Supporting Information

Pharmacophore-Directed Retrosynthesis Applied to Rameswaralide: Synthesis and Bioactivity of *Sinularia* Natural Product Tricyclic Cores

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General

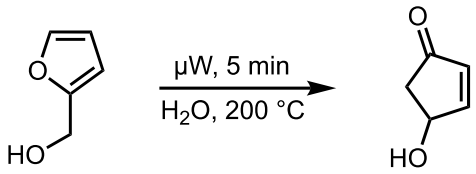
^{1}H NMR and ^{13}C NMR were recorded at 25 °C using either a 600 MHz NMR equipped with Prodigy Cold Probe NMR (^{1}H NMR at 600 MHz, ^{13}C NMR at 150 MHz), or 400 MHz NMR (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz). Chemical shifts are reported in ppm using the residual solvent resonance as the internal standard (^{1}H NMR $CDCl_3$: δ 7.26 ppm, ^{13}C NMR $CDCl_3$: δ 77.16 ppm) Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet (or any combination of these), app = apparent when multiplicity arises from coincidental equivalence of coupling constants, or there is obviously higher-order coupling than cannot be resolved within a given resonance *e.g*. app t = apparent triplet), coupling constants (Hz) and integration. Infrared spectra (IR) were obtained using both ATR and thin film (NaCl plates) sampling techniques (as stated in line listing) and recorded in wavenumbers (cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), and weak (w) or intermediate absorptions *i.e.* w-m, m-s. High Resolution Mass Spectrometry (HRMS) analysis was obtained using a Thermo Orbitrap Discovery utilizing Electrospray Ionization (ESI) and are reported as *m/z* (relative intensity).

All non-aq. reactions were performed under a nitrogen atmosphere in oven-dried (125 °C) or flame-dried glassware unless otherwise indicated. Reaction solvents used were pre-dried by passing through activated molecular sieves or alumina (JC Meyer Solvent Drying System). Both diisopropylethylamine (DIPEA) and triethylamine (Et_3N) were distilled over CaH_2 prior to use. All work-up and purifications were completed using ACS grade solvents and no precautions were taken to exclude air. Thin Layer Chromatography (TLC) was performed using glass-backed silica gel F_{254} (Silicycle, 250 µm thickness). TLCs were visualized under UV irradiation (254 nm) or by the use of *p*-anisaldehyde (PAA), Hannesian's, or $KMnO_4$ staining solutions as specified for each reaction. Standard flash column chromatography was completed using Silicycle ultrapure SiliaFlash silica gel, 40-63 µm, 60 Å pore size. Medium pressure liquid chromatography (MPLC) was performed using a Teledyne Isco CombiFlash Rf automated flash chromatography system. Microwave reactions were completed using a CEM discover SP equipped with an Explorer. Microwave vessels used were 35 mL borosilicate glass with a 35 mL silicon cap compatible with the Discover SP (part # 909235). Temperature was monitored using an infrared sensor.

Reagent List:

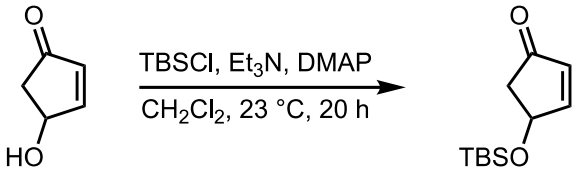
Furfuryl alcohol (Alfa Aesar)
TBSCl (Oakwood)
DMAP (Oakwood)
K_2CO_3 (Oakwood)
I_2 (Alfa Aesar)
Ethoxy vinyl tin (Oakwood)
$Pd_2(dba)_3$ (Oakwood)
$AsPh_3$ (Sigma-Aldrich)
CuTC (Sigma-Aldrich)
MeLi, 3.1 M in diethoxymethane (Sigma-Aldrich)
TBAF, 1 M in THF (Sigma-Aldrich)
Acryloyl chloride (Sigma-Aldrich)
BTM catalyst (prepared according to literature procedure[1])
IBX (prepared according to literature procedure[2])
AIBN (Sigma-Aldrich)
Bu_3SnH (Alfa Aesar)
NBS (recrystallized from Sigma-Aldrich)
TESOTf (Oakwood)
2,6-Lutidine (Sigma-Aldrich)
$ZnEt_2$, 1 M in hexanes (Sigma-Aldrich)
CH_2I_2 (Distilled prior to use from Oakwood)
$CHBr_3$ (Sigma-Aldrich)
Acetic Acid, glacial (Sigma-Aldrich)
$AgBF_4$ (Strem)
CAN (Alfa Aesar)
DBU (Sigma-Aldrich)

Experimental Procedures



furfuryl alcohol (11) **10**

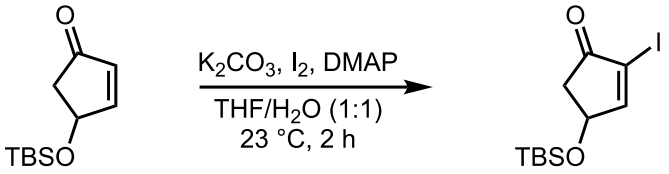
4-hydroxycyclopent-2-en-1-one (10): Cyclopentenone **10** was prepared based on a modified procedure reported by Ulbrich and co-workers as well as Saitman and co-workers.[3,4] Furfuryl alcohol (1.000 mL, 12.57 mmol, 1.0 equiv) was delivered into 48 microwave vials (35 mL volume) utilizing a micropipette (total of 555.4 mmol). The alcohol was then dissolved in deionized (DI) H_2O (20 mL per vial). *Note: the vials were not equipped with a stir bar and caps were applied to vials without exclusion of air.* Each vial was then submitted to microwave irradiation at 300 W, 200 °C for 5 min. After all 48 vials had been irradiated, the cloudy brown mixture in each vial was combined in a separatory funnel, each vial with rinsed with EtOAc (~2 mL) to ensure quantitative transfer. The aq. layer was then washed with EtOAc (3x 250 mL). At this stage, the *aq. layer was a clear, light orange solution. If aq. layer is dark and cloudy, polymeric side product is still present in the aq. layer and further rounds of EtOAc washes are required to remove the polymer which is essential at this stage.* The combined organic layers were then back extracted with DI H_2O (2x 200 mL). The combined aq. layers were evaporated under reduced pressure, utilizing a high vacuum (Welch DuoSeal 1400) connected directly to a rotovap. The resulting oil was azeotropically dried with toluene (3x ~10 mL) to yield cyclopentenone **10** as a light brown/red non-viscous oil (25.99 g, 264.9 mmol, 47%) which was of sufficient purity (by ^{1}H NMR) taken directly to the alcohol protection step without further purification. Spectral data matched that previously reported.[5,6]



10 **S1**

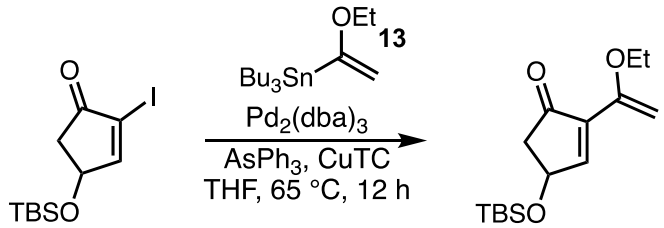
4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (S1): TBS protected enone **S1** was prepared based on a modified procedure previously reported by Song and co-workers.[7] A 1 L round-bottomed flask containing cyclopentenol **10** (50.73 g, 517.1 mmol, 1.0 equiv) was equipped with a 250 mL addition funnel. The entire apparatus was evacuated and refilled with N_2 (3x) and was maintained under a positive pressure of N_2. In the round-bottom flask, the dark red/brown oil was then dissolved in CH_2Cl_2 (345 mL, *Note: Used HPLC grade CH_2Cl_2 that had been stored over 3 Å mol. sieves for one week prior to use*) before adding Et_3N (108 mL, 775.7 mmol, 1.5 equiv) and DMAP (6.30 g, 51.7 mmol, 10 mol %). The dark red/brown homogeneous solution was then cooled to 0 °C (ice/water bath) and a solution of TBSCl (93.50 g, 620.6 mmol, 1.2 equiv) in CH_2Cl_2 (172 mL) was added dropwise over *ca.* 45 mins (using equipped addition funnel). After complete addition of the TBSCl solution, the reaction mixture was now a light red/brown heterogeneous mixture. The mixture was allowed to warm to ambient temperature (23°C) and was stirred until full consumption of alcohol **10**, as determined by TLC (typically 16 h). The red/brown heterogeneous mixture was then transferred to a 2 L separatory funnel, washing with CH_2Cl_2 (250 mL) and DI H_2O (100 mL) to ensure quantitative transfer. Additional DI H_2O (300 mL) was added to the separatory funnel before shaking vigorously. The layers were then separated, and the organic layer was treated with aq. 1 M HCl (2 x 250 mL) followed by satd. aq. $NaHCO_3$ (3 x 250 mL). The organic layer was then washed with brine, dried over anhyd. Na_2SO_4, decanted, and the solvent was removed *in vacuo* to yield a dark red/brown crude oil. The oil was purified by flash chromatography (5 inch column, ~5 inch height of silica, dry loaded) eluting 0 → 20% EtOAc in hexanes (1.5 L hexanes then 5% increments, 1 L each) to yield TBS protected

cyclopentene **S1** as a non-viscous, light yellow oil (85.34 g, 401.9 mmol, 78% yield). Spectral data matched that previously reported.[7]



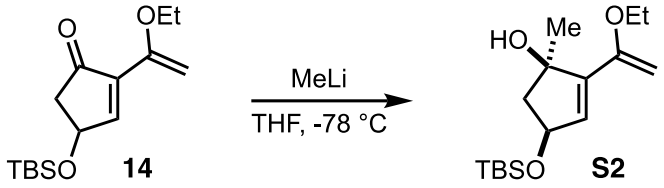
S1 **12**

4-((tert-butyldimethylsilyl)oxy)-2-iodocyclopent-2-en-1-one (12): α-Iodo enone **12** was synthesized by scaling-up the method previously reported by Yang and co-workers.[8] Purification by flash chromatography (0 → 20% Et_2O in hexanes) provided α-iodo enone **12** as a light yellow waxy solid. Spectral data matched that previously reported.[8]



12 **14**

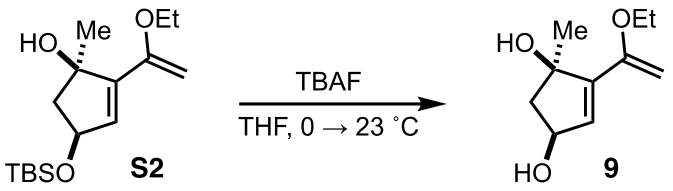
4-((*tert*-butyldimethylsilyl)oxy)-2-(1-ethoxyvinyl)cyclopent-2-en-1-one (14): Vinyl iodide **12** (18.17 g, 53.71 mmol, 1.0 equiv), as a waxy solid, was weighed into an oven-dried, 1 L three-necked, round-bottomed flask. The flask was then equipped with a reflux condenser and the entire apparatus was evacuated and refilled with N_2 (3x) and was maintained under a positive pressure of N_2. The solid was dissolved in THF (212 mL) prior to the addition of $Pd_2(dba)_3$ (1.22 g, 1.33 mmol, 2.5 mol %), $AsPh_3$ (0.815 g, 2.66 mmol, 5.0 mol %) and CuTC (0.507 g, 2.66 mmol, 5.0 mol %) sequentially. Ethoxy vinyl tin **13** (18.5 mL, 55.3 mmol, 1.03 equiv) was then added over *ca.* 1 min via plastic syringe. The reaction mixture was then heated to reflux (65 °C) and stirred. Upon full consumption of iodide **12**, as judged by TLC (typically 12 h), the dark red mixture was filtered through a pad of celite, washing with CH_2Cl_2 (~20 mL) and the solvent was removed by rotary evaporation. The viscous oil was purified by flash chromatography (0 → 10% Et_2O in hexanes) to yield a light-yellow oil (12.99 g, 45.99 mmol, 86%): *Note: the cross coupling was performed on up to 50 g scale, but isolated yields were inconsistent on larger scales.* TLC (1:19 EtOAc:hexanes) R_f = 0.46; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11-0.15 (m, 6H), 0.91 (s, 9H), 1.36 (t, *J* = 7.0 Hz, 3H), 2.39 (dd, *J* = 18.2, 2.4 Hz, 1H), 2.84 (dd, *J* = 18.2, 6.1 Hz, 1H), 3.82 (q, *J* = 7.0 Hz, 2H), 4.39-4.42 (m, 1H), 4.89 (app dt, *J* = 5.3, 2.2 Hz, 1H), 5.38 (d, *J* = 1.5 Hz, 1H), 7.50 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ -4.5, -4.6, 14.5, 18.3, 25.9 (3), 47.2, 62.4, 67.8, 89.2, 139.3, 151.6, 157.5, 202.5;FT-IR (thin film): 2956 (m), 2930 (m), 2858 (m), 1720 (s) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{27}O_3Si^+$ ([M + H]$^+$): 283.1724; found 283.1725.

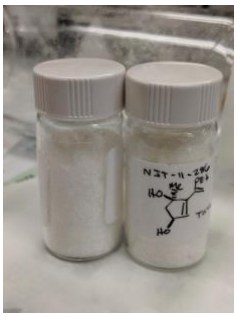


14 **S2**

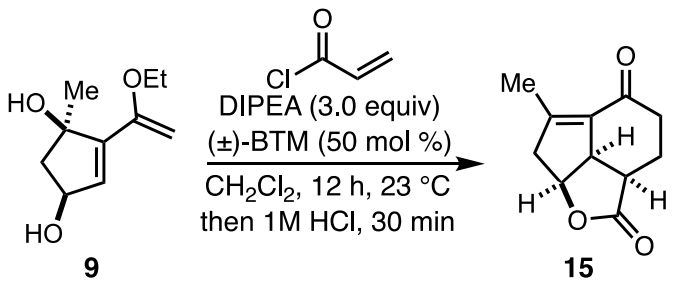
4-((*tert*-butyldimethylsilyl)oxy)-2-(1-ethoxyvinyl)-1-methylcyclopent-2-en-1-ol (S2): A 1-L round-bottomed flask containing enone **14** (40.34 g, 142.8 mmol, 1.0 equiv) was equipped with a septum and was evacuated and filled with N_2 (3x) using an 18G needle. The flask was then maintained under a positive pressure of N_2. The light-yellow oil was then dissolved in THF (480 mL) and cooled to -78 °C (dry

ice:acetone bath). MeLi (3.1 M in diethoxymethane, 50.7 mL, 157 mmol, 1.1 equiv) was then added dropwise over 30 min via syringe pump. After complete addition, the reaction was stirred at -78 °C until starting enone was consumed as judged by TLC (typically 2.5 h). The -78 °C stirred solution was quenched by slow addition of DI H_2O (200 mL). The biphasic mixture was then allowed to warm to 23 °C by removing the dry ice acetone bath. Satd. aq. NH_4Cl (550 mL) was then added and the bulk of the THF was removed by rotary evaporation. The resulting solution was transferred to a separatory funnel, rinsing with EtOAc (~200 mL). The biphasic mixture was shaken vigorously, and the layers were separated. The aq. layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (~200 mL) and dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to yield a red/orange viscous oil. The oil was purified by MPLC (330 g silica, eluting 0 → 60% EtOAc in hexanes) to yield tertiary alcohol **S2** as a clear, light yellow oil (18.88 g, 63.25 mmol, 44%, >19:1 dr): TLC (1:9 EtOAc:hexanes) R_f = 0.24; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.08, 0.09 (overlapping s, 6H), 0.89 (s, 9H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.42 (s, 3H), 1.92 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.41-2.44 (m, 1H), 2.46 (dd, *J* = 13.0, 6.9 Hz, 1H), 3.80 (app qd, *J* = 7.0, 4.7 Hz, 2H), 4.21 (d, *J* = 2.23 Hz, 1H), 4.63 (ddd, *J* = 7.3, 5.5, 2.1 Hz, 1H), 4.71 (d, *J* = 2.2 Hz, 1H), 6.00 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ -4.52, -4.50, 14.6, 18.3, 26.0(3), 27.4, 53.2, 62.8, 72.6, 80.9, 86.0, 132.2, 145.4, 155.3;FT-IR (ATR): 3424 (w-m), 2930 (m), 1637 (w), 1587 (m) cm^{-1}; HRMS (ESI) *m/z* cald for $C_{16}H_{31}O_3Si^+$ ($[M + H]^+$): 299.2037; found 299.2035.

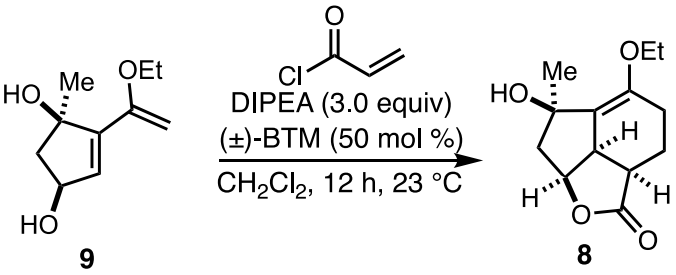




5-(1-ethoxyvinyl)-1-methylcyclopent-4-ene-1,3-diol (**9**): A 500 mL round-bottomed flask containing **S2** (18.88 g, 63.3 mmol, 1.0 equiv) was equipped with a septum and evacuated and refilled with N_2 (3x) using an 18G needle. The flask was then maintained under a positive pressure of N_2. The light-yellow oil was then dissolved in THF (320 mL) and cooled to 0 °C (ice water bath). TBAF (1.0 M in THF, 70 mL, 70 mmol, 1.1 equiv) was then added over *ca.* 10 min. The ice bath was then removed, and the reaction was allowed to warm to ambient temperature (23 °C) and was stirred until complete consumption of **S2**, as judged by TLC (typically 2.5 – 4 h). The solvent was then removed *in vacuo* to yield a viscous dark red oil. The oil was then run through a silica plug (4-in diameter, 4-in tall) eluting with 60% EtOAc in hexanes (1 L), 80% EtOAc in hexanes (1 L), and EtOAc until all product was eluted (judging by TLC). After evaporation of solvent, the resulting light-yellow fibrous/needle crystals were dissolved in minimal hot EtOAc and cooling to ambient temperature open to air provided colorless needles (8.75 g, 47.5 mmol, 75%) after collection of 3 crops of crystals: TLC (1:1 EtOAc:hexanes) R_f = 0.18; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 3H), 1.82, (d, *J* = 8.4 Hz, 1H, -OH detd. by D_2O exchange), 1.93 (dd, *J* = 13.7, 4.3 Hz, 1H), 2.48 (ddd, *J* = 13.7, 7.0, 2.5 Hz, 1H), 2.68 (s, 1H, -OH detd. by D_2O exchange), 3.82 (app qd, *J* = 7.0, 2.5 Hz, 2H), 4.22 (d, *J* = 2.4 Hz, 1H), 4.60-4.64 (m, 2H), 6.09 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): 14.6, 27.5, 51.8, 63.0, 72.8, 81.1, 86.2, 131.8, 146.6, 155.7;FT-IR (ATR): 3239 (m), 3922 (m), 1660 (m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{16}O_3Na^+$ ($[M + Na]^+$): 207.0992; found 207.0993.



4-methyl-2a,2a1,3,6,7,7a-hexahydroindeno[1,7-*bc*]furan-1,5-dione (**15**): Diene diol **9** (100.0 mg, 0.5430 mmol, 1.0 equiv) was weighed into an oven dried (or flame dried) 10 mL round-bottomed flask. Solid (±)-BTM (68.0 mg, 0.271 mmol, 0.5 equiv) was then added. The flask was then equipped with a septum and was evacuated and refilled with N_2 (3x) using an 18G needle. The flask was then maintained under a positive pressure of N_2. The solids were then dissolved in CH_2Cl_2 (4.7 mL) and DIPEA (0.28 mL, 1.6 mmol, 3.0 equiv) was added. A freshly prepared 1.2 M solution of acryloyl chloride (66 µL, 0.82 mmol, 1.5 equiv) in CH_2Cl_2 (0.66 mL) at 23 °C was then added over 8 h via a plastic syringe fitted onto a syringe pump. After stirring for 12 h, 1 M aq. HCl (5.0 mL) was added over *ca.* 30 s at ambient temperature (23 °C). The mixture was then stirred for 30 min. The biphasic mixture was then transferred to a separatory funnel with the aid of CH_2Cl_2 (~5 mL) and the layers were separated. The aq. layer was then extracted with CH_2Cl_2 (3x ~5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to yield a dark orange sticky solid. The material was then purified by MPLC (4 g silica gold, dry loaded) eluting 0 → 75% EtOAc in hexanes to afford tricyclic enone **15** as a light yellow oil which upon successive azeotropic removal of EtOAc with CH_2Cl_2/hexanes became a light yellow solid (66.6 mg, 0.346 mmol, 64%): TLC (1:1 EtOAc:hexanes) R_f = 0.25; mp 61-64 °C (CH_2Cl_2/hexanes, diffusion method); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.84-1.92 (m, 1H), 2.12 (s, 3H), 2.28-2.35 (m, 1H), 2.36-2.45 (m, 2H), 2.72 (d, *J* = 19.4 Hz, 1H), 2.95 (ddt, *J* = 19.4, 5.2, 1.6 Hz, 1H), 3.13-3.19 (m, 1H), 3.69-3.74 (m, 1H), 5.02 (app t, *J* = 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.8, 22.1, 38.4, 39.0, 46.1, 48.8, 80.5, 129.6, 151.8, 178.5, 198.9;FT-IR (ATR): 2944 (w), 1759 (s), 1679 (s), 1626 (s) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}O_3Na^+$ ([M + Na]$^+$): 215.0679; found 215.0678.

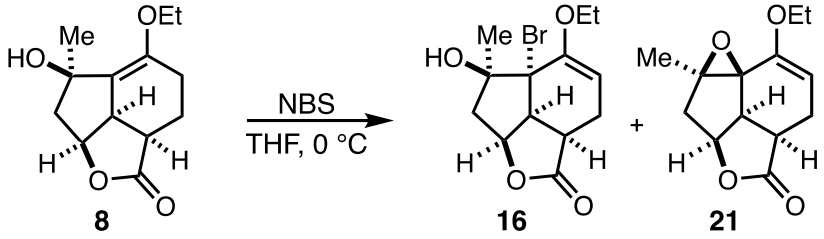


5-ethoxy-6-hydroxy-6-methyl-2a1,3,4,6,7,7a-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one (8): Diene diol **9** (1.50 g, 8.14 mmol, 1.0 equiv) was weighed into an oven dried (or flame dried under vacuum) 200 mL round-bottomed flask. Solid (±)-BTM (1.03 g, 4.07 mmol, 0.5 equiv) was then added. The flask was equipped with a septum and was evacuated and refilled with N_2 (3x) using an 18G needle. The flask was then maintained under a positive pressure of N_2. The colorless solids were dissolved in CH_2Cl_2 (65 mL) and DIPEA (4.25 mL, 24.4 mmol, 3.0 equiv) was added, prior to the addition of a freshly prepared 0.81 M solution of acryloyl chloride (1.0 mL, 12 mmol, 1.5 equiv) in CH_2Cl_2 (15.0 mL) at 23 °C over 8 h using a plastic syringe fitted to a syringe pump. After stirring for 12 h the red solution was treated with satd. aq. $NaHCO_3$ (~ 30 mL) and was stirred for ~5 min. The biphasic mixture was then transferred to a separatory funnel, rinsing with CH_2Cl_2 (~10 mL) to ensure quantitative transfer. The aq. layer was then extracted with CH_2Cl_2 (3x ~30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to yield a dark red sticky oil. The material was then purified by MPLC (80 g silica, dry loaded) eluting 0 → 100% Et_2O in hexanes over 25 min, followed by an additional 10 min held at 100% Et_2O to give a light yellow viscous oil. *Trace DIPEA was extremely detrimental to the following*

reaction thus the material was then taken up in equal portions of MeCN and H_2O and was lyophilized to yield the desired enol ether **8** as a fluffy light yellow solid (1.50 g, 6.30 mmol, 77% yield):

Note: *For reproducible yields, a new bottle of acryloyl chloride stored under argon gave optimal and reproducible yields of the enol ether **8** avoiding subsequent elimination leading to enone **15**.*

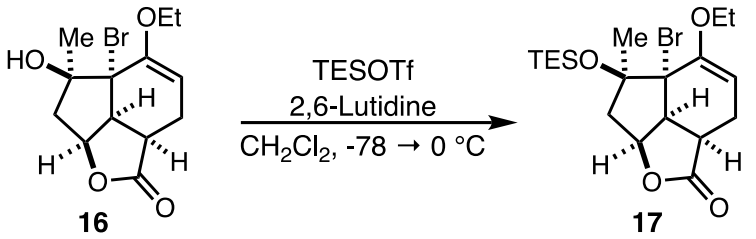
TLC (1:1 EtOAc:hexanes, PAA stain) R_f = 0.20; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 3H), 1.91-1.99 (m, 1H), 2.12 (dd, *J* = 15.6, 5.7 Hz, 1H), 2.16-2.22 (m, 1H), 2.27-2.35 (m, 3H), 2.96 (ddd, *J* = 6.5, 5.5, 2.6 Hz, 1H), 3.12 (ddt, *J* = 7.1, 4.9, 2.6 Hz, 1H), 3.82-3.91 (m, 2H), 4.53 (s, 1H), 4.74 (ddd, *J* = 5.6, 4.6, 1.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.4, 20.3, 21.1, 30.4, 39.4, 43.8, 46.6, 63.5, 79.6, 81.4, 121.4, 148.6, 177.5;FT-IR (ATR): 3514 (w), 2962 (w), 1754 (m-s), 1147 (s), 1605 (s) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_4Na^+$ ([M + Na]$^+$): 261.1097; found 261.1103.



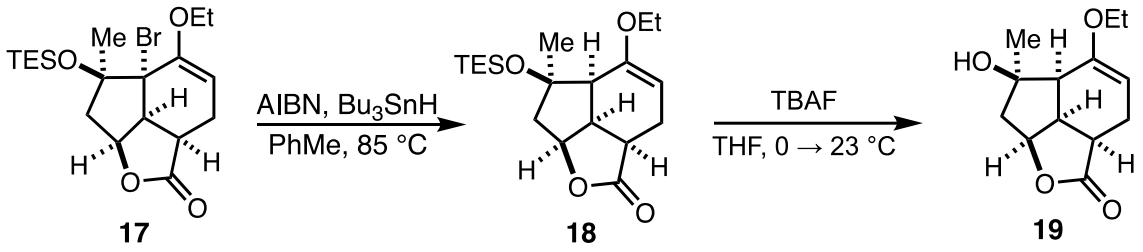
5a-bromo-5-ethoxy-6-hydroxy-6-methyl-2a1,3,5a,6,7,7a-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one (16): A 50-mL round-bottomed flask containing enol ether **8** (2.16 g, 9.06 mmol, 1.0 equiv) was equipped with a rubber septum and was evacuated and refilled with N_2 (3x) using an 18G needle. The flask was then maintained under a positive pressure of N_2. The solid was then dissolved in THF (90 mL) and was cooled to 0 °C using an ice water bath. The septum was then removed and solid NBS (1.61 g, 9.06 mmol, 1.0 equiv) was added in a single portion and the septum was quickly replaced. The flask was then covered with aluminum foil (to shield reaction vessel from light) and the reaction was stirred at 0 °C. Upon full consumption of enol ether **8**, as judged by TLC (typically 1 h), the reaction was treated with satd. aq. $NaHCO_3$ (90 mL) at 0 °C. A colorless precipitate immediately formed, and the precipitate was removed by filtration through celite. The filtrate was then transferred to a separatory funnel, rinsing with Et_2O (~10 mL). The biphasic mixture was then extracted with Et_2O (3x ~50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to yield a light yellow solid. The solid was purified by MPLC (24 g silica, dry loaded) eluting 0 → 70% EtOAc in hexanes to yield allylic bromide **16** mixed with epoxide **21** as an inseparable mixture and as a colorless crystalline solid (2.44 g total, 7.08 mmol desired product, 78% yield of **16**, 0.818 mmol, 9% yield of **21**). *Note: mmol and yield determined based on ratio of signal integration in the ^{1}H NMR of the two compounds. Formation of epoxide **21** is not always noted but is typically more prevalent on reactions larger than 1 g scale. The epoxide was not detrimental to the subsequent reaction and can be separated at that point.* Characterization data for the desired allylic bromide **16**: TLC (Et_2O) R_f = 0.38; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.0 Hz, 3H), 1.69 (s, 3H), 2.02 (s, 1H), 2.33 (d, *J* = 14.8 Hz, 1H), 2.42 (ddd, *J* = 14.8, 5.1, 2.1 Hz, 1H), 2.58 (ddd, *J* = 18.0, 8.2, 2.8 Hz, 1H), 2.73 (dd, *J* = 18.0, 5.7 Hz, 1H), 2.89 (app t, *J* = 9.5 Hz, 1H), 3.78 (dq, *J* = 8.9, 6.9 Hz, 1H), 3.87 (dq, *J* = 9.6, 7.0 Hz, 1H), 3.97 (dd, *J* = 10.9, 6.7 Hz, 1H), 4.99 (dd, *J* = 5.9, 2.8 Hz, 1H), 5.07 (app t, *J* = 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.5, 21.9, 27.5, 37.9, 43.2, 55.2, 63.4, 69.7, 81.5, 84.3, 98.9, 151.7, 177.5;FT-IR (ATR): 3489 (w), 2971 (w), 1764 (s), 1665 (m), 1150 (s) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_4BrNa^+$ ([M + Na]$^+$): 339.0202, 341.0182; found 339.0203, 341.0182.

7-ethoxy-1a-methyl-1a,2,2a,2a1,4a,5-hexahydro-4*H*-oxireno[2',3':3,3a]indeno[1,7-*bc*]furan-4-one (21): A sample of epoxide **21** (devoid of the co-eluting allylic bromide **16** as described above) was prepared for characterization by removing an aliquot from a transposition reaction described above. The aliquot was treated with satd. aq. $NaHCO_3$ (to induce further cyclization to the epoxide) and was stirred at 23 °C for 2 hours prior to filtering the colorless precipitate through a cotton plug. The resulting biphasic mixture was transferred to a separatory funnel and was extracted with Et_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to yield a colorless crystalline solid. The solid was then purified by flash chromatography eluting 0 → 100% Et_2O in hexanes to yield epoxide **21** as

colorless flaky or plate like crystals; TLC (Et_2O, PAA stain) R_f = 0.38; ^1H NMR (600 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.65 (s, 3H), 2.08 (dd, *J* = 15.6, 5.7 Hz, 1H), 2.47 (d, *J* = 15.6 Hz, 1H), 2.70 (ddd, *J* = 17.6, 9.9, 6.0 Hz, 1H), 2.79 (dt, *J* = 17.6, 2.7 Hz, 1H), 2.92-2.99 (m, 2H), 3.71-3.76 (m, 2H), 4.75 (app t, *J* = 5.5 Hz, 1H), 4.82 (dd, *J* = 6.0, 2.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.4, 16.2, 22.8, 35.3, 40.4, 46.0, 62.8, 67.9, 73.1, 78.4, 99.4, 151.7, 179.2;FT-IR (thin film): 2976 (w), 2930 (w), 1769 (s), 1642 (w-m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_4Na^+$ ([M + Na]$^+$): 259.0941; found 259.0942.



5a-bromo-5-ethoxy-6-methyl-6-((triethylsilyl)oxy)-2a1,3,5a,6,7,7a-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one (17): A 250-mL round-bottomed flask containing tertiary alcohol **16** (2.44 g total, 7.08 mmol, 1.0 equiv of **16**, containing 0.818 mmol of **21** (by ^1H NMR), see previous reaction for details) was equipped with a septum and evacuated and refilled with N_2 (3x) using an 18G needle. The flask was then maintained under a positive pressure of N_2. The solid was then dissolved in CH_2Cl_2 (77 mL) and the resulting clear colorless solution was cooled to -78 °C (dry ice acetone bath). 2,6-Lutidine (4.49 mL, 38.3 mmol, 5.4 equiv) was then added followed by the dropwise addition of TESOTf (3.5 mL, 15 mmol, 2.2 equiv) over *ca.* 1 min using a plastic syringe. After complete addition, the reaction was stirred at -78 °C for 10 min prior to replacing the -78 °C bath with a 0 °C bath (ice water). After complete consumption of alcohol **16** as judged by TLC (typically 2 h), the reaction mixture was treated with satd. aq. $NaHCO_3$ (~60 mL) at 0 °C. The biphasic mixture was then transferred to a separatory funnel, rinsing with CH_2Cl_2 (~10 mL). After vigorous shaking the layers were separated. The aq. layer was then extracted with CH_2Cl_2 (3x ~30 mL). The combined organic layers were then washed with 1 M aq. HCl (20 mL) and then washed with satd. aq. $NaHCO_3$ (20 mL). The combined organic layers were then washed with brine, dried over Mg_2SO_4, filtered, and the solvent was removed *in vacuo* to yield a light-yellow oil. The material was purified by silica gel flash chromatography (1.5-inch column, ~7 inches silica, wet loaded in CH_2Cl_2) eluting 0 → 20% Et_2O in hexanes (5% increments, 250 mL each) to yield the title compound as a colorless waxy solid (2.47 g, 5.73 mmol, 81% yield based on calculated amount of tertiary alcohol **16**) (*Note: the product is weakly UV active, therefore many product-containing fractions will be missed if PAA stain is not used)*. TLC (Et_2O, UV active/PAA stain) R_f = 0.71; ^1H NMR (600 MHz, $CDCl_3$): δ 0.59 (q, *J* = 8.0 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.55 (s, 3H), 2.03 (dd, *J* = 15.1, 2.7 Hz, 1H), 2.42 (ddd, *J* = 17.1, 4.3, 2.1 Hz, 1H), 2.49 (ddd, *J* = 17.0, 6.1, 2.9 Hz, 1H), 2.75-2.82 (m, 2H), 3.19 (app dt, *J* = 5.1, 2.8 Hz, 1H), 3.76-3.83 (m, 2H), 4.81 (ddd, *J* = 9.2, 6.3, 2.7 Hz, 1H), 4.93 (dd, *J* = 6.1, 2.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 4.8 (3), 6.9 (3), 14.5, 21.2, 29.5, 41.3, 47.2, 54.4, 63.5, 69.8, 70.5, 92.8, 97.8, 150.3, 173.2;FT-IR (thin film): 2954 (m), 1749 (s), 1648 (w-m) cm^{-1}; HRMS (ESI) *m/z* cald for $C_{19}H_{31}O_4BrNa^+$ ([M + Na]$^+$): 453.1067, 455.1047; found 453.1070, 455.1048.

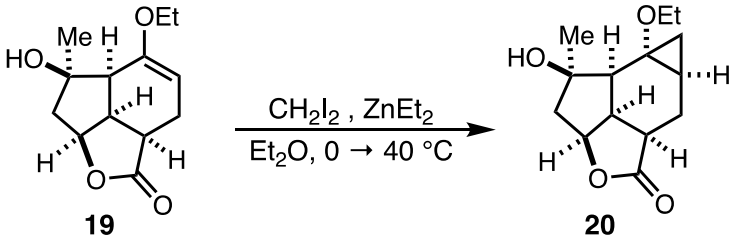


5-ethoxy-6-hydroxy-6-methyl-2a1,3,5a,6,7,7a-hexahydroindeno[1,7-*bc*]furan-2(2a*H*)-one (19): To a 250-mL round-bottomed flask containing allylic bromide **17** (2.46 g, 5.70 mmol, 1.0 equiv) was added AIBN (187 mg, 1.14 mmol, 0.2 equiv). The round-bottomed flask was fitted with a reflux condenser and the entire apparatus was evacuated and refilled with N_2 (3x) and was subsequently maintained under a positive

pressure of N_2. The mixture was dissolved in PhMe (57 mL) and the reflux condenser was removed, Bu_3SnH (1.7 mL, 6.3 mmol, 1.1 equiv) was added over *ca.* 20 s and the condenser was quickly refitted to the round-bottomed flask. The clear colorless solution was heated to 85 °C and was stirred at that temperature until full consumption of allylic bromide **17** (as determined by TLC, typically 1-2 h). The solvent was then removed *in vacuo* to yield a viscous, clear, colorless oil. The oil which contained some trace tin by-products was utilized without further purification in the subsequent deprotection reaction.

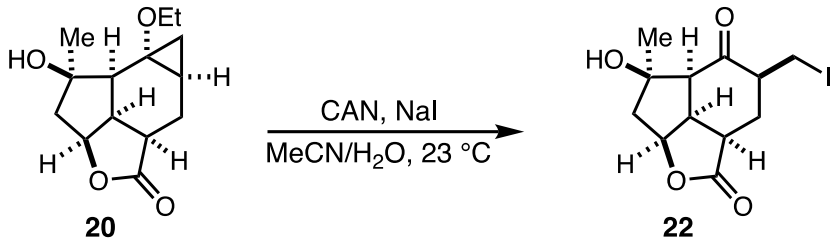
*When using enol ether **18** for attempted cyclopropanation reactions, purification was completed by MPLC (wet loaded using CH_2Cl_2) eluting 0 → 60% Et_2O in hexanes to yield debrominated silylether **18** as a clear colorless oil. Characterization data for purified debrominated silylether **18**:* TLC (30% Et_2O in hexanes, PAA stain) R_f = 0.35; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.56 (q, *J* = 8.0 Hz, 6H), 0.93 (t, *J* = 8.0 Hz, 9H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.40 (s, 3H), 2.00 (dd, *J* = 14.9, 2.4 Hz, 1H), 2.15 (dd, *J* = 14.9, 9.5 Hz, 1H), 2.24 (d, *J* = 5.1 Hz, 1H), 2.36 (dd, *J* = 16.8, 4.2 Hz, 1H), 2.43 (ddd, *J* = 7.0, 5.5, 2.3 Hz, 1H), 2.47 (ddd, *J* = 17.0, 5.5, 2.6 Hz, 1H), 3.07 (bs, 1H), 3.64-3.78 (m, 2H), 4.48 (ddd, *J* = 9.3, 6.6, 2.4 Hz, 1H), 4.74 (dd, *J* = 5.6, 2.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 4.7, 6.7, 14.6, 22.4, 29.4, 29.4, 37.0, 44.0, 46.7, 49.0, 62.4, 70.0, 88.8, 94.8, 151.3, 174.6;FT-IR (thin film): 2956 (m-s), 2877 (m), 1739 (s), 1662 (w) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{32}O_4SiNa^+$ ([M + Na]$^+$): 375.1962; found 375.1964.

The round-bottomed flask containing enol ether **18** as a crude oil was equipped with a septum and was evacuated and refilled with N_2 (3x) using an 18G needle. The flask was then maintained under a positive pressure of N_2.The oil was then dissolved in THF (57 mL) and the resulting clear colorless solution was cooled to 0 °C (ice water bath) prior to adding TBAF (1M in THF, 14.3 mL, 14.3 mmol, 2.5 equiv) over *ca.* 45 s (*Note: when using crude **18**, tin-containing byproducts which remained from the previous reaction made it necessary to use an excess of TBAF to achieve full conversion to **19**)*. The reaction was stirred at 0 °C for 5 min, after which the 0 °C bath was removed allowing the reaction to warm to ambient temperature (23 °C). After TES protected alcohol **19** was fully consumed (as judged by TLC, typically 2-3 h) the solvent was removed *in vacuo* to yield a light brown viscous oil. The material was then purified by flash chromatography (1.5 inch column, ~7 inches of silica, wet loaded with CH_2Cl_2) eluting 0 → 60% EtOAc in hexanes (10% increments, 250 mL each) to yield tertiary alcohol **19** as a colorless powder (1.222 g, 5.128 mmol, 90% yield over 2 steps); TLC (EtOAc, PAA stain) R_f = 0.53; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 3H), 1.51 (d, *J* = 1.9 Hz, 1H, -OH detd. by D_2O exchange), 1.83 (ddd, *J* = 14.9, 5.1, 1.7 Hz, 1H), 2.37 (d, *J* = 14.9 Hz, 1H), 2.45-2.54 (m, 2H), 2.70 (ddd, *J* = 18.3, 4.4, 1.9 Hz, 1H), 2.86 (ddd, *J* = 10.9, 9.2, 2.0 Hz, 1H), 3.2 (td, *J* = 10.5, 6.4 Hz, 1H), 3.69-3.79 (m, 2H), 4.82 (app t, *J* = 4.0 Hz, 1H), 5.00 (dd, *J* = 6.4, 5.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.8, 22.6, 28.3, 36.3, 41.5, 46.3, 48.9, 62.2, 80.1, 83.0, 94.8, 151.3, 178.9; FT-IR (ATR): 3428 (w-m), 2871 (w), 1748 (m-s) 1673 (m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_4Na^+$ ([M + Na]$^+$): 261.1097; found 261.1098.



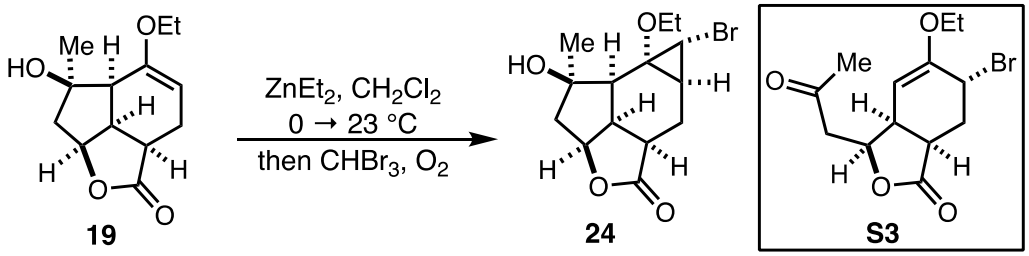
6a-ethoxy-1-hydroxy-1-methyldecahydro-4*H*-cyclopropa[4,5]indeno[1,7-*bc*]furan-4-one (20): Enol ether **19** (26.9 mg, 0.113 mmol, 1.0 equiv) as a colorless solid was weighed into a flame-dried 1.5 dram vial. The vial was equipped with a septum and then evacuated and refilled with N_2 (3x) through an 18G needle. The reaction was maintained under a positive pressure of N_2. The enol ether **19** was dissolved in Et_2O (0.84 mL) and the solution was cooled to 0 °C. $ZnEt_2$ (1 M in hexanes, 0.84 mL, 0.84 mmol, 10 equiv) was then added dropwise over *ca.* 1 min. The reaction was then stirred at 0 °C for 5 min prior to the addition of CH_2I_2 (64 µL, 0.78 mmol, 9.5 equiv). The reaction was then allowed to warm to ambient temperature (23 °C) over 1 h, after which the vial was sealed and heated to 40 °C (*Note: heating a reaction in a sealed container is dangerous and can lead to an explosion. A blast shield should be employed in addition to your hood sash for protection*). After full consumption of starting enol ether **19**, as determined by TLC (~5 h), the

reaction was cooled to 0 °C. While the reaction mixture was stirring vigorously, 1 M aq. HCl (~1-2 mL) was added slowly until all colorless precipitate had dissolved (*Note: Add aq. HCl slowly, if $ZnEt_2$ is still present in solution the reaction will bubble over the top of the reaction flask*). The reaction mixture was then transferred to a separatory funnel with Et_2O (~2 mL) to ensure quantitative transfer. The layers were separated, and the aq. layer was extracted with Et_2O (3x ~3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to yield a light-yellow solid. The solid was then purified by flash chromatography (Monstr-Pette (Kimble p1005, 10 mm O.D.) pipette column, wet loaded with CH_2Cl_2) eluting 0 → 40% EtOAc in hexanes (5% increments, 2 mL each), then 45 → 70% EtOAc in hexanes (5% increments, 4 mL each) to yield the product as a colorless crystalline solid (10.7 mg, 0.0421 mmol, 38% yield) (*Note: reaction yields ranged from 35 to 69% and were highly dependent on CH_2I_2 purity; ~40% was a typical yield)*: TLC (5:1 EtOAc:hexanes, PAA stain) R_f = 0.35; mp 118-121 °C (CH_2Cl_2/hexanes, diffusion method); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.71 (app t, *J* = 6.5 Hz, 1H), 0.98 (ddd, *J* = 10.5, 7.4, 1.7 Hz, 1H), 1.14 (t, *J* = 7.0 Hz, 3H), 1.23 (ddt, *J* = 9.4, 6.0, 3.2 Hz, 1H), 1.33 (s, 3H), 2.12 (ddd, *J* = 14.5, 7.5, 3.6 Hz, 1H), 2.18 (dd, 14.1, 5.8 Hz, 1H), 2.28-2.35 (m, 2H), 2.64-2.69 (m, 2H) 3.11 (dt, *J* = 12.0, 9.7 Hz, 1H), 3.33 (dq, *J* = 8.8, 7.1 Hz, 1H), 3.65 (dq, *J* = 8.8, 7.0 Hz, 1H), 4.30 (s, 1H), 4.80 (ddd, *J* = 8.4, 7.6, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.66, 14.74, 15.7, 22.2, 30.8, 34.7, 38.0, 43.1, 46.6, 60.5, 61.9, 80.7, 81.5, 180.1;FT-IR (thin film): 3479 (w-m), 2926 (m-s), 1764 (s), 1259 (m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_4Na^+$ ([M + Na]$^+$): 275.1254; found 275.1256.



20 **22**

6-hydroxy-4-(iodomethyl)-6-methyloctahydroindeno[1,7-*bc*]furan-2,5-dione (22): To a 2 dram vial containing cyclopropane **20** (16.2 mg, 0.0642 mmol, 1.0 equiv), was added CAN (79.9 mg, 0.146 mmol, 2.3 equiv) and NaI (20.6 mg, 0.137 mmol, 2.1 equiv) sequentially. The vial was then fitted with a septum and was evacuated and refilled with N_2 (3x). The solids were dissolved in MeCN (0.5 mL) and H_2O (0.1 mL) and the red/brown reaction mixture was stirred at ambient temperature (23 °C). *Note: both MeCN and H_2O were degassed by bubbling Ar through the solvents for 20 min prior to use.* After 3 h mass spec revealed the prevalence of starting cyclopropane **20** (*TLC difficult to interpret as product decomposes and streaks*). At this point additional CAN (81.7 mg, 0.149 mmol, 2.3 equiv) was added by removing the septum, adding solid CAN and then quickly refitting the septum on the vial. After 30 min, mass spec showed no starting material. DI H_2O (~2 mL) was added to the vial and the and the orange mixture was extracted with CH_2Cl_2 (3x ~2 mL) using a pipet to remove the layer from the vial. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to yield iodide **22** as an orange solid. Unfortunately, this compound was not stable to silica gel and therefore could not be purified to homogeneity and a yield is not provided. Data for the crude product is provided: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.60 (s, 3H), 1.88 (dd, *J* = 15.2, 6.1 Hz, 1H), 2.01 (td, *J* = 13.6, 9.9 Hz, 1H), 2.26 (d, *J* = 15.2 Hz, 1H), 2.45 (app ddt, *J* = 14.1, 7.5, 4.6 Hz, 1H), 2.56 (d, *J* = 9.7 Hz, 1H), 2.64 (ddd, *J* = 13.5, 10.0, 4.6 Hz, 1H), 3.05 (dd, *J* = 10.4, 7.5 Hz, 1H), 3.31 (dt, *J* = 12.2, 9.9 Hz, 1H), 3.48 (ddd, *J* = 12.4, 9.7, 7.7 Hz, 1H), 3.57 (dd, *J* = 10.4, 4.5 Hz, 1H), 5.10 (dd, *J* = 7.6, 6.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 2.7, 26.9, 27.8, 37.6, 40.8, 48.0, 49.8, 58.5, 82.4, 82.8, 179.1, 207.4; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}IO_4Na^+$ ([M + Na]$^+$): 372.9907; found 372.9908.

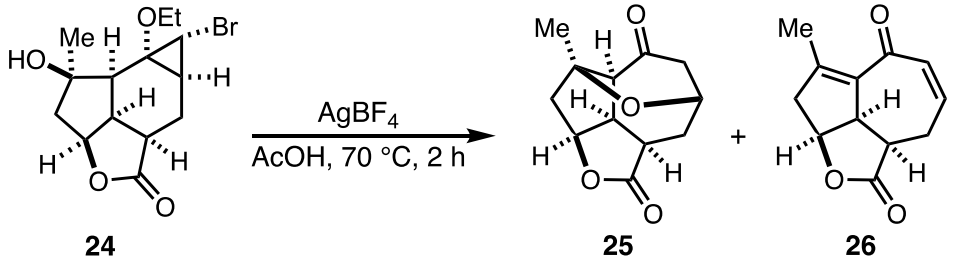


19 **24** **S3**

6-bromo-6a-ethoxy-1-hydroxy-1-methyldecahydro-4*H*-cyclopropa[4,5]indeno[1,7-*bc*]furan-4-one (24): Enol ether **19** (90.0 mg, 0.378 mmol, 1.0 equiv) was weighed into an oven-dried 2 dram vial. The vial was equipped with a septum and was evacuated and refilled with N_2 (3x) using an 18G needle. The vial was then maintained under a positive pressure of N_2. The colorless solid was dissolved in CH_2Cl_2 (3.8 mL) and the resulting homogenous, colorless solution was cooled to 0 °C before adding $ZnEt_2$ (1M in hexanes, 0.94 mL, 0.94 mmol, 2.5 equiv) dropwise over *ca.* 2 min (*white vapor forms in the headspace above the reaction mixture as $ZnEt_2$ is added*). After complete addition, the reaction was stirred at 0 °C for *ca.* 5 min prior to warming the reaction to ambient temperature (23 °C) by removing the ice bath. The reaction was then stirred at 23 °C for 30 min (*Note: this premixing time is absolutely essential to the success of the reaction; failure to premix the $ZnEt_2$ and the tertiary alcohol for 30 min will result in increased side reactions and low yields of cyclopropane **24***). After stirring for 30 min at 23 °C, $CHBr_3$ (66 µL, 0.76 mmol, 2.0 equiv) was added dropwise over *ca.* 1 min at the same temperature and the N_2 inlet was replaced with an O_2 balloon through a 18 G needle (*Note: the headspace was NOT purged, O_2 was allowed to passively diffuse into the existing N_2 atmosphere. A white cloud forms directly above the reaction mixture and remains until the reaction is complete*). Stirring was continued with the attached O_2 balloon at 23 °C for 2 h (*Note: the reaction now contained a colorless precipitate)* at which time the reaction was quenched by slow addition of satd. aq. NH_4Cl solution (enough to dissolve all precipitate upon vigorous stirring). The biphasic mixture was then transferred to a separatory funnel, rinsing with CH_2Cl_2 (~5 mL) and the layers were separated. If solid persisted, additional satd. aq. NH_4Cl solution was added accordingly. The aq. layer was then extracted with CH_2Cl_2 (3x ~6 mL) and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to yield a colorless solid which was purified by MPLC (4 g silica gold, dry loaded) eluting 0 → 75% EtOAc in hexanes to give bromocyclopropane **24** as a colorless crystalline solid (87.6 mg, 0.265 mmol, 70% yield); TLC (EtOAc, PAA stain) R_f = 0.53; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.42 (ddd, *J* = 6.3, 4.6, 4.0 Hz, 1H), 1.45 (s, 3H), 2.10-2.17 (m, 3H), 2.26 (ddd, *J* = 15.0, 8.8, 6.3 Hz, 1H), 2.47 (s, 1H), 2.62 (d, *J* = 10.6 Hz, 1H), 2.74 (ddd, *J* = 11.7, 8.8, 4.6 Hz, 1H), 3.10 (app td, *J* = 11.1, 10.9, 7.8 Hz, 1H), 3.22 (d, *J* = 4.6 Hz, 1H), 3.48 (dq, *J* = 8.8, 7.0, Hz, 1H), 3.73 (dq, *J* = 8.7, 7.0 Hz, 1H), 4.90 (ddd, *J* = 7.7, 5.3, 4.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.4, 21.3, 24.1, 27.4, 29.5, 35.0, 38.8, 44.5, 47.5, 60.4, 63.1, 81.0, 82.0, 179.4;FT-IR (thin film): 3449 (w-m), 2974 (w-m), 1760 (s), 735 (m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}O_4BrNa^+$ ([M + Na]$^+$): 353.0359, 355.0338; found 353.0363, 355.0338.

The purity of bromoform is important. The presence of bromine from bromoform's decomposition leads to α-bromination/retro aldol side reaction, providing methyl ketone S3. For reproducible results, we used "Bromoform, contains 60-120 ppm 2-methyl-2-butene as stabilizer, 99%" from Sigma-Aldrich (SKU: 241032) without further purification.

Data for methyl ketone **S3**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.0 Hz, 3H), 2.21 (s, 3H), 2.38-2.50 (m, 2H), 2.71 (dd, *J* = 17.4, 6.9 Hz, 1H), 2.85 (dd, *J* = 17.4, 6.7 Hz, 1H), 3.10 (app td, *J* = 9.0, 5.4 Hz, 1H), 3.51 (app td, *J* = 8.0, 3.9 Hz, 1H), 3.70-3.78 (m, 2H), 4.45 (d, *J* = 3.8 Hz, 1H), 4.55 (t, *J* = 5.2 Hz, 1H), 5.09 (app q, 7.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.4, 30.8, 32.7, 36.6, 36.9, 42.6, 45.9, 63.5, 77.7, 92.1, 156.2, 177.1, 204.9;FT-IR (thin film): 2978 (w), 2933 (w), 1771 (s), 1717 (m), 1197 (m) cm^{-1}



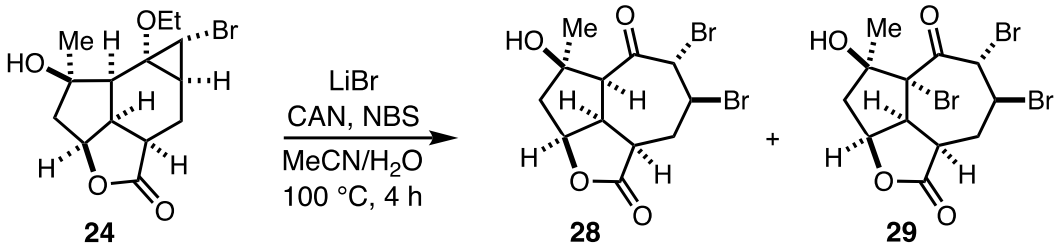
24 **25** **26**

4-methyloctahydro-1H-4,7-epoxyazuleno[1,8-bc]furan-1,5(2aH)-dione and **4-methyl-2a1,3,8,8a-tetrahydro-1H-azuleno[1,8-bc]furan-1,5(2aH)-dione, (25 and 26):** To a 1.5-dram vial containing bromo cyclopropane **24** (32.4 mg, 0.0980 mmol, 1.0 equiv) was added $AgBF_4$ (76.0 mg, 0.391 mmol, 4.0 equiv). The vial was subsequently equipped with a septum and was evacuated and refilled with N_2 (3x) using an

18G needle. The vial was then maintained under a positive pressure of N_2. The solids were dissolved in AcOH (1.0 mL) and 3 drops DI H_2O (from 20 G needle). The septum was replaced with a cap, the joint was sealed with Teflon tape, then parafilm and the vial was heated to 80 °C and was stirred (*Note: heating a reaction in a sealed container is dangerous and can lead to an explosion. A blast shield should be employed in addition to your hood sash for protection*). After full consumption of starting cyclopropane **24** as determined by TLC (typically 1.5 h), the reaction mixture was allowed to cool to ambient temperature (23 °C) and was neutralized by slow addition of satd. aq. $NaHCO_3$ until a pH of ~7 was achieved. The dark grey/black precipitate (Ag_2O) that had formed during the reaction was removed by filtration through celite and the filtrate was transferred to a separatory funnel, rinsing with CH_2Cl_2 (~3 mL). The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3x ~3 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to yield a gray oil. The oil was purified by flash chromatography (1/2 inch column, ~7 inch height of silica, dry loaded) eluting 0 → 25% EtOAc in CH_2Cl_2 (2.5% increments, 25 mL each) to yield pyranone **25** as a clear colorless oil (8.1 mg, 0.036 mmol, 37% yield) and cross conjugated dienone **26** as a colorless solid (2.4 mg, 0.012 mmol, 12% yield);

Pyranone **25:** TLC (70% EtOAc in hexanes, PAA stain) R_f = 0.27; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.38 (s, 3H), 2.04-2.14 (m, 2H), 2.37 (dd, *J* = 15.8, 2.0 Hz, 1H), 2.42 (dd, *J* = 17.8, 1.8 Hz, 1H), 2.61 (d, *J* = 7.1 Hz, 1H), 2.74 (app ddt, *J* = 15.2, 7.4, 2.3 Hz, 1H), 2.80 (td, *J* = 10.9, 3.0 Hz, 1H), 2.98 (app dd, *J* = 17.9, 4.5 Hz, 1H), 3.48 (dt, *J* = 11.2, 7.4 Hz, 1H), 4.58-4.62 (m, 1H), 5.09 (ddd, *J* = 9.3, 7.6, 1.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ. 26.8, 35.4, 35.9, 45.8, 46.6, 48.9, 59.5, 67.5, 82.0, 83.0, 180.2, 206.1;FT-IR (thin film): 2937 (w), 1763 (s), 1716 (m)1214 (w-m), 1012 (w-m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}O_4Na^+$ ([M + Na]$^+$): 245.0784; found 245.0785.

Dienone **26:** TLC (30% EtOAc in CH_2Cl_2) R_f = 0.66; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.18 (app dt, *J* = 2.2, 1.3 Hz, 3H), 2.42 (app tdd, *J* = 13.6, 6.0, 2.3 Hz, 1H), 2.73 (ddd, *J* = 13.8, 8.7, 5.2 Hz, 1H), 2.85 (br d, *J* = 20.1 Hz, 1H), 2.99 (ddt, *J* = 20.0, 7.0, 1.4 Hz, 1H), 3.21 (ddd, *J* = 13.3, 10.4, 5.2 Hz, 1H), 3.83-3.88 (m, 1H), 5.15 (td, *J* = 7.1, 1.3 Hz, 1H), 6.10 (ddd, *J* = 11.3, 2.2, 0.9 Hz, 1H), 6.69 (ddd, *J* = 11.2, 8.9, 6.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.6, 26.9, 43.8, 47.2, 49.7, 79.4, 133.2, 135.3, 140.7, 155.9, 177.1, 192.1;FT-IR (thin film): 2920 (m), 2851 (m), 1764 (s), 1737 (m), 1684 (m), 1603 (m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{12}O_3Na^+$ ([M + Na]$^+$): 227.0679; found 227.0679.

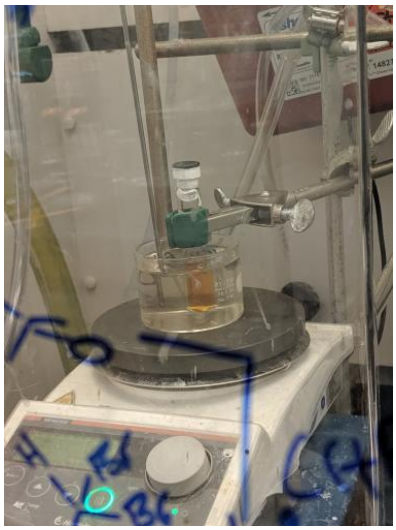


24 28 29

6,7-dibromo-4-hydroxy-4-methyloctahydro-1H-azuleno[1,8-bc]furan-1,5(2aH)-dione and **4a,6,7-tribromo-4-hydroxy-4-methyloctahydro-1H-azuleno[1,8-bc]furan-1,5(2aH)-dione (28 and 29):** Bromo cyclopropane **24** (30.8 mg, 0.0930 mmol, 1.0 equiv) was weighed into a Pyrex threaded culture tube. CAN (104.5 mg, 0.1906 mmol, 2.0 equiv), LiBr (11.6 mg, 0.134 mmol, 1.4 equiv) and NBS (53.7 mg, 0.302 mmol, 3.2 equiv) were added to the vial as solids. The culture tube was fitted with a septum and evacuated and refilled with argon (3x) using an 18G needle. The culture tube was then maintained under a positive pressure of argon. The solids were then dissolved in MeCN (0.9 mL) and 2 drops of DI H_2O (20 G needle, ~36 μL). *Note: MeCN and DI H_2O were degassed by bubbling argon through solvent for ca. 20 min. Without degassing the reaction does not proceed*. The septum was then replaced with the tube cap and the joint was sealed with Teflon tape. The orange homogeneous reaction was then heated to 100 °C (*Note: heating a reaction in a sealed container is dangerous and can lead to an explosion. A blast shield should be employed in addition to your hood sash for protection*) and stirred for 4 h. At this point, the reaction was usually a homogeneous yellow solution (see image below) at which point the reaction was cooled to ambient temperature (23 °C). CH_2Cl_2 (1 mL) was added and the vial was shaken vigorously. The organic layer was removed from the vial using a pipette. The aq. layer was then extracted with CH_2Cl_2 (3x 2 mL) and the layers were again separated by pipette. The combined organic layers were dried over $MgSO_4$,

filtered and the solvent was removed *in vacuo* to yield a clear, light yellow film that was purified by flash chromatography (1/2 inch column, dry loaded) eluting 0 → 60% EtOAc in hexanes (10% increments, 50 mL each) to yield dibromo cycloheptanone **28** as a colorless crystalline solid (4.8 mg, 0.013 mmol, 14% yield) and tribromo cycloheptanone **29** as a colorless crystalline solid (19.6 mg, 0.0425 mmol, 46% yield).

t = 0

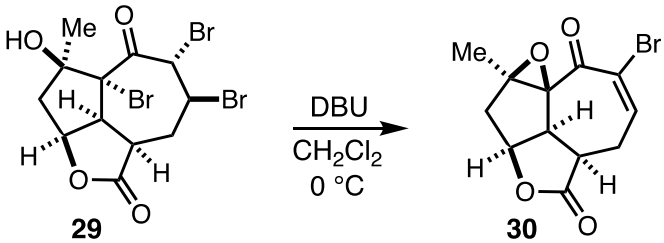


t = 2 h

t = 4 h

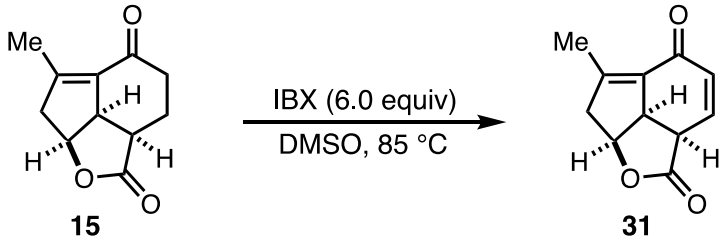
Dibromocycloheptanone **28.** TLC (50% EtOAc in CH_2Cl_2, PAA stain) R_f = 0.68; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.62 (s, 3H), 1.86 (dd, *J* = 15.3, 6.3 Hz, 1H), 2.33-2.43 (m, 2H), 2.77 (app br dt, *J* = 15.3, 4.1 Hz, 1H), 3.15 (ddd, *J* = 12.6, 11.5, 5.0 Hz, 1H), 3.24 (d, *J* = 10.3 Hz, 1H), 4.14 (td, *J* = 10.9, 7.8 Hz, 1H), 4.47 (ddd, *J* = 13.3, 3.5, 2.1 Hz, 1H), 4.83 (dd, *J* = 2.2, 0.9 Hz, 1H), 5.06 (dd, *J* = 7.7, 6.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 27.0, 35.5, 40.7, 42.9, 46.7, 48.6, 56.7, 59.9, 80.3, 81.5, 175.8, 201.3;FT-IR (thin film): 3468 (br w), 2930 (w), 1759 (s), 1703 (m), 1193 (m), 731 (w) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}O_4Br_2Na^+$ ([M + Na]$^+$): 402.9151, 404.9131, 406.9110; found 402.9158, 404.9136, 406.9112.

Tribromocycloheptanone **29**. TLC (70% EtOAc in hexanes: UV and Hanessians' stain) R_f = 0.78; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.90 (s, 3H), 2.25 (br s, 1H), 2.30 (d, *J* = 15.5 Hz, 1H), 2.62-2.70 (m, 2H), 2.83 (dddd, *J* = 15.4, 5.1, 3.9, 1.08 Hz, 1H), 3.20 (ddd, *J* = 13.2, 12.4, 3.8 Hz, 1H), 4.60 (dd, *J* = 12.4, 8.3 Hz, 1H), 4.72 (ddd, *J* = 13.0, 5.3, 1.1 Hz, 1H), 4.93 (app t, *J* = 1.0 Hz, 1H), 5.24 (dd, *J* = 8.3, 6.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.6, 35.8, 43.8, 44.9, 49.6, 51.9, 52.0, 69.3, 80.4, 85.9, 175.7, 195.1;FT-IR (thin film): 3400 (br w), 2981 (w), 1761 (s), 1705 (m), 1215 (m-s), 733 (w-m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}O_4Br_3Na^+$ ([M + Na]$^+$): 480.8256, 482.8236, 484.8215, 486.8195; found 480.8259, 482.8236, 484.8213, 486.8189.

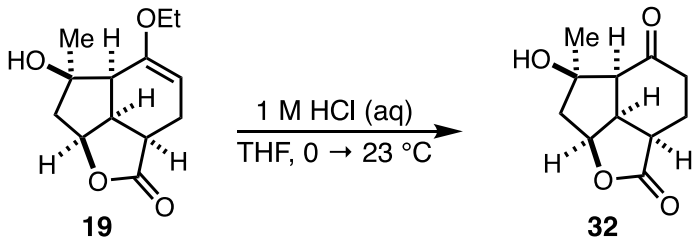


7-bromo-1a-methyl-1a,2,2a,2a1,4a,5-hexahydrooxireno[2',3':3,3a]azuleno[1,8-bc]furan-4,8-dione (30): A vial containing tribromo cycloheptanone **29** (35.1 mg, 0.0762 mmol, 1.0 equiv) was equipped with a septum and was evacuated and refilled N_2 (3x) using an 18G needle. The vial was then maintained under a positive pressure of N_2. The solid was then dissolved in CH_2Cl_2 (0.4 mL) and the clear colorless solution was cooled to 0 °C. DBU (23 µL, 0.15 mmol, 2.0 equiv) was then added dropwise and the solution immediately turned to a dark brown color. The reaction was stirred for 15 min and was quenched at 0 °C

by the addition of satd. aq. NH_4Cl (~5 mL). The biphasic mixture was transferred to a separatory funnel, rinsing with CH_2Cl_2 (~3 mL) for quantitative transfer, and the layers were separated. The aq. layer was then extracted with CH_2Cl_2 (3x ~5 mL) and the combined organic layers were dried over Mg_2SO_4, filtered and the solvent was removed *in vacuo* to yield a light brown solid. The crude material was then purified by flash chromatography (1/2 inch column, dry loaded) eluting 0 → 60% EtOAc in hexanes (10% increments, 50 mL each) to yield α-bromo enone **30** as colorless crystalline solid (16.0 mg, 0.0535 mmol, 70% yield); TLC (70% EtOAc in hexanes, UV) R_f = 0.54; A small sample was recrystallized from EtOAc/hexanes (diffusion) to give a cluster of colorless prism-shaped crystals, mp 153-154 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.74 (s, 3H), 2.29 (dd, *J* = 16.2, 7.0 Hz, 1H), 2.52 (d, *J* = 16.2 Hz, 1H), 2.92 (ddd, *J* = 14.6, 10.1, 6.2 Hz, 1H), 3.01 (ddd, *J* = 14.6, 11.7, 5.9 Hz, 1H), 3.20 (ddd, *J* = 11.8, 9.8, 6.3 Hz, 1H), 3.26 (dd, *J* = 9.8, 7.1 Hz, 1H), 4.94 (t, *J* = 7.1 Hz, 1H), 7.54 (dd, *J* = 10.1, 5.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.7, 27.9, 38.7, 39.5, 44.0, 69.5, 75.3, 79.0, 127.6, 146.6, 176.1, 188.6;FT-IR (thin film): 2930 (w), 1763 (s), 1691 (m), 734 (w-m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}O_4BrNa^+$ ([M + Na]$^+$): 320.9733, 322.9712; found 320.9736, 322.9713.

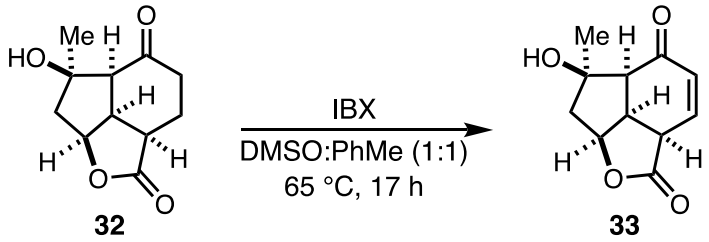


4-methyl-2a,2a1,3,7a-tetrahydroindeno[1,7-*bc*]furan-1,5-dione (31): Enone **15** (50.0 mg, 0.260 mmol, 1.0 equiv) was weighed into an oven dried Pyrex threaded culture tube. The light-yellow solid was then dissolved in DMSO (5.2 mL, 0.3 M based on IBX). IBX (437 mg, 1.56 mmol, 6.0 equiv) was then added, the tube was then sealed (*under an atmosphere of air*) and the solution was heated to 85 °C (*Note: heating a reaction in a sealed container is potentially dangerous and can lead to explosion. A blast shield should be employed in addition to your hood sash for protection*). After stirring at that temperature for 6 h, the reaction was allowed to cool to ambient temperature (23 °C) and the reaction mixture was transferred to a separatory funnel, rinsing with Et_2O (~5 mL). The solution was then diluted with Et_2O (50 mL) and was washed with 5% $NaHCO_3$ solution (50 mL). The biphasic mixture was shaken vigorously before separating the layers. The aq. layer was then extracted with Et_2O (5x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to yield a clear colorless oil. The oil was purified by MPLC (4g silica gold, dry loaded) eluting 0 → 90% EtOAc in hexanes to yield dienone **31** as a clear colorless oil (26.7 mg, 0.140 mmol, 54% yield); TLC (70% EtOAc in hexanes) R_f = 0.25; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.74 (d, *J* = 19.3 Hz, 1H), 2.95 (ddt, *J* = 19.1, 4.7, 1.7 Hz, 1H), 3.60 (ddd, *J* = 8.4, 5.9, 1.7 Hz, 1H), 3.99-4.04 (m, 1H), 5.06 (app t, *J* = 4.8 Hz, 1H), 6.17 (dd, *J* = 10.0, 1.72 Hz, 1H) 6.84 (dd, *J* = 10.0, 5.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.7, 41.8, 45.5, 50.6, 81.0, 127.9, 133.7, 139.5, 150.0, 172.5, 186.0;FT-IR (thin film): 2913 (w), 1767 (s), 1665 (s), 1635 (m) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{10}O_3Na^+$ ([M + Na]$^+$): 213.0522; found 213.0523.

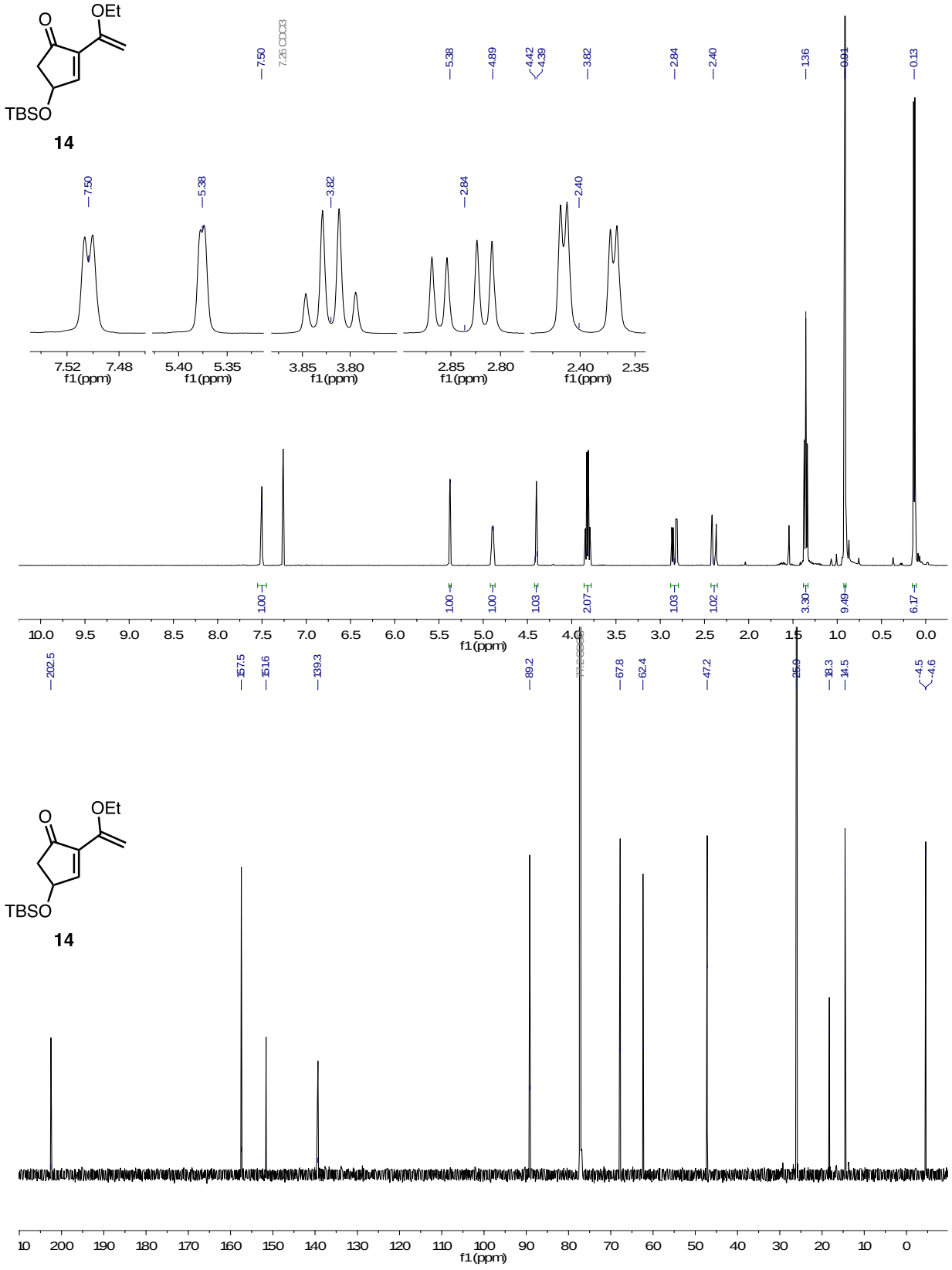


6-hydroxy-6-methyloctahydroindeno[1,7-*bc*]furan-2,5-dione (32): Ethyl enol ether **19** (100.0 mg, 0.4197 mmol, 1.0 equiv) was weighed into a 2 dram vial. The vial was equipped with a septum and was evacuated and refilled with N_2 (3x) using an 18G needle. The vial was then maintained under a positive pressure of N_2. The colorless solid was then dissolved in THF (3.0 mL) and was cooled to 0 °C (ice water

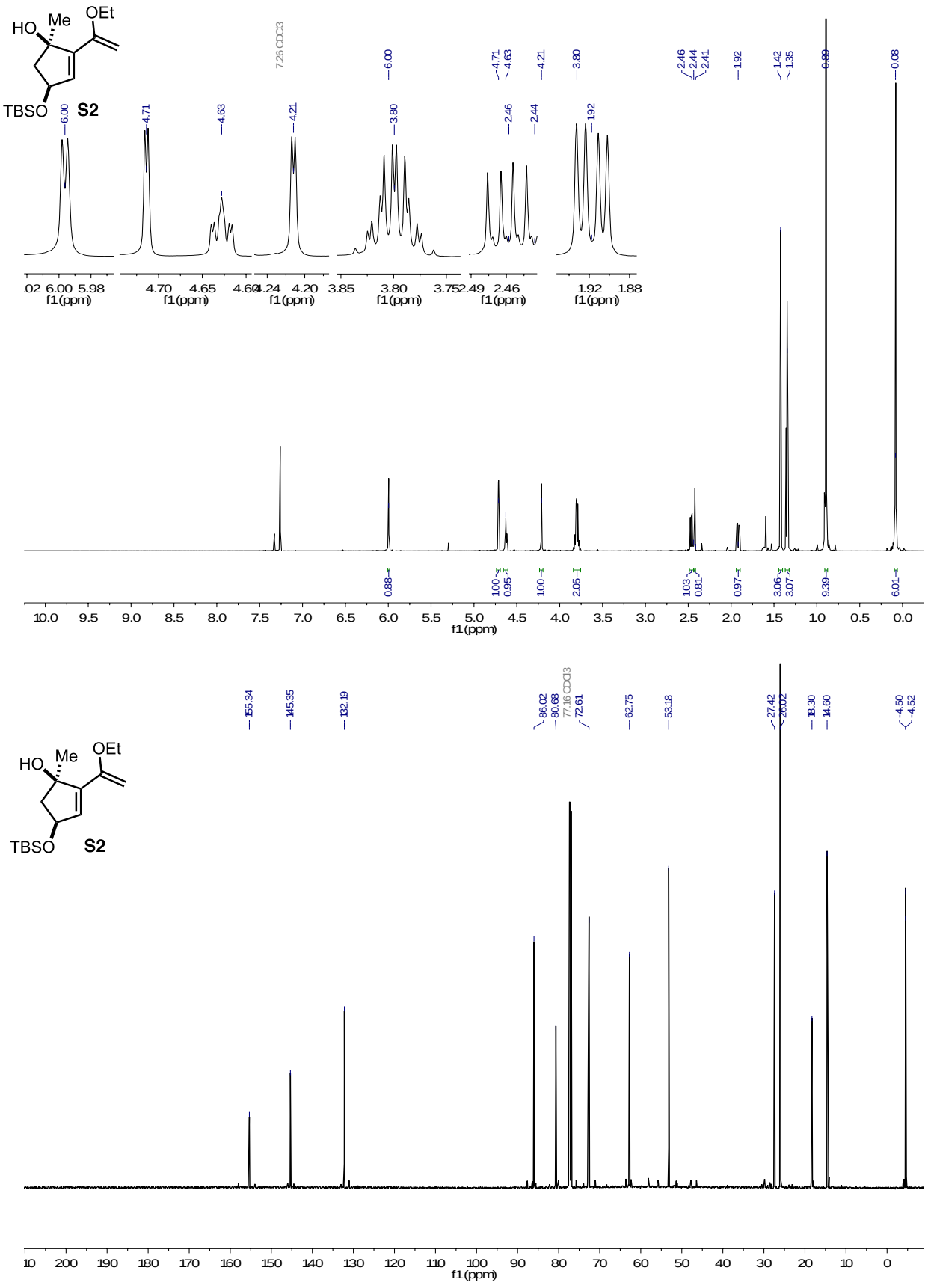
bath). Aq. HCl (1 M, 0.8 mL, 0.8 mmol, 1.9 equiv) was then added over *ca.* 30 s and the resulting clear colorless solution was stirred at 0 °C for 10 min. The ice bath was removed, and the reaction was allowed to warm to ambient temperature (23 °C) until full consumption of starting enol ether **19**, as determined by TLC (1.5 h). The reaction was then neutralized by the slow addition of satd. aq. $NaHCO_3$ until a pH of ~7 was achieved. The reaction was then transferred to a separatory funnel using CH_2Cl_2 (~3 mL) to ensure quantitative transfer. The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3x ~4 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to yield a colorless solid. The solid was purified by flash chromatography (1/2 inch column, ~6 inch height of silica, dry loaded) eluting 0 → 100% EtOAc in hexanes (10% increments, 50 mL each) to yield ketone **32** as a colorless solid (71.3 mg, 0.339 mmol, 81% yield); Spectral data matched that previously reported by Deng and co-workers[9] and is included here since NMR data was taken at higher field strength. TLC (70% EtOAc in hexanes, PAA stain) R_f = 0.24; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.46 (s, 3H), 1.86-1.94 (m, 2H), 2.08 (dddd, *J* = 14.1, 13.1, 6.2, 4.4 Hz, 1H), 2.28-2.37 (m, 2H), 2.45-2.61 (m, 3H), 3.02 (ddd, *J* = 10.0, 6.1, 3.4 Hz, 1H), 3.40 (td, *J* = 10.6, 6.4 Hz, 1H), 5.07 (dd, *J* = 6.4, 4.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.7, 27.1, 38.1, 38.8, 43.7, 47.3, 58.3, 82.4, 83.4, 177.8, 209.8;FT-IR (thin film): 3516 (w-m), 2919 (w), 1765 (s), 1692 (s) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}O_4Na^+$ ([M + Na]$^+$): 233.0784; found 233.0785.



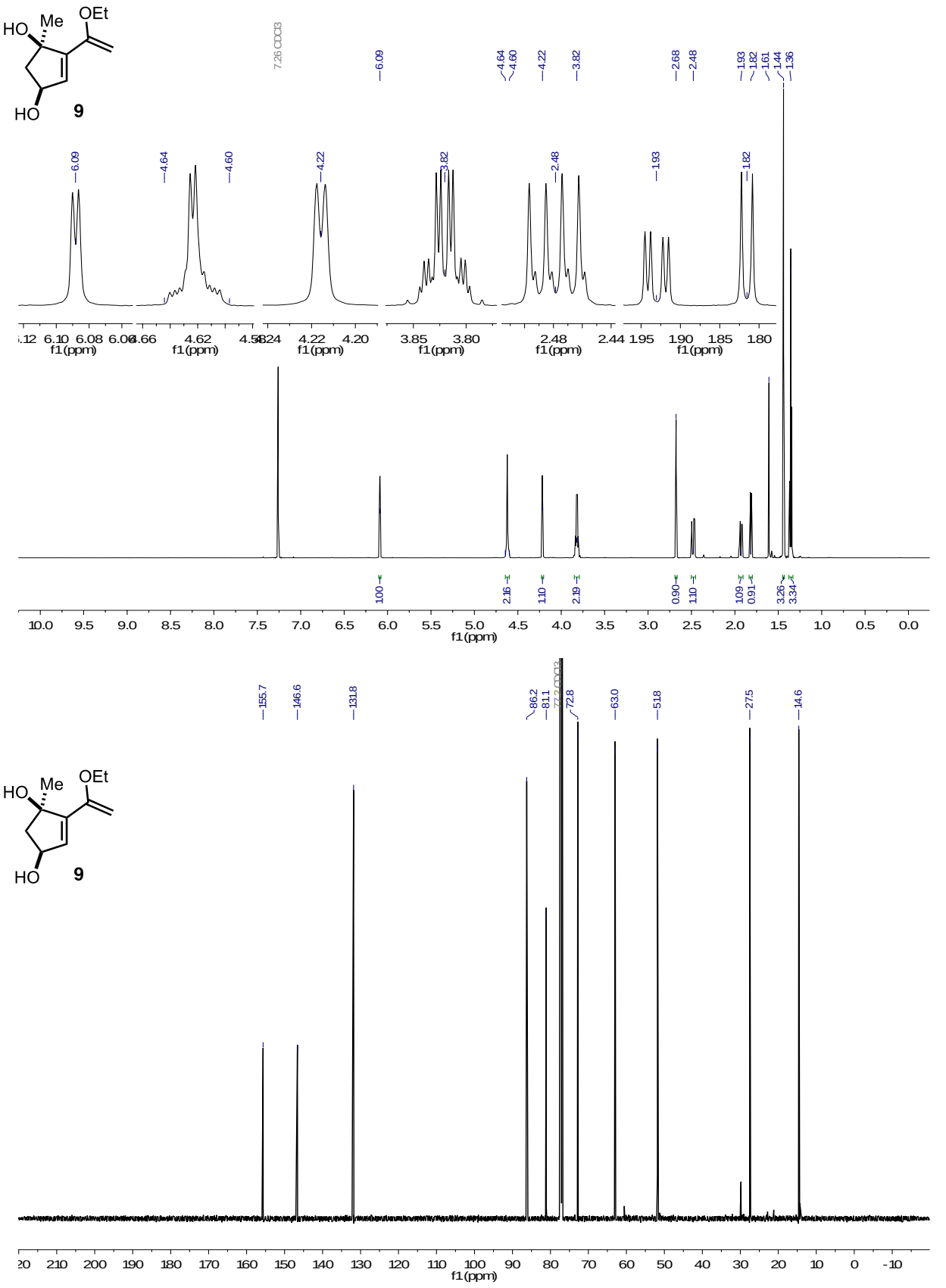
6-hydroxy-6-methyl-2a,2a1,5a,6,7,7a-hexahydroindeno[1,7-*bc*]furan-2,5-dione (33): Ketone **32** (10.5 mg, 0.0499 mmol, 1.0 equiv) was weighed into a 1.5 dram vial. IBX (71.4 mg, 0.255 mmol, 5.1 equiv) was then added. DMSO (0.4 mL) and PhMe (0.4 mL) were then added, creating a white suspension. The vial was capped under an air atmosphere and was sealed with Teflon tape. The suspension was then heated to 65 °C and was covered with aluminum foil (IBX is sensitive to light) and was stirred. *Note: upon heating all solids dissolved, resulting in a clear colorless solution*. After stirring at that temperature for 17 h, a colorless solid had precipitated. The mixture was cooled to 23 °C and 5% aq. $NaHCO_3$ (~4 mL) was added. Using a pipette, the organic layer was removed. The aq. layer was then extracted with EtOAc (3x ~3 mL) using a pipette to remove the organic layer (in vial extraction). The combined organic layers were then dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to yield a colorless solid. The solid was purified by flash chromatography (Monstr-Pette (Kimble p1005, 10 mm O.D.) pipette column, wet loaded in CH_2Cl_2) eluting 0 → 40% EtOAc in hexanes (5% increments, 2 mL each), then 45 → 100% EtOAc in hexanes (5% increments, 4 mL each) to yield an inseparable mixture of starting ketone **32** and enone **33** as a colorless solid (7.9 mg, NMR ratio 1.0:1.6, **32**:**33**, NMR yield of **33** 48%, 79% brsm). To obtain a sample of pure enone **33** for biological testing, the mixture was further purified by semi-prep HPLC using a gemini 5 μM C18 110 Å 250 x 21.2 mm column (isocratic: 97.5% H_2O, 2.5% MeCN). Enone **33** eluted at 29.9 min and ketone **32** at 31.1 min. As there was significant shouldering, only fractions at the very beginning of the first peak were combined to give pure enone **33** for biological testing and characterization: TLC (EtOAc, UV and PAA stain) R_f = 0.49; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (s, 1H, likely -OH based on absence of cross peak in HSQC (^{1}H-^{13}C)), 1.48 (s, 3H), 1.93 (dd, *J* = 15.1, 5.7 Hz, 1H), 2.31 (d, *J* = 15.0 Hz, 1H), 2.57 (d, *J* = 10.0 Hz, 1H), 3.61 (ddd, *J* = 11.3, 5.0, 2.1 Hz, 1H), 3.65 (ddd, *J* = 10.9, 9.5, 6.9 Hz, 1H), 5.15 (dd, *J* = 7.0, 5.6 Hz, 1H) 6.22 (dd, *J* = 10.3, 2.1 Hz, 1H), 7.00 (dd, *J* = 10.3, 4.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.2, 39.9, 41.2, 47.4, 55.8, 82.8, 82.9, 131.0, 142.5, 174.1, 196.0;FT-IR (thin film): 3448 (m), 1751 (s), 1663 (s) cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}O_4Na^+$ ([M + Na]$^+$): 231.0628; found 231.0629.



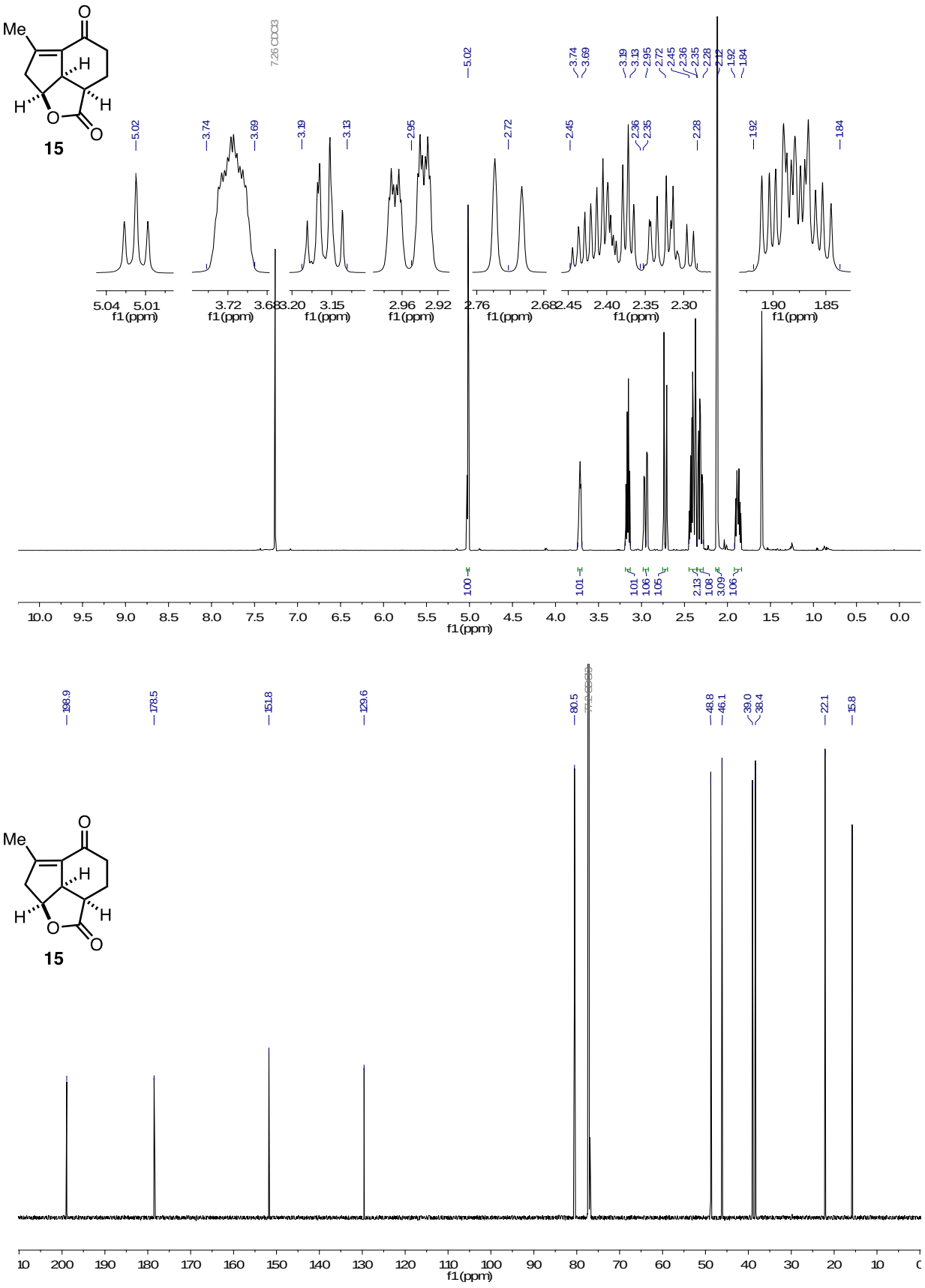
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR of diene **14**.



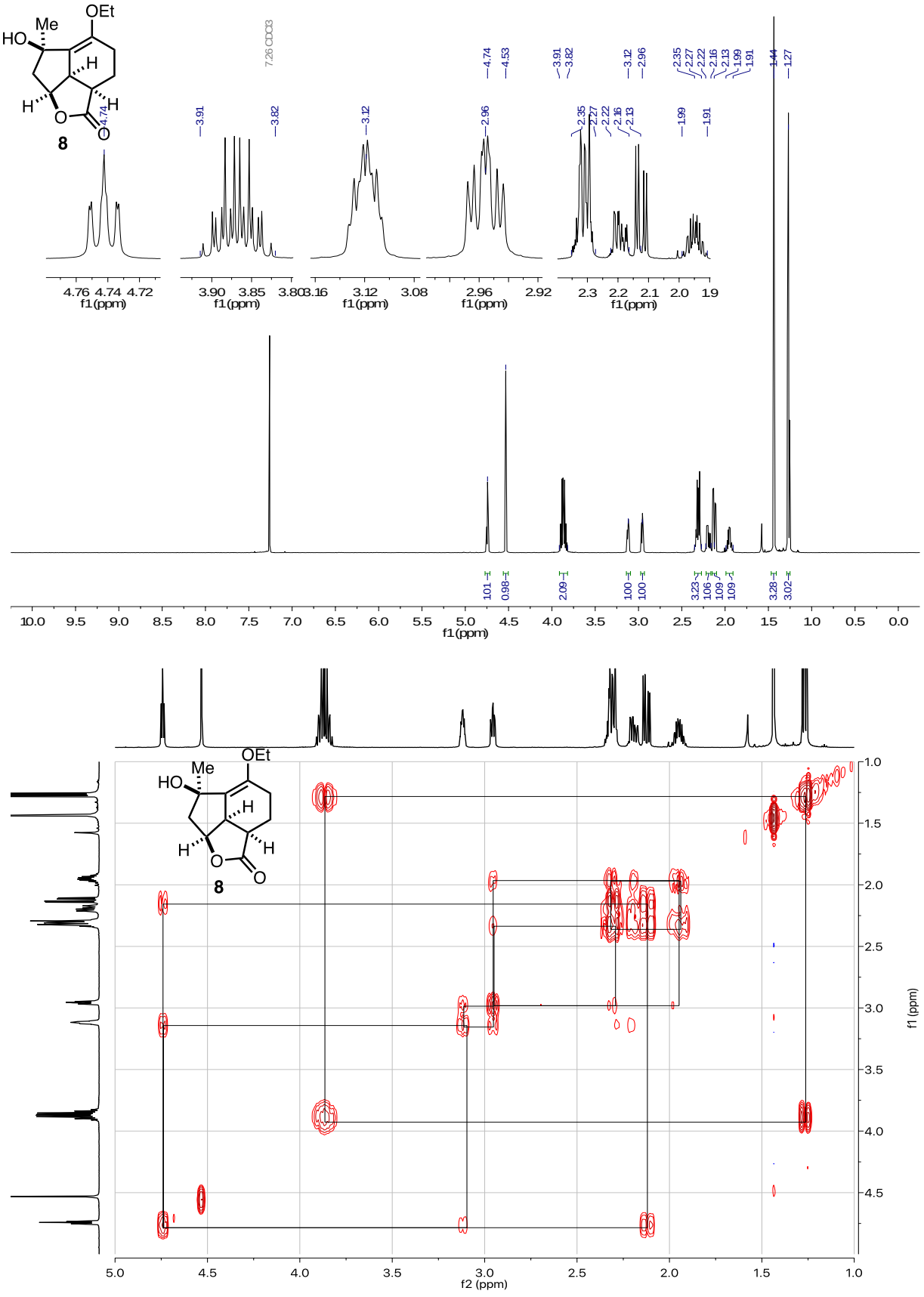
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of tertiary alcohol **S2**.



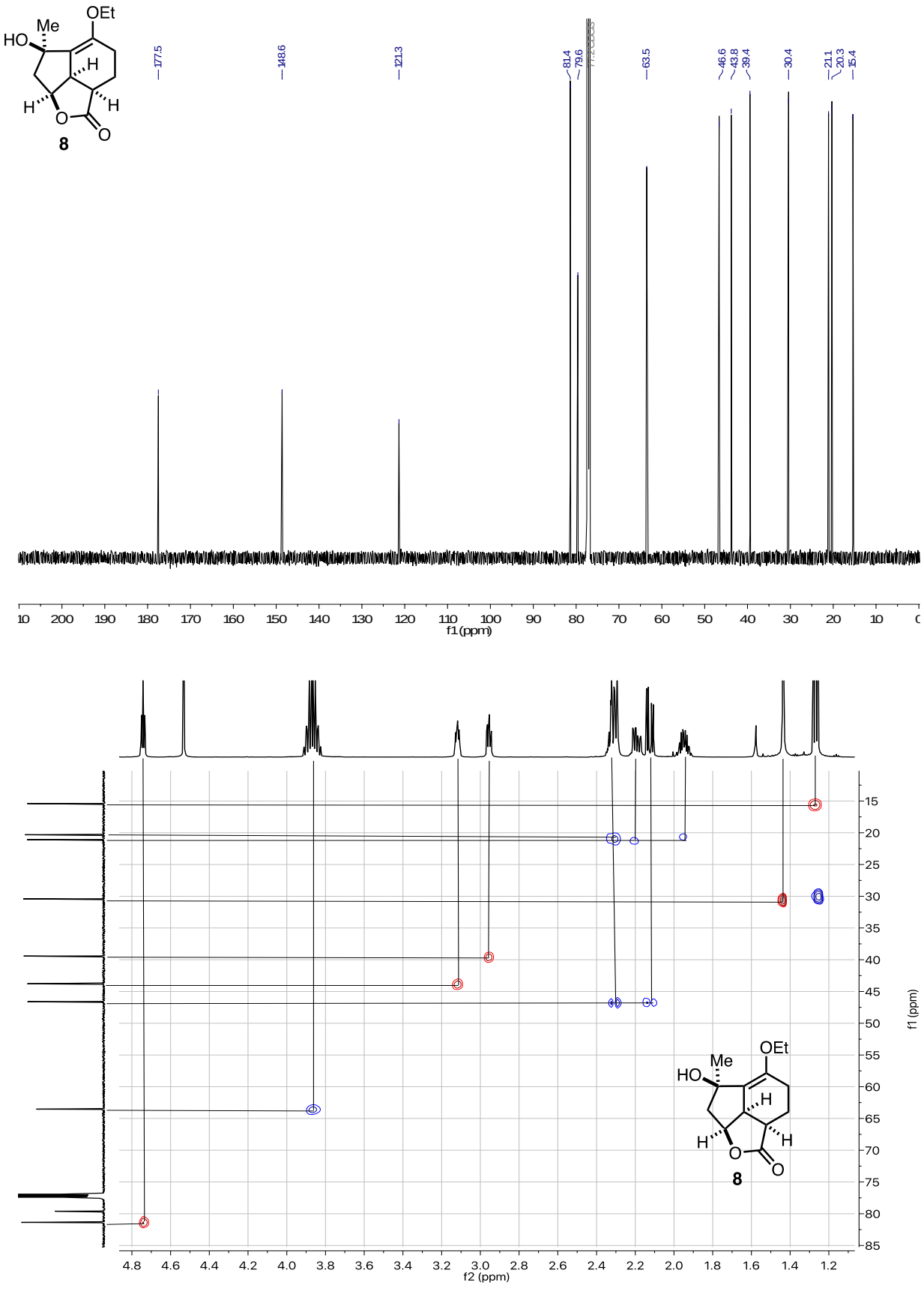
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of diene diol **9**.



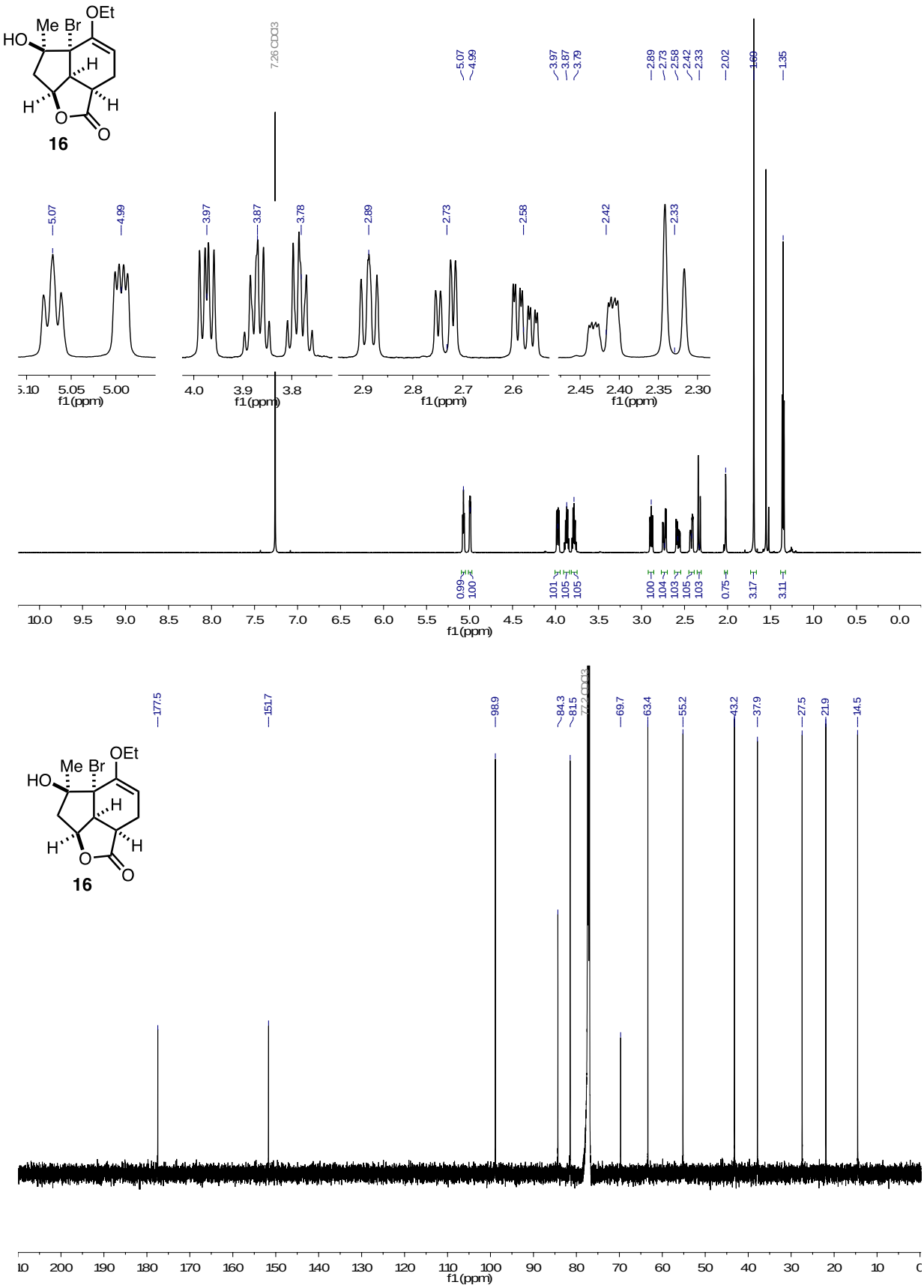
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of tricyclic enone **15**.



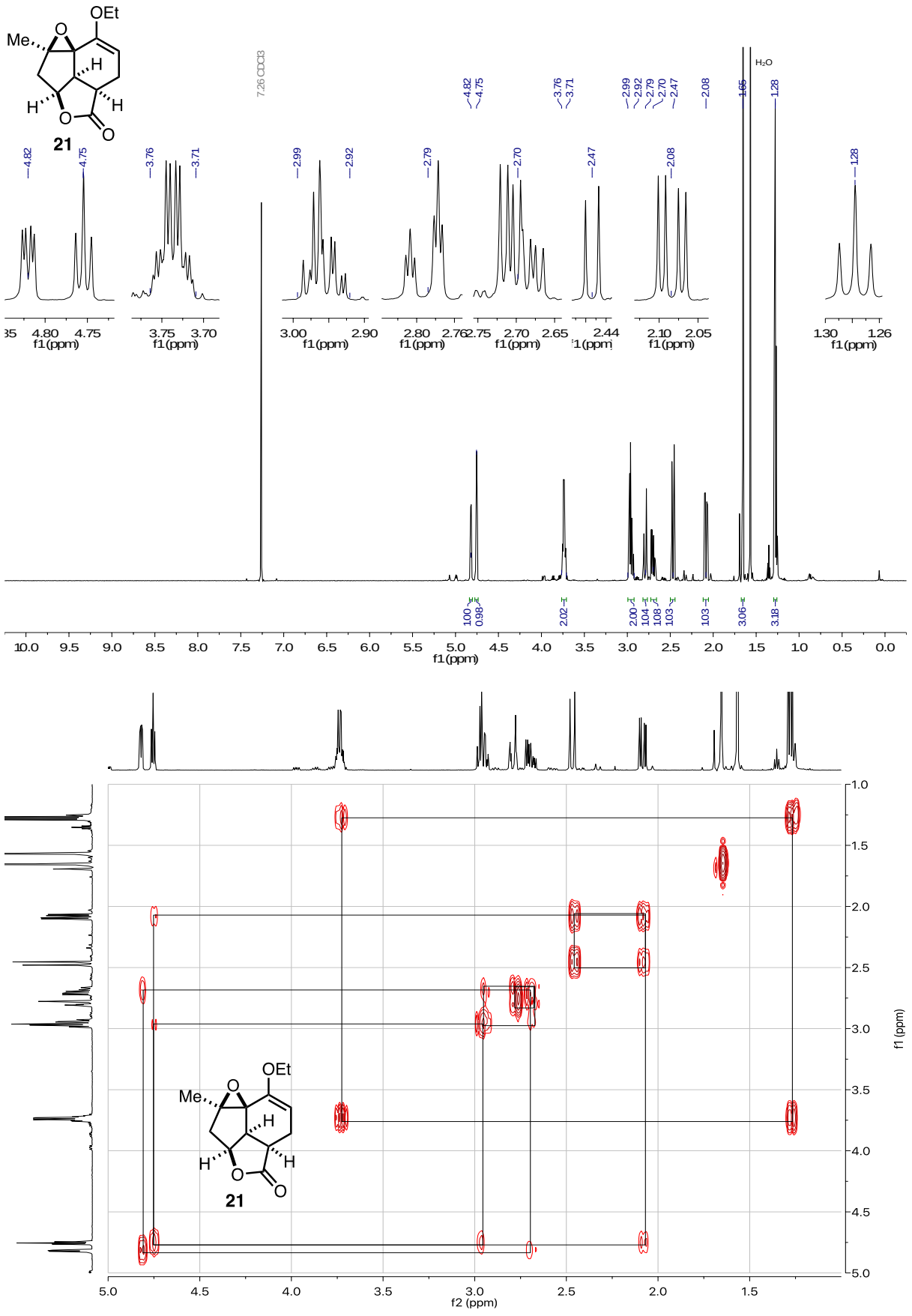
^{1}H (600 MHz) and COSY (400 MHz) NMR of tricyclic lactone **8**.



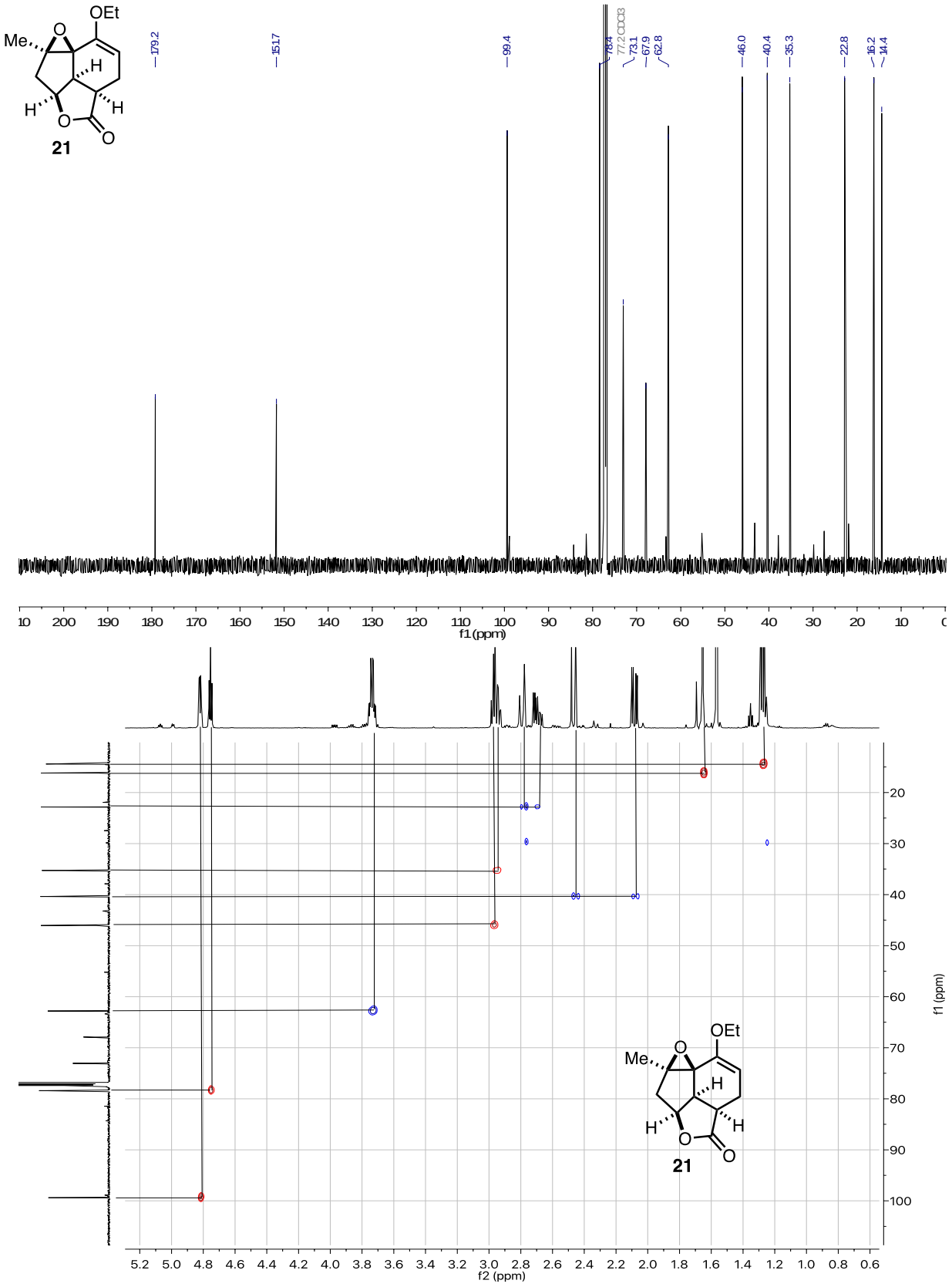
^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) (400 MHz) NMR of tricyclic lactone **8**.



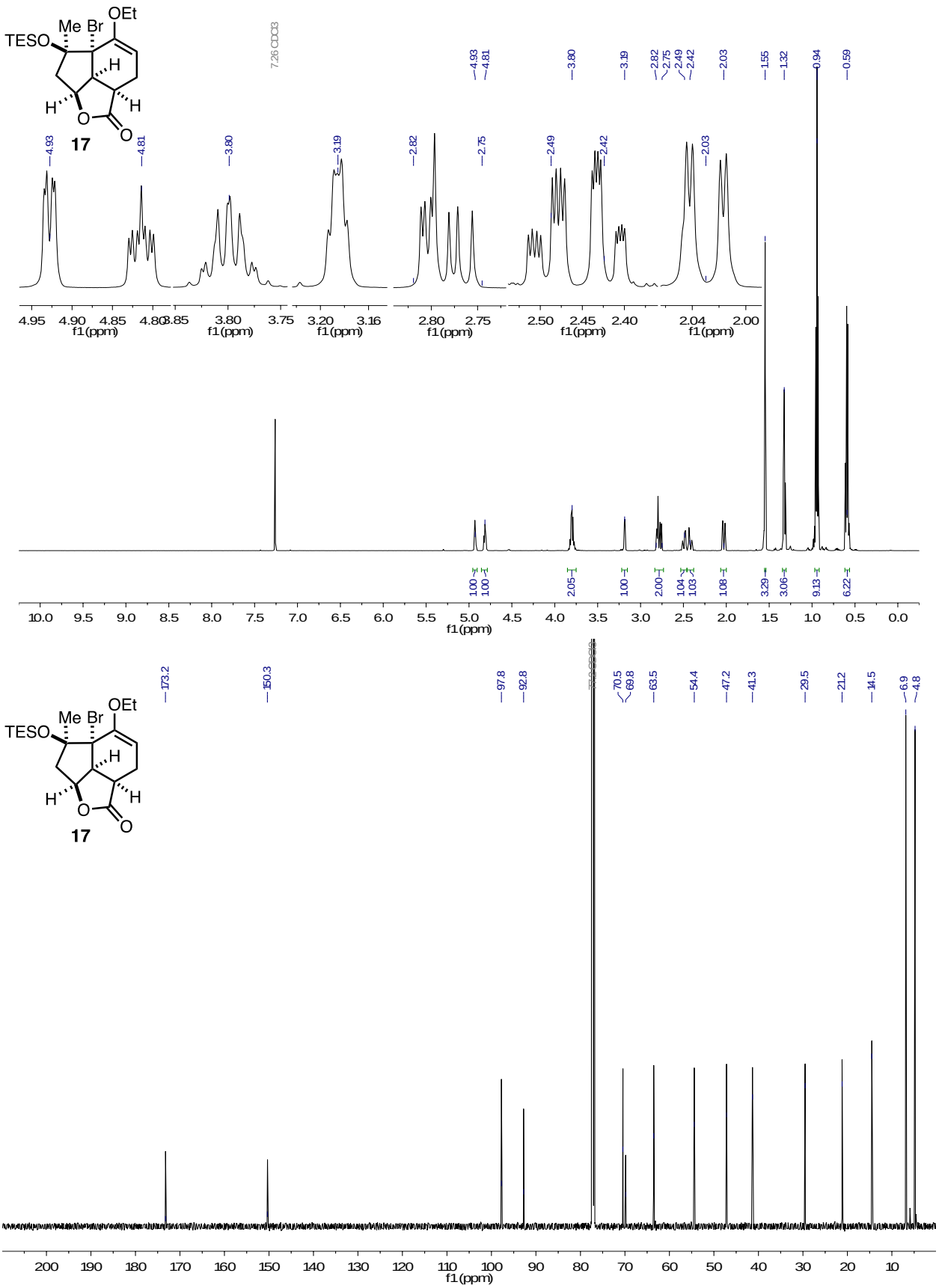
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of allylic bromide **16**.



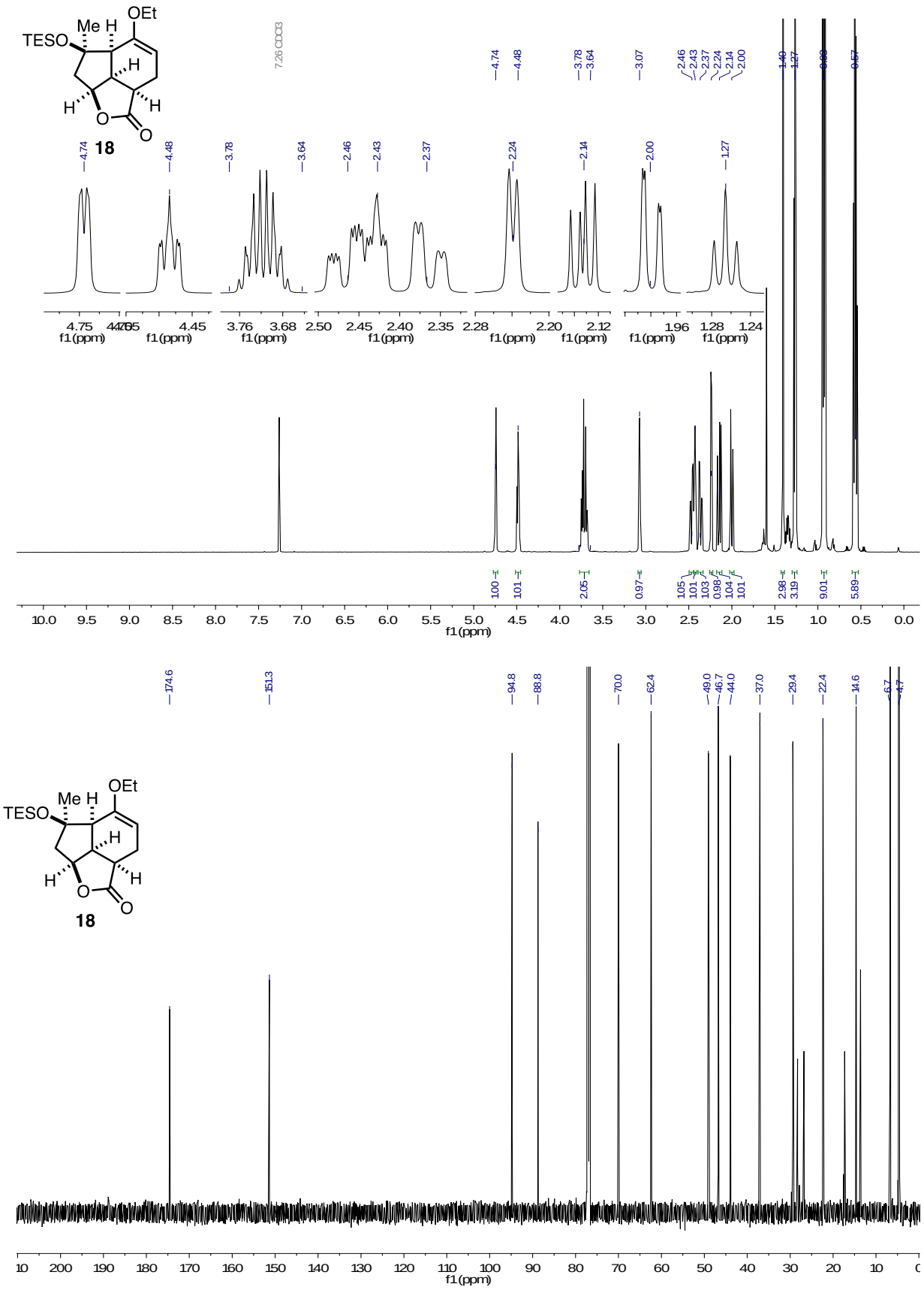
^{1}H (600 MHz) and COSY (600 MHz) NMR of 5,5,6 epoxide **21** with trace allylic bromide **16**.



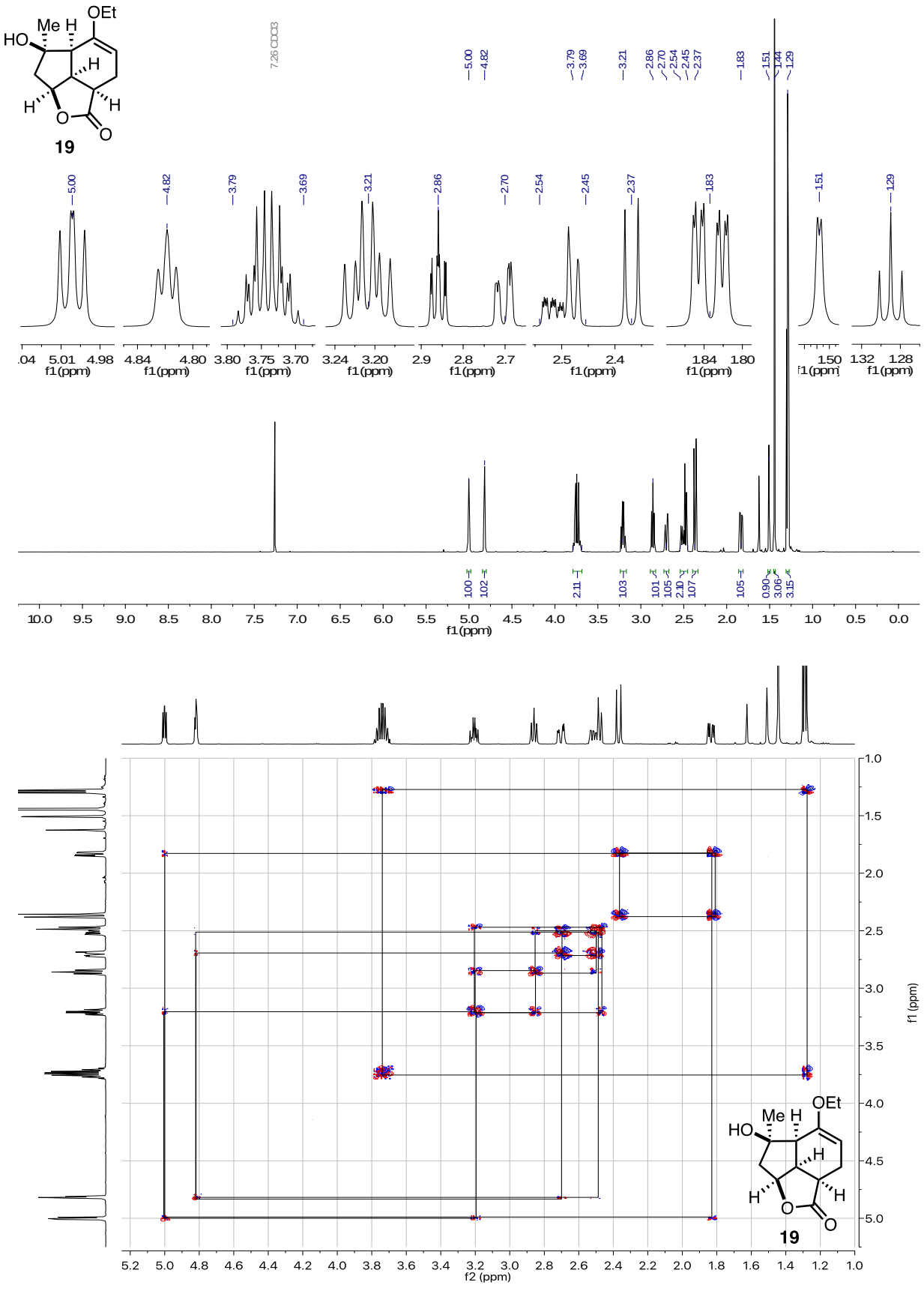
^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) (600 MHz) NMR of epoxide **21** with trace allylic bromide **16**.



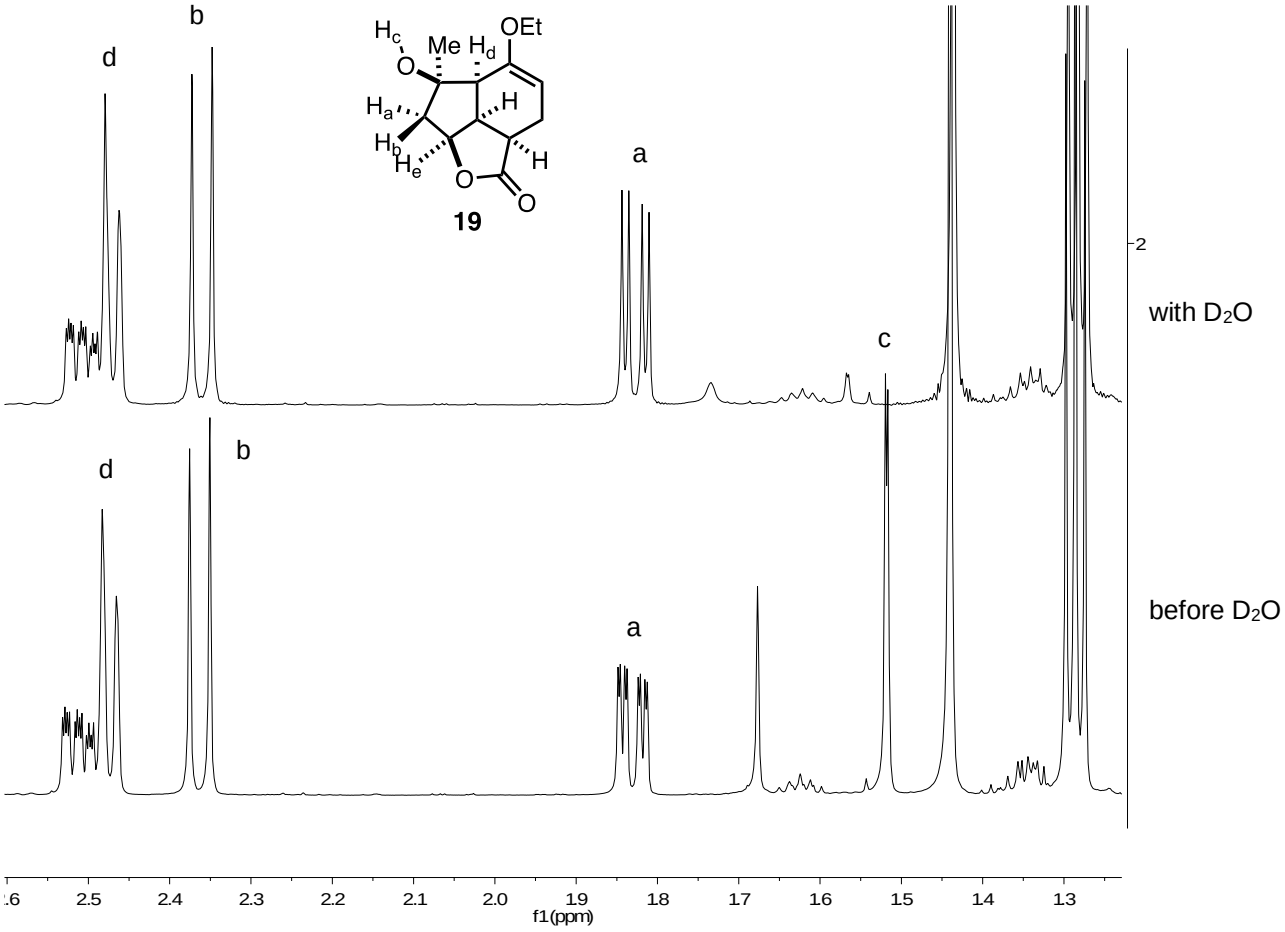
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of TES protected allylic bromide **17**.



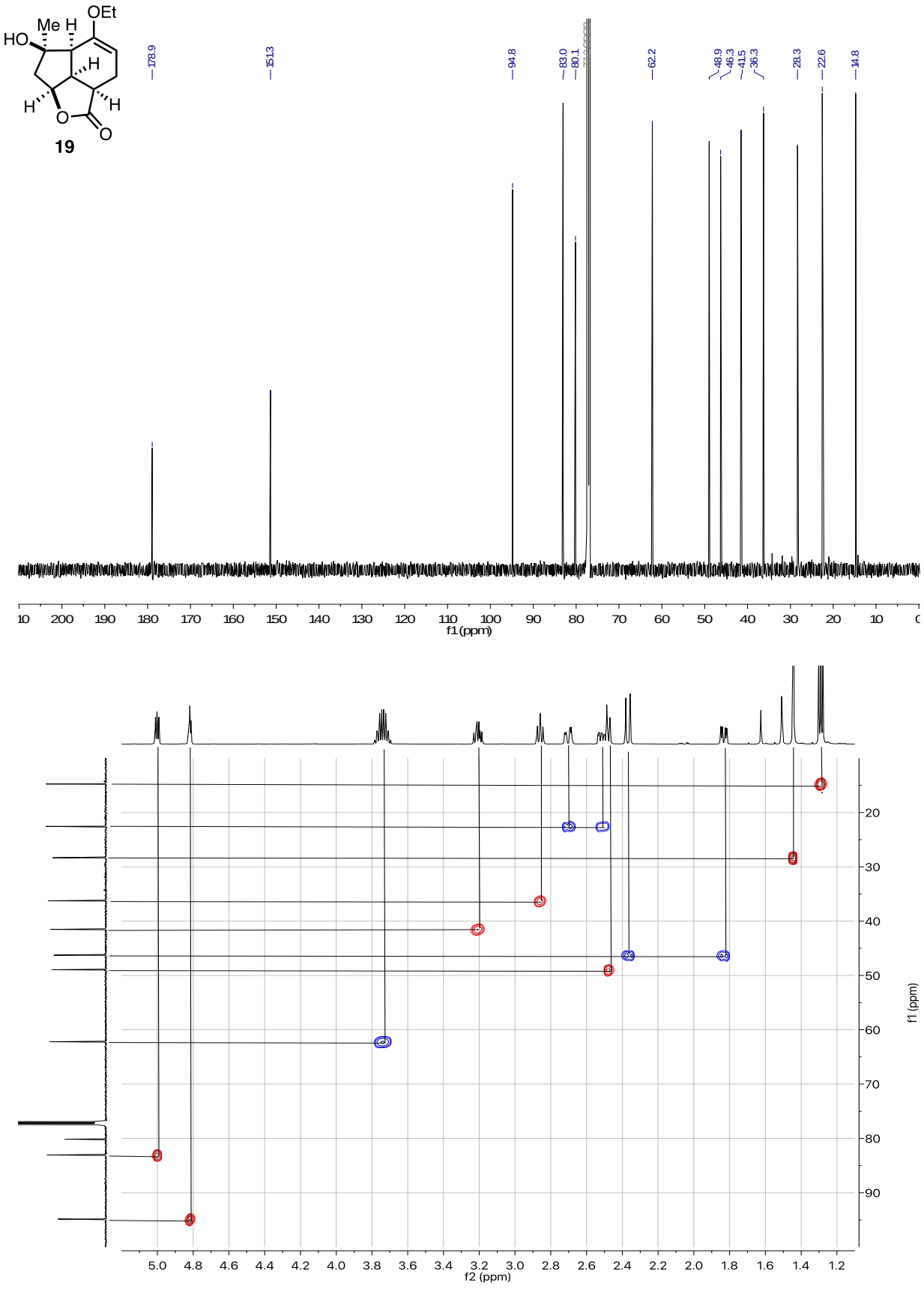
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of TES enol ether **18**, tin byproduct present in spectra.



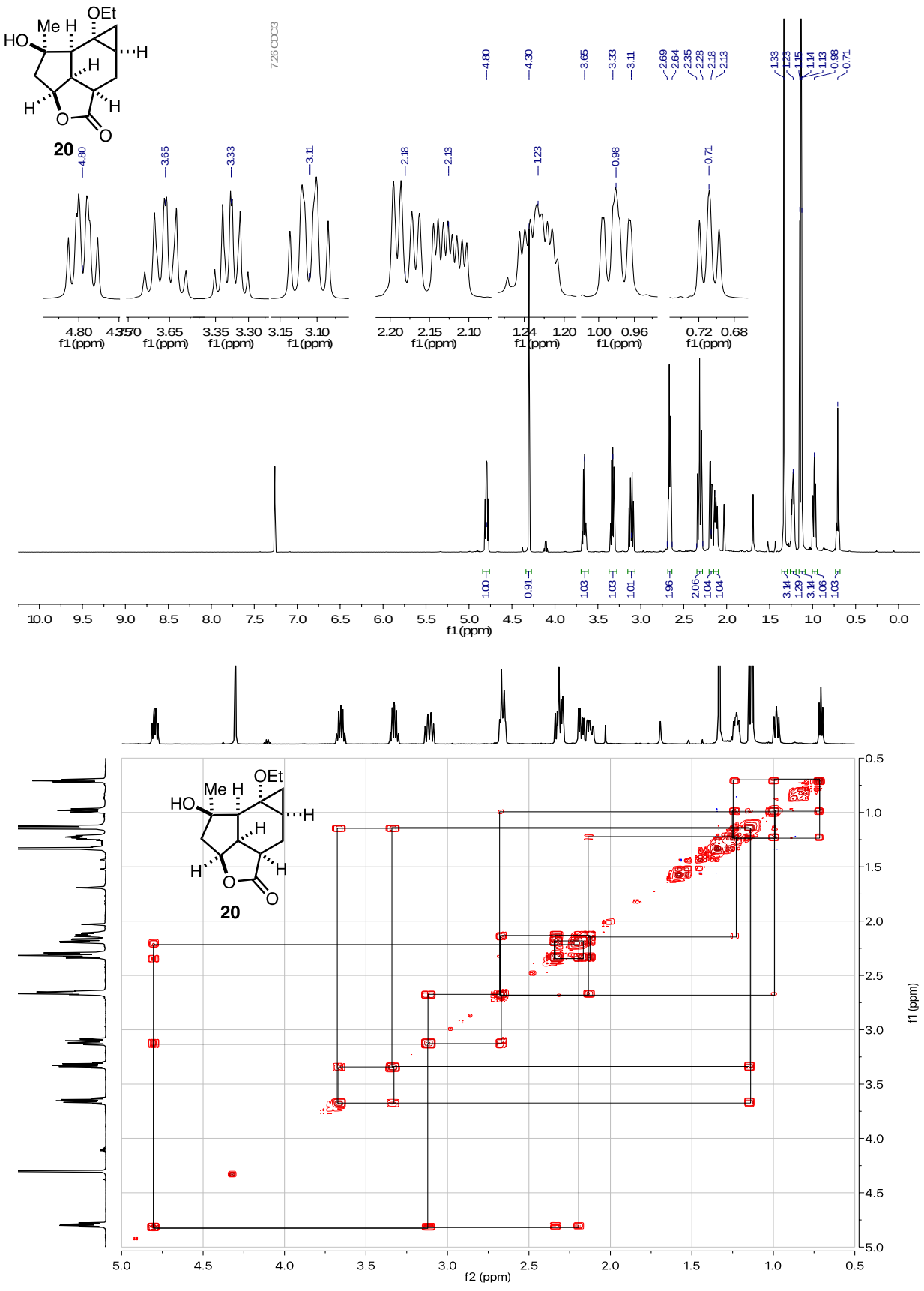
^{1}H (600 MHz) and COSY quantum filtered (600 MHz) NMR of enol ether **19**.



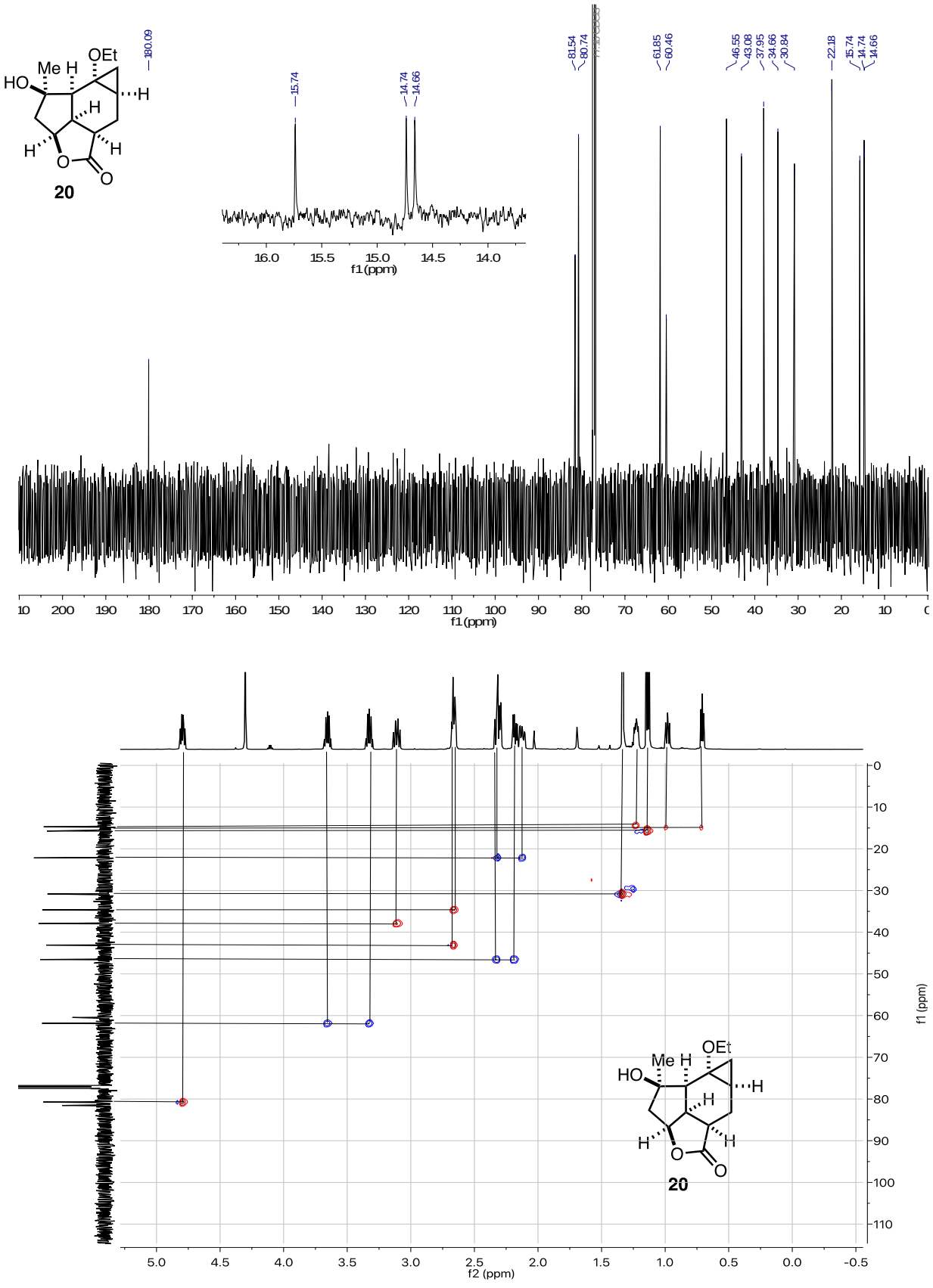
D_2O Exchange: ^1H NMR (600 MHz) before and after adding one drop of D_2O to a NMR sample. Coupling of ROH_c presumably the result of W-coupling to H_a. Diastereotopic protons H_a and H_b were assigned based on the observed W-coupling, bond angles and the Karplus curve and predicted coupling constants with proton H_e.



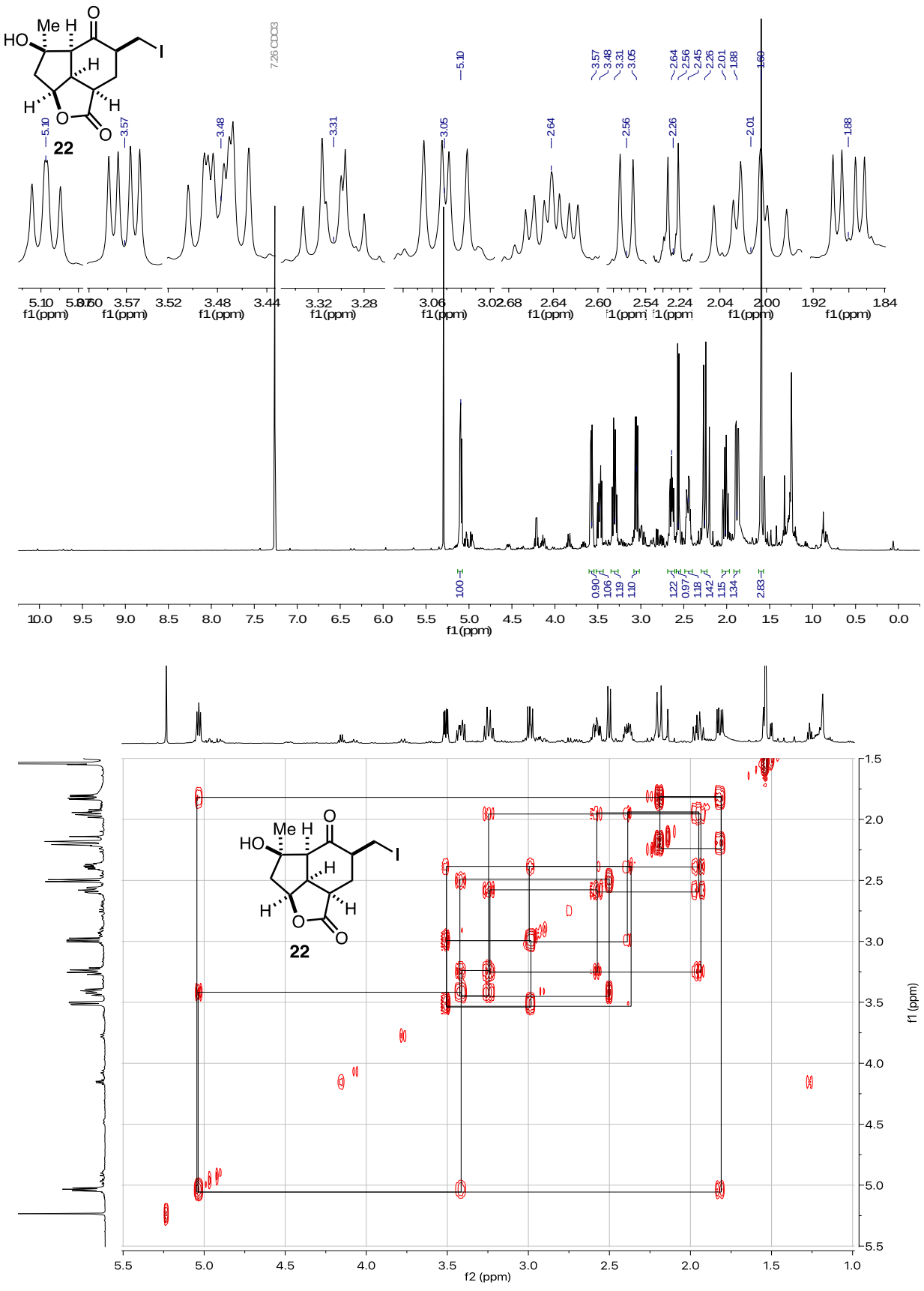
^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) (600 MHz) NMR of enol ether **19**.



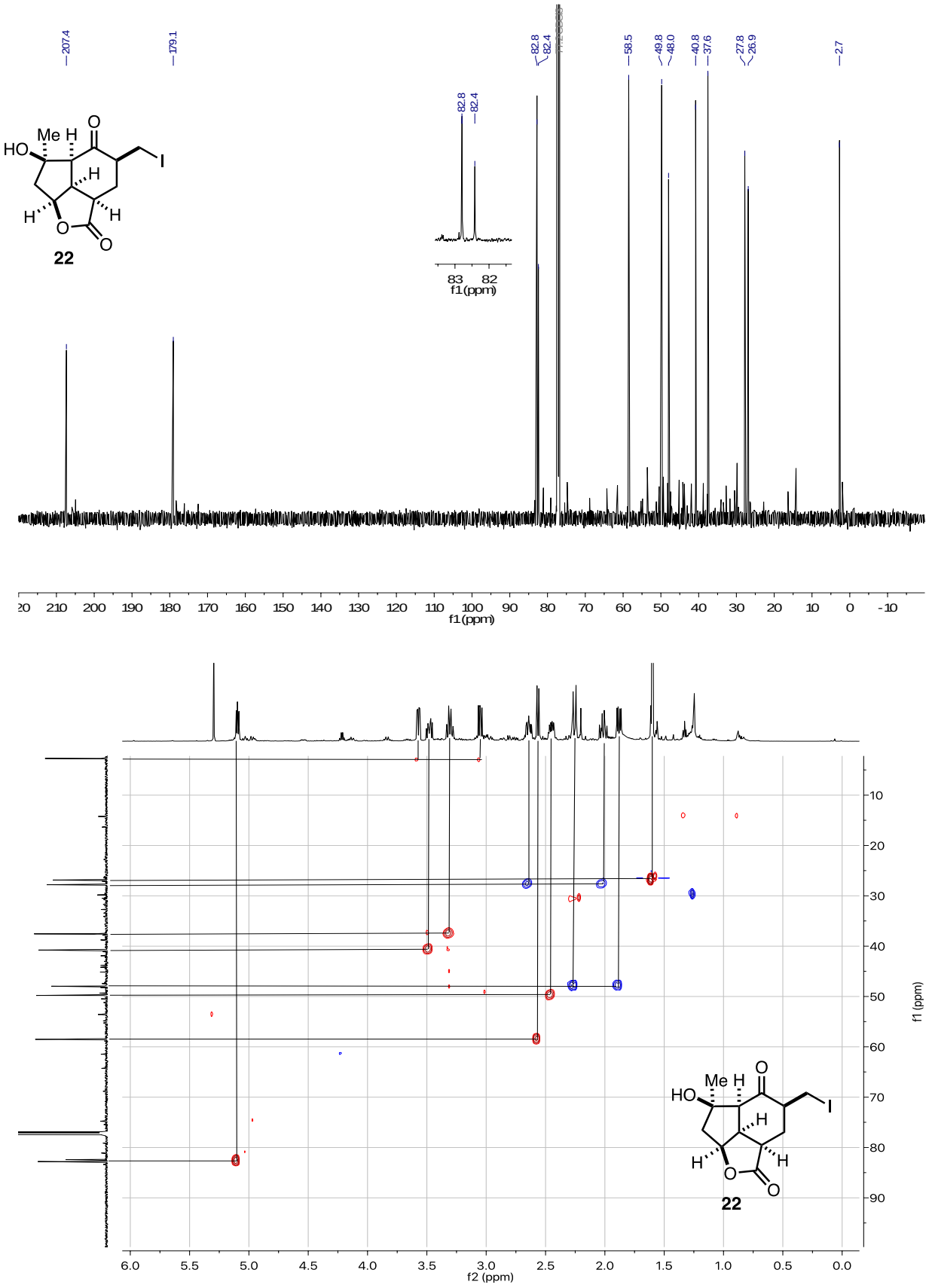
^{1}H (600 MHz) and COSY (600 MHz) NMR of cyclopropane **20**.



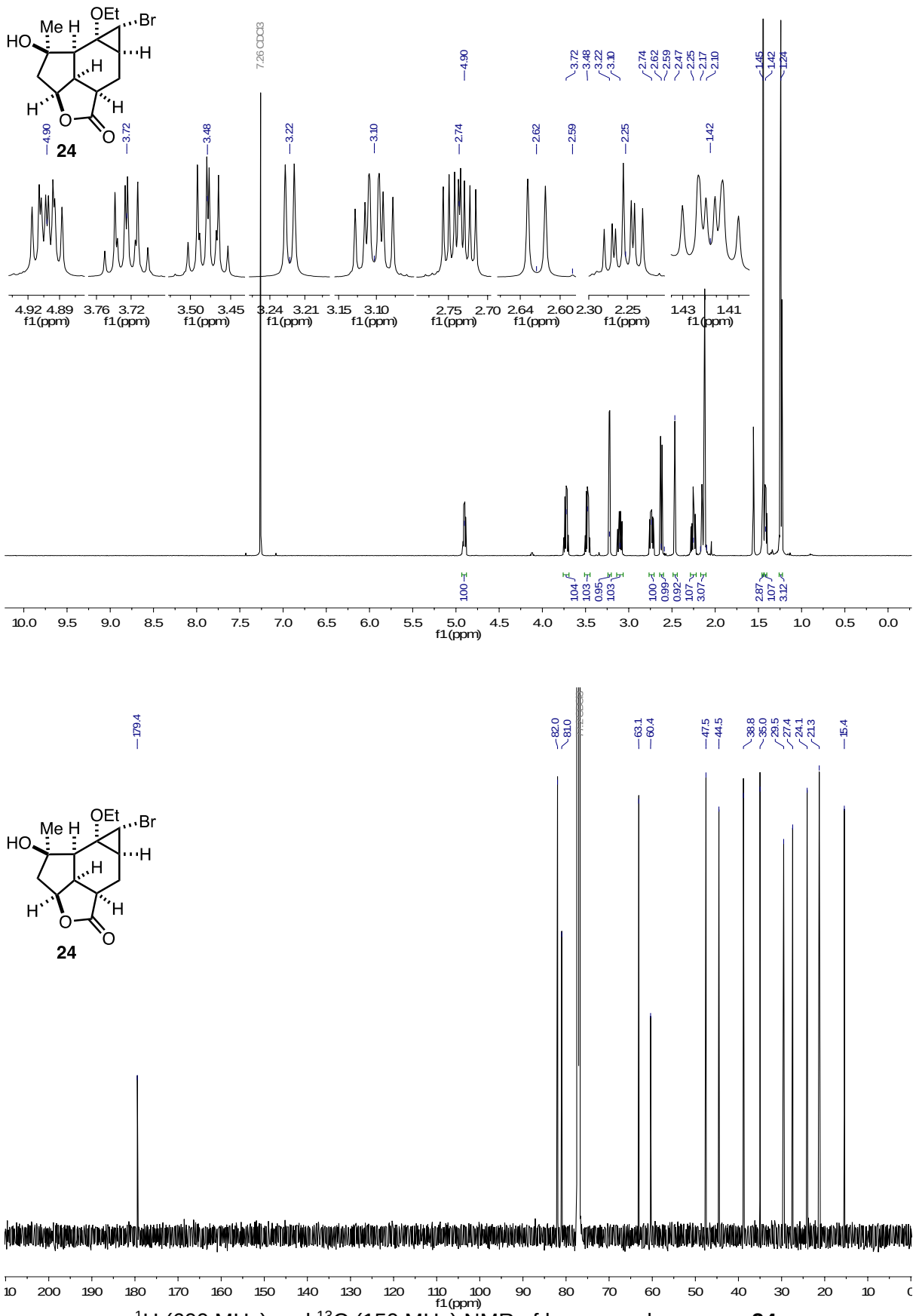
^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) (600 MHz) NMR of cyclopropane **20**



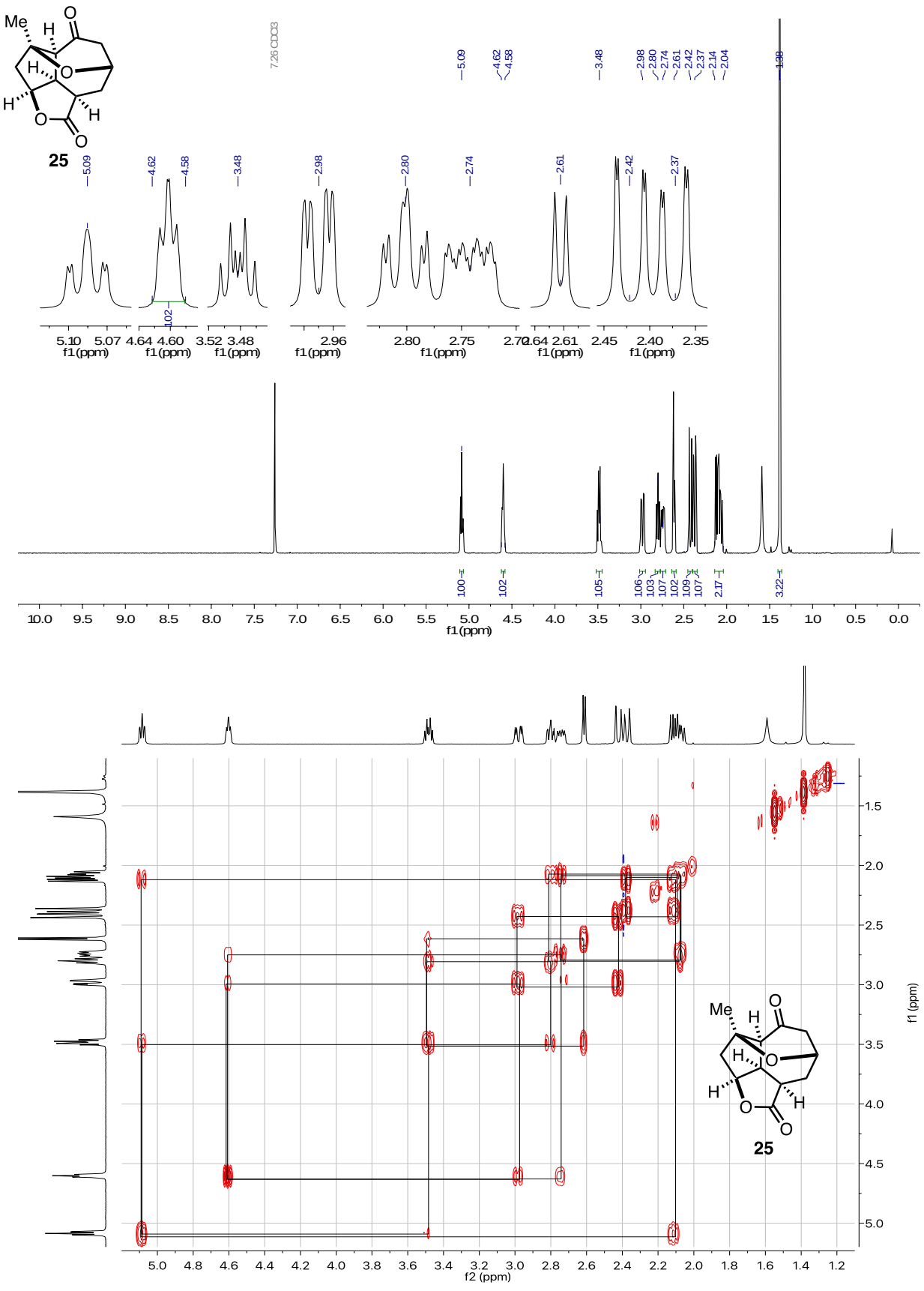
^{1}H (600 MHz) and COSY NMR of crude primary iodide **22**.



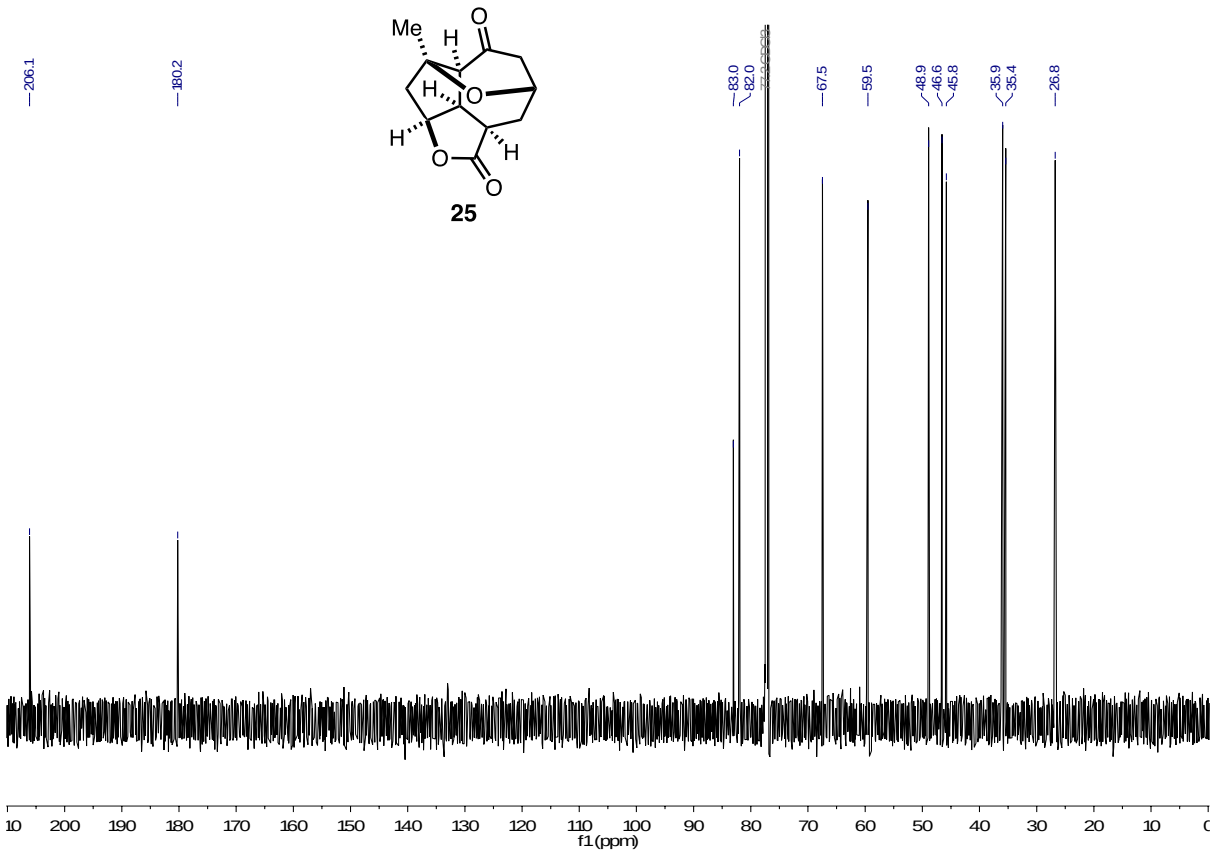
^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) NMR of crude primary iodide **22**.

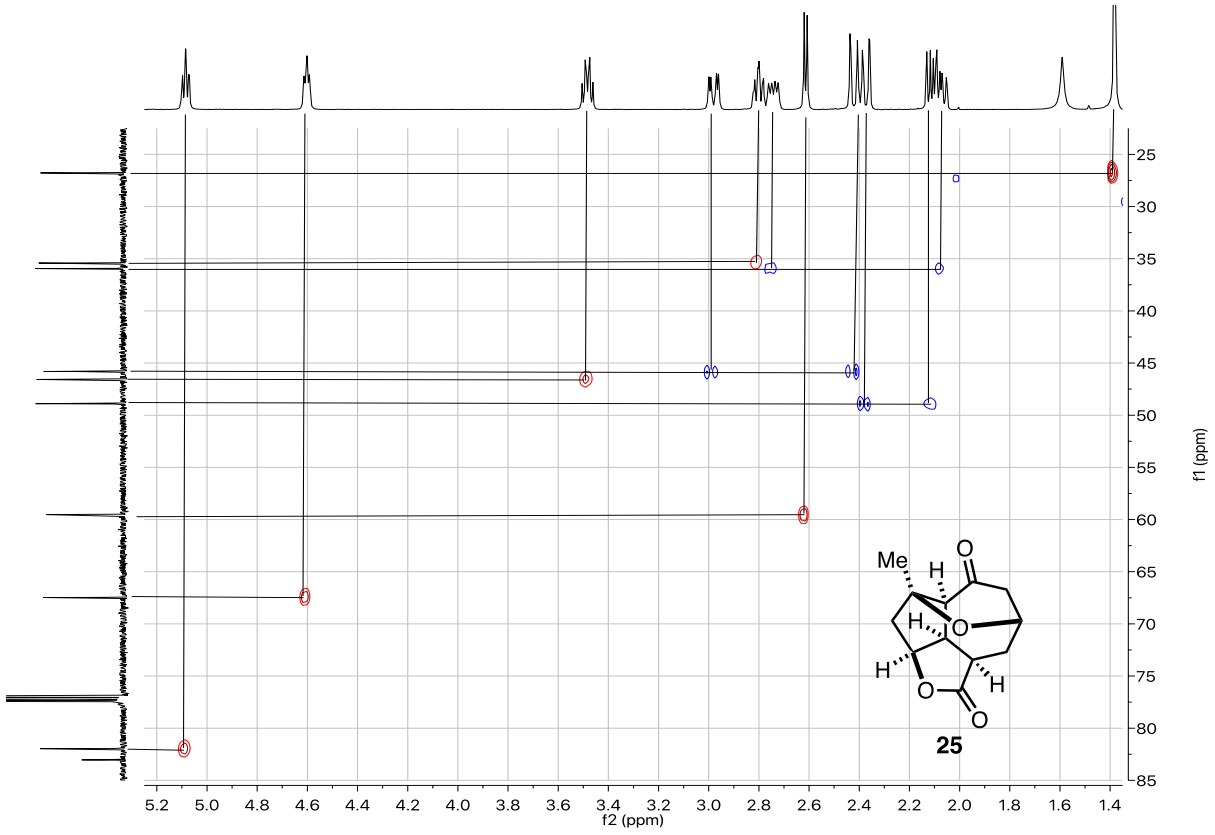


^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of bromo cyclopropane **24**.

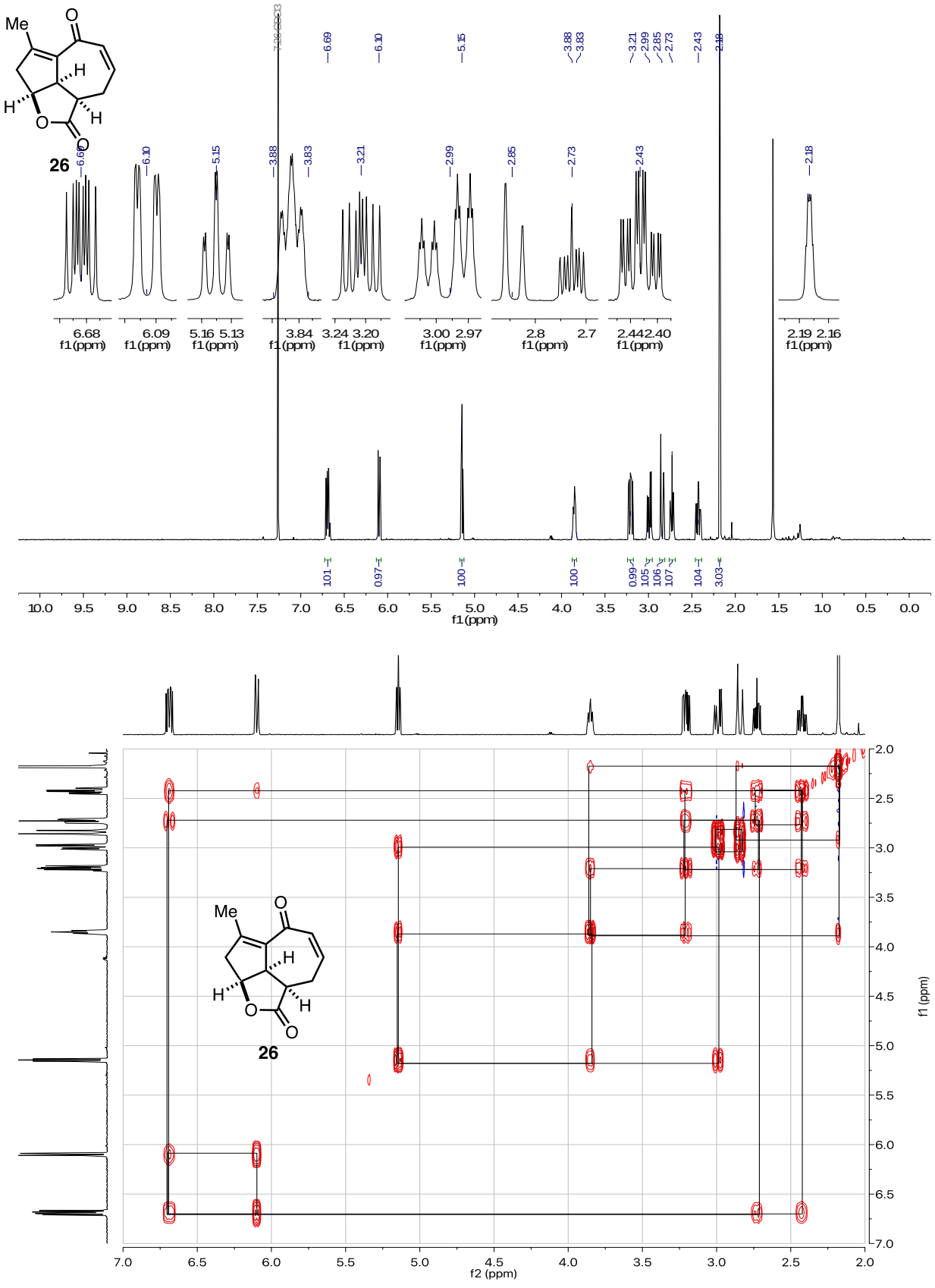


^{1}H (600 MHz) and COSY (600 MHz) NMR of saturated pyranone **25**.

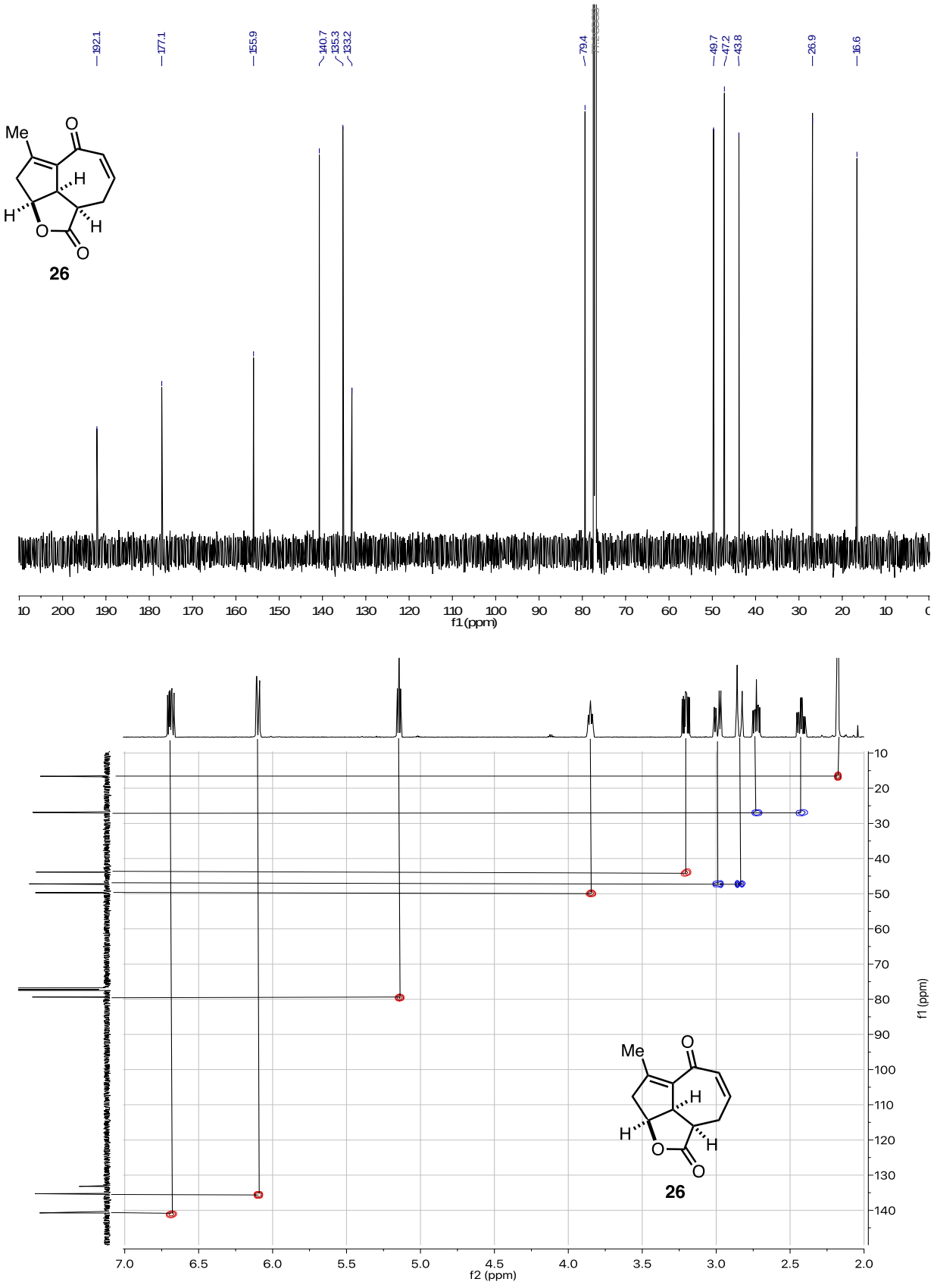




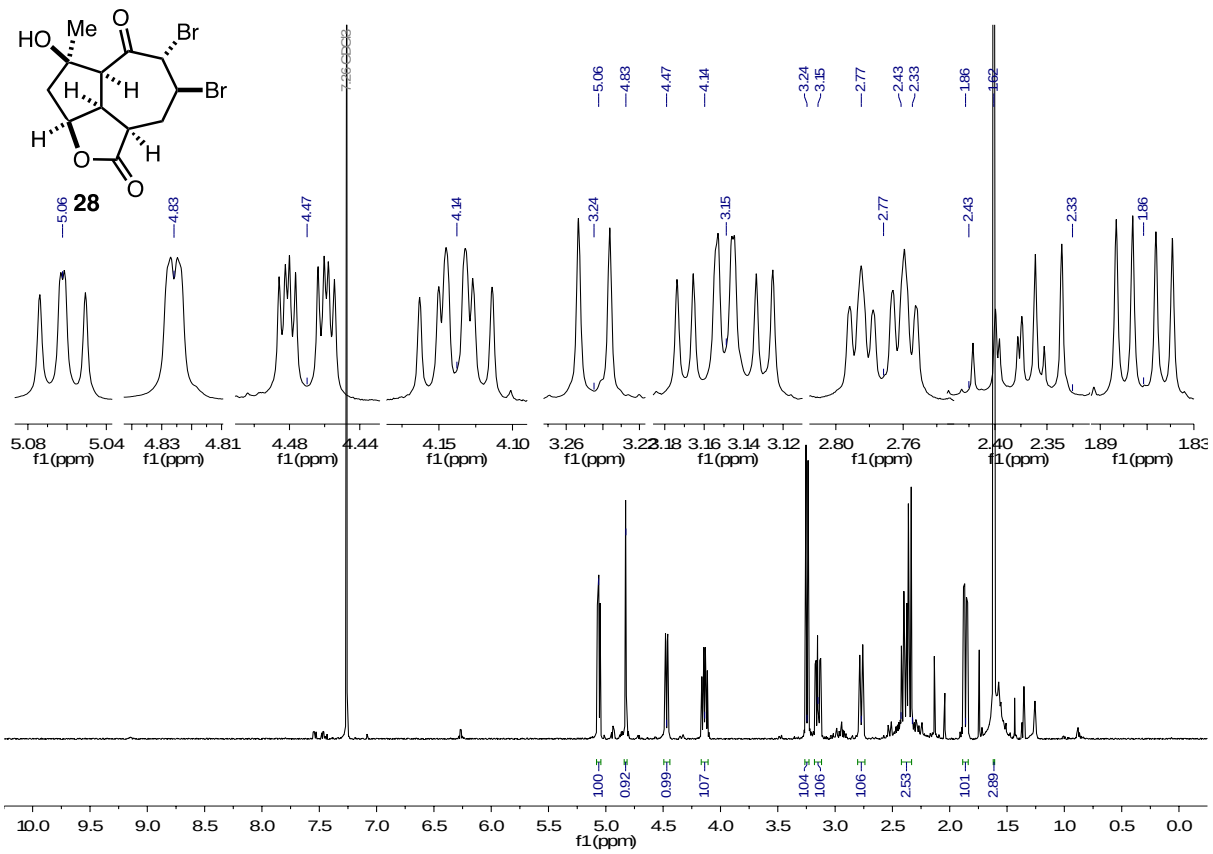
^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) (600 MHz) NMR of saturated pyranone **25**.

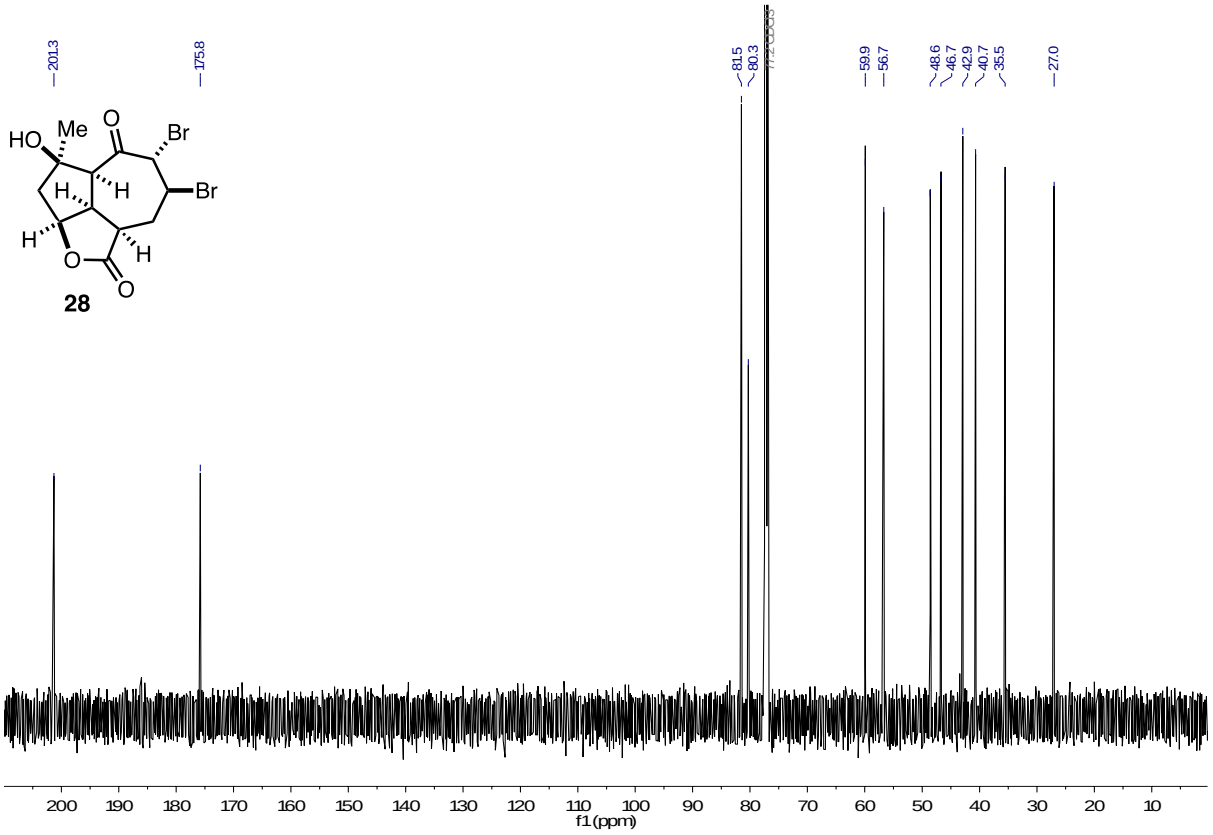


^{1}H (600 MHz) and COSY (600 MHz) NMR of cross conjugated dienone **26**.

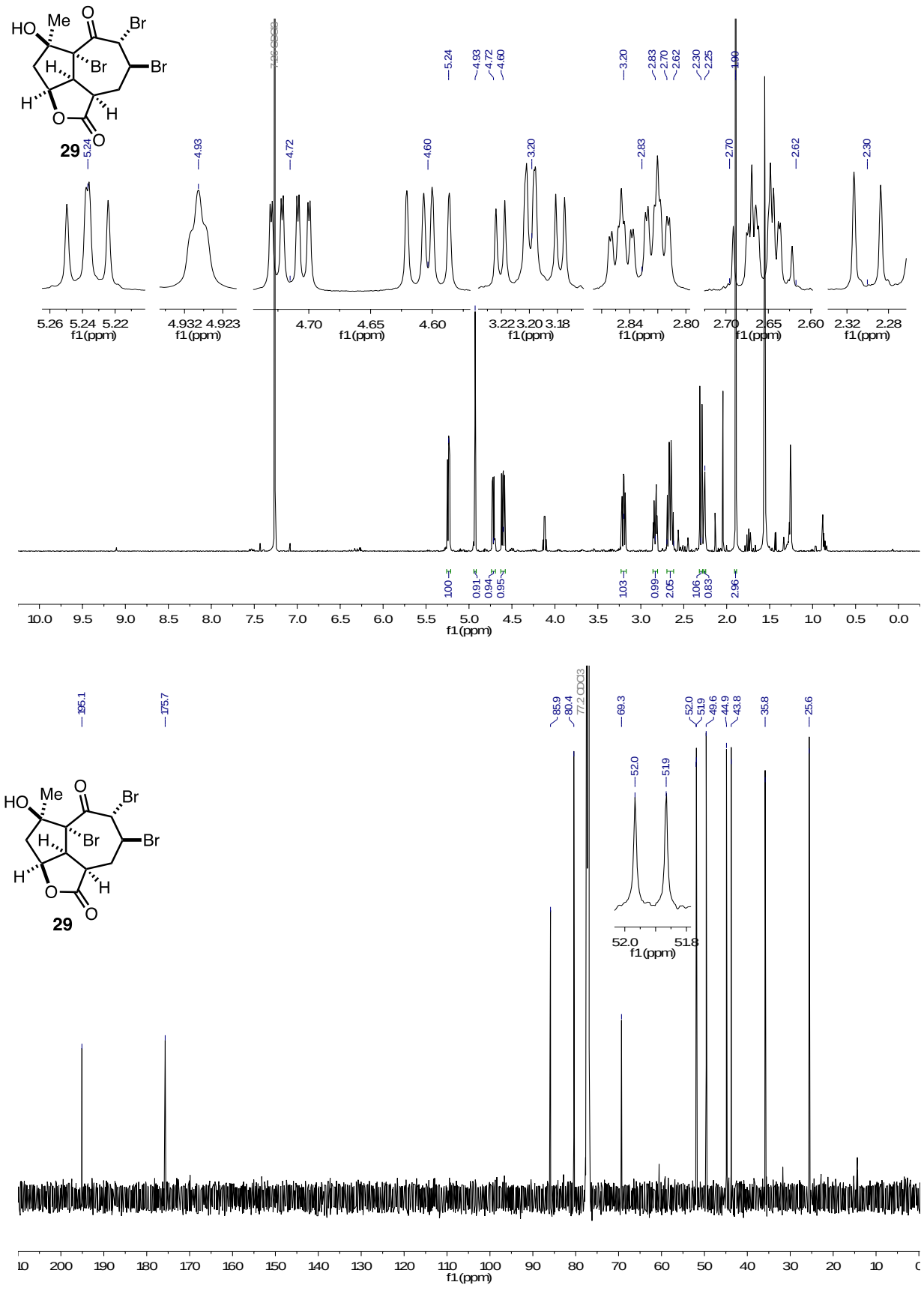


^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) (600 MHz) NMR of cross conjugated dienone **26**.

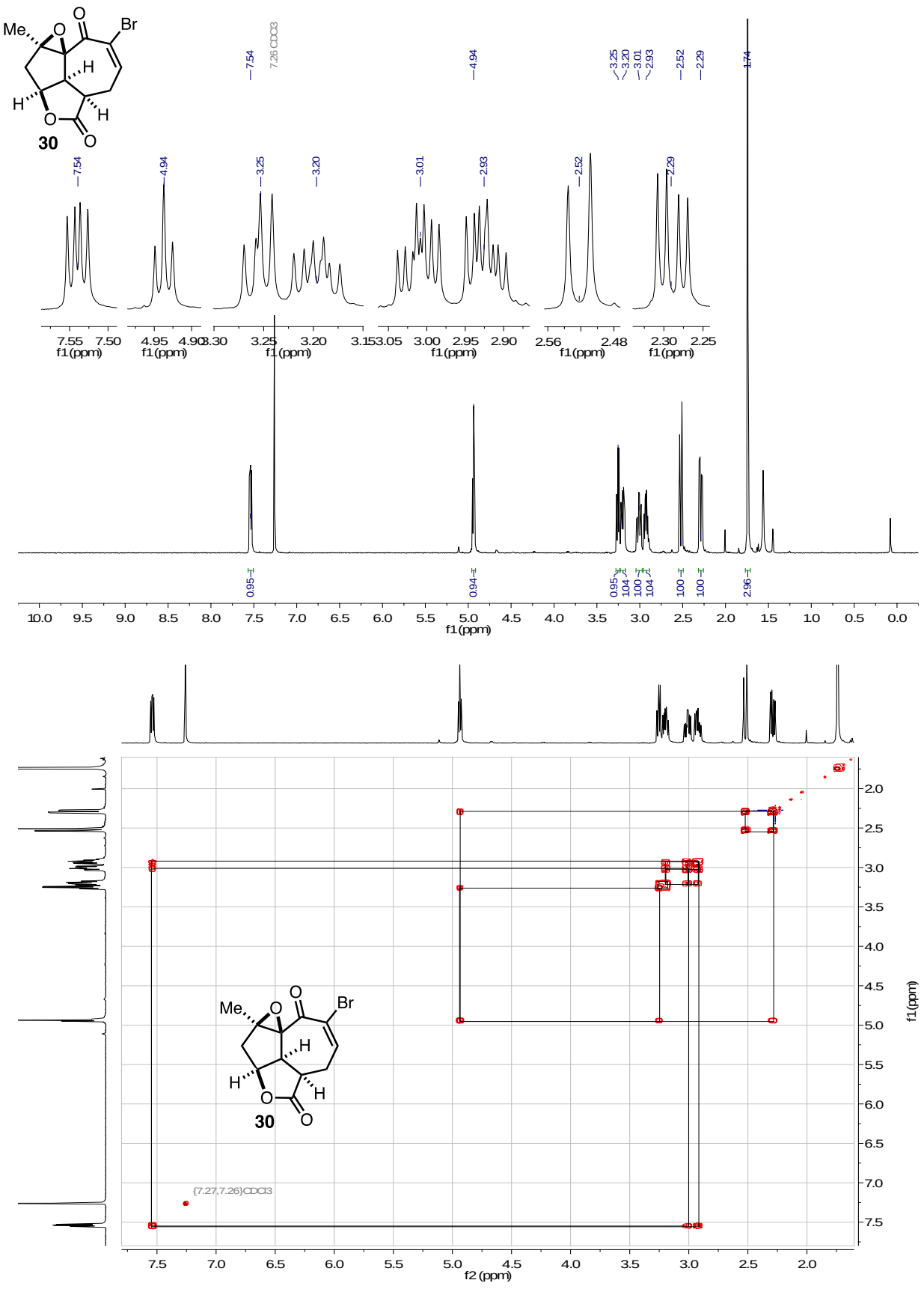




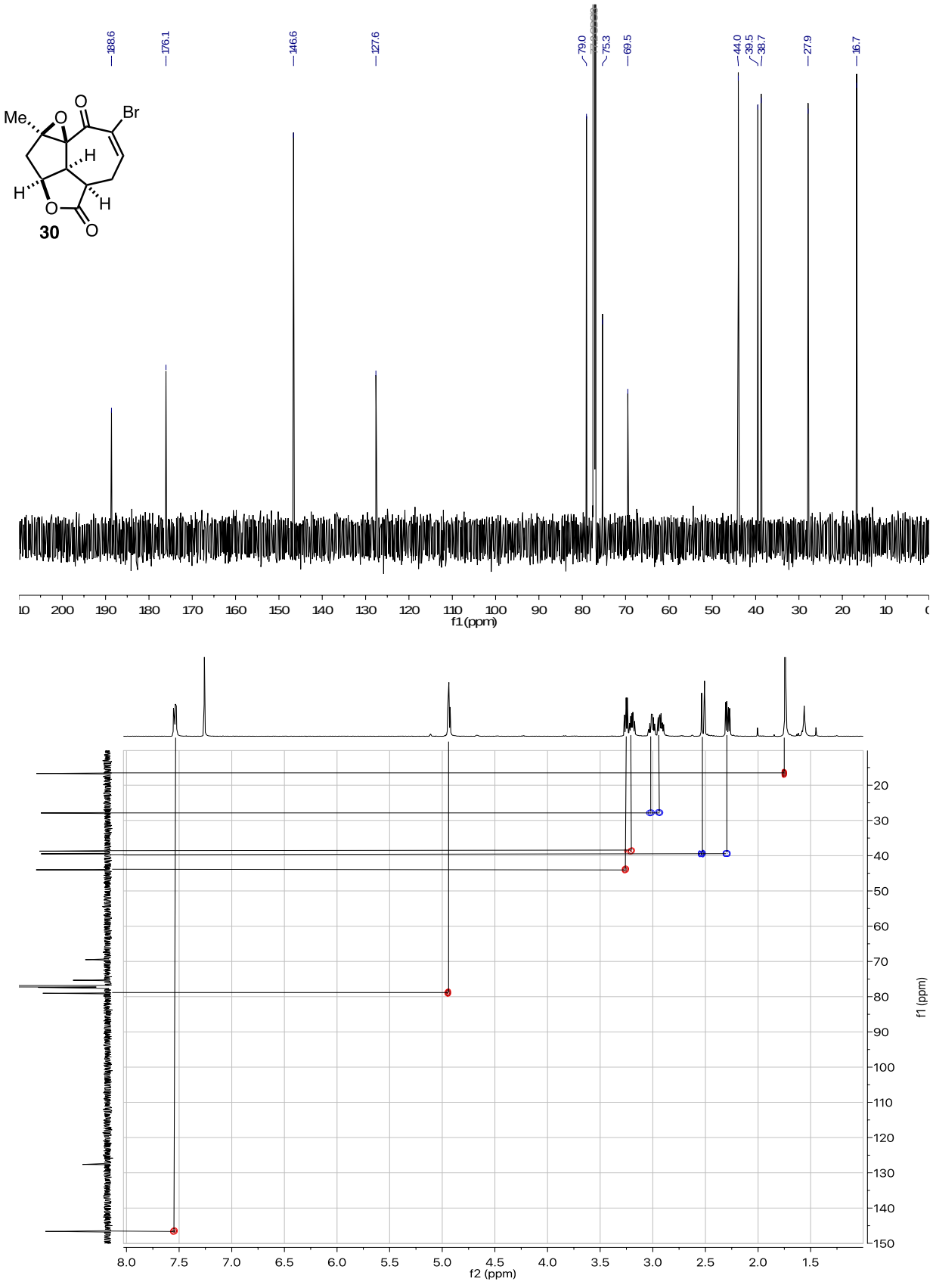
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of 5,5,7 dibromide core **28**.



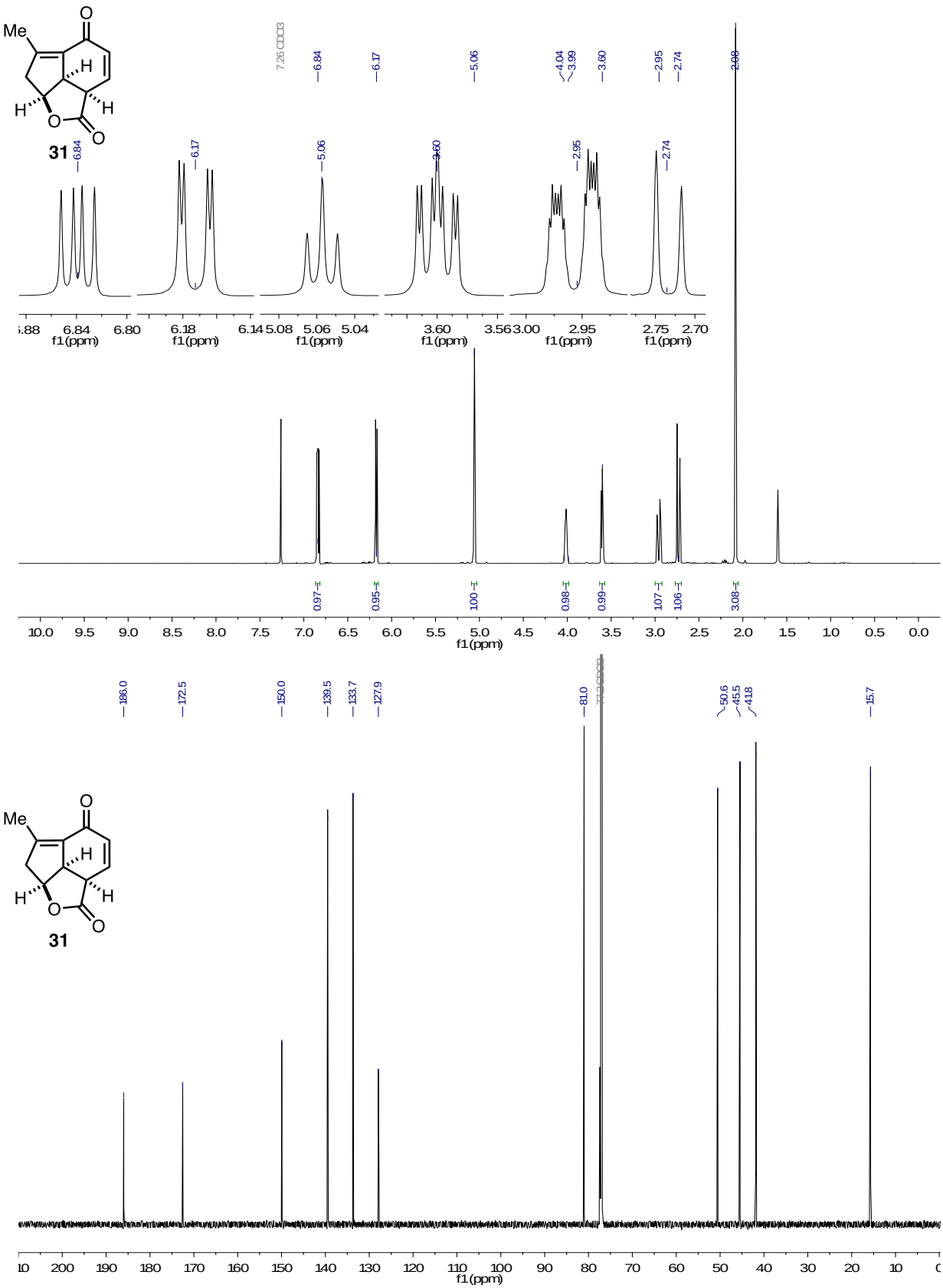
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of 5,5,7 core tribromide **29**.



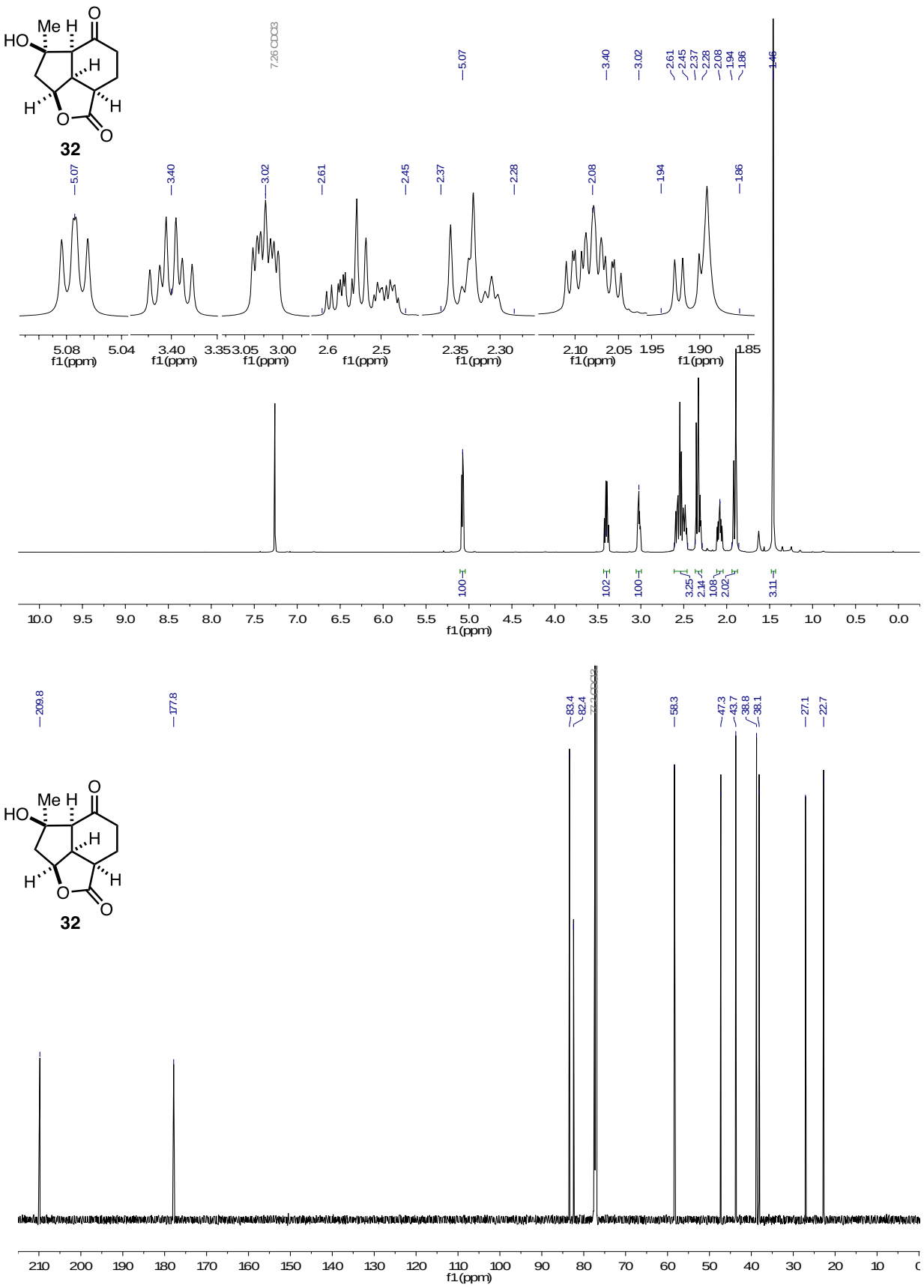
^{1}H (600 MHz) and COSY (600 MHz) NMR of α-bromo enone **30**.



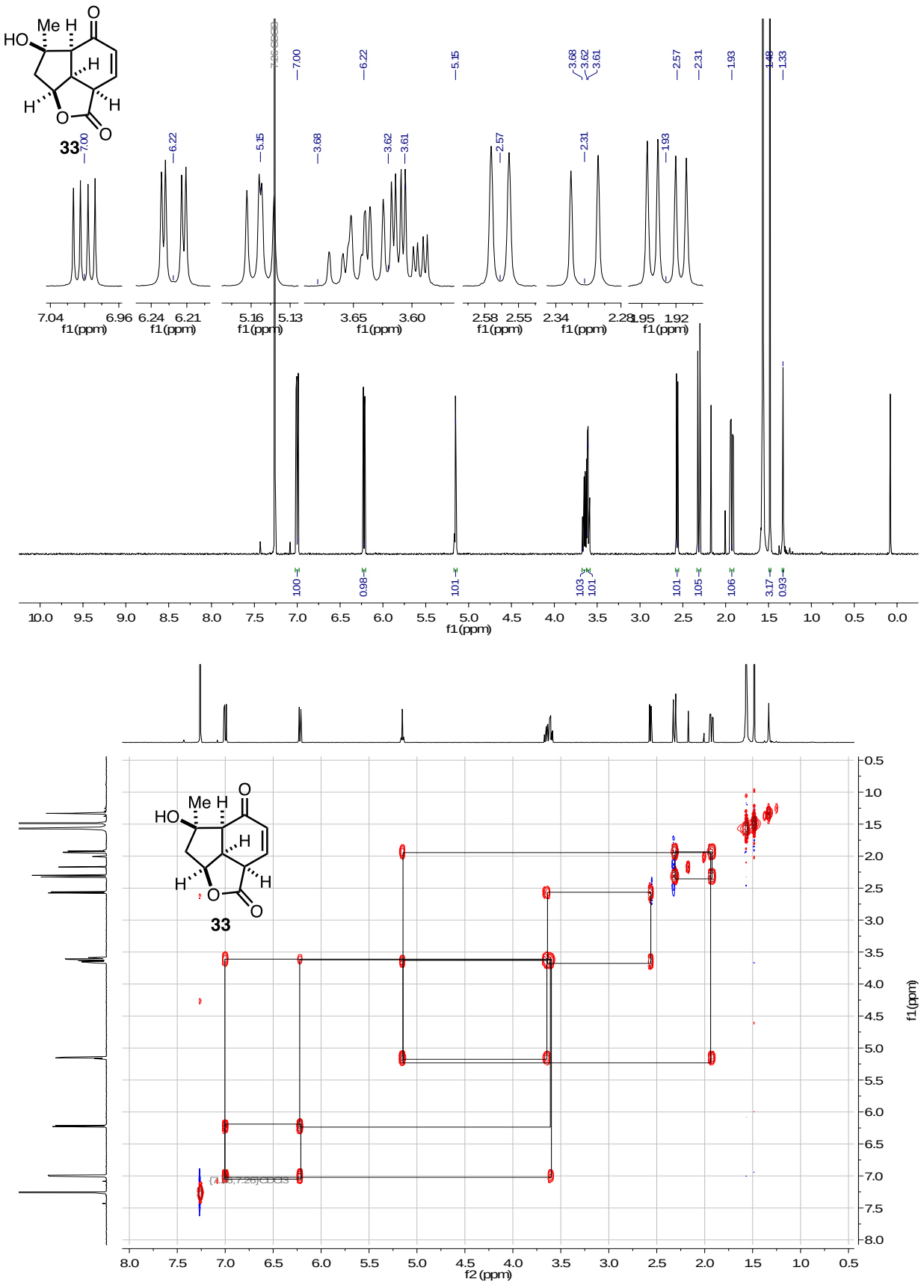
^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) (600 MHz) NMR of α-bromo enone **30**.



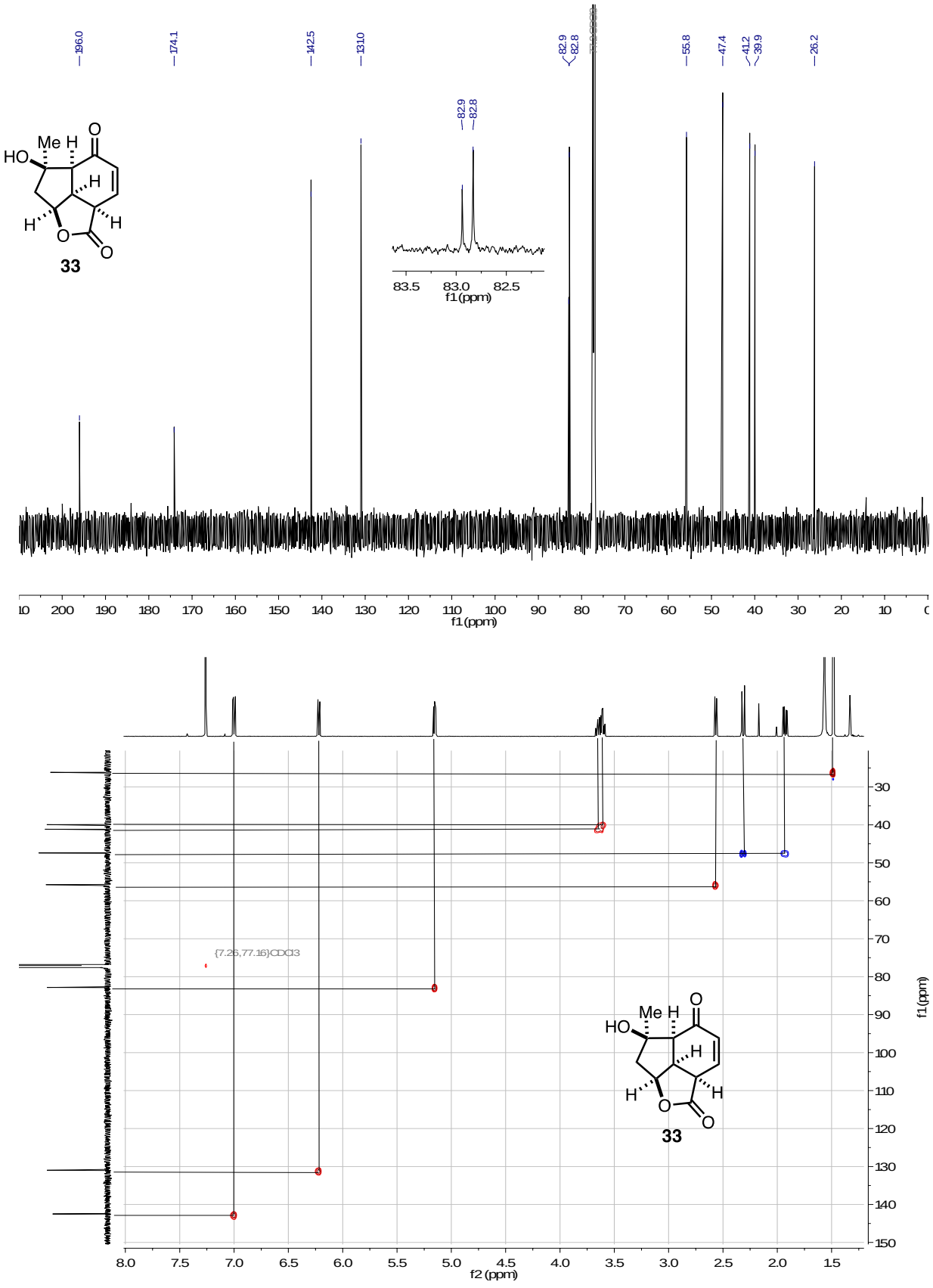
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of cross-conjugated dieneone **31**.



^{1}H (600 MHz) and ^{13}C (150 MHz) NMR of tricyclic ketone **32**.



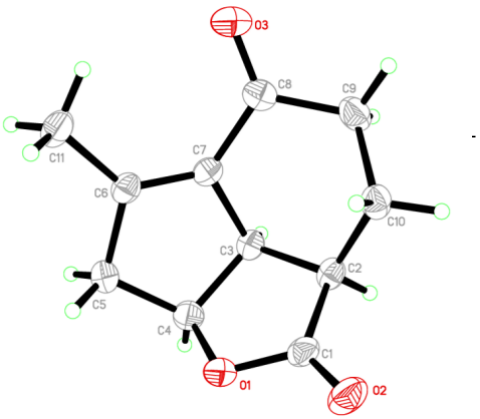
^{1}H (600 MHz) and COSY (600 MHz) NMR of tricyclic enone **33**.



^{13}C (150 MHz) and HSQC (^{1}H-^{13}C) (600 MHz) NMR of tricyclic enone **33**.

X-ray structure and crystallographic data

Table S1. X-ray crystallographic data of tricyclic enone **15**

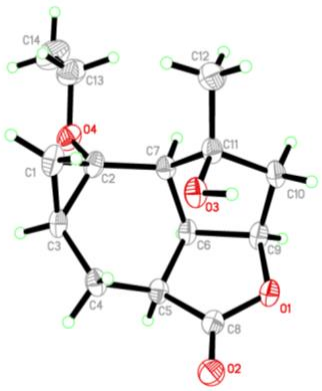


Identification code	DR43	
Empirical formula	C11 H12 O3	
Formula weight	192.21	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 14.8138(15) Å	α = 90°.
	b = 8.1344(9) Å	β = 90°.
	c = 15.3521(16) Å	γ = 90°.
Volume	1849.9(3) $Å^3$	
Z	8	
Density (calculated)	1.380 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	816	
Crystal size	0.232 x 0.215 x 0.142 mm^3	
Theta range for data collection	2.653 to 26.362°.	
Index ranges	-18<=h<=18, -10<=k<=10, -19<=l<=19	
Reflections collected	55825	
Independent reflections	1895 [R(int) = 0.0482]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.864 and 0.857	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1895 / 0 / 128	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.0354, wR2 = 0.0900	
R indices (all data)	R1 = 0.0385, wR2 = 0.0927	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.315 and -0.139 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DR43 (enone **15**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6270(1)	2997(1)	2564(1)	29(1)
O(2)	7190(1)	880(1)	2781(1)	36(1)
O(3)	4504(1)	2223(1)	5622(1)	32(1)
C(1)	6803(1)	2063(2)	3070(1)	25(1)
C(2)	6809(1)	2677(2)	3999(1)	22(1)
C(3)	6066(1)	3985(1)	4006(1)	22(1)
C(4)	5873(1)	4364(2)	3043(1)	26(1)
C(5)	4850(1)	4337(2)	2938(1)	28(1)
C(6)	4509(1)	3493(2)	3746(1)	23(1)
C(7)	5176(1)	3324(1)	4330(1)	21(1)
C(8)	5174(1)	2460(2)	5176(1)	24(1)
C(9)	6100(1)	1853(2)	5440(1)	31(1)
C(10)	6636(1)	1267(2)	4646(1)	26(1)
C(11)	3546(1)	2967(2)	3816(1)	31(1)

Table S3. X-ray crystallographic data of cyclopropane (±)-**20**

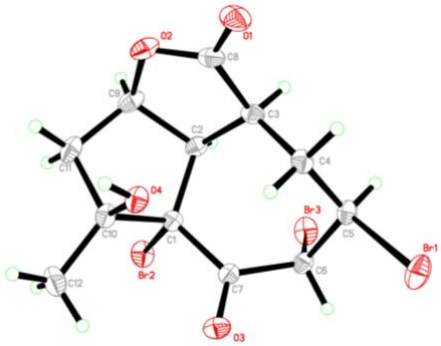


dentification code	dr36	
Empirical formula	C14 H20 O4	
Formula weight	252.30	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 14.6382(8) Å	α = 90°.
	b = 6.1795(3) Å	β = 94.350(3)°.
	c = 14.2319(12) Å	γ = 90°.
Volume	1283.66(14) $Å^3$	
Z	4	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	544	
Crystal size	0.324 x 0.128 x 0.032 mm^3	
Theta range for data collection	2.791 to 26.401°.	
Index ranges	-18<=h<=18, -7<=k<=7, -17<=l<=17	
Reflections collected	14218	
Independent reflections	2636 [R(int) = 0.0459]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9197 and 0.8947	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2636 / 0 / 169	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0425, wR2 = 0.0988	
R indices (all data)	R1 = 0.0596, wR2 = 0.1076	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.278 and -0.167 $e.Å^{-3}$	

Table S4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for dr36 (cyclopropane **20**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	207(1)	6979(2)	4292(1)	24(1)
O(2)	-381(1)	9754(2)	3472(1)	31(1)
O(3)	1621(1)	10159(2)	5070(1)	24(1)
O(4)	3854(1)	8084(2)	3329(1)	30(1)
C(1)	3148(1)	11510(3)	3835(1)	31(1)
C(2)	3088(1)	9111(3)	3699(1)	24(1)
C(3)	2573(1)	10560(3)	3003(1)	26(1)
C(4)	1538(1)	10590(3)	2977(1)	26(1)
C(5)	1113(1)	8333(2)	3119(1)	22(1)
C(6)	1701(1)	6660(2)	3691(1)	21(1)
C(7)	2540(1)	7581(2)	4279(1)	21(1)
C(8)	247(1)	8494(3)	3626(1)	23(1)
C(9)	1067(1)	5785(3)	4434(1)	23(1)
C(10)	1544(1)	6312(3)	5392(1)	25(1)
C(11)	2171(1)	8247(3)	5227(1)	23(1)
C(12)	2913(1)	8636(3)	6015(1)	35(1)
C(13)	4624(1)	7901(4)	3998(2)	39(1)
C(14)	5339(1)	6573(4)	3562(2)	50(1)

Table S5. X-ray crystallographic data of dibromide **29**

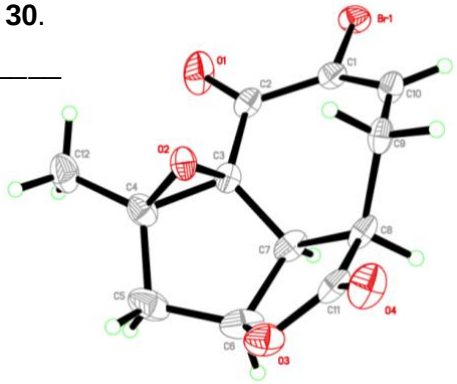


_____ Identification code	dr40	
Empirical formula	C12 H13 Br3 O4	
Formula weight	460.95	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.3345(2) Å	□= 84.4638(12)°.
	b = 9.2517(4) Å	□= 75.5671(17)°.
	c = 12.3961(5) Å	□ = 82.1279(12)°.
Volume	695.44(5) $Å^3$	
Z	2	
Density (calculated)	2.201 Mg/m^3	
Absorption coefficient	8.707 mm^{-1}	
F(000)	444	
Crystal size	0.350 x 0.222 x 0.132 mm^3	
Theta range for data collection	2.713 to 28.353°.	
Index ranges	-8<=h<=8, -12<=k<=12, -16<=l<=16	
Reflections collected	33238	
Independent reflections	3477 [R(int) = 0.0308]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.179 and 0.069	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3477 / 0 / 177	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0190, wR2 = 0.0472	
R indices (all data)	R1 = 0.0206, wR2 = 0.0479	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.660 and -0.443 $e.Å^{-3}$	

Table S6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for dr40 (tribromide **29**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	14248(1)	-1062(1)	6632(1)	30(1)
Br(2)	6738(1)	3020(1)	9708(1)	23(1)
Br(3)	7709(1)	-592(1)	8962(1)	25(1)
O(1)	9385(2)	2918(2)	4414(1)	27(1)
O(2)	7013(2)	4132(1)	5745(1)	24(1)
O(3)	12187(2)	2162(1)	8481(1)	21(1)
O(4)	10820(2)	4240(1)	6718(1)	18(1)
C(1)	8618(3)	2924(2)	8161(1)	15(1)
C(2)	7237(3)	2528(2)	7386(1)	16(1)
C(3)	8500(3)	1781(2)	6306(1)	17(1)
C(4)	10878(3)	1067(2)	6164(1)	18(1)
C(5)	11137(3)	-227(2)	6998(1)	18(1)
C(6)	10497(3)	156(2)	8227(1)	18(1)
C(7)	10539(3)	1796(2)	8323(1)	15(1)
C(8)	8393(3)	2973(2)	5385(1)	20(1)
C(9)	6197(3)	4029(2)	6958(2)	22(1)
C(10)	9178(3)	4500(2)	7738(1)	18(1)
C(11)	7025(3)	5207(2)	7464(2)	23(1)
C(12)	10027(3)	5377(2)	8482(2)	26(1)

Table S7. X-ray crystallographic data of epoxy bromo enone **30**.



Identification code	DR45	
Empirical formula	C12 H11 Br O4	
Formula weight	299.12	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pna2_1$	
Unit cell dimensions	a = 17.7546(7) Å	α = 90°.
	b = 4.9613(2) Å	β = 90°.
	c = 13.0346(4) Å	γ = 90°.
Volume	1148.16(7) $Å^3$	
Z	4	
Density (calculated)	1.730 Mg/m^3	
Absorption coefficient	3.580 mm^{-1}	
F(000)	600	
Crystal size	0.104 x 0.091 x 0.050 mm^3	
Theta range for data collection	2.776 to 28.293°.	
Index ranges	-23<=h<=23, -6<=k<=6, -17<=l<=17	
Reflections collected	27717	
Independent reflections	2851 [R(int) = 0.0448]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.797 and 0.670	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2851 / 1 / 156	
Goodness-of-fit on F^2	1.075	
Final R indices [I>2sigma(I)]	R1 = 0.0247, wR2 = 0.0507	
R indices (all data)	R1 = 0.0304, wR2 = 0.0522	
Absolute structure parameter	0.020(11)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.459 and -0.255 $e.Å^{-3}$	

Table S8. Atomic coordinates (Å x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for dr40 (epoxy enone **30**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	10760(1)	-2803(1)	9320(1)	27(1)
O(1)	9699(2)	724(5)	8135(2)	40(1)
O(2)	8841(1)	5173(4)	9453(2)	20(1)
O(3)	7696(1)	4453(5)	11122(2)	29(1)
O(4)	8453(1)	5994(5)	12339(2)	30(1)
C(1)	10094(2)	-127(6)	9833(2)	21(1)
C(2)	9578(2)	939(6)	9044(2)	22(1)
C(3)	8854(2)	2224(5)	9433(3)	18(1)
C(4)	8310(2)	3731(7)	8790(3)	25(1)
C(5)	7543(2)	3484(7)	9294(4)	35(1)
C(6)	7680(2)	2311(7)	10352(3)	32(1)
C(7)	8471(2)	1058(6)	10362(2)	23(1)
C(8)	8823(2)	1998(6)	11374(2)	22(1)
C(9)	9654(2)	2818(6)	11299(2)	24(1)
C(10)	10134(2)	648(6)	10811(3)	24(1)
C(11)	8331(2)	4346(6)	11684(2)	24(1)
C(12)	8369(2)	4356(8)	7666(3)	35(1)

Cytotoxicity assays of *Sinularia* natural product intermediates 15, 25-26, 30-36.

The cell lines, MDA MB 231, HCT 116, A549, and HUVEC were obtained from American Tissue Culture Collection (ATCC). MDA MB 231 cells were cultured in DMEM (ThermoFisher Scientific; Waltham, MA) supplemented with 10% fetal bovine serum (FBS; ThermoFisher Scientific; Waltham, MA). HCT 116 cells were cultured in McCoy's 5A (ThermoFisher Scientific; Waltham, MA) supplemented with 10% FBS. A549 cells were cultured in F12-K (ATCC; Manassas, VA) supplemented with 10% FBS. HUVEC cells were cultured in EBM-2 (Lonza; Basel Switzerland) supplemented with an EGM-2 bullet kit (Lonza; Basel Switzerland). All cell lines were maintained in a humidified incubator at 37 °C with 5% CO_2.

Cell viability assays were performed using resazurin sodium salt (Sigma; St. Louis, MO) in 96 well plates. The cells were seeded at varying cell densities per well: MDA MB 231, 2,500 cells/well; HCT 116, 4,000 cells/well; A549, 4,000 cells/well; and HUVEC, 2,000 cells per well. All compounds were dissolved in DMSO and diluted in media to a final maximum concentration of 100 µM. After incubation with drugs for 72 h, resazurin was added to each well to a final concentration of 10 µg/ml. After incubation at 37 °C for another 4-6 h away from direct light, fluorescence was measured using BMG Fluostar Optima Microplate Reader (Ortenberg, Germany). The data was analyzed using Microsoft Excel (Redmond, WA) and Graphpad Prism (San Diego, California).

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