Supplementary Information for

Total Synthesis of Diplofuranone A and Diapolic Acid A

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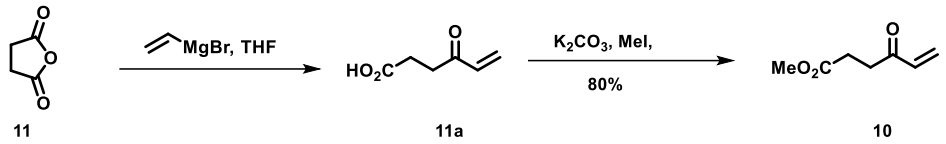
Contents:

1. General Information

General Aspects: Experiments involving moisture andair sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification unless otherwise noted. Yields refer to chromatographically pure compounds, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as a visualizing agent and an p-anisaldehyde or ninhydrin stain, and heat as developing agents. Merck silica gel (particle size 100-200 and 230-400 mesh) was used for flash column chromatography. Neat compounds were used for record IR spectra. NMR spectra were recorded on either a BrukerAvance 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), BrukerAvance 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz), or JEOL DELTA (ECX) 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz). Mass spectrometric data were obtained using WATERS-Q-Tof-Premier-HAB213 and WATERS-QTof-Premier-APCI-MS instruments and IR data recorded from PerkinElmer, FT-IR spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, mspt= septet, dd = doublet of doublet, ddd = doublet of a doublet of a doublet, dt = doublet of a triplet, td = triplet of a doublet, m = multiplet, br = broad.

2. Synthesis of Diplofuranone A, 1

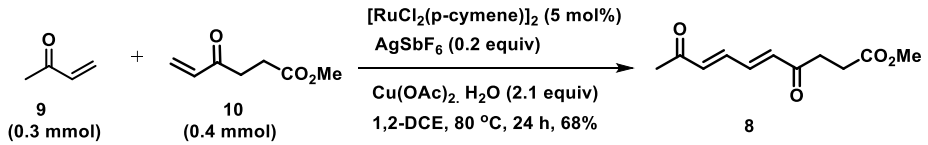
Synthesis of Compound 10:



To a magnetically stirred solution of compound **11** (1.25 g, 12.5mmol, 1.0 equiv.) in dry THF (15 ml) at -78°C was added vinyl magnesium bromide (13.70 ml, 1.0 M in THF, 13.7 mmol, 1.1 equiv.) dropwise. After 30 min, the reaction mixture was quenched by saturated ammonium chloride and mixture was extracted with EtOAc (3 x 20 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated the crude compound which was quickly purified via silica gel column chromatography to give **11a** (960 mg, 7.5 mmol, 60%) and used for the next step.

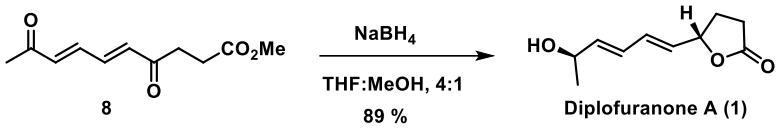
To a stirred solution of compound **11a** (960 mg, 7.5 mmol, 1.0 equiv.) in acetone (8 ml) were added sequentially K_2CO_3 (1.12g, 8.25 mmol, 1.1 equiv) and MeI (0.6 ml, 9.75 mmol, 1.3 equiv) at 0 °C. The resulting mixture was stirred at room temperature for 4 h. Then acetone was removed under reduced pressure, and the mixture was diluted with ethyl acetate, filtered and concentrated to give the crude compound which was directly purified by column chromatography using 5% EtOAc in pet ether to afford compound **10** as a pale yellow liquid (853 mg, 6.0mmol, 80%). **IR** (neat): ν_{max}/cm^{-1} 2986, 2305, 1734, 1682, 1585, 1422, 1265, 1043, 909. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 17.7, 10.4 Hz, 1H), 6.26 (dd, *J* = 17.6, 0.9 Hz, 1H), 5.87 (dd, *J* = 10.4, 1.0 Hz, 1H), 3.68 (s, 3H), 2.92 (t, *J* = 6.7 Hz, 2H), 2.64 (t, *J* = 6.7 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.61, 173.34, 136.25, 128.71, 51.93, 34.19, 27.71. **HRMS** (APCI-TOF) m/z calcd. for $C_7H_{11}O_3$ $[M+H]^+$: 143.0708; found 143.0710

Synthesis of compound 8:



A 5 mL screw-cap vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (21.45 mg, 0.035 mmol, 5.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ (292 mg, 1.47 mmol, 2.1 equiv), $AgSbF_6$ (48 mg, 0.14 mmol, 20 mol%) and 1,2-dichloroethane (5 mL). The vial was sealed under nitrogen and allowed to stir at room temperature under nitrogen atmosphere for 10 minutes. To this, vinyl ketone **10** (100mg, 0.70 mmol, 1.0 equiv) and methyl vinyl ketone **9** (0.09 ml, 1.05 mmol, 1.5 equiv) were added into the solution in sequence via syringe. Then the reaction mixture was heated to 80 °C (using an oil bath) with stirring for 24 h. After cooling down, the mixture was diluted with ethyl acetate, filtered and concentrated to give the crude compound which was directly purified by column chromatography using 10% EtOAc in pet ether to afford compound **8** as a brown liquid (99 mg, 0.47 mmol, 68%) and 10% homodimer of methyl vinyl ketone **9**. **IR** (neat): ν_{max}/cm^{-1} 2924, 2854, 1737, 1670, 1589, 1359, 1255, 1002, 802. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 - 7.07 (m, 2H), 6.48 (dd, *J* = 19.5, 15.1 Hz, 2H), 3.68 (s, 3H), 2.93 (t, *J* = 6.5 Hz, 2H), 2.66 (t, *J* = 6.6 Hz, 2H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.81, 197.62, 173.19, 139.64, 139.38, 137.06, 135.66, 52.00, 35.68, 28.00, 27.78. **HRMS** (APCI-TOF) m/z calcd. for $C_{11}H_{15}O_4$ $[M+H]^+$: 211.0970; found 211.0962.

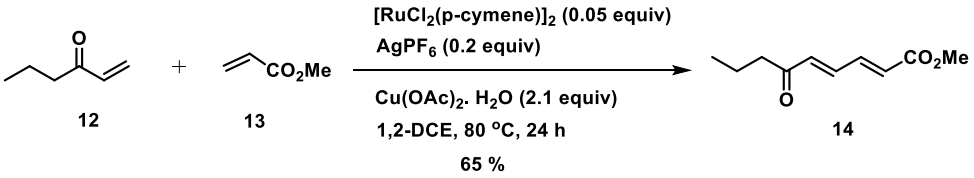
Synthesis of Diplofuranone A, 1:



To a magnetically stirred solution of diene **8** (35 mg, 0.16 mmol, 1.0 equiv) in THF:MeOH (4:1 ratio, 4 ml), was added $NaBH_4$ (13 mg, 0.33 mmol, 2.0 equiv) at 0 °C and the reaction mixture was allowed to stirred at room temperature for 30 minutes. Then reaction mixture was quenched with water and extracted with ethyl acetate (10 ml X 2), washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography using 30 % EtOAc in pet ether to furnish diplofuranone A **1** as a colourless liquid (26 mg, 0.14 mmol, 89%). **IR** (neat): ν_{max}/cm^{-1} 3365, 2924, 2853, 1769, 1661, 1328, 1182, 994, 915, 800. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.33 – 6.25 (m, 1H), 6.21 (dd, J = 15.2, 10.7 Hz, 1H), 5.82 (dd, J = 15.0, 6.0 Hz, 1H), 5.68 (dd, J = 15.0, 6.6 Hz, 1H), 4.97 (q, J = 7.0 Hz, 1H), 4.38 (dd, J = 12.5, 6.2 Hz, 1H), 2.56 – 2.52 (m, 2H), 2.44 – 2.37 (m, 1H), 2.02 – 1.97 (m, 1H), 1.29 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.98, 139.69, 132.35, 129.99, 127.73, 80.34, 68.27, 28.85, 28.60, 23.34. **HRMS** (APCI-TOF) m/z calcd. for $C_{10}H_{15}O_3$ $[M+H]^+$: 183.1021; found 183.1040.

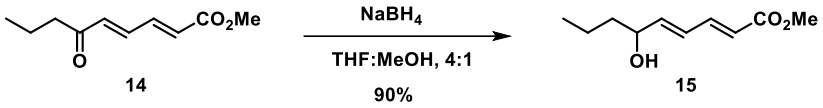
3. Synthesis of Diapolic acid A, 7

Synthesis of Compound 14:



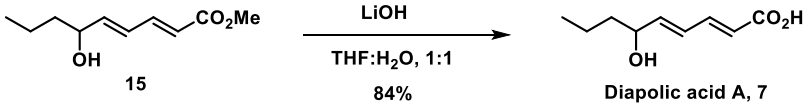
A 5 mL screw-cap vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.02 mmol, 5.0 mol%), $Cu(OAc)_2{\cdot}H_2O$ (213 mg, 1.0 mmol, 2.1 equiv), $AgPF_6$ (26 mg, 0.1 mmol, 20 mol%) and 1,2-dichloroethane (2 mL). The vial was sealed under nitrogen and allowed to stir at room temperature under nitrogen atmosphere for 10 minutes. To this methylacrylate **13** (66 mg, 70 µl, 0.77 mmol, 1.5 equiv) and propyl vinyl ketone **12** (50 mg, 60 µl, 0.51 mmol, 1.0 equiv) was added into the solution in sequence via syringe. Then the reaction mixture was heated to 80 °C (using an oil bath) while stirring for 24 h. After cooling down, the mixture was diluted with ethyl acetate, filtered, and concentrated to give the crude compound which was directly purified by column chromatography using 15% EtOAc in pet ether to afford compound **14** as a as a colourless solid (60 mg, 0.33 mmol, 65%). **IR** (neat): ν_{max}/cm^{-1} 2963, 2934, 2876, 1723, 1693, 1597, 1436, 1328, 1235, 1195, 1004, 873. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 15.3, 11.4 Hz, 1H), 7.16 (dd, *J* = 15.5, 11.4 Hz, 1H), 6.43 (d, *J* = 15.4 Hz, 1H), 6.22 (d, *J* = 15.3 Hz, 1H), 3.77 (s, 3H), 2.56 (t, *J* = 7.3 Hz, 2H), 1.68 – 1.63 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.09, 166.37, 141.75, 138.16, 135.66, 128.46, 52.01, 43.24, 17.52, 13.80. **HRMS** (ESI-TOF) m/z calcd. for $C_{10}H_{15}O_3$ $[M+H]^+$ 183.1021; found 183.1029.

Synthesis of Compound 15:



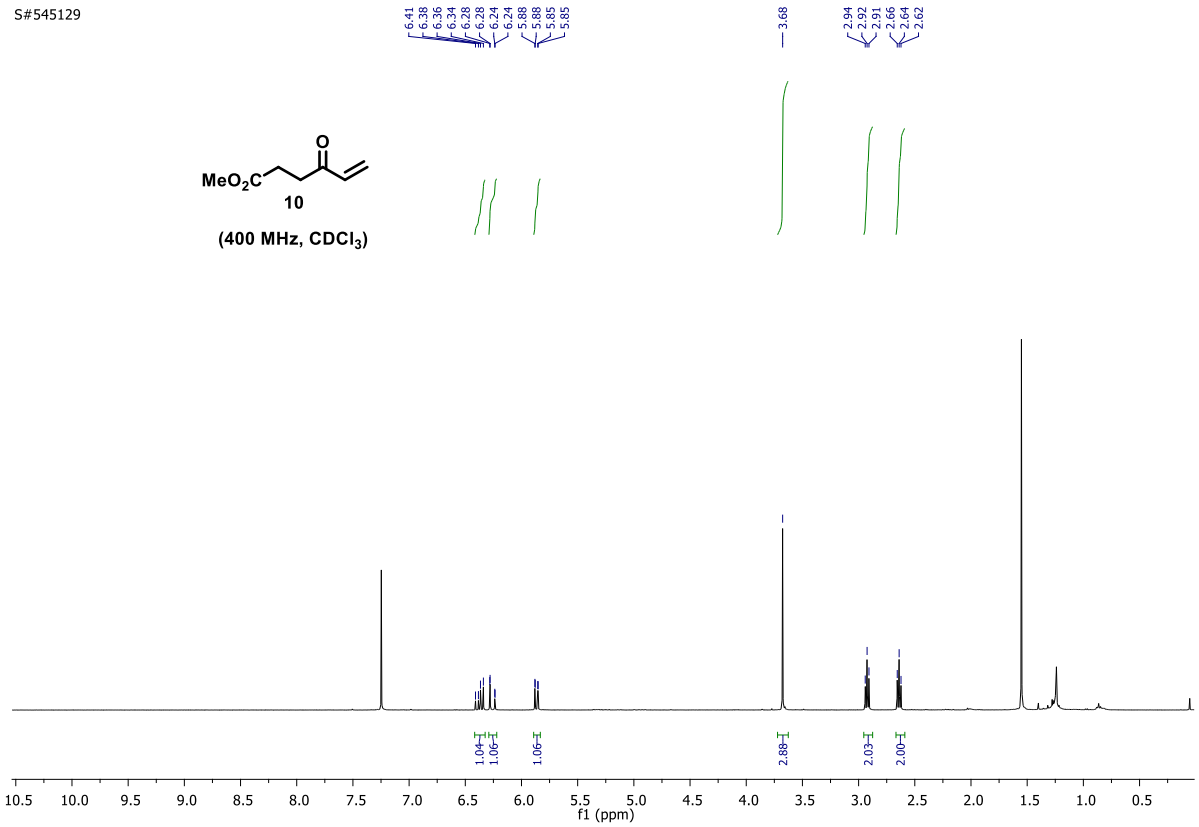
To a solution of **14** (35 mg, 0.19 mmol, 1.0 equiv) in THF:MeOH (4:1 ratio, 1.0 ml), was added $NaBH_4$ (8 mg, 0.20 mmol, 1.1 equiv) at 0 °C and the reaction mixture was allowed to stirred at room temperature for 30 minutes. Then reaction mixture was quenched with water and extracted with ethyl acetate (10 ml X 2), washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography using 20% EtOAc in pet ether to furnish compound **15** as a colourless solid (32 mg, 0.17 mmol, 90%). **IR** (neat): ν_{max}/cm^{-1} 3441, 2957, 2932, 2873, 1721, 1645, 1618, 1435, 1309, 1266, 1142, 1000, 872. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 15.4, 11.0 Hz, 1H), 6.35 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.10 (dd, *J* = 15.3, 5.9 Hz, 1H), 5.87 (d, *J* = 15.3 Hz, 1H), 4.24 (q, *J* = 6.1 Hz, 1H), 3.73 (s, 3H), 1.71 (s, 1H, br-OH), 1.58 – 1.50 (m, 2H), 1.44 – 1.36 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.40, 145.17, 144.13, 127.24, 120.93, 71.70, 51.56, 39.13, 18.49, 13.91. **HRMS** (ESI-TOF) m/z calcd. for $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1178; found 185.1175.

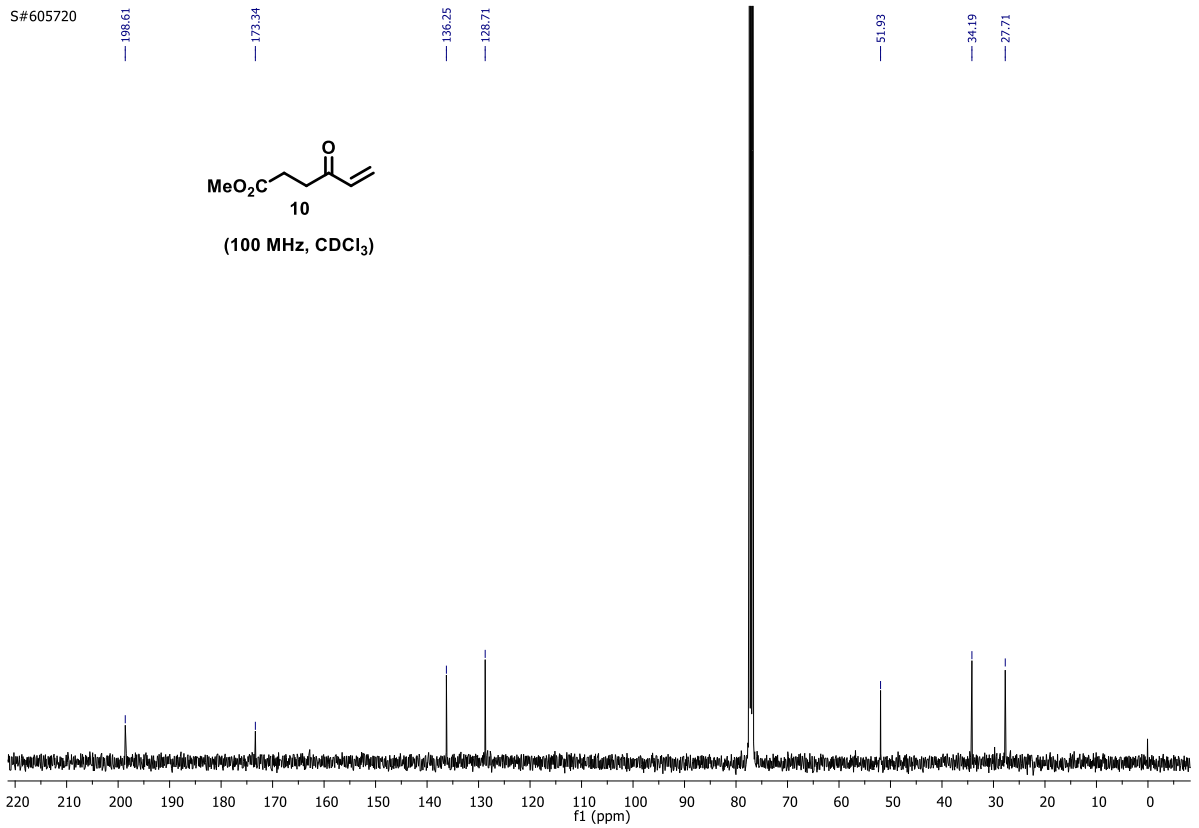
Synthesis of Diapolic acid A (7):

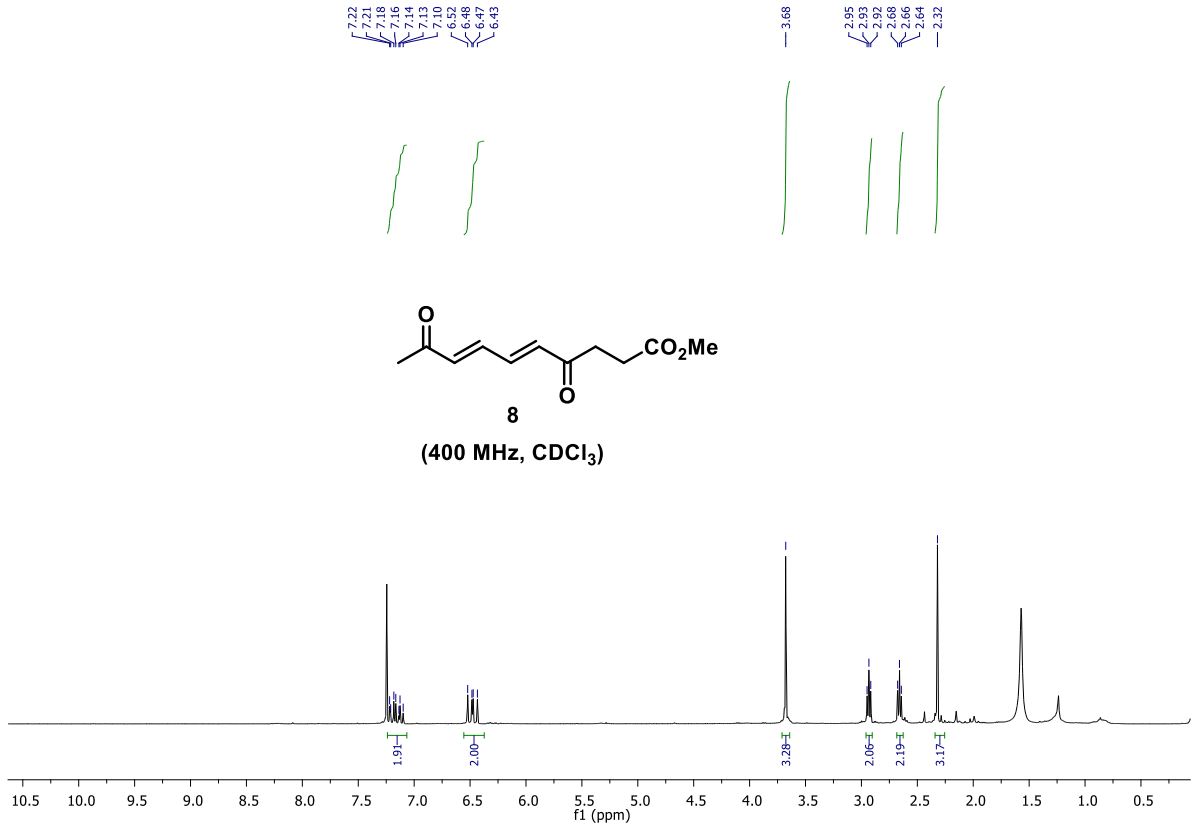


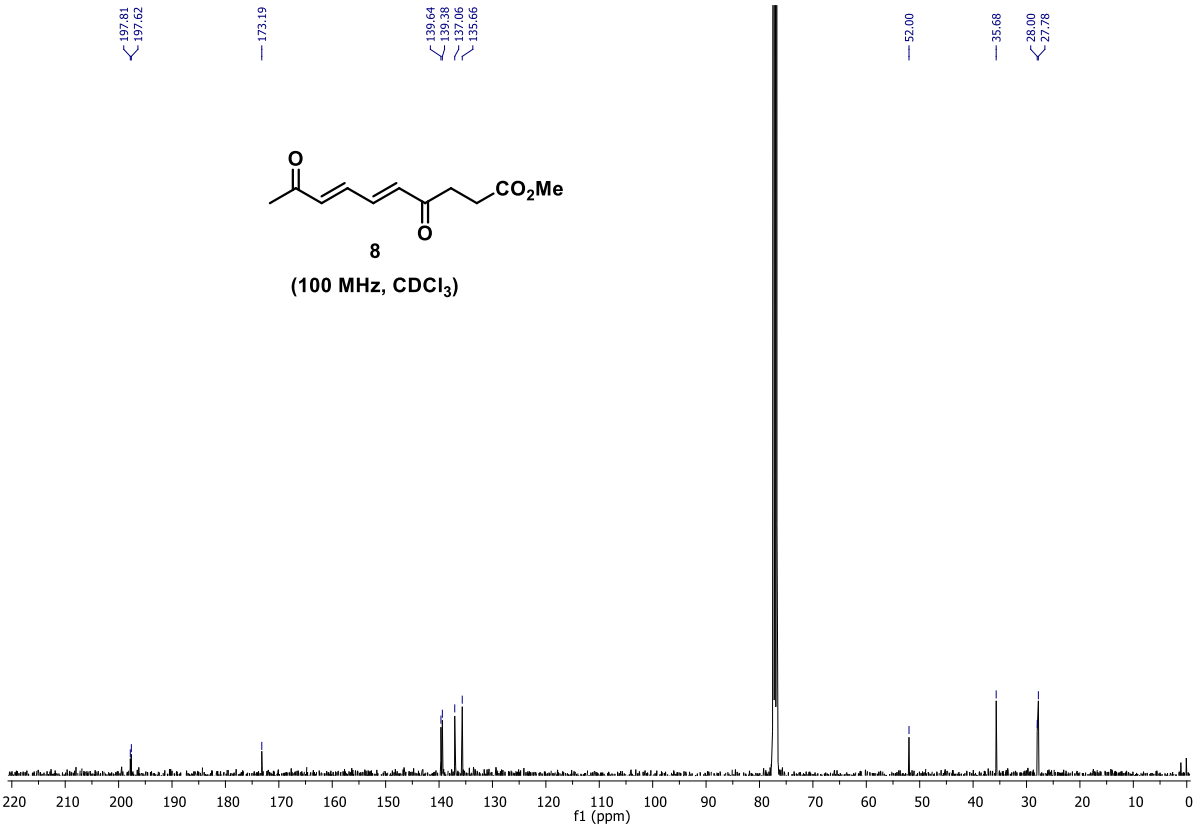
A mixture of compound **15** (30 mg, 0.16 mmol, 1.0 equiv) and LiOH (12 mg, 0.48 mmol, 3.0 equiv) in THF: H_2O, (1:1, 1.0 mL) at 0 ^{0}C and the reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was acidified with aqueous HCl (1N HCl), extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo and purified by neutral-alumina column chromatography using 40% EtOAc in pet ether to afford diapolic acid A **7** as a colourless solid (22 mg, 0.13 mmol, 84%). **IR** (neat): ν_{max}/cm^{-1} 3383, 2959, 2927, 2873, 1693, 1644, 1619, 1416, 1304, 1260, 1135, 1001, 847. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.38 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.15 (dd, *J* = 15.3, 5.8 Hz, 1H), 5.87 (d, *J* = 15.3 Hz, 1H), 4.26 (q, *J* = 6.1 Hz, 1H), 1.59 – 1.51 (m, 2H), 1.40 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.79, 146.15 (2C), 127.13, 120.54, 71.71, 39.07, 18.48, 13.89. **HRMS** (ESI-TOF) m/z calcd. for $C_9H_{15}O_3$ $[M+H]^+$ 171.1021; found 171.1026.

4. ^{1}H and ^{13}C NMR Spectra for the Synthesis of Diplofuranone A, 1






7.22
7.21
7.18
7.16
7.14
7.13
7.10
6.52
6.48
6.47
6.43
3.68
2.95
2.93
2.92
2.68
2.66
2.64
2.32
O
CO2Me
O
8
(400 MHz, CDCl3)
1.91
2.00
3.28
2.06
2.19
3.17
10.5 10.0 9.5 9.0 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
f1 (ppm)


197.81
197.62
173.19
139.64
139.38
137.06
135.66
52.00
35.68
28.00
27.78
O
CO2Me
O
8
(100 MHz, CDCl3)
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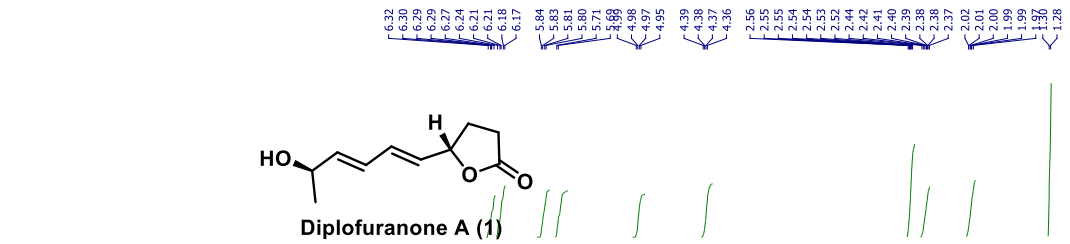
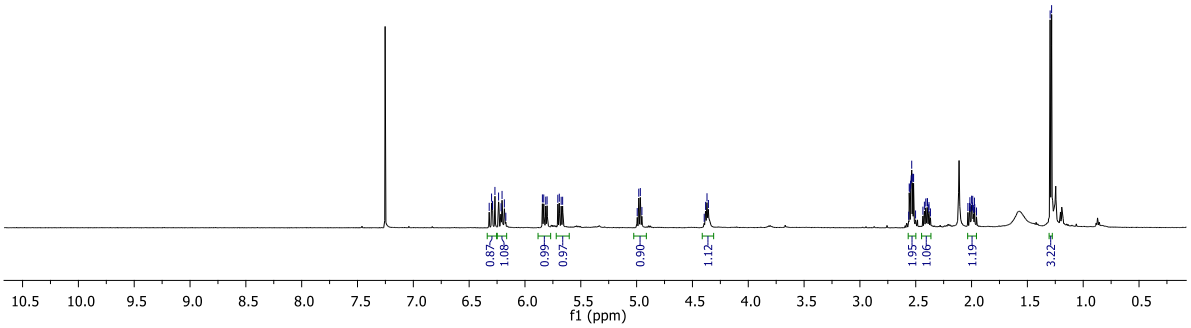
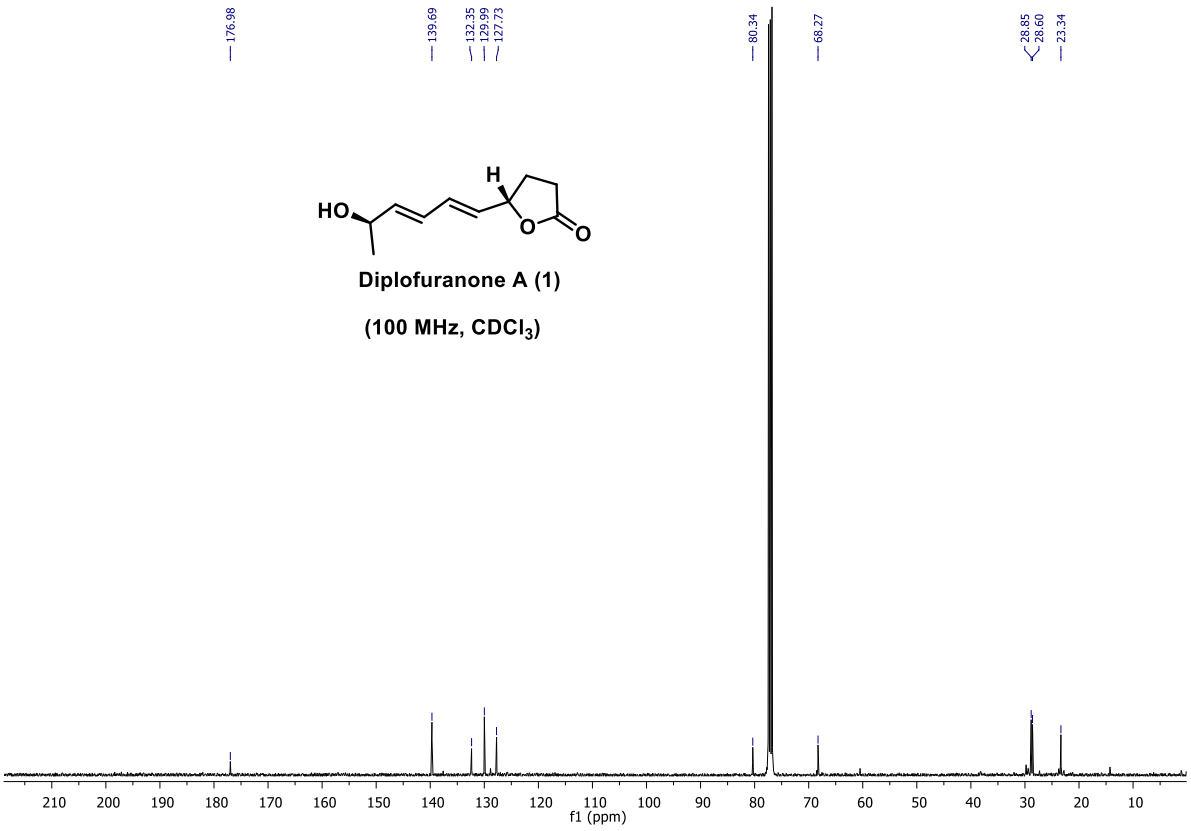
f1 (ppm)



Diplofuranone A (1)

(500 MHz, $CDCl_3$)

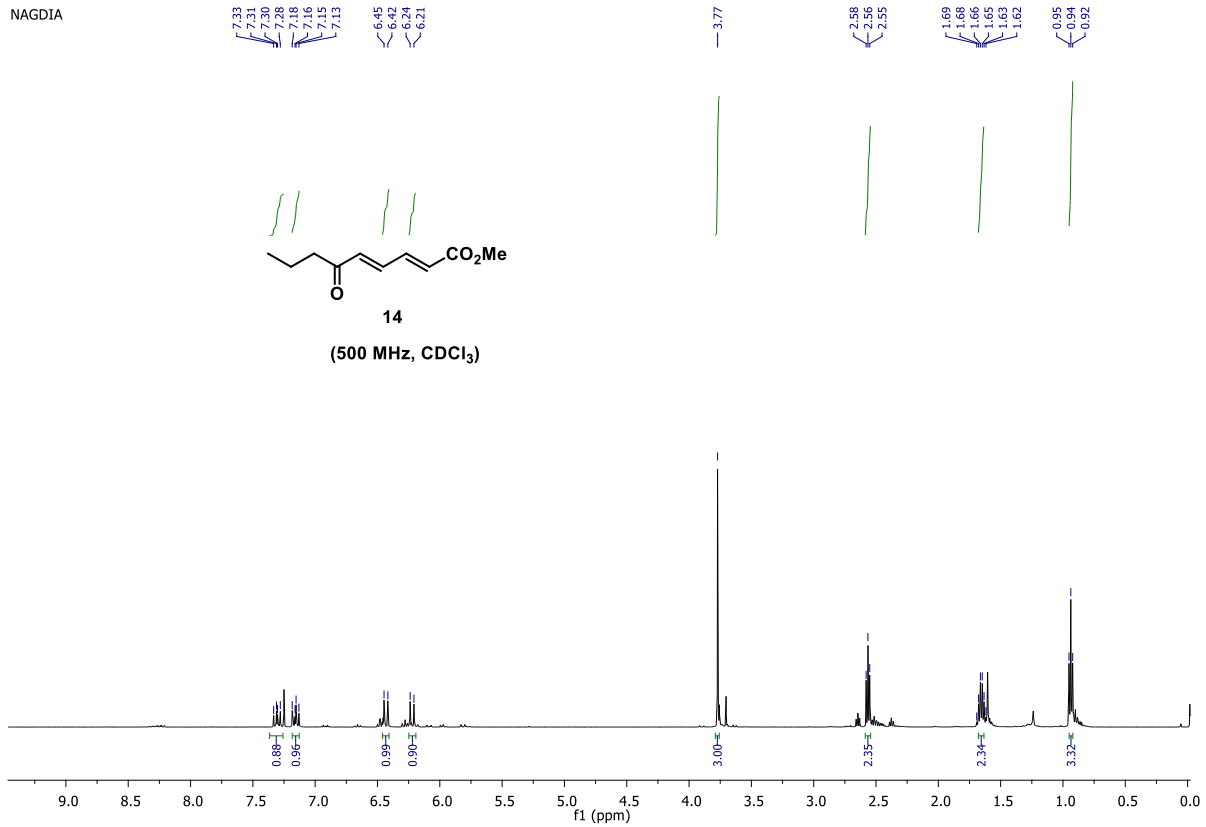


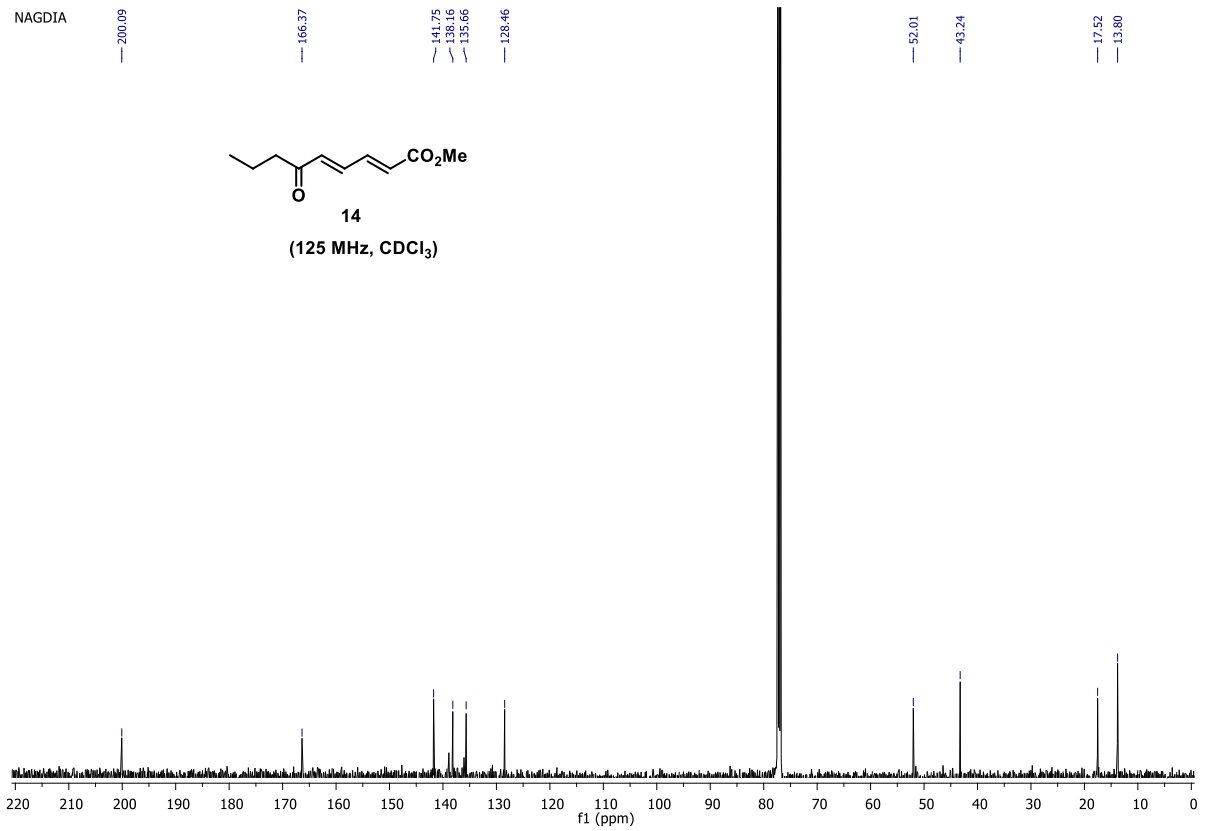


Diplofuranone A (1)

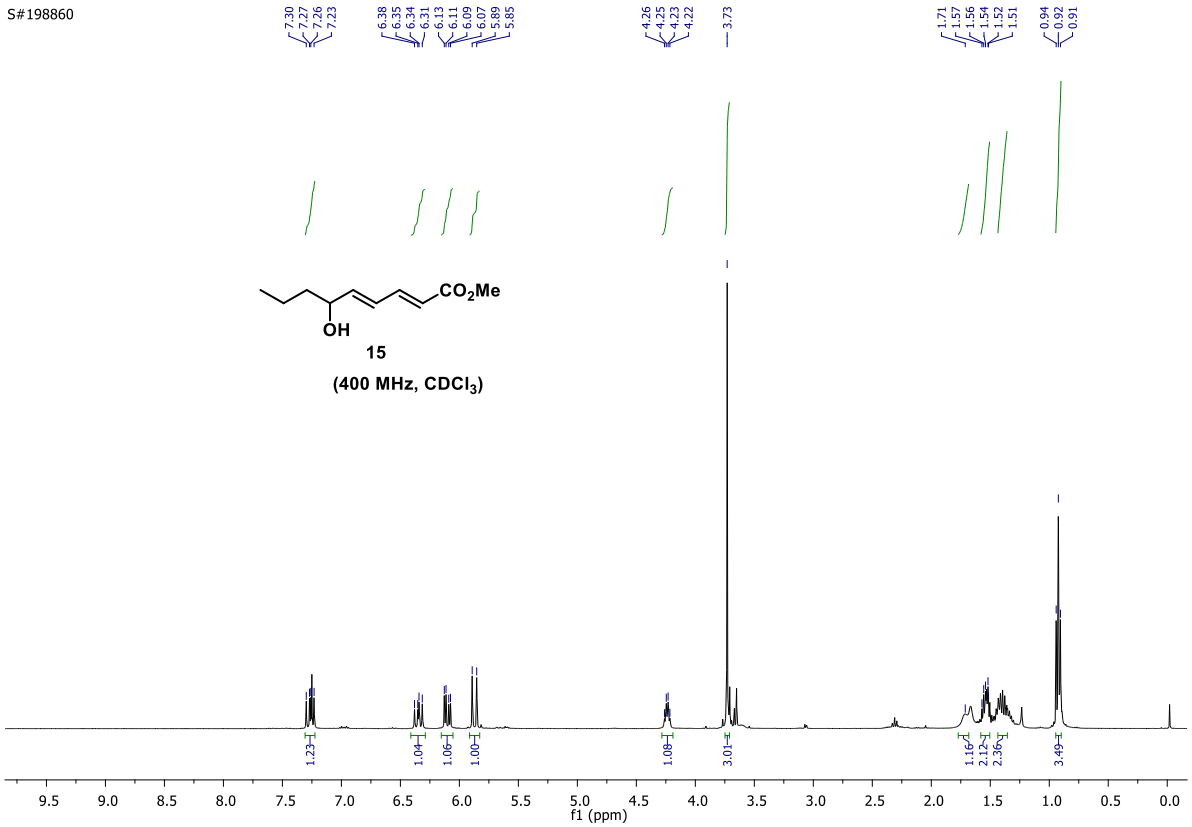
(100 MHz, $CDCl_3$)

5. ^{1}H and ^{13}C NMR Spectra for the Synthesis of Diapolic acid A, 7





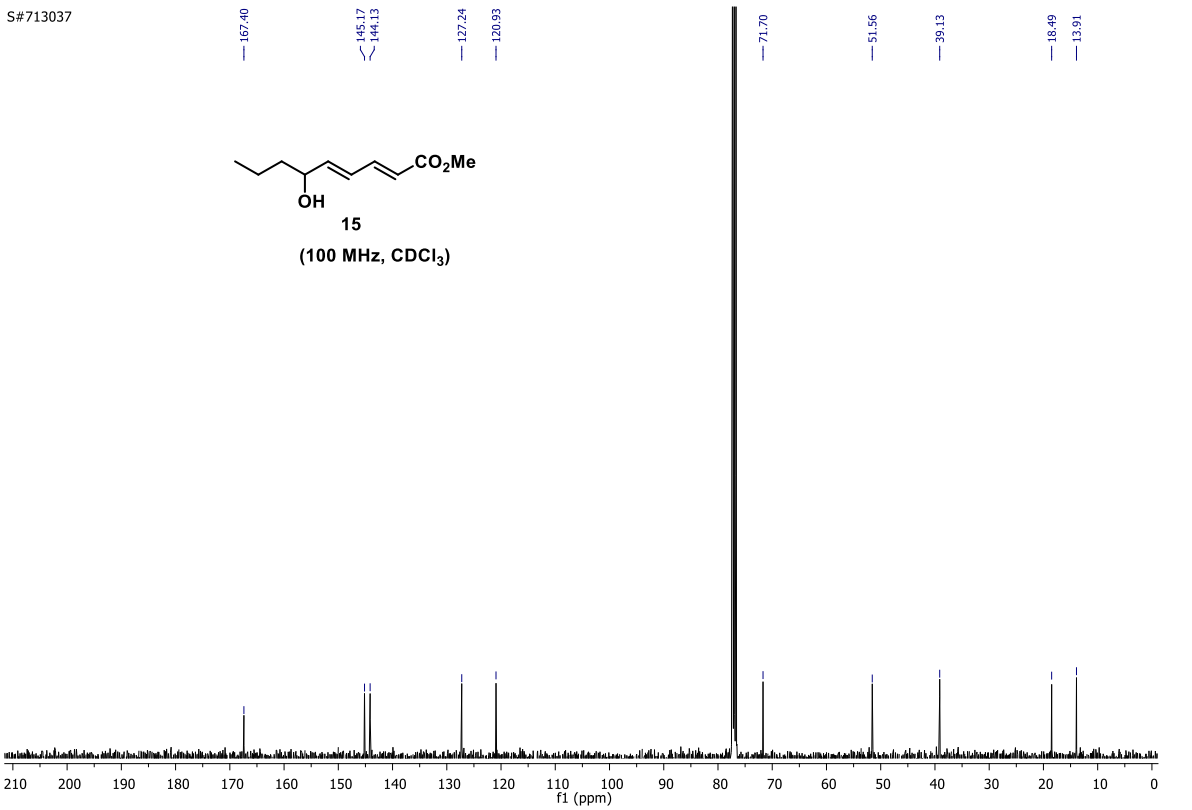
S#198860



15

(400 MHz, $CDCl_3$)

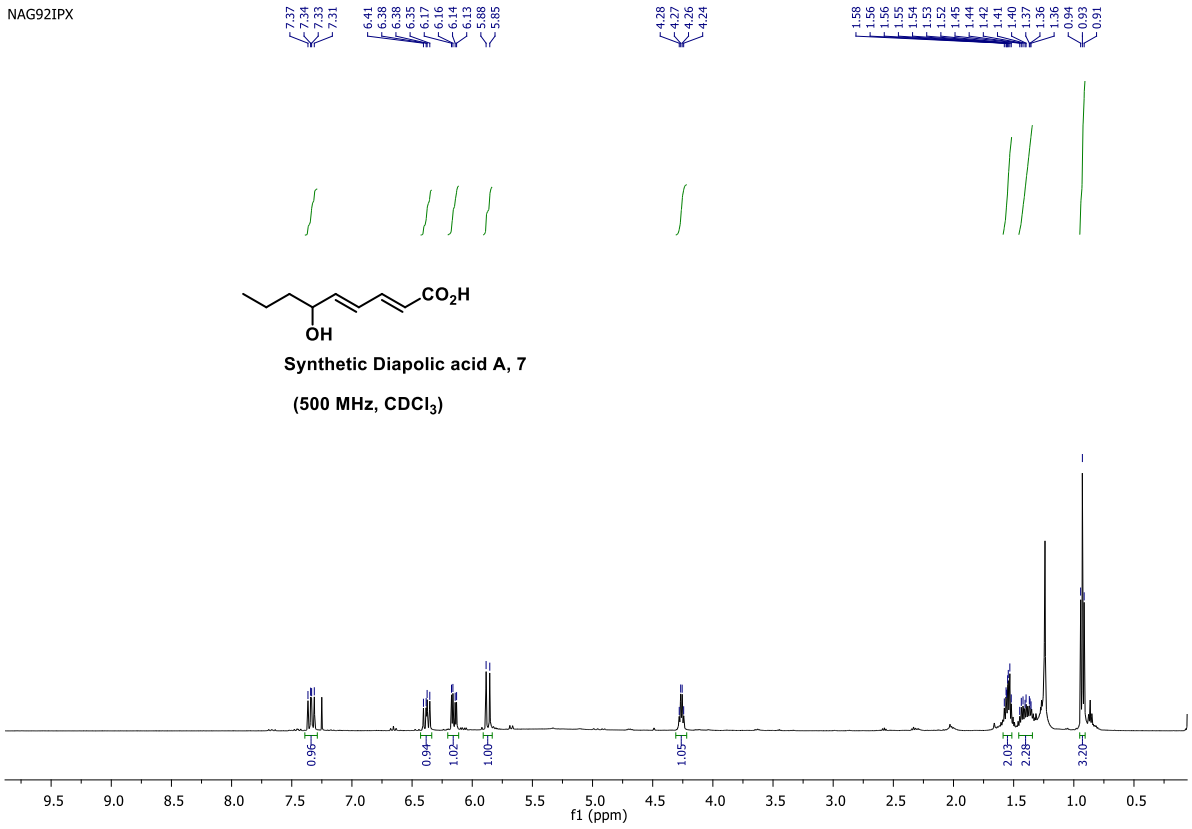
S#713037



15

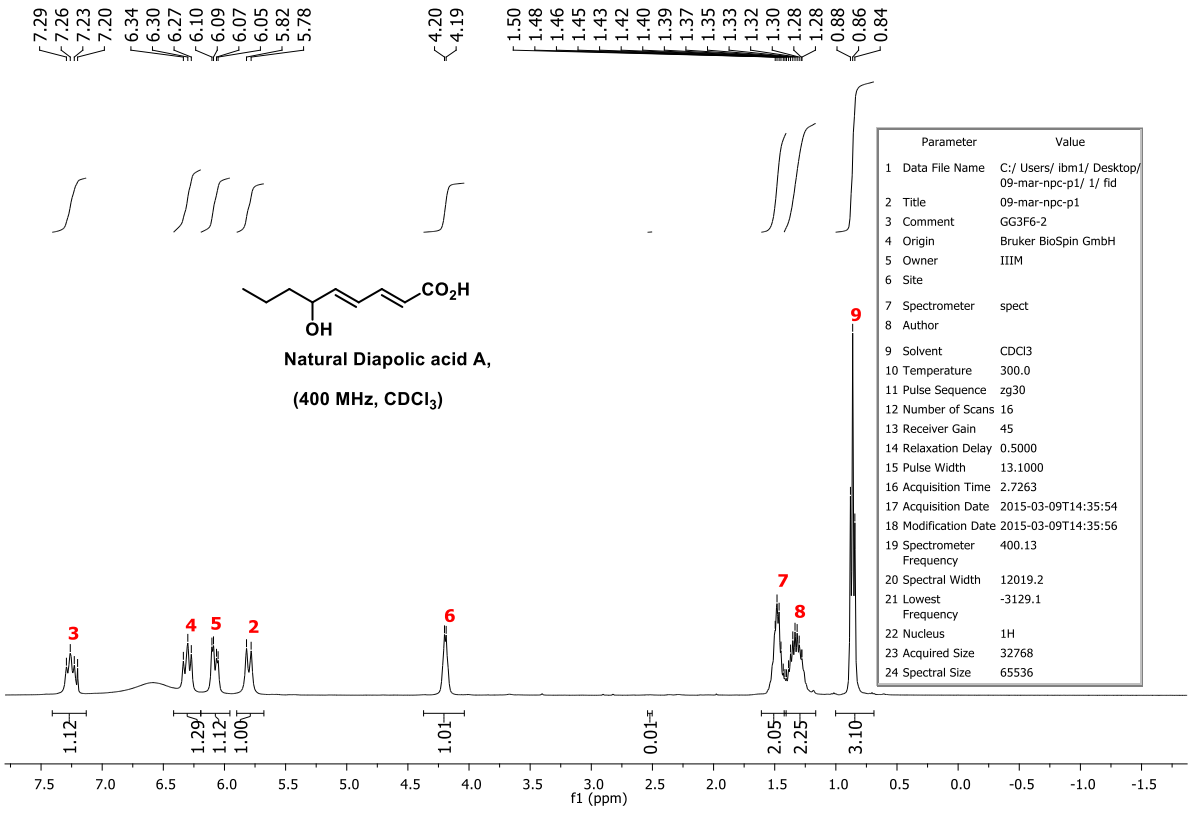
(100 MHz, $CDCl_3$)

NAG92IPX



Synthetic Diapolic acid A, 7

(500 MHz, $CDCl_3$)



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8	Author	
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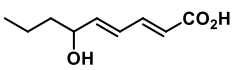
Natural Diapolic acid A,

(400 MHz, $CDCl_3$)

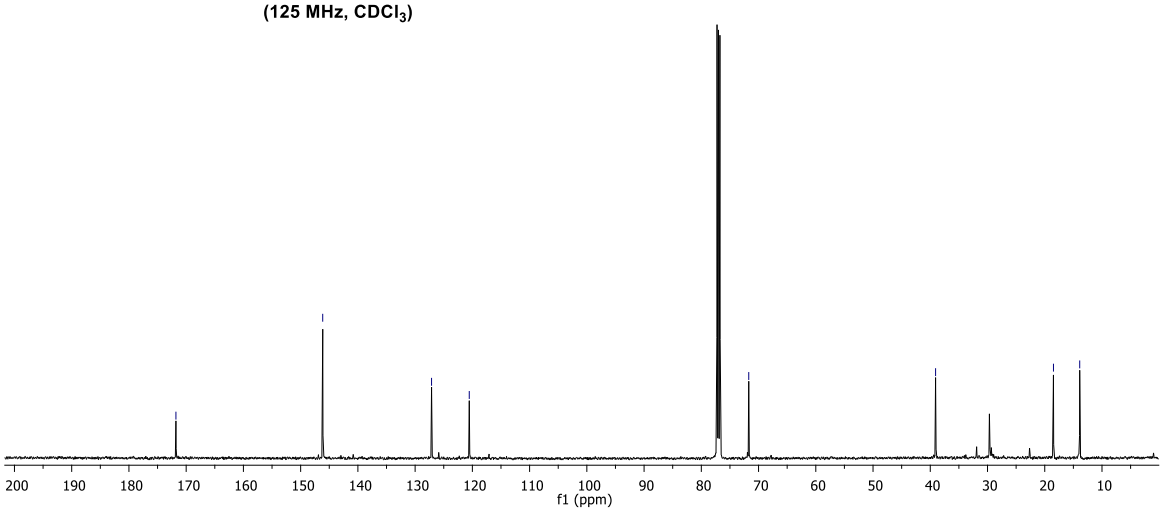
NAG927PX

171.79 146.15 127.13 120.54 71.71 39.07 18.48 13.89

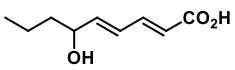


Synthetic Diapolic acid A, 7

(125 MHz, $CDCl_3$)

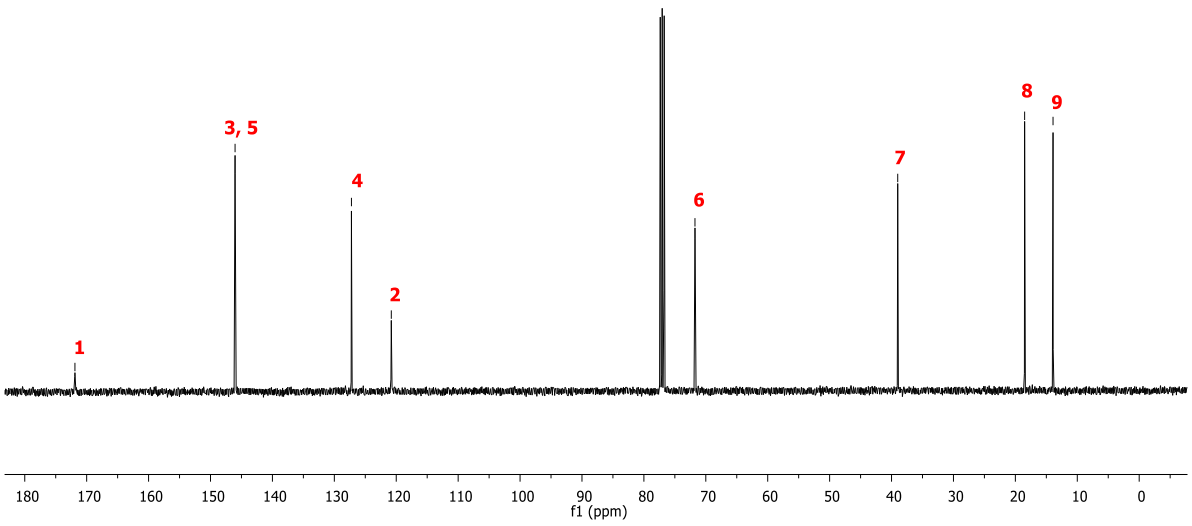


171.90 146.03 127.24 120.80 71.75 39.00 18.50 13.92



Natural Diapolic acid A,

(100 MHz, $CDCl_3$)



6. ^{1}H and ^{13}C NMR comparison tables for Diplofuranone A, 1 and Diapolic acid A, 7

^{1}H and ^{13}C NMR comparison tables: Diplofuranone A (1)

^{1}H-NMR in $CDCl_3$		^{13}C-NMR in $CDCl_3$	
Natural 400 MHz	**Synthetic 500 MHz**	**Natural 100 MHz**	**Synthetic 100 MHz**
1.30 (d, *J* =6.4 Hz)	1.29 (d, *J* =6.5, Hz)	176.8	176.98
2.41 - 2.00 (m)	2.40 - 2.00 (m)	139.7	139.69
2.55 - 2.00 (m,)	2.56 - 2.00 (m)	132.2	132.35
4.37 (dq, *J* = 6.4, 6.1, Hz)	4.39 - 4.36 (m)	129.9	129.99
4.98 (q, *J* = 6.6, Hz)	4.97 (q, *J* = 7.0 Hz)	127.6	127.73
5.65 (dd, *J* = 14.7, 6.6, Hz)	5.68 (dd, *J* = 15.0, 6.6, Hz)	80.3	80.34
5.83 (dd, *J* = 14.9, 6.1, Hz)	5.82 (dd, *J* = 15.0, 6.0, Hz)	68.2	68.27
6.25 (dd, *J* = 14.9, 10.6, Hz)	6.21 (dd, *J* = 15.2, 10.7 Hz)	28.7	28.85
6.27 (dd, *J* = 14.7, 10.6, Hz)	6.33 – 6.25 (m, 1H),	28.5	28.60
		23.2	23.34

^{1}H and ^{13}C NMR comparison tables: Diapolic acid A (7)

^{1}H-NMR		^{13}C-NMR in $CDCl_3$	
Natural Diapolic acid A 400 MHz, $CDCl_3$	**Synthetic Diapolic acid A 500 MHz, $CDCl_3$**	**Natural Diapolic acid A 100 MHz, $CDCl_3$**	**Synthetic Diapolic acid A 125 MHz, $CDCl_3$**
7.41–7.13 (m, 1H)	7.34 (dd, *J* = 15.3, 11.1 Hz, 1H)	171.9	171.79
6.42–6.19 (m, 1H)	6.38 (dd, *J* = 15.2, 11.1 Hz, 1H)	146.0	146.15
6.05–6.10 (m, 1H)	6.15 (dd, *J* = 15.3, 5.8 Hz, 1H)	146.0	146.15
5.80 (d, 15.1 Hz, 1H)))	5.87 (d, *J* = 15.3 Hz, 1H)	127.2	127.13
4.19 (d, 5.5 Hz, 1H))	4.26 (q, *J* = 6.1 Hz, 1H)	120.8	120.54
1.45–1.50 (m, 2H)	1.59 – 1.51 (m, 2H)	71.7	71.71
1.28–1.37 (m, 2H)	1.40 (m, 2H)	39.0	39.07
0.86 (t, 7.2 Hz, 3H))	0.93 (t, *J* = 7.3 Hz, 3H)	18.5	18.48
		13.9	13.89