Rhodium Carbenoid Initiated O−H Insertion/Aldol/Oxy-Cope Cascade for the Stereoselective Synthesis of Functionalized Oxacycles

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A. MATERIALS AND METHODS

Reagents

Reagents and solvents were obtained from Sigma-Aldrich (www.sigma-aldrich.com), Chem-Impex (www.chemimpex.com) or Acros Organics (www.fishersci.com) and used without further purification unless otherwise indicated. Dry solvents such as dichloromethane was distilled over CaH under N_2 unless otherwise indicated. THF purchased from Sigma-Aldrich was distilled over Na metal with benzophenone indicator. Dry toluene and acetonitrile were obtained from Acros Organics (www.fishersci.com) in 1 L bottles stored over molecular sieves.

Reactions

All reactions were performed in flame-dried glassware under positive N_2 pressure with magnetic stirring unless otherwise noted. Liquid reagents and solutions were transferred through rubber septa via syringes flushed with N_2 prior to use. Cold baths were generated as follows: 0 °C with wet ice/water and −78 °C with dry ice/acetone. Syringe pump addition reactions were conducted using a Harvard Apparatus (Model: 55-1111) or a New Era Pump Systems, Inc. (Model: NE-300) syringe pump.

Chromatography

TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$), cerium ammonium molybdenate (CAM), phosphomolybdic acid (PMA), and ninhydrin. Silica flash chromatography was performed on Sorbtech 230–400 mesh silica gel 60.

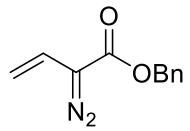
Analytical Instrumentation

IR spectra were recorded on a Shimadzu IRAffinity-1 FTIR spectrometer with peaks reported in cm^{-1}. NMR spectra were recorded on a Varian VNMRS 400 and 500 MHz NMR spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ ((^1H, 7.26 ppm, ^{13}C, 77.0 ppm); coupling constants are expressed in Hz. NMR spectra were processed using Mnova (www.mestrelab.com/software/mnova-nmr). Mass spectra were obtained at the OU Analytical Core Facility on an Agilent 6538 High-Mass-Resolution QTOF Mass Spectrometer and an Agilent 1290 UPLC. X-ray crystallography analysis was carried out at the University of Oklahoma using a Bruker APEX ccd area detector (1) and graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) source. Crystal structures were visualized using CCDC Mercury software (http://www.ccdc.cam.ac.uk/products/mercury/).

Nomenclature

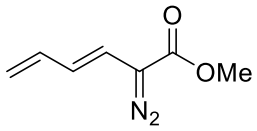
N.B.: Atom numbers shown in chemical structures herein correspond to IUPAC nomenclature, which was used to name each compound.

B. SYNTHESIS OF DIAZO ESTERS 1a, 1b



1a

Benzyl 2-diazobut-3-enoate (1a). Compound was prepared using known literature procedure.[1]



1b

Methyl (E)-2-diazohexa-3,5-dienoate (1b). To a stirred solution of diisopropylamine (1.1 mL, 8.09 mmol, 1.2 equiv) in dry THF (10 mL) at –78 °C was added *n*-BuLi (4.6 mL, 7.44 mmol, 1.1 equiv, 1.6 M) and stirred for 30 minutes at –78 ºC. Then HMPA (2.3 mL, 13.5 mmol, 2.0 equiv) was added and allowed to stir for an additional 5 minutes. Methyl (E)-hexa-3,5-dienoate, prepared from known literature procedures[2] was then added (850 mg, 6.70 mmol, 1.0 equiv) in 10 mL THF and allowed to stir for 30 minutes at −78 °C. Once enolate formation was complete, a solution of 4-Acetamidobenzenesulfonyl azide (*p*-ABSA) (1.94 g, 8.09 mmol) in 8 mL THF was added and the reaction was allowed to stir for an additional 30 minutes at −78 °C. The reaction was then allowed to slowly reach −20 °C over 1.5 h before it was quenched with saturated solution of NH_4Cl (10 mL). The reaction mixture was then extracted with EtOAc (3 × 30 mL), and the combined EtOAc layers were washed with water (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound. Column chromatographic purification of the crude compound over silica gel (9:1 hexanes/EtOAc) afforded the compound **1b** (622 mg, 65%) as a red oil. **TLC**: R_f 0.50 (9:1 hexanes/EtOAc). **IR** (NaCl): 3005, 2085, 1710, 1627, 1436, 1327, 1168, 1103, 999, 742. **^{1}H NMR** (400 MHz) δ 6.57–6.30 (m, 1H), 5.93 (m, J = 1.6 Hz, 2H), 5.14–5.07 (dd, 1H), 4.99 (dd, J = 10.1, 1.6 Hz, 1H), 3.80 (s, 3H). **^{13}C NMR** (101 MHz) δ 165.3, 136.0, 124.2, 115.1, 114.9, 52.2.

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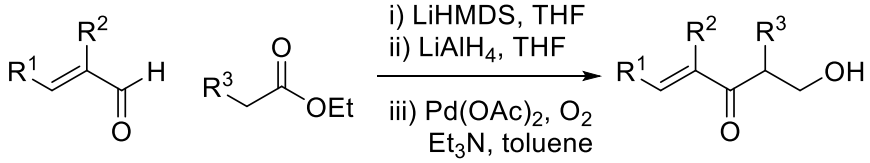
1. Wu, J. Q.; Yang, Z.; Zhang, S. S.; Jiang, C. Y.; Li, Q. J.; Huang, Z. S.; Wang, H. G. *ACS Catal.* **2015**, *5*, 6453−6457.
2. Iosub, A. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2015**, *137*, 3454−3457.

C. SYNTHESIS OF *β*-HYDROXY VINYL KETONES 2a–2f

Method A

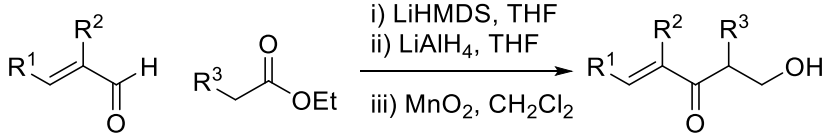


To a stirred solution of ethyl ester (1.0 equiv, commercial available) in THF (0.55 M) was added LiHMDS (1.1 equiv, 1.0 M) at −78 °C. The resulting mixture was stirred for 1 h at −78 °C. Corresponding aldehyde (1.0 equiv, commercially available) was then added *via* syringe and the temperature was maintained for 3 h at −78 °C. Reaction was then quenched at –78 °C with saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with ethyl acetate (3x). The combined extracts were dried over Na_2SO_4. The crude reaction extract was filtered through a silica gel plug, evaporated under reduced pressure and the residue was taken forward without further purification.

To a stirred suspension of $LiAlH_4$ (1.2 equiv, 0.25 M) in dry THF at 0 °C was added a solution of crude aldol product (1.0 equiv, 0.4 M) in freshly distilled THF (0.4 M). Reaction was monitored by TLC until completion (1-2 h). Reaction was quenched by adding copious amounts of ethyl acetate followed by 15% aqueous NaOH solution at 0 °C. The crude mixture was filtered through a celite pad and extracted with ethyl acetate (3x). The combined organic layers were then dried over sodium sulfate, filtered through a silica gel plug and concentrated by rotary evaporation to afford the crude diol that was taken forward without further purification.

$Pd(OAc)_2$ (0.01 equiv) and Et_3N (0.03 equiv) were dissolved in THF–toluene (15%; 3.4 mL). Crude diol (1.0 mmol) was added and the reaction mixture was heated to 45 °C under 1 atm of O_2 (balloon) for 20 h. After completion of reaction, solvent was evaporated under reduced pressure. Purification by silica gel flash chromatography using hexanes-ethyl acetate (30-40%, gradient elution) afforded *β*-hydroxy vinyl ketone.

Method B

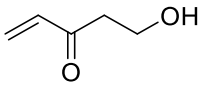


To a stirred solution of ethyl ester (1.0 equiv, commercial available) in THF (0.55 M) was added LiHMDS (1.1 equiv, 1.0 M) at −78 °C. The resulting mixture was stirred for 1 h at −78 °C. Corresponding aldehyde (1.0 equiv, commercially available) was then added *via* syringe and the temperature was maintained for 3 h at −78 °C. Reaction was then quenched at –78 °C with saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with ethyl acetate (3x). The combined extracts were dried over Na_2SO_4. The crude reaction extract was filtered through a silica gel plug, evaporated under reduced pressure and the residue was taken forward without further purification.

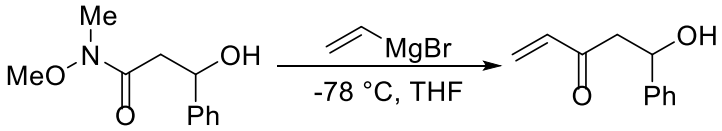
To a stirred suspension of $LiAlH_4$ (1.2 equiv, 0.25 M) in dry THF at 0 °C was added a solution of crude aldol product (1.0 equiv, 0.4 M) in freshly distilled THF (0.4 M). Reaction was monitored by TLC until completion (1-2 h). Reaction was quenched by adding copious amounts of ethyl acetate followed by 15% aqueous NaOH solution at 0 °C. The crude mixture was filtered

through a celite pad and extracted with ethyl acetate (3x). The combined organic layers were then dried over sodium sulfate, filtered through a silica gel plug and concentrated by rotary evaporation to afford the crude diol that was taken forward without further purification.

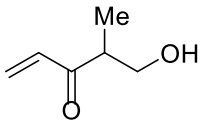
To a stirred solution of crude diol (1.0 equiv) in CH_2Cl_2 (0.1 M) was added MnO_2 (20.0 equiv) all at once. The reaction was stirred overnight. Then the mixture was filtered over a celite pad and concentrated by rotary evaporation to afford the crude product. Purification by silica gel flash chromatography using hexanes-ethyl acetate (30-40%, gradient elution) afforded β-hydroxy vinyl ketone.



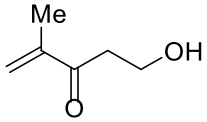
5-hydroxypent-1-en-3-one (2a). Prepared from acrolein and ethyl acetate using general procedure **A**. Pale yellow oil (392 mg, 80%). **TLC**: R_f 0.28 (1:1 hexanes/EtOAc). **IR** (NaCl): 3410, 3394, 2947, 2893, 1672, 1614, 1406, 1197, 1049, 972, 621. **^{1}H NMR** (500 MHz) δ 6.33 (dd, J = 17.7, 10.5 Hz, 1H), 6.23 (dd, J = 17.7, 1.1 Hz, 1H), 5.88 (dd, J = 10.4, 1.1 Hz, 1H), 3.87 (t, J = 5.5 Hz, 2H), 2.84 (t, J = 5.0 Hz, 2H), 2.78 (s, 1H). **^{13}C NMR** (126 MHz) δ 200.9, 136.5, 129.1, 57.6, 41.1.



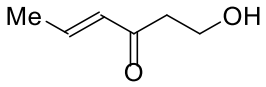
5-hydroxy-5-phenylpent-1-en-3-one (2b). To a solution of Weinreb amide (600 mg, 2.87 mmol 1.0 equiv, prepared from known literature protocol[3]) in THF (48 mL) was added vinyl magnesium bromide solution (6.9 mL, 6.90 mmol, 2.4 equiv, 1.0 M) at −78 °C over the course of 10 minutes. The temperature was maintained at −78 °C for six hours prior to quenching with ammonium chloride at −78 °C. The aqueous layer was separated and extracted with ethyl acetate (3x). The combined extracts were dried over Na_2SO_4 and concentrated by rotary evaporation to afford crude product. Purification by silica gel flash chromatography using hexanes-ethyl acetate (25-30%, gradient elution) afforded pure **2f** as a pale yellow oil (121 mg, 24%). **TLC**: R_f 0.40 (7:3 hexanes/EtOAc). **IR** (NaCl): 3458, 1682, 1614, 1402, 760, 702. **^{1}H NMR** (400 MHz) δ 7.41–7.31 (m, 4H), 7.31–7.23 (m, 1H), 6.35 (dd, J = 17.7, 10.4 Hz, 1H), 6.22 (dd, J = 17.8, 1.1 Hz, 1H), 5.89 (dd, J = 10.5, 1.1 Hz, 1H), 5.19 (dt, J = 8.8, 2.6 Hz, 1H), 3.51 (d, J = 2.9 Hz, 1H), 3.09–2.89 (m, 2H). **^{13}C NMR** (101 MHz) δ 200.4, 142.8, 136.5, 129.4, 128.4, 127.5, 125.6, 69.7, 47.8. Data matches known literature values.[4]



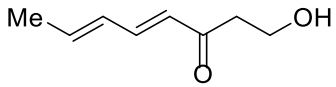
5-hydroxy-4-methylpent-1-en-3-one (2c). Prepared from acrolein and ethyl propionate using general procedure **A**. Pale yellow oil (127 mg, 16% isolated over three steps). **TLC**: R_f 0.30 (2:3 hexanes/EtOAc). **IR** (NaCl): 3491, 2972, 2935, 2882, 1738, 1686, 1516, 1462, 1406, 1030, 980. **^{1}H NMR** (400 MHz) δ 6.39 (dd, J = 17.5, 10.5 Hz, 1H), 6.24 (dd, J = 17.6, 1.3 Hz, 1H), 5.78 (dd, J = 10.5, 1.3 Hz, 1H), 3.77–3.57 (m, 2H), 3.00 (pd, J = 7.2, 4.5 Hz, 1H), 1.07 (d, J = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz) δ 203.8, 135.1, 128.9, 64.0, 45.2, 13.4. Data matches known literature values.[5]



5-hydroxy-2-methylpent-1-en-3-one (2d). Prepared from methacrolein and ethyl acetate using general procedure **B**. Pale yellow oil (347 mg, 27% isolated over three steps). **TLC**: R_f 0.20 (3:2 hexanes/EtOAc). **IR** (NaCl): 3445, 2957, 2928, 2889, 2357, 2326, 1672, 1373, 1053, 939, 737. **^{1}H NMR** (400 MHz) δ 6.00 (s, 1H), 5.85–5.83 (m, 1H), 3.91 (q, J = 5.3 Hz, 2H), 2.95 (t, J = 5.4 Hz, 2H), 2.53 (s, 1H), 1.92–1.86 (m, 3H). **^{13}C NMR** (101 MHz) δ 201.4, 144.1, 125.3, 57.6, 39.3, 16.9.



(E)-1-hydroxyhex-4-en-3-one (2e). Prepared from predominately trans crotonaldehyde and ethyl acetate using general procedure **B**. Pale yellow oil (726 mg, 61% isolated over three steps). **TLC**: R_f 0.48 (1:1 hexanes/EtOAc). **IR** (NaCl): 3443, 3422, 3398, 2965, 2945, 2889, 1661, 1632, 1443, 1373, 1055, 972, 737. **^{1}H NMR** (400 MHz) δ 6.89 (dq, J = 15.8, 6.8 Hz, 1H), 6.13 (dq, J = 15.8, 1.7 Hz, 1H), 3.88 (t, J = 5.4 Hz, 2H), 2.79 (t, J = 5.4 Hz, 2H), 2.61 (s, 1H), 1.92 (dd, J = 6.8, 1.7 Hz, 3H). **^{13}C NMR** (101 MHz) δ 200.6, 143.9, 132.1, 58.1, 41.2, 18.3. Data matches known literature values.[6]



(4E,6E)-1-hydroxyocta-4,6-dien-3-one (2f). Prepared from sorbaldehyde and ethyl acetate using general procedure **B**. Pale yellow oil (412 mg, 35% isolated over three steps). **TLC**: R_f 0.2 (3:2 hexanes/EtOAc). **IR** (NaCl): 3441, 3416, 2963, 2938, 2913, 2886, 2359, 1678, 1636, 1591, 1377, 1190, 1055, 999. **^{1}H NMR** (500 MHz) δ 7.19–7.12 (m, 1H), 6.29–6.13 (m, 2H), 6.07 (d, J = 15.7 Hz, 1H), 3.89 (t, J = 5.4 Hz, 2H), 2.82 (t, J = 5.4 Hz, 2H), 2.65 (s, 1H), 1.88 (d, J = 5.1 Hz, 3H). **^{13}C NMR** (126 MHz) δ 201.0, 143.9, 141.2, 130.1, 127.6, 58.2, 41.7, 18.8.

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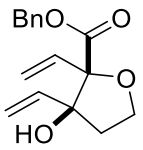
3. Roche, C.; Labeeuw, O.; Haddad, M.; Ayad, T.; Genet, J.-P.; Ratovelomanana-Vidal, V.; Phansavath, P. *Eur. J. Org. Chem.* **2009**, 3977.
4. Hong, B. C.; Chin, S. F. *Synthetic Communications* **1997**, *27*, 1191–1197.
5. Batt, F.; Bourcet, E.; Kassab, Y.; Fache, F. *Synlett* **2007**, *12*, 1869–1872.
6. Prandi, C.; Venturello, P. *J. Org. Chem.* **1994**, *59*, 3494–3496.

D. SYNTHESIS OF ALDOL CASCADE INTERMEDIATE 3a



Benzyl 3-hydroxy-2,3-divinyltetrahydrofuran-2-carboxylate (3a). To a flame dried 15 mL pear shaped round bottom with stir bar was added $Rh_2(esp)_2$ (1 mol%). A solution of *β*-hydroxy vinyl ketone (25 mg, 0.25 mmol) in 1.5 mL CH_2Cl_2 was then added, the flask was equipped with a reflux condenser, and set to stirring while at reflux. While at reflux, a solution of vinyl diazo (76 mg, 0.37 mmol) in 1 mL CH_2Cl_2 was added over 3 h *via* syringe pump at this temperature. After the addition was completed, the reaction was left to reflux for an additional 1 hour. After reaction was completed, the crude reaction mixture was concentrated using rotary evaporation and then purified using flash column chromatography eluting with 1:3 ethyl acetate: hexanes to afford aldol product **3a** as a colorless liquid (49 mg, 72%). **TLC**: R_f 0.21 (7:3 hexanes/EtOAc). **IR** (NaCl): 3522, 3496, 3481, 3466, 2981, 2951, 2893, 1734, 1718, 1639, 1456, 1375, 1267, 1151, 1056, 991, 929, 742. **^{1}H NMR** (400 MHz) δ 7.36–7.31 (m, 5H), 6.09–5.98 (m, 2H), 5.51 (dd, J = 17.0, 1.4 Hz, 1H), 5.33 (dd, J = 17.3, 1.1 Hz, 1H), 5.29–5.15 (m, 4H), 4.33–4.25 (m, 1H), 4.20–4.15 (m, 1H), 2.43 (d, J = 2.8 Hz, 1H), 2.25–2.16 (m, 1H), 1.90 (ddd, J = 12.8, 6.1, 1.7 Hz, 1H). **^{13}C NMR** (101 MHz): δ 170.2, 137.4, 135.5, 135.3, 128.5, 128.2, 128.1, 116.5, 115.8, 91.9, 84.3, 67.0, 66.9, 37.2. **ESI-MS** *m/z* calcd for $C_{16}H_{18}O_4Na$ ($[M+Na]^+$) 297.1102; found 296.5. Relative stereochemistry was assigned based on previous literature reports.[7]

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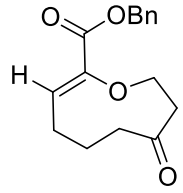
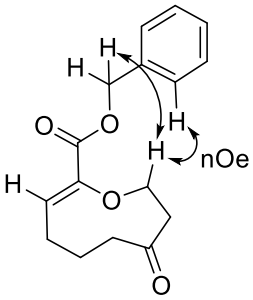
7. Nicolle, S. M.; Christopher W. L.; Hayes, J.; Moody, C. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 8485–8489.

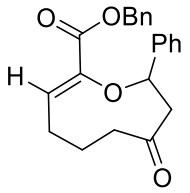
E. General Procedure for the Synthesis of Oxacycles 4a–4k

To a flame dried 15 mL pear shaped round bottom with stir bar was added $Rh_2(OAc)_4$ (1 mol%). A solution of *β*-hydroxy vinyl ketone (0.25 mmol) in 1.5 mL toluene was then added, the flask was equipped with a reflux condenser, and set to stirring while at reflux. While at reflux a solution of vinyl diazo (0.37 mmol) in 1 mL toluene was added over 3 h *via* syringe pump at this temperature. After the addition was completed, the reaction was left to reflux for an additional 1 hour. After reaction was completed, the crude reaction mixture was purified using flash column chromatography eluting with 1:3 ethyl acetate: hexanes to afford oxacycle **4a–4k**.

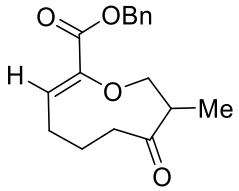




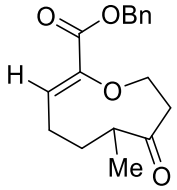
Benzyl (Z)-7-oxo-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4a). Colorless liquid (47 mg, 68%). **TLC**: R_f 0.34 (7:3 hexanes/EtOAc). **IR** (NaCl): 3496, 2953, 2937, 1726, 1712, 1647, 1498, 1454, 1269, 1170, 1101, 769, 752, 738, 698. **^{1}H NMR** (400 MHz) δ 7.40–7.34 (m, 5H), 6.39 (t, J = 8.4 Hz, 1H), 5.23 (s, 2H), 4.34 (t, J = 6.0 Hz, 2H), 2.67 (t, J = 6.0 Hz, 2H), 2.47–2.44 (m, 2H), 2.26–2.20 (m, 2H), 1.94–1.88 (m, 2H). **^{13}C NMR** (101 MHz): δ 212.6, 163.4, 146.8, 135.6, 128.6, 128.3, 128.2, 127.4, 69.8, 66.8, 44.6, 37.6, 23.0. **HRMS** (ESI) *m/z* calcd for $C_{16}H_{18}O_4Na$ ($[M+Na]^+$) 297.1102; found 297.1105.



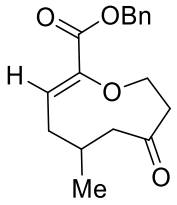
Benzyl (Z)-7-oxo-9-phenyl-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4b). Colorless liquid (34.6 mg, 58%). **TLC**: R_f 0.46 (7:3 hexanes/EtOAc). **IR** (NaCl): 3061, 3032, 2947, 1712, 1649, 1498, 1452, 1379, 1263, 975, 916, 744, 698. **^{1}H NMR** (400 MHz) δ 7.40–7.26 (m, 8H), 7.17–7.15 (m, 2H), 6.37 (t, J = 7.9 Hz, 1H), 5.27 (dd, J = 11.2, 3.5 Hz, 1H), 5.06 (q, J = 12.3 Hz, 2H), 3.18 (dd, J = 14.3, 11.3 Hz, 1H), 2.66–2.57 (m, 3H), 2.55–2.49 (m, 1H), 2.39 (dt, J = 17.0, 6.5 Hz, 1H), 2.13 (dtd, J = 14.8, 7.6, 2.8 Hz, 1H), 1.80–1.71 (m, 1H). **^{13}C NMR** (101 MHz): δ 211.7, 163.3, 146.5, 141.4, 135.4, 128.4, 128.3, 128.2, 128.1, 127.6, 127.0, 125.5, 82.4, 66.7, 52.5, 41.4, 24.6, 22.9. **HRMS** (ESI) *m/z* calcd for $C_{22}H_{22}O_4Na$ ($[M+Na]^+$) 373.1415; found 373.1419.



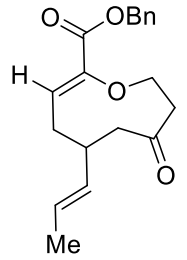
Benzyl (Z)-8-methyl-7-oxo-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4c). Colorless liquid (35 mg, 60%). **TLC**: R_f 0.44 (7:3 hexanes/EtOAc). **IR** (NaCl): 3977, 2960, 2933, 1743, 1718, 1647, 1456, 1269, 1170, 1103, 752, 738, 698. **^{1}H NMR** (400 MHz) δ 7.39–7.33 (m, 5H), 6.36 (t, J = 8.5 Hz, 1H), 5.22 (s, 2H), 4.33 (dd, J = 11.7, 5.4 Hz, 1H), 3.94 (dd, J = 11.6, 8.6 Hz, 1H), 2.87 (ddd, J = 8.4, 7.0, 5.4 Hz, 1H), 2.44–2.40 (m, 2H), 2.19 (dtd, J = 12.7, 8.5, 4.3 Hz, 2H), 1.93 (td, J = 7.7, 3.9 Hz, 1H), 1.89–1.78 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz): δ 214.6, 163.4, 147.4, 135.6, 128.6, 128.3, 128.2, 126.7, 76.0, 66.8, 48.0, 35.5, 22.8, 22.4, 12.6. **HRMS** (ESI) *m/z* calcd for $C_{17}H_{20}O_4Na$ ($[M+Na]^+$) 311.1259; found 311.1263.



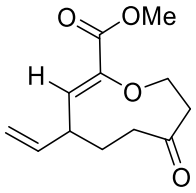
Benzyl (Z)-6-methyl-7-oxo-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4d). Colorless liquid (45 mg, 71%). **TLC**: R_f 0.43 (7:3 hexanes/EtOAc). **IR** (NaCl): 3859, 3741, 3647, 1737, 1712, 1647, 1543, 1512, 1456, 1265, 1165, 1095, 893, 842, 740. **^{1}H NMR** (400 MHz) δ 7.38–7.32 (m, 5H), 6.40 (dd, J = 9.2, 7.7 Hz, 1H), 5.26–5.18 (m, 2H), 4.46 (dt, J = 12.0, 5.2 Hz, 1H), 4.18 (ddd, J = 12.0, 8.9, 4.3 Hz, 1H), 2.88 (ddt, J = 9.9, 7.4, 3.7 Hz, 1H), 2.73 (ddd, J = 15.2, 5.5, 4.3 Hz, 1H), 2.62 (ddd, J = 15.0, 8.9, 5.0 Hz, 1H), 2.43–2.33 (m, 1H), 2.11–2.04 (m, 1H), 1.87 (tdd, J = 10.9, 5.8, 3.6 Hz, 1H), 1.68–1.60 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz): δ 215.7, 163.4, 146.3, 135.6, 128.6, 128.3, 128.2, 69.4, 66.8, 43.2, 42.5, 31.9, 22.7, 17.7. **HRMS** (ESI) *m/z* calcd for $C_{17}H_{20}O_4Na$ ($[M+Na]^+$) 311.1259; found 311.1263.



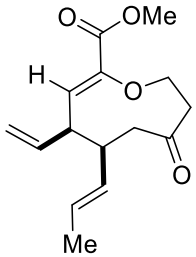
Benzyl (Z)-5-methyl-7-oxo-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4e). Colorless liquid (48.5 mg, 64%). **TLC**: R_f 0.45 (7:3 hexanes/EtOAc). **IR** (NaCl): 2956, 2929, 1726, 1716, 1456, 1267, 1093, 750, 738, 698. **^{1}H NMR** (400 MHz) δ 7.38–7.33 (m, 5H), 6.44 (t, J = 8.5 Hz, 1H), 5.27–5.18 (m, 2H), 4.47 (dt, J = 11.8, 5.0 Hz, 1H), 4.20 (ddd, J = 11.8, 9.6, 4.3 Hz, 1H), 2.70 (ddd, J = 14.9, 9.6, 5.1 Hz, 1H), 2.58 (dt, J = 15.5, 4.6 Hz, 1H), 2.52–2.45 (m, 1H), 2.45–2.36 (m, 2H), 2.22–2.18 (m, 1H), 2.02 (ddd, J = 13.5, 8.3, 6.0 Hz, 1H), 1.05 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz): δ 211.9, 163.3, 146.5, 135.6, 128.6, 128.3, 128.1, 126.5, 69.7, 66.8, 45.7, 44.8, 31.3, 30.1, 21.4. **HRMS** (ESI) *m/z* calcd for $C_{17}H_{20}O_4Na$ ($[M+Na]^+$) 311.1259; found 311.1263.



Benzyl (Z)-7-oxo-5-((E)-prop-1-en-1-yl)-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4f). Colorless liquid (34 mg, 61%). **TLC**: R_f 0.57 (7:3 hexanes/EtOAc). **IR** (NaCl): 3747, 3736, 3469, 2960, 1747, 1710, 1649, 1558, 1541, 1521, 1506, 1454, 1265, 1101, 752, 738, 698. **^{1}H NMR** (400 MHz) δ 7.39–7.32 (m, 5H), 6.42 (dd, J = 9.3, 8.0 Hz, 1H), 5.49–5.45 (m, 1H), 5.29–5.18 (m, 2H), 4.49 (dt, J = 11.8, 4.9 Hz, 1H), 4.20 (ddd, J = 11.8, 9.6, 4.5 Hz, 1H), 2.95 (ddd, J = 12.2, 8.0, 4.2 Hz, 1H), 2.74–2.66 (m, 1H), 2.65–2.61 (m, 1H), 2.58 (t, J = 4.6 Hz, 1H), 2.47 (ddd, J = 13.1, 9.3, 4.0 Hz, 1H), 2.22 (dd, J = 13.5, 4.5 Hz, 1H), 2.10 (ddd, J = 13.4, 8.0, 5.7 Hz, 1H), 1.89–1.86 (m, 1H), 1.66 (d, J = 8.0, 3H). **^{13}C NMR** (101 MHz): δ 211.5, 163.3, 146.7, 135.6, 133.5, 128.6, 128.3, 128.1, 126.4, 124.8, 69.7, 66.8, 44.8, 43.4, 38.8, 28.9, 17.9. **HRMS** (ESI) *m/z* calcd for $C_{19}H_{22}O_4Na$ ($[M+Na]^+$) 337.1415; found 337.1417.

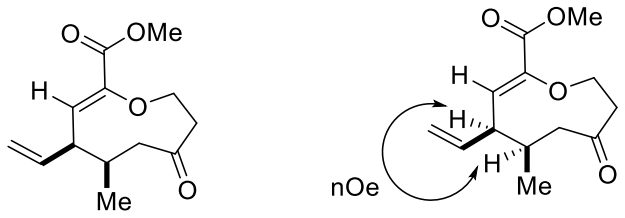


Methyl (Z)-7-oxo-4-vinyl-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4g). Colorless liquid (34.5 mg, 64%). **TLC**: R_f 0.44 (7:3 hexanes/EtOAc). **IR** (NaCl): 3745, 2954, 1722, 1647, 1541, 1512, 1433, 1340, 1309, 1292, 1246, 1097, 1001, 918, 775. **^{1}H NMR** (400 MHz) δ 6.17 (dd, J = 9.4, 0.9 Hz, 1H), 5.79–5.70 (m, 1H), 5.09–5.00 (m, 2H), 4.54–4.49 (m, 1H), 4.21–4.14 (m, 1H), 3.80 (s, 3H), 3.33–3.24 (m, 1H), 2.78–2.69 (m, 2H), 2.64–2.58 (m, 1H), 2.25–2.14 (m, 2H), 1.62–1.50 (m, 1H). **^{13}C NMR** (101 MHz): δ 212.2, 163.9, 145.5, 139.5, 129.4, 115.1, 69.5, 52.1, 44.5, 37.9, 37.1, 30.0. **HRMS** (ESI) ***m/z*** calcd for $C_{12}H_{16}O_4Na$ ($[M+Na]^+$) 247.0946; found 247.0948.

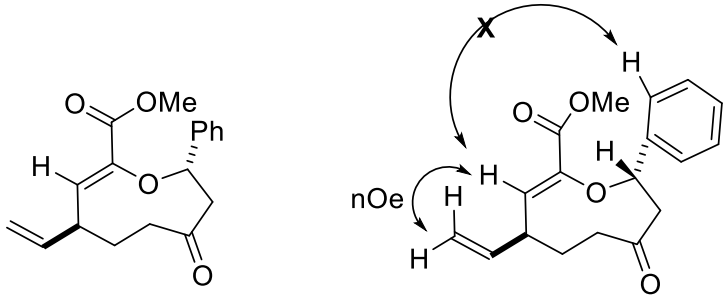


Methyl (4*R*,5*S*,Z)-7-oxo-5-((E)-prop-1-en-1-yl)-4-vinyl-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4h). Colorless liquid (32 mg, 59%, (dr > 98:2)). **TLC**: R_f 0.53 (7:3 hexanes/EtOAc). **IR** (NaCl): 2954, 2927, 2872, 1714, 1639, 1456, 1435, 1315, 1271, 1238, 1195, 1087, 974, 777, 732. **^{1}H NMR** (400 MHz) δ 6.72 (d, J = 10.8 Hz, 1H), 6.09–6.02 (m, 1H), 5.86 (ddd, J = 15.4, 8.3, 6.3 Hz, 1H), 5.38–5.21 (m, 2H), 4.29 (ddd, J = 12.4, 8.1, 2.0 Hz, 1H), 4.20 (ddd, J = 12.4, 6.4, 2.2 Hz, 1H), 3.77 (s, 3H), 3.01 (d, J = 7.4 Hz, 2H), 2.70 (ddd, J = 19.0,

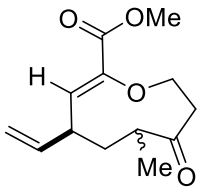
8.2, 2.2 Hz, 1H), 2.57 (ddd, *J* = 18.9, 6.4, 2.0 Hz, 1H), 2.22–2.11 (m, 2H), 1.91–1.82 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz): *δ* 204.4, 164.4, 141.4, 140.0, 136.9, 127.9, 127.7, 122.0, 64.1, 51.9, 47.1, 40.3, 39.0, 37.0, 20.6. **HRMS** (ESI) *m/z* calcd for $C_{15}H_{20}O_4Na$ ($[M+Na]^+$) 287.1259; found 287.1261.



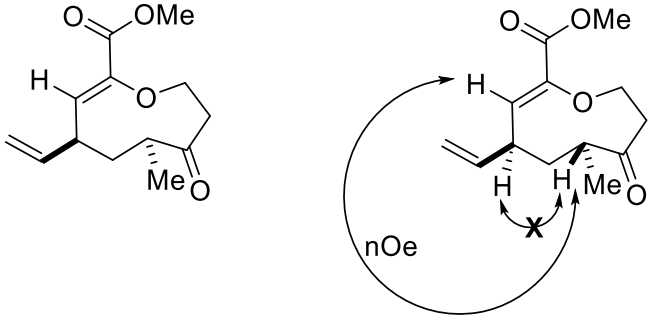
Methyl (4*R*,5*R*,*Z*)-5-methyl-7-oxo-4-vinyl-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4i). (36 mg, 60%, (dr > 98:2)). Recrystallization from hexanes (slow evaporation method) yielded monoclinic colorless crystal (mp 72–74 °C). **TLC**: R_f 0.40 (7:3 hexanes/EtOAc). **IR** (NaCl): 2962, 1720, 1641, 1442, 1429, 1300, 1238, 1161, 1095, 1004, 767, 723, 671, 644. **^{1}H NMR** (400 MHz) *δ* 6.31 (d, *J* = 10.0 Hz, 1H), 5.81 (ddd, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.13–4.98 (m, 2H), 4.57 (ddd, *J* = 11.9, 5.8, 3.1 Hz, 1H), 4.11 (td, *J* = 11.6, 4.2 Hz, 1H), 3.82 (s, 3H), 3.43 (dtt, *J* = 9.5, 3.6, 1.8 Hz, 1H), 2.83–2.75 (m, 1H), 2.64–2.43 (m, 3H), 2.10 (dd, *J* = 13.7, 4.5 Hz, 1H), 0.88 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz): *δ* 211.6, 163.8, 146.5, 138.8, 126.7, 115.9, 77.3, 77.0, 76.7, 69.8, 52.2, 45.1, 44.5, 40.7, 36.1, 15.2. **HRMS** (ESI) *m/z* calcd for $C_{13}H_{18}O_4Na$ ($[M+Na]^+$) 261.1102; found 261.1100.



Methyl (4*S*,9*S*,*Z*)-7-oxo-9-phenyl-4-vinyl-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4j). Colorless liquid (33 mg, 67%, (dr > 98:2)). **TLC**: R_f 0.41 (7:3 hexanes/EtOAc). **IR** (NaCl): 3734, 2312, 1722, 1647, 1541, 1508, 1436, 1352, 1300, 1247, 1203, 1143, 1097, 1001, 925, 877, 761, 694, 671. **^{1}H NMR** (400 MHz) *δ* 7.44–7.34 (m, 4H), 7.33–7.27 (m, 1H), 6.17 (d, *J* = 9.3 Hz, 1H), 5.80 (ddd, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.25 (dd, *J* = 11.2, 3.8 Hz, 1H), 5.16–5.02 (m, 2H), 3.58 (s, 3H), 3.49–3.38 (m, 1H), 3.08 (dd, *J* = 15.3, 11.2 Hz, 1H), 2.82–2.70 (m, 2H), 2.44 (ddd, *J* = 13.9, 6.5, 4.4 Hz, 1H), 2.28–2.20 (m, 1H), 1.69–1.57 (m, 1H). **^{13}C NMR** (101 MHz): *δ* 210.9, 163.8, 145.6, 141.5, 139.8, 129.2, 128.3, 127.6, 125.4, 115.1, 81.9, 77.3, 77.0, 76.7, 53.1, 51.8, 38.4, 38.2, 30.0. **HRMS** (ESI) *m/z* calcd for $C_{18}H_{20}O_4Na$ ($[M+Na]^+$) 323.1259; found 323.1255



Methyl (4*S*,6*S*,*Z*)-6-methyl-7-oxo-4-vinyl-4,5,6,7,8,9-hexahydrooxonine-2-carboxylate (4k). (41 mg, 68%, (dr = 3:1);

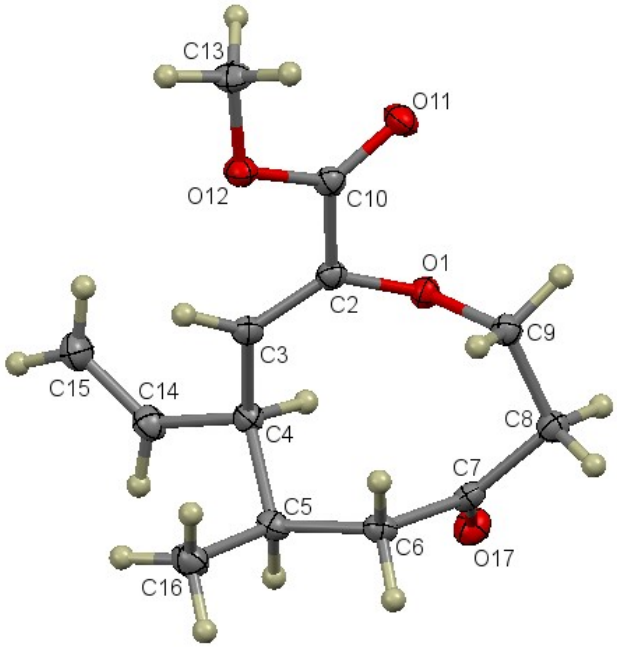


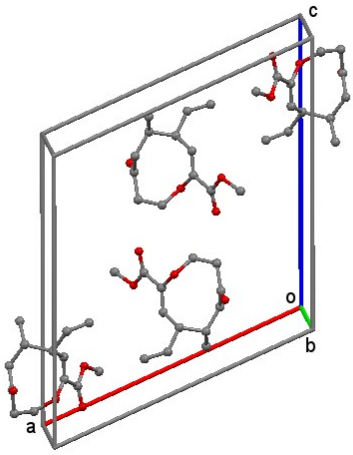
4k (Major diastereomer): White solid mp 49–50 °C). **TLC**: R_f 0.50 (7:3 hexanes/EtOAc). **IR** (NaCl): 2962, 1722, 1645, 1460, 1294, 1246, 1093, 999, 923, 775, 675, 624. **^{1}H NMR** (400 MHz) δ 6.20 (d, J = 9.7 Hz, 1H), 5.77–5.63 (m, 1H), 5.08–4.94 (m, 2H), 4.55–4.48 (m, 1H), 4.21–4.11 (m, 1H), 3.78 (s, 3H), 3.32–3.23 (m, 1H), 2.94–2.86 (m, 1H), 2.74–2.62 (m, 2H), 1.99–1.90 (m, 1H), 1.49–1.39 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz): δ 215.4, 163.9, 145.4, 139.5, 129.9, 114.9, 77.3, 77.0, 76.7, 69.2, 52.1, 43.3, 40.9, 38.7, 37.3, 17.8. **HRMS** (ESI) *m/z* calcd for $C_{13}H_{18}O_4Na$ ($[M+Na]^+$) 261.1102; found 261.1107.

4k (Minor diastereomer): isolated as pale yellow liquid along with major diastereomer (dr = 1:1); **^{1}H NMR** (400 MHz) δ 6.21 (d, J = 9.6 Hz, 1H), 6.11 (d, J = 9.5 Hz, 1H), 5.72 (dddd, J = 17.1, 10.4, 6.8, 5.1 Hz, 2H), 5.06–4.98 (m, 4H), 4.52 (dd, J = 11.2, 5.8 Hz, 1H), 4.35–4.23 (m, 2H), 4.17 (ddd, J = 11.9, 9.1, 4.9 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.41–3.25 (m, 2H), 2.96–2.83 (m, 2H), 2.75–2.64 (m, 2H), 1.99–1.86 (m, 3H), 1.79 (ddd, J = 14.0, 4.8, 2.5 Hz, 1H), 1.46 (td, J = 12.8, 4.0 Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H). **^{13}C NMR** (101 MHz): δ 215.59, 215.35, 163.94, 145.39, 143.44, 139.87, 139.54, 130.70, 129.97, 114.98, 114.69, 77.32, 77.00, 76.68, 69.18, 68.66, 52.11, 52.09, 46.56, 43.34, 42.67, 41.00, 40.98, 39.54, 38.77, 37.35, 17.85, 17.82.

F. X-RAY DIFFRACTION DATA FOR OXACYCLE 4i

Sample: KC-508
CCDC 1510906
User: Kiran
Formula: C_{13} H_{18} O_4





Comment

The displacement ellipsoids were drawn at the 50% probability level.

Experimental

A colorless, needle-shaped crystal of dimensions 0.05 x 0.08 x 0.58 mm was selected for structural analysis. Intensity data for this compound were collected using a diffractometer with a Bruker APEX ccd area detector[8] and graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The sample was cooled to 100(2) K. Cell parameters were determined from a non-linear least squares fit of 3066 peaks in the range $2.36 < \theta < 27.28°$. A total of 9302 data were measured in the range $1.543 < \theta < 27.503°$ using ϕ and ω oscillation frames. The data were

corrected for absorption by the empirical method giving minimum and maximum transmission factors of 0.948 and 0.995.[9] The data were merged to form a set of 2838 independent data with R(int) = 0.0239 and a coverage of 99.7 %.

The monoclinic space group $P2_1/n$ was determined by systematic absences and statistical tests and verified by subsequent refinement. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2.[10] The positions of hydrogens were initially determined by geometry and were refined using a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom displacement parameters were set to 1.2 (1.5 for methyl) times the isotropic equivalent displacement parameters of the bonded atoms. A total of 154 parameters were refined against 2838 data to give $wR(F^2)$ = 0.1232 and S = 0.973 for weights of $w = 1/[\sigma^2 (F^2) + (0.0850\ P)^2 + 0.2000\ P]$, where $P = [F_o^2 + 2F_c^2] / 3$. The final $R(F)$ was 0.0431 for the 2334 observed, $[F > 4\sigma(F)]$, data. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.338 and -0.211 e/Å^3, respectively.

Acknowledgment

The authors thank the National Science Foundation (grant CHE-0130835) and the University of Oklahoma for funds to purchase of the X-ray instrument and computers. This structure was determined by Douglas R. Powell.

References

8. (a) Data Collection: APEX2 (2007) Bruker AXS Inc., Madison, Wisconsin, USA. (b) Data Reduction: SAINT (2007) Bruker AXS Inc., Madison, Wisconsin, USA.
9. L. Krause, R. Herbst-Irmer, G. M. Sheldrick, and D. Stalke (2015). *J. Appl. Cryst., 48*, 3-10.
10. (a) G. M. Sheldrick (2015). *Acta Cryst., A71*, 3-8. (b) G. M. Sheldrick (2015). *Acta Cryst., C71*, 3-8.

Table 1. Crystal data and structure refinement for KC-508

Empirical formula	$C_{13}H_{18}O_4$	
Formula weight	238.27	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 15.381(2) Å	α= 90°
	b = 5.4641(7) Å	β= 113.595(2)°
	c = 16.210(2) Å	γ= 90°
Volume	1248.4(3) $Å^3$	
Z, Z'	4, 1	
Density (calculated)	1.268 Mg/m^3	
Wavelength	0.71073 Å	
Temperature	100(2) K	
F(000)	512	
Absorption coefficient	0.093 mm^{-1}	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.995 and 0.948	
Theta range for data collection	1.543 to 27.503°	
Reflections collected	9302	
Independent reflections	2838 [R(int) = 0.0239]	
Data / restraints / parameters	2838 / 0 / 154	
$wR(F^2$ all data)	$wR2$ = 0.1232	
R(F obsd data)	$R1$ = 0.0431	
Goodness-of-fit on F^2	0.973	
Observed data [I > 2s(I)]	2334	
Largest and mean shift / s.u.	0.000 and 0.000	
Largest diff. peak and hole	0.338 and -0.211 $e/Å^3$	

$wR2 = \{ \Sigma [w(F_o2 - F_c2)2] / \Sigma [w(F_o 2)2] \}^{1/2}$

$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters for KC-508. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	0.46907(6)	0.10996(16)	0.60579(6)	0.0178(2)
C(2)	0.42734(8)	0.2668(2)	0.64565(8)	0.0169(3)
C(3)	0.43172(8)	0.2249(2)	0.72827(8)	0.0176(3)
C(4)	0.48388(8)	0.0095(2)	0.78505(8)	0.0174(3)
C(7)	0.64307(8)	-0.0454(2)	0.72005(9)	0.0179(3)
C(6)	0.64721(8)	0.1400(2)	0.79107(9)	0.0178(3)
C(5)	0.58961(8)	0.0672(2)	0.84585(8)	0.0179(3)
C(9)	0.54699(8)	0.2188(2)	0.58841(9)	0.0180(3)
C(8)	0.63172(8)	0.0466(2)	0.62814(9)	0.0192(3)
C(10)	0.36759(8)	0.4617(2)	0.58420(8)	0.0175(3)
O(11)	0.34903(6)	0.46664(17)	0.50434(6)	0.0226(2)
O(12)	0.33447(6)	0.62443(16)	0.62668(6)	0.0198(2)
C(13)	0.26974(9)	0.8043(2)	0.56842(9)	0.0219(3)
C(14)	0.43403(9)	-0.0960(2)	0.84073(9)	0.0215(3)
C(15)	0.34565(10)	-0.0569(3)	0.83131(10)	0.0263(3)
C(16)	0.59979(10)	0.2650(3)	0.91594(9)	0.0245(3)
O(17)	0.64891(6)	-0.26361(16)	0.73678(7)	0.0232(2)

Table 3. Bond lengths [Å] and angles [°] for KC-508.

O(1)-C(2)	1.3769(14)	C(9)-H(9A)	0.9900
O(1)-C(9)	1.4630(14)	C(9)-H(9B)	0.9900
C(2)-C(3)	1.3335(18)	C(8)-H(8A)	0.9900
C(2)-C(10)	1.4959(17)	C(8)-H(8B)	0.9900
C(3)-C(4)	1.5115(17)	C(10)-O(11)	1.2092(15)
C(3)-H(3)	0.9500	C(10)-O(12)	1.3436(15)
C(4)-C(14)	1.5130(17)	O(12)-C(13)	1.4477(15)
C(4)-C(5)	1.5596(17)	C(13)-H(13A)	0.9800
C(4)-H(4)	1.0000	C(13)-H(13B)	0.9800
C(7)-O(17)	1.2181(15)	C(13)-H(13C)	0.9800
C(7)-C(8)	1.5148(18)	C(14)-C(15)	1.3231(19)
C(7)-C(6)	1.5156(18)	C(14)-H(14)	0.9500
C(6)-C(5)	1.5367(17)	C(15)-H(15A)	0.9500
C(6)-H(6A)	0.9900	C(15)-H(15B)	0.9500
C(6)-H(6B)	0.9900	C(16)-H(16A)	0.9800
C(5)-C(16)	1.5302(18)	C(16)-H(16B)	0.9800
C(5)-H(5)	1.0000	C(16)-H(16C)	0.9800
C(9)-C(8)	1.5254(17)		

C(2)-O(1)-C(9)	114.14(9)	C(16)-C(5)-C(4)	112.51(10)
C(3)-C(2)-O(1)	121.25(11)	C(6)-C(5)-C(4)	112.56(10)
C(3)-C(2)-C(10)	124.16(11)	C(16)-C(5)-H(5)	107.3
O(1)-C(2)-C(10)	114.09(10)	C(6)-C(5)-H(5)	107.3
C(2)-C(3)-C(4)	123.11(11)	C(4)-C(5)-H(5)	107.3
C(2)-C(3)-H(3)	118.4	O(1)-C(9)-C(8)	107.17(10)
C(4)-C(3)-H(3)	118.4	O(1)-C(9)-H(9A)	110.3
C(3)-C(4)-C(14)	112. 81(10)	C(8)-C(9)-H(9A)	110.3
C(3)-C(4)-C(5)	113. 12(10)	O(1)-C(9)-H(9B)	110.3
C(14)-C(4)-C(5)	110.44(10)	C(8)-C(9)-H(9B)	110.3
C(3)-C(4)-H(4)	106.7	H(9A)-C(9)-H(9B)	108.5
C(14)-C(4)-H(4)	106.7	C(7)-C(8)-C(9)	111.26(10)
C(5)-C(4)-H(4)	106.7	C(7)-C(8)-H(8A)	109.4
O(17)-C(7)-C(8)	120.87(12)	C(9)-C(8)-H(8A)	109.4
O(17)-C(7)-C(6)	120.53(12)	C(7)-C(8)-H(8B)	109.4
C(8)-C(7)-C(6)	118.59(11)	C(9)-C(8)-H(8B)	109.4
C(7)-C(6)-C(5)	114.04(10)	H(8A)-C(8)-H(8B)	108.0
C(7)-C(6)-H(6A)	108.7	O(11)-C(10)-O(12)	123.95(11)
C(5)-C(6)-H(6A)	108.7	O(11)-C(10)-C(2)	123.20(11)
C(7)-C(6)-H(6B)	108.7	O(12)-C(10)-C(2)	112.81(10)
C(5)-C(6)-H(6B)	108.7	C(10)-O(12)-C(13)	114.69(10)
H(6A)-C(6)-H(6B)	107.6	O(12)-C(13)-H(13A)	109.5
C(16)-C(5)-C(6)	109.56(10)	O(12)-C(13)-H(13B)	109.5

H(13A)-C(13)-H(13B)	109.5	C(14)-C(15)-H(15B)	120.0
O(12)-C(13)-H(13C)	109.5	H(15A)-C(15)-H(15B)	120.0
H(13A)-C(13)-H(13C)	109.5	C(5)-C(16)-H(16A)	109.5
H(13B)-C(13)-H(13C)	109.5	C(5)-C(16)-H(16B)	109.5
C(15)-C(14)-C(4)	127.75(13)	H(16A)-C(16)-H(16B)	109.5
C(15)-C(14)-H(14)	116.1	C(5)-C(16)-H(16C)	109.5
C(4)-C(14)-H(14)	116.1	H(16A)-C(16)-H(16C)	109.5
C(14)-C(15)-H(15A)	120.0	H(16B)-C(16)-H(16C)	109.5

Table 4.

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for KC-508. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	17(1)	19(1)	19(1)	-1(1)	8(1)	-1(1)
C(2)	14(1)	18(1)	17(1)	-2(1)	5(1)	-1(1)
C(3)	15(1)	19(1)	17(1)	-1(1)	5(1)	-1(1)
C(4)	18(1)	18(1)	16(1)	0(1)	7(1)	1(1)
C(7)	11(1)	20(1)	21(1)	0(1)	5(1)	0(1)
C(6)	17(1)	18(1)	17(1)	1(1)	4(1)	-1(1)
C(5)	19(1)	18(1)	15(1)	1(1)	5(1)	1(1)
C(9)	18(1)	20(1)	17(1)	1(1)	7(1)	-1(1)
C(8)	17(1)	21(1)	19(1)	-1(1)	7(1)	-1(1)
C(10)	15(1)	19(1)	17(1)	-1(1)	5(1)	-2(1)
O(11)	26(1)	26(1)	15(1)	1(1)	6(1)	3(1)
O(12)	20(1)	21(1)	17(1)	0(1)	6(1)	4(1)
C(13)	20(1)	19(1)	22(1)	2(1)	4(1)	4(1)
C(14)	25(1)	21(1)	20(1)	3(1)	10(1)	1(1)
C(15)	26(1)	32(1)	23(1)	4(1)	13(1)	1(1)
C(16)	25(1)	26(1)	19(1)	-3(1)	6(1)	0(1)
O(17)	24(1)	18(1)	28(1)	1(1)	12(1)	2(1)

Table 5. Hydrogen coordinates and isotropic displacement parameters for KC-508.

	x	y	z	U(eq)
H(3)	0.4006	0.3357	0.7526	0.021
H(4)	0.4844	-0.1218	0.7423	0.021
H(6A)	0.6233	0.2989	0.7613	0.021
H(6B)	0.7143	0.1632	0.8329	0.021
H(5)	0.6184	-0.0861	0.8793	0.022
H(9A)	0.5631	0.3821	0.6170	0.022
H(9B)	0.5287	0.2380	0.5228	0.022
H(8A)	0.6229	-0.0944	0.5872	0.023
H(8B)	0.6901	0.1338	0.6334	0.023
H(13A)	0.3015	0.8959	0.5365	0.033
H(13B)	0.2501	0.9173	0.6047	0.033
H(13C)	0.2138	0.7213	0.5247	0.033
H(14)	0.4706	-0.2030	0.8881	0.026
H(15A)	0.3056	0.0485	0.7851	0.032
H(15B)	0.3222	-0.1343	0.8708	0.032
H(16A)	0.6667	0.2814	0.9568	0.037
H(16B)	0.5626	0.2190	0.9505	0.037
H(16C)	0.5766	0.4214	0.8855	0.037

Table 6. Torsion angles [°] for KC-508.

C(9)-O(1)-C(2)-C(3)	-115.44(13)
C(9)-O(1)-C(2)-C(10)	72.37(13)
O(1)-C(2)-C(3)-C(4)	1.56(19)
C(10)-C(2)-C(3)-C(4)	172.93(11)
C(2)-C(3)-C(4)-C(14)	-143.28(12)
C(2)-C(3)-C(4)-C(5)	90.46(15)
O(17)-C(7)-C(6)-C(5)	-42.40(16)
C(8)-C(7)-C(6)-C(5)	137.71(11)
C(7)-C(6)-C(5)-C(16)	179.32(10)
C(7)-C(6)-C(5)-C(4)	-54.69(14)
C(3)-C(4)-C(5)-C(16)	63.69(14)
C(14)-C(4)-C(5)-C(16)	-63.83(14)
C(3)-C(4)-C(5)-C(6)	-60.69(14)

C(14)-C(4)-C(5)-C(6)	171.79(10)
C(2)-O(1)-C(9)-C(8)	128.70(10)
O(17)-C(7)-C(8)-C(9)	127.43(12)
C(6)-C(7)-C(8)-C(9)	-52.68(14)
O(1)-C(9)-C(8)-C(7)	-43.05(13)
C(3)-C(2)-C(10)-O(11)	-164.40(12)
O(1)-C(2)-C(10)-O(11)	7.52(17)
C(3)-C(2)-C(10)-O(12)	13.47(17)
O(1)-C(2)-C(10)-O(12)	-174.60(9)
O(11)-C(10)-O(12)-C(13)	2.86(17)
C(2)-C(10)-O(12)-C(13)	-174.99(10)
C(3)-C(4)-C(14)-C(15)	15.1(2)
C(5)-C(4)-C(14)-C(15)	142.77(15)

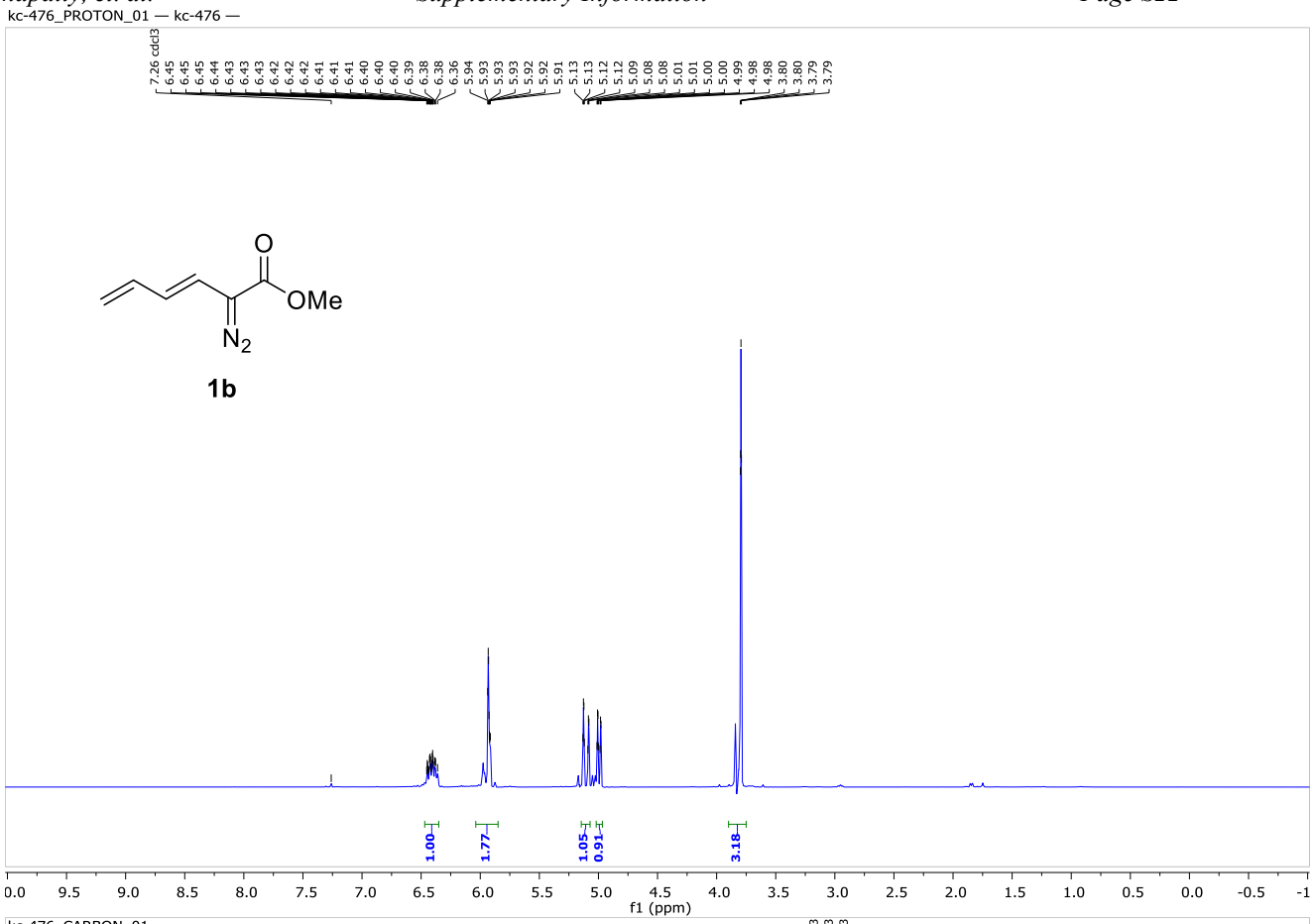
Table 7. Hydrogen bonds for KC-508[Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(6)-H(6A)...O(17)#1	0.99	2.48	3.3784(16)	150.6
C(8)-H(8A)...O(11)#2	0.99	2.65	3.6156(16)	164.1
C(8)-H(8B)...O(17)#3	0.99	2.59	3.3675(15)	135.5
C(13)-H(13A)...O(1)#1	0.98	2.64	3.3272(16)	127.6

Symmetry transformations used to generate equivalent atoms:
#1 x, y+1, z #2 -x+1, -y, -z+1 #3 -x+3/2, y+1/2, -z+3/2

G. ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, AND nOe SPECTRA

1. Diazo ester **1b** S22
2. *β*-Hydroxy vinyl ketones **2a–2f** S23
3. Cascade intermediate **3a** S29
4. Oxacycles **4a–4k** S32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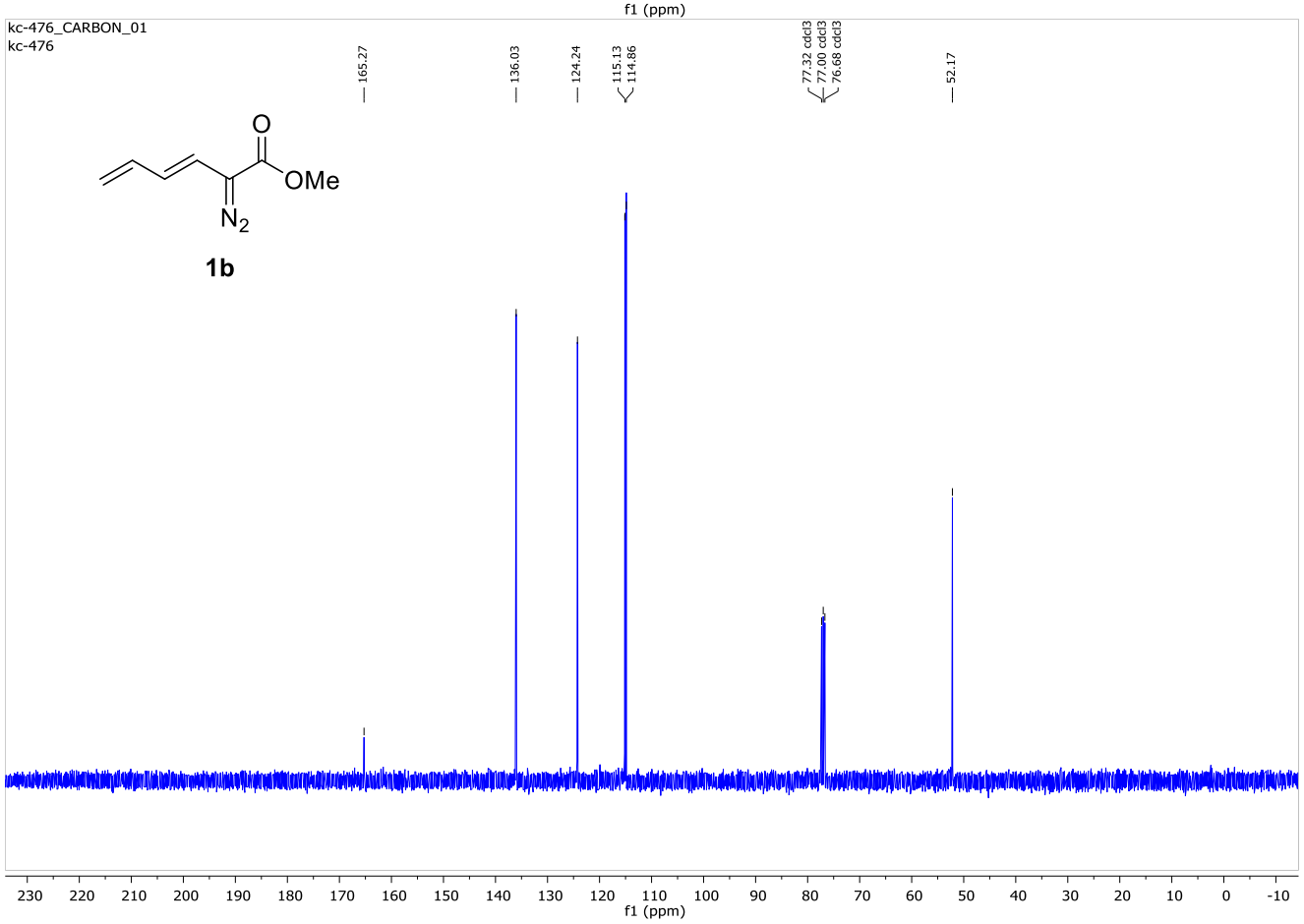
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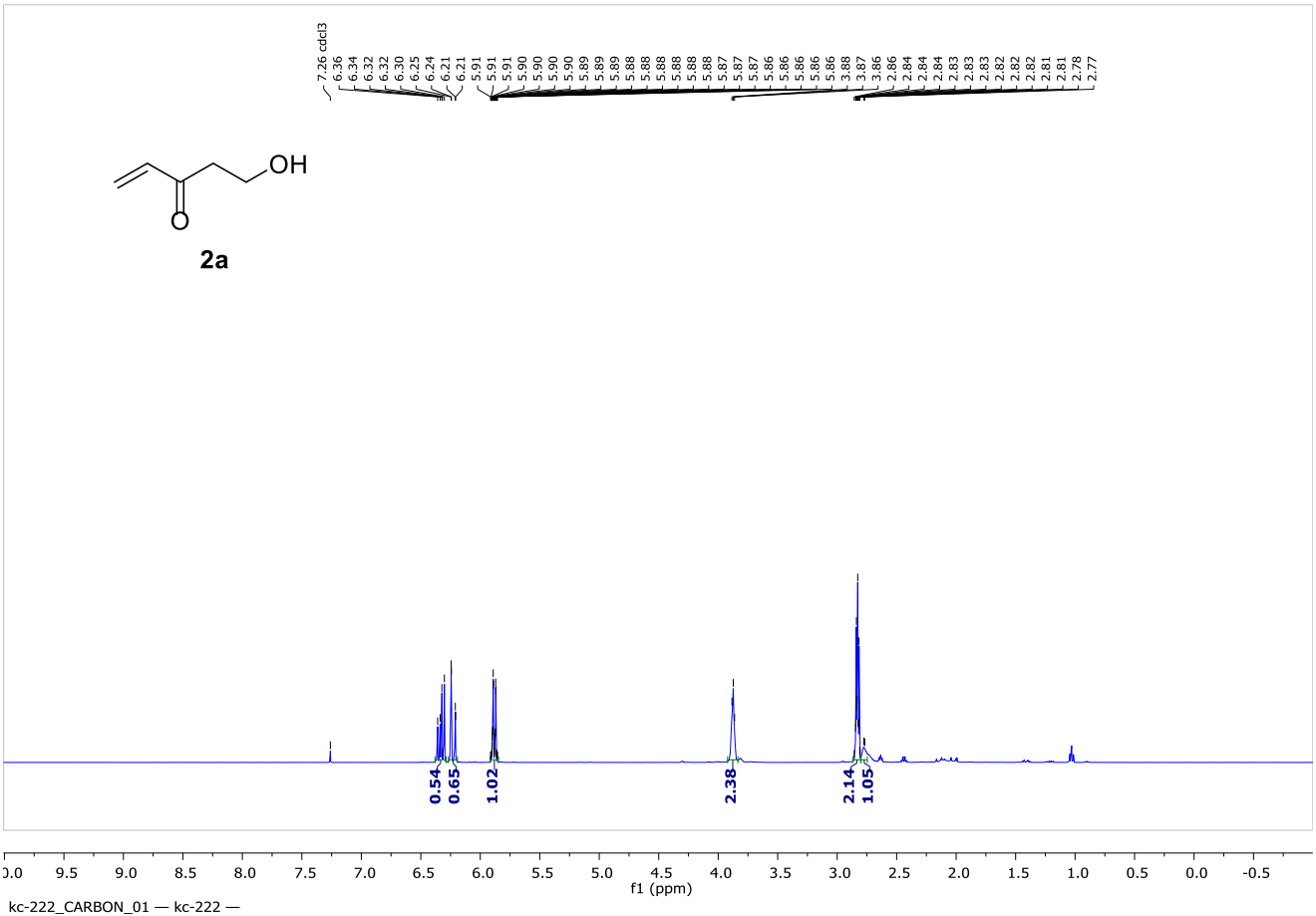

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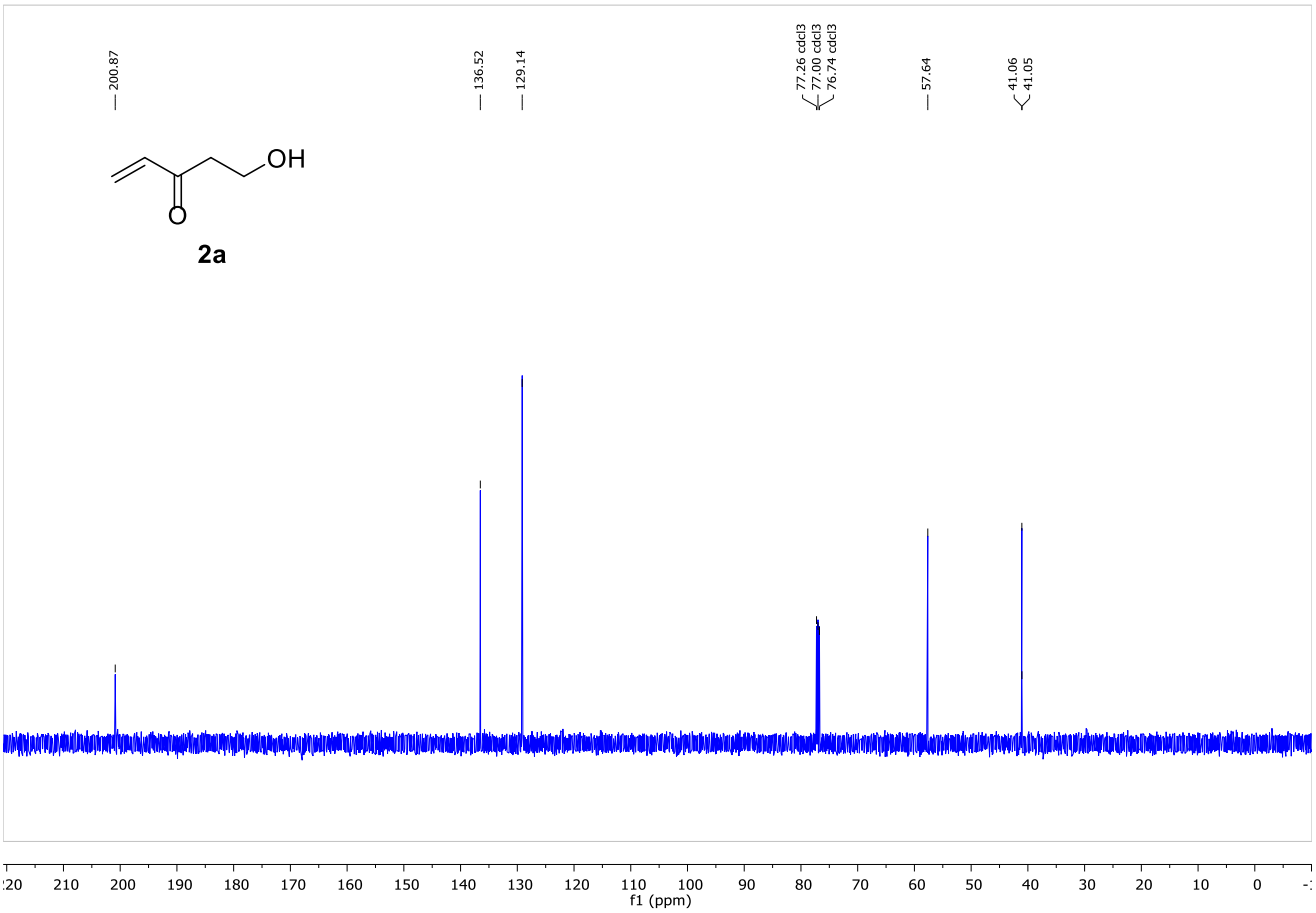

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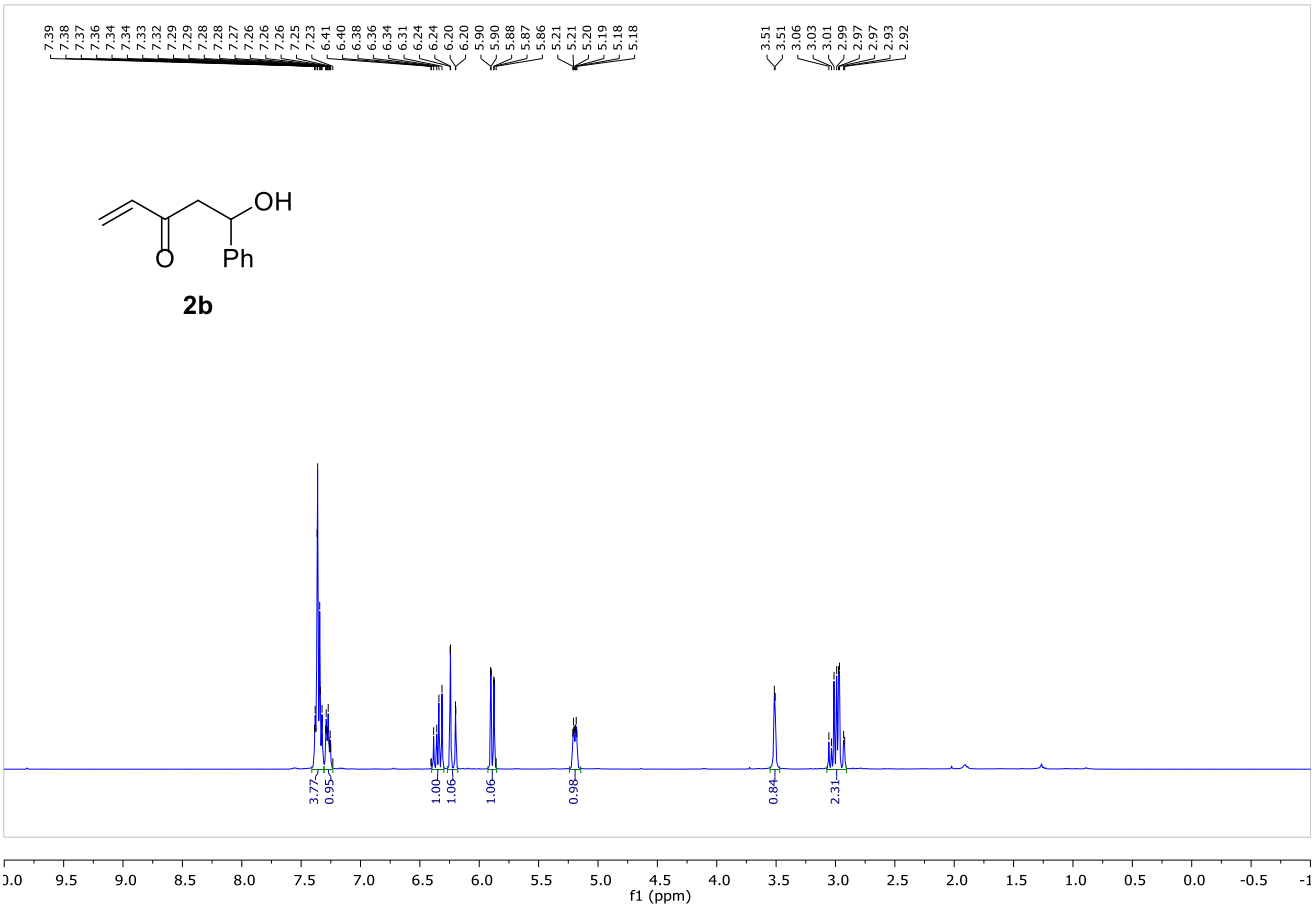

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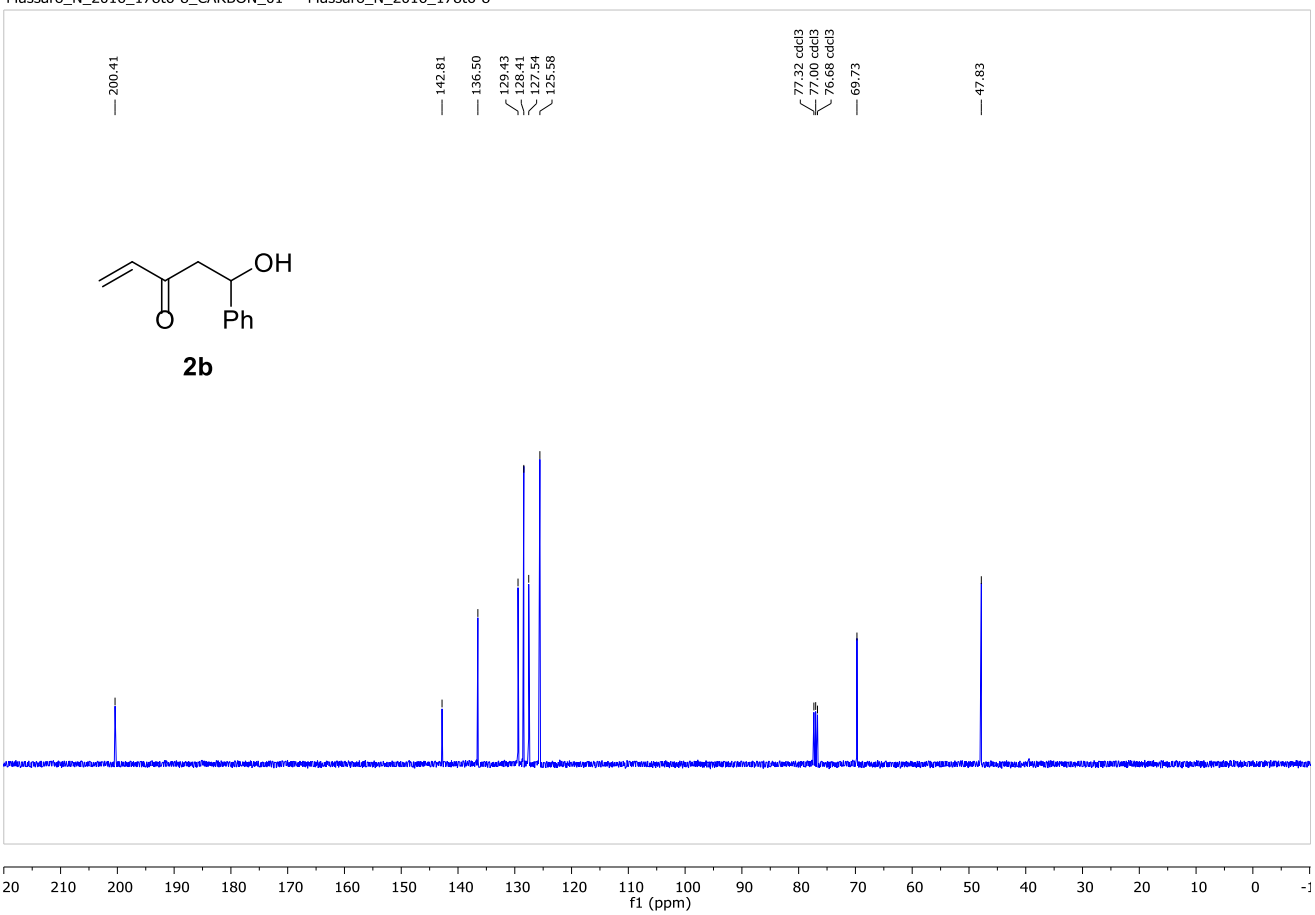

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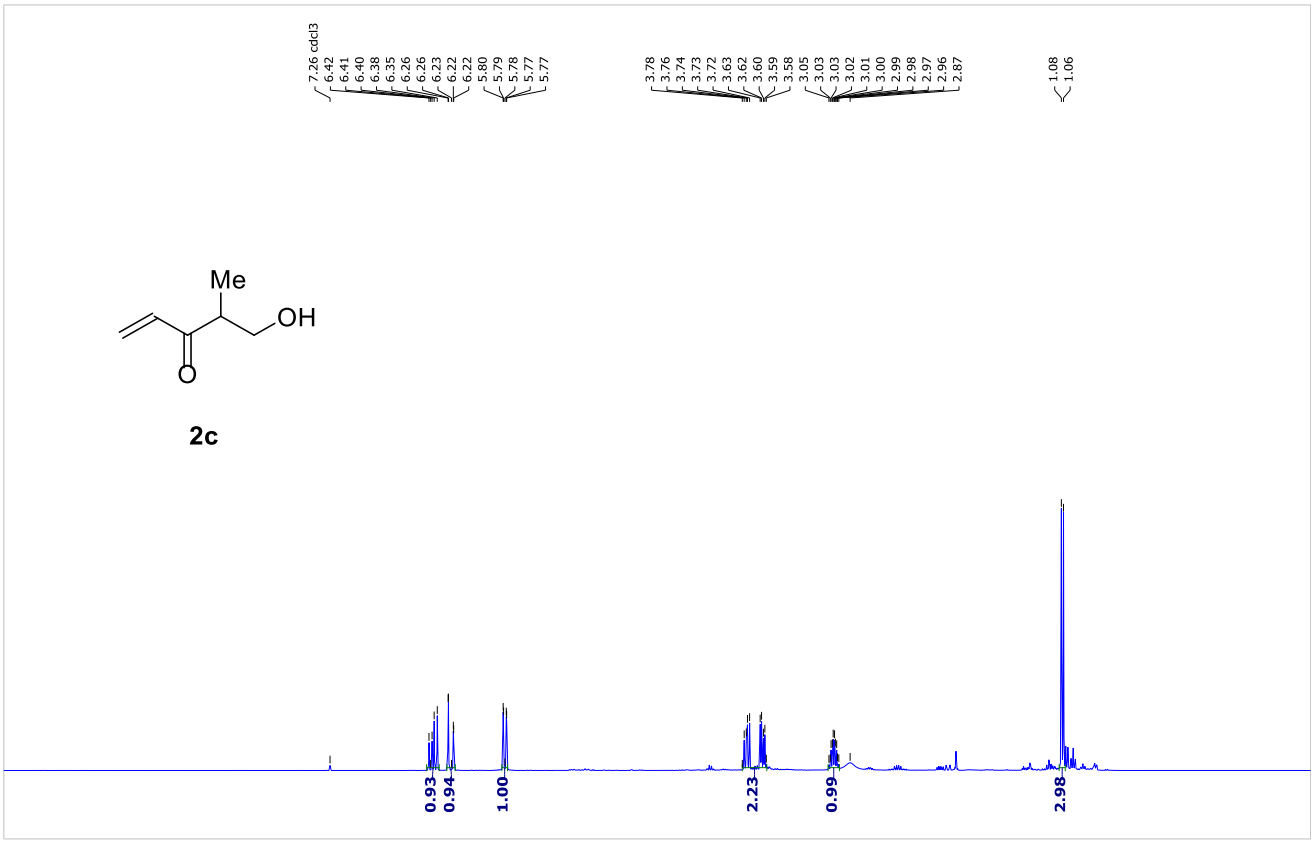

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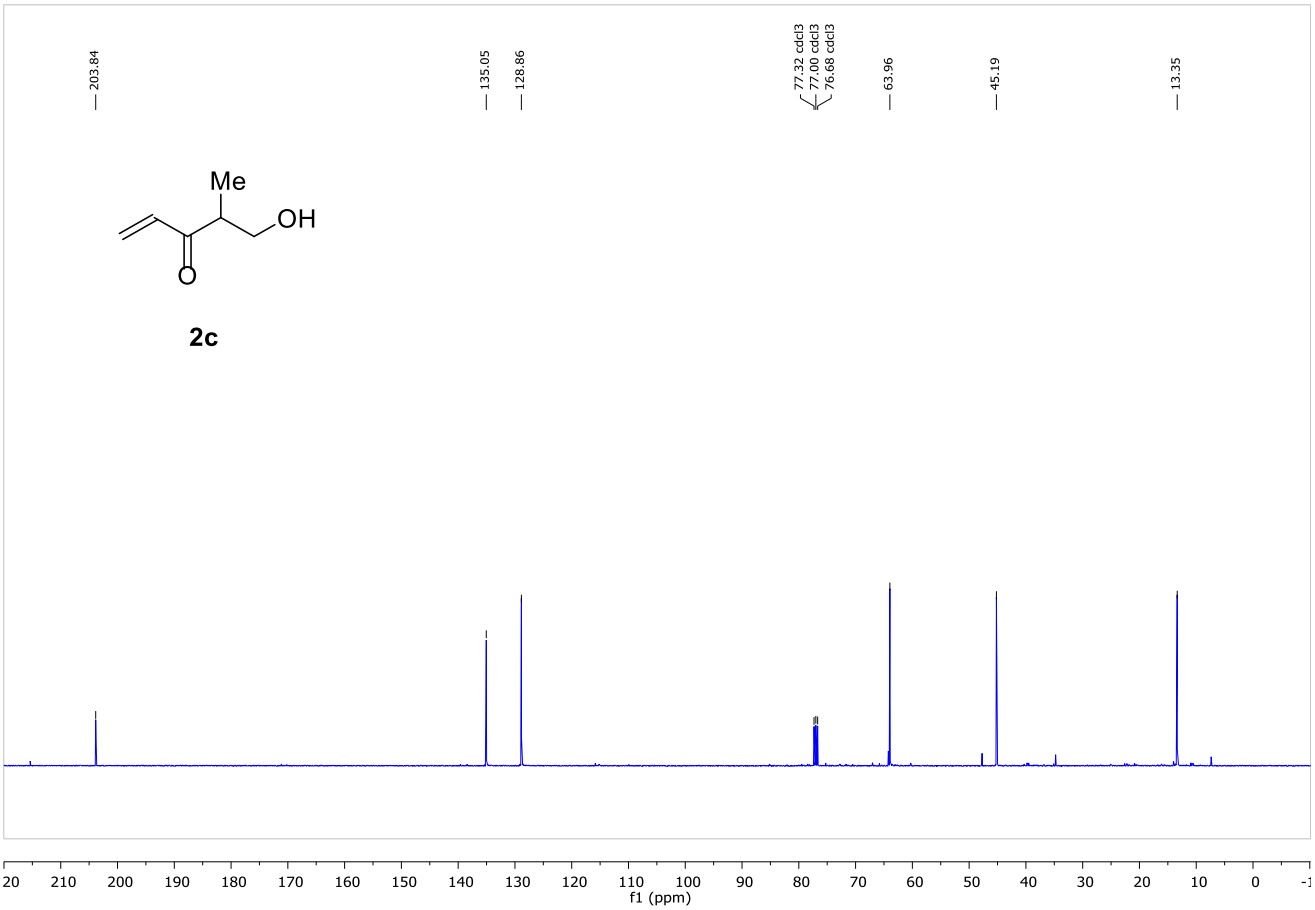

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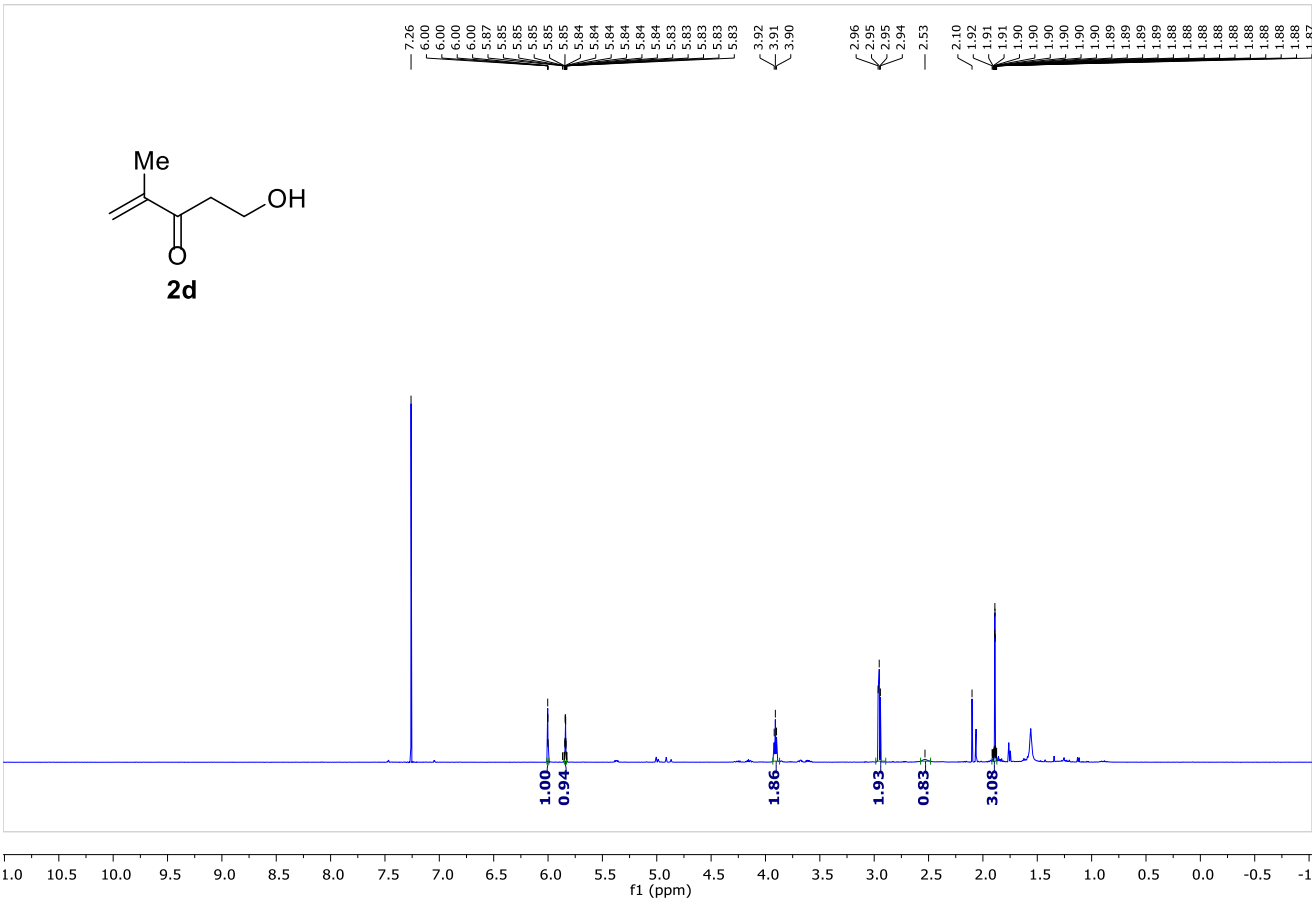

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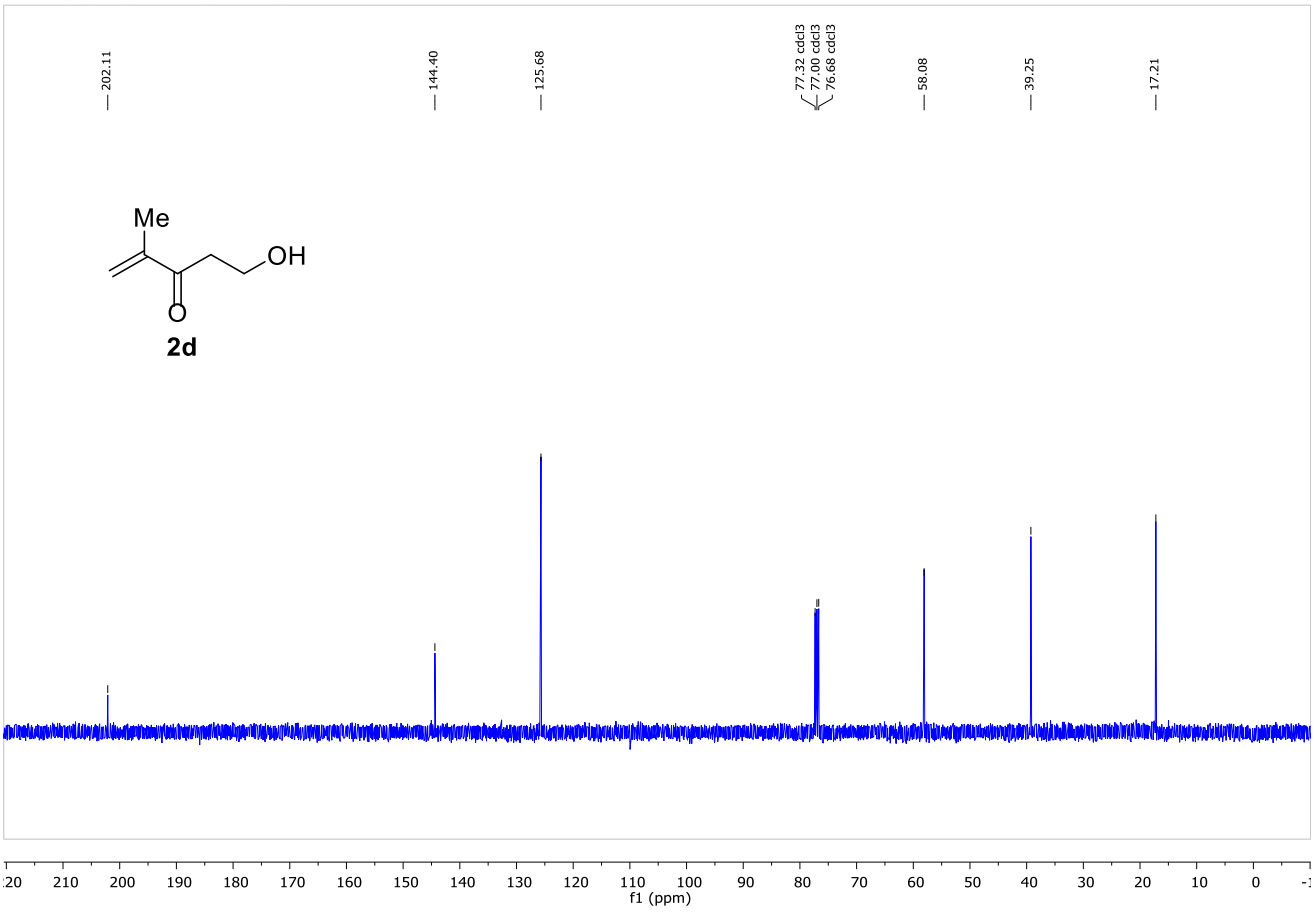

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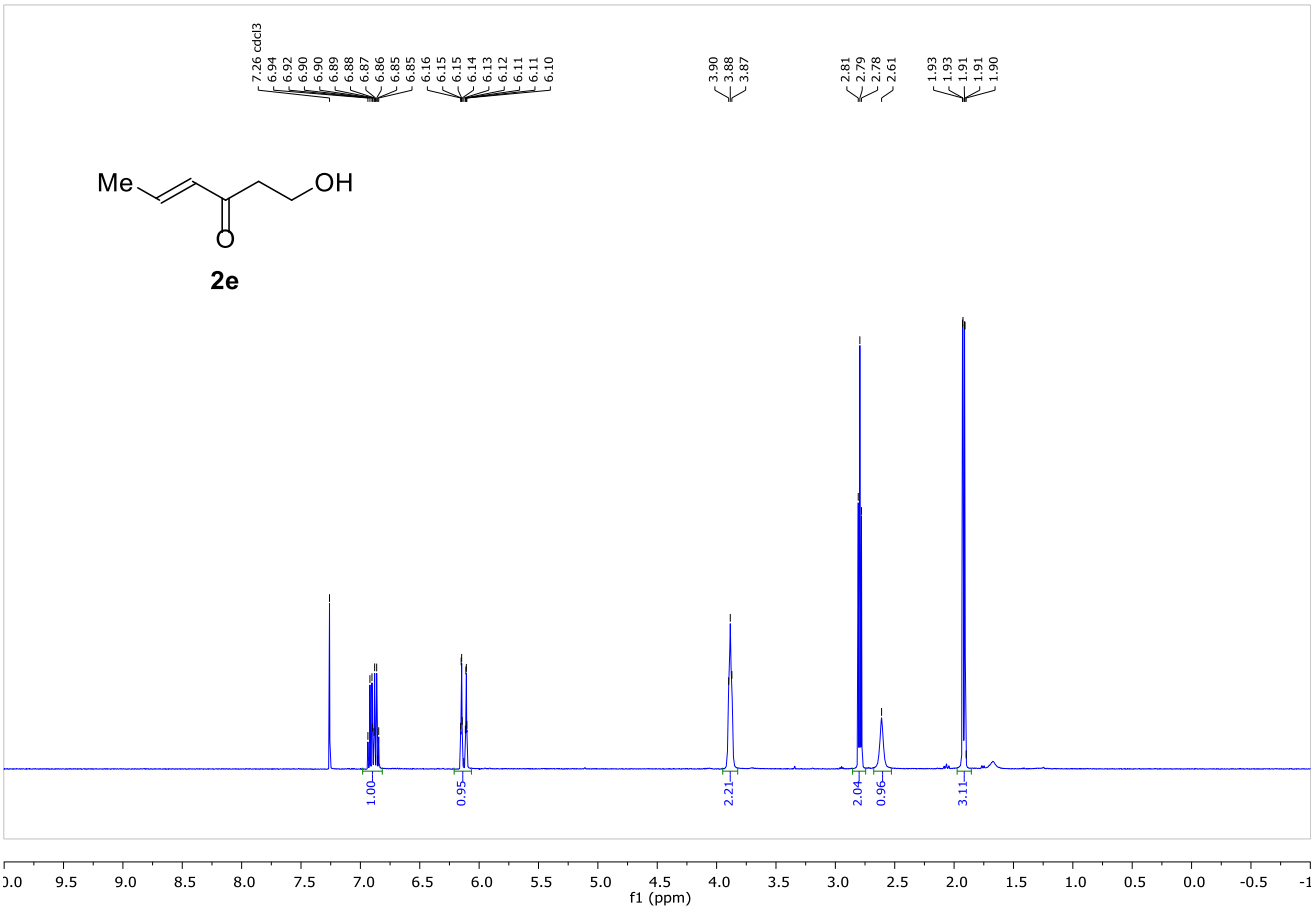

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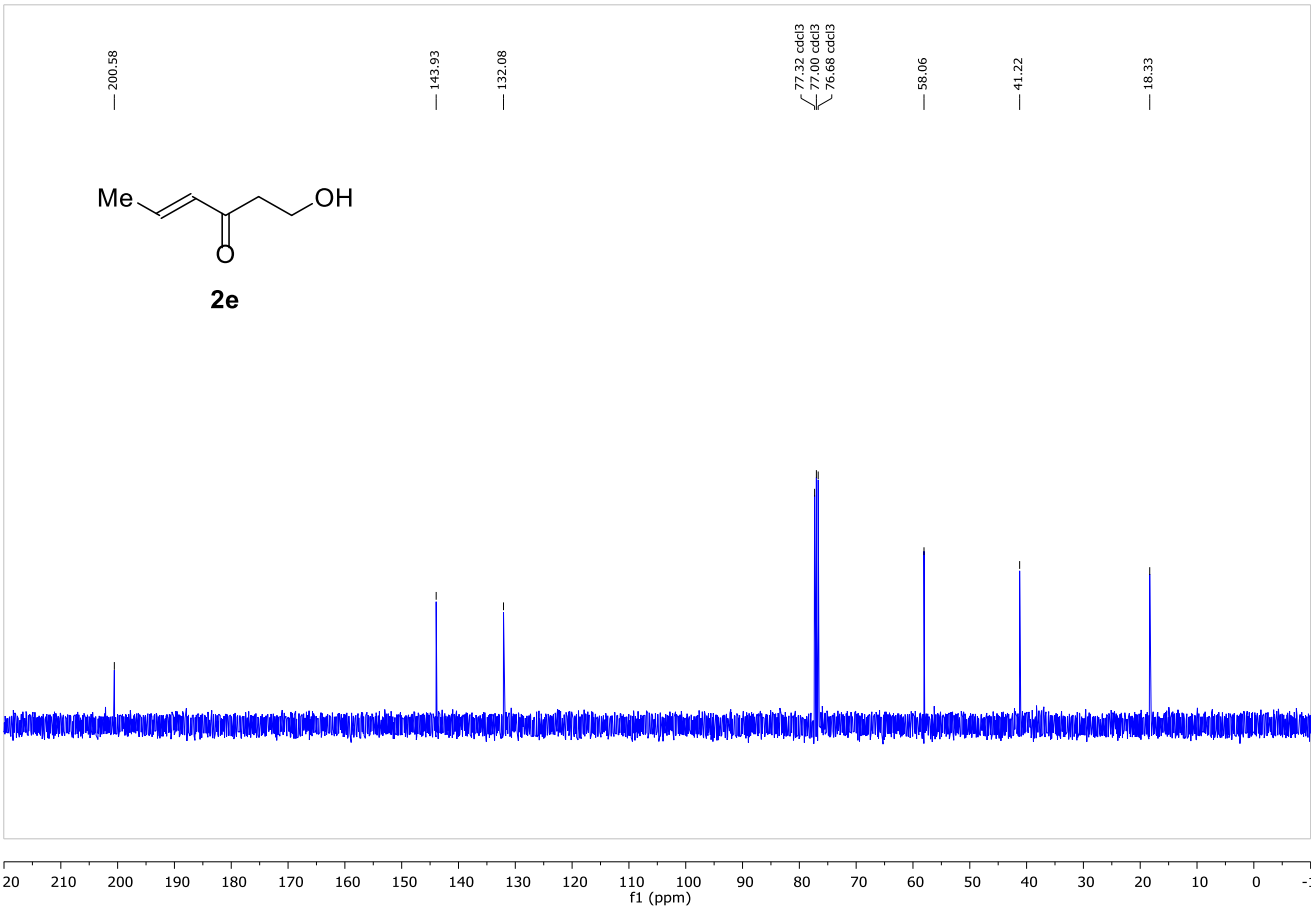

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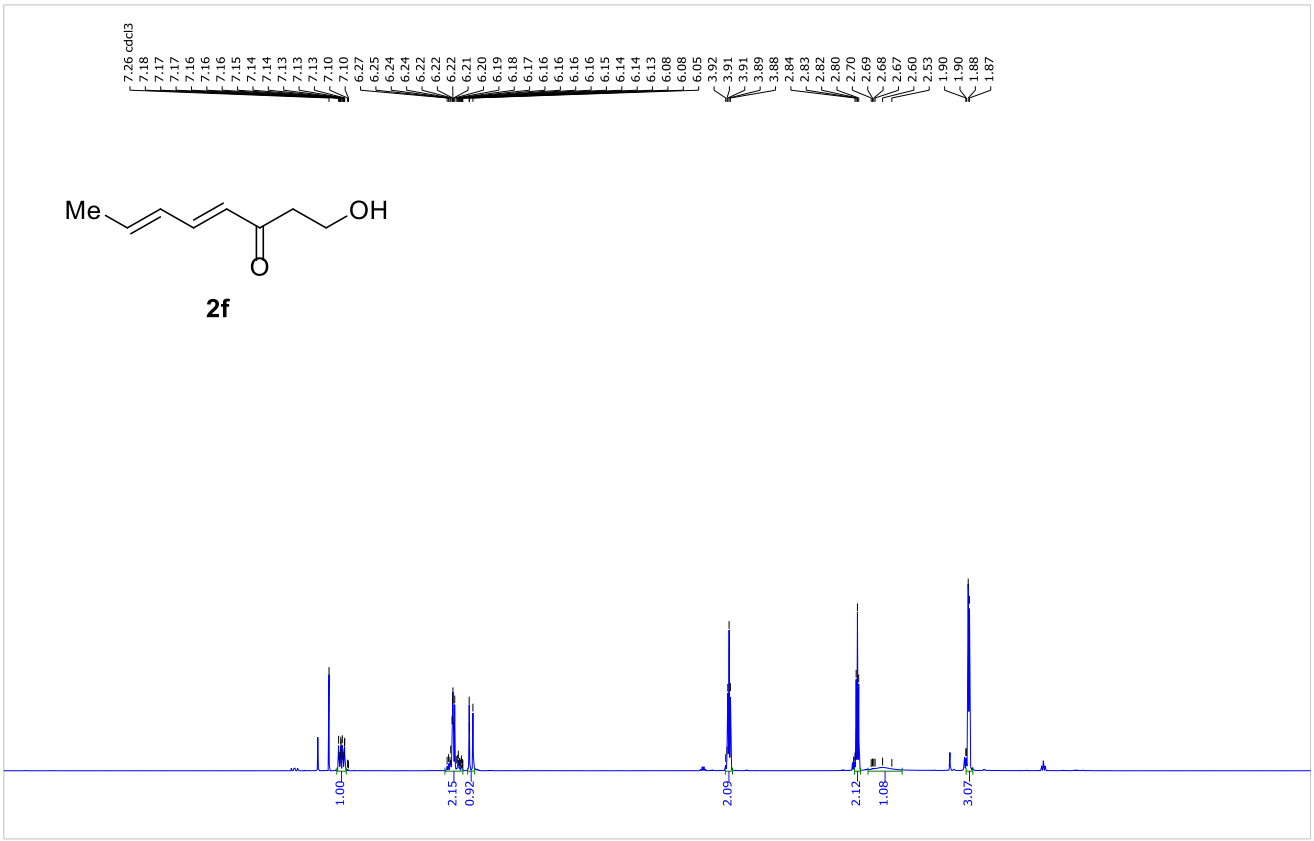

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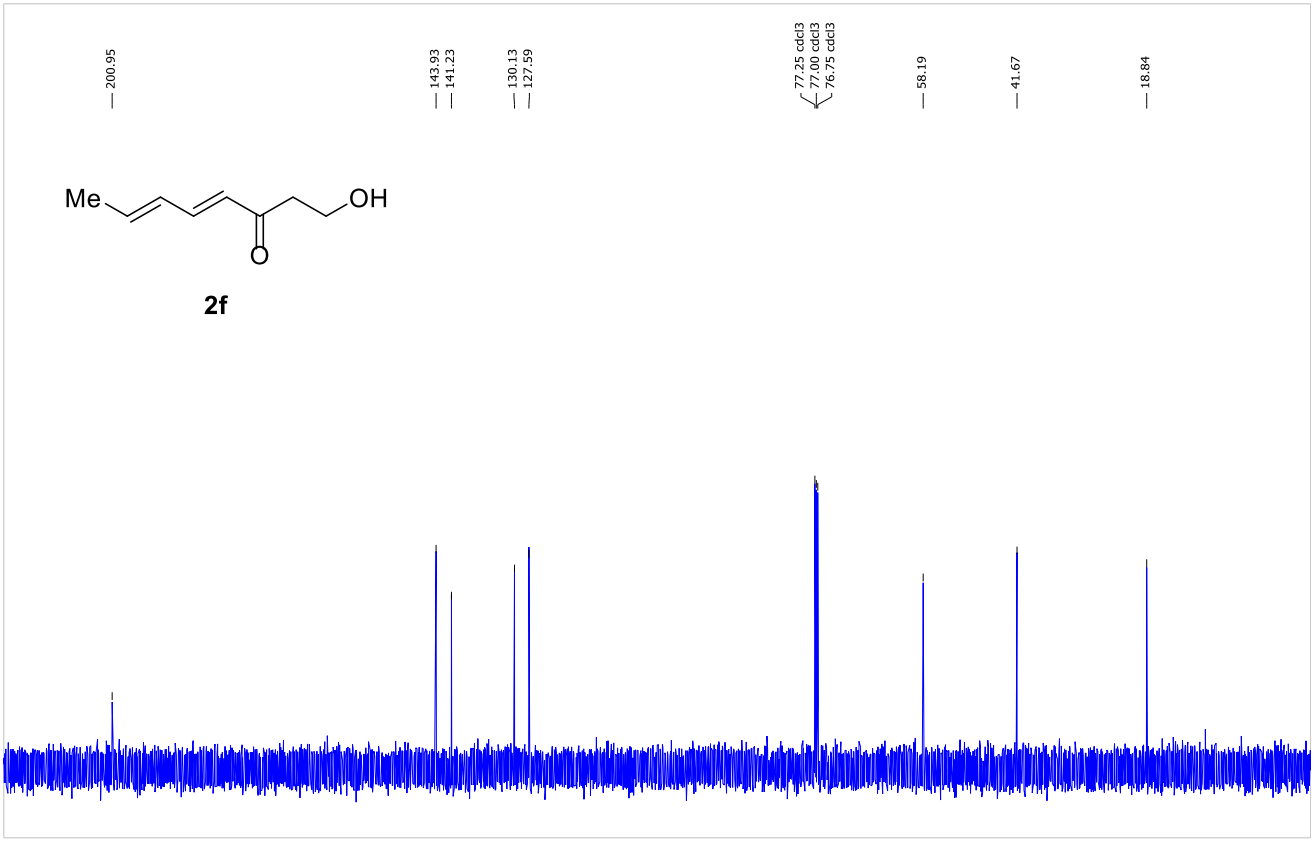

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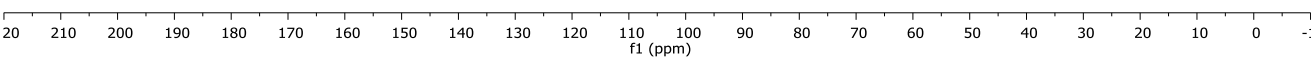

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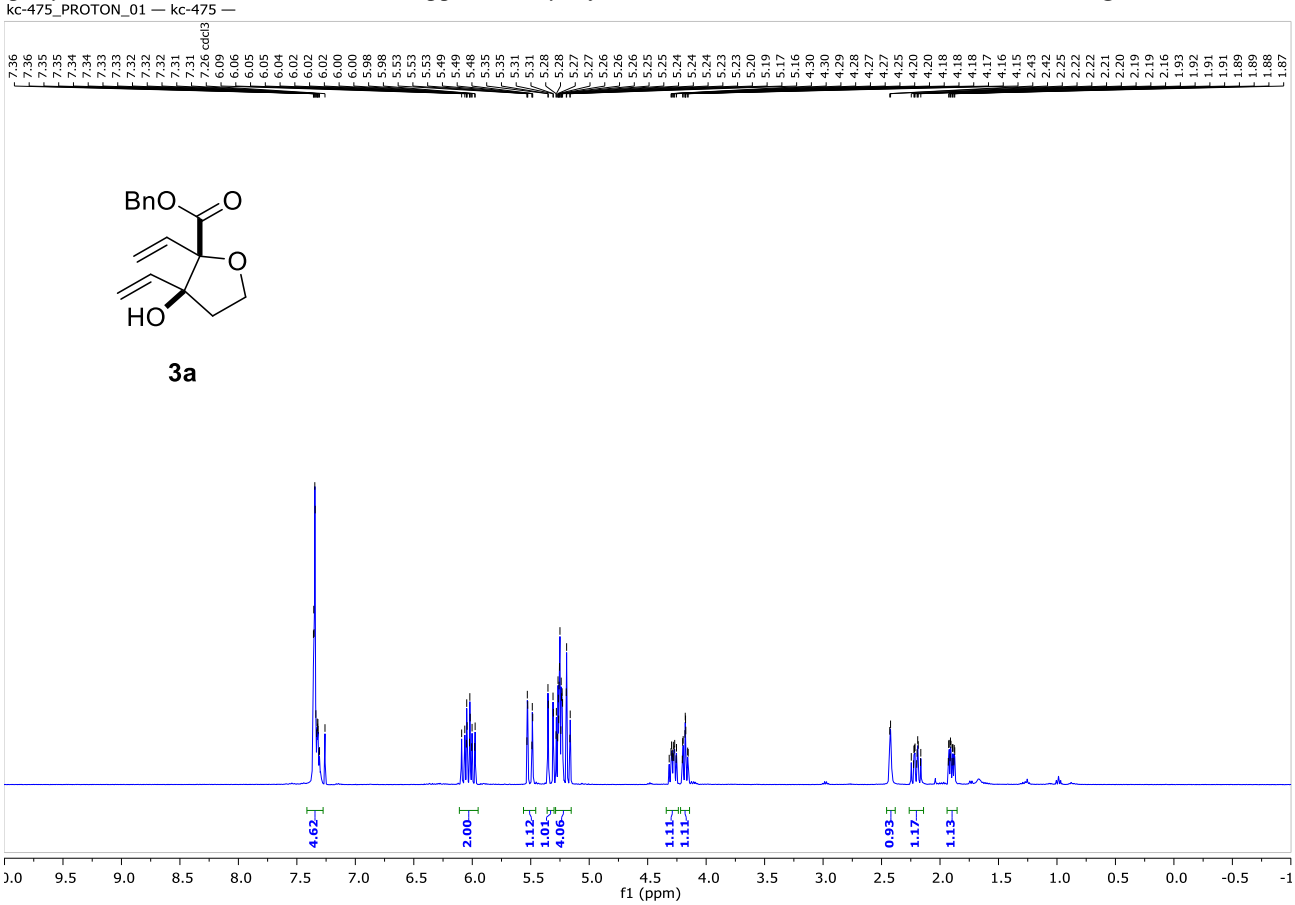

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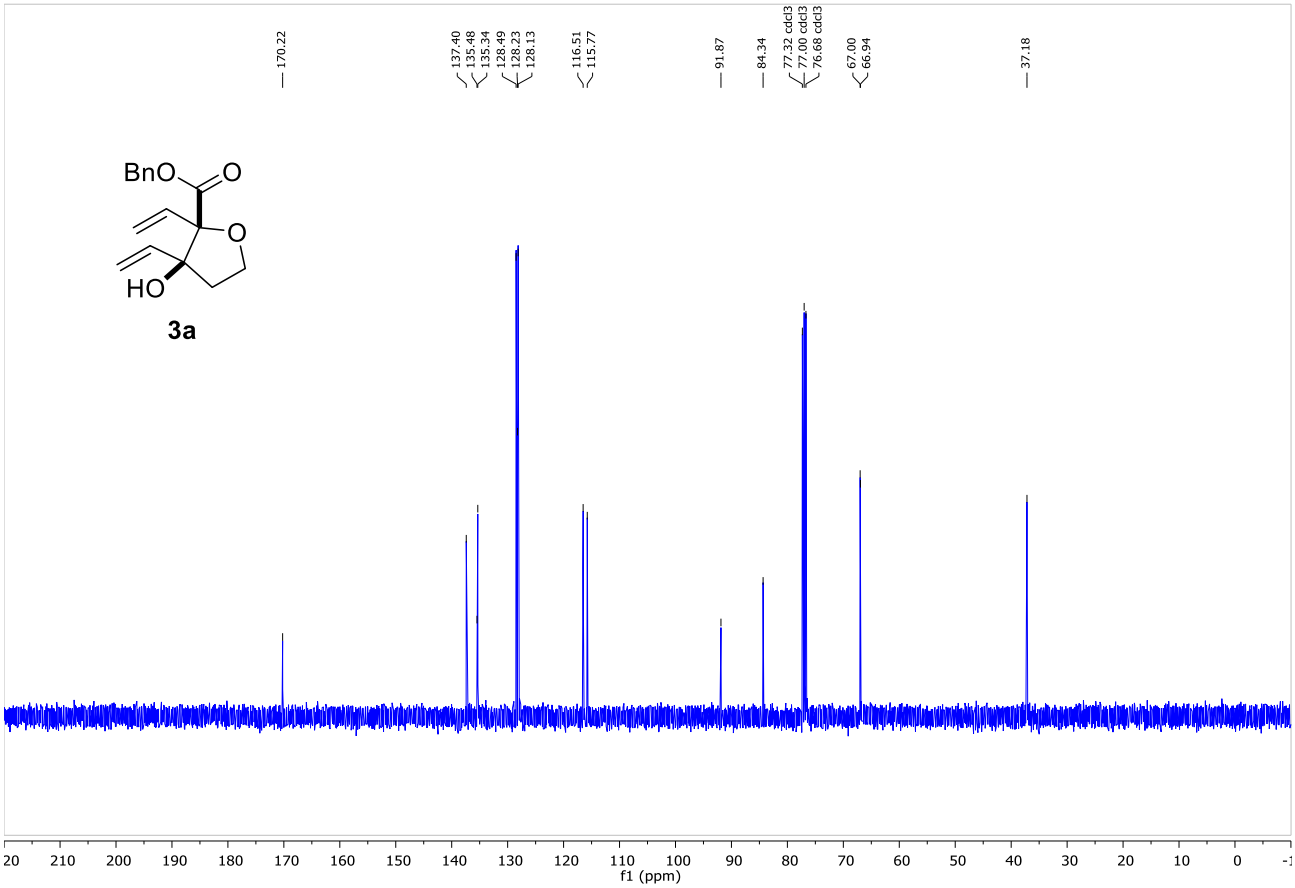

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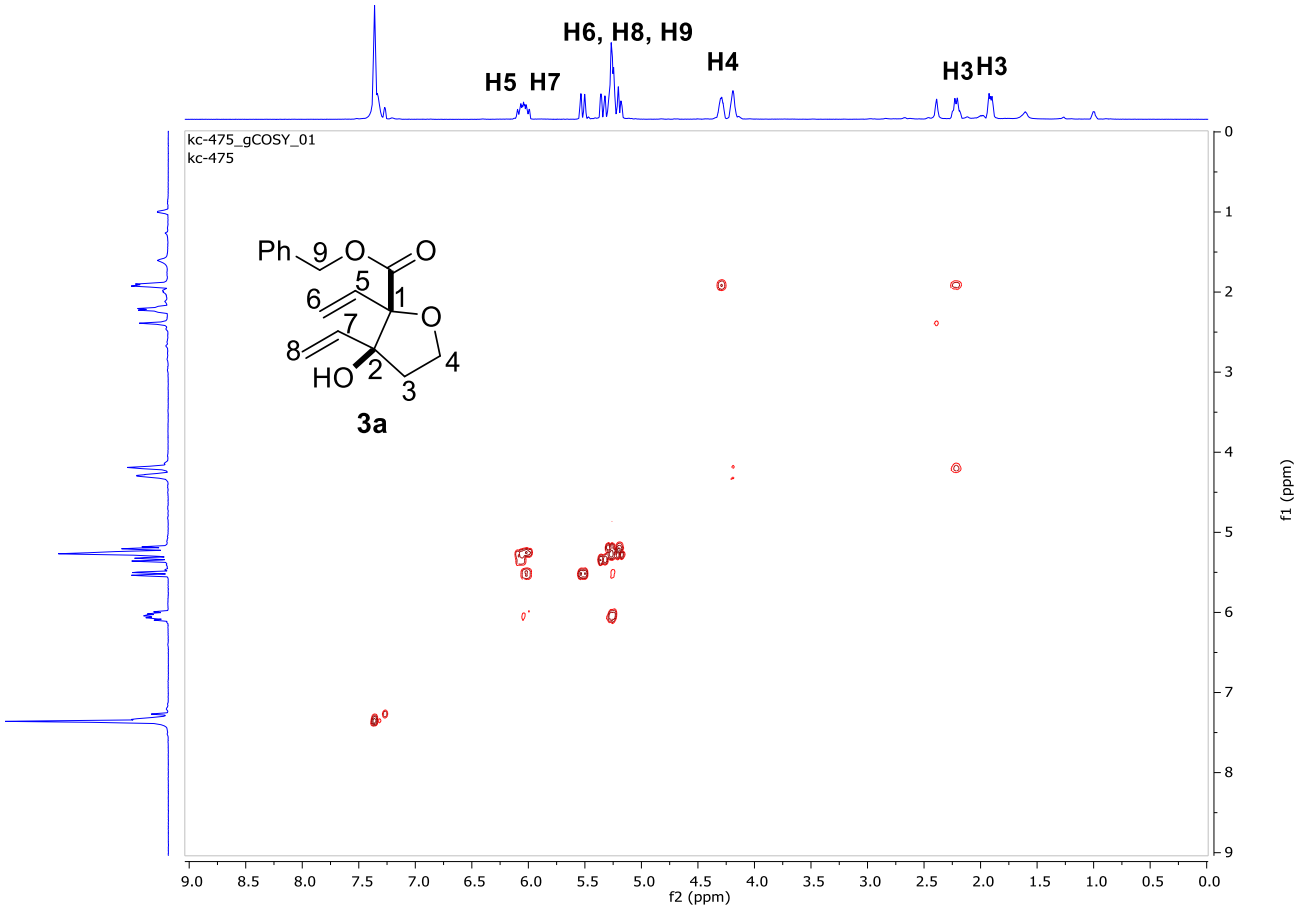
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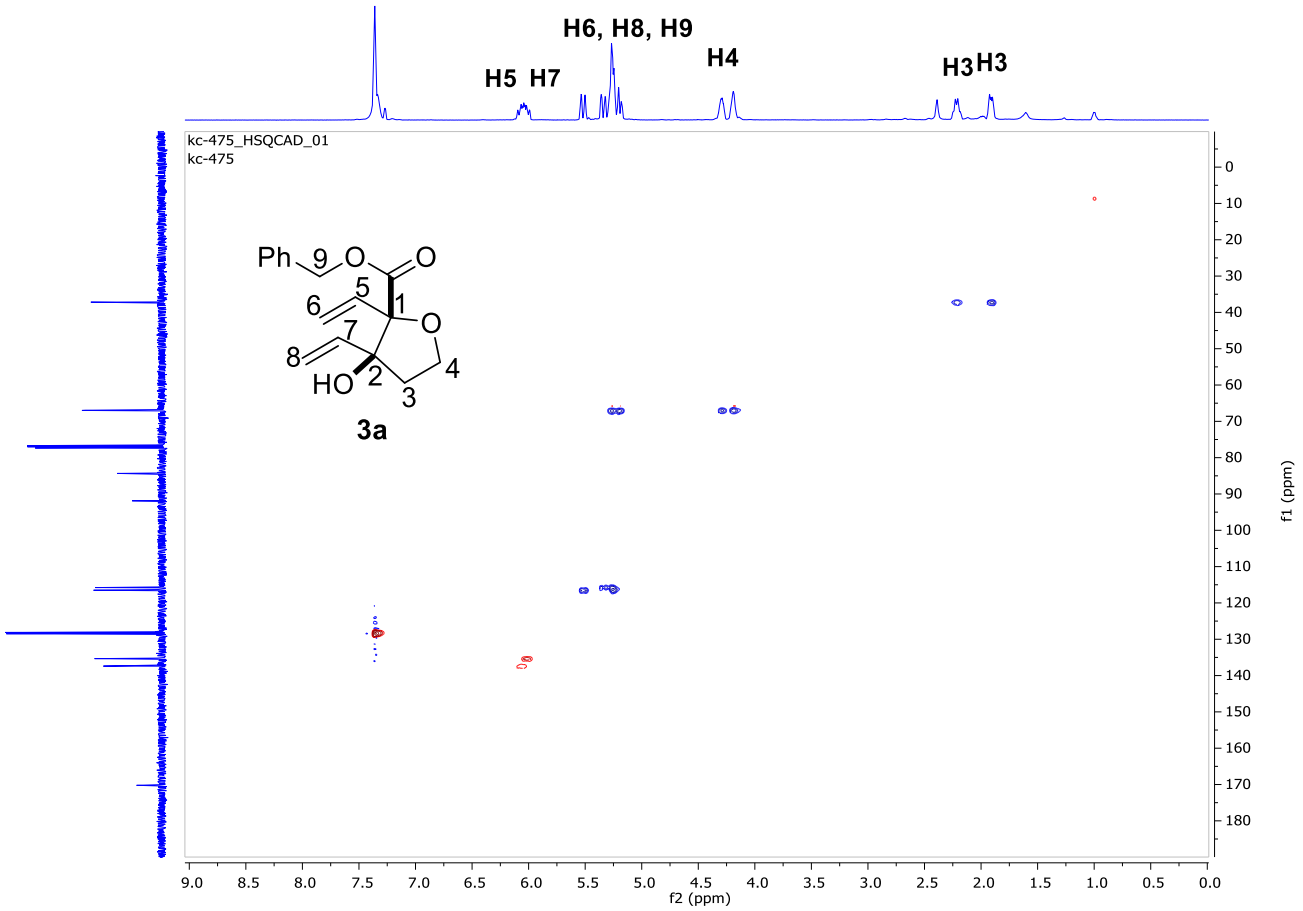
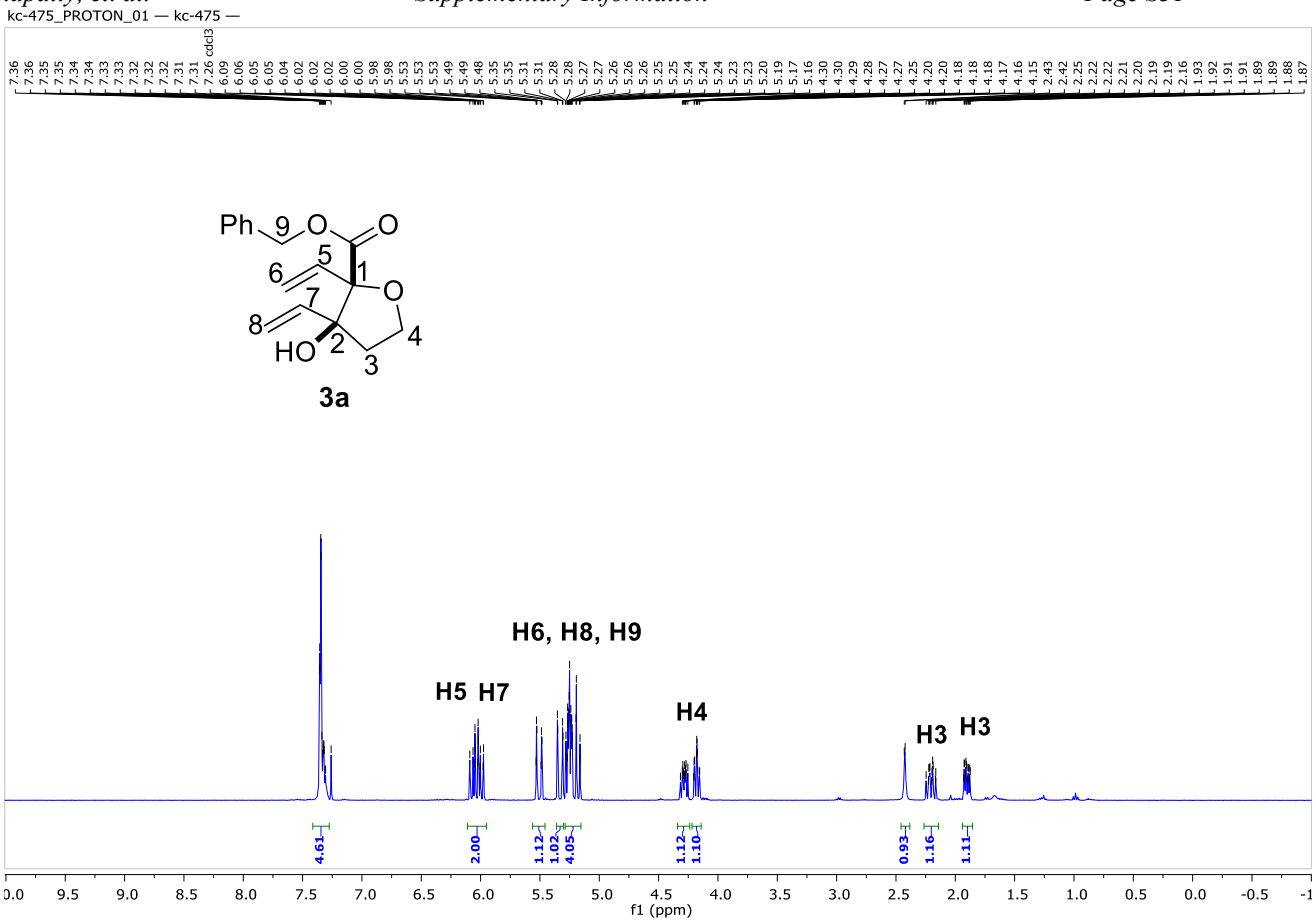
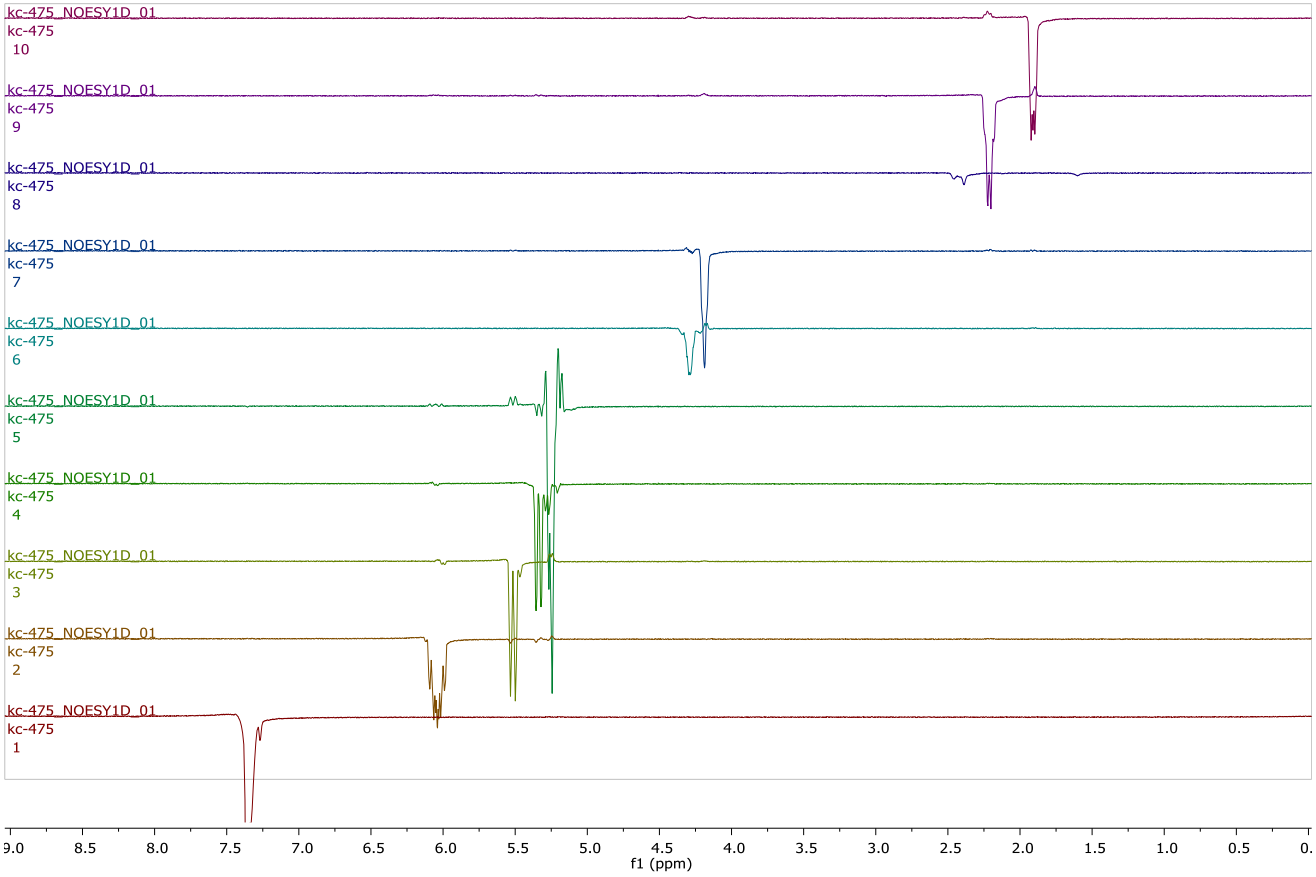
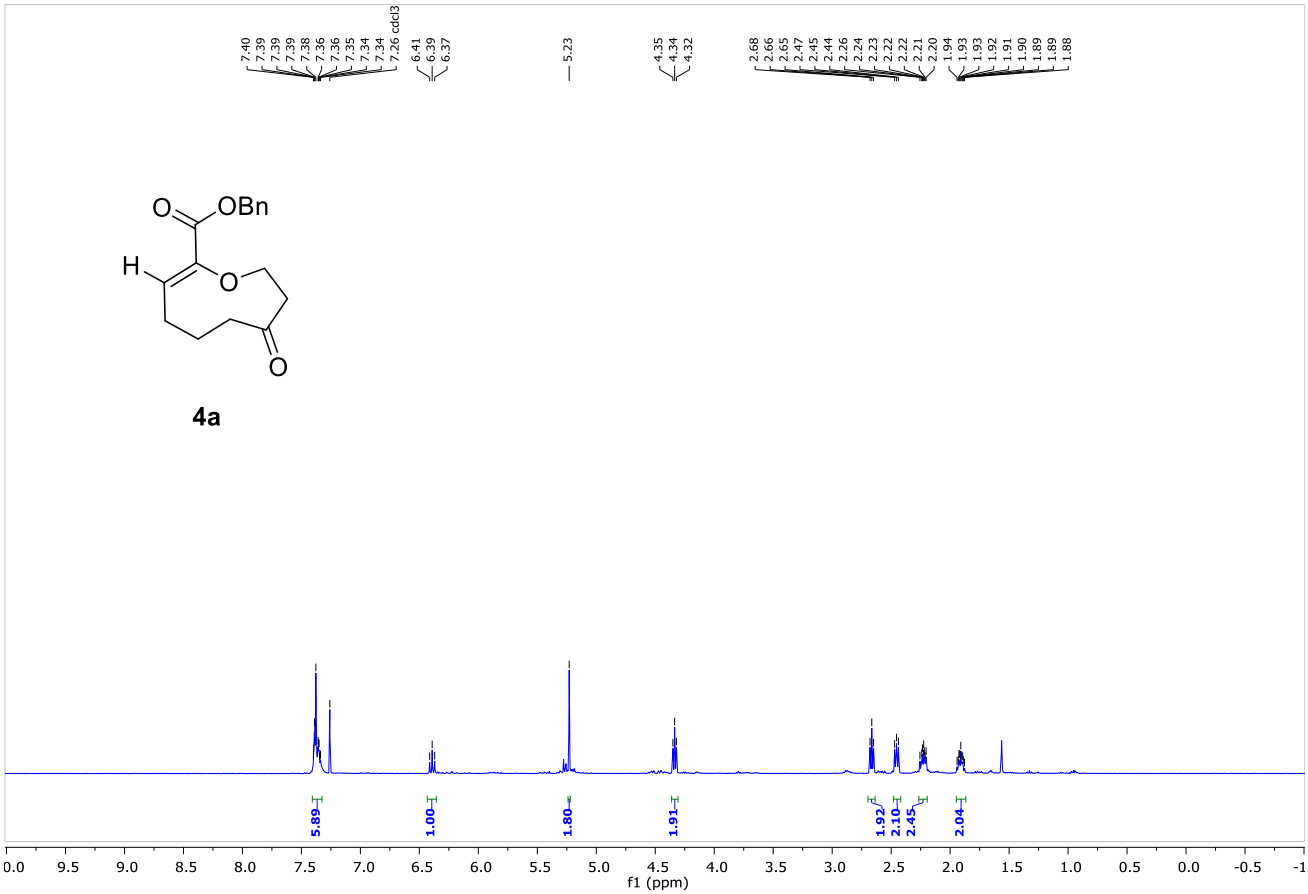
f2 (ppm)
f1 (ppm)


H6, H8, H9
H4
H5 H7
H3 H3
kc-475_HSQCAD_01
kc-475
Ph 9 O O
5
6 1 O
7
8 4
HO 2 3
3a
f2 (ppm)
f1 (ppm)


kc-475_PROTON_01 — kc-475 —
Ph
9
O
O
5
6
1
7
O
8
HO
2
4
3
3a
H6, H8, H9
H5 H7
H4
H3 H3
4.61
2.00
1.12
1.02
4.05
1.12
1.10
0.93
1.16
1.11
f1 (ppm)

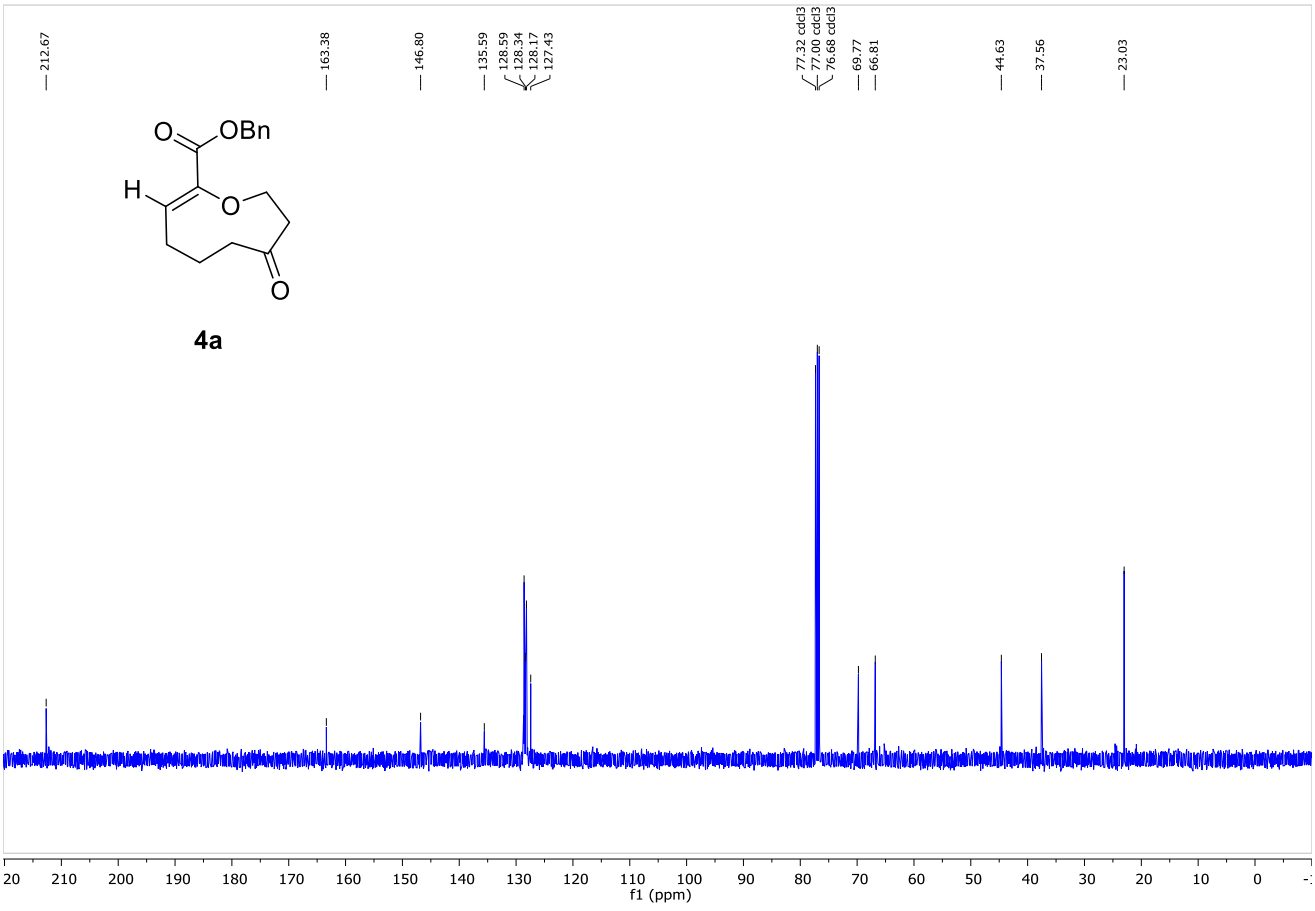

kc-475_NOESY1D_01
kc-475
10
kc-475_NOESY1D_01
kc-475
9
kc-475_NOESY1D_01
kc-475
8
kc-475_NOESY1D_01
kc-475
7
kc-475_NOESY1D_01
kc-475
6
kc-475_NOESY1D_01
kc-475
5
kc-475_NOESY1D_01
kc-475
4
kc-475_NOESY1D_01
kc-475
3
kc-475_NOESY1D_01
kc-475
2
kc-475_NOESY1D_01
kc-475
1
f1 (ppm)

kc-247-3_PROTON_01 — kc-247-3 —

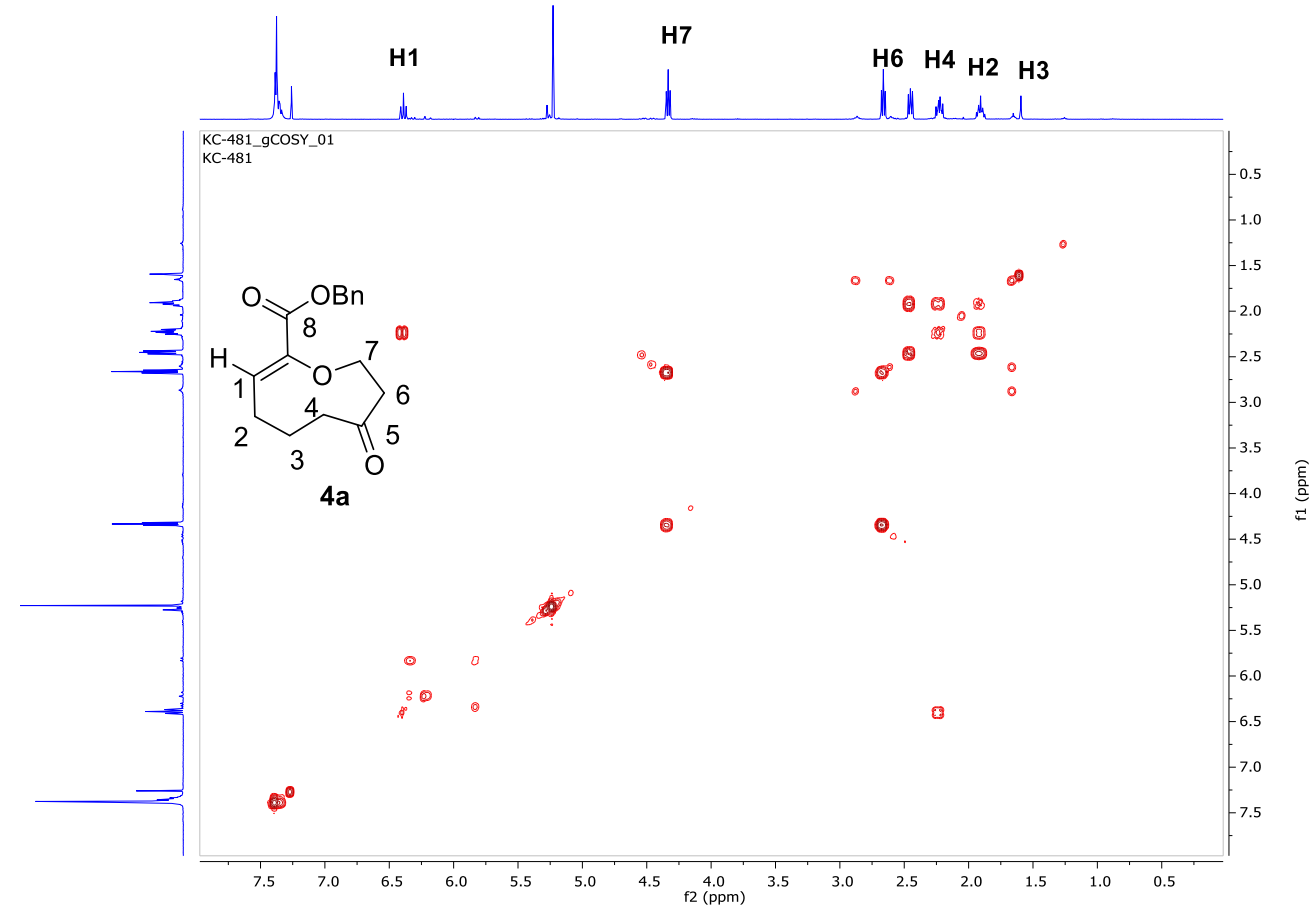


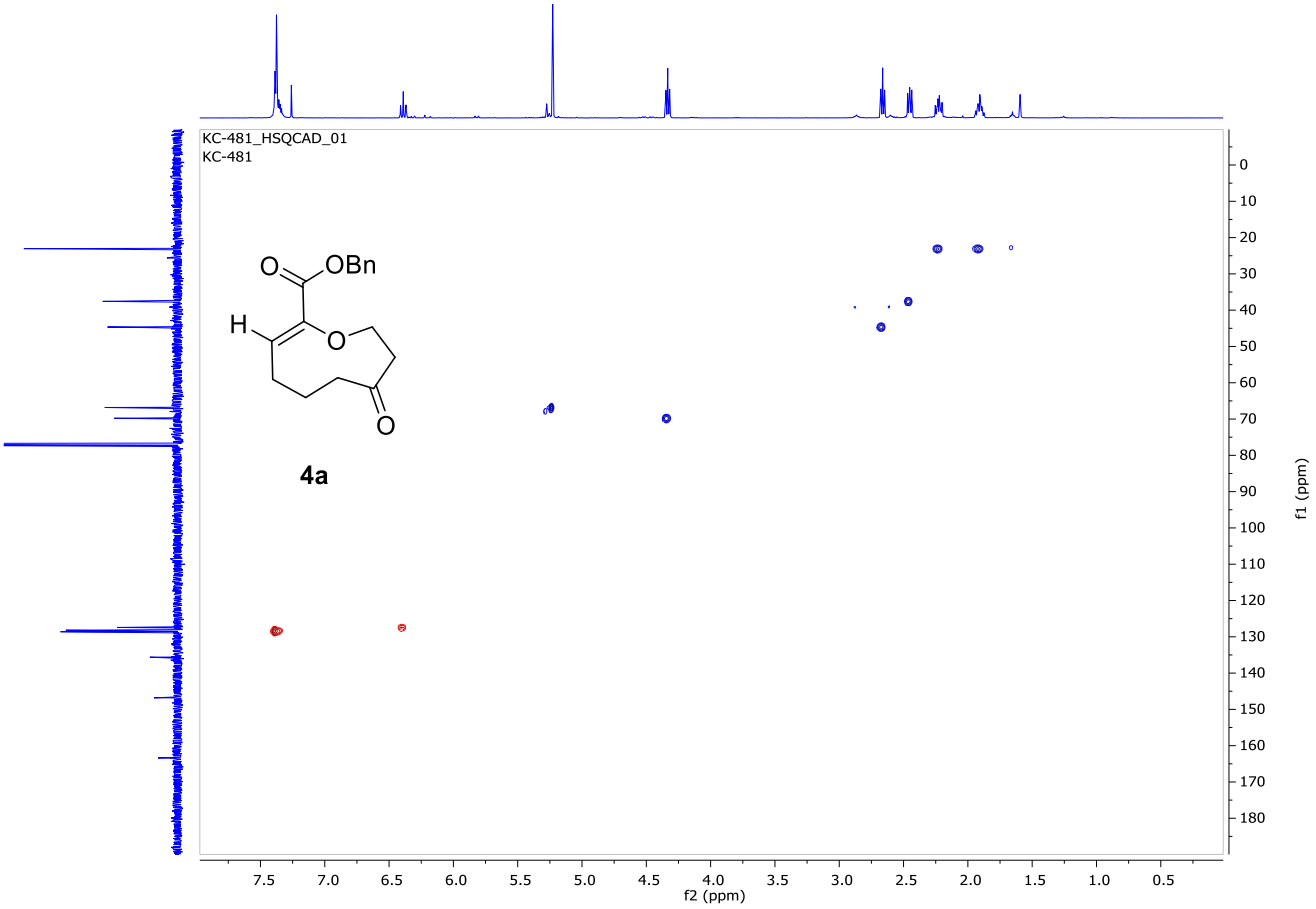
4a

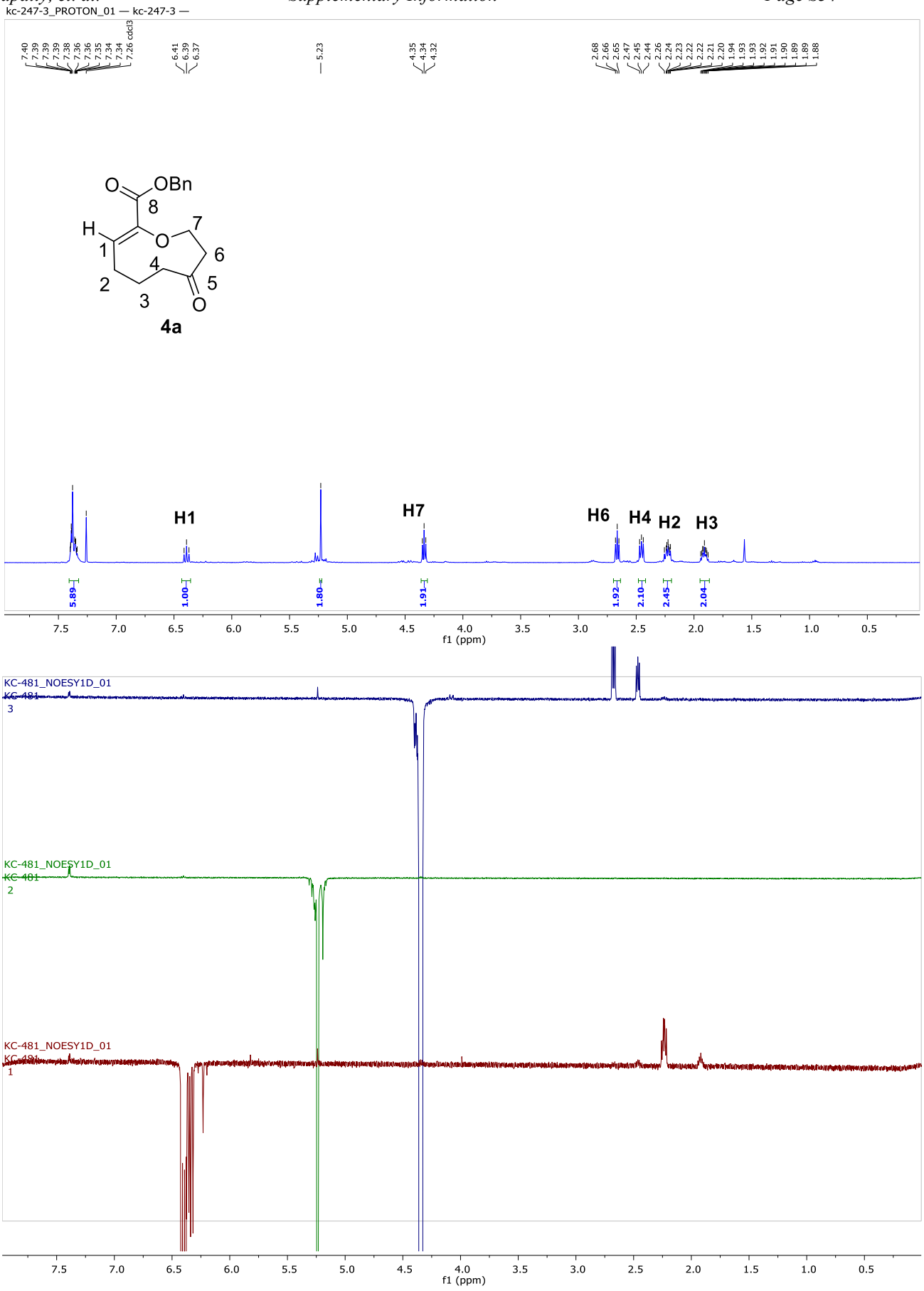
kc-247_CARBON_01 — kc-247 —



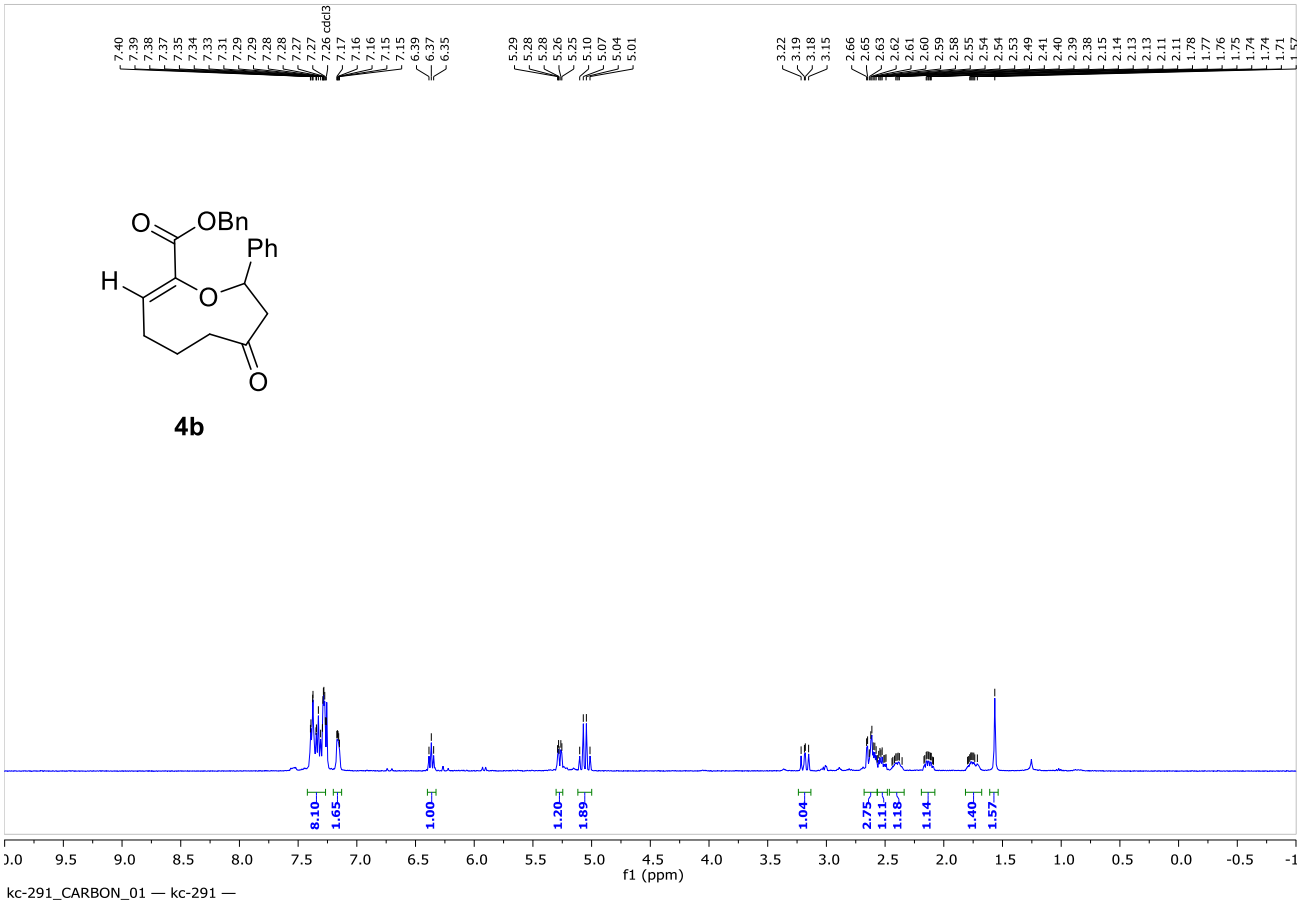
4a


H1
H7
H6
H4
H2
H3
KC-481_gCOSY_01
KC-481
O
OBn
8
H
7
1
O
6
4
2
5
3
O
4a
f1 (ppm)
f2 (ppm)

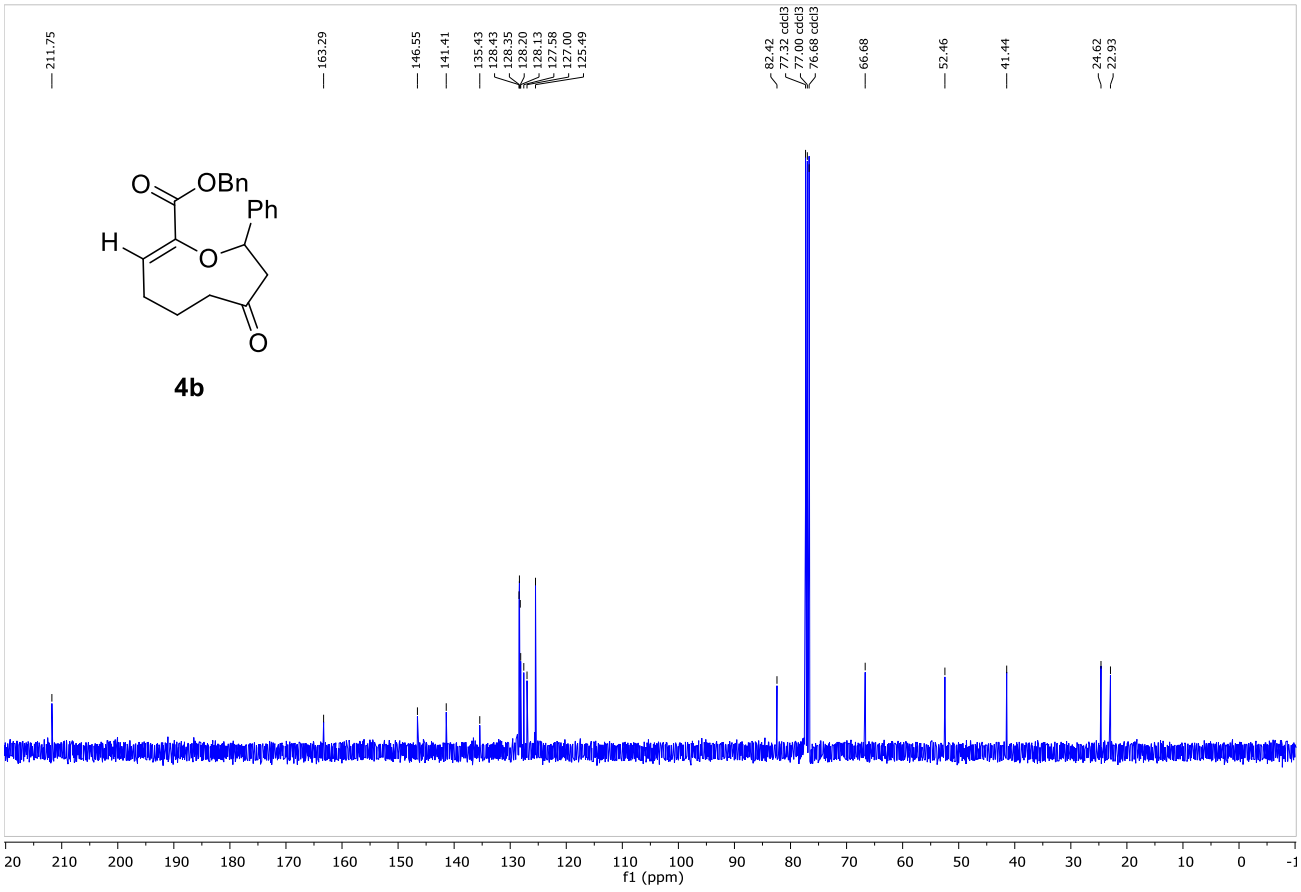

KC-481_HSQCAD_01
KC-481
O
OBn
H
O
O
4a
f1 (ppm)
f2 (ppm)


kc-247-3_PROTON_01 — kc-247-3 —
7.40 7.39 7.39 7.38 7.36 7.36 7.35 7.34 7.34 7.26 cdcl3
6.41 6.39 6.37
5.23
4.35 4.34 4.32
2.68 2.66 2.65 2.47 2.45 2.44 2.26 2.24 2.23 2.22 2.22 2.21 2.20 1.94 1.93 1.93 1.92 1.91 1.90 1.89 1.89 1.88
O
OBn
8
H
7
1
O
6
4
2
5
3
O
4a
H1
H7
H6
H4
H2
H3
5.89
1.00
1.80
1.91
1.92
2.10
2.45
2.04
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)
KC-481_NOESY1D_01
KC-481
3
KC-481_NOESY1D_01
KC-481
2
KC-481_NOESY1D_01
KC-481
1
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)

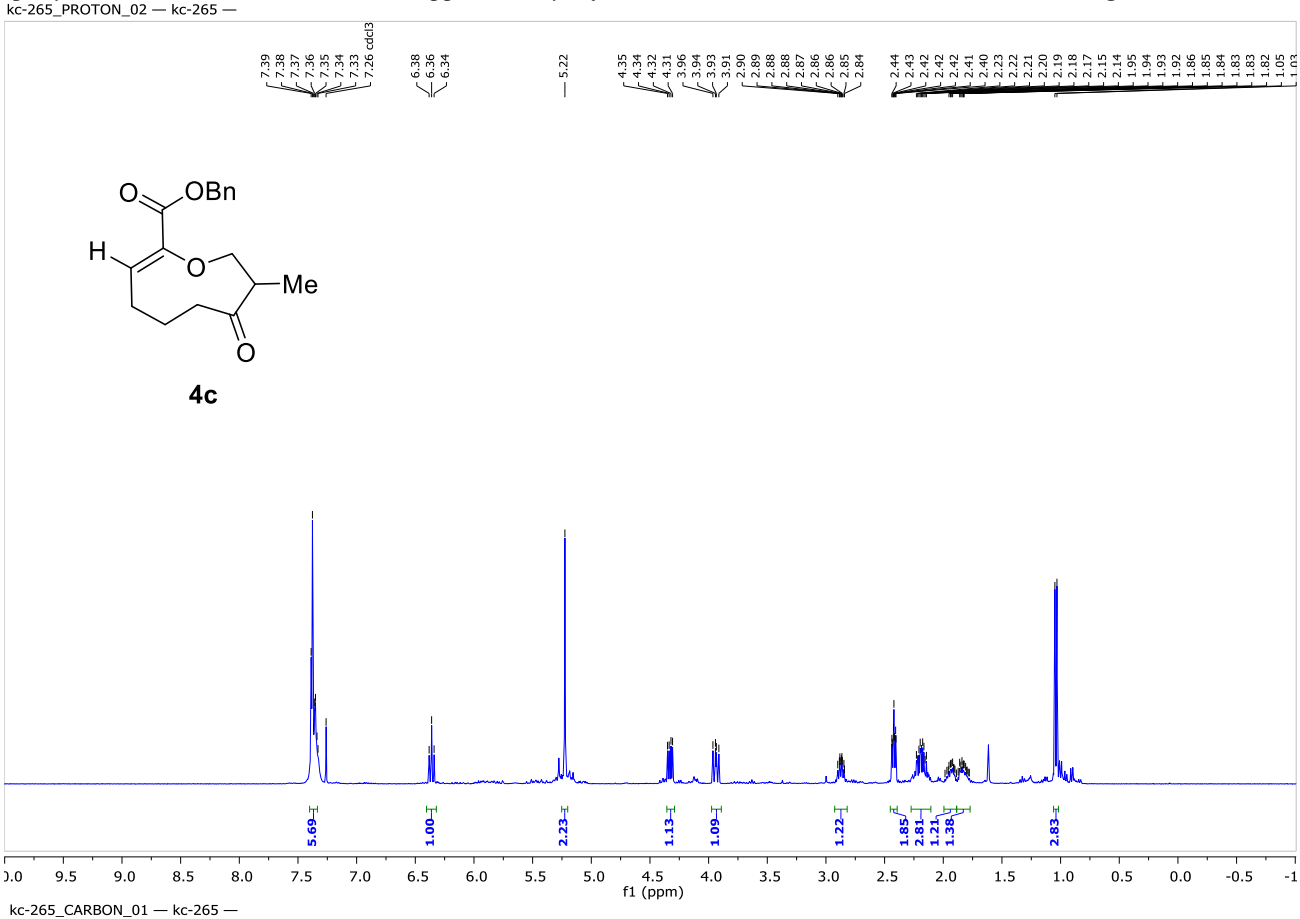
kc-291_PROTON_01 — kc-291 —



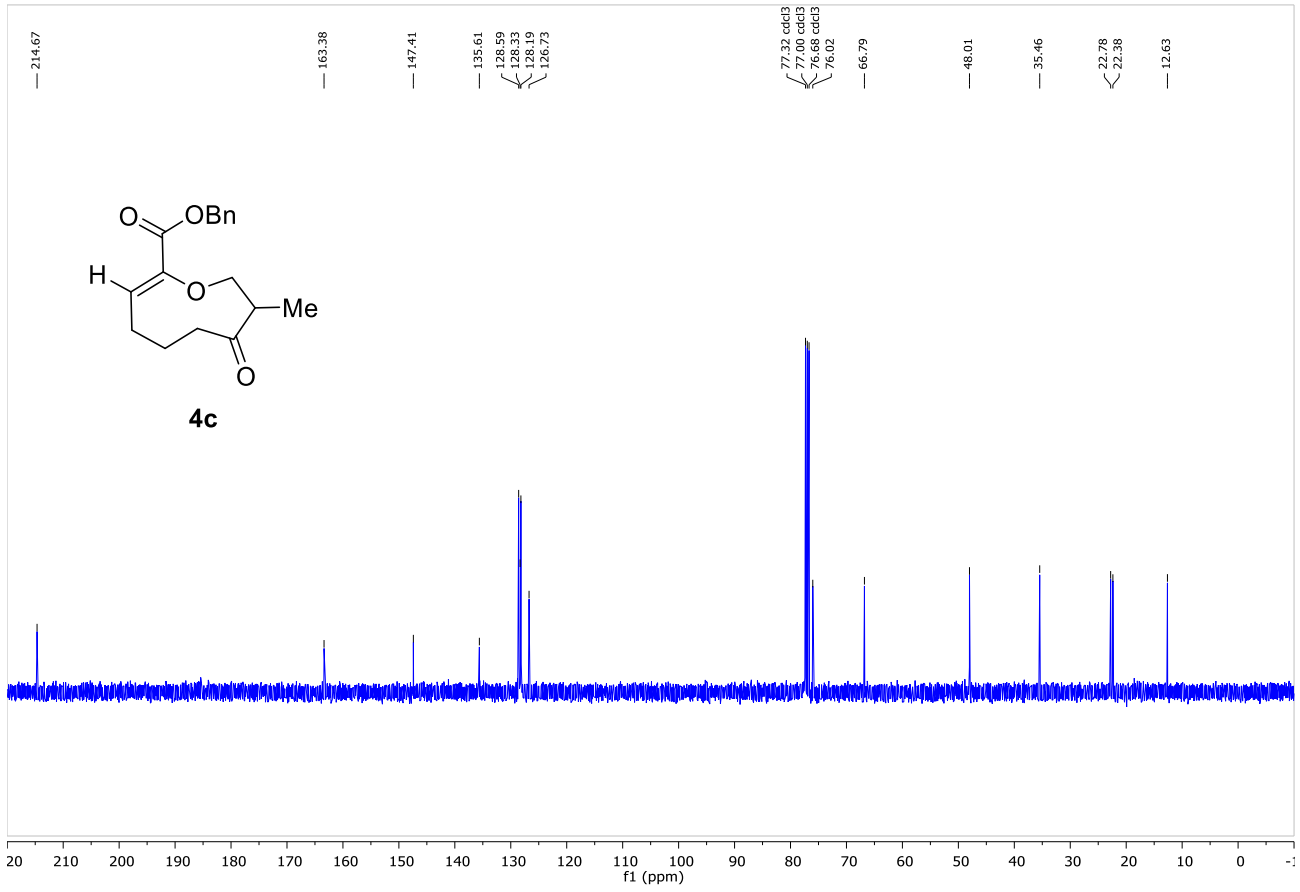
kc-291_CARBON_01 — kc-291 —



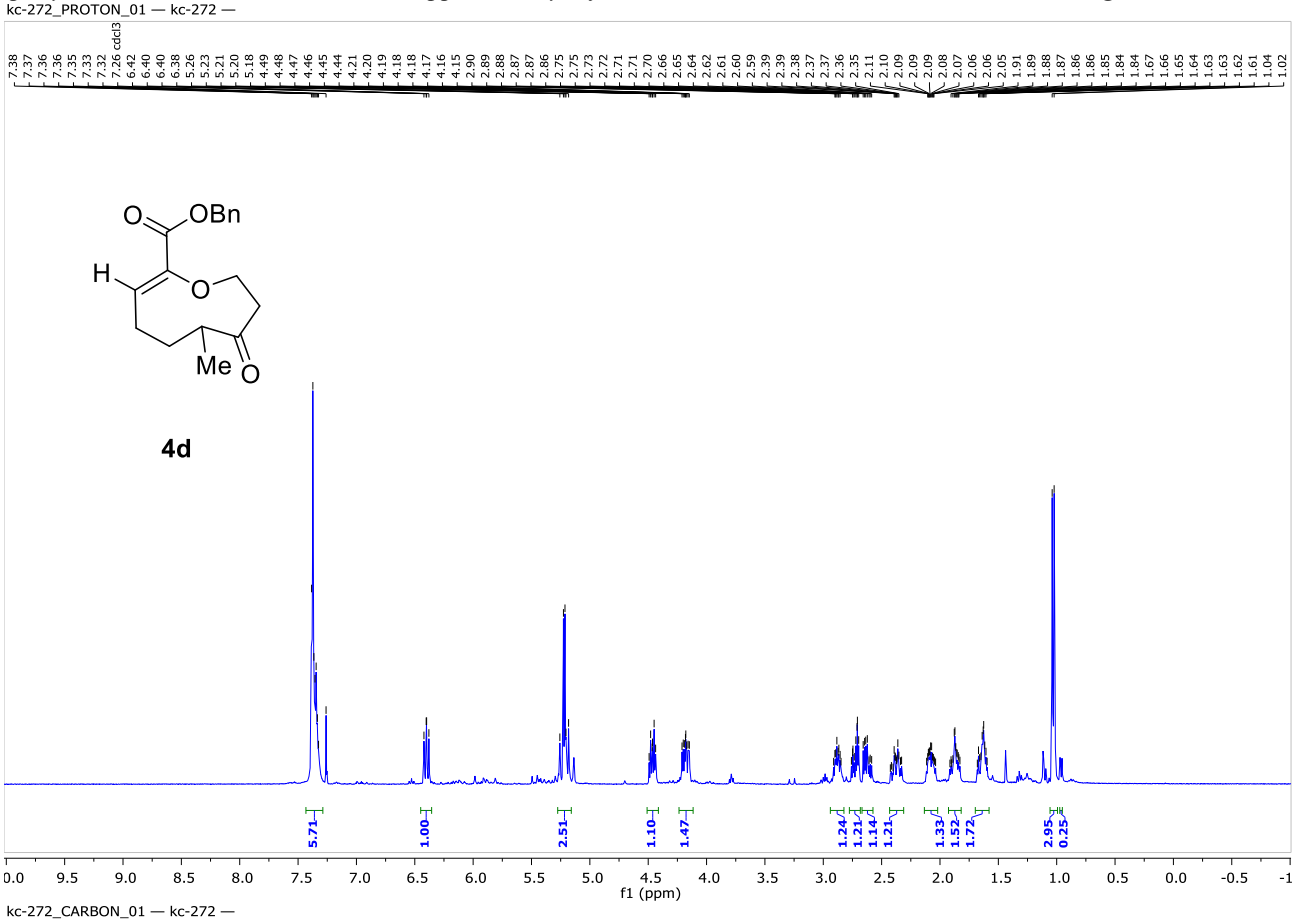
kc-265_PROTON_02 — kc-265 —



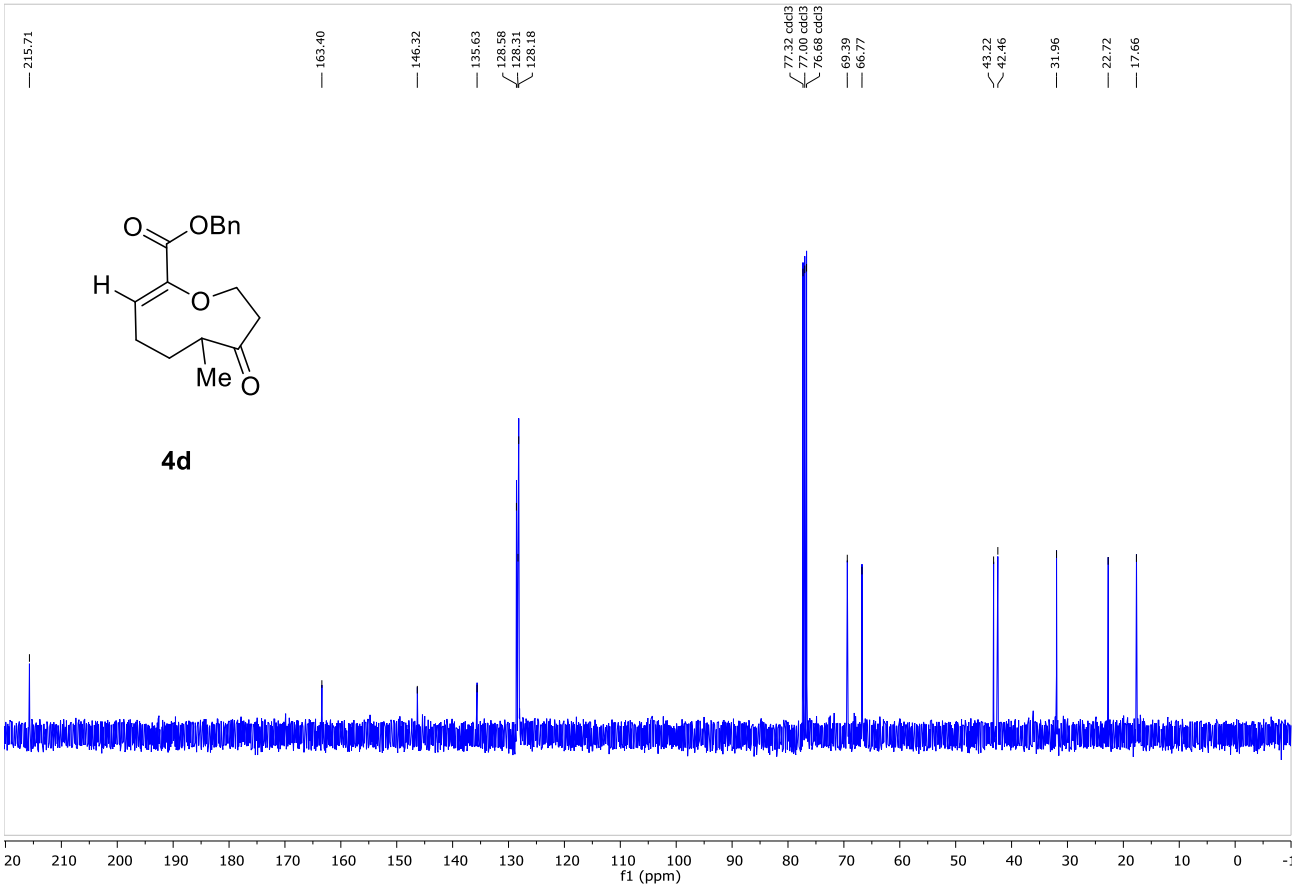
kc-265_CARBON_01 — kc-265 —

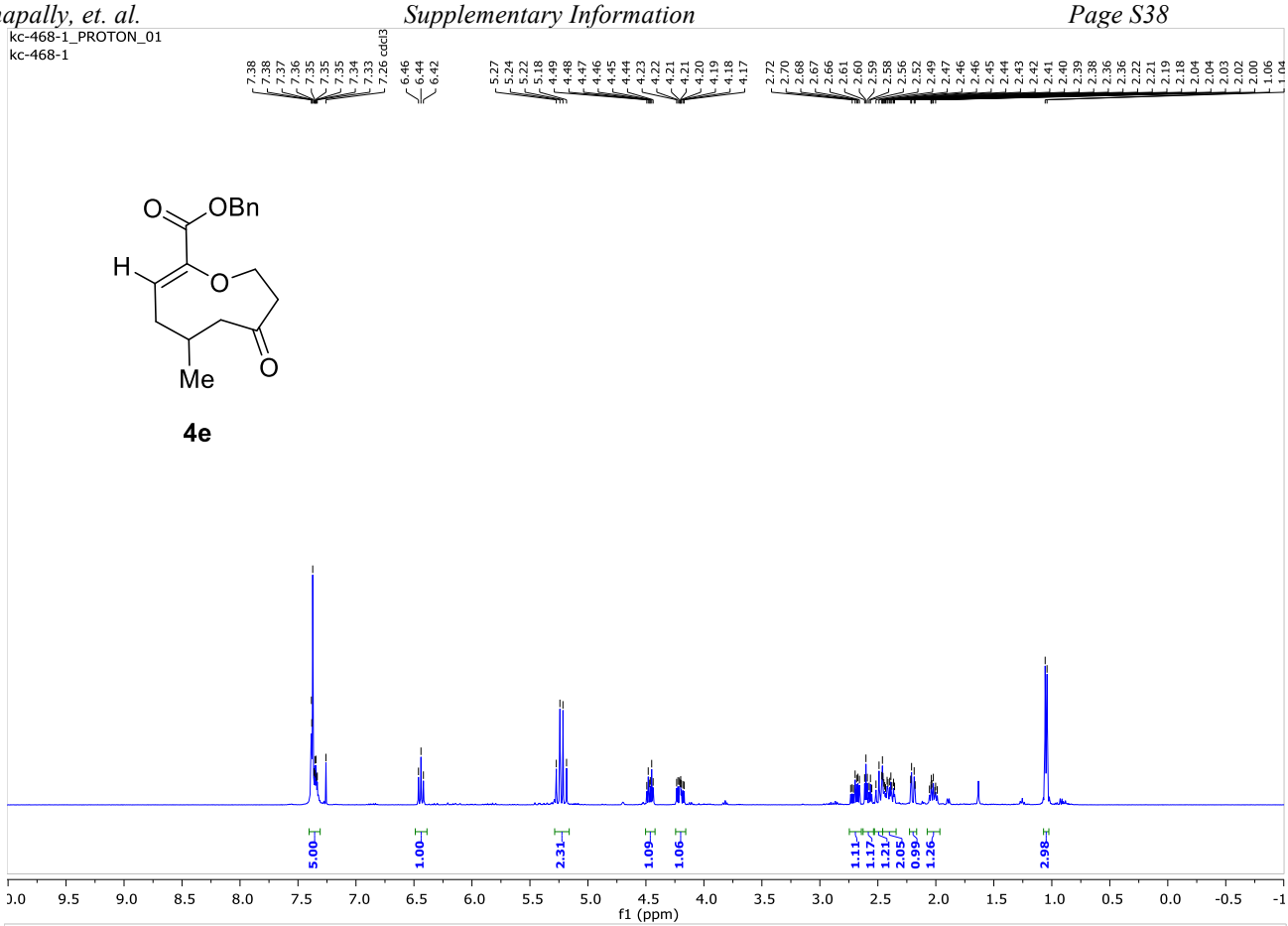


kc-272_PROTON_01 — kc-272 —

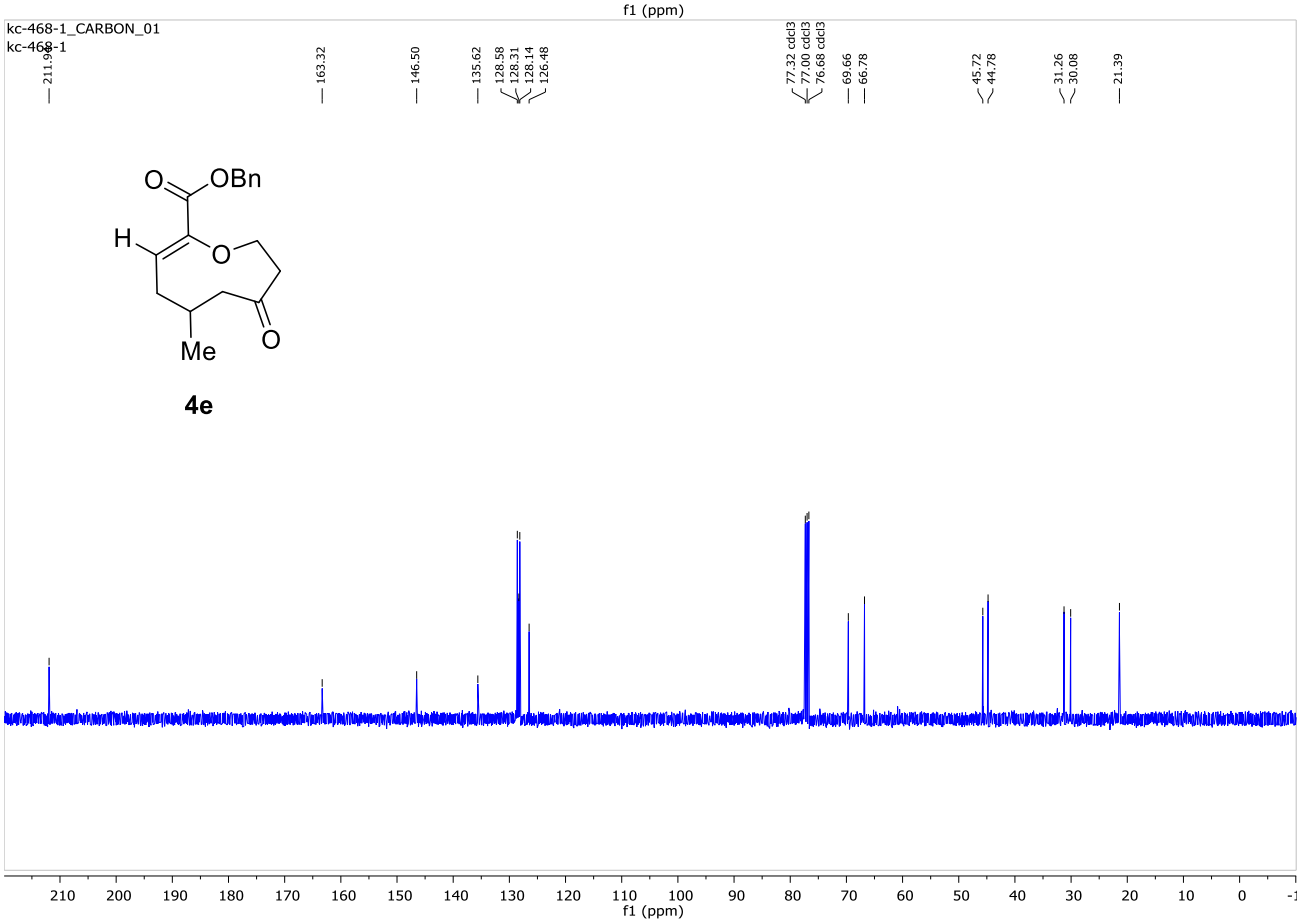


kc-272_CARBON_01 — kc-272 —

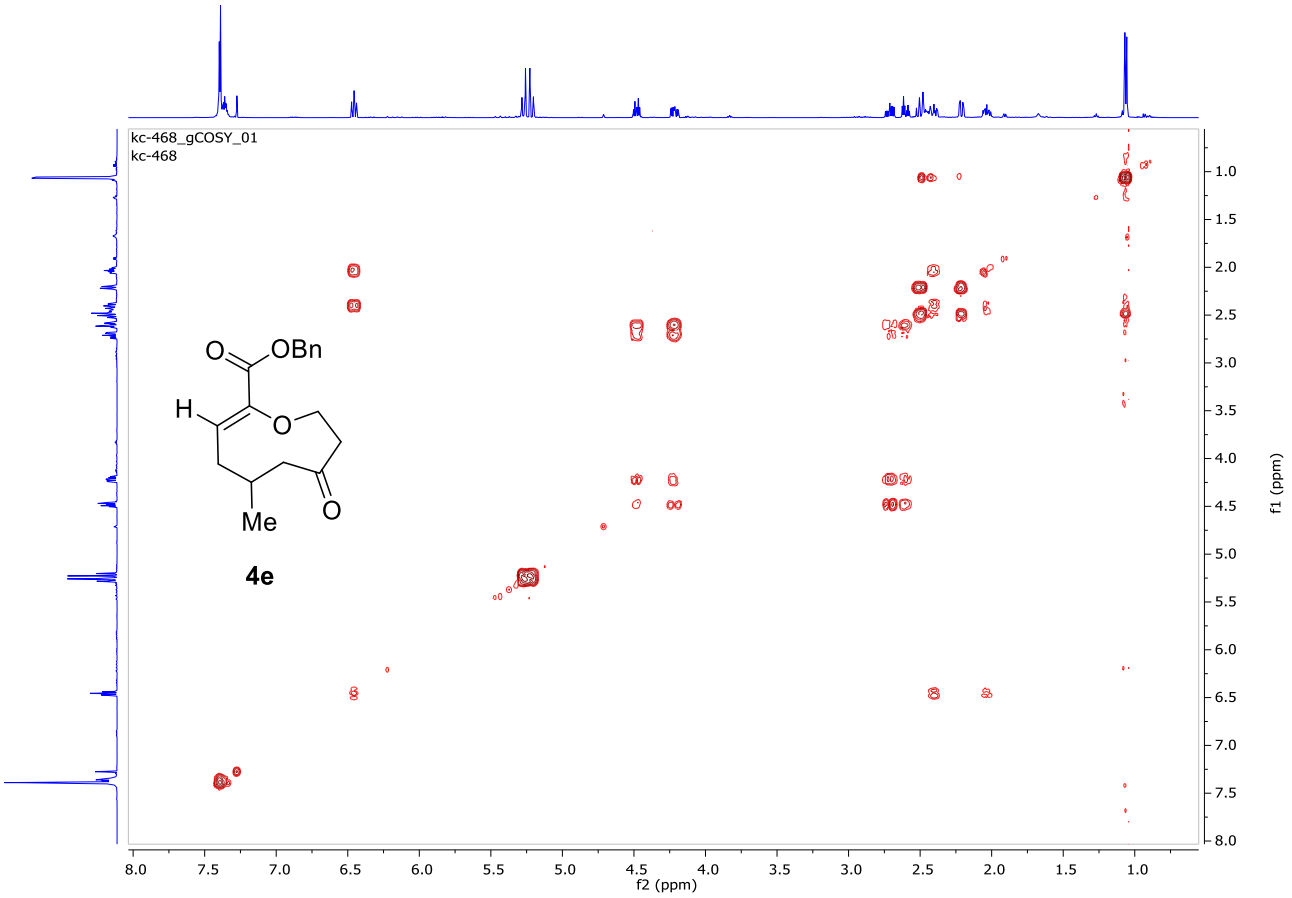


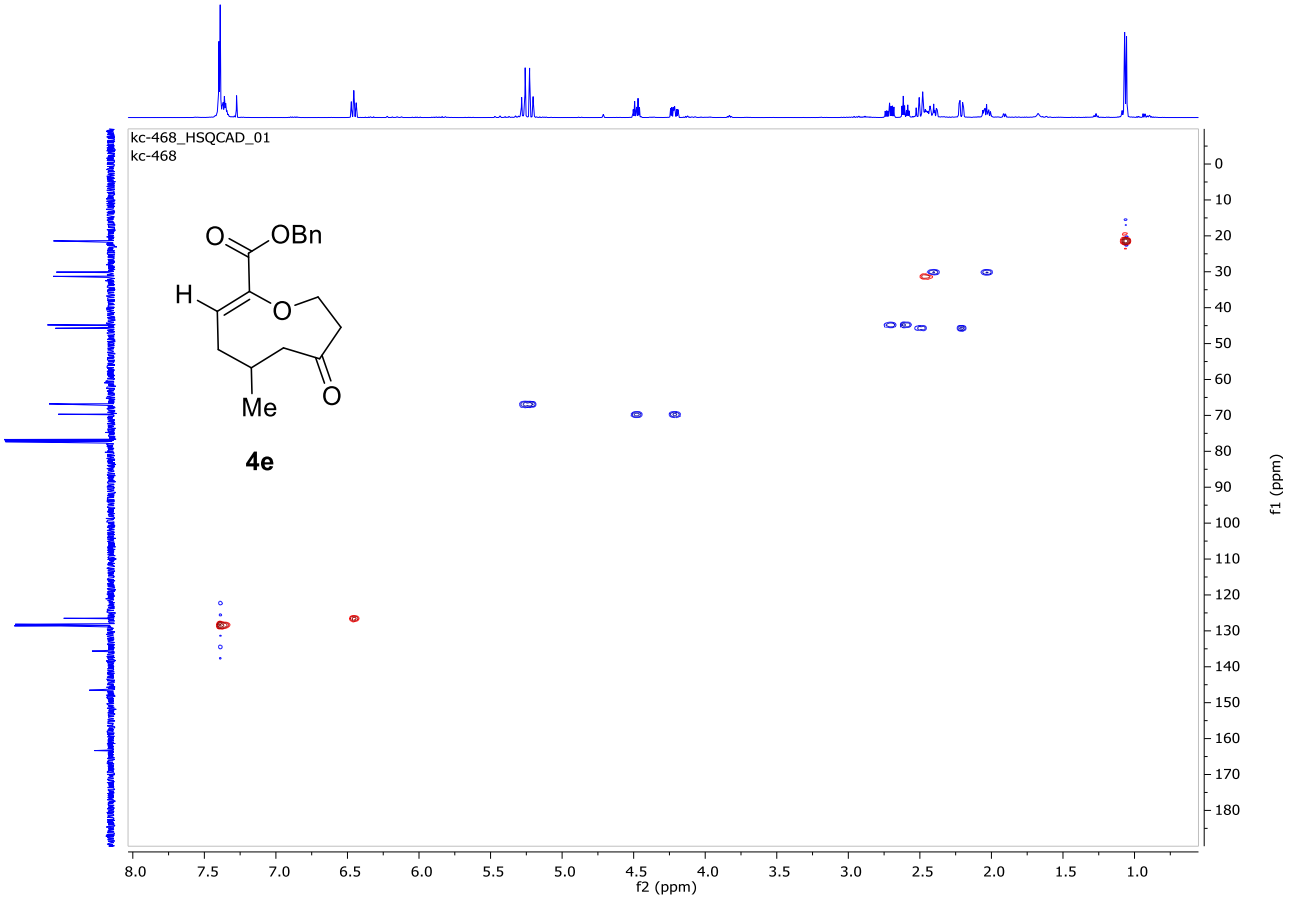

kc-468-1_PROTON_01
kc-468-1
O
OBn
H
O
Me
O
5.00
1.00
2.31
1.09
1.06
1.11
1.17
1.21
2.05
0.99
1.26
2.98
f1 (ppm)

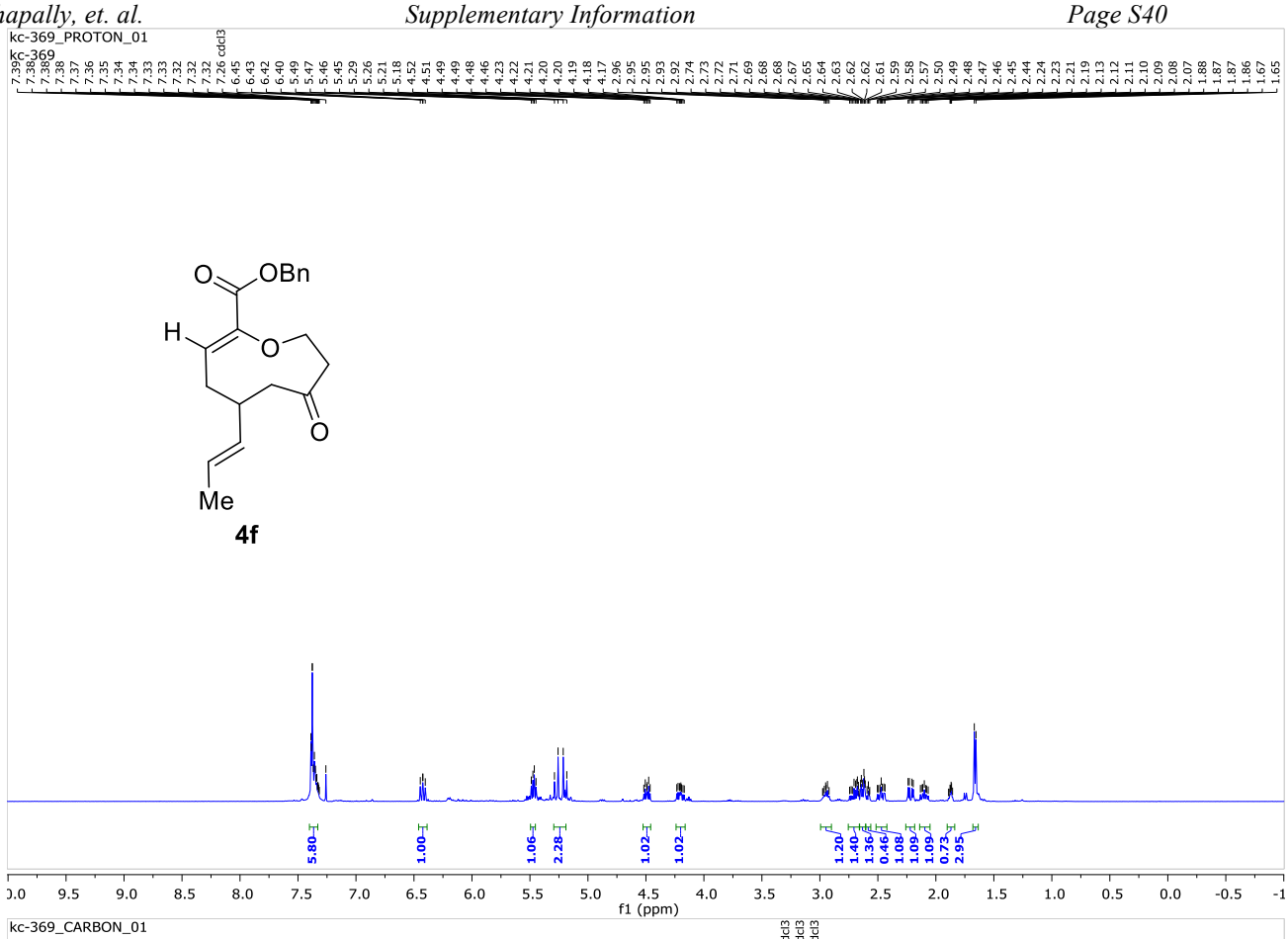
4e

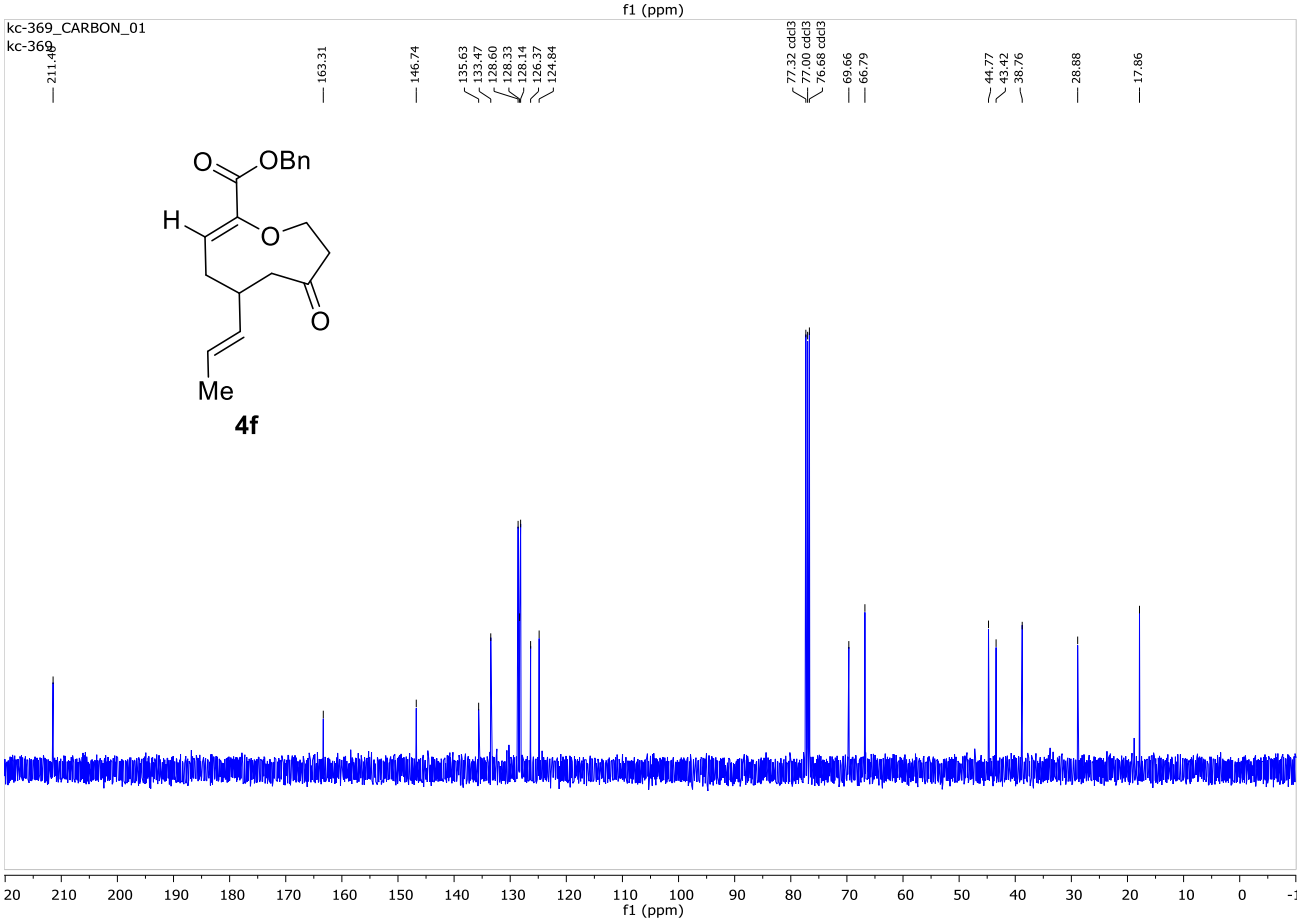

kc-468-1_CARBON_01
kc-468-1
211.98
163.32
146.50
135.62
128.58
128.31
128.14
126.48
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
69.66
66.78
45.72
44.78
31.26
30.08
21.39
O
OBn
H
O
Me
O
f1 (ppm)

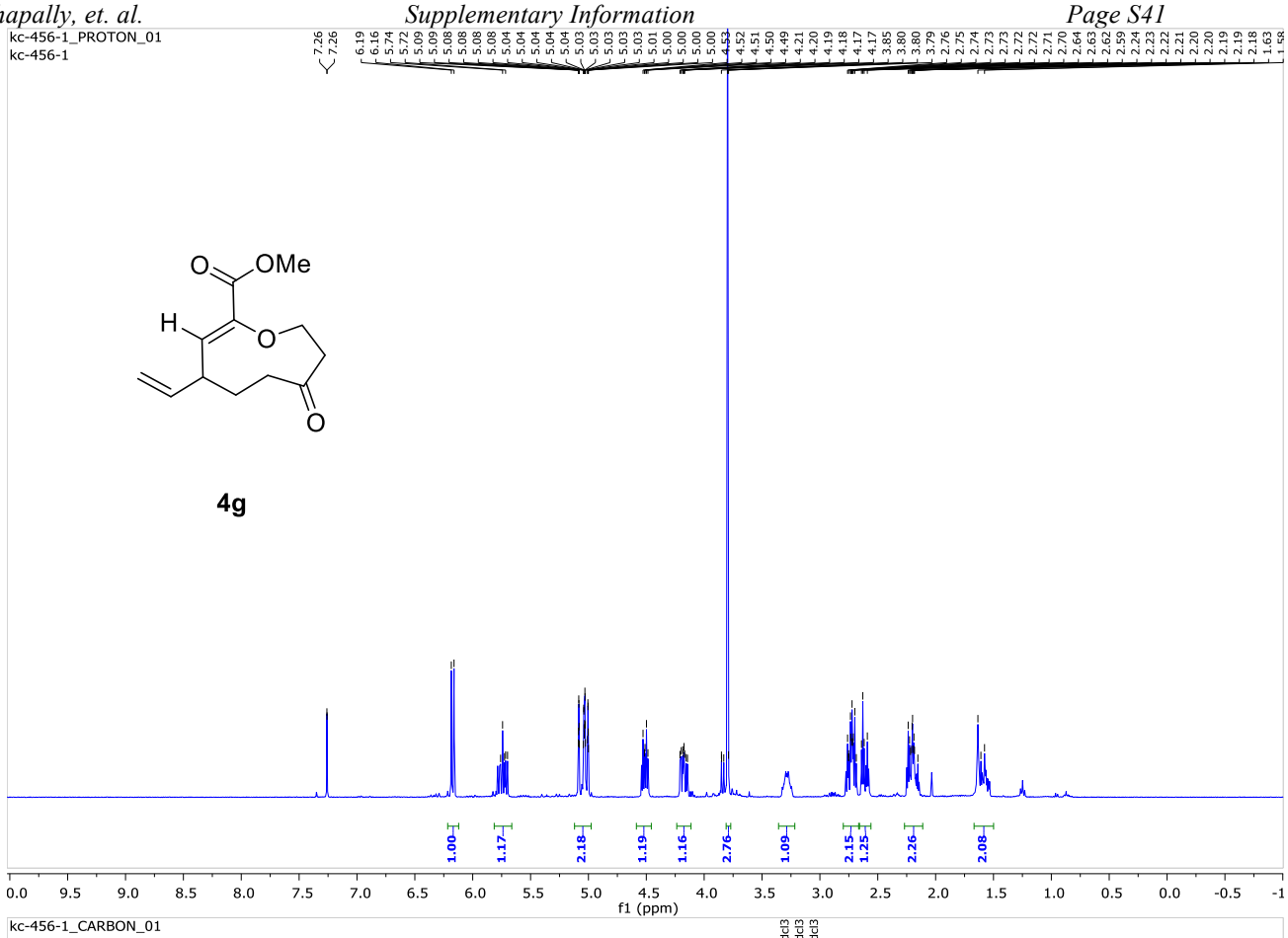
4e


kc-468_gCOSY_01
kc-468
O
OBn
H
O
O
Me
4e
f2 (ppm)
f1 (ppm)

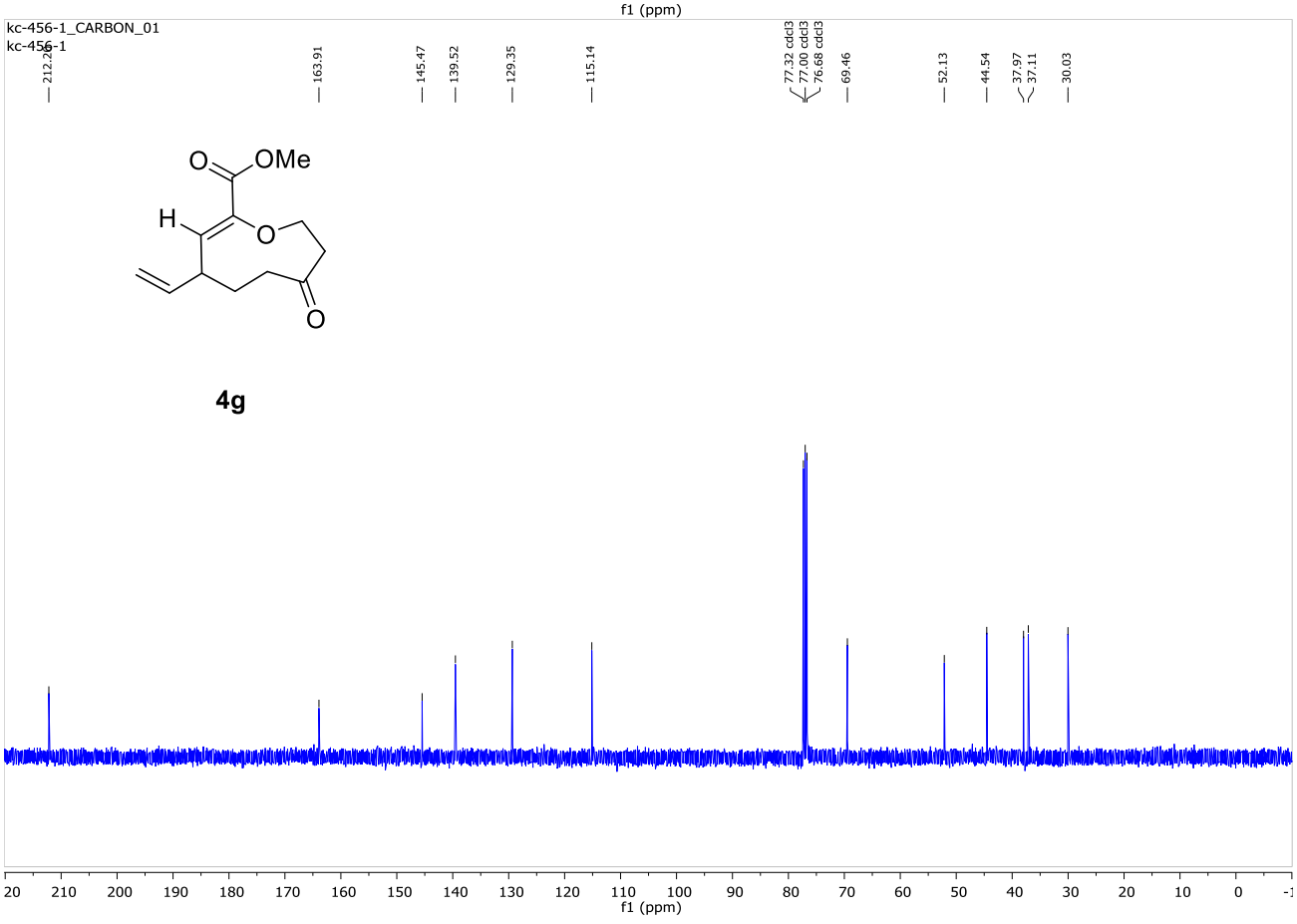

kc-468_HSQCAD_01
kc-468
O
OBn
H
O
O
Me
4e
f2 (ppm)
f1 (ppm)


kc-369_PROTON_01
kc-369
O
OBn
H
O
O
Me
4f
5.80
1.00
1.06
2.28
1.02
1.02
1.20
1.40
1.36
0.46
1.08
1.09
1.09
0.73
2.95
f1 (ppm)

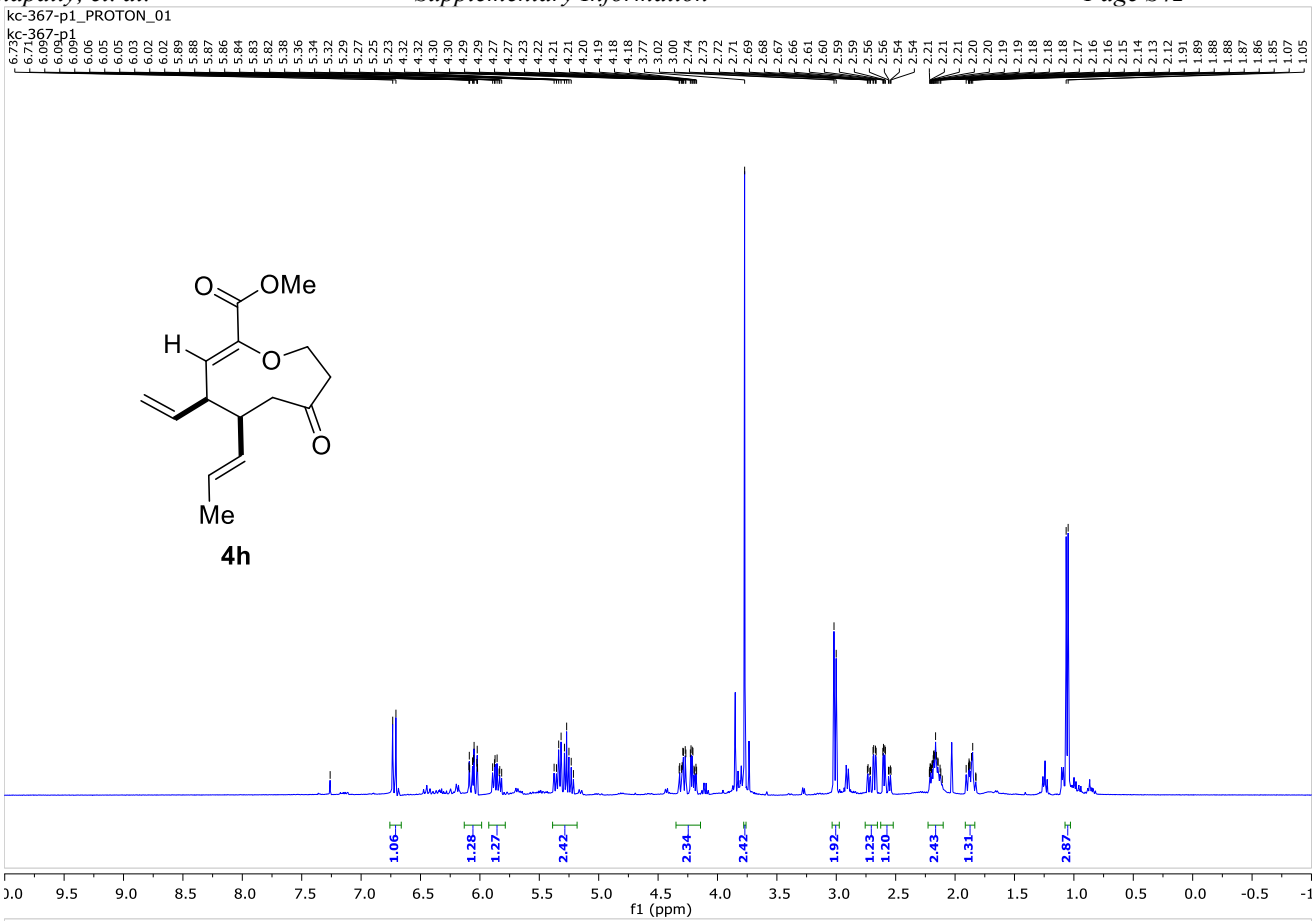

kc-369_CARBON_01
kc-369
211.49
163.31
146.74
135.63
133.47
128.60
128.33
128.14
126.37
124.84
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
69.66
66.79
44.77
43.42
38.76
28.88
17.86
O
OBn
H
O
O
Me
4f
f1 (ppm)

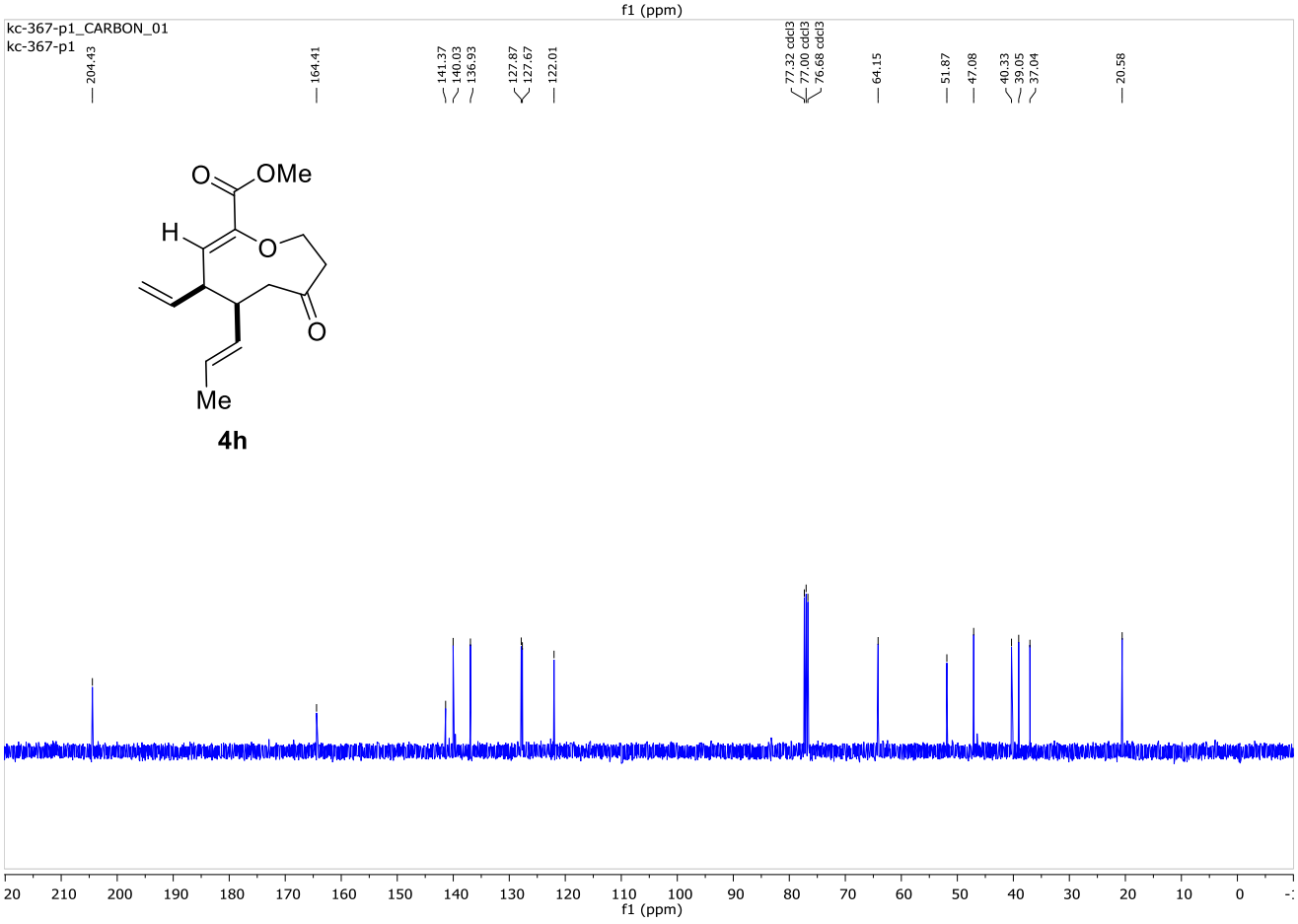

kc-456-1_PROTON_01
kc-456-1
O
OMe
H
O
O
1.00
1.17
2.18
1.19
1.16
2.76
1.09
2.15
1.25
2.26
2.08
f1 (ppm)

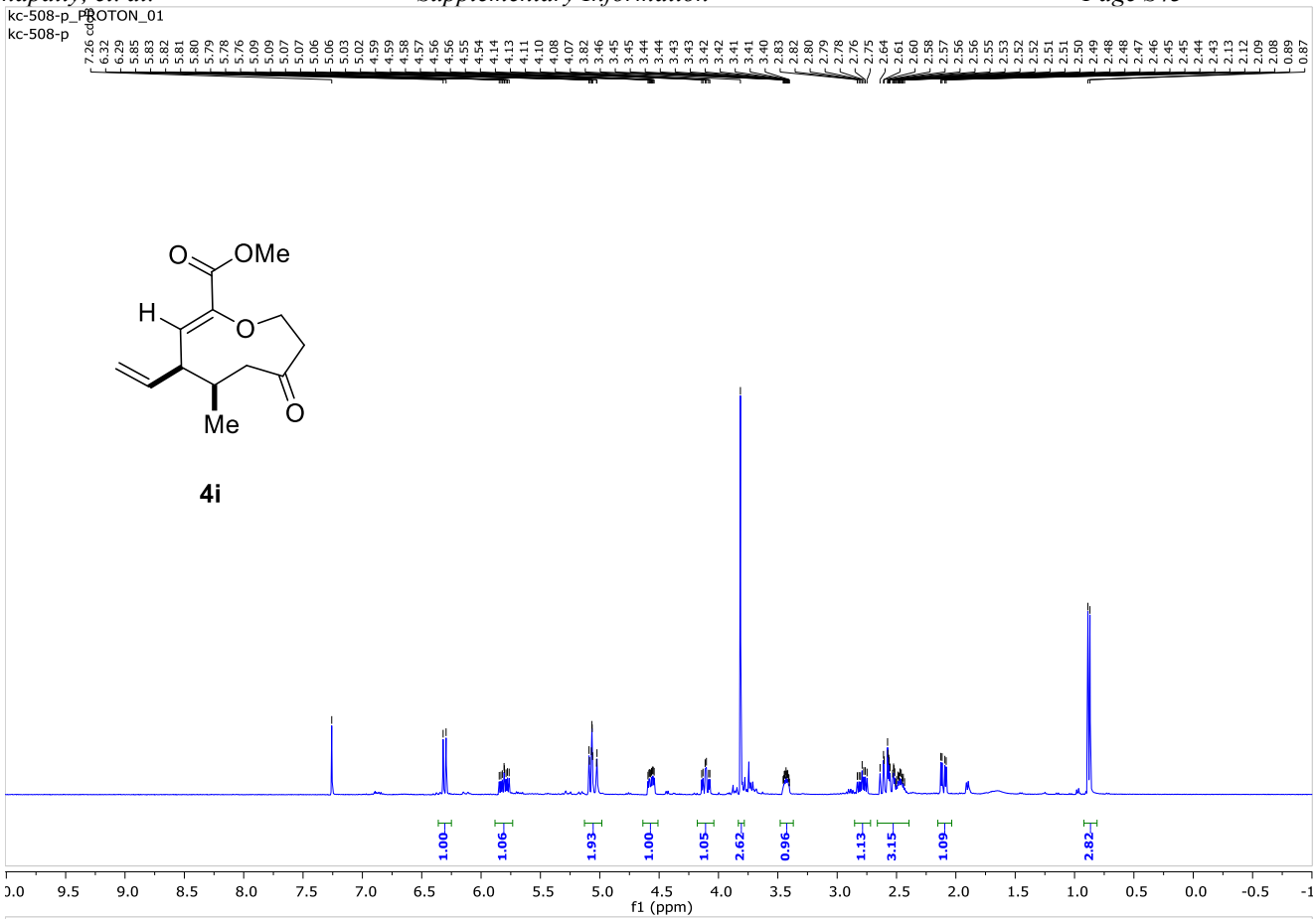
4g


kc-456-1_CARBON_01
kc-456-1
212.26
163.91
145.47
139.52
129.35
115.14
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
69.46
52.13
44.54
37.97
37.11
30.03
O
OMe
H
O
O
f1 (ppm)

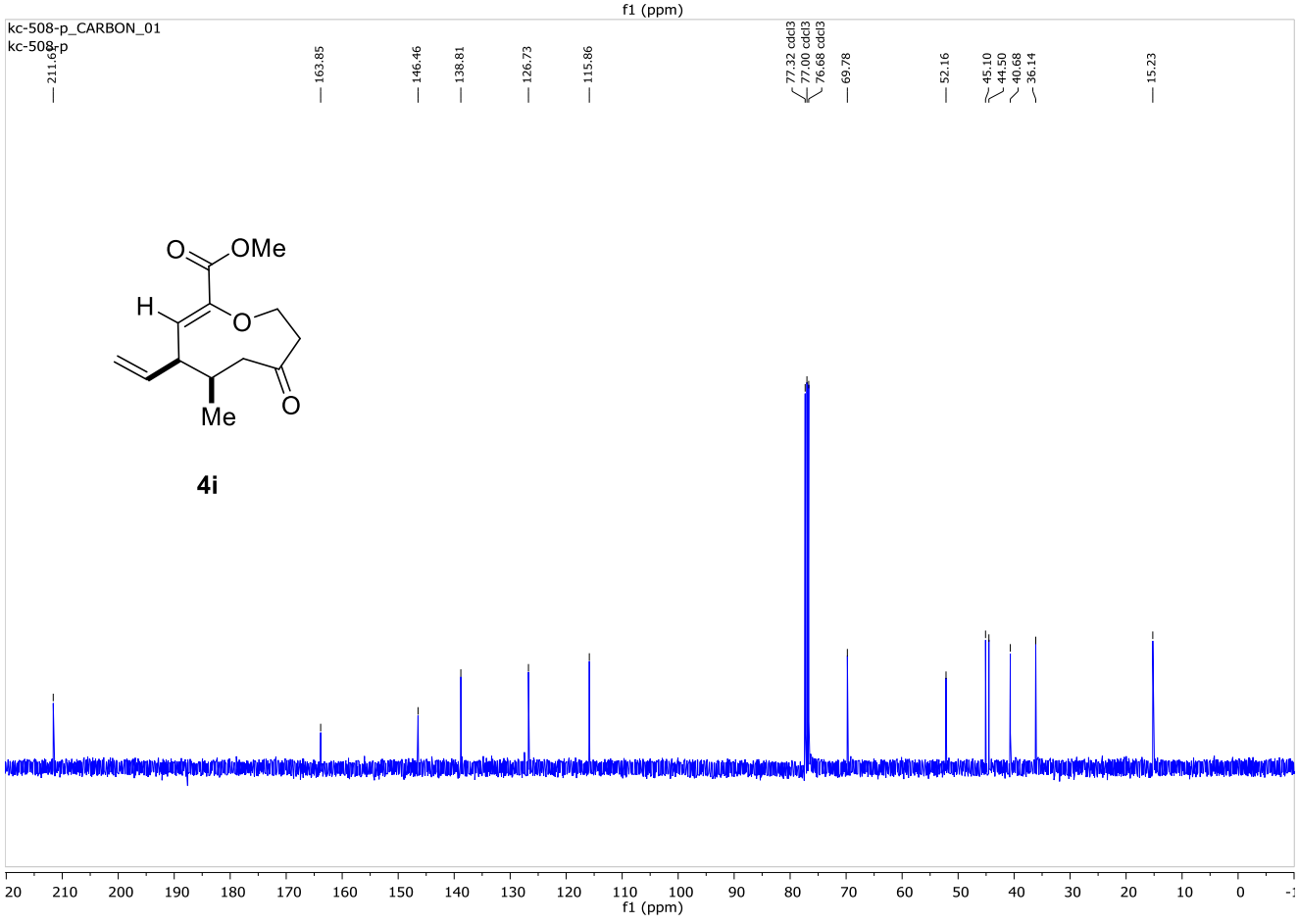
4g


kc-367-p1_PROTON_01
kc-367-p1
O
OMe
H
O
O
Me
4h
1.06
1.28
1.27
2.42
2.34
2.42
1.92
1.23
1.20
2.43
1.31
2.87
f1 (ppm)

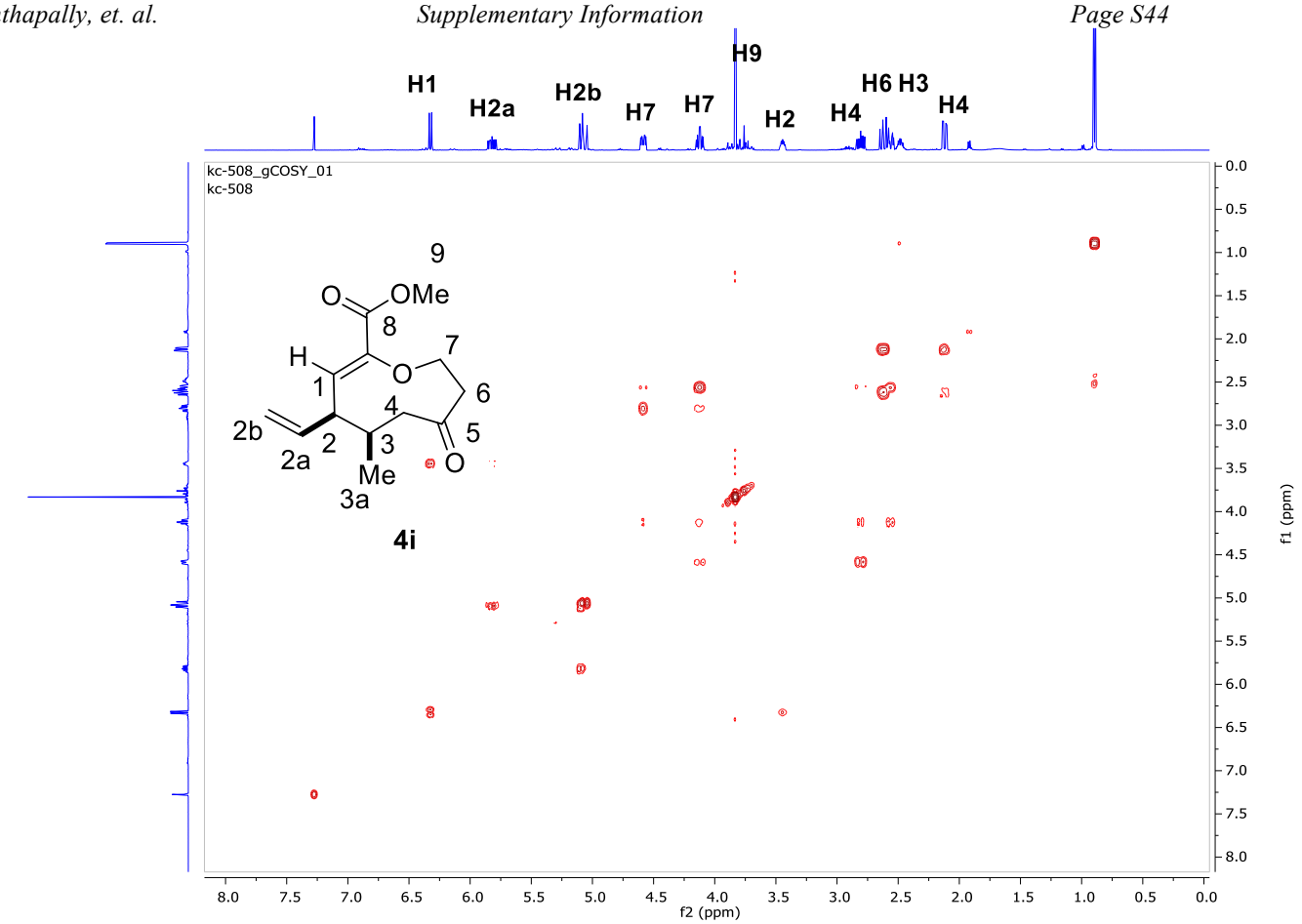

kc-367-p1_CARBON_01
kc-367-p1
204.43
164.41
141.37
140.03
136.93
127.87
127.67
122.01
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
64.15
51.87
47.08
40.33
39.05
37.04
20.58
O
OMe
H
O
O
Me
4h
f1 (ppm)

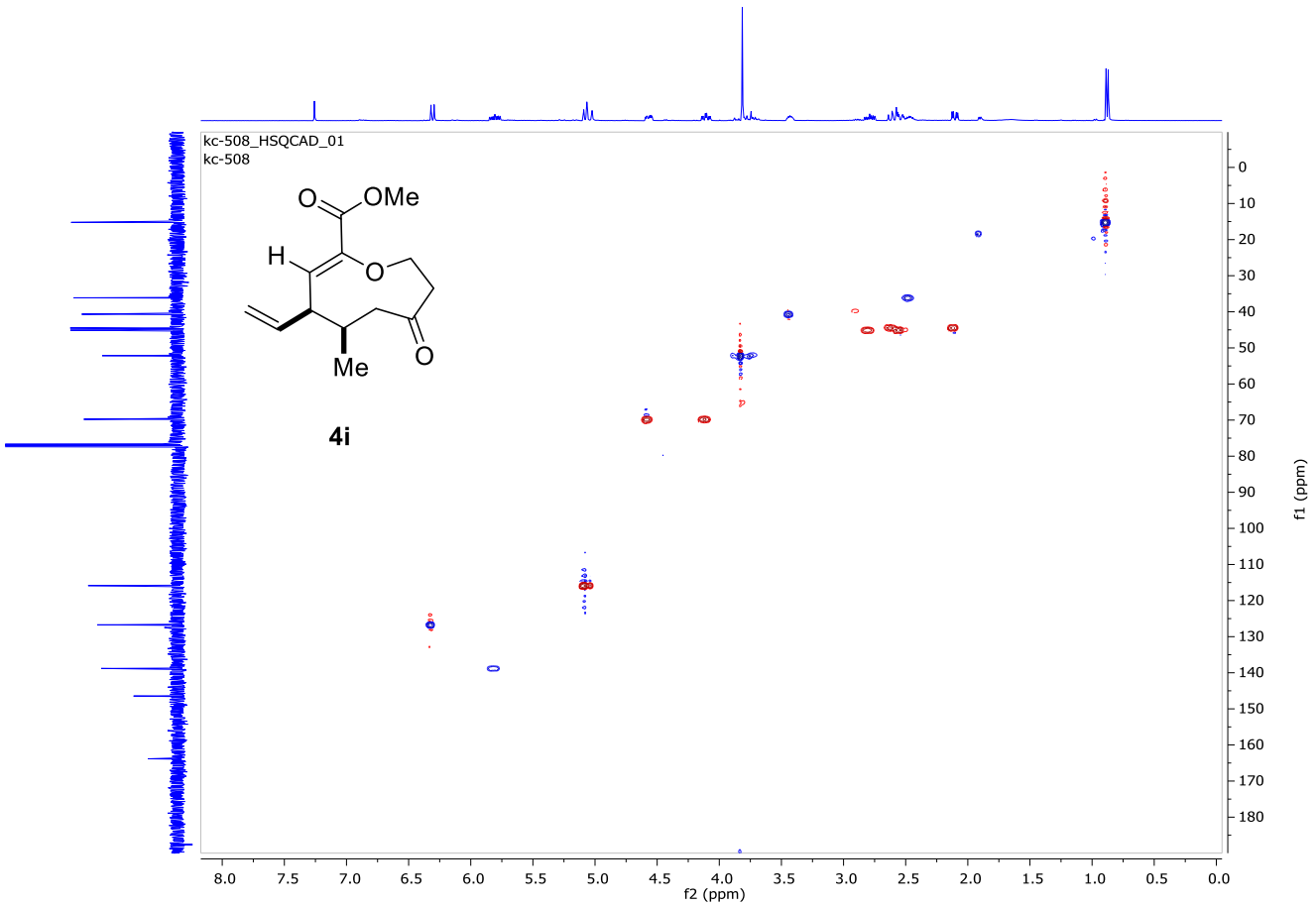

kc-508-p_PROTON_01
kc-508-p
O
OMe
H
O
Me
O
1.00
1.06
1.93
1.00
1.05
2.62
0.96
1.13
3.15
1.09
2.82
f1 (ppm)

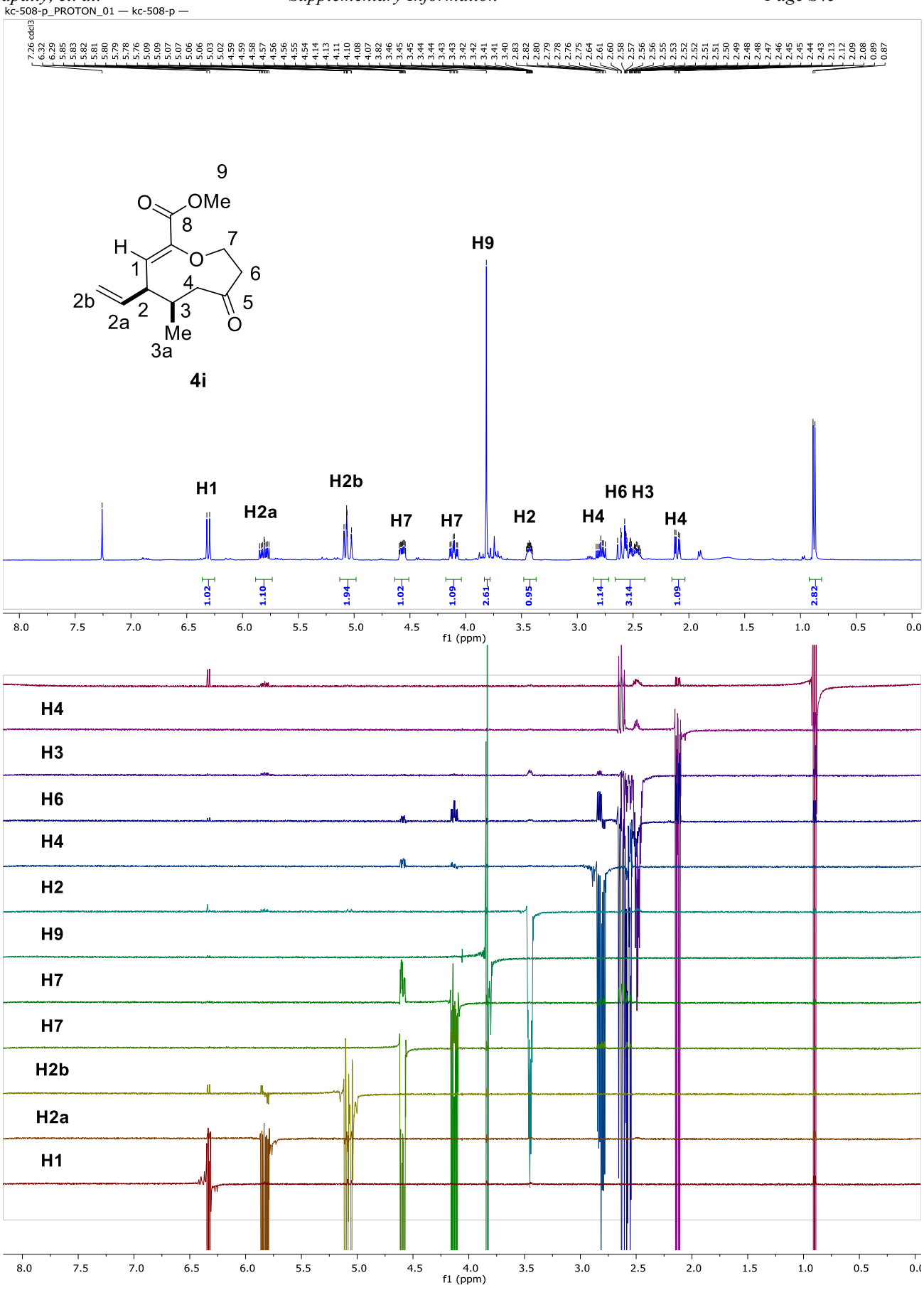
4i

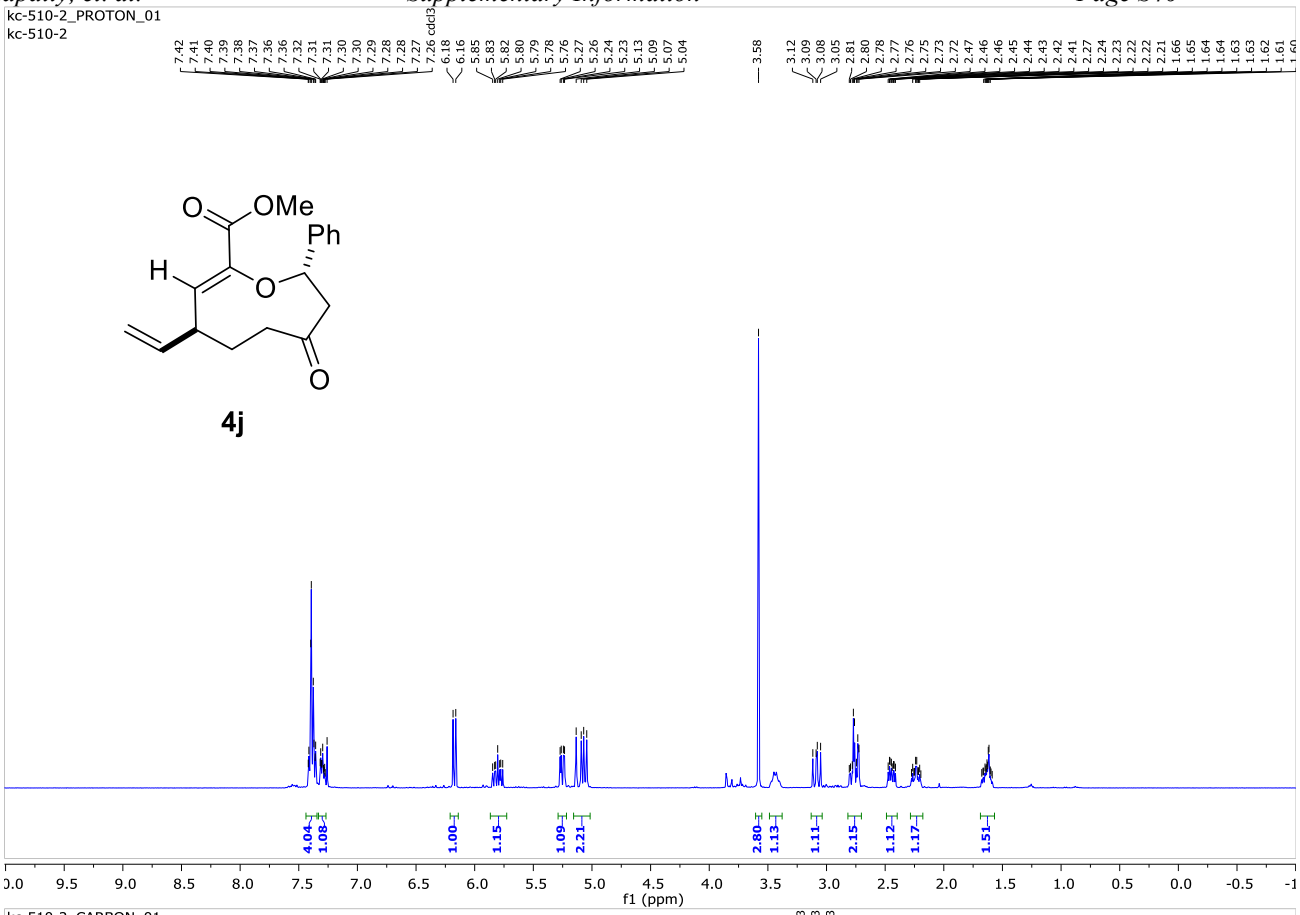

kc-508-p_CARBON_01
kc-508-p
211.63
163.85
146.46
138.81
126.73
115.86
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
69.78
52.16
45.10
44.50
40.68
36.14
15.23
O
OMe
H
O
Me
O
f1 (ppm)

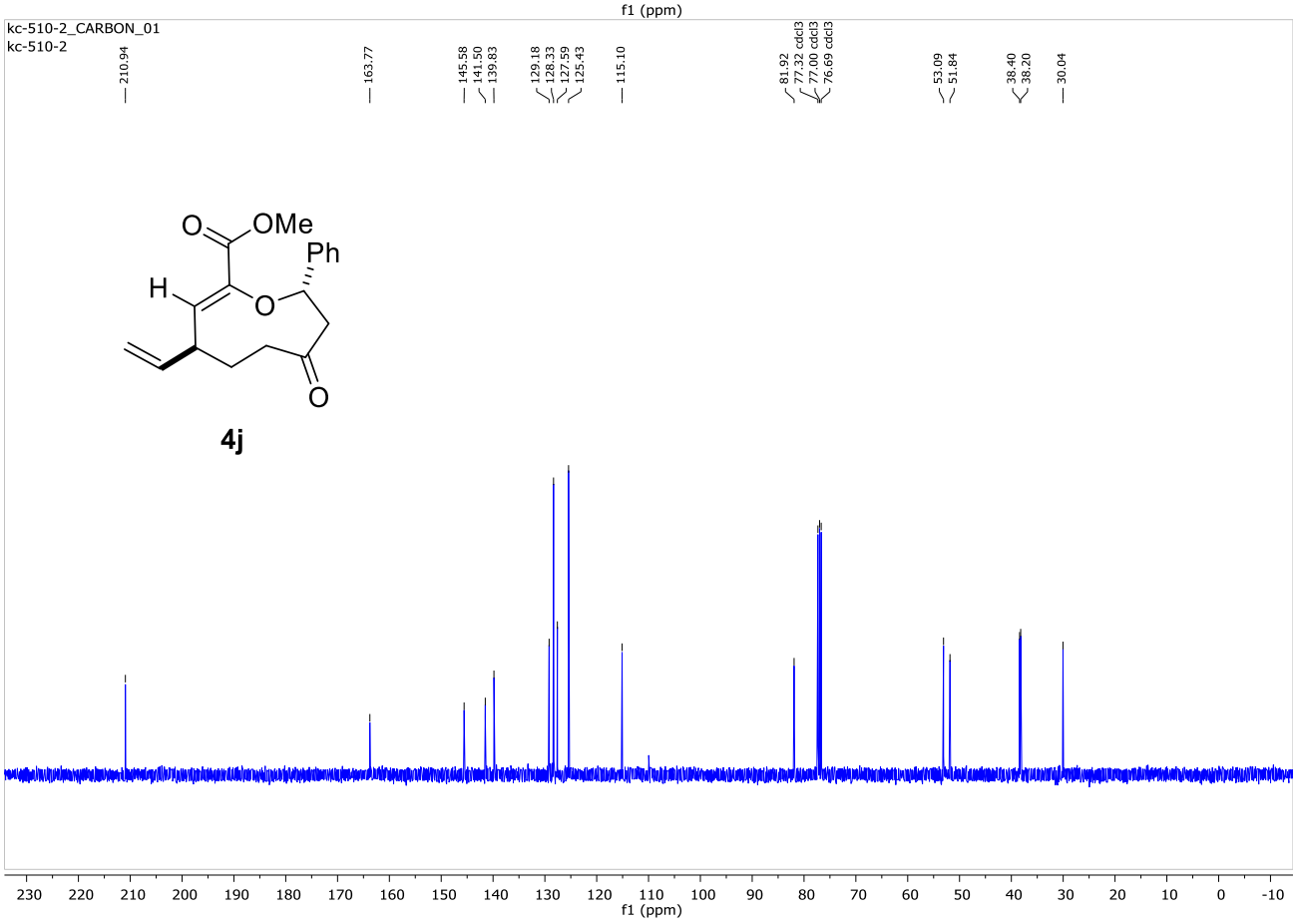
4i

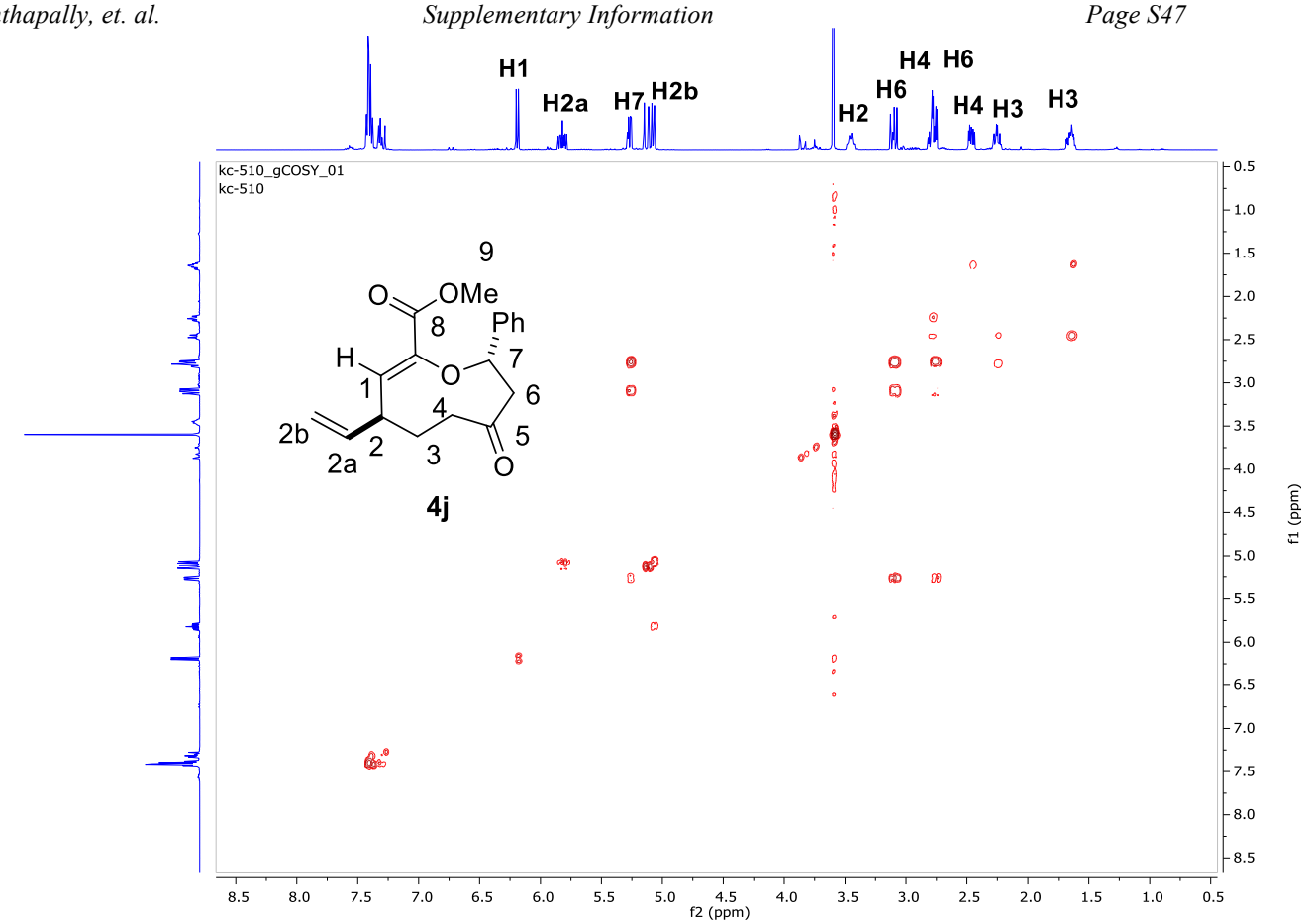

H1
H2a
H2b
H7
H7
H9
H2
H4
H6 H3
H4
kc-508_gCOSY_01
kc-508
9
O
OMe
8
7
H
1
O
6
4
2b
2
3
5
2a
O
Me
3a
4i
f2 (ppm)
f1 (ppm)

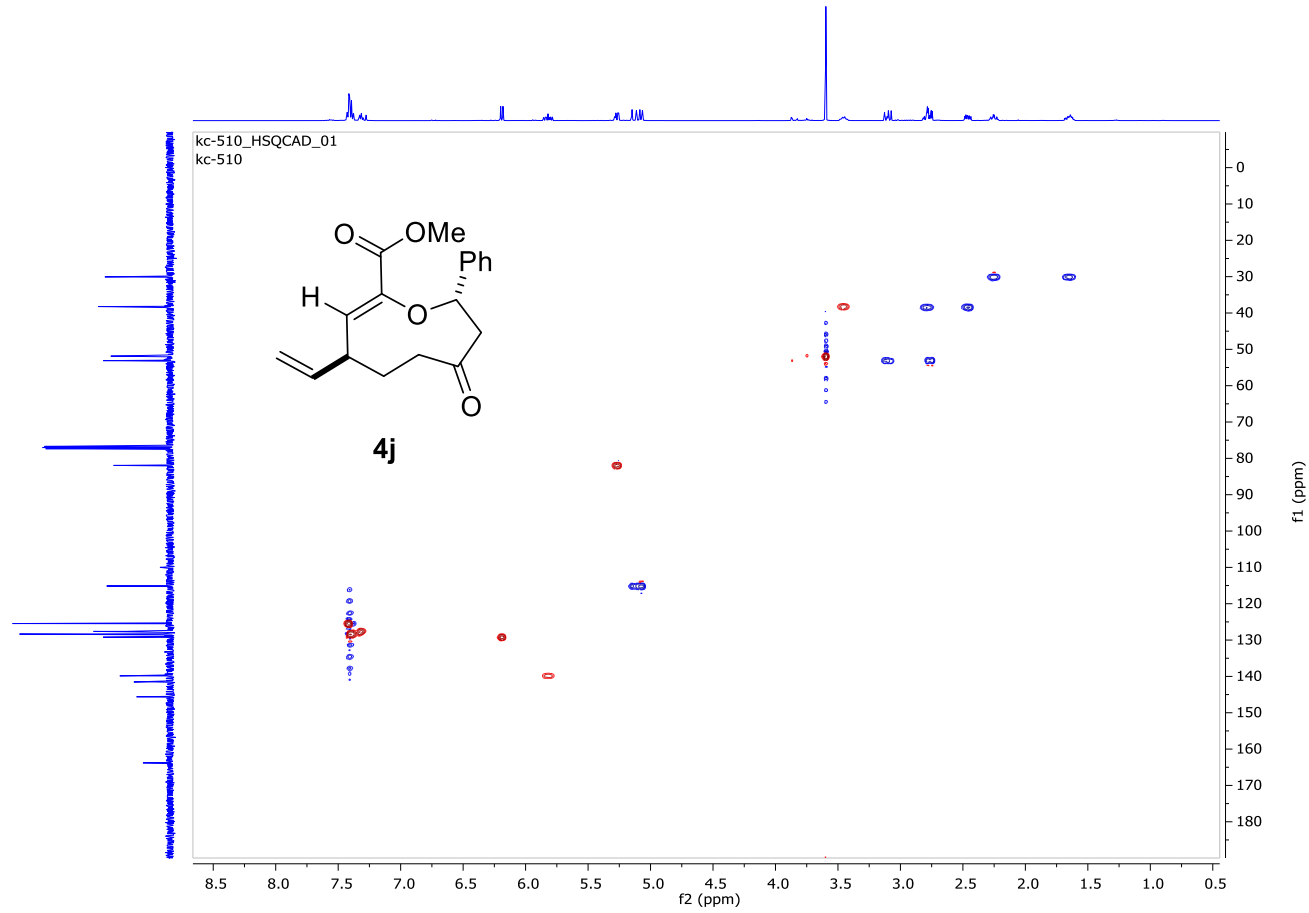

kc-508_HSQCAD_01
kc-508
O
OMe
H
O
Me
O
4i
f2 (ppm)
f1 (ppm)

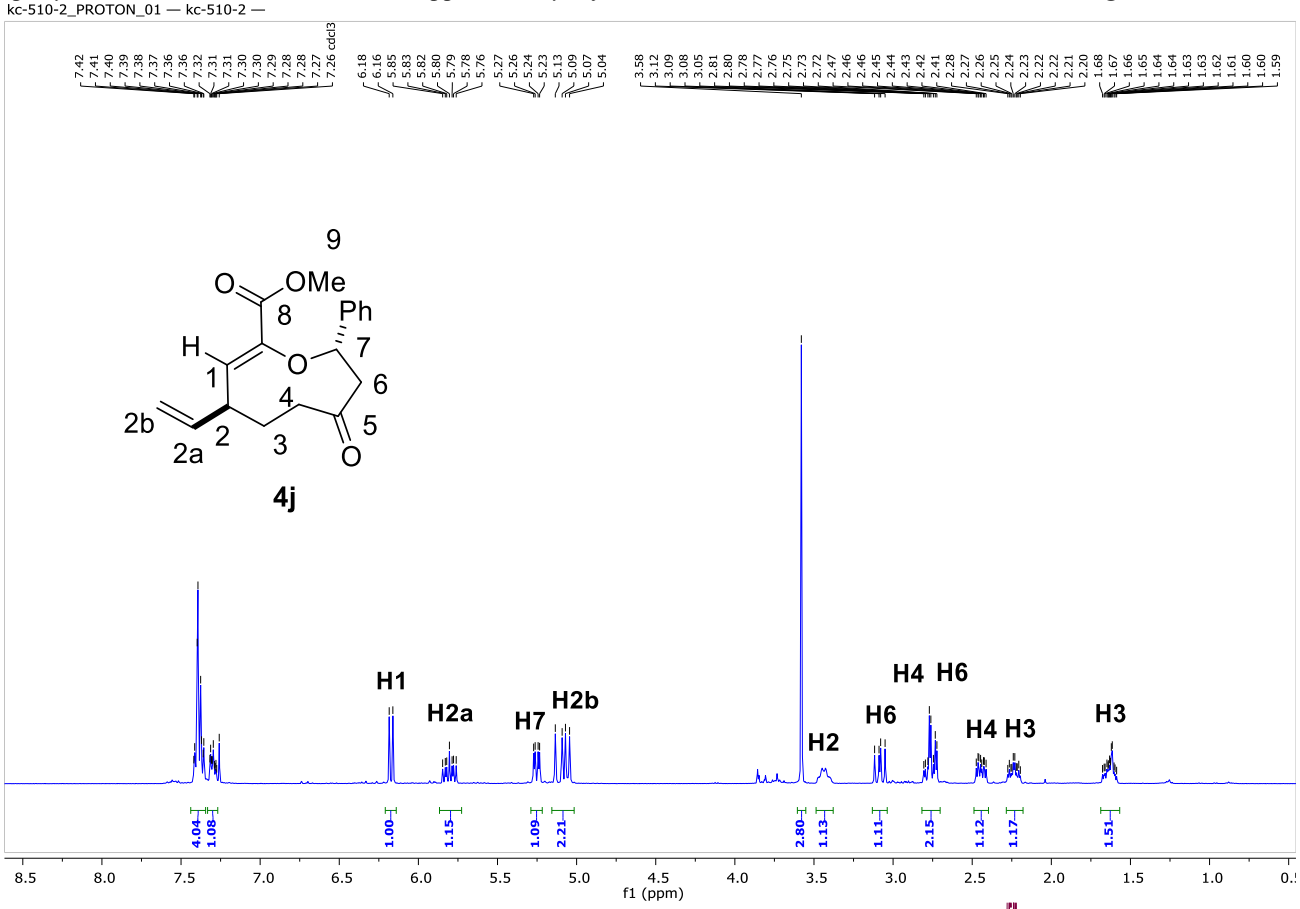

kc-508-p_PROTON_01 — kc-508-p —
4i
H1
H2a
H2b
H7
H7
H9
H2
H4
H6 H3
H4
1.02
1.10
1.94
1.02
1.09
2.61
0.95
1.14
3.14
1.09
2.82
f1 (ppm)
H4
H3
H6
H4
H2
H9
H7
H7
H2b
H2a
H1
f1 (ppm)

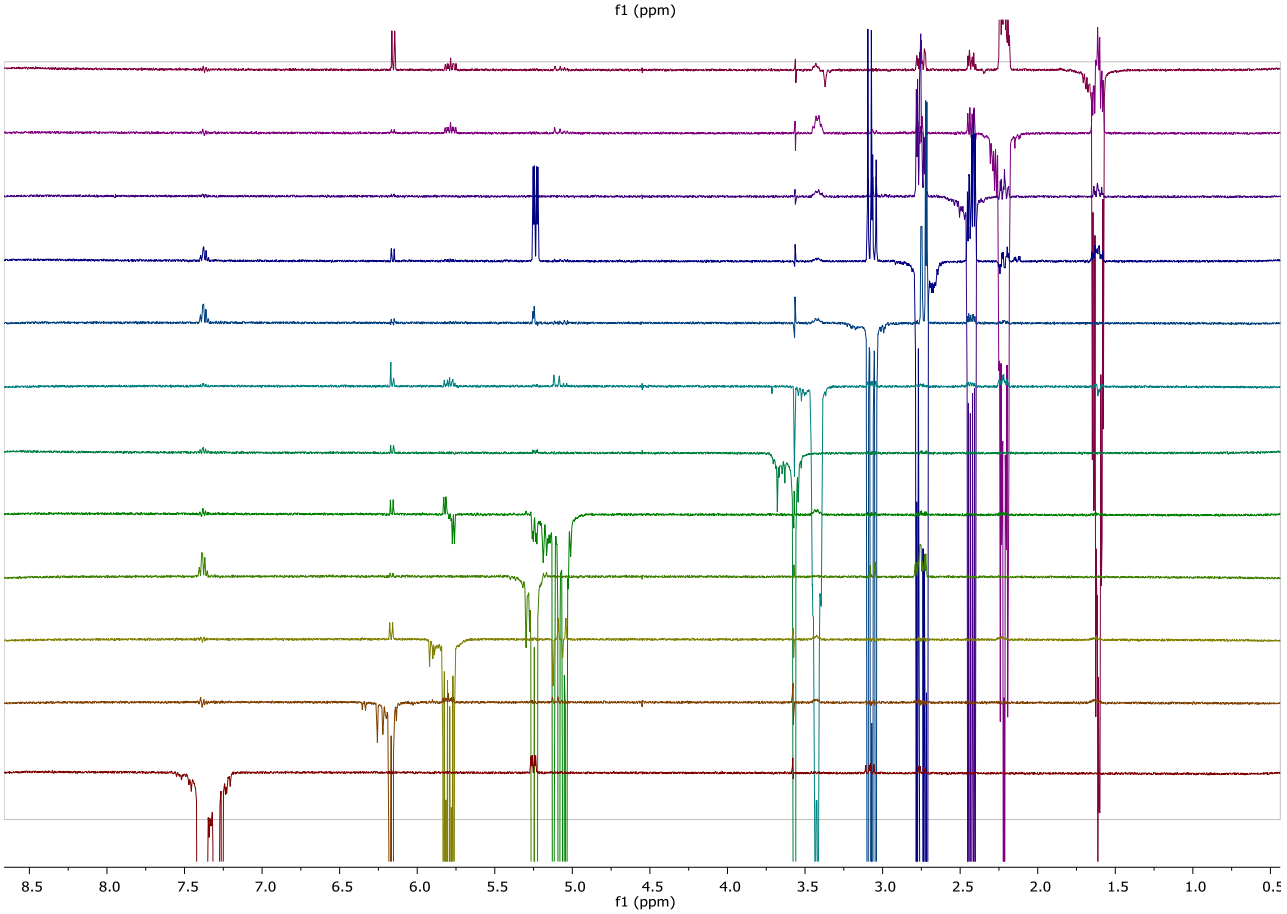

kc-510-2_PROTON_01
kc-510-2
O
OMe
Ph
H
O
O
4j
4.04
1.08
1.00
1.15
1.09
2.21
2.80
1.13
1.11
2.15
1.12
1.17
1.51
f1 (ppm)


kc-510-2_CARBON_01
kc-510-2
210.94
163.77
145.58
141.50
139.83
129.18
128.33
127.59
125.43
115.10
81.92
77.32 cdcl3
77.00 cdcl3
76.69 cdcl3
53.09
51.84
38.40
38.20
30.04
O
OMe
Ph
H
O
O
4j
f1 (ppm)

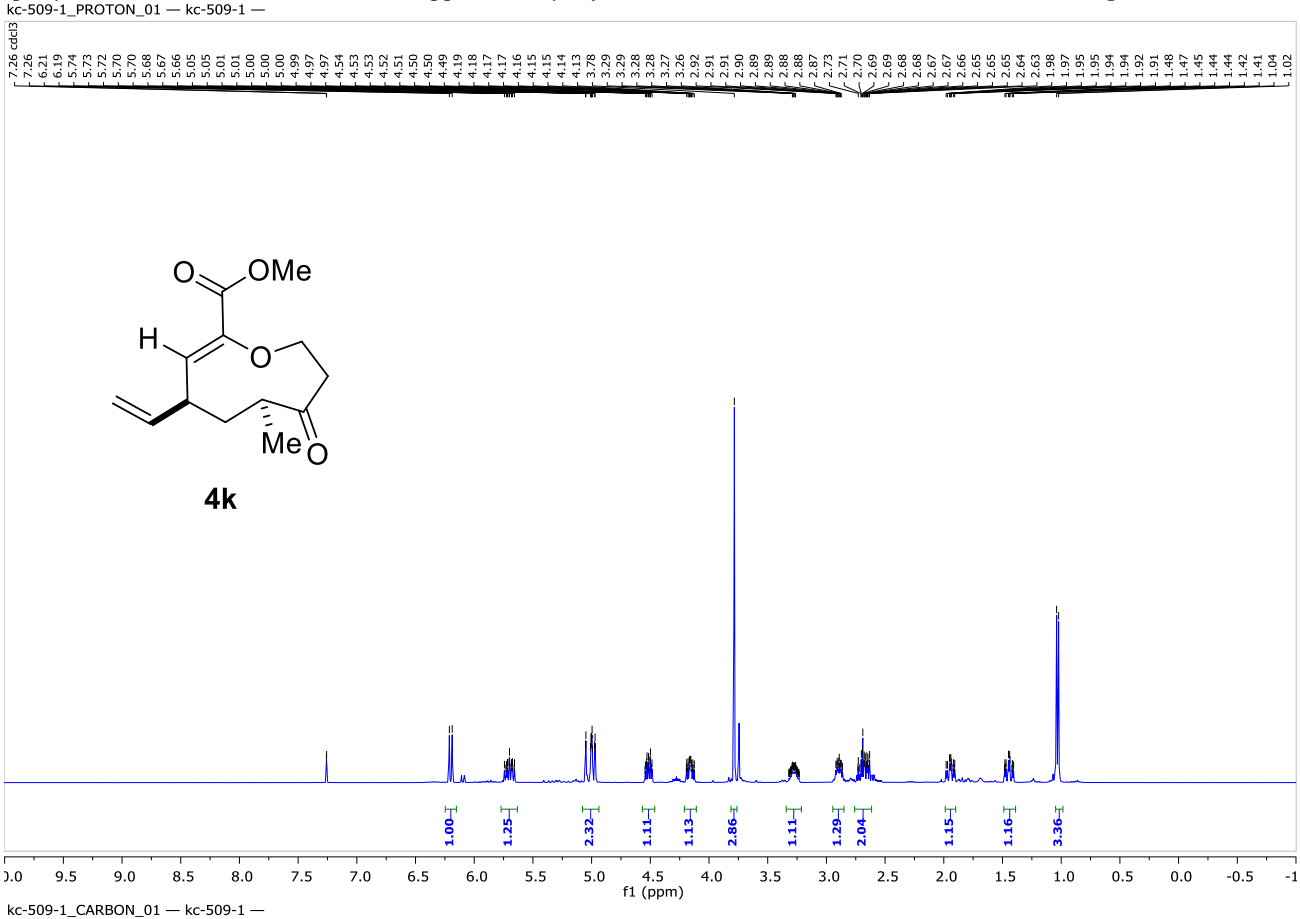

H1
H2a
H7
H2b
H2
H6
H4
H6
H4
H3
H3
kc-510_gCOSY_01
kc-510
9
O
OMe
8
Ph
H
7
1
O
6
4
2b
5
2a
2
3
O
4j
f2 (ppm)
f1 (ppm)


kc-510_HSQCAD_01
kc-510
O
OMe
Ph
H
O
O
4j
f2 (ppm)
f1 (ppm)


kc-510-2_PROTON_01 — kc-510-2 —
9
O
OMe
8
Ph
H
7
1
O
6
4
2b
5
2
2a
3
O
4j
H1
H2a
H7
H2b
H2
H6
H4 H6
H4 H3
H3
4.04
1.08
1.00
1.15
1.09
2.21
2.80
1.13
1.11
2.15
1.12
1.17
1.51
f1 (ppm)

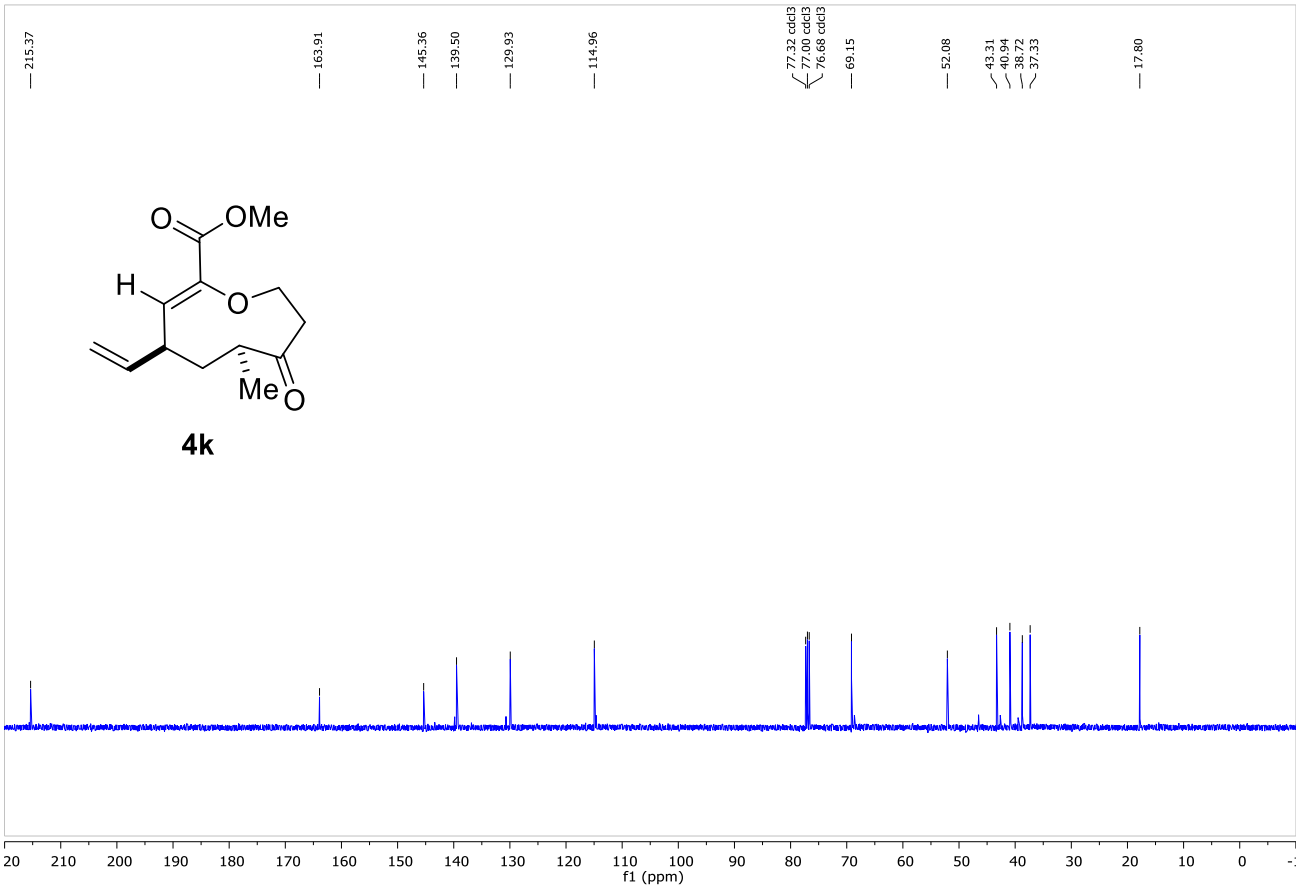

f1 (ppm)

kc-509-1_PROTON_01 — kc-509-1 —

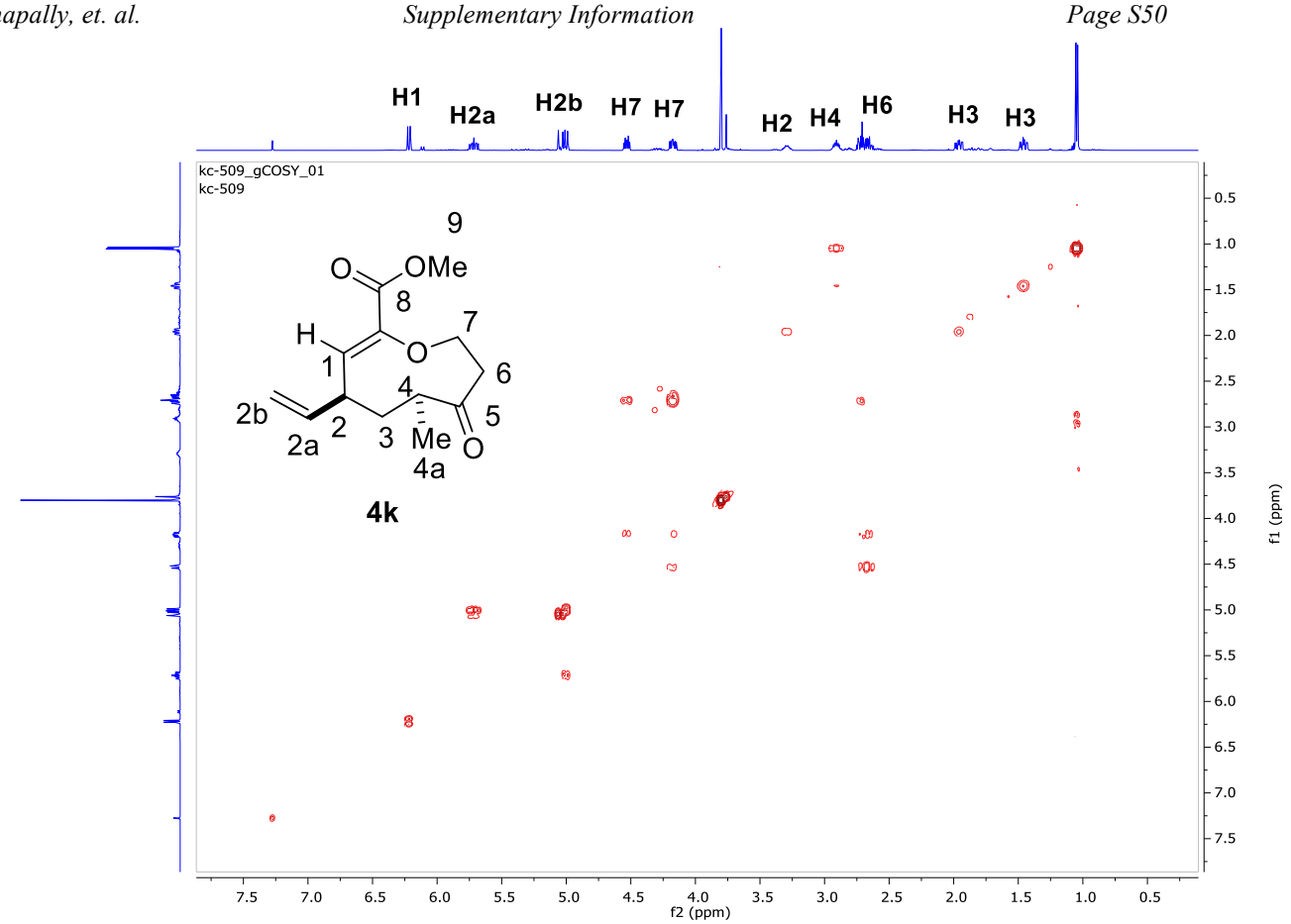


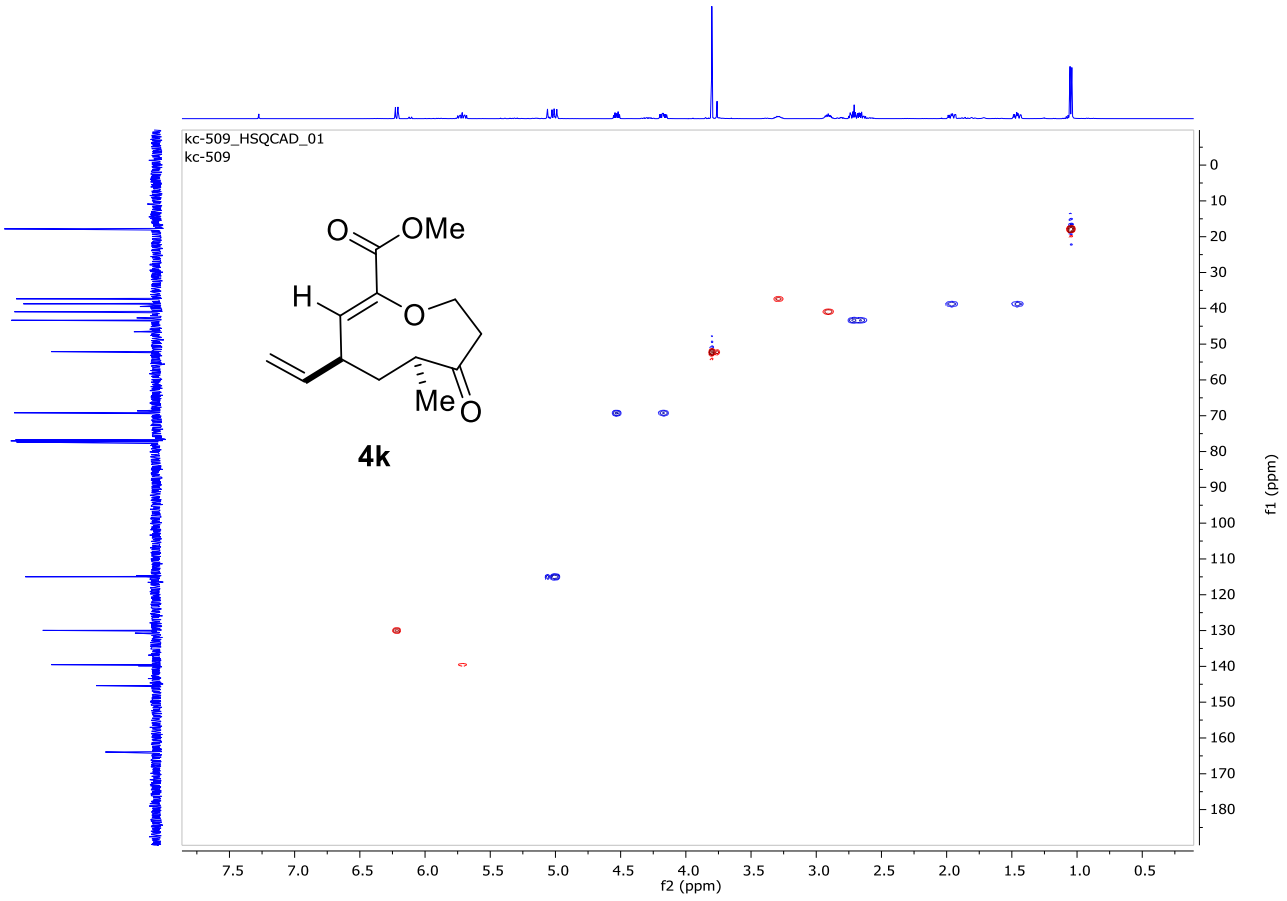
4k

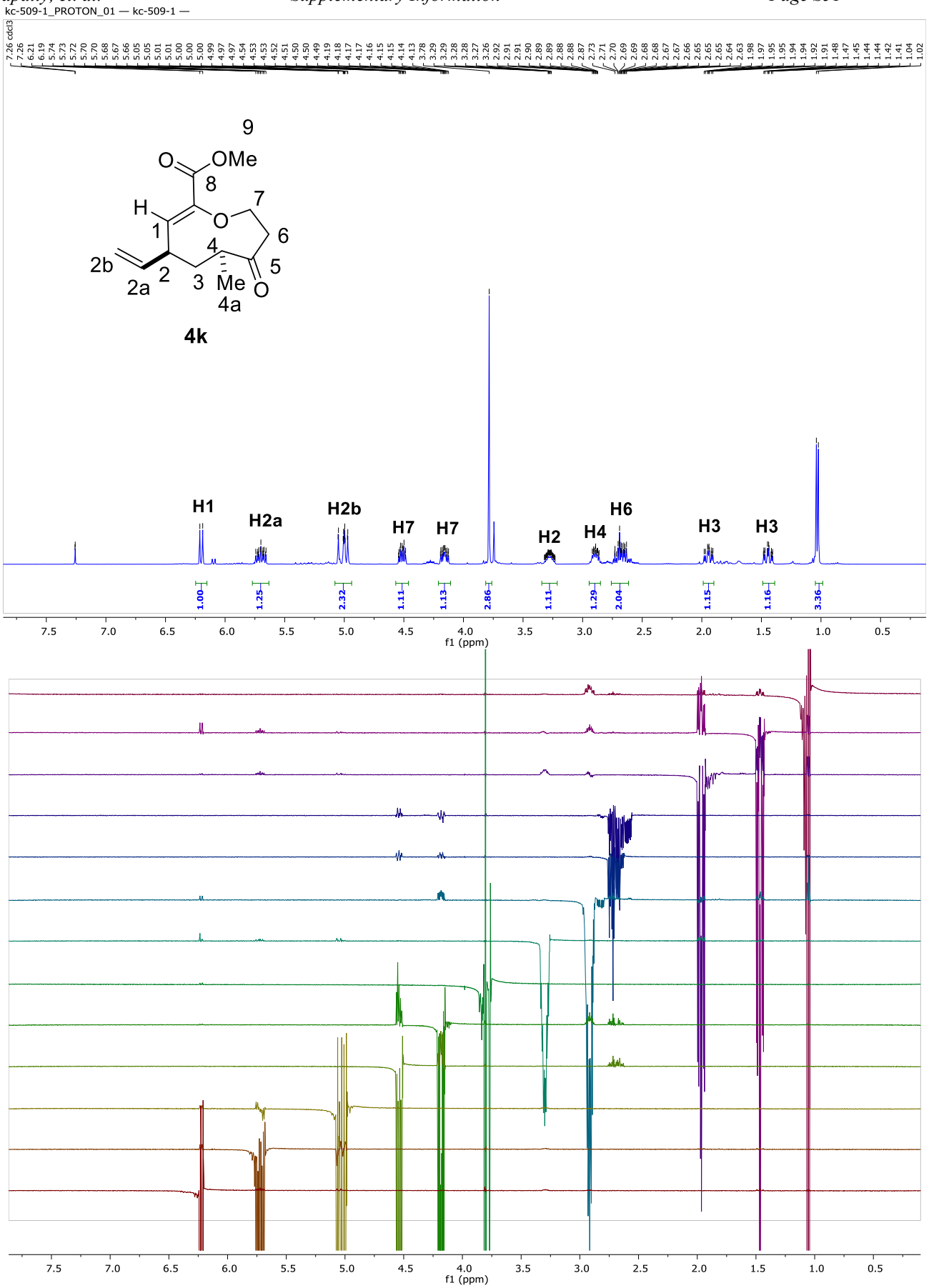
kc-509-1_CARBON_01 — kc-509-1 —



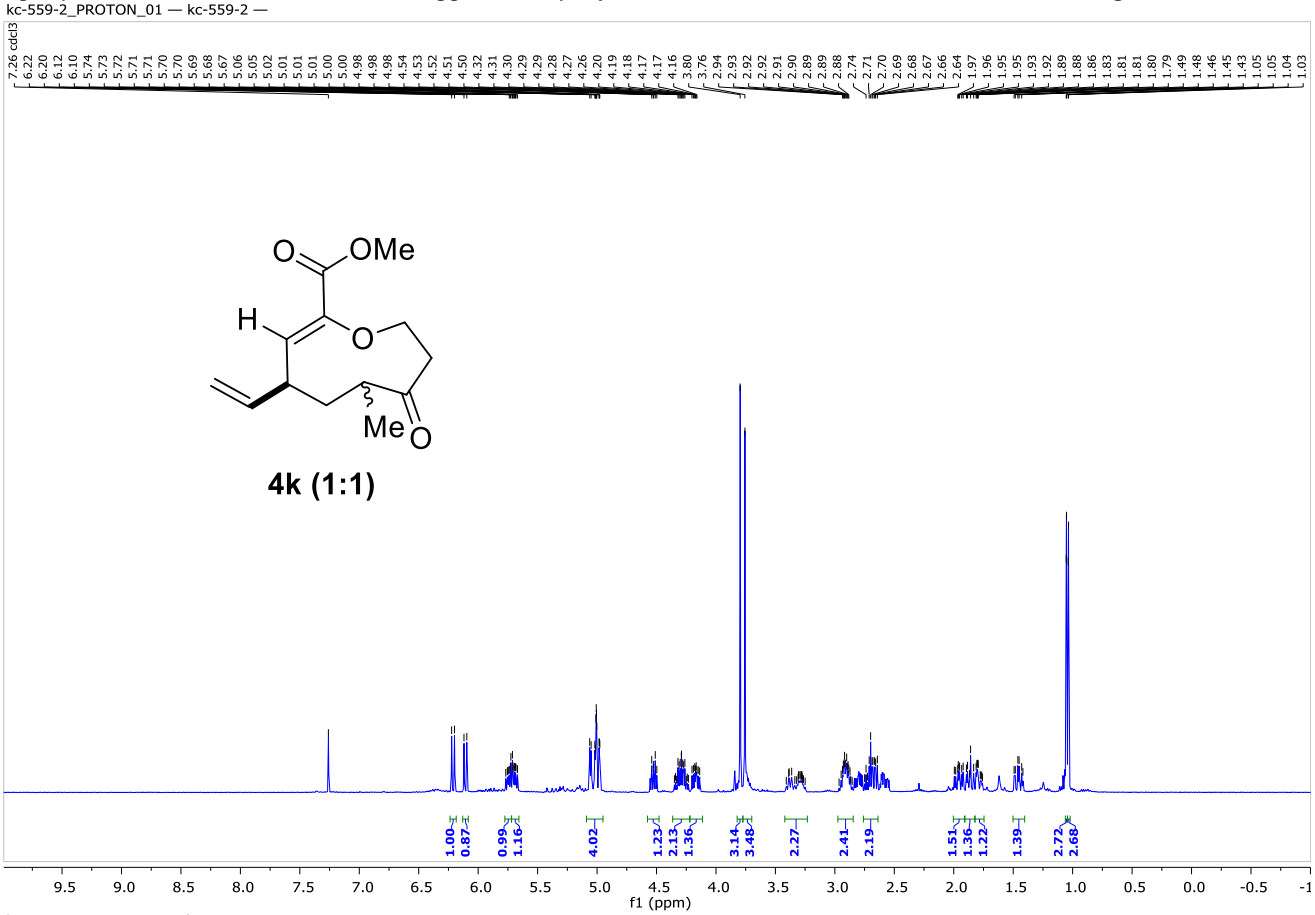
4k


H1
H2a
H2b
H7
H7
H2
H4
H6
H3
H3
kc-509_gCOSY_01
kc-509
9
O
OMe
8
7
H
1
O
6
4
2b
5
2
3
Me
O
2a
4a
4k
f2 (ppm)
f1 (ppm)


kc-509_HSQCAD_01
kc-509
O
OMe
H
O
Me
O
4k
f2 (ppm)
f1 (ppm)


kc-509-1_PROTON_01 — kc-509-1 —
9
O
OMe
8
H
7
1
O
6
4
2b
5
2a
2
3
Me
O
4a
4k
H1
H2a
H2b
H7
H7
H2
H4
H6
H3
H3
1.00
1.25
2.32
1.11
1.13
2.86
1.11
1.29
2.04
1.15
1.16
3.36
f1 (ppm)
f1 (ppm)

kc-559-2_PROTON_01 — kc-559-2 —



kc-559-2_CARBON_01 — kc-559-2 —