

Laccase-catalyzed oxidative phenolic coupling of vanillidene derivatives

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Electronic Supplementary Information

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1. General remarks

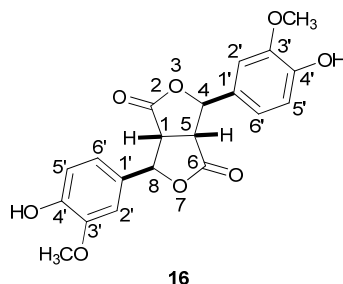
All commercially available reagents were used without further purification. Solvents used for extraction and purification were distilled prior to use. Reaction temperatures are reported as bath temperatures.

Melting points were obtained on a Büchi melting point apparatus B-545 with open capillary tubes and are uncorrected. IR spectra were measured on a Perkin Elmer *Spectrum One* (FT-IR spectrometer). UV/VIS spectra were recorded with a Varian Cary 50. ^1H and ^{13}C NMR spectra were recorded at 500 (125) and 300 (75) MHz on a Varian ^{Unity}Inova 500 MHz spectrometer and the chemical shifts were referenced to CDCl_3 ($\delta = 7.26$ ppm in ^1H NMR spectra and $\delta = 77.00$ in ^{13}C NMR spectra) and DMSO-d_6 ($\delta = 2.50$ ppm in ^1H NMR spectra and $\delta = 39.52$ in ^{13}C NMR spectra) as the solvents. HSQC-, HMBC-, HSQMBC- and COSY spectra were recorded on Varian ^{Unity}Inova spectrometers (500 MHz or 300 MHz). Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), m (multiplet), br (broad) and ov (overlapped). Low resolution impact mass spectra (EI-LRMS) and exact mass electron impact mass spectra (HRMS) were obtained at 70 eV on a Finnigan Mat 95 instrument. Gas-chromatography mass spectra (GC-MS) were done on a Thermo Polaris Q equipped with a Varian Trace GC Ultra and a column DB5 (TGC/50/5/10/280). ESI-MS spectra were measured on a Bruker Microtof Q. The intensities are reported as percentages relative to the base peak ($I = 100\%$).

Thin-layer chromatography (TLC) was performed on TLC silica gel 60 F₂₅₄ (Merck). Products were purified by column chromatography on silica gel MN 60, 0.063-0.200 mm (Macherey and Nagel) or by flash column chromatography on silica gel MN 60, 0.04-0.053 mm (Macherey and Nagel). Analytical HPLC was performed using a Knauer K-501 pump equipped with a Bischoff LAMBDA 1000 detector. The chiral HPLC column used was from Daicel Chemical Industries (Chiralpak IB; 250 mm x 4.6 mm; 5 μm)

Laccases from *Trametes versicolor* and *Agaricus bisporus* were from Sigma (EC 1.10.3.2). The pH of the buffer was adjusted using a pH 330/SET-1 pH-meter.

2. Oxidative dimerization of ferulic acid [(*E*)-1] using laccase as the catalyst



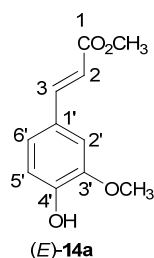
A solution of ferulic acid [(*E*)-1] (500 mg, 2.6 mmol) in DMSO (9 mL) was added to NaOAc buffer (430 mL, 0.1 M, pH 5.0). Laccase from *Trametes versicolor* (2.5 mg, 27 U) was added and the reaction mixture was stirred under air at room temperature for 2 h. The reaction mixture was acidified with 5M HCl (25 mL) and the solution was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic phases were dried over MgSO₄, filtered, and evaporated in *vacuo*. The crude product was purified by repeated crystallization from EtOAc/cyclohexane (2:1) to give 4-*cis*,8-*cis*-bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-2,6-dione (**16**) (80 mg, 0.21mmol, 16%) as a white solid. mp 199-200 °C (lit.,¹ 206-208 °C); UV λ_{max} (EtOH)/nm 235 and 281 (log ε/dm³ mol⁻¹ cm⁻¹ 4.19 and 3.88); IR (ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3017 (OH), 1764 (lactone), 1612 (arom. C=C), 1520 (arom. C=C), 1280 (arom. C-O), 861 (arom. C-H) and 826 (arom. C-H); ¹H NMR δ_H (300 MHz; DMSO-d₆) 3.80 (6H, s, OCH₃), 4.40 (2H, s, 1-H and 5-H), 5.73 (2H, s, 4-H and 8-H), 6.80 (2H, d, ³J_{5'-H,6'-H} 8.1 Hz, 5'-H), 6.87 (2H, dd, ⁴J_{2'-H,6'-H} 2.0 Hz, ³J_{5'-H,6'-H} 8.3 Hz, 6'-H), 6.99 (2H, d, ⁴J_{2'-H,6'-H} 1.8 Hz, 2'-H) and 9.24 (s, 2H, OH); ¹³C NMR δ_c (75 MHz; DMSO-d₆) 48.08 (C-1 and C-5), 55.80 (OCH₃), 82.07 (C-4 and C-8), 110.64 (C-2'), 115.45 (C-5'), 119.22 (C-6'), 129.01 (C-1'), 147.36 (C-4'), 147.86 (C-3') and 175.42 (C-2 and C-6); MS (ESI, pos.) *m/z* 409 [(M+Na)⁺, 100%].

3. Synthesis of vanillidene derivatives 14a-f and 15a-d

3.1 General procedure I for the synthesis of (*E*)-ferulic acid esters of type 14

(*E*)-ferulic acid esters were prepared according to the method described by Ralph et al.² A solution of ferulic acid [(*E*)-1] (5.0 g, 26 mmol) in the corresponding alcohol was treated with acetyl chloride (6 mL, 84 mmol) with cooling. The mixture was stirred at room temperature until the substrate was consumed (TLC). The solvent was removed in *vacuo* and the crude product was purified by column chromatography over silica gel using EtOAc/cyclohexane as eluent to give the ferulic acid esters in analytical pure form.

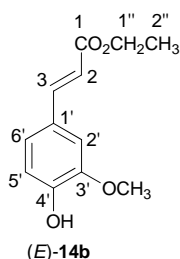
3.1.1 Methyl-(*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate [(*E*)-14a]



According to the general procedure **I** ferulic acid [(*E*)-**1**] (5.0 g, 26 mmol) and distilled methanol (90 mL, 2.2 mol) were reacted for 24 h. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (cyclohexane/EtOAc = 1:1) to afford methyl-(*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate [(*E*)-**14a**] (4.9 g, 24 mmol, 93%) as a white solid: mp 65 °C (lit.,³ 67-68 °C); R_f 0.40 (cyclohexane/EtOAc = 1:1); UV λ_{max} (EtOH)/nm 203, 218, 237 and 327 (log $\epsilon/dm^3 mol^{-1} cm^{-1}$ 4.00, 4.05, 4.02 and 4.00); IR (ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3332 (OH), 2947 (CH₃), 1699 (C=O), 1634 (C=C), 1589 (arom. C=C), 1512 (arom. C=C), 1256 (arom. C-O), 1183 (alkyl C-O), 979 (*trans* -CH=CH-), 861 (arom. C-H) and 813 (arom. C-H); ¹H NMR δ_H (300 MHz; CDCl₃) 3.75 (3H, s, CO₂CH₃), 3.83 (3H, s, OCH₃), 6.25 (1H, d, ³ $J_{2-H,3-H}$ 15.9 Hz, 2-H), 6.38 (1H, s, OH), 6.87 (1H, d, ³ $J_{5'-H,6'-H}$ 8.2 Hz, 5'-H), 6.96 (1H, d, ⁴ $J_{2'-H,6'-H}$ 1.5 Hz, 2'-H), 7.00 (1H, dd, ³ $J_{5'-H,6'-H}$ 8.2 Hz, ⁴ $J_{2'-H,6'-H}$ 1.7 Hz, 6'-H) and 7.58 (1H, d, ³ $J_{2-H,3-H}$ 15.9 Hz, 3-H); ¹³C NMR δ_C (75 MHz; CDCl₃) 51.42 (CO₂CH₃), 55.86 (OCH₃), 109.39 (C-2'), 114.72 (C-5'),* 114.74 (C-2),* 122.78 (C-6'), 126.63 (C-1'), 144.91 (C-3), 146.76 (C-3'), 147.97 (C-4') and 167.71 (C-1); MS (EI, 70 eV) m/z 208 (M⁺, 100%), 177 (46) and 145 (18).

* value may be interchanged

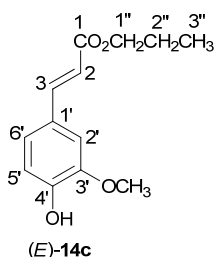
3.1.2 Ethyl-(*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate [(*E*)-14b]



According to the general procedure **I** ferulic acid [(*E*)-**1**] (5.0 g, 26 mmol) and distilled ethanol (90 mL, 1.5 mol) were reacted for 48 h. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (cyclohexane/EtOAc = 7:5) to afford ethyl-(*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate [(*E*)-**14b**] (4.9 g, 22

mmol, 86%) as a white solid: mp 57-58 °C (petroleum ether) (lit.,⁴ 58 °C); R_f 0.34 (cyclohexane/EtOAc = 7:5); UV λ_{max} (EtOH)/nm 218, 236 and 327 ($\log \epsilon/dm^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 4.06, 4.01 and 4.24); IR (ATR) $\tilde{\nu}_{max}/\text{cm}^{-1}$ 3169 (OH), 2977 (CH₂, CH₃), 1671 (C=O), 1629 (C=C), 1588 (arom. C=C), 1515 (arom. C=C), 1281 (arom. C-O), 1251 (arom. C-O), 975 (*trans* -CH=CH-), 842 (arom. C-H) and 812 (arom C-H); ¹H NMR δ_H (300 MHz; CDCl₃) 1.33 (3H, t, ³ $J_{1''-H,2''-H}$ 7.0 Hz, 2''-H), 3.91 (3H, s, OCH₃), 4.25 (2H, q, ³ $J_{1''-H, 2''-H}$ 7.1 Hz, 1''-H), 5.90 (1H, s, OH), 6.28 (1H, d, ³ $J_{2-H,3-H}$ 16.0 Hz, 2-H), 6.91 (1H, d, ³ $J_{5'-H,6'-H}$ 8.0 Hz, 5'-H), 7.02 (1H, d, ⁴ $J_{2'-H,6'-H}$ 1.6 Hz, 2'-H), 7.06 (1H, dd, ³ $J_{5'-H,6'-H}$ 8.2 Hz, ⁴ $J_{2'-H,6'-H}$ 1.7 Hz, 6'-H) and 7.61 (1H, d, ³ $J_{2-H,3-H}$ 16.0 Hz, 3-H); ¹³C NMR δ_c (75 MHz; CDCl₃) 14.32 (C-2''), 55.89 (OCH₃), 60.33 (C-1''), 109.29 (C-2'), 114.69 (C-5'), 115.60 (C-2), 122.98 (C-6'), 126.99 (C-1'), 144.65 (C-3), 146.75 (C-4'), 147.89 (C-3') and 167.28 (C-1); MS (GC-MS) m/z 222 (M⁺, 100%), 177 (47), 145 (74), 117 (30), 89 (35) and 77 (27).

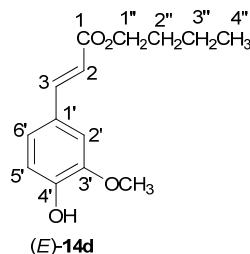
3.1.3 *n*-Propyl-(*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate [(*E*)-14c]



According to the general procedure **I** ferulic acid [(*E*)-**1**] (5.0 g, 26 mmol) and *n*-propanol (120 mL, 1.6 mol) were reacted for 48 h. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (cyclohexane/EtOAc = 2:1) to afford *n*-propyl-(*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate [(*E*)-**14c**] (5.5 g, 23 mmol, 90%) as a white solid: mp 40-41 °C (petroleum ether) (lit.,⁵ 34-36 °C); R_f 0.6 (cyclohexane/EtOAc = 1:2); UV λ_{max} (EtOH)/nm 201, 217, 236 and 326 ($\log \epsilon/dm^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 4.15, 4.08, 4.03 and 4.25); IR (ATR) $\tilde{\nu}_{max}/\text{cm}^{-1}$ 3401 (OH), 2967 (CH₃, CH₂), 1679 (C=O), 1632 (C=C), 1590 (arom. C=C), 1511 cm^{-1} (arom. C=C), 1264 (arom. C-O), 1153 (alkyl C-O), 979 (*trans* -CH=CH-), 845 (arom. C-H) and 815 (arom. C-H); ¹H NMR δ_H (300 MHz; CDCl₃) 0.99 (3H, t, ³ $J_{2''-H,3''-H}$ 7.5 Hz, 3''-H), 1.71 (2H, sex, ³ $J_{1''-H,2''-H}$ 7.0 Hz, 2''-H), 3.91 (3H, s, OCH₃), 4.15 (2H, t, ³ $J_{1''-H,2''-H}$ 7.0 Hz, 1''-H), 5.94 (1H, s, OH), 6.29 (1H, d, ³ $J_{2-H,3-H}$ 15.8 Hz, 2-H), 6.91 (1H, d, ³ $J_{5'-H,6'-H}$ 8.0 Hz, 5'-H), 7.03 (1H, d, ⁴ $J_{2'-H,6'-H}$ 1.6 Hz, 2'-H), 7.07 (1H, dd, ³ $J_{5'-H,6'-H}$ 8.1 Hz, ⁴ $J_{2'-H,6'-H}$ 1.8 Hz, 6'-H) and 7.61 (1H, d, ³ $J_{2-H,3-H}$ 16.0 Hz, 3-H); ¹³C NMR δ_c (75 MHz; CDCl₃) 10.42 (C-3''), 22.08 (C-2''), 55.90 (OCH₃), 66.00 (C-1''), 109.31 (C-2'), 114.70 (C-5'), 115.57 (C-2), 122.99 (C-6'), 126.99 (C-1'), 144.64 (C-3), 146.75 (C-

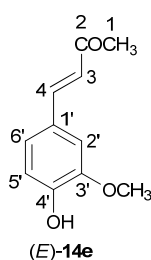
4'), 147.89 (C-3') and 167.40 (C-1); MS (EI, 70 eV) m/z 236 (M^+ , 100%), 194 (65), 177 (75), 145 (41), 117 (13), 89 (10) and 77 (5).

3.1.4 *n*-Butyl-(*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate [(*E*)-14d]



According to the general procedure **I** ferulic acid [(*E*)-**1**] (5.0 g, 26 mmol) and *n*-butanol (137 mL, 1.5 mol) were reacted for 6 d. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (cyclohexane/EtOAc = 7:3) to afford *n*-butyl-(*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate [(*E*)-**14d**] (5.7 g, 23 mmol, 90%): mp 50-51 °C (lit.,⁶ 46-48 °C); R_f 0.33 (cyclohexane/EtOAc = 7:3); UV λ_{max} (EtOH)/nm 218, 236 and 326 (log $\epsilon/dm^3 mol^{-1} cm^{-1}$ 4.05, 4.00 and 4.24); IR (ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3396 (OH), 2959 (CH₃, CH₂), 1679 (C=O), 1632 (C=C), 1590 (arom. C=C), 1511 (arom. C=C), 1264 (arom. C-O), 1154 (alkyl C-O), 978 (*trans* -CH=CH-), 845 (arom. C-H) and 815 (arom. C-H); ¹H NMR δ_H (300 MHz; CDCl₃) 0.93 (3H, t, ³ $J_{3''-H,4''-H}$ 7.3 Hz, 4''-H), 1.45 (2H, sex., ³ $J_{3''-H,4''-H}$ 7.5 Hz, 3''-H), 1.69 (2H, q, ³ $J_{2''-H,3''-H}$ 6.7 Hz, 2''-H), 3.92 (3H, s, OCH₃), 4.20 (2H, t, ³ $J_{1''-H,2''-H}$ 6.7 Hz, 1''-H), 5.91 (1H, s, OH), 6.29 (1H, d, ³ $J_{2-H,3-H}$ 16.0 Hz, 2-H), 6.91 (1H, d, ³ $J_{5'-H,6'-H}$ 8.2 Hz, 5'-H), 7.03 (1H, d, ⁴ $J_{2'-H,6'-H}$ 1.6 Hz, 2'-H), 7.06 (1H, dd, ³ $J_{5'-H,6'-H}$ 8.2 Hz, ⁴ $J_{2'-H,6'-H}$ 1.8 Hz, 6'-H) and 7.61 (1H, d, ³ $J_{2-H,3-H}$ 15.8 Hz, 3-H); ¹³C NMR δ_c (75 MHz; CDCl₃) 13.73 (C-4''), 19.87 (C-3''), 30.79 (C-2''), 55.90 (OCH₃), 64.28 (C-1''), 109.28 (C-2'), 114.68 (C-5'), 115.64 (C-2), 123.00 (C-6'), 127.02 (C-1'), 144.60 (C-3), 146.74 (C-3'), 147.88 (C-4') and 167.38 (C-1); MS (GC-MS) m/z 250 (M^+ , 46%), 194 (100), 177 (38), 145 (50), 117 (29), 89 (28) and 77 (21).

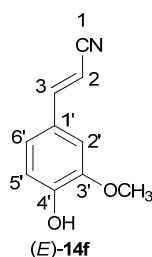
3.2 Synthesis of (*E*)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one [(*E*)-14e]⁷



A solution of vanillin (**18**) (2.5 g, 16 mmol) in acetone (30 mL) was treated with 8 M HCl (8

mL) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was neutralized with 2.5 M NaOH (ca. 20 mL), H₂O (100 mL) was added and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers was dried over Na₂SO₄, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography over silica gel (CH₂Cl₂/MeOH = 20:0.1) to afford (*E*)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one [(*E*)-**14e**] (1.5 g, 7.8 mmol, 48%) as a yellow solid. mp 125-126 °C (lit.,⁷ 124-125 °C); R_f 0.26 (CH₂Cl₂/MeOH = 20:0.1); UV λ_{max} (MeCN)/nm 221, 238 and 328 (log ε/dm³ mol⁻¹ cm⁻¹ 4.06, 4.05 and 4.31); IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3241 (OH), 3003 (CH₃), 1674 (C=O), 1635 (C=C), 1581 (arom. C=C), 1516 (arom. C=C), 1262 (arom. C-O), 1165 (alkyl C-O), 979 (*trans* -CH=CH-), 839 (arom. C-H) and 823 (arom. C-H); ¹H NMR δ_H (300 MHz; CDCl₃) 2.36 (3H, s, 1-H), 3.93 (3H, s, OCH₃), 5.94 (1H, s, OH), 6.58 (1H, d, ³J_{H₃,4-H} 16.3 Hz, 3-H), 6.93 (1H, d, ³J_{5'-H,6'-H} 8.0 Hz, 5'-H), 7.06 (1H, d, ⁴J_{2'-H,6'-H} 1.9 Hz, 2'-H), 7.09 (1H, dd, ³J_{5'-H,6'-H} 8.1 Hz, ⁴J_{2'-H,6'-H} 1.8 Hz, 6'-H) and 7.45 (1H, d, ³J_{3-H,4-H} 16.1 Hz, 4-H); ¹³C NMR δ_C (75 MHz; CDCl₃) 27.28 (C-1), 55.94 (OCH₃), 109.28 (C-2'), 114.80 (C-5'), 123.50 (C-6'), 124.98 (C-3), 126.91 (C-1'), 143.72 (C-4), 146.86 (C-3'), 148.24 (C-4') and 198.40 (C-2); MS (EI, 70 eV) *m/z* 192 (M⁺, 100%), 145 (64), 134 (8), 117 (17) and 89 (8).

3.3 Synthesis of (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylonitrile [(*E*)-**14f**]⁸



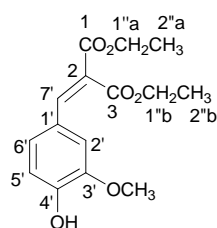
A suspension of KOH (1.8 g, 32 mmol) and 18-crown-6 (442 mg, 16 mol) in acetonitrile (30 mL) was refluxed under argon for 10 min. A solution of vanillin (**18**) (2.5 g, 16 mmol) in acetonitrile (30 mL) was added to the suspension and the resulting mixture was refluxed under argon for 48 h. After cooling to room temperature, ice (100 g) was added and the mixture was neutralized with 5 M HCl (ca. 8 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 70 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography over silica gel (cyclohexane/EtOAc = 1:1) to afford (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylonitrile [(*E*)-**14f**] (1.5 g, 8.6 mmol, 52%) as a yellow solid. mp 97-98 °C (lit.,⁸ 93-96 °C); R_f 0.34 (cyclohexane/EtOAc = 1:1); UV λ_{max} (MeCN)/nm 215, 235, 293 and 319 (log ε/dm³ mol⁻¹ cm⁻¹ 4.08, 4.06, 4.11 and 4.20); IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3391 (OH), 2208 (CN), 1598 (arom. C=C),

1509 (arom. C=C), 1278 (arom. C-O), 1158 (alkyl C-O), 968 (*trans* -CH=CH-), 849 (arom. C-H) and 797 (arom. C-H); $^1\text{H NMR } \delta_{\text{H}}$ (300 MHz; CDCl_3) 3.93 (3H, s, OCH_3), 5.95 (1H, s, OH), 5.70 (1H, d, $^3J_{2\text{-H},3\text{-H}}$ 16.6 Hz, 2-H), 6.92 (1H, d, $^4J_{2'\text{-H},6'\text{-H}}$ 2.0 Hz, 2'-H), 6.93 (1H, d, $^3J_{5'\text{-H},6'\text{-H}}$ 8.1 Hz, 5'-H), 7.00 (1H, dd, $^3J_{5'\text{-H},6'\text{-H}}$ 8.3 Hz, $^4J_{2'\text{-H},6'\text{-H}}$ 1.9 Hz, 6'-H) and 7.30 (1H, d, $^3J_{2\text{-H},3\text{-H}}$ 16.4 Hz, 3-H); $^{13}\text{C NMR } \delta_{\text{C}}$ (75 MHz; CDCl_3) 56.00 (OCH_3), 93.28 (C-2), 108.62 (C-2'), 114.87 (C-5'), 118.62 (C-1), 122.39 (C-6'), 126.18 (C-1'), 146.87 (C-3'), 148.69 (C-4') and 150.37 (C-1); MS (EI, 70 eV) m/z 175 (M^+ , 100%), 145 (32), 132 (80), 104 (24) and 77 (18).

3.4 General experimental procedure II for the preparation of trisubstituted vanillidene derivatives of type 15

A solution of vanillin (**18**) (2.5 g, 16 mmol) and the β -dicarbonyl (16 mmol) in CH_2Cl_2 (40 mL) was treated with piperidine (70 μL , 0.70 mmol) and acetic acid (40 μL , 0.70 mmol). The solution was refluxed using a Dean Stark apparatus until the vanillin was consumed. The solvent was removed *in vacuo* and the crude product was purified by column chromatography over silica gel to give the trisubstituted vanillidene derivative.

3.4.1 Diethyl 2-(4-hydroxy-3-methoxybenzylidene)malonate (**15a**)

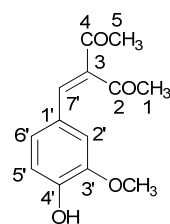


15a

According to the general procedure **II** vanillin (**18**) (2.5 g, 16 mmol) and diethyl malonate (2.5 g, 16 mmol) were reacted for 14 h. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (EtOAc/cyclohexane = 4:1) to afford diethyl 2-(4-hydroxy-3-methoxybenzylidene)malonate (**15a**) (4.3 g, 14 mmol, 90%) as a white solid. mp 104-105 °C (lit.,⁹ 108-109 °C); R_f 0.60 (EtOAc/cyclohexane = 5:1); UV λ_{max} (MeCN)/nm 326 (log $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 4.31); IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3478 (OH), 2975 (CH_2 , CH_3), 1730 (C=O), 1682 (C=C), 1585 (arom. C=C), 1519 (arom. C=C), 1291 (arom. C-O), 1175 (C-O), 857 (arom. C-H) and 815 (arom. C-H); $^1\text{H NMR } \delta_{\text{H}}$ (300 MHz; CDCl_3) 1.32 (6H, t, $^3J_{1''\text{a-H},2''\text{a-H}}$ 7.2 Hz, 2''a-H and 2''b-H), 3.88 (3H, s, OCH_3), 4.25-4.38 (4H, m, 1''a-H and 1''b-H), 6.90 (1H, d, $^3J_{6'\text{-H},5'\text{-H}}$ 8.1 Hz, 5'-H), 7.02 (1H, d, $^4J_{2'\text{-H},6'\text{-H}}$ 2.0 Hz, 2'-H), 7.05

(1H, dd, $^3J_{5'-H,6'-H}$ 8.0 Hz, $^4J_{2'-H,6'-H}$ 2.1 Hz, 6'-H) and 7.64 (1H, s, 7'-H); ^{13}C NMR δ_C (75 MHz; CDCl₃) 13.97 (C-2''a or C-2''b), 14.14 (C-2''a or C-2''b), 55.84 (OCH₃), 61.44 (C-1''a or C-1''b), 61.61 (C-1''a or C-1''b), 111.36 (C-2'), 114.73 (C-5'), 123.55 (C-2), 124.77 (C-6'), 125.21 (C-1'), 142.09 (C-7'), 146.51 (C-3'), 148.20 (C-4'), 164.44 (C-1 or C-3), 167.27 (C-1 or C-3); MS (EI, 70 eV) m/z 294 (M⁺, 100%), 249 (38), 220 (24), 176 (14), 148 (36); HRMS (EI, M⁺) found: 294.1102 calc. for C₁₅H₁₈O₆: 294.1103.

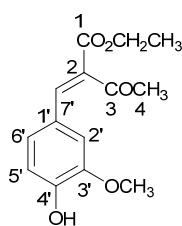
3.4.2 3-(4-Hydroxy-3-methoxybenzylidene)pentene-2,4-dione (15b)



15b

According to the general procedure **II** vanillin (**18**) (2.5 g, 16 mmol) and pentane-2,4-dione (2.0 g, 16 mmol) were reacted for 15 h. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (CH₂Cl₂/MeOH = 40:1) to afford 3-(4-hydroxy-3-methoxybenzylidene)pentane-2,4-dione (**15b**) (3.7 g, 16 mmol, 96%) as a yellow solid. mp 132-133 °C (lit.,¹⁰ 128-129 °C); R_f 0.60 (CH₂Cl₂/MeOH = 40:1); UV λ_{max} (MeCN)/nm 222, 246 and 332 (log $\epsilon/dm^3 mol^{-1} cm^{-1}$ 4.05, 4.06 and 4.32); IR (ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3367 (OH), 1693 (C=O), 1578 (arom. C=C), 1515 (arom. C=C), 1265 (arom. C-O), 1173 (C-O), 853 (arom. C-H) and 819 (arom. C-H); 1H NMR δ_H (300 MHz; CDCl₃) 2.32 (3H, s, 1-H or 5-H), 2.40 (3H, s, 1-H or 5-H), 3.88 (3H, s, OCH₃), 6.02 (1H, s, OH), 6.91 (1H, d, $^3J_{5'-H,6'-H}$ 8.2 Hz, 5'-H), 6.92 (1H, d, $^3J_{2'-H,6'-H}$ 2.1 Hz, 2'-H), 6.98 (1H, dd, $^3J_{5'-H,6'-H}$ 8.2 Hz, $^4J_{2'-H,6'-H}$ 2.1 Hz, 6'-H) and 7.40 (s, 1H, 7'-H); ^{13}C NMR δ_C (75 MHz; CDCl₃) 26.32 (C-1 or C-5), 31.70 (C-1 or C-5), 55.94 (OCH₃), 111.49 (C-2'), 114.96 (C-5'), 125.03 (C-6'), 125.13 (C-1'), 140.08 (C-7'), 140.64 (C-3), 146.72 (C-3'), 148.35 (C-4'), 196.45 (C-2 or C-4) and 206.42 (C-2 or C-4); MS (EI, 70 eV) m/z 234 (M⁺, 100%), 177 (62), 145 (26) and 43 (51); HRMS (EI, M⁺) found: 234.0915 calc. for C₁₃H₁₄O₄: 234.0892.

3.4.3 Ethyl 2-(4-hydroxy-3-methoxybenzylidene)-3-oxo-butanoate (15c)

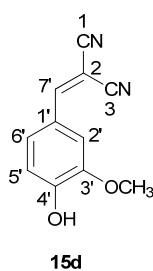


15c

According to the general procedure **II** vanillin (**18**) (2.5 g, 16 mmol) and ethyl-3-oxobutanoate (2.0 g, 16 mmol) were reacted for 16 h. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (CH₂Cl₂/MeOH = 40:1) to afford ethyl 2-(4-hydroxy-3-methoxybenzylidene)-3-oxobutanoate (**15c**) as an *E/Z* mixture (*E:Z* = 4:6; ¹H NMR) (2.45 g, 11 mmol, 67%) as a white solid. mp 109-110 °C (lit.,¹⁰ 110 °C); R_f 0.46 (CH₂Cl₂/MeOH = 40:1); UV λ_{max} (MeCN)/nm 222, 243 and 331 (log ε/dm³ mol⁻¹ cm⁻¹ 4.24, 4.06 and 4.01); IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3395 (OH), 3013 (CH₂), 1725 (C=O), 1578 (arom. C=C), 1518 (arom. C=C), 1265 (arom. C-O), 1173 (C-O), 853 (arom. C-H) and 811 (arom. C-H); ¹H NMR (*E*)-**15c** δ_H (500 MHz; CDCl₃) 1.29-1.32 (3H, t, ³J_{H,H} 7.2 Hz, CH₂CH₃), 2.37 (3H, s, 4-H), 4.27 (2H, m, CH₂CH₃), 3.85 (3H, s, OCH₃), 5.98 (1H, s, OH), 6.88 (1H, d, ³J_{5'-H,6'-H} 8.0 Hz, 5'-H), 6.92 (1H, d, ⁴J_{2'-H,6'-H} 1.9 Hz, 2'-H), 6.96 (1H, dd, ³J_{5'-H,6'-H} 1.8 Hz, ³J_{5'-H,6'-H} 7.9 Hz, 6'-H) and 7.57 (1H, s, 7'-H); ¹H NMR (*Z*)-**15c** δ_H (500 MHz; CDCl₃) 1.29-1.32 (3H, t, ³J_{H,H} 7.2 Hz, CH₂CH₃), 2.38 (3H, s, 4-H), 4.27 (2H, m, CH₂CH₃), 3.86 (3H, s, OCH₃), 5.98 (1H, s, OH), 6.90 (1H, d, ³J_{5'-H,6'-H} 7.9 Hz, 5'-H), 7.00 (1H, d, ⁴J_{2'-H,6'-H} 1.9 Hz, 2'-H), 7.03 (1H, dd, ⁴J_{2'-H,6'-H} 1.8 Hz, ³J_{5'-H,6'-H} 7.9 Hz, 6'-H) and 7.47 (1H, s, 7'-H); ¹³C NMR (*E*)-**15c** δ_C (125 MHz; CDCl₃) 13.93 (CH₂CH₃),* 31.24 (C-4), 55.80 (OCH₃),* 61.34 (CH₂CH₃), 111.64 (C-2'), 114.82 (C-5'), 124.78 (C-6'), 125.06 (C-1'),* 131.38 (C-2), 140.66 (C-7'), 146.60 (C-3'), 148.11 (C-4'), 164.70 (C-1) and 204.16 (C-3); ¹³C NMR (*Z*)-**15c** δ_C (125 MHz; CDCl₃) 14.13 (CH₂CH₃),* 26.33 (C-4), 55.87 (OCH₃),* 61.63 (CH₂CH₃), 111.38 (C-2'), 114.83 (C-5'), 125.06 (C-1'),* 125.08 (C-6'),* 132.16 (C-2), 140.65 (C-7'), 146.63 (C-3'), 148.50 (C-4'), 168.40 (C-1) and 194.70 (C-3); MS (EI, 70 eV) *m/z* 264 (M⁺, 100%), 249 (44), 219 (20) and 177 (23); HRMS (EI, M⁺) found: 264.1006 calc. for C₁₄H₁₆O₅; 264.0998.

* value may be interchanged

3.4.4 2-(4-Hydroxy-3-methoxybenzylidene)malononitrile (**15d**)



According to the general procedure **II** vanillin (**18**) (2.5 g, 16 mmol) and malononitrile (1.06 g, 16 mmol) were reacted for 16 h. After evaporation of the volatiles *in vacuo* the crude

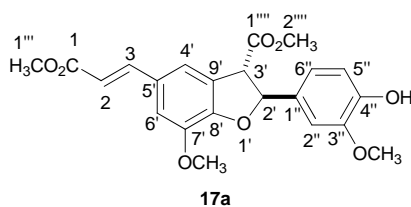
product was purified by column chromatography over silica gel (EtOAc/cyclohexane = 5:2) to afford 2-(4-hydroxy-3-methoxybenzylidene)malononitrile (**15d**) (2.93 g, 15 mmol, 89%) as a yellow solid. mp 131-132 °C (lit.,¹¹ 136-137 °C); R_f 0.80 (EtOAc/cyclohexane = 5:2); UV λ_{max} (MeCN)/nm 245, 368 and 460 ($\log \epsilon/dm^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 3.89, 4.28 and 3.34); IR (ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3298 (OH), 2222 (CN), 1605 (C=C), 1514 (arom. C=C), 1291 (arom. C-O), 1187 (C-O), 867 (arom. C-H) and 818 (arom. C-H); 1H NMR δ_H (300 MHz; $CDCl_3$) 3.98 (s, 3H, OCH₃), 7.02 (1H, d, $^3J_{6'-H,5'-H}$ 8.3 Hz, 5'-H), 7.31 (1H, dd, $^4J_{2'-H,6'-H}$ 2.0 Hz, $^3J_{5'-H,6'-H}$ 8.3 Hz, 6'-H), 7.63 (1H, s, 7'-H) and 7.72 (1H, d, $^4J_{2'-H,6'-H}$ 1.9 Hz, 2'-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$) 56.19 (OCH₃), 78.14 (C-2), 110.41 (C-2'), 113.61 (C-1 or C-3), 114.37 (C-1 or C-3), 115.21 (C-5'), 123.95 (C-1'), 128.98 (C-6'), 147.04 (C-3'), 152.15 (C-4') and 159.21 (C-7'); MS (EI, 70 eV) m/z 200 (M^+ , 100%), 185 (14), 157 (82) and 129 (25); HRMS (EI, M^+) found: 200.0591 calc. for $C_{11}H_8N_2O_2$: 200.0586.

4 Laccase-catalyzed dimerization of disubstituted vanillidene derivatives

4.1 General procedure III for the laccase-catalyzed oxidation of (*E*)-ferulic acid esters

A solution of a ferulic acid ester in an organic solvent was added to 0.1 M NaOAc buffer (pH 5.0). The laccase was added and the reaction was stirred under air at room temperature for different reaction times. After extraction with CH_2Cl_2 (3 × 40 mL) the combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography over silica gel (cyclohexane/EtOAc) to afford the dihydrobenzofuran in analytical pure form.

4.1.1 Methyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-methoxycarbonyl-1-benzofuran-5yl]propenoate (**17a**)

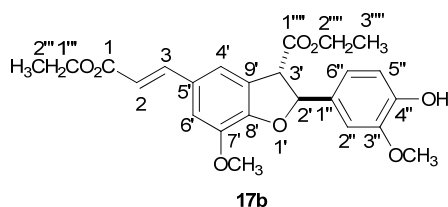


According to the general procedure **III** a solution of **14a** (80 mg, 0.4 mmol) in DMSO (1.6 mL) and laccase from *Trametes versicolor* (4 U, 0.4 mg) were reacted in NaOAc buffer (0.1 M, pH 5.0, 78.4 mL) for 1 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc = 7:5) to afford methyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-

methoxy-3-methoxycarbonyl-1-benzofuran-5yl]propenoate (**17a**) (30 mg, 0.07 mmol, 38%) as a white solid: mp 155 °C (from MeOH) (lit.,¹² 151-152 °C); R_f 0.20 (cyclohexane/EtOAc = 7:5); UV λ_{max} (EtOH)/nm 326 (log $\epsilon/dm^3 mol^{-1} cm^{-1}$ 4.26); IR (ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3374 (OH), 2949 (CH₃), 1741 (C=O), 1633 (C=C), 1520 (arom. C=C), 1264 (arom. C-O), 1162 (alkyl C-O), 987 (*trans* -CH=CH-), 856 (arom. C-H) and 831 (arom. C-H); ¹H NMR δ_H (300 MHz; CDCl₃) 3.76 (3H, s, 1''''-H), 3.79 (3H, s, 2''''-H), 3.92 (3H, s, OCH₃''), 3.98 (3H, s, OCH₃'), 4.34 (1H, d, ³ $J_{2'-H,3'-H}$ 8.2 Hz, 3'-H), 5.74 (1H, s, OH), 6.11 (1H, d, ³ $J_{2'-H,3'-H}$ 8.21 Hz, 2'-H), 6.32 (1H, d, ³ $J_{2-H,3-H}$ 16.0 Hz, 2-H), 6.90 (3H, s, 2'', 6'', 5''-H), 7.02 (1H, s, 6'-H), 7.18 (1H, s, 4'-H) and 7.64 (1H, d, ³ $J_{2-H,3-H}$ 16.0 Hz, 3-H); ¹³C NMR δ_C (75 MHz; CDCl₃) 51.92 (C-1'''), 53.15 (C-2'''), 55.76 (C-3'), 56.29 (OCH₃''), 56.41 (OCH₃'), 87.74 (C-2'), 108.99 (C-2''),* 112.36 (C-6'), 114.79 (C-5''), 115.85 (C-2), 118.17 (C-4'), 119.73 (C-6''),* 125.97 (C-9'), 128.86 (C-5'), 131.63 (C-1''), 145.00 (C-3), 145.03 (C-7'), 146.34 (C-4''), 146.97 (C-3''), 150.23 (C-8'), 167.90 (C-1) and 171.02 (C-1'''); MS (EI, 70 eV) m/z 414 (M⁺, 76%), 382 (95) and 350 (100).

* value may be interchanged

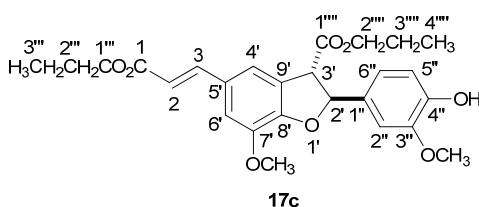
4.1.2 Ethyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-ethoxycarbonyl-1-benzofuran-5yl]propenoate (**17b**)



According to the general procedure **III** a solution of **14b** (90 mg, 0.4 mmol) in DMSO (1.6 mL) and laccase from *Trametes versicolor* (4 U, 0.4 mg) were reacted in NaOAc buffer (0.1 M, pH 5.0, 78.4 mL) for 16 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc = 3:1) to afford ethyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-ethoxycarbonyl-1-benzofuran-5yl]propenoate (**17b**) (26 mg, 0.06 mmol, 29%) as a white solid: mp 150-151 °C (lit.,² 153°C); R_f 0.10 (cyclohexane/EtOAc = 3:1); UV λ_{max} (CH₂Cl₂)/nm 326 (log $\epsilon/dm^3 mol^{-1} cm^{-1}$ 4.28); IR (ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3411 (OH), 2980 (CH₂, CH₃), 1737 (C=O), 1709 (C=O), 1636 (C=C), 1520 (arom. C=C), 1491 (arom. C=C), 1262 (arom. C-O), 1235 (arom. C-O), 1161 (alkyl C-O), 1139 (alkyl C-O), 1016 (*trans* -CH=CH-), 856 (arom. C-H) and 838 (arom. C-H); ¹H NMR δ_H (300 MHz; CDCl₃) 1.34 (6H, t, ³ $J_{1''''-H,2''''-H}$ 7.2 Hz, 2''''-H, 3''''-H), 3.87 (3H, s, OCH₃''), 3.91 (3H, s, OCH₃'), 4.24-4.25 (5H, m, 3'-H,

2''''-H, 1''''-H), 5.67 (1H, s, OH), 6.11 (1H, d, $^3J_{2'-H,3'-H}$ 8.2 Hz, 2'-H), 6.30 (1H, d, $^3J_{2-H,3-H}$ 15.8 Hz, 2-H), 6.90 (3H, s, 2''-H, 5''-H, 6''-H), 7.02 (1H, s, 6'-H), 7.20 (1H, s, 4'-H) and 7.64 (1H, d, $^3J_{2-H,3-H}$ 16.0 Hz, 3-H); ^{13}C NMR δ_{C} (75 MHz; CDCl_3) 14.25 (C-2'''' or C-3''''), 14.32 (C-2'''' or C-3''''), 55.54 (C-3'), 55.98 (OCH_3 ''), 56.08 (OCH_3 '), 60.39 (C-1'''), 61.85 (C-2''''), 87.46 (C-2'), 108.73 (C-6''), 111.88 (C-6'), 114.68 (C-5''), 115.93 (C-2), 117.86 (C-4'), 119.46 (C-2''), 125.84 (C-9'), 128.64 (C-5'), 131.43 (C-1''), 144.51 (C-3), 144.69 (C-7'), 146.02 (C-4''), 146.68 (C-3''), 149.89 (C-8'), 167.20 (C-1) and 170.21 (C-1'''''); MS (EI, 70 eV) m/z 442 (M^+ , 74%), 396 (78) and 350 (100).

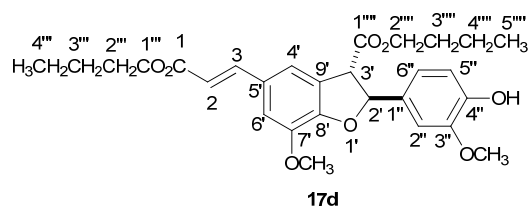
4.1.3 *n*-Propyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-propioxycarbonyl-1-benzofuran-5yl]propenoate (**17c**)



According to the general procedure **III** a solution of **14c** (97 mg, 0.4 mmol) in DMSO (1.6 mL) and laccase from *Trametes versicolor* (4 U, 0.4 mg) were reacted in NaOAc buffer (0.1 M, pH 5.0, 78.4 mL) for 16 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (cyclohexane/EtOAc = 3:1) to afford *n*-propyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-propioxycarbonyl-1-benzofuran-5yl]propenoate (**17c**) (23 mg, 0.05 mmol, 23%) as a white solid. mp 122-123 °C; R_f 0.15 (cyclohexane/EtOAc = 3:1); UV λ_{max} (CH_2Cl_2)/nm 325 ($\log \varepsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 4.29); IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ 3408 (OH), 2971 (CH_2 , CH_3), 1734 (C=O), 1717 (C=O), 1634 (C=C), 1519 (arom. C=C), 1489 (arom. C=C), 1262 (arom. C-O), 1162 (alkyl C-O), 1139 (alkyl C-O), 996 (*trans* -CH=CH-), 856 (arom. C-H) and 829 (arom. C-H); ^1H NMR δ_{H} (300 MHz; CDCl_3) 1.02 (3H, t, $^3J_{3''''-H,4''''-H}$ 7.2 Hz, 4''''-H), 1.04 (3H, t, $^3J_{3''''-H,2''''-H}$ 7.3 Hz, 3''''-H), 1.76 (2H, q, $^3J_{3''''-H,4''''-H}$ 7.2 Hz, 3''''-H), 1.78 (2H, q, $^3J_{3''''-H,2''''-H}$ 7.3 Hz, 2''''-H), 4.17 (4H, m, 1''''-H, 2''''-H), 3.87 (3H, s, OCH_3 ''), 3.92 (3H, s, OCH_3 '), 4.33 (1H, d, $^3J_{2'-H,3'-H}$ 8.2 Hz, 3'-H), 5.65 (1H, s, OH), 6.11 (1H, d, $^3J_{2'-H,3'-H}$ 8.2 Hz, 2'-H), 6.31 (1H, d, $^3J_{2-H,3-H}$ 15.8 Hz, 2-H), 6.90 (3H, s, 2''-H, 5''-H, 6''-H), 7.03 (1H, s, 6'-H), 7.19 (1H, s, 4'-H) and 7.63 (1H, d, $^3J_{2-H,3-H}$ 16.0 Hz, 3-H); ^{13}C NMR δ_{C} (75 MHz; CDCl_3) 10.40 (C-3'''' or C-4''''), 10.44 (C-3'''' or C-4''''), 21.99 (C-2'''' or C-3''''), 22.11 (C-2'''' or C-4''''), 55.62 (C-3'), 55.98 (OCH_3 ''), 56.08 (OCH_3 '), 66.05 (C-1'''), 67.44

(C-2'''''), 87.47 (C-2'), 108.71 (C-2''), 111.88 (C-6'), 114.48 (C-5''), 115.96 (C-2), 117.94 (C-4'), 119.47 (C-6''), 125.84 (C-9'), 128.63 (C-5'), 131.48 (C-1''), 144.48 (C-3), 144.70 (C-7'), 146.02 (C-3''), 146.67 (C-4''), 149.89 (C-8'), 167.30 (C-1) and 170.29 (C-1'''''); MS (EI, 70 eV) m/z 470 (M^+ , 86%), 410 (97) and 350 (100); HRMS (EI, M^+) found: 470.1949 calc. for $C_{26}H_{30}O_8$: 470.1941.

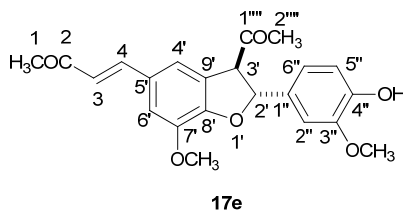
4.1.4 *n*-Butyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-butoxycarbonyl-1-benzofuran-5yl]propenoate (**17d**)



According to the general procedure **III** a solution of **14d** (530 mg, 2.1 mmol) in DMSO (8 mL) and laccase from *Trametes versicolor* (120 U, 12 mg) were reacted in NaOAc buffer (0.1 M, pH 5.0, 482 mL) as the solvent for 3 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (CH_2Cl_2) to afford *n*-butyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-butoxycarbonyl-1-benzofuran-5yl]propenoate (**17d**) (117 mg, 0.23 mmol, 22%) as a white solid: mp 121-123°C; R_f 0.28 (cyclohexane/EtOAc = 7:3); UV λ_{max} (CH_2Cl_2)/nm 325 ($\log \epsilon/dm^3 mol^{-1} cm^{-1}$ 4.30); IR (ATR) $\tilde{\nu}_{max}/cm^{-1}$ 3532 (OH), 2958 (CH_2 , CH_3), 1724 (C=O), 1705 (C=O), 1630 (C=C), 1515 (arom. C=C), 1502 (arom. C=C), 1263 (arom. C-O), 1140 (alkyl C-O), 982 (*trans* -CH=CH-), 858 (arom. C-H) and 823 (arom. C-H); 1H NMR δ_H (300 MHz; $CDCl_3$) 0.95 (3H, t, $^3J_{4''''-H,5''''-H}$ 7.4 Hz, 5''''-H), 0.97 (3H, t, $^3J_{3''''-H,4''''-H}$ 7.4 Hz, 4''''-H), 1.42 (2H, ov, 4''''-H), 1.44 (2H, ov, 3''''-H), 1.68 (2H, ov, 2''''-H), 1.69 (2H, ov, 3''''-H), 3.88 (3H, s, OCH_3''), 3.92 (3H, s, OCH_3'), 4.20 (2H, ov, 1''-H), 4.21 (2H, ov, 2''''-H), 4.32 (1H, d, $^3J_{2'-H,3'-H}$ 8.3 Hz, 3'-H), 5.63 (1H, s, OH), 6.11 (1H, d, $^3J_{2'-H,3'-H}$ 8.2 Hz, 2'-H), 6.31 (1H, d, $^3J_{2-H,3-H}$ 15.8 Hz, 2-H), 6.90 (3H, s, 2''-H, 5''-H, 6''-H), 7.02 (1H, s, 6'-H), 7.19 (1H, s, 4'-H) and 7.63 (1H, d, $^3J_{2-H,3-H}$ 15.8 Hz, 3-H); ^{13}C NMR δ_C (75 MHz; $CDCl_3$) 13.64 (C-4'''' or C-5'''''), 13.76 (C-4'''' or C-5'''''), 19.17 (C-4'''''), 19.21 (C-3'''''), 30.63 (C-3'''''), 30.81 (C-1'''''), 55.63 (C-3'), 56.01 (OCH_3''), 56.13 (OCH_3'), 64.34 (C-2'''), 65.74 (C-2'''''), 87.48 (C-2'), 108.72 (C-2''), 111.98 (C-6'), 114.49 (C-5''), 116.00 (C-2), 117.86 (C-4'), 119.49 (C-6''), 125.87 (C-9'), 128.64 (C-5'), 131.50 (C-1''), 144.47 (C-3), 144.71 (C-7'), 146.04 (C-4'), 146.69 (C-3''), 149.90 (C-8'), 167.32 (C-1) and 170.31 (C-1''); MS (EI, 70 eV) m/z 498

(M⁺, 44%), 424 (97) and 350 (100); HRMS (EI, M⁺) found: 498.2258 calc. for C₂₈H₃₄O₈: 498.2254.

4.1.5 4-(E)-[(2R*,3R*)-2,3-Dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-acetyl-1-benzofuran-5yl]but-3-en-2-one (17e)



According to the general procedure **III** a solution of **14e** (80 mg, 0.4 mmol) in DMSO (1.6 mL) and laccase from *Trametes versicolor* (4U, 0.4 mg) were reacted in NaOAc buffer (0.1 M, pH 5.0, 78.4 mL) as the solvent for 9 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (CH₂Cl₂/MeOH = 20:0.1) to afford 4-(E)-[(2R*,3R*)-2,3-dihydro-2-(4-hydroxy-3-methoxy-phenyl)-7-methoxy-3-acetyl-1-benzofuran-5yl]but-3-ene-2-one (**17e**) (20 mg, 0.05 mmol, 25%) as a white oil: R_f 0.12 (CH₂Cl₂/MeOH = 20:0.1); UV λ_{max} (CH₂Cl₂)/nm 336 (log ε/dm³ mol⁻¹ cm⁻¹ 1.21); IR (ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3377 (OH), 2963 (CH₃), 1713 (C=O), 1665 (C=O), 1588 (arom. C=C), 1259 (arom. C-O), 1145 (alkyl C-O), 1030 (*trans* -CH=CH-), 909 (arom. C-H) and 801 (arom. C-H); ¹H NMR δ_H (300 MHz; CDCl₃) 2.35 (3H, s, 2''''-H), 2.37 (3H, s, 1-H), 3.86 (3H, s, OCH₃''), 3.96 (3H, s, OCH₃'), 4.39 (1H, d, ³J_{2'-H,3'-H} 6.7 Hz, 3'-H), 5.70 (1H, s, OH), 6.07 (1H, d, ³J_{2'-H,3'-H} 6.7 Hz, 2'-H), 6.60 (1H, d, ³J_{2-H,3-H} 16.3 Hz, 3-H), 6.84 (2H, s, 2''-H, 6''-H), 6.87 (1H, s, 5''-H), 7.06 (1H, s, 6'-H), 7.11 (1H, s, 4'-H) and 7.46 (1H, d, ³J_{2-H,3-H} 16.3 Hz, 4-H); ¹³C NMR δ_C (75 MHz; CDCl₃) 27.44 (C-1), 28.77 (C-2'''''), 55.98 (OCH₃''), 56.11 (OCH₃'), 63.78 (C-3'), 86.80 (C-2'), 108.58 (C-6'' or C-2''), 112.14 (C-6'), 114.60 (C-5''), 117.78 (C-4'), 119.11 (C-6'' or C-2''), 125.29 (C-3), 125.92 (C-9'), 128.64 (C-5'), 131.58 (C-1''), 143.23 (C-4), 145.03 (C-7'), 146.10 (C-4''), 146.74 (C-3''), 150.45 (C-8'), 198.17 (C-2) and 203.56 (C-1'''''); MS (EI, 70 eV) *m/z* 382 (M⁺, 40%), 380 (12), 365 (8), 340 (100) and 311 (16); HRMS (EI, M⁺) found: 382.1411 calc. for C₂₂H₂₂O₆: 382.1416.

4.2 Treatment of **14a** with aerial O₂ in the absence of any catalyst

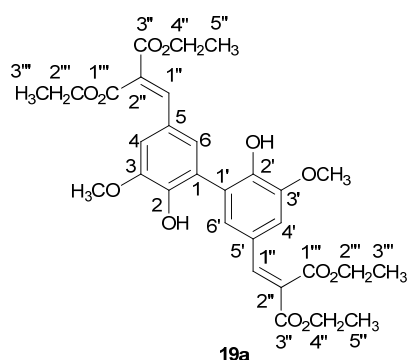
A solution of **14a** (84 mg, 0.4 mmol) in DMSO (1.6 mL) was stirred in NaOAc buffer (0.1 M, pH 5.0, 78.4 mL) as the solvent for 1 h under air at room temperature. After extraction with CH₂Cl₂ (3 × 30 mL) the combined organic phases were analyzed by TLC. Only **14a** could be detected.

5 Laccase-catalyzed dimerization of trisubstituted vanillidene derivatives

5.1 General experimental procedure IV for the laccase-catalyzed oxidation of trisubstituted vanillidene derivatives of type 15

A solution of a vanillidene derivative **15** in DMSO (8 mL) was added to NaOAc buffer (0.1 M, pH 5.0, 72 mL). Laccase from *Trametes versicolor* (4 U, 0.4 mg) was added and the reaction mixture was stirred under air at room temperature. After extraction with CH₂Cl₂ (3 × 30 mL) the combined organic phases were dried over MgSO₄, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography over silica gel to afford the product in analytical pure form.

5.1.1 5,5'-Di(2,2-diethoxycarbonylviny)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (**19a**)

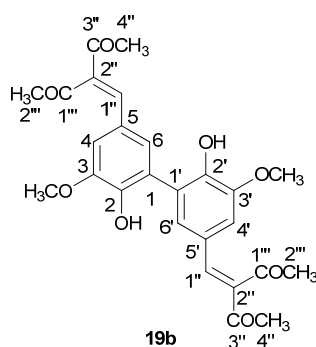


According to the general procedure **IV** a solution of **15a** (118 mg, 0.4 mmol) and laccase were reacted in NaOAc buffer for 22 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was purified by flash chromatography over silica gel (CH₂Cl₂/MeOH =40:0.5) to afford 5,5'-di(2,2-diethoxycarbonylviny)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (**19a**) (93 mg, 0.16 mmol, 79%) as a yellow oil: R_f 0.1 (CH₂Cl₂/MeOH =40:0.5); UV λ_{max} (MeCN)/nm 242, 332 and 387 (log ε/dm³ mol⁻¹ cm⁻¹ 3.11, 3.21 and 2.86); IR (ATR) $\tilde{\nu}_{\max}$ /cm⁻¹ 3418 (OH), 2982 (CH₂, CH₃), 1717 (C=O), 1592 (arom. C=C), 1212 (arom. C-O), 1178 (alkyl C-O), 859 (arom. C-H) and 728 (arom. C-H); ¹H NMR δ_H (300 MHz; DMSO-*d*₆) 1.25-1.36 (12H, t, ³J_{4''-H,5''-H} 7.0 Hz, 3''-H and 5''-H), 3.92 (6H, s, OCH₃ and OCH₃'), 4.25-4.36 (8H, m, 2''-H and 4''-H), 7.04 (4H, s, 4-H, 4'-H, 6-H and 6'-H) and 7.65 (2H, s, 1''-H); ¹³C NMR δ_C (75MHz; DMSO-*d*₆) 13.96 (C-3'' or C-5''), 14.14 (C-3''a or C-5''), 56.09 (OCH₃ and OCH₃'), 61.47 (C-2'' or C-4''), 61.65 (C-2'' or C-4''), 110.42 (C-4, C-4' or C-6, C-6'), 123.29 (C-1 and C-1'), 123.97 (C-2''),* 124.84 (C-5 and C-5')*, 126.94 (C-4, C-4' or C-6, C-6'), 141.84 (C-1''), 145.50 (C-3 and C-3'), 147.01 (C-2 and C-

2'), 164.37 (C-1''' or C-3'') and 167.14 (C-1''' or C-3''); MS (ESI, pos.) m/z 609 [(M + Na)⁺, 84%], 604 [(M + NH₄)⁺, 100] and 587 [(M + H)⁺, 81]; HRMS (ESI, pos.) found: 587.2123 [C₃₀H₃₄O₁₂ + H]⁺ calc. for C₃₀H₃₅O₁₂: 587.2129.

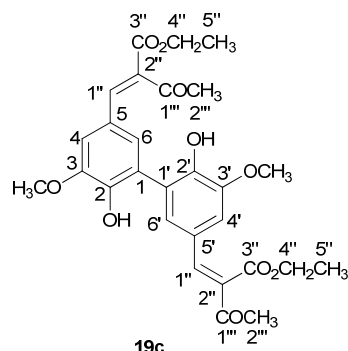
* value may be interchanged

5.1.2 5,5'-Di(2,2-diacetylviny)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (19b)



According to the general procedure **IV** a solution of **15b** (98 mg, 0.4 mmol) and laccase were reacted in NaOAc buffer for 5 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was purified by flash chromatography over silica gel (CH₂Cl₂/MeOH = 40:1) to afford 5,5'-di(2,2-diacetylviny)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (**19b**) (91 mg, 0.2 mmol, 93%) as a yellow solid: mp 210-213 °C; R_f 0.20 (CH₂Cl₂/MeOH = 40:1); UV λ_{max} (MeCN)/nm 220, 248 and 337 (log ε/dm³ mol⁻¹ cm⁻¹ 4.34, 4.35 and 4.52); IR (ATR) $\tilde{\nu}_{\text{max}}$ /cm⁻¹ 3379 (OH), 1707 (C=O), 1581 (arom. C=C), 1501 (arom. C=C), 1260 (arom. C-O), 1175 (alkyl C-O) and 815 (arom. C-H); ¹H NMR δ_H (300 MHz; DMSO-d₆) 2.23 (6H, s, 2'''-H or 4'''-H), 2.35 (6H, s, 2'''-H or 4'''-H), 3.80 (6H, s, OCH₃ and OCH₃'), 6.90 (2H, s, 6-H and 6'-H), 7.04 (2H, s, 4-H and 4'-H) and 7.60 (s, 2H, 1''-H); ¹³C NMR δ_C (75MHz; DMSO-d₆) 26.09 (C-2''' or C-4'''), 31.40 (C-2''' or C-4'''), 55.87 (OCH₃ and OCH₃'), 112.33 (C-4 and C-4'), 123.03 (C-5 and C-5'), 125.06 (C-1 and C-1'), 126.16 (C-6 and C-6'), 139.65 (C-2''), 140.14 (C-1''), 147.08 (C-2 and C-2'), 147.69 (C-3 and C-3'), 197.20 (C-1''' or C-3'') and 206.37 (C-1''' or C-3''); MS (ESI, pos.) m/z 489 [(M + Na)⁺, 100%]; 484 [(M + NH₄)⁺, 18] and 467 [(M + H)⁺, 65]; HRMS (ESI, pos.) found: 467.1700 [C₂₆H₂₆O₈ + H]⁺ calc. for C₂₆H₂₇O₈: 467.1706.

5.1.3 5,5'-Di(2-acetyl-2-ethoxycarbonylvinyl)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (19c)

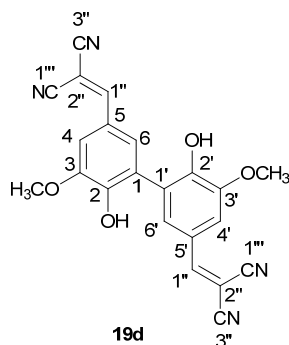


According to the general procedure **IV** a solution of **15c** (88 mg, 0.4 mmol) and laccase were reacted in NaOAc buffer for 3 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was purified by column chromatography over silica gel (CH₂Cl₂/MeOH = 40:1) to afford a mixture of the three *E/Z*-isomers of 5,5'-di(2-acetyl-2-ethoxycarbonylvinyl)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (**19c**) (76 mg, 0.17 mmol, 86%) as a yellow oil: R_f 0.30 (CH₂Cl₂/MeOH = 30:1); UV λ_{max} (MeCN)/nm 248 and 335 (log ε/dm³ mol⁻¹ cm⁻¹ 4.21 and 4.37); IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ 3359 (OH), 2982 (CH₂, CH₃), 1716 (C=O), 1586 (arom. C=C), 1492 (arom. C=C), 1213 (arom. C-O), 1181 (alkyl C-O), 857 (arom. C-H) and 814 (arom. C-H); ¹H NMR (*E*)/(*E*)-**19c** δ_H (500 MHz; CDCl₃) 1.30 (6H, t, ³J_{4''-H,5''-H} 7.03 Hz, 5''-H), 2.59 (6H, s, 2''''-H), 3.89 (6H, s, OCH₃ and OCH₃''),* 4.26 (4H, q, ³J_{4''-H,5''-H} 6.98 Hz, 4''-H), 6.95 (2H, d, ⁴J_{4-H,6-H} 1.85, ⁴J_{4'-H,6'-H} 1.85 Hz, 6-H and 6'-H), 7.00 (2H, d, ⁴J_{4-H,6-H} 2.00, ⁴J_{4'-H,6'-H} 2.00 Hz, 4-H and 4'-H) and 7.57 (2H, s, 1''-H); ¹³C NMR (*E*)/(*E*)-**19c** δ_C (125MHz; CDCl₃) 14.13 (C-5''), 31.26 (C-2'''), 56.059(OCH₃ and OCH₃''),* 61.32 (C-4''), 126.72 (C-6 and C-6'), 124.63 (C-1 and C-1'), 124.68 (C-5 and C-5'), 110.83 (C-4 and C-4'), 131.72 (C-2''), 141.15 (C-1''), 147.13 (C-3 and C-3'), 145.51 (C-2 and C-2'), 164.61 (C-3'') and 203.93 (C-1'''); ¹H NMR (*Z*)/(*Z*)-**19c** δ_H (500 MHz; CDCl₃) 1.27 (6H, t, ³J_{4''-H,5''-H} 7.03 Hz, 5''-H), 2.37 (6H, s, 2''''-H), 3.89(6H, s, OCH₃ and OCH₃''),* 4.26 (4H, q, ³J_{4''-H,5''-H} 6.98 Hz, 4''-H), 7.05 (2H, d, ⁴J_{4-H,6-H} 2.07, ⁴J_{4'-H,6'-H} 2.07 Hz, 6-H and 6'-H), 7.07 (2H, d, ⁴J_{4-H,6-H} 2.00, ⁴J_{4'-H,6'-H} 2.00 Hz, 4-H and 4'-H) and 7.46 (2H, s, 1''-H); ¹³C NMR (*Z*)/(*Z*)-**19c** δ_C (125 MHz; CDCl₃) 13.91 (C-5''), 26.29 (C-2'''), 56.11(OCH₃ and OCH₃''),* 61.62 (C-4''), 127.23 (C-6 and C-6'), 123.43 (C-1 and C-1'), 124.61 (C-5 and C-5'), 110.43 (C-4 and C-4'), 132.49 (C-2''), 140.41 (C-1''), 147.27 (C-3 and C-3'), 145.93 (C-2 and C-2'), 168.23 (C-3'') and 194.59 (C-1'''); MS (ESI, pos.) *m/z* 549 [(M + Na)⁺, 100%], 544 [(M + NH₄)⁺, 21] and 527 [(M + H)⁺, 44]; HRMS (ESI, pos.) found: 527.1912 [C₂₈H₃₀O₁₀ + H]⁺ calc. for C₂₈H₃₁O₁₀: 527.1917.

* value may be interchanged

The signals of (*E*)/(*Z*)-isomer are overlapped with the signals of the (*E*)/(*E*)- and the (*Z*)/(*Z*)-isomer.

5.1.4 5,5'-Di(2,2-dicyanovinyl)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (**19d**)



According to the general procedure **IV** a solution of **15d** (80 mg, 0.4 mmol) and laccase were reacted in NaOAc buffer for 21 h at room temperature. After evaporation of the volatiles *in vacuo* the crude product was washed with EtOAc/cyclohexane (5:2) (3 × 3 mL) to afford 5,5'-di(2,2-dicyanovinyl)-2,2'-dihydroxy-3,3'-dimethoxybiphenyl (**19d**) (85 mg, 0.2 mmol, quantitativ) as a yellow solid: mp > 300 °C (lit.,¹³ > 300 °C); UV λ_{\max} (MeCN)/nm 259, 376 and 446 (log $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 4.15, 4.49 and 4.00); IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ 3388 (OH), 2227 (CN), 1593 (C=C), 1504 (arom. C=C), 1293 (arom. C-O), 1184 (alkyl C-O) and 845 (arom. C-H); ¹H NMR δ_{H} (300 MHz; DMSO-*d*₆) 3.90 (6H, s, OCH₃ and OCH₃'), 7.46 (2H, d, ⁴*J*_{4-H,6-H} 1.9 Hz, 6-H and 6'-H), 7.71 (2H, d, ⁴*J*_{4-H,6-H} 1.9 Hz, 4-H and 4'-H) and 8.31 (2H, s, 1''-H); ¹³C NMR δ_{C} (75 MHz; DMSO-*d*₆) 55.96 (OCH₃ and OCH₃'), 75.33 (C-2''), 111.72 (C-4 and C-4'), 114.30 (C-1''' or C-3''), 115.08 (C-1''' or C-3''), 122.23 (C-5 and C-5'), 124.92 (C-1 and C-1'), 129.22 (C-6 and C-6'), 147.94 (C-3 and C-3'), 151.61 (C-2 and C-2') and 160.44 (C-1''); MS (ESI, pos.) *m/z* 421 [(M + Na)⁺ 100%]; HRMS (ESI, pos.) found: 421.0907 [C₂₂H₁₄N₄O₄ + Na]⁺ calc. for C₂₂H₁₄N₄O₄Na: 421.0913.

5.2 Treatment of trisubstituted vanillidene derivatives **15** with aerial O₂ in the absence of any catalyst

A solution of **15** (0.4 mmol) in DMSO (8 mL) was stirred in NaOAc buffer (0.1 M, pH 5.0, 72 mL) as the solvent under air at room temperature for the reaction times given in Table 3. After extraction with CH₂Cl₂ (3 × 30 mL) the combined organic phases were analyzed by TLC. Only **15** could be detected.

6 Enantiomeric analysis of 17a-d by chiral HPLC

The enantiomers of **17a** were separated by chiral HPLC (CHIRALPAK IB column; 250 mm × 4.60 mm, 5 μ; *n*-hexane/EtOAc = 4:6; flow rate 1 mL/min; UV detection λ 280 nm) to afford the two enantiomers ($t_R = 5.38$ min, $t_R = 6.27$ min) (Fig. 1). The enantiomeric excess was calculated from the peak areas to ee (%) = 1.30.

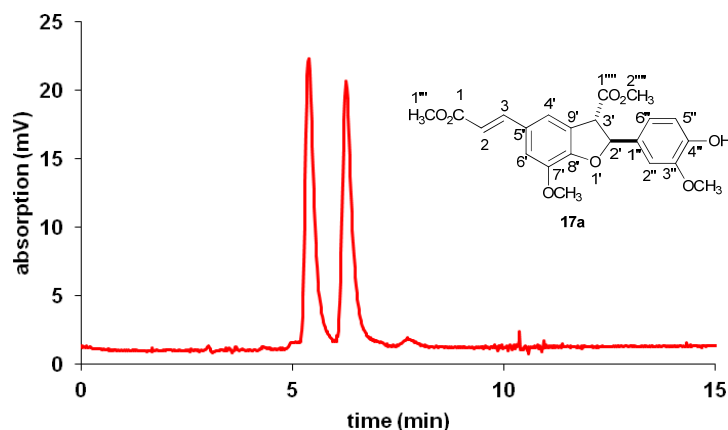


Fig. 1. HPLC chromatogram of the separation of the enantiomers of **17a** on an analytical column with a chiral stationary phase.

The enantiomers of **17b** were separated by chiral HPLC (CHIRALPAK IB column; 250 mm × 4.60 mm, 5 μ; *n*-hexane/EtOH = 5:2; flow rate 1 mL/min; UV detection λ 280 nm) to afford the two enantiomers ($t_R = 7.05$ min, $t_R = 8.05$ min) (Fig. 2). The enantiomeric excess was calculated from the peak areas to ee (%) = 0.66.

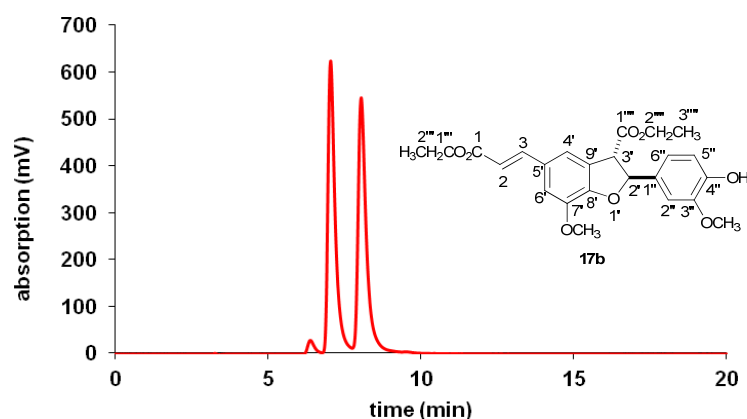


Fig. 2. HPLC chromatogram of the separation of the enantiomers of **17b** on an analytical column with a chiral stationary phase.

The enantiomers of **17c** were separated by chiral HPLC (CHIRALPAK IB column; 250 mm × 4.60 mm, 5 μ; *n*-hexane/EtOH = 5:1; flow rate 1 mL/min; UV detection λ 280 nm) to afford the two enantiomers ($t_R = 10.29$ min, $t_R = 11.95$ min) (Fig. 3). The enantiomeric excess was calculated from the peak areas to ee (%) = 6.00.

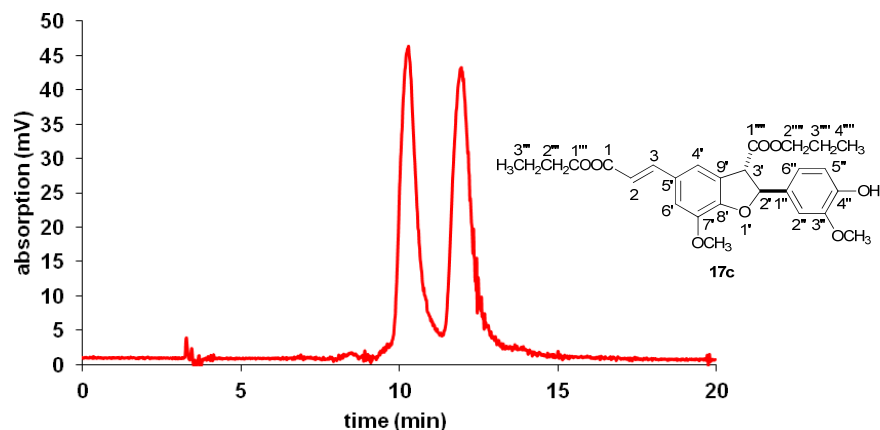


Fig. 3. HPLC chromatogram of the separation of the enantiomers of **17c** on an analytical column with a chiral stationary phase.

The enantiomers of **17d** were separated by chiral HPLC (CHIRALPAK IB column; 250 mm × 4.60 mm, 5 μ; *n*-hexane/EtOAc = 3:1; flow rate 1 mL/min; UV detection λ 280 nm) to afford the two enantiomers ($t_R = 10.56$ min, $t_R = 12.06$ min) (Fig. 4). The enantiomeric excess was calculated from the peak areas to ee (%) = 6.00.

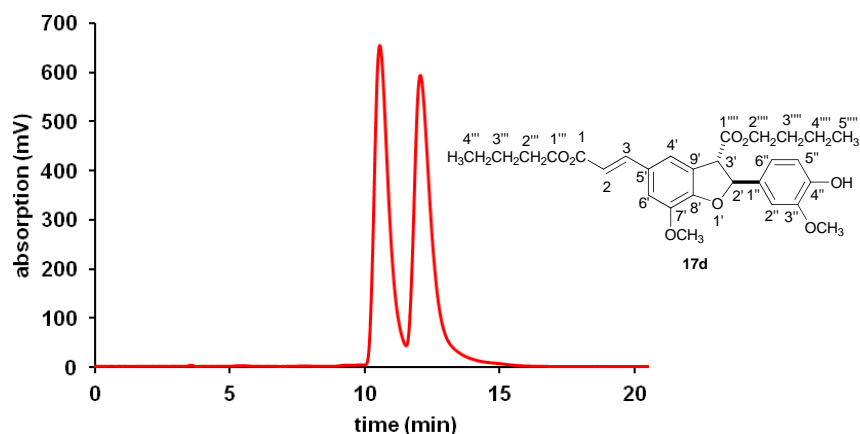


Fig. 4. HPLC chromatogram of the separation of the enantiomers of **17d** on an analytical column with a chiral stationary phase.

7 Copies of ^1H and ^{13}C NMR spectra¹⁴

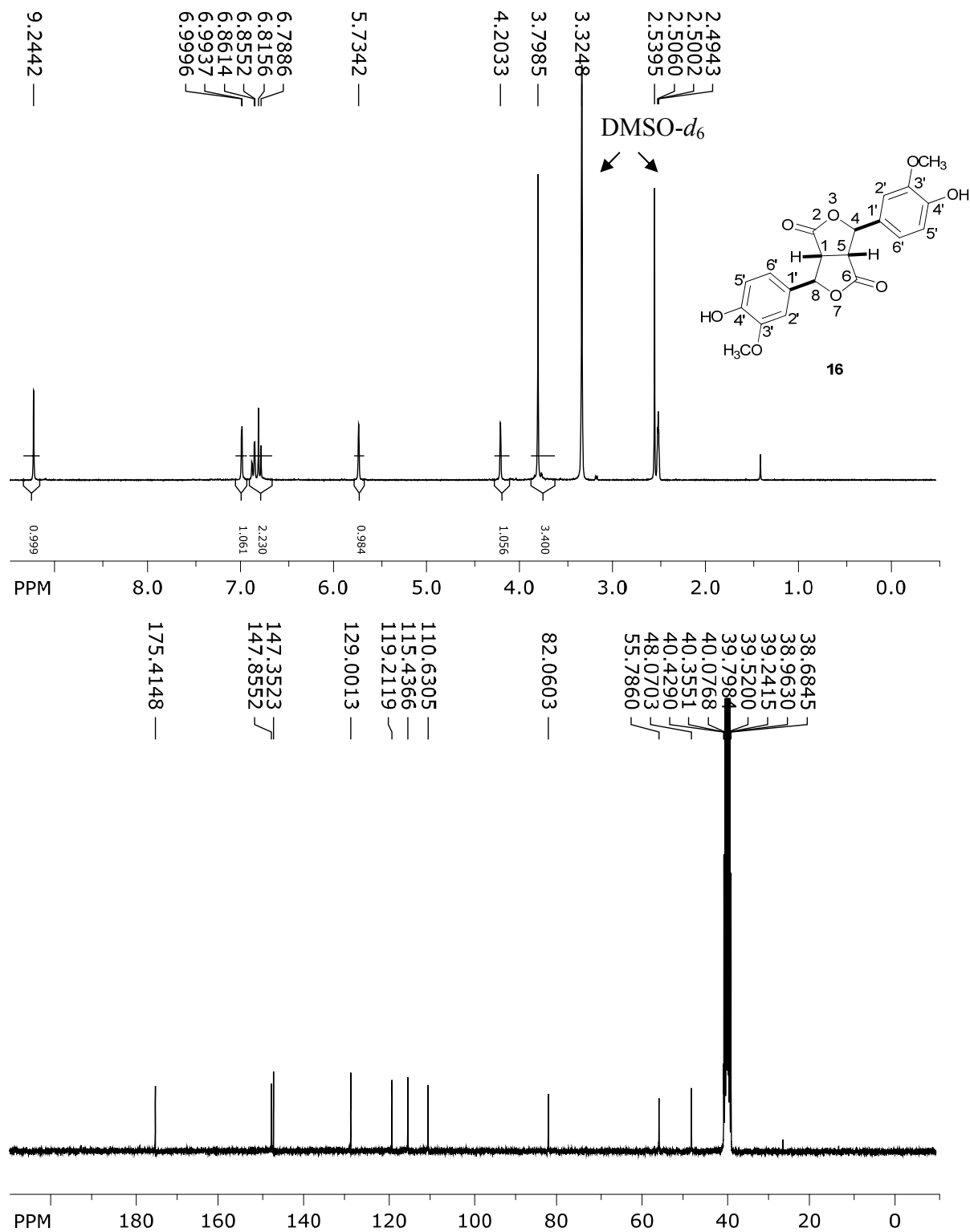


Fig. 5. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of **16** in $\text{DMSO-}d_6$.

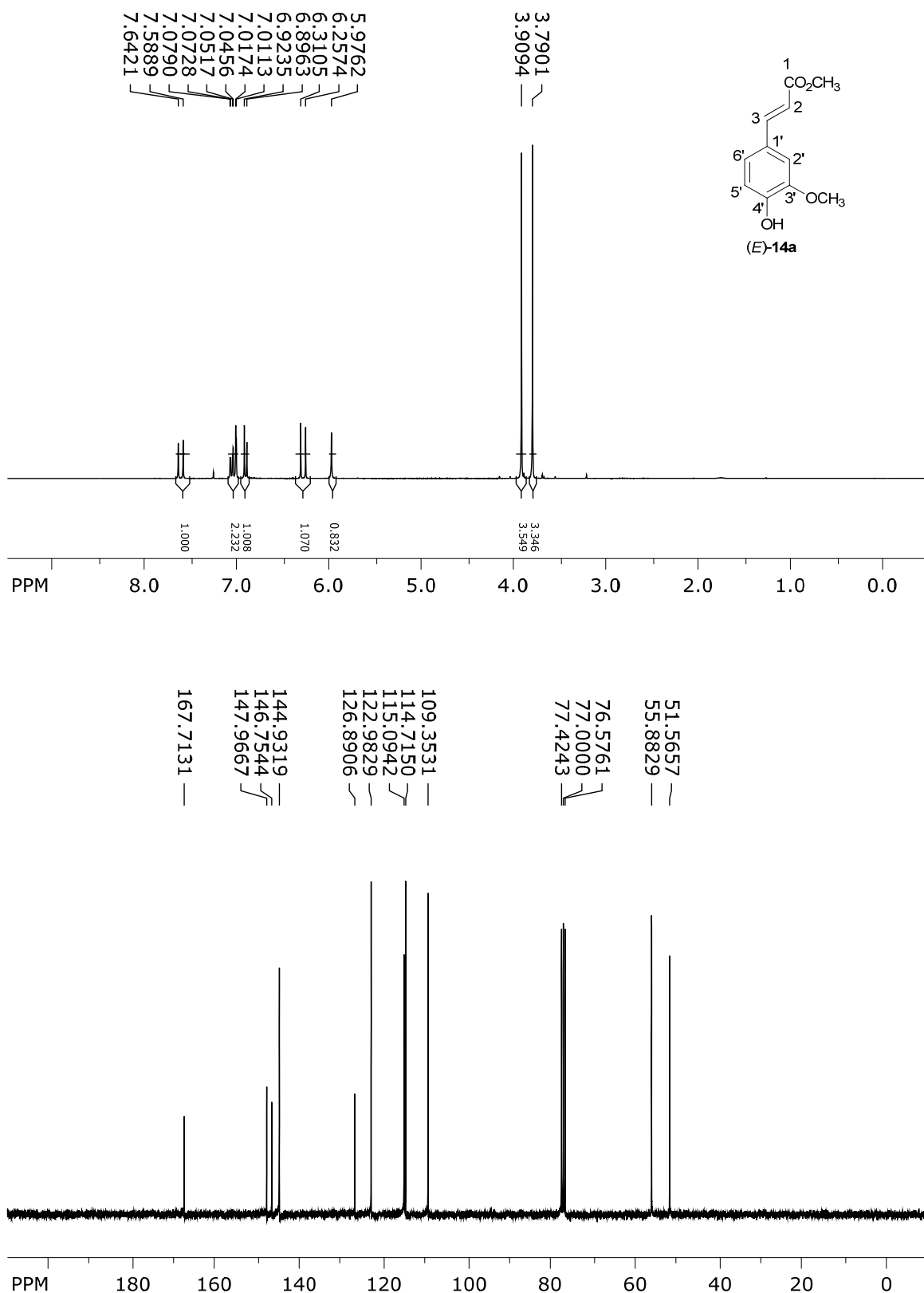


Fig. 6. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of *(E)*-14a in CDCl₃.

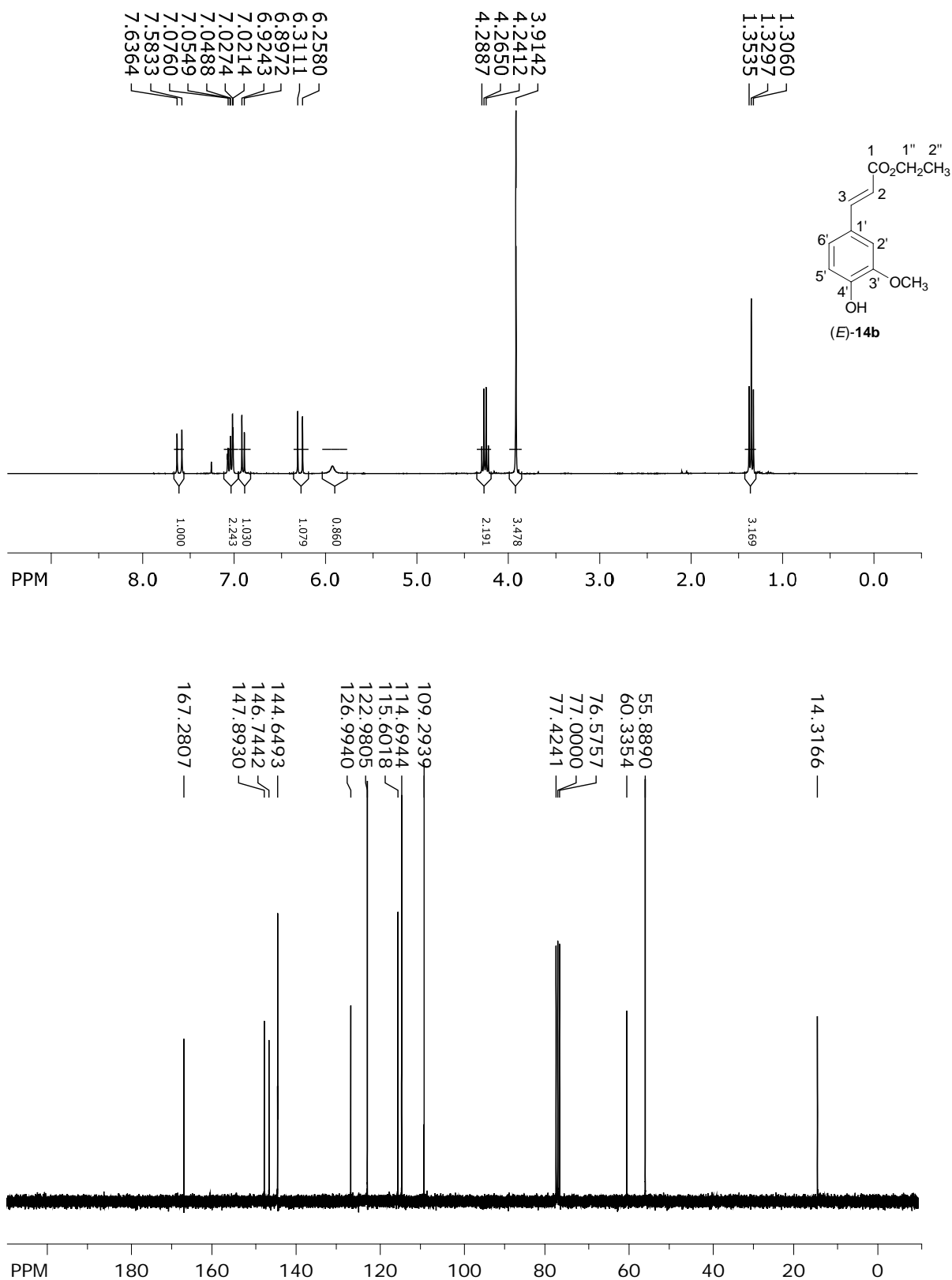


Fig. 7. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of *(E)*-14b in CDCl₃.

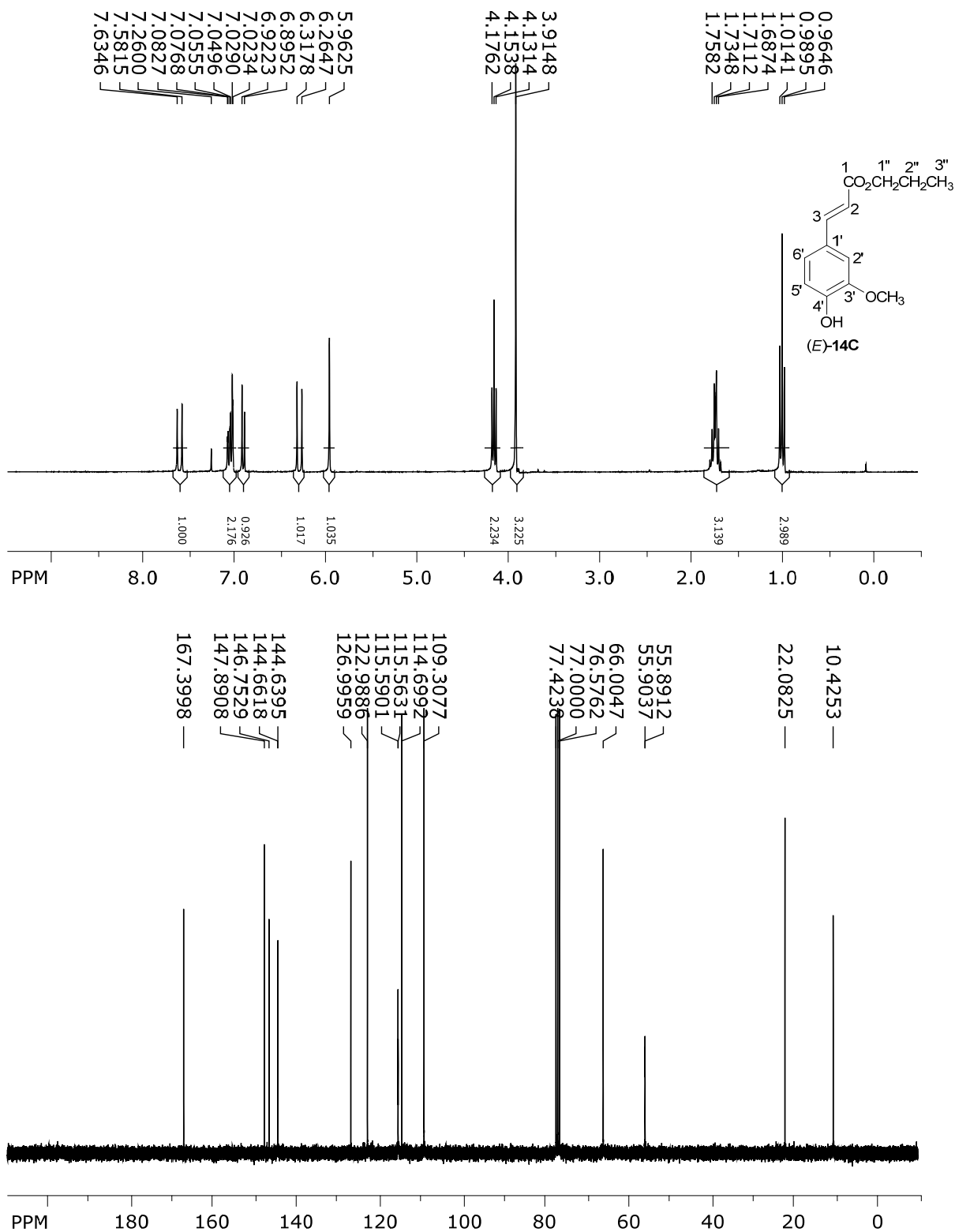


Fig. 8. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of *(E)*-14c in CDCl₃.

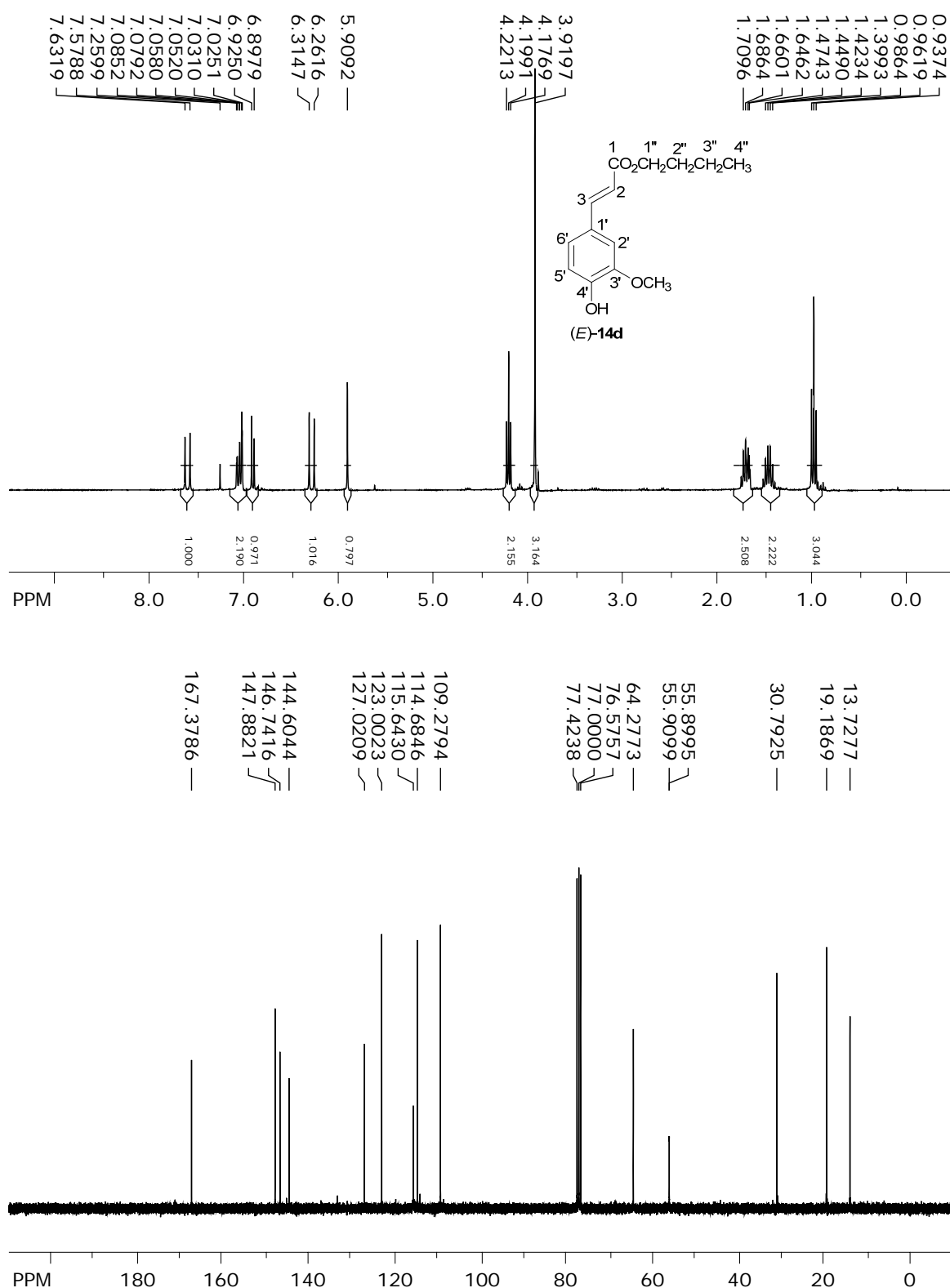


Fig. 9. ¹H (300 MHz) and ¹³C (75 MHz) of (E)-14d in CDCl₃.

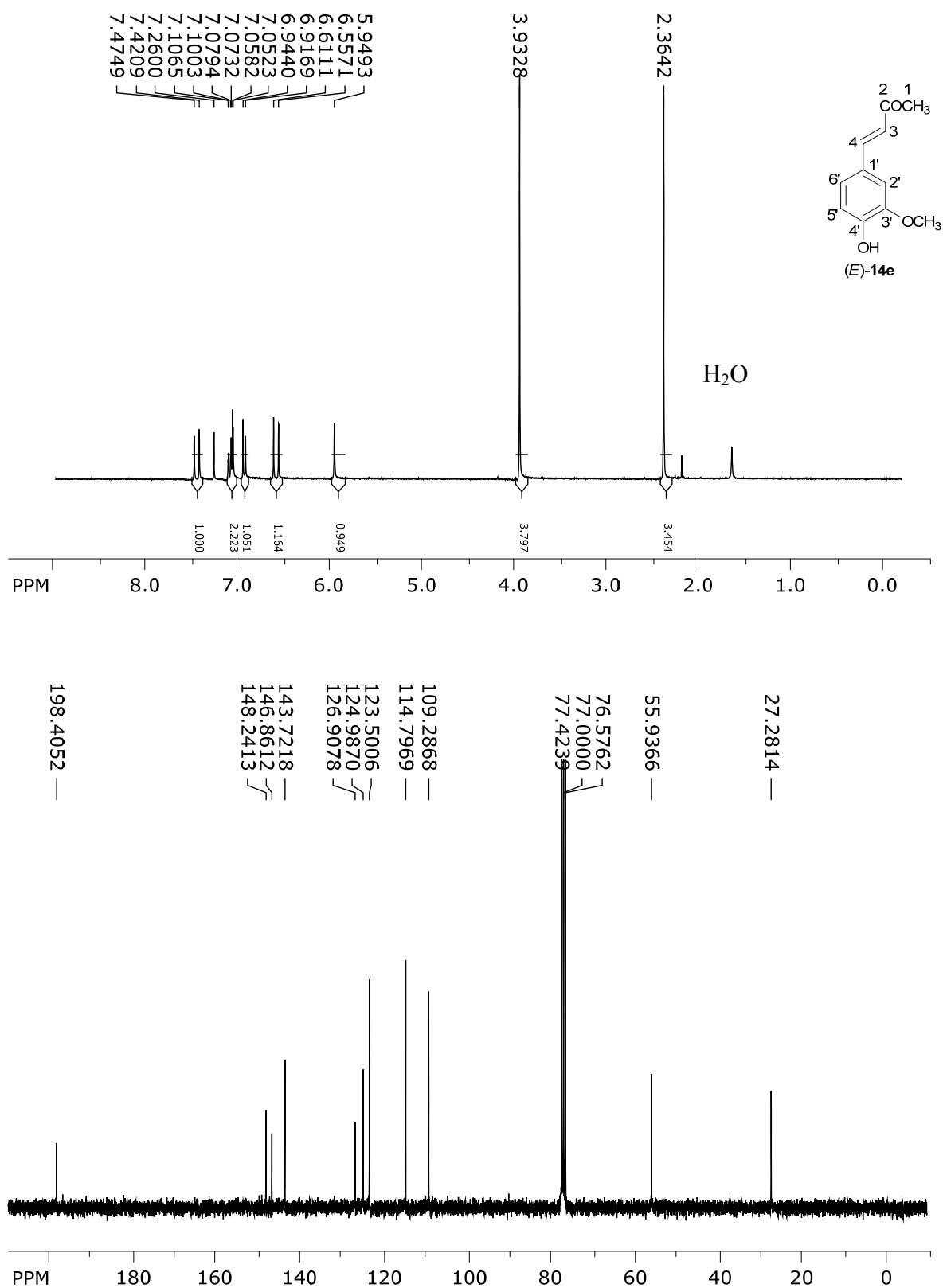


Fig. 10. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of (E)-14e in CDCl₃.

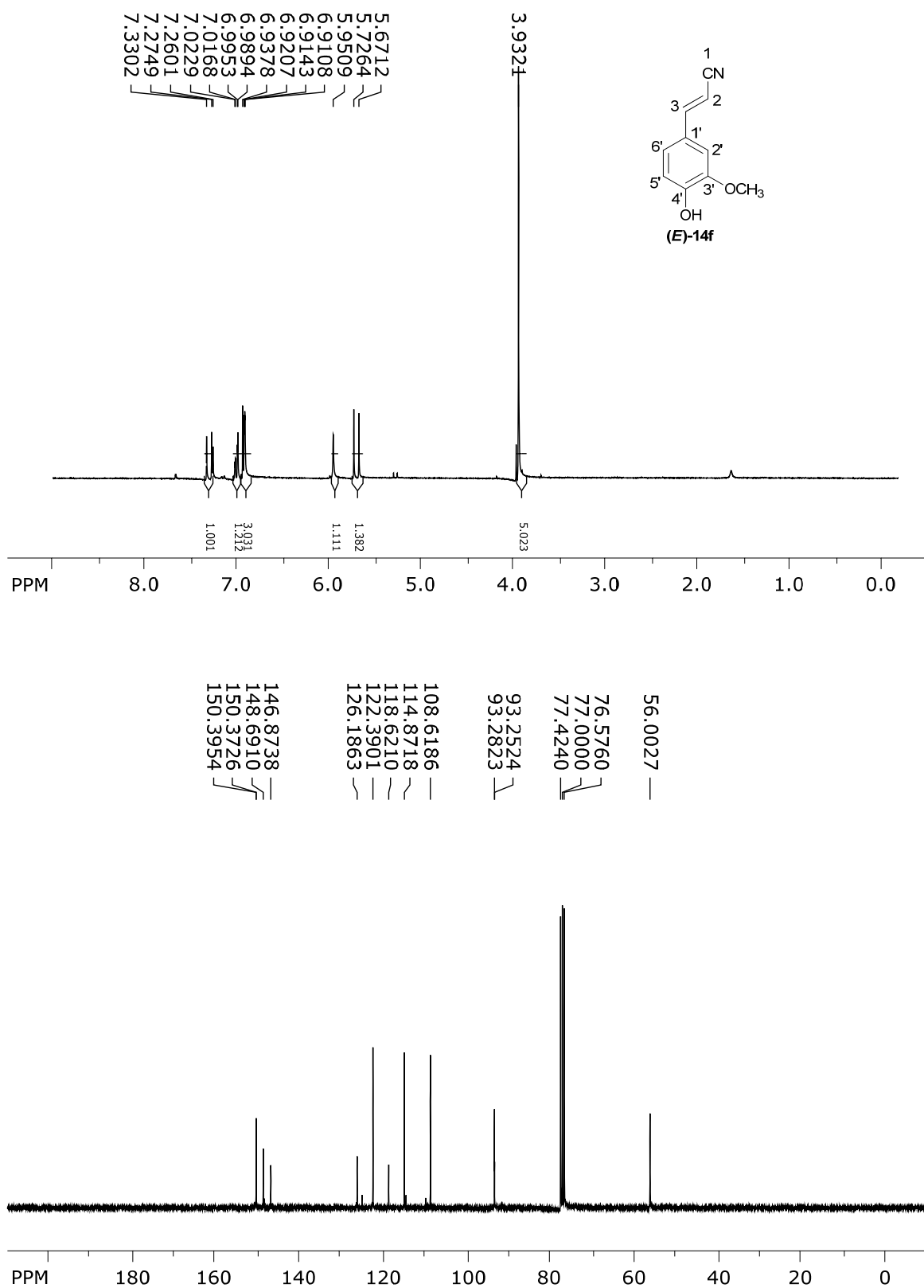


Fig. 11. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of (E)-14f in CDCl₃.

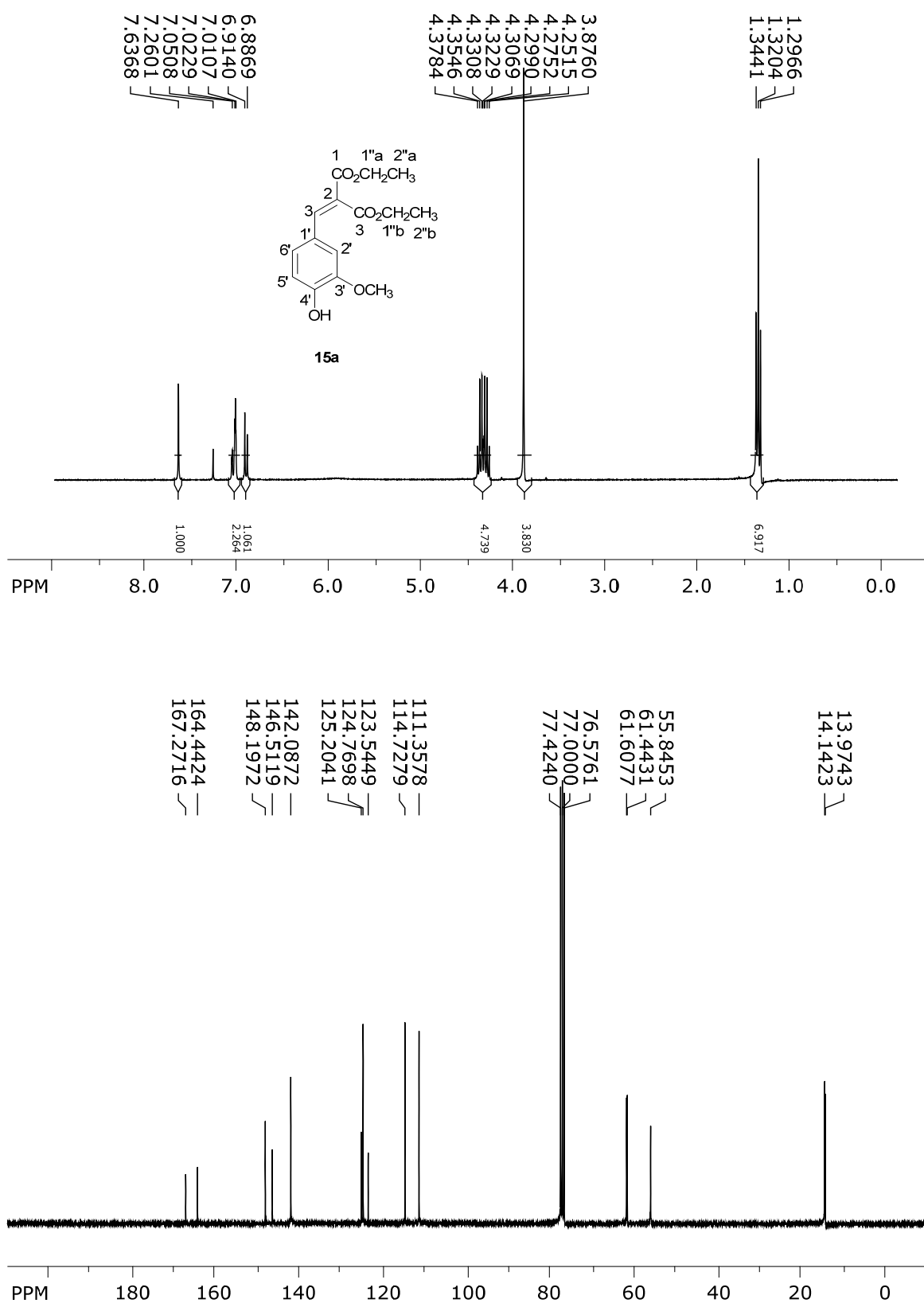


Fig. 12. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **15a** in CDCl₃.

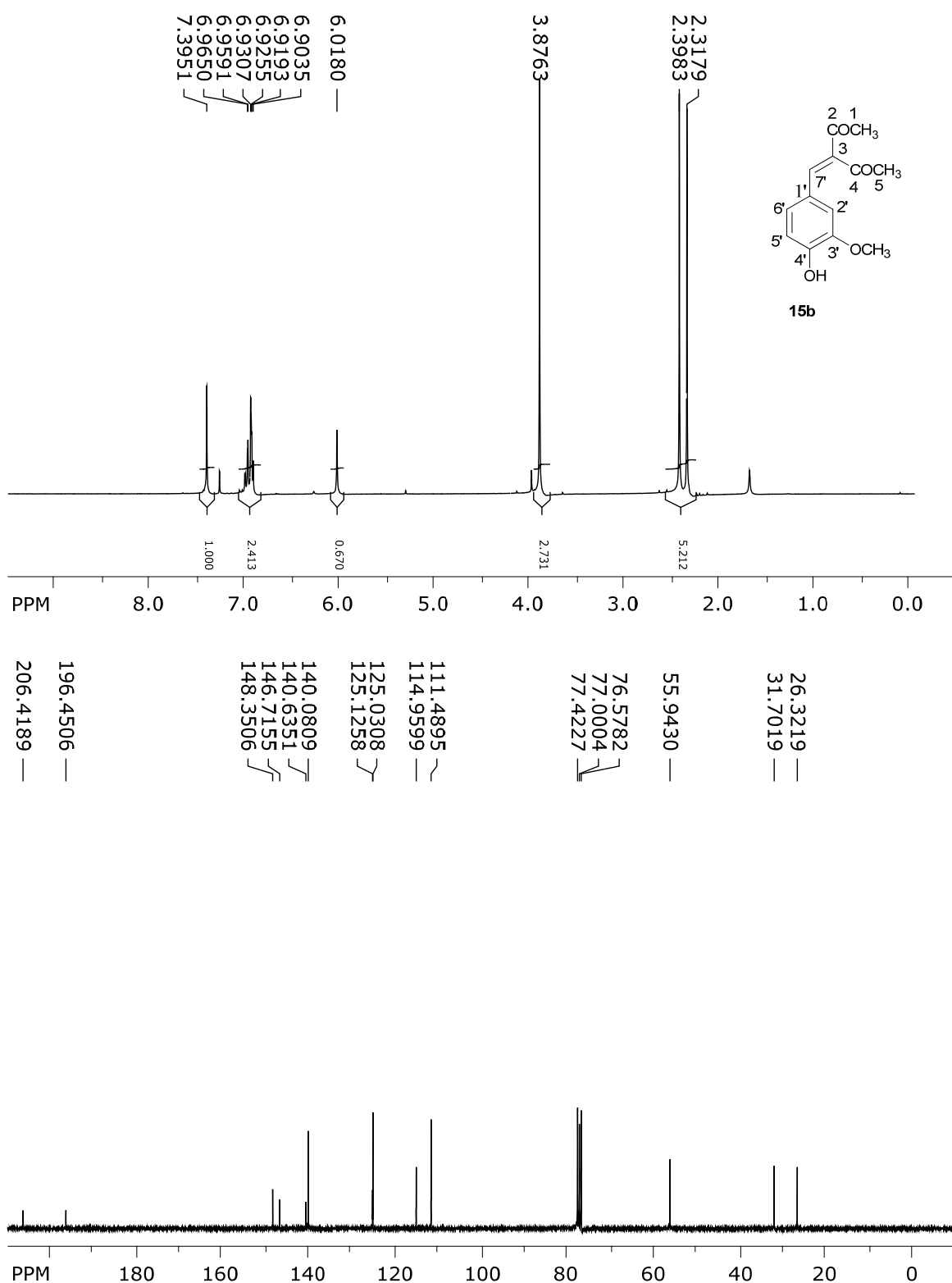


Fig. 13. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **15b** in CDCl₃.

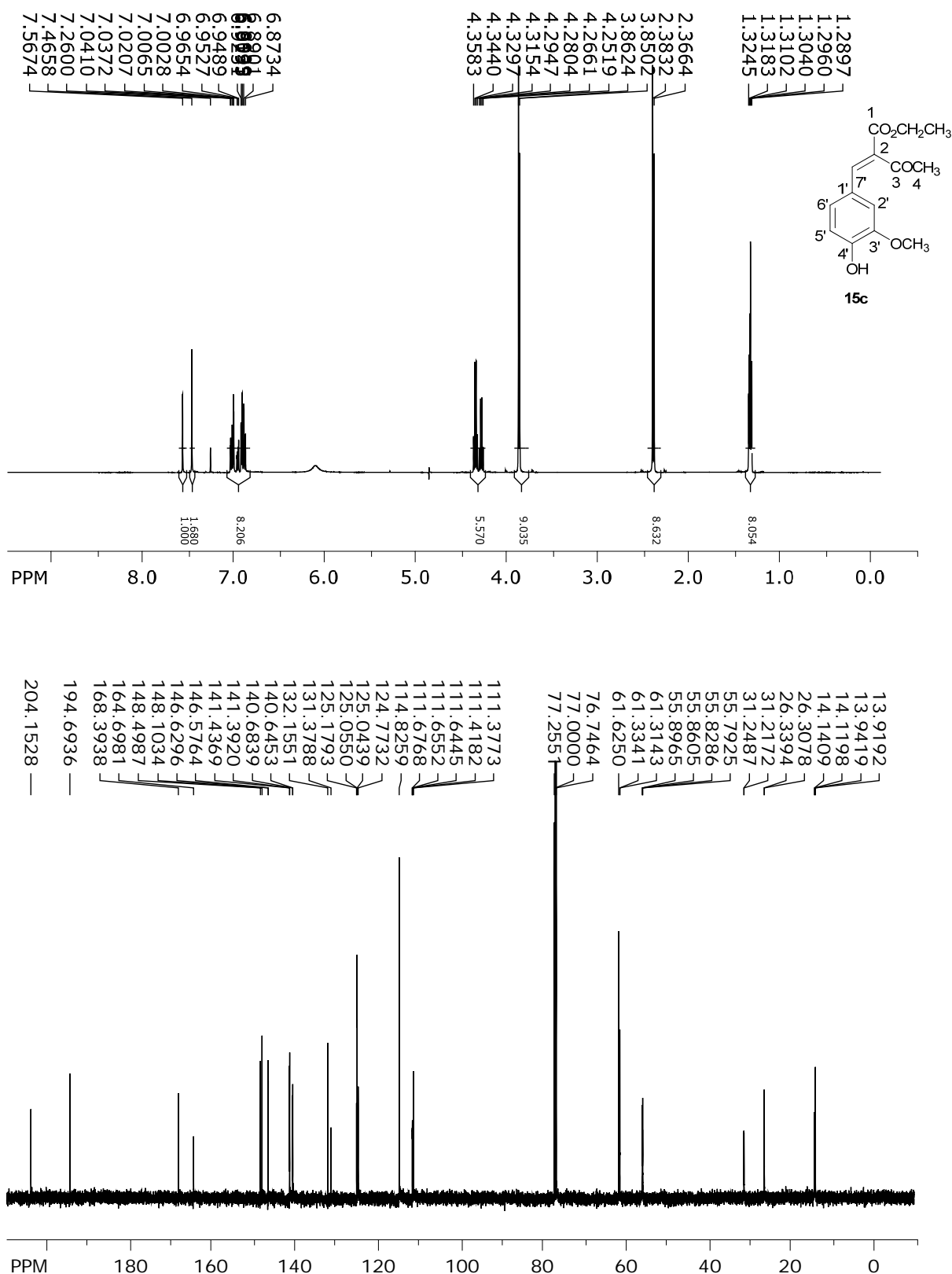


Fig. 14. ¹H (500 MHz) and ¹³C (125 MHz) NMR spectra of **15c** in CDCl₃.

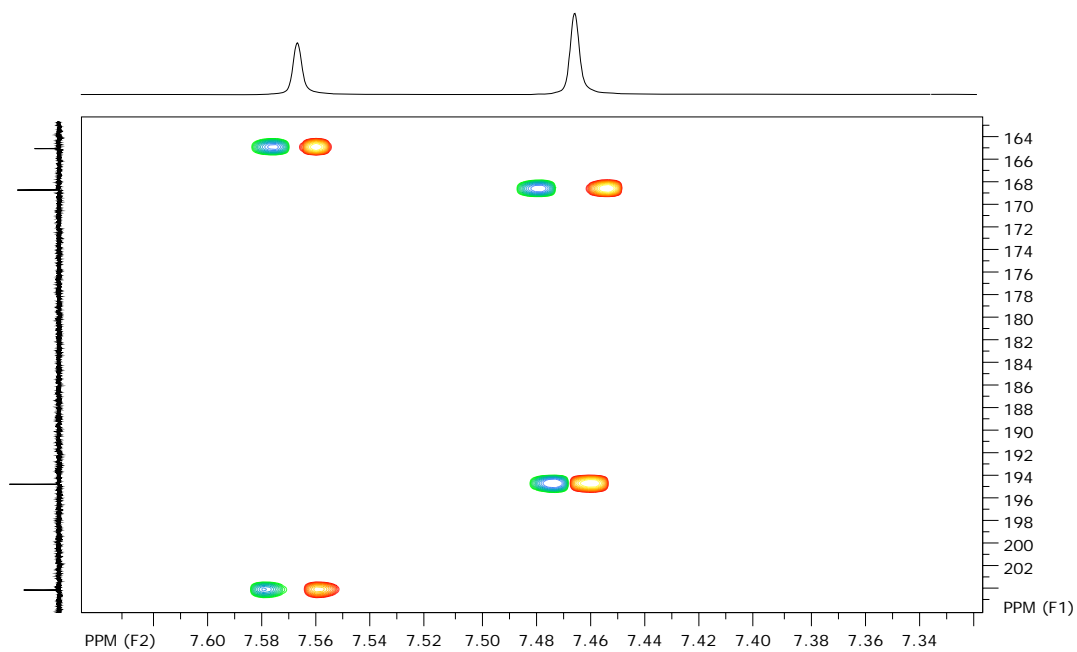


Fig. 15. Part of HSQMBC (500, 125 MHz) NMR spectrum of **15c** in CDCl₃ used for the determination of *E* and *Z* isomers from the mixture.

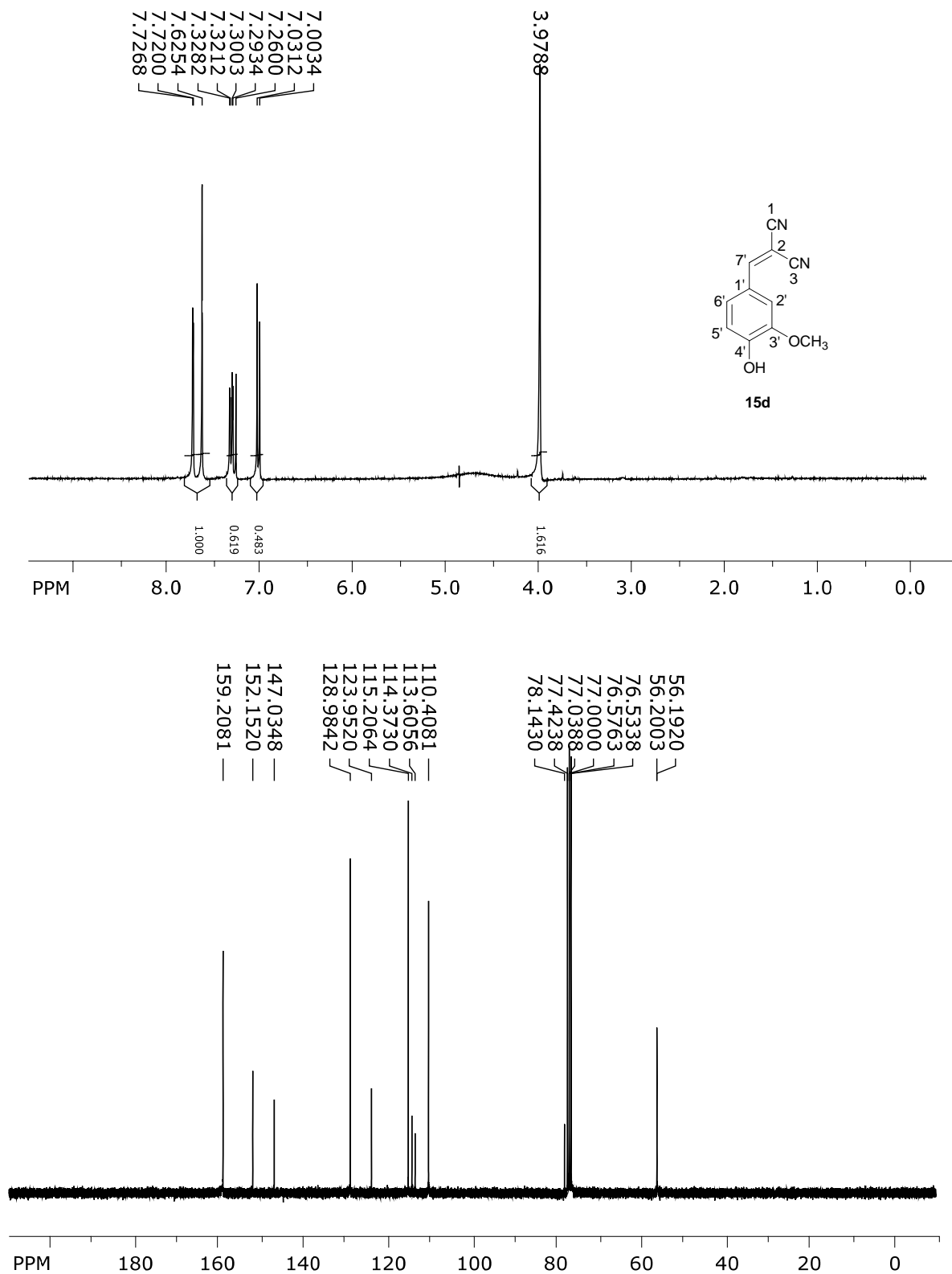


Fig. 16. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **15d** in CDCl₃.

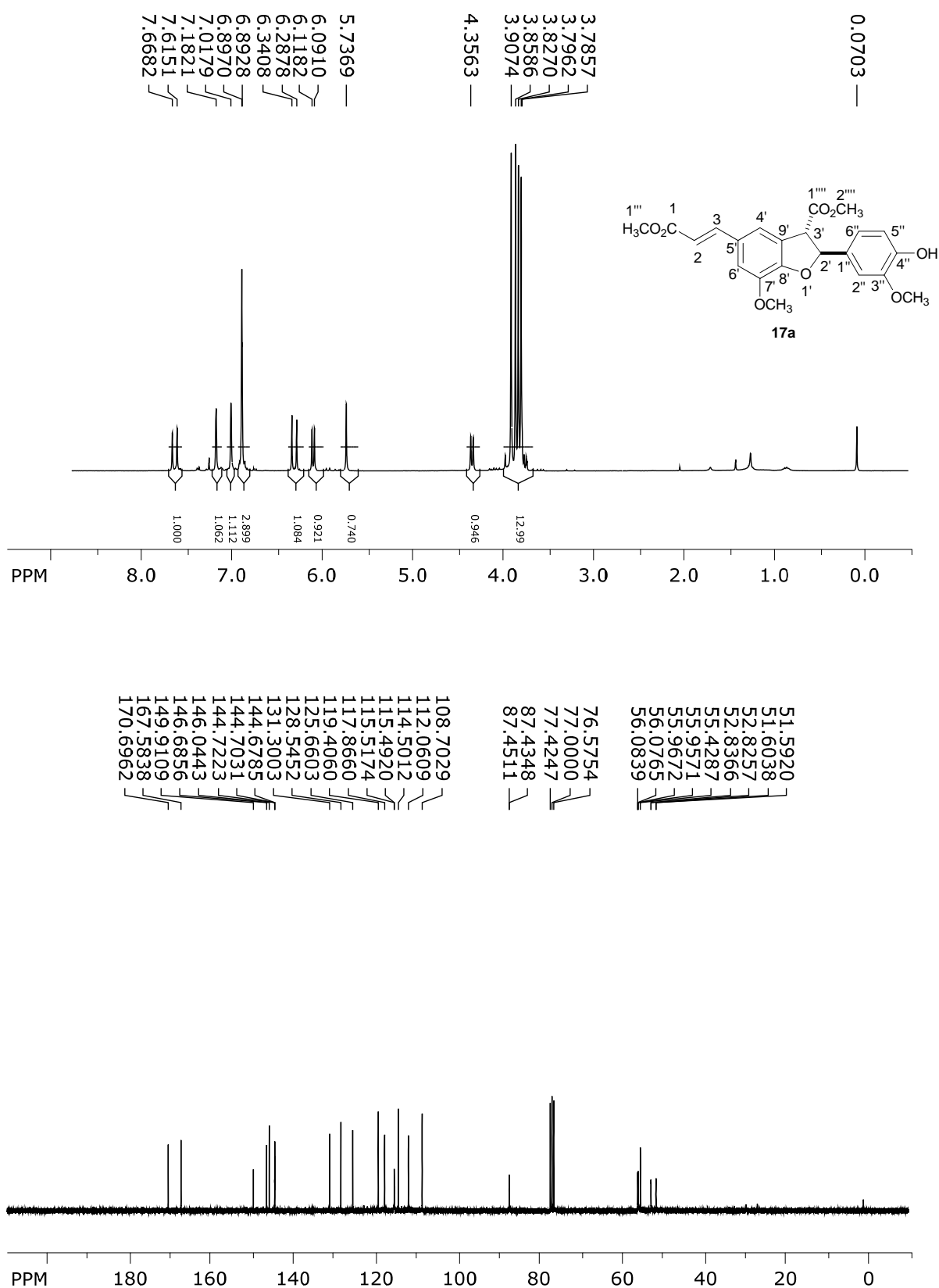


Fig. 17. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **17a** in CDCl₃.

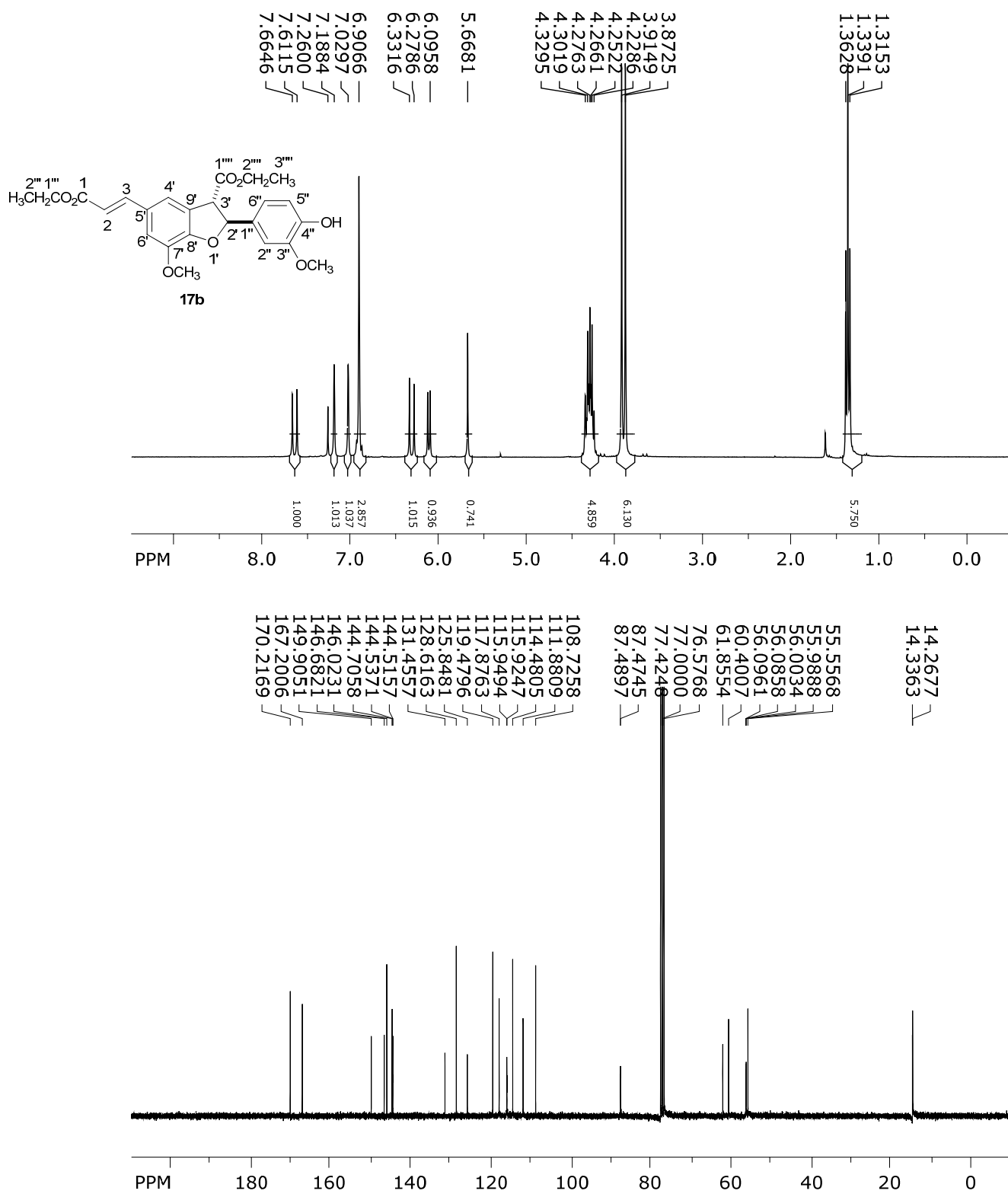


Fig. 18. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **17b** in CDCl₃.

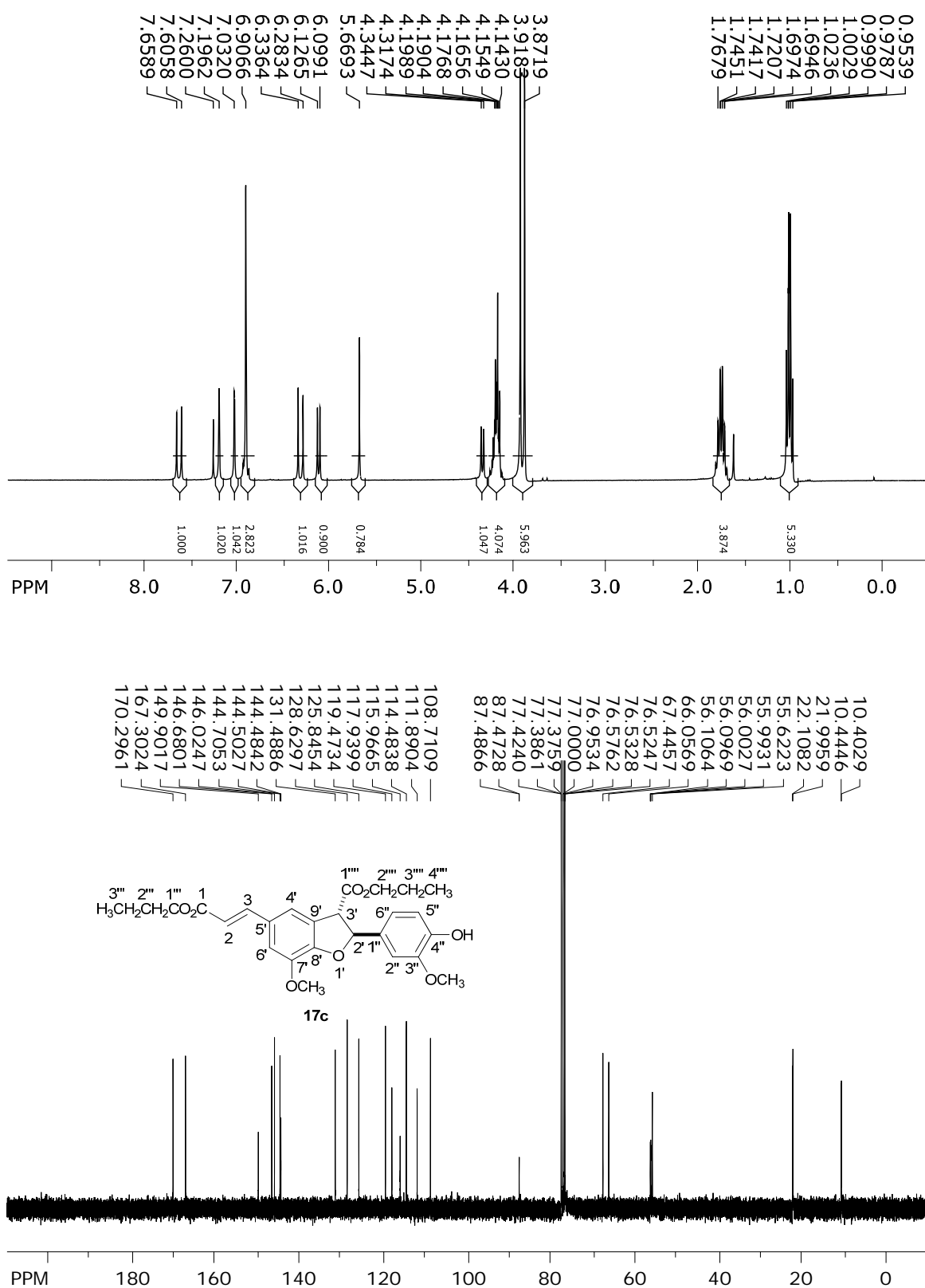


Fig. 19. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **17c** in CDCl₃.

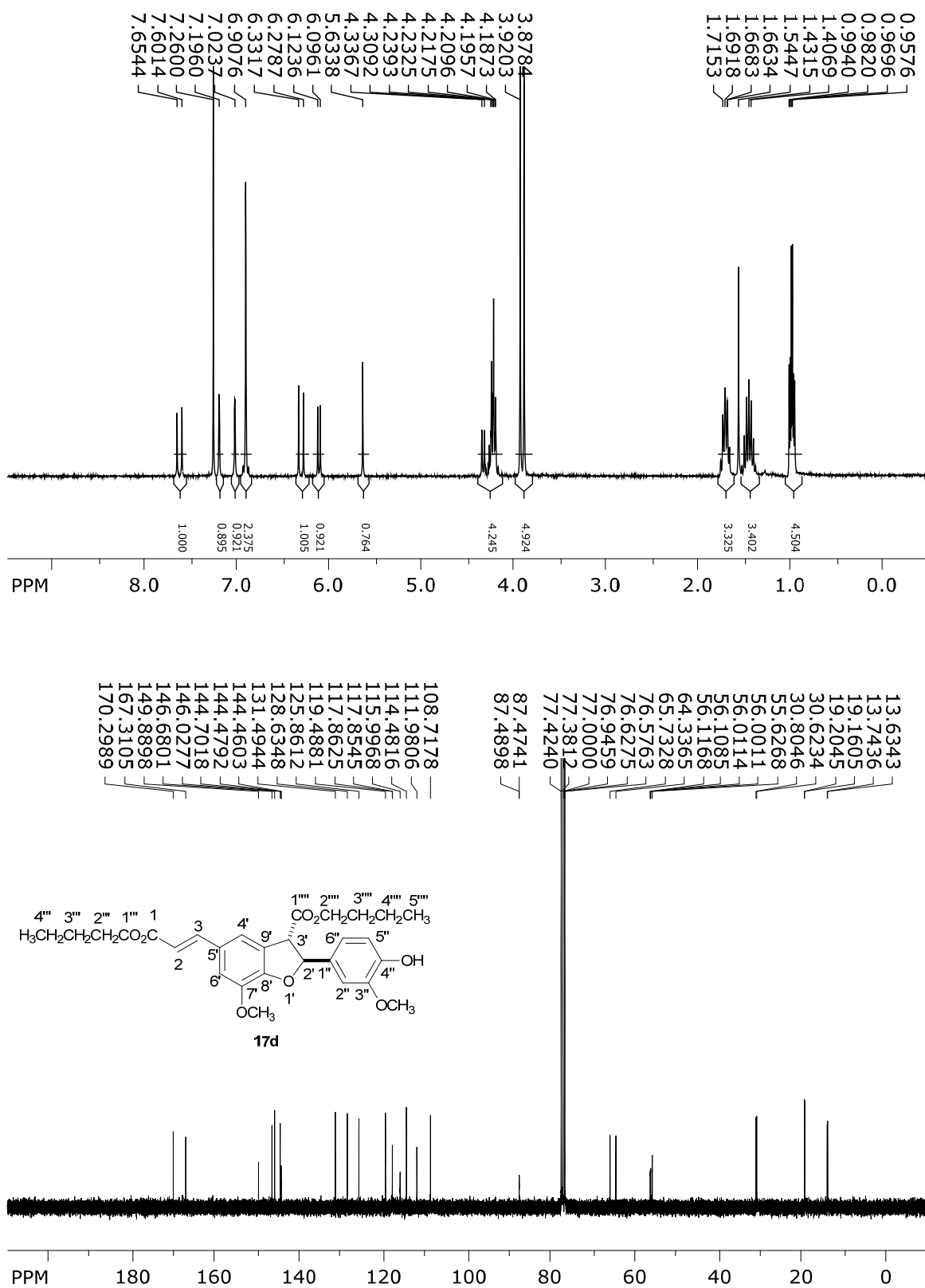


Fig. 20. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **17d** in CDCl₃.

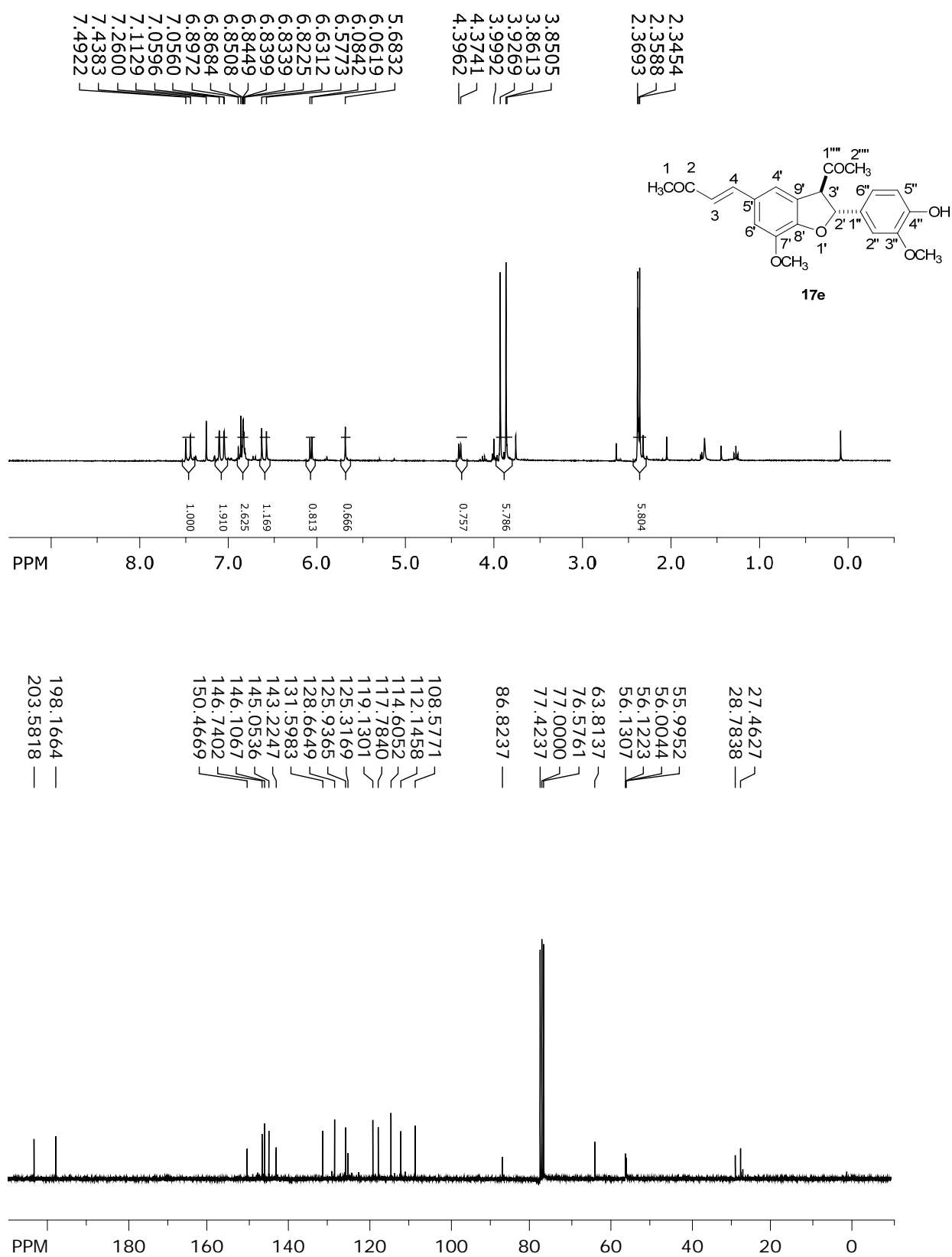


Fig. 21. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **17e** in CDCl₃.

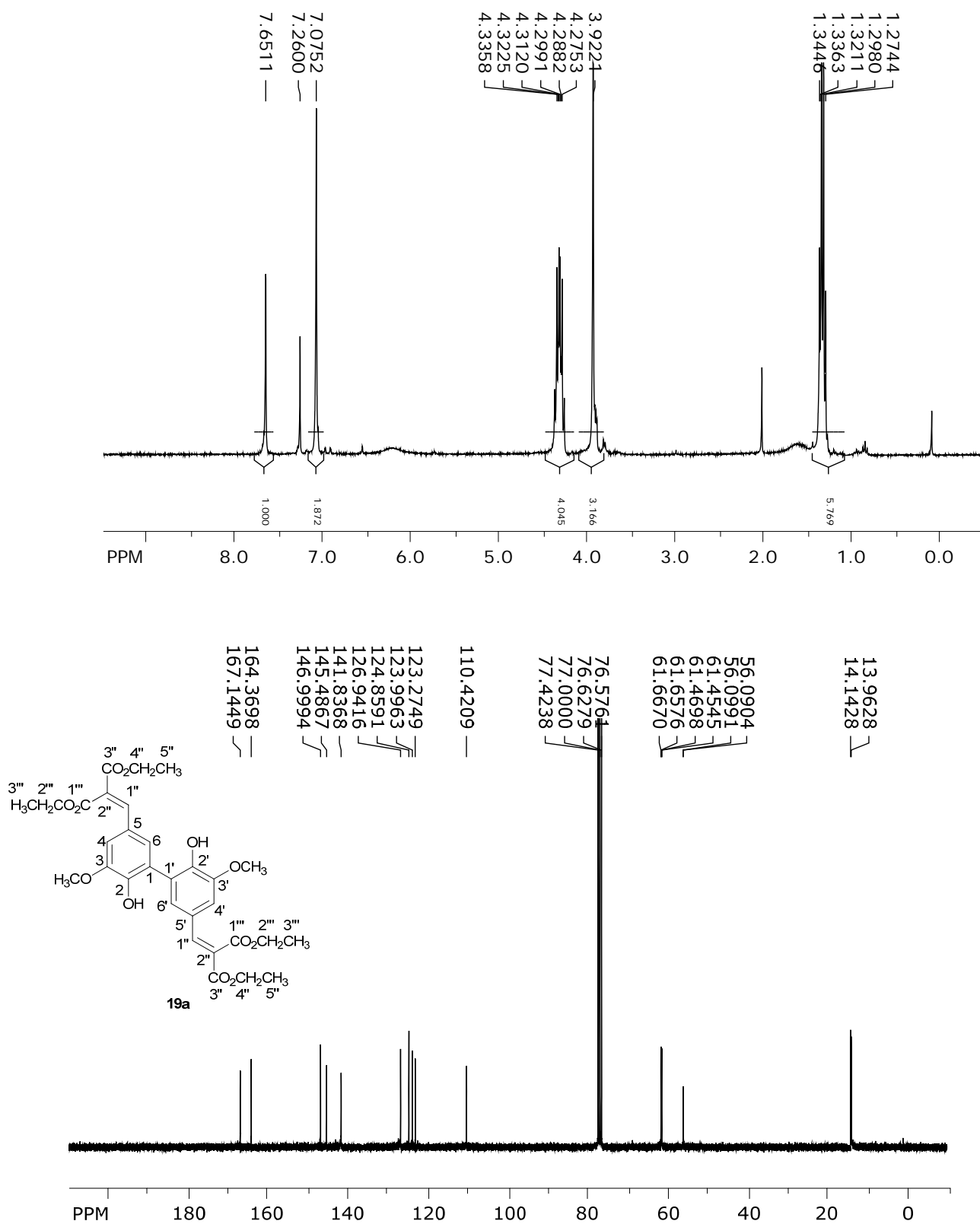


Fig. 22. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **19a** in CDCl₃.

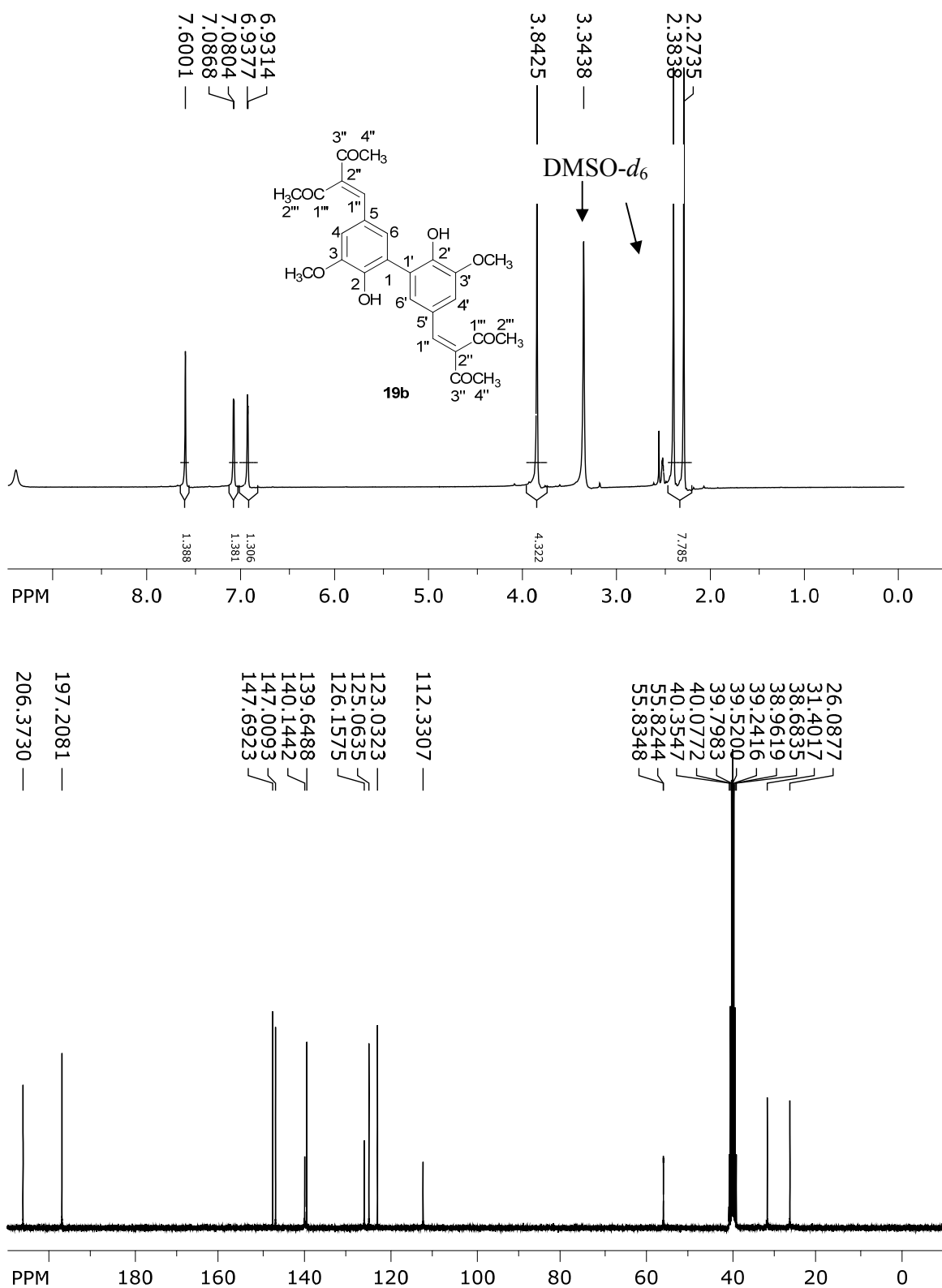


Fig. 23. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **19b** in DMSO-*d*₆.

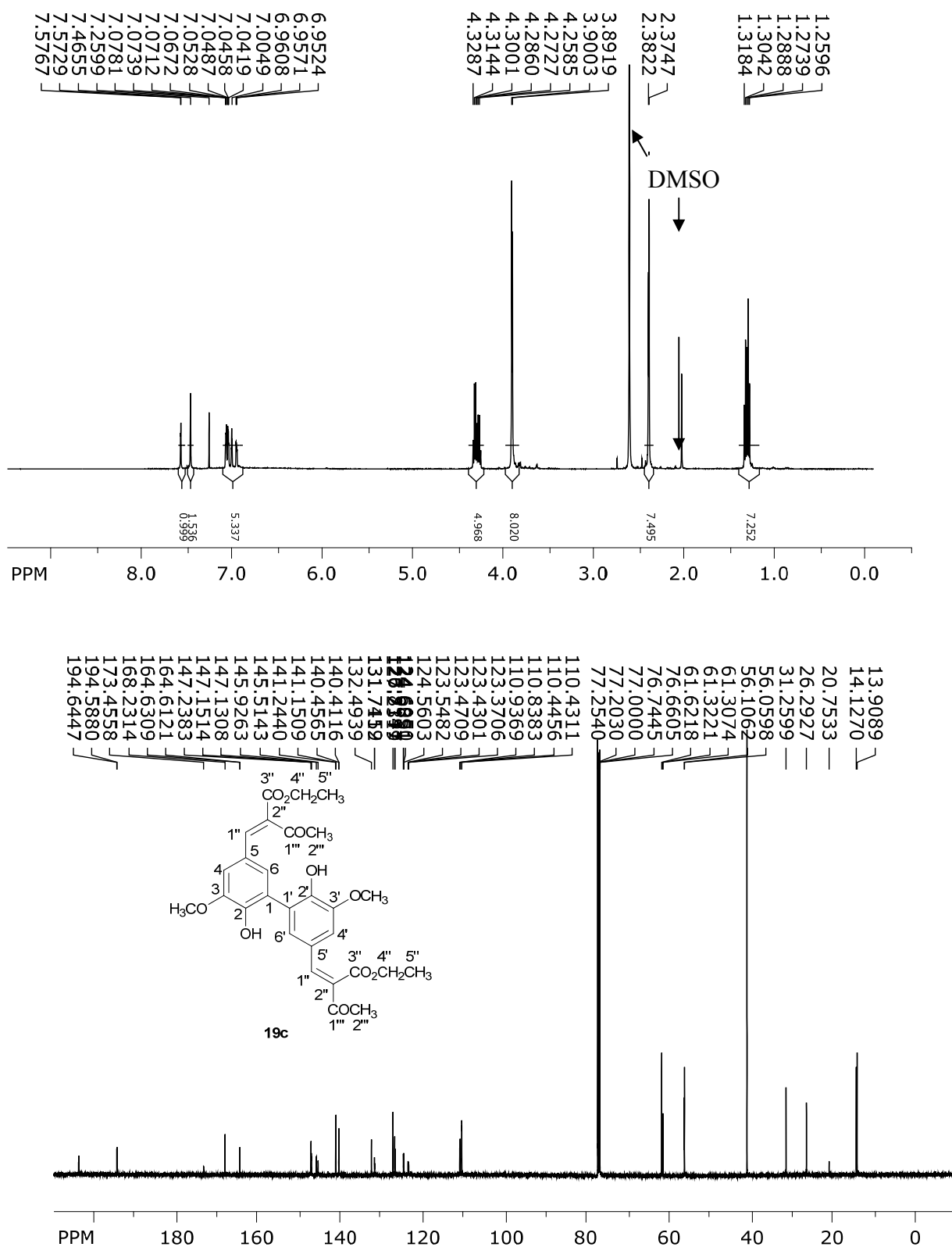


Fig. 24. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra of **19c** in CDCl₃.

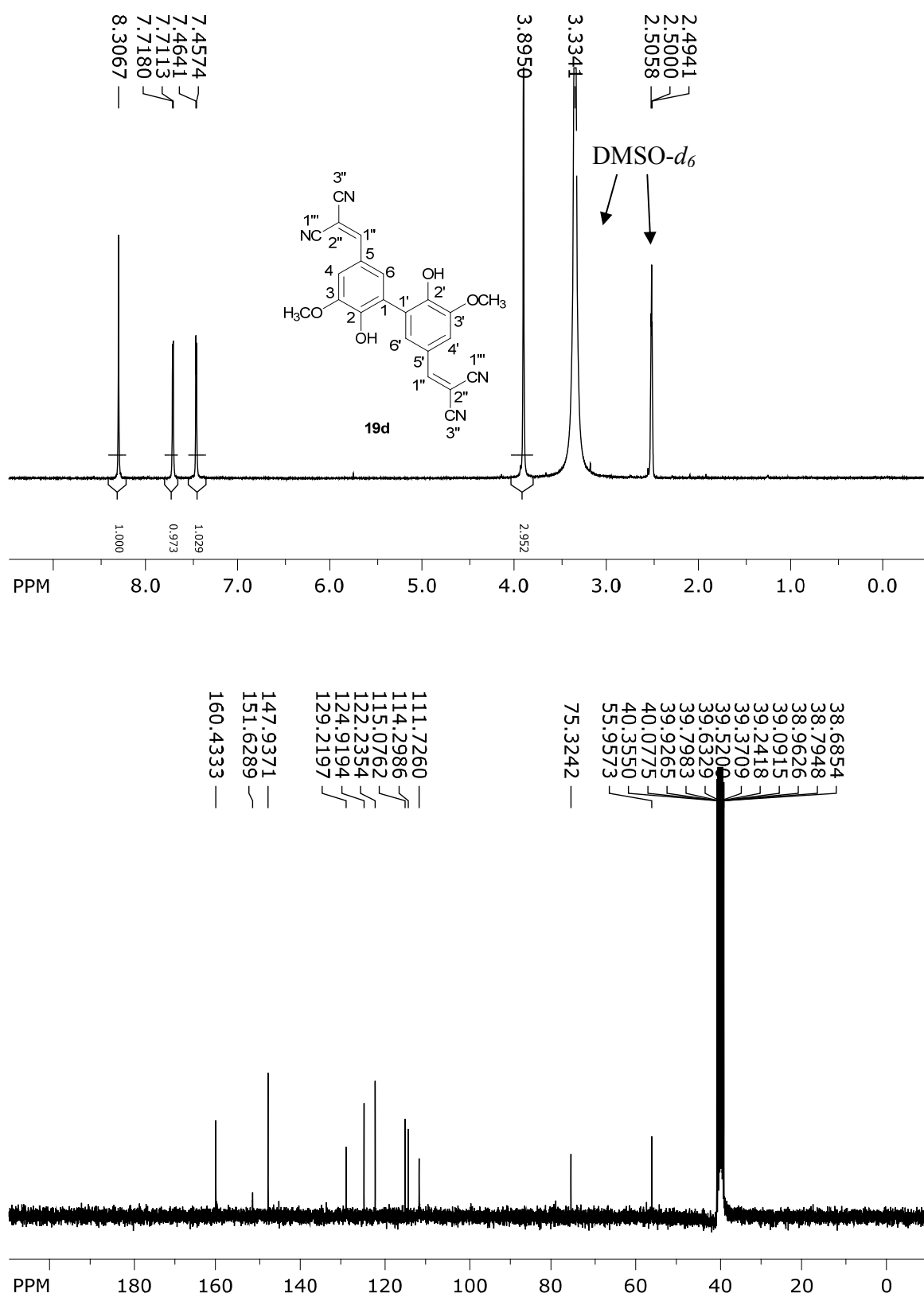


Fig. 25. ^1H and ^{13}C NMR spectra (300, 75 MHz) of **19d** in $\text{DMSO-}d_6$.

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