Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.


# A multifunctional divergent scaffold to access the formal syntheses of various sesquiterpenoids

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**Supporting Information**

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## Abbreviations

| | |
|---|---|
| AIBN | Azobisisobutyronitrile |
| DCM | Dichloromethane |
| DIBAL | Diisobutylaluminium hydride |
| DMAP | 4-Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMS | Dimethyl sulfide |
| DMSO | Dimethyl sulfoxide |
| HMPA | Hexamethylphosphoramide |
| IBX | 2-Iodoxybenzoic acid |
| KHMDS | Potassium bis(trimethylsilyl)amide |
| L-Selectride | Lithium tri-sec-butylborohydride |
| LiHMDS | Lithium bis(trimethylsilyl)amide |
| MB | Methylene blue |
| *m*CPBA | Meta-Chloroperoxybenzoic acid |
| NBS | N-Bromosuccinimide |
| NCS | N-Chlorosuccinimide |
| NIS | N-Iodosuccinimide |
| NMO | N-Methylmorpholine N-oxide |
| o/n | Overnight |
| PCC | Pyridinium chlorochromate |
| PDC | Pyridinium dichromate |
| PIDA | (Diacetoxyiodo)benzene |
| *p*TSA | p-Toluenesulfonic acid |
| TEMPO | (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl |
| TMAO | Trimethylamine N-oxide |
| TMSCl | Trimethylsilyl chloride |

**1. Materials and Methods**

All reactions were carried out under an argon (Ar) atmosphere with dry solvents under anhydrous conditions. Anhydrous solvents were either obtained from commercial sources (dry DMF, dioxane, DMSO and MeOH) or dried accordingly. Dry diethyl ether ($Et_2O$), and tetrahydrofuran (THF), were obtained by refluxing the solvents with sodium metal as drying agent and benzophenone as indicator for several hours, dry acetonitrile was dried by distillation from $P_2O_5$, whereas methylene chloride ($CH_2Cl_2$) from $CaH_2$. The solvents were kept under Ar using molecular sieves 4Å in their bottles. Petroleum ether refers to the 40-60°C boiling fraction. Commercially available reagents were purchased at the highest commercial quality and used without further purification or where specified, purified by standard techniques.

Reactions were monitored by thin-layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent ($\lambda_{max}$= 254 nm or 360 nm) and ethanolic *p*-anisaldehyde as developing agent or by *Seebach* TLC stain solution, followed by heating. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative TLC plates (S-2 0.5mm E. Merck silica gel plates precoated with silica gel 60-F254) were used in cases where the separation with usual flash column chromatography were inadequate.

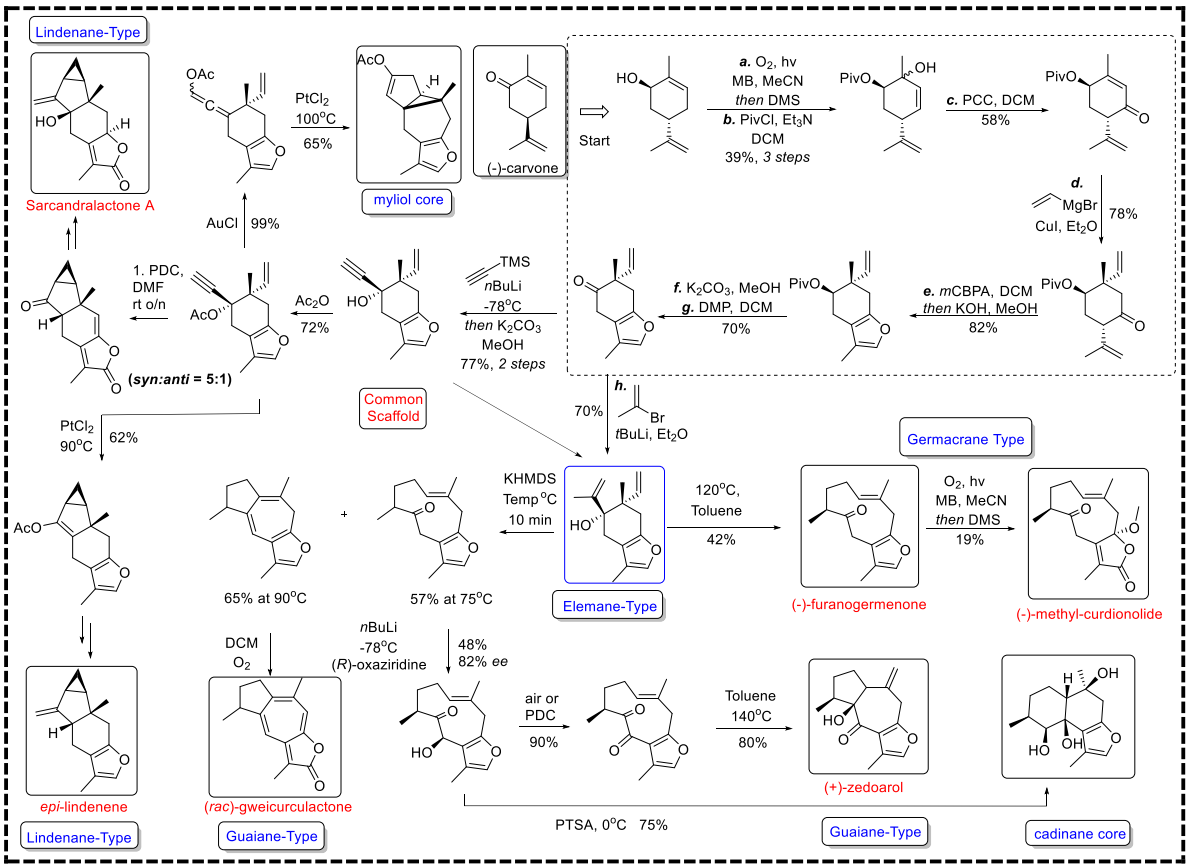
NMR spectra were recorded at 298 K using an Agilent Technologies DD2 500 spectrometer and calibrated by residual solvent peaks. $^1$H NMR spectra were recorded at 500 MHz and residual solvent peaks were used as an internal reference ($CDCl_3$ δ 7.26). Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, brs = broad singlet, d = doublet, brd = broad doublet, t = triplet, brt = broad triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances, coupling constants are reported in Hz, integration is included. $^{13}$C NMR spectra were recorded at 125 MHz and residual solvent peaks were used as an internal reference ($CDCl_3$ δ 77.00). Data are reported as follows: chemical shift in ppm, multiplicity deduced. The assignment of $^1$H and $^{13}$C signals was assisted by COSY, HSQC, HMBC and NOESY experiments where necessary.

High Pressure Liquid Chromatography (HPLC) was performed on an Agilent 1260 Infinity II spectrometer to monitor reaction kinetics. Optical rotations were recorded on a Krüss Optronic polarimeter at 589 nm and are reported in units of 10–1(deg cm2 g–1).

Infusion experiments were carried out on an Agilent Q-TOF Mass Spectrometer, G6540B model with Dual AJS ESI-MS. All the compounds (dissolved in LC-MS grade, methanol) were introduced into the ESI source of the MS with a single injection of 15 µL of the sample and with a flow rate of 300 µL/min of 100% methanol as a solvent in the binary pump. The experiments were run using a Dual AJS ESI source, operating in a positive ionization mode. Source operating conditions were 330 $^o$C Gas Temp, 8 l/min Gas Flow, Sheath Gas Temp 250 $^o$C, Sheath Gas Flow 10 l/min and 150 V Fragmentor. Data-dependent MS/MS analysis was performed in

parallel with the MS analysis, in a centroid mode, using different collision energies (10, 20, 30, 40 V). All accurate mass measurement of the $[M+H]^+$ ions, were carried out by scanning from 100 to 500 m/z. The Q-TOF was calibrated 1 h prior to the infusion experiments by using a calibration mixture. Data were acquired in an external calibration mode.

**2. Synopsis of Zografos's divergent total synthesis of sesquiterpenoids (Org. Lett., 2013, 15, 152; Chem. Comm., 2015, 51, 2364; Org. Biomol. Chem., 2016, 14, 6942)** [1]



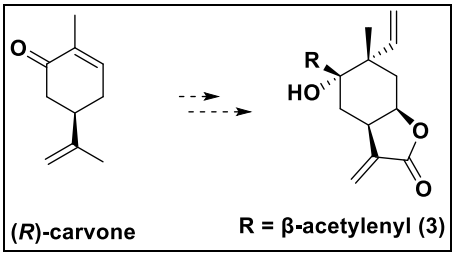

**Scheme S1.** Synthetic routes to furo-sesquiterpenoids

Our previously published synthetic route utilizes furan-elemanes as common synthetic scaffolds to access various carbocyclic cores of sesquiterpeneoids. The selection of furan-elemane common scaffolds relied on the ability of *trans*-positioned unsaturations (diene and enyne) to succeed: 1. a non-reversible, non-biomimetic, enantioselective oxy-Cope reaction for the synthesis of a crucial biosynthetic germacrane intermediate and 2. highly selective cycloisomerizations to deliver cyclopropane sesquiterpenoids. Biomimetic utilization of the germacrane intermediate enriched the route with furoguaiane and furocadinane sesquiterpenoids. Further oxidation steps allowed the addition of further functionality following the biomimetic two-phase protocol (cyclase-oxidase phase).

Major drawback of the described plan is the inaccessibility to *α*-methylene-*γ*-butyrolactone sesquiterpenoids. Direct oxidation of furan functionality resulted in only poor yields of *α*,*β*-unsaturated-*γ*-

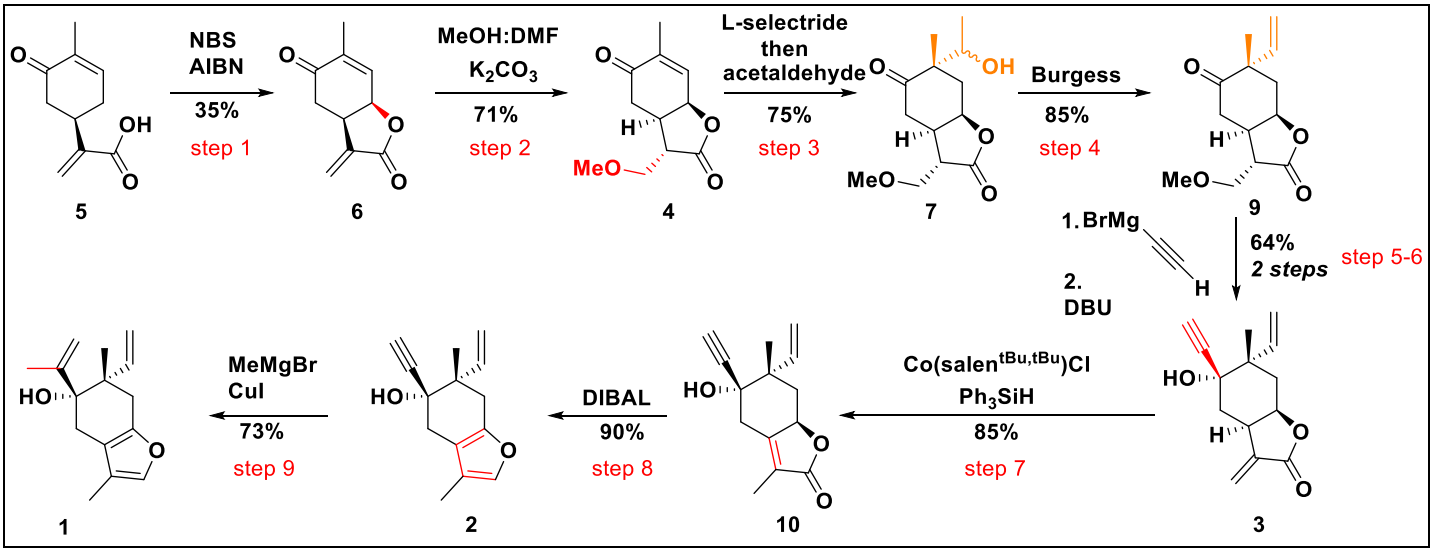
butenolides, which we were unable to transform into the desired exocyclic methylene lactone. Also, despite the undeniable success of this plan to provide diversity, it lacks scalability majorly due to the incorporation of a photochemical oxidation and the instability of furo-ketone *en-route* to the common synthetic scaffold. Considering these facts, we turned our attention to alternative synthetic routes that can still provide the described diversity, enriching it with the ability to introduce the biologically important *α*-methylene-*γ*-butyrolactone cores.

### 3. Designing divergent scaffolds. The logic behind the selection




**Scheme S2.** Divergent scaffold

Wishing to overpass the drawbacks of our previous plan, we considered the synthesis of divergent scaffold **3**, bearing the *syn*-*α*-methylene-*γ*-butyrolactone functionality. The *syn*-conformation of the lactone moiety was selected based on the lower rigidity of the structure that favours better biological profiles.[2] *Syn*-relation between methyl group and lactone moiety is crucial to retain the access to lindenane and myliol sesquiterpenoids (see plan above). Finally, β-side is required for 2-propenyl-chain to gain access to germacrene and guaiane natural products and β-side for acetylenyl-chain to allow synthesis of lindenane and myliol natural products. Its construction was envisioned directly from the acrylic acid functionality, through a CH-lactonization protocol. A synopsis of the synthetic plan used is shown below.




**Scheme S3.** Synthetic plan synopsis

## 4. Experimental procedures

### 4.1 Early-stage introduction of *α*-methylene-*γ*-butenolide core from carvonic acid 5-Optimization for CH-lactonization (Step 1)

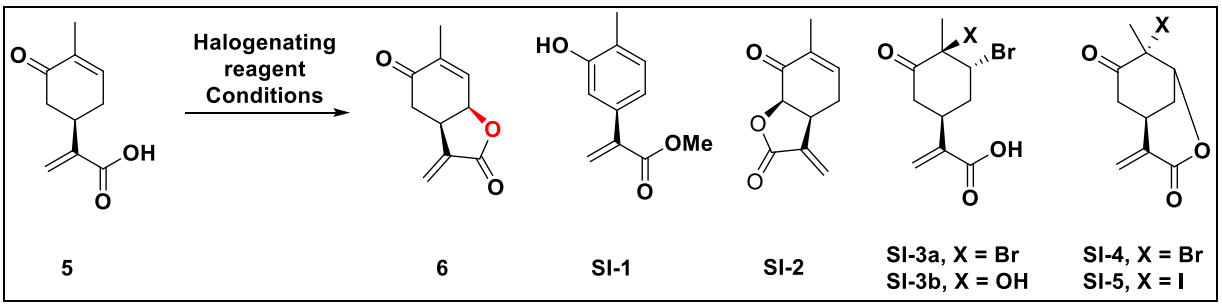
Carvonic acid **5** was intended to play a dual role, firstly to selectively deliver syn-*α*-methylene-*γ*-butenolide by utilizing its allylic functionality and secondly to orient the introduction of vinyl- and acetylene chains accordingly, as the *syn*-locked conformation of the lactone moiety was expected by DFT calculations to be oriented vertically to the cyclohexane carbocycle (conducted by Gaussian b3lyp/m06).

Although both 6- and 8-positions are activated enough to enable their functionalization in carvonic acid **5**, several methods to introduce substituents as halogens or hydroxyls failed to deliver clean reactions. Below are given selected examples of our failed routes towards **6** and the optimization protocol to deliver it.

#### 4.1.1 Attempting allylic halogenation

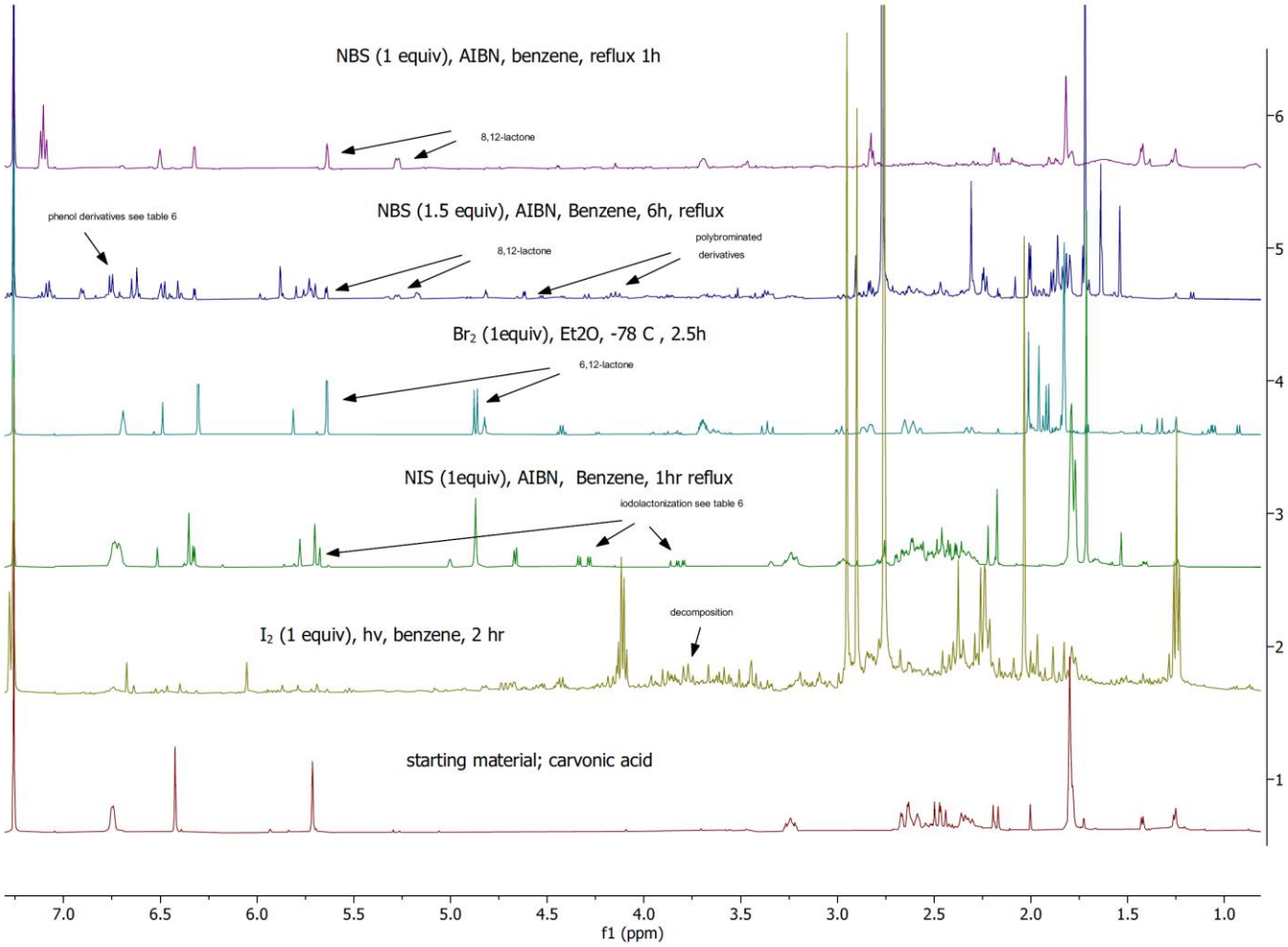
Several halogenation protocols have been attempted for the allylic halogenation of carvonic acid and its subsequent lactonization to **6**. In most cases, reactions provided multiple products deriving from polyhalogenation ex. **SI-3**, and halolactonization reactions ex. **SI-4** and **SI-5**. In some cases, the promising for the synthesis of 6,12-SQLs 6,12-lactone **SI-2** (Table S1) was obtained in low to moderate yields. Moderate yields of 6,12-lactone **SI-2** were isolated chemoselectively by using a base (LHMDS) and iron or copper chloride. Mechanistic investigation reveals formation of *α*-chlorinated ketone intermediate instead of a radical initiated process that leads to compound **SI-2**. Also, compound **SI-2** was obtained when bromine under ionic conditions was utilized, albeit in non reproducible yields that vary from 40 to 15%. In cases where the desired **6** was delivered, commonly the yields are low due to overoxidation products ex. **SI-1**. Crucial factor for obtaining decent yield of **6** was the carefully controlled heating conditions and the accurate reaction time. Beneficial was found the exclusion of molecular oxygen from reaction mixture to avoid part of overoxidized products.

**Table S1.** Attempts for the synthesis of **6** utilizing halogenating reagents.

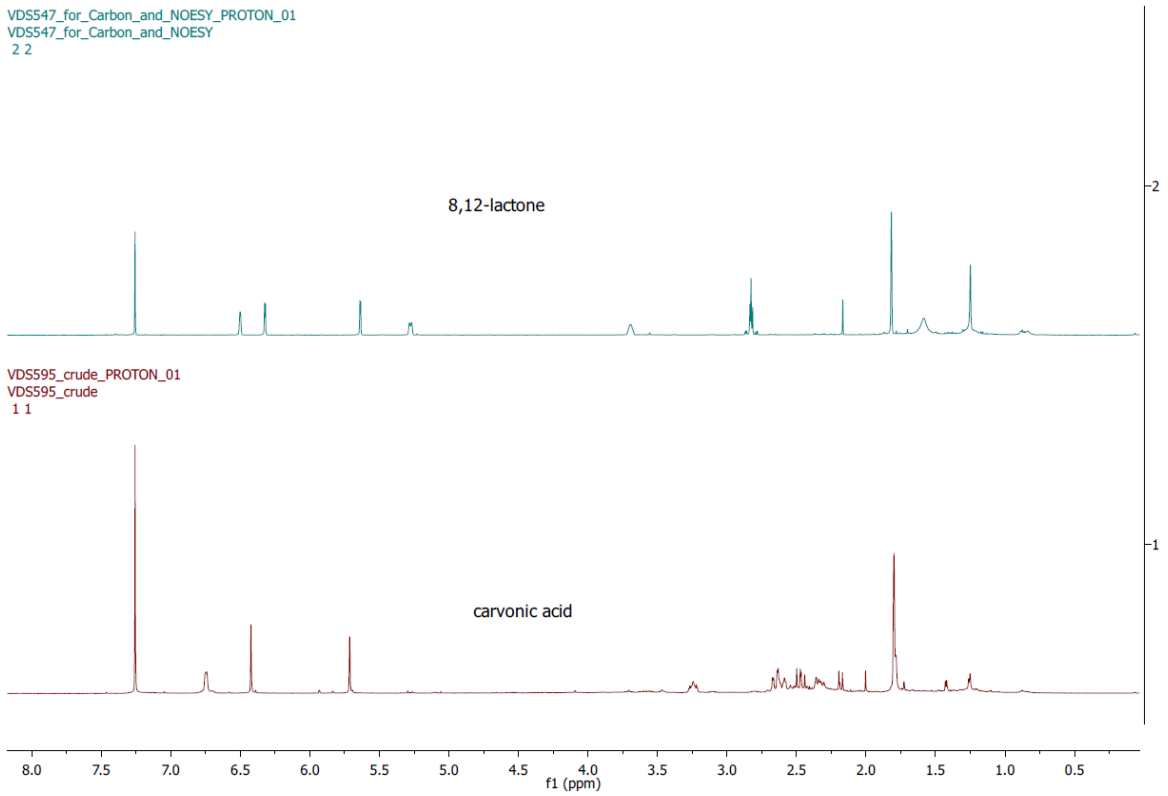


| Entry [a] | Conditions | Products | Conversion | Yields for major products |
|---|---|---|---|---|
| 1 | NBS (1.1 equiv), AIBN (25 mol%) two portions, $CCl_4$, 80 °C, 105 min | **6, SI-1, SI-2** | 66% | **6** (10%), **SI-1** (21%), **SI-2** (3%) |
| 2 | NBS (1.1 equiv), AIBN (15 mol%), $CCl_4$, 80 °C, 1 h, deoxygenation | Polybrominated products, **6, SI-2** | 55% | **6** (10%), **SI-2** (3%) |
| 3 | NBS (1.1 equiv), AIBN (15 mol%), $CCl_4$, 80 °C, 2 h, deoxygenation, microwave | **6, SI-1, SI-2** | 52% | **6** (10%), **SI-1** (30%), **SI-2** (6%) |
| 4 | NBS (1 equiv), AIBN (15 mol%), $CCl_4$, 80 °C, 7 h | **6, SI-1, SI-2** | 100% | **6** (12%), **SI-1** (80%), **SI-2** (4%) |
| 5 | NBS (1.5 equiv), AIBN (15 mol%), Benzene, 80 °C, 1 h | **6, SI-5** | 100% | **6** (19%), **SI-4** (70%) |
| 6[b] | NBS (1 equiv), AIBN (10 mol%), Benzene, 80 °C, 1.5 h, deoxygenation | **6, SI-1, SI-2** | 57% | **6** (35%), **SI-1** (19%), **SI-2** (5%) |
| 7 | NIS (1 equiv), AIBN (10 mol%), Benzene, 80 °C, 1 h, deoxygenation | **SI-5, unidentified products** | 60% | **SI-5** (31%) |
| 8 | NCS (1 equiv), AIBN (10 mol%), Benzene, 80 °C, 1 h, deoxygenation | Complex mixture of products | 75% | - |
| 9 | NBS (1 equiv), UV light, Benzene, rt, 2 h | Complex mixture of products | - | - |
| 10 | NBS (1 equiv), $Et_3B$, Benzene, -20 °C, 1 h | Complex mixture of products | - | - |
| 11 | NBS (1 equiv), benzoyl peroxide (10 mol%), Benzene, 80 °C, 1.5 h, deoxygenation[3] | **6, SI-1, SI-2** | 73% | **6** (22%), **SI-1** (19%), **SI-2** (7%) |
| 12 | $Br_2$ (1 equiv), in two portions $Et_2O$, -78 °C to -30 °C 100 min and then rt for 30 min | **SI-2, SI-3, SI-4** | 82% | **SI-2** (40%), **SI-3a** (16%) **SI-3b** (8%), **SI-4** (18%) |
| 13 | $I_2$ (1 equiv), in two portions $Et_2O$, -78 °C to -30 °C 100 min and then rt for 30 min | Complex mixture of products | - | - |
| 14 | $I_2$ (1 equiv) UV-VIS light, Benzene, | **SI-5 and minor polyiodination** | 78% | **SI-5** (28%) |
| 15 | LHMDS (2 equiv), $FeCl_3$ (4 equiv), THF, -78 to -15 °C, o/n | **SI-2** | 30% | **SI-2** (20%) |
| 16 | LHMDS (2 equiv), CuOTf (4 equiv), THF, -78 to -15 °C, o/n | - | 0 | - |
| 17 | LHMDS (2 equiv), $Fe(acac)_3$ (4 equiv), THF, -78 to 5 °C, o/n | - | 0 | - |
| 18 | LHMDS (2 equiv), $CuCl_2$ (4 equiv), THF, -78 °C to rt, o/n | **SI-2** | 35% | **SI-2** (35%) |
| 19 | LHMDS (2 equiv), $TiCl_4$ (4 equiv), THF, -78 °C to rt, o/n | - | 0 | - |
| 20 | LHMDS (2 equiv), $ZnCl_2$ (4 equiv), THF, -78 °C to rt, o/n | - | 0 | - |
| 21 | KHMDS (2 equiv), $CuCl_2$ (4 equiv), THF, -78 °C to rt, o/n | **SI-2** | 18% | **SI-2** (15%) |
| 22 | LHMDS (2 equiv), CuI (4 equiv), THF, -78 °C to rt, o/n | - | 0 | - |

[a] All reactions were conducted in up to 2.22 mmol scale unless otherwise noted. [b] Reaction was scaled up to 5.6 mmol.

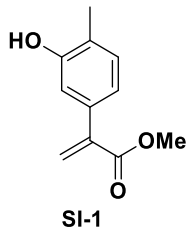



**Spectra 1.** Comparison of different methods to achieve 8,12-lactonization




**Spectra 2.** H[1]NMR comparison of carvonic acid **5** and the desired 8,12-lactone **6**.

**Methyl 2-(3-hydroxy-4-methylphenyl)acrylate (SI-1)**




SI-1

MW: 192.21 g/mol Formula: $C_{11}H_{12}O_3$

To a stirring solution of **Compound 5** (100 mg, 0.55 mmol, 1.0 eq) in $CCl_4$ (10 mL), AIBN (14 mg, 0.08 mmol, 0.15 eq) and NBS (98 mg, 0.55 mmol, 1.0 eq) were added successively and the reaction mixture was left at reflux for 7h. After being cooled down, the reaction was treated with saturated aqueous $NaHCO_3$ and after separation, the aqueous layer was acidified by HCl 6N and extracted three times with EtOAc (3x20 mL). The combined organic extracts were washed three times with water (3x10 mL) to remove succinimide, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was recrystallized from MeOH to afford pure **Compound SI-1** (85 mg, 80%).

**Physical state:** white solid.

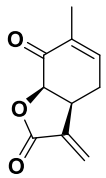
**TLC:** $R_f$ = 0.51 (hexane:EtOAc = 1:3, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 7.13 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.51 (d, *J* = 1.0 Hz, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 3.84 (s, 3H), 2.23 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 172.29, 157.39, 140.79, 134.95, 130.37, 128.88, 127.23, 120.52, 110.32, 55.43, 16.15.

**HRMS (ESI, m/z):** calcd. for $C_{11}H_{13}O_3^+$ ($[M+H]^+$): 193.0865, found: 193.0870.

**(3a*S*,7a*R*)-6-methyl-3-methylene-3a,7a-dihydrobenzofuran-2,7(3H,4H)-dione (SI-2)**




MW: 178.19 g/mol Formula: $C_{10}H_{10}O_3$

**Method for entry 14: Compound 5** (135 mg, 0.75 mmol, 1.0 eq) was dissolved in $Et_2O$ (13 mL) and the mixture was brought to -78 °C and $Br_2$ (19 µL, 0.37 mmol, 0.5 eq) was added dropwise. The reaction mixture was left stirring for 40 min at the same temperature before $Br_2$ (19 µL, 0.37 mmol, 0.5 eq) dissolved in 1 mL of $Et_2O$ was added slowly and the reaction was left stirring for 1h until -40 °C and was then brought to room

temperature for additional 30 min. Addition of saturated aqueous $NaHCO_3$ followed and after separation of the two layers, the aqueous phase was extracted three times with $Et_2O$ (3x10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure, affording pure **Compound SI-2** (54 mg, 40%).

**Method for entry 20:** In a flame-dried round-bottom flask, **Compound 5** (67 mg, 0.37 mmol, 1.0 eq) was dissolved in THF (7 mL) under Ar atmosphere and the mixture was brought to -78 °C. Addition of LiHMDS (0.8 mL, 0.74 mmol, 1M in THF, 2 eq) followed and the reaction mixture was left stirring at the same temperature for 45 min. Then, $CuCl_2$ (150 mg, 1.12 mmol, 3 eq) was added quickly and the resulting mixture was left stirring until rt overnight. The reaction was diluted with ethyl acetate and was quench by aqueous EDTA. After separation, the organic layer was washed with aqueous $NaHCO_3$, dried over $Na_2SO_4$ and concentrated under reduced pressure, affording pure **Compound SI-2** (23 mg, 35%).

**Physical state:** white solid.

**TLC:** $R_f$ = 0.42 (hexane:EtOAc = 1:3, UV active on TLC, stains pink upon *p*-anisaldehyde staining).

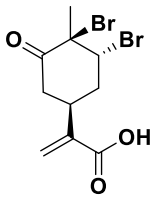
**$[\alpha]^{20}_D$** = -57.8 (*c* 1.35, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.69 (s, 1H), 6.29 (s, 1H), 5.64 (s, 1H), 4.86 (d, *J* = 8.2 Hz, 1H), 3.70 (dq, *J* = 7.6, 3.9 Hz, 1H), 2.93 – 2.80 (m, 1H), 2.70 – 2.55 (m, 1H), 1.82 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 191.1, 168.8, 143.0, 136.8, 136.2, 121.6, 76.4, 38.4, 25.7, 16.0.

**HRMS (ESI, m/z):** calcd. for $C_{10}H_{11}O_3^+$ ($[M+H]^+$): 179.0708, found: 179.0722.

**2-((1*S*,3*R*,4*R*)-3,4-dibromo-4-methyl-5-oxocyclohexyl)acrylic acid (SI-3a)**




MW: 340.01 g/mol Formula: $C_{10}H_{12}Br_2O_3$

**Compound 5** (400 mg, 1.66 mmol, 1.0 eq) was dissolved in $Et_2O$ (30 mL) and the mixture was brought to -78 °C and before a solution of $Br_2$ (43 µL, 0.37 mmol, 0.5 eq) in 1 mL $Et_2O$ was added dropwise. The reaction mixture was left stirring for 45 min until the temperature reached -55 °C, before a second solution of $Br_2$ (19 µL, 0.37 mmol, 0.5 eq) in 1 mL $Et_2O$ was added slowly and the reaction was left stirring for 2h until -30 °C. Addition of saturated aqueous $NaHCO_3$ followed and after separation, the aqueous layer was brought to pH 3.0 and was extracted three times with $Et_2O$ (3x10 mL). The residue was chromatographed (silica gel) with gradient from 5:1 hexane: EtOAc to 1:1 hexane: EtOAc to afford pure **Compound SI-3a** (90 mg, 16%).

**Physical state:** yellow oil.

**TLC:** $R_f$ = 0.48 (hexane:EtOAc = 1:3, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

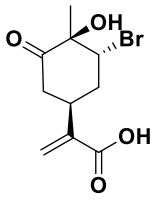
**$[\alpha]^{20}_D$** = +36.4 (*c* 1.5, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDC_3$)** δ = 6.51 (s, 1H), 5.83 (s, 1H), 4.82 (t, *J* = 3.0 Hz, 1H), 3.72 – 3.57 (m, 1H), 3.36 (dd, *J* = 14.6, 13.6 Hz, 1H), 2.98 (ddd, *J* = 14.9, 12.3, 2.8 Hz, 1H), 2.59 (ddd, *J* = 14.5, 4.4, 2.1 Hz, 1H), 2.32 (dd, *J* = 14.6, 2.8 Hz, 1H), 2.01 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 200.6, 171.3, 141.1, 128.0, 63.0, 59.0, 40.3, 36.0, 35.2, 28.2.

**HRMS (ESI, m/z):** calcd. for $C_{10}H_{12}Br_2O_3Na^+$ ($[M+Na]^+$): 362.9031, found: 362.9012.

**2-((1*S*,3*R*,4*R*)-3-bromo-4-hydroxy-4-methyl-5-oxocyclohexyl)acrylic acid (SI-3b)**




MW: 277.11 g/mol Formula: $C_{10}H_{13}BrO_4$

**Compound 5** (400 mg, 1.66 mmol, 1.0 eq) was dissolved in $Et_2O$ (30 mL) and the mixture was brought to -78 °C and before a solution of $Br_2$ (43 µL, 0.37 mmol, 0.5 eq) in 1 mL $Et_2O$ was added dropwise. The reaction mixture was left stirring for 45 min until the temperature reached -55 °C, before a second solution of $Br_2$ (19 µL, 0.37 mmol, 0.5 eq) in 1 mL $Et_2O$ was added slowly and the reaction was left stirring for 2h until -30 °C. Addition of saturated aqueous $NaHCO_3$ followed and after separation, the aqueous layer was brought to pH 3.0 and was extracted three times with $Et_2O$ (3x10 mL). The residue was chromatographed (silica gel) with gradient from 5:1 hexane: EtOAc to 1:1 hexane: EtOAc to afford pure **Compound SI-3b** (37 mg, 8%).

**Physical state:** yellow oil.

**TLC:** $R_f$ = 0.40 (hexane:EtOAc = 1:3, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

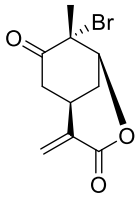
**$[\alpha]^{20}_D$** = +40.7 (*c* 1.2, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.46 (s, 1H), 5.84 (s, 1H), 4.62 (t, *J* = 3.1 Hz, 1H), 3.58 (tt, *J* = 12.6, 4.4 Hz, 1H), 2.92 (t, *J* = 13.5 Hz, 1H), 2.73 – 2.56 (m, 2H), 2.38 – 2.27 (m, 1H), 1.62 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 208.9, 171.1, 140.3, 129.2, 77.3, 62.7, 41.2, 38.0, 36.0, 24.5.

**HRMS (ESI, m/z):** calcd. for $C_{10}H_{13}BrO_4Na^+$ ($[M+Na]^+$): 298.9895, found: 298.9877.

**(1*S*,5*R*,8*R*)-8-bromo-8-methyl-4-methylene-2-oxabicyclo[3.3.1]nonane-3,7-dione (SI-4)**




MW: 259.10 g/mol Formula: $C_{10}H_{11}BrO_3$

To a stirring solution of **compound 5** (400 mg, 2.22 mmol, 1.0 eq) in benzene (25 mL), AIBN (76 mg, 0.44 mmol, 0.2 eq) and NBS (592 mg, 3.33 mmol, 1.5 eq) were added successively and the reaction mixture was left at reflux for 1h. After being cooled down, the reaction was treated with saturated aqueous $NaHCO_3$ and after separation, the aqueous layer was extracted three times with Et2O (3x15 mL). The combined organic extracts were washed three times with water (3x10 mL) to remove succinimide, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 5:1 hexane: EtOAc to 1:1 hexane: EtOAc to afford pure **Compound SI-4** (403 mg, 70%).

**Physical state:** yellowish solid.

**TLC:** $R_f$ = 0.65 (hexane:EtOAc = 1:3, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

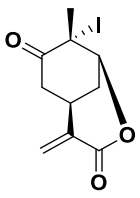
**$[\alpha]^{20}_D$** = -48.9 (*c* 1.7, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.53 (s, 1H), 5.69 (s, 1H), 4.93 (dt, *J* = 4.2, 2.2 Hz, 1H), 3.57 (dd, *J* = 15.0, 5.0 Hz, 1H), 3.35 (dp, *J* = 5.8, 3.0 Hz, 1H), 3.06 (dt, *J* = 14.5, 2.3 Hz, 1H), 2.49 (dt, *J* = 14.9, 2.7 Hz, 1H), 2.34 (dq, *J* = 14.6, 3.4 Hz, 1H), 1.93 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 200.9, 162.0, 136.5, 131.7, 84.0, 60.6, 44.7, 36.1, 27.0, 23.6.

**HRMS (ESI, m/z):** calcd. for $C_{10}H_{12}BrO_3^+$ ($[M+H]^+$): 258.9970, found: 258.9989.

**(1*S*,5*R*,8*R*)-8-iodo-8-methyl-4-methylene-2-oxabicyclo[3.3.1]nonane-3,7-dione (SI-5)**




MW: 306.10 g/mol Formula: $C_{10}H_{11}IO_3$

To a stirring solution of **Compound 5** (400 mg, 2.22 mmol, 1.0 eq) in benzene (25 mL), AIBN (76 mg, 0.44 mmol, 0.2 eq) and NIS (499 mg, 2.22 mmol, 1.0 eq) were added successively and the reaction mixture was left at reflux for 1h. After being cooled down, the reaction was treated with saturated aqueous $NaHCO_3$ and after separation, the aqueous layer was extracted three times with Et2O (3x15 mL). The combined organic

extracts were washed three times with water (3x10 mL) to remove succinimide, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 10:1 hexane: EtOAc to 6:1 hexane: EtOAc to afford pure **Compound SI-5** (211 mg, 31%).

**Physical state:** yellow solid.

**TLC:** $R_f$ = 0.6 (hexane:EtOAc = 1:3, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

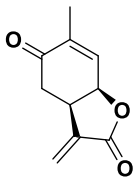
**$[\alpha]^{20}_D$** = -51.2 (*c* 1.2, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.52 (s, 1H), 5.68 (s, 1H), 5.01 (dt, *J* = 3.8, 2.1 Hz, 1H), 3.89 – 3.78 (m, 1H), 3.38-3.33 (m, 1H), 3.23 (dt, *J* = 14.4, 2.3 Hz, 1H), 2.48 (ddt, *J* = 25.0, 14.4, 2.9 Hz, 2H), 2.18 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 191.1, 168.8, 143.0, 136.8, 136.2, 121.6, 76.4, 38.4, 25.7, 16.0.

**HRMS (ESI, m/z):** calcd. for $C_{10}H_{12}IO_3^+$ ($[M+H]^+$): 306.9831, found: 306.9820.

**(3a*R*,7a*R*)-6-methyl-3-methylene-3a,7a-dihydrobenzofuran-2,5(3H,4H)-dione (6).**



MW: 178.19 g/mol Formula: $C_{10}H_{10}O_3$

**Compound 5** (500 mg, 2.77 mmol, 1.0 eq) To a stirring solution of **compound 5** (400 mg, 2.22 mmol, 1.0 eq) in thoroughly degassed benzene (40 mL) equipped by refluxed condenser and argon balloon, AIBN (76 mg, 0.44 mmol, 0.2 eq) and NBS (395 mg, 2.22 mmol, 1.0 eq) were added successively and the reaction mixture was left at reflux for 1h sharp. After being cooled down, the reaction was treated with saturated sodium thiosulfate and after separation aqueous $NaHCO_3$. The two layers were separated and the aqueous layer was extracted one time with benzene (25 mL). The combined organic extracts were washed three times with water (3x10 mL) to remove succinimide, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 5:1 hexane: EtOAc to 1:1 hexane: EtOAc to afford pure c**ompound 6** (173 mg, 35%).

**Physical state**: white solid.

**TLC:** $R_f$ = 0.5 (hexane:EtOAc = 1:3, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

**$[\alpha]^{20}_D$** = -68.6 (*c* 0.7, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.53 – 6.48 (m, 1H), 6.33 (d, *J* = 3.1 Hz, 1H), 5.64 (d, *J* = 3.1 Hz, 1H), 5.31 – 5.25 (m, 1H), 3.74 – 3.66 (m, 1H), 2.89 – 2.80 (m, 2H), 1.82 (s, 3H).

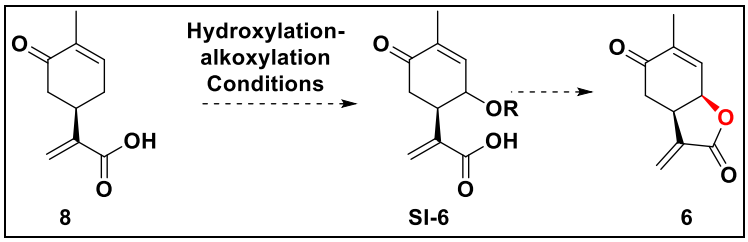
**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 195.0, 168.8, 138.5 137.2, 136.5, 122.7, 73.1, 38.3, 37.1, 15.9.

**HRMS (ESI, m/z):** calcd. for $C_{10}H_{11}O_3^+$ ($[M+H]^+$): 179.0708, found: 179.0712.

### 4.1.2 Attempting allylic hydroxylation-alkoxylation

Despite the extended literature present on the topic of allylic hydroxylation and alkoxylation, none of the tested methods provided even traces of the desired products. Utilization of singlet oxygen and selenium dioxide resulted inseparable complex mixture of products while radical lactonization with the aid of strong oxidants as $K_2S_2O_8$ led to decomposition. Attempts to hydroxylate the allylic position by the oxidation of the *γ*-stabilized enol form provided only traces of hydroxylated intermediate **SI-6 (Table S2)**. Efforts to use carboxylic acid as directing group for palladium-mediated CH-activation of allylic position,[4] resulted only in unreacted starting material.

**Table S2.** Selected attempts for hydroxylation and CH-lactonization of carvonic acid **5**.



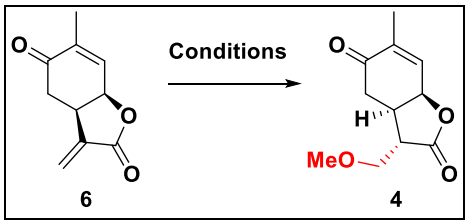

| Entry | Hydroxylation reagent | Products | Conversion | Yield |
|---|---|---|---|---|
| 1 | $O_2$, methylene blue, VIS light 300W, $CH_3CN$, rt, 3 days | Unreacted SM | - | - |
| 3 | t-BuOK (2 equiv), EtOH, rt, $O_2$[5] | SM | 0 | - |
| 4 | MeMgBr (5 equiv), $FeCl_3$ (1.2 equiv), TMSCl, (1.2 equiv), nitrosobenzene (1.5 equiv), 0 °C to rt, 5 hr[6] | Hydroxylated product **SI-6** | 40% | 15% |
| 5 | $K_2S_2O_8$ (2 equiv), $Cu(OAc)_2$ (10 mol%), $CH_3CN$, 80 °C, o/n[7] | Decomposition | - | - |
| 6 | $K_2S_2O_8$ (2 equiv), $Cu(OAc)_2$ (10 mol%), DMF/$H_2O$ 5:1, 80 °C, o/n[7] | Decomposition | - | - |
| 7 | $SeO_2$ (0.5 eq), t-BuOOH (3 equiv), $CH_3CN$/$H_2O$, rt to 50 °C, o/n[8] | Complex mixture of products | - | - |
| 8 | $Pd(OAc)_2$ (10 mol%), oxone (1.5 equiv), $K_2CO_3$ (1 equiv), dioxane, rt, o/n | Unreacted SM | - | - |
| 9 | $Pd(Oac)_2$ (5 mol%), oxone (1.5 equiv), $K_2CO_3$ (1 equiv), DMSO 110 °C, o/n | SM | - | - |
| 10 | $Pd(OAc)_2$ (10 mol%), benzoquinone (2 equiv), DMSO 130 °C, o/n | **SI-2** | 20% | 8% |
| 11 | $Pd(OAc)_2$ (10 mol%), benzoquinone (2 equiv), DMSO, AcOH 70 °C, o/n | **SI-2** | 20% | 8% |
| 12 | $Pd(OAc)_2$ (10 mol%), PIDA (1.5 equiv), tBuOK (2 equiv), t-BuOH, 80 °C, o/n | Unreacted SM | - | - |

### 4.2 Optimization for the protection of α-methylene-γ-butenolide (step 2)

Attempts to introduce the alkyl chains in the presence of *α*-methylene-*γ*-butenolide functionality failed, due to the highly reactive nature of the lactone. Based on that, protection of methylene group was surveyed. The chemoselective protection of *α*-methylene side was accomplished by the reversible introduction of methyl ether with $K_2CO_3$ and MeOH in a mixture of DMF. The dilution of the substrate (<0.1M) and the ratio of DMF

(DMF:MeOH= 3:1) is a crucial factor for the completion of the reaction (Table S3). We must note that unreacted starting material is inseparable from the product.

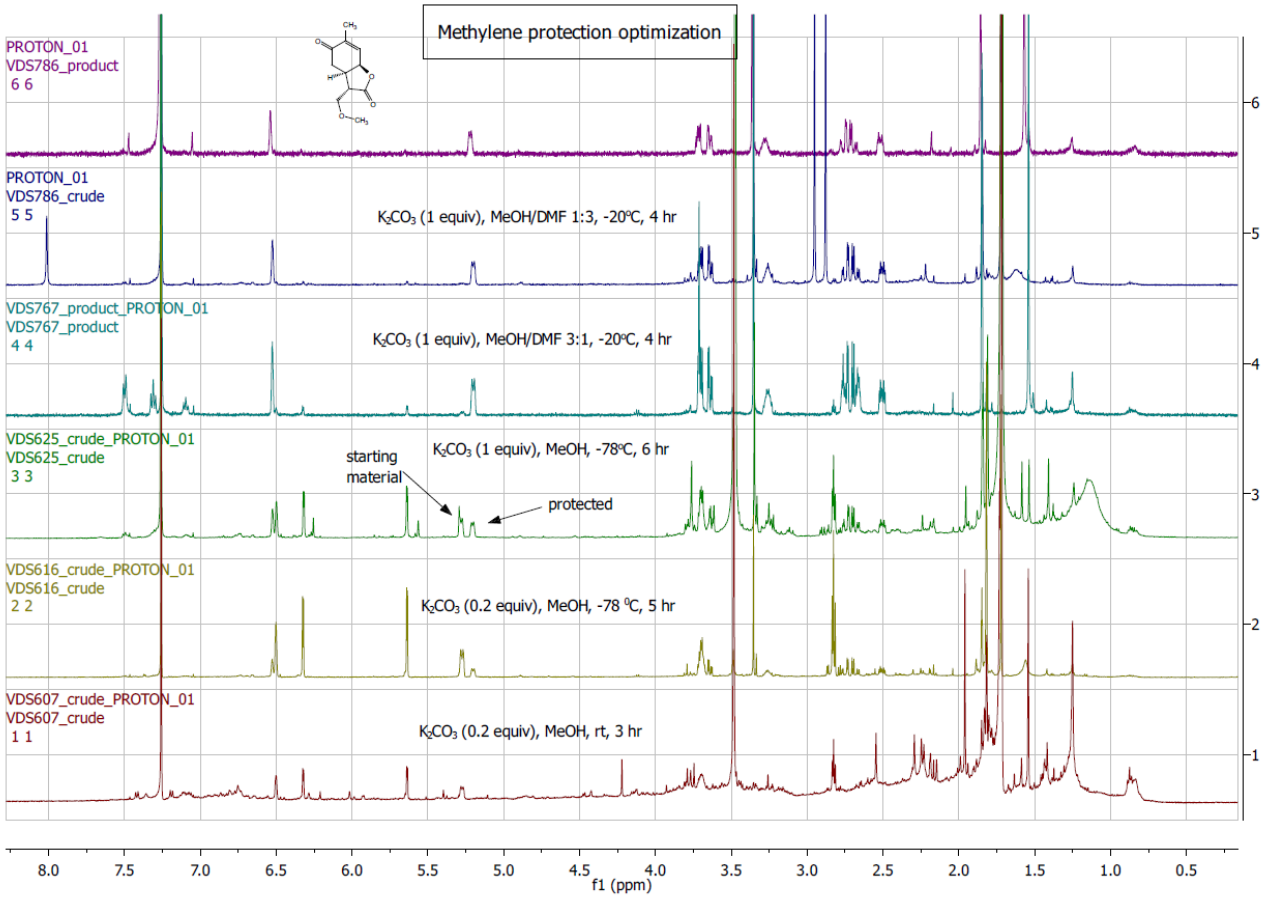
**Table S3**. Optimization for the protection of **6**.




| Entry[1] | Base | Solvent | Conversion | Yield of 4 |
|---|---|---|---|---|
| 1 | MeONa (1.5 equiv), rt, 2 h | MeOH | 100% | Complex mixture of products |
| 2 | $K_2CO_3$ (0.2 equiv), rt, 3 h | MeOH | 55% | Complex mixture of products |
| 3 | $K_2CO_3$ (0.2 equiv), -78 °C to rt, 5 h | MeOH | 30% | 25% |
| 4 | Substrate >0.2M $K_2CO_3$ (1 equiv), -78 °C, 6 h | MeOH | 68% | 45% |
| 5 | Substrate <0.1M, $K_2CO_3$ (1 equiv), -20 °C, 4 h | MeOH/DMF 3:1 | 84% | 59% |
| 6 | Substrate <0.1M, $K_2CO_3$ (2 equiv), -20 °C, 4 h | MeOH/DMF 1:3 | 100% | 71% |

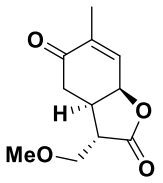
[1] Yields reported as calculated by $H^1$NMR with internal standard.

Optimization attempts as monitored by NMR are shown below (Spectra 3).




**Spectra 3.** Screening conditions for *α*-methylene protection.

**(3*S*,3a*R*,7a*S*)-3-(methoxymethyl)-6-methyl-3a,7a-dihydrobenzofuran-2,5(3H,4H)-dione (4)**




MW: 210.23 g/mol Formula: $C_{11}H_{14}O_4$

To a stirring solution of **compound 6** (3 g, 16.83 mmol, 1.0 eq) in a mixture of DMF/MeOH 3:1 (250/83 mL) at -20 °C, $K_2CO_3$ (4.6 g, 33.66 mmol, 2 eq) was added in one portion and the reaction mixture was left stirring at that temperature for 4 h. Upon completion, 100 mL of $Et_2O$ were added and the reaction mixture was left at rest without stirring at -20 °C for 30 min for any excess of $K_2CO_3$ to be precipitated, before it was filtered under vacuum and quenched with saturated aqueous $NH_4Cl$ (90mL). After separation, the aqueous layer was extracted two times with $Et_2O$ (2x150 mL) and two times with EtOAc (2x50 mL). The combined organic extracts were washed once with $H_2O$ (120 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 3:1 hexane: EtOAc to 1:1 hexane: EtOAc to afford pure **Compound 4** (2.5 g, 71%).

**Physical state:** white solid.

**TLC:** $R_f$ = 0.67 (hexane:EtOAc = 1:3, UV inactive on TLC, stains brown upon *p*-anisaldehyde staining).

**$[\alpha]^{20}_D$** = -70 (*c* 0.2, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.54 – 6.50 (m, 1H), 5.19 (dt, *J* = 7.0, 2.1 Hz, 1H), 3.69 (dd, *J* = 9.8, 4.8 Hz, 1H), 3.63 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.34 (s, 3H), 3.30 – 3.21 (m, 1H), 2.70 (qd, *J* = 17.2, 4.8 Hz, 2H), 2.50 (dt, *J* = 10.5, 4.1 Hz, 1H), 1.84 (s, 3H).

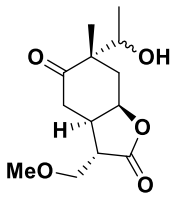
**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 196.0, 175.2, 138.5, 137.6, 73.7, 68.9, 59.3, 44.7, 37.2, 36.9, 15.8.

**HRMS (ESI, m/z):** calcd. for $C_{11}H_{15}O_4^+$ ($[M+H]^+$): 211.0970, found: 211.0967.

**4.3 Introduction of vinyl alkyl chain (steps 3-4)**

Following the protection, conjugated reduction of **4** by L-selectride and subsequent addition of acetaldehyde provided compound **7** in 75% yield, as a mixture of diastereoisomers majoring the Zimmerman-Traxler predicted alcohol in a ratio of 4:1. Dehydration by Burgess reagent provided compound **7** in 85% yield after trituration with 1% triethylamine based silica gel. Crude NMR of reaction mixtures reveal a complex reaction profile that refer to Burgess-**7** hybrids, separated in cases of carvone-based dehydrations. Hybrid Burgess-**7** although traceable in crude reactions were never succeeded to be isolated.

**(3*S*,3a*R*,6*R*,7a*R*)-6-(1-hydroxyethyl)-3-(methoxymethyl)-6-methyltetrahydrobenzofuran-2,5(3H,4H)-dione (7)**




MW: 256.30 g/mol Formula: $C_{13}H_{20}O_5$

To a flame-dried round-bottom flask, **compound 4** (3 g, 14.27 mmol, 1.0 eq) was dissolved in THF (100 mL) under Ar atmosphere and was cooled to -78 °C. L-Selectride (14.3 mL, 14.27 mmol, 1.0 M in THF, 1.0 eq) was then added and the resulting mixture was stirred for 1 h at -78 °C. Acetaldehyde (4.8 mL, 85.62 mmol, 6eq) was then added and the reaction mixture was stirred for 1 h at the same temperature before it was quenched with saturated aqueous $NH_4Cl$ (15 mL). The resulting mixture was allowed to warm to room temperature and stir vigorously for an additional hour. The aqueous layer was separated and extracted three times with EtOAc (3x80 mL). The combined organic extracts were dried over $NaSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 8:1 hexane: EtOAc to 1:2 hexane: EtOAc to afford pure **compound 7** (2.7 g, 75%).

**Physical state:** white solid.

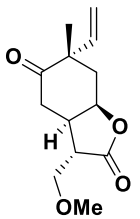
**TLC:** $R_f$ = 0.47 (hexane:EtOAc = 1:3, UV inactive on TLC, stains brown upon *p*-anisaldehyde staining).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 4.96 (td, *J* = 7.7, 5.5 Hz, 1H), 3.84 (dq, *J* = 6.6, 3.8 Hz, 1H), 3.70 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.60 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.34 (s, 3H), 3.06 (m, 1H), 2.68 (dd, *J* = 14.7, 6.8 Hz, 1H), 2.55 – 2.45 (m, 2H), 2.30 (dd, *J* = 15.0, 5.5 Hz, 1H), 1.98 (dd, *J* = 15.1, 7.6 Hz, 1H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.10 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 214.8, 176.1, 75.5, 71.3, 70.8, 59.2, 50.2, 48.0, 41.3, 37.9, 37.5, 18.7, 17.6.

**HRMS (ESI, m/z):** calcd. for $C_{13}H_{20}O_5Na^+$ ($[M+Na]^+$): 279.1208, found: 279.1233.

**(3*S*,3a*R*,6*S*,7a*R*)-3-(methoxymethyl)-6-methyl-6-vinyltetrahydrobenzofuran-2,5(3H,4H)-dione (9)**




MW: 238.28 g/mol Formula: $C_{13}H_{18}O_4$

**Compound 7** (2.6 g, 10.14 mmol, 1.0 eq) was dissolved in toluene (30 mL) in a sealed tube, before Burgess reagent (7.2 g, 30.42 mmol, 3.0 eq) was added and the reaction mixture was left stirring at 80 °C for 12 h.

Then, silica gel triturated by triethylamine was added (2.8 mL, 20.28 mmol, 2 eq) and the resulting mixture was left stirring at 80 °C for additional 12 h. The reaction was quenched with NH4Cl (10 mL) and the aqueous layer was separated and extracted three times with EtOAc (3x20 mL). The combined organic extracts were dried over $NaSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 10:1 hexane: EtOAc to 1:2 hexane: EtOAc to afford pure **Compound 9** (2.1 g, 85%).

**Physical state:** white solid.

**TLC:** $R_f$ = 0.65 (hexane:EtOAc = 1:3, UV active on TLC, stains greenish upon *p*-anisaldehyde staining).

**$[\alpha]^{20}_D$** = +73.7 (*c* 0.7, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 5.82 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.19 (d, *J* = 10.7 Hz, 1H), 5.09 (d, *J* = 17.6 Hz, 1H), 4.91 (ddd, *J* = 9.7, 7.9, 6.4 Hz, 1H), 3.71 (dd, *J* = 9.3, 4.6 Hz, 1H), 3.61 (dd, *J* = 9.3, 3.4 Hz, 1H), 3.35 (s, 3H), 2.99 – 2.89 (m, 1H), 2.64 (dd, *J* = 15.9, 6.2 Hz, 1H), 2.58 – 2.46 (m, 3H), 1.92 (dd, *J* = 14.3, 9.9 Hz, 1H), 1.20 (s, 3H).

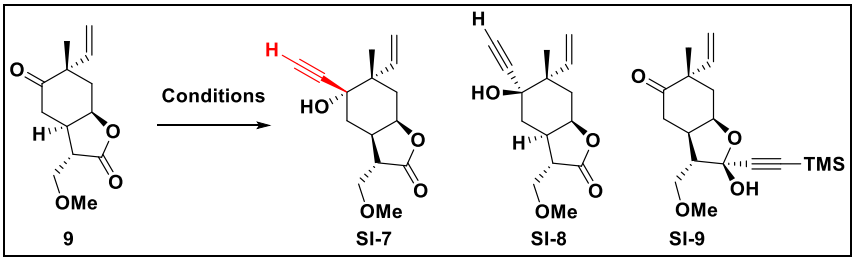
**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 210.5, 176.1, 139.6, 115.6, 75.0, 70.9, 59.3, 49.7, 47.4, 40.3, 38.3, 36.2, 24.9.

**HRMS (ESI, m/z):** calcd. for $C_{13}H_{19}O_4^+$ ([M+H]$^+$): 239.1283, found: 239.1270.

### 4.4 Introduction of acetylene chain and deprotection (steps 5-6)

Addition of lithium TMS-acetylene in **9** in THF followed by the subsequent basic hydrolysis of TMS- resulted in compounds **SI-7** and **SI-8** in a ratio of 1.5:1. Performing the addition reaction in different solvents and temperatures utilizing different metals did not led to improvement of the diastereomeric ratio of the addition (Table 10). It is interesting to notice that when ether was used as solvent, the delivery of a significant amount of compound **SI-9** was delivered, corresponding to the addition of acetylene to lactone functionality without its ring opening. The latter reveals the special thermodynamics even of lactole for its closed form. Finally, the use of ethynyl magnesium bromide for the desired alkylation delivered compounds **SI-7** and **SI-8** in a 3.5:1 diastereomeric ratio, majoring the desired anti-positioned **SI-7** (Table S4).

**Table S4.** Optimization for the addition of chain.



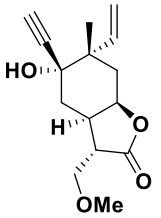

| Entry | Conditions | Conversion | Products and Yields |
|---|---|---|---|
| 1* | **9**, TMS-acetylene (1.5 equiv), n-BuLi (1.3 equiv), $Et_2O$, -78 °C, 1 h, followed by $K_2CO_3$, MeOH, rt, 1 h | 87% | **SI-7** (25%), **SI-8** (11%), **SI-9** (35%) |

| | | | |
|---|---|---|---|
| 2 | **9**, TMS-acetylene (1 equiv), n-BuLi (1 equiv), THF, -78 °C, followed by $K_2CO_3$, MeOH, rt, 1 h | 75% | **SI-7** (45%), **SI-8** (30%) |
| 3 | **9**, TMS-acetylene (1.8 equiv), n-BuLi (1.5 equiv), THF-hexane (1:0.3), -78 °C, 1 h, followed by $K_2CO_3$, MeOH, rt, 1 h | 70% | **SI-7** (35%), **SI-8** (35%) |
| 4 | **9**, ethynyl magnesium bromide 0.5M (1.1 equiv), THF, -78 °C, 3 h | 85% | **SI-7** (70%), **SI-8** (15%) |

* Compound **SI-8** was isolated prior to TMS- removal.

DBU-promoted deprotection of MeO- of compound **SI-7** followed, resulting in the formation of compound **3** in 64% yield over the two steps.

**(3*S*,3a*R*,5*R*,6*S*,7a*R*)-5-ethynyl-5-hydroxy-3-(methoxymethyl)-6-methyl-6-vinylhexahydrobenzofuran-2(3H)-one (SI-7)**




MW: 264.32 g/mol Formula: $C_{15}H_{20}O_4$

A solution of **compound 9** (50 mg, 0.21 mmol, 1 eq) in 3 mL THF was brought to -78 °C, before a solution of ethynyl magnesium bromide (0.46 mL, 0.5M in THF, 1.1 eq) was added slowly to the above mixture. The reaction was left stirring at the same temperature for 3 h, before it was quenched with saturated aqueous $NH_4Cl$ (5 mL). The aqueous layer was separated and extracted three times with $Et_2O$ (3x5 mL). The combined organic extracts were dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 10:1 hexane: EtOAc to 1:1 hexane: EtOAc to afford pure **Compound SI-7** (39 mg, 70%).

**Physical state:** white solid.

**TLC:** $R_f$ = 0.38 (hexane:EtOAc = 1:1, UV inactive on TLC, stains purple upon *p*-anisaldehyde staining).

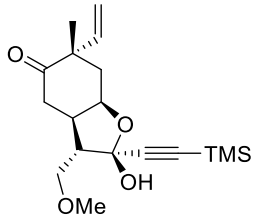
**$[\alpha]^{20}_D$** = +45.7 (*c* 1.2, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.11 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.28 (d, *J* = 11.0 Hz, 1H), 5.19 (d, *J* = 17.7 Hz, 1H), 4.82 (q, *J* = 5.0 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.62 (dd, *J* = 9.5, 3.2 Hz, 1H), 3.34 (s, 3H), 2.74 (dt, *J* = 5.0, 2.5 Hz, 2H), 2.53 (d, *J* = 1.2 Hz, 1H), 2.18 (dd, *J* = 15.3, 4.9 Hz, 1H), 2.15 – 2.06 (m, 2H), 1.96 – 1.89 (m, 1H), 1.28 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 177.4, 142.2, 116.1, 85.7, 77.1, 74.4, 73.8, 71.0, 59.4, 48.4, 42.6, 35.6, 35.2, 32.3, 24.0.

**HRMS (ESI, m/z):** calcd. for $C_{15}H_{20}O_4Na^+$ ($[M+Na]^+$): 287.1259, found: 287.1250.

**(2*S*,3*S*,3a*R*,6*S*,7a*R*)-2-hydroxy-3-(methoxymethyl)-6-methyl-2-((trimethylsilyl)ethynyl)-6-vinylhexahydrobenzofuran-5(4H)-one (SI-9)**




MW: 336.50 g/mol Formula: $C_{18}H_{28}O_4Si$

A solution of TMS-acetylene (33 µL, 0.233 mmol, 1.5 eq) in 1 mL $Et_2O$ was added to a flame-dried round-bottom flask under Ar atmosphere and the solution was cooled to 0 °C before n-BuLi (80 µL, 0.202 mmol, 2.5M in THF, 1.3 eq) was added dropwise. The resulting mixture was left stirring for 5 min at 0 °C and for additional 15 min at room temperature whereupon it was brought to -78 °C, before a solution of compound **9** (37 mg, 0.155 mmol, 1 eq) in 3 mL $Et_2O$ was added slowly to the above mixture. The reaction was left stirring at the same temperature for 1 h, before it was quenched with saturated aqueous $NH_4Cl$ (5 mL). The aqueous layer was separated and extracted three times with $Et_2O$ (3x5 mL). The combined organic extracts were dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 80:1 hexane: EtOAc to 50:1 hexane: EtOAc to afford pure **Compound SI-9** (18 mg, 35%).

**Physical state:** yellowish oil.

**TLC:** $R_f$ = 0.59 (hexane:EtOAc = 1:1, UV inactive on TLC, stains red upon *p*-anisaldehyde staining).

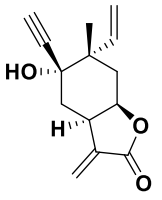
**$[\alpha]^{20}_D$** = -36.3 (*c* 0.7, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 5.77 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.09 (d, *J* = 10.7 Hz, 1H), 5.04 (d, *J* = 17.6 Hz, 1H), 4.56 (td, *J* = 11.1, 4.1 Hz, 1H), 4.04 (s, 1H), 3.66 (m, 2H), 3.38 (s, 3H), 2.68 – 2.58 (m, 2H), 2.47 – 2.37 (m, 1H), 2.36 – 2.25 (m, 2H), 1.21 (s, 3H), 0.18 (s, 9H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 213.1, 140.3, 114.4, 102.6, 97.4, 88.6, 73.7, 70.2, 59.2, 56.8, 48.9, 41.8, 37.8, 37.1, 25.4, -0.3.

**HRMS (ESI, m/z):** calcd. for $C_{18}H_{28}O_4SiNa^+$ ($[M+Na]^+$): 359.1655, found: 359.1680.

**(3a*R*,5*S*,6*R*,7a*R*)-5-ethynyl-5-hydroxy-6-methyl-3-methylene-6-vinylhexahydrobenzofuran-2(3H)-one (3)**



MW: 232.28 g/mol Formula: $C_{14}H_{16}O_3$

Compound **SI-7** (31 mg, 0.117 mmol, 1eq) was dissolved in toluene (5 mL) in a sealed tube before DBU (0.7 mL, 4.457 mmol, 38 eq) was added and the reaction mixture was left stirring at 120 °C overnight. The reaction was quenched with HCl 1N (1 mL) and extracted three times with ethyl acetate (3x5 mL). The combined organic extracts were dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed (silica gel) with gradient from 10:1 hexane: EtOAc to 4:1 hexane: EtOAc to afford pure **Compound 3** (24 mg, 90%).

**Physical state:** white solid.

**TLC:** $R_f$ = 0.45 (DCM:MeOH = 20:1, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

**$[\alpha]^{20}_D$** = +52.6 (*c* 1.5, $CHCl_3$).

**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.18 (d, *J* = 1.5 Hz, 1H), 6.12 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.62 (d, *J* = 1.2 Hz, 1H), 5.30 (d, *J* = 11.0 Hz, 1H), 5.19 (d, *J* = 17.6 Hz, 1H), 4.61 (td, *J* = 5.2, 2.9 Hz, 1H), 3.23 (ddd, *J* = 11.3, 7.1, 5.6 Hz, 1H), 2.50 (s, 1H), 2.25 – 2.13 (m, 2H), 2.02 – 1.91 (m, 2H), 1.29 (s, 3H).

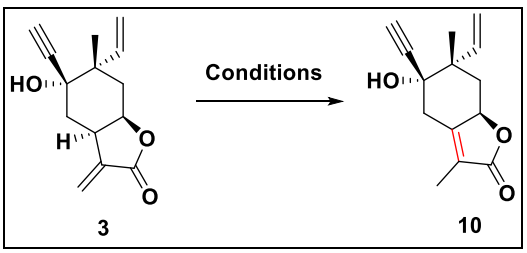
**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 170.2, 142.8, 140.4, 121.8, 115.8, 84.9, 75.8, 74.2, 70.7, 41.9, 36.2, 35.8, 31.0, 23.8.

**HRMS (ESI, m/z):** calcd. for $C_{14}H_{16}O_3Na^+$ ($[M+Na]^+$): 255.0997, found: 255.0981.

### 4.5 Isomerization of *α*-methylene-*γ*-butenolide to *α,β*-unsaturated butanolide (step 7)

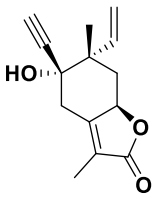
Several conditions were screened for the isomerization of exomethylene group to compound **10**, all providing unreacted starting material (Table S5). Fortuitously, conditions reported by Shenvi's group allowed the clean isomerization to unsaturated lactone **10** in 85% yield. Direct reduction by DIBAL resulted the common scaffold **1**.

**Table S5.** Selected reactions for isomerization of **3**.




| Entry | Conditions | Conversion | Yield |
|---|---|---|---|
| **1** | Grubbs 2$^{nd}$ gen., $CHCl_3$, 40 °C, 4 h | 0% | - |
| **2** | Wilkinson cat., toluene, 80 °C, o/n | 0% | - |
| **3** | Co(Salen$^{tBu,tBu}$)Cl, $PhSiH_3$, benzene, 60 °C, 1 h | 100% | **10** (85%) |

**(5*S*,6*R*,7a*R*)-5-ethynyl-5-hydroxy-3,6-dimethyl-6-vinyl-5,6,7,7a-tetrahydrobenzofuran-2(4H)-one (10)**




MW: 232.28 g/mol Formula:$C_{14}H_{16}O_3$

A solution of **compound 3** (24 mg, 0.096 mmol, 1.0 eq) in 2 mL benzene was charged in a flame-dried Schlenk apparatus and degassed under an Ar atmosphere for 5 minutes before Co(Salen$^{tBu,tBu}$)Cl (6 mg, 10 mol%) was added very quickly to the above solution. The resulting dark green mixture was further deggased for 10 min before phenylsilane (1.2 µL, 10 mol%) was added. The reaction was then left at 60 °C until completion for 80 min, whereupon it was partially evaporated and directly chromatographed (silica gel) with gradient from 6:1 hexane: EtOAc to 2:1 hexane: EtOAc to afford pure **compound 10** (19 mg, 85%).

**Physical state:** white solid.

**TLC:** $R_f$ = 0.42 (hexane:EtOAc = 1:1, UV active on TLC, stains pink upon *p*-anisaldehyde staining).

**[α]$^{20}_D$** = +45.7 (*c* 1.2, $CHCl_3$).

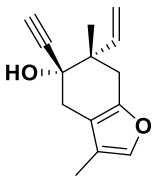
**$^1$H NMR (500 MHz, $CDCl_3$)** δ = 6.25 (dd, *J* = 17.9, 11.1 Hz, 1H), 5.36 (d, *J* = 2.1 Hz, 1H), 5.33 (d, *J* = 4.3 Hz, 1H), 4.95 – 4.88 (m, 1H), 3.09 (d, *J* = 13.2 Hz, 1H), 2.63 (d, *J* = 13.5 Hz, 1H), 2.54 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.51 (s, 1H), 2.27 (s, 1H), 1.85 (s, 3H), 1.59 (d, *J* = 12.4 Hz, 1H), 1.26 (s, 3H).

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ = 174.86, 158.28, 138.33, 123.38, 116.83, 83.68, 77.09, 75.58, 75.06, 45.54, 39.95, 38.28, 24.32, 8.31.

**HRMS (ESI, m/z):** calcd. for $C_{14}H_{16}O_3Na^+$ ([M+Na]$^+$): 255.0997, found: 255.0982.

**4.6 Reduction of *α,β*-unsaturated butanolide to common scaffold 1 (step 8)**

**(5*S*,6*R*)-5-ethynyl-3,6-dimethyl-6-vinyl-4,5,6,7-tetrahydrobenzofuran-5-ol (2)[1c]**




MW: 216.28 g/mol Formula: $C_{14}H_{16}O_2$

**Compound 10** (18 mg, 0.078 mmol, 1 eq) was dissolved in $Et_2O$ (2 mL) under Ar atmosphere and the mixture was cooled to -20 °C, before diisobutylaluminum hydride (48 µL, 0.086 mmol, 25% w/w in hexane, 1.1 eq) was added slowly. Once the addition was complete, the mixture was allowed to stir at -20 °C for 1 h before

quenching the reaction with 10% aqueous $H_2SO_4$ (60 µL). After warming to rt, the two layers were separated, and the aqueous phase was extracted four times with $Et_2O$ (4x5 mL). The combined organic extracts were dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed (neutralized silica gel) with gradient from 100:1 hexane: EtOAc to 80:1 hexane: EtOAc to afford pure **Compound 2** (15 mg, 90%).

**Physical state:** colorless oil.

**TLC:** $R_f$ = 0.46 (hexane:$Et_2O$ = 3:1, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

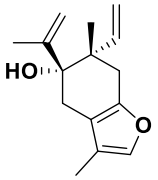
**Optical rotation and Spectra identical to the one reported earlier[1c]**

**$^1$H NMR (500 MHz, $CDCl_3$)** δ =7.09 (brs, 1H), 6.19 (brs, 1H), 5.25 (d, *J* = 12 Hz, 1H), 5.21 (d, *J* = 17 Hz, 1H), 2.95-2.80 (m, 2H), 2.77-2.53 (m, 2H), 2.49 (s, 1H), 1.93 (s, 3H), 1.26 (s, 3H)

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ=148.4, 148.3, 137.8, 119.5, 119.4, 115.4, 85.4, 73.0, 72.3, 44.7, 33.8, 26.9, 21.8, 8.1

### 4.7 Unifying the two common scaffolds 2 and 1 (step 9)

**(5R,6S)-3,6-dimethyl-5-(prop-1-en-2-yl)-6-vinyl-4,5,6,7-tetrahydrobenzofuran-5-ol (1)[1a]**




MW: 232.32 g/mol Formula: $C_{15}H_{20}O_2$

Freshly purified CuI (52 mg, 0.54 mmol, 2.0 eq) (Freshly precipitated[9] and dried CuI seemed to be crucial for a complete conversion of the reaction) was added to a flask under argon. Then dry THF (2 ml) was added and the mixture was cooled to –25 °C. Then methylmagnesium chloride (0.45 ml, 1.1 mmol, 2.5M solution in THF, 4.0 eq.) was added slowly by syringe pump addition within 100 min. The yellow mixture was stirred for 30 min at –20 °C. Next a solution of propargylic alcohol **1** (60 mg, 0.27 mmol, 1.0 eq.) in THF (2 ml) was added slowly within 10 min. The reaction mixture was allowed to warm to RT and stirred
for further 12 h. Subsequently the reaction mixture was poured into a beaker with ice cold sat. aqueous $NH_4Cl$-solution (1.5 ml) and water (0.5 ml). The black precipitate formed was filtered off through a silica plug and sand and the blue colored filtrate was extracted with $Et_2O$ (3 x 10 ml). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexane/Et2O 5:1-4:1) gave the title **compound 1** (47 mg, 73%)

**Physical state:** light yellow oil.

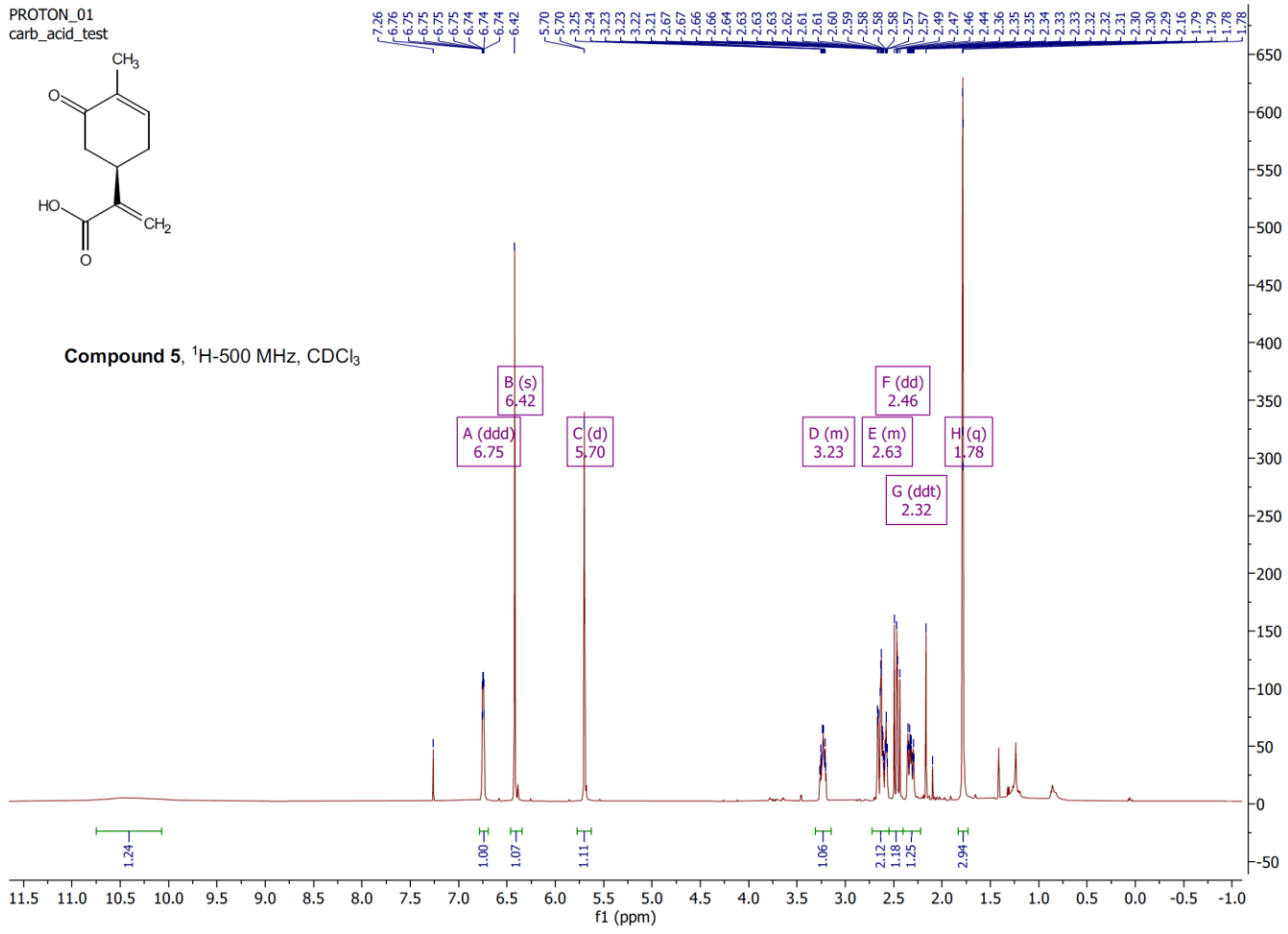
**TLC:** $R_f$ = 0.51 (hexane:$Et_2O$ = 3:1, UV active on TLC, stains purple upon *p*-anisaldehyde staining).

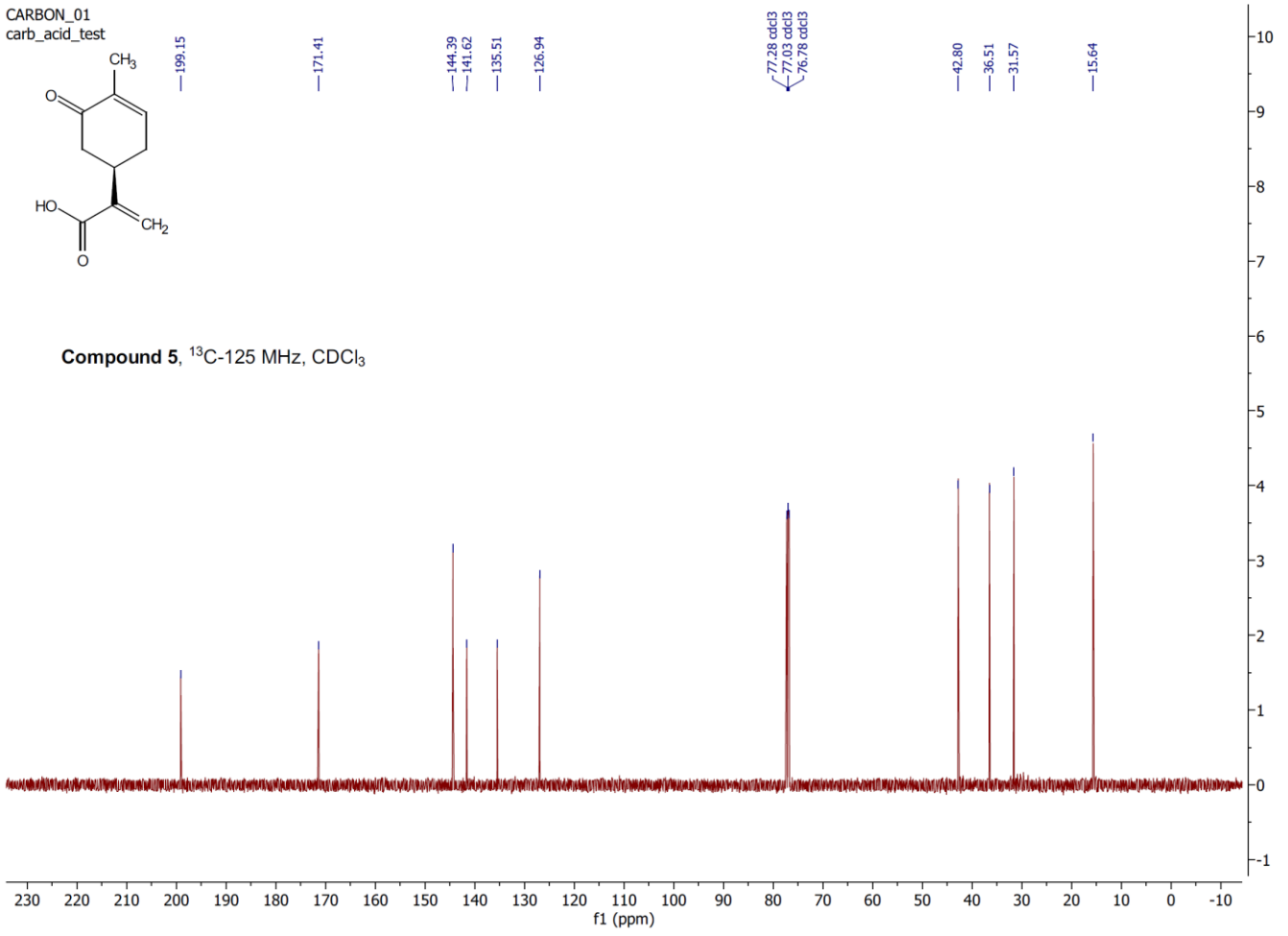
**Optical rotation and spectra identical to the one reported earlier[1a]**

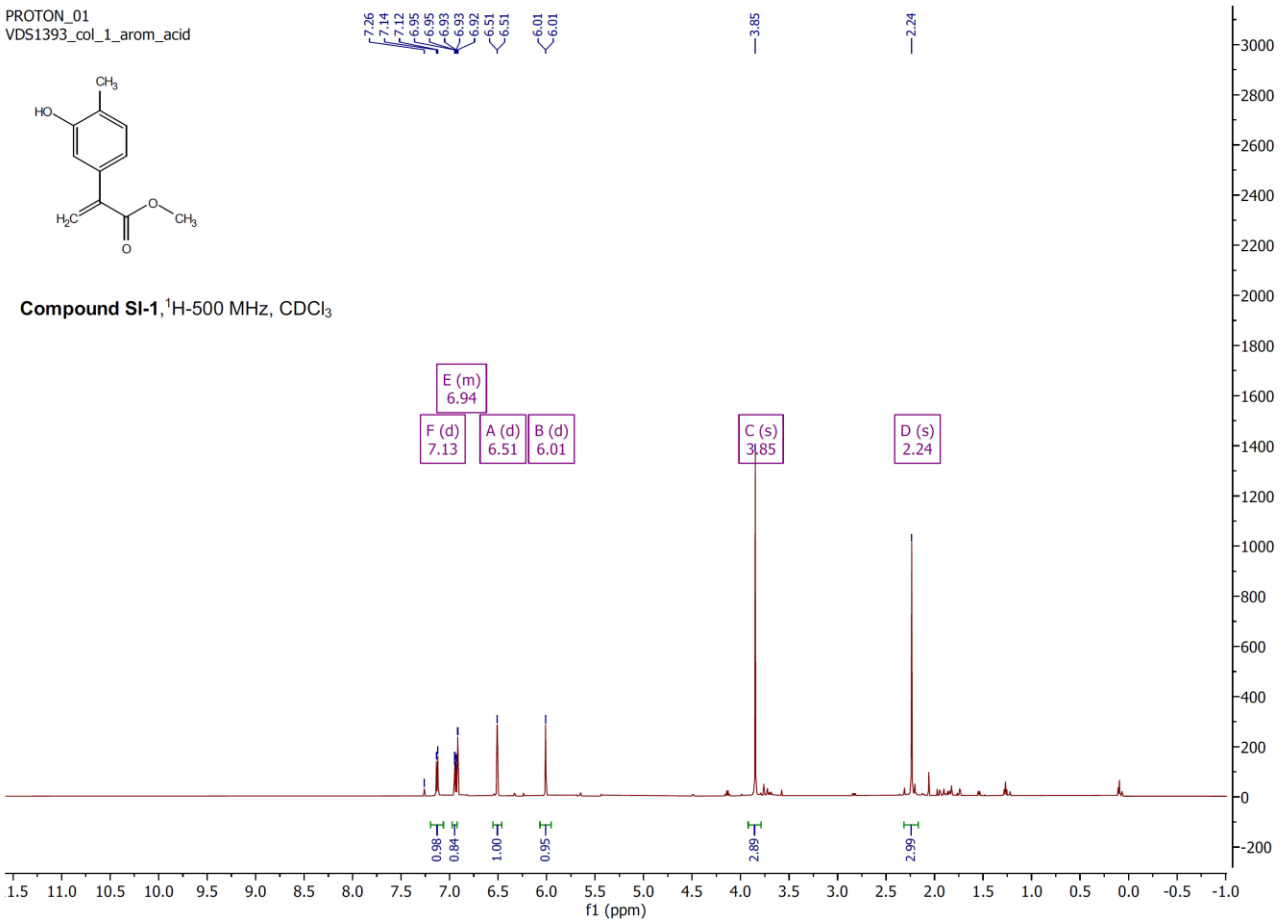
**$^{1}$H NMR (500 MHz, $CDCl_3$)** δ = 7.09 (s, 1H), 6.08 (dd, *J* = 15Hz, 10Hz, 1H), 5.14 (d, *J* = 10Hz, 1H), 5.12 (d, *J* = 15Hz, 1H), 5.06 **–** 5.0 (m, 1H), 4.95 (s, 1H), 2.90 (dd, *J* = 15Hz, 10Hz, 2H), 2.37 (dd, 20Hz, 15Hz, 2H), 1.91 (s, 3H), 1.86 (s, 3H), 1.13 (s, 3H);

**$^{13}$C NMR (125 MHz, $CDCl_3$)** δ= 148.7, 148.2, 143.5, 137.7, 119.6, 113.5, 113.2, 113.1, 77.9, 45.0, 33.3, 32.6, 22.3, 20.8, 8.0

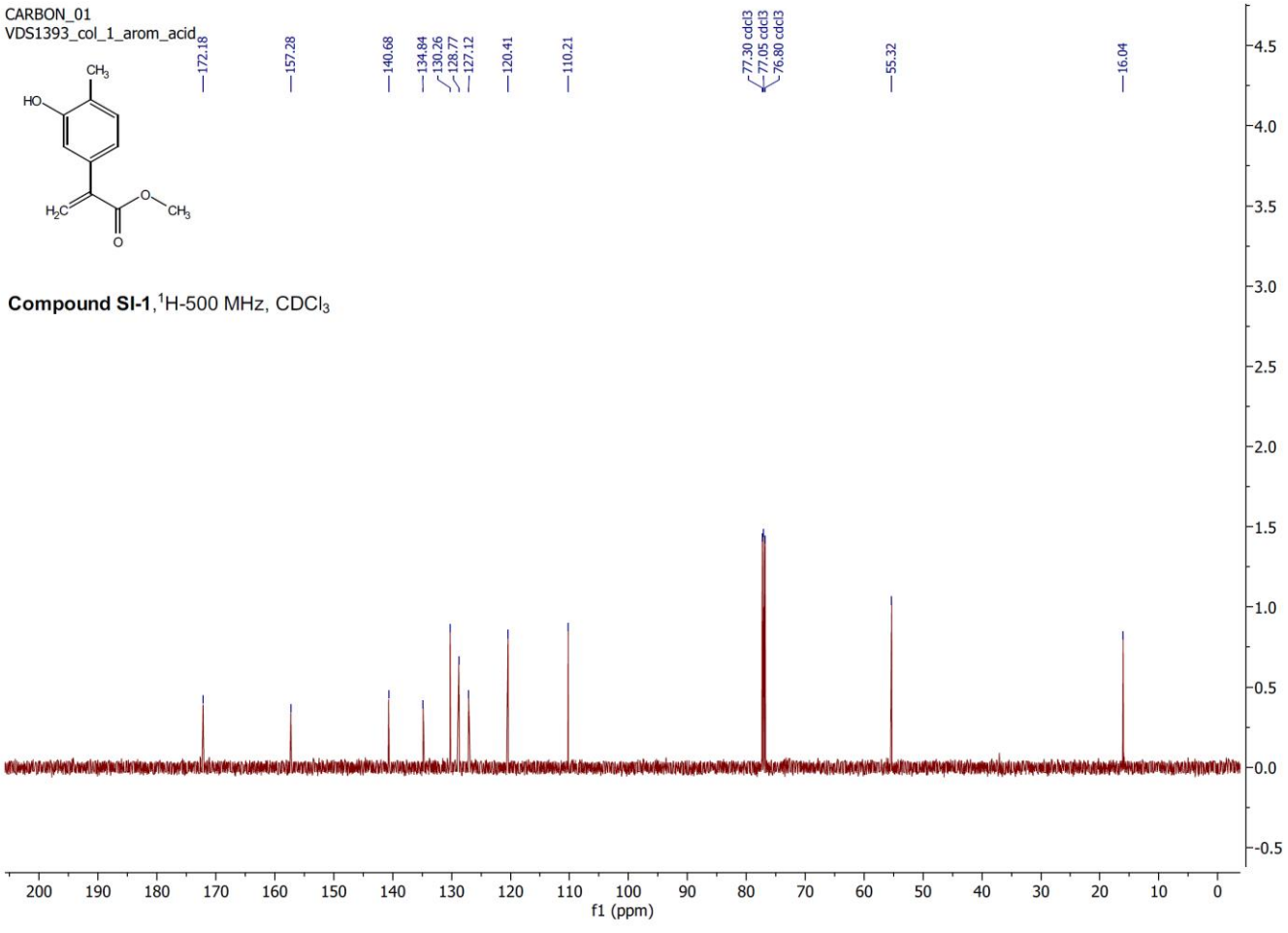
5. **NMR Spectra**



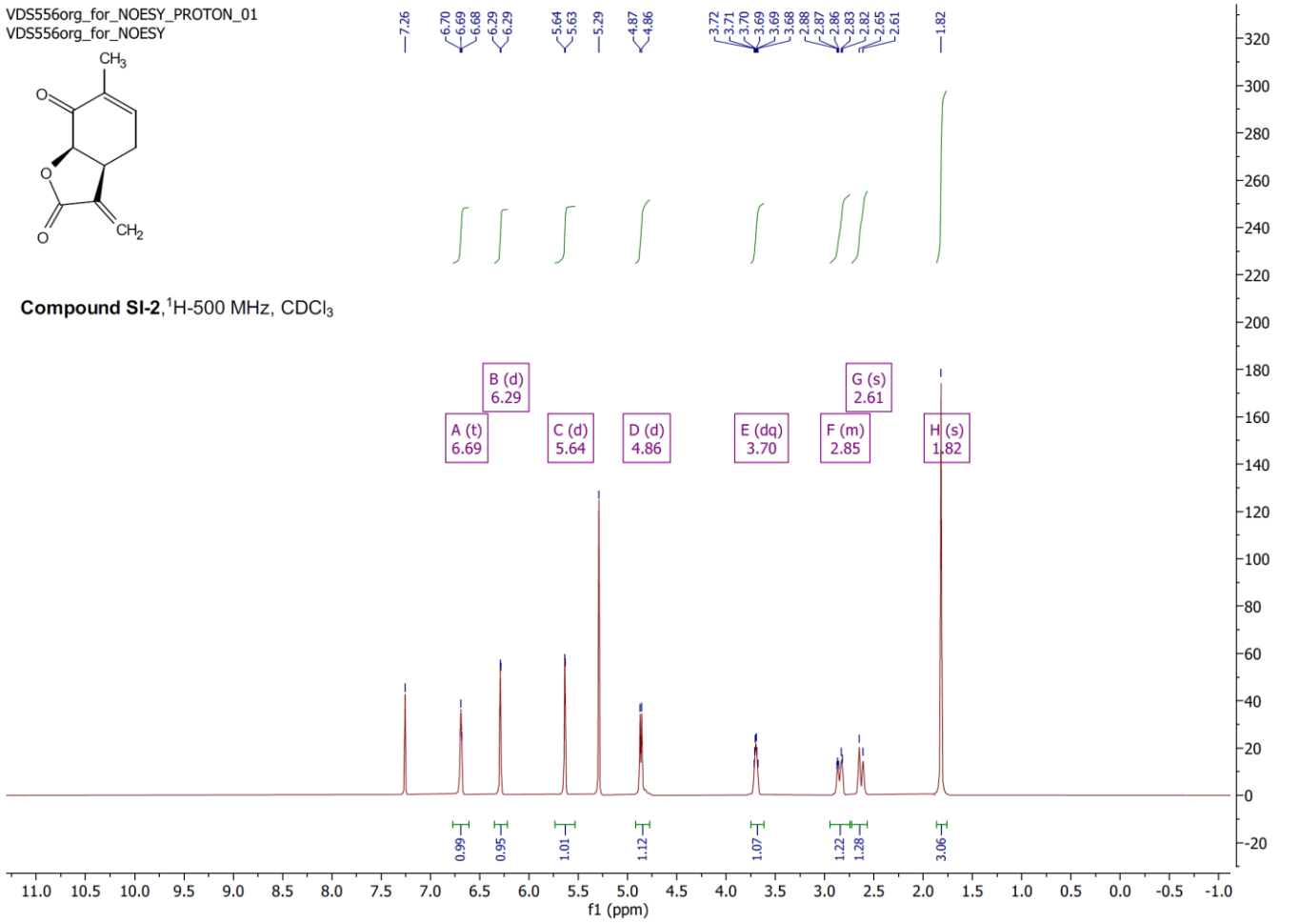





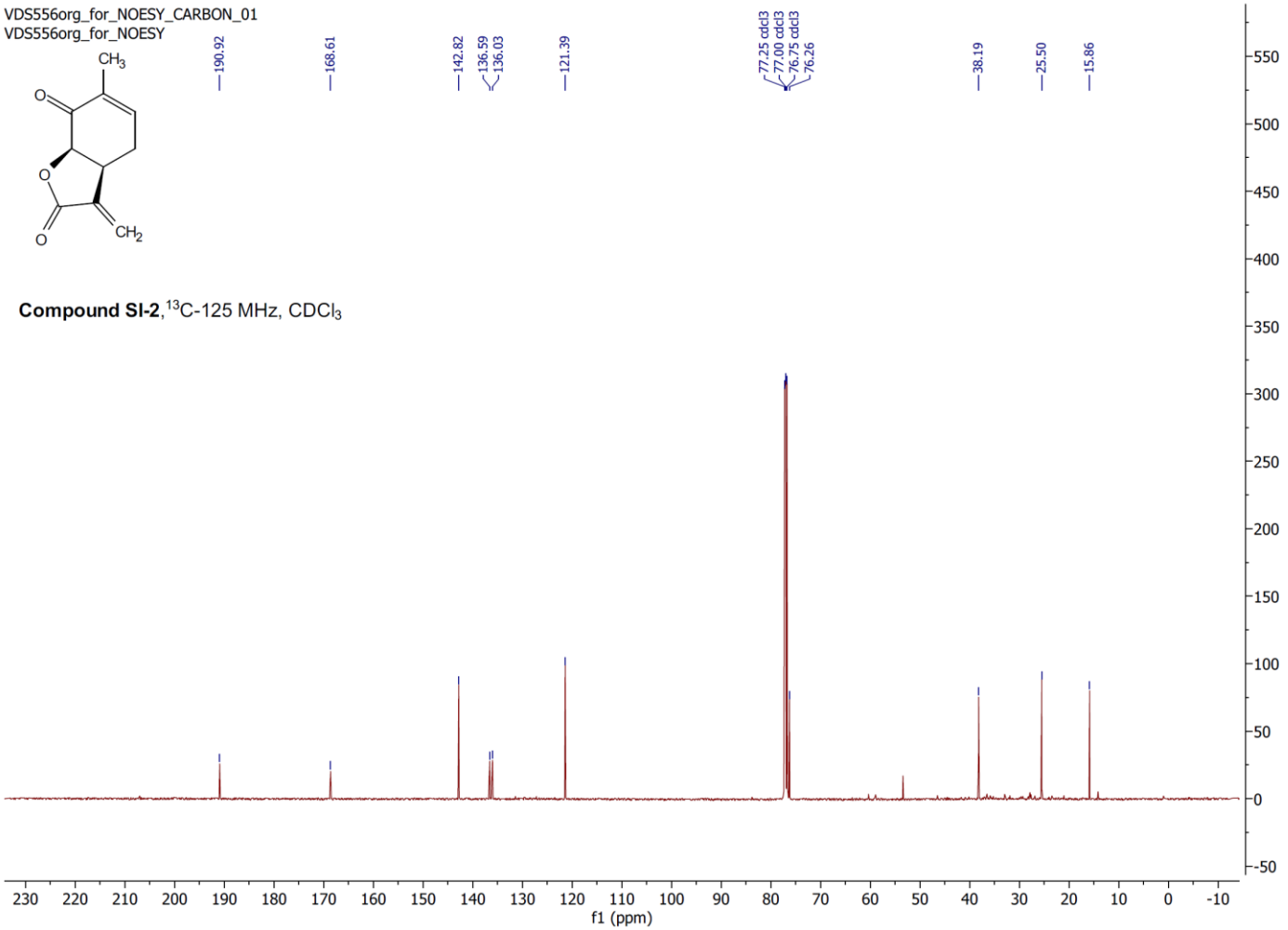

**Compound SI-1**, $^{1}$H-500 MHz, $CDCl_3$



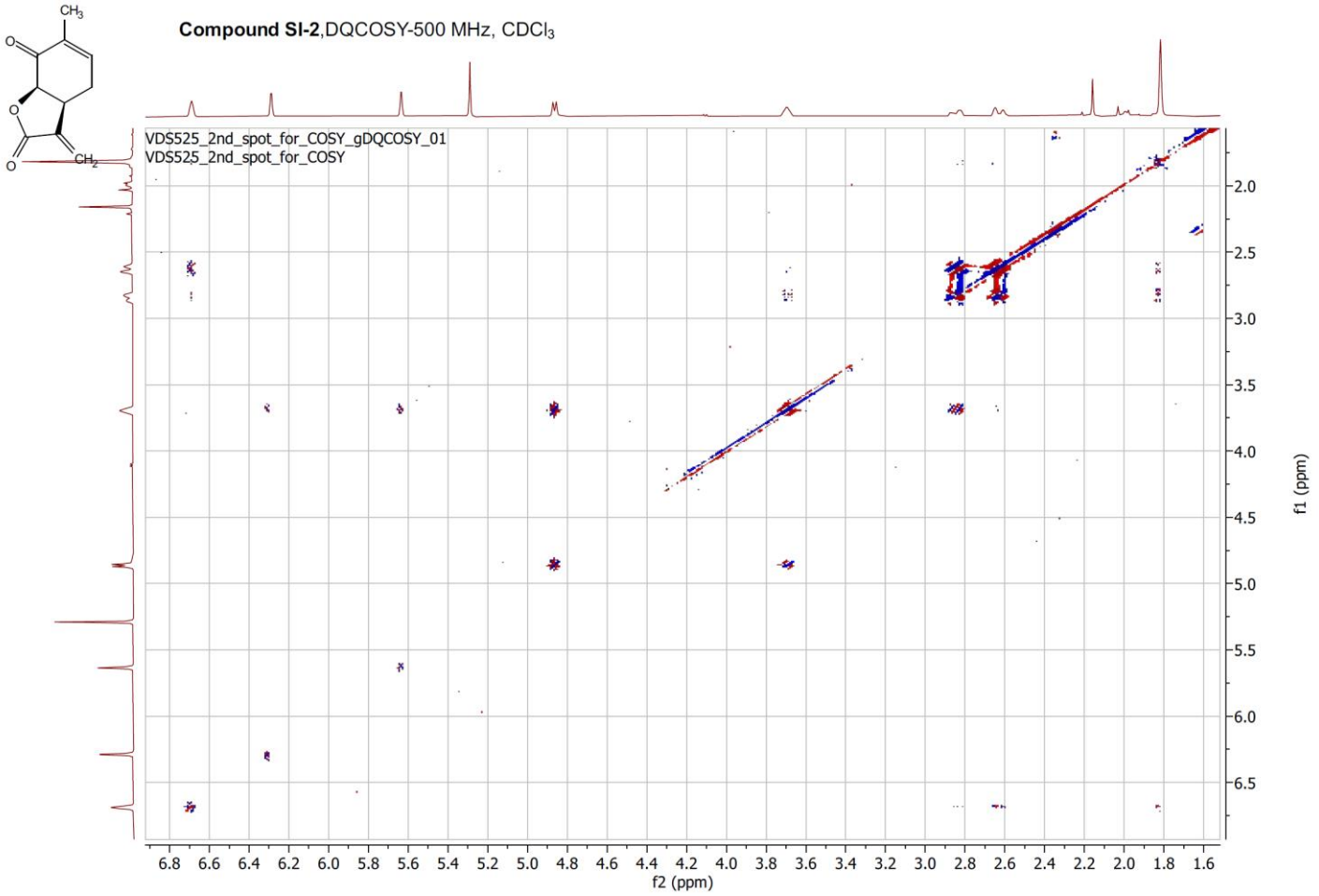

**Compound SI-1**, $^{1}$H-500 MHz, $CDCl_3$

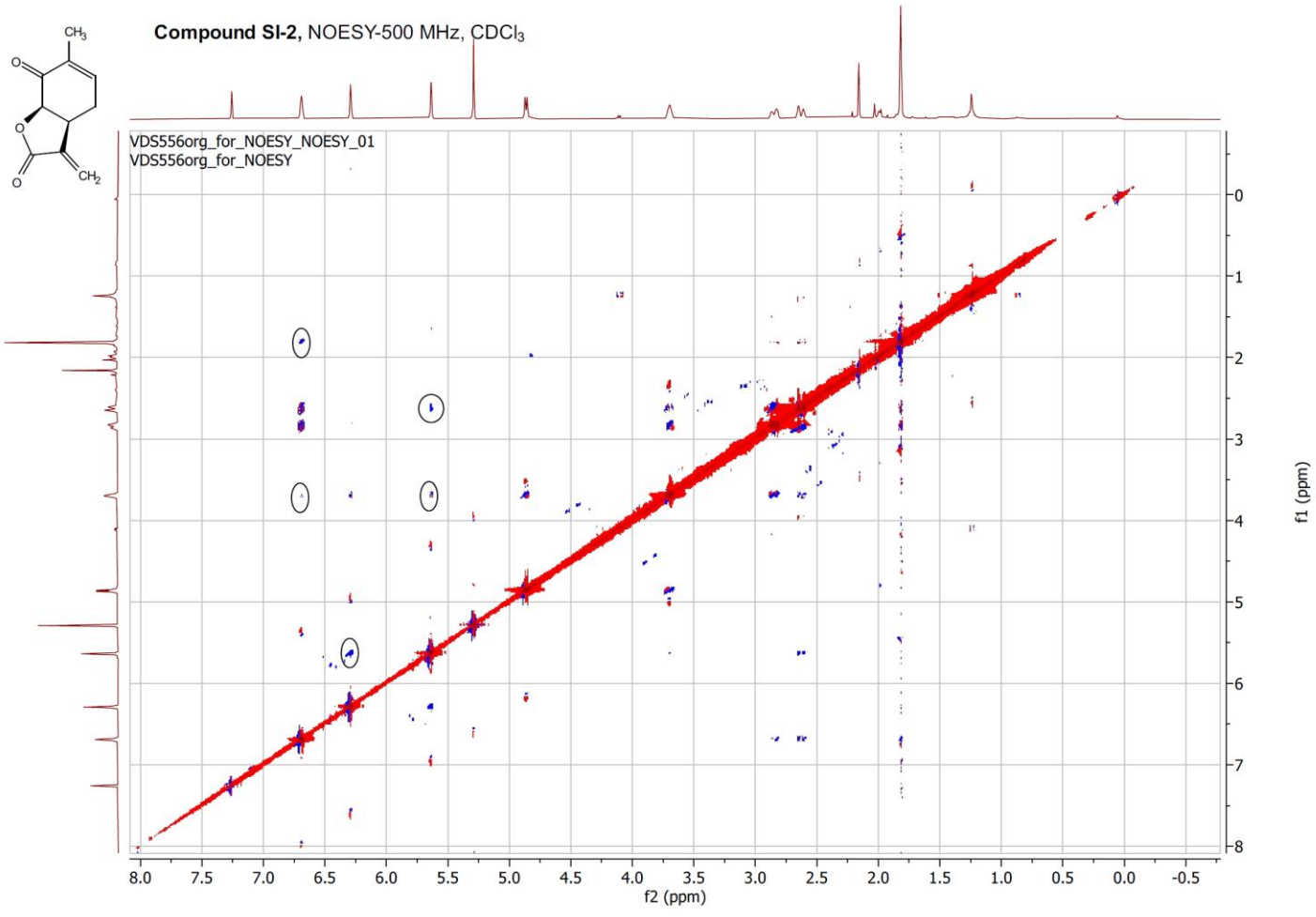


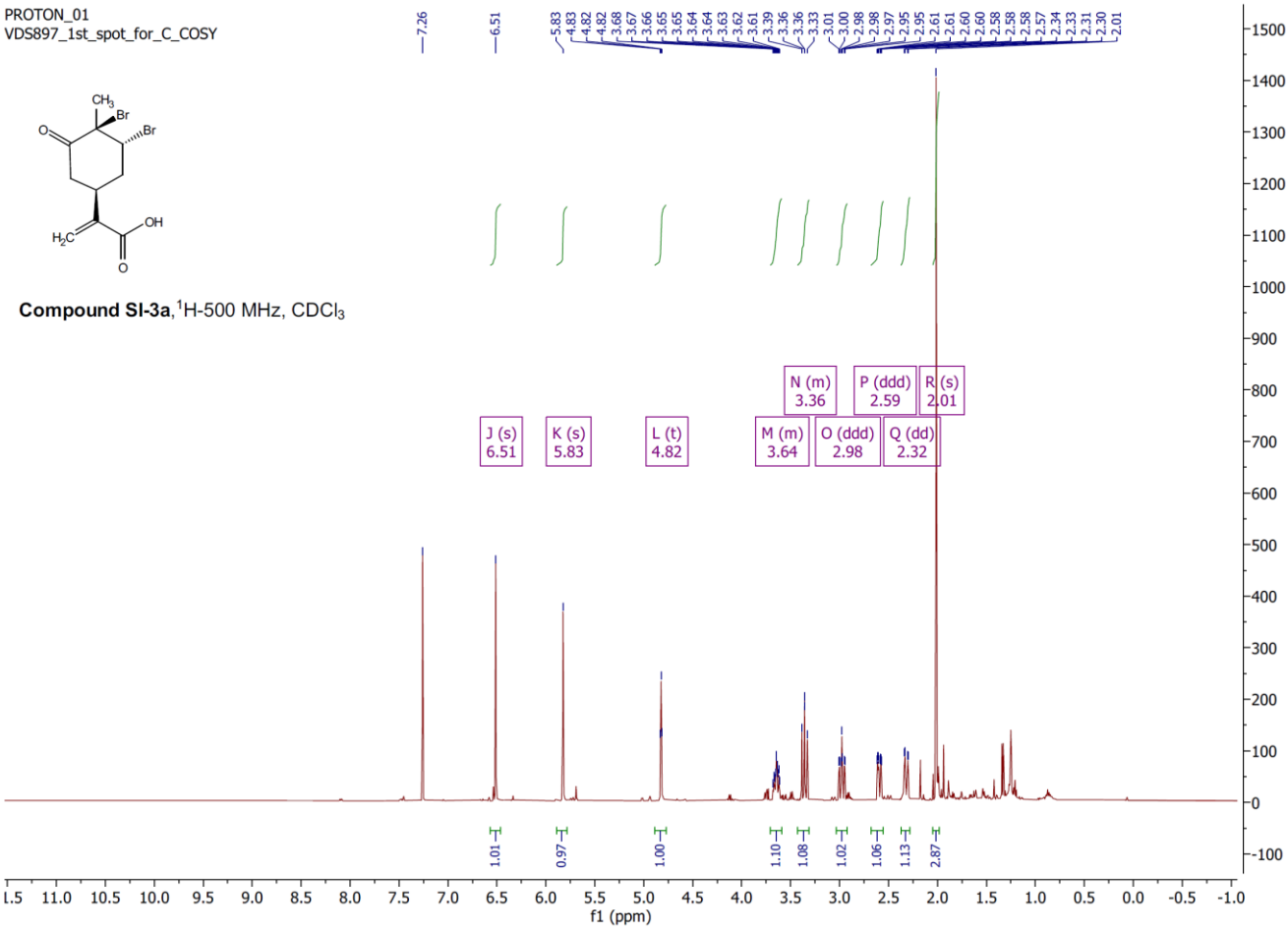

**Compound SI-2**, $^{1}$H-500 MHz, $CDCl_3$



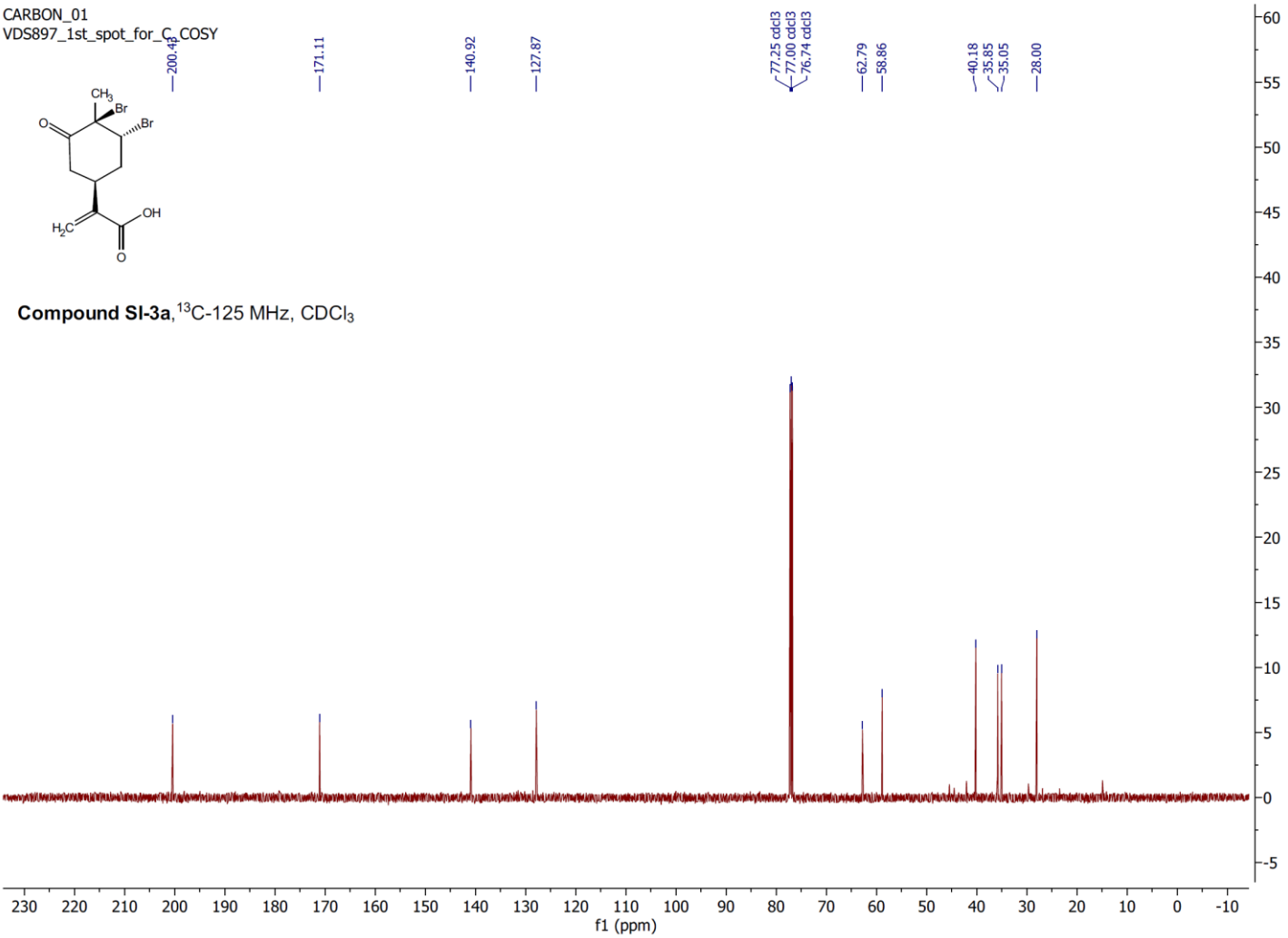

**Compound SI-2**, $^{13}$C-125 MHz, $CDCl_3$


Compound SI-2,DQCOSY-500 MHz, CDCl3
VDS525_2nd_spot_for_COSY_gDQCOSY_01
VDS525_2nd_spot_for_COSY
f2 (ppm)
f1 (ppm)

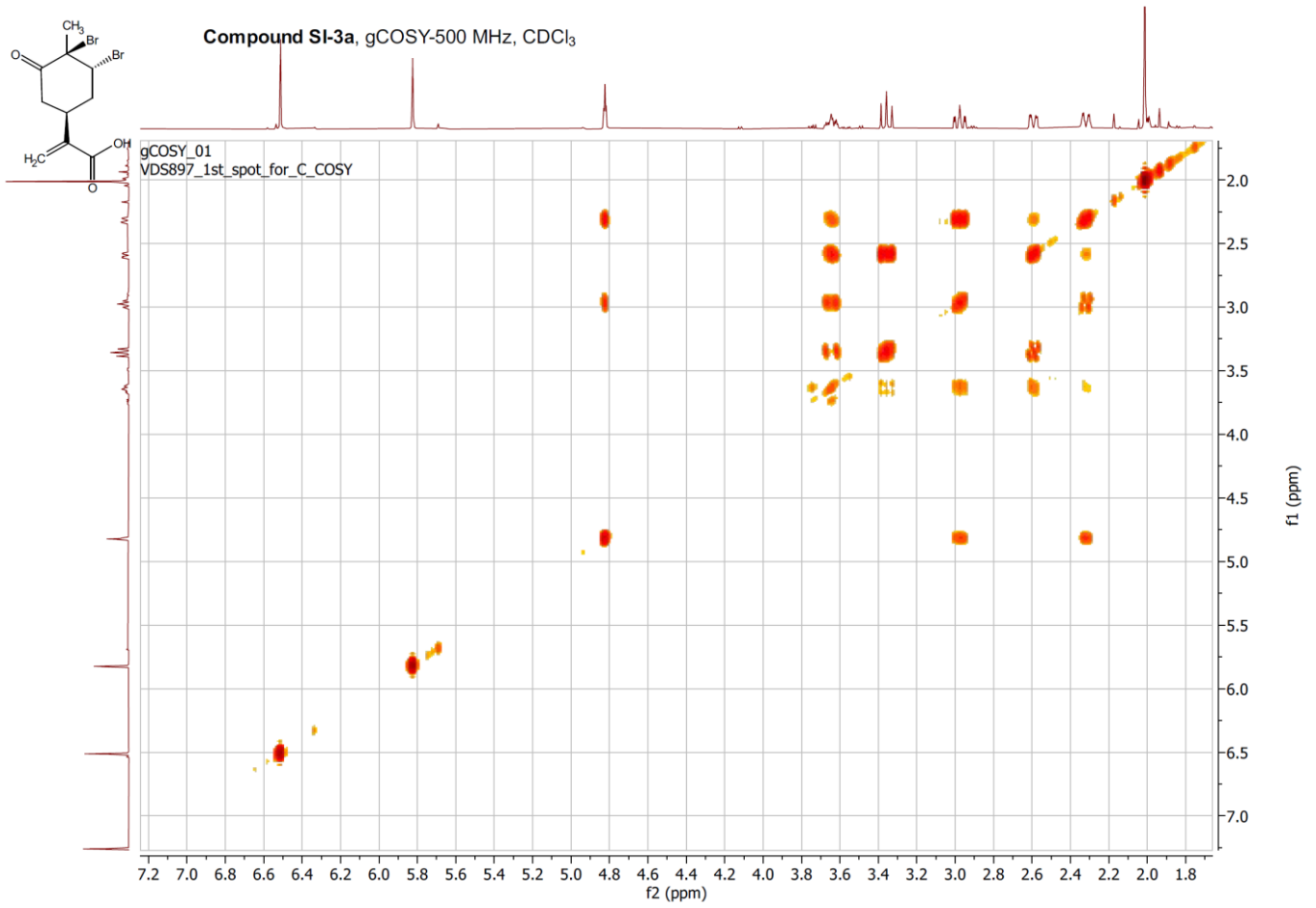

Compound SI-2, NOESY-500 MHz, CDCl3
VDS556org_for_NOESY_NOESY_01
VDS556org_for_NOESY
f2 (ppm)
f1 (ppm)

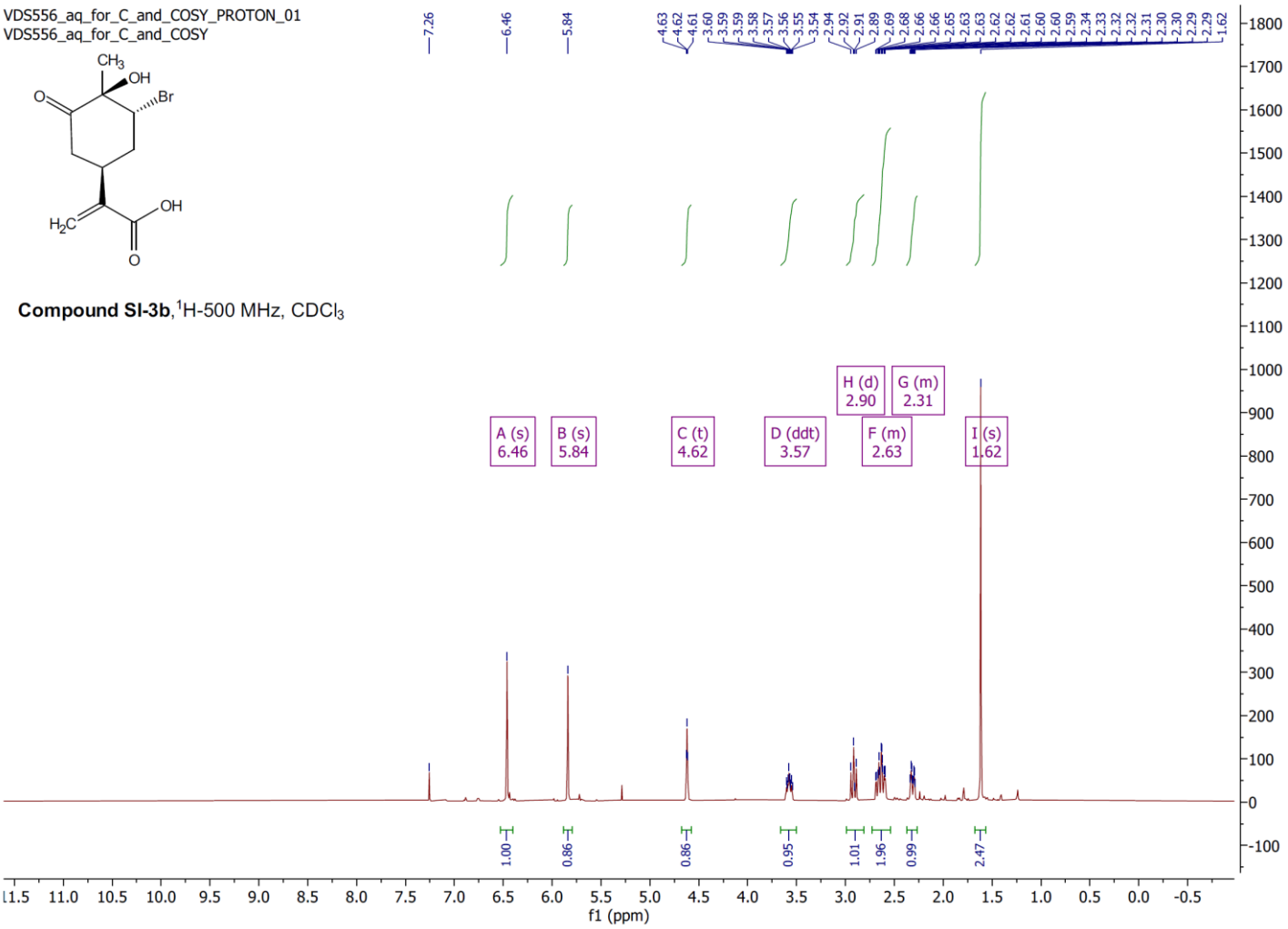


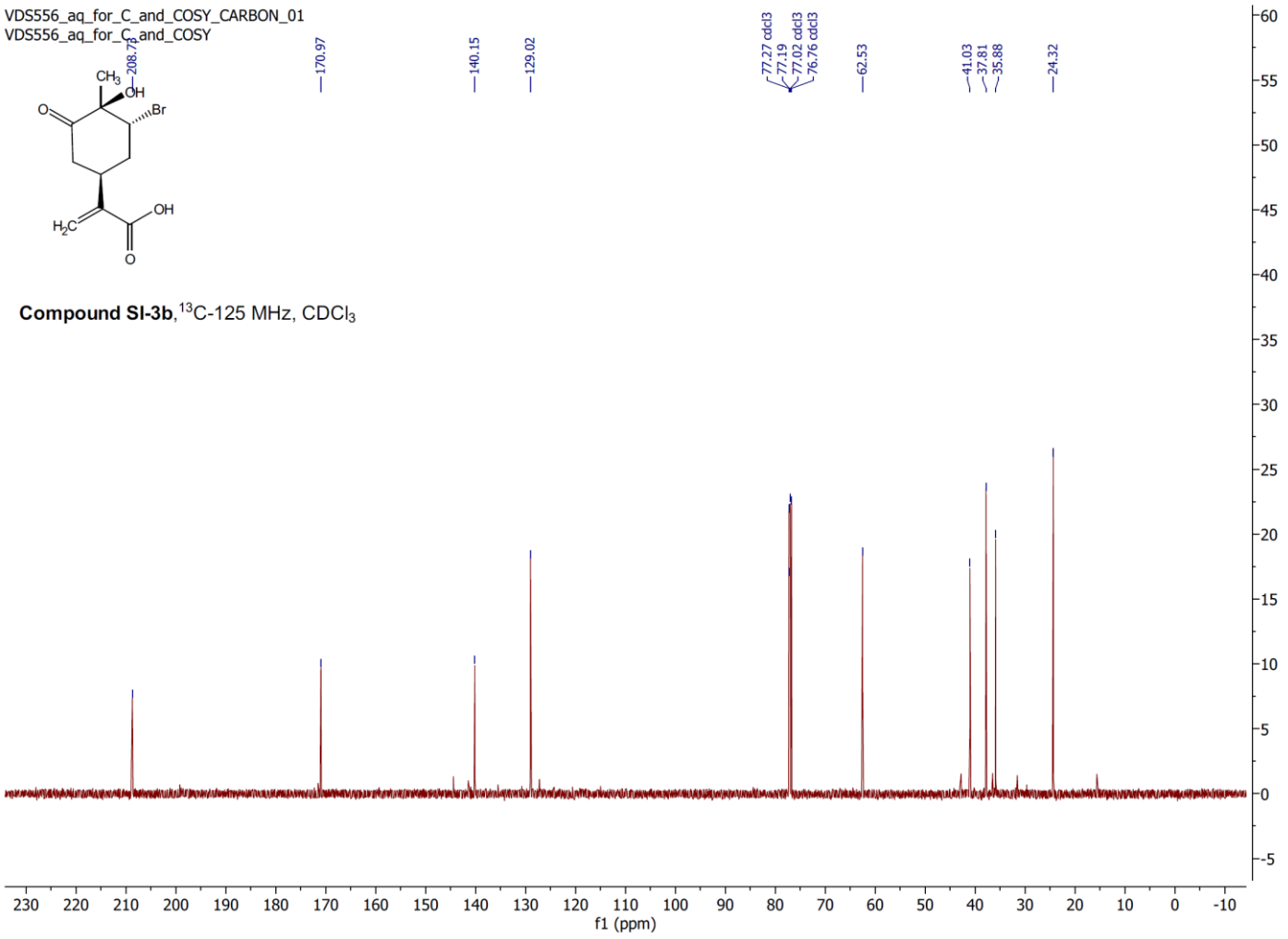

**Compound SI-3a**, $^{1}$H-500 MHz, $CDCl_3$



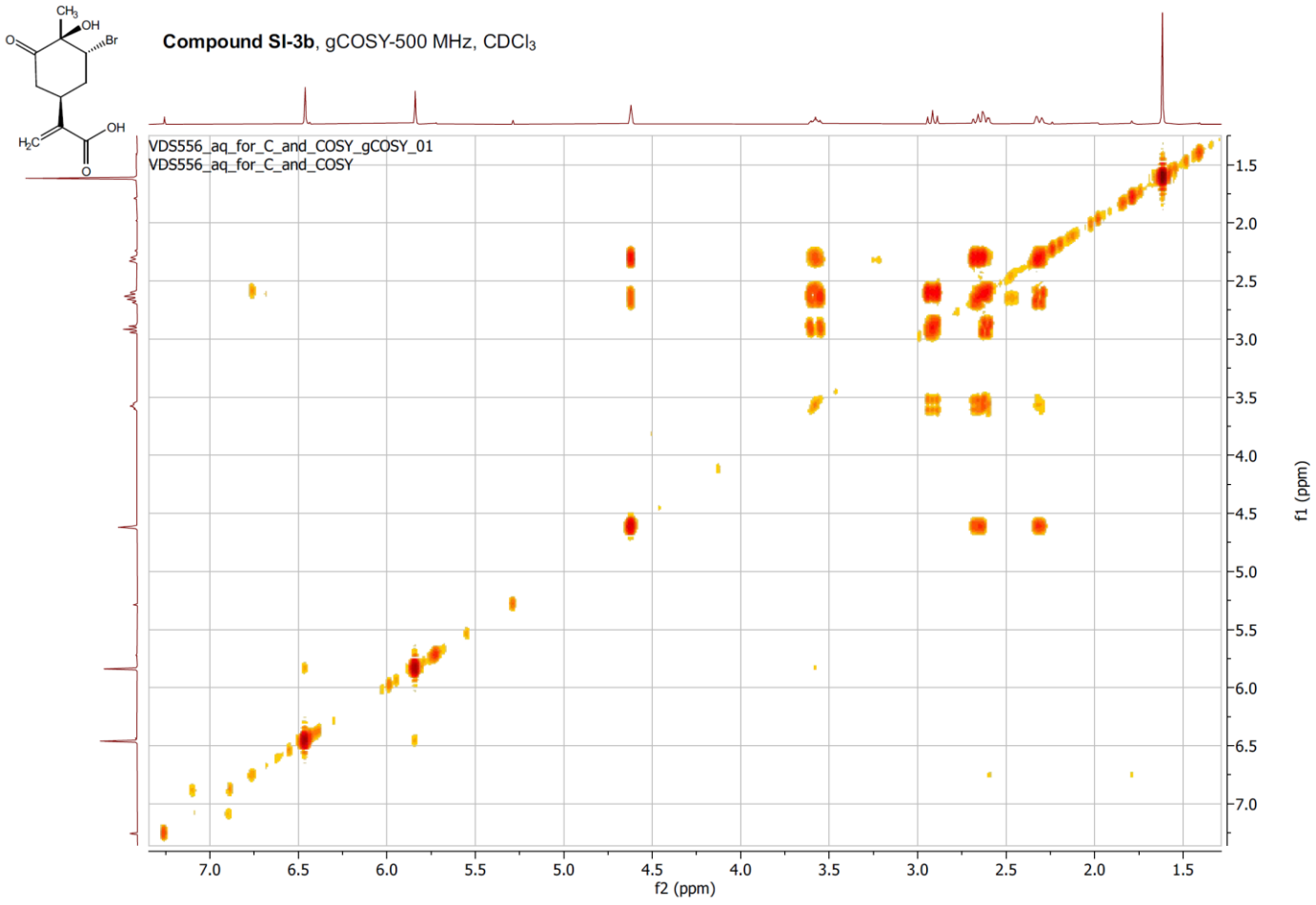

**Compound SI-3a**, $^{13}$C-125 MHz, $CDCl_3$


Compound SI-3a, gCOSY-500 MHz, CDCl3
gCOSY_01
VDS897_1st_spot_for_C_COSY
f2 (ppm)
f1 (ppm)

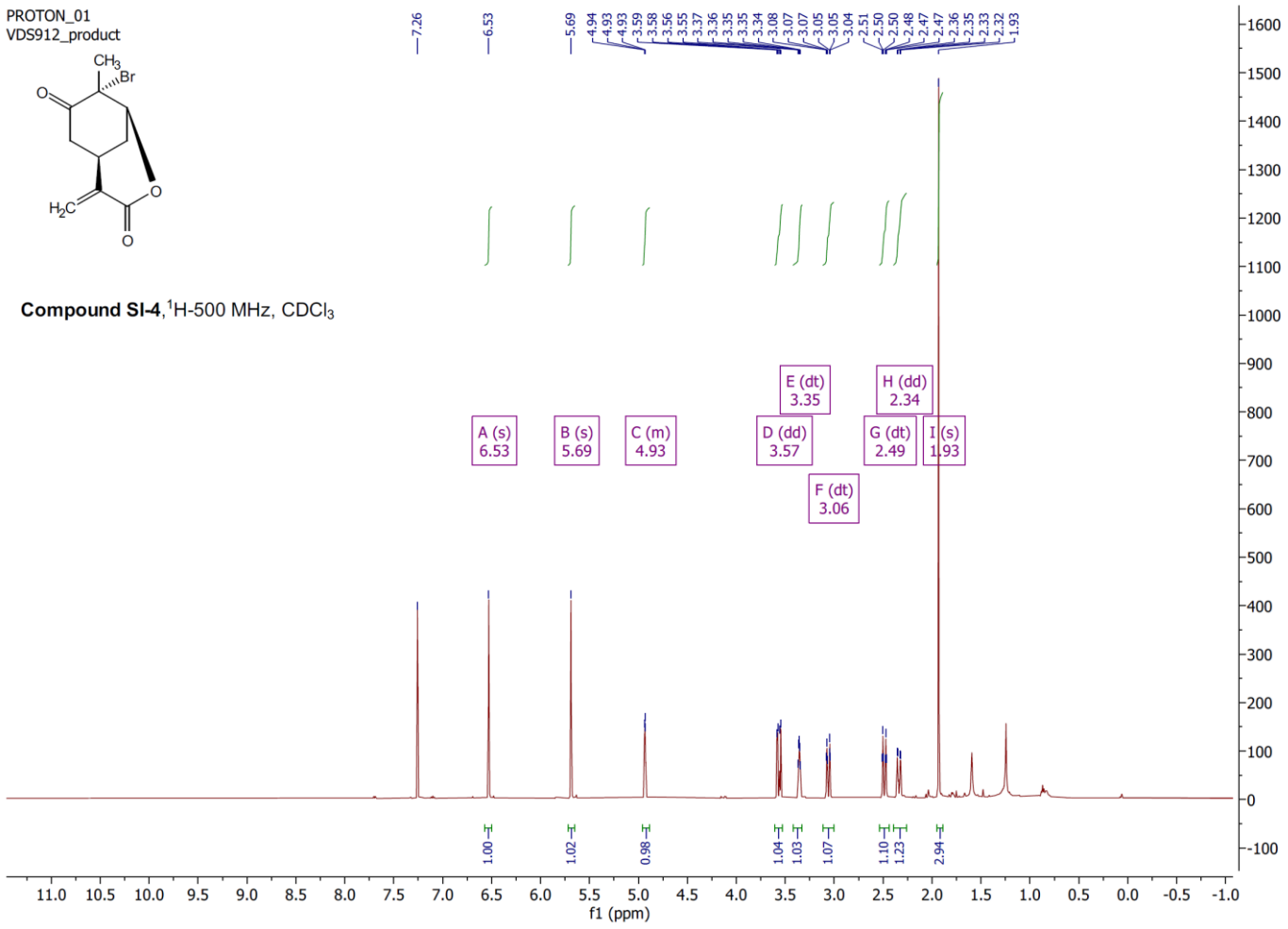

VDS556_aq_for_C_and_COSY_PROTON_01
VDS556_aq_for_C_and_COSY
Compound SI-3b, 1H-500 MHz, CDCl3
A (s) 6.46
B (s) 5.84
C (t) 4.62
D (ddt) 3.57
F (m) 2.63
G (m) 2.31
H (d) 2.90
I (s) 1.62
f1 (ppm)

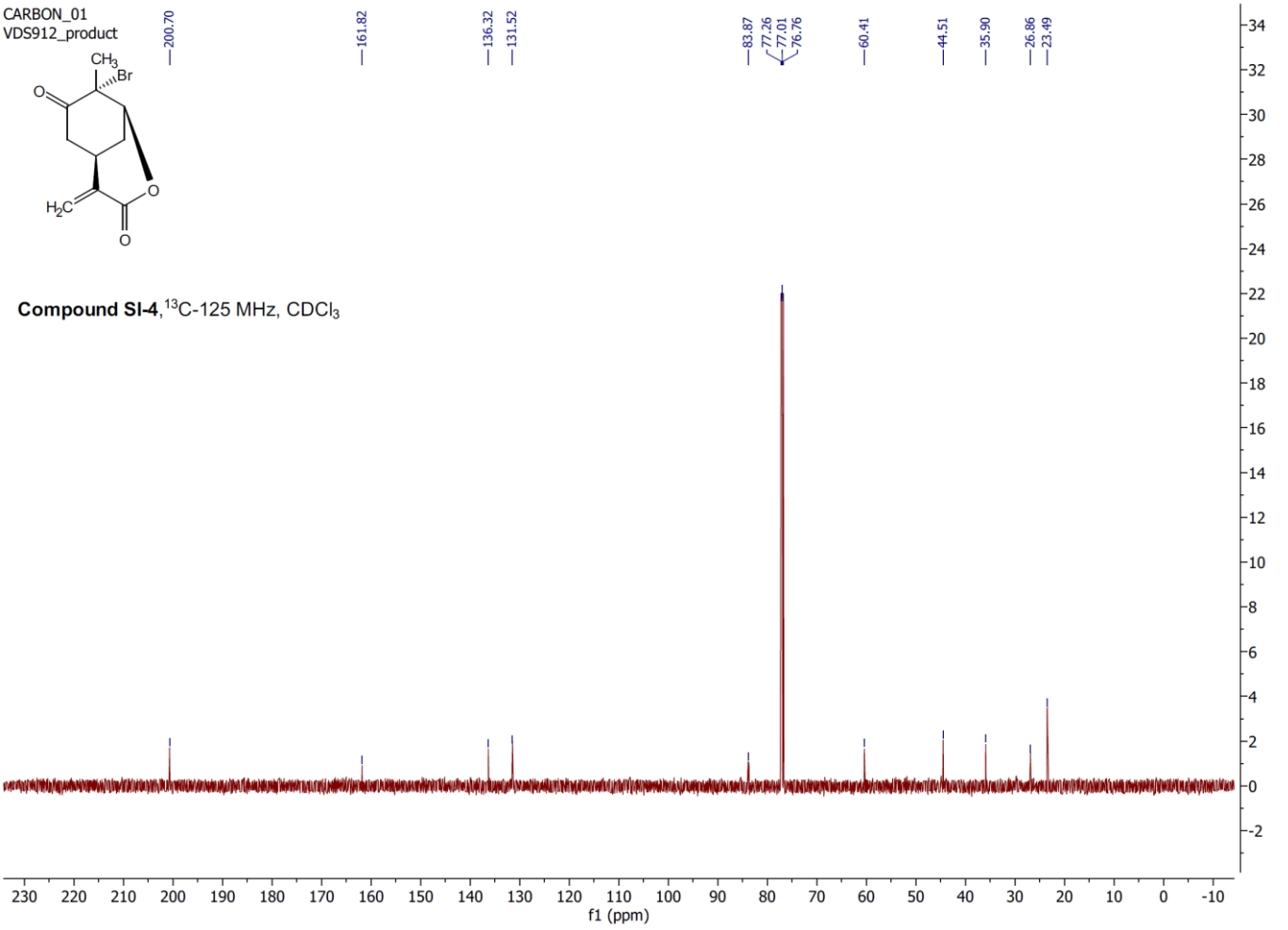


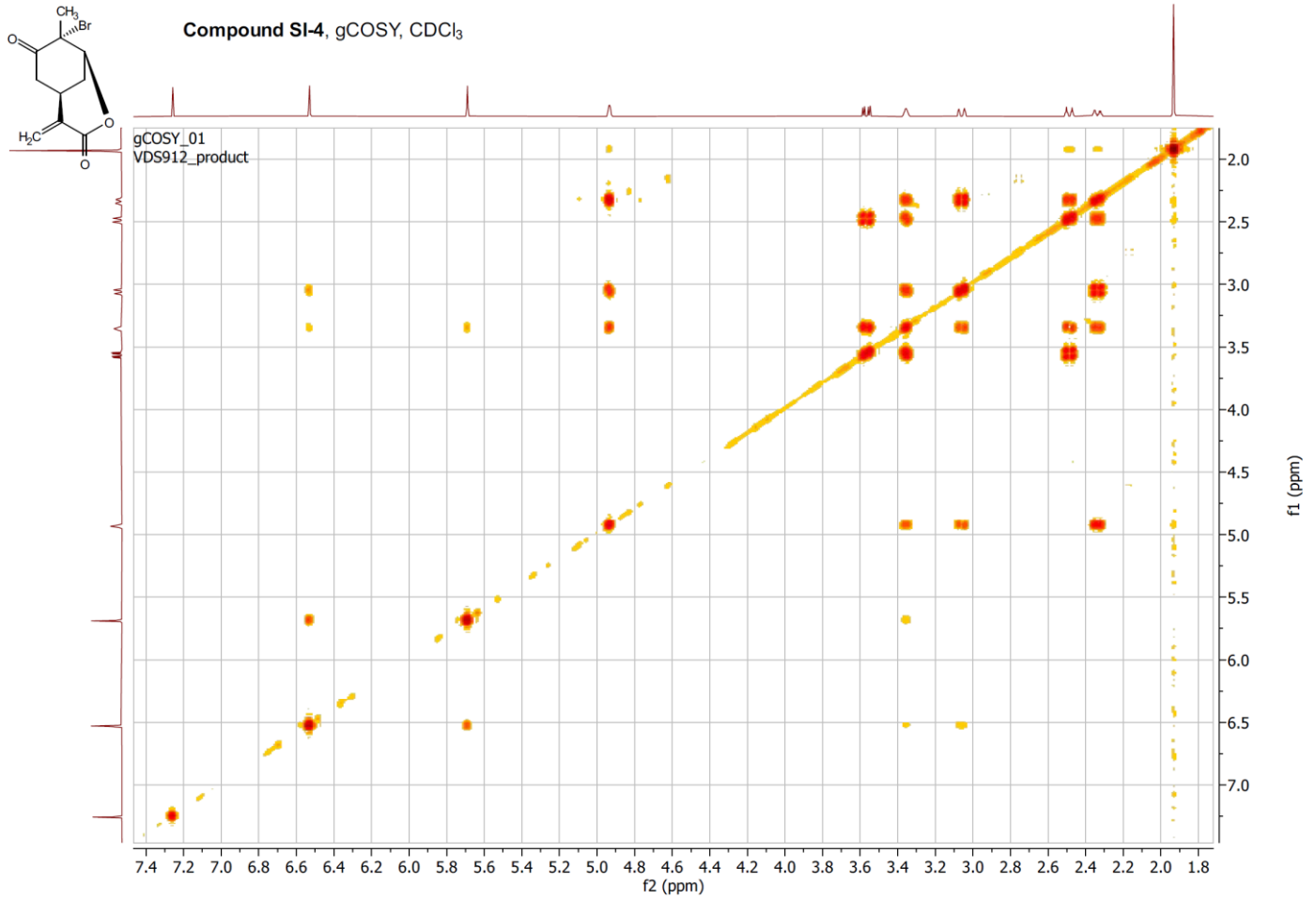

**Compound SI-3b**,$^{13}$C-125 MHz, $CDCl_3$

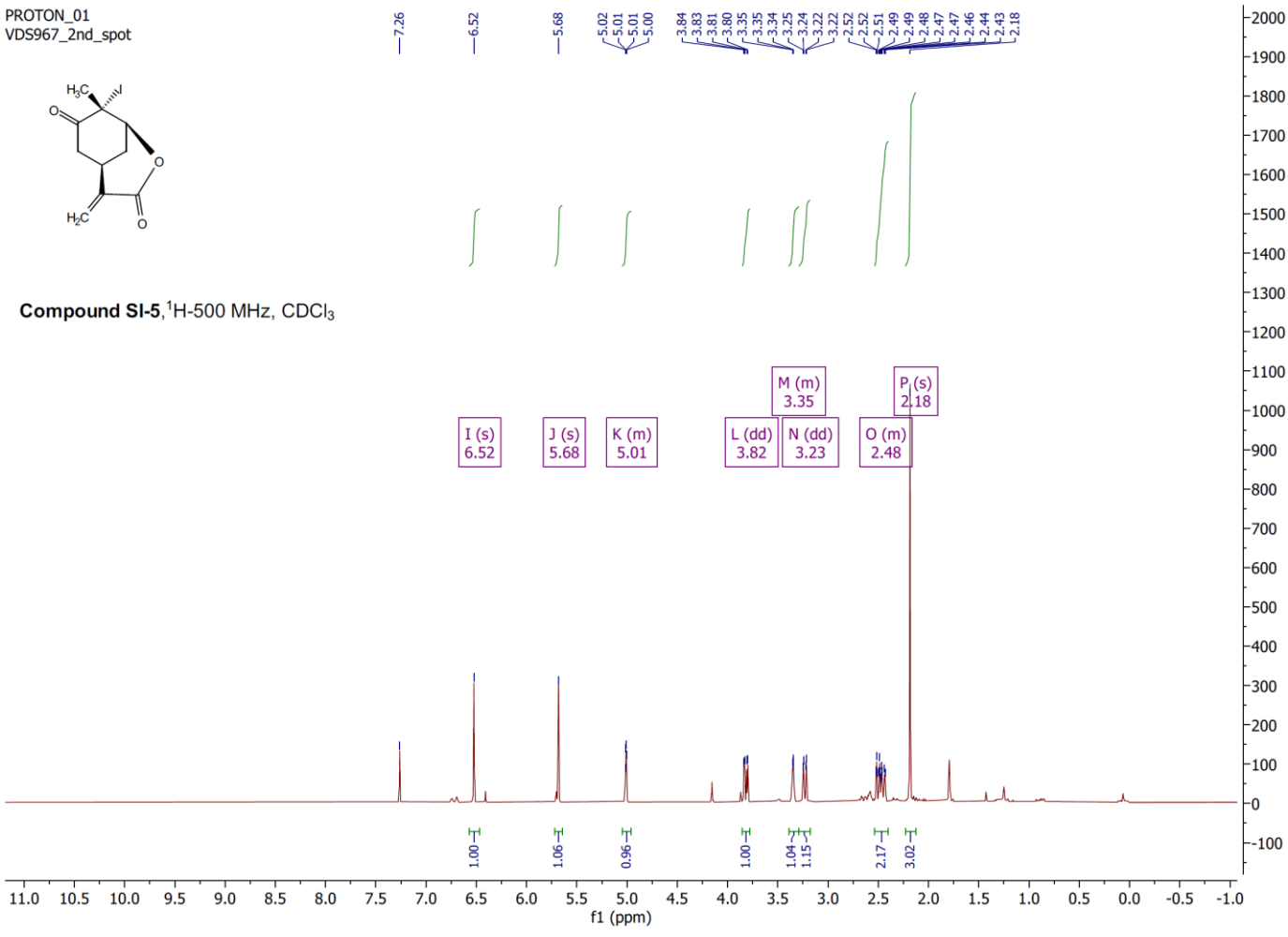


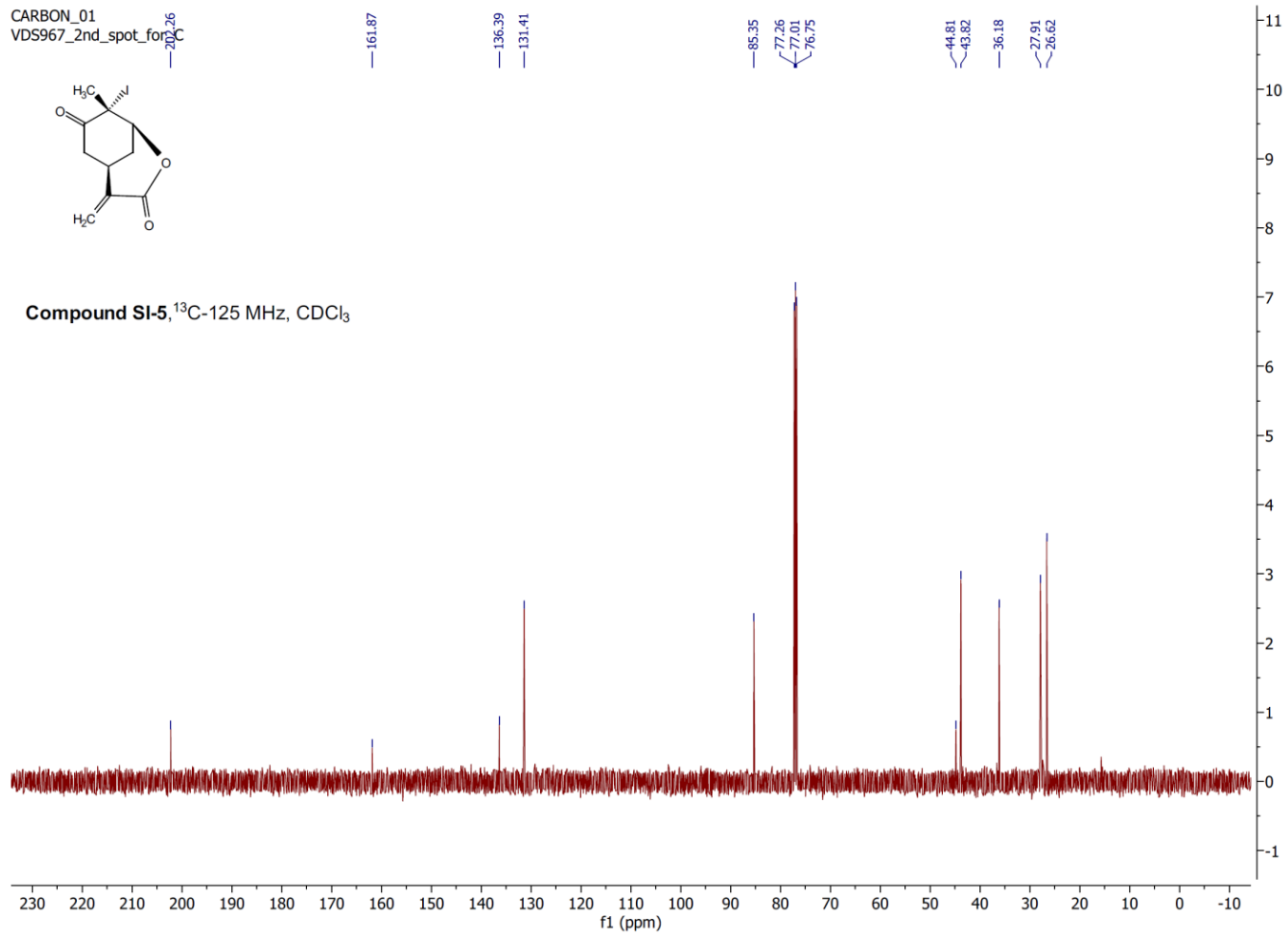

**Compound SI-3b**, gCOSY-500 MHz, $CDCl_3$

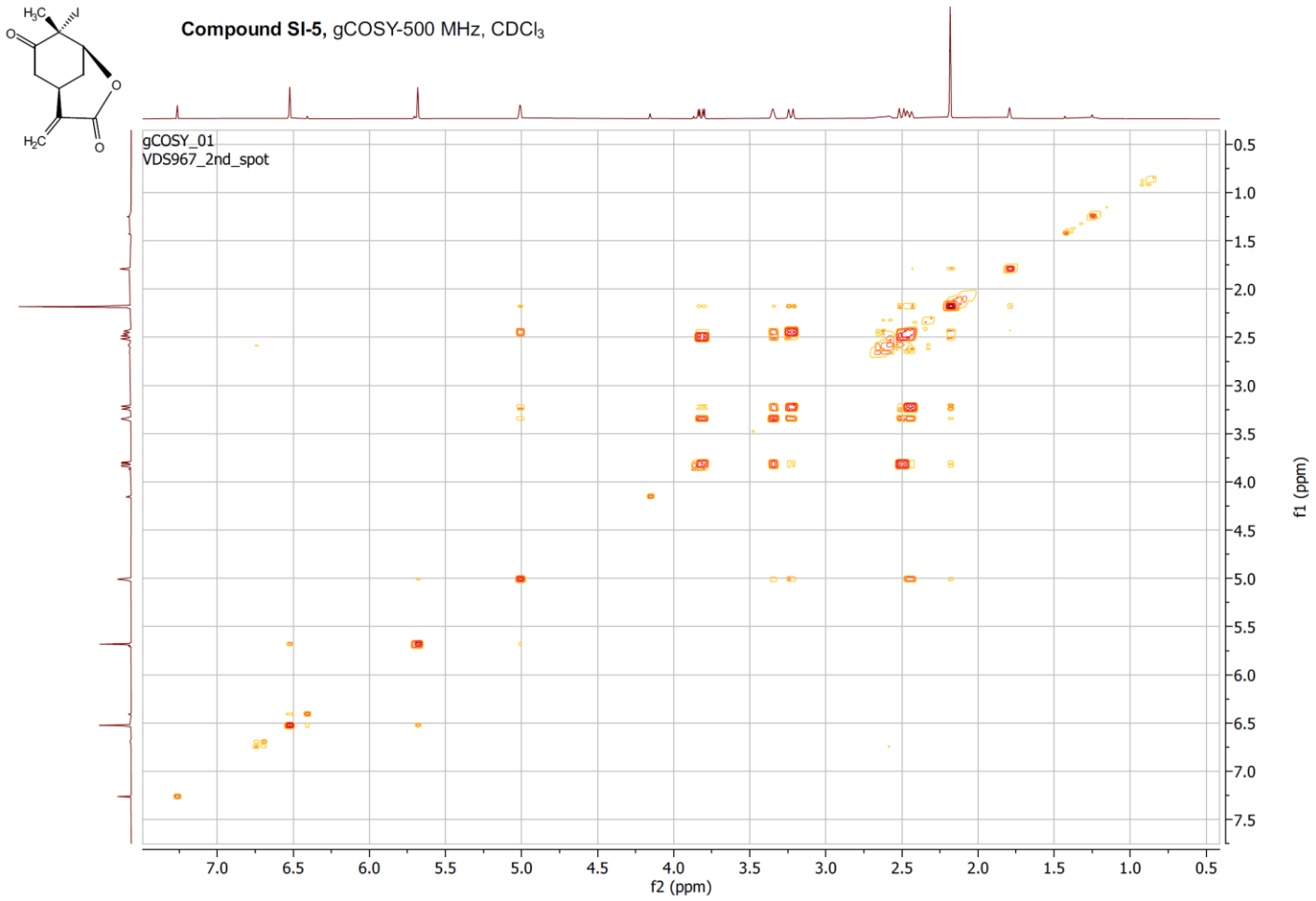

PROTON_01
VDS912_product
Compound SI-4,1H-500 MHz, CDCl3
A (s) 6.53
B (s) 5.69
C (m) 4.93
D (dd) 3.57
E (dt) 3.35
F (dt) 3.06
G (dt) 2.49
H (dd) 2.34
I (s) 1.93
f1 (ppm)

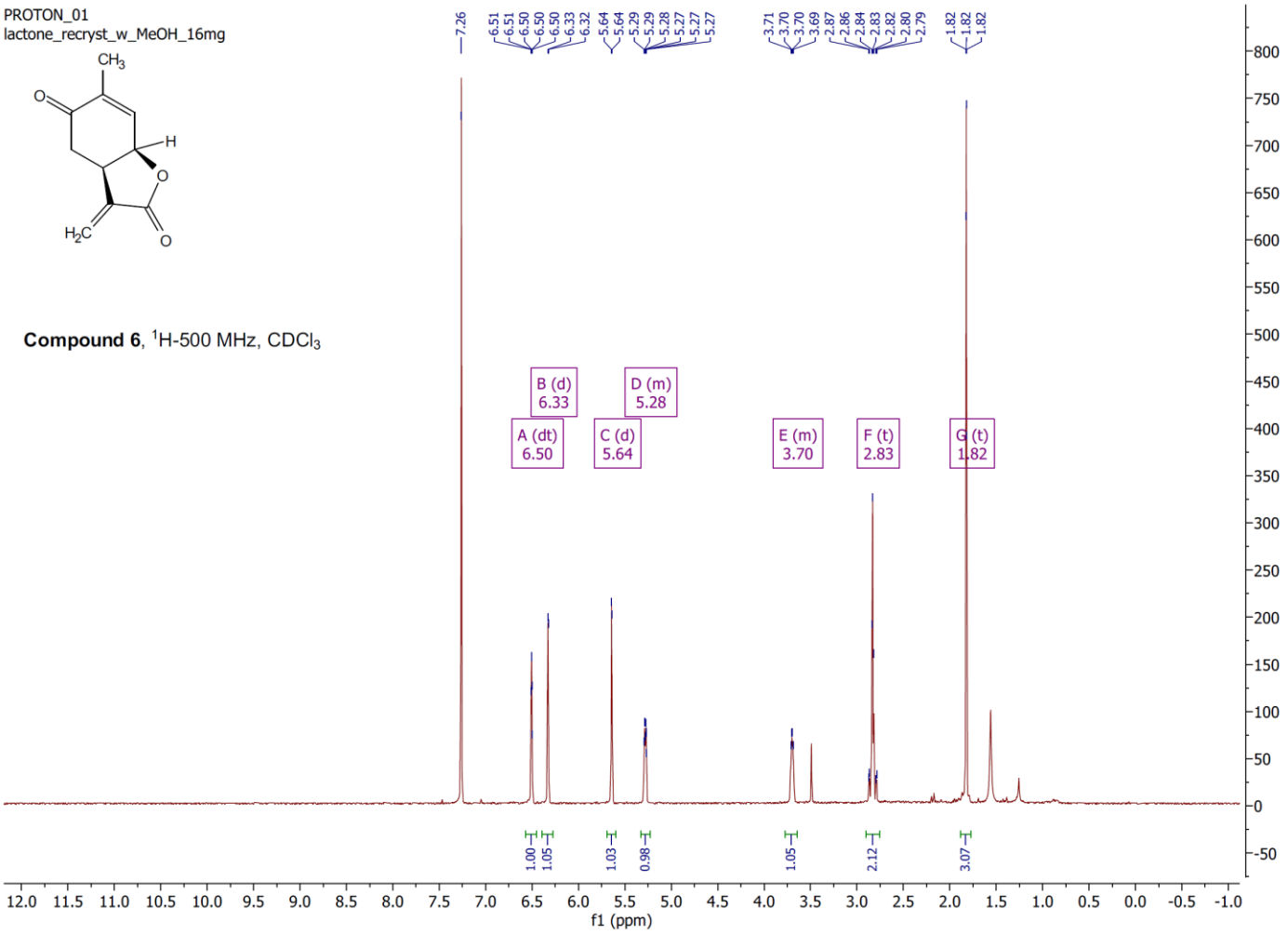

CARBON_01
VDS912_product
Compound SI-4,13C-125 MHz, CDCl3
f1 (ppm)

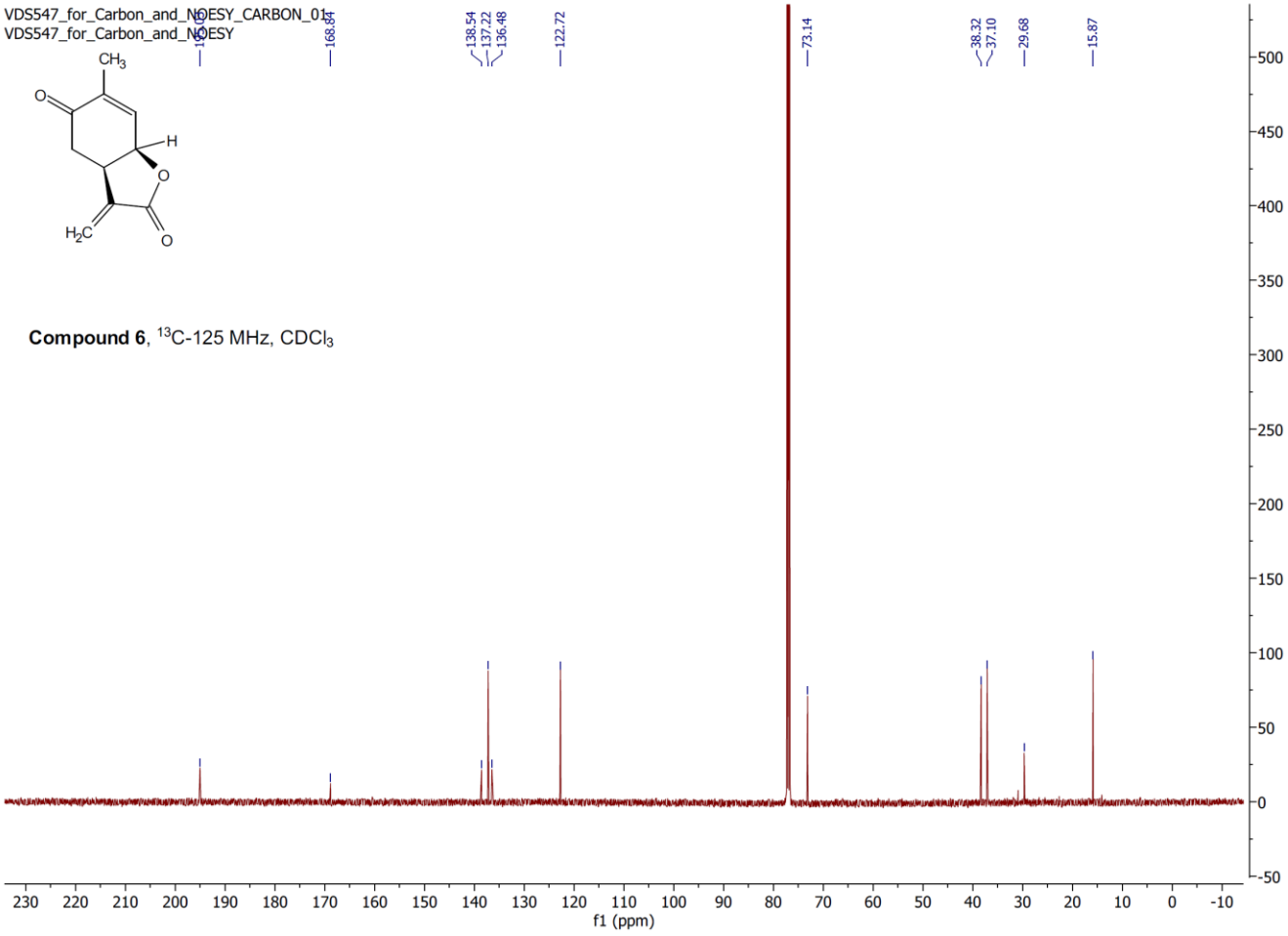

Compound SI-4, gCOSY, CDCl3
gCOSY_01
VDS912_product
f2 (ppm)
f1 (ppm)

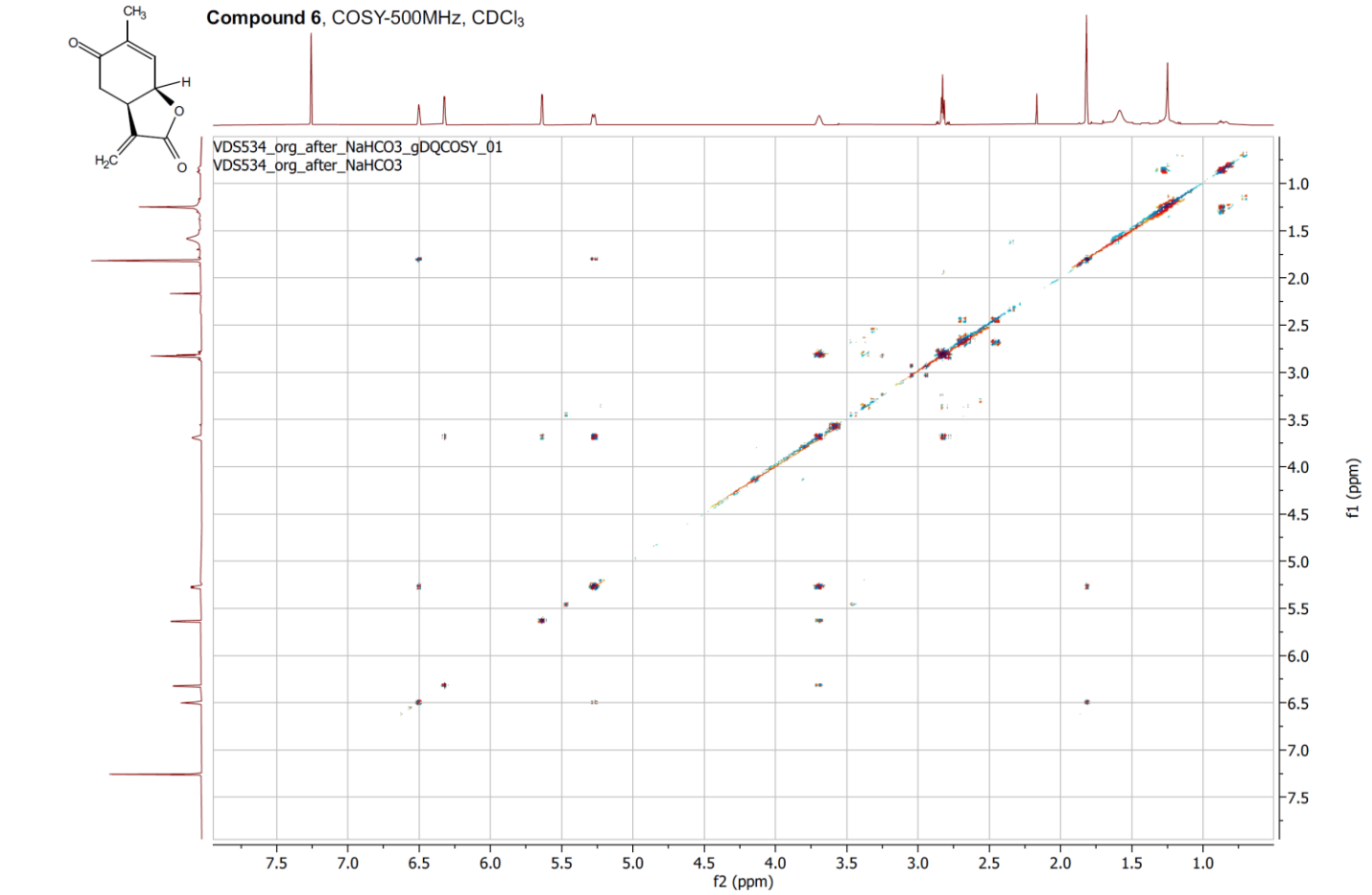

PROTON_01
VDS967_2nd_spot
Compound SI-5, 1H-500 MHz, CDCl3
I (s) 6.52
J (s) 5.68
K (m) 5.01
L (dd) 3.82
M (m) 3.35
N (dd) 3.23
O (m) 2.48
P (s) 2.18
f1 (ppm)

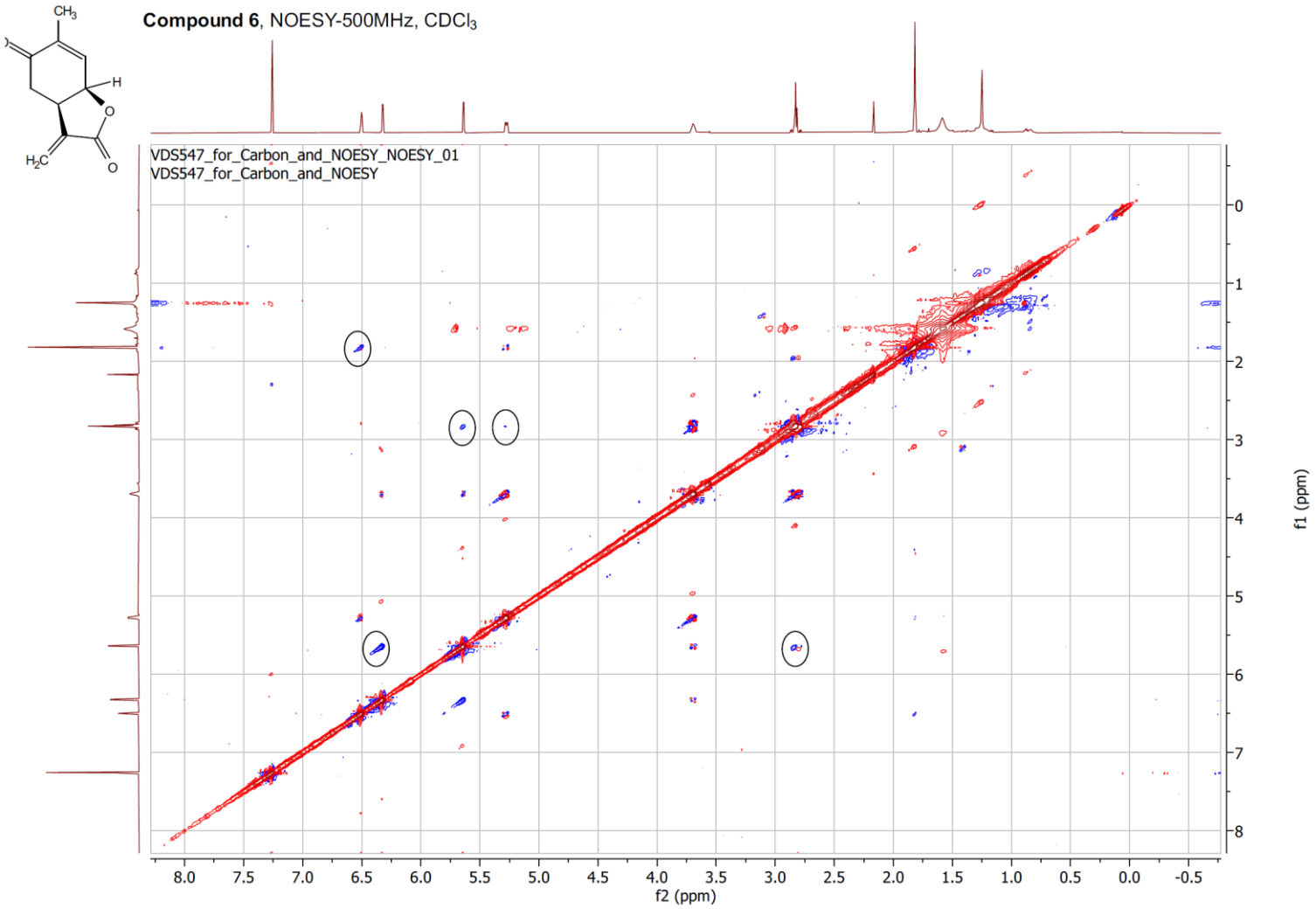

CARBON_01
VDS967_2nd_spot_for_C
202.26
161.87
136.39
131.41
85.35
77.26
77.01
76.75
44.81
43.82
36.18
27.91
26.62
Compound SI-5, 13C-125 MHz, CDCl3
f1 (ppm)

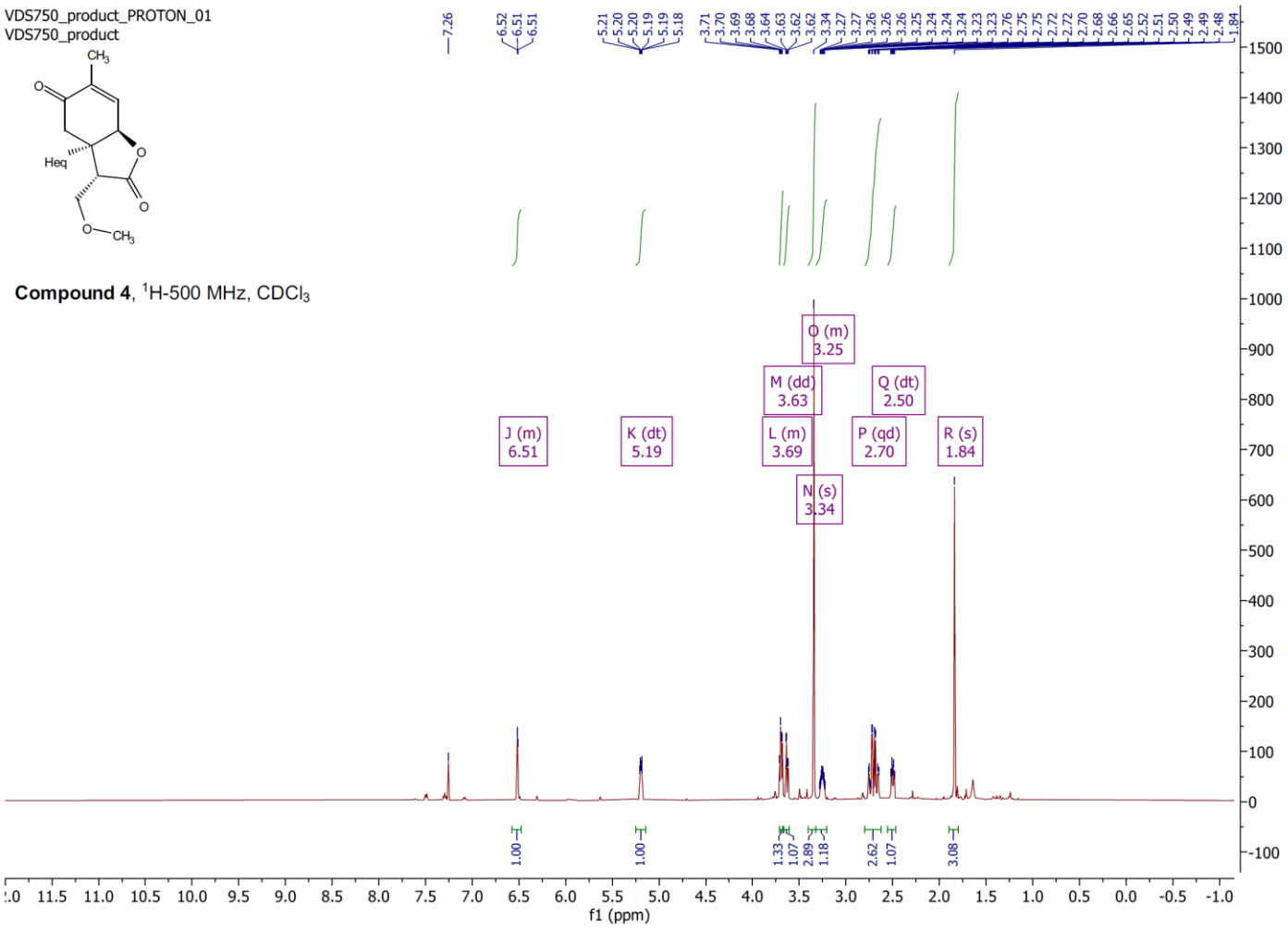

Compound SI-5, gCOSY-500 MHz, CDCl3
gCOSY_01
VDS967_2nd_spot
f2 (ppm)
f1 (ppm)

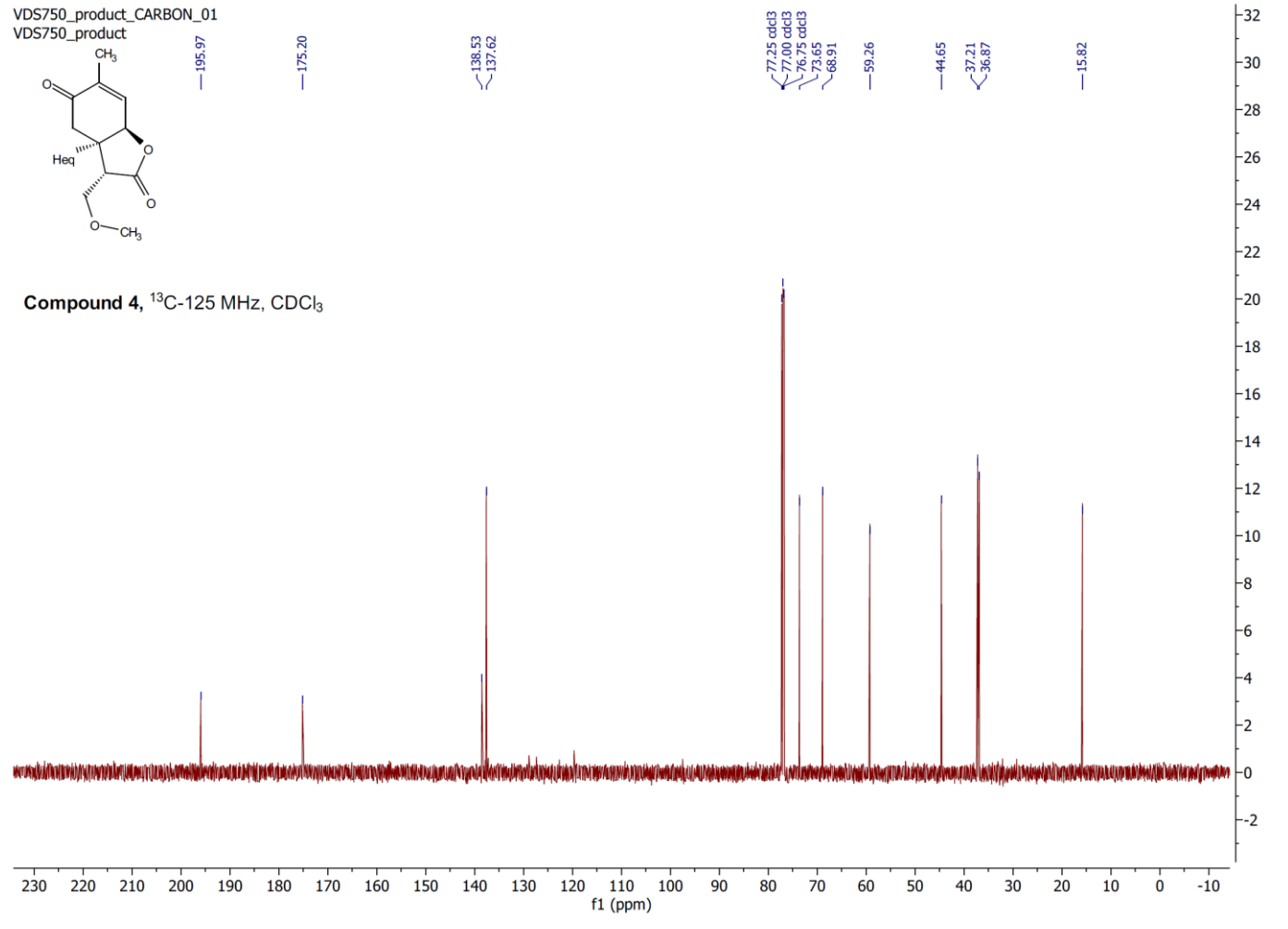

PROTON_01
lactone_recryst_w_MeOH_16mg
CH3
O
H
O
H2C
O
Compound 6, 1H-500 MHz, CDCl3
B (d) 6.33
D (m) 5.28
A (dt) 6.50
C (d) 5.64
E (m) 3.70
F (t) 2.83
G (t) 1.82
1.00
1.05
1.03
0.98
1.05
2.12
3.07
f1 (ppm)

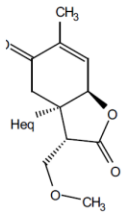

VDS547_for_Carbon_and_NOESY_CARBON_01
VDS547_for_Carbon_and_NOESY
CH3
O
H
O
H2C
O
Compound 6, 13C-125 MHz, CDCl3
168.84
138.54
137.22
136.48
122.72
73.14
38.32
37.10
29.68
15.87
f1 (ppm)


Compound 6, COSY-500MHz, CDCl3
VDS534_org_after_NaHCO3_gDQCOSY_01
VDS534_org_after_NaHCO3
f2 (ppm)
f1 (ppm)


Compound 6, NOESY-500MHz, CDCl3
VDS547_for_Carbon_and_NOESY_NOESY_01
VDS547_for_Carbon_and_NOESY
f2 (ppm)
f1 (ppm)

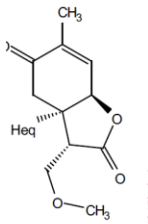

VDS750_product_PROTON_01
VDS750_product
Heq
Compound 4, 1H-500 MHz, CDCl3
O (m)
3.25
M (dd)
3.63
Q (dt)
2.50
J (m)
6.51
K (dt)
5.19
L (m)
3.69
P (qd)
2.70
R (s)
1.84
N (s)
3.34
f1 (ppm)


VDS750_product_CARBON_01
VDS750_product
Heq
Compound 4, 13C-125 MHz, CDCl3
f1 (ppm)

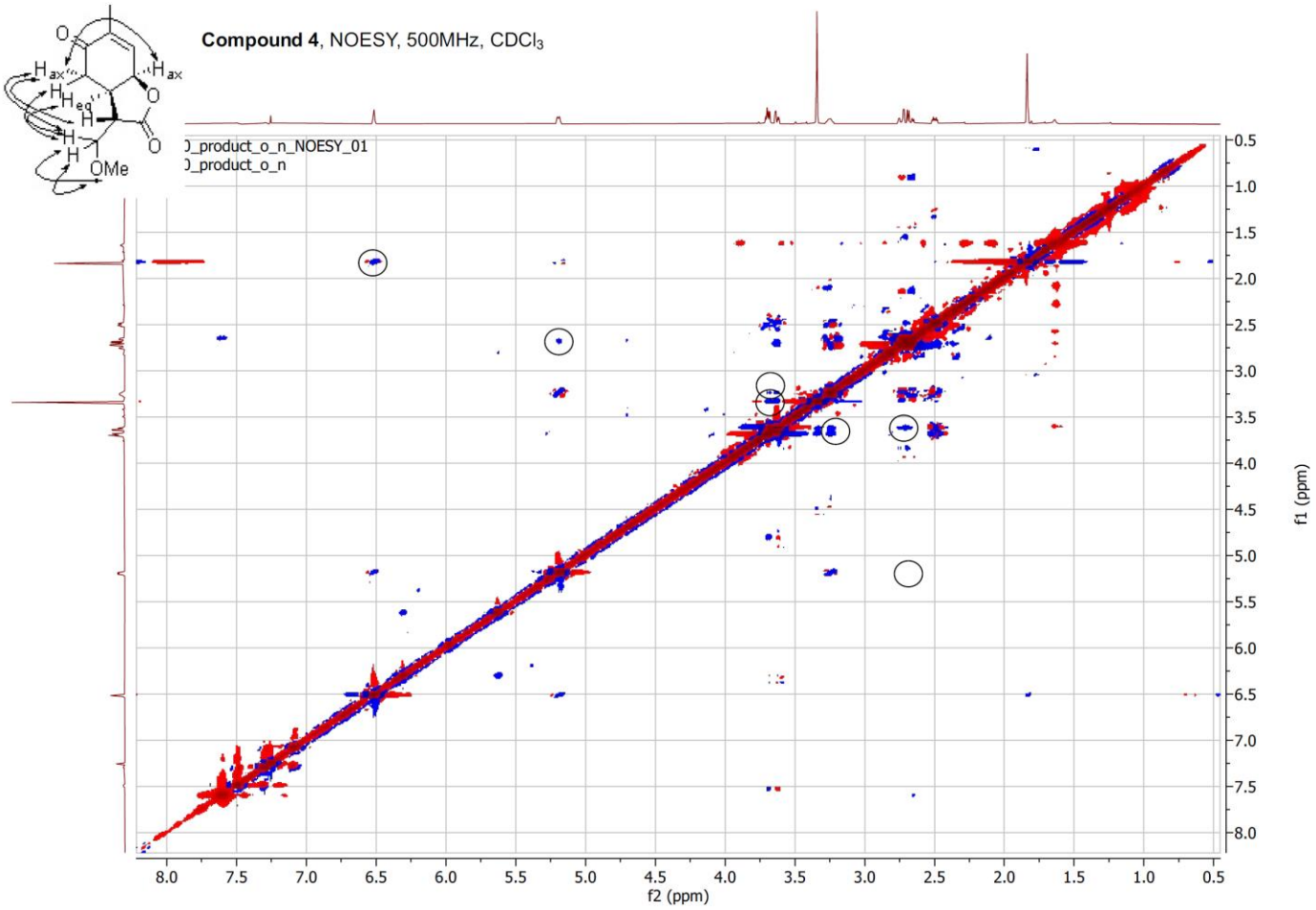


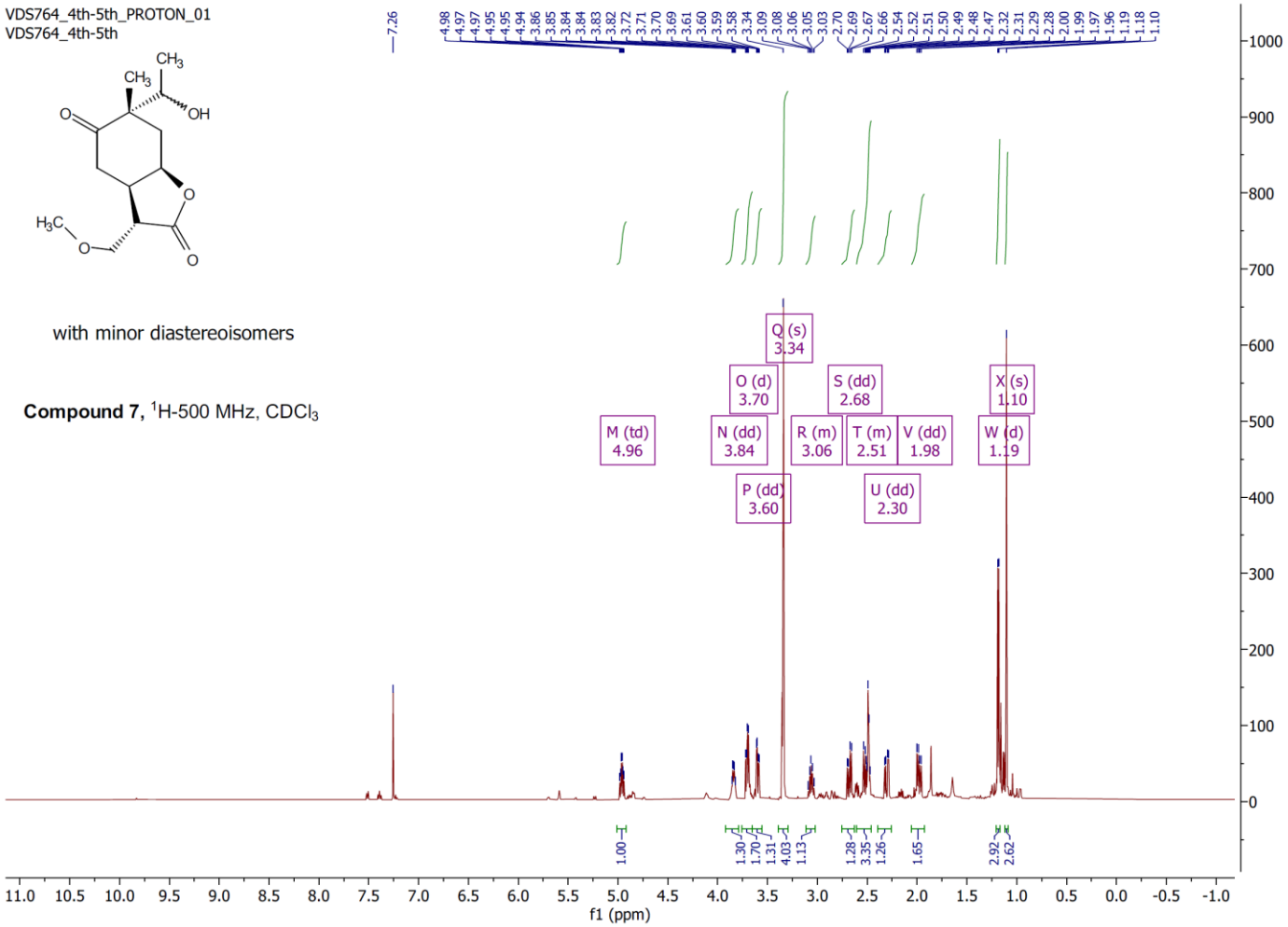

**Compound 4**, gCOSY, 500MHz, $CDCl_3$

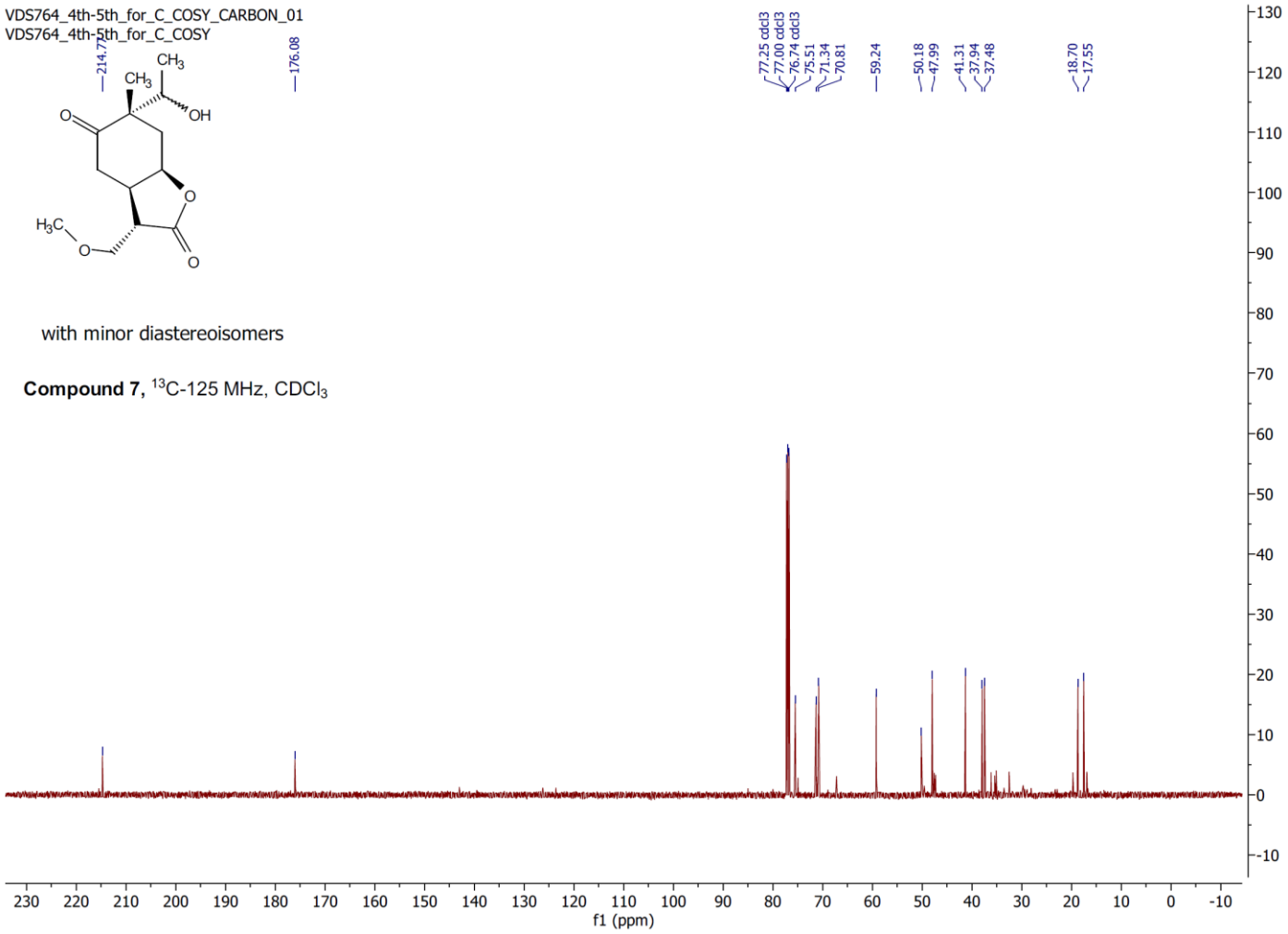



**Compound 4**, HSQCAD, $CDCl_3$

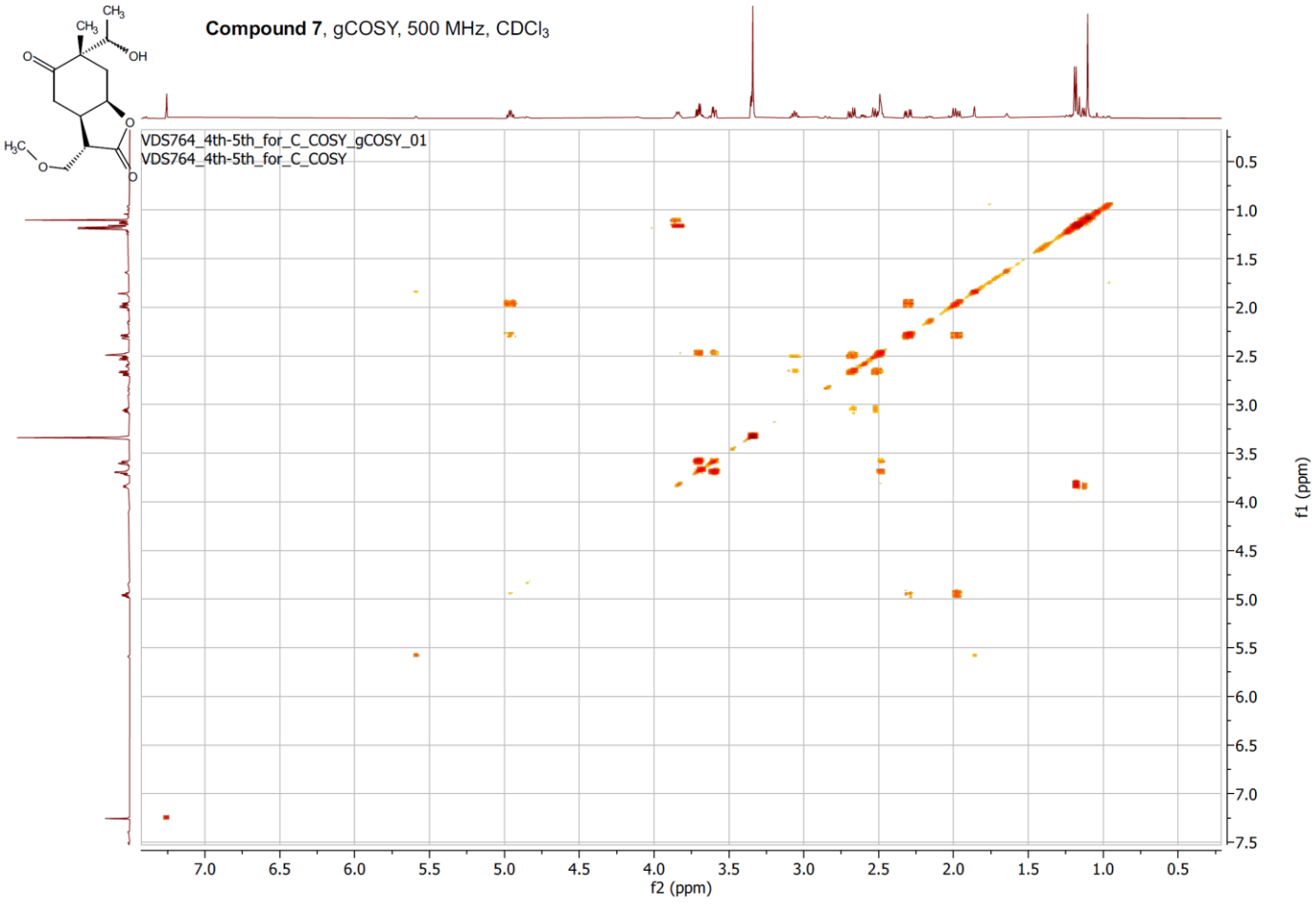

Compound 4, NOESY, 500MHz, CDCl3
f2 (ppm)
f1 (ppm)

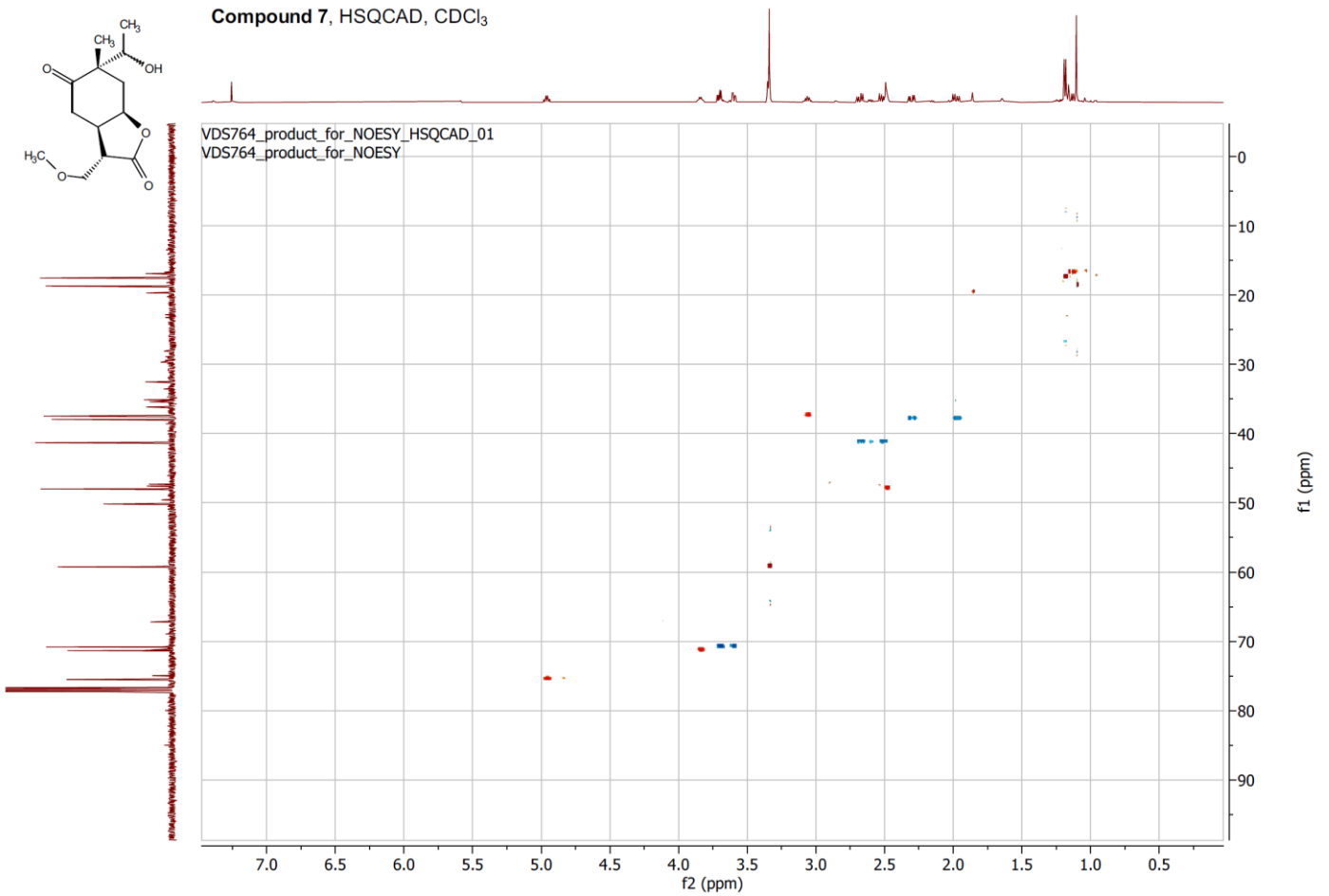

VDS764_4th-5th_PROTON_01
VDS764_4th-5th
with minor diastereoisomers
Compound 7, 1H-500 MHz, CDCl3
Q (s) 3.34
O (d) 3.70
S (dd) 2.68
X (s) 1.10
M (td) 4.96
N (dd) 3.84
R (m) 3.06
T (m) 2.51
V (dd) 1.98
W (d) 1.19
P (dd) 3.60
U (dd) 2.30
f1 (ppm)

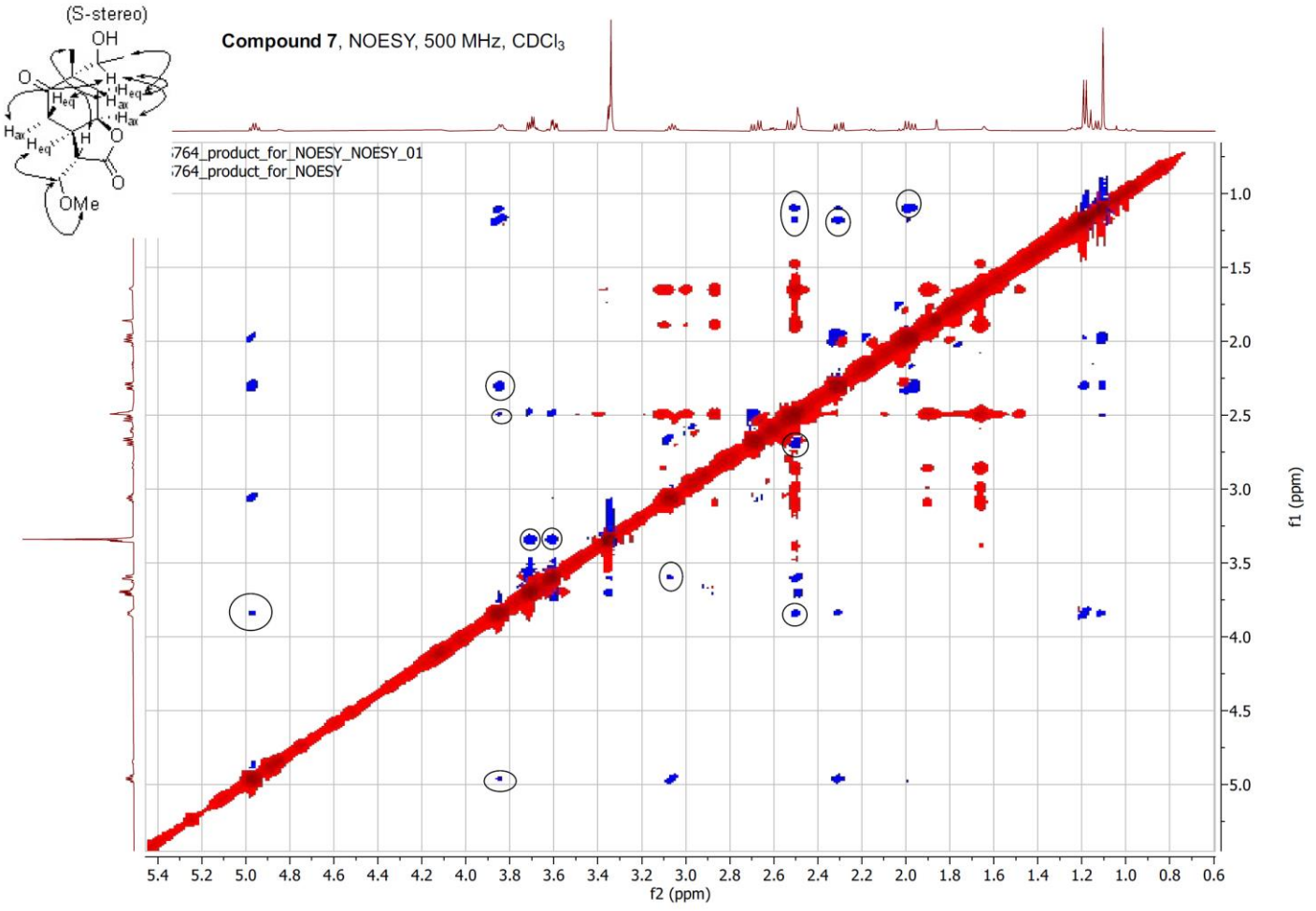


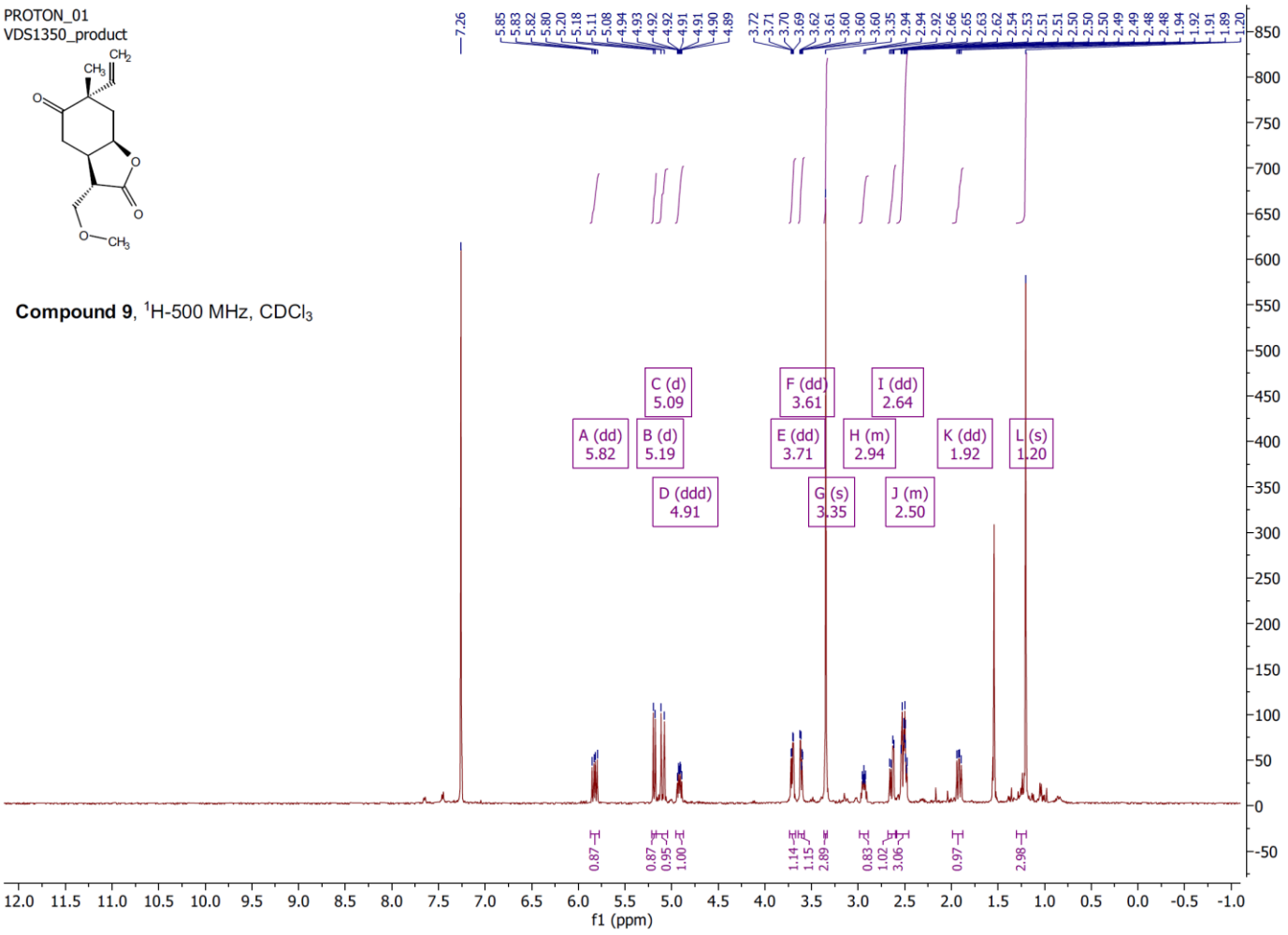

with minor diastereoisomers

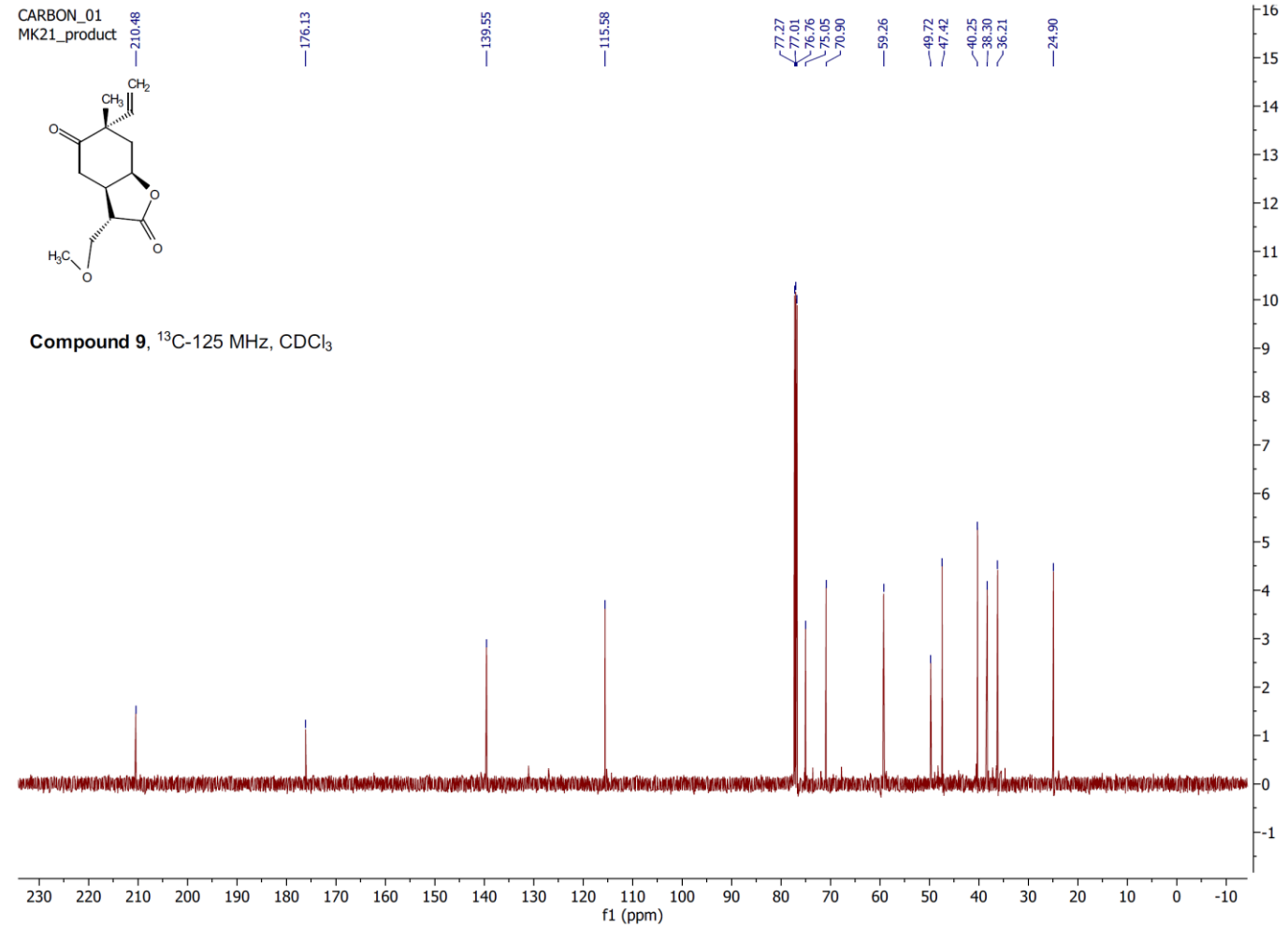
**Compound 7,** $^{13}$C-125 MHz, $CDCl_3$

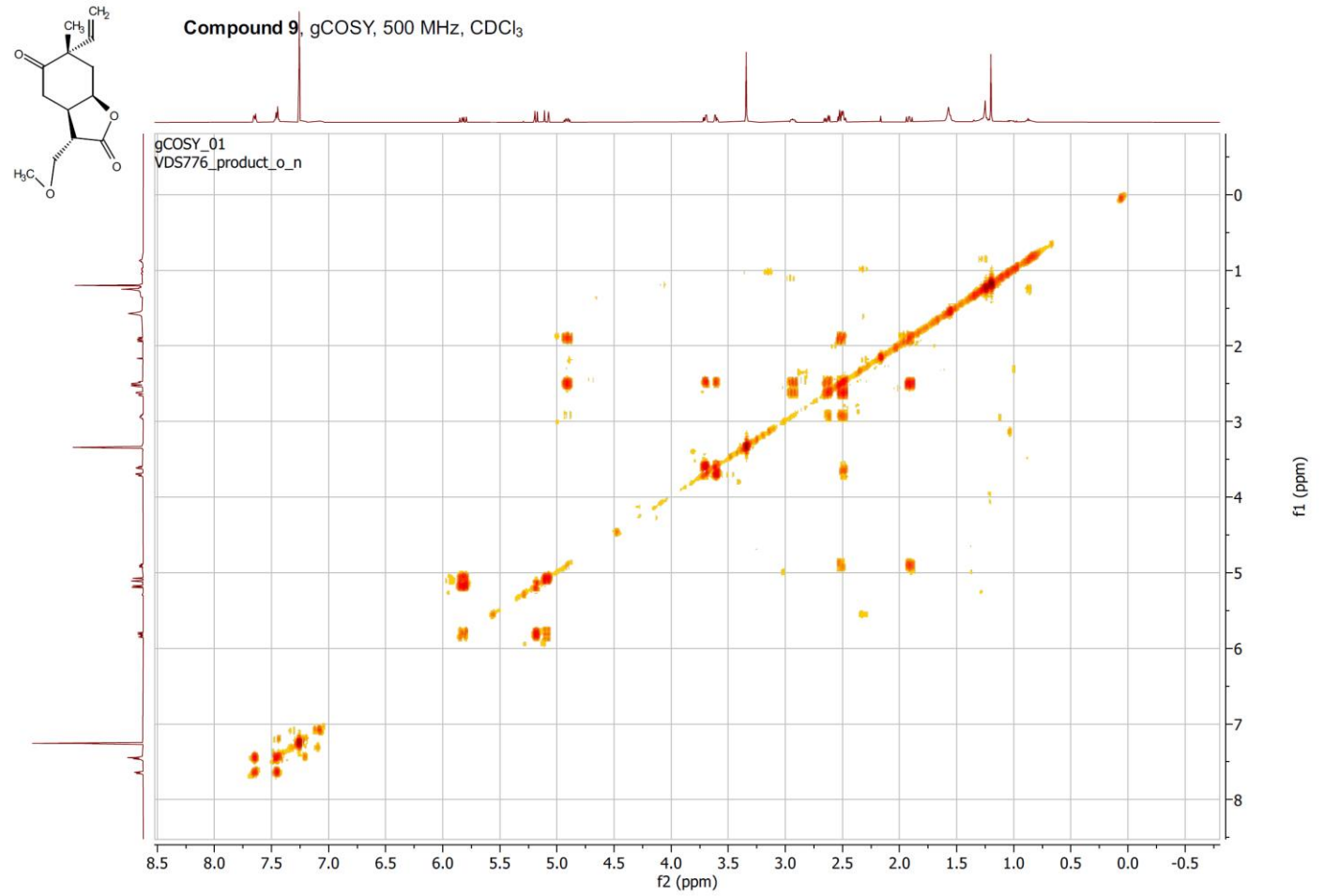


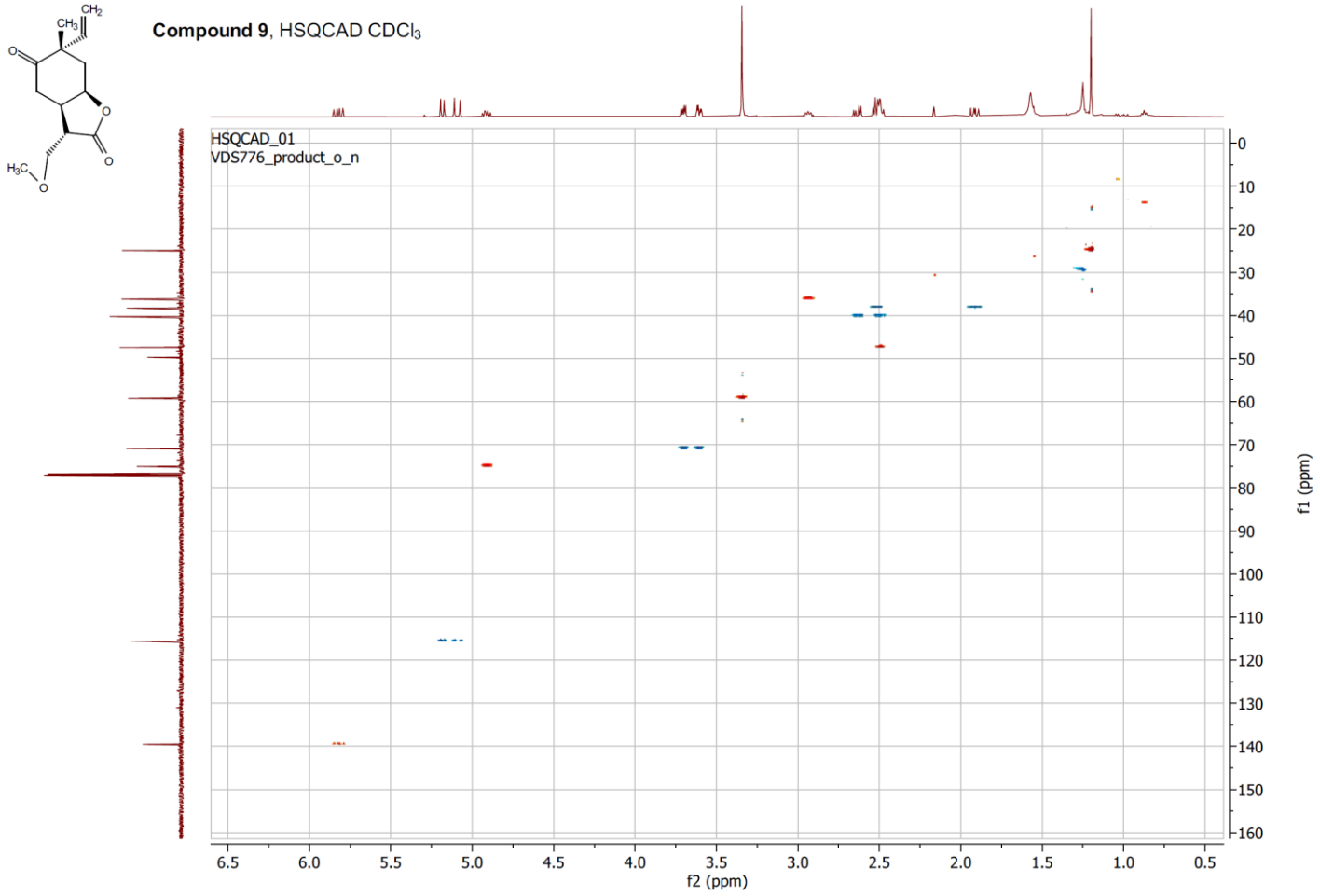

Compound 7, HSQCAD, CDCl3
VDS764_product_for_NOESY_HSQCAD_01
VDS764_product_for_NOESY
f2 (ppm)
f1 (ppm)

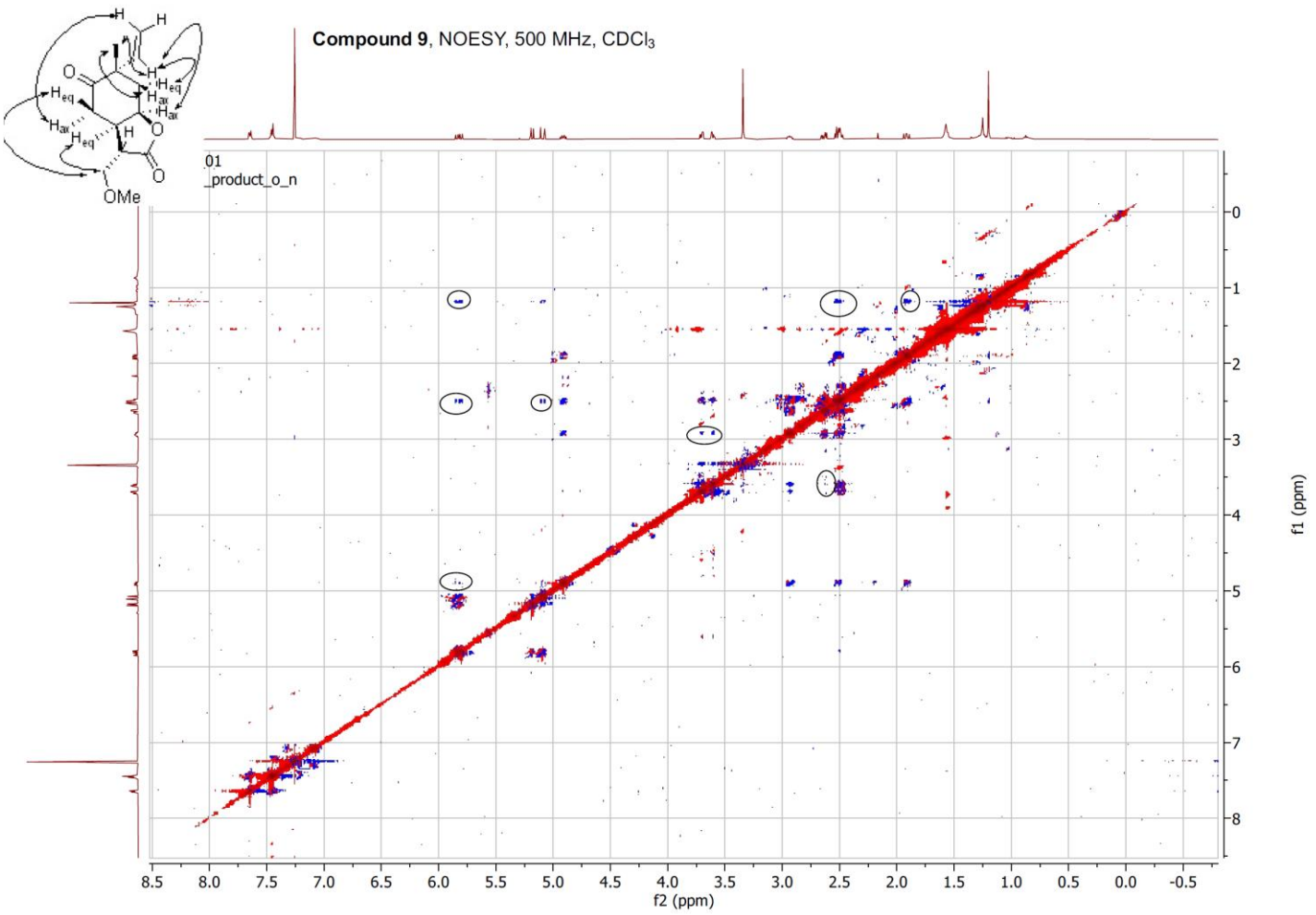

(S-stereo)
OH
OMe
Compound 7, NOESY, 500 MHz, CDCl3
764_product_for_NOESY_NOESY_01
764_product_for_NOESY
f2 (ppm)
f1 (ppm)

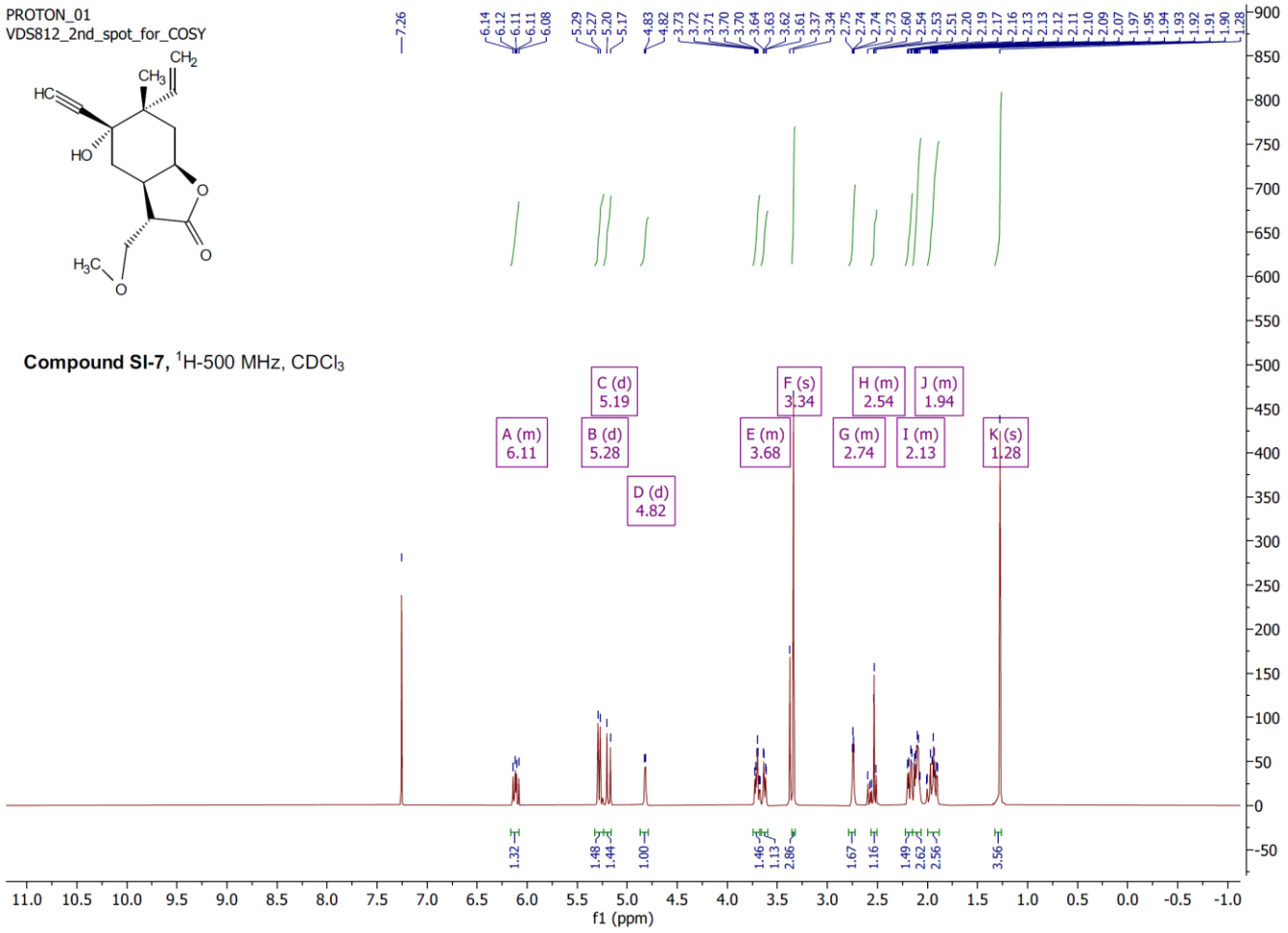

PROTON_01
VDS1350_product
Compound 9, $^{1}$H-500 MHz, $CDCl_3$
A (dd) 5.82
B (d) 5.19
C (d) 5.09
D (ddd) 4.91
E (dd) 3.71
F (dd) 3.61
G (s) 3.35
H (m) 2.94
I (dd) 2.64
J (m) 2.50
K (dd) 1.92
L (s) 1.20
f1 (ppm)

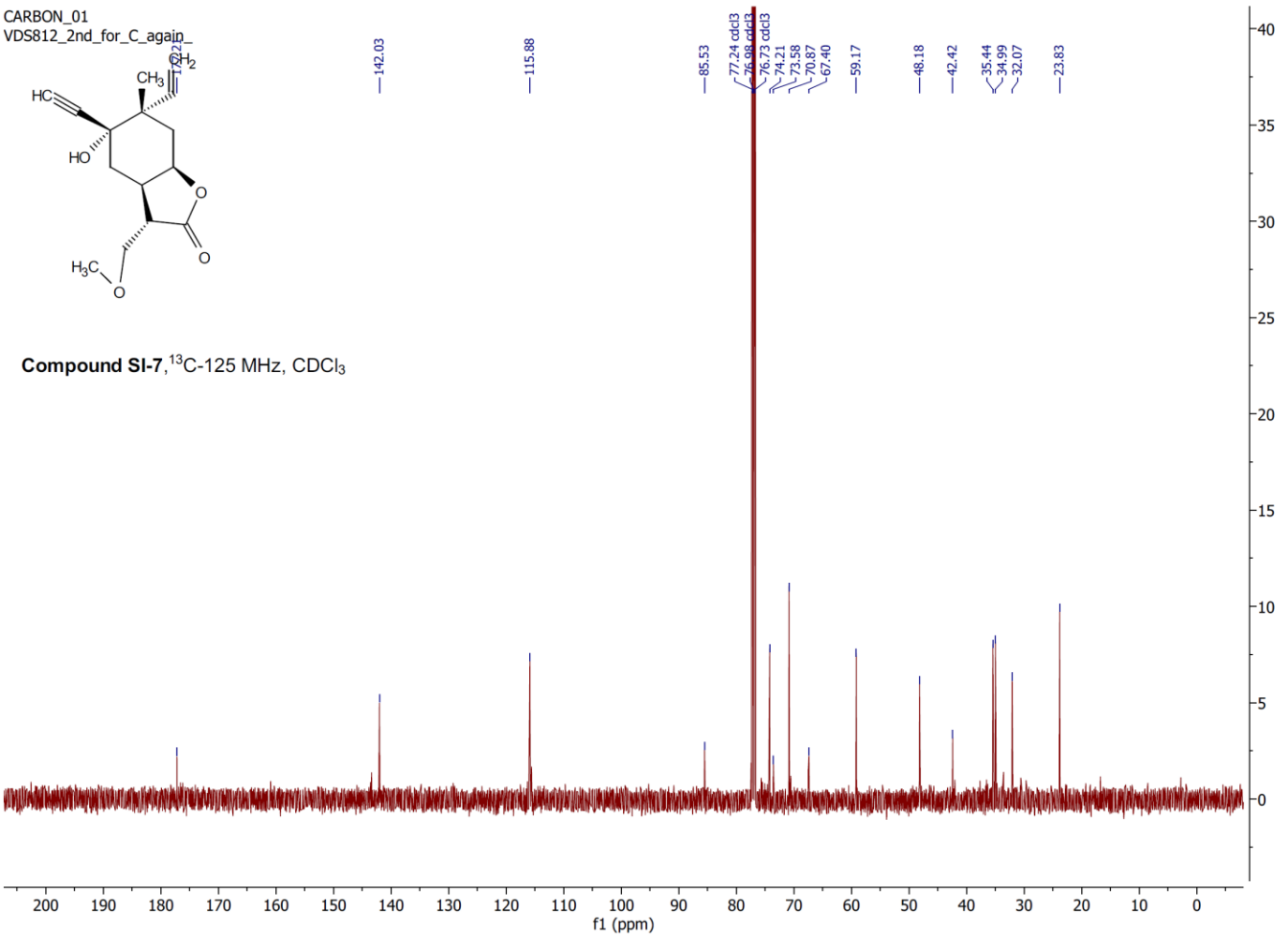

CARBON_01
MK21_product
Compound 9, $^{13}$C-125 MHz, $CDCl_3$
210.48
176.13
139.55
115.58
77.27
77.01
76.76
75.05
70.90
59.26
49.72
47.42
40.25
38.30
36.21
24.90
f1 (ppm)


Compound 9, gCOSY, 500 MHz, CDCl3
gCOSY_01
VDS776_product_o_n
f2 (ppm)
f1 (ppm)

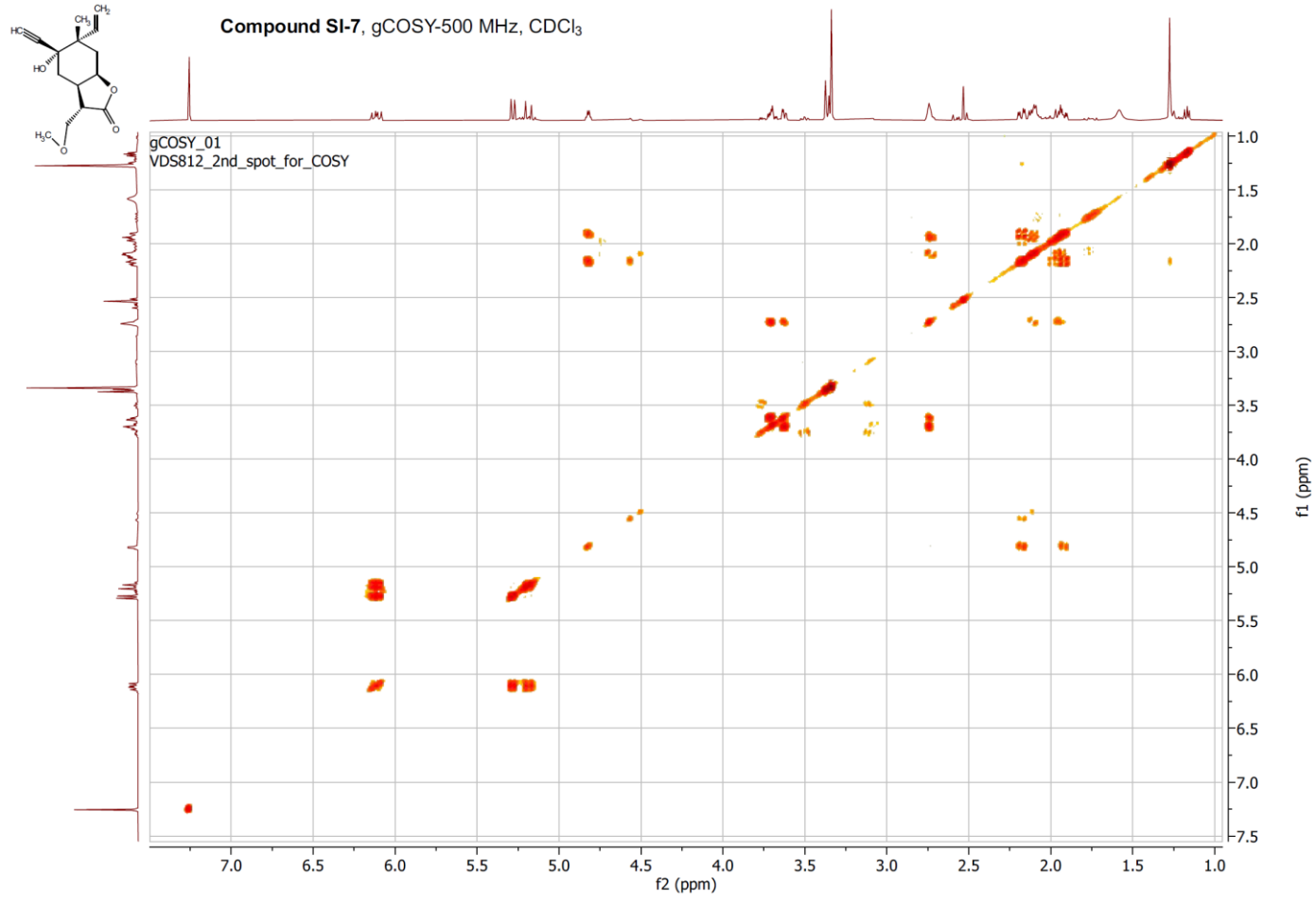

Compound 9, HSQCAD CDCl3
HSQCAD_01
VDS776_product_o_n
f2 (ppm)
f1 (ppm)


Compound 9, NOESY, 500 MHz, CDCl3
01
_product_o_n
OMe
f2 (ppm)
f1 (ppm)

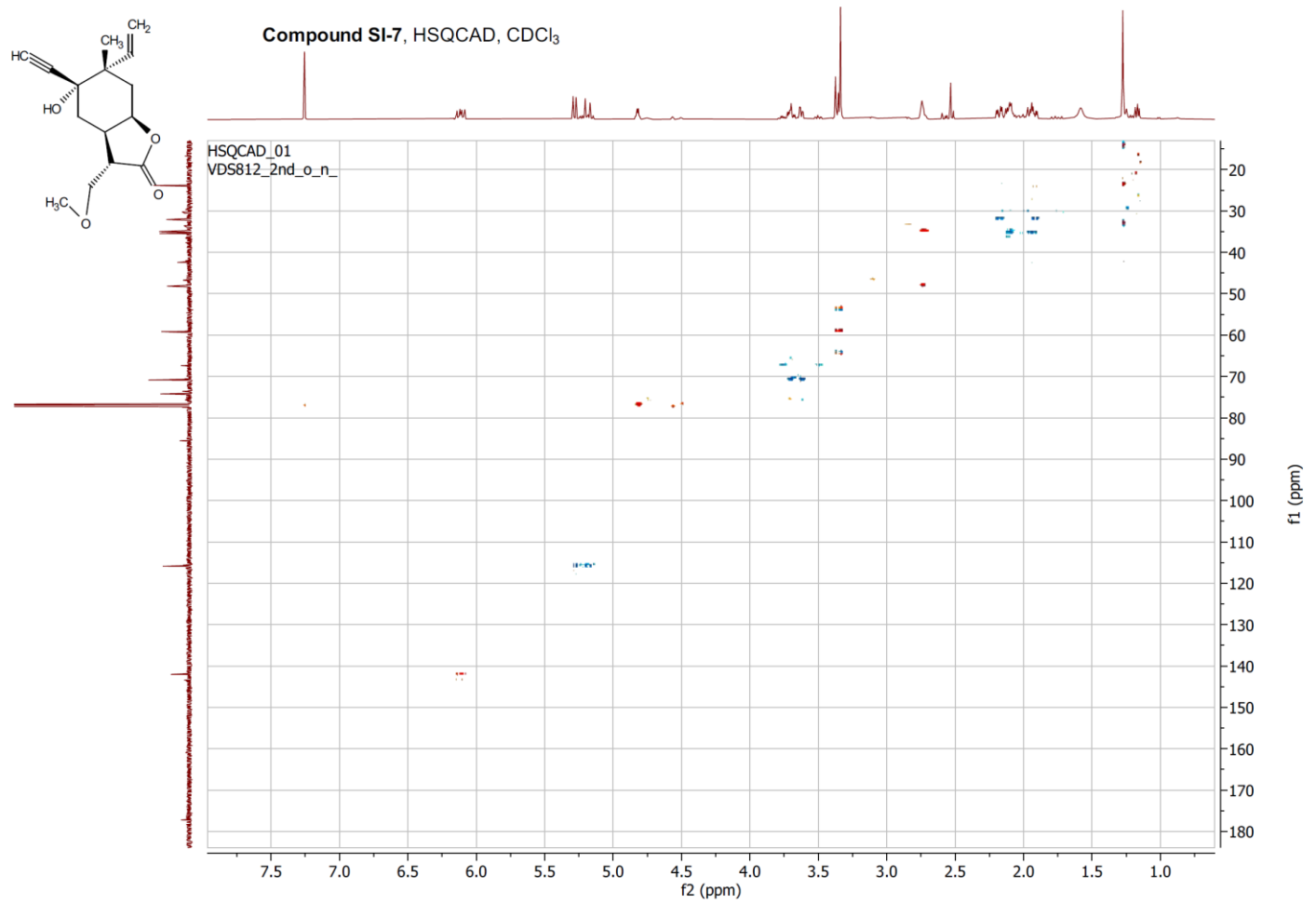

PROTON_01
VDS812_2nd_spot_for_COSY
Compound SI-7, 1H-500 MHz, CDCl3
A (m) 6.11
B (d) 5.28
C (d) 5.19
D (d) 4.82
E (m) 3.68
F (s) 3.34
G (m) 2.74
H (m) 2.54
I (m) 2.13
J (m) 1.94
K (s) 1.28
f1 (ppm)

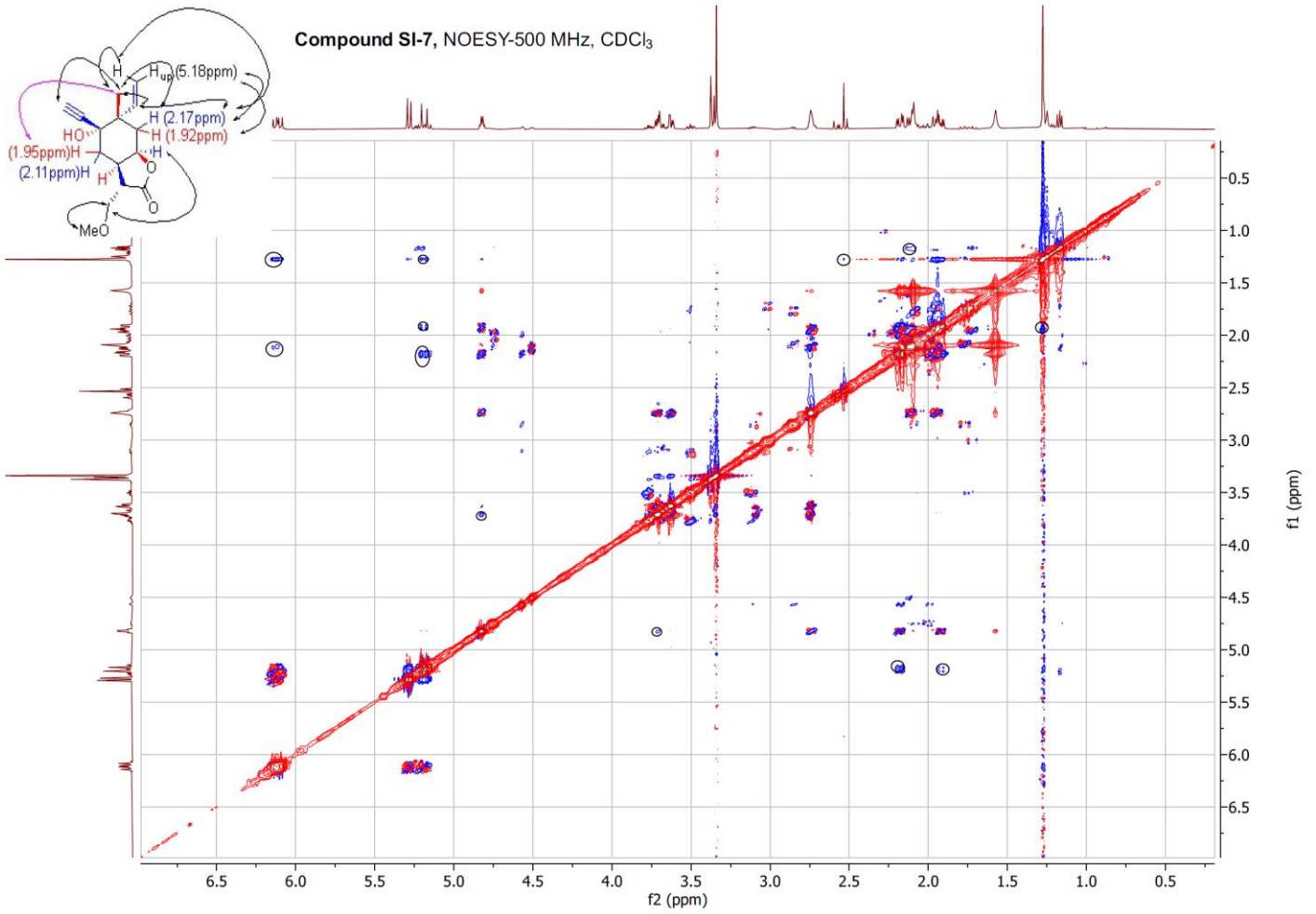


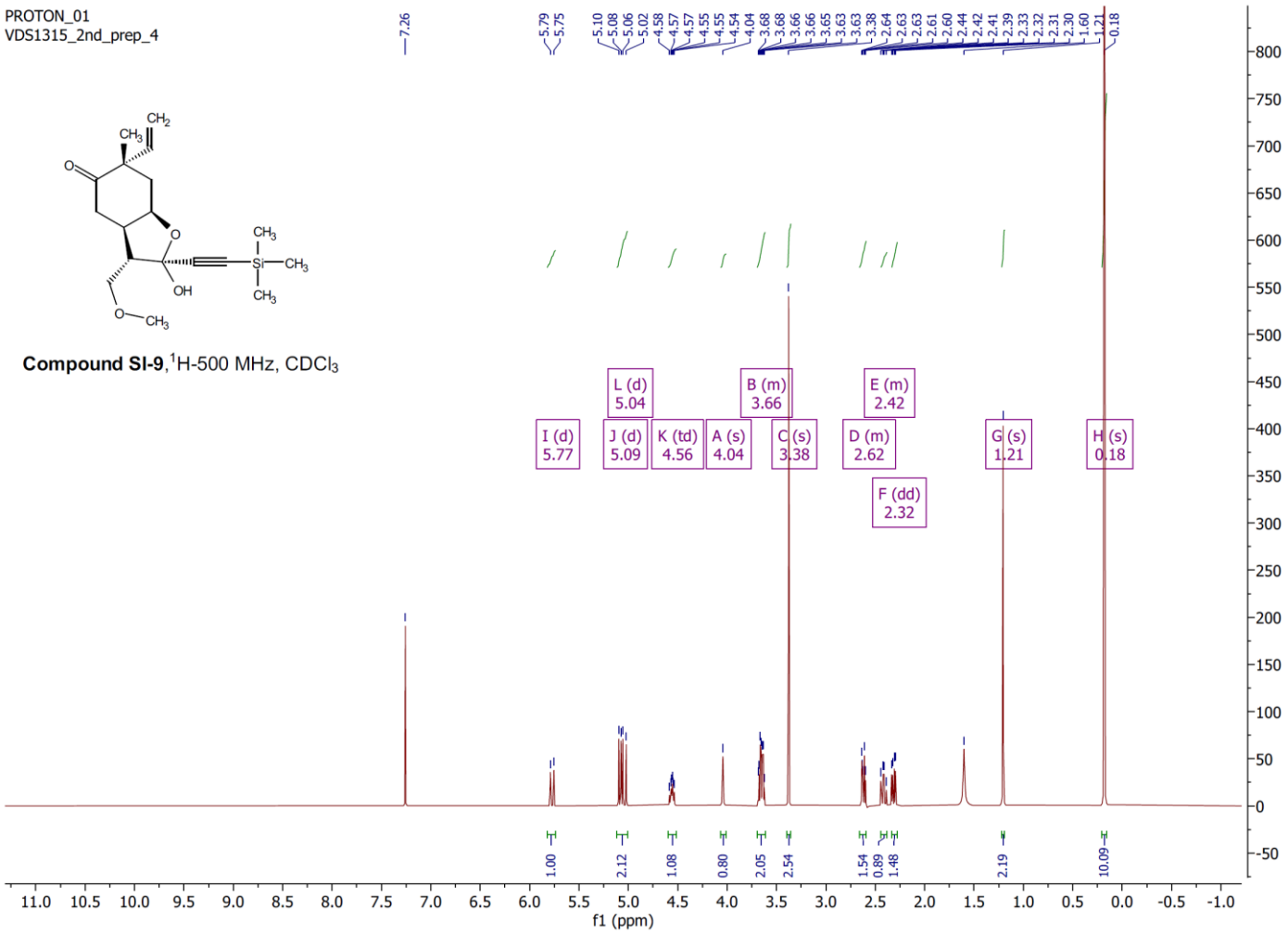

**Compound SI-7**, $^{13}$C-125 MHz, $CDCl_3$



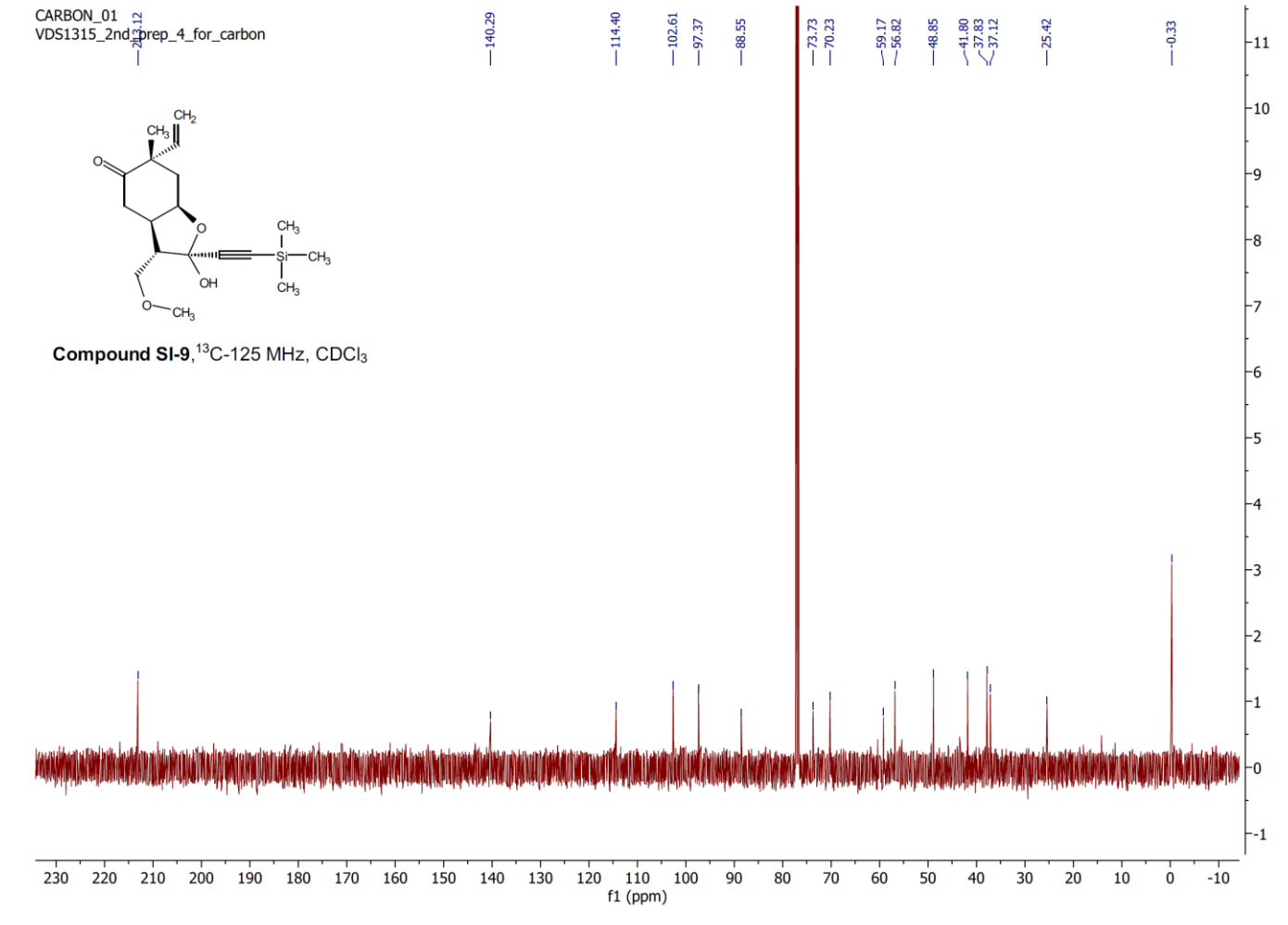

**Compound SI-7**, gCOSY-500 MHz, $CDCl_3$


Compound SI-7, HSQCAD, CDCl3
HSQCAD_01
VDS812_2nd_o_n_
f2 (ppm)
f1 (ppm)

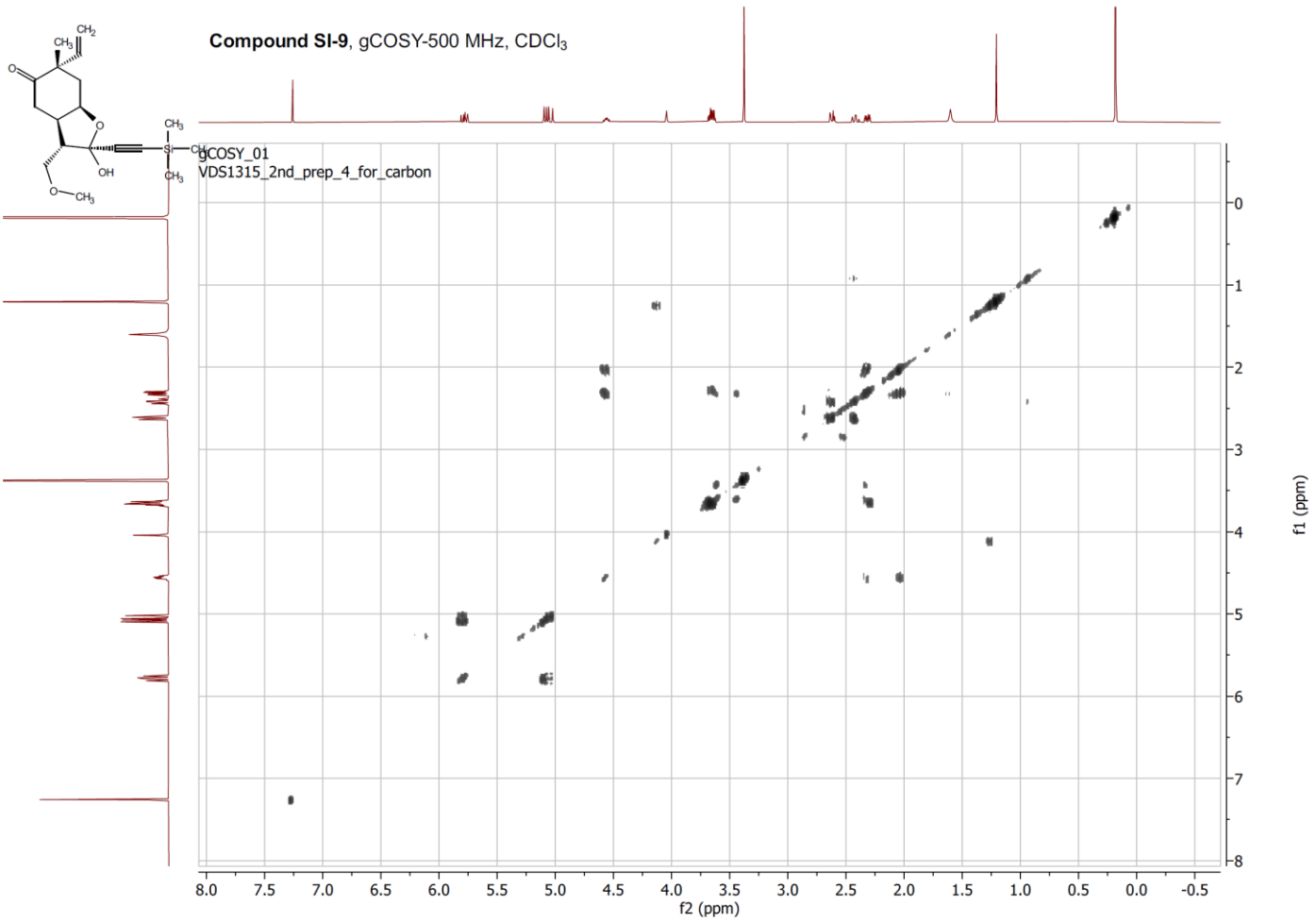

Compound SI-7, NOESY-500 MHz, CDCl3
H (5.18ppm)
H (2.17ppm)
H (1.92ppm)
(1.95ppm)H
(2.11ppm)H
MeO
f2 (ppm)
f1 (ppm)

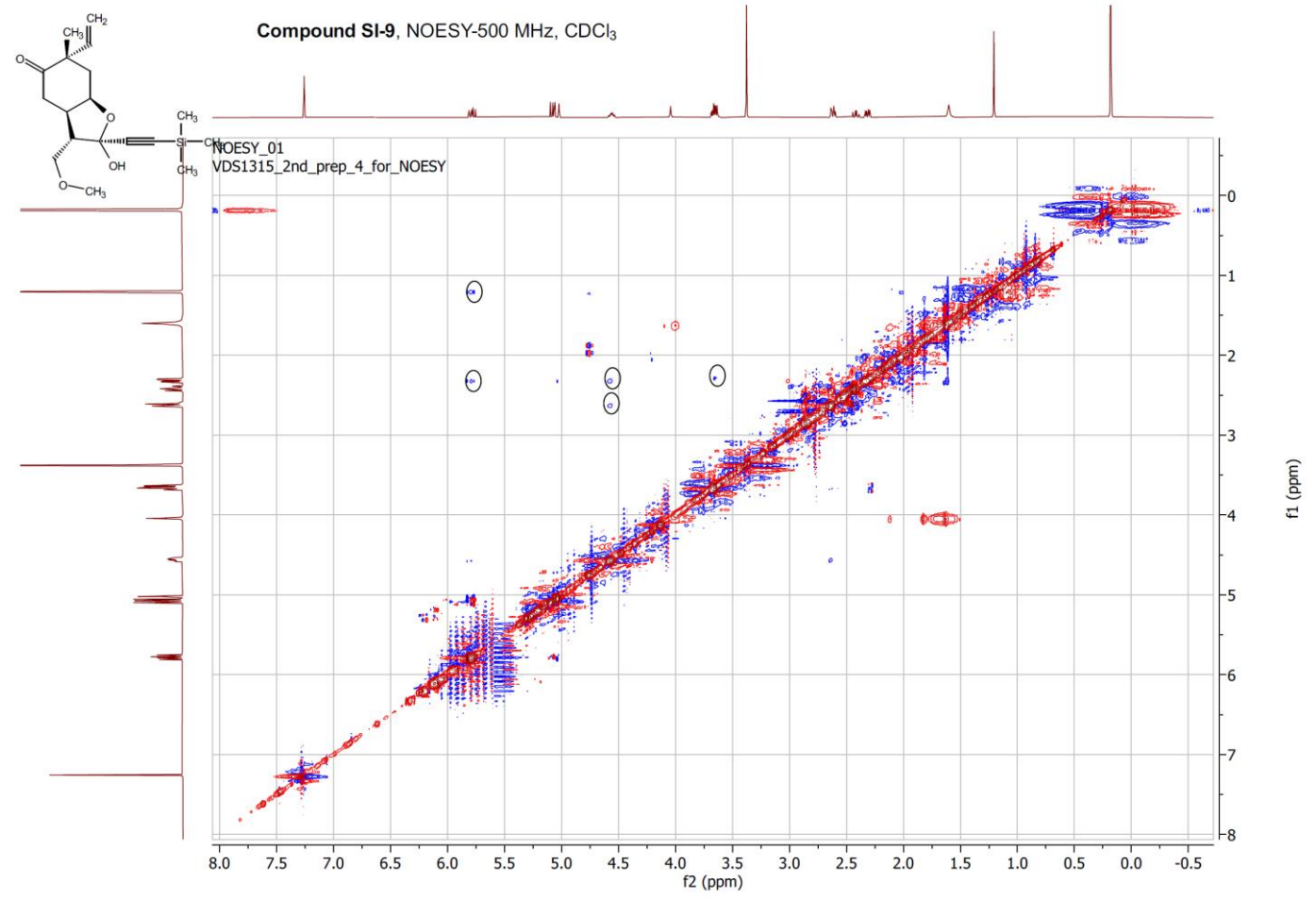


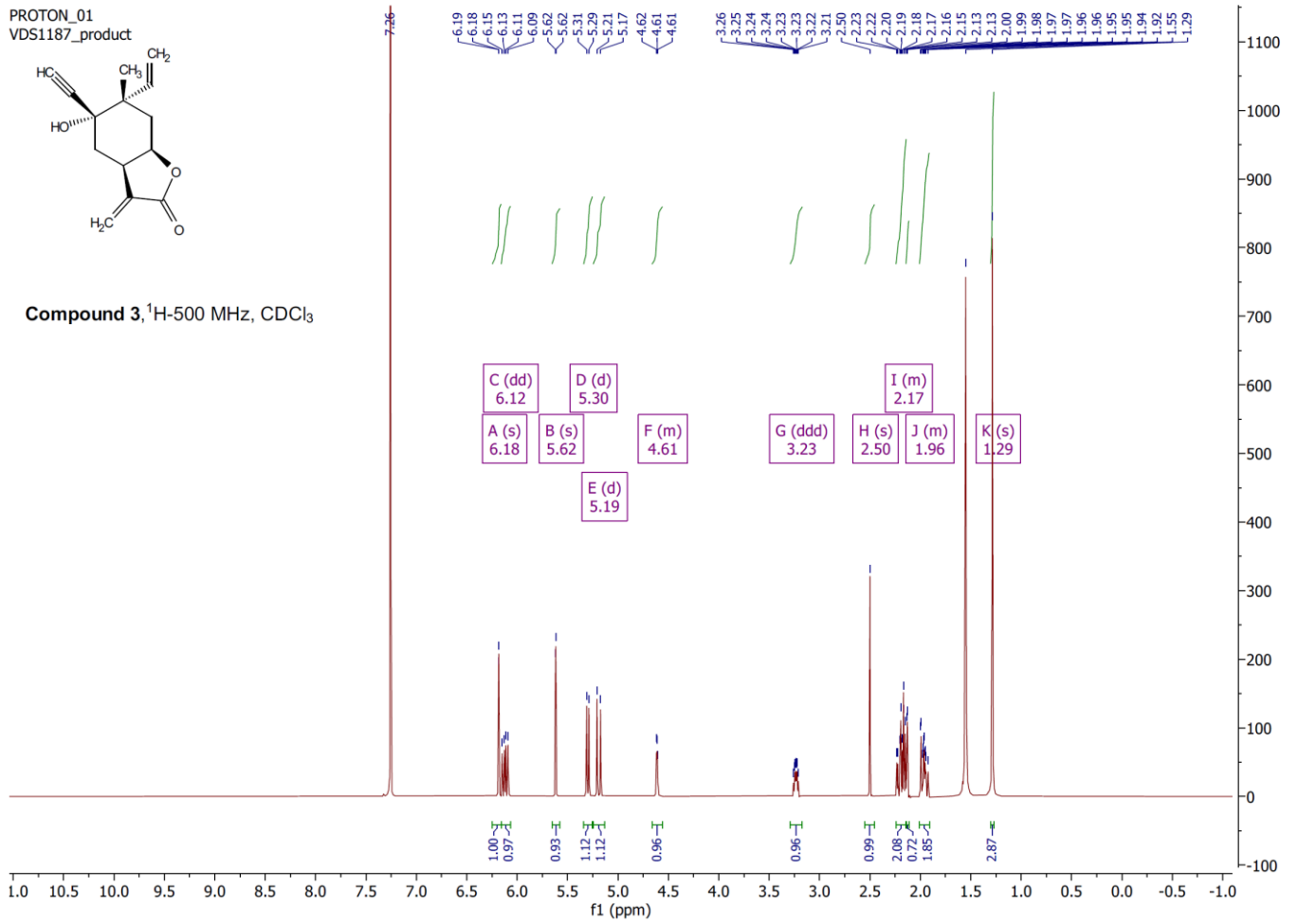

**Compound SI-9**,$^{1}$H-500 MHz, $CDCl_3$

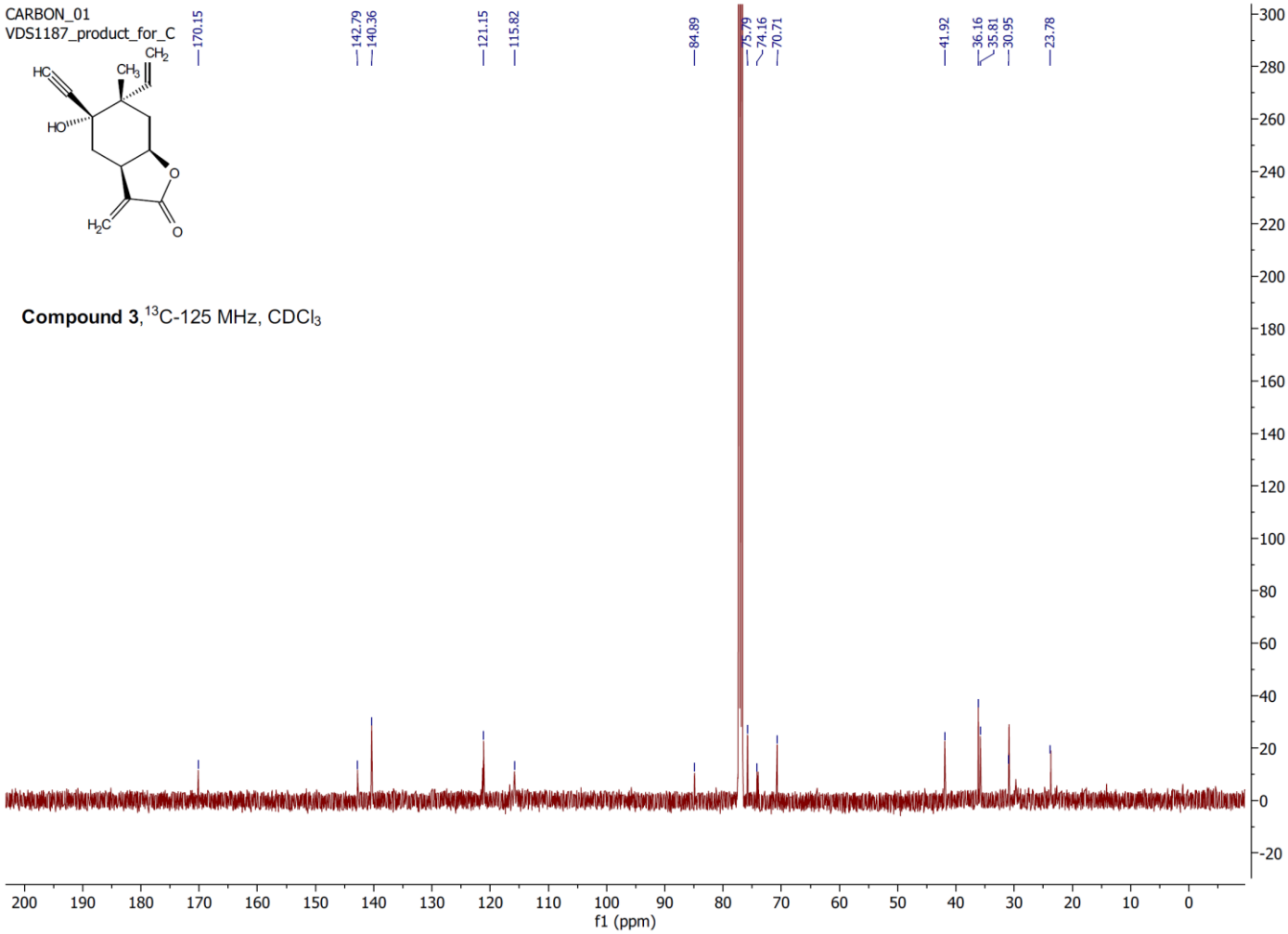


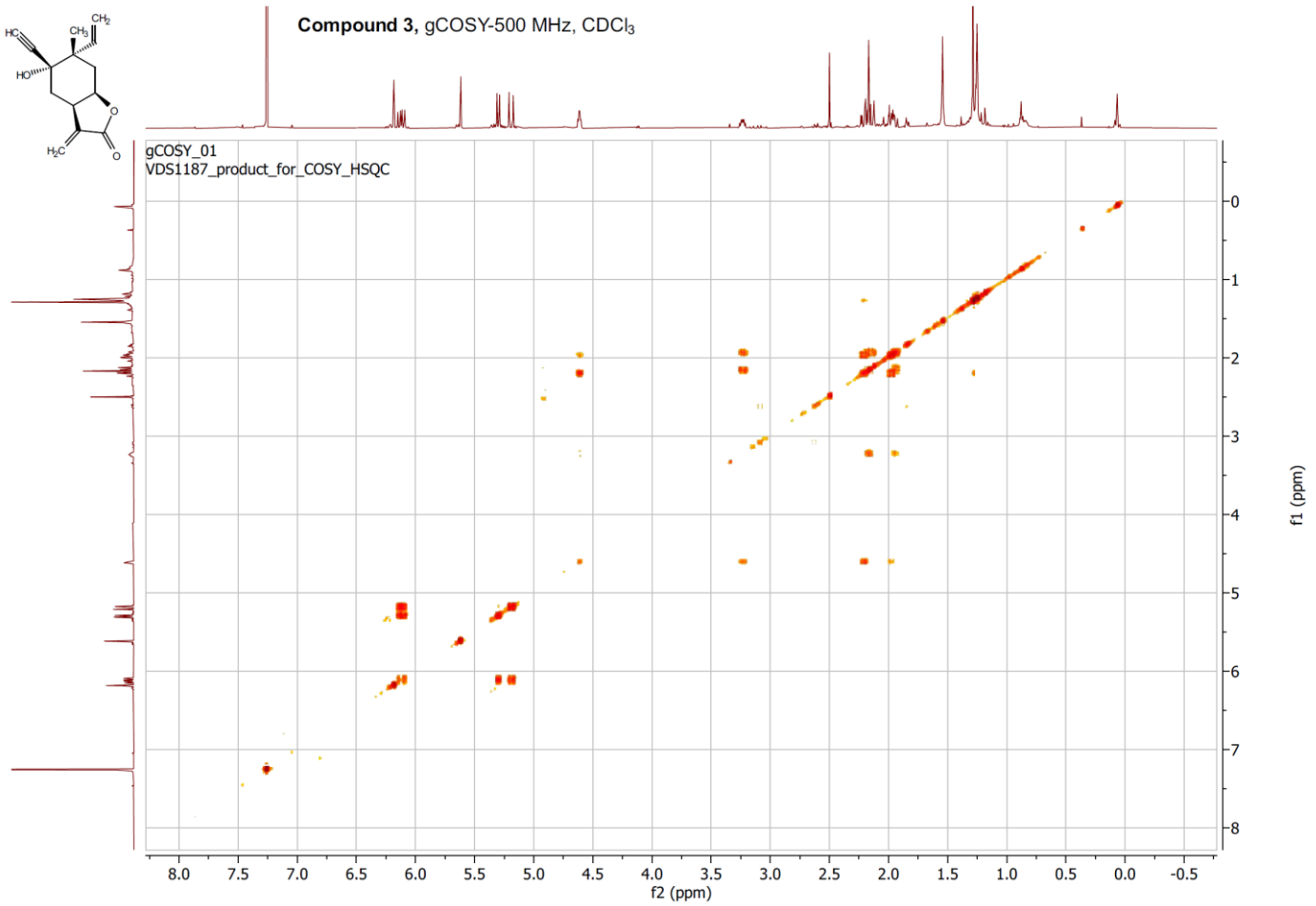

**Compound SI-9**,$^{13}$C-125 MHz, $CDCl_3$

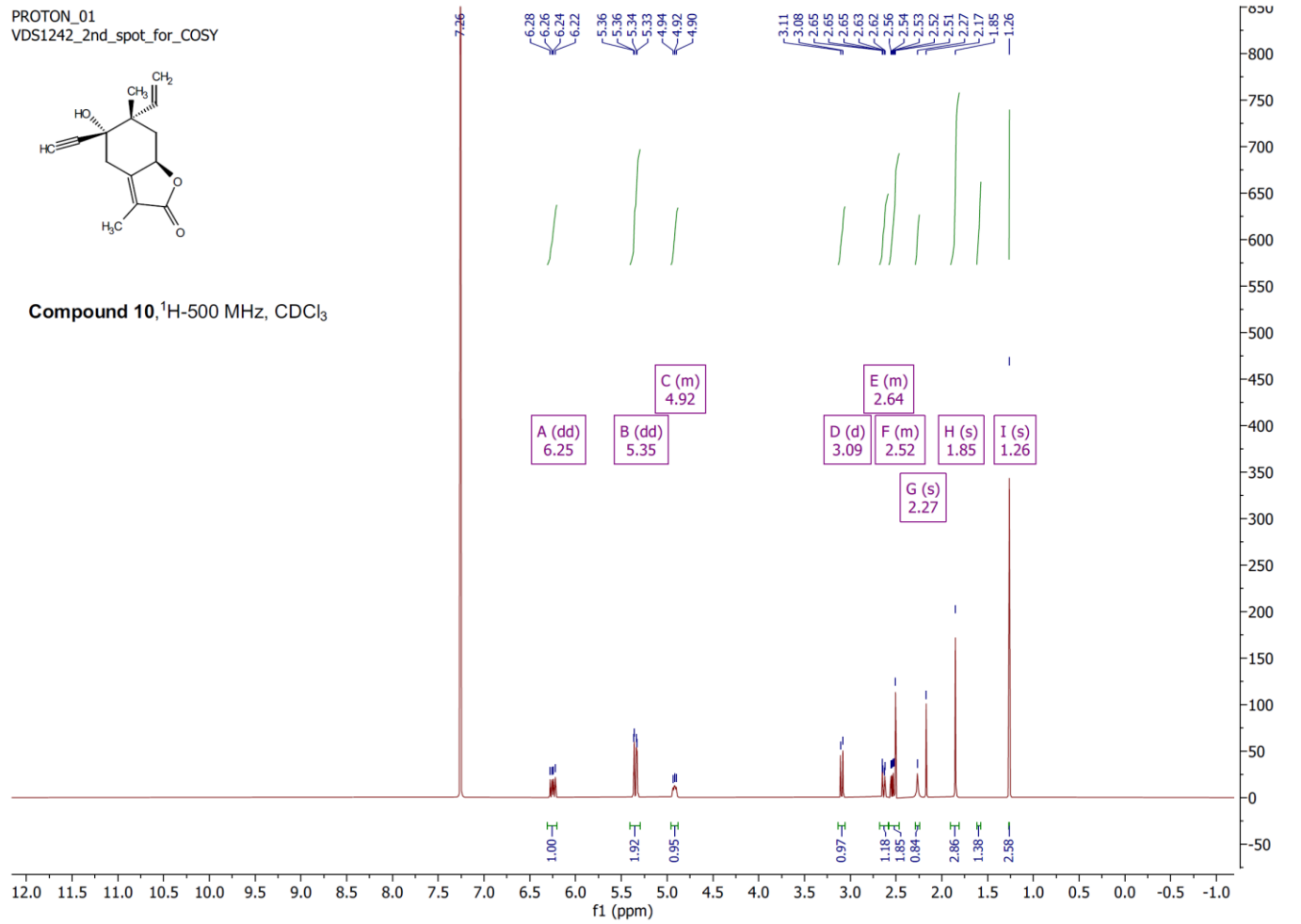

Compound SI-9, gCOSY-500 MHz, CDCl3
gCOSY_01
VDS1315_2nd_prep_4_for_carbon
f2 (ppm)
f1 (ppm)

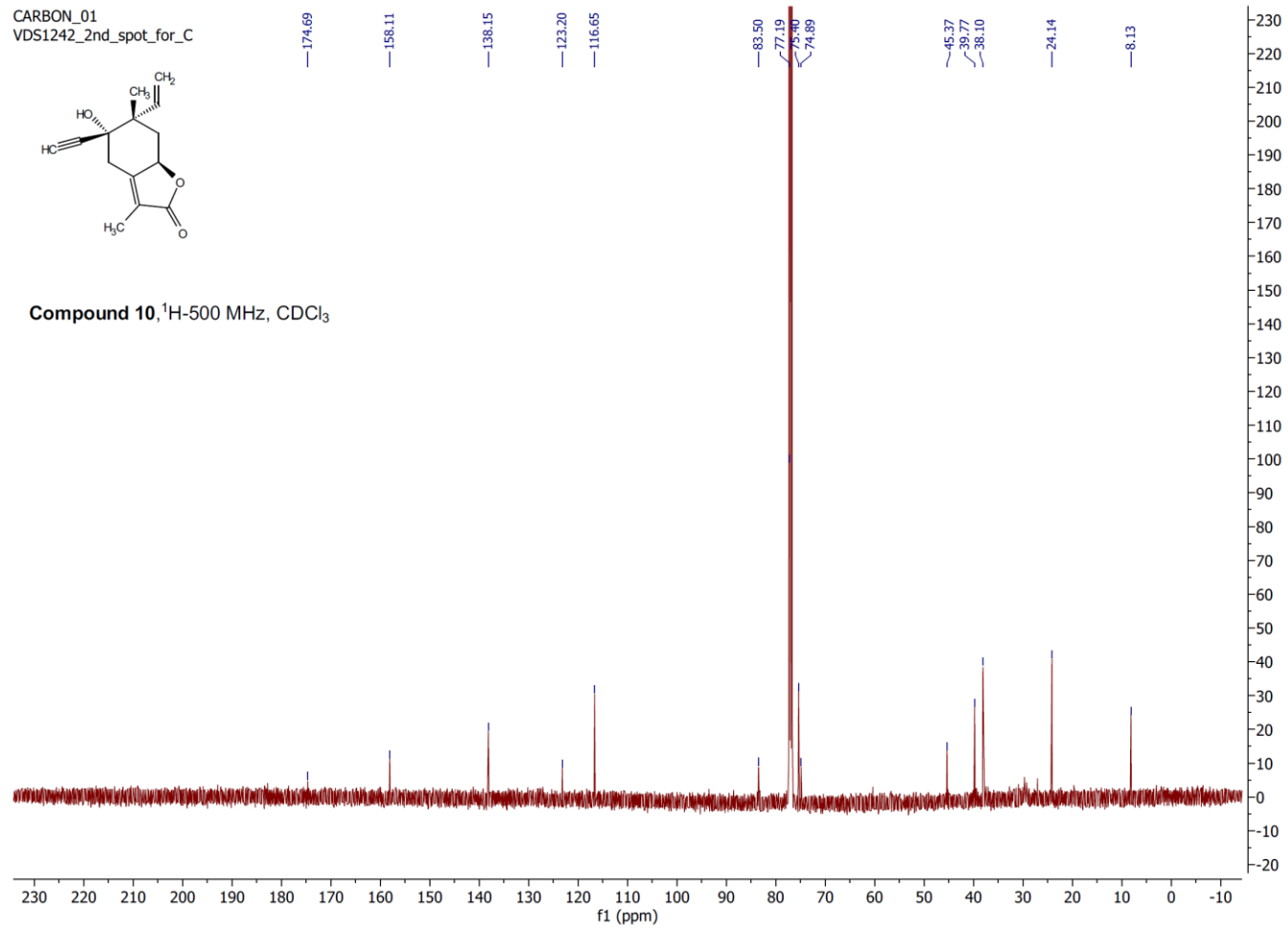

Compound SI-9, NOESY-500 MHz, CDCl3
NOESY_01
VDS1315_2nd_prep_4_for_NOESY
f2 (ppm)
f1 (ppm)


PROTON_01
VDS1187_product
Compound 3,1H-500 MHz, CDCl3
C (dd) 6.12
D (d) 5.30
I (m) 2.17
A (s) 6.18
B (s) 5.62
F (m) 4.61
G (ddd) 3.23
H (s) 2.50
J (m) 1.96
K (s) 1.29
E (d) 5.19
f1 (ppm)

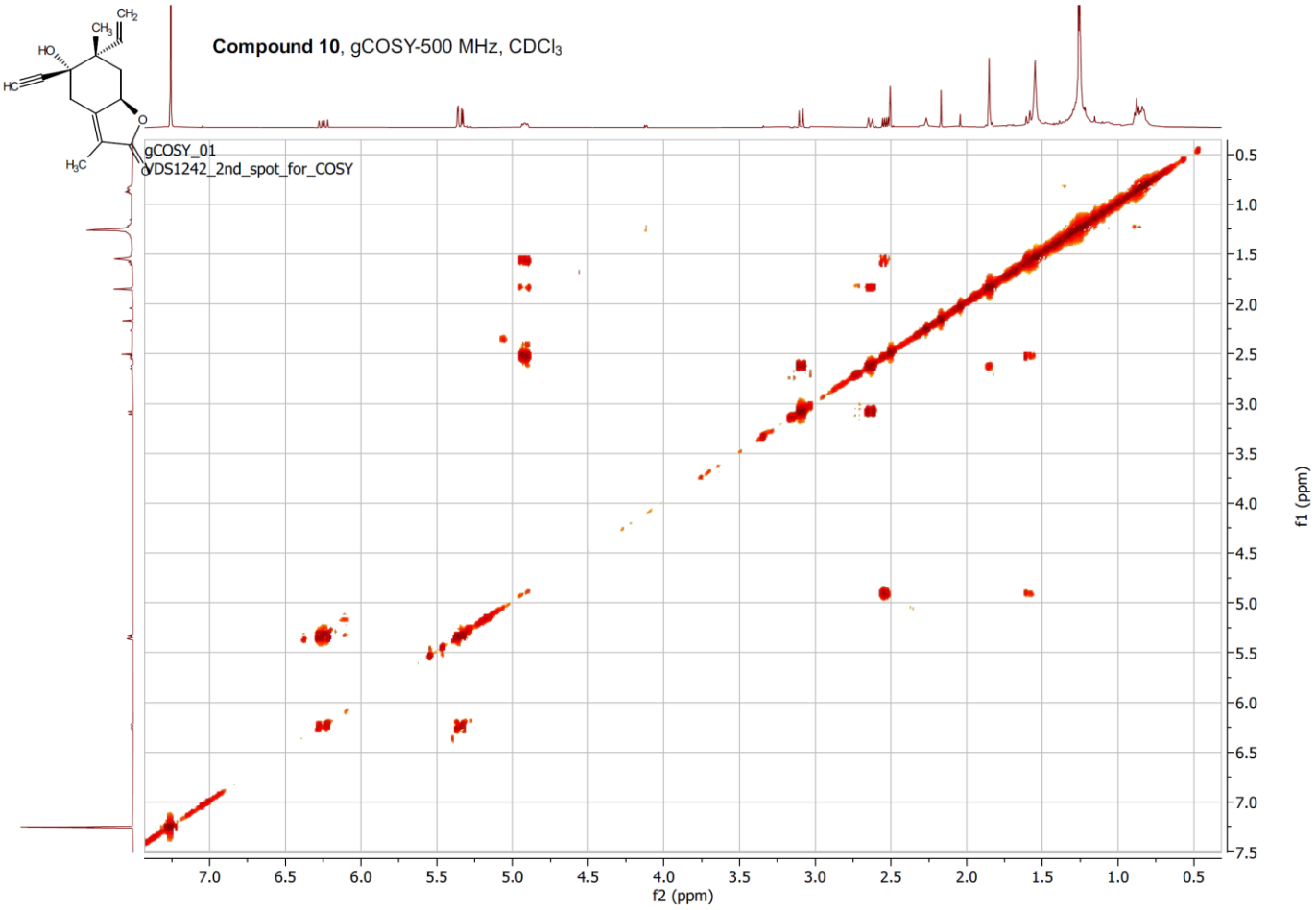

CARBON_01
VDS1187_product_for_C
Compound 3,13C-125 MHz, CDCl3
f1 (ppm)


Compound 3, gCOSY-500 MHz, CDCl3
gCOSY_01
VDS1187_product_for_COSY_HSQC
f2 (ppm)
f1 (ppm)


PROTON_01
VDS1242_2nd_spot_for_COSY
Compound 10,1H-500 MHz, CDCl3
A (dd) 6.25
B (dd) 5.35
C (m) 4.92
D (d) 3.09
E (m) 2.64
F (m) 2.52
G (s) 2.27
H (s) 1.85
I (s) 1.26
f1 (ppm)

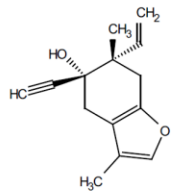



**Compound 10**, $^{1}$H-500 MHz, $CDCl_3$




**Compound 10**, gCOSY-500 MHz, $CDCl_3$

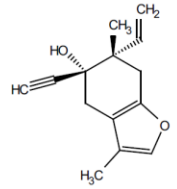
VDS1255



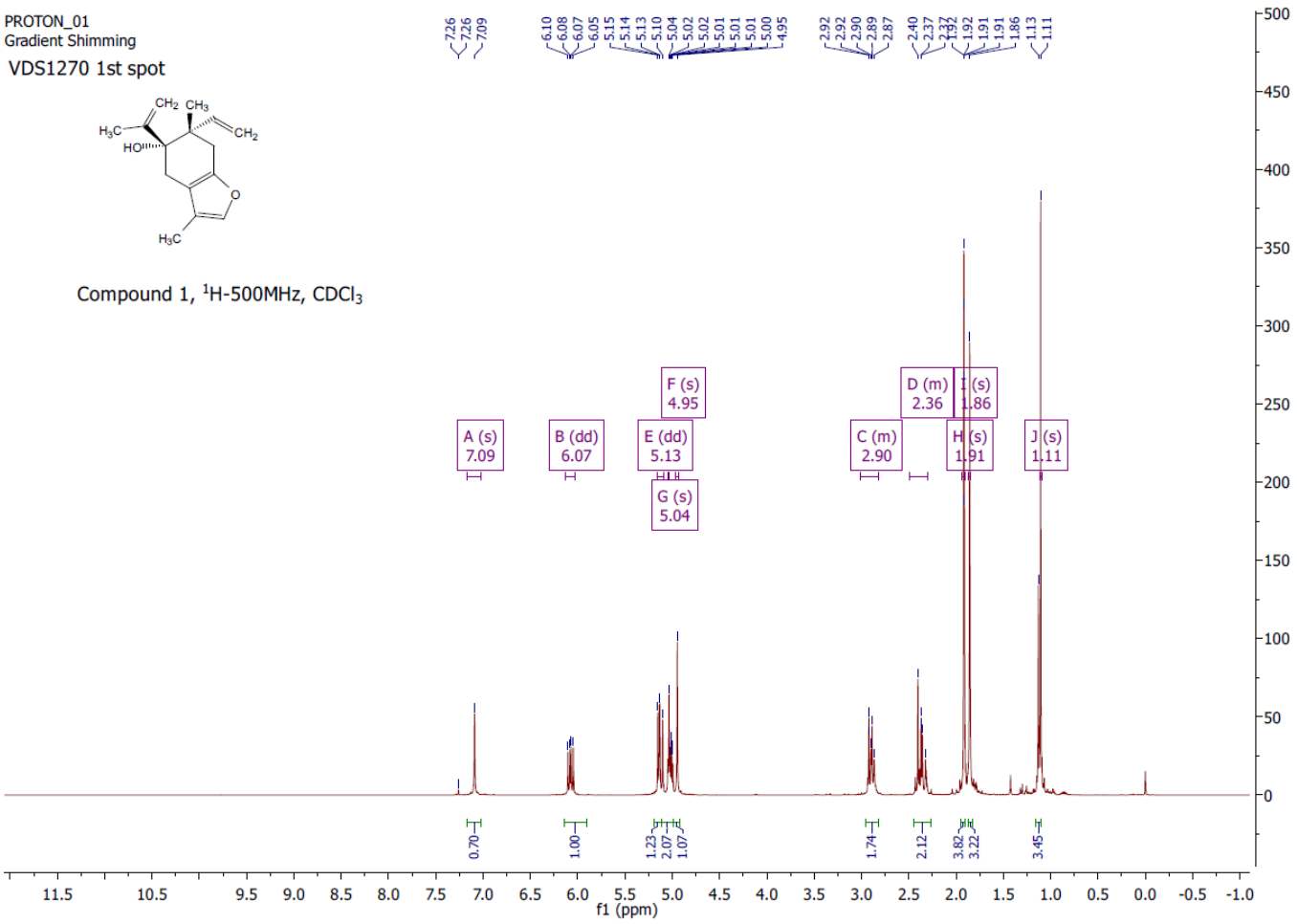
**Compound 2**,$^{1}$H-500 MHz, $CDCl_3$

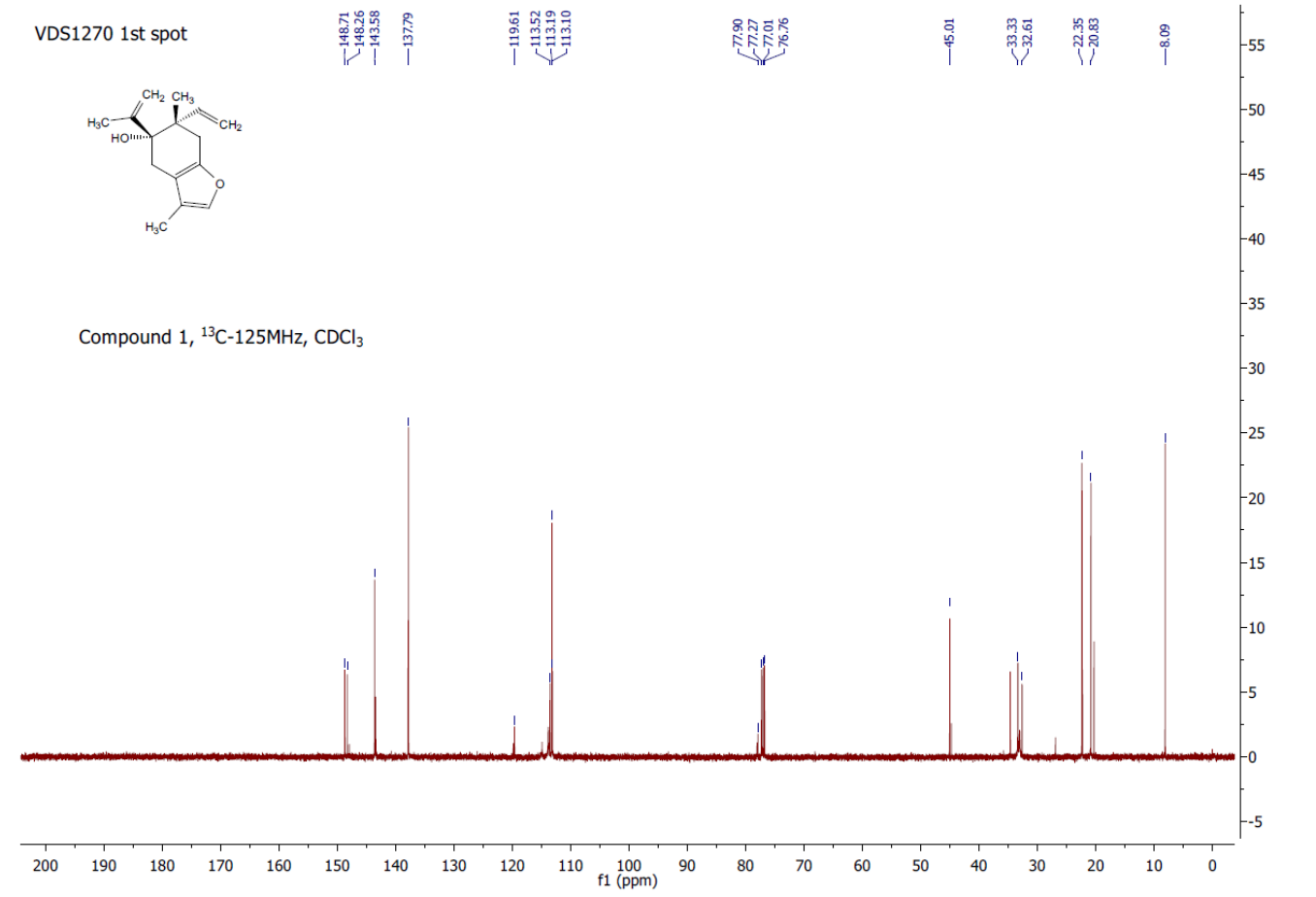



VDS1255



**Compound 2**,$^{13}$C-125 MHz, $CDCl_3$


PROTON_01
Gradient Shimming
VDS1270 1st spot
Compound 1, $^{1}$H-500MHz, $CDCl_3$
A (s) 7.09
B (dd) 6.07
E (dd) 5.13
F (s) 4.95
G (s) 5.04
C (m) 2.90
D (m) 2.36
H (s) 1.91
I (s) 1.86
J (s) 1.11
f1 (ppm)


VDS1270 1st spot
Compound 1, $^{13}$C-125MHz, $CDCl_3$
f1 (ppm)

## 6. References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