Supporting Information

Semisynthetic Derivatives of Sesquiterpene Lactones by Palladium-Catalyzed Arylation of the α-Methylene-γ-lactone Substructure

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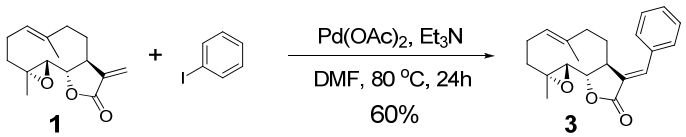
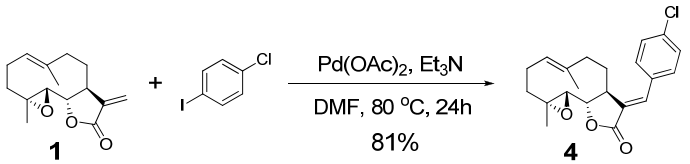
I. Experimental Procedures and Characterization Data

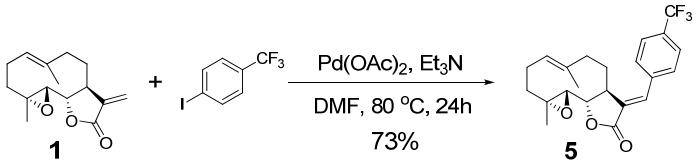
Representative Reaction Procedure. A mixture of parthenolide (10 mg, 0.04 mmol), triethylamine (17 μL, 0.12 mmol), and iodobenzene (5 μL, 0.045 mmol) in DMF (200 μL) was treated with palladium (II) acetate (0.5 mg, 0.002 mmol) and then heated at 80 °C under air. After 24 h, the reaction mixture was allowed to cool to rt, water (2 mL) was added, and the resultant mixture was extracted with Et_2O (2 mL × 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (19:1–7:3 hexanes/EtOAc) afforded the (*E*)-13-phenylparthenolide product **3** as a solid (7.8 mg) in 60% yield.



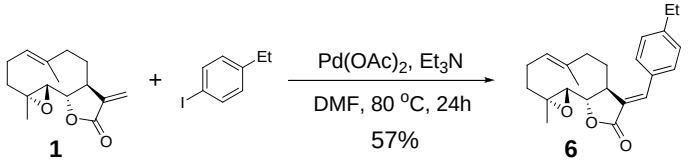
(*E*)-13-phenylparthenolide 3. See representative reaction procedure: mp 196–198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 3.6 Hz, 1H), 7.46–7.35 (m, 5H), 5.29 (d, *J* = 11.5 Hz, 1H), 3.96 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.32 (m, 1H), 2.84 (d, *J* = 8.9 Hz, 1H), 2.42 (m, 1H), 2.27–2.09 (m, 5H), 1.68 (s, 3H), 1.42 (m, 1H), 1.31 (s, 3H), 1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 138.2, 134.8, 133.5, 129.8 (2), 129.7, 129.0, 128.5 (2), 125.0, 83.0, 66.5, 61.6, 46.8, 41.8, 36.1, 30.1, 24.3, 17.5, 17.4; IR (film) ν_{max} 2928, 1753, 1644, 1193 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{24}O_3$ $(M)^+$ 324.1725, found 324.1732; $[\alpha]^{25}_D$ +142 (*c* 0.73, $CHCl_3$).



(*E*)-13-(4-chlorophenyl)-parthenolide 4. See representative reaction procedure. Triethylamine (6 equiv.) and 1-chloro-4-iodobenzene (2 equiv.) were used. SiO_2 flash chromatography (8:2 hexanes/EtOAc) afforded the title compound as a solid in 81% yield: mp 188–190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 3.6 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 5.28 (dd, *J* = 12.1, 2.4 Hz, 1H), 3.96 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.27 (m, 1H), 2.83 (d, *J* = 8.8 Hz, 1H), 2.43 (m, 1H), 2.27–2.14 (m, 4H), 2.11–2.04 (m, 1H), 1.68 (s, 3H), 1.49–1.40 (m, 1H), 1.31 (s, 3H), 1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 136.7, 135.7, 134.6, 132.0, 131.0 (2), 129.7, 129.0 (2), 125.2, 83.0, 66.5, 61.7, 46.7, 41.8, 36.1, 30.0, 24.3, 17.5, 17.4; IR (film) ν_{max} 2929, 1752, 1646, 1191, 1089 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{23}ClO_3$ $(M)^+$ 358.1336, found 358.1333; $[\alpha]^{26}_D$ +202 (*c* 0.56, $CHCl_3$).

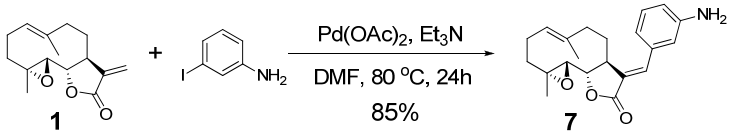


(*E*)-13-(4-trifluoromethylphenyl)-parthenolide 5. See representative reaction procedure. Triethylamine (6 equiv.) and 4-iodobenzotrifluoride (1.5 equiv.) were used. SiO_2 flash chromatography (75:20:5 hexanes/EtOAc/THF) afforded the title compound as a solid in 73% yield: mp 182–184 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 3.7 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 5.28 (d, *J* = 11.5 Hz, 1H), 3.97 (dd, *J* = 8.9, 6.8 Hz, 1H), 3.32 (m, 1H), 2.84 (d, *J* = 8.9 Hz, 1H), 2.42 (m, 1H), 2.27–2.14 (m, 4H), 2.04–1.98 (m, 1H), 1.67 (s, 3H), 1.45 (m, 1H), 1.31 (s, 3H), 1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 137.1, 136.2, 134.6, 131.7, 131.2 (q, $^2J_{CF}$ = 33 Hz, 1C), 129.8 (2), 125.5 (q, $^3J_{CF}$ = 3 Hz, 2C), 125.2, 123.7 (q, $^1J_{CF}$ = 247 Hz, 1C), 83.1, 66.4, 61.7, 46.7, 41.8, 36.1, 30.2, 24.3, 17.4, 17.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.9; IR (film) ν_{max} 2931, 1754, 1324, 1066 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}F_3O_3$ $(M+Na)^+$ 415.1497, found 415.1499; $[\alpha]^{25}_D$ +108 (*c* 1.15, $CHCl_3$).

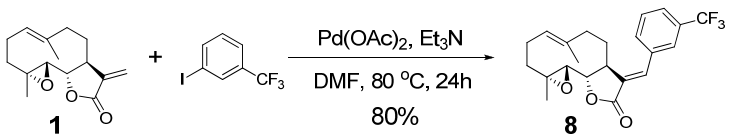


(*E*)-13-(4-ethylphenyl)-parthenolide 6. See representative reaction procedure. Triethylamine (6 equiv.) and 1-ethyl-4-iodobenzene (2 equiv.) were used. SiO_2 flash chromatography (6:2:2 hexanes/Et_2O/EtOAc) afforded the title compound as a solid in 57% yield: mp 160–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 3.4 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 5.30 (dd, *J* = 12.0, 2.1 Hz, 1H), 3.96 (dd, *J* = 8.7, 6.7 Hz, 1H), 3.33–3.29 (m, 1H), 2.86 (d, *J* = 8.8 Hz, 1H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.48–2.40 (m, 1H), 2.25–2.17 (m, 5H), 1.68 (s, 3H), 1.46–1.38 (m, 1H), 1.31 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 146.4, 138.3, 134.8, 130.8, 130.1 (2), 128.1 (2), 127.8, 125.1, 82.9, 66.5, 61.6,

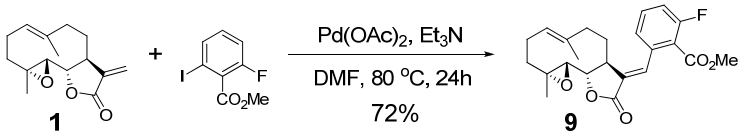
46.8, 41.9, 36.1, 30.0, 28.8, 24.3, 17.5, 17.4, 15.2; IR (film) ν_{max} 2963, 2930, 1750, 1643, 1193 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{23}H_{28}O_3$ $(M+H)^+$ 353.2117, found 353.2115; $[\alpha]^{22}_D$ +99 (*c* 0.67, $CHCl_3$).



(*E*)-13-(3-aminophenyl)-parthenolide 7. See representative reaction procedure. Triethylamine (6 equiv.) and 3-iodoaniline (2 equiv.) were used. SiO_2 flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 85% yield: mp 95–98 °C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.58 (d, *J* = 3.5 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.70 (s, 1H), 6.69 (m, 1H), 5.27 (d, *J* = 12.2 Hz, 1H), 3.91 (dd, *J* = 8.7, 6.9 Hz, 1H), 3.78 (br s, 2H), 3.27 (m, 1H), 2.83 (d, *J* = 8.9 Hz, 1H), 2.42 (m, 1H), 2.25–2.15 (m, 5H), 1.68 (s, 3H), 1.40 (m, 1H), 1.31 (s, 3H), 1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 146.5, 138.6, 134.9, 134.5, 129.3, 128.8, 124.9, 119.8, 116.3, 116.1, 83.0, 66.6, 61.6, 46.8, 41.9, 36.1, 30.2, 24.3, 17.5, 17.4; IR (film) ν_{max} 3460, 3368, 2928, 1743, 1640, 1208 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{25}NO_3$ $(M)^+$ 339.1834, found 339.1836; $[\alpha]^{22}_D$ +87 (*c* 0.99, $CHCl_3$).

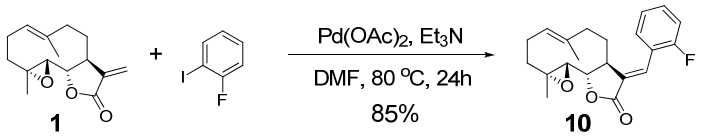


(*E*)-13-(3-trifluoromethylphenyl)-parthenolide 8. See representative reaction procedure. Triethylamine (6 equiv.) and 3-iodobenzotrifluoride (2 equiv.) were used. SiO_2 flash chromatography (1:1 hexanes/EtOAc) afforded the title compound as a solid in 80% yield. Recrystallization from hexanes/chloroform provided a crystalline solid suitable for X-ray structure analysis: mp 118–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.56 (m, 5H), 5.30 (dd, *J* = 12.1, 2.2 Hz, 1H), 3.98 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.33 (m, 1H), 2.85 (d, *J* = 8.9 Hz, 1H), 2.43 (m, 1H), 2.25–2.12 (m, 4H), 2.03 (m, 1H), 1.67 (s, 3H), 1.45 (m, 1H), 1.32 (s, 3H), 1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 136.2, 134.5, 134.3, 133.3, 131.2, 131.1 (q, $^2J_{CF}$ = 33 Hz, 1C), 129.3, 126.1 (q, $^3J_{CF}$ = 4 Hz, 1C), 125.8 (q, $^3J_{CF}$ = 4 Hz, 1C), 125.2, 123.7 (q, $^1J_{CF}$ = 271 Hz, 1C), 83.1, 66.4, 61.7, 46.7, 41.6, 36.1, 30.0, 24.2, 17.4, 17.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.7; IR (film) ν_{max} 2933, 1755, 1651, 1329, 1193 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}F_3O_3$ $(M+H)^+$ 393.1678, found 393.1680; $[\alpha]^{25}_D$ +18 (*c* 1.10, $CHCl_3$).

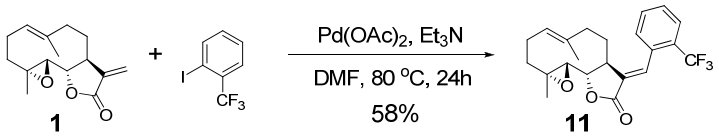


(*E*)-13-(3-fluoro-2-methoxycarbonyl)-parthenolide 9. See representative reaction procedure. Triethylamine (6 equiv.) and methyl 2-fluoro-6-iodobenzoate (2 equiv.) were used. SiO_2 flash chromatography (7:3 hexanes/THF) afforded the title compound as a solid in 72% yield: mp 180–183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.8 Hz, 1H), 7.49 (td, *J* = 8.1, 5.4 Hz, 1H), 7.20–7.15 (m, 2H), 5.20 (dd, *J* = 12.1, 2.2 Hz, 1H), 3.94 (s, 3H), 3.96–3.92 (m, 1H), 3.22–3.19 (m, 1H), 2.79 (d, *J* = 9.0 Hz, 1H), 2.44–2.35 (m, 1H), 2.22–2.14 (m, 2H), 1.93–1.89 (m,

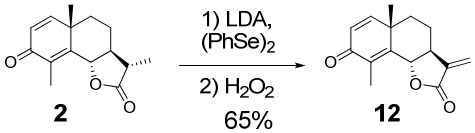
2H), 1.84–1.80 (m, 1H), 1.62 (s, 3H), 1.44–1.37 (m, 1H), 1.28 (s, 3H), 1.32–1.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 164.6, 160.5 (d, $^1J_{CF}$ = 254 Hz, 1C), 135.9, 135.1, 134.8, 132.5, 131.9 (d, $^3J_{CF}$ = 9 Hz, 1C), 124.7, 124.0, 121.0 (d, $^2J_{CF}$ = 15 Hz, 1C), 117.0 (d, $^2J_{CF}$ = 22 Hz, 1C), 83.0, 66.6, 61.6, 52.9, 46.4, 41.3, 36.2, 30.4, 24.1, 17.3 (2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.1; IR (film) ν_{max} 2952, 2931, 1756, 1731, 1657, 1469, 1204 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}FO_5$ $(M+Na)^+$ 423.1584, found 423.1580; $[\alpha]^{26}_D$ +42 (*c* 0.97, $CHCl_3$).



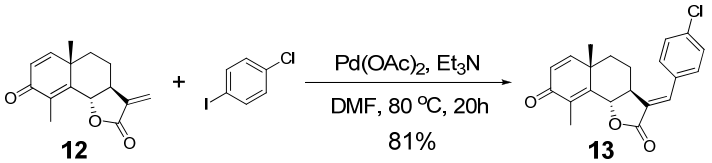
(*E*)-13-(2-fluorophenyl)-parthenolide 10. See representative reaction procedure. Triethylamine (6 equiv.) and 1-fluoro-2-iodobenzene (2 equiv.) were used. SiO_2 flash chromatography (8:2 hexanes/EtOAc) afforded the title compound as a solid in 85% yield: mp 184–186 °C; ^{1}H NMR (500 MHz,) δ 7.70 (d, *J* = 3.8 Hz, 1H), 7.42–7.35 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 9.4 Hz, 1H), 5.27 (dd, *J* = 12.1, 2.4 Hz, 1H), 3.93 (dd, *J* = 8.6, 7.3 Hz, 1H), 3.24 (m, 1H), 2.84 (d, *J* = 8.9 Hz, 1H), 2.41 (m, 1H), 2.33–2.12 (m, 3H), 2.04 (dd, *J* = 13.0, 6.0 Hz, 1H), 1.95 (dd, *J* = 15.1, 5.8 Hz, 1H),1.65 (s, 3H), 1.42–1.38 (m, 1H), 1.30 (s, 3H), 1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 160.3 (d, $^1J_{CF}$ = 250 Hz, 1C), 134.8, 132.1, 131.5 (d, $^3J_{CF}$ = 8 Hz, 1C), 131.0, 130.4, 124.9, 124.1, 121.8 (d, $^2J_{CF}$ = 14 Hz, 1C), 116.0 (d, $^2J_{CF}$ = 22 Hz, 1C), 83.0, 66.5, 61.6, 47.2, 41.2, 36.2, 29.9, 24.2, 17.4, 17.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.5; IR (film) ν_{max} 2930, 1755, 1650, 1208 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{23}FO_3$ $(M)^+$ 342.1631, found 342.1629; $[\alpha]^{24}_D$ +134 (*c* 0.51, $CHCl_3$).



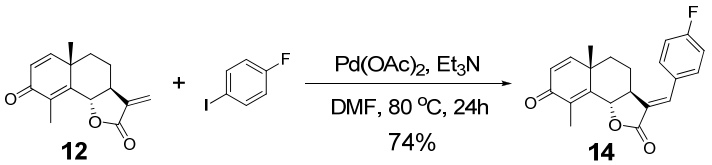
(*E*)-13-(2-trifluoromethylphenyl)-parthenolide 11. See representative reaction procedure. Triethylamine (6 equiv.) and 2-iodobenzotrifluoride (2 equiv.) were used. SiO_2 flash chromatography (7:3 hexanes/THF) afforded the title compound as a solid in 58% yield. Recrystallization from $CDCl_3$ provided a crystalline solid suitable for X-ray structure analysis: mp 229–232 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.52–7.45 (m, 2H), 5.21 (d, *J* = 10.4 Hz, 1H), 3.95 (dd, *J* = 9.0, 7.1 Hz, 1H), 3.25–3.21 (m, 1H), 2.80 (d, *J* = 6.7 Hz, 1H), 2.43–2.35 (m, 1H), 2.25–2.15 (m, 2H), 1.90–1.84 (m, 2H), 1.73 (m, 1H), 1.61 (s, 3H), 1.39–1.33 (m, 1H), 1.28 (s, 3H), 1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 134.8, 134.4, 133.1, 132.9, 131.6, 129.1, 129.0, 128.7 (q, $^2J_{CF}$ = 44 Hz, 1C), 126.3 (q, $^3J_{CF}$ = 5 Hz, 1C), 124.7, 123.6 (q, $^1J_{CF}$ = 272 Hz, 1C), 83.0, 66.6, 61.5, 46.4, 41.3, 36.2, 30.0, 24.1, 17.3(2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.7; IR (film) ν_{max} 2930, 1759, 1655, 1316, 1163 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}F_3O_3$ $(M+H)^+$ 393.1678, found 393.1685; $[\alpha]^{25}_D$ +43 (*c* 0.77, $CHCl_3$).



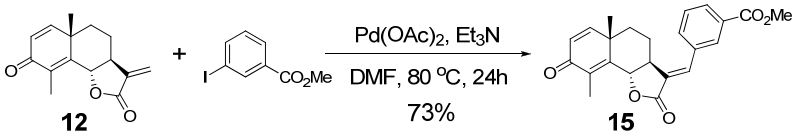
11,13-dehydrosantonin 12. The synthesis of the title compound was accomplished using literature procedure.[1] All spectral and characterization data matched the reported data.



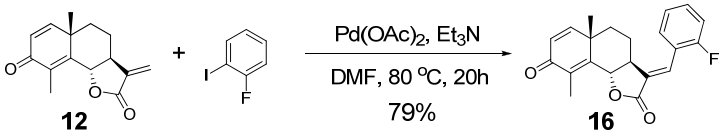
(*E*)-13-(4-chlorophenyl)-11,13-dehydrosantonin 13. See representative reaction procedure. The 11,13-dehydrosantonin **12**, triethylamine (6 equiv.), and 1-chloro-4-iodobenzene (2 equiv.) were used and the reaction was heated at 80 °C for 20 h. SiO_2 flash chromatography (7:3 hexanes/EtOAc) afforded the title compound as a solid in 81% yield: mp 232–234 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 3.4 Hz, 1H), 7.39 (d, *J* = 14.8 Hz, 2H), 7.27 (m, 2H), 6.69 (d, *J* = 13.3 Hz, 1H), 6.27 (d, *J* = 9.9 Hz, 1H), 4.80 (dd, *J* = 11.3, 1.3 Hz, 1H), 3.02 (tt, *J* = 11.4, 3.2 Hz, 1H), 2.27–2.21 (m, 1H), 2.19 (d, *J* = 1.3 Hz, 3H), 1.81 (m, 1H), 1.54 (m, 1H), 1.42 (m, 1H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.1, 170.4, 154.6, 150.7, 136.8, 135.6, 131.9, 130.6 (2), 129.1, 129.0, 128.7 (2), 126.0, 81.8, 49.6, 41.1, 38.0, 25.2, 22.0, 10.8; IR (film) ν_{max} 2929, 1760, 1661, 1251, 1049 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{19}ClO_3$ $(M)^+$ 354.1023, found 354.1021; $[\alpha]^{27}_D$ +258 (*c* 0.67, $CHCl_3$).



(*E*)-11,13-dehydro-13-(4-fluorophenyl)-santonin 14. See representative reaction procedure. The 11,13-dehydrosantonin **12**, triethylamine (6 equiv.), and 1-fluoro-4-iodobenzene (2 equiv.) were used. SiO_2 flash chromatography (7:3 hexanes/EtOAc) afforded the title compound as a solid in 74% yield: mp 220–222 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.3 Hz, 1H), 7.35–7.29 (m, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 6.69 (d, *J* = 9.9 Hz, 1H), 6.27 (d, *J* = 9.9 Hz, 1H), 4.80 (dd, *J* = 11.3, 1.3 Hz, 1H), 3.03 (tt, *J* = 11.4, 3.2 Hz, 1H), 2.26 (m, 1H), 2.19 (d, *J* = 1.2 Hz, 3H), 1.88–1.78 (m, 1H), 1.58–1.51 (m, 1H), 1.47–1.38 (m, 1H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 170.5, 163.2 (d, $^1J_{CF}$ = 250 Hz, 1C), 154.6, 150.8, 137.1, 131.3 (d, $^3J_{CF}$ = 8 Hz, 2C), 129.6, 129.0, 128.4, 126.0, 115.7 (d, $^2J_{CF}$ = 28 Hz, 2C), 81.8, 49.6, 41.1, 38.1, 25.2, 22.0, 10.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.1; IR (film) ν_{max} 2929, 1762, 1662, 1508 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{19}FO_3$ $(M)^+$ 338.1318, found 338.1321; $[\alpha]^{27}_D$ +196 (*c* 0.72, $CHCl_3$).



(*E*)-11,13-dehydro-13-(3-methoxycarbonylphenyl)-santonin 15. See representative reaction procedure. The 11,13-dehydrosantonin **12**, triethylamine (6 equiv.), and methyl 3-iodobenzoate (2 equiv.) were used. SiO_2 flash chromatography (7:3 hexanes/EtOAc) afforded the title compound as a solid in 73% yield: mp 186–188 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (m, 1H), 8.00 (br s, 1H), 7.76 (d, *J* = 3.4 Hz, 1H), 7.53–7.46 (m, 2H), 6.68 (d, *J* = 9.9 Hz, 1H), 6.27 (d, *J* = 9.9 Hz, 1H), 4.81 (dd, *J* = 11.3, 1.1 Hz, 1H), 3.93 (s, 3H), 3.10 (tt, *J* = 11.5, 3.3 Hz, 1H), 2.21–2.17 (m, 1H), 2.20 (d, *J* = 16.0 Hz, 3H), 1.80 (m, 1H), 1.56 (td, *J* = 13.3, 4.5 Hz, 1H), 1.46–1.36 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.1, 170.3, 166.3, 154.6, 150.7, 136.8, 133.8, 133.6, 130.4, 130.3, 130.2, 129.7, 129.1, 128.6, 126.0, 81.8, 52.4, 49.6, 41.1, 38.0, 25.2, 22.0, 10.8; IR (film) ν_{max} 2951, 1766, 1722, 1662, 1250 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{23}H_{22}O_5$ $(M+H)^+$ 379.1546, found 379.1544; $[\alpha]^{28}_D$ +139 (*c* 0.75, $CHCl_3$).



(*E*)-11,13-dehydro-13-(2-fluorophenyl)-santonin 16. See representative reaction procedure. The 11,13-dehydrosantonin **12**, triethylamine (6 equiv.), and 1-fluoro-2-iodobenzene (2 equiv.) were used and the reaction was heated at 80 °C for 20 h. SiO_2 flash chromatography (7:3 hexanes/EtOAc) afforded the title compound as a solid in 79% yield: mp 240–242 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 3.4 Hz, 1H), 7.43–7.36 (m, 1H), 7.29 (td, *J* = 7.4, 1.6 Hz, 1H), 7.19 (td, *J* = 7.5, 1.1 Hz, 1H), 7.13 (m, 1H), 6.67 (d, *J* = 9.8 Hz, 1H), 6.27 (d, *J* = 9.9 Hz, 1H), 4.80 (dd, *J* = 11.4, 1.2 Hz, 1H), 2.99 (m, 1H), 2.19 (d, *J* = 1.5 Hz, 3H), 2.09–2.06 (m, 1H), 1.82–1.75 (m, 1H), 1.54 (td, *J* = 13.4, 4.3 Hz, 1H), 1.48–1.37 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 170.1, 160.2 (d, $^1J_{CF}$ = 250 Hz, 1C), 154.6, 150.8, 131.5 (d, $^3J_{CF}$ = 8 Hz, 1C), 131.0, 130.8, 130.7, 129.0, 126.0, 124.0, 121.6 (d, $^2J_{CF}$ = 15 Hz, 1C), 115.9 (d, $^2J_{CF}$ = 21 Hz, 1C), 81.7, 50.1, 41.1, 38.1, 25.2, 21.7, 10.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.2; IR (film) ν_{max} 2926, 1767, 1662, 1250, 1200 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{19}FO_3$ $(M)^+$ 338.1318, found 338.1319; $[\alpha]^{27}_D$ +105 (*c* 0.72, $CHCl_3$).

Table S1. Diagnostic Vinyl Protons in **3–11** and **13–16**.

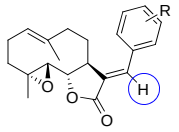
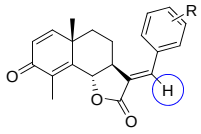
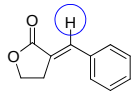
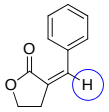
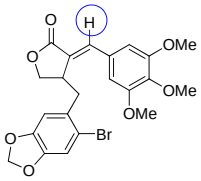
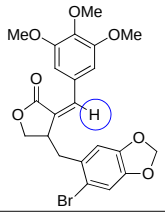
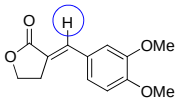
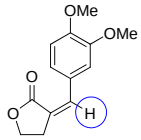
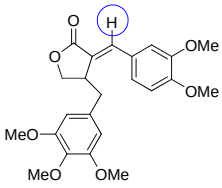
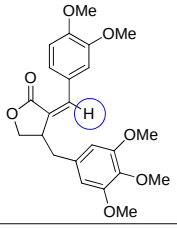
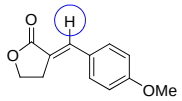
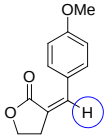
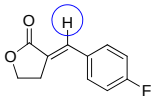
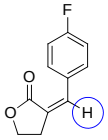
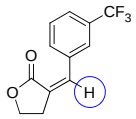
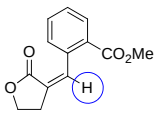
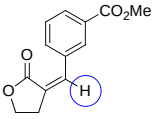
Structure	R =	Compound	Chemical Shift of Vinyl Proton	Notes
	H	**3**	7.68 ppm	COSY, NOESY data
	4-Cl	**4**	7.61 ppm	
	4-CF_3	**5**	7.67 ppm	
	4-Et	**6**	7.65 ppm	
	3-NH_2	**7**	7.58 ppm	
	3-CF_3	**8**	7.67-7.56 ppm	X-ray data
	3-F, 2-CO_2Me	**9**	7.71 ppm	
	2-F	**10**	7.70 ppm	
	2-CF_3	**11**	7.91 ppm	X-ray data
	4-Cl	**13**	7.69 ppm	
	4-F	**14**	7.71 ppm	
	3-CO_2Me	**15**	7.76 ppm	
	2-F	**16**	7.68 ppm	

Table S2. Diagnostic Vinyl Protons in α-Methylene-γ-lactones.[a]

E-olefin Structure	Chemical Shift of Vinyl Proton	*Z*-olefin Structure	Chemical Shift of Vinyl Proton	Questionable Structures	Chemical Shift of Vinyl Proton
	7.52 ppm[2] 7.60 ppm[3]		6.99 ppm[3]		
	7.51 ppm[4]		6.63 ppm[4]		
	8.13 ppm[5]		6.90 ppm[5]		
	7.55 ppm[5]		6.53 ppm[5]		
	7.45 ppm[2]				7.38 ppm[6]
	7.44-7.38 ppm[2]				7.46 ppm[6]
					7.60 ppm[6]
					8.10 ppm[6]
					8.10 ppm[6]

[a] All chemical shifts were obtained from the literature. Refer to the references section (III) for corresponding citations.

II. Biological Evaluation

Cell Culture.[7] HeLa (cervical cancer) cells were maintained in logarithmic phase of growth in Dulbecco's Modified Eagle Medium (D-MEM) supplemented with 10% fetal bovine serum, L-glutamine (2 mM), streptomycin (50 μg/mL), and penicillin (50 IU/mL). They were cultured at 37 °C in a humidified incubator under 5% CO_2 in air.

Cell Proliferation Assay.[7] The 50% inhibitory concentration (IC_{50}) of the sesquiterpene lactones **1**, **3**–**16** on HeLa cells was determine by the MTT assay. HeLa cells were plated into a 96-well plate at 10,000 cells per well in growth medium (150 μL) and incubated at 37 °C in a humidified incubator under 5% CO_2 in air. After 24 h, the growth medium was removed and the HeLa cells were treated with 100 μL of a solution of test compound in 1% DMSO in growth medium. Eight concentrations of each test compound were used and each concentration was repeated in triplicate. After incubation for 48 h, 20 μL of MTT solution (5 mg/mL) in PBS was added to each well and the plate was incubated further for 1 h. The medium was removed, and 200 μL of DMSO was added to each well. The OD was measured at 570 nm. The IC_{50} values on HeLa cell proliferation were calculated by GraphPad Prism 5 software.

III. References

(1) Rossi, C.; Ambrogi, V.; Grandolini, G.; Scarcia, V. *J. Pharm. Sci.* **1986**, *75*, 784–786.
(2) Moise, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 1695–1698.
(3) Lewis, F. D.; Oxman, J. D.; Gibson, L. L.; Hampsch, H. L.; Quillen, S. L. *J. Am. Chem. Soc.* **1986**, *108*, 3005–3015.
(4) Ishibashi, H.; Ito, K.; Hirano, T.; Tabuchi, M.; Ikdea, M. *Tetrahedron* **1993**, *49*, 4173–4182.
(5) Sai, H.; Ogiku, T.; Ohmizu, H. *Tetrahedron* **2007**, *63*, 10345–10353.
(6) Arcadi, A.; Chiarini, M.; Marinelli, F.; Berente, Z.; Kollár, L. *Eur. J. Org. Chem.* **2001**, *16*, 3165–3173. Arcadi, A.; Chiarini, M.; Marinelli, F.; Berente, Z.; Kollar, L. *Org. Lett.* **2000**, *2*, 69–72.
(7) Recent reference: Sun, H.-X.; Zheng, Q.-F.; Tu, J. *Bioorg. Med. Chem.* **2006**, *14*, 1189–1198.

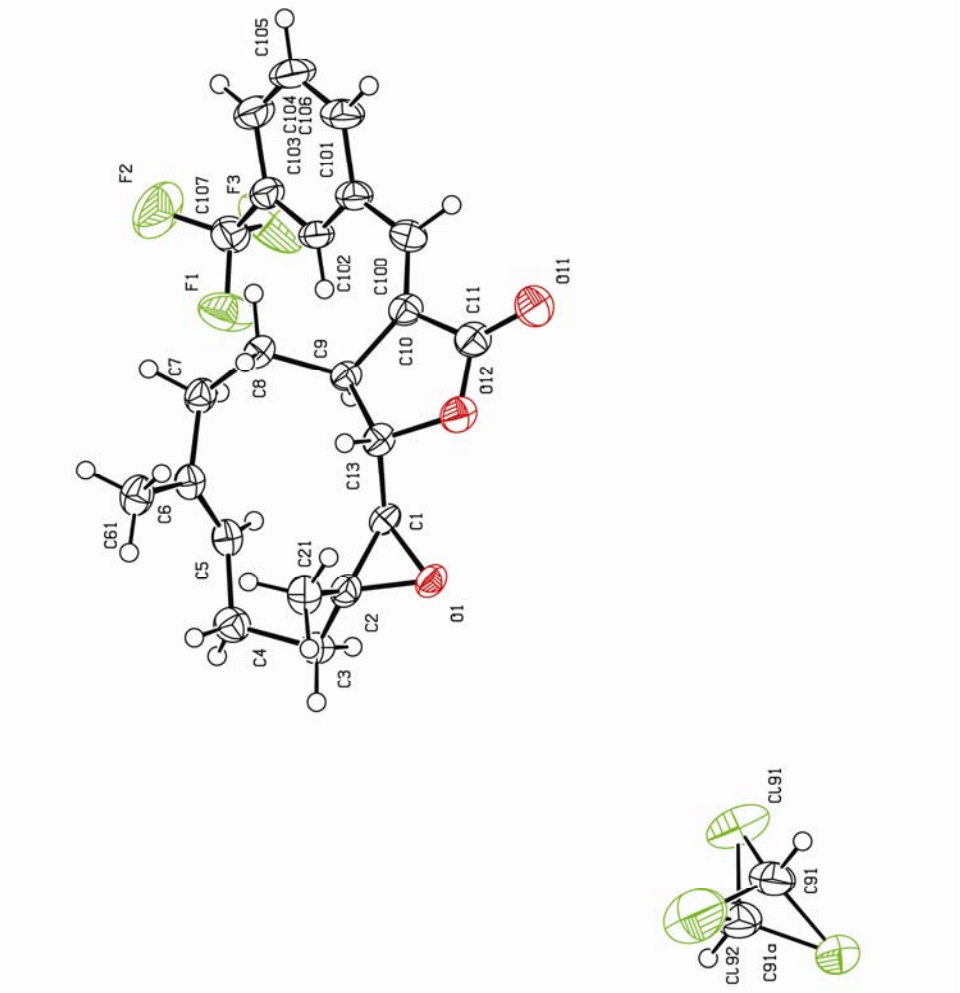


Figure S1. ORTEP Diagram of 8.

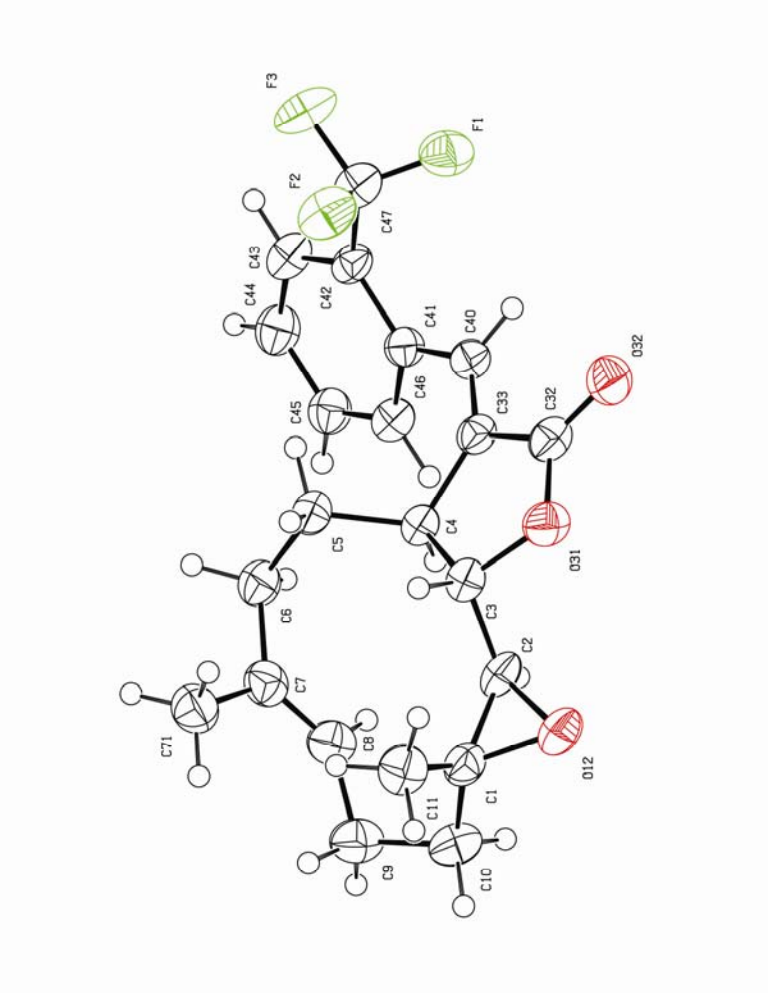
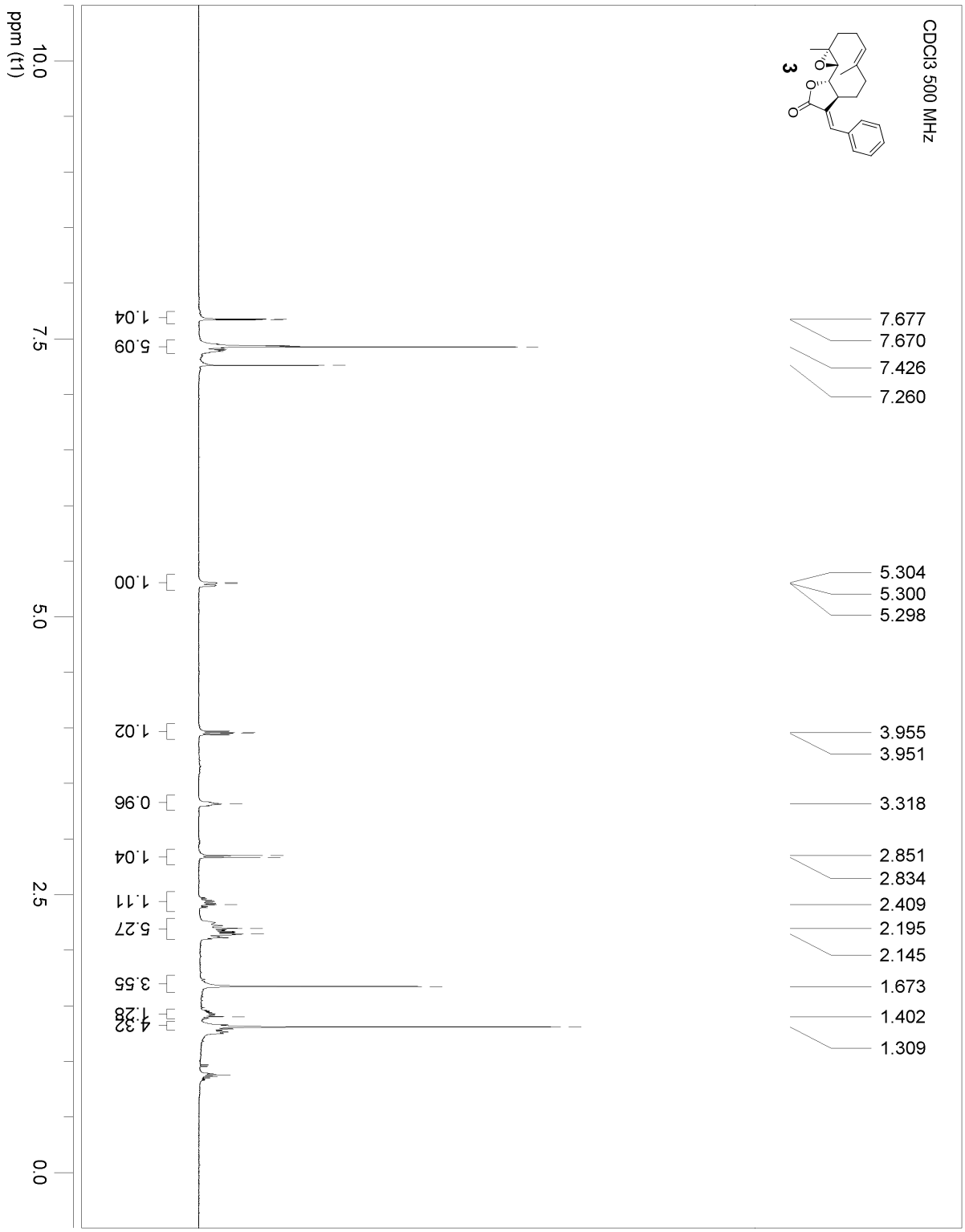


Figure S2. ORTEP Diagram of **11**.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3.951
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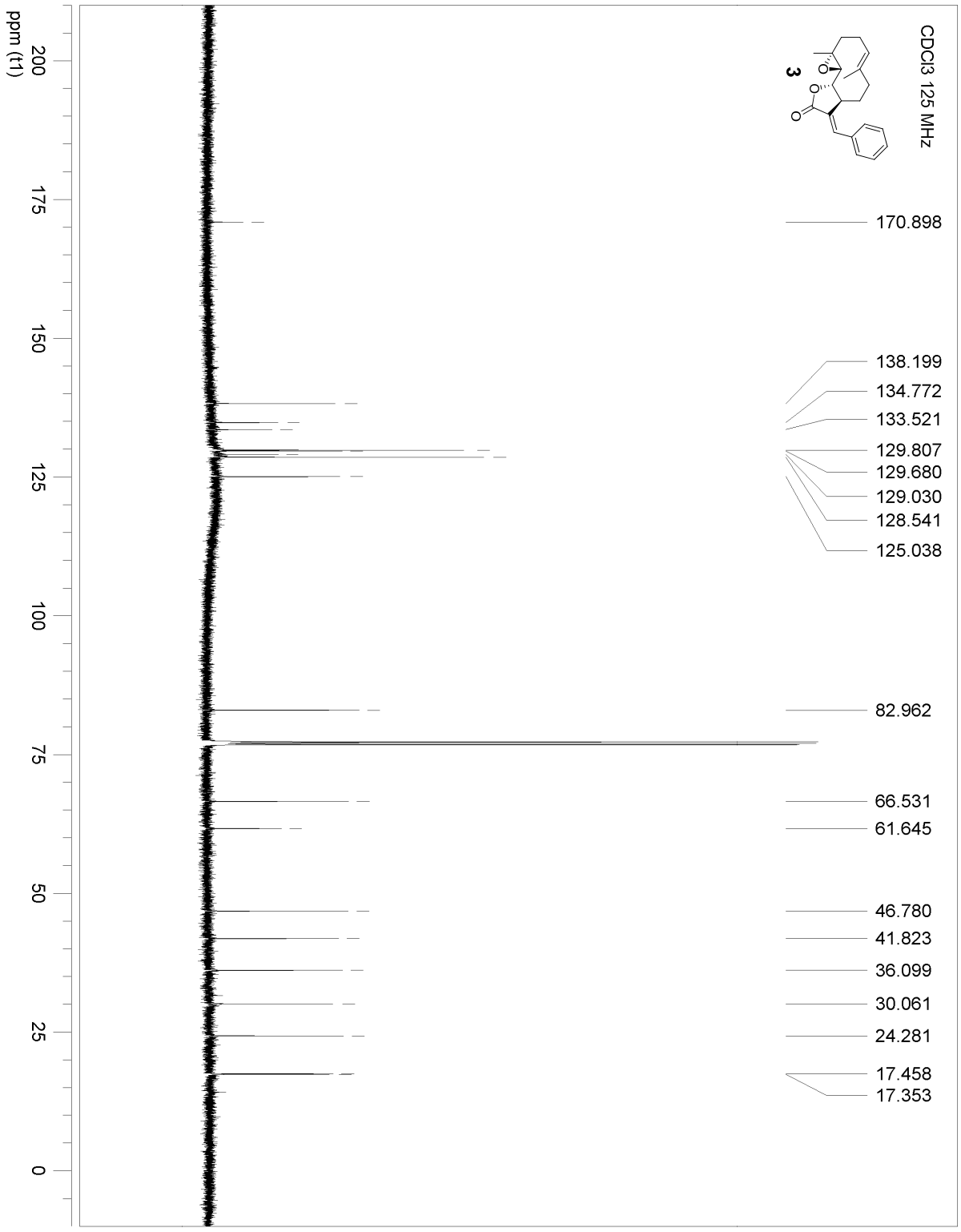
2.851
2.834
2.409
2.195
2.145
1.673
1.402
1.309
1.04
5.09
1.00
1.02
0.96
1.04
1.11
5.27
3.55
4.32
1.28
10.0
7.5
5.0
2.5
0.0
ppm (t1)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125.038
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61.645
46.780
41.823
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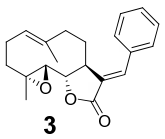
200
175
150
125
100
75
50
25
0



3

H1-Gradient COSY standard parameters, NS=1, TXI_HCN_XYZ probe.
Turn sample spinning off.
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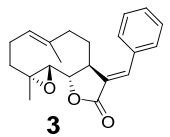
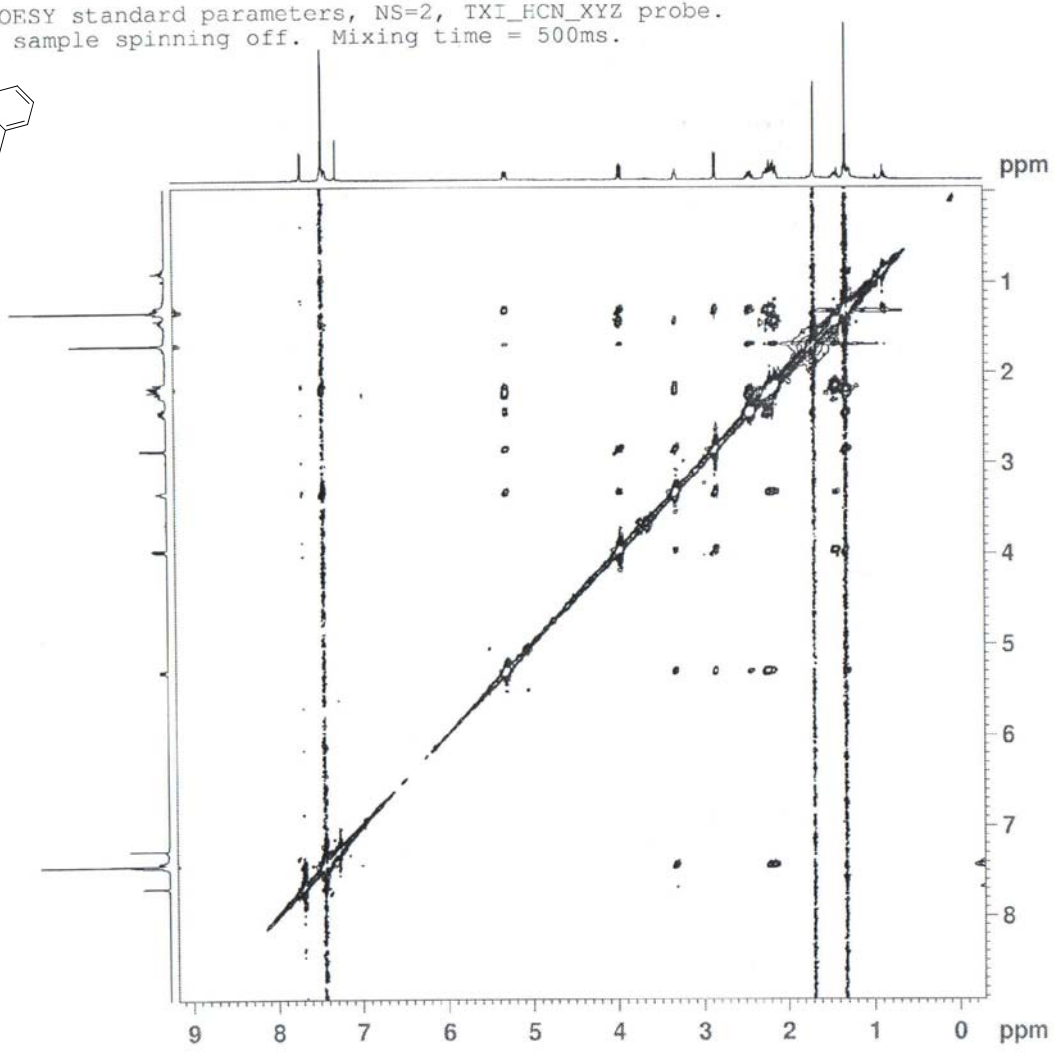
2
4
6
ppm

H1-NOESY standard parameters, NS=2, TXI_HCN_XYZ probe.
Turn sample spinning off. Mixing time = 500ms.



3

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PROCNO                   1

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TD                    2048
SOLVENT               CDCl3
NS                      16
DS                      16
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FIDRES             2.311938 Hz
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RG                      40
DW                  105.600 usec
DE                    6.00 usec
TE                   294.1 K
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D1                 3.00000000 sec
D8                 0.50000000 sec
D16                0.00020000 sec
IN0                0.00022228 sec
MCREST             0.00000000 sec
MCWRK              3.00000000 sec
TAU                0.24879999 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    10.20 usec
P2                    20.40 usec
PL1                    0.00 dB
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====== GRADIENT CHANNEL =====
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GPNAM2              SINE.100
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GPX2                   0.00 %
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GPY2                   0.00 %
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GPZ2                 -40.00 %
P16                1000.00 usec

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GB                       0
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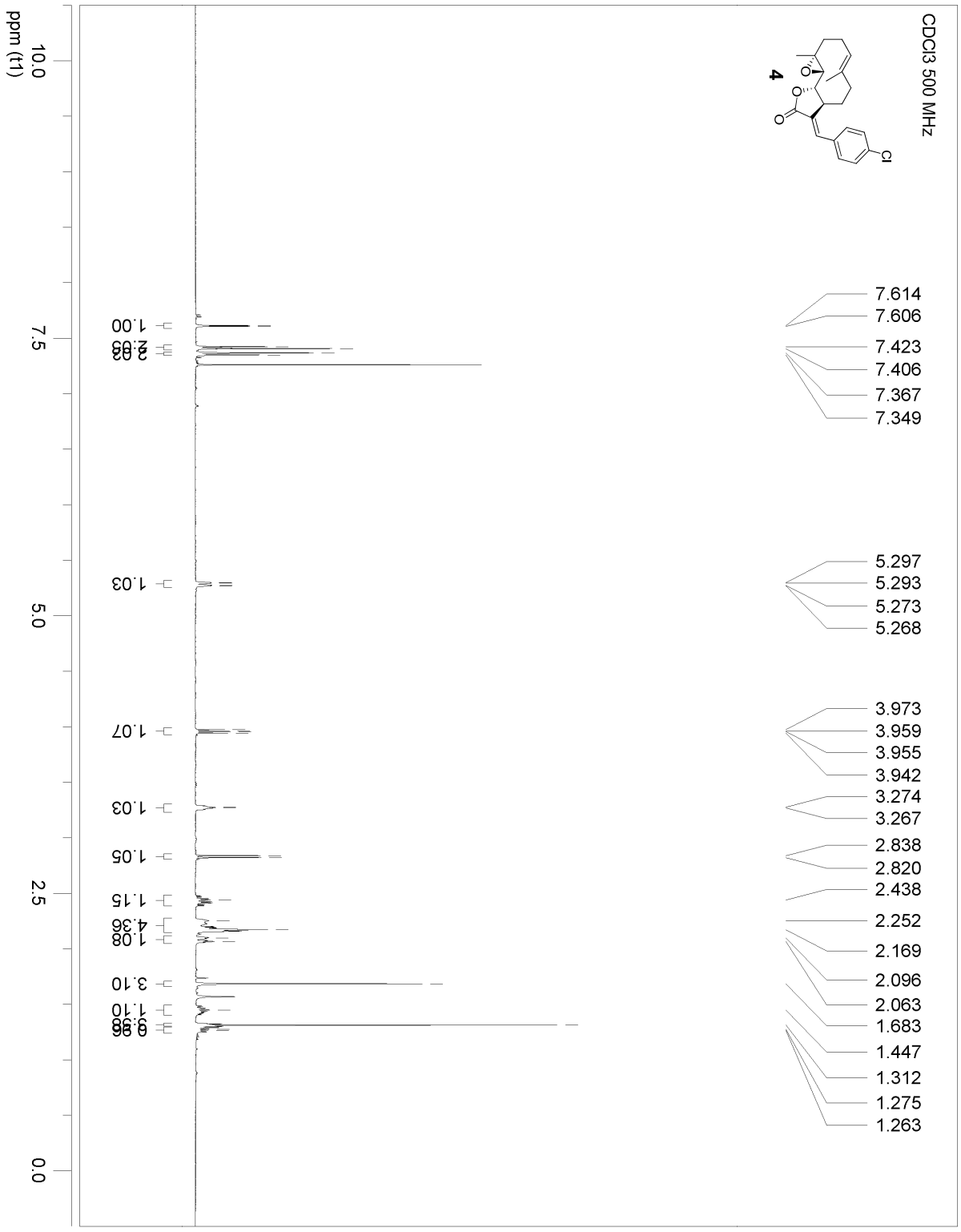
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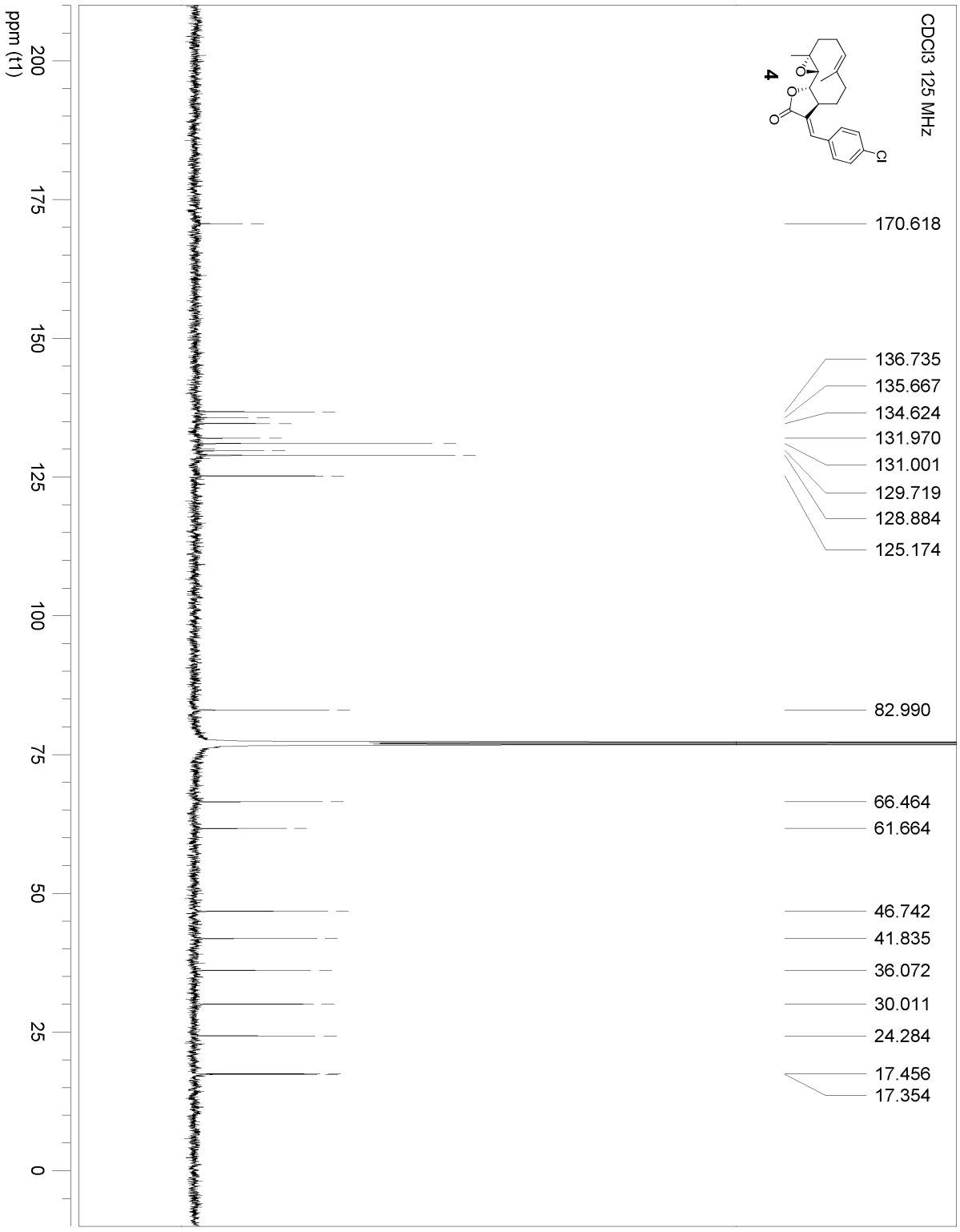
8.96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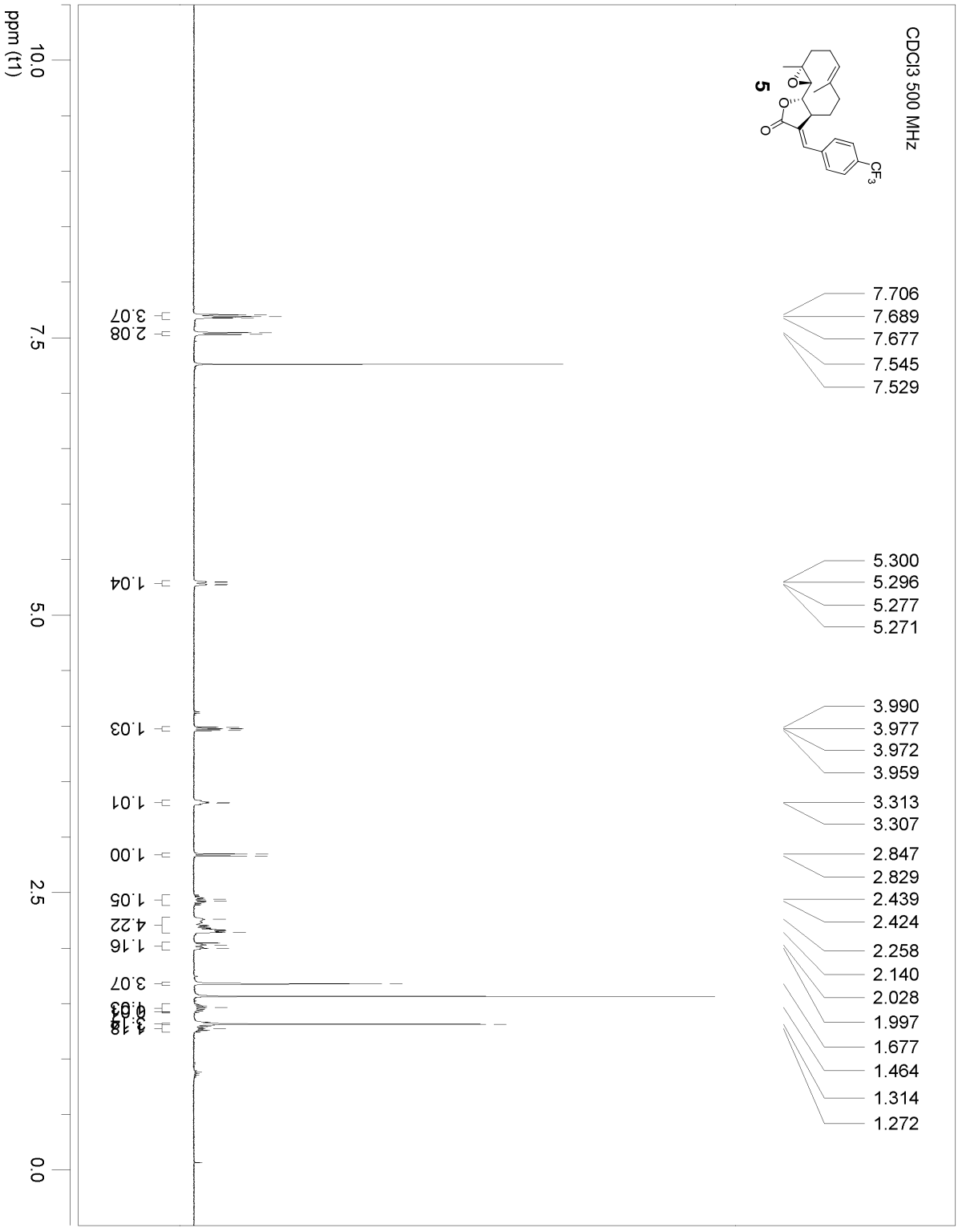
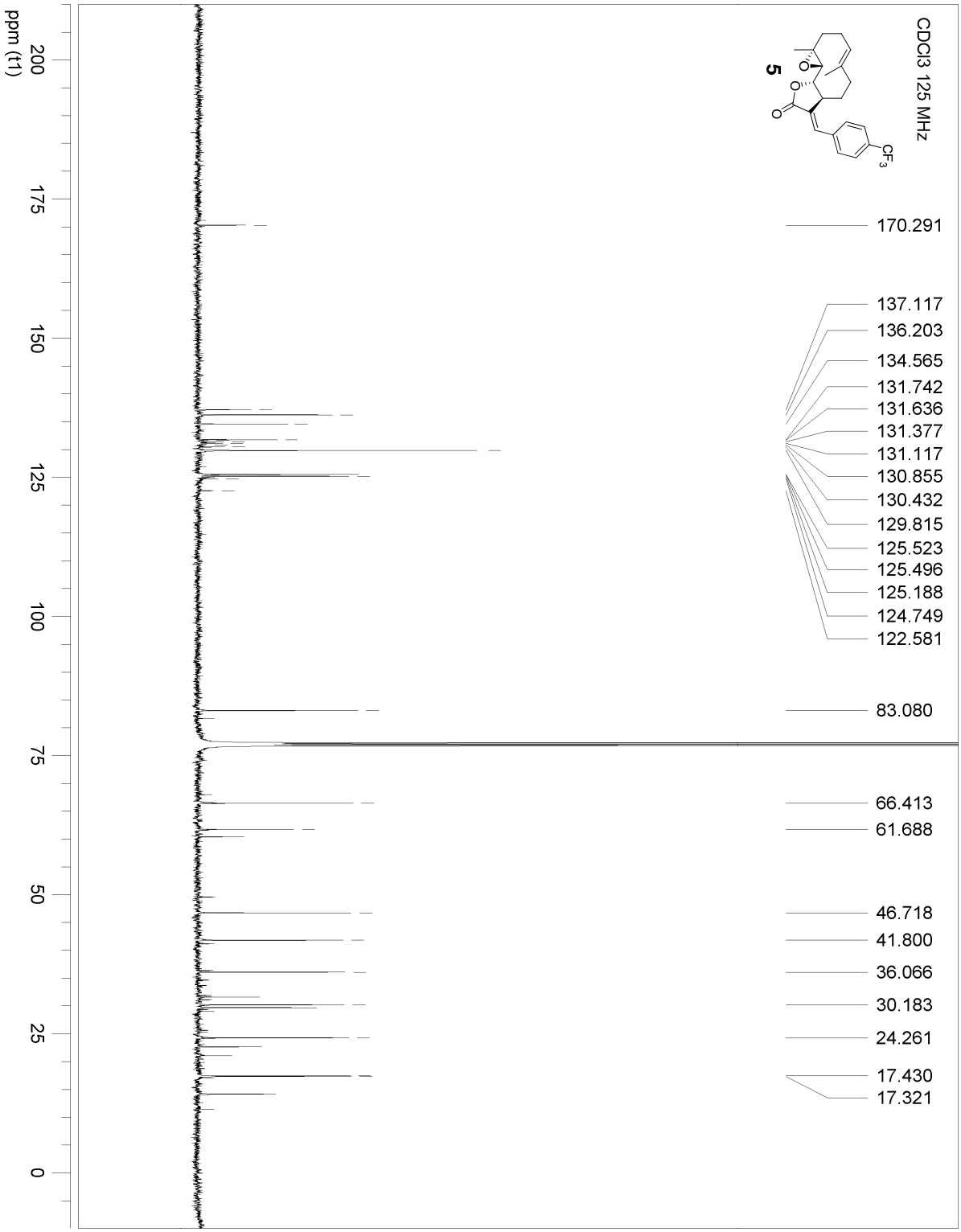
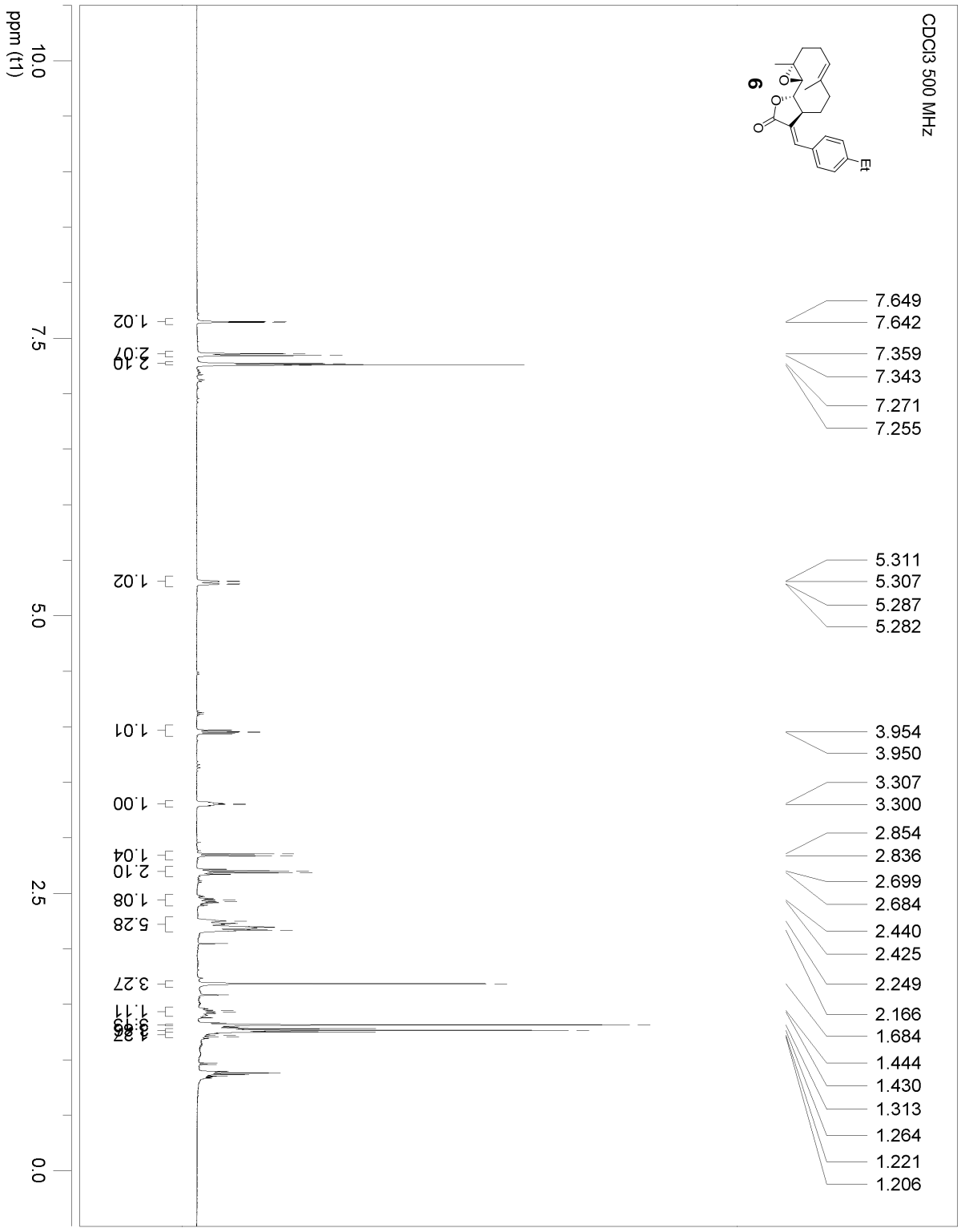
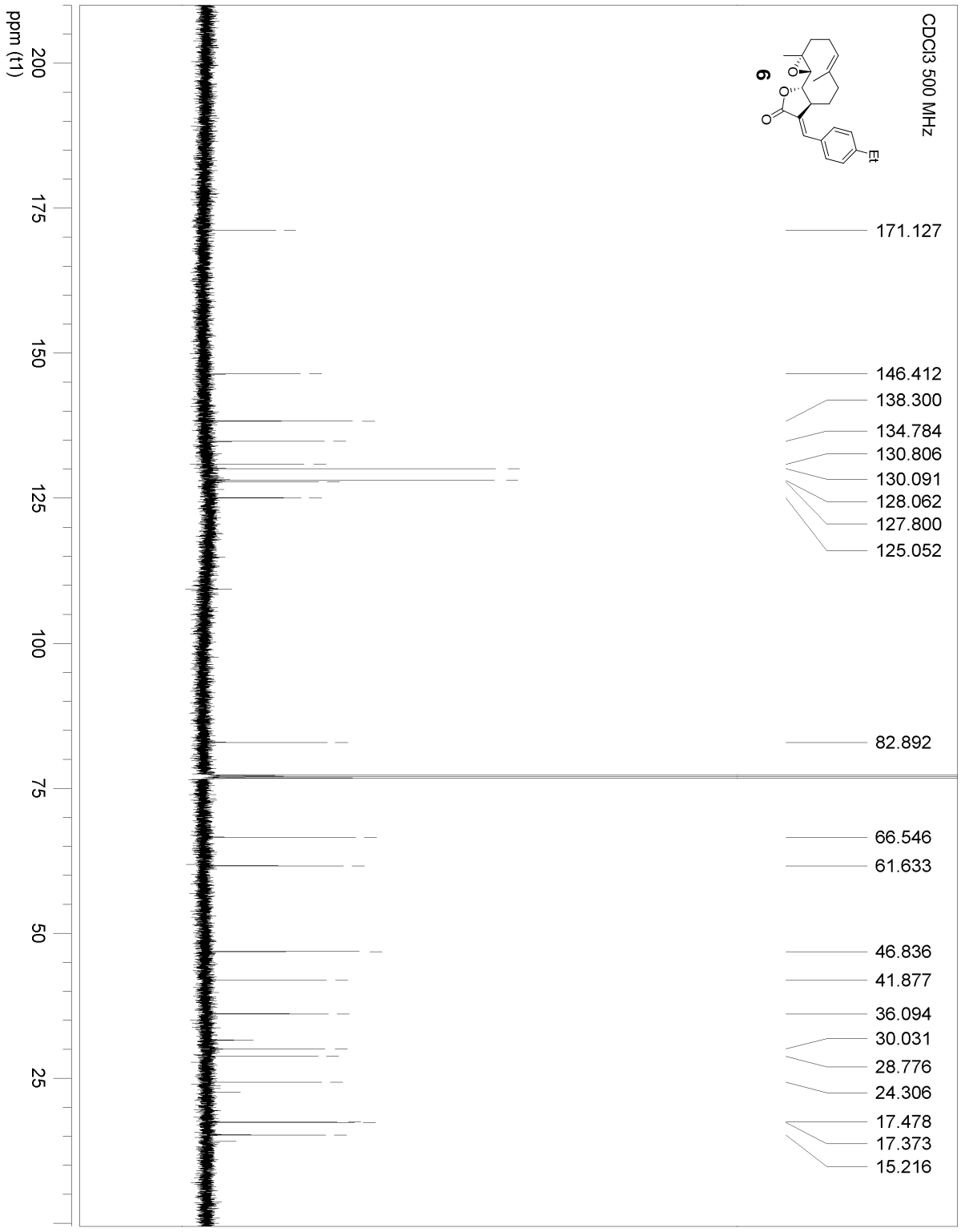
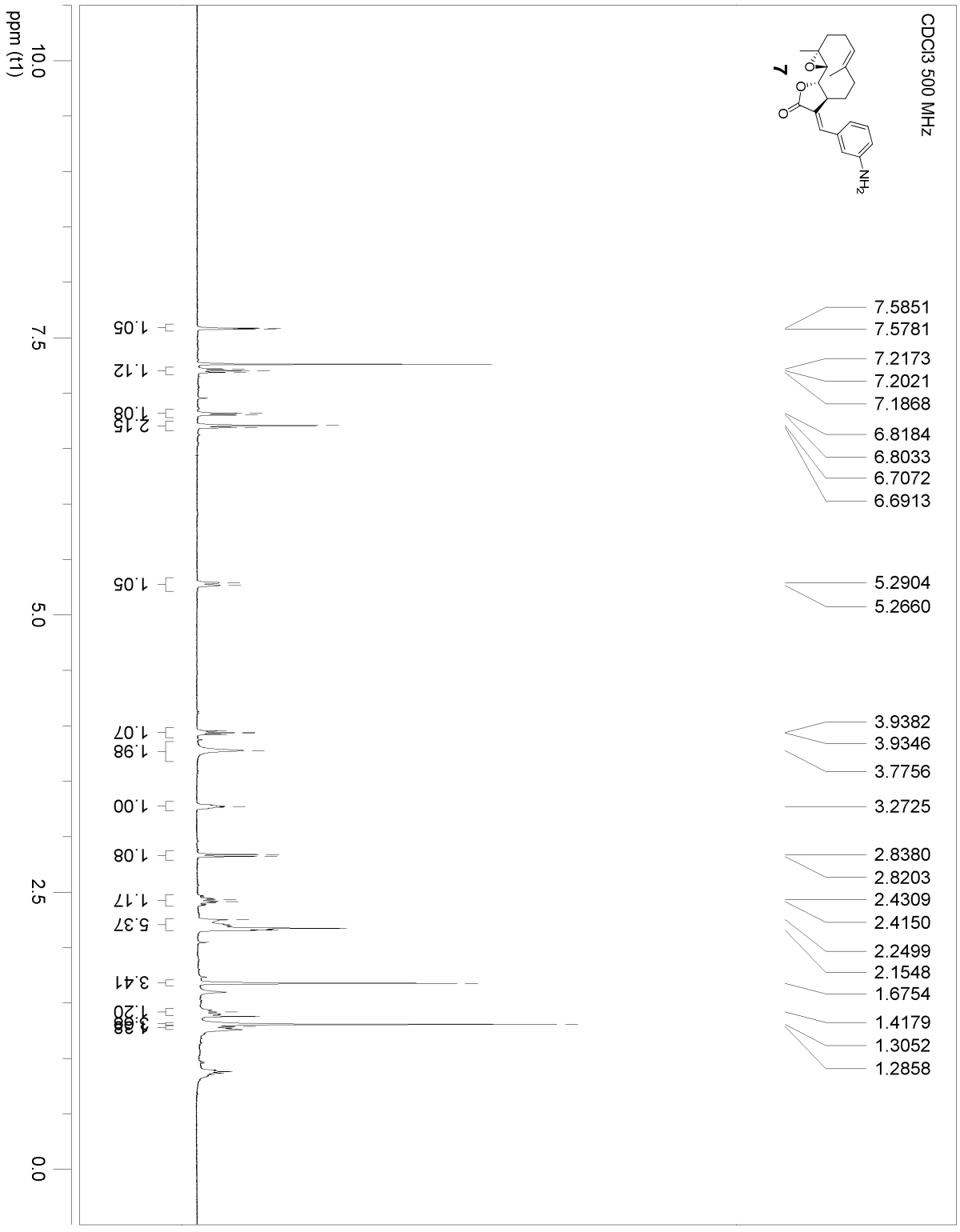
17.456
17.354

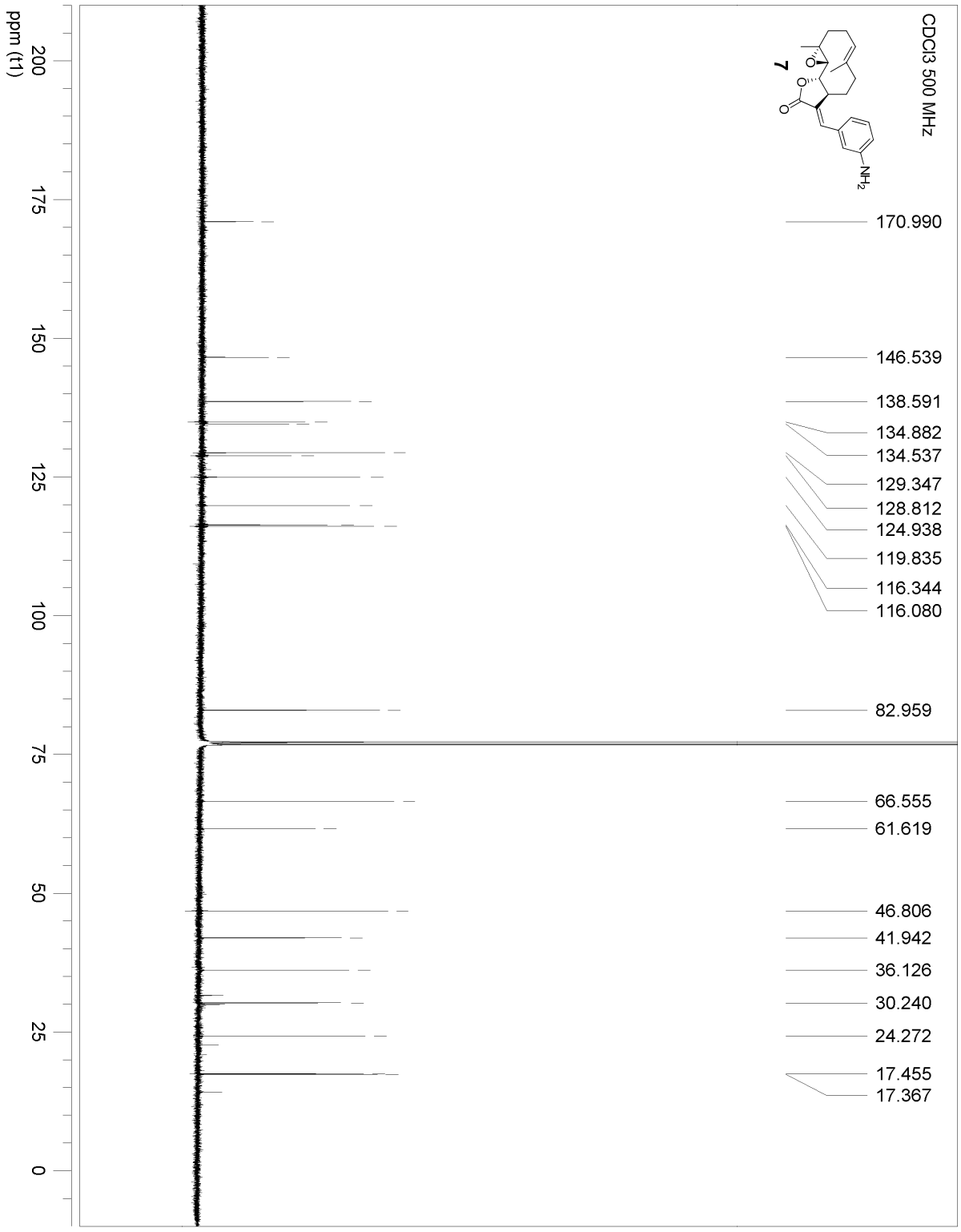

CDCl3 500 MHz
5
7.706
7.689
7.677
7.545
7.529
5.300
5.296
5.277
5.271
3.990
3.977
3.972
3.959
3.313
3.307
2.847
2.829
2.439
2.424
2.258
2.140
2.028
1.997
1.677
1.464
1.314
1.272
3.07
2.08
1.04
1.03
1.01
1.00
1.05
4.22
1.16
3.07
10.0
7.5
5.0
2.5
0.0
ppm (t1)

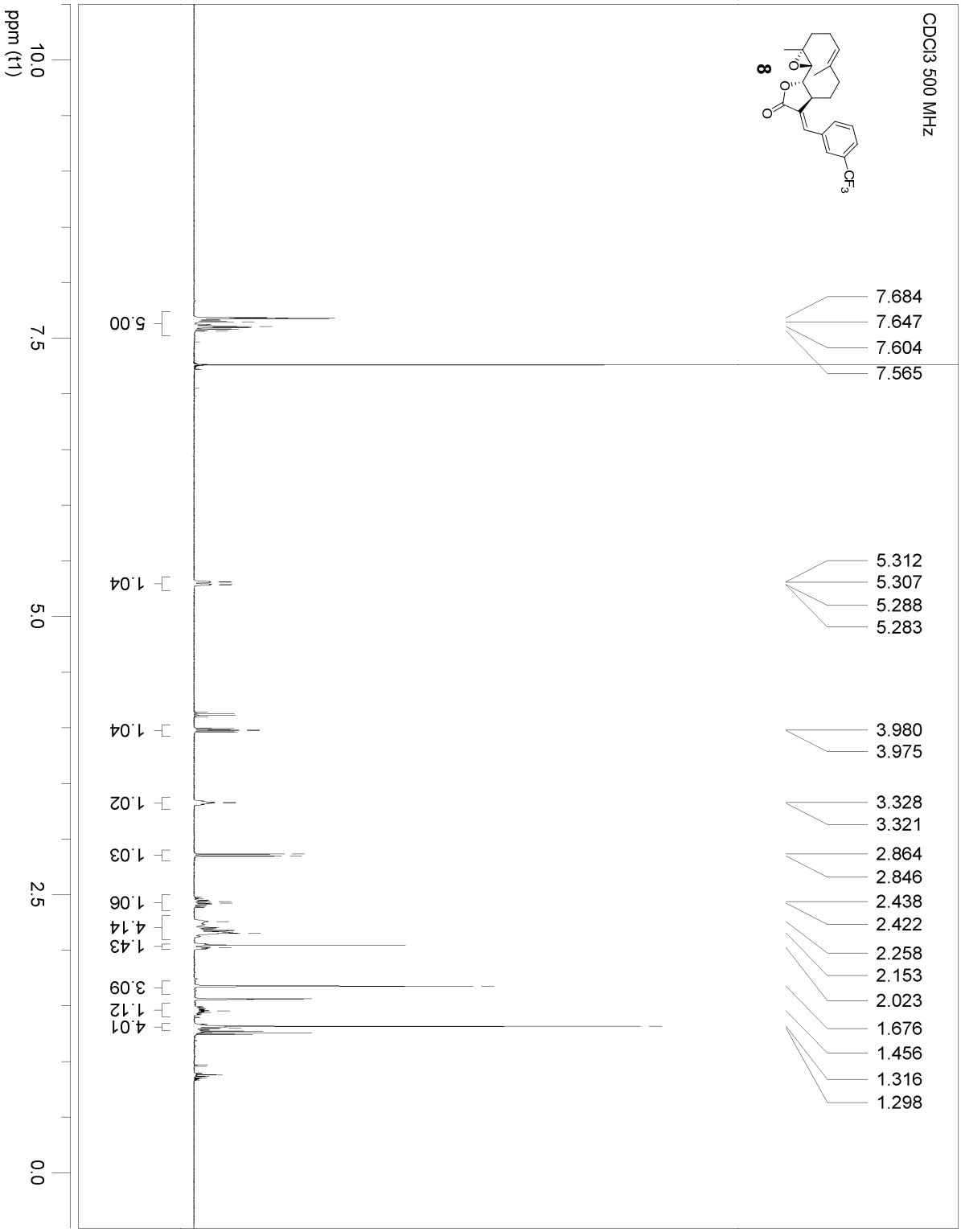

CDCl3 125 MHz
5
170.291
137.117
136.203
134.565
131.742
131.636
131.377
131.117
130.855
130.432
129.815
125.523
125.496
125.188
124.749
122.581
83.080
66.413
61.688
46.718
41.800
36.066
30.183
24.261
17.430
17.321
ppm (t1)
200
175
150
125
100
75
50
25
0

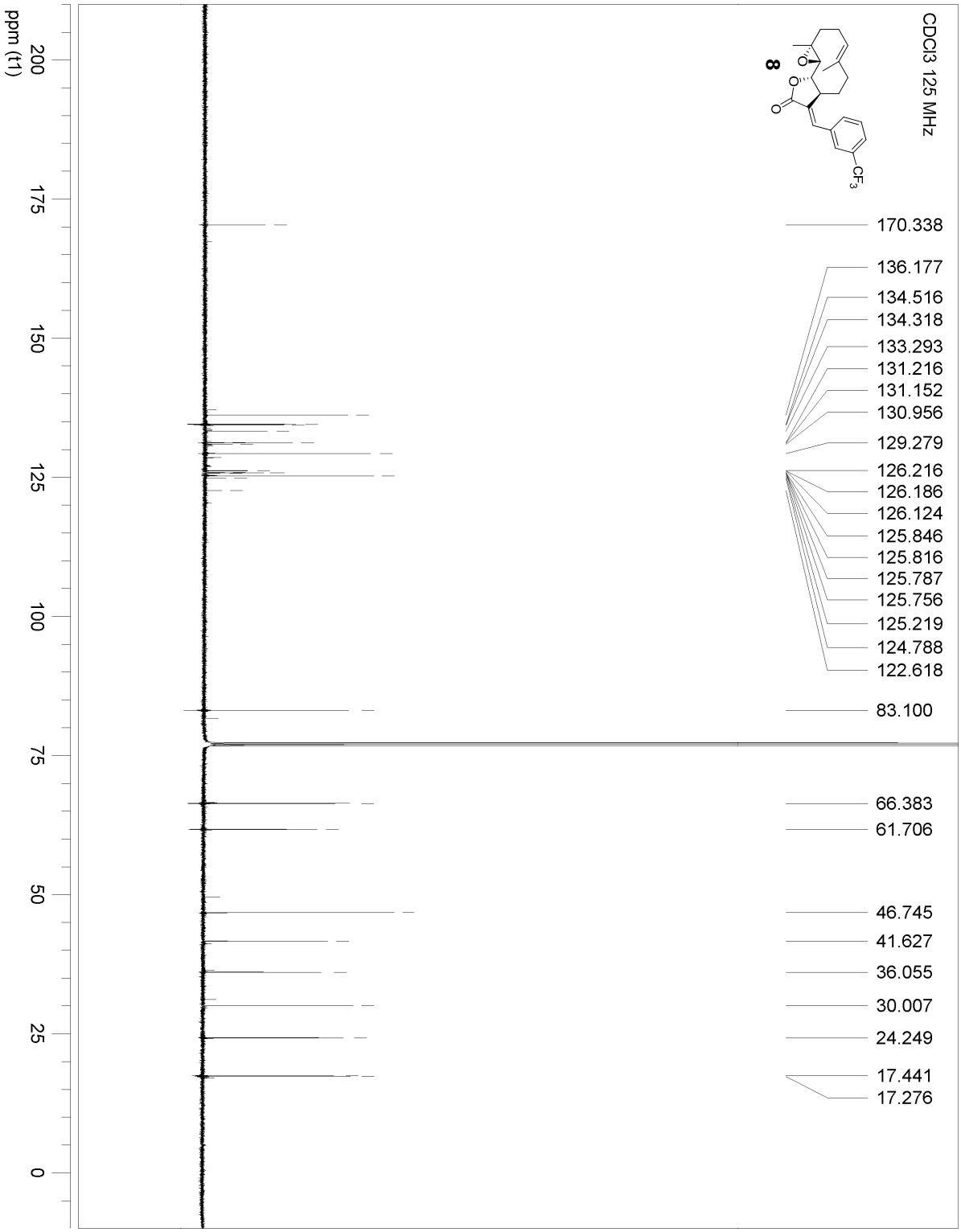

CDCl3 500 MHz
6
Et
7.649
7.642
7.359
7.343
7.271
7.255
5.311
5.307
5.287
5.282
3.954
3.950
3.307
3.300
2.854
2.836
2.699
2.684
2.440
2.425
2.249
2.166
1.684
1.444
1.430
1.313
1.264
1.221
1.206
1.02
2.07
2.10
1.02
1.01
1.00
1.04
2.10
1.08
5.28
3.27
1.11
10.0
7.5
5.0
2.5
0.0
ppm (t1)

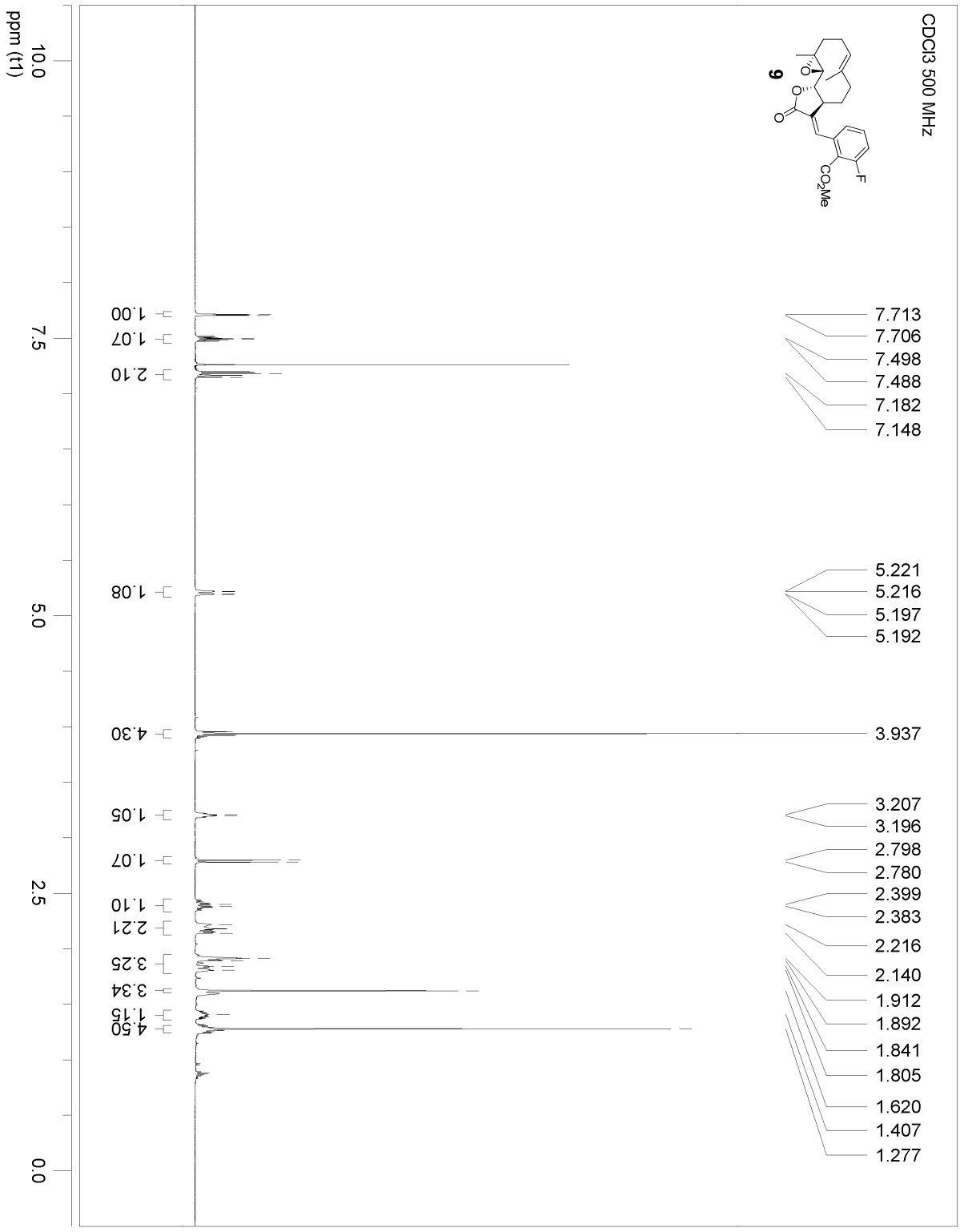

CDCl3 500 MHz
9
Et
ppm (t1)
200
175
150
125
100
75
50
25
171.127
146.412
138.300
134.784
130.806
130.091
128.062
127.800
125.052
82.892
66.546
61.633
46.836
41.877
36.094
30.031
28.776
24.306
17.478
17.373
15.216

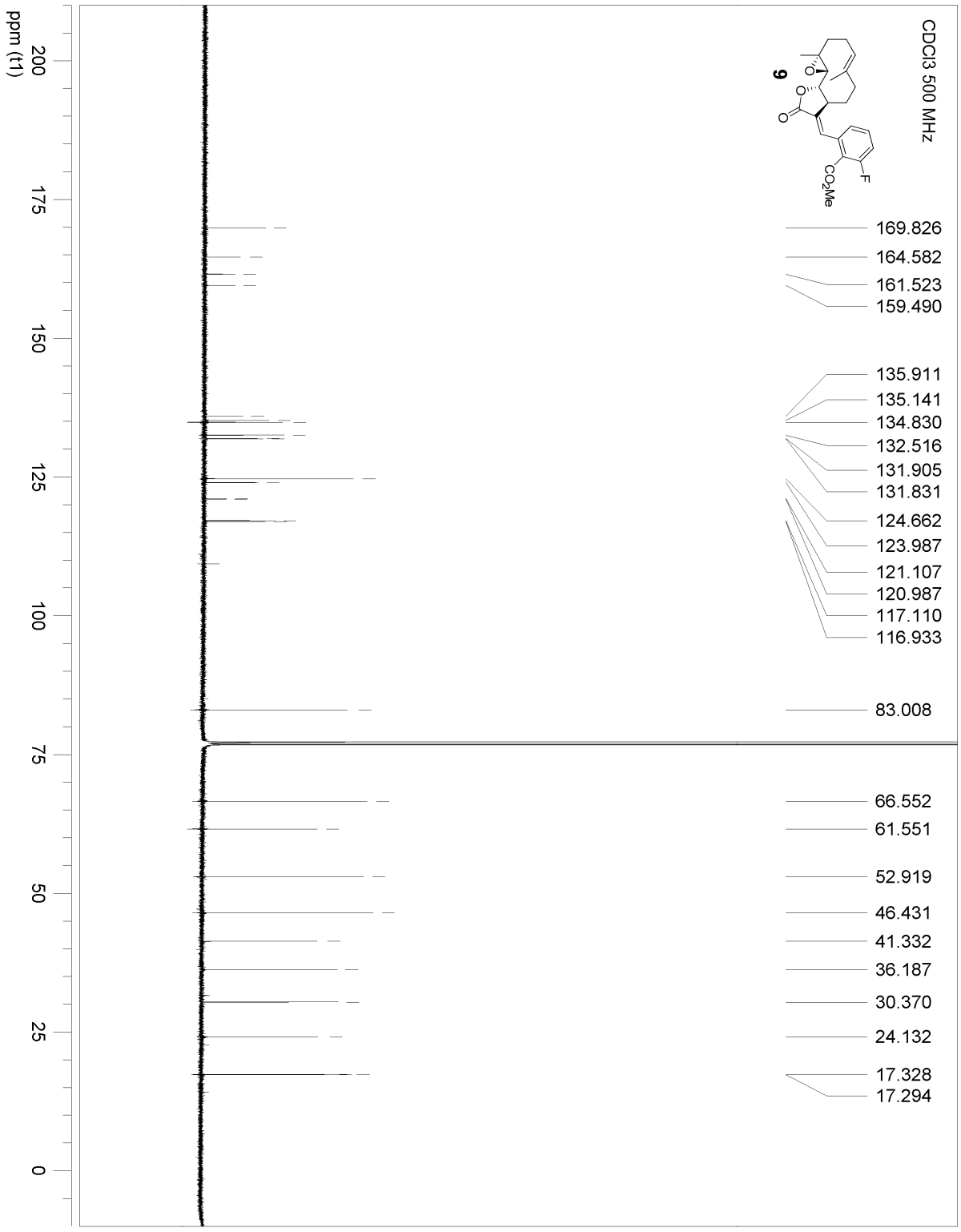

CDCl3 500 MHz
7
NH2
7.5851
7.5781
7.2173
7.2021
7.1868
6.8184
6.8033
6.7072
6.6913
5.2904
5.2660
3.9382
3.9346
3.7756
3.2725
2.8380
2.8203
2.4309
2.4150
2.2499
2.1548
1.6754
1.4179
1.3052
1.2858
1.05
1.12
1.08
2.15
1.05
1.07
1.98
1.00
1.08
1.17
5.37
3.41
1.20
3.08
10.0
7.5
5.0
2.5
0.0
ppm (t1)

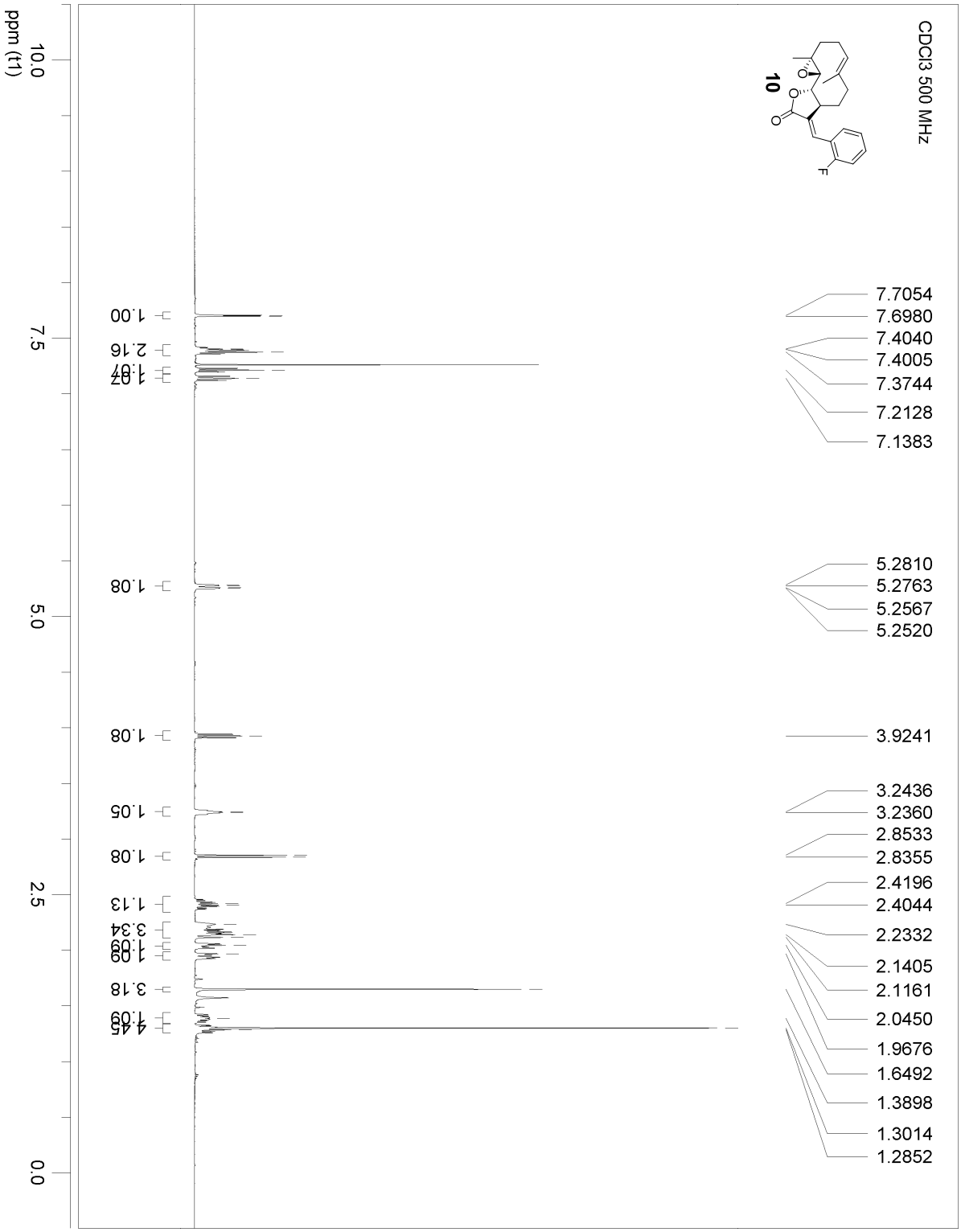

CDCl3 500 MHz
7
NH2
170.990
146.539
138.591
134.882
134.537
129.347
128.812
124.938
119.835
116.344
116.080
82.959
66.555
61.619
46.806
41.942
36.126
30.240
24.272
17.455
17.367
ppm (t1)
200
175
150
125
100
75
50
25
0

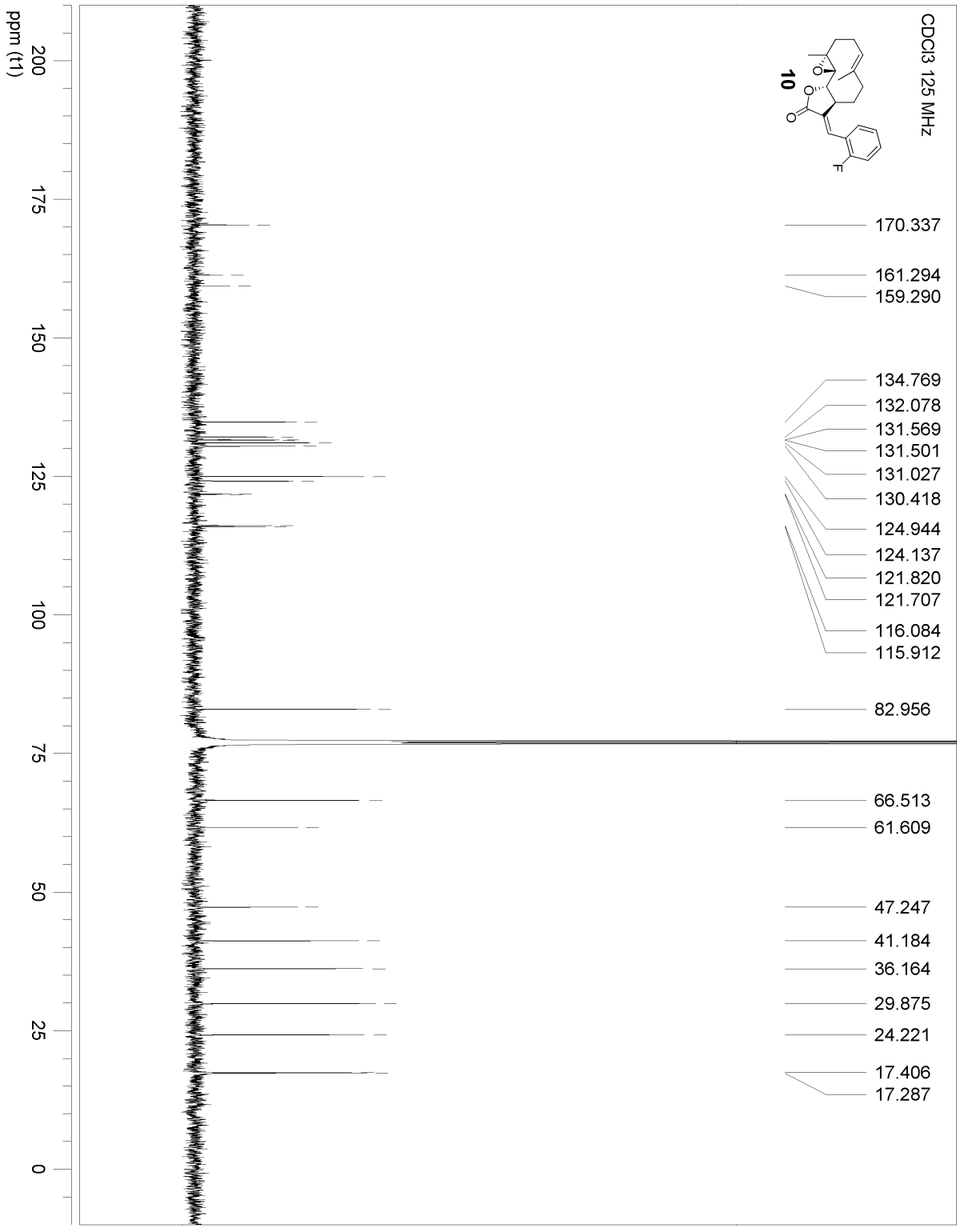

CDCl3 500 MHz
8
CF3
O
O
O
10.0
7.5
5.0
2.5
0.0
ppm (t1)
5.00
1.04
1.04
1.02
1.03
1.06
4.14
1.43
3.09
1.12
4.01
7.684
7.647
7.604
7.565
5.312
5.307
5.288
5.283
3.980
3.975
3.328
3.321
2.864
2.846
2.438
2.422
2.258
2.153
2.023
1.676
1.456
1.316
1.298

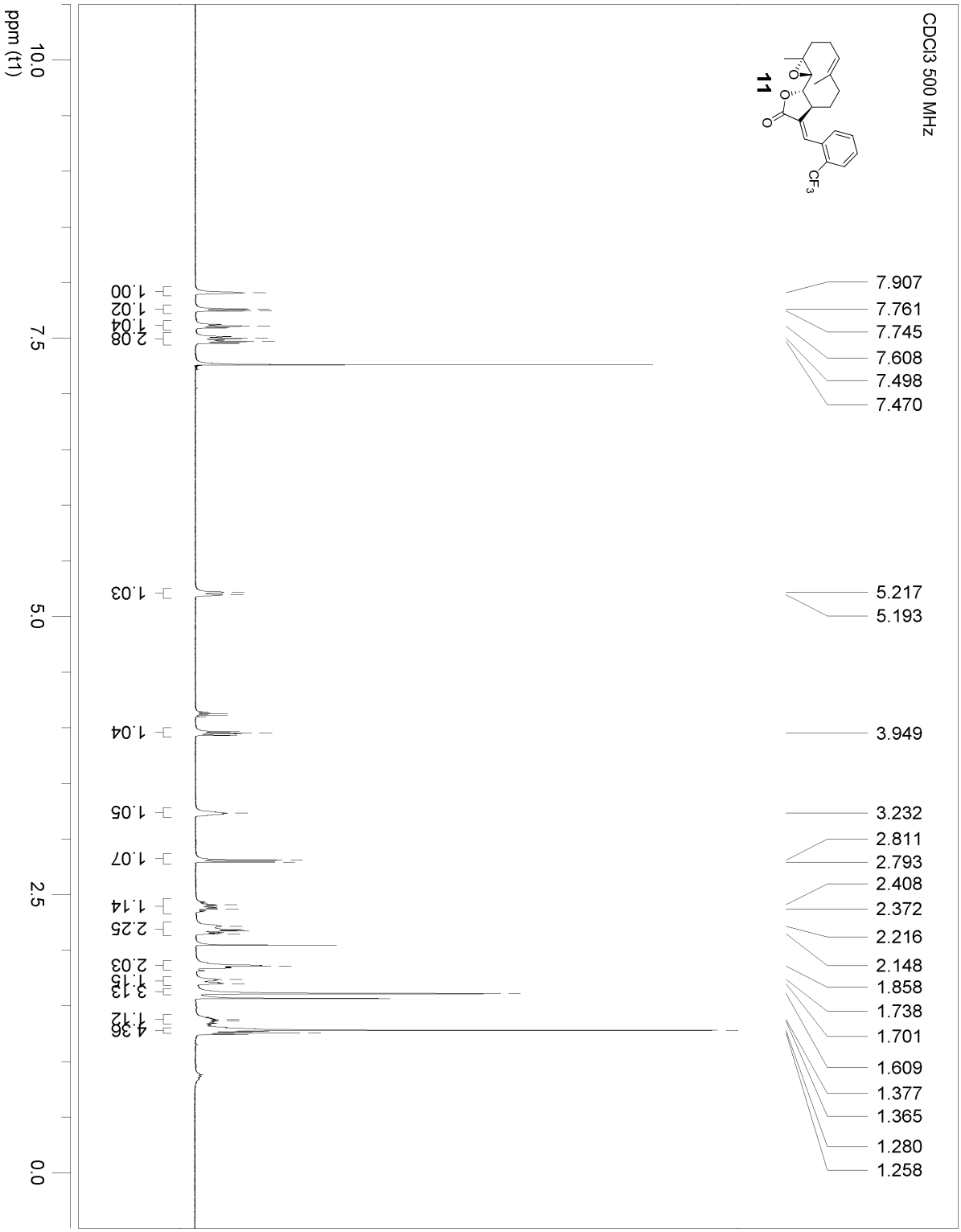

CDCl3 125 MHz
8
170.338
136.177
134.516
134.318
133.293
131.216
131.152
130.956
129.279
126.216
126.186
126.124
125.846
125.816
125.787
125.756
125.219
124.788
122.618
83.100
66.383
61.706
46.745
41.627
36.055
30.007
24.249
17.441
17.276
ppm (t1)
200
175
150
125
100
75
50
25
0

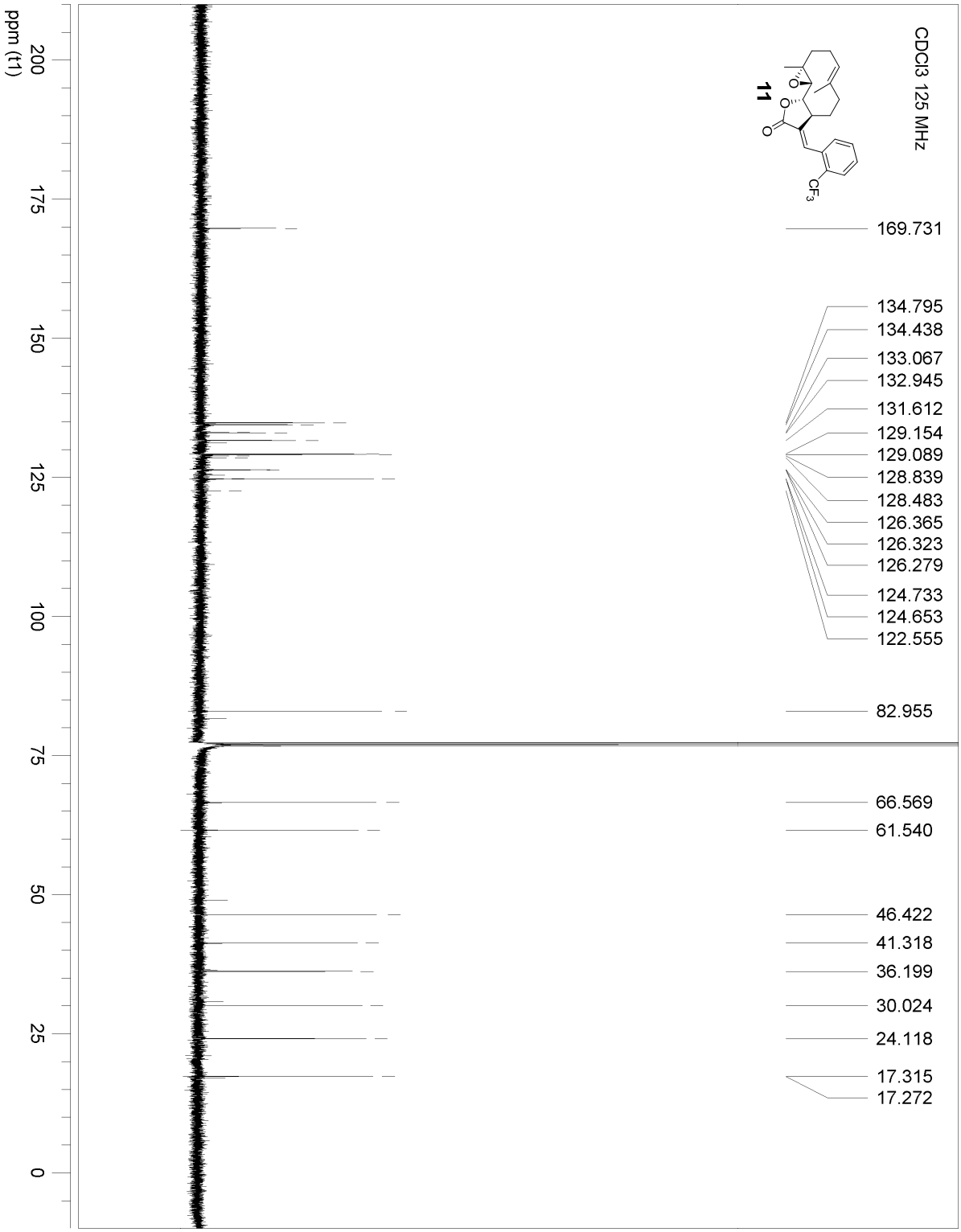

CDCl3 500 MHz
9
F
CO2Me
O
O
O
10.0
7.5
5.0
2.5
0.0
ppm (t1)
1.00
1.07
2.10
1.08
4.30
1.05
1.07
1.10
2.21
3.25
3.34
1.15
4.50
7.713
7.706
7.498
7.488
7.182
7.148
5.221
5.216
5.197
5.192
3.937
3.207
3.196
2.798
2.780
2.399
2.383
2.216
2.140
1.912
1.892
1.841
1.805
1.620
1.407
1.277

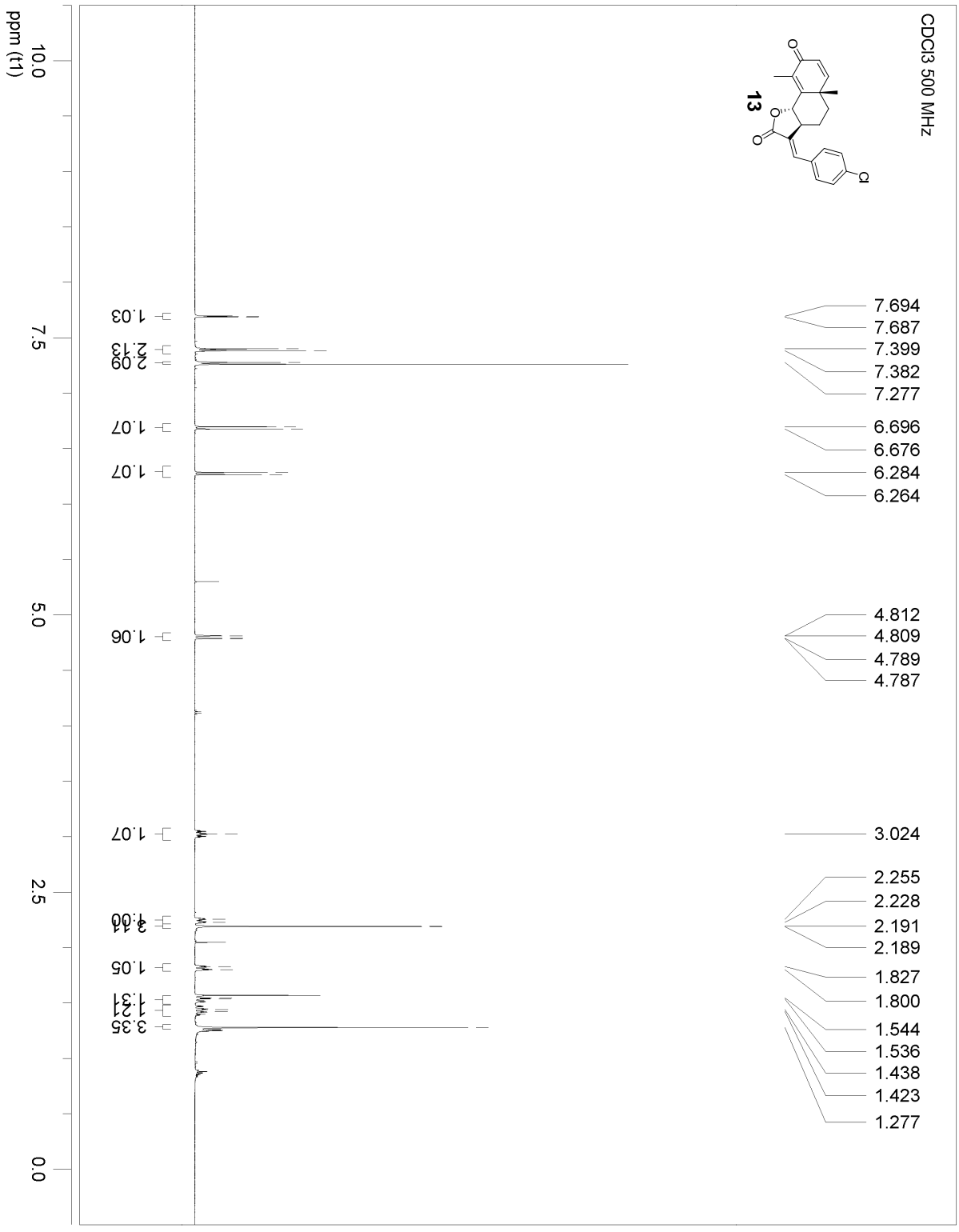

CDCl3 500 MHz
6
169.826
164.582
161.523
159.490
135.911
135.141
134.830
132.516
131.905
131.831
124.662
123.987
121.107
120.987
117.110
116.933
83.008
66.552
61.551
52.919
46.431
41.332
36.187
30.370
24.132
17.328
17.294
ppm (t1)
200
175
150
125
100
75
50
25
0

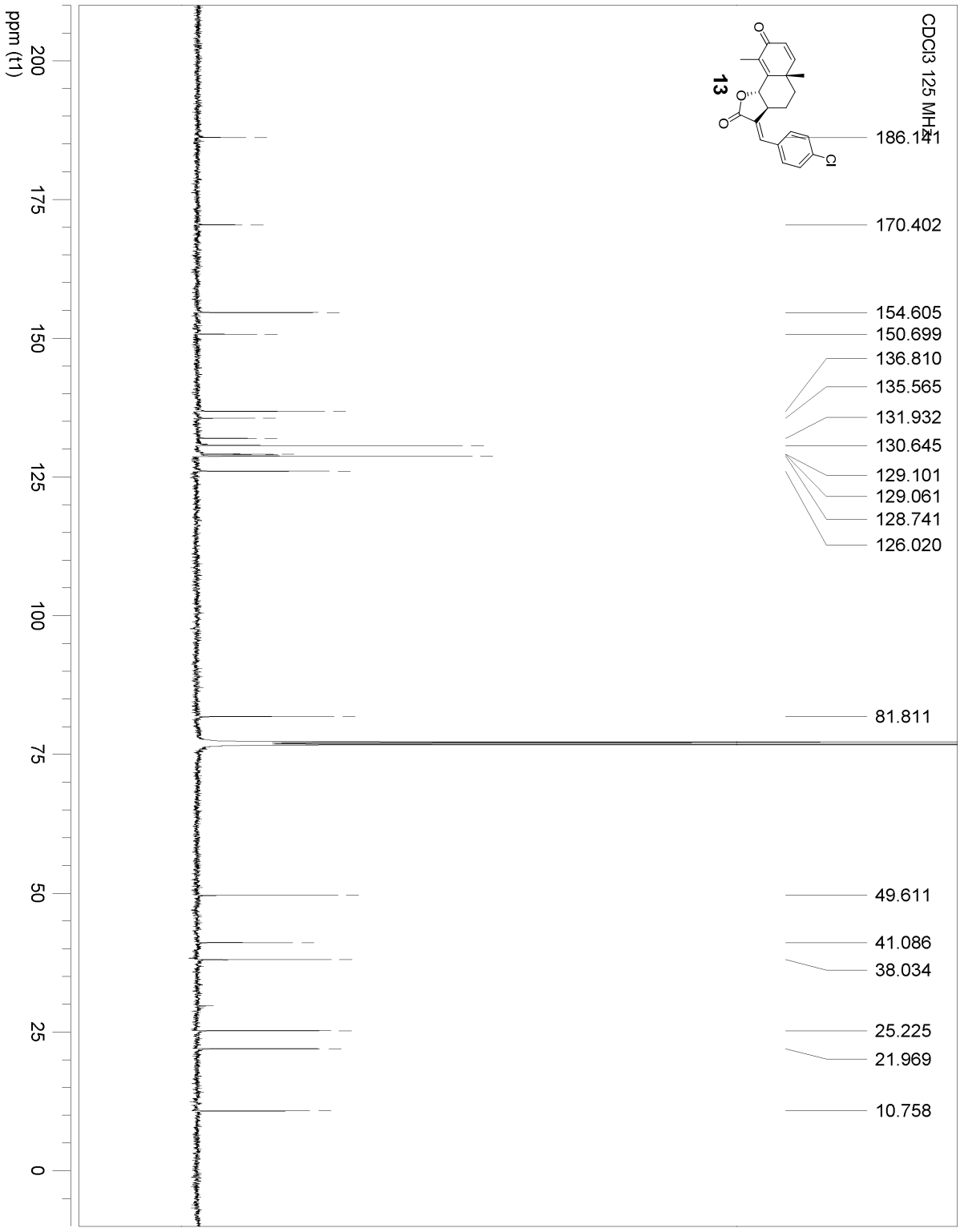

CDCl3 500 MHz
10
ppm (t1)
10.0
7.5
5.0
2.5
0.0
1.00
2.16
1.07
1.08
1.08
1.05
1.08
1.13
3.34
1.09
1.09
3.18
1.09
4.45
7.7054
7.6980
7.4040
7.4005
7.3744
7.2128
7.1383
5.2810
5.2763
5.2567
5.2520
3.9241
3.2436
3.2360
2.8533
2.8355
2.4196
2.4044
2.2332
2.1405
2.1161
2.0450
1.9676
1.6492
1.3898
1.3014
1.2852

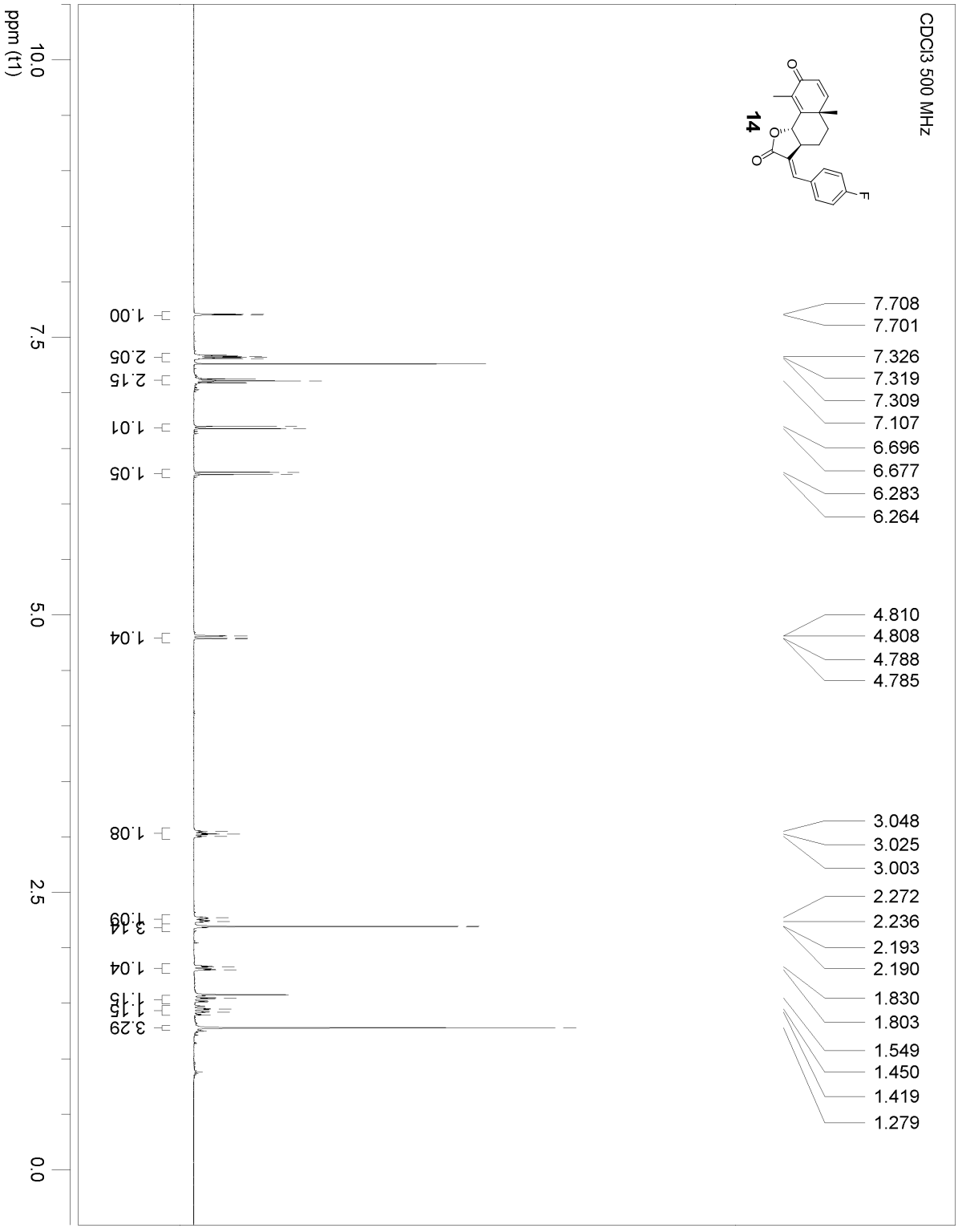

CDCl3 125 MHz
10
F
170.337
161.294
159.290
134.769
132.078
131.569
131.501
131.027
130.418
124.944
124.137
121.820
121.707
116.084
115.912
82.956
66.513
61.609
47.247
41.184
36.164
29.875
24.221
17.406
17.287
ppm (t1)
200
175
150
125
100
75
50
25
0

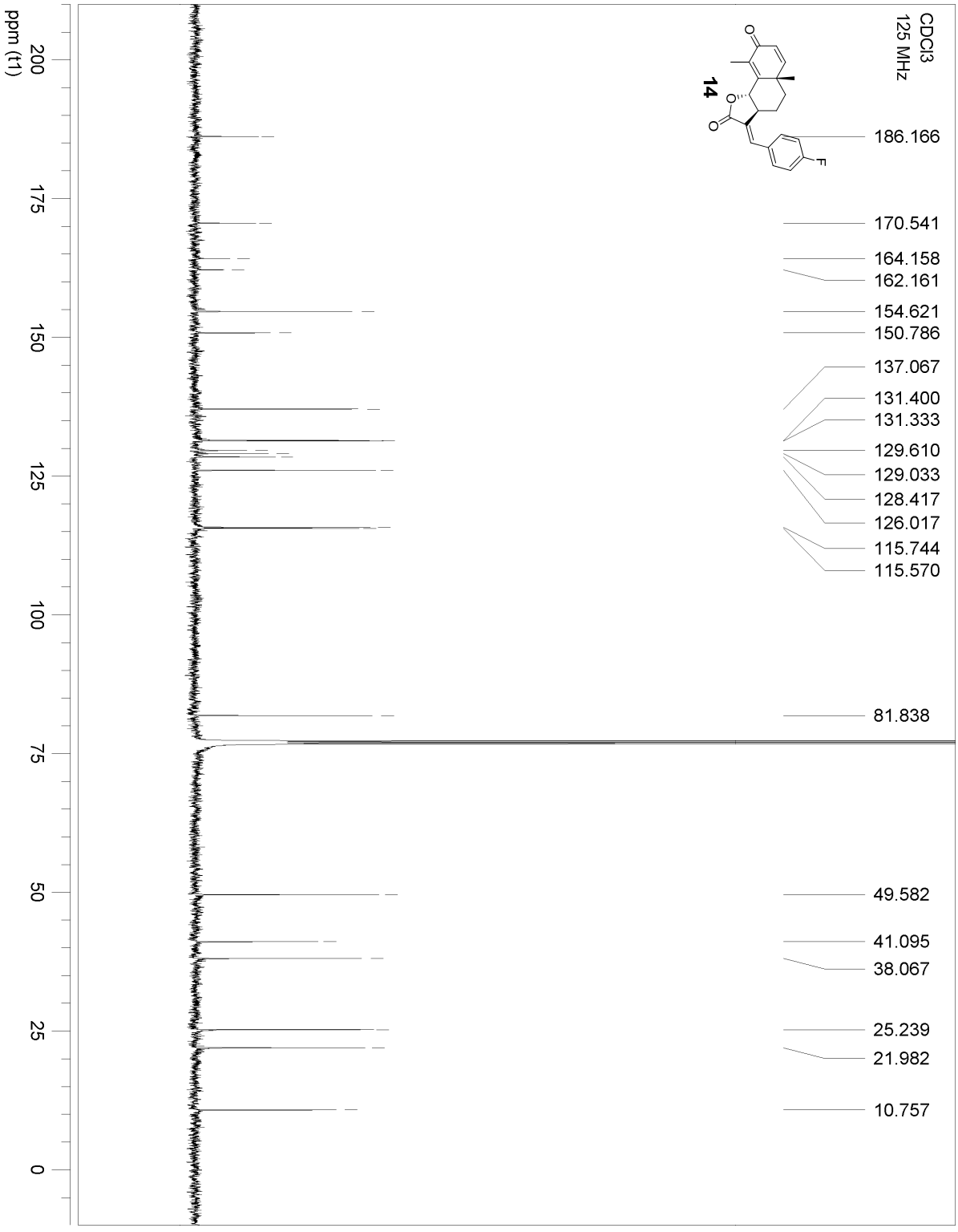

CDCl3 500 MHz
11
CF3
7.907
7.761
7.745
7.608
7.498
7.470
5.217
5.193
3.949
3.232
2.811
2.793
2.408
2.372
2.216
2.148
1.858
1.738
1.701
1.609
1.377
1.365
1.280
1.258
1.00
1.02
1.04
2.08
1.03
1.04
1.05
1.07
1.14
2.25
2.03
3.13
1.12
4.36
10.0
7.5
5.0
2.5
0.0
ppm (t1)

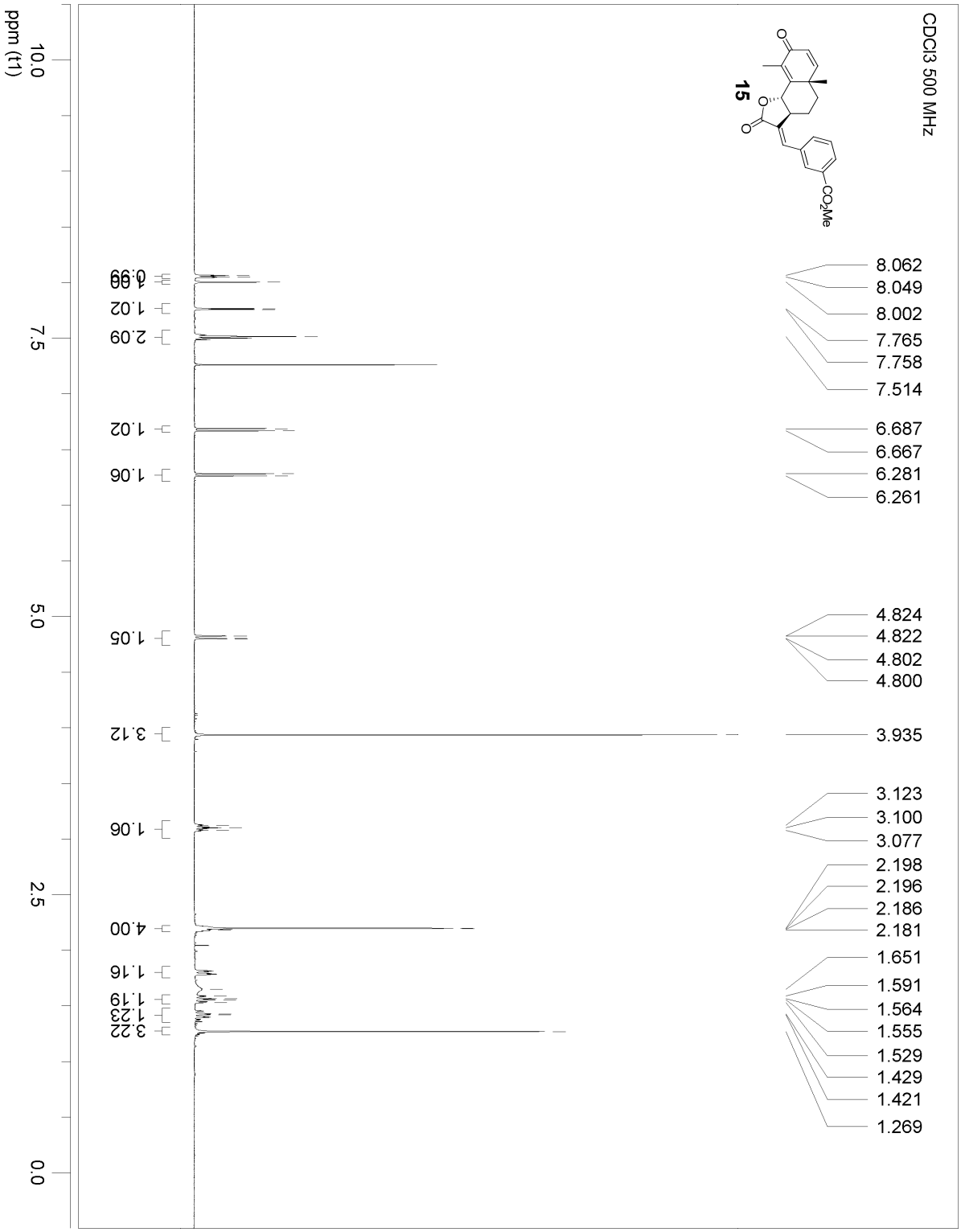

CDCl3 125 MHz
11
169.731
134.795
134.438
133.067
132.945
131.612
129.154
129.089
128.839
128.483
126.365
126.323
126.279
124.733
124.653
122.555
82.955
66.569
61.540
46.422
41.318
36.199
30.024
24.118
17.315
17.272
ppm (t1)
200
175
150
125
100
75
50
25
0

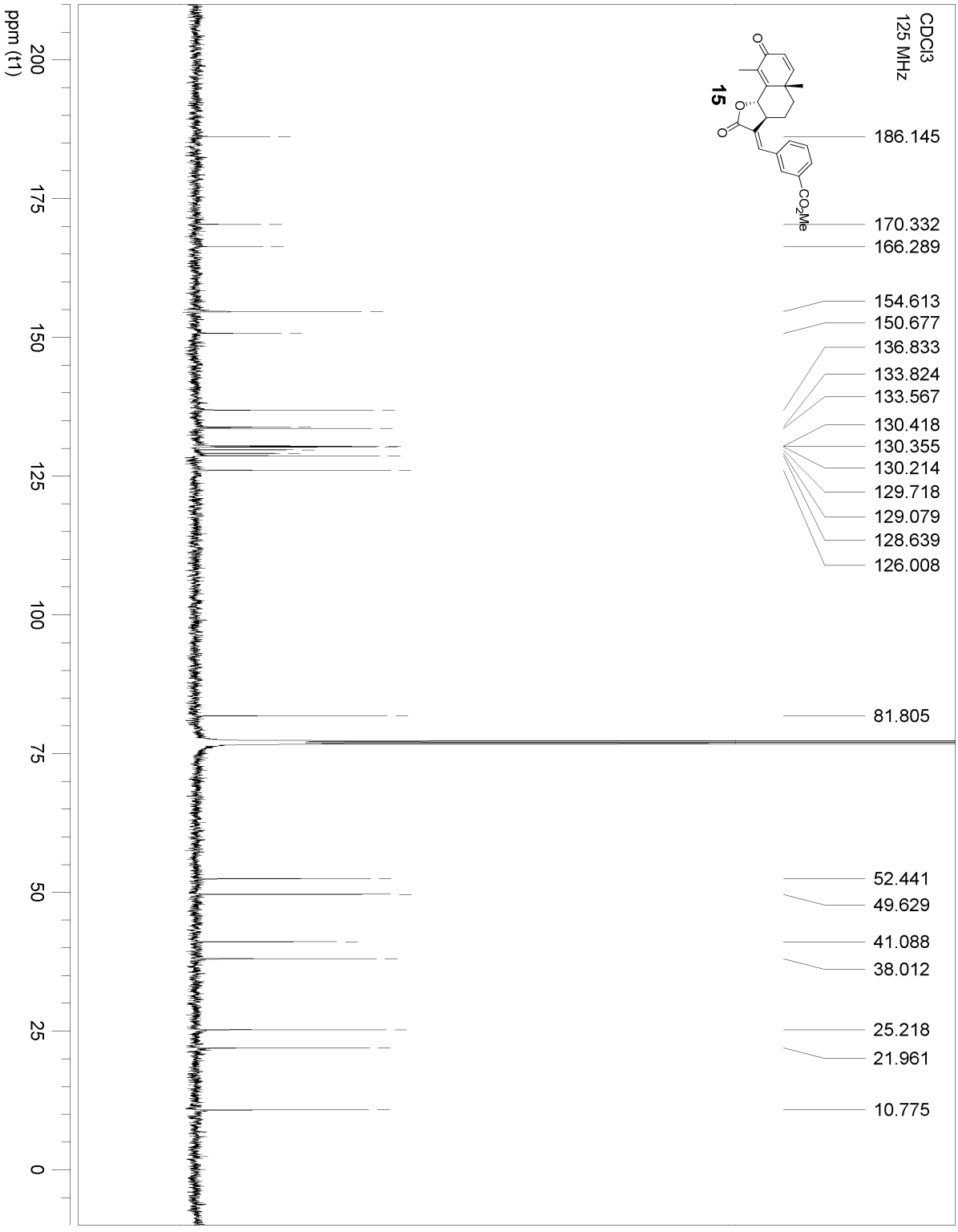

CDCl3 500 MHz
13
7.694
7.687
7.399
7.382
7.277
6.696
6.676
6.284
6.264
4.812
4.809
4.789
4.787
3.024
2.255
2.228
2.191
2.189
1.827
1.800
1.544
1.536
1.438
1.423
1.277
1.03
2.13
2.09
1.07
1.07
1.06
1.07
3.11
1.00
1.05
1.31
1.21
3.35
10.0
7.5
5.0
2.5
0.0
ppm (t1)

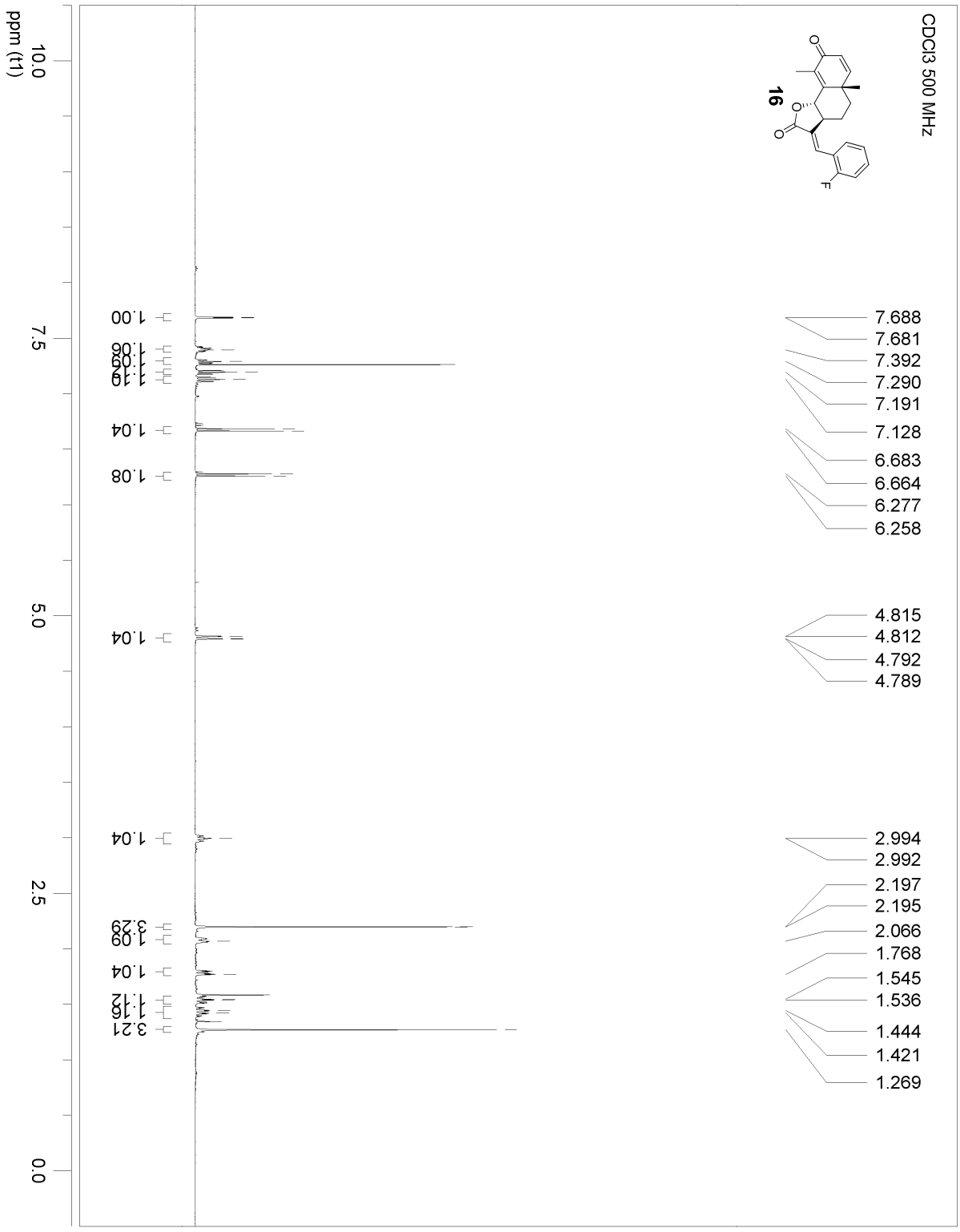

CDCl3 125 MHz
13
Cl
186.141
170.402
154.605
150.699
136.810
135.565
131.932
130.645
129.101
129.061
128.741
126.020
81.811
49.611
41.086
38.034
25.225
21.969
10.758
ppm (t1)
200
175
150
125
100
75
50
25
0

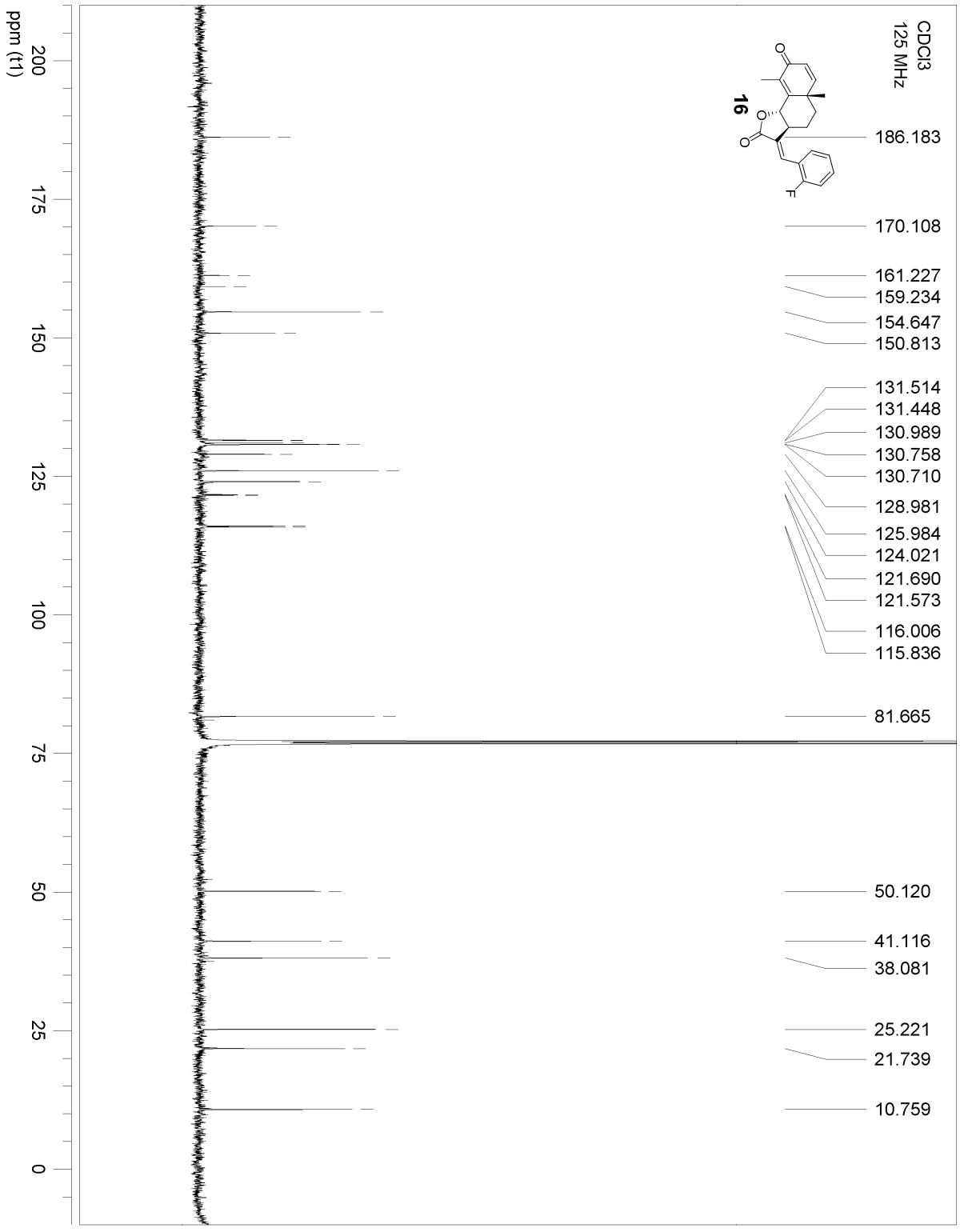

CDCl3 500 MHz
14
7.708
7.701
7.326
7.319
7.309
7.107
6.696
6.677
6.283
6.264
4.810
4.808
4.788
4.785
3.048
3.025
3.003
2.272
2.236
2.193
2.190
1.830
1.803
1.549
1.450
1.419
1.279
1.00
2.05
2.15
1.01
1.05
1.04
1.08
3.14
1.09
1.04
1.15
1.15
3.29
10.0
7.5
5.0
2.5
0.0
ppm (t1)


CDCl3
125 MHz
14
186.166
170.541
164.158
162.161
154.621
150.786
137.067
131.400
131.333
129.610
129.033
128.417
126.017
115.744
115.570
81.838
49.582
41.095
38.067
25.239
21.982
10.757
ppm (t1)
200
175
150
125
100
75
50
25
0


CDCl3 500 MHz
15
CO2Me
8.062
8.049
8.002
7.765
7.758
7.514
6.687
6.667
6.281
6.261
4.824
4.822
4.802
4.800
3.935
3.123
3.100
3.077
2.198
2.196
2.186
2.181
1.651
1.591
1.564
1.555
1.529
1.429
1.421
1.269
0.99
1.02
2.09
1.02
1.06
1.05
3.12
1.06
4.00
1.16
1.19
1.23
3.22
10.0
7.5
5.0
2.5
0.0
ppm (t1)


CDCl3
125 MHz
15
CO2Me
186.145
170.332
166.289
154.613
150.677
136.833
133.824
133.567
130.418
130.355
130.214
129.718
129.079
128.639
126.008
81.805
52.441
49.629
41.088
38.012
25.218
21.961
10.775
ppm (t1)
200
175
150
125
100
75
50
25
0


CDCl3 500 MHz
16
7.688
7.681
7.392
7.290
7.191
7.128
6.683
6.664
6.277
6.258
4.815
4.812
4.792
4.789
2.994
2.992
2.197
2.195
2.066
1.768
1.545
1.536
1.444
1.421
1.269
1.00
1.06
1.09
1.19
1.04
1.08
1.04
1.04
3.29
1.09
1.04
1.12
1.16
3.21
10.0
7.5
5.0
2.5
0.0
ppm (t1)


CDCl3
125 MHz
16
186.183
170.108
161.227
159.234
154.647
150.813
131.514
131.448
130.989
130.758
130.710
128.981
125.984
124.021
121.690
121.573
116.006
115.836
81.665
50.120
41.116
38.081
25.221
21.739
10.759
ppm (t1)
200
175
150
125
100
75
50
25
0