Supplementary Information

Functionalized Dienes: A New Series of Potential Agents for the Treatment of Alzheimer's Disease

Aldo S. Oliveira, *,[a] *Lidiane Meier,*[a] *Eduardo Zapp,*[a] *Daniela Brondani,*[a] *Inês M. C. Brighente*[b] *and Marcus M. Sá*[b]

[a]*Departamento de Ciências Exatas e Educação, Universidade Federal de Santa Catarina (UFSC), 89036-004 Blumenau-SC, Brazil*

[b]*Departamento de Química, Universidade Federal de Santa Catarina (UFSC), 88040-900 Florianópolis-SC, Brazil*

General considerations

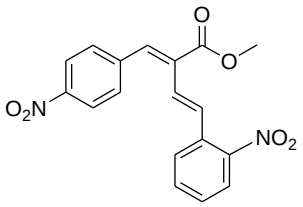
All chemicals were of reagent grade and were used as received. Melting points were determined using a hot plate apparatus and are uncorrected. Infrared spectra were acquired with a FTIR spectrometer (range 4000-400 cm^{-1}) using KBr for solids and film for liquid samples. Elemental analyses were conducted in a CHNS microanalyzer and the analytical results were within ± 0.4% of the theoretical values for all compounds. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra (fully decoupled) were recorded at 100 MHz. Splitting patterns are designated as s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), t (triplet), or m (multiplet). Coupling constants (*J*) are measured in hertz (Hz). Chemical shifts were recorded in parts *per* million (ppm, δ) relative to solvent ($CDCl_3$ at 7.26 ppm for ^{1}H NMR, and $CDCl_3$ at 77.16 ppm for ^{13}C NMR) as the internal standard. Column chromatography was performed using silica gel (70-230 mesh) and hexane/ethyl acetate as the eluent. Thin layer chromatography analysis was performed on silica gel plates, using a UV lamp for visualization.

General procedure for the preparation of dienes **1**[1]

To a stirred mixture containing phosphonium salt **2** (1.0 mmol), and a given aldehyde (1.0 mmol) in DMSO (2.2 mL), it was added a solution of $NaHCO_3$ (5.0 mmol) in H_2O (5.0 mL) and the reaction mixture was stirred at 25 °C for 24-45 h (see below). Next, the reaction was quenched with the addition of 1 M HCl, the aqueous mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed twice with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. In most cases, the crude product was purified by simple trituration with 2-propanol (or crystallization from the same solvent) to give pure (*E*,*E*)-dienes. Purification by column chromatography on silica gel (9:1 hexane/EtOAc) also furnished dienes **1** in comparable yields and purity.

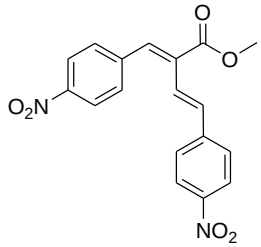
*e-mail: aldo.sena@ufsc.br

(1*E*,3*E*)-2-Methoxycarbonyl-4-(4-nitrophenyl)-1-(2-nitrophenyl)-1,3-butadiene (**1a**)



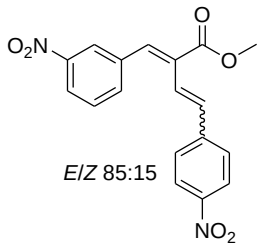
24 h, yellow solid; mp: 174.5-175.0 °C; IR (KBr) ν_{max} / cm^{-1} 3101, 3033, 2956, 1713, 1603, 1588, 1526, 1513, 1343, 1252, 1133, 852, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H, CH_3), 6.84 (dd, *J* 16.2, 1.2 Hz, 1H, HC), 7.42-7.61 (m, 4H, HAr), 7.70 (s, 1H, HC), 7.71 (d, *J* 16.2 Hz, 1H, HC), 7.98 (dd, *J* 8.0, 1.2 Hz, 1H, H_{Ar}), 8.27 (d, *J* 8.6 Hz, 2H, HAr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9 (CH_3), 124.1 (2 × CH), 125.1 (CH), 125.2 (CH), 128.4 (CH), 129.1 (CH), 130.9 (2 × CH), 132.6 (CH), 132.7 (C), 132.9 (C), 133.5 (CH), 138.0 (CH), 141.8 (C), 147.8 (C), 148.3 (C), 167.0 (C). Anal. calcd. for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found: C, 61.00; H, 4.20; N, 7.90.

(1*E*,3*E*)-2-Methoxycarbonyl-1,4-*bis*(4-nitrophenyl)-1,3-butadiene (**1b**)



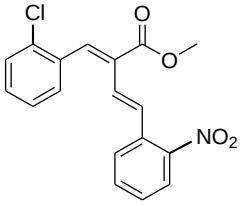
24 h, yellow solid; mp: 198.0-200.0 °C; IR (KBr) ν_{max} / cm^{-1} 3107, 2959, 1723, 1591, 1513, 1344, 1248, 1126, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H, CH_3), 7.06 (d, *J* 16.4 Hz, 1H, HC), 7.43 (d, *J* 16.4 Hz, 1H, HC), 7.52 (d, *J* 8.8 Hz, 2H, H_{Ar}), 7.59 (d, *J* 8.8 Hz, 2H, H_{Ar}), 7.71 (s, 1H, HC), 8.20 (d, *J* 8.8 Hz, 2H, H_{Ar}), 8.30 (d, *J* 8.8 Hz, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9 (CH_3), 124.1 (2 × CH), 124.4 (2 × CH), 124.7 (CH), 127.6 (2 × CH), 130.9 (2 × CH), 132.2 (C), 134.7 (CH), 138.4 (CH), 141.7 (C), 143.3 (C), 147.6 (C), 147.9 (C), 166.9 (C). Anal. calcd. for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.65; H, 4.32; N, 7.77.

(1*E*,3*E*)-2-Methoxycarbonyl-1-(3-nitrophenyl)-4-(4-nitrophenyl)-1,3-butadiene (**1c**)



30 h, yellow solid (obtained as a 85:15 mixture of (*E*,*E*):(*E*,*Z*) isomers); mp: 160-164 °C; IR (KBr) ν_{max} / cm^{-1} 3057, 2954, 1722, 1595, 1526, 1509, 1345, 1250, 1126, 836, 743; ^{1}H NMR (400 MHz, $CDCl_3$) [data for major (*E*,*E*)-diene **1c**] δ 3.94 (s, 3H, CH_3), 7.07 (dd, *J* 16.4, 1.0 Hz, 1H, HC), 7.43 (d, *J* 16.4 Hz, 1H, HC), 7.53 (d, *J* 9.0 Hz, 2H, H_{Ar}), 7.63 (t, *J* 8.0 Hz, 1H, H_{Ar}), 7.71 (s, 1H, HC), 7.74 (d, *J* 8.0 Hz, 1H, H_{Ar}), 8.19 (d, *J* 9.0 Hz, 2H, H_{Ar}), 8.23-8.33 (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) [data for major (*E*,*E*)-diene **1c**] δ 52.8 (CH_3), 123.9 (CH), 124.4 (2 × CH), 124.6 (CH), 124.8 (CH), 127.5 (2 × CH), 130.0 (CH), 131.6 (C), 134.5 (CH), 135.8 (CH), 136.9 (C), 138.2 (CH), 143.4 (C), 147.5 (C), 148.7 (C), 166.9 (C). Anal. calcd. for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found: C, 61.32; H, 3.75; N, 7.84.

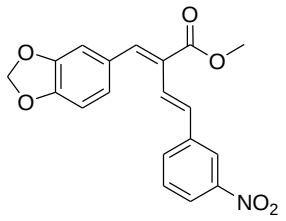
(1*E*,3*E*)-1-(2-Chlorophenyl)-2-methoxycarbonyl-4-(2-nitrophenyl)-1,3-butadiene (**1d**)



30 h, yellow solid; mp: 112.5-113.5 °C; IR (KBr) ν_{max} / cm^{-1} 3069, 2952, 1717, 1605, 1566, 1515, 1342, 1243, 1118, 776, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H, CH_3), 6.80 (dd, *J* 16.2, 1.0 Hz, 1H, HC), 7.26-7.41 (m, 4H, H_{Ar}), 7.45-7.53 (m, 3H, H_{Ar}), 7.71 (d, *J* 16.2 Hz, 1H, HC), 7.79 (s, 1H, CH), 7.93 (d, *J* 8.0 Hz, 1H, HAr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7 (CH_3), 124.9 (CH),

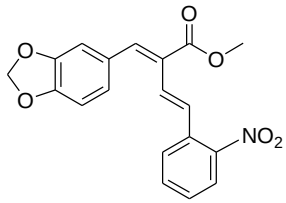
126.1 (CH), 126.8 (CH), 128.5 (CH), 128.6 (CH), 130.1 (CH), 130.4 (CH), 130.9 (CH), 131.0 (C), 131.7 (CH), 133.3 (CH), 133.9 (C), 134.6 (C), 138.2 (C), 138.3 (CH), 148.3 (C), 167.3 (C). Anal. calcd. for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.07. Found: C, 62.96; H, 3.87; N, 4.38.

(1*E*,3*E*)-2-Methoxycarbonyl-1-(3,4-methylenedio-xyphenyl)-4-(3-nitrophenyl)-1,3-butadiene (**1e**)



40 h, yellow solid; mp: 129.0-130.5 °C; IR (KBr) ν_{max} / cm^{-1} 3085, 2950, 1709, 1583, 1528, 1490, 1352, 1237, 1120, 1038, 930, 823, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, CH_3), 6.04 (s, 2H, CH_2), 6.88 (d, *J* 8.0 Hz, 1H, H_{Ar}), 6.94-6.98 (m, 2H, H_{Ar}), 7.11 (dd, *J* 16.2, 1.0 Hz, 1H, HC), 7.35 (d, *J* 16.2 Hz, 1H, HC), 7.50 (t, *J* 8.0 Hz, 1H, H_{Ar}), 7.64 (s, 1H, HC), 7.72 (d, *J* 8.0 Hz, 1H, H_{Ar}), 8.08-8.27 (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4 (CH_3), 101.8 (CH_2), 108.8 (CH), 110.1 (CH), 121.3 (CH), 122.5 (CH), 124.9 (CH), 125.7 (CH), 127.5 (C), 129.4 (C), 129.8 (CH), 132.3 (CH), 132.5 (CH), 139.6 (C), 141.3 (CH), 148.2 (C), 148.9 (2 × C), 167.8 (C). Anal. calcd. for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.21; H, 4.52; N, 4.03.

(1*E*,3*E*)-2-Methoxycarbonyl-1-(3,4-methylenedio-xyphenyl)-4-(2-nitrophenyl)-1,3-butadiene (**1f**)



45 h, yellow solid; mp: 100.5-101.0 °C; IR (KBr) ν_{max} / cm^{-1} 3096, 2957, 1702, 1605, 1589, 1517, 1507, 1352, 1240, 1036, 925, 804, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H, CH_3), 6.01 (s, 2H, CH_2), 6.85 (d, *J* 8.5 Hz, 1H, H_{Ar}), 6.92-6.98 (m, 3H, HC and 2H_{Ar}), 7.39 (ddd, *J* 8.0, 7.5, 1.3 Hz, 1H, H_{Ar}), 7.54-7.68 (m, 4H, 2HC and 2H_{Ar}), 7.94 (dd, *J* 8.0, 1.3 Hz, 1H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5 (CH_3), 101.7 (CH_2), 108.8 (CH), 110.2 (CH), 125.0 (CH), 125.8 (CH), 126.7 (CH), 127.9 (C), 128.4 (CH), 129.4 (C), 130.1 (CH), 133.3 (CH), 133.5 (C), 141.4 (CH), 141.5 (CH), 148.1 (C), 148.3 (C), 148.8 (C), 167.8 (C). Anal. calcd. for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.27; H, 4.53; N, 3.83.

Reference

1. Sá, M. M.; Meier, L.; *Heteroat. Chem.* **2013**, *24*, 384.

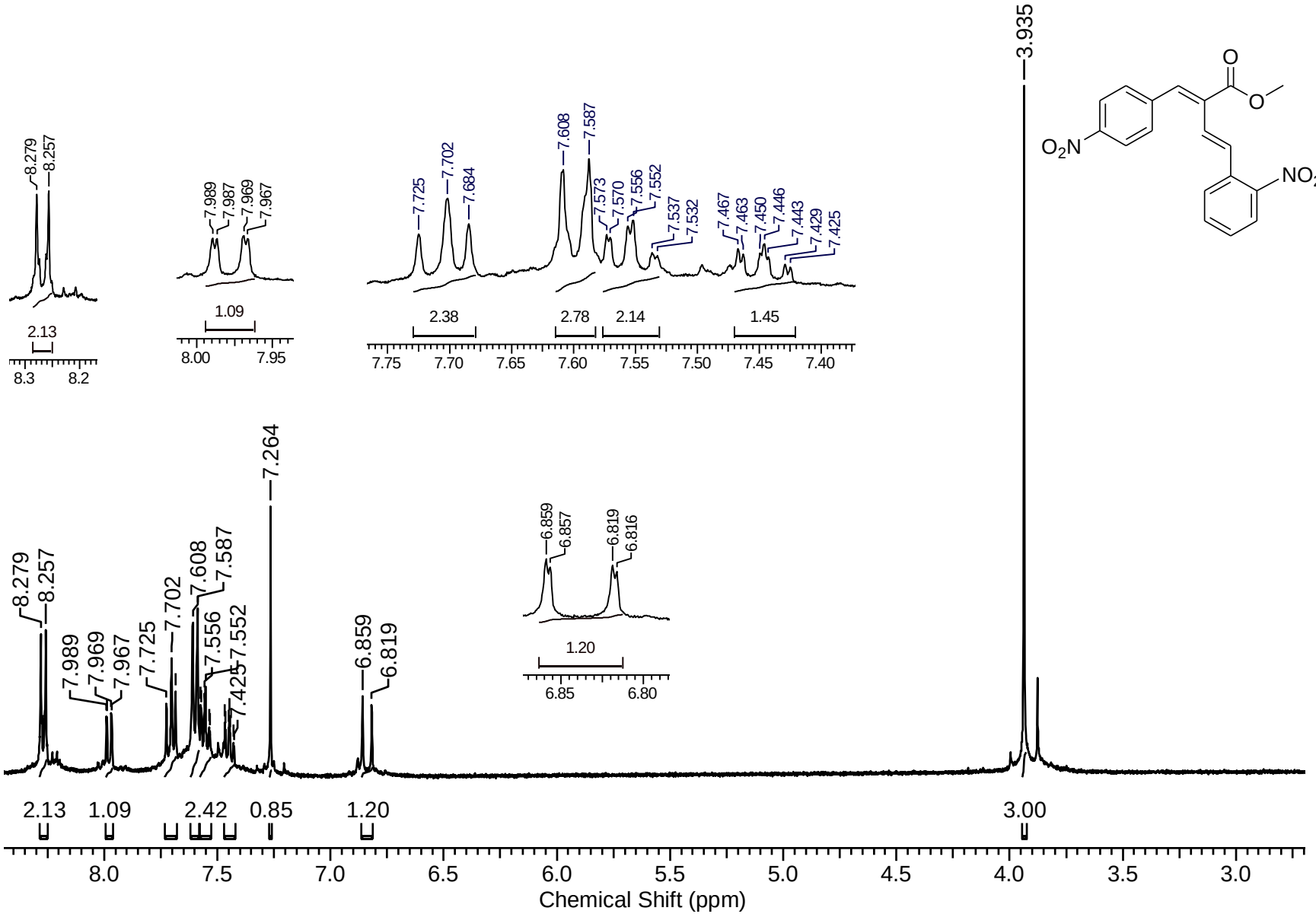


Figure S1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-4-(4-nitrophenyl)-1-(2-nitrophenyl)-1,3-butadiene (**1a**).

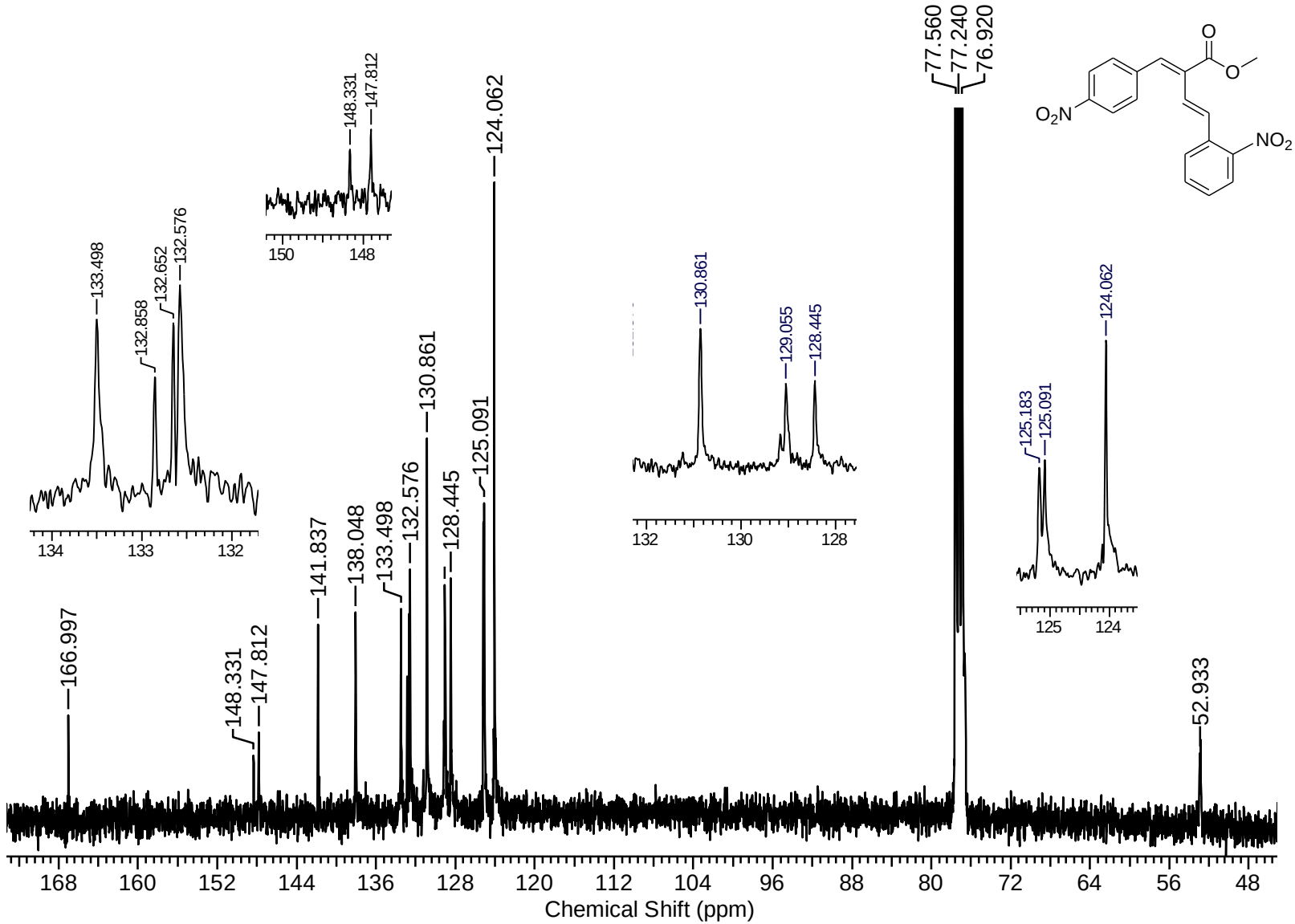


Figure S2. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-4-(4-nitrophenyl)-1-(2-nitrophenyl)-1,3-butadiene (**1a**).

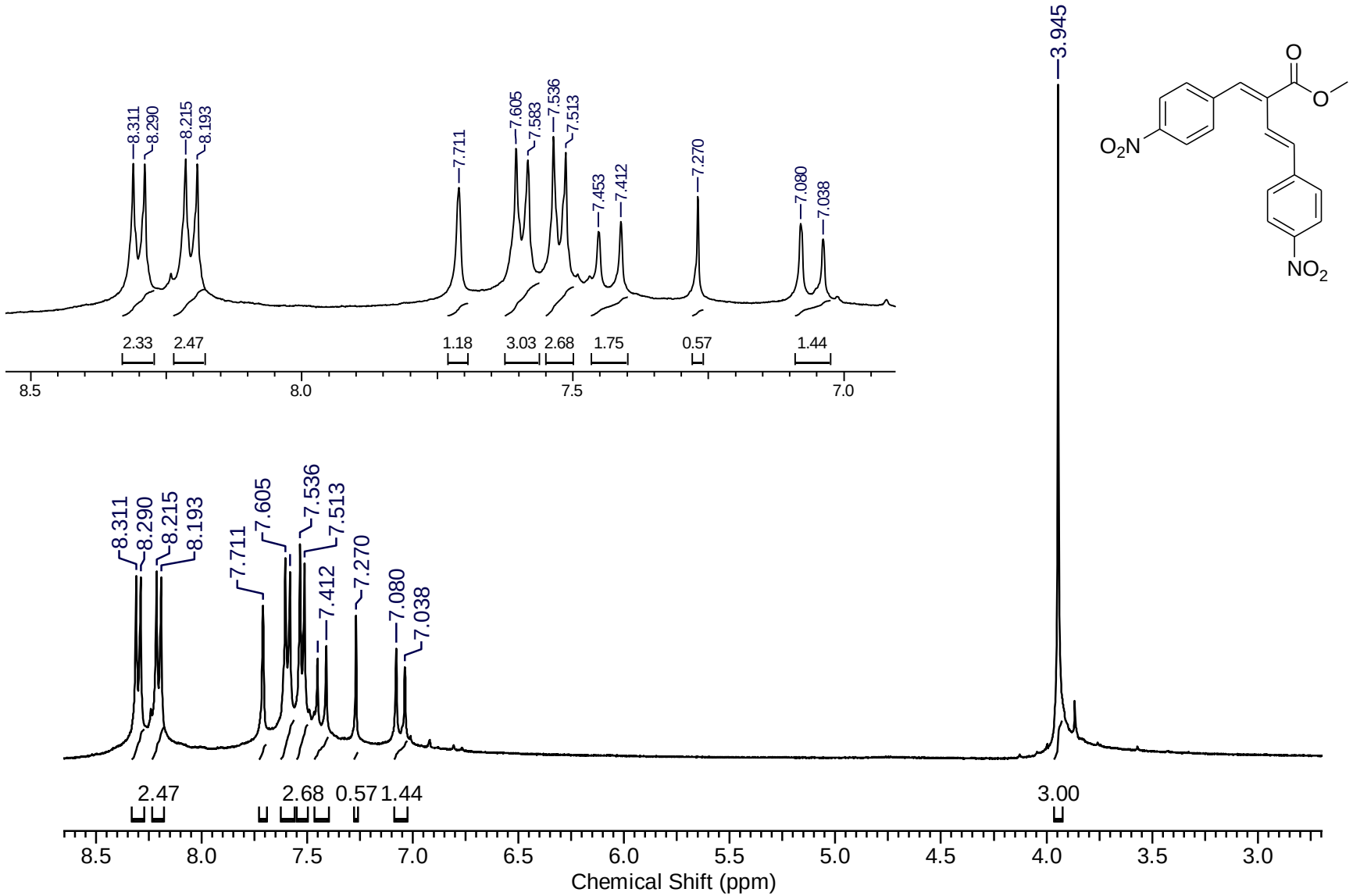


Figure S3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-1,4-*bis*(4-nitrophenyl)-1,3-butadiene (**1b**).

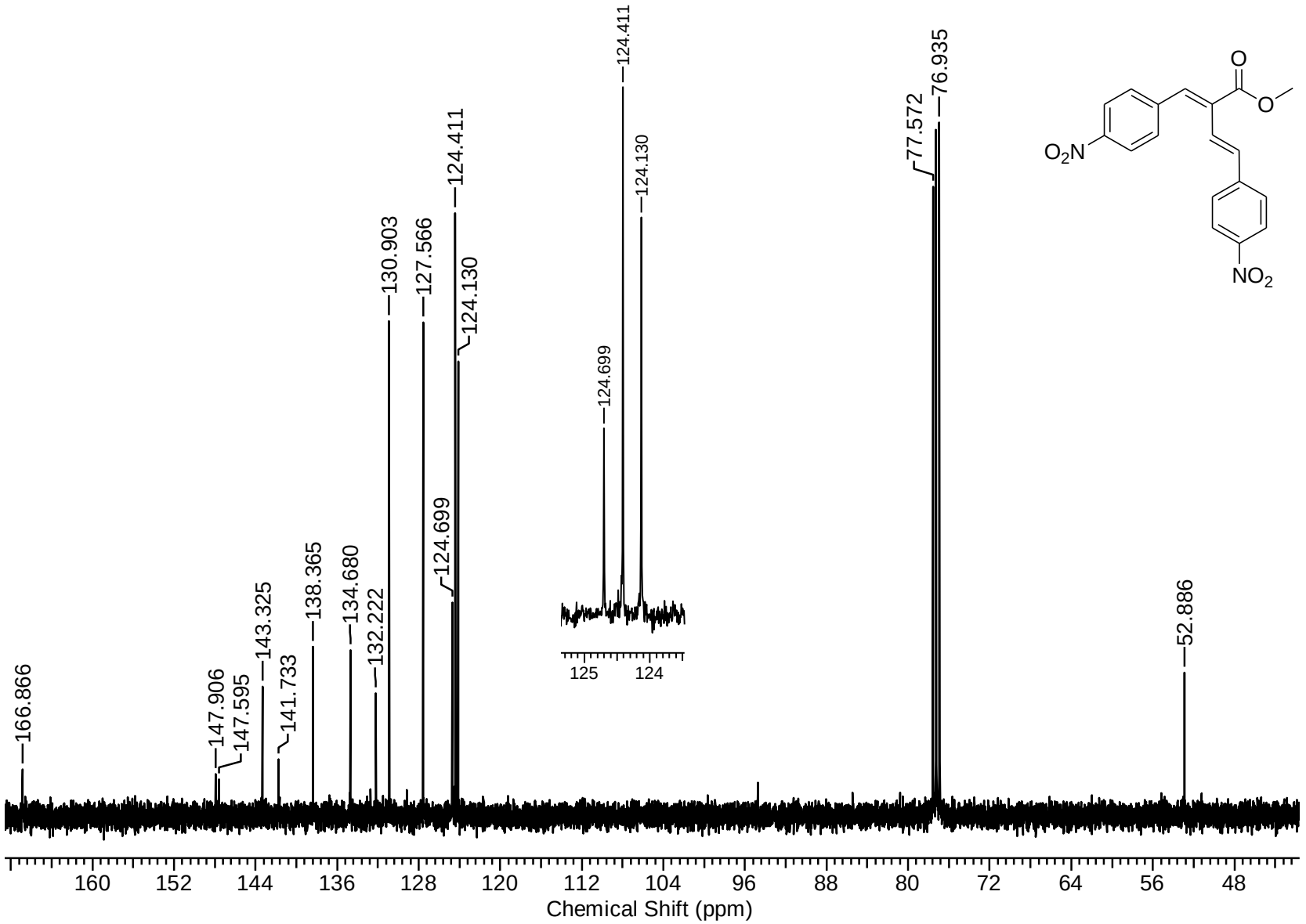


Figure S4. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-1,4-*bis*(4-nitrophenyl)-1,3-butadiene (**1b**).

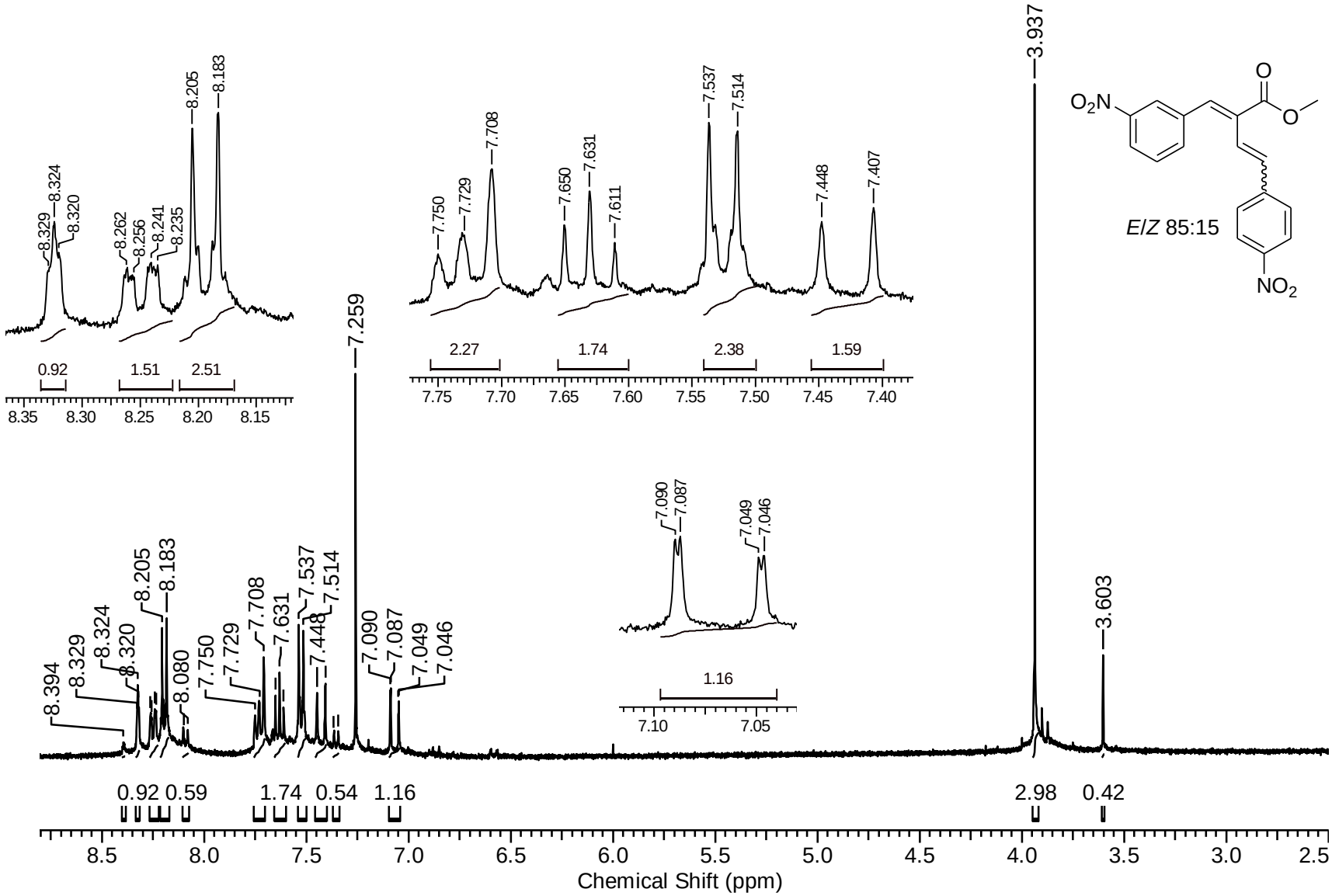


Figure S5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-1-(3-nitrophenyl)-4-(4-nitrophenyl)-1,3-butadiene (**1c**).

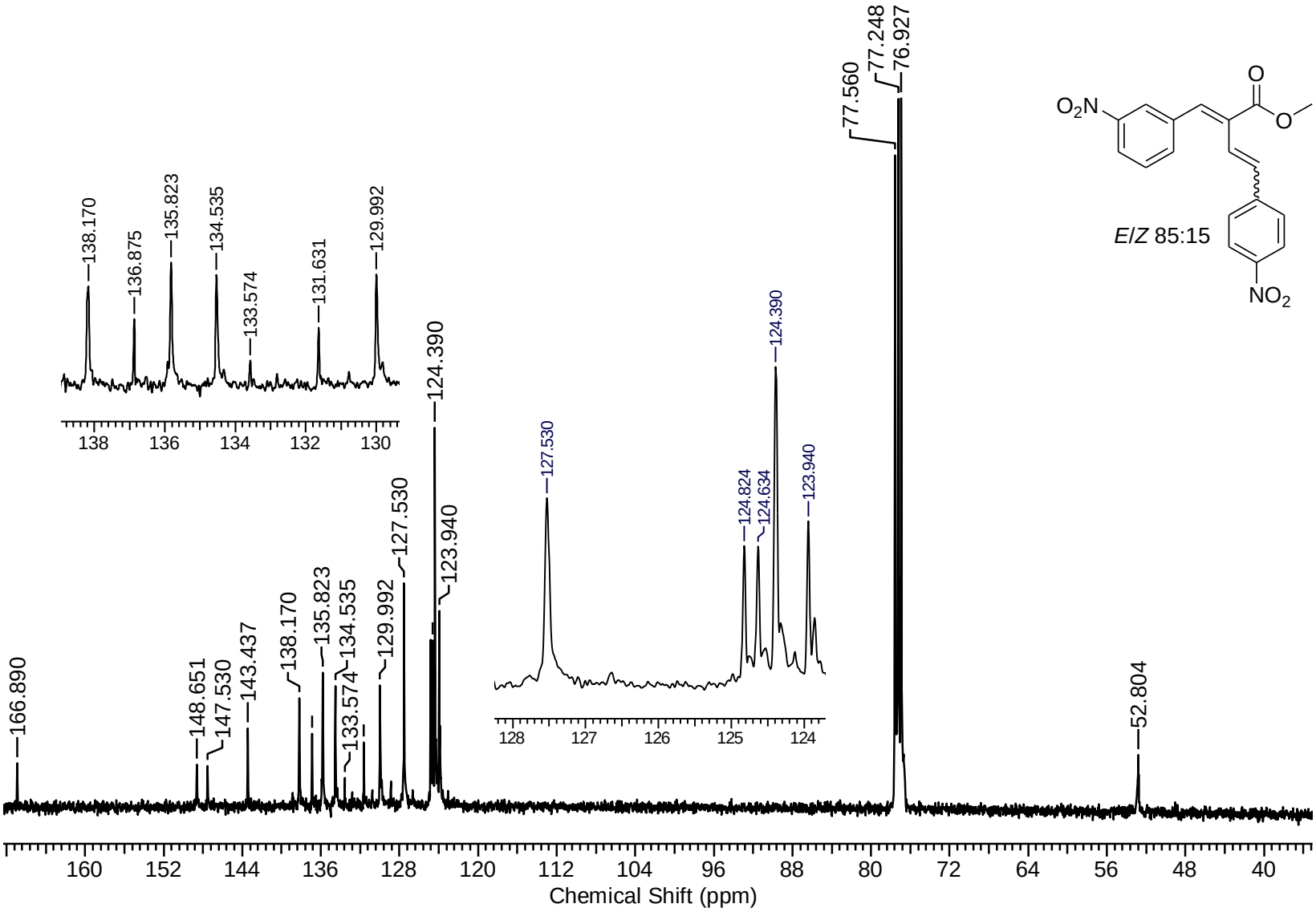


Figure S6. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-1-(3-nitrophenyl)-4-(4-nitrophenyl)-1,3-butadiene (**1c**).

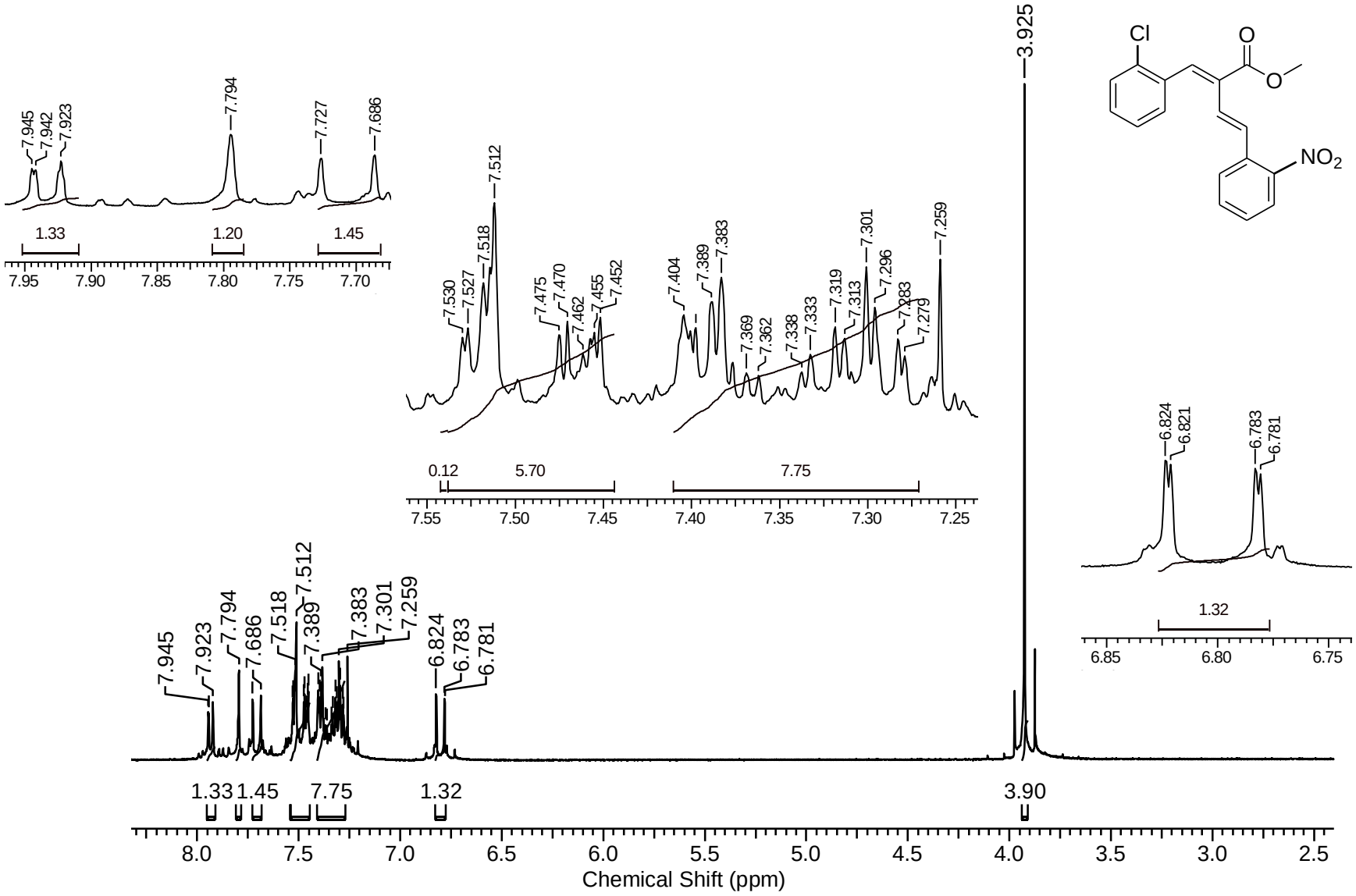


Figure S7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (1*E*,3*E*)-1-(2-chlorophenyl)-2-methoxycarbonyl-4-(2-nitrophenyl)-1,3-butadiene (**1d**).

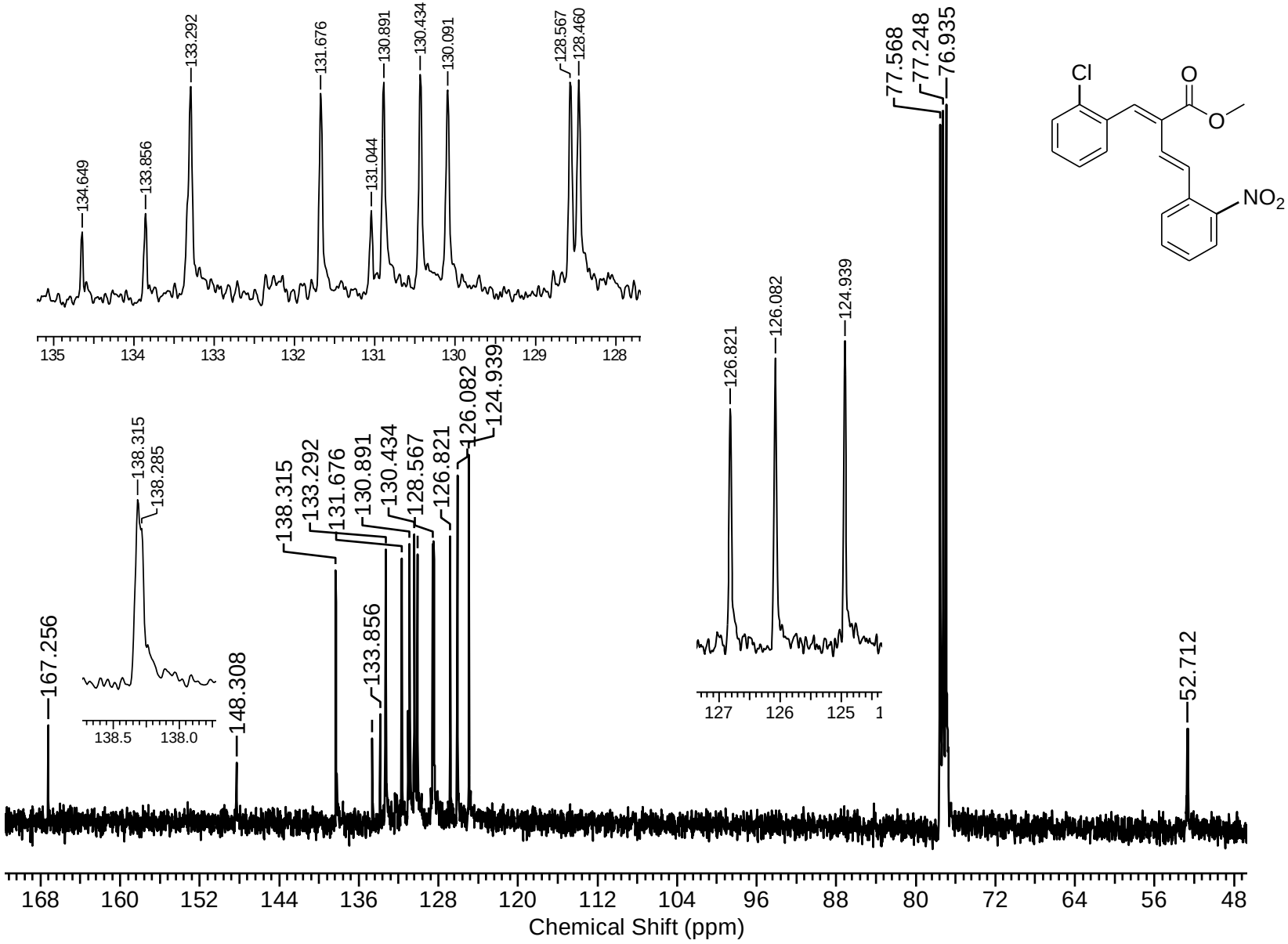


Figure S8. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (1*E*,3*E*)-1-(2-chlorophenyl)-2-methoxycarbonyl-4-(2-nitrophenyl)-1,3-butadiene (**1d**).

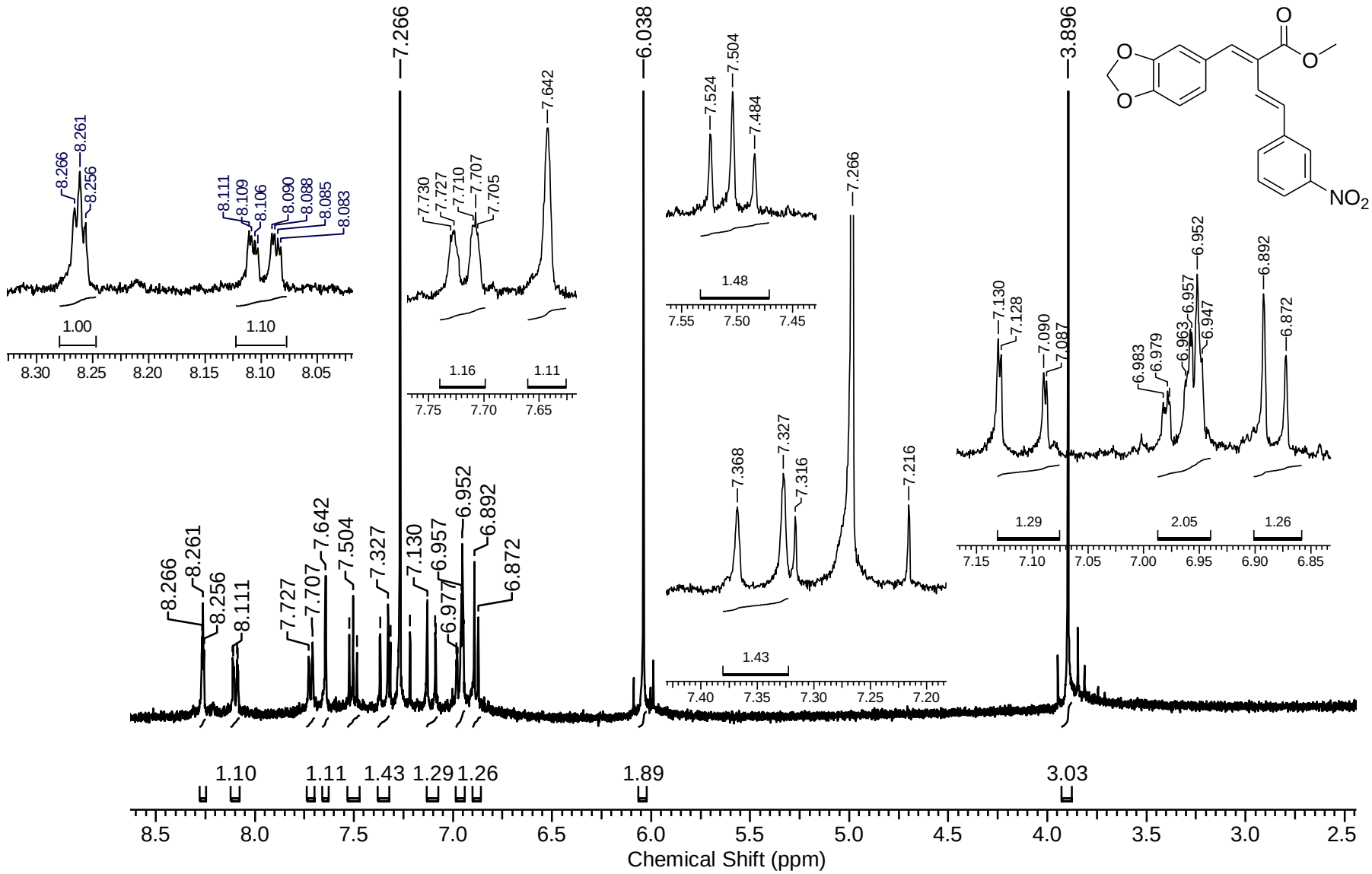


Figure S9. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-1-(3,4-methylenedioxyphenyl)-4-(3-nitrophenyl)-1,3-butadiene (**1e**).

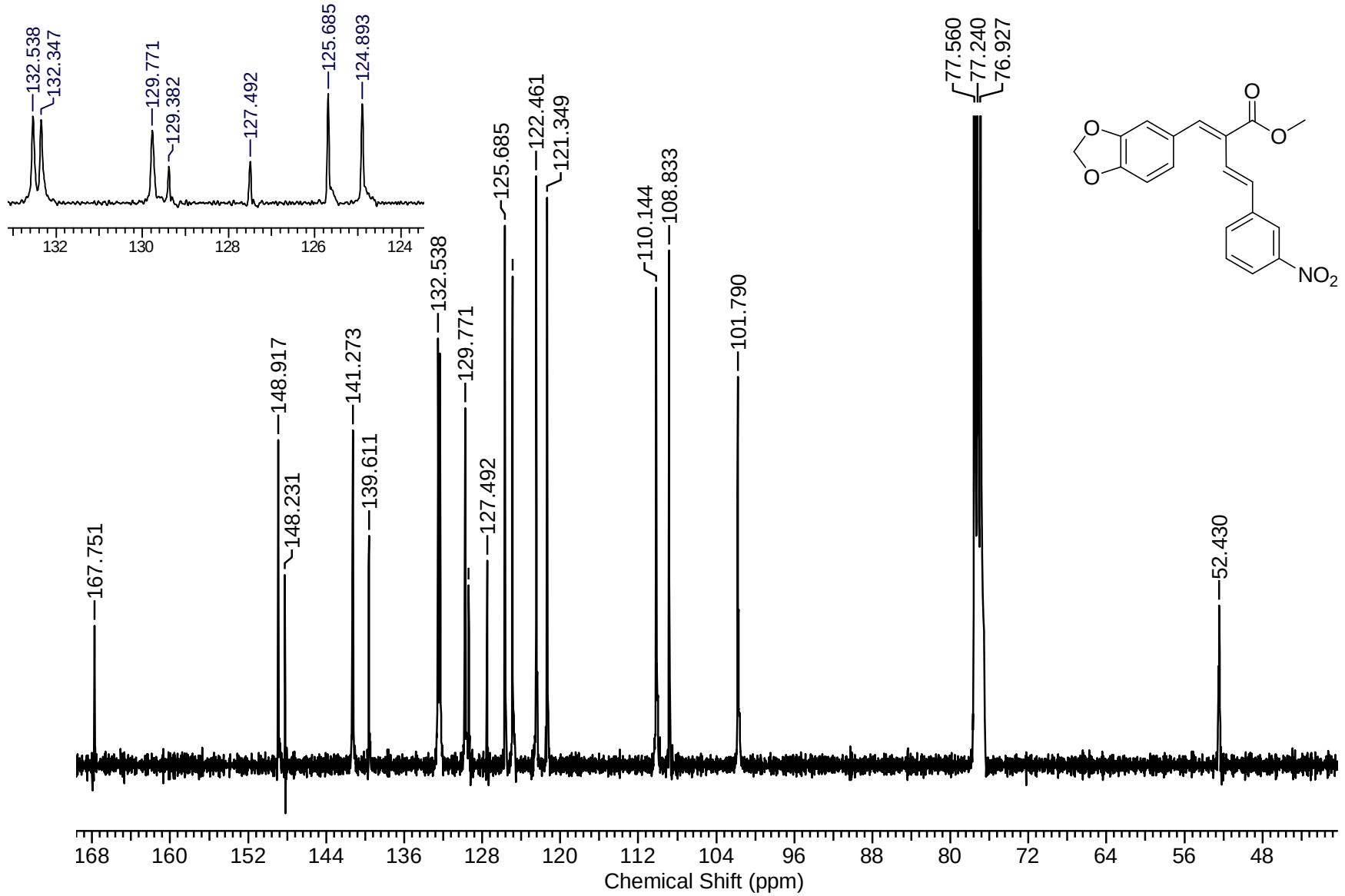


Figure S10. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-1-(3,4-methylenedioxyphenyl)-4-(3-nitrophenyl)-1,3-butadiene (**1e**).

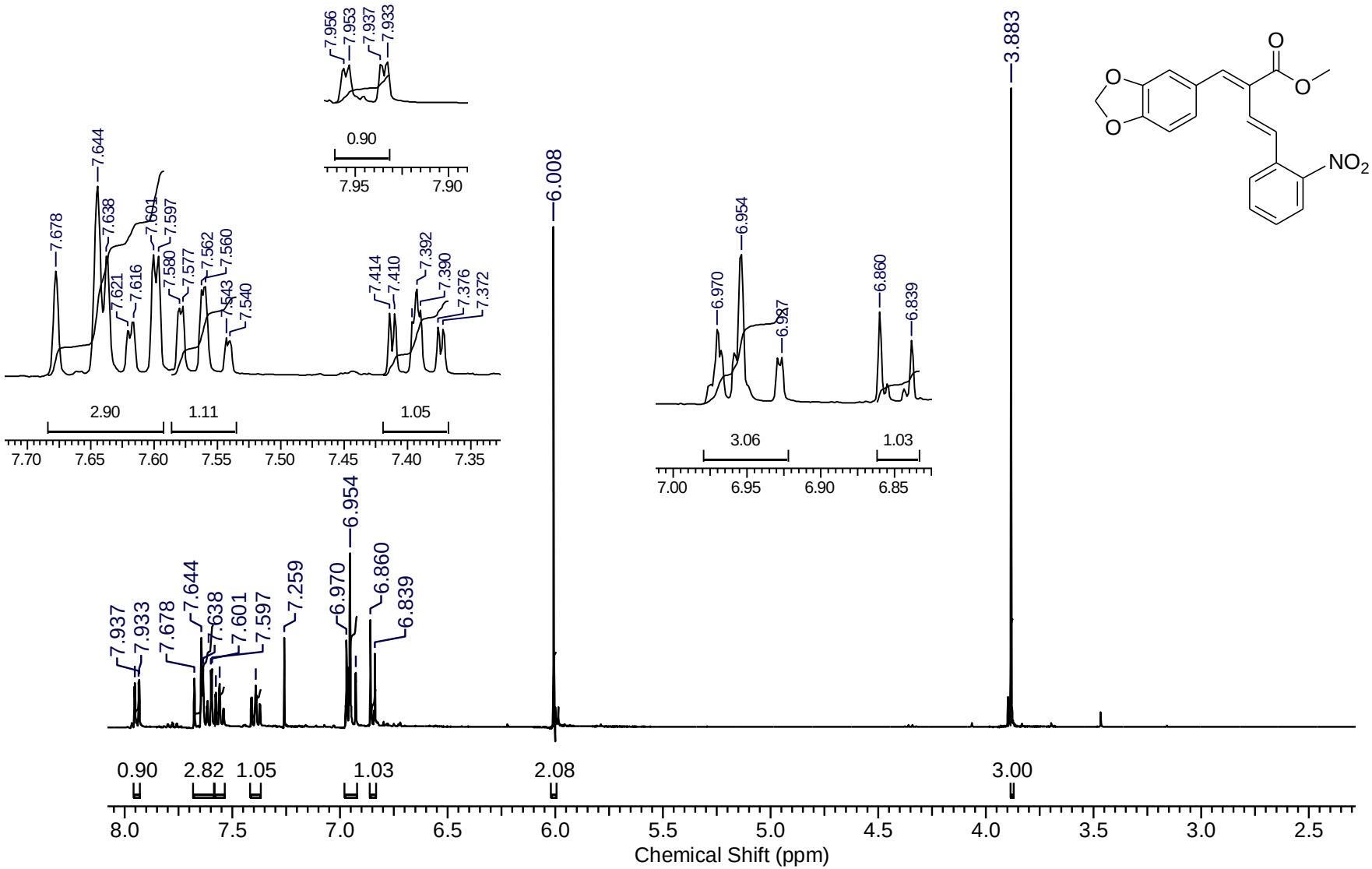


Figure S11. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-1-(3,4-methylenedioxyphenyl)-4-(2-nitrophenyl)-1,3-butadiene (**1f**).

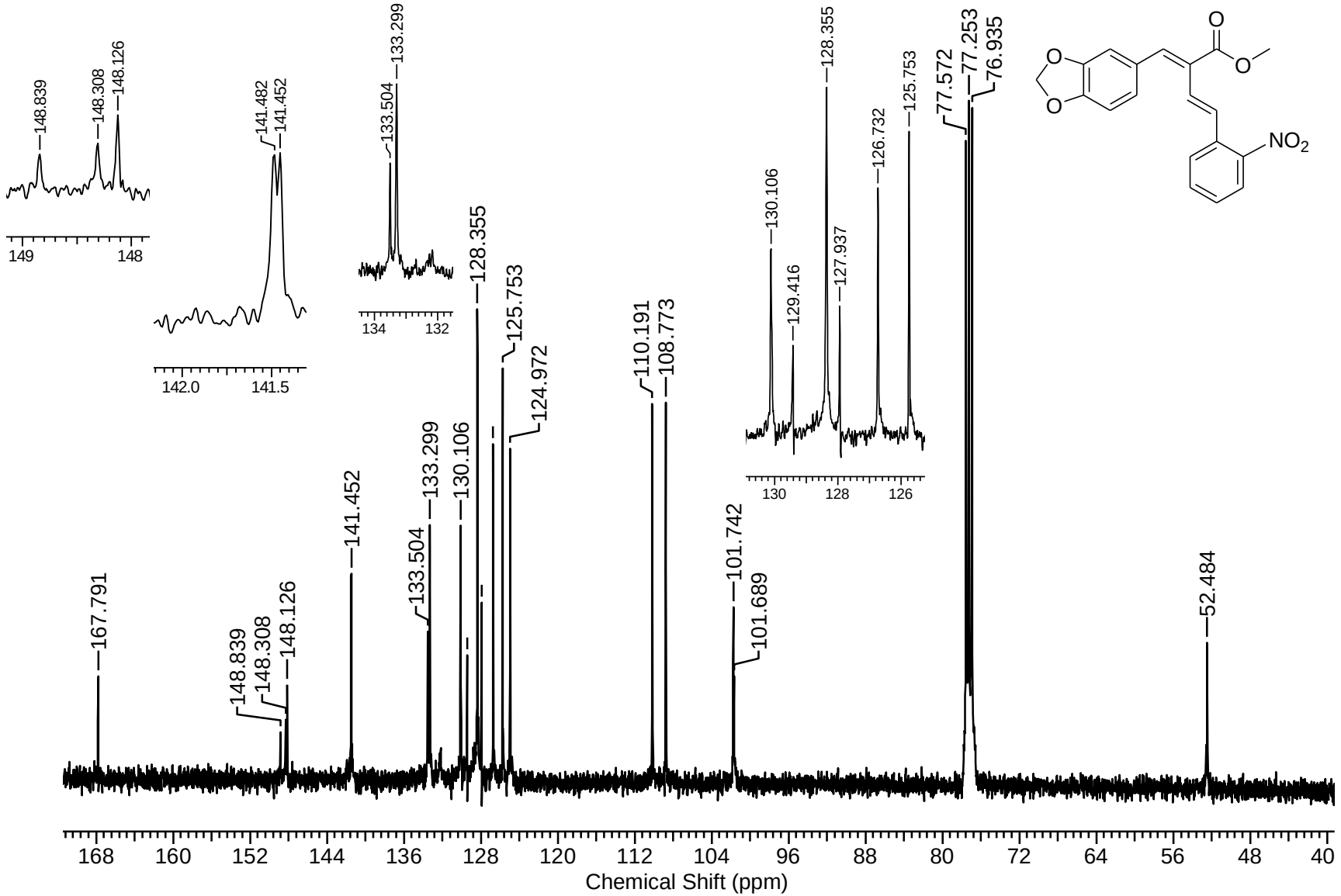


Figure S12. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (1*E*,3*E*)-2-methoxycarbonyl-1-(3,4-methylenedioxyphenyl)-4-(2-nitrophenyl)-1,3-butadiene (**1f**).