

Supporting Information

From α -bromomethylbutenolide to fused tri(four)cyclidihydro-furandiones through Barbier reaction-Heck arylation-oxidation sequence

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1. General information

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under nitrogen and argon atmosphere with magnetic stirring. ¹H and ¹³C-NMR spectra were recorded on a Bruker AMX 300 spectrometer working at 300 MHz, 75 MHz respectively for ¹H and ¹³C with chloroform-d as solvent. Chemical shifts were reported in δ , parts per million (ppm), relative to chloroform (δ = 7.28 ppm) as international standards unless otherwise stated for proton nuclear magnetic resonance (¹H-NMR). Chemical shifts for carbon nuclear magnetic resonance (¹³C-NMR) were reported in δ , parts per million (ppm), relative to the center line of the chloroform triplet (δ = 77.07 ppm). Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. The abbreviations s, d, dd, t, q, br and m stand for resonance multiplicities singlet, doublet, doublet of doublet,

triplet, quartet, broad and multiplet, respectively. Allylation diastereoselectivity was determined by ^1H -NMR integrations of the methylene signals in the crude products. High Resolution Mass spectroscopy data were recorded on an Autospec Ultima (Waters/Micromass) device with a resolution of 5000 RP at 5%. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel plates (Fluka Kiesel gel 60 F254, Merck) and visualized by a 254 nm UV lamp and potassium permanganate. Melting points (Mp) were determined on a System Kofler type WME apparatus.

2. Representative procedure for allylation of aldehydes with 3-bromomethyl-5H-furan-2-one

To a reaction vessel were added sequentially 3-bromomethyl-5H-furan-2-one **1** (400 mg, 2.26 mmol), aldehyde **2** (1.53 mmol, 0.68 equiv.), THF (2 mL) saturated aqueous NH_4Cl (1 mL) and activated zinc powder [30] (2.64 mmol, 1.17 equiv.). The mixture was stirred vigorously at ambient temperature. After 16h, the reaction was filtered through diatomite, extracted with diethyl ether (2 x 20 mL for each extraction), washed with brine (20 mL) and dried over anhydrous MgSO_4 . Evaporation *in vacuo* followed by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 7:3) afforded homoallylic alcohols **3**, **12**, **13** and **14**

3. Characterization data for the lactone **3**, **12**, **13**, **14**

4-((2-Bromophenyl)(hydroxyl)methyl)-3-methylenedihydrofuran-2(3H)-one **3**. White solid; Mp: 111-115 °C; Yield: (281, 65%); dr: (85:5); ^1H -NMR (300 MHz, CDCl_3): δ = 7.55 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.23 (d, J = 2.1 Hz, 1H), 5.22 (d, J = 2.4 Hz, 1H), 5.21 (d, J = 3.90 Hz, 1H), 4.34-4.32 (m, 2H), 3.52-3.48 (m, 1H), 2.98 (s (*br.*), 1H) ppm; Discernable data for minor diastereoisomer: δ = 6.28 (d, J = 2.4 Hz, 1H), 5.48 (d, J = 2.1 Hz, 1H), 5.25 (d, J = 4.8 Hz, 1H), 4.51 (dd, J = 9.3 Hz, J = 4.20 Hz, 1H), 4.19-4.13 (m, 1H) ppm; ^{13}C -NMR (75 MHz, CDCl_3): δ = 171.0 (C=O), 139.5 (*aromatic* =C), 133.7 ($\text{H}_2\text{C}=\text{C}$), 132.9 (*aromatic* =CH), 129.7 (*aromatic* =CH), 128.8 (*aromatic* =CH), 127.6 (*aromatic* =CH), 125.4 (*aromatic* =C-Br), 122.0 ($\text{H}_2\text{C}=\text{C}$), 74.0 (CH-OH), 68.5 (OCH_2), 43.6 (CH) ppm; HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_3\text{Br}$ $[\text{M}+\text{H}]^+$ 282.9970, found 282.9979.

4-((1-Bromonaphthalen-2-yl)(hydroxyl)methyl)-3-methylenedihydrofuran-2(3H)-one **12**. Light yellow solid; Mp: 140-142 °C; Yield: (305 mg, 60%); dr: (87:13); ^1H -NMR (300 MHz, CDCl_3): δ = 8.35 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.63-7.59 (m, 3H), 6.34 (d, J = 2.1 Hz, 1H), 5.56 (d, J = 6.6 Hz, 1H), 5.48 (d, J = 1.5 Hz, 1H), 4.31-4.29 (m, 2H), 3.63-3.56 (m, 1H), 2.71 (s (*br.*), 1H) ppm; Discernable data for minor diastereoisomer: δ = 6.28 (d, J = 2.4 Hz, 1H), 5.60 (d, J = 5.4 Hz, 1H), 5.38 (d, J = 2.4 Hz, 1H), 4.65 (dd, J = 9.6 Hz, J = 4.2 Hz, 1H), 4.31-4.25 (m, 1H) ppm; ^{13}C -NMR (75 MHz, CDCl_3): δ = 170.9 (C=O), 137.6 ($\text{H}_2\text{C}=\text{C}$), 134.4 (*aromatic* =C), 134.3 (*aromatic* =C), 132.0 (*aromatic* =C), 128.2 (*aromatic* =CH), 128.1 (*aromatic* =CH), 127.9 (*aromatic* =CH), 127.5 (*aromatic* =CH), 127.2 (*aromatic* =CH), 125.7 (*aromatic* =CH), 125.1 (*aromatic* =C-Br), 122.5 ($\text{H}_2\text{C}=\text{C}$), 74.8 (CH-OH), 68.2 (OCH_2), 44.2 (CH) ppm; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_3\text{Br}$ $[\text{M}+\text{H}]^+$ 333.0126, found 333.0138.

4-((1-Chloro-3,4-dihydronaphthalen-2-yl)(hydroxyl)methyl)-3-methylenedihydrofuran-2(3H)-one **13**. Colorless oil; Yield: (357 mg, 80%); dr: (89:11); ^1H -NMR (300 MHz, CDCl_3): δ = 7.67-7.64 (m, 1H), 7.30-7.27 (m, 2H), 7.26-7.19 (m, 1H), 6.41 (d, J = 2.1 Hz, 1H), 6.10 (d, J = 1.5 Hz, 1H), 5.09 (d, J = 9.6 Hz, 1H), 4.25 (t, J = 9.6 Hz, 1H), 4.10 (dd, J = 9.6 Hz, J = 4.5 Hz, 1H), 3.35-3.32 (m, 1H), 2.89-2.81 (m, 2H), 2.72-2.62 (m, 1H), 2.44 (s (*br.*), 1H), 2.39-2.28 (m, 1H) ppm; Discernable data for minor diastereoisomer: δ = 6.30 (d, J = 2.4 Hz, 1H), 5.57 (d, J = 2.1 Hz, 1H), 4.57 (dd, J = 9.3 Hz, J = 4.20 Hz, 1H), 4.47 (t, J = 9.3 Hz, 1H) ppm; ^{13}C -NMR (75 MHz, CDCl_3): δ = 170.7 (C=O), 136.3 (*aromatic* =C), 135.4 ($\text{H}_2\text{C}=\text{C}$), 134.7 (*aromatic* =C), 132.2 (Cl-C=C), 128.7 (*aromatic* =CH), 128.5 (*aromatic* =CH), 127.2 (*aromatic* =CH), 126.9 (=C-Cl), 125.6 (*aromatic* =CH), 125.1 ($\text{H}_2\text{C}=\text{C}$), 72.1 (CH-OH), 67.0 (OCH_2), 42.2 (CH), 27.7 (CH_2), 23.4 (CH_2) ppm; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_3\text{Cl}$ $[\text{M}+\text{H}]^+$ 291.0782, found 291.0776.

4-((1-Bromo-3,4-dihydronaphthalen-2-yl)(hydroxyl)methyl)-3-methylenedihydrofuran-2(3H)-one **14**. Grayish solid; Mp: 135-137 °C; Yield: (457 mg, 89%); dr: (94:6); ^1H -NMR (300 MHz, CDCl_3): δ = 7.67-7.66 (m, 1H), 7.30-7.23 (m, 3H), 7.17-7.15 (m, 1H), 6.43 (d, J = 2.1 Hz, 1H), 6.10 (d, J = 1.5 Hz, 1H), 5.09 (d, J = 9.6 Hz, 1H), 4.26 (t, J = 9.3 Hz, 1H), 4.13 (dd, J = 9.6 Hz, J = 4.6 Hz, 1H), 3.37-3.34 (m, 1H), 2.92-2.81 (m, 2H), 2.72-2.62 (m, 1H), 2.37-2.26 (m, 1H) ppm; ^{13}C -NMR (75 MHz, CDCl_3): δ = 170.6 (C=O), 137.9 ($\text{H}_2\text{C}=\text{C}$), 136.4 (Br-C=C), 135.3 (*aromatic* =C), 133.1 (*aromatic* =C), 128.8 (*aromatic* =CH), 127.7 (*aromatic* =CH), 127.1 (*aromatic* =CH), 127.0 (*aromatic* =CH), 125.6 ($\text{H}_2\text{C}=\text{C}$), 121.6 (=C-Br), 75.1 (CH-OH), 66.9 (OCH_2), 42.2 (CH), 27.8 (CH_2), 24.5 (CH_2) ppm; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_3\text{Br}$ $[\text{M}+\text{H}]^+$ 335.0277, found 335.0271.

4. General procedure for Pd-catalyzed Heck reaction of bromoderivative **3**

Procedure A

A mixture of lactone **3** (100 mg, 0.35 mmol), PdCl₂(PPh₃)₂ (12.5 mg, 0.017 mmol), and K₂CO₃ (98 mg, 0.71 mmol) in solvent (3mL) was purged under argon atmosphere and stirred at 95 °C for 16 h. After completion of the reaction (as monitored by TLC), the mixture was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over anhydrous MgSO₄, concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with CH₂Cl₂/petroleum ether, (8:2) to give the expected product **4**.

3-Methylene-3a,9b-dihydro-4H-furo[3,2-c]chromen-2(3H)-one 4. Yellow oil; Yield: (29 mg, 40%); ¹H-NMR (300 MHz, CDCl₃): δ = 7.60 (d, *J* = 7.8 Hz, 1H), 7.39-7.20 (m, 3H), 6.47 (d, *J* = 2.1 Hz, 1H), 5.81 (d, *J* = 1.8 Hz, 1H), 5.71 (d, *J* = 3.3 Hz, 1H), 4.10 (dd, *J* = 12.0 Hz, *J* = 6.0 Hz, 1H), 3.97 (dd, *J* = 9.0 Hz, *J* = 6.0 Hz, 1H), 3.18-3.11 (m, 1H) ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 170.0 (C=O), 138.8 (*aromatic* =C), 135.3 (H₂C=C), 133.2 (*aromatic* =CH), 129.9 (*aromatic* =CH), 128.0 (*aromatic* =C), 126.8 (*aromatic* =CH), 124.7 (H₂C=C), 121.1 (*aromatic* =CH), 79.4 (OCH), 64.0 (OCH₂), 49.6 (=C-CH) ppm; HRMS (ESI) calcd. for C₁₂H₁₁O₃ [M+H]⁺ 203.0708, found 203.0706.

(10a)-Methyl-7a,10a-dihydro-7H-benzo[6,7]indeno[1,2-c]furan-7,10(8H)-dione 15. Yellow solid; Mp: 206-207 °C; Yield: (46 mg, 60%); ¹H-NMR (300 MHz, CDCl₃): δ = 8.95 (d, *J* = 9.9 Hz, 1H), 7.99-7.94 (m, 2H), 7.78-7.72 (m, 3H), 4.77 (t, *J* = 9.3 Hz, 1H), 4.45 (dd, *J* = 9.9 Hz, *J* = 5.10 Hz, 1H), 3.47 (dd, *J* = 10.5 Hz, *J* = 5.1 Hz, 1H), 2.08 (s, 3H) ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 202.9 (C=O), 176.5 (CO₂), 153.9 (*aromatic* =C), 138.2 (*aromatic* =C), 133.0 (*aromatic* =C), 131.4 (*aromatic* =C), 129.7 (*aromatic* =CH), 129.6 (*aromatic* =CH), 129.3 (*aromatic* =CH), 127.8 (*aromatic* =CH), 127.6 (*aromatic* =CH), 119.2 (*aromatic* =CH), 66.4 (OCH₂), 56.3 (CH), 52.0 (CCH₃), 23.5 (CH₃) ppm; HRMS (ESI) calcd. for C₁₆H₁₁O₃ [M-H]⁻ 251.0708, found 251.0710.

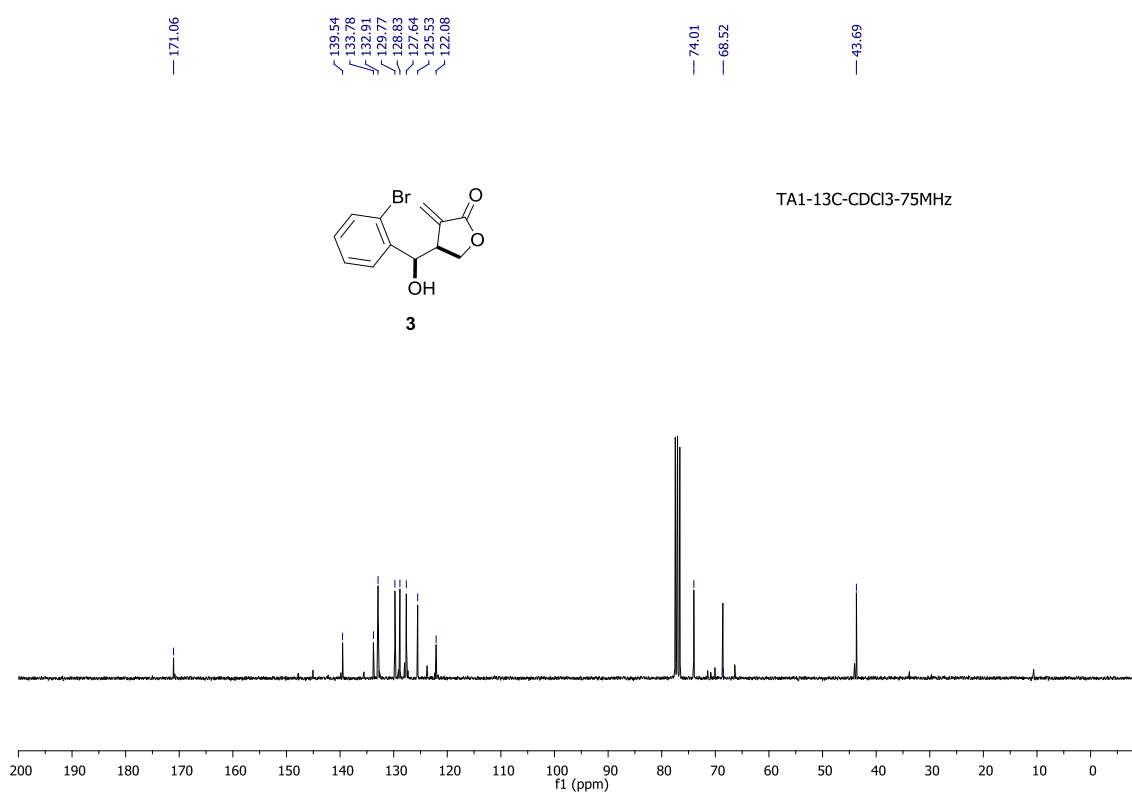
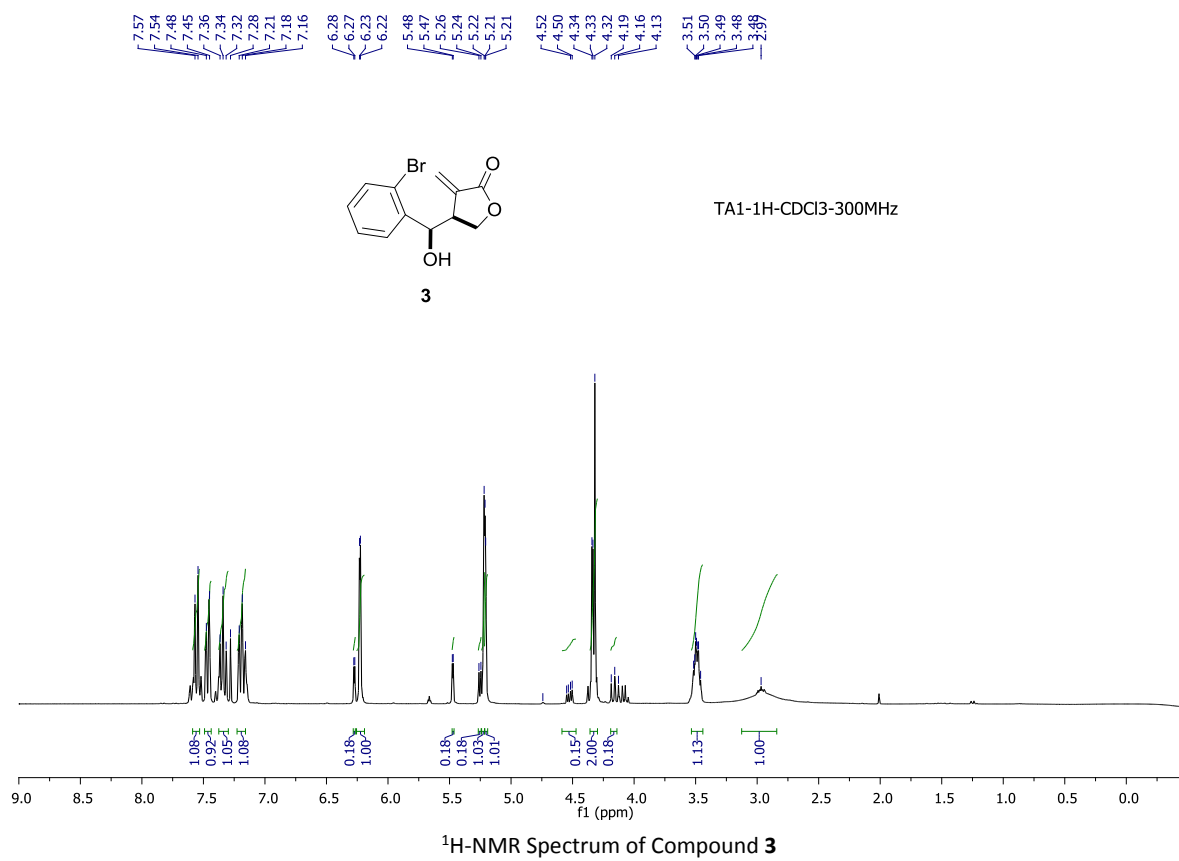
(10a)-Methyl-6,7a,8,10a-tetrahydro-7H-benzo[6,7]indeno[1,2-c]furan-7,10(5H)-dione 16. Yellow solid; Mp: 122-124 °C; Yield: (46 mg, 60%); ¹H-NMR (300 MHz, CDCl₃): δ = 8.42 (d, *J* = 9.3 Hz, 1H), 7.40-7.30 (m, 3H), 4.64 (t, *J* = 9.9 Hz, 1H), 4.50 (dd, *J* = 9.9 Hz, *J* = 3.9 Hz, 1H), 3.19 (dd, *J* = 9.6 Hz, *J* = 3.6 Hz, 1H), 2.97-2.91 (m, 2H), 2.73-2.64 (m, 1H), 2.49-2.37 (m, 1H), 1.87 (s, 3H) ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 203.5 (C=O), 176.3 (CO₂), 165.2 (=C-CO), 139.9 (*aromatic* =C), 138.0 (*aromatic* =C), 131.3 (=C), 129.3 (*aromatic* =CH), 128.7 (*aromatic* =CH), 128.5 (*aromatic* =CH), 127.1 (*aromatic* =CH), 66.4 (OCH₂), 55.4 (CCH₃), 52.0 (CH), 28.1 (CH₂), 22.0 (CH₂), 18.4 (CH₃) ppm; HRMS (ESI) calcd. for C₁₆H₁₅O₃ [M+H]⁺ 255.1011, found 255.1016.

Procedure B

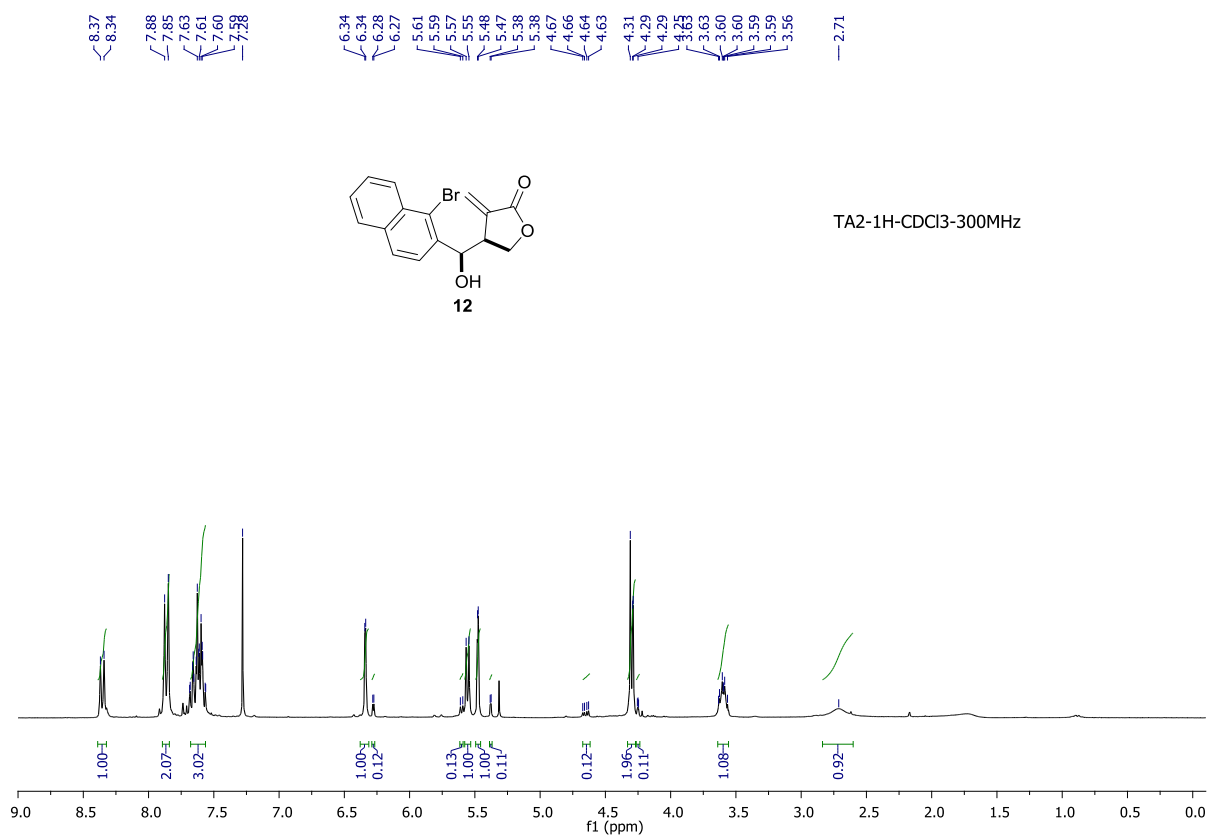
A mixture of lactone **3** (100 mg, 0.35 mmol), PdCl₂(PPh₃)₂ (12.5 mg, 0.017 mmol) and KOAc (69.6 mg, 0.71 mmol) in CH₃CN (3mL). The mixture was purged under argon atmosphere and stirred at 95 °C for 16 h. After completion of the reaction (as monitored by TLC), the mixture was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure and purified by flash column chromatography on silica gel eluting with CH₂Cl₂/petroleum ether, (8:2) to give the expected product **5**.

(3a)-Methyl-3a,8a-dihydro-1H-indeno[1,2-c]furan-3,8-dione 5. Yellow solid; Mp: 122-124 °C; Yield: (29 mg, 40%). ¹H-NMR (300 MHz, CDCl₃): δ = 7.83-7.74 (m, 3H), 7.55 (d, *J* = 7.2 Hz, 1H), 4.66 (t, *J* = 9.9 Hz, 1H), 4.51 (dd, *J* = 9.9 Hz, *J* = 7.2 Hz, 1H), 3.30 (dd, *J* = 9.0 Hz, *J* = 3.3 Hz, 1H), 1.83 (s, 3H) ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 203.4 (C=O), 177.2 (CO₂), 154.2 (*aromatic* =C), 136.5 (*aromatic* =C), 134.4 (*aromatic* =CH), 129.6 (*aromatic* =CH), 125.1 (*aromatic* =CH), 124.1 (*aromatic* =CH), 66.4 (OCH₂), 54.7 (CCH₃), 29.6 (CH), 22.2 (CH₃) ppm; HRMS (ESI) calcd. for C₁₂H₁₁O₃ [M+H]⁺ 203.0708, found 203.0706.

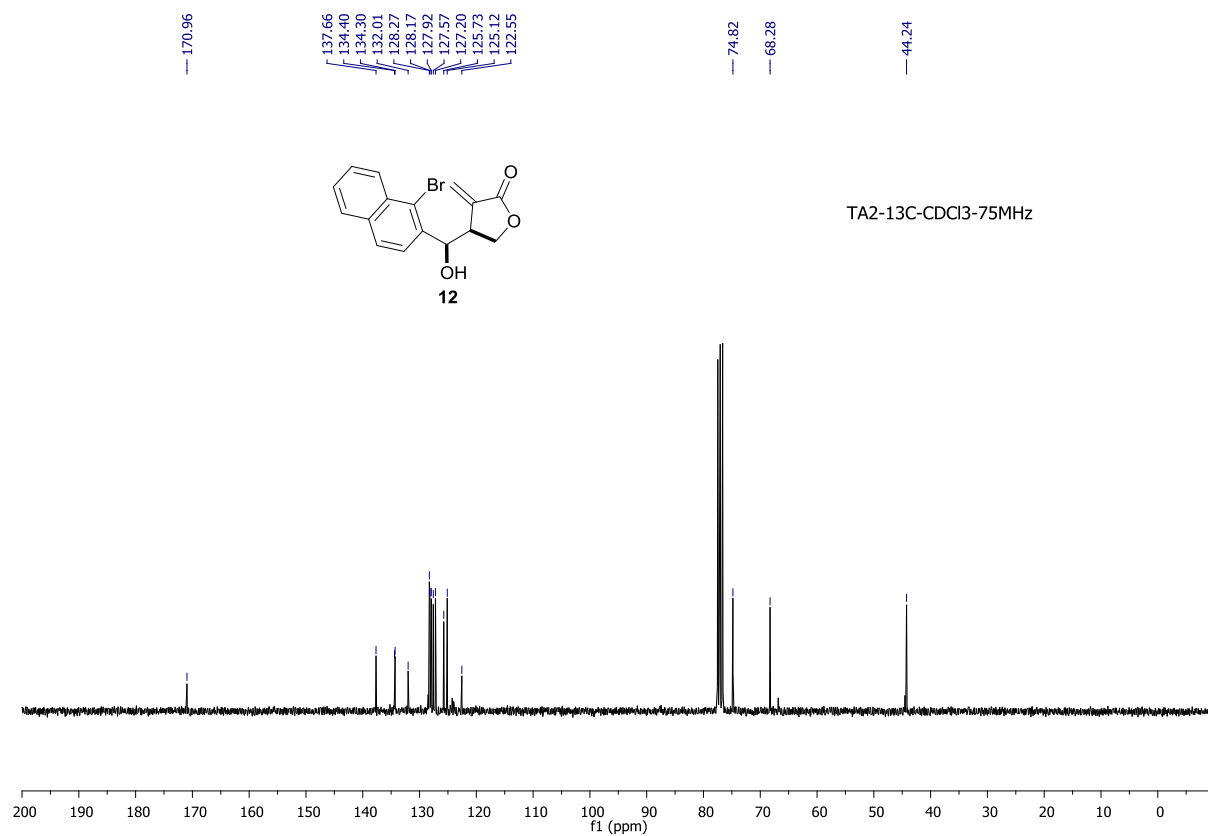
9. ¹H and ¹³C-NMR Spectra



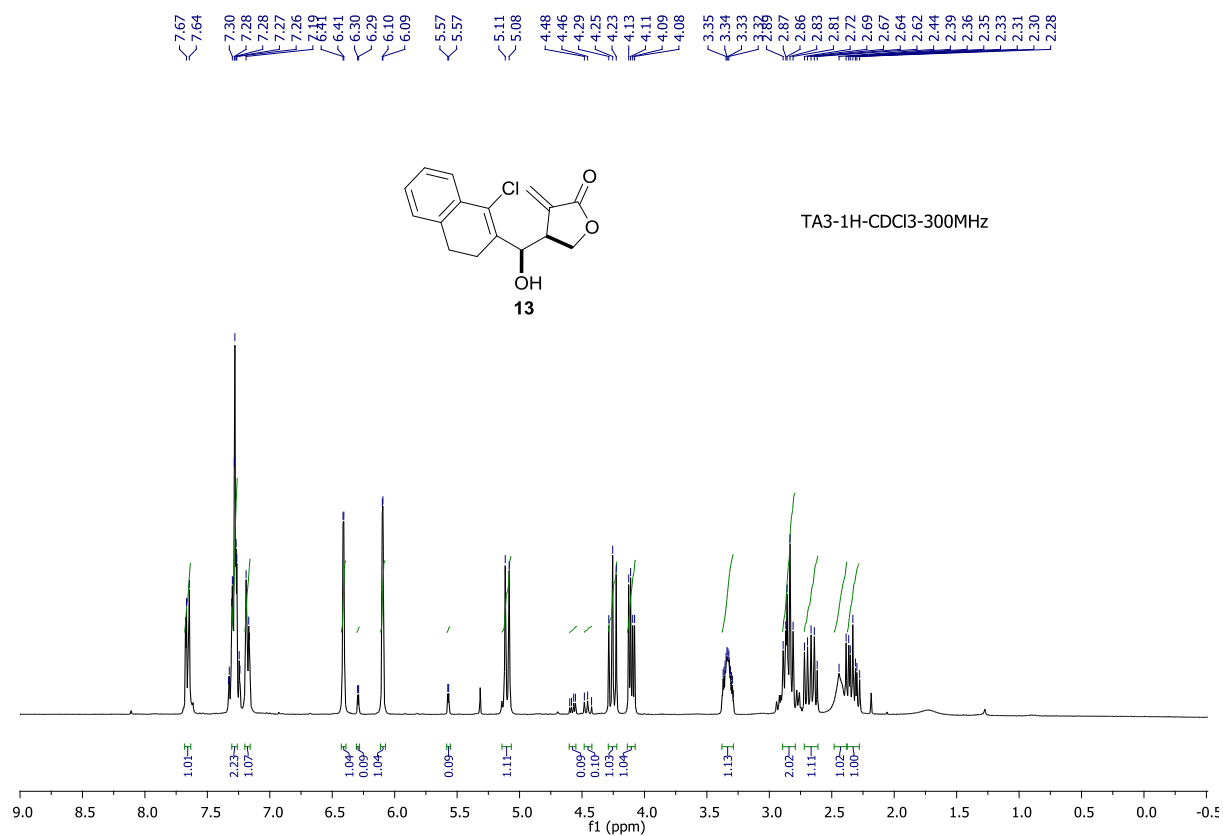
¹³C-NMR Spectrum of Compound **3**



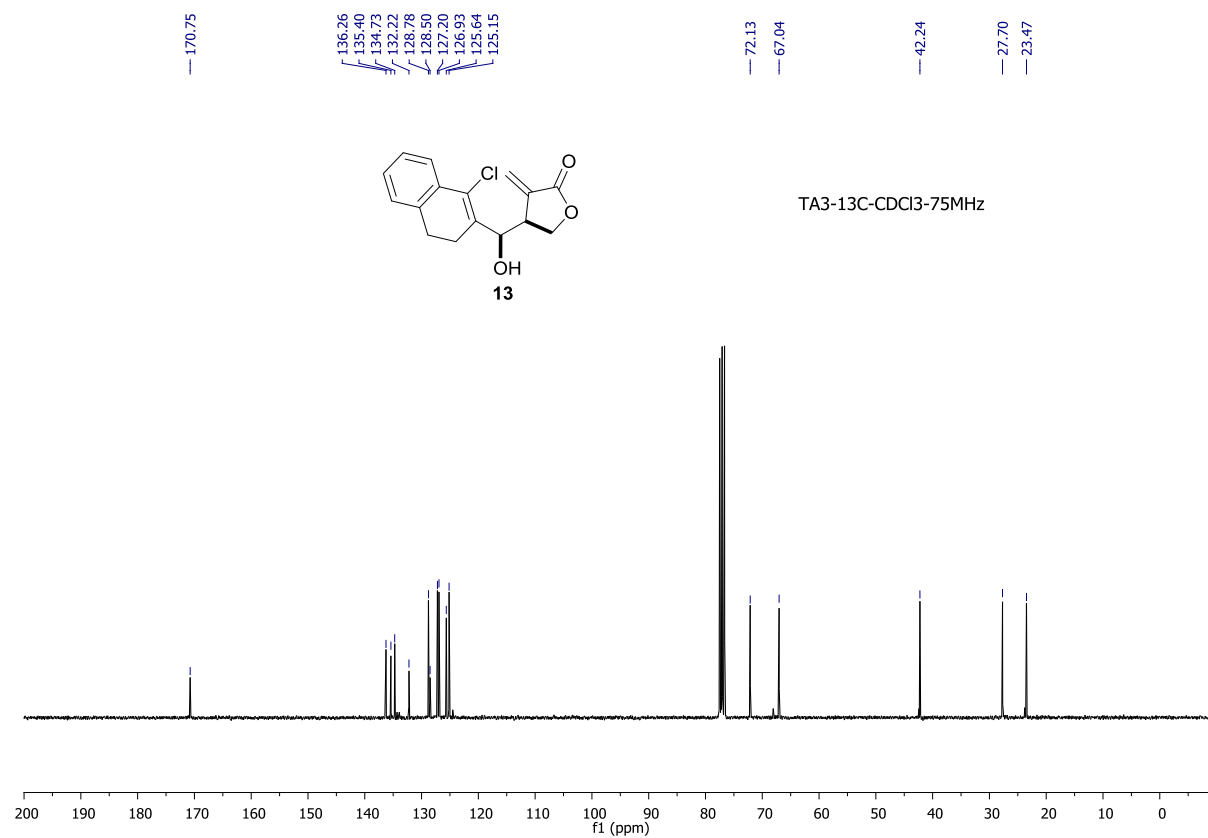
^1H -NMR Spectrum of Compound **12**



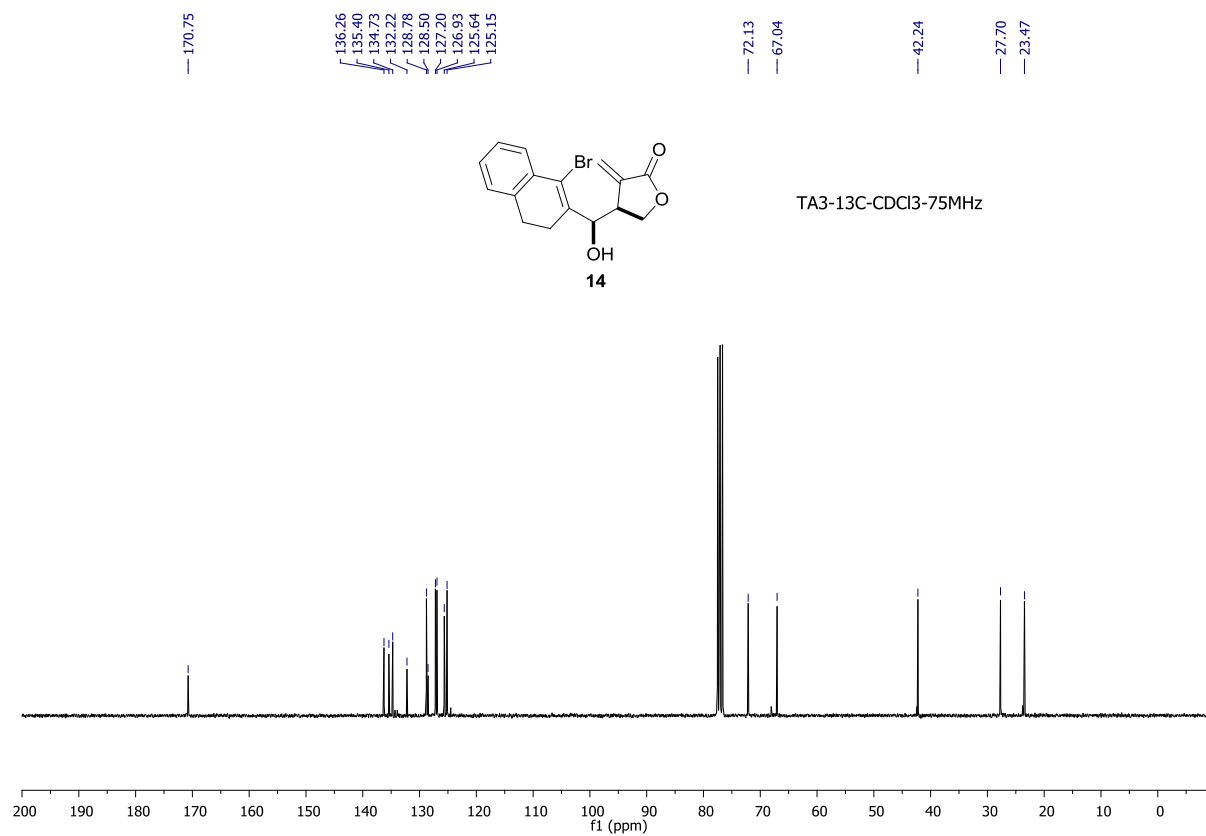
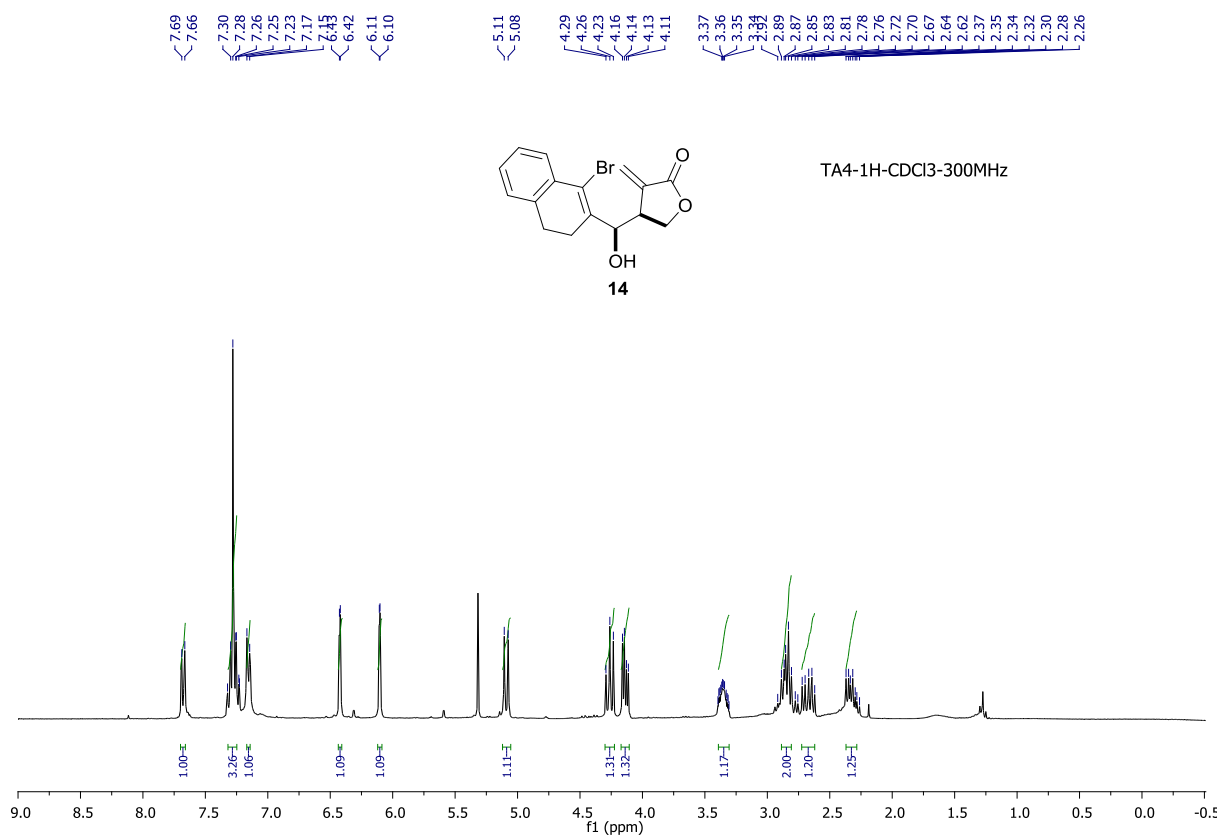
^{13}C -NMR Spectrum of Compound **12**

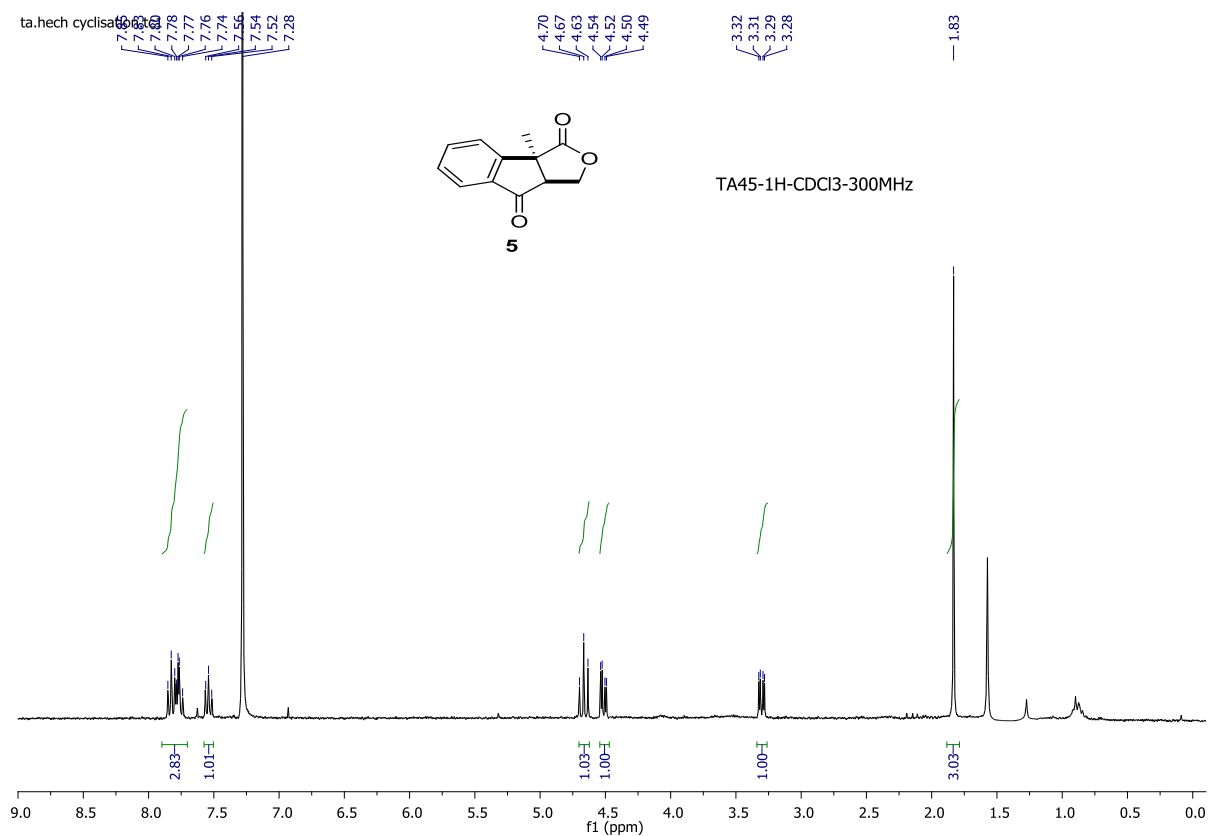


¹H-NMR Spectrum of Compound **13**

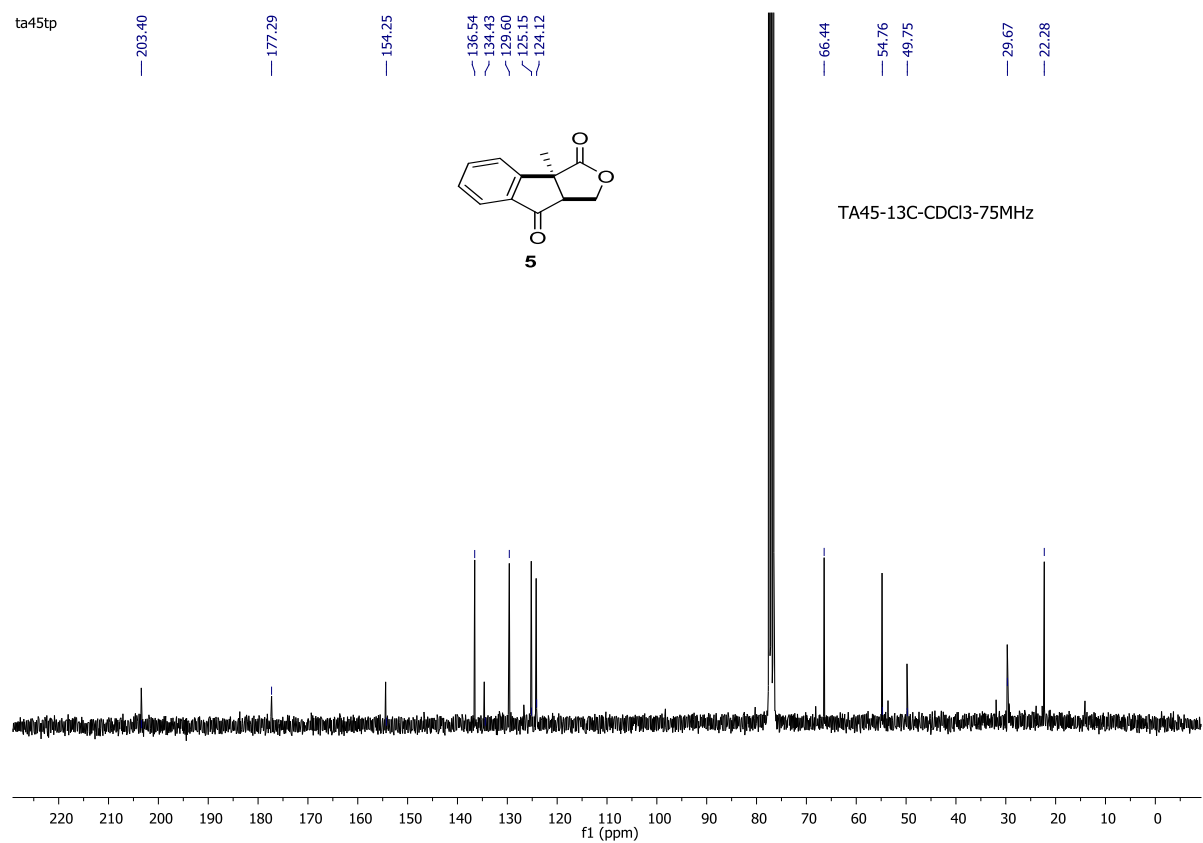


¹³C-NMR Spectrum of Compound **13**

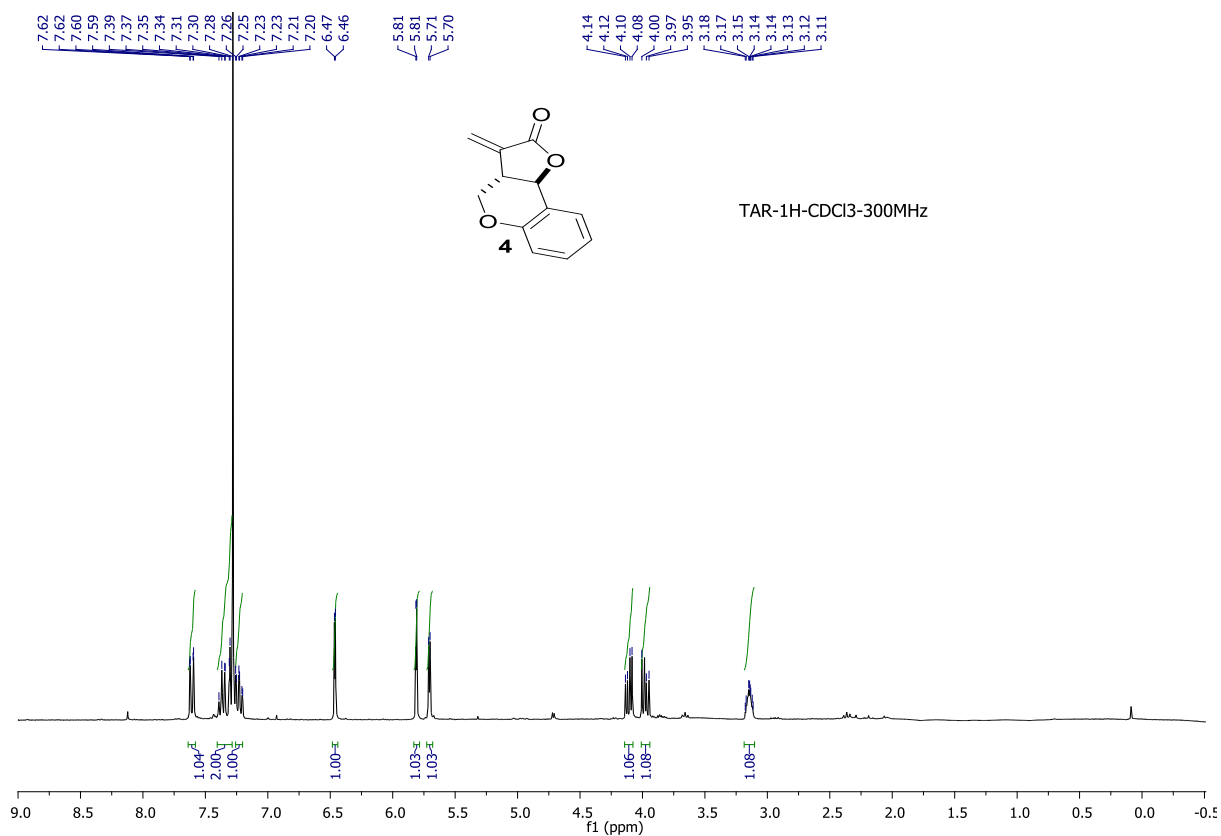




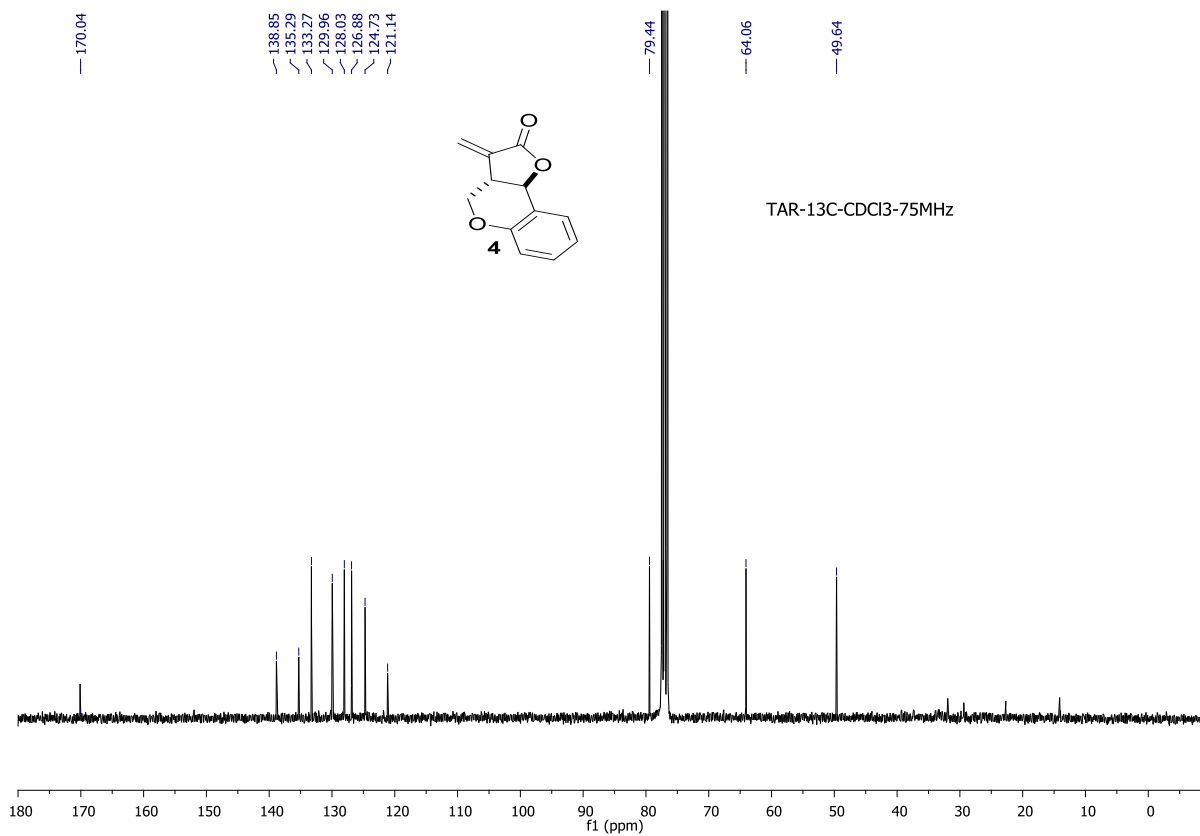
¹H-NMR Spectrum of Compound 5



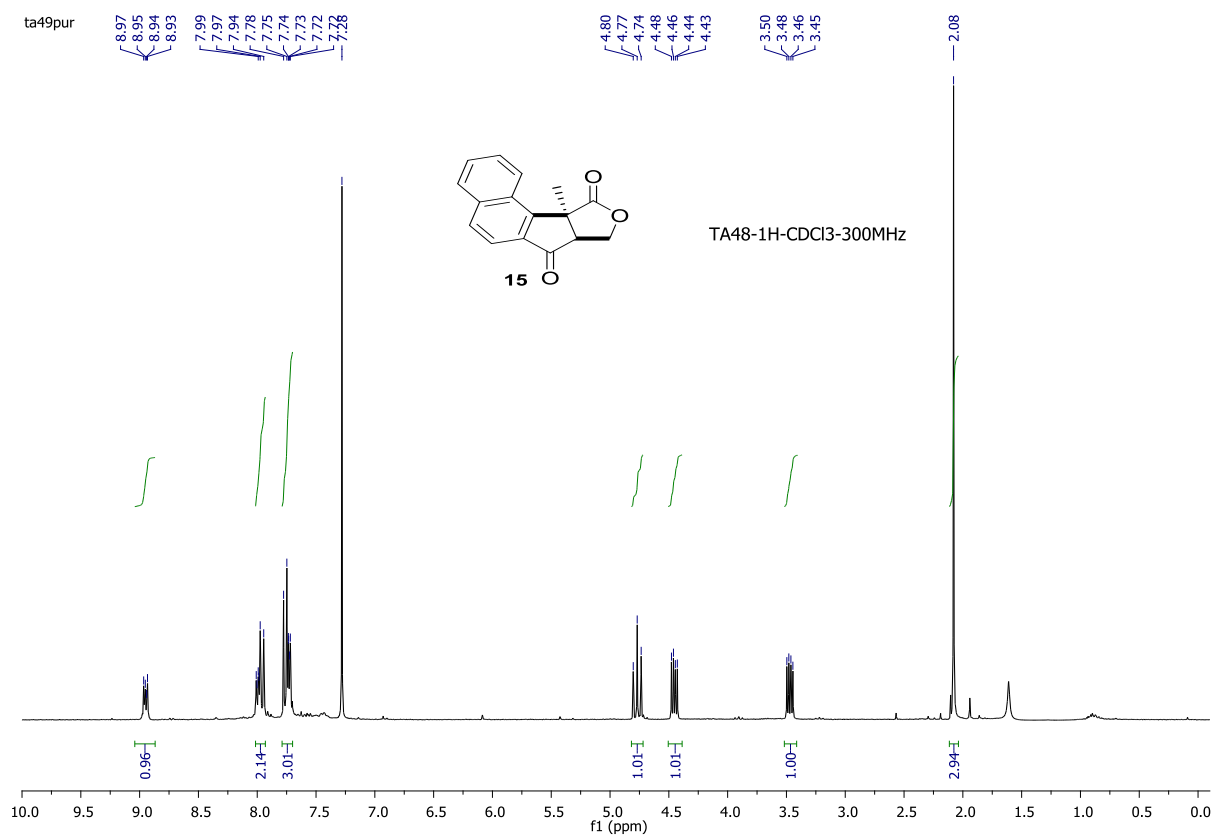
¹³C-NMR Spectrum of Compound 5



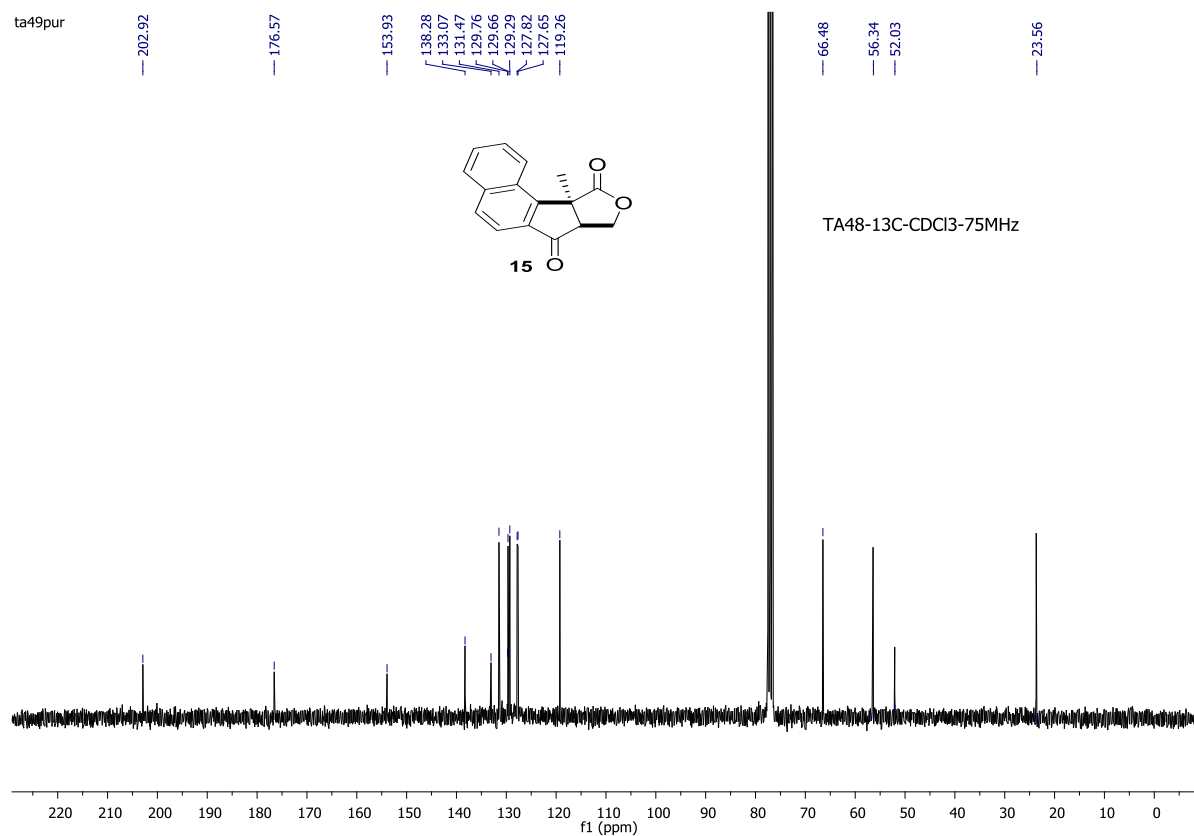
¹H-NMR Spectrum of Compound **4**



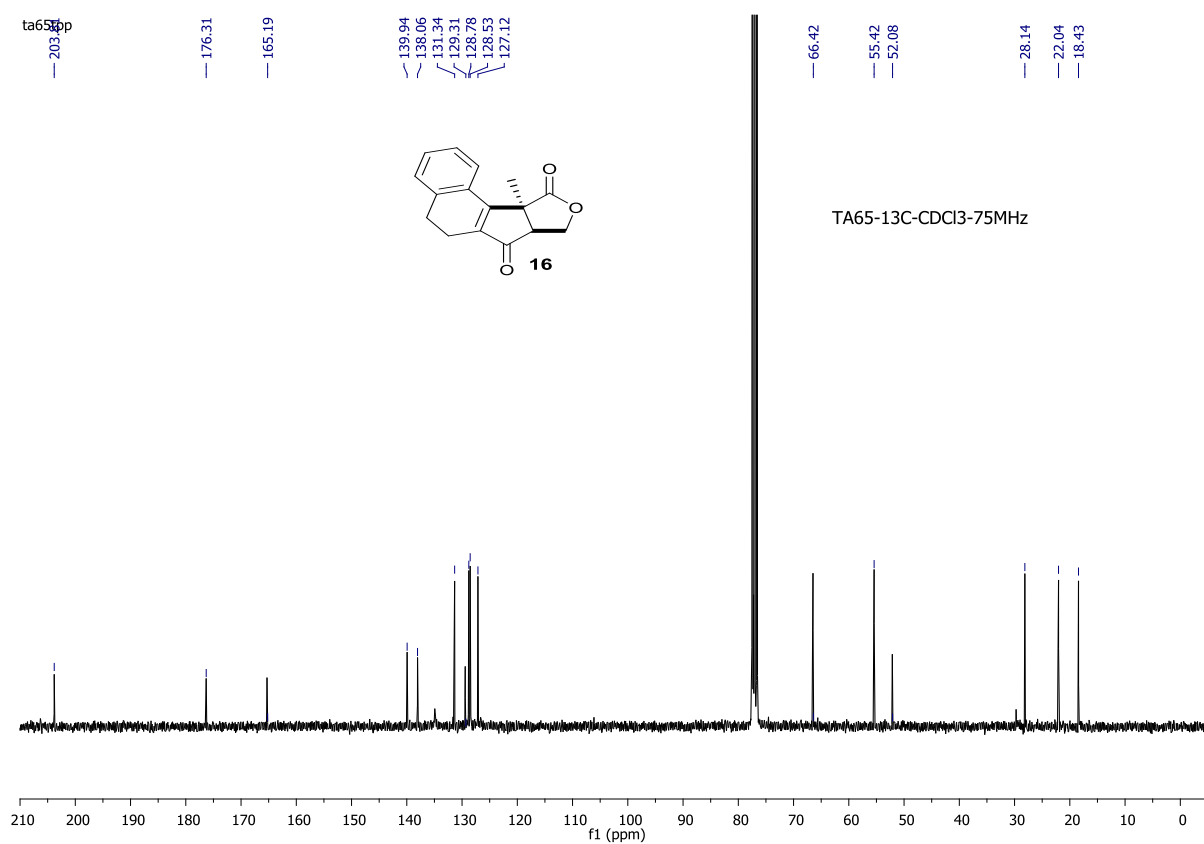
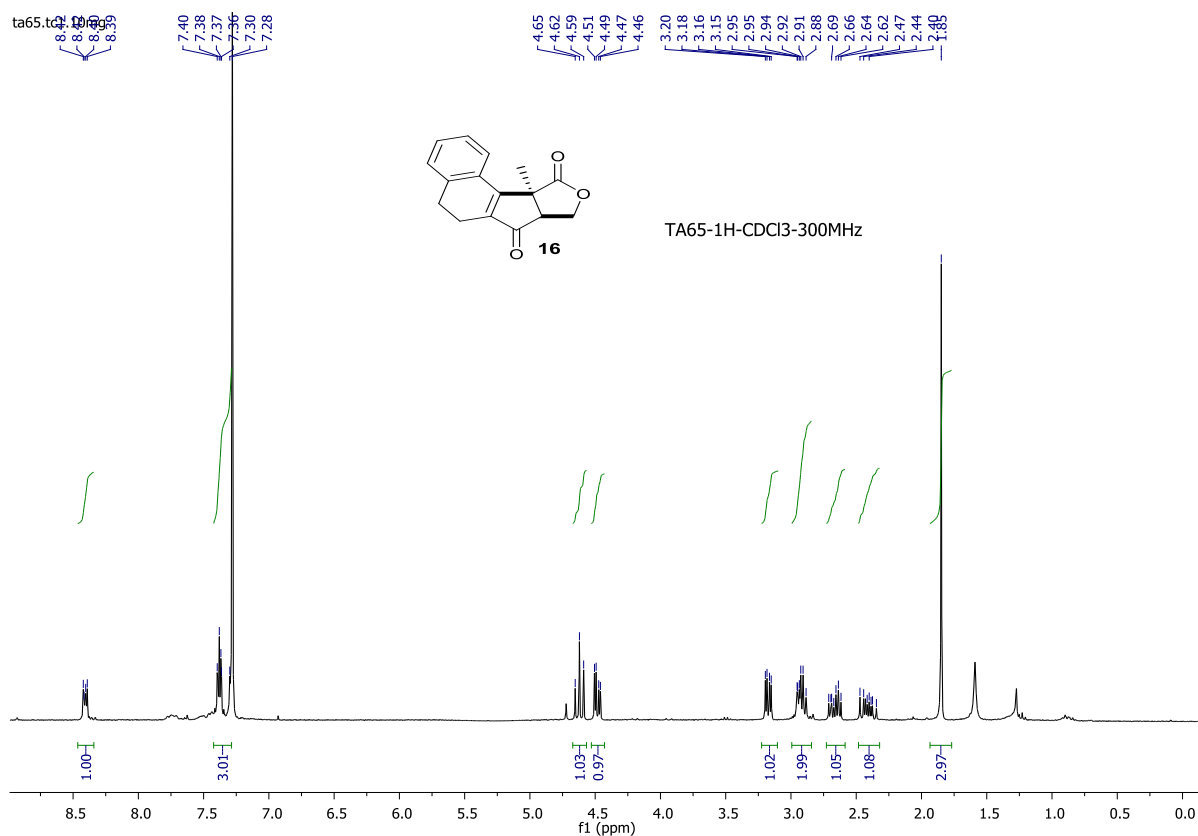
¹³C-NMR Spectrum of Compound **4**



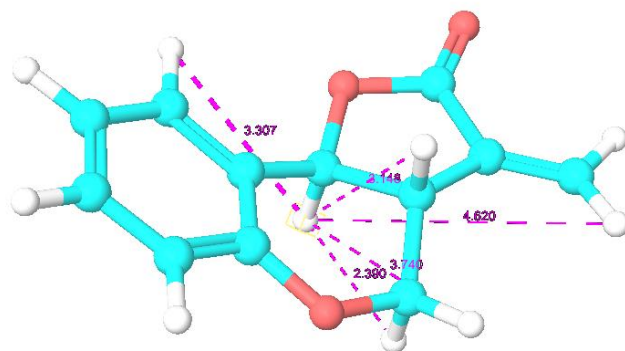
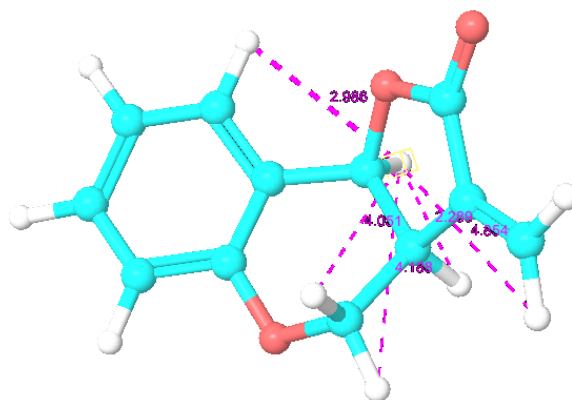
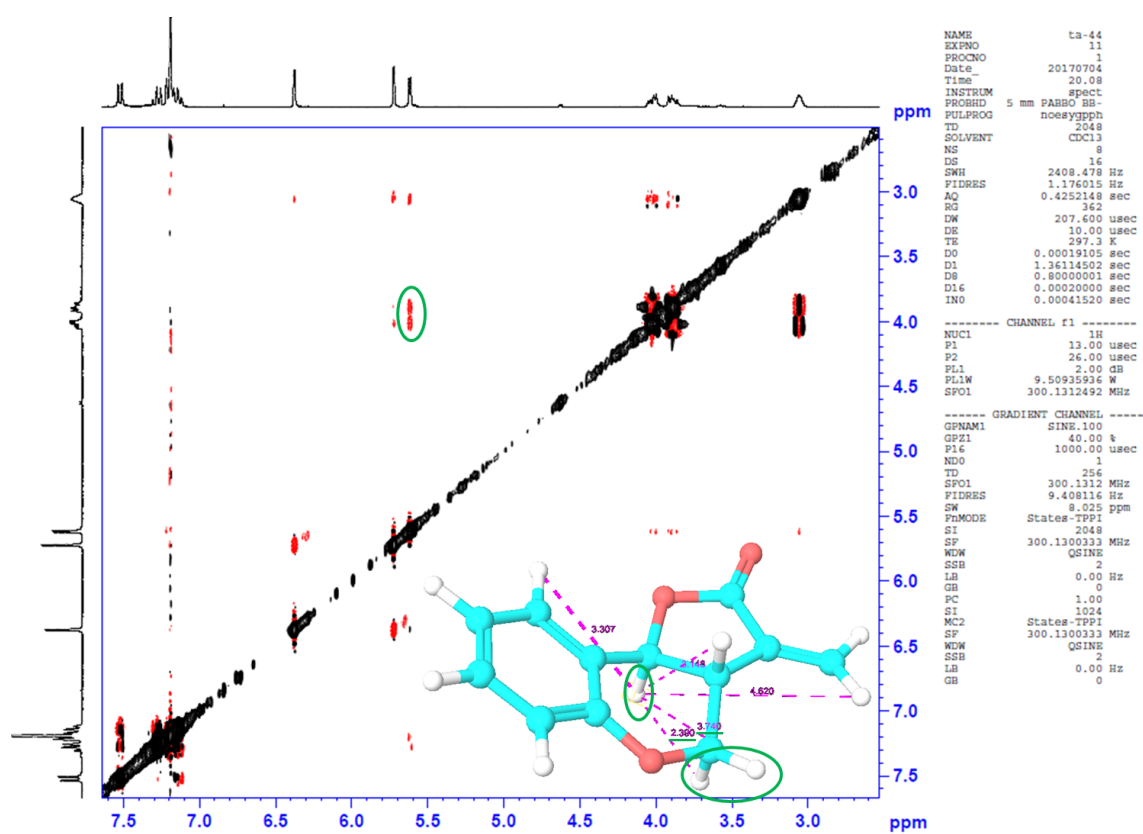
¹H-NMR Spectrum of Compound **15**



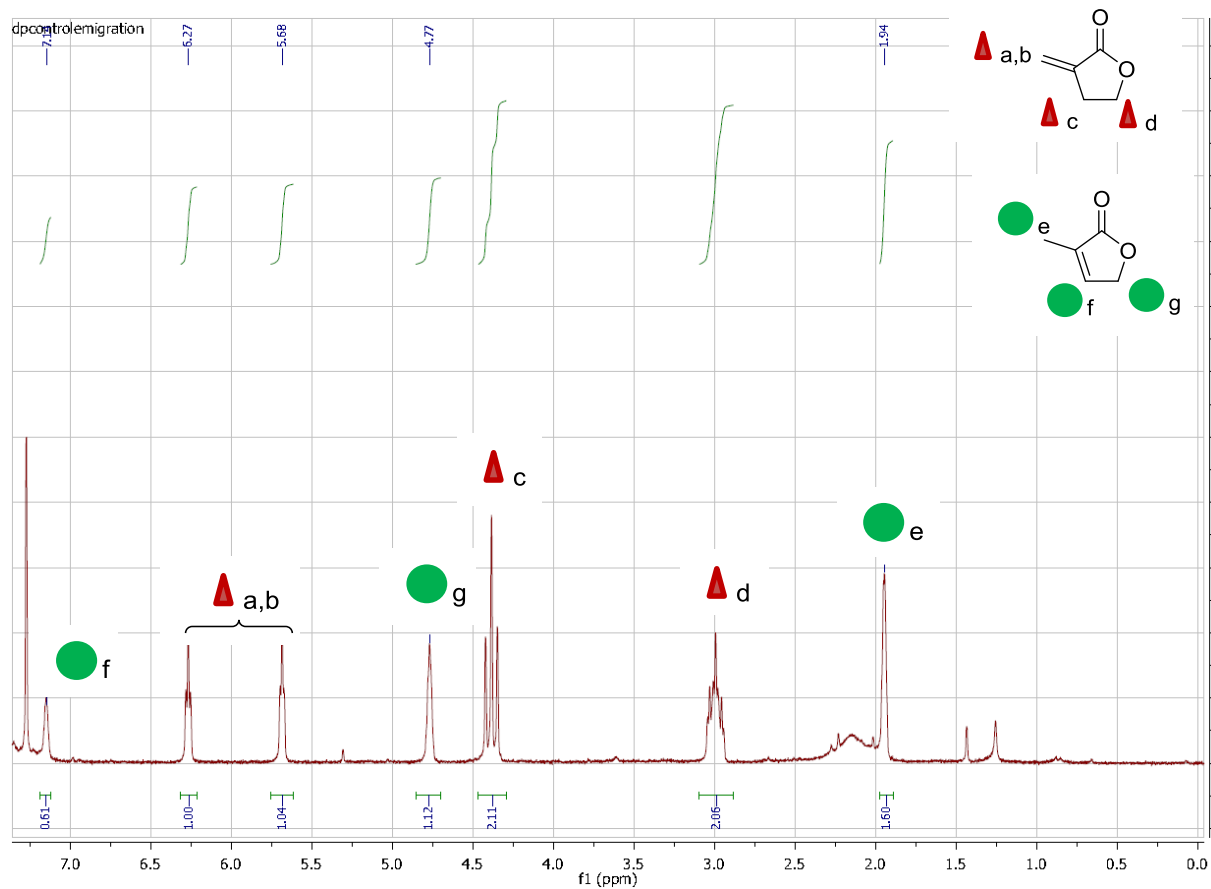
¹³C-NMR Spectrum of Compound **15**



10. Noesy experiments: compound 4



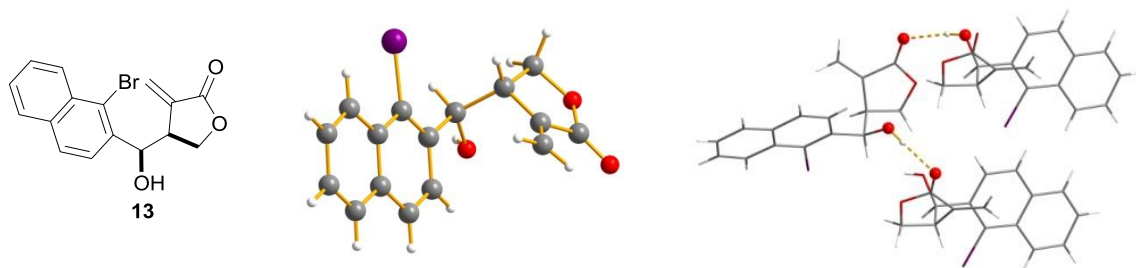
11. Control experiment : olefin migration



Chemical shifts in agreement with Jefford, C.W.; Rossier, J.-C.; Boukouvalas, J.; Sledeski, A.W.; Huang, P.-Z. A concise synthesis of siphonodictidine. *J. Nat. Prod.* **2004**, *67*, 1383–1386. DOI: 10.1021/np0400860.

12. X-ray crystal structure for lactone 12 and 16

Structure of 12 CCDC 1565162



Structure of 16 CCDC 1565163

