Synthesis of Rumphellaone A and Hushinone by a Gold-Catalyzed [2+2] Cycloaddition

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Supporting Information

Table of contents

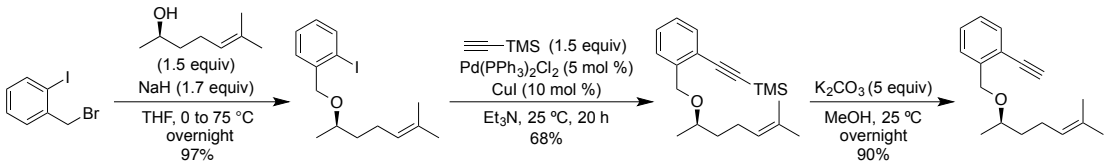
1. General Information

Unless otherwise stated, reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolv^{TM} solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF234) using UV light as the visualizing agent and an acidic solution of vanillin in ethanol as the developing agent. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-63 μm). Silver nitrate-impregnated silica was prepared dissolving 40 g of $AgNO_3$ in 400 mL of water for 213 g of silica and, after removal of water by rotary evaporation, the silica was heated at 130 °C under vacuum overnight. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.
NMR spectra were recorded at 298 K on a Bruker Avance 300 Ultrashield, Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatuses. Spectra were referenced to the solvent residual signal (28.0 ppm of CDCl3). ^{1}H and ^{13}C NMR assignments are corroborated by 1D and 2D experiments (gCOSY, gHSQC and DEPTq135 sequences).
Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers.
HPLC analysis was carried out in an Agilent Tehcnologies instrument HPLC 1200 series with DAD detector. Chiral GC analysis was carried out in an Agilent 6890N (GC) 5973(MSD) instrument with Electron impact (EI) ionization mode. Specific rotation was measured using Jasco P1030 polarimeter in the indicated solvents, concentrations and temperature. Chemicals were purchased from Sigma Aldrich, TCI, Alfa Aesar, Fluorochem and used without further purification unless otherwise reported. The catalyst [IPrAu(PhCN)]BARF was synthesized according reported procedure.[1] (*S*)-BINOL was purchased from Fluka and put under vacuum prior to use. Tetraallyltin was purchased from TCI, Ti(O*i*Pr)$_4$ was purchased from Sigma Aldrich stored in the glovebox and used without further purification.

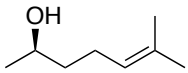
[1] Huguet, N.; Leboeuf, D.; Echavarren, A. M. *Chem. Eur. J.* **2013**, *19*, 6581−6585.

2. Procedures for the preparation of the substrates and characterizations

Synthesis of (*R*)-6-(2-ethynyl)-benzyloxy-2-methylhept-2-ene (6)

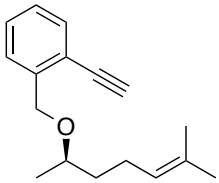


(*R*)-6-methylhept-5-en-2-ol



The alcohol is commercially available (common suppliers) but it can be prepared according to a published procedure.[2] The enantiomeric excess was determined by chiral GC-MS analysis (Betadex 120 30 × 0.25mm, 0.25µm; Tinj/aux 280 °C; flow 1.5mL/min; split 100:1 (0.2µL); isotherm 130 °C; sample in DCM); t_R (minor) 53.923 min, t_R (major) 56.381 min, 98% *ee*.

(*R*)-6-(2-ethynyl)-benzyloxy-2-methylhept-2-ene (6)



To a slurry of sodium hydride (1 g, 26.9 mmol) in THF (81 mL) at 0 °C, a solution of (*R*)-6-methylhept-5-en-2-ol (2.6 g, 20.2 mmol) in THF (81 mL) was added dropwise and stirred for 15 min. Thereafter, 1-(bromomethyl)-2-iodobenzene (5 g, 16.8 mmol) in THF (81 mL) was added over 10 minutes. The mixture was then stirred for 30 min at 0 °C and subsequently the temperature was increased to 75 °C and further stirred for 17 h. The reaction was quenched by addition of methanol followed by water and acidification with HCl 10 %. After complete evaporation of solvents and water, the residue was filtered through a plug of silica and washed with dichloromethane. (*R*)-6-(2-iodo)-benzyloxy-2-methylhept-2-ene was used as it was in the next step (97% yield).

To a solution of (*R*)-6-(2-iodo)-benzyloxy-2-methylhept-2-ene (5.65 g, 16.41 mmol) in triethylamine (15.7 mL, 113 mmol) was added bis(triphenylphosphine)palladium dichloride (0.58 g, 0.82 mmol) and copper(I) iodide (0.313 g, 1.64 mmol) under argon and the mixture was degassed. Ethynyltrimethylsilane (3.5 mL, 24,62 mmol) was then added to the reaction mixture. The solution was stirred at room temperature overnight. After filtration over a pad of silica, the solvent was removed by rotary evaporation. The crude product was purified using CombiFlash chromatographer (100% to 98:2 cyclohexane:diethyl ether) to give (*R*)-6-[2-(trimethylsilyl)ethynyl]-benzyloxy-2-methylhept-2-ene (3.5 g, 68% yield, orange oil).

[2] Chatterjee, S.; Ghadigaonkar, S.; Sur, P.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* **2014**, *79*, 8067−8076.

To a solution of (*R*)-6-[2-(trimethylsilyl)ethynyl]-benzyloxy-2-methylhept-2-ene (3.45 g, 11,48 mmol) in methanol (29 mL) was added potassium carbonate (7.9 g, 57.4 mmol). The reaction mixture was stirred at 24 °C overnight and then quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and filtered. The solvent was removed by rotary evaporation. Purification using CombiFlash chromatographer (100% to 95:5 cyclohexane: diethyl ether) gave (*R*)-6-(2-ethynyl)-benzyloxy-2-methylhept-2-ene (**6**) (2.35 g, 90% yield, orange oil).

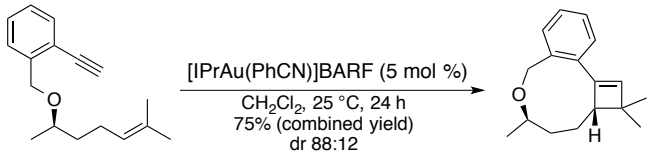
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.54 (m, 1H), 7.51 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.38 (td, *J* = 7.6, 1.4 Hz, 1H), 7.25 (td, *J* = 7.6, 1.4 Hz, 1H), 5.15 – 5.12 (m, 1H), 4.77 (d, *J* = 12.8 Hz, 1H), 4.65 (d, *J* = 12.8 Hz, 1H), 3.63 – 3.55 (m, 1H), 3.31 (s, 1H), 2.21 – 2.02 (m, 2H), 1.75 – 1.66 (m and s, 1H + 3H), 1.63 (s, 3H), 1.51 (dddd, *J* = 13.6, 9.0, 6.8, 5.4 Hz, 1H), 1.25 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 141.7 (Cq), 132.6 (CH, Ar), 131.6 (Cq), 128.9 (CH, Ar), 127.6 (CH, Ar), 127.0 (CH, Ar), 124.4 (CH), 120.4 (Cq), 81.6 (CH), 81.5 (Cq), 74.9 (CH), 68.2 (CH_2), 36.8 (CH_2), 25.7 (CH_3), 24.2 (CH_2), 19.7 (CH_3), 17.7 (CH_3).

$[\alpha]_D$ ($CHCl_3$, *c* 0.23, 25 °C) = −18.4 °

HRMS (ESI+) calculated for $[C_{17}H_{22}ONa]^+$ *m/z* 265.1563; found $[M + Na]^+$ *m/z* 265.1561

(2a*S*,5*R*)-2,2,5-trimethyl-2,2a,3,4,5,7-hexahydrobenzo[*c*]cyclobuta[*e*]oxonine (7)



Inside the glove box, to a solution of (*R*)-6-(2-ethynyl)-benzyloxy-2-methylhept-2-ene (**6**) (650 mg, 2.68 mmol) in CH_2Cl_2 (18 ml) at 23 °C was added catalyst **D** (208 mg, 0.134 mmol). The solution was stirred for 24 h. The reaction was quenched with NEt_3 (500 µL) and the solvent removed under reduced pressure. Separation of the major isomer was obtained by purification on $AgNO_3$-impregnated silica gel (slow elution 300:1 cyclohexane: diethyl ether). (75% overall yield, four runs average).

Data for the major isomer

Physical aspect: light yellow oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 1H), 7.36 – 7.31 (m, 1H), 7.30 – 7.27 (m, 2H), 6.51 (s, 1H), 5.01 (d, *J* = 12.3 Hz, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 3.38 (pd, *J* = 6.4, 2.4 Hz, 1H), 3.08 (dd, *J* = 11.6, 1.7 Hz, 1H), 1.97 – 1.89 (m, 1H), 1.83 (ddt, *J* = 15.0, 5.4, 2.6 Hz, 1H), 1.69 (dddd, *J* = 14.9, 12.3, 6.7, 2.6 Hz, 1H), 1.45 – 1.37 (m, 1H), 1.26 (s, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.13 (s, 3H).

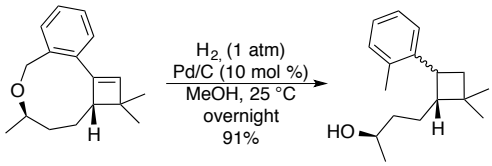
^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0 (Cq), 140.0 (CH), 136.1 (Cq), 133.7 (Cq), 131.2 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, Ar), 127.6 (CH, Ar), 71.6 (CH), 66.4 (CH_2), 57.2 (CH), 42.6 (Cq), 37.1 (CH_2), 28.7 (CH_2), 27.1 (CH_3), 22.6 (CH_3), 22.36 (CH_3).

$[\alpha]_D$ ($CHCl_3$, *c* 0.48, 25 °C) = −158.7 °

HRMS (ESI+) calculated for $[C_{17}H_{22}ONa]^+$ *m/z* 265.1563; found $[M + Na]^+$ *m/z* 265.1568

HPLC Chiralcel OD-H (4.6 mm × 250 mm); hexane:IPA 98:2; 0.8 mL/min; λ = 254 nm, 1 μL injection; t_R (major) 15.263 min, t_R (minor) 16.363 min, 95% *ee*.

(*R*)-4-[(*R*)-2,2-dimethyl-4-(*o*-tolyl)cyclobutyl]butan-2-ol (10)



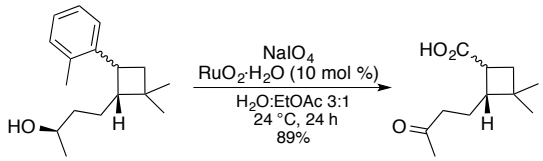
To a solution of compound **7** (350 mg, 1.44 mmol) in MeOH (17.2 mL) was added palladium on carbon (184 mg, 0.17 mmol). The resulting suspension was stirred at 26 °C under H_2 atmosphere (balloon) overnight. The mixture was filtered through a pad of celite, washed with EtOAc, and the solvent was removed under reduced pressure. Purification on slica gel flash column chromatography (4:1 cyclohexane: ethyl acetate) delivered (*R*)-4-[(*R*)-2,2-dimethyl-4-(*o*-tolyl)cyclobutyl]butan-2-ol (**10**) (91% three runs average, colorless resin). Rotamer of the major diastereoisomer (*cis*) is also visible due to high rotational energy barrier.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 0.44H), 7.26 – 7.18 (m, 2.43H), 7.16 – 7.08 (m, 2.79H), 3.85 (dt, *J* = 10.7, 8.4 Hz, 1H), 3.75 (q, *J* = 6.1 Hz, 0.42H), 3.57 – 3.45 (m, 1H), 3.17 (q, *J* = 9.5 Hz, 0.41H), 2.30 (s, 1.75H), 2.27 (s, 3H), 2.25 – 2.17 (m, 1.27H), 2.12 (ddd, *J* = 10.6, 8.5, 0.8 Hz, 0.45H), 1.86 (ddd, *J* = 11.1, 8.2, 3.2 Hz, 1H), 1.64 – 1.48 (m, 1.32H), 1.41 – 1.35 (m, 4H), 1.28 – 1.21 (m, 1.46H), 1.21 – 1.13 (m, 4.47H), 1.07 −1.03 (m, 3.72H), 0.99 (d, *J* = 6.2 Hz, 3H), 0.95 (d, *J* = 6.2 Hz, 0.77H), 0.93 – 0.80 (m, 1.93H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0 (Cq *trans*), 139.5 (Cq *cis*), 136.9 (Cq *cis*), 136.8 (Cq rotamer), 135.8 (Cq *trans*), 129.9 (CH *trans*), 129.6 (CH *cis*), 129.5 (CH rotamer), 126.8 (CH *cis*), 126.75 (rotamer), 125.9 (CH *trans*), 125.8 (CH *cis*), 125.78 (CH rotamer), 125.55 (CH *trans*), 125.53 (CH rotamer), 125.51 (CH *cis*), 125.4 (CH *trans*), 68.4 (CH *trans*), 68.2 (CH rotamer), 68.19 (CH *cis*), 49.9 (CH_3 *trans*), 47.7 (CH_3 rotamer), 47.6 (CH_3 *cis*), 41.51 (CH_2 *trans*), 38.1 (CH *trans*), 30.0 (CH_2 *cis*), 37.9 (CH_2 rotamer), 37.6 (CH_2 *trans*), 35.1 (CH_2 *cis*), 35.08 (rotamer), 34.62 (rotamer), 34.61 (CH *cis*), 34.1 (Cq *trans*), 33.9 (rotamer), 33.89 (Cq *cis*), 31.2 (CH_3 *trans*), 30.3 (CH_3 *cis*), 26.9 (CH_2 *trans*), 25.0 (rotamer), 24.98 (CH_3 *cis*), 23.3 (CH_3 *trans*), 23.28 (CH *cis*), 23.13 (rotamer), 23.1 (CH_2 *cis*), 22.4 (CH *trans*), 19.7 (CH_3 *trans*), 19.66 (CH_3 *cis*). Some peaks of the *cis* rotamer are missing for overlapping.

HRMS (ESI+) calculated for $[C_{17}H_{26}ONa]^+$ *m/z* 269.1876; found $[M + Na]^+$ *m/z* 269.1863

(2*R*)-3,3-dimethyl-2-(3-oxobutyl)cyclobutane-1-carboxylic acid (11)



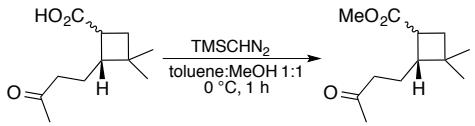
To a round 500 mL round bottom flask (*R*)-4-[(*R*)-2,2-dimethyl-4-(*o*-tolyl)cyclobutyl]butan-2-ol (**10**) (356 mg, 1.44 mmol) dissolved in ethyl acetate (40 ml) was added followed by water (168 ml). The biphasic system was cooled down to 0 °C. Sodium periodate (4.6 g, 21,67 mmol) and ruthenium(IV) oxide hydrate (21.8 mg, 0.14 mmol) were added sequentially. The reaction was stirred vigorously (1200 rpm) for 24 h at 24 °C. The reaction was initially extracted with EtOAc (100 mL × 4) and concentrated to a minimum amount of EtOAc (10 mL). The organic layer was washed with a solution of brine: aqueous saturated solution of Na_2SO_3 10:1 (10 mL). The aqueous layer was separated and acidified with conc. HCl to pH=2 and extracted with EtOAc (10 mL × 4). The combined organic layers were washed with aqueous saturated solution of Na_2CO_3 (20 mL) followed by extraction in DCM (20 mL × 1). The aqueous phases were acidified again with conc. HCl conc. to pH=2 and extracted with EtOAc (20 mL × 5). The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Compound **11** was used for the next step without futher purification (89% three runs average, orange resin).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (ddd, *J* = 10.2, 8.9, 6.0 Hz, 1H), 2.70 (q, *J* = 9.3 Hz, 1H), 2.57 – 2.28 (m, 6H), 2.15 (s, 6H), 2.13 – 2.09 (m, 1H), 1.97 – 1.81 (m, 3H), 1.80 – 1.64 (m, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3 (Cq. Ketone), 209.2 (Cq, ketone), 181.4 (Cq, COOH), 180.5 (Cq, COOH), 47.7 (CH), 46.4 (CH), 42.0 (Cq), 41.2 (CH_2), 39.1 (CH), 36.4 (CH), 35.9 (CH_2), 35.8 (CH_2), 34.5 (Cq), 33.8 (CH_2), 31.0 (CH_3), 30.1 (CH_3), 29.9 (CH_3), 29.9 (CH_3), 23.9 (CH_2), 23.2 (CH_3), 22.3 (CH_3), 21.4 (CH_2).

HRMS (ESI+) calculated for $[C_{11}H_{17}O_3]^+$ *m/z* 197.1183; found $[M + H]^+$ *m/z* 197.1190

Methyl (2*R*)-3,3-dimethyl-2-(3-oxobutyl)cyclobutane-1-carboxylate



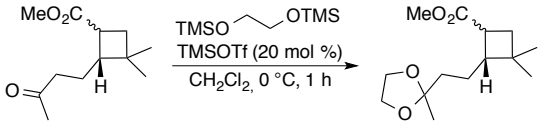
(2*R*)-3,3-dimethyl-2-(3-oxobutyl)cyclobutane-1-carboxylic acid **11** (250 mg, 1.26 mmol) was dissolved in a mixture of toluene (3.3 ml) and methanol (3.3 ml) under argon. The solution was cooled down to 0 °C and trimethylsilyldiazomethane (2.5 ml, 5.04 mmol) was added dropwise. The reaction was stirred at the same temperature for 1.5 h and then concentrated under vacuum. Methyl (2*R*)-3,3-dimethyl-2-(3-oxobutyl)cyclobutane-1-carboxylate was used in the next step without further purification (98% three runs average, colorless resin).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 – 3.58 (2s, 3 + 1.28H), 3.16 (ddd, *J* = 10.0, 8.9, 6.2 Hz, 1H), 2.63 (q, *J* = 9.3 Hz, 0.42H), 2.39 – 2.22 (m, 4.28H), 2.15 – 2.03 (m, 6H), 1.95 – 1.72 (m, 2H), 1.69 – 1.61 (m, 2.8H), 1.11 (s, 2.83H), 1.05 (s, 1.25H), 1.04 –1.02 (m, 4.35H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6 (Cq, ketone *trans*), 208.4 (Cq, ketone *cis*), 175.8 (Cq, ester *trans*), 175.0 (Cq, ester *cis*), 51.6 (CH_3 *trans*), 51.4 (CH_3 *cis*), 47.6 (CH, *trans*), 46.2 (CH *cis*), 41.9 (CH_2 *cis*), 41.3 (CH_2 *trans*), 39.1 (CH, *trans*), 36.2 (CH *cis*), 36.0 (Cq *trans*), 35.6 (Cq *cis*), 34.5 (CH_2 *trans*), 34.0 (CH_2 *cis*), 31.0 (CH_3 *cis*), 30.1 (CH_3 *trans*), 29.9 (CH_3 *trans*), 29.86 (CH_3 *cis*), 23.9 (CH_2 *trans*), 23.2 (CH_3 *cis*), 22.2 (CH_3 *trans*), , 21.5 (CH_2 *cis*).

HRMS (ESI+) calculated for $[C_{12}H_{20}O_3Na]^+$ *m/z* 235.1305; found $[M + Na]^+$ *m/z* 235.1300

Methyl (2*R*)-3,3-dimethyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclobutane-1-carboxylate (12)



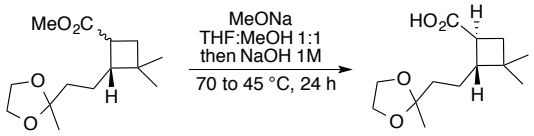
Methyl (2*R*)-3,3-dimethyl-2-(3-oxobutyl)cyclobutane-1-carboxylate (268 mg, 1.26 mmol) was dissolved in CH_2Cl_2 (3.3 mL) under argon and cooled down to 0 °C. Trimethylsilyl trifluoromethanesulfonate (45.6 µl, 0.25 mmol) and 2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane (619 µl, 2.52 mmol) were added in this order. The reaction was stirred at 0 °C for 1.5 h then quenched with pyridine. The solution was diluted with CH_2Cl_2, washed with saturated aqueous solution of $NaHCO_3$, $CuSO_4$ 10% and water sequentially. The organic layers were dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Compound **12** was used in the next step without further purification (95% three runs average, yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$ δ 4.01 – 3.84 (m, 6H), 3.67 (s, 3H), 3.66 (s, 1.5H), 3.18 (ddd, *J* = 9.8, 8.8, 6.4 Hz, 1H), 2.62 (q, *J* = 9.2 Hz, 0.45H), 2.31 – 2.22 (m, 1H), 2.16 – 2.10 (m, 1.5H), 1.94 – 1.84 (m, 0.48H), 1.85 – 1.73 (m, 1.5H), 1.57 – 1.43 (m, 6.2H), 1.33 – 1.28 (m, 4.7H), 1.13 (s, 3H), 1.08 (s, Hz, 1.4H), 1.06 (s, 3H), 1.04 (s, 1.7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (Cq *trans*), 175.1 (Cq *cis*), 109.9 (Cq *cis*), 109.86 (Cq *trans*), 64.6 ($2CH_2$ *cis*), 64.58 ($2CH_2$ *trans*), 51.5 (CH_3 *trans*), 51.2 (CH_3 *cis*), 48.3 (CH *trans*), 47.0 (CH *cis*), 39.3 (CH *trans*), 37.5 (CH_2 *cis*), 36.7 (CH_2 *trans*), 36.4 (CH *cis*), 35.9 (CH_2 *trans*), 35.6 (Cq *cis*), 34.5 (Cq *trans*), 33.9 (CH_2 *cis*), 31.2 (CH_3 *cis*), 30.4 (CH_3 *trans*), 24.7 (CH_2 *trans*), 23.7 (CH_3 *trans*), 23.7 (CH_3 *cis*), 23.3 (CH_3 *cis*), 22.2 (CH_3 *trans*), 21.9 (CH_2 *cis*).

HRMS (ESI+) calculated for $[C_{14}H_{24}O_4Na]^+$ *m/z* 279.1567; found $[M + Na]^+$ *m/z* 279.1560

(1*S*,2*R*)-3,3-dimethyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclobutane-1-carboxylic acid (13)



Inside the glovebox, methyl (2R)-3,3-dimethyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclobutane-1-carboxylate (**12**) (145 mg, 0.57 mmol) was dissolved in THF (1.2 mL) in a microwave vial. Then sodium methoxide (33.7 mg, 0.62 mmol) and MeOH (1.2 mL) were added and the vial was sealed. The resulting mixture was stirred outside the glovebox for 20 h at 70 °C (the reaction monitored by GC-MS). An aqueous solution of sodium hydroxide 1M (1.1 mL, 1.13 mmol) was then added and the reaction stirred a 45 °C until consumption of the starting material (TLC 1:1 cyclohexane:ethyl acetate; 2-3 h). The reaction was cooled down to 0 °C , diluted with EtOAc (10 mL) and quenched with aqueous saturated solution of NH_4Cl and extracted with EtOAc (5 × 10 mL). The aqueous solutions were acidified with HCl 1M to pH = 6/5 (warning: lower pH caused the acetal cleavage) and extracted with EtOAc (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. Compound **13** was used in the next step without further purification (86% three runs average, brown resin).

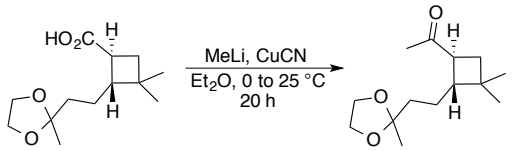
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.87 (brs, 1), 4.02 – 3.85 (m, 4H), 2.65 (q, J = 9.2 Hz, 1H), 2.22 – 2.14 (m, 1H), 2.00 – 1.74 (m, 2H), 1.66 – 1.45 (m, 4H), 1.31 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5 (Cq, CO), 109.9 (Cq), 64.6 ($2CH_2$), 48.3 (CH), 39.2 (CH), 36.6 (CH_2), 35.8 (CH_2), 34.5 (Cq), 30.4 (CH_3), 24.7 (CH_2), 23.7 (CH_3), 22.2 (CH_3).

$[\alpha]_D$ (acetone, c 0.15, 25 °C) = −149.9 °

HRMS (ESI−) calculated for $[C_{13}H_{21}O_4]^-$ m/z 241.1445; found $[M - H]^-$ m/z 241.1438

1-{(1*S*,2*R*)-3,3-dimethyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclobutyl}ethan-1-one (8)



To a flame dried (under *vacuum*) 25 mL round-bottomed flask equipped with stirbar under argon atmosphere was added solid cyanocopper (444 mg, 4.95 mmol) followed by diethyl ether (1.7 ml). The flask was cooled down to 0 °C and a methyllithium (6.6 mL, 9.90 mmol) was added dropwise *via* syringe. The reaction was stirred for 5 min at 0 °C and a solution of (1S,2R)-3,3-dimethyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclobutane-1-carboxylic acid **13** (240 mg, 0.99 mmol) in diethyl ether (5 ml) was added dropwise at a rate of approximately 1 mL/min. The reaction was allowed to warm to 25 °C over a period of 1 hour, and was stirred at the same temperature for 14 hours. The reaction was determined to be completed by TLC analysis (TLC 1:1 cyclohexane:ethyl acetate; 2-3 h), and was quenched with aqueous saturated solution of NH_4Cl. The biphasic mixture was transferred to a separatory funnel, and

the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Compound **8** was purified by silica gel flash column chromatography (7:3 cyclohexane: ethyl acetate) (65% two runs average, light yellow oil).

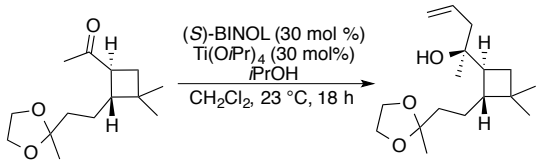
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 – 3.81 (m, 4H), 2.74 (q, *J* = 9.2 Hz, 1H), 2.15 – 2.07 (m, 4H), 1.80 – 1.75 (m, 2H), 1.59 – 1.40 (m, 4H), 1.30 (s, 3H), 1.05 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1 (Cq, CO), 109.8 (Cq), 64.6 ($2CH_2$), 47.4 (CH), 46.8 (CH), 37.0 (CH_2), 36.1 (CH_2), 33.8 (Cq), 30.5 (CH_3), 28.3 (CH_3), 24.9 (CH_2), 23.7 (CH_3), 22.4 (CH_3).

$[\alpha]_D$ ($CHCl_3$, *c* 0.21, 23 °C) = +499.0 °

HRMS (ESI+) calculated for $[C_{14}H_{24}O_3Na]^+$ *m/z* 263.1618; found $[M + Na]^+$ *m/z* 263.1623

(*S*)-2-{(1*S*,2*R*)-3,3-dimethyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclobutyl}pent-4-en-2-ol (9)



Titanium(IV) isopropoxide (47.5 µl, 0.16 mmol) was added to a solution of (*S*)-[1,1'-binaphthalene]-2,2'-diol (46.5 mg, 0.16 mmol) in CH_2Cl_2 (1300 µl) and the orange solution was stirred at 25 °C for several minutes. Propan-2-ol (828 µl, 10.82 mmol) was added, followed by 1-{(1*S*,2*R*)-3,3-dimethyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclobutyl}ethan-1-one (**8**) (130 mg, 0.54 mmol) and tetraallylstannane (195 µl, 0.81 mmol). After an initial induction period, the color of the solution lightened from orange to yellow. After 16 h stirring at the same temperature, the reaction was quenched with aqueous saturated solution of NH_4Cl and extracted in CH_2C_2 (4 × 10 mL). After removal of the solvent under reduced pressure, the resulting oily residue was extracted with cyclohexane, dried over Na_2SO_4, filtered through celite and concentrated under reduced pressure. Purification by $AgNO_3$-impregnated silica gel flash column chromathography (slow elution 6:4 cyclohexane: diethyl ether) afforded pure **9** and a minor fraction of a mixture of both isomers (combined yield 80%).

Data for the major isomer

Physical aspect: light yellow oil

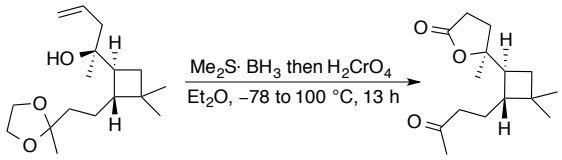
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.5, 10.3, 7.5 Hz, 1H), 5.19 – 5.05 (m, 2H), 4.02 – 3.89 (m, 4H), 2.20 – 2.02 (m, 2H), 1.95 – 1.82 (m, 2H), 1.69 – 1.46 (m, 6H), 1.32 (s, 3H), 1.12 (s, 3H), 1.07 – 1.06 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2 (CH), 118.4 (CH_2), 110.0 (Cq), 72.0 (Cq), 64.6 ($2CH_2$), 45.0 (CH_2), 44.9 (CH), 44.5 (CH), 37.6 (CH_2), 33.6 (CH_2), 33.0 (Cq), 31.2 (CH_3), 26.2 (CH_2), 25.1 (CH_3), 23.5 (CH_3), 22.5 (CH_3).

$[\alpha]_D$ (acetone, *c* 0.27, 23 °C) = +351.6 °

HRMS (ESI+) calculated for $[C_{17}H_{30}O_3Na]^+$ *m/z* 305.2087; found $[M + Na]^+$ *m/z* 305.2094

(*S*)-5-[(1*S*,2*R*)-3,3-dimethyl-2-(3-oxobutyl)cyclobutyl]-5-methyldihydrofuran-2(3*H*)-one (rumphellaone A) (1)



To a stirred solution of (S)-2-{(1S,2R)-3,3-dimethyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclobutyl}pent-4-en-2-ol (**9**) (81 mg, 0.29 mmol) in diethyl ether (290 µl), cooled to −78 °C wass added BMS (186 µl, 0.37 mmol). The mixture was allowed to warm up to 25 °C (warning: hydrogen formation) and was stirred at the same temperature for 12 h. A solution chromic acid (1 mL, 0.86 mmol) [prepared from $Na_2Cr_2O_7$•H_2O 2.6 g, conc. H_2SO_4 1.9 ml and then diluted to volume (10 mL) with water] was added dropwise to the mixture at 0 °C. The mixture was refluxed for 1 h and cooled down to 25 °C. The reaction was diluted with ethyl acetate, the organic phase was and the aqueous layer were extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Purification by silica gel flash column chromatography (6:4 diethyl ether:cyclohexane) afforded compound **1** (38 mg, 53%, colorless resin which solidified upon standing).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 – 2.48 (m, 2H), 2.42 – 2.33 (m, 2H), 2.17 – 1.98 (s + m, 5H), 1.94 – 1.81 (m, 2H), 1.74 – 1.53 (m, 3H), 1.51 – 1.38 (m, 1H), 1.32 (s, 3H), 1.07 – 1.04 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5 (Cq), 176.9 (Cq), 87.2 (Cq), 44.5 (CH), 44.2 (CH), 42.0 (CH_2), 33.5 (CH_2), 33.0 (Cq), 30.9 (CH_3), 30.6 (CH_2), 29.9 (CH_3), 29.1 (CH_2), 25.1 (CH_2), 24.9 (CH_3), 22.5 (CH_3).

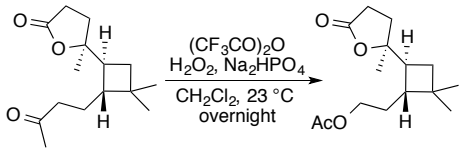
$[\alpha]_D$ ($CHCl_3$, *c* 1.11, 25 °C) = +65.6 °; lit.[3] $[\alpha]_D$ ($CHCl_3$, *c* 1.11, 30 °C) = +75.8 °

HRMS (ESI+) calculated for $[C_{15}H_{25}O_3]^+$ *m/z* 253.1798; found $[M + H]^+$ *m/z* 253.1806

Chiral GC-MS analysis (HP5-MS 30m × 0.25mm, 0.25µm Tinj/Aux 280 °C; flow 1.5mL/min split 50:1 (1µL); method: 50-325(5')/10 °C min; sample in DCM); t_R (minor) 15.580 min, t_R (major) 15.646 min, 97% *ee*.

(*S*)-5-[(1*S*,2*R*)-2-(2-acetoxyethyl)-3,3-dimethylcyclobutyl]-5-methyldihydrofuran-2(3*H*)-one (14)

[3] Hirokawa, T.; Nagasawa, T.; Kuwahara, S. *Tetrahedron Lett.* **2012**, *53*, 705−706.



Trifluoroacetic anhydride (121 µl, 0.86 mmol) was added to a csuspension of hydrogen peroxide (35.0 µl, 0.57 mmol) in CH_2Cl_2 (274 µl) at 0 °C. The resulting solution was stirred for 5 min at 0 °C, and then sodium phosphate dibasic (122 mg, 0.86 mmol) was added followed by a solution of 5-[(1*R*,2*S*)-3,3-dimethyl-2-(3-oxobutyl)cyclobutyl]-5-methyldihydrofuran-2(3*H*)-one (18 mg, 0.07 mmol) in CH_2Cl_2 (274 µl) (plus rinse 0.2 mL × 2). The resulting suspension was stirred at 23 °C overnight, poured into 1 mL of saturated $NaHCO_3$ and extracted with EtOAc (3 × 2 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by silica gel flash column chromatography (35:15 cyclohexane: ethyl acetate) afforded compound **14** (60%, three runs average, colorless resin).

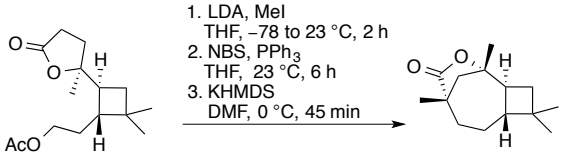
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 – 3.89 (m, 2H), 2.74 – 2.45 (m, 2H), 2.14 – 1.99 (m and s, 6H), 1.97 – 1.71 (m, 3H), 1.60 (dd, *J* = 10.7, 7.8 Hz, 1H), 1.55 – 1.43 (m, 1H), 1.33 (s, 3H), 1.07 (m, 3H + 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (Cq), 171.0 (Cq), 87.1 (Cq), 63.0 (CH_2), 43.9 (CH), 42 (CH), 33.6 (CH_2), 33.1 (Cq), 30.7 (CH_2), 30.6 (CH_3), 30.3 (CH_2), 29.2 (CH_2), 24.8 (CH_3), 22.7 (CH_3), 21.0 (CH_3).

$[\alpha]_D$ ($CHCl_3$, *c* 0.42, 26 °C) = +65.5 °

HRMS (ESI+) calculated for $[C_{15}H_{24}O_4Na]^+$ *m/z* 291.1567; found $[M + Na]^+$ *m/z* 291.1574

(1*S*,2*S*,5*R*,8*S*)-1,4,4,8-tetramethyl-10-oxatricyclo[6.2.1.0^{2,5}]undecan-9-one (hushinone) (2)



To a solution of diisopropylamine (17.8 µl, 0.125 mmol) in dry THF (145 µl) at 0 °C was added *n*-butyllithium (44.7 µl, 0.125 mmol) dropwise. The solution was stirred at 0 °C 5 min and then cooled down to −78 °C at which time (*S*)-5-[(1*S*,2*R*)-2-(2-acetoxyethyl)-3,3-dimethylcyclobutyl]-5-methyldihydrofuran-2(3*H*)-one (**14**) (32 mg, 0.12 mmol) in dry THF (145 µl × 2) was added over 10 min. The mixture was stirred at −78 °C for 20 min then iodomethane (8.2 µl, 0.11 mmol) was added in one portion. The mixture was allowed to warm to 23 °C, stirred for 2 h and then partitioned between EtOAc and saturated aqueous solution of NH_4Cl. The phases were separated, and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (1:1 cyclohexane: ethyl acetate) afforded 5-[(1*S*,2*R*)-2-(2-

hydroxyethyl)-3,3-dimethylcyclobutyl]-3,5-dimethyldihydrofuran-2(3*H*)-one (34%, colorless resin). The NMR spectra matched with those previously reported in the literature.[4]

To a stirred solution of 5-[(1*S*,2*R*)-2-(2-hydroxyethyl)-3,3-dimethylcyclobutyl]-3,5-dimethyldihydrofuran-2(3*H*)-one (9.7 mg, 0.04 mmol) and triphenylphosphine (15 mg, 0.06 mmol) in THF (404 µl) was added N-bromosuccinimide (9.3 mg, 0.05 mmol) at 23 °C. After 6 h, the mixture was quenched with water and extracted with EtOAc (3 × 2 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (5:1 cyclohexane: ethyl acetate) afforded 5-[(1*S*,2*R*)-2-(2-bromoethyl)-3,3-dimethylcyclobutyl]-3,5-dimethyldihydrofuran-2(3*H*)-one (61%, colorless resin). The NMR spectra matched with those previously reported in the literature.[4]

To a stirred solution of 5-[(1*S*,2*R*)-2-(2-bromoethyl)-3,3-dimethylcyclobutyl)-3,5-dimethyldihydrofuran-2(3*H*)-one (7.5 mg, 0.025 mmol) in N,N-Dimethylformamide (102 µl) at 0 °C was added potassium hexamethyldisilazide (99 µl, 0.05 mmol). After 45 min the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate (3 × 1 mL). The organic phase was washed with a saturated aqueous solution of NH_4Cl, water and brine, dried over $MgSO_4$ and concentrated reduced pressure. Purification by silica gel flash column chromatography (9:1 cyclohexane: ethyl acetate) afforded hushinone **2** (99%, white solid).[4]

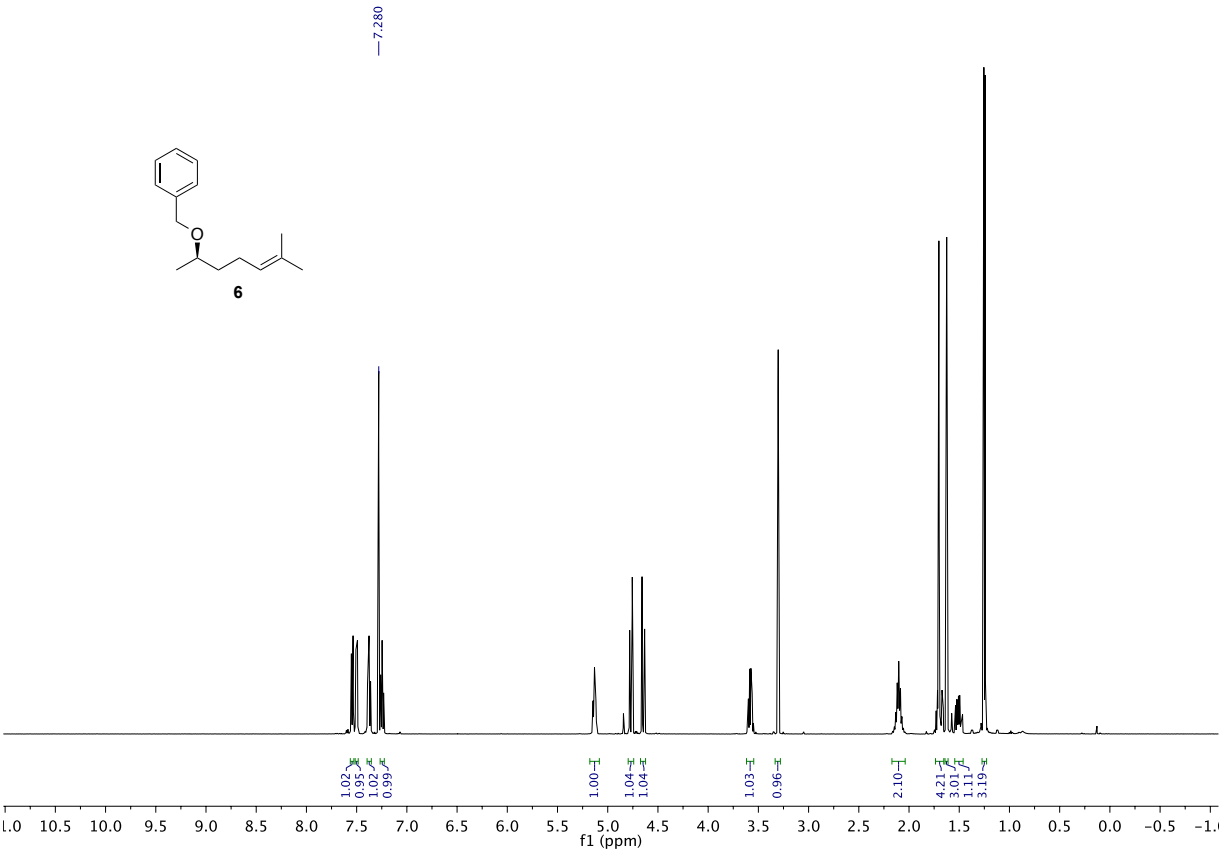
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (d, *J* = 12.9 Hz, 1H), 2.21 (td, *J* = 11.7, 7.8 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.86 – 1.62 (m, 4H), 1.55 – 1.49 (m, 1H), 1.35 (s, 4H), 1.33 – 1.21 (m, 5H), 1.03 – 1.028 (m, 6H).

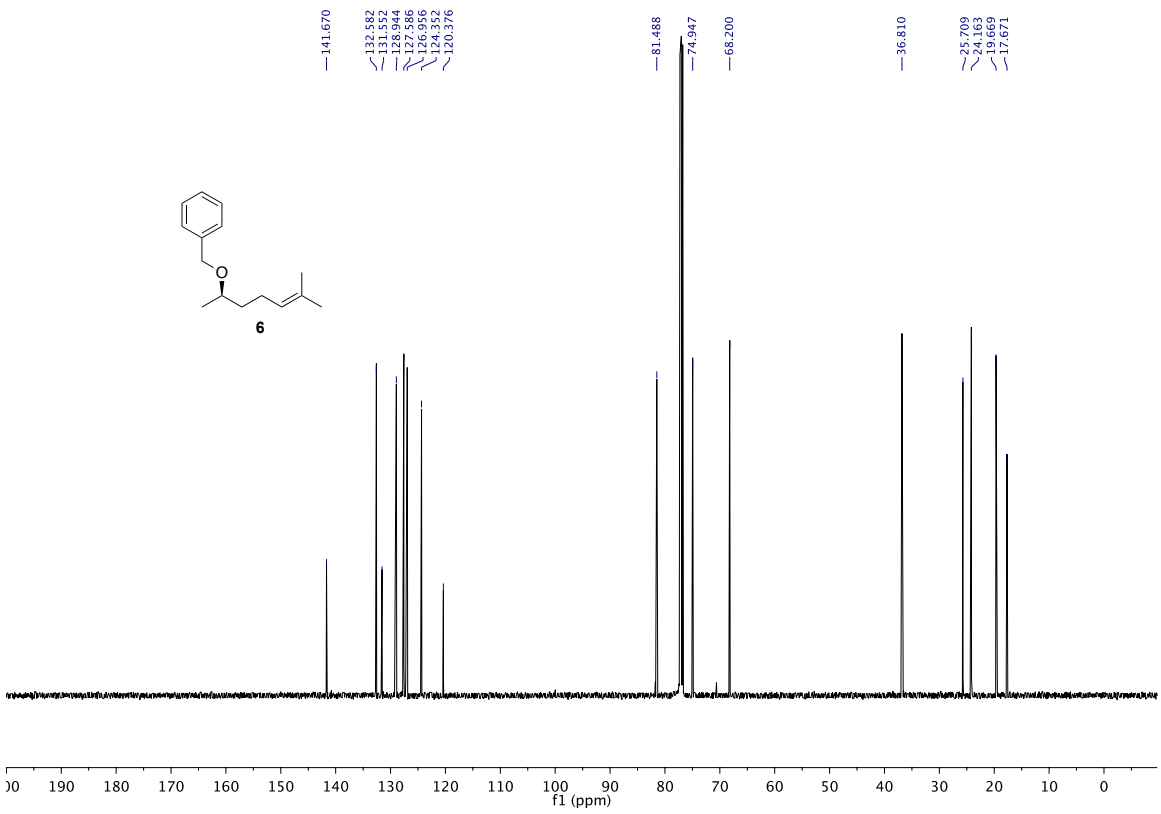
^{13}C NMR (101 MHz, $CDCl_3$) δ 181.8 (Cq), 86.0 (Cq), 50.8 (CH), 48.8 (CH), 46.6 (Cq), 46.58 (CH_2), 39.4 (CH_2), 37.8 (CH_2), 35.5 (Cq), 30.2 (CH_3), 28.1 (CH_3), 26.7 (CH_2), 22.3 (CH_3), 19.8 (CH_3).

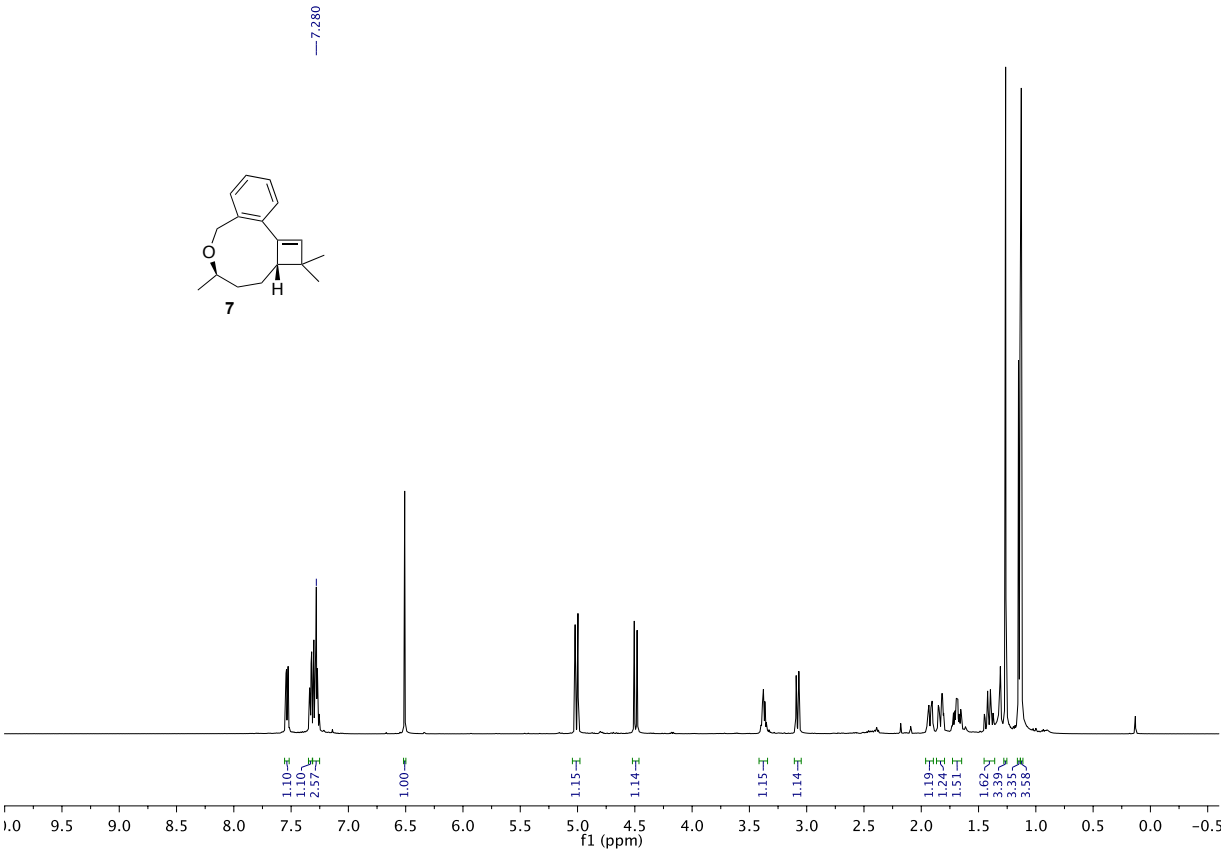
$[\alpha]_D$ (EtOH, *c* 0.35, 25 °C) = +32.0 °; lit. [4]$[\alpha]_D$ (EtOH, *c* 1.00, 23 °C) = +24.1 °

[4] Hirokawa, T.; Kuwahara, S. *Eur. J. Org. Chem.* **2013**, 2780−2782.

3. NMR spectra



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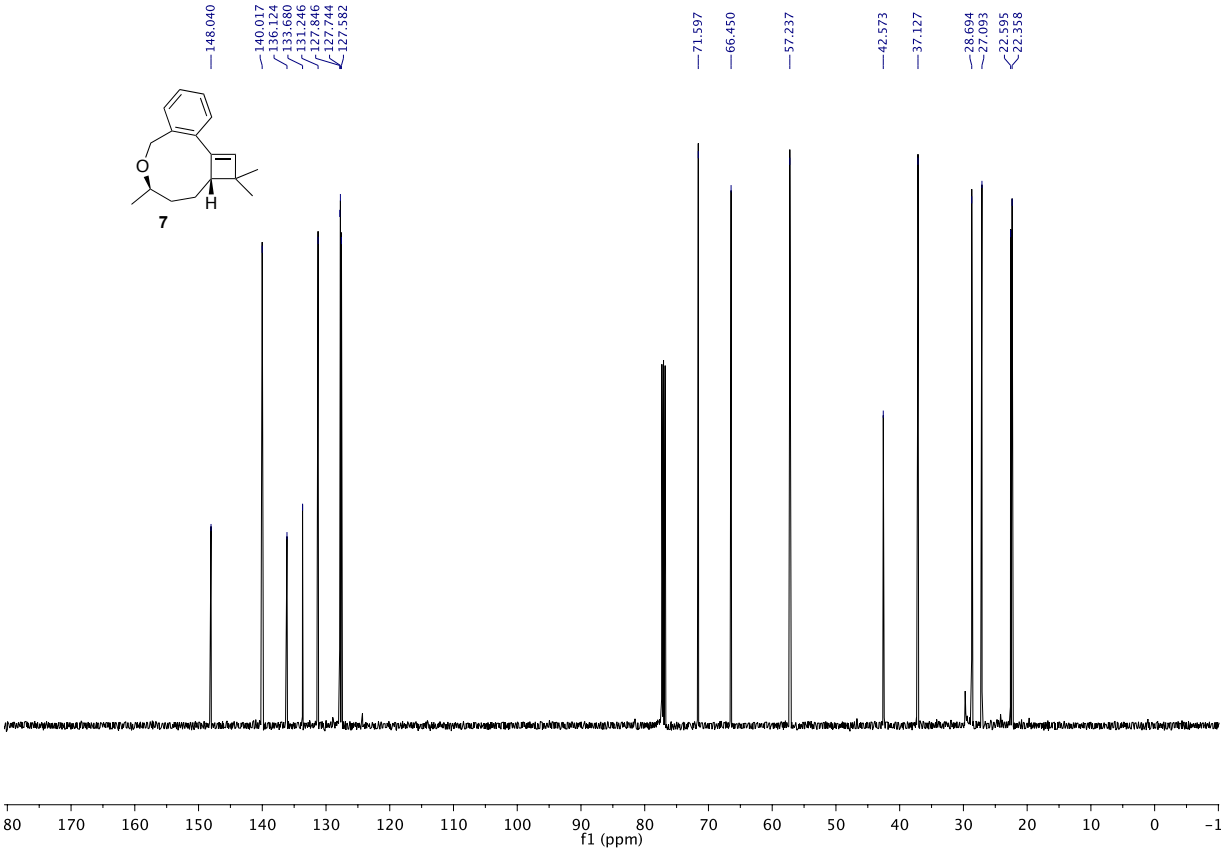
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H
7
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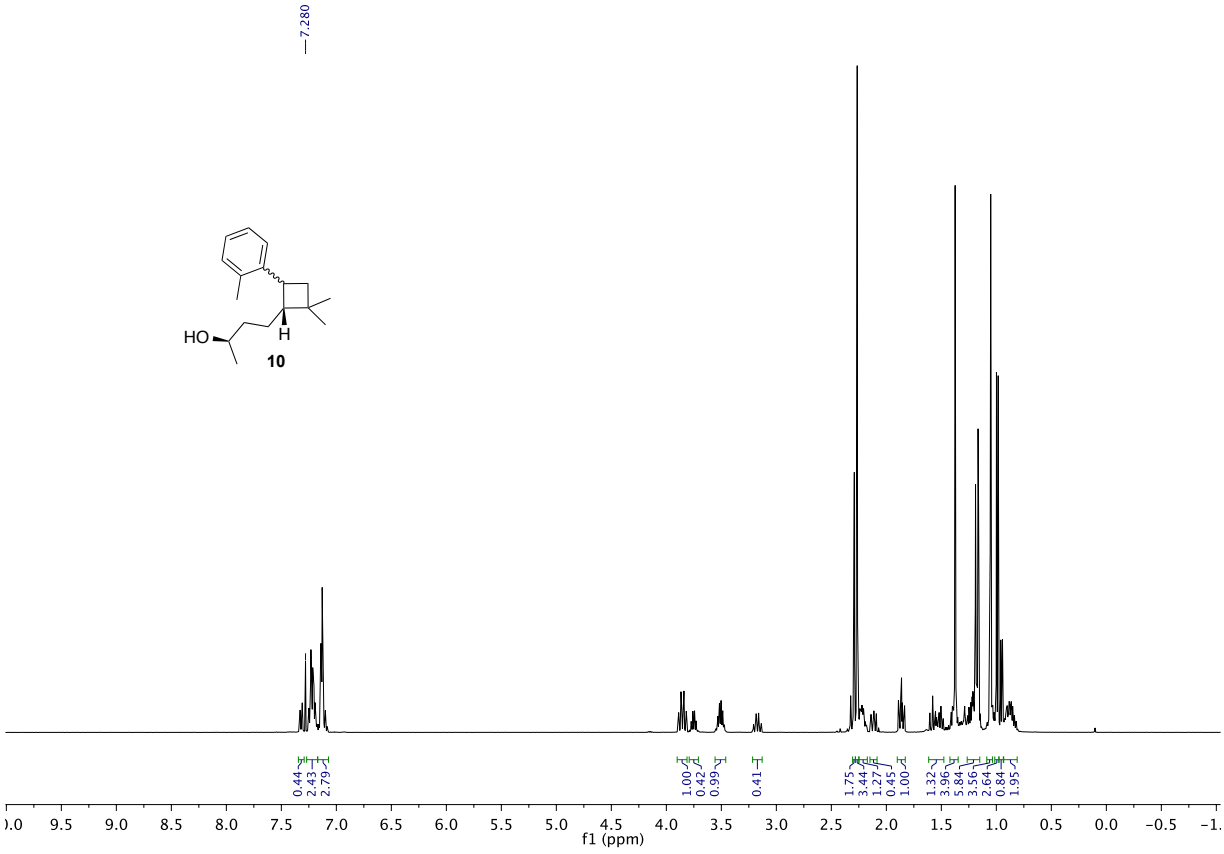
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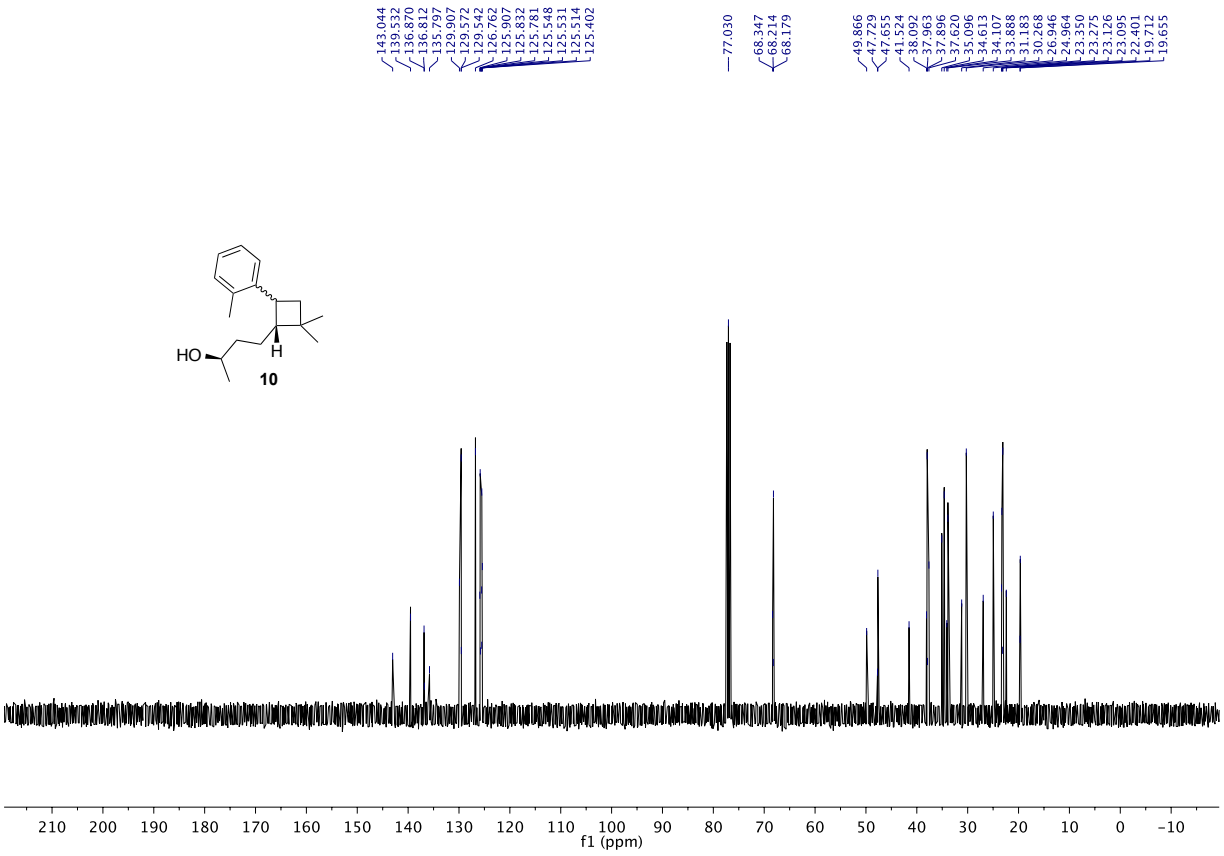
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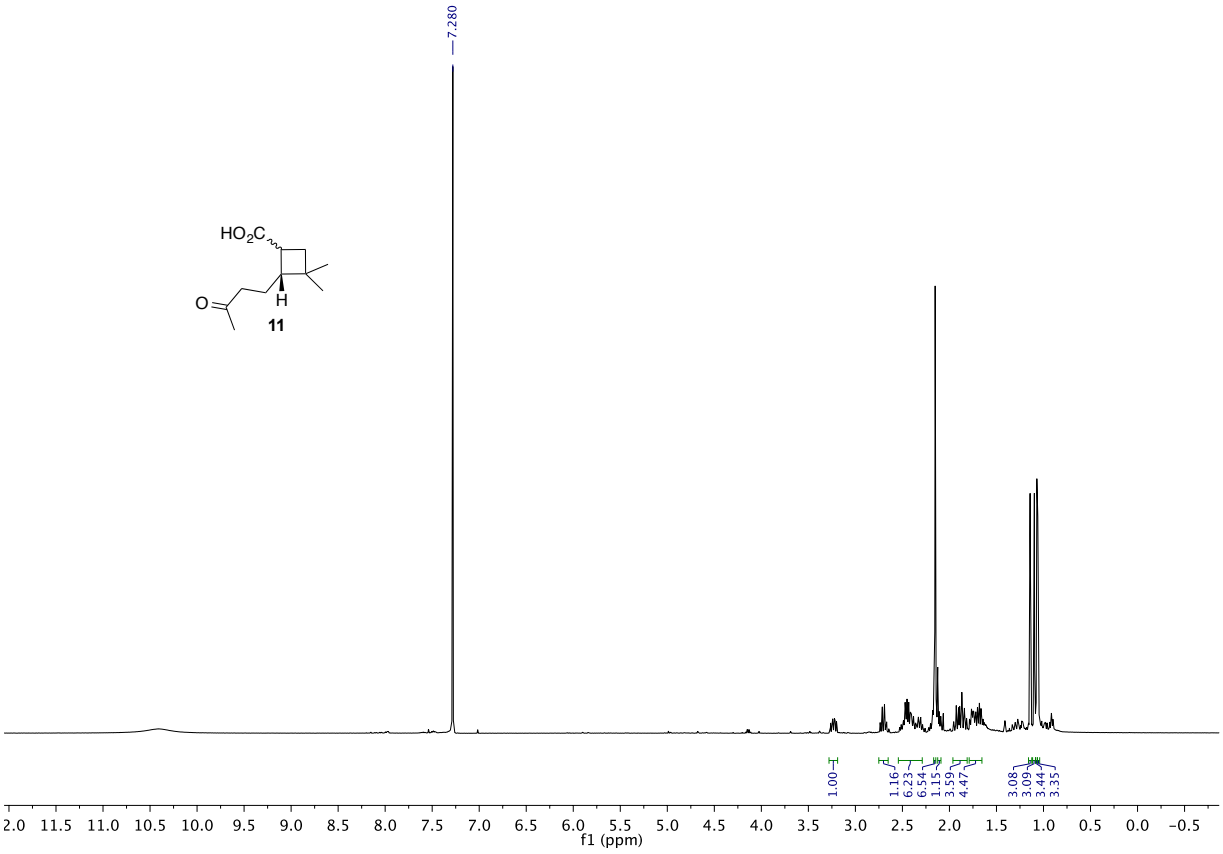
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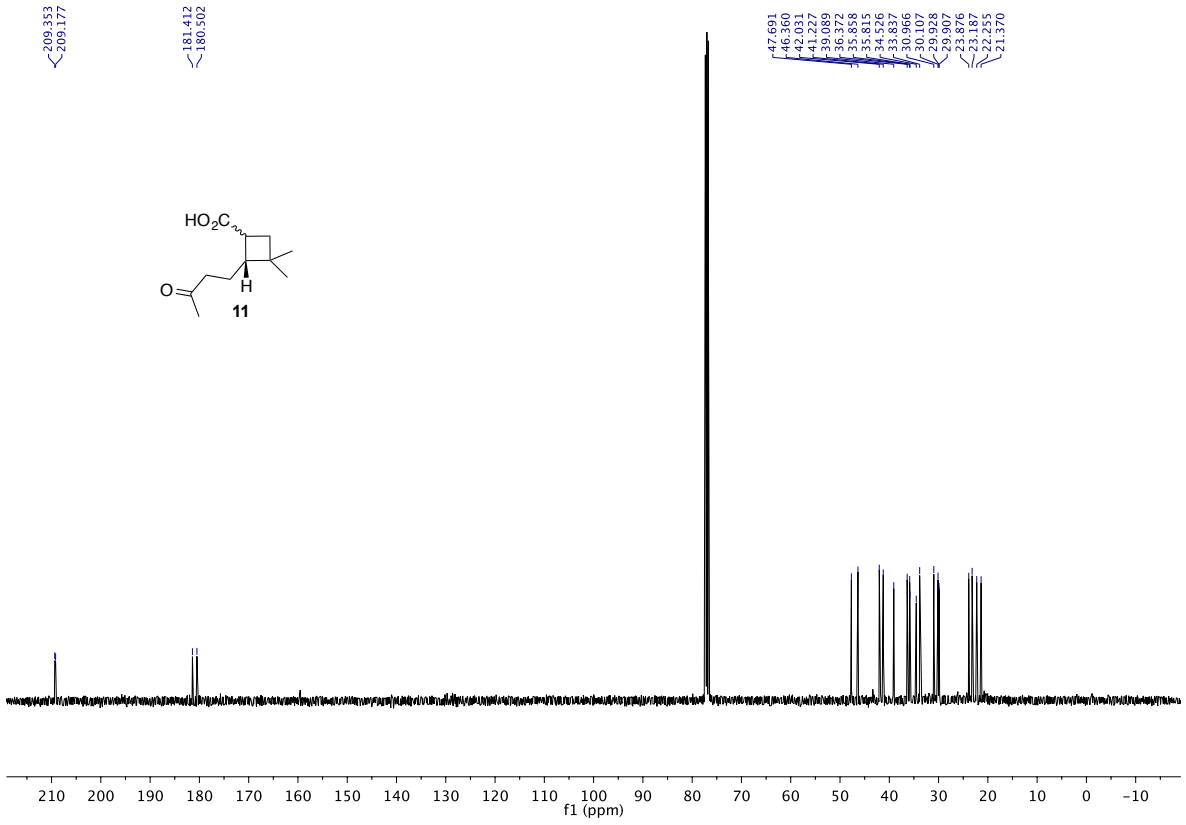
f1 (ppm)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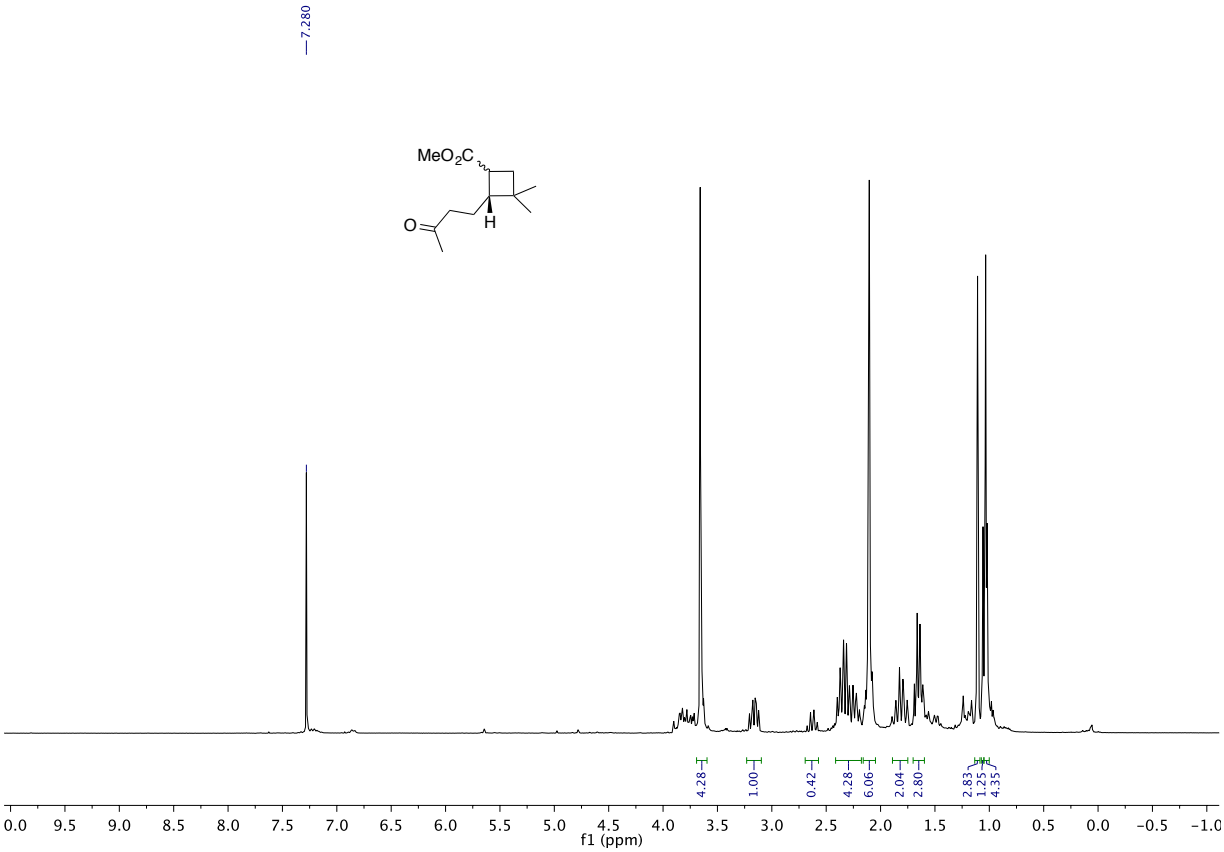
f1 (ppm)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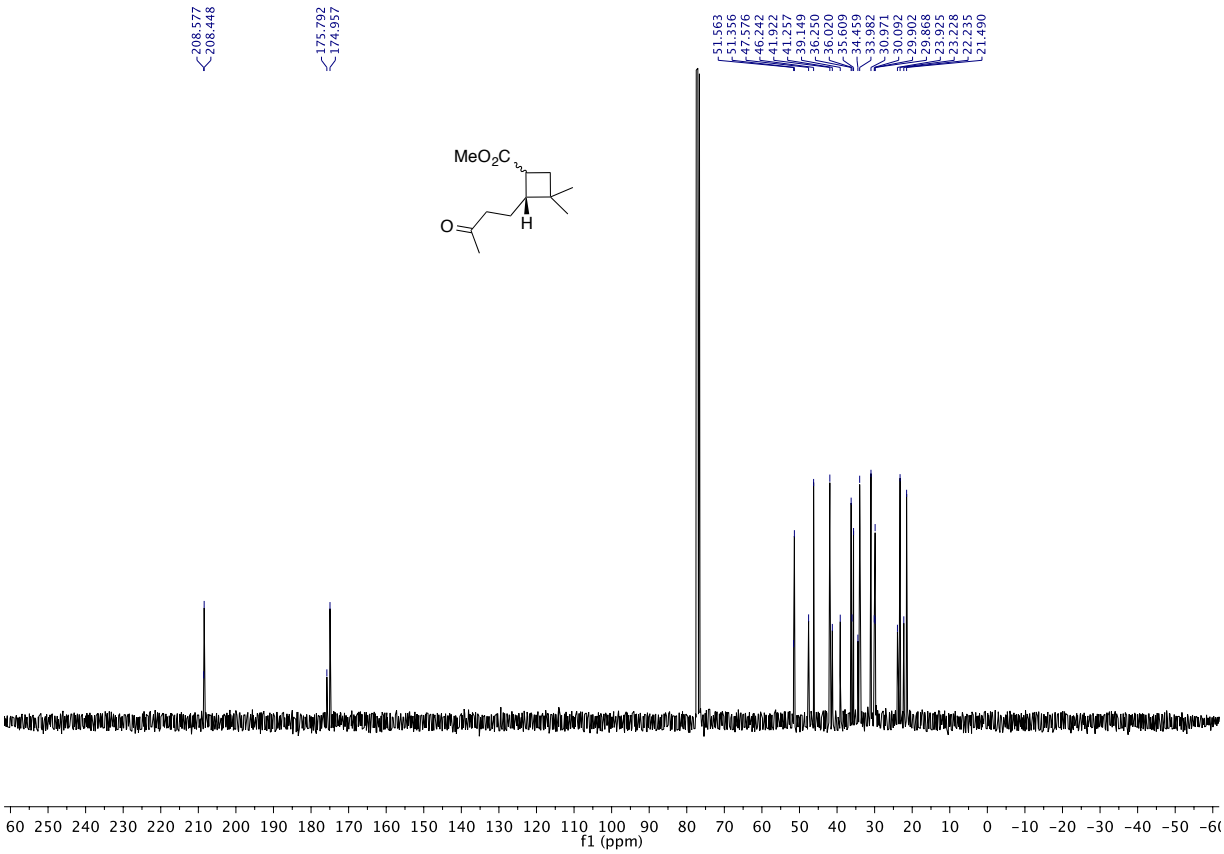
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MeO2C
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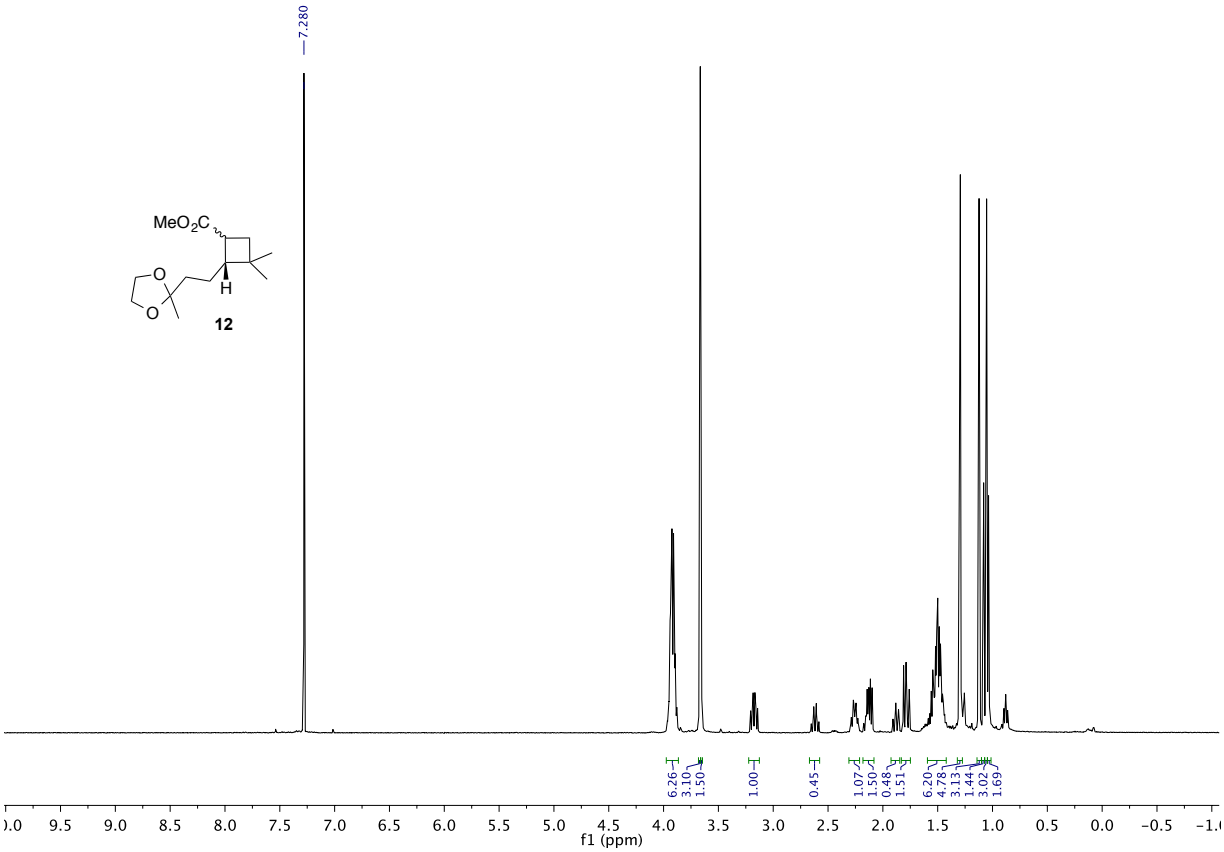
H
f1 (ppm)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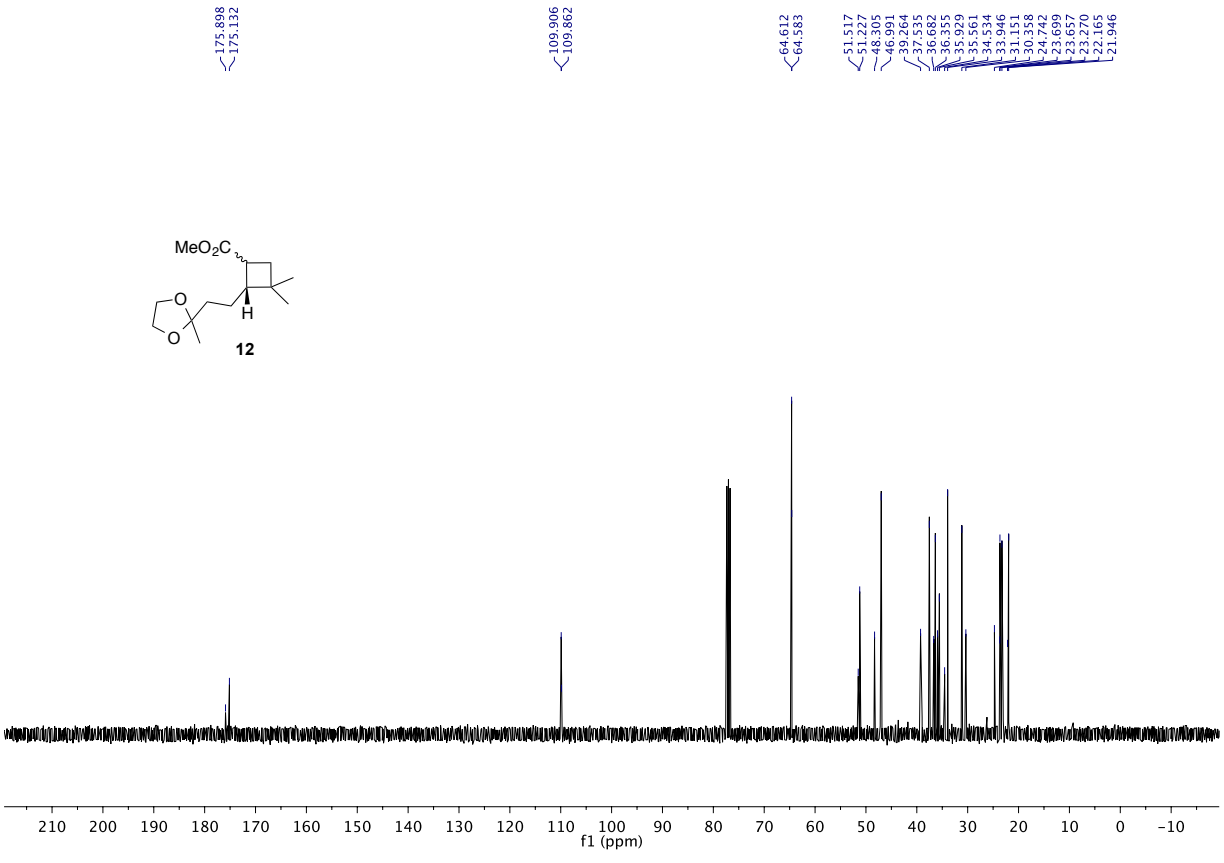
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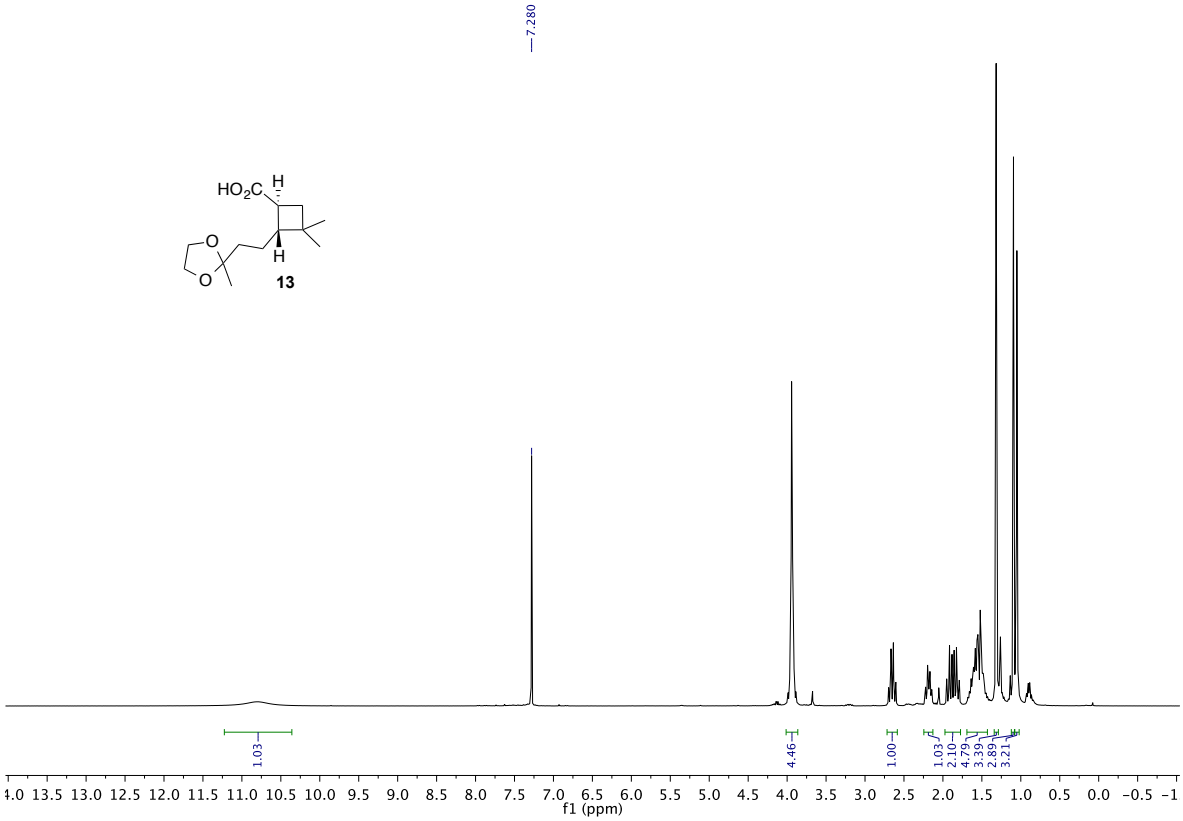
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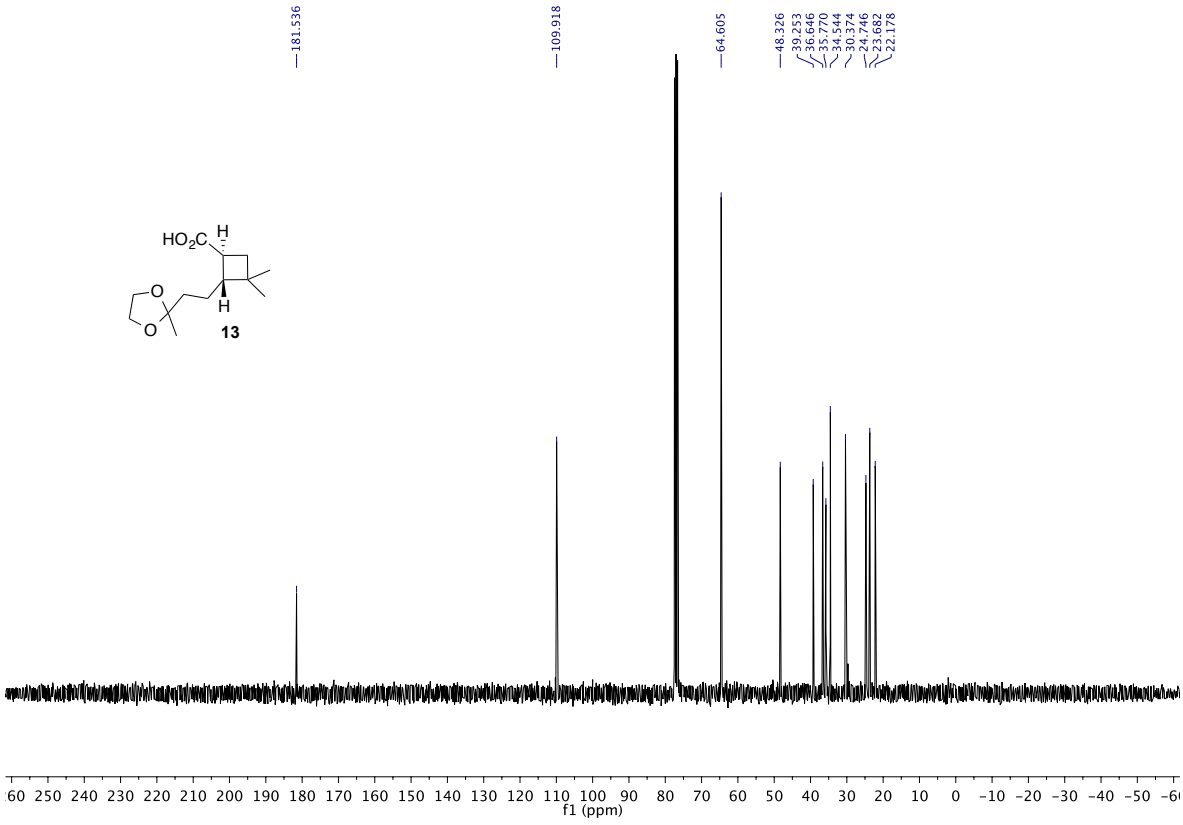
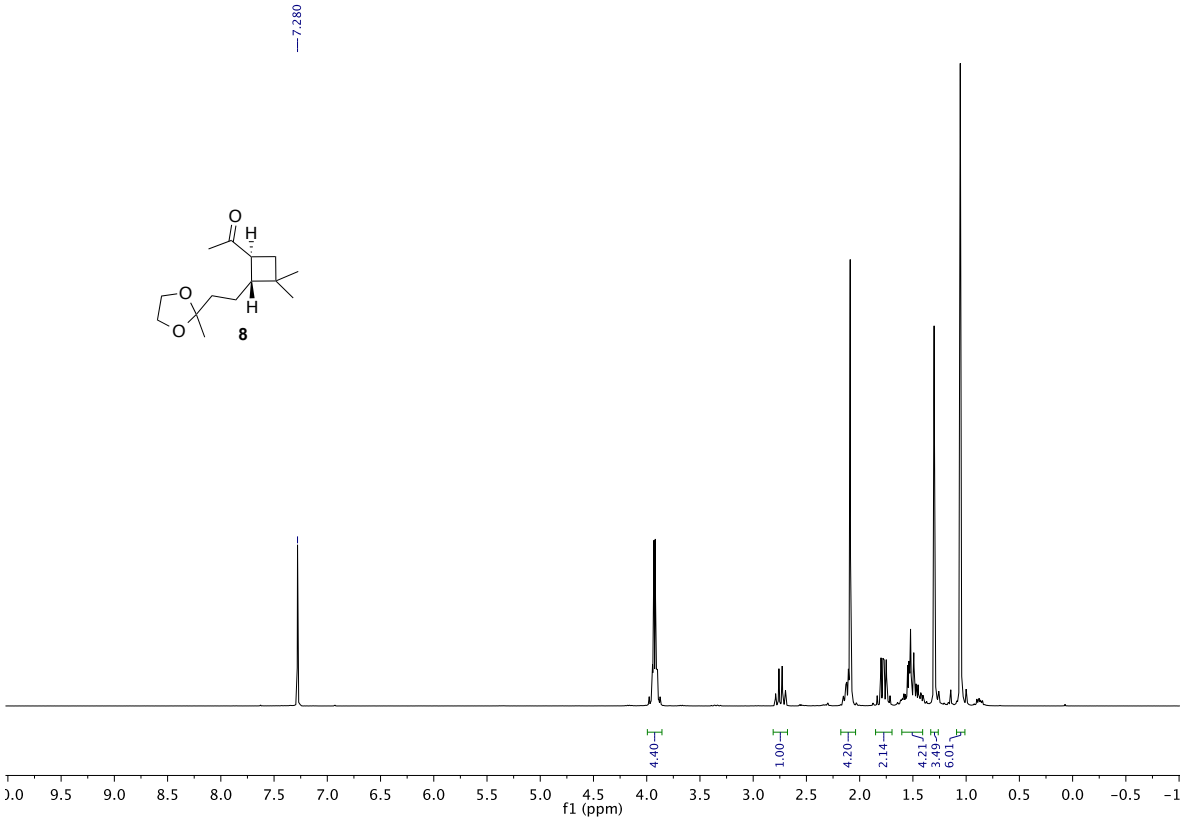
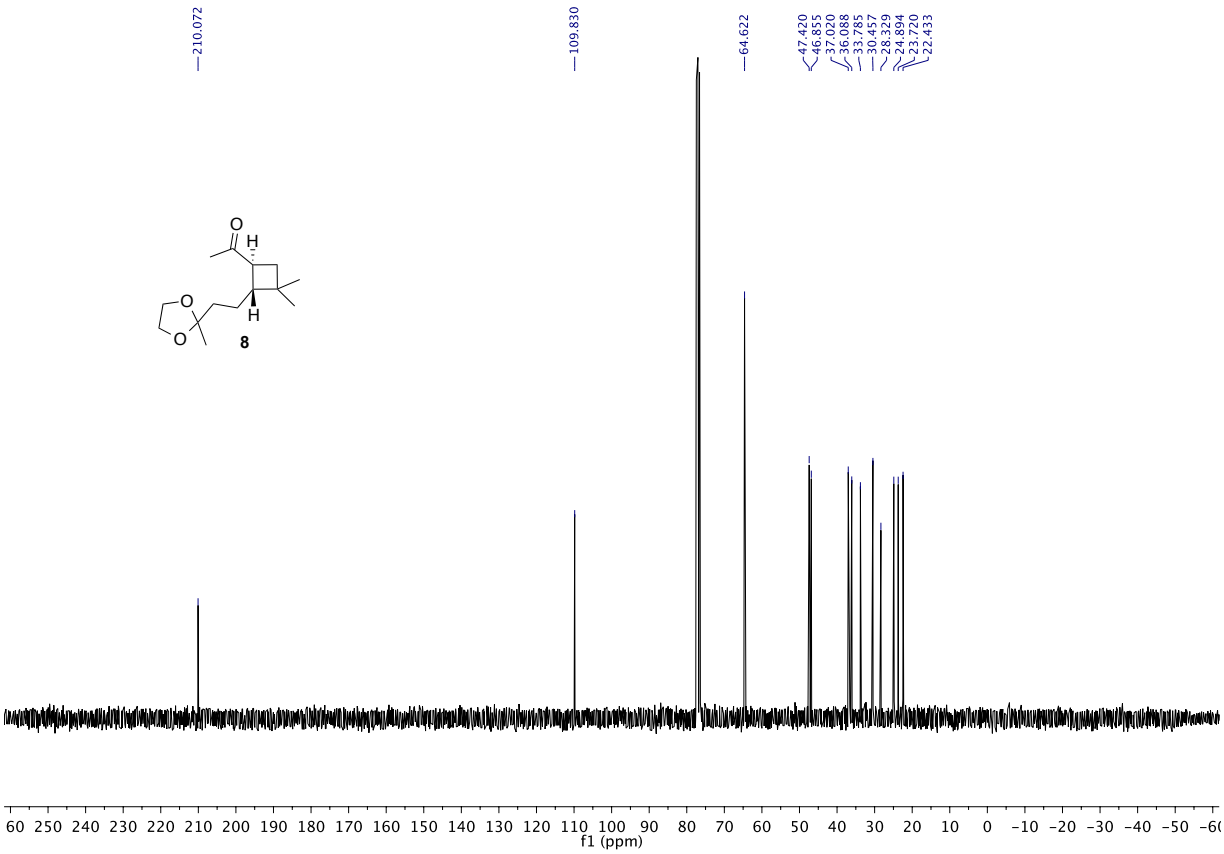
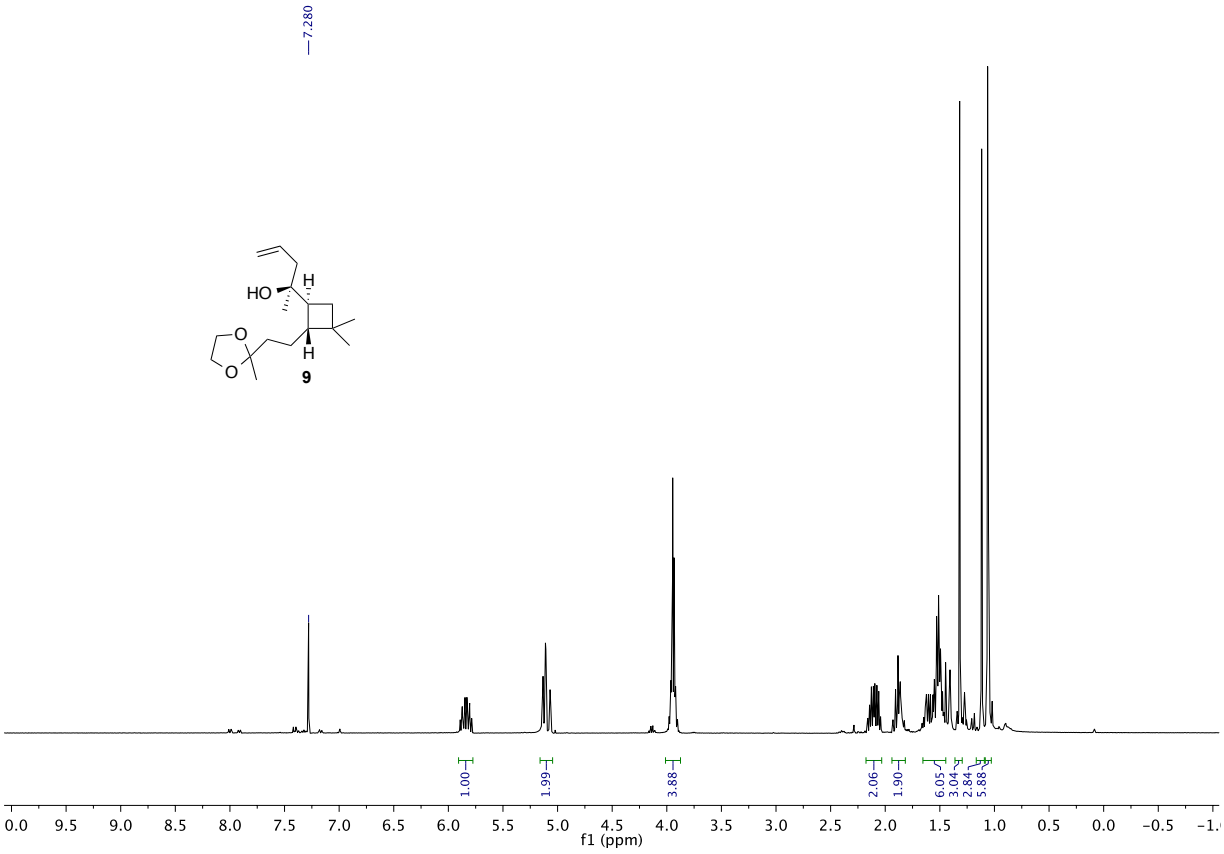
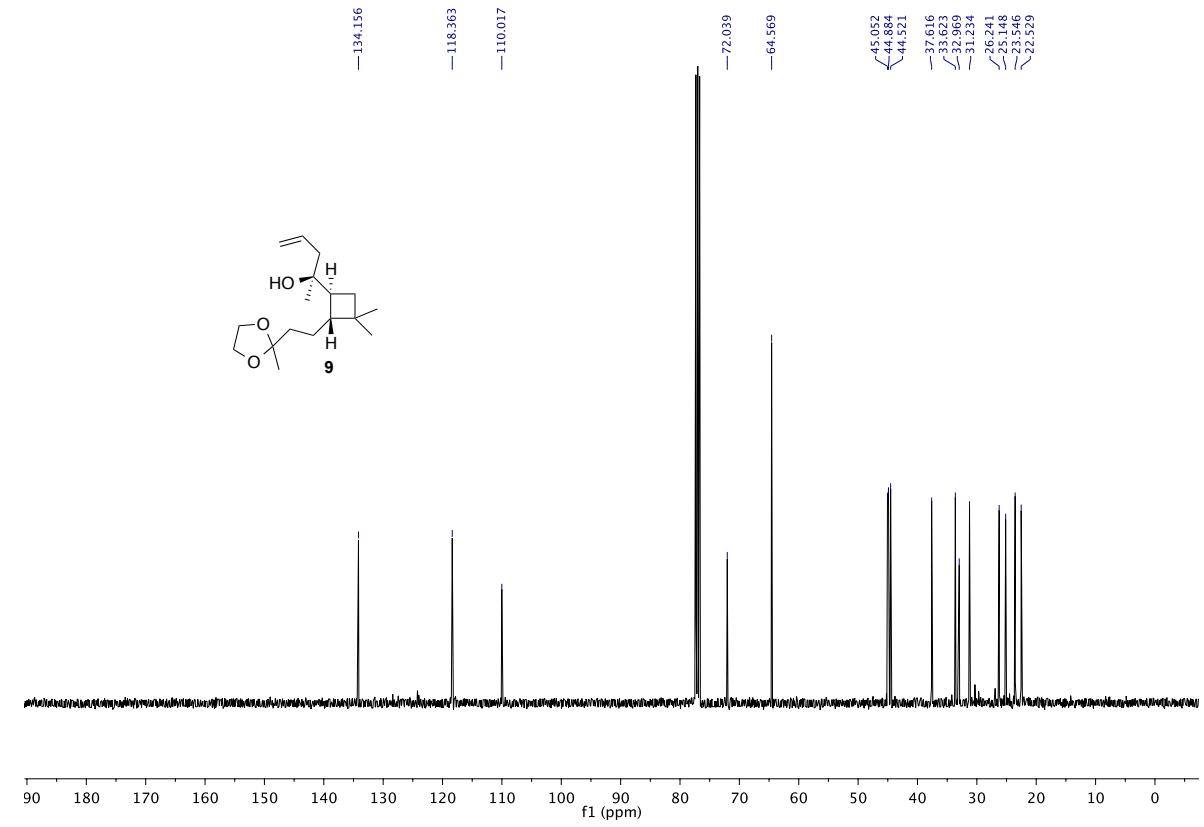
3.21
f1 (ppm)

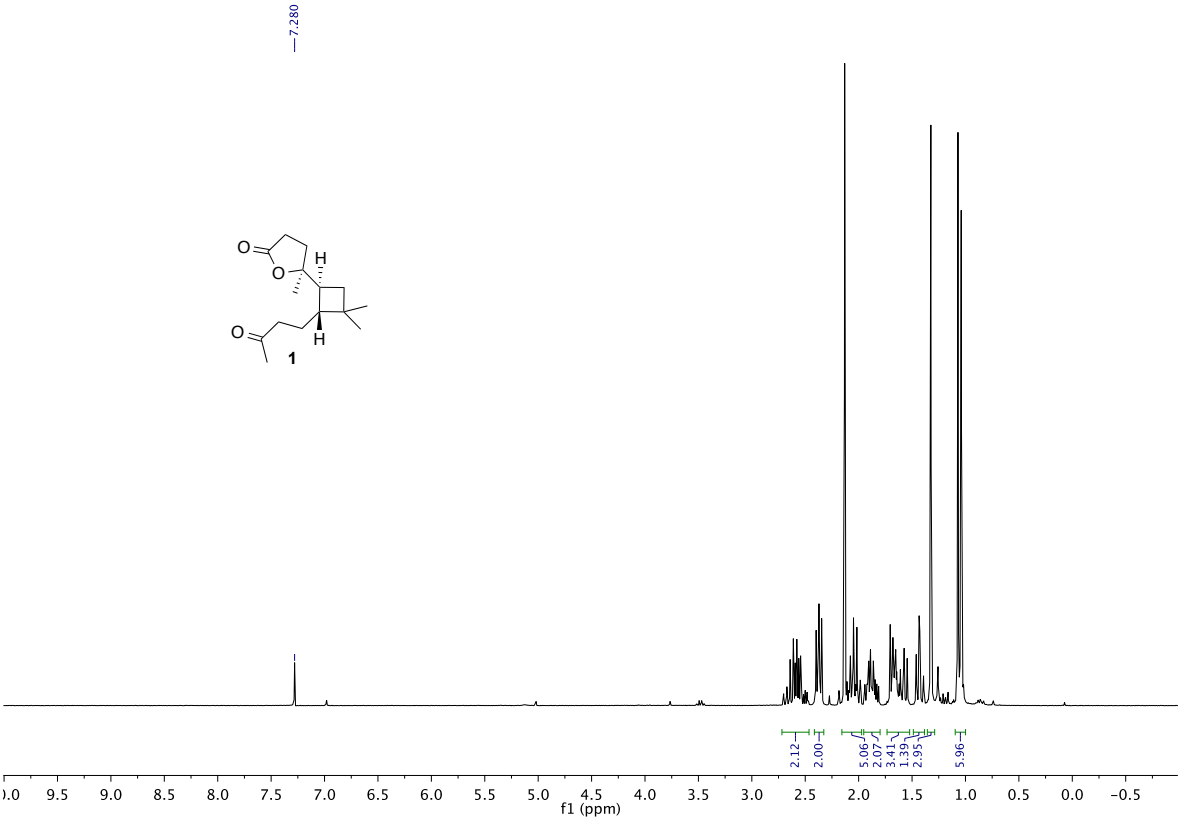

181.536
109.918
64.605
48.326
39.253
36.646
35.770
34.544
30.374
24.746
23.682
22.178
HO2C
H
O
O
H
13
f1 (ppm)

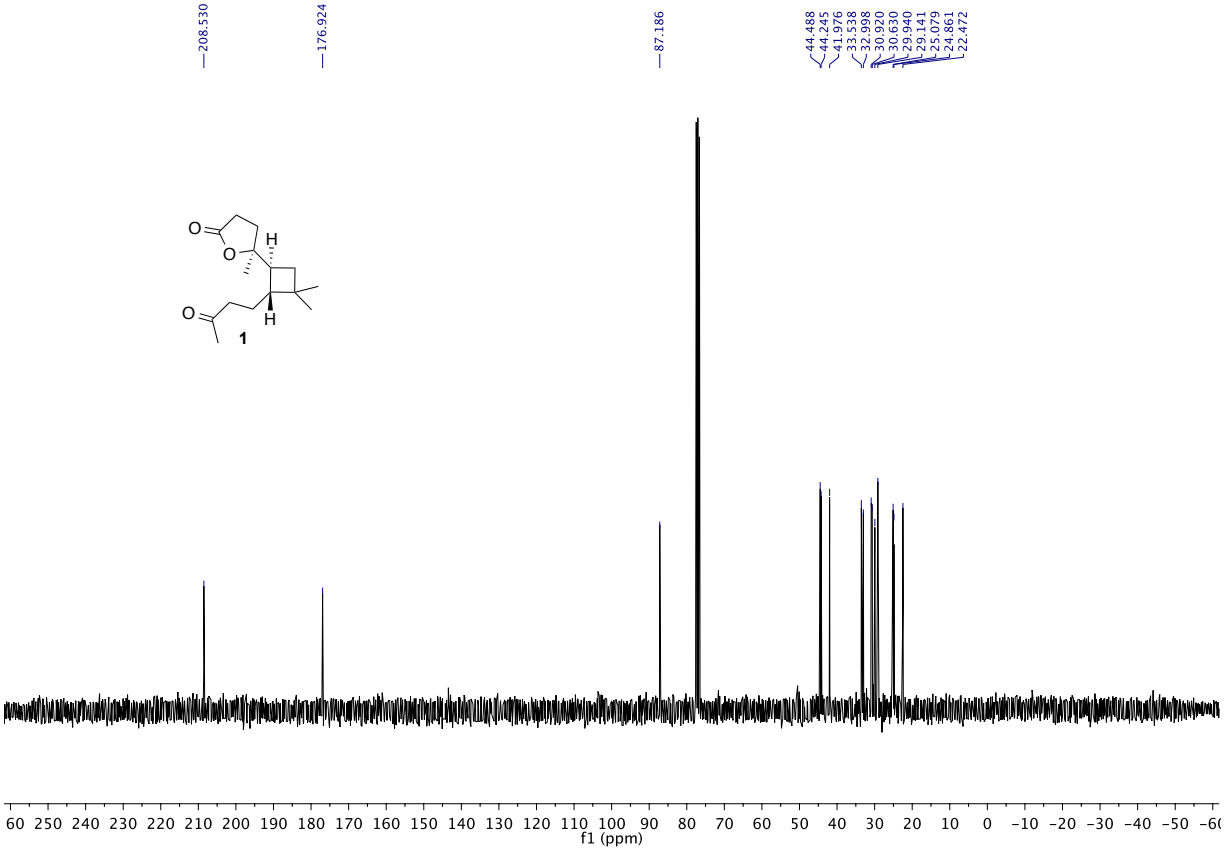

7.280
O
H
O
O
H
8
4.40
1.00
4.20
2.14
4.21
3.49
6.01
f1 (ppm)

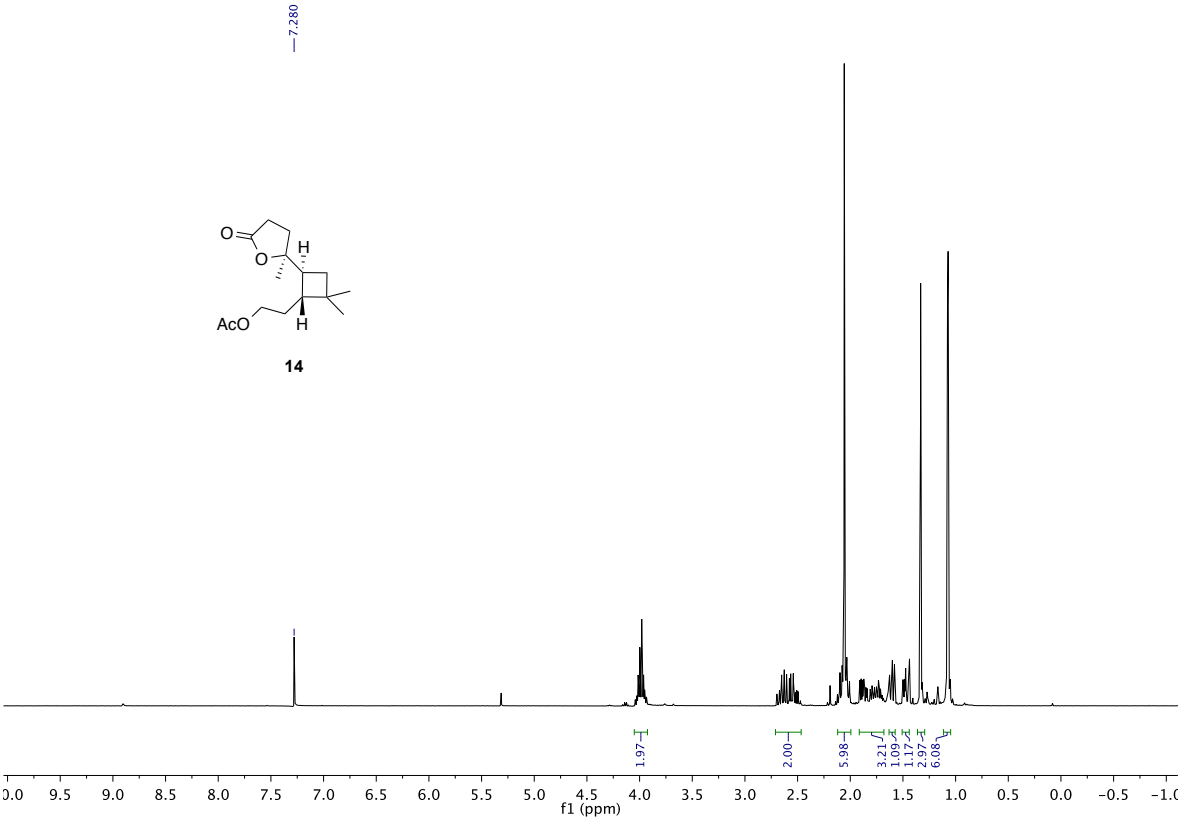

210.072
109.830
64.622
47.420
46.855
37.020
36.088
33.785
30.457
28.329
24.894
23.720
22.433
O
H
O
O
H
8
f1 (ppm)

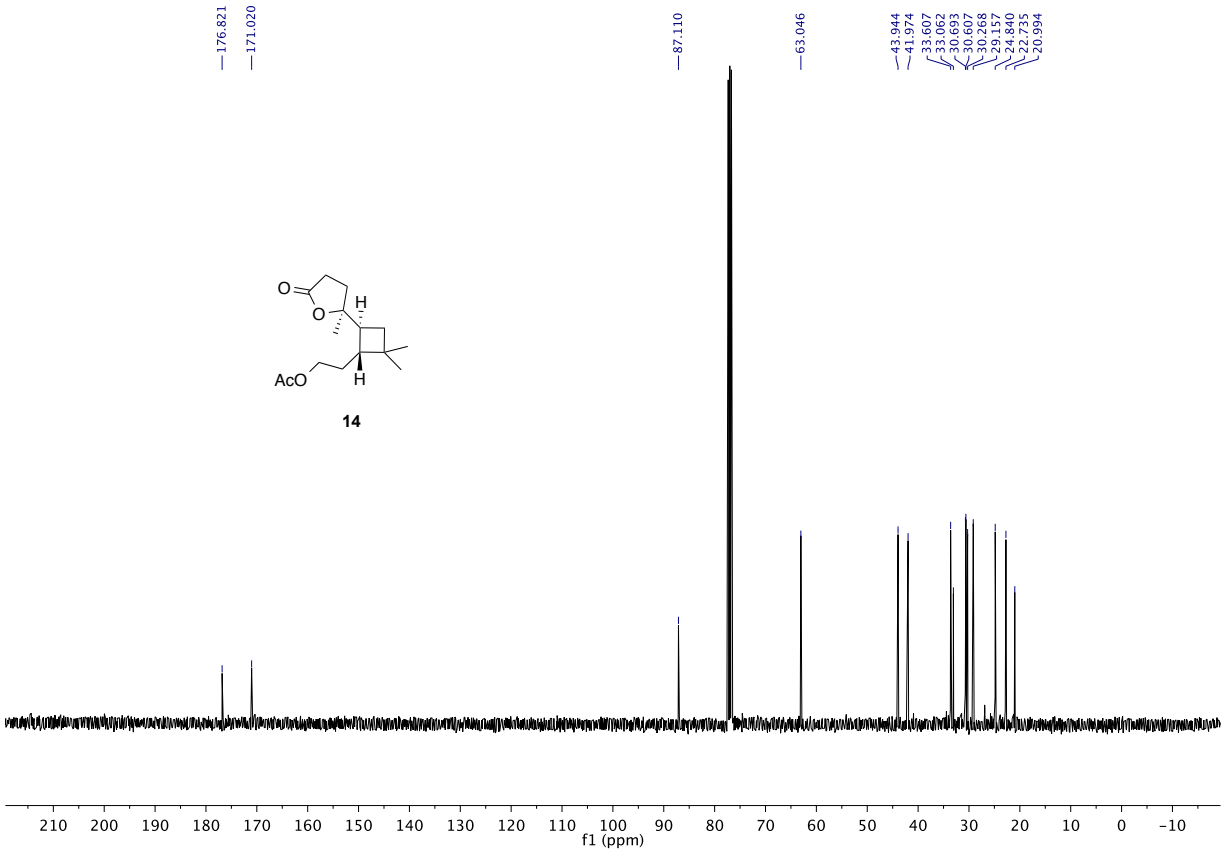

7.280
HO
H
O
O
H
9
1.00
1.99
3.88
2.06
1.90
6.05
3.04
2.84
5.88
f1 (ppm)

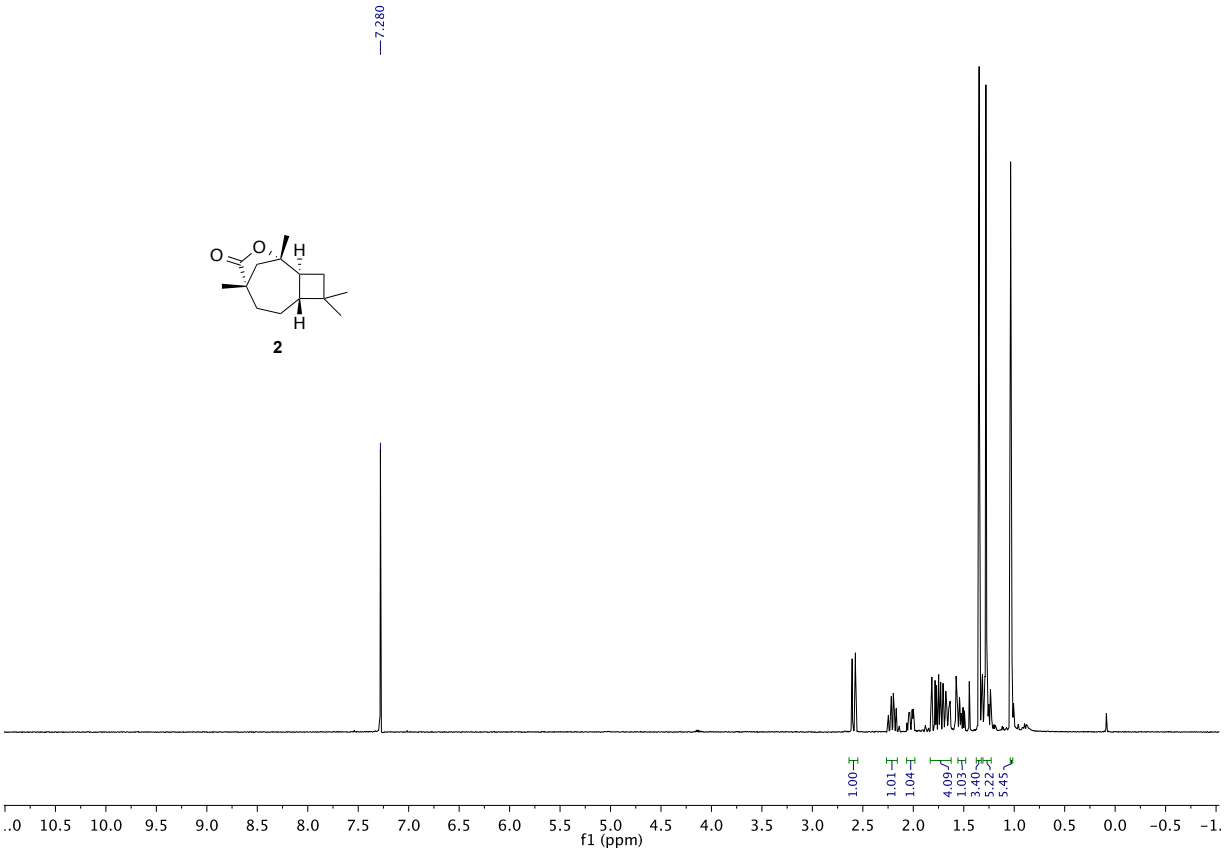

134.156
118.363
110.017
72.039
64.569
45.052
44.884
44.521
37.616
33.623
32.969
31.234
26.241
25.148
23.546
22.529
HO
H
O
O
H
9
f1 (ppm)

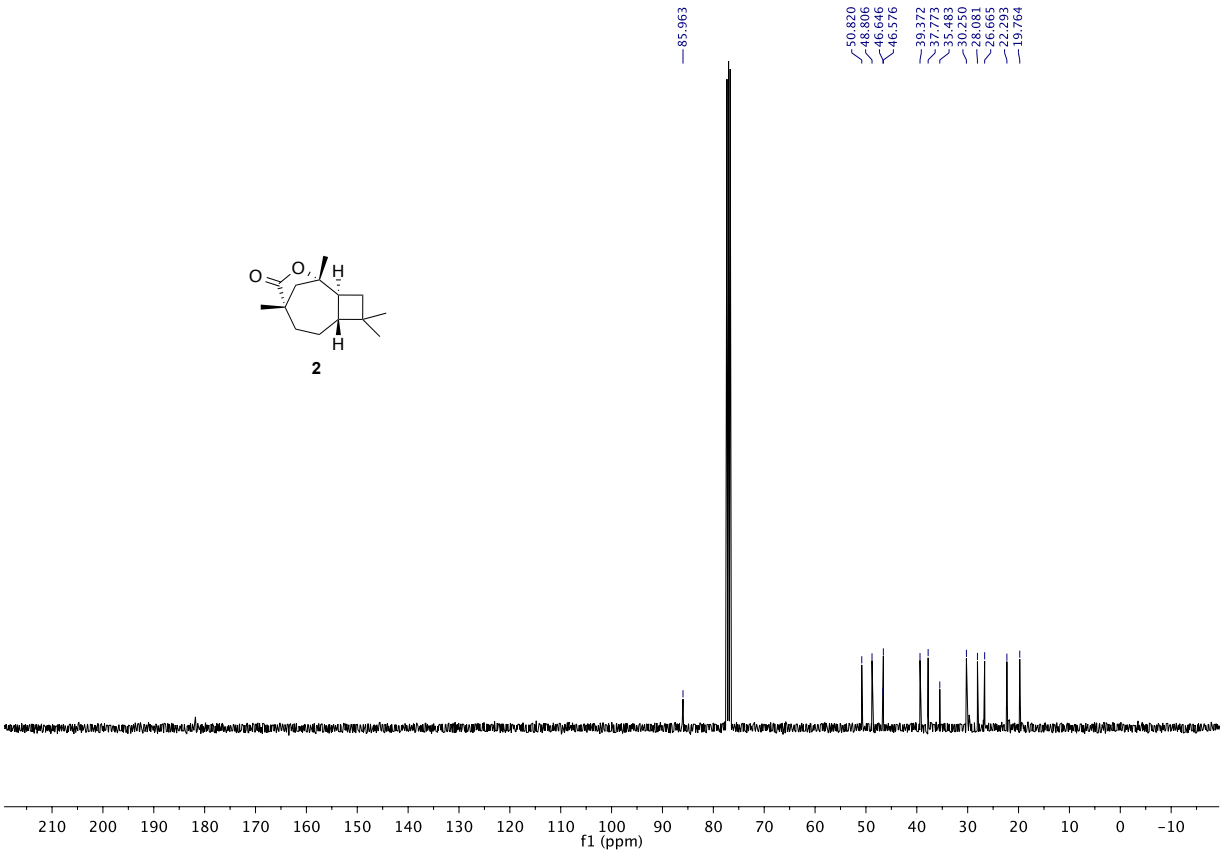

7.280
O
O
H
O
H
1
2.12
2.00
5.06
2.07
3.41
1.39
2.95
5.96
f1 (ppm)


208.530
176.924
87.186
44.488
44.245
41.976
33.538
32.998
30.920
30.630
29.940
29.441
25.079
24.861
22.472
O
O
H
O
H
1
f1 (ppm)


7.280
O
O
H
AcO
H
14
1.97
2.00
5.98
3.21
1.09
1.17
2.97
6.08
f1 (ppm)

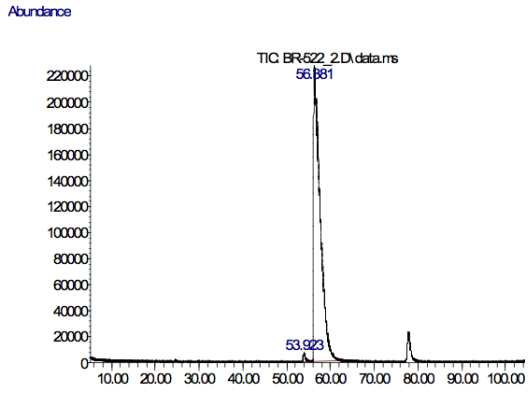

176.821
171.020
87.110
63.046
43.944
41.974
33.607
33.062
30.693
30.607
30.268
29.157
24.840
22.735
20.994
O
O
H
AcO
H
14
f1 (ppm)

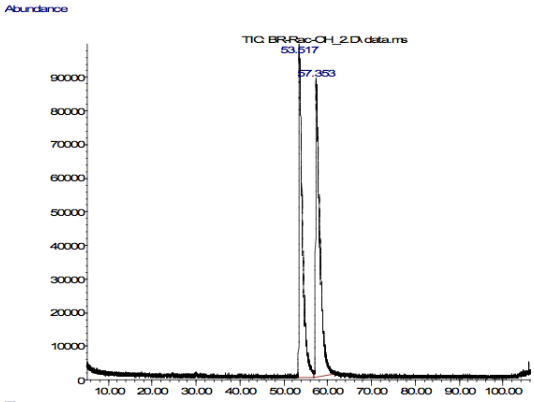

7.280
O
O
H
H
2
1.00
1.01
1.04
4.09
1.03
3.40
5.22
5.45
f1 (ppm)


85.963
50.820
48.806
46.646
46.576
39.372
37.773
35.483
30.250
28.081
26.665
22.293
19.764
O
O
H
H
2
f1 (ppm)

4. Chiral GC-MS traces

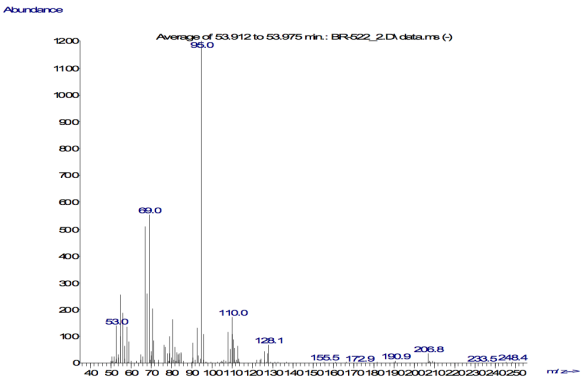
(*R*)-6-methylhept-5-en-2-ol

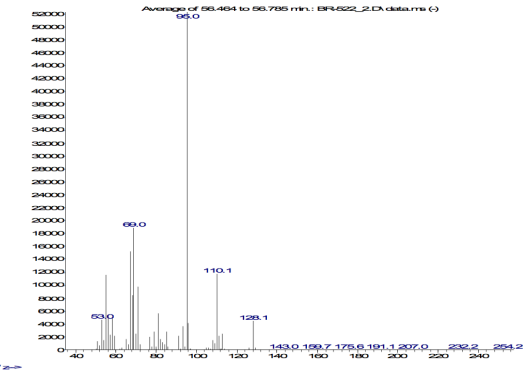




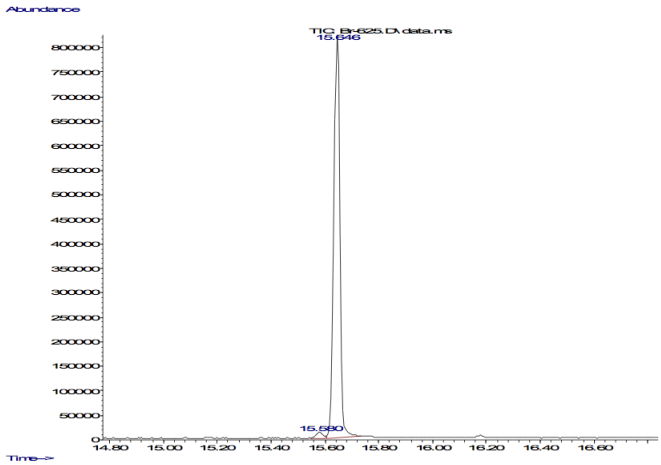
peak #	R.T. first min	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	53.923	8460	8536	8735 M	7390	2238322	0.97%	0.962%
2	56.381	8893	8965	10017 M6	226778	230484762	100.00%	99.038%

peak #	R.T. first min	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	53.517	8386	8465	9050 M7	99171	54860834	93.93%	48.435%
2	57.353	9056	9135	9844 M6	88801	58407013	100.00%	51.565%

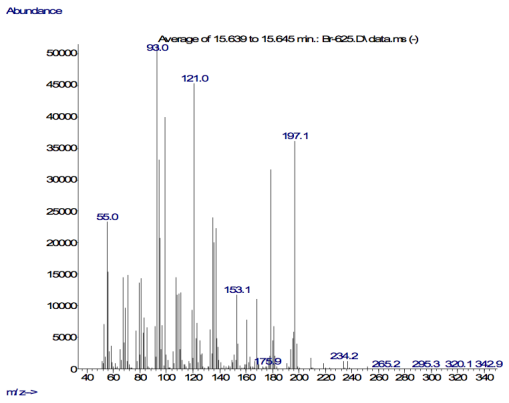


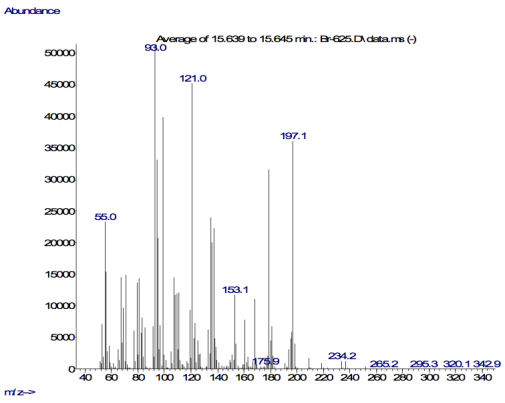


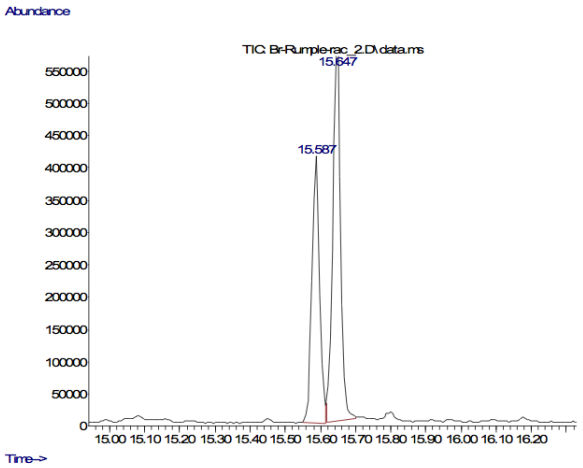
Rumphellaone (1)



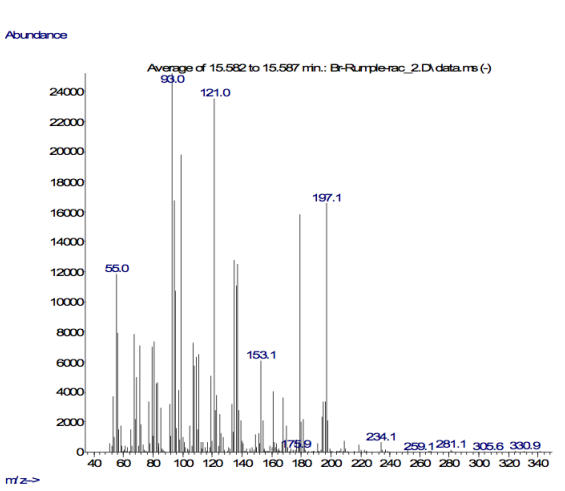
peak #	R.T. first min	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	15.580	2266	2272	2276 M3	12519	193605	1.55%	1.527%
2	15.646	2276	2283	2298 M	829208	12485681	100.00%	98.473%

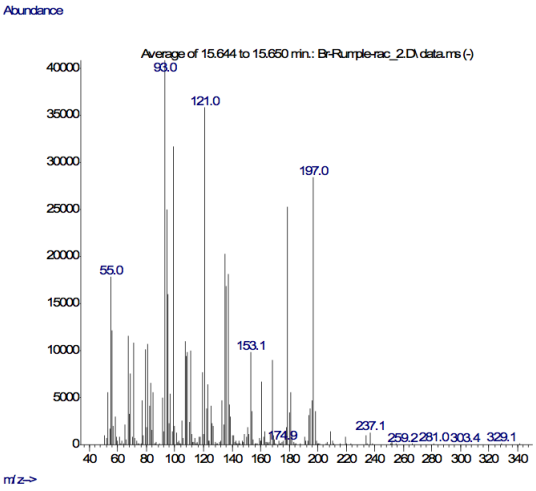




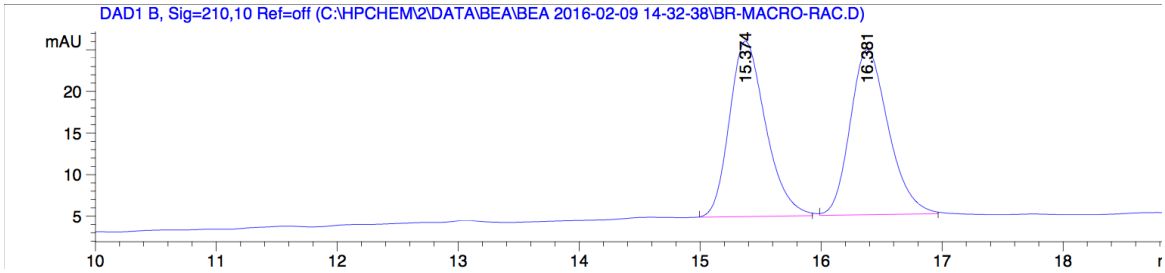


peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	15.587	2266	2273	2278	M	414270	6412418	68.51%	40.658%
2	15.647	2278	2283	2293	M	610158	9359375	100.00%	59.342%

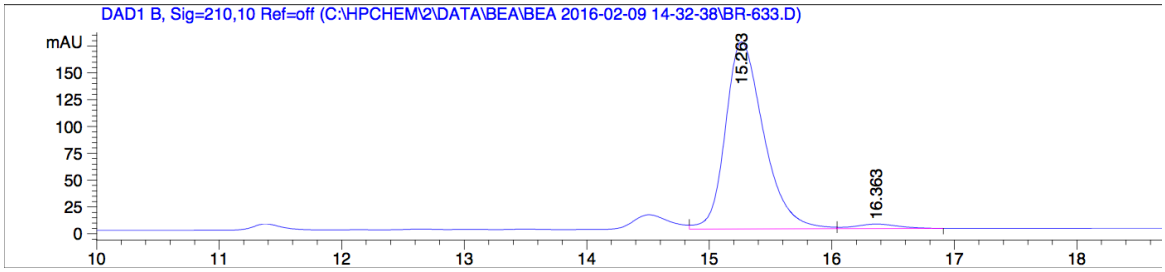




5. Chiral HPLC traces

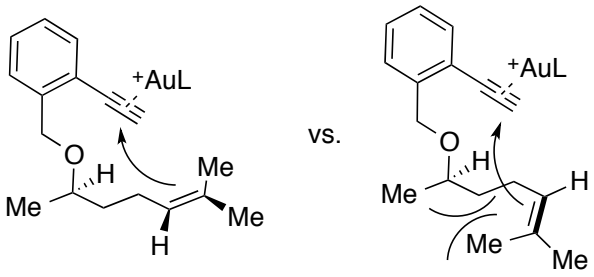


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.374	BB	0.3206	438.52158	21.08517	50.1493
2	16.381	BB	0.3379	435.90970	19.87548	49.8507
Totals :				874.43127	40.96064	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.263	VB	0.3289	3779.69873	174.34738	97.3011
2	16.363	BB	0.3703	104.83819	4.24297	2.6989
Totals :				3884.53692	178.59035	

Gold-catalyzed [2+2] cycloaddition: Postulated transition states



(*R*)-alcohol shown.