Electronic Supplementary Material (ESI) for Chemical Science

Organocatalytic C–H Hydroxylation with Oxone® Enabled by an Aqueous Fluoroalcohol Solvent System

Supplementary Material

(*16 pages*)

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General. All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive solutions were transferred via syringe. Solvent removal was effected by concentration of organic solutions under reduced pressure (ca. 20 Torr) by rotary evaporation. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were passed through two columns of activated alumina prior to use. *tert*-Butyl alcohol was purified by distillation over CaH_2 and stored over activated 3Å molecular sieves. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP, Oakwood HO242) and 2,2,2-trifluoroethanol (TFE) were used without further purification. Chromatographic purification of products was accomplished using forced flow chromatography on Silicycle silica gel 60 (40-63 μm). Thin layer chromatography was performed on EM science silica gel 60 F254 plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching and by staining with ethanolic anisaldehyde, aqueous potassium permanganate, or aqueous ceric ammonium molybdate (CAM) solution.

Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Mercury 400 operating at 400, 100, and 376 MHz for ^1H, ^{13}C, and ^{19}F, respectively. ^1H and ^{13}C spectra are referenced internally according to residual solvent signals ($CHCl_3$ δ = 7.26 ppm, $^{13}CDCl_3$ δ = 77.23 ppm). ^{19}F NMR spectra are referenced internally using α,α,α-trifluorotoluene as a standard (δ = –63.72 ppm). Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), integration, and coupling constant (Hz). Data for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shift (δ, ppm). Infrared (IR) spectra were recorded as either thin films using NaCl plates on a Thermo-Nicolet 300 FT-IR spectrometer and are reported in frequency of absorption. High resolution mass spectra were obtained from the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University.

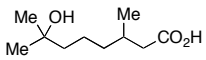
Oxaziridine **1** and benzoxathiazinane **2** were prepared as described by Brodsky and Du Bois.[1] Characterization data for compounds appearing in entries 2, 3, and 6a (Table 2) has been previously reported.[1,2]

Oxaziridine Stability Measurements

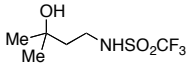
To a 0.5 dram vial was added oxaziridine **1** (20 mg, 66 μmol), 1.3 mL of solvent, and a stir bar. After stirring for the given amount of time at 50 °C, the solution was cooled to room temperature and transferred to a 20 mL scintillation vial using 0.25 mL of CH_2Cl_2. This mixture was concentrated in vacuo (40 °C) to an oily residue. The percentage of **1** was determined by integration of the ^1H NMR spectrum using pyrazine as an internal standard and by ^{19}F NMR.

General Procedure for C–H Hydroxylation

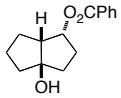
To a 10 mL round bottom flask containing substrate (1.0 mmol), catalyst (58 mg, 0.20 mmol, 0.2 equiv), and Oxone (768 mg, 2.5 mmol, 2.5 equiv) was added 4.0 mL of a 9:1 H_2O/HFIP solution. The flask was fitted with a Teflon cap, sealed, and placed in an oil bath pre-heated to 70 °C. The reaction mixture was stirred vigorously at this temperature for 12-24 h, then cooled to ambient temperature and transferred to a separatory funnel containing 7 mL of H_2O and 10 mL EtOAc. The organic layer was collected and the aqueous layer was extracted with 10 mL of EtOAc. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the isolated material by chromatography on silica gel (conditions given below) furnished the desired product.



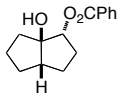
7-Hydroxy-3,7-dimethyloctanoic acid (Entry 1, Table 2). Purified by chromatography on silica gel using 30% acetone/hexanes (colorless oil, 85%). TLC R_f = 0.22 (3:1 hexanes/acetone); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.36 (dd, 1H, *J* = 14.8, 6.0 Hz), 2.18 (dd, 1H, *J* = 15.2, 8.0 Hz), 2.04-1.95 (m, 1H), 1.50-1.30 (m, 6H), 1.31-1.25 (m, 6H), 1.26-1.19 (m, 1H), 0.94 (d, 3H, *J* = 6.6 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.4, 72.1, 44.3, 42.2, 37.7, 30.7, 29.8, 29.7, 21.2, 20.4 ppm; IR (thin film) ν 3745, 2968, 2341, 1707, 1458, 1380, 907 cm^{-1}; HRMS (ES^+) calcd for $C_{10}H_{20}O_3Na^+$ 211.1130 found 211.23 [MNa^+].



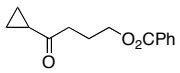
1,1,1-Trifluoro-*N*-(3-hydroxy-3-methylbutyl)methanesulfonamide (Entry 2c, Table 2). Purified by chromatography on silica gel using 25% EtOAc/hexanes (pale yellow oil, 40%). TLC R_f = 0.12 (7:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.51 (br s, 1H), 3.48 (m, 2H), 1.79-1.76 (m, 2H), 1.67 (s, 1H), 1.31 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.3, 72.8, 41.5, 41.9, 30.2 ppm; IR (thin film) ν 3548, 3315, 3125, 2976, 2934, 1425, 1370, 1298, 1077 cm^{-1}; HRMS (ES^-) calcd for $C_6H_{12}F_3NO_3S$ 234.04 found 234.1 [M^-].



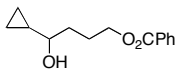
3α-Hydroxyoctahydropentalen-1-yl benzoate (Entry 4a, Table 2). Purified by chromatography on silica gel using 10% EtOAc/hexanes (colorless oil, 38%). TLC R_f = 0.13 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-8.01 (m, 2H), 7.56 (tt, 1H, *J* = 7.4, 1.5 Hz), 7.47-7.43 (m, 2H), 5.49 (dt, 1H, *J* = 7.6, 5.8 Hz), 2.59-2.55 (m, 1H), 2.26-2.20 (m, 1H), 1.99-1.69 (m, 9H), 1.65-1.59 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 133.0, 130.5, 129.6, 128.7, 128.5, 90.5, 76.9, 55.2, 42.5, 42.4, 37.9, 31.9, 26.9, 26.8 ppm; IR (thin film) ν 3409, 2955, 2870, 1718, 1451, 1315, 1276, 1116, 984 cm^{-1}; HRMS (ES^+) calcd for $C_{15}H_{18}O_3Na^+$ 269.1154 found 269.1143 [MNa^+].



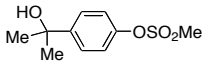
6α-Hydroxyoctahydropentalen-1-yl benzoate (Entry 4b, Table 2). Purified by chromatography on silica gel using 10% EtOAc/hexanes (colorless oil, 7%). TLC R_f = 0.21 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, 2H, 8.2, 1.0 Hz), 7.63-7.59 (m, 1H), 7.48 (dt, 2H, *J* = 12.0, 5.7 Hz), 5.06 (dd, 1H, *J* = 10.3, 6.6 Hz), 2.40-2.36 (m, 1H), 2.17-2.10 (m, 2H), 2.03-1.90 (m, 2H), 1.77-1.66 (m, 3H), 1.63-1.51 (m, 1H), 1.51-1.41 (m, 1H, 1.32-1.26 (m, 1H), 1.25-1.14 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 133.6, 130.4, 130.0 128.8, 91.0, 87.1, 50.9, 37.8, 35.2, 30.2, 26.6, 26.1 ppm; IR (thin film) ν 3447, 2953, 2870, 1781, 1451, 1378, 1274, 1070, 1011 cm^{-1}; HRMS (ES^+) calcd for $C_{15}H_{18}O_3Na^+$ 269.1154 found 269.11 [MNa^+].



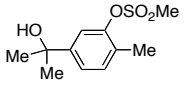
4-Cyclopropyl-4-oxobutyl benzoate (Entry 5a, Table 2). Purified by chromatography on silica gel using 10% EtOAc/hexanes (white solid, 29%). TLC R_f = 0.49 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07-8.05 (m, 2H), 7.58-7.54 (m, 1H), 7.47-7.43 (m, 2H), 4.34 (t, 2H, *J* = 6.7 Hz), 2.73 (t, 2H, *J* = 7.2 Hz), 2.11-2.05 (m, 2H), 2.05-1.90 (m, 1H), 1.02 (m, 2H), 0.88-0.85 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.0, 166.7, 133.1, 130.3, 129.7, 128.5, 64.4, 39.8, 23.1, 20.7, 10.9 ppm; IR (thin film) ν 3379, 1716, 1601, 1451, 1387, 1273, 1777, 1111, 1068 cm^{-1}; HRMS (ES^+) calcd for $C_{14}H_{17}O_3^+$ 233.1177 found 233.1170 [MH^+].



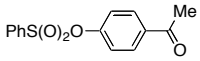
4-Cyclopropyl-4-hydroxybutyl benzoate (Entry 5b, Table 2). Purified by chromatography on silica gel using 10% EtOAc/hexanes (colorless oil, 11%). TLC R_f = 0.17 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07-8.04 (m, 2H), 7.59-7.55 (m, 1H), 7.47-7.43 (m, 2H), 4.38 (t, 2H, *J* = 6.6 Hz), 2.94 (ddd, 1H, *J* = 8.5, 7.3, 5.2 Hz), 2.07-1.83 (m, 2H), 1.86-1.74 (m, 2H), 0.99-0.89 (m, 2H), 0.62-0.50 (m, 2H), 0.33-0.23 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 133.0, 130.5, 129.7, 115.2, 76.7, 65.2, 33.6, 25.3, 18.1, 3.0, 2.7 ppm; IR (thin film) ν 3443, 3078, 3003, 2926, 2360, 1717, 1277, 1179, 1117 cm^{-1}; HRMS (ES^+) calcd for $C_{14}H_{18}O_3Na^+$ 257.1154 found 257.1148 [MH^+].



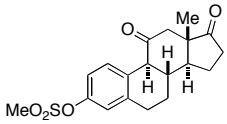
4-(2-Hydroxypropan-2-yl)phenyl methanesulfonate (Entry 6b, Table 2). Purified by chromatography on silica gel using 25% EtOAc/hexanes (white solid, 55%). TLC R_f = 0.18 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, 2H, *J* = 4.6 Hz), 7.23 (d, 2H, *J* = 4.6 Hz), 3.12 (s, 3H), 1.57 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 147.9, 126.4, 121.7, 73.4, 37.4, 31.9 ppm; IR (thin film) ν 3278, 3038, 3028, 3973, 2940, 2360, 1502, 1375, 1170, 1152, 871 cm^{-1}; HRMS (ES$^+$) calcd for $C_{10}H_{14}O_4SNa^+$ 253.0511 found 253.0505 [MNa^+].



5-(2-Hydroxypropan-2-yl)-2-methylphenyl methanesulfonate (Entry 7, Table 2). Purified by chromatography on silica gel using 25% EtOAc/hexanes (colorless oil, 30%). TLC R_f = 0.17 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 1H, *J* = 1.8 Hz), 7.29 (dd, 1H, *J* = 8.0, 1.8 Hz), 7.22 (d, 1H, *J* = 8.0 Hz), 3.19 (s, 3H), 2.34 (s, 3H), 1.50 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.2, 147.8, 131.7, 129.5, 123.5, 118.5, 72.3, 38.3, 31.8, 16.4 ppm; IR (thin film) ν 3530, 2976, 2935, 1506, 1400, 1353, 1186, 1165, 1120, 969, 932, 852, 811 cm^{-1}; HRMS (ES$^+$) calcd for $C_{11}H_{16}O_4SNa^+$ 267.0667 found 267.18 [MNa^+].



4-Acetylphenyl benzenesulfonate (Entry 8, Table 2). Purified by chromatography on silica gel using 15% acetone/hexanes (yellow oil, 53%). TLC R_f = 0.42 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90-7.87 (m, 2H), 7.83-7.81 (m, 2H), 7.69-7.65 (m, 1H), 7.55-7.51 (m, 2H), 7.08-7.05 (m, 2H), 2.55 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8, 152.9, 135.8, 135.1, 134.7, 130.2, 129.4, 128.5, 122.5, 26.7 ppm; IR (thin film) ν 3069, 3006, 1687, 1596, 1377, 1202, 1155, 1092, 865 cm^{-1}.

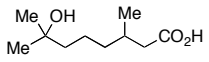


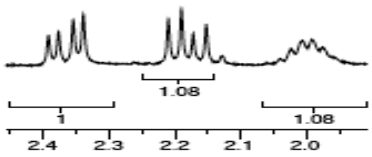
(8*S*,9*S*,13*S*,14*S*)-13-methyl-11,17-dioxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl methanesulfonate (Figure 2). Purified by chromatography on silica gel using 5% acetone/hexanes (white foam, 30%). TLC R_f = 0.28 (2:1 hexanes/acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (s, 1H), 6.99 (d, 2H, *J* = 1.6 Hz), 3.70 (d, 1H, *J* = 5.4 Hz), 3.12 (s, 3H), 2.55-2.39 (m, 3H), 2.25-2.02 (m, 6H), 1.86–1.76 (m, 3H), 0.92 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.2, 210.5, 148.0, 138.1, 130.3, 129.5, 123.5, 120.3, 54.2, 50.6, 46.7, 41.8, 37.7, 36.2, 32.8, 24.8, 22.9, 21.6, 15.0 ppm; IR (thin film) ν 2934, 1739, 1701, 1492, 1473, 1179, 1167, 1139, 1026, 857, 731 cm^{-1}; HRMS (ES$^+$) calcd for $C_{19}H_{22}O_5SNa^+$ 385.1086 found 385.15 [MNa^+].

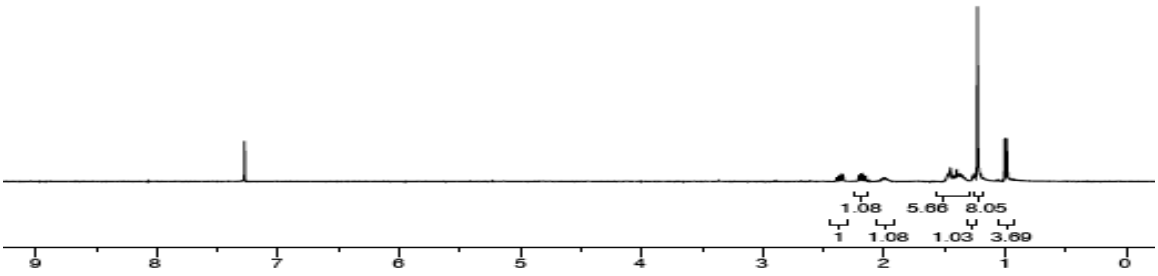
1. Brodsky, B. H.; Du Bois, J. *J. Am. Chem. Soc.* **2005**, *127*, 15391-15393.

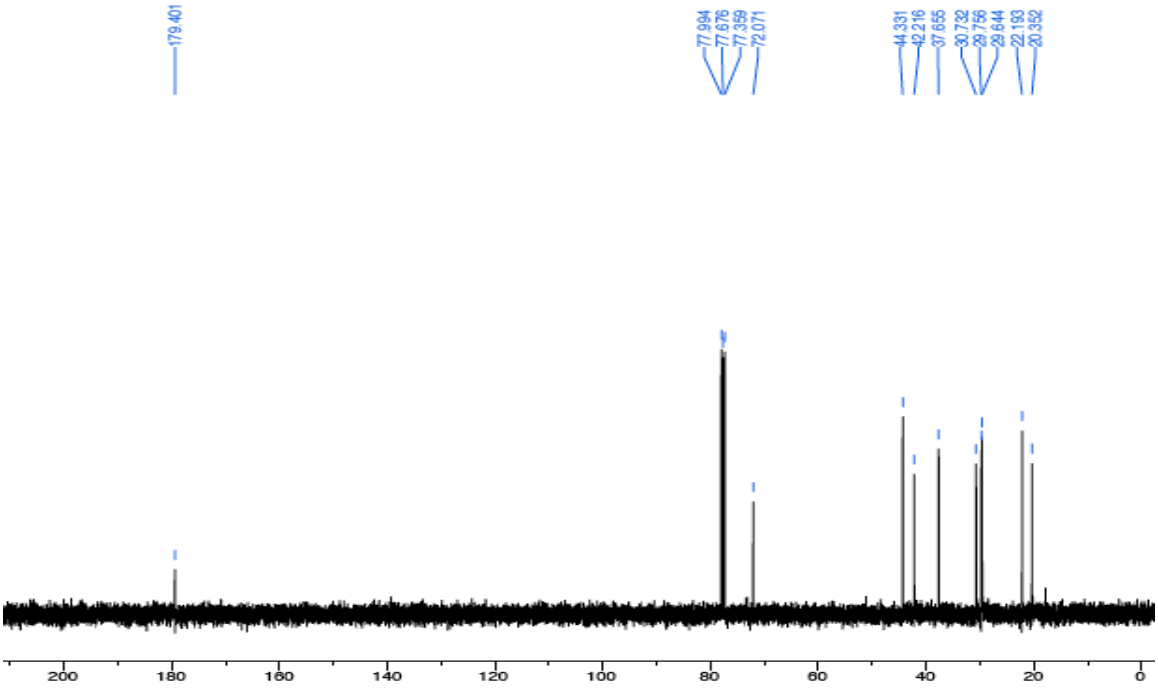
2. McNeill, E.; Du Bois, J. *Chem. Sci.*, **2012**, *3*, 1810-1813.

7-Hydroxy-3,7-dimethyloctanoic acid

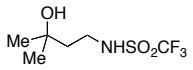


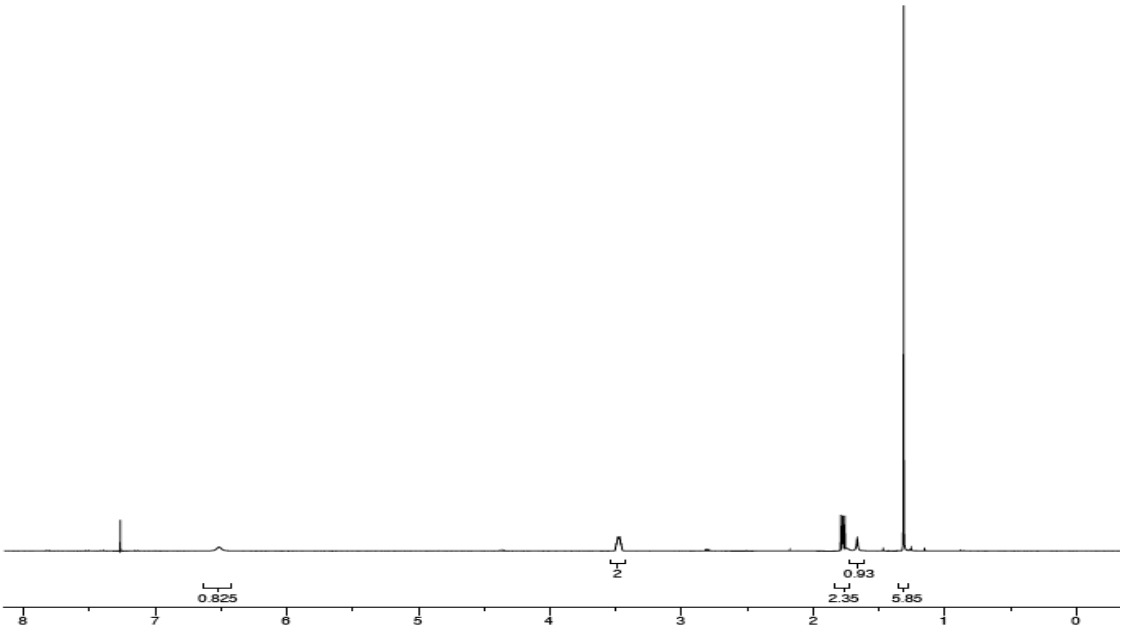


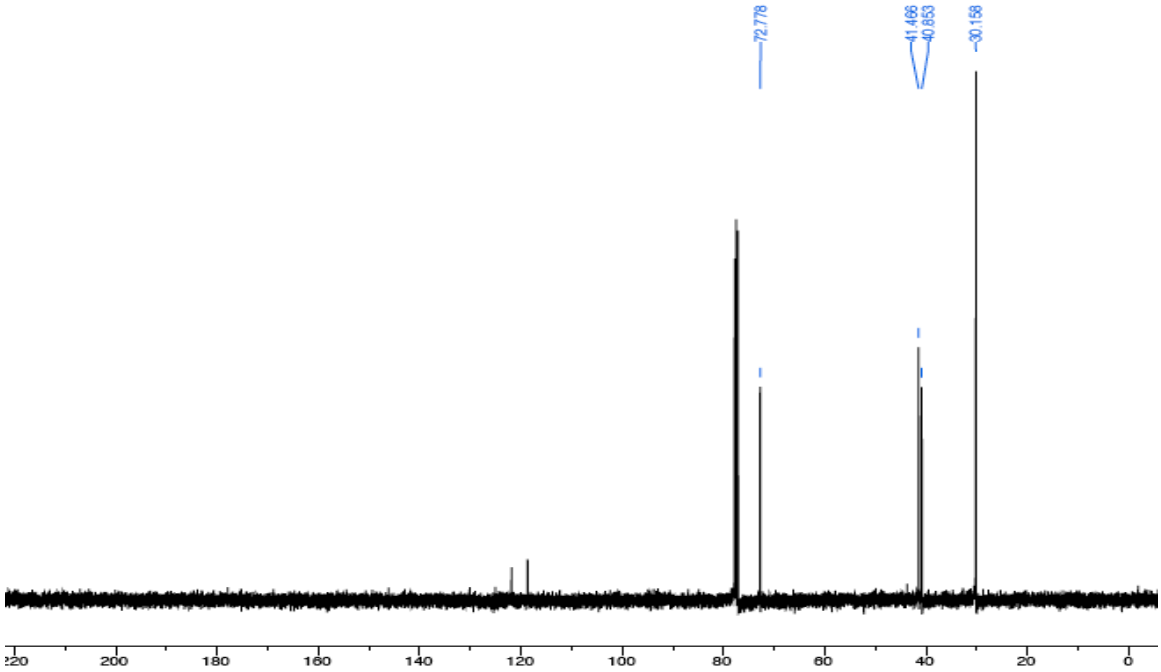




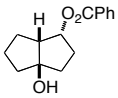
1,1,1-Trifluoro-*N*-(3-hydroxy-3-methylbutyl)methanesulfonamide

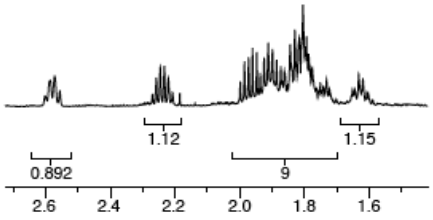


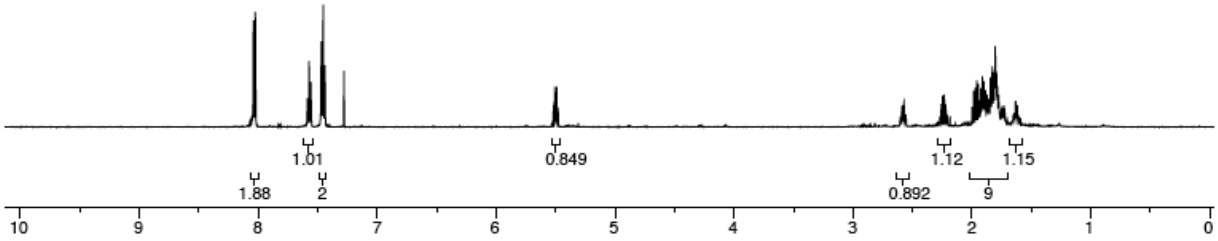


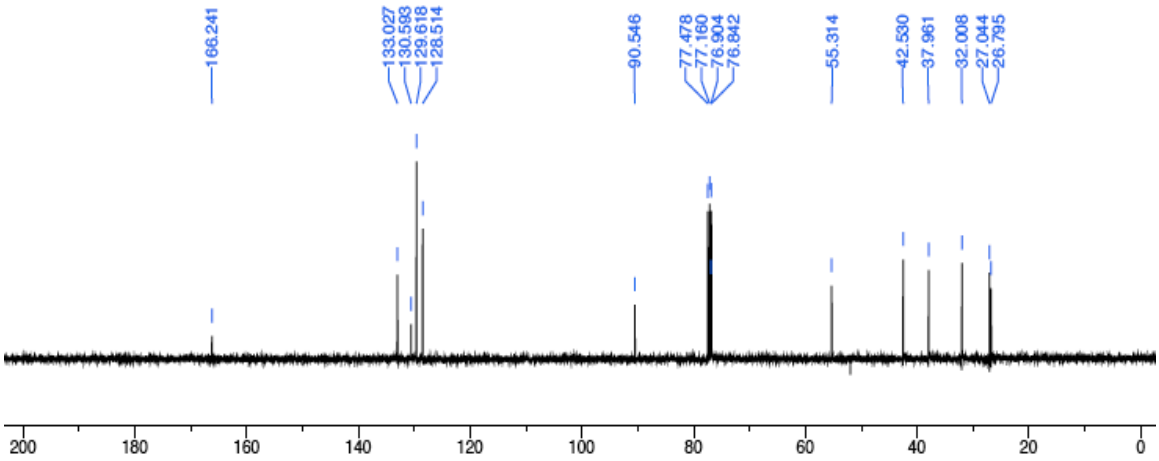


3α-Hydroxyoctahydropentalen-1-yl benzoate

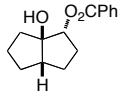


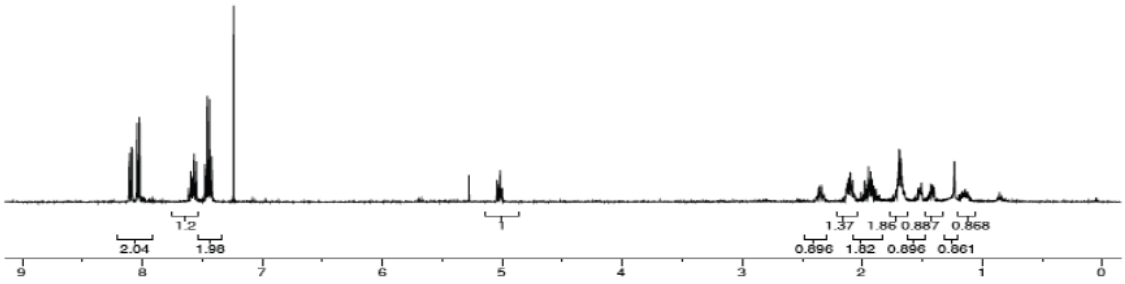


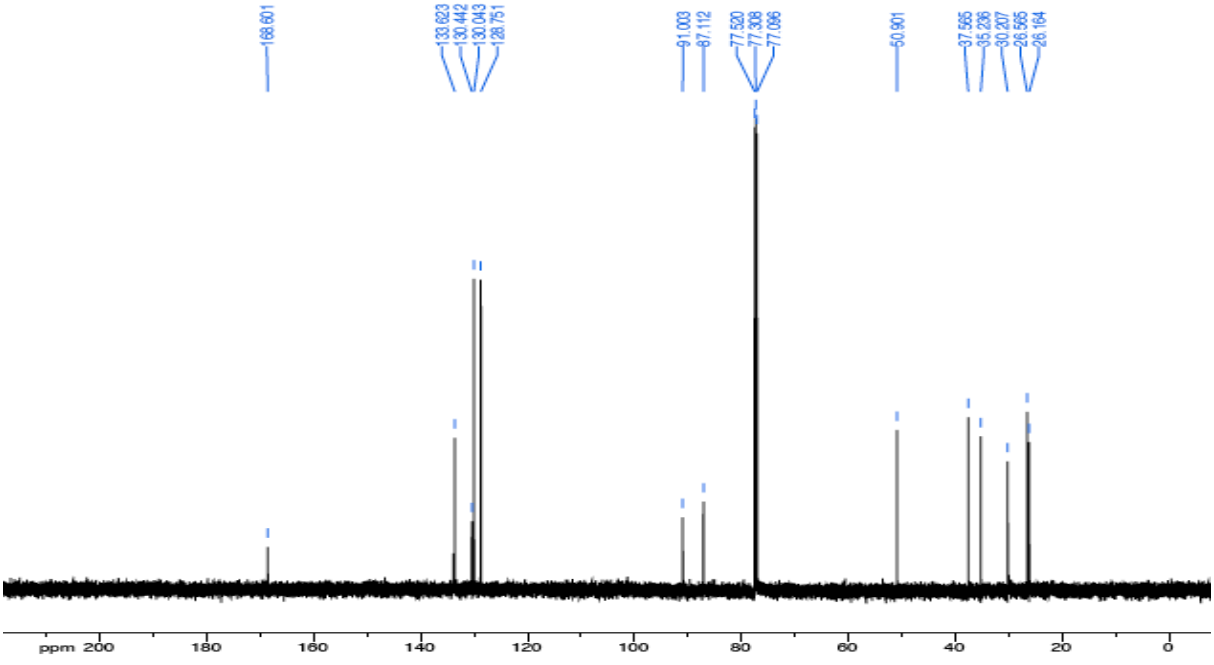




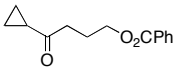
6α-Hydroxyoctahydropentalen-1-yl benzoate

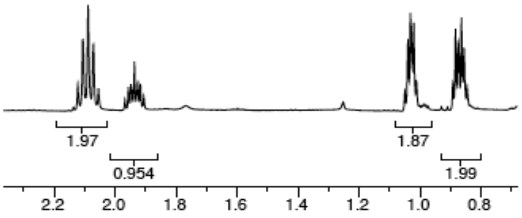


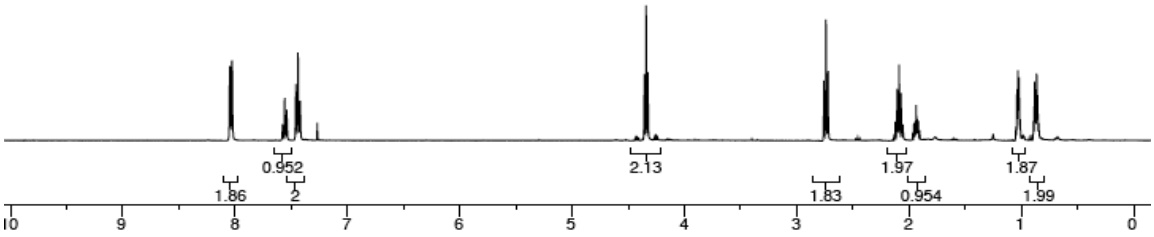


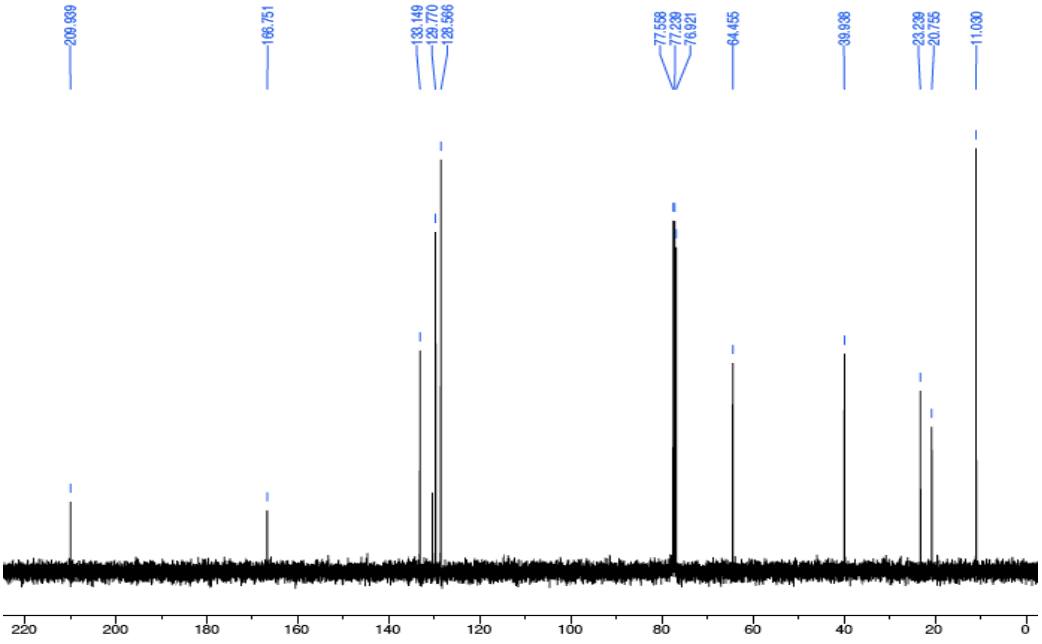


4-Cyclopropyl-4-oxobutyl benzoate

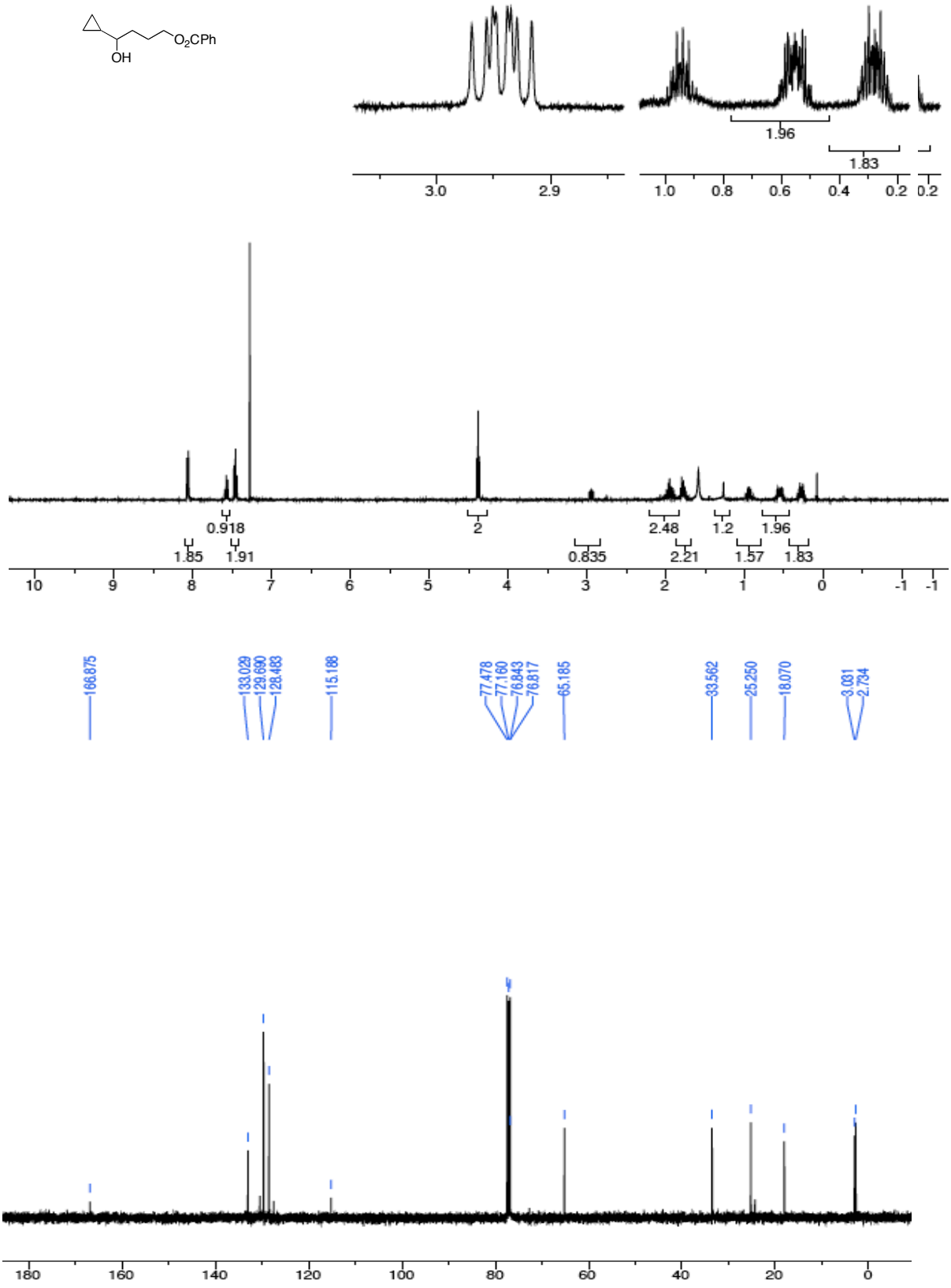




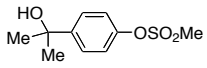


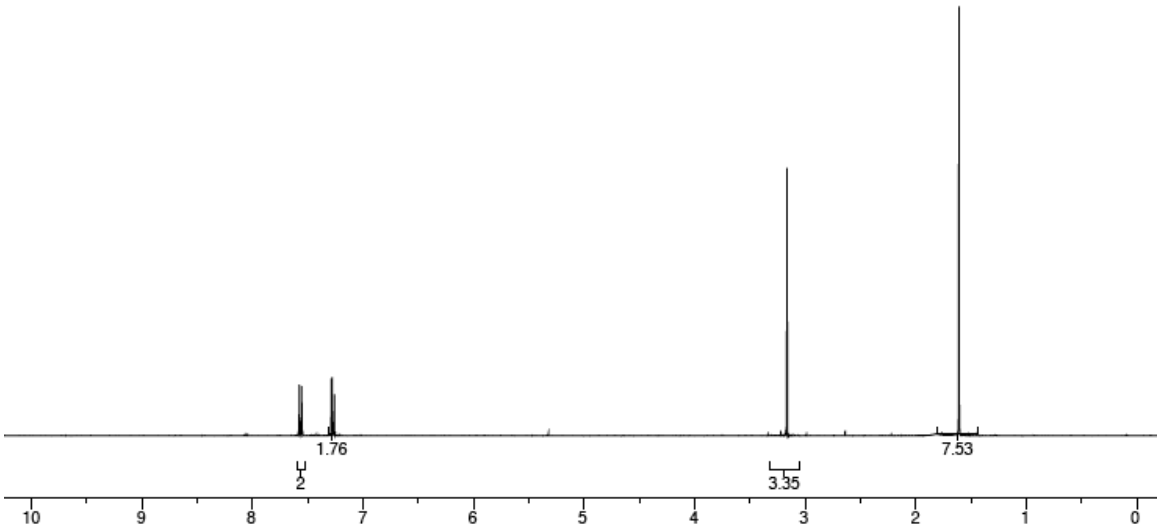


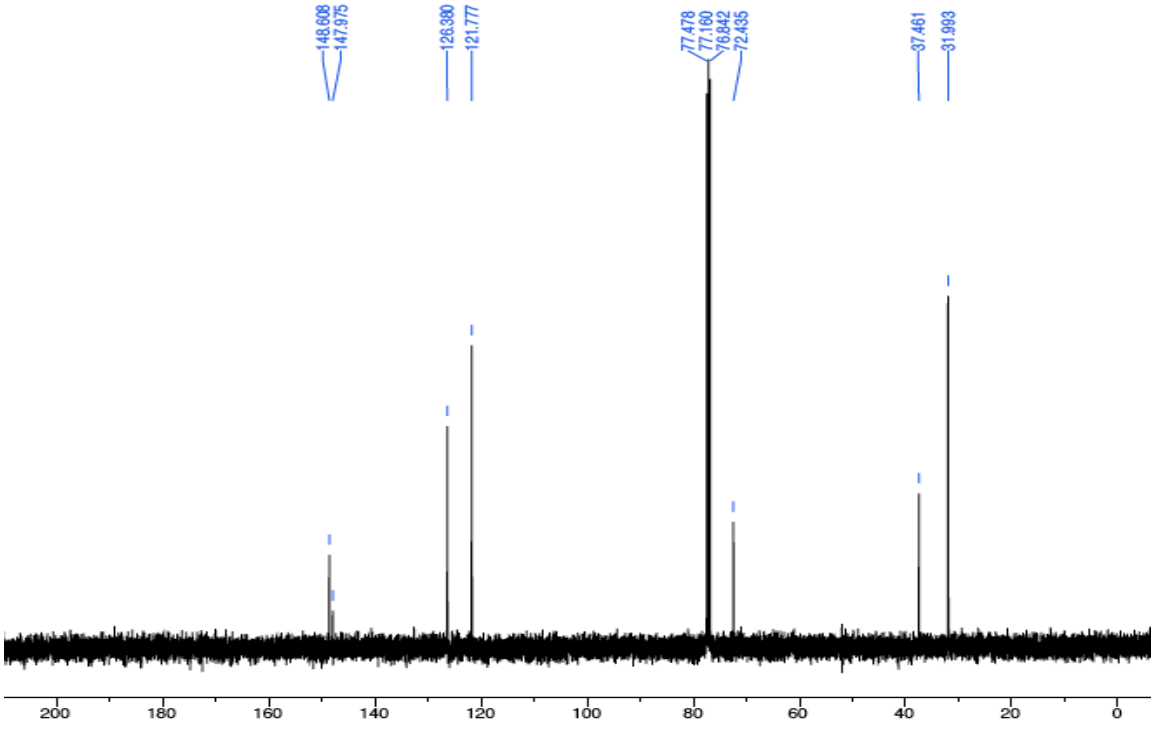
4-Cyclopropyl-4-hydroxybutyl benzoate



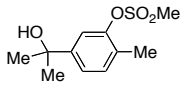
4-(2-Hydroxypropan-2-yl)phenyl methanesulfonate

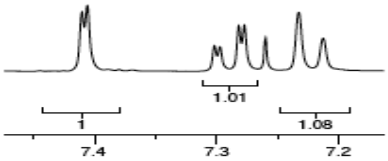


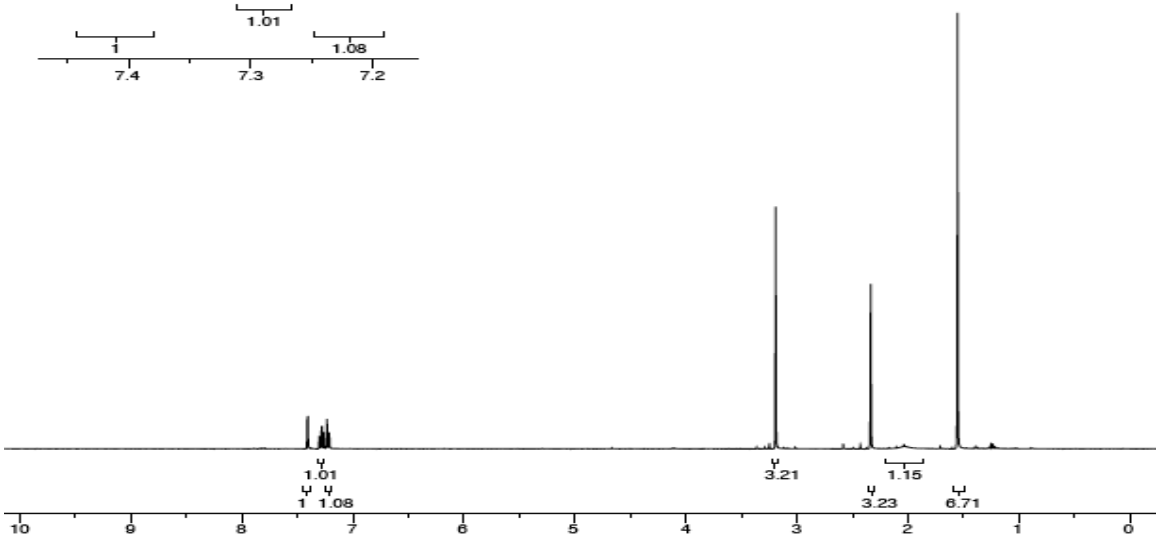


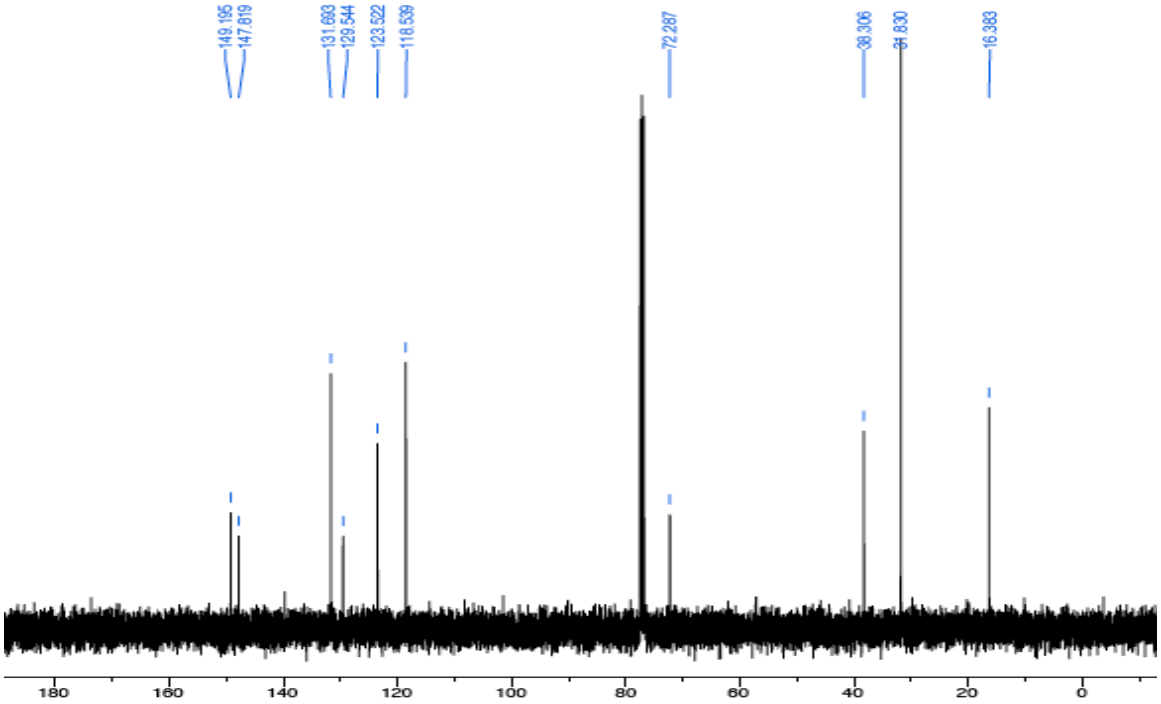


5-(2-Hydroxypropan-2-yl)-2-methylphenyl methanesulfonate

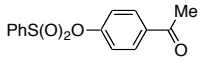


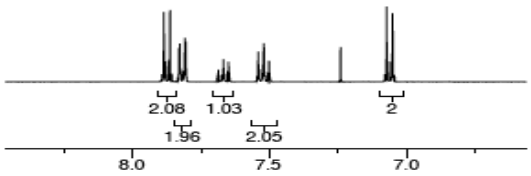


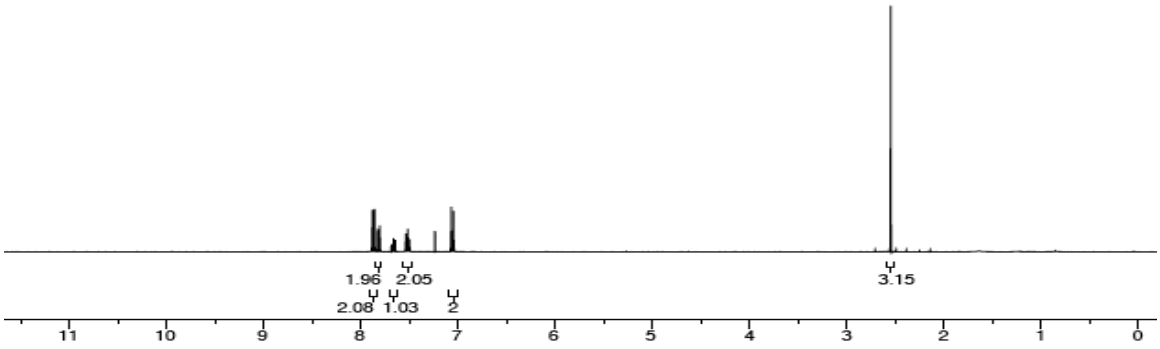


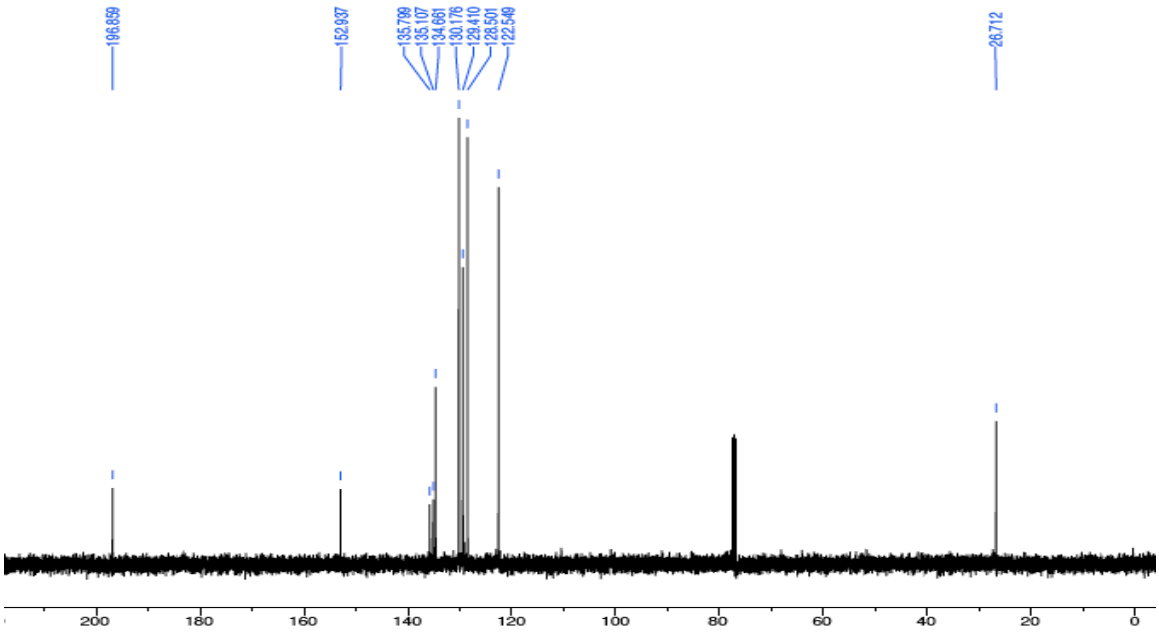


4-Acetylphenyl benzenesulfonate

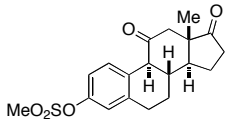


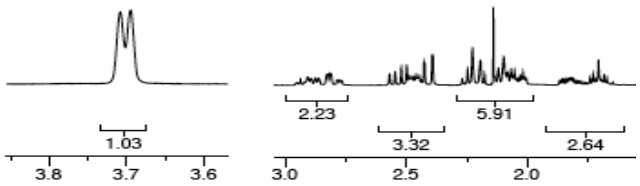


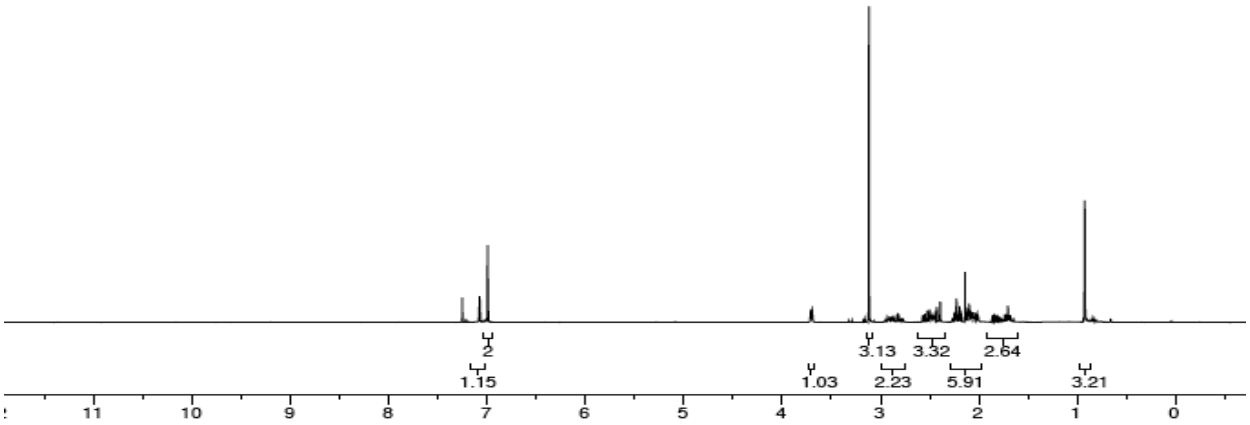


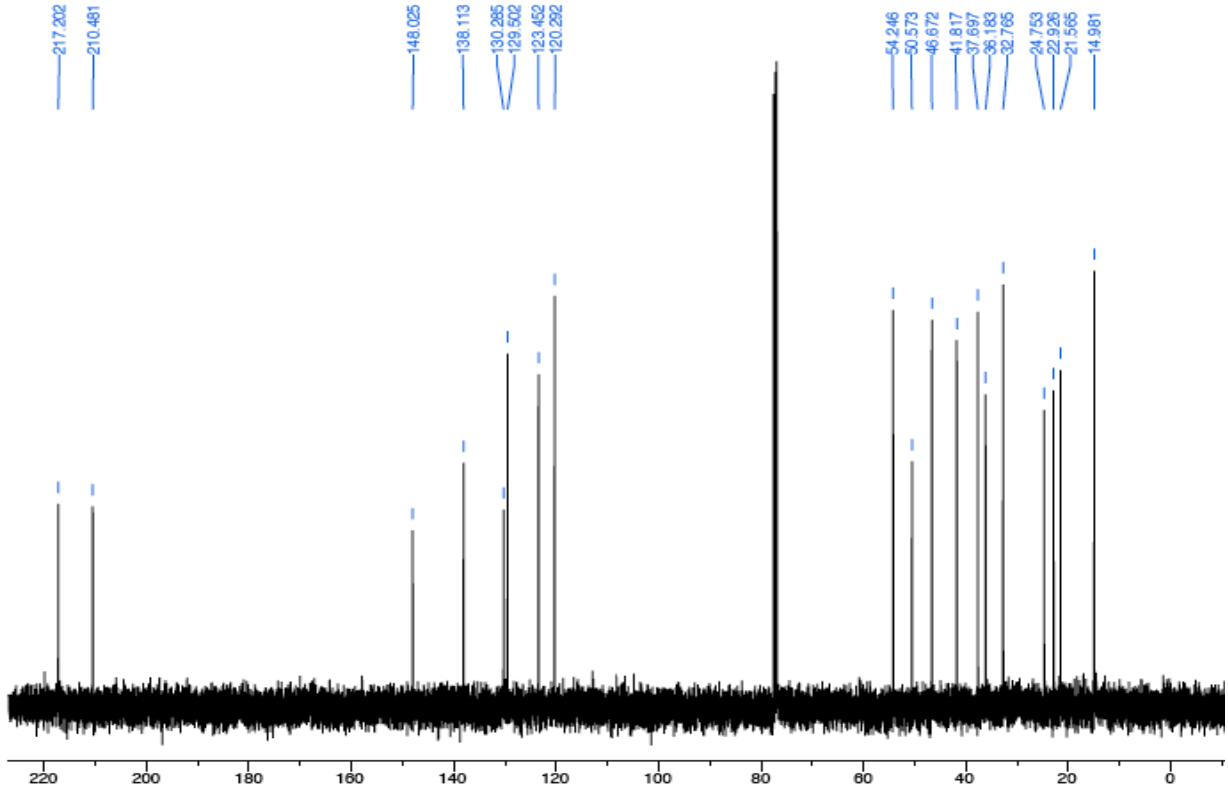


(8*S*,9*S*,13*S*,14*S*)-13-Methyl-11,17-dioxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl methanesulfonate.



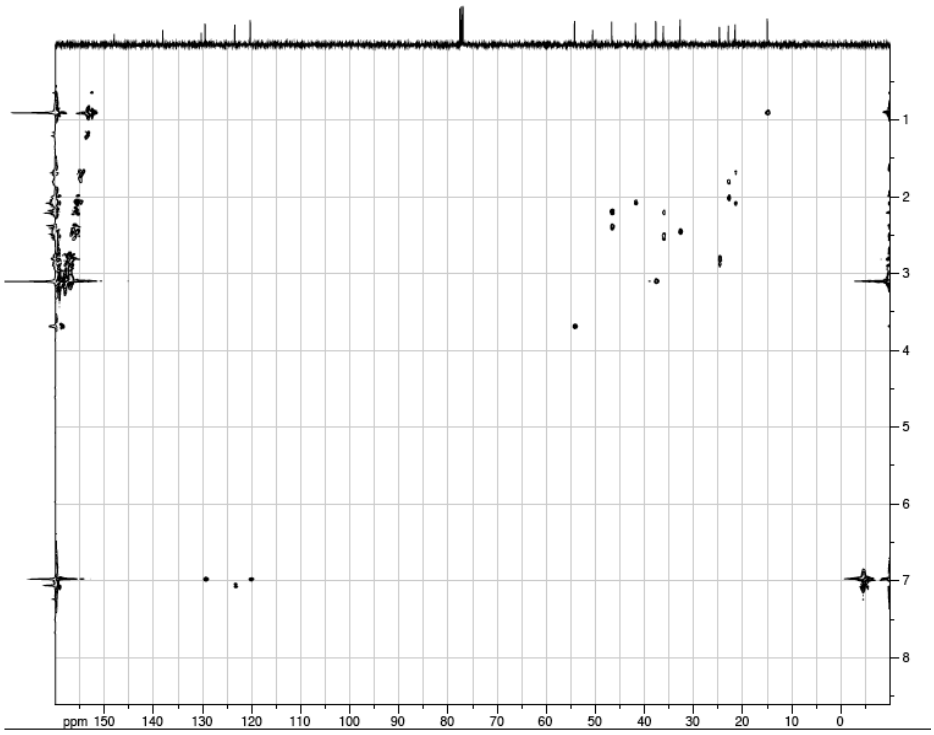




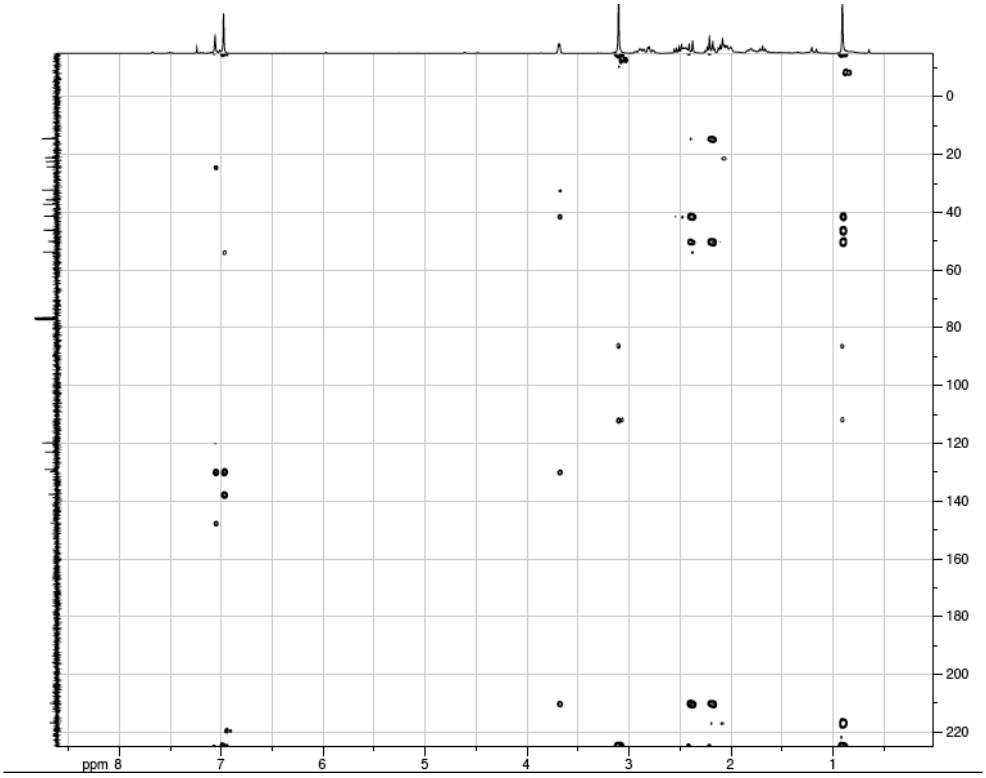


2D NMR Spectra for product appearing in Figure 2:

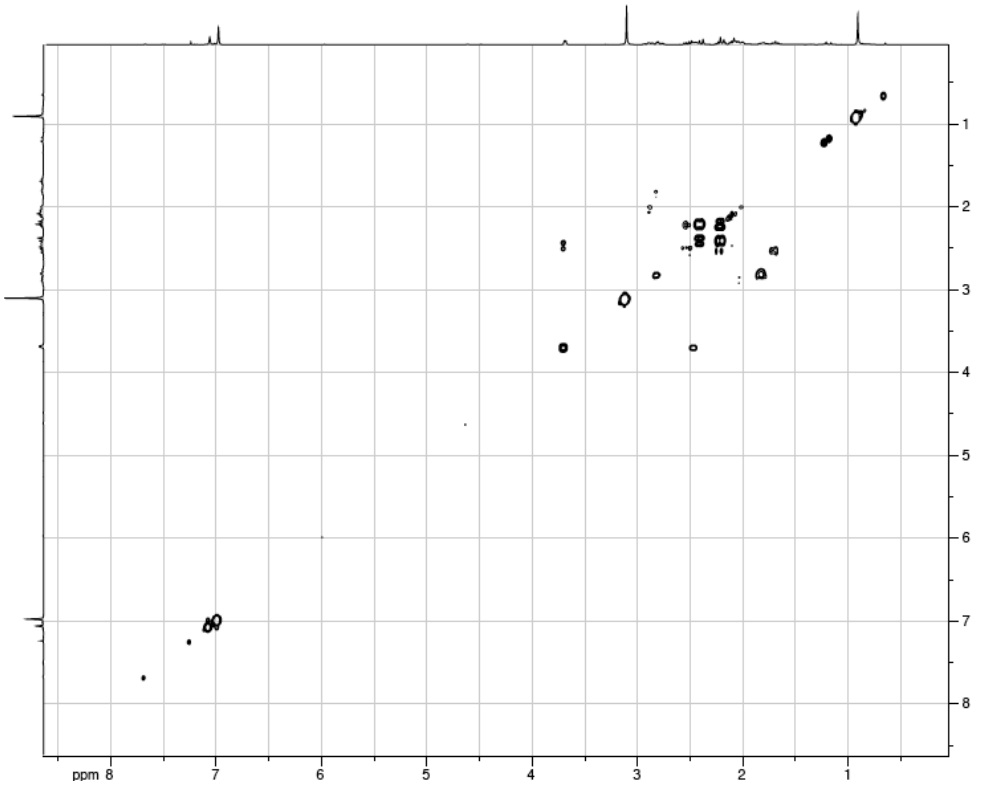
HSQC



HMBC



COSY



Zoomed in: