Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Syntheses and biological effects of natural Morinda lactone and derivatives

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Table of Contents:

Morinda lactone (1a). Based on a procedure described by Poss and Belter [1], allylic alcohol **3a** (0.315 g, 1.01 mmol, 1.0 equiv) was added to a solution of ascorbic acid (0.573 g, 3.25 mmol, 3.2 equiv) in H_2O (2 mL). The mixture was stirred at room temperature for 4 days. The yellow solution was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/n-hexane 80:20) to give a light yellow, foamy solid. Yield: 0.049 g (0.15 mmol, 15%). ^{1}H NMR (300 MHz, MeOD): δ = 6.85 (s, 1H), 6.69 – 6.68 (m, 2H), 6.35 (d, *J* = 16.2 Hz, 1H), 6.02 (dt, *J* = 15.9, 7.6 Hz, 1H), 4.43 (br s, 1H), 4.38 (dd, *J* = 5.8, 3.5 Hz, 1H), 4.21 (dd, *J* = 9.6, 5.7 Hz, 1H), 4.05 (dd, *J* = 9.5, 3.5 Hz, 1H), 2.64 (m, 2H) ppm. ^{13}C NMR (100 MHz, MeOD) δ = 177.7, 146.3, 146.2, 135.9, 130.8, 120.0, 119.7, 116.3, 113.8, 108.5, 88.7, 80.3, 75.9, 75.7, 39.5 ppm.

5,6-*O*-isopropylidene-L-ascorbic acid (2). Compound **2** was prepared according to a literature procedure [2] from L-ascorbic acid (100.761 g, 0.572 mol, 1.0 equiv), 2,2-dimethoxypropane (125 mL, 1.42 mol, 2.5 equiv) in acetone (500 mL) by using a stream of gaseous HCl for 10 min and stirring the resulting suspension for 1.5 h. **2** was isolated as a colorless solid. Yield: 117.494 g (0.544 mol, 95%). $[\alpha]^{25}_D$ = +20.1 (c = 5.0; MeOH). ^{1}H NMR (500 MHz, acetone-d6): δ = 4.71 (d, *J* = 3.2 Hz, 1H), 4.34 (dt, *J* = 6.6, 3.2 Hz, 1H), 4.17 (t, *J* = 7.4 Hz, 1H), 4.00 (t, *J* = 7.4 Hz, 1H), 3.88 (br. s., 2H), 1.29 (s, 3H), 1.28 (s, 3H) ppm. ^{13}C NMR (126 MHz, acetone-d6) δ = 170.3, 151.1, 119.7, 110.2, 75.4, 74.9, 65.9, 26.2, 25.7 ppm. Analytical data match those previously reported [3,4].

$KHSO_4$·SiO_2. Following a literature procedure [5], $KHSO_4$ (4.157 g, 30.53 mmol) was dissolved in H_2O (20 mL) and SiO_2 (10.366 g) was added. The resulting suspension was stirred for 15 min at

room temperature and warmed to 120° C within 2 h. The temperature was maintained at 120° C for a further 58 h and a free-flowing solid was obtained.

3,4-bis((trimethylsilyl)oxy)benzaldehyde (21). According to a literature procedure [6], a solution of 3,4-dihydroxybenzaldehyde (5.173 g, 37.45 mmol, 1.0 equiv) in pyridine (21 mL, 265 mmol, 7.1 equiv) was added dropwise within 10 min to a solution of trimethylsilyl chloride (11 mL, 118 mmol, 3.2 equiv) in toluene (34 mL) under an argon atmosphere. The mixture was stirred at 65 °C (bath temperature) for 2 h. After cooling to room temperature, the pyridinium chloride was separated by filtration and washed with toluene (150 mL). The filtrate was concentrated *in vacuo* and the yellow residue was distilled to obtain a colorless liquid at 93 °C-97 °C ($3.4 \cdot 10^{-2}$ mbar). Yield: 9.700 g (34.34 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.81 (s, 1H), 7.40 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.36 (d, *J* = 1.9 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 0.29 (s, 9H), 0.27 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 191.1, 153.1, 147.5, 131.2, 125.8 121.0, 120.8, 0.5, 0.4 ppm. Analytical data match those previously reported [6].

1-(3,4-bis((trimethylsilyl)oxy)phenyl)prop-2-en-1-ol (3a). Following a literature procedure [7], to a stirred solution of 3,4-bis((trimethylsilyl)oxy)benzaldehyde (**21**) (2.886 g, 10.22 mmol, 1.0 equiv) in dry THF (15 mL) was added vinylmagnesium bromide (1 M solution in THF, 11.2 mL, 11.2 mmol, 1.1 equiv) at 0 °C. The mixture was stirred for 3 h at 0 °C. Saturated, aq. NH_4Cl (120 mL) was added and the aq. phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with sat., aq. NaCl (40 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **3a** as an orange oil. Yield: 3.072 g (9.893 mmol, 97%). **3a** was a sensitive compound that decomposed in solution or after prolonged storage in the fridge under an argon atmosphere. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.85 - 6.81 (m, 3H), 6.03 (ddd, *J* = 17.3, 10.3, 5.9 Hz, 1H), 5.32 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.18 (dt, *J* = 10.3, 1.3 Hz, 1H), 5.10 (m,

1H), 0.24 (s, 20H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.7, 146.3, 140.4, 136.4, 121.0, 120.0, 119.5, 115.0, 75.0, 0.5, 0.5 ppm. MS (DIP): *m/z* calculated for $C_{15}H_{26}O_3Si_2$ [M]: 310.14205. Found: 310.

1-(3,4-dimethoxyphenyl)prop-2-en-1-ol (3b). Allylic alcohol **3b** was prepared according to a literature procedure [7] from 3,4-dimethoxybenzaldehyde (2.568, 15.45 mmol, 1.0 equiv) dissolved in THF (22 mL) and vinylmagnesium bromide (1 M solution in THF, 16.5 mL, 16.5 mmol, 1.1 equiv) by stirring at 0 °C for 3 h. **3b** was obtained as a yellow oil. Yield: 2.938 g (15.13 mmol, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.92 - 6.88 (m, 2H), 6.84 - 6.83 (m, 1H), 6.04 (ddd, *J* = 17.1, 10.1, 5.9 Hz, 1H), 5.34 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.19 (dt, *J* = 10.3, 1.2 Hz, 1H), 5.15 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.02 (d, *J* = 3.2 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 149.2, 148.7, 140.4, 135.4, 118.8, 115.0, 111.1, 109.5, 75.2, 56.0, 56.0 ppm. HRMS (ESI): *m/z* calculated for $C_{11}H_{12}O_2 + H^+$ [M + H^+ - H_2O]: 177.09101. Found: 177.09062. Analytical match those previously reported [8].

1-(2,3,4-trimethoxyphenyl)prop-2-en-1-ol (3c). Allylic alcohol **3c** was prepared according to a literature procedure [7] from a solution of 2,3,4-trimethoxybenzaldehyde (1.97, 10.0 mmol, 1.0 equiv) in THF (15 mL) and vinylmagnesium bromide (1 M solution in THF, 12 mL, 12.0 mmol, 1.2 equiv) by stirring at 0 °C for 3 h. **3c** was obtained as a yellow oil. Yield: 2.311 g (10.3 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.04 (ddd, *J* = 17.0, 10.3, 5.5 Hz, 1H), 5.35 – 5.29 (m, 2H), 5.19 (d, *J* = 10.3 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.62 – 2.61 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 153.6, 151.6, 142.2, 140.4, 128.6, 122.0, 114.5, 107.3, 71.5, 61.3, 60.9, 56.1 ppm. HRMS (ESI): *m/z* calculated for $C_{12}H_{14}O_3 + H^+$ [M + H^+ - H_2O]: 207.10157. Found: 207.10093.

1-(2,4,5-trimethoxyphenyl)prop-2-en-1-ol (3d). Allylic alcohol **3d** was prepared according to a literature procedure [7] from a solution of 2,4,5-trimethoxybenzaldehyde (5.040, 25.69 mmol, 1.0 equiv) in THF (36 mL) and vinylmagnesium bromide (1 M solution in THF, 25.4 mL, 25.4 mmol, 1.0 equiv) by stirring at 0 °C for 3 h. **3d** was obtained as a yellow solid. Yield: 4.844 g (21.60 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.86 (s, 1H), 6.52 (s, 1H), 6.09 (ddd, *J* = 17.1, 10.4, 5.5 Hz, 1H), 5.39 (m, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.16 (d, *J* = 10.3 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 6H), 2.64 (d, *J* = 5.0 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 151.0, 149.1, 143.2, 139.7, 122.4, 114.5, 111.4, 97.7, 70.8, 56.6, 56.5, 56.3 ppm. ^{1}H and ^{13}C NMR spectra match those previously reported [9].

1-(3,4,5-trimethoxyphenyl)prop-2-en-1-ol (3e). Allylic alcohol **3e** was prepared according to a literature procedure [7] from a solution of 3,4,5-trimethoxybenzaldehyde (1.962, 10.00 mmol, 1.0 equiv) in THF (15 mL) and vinylmagnesium bromide (1 M solution in THF,12 mL, 12.0 mmol, 1.2 equiv) by stirring at 0 °C for 3 h. **3e** was purified by flash chromatography (silica gel, n-hexane/EtOAc 80:20) to give a light yellow oil. Yield: 1.270 g (5.663 mmol, 57%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.60 (s, 2H), 6.03 (ddd, *J* = 17.0, 10.4, 6.1 Hz, 1H), 5.37 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.21 (dt, *J* = 10.4, 1.3 Hz, 1H), 5.13 (d, *J* = 6.0 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 2.07 (br s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 153.4, 140.1, 138.4, 137.4, 115.4, 103.2, 75.6, 60.9, 56.2 ppm. HRMS (ESI): *m/z* calculated for $C_{12}H_{14}O_3$+ H^+ [M + H^+ - H_2O]: 207.10157. Found: 207.10127. ^{1}H and ^{13}C NMR spectra match those previously reported [10].

1-*tert*-Butoxycarbonylindole-3-carboxyldehyde (6). Aldehyde **6** was prepared according to a literature procedure [11] from indole-3-carboxaldehyde (1.051 g, 7.240 mmol, 1.0 equiv), DMAP (0.087 g, 0.71 mmol, 0.1 equiv) and di-*tert*-butyl dicarbonate (1.929 g, 8.838 mmol, 1.2 equiv) in CH_2Cl_2 (14 mL). The solution was stirred at room temperature for 22 h. **6** was recrystallized from

abs. EtOH (10 mL) to obtain the product as a colorless solid. Yield: 1.373 g (5.598 mmol, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.10 (s, 1H), 8.29 (d, *J* = 7.5 Hz, 1H), 8.23 (s, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.43 – 7.36 (m, 2H), 1.71 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 186.0, 148.9, 136.7, 136.1, 126.2, 124.8, 122.3, 121.7, 115.3, 85.8, 28.2 ppm. Analytical data match those previously reported [11].

***tert*-Butyl 3-(1-hydroxyallyl)-1H-indole-1-carboxylate (7).** Allylic alcohol **7** was prepared according to a literature procedure [11] from a solution of the aldehyde **6** (1.231 g, 5.019 mmol, 1.0 equiv) in THF (7.5 mL) and vinylmagnesium bromide (1 M solution in THF, 6 mL, 6.0 mmol, 1.2 equiv) by stirring at 0 °C for 3 h. **7** was isolated as a red-orange oil. Yield: 1.339 g (4.899 mmol, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 6.2 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.34 – 7.31 (m, 1H), 7.26 – 7.22 (m, 1H), 6.21 (ddd, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.49 – 5.46 (m, 2H), 5.30 – 5.28 (m, 1H), 1.98 (br s, 1H), 1.67 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 149.8, 139.0, 136.1, 128.6, 124.8, 123.1, 122.7, 122.3, 120.1, 116.1, 115.5, 83.9, 69.1, 28.3 ppm. Analytical data match those previously reported [11].

Methyl indole-2-carboxylate (22). Ester **22** was prepared according to a literature procedure [12] from indole-2-carboxylic acid (5.02 g, 31.1 mmol, 1.0 equiv) and a catalytic amount of conc. H_2SO_4 (0.1 mL) by refluxing overnight in MeOH (50 mL). **22** was obtained as a colorless solid. Yield: 4.83 g (27.6 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.02 (br s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.32 (m, 1H), 7.24 – 7.23 (m, 1H), 3.96 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.2, 137.0, 127.6, 127.2, 125.6, 122.8, 121.0, 112.0, 108.9, 52.2 ppm. Analytical data match those previously reported [13].

Indole-2-carbaldehyde (23). Aldehyde **23** was synthesized in two steps according to literature procedures [14,15] from ester **22**. In the first step, methyl indole-2-carboxylate (3.99 g, 22.8 mmol,

1.0 equiv) was reduced to the alcohol (1H-indol-2-yl)methanol by $LiAlH_4$ (2.60 g, 68.5 mmol, 3.0 equiv) in THF (69 mL) at 5 °C for 1 h. Yield: 2.85 g (19.4 mmol, 85%).In the second step, (1H-indol-2-yl)methanol (2.70 g, 18.3 mmol, 1.0 equiv) was oxidized to **23** with MnO_2 (7.84 g, 90.2 mmol, 4.9 equiv.) in CH_2Cl_2 (40 mL) and purified by column chromatography (silica gel, CH_2Cl_2/EtOAc 20:80). Yield: 0.770 g (5.30 mmol, 29%; yield over two steps: 25%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.87 (s, 1H), 9.40 (br s, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.30 (d, *J* = 1.1 Hz, 1H), 7.21 – 7.18 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 182.4, 138.2, 136.1, 127.5, 127.4, 123.6, 121.4, 115.1, 112.7 ppm. Analytical data match those previously reported [16].

1-*tert*-Butoxycarbonylindole-2-carboxyldehyde (24). Aldehyde **24** was prepared according to a literature procedure [11] from indole-2-carboxaldehyde (**23**) (0.588 g, 4.05 mmol, 1.0 equiv), DMAP (0.053 g, 0.43 mmol, 0.1 equiv) and di-*tert*-butyl dicarbonate (1.2 mL, 4.8 mmol, 1.2 equiv) in CH_2Cl_2 (8 mL). The solution was stirred at room temperature for 17 h. **24** was obtained as a light-orange solid. Yield: 0.941 g (3.84 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.44 (s, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.49 (m, 1H), 7.44 (s, 1H), 7.30 (m, 1H), 1.72 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 184.3, 150.0, 138.0, 138.0, 128.3, 127.7, 124.0, 123.3, 116.6, 116.2, 85.7, 28.3 ppm. Analytical data match those previously reported [17].

***tert*-Butyl 2-(1-hydroxyallyl)-1H-indole-1-carboxylate (11).** Allylic alcohol **11** was prepared according to a literature procedure [7] from a solution of the aldehyde **24** (0.742 g, 3.03 mmol, 1.0 equiv) in THF (4.4 mL) and vinylmagnesium bromide (1 M solution in THF, 3.6 mL, 3.6 mmol, 1.2 equiv) by stirring at 0 °C for 3 h. **11** was isolated as a red-orange oil. Yield: 0.740 g (2.71 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.30 – 7.27 (m, 1H), 7.24 – 7.20 (m, 1H), 6.60 (s, 1H), 6.25 (ddd, *J* =

17.2, 10.3, 5.1 Hz, 1H), 5.58 (d, *J* = 4.8 Hz, 1H), 5.44 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.31 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.48 (br s, 1H), 1.72 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 151.7, 142.1, 137.5, 136.5, 131.7, 129.0, 124.6, 123.2, 121.1, 116.1, 115.8, 113.0, 109.6, 85.4, 68.5, 28.4 ppm. Analytical data match those previously reported [18].

2-(2,2-Diethoxyethoxy)benzaldehyde (25). Aldehyde **25** was prepared according to a literature[19] procedure from salicylaldehyde (10.5 mL, 101 mmol, 1.0 equiv), bromoacetaldehyde diethyl acetal (16 mL, 106 mmol, 1.05 equiv), K_2CO_3 (27.643 g, 200 mmol, 2.0 equiv) in dry DMF (50 mL) by stirring the mixture at 100 °C for 19 h. **25** was isolated as a pale yellow oil. Yield: 20.952 g (87.93 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.51 (d, *J* = 0.6 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 8.6, 6.8, 1.9 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 4.88 (t, *J* = 5.3 Hz, 1H), 4.11 (d, *J* = 5.4 Hz, 1H), 3.82 – 3.76 (m, 2H), 3.68 – 3.62 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 189.8, 161.1, 136.1, 128.4, 125.2, 121.3, 112.9, 100.6, 69.3, 63.3, 15.5 ppm. Analytical data match those previously reported[19].

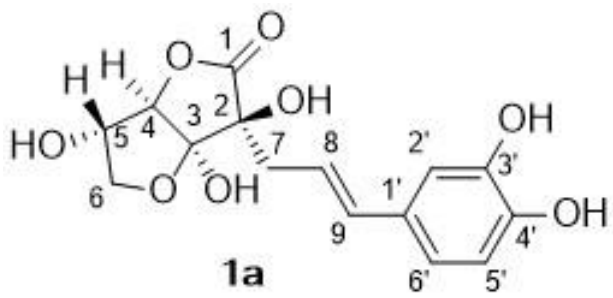
Benzofuran-2-carbaldehyde (26). Aldehyde **26** was prepared according to a literature procedure[19] from refluxing a solution of aldehyde **25** (9.533 g, 40.01 mmol, 1.0 equiv), acetic acid (16 mL) and H_2O (2.2 mL) for 65 h. **26** was isolated as a pale yellow oil. Yield: 1.848 g (12.65 mmol, 32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.87 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.52 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 179.9, 156.4, 152.8, 129.4, 126.8, 124.3, 123.8, 118.0, 112.9 ppm. Analytical data match those previously reported [19].

1-(Benzofuran-2-yl)prop-2-en-1-ol (15). Allylic alcohol **15** was prepared according to a literature procedure [7] from a solution of the aldehyde **26** (1.046 g, 7.157 mmol, 1.0 equiv) in THF (10 mL)

and vinylmagnesium bromide (1 M solution in THF, 8.2 mL, 8.2 mmol, 1.2 equiv) by stirring at 0 °C for 3 h. **15** was purified by flash chromatography (silica gel, n-hexane/EtOAc 80:20) and isolated as a yellow oil. Yield: 0.761 g (4.366 mmol, 61%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.5 Hz, 1H), 7.48 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.30 - 7.21 (m, 2H), 6.65 (s, 1H), 6.20 (ddd, *J* = 17.0, 10.2, 5.8 Hz, 1H), 5.51 (dt, *J* = 17.2, 1.0 Hz, 1H), 5.37 – 5.35 (m, 2H), 2.26 (d, *J* = 5.5 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 157.6, 155.1, 136.5, 128.1, 124.5, 123.0, 121.3, 117.4, 111.4, 103.5, 69.3 ppm. HRMS (ESI): *m/z* calculated for $C_{11}H_8O + H^+$ [$M + H^+ - H_2O$]: 157.06479. Found: 157.06459. ^{1}H and ^{13}C NMR spectra match those previously reported [20].

1-(Benzo[*b*]thiophen-3-yl)prop-2-en-1-ol (18). Allylic alcohol **18** was prepared according to a literature procedure [21] from a solution of benzo[*b*]thiophene-3-carbaldehyde (0.515 g, 3.17 mmol, 1.0 equiv) in THF (6.2 mL) and vinylmagnesium bromide (1 M solution in THF, 3.4 mL, 3.4 mmol, 1.1 equiv) by stirring at -78 °C for 1 h. **18** was isolated as a yellow oil. Yield: 0.579 g (3.04 mmol, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 – 7.91 (m, 1H), 7.87 – 7.86 (m, 1H), 7.40 (s, 1H), 7.39 – 7.35 (m, 2H), 6.20 (ddd, *J* = 17.1, 10.3, 5.8 Hz, 1H), 5.57 (d, *J* = 5.7 Hz, 1H), 5.48 (d, *J* = 17.1 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 2.12 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.1, 138.8, 137.6, 137.3, 124.6, 124.2, 123.4, 123.0, 122.7, 116.3, 70.9 ppm. Analytical data match those previously reported [9].

Table S1. Comparison of NMR data of natural and synthetic morinda lactone (**1a**).



1a

	1a (natural)[a]		**1a** (synthetic, procedure A)[b]		**1a** (synthetic, procedure B)[b]	
position	δ_H (mult. , *J* [Hz])	δ_C	δ_H (mult. , *J* [Hz])	δ_C	δ_H (mult. , *J* [Hz])	δ_C
1		175.8		175.5		175.5
2		78.9		78.5		78.5
3		107.5		107.1		107.1
4	4.33 (s)	87.8	4.33 (s)	87.4	4.33 (s)	87.4
5	4.23 (br t, 5.2)	74.5	4.23 (m)	74.1	4.23 (br s)	74.2
6a	4.13 (dd, 9.4, 6.2)	74.4	4.13 (dd, 9.3, 6.4)	74.0	4.15 – 4.12 (m)	74.0
6b	3.86 (dd, 9.4, 4.2)		3.85 (dd, 9.3, 4.3)		3.86 – 3.84 (m)	
7	2.51 (m)[c]	39.5	2.56 – 2.46 (m)[c]	38.4	2.50 (m)[c]	38.4

8	5.92 (dt, 16.0, 15.6)	129.0	5.91 (dt, 15.8, 7.6)	119.6	5.92 (dt, 15.7, 7.6)	119.7
9	6.22 (d, 16.0)	133.7	6.22 (d, 15.8)	133.3	6.22 (d, 15.8)	133.3
1’		129.0		128.6		128.6
2’	6.78 (d, 1.4)	113.0	6.78 (d, 1.6)	112.6	6.78 (m)	112.6
3’		145.7		145.5		145.4
4’		145.5		145.2		145.2
5’	6.66 (d, 8.0)	116.0	6.65 (d, 8.0)	115.6	6.66 – 6.65 (m)	115.6
6’	6.59 (dd, 8.0, 1.4)	118.4	6.59 (dd, 8.1, 1.5)	118.0	6.59 – 6.58 (m)	118.0
OH			8.93 (br s), 8.87 – 8.59 (m), 6.93 (br s), 5.71 (br s), 5.58 (br s)		8.95 – 8.71 (m), 6.95 – 6.93 (m), 5.71 (br s), 5.61 – 5.58 (br s)	

[a] Data and assignments taken from literature [22], spectra were recorded at ^{1}H (400 MHz) and ^{13}C (100 MHz) in DMSO-d_6.

[b] Spectra were recorded at ^{1}H (500 MHz) and ^{13}C (126 MHz) in DMSO-d_6 and calibrated to the solvent residual peaks of DMSO-d_6 (δ_H = 2.50 and δ_C = 39.52 ppm).

[c] This signal overlaps with the solvent residual signals. Additional spectra in acetone-d_6 are provided.

Morinda lactone (1a, procedure A). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.92 (br s, 3H), 6.92 (d, *J* = 1.5 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.72 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 6.07 (dt, *J* = 15.8, 7.7 Hz, 1H), 5.83 (br s, 1H), 4.76 (br s, 1H), 4.51 (br s, 1H), 4.47 (s, 1H), 4.44 – 4.42 (m, 1H), 4.16 (dd, *J* = 9.7, 5.5 Hz, 1H), 4.06 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.06 (br s, 3H), 2.70 – 2.61 (m, 2H) ppm. ^{13}C NMR (126 MHz, acetone-d_6) δ = 175.7, 146.0, 145.8, 134.9, 130.6, 120.5, 119.5, 116.1, 113.4, 108.3, 87.6, 79.5, 75.6, 75.5, 38.9 ppm.

Morinda lactone (1a, procedure B). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.93 – 7.76 (m, 5H), 6.91 (d, *J* = 1.9 Hz, 1H), 6.77 – 6.74 (m, 1H), 6.73 -6.71 (m, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.07 (dt, *J* = 15.9, 7.6 Hz, 1H), 4.76 (br s, 1H), 4.49 (m, 1H), 4.46 (s, 1H), 4.43 – 4.41 (m, 1H), 4.16 (dd, *J* = 9.7, 5.6 Hz, 1H), 4.05 (dd, *J* = 9.7, 3.3 Hz, 1H), 2.70 – 2.60 (m, 2H) ppm. ^{13}C NMR (126 MHz, acetone-d_6) δ = 175.7, 146.0, 145.8, 134.9, 130.6, 120.5, 119.5, 116.1, 113.4, 108.3, 87.6, 79.5, 75.6, 75.5, 39.0 ppm.

Some compounds of type **1** show additional signals in their ^{13}C NMR spectra. Comparing with the data of similar compounds [1,23,24], it seems likely that the open form **1'** is present in solution. Usually, not all signals of the minor isomer **1'** are visible.

Scheme S1. Equilibrium between the closed form **1** and the open form **1'**.

Morinda lactone (1'a, procedure A, minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 132.8, 122.3, 120.8, 120.7, 119.1, 117.8, 116.6, 116.4, 115.5, 84.6, 78.6, 76.3 ppm.

Morinda lactone (1'a, procedure B, minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 123.2, 118.8, 115.5, 86.9, 76.3, 40.8 ppm.

1'b (minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 134.3, 79.5, 73.2 ppm.

1'b (minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 134.3, 79.5, 73.2 ppm.

1'c (minor form). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 132.2, 130.7, 121.7, 117.4, 84.3, 70.4, 66.0, 65.0, 35.2 ppm.

1'd (minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 131.0, 118.5, 83.6, 71.6, 62.4, 41.9 ppm.

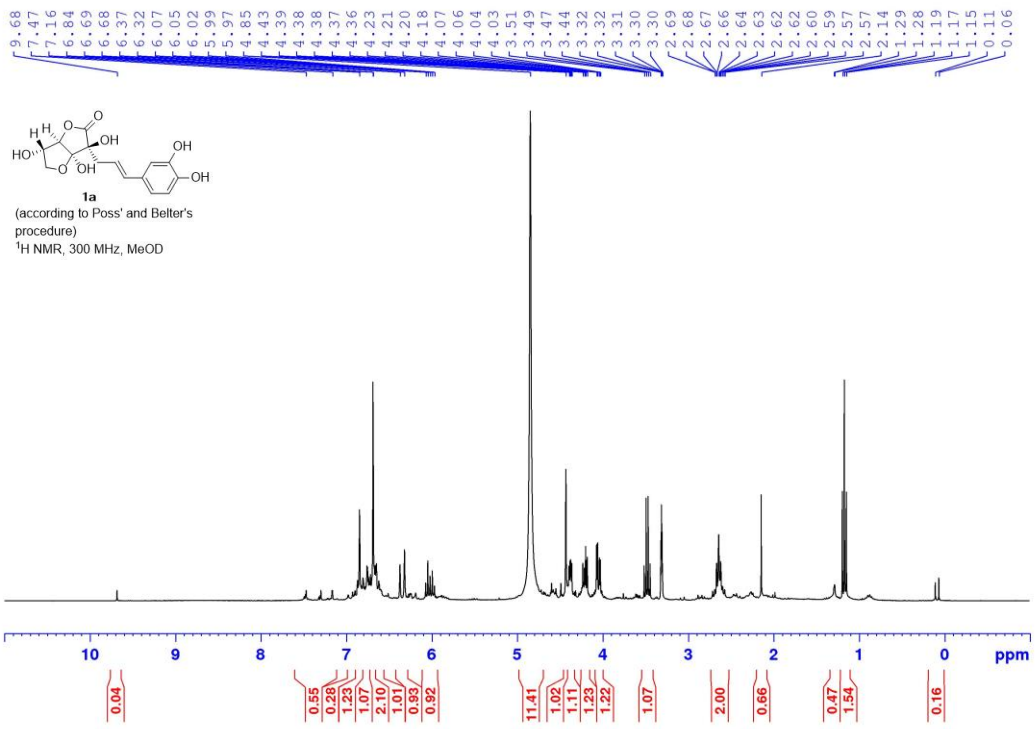
1'e (minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 134.6, 134.5, 123.8, 123.7, 89.4, 84.5, 76.5, 74.2, 73.2, 71.0, 35.4 ppm.

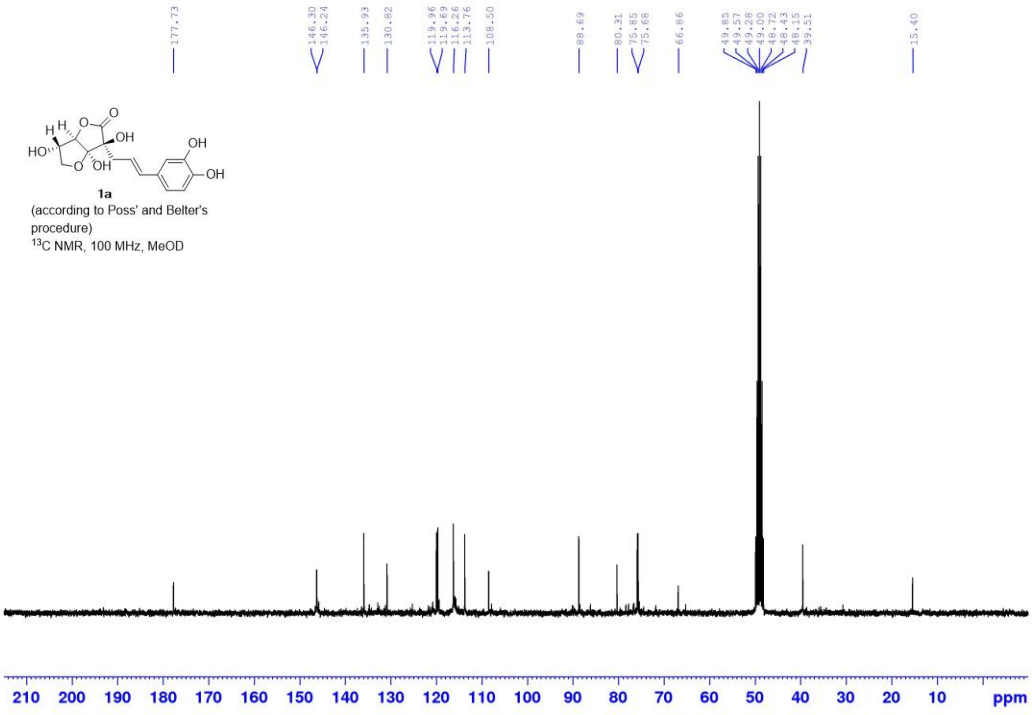
9' (minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 132.7, 125.5, 125.3, 125.2, 125.1, 124.2, 123.6, 121.1, 120.7, 120.5, 115.9, 98.4, 84.6, 76.5, 74.2, 73.2, 71.0, 36.1 ppm.

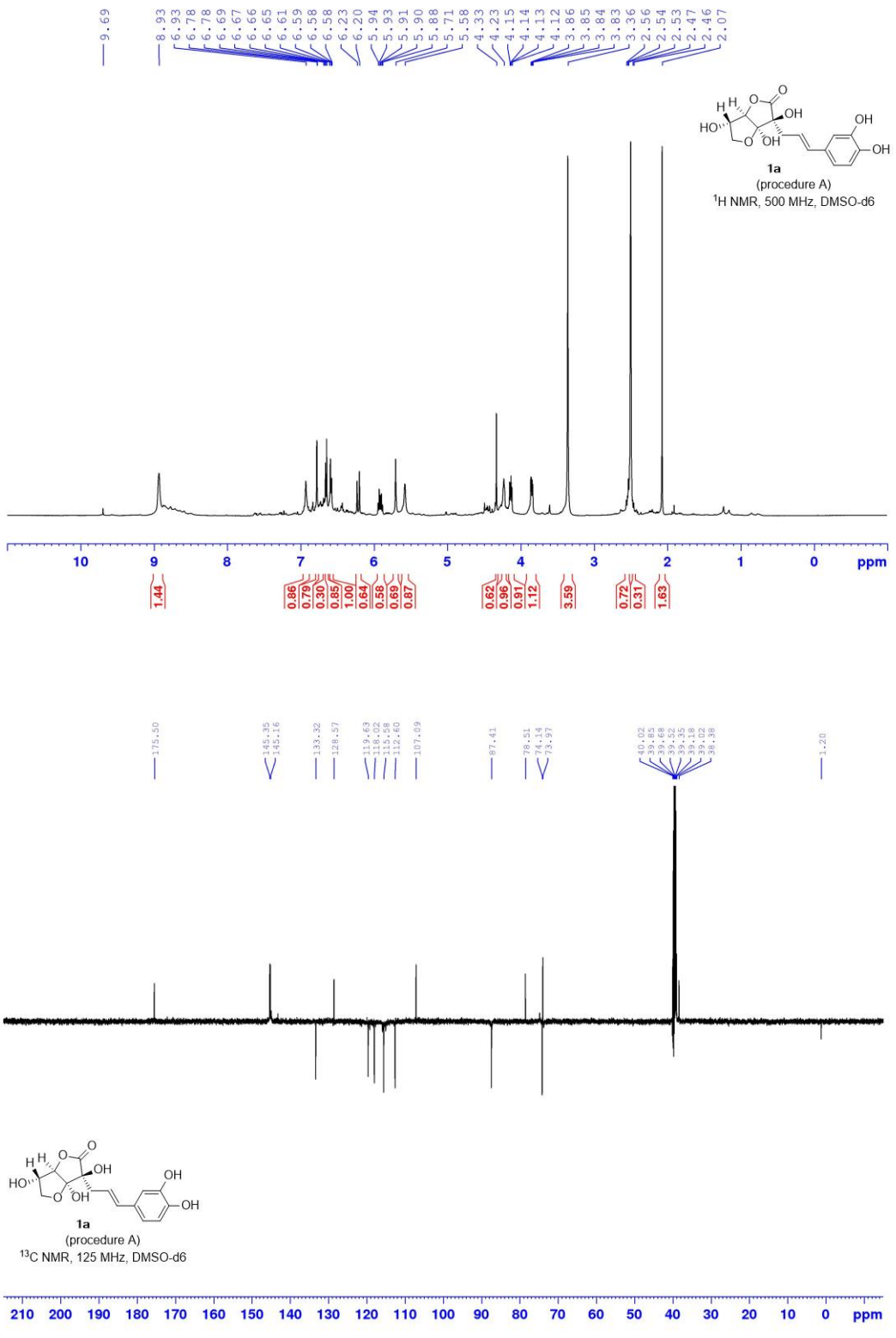
13' (minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 127.6, 126.2, 125.2, 124.6, 122.7, 122.5, 120.9, 120.1, 111.6, 102.8, 84.5, 74.6, 73.2, 71.0, 39.2 ppm.

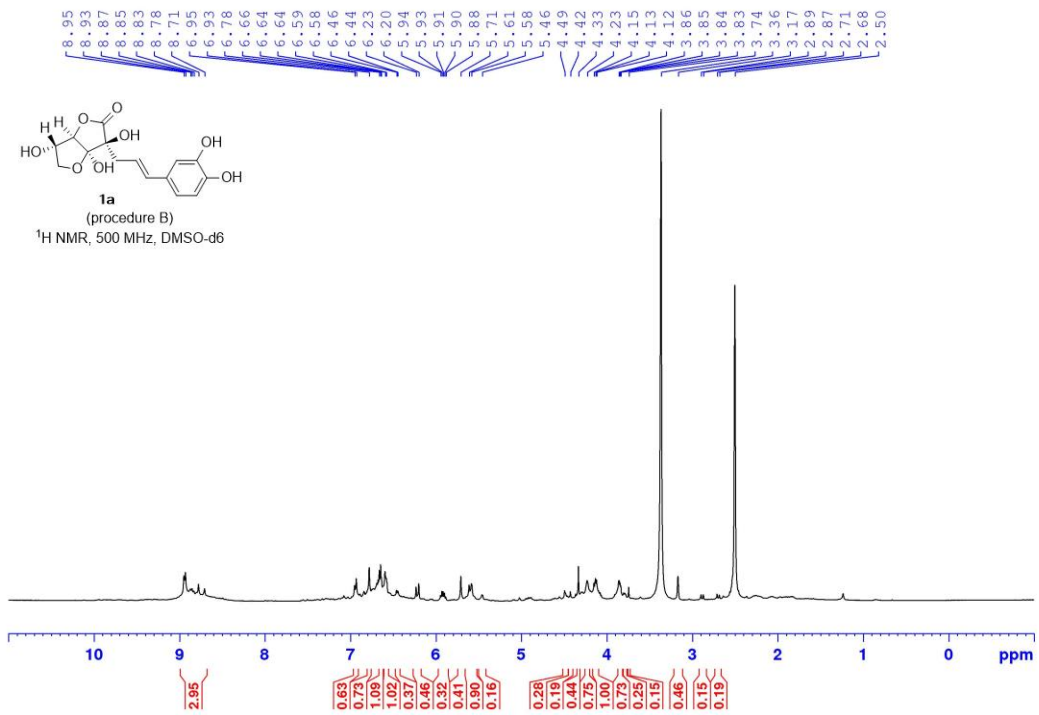
17' (minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 132.8, 132.7, 129.6, 129.5, 128.4, 127.8, 127.6, 125.2, 123.7, 122.9, 122.8, 121.7, 120.1, 111.5, 104.3, 89.5, 84.7, 76.4, 74.3, 73.3, 71.0, 35.5 ppm.

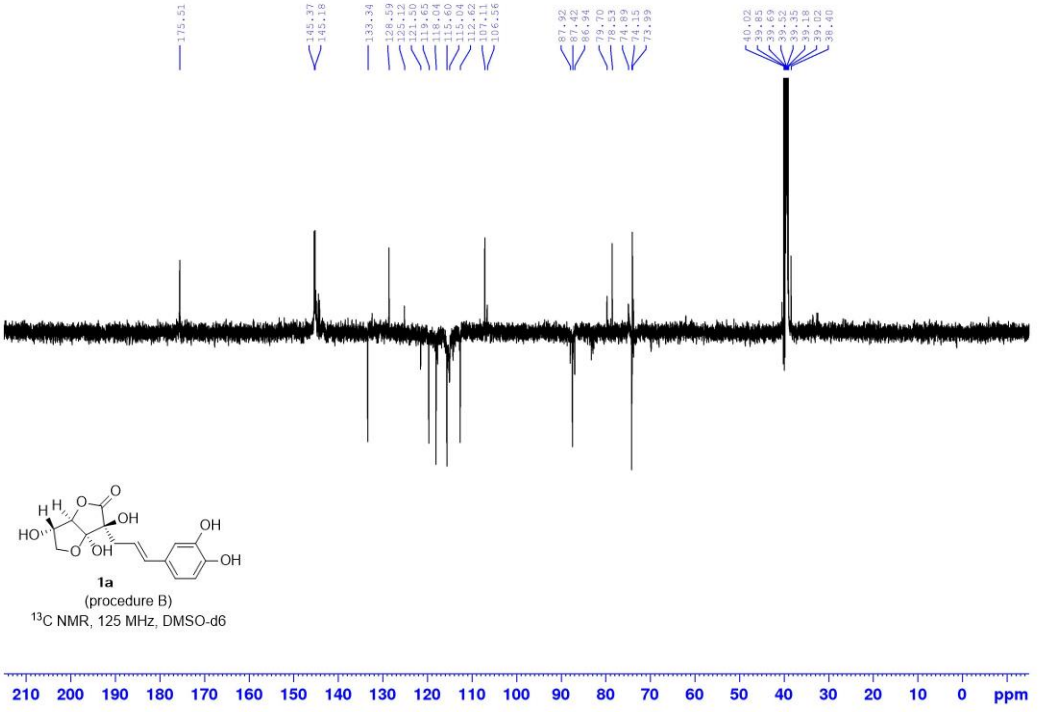
20' (minor form). ^{13}C NMR (126 MHz, acetone-d_6) δ = 126.7, 126.7, 126.5, 125.3, 125.1, 123.6, 123.1, 89.5, 84.6, 76.4, 74.3, 73.2, 71.0, 35.9 ppm.

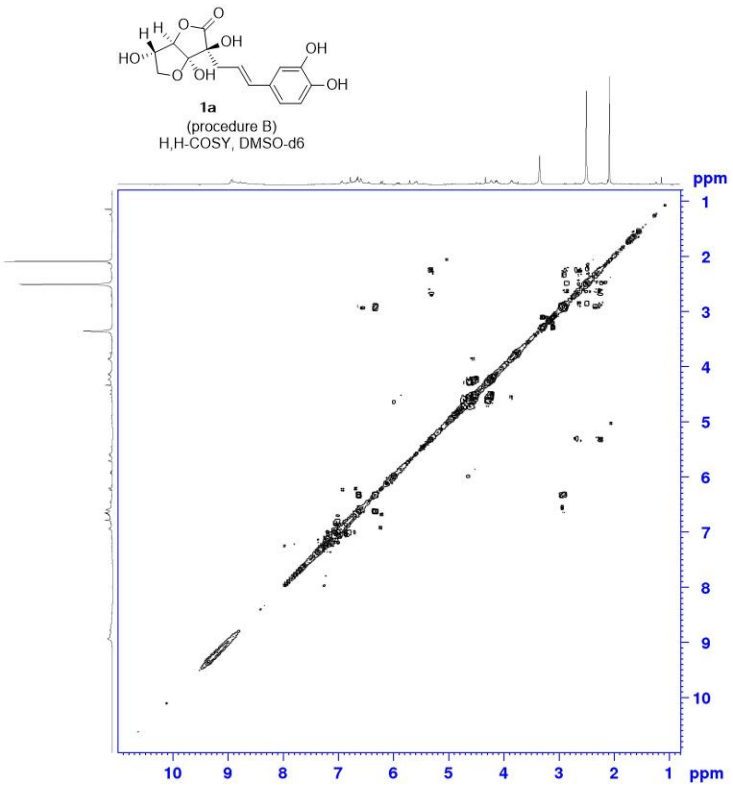

9.68
7.47
7.16
6.84
6.69
6.68
6.37
6.32
6.07
6.05
6.02
5.99
5.97
4.85
4.43
4.39
4.38
4.38
4.37
4.36
4.23
4.21
4.20
4.18
4.07
4.06
4.04
4.03
3.51
3.49
3.47
3.44
3.32
3.32
3.31
3.30
3.30
2.69
2.68
2.67
2.66
2.64
2.63
2.62
2.62
2.60
2.59
2.57
2.57
2.14
1.29
1.28
1.19
1.17
1.15
0.11
0.06
1a
(according to Poss' and Belter's procedure)
1H NMR, 300 MHz, MeOD
10
9
8
7
6
5
4
3
2
1
0
ppm
0.04
0.55
0.28
1.23
1.07
2.10
1.01
0.93
0.92
11.41
1.02
1.11
1.23
1.22
1.07
2.00
0.66
0.47
1.54
0.16

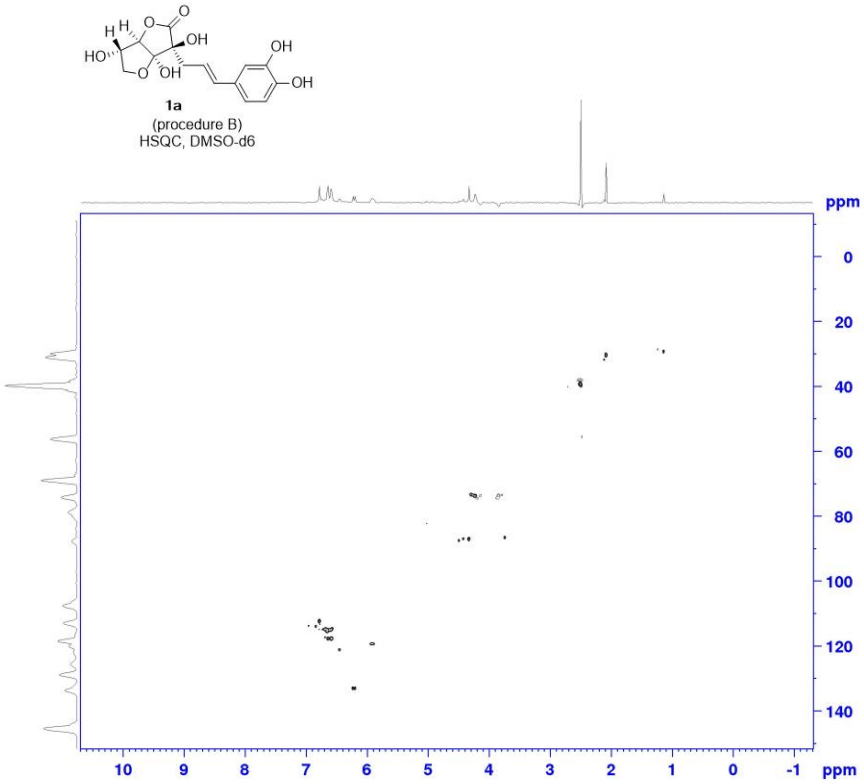

177.73
146.30
146.24
135.93
130.82
119.96
119.69
116.26
113.76
108.50
88.69
80.31
75.85
75.68
66.86
49.85
49.57
49.28
49.00
48.72
48.43
48.15
39.51
15.40
1a
(according to Poss' and Belter's procedure)
13C NMR, 100 MHz, MeOD
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

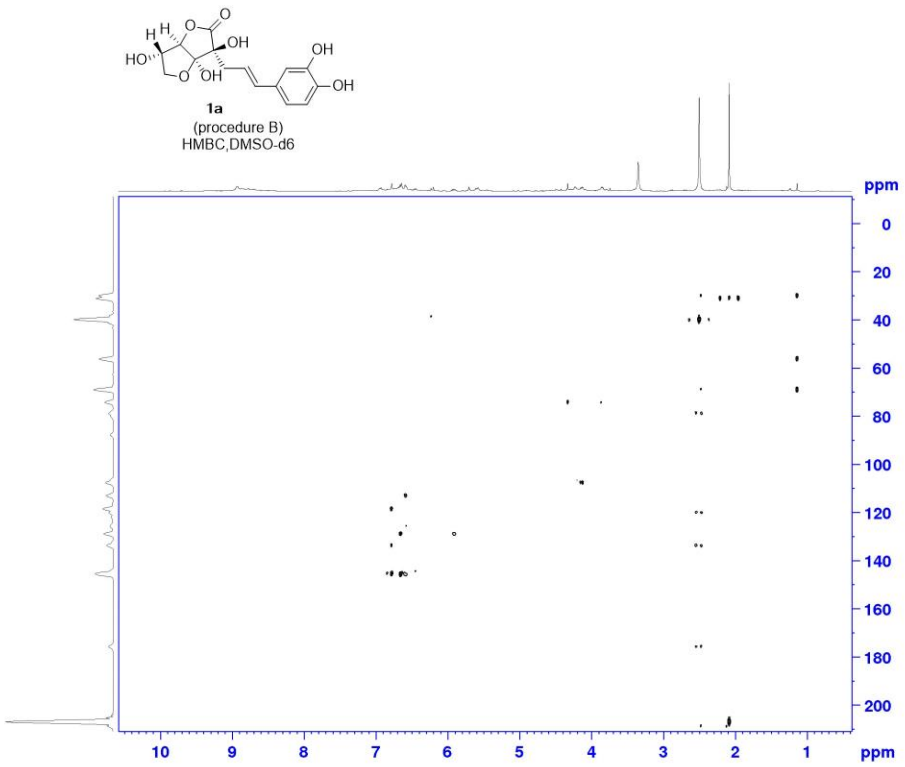

9.69
8.93
6.93
6.78
6.78
6.69
6.67
6.66
6.65
6.61
6.59
6.58
6.58
6.23
6.20
5.94
5.93
5.91
5.90
5.88
5.71
5.58
4.33
4.23
4.15
4.14
4.13
4.12
3.86
3.85
3.84
3.83
3.36
2.56
2.54
2.53
2.47
2.46
2.07
1a
(procedure A)
1H NMR, 500 MHz, DMSO-d6
10 9 8 7 6 5 4 3 2 1 0 ppm
1.44
0.86 0.79 0.30 0.85 1.00 0.64 0.58 0.69 0.87
0.62 0.96 0.91 1.12
3.59
0.72 0.31
1.63
175.50
145.35
145.16
133.32
128.57
119.63
116.02
115.58
112.60
107.09
87.41
78.51
74.14
73.97
40.02
39.85
39.68
39.52
39.35
39.18
39.02
38.98
38.38
1.20
1a
(procedure A)
13C NMR, 125 MHz, DMSO-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

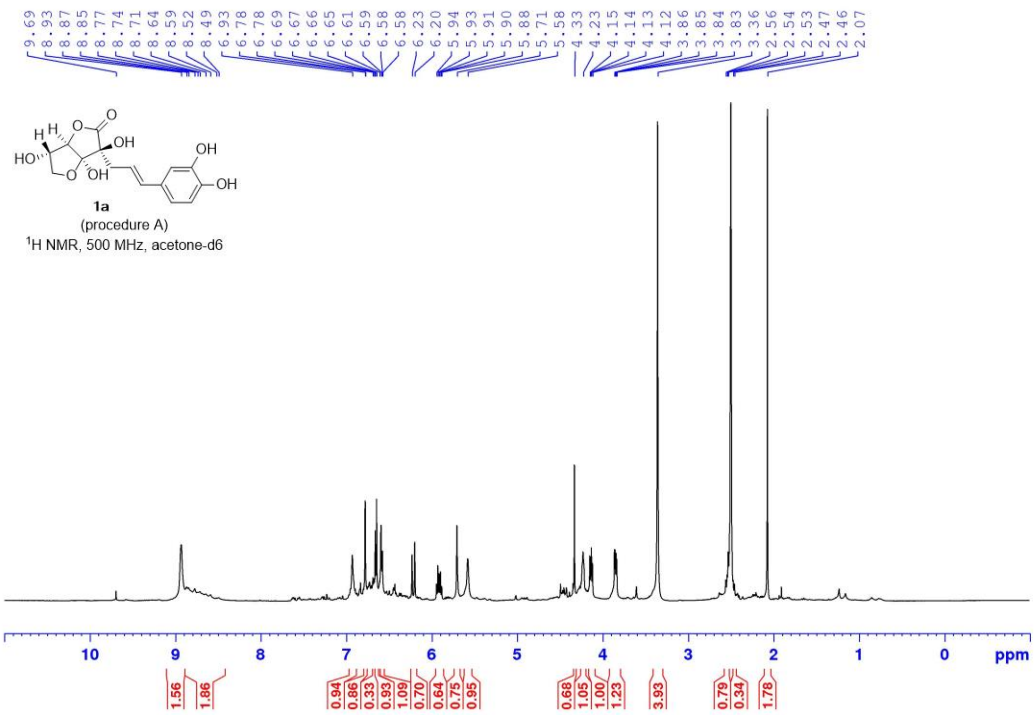

8.95
8.93
8.87
8.85
8.83
8.78
8.71
6.95
6.93
6.78
6.66
6.64
6.64
6.59
6.58
6.46
6.44
6.23
6.20
5.94
5.93
5.91
5.90
5.88
5.71
5.61
5.58
5.46
4.49
4.42
4.33
4.23
4.15
4.13
4.12
3.86
3.85
3.84
3.83
3.74
3.36
3.17
2.89
2.87
2.71
2.68
2.50
1a
(procedure B)
1H NMR, 500 MHz, DMSO-d6
10
9
8
7
6
5
4
3
2
1
0
ppm
2.95
0.63
0.73
1.09
1.02
0.37
0.46
0.32
0.41
0.90
0.16
0.28
0.19
0.44
0.75
1.00
0.73
0.25
0.15
0.46
0.15
0.19

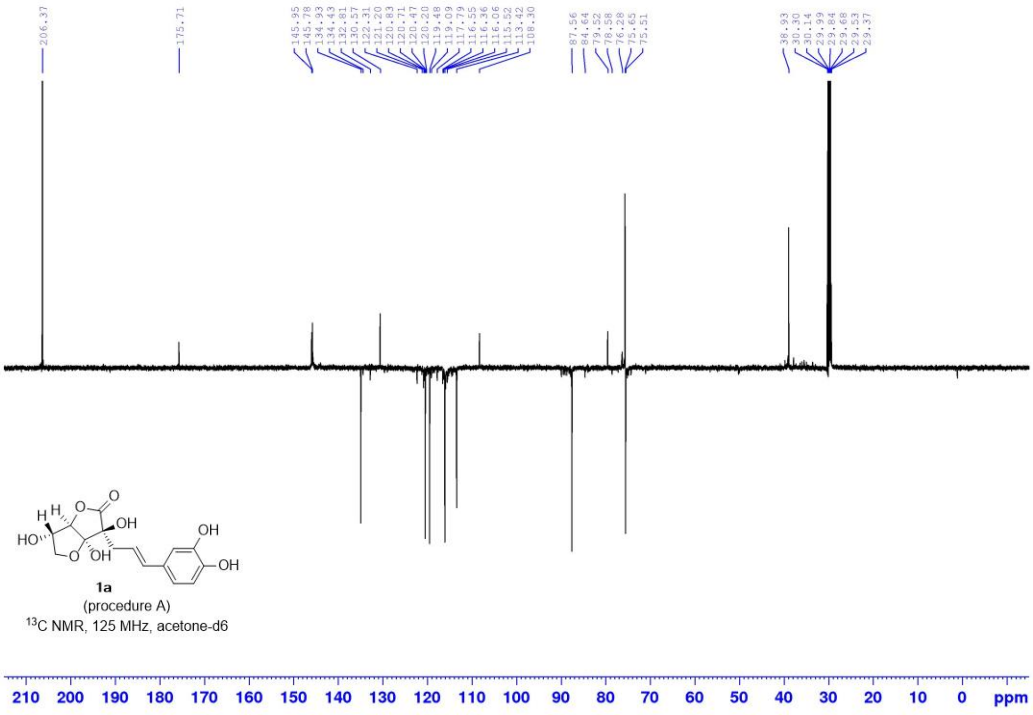

175.51
145.37
145.18
133.34
128.59
125.12
121.30
119.65
118.44
115.60
115.04
112.62
107.11
106.56
87.92
87.42
86.94
79.70
78.53
74.89
74.15
73.99
40.02
39.85
39.69
39.52
39.35
39.18
39.02
38.40
1a
(procedure B)
13C NMR, 125 MHz, DMSO-d6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

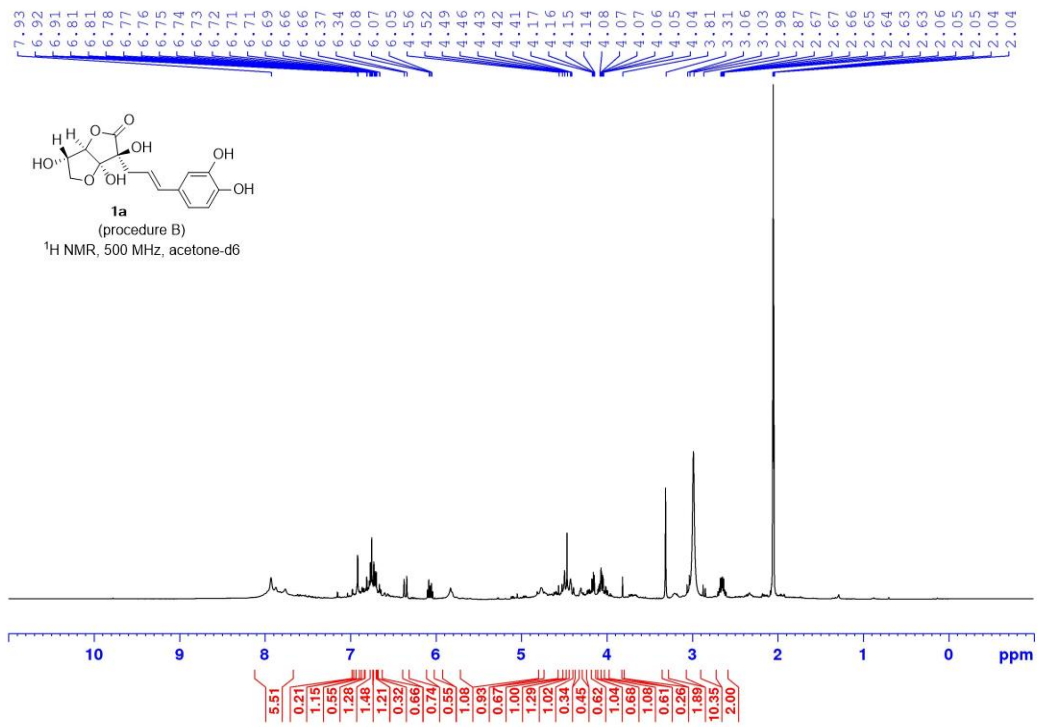

1a
(procedure B)
H,H-COSY, DMSO-d6
ppm
1
2
3
4
5
6
7
8
9
10
10 9 8 7 6 5 4 3 2 1 ppm

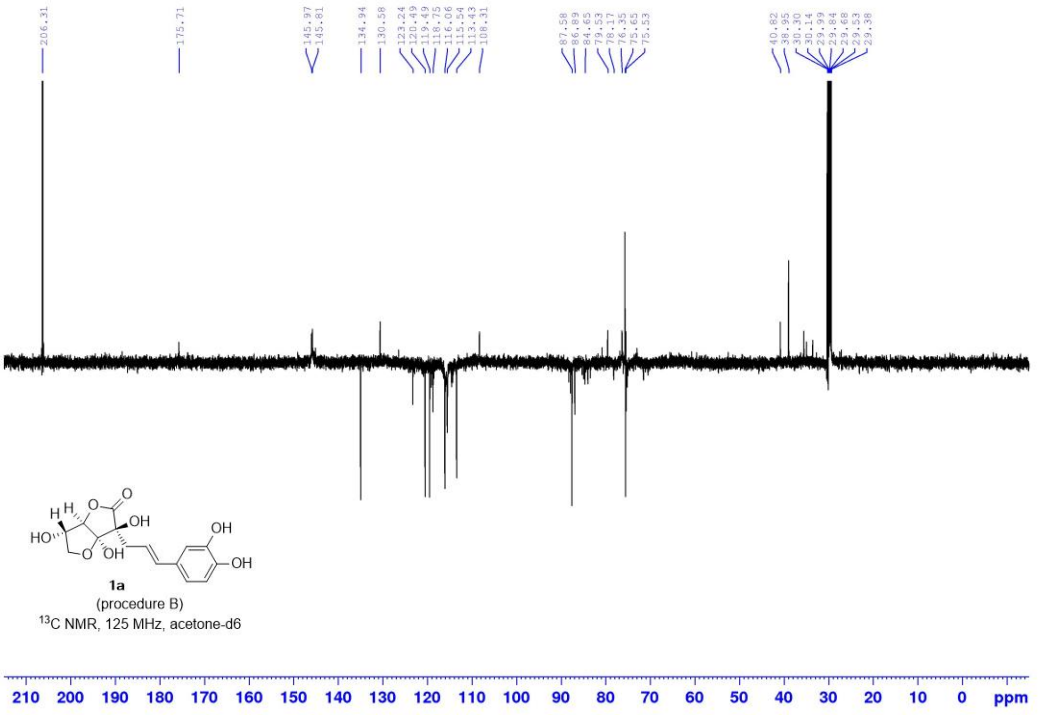

1a
(procedure B)
HSQC, DMSO-d6
ppm
0
20
40
60
80
100
120
140
10 9 8 7 6 5 4 3 2 1 0 -1 ppm

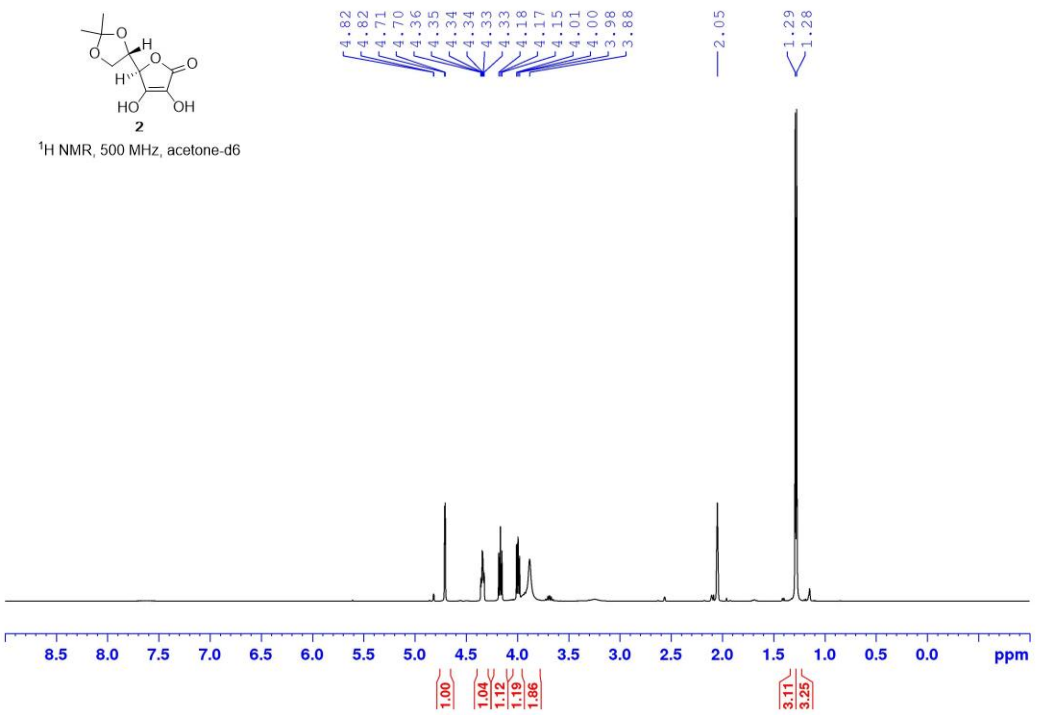

1a
(procedure B)
HMBC,DMSO-d6
ppm
0
20
40
60
80
100
120
140
160
180
200
10
9
8
7
6
5
4
3
2
1
ppm


9.69
8.93
8.87
8.85
8.77
8.74
8.71
8.64
8.59
8.52
8.49
6.93
6.78
6.78
6.69
6.67
6.66
6.65
6.61
6.59
6.58
6.58
6.23
6.20
5.94
5.93
5.91
5.90
5.88
5.71
5.58
4.33
4.23
4.15
4.14
4.13
4.12
3.86
3.85
3.84
3.83
3.36
2.56
2.54
2.53
2.47
2.46
2.07
1a
(procedure A)
1H NMR, 500 MHz, acetone-d6
10
9
8
7
6
5
4
3
2
1
0
ppm
1.56
1.86
0.94
0.86
0.33
0.93
1.09
0.70
0.64
0.75
0.95
0.66
1.05
1.00
1.23
3.93
0.79
0.34
1.78


206.37
175.71
145.95
145.78
134.93
134.43
132.81
132.37
132.31
121.20
120.83
120.71
120.47
120.20
119.88
119.09
117.79
116.55
116.36
116.16
115.92
113.42
108.30
87.56
84.64
79.52
78.58
76.28
75.65
75.51
38.93
30.30
30.14
29.99
29.84
29.68
29.53
29.37
1a
(procedure A)
13C NMR, 125 MHz, acetone-d6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

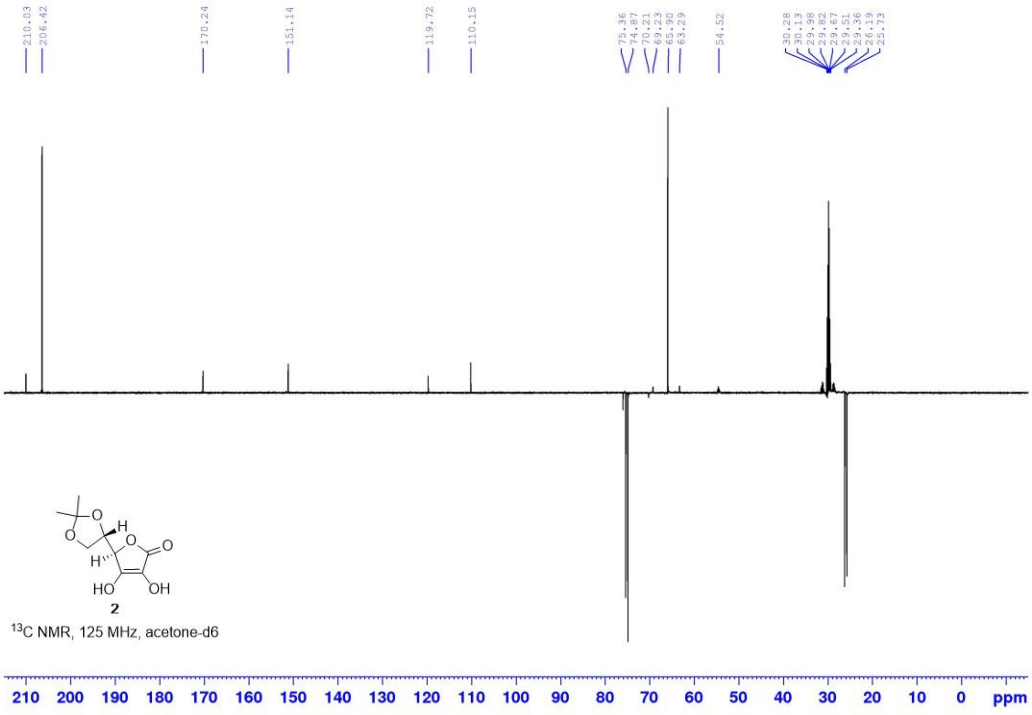

1a
(procedure B)
1H NMR, 500 MHz, acetone-d6
ppm


1a
(procedure B)
13C NMR, 125 MHz, acetone-d6
ppm



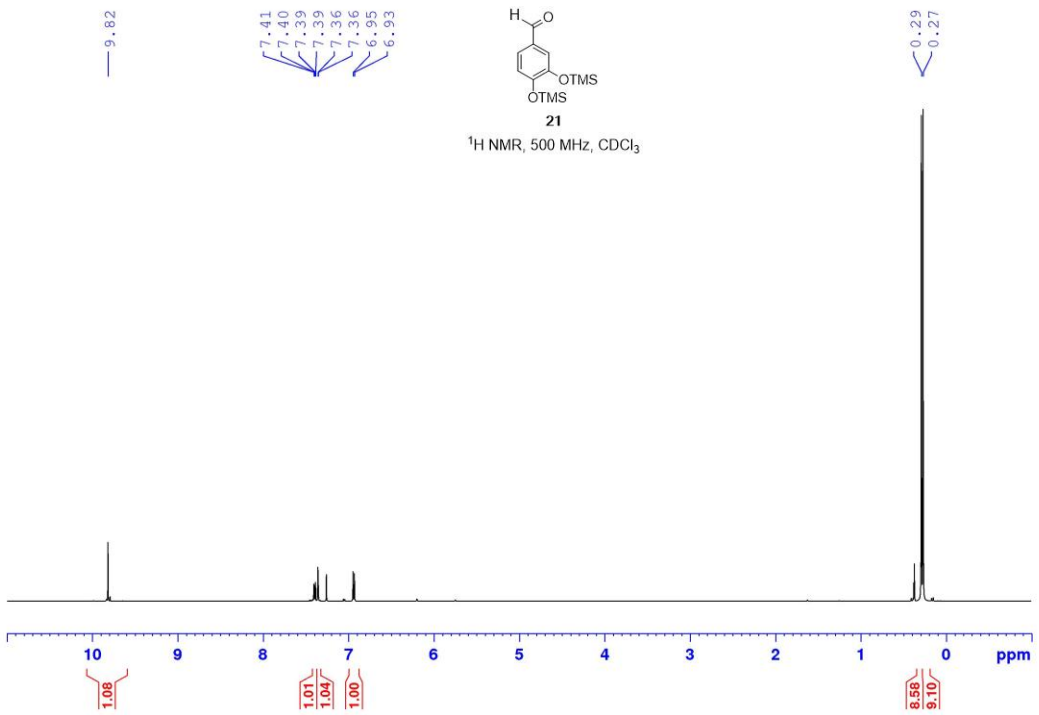
2

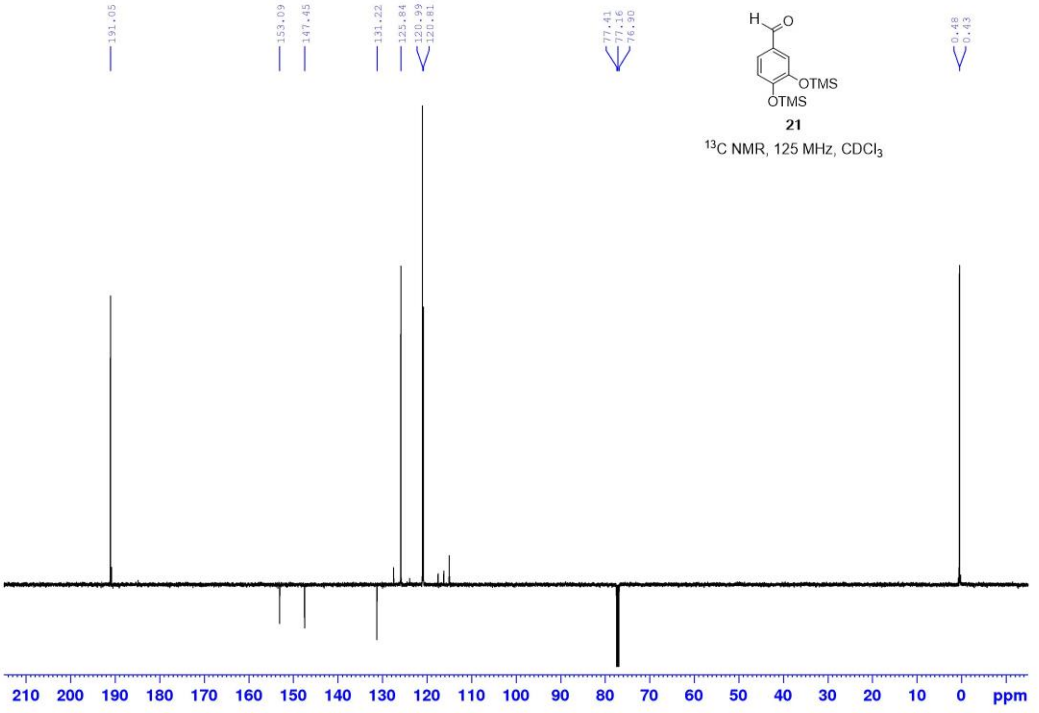
^{1}H NMR, 500 MHz, acetone-d6

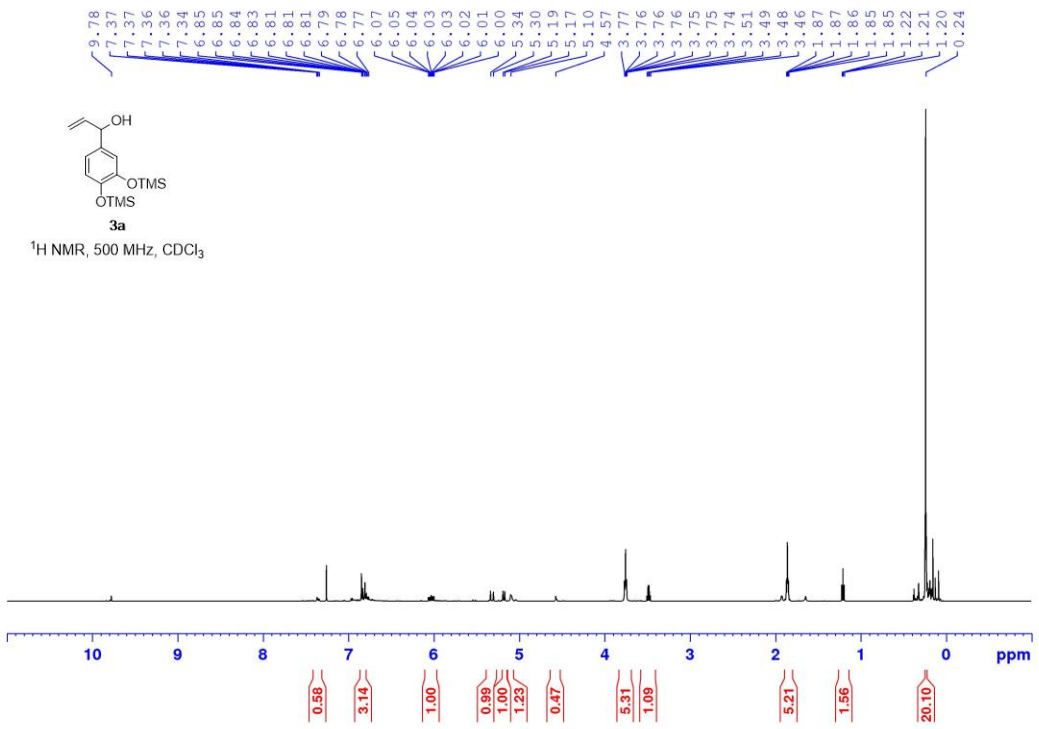


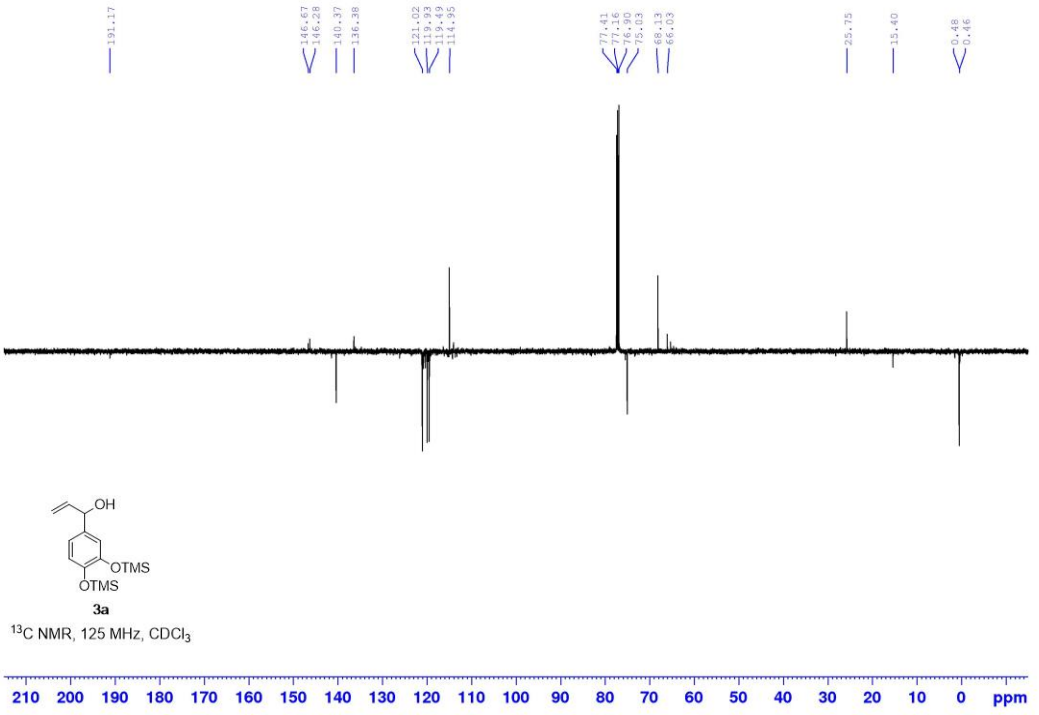
2

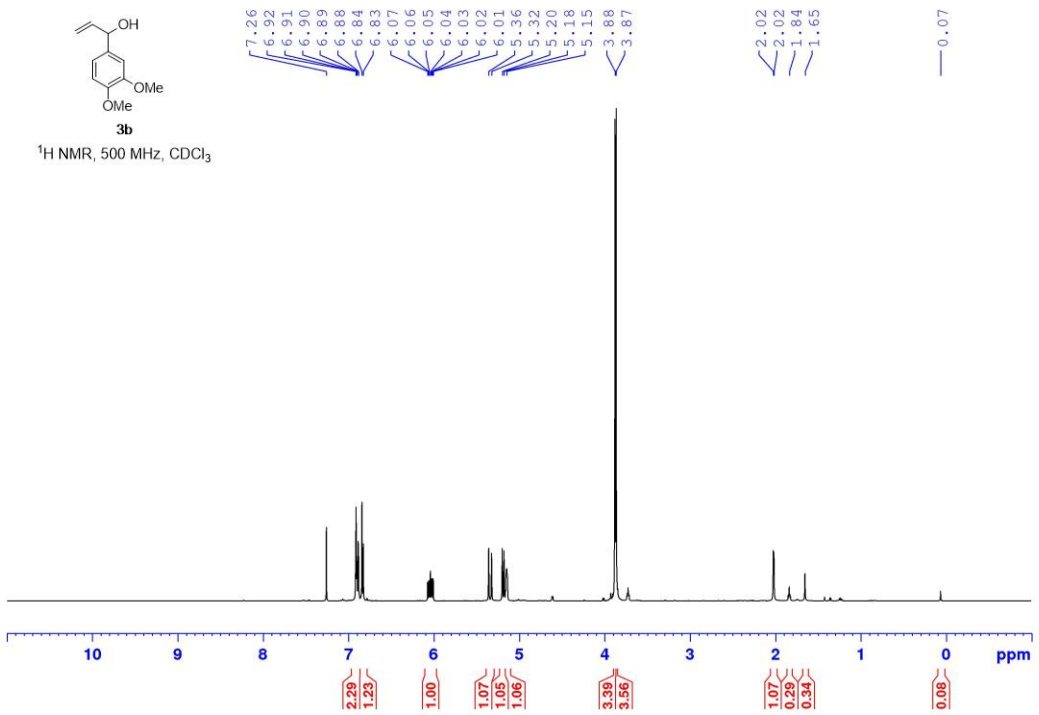
^{13}C NMR, 125 MHz, acetone-d6

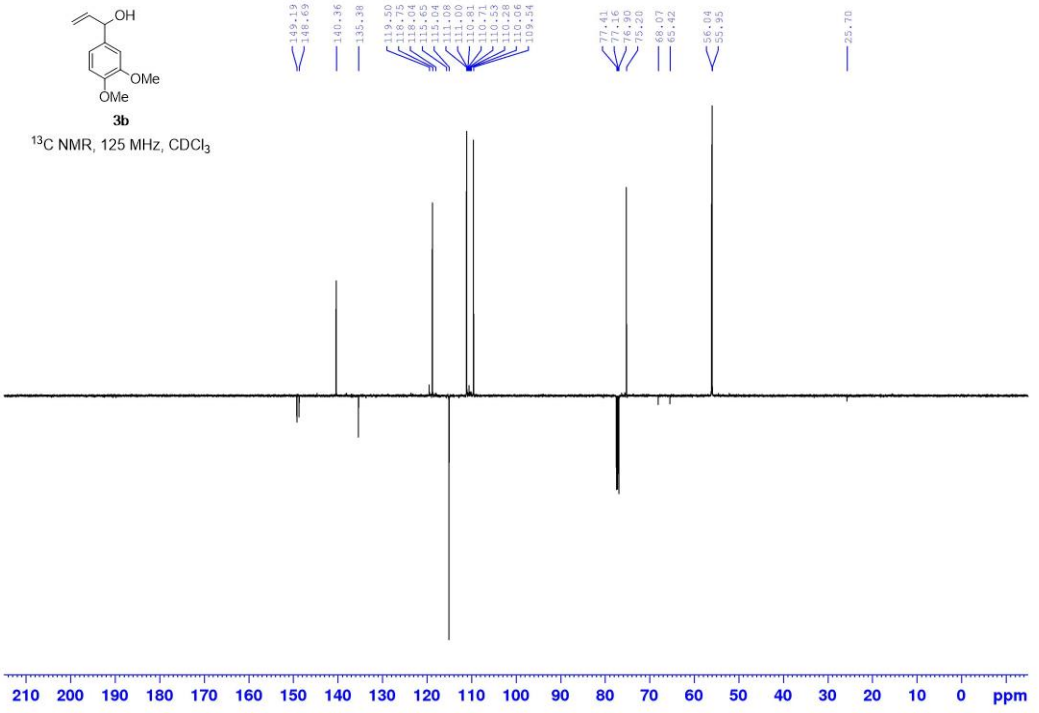

9.82
7.41
7.40
7.39
7.39
7.36
7.36
6.95
6.93
0.29
0.27
OTMS
OTMS
21
1H NMR, 500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.08
1.01
1.04
1.00
8.56
9.10

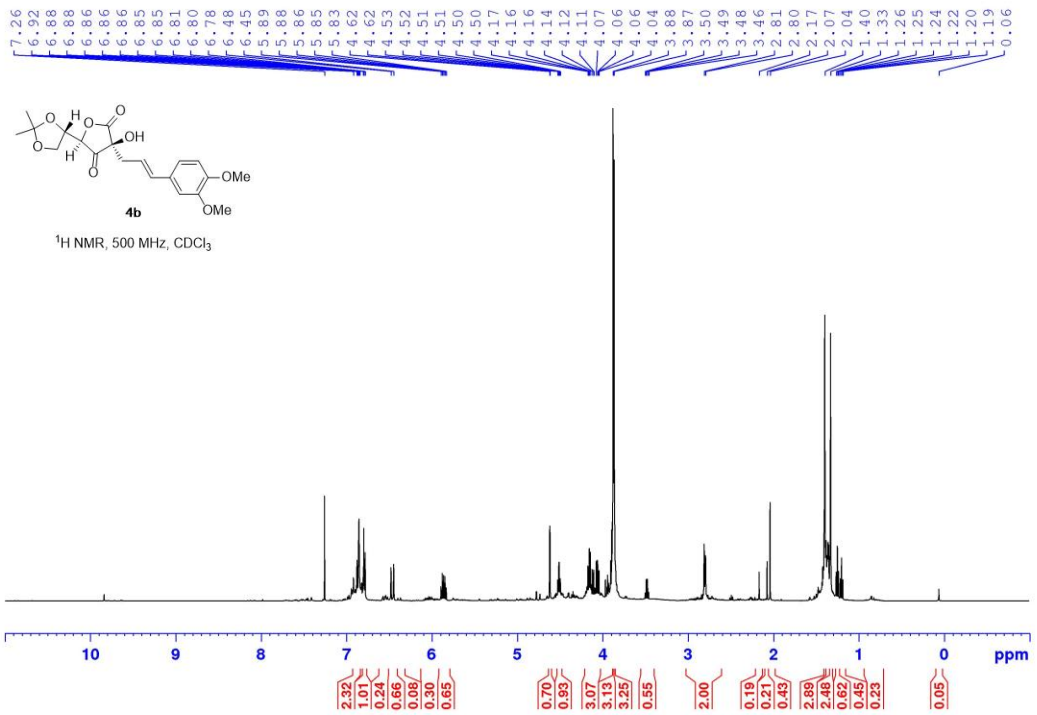

191.05
153.09
147.45
131.22
125.84
120.99
120.81
77.41
77.16
76.90
0.48
0.43
OTMS
OTMS
21
13C NMR, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


9.78
7.37
7.37
7.36
7.36
7.34
6.85
6.84
6.83
6.81
6.81
6.81
6.79
6.78
6.77
6.07
6.05
6.04
6.03
6.03
6.02
6.01
6.00
5.34
5.30
5.19
5.17
5.10
4.57
3.77
3.76
3.76
3.76
3.75
3.75
3.74
3.51
3.49
3.48
3.46
1.87
1.87
1.86
1.85
1.85
1.22
1.21
1.20
0.24
OH
OTMS
OTMS
3a
1H NMR, 500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
0.58
3.14
1.00
0.99
1.00
1.23
0.47
5.31
1.09
5.21
1.56
20.10

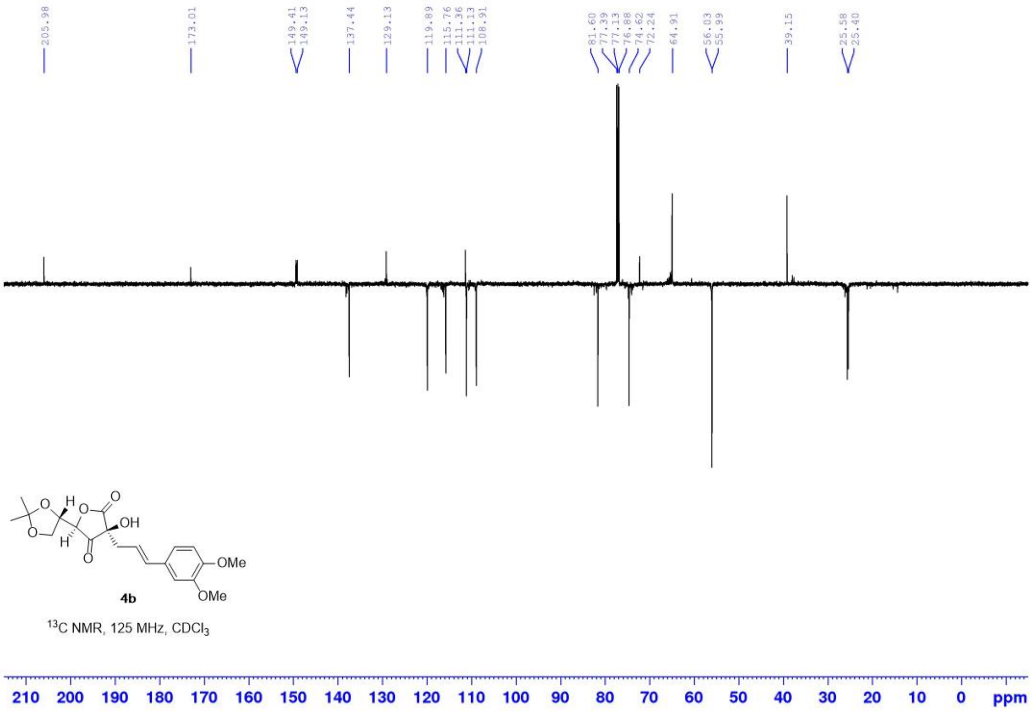

191.17
146.67
146.28
140.37
136.38
121.02
119.93
119.49
114.95
77.41
77.16
76.90
75.03
68.13
66.03
25.75
15.40
0.48
0.46
OH
OTMS
OTMS
3a
13C NMR, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OH
OMe
OMe
3b
^{1}H NMR, 500 MHz, CDCl$_3$
7.26
6.92
6.91
6.90
6.89
6.88
6.84
6.83
6.07
6.06
6.05
6.04
6.03
6.02
6.01
5.36
5.32
5.20
5.18
5.15
3.88
3.87
2.02
2.02
1.84
1.65
0.07
10 9 8 7 6 5 4 3 2 1 0 ppm
2.29
1.23
1.00
1.07
1.05
1.06
3.39
3.56
1.07
0.29
0.34
0.08

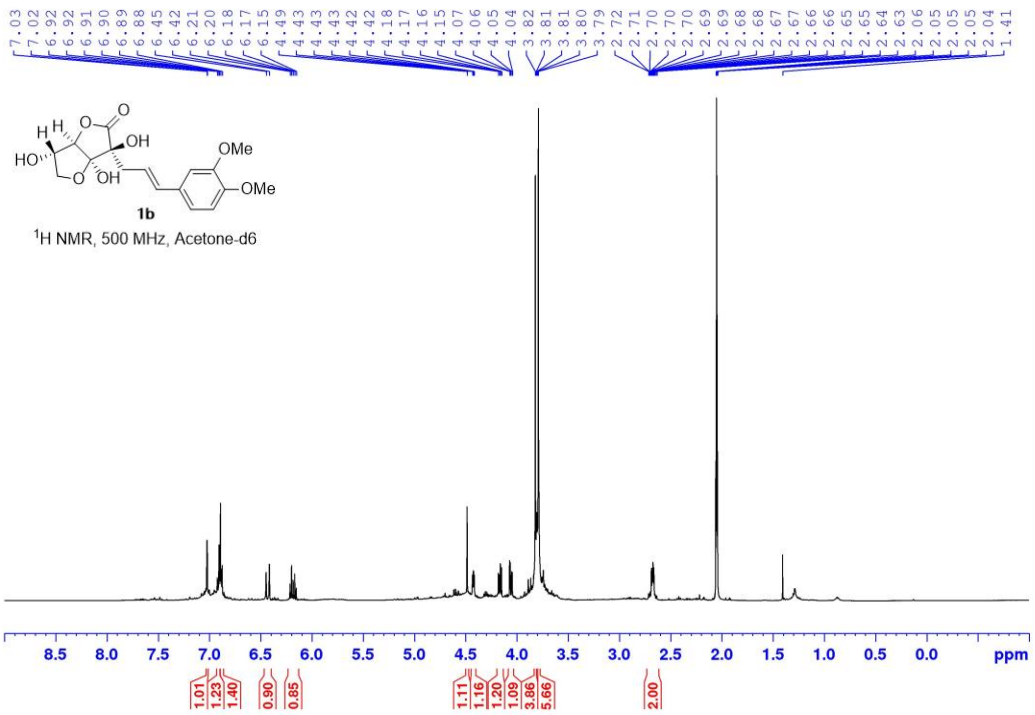

OH
OMe
OMe
3b
^{13}C NMR, 125 MHz, CDCl$_3$
149.19
148.69
140.36
135.38
119.50
118.75
118.64
115.65
115.04
111.08
111.00
110.81
110.71
110.53
110.38
110.06
109.54
77.41
77.16
76.90
75.20
68.07
65.42
56.04
55.95
25.70
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

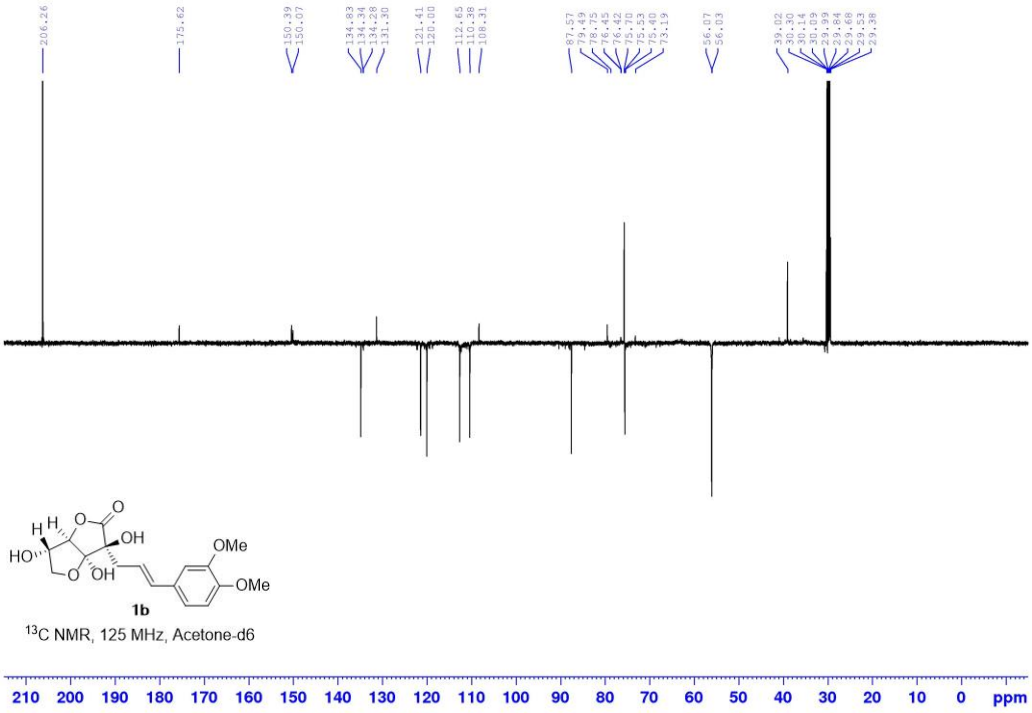


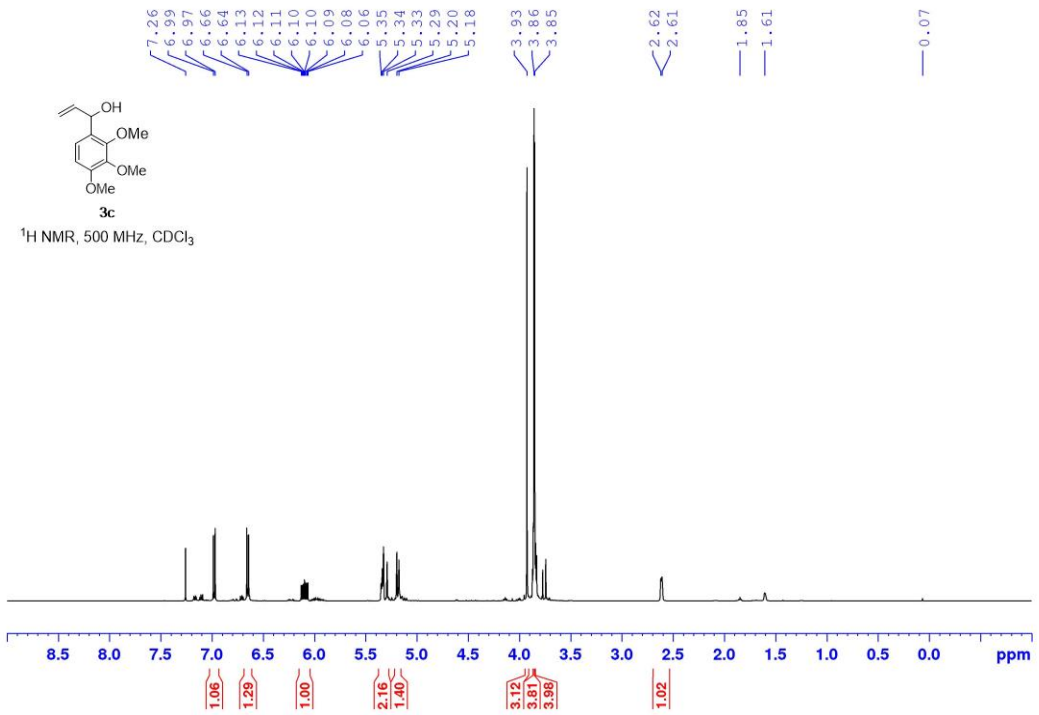
^{1}H NMR, 500 MHz, $CDCl_3$

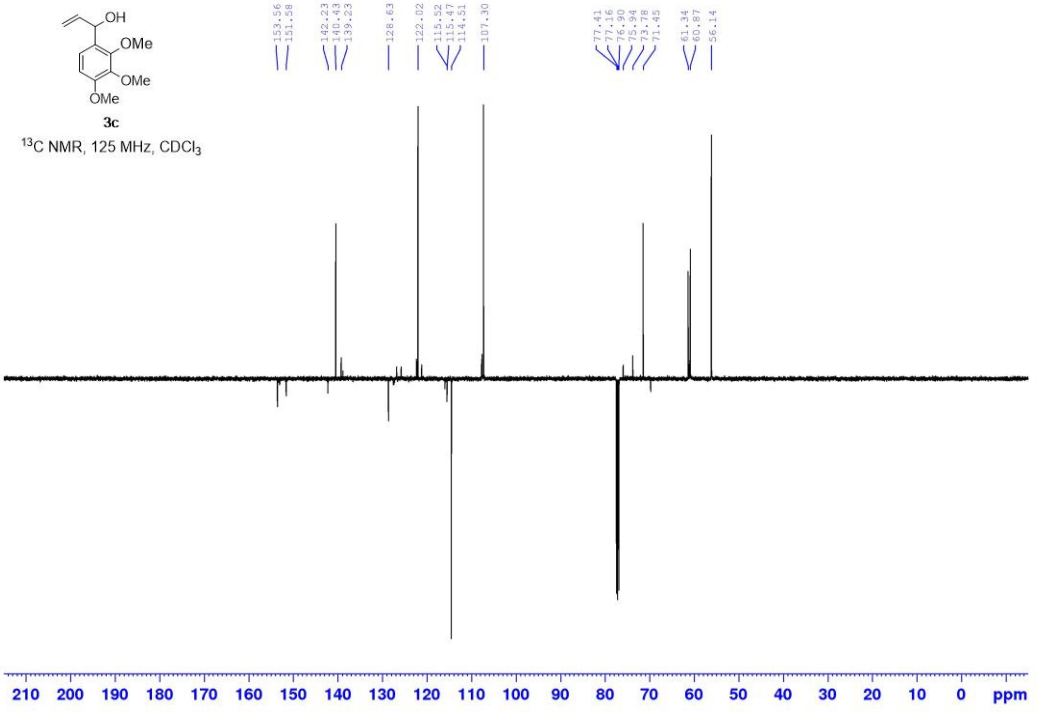


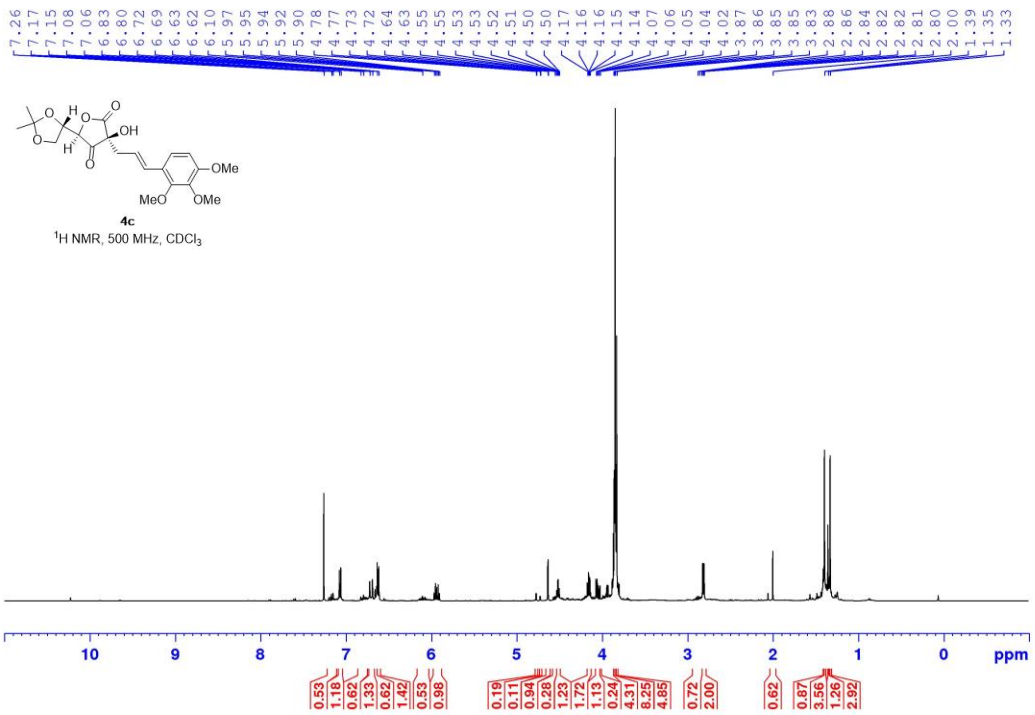
^{13}C NMR, 125 MHz, $CDCl_3$

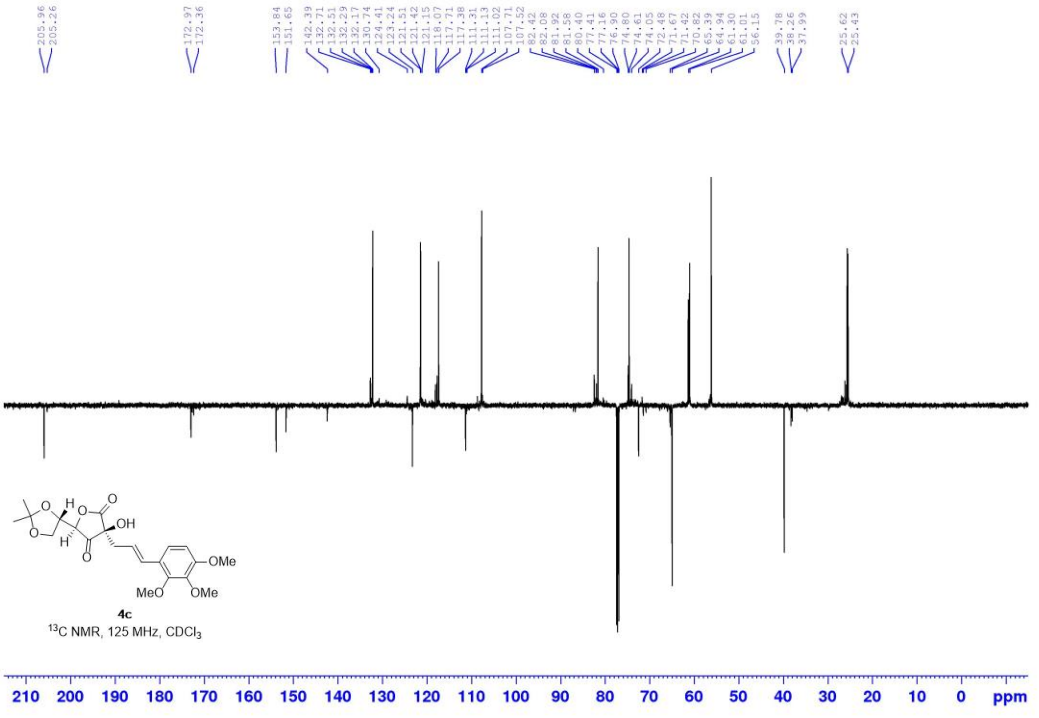

1b
1H NMR, 500 MHz, Acetone-d6
ppm

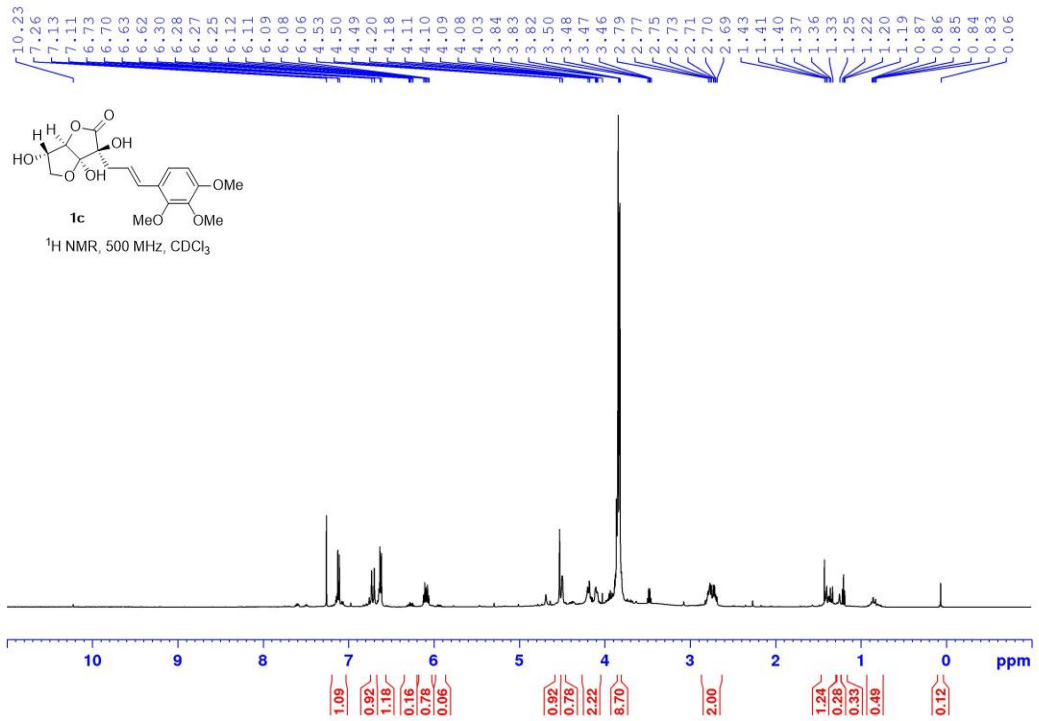

1b
13C NMR, 125 MHz, Acetone-d6
ppm

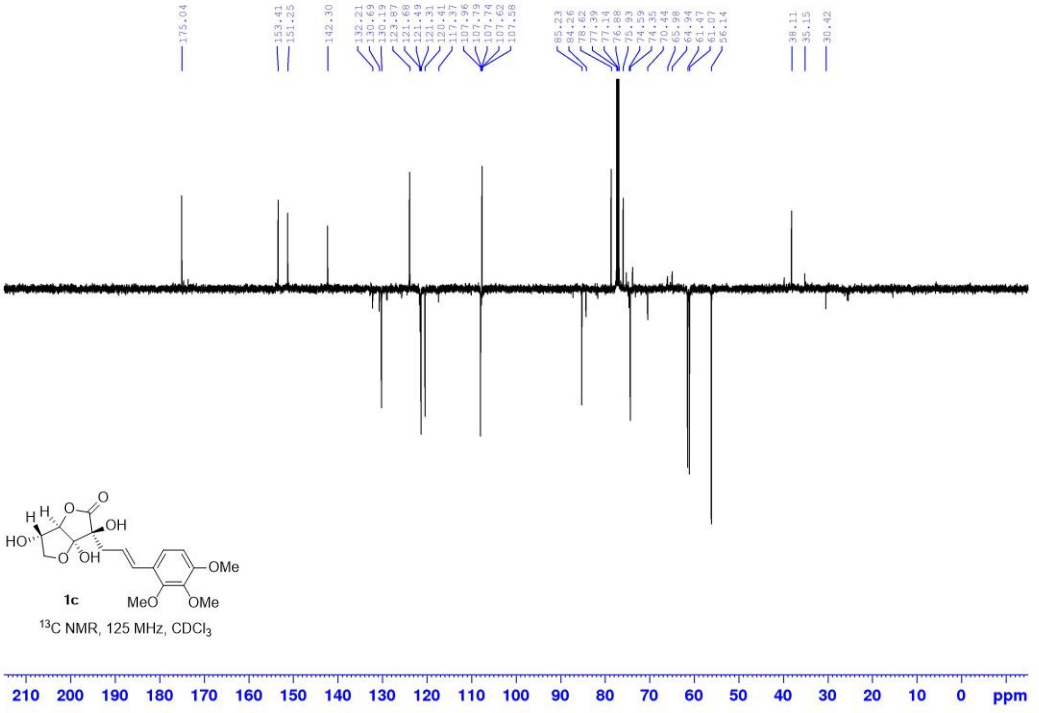

7.26
6.99
6.97
6.66
6.64
6.13
6.12
6.11
6.10
6.10
6.09
6.08
6.06
5.35
5.34
5.33
5.29
5.20
5.18
3.93
3.86
3.85
2.62
2.61
1.85
1.61
0.07
OH
OMe
OMe
OMe
3c
1H NMR, 500 MHz, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.06
1.29
1.00
2.16
1.40
3.12
3.81
3.98
1.02

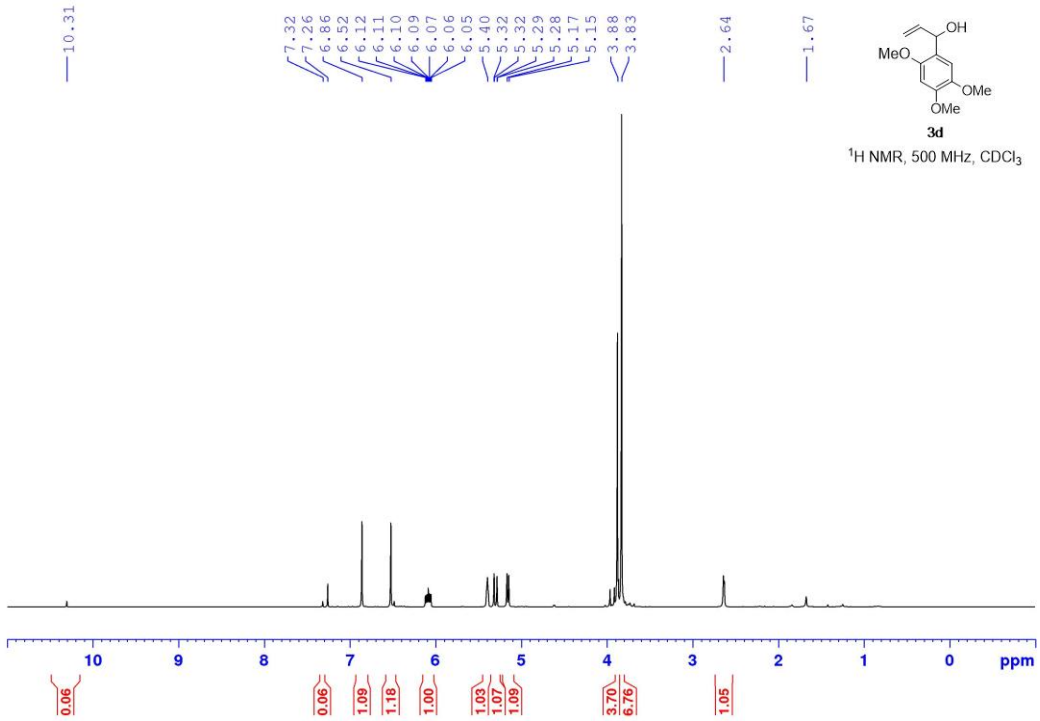

153.56
151.58
142.23
140.43
139.23
128.63
122.02
115.52
115.47
114.51
107.30
77.41
77.16
76.90
76.64
73.78
71.45
61.34
60.87
56.14
OH
OMe
OMe
OMe
3c
13C NMR, 125 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

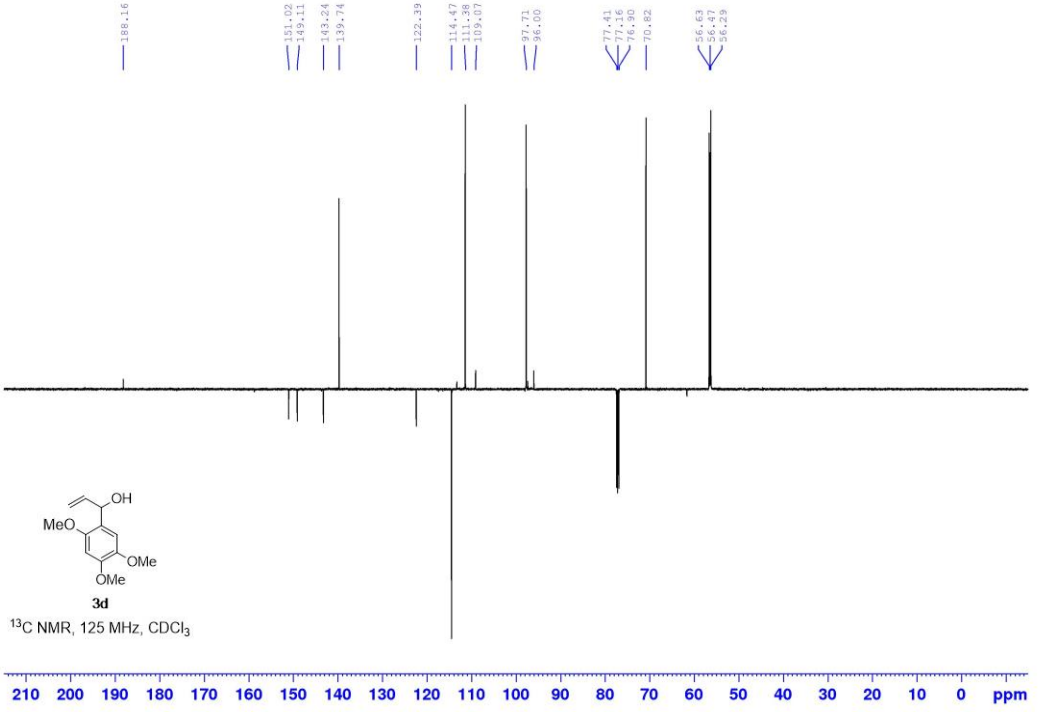

4c
^{1}H NMR, 500 MHz, $CDCl_3$

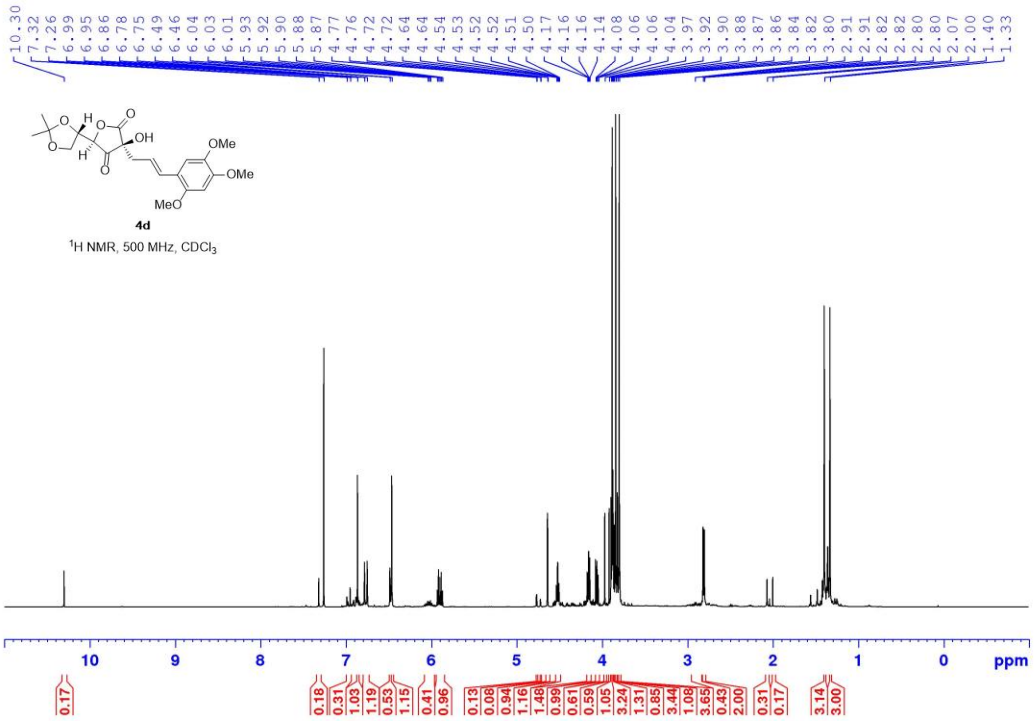

4c
^{13}C NMR, 125 MHz, $CDCl_3$

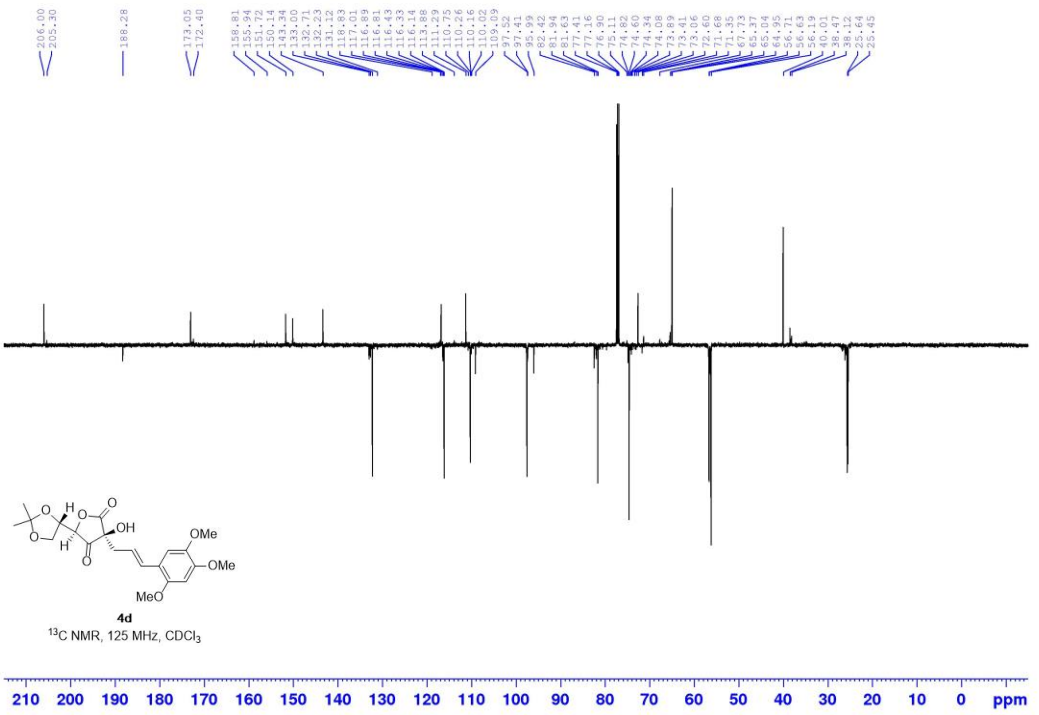

10.23
7.26
7.13
7.11
6.73
6.70
6.63
6.62
6.30
6.28
6.27
6.25
6.12
6.11
6.09
6.08
6.06
4.53
4.50
4.49
4.20
4.18
4.11
4.10
4.09
4.08
4.03
3.84
3.83
3.82
3.50
3.48
3.47
3.46
2.79
2.77
2.75
2.73
2.71
2.70
2.69
1.43
1.41
1.40
1.37
1.36
1.33
1.25
1.22
1.20
1.19
0.87
0.86
0.85
0.84
0.83
0.06
1c
MeO
OMe
OMe
1H NMR, 500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.09
0.92
1.18
0.16
0.78
0.06
0.92
0.78
2.22
8.70
2.00
1.24
0.28
0.33
0.49
0.12

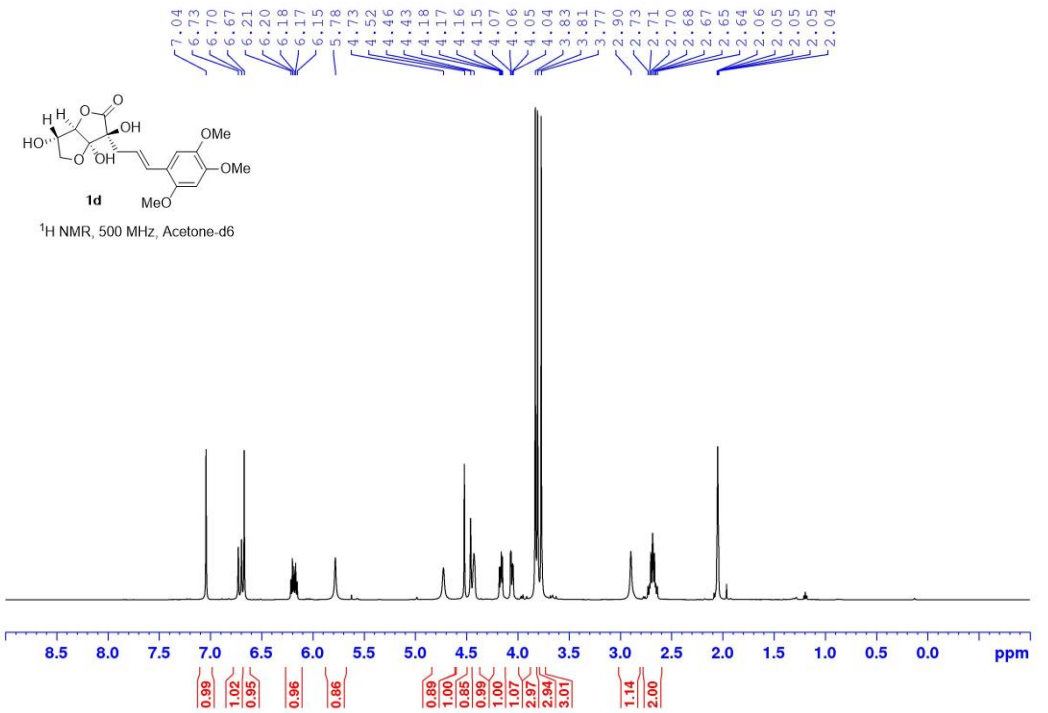

175.04
153.41
151.25
142.30
132.21
130.69
130.39
123.87
121.68
121.49
121.31
120.41
117.37
110.96
107.79
107.74
107.62
107.58
85.23
84.26
78.62
77.39
77.14
76.88
75.93
74.59
74.35
70.44
66.98
64.94
61.47
61.07
56.14
38.11
35.15
30.42
1c
MeO
OMe
OMe
13C NMR, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

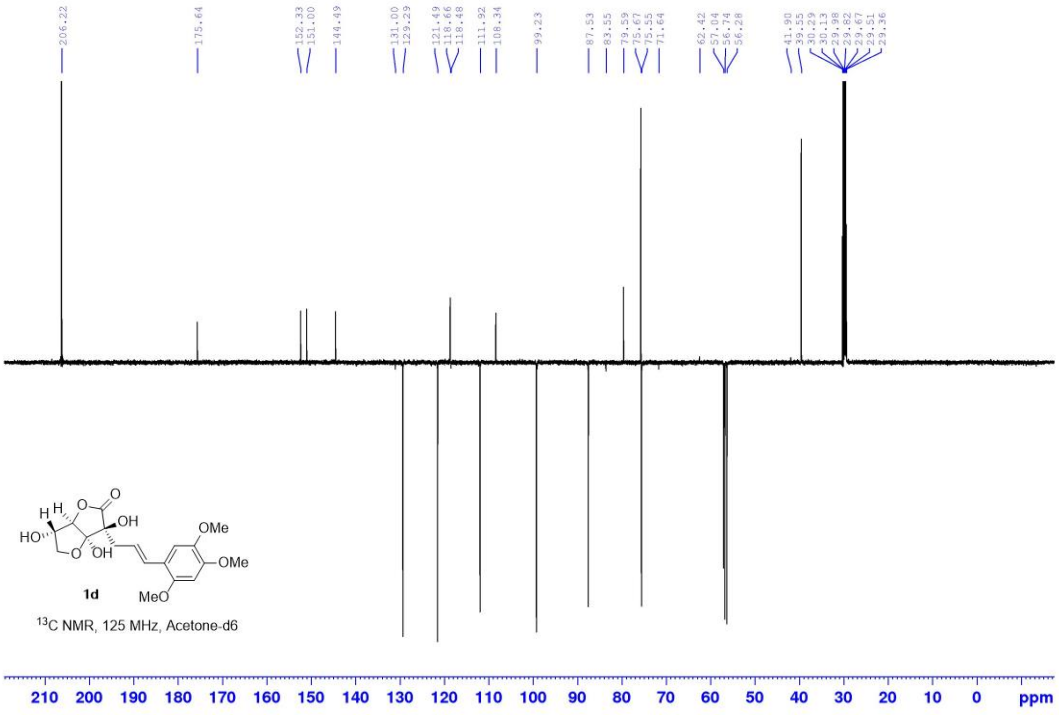

10.31
7.32
7.26
6.86
6.52
6.12
6.11
6.10
6.09
6.07
6.06
6.05
5.40
5.32
5.32
5.29
5.28
5.17
5.15
3.88
3.83
2.64
1.67
OH
MeO
OMe
OMe
3d
1H NMR, 500 MHz, CDCl3
10 9 8 7 6 5 4 3 2 1 0 ppm
0.06
0.06
1.09
1.18
1.00
1.03
1.07
1.09
3.70
6.76
1.05

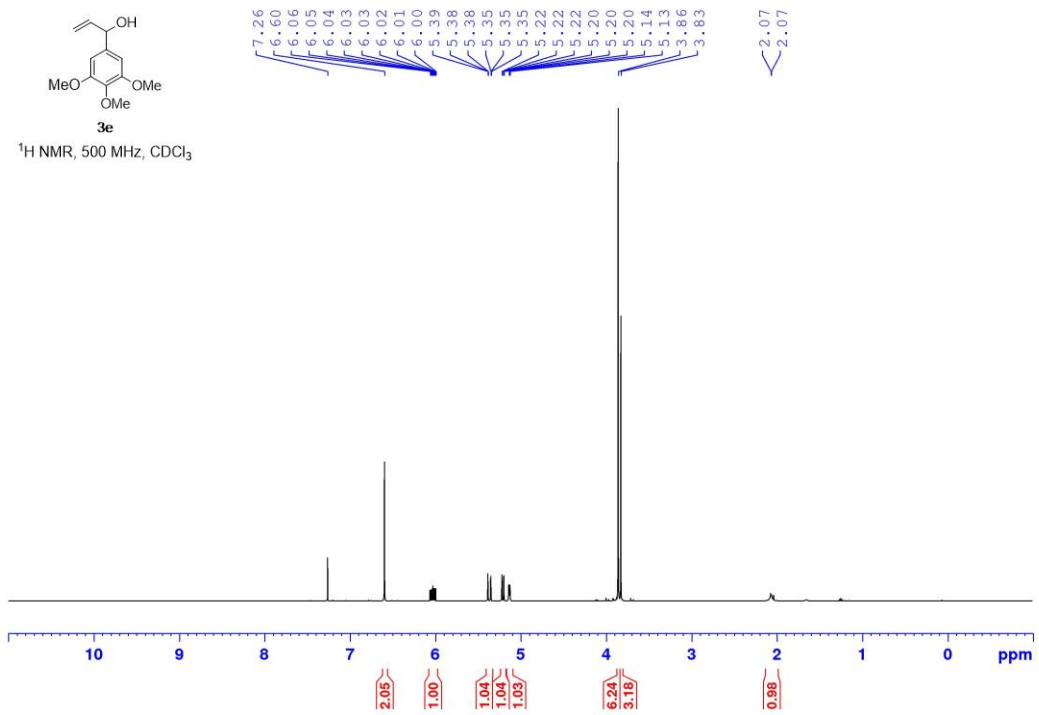

188.16
151.02
149.11
143.24
139.74
122.39
114.47
113.38
109.07
97.71
96.00
77.41
77.16
76.90
70.82
56.63
56.47
56.29
OH
MeO
OMe
OMe
3d
13C NMR, 125 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

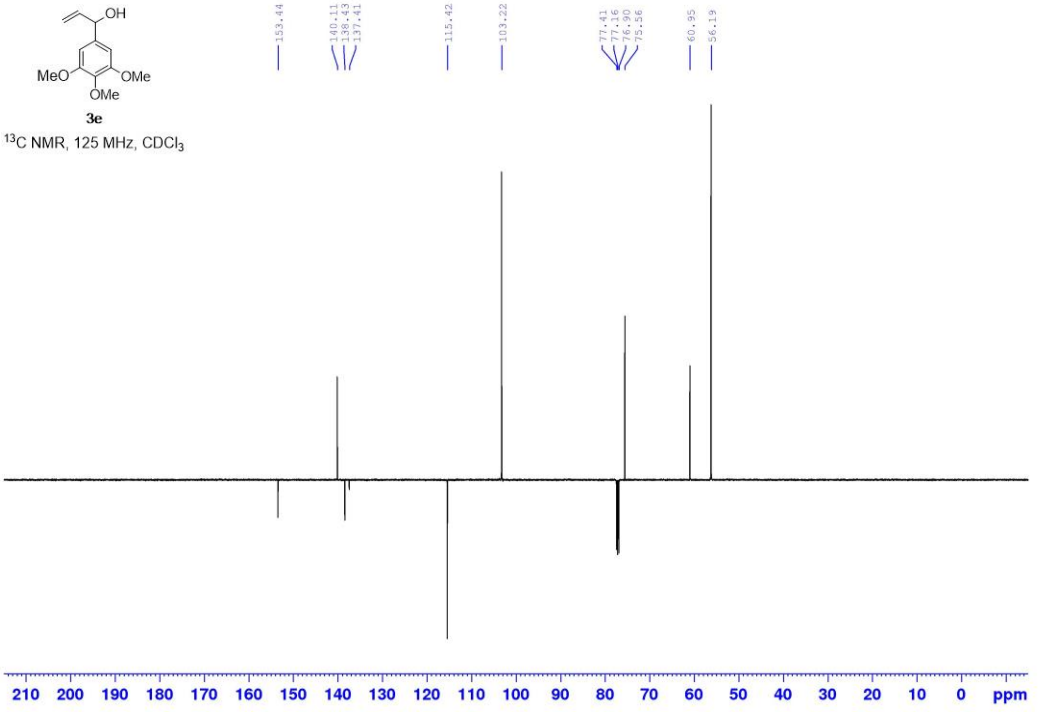

4d
^{1}H NMR, 500 MHz, $CDCl_3$
ppm

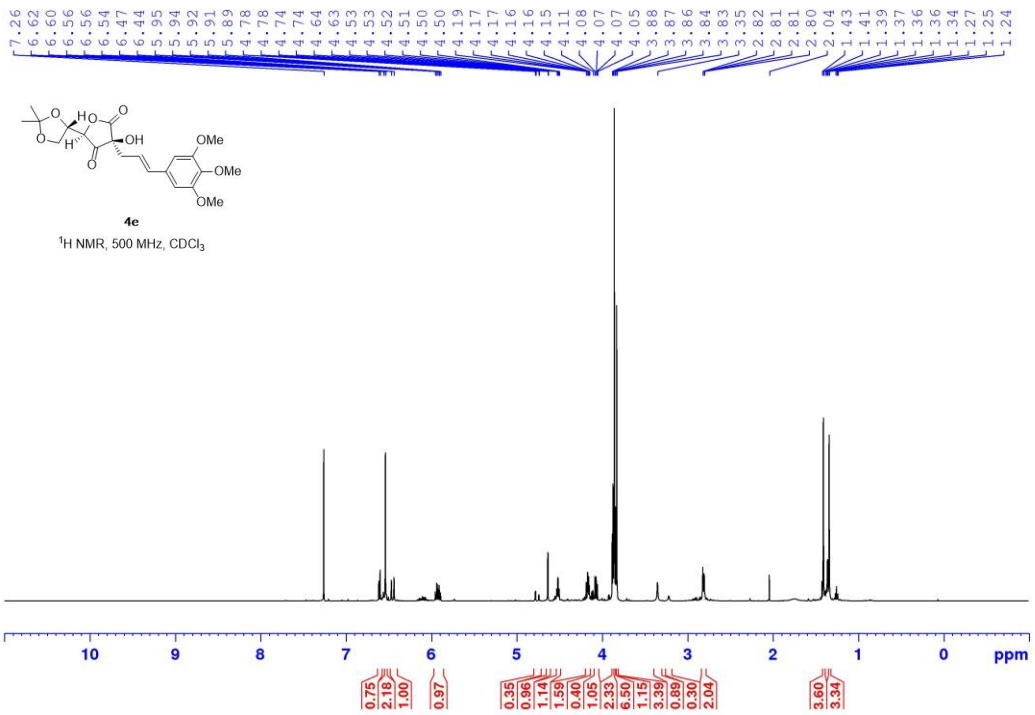

4d
^{13}C NMR, 125 MHz, $CDCl_3$
ppm

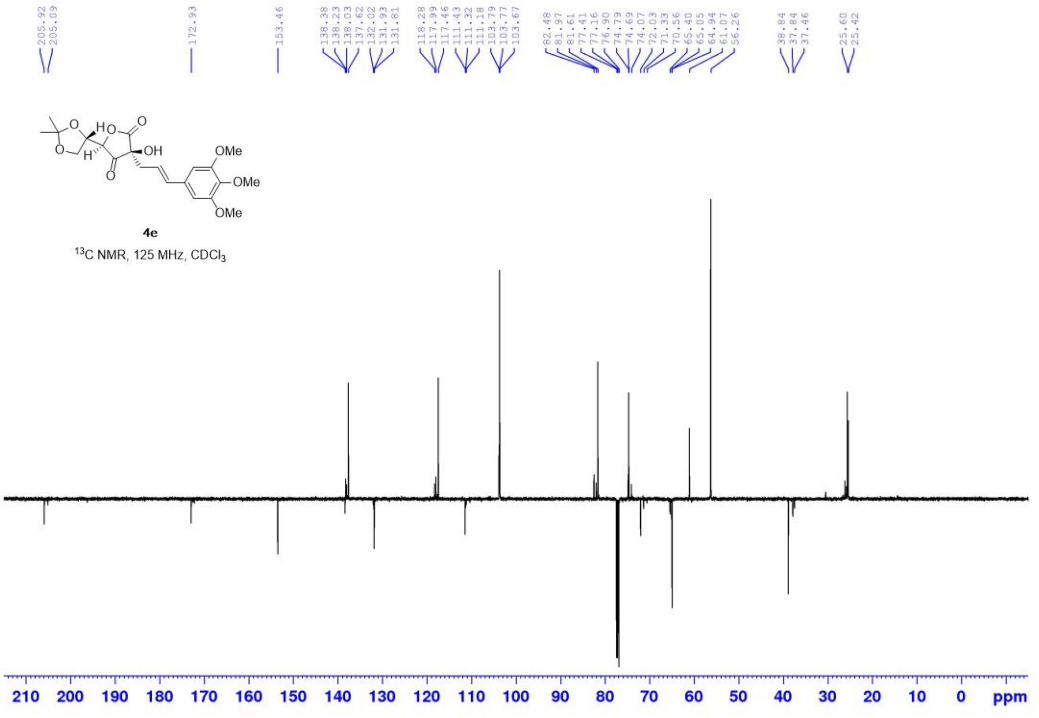

7.04
6.73
6.70
6.67
6.21
6.20
6.18
6.17
6.15
5.78
4.73
4.52
4.46
4.43
4.18
4.17
4.16
4.15
4.07
4.06
4.05
4.04
3.83
3.81
3.77
2.90
2.73
2.71
2.70
2.68
2.67
2.65
2.64
2.06
2.05
2.05
2.05
2.04
OMe
OMe
MeO
OH
OH
HO
1d
1H NMR, 500 MHz, Acetone-d6
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.99
1.02
0.95
0.96
0.86
0.89
1.00
0.85
0.99
1.00
1.07
2.97
2.94
3.01
1.14
2.00

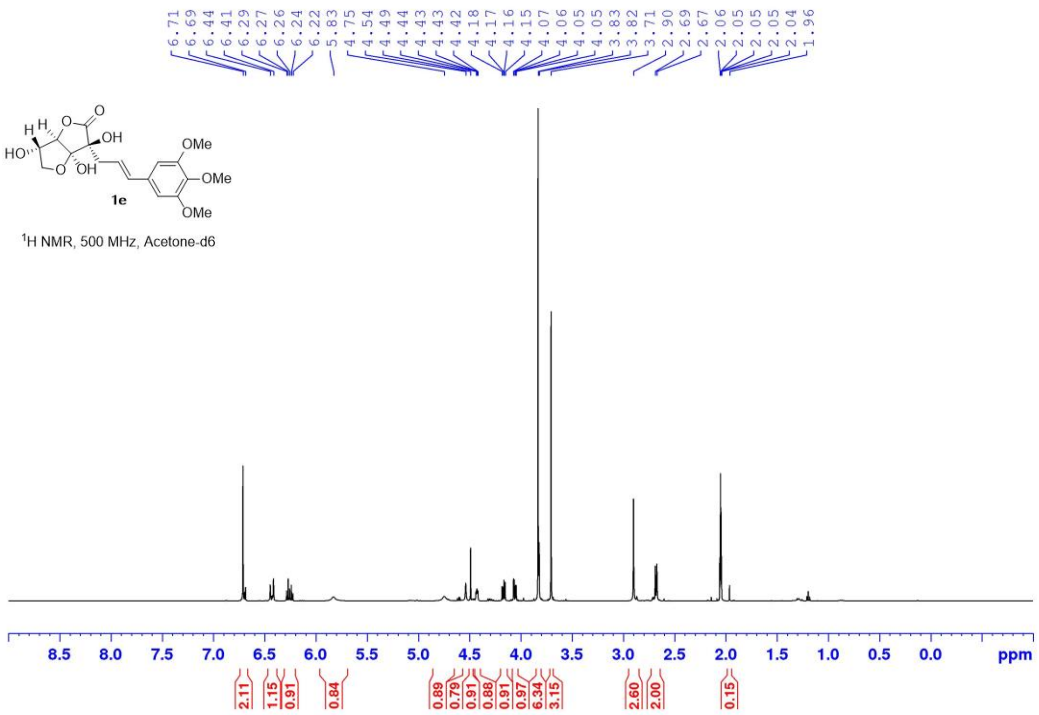

206.22
175.64
152.33
151.00
144.49
131.00
129.29
121.49
116.46
118.48
111.92
108.34
99.23
87.53
83.55
79.59
75.67
75.55
71.64
62.42
62.04
56.74
56.28
41.90
38.55
30.29
30.13
29.98
29.82
29.67
29.51
29.36
OMe
OMe
MeO
OH
OH
HO
1d
13C NMR, 125 MHz, Acetone-d6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

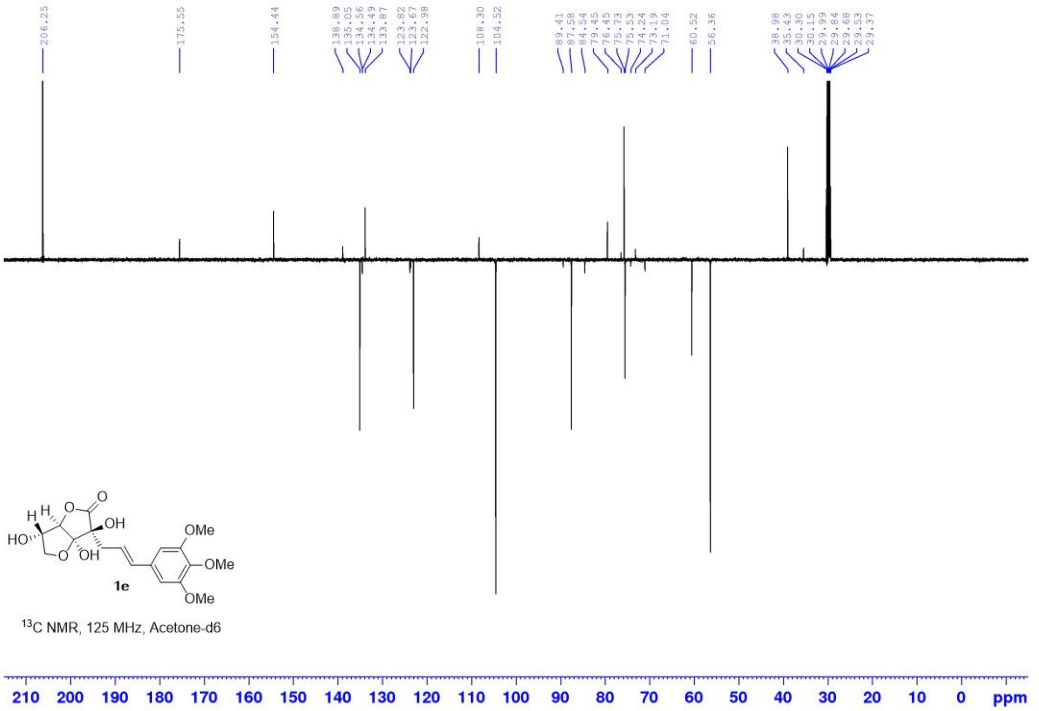

OH
MeO
OMe
OMe
3e
^{1}H NMR, 500 MHz, $CDCl_3$
7.26
6.60
6.06
6.05
6.04
6.03
6.03
6.02
6.01
6.00
5.39
5.38
5.38
5.35
5.35
5.35
5.22
5.22
5.22
5.20
5.20
5.20
5.14
5.13
3.86
3.83
2.07
2.07
10 9 8 7 6 5 4 3 2 1 0 ppm
2.05
1.00
1.04
1.04
1.03
6.24
3.18
0.98

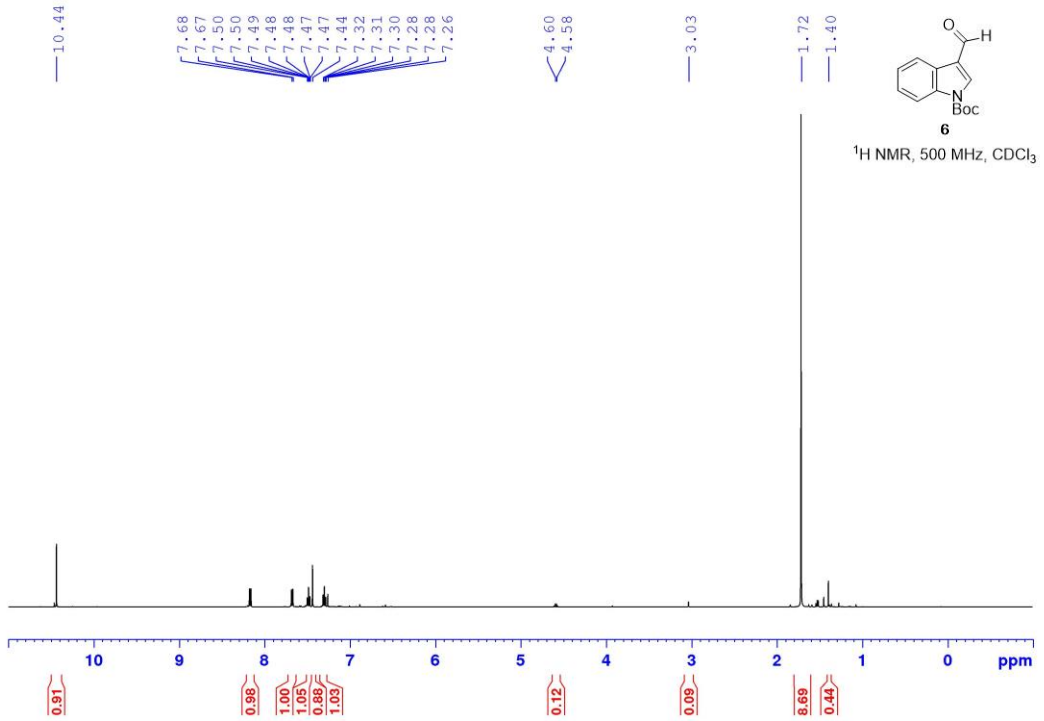

OH
MeO
OMe
OMe
3e
^{13}C NMR, 125 MHz, $CDCl_3$
153.44
140.11
138.43
137.41
115.42
103.22
77.41
77.16
76.90
75.56
60.95
56.19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

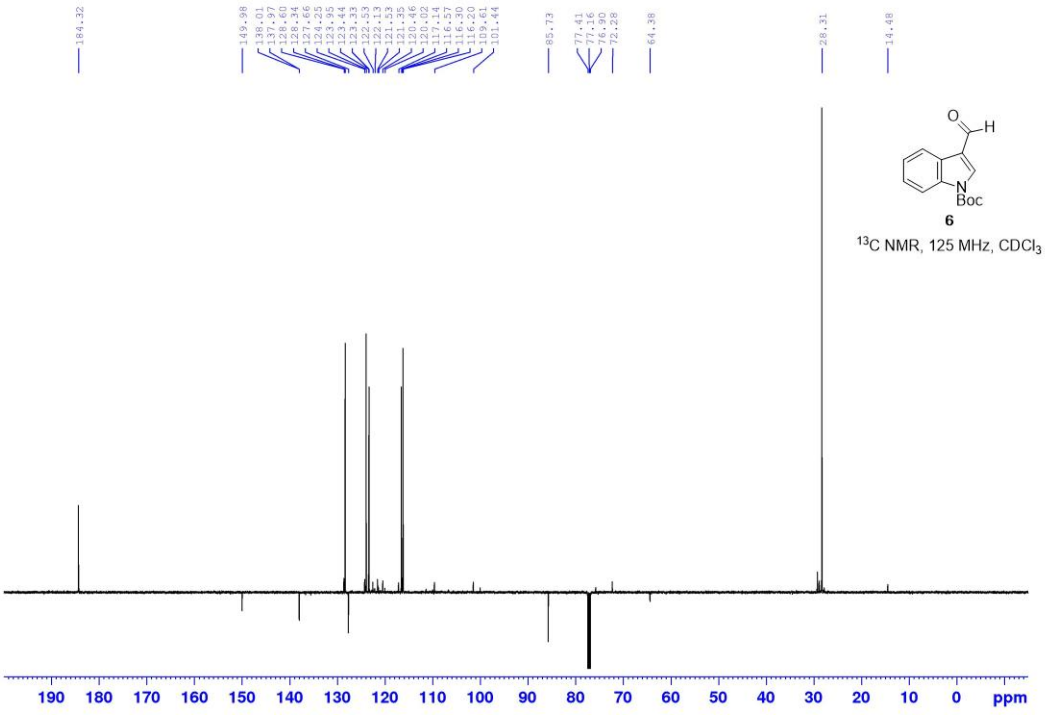

4e
1H NMR, 500 MHz, CDCl3
OMe
OMe
OMe
OH
10 9 8 7 6 5 4 3 2 1 0 ppm

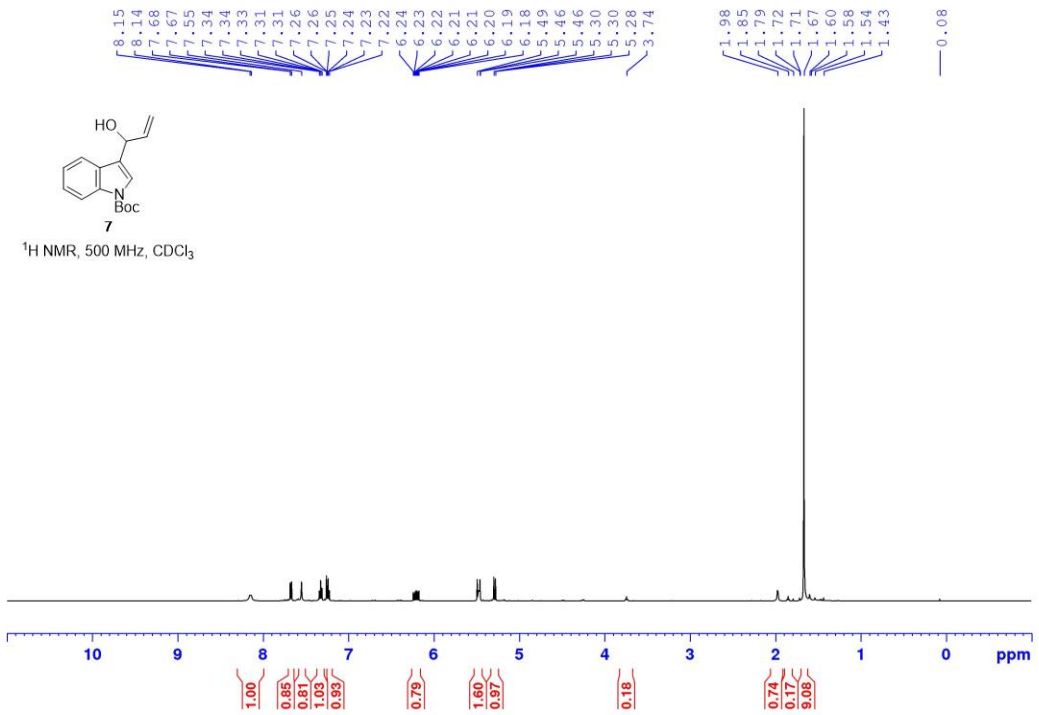

4e
13C NMR, 125 MHz, CDCl3
OMe
OMe
OMe
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

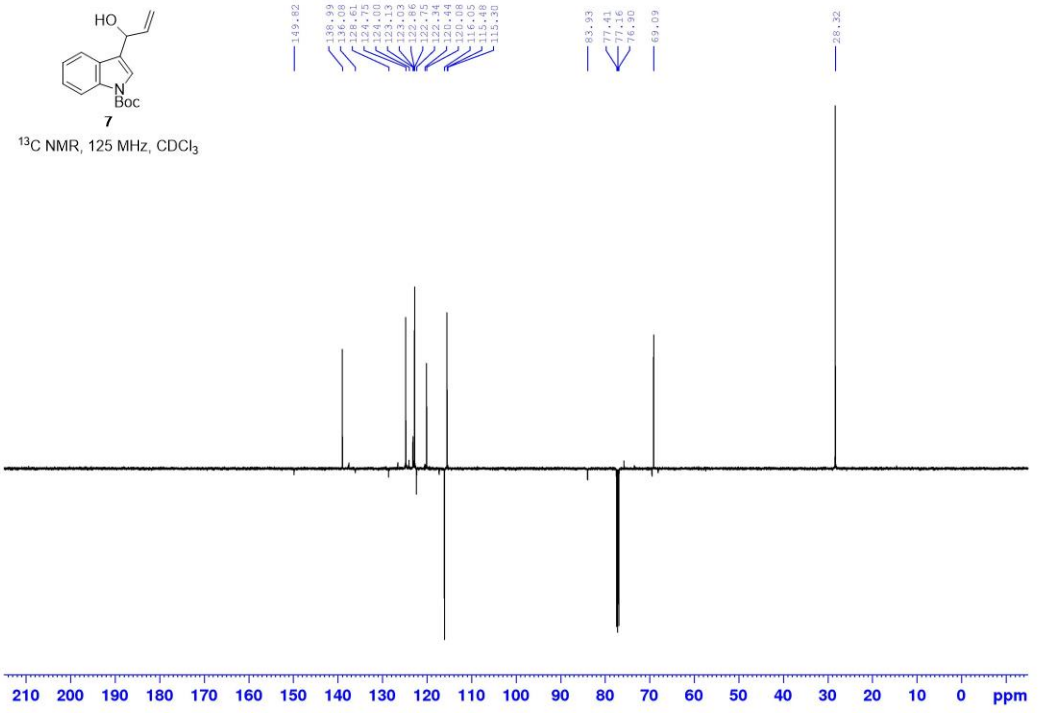

6.71
6.69
6.44
6.41
6.29
6.27
6.26
6.24
6.22
5.83
4.75
4.54
4.49
4.44
4.43
4.42
4.18
4.17
4.16
4.15
4.07
4.06
4.05
4.05
3.83
3.82
3.71
2.90
2.69
2.67
2.06
2.05
2.05
2.05
2.04
1.96
OMe
OMe
OMe
OH
OH
1e
1H NMR, 500 MHz, Acetone-d6
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.11
1.15
0.91
0.84
0.89
0.79
0.91
0.88
0.91
0.97
6.34
3.15
2.60
2.00
0.15

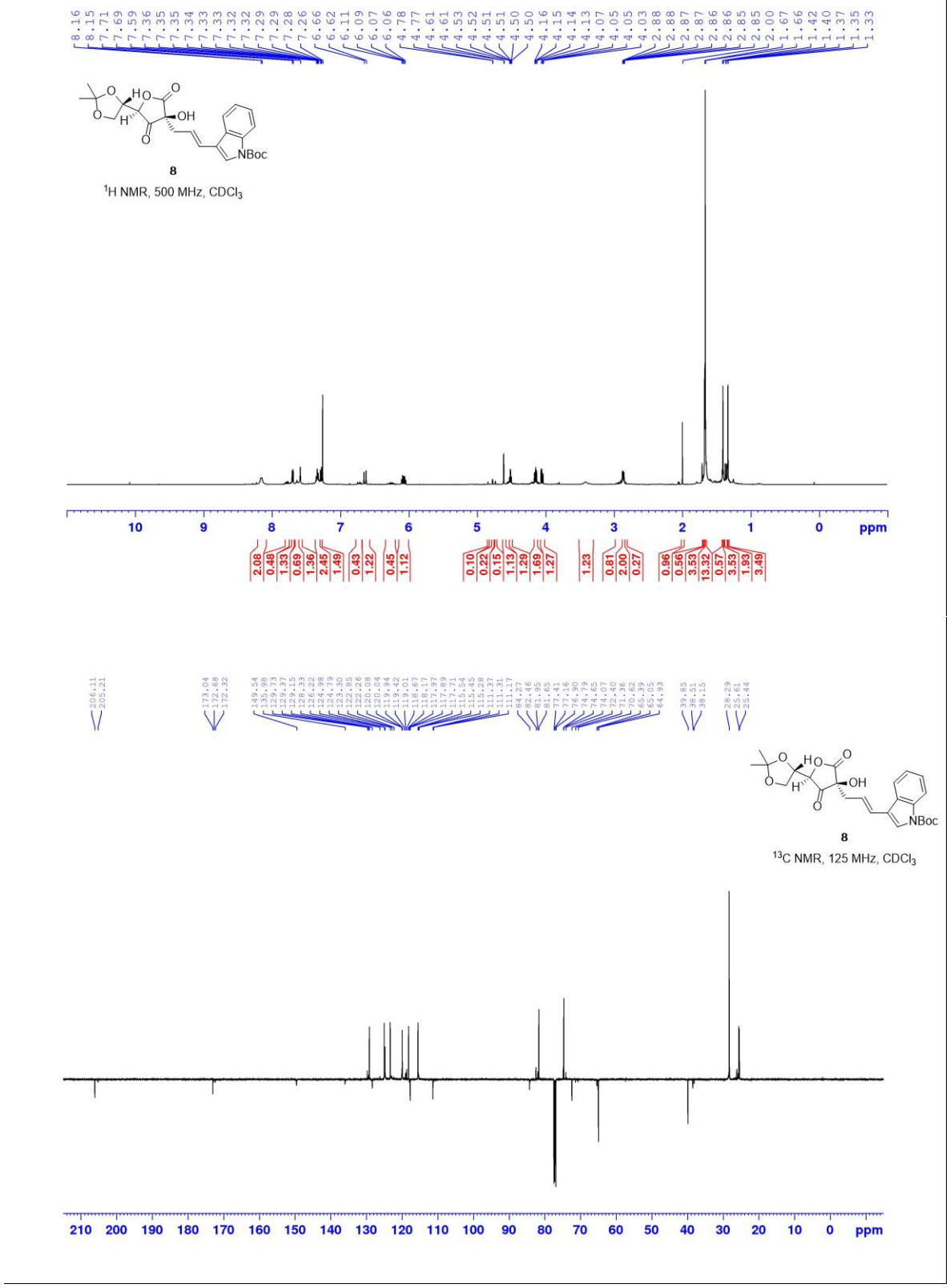

206.25
175.55
154.44
138.89
135.05
134.56
134.49
133.87
123.82
123.67
122.98
108.30
104.52
89.41
87.58
84.54
79.45
76.43
75.73
75.53
74.24
73.19
71.04
60.52
56.36
38.98
35.43
30.30
30.15
29.99
29.84
29.68
29.53
29.37
OMe
OMe
OMe
OH
OH
1e
13C NMR, 125 MHz, Acetone-d6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

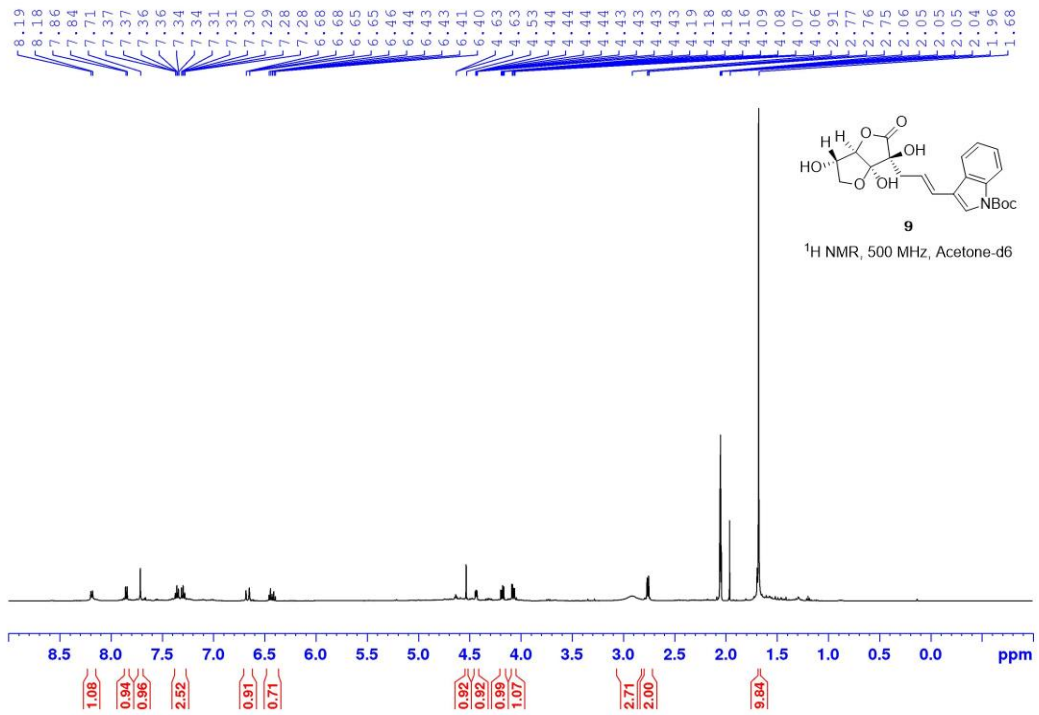

10.44
7.68
7.67
7.50
7.50
7.49
7.48
7.48
7.47
7.47
7.44
7.32
7.31
7.30
7.28
7.28
7.26
4.60
4.58
3.03
1.72
1.40
O
H
N
Boc
6
^{1}H NMR, 500 MHz, CDCl$_3$
10 9 8 7 6 5 4 3 2 1 0 ppm
0.91
0.98
1.00
1.05
0.88
1.03
0.12
0.09
8.69
0.44

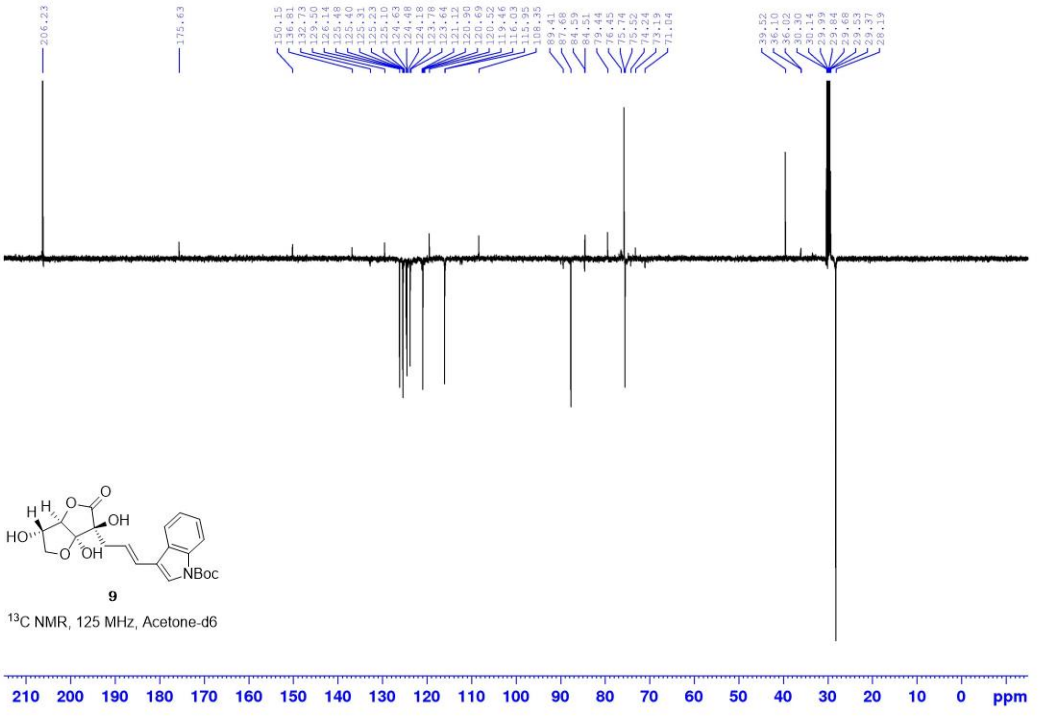

184.32
149.96
138.01
137.97
128.60
128.34
127.66
124.25
123.95
123.44
123.33
122.53
122.13
121.53
121.35
120.46
120.02
119.14
116.57
116.30
116.20
109.61
101.44
85.73
77.41
77.16
76.90
72.28
64.38
28.31
14.48
O
H
N
Boc
6
^{13}C NMR, 125 MHz, CDCl$_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

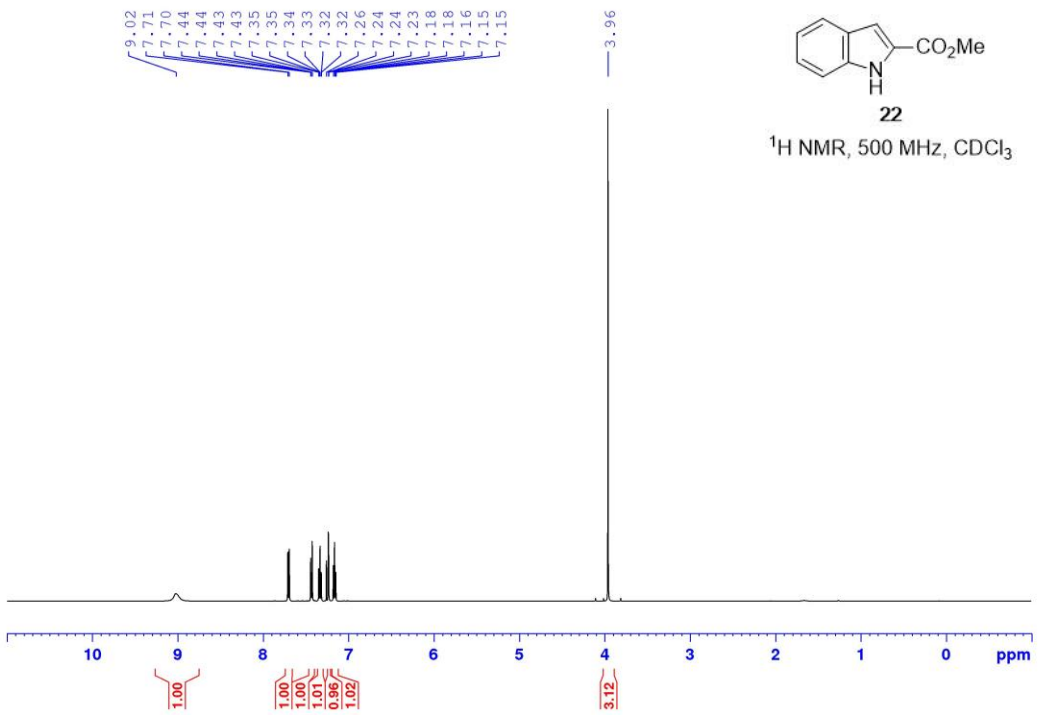

HO
N
Boc
7
1H NMR, 500 MHz, CDCl3
8.15
8.14
7.68
7.67
7.55
7.34
7.34
7.33
7.31
7.31
7.26
7.26
7.25
7.24
7.23
7.22
6.24
6.23
6.22
6.21
6.21
6.20
6.19
6.18
5.49
5.46
5.46
5.30
5.30
5.28
3.74
1.98
1.85
1.79
1.72
1.71
1.67
1.60
1.58
1.54
1.43
0.08
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.85
0.81
1.03
0.93
0.79
1.60
0.97
0.18
0.74
0.17
9.08

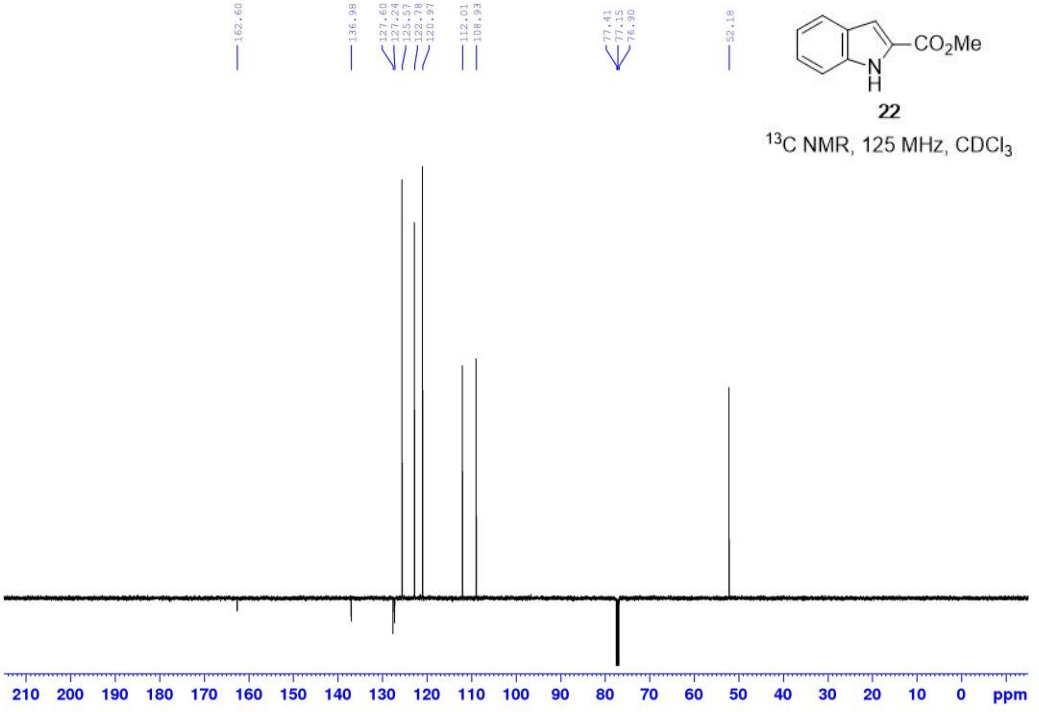

HO
N
Boc
7
13C NMR, 125 MHz, CDCl3
149.82
138.99
136.08
129.51
124.75
124.00
123.13
123.03
122.86
122.35
122.34
120.44
120.08
116.05
115.48
115.30
83.93
77.41
77.16
76.90
69.09
28.32
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

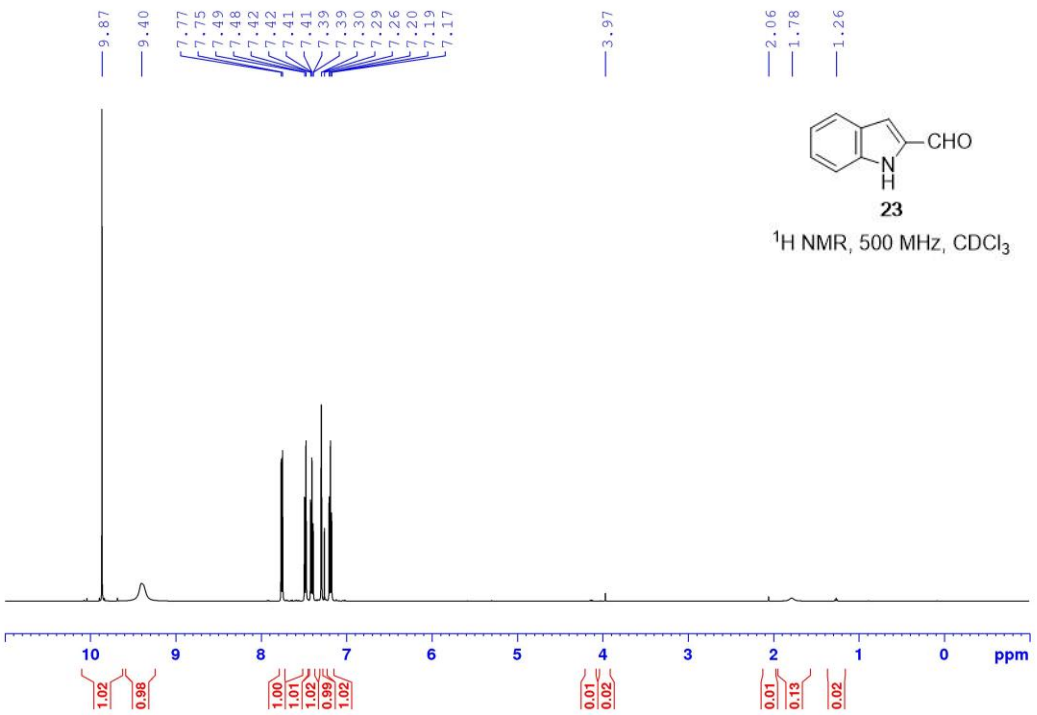

8.16
8.15
7.71
7.69
7.59
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.29
7.29
7.28
7.26
6.66
6.62
6.11
6.09
6.07
6.06
4.78
4.77
4.61
4.61
4.53
4.52
4.51
4.51
4.50
4.50
4.16
4.15
4.14
4.13
4.07
4.05
4.05
4.03
2.88
2.88
2.87
2.87
2.86
2.86
2.85
2.85
2.00
1.67
1.66
1.42
1.40
1.37
1.35
1.33
8
1H NMR, 500 MHz, CDCl3
10 9 8 7 6 5 4 3 2 1 0 ppm
2.08 0.48 1.33 0.69 1.36 2.45 1.49 0.43 1.22 0.45 1.12 0.10 0.22 0.15 1.13 1.29 1.69 1.27 1.23 0.81 2.00 0.27 0.96 0.56 3.53 13.32 0.57 3.53 1.93 3.49
206.11
205.21
173.04
172.68
172.32
149.54
135.98
129.73
129.37
129.15
128.33
126.22
124.88
124.79
123.30
122.85
122.26
120.08
120.04
119.94
119.42
119.01
118.67
118.17
117.89
117.69
117.71
115.54
115.45
115.28
111.37
111.31
111.17
84.27
82.46
81.95
81.65
81.41
77.16
76.90
74.79
74.65
74.07
72.40
71.96
70.62
65.39
65.05
64.93
39.85
38.51
38.15
28.29
25.61
25.44
8
13C NMR, 125 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


9
1H NMR, 500 MHz, Acetone-d6
ppm


9
13C NMR, 125 MHz, Acetone-d6
ppm

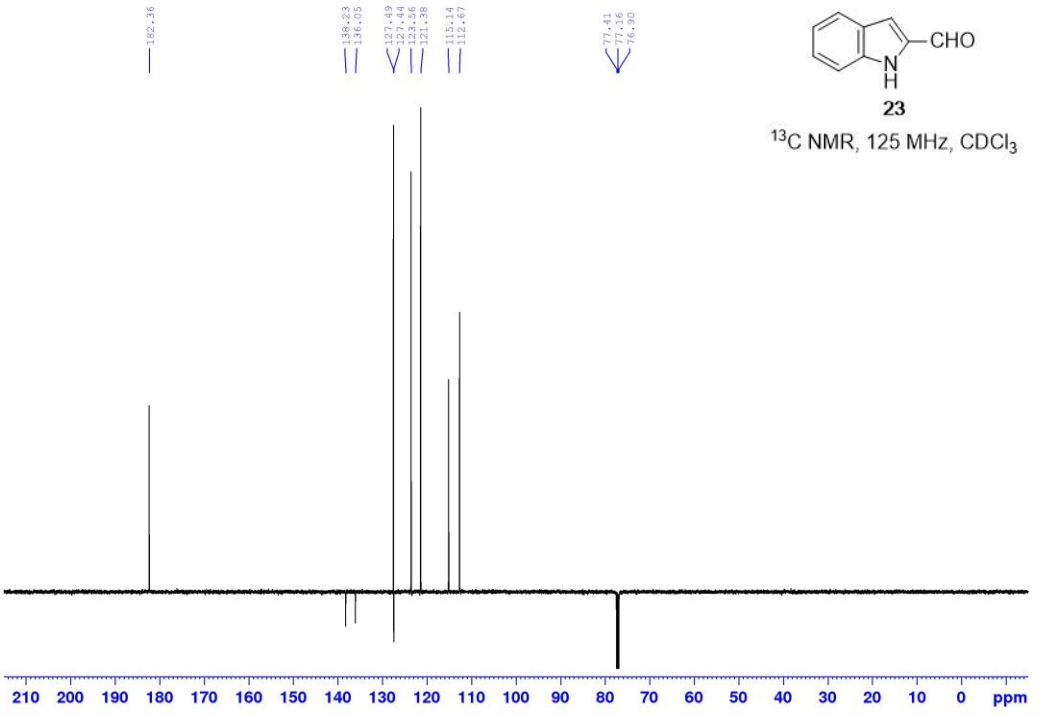

9.02
7.71
7.70
7.44
7.44
7.43
7.43
7.35
7.35
7.34
7.33
7.32
7.32
7.26
7.24
7.24
7.23
7.18
7.18
7.16
7.15
7.15
3.96
CO2Me
N
H
22
1H NMR, 500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.00
1.01
0.96
1.02
3.12


162.60
136.98
127.60
127.24
125.57
122.78
120.97
112.01
108.93
77.41
77.15
76.90
52.18
CO2Me
N
H
22
13C NMR, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



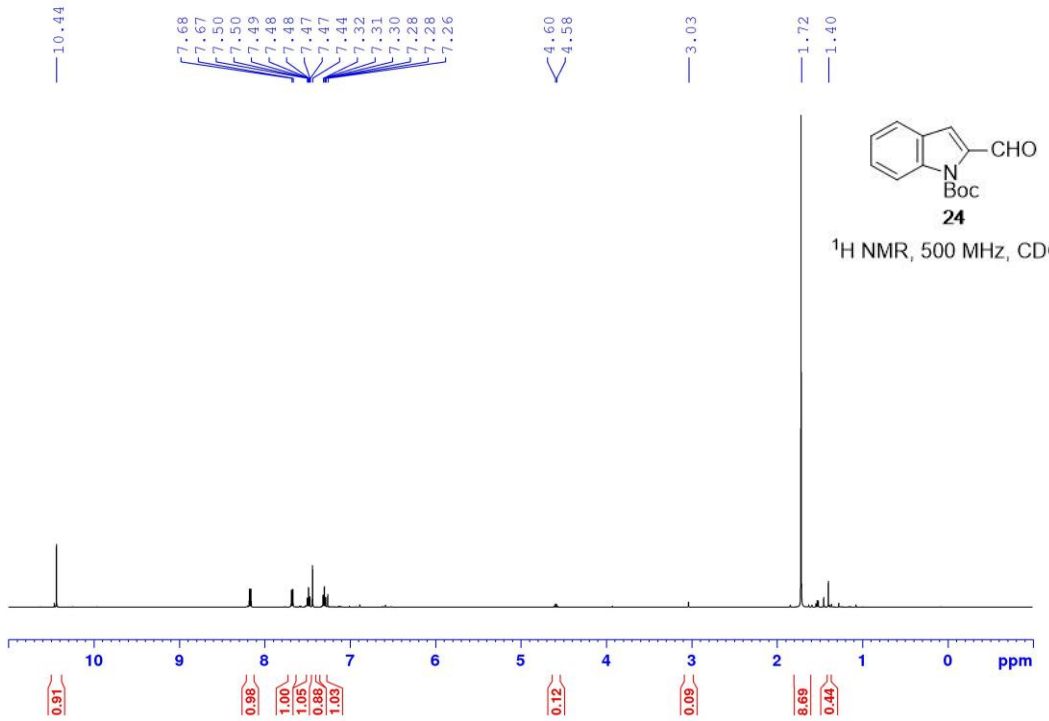
23

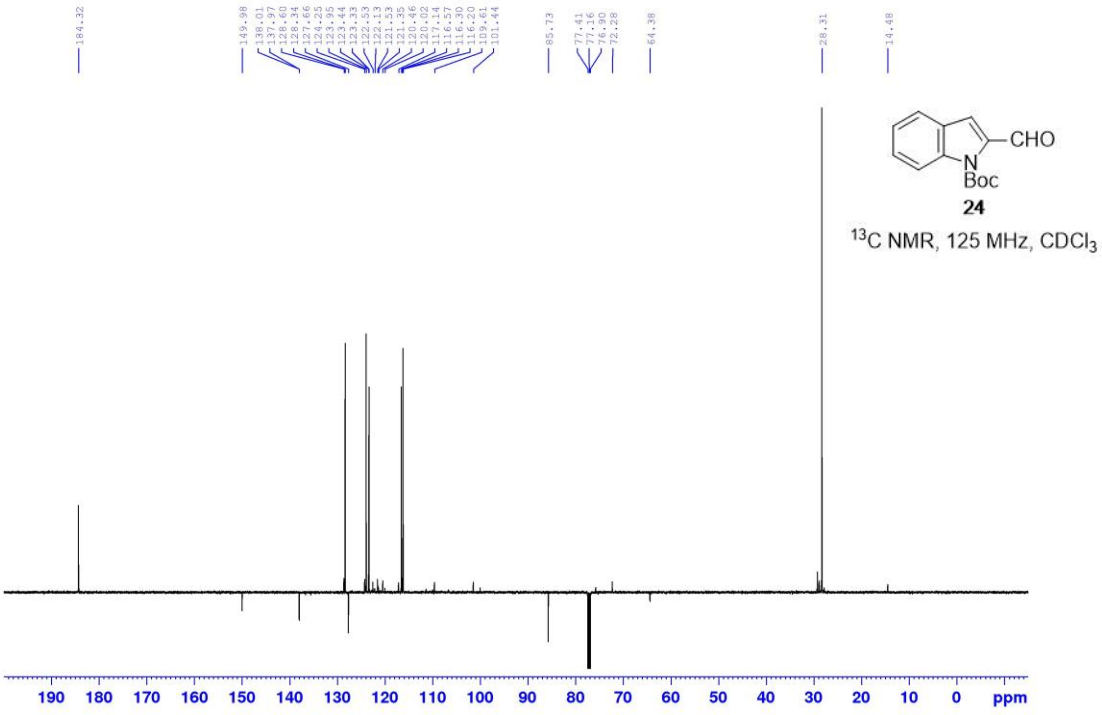
^{1}H NMR, 500 MHz, $CDCl_3$

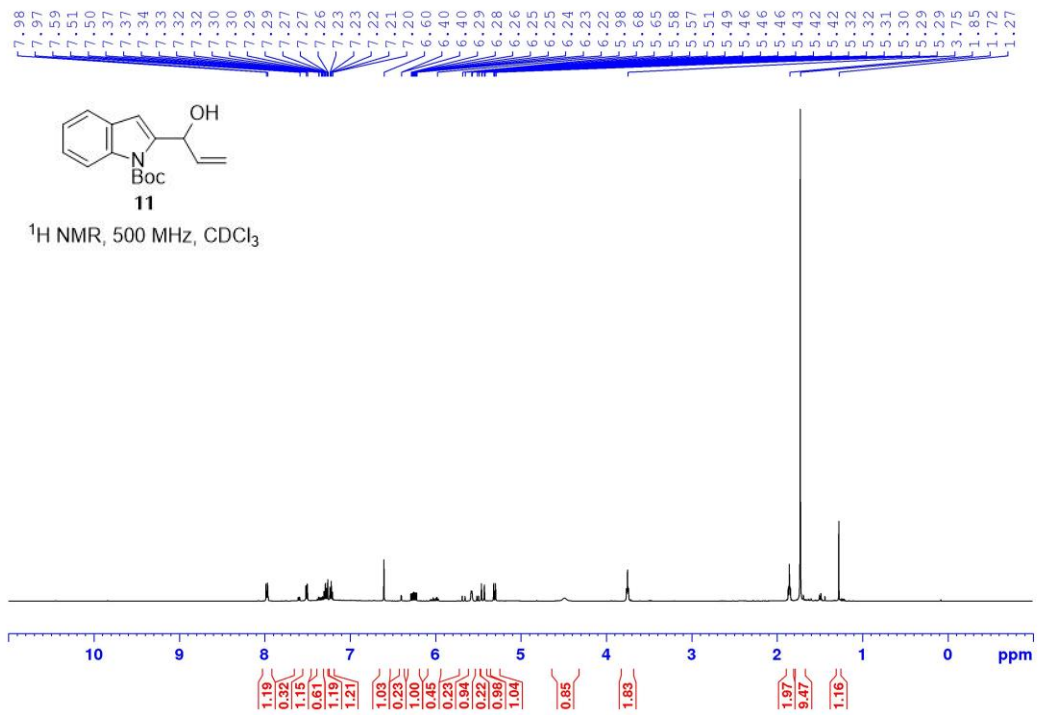


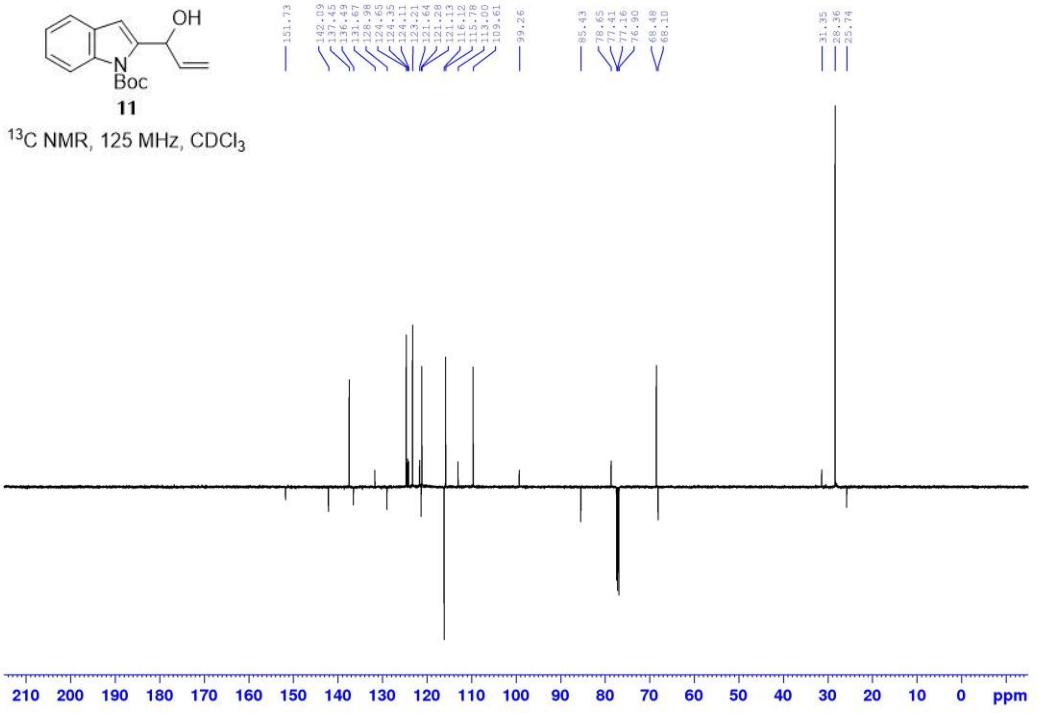
23

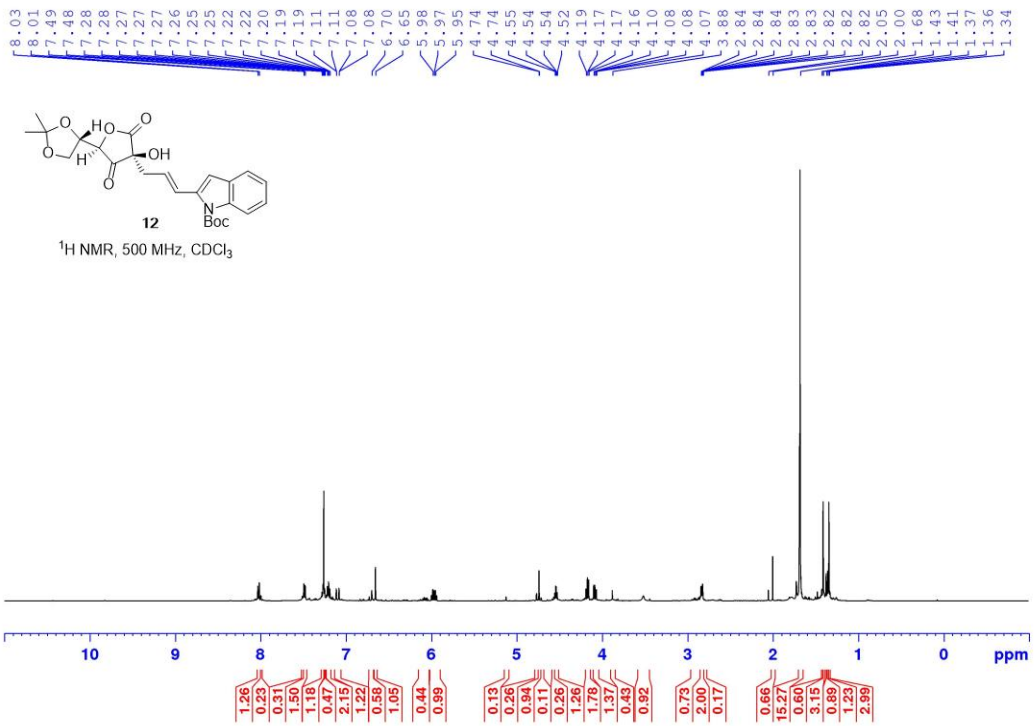
^{13}C NMR, 125 MHz, $CDCl_3$

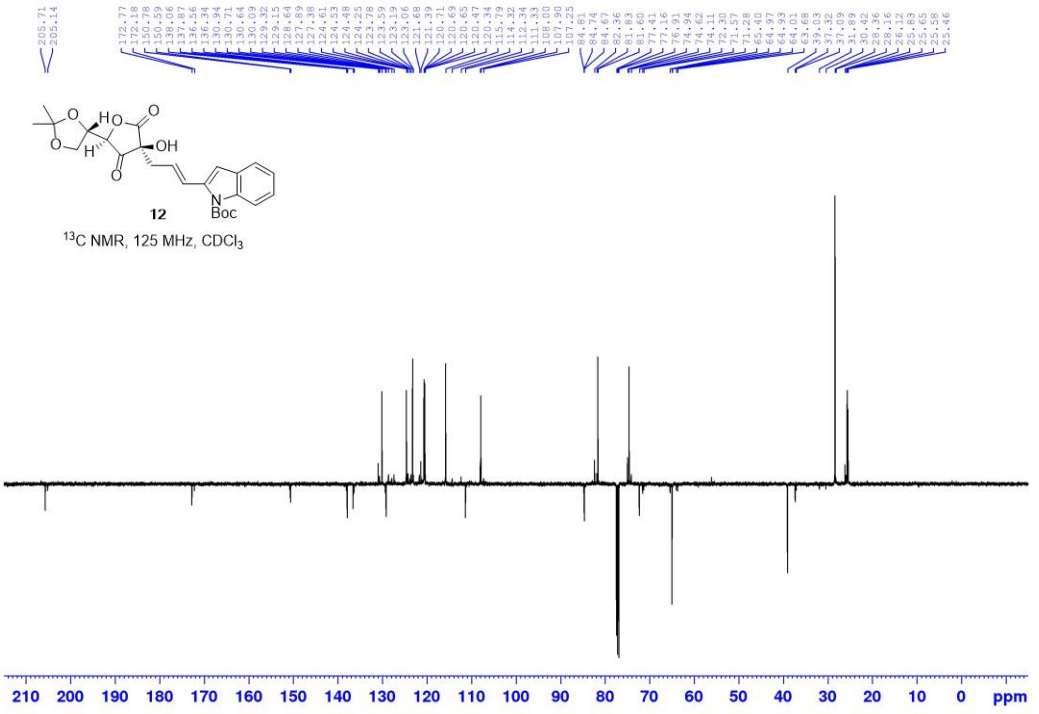

10.44
7.68
7.67
7.50
7.50
7.49
7.48
7.48
7.47
7.47
7.44
7.32
7.31
7.30
7.28
7.28
7.26
4.60
4.58
3.03
1.72
1.40
CHO
N
Boc
24
^{1}H NMR, 500 MHz, $CDCl_3$
10
9
8
7
6
5
4
3
2
1
0
ppm
0.91
0.98
1.00
1.05
0.88
1.03
0.12
0.09
8.69
0.44

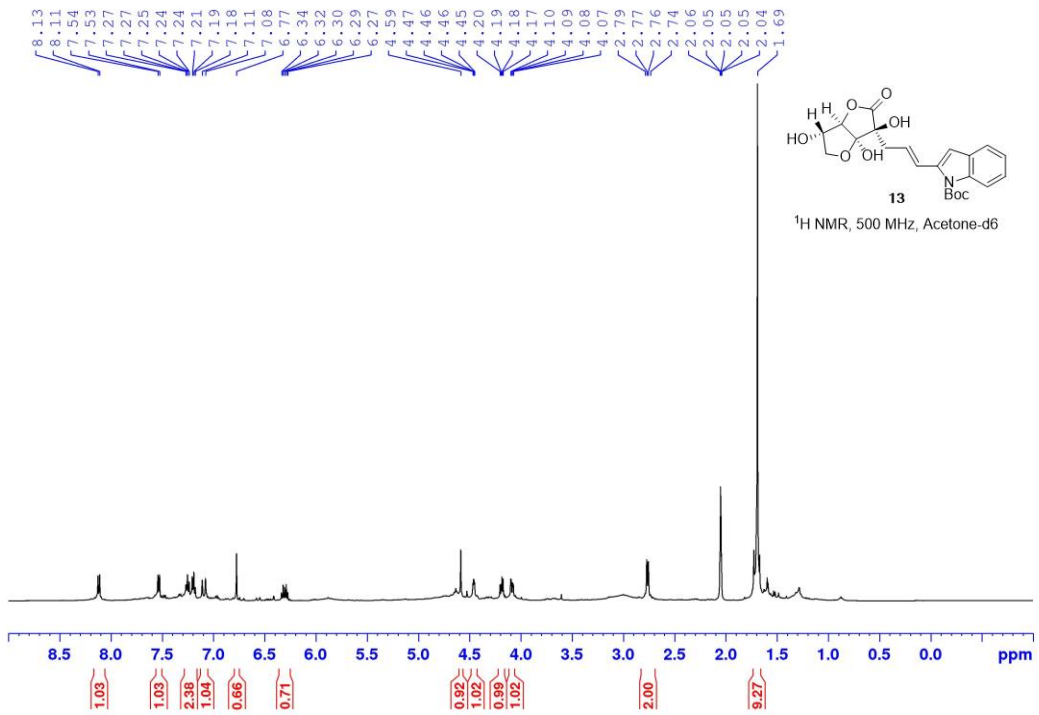

184.32
149.96
138.01
137.97
128.60
128.34
127.66
124.25
123.95
123.44
123.33
122.53
122.13
121.53
121.35
120.46
120.02
119.54
116.57
116.30
116.20
109.61
101.44
85.73
77.41
77.16
76.90
72.28
64.38
28.31
14.48
CHO
N
Boc
24
^{13}C NMR, 125 MHz, $CDCl_3$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

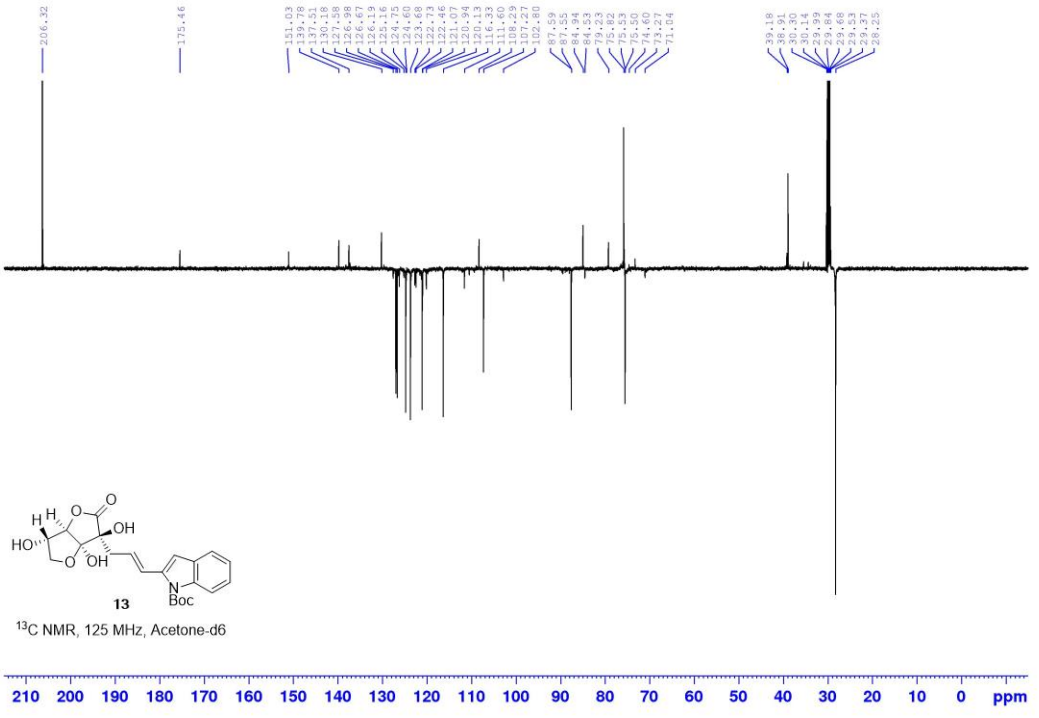

OH
N
Boc
11
1H NMR, 500 MHz, CDCl3
ppm

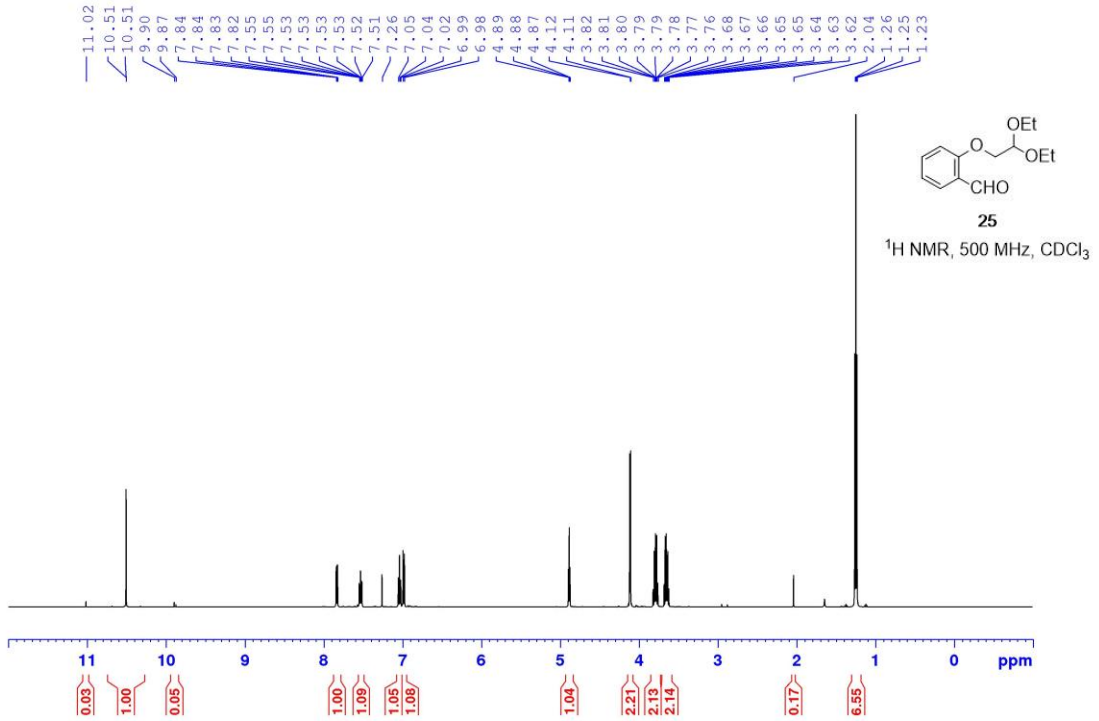

OH
N
Boc
11
13C NMR, 125 MHz, CDCl3
ppm

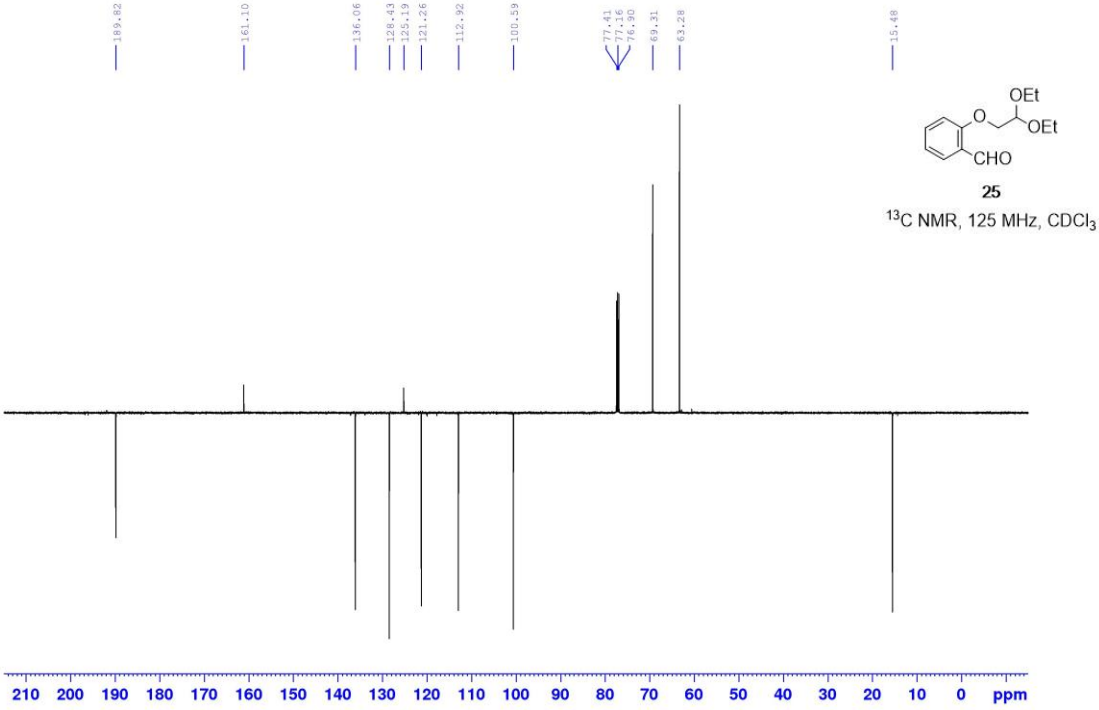

12
Boc
1H NMR, 500 MHz, CDCl3
ppm

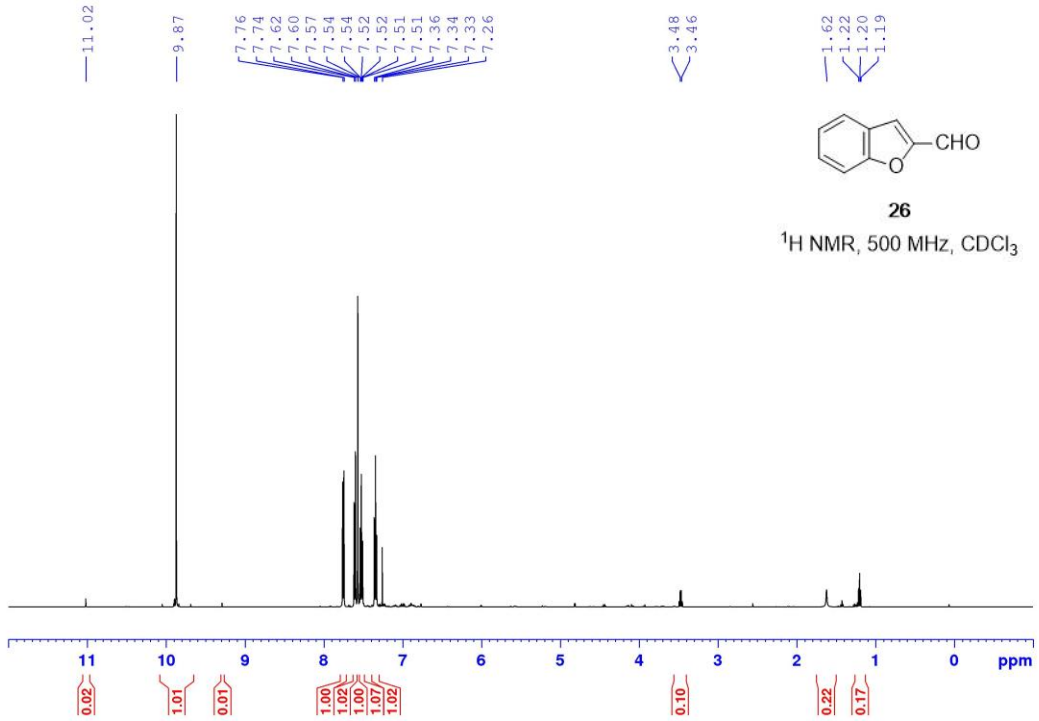

12
Boc
13C NMR, 125 MHz, CDCl3
ppm

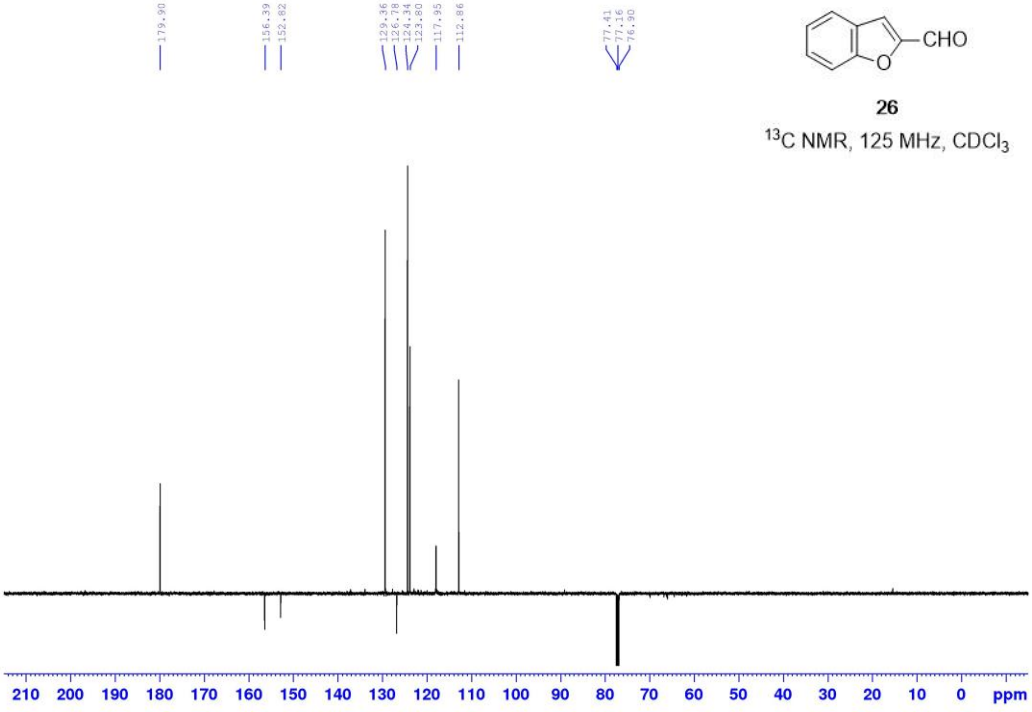

8.13
8.11
7.54
7.53
7.27
7.27
7.25
7.24
7.24
7.21
7.19
7.18
7.11
7.08
6.77
6.34
6.32
6.30
6.29
6.27
4.59
4.47
4.46
4.46
4.45
4.20
4.19
4.18
4.17
4.10
4.09
4.08
4.07
2.79
2.77
2.76
2.74
2.06
2.05
2.05
2.05
2.04
1.69
H
H
O
O
OH
HO
O
OH
N
Boc
13
1H NMR, 500 MHz, Acetone-d6
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.03
1.03
2.38
1.04
0.66
0.71
0.92
1.02
0.99
1.02
2.00
9.27

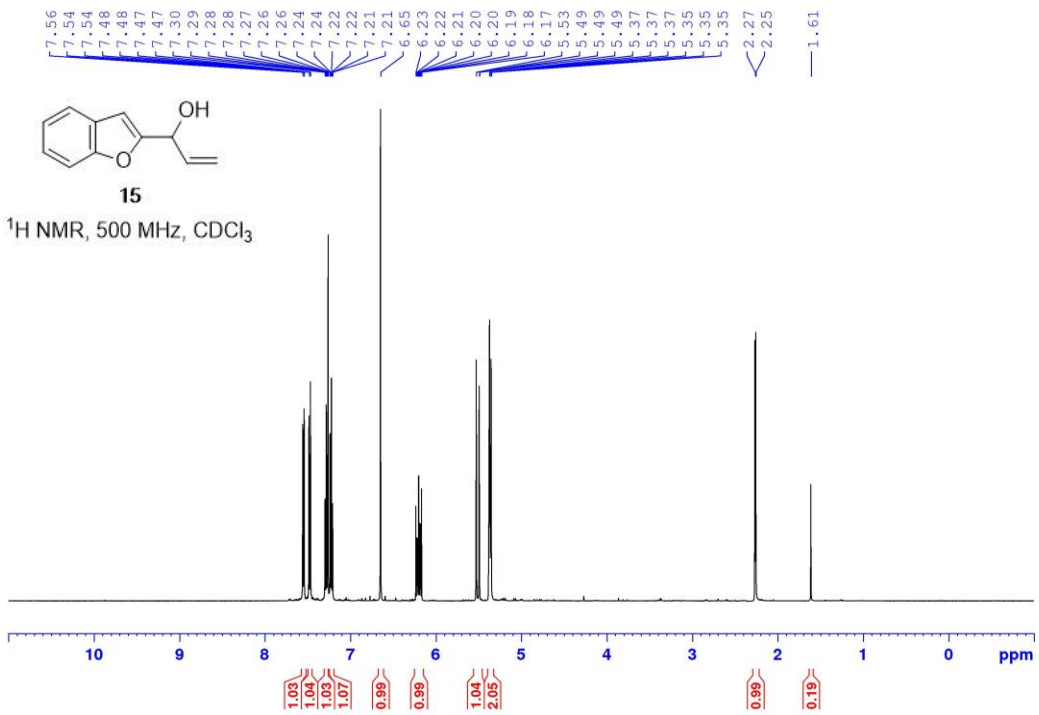

206.32
175.46
151.03
139.78
137.51
130.18
127.58
126.98
126.67
126.19
125.16
124.75
124.60
123.68
122.73
122.46
121.07
120.94
120.13
116.33
111.60
108.29
107.27
102.80
87.59
87.55
84.94
84.53
79.23
75.82
75.53
74.66
74.60
73.27
71.04
39.18
38.91
30.30
30.14
29.99
29.84
29.68
29.53
29.37
28.25
H
H
O
O
OH
HO
O
OH
N
Boc
13
13C NMR, 125 MHz, Acetone-d6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

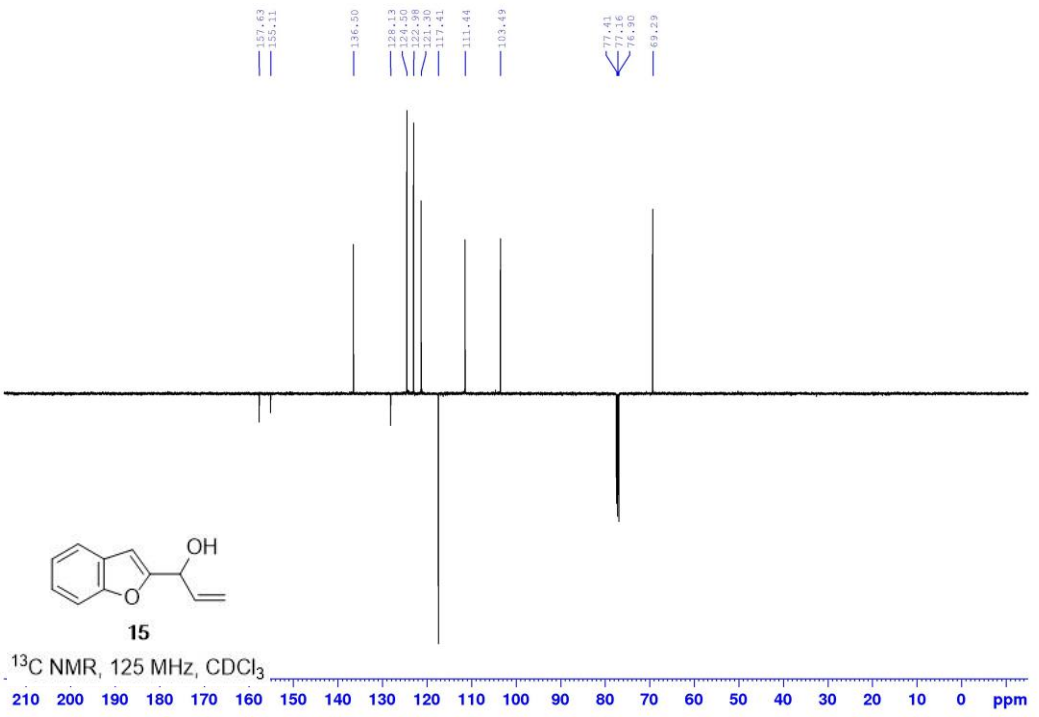

11.02
10.51
10.51
9.90
9.87
7.84
7.84
7.83
7.82
7.55
7.55
7.53
7.53
7.53
7.53
7.52
7.51
7.26
7.05
7.04
7.02
6.99
6.98
4.89
4.88
4.87
4.12
4.11
3.82
3.81
3.80
3.79
3.79
3.78
3.77
3.76
3.68
3.67
3.66
3.65
3.65
3.64
3.63
3.62
2.04
1.26
1.25
1.23
OEt
OEt
O
CHO
25
1H NMR, 500 MHz, CDCl3
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.03
1.00
0.05
1.00
1.09
1.05
1.08
1.04
2.21
2.13
2.14
0.17
6.55

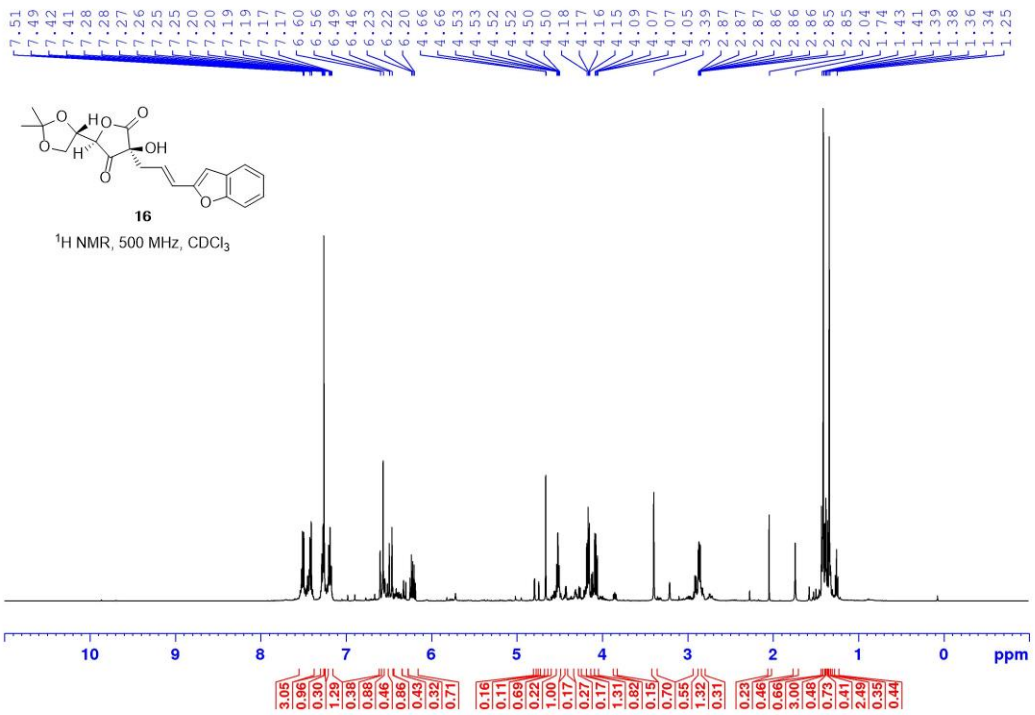

189.82
161.10
136.06
128.43
125.19
121.26
112.92
100.59
77.41
77.16
76.90
69.31
63.28
15.48
OEt
OEt
O
CHO
25
13C NMR, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

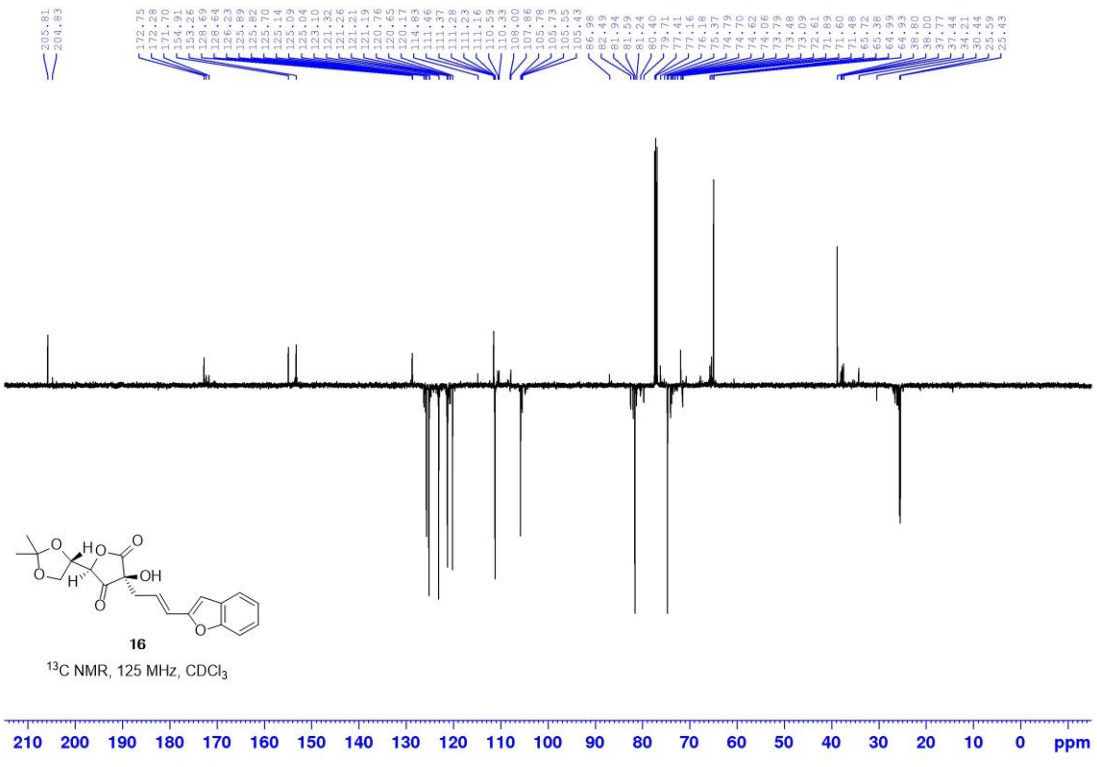

11.02
9.87
7.76
7.74
7.62
7.60
7.57
7.54
7.54
7.52
7.52
7.51
7.51
7.36
7.34
7.33
7.26
3.48
3.46
1.62
1.22
1.20
1.19
CHO
26
1H NMR, 500 MHz, CDCl3
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.02
1.01
0.01
1.00
1.02
1.00
1.07
1.02
0.10
0.22
0.17

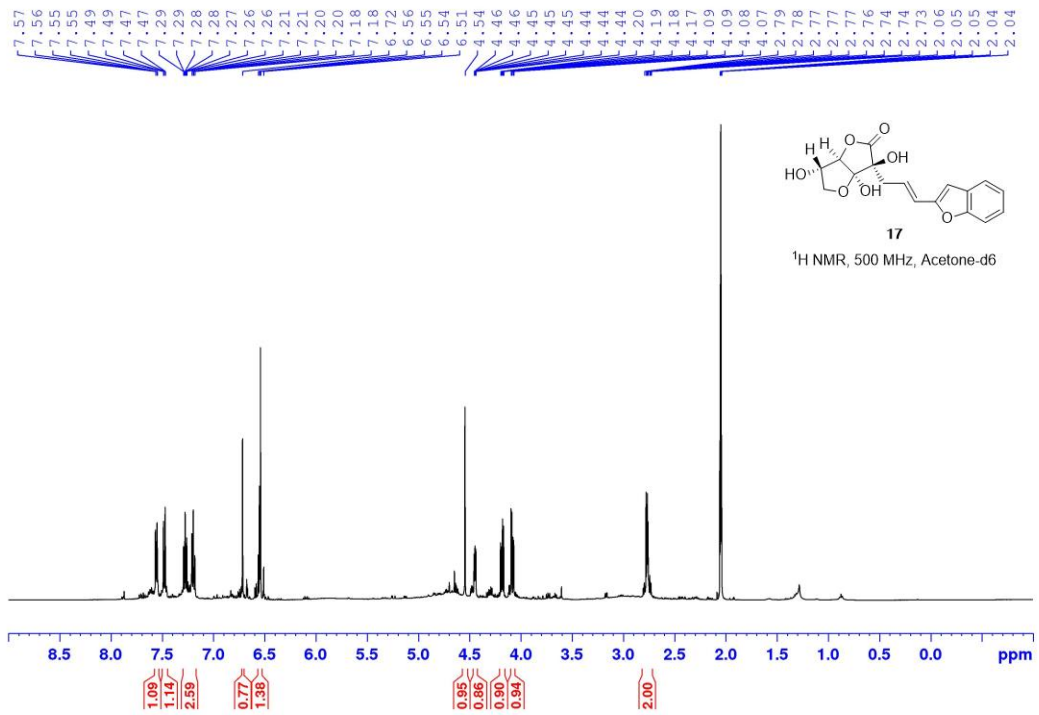

179.90
156.39
152.82
129.36
127.38
124.34
123.80
117.95
112.86
77.41
77.16
76.90
CHO
26
13C NMR, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

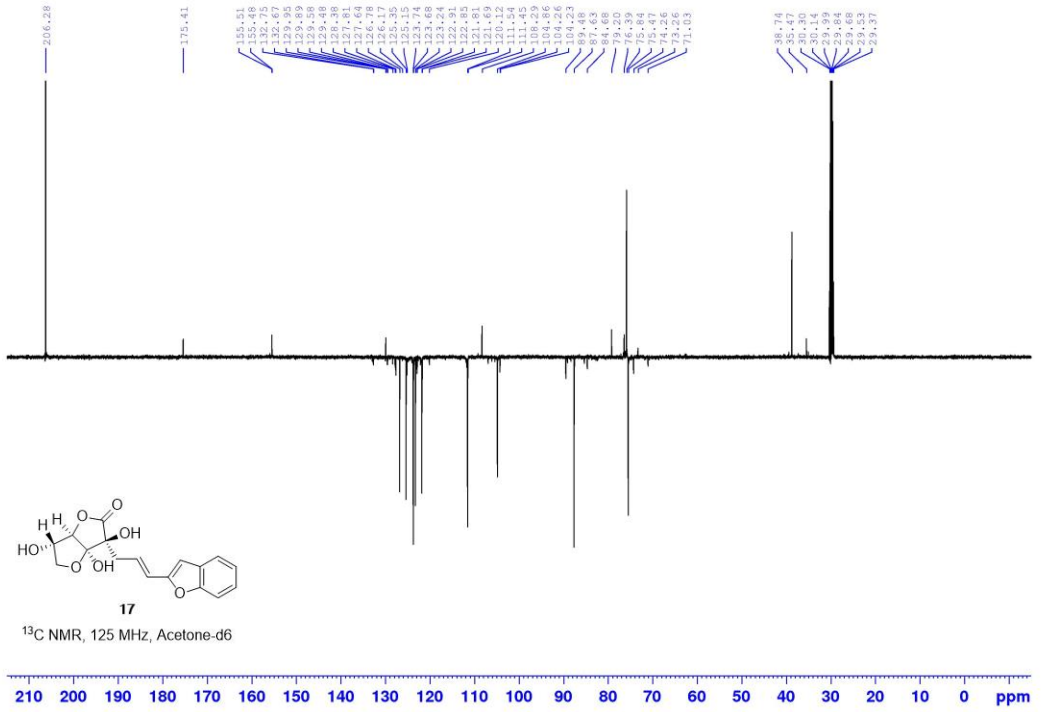

7.56
7.54
7.54
7.48
7.48
7.47
7.47
7.30
7.29
7.28
7.28
7.27
7.26
7.26
7.24
7.24
7.22
7.22
7.21
7.21
6.65
6.23
6.22
6.21
6.20
6.20
6.19
6.18
6.17
5.53
5.49
5.49
5.49
5.37
5.37
5.37
5.35
5.35
5.35
2.27
2.25
1.61
OH
O
15
1H NMR, 500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.03
1.04
1.03
1.07
0.99
0.99
1.04
2.05
0.99
0.19


157.63
155.11
136.50
128.13
124.50
122.98
121.30
117.41
111.44
103.49
77.41
77.16
76.90
69.29
OH
O
15
13C NMR, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


16
1H NMR, 500 MHz, CDCl3
ppm


16
13C NMR, 125 MHz, CDCl3
ppm


17
1H NMR, 500 MHz, Acetone-d6
ppm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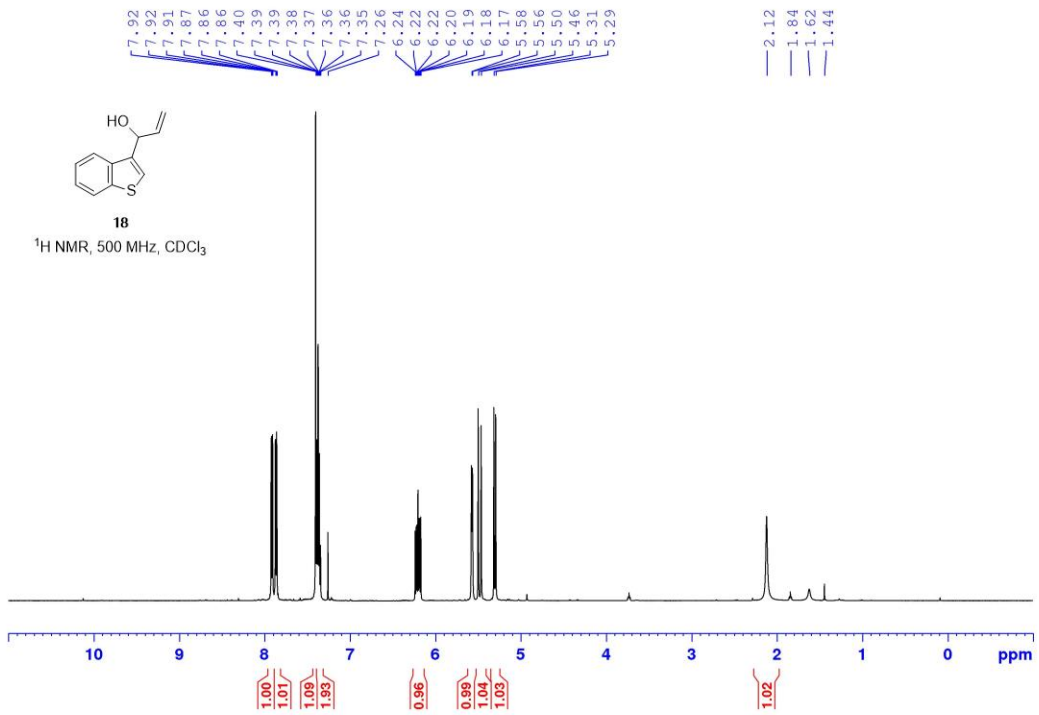
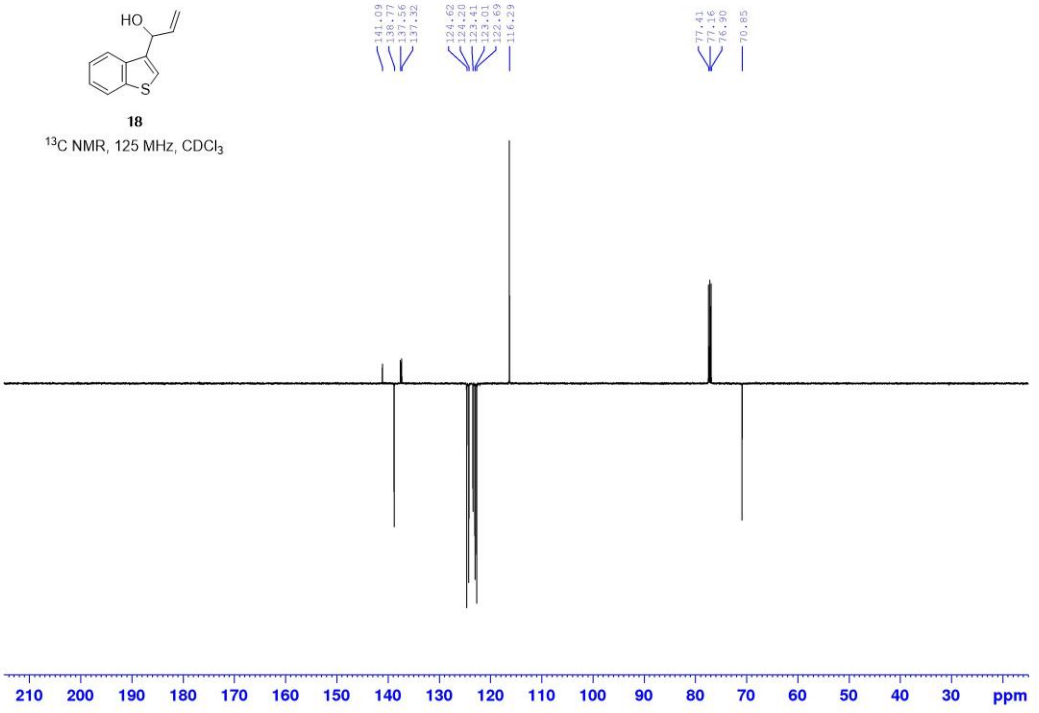
13C NMR, 125 MHz, Acetone-d6
ppm


7.92
7.92
7.91
7.87
7.86
7.86
7.40
7.39
7.39
7.38
7.37
7.36
7.36
7.35
7.26
6.24
6.22
6.22
6.20
6.19
6.18
6.17
5.58
5.56
5.50
5.46
5.31
5.29
2.12
1.84
1.62
1.44
HO
S
18
1H NMR, 500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.01
1.09
1.93
0.96
0.99
1.04
1.03
1.02


HO
S
18
13C NMR, 125 MHz, CDCl3
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138.77
137.56
137.32
124.62
124.20
123.41
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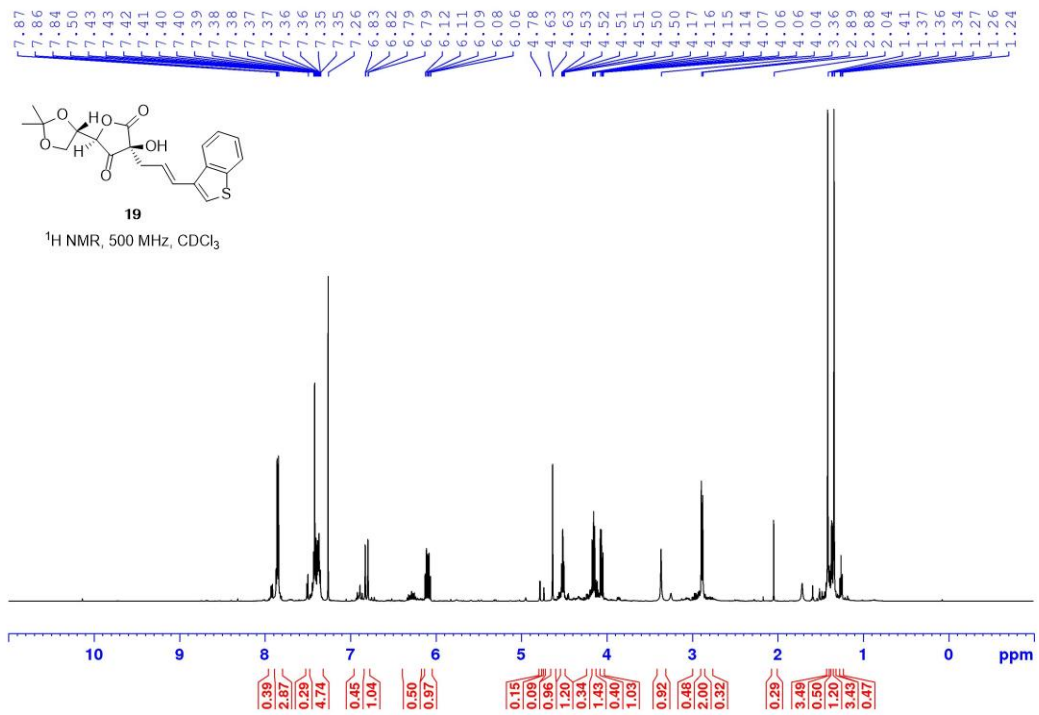
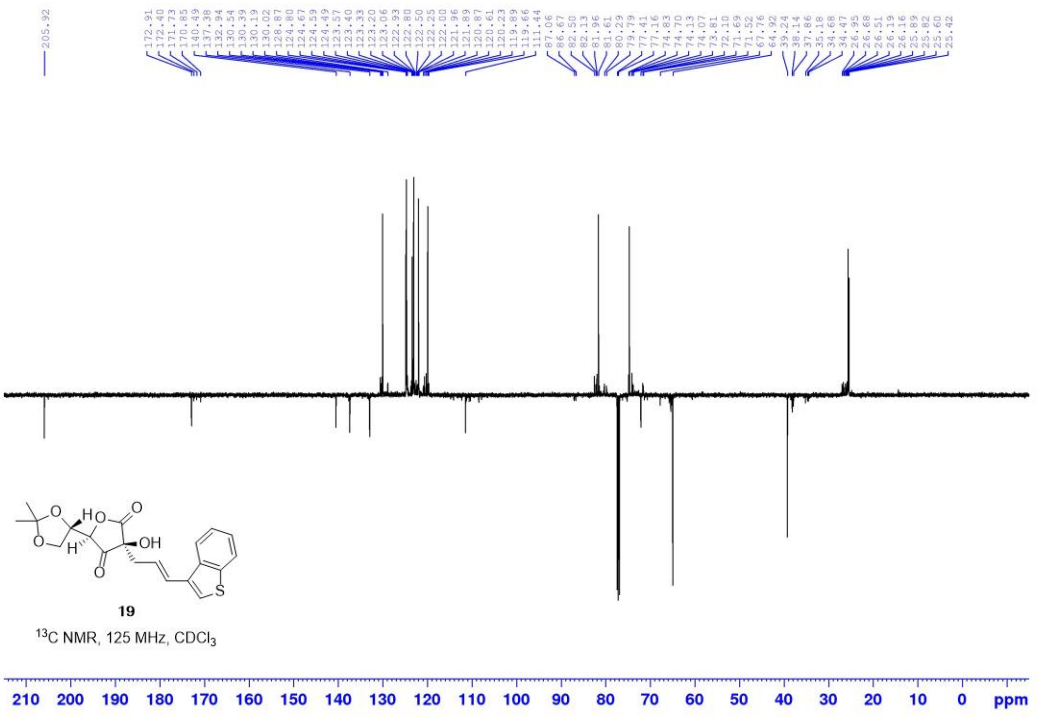
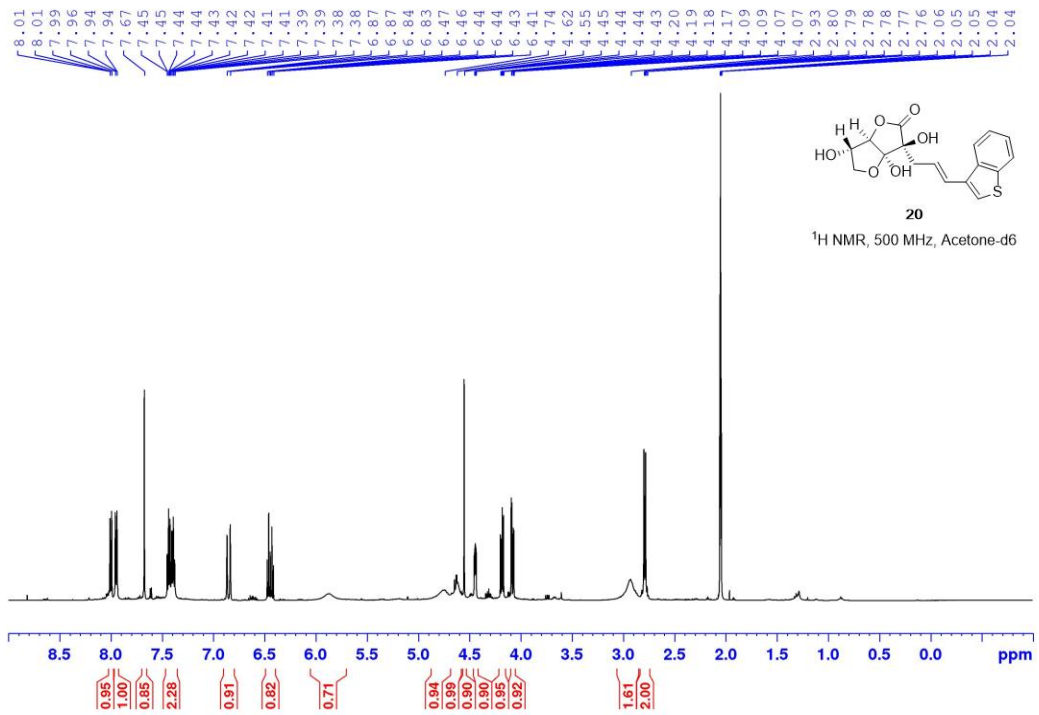
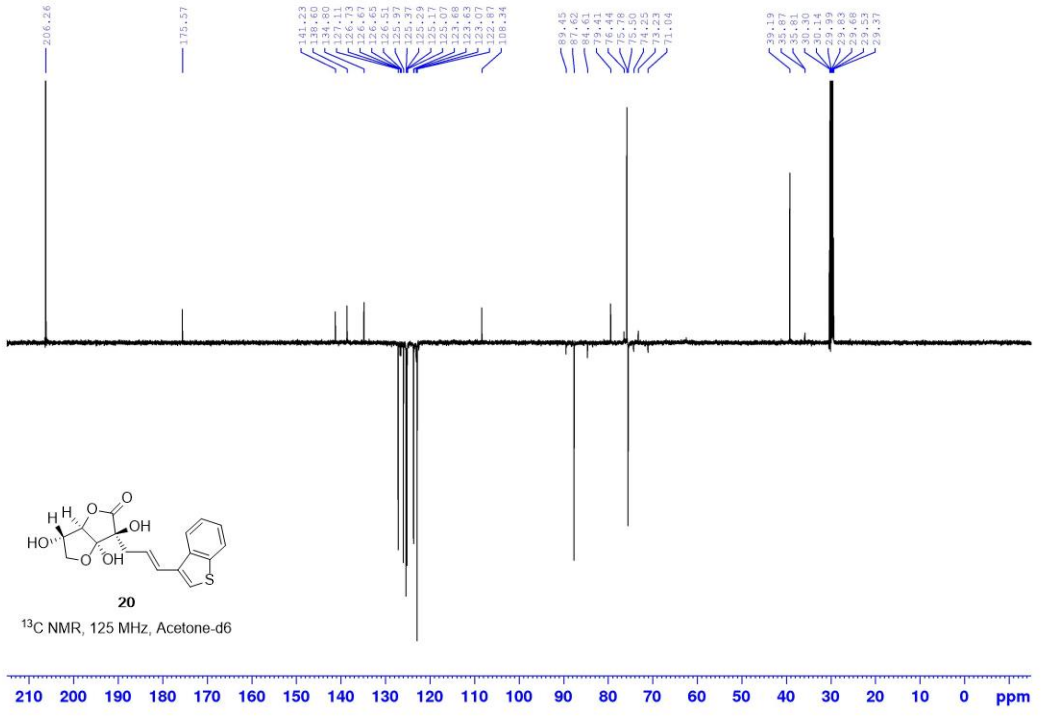
122.69
116.29
77.41
77.16
76.90
70.85
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


19
^{1}H NMR, 500 MHz, $CDCl_3$


19
^{13}C NMR, 125 MHz, $CDCl_3$


20
1H NMR, 500 MHz, Acetone-d6
ppm


20
13C NMR, 125 MHz, Acetone-d6
ppm

Antimicrobial assay

Minimum Inhibitory Concentrations (MIC) of Morinda lactone (**1a**) and derivatives were determined via serial dilution assays as described previously [25,26]. They were tested on the following organisms: *Pichia anomala, Schizosaccharomyces pombe, Mucor hiemalis, Candida albicans,* and *Rhodotulas glutinis* for fungal microorganisms; *Bacillus subtilis, Staphyloccocus aureus* and *Mycobacterium smegmatis* for Gram-positive bacteria, *Acinetobacter baumannii*, *Chromobacterium violaceum, Escherichia coli* and *Pseudomonas aeruginosa* for Gram-negative bacteria.

Table S2. Antimicrobial activity of morinda lactone (**1a**) and derivatives **1b-e**, **9**, **13**, **17**, and **20**.

		MIC [µg/mL]									
organisms	**Strain No.**	**1a**	**1b**	**1c**	**1d**	**1e**	**9**	**13**	**17**	**20**	**Reference**
Bacteria											
B. subtilis	DSM 10	–	–	–	–	–	–	–	–	–	8.3[a]
S. aureus	DSM 346	–	–	–	–	–	–	66.6	–	–	1.7[a]
M. smegmatis	ATCC 700084	–	–	–	–	–	66.6	–	–	–	1.7[b]
A. baumannii	DSM 30008	–	–	–	–	–	–	–	–	–	0.3[c]
C. violaceum	DSM 30191	–	–	–	–	–	–	–	–	–	0.8[a]
E. coli	DSM 1116	–	–	–	–	–	–	–	–	–	1.7[a]
P. aeruginosa	PA14	–	–	–	–	–	–	–	–	–	0.1[d]
Fungi											
M. hiemalis	DSM 2656	66.6	66.6	66.6	66.6	–	–	66.6	–	–	4.2[e]
P. anomala	DSM 6766	–	–	–	–	–	–	–	–	–	8.3[e]
R. glutinis	DSM 10134	–	–	–	–	–	–	–	–	–	4.2[e]
C. albicans	DSM 1665	–	–	–	–	–	–	–	–	–	8.3[e]
S. pombe	DSM 70572	–	–	–	–	–	–	–	–	–	4.2[e]

References: [a] oxytetracycline, [b] kanamycin, [c] ciprobay, [d] gentamicin, [e] nystatin; – : not active.

Biofilm inhibition assay

Staphylococcus aureus DSM 1104 (from stock at –20 °C) was incubated in 25 mL casein-peptone soymeal-peptone (CASO) medium at 37 °C on a rotary shaker (100 rpm) for 18 h. The OD_{600} of the culture solution was adjusted to match the turbidity of a 0.001 McFarland standard. 150 µL of CASO with 4% glucose broth was added together with the serially diluted compounds (250 – 2 µg/mL) and incubated in 96 well microtiter plates (TPP tissue culture ref. no 92196) at 37 °C for 18 h. The anti-biofilm activity was assessed via 0.1% crystal violet staining (Thermo Fisher, Waltham, USA) following protocols established previously [27,28]. Briefly, the supernatant was discarded, the biofilm was stained at room temperature for 15 min and then washed thrice with PBS (phosphate-buffered saline) buffer. The dye together with biofilm was dissolved in acetic acid (30%), and the absorbance was determined with a plate reader (Synergy 2, BioTek, Santa Clara, USA) at 530 nm. Methanol (2.5%) was employed as a negative control and microporenic acid A [27] (250-0.2 µg/mL) as positive control.

P. aeruginosa (PA 14) DSM 19882 was precultured in 25 mL LB medium (Luria-Bertani Broth) with a 250 mL flask at 37 °C with shaking 100 rpm overnight. The OD_{600} of the suspended solution

was measured and adjusted to 0.1 McFarland standard in M63 medium, which is supplemented with magnesium sulfate, glucose and casamino acids as previously described. The compounds were added into 150 µL bacterial solution at the concentration (250–2 µg/mL) then the solution was added in U-bottom 96 well plate (Falcon non-tissue plate with U-Bottom ref.no 351177). The plates were incubated at 37 °C at 150 rpm for 24 h and biofilms were established at the air liquid interface. The plates were rinsed once by using PBS buffer, the biofilms were stained by 150 µL 0.1% CV at room temperature for 15 min and then rinsed two times by using PBS buffer. The absorbance was quantified with the plate reader (Synergy 2, BioTek, Santa Clara, USA) at 550 nm using ethanol (95%). Methanol (2.5 %) and Myxovalargin A (250–2 µg/mL) were used as negative control and positive control, respectively.

Biofilm dispersion assay

A cell suspension of *Staphylococcus aureus* strain DSM 1104 was adjusted to match the turbidity of a 0.001 McFarland standard. It was incubated in 96 well tissue microtiter plates for 18 h in CASO with 4% glucose broth. The supernatant was removed from and the wells were washed with 150 µL PBS buffer, then 150 µL of the fresh media (CASO with 4% glucose broth) was added together with the serially diluted compounds (250 – 2 µg/mL) to the wells. The plates were incubated at 37 °C for a further 24 h. Staining of the preformed biofilms and controls was carried out as described above for the biofilm inhibition [28].

Candida albicans DSM 11225 was grown in 25 mL Yeast extract Peptone Dextrose (YPED) medium in a 250 mL flask at 30 °C in a shaker (100 rpm) for 18 h. The OD_{600} of the bacterial suspension was adjusted to 0.05 McFarland standard in RPMI 1640 medium. The 150 µL bacterial solution was added to 96 well non-tissue microtiter plates (Falcon non-tissue plate ref.no 351172) at 37 °C (150 rpm). After 90 min incubation, the supernatant was discarded and the wells rinsed twice with PBS buffer. Compounds were serially diluted in 150 µL of fresh media (RPMI 1640) at concentrations ranging from 250–2 µg/mL and added to the wells of 96 wells plates. Methanol (2.5%) and farnesol (250–2 µg/mL) were used as a negative and positive control, respectively. The plates were incubated at 37 °C and 150 rpm for a further 24 h. The supernatant was removed and washed by PBS buffer. Biofilms were stained by 150 µL 0.1% CV for 25 min at room temperature. The plates were washed four times with PBS buffer and 150 µL ethanol (95%) was added to wells to dissolve the biofilms. The absorbance was measured with a plate reader (Synergy 2, BioTek, Santa Clara, USA) at 610 nm. SD of two repeats with duplicates each were 10% or less [28].

Table S3. Antibiofilm effects of morinda lactone (**1a**) and derivatives **1b-e**, **9**, **13**, **17**, and **20**

Cmpd	Biofilm inhibition (*S. aureus*)[a] [% ± SD]	Biofilm dispersion (*S. aureus*)[b] [% ± SD]	Biofilm dispersion (*C. albicans*)[c] [% ± SD]
1a	-	-	52±10 (250 µg/mL)
1b	26±9 (250 µg/mL)	-	59±6 (250 µg/mL)
1c	65±10 (250 µg/mL)	-	64±5 (250 µg/mL)
1d	-	-	63±6 (250 µg/mL)
1e	-	-	73±9 (250 µg/mL)
			35±3 (31.3 µg/mL)
9	80±4 (250 µg/mL)	50±8 (250 µg/mL)	86±5 (250 µg/mL)
	57±4 (125 µg/mL)		66±5 (62.5 µg/mL)
			21±4 (15.6 µg/mL)
13	72±9 (250 µg/mL)* 21±10 (125 µg/mL)*	24±4 (250 µg/mL)*	77±2 (250 µg/mL)
			42±8 (31.3 µg/mL)
17	79±2 (250 µg/mL)	50±7 (250 µg/mL)	80±6 (250 µg/mL)
	28±8 (125 µg/mL)		57±8 (62.5 µg/mL)
			23±8 (15.6 µg/mL)
20	80±6 (250 µg/mL)	-	-
	23±2 (61.5 µg/mL)		
(-) no activity, SD: standard deviation			

References [%]: [a] microporenic acid A (MAA): 82 ± 6 (250 µg/mL), 79 ± 10(7.8 µg/mL), 25 ± 9 (3.9 µg/mL); [b] microporenic acid A (MAA): 50 ± 10 (250 µg/mL), 29 ± 10 (15.6 µg/mL); [c] farnesol: 75 ± 6 (250 µg/mL), 62 ± 10 (31.3 µg/mL), 50 ± 10 (15.6 µg/mL); *activity below MIC values.

Cytotoxicity assay

The evaluation of in *vitro* cytotoxicity (IC_{50}) of the isolated compounds was performed with mouse fibroblast cell line L929 (ACC2) and mammalian HeLa KB3.1 (ACC158) cancer cells. Therefore, compounds **1a-1e, 9, 13, 17,** and **20** were tested as previously described [16]. 6×10^3 cells/well were selected in 96-well microtiter plates. The compounds were dissolved in MeOH (1 mg/mL) which was used as negative control in this study; epothilon B (1 mg/mL) was used as positive control. The cell lines were incubated with a serial dilution of the test compounds (final range from 37 to 0.6 x 10^{-3} µg/mL) for five days. Afterwards, they were dyed using 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT), which is only converted to its purple formazan derivative by living cells. To calculate the percentage of cell viability, absorption at 595 nm was measured using a microplate reader. Results were expressed as IC_{50}, the half maximal inhibitory concentration (µM).

Table S4. Cytotoxicity of morinda lactone (**1a**) and derivatives **1b-e**, **9**, **13**, **17**, and **20**.

	IC50 [µg/ml]			
	L929 (ACC2)	Tox.Nr.	KB3.1 (ACC158)	Tox-Nr.
1a	68	**3640**	–	**3630**
1b	–	**3639**	–	**3633**
1c	–	**3640**	–	**3630**
1d	–	**3639**	–	**3633**
1e	–	**3638**	–	**3634**
9	–	**3638**	76	**3634**
13	–	**3637**	67	**3631**
17	–	**3637**	–	**3631**
20	–	**3635**	75	**3632**
Epo B	0.00024	**3483**	0.000017	**3485**

References: Epo B: epothilon B; – : not active.

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