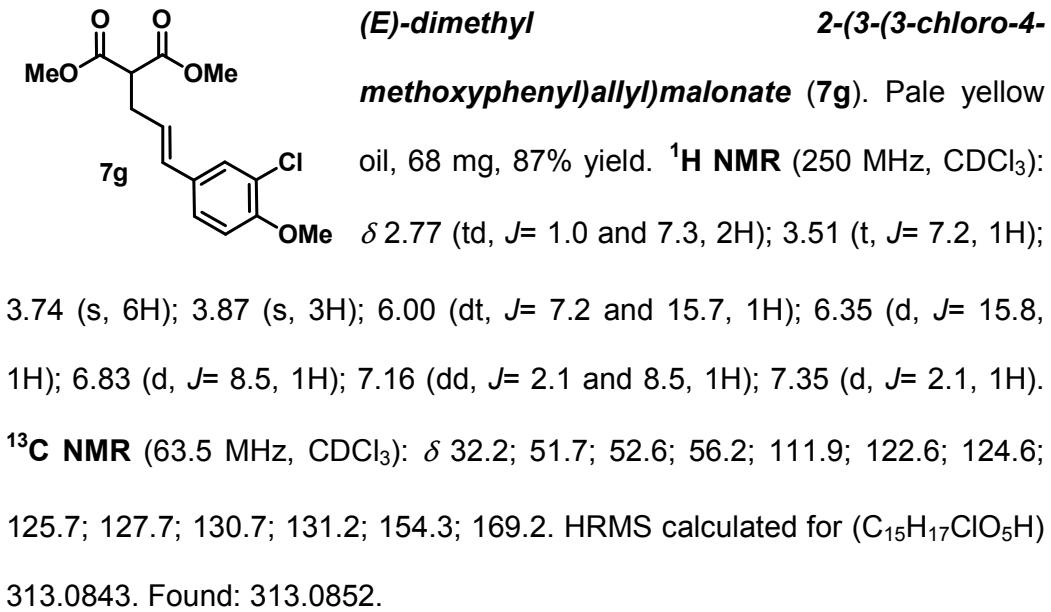
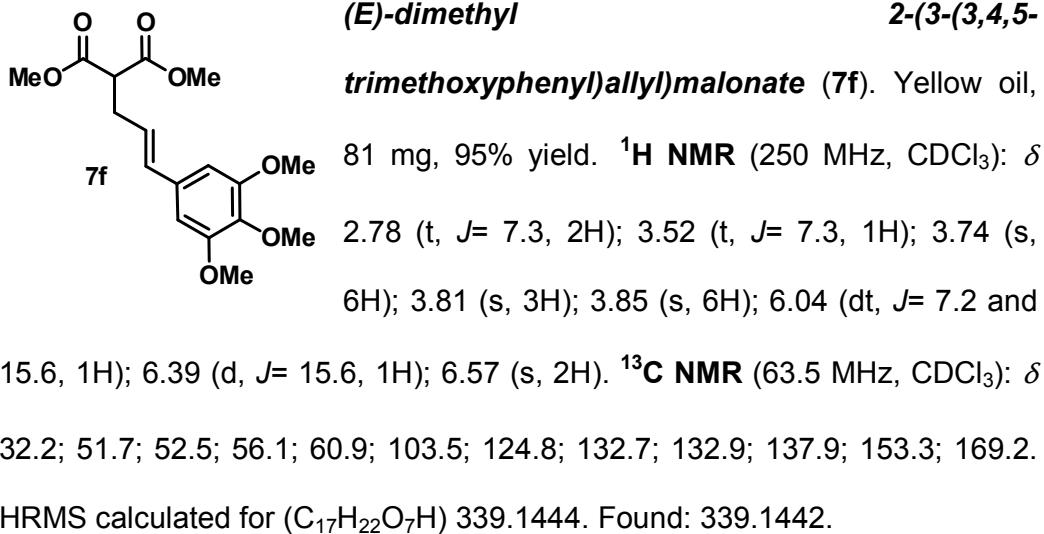
(*E*)-dimethyl

2-(3-(2,4-

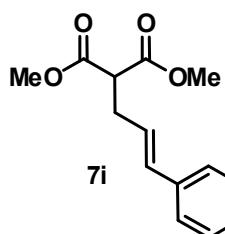
dimethoxyphenyl)allyl)malonate (7c). Pale yellow oil, 47 mg, 61% yield. **^1H NMR** (250 MHz, CDCl_3): δ 2.79 (td, $J= 1.2$ and $7.3, 2\text{H}$); 3.52 (t, $J= 7.6, 1\text{H}$);

3.74 (s, 6H); 3.79 (s, 3H); 3.80 (s, 3H); 6.00 (dt, $J= 7.1$ and 15.9 , 1H); 6.44 (m, 2H); 6.69 (d, $J= 15.9$, 1H); 7.28 (d, $J= 8.3$, 1H). **^{13}C NMR** (63.5 MHz, CDCl_3): δ 32.7; 51.8; 52.1; 55.3; 55.4; 98.4; 104.7; 119.2; 123.7; 127.3; 127.4; 157.5; 160.3; 169.4. HRMS calculated for ($\text{C}_{16}\text{H}_{20}\text{O}_6\text{H}$) 309.1338. Found: 309.1341.



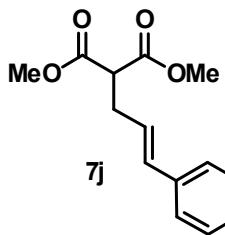


132.3; 159.2; 169.4. HRMS calculated for ($C_{14}H_{16}O_5Na$) 287.0895. Found: 287.0883.



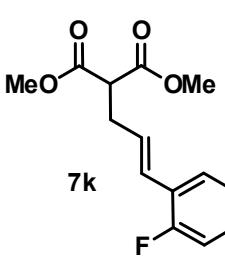
(*E*)-dimethyl 2-(3-(4-chlorophenyl)allyl)malonate

(7i). Pale yellow oil, 64 mg, 84% yield. **1H NMR** (250 MHz, $CDCl_3$): δ 2.79 (t, $J= 7.6$, 2H); 3.54 (t, $J= 7.5$, 1H); 3.74 (s, 6H); 6.12 (dt, $J= 7.1$ and 15.7, 1H); 6.43 (d, $J= 15.5$, 1H); 7.25 (m, 4H); 7.27. **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.2; 51.6; 52.6; 126.1; 127.4; 128.6; 131.7; 133.0; 135.4; 169.2. HRMS calculated for ($C_{14}H_{15}ClO_4Na$) 305.0557. Found: 305.0569.



(*E*)-dimethyl 2-(3-(4-fluorophenyl)allyl)malonate

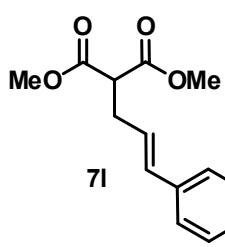
(7j). Colorless oil, 69 mg, 62% yield. **1H NMR** (250 MHz, $CDCl_3$): δ 2.78 (t, $J= 7.6$, 2H); 3.52 (t, $J= 7.5$, 1H); 3.74 (s, 6H); 6.04 (dt, $J= 7.1$ and 15.7, 1H); 6.43 (d, $J= 15.8$, 1H); 7.00 (m, 2H); 7.27 (m, 2H). **^{13}C NMR** (63.5 MHz, $CDCl_3$): δ 32.2; 51.7; 52.5; 115.4 (d, $J= 2.1$); 125.1 (d, $J= 2.5$); 127.7 (d, $J= 4$); 131.7; 133.1; 162.20 (d, $J= 245$); 169.18. HRMS calculated for ($C_{14}H_{15}NO_4FNa$) 289.0852. Found: 289.0829. The spectroscopic data obtained for this compound were consistent with the data available in the literature: Doucet, H.; Lemhadri, M.; Battace, A.; Zair, T.; Santelli, M. *J. Organomet. Chem.* **2007**,



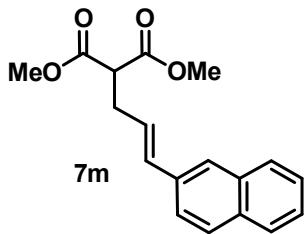
692, 2270

(*E*)-dimethyl 2-(3-(4-fluorophenyl)allyl)malonate (7k).

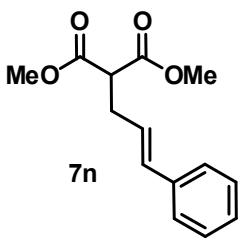
Pale yellow oil, 48 mg, 66% yield. **¹H NMR** (250 MHz, CDCl₃): δ 2.83 (t, *J*= 7.2, 2H); 3.55 (t, *J*= 7.5, 1H); 3.75 (s, 6H); 6.22 (dt, *J*= 7.2 and 15.9, 1H); 6.63 (d, *J*= 15.9, 1H); 7.04 (m, 2H); 7.18 (m, 1H); 7.40 (td, *J*= 1.7 and 7.6, 1H). **¹³C NMR** (63.5 MHz, CDCl₃): δ 32.6; 51.6; 52.6; 55.1; 115.6 (d, *J*=22); 124.0 (d, *J*=3.5); 124.7 (d, *J*=22.2); 125.4 (d, *J*=3.5); 127.3 (d, *J*=5.8); 128.1 (d, *J*=4.6); 128.6 (d, *J*=8.3); 160.0 (d, *J*=247.5); 169.2. HRMS calculated for (C₁₄H₁₅NO₄FNa) 289.0852. Found: 289.0864.



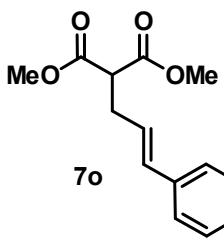
(E)-dimethyl 2-(3-([1,1'-biphenyl]-4-yl)allyl)malonate (7l). Colorless oil, 61 mg, 70% yield. **¹H NMR** (250 MHz, CDCl₃): δ 2.84 (t, *J*= 7.4, 2H); 3.56 (t, *J*= 7.6, 1H); 3.76 (s, 6H); 6.20 (dt, *J*= 7.3 and 15.8, 1H); 6.53 (d, *J*= 15.8, 1H); 7.40 (m, 5H); 7.57 (m, 4H). **¹³C NMR** (63.5 MHz, CDCl₃): δ 32.3; 51.8; 52.6; 125.5; 126.6; 126.9; 127.2; 121.3; 128.8; 132.5; 136.0; 140.2; 140.7; 169.3. HRMS calculated for (C₂₀H₂₀O₄Na) 347.1259. Found: 347.1259.



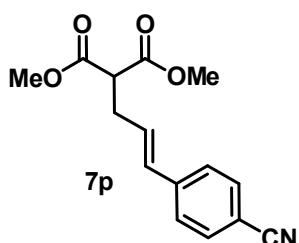
(E)-dimethyl 2-(3-(naphthalen-2-yl)allyl)malonate (7m). Colorless oil, 66 mg, 82% yield. **¹H NMR** (250 MHz, CDCl₃): δ 2.88 (td, *J*= 1.0 and 7.3, 2H); 3.59 (t, *J*= 7.5, 1H); 3.77 (s, 6H); 6.23 (dt, *J*= 7.2 and 15.7, 1H); 6.65 (d, *J*= 15.9, 1H); 7.45 (m, 2H); 7.55 (dd, *J*= 1.6 and 8.6, 2H); 7.69 (s, 1H); 7.78 (m, 2H). **¹³C NMR** (63.5 MHz, CDCl₃): δ 32.4; 51.8; 52.6; 123.5; 125.8; 126.0; 126.2; 127.6; 127.9; 128.1; 132.9; 133.1; 133.6; 134.4; 169.3. HRMS calculated for (C₁₈H₁₈O₄Na) 321.1103. Found: 321.1100.



dimethyl 2-cinnamylmalonate (7n). Colorless oil, 56 mg, 90% yield. **¹H NMR** (250 MHz, CDCl₃): δ 2.81 (td, *J*= 1.2 and 7.3, 2H); 3.54 (t, *J*= 7.5, 1H); 3.74 (s, 6H); 6.14 (dt, *J*= 7.2 and 15.8, 1H); 6.48 (d, *J*= 15.8, 1H); 7.27 (m, 5H). **¹³C NMR** (63.5 MHz, CDCl₃): δ 32.2; 51.7; 52.6; 125.4; 126.2; 127.4; 128.6; 132.9; 137.0; 169.2. HRMS calculated for (C₁₄H₁₆O₄H) 249.1127. Found: 249.1140. The spectroscopic data obtained for this compound were consistent with the data available in the literature: Doucet, H.; Lemhadri, M.; Battace, A.; Zair, T.; Santelli, M. *J. Organomet. Chem.* **2007**, 692, 2270.

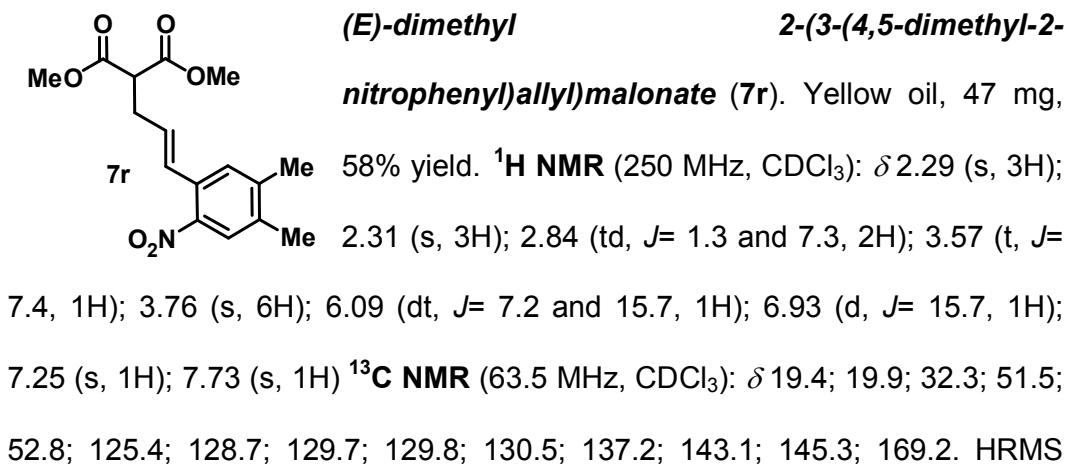
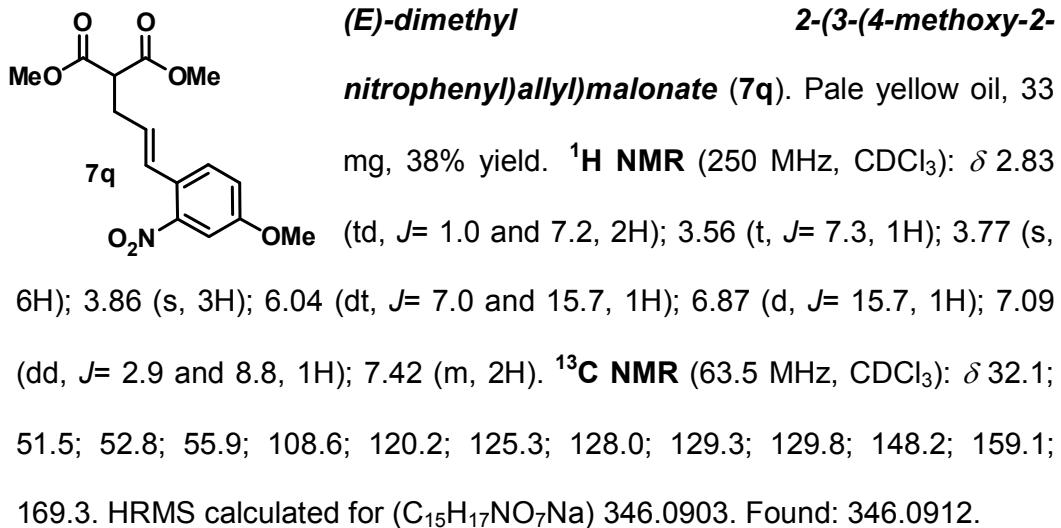


(E)-dimethyl 2-(3-(3,4-dichlorophenyl)allyl)malonate (7o). Pale yellow oil, 69 mg, 87% yield. **¹H NMR** (250 MHz, CDCl₃): δ 2.80 (td, *J*= 1.0 and 7.3, 2H); 3.52 (t, *J*= 7.4, 1H); 3.75 (s, 6H); 6.15 (dt, *J*= 7.1 and 15.8, 1H); 6.38 (d, *J*= 15.8, 1H); 7.13 (dd, *J*= 2.0 and 8.4, 1H); 7.34 (d, *J*= 8.4, 1H); 7.39 (d, *J*= 2.0, 1H). **¹³C NMR** (63.5 MHz, CDCl₃): δ 32.1; 51.5; 52.7; 125.4; 127.6; 127.9; 130.4; 130.7; 131.1; 132.6; 137.1; 169.2. HRMS calculated for (C₁₄H₁₄Cl₂O₄H) 317.0347. Found: 317.0352.

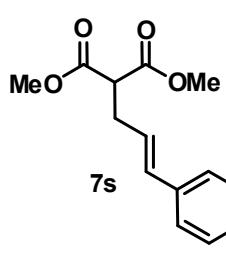


(E)-dimethyl 2-(3-(4-cyanophenyl)allyl)malonate (7p). Colorless oil, 41 mg, 60% yield. **¹H NMR** (250 MHz, CDCl₃): δ 2.83 (t, *J*= 7.3, 2H); 3.54 (t, *J*= 7.4,

1H); 3.74 (s, 6H); 6.28 (dt, J = 7.0 and 15.8, 1H); 6.49 (d, J = 16.0, 1H); 7.39 (d, J = 8.3, 2H); 7.56 (d, J = 8.4, 2H). **^{13}C NMR** (63.5 MHz, CDCl_3): δ 32.2; 51.3; 52.7; 110.7; 118.9; 126.7; 129.7; 131.4; 132.4; 141.4; 146.9; 169.0. HRMS calculated for ($\text{C}_{15}\text{H}_{15}\text{NO}_4\text{H}$) 274.1079. Found: 274.1096. The spectroscopic data obtained for this compound were consistent with the data available in the literature: Doucet, H.; Lemhadri, M.; Battace, A.; Zair, T.; Santelli, M. *J. Organomet. Chem.* **2007**, 692, 2270.

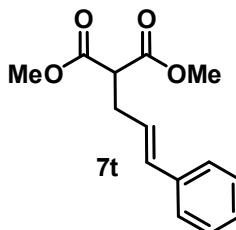


calculated for (C₁₆H₁₉NO₆H) 322.1291. Found: 322.1295.



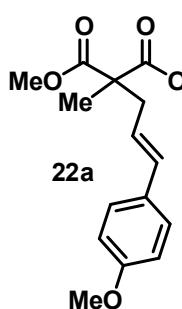
(E)-dimethyl 2-(3-(4-nitrophenyl)allyl)malonate -

(7s). Pale yellow oil, 70 mg, 95% yield. **¹H NMR** (250 MHz, CDCl₃): δ 2.86 (t, J= 7.2, 2H); 3.56 (t, J= 7.4, 1H); 3.74 (s, 6H); 6.35 (dt, J= 7.1 and 15.8, 1H); 6.54 (d, J= 16.0, 1H); 7.44 (d, J= 8.8, 2H); 8.14 (d, J= 8.8, 2H). **¹³C NMR** (63.5 MHz, CDCl₃): δ 32.2; 51.2; 52.7; 123.9; 126.7; 130.7; 131.0; 143.3; 146.7; 169.0. HRMS calculated for (C₁₄H₁₅NO₆H) 294.0977. Found: 294.0976.



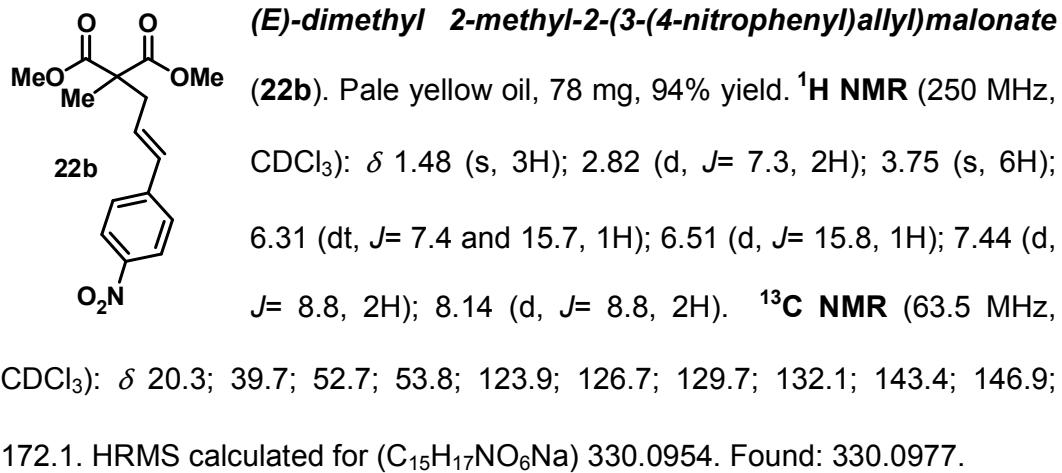
(E)-dimethyl 2-(3-(3-nitrophenyl)allyl)malonate -

(7t). Pale yellow oil, 22 mg, 30% yield. **¹H NMR** (250 MHz, CDCl₃): δ 2.84 (t, J= 6.8, 2H); 3.56 (t, J= 7.3, 1H); 3.76 (s, 6H); 6.30 (dt, J= 7.1 and 15.8, 1H); 6.53 (d, J= 15.7, 1H); 7.41 (t, J= 7.9, 1H); 7.62 (d, J= 7.7, 1H); 8.05 (dd, J= 1.0 and 8.1, 1H); 8.16 (s, 1H). **¹³C NMR** (63.5 MHz, CDCl₃): δ 32.1; 51.3; 52.7; 120.8; 122.0; 128.9; 129.4; 130.8; 132.1; 138.7; 148.6; 169.0. HRMS calculated for (C₁₄H₁₅NO₆H) 294.0977. Found: 294.0947.

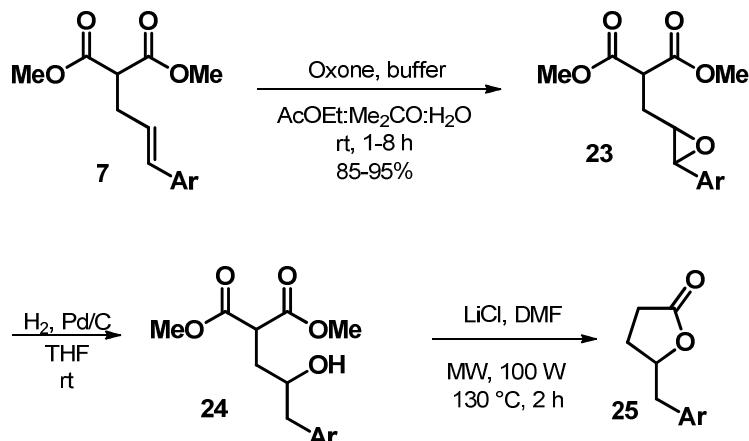


(E)-dimethyl 2-methyl-2-(3-(4-methoxyphenyl)allyl)malonate (22a). Colorless oil, 72 mg, 92% yield. **¹H NMR** (250 MHz, CDCl₃): δ 1.45 (s, 3H); 2.74 (dd, J= 1.0 and 7.5, 2H); 3.73 (s, 6H); 3.79 (s, 3H);

5.93 (dt, $J= 7.5$ and 15.8 , 1H); 6.38 (d, $J= 15.9$, 1H); 6.82 (d, $J= 8.8$, 2H); 7.25 (d, $J= 8.7$, 2H). ^{13}C NMR (63.5 MHz, CDCl_3): δ 20.0; 39.5; 52.5; 54.0; 55.3; 113.9; 121.8; 127.4; 129.9; 133.5; 159.1; 172.4. HRMS calculated for ($\text{C}_{16}\text{H}_{20}\text{O}_5\text{Na}$) 315.1208. Found: 315.1223.

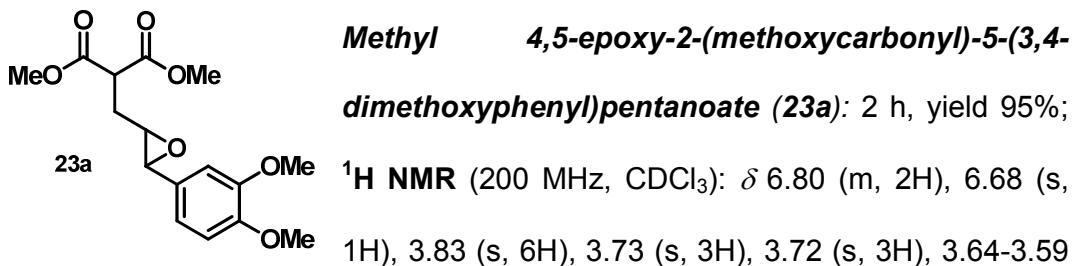


General procedure for the synthesis of 5-arylmethyl- γ -lactones 25 from 7.

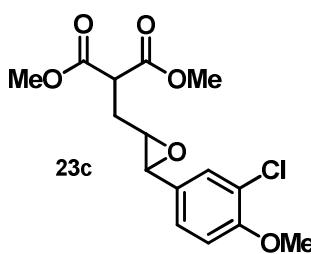


1. Epoxidation of alkenes 7: To a stirred solution of alkene **7** (1.0 mmol), ethyl acetate (10 mL), acetone (5.0 mL) and phosphate buffer (1.0 mol L⁻¹ K₂HPO₄/KH₂PO₄, pH 8, 10 mL) at 25 °C was added dropwise a solution of Oxone (1.3 mmol) in H₂O (5.0 mL). The reaction mixture was stirred until TLC (8:2 or 6:4 hexane:EtOAc) showed completion of the reaction (1-8 h). The insoluble solid was separated by filtration under reduced pressure and washed with EtOAc. The filtrate was washed with 1.0 mol L⁻¹ Na₂S₂O₃ and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give the epoxides as pale yellow oil, which were used in the next step without further purification. Representative data for epoxides **23a** and **23c** are included below.

Epoxides **23b** and **23d** were prepared according to literature: Marques, M. V.; Sá, M. M. *J. Org. Chem.* **2014**, 79, 4650.

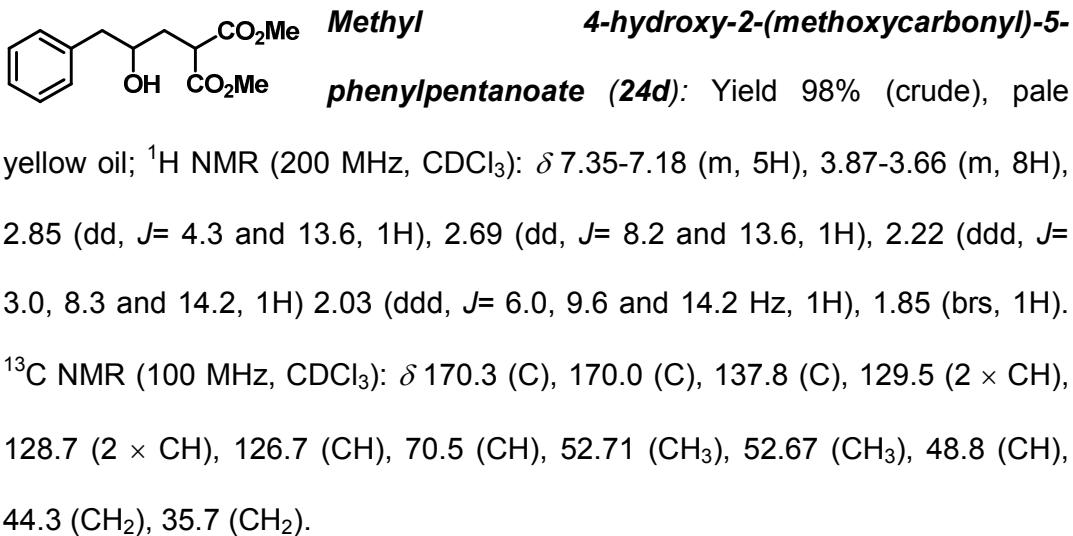


(m, 2H), 3.01 (ddd, J = 2.0, 4.8 and 6.7, 1H), 2.36 (ddd, J = 4.8, 8.6 and 14.2, 1H), 2.14 (appdt, J = 6.1 and 14.2, 1H). **^{13}C NMR** (50 MHz, CDCl_3): δ 169.24 (C), 169.19 (C), 149.4 (C), 149.3 (C), 129.5 (C), 118.5 (CH), 111.3 (CH), 108.3 (CH), 59.8 (CH), 59.0 (CH), 56.03 (CH_3), 55.97 (CH_3), 52.8 (CH_3), 52.7 (CH_3), 48.5 (CH), 31.5 (CH_2).

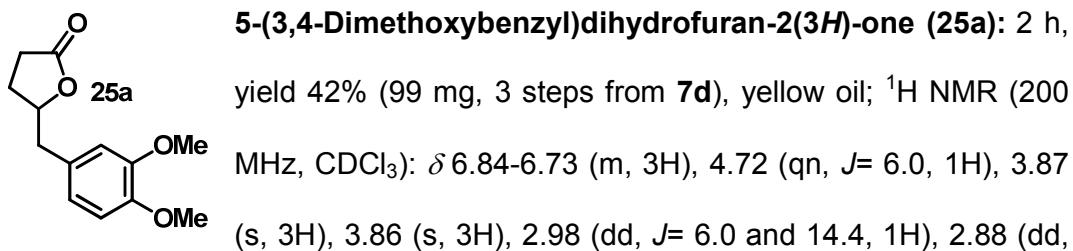


Methyl 4,5-epoxy-2-(methoxycarbonyl)-5-(3-chloro-4-methoxyphenyl)pentanoate (23c): 2 h, yield 90%; ^1H NMR (200 MHz, CDCl_3): δ 7.22 (d, J = 2.4, 1H), 7.10 (dd, J = 2.4 and 8.6, 1H), 6.87 (d, J = 8.6, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.63 (dd, J = 5.3 and 8.7, 1H), 3.58 (d, J = 1.6, 1H), 3.01 (ddd, J = 1.6, 4.7 and 6.5, 1H), 2.38 (ddd, J = 4.7, 8.7 and 14.0, 1H), 2.15 (appdt, J = 6.2 and 14.0, 1H).

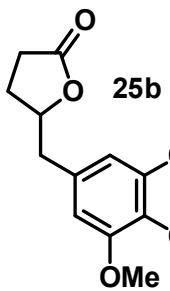
2. Hydrogenolysis of epoxides 23: To a stirred solution of the freshly prepared epoxide **23** (0.85-0.95 mmol) in THF (10 mL) was added Pd/C 10% (10% m/m) then the system was charged with H_2 (balloon) and the mixture was stirred at 25 °C until TLC (8:2 or 6:4 hexane: EtOAc) showed completion of the reaction (1 h for **23c,d** and 8 h for **23a,b**). The reaction mixture was filtered through a Celite pad and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure to provide the secondary alcohols **24** as pale yellow oil which was used in the next step without further purification. Representative data for alcohol **24d** is included below.



3. Domino lactonization/Krapcho decarboxylation step: To a 10 mL glass tube containing a solution of alcohol **24** (0.75-0.90 mmol) in DMF (3.5 mL) were added LiCl (5.0 mmol) and water (2.0 mmol). The vessel was sealed with a septum, placed into the microwave cavity, and the mixture was heated to 130 °C (maximum power = 100 W) under stirring until TLC (6:4 hexane:EtOAc) showed completion of the reaction (2 h). After cooling to 25 °C, the mixture was diluted with EtOAc and washed with water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with 0.1 mol L⁻¹ HCl and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 5-arylmethyl- γ -lactones **25** as brown oil. Purification by column chromatography on silica gel (6:4 hexane/EtOAc) gave pure lactones.

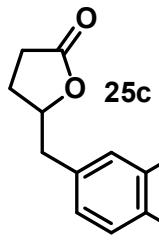


J = 6.0 and 14.4, 1H), 2.55-2.16 (m, 3H), 2.03-1.84 (m, 1H). ^{13}C NMR (50 MHz, CDCl_3): δ 177.1 (C), 148.9 (C), 148.0 (C), 128.4 (C), 121.5 (CH), 112.7 (CH), 111.4 (CH), 80.8 (CH), 55.8 (2 x CH₃), 40.7 (CH₂), 28.5 (CH₂), 26.8 (CH₂). IR (ZnSe, cm^{-1}): ν = 2937, 2835, 1770, 1590, 1518, 1260, 1236, 1176, 1026, 804, 765. HRMS calculated for ($\text{C}_{13}\text{H}_{16}\text{O}_4\text{H}$) 237.1121. Found: 237.1124. The spectroscopic data obtained for this compound were consistent with the data available in the literature: Lambert, J. D.; Rice, J. E.; Hong, J.; Hou, Z.; Yang, C. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 873.



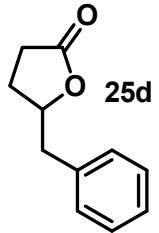
5-(3,4,5-Trimethoxybenzyl)dihydrofuran-2(3*H*)-one (25b):

2 h, yield 44% (117 mg, 3 steps from **7f**), yellow oil; ^1H NMR (200 MHz, CDCl_3): δ 6.40 (s, 2H), 4.70 (qn, J = 6.2, 1H), 3.80 (s, 6H), 3.78 (s, 3H), 2.92 (dd, J = 6.2 and 14.2, 1H), 2.83 (dd, J = 6.2 and 14.2, 1H), 2.44-2.15 (m, 3H), 2.00-1.81 (m, 1H). ^{13}C NMR (50 MHz, CDCl_3): δ 177.0 (C), 153.3 (2 x C), 137.1 (C), 131.7 (C), 106.6 (2 x CH), 80.7 (CH), 60.8 (CH₃), 56.2 (2 x CH₃), 41.6 (CH₂), 28.6 (CH₂), 27.1 (CH₂). IR (ZnSe, cm^{-1}): ν = 2938, 2839, 1769, 1589, 1504, 1462, 1423, 1332, 1244, 1179, 1083, 1006. HRMS calculated for ($\text{C}_{14}\text{H}_{18}\text{O}_5\text{H}$) 267.1227. Found: 267.1225. The spectroscopic data obtained for this compound were consistent with the data available in the literature: Lambert, J. D.; Rice, J. E.; Hong, J.; Hou, Z.; Yang, C. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 873.



5-(3-Chloro-4-methoxybenzyl)dihydrofuran-2(3H)-one

(25c): 2 h, yield 56% (135 mg, 3 steps from **7g**), yellow solid; Mp: 72.2-73.3 °C. ^1H NMR (200 MHz, CDCl_3): δ 7.19 (d, $J= 2.0$, 1H), 7.05 (dd, $J= 2.0$ and 8.0, 1H), 6.83 (d, $J= 8.0$, 1H), 4.62 (qn, $J= 6.3$, 1H), 3.82 (s, 3H), 2.91 (dd, $J= 6.3$ and 14.2, 1H), 2.80 (dd, $J= 6.3$ and 14.2, 1H), 2.50-2.35 (m, 2H), 2.30-2.14 (m, 1H), 1.97-1.77 (m, 1H). ^{13}C NMR (50 MHz, CDCl_3): δ 176.8 (C), 153.9 (C), 130.9 (CH), 129.2 (C), 128.8 (CH), 122.3 (C), 112.2 (CH), 80.6 (CH), 56.1 (CH_3), 40.1 (CH_2), 28.6 (CH_2), 27.1 (CH_2). IR (ZnSe, cm^{-1}): $\nu = 2968, 2915, 1776, 1503, 1258, 1177, 1067, 1025$. HRMS calculated for ($\text{C}_{12}\text{H}_{13}\text{ClO}_3\text{Na}$) 263.0445. Found: 263.0446.



5-Benzylidihydrofuran-2(3H)-one (25d): 2 h, yield 59% (104 mg,

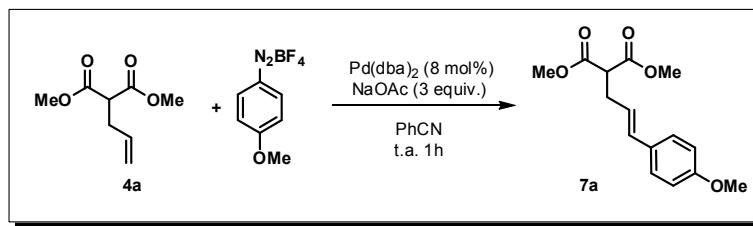
3 steps from **7n**), colorless oil; ^1H NMR (200 MHz, CDCl_3): δ 7.36-7.20 (m, 5H), 4.70 (qn, $J= 6.3$, 1H), 3.04 (dd, $J= 6.3$ and 14.2, 1H), 2.90 (dd, $J= 6.3$ and 14.2, 1H), 2.53-2.33 (m, 2H), 2.31-2.13 (m, 1H), 2.06-1.81 (m, 1H). ^{13}C NMR (50 MHz, CDCl_3): δ 176.9 (C), 136.0 (C), 129.3 (2 x CH), 128.5 (2 x CH), 126.8 (CH), 80.7 (CH), 41.2 (CH_2), 28.5 (CH_2), 27.0 (CH_2). IR (ZnSe, cm^{-1}): $\nu = 3025, 2942, 1772, 1762, 1496, 1453, 1352, 1176, 1024, 700$. HRMS calculated for ($\text{C}_{11}\text{H}_{12}\text{O}_2\text{H}$) 177.0910. Found: 177.0916. The spectroscopic data obtained for this compound were consistent with the data available in the literature: Ube, H.; Shimada, N.; Terada, M. *Angew. Chem. 2010*, 122, 1902.

Monitoring the Substrate-Directable Heck-Matsuda Reaction by Electrospray Ionization-Mass Spectrometry (ESI-MS).

General procedure for the ESI-MS and ESI-MS/MS experiments. All experiments were performed on a Q-TOF mass spectrometer (Waters Micromass, Manchester, UK) equipped with an electrospray ionization (ESI) source. For typical ESI conditions, the samples were directly infused using a syringe pump at a flow rate of the $10 \mu\text{L}\cdot\text{min}^{-1}$. The main conditions in positive ion mode were as following: capillary voltage 3000 eV; cone voltage 30 eV; source temperature 100°C; desolvation temperature 100°C. The cationic species were subjected to collision-induced dissociation (CID) with argon by using collision energies ranging from 5 to 45 eV.

Electrospray Ionization-Mass Spectrometry (ESI-MS).

To a round-bottomed flask were added $\text{Pd}(\text{dba})_2$ (8 mol%), sodium acetate (3 equiv) and benzonitrile (0,1 mol/L). To the resulting suspension, it was then added the olefin **4** (1 equiv) followed by addition of the arenediazonium tetrafluoroborate (1 equiv.). Next, the ESI/MS monitoring was made by periodically taken 1 μL aliquots, diluting those in acetonitrile (1 mL) containing 0.1% of HCOOH, followed by injection into the Mass spectrometer. MS spectra were recorded as indicated in the general procedure for ESI/MS(/MS) experiments.



1 minute

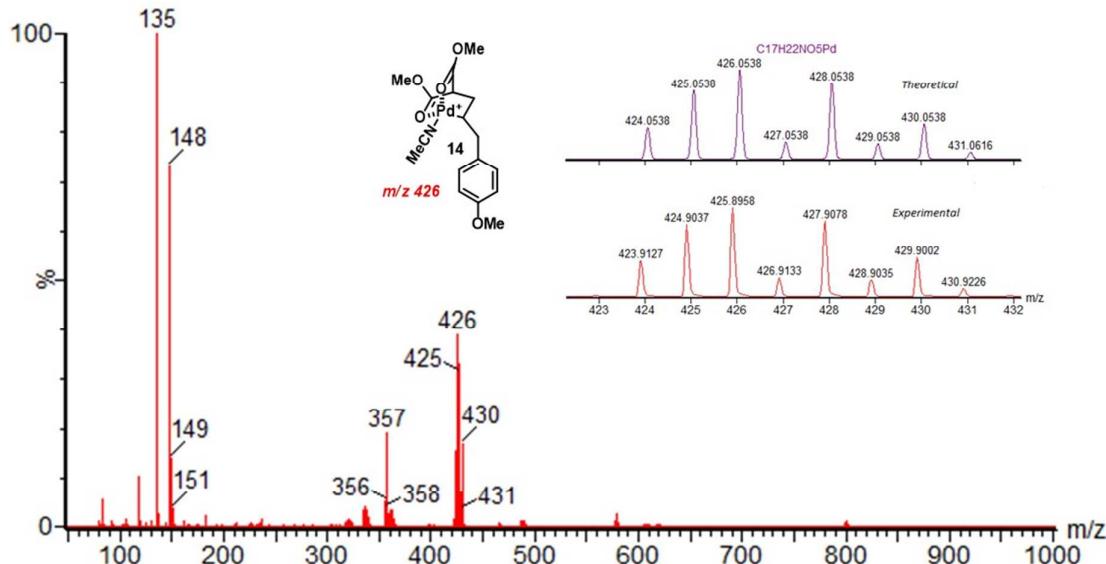


Figure S1: ESI(+)-MS of reaction solution at the 1 minute.

10 minutes

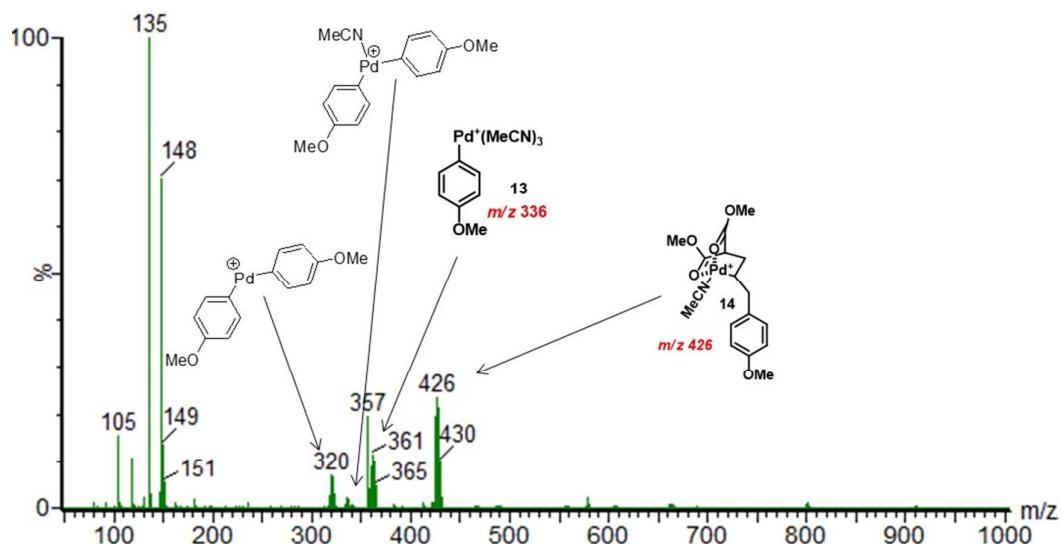


Figure S2: ESI(+)-MS of reaction solution after 10 minutes.

20 minutes

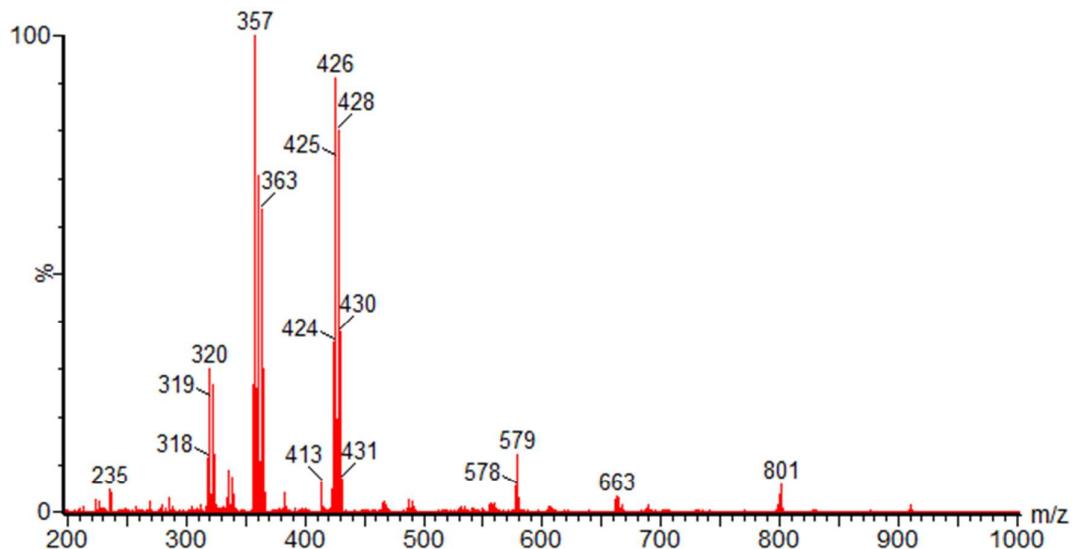


Figure S3: ESI(+)-MS of reaction solution at the 20 minutes.

30 minutes

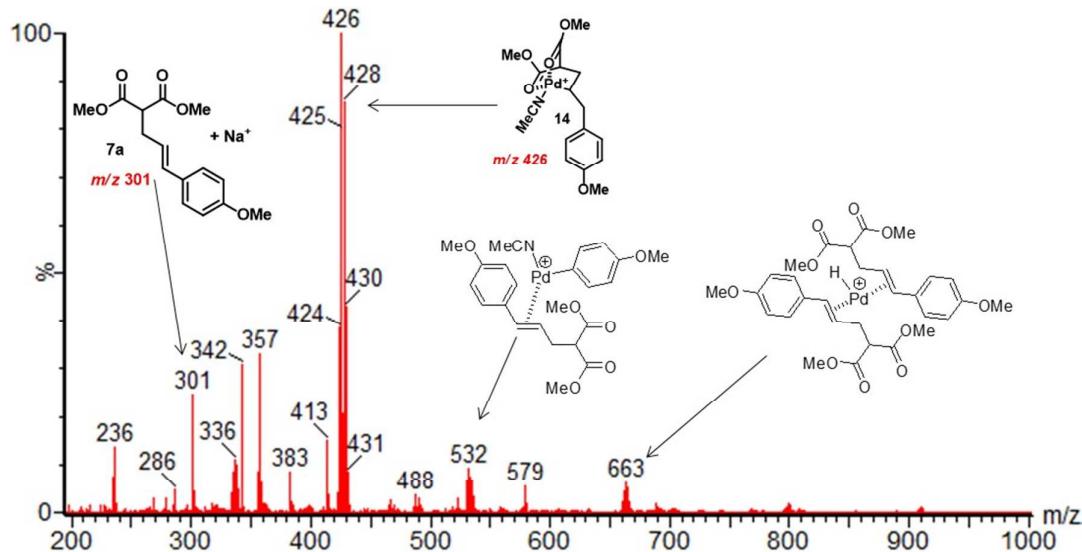


Figure S4: ESI(+)-MS of reaction solution at the 30 minutes.

40 minutes

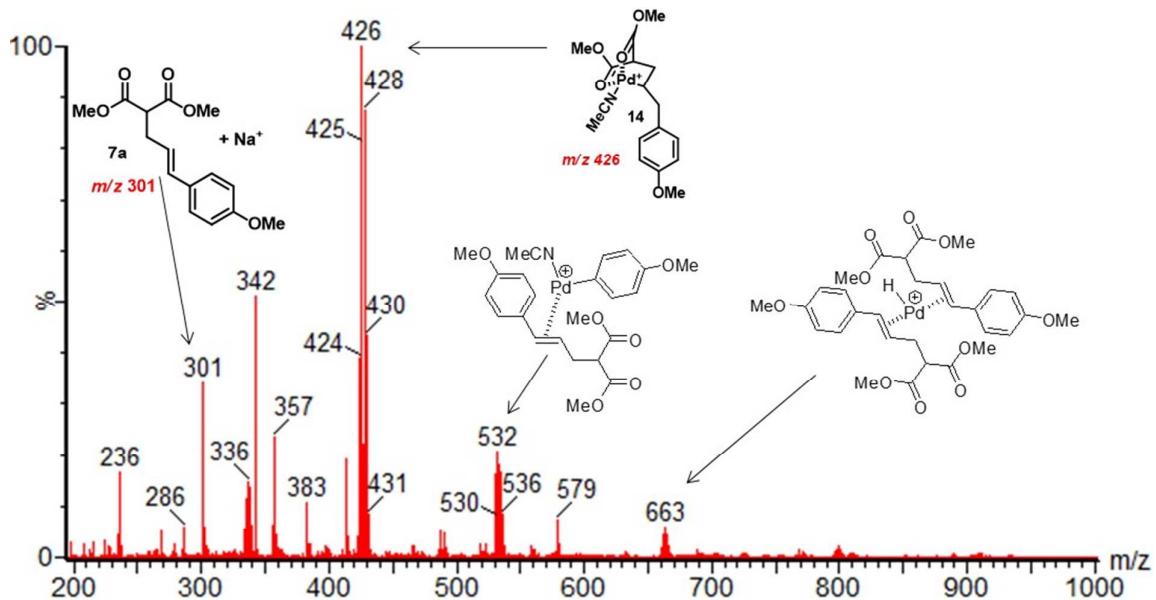


Figure S5: ESI(+)-MS of reaction solution at the 40 minutes.

50 minutes

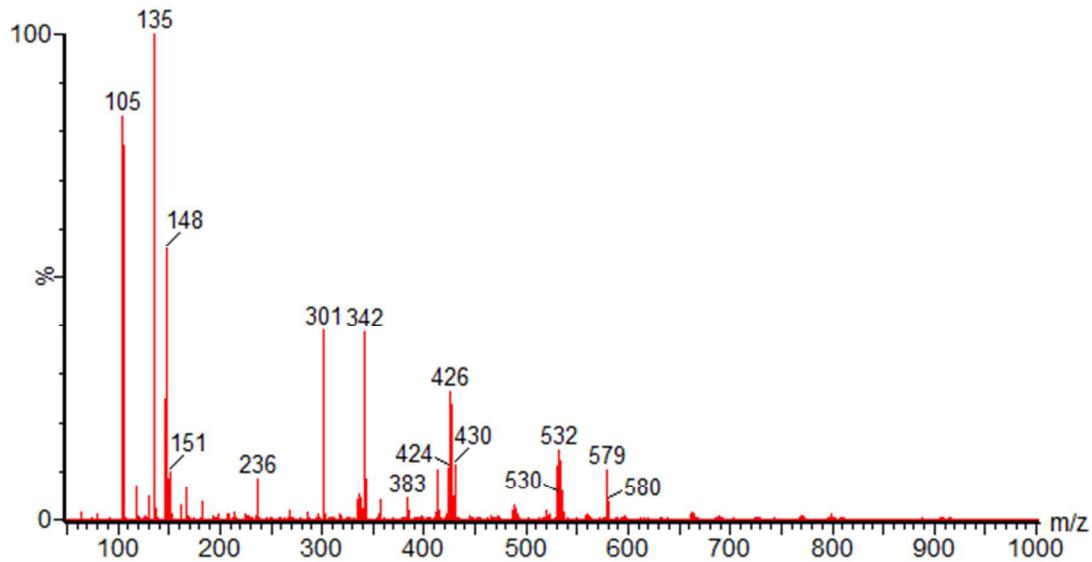


Figure S6: ESI(+)-MS of reaction solution at the 50 minutes.

65 minutes

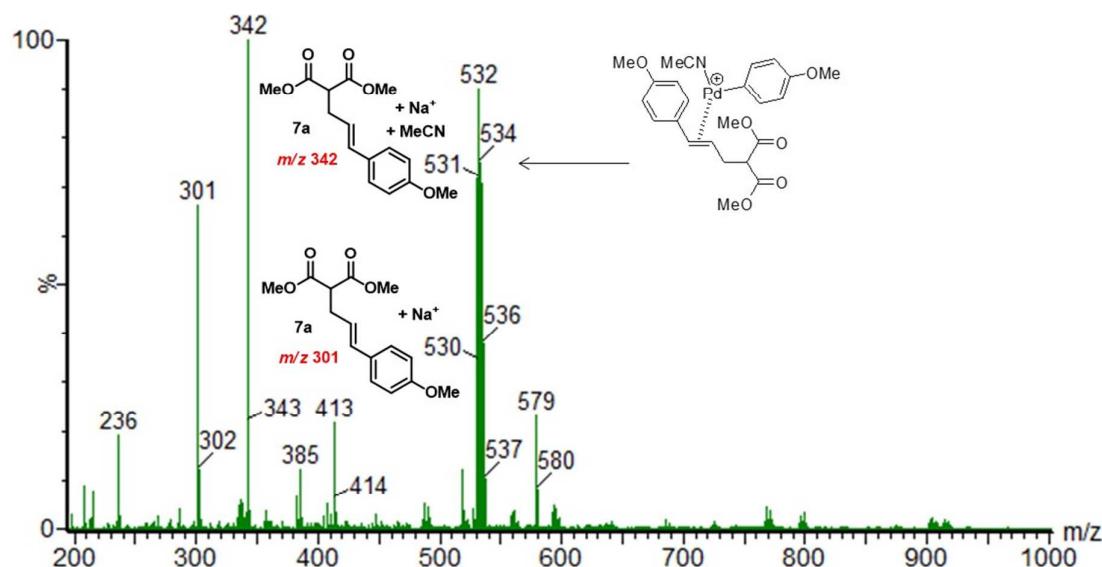


Figure S7: ESI(+)-MS of reaction solution at the 65 minutes.

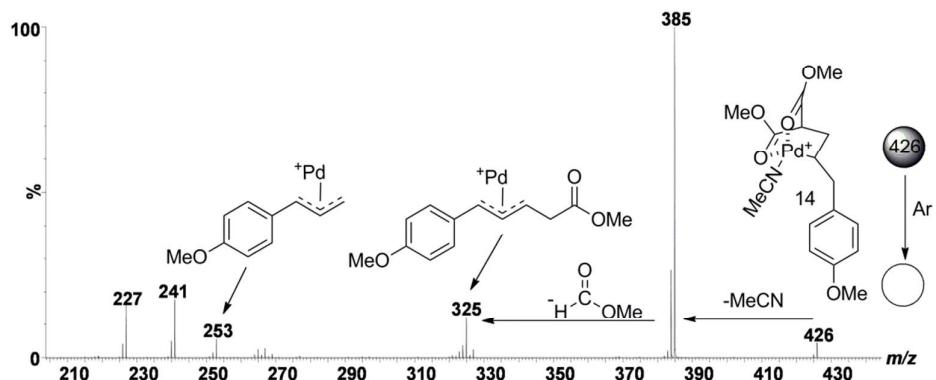
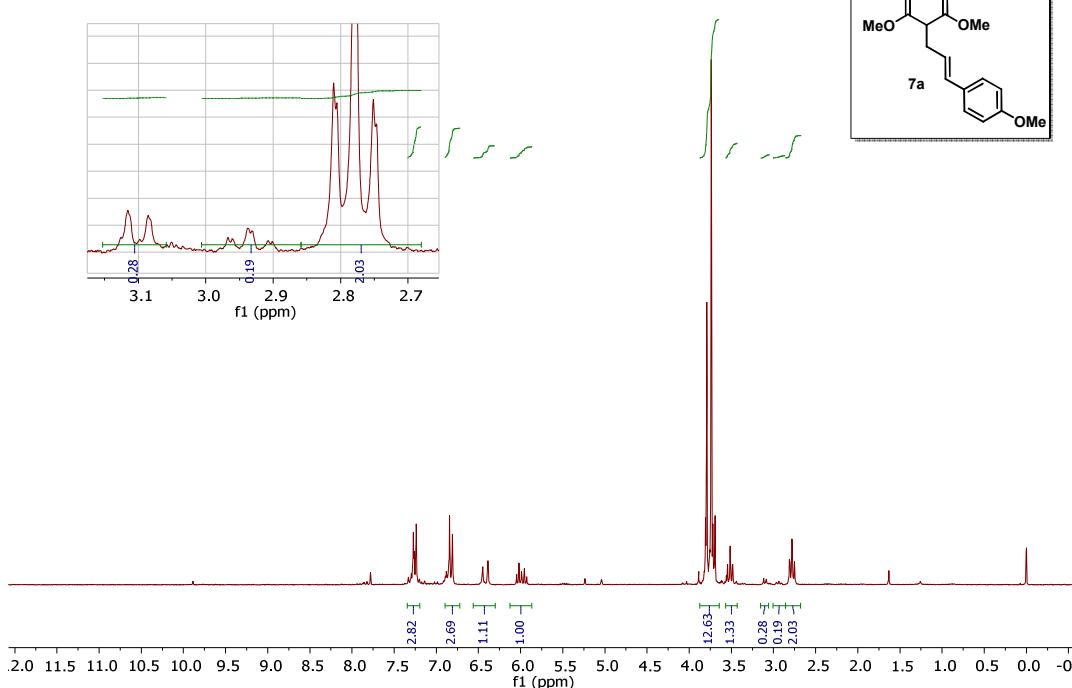


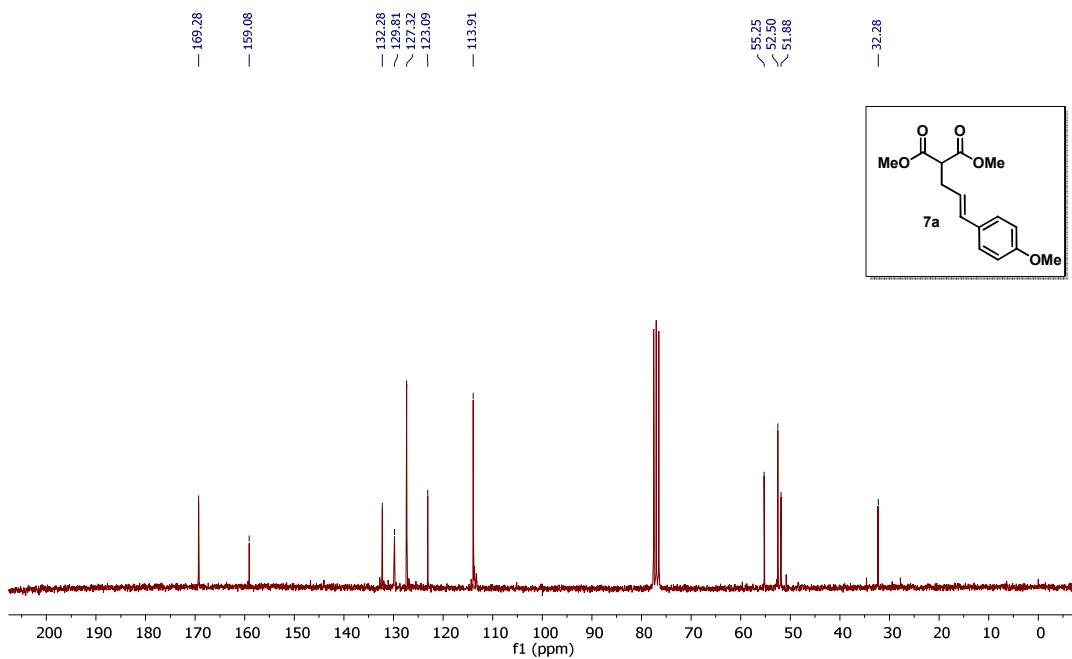
Figure S8: ESI(+)-MS/MS of m/z 426.

NMR Spectra

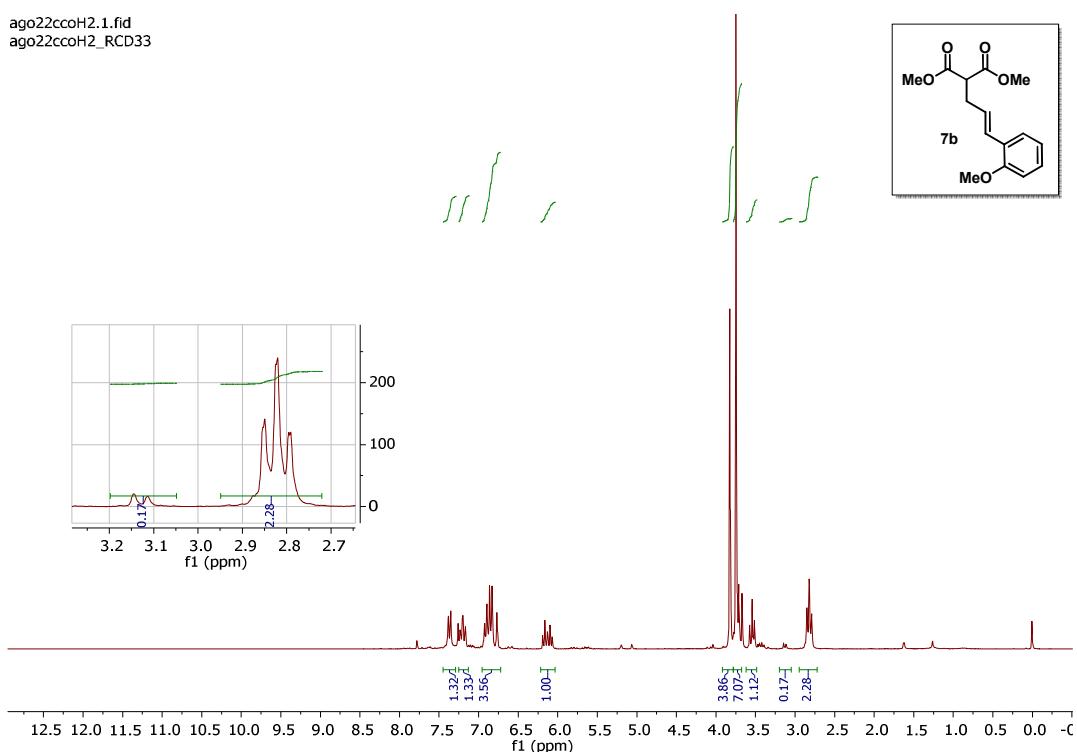
set12ccoH2.1.fid
Caio- CDCl₃- RCD-24-set12ccoH2- 250 MHz



set12ccoC1.1.fid
Caio- CDCl₃- RCD-24-set12ccoC1- 250 mHz

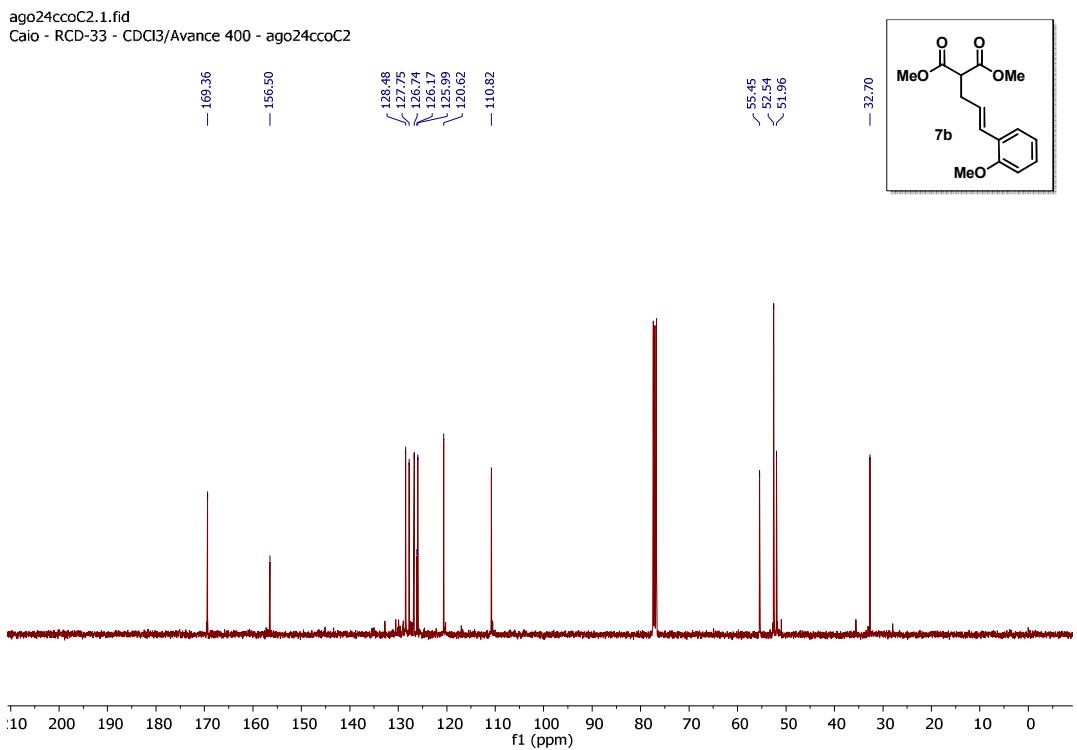


ago22ccoH2.1.fid
ago22ccoH2_RCD33



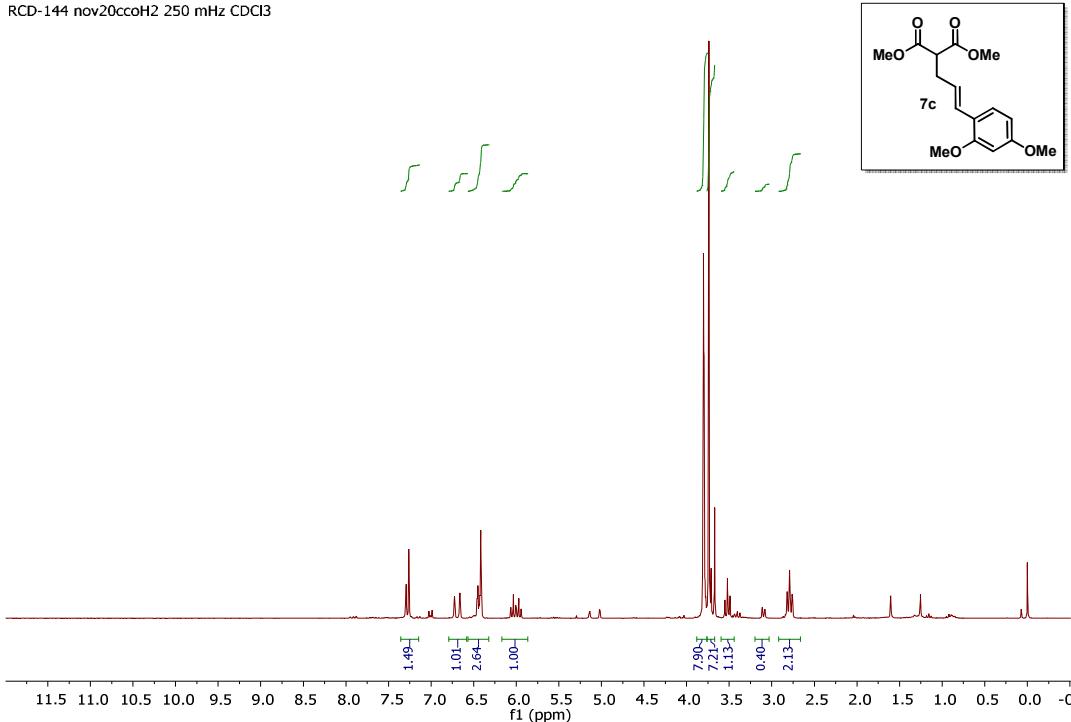
¹H NMR spectrum of 7b (250 MHz, CDCl₃)

ago24ccoC2.1.fid
Caio - RCD-33 - CDCl₃/Avance 400 - ago24ccoC2



¹³C NMR spectrum of 7b (62.5 MHz, CDCl₃)

nov20ccoH2.1.fid
RCD-144 nov20ccoH2 250 mHz CDCl₃

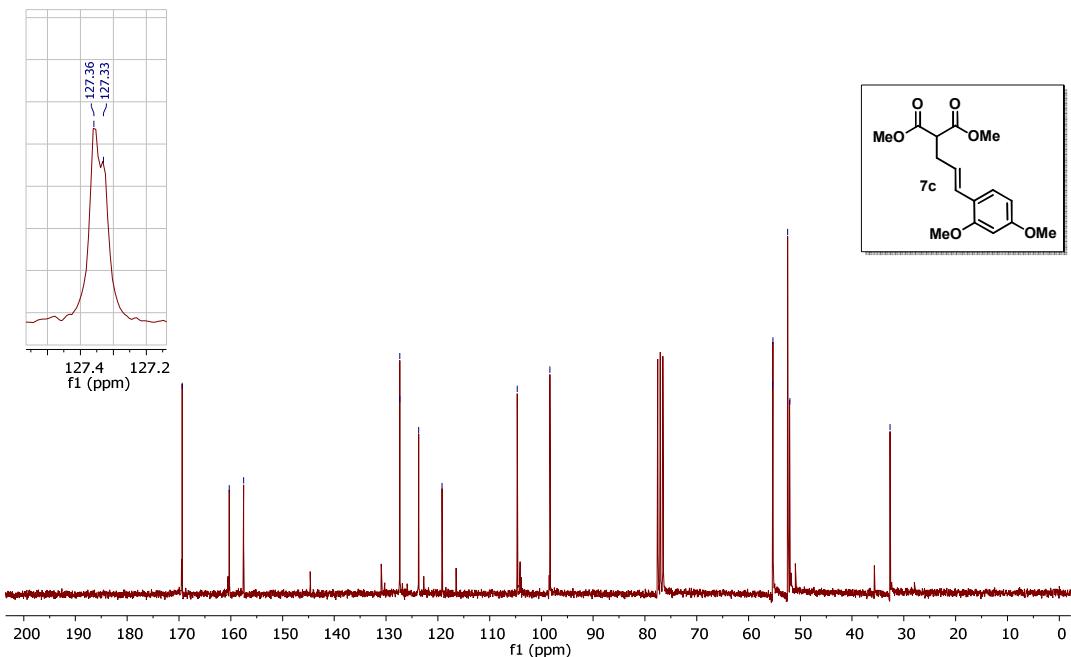


¹H NMR spectrum of 7c (250 MHz, CDCl₃)

dez11ccoC2.1.fid
RCD-170 dez11ccoC2

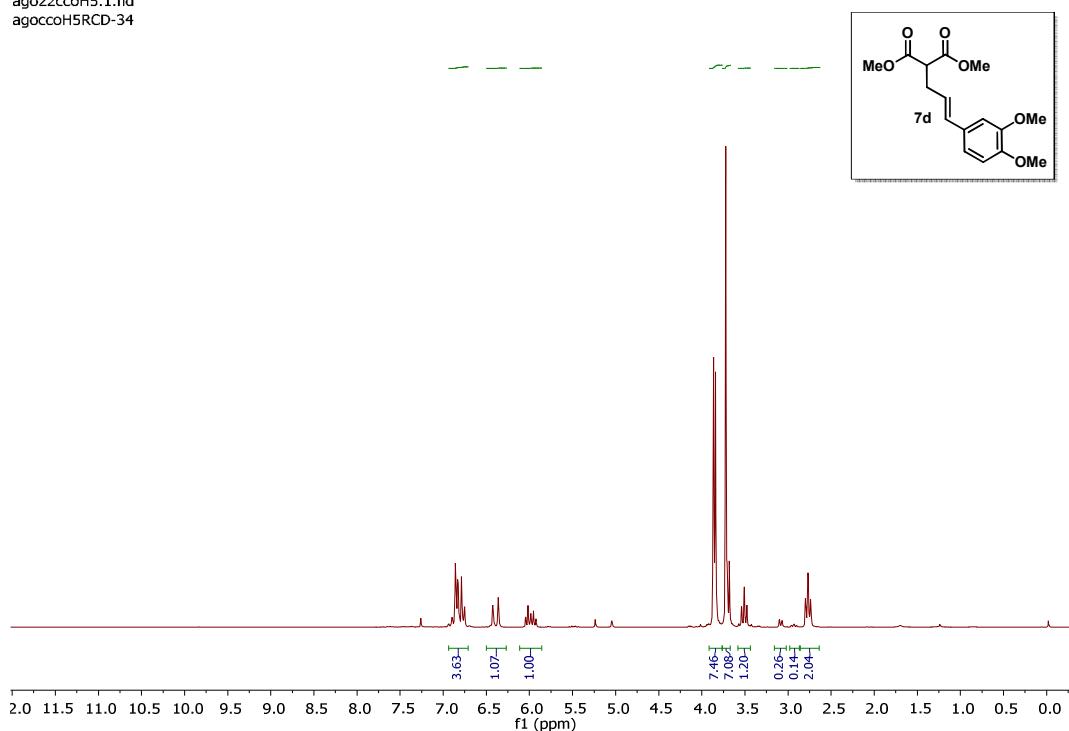
— 169.36
— 160.27
— 157.53
— 127.36
— 127.33
— 123.73
— 119.19
— 104.69
— 98.35

— 55.37
— 55.31
— 52.44
— 52.05
— 32.70



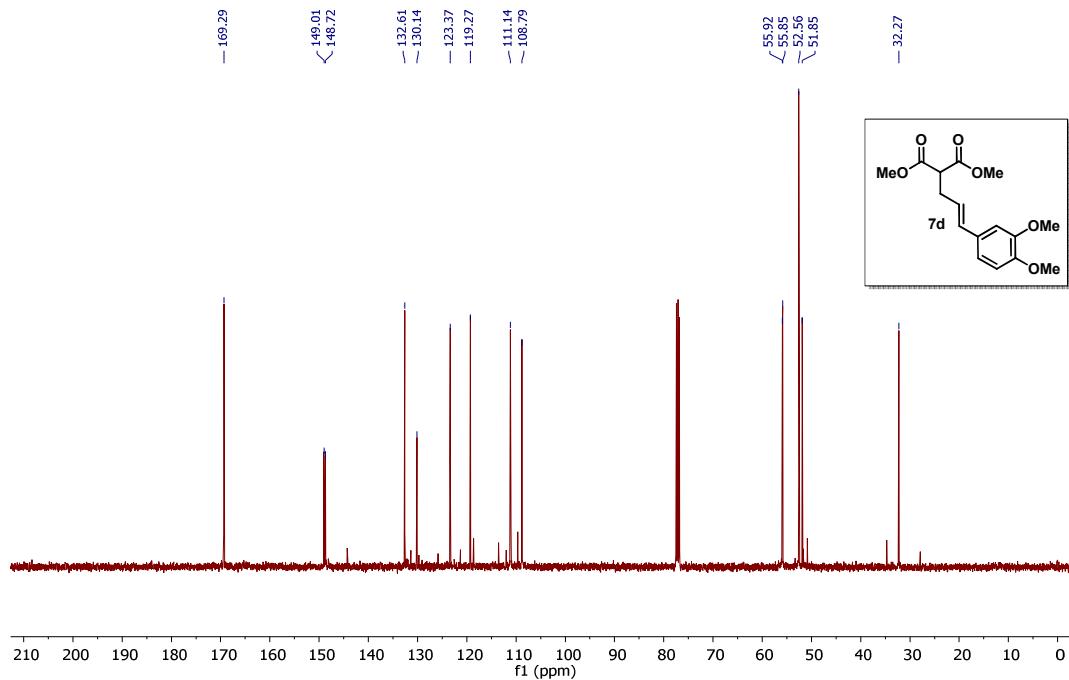
¹³C NMR spectrum of 7c (62.5 MHz, CDCl₃)

ago22ccoH5.1.fid
agoccoH5RCD-34



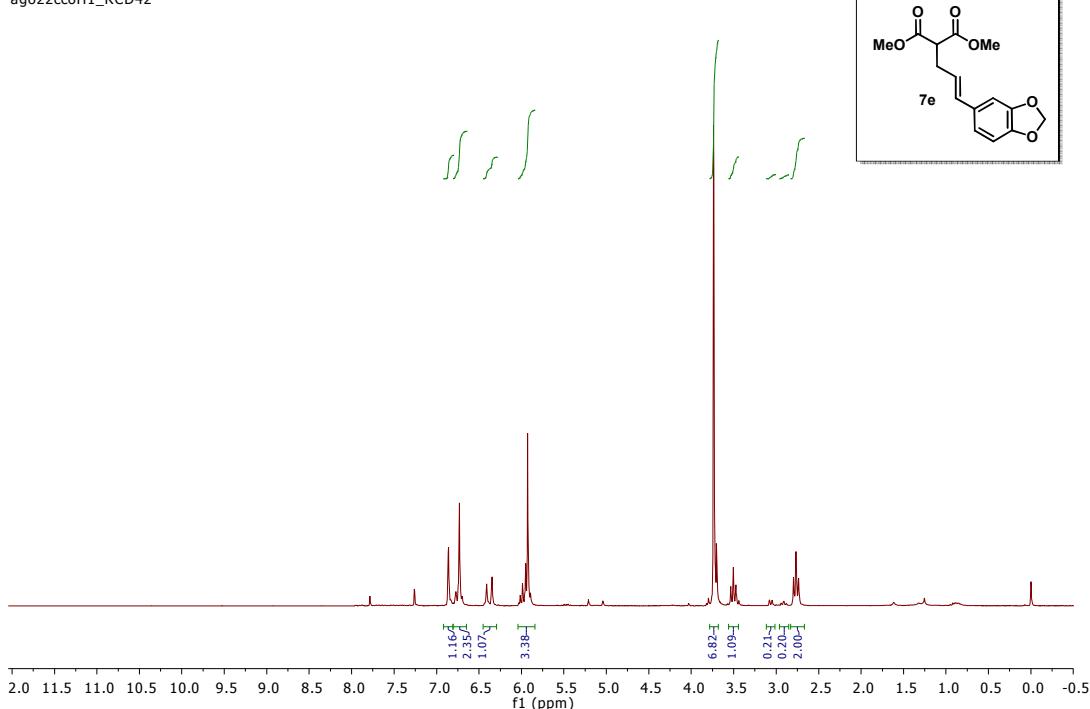
¹H NMR spectrum of 7d (250 MHz, CDCl₃)

ago24ccoC1.1.fid
Caio - RCD-34 - CDCl₃/Avance 400 - ago24ccoC1



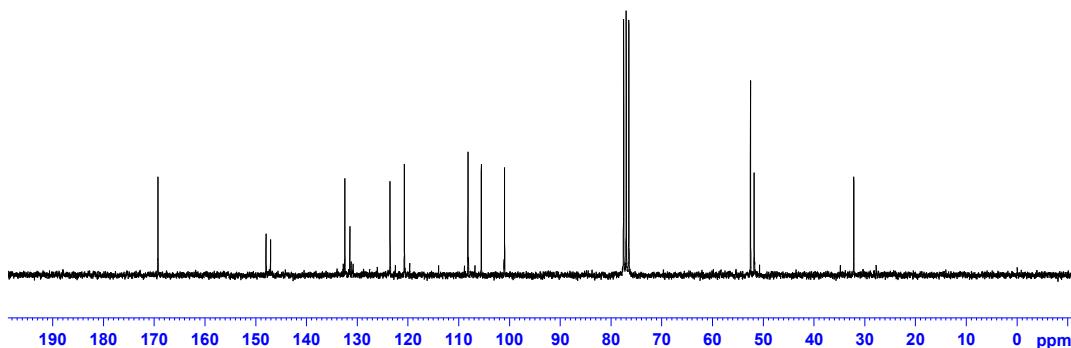
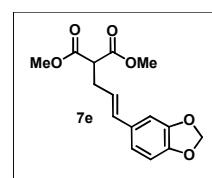
¹³C NMR spectrum of 7d (62.5 MHz, CDCl₃)

ago22ccoH1.1.fid
ago22ccoH1_RCD42



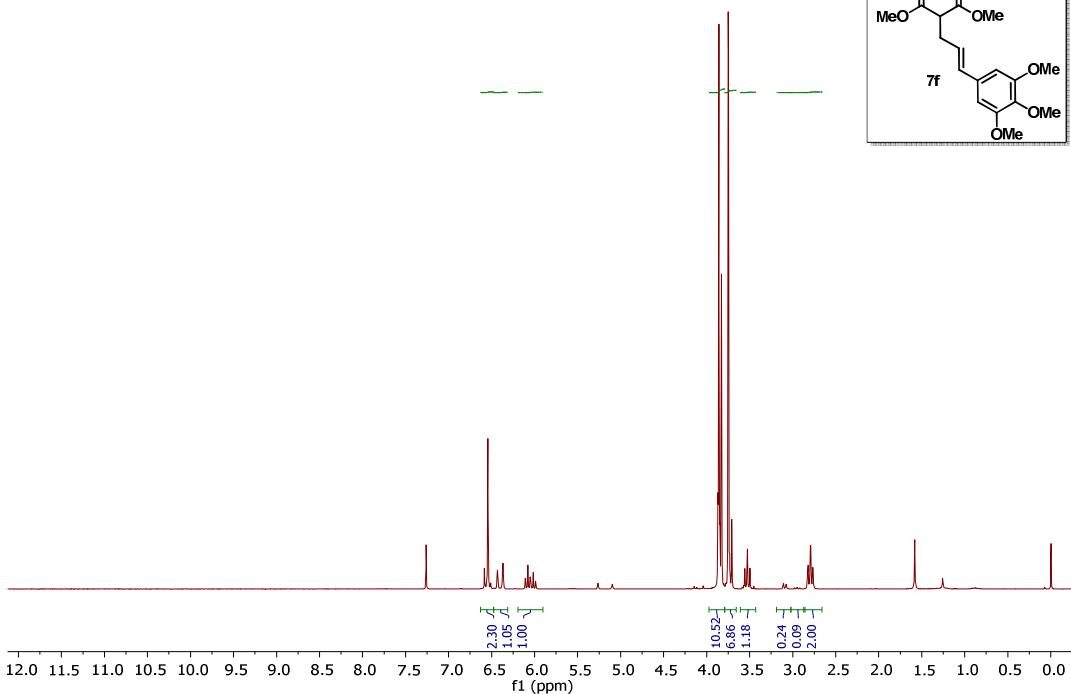
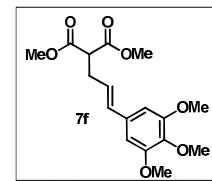
¹H NMR spectrum of 7e (250 MHz, CDCl₃)

Caio - RCD-42 - CDC13/250 MHz - ago24ccoC1
169.23 147.96 147.05 132.41 131.40 123.55 120.73 108.18 105.55 100.99 77.52 77.51 76.50 52.52 51.79 32.16



¹³C NMR spectrum of 7e (62.5 MHz, CDCl₃)

dez09ccoH3/1
rcd-32 (trimetoxi) CDCl₃ 250MHz dez09ccoH3

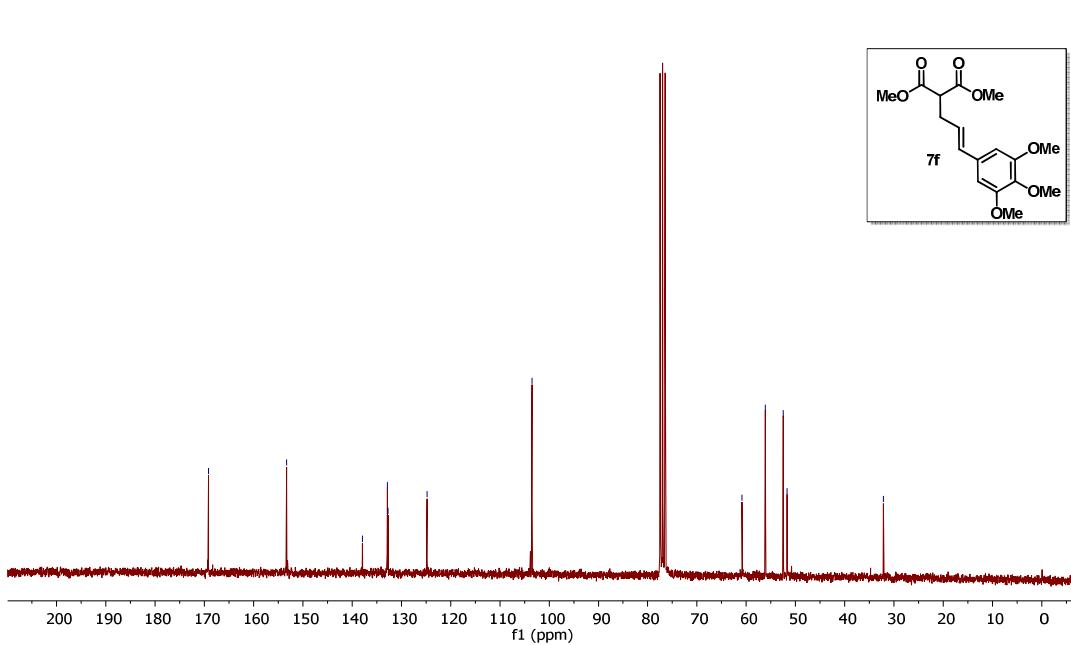
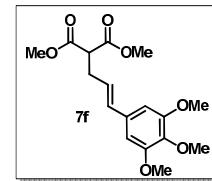


¹H NMR spectrum of 7f (250 MHz, CDCl₃)

dez09ccoC1.1.fid
rcd-32 (trimetoxi) CDCl₃ 250MHz dez09ccoC1

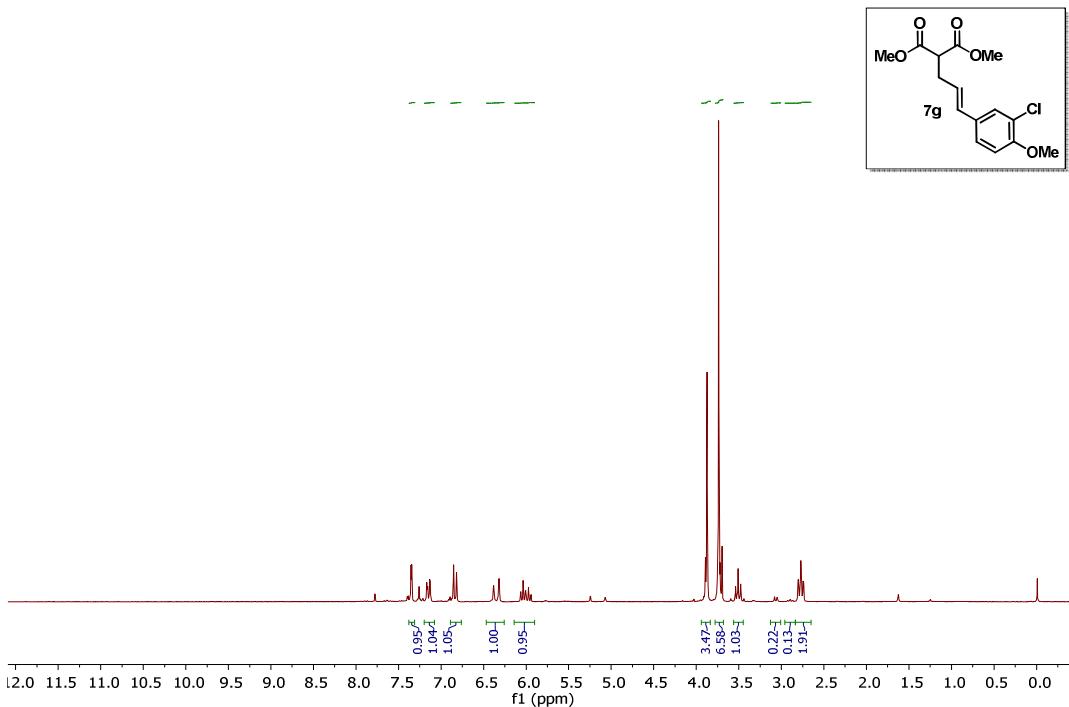
— 137.91
— 132.86
— 132.70
— 124.81
— 103.48
— 60.94
— 56.11
— 52.51
— 51.72

— 32.14



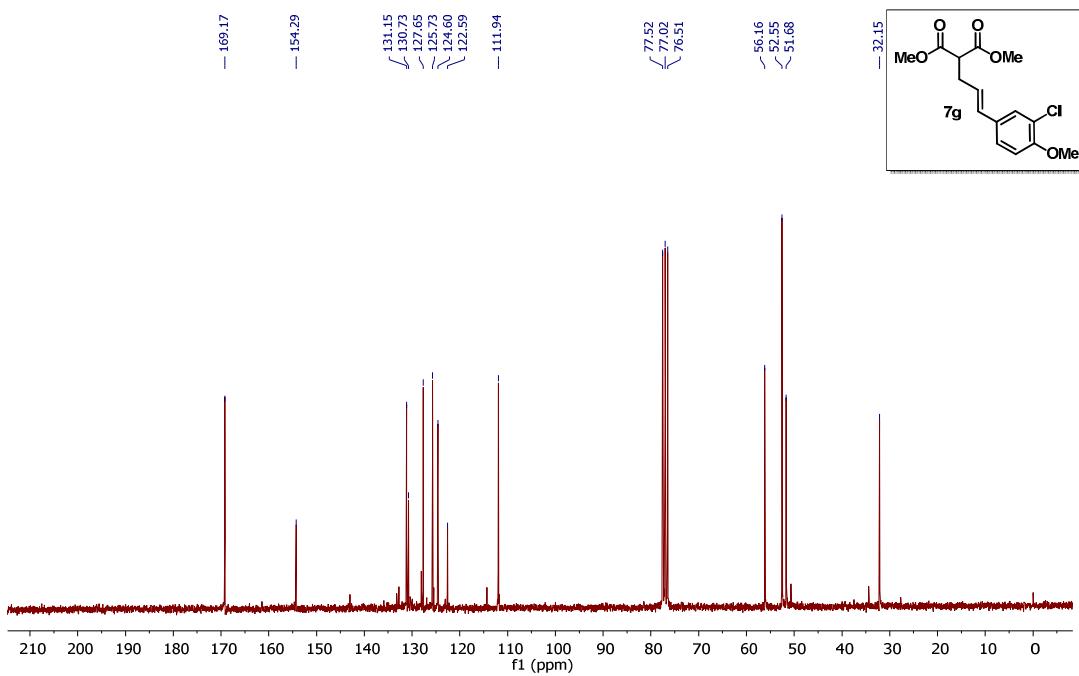
¹³C NMR spectrum of 7f (62.5 MHz, CDCl₃)

nov07resH1.1.fid
nov07resH1

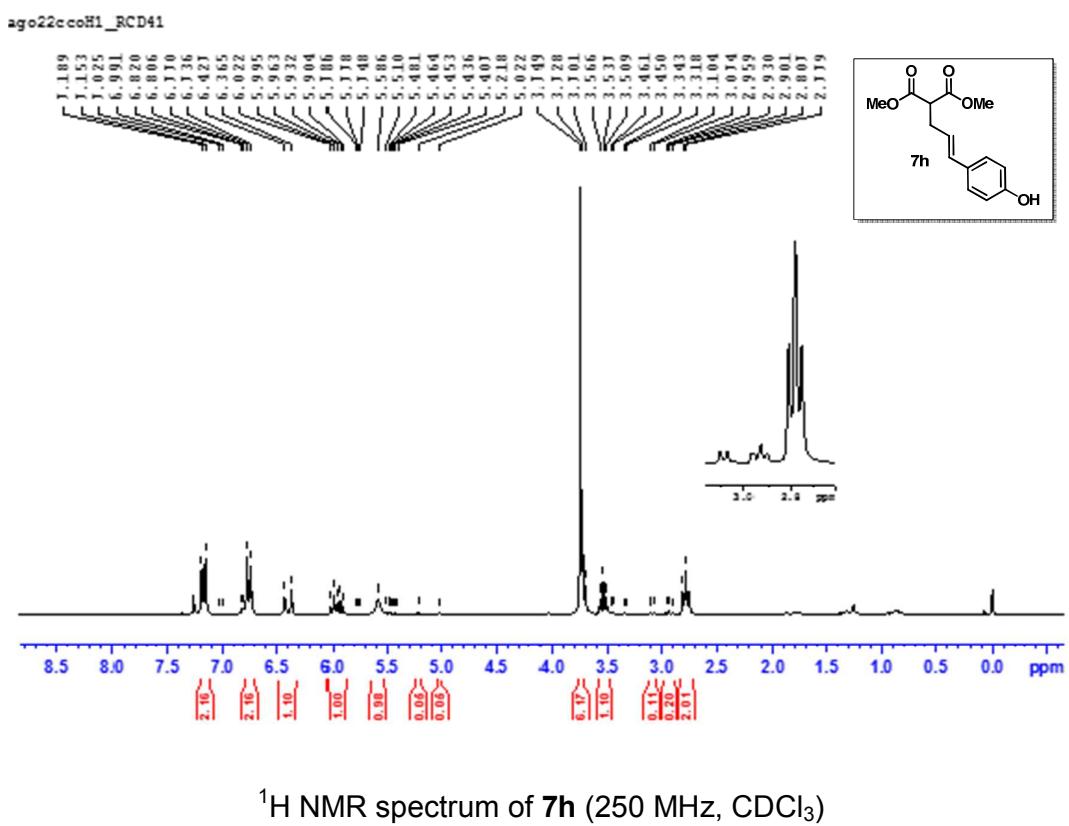


¹H NMR spectrum of 7g (250 MHz, CDCl₃)

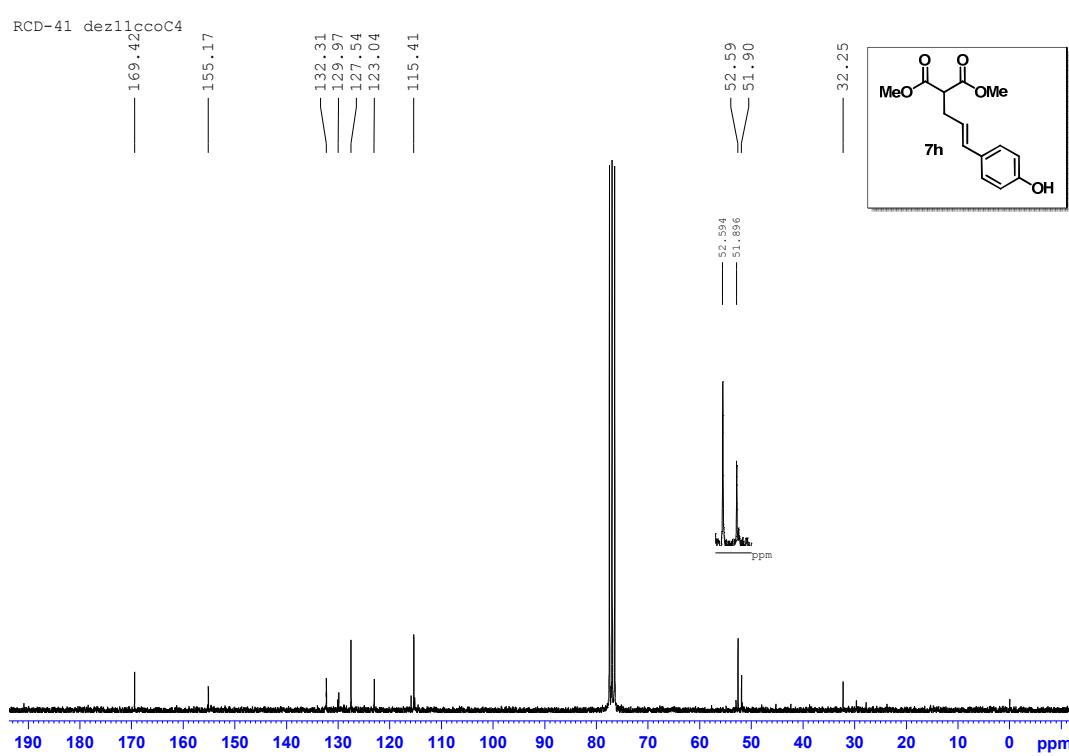
nov07resC1.1.fid
nov07resC1 250 mHz 07/11/2010 RES-5



¹³C NMR spectrum of 7g (62.5 MHz, CDCl₃)

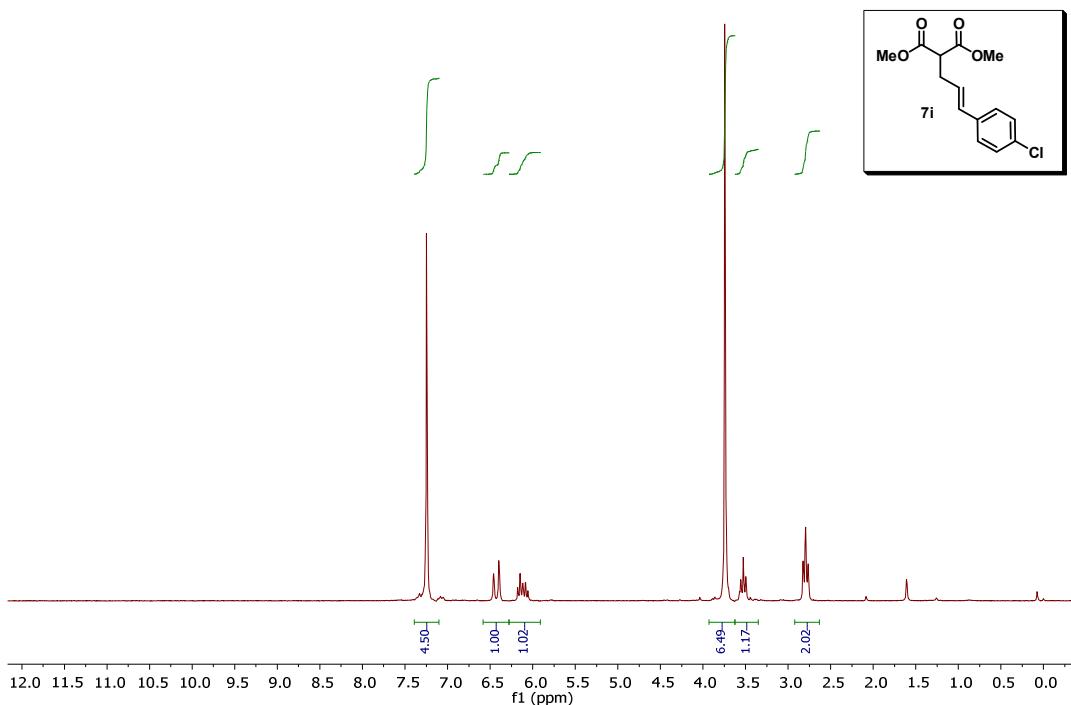


¹H NMR spectrum of **7h** (250 MHz, CDCl₃)

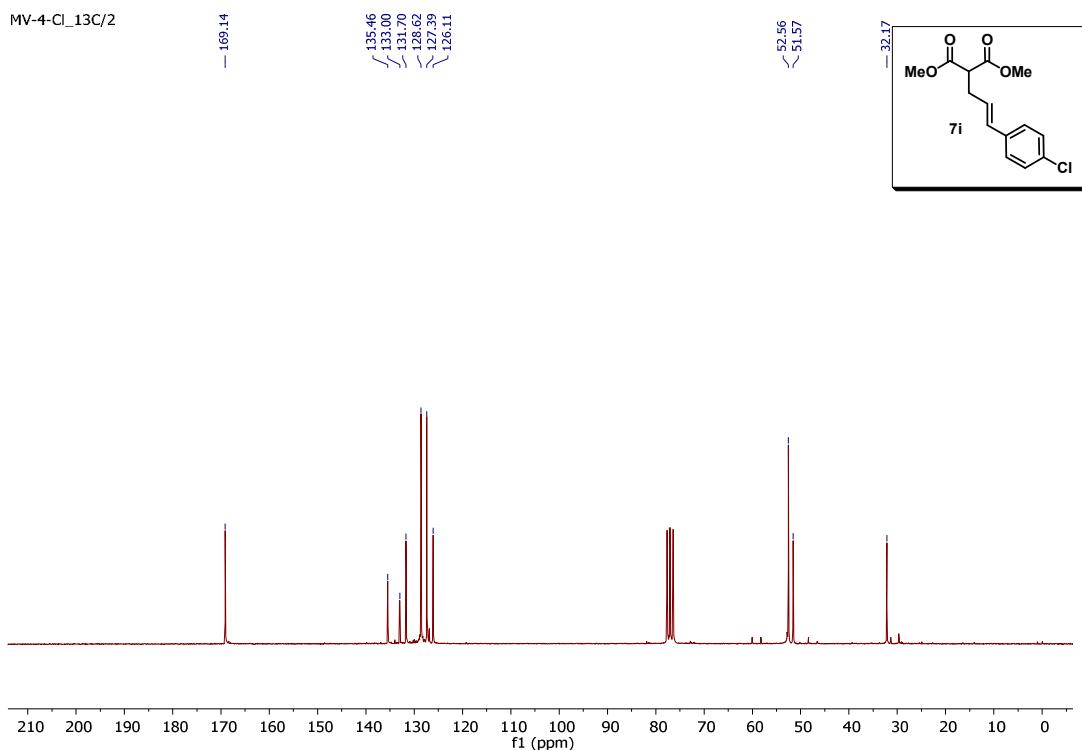


¹³C NMR spectrum of **7h** (62.5 MHz, CDCl₃)

mai27ccoH2.2.fid
4-Cl CDCl₃ 250MHz mai27ccoH2-2012

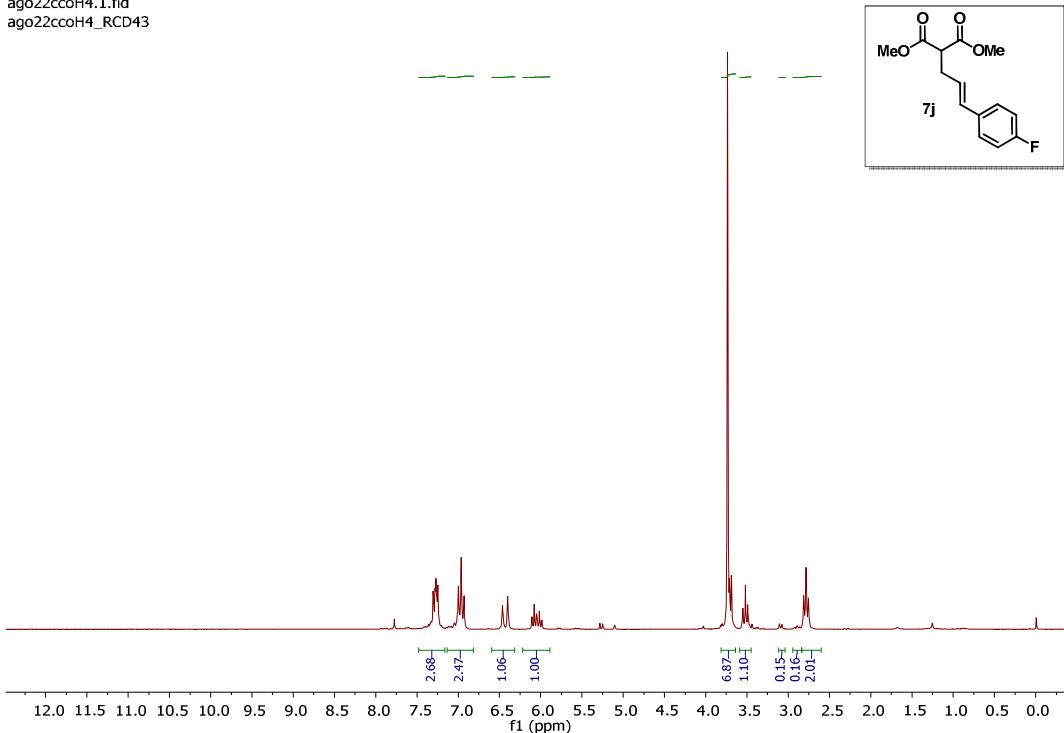


¹H NMR spectrum of 7i (250 MHz, CDCl₃)



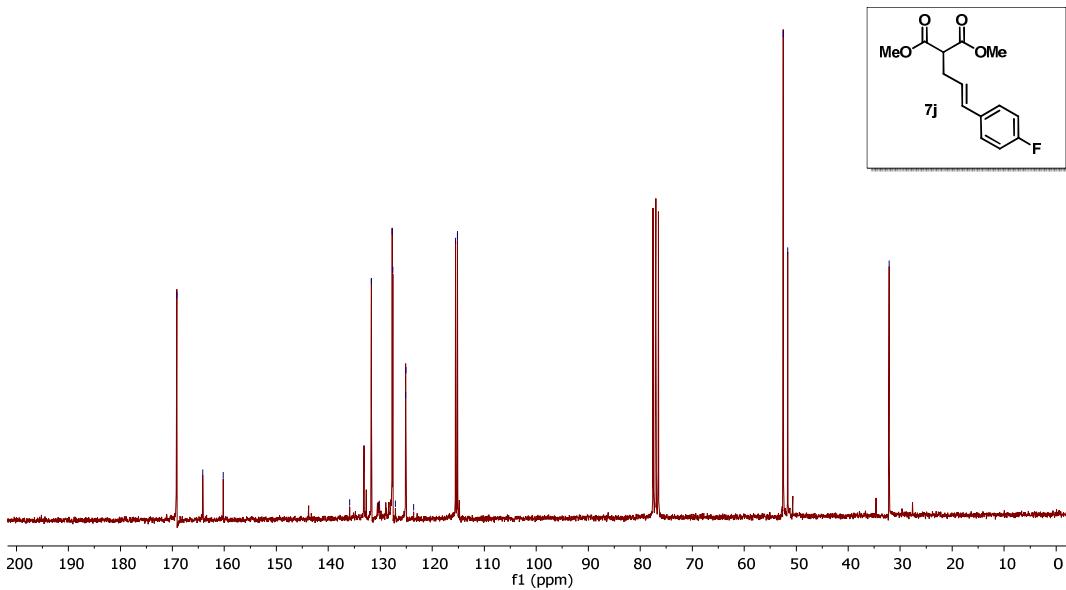
¹³C NMR spectrum of 7i (50 MHz, CDCl₃)

ago22ccoH4.1.fid
ago22ccoH4_RCD43



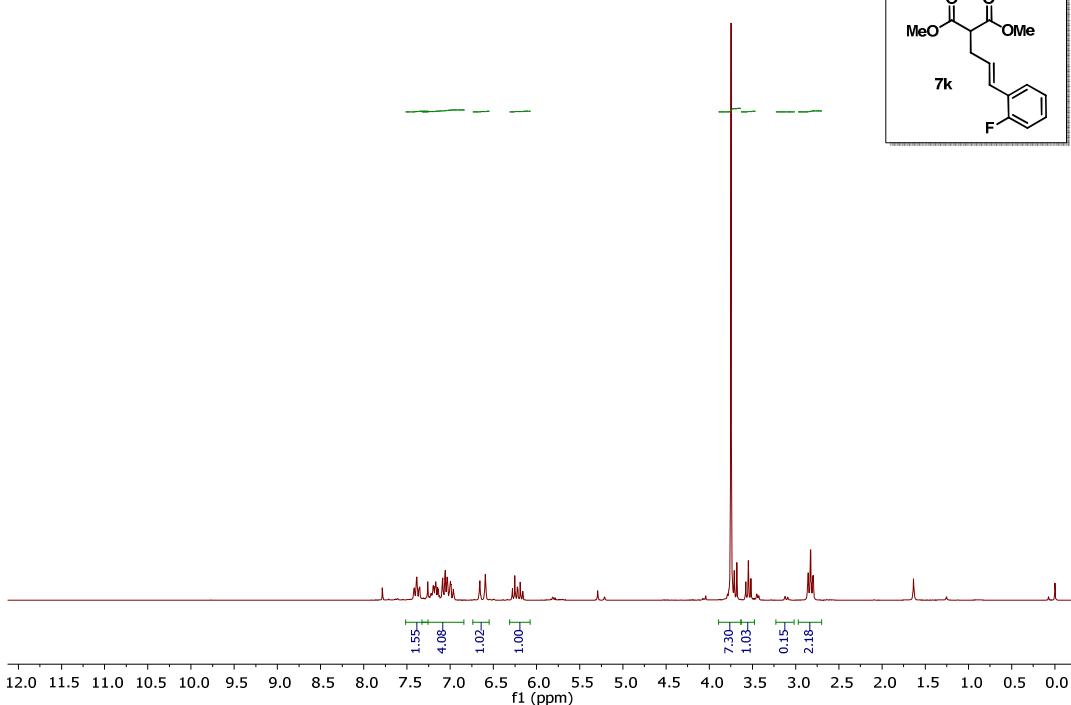
¹H NMR spectrum of 7j (250 MHz, CDCl₃)

ago23ccoC2.1.fid
Caio - RCD-43 - CDCl₃/250.14 Hz - ago23ccoC2.1
171.17, 169.14, 168.22, 143.92, 130.33, 127.71, 127.72, 127.60, 127.08, 125.13, 125.09, 123.98, 123.82, 115.92, 115.17, 52.52, 51.66, -32.15



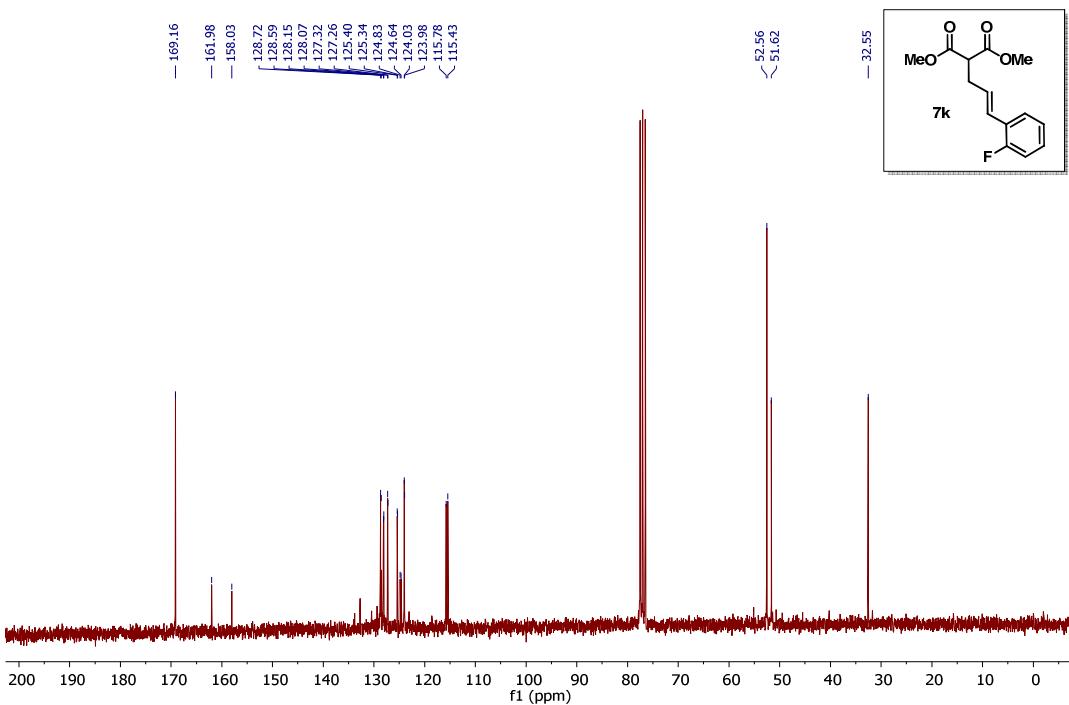
¹³C NMR spectrum of 7j (62.5 MHz, CDCl₃)

nov26ccoH2.1.fid
RES-08 nov26ccoH2 250mHz



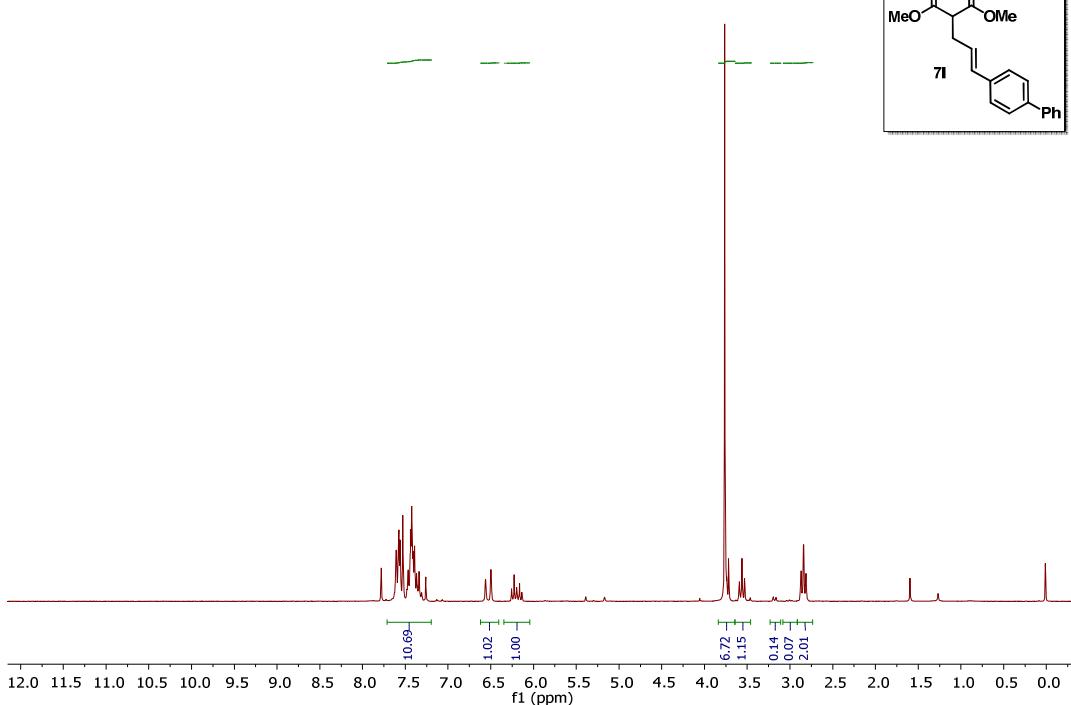
¹H NMR spectrum of 7k (250 MHz, CDCl₃)

nov29ccoC1.1.fid
RES 08 nov29ccoC1Cdcl3 250mHz



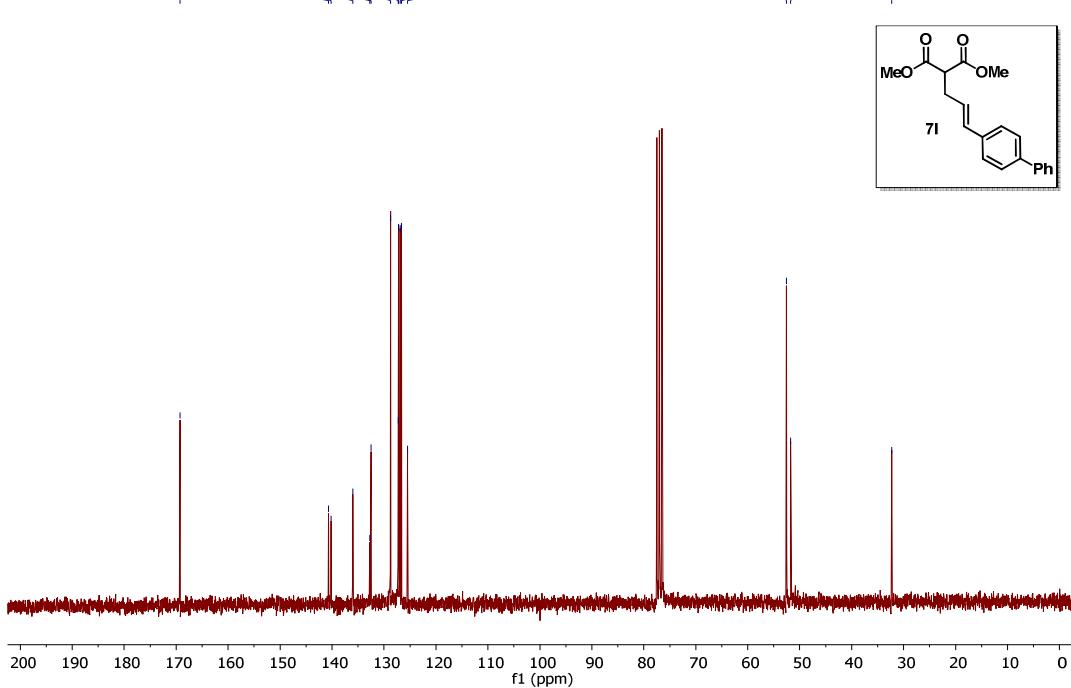
¹³C NMR spectrum of 7k (62.5 MHz, CDCl₃)

nov23ccoH2.1.fid
RCD-152 CDCl₃ 250 mHz nov23ccoH2



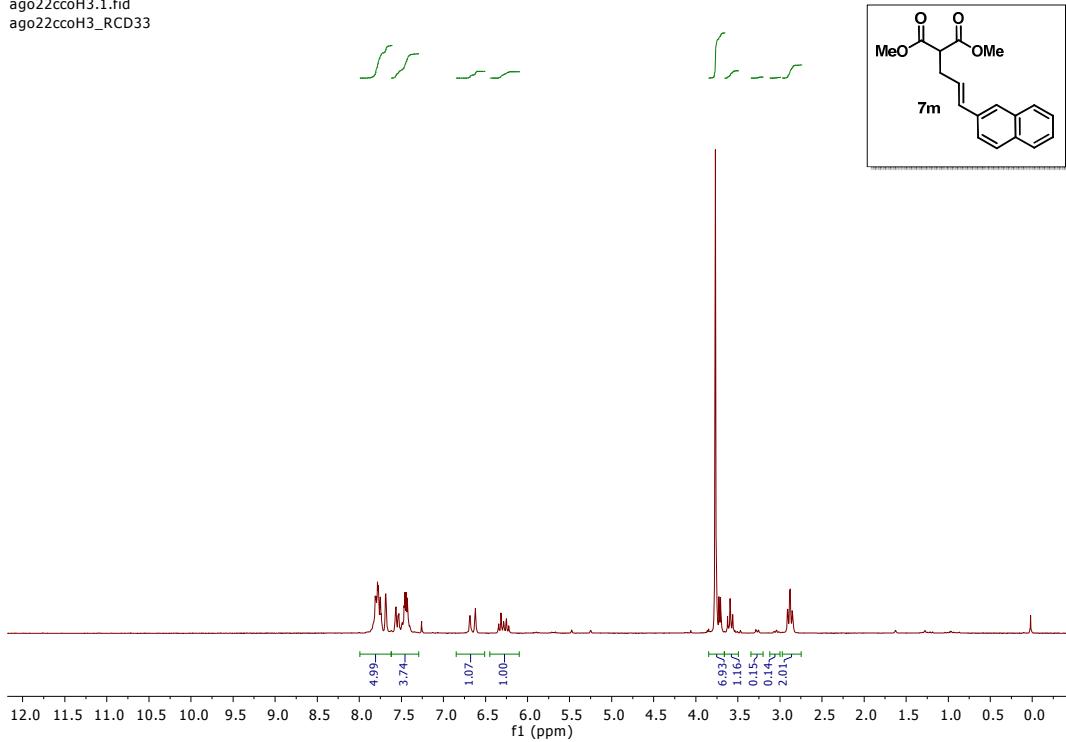
¹H NMR spectrum of 7I (250 MHz, CDCl₃)

nov23ccoC1.1.fid
nov23ccoC1 RCD 152



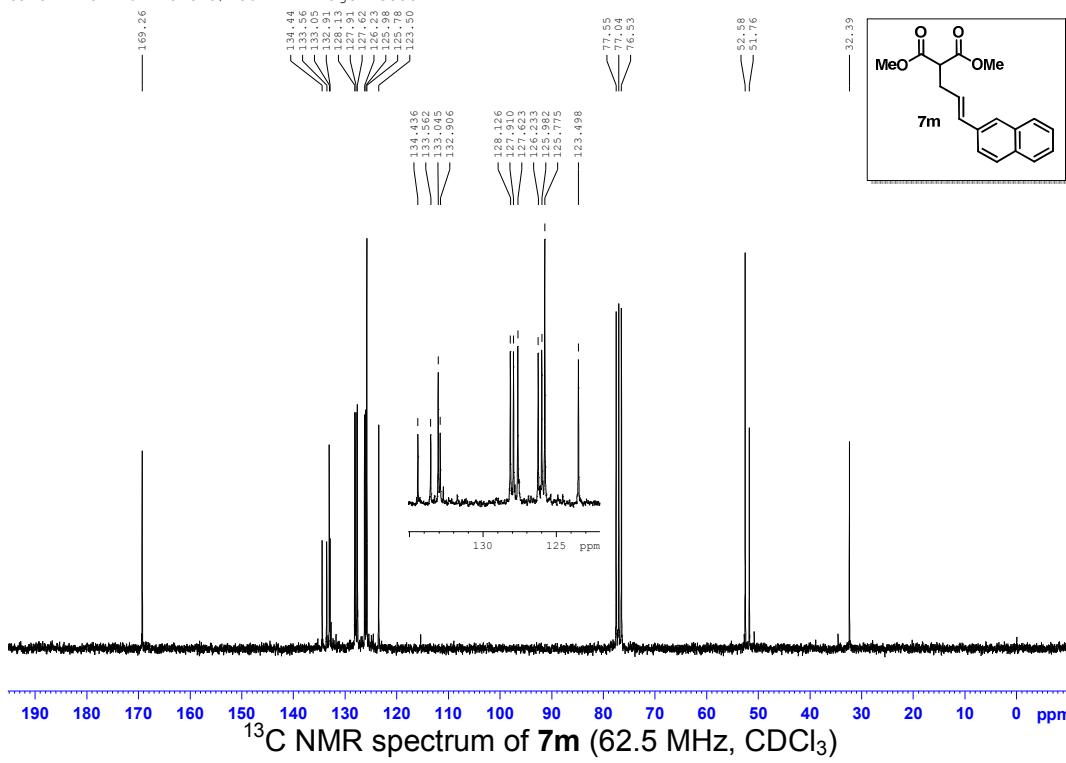
¹³C NMR spectrum of 7I (62.5 MHz, CDCl₃)

ago22ccoH3.1.fid
ago22ccoH3_RCD33



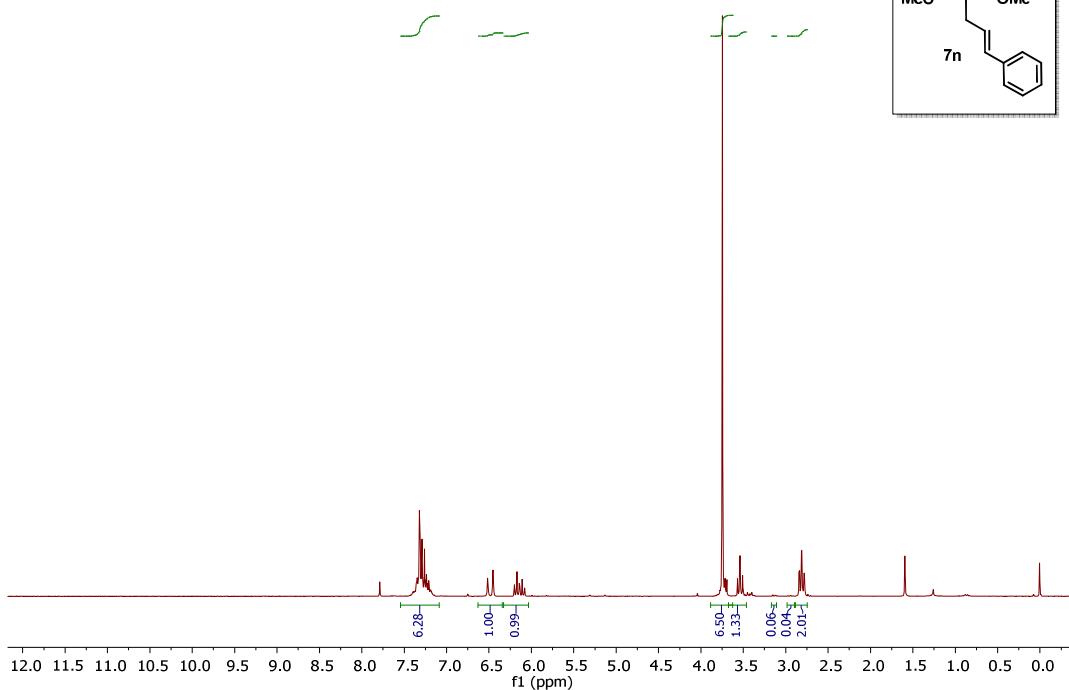
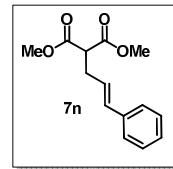
¹H NMR spectrum of 7m (250 MHz, CDCl₃)

Caio - RCD-40 - CDC13/250 MHz - ago24ccoC2



¹³C NMR spectrum of 7m (62.5 MHz, CDCl₃)

dez07cc0H2/1
RCD-72 dez07cc0H2 250mHz CDCl₃

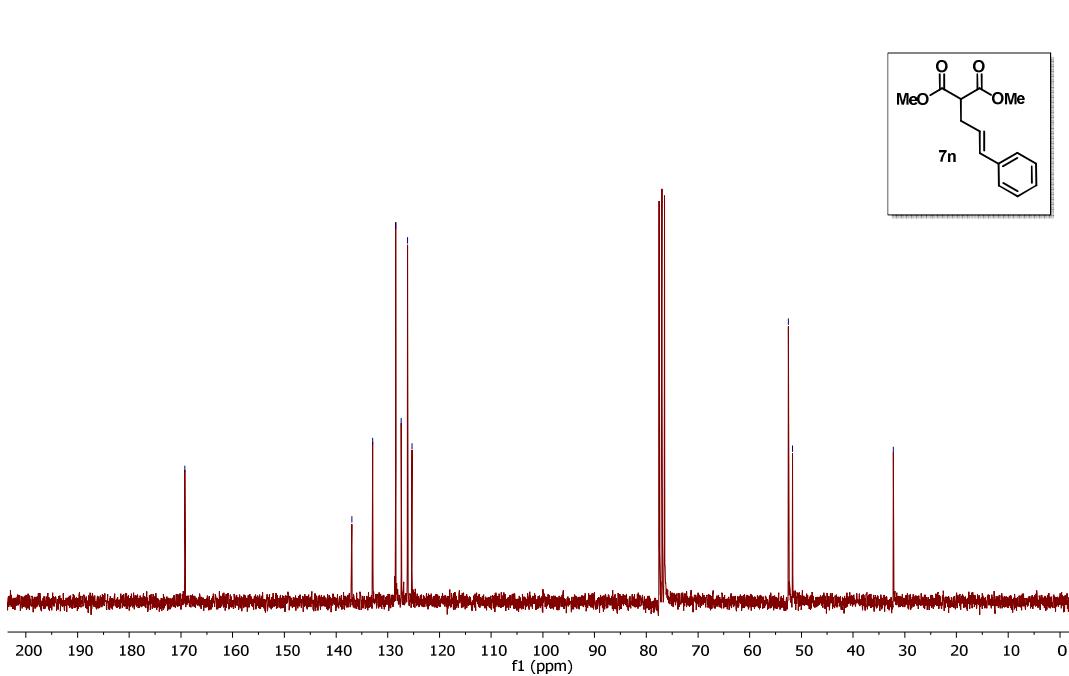
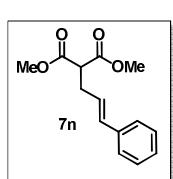


¹H NMR spectrum of 7n (250 MHz, CDCl₃)

dez11cc0C3/1
rcd-72 dez11cc0C3 CDCl₃ 62.523

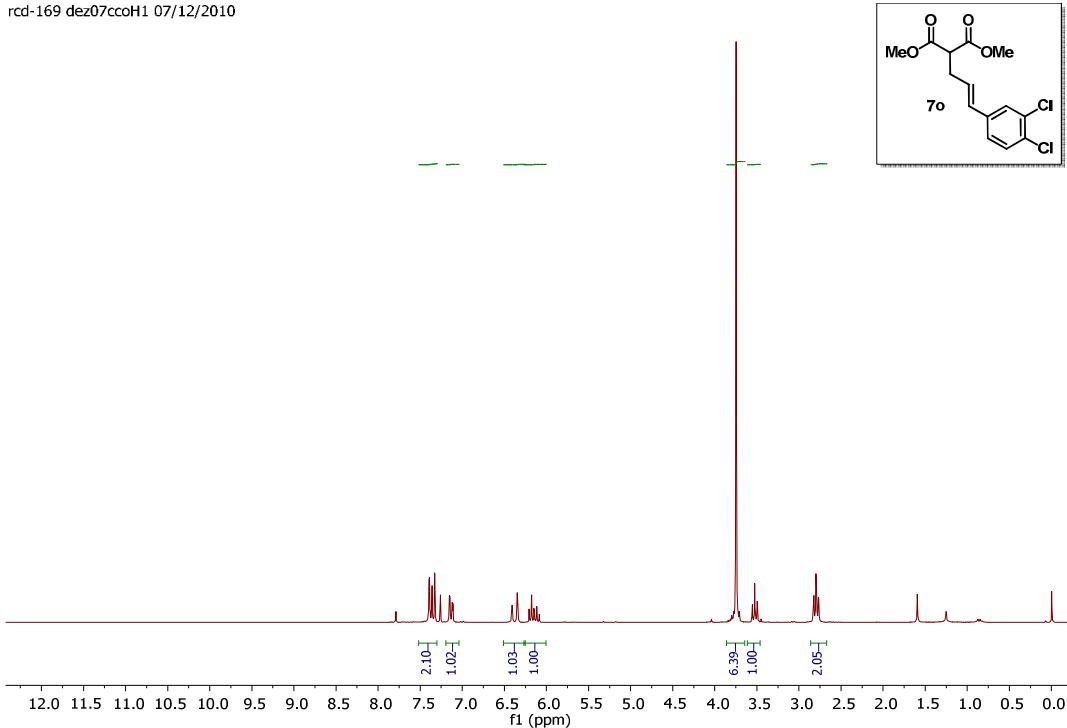
136.97
122.91
129.48
127.40
126.18
125.34

52.55
51.72



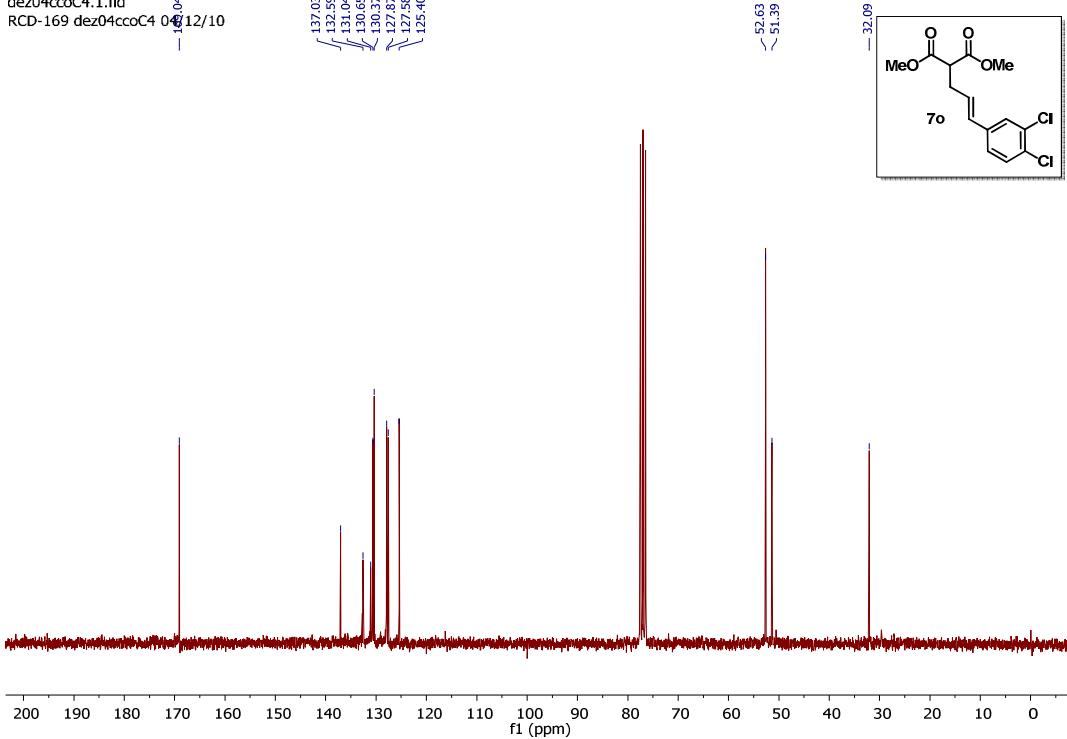
¹³C NMR spectrum of 7n (62.5 MHz, CDCl₃)

dez07ccoH1/1
rcd-169 dez07ccoH1 07/12/2010



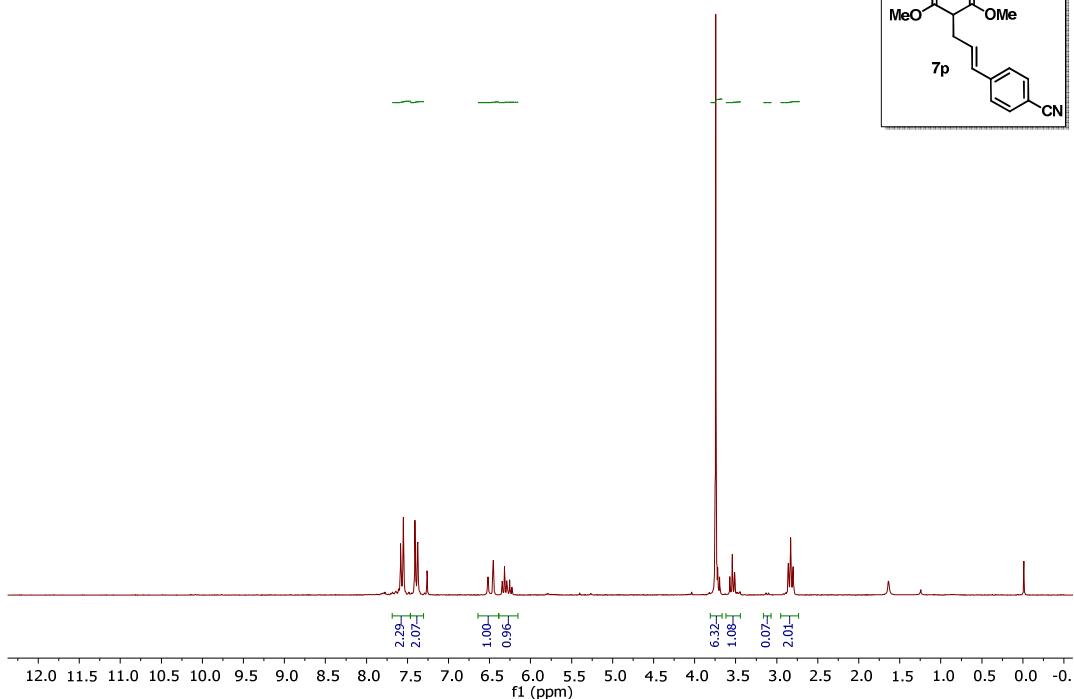
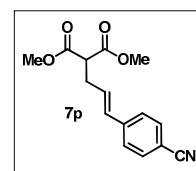
¹H NMR spectrum of 7o (250 MHz, CDCl₃)

dez04ccoC4.1.fid
RCD-169 dez04ccoC4 07/12/10



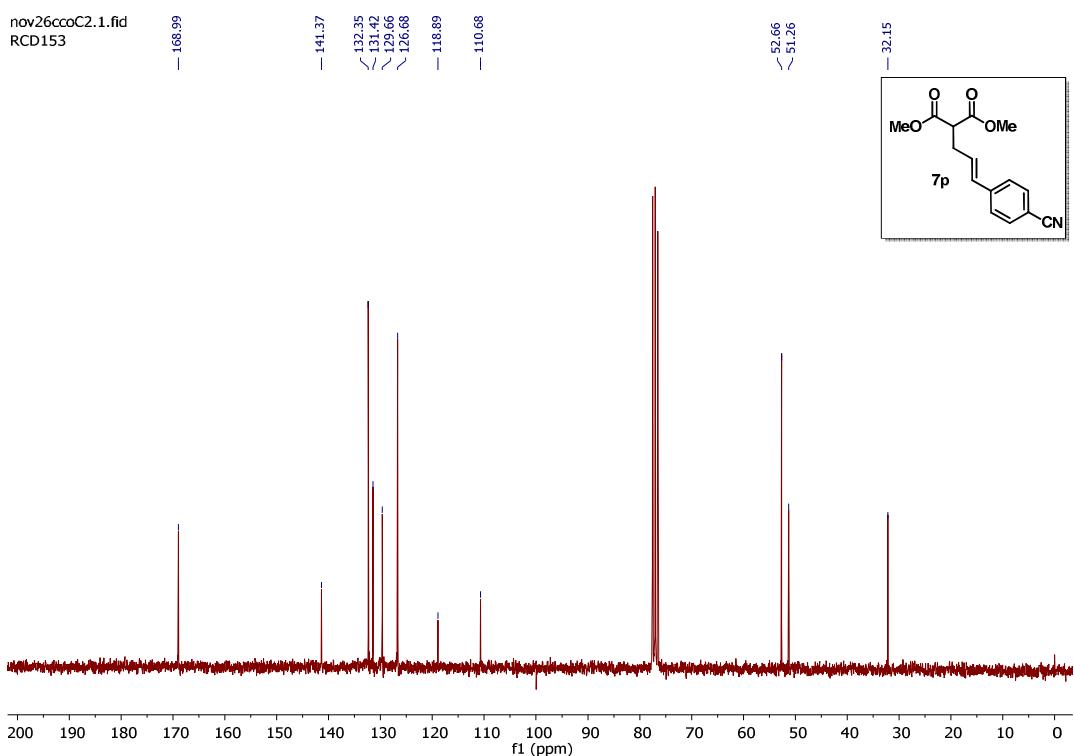
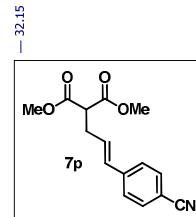
¹³C NMR spectrum of 7o (62.5 MHz, CDCl₃)

nov26ccoH3.1.fid
rcd-153 nov26ccoH3 250mHz CDCl₃



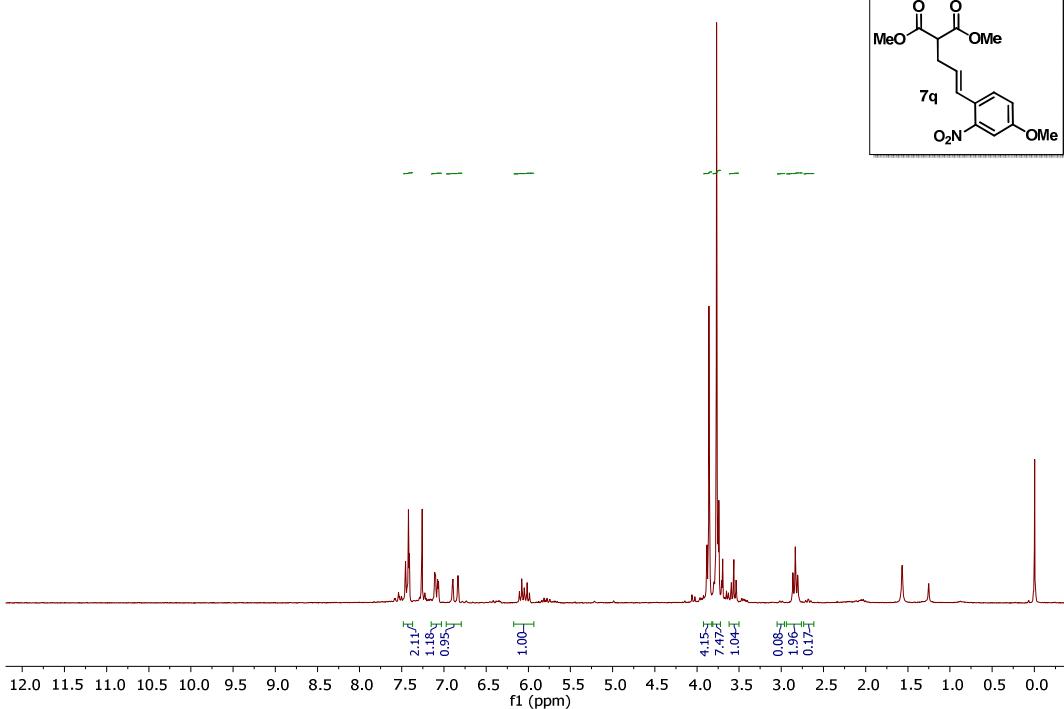
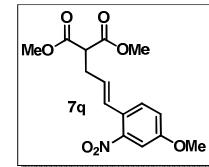
¹H NMR spectrum of 7p (250 MHz, CDCl₃)

nov26ccoC2.1.fid
RCF153



¹³C NMR spectrum of 7p (62.5 MHz, CDCl₃)

nov22ccoH1.1.fid
RCD-145 nov22ccoH1CDCl₃ 250mHz

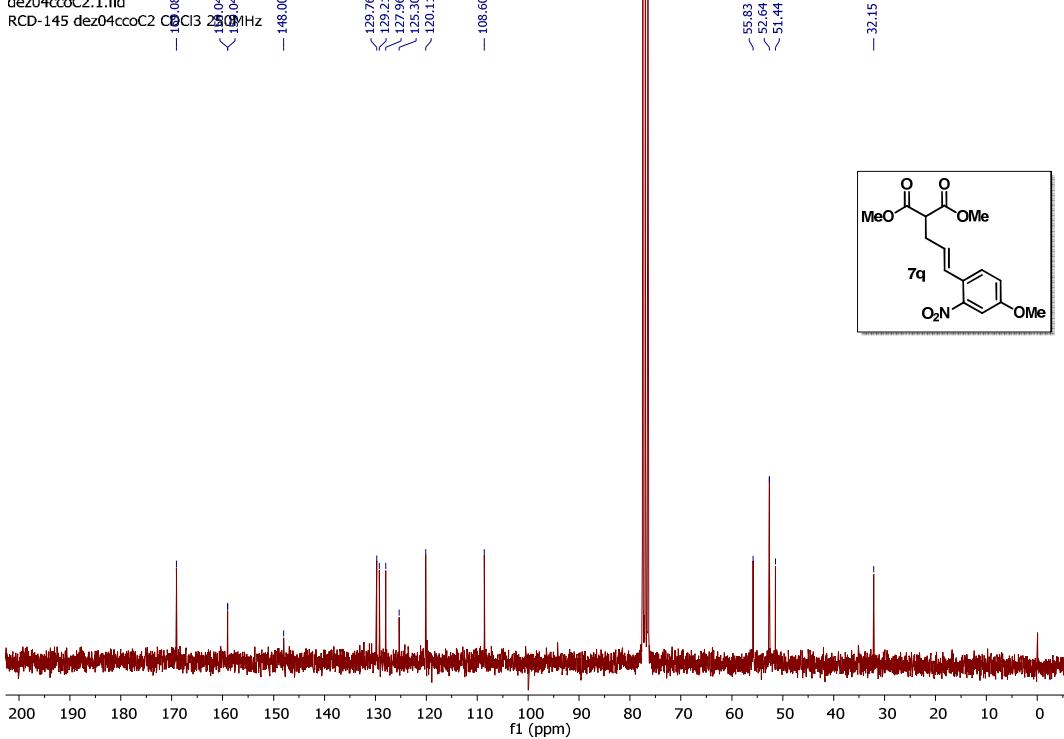
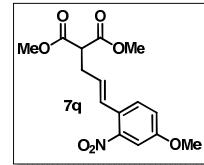


¹H NMR spectrum of 7q (250 MHz, CDCl₃)

dez04ccoC2.1.fid
RCD-145 dez04ccoC2 CDCl₃ 250MHz
— 10.08 < 10.04 — 148.00

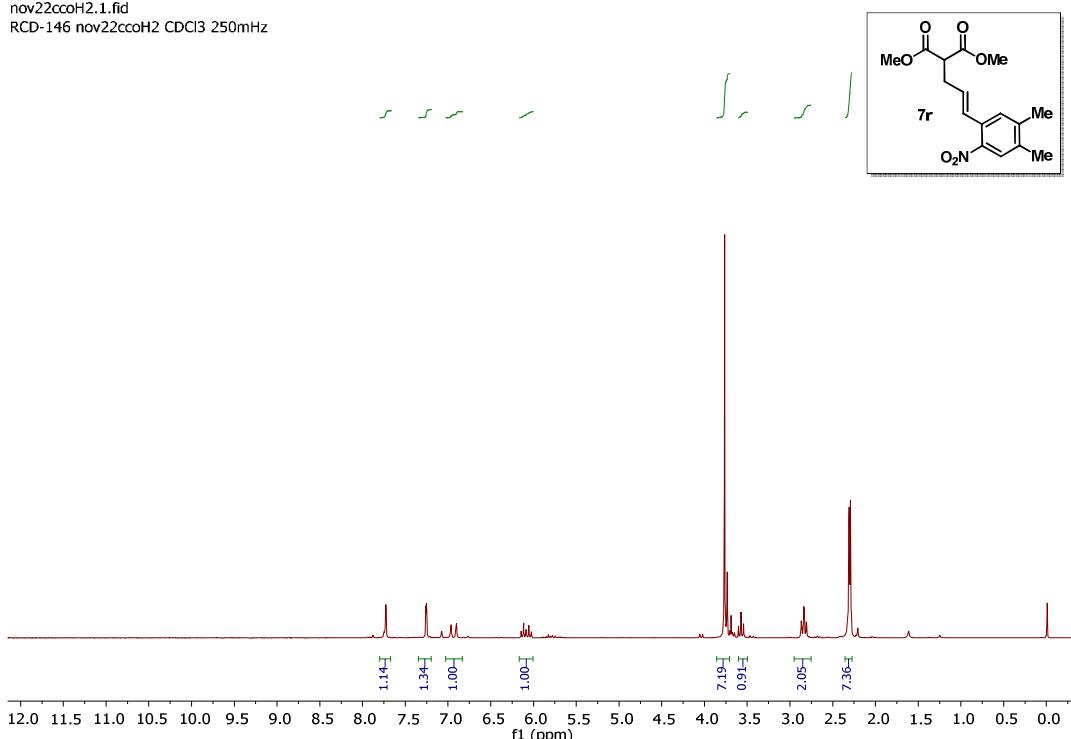
— 129.76 < 129.21 < 127.96 < 125.30 < 120.11 — 108.60

< 55.83 < 52.64 < 51.44 — 32.15



¹³C NMR spectrum of 7q (62.5 MHz, CDCl₃)

nov22ccoH2.1.fid
RCD-146 nov22ccoH2 CDCl₃ 250MHz

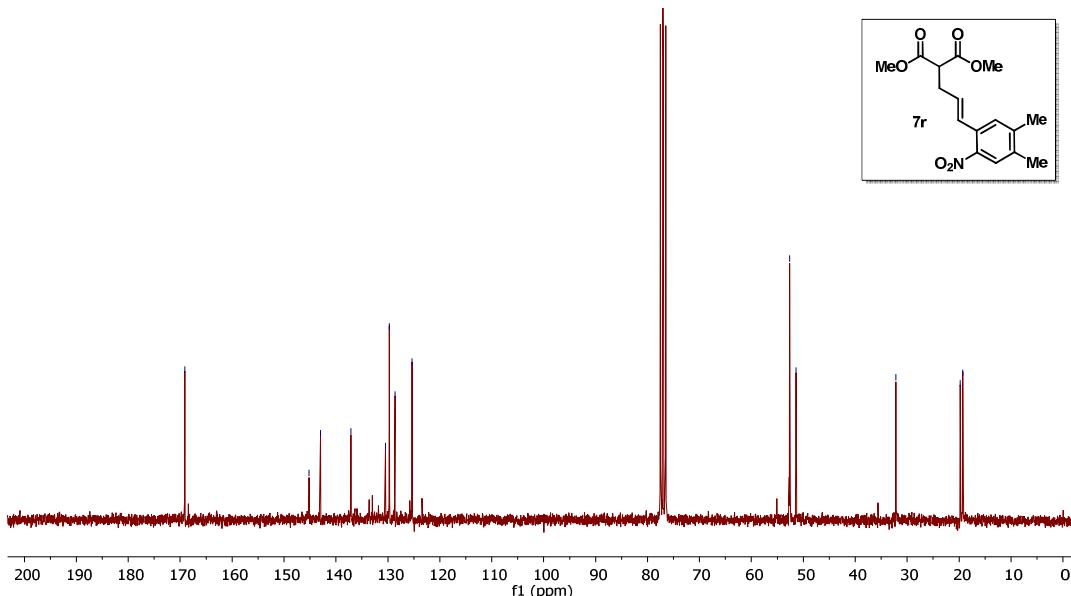


¹H NMR spectrum of 7r (250 MHz, CDCl₃)

dez04ccoC1.1.fid
RCD-146 dez04ccoC1 250MHz

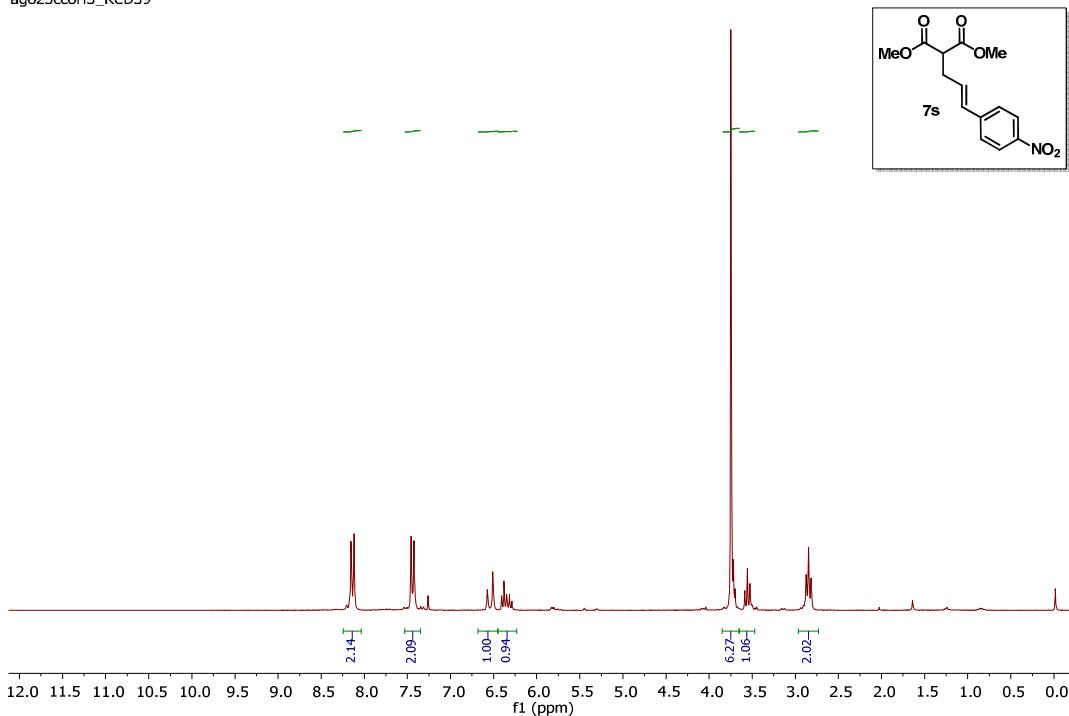
> 145.18
~ 143.00
~ 137.09
< 130.45
> 129.70
> 128.64
> 125.33

< 52.64
~ 51.41
~ 32.16
< 19.80
< 19.31

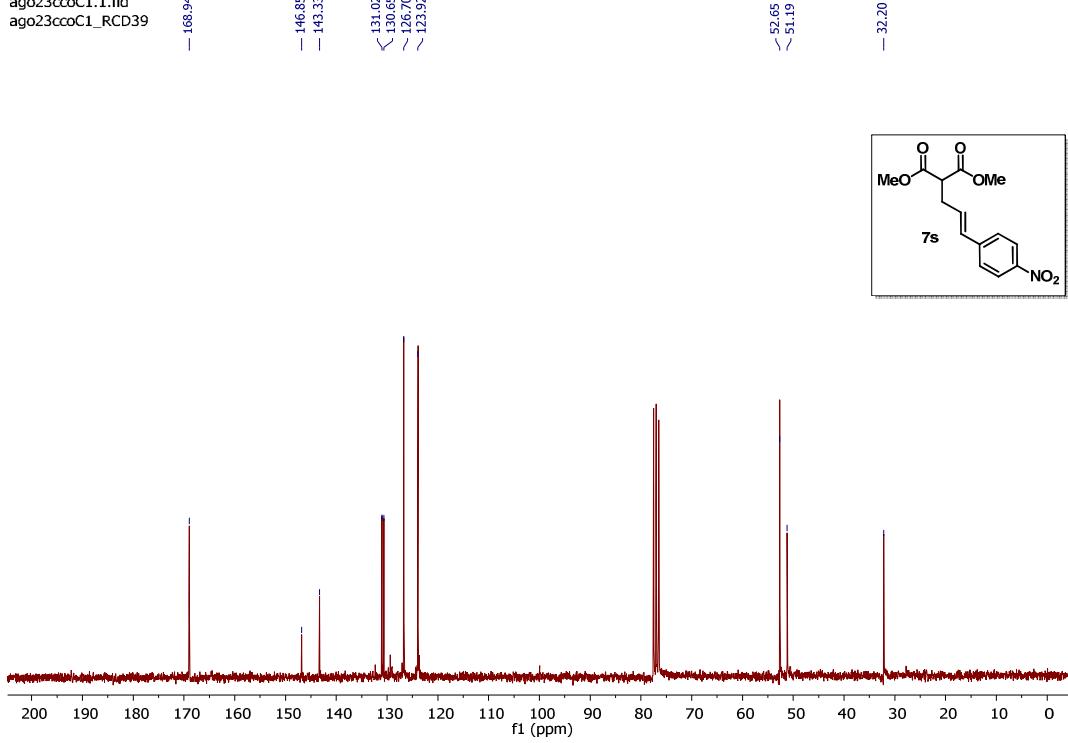


¹³C NMR spectrum of 7r (62.5 MHz, CDCl₃)

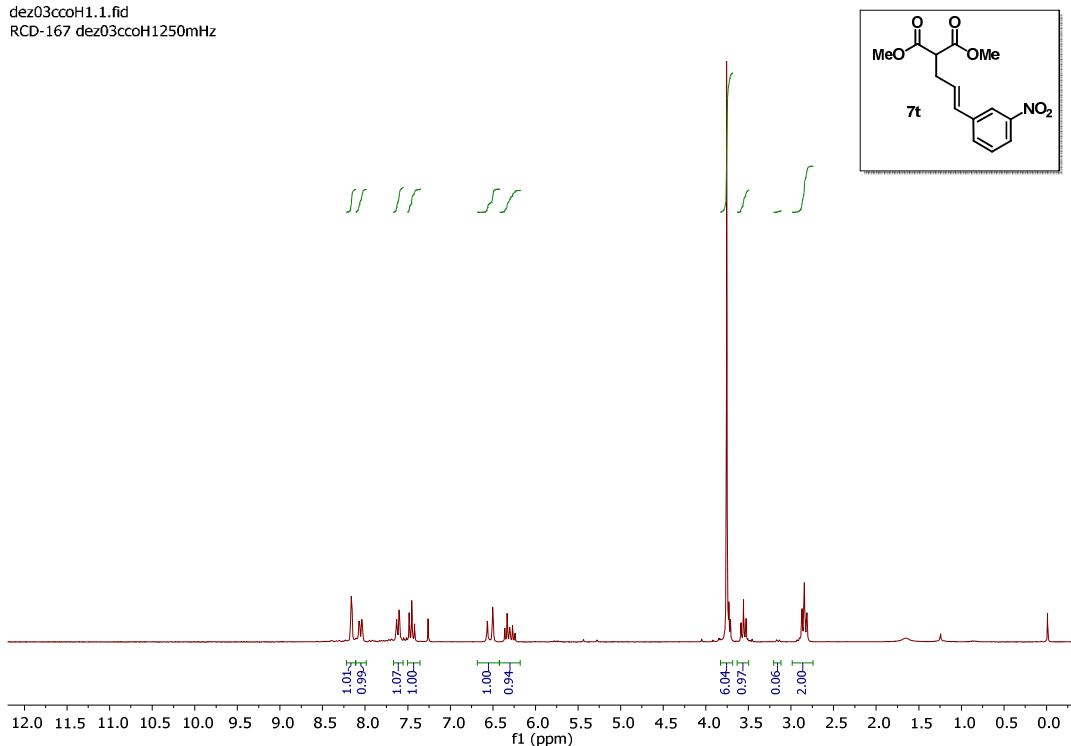
ago23ccoH3.1.fid
ago23ccoH3_RCD39



ago23ccoC1.1.fid
ago23ccoC1_RCD39

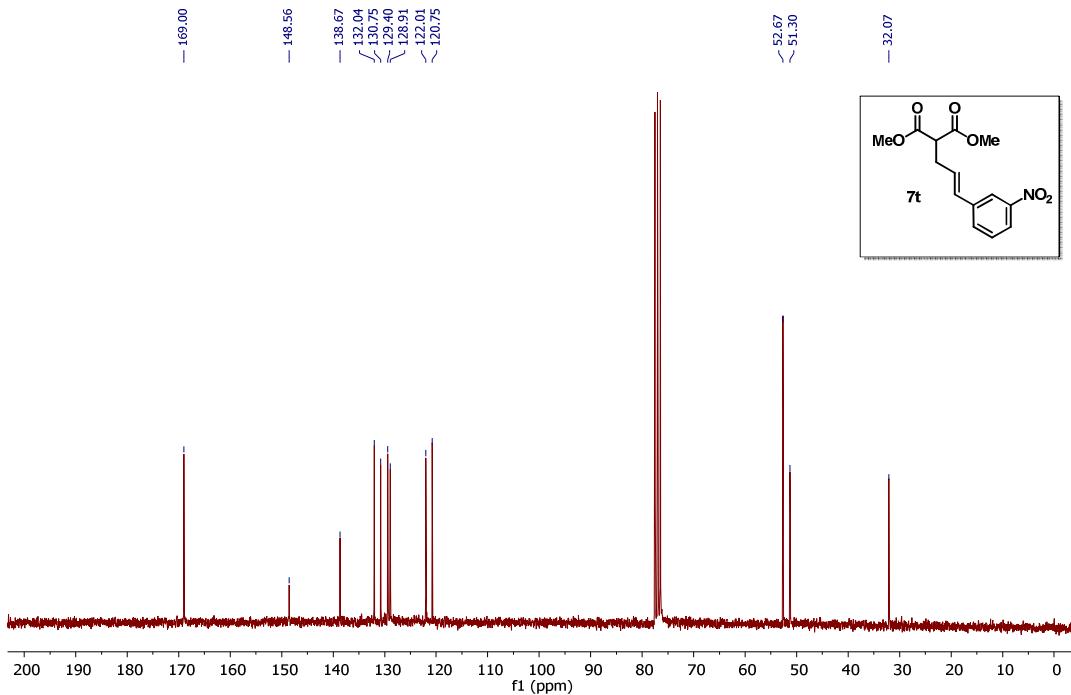


dez03ccoH1.1.fid
RCD-167 dez03ccoH1250mHz



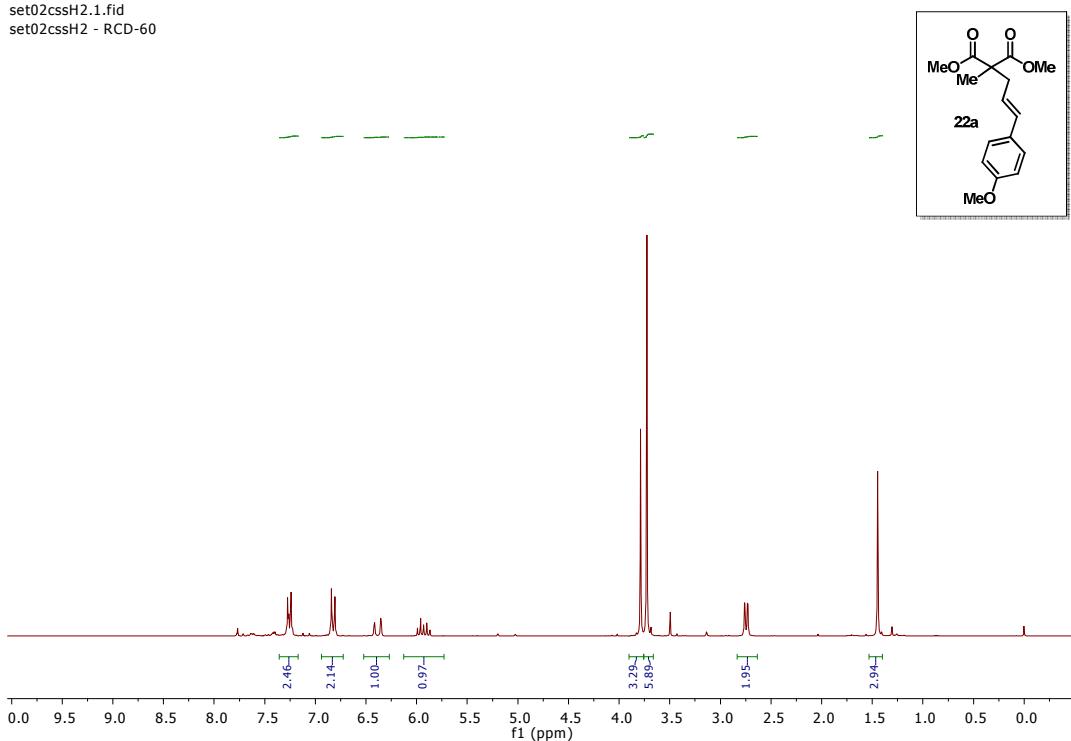
¹H NMR spectrum of 7t (250 MHz, CDCl₃)

dez03ccoC1.1.fid
RCD-167 dez03ccoC1250mHz



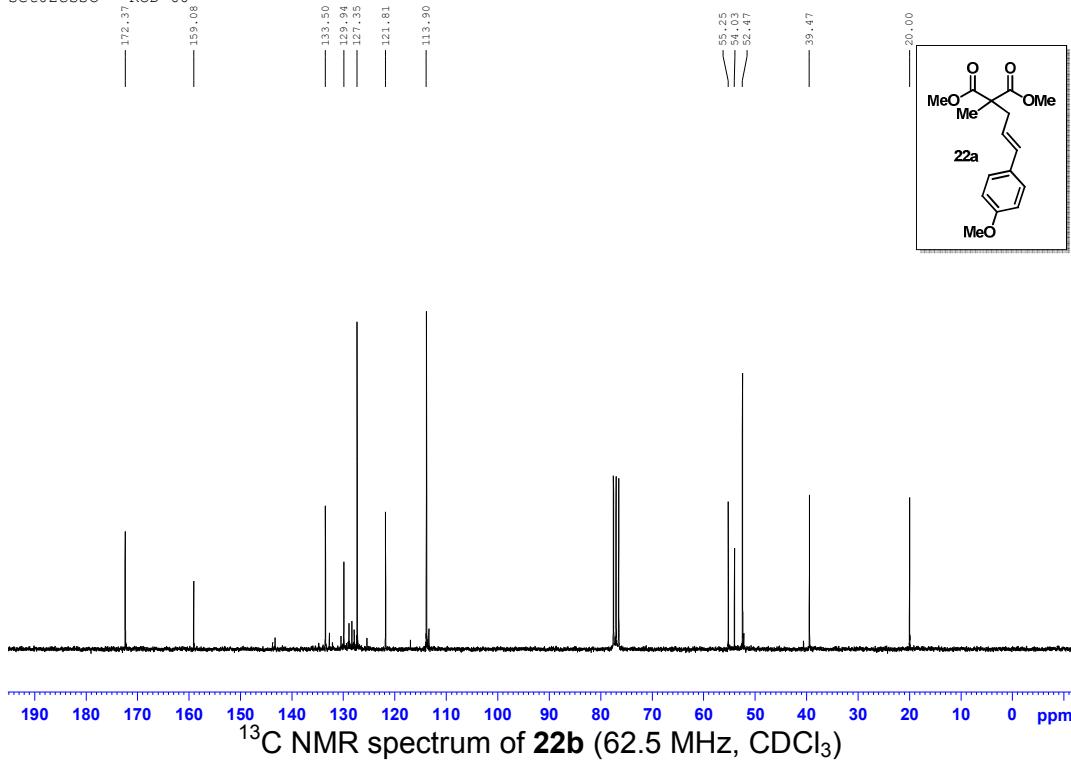
¹³C NMR spectrum of 7t (62.5 MHz, CDCl₃)

set02cssH2.1.fid
set02cssH2 - RCD-60

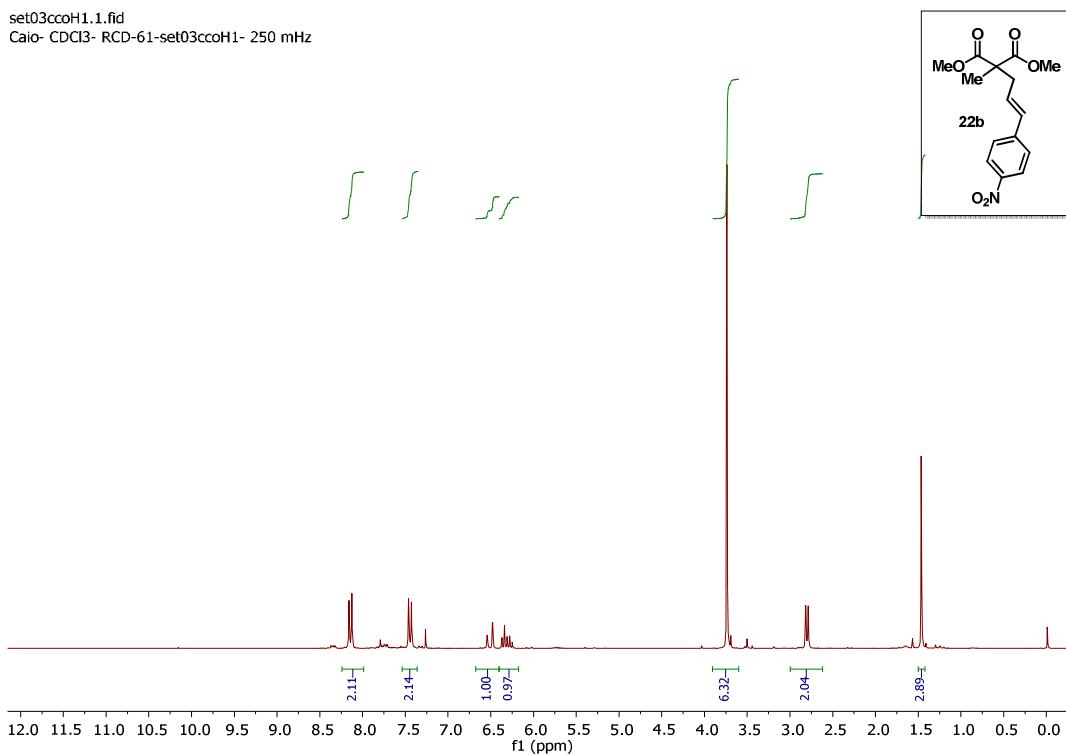


¹H NMR spectrum of **22a** (250 MHz, CDCl₃)

set02cssC - RCD-60

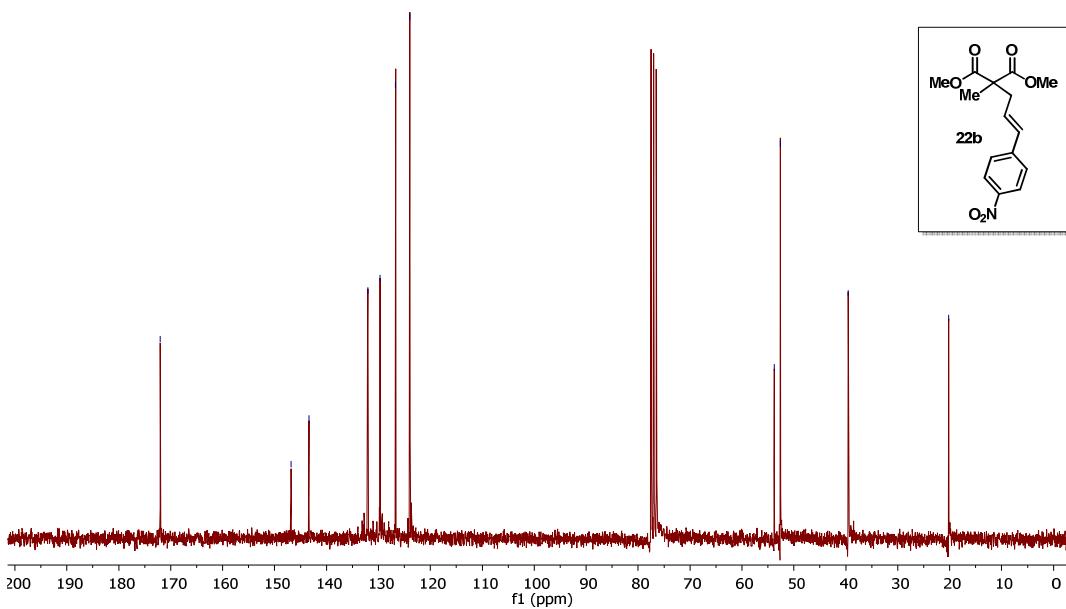


set03ccoH1.1.fid
Caio- CDCl₃- RCD-61-set03ccoH1- 250 mHz

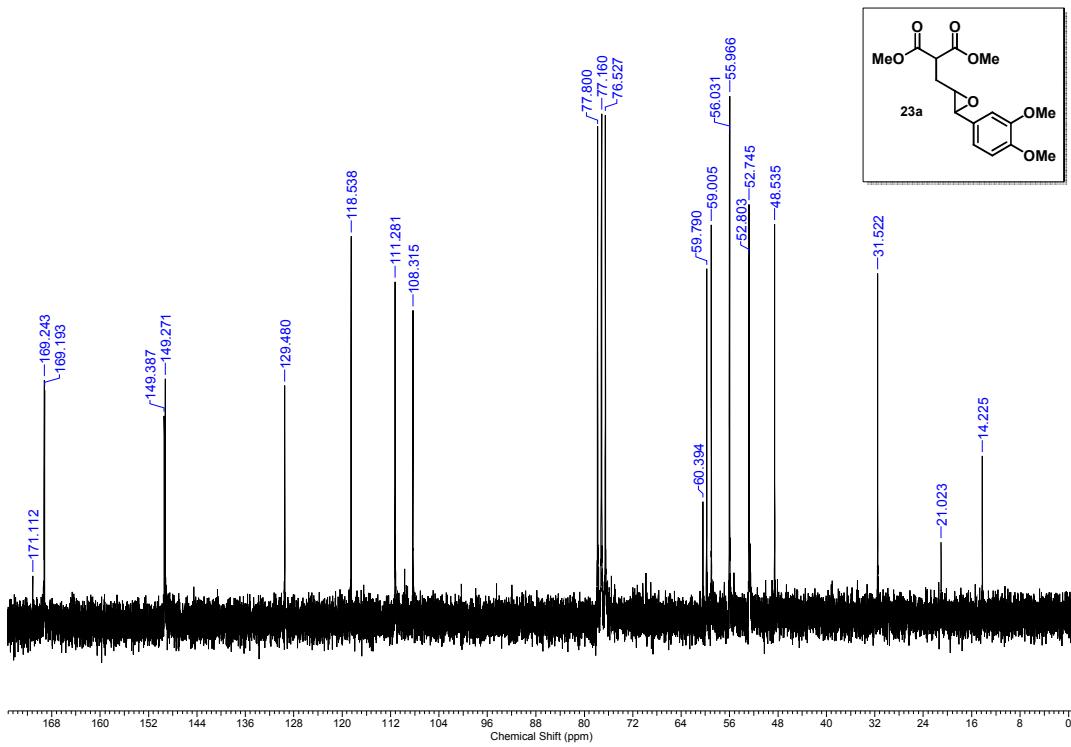
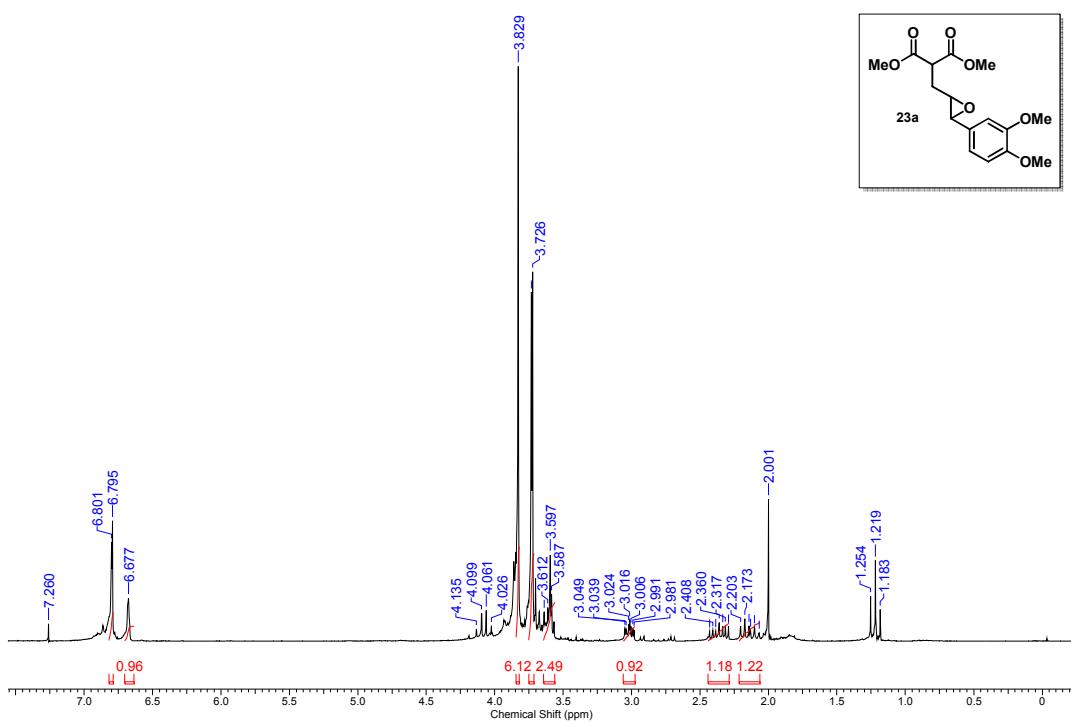


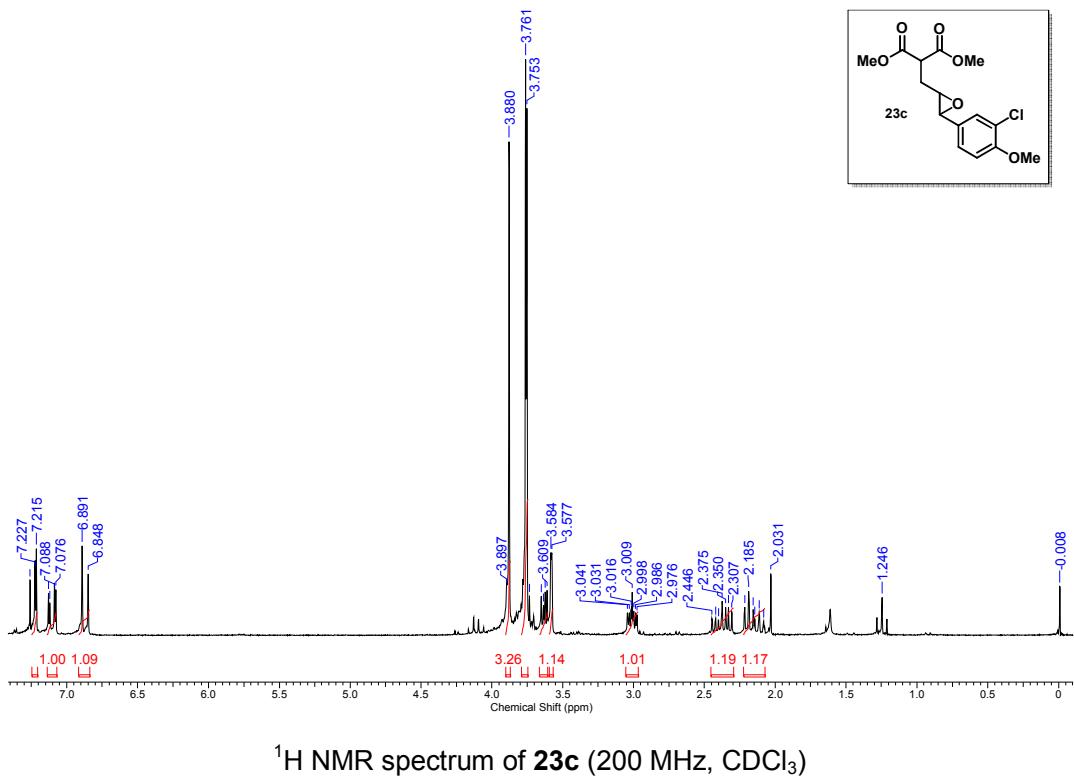
¹H NMR spectrum of **22b** (250 MHz, CDCl₃)

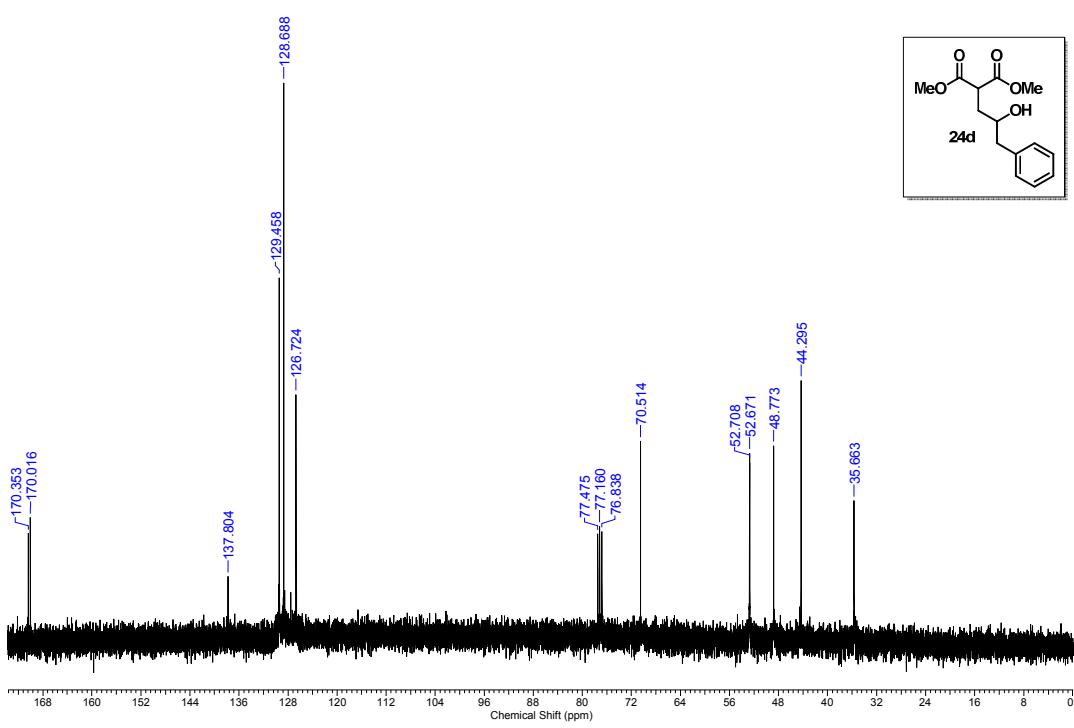
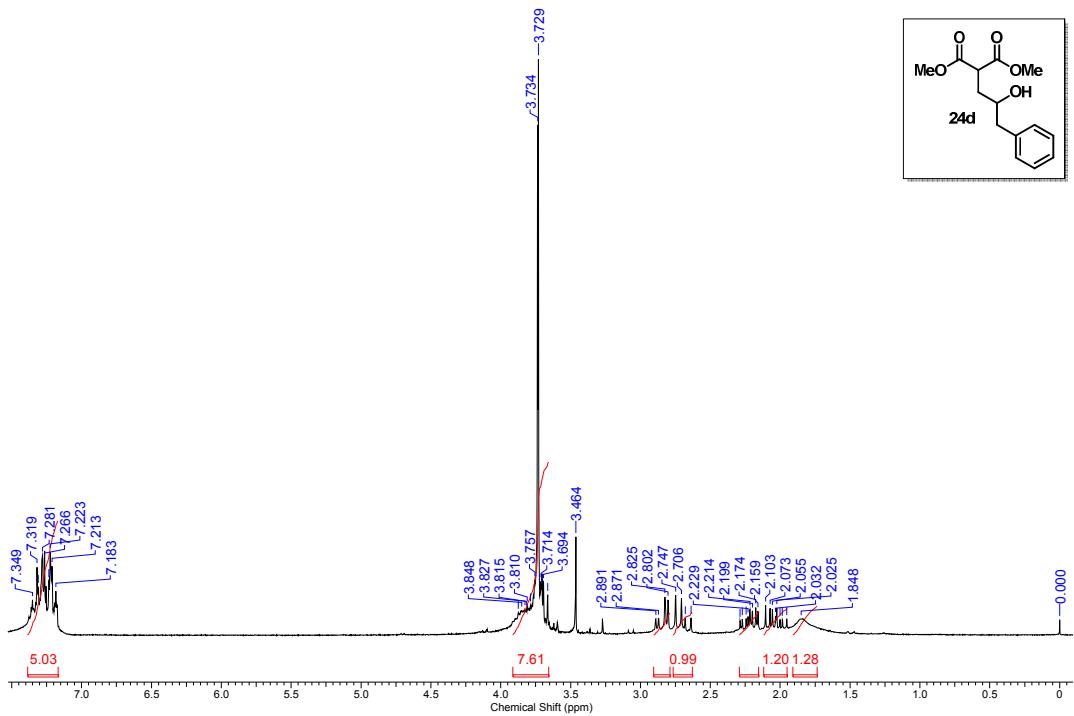
set03ccoC1.1.fid
Caio- CDCl₃- RCD-61-set03ccoC1- 250 mHz
— 197.01
— 195.38
— 132.06
— 129.69
— 126.71
— 123.93
— < 52.62
— 39.56
— 20.22

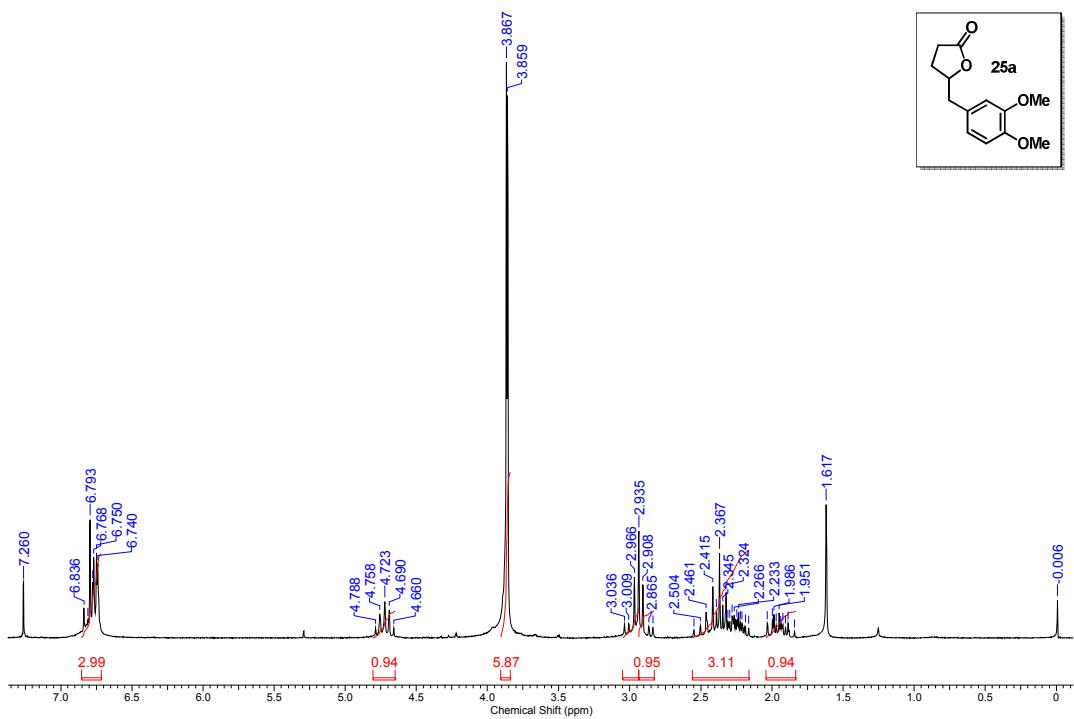


¹³C NMR spectrum of **22b** (62.5 MHz, CDCl₃)

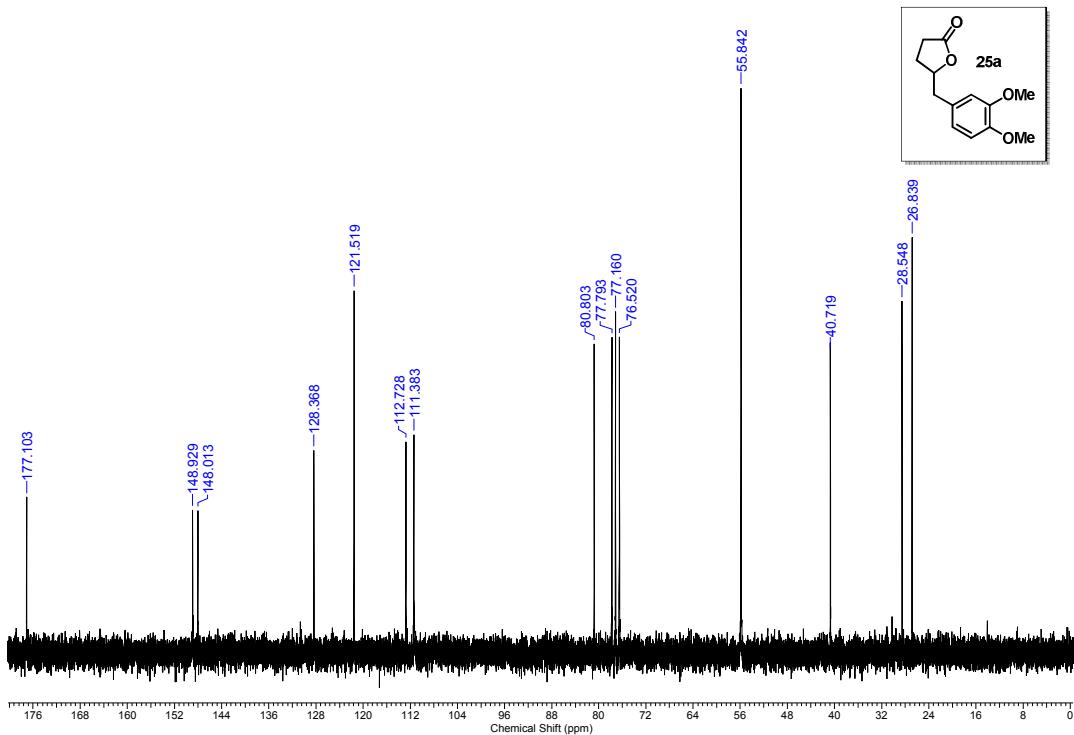




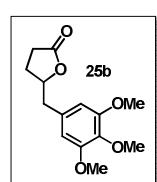
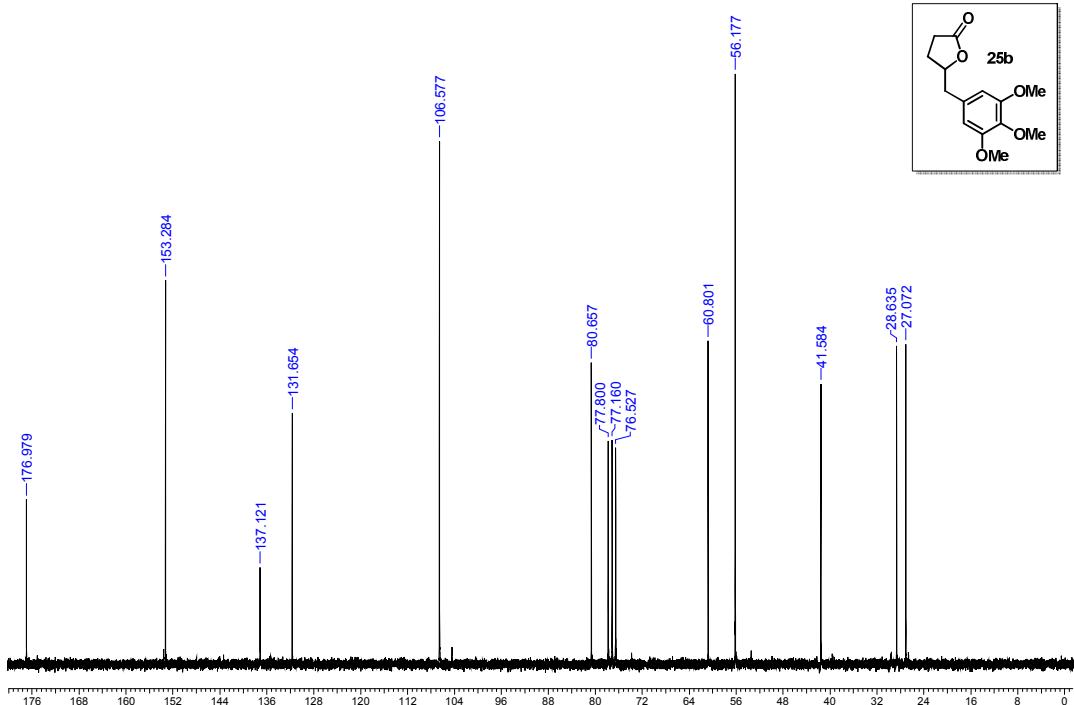
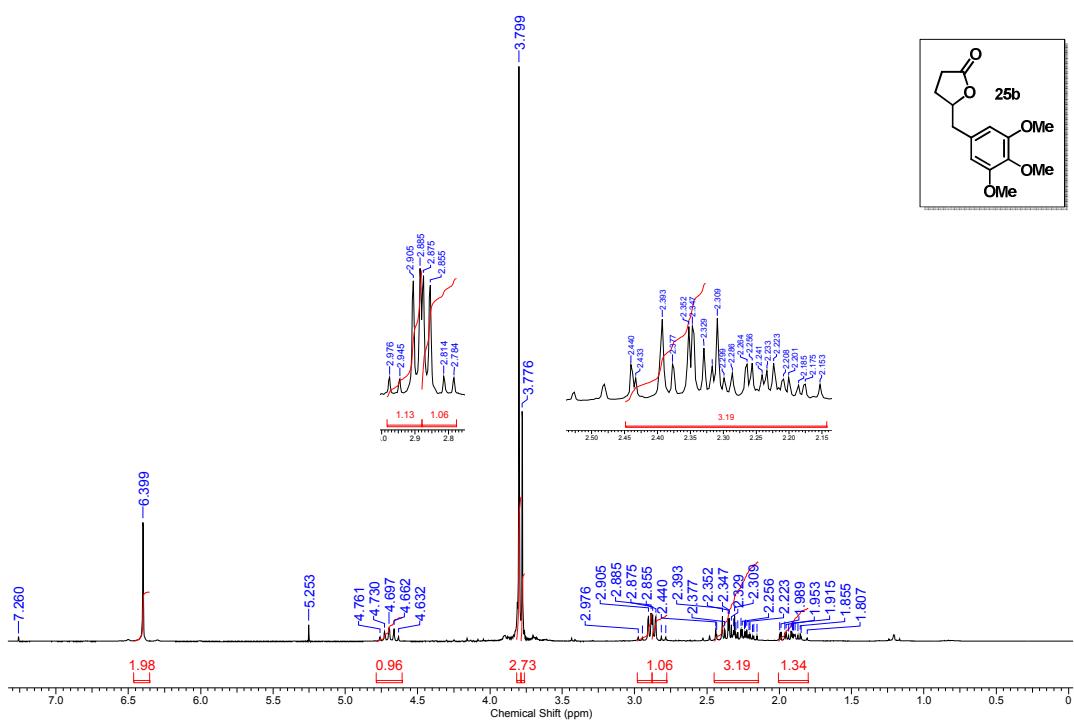


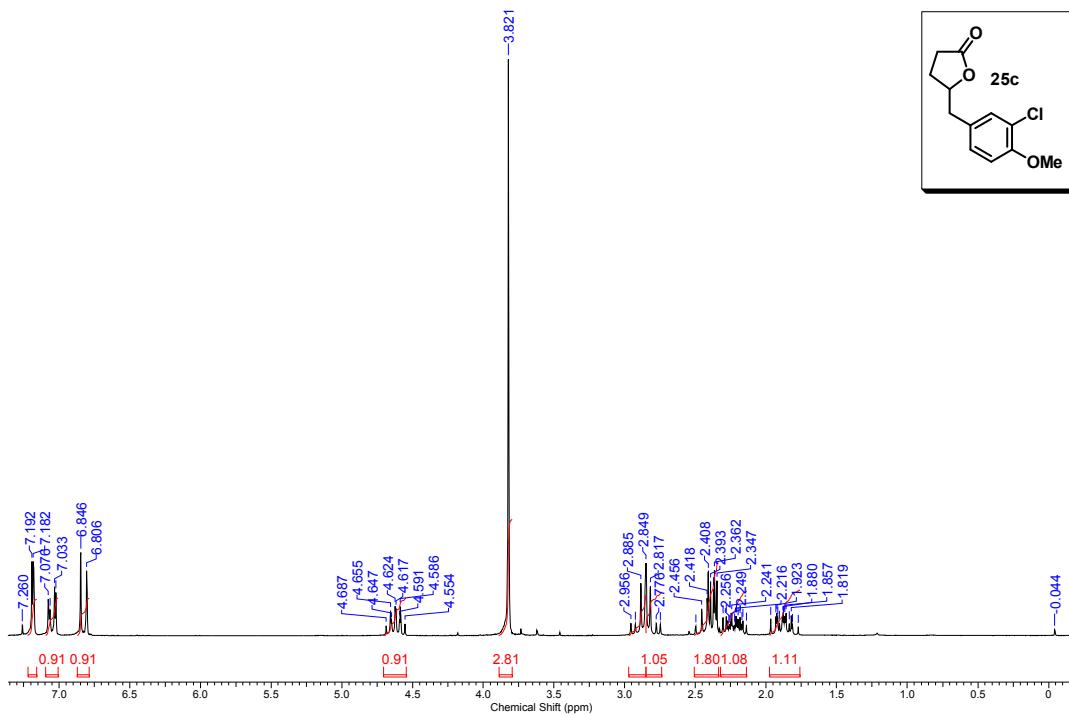
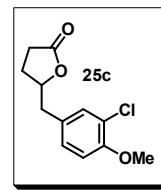


¹H NMR spectrum of **25a** (200 MHz, CDCl₃)

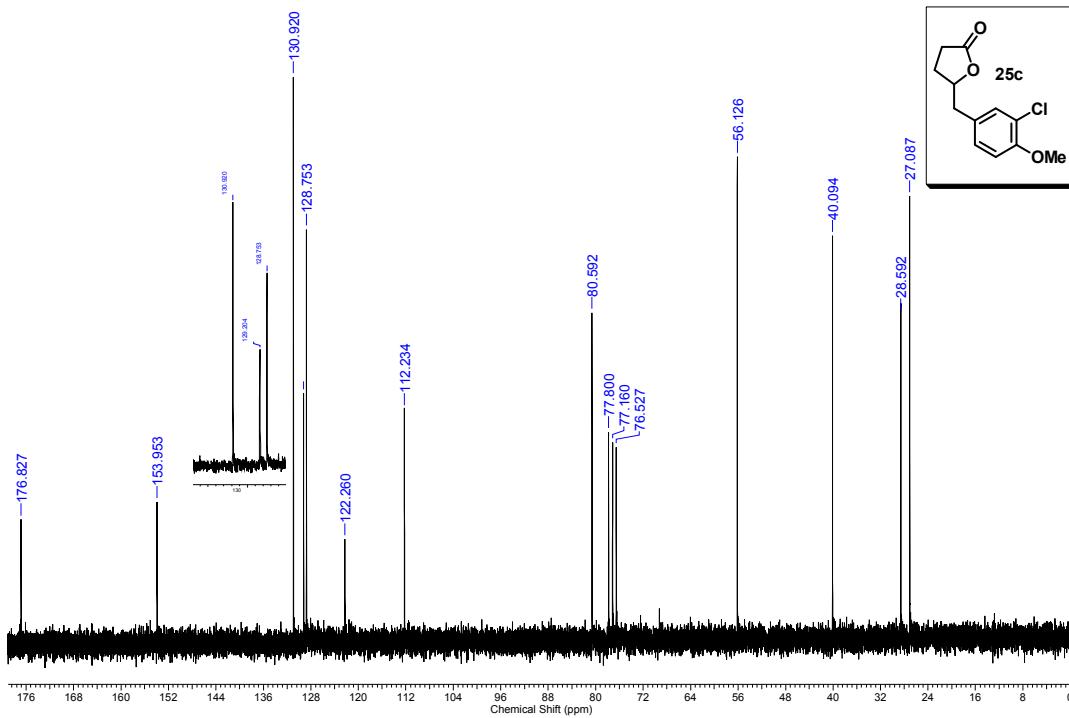
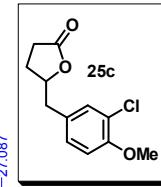


¹³C NMR spectrum of **25a** (50 MHz, CDCl₃)





¹H NMR spectrum of **25c** (200 MHz, CDCl₃)



¹³C NMR spectrum of **25c** (50 MHz, CDCl₃)

