

Synthesis of (±)-γ-Rubromycin via a New Hypoiodite-Catalytic Oxidative Cycloetherification

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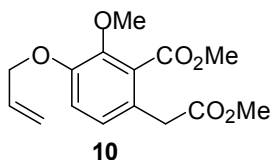
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General Information

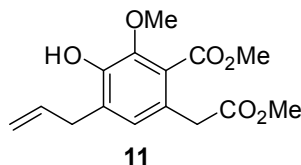
All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on GF254 plates. The silica gel (200–300 meshes) was used for column chromatography, and the distillation range of petro ether was 60–90 °C. CH₂Cl₂ was dried by distillation over CaH₂ and THF was dried by distillation over LiAlH₄. ¹H and ¹³C NMR spectra were recorded in CDCl₃ solution on Bruker AX-400 MHz instruments or Varian Mercury-600 MHz instruments and spectral data were reported in ppm relative to tetramethylsilane (TMS) as internal standard. IR spectra were recorded on a fourier transform infrared spectrometer. High-resolution mass spectral analysis (HRMS) data were measured on the Bruker Apex II by means of the ESI technique.

Experimental and Spectral Data

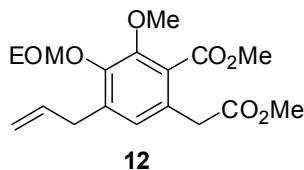


Compound 10: To a solution of methyl 3-hydroxy-2-methoxy-6-(2-methoxy-2-oxoethyl) benzoate **9** (2.5 g, 10.0 mmol) in acetone (100 ml) was added K₂CO₃ (1.7 g, 12 mmol) and allyl bromide (1.0 mL, 12 mmol) slowly over 5 min and the resulting mixture was stirred reflux overnight. After removal of the solvent in vacuo, the resultant residue was taken up in water (50 mL) and the aqueous mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 8:1) of the crude product afforded a yellow oil in 98% yield (2.88 g, 9.8 mmol). IR (film) ν_{max} 2952, 1736, 1490, 1273, 1148, 1056 cm⁻¹; ¹H NMR (400 MHz,

CDCl₃): δ = 6.92 (dd, J = 12.4, 8.4 Hz, 2H), 6.08–5.99 (m, 1H), 5.43–5.26 (m, 2H), 4.57 (d, J = 4.8 Hz, 2H), 3.88 (s, 6H), 3.66 (s, 3H), 3.60 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) 171.5, 167.6, 150.9, 147.2, 132.8, 128.9, 126.1, 124.5, 117.6, 115.5, 69.6, 61.4, 52.1, 51.9, 38.2 ppm; HRMS (ESI) C₁₅H₁₉O₆ [M+H]⁺ calcd for 295.1176, found 295.1170.

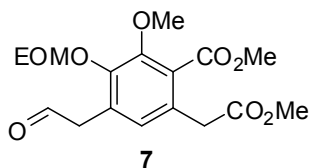


Compound 11: Methyl 3-(allyloxy)-2-methoxy-6-(2-methoxy-2-oxoethyl) benzoate **10** (2.88 g, 9.8 mmol) combined with PhNEt₂ (1 mL) was heated neat at 240 °C under a nitrogen atmosphere for 6 h. The reaction mixture changed from a clear oil to a dark brown oil, the reaction mixture was allowed to cool, and the thick brown oil subjected to chromatography in a silica gel (Petro Ether/EtOAc 8:1) afforded a clear oil in 95% yield (2.74 g, 9.3 mmol). IR (film) ν_{max} 2953, 1731, 1432, 1292, 1198, 1054 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 6.79 (s, 1H), 6.00–5.90 (m, 2H), 5.11–5.06 (m, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.66 (s, 3H), 3.65 (s, 2H), 3.39 (d, J = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) 171.8, 167.3, 146.1, 145.2, 135.5, 129.3, 127.9, 124.3, 124.1, 116.3, 62.3, 52.2, 51.9, 38.8, 33.9 ppm; HRMS (ESI) C₁₅H₁₉O₆ [M+H]⁺ calcd for 295.1176, found 295.1169.



Compound 12: Methyl 4-allyl-3-hydroxy-2-methoxy-6-(2-methoxy-2-oxoethyl) benzoate **11** (2.5 g, 8.5 mmol) was dissolved in dry dichloromethane (50 mL) and

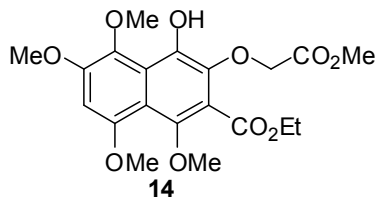
cooled to 0 °C under nitrogen. Diisopropylethylamine (1.48 mL, 8.5 mmol) was added, followed by ethoxymethyl chloride (1.2 mL, 12.8 mmol). The cooling bath was removed after 30 min, and the reaction allowed to stir for a further 4 h at room temperature. Water (100 mL) was then added, and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 8:1) of the crude product afforded a clear oil in 90% yield (2.7 g, 7.7 mmol). IR (film) $\nu_{\max}$ 2952, 1737, 1433, 1291, 1161, 1046 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 6.86 (s, 1H), 6.00–5.90 (m, 1H), 5.14 (s, 2H), 5.11–5.06 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.85–3.80 (m, 2H), 3.68 (s, 3H), 3.63 (s, 2H), 3.45 (d, J = 6.4 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 171.4, 167.4, 150.8, 147.6, 136.9, 136.1, 128.1, 127.7, 127.1, 116.5, 97.7, 65.7, 61.4, 52.2, 52.0, 38.7, 34.0, 15.1 ppm; HRMS (ESI) C₁₈H₂₅O₇ [M+H]⁺ calcd for 353.1595, found 353.1588.



Compound 7: Methyl 4-allyl-3-(ethoxymethoxy)-2-methoxy-6-(2-methoxy-2-

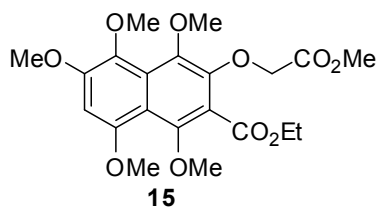
oxoethyl) benzoate **12** (2.0 g, 5.7 mmol) was dissolved in methanol (20 ml) and cooled to -78 °C. Ozone was bubbled through the solution for 1 h, then Me₂S were added and the cooling bath removed. The reaction mixture was stirred at room temperature for 2 h. Then the solvent was removed in vacuo, chromatography in a silica gel (Petro Ether/EtOAc 8:1) of the crude product afforded a clear oil in 92% yield (1.9 g, 5.2 mmol). IR (film) $\nu_{\max}$ 2952, 1736, 1452, 1291, 1160, 1053 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 9.72 (s, 1H), 6.87 (s, 1H), 5.15 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.76–3.64 (m, 9H), 1.22 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃)

198.8, 171.1, 167.1, 150.7, 148.5, 129.5, 128.7, 128.6, 128.5, 97.8, 65.9, 61.4, 52.3, 52.1, 45.2, 38.5, 15.0 ppm; HRMS (ESI) $C_{17}H_{23}O_8$ $[M+H]^+$ calcd for 355.1387, found 355.1383.

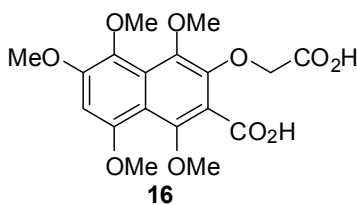


Compound 14: Following the literature's procedure,¹ Ortho-Quinone **13** (3.5 g, 10 mmol) was dissolved in PhH (150 mL) and combined with 10% $Na_2S_2O_4$ (150 mL). After 30 min of stirring, the layers were separated. The organic layer was dried and concentrated to afford the catechol, which was used immediately. The residue was dissolved in thoroughly deoxygenated DMF (100 mL), and $KHCO_3$ (1 g, 10 mmol) and methyl bromoacetate (0.93 mL, 10 mmol) were added. After stirring overnight, the reaction was quenched with saturated NH_4Cl , extracted with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 2:1) of the crude product afforded a yellow oil in 82% yield (3.5 g, 8.2 mmol). IR (film) ν_{max} 3623, 2941, 1763, 1732, 1612, 1378, 1271, 1213, 1114, 1056, 1036 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1H), 6.60 (s, 1H), 4.78 (s, 2H), 4.40 (q, J = 7.2Hz, 2H), 3.97 (s, 3H), 3.95 (s, 6H), 3.79 (s, 6H), 1.37 (t, J = 7.2Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.7, 165.7, 154.2, 148.4, 146.0, 140.8, 137.5, 136.4, 121.8, 120.8, 113.6, 96.3, 69.7, 63.9, 62.3, 61.3, 56.7, 56.6, 51.8, 14.2 ppm; HRMS (ESI) $C_{20}H_{24}NaO_{10}$ $[M+Na]^+$ calcd for 447.1262, found 447.1625.

(1) Lowell, A. N.; Fennie, M. W.; Kozlowski, M. C., *J. Org. Chem.* **2008**, 73, 1911.

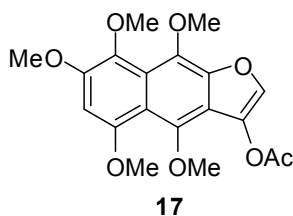


Compound 15: To a solution of Ethyl 4-hydroxy-1,5,6,8-tetramethoxy-3-(2-methoxy-2-oxoethoxy)-2-naphthoate **14** (1.9 g, 4.5 mmol) in acetone (100 ml) was added K_2CO_3 (6.1 g, 45 mmol) and CH_3I (2.8 mL, 45 mmol) slowly over 5 min and the resulting mixture was stirred reflux overnight. After removal of the solvent in vacuo, the resultant residue was taken up in water (50 mL) and the aqueous mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 4:1) of the crude product afforded a yellow oil in 98% yield (2.0 g, 4.4 mmol). IR (film) ν_{max} 2940, 1734, 1623, 1603, 1459, 1306, 1266, 1212, 1114, 1060 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 6.67(s, 1H), 4.79 (s, 2H), 4.41 (q, J = 7.2Hz, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 3.83 (s, 6H), 3.80 (s, 3H), 3.78 (s, 3H), 1.37 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.5, 165.6, 153.8, 151.0, 150.5, 146.0, 142.9, 136.5, 127.1, 120.8, 114.3, 96.4, 70.5, 63.9, 62.2, 61.9, 61.5, 56.8, 56.6, 51.9, 14.2 ppm; HRMS (ESI) $C_{21}H_{27}O_{10}$ $[M+H]^+$ calcd for 439.1599, found 439.1606.

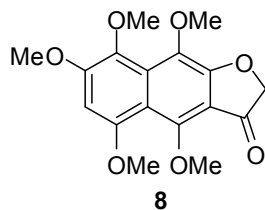


Compound 16: To a solution of ethyl 1,4,5,6,8-pentamethoxy-3-(2-methoxy-2-oxoethoxy)-2-naphthoate **15** (1.2 g, 2.7 mmol) in methanol (16 mL) was added 10% aqueous KOH (5.2 mL). The mixture was stirred for 1.5 h at 80 °C. The product formed by adding 1 N HCl, the aqueous mixture was extracted with DCM. The

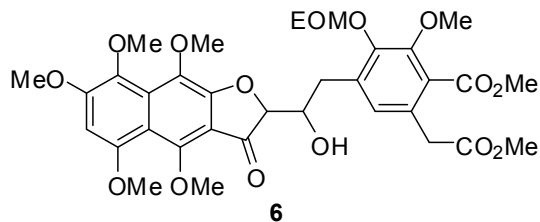
combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 1:1) of the crude product afforded a yellow oil in 90% yield (0.95 g, 2.4 mmol). IR (film) ν_{max} 2939, 1733, 1603, 1460, 1360, 1058, 910 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 10.79 (s, 2H), 6.69 (s, 1H), 4.94 (s, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 173.1, 168.7, 154.1, 152.1, 146.02, 145.98, 142.6, 136.1, 127.5, 117.1, 113.5, 96.4, 70.6, 64.3, 62.1, 61.9, 56.7, 56.5 ppm; HRMS (ESI) C₁₈H₂₁O₁₀ [M+H]⁺ calcd for 397.1129, found 397.1136.



Compound 17: A mixture of acetic anhydride (20 mL), acetic acid (4 mL), anhydrous sodium acetate (2.3 g, 28.0 mmol), and 3-(carboxymethoxy)-1,4,5,6,8-pentamethoxy-2-naphthoic acid **16** (340 mg, 0.86 mmol) was heated to reflux for 5 h. Water (100 mL) was then added, and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 2:1) of the crude product afforded a yellow solid in 85% yield (274 mg, 0.73 mmol). m.p. 151-152°C IR (film) ν_{max} 2937, 1732, 1602, 1362, 1205, 1050 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.88 (s, 1H), 6.67 (s, 1H), 4.06 (s, 3H), 4.02 (s, 6H), 3.93 (s, 3H), 3.88 (s, 3H), 2.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 167.9, 153.8, 148.8, 145.1, 136.7, 135.2, 134.8, 133.8, 123.9, 115.2, 114.5, 95.6, 63.7, 62.8, 62.0, 57.1, 56.7, 29.7, 20.7 ppm; HRMS (ESI) C₁₉H₂₁O₈ [M+H]⁺ calcd for 377.1231, found 377.1226.

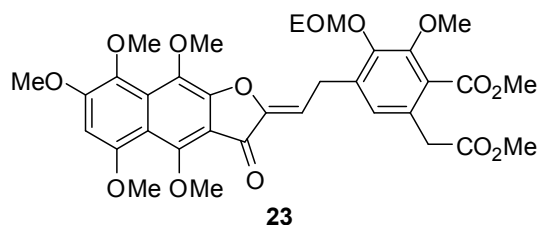


Compound 8: A mixture of 4,5,7,8,9-pentamethoxynaphtho[2,3-b]furan-3-yl acetate **17** (188 mg, 0.5 mmol), methanol (3 mL), water (1 mL), and 1 N HCl (0.2 mL) was heated to reflux for 2 h. The mixture was extracted with DCM. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 2:1) of the crude product afforded a yellow oil in 88% yield (165 mg, 0.44 mmol). IR (film) ν_{max} 2924, 1718, 1624, 1364, 1261, 1052 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 6.56 (s, 1H), 4.68 (s, 2H), 4.07 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 196.4, 159.2, 157.6, 154.3, 153.4, 135.8, 133.4, 132.3, 113.2, 111.5, 94.4, 75.0, 63.2, 62.3, 62.0, 56.8, 56.4 ppm; HRMS (ESI) C₁₇H₁₉O₇ [M+H]⁺ calcd for 335.1125, found 335.1115.



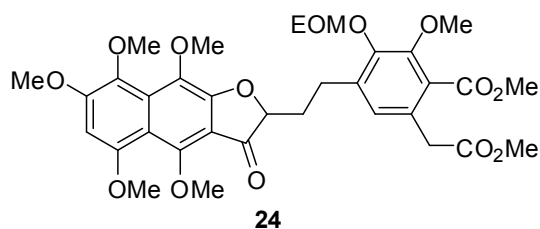
Compound 6: To a solution of 4,5,7,8,9-pentamethoxynaphtho [2,3-b] furan-3-yl acetate **17** (50 mg, 0.13 mmol) in anhydrous THF (5 mL) at -78 °C was added LDA (2 N in THF, 0.085 mL, 0.17 mmol, 1.5 equiv) slowly over 5 min and the resulting mixture was stirred at -78 °C for 1 h. Methyl 3-(ethoxymethoxy)-2-methoxy-6-(2-methoxy-2-oxoethyl)-4-(2-oxoethyl) benzoate **7** (69 mg, 0.2 mmol, in 2mL THF, 1.5 equiv) was added to the reaction mixture and the resulting solution was stirred at -78 °C for 30 min and at -40 °C for 4 h. The reaction mixture was quenched by

addition of saturated aqueous NH_4Cl (2 mL). And the aqueous mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 4:1) of the crude product afforded a yellow oil in 85% yield (76 mg, 0.11 mmol). IR (film) ν_{max} 2937, 1717, 1579, 1453, 1388, 1364, 1264, 1053 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.00 (s, 1H), 6.55 (s, 1H), 5.22–5.16 (m, 2H), 4.70–4.38 (m, 2H), 4.06–3.84 (m, 23H), 3.36–3.61 (m, 5H), 3.36–2.95 (m, 3H), 1.27–1.21 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) 196.7, 171.2, 167.3, 158.0, 154.5, 153.6, 150.6, 148.6, 135.8, 134.5, 133.0, 128.7, 128.4, 128.3, 127.7, 127.6, 113.1, 111.9, 97.9, 94.3, 86.8, 72.4, 66.0, 63.2, 62.1, 61.4, 56.8, 56.4, 52.2, 52.0, 38.6, 34.6, 32.3, 15.0 ppm; HRMS (ESI) $\text{C}_{34}\text{H}_{41}\text{O}_{15}$ $[\text{M}+\text{H}]^+$ calcd for 689.2440, found 689.2445.

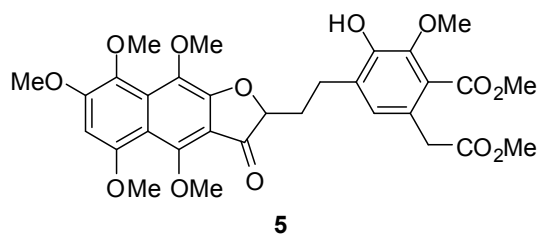


Compound 23: To a solution of methyl 3-(ethoxymethoxy)-4-(2-hydroxy-2-(4,5,7,8,9-pentamethoxy-3-oxo-2,3-dihydronaphtho[2,3-b]furan-2-yl)ethyl)-2-methoxy-6-(2-methoxy-2-oxoethyl)benzoate **6** (55 mg, 0.08 mmol) and methanesulfonyl chloride (2 equiv, 0.16 mmol, 12.37 μ L) in CH_2Cl_2 (2 mL) was added dropwise Et_3N (2.0 equiv, 0.16 mmol, 22.24 μ L) at -78°C . After being stirred at 0°C for 1 h, 1 N HCl (0.5 mL) was added, and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 2:1) of the crude product afforded a yellow oil in 72% yield (39 mg, 0.058 mmol). IR (film) ν_{max} 2940, 1736, 1576, 1454, 1366, 1266, 1053 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 6.95 (s, 1H), 6.60 (s, 1H),

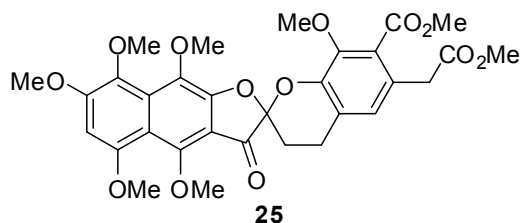
6.17 (t, $J = 8.0$ Hz, 1H), 5.22 (s, 2H), 4.13 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.90–3.85 (m, 13H), 3.66 (s, 3H), 3.64 (s, 2H), 1.27 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 180.8, 171.2, 167.3, 157.7, 155.4, 153.7, 152.0, 150.8, 149.8, 147.9, 136.4, 135.6, 132.7, 131.6, 128.4, 127.7, 127.6, 113.5, 112.0, 110.7, 97.8, 94.8, 65.8, 63.3, 62.4, 62.0, 61.5, 56.9, 56.4, 52.2, 52.0, 38.7, 26.4, 15.2 ppm; HRMS (ESI) $\text{C}_{34}\text{H}_{39}\text{O}_{14}$ $[\text{M}+\text{H}]^+$ calcd for 671.2334, found 671.2338.



Compound 24: A solution of (Z)-methyl 3-(ethoxymethoxy)-2-methoxy-6-(2-methoxy-2-oxoethyl)-4-(2-(4,5,7,8,9-pentamethoxy-3-oxonaphtho[2,3-b]furan-2(3H)-ylidene)ethyl)benzoate **23** (40 mg, 0.059 mmol) in 4 mL of methanol and 1 mL of dioxane was hydrogenated over 10% Pd/C (4 mg) at atmospheric pressure for 2 h. After filtration and evaporation chromatography in a silica gel (Petro Ether/EtOAc 2:1) of the crude product afforded a yellow oil in 98% yield (39 mg, 0.058 mmol). IR (film) ν_{max} 2922, 1796, 1599, 1467, 1366, 1053 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 6.92 (s, 1H), 6.56 (s, 1H), 5.17 (s, 2H), 4.68–4.65 (m, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 3.87–3.80 (m, 8H), 3.67 (s, 3H), 3.61 (s, 2H), 2.93 (t, $J = 7.6$ Hz, 2H), 2.41–2.11 (m, 2H), 1.21 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 198.0, 171.2, 167.3, 157.8, 157.5, 154.3, 153.3, 150.7, 147.9, 137.7, 135.7, 133.1, 132.2, 128.0, 127.7, 127.2, 113.0, 111.4, 97.6, 94.2, 84.8, 65.7, 63.1, 62.0, 61.3, 56.8, 56.3, 52.1, 52.0, 51.9, 38.6, 32.0, 25.6, 15.0 ppm; HRMS (ESI) $\text{C}_{34}\text{H}_{41}\text{O}_{14}$ $[\text{M}+\text{H}]^+$ calcd for 673.2491, found 673.2489.

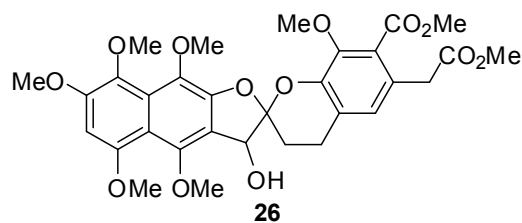


Compound 5: To a solution of methyl 3-(ethoxymethoxy)-2-methoxy-6-(2-methoxy-2-oxoethyl)-4-(2-(4,5,7,8,9-pentamethoxy-3-oxo-2,3-dihydronaphtho[2,3-b]furan-2-yl)ethyl)benzoate **24** (30 mg, 0.045 mmol) in CH₂Cl₂ (2 mL) was added dropwise TFA (2.0 equiv, 0.09 mmol, 6.7 μ L) at 0 °C. After being stirred at 0 °C for 30 min, sat NaHCO₃ (0.5 mL) was added, and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 1:1) of the crude product afforded a yellow oil in 98% yield (27 mg, 0.044 mmol). IR (film) ν_{max} 2939, 1723, 1623, 1601, 1578, 1456, 1433, 1363, 1291, 1054 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 6.85 (s, 1H), 6.55 (s, 1H), 6.15 (s, 1H), 4.65–4.62 (m, 1H), 4.04 (s, 3H), 4.02 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.66 (s, 3H), 3.61 (s, 2H), 2.93 (t, J = 7.6 Hz, 2H), 2.37–2.12 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) 198.3, 171.6, 167.2, 157.8, 157.5, 154.3, 153.3, 146.5, 145.3, 135.7, 133.0, 132.2, 130.0, 128.1, 124.3, 124.1, 113.0, 111.4, 94.2, 84.6, 63.1, 62.2, 62.0, 61.9, 56.7, 56.3, 52.2, 51.9, 38.7, 31.2, 25.3 ppm; HRMS (ESI) C₃₁H₃₄NaO₁₃ [M+Na]⁺ calcd for 637.1892, found 637.1904.



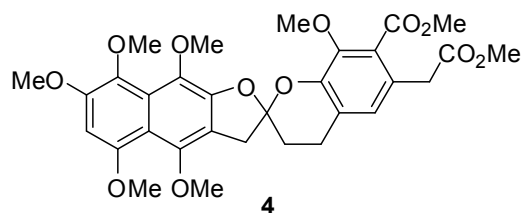
Compound 25: TBAI 5 mg (15 mol%) was added to a stirring solution of methyl

3-hydroxy-2-methoxy-6-(2-methoxy-2-oxoethyl)-4-(2-(4,5,7,8,9-pentamethoxy-3-oxo-2,3-dihydronaphtho[2,3-b]furan-2-yl)ethyl)benzoate **5** 24 mg (0.039 mmol) in 5 mL THF and then the solution of *m*CPBA 13 mg (2.0 eq.) and TBAF 20 mg (2.0 eq.) in 5 mL THF at room temperature was added dropwise in 5 min. The resulting solution was quenched with water, extracted (DCM), washed with Na₂SO₃, NaHCO₃ and brine, dried with Na₂SO₄, filtered, and concentrated. Chromatography on silica gel (Petro Ether/EtOAc 2:1) of the crude product afforded a yellow oil in 88% yield (21 mg, 0.034 mmol). IR (film) ν_{max} 2950, 1737, 1624, 1620, 1480, 1458, 1287, 1212, 1049 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 6.85 (s, 1H), 6.57 (s, 1H), 4.13 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 3.64 (d, *J* = 4.8 Hz, 2H), 3.25 (td, *J* = 17.2, 5.6 Hz, 1H), 2.96 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.32 (td, *J* = 13.6, 5.6 Hz, 1H), 2.14 (dd, *J* = 13.6, 2.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) 191.0, 171.6, 167.4, 157.9, 156.3, 154.3, 154.2, 146.4, 144.7, 136.2, 132.8, 132.6, 127.0, 126.1, 125.0, 124.98, 113.2, 108.6, 102.3, 94.5, 63.3, 62.2, 62.1, 61.58, 61.55, 56.83, 56.3, 52.13, 52.10, 38.4, 25.5, 20.6 ppm; HRMS (ESI) C₃₂H₃₆NO₁₃ [M+NH₄]⁺ calcd for 630.2181, found 630.2194.



Compound 26: To a stirring solution of methyl 4',5',7',8,8',9'-hexamethoxy-6-(2-methoxy-2-oxoethyl)-3'-oxo-3'H-spiro[chroman-2,2'-naphtho[2,3-b]furan]-7-carboxylate **25** (20 mg, 0.032 mmol) in MeOH (1.5 mL) (2 mL) was added NaBH₄ (1.2 mg, 0.032 mmol), and the reaction mixture was stirred at 0 °C for 10 min quenched by the addition of water and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried with Na₂SO₄, filtered, and concentrated.

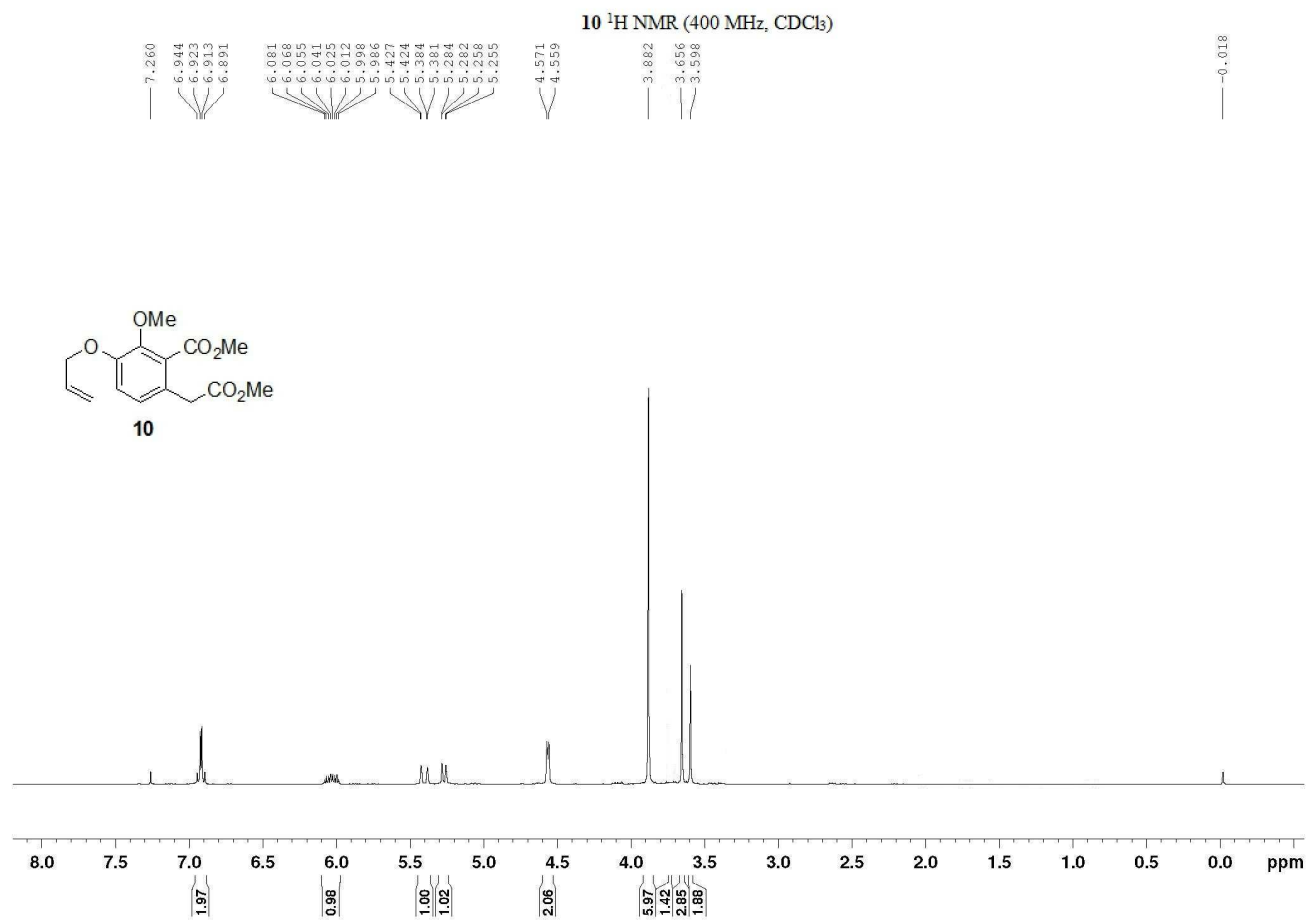
Chromatography in a silica gel (Petro Ether/EtOAc 2:1) of the crude product afforded a yellow oil in 95% yield (18 mg, 0.03 mmol). IR (film) $\nu_{\max}$ 2946, 1736, 1652, 1620, 1459, 1355, 1288, 1221, 1040 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 6.85 (s, 1H), 6.61 (s, 1H), 5.41 (s, 1H), 3.99 (s, 6H), 3.97 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.69 (s, 6H), 3.64 (d, J = 6.0 Hz, 2H), 3.34–3.25 (m, 1H), 2.88 (ddd, J = 8.0, 5.2, 2.4 Hz, 1H), 2.42 (ddd, J = 8.8, 6.0, 2.8 Hz, 1H), 2.24 ppm (dt, J = 12.8, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) 171.5, 167.3, 154.0, 151.5, 150.7, 147.3, 146.4, 144.2, 136.9, 133.1, 128.2, 126.8, 126.2, 125.3, 125.1, 118.6, 113.9, 107.3, 95.2, 76.3, 62.9, 61.94, 61.88, 61.6, 56.8, 56.6, 52.1, 52.0, 38.4, 27.8, 21.5 ppm; HRMS (ESI) $\text{C}_{31}\text{H}_{38}\text{NO}_{13}$ $[\text{M}+\text{NH}_4]^+$ calcd for 632.2338, found 632.2324.



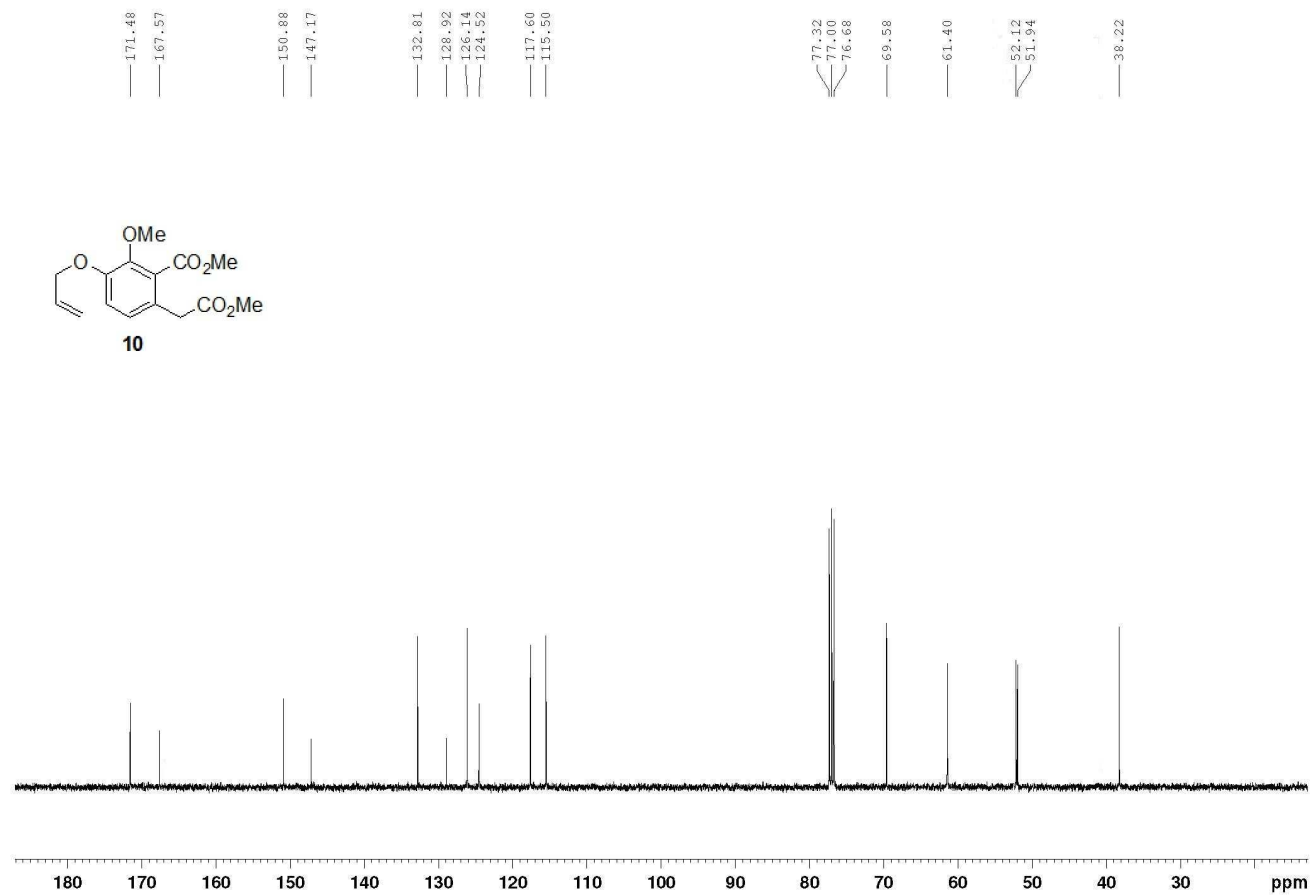
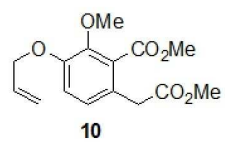
Compound 4: To a stirring solution of methyl 3'-hydroxy-4',5',7',8,8',9'-hexamethoxy-6-(2-methoxy-2-oxoethyl)-3'H-spiro[chroman-2,2'-naphtho[2,3-b]furan]-7-carboxylate **26** (10 mg, 0.016 mmol) in TFA (0.5 mL) was added Et_3SiH (2.6 μL , 0.016 mmol), and the reaction mixture was stirred at 50 $^\circ\text{C}$ for 5 min. Then sat NaHCO_3 (0.5 mL) was added, and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. Chromatography in a silica gel (Petro Ether/EtOAc 2:1) of the crude product afforded a yellow oil in 81% yield (8 mg, 0.013 mmol). IR (film) $\nu_{\max}$ 2925, 1736, 1643, 1603, 1457, 1355, 1257, 1204, 1059 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 6.83 (s, 1H), 6.60 (s, 1H), 3.98 (s, 6H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.69–3.67 (m, 4H), 3.63 (s, 3H), 3.62 (s, 2H), 3.43 (d, J = 16.8 Hz, 1H), 3.38–3.32 (m,

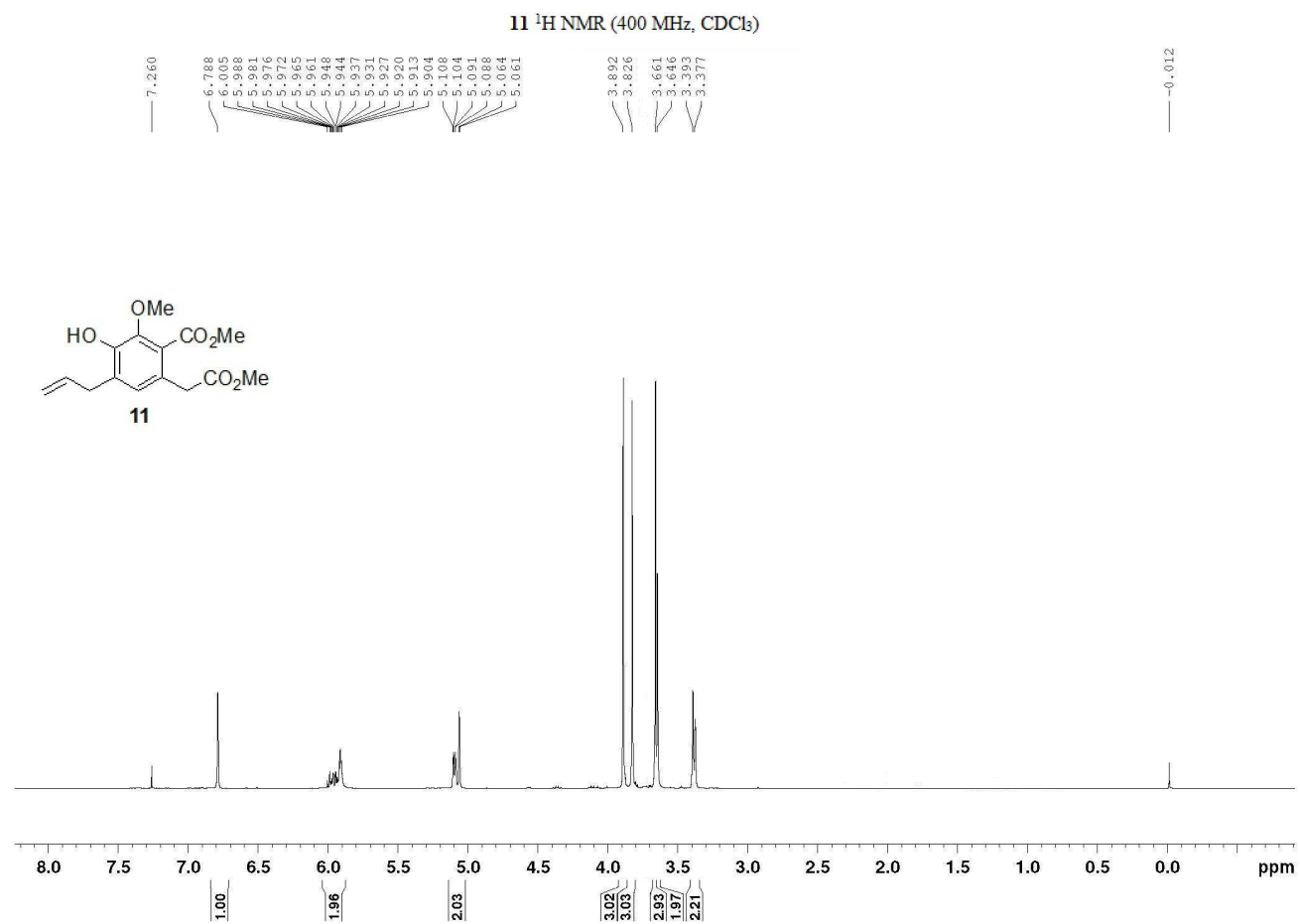
1H), 2.86 (dd, $J = 16.8, 3.6$ Hz, 1H), 2.42 (ddd, $J = 11.4, 6.0, 3.6$ Hz, 1H), 2.24 ppm (dt, $J = 13.2, 6.0$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) 171.7, 167.6, 153.3, 145.0, 149.1, 148.8, 146.5, 144.6, 137.0, 133.0, 127.2, 126.6, 126.2, 125.0, 124.5, 117.7, 113.6, 109.8, 95.1, 61.9, 61.8, 61.5, 61.4, 56.8, 56.7, 52.1, 52.0, 39.6, 38.4, 29.7, 22.0 ppm; HRMS (ESI) $\text{C}_{31}\text{H}_{35}\text{O}_{12}$ $[\text{M}+\text{H}]^+$ calcd for 599.2123, found 599.2110. Matches previously reported data.²

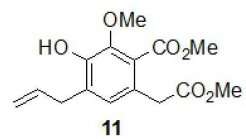
(2) Rathwell, D. C. K.; Yang, S.; Tsang, K. Y.; Brimble, M. A., *Angew. Chem., Int. Ed.* **2009**, 48, 7996.



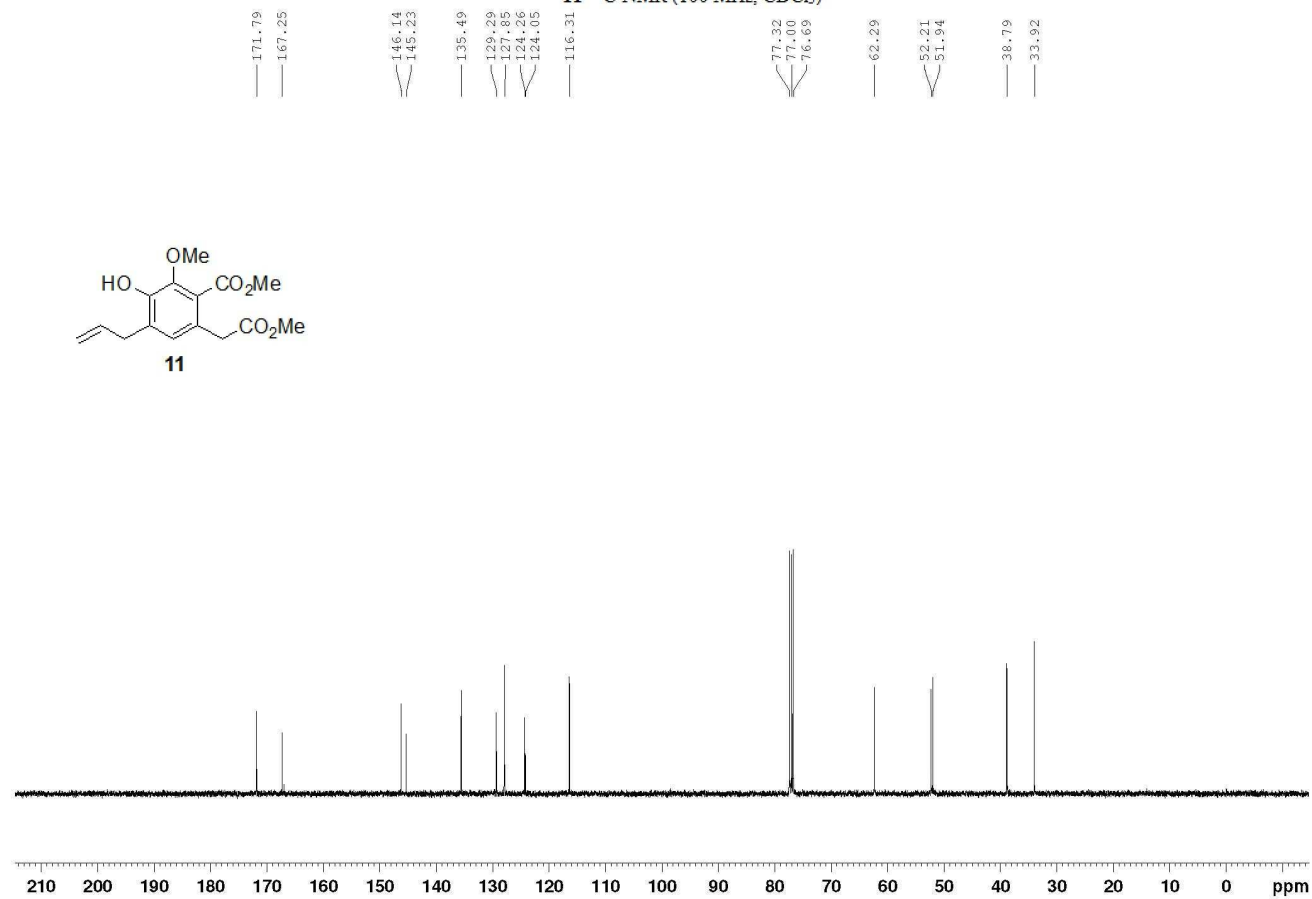
10 ^{13}C NMR (100 MHz, CDCl_3)

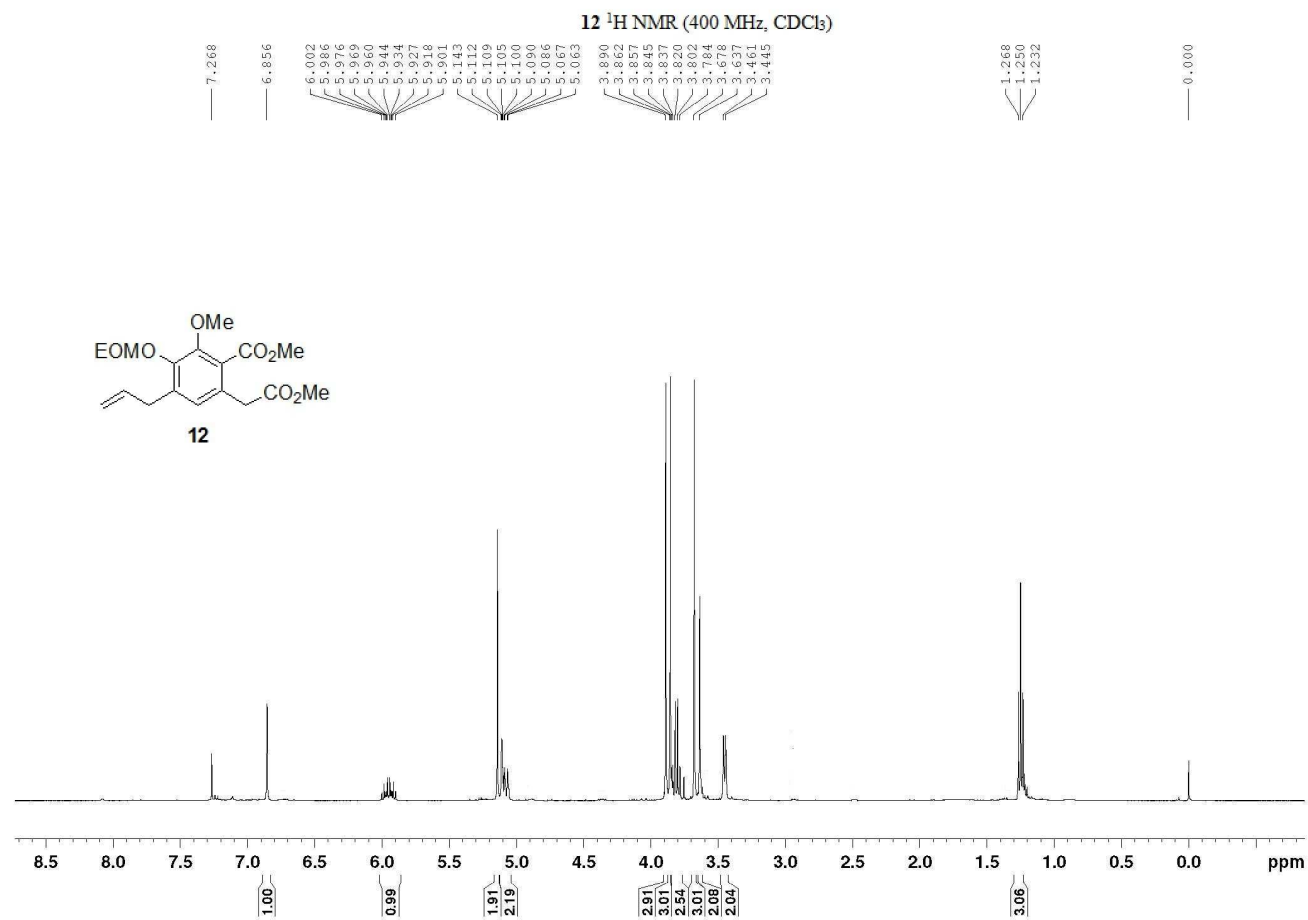


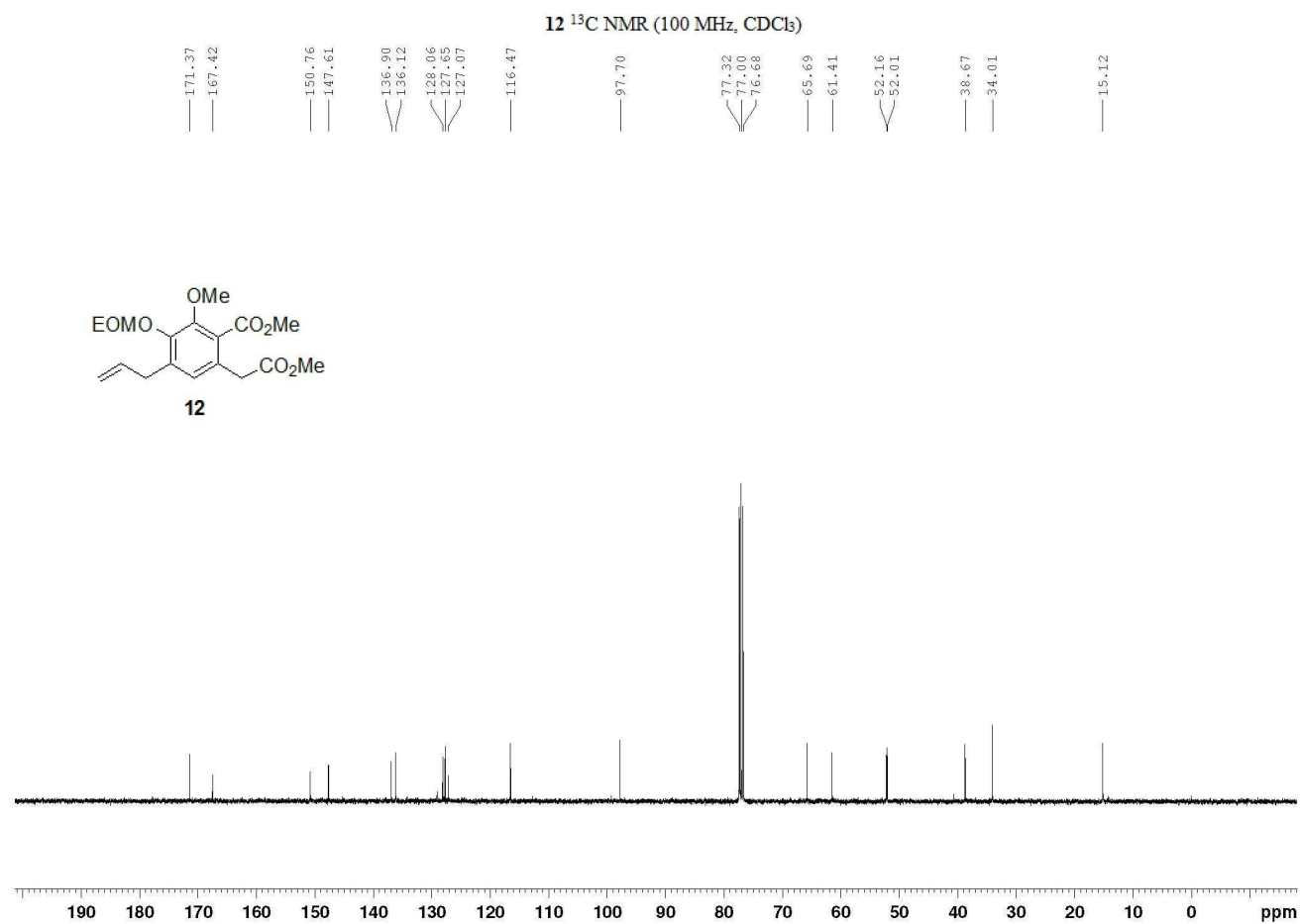


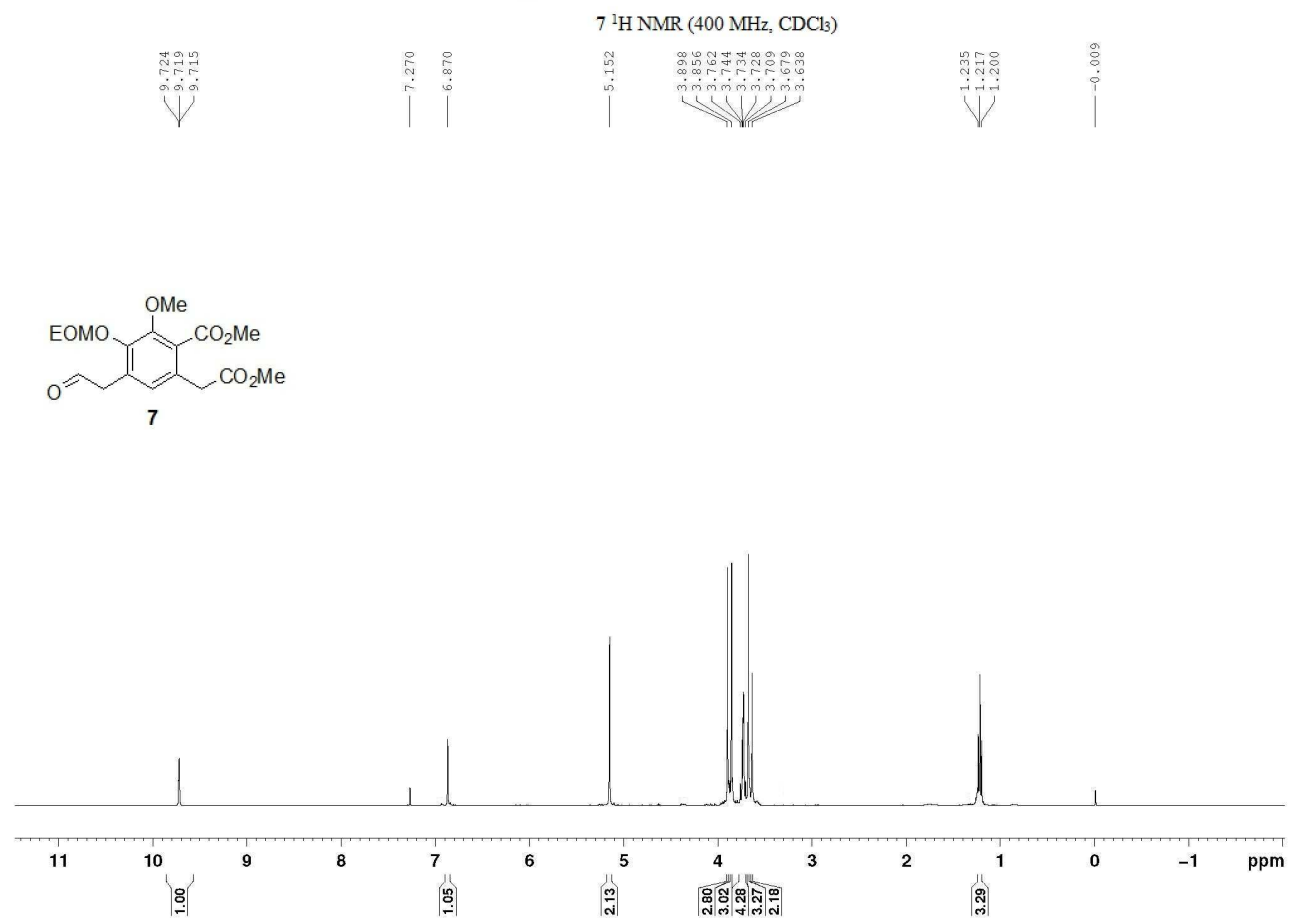


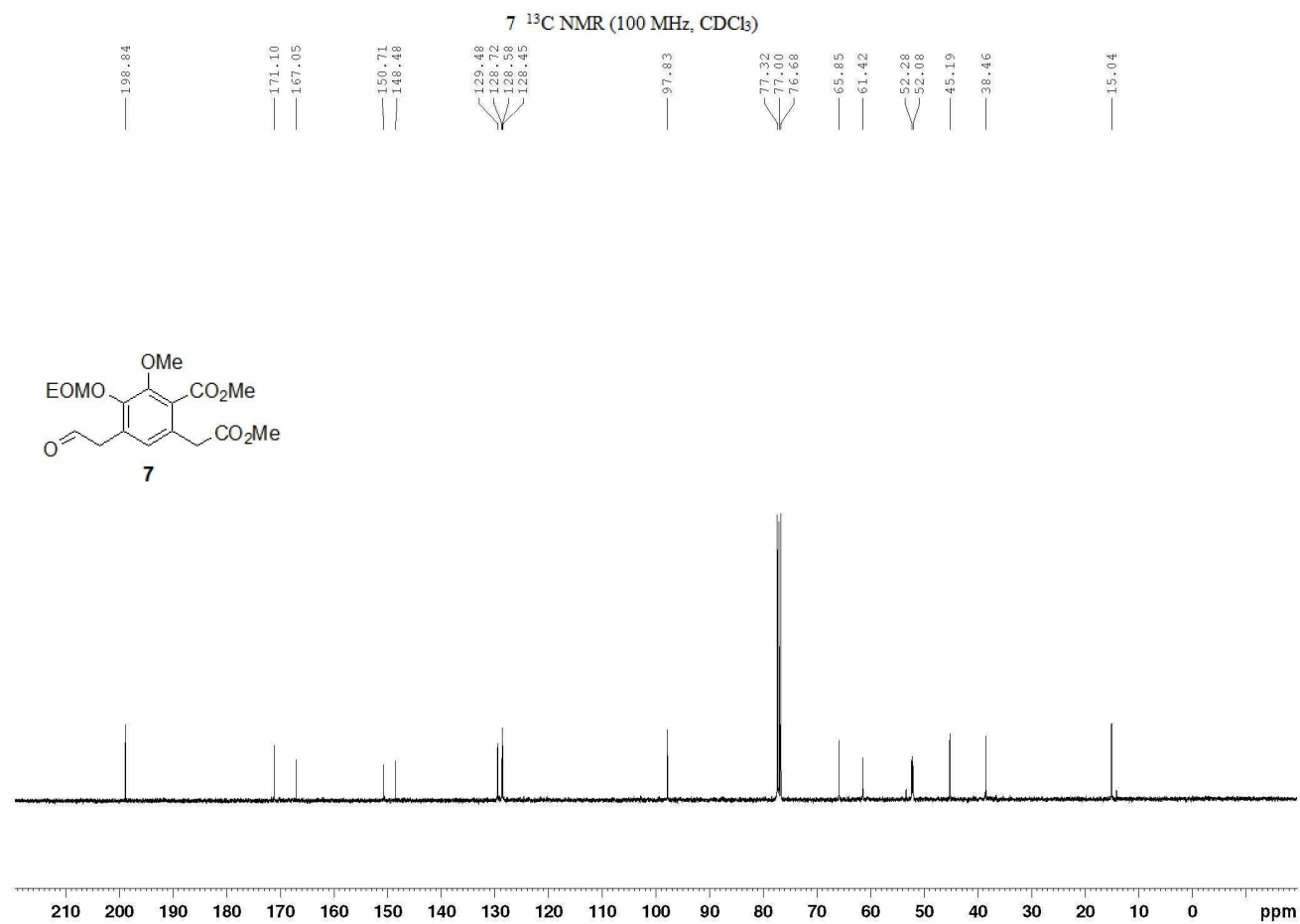
11 ^{13}C NMR (100 MHz, CDCl_3)

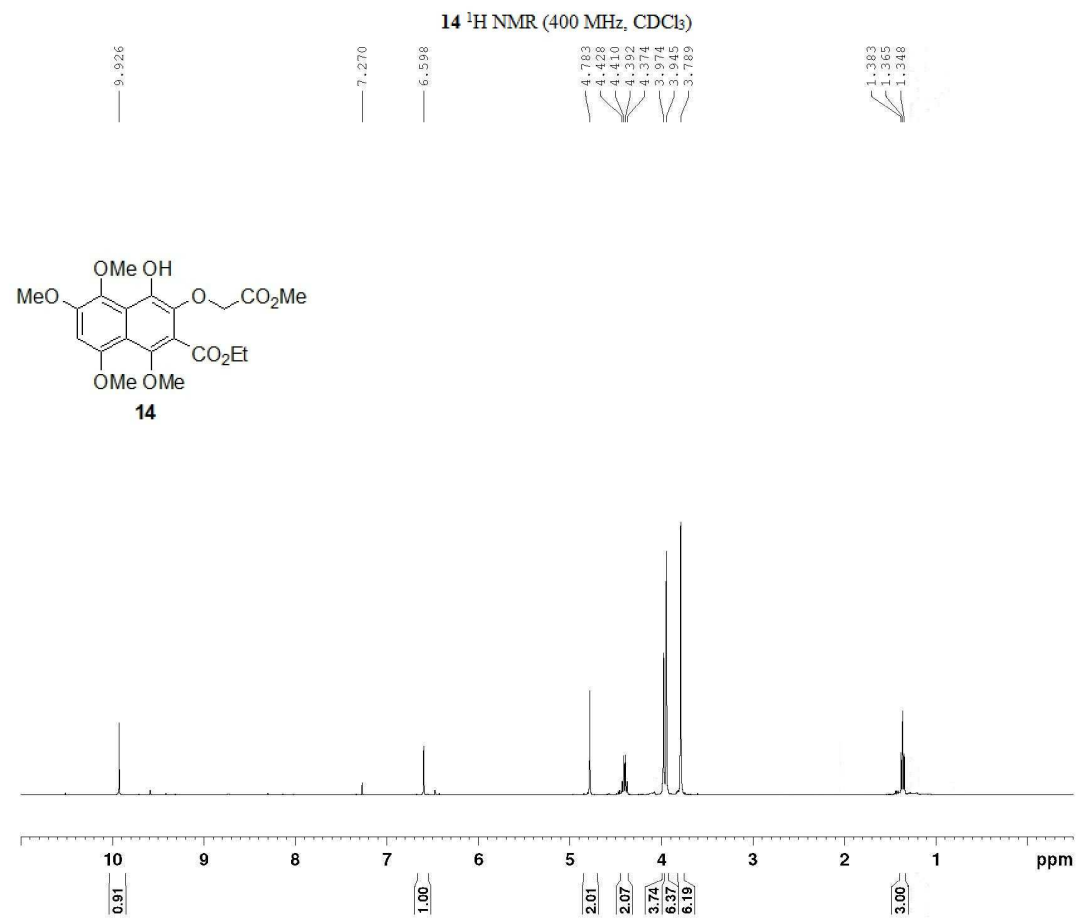




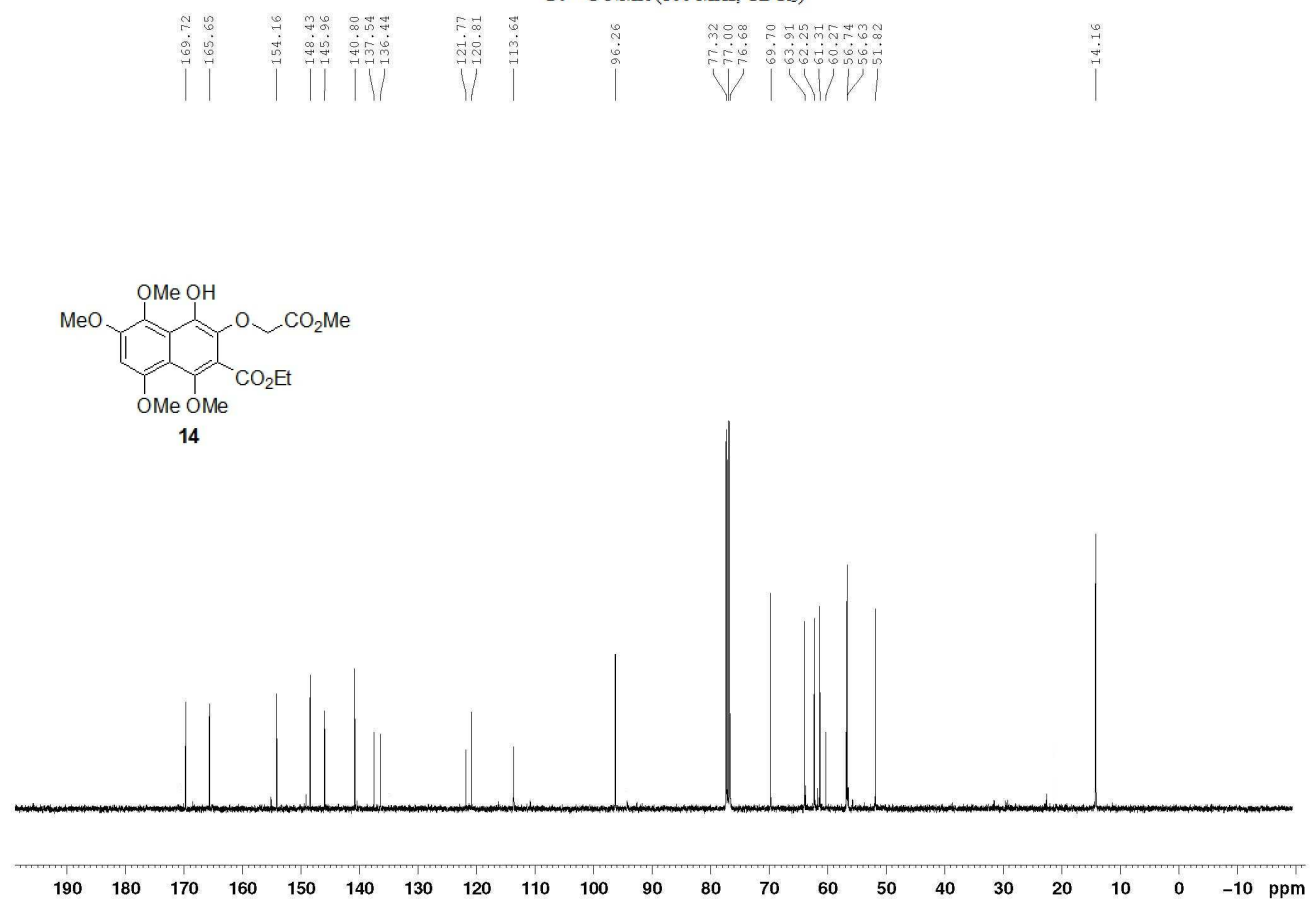


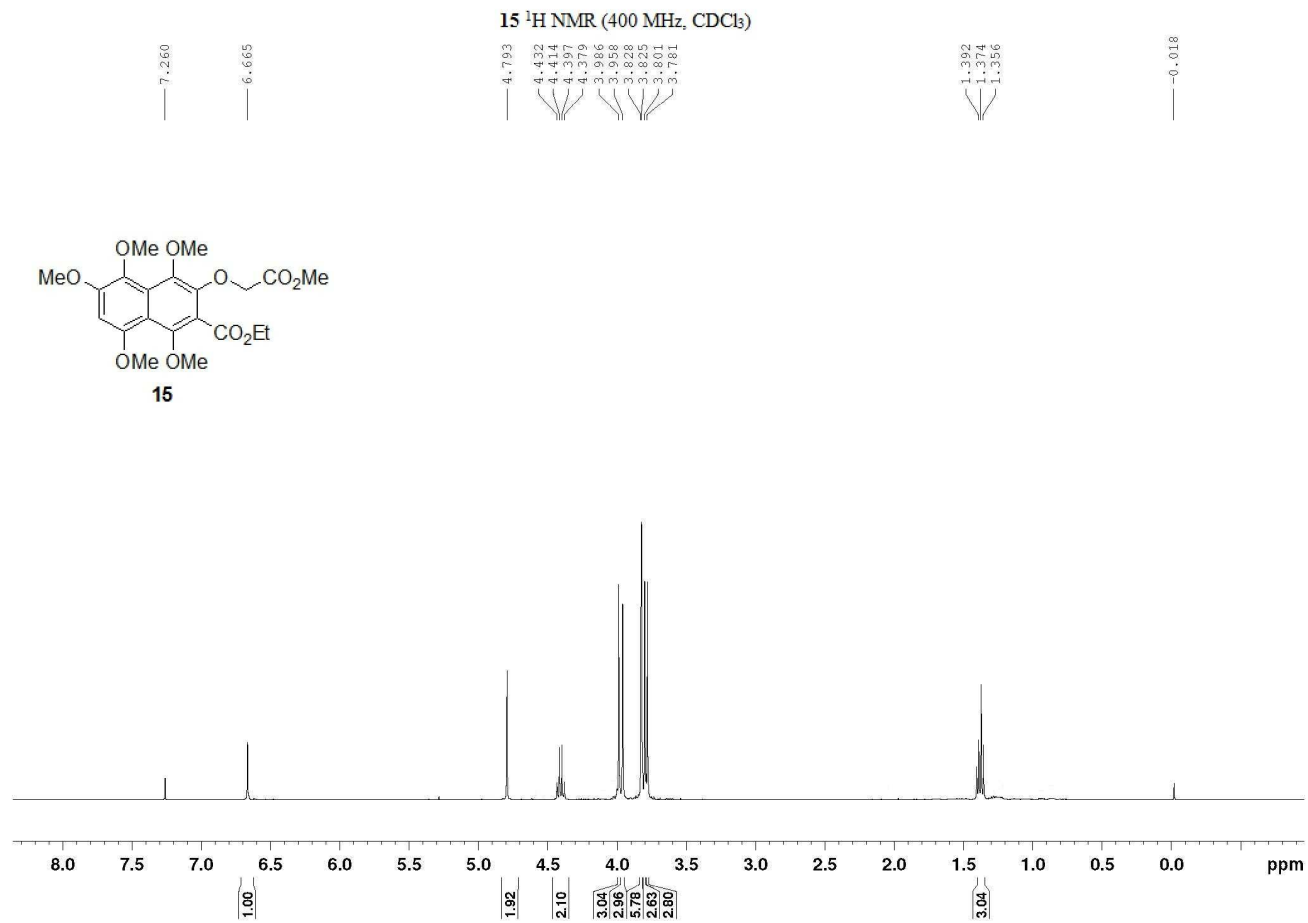


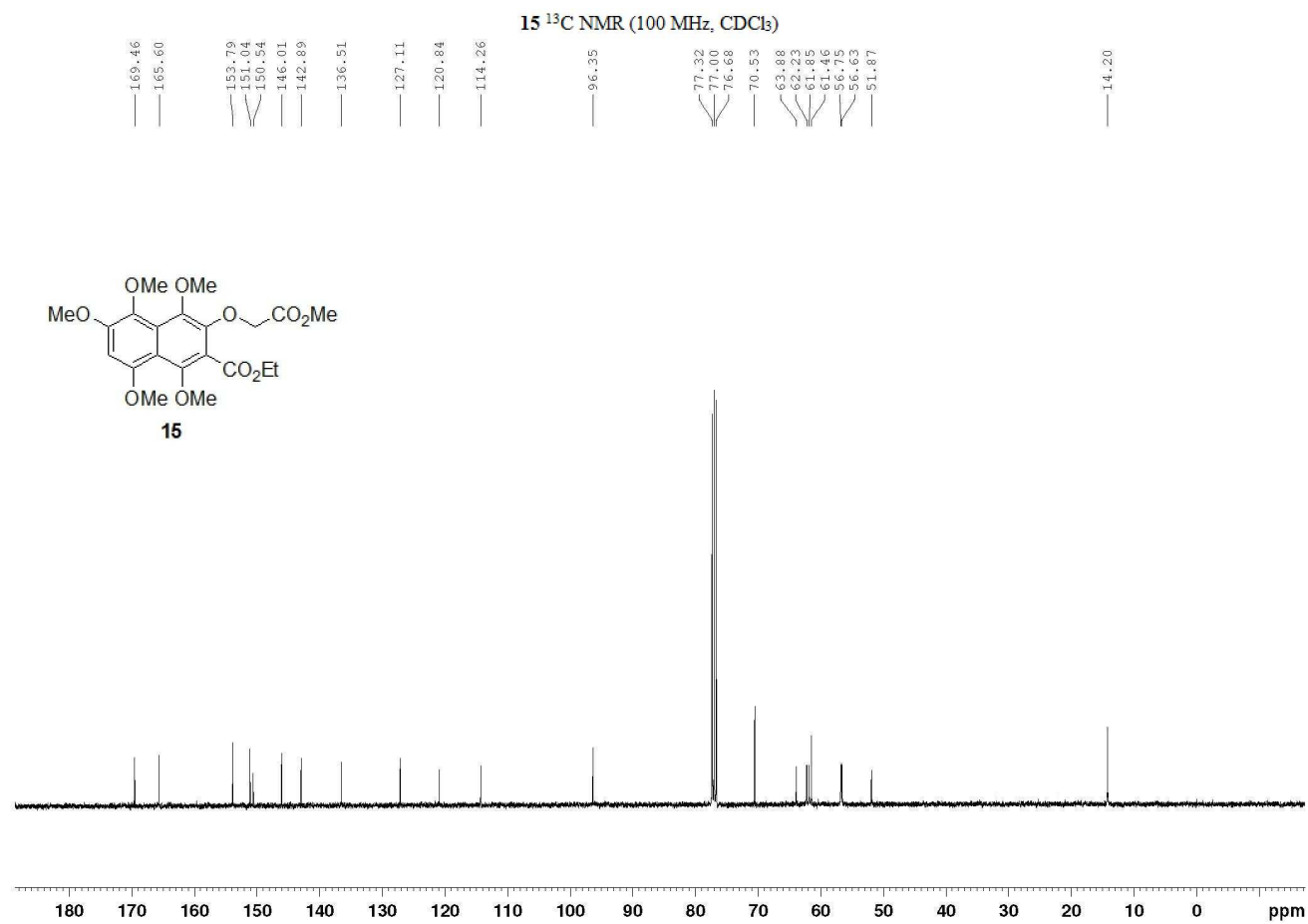


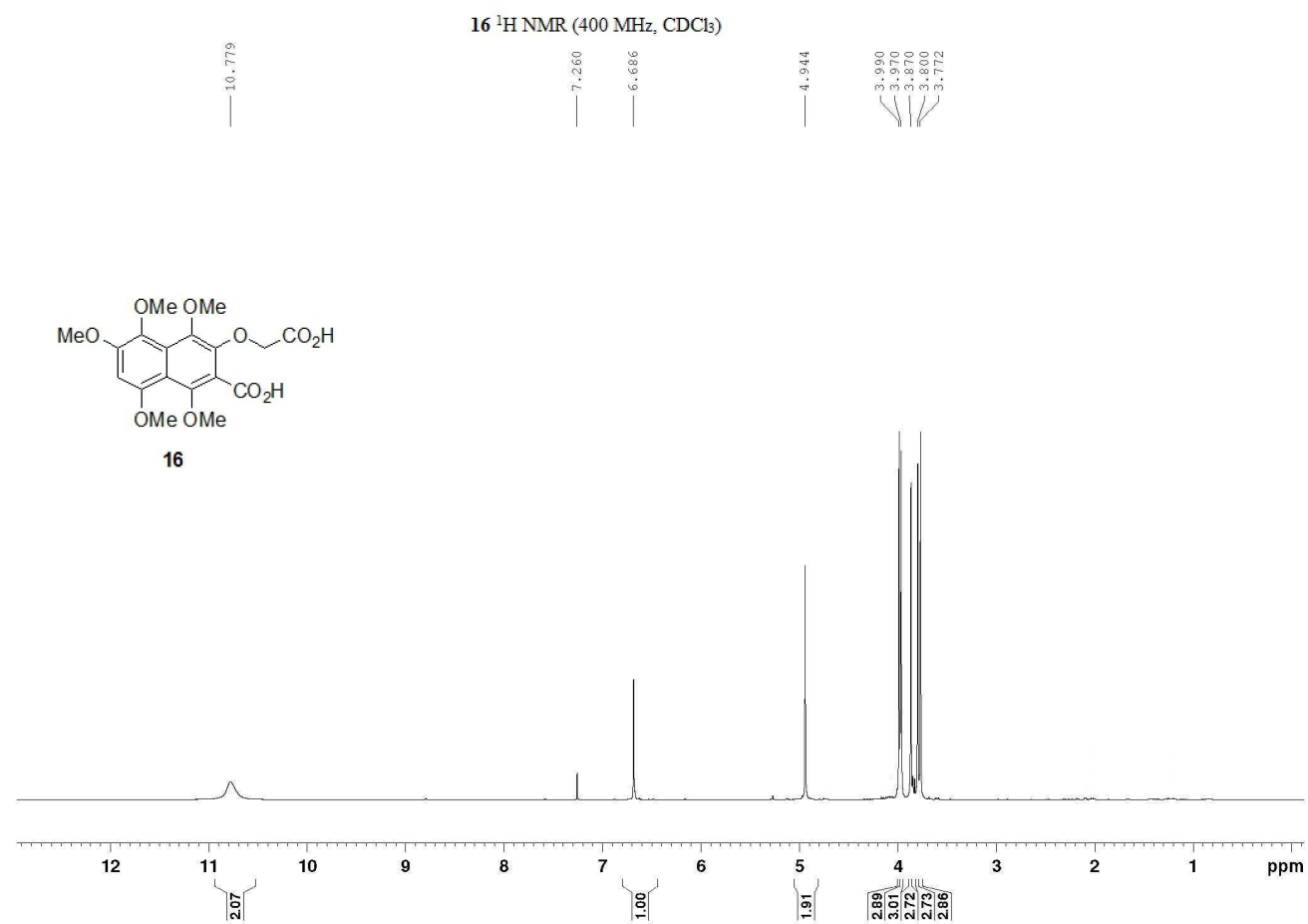


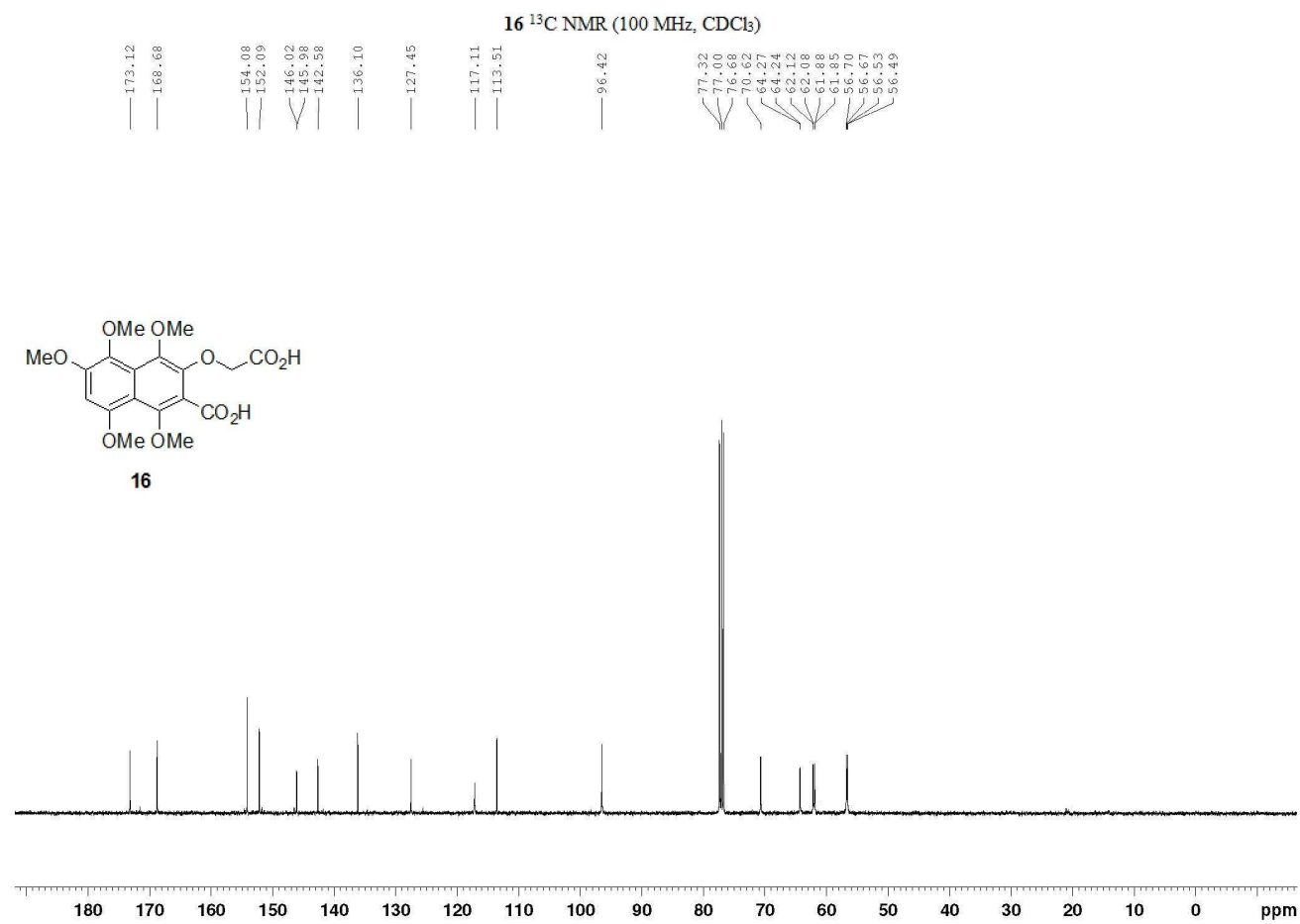
14 ^{13}C NMR (100 MHz, CDCl_3)











17 ^1H NMR (400 MHz, CDCl_3)

