An Oxidopyrylium Cyclization/Ring-Opening Route to Polysubstituted α-Hydroxytropolones

Christine Meck[†,‡], Noushad Mohd[†] and Ryan P. Murelli[†,‡,*]

[†]*Department of Chemistry, Brooklyn College,The City University of New York, 2900 Bedford Avenue, Brooklyn College 11210*

[‡]*Department of Chemistry, The Graduate Center, The City University of New York, 365 Fifth Avenue, New York, NY 10016*

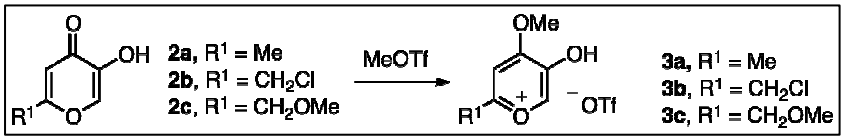
Supporting Information

Table of Contents

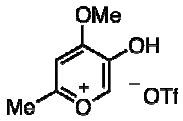
I. General Information

All starting materials and reagents were purchased from commercially available sources and used without further purification, with exception of CH_2Cl_2 and benzene, which was purified on a solvent purification system prior to the reaction. ^{1}H NMR shifts are measured using the solvent residual peak as the internal standard ($CHCl_3$ δ 7.26, D_2O δ 4.79), and reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR shifts are measured using the solvent residual peak as the internal standard ($CDCl_3$ δ 77.20), and reported as chemical shifts. Infrared (IR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w). Microwave reactions were preformed via the Biotage Initiator 2.5. Purification via reverse phase column chromatography was performed on the Biotage Isolera Prime, with Biotage SNAP 12g cartridges, in a solvent system of acetonitrile in water, each solvent containing 0.05% trifluoroacetic acid (TFA).

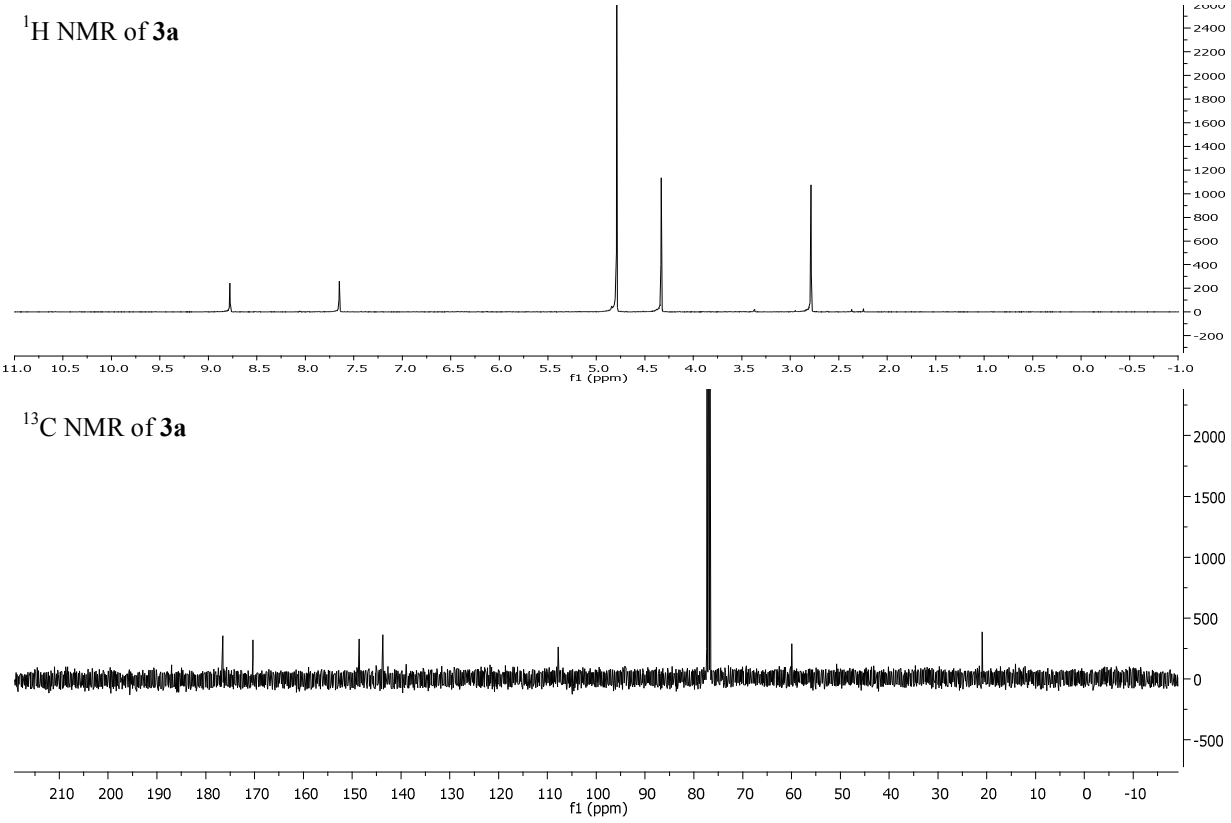
II. Synthesis and characterization of oxidopyrylium salts (3a-c)[1]



5-hydroxy-4-methoxy-2-methylpyrylium (3a). To a solution of **2a**[2] (1.31 g, 10.3 mmol) in CH_2Cl_2 (5.25 ml) was added methyl trifluoromethanesulfonate (MeOTf), (1.77 ml, 15.6 mmol). Reaction stirred at reflux for 4 h, cooled to rt, and then evaporated under reduced pressure to yield crude **3a** as an orange to red tinted oil. Crystallization from Ethyl Acetate (EtOAc) yielded pure **3a** as an orange solid (1.0g, 33% yield). **^{1}H NMR (400 MHz, D_2O)** δ 8.78 (s, 1H), 7.65 (s, 1H), 4.33 (s, 3H), 2.79 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.52 (s), 170.34 (s), 148.59 (s), 143.72 (s), 107.80 (s), 59.94 (s), 20.91 (s).



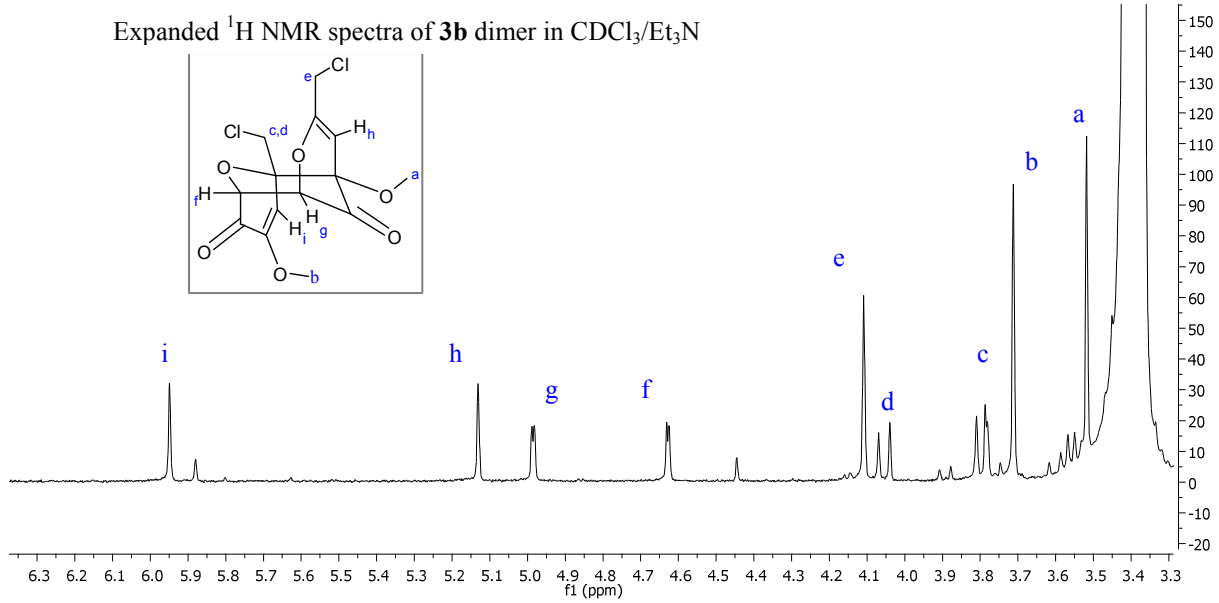
[1] The procedure for the synthesis of **3a-3c** was modified from a published procedure for **3a**: Wender, P. A.; Mascarenas, J. L. *Tetrahedron Lett*. **1992**, 33, 2115-2118.
[2] For preparation of **2a** and **2b**, see: Hider, R. C; et al. *J. Med. Chem.* **2008**, 51, 4539-4552.



2-(chloromethyl) -5-hydroxy-4-methoxypyrylium (3b). To a solution of **2b**[2] (500 mg, 3.1 mmol) in benzene (1.6 ml) was added MeOTf, (1.03 ml, 9.3 mmol). Reaction was run under microwave irradiation for 20 min at 80 °C, and then evaporated under reduced pressure to yield crude **3b** as an off white solid (999 mg, >95% yield). Crystallization from Ethyl Acetate (EtOAc) yielded pure **3b** as an off white solid (156 mg, 16% yield), which was incompatible in standard deuterated solvents due to insolubility ($CDCl_3$) or instability (d-DMSO and D_2O). MP=74-80°C. **IR (thin film, KBr)** 2853 (w), 1622 (m), 1569 (m), 1544 (m), 1503 (m), 1459 (w), 1254 (s), 1227 (s), 1172 (m), 1028 (s), 991 (m), 637 (s), 574 (w). **HRMS (ESI +)** m/z calc'd for $C_7H_8O_3Cl$: 175.0156. Found: 175.0159. Due to incompatibility with deuterated solvents, NMR verification was found by conversion to dimer and subsequent analysis. To do this, an aliquot of the salt was placed in approximately 10-20% solution of N,N-diethylaniline (Et_2NPh) in $CDCl_3$, and signature peaks consistent with those of known dimer **7** were observed. **^{1}H NMR (400 MHz, $CDCl_3$)**[3] δ 5.95 (s, 1H), 5.13 (s, 1H), 4.98 (d, *J* = 2.6 Hz, 1H), 4.63 (d, *J* = 2.6 Hz, 1H), 4.11 (s, 2H), 4.05 (d, *J* = 11.8 Hz, 1H), 3.80 (d, *J* = 11.1 Hz, 1H), 3.66 (s, 3H), 3.50 (s, 3H).

[3] Partial ^{1}H NMR shown to reflect key protons distinguishable from base.

Expanded ^{1}H NMR spectra of **3b** dimer in $CDCl_3/Et_3N$

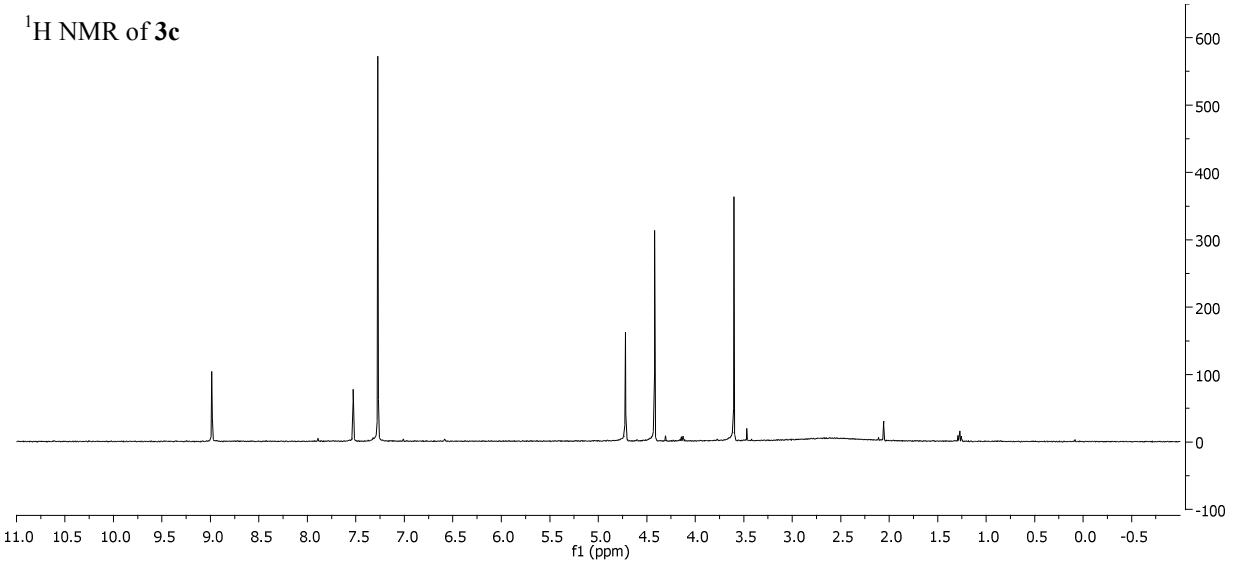


5-hydroxy-4-methoxy-2-(methoxymethyl)pyrylium (3c). To a solution of **2c**[4] (153 mg, 0.994 mmol) in CH_2Cl_2 (502 µL) was added MeOTf, (167 µL, 1.49 mmol). Reaction stirred at reflux for 3.5 h, cooled to rt, and then evaporated under reduced pressure to yield crude **3c** as an orange to red tinted oil [5] (282 mg, 87%). The oil was taken up in hot chloroform, to which was added several drops of EtOAc while hot until the solution became cloudy. Solution was placed on ice, and a white solid crystallized out **3c** (20 mg, 6%) which decomposes at temperatures of 235 °C. **IR (thin film, KBr)** 3486 (br), 1634 (m), 1259 (s), 1174 (m), 1035 (s), 764 (w), 643 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.99 (s, 1H), 7.53 (s, 1H), 4.72 (s, 2H), 4.42 (s, 3H), 3.60 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 174.37 (s), 171.16 (s), 149.51 (s), 145.13 (s), 105.07 (s), 69.82 (s), 60.01 (s), 59.96 (s). **HRMS (ESI+)** *m/z* calc'd for $C_8H_{11}O_4$: 171.0652. Found: 171.0653.

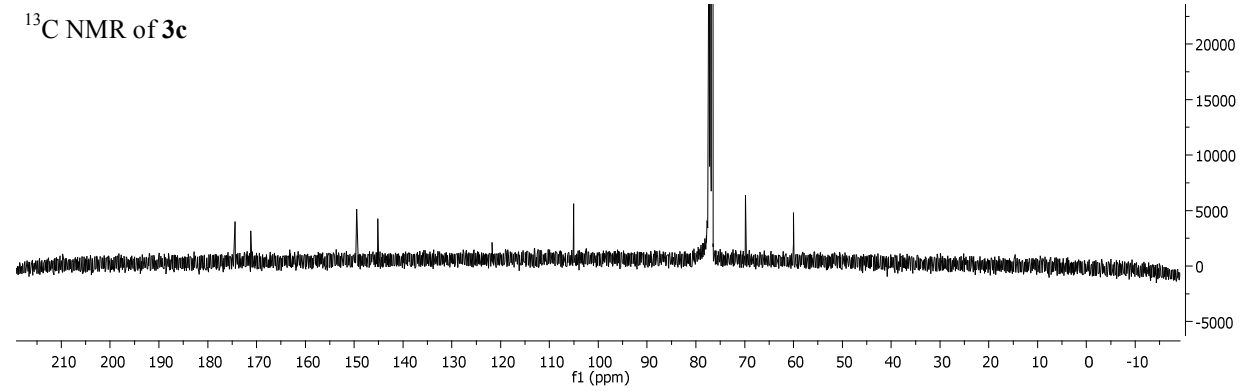
[4] Prepared from a solution of **2b** in a 0.2 M solution of methanol (MeOH) and 5eq of Na° and stirred at rt over a 72 h period.

[5] Oil decomposes when stored neat in the freezer. Long-term storage in $CHCl_3$ is recommended.

^{1}H NMR of **3c**

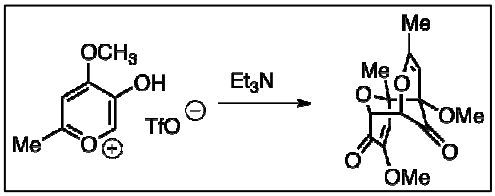


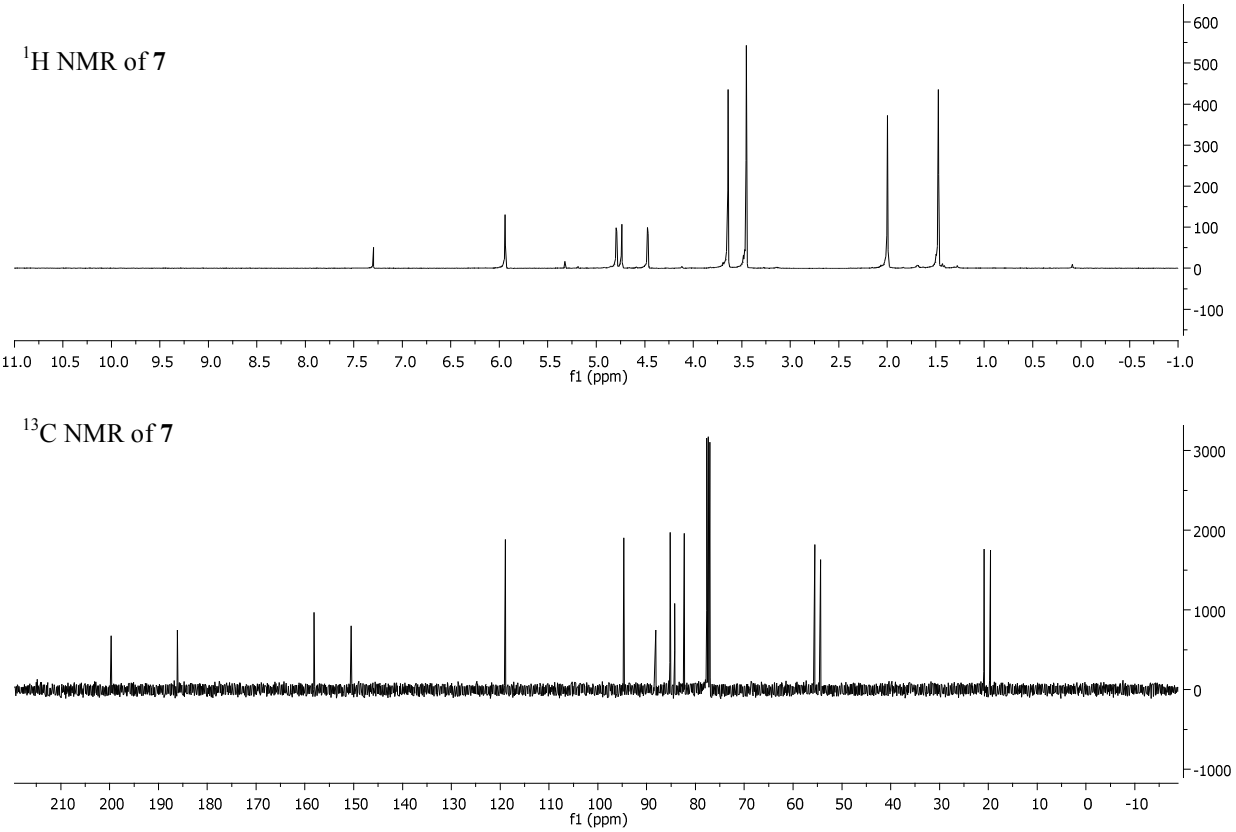
^{13}C NMR of **3c**



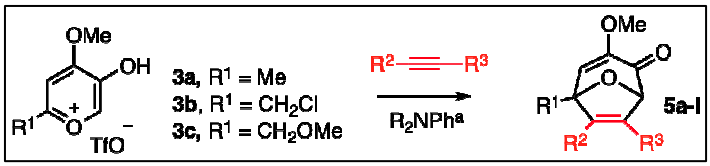
III. Synthesis and characterization of oxidopyrylium dimer (7)

(1R,2S,6S,7R)-6,9-dimethoxy-4,7-dimethyl-3,11-dioxatricyclo[5.3.1.12,6]dodeca-4,8-diene-10,12-dione (7). To a solution of **14a** (69.8 mg, 0.240 mmol) in $CHCl_3$ (1.2 ml) was added triethylamine (29.1 mg, 0.288 mmol). After a short mixing time (~10 s) at rt, the reaction mixture was washed with NH_4Cl_{aq} (6 x 2mL) to yield **3a** (24.4 mg, 73% yield) as a pale yellow solid that decomposes at 161°C. Rf= 0.29 in 30% ethyl acetate (EtOAc) in hexanes. **IR (thin film, KBr)** 3078 (w), 2982 (w), 1744 (s), 1704 (s), 1663 (m), 1617 (m), 1454 (m) 1367 (m) , 1289 (m), 1249 (m), 1186 (s), 1162 (m), 1133 (m), 1094 (m), 991 (m), 870 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.94 (s, 1H), 4.79 (d, *J* = 2.7 Hz, 1H), 4.74 (s,1H), 4.47 (d, *J* = 2.7 Hz, 1H), 3.64 (s, 3H), 3.45 (s, 3H), 2.00 (s, 3H), 1.47 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 199.67 (s), 186.12 (s), 158.15 (s), 150.52 (s), 118.91 (s), 94.67 (s), 88.15 (s), 85.19 (s), 84.27 (s), 82.28 (s), 55.56 (s), 54.37 (s), 20.86 (s), 19.58 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{14}H_{16}O_6Na^+$: 303.08391 Found: 303.08455.





IV. Synthesis and characterization of 8-oxabicyclo[3.2.1]octenes (5a-i)



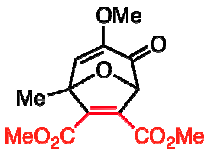
General Procedure A. To a solution of salt **3a** and alkyne **(**20 equiv) in CH_2Cl_2 (0.2 M) was added N,N-dimethylaniline (2 equiv). The reaction stirred at rt and was monitored periodically by ^{1}H NMR until dimer **7** was completely consumed. Reaction mixture was then loaded directly onto column for chromatography and purified.

General Procedure B. To a solution of salts **3a-3c** and alkyne **(**5-20 equiv) in $CHCl_3$ (0.5 M) was added N,N-diisopropylaniline (1.2 equiv). The reaction mixture was subjected to microwave irradiation at 100 °C and was monitored periodically by ^{1}H NMR until dimer **7** was completely consumed. Reaction mixture was then loaded directly onto column for chromatography and purified.

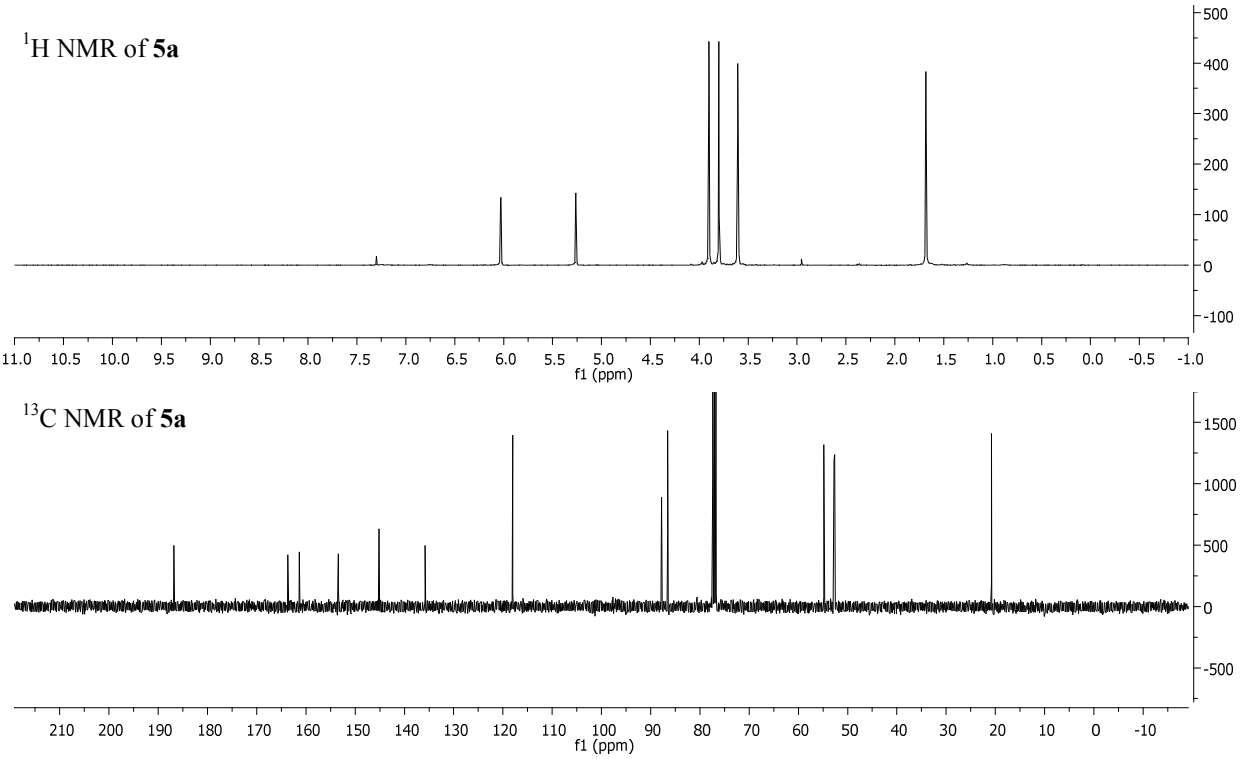
Dimethyl 3-methoxy-1-methyl-4-oxo-8-oxabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate (5a).

Procedure A: To a solution of **3a** (100 mg, 0.34 mmol) and dimethyl acetylenedicarboxylate **(**DMAD) (832 µL, 6.8 mmol) in CH_2Cl_2 (1.7 mL) was added N,N-dimethylaniline (86 µL, 0.68 mmol). After stirring at rt for 17 h, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: 5% EtOAc in hexanes (100 mL); 10% EtOAc in hexanes (200 mL); 20% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5a** as an orange solid (71 mg, 74% yield).

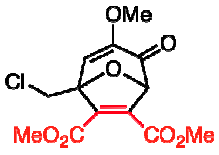
Procedure B: To a solution of **3a** (110.4 mg, 0.381 mmol) and DMAD (939 µL, 7.62 mmol) in $CHCl_3$ (762 µL) was added N,N-diisopropylaniline (88 µL, 0.457 mmol). After microwave irradiation at 100 °C for 5 min, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (100 mL); 20% EtOAc in hexanes (100 mL); 25% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5a** as an orange solid (96.8 mg, 90% yield).



Characterization of **5a**: Melting Point (MP)= 94-97°C. Rf= 0.35 in 25%EtOAc in hexanes. **IR (thin film, KBr)** 2956 (m), 1723 (s), 1653 (m), 1608 (s), 1437 (s), 1323 (s), 1286 (s), 1129 (s), 1073 (m), 1031 (m), 980 (w), 866 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.03 (s, 1H), 5.26 (s, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.61 (s, 3H), 1.68 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 186.86 (s), 163.72 (s), 161.38 (s), 153.46 (s), 145.20 (s), 135.82 (s), 118.03 (s), 87.79 (s), 86.54 (s), 54.82 (s), 52.76 (s), 52.61 (s), 20.80 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{13}H_{14}O_7H^+$: 283.08123, Found: 283.08170.

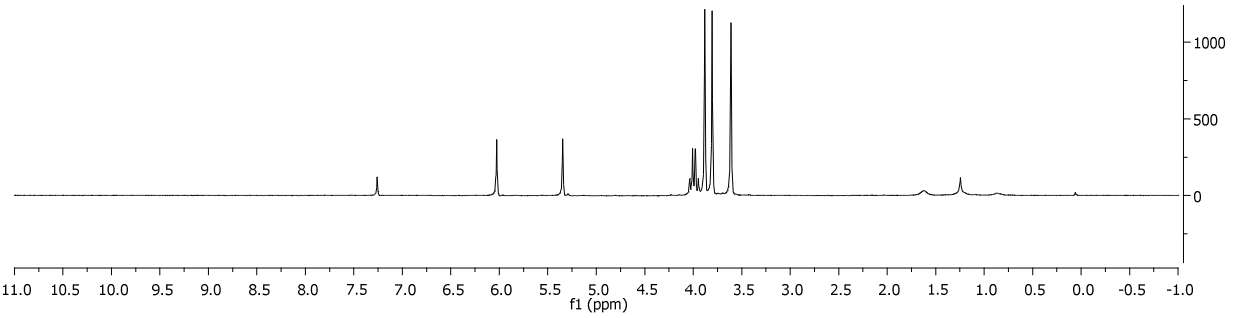


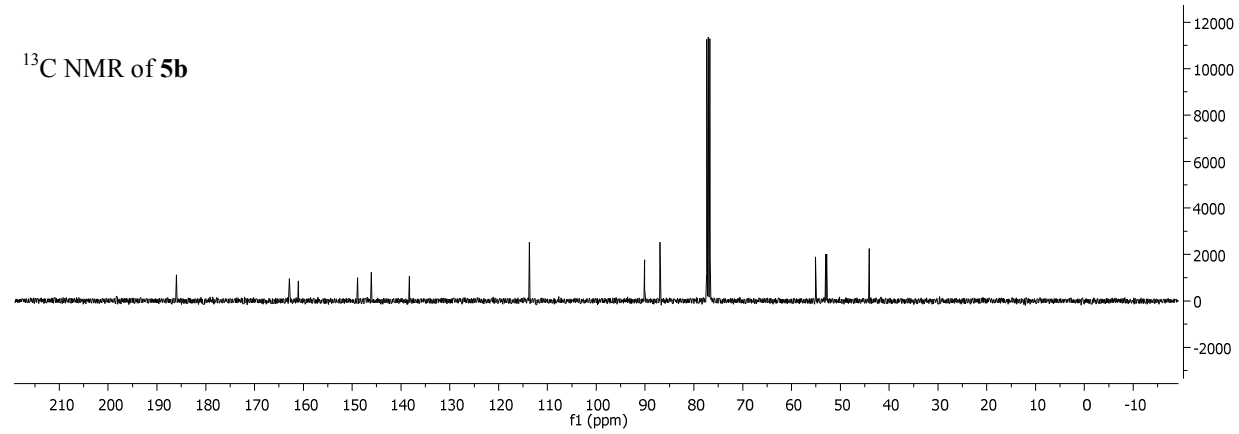
Dimethyl 1-(chloromethyl)-3-methoxy-4-oxo-8-oxabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate (5b).



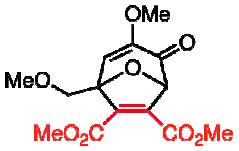
Following procedure B: To a solution of **3b** (102.7 mg, 0.317 mmol) and DMAD (783 µL, 6.34 mmol) in $CHCl_3$ (634 µL) was added N,N-diisopropylaniline (74 µL, 0.380 mmol). After microwave irradiation at 100 °C for 60 min, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (100 mL); 20% EtOAc in hexanes (100 mL); 25% EtOAc in hexanes(100 mL)). Product fractions were concentrated to yield **5b** as a light yellow solid (76 mg, 76% yield). MP= 127-130°C. Rf= 0.33 in 40% in EtOAc in hexanes. **IR (thin film, KBr)** 2956 (w), 1720 (s), 1649 (w), 1610 (s), 1437 (s), 1278 (s), 1219 (m), 1129 (s), 1079 (m), 985 (m), 797 (w), 727 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.03 (s, 1H), 5.35 (s, 1H), 3.99 (dd, *J* = 12.3, 12.3 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.61 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 185.98 (s), 162.87 (s), 161.01 (s), 148.90 (s), 146.05 (s), 138.27 (s), 113.71 (s), 90.08 (s), 86.92 (s), 55.06 (s), 53.00 (s), 52.81 (s), 44.10 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{13}H_{13}ClO_7Na^+$: 339.02420. Found: 339.02506.

^{1}H NMR of **5b**

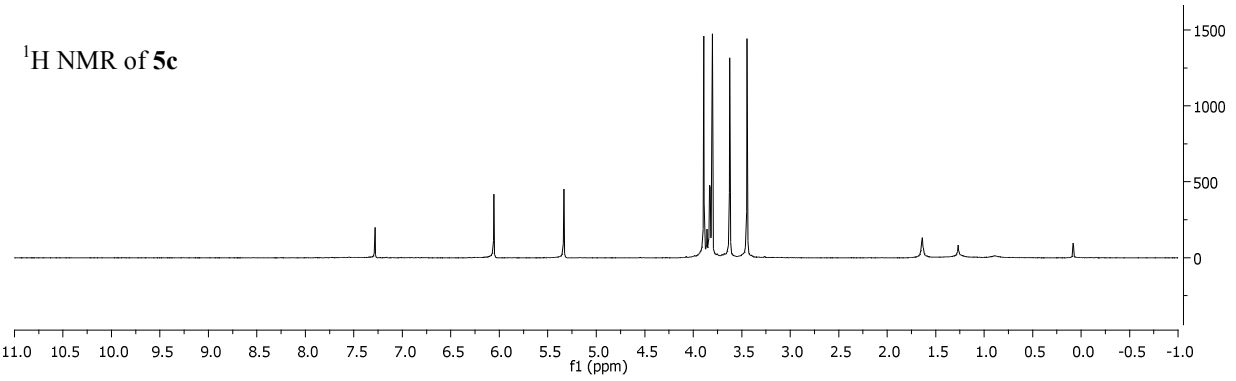


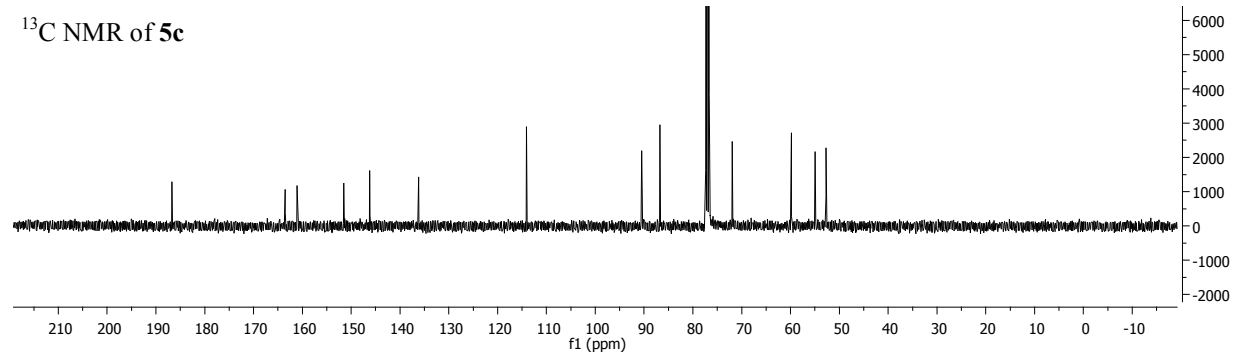


Dimethyl 3-methoxy-1-(methoxymethyl)-4-oxo-8-oxabicyclo[3.2.1]octa-2,6-diene-6,7-dicarboxylate (5c).



Following procedure B: To a solution of **3c** (114.6 mg, 0.358 mmol) and DMAD (870 µL, 7.16 mmol) in $CHCl_3$ (716 µL) was added N,N-diisopropylaniline (84 µL, 0.430 mmol). After microwave irradiation at 100 °C for 15 min, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (100 mL); 20% EtOAc in hexanes (100 mL); 25% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5c** as a light yellow oil (68.3 mg, 58% yield). Rf= 0.22 in 26% EtOAc in hexanes. **IR (thin film, KBr)** 2954 (w), 2841 (w), 1723 (s), 1610 (m), 1437 (m), 1263 (br/s), 1134 (m), 1110 (m), 1080 (w), 1029(w), 977 (w), 809 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.03 (s, 1H), 5.31 (s, 1H), 3.87 (s, 3H), 3.81 (dd, *J* = 3.1, 3.1 Hz, 2H), 3.78 (s, 3H), 3.60 (s, 3H), 3.42 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 186.75 (s), 163.54 (s), 161.11 (s), 151.49 (s), 146.19 (s), 136.16 (s), 114.06 (s), 90.51 (s), 86.73 (s), 71.94 (s), 59.81 (s), 54.95 (s), 52.73 (s), 52.65 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{14}H_{16}O_8H^+$: 313.0918. Found: 313.0922.



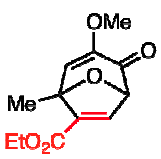


Ethyl-3-methoxy-5-methyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (5d).

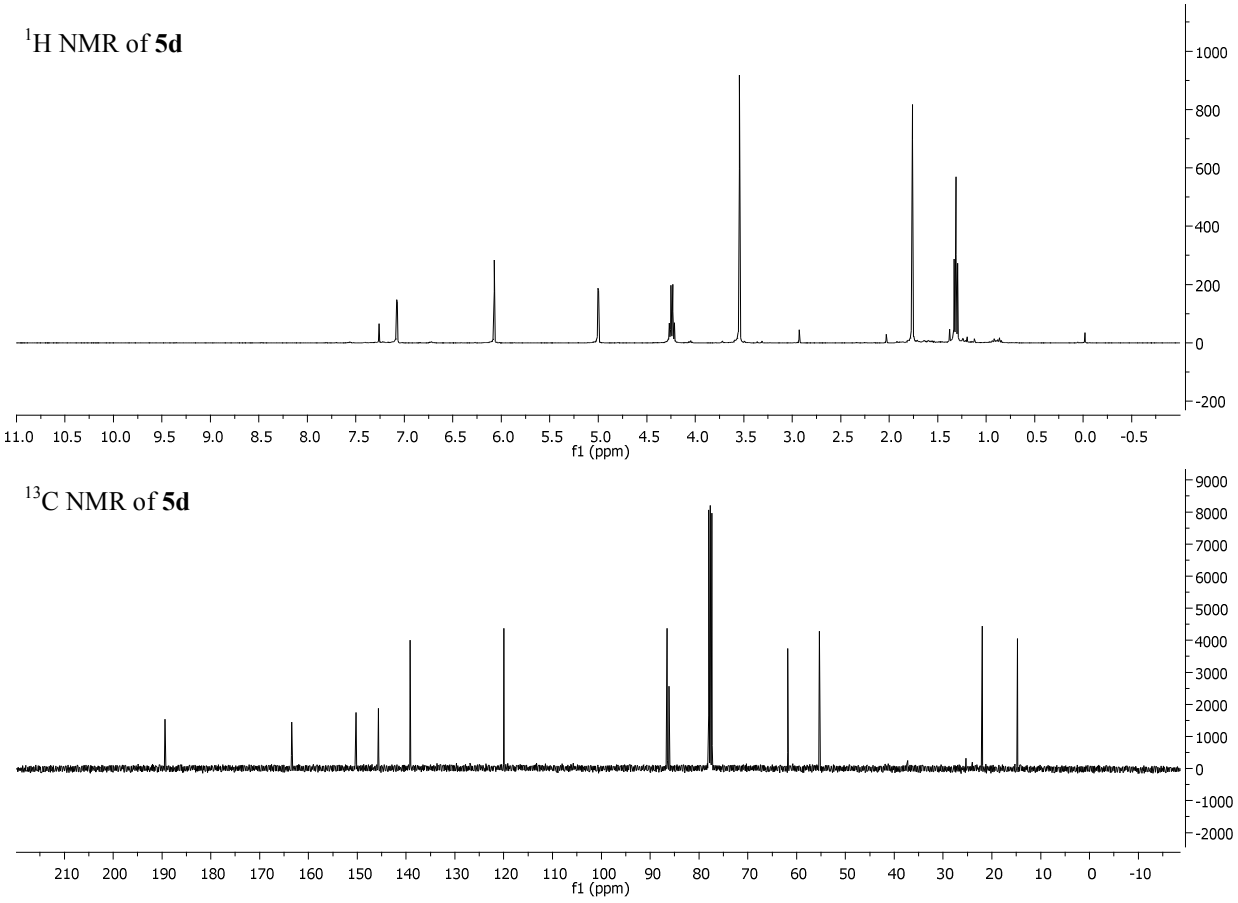
Procedure A: To a solution of **3a** (100 mg, 0.34 mmol) and ethyl propiolate (694 µL, 6.8 mmol) in CH_2Cl_2 (1.7 mL) was added N,N-dimethylaniline (86 µL, 0.68 mmol). After stirring at rt for 21 h, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 10% EtOAc in hexanes (100 mL); 25% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5d** as an off white solid (36 mg, 44% yield).

Procedure B: To a solution of **3a** (104 mg, 0.359 mmol) and ethyl propiolate (726 µL, 7.18 mmol) in $CHCl_3$ (718 µl) was added N,N-diisopropylaniline (84 µL, 0.431 mmol). After microwave irradiation at 100°C for 15 min, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (200 mL); Product fractions were concentrated to yield **5d** as an off white solid (75.5 mg, 88% yield).

Characterization of **5d**: MP= 52-55°C. Rf= 0.38 in 25% EtOAc in hexanes. **IR (thin film, KBr)** 2982 (w), 2938 (w), 1711 (s), 1604 (m), 1452 (w), 1317 (m), 1128 (m), 1073 (m), 987 (w), 783 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.08 (d, *J* = 2.5 Hz, 1H), 6.07 (s, 1H), 5.00 (d, *J* = 2.5 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.54 (s, 3H), 1.76 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz,**



$CDCl_3$) δ 189.41 (s), 163.46 (s), 150.25 (s), 145.64 (s), 139.18 (s), 119.99 (s), 86.51 (s), 86.13 (s), 61.80 (s), 55.30 (s), 21.96 (s), 14.78 (s). **HRMS (ESI+) *m/z*** calc'd for $C_{12}H_{14}O_5H^+$: 239.0914. Found: 239.09073.

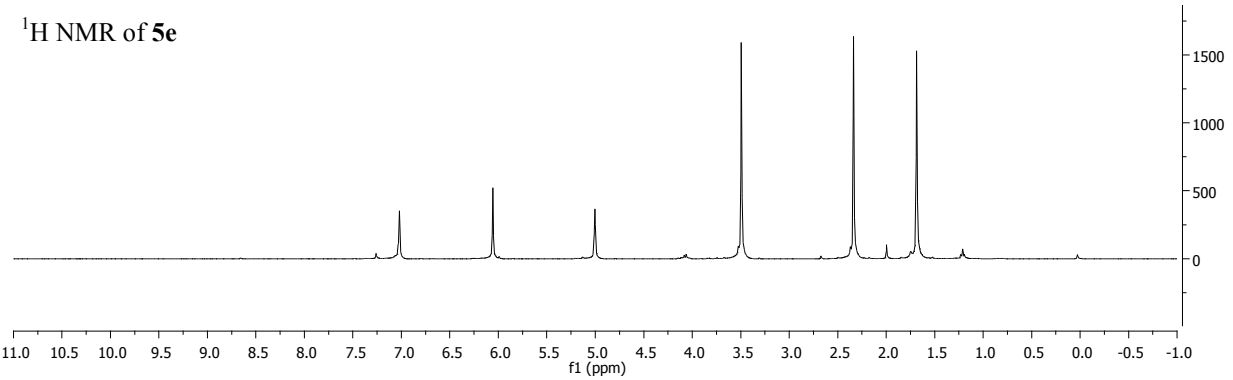


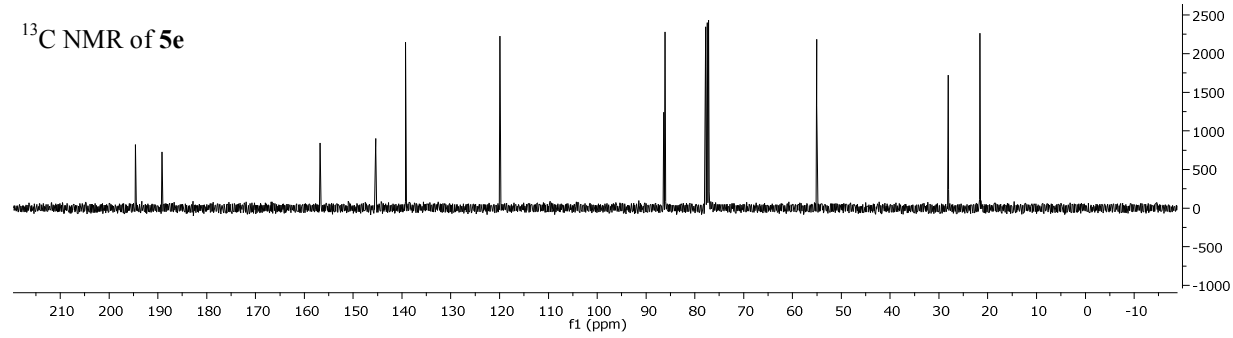
6-Acetyl-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (5e).

Procedure A: To a solution of **3a** (50 mg, 0.172 mmol) and 3-butyn-2-one (270 µL, 3.4 mmol) in CH_2Cl_2 (862 µL) was added N,N-dimethylaniline (44 µL, 0.34 mmol). After stirring at rt for 70 h, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5e** as a white solid (16 mg, 44% yield).

Procedure B: To a solution of **3a** (102.4 mg, 0.353 mmol) and 3-butyn-2-one (540 µL, 7.06 mmol) in $CHCl_3$ (706 µL) was added N,N-diisopropylaniline (82 µL, 0.424 mmol). After microwave irradiation at 100 °C for 15 min, reaction was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5e** as a white solid (71 mg, 97% yield).

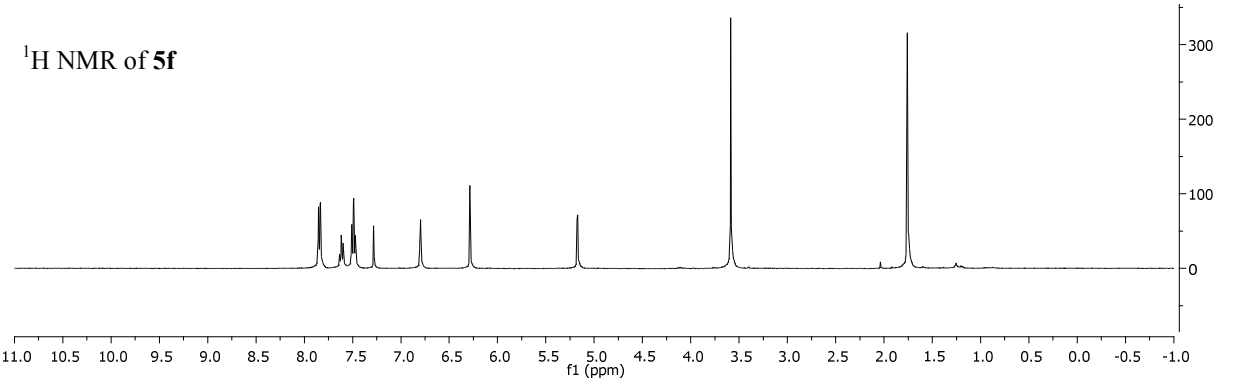
Characterization of **5e**: MP=146-150°C. Rf= 0.23 in 25% EtOAc in hexanes. **IR (thin film, KBr)** 3074 (s), 2931 (w), 1708 (s), 1663 (s), 1608 (s), 1441 (w), 1228 (m). 1129 (m). 1063 (m), 990 (w), 881 (w), 660 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.07 (d, J=1.4 Hz. 1H), 6.08 (s, 1H), 5.03 (d, *J* = 1.4 Hz, 1H), 3.52 (s, 3H), 2.36 (s, 3H), 1.71 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 194.63 (s), 189.16 (s), 156.78 (s), 145.40 (s), 139.26 (s), 119.94 (s), 86.40 (s), 86.13 (s), 55.03 (s), 28.07 (s), 21.63 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{11}H_{12}O_4Na^+$: 231.06278. Found: 231.06338.

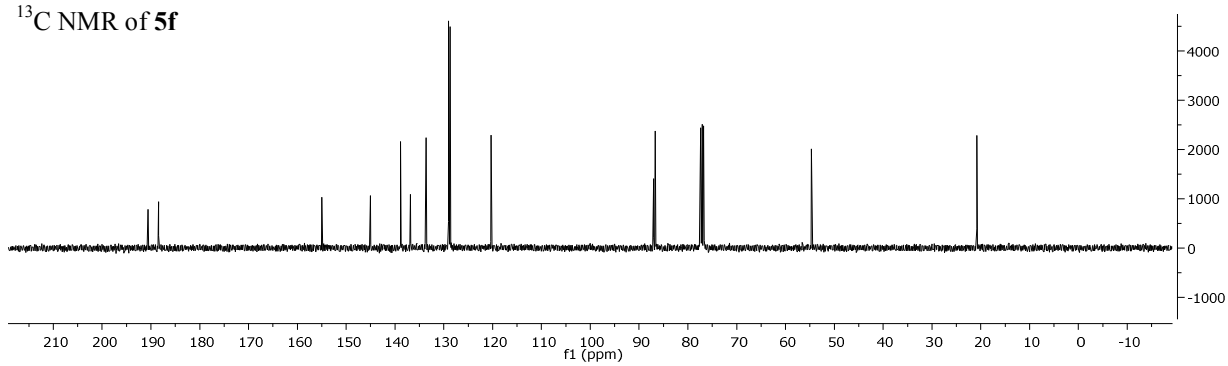




6-Benzoyl-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (5f). Following procedure B: To a solution of **3a** (100 mg, 0.340 mmol) and benzyl acetylene (225 mg, 1.72 mmol) in $CHCl_3$ (680 µL) was added N,N-diisopropylaniline (80 µL, 0.408 mmol). After microwave irradiation at 100 °C for 10 min, the reaction mixture was purified by chromatography (silica gel, 26 cm x 2.6 cm, solvent gradient: hexanes (50 mL); 2% EtOAc in hexanes (100 mL), 5% EtOAc in hexanes (100mL), 10% EtOAc in hexanes (100 mL); 20%-25% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5f** as a light yellow solid (78 mg, 85% yield). Due to high value of benzyl acetylene, fractions containing it were also concentrated (125 mg, 70% recovery (180 mg would be 100% theoretical yield of un-reacted product)). MP= 93-95°C. Rf=0.50 in 30% EtOAc in hexanes. **IR (thin film, KBr)** 3068 (w), 2978 (w), 2936 (w), 1711 (s), 1643 (s), 1608 (s), 1448 (m), 1325 (s), 1227 (m), 1180 (m), 1126 (s), 1075 (m), 988 (m), 819 (m), 843 (m), 701 (m), 667 (m) , 654 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (dd, *J* =7.6, 7.6 Hz, 2H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.26 (s, 1H), 5.15 (d, *J* = 2.5 Hz, 1H), 3.56 (s, 3H), 1.74 (s,

3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 190.59 (s), 188.44 (s), 155.01 (s), 145.05 (s), 138.84 (s), 136.82 (s), 133.61 (s), 129.01 (s), 128.73 (s), 120.31 (s), 87.04 (s), 86.70 (s), 54.71 (s), 20.80 (s). **HRMS (ESI+) *m/z*** calc'd for $C_{16}H_{14}O_4H^+$: 271. 0965. Found: 271.0964.



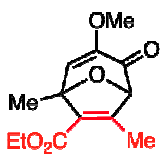


Ethyl3-methoxy-5,7-dimethyl-2-oxo-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (5g).

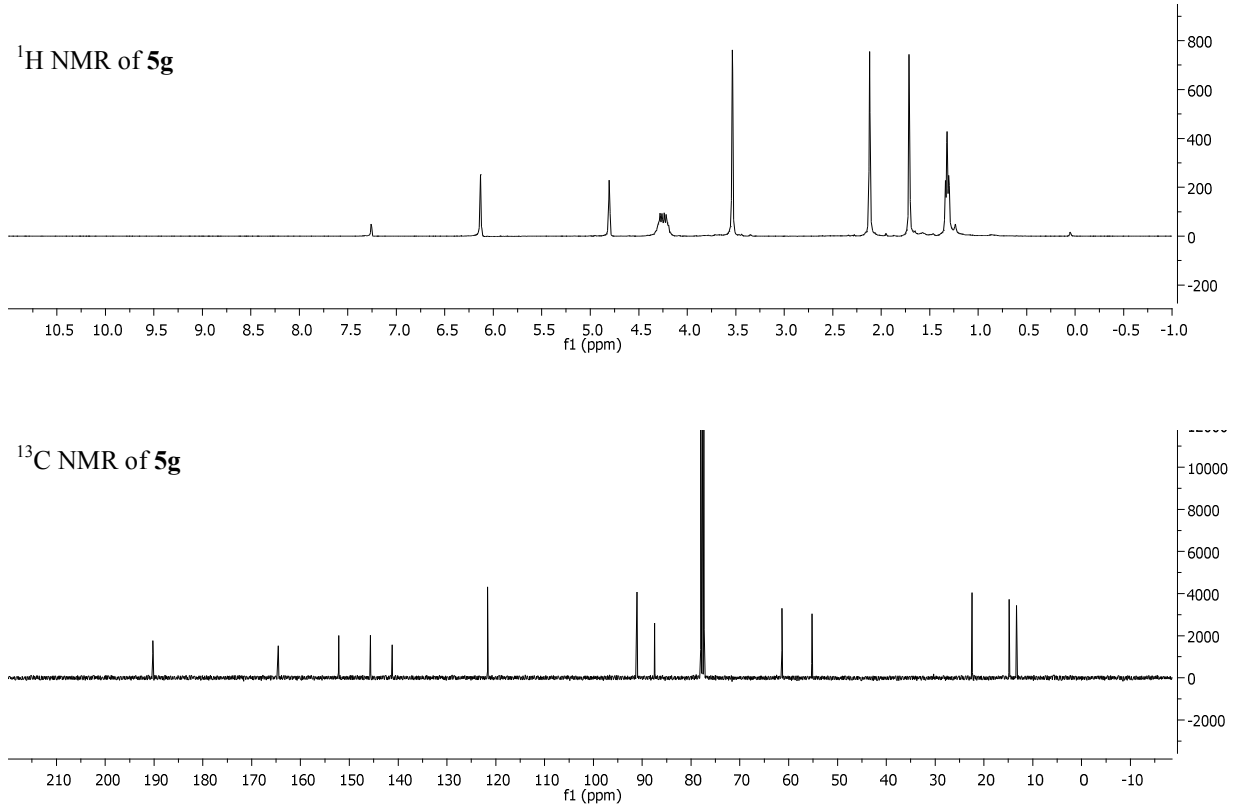
Procedure A: To a solution of **3a** (50 mg, 0.17 mmol) and ethyl but-2-ynoate (402 µL, 3.4 mmol) in CH_2Cl_2 (862 µL) was added N,N-dimethylaniline (44 µL, 0.34 mmol). After stirring at rt for 70 h, no conversion to product **5g** was observed.

Procedure B: To a solution of **3a** (106.3 mg, 0.367 mmol) and ethyl but-2-ynoate (855 µL, 7.34 mmol) in $CHCl_3$ (734 µL) was added N,N-diisopropylaniline (86 µL, 0.440 mmol). After microwave irradiation at 100 °C for 60 min, the reaction mixture was purified by chromatography (silica gel, 18cm x 1.8cm, solvent gradient: hexanes (50 mL); 2% EtOAc in hexanes (50 mL); 5% EtOAc in hexanes (200 mL); 10% EtOAc in hexanes (300 mL)). Product fractions were concentrated to yield **5g** as a white solid (29.3 mg, 32% yield).

Characterization of **5g**: MP=64-66°C. Rf= 0.53 in 25% EtOAc in hexanes. **IR (thin film, KBr)** 2981 (w), 2937 (w), 1706 (s), 1606 (m), 1446 (w), 1328 (m), 1132 (m), 1083 (m), 1048 (m), 871 (w), 785 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.13 (s, 1H), 4.80 (s, 1H), 4.36 – 4.15 (m, 2H), 3.54 (s, 3H), 2.12 (s, 3H), 1.71 (s, 3H), 1.32 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 190.23 (s), 164.58 (s), 152.19 (s), 145.66 (s), 141.22 (s), 121.66 (s), 91.06 (s), 87.45 (s), 61.36 (s), 55.25 (s),



22.45 (s), 14.86 (s), 13.33 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{13}H_{16}O_5H^+$: 253.1071. Found: 253.1059.



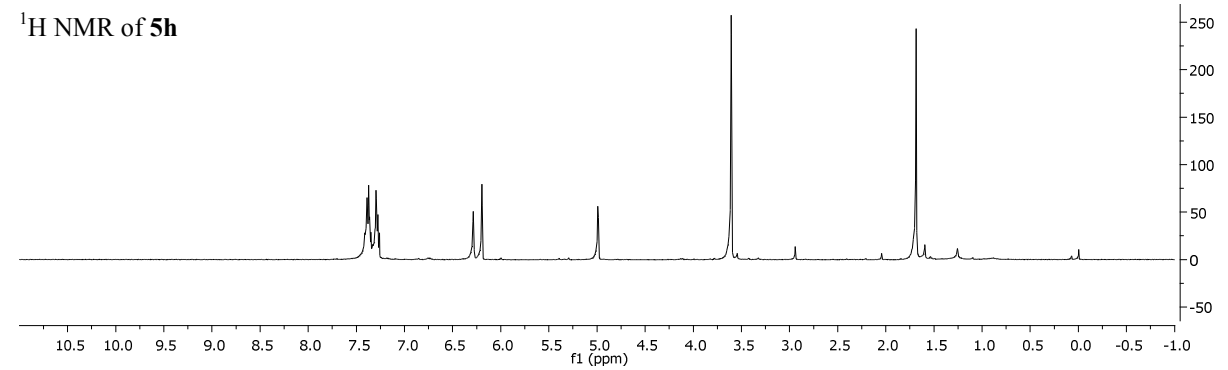
3-methoxy-5-methyl-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (5h).

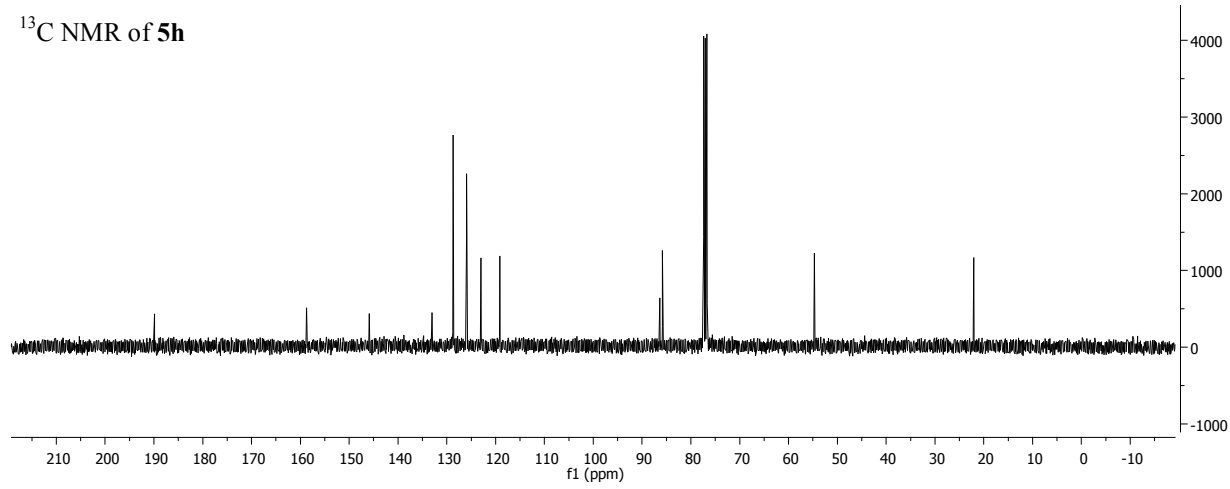
Procedure A: To a solution of **3a** (100 mg, 0.34 mmol) and phenylacetylene (745 µL, 6.8 mmol) in CH_2Cl_2 (1.7 mL) was added N,N-dimethylaniline (86 µL, 0.68 mmol). After stirring at rt for 1 week, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL), 10% EtOAc in hexanes (100 mL); 25% EtOAc in hexanes (100 mL)). Product fractions were concentrated to yield **5h** as an off white solid (29 mg, 35% yield).

Procedure B[6]: To a solution of **3a** (102.8 mg, 0.354 mmol) and phenylacetylene (776 µL, 7.08 mmol) in $CHCl_3$ (708 µl) was added N,N-diisopropylaniline (83 µL, 0.425 mmol). After microwave irradiation at 100 °C for 30 min, the reaction mixture was purified by chromatography (silica gel, 18 cm x 1.8 cm, solvent gradient: hexanes (50 mL); 10% EtOAc in hexanes (75 mL); 15% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5h** as an off white solid (49 mg, 57% yield).

[6] 5 equiv of alkyne conditions the same as stated with the following amounts: **3a** (97 mg, 0.334 mmol), phenylacetylene (183 µL, 1.67 mmol), N,N-diisopropylaniline (78 µL. 0.400 mmol), neat. Yielded **5h** (34 mg, 42%).

Characterization of **5h**: MP= 76-84°C. Rf=0.56 in 26% EtOAc in hexanes. **IR (thin film, KBr)** 2977 (w), 2934 (w), 2836 (w), 1711 (s), 1606 (m), 1491 (w), 1446 (w), 1130 (m), 1058 (w), 864 (m), 755 (m), 977 (w), 697 (w), 661 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 – 7.34 (m, 3H), 7.29 (dd, *J* = 5.1, 2.8 Hz, 2H), 6.28 (d, *J* = 2.4 Hz, 1H), 6.19 (s, 1H), 4.99 (d, *J* = 2.5 Hz, 1H), 3.60 (s, 3H), 1.68 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.89 (s), 158.72 (s), 145.91 (s), 133.02 (s), 128.73 (s), 128.70 (s), 125.97 (s), 123.00 (s), 119.13 (s), 86.39 (s), 85.81 (s), 54.71 (s), 22.08 (s). **HRMS** (ESI+) *m/z* calc'd for $C_{15}H_{14}O_3Na^+$: 265.0835. Found: 265.0836.

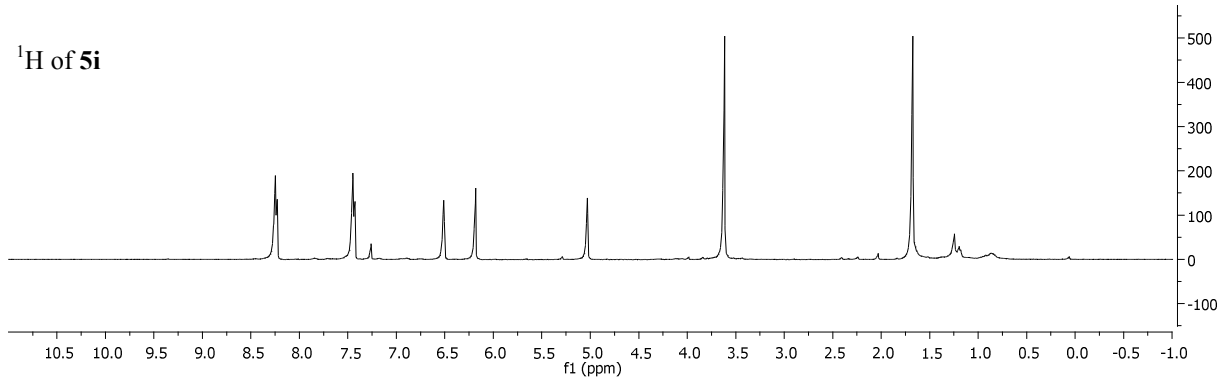


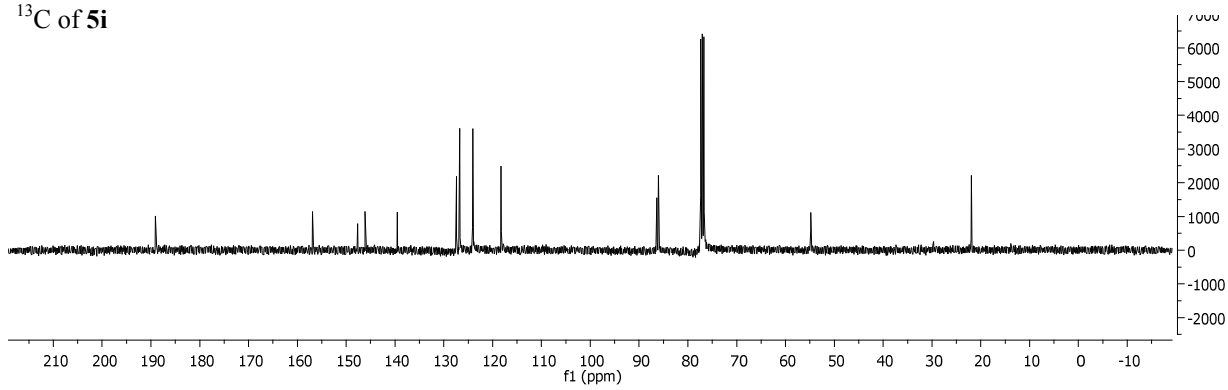


3-Methoxy-5-methyl-6-(4-nitrophenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (5i). Following procedure B: To a solution of **3a** (100 mg, 0.355 mmol) and 1-ethynyl-4-nitrobenzene (1.05 g, 7.10 mmol) in $CHCl_3$ (2.80 mL)[7] was added N,N-diisopropylaniline (83.5 µL, 0.426 mmol). After microwave irradiation at 100 °C for 30 min, reaction was purified by chromatography (silica gel, 26 cm x

[7] Added solvent needed due to poor solubility.

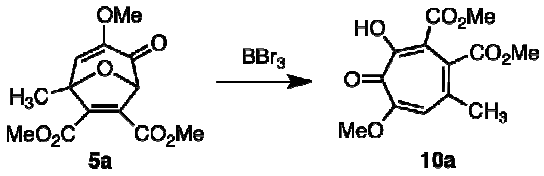
2.6 cm solvent gradient, dry loaded,[8] hexanes (50 mL); 10% EtOAc in hexanes (100 mL); 15% EtOAc in hexanes (100 mL); 20% EtOAc in hexanes (100 mL); 25% EtOAc in hexanes (200 mL)). Product fractions were concentrated to yield **5i** as a yellow solid (65 mg, 64% yield). MP= 145-148°C. Rf=0.27 in 16% EtOAc in hexanes. **IR (thin film, KBr)** 3075 (w), 2935 (w), 1712 (s), 1604 (m), 1516 (s), 1453 (w), 1341 (s), 1129 (m), 1108 (w), 987 (w), 865 (w), 851 (m), 750 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.24 (d, J=8.7 Hz, 2H), 7.44 (d, J=8.7, 2H), 6.51 (d, *J* = 2.5 Hz, 1H), 6.18 (s, 1H), 5.03 (d, *J* = 2.5 Hz, 1H), 3.61 (s, 3H), 1.67 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.08 (s), 156.93 (s), 147.67 (s), 146.13 (s), 139.53 (s), 127.42 (s), 126.77 (s), 124.07 (s), 118.26 (s), 86.33 (s), 86.00 (s), 54.84 (s), 21.95 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{15}H_{13}NO_5H^+$: 288.0866. Found: 288.0866.





V. Synthesis and characterization of methoxytropolone 10a via BBr_3

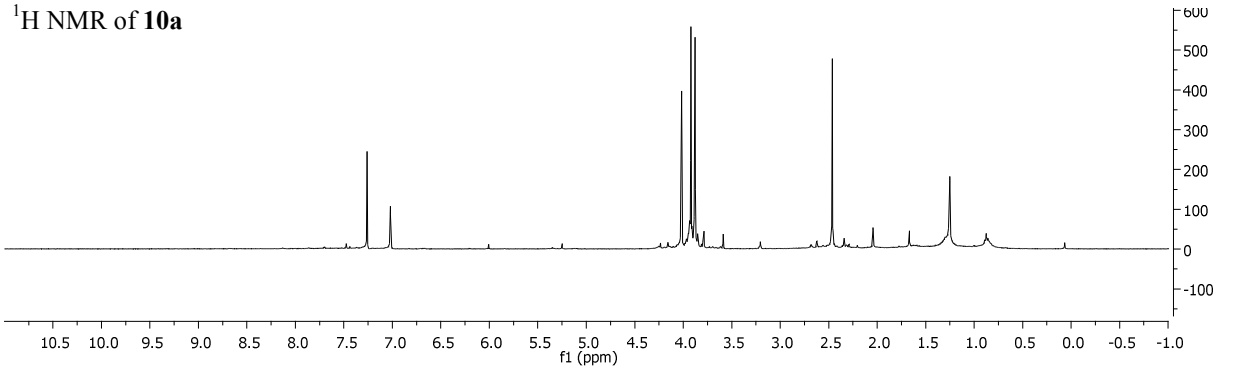
Dimethyl 7-hydroxy-5-methoxy-3-methyl-6-oxocyclohepta-2,4,7-triene-1,2-dicarboxylate (10a). To a solution of **5a** (50 mg, 0.17 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added BBr_3 in CH_2Cl_2 (102 μL of 1.0 M solution, 0.1 mmol). The reaction ran for 10 min, and a second portion of the BBr_3 solution was added (102 μL, 0.1 mmol). The reaction ran for



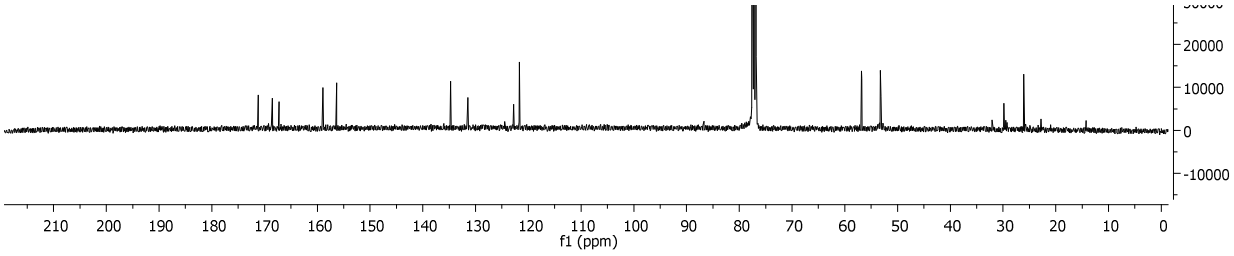
[8] Reaction mixture absorbed onto silica gel (500mg) in a round bottom flask directly after microwave irradiation. Evaporated off any excess solvent and dried under vacuum for ~ 30 min. Dried silica with mixture absorbed was loaded directly onto column.

an additional 10 min, at which time the reaction mixture was quenched with $NaHCO_{3aq}$ (5 mL). The aqeuous layer was extracted with CH_2Cl_2 (3 x 5 mL), and then acidified to a pH of 7 by dropwise addition of a 2M HCl solution. The acidified solution was then extracted with CH_2Cl_2 (5 x 5 mL), dried over Na_2SO_4, filtered and concentrated to yield **10a** as a yellow oil (16 mg, 0.56 mmol, 33% yield). MP=129-134. **IR (thin film, KBr)** 3225 (br), 2953 (w), 2852 (w), 1738 (s), 1571 (m), 1437 (m), 1320 (w), 1263 (s), 1156 (m), 1068 (m), 939 (w), 763 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.02 (s, 1H), 4.02 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 2.46 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.22 (s), 168.52 (s), 167.26 (s), 158.96 (s), 156.35 (s), 134.72 (s), 131.45 (s), 122.78 (s), 121.71 (s), 56.81 (s), 53.27 (s), 53.12 (s), 26.08 (s). **HRMS (ESI+) *m/z*** calc'd for $C_{13}H_{14}O_7Na^+$: 305.06317. Found: 305.06278.

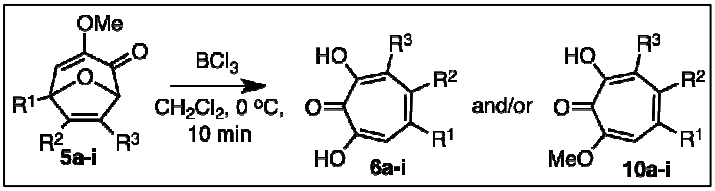
^{1}H NMR of **10a**

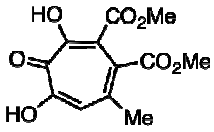


^{13}C NMR of **10a**

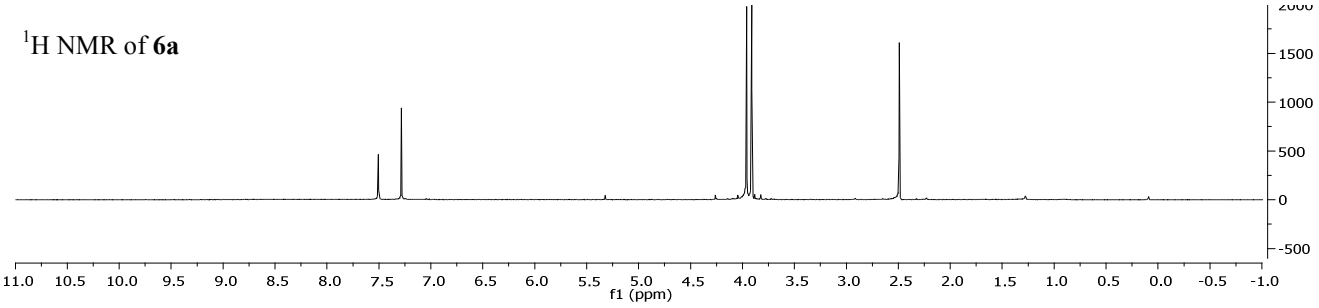


VI. Synthesis and characterization of α-hydroxy and α-methoxytropolones via BCl_3



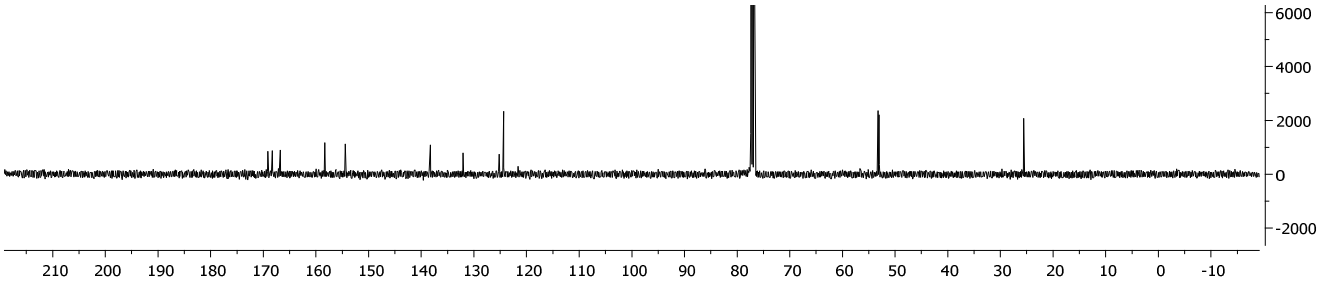


Dimethyl 5,7-dihydroxy-3-methyl-6-oxocyclohepta-2,4,7-triene-1,2-dicarboxylate (6a). A solution of BCl_3 (1.0 M in CH_2Cl_2) (588 μL, 0.588 mmol) was diluted with CH_2Cl_2 (6.0 mL) and cooled to 0 °C. In a separate roundbottom flask, **5a** (23.7 mg, 0.084 mmol) was dissolved in CH_2Cl_2 (6.0 mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 min of stirring at 0 °C, the reaction mixture was quenched with H_2O (12.0 mL), stirred for 2 min at 0 °C, and then warmed to rt where it continued to stir for 60 min. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2, (5 x 10 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **6a** as a yellow solid (17.4 mg, 77%).[9] MP= 159-161°C. **IR (thin film, KBr)** 3260 (br), 2957 (w), 1738 (s), 1543 (m), 1436 (w), 1256 (br/s), 1154 (m), 1065 (w), 1029 (w), 962 (w), 754 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 2.46 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.27 (s), 168.41 (s), 166.90 (s), 158.40 (s), 154.56 (s), 138.42 (s), 132.18 (s), 125.28 (s), 124.48 (s), 53.40 (s), 53.20 (s), 25.74 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{12}H_{12}O_7Na^+$: 291.04752. Found: 291.04831.



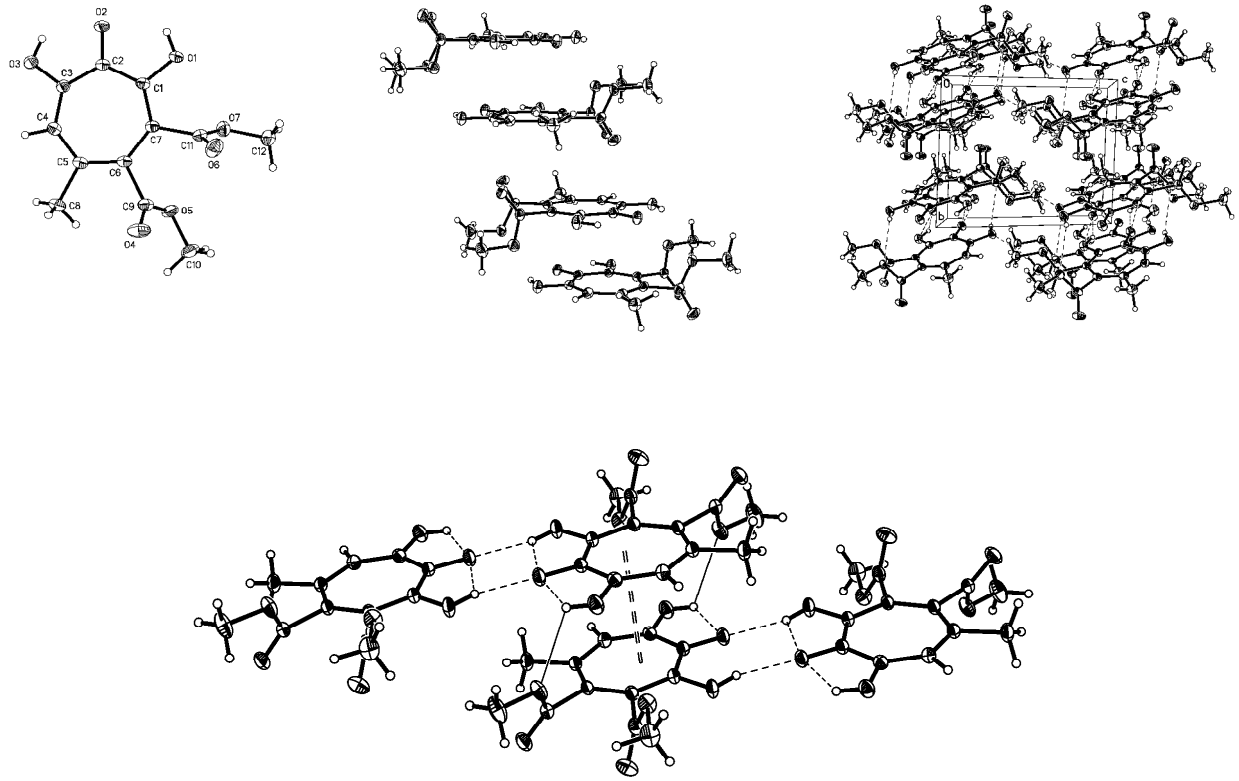
[9] If desired, compound can be further purified via reverse phase column chromatography (C-18) with a gradient of 20-27% over 16 column volumes (CV).

^{13}C NMR of **6a**

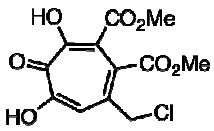


Select Crystal Structure images of 6a

(Images courtesy of William W. Brennesel, University of Rochester Chemistry Department)

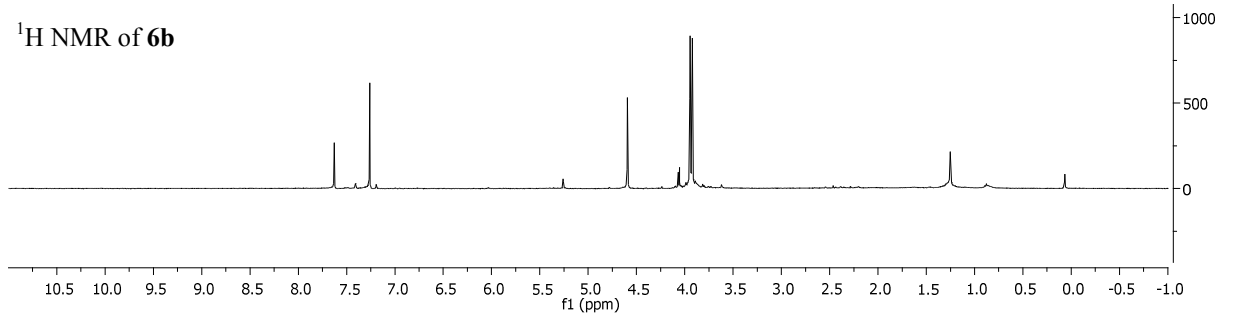


Dimethyl 3-(chloromethyl)-5,7-dihydroxy-6-oxocyclohepta-2,4,7-triene-1,2-dicarboxylate (6b). A solution of

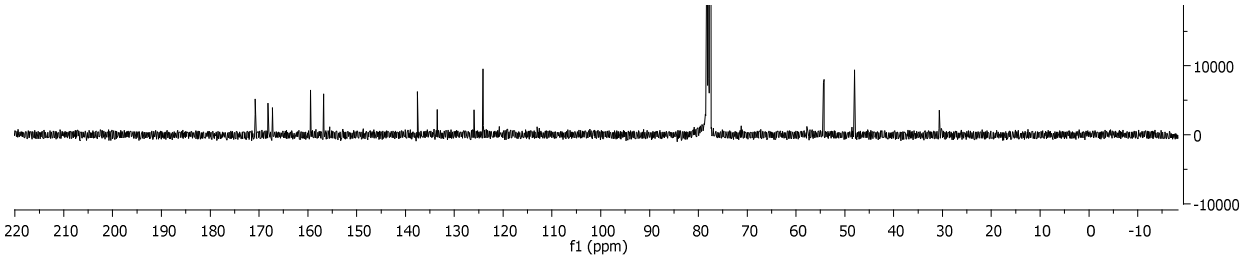


BCl_3 (1.0 M in CH_2Cl_2) (1.26 mL, 1.26 mmol) was diluted with CH_2Cl_2 (6.0 mL) and cooled to 0 °C. In a separate roundbottom flask, **5b** (26.5 mg, 0.084 mmol) was dissolved in CH_2Cl_2 (6.0 mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 min of stirring at 0 °C, the reaction mixture was quenched with H_2O (12.0 mL), stirred for 2 min at 0 °C, and then warmed to rt where it continued to stir for 30 min. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2, (5 x 10 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **6b** as a yellow solid (22 mg, 87%). Compound can be further purified via reverse phase column chromatography (C-18) with a gradient of 20-27% over 16 CV (7.7 mg after purification). Decomposes at temperatures 171-180°C. **IR (thin film, KBr)** 3261 (br), 2956 (w), 1737 (s), 1557 (m), 1436 (m), 1260 (br/s), 1153 (m), 989 (w), 668 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (s, 1H), 4.59 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.79 (s), 168.17 (s), 167.28 (s), 159.48 (s), 156.78 (s), 137.55 (s), 133.51 (s), 125.94 (s), 124.11 (s), 54.40 (s), 54.27 (s), 48.03 (s). **HRMS (ESI+) *m/z*** calc'd for $C_{12}H_{11}O_7^+$[10]: 267.0499. Found: 267.0502.

^{1}H NMR of **6b**

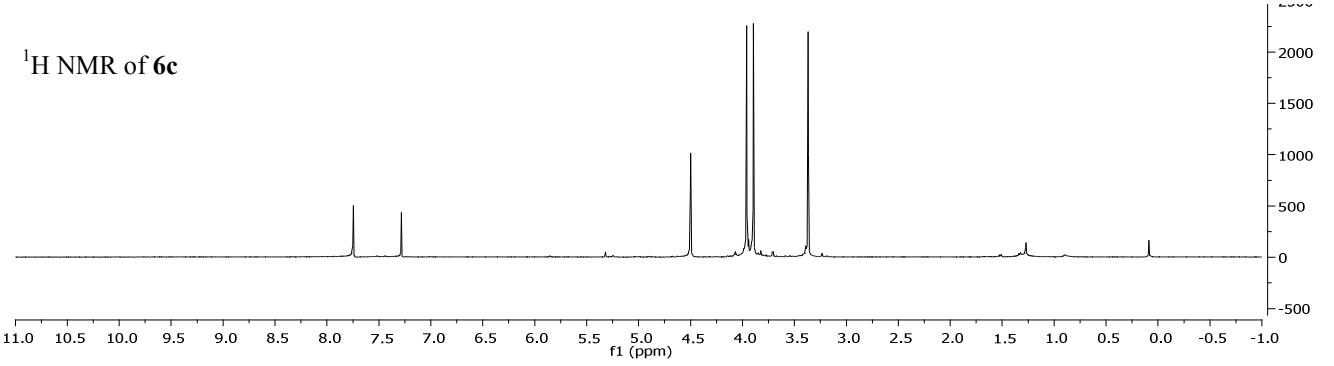


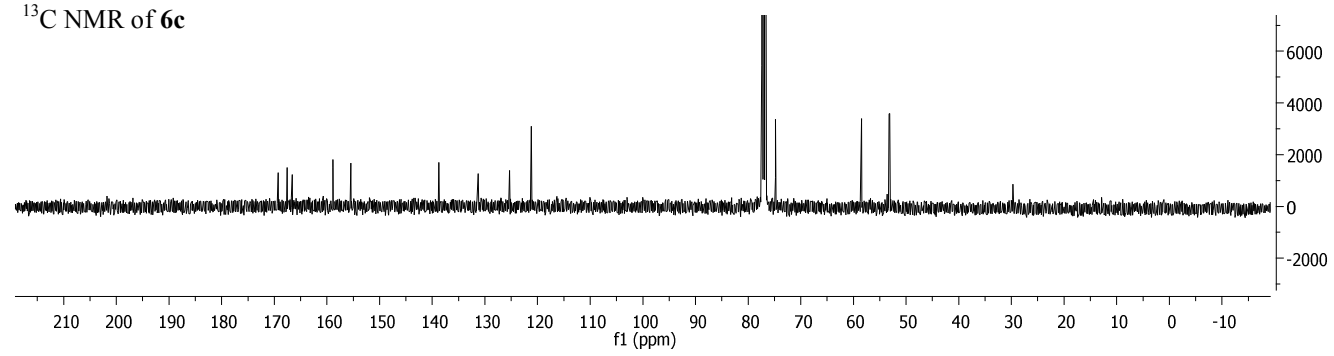
^{13}C NMR of **6b**



[10] Chlorine fragmentation, or mass minus Cl. Confirmation of chlorine was done qualitatively through a halogen flame test (Beilstein Test), with chlorokojic acid **2b** and hydroxytropolone **6a** as positive and negative controls respectively.

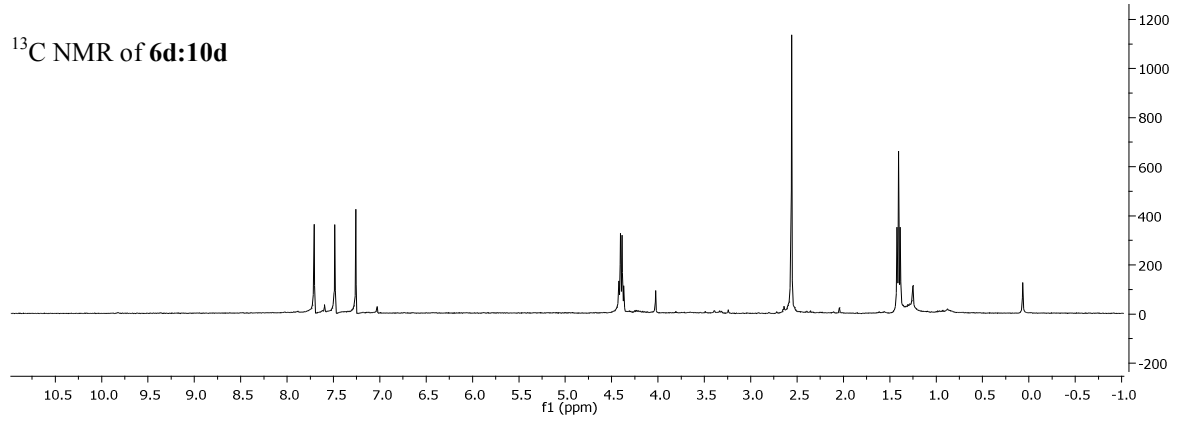
Dimethyl 5,7-dihydroxy-3-(methoxymethyl)-6-oxocyclohepta-2,4,7-triene-1,2-dicarboxylate (6c). A solution of BCl_3 (1.0 M in CH_2Cl_2) (459 µL, 459 mmoll) was diluted with CH_2Cl_2 (4.7 mL) and cooled to 0 °C. In a separate roundbottom flask, **5c** (20.5 mg, 0.066 mmol) was dissolved in CH_2Cl_2 (4.7 mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 min of stirring at 0 °C, the reaction mixture was quenched with H_2O (9.4 mL), stirred for 2 min at 0 °C, and then warmed to rt where it continued to stir for 1 h. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2, (5 x 10 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **6c** as a yellow oil (16.6 mg, 85%). **IR (thin film, KBr)** 3261 (br), 2953 (w), 1738 (s), 1548 (m), 1436 (m), 1343 (m), 1259 (s), 1148 (m), 1100 (m), 1061 (m), 890 (w), 734 (w), 668 (w) cm^1. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73 (s, 1H), 4.48 (s, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 3.35 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.26 (s), 167.57 (s), 166.58 (s), 158.84 (s), 155.45 (s), 138.76 (s), 131.26 (s), 125.32 (s), 121.17 (s), 74.79 (s), 58.47 (s), 53.25 (s), 53.13 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{13}H_{14}O_8H^+$: 299.0761. Found: 299.0757.





Ethyl 4,6-dihydroxy-2-methyl-5-oxocyclohepta-1,3,6-trienecarboxylate (6d) and Ethyl 6-hydroxy-4-methoxy-2-methyl-5-oxocyclohepta-1,3,6-trienecarboxylate (10d). A solution of BCl_3 (1.0 M in CH_2Cl_2) (627 µL, 0.627 mmol) was diluted with CH_2Cl_2 (6.4 mL) and cooled to 0 °C. In a separate roundbottom flask, **5d** (21.3 mg, 0.089 mmol) was dissolved in CH_2Cl_2 (6.4 mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 min of stirring at 0 °C, the reaction mixture was quenched with H_2O (12.8 mL), stirred for 2 min at 0 °C, and then warmed to rt where it continued to stir for 30

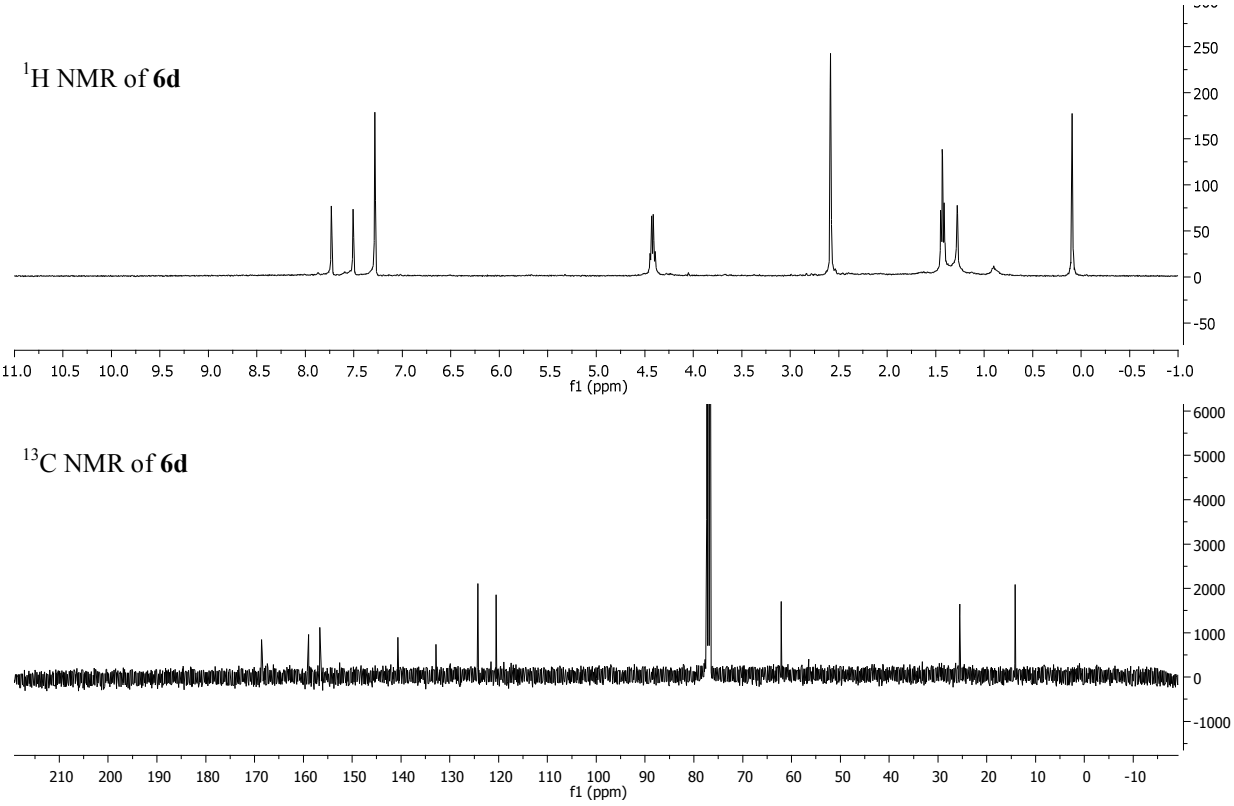
mintues. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2, (3 x 10 mL) and EtOAc (2 x 10 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the resulting solid was added $CHCl_3$ where a white solid precipitated out. The organic layer was decanted off and concentrated under reduced pressure to yield a mixture of **6d:10d**[11] as a brownish green solid (7.9 mg, 39%).



Homogenization of 6d/10d solution with HBr/AcOH

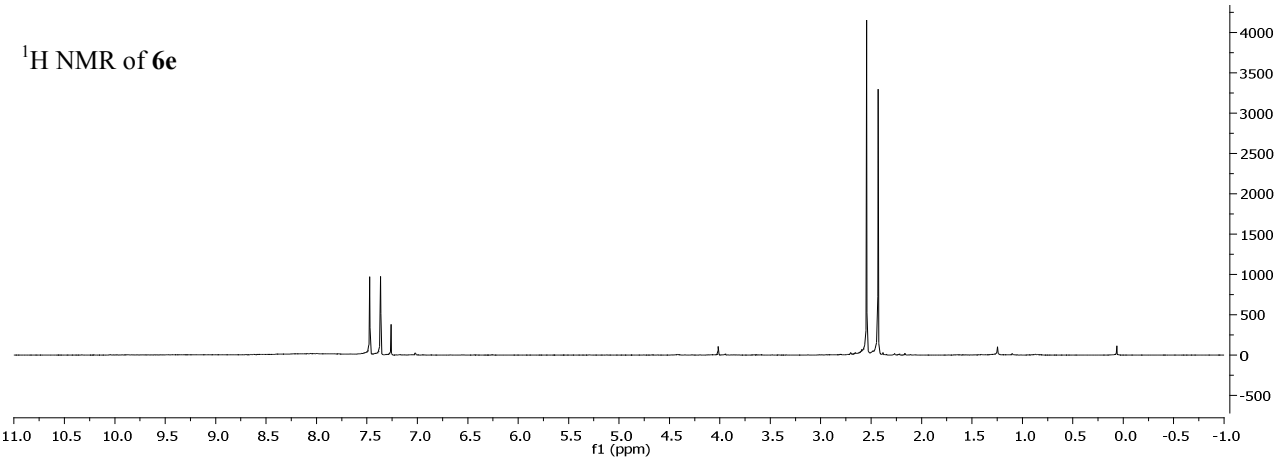
To the mixture of **6d:10d** (7.9 mg, 0.033 mmol) was added acetic acid (192 µl) and 33% HBr in acetic acid (224 µl), and reaction was left to stir at 90 °C for 3 h. After 3 h, reaction mixture was let to cool to rt. The reaction was quenched with 7 pH phosphate buffer, and diluted with CH_2Cl_2. The organic layer was washed several times with the phosphate buffer. The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to yield a brown solid **6d** (3.1 mg, 42% yield). Decomposes at temperatures above 80 °C. **IR (thin film, KBr)** 3260 (br), 2917 (w), 2849 (w), 1718 (s), 1500 (w), 1462 (w), 1217 (br/s), 1094 (m), 922 (w), 785 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** $^1\delta$ 7.68 (s, 1H), 7.45 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.53 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.72 (s), 168.65 (s), 159.04 (s), 156.74 (s), 140.73 (s), 132.94 (s), 124.35 (s), 120.54 (s), 62.28 (s), 25.67 (s), 14.33 (s). **HRMS (ESI+) *m/z*** calc'd for $C_{11}H_{12}O_5H^+$: 225.07575. Found: 225.07611

[11] Compound can be purified via reverse phase column chromatography (C-18) with a gradient of 20-27% for 1.9 CV, 27-30% for 5 CV, 30-45% for 7 CV.

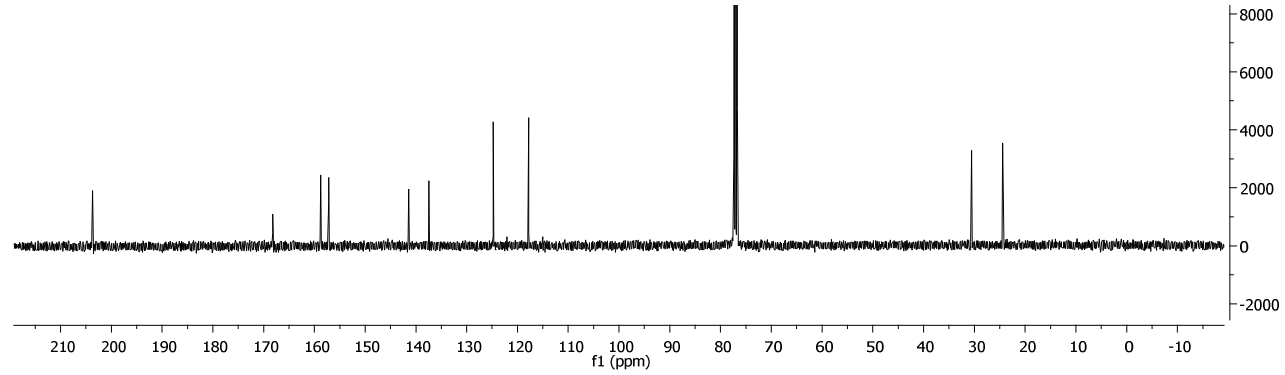


4-Acetyl-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trienone (6e). A solution of BCl_3 (1.0 M in CH_2Cl_2) (673 µL, 0.673 mmol) was diluted with CH_2Cl_2 (6.9 mL) and cooled to 0°C. In a separate roundbottom flask, **5e** (20.0 mg, 0.096 mmol) was dissolved in CH_2Cl_2 (6.9 mL), was cooled to 0°C and was added to the BCl_3 solution. After 10 min of stirring at 0°C, the reaction mixture was quenched with H_2O (13.7 mL), stirred for 2 min at 0 °C, and then warmed to rt where it continued to stir for 1 h. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2, (5 x 10 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **6e** as an orange solid (19.6 mg, >95% yield). MP= 106-110°C. **IR (thin film, KBr)** 3240 (br), 2918 (w), 2852 (w), 1700 (s), 1536 (s), 1446 (w), 1283 (m), 1203 (s), 1134 (m), 1031 (w), 893 (w), 785 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$** δ 7.44 (s, 1H), 7.36 (s, 1H), 2.55 (s, 3H), 2.43 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$** δ 204.08 (s), 168.56 (s), 159.03 (s), 157.48 (s), 141.72 (s), 137.77 (s), 125.04 (s), 118.06 (s), 30.92 (s), 24.80 (s). **HRMS (ESI+) *m/z*** calc'd for $C_{10}H_{10}O_4H^+$: 195.06519. Found: 195.06531.

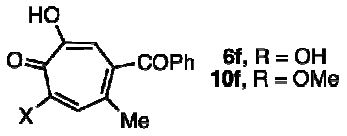
^{1}H NMR of **6e**



^{13}C NMR of **6e**



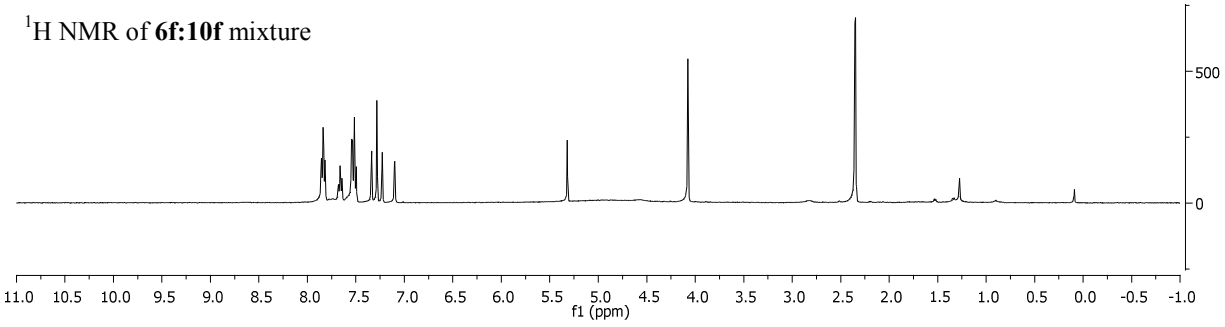
4-benzoyl-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trienone (6f) and 4-benzoyl-2-hydroxy-7-methoxy-5-methylcyclohepta-2,4,6-trienone (10f). A solution of BCl_3 (1.0 M in CH_2Cl_2) (503 µL, 0.503 mmol) was diluted with CH_2Cl_2 (5.2 mL) and cooled to 0°C. In a separate roundbottom flask, **5f** (19.4 mg, 0.072 mmol) was dissolved in CH_2Cl_2 (5.2 mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 min of stirring at 0 °C, the reaction mixture was quenched with H_2O (10.3 mL), stirred for 2 min at 0°C, and then warmed to rt where it continued to stir for 1 h. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2, (5 x 10 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **6f:10f** as a yellow solid (19.6 mg, >95% yielded) in a 1:1 ratio. The mixture of compounds **6i: 10i** can be purified for characterization via reverse phase column chromatography (C-18) with a gradient of 27-35% for 5 column volumes, and 35-65% for 8 column volumes, **10i** collected on fractions 2-7; **6i** was collected on fractions 10-13.



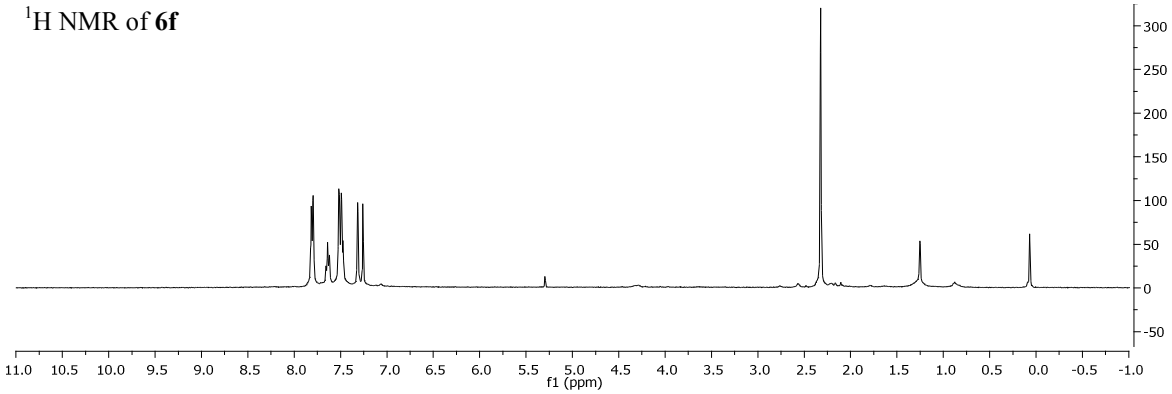
4-Benzoyl-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trienone (6f) decomposed at temperature of 45-50°C. **IR (thin film, KBr)** 3279 (br), 2918 (w), 2849 (w), 1674 (s), 1595 (w), 1536 (m), 1448 (m), 1284 (m), 1231 (s), 1084 (m), 829 (w), 725 (w), 688 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 7.7 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.52 (s, 1H), 7.49 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.32 (s, 1H), 2.32 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 197.09 (s), 168.38 (s), 158.69 (s), 156.94 (s), 139.71 (s), 138.08 (s), 135.58 (s), 134.36 (s), 130.10 (s), 129.03 (s), 124.31 (s), 118.83 (s), 24.48 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{15}H_{12}O_4H^+$: 257.0808. Found: 257.0806.

4-Benzoyl-2-hydroxy-7-methoxy-5-methylcyclohepta-2,4,6-trienone (10f) melted at 143-145°C. **IR (thin film, KBr)** 3209 (br), 2918 (w), 2847 (w), 1673 (s), 1560 (s), 1448 (w), 1262 (s), 1241 (s), 1145 (m), 1087 (m), 828 (w), 725 (w), 688 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.49 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.24 (s, 1H), 7.11 (s, 1H), 4.05 (s, 3H), 2.34 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.18 (s), 170.53 (s), 159.26 (s), 158.90 (s), 139.39 (s), 135.52 (s), 134.75 (s), 134.37 (s), 130.09 (s), 129.03 (s), 122.00 (s), 116.76 (s), 56.54 (s), 24.83 (s). **HRMS (ESI+)** *m/z* calc'd for $C_{16}H_{14}O_4$: 271.0965. Found: 271.0957.

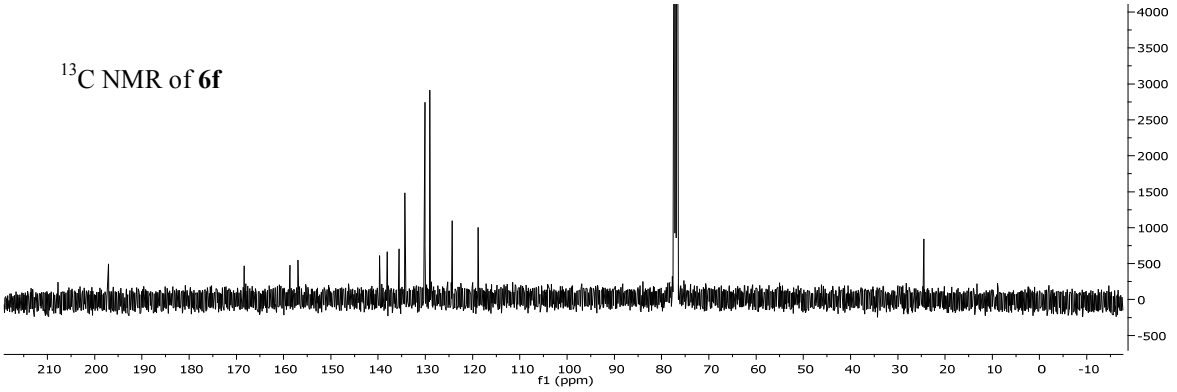
^{1}H NMR of **6f:10f** mixture



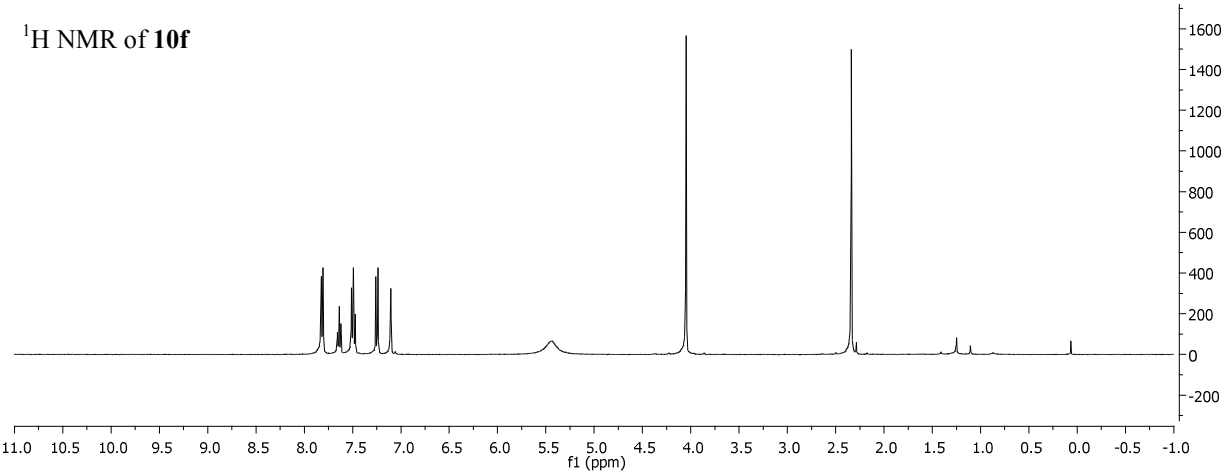
^{1}H NMR of **6f**



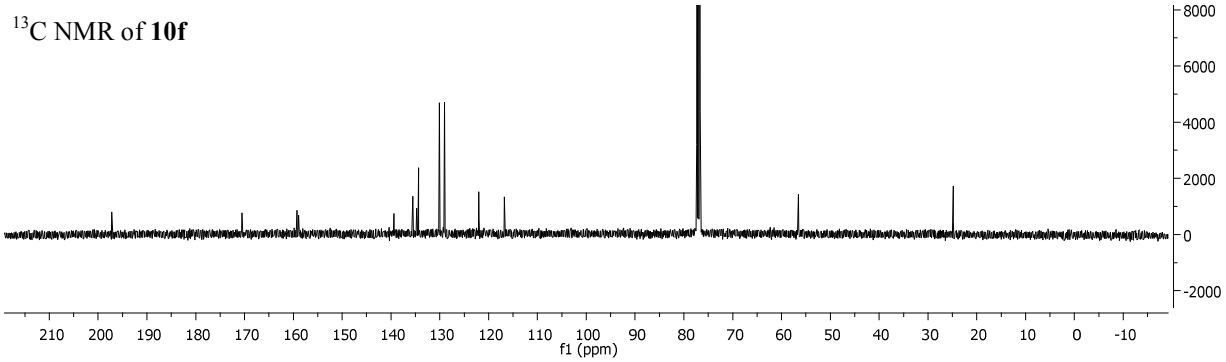
^{13}C NMR of **6f**



^{1}H NMR of **10f**



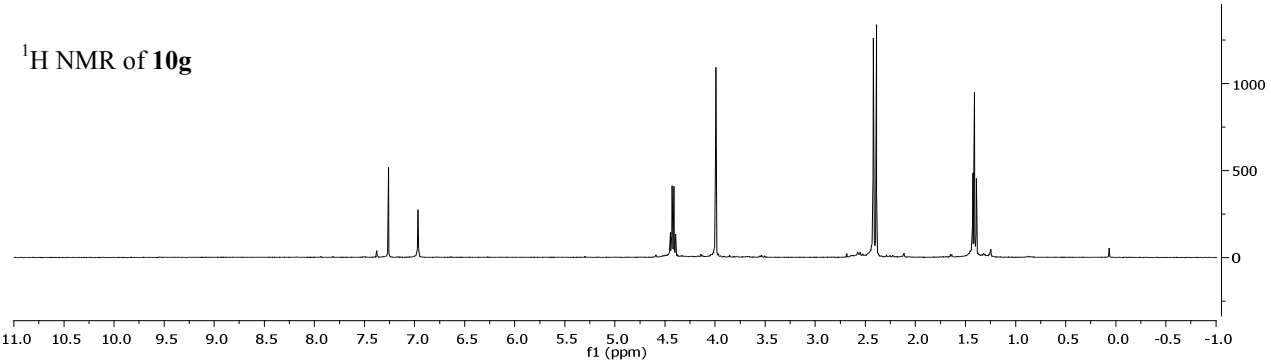
^{13}C NMR of **10f**

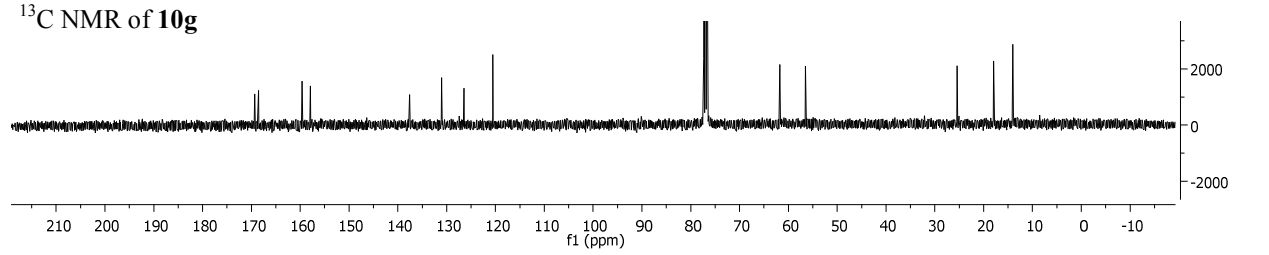


Homogenization of 6f/10f solution with HBr/AcOH

To the mixture of **6f:10f** (16.9 mg, 0.062 mmol) was added acetic acid (364 µl) and 33% HBr in acetic acid (425 µl), and reaction was left to stir at 90 °C for 3 h. After 3 h, reaction mixture was let to cool to rt. The reaction was quenched with 7 pH phosphate buffer, and diluted with CH_2CL_2. The organic layer was washed several times with the phosphate buffer. The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to yield a brown solid **6f** (9.5 mg, 60% yield).

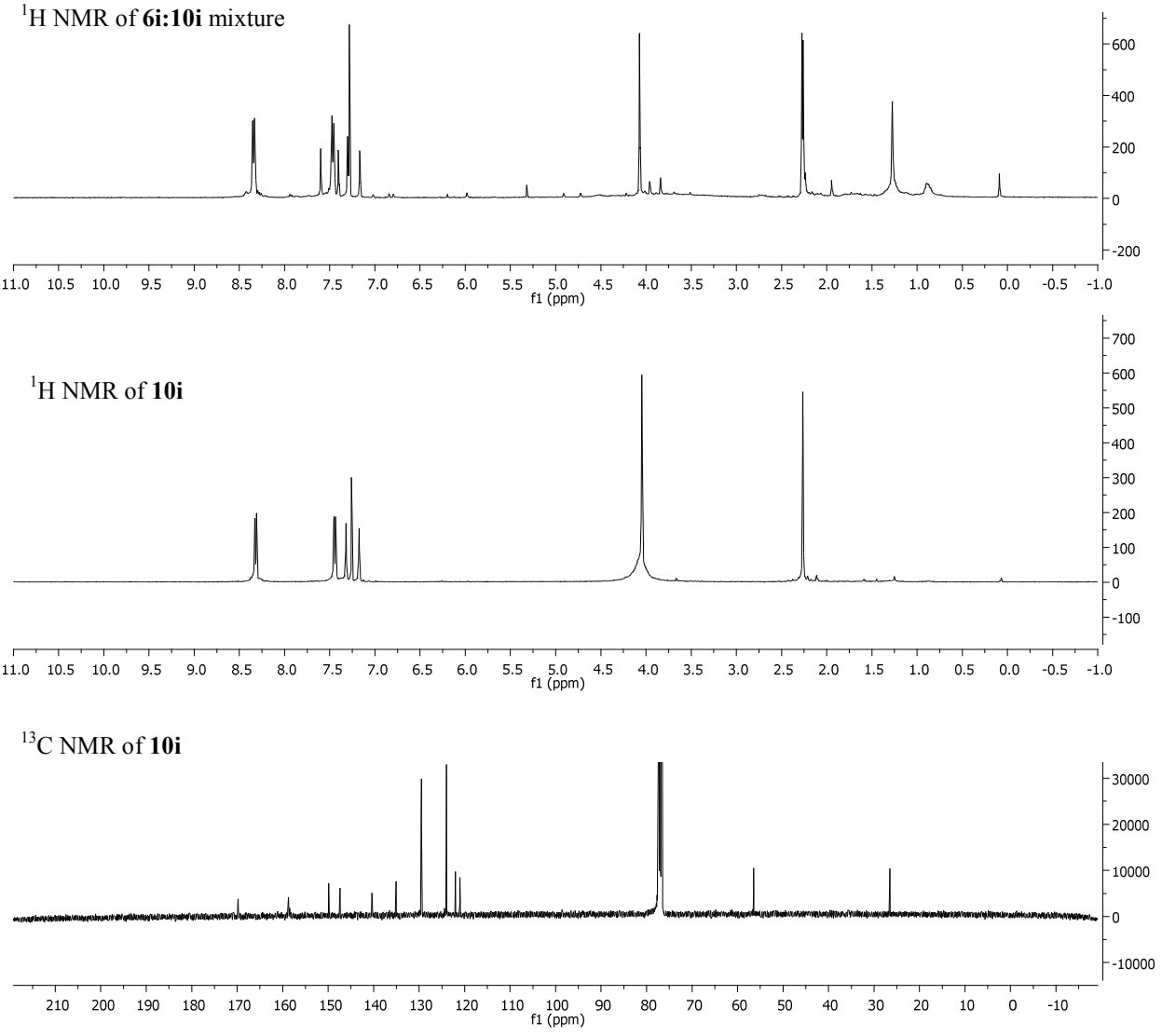
Ethyl 6-hydroxy-4-methoxy-2,7-dimethyl-5-oxocyclohepta-1,3,6-trienecarboxylate (10g). A solution of BCl_3 (1.0 M in CH_2Cl_2) (486 µL, 0.486 mmol) was diluted with CH_2Cl_2 (5 mL) and cooled to 0 °C. In a separate roundbottom flask, **5g** (17.5 mg, 0.069 mmol) was dissolved in CH_2Cl_2 (5 mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 min of stirring at 0 °C, the reaction mixture was quenched with H_2O (10 mL), stirred for 2 min at 0 °C, and then warmed to rt where it continued to stir for 1 h. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2, (5 x 10 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield **10g** as a yellow solid (13.4 mg, 77% yield). MP= 64-70°C. **IR (thin film, KBr)** 3381 (w), 2917 (w), 2848 (w), 1727 (s), 1551 (w), 1454 (w), 1317 (m), 1223 (s), 1146 (m), 1037 (m), 876 (w), 791 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.95 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.70 (s), 168.91 (s), 160.01 (s), 158.30 (s), 137.98 (s), 131.45 (s), 126.86 (s), 120.88 (s), 62.14 (s), 56.87 (s), 25.79 (s), 18.32 (s), 14.41 (s). **HRMS (ESI+)** ***m/z*** calc'd for $C_{13}H_{16}O_5Na^+$: 275.08899. Found: 275.08788.





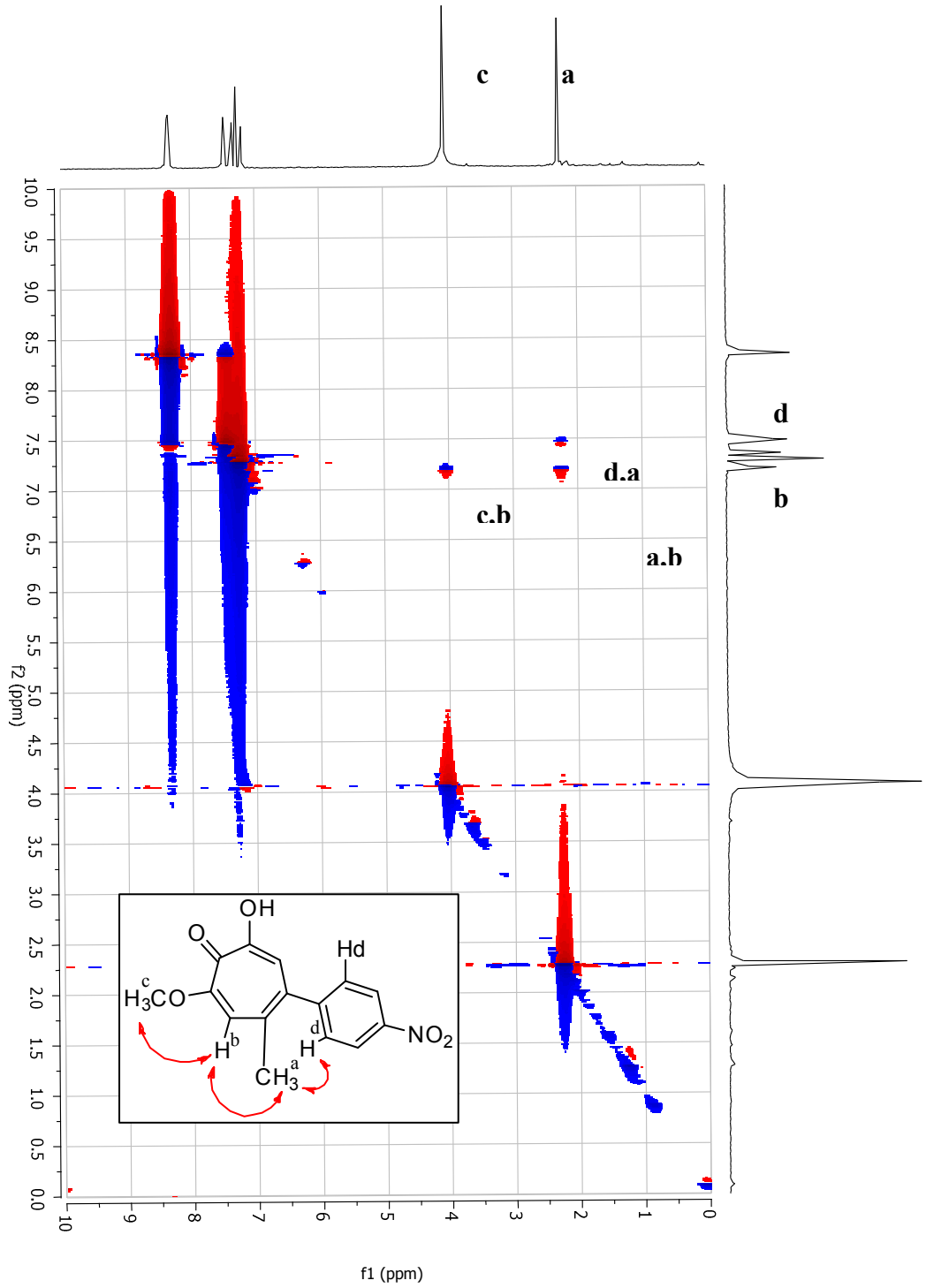
2,7-dihydroxy-4-methyl-5-(4-nitrophenyl)cyclohepta-2,4,6-trienone (6i) and 2-hydroxy-7-methoxy-5-methyl-4-(4- nitrophenyl)cyclohepta-2,4,6-trienone (10i). A solution of BCl_3 (1.0 M in CH_2Cl_2) (728 µL, 0.728 mmol) was diluted with CH_2Cl_2 (7.4 mL) and cooled to 0 °C. In a separate roundbottom flask, **5i** (29.8 mg, 0.104 mmol) was dissolved in CH_2Cl_2 (7.4 mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 min of stirring at 0 °C, the reaction mixture was quenched with H_2O (15 mL), stirred for 2 min at 0 °C, and then warmed to rt where it continued to stir for 1 h. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2, (5 x 10 mL). Combined organics were dried over Na_2SO_4, filtered, and

concentrated under reduced pressure to yield **6i:10i** as a yellow solid (23.3 mg, 81%) in a 1:1 mixture. Compound mixture **10i**[12] was purified for characterization via reverse phase column chromatography (C-18) with a gradient of 35-55% . Fractions 2-4 were concentrated to generate **2-hydroxy-7-methoxy-5-methyl-4-(4-nitrophenyl)cyclohepta-2,4,6-trienone (10i)** as a yellow solid with a melting point range of 210-214°C. **IR (thin film, KBr)** 3229 (br), 2917 (w), 2848 (w), 1558 (s), 1514 (s), 1480 (m), 1344 (s), 1265 (s), 1229 (s), 1133 (s), 855 (w), 725 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.32 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.32 (s, 1H), 7.18 (s, 1H), 4.05 (s, 3H), 2.26 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.81 (s), 158.72 (s), 158.57 (s), 149.86 (s), 147.38 (s), 140.37 (s), 135.05 (s), 129.51 (s), 124.00 (s), 122.04 (s), 121.03 (s), 56.48 (s), 26.53 (s).**HRMS (ESI+)** *m/z* calc'd for $C_{15}H_{13}NO_5H^+$: 288.0866. Found: 288.0872



[12] Compound **6i** decomposes on reverse phase column and could not be isolated cleanly. To isolate **10i**, the mixture of **6i:10i** was dissolved in chloroform, applied to a dry loaded samplet, and allowed to dry under vacuum for an h prior to running column.

NOESY of 2-hydroxy-7-methoxy-5-methyl-4-(4-nitrophenyl)cyclohepta-2,4,6-trienone (10i)



Homogenization of 6f/10f mixture with HBr/AcOH

To the mixture of **6i:10i** (23.3 mg, 0.081 mmol) was added acetic acid (473 µl) and 33% HBr in acetic acid (552 µl), and reaction was left to stir at 90 °C for 3 h. After 3 h, reaction mixture was let to cool to rt. The reaction was quenched with 7 pH phosphate buffer, and diluted with CH_2Cl_2. The organic layer was washed several times with the phosphate buffer. The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to yield 2,7-dihydroxy-4-methyl-5-(4-nitrophenyl)cyclohepta-2,4,6-trienone **(6i)** as a brown solid (17.8 mg, 80% yield) that decomposes at 200 °C. **IR (thin film, KBr)** 3229 (br), 2917 (w), 1595 (m), 1518 (s), 1344 (s), 1279 (m), 1260 (m), 1194 (m), 1092 (m), 855 (w), 702 (w) cm^{-1}.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.32 (d, *J* = 8.3 Hz, 2H), 7.57 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.38 (s, 1H), 2.24 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.65 (s), 158.14 (s), 156.43 (s), 149.96 (s), 147.38 (s), 140.57 (s), 138.29 (s), 129.53 (s), 124.08 (s), 123.99 (s), 122.79 (s), 26.25 (s). **HRMS (ESI+)** ***m/z*** calc'd for $C_{14}H_{11}NO_5H^+$: 274.0710. Found: 274.0705.