

A Simple Model for the Biosynthesis of the Strigolactone ABC Ring System

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and Aaron Aponick*

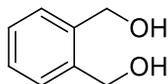
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Supporting information

General:

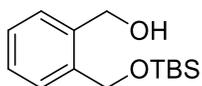
All reactions requiring anhydrous or oxygen-free conditions were carried out under an atmosphere of argon in oven-dried glassware. Anhydrous solvents were purchased from Sigma-Aldrich in sure-seal bottles and used as received. Thin layer chromatography was performed using 250 μm Silica Gel 60 F₂₅₄ pre-coated plates (Whatman) and the plates were visualized with UV or permanganate stain. Flash column chromatography was performed using 230-400 Mesh 60A Silica Gel (Whatman). Proton nuclear magnetic resonance (¹H NMR) and carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded in deuterated chloroform, CDCl₃ at the frequency indicated. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS, 0.0 ppm) or CDCl₃ (7.27 ppm in ¹H NMR and 77.0 ppm in ¹³C NMR). Multiplicities are reported using the following abbreviations: s, singlet; d doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; br, broad. Infrared spectra were obtained on a Bruker Vector 22 IR spectrometer and are reported in wavenumbers. High resolution mass spectra (HRMS) were obtained by Mass Spectrometry Core Laboratory of University of Florida.



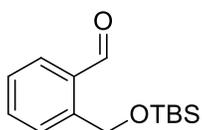
1,2-phenylenedimethanol.¹ A solution of phthalic anhydride (5.04 g, 34.0 mmol) in tetrahydrofuran (50 mL) was added at 0 °C to the suspension of lithium aluminium hydride (2.37 g, 62.4 mmol) in tetrahydrofuran (80 mL), and the mixture was stirred at room temperature for 30 min and then at reflux for 3 h. The mixture was cooled to 0 °C and water (2.4 mL) was added in a dropwise fashion at 0 °C, followed by 15 % aqueous sodium hydroxide solution (2.4 mL) and water (6 mL). The mixture was diluted with ethyl acetate (100 mL), filtered through a plug of celite, and eluted with ethyl acetate. The solvents were evaporated and the crude was purified by column chromatography with hexanes-ethyl

¹ W. K. Anderson and F. R. Kinder Jr., *J. Heterocyclic Chem.*, 1990, **27**, 975-979.

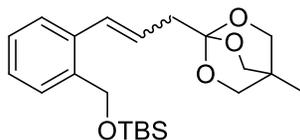
acetate (5:1 to 1:1 gradient) to yield 3.36 g (71 %) of the product as a white solid; ^1H NMR (CDCl_3 , 300 MHz): δ 7.33 (m, 4H); 4.68 (s, 4H), 3.43 (s, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 139.3, 129.7, 128.5, 64.1.



(2-(((*tert*-butyldimethylsilyloxy)methyl)phenyl)methanol).¹ Using a literature procedure,² A solution of 1,2-phenylenedimethanol (539 mg, 3.90 mmol) in tetrahydrofuran (10 mL) was added to a suspension of sodium hydride (154 mg of a 60 % dispersion in mineral oil, 3.85 mmol) in tetrahydrofuran (25 mL) at room temperature and the mixture was stirred overnight. The resulting solution was then cooled to 0 °C and *t*-butyldimethylsilyl chloride (580 mg, 3.85 mmol) was added in one portion. After 10 min at 0 °C, the reaction mixture was stirred at room temperature for 1.5 h. Saturated aqueous ammonium chloride (40 mL) was added and the mixture was extracted with ether. The combined extracts were washed with brine, dried (MgSO_4) and evaporated. The crude product was purified by column chromatography with hexanes:ethyl-acetate 10:1 as eluent to yield 877 mg (90 %) of the title compound; ^1H NMR (CDCl_3 , 300 MHz): δ 7.25-7.37 (m, 4H); 4.80 (s, 2H); 4.67 (d, 2H); 3.25 (t, 1H); 0.92 (s, 9H); 0.12 (s, 6H); ^{13}C NMR: δ 139.8, 138.6, 129.4, 128.6, 127.9, 64.7, 63.8, 25.8, 18.2, -5.3.



2-(((*tert*-butyldimethylsilyloxy)methyl)benzaldehyde (7).¹ Activated manganese dioxide (2.0 g, 90 % technical oxidation grade) was added to the solution of the alcohol obtained above (237 mg, 0.94 mmol) in petroleum ether (10 mL) at 0 °C, and the mixture was stirred at 0-10 °C for 3 h. The solids were then removed by filtration through a celite plug and the solvent evaporated to yield 220 mg (94 %) of the title compound as a colorless oil; ^1H NMR (CDCl_3 , 300 MHz): δ 10.18 (s, 1H); 7.82 (m, 2H); 7.63 (m, 1H); 7.45 (m, 1H); 5.16 (s, 2H); 0.97 (s, 9H); 0.14 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 193.3, 144.3, 133.9, 133.4, 132.6, 127.0, 126.6, 62.9, 25.9, 18.4, -5.3.



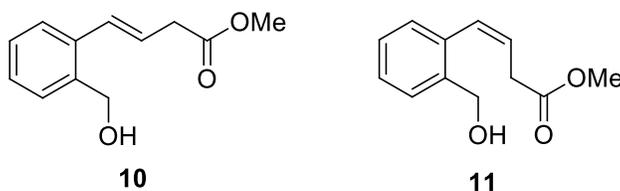
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***Tert*-butyldimethyl((2-(3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)prop-1-en-1-yl)benzyl)oxy)silane (9).** According to a modified literature procedure for Wittig reaction of **8**,³ Lithium hexamethyldisilazide 1 M in THF (53.0 mL, 53.0 mmol) was added at room temperature to a suspension of phosphonium bromide salt **8**³ (27.35 g, 54.8 mmol) in tetrahydrofuran (200 mL) and the mixture was heated to reflux for 1 h. The mixture was then cooled down to -78 °C and a solution of aldehyde **7** (9.14 g, 36.5 mmol) in tetrahydrofuran (100 mL) was added. The reaction mixture was then stirred at -78 °C

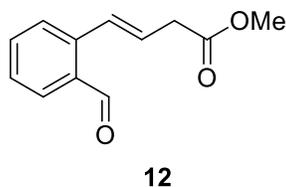
² C. Aissa and A. Furstner, *J. Am. Chem. Soc.*, 2007, **129**, 14836-14837.

³ K. J. Lee, K. C. Joo, E. J. Kim, M. Lee, D. H. Kim, *Bioorg. Med. Chem.*, 1997, **5**, 1989-1998.

for 1 h, and room temperature for 2 h. Water (70 mL) was added and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried (MgSO_4) and evaporated. The crude product was purified by column chromatography pretreated with 3 % triethylamine in hexane and eluted with 0.5 % triethylamine in hexane to yield 13.83 g of the product as 1:1 mixture (97 % yield) of E/Z isomers; ^1H NMR (CDCl_3 , 300 MHz): δ 7.22-7.55 (m, 4H); 6.60 (d, J = 11.3 Hz) and 6.65 (d, 1H, J = 15.9 Hz); 5.89 (dt, J = 7.1, 11.3 Hz) and 6.17 (dt, 1H, J = 7.1, 15.9 Hz); 4.72 and 4.82 (s, 2H); 3.93 and 3.94 (s, 6H); 2.58 and 2.68 (dd, 2H, J = 7.1, 1.7 Hz); 0.98 (s, 9H); 0.81 and 0.82 (s, 3 H); 0.13 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 139.1, 137.7, 135.2, 134.2, 133.8, 133.5, 129.4, 129.0, 128.8, 128.6, 128.5, 128.4, 126.9, 126.6, 126.3, 125.8, 125.7, 125.6, 125.3, 108.6, 108.4, 72.7, 63.0, 62.8, 40.7, 35.9, 30.4, 30.3, 25.9, 18.3, 14.5, -5.3, -5.4; IR (neat): 3018 cm^{-1} , 2931 cm^{-1} , 2881 cm^{-1} , 1472 cm^{-1} , 1397 cm^{-1} , 1356 cm^{-1} , 1259 cm^{-1} , 1119 cm^{-1} , 994 cm^{-1} , 839 cm^{-1} ; HRMS (DART): calculated for $\text{C}_{22}\text{H}_{35}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 391.2299, found: 391.2300.

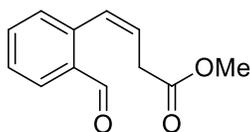


(E)-methyl 4-(2-hydroxymethyl)phenylbut-3-enoate (10) and (Z)-methyl 4-(2-hydroxymethyl)phenylbut-3-enoate (11). The orthoester **9** (9.00 g, 23.0 mmol) was stirred in 0.2 M sulfuric acid methanolic solution (200 mL) at room temperature for 1 h. Water was then added and the resulting mixture was extracted with methylene chloride. The combined organic layers were washed with brine, dried (MgSO_4), and evaporated. The crude product was purified by column chromatography (hexane/ethyl acetate 4:1) to give 1.646 g of **10** and 1.474 g of **11** (66 %). Data for **10**: R_f 0.21 (hexane:ethyl acetate :4:1); ^1H NMR (CDCl_3 , 300 MHz): δ 7.47 (m, 1H); 7.19-7.32 (m, 3H); 6.78 (d, 1H, J = 15.9 Hz); 6.19 (m, 1H); 4.66 (s, 2H); 3.68 (s, 3H); 3.25 (dd, 2H, J = 7.2, 1.5 Hz); 2.01 (br s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 172.0, 137.4, 135.6, 130.3, 128.2, 127.9, 127.5, 126.1, 123.9, 63.0, 51.8, 38.2; IR (neat): 3461 cm^{-1} , 1733 cm^{-1} ; HRMS (DART): calculated for $\text{C}_{12}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$: 207.1016, found: 207.1018. Data for **11**: R_f 0.27 (hexane:ethyl acetate :4:1); ^1H NMR (CDCl_3 , 300 MHz): δ 7.39-7.42 (m, 1H); 7.23-7.31 (m, 2H); 7.12-7.15 (m, 1H); 6.76 (d, 1H, J = 11.1 Hz); 5.92 (dt, 1H, J = 7.3, 11.1 Hz); 4.59 (d, 2H, J = 5.4 Hz); 3.64 (s, 3H); 3.14 (dd, 2H, J = 7.3, 1.5 Hz); 2.11 (br s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 172.2, 138.9, 134.7, 130.6, 128.9, 127.9, 127.6, 127.4, 124.5, 62.9, 51.9, 33.6; IR (neat): 3466 cm^{-1} , 1726 cm^{-1} ; HRMS (DART): calculated for $[\text{M}+\text{H}]^+$: 207.1016, found: 207.1010.



(E)-methyl 4-(2-formylphenyl)but-3-enoate (12). A solution of alcohol **10** (470 mg, 2.28 mmol) in DCM (4 mL) was added to a mixture of PCC (688 mg, 3.19 mmol) and celite (688 mg) in DCM (13 mL) at room temperature. After 1 h, the mixture was diluted with diethyl ether, filtered through celite, and the

solvents were evaporated. Flash column chromatography (hexane-ethyl acetate 10:1) provided 432 mg of **12** as a colorless oil (93 %); ^1H NMR (CDCl_3 , 300 MHz): δ 10.26 (s, 1H); 7.81 (m, 1H); 7.34-7.59 (m, 4H); 6.28 (dt, 1H, $J = 7.2, 15.9$ Hz); 3.74 (s, 3H); 3.35 (dd, 2H, $J = 7.2, 1.6$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz): δ 192.4, 171.6, 139.3, 133.7, 132.6, 131.7, 129.6, 127.7, 127.6, 127.2, 51.9, 38.2; IR (neat): 2849 cm^{-1} , 2745 cm^{-1} , 1735 cm^{-1} , 1698 cm^{-1} ; HRMS (DART): calculated for $\text{C}_{12}\text{H}_{13}\text{O}_3$ $[\text{M}+\text{H}]^+$: 205.0859, found: 205.0868.



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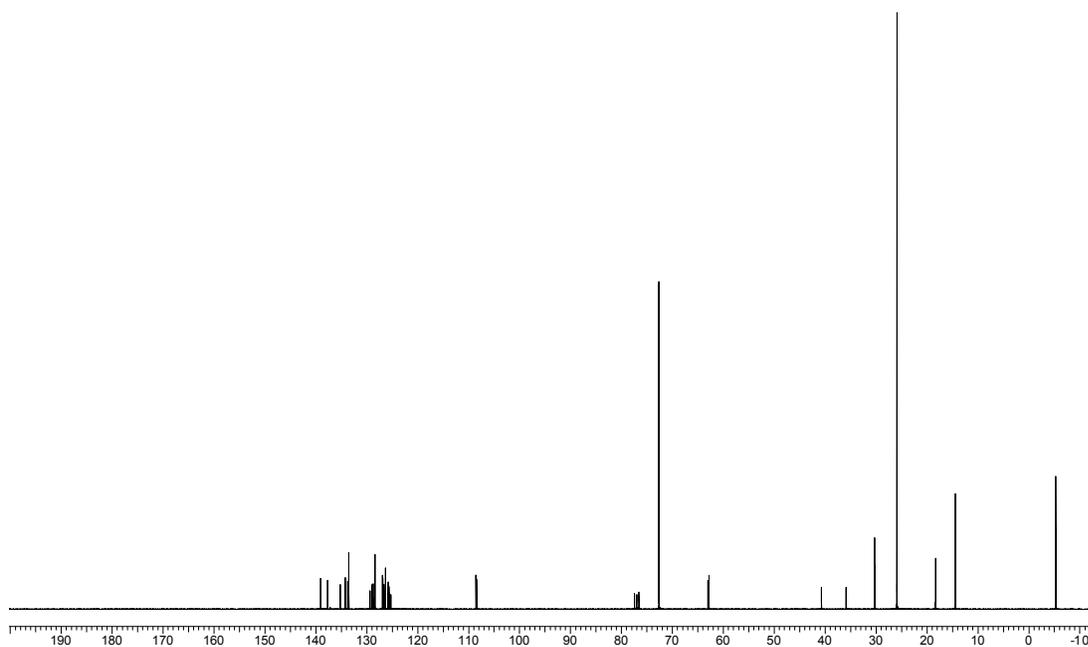
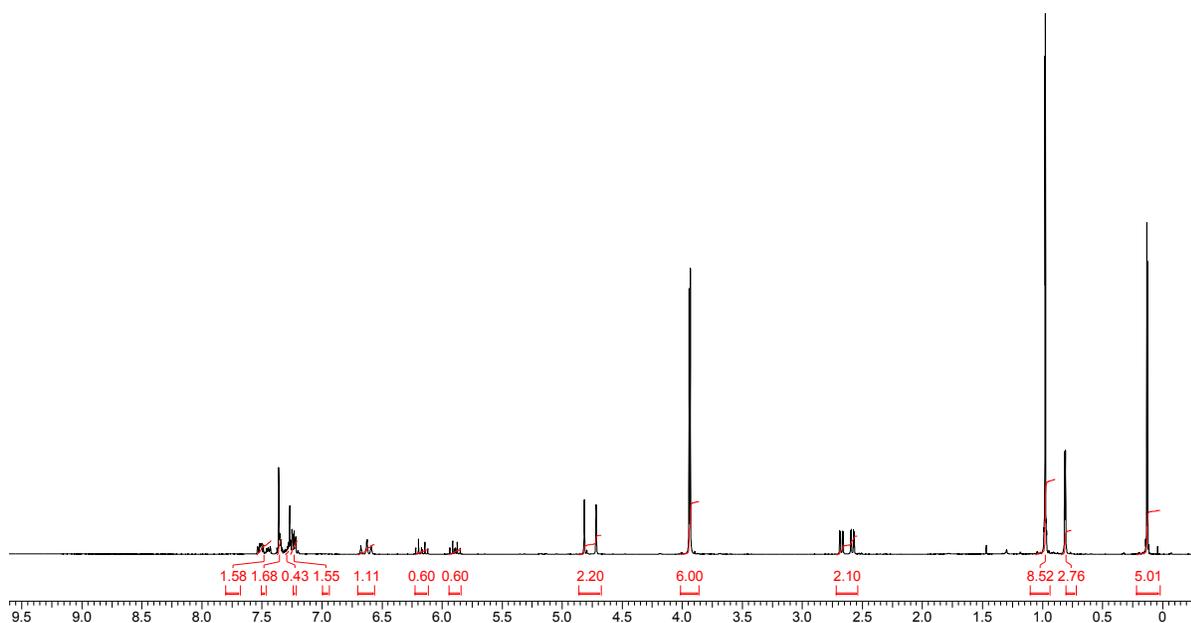
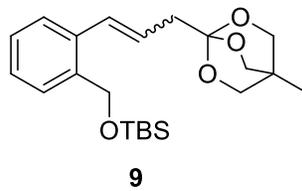
(Z)-methyl 4-(2-formylphenyl)but-3-enoate (13). A solution of alcohol **11** (1.074 g, 5.21 mmol) in DCM (15 mL) was added to a mixture of PCC (1.590 g, 7.38 mmol) and celite (1.590 mg) in DCM (35 mL) at room temperature. After 1 h, the mixture was diluted with diethyl ether, filtered through celite, and the solvents evaporated. Flash column chromatography (hexane-ethyl acetate 10:1) yielded 994 mg of **13** as a colorless oil (93 %); ^1H NMR (CDCl_3 , 300 MHz): δ 10.21 (s, 1H); 7.90 (d, 1H, $J = 7.8$ Hz); 7.58 (m, 1H); 7.44 (m, 1H); 7.29 (d, 1H, $J = 7.5$ Hz); 7.06 (d, 1H, $J = 11.7$ Hz); 6.07-6.16 (m, 1H); 3.68 (s, 3H); 3.11 (dd, 2H, $J = 7.6, 1.1$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz): δ 191.5, 171.1, 138.8, 133.4, 133.4, 129.9, 129.2, 128.9, 127.6, 126.1, 51.6, 33.5; IR (neat): 2854 cm^{-1} , 2740 cm^{-1} , 1731 cm^{-1} , 1695 cm^{-1} ; HRMS (DART): calculated for $\text{C}_{12}\text{H}_{13}\text{O}_3$ $[\text{M}+\text{H}]^+$: 205.0859, found: 205.0867.

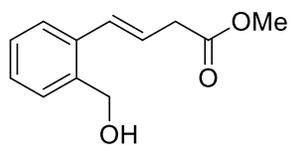
Representative procedure for trimethylsilyl triflate catalyzed cyclization: Trimethylsilyl triflate (0.85 mL of a 0.11 M solution in CH_2Cl_2 , 0.094 mmol) was added to solution of **12** (0.098 g, 0.48 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After 2h, when thin layer chromatographic analysis indicated complete consumption of **12**, water was added and the reaction mixture was extracted with CH_2Cl_2 . The combined organic extract was washed with brine, dried over magnesium sulfate, and concentrated to 1 mL. Flash chromatography (gradient, hexanes:ethyl acetate 10:1 to 4:1) afforded 0.060 g of a mixture of **14** and **15** in an 80:20 ratio (60 % yield) and 0.007 g of **16** (7%); data for **14**: ^1H NMR (CDCl_3 , 300 MHz): δ 7.43-7.54 (m, 4H), 6.04 (d, 1H, $J = 7.2$ Hz), 4.72 (s, 1H), 3.44 (s, 3H), 3.32 (m, 1H), 2.94 (dd, 1H, $J = 18.2, 10.6$ Hz), 2.35 (dd, 1H, $J = 18.2, 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz): δ 176.1, 141.1, 139.6, 130.1, 130.1, 126.5, 126.3, 88.3, 85.9, 56.6, 44.4, 32.9; IR (neat) 1773 cm^{-1} , 1172 cm^{-1} , 1092 cm^{-1} , 1024 cm^{-1} ; HRMS (DART) calculated for $\text{C}_{12}\text{H}_{13}\text{O}_3$ $[\text{M}+\text{H}]^+$: 205.0859, found: 205.0857; data for **15**: ^1H NMR (CDCl_3 , 300 MHz): δ 7.35-7.49 (m, 4H), 5.72 (d, 1H, $J = 7.2$ Hz), 4.82 (d, 1H, $J = 6.9$ Hz), 3.55-3.66 (m, 1H), 3.48 (s, 3H), 2.73 (dd, 1H, $J = 18.2, 7.2$ Hz), 2.58 (dd, 1H, $J = 18.2, 10.2$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz): δ 176.9, 141.9, 137.9, 130.0, 129.4, 126.0, 125.5, 83.6, 82.0, 57.7, 41.9, 28.0; IR (neat) 1773 cm^{-1} , 1176 cm^{-1} , 1112 cm^{-1} , 1092 cm^{-1} , 1025 cm^{-1} ; MS (DART) calculated for $\text{C}_{12}\text{H}_{13}\text{O}_3$ $[\text{M}+\text{H}]^+$: 205.0859, found: 205.0859; Data for **16**: ^1H NMR (CDCl_3 , 300 MHz): δ 7.45 (d, 1H, $J = 7.5$ Hz), 7.16-7.28 (m, 3H), 6.69 (s, 1H), 5.09 (s, 1H), 3.74 (s, 3H), 3.46 (d, 1H, $J = 17.0$ Hz), 3.39 (d, 1H, $J = 17.0$ Hz), 3.06 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.2, 142.9, 141.8, 141.2, 131.3, 128.5, 125.4, 123.9, 121.1, 83.8, 52.4, 52.0, 33.6; IR (neat) 1735 cm^{-1} ; MS (DART) calculated for $\text{C}_{13}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$: 219.1016, found: 219.1011.

Representative procedure for triflic acid catalyzed cyclization: Triflic acid (0.21 mL of a 0.23 M solution in CH₂Cl₂, 0.048 mmol) was added to solution of **12** (0.098 g, 0.48 mmol) in CH₂Cl₂ (4.0 mL) at -78 °C. After 1h, the mixture was warmed to 0 °C and stirred for 3 h, when thin layer chromatographic analysis indicated complete consumption of **12**. The reaction mixture was then poured onto ice and extracted with CH₂Cl₂. The combined organic extract was washed with brine, dried over magnesium sulfate, and concentrated to 1 mL. Flash chromatography (gradient, hexanes:ethyl acetate 10:1 to 4:1) afforded 0.067 g of a mixture of **14** and **15** in a 99:1 ratio (68% yield) and 0.002 g of **16** (2%). The compounds exhibited spectral data identical to those obtained above.

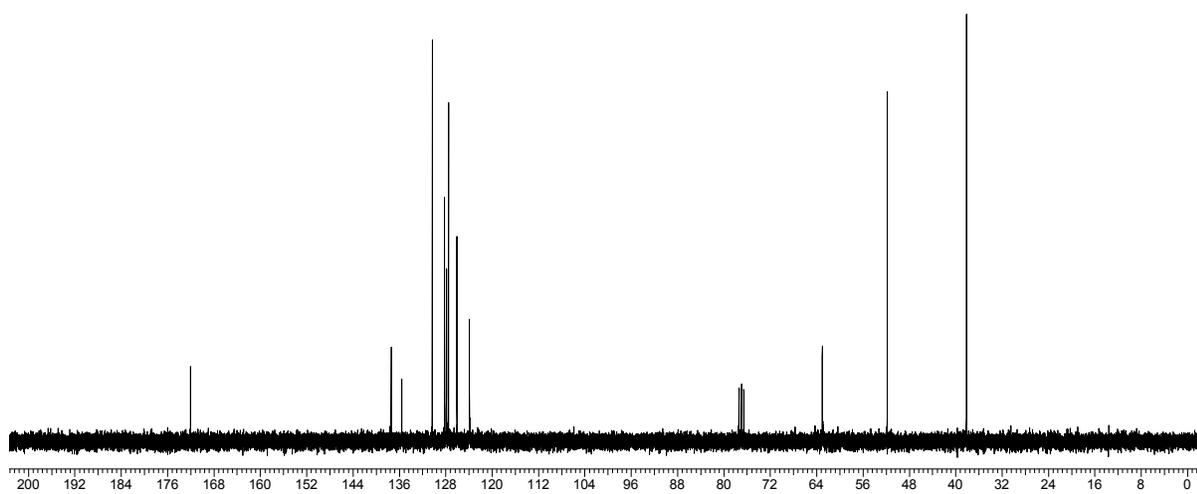
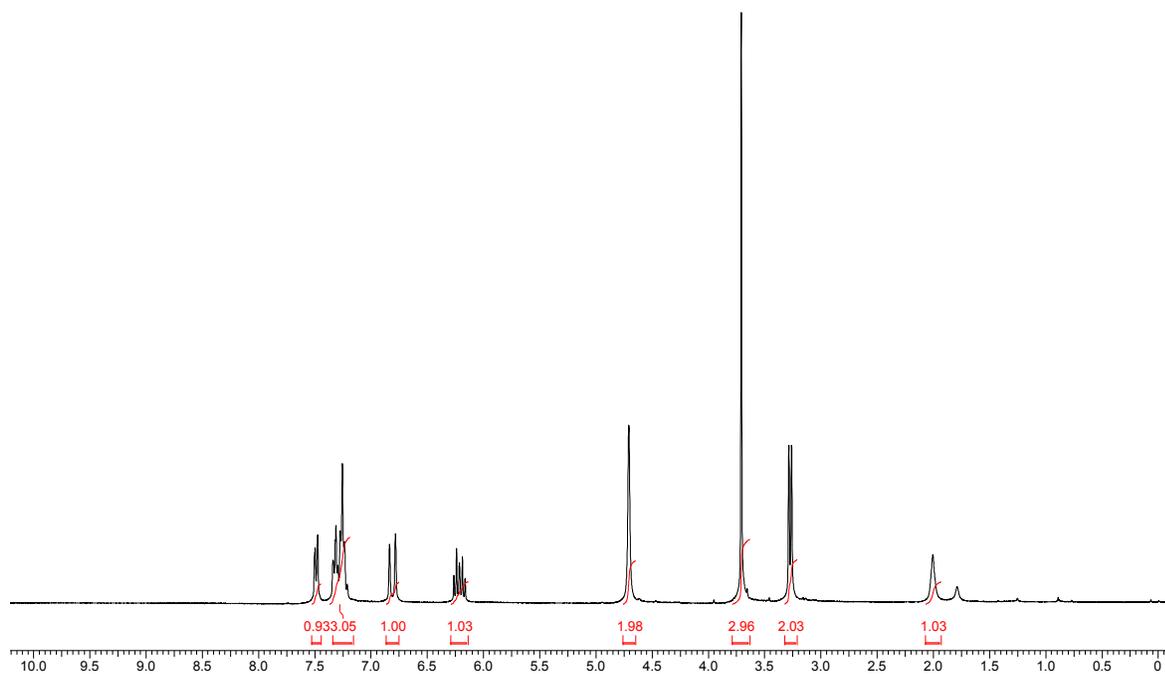
Computational methods

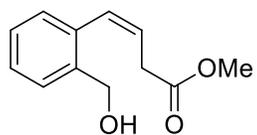
Geometry optimizations of protonated aldehydes, transition states and cyclized structures employed the 6-31G(*d,p*) basis set for all atoms. Single-point energy calculations were then performed for each of these optimized structures with the 6-311+G(2*d*,2*p*) basis set. Solvation effects were taken into account by performing single-point calculations on the optimized structures using the conductorlike polarizable continuum model (CPCM) method with the UAKS radii. The parameters for CH₂Cl₂ were used for all solvation calculations. All stationary point structures were confirmed either as minima (no imaginary frequencies) or transition states (only one imaginary frequency) by analytical frequency calculations at the same theory level as the geometry optimizations. All energies reported for the transition states have been corrected for solvation and zero-point vibrational effects.



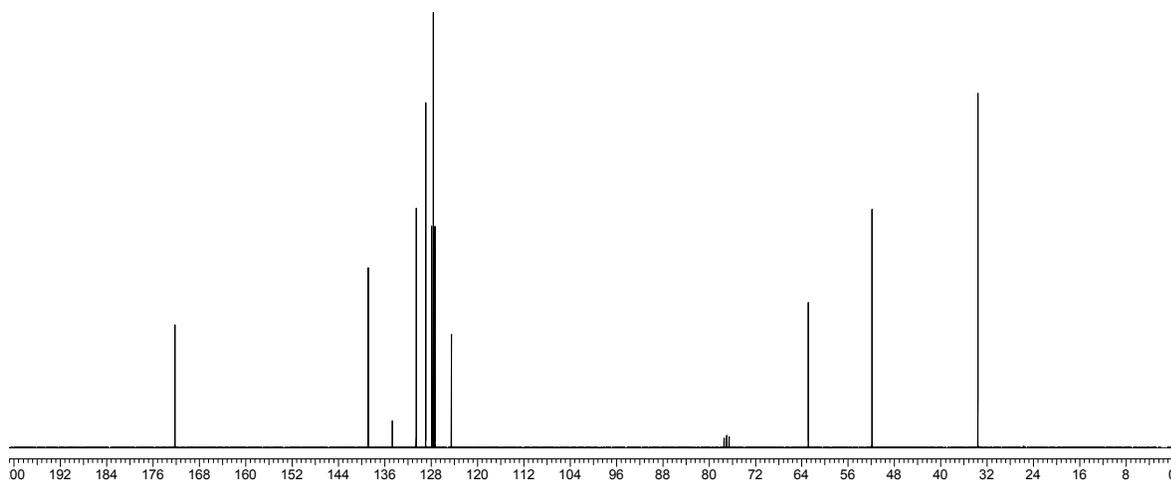
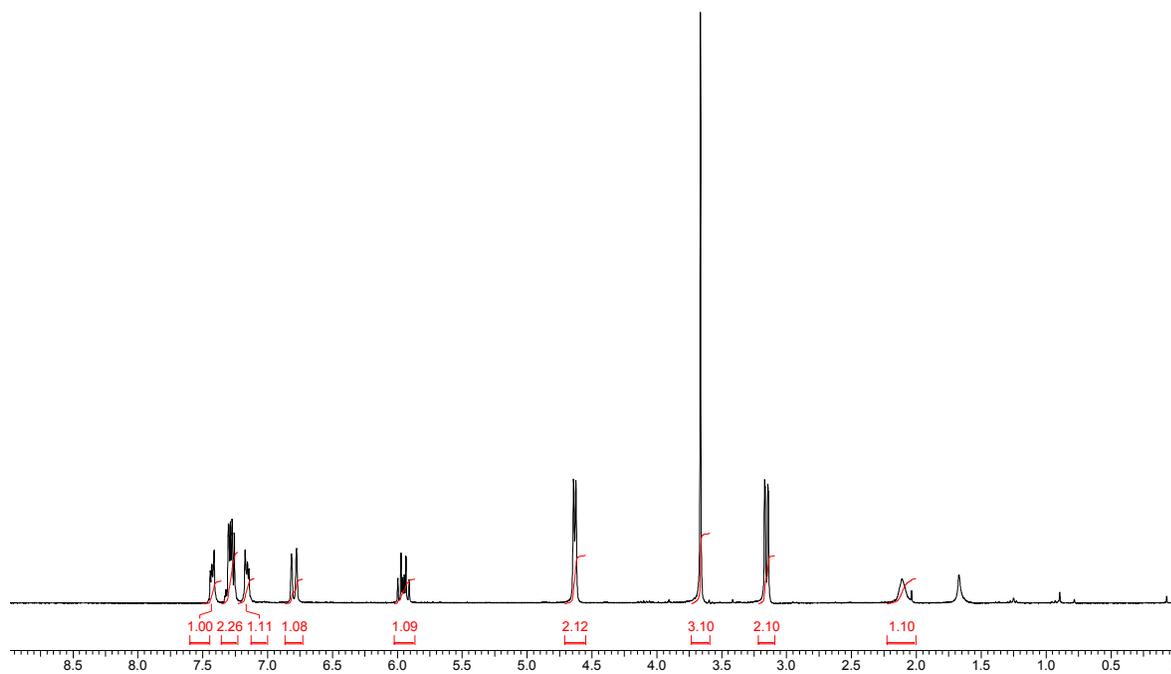


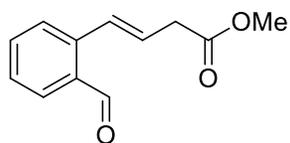
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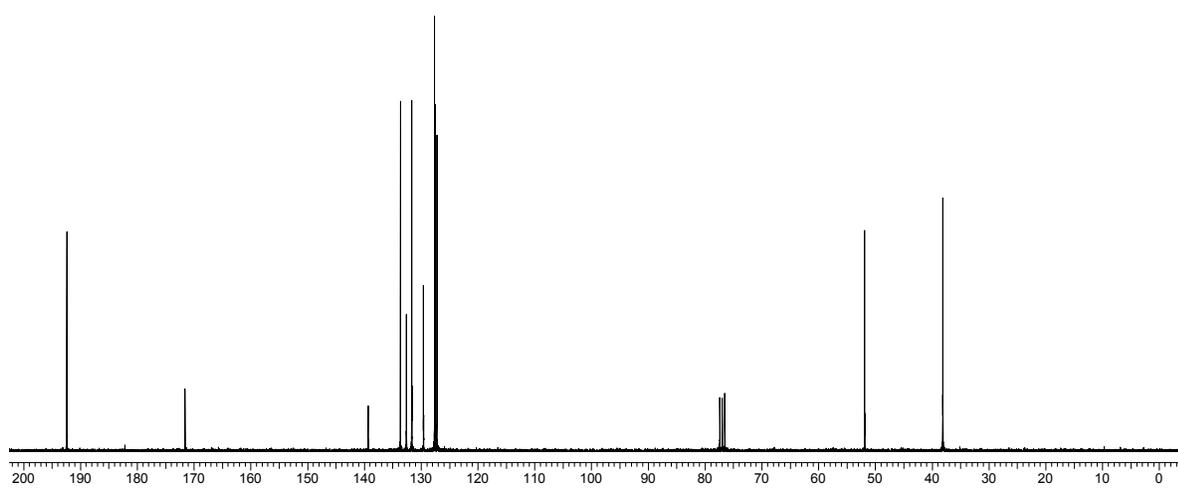
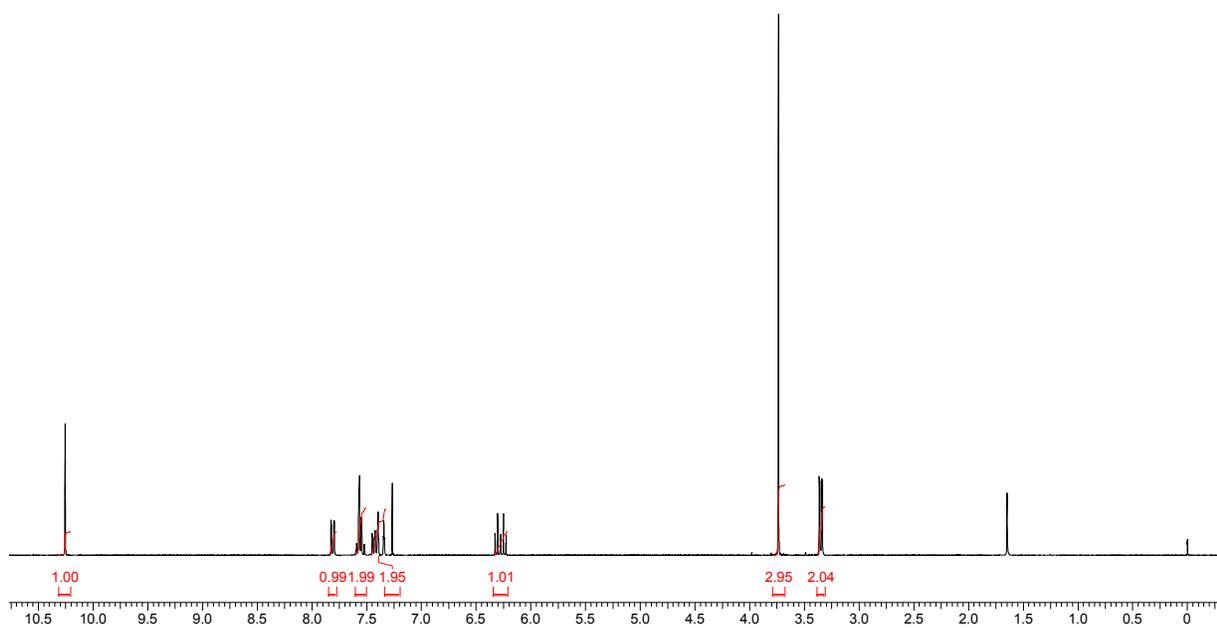


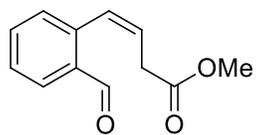
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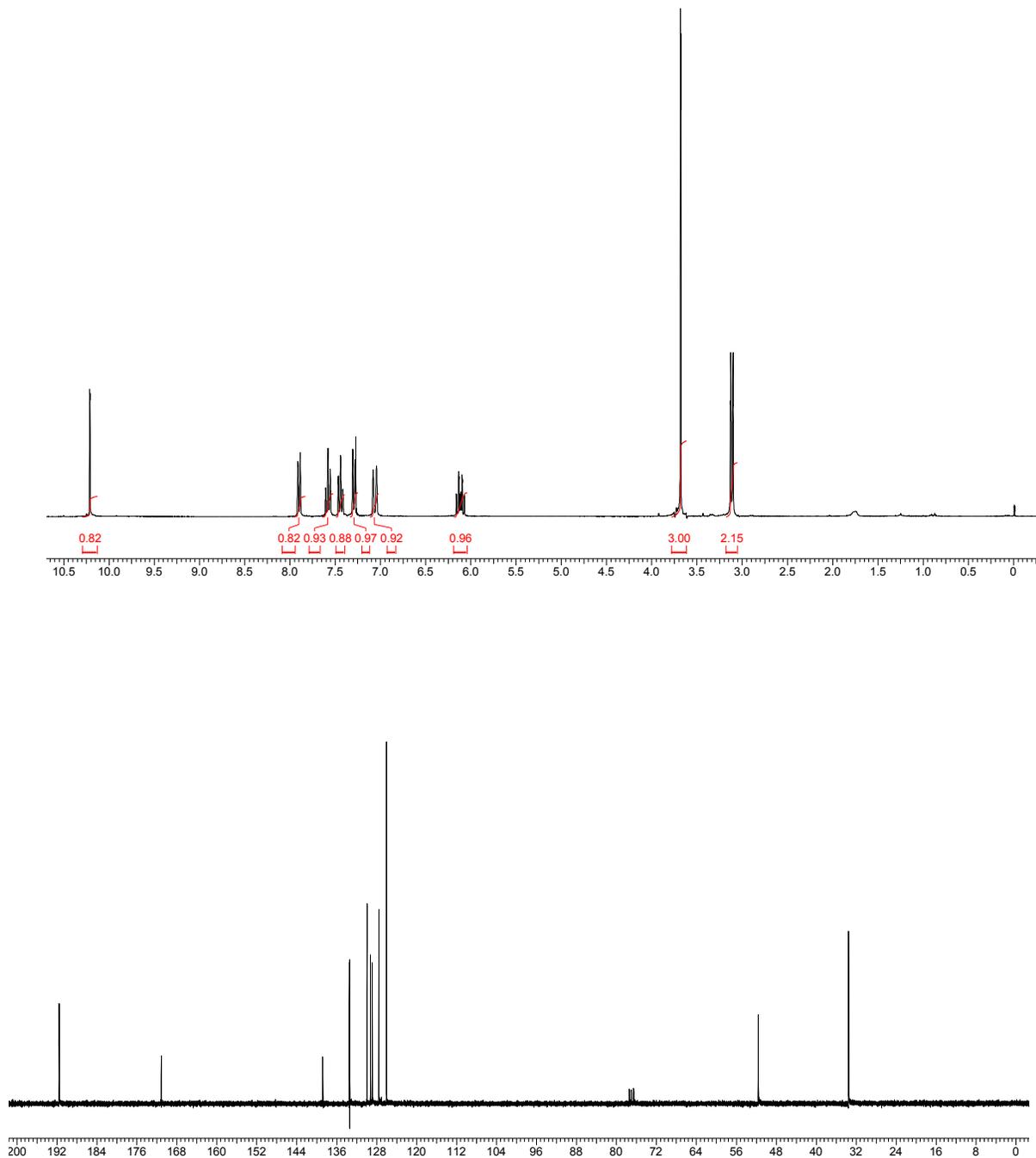


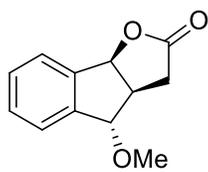
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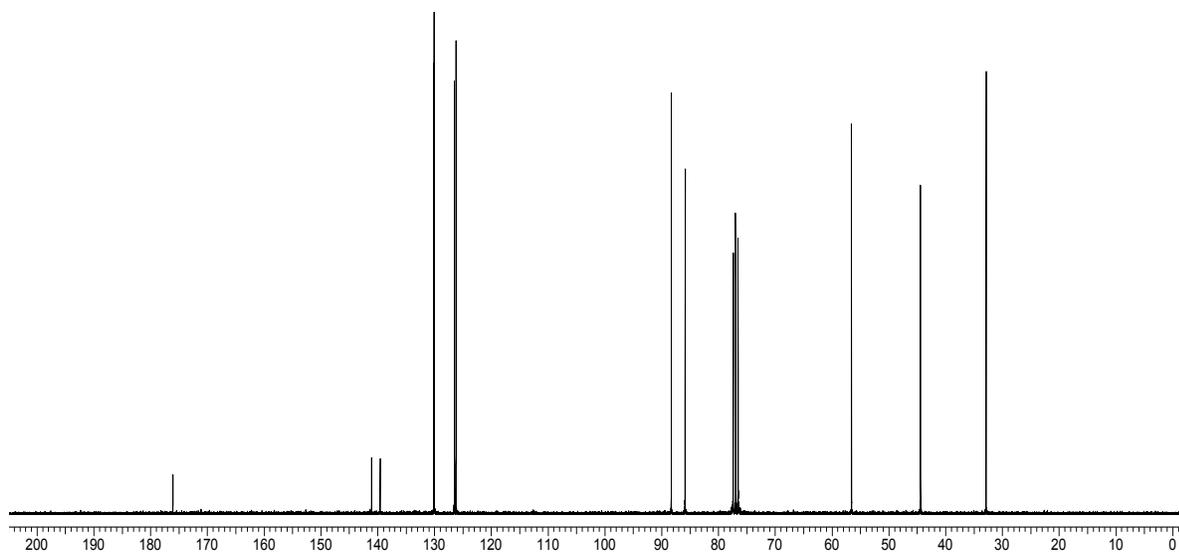
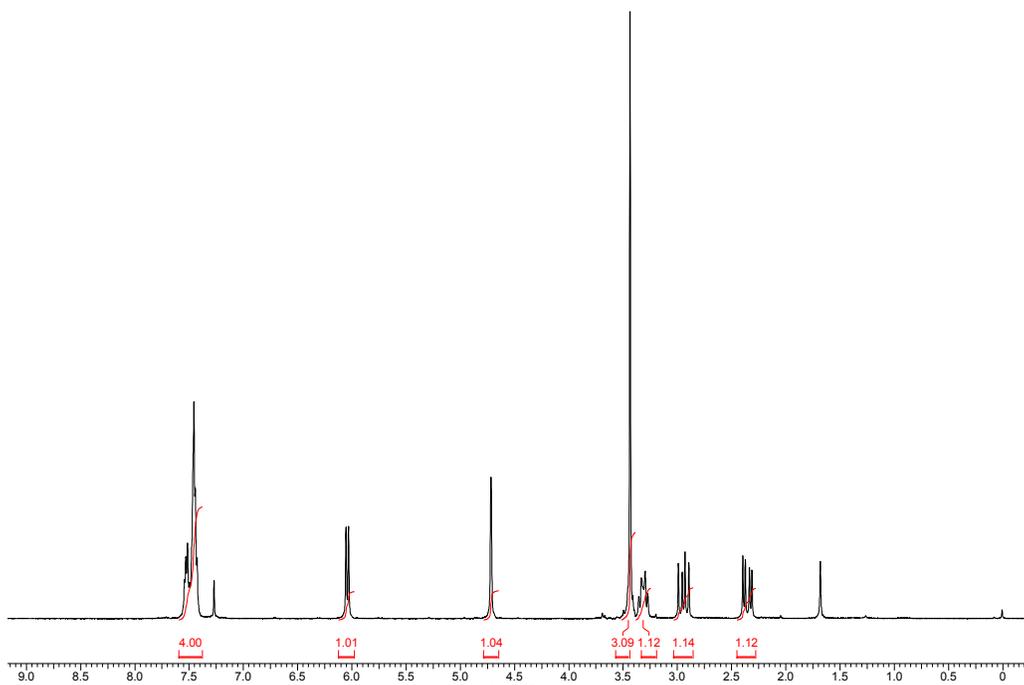


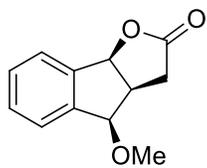
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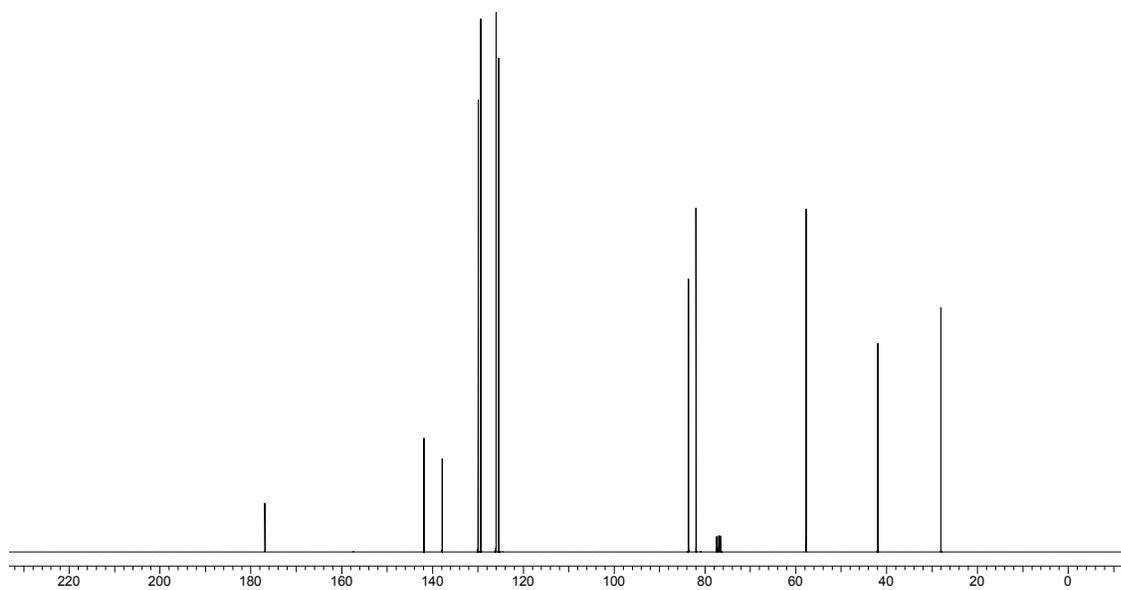
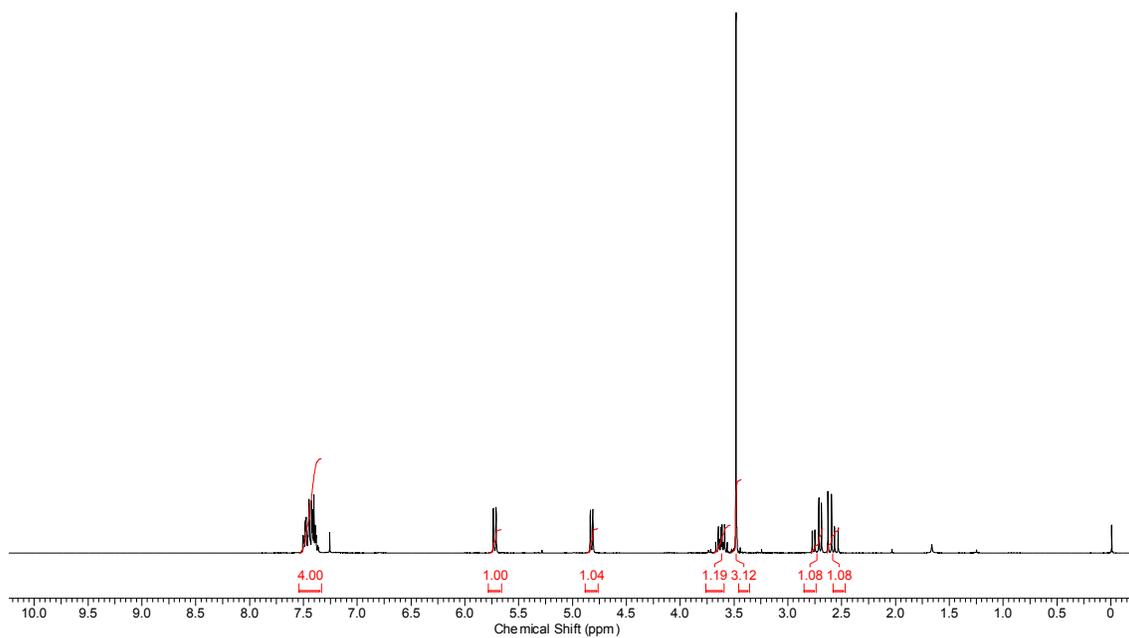


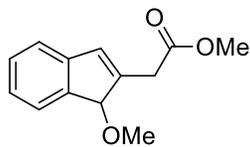
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