Supporting Information

A practical deca-gram scale ring expansion of (*R*)-(–)-carvone to (*R*)-(+)-3-methyl-6-isopropenyl-cyclohept-3-enone-1.

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Table of Contents

1. General Information

All water sensitive reactions were performed using oven-dried (130 °C) and then flame dried glassware. The reactions were performed under an atmosphere of dry argon, unless otherwise stated. The final extracted solutions were concentrated on a Büchi Labortechnik AG rotary evaporator model R-215 at 200–100 mBar and 35–40 ^{o}C.

Solvents and reagents: DMSO and DMF (for the batch reactions) were treated with CaH_2, distilled and stored over 3Å molecular sieves under an argon atmosphere, whereas DMSO 99%+ for flow reactions was purchased from Alfa-Aesar and used as supplied. THF was distilled from sodium-benzophenone and used directly. Hexanes and EtOAc were distilled before use, and other reagents were used as supplied from commercial sources without further purification. The *R*-(–)-carvone used in these experiments has a chemical purity of 98% (by GC and NMR), an enantiomeric purity of 99.5% (by chiral column GC) and specific rotation $[\alpha]_D^{25} = –60.8$ (neat); lit.[1] $[\alpha]_D^{25} = –61.0$ (neat), and was kindly donated by Firmenich S.A. (São Paulo, Brazil).

NMR spectroscopy: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 (400 MHz) or Bruker DRX-600 (600 MHz) spectrometer at room temperature in $CDCl_3$ (99.8% atom-D); the residual solvent signals served as internal standard (^{1}H NMR spectra at d 7.26 ppm and ^{13}C NMR spectra at d 77.16 ppm. Chemical shifts are reported in parts per million (ppm). The multiplicity of a signal is reported as: s – singlet; d – doublet; t – triplet; br – broad; m – multiplet. Coupling constants (*J*) are given in Hertz (Hz). The centre of each peak is reported with the exception of multiplet signals where a range of ppm values are given. Spectra are assigned in full with the aid of ^{1}H-COSY, ^{13}C DEPT-135, HMQC, HSQC, HMBC and nOe-diff data where appropriate.

High resolution mass spectrometry (HRMS): Measurements were recorded on a Waters Micromass LCT Premier spectrometer using positive electrospray ionization (ESI+). Measured values are reported to 4 decimal places and are within ±5 ppm of the calculated value. The calculated values are based on the most abundant isotopes.

Microwave apparatus: A Biotage® Initiator Microwave Synthesiser was used to perform the microwave reactions.

Gas chromatography (GC): Analyses were performed using a Shimadzu Corp. GC-17A model equipped with a 30.0 m × 250 μm × 0.25 μm DB-5 capillary column, in the split mode (ratio 26:1) using nitrogen as carrier gas at a flow rate of 49 mL/min (100 kPa). The injection port temperature was maintained at 250 °C, the oven temperature was started at an initial temperature of 70 °C, with a ramp of 8 °C/min to a final temperature of 250 °C where it was held for 10 minutes. The FID detector temperature was maintained at 280 °C.

Gas chromatography coupled to mass spectrometry (GC-MS): Analyses were performed using a Shimadzu Corp. GC-17A model coupled to a GCMS-QP5000, equipped with a 30.0 m × 250 μm × 0.25 μm DB-5 capillary column. The GCMS analyses were carried out in the split mode (ratio 26:1) using helium as carrier gas at a flow rate of 49 mL/min (100 kPa). The GC temperatures were the same as described above.

Gas chromatography with a chiral column: Measurements were performed using a Shimadzu Corp. GC-17A model, equipped with a 30.0 m × 320 μm gamma-cyclodextrin capillary column. The GC analyses were carried out in the split mode (ratio 26:1) using nitrogen as carrier gas at a flow rate of 49 mL/min (100 kPa). The injection port temperature was maintained at 250 °C; the oven was maintained at an

initial temperature of 60 °C, and then increased at 0.5 °C/min to a final temperature of 180 °C where it was held for 10 minutes. The FID detector was maintained at 280 °C.

Infrared (IR) spectroscopy: Spectra were recorded using a Perkin-Elmer Spectrum One FTIR ATR spectrometer. Samples were deposited neat over the ATR. Only the significant peaks are reported, and those corresponding to key functional groups are assigned.

Melting points (mp): Measurements were recorded, without correction, on a MicroQuimica MQAPF-301.

Optical rotation: Measurements were recorded on a Perkin-Elmer Model 241 digital polarimeter using a Na/halogen lamp (589 nm) as the light source over a pathlength of 100 mm. $[\alpha]_D$; values are reported in deg cm^2/g at specified concentrations (c) in g/100 mL and temperature (T).

Column chromatography: When necessary the reaction products were purified by column chromatography on flash silica gel (pore size 60 Å, 230–400 mesh, 40–63 μm particle size).[2] Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (Merck no. 1055540001).

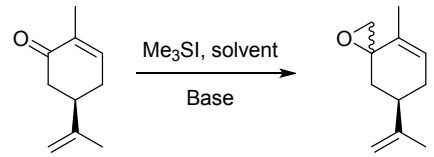
Flow equipment: Flow reactions were performed on a Vapourtec E series Flow Chemistry system equipped with standard PTFE tubing (i.d. 1.0 mm and 2.0 mm, o.d. 1.6 mm and 3.0 mm, respectively). The red end crimped tubing was used to pump the *n*-BuLi solution, and the blue end crimped tubing to pump the other reagent solutions.[3]

General procedure for setting up and cleaning down the peristaltic flow system: To prepare the Vapourtec E series for an organometallic reagent flow-reaction, the procedure used by the Cambridge group was adopted.[3]

2. Experimental Details

Trimethylsulfonium Iodide.[4]

Me_2S (50.7 mL, 0.69 mol, 1.15 equiv) and MeI (37.4 mL, 0.60 mol, 1.0 equiv) were reacted, and the solid product was recrystallized from hot EtOH to furnish white crystals (110.40 g, 0.54 mol) in 90% yield: m.p. 206.8–206.9 °C; lit.[5] m.p. 215–220 °C.



(*R*)-(–)-carvone
1

6a/6b

Compounds 6a/6b: *Batch Procedure with NaH.*

NaH (2.40 g, 60 mmol, 2.0 equiv, 60% mineral oil dispersion, Sigma-Aldrich) was placed in a two-necked round-bottomed flask fitted with a reflux condenser and a septum, maintained under dry argon, with magnetic stirring. The mineral oil was removed with 40–60 petroleum ether (4 × 5 mL) by washing and decantation. Dry DMSO (24 mL) was introduced via syringe and the mixture was heated at 70–75 ˚C until the evolution of hydrogen ceased (~1 h) to give a cloudy yellow-grey solution of dimsyl-Na. The system was cooled down to room temperature, diluted with THF (24 mL), and then cooled to –10 °C (NaCl-ice bath). A previously prepared solution of $Me_3S^+I^-$ (12.24 g, 60 mmol, 2.0 equiv) in DMSO (48 mL) was added over a period of about 3 min. The mixture was stirred for 1 min before adding neat (*R*)-(–)-carvone (4.51 g, 30 mmol, 1.0 equiv.) via syringe during 5 min. Stirring was continued at –10 °C for 1 h and then for a further 1 h with the bath removed. The reaction mixture was

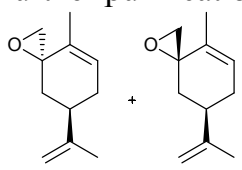
diluted with water (40 mL), extracted with hexane (5 × 20 mL) and washed with brine (3 × 20 mL). The combined organic phases were dried over $NaSO_4$ and solvent removed *in vacuo* to furnish epoxides **6a**/**6b** (4.30 g, 26 mmol, 90:10 ratio by GC and NMR) as a colourless oil in 87% yield.

Compound 6a/6b: *Batch Procedure with n-BuLi in DMSO.*

n-BuLi (100 mL, 250 mmol, 2.0 equiv. 2.5 M in hexanes) was added drop-wise to dry DMSO (75 mL) with magnetic stirring and an argon atmosphere at room temperature. Evolution of gas was observed and monitored by a standard mercury bubbler. After 1 h a biphasic mixture was formed, and the dimsyl-Li solution in DMSO (heavier phase) was added drop-wise via cannula to a solution of $Me_3S^+I^-$ (48.98 g, 240 mmol, 2.0 equiv.) in THF/DMSO (290 mL/75 mL) at –10 °C. The white suspension was stirred for 30 min before addition of a solution of (*R*)-(–)-carvone (18.02 g, 120 mmol, 1.0 equiv) in THF (10 mL) using a syringe pump (1.7 mL/min), over the course of 18 min. The stirring was maintained for 3 h at –10 °C, and then diluted with cold water (150 mL) and hexane (100 mL). The aqueous phase was extracted with hexane (5 × 100 mL). The combined organic phase was washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. A mixture of the epoxides **6a**/**6b** was obtained as a yellowish oil (23.1 g), which was used directly in the next step without any further purification. This crude product was not purified further due to previous difficulties observed with chromatography and distillation.

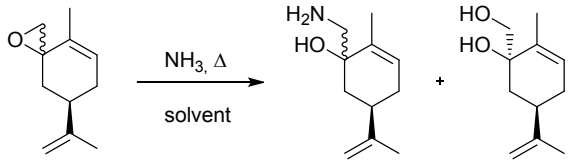
Compound 6a/6b: *Flow Procedure.*

The continuous flow preparation of the epoxides **6a/6b** was carried out using a three-stream reactor assembly. The Vapourtec E-Series machine was charged with a 0.5 M solution of (*R*)-(–)-carvone in DMSO (pump A) at the rate of 1.0 mL.min^{-1}, a 0.4 M solution of $Me_3S^+I^-$ in DMSO (pump B) at the rate of 1.88 mL.min^{-1} and a solution of *n*-BuLi (2.25 M in hexanes) pumped direct from the bottle through C at the rate of 0.340 mL.min^{-1}. The DMSO was used directly without any purification. The desired flow rates were set and all pumps begun and DMSO and hexane were pumped for 5 min. Pump C was timed to switch to pumping *n*-BuLi for 5 min before switching pumps A and B simultaneously to (*R*)-(–)-carvone and $Me_3S^+I^-$ at the rates as determined above. The streams of pumps B and C were mixed through a T-piece generating the ylide, which was mixed with a stream of (*R*)-(–)-carvone from pump A. A PTFE tubing of 2.00 mm i.d. was used between pump C and the second T-piece. The resulting stream was driven to a 10 mL coil reactor at room temperature with residence time of 3.1 min at these flow rates. The quench was made by continuously collecting the output in a conical flask with stirred cold water (50 mL) for 2 h. The reaction mixture was then diluted with cold water (200 mL) and Et_2O (80 mL). The aqueous phase was extracted with Et_2O (4 × 80 mL) and washed with cold water (2 × 80 mL) and brine (2 × 80 mL). The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo* to furnish the epoxides **6a**/**6b** as a pale yellowish oil (9.30 g, 57 mmol) in 95% yield. The crude product was used in the next step without any further purification.



6a **6b**

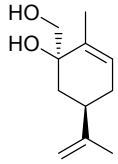
Compounds 6a/6b data: R_f 0.59 (*n*-hexane–EtOAc, 95:5); **Ratio 6a/6b**: 90:10 (^{1}H NMR and GC); $[\alpha]_D^{25}$ = +24.3 (*c* 1.42, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz) major isomer: δ 5.82–5.70 (1H, m), 4.74 (1H, br s), 4.72 (1H, br s), 2.93 (1H, dd, *J* = 4.9, 1.4 Hz), 2.67 (1H, d, *J* = 5.0 Hz), 2.44–2.56 (1H, m), 2.16–2.26 (1H, m), 2.06–2.12 (1H, m), 1.98–2.05 (1H, m), 1.73 (3H, br s), 1.50 (3H, br s), 1.45–1.56 (1H, m); **^{13}C NMR** ($CHCl_3$, 100 MHz) major isomer: δ 148.4, 133.0, 128.7, 109.5, 59.0, 53.3, 41.6, 36.8, 31.4, 20.6, 15.6; **IR** (neat, cm^{-1}): 2971, 2919, 1645, 1450, 1436, 888; **LRMS**: *m/z* 164, 149, 135, 121, 107, 93, 91, 77, 55, 41; **HRMS** (ESI+): *m/z* calc. for $C_{11}H_{17}O$ $[M+H]^+$ 165.1279, found 165.1278; **GC**: 9.975 min = **6a**, 9.817 min = **6b**.



6a/6b **4a/4b** **8**

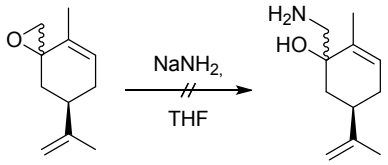
Compounds 4a/4b and 8: *Representative procedure for the epoxide opening with ammonia.*

A commercial ammonia solution in H_2O was used (25–30%, Fisher Scientific). Other ammonia solutions were prepared by bubbling ammonia gas, at room temperature, into the desired solvent for 2 h, to give ammonia solutions in MeOH (8.0 N), isopropanol (4.0 M), dimethoxyethane (2.9 M) and dioxane (2.3 M). The final solutions were analysed by titration with a 0.12 M HCl standard aqueous solution containing bromocresol green as the pH indicator (orange below pH 3.8, blue above pH 5.4 and green at intermediate pH). A screw-cap pressure tube was charged with the epoxides **6a**/**6b** [(**a**) 2.0 g, 12.2 mmol; (**b**) 0.20 g, 1.2 mmol; (**c**) 0.16 g, 1.0 mmol; (**d**) 0.33 g, 2.0 mmol; (**e**) 0.16 g, 1.0 mmol] and ammonia solution [(**a**) 25-30% in H_2O (12.1 mL) and THF (4.0 mL); (**b**) 8.0 N in MeOH (3.0 mL); (**c**) 4.0 M in isopropanol (2.5 mL); (**d**) 2.9 M in dimethoxyethane (7.0 mL); (**e**) 2.3 M in dioxane (4.3 mL)]. The pressure tubes were stoppered and heated at [(**a**) 90–100 °C for 6 h; (**b**) 90 °C for 2.5 h; (**c**) 90 °C for 2.0 h; (**d**) 90 °C for 1.5 h; (**e**) 130 °C for 25 min (MW)]. The mixtures were cooled down to room temperature, the pressure tubes were opened and gently heated at 45 °C for 10–15 min in order to remove the residual ammonia. The crude mixtures were neutralized with AcOH 5% (v/v) solution as measured by pH paper, extracted with EtOAc (5 × 10 mL), and the solvent removed *in vacuo*. The conversions were calculated by ^{1}H NMR analysis of the crude products.



8

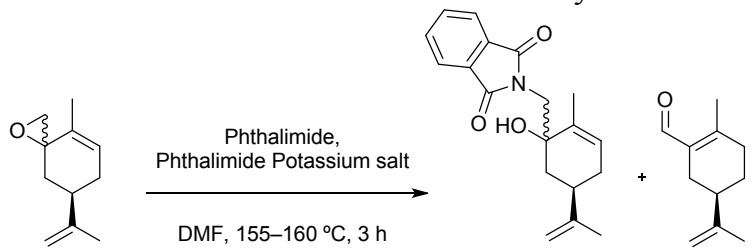
Compound 8 data: R_f 0.43 (*n*-hexane–EtOAc, 50:50); $[\alpha]_D^{25}$ = –0.71 (*c* 0.11, $CHCl_3$); **m.p.** 103.6–104.5 °C; **^{1}H NMR** (400 MHz): δ 5.66–5.74 (1H, m), 4.74–4.77 (2H, m), 3.70 (1H, d, *J* = 10.7 Hz), 3.54 (1H, d, *J* = 10.7 Hz), 2.29–2.40 (1H, m), 2.12–2.20 (1H, m), 1.90–1.96 (1H, m), 1.82–1.89 (1H, m), 1.73–1.79 (6H, m), 1.55–1.64 (1H, m), 1.49–2.45 (2H, m, after D_2O exchange this resonance disappears); **^{13}C NMR** (100 MHz): δ 149.1, 134.2, 128.7, 109.3, 72.8, 68.8, 39.2, 37.1, 31.4, 21.0, 18.0; **IR** (neat, cm^{-1}): 3305, 2946, 2911, 2854, 1645, 1445, 1359, 1011, 889; **LRMS**: *m/z* 182, 164, 151, 123, 109, 93, 91, 67, 55, 41; **HRMS** (ESI+): *m/z* calc. for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1205, found 205.1201; **GC**: 12.983 min = **8**.



6a/6b **4a/4b**

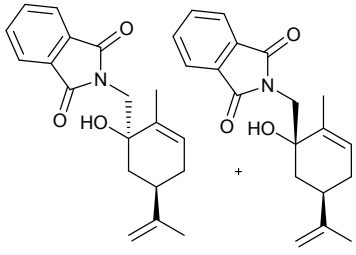
Compounds 4a/4b: *Representative procedure for the epoxide opening with sodium amide.*

A 15 mL screw cap pressure tube was charged with the epoxides **6a**/**6b** (0.40 g, 2.4 mmol), THF (5 mL) and sodium amide (0.17 g, 4.35 mmol, 1.8 equiv.). Ammonia (7 mL) was condensed from the cylinder with a cold-finger condenser and added to a screw cap tube maintained at –78 ˚C with magnetic stirring. The pressure tube was closed and allowed to warm to room temperature, and left stirring for 12 h. After this time, the tube was opened and gentle heated at 45 ˚C in order to remove the residual ammonia. The amino-alcohols **4a**/**4b** were not observed by TLC.



6a/6b **9a/9b** **10**

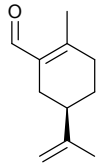
Compounds 9a/9b and 10: To a 1000 mL two necked round-bottomed flask, connected with a condenser, were added sequentially phthalimide (13.76 g, 94 mmol, 0.85 equiv.), potassium phthalimide (3.05 g, 17 mmol, 0.15 equiv.), the epoxides **6a**/**6b** (18.72 g, 110 mmol, 1.0 equiv.) and DMF (240 mL), at room temperature with vigorous magnetic stirring. The suspension was heated at 160 ˚C for 3 h and after cooling down to room temperature the reaction mixture was diluted with EtOAc (150 mL), water (300 mL) and brine (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (5 × 150 mL) and washed with water (2 × 150 mL). The solvent was removed *in vacuo* to afford a brown oil (crude mass 54.10 g). The crude product was used in the next step without any further purification. A small analytical sample was purified by column chromatography (*n*-hexane–EtOAc, 90:10) to affording the pure compounds **9a**/**9b** and **10**.



9a **9b**

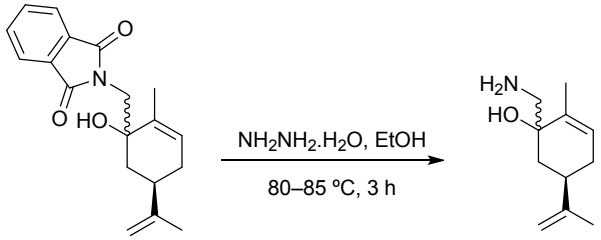
Compounds 9a/9b data: R_f 0.30 (*n*-hexane–EtOAc, 80:20); **Ratio 9a**/**9b**: 85:15 (^{1}H NMR); $[\alpha]_D^{25}$ = –34.4 (*c* 1.40, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz) major isomer: δ 7.81–7.90 (2H, m), 7.68–7.75 (2H, m), 5.58 (1H, br s), 4.76 (1H, br s), 4.70 (1H, br s), 3.98 (1H, d, *J* = 14.6 Hz), 3.84 (1H, d, *J* = 14.6 Hz), 3.18 (1H, s, after D_2O exchange this resonance disappears), 2.52–2.65 (1H, m), 2.07–2.17 (1H, m), 1.92–2.02 (1H, m), 1.85 (3H, br s), 1.77–1.87 (1H, m), 1.70 (3H, br s), 1.44-1.53 (1H, m); **^{13}C NMR**

($CHCl_3$, 100 MHz) major isomer: δ 169.5, 148.7, 135.7, 134.3, 131.9, 126.0, 123.6, 109.5, 75.0, 44.4, 39.0, 38.1, 31.1, 20.5, 17.2; **IR** (neat, cm^{-1}): 3486, 2940, 2920, 1772, 1705, 890, 716; **LRMS:** *m/z* 311, 293, 268, 252, 238, 196, 178, 161, 151, 133, 123, 109, 91, 77, 67, 41; **HRMS** (ESI+): *m/z* calc. for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.1600, found 312.1594; **GC**: 26.925 min = **9a**, 27.025 min = **9b**.



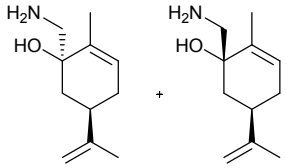
10

Compound 10 data: R_f 0.33 (*n*-hexane–EtOAc, 90:10); $[\alpha]_D^{25}$ = +113 (c 1.16, $CHCl_3$); **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 10.13 (1H, s), 4.73 (1H, br s), 4.69 (1H, br s), 2.44–2.65 (1H, m), 2.26–2.37 (2H, m), 2.13 (3H, s), 2.01–2.10 (1H, m), 1.87–1.95 (1H, m), 1.78–1.86 (1H, m), 1.73 (3H, br s), 1.38–1.51 (1H, m); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 191.0, 155.7, 149.0, 133.3, 109.2, 40.3, 34.8, 27.6, 26.9, 20.9, 18.1; **IR** (neat, cm^{-1}): 2933, 2865, 1666, 1643, 1438, 1232, 888; **LRMS**: *m/z* 164, 149, 123, 121, 95, 93, 68, 53, 41; **HRMS**: *m/z* calc. mass for $C_{11}H_{17}O$ $[M+H]^+$ 165.1279, found 165.1273; **GC**: 11.825 min = **10**.



9a/9b **4a/4b**

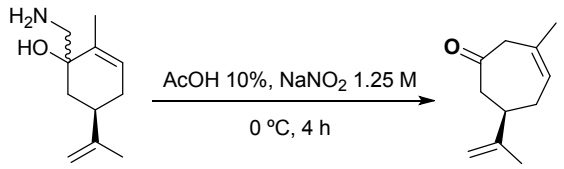
Compounds 4a/4b from 9a/9b: To a suspension of the crude products **9a**/**9b** (54.10 g) in EtOH (500 mL) was added $NH_2NH_2.H_2O$ (14.4 mL, 0.24 mol). The reaction system was heated at 80–85 ºC for 3 h, cooled down to room temperature, and the white solid formed (phthalyl hydrazide) was filtered off in a sintered funnel and washed with EtOH (3 × 30 mL). The ethanolic filtrate afforded after evaporation *in vacuo*, a yellowish oil mixed with a solid characterized as **4a**/**4b** (13.9 g, 76.7 mmol) in 70% yield for the last 2 steps. This mixture was recrystallized from hot *n*-hexane to give **4a** as yellowish crystals (12.16 g, 70.4 mmol) in 64% yield for the last 2 steps. The crude mixture of amino-alcohols **4a**/**4b** can be used directly in next step.



4a **4b**

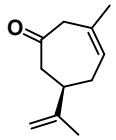
Compound 4a data: R_f 0.29 (MeOH–EtOAc, 50:50); **Ratio 4a**/**4b**: 85:15 (^{1}H NMR and GC); $[\alpha]_D^{25}$ = –118 (*c* 1.03, $CHCl_3$) {lit.[6] $[\alpha]_D^{25}$ = –92.2 (*c* 2.0 $CHCl_3$)}; **m.p.** 100.9–101.5 °C {lit.[6] m.p. 99.2–99.7 °C}; **^{1}H NMR** (600 MHz): δ 5.51 (1H, br s), 4.72 (1H, br s), 4.71 (1H br s), 2.78 (1H, d, *J* = 13.0 Hz), 2.72 (1H, d, *J* = 13.0), 2.21–2.29 (1H, m), 2.04–2.11 (1H, m) 1.88–1.96 (2H, m), 1.72 (3H, br s), 1.70 (3H, br s), 1.45–1.54 (1H, m,), 0.5–3.5 (3H, m, after D_2O exchange this resonance disappears). **^{13}C NMR** (125 MHz): δ 149.1, 137.2, 125.2, 109.2, 73.0, 46.6, 39.5, 38.3, 31.3, 20.6, 17.3; **IR** (film, cm^{-1}): 3372, 3309, 3082, 2955, 2914, 1645, 1596, 940, 891; **LRMS**:

m/z 181, 164, 151, 123, 109, 91, 81, 67, 55, 41; **HRMS** (ESI+): *m/z* calc. for $C_{11}H_{20}NO$ $[M+H]^+$ 182.1545, found 182.1541; **GC**: 12.958 min = **4a**, 13.017 min = **4b**.



4a/4b **2**

Compound 2: *on a 4.94 g (27.6 mmol) scale*.
A solution of the amino-alcohols **4a**/**4b** (4.94 g, 27.6 mmol, 1 equiv.) in 10% (v/v) aqueous AcOH (57.5 mL) at 0 ˚C was treated with a 1.25 M aqueous solution of $NaNO_2$ (39.7 mL, 49.6 mmol, 1.8 equiv). The reaction mixture was stirred for 4 h at 0 ˚C. The aqueous phase was extracted with EtOAc (5 × 20 mL) and the combined organic extracts were washed with 10% (m/v) solution of $NaHCO_3$ (1 × 30 mL), brine (2 × 30 mL), water (2 × 30 mL) and dried over Mg_2SO_4. The solvent was removed *in vacuo* and the residue was immediately purified by flash column chromatography (eluent *n*-hexane–EtOAc 95:5) to afford **2** (3.21 g, 19.5 mmol) in 71% yield.
Compound 2: *on an overall 38.7 g (213.9 mmol) scale, performed simultaneously in 3 flasks with 12.90 g (71.3 mmol) each of crude mixture **4a**/**4b***.
A solution of the amino-alcohols **4a**/**4b** (12.90 g, 71.3 mmol, 1 equiv.) in 10% (v/v) aqueous AcOH (150 mL) at 0 ˚C was treated with a 1.25 M aqueous solution of $NaNO_2$ (103 mL, 128 mmol, 1.8 equiv). The reaction mixture was stirred for 4 h at 0 ˚C. The contents of three 3 flasks were combined, the aqueous phase was extracted with EtOAc (5 × 50 mL) and the organic extracts were washed with 10% (m/v) solution of $NaHCO_3$ (3 × 50 mL), brine (2 × 50 mL), water (2 × 50 mL) and dried over Mg_2SO_4. The solvent was removed *in vacuo* and the residue was immediately purified by flash column chromatography (eluent *n*-hexane–EtOAc 95:5) to afford **2** (15.9 g, 96 mmol) in 35% yield.



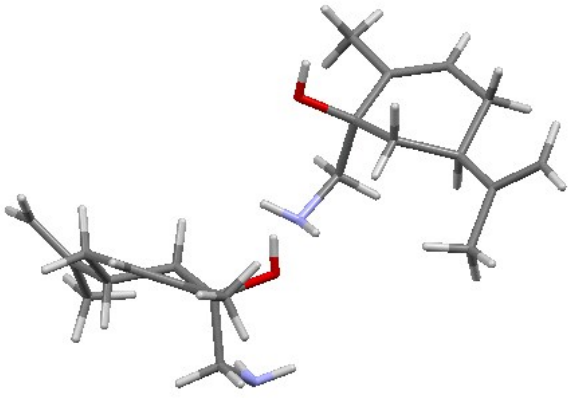
2

Compound 2 data: $\boldsymbol{R_f}$ 0.53 (*n*-hexane–EtOAc, 90:10); $\boldsymbol{[\alpha]_D^{25}}$= +44.3 (*c* 1.15, $CHCl_3$) {lit.[6] $[\alpha]_D^{25}$ = +30.0 (*c* 0.26 $CHCl_3$)}; **^{1}H NMR** ($CHCl_3$, 400 MHz): δ 5.51–5.59 (1H, m), 4.75 (1H, br s), 4.72 (1H, br s), 3.30 (1H, d, J = 14.8 Hz), 2.99 (1H, d, J = 14.8 Hz), 2.70–2.80 (1H, m), 2.60 (1H, br s), 2.58 (1H, br s), 2.16–2.35 (2H, m), 1.77 (3H, br s), 1.72 (3H, br s); **^{13}C NMR** ($CHCl_3$, 100 MHz): δ 208.0, 148.3, 130.4, 124.5, 110.2, 49.0, 48.3, 43.3, 33.1, 26.1, 20.5; **IR** (neat, cm^{-1}): 2969, 2913, 1704, 890; **LRMS**: *m/z* 164, 149, 136, 122, 107, 93, 80, 68, 53, 41; **HRMS**: *m/z* calc. for $C_{11}H_{17}O$ $[M+H]^+$ 165.1279, found 165.1278; **GC**: 10.242 min = **2**.

3. X-ray data 4a: File reference SL1309

Table 1 – Crystal data and structure refinement of **4a**

Empirical formula	$C_{11}H_{19}NO$
Formula weight	181.27
Temperature	180(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P2(1)
Unit cell dimensions	a = 7.7588(3) Å b = 5.5583(2) Å c = 12.2776(6) Å β = 97.980(2)º
Volume	524.35(4) $Å^3$
Z	2
Density (calculated)	1.148 Mg/m^3
Absorption coefficient	0.073 mm^{-1}
F(000)	200
Crystal size	0.46 × 0.07 ×0.05 mm^3
θ range for data collection	3.97 t0 27.75º
Index ranges	$-10 \le h \le 10$, $-5 \le k \le 7$, $-12 \le 1 \le 15$
Reflections collected	3767
Independent reflections	1347 [R_{int} = 0.0792]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1347 / 1 / 129
Goodness-of-fit on F^2	1.020
Final R indices [I>2σ(I)]	R1 = 0.0445, wR2 = 0.1052
R indices (all data)	R1 = 0.0567, wR2 = 0.1097
Largest diff. peak and hole	0.223 and –0.188 $eÅ^3$



4. NMR Spectra

	Parameter	Value
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3	Pulse Sequence	zg30
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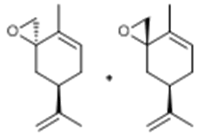
5	Receiver Gain	64
6	Relaxation Delay	1.0000
7	Pulse Width	7.8000
8	Acquisition Time	2.7329
9	Acquisition Date	2013-12-27T17:55:00
10	Modification Date	2013-12-27T14:55:24
11	Spectrometer Frequency	399.57
12	Spectral Width	5995.2
13	Lowest Frequency	-403.1
14	Nucleus	1H
15	Acquired Size	16384
16	Spectral Size	16384



6a 6b

	Parameter	Value
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2	Temperature	298.2
3	Pulse Sequence	zgpg30
4	Number of Scans	256
5	Receiver Gain	8192
6	Relaxation Delay	1.0000
7	Pulse Width	8.7000
8	Acquisition Time	2.5035
9	Acquisition Date	2013-12-27T18:11:00
10	Modification Date	2013-12-27T15:11:10
11	Spectrometer Frequency	100.47
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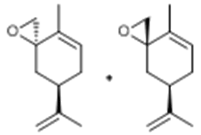
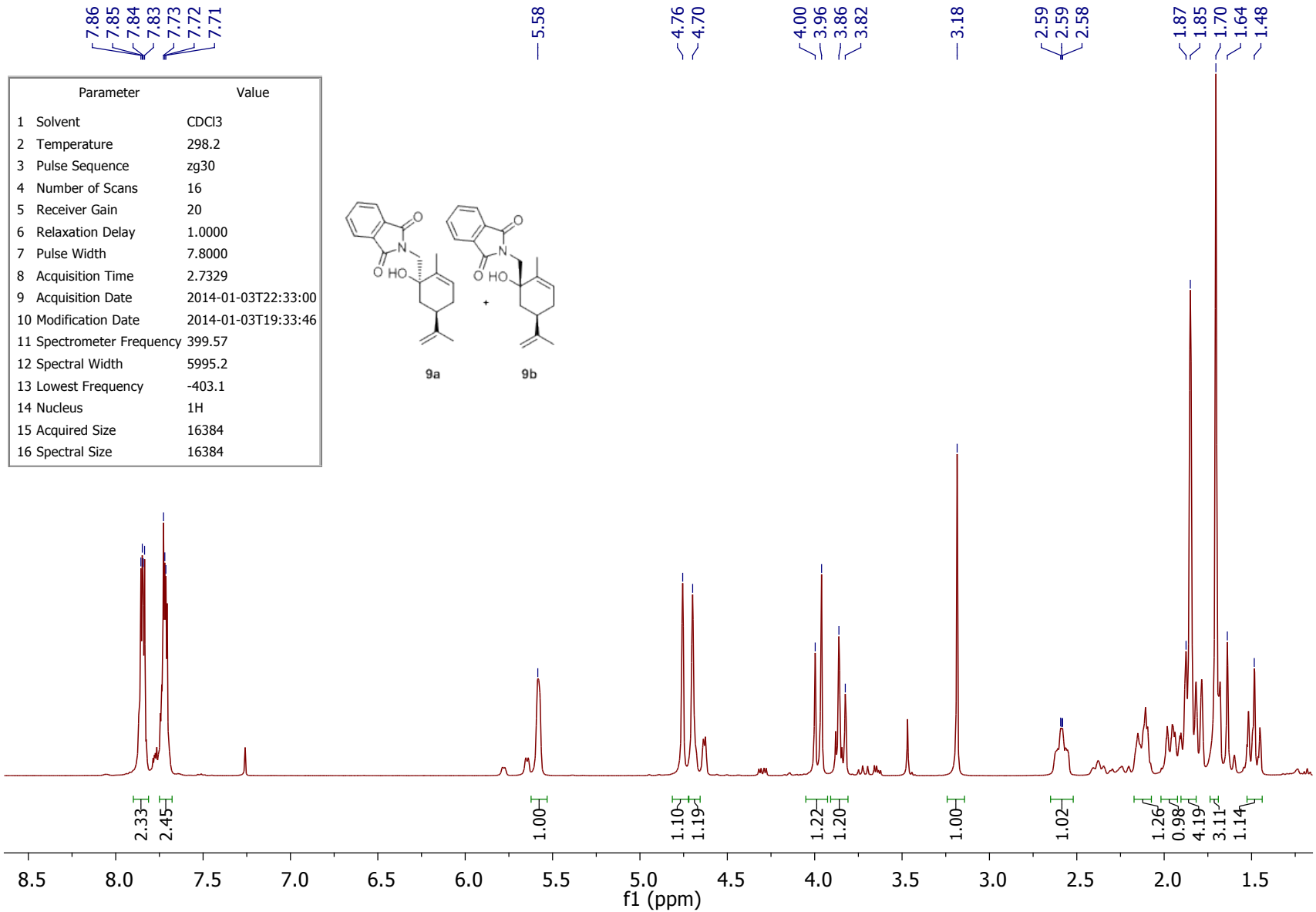
14	Nucleus	13C
15	Acquired Size	65536
16	Spectral Size	65536



6a 6b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7.83
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7.72
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5.58
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4.70
4.00
3.96
3.86
3.82
3.18
2.59
2.59
2.58
1.87
1.85
1.70
1.64
1.48
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2 Temperature 298.2
3 Pulse Sequence zg30
4 Number of Scans 16
5 Receiver Gain 20
6 Relaxation Delay 1.0000
7 Pulse Width 7.8000
8 Acquisition Time 2.7329
9 Acquisition Date 2014-01-03T22:33:00
10 Modification Date 2014-01-03T19:33:46
11 Spectrometer Frequency 399.57
12 Spectral Width 5995.2
13 Lowest Frequency -403.1
14 Nucleus 1H
15 Acquired Size 16384
16 Spectral Size 16384
9a
9b
2.33
2.45
1.00
1.10
1.19
1.22
1.20
1.00
1.02
1.26
0.98
4.19
3.11
1.14
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

	Parameter	Value
1	Solvent	CDCl3
2	Temperature	298.2
3	Pulse Sequence	zgpg30
4	Number of Scans	256
5	Receiver Gain	8192
6	Relaxation Delay	1.0000
7	Pulse Width	8.7000
8	Acquisition Time	2.5035
9	Acquisition Date	2014-01-03T22:49:00
10	Modification Date	2014-01-03T19:49:32
11	Spectrometer Frequency	100.47
12	Spectral Width	26178.0
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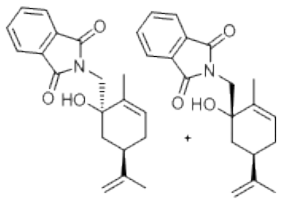
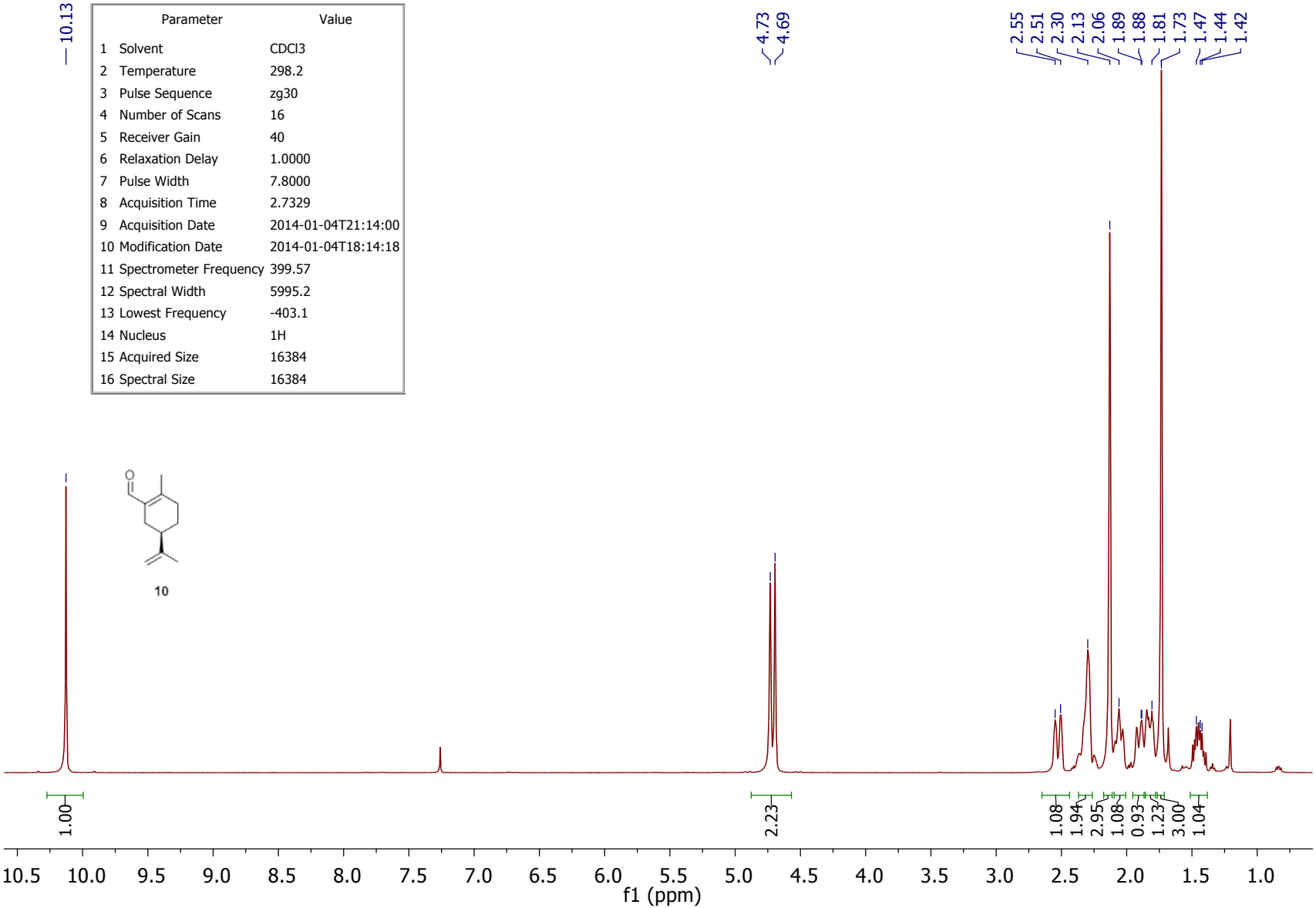
14	Nucleus	13C
15	Acquired Size	65536
16	Spectral Size	65536



9a

9b



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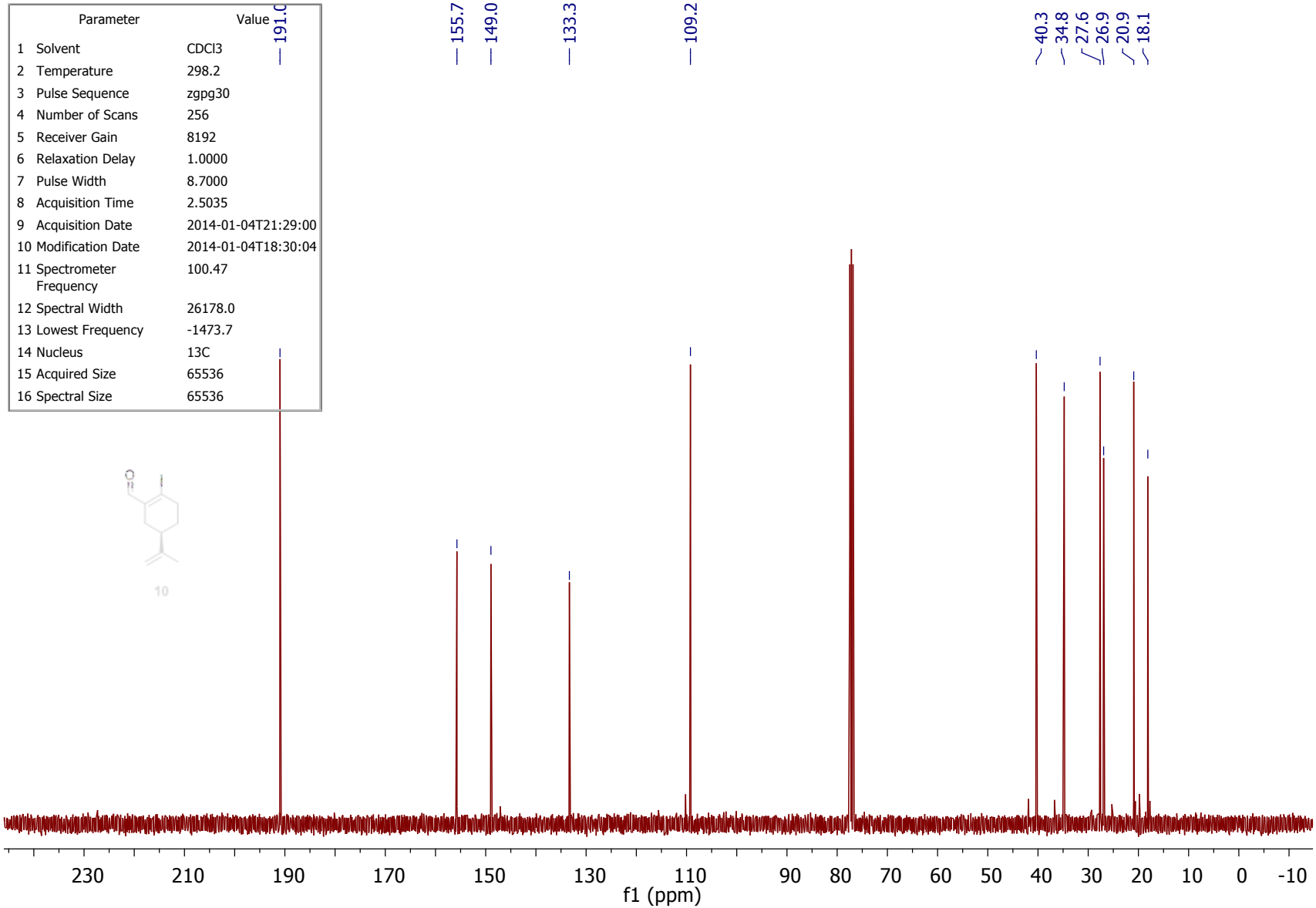
3	Pulse Sequence	zg30
4	Number of Scans	16
5	Receiver Gain	40
6	Relaxation Delay	1.0000
7	Pulse Width	7.8000
8	Acquisition Time	2.7329
9	Acquisition Date	2014-01-04T21:14:00
10	Modification Date	2014-01-04T18:14:18
11	Spectrometer Frequency	399.57
12	Spectral Width	5995.2
13	Lowest Frequency	-403.1
14	Nucleus	1H
15	Acquired Size	16384
16	Spectral Size	16384


Parameter Value
1 Solvent CDCl3
2 Temperature 298.2
3 Pulse Sequence zgpg30
4 Number of Scans 256
5 Receiver Gain 8192
6 Relaxation Delay 1.0000
7 Pulse Width 8.7000
8 Acquisition Time 2.5035
9 Acquisition Date 2014-01-04T21:29:00
10 Modification Date 2014-01-04T18:30:04
11 Spectrometer Frequency 100.47
12 Spectral Width 26178.0
13 Lowest Frequency -1473.7
14 Nucleus 13C
15 Acquired Size 65536
16 Spectral Size 65536
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155.7
149.0
133.3
109.2
40.3
34.8
27.6
26.9
20.9
18.1
10
230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

	Parameter	Value
1	Solvent	CDCl3
2	Temperature	300.0
3	Pulse Sequence	zg30
4	Number of Scans	16
5	Receiver Gain	51
6	Relaxation Delay	1.0000
7	Pulse Width	7.8000
8	Acquisition Time	1.8219
9	Acquisition Date	2013-06-03T12:35:45
10	Modification Date	2013-06-03T12:35:48
11	Spectrometer Frequency	600.13
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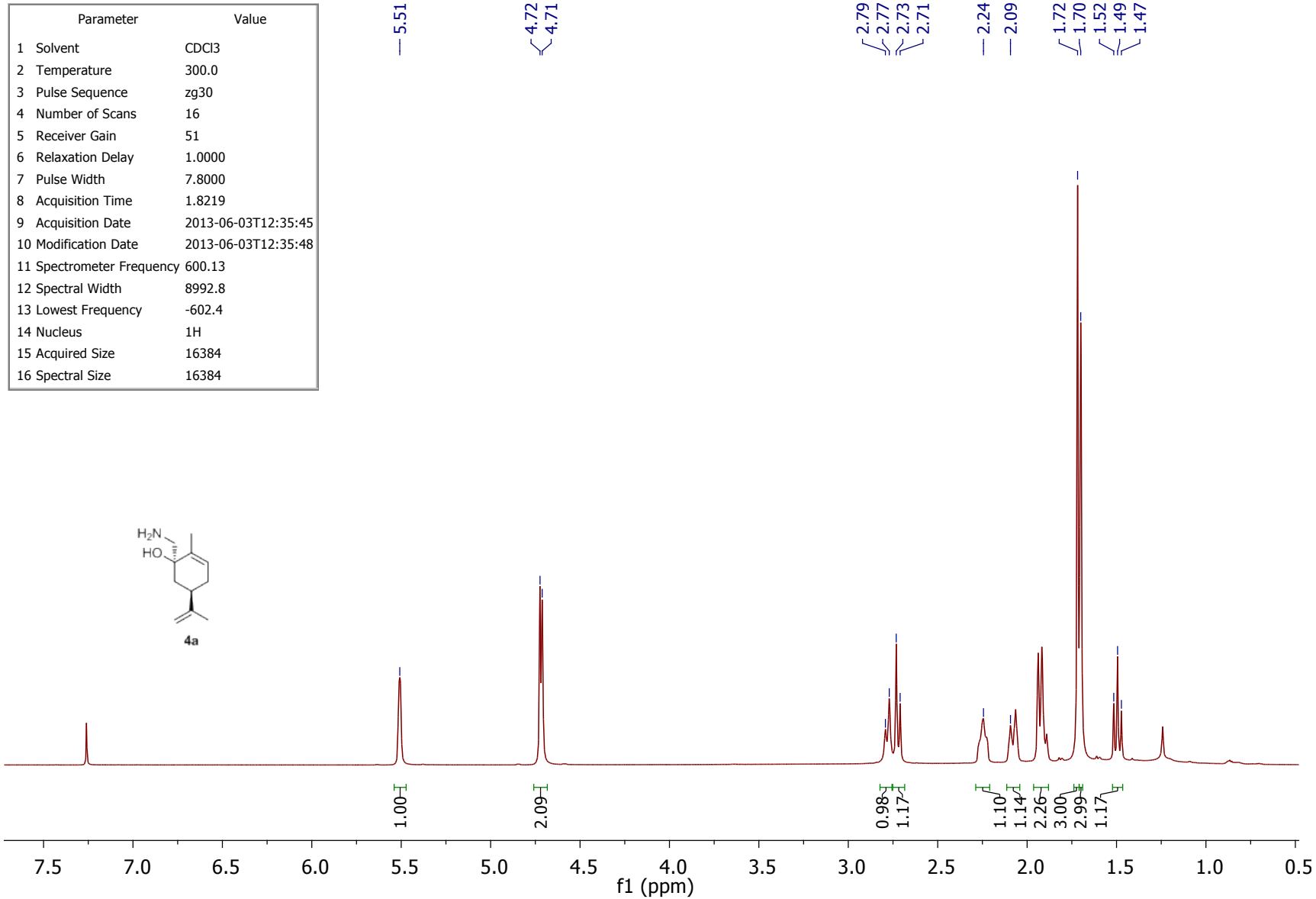
13	Lowest Frequency	-602.4
14	Nucleus	1H
15	Acquired Size	16384
16	Spectral Size	16384



	Parameter	Value
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2	Temperature	300.0
3	Pulse Sequence	zgpg
4	Number of Scans	512
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7	Pulse Width	5.0000
8	Acquisition Time	1.7433
9	Acquisition Date	2013-06-03T13:10:48
10	Modification Date	2013-06-03T13:10:51
11	Spectrometer Frequency	150.92
12	Spectral Width	37594.0
13	Lowest Frequency	-3748.1
14	Nucleus	13C
15	Acquired Size	65536
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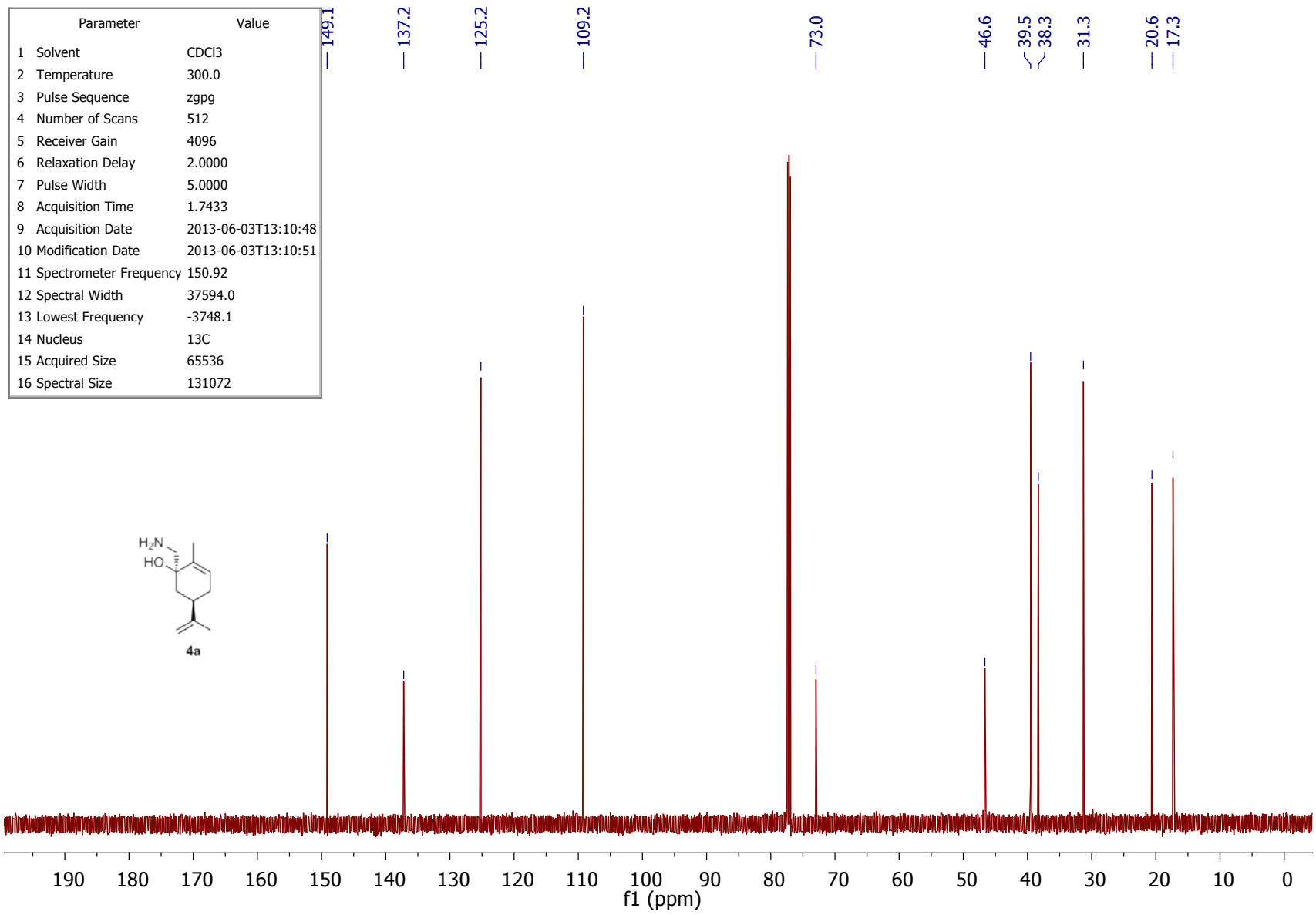
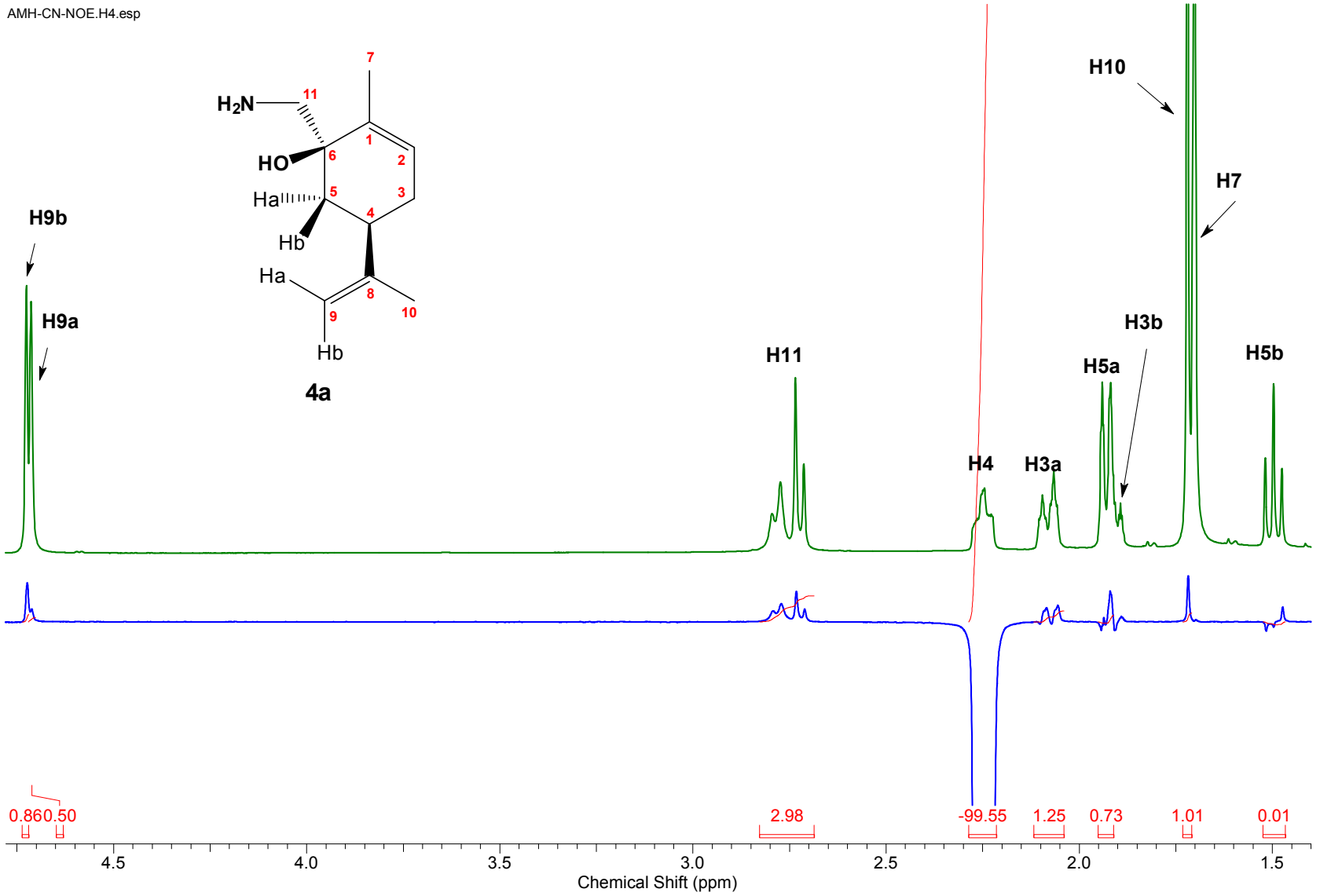
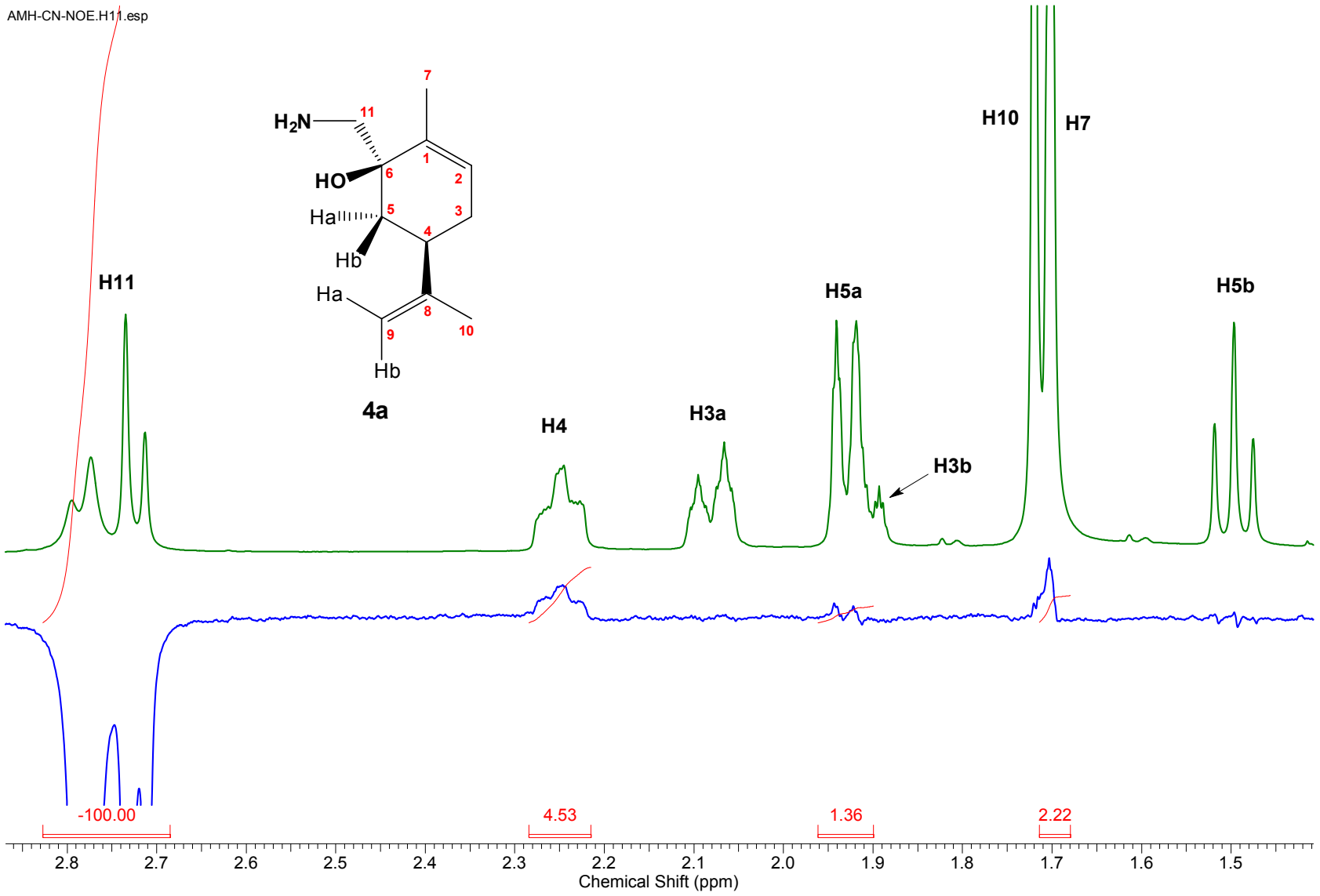


nOe-diff for compound **4a** – H4 irradiated.



nOe-diff for compound **4a** – H11 irradiated.



4a

	Parameter	Value
1	Solvent	CDCl3
2	Temperature	297.5
3	Pulse Sequence	zg30
4	Number of Scans	16
5	Receiver Gain	114
6	Relaxation Delay	1.0000
7	Pulse Width	8.7600
8	Acquisition Time	3.7225
9	Acquisition Date	2013-03-12T08:25:00
10	Modification Date	2013-03-12T22:11:00
11	Spectrometer Frequency	400.15
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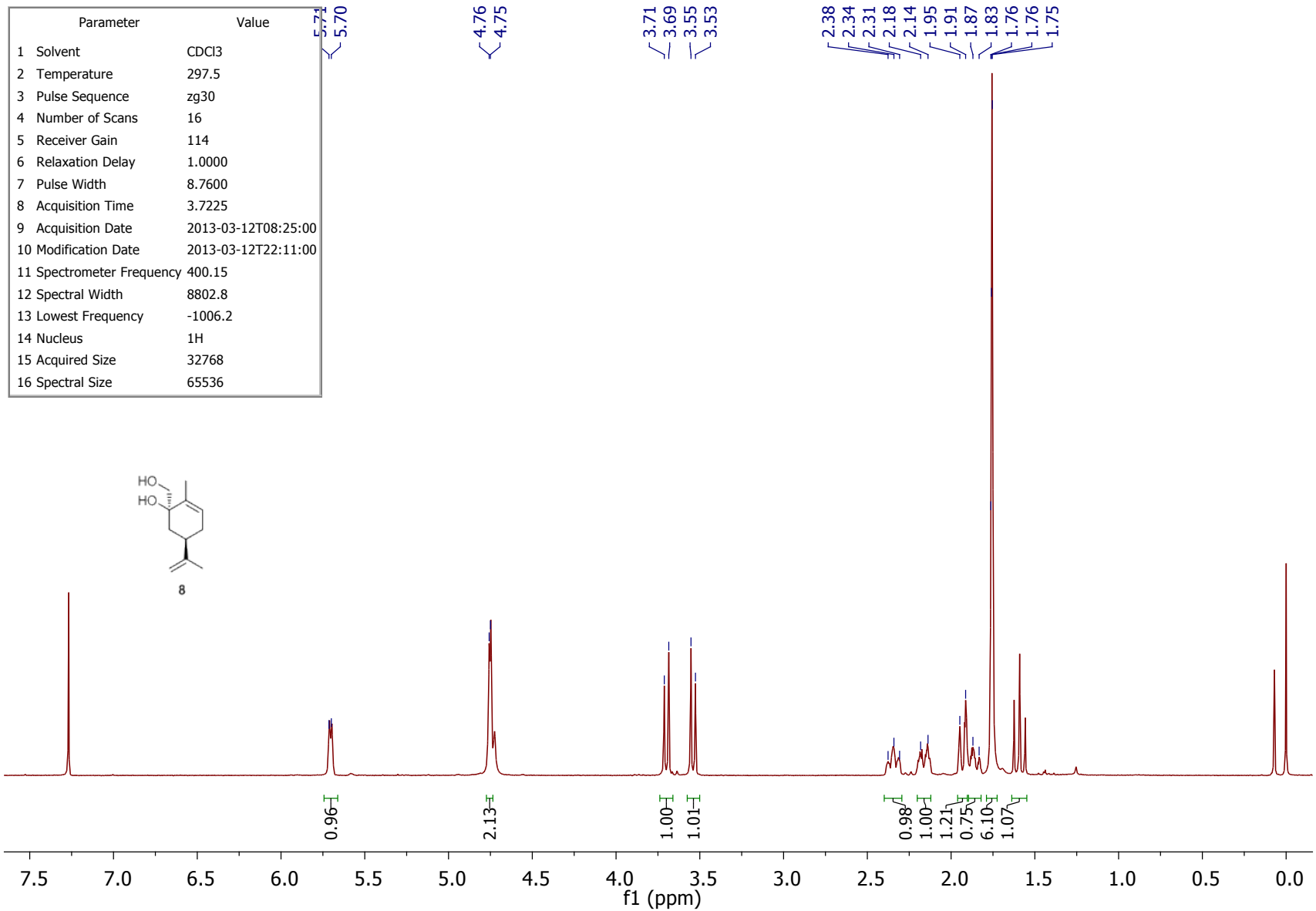
13	Lowest Frequency	-1006.2
14	Nucleus	1H
15	Acquired Size	32768
16	Spectral Size	65536



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3	Pulse Sequence	zgpg30
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7	Pulse Width	8.7500
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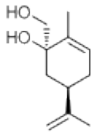
14	Nucleus	13C
15	Acquired Size	16384
16	Spectral Size	32768



8

	Parameter	Value
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4	Number of Scans	16
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6	Relaxation Delay	1.0000
7	Pulse Width	7.8000
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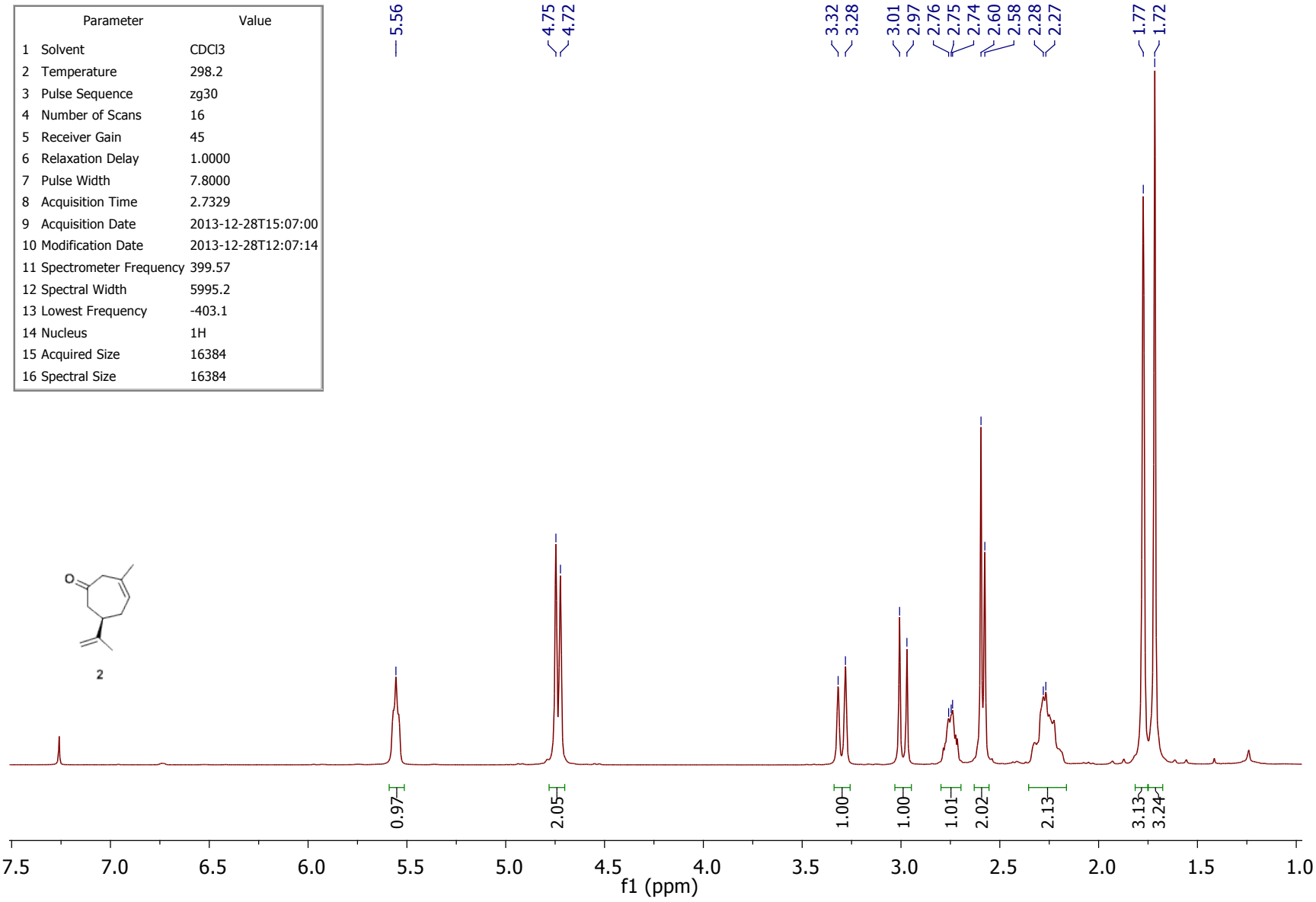
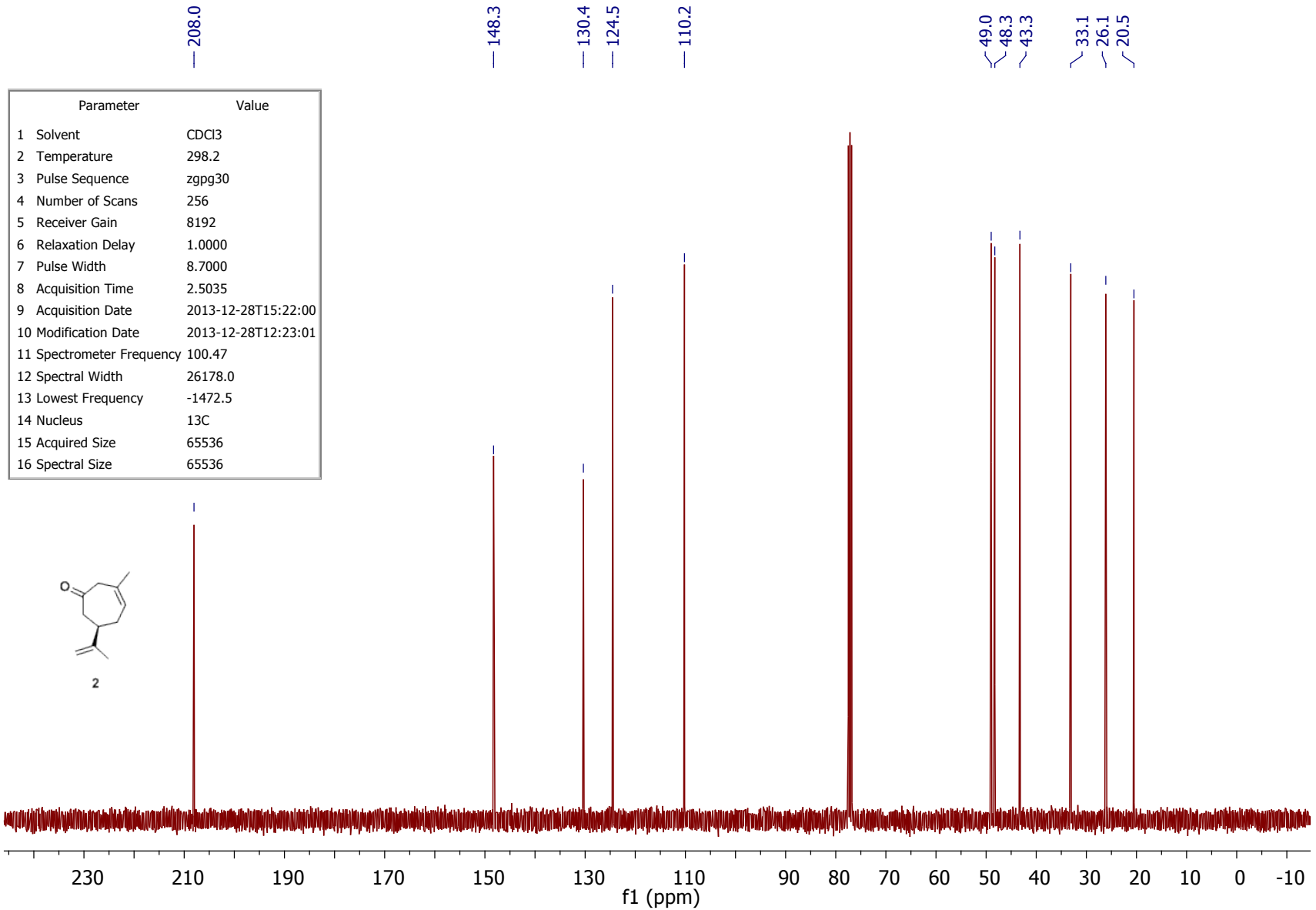
15	Acquired Size	16384
16	Spectral Size	16384

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124.5
110.2
49.0
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43.3
33.1
26.1
20.5
Parameter Value
1 Solvent CDCl3
2 Temperature 298.2
3 Pulse Sequence zgpg30
4 Number of Scans 256
5 Receiver Gain 8192
6 Relaxation Delay 1.0000
7 Pulse Width 8.7000
8 Acquisition Time 2.5035
9 Acquisition Date 2013-12-28T15:22:00
10 Modification Date 2013-12-28T12:23:01
11 Spectrometer Frequency 100.47
12 Spectral Width 26178.0
13 Lowest Frequency -1472.5
14 Nucleus 13C
15 Acquired Size 65536
16 Spectral Size 65536
O
2
230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5. References

[1] http://www.sigmaaldrich.com/catalog/product/aldrich/124931?lang=en&region=GB (accessed December 2014).

[2] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923–2925.

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