Importance of Lipophilicity for Potent Anti-Herpes Simplex Virus-1 Activity of α-Hydroxytropolones

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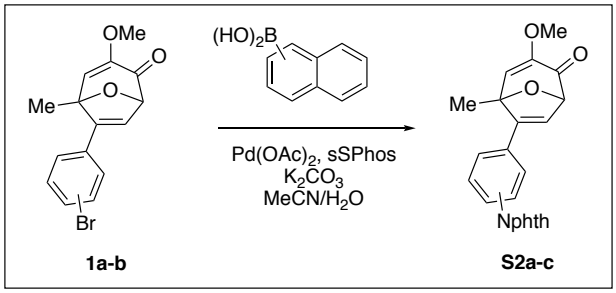
I. General Information

All starting materials and reagents were purchased from commercially available sources and used without further purification. Hydroxytropolones tested in the manuscript that are not described in the following supporting information have been reported previously.[1] ^{1}H NMR shifts are measured using the solvent residual peak as the internal standard ($CDCl_3$ δ 7.26), 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 77.16), and reported as chemical shifts. Infrared (IR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w). Microwave reactions were performed via the Biotage Initiator 2.5. Purification via column chromatography was performed on the Biotage Isolera Prime, with Biotage SNAP 10g cartridges, in a solvent system of ethyl acetate and hexanes. Reversed-phase chromatography was also performed on the Biotage Isolera Prime, with Biotage SNAP 12g C_{18} cartridges, in a solvent system of acetonitrile and water, with each containing .05% trifluoroacetic acid.

II. Biaryl αHT Synthesis

IIa. Synthesis and characterization of 8-oxabicyclo[3.2.1]octenes (s2a-c)

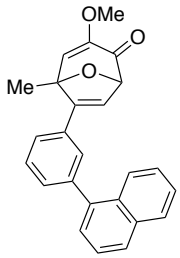


General Procedure. To a solution of 8-oxabicyclo[3.2.1]octene **1a-b** in acetonitrile (.03M) was added palladium(II) acetate (0.5 equiv) and sSPhos (1 equiv). The reaction mixture was stirred at room temperature for 5 minutes at

[1] Please see: Lomonosova, E.; Daw, J.; Garimallaprabhakaran, A. K.; Agyemang N. B.; Ashani, Y.; Murelli, R. P.; Tavis, J. E. *Antiviral Res.* **2017**, *144*, 164-172 and references therein.

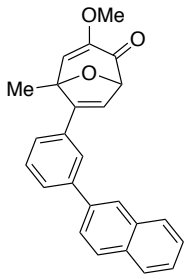
which point a solution of napthylboronic acid (10 equiv) and potassium carbonate (10 equiv) in H_2O (.02M with respect to 8-oxabicyclo[3.2.1]octene) was added. The reaction mixture was then heated in a 50 °C mineral oil bath for 2.5 hours and was subsequently allowed to cool to room temperature and concentrated *in vacuo* to remove acetonitrile. To the concentrated solution was added sat. NaCl (aq), and the organic material was extracted with $CHCl_3$ (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield crude 8-oxabicyclo[3.2.1]octene **S2a-c**. The reaction mixture was then loaded directly onto column for chromatography and purified.

3-methoxy-5-methyl-6-(3-(naphthalen-1-yl)phenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (S2a). To a solution



of 6-(3-bromophenyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one **1a**[2] (25 mg, 0.078 mmol) in acetonitrile (2.5 mL) was added palladium(II) acetate (8.6 mg, 0.039 mmol) and sSPhos (40 mg, 0.078 mmol). The reaction mixture was stirred at room temperature for 5 minutes at which point a solution of 1-napthylboronic acid (134 mg, 0.78 mmol) and potassium carbonate (108 mg, 0.78 mmol) in H_2O (5 mL) was added. The reaction mixture was then heated in a 50 °C mineral oil bath for 2.5 hours and was subsequently allowed to cool to room temperature and concentrated *in vacuo* to remove acetonitrile. To the concentrated solution was added sat. NaCl (aq) (10 mL), and the organic material was extracted with $CHCl_3$ (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield crude 3-methoxy-5-methyl-6-(3-(naphthalen-1-yl)phenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2a). The reaction mixture was purified by chromatography (Biotage Isolera Prime, 10 g silica gel column, solvent gradient: 0% EtOAc in hexanes (3 CV); 0-50% EtOAc in hexanes (35 CV)). Product fractions were concentrated to yield **S2a** as a clear oil (8 mg, 28% yield). Rf= 0.34 in 30% EtOAc in hexanes. **IR (thin film, KBr)** 3053 (w), 2954 (w), 2930 (m), 2850 (w), 1710 (s), 1605 (m), 1341 (w), 1173 (w), 1131 (m), 1057 (w), 989 (w), 865 (m), 779 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 – 7.84 (m, 3H), 7.57 – 7.36 (m, 8H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.16 (s, 1H), 5.01 (d, *J* = 2.5 Hz, 1H), 3.56 (s, 3H), 1.74 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.94, 158.70, 146.12, 141.40, 139.60, 133.97, 133.10, 131.64, 130.54, 128.96, 128.59, 128.19, 127.43, 127.10, 126.42, 126.13, 125.79, 125.57, 125.19, 123.56, 119.22, 86.54, 85.98, 54.90, 22.31. **HRMS (ESI+)** *m/z* calc'd for $C_{25}H_{20}O_3Na^+$: 391.1305. Found: 391.1307.

3-methoxy-5-methyl-6-(3-(naphthalen-2-yl)phenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (S2b). To a solution

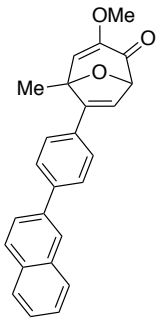


of 6-(3-bromophenyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one **1a** (25 mg, 0.078 mmol) in acetonitrile (2.5 mL) was added palladium(II) acetate (8.6 mg, 0.039 mmol) and sSPhos (40 mg, 0.078 mmol). The reaction mixture was stirred at room temperature for 5 minutes at which point a solution of 2-napthylboronic acid (134 mg, 0.78 mmol) and potassium carbonate (108 mg, 0.78 mmol) in H_2O (5 mL) was added. The reaction mixture was then heated in a 50 °C mineral oil bath for 2.5 hours and was subsequently allowed to cool to room temperature and concentrated *in vacuo* to remove acetonitrile. To the concentrated solution was

[2] Williams, Y. D.; Meck, C.; Mohd, N.; Murelli, R. P. *J. Org. Chem.*, 2013, **78**, 11707–11713.

added sat. NaCl (aq) (10 mL), and the organic material was extracted with $CHCl_3$ (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield crude 3-methoxy-5-methyl-6-(3-(naphthalen-1-yl)phenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2a). The reaction mixture was purified by chromatography (Biotage Isolera Prime, 10 g silica gel column, solvent gradient: 0% EtOAc in hexanes (3 CV); 0-50% EtOAc in hexanes (35 CV)). Product fractions were concentrated to yield **S2b** as a yellow oil (13 mg, 45% yield). Rf= 0.28 in 30% EtOAc in hexanes. **IR (thin film, KBr)** 3052 (w), 2940 (w), 2936 (m), 2838 (w), 1709 (s), 1604 (m), 1438 (w), 1342 (w), 1269 (w), 1173 (w), 1130 (s), 1059 (w), 987 (w), 856 (m), 796 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.03 – 8.01 (m, 1H), 7.97 – 7.87 (m, 3H), 7.73 – 7.68 (m, 2H), 7.61 (m, 1H), 7.56 – 7.48 (m, 3H), 7.29 (m, 1H), 6.39 (d, J = 2.5 Hz, 1H), 6.23 (s, 1H), 5.03 (d, J = 2.5 Hz, 1H), 3.62 (s, 3H), 1.76 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.96, 158.83, 146.12, 142.05, 138.08, 133.79, 133.74, 132.90, 129.33, 128.81, 128.34, 128.01, 127.84, 126.67, 126.39, 126.15, 125.53, 125.42, 124.84, 123.64, 119.25, 86.62, 86.01, 54.92, 22.36. **HRMS (ESI+)** *m/z* calc'd for $C_{25}H_{20}O_3Na^+$: 391.1305. Found: 391.1307.

3-methoxy-5-methyl-6-(4-(naphthalen-2-yl)phenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (S2c). To a solution of 6-(4-bromophenyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one **1b**[3] (25 mg, 0.078 mmol) in acetonitrile (2.5 mL) was added palladium(II) acetate (8.6 mg, 0.039 mmol) and sSPhos (40 mg, 0.078 mmol). The reaction mixture was stirred at room temperature for 5 minutes at which point a solution of 2-napthylboronic acid (134 mg, 0.78 mmol) and potassium carbonate (108 mg, 0.78 mmol) in H_2O (5 mL) was added. The reaction mixture was then heated in a 50 °C mineral oil bath for 2.5 hours and was subsequently allowed to cool to room temperature and concentrated *in vacuo* to remove acetonitrile. To the concentrated solution was added sat. NaCl (aq) (10 mL), and the organic material was extracted with $CHCl_3$ (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield crude 3-methoxy-5-methyl-6-(3-(naphthalen-1-yl)phenyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (2a). The reaction mixture was purified by chromatography (Biotage Isolera Prime, 10 g silica gel column, solvent gradient: 0% EtOAc in hexanes (3 CV); 0-50% EtOAc in hexanes (35 CV)). Product fractions were concentrated to yield **S2c** as a pale yellow solid (19 mg, 66% yield). MP= 197-200°C. Rf= 0.26 in 30% EtOAc in hexanes. **IR (thin film, KBr)** 3053 (w), 2940 (w), 2931 (w), 2833 (w), 1710 (s), 1600 (m), 1499 (w), 1437 (w), 1341 (w), 1264 (w), 1173 (m), 1131 (s), 1057 (w), 988 (w), 863 (m), 818 (m), 732 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 – 8.04 (m, 1H), 7.97 – 7.85 (m, 3H), 7.77 – 7.72 (m, 3H), 7.55 – 7.47 (m, 2H), 7.45 – 7.39 (m, 2H), 6.36 (d, *J* = 2.6 Hz, 1H), 6.24 (s, 1H), 5.03 (d, *J* = 2.5 Hz, 1H), 3.63 (s, 3H), 1.76 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.91, 158.47, 146.11, 141.60, 137.64, 133.75, 132.91, 132.08, 128.76, 128.35, 127.81, 127.77, 126.64, 126.60, 126.34, 125.93, 125.29, 123.11, 119.18, 86.52, 85.97, 54.86, 22.34. **HRMS (ESI+)** *m/z* calc'd for $C_{25}H_{20}O_3Na^+$: 391.1305. Found: 391.1303.

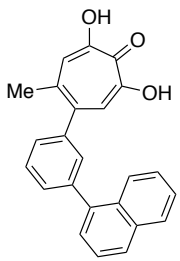


[3] Tavis, J. E.; Morrison, L. A.; Murelli, R. P. Preparation of Hydroxylated Tropolone Inhibitors of Nucleotidyl Transferases in Treatment of Herpesvirus and Hepatitis B. U. S. Patent WO 2016201243, Dec 15, 2016.

IIb. Synthesis and characterization of biaryl α-hydroxytropolones via TfOH/HBr/AcOH

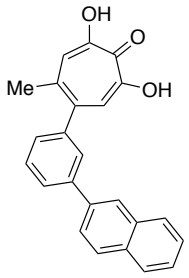
General Procedure. To a solution of 8-oxabicyclo[3.2.1]octene **S2a-c** in $CHCl_3$ (0.1 M) was added triflic acid (4 equiv). The mixture was stirred for 30 minutes at room temperature before quenching with an equivalent volume of pH 7 phosphate buffer. Extraction with $CHCl_3$ followed by concentration under reduced pressure isolated the methoxytropolone. To this compound was added HBr in AcOH (33%), and the solution was heated in a mineral oil bath at 120°C for 2 hours. The reaction mixture was then quenched with pH 7 phosphate buffer and filtered. The precipitate was azeotroped with $CHCl_3$ (3x) and concentrated under reduced pressure to afford α-hydroxytropolone **233-235**.

2,7-dihydroxy-4-methyl-5-(3-(naphthalen-1-yl)phenyl)cyclohepta-2,4,6-trien-1-one (235). To a solution of



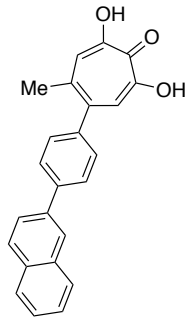
bicycle **S2a** (7 mg, 0.019 mmol) in $CHCl_3$ (190 µL) was added triflic acid (6.7 µL, 0.076 mmol). The mixture was stirred for 30 minutes at room temperature before quenching with an equivalent volume of pH 7 phosphate buffer. Extraction with $CHCl_3$ followed by concentration under reduced pressure isolated the methoxytropolone. To this compound was added 285 µL of a solution of HBr in AcOH (33%), and the solution was heated in a mineral oil bath at 120°C for 2 hours. The reaction mixture was then quenched with pH 7 phosphate buffer and filtered. The precipitate was azeotroped with $CHCl_3$ (3x) and concentrated under reduced pressure to yield **235** as a brown oil (5.1 mg, 76% yield over two steps). **IR (thin film, KBr)** 3236 (br), 3052 (w), 2917 (w), 2846 (w), 1700 (s), 1634 (w), 1617 (w), 1559 (m), 1520 (w), 1388 (w), 1279 (w), 1224 (m), 1125 (w), 1086 (w), 797 (m), 668 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 (s, 1H), 7.96 – 7.85 (m, 4H), 7.77 – 7.75 (m, 2H), 7.62 – 7.49 (m, 6H), 2.34 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.36, 157.85, 156.58, 144.32, 143.70, 141.68, 139.14, 137.91, 133.78, 132.90, 129.29, 128.75, 128.34, 127.81, 127.39, 127.34, 126.82, 126.60, 126.32, 126.10, 125.50, 124.43, 124.22, 26.68. **HRMS (ESI+)** *m/z* calc'd for $C_{24}H_{19}O_3^+$: 355.1329. Found: 355.1258.

2,7-dihydroxy-4-methyl-5-(3-(naphthalen-2-yl)phenyl)cyclohepta-2,4,6-trien-1-one (233). To a solution of



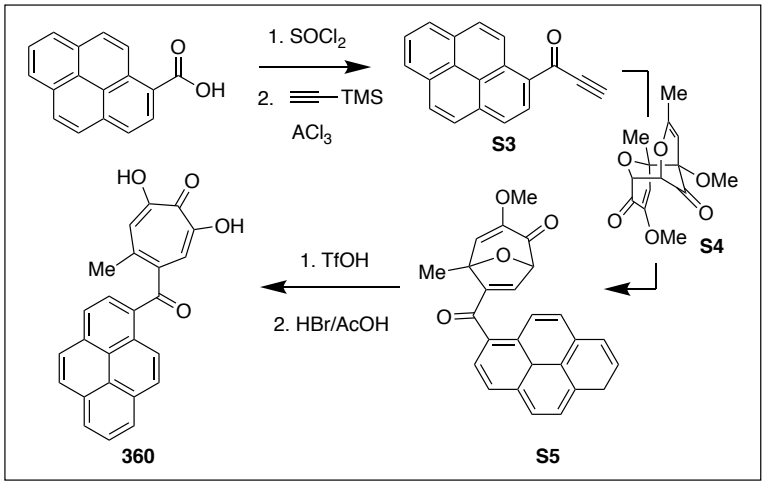
bicycle **S2b** (19 mg, 0.0516 mmol) in $CHCl_3$ (516 µL) was added triflic acid (18.2 µL, 0.206 mmol). The mixture was stirred for 30 minutes at room temperature before quenching with an equivalent volume of pH 7 phosphate buffer. Extraction with $CHCl_3$ followed by concentration under reduced pressure isolated the methoxytropolone. To this compound was added 500 µL of a solution of HBr in AcOH (33%), and the solution was heated in a mineral oil bath at 120°C for 2 hours. The reaction mixture was then quenched with pH 7 phosphate buffer and filtered. The precipitate was azeotroped with $CHCl_3$ (3x) and concentrated under reduced pressure to yield **233** as a black oil (8 mg, 44% yield over two steps). **IR (thin film, KBr)** 3240 (br), 3045 (w), 2919 (w), 2846 (w), 1700 (s), 1653 (m), 1506 (m), 1437 (w), 1387 (m), 1223 (m), 1124 (w), 1088 (w), 798 (m), 667 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 (s, 1H), 7.96 – 7.86 (m, 3H), 7.76 (m, 2H), 7.62 – 7.50 (m, 7H), 2.34 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.29, 157.87, 156.60, 144.32, 143.72, 141.68, 139.17, 137.91, 133.77, 132.90, 129.29, 128.76, 128.34, 127.81, 127.39, 127.34, 126.83, 126.61, 126.32, 126.10, 125.50, 124.46, 124.25, 26.69. **HRMS (ESI+)** *m/z* calc'd for $C_{24}H_{19}O_3^+$: 355.1329. Found: 391.1330.

2,7-dihydroxy-4-methyl-5-(4-(naphthalen-2-yl)phenyl)cyclohepta-2,4,6-trien-1-one (234). To a solution of

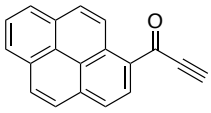


bicycle **S2c** (13 mg, 0.0353 mmol) in $CHCl_3$ (350 µL) was added triflic acid (12.5 µL, 0.141 mmol). The mixture was stirred for 30 minutes at room temperature before quenching with an equivalent volume of pH 7 phosphate buffer. Extraction with $CHCl_3$ followed by concentration under reduced pressure isolated the methoxytropolone. To this compound was added 500 µL of a solution of HBr in AcOH (33%), and the solution was heated in a mineral oil bath at 120°C for 2 hours. The reaction mixture was then quenched with pH 7 phosphate buffer and filtered. The precipitate was azeotroped with $CHCl_3$ (3x) and concentrated under reduced pressure to yield crude **3c** as a black oil. The product was purified via chromatography (Biotage Isolera Prime, 12 g C_{18} reversed-phase silica gel column, solvent gradient: 10% acetonitrile in H_2O (3 CV); 10-75% acetonitrile in H_2O (25 CV); 100% acetonitrile (10 CV)). Product fractions were concentrated to yield **234** as a yellow oil (1 mg, 8% yield over two steps). **IR (thin film, KBr)** 3251 (br), 2925 (w), 2844 (w), 1700 (m), 1653 (m), 1512 (m), 1387 (w), 1135 (w), 1088 (w), 811 (w), 668 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (s, 1H), 7.97 – 7.88 (m, 3H), 7.82 – 7.78 (m, 2H), 7.61 (s, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 2.34 (s, 3H). **Partial ^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.57, 140.65, 137.82, 133.82, 132.91, 129.04, 128.76, 128.38, 127.84, 127.67, 126.60, 126.31, 126.04, 125.48, 26.69. **HRMS (ESI+)** *m/z* calc'd for $C_{24}H_{19}O_3^+$: 355.1329. Found: 391.1332

III. Synthesis and characterization of pyrene-1-carbonyl αHT (360)

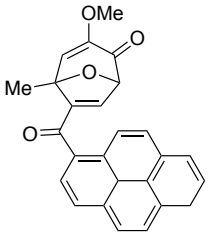


1-(pyren-1-yl)prop-2-yn-1-one (S3). Pyrene-1-carboxylic acid (5g, 20mM, 1eq) was stirred with thionyl chloride



(2 eq) for an hour at room temperature. After removing the thionyl chloride under reduced pressure, the crude reaction mixture was taken to next step as such. Closely following literature precedent,[4] in a round bottom flask, to a solution of acid chloride in CH_2Cl_2 (0.06M), TMS acetylene (2.1g, 22 mmol, 1.1 eq) is added. The flask was cooled to 0 ^{0}C, then $AlCl_3$ (9.36g, 70mmol, 3.2 eq) is added with vigorous stirring and left at 0 ^{o}C for 30 minutes. Then, the temperature was raised to room temperature, for 30 minutes. The reaction was quenched with 2M HCl and extracted with CH_2Cl_2. The organic layers were washed twice with saturated $NaHCO_3$ solution, followed by brine wash. After drying with Na_2SO_4, organic layers were filtered and concentrated under reduced pressure, to be used as such in next step (Crude yields >100%).

6-(3a[1],6-dihydropyrene-1-carbonyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (S5). To a

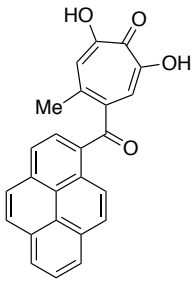


solution of (1R, 2S, 6S, 7R)-6,9-dimethoxy-4,7-dimethyl-3,11-dioxatricyclo[5.3.1.12,6]dodeca-4,8-diene-10,12-dione **S4**[5] (280 mg,1mmol, 1 eq) in $CDCl_3$ (0.5 M, 2 mL) in a sealed tube, was added crude alkynone **S3** (2000mg, 8mmol, 8 eq). After stirring at 120 ^{0}C, for 3 hours in an oil bath, the solvent was evaporated and crude material loaded onto column cartridge using 1-1.5 mL toluene, was purified by chromatography (Biotage Isolera Prime, SNAP 10g silica gel, 18cm x 1.8cm, 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 **S5** as a pale yellow solid (434 mg, 1.1mmol, 55 % yield). **MP:** 202-205 ^{o}C. **IR (ATR, ZnSe)** 3041 (w), 3011(w), 2977 (w), 2932 (w), 1708(s), 1638(s), 1605(s), 1587(s), 1501(m), 1447(w), 1380(w), 1179(w), 1124(s), 1057(m), 981(w), 908(s), 844(s). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.65 (d, *J* = 9.3 Hz, 1H), 8.25 (d, *J* = 7.7

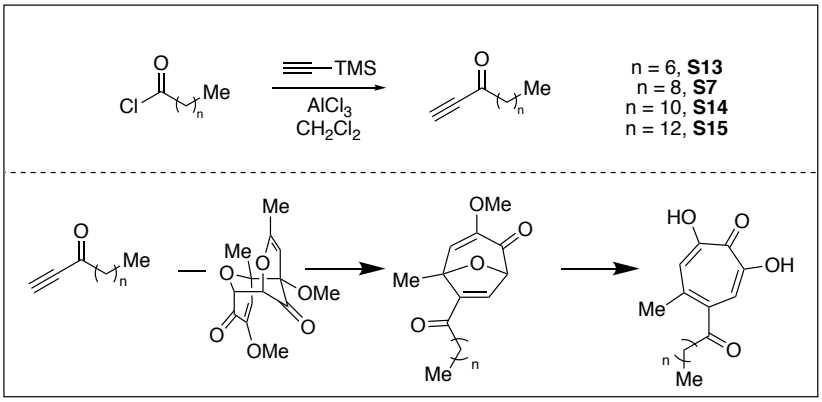
[4] Schubert, T.; Werner, H.; Maria-Regina, K.; Müller, M. *Eur. J. Org. Chem.* **2001**, *22*, 4181–4187.
[5] Meck, C.; Mohd, N.; Murelli, R. P. *Org. Lett.* **2012**, 14, 5988–5991.

Hz, 2H), 8.17 (ddd, *J* = 13.8, 9.5, 7.0 Hz, 4H), 8.10 – 8.00 (m, 2H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.42 (s, 1H), 5.16 (d, *J* = 2.5 Hz, 1H), 3.67 (s, 3H), 1.96 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 192.88, 188.58, 157.96, 145.29, 140.46, 134.20, 131.07, 130.55, 129.97, 129.77, 129.74, 127.75, 127.09, 126.62, 126.60, 126.37, 124.92, 124.23, 124.19, 123.76, 120.27, 86.90, 86.58, 54.87, 21.16. **HRMS (ESI+)**: *m/z* calc'd for $C_{26}H_{18}O_4H^+$: 395.1278. Found: 395.1293.

2,7-dihydroxy-4-methyl-5-(pyrene-1-carbonyl)cyclohepta-2,4,6-trien-1-one (360). A solution of BCl_3 (1.0 M in CH_2Cl_2, 2.1 mL, 2.1 mmol, 7 eq) was diluted with CH_2Cl_2 (0.21M, 10 mL) and cooled to 0°C. In a separate round bottom flask, **S5** (120 mg, 0.30 mmol, 1 eq) was dissolved in CH_2Cl_2 (0.028M, 10mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 minutes of stirring at 0 °C, the reaction mixture was quenched with H_2O (20 mL), stirred for 2 minutes at 0 °C, and then warmed to room temperature where it continued to stir for 1 hour. 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 2-hydroxy-7-methoxy-5-methyl-4-(pyrene-1-carbonyl)cyclohepta-2,4,6-trien-1-one (100 mg, 0.25mmol). The methoxytropolone was immediately transferred to a round bottom flask, fitted with reflux condenser and base trap, and a 33% HBr in acetic acid (0.09 M) was added to flask. The reaction was stirred at 120 °C for 1 hour. After 1 hour, reaction mixture was let to cool to room temperature. The reaction mixture was further cooled to 0 ^{o} C, to which phosphate buffer solution (pH =7), diluted with ice cold water was added. On standing at below 0^{o} C, a greenish yellow precipitate was filtered with a fritted funnel and dried under reduced pressure to yield **360** (23mg, 0.06 mmol, 23% yield) as a greenish-yellow solid. **MP**: >290 ^{o}C. **IR (ATR, ZnSe)** 3333 (br), 2919 (w), 2849 (w), 1617(s), 1657 (s), 1587 (s), 1498 (m), 1383(m), 1291(w), 1209(s), 1188(m), 1075(m), 908(s), 834(s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.34 (d, *J* = 9.4 Hz, 1H), 8.40 – 8.30 (m, 3H), 8.26 (d, *J* = 9.0 Hz, 1H), 8.16 – 8.07 (m, 3H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.58 (s, 1H), 7.53 (s, 1H), 2.42 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 199.52, 168.34, 158.79, 156.92, 141.91, 138.79, 135.25, 131.39, 131.02, 130.95, 130.78, 130.50, 130.09, 128.81, 127.11, 126.87, 126.77, 125.18, 124.62, 124.59, 124.10, 124.03, 119.87, 24.82. **HRMS (ESI+)**: *m/z* calc'd for $C_{25}H_{16}O_4H^+$: 381.1121. Found: 381.1118



IV. Aliphatic ketone αHT Synthesis



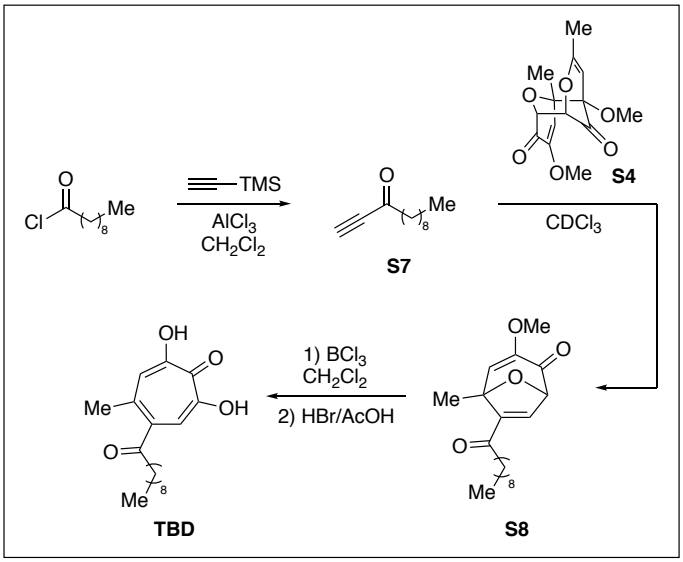
General Alkynone Procedure. In a round bottom flask, to a solution of acid chloride (1.0 eq) in CH_2Cl_2 (0.056 M), TMS acetylene (1.1 eq) is added. The flask was cooled to 0 °C, then $AlCl_3$ (14-28 mmol, 3.1 eq) is added with vigorous stirring and left at 0 °C for 30 minutes. Then, the temperature was raised to room temperature, for 30 minutes. The reaction was quenched with 2M HCl and extracted with CH_2Cl_2. The organic layers were washed twice with saturated $NaHCO_3$ solution, followed by brine wash. After drying with Na_2SO_4, organic layers were filtered and concentrated under reduced pressure, to be used as such in next step (Crude yields 80->100%).

IVa. Synthesis and characterization of heptane ketone αHT (380)

3-methoxy-5-methyl-6-octanoyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (S6). To a solution of (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 **S4** (280 mg, 1 mmol, 1 eq) in $CDCl_3$ (0.5 M, 2 mL) in a sealed tube, was added crude alkynone **S13** (1.2 g, 8 mmol, 8 eq). After stirring at 120 °C, for 30 minutes under microwave irradiation, the solvent was evaporated and crude material loaded onto column cartridge using 1-1.5 mL toluene, was purified by chromatography (Biotage Isolera Prime, SNAP 10g silica gel, 18cm x 1.8cm, 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 **S6** as a pale brown oil (406 mg, 70% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.99 (d, *J* = 2.5 Hz, 1H), 6.10 (s, 1H), 5.04 (d, *J* = 2.6 Hz, 1H), 3.53 (s, 3H), 2.74 – 2.56 (m, 2H), 1.71 (s, 3H), 1.67 – 1.50 (m, 3H), 1.28 (dd, *J* = 8.8, 4.7 Hz, 6H), 0.87 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.20, 188.74, 155.93, 144.80, 137.56, 119.63, 85.97, 85.68, 54.43, 39.95, 31.44, 28.89, 28.86, 23.89, 22.39, 21.02, 13.88. **HRMS (ESI+)**: *m/z* calc'd for $C_{17}H_{24}O_4Na^+$:315.1567. Found: 315.1571.

2,7-dihydroxy-4-methyl-5-octanoylcyclohepta-2,4,6-trien-1-one (380). A solution of BCl_3 (1.0 M in CH_2Cl_2, 0.93-1.19 mL, 0.93-1.19 mmol, 7 eq) was diluted with CH_2Cl_2 (0.18M, 5 mL) and cooled to 0 °C. In a separate round bottom flask, **S6** (50 mg, 0.17 mmol, 1 eq) was dissolved in CH_2Cl_2 (0.028M, 5mL), was cooled to 0 °C and was added to the BCl_3 solution. After 10 minutes of stirring at 0 °C, the reaction mixture was quenched with H_2O (10 mL), stirred for 2 minutes at 0 °C, and then warmed to room temperature where it continued to stir for 1 hour. 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 a mixture of hydroxytropolone and methoxytropolone. This mixture was added to a round bottom flask fitted with reflux condenser and base trap, and a 33% HBr in acetic acid (0.09 M) was added to flask, and the reaction was heated to 120 °C for 1 hour. After 1 hour, reaction mixture was let to cool to room temperature. The reaction mixture was further cooled to below 0 ^{o} C, to which phosphate buffer solution (pH =7), diluted with ice cold water was added. On standing at below 0^{o}C, a brown precipitate was filtered with a fritted funnel and dried under reduced pressure. They were further purified using reverse phase column chromatography conditions (Biotage Isolera Prime, SNAP 12g C18 silica gel column, solvent gradient: 2-85% acetonitrile in water (35 CV); acetonitrile and water each contained 0.05% TFA)). Crude material loaded onto column cartridge using 1-1.5 mL DMSO. Product fractions were concentrated to yield **380** (2.1 mg, 4.4 % yield). **IR (ATR, ZnSe)** 3080 (w), 2960 (br), 2922 (br), 2849 (br), 1696(s), 1647 (s), 1538(s), 1511 (s), 1057(m), 896(w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.28 (s, 1H), 2.78 (t, *J* = 7.4 Hz, 2H), 2.39 (s, 3H), 1.70 (d, *J* = 7.4 Hz, 3H), 1.42 – 1.14 (m, 8H), 0.97 – 0.66 (m, 5H). **Partial ^{13}C NMR (100 MHz, $CDCl_3$)** δ 117.43, 43.19, 31.64, 29.71, 29.15, 29.06, 24.29, 23.83, 22.60, 14.06. **HRMS (ESI+)**: *m/z* calc'd for $C_{16}H_{23}O_4Na^+$: 279.1591. Found: 279.1589.

IVb. Synthesis and characterization of nonane ketone αHT (792)



Dodec-1-yn-3-one (S7). To a solution of decanoyl chloride (919 µL, 5.24 mmol) in CH_2Cl_2 (87 mL) was added trimethylsilyl acetylene (800 µL, 5.77 mmol), and the mixture was cooled to 0 °C. To this mixture was added aluminum chloride (2.24 g, 16.77 mmol) was added, and the

mixture was stirred at 0 °C for 30 min. The solution was then allowed to come to rt, at which point it was stirred for an additional 30 min. The reaction was quenched with 30 mL of 2M HCl, and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *en vacuo* to yield crude **S7** as an orange oil (84% crude yield). The crude alkynone was used without further purification in the next step.

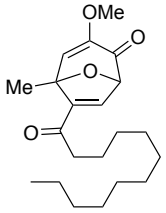
6-decanoyl-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (S8). To a solution of dimer **S4** (69 mg, .25 mmol) in $CDCl_3$ (500 μL) was dodec-1-yn-3-one **S7** (355 mg, 1.97 mmol). The reaction mixture was subjected to microwave irradiation at 120 °C for 30 min, at which point the solution was concentrated *en vacuo*. The residue was then dissolved in ~1 mL of CH_2Cl_2, and subjected to normal-phase column chromatography conditions (Biotage Isolera Prime, SNAP 10g silica gel column, solvent gradient: 5% EtOAc in hexane (6 CV); 10% EtOAc in hexane (12 CV); 20% EtOAc in hexane (12 CV); 100% EtOAc (5 CV)). Product fractions were concentrated *en vacuo* to yield **S8** as a yellow oil (126.3 mg, 79% yield). Rf= 0.15 in 10% EtOAc in hexanes. **IR (thin film, KBr)** 2926 (s), 2855 (m), 1715 (s), 1671 (m), 1610 (m), 1456 (m), 1376 (w), 1342 (w), 1128 (s), 1049 (w), 989 (w), 868 (m), 656 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.99 (d, *J* = 2.6 Hz, 1H), 6.09 (s, 1H), 5.02 (d, *J* = 2.6 Hz, 1H), 3.51 (s, 3H), 2.70 – 2.60 (m, 2H), 1.69 (s, 3H), 1.60 – 1.51 (m, 2H), 1.27 – 1.22 (m, 12H), 0.85 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.48, 189.06, 156.26, 145.06, 137.61, 119.84, 86.27, 85.91, 54.74, 40.27, 31.92, 29.47, 29.46, 29.32, 29.23, 24.17, 22.73, 21.30, 14.18. **HRMS (ESI+)** *m/z* calc'd for $C_{19}H_{28}O_4Na^+$: 343.1880. Found: 343.1862.

4-decanoyl-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (792). A solution of bicycle **S8** (66.1 mg, 0.206 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C. In a separate flask, a 1.0M solution of boron trichloride in CH_2Cl_2 (1.44 mL, 1.44 mmol) had CH_2Cl_2 (15 mL) added, and was cooled to 0 °C. The solution containing **S8** was added to the boron trichloride solution, and the mixture was stirred for 10 minutes at 0 °C. To this mixture was added H_2O (10 mL), and the solution was stirred for 2 minutes at 0 °C. The reaction was then allowed to come to rt and stirred for an additional 60 minutes. The organic layer was pipetted out, extracted with CH_2Cl_2 (3 x 5 mL), and concentrated *en vacuo* to yield the methoxytropolone as an orange solid. To this compound was added 2.3 mL of a solution of HBr in AcOH (33%), and the solution was heated in a mineral oil bath at 120 °C for 1 hour. The reaction mixture was then quenched with pH 7 phosphate buffer, and extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *en vacuo* to yield crude **S9** as a brown oil. This residue was then dissolved in methanol (5 mL), and washed with hexane (3 x 2 mL). The methanol layer was then concentrated *en vacuo* to yield **792** as a brown oil (7 mg, 11% yield over two steps). **IR (thin film, KBr)** 3234 (br), 2954 (s), 2854 (m), 1705 (s), 1608 (w), 1533 (m), 1457 (w), 1395 (m), 1283 (w), 1157 (w), 1132 (m), 1065 (s), 897 (m), 722 (m), 669 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.28 (s, 1H), 2.78 (t, *J* = 7.4 Hz, 2H), 2.39 (s, 3H), 1.73 – 1.68 (m, 2H), 1.28 – 1.24 (m, 12H), 0.90 – 0.86 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.81, 168.19, 158.74, 157.37, 142.06, 137.32, 124.87, 117.85, 43.33, 31.99, 31.74,

29.54, 29.39, 29.33, 24.43, 23.97, 22.81, 14.25. **HRMS (ESI+)** *m/z* calc'd for $C_{18}H_{27}O_4^+$: 307.1904. Found: 307.1890.

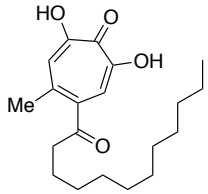
IVc. Synthesis and characterization of undecane ketone αHT (351)

6-(dodecanoyl)-3-methoxy-5-methyl-8-oxabicyclo [3.2.1] octa-3,6-dien-2-one (S9). To a solution of dimer **S4**



(280 mg, 1 mmol, 1 eq) in $CDCl_3$ (0.5 M, 2 mL) in a sealed tube, was added crude alkynone **S14** (1.66 g, 8 mmol, 8 eq). After stirring at 120 ^{0}C for 30 minutes under microwave irradiation, the solvent was evaporated and crude material loaded onto column cartridge using 1-1.5 mL toluene, was purified by chromatography (Biotage Isolera Prime, SNAP 10g silica gel, 18cm x 1.8cm, 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 **S9** (400 mg, 1.15 mmol, 57%) as a pale brown solid. MP= 59-62 ^{o}C. **IR (ATR, ZnSe)** 3087 (w), 2919 (br), 2950 (br), 2852 (br), 1711 (s), 1666 (s), 1608 (s), 1456 (s), 1377(m), 1118(s), 1051(m), 987(m), 859(m), 841(m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.02 (d, *J* = 2.6 Hz, 1H), 6.11 (s, 1H), 5.05 (d, *J* = 2.6 Hz, 1H), 3.54 (s, 3H), 2.75 – 2.58 (m, 2H), 1.72 (s, 3H), 1.66 – 1.51 (m, 2H), 1.40 – 1.13 (m, 18H),0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.32, 188.90, 156.16, 144.97, 137.49, 119.70, 86.16, 85.82, 54.63, 40.16, 31.87, 29.56, 29.41, 29.36, 29.30, 29.13, 24.06, 22.65, 21.20, 14.09. **HRMS (ESI+)**: *m/z* calc'd for $C_{21}H_{32}O_4H^+$: 349.2373. Found: 349.2363.

4-dodecanoyl-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (351). A solution of BCl_3 (1.0 M in CH_2Cl_2,



1.3 mL, 1.3 mmol, 7 eq) was diluted with CH_2Cl_2 (13 mL) and cooled to 0°C. In a separate round bottom flask, **S9** (64 mg, 0.18 mmol, 1 eq) was dissolved in CH_2Cl_2 (13 mL), was cooled to 0°C and was added to the diluted BCl_3 solution. After 10 minutes of stirring at 0°C, the reaction mixture was quenched with H_2O (10 mL), stirred for 2 minutes at 0°C, and then warmed to room temperature where it continued to stir for 1 hour. 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 a mixture of hydroxytropolone and methoxytropolone. This mixture was added to a round bottom flask fitted with reflux condenser and base trap, and a 33% HBr in acetic acid (0.09 M) was added to flask, and the reaction was heated to 120 °C for 1 hour. After 1 hour, reaction mixture was let to cool to room temperature. The reaction mixture was further cooled to below 0 ^{o} C, to which phosphate buffer solution (pH =7), diluted with ice cold water was added. On standing at below 0^{o}C, a brown precipitate was filtered with a fritted funnel and dried under reduced pressure. They were further purified using reverse phase column chromatography conditions (Biotage Isolera Prime, SNAP 12g C18 silica gel column, solvent gradient: 2-85% acetonitrile in water (35 CV); acetonitrile and water each contained 0.05% TFA)). Crude material loaded onto column cartridge using 1-1.5 mL DMSO to yield **351** (7.6 mg, 6% yield) as a pale brown solid. MP= 62-65 ^{o}C. **IR (ATR, ZnSe)** 3233 (w), 2955 (br), 2922 (br), 2852 (br), 1688 (s), 1555 (s), 1503 (s), 1468 (w), 1403 (w), 1290 (m), 1223(m), 1162(s), 1098(m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.28 (s, 1H), 2.78 (t, *J* = 7.4 Hz, 2H), 2.39 (s, 3H), 1.76 – 1.62 (m, 2H),1.40 – 1.17 (m, 18H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ

206.65, 168.11, 158.58, 157.22, 141.90, 137.13, 124.67, 117.65, 43.18, 31.90, 29.58, 29.44, 29.39, 29.32, 29.19, 24.28, 23.83, 22.68, 14.11. **HRMS (ESI+)**: *m/z* calc'd for $C_{20}H_{30}O_4H^+$: 335.2217. Found: 335.2216.

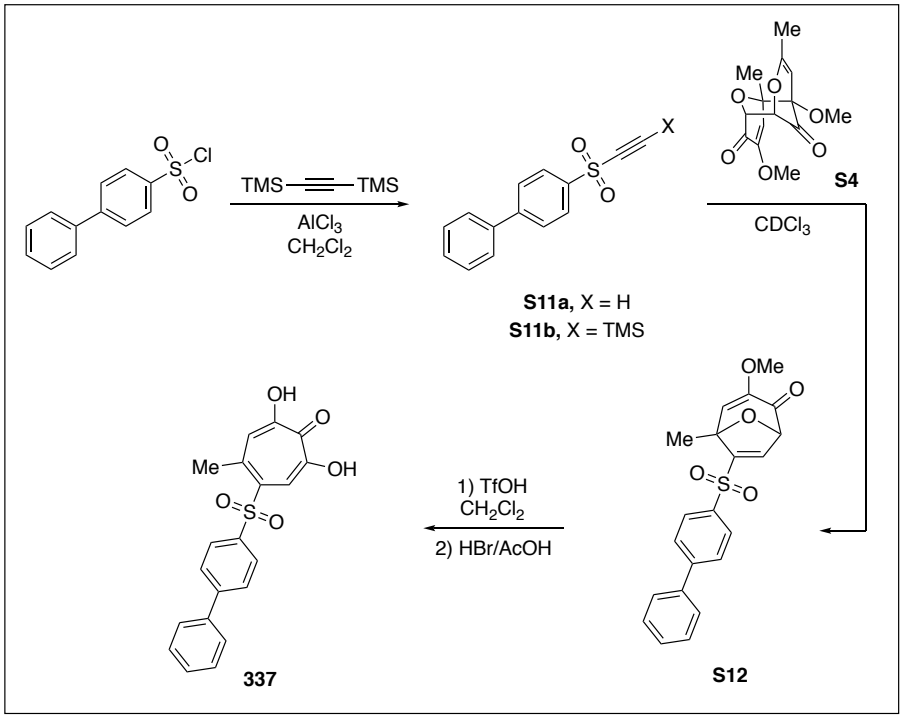
IVd. Synthesis and characterization of tridecane ketone αHT (381)

3-methoxy-5-methyl-6-tetradecanoyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (S10). To a solution of dimer **S4** (280 mg, 1 mmol, 1 eq) in $CDCl_3$ (0.5 M, 2 mL) in a sealed tube, was added crude alkynone **S15** (1.88 g, 8 mmol, 8 eq). After stirring at 120 ^{0}C, for 30 minutes under microwave irradiation, the solvent was evaporated and crude material loaded onto column cartridge using 1-1.5 mL toluene, was purified by chromatography (Biotage Isolera Prime, SNAP 10g silica gel, 18cm x 1.8cm, 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 **S10** as a pale brown solid (360 mg, 48% yield). **IR (ATR, ZnSe)** 3090(w), 2959 (br), 2922 (br), 2855 (br), 1711(s), 1663 (s), 1605(s), 1447 (br), 1374 (br), 1337(w), 1285(m), 1124(s), 1045(m), 984(m), 911(s), 862(m), 847(w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.98 (s, 1H), 6.09 (d, *J* = 1.2 Hz, 1H), 5.10 – 4.96 (m, 1H), 3.60 – 3.43 (m, 3H), 2.65 (dd, *J* = 11.0, 3.8 Hz, 2H), 1.70 (d, *J* = 1.6 Hz, 3H), 1.59 (s, 2H), 1.23 (s, 21H), 0.91 – 0.75 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.59, 189.17, 156.44, 145.24, 137.73, 119.96, 86.42, 86.09, 54.90, 40.43, 32.16, 29.91, 29.88, 29.83, 29.68, 29.62, 29.59, 29.40, 24.32, 22.93, 21.47, 14.36. **HRMS (ESI+)**: *m/z* calc'd for $C_{23}H_{36}O_4Na^+$: 399.2506. Found: 399.2508.

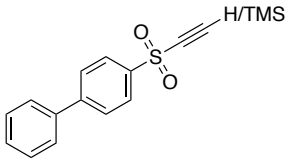
2,7-dihydroxy-4-methyl-5-tetradecanoylcyclohepta-2,4,6-trien-1-one (381). A solution of BCl_3 (1.0 M in CH_2Cl_2, 0.93-1.19 mL, 0.93-1.19 mmol, 7 eq) was diluted with CH_2Cl_2 (0.18M, 5 mL) and cooled to 0°C. In a separate round bottom flask, **S10** (50 mg, 0.13 mmol, 1 eq) was dissolved in CH_2Cl_2 (0.028M, 5mL), was cooled to 0°C and was added to the BCl_3 solution. After 10 minutes of stirring at 0°C, the reaction mixture was quenched with H_2O (10 mL), stirred for 2 minutes at 0°C, and then warmed to room temperature where it continued to stir for 1 hour. 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 a mixture of hydroxytropolone and methoxy tropolone (39 mg crude yield). This mixture was added to a round bottom flask fitted with reflux condenser and base trap, and a 33% HBr in acetic acid (0.09 M) was added to flask, and the reaction was heated to 120 °C for 1 hour. After 1 hour, reaction mixture was let to cool to room temperature. The reaction mixture was further cooled to below 0 ^{o} C, to which phosphate buffer solution (pH =7), diluted with ice cold water was added. On standing at below 0^{o}C, a brown precipitate was filtered with a fritted funnel and dried under reduced pressure. They were further purified using reverse phase column chromatography conditions (Biotage Isolera Prime, SNAP 12g C18 silica gel column, solvent gradient: 2-85% acetonitrile in water (35 CV); acetonitrile and water each contained 0.05% TFA)). Crude material loaded onto column cartridge using 1-1.5 mL DMSO. Product fractions were concentrated to yield **381** as a browl oil (8.7 mg, 0.024 mmol, 23 % yield). **IR (ATR, ZnSe)** 2950 (w), 2935 (br), 2901 (w), 2846 (br), 1702(s), 1538 (s), 1459 (s), 1383 (br), 1273(m), 1097(m), 914 (w) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.28 (s, 1H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 1.69 (d, *J* = 7.1 Hz, 2H), 1.26 (s, 24H),

0.88 (t, J = 6.6 Hz, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.69, 168.25, 157.21, 141.88, 137.12, 124.66, 117.63, 77.34, 77.23, 77.03, 76.71, 43.19, 31.93, 29.67, 29.64, 29.59, 29.45, 29.40, 29.36, 29.20, 24.29, 23.83, 22.70, 14.13. **HRMS (ESI+)**: *m/z* calc'd for $C_{22}H_{35}O_4^+$: 363.2530. Found: 363.2509.

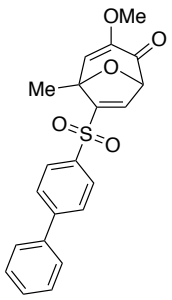
V. Synthesis and characterization of biphenyl sulfonyl αHT (337)



4-(ethynylsulfonyl)-1,1'-biphenyl (S11a/b). To a solution of (1,1'-biphenyl)-4-sulfonyl chloride (1.0 g, 3.96 mmol) in CH_2Cl_2 (12 mL) was added aluminum chloride (528 mg, 3.96 mmol). After stirring at rt for 30 min, bis(trimethylsilyl)acetylene (797 µL, 3.96 mmol) was added, and the mixture was allowed to stir overnight at rt. The solution was then concentrated *en vacuo*, dissolved in ~1 mL of CH_2Cl_2, and subjected to normal-phase column chromatography conditions (Biotage Isolera Prime, SNAP 10g silica gel column, solvent gradient: 100% hexane (7 CV); 5% EtOAc in hexane (12 CV); 10% EtOAc in hexane (1 CV); 20% EtOAc in hexane (16 CV); 100% EtOAc (15 CV)). Product fractions were concentrated *en vacuo* to yield a 70:30 mixture of **S11a** and **S11b** as an orange oil. The mixture was used without further purification in the following step.

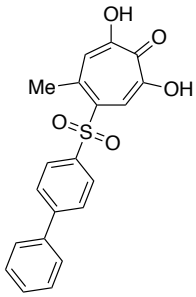


6-([1,1'-biphenyl]-4-ylsulfonyl)-3-methoxy-5-methyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (S12). To a solution of dimer **S4** (93 mg, .332 mmol) in $CDCl_3$ (664 µL) was added 4-(ethynylsulfonyl)-1,1'-biphenyl **S11a/b** (112.7 mg, .465 mmol based on **S11a**). The reaction mixture was subjected to microwave irradiation at 120 °C for 30 min, at which point the solution was concentrated *en vacuo*. The residue was then dissolved in ~1 mL of CH_2Cl_2, and subjected to normal-phase column chromatography conditions (Biotage Isolera Prime, SNAP 10g silica gel column, solvent gradient: 5% EtOAc in hexane (13 CV); 10% EtOAc in hexane (11 CV); 20% EtOAc in hexane (5 CV); 25% EtOAc in hexane (6 CV); 100% EtOAc (5 CV)). Product fractions were concentrated en vacuo to yield **S12** as a clear oil (63.5 mg, 36% yield based on S2a). **IR (ATR, ZnSe)** 2983 (w), 2937 (w), 2829 (w), 1720 (s), 1603 (s), 1475 (m), 1394 (m), 1312 (s), 1273 (w), 1158 (s), 1106 (s), 991 (m), 861 (m), 759 (m), 729 (m) cm^{-1}. **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.63 – 7.44 (m, 5H), 6.98 (d, *J* = 2.5 Hz, 1H), 5.81 (s, 1H), 5.05 (d, *J* = 2.5 Hz, 1H), 3.43 (s, 3H), 1.70 (s, 3H). **^{13}C NMR (50 MHz, $CDCl_3$)** δ 187.17, 158.64, 147.52, 145.35, 138.77, 138.56, 137.23, 129.35, 129.13, 129.08, 128.17, 127.47, 118.99, 86.13, 85.69, 54.82, 21.51. **HRMS (ESI+)** *m/z* calc'd for $C_{21}H_{19}O_5S^+$: 383.0948. Found: 383.0950.



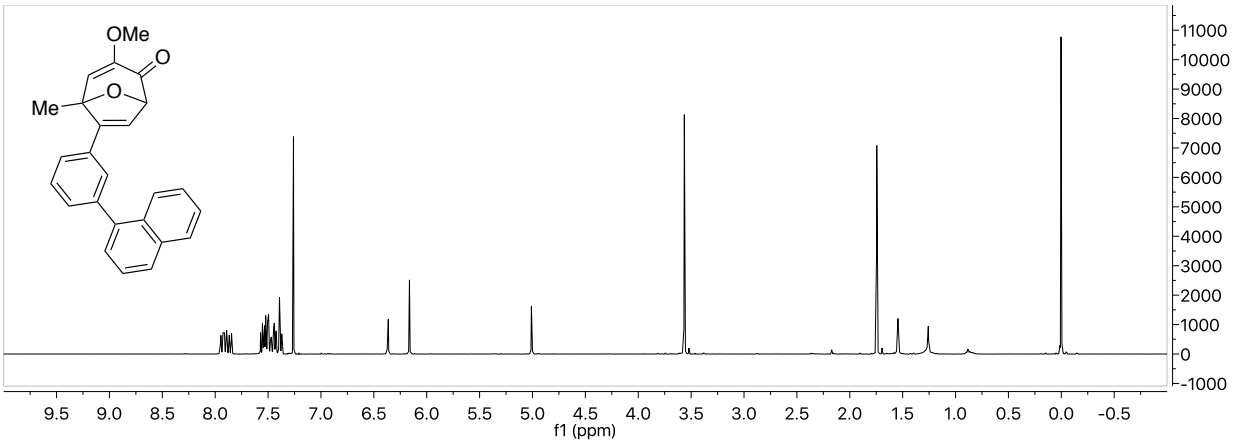
4-([1,1'-biphenyl]-4-ylsulfonyl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (337).

To a solution of bicycle **S12** (32 mg, 0.084 mmol) in CH_2Cl_2 (840 µL) was added triflic acid (29.5 µL, 0.335 mmol). The mixture was stirred for 30 minutes at rt before quenching with 10 mL pH 7 phosphate buffer. Extraction with CH_2Cl_2 (3 x 5 mL) followed by concentration *en vacuo* isolated the methoxytropolone as an orange solid. To this compound was added 933 µL of a solution of HBr in AcOH (33%), and the solution was heated in a mineral oil bath at 120 °C for 1 hour. The reaction mixture was then quenched with pH 7 phosphate buffer, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *en vacuo* to yield **337** as a yellow oil (4.2 mg, 14% yield over two steps). **IR (thin film, KBr)** 3254 (br), 2924 (m), 1593 (w), 1549 (s), 1394 (m), 1314 (s), 1287 (s), 1159 (s), 1087 (m), 981 (w), 721 (w), 680 (m), 614 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.75 (s, 1H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.61 – 7.56 (m, 2H), 7.50 – 7.42 (m, 4H), 2.64 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.76, 160.35, 155.89, 146.80, 142.49, 139.15, 139.06, 138.99, 129.29, 128.97, 128.26, 128.06, 127.51, 124.97, 119.77, 25.88. **HRMS (ESI+)** *m/z* calc'd for $C_{20}H_{17}O_5S^+$: 369.0791. Found: 369.0787.

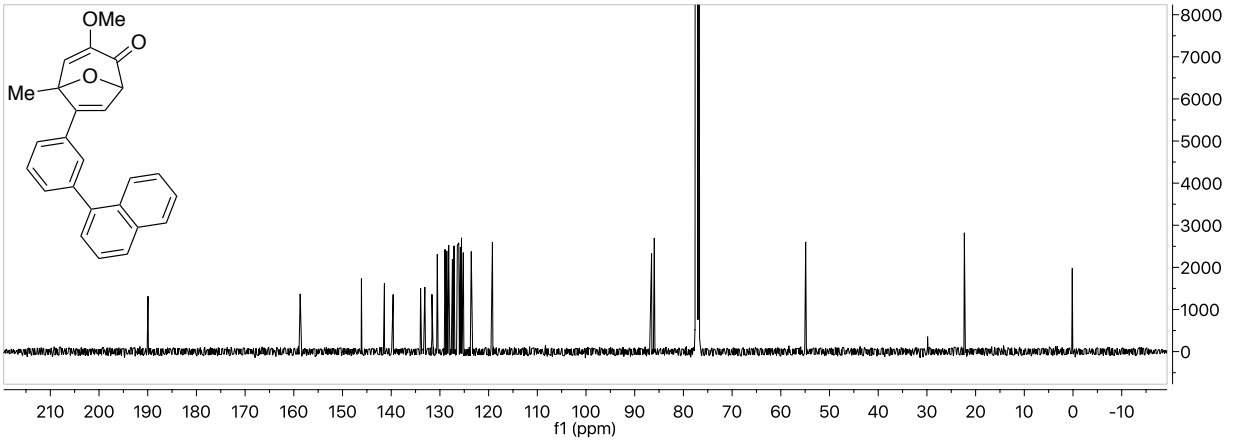


VI. NMR Spectra of new compounds (in order of table of contents)

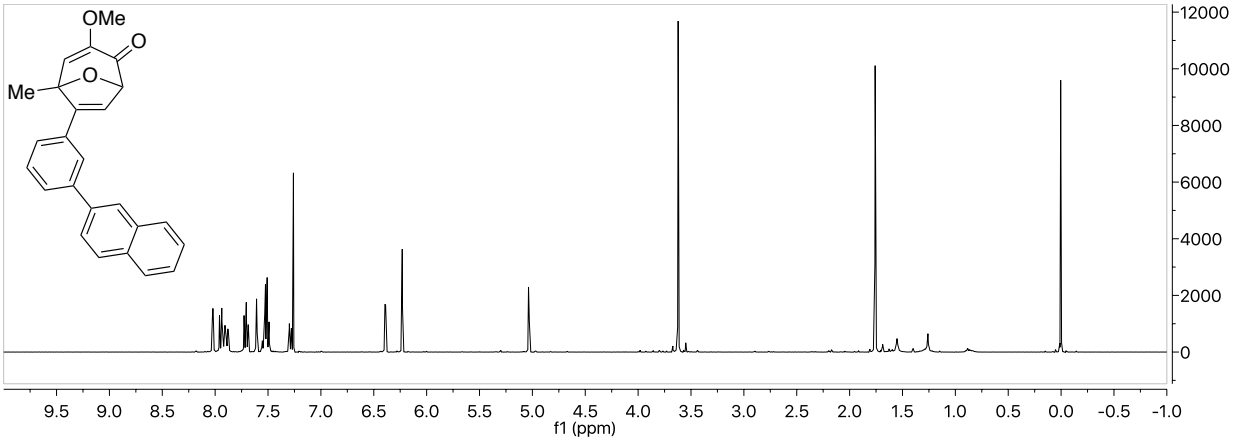
^{1}H NMR of S2a



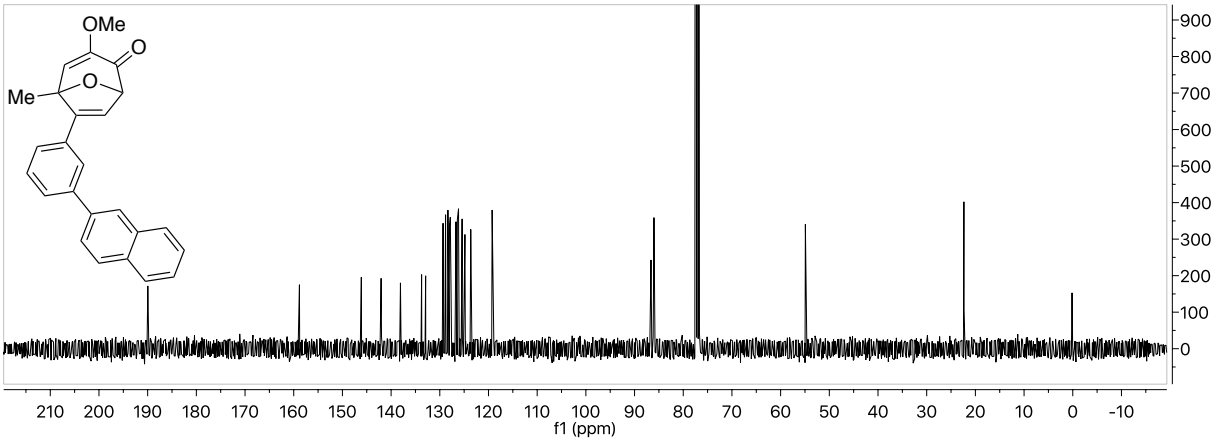
^{13}C NMR of S2a



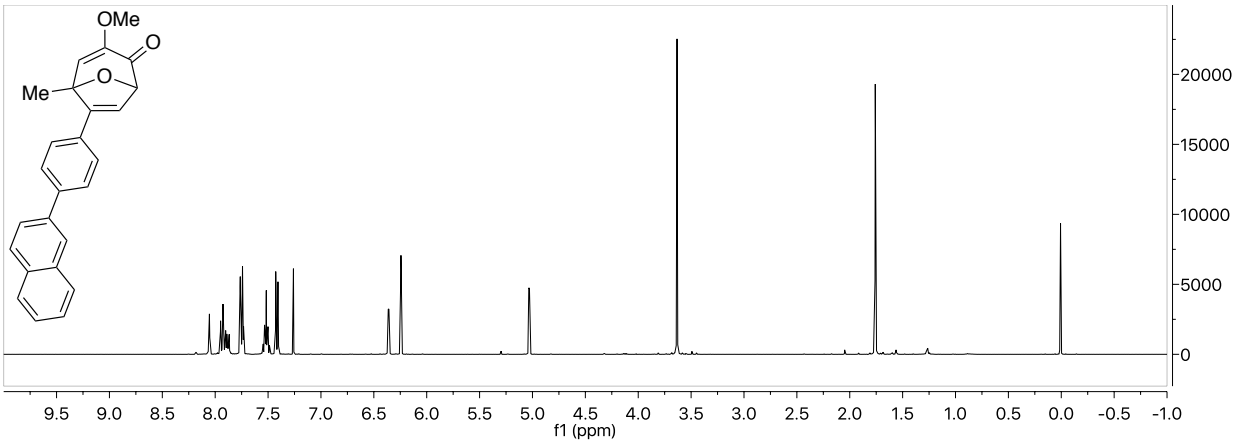
^{1}H NMR of S2b



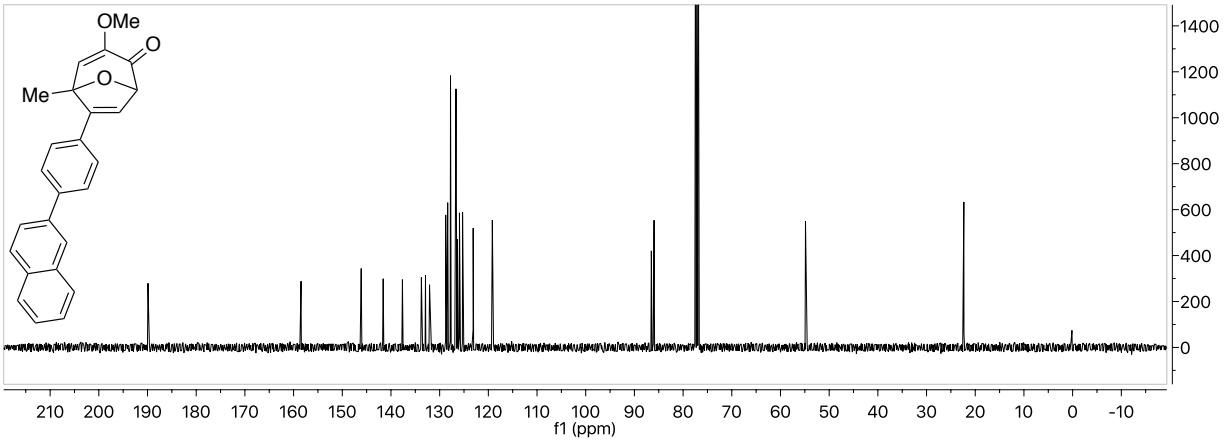
^{13}C NMR of S2b



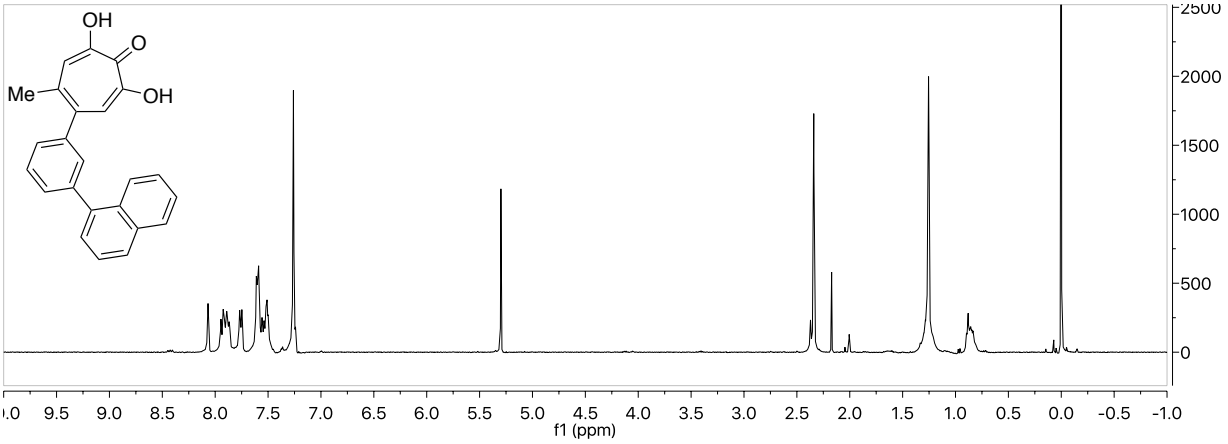
^{1}H NMR of S2c



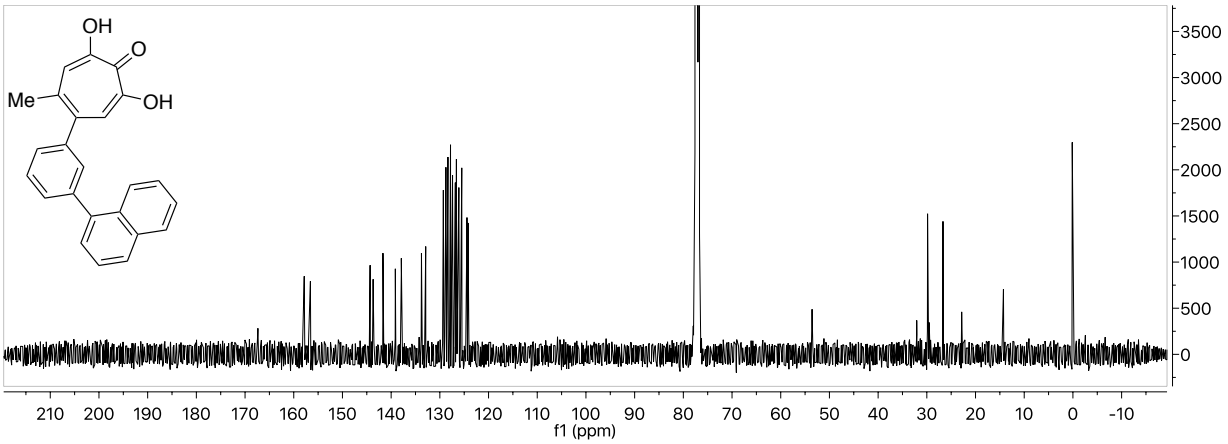
^{13}C NMR of S2c



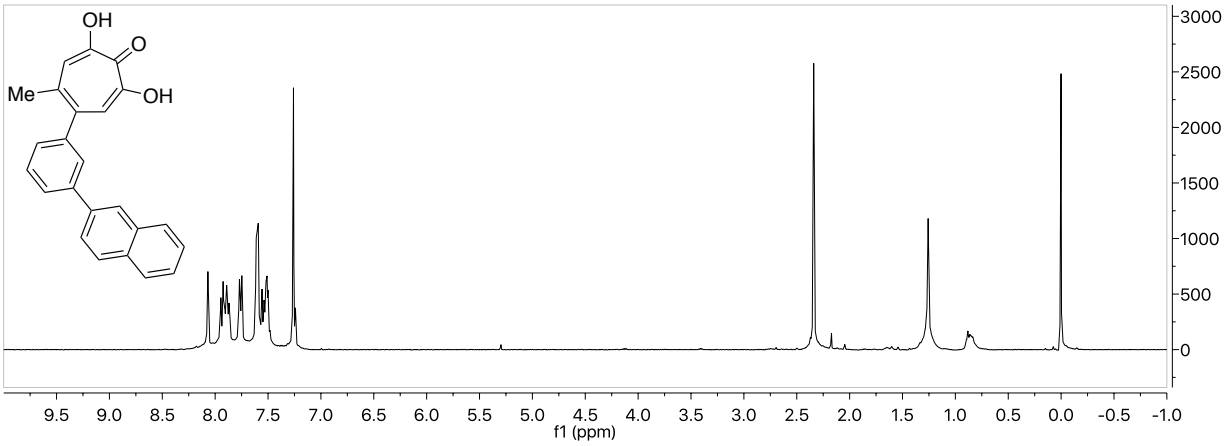
^{1}H NMR of 235



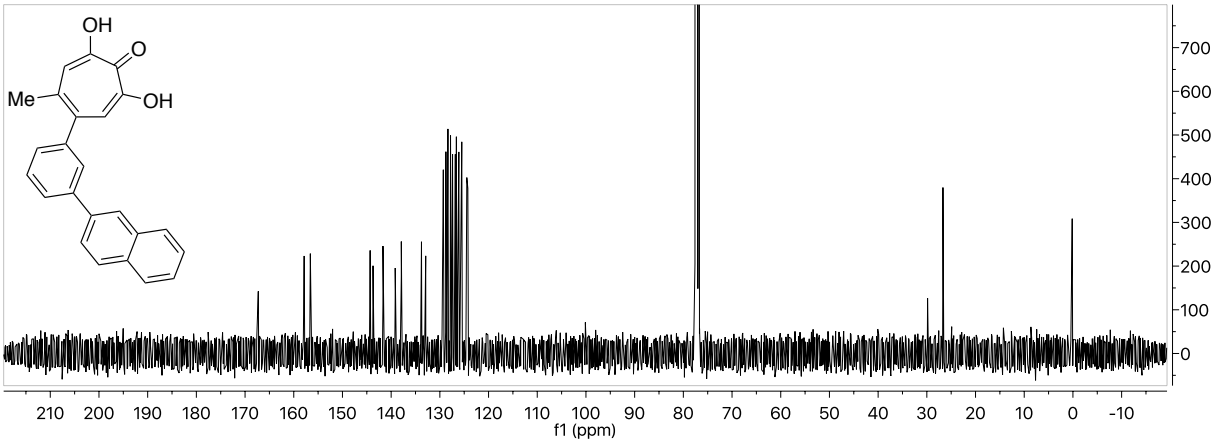
^{13}C NMR of 235



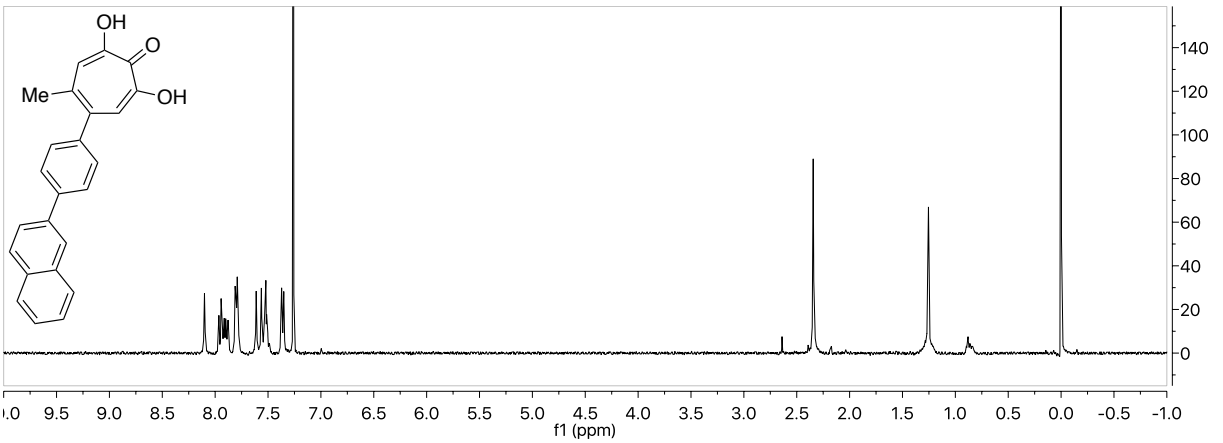
^{1}H NMR of 233



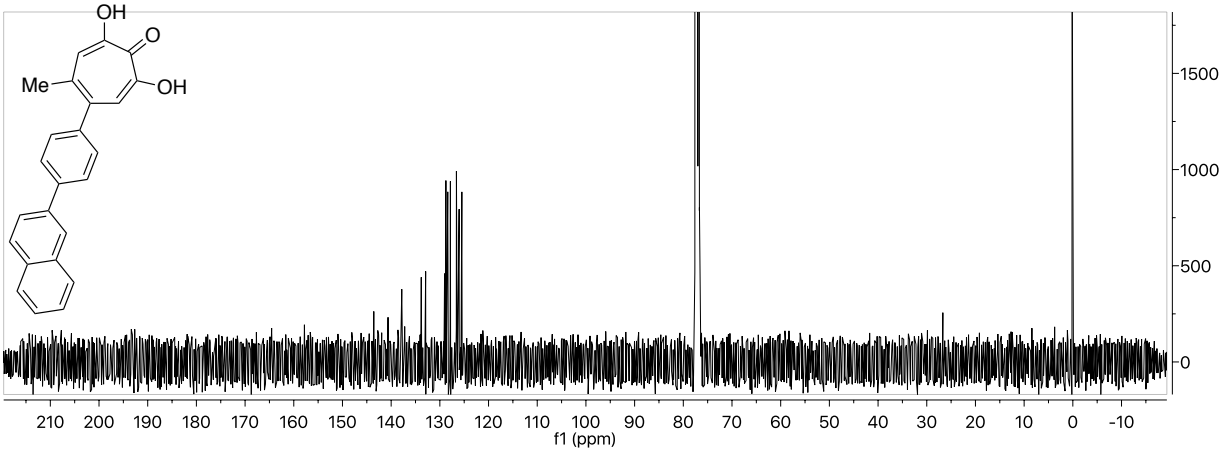
^{13}C NMR of 233



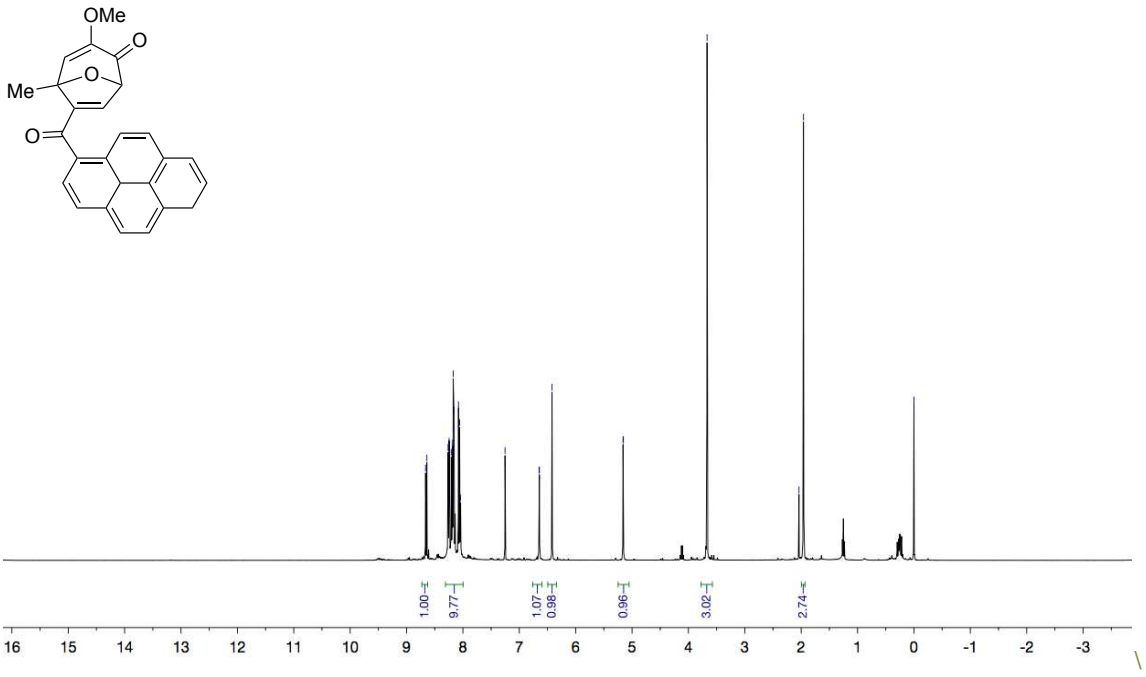
^{1}H NMR of 234



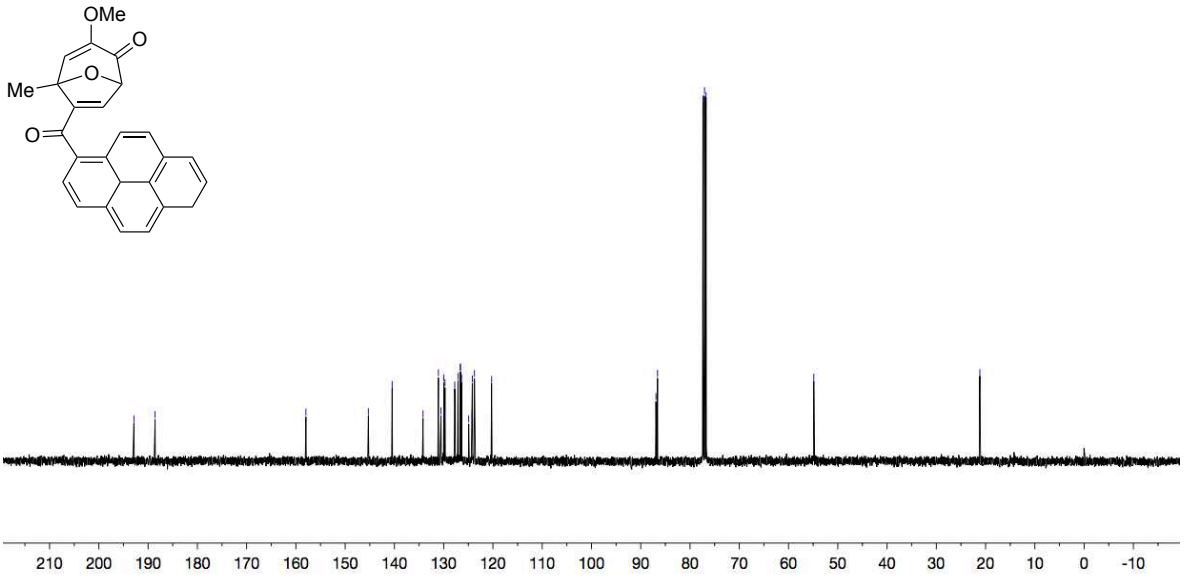
^{13}C NMR of 234 (partial)



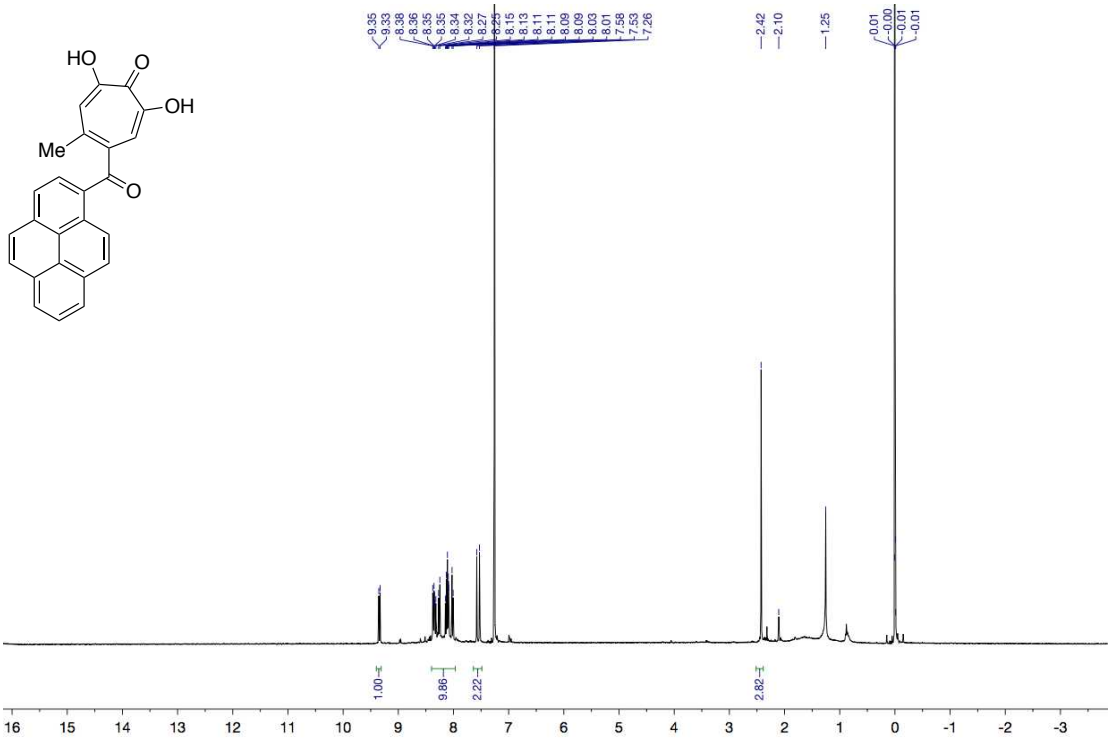
^{1}H NMR of S5



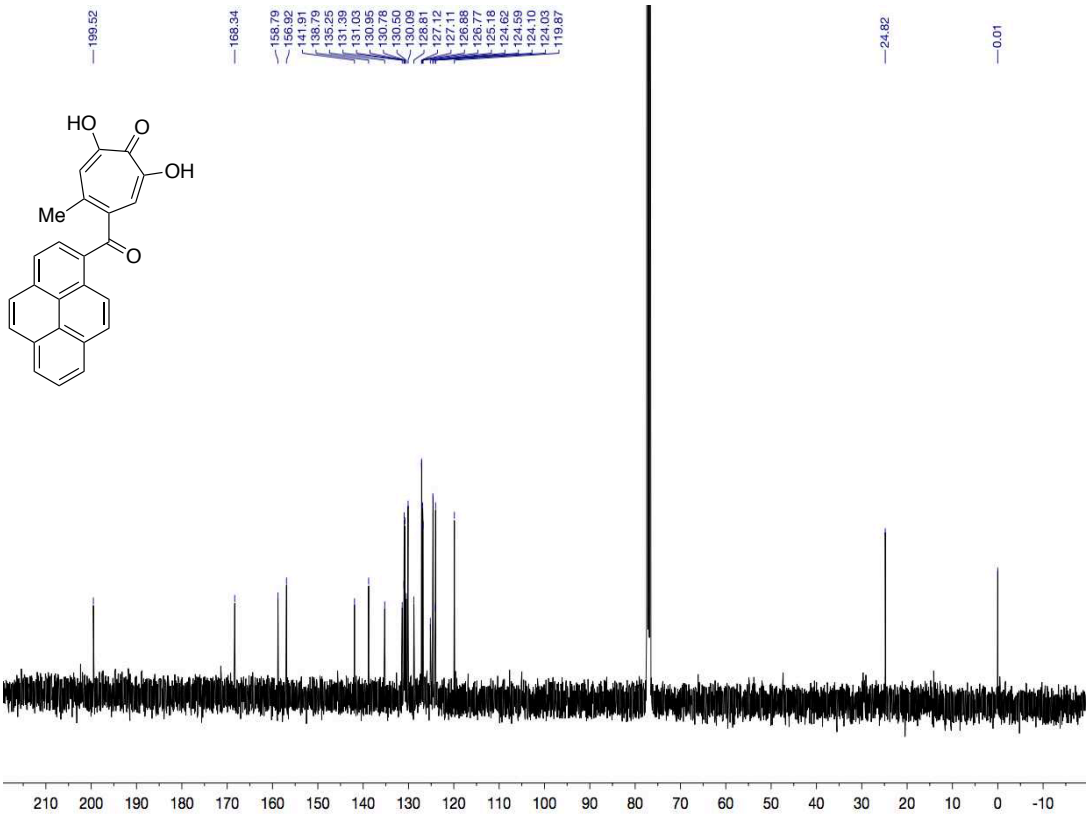
^{13}C NMR of S5



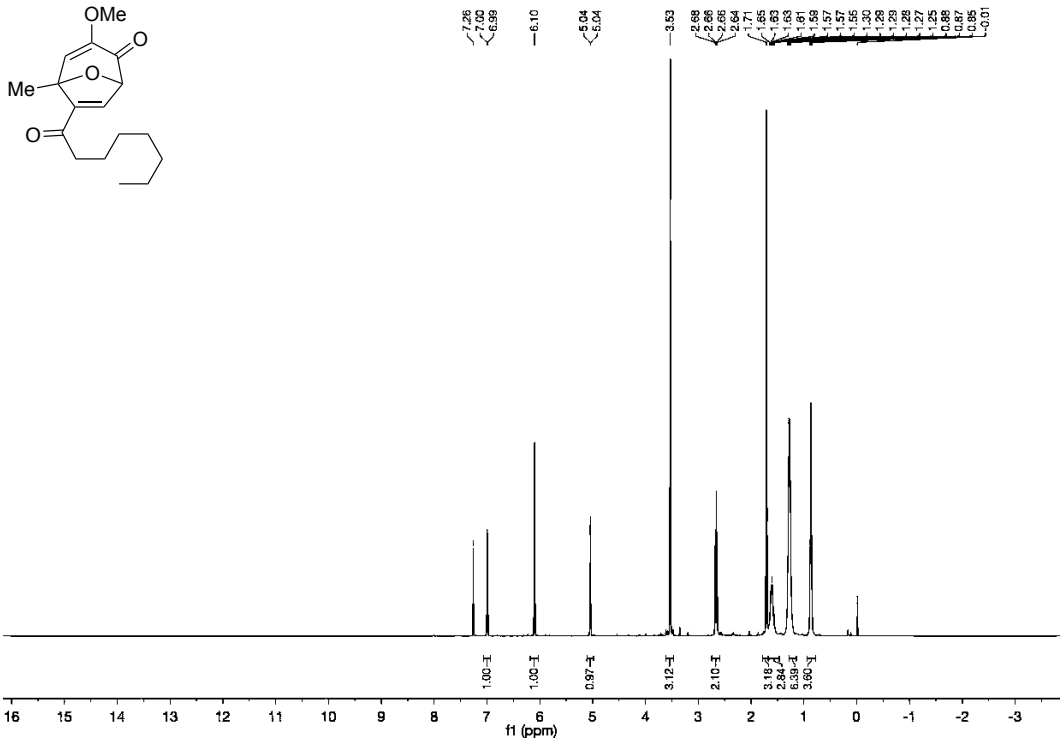
^{1}H NMR of 360



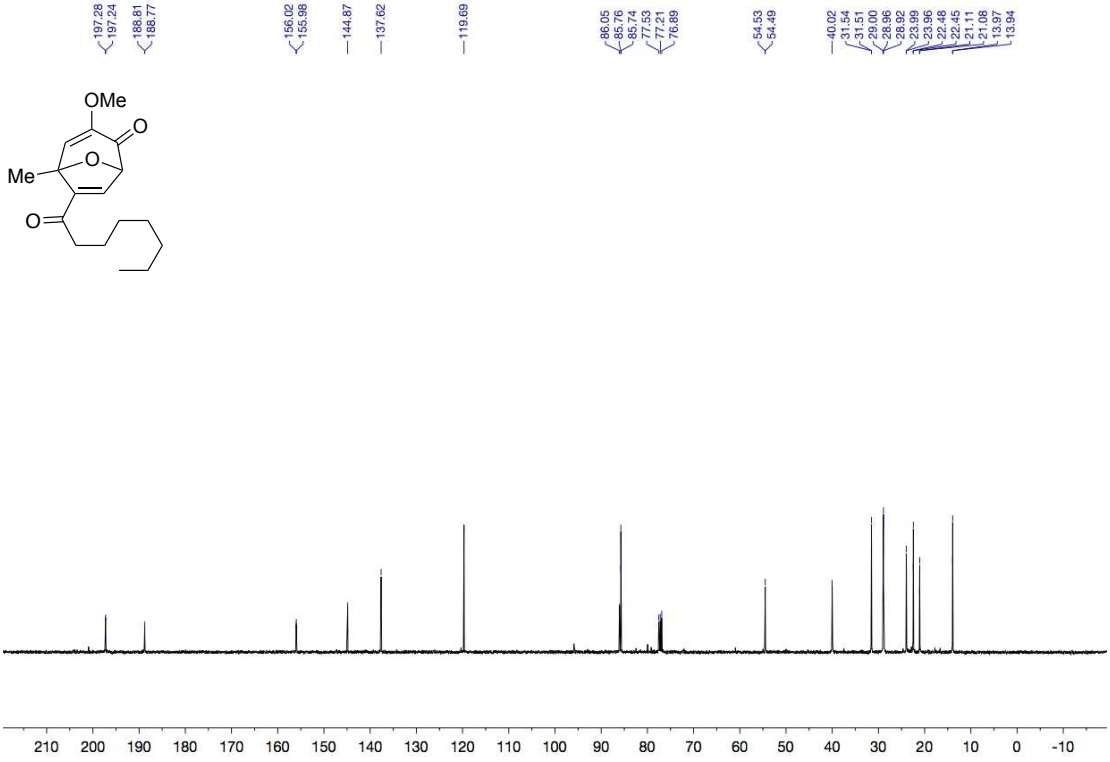
^{13}C NMR of 360



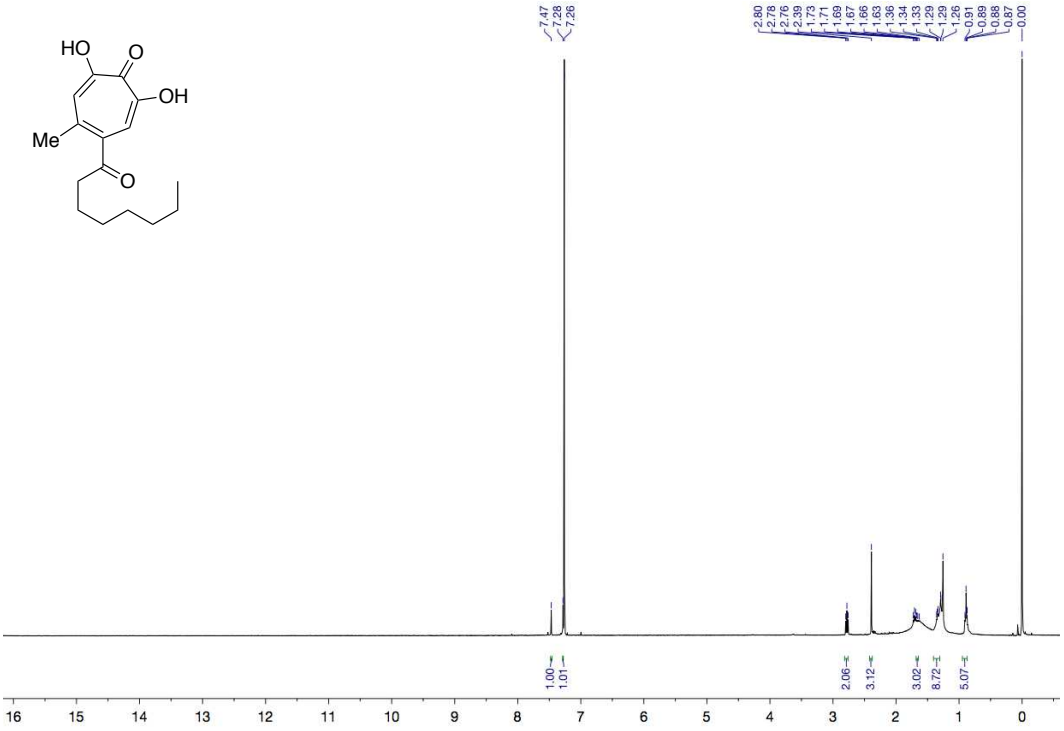
^{1}H NMR of S6



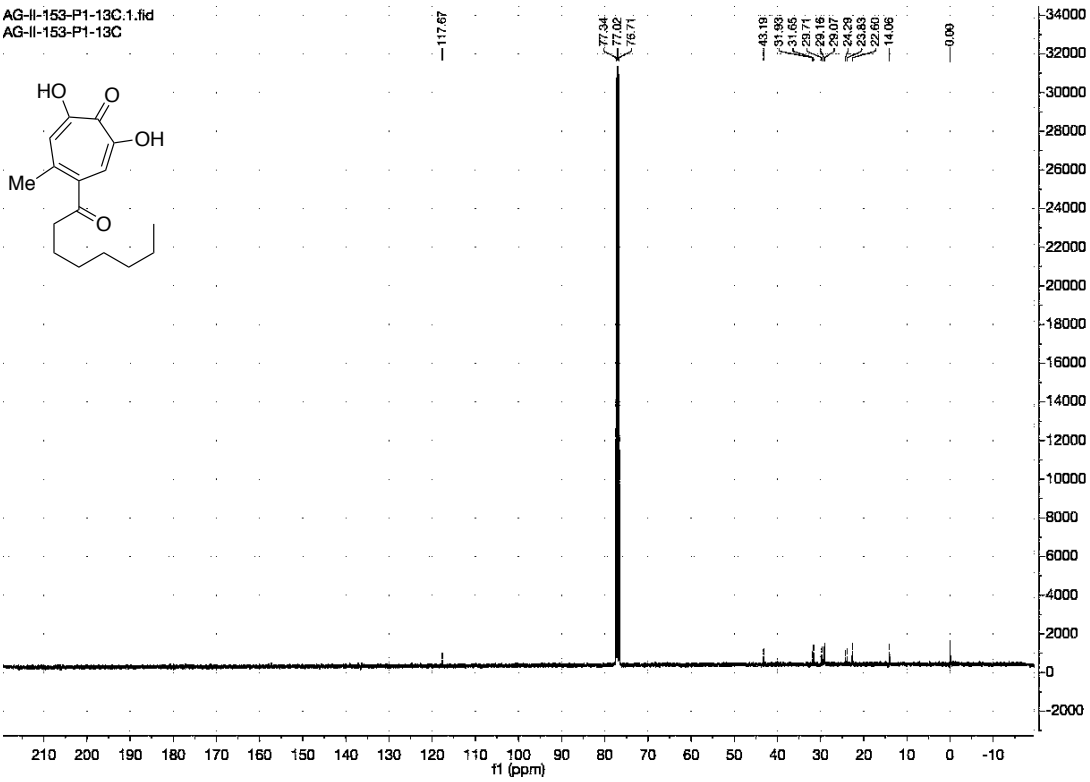
^{13}C NMR of S6



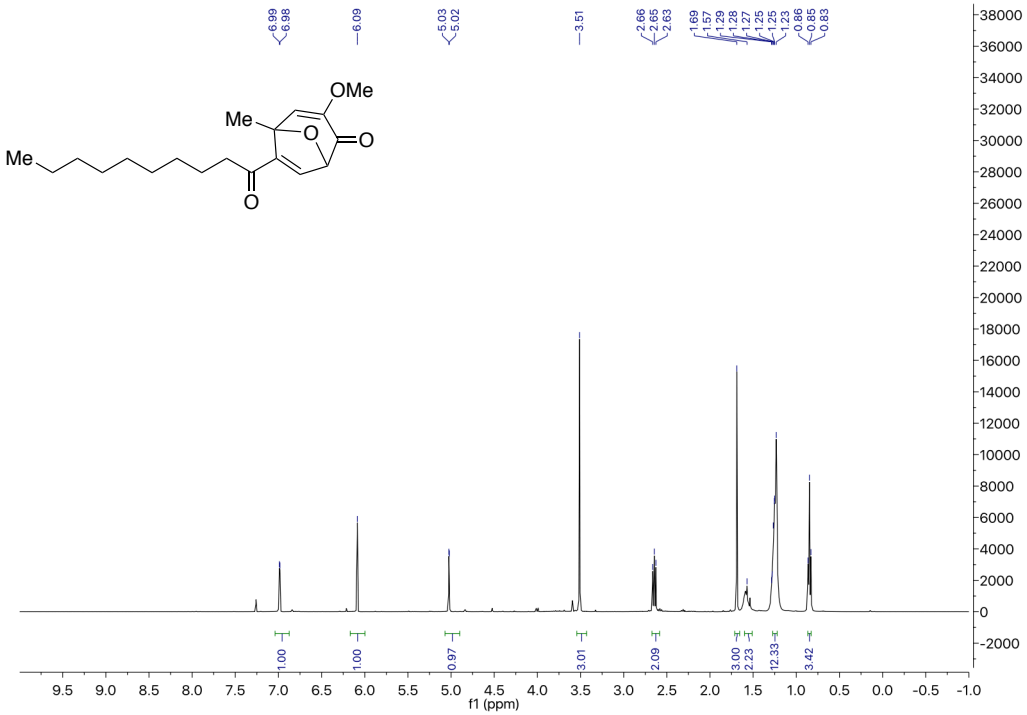
^{1}H NMR of 380



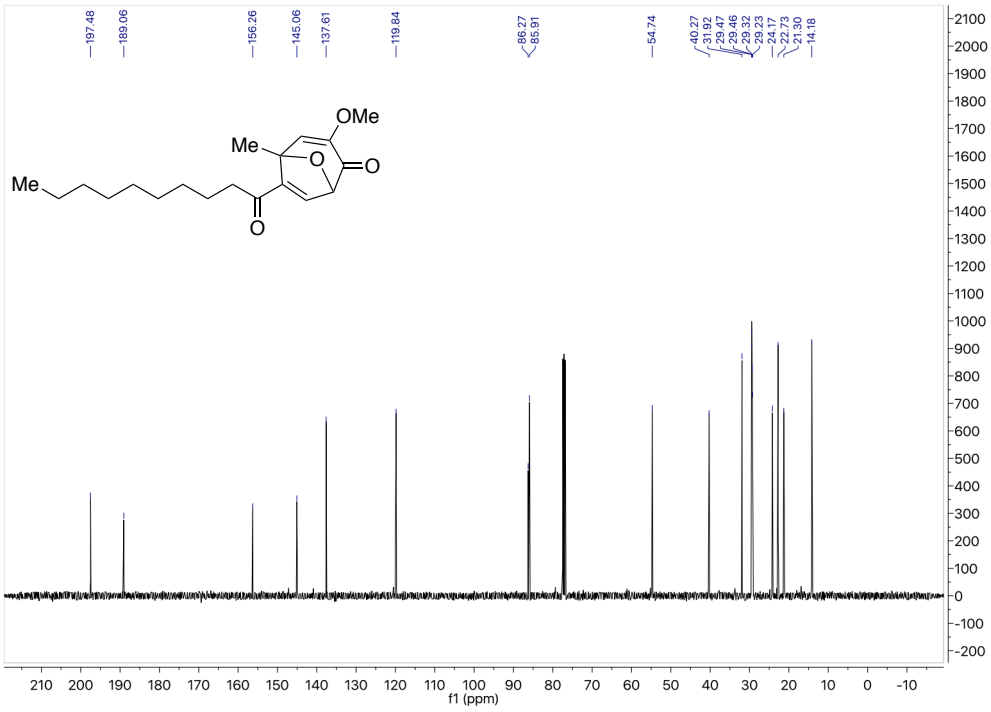
^{13}C NMR of 380 (partial)



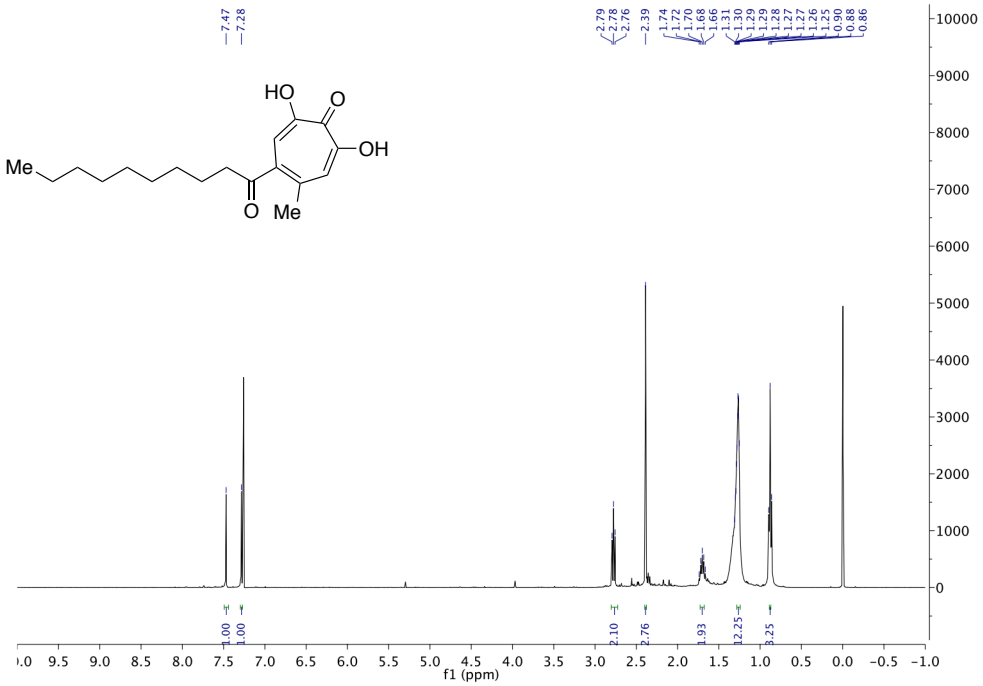
^{1}H NMR of S8



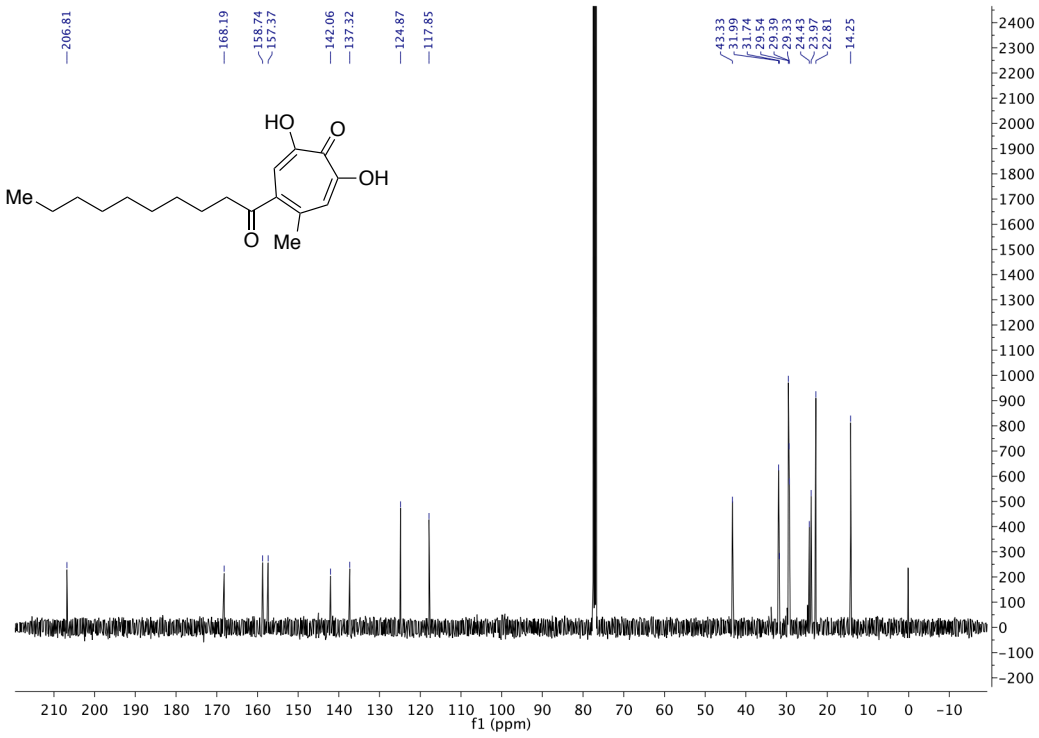
^{13}C NMR of S8



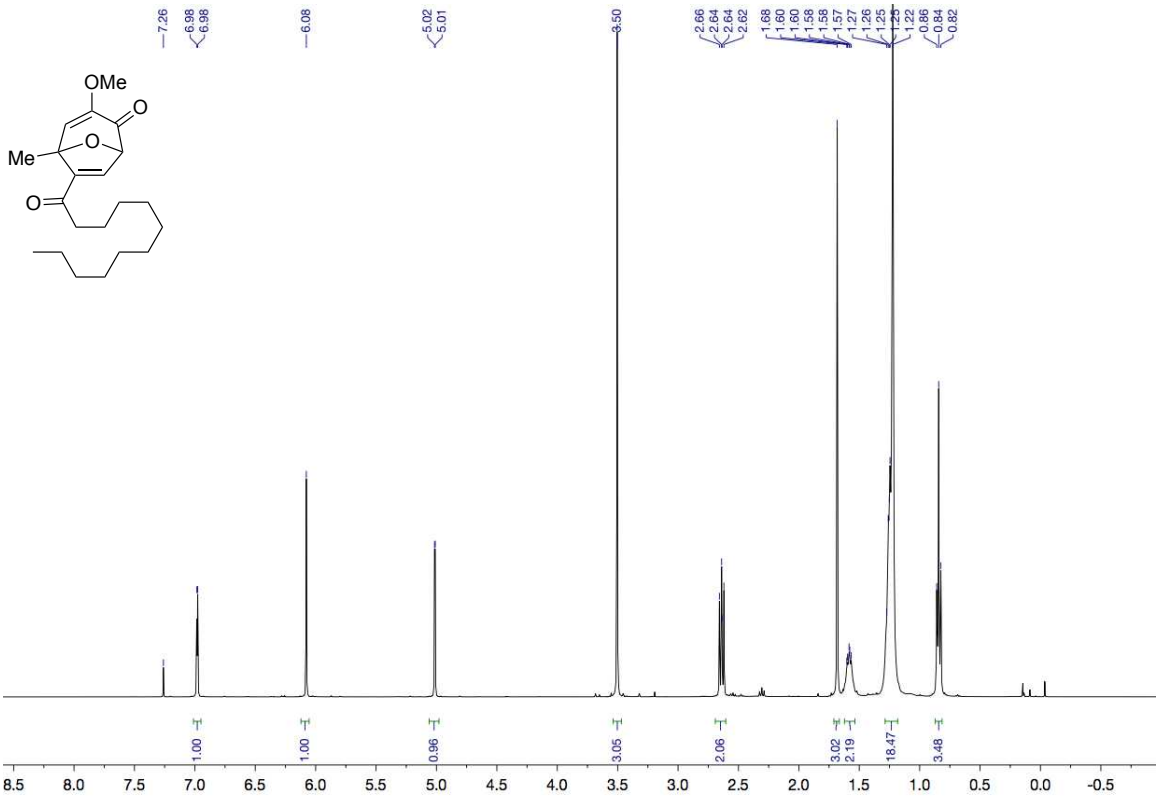
^{1}H NMR of 792



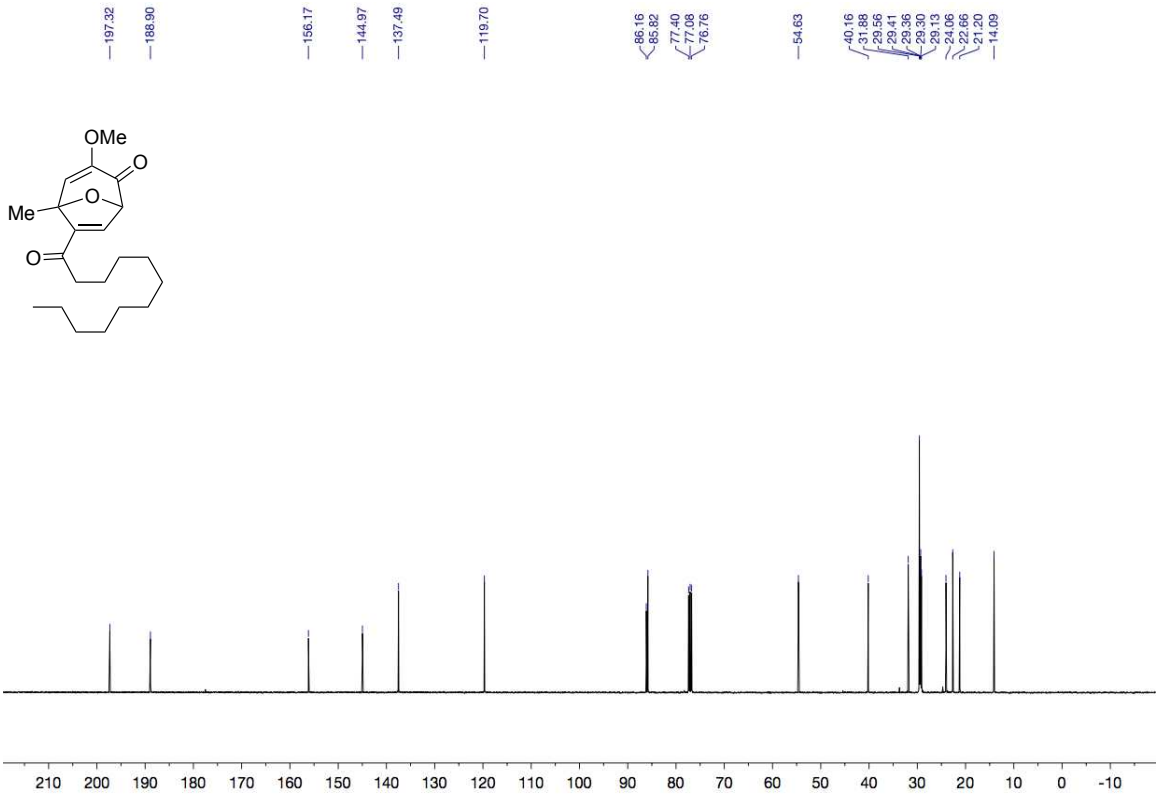
^{13}C NMR of 792



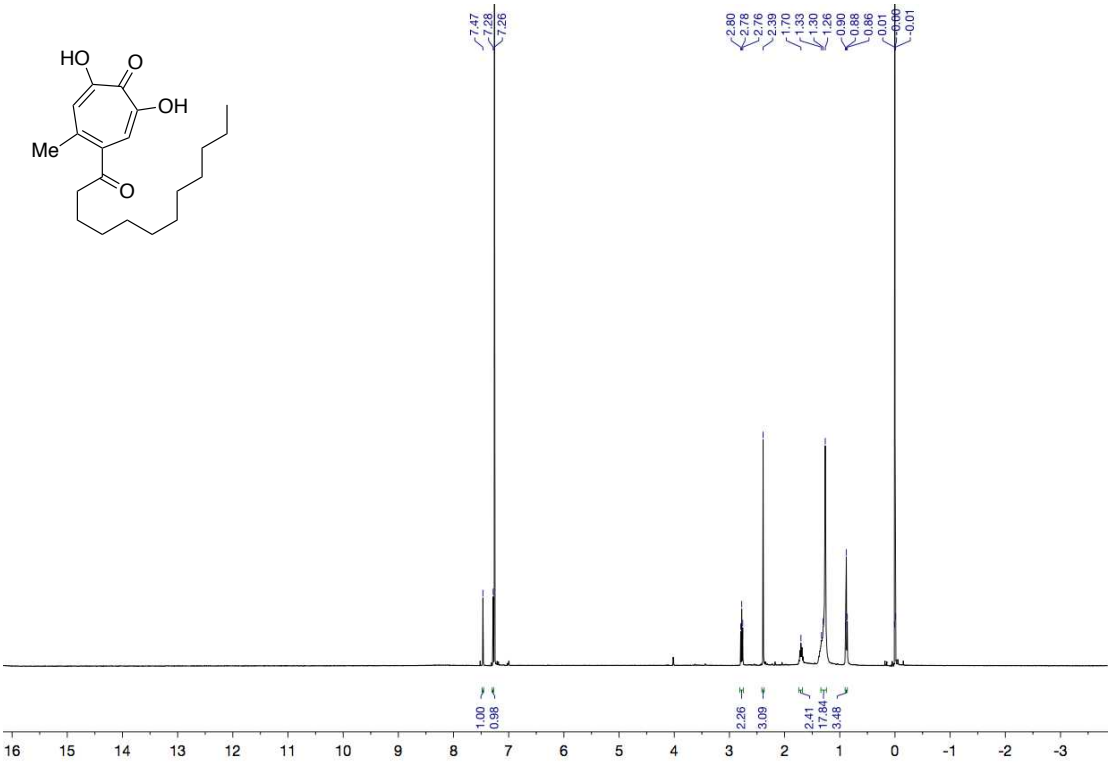
^{1}H NMR of S9



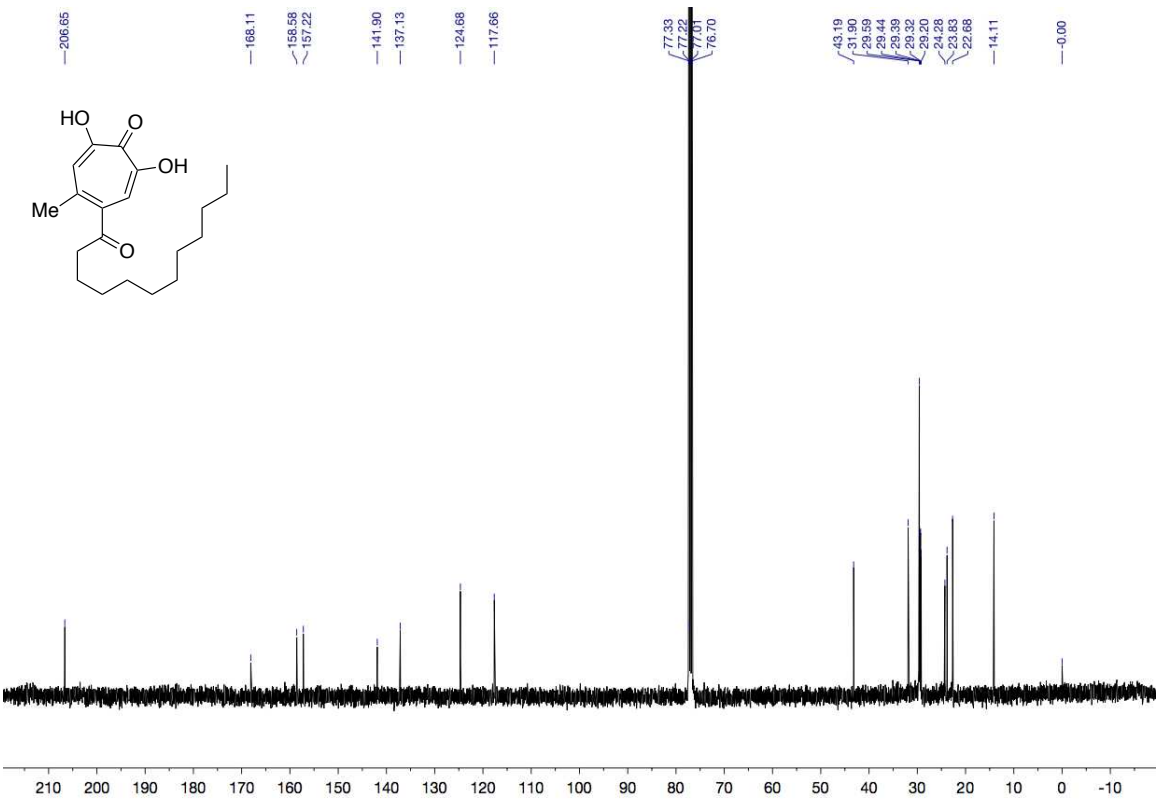
^{13}C NMR of S9



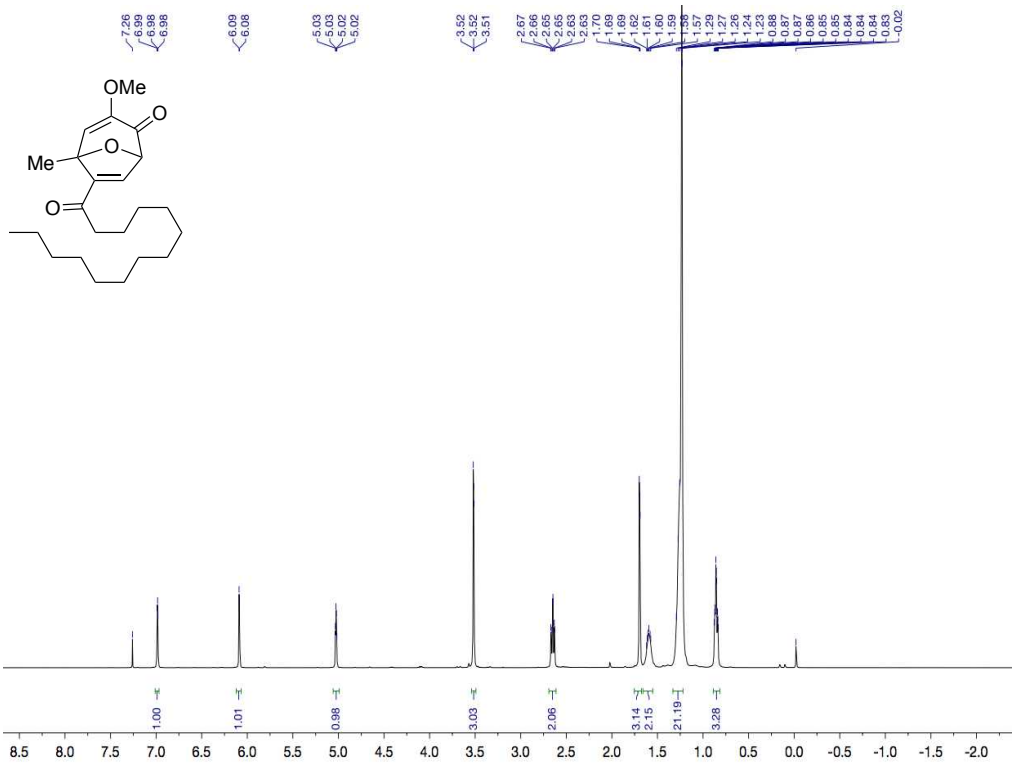
^{1}H NMR of 351



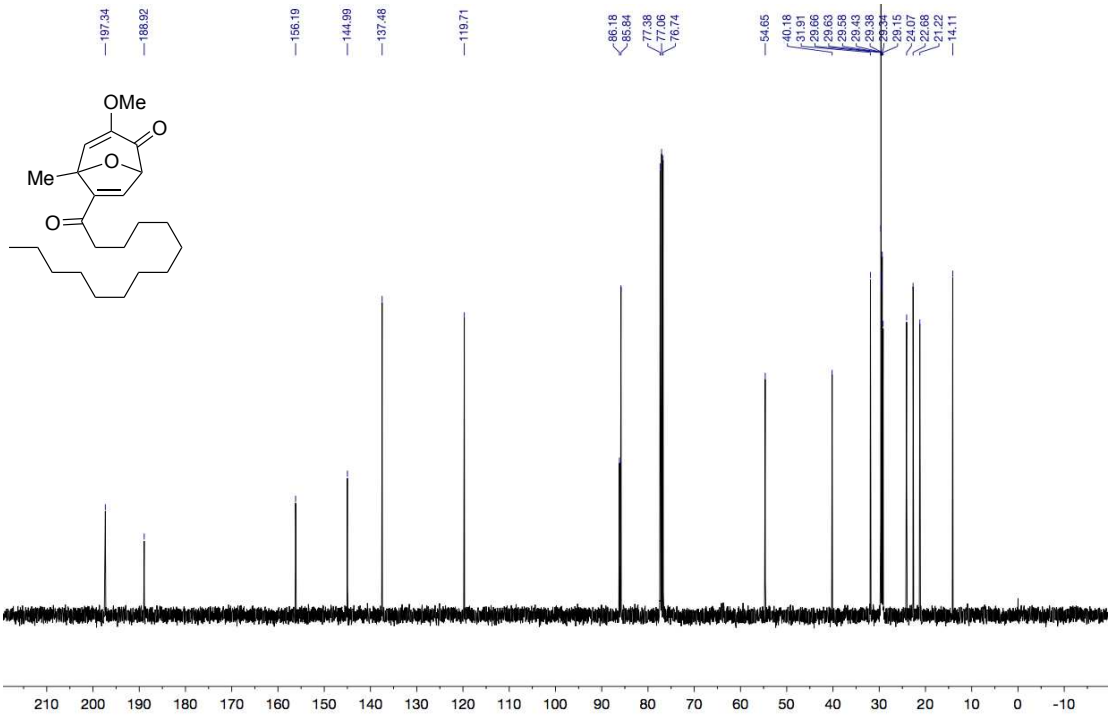
^{13}C NMR of 351



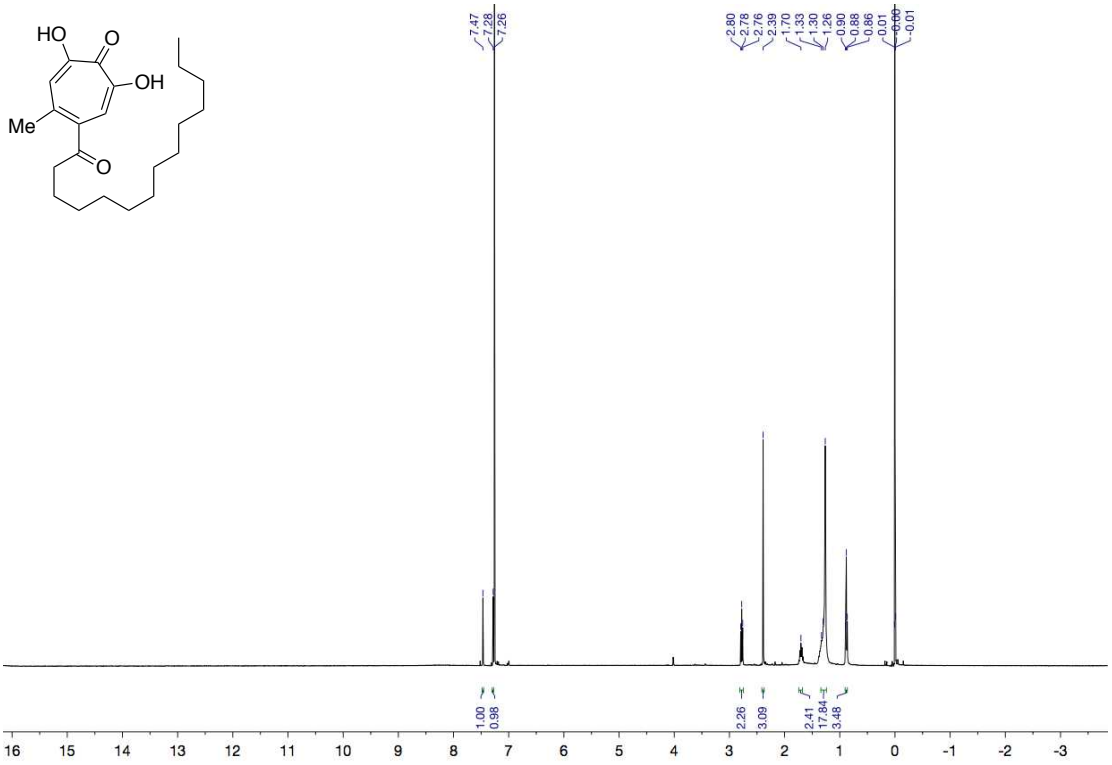
^{1}H NMR of S10



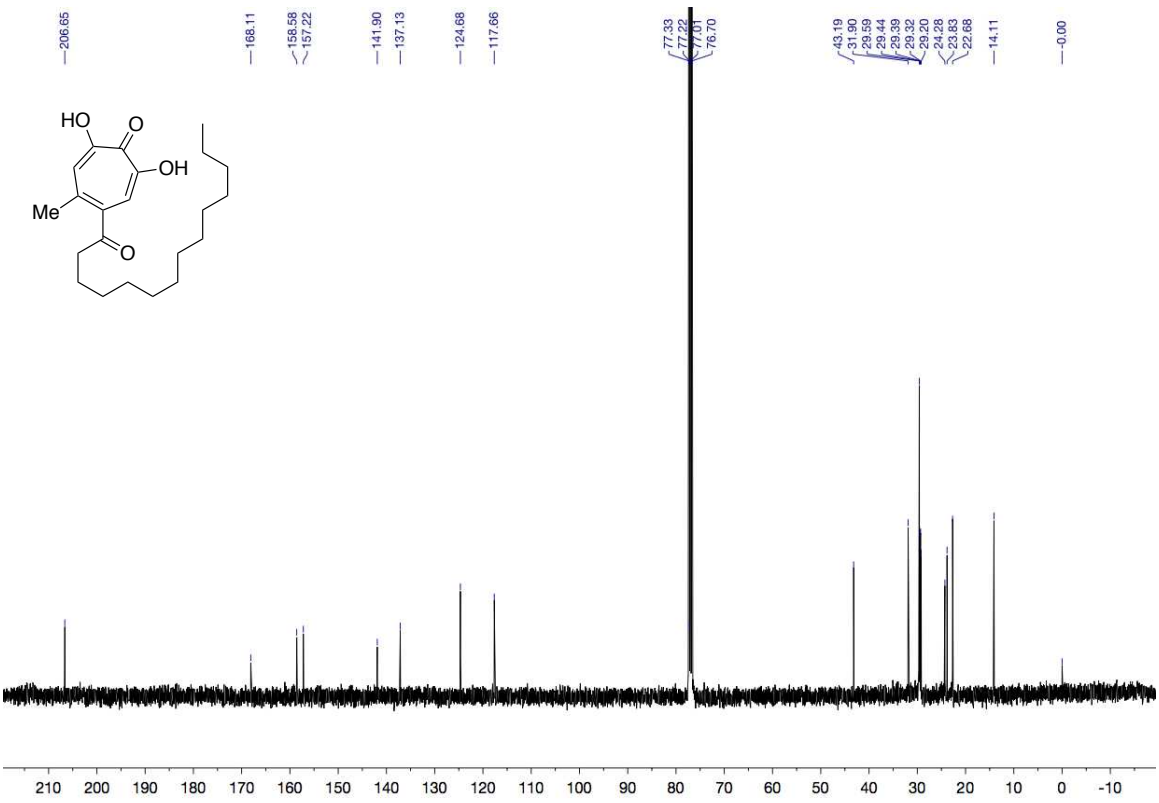
^{13}C NMR of S10



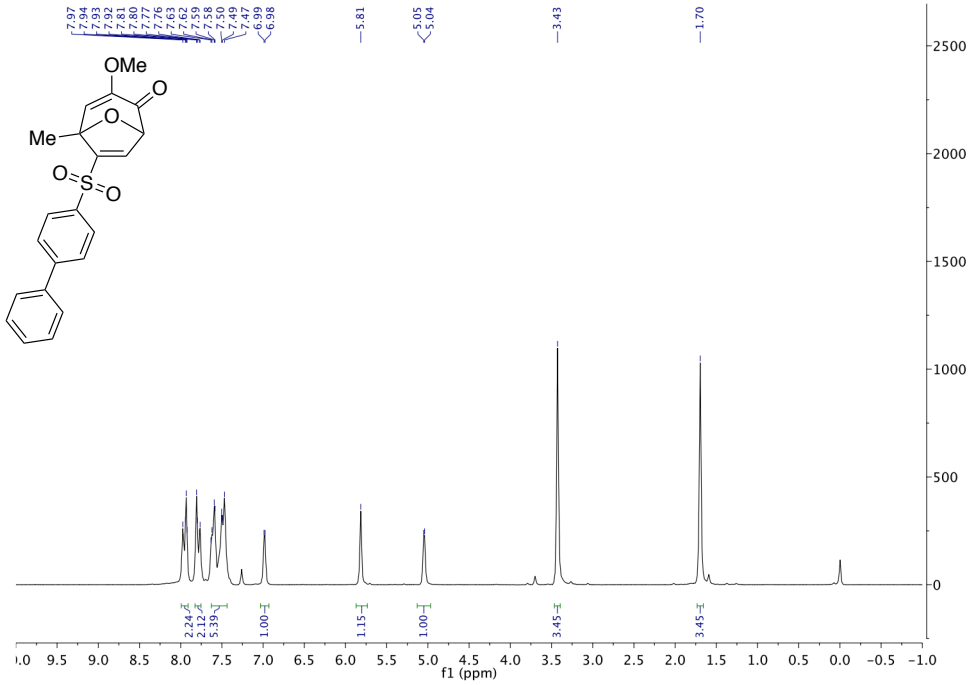
^{1}H NMR of 381



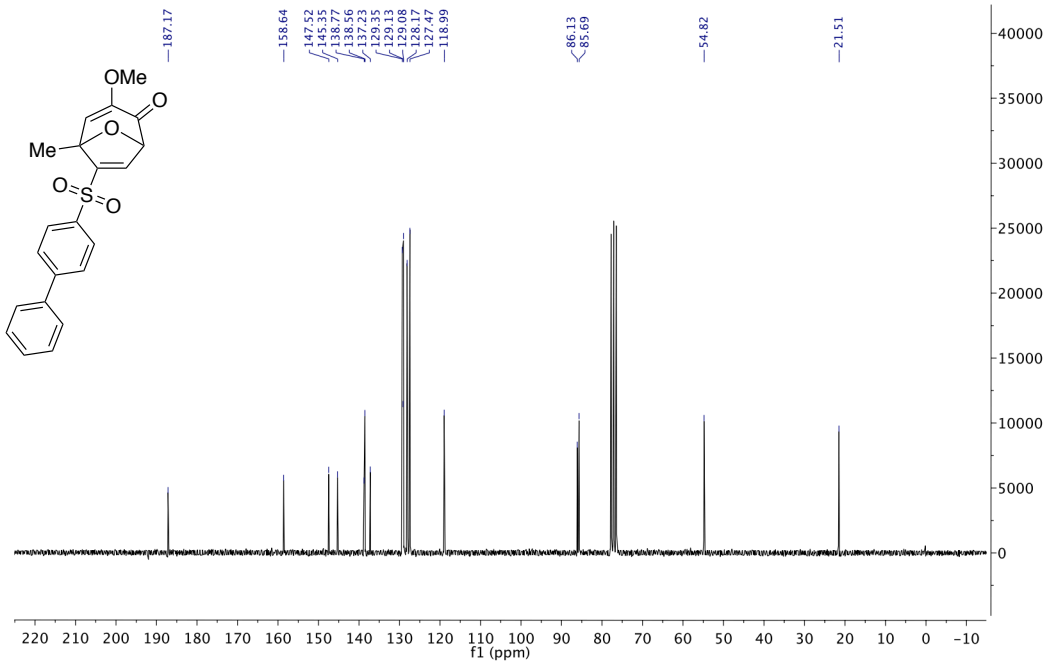
^{13}C NMR of 381



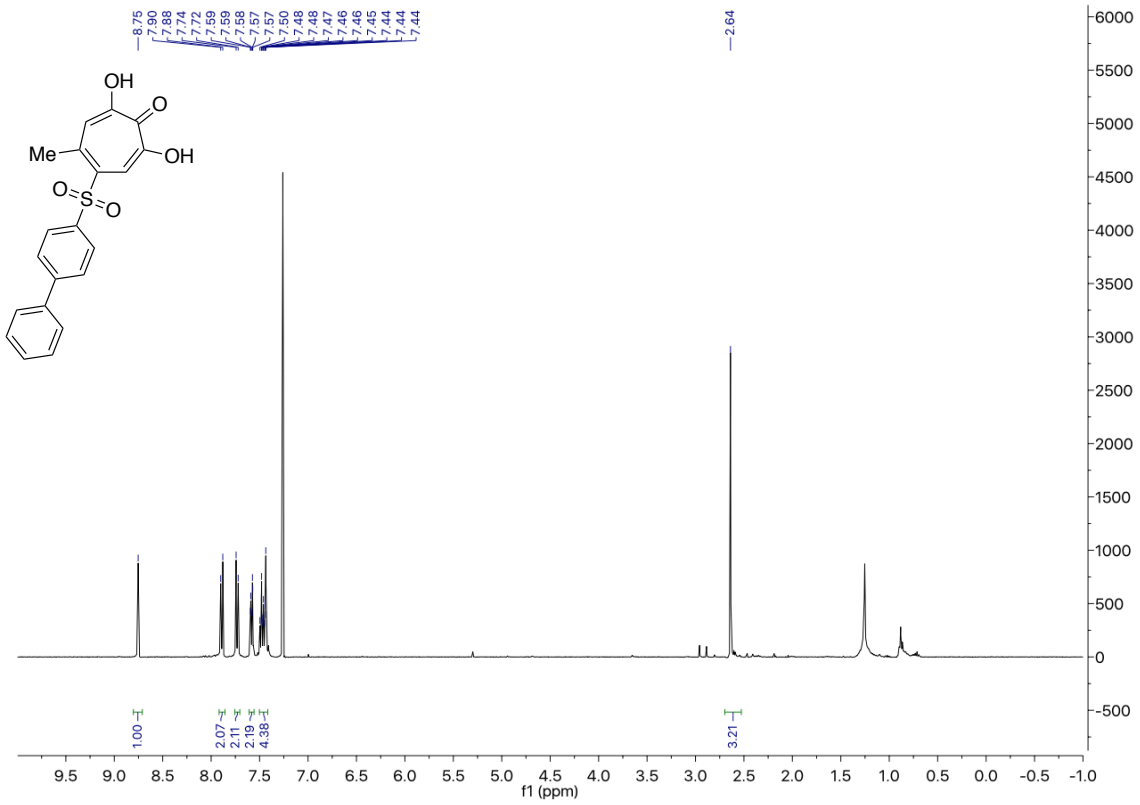
^{1}H NMR of S12



^{13}C NMR of S12



^{1}H NMR of 337



^{13}C NMR of 337