Asymmetric Synthesis of Seven-Membered Carbocyclic Rings via a Sequential Oxyanionic 5-Exo Dig Cyclization/Claisen Rearrangement Process. Total Synthesis of (–)-Frondosin B

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Supporting Information

Contents:

General Experimental.

^{1}H and ^{13}C NMR spectra were obtained using a Varian INOVA NMR 500 MHz spectrometer. Chemical shifts are reported in units of parts per million (ppm), relative to tetramethylsilane at $\delta = 0.00$ ppm. Coupling constants *J* are reported in hertz (Hz).

Infrared spectra were recorded on a Pelkin Elmer 1600 series FT-IR and reported in cm^{-1}. Melting points were observed using a Melt-Temp in an open Pyrex capillary tube and are uncorrected. High resolution mass spectra were analyzed by the Mass Spectrometry Laboratory at the University of Illinois, Urbana Champaign, Illinois.

Optical rotations were measured at 589 nm on a Jasco P-1010 digital polarimeter. Sample concentrations are reported in g/100 mL ($CHCl_3$). Enantiomer ratios were determined either by chiral HPLC or chiral GC. The HPLC measurements were done on an Agilent 1100 series instrument equipped with a DAICEL OD (cellulose tris-(3,5-dimethylphenyl) carbamate) chiral column and a diode array detector measured at 283 nm. Eluting solvent was a mixture of 2-propanol and hexane at a flow rate of 1 mL/min. The GC measurements were done on a Hewlett-Packard P 5890 II chromatograph equipped with a flame ionization detector, ChemStation software (version A.03.00), and Chiradex B-DM (*beta*-cyclodextrin) chiral column (30 m x 0.25 mm i.d., split ratio 100:1, He carrier gas average linear velocity at 60 cm/sec).

All microwave experiments were conducted in a CEM Focused Microwave™ Synthesis System, Model Discover microwave oven, equipped with an infrared temperature control system. All microwave reactions were performed in sealed 10 mL microwave vials.

Tetrahydrofuran (THF) was freshly distilled under N_2 from dark blue solutions of sodium benzophenone ketyl. Phenetole (PhOEt), CH_2Cl_2 (DCM), TMSCl, and Et_3N were freshly distilled from calcium hydride. Bulk solvents were purchased from Fisher or VWR.

All starting reagents were purchased from Aldrich, Acros or Strem. The concentrations of solutions of *n*-BuLi were determined by titrations with *sec*-butyl alcohol using 1,10-phenantroline as the indicator following the method of Watson and Eastham.[1] All glassware was flame-dried under an inert atmosphere and all reactions were performed under an atmosphere of dry argon or nitrogen.

[1] S. C. Watson, J. F. Eastham, *J. Organomet. Chem.* **1967**, *9*, 165-168.

Experimental Procedures

1-Cyclopentenyl-4-pentyn-1-one (2a)

Following the general procedure of Bobbitt et al.,[2] silica gel (2.0 g) was added to a solution of 1-cyclopentenyl-4-pentyn-1-ol (1.00 g, 6.66 mmol) in CH_2Cl_2 (65 mL), and the resulting slurry was stirred for 3 min. 4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (2.10 g, 7.00 mmol) was then added and the reaction mixture was stirred vigorously at room temperature for 4h. The mixture was then filtered through a short pad (10 mm) of silica gel, washing with more CH_2Cl_2. The filtrate was concentrated under vacuum and the residue was purified by column chromatography on silica gel (6% EtOAc in hexanes) to afford ketone **2a** as a pale yellow oil (0.937 g, 77%). IR (neat) 3291, 2953, 2115, 1668, 1612, 1432, 1378, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.75-6.73 (m, 1 H), 2.92-2.88 (m, 2 H), 2.57-2.50 (m, 4H), 2.49-2.44 (m, 2H), 1.94-1.88 (overlapping patterns, 3H); ^{13}C NMR 196.2, 145.2, 143.8, 83.5, 68.5, 37.7, 33.9, 30.5, 22.7, 13.2; HRMS (EI) calcd for $C_{10}H_{11}O$ (M^+–1) *m/z* 147.0810, found 147.0810.

1-Cyclohexenyl-4-pentyn-1-one (2b)

Following the procedure described for the synthesis of **2a**, ketone **2b** was prepared from 1-cyclohexenyl-4-pentyn-1-ol as a pale yellow oil in 94% yield. IR (neat) 3299, 2934, 2120, 1667, 1638, 1434, 1389, 990 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.92-6.90 (m, 1H), 2.91-2.86 (m, 2H), 2.50-2.45 (m, 2H), 2.26-2.20 (m, 4H), 1.94 (t, *J*=2.68 Hz, 1H), 1.64-1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.6, 140.3, 138.9, 83.7, 68.4, 35.9, 26.0, 23.0, 21.9, 21.5, 13.4; HRMS (EI) calcd for $C_{11}H_{14}O$ (M^+) *m/z* 162.1045, found 162.1046.

1-Cyclohexenyl-5-phenyl-4-pentyn-1-one (2c)

Following the procedure described for the synthesis of **2a**, ketone **2c** was prepared from 1-cyclohexenyl-5-phenyl-4-pentyn-1-ol as a pale yellow oil in 77% yield. IR (neat) 2931, 2286, 1666, 1490, 1189, 756, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.39 (m, 2H), 7.29-7.27 (m, 3H), 6.96 (t, *J*=1.7 Hz, 1H), 2.99-2.96 (m, 2H), 2.73-2.70 (m, 2H), 2.28-2.25 (m, 4H), 1.67-1.64 (m, 4H); ^{13}C NMR (CDCl3, 125 MHz) δ 198.9, 140.2, 139.0, 131.5, 128.1, 127.5, 123.7, 89.2, 80.8, 36.1, 26.0, 23.0, 21.8, 21.5, 14.5; HRMS (EI) calcd for $C_{17}H_{18}O$ (M^+) *m/z* 238.1358, found 238.1359.

[2] J. M. Bobbitt. *J. Org. Chem.* **1998**, *63,* 9367–9374.

1-Cyclohexenyl-5-(2,5-dimethoxyphenyl)-4-pentyn-1-one (2d)

To a solution of oxalyl chloride (0.25 mL, 2.9 mmol) in 8 mL of CH_2Cl_2 was added DMSO (0.41 mL, 5.8 mmol) at –78˚C and the resulting mixture was stirred for 20 minutes. 1-Cyclohexenyl-5-(2,5-dimethoxyphenyl)-4-pentyn-1-ol (345 mg, 1.15 mmol) in CH_2Cl_2 (10 mL) was then added via cannula at –78˚C and the resulting mixture was allowed to stir for an additional 30 min. Triethylamine (1.60 mL, 11.5 mmol) was then added dropwise to the reaction mixture and stirring was continued thereafter for 1h at –78˚C. Upon warming to room temperature, the solvent was removed under reduced pressure and the resulting yellow slurry was passed through a short pad of Celite, washing the solids several times with diethyl ether (3 x 30 mL). The ethereal solution was then washed with saturated aq. NH_4Cl (1 x 100 mL), the layers were separated and the aqueous layer was extracted with diethyl ether (1 x 15 mL). The combined organic extracts were washed with brine (1 x 100 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (16% EtOAc in hexane) to give ketone **2d** as a pale yellow solid (307 mg, 90%). Mp. 68-71°C; IR (neat) 2933, 1666, 1500; 1464, 1417, 1270, 1232, 1046, 804, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.85-6.93 (m, 1H), 6.89 (d, *J*= 2.9 Hz, 1H), 6.78 (d, *J*= 2.9 Hz, 1H), 6.77 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.00-2.96 (m, 2H), 2.77-2.73 (m, 2H), 2.25-2.21 (m, 4H), 1.63-1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.0, 154.3, 153.2, 140.3, 139.0, 118.4, 114.9, 113.3, 111.9, 93.5, 76.9, 56.4, 55.7, 36.3, 26.1, 23.1, 21.9, 21.5, 14.9; HRMS (EI) calcd for $C_{19}H_{22}O_3$ (M^+) *m/z* 298.1569, found 298.1569.

1-Cyclopentenyl-5-phenyl-4-pentyn-1-one (2e)

Following the procedure described for the synthesis of **2d**, ketone **2e** was prepared from 1-cyclopentenyl-5-phenyl-4-pentyn-1-ol as a pale yellow oil in 89% yield. IR (neat) 2914, 1661, 1614, 1490, 1428, 1377, 1179, 984, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.35 (m, 2H), 7.28-7.25 (m, 3H), 6.80 (br. s, 1H), 3.02-2.97 (m, 2H), 2.74-2.69 (m, 2H), 2.59-2.54 (m, 4H), 1.93 (quin., *J*=7.56 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.6, 145.3, 144.0, 131.5, 128.2, 127.6, 123.7, 89.0, 80.9, 38.0, 34.0, 30.6, 22.7, 14.4; HRMS (EI) calcd for $C_{16}H_{16}O$ (M^+) m/z 224.1201, found 224.1200.

5-(2,5-dimethoxyphenyl)-1-(6,6-dimethylcyclohexenyl)-4-pentyn-1-one (2f)

Following the procedure described for the synthesis of **2a**, ketone **2f** was prepared from 5-(2,5-dimethoxyphenyl)-1-(6,6-dimethylcyclohexenyl)-4-pentyn-1-ol as an off-white solid in 92% yield. Mp 54-55°C; IR (neat) 2930, 2191, 1707, 1610, 1499, 1463, 1272, 1209, 1176, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.89 (d, *J*=2.69 Hz, 1H), 6.77 (d, *J*=2.69 Hz, 1H), 6.76 (s, 1H), 6.74 (app t, *J*=3.91 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.95-2.92 (m, 2H), 2.73-2.70 (m, 2H), 2.20-2.17 (m, 2H), 1.63-1.58 (m, 2H), 1.45-1.42 (m, 2H), 1.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.2, 154.3, 153.1, 147.1, 139.4, 118.4, 114.9, 111.8, 93.5, 76.9, 56.4, 55.7, 40.4, 38.4, 33.4, 27.9, 26.6, 18.1, 15.0; HRMS (EI) calcd for $C_{21}H_{26}O$ (M^+) m/z 326.1882, found 326.1884.

(*R*)-1-Cyclopentenyl-4-pentyn-1-ol (3a).

General procedure for the asymmetric reduction of enones[3] 3a-f:

A solution of ketone **2a** (701 mg, 4.72 mmol) in 49 mL of toluene was added to (-)-(S)-CBS reagent (1M, 0.708 mL, 0.708 mmol) in toluene (21 mL) and the resulting mixture was cooled to –78˚C. After 15 min, catecholborane (849 mg, 7.08 mmol) was added and the reaction was stirred for an additional 40 h at –78 °C. Methanol (3.6 mL) was then added to quench the reaction. Upon warming warm to room temperature, the mixture was diluted with diethyl ether (400 mL) and transferred to a beaker along with 1M aq. NaOH/saturated $NaHCO_3$ (2:1 by volume) solution (300 mL). The resulting heterogeneous mixture was stirred vigorously for 15 minutes, the layers were separated and the organic layer was washed again with the 1M NaOH/ saturated $NaHCO_3$ (2:1) solution until the aqueous layers remained clear. The dark aqueous layers were extracted with ether (2 x 100 mL), the combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a volume of ~40 mL. A solution of HCl/MeOH (1.25 M, 0.76 mL, 0.95 mmol) was then added and the resulting precipitate was removed by filtration. After solvent removal under reduced pressure, the crude product was purified by column chromatography on silica gel (15% EtOAc in hexane) to give alcohol **3a** as a pale yellow oil (612 mg, 86%). The observed enantiomer ratio of 93.5% : 6.5% (87% *ee*) was determined by chiral GC. $[\alpha]^{21}_D$ = +8.6 (*c* 0.465, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **3a**.[4]

[3] E. J. Corey, C. J. Helal, *Angew. Chem., Int. Ed.* **1998**, *37*, 1986-2012.
[4] X. Li, R. E. Kyne, T. V. Ovaska, *J. Org. Chem.* **2007**, *72*, 6624-6627.

(*R*)-1-Cyclohexenyl-4-pentyn-1-ol (3b).

Following the procedure described for the synthesis of **3a**, alcohol **3b** was prepared from **2b** as a pale yellow oil in 66% yield. The observed enantiomer ratio of 94.5% : 5.5% (89% *ee*) was determined by chiral GC. $[\alpha]^{20}_{D} = -3.9$ (*c* 1.50, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **3b**.[4]

(*R*)-1-Cyclohexenyl-5-phenyl-4-pentyn-1-ol (3c).

Following the procedure described for the synthesis of **3a**, alcohol **3c** was prepared from **2c** as a pale yellow oil in 95% yield. The observed enantiomer ratio of 95.5% : 4.5% (91% *ee*) was determined by chiral GC. $[\alpha]^{21}_{D} = -23.8$ (*c* 0.875, $CHCl_3$). IR (neat) 3368, 3056, 3032, 2926, 2857, 2234, 1599, 1491, 1263, 1054, 756, 692; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.30 (m, 2H), 7.30-7.25 (m, 3H), 2.76-2.75 (m, 1H), 4.19 (t, *J*= 6.3 Hz, 1H), 2.55-2.45 (m, 2H), 2.15-2.06 (m, 2H), 2.01-1.93 (m, 1H), 1.85 (app. q, *J*=6.8 Hz, 2H), 1.75-1.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.3, 131.5, 128.2, 127.6, 123.8, 123.5, 89.7, 80.9, 75.5, 33.8, 25.0, 23.6, 22.6 (two peaks), 16.1; HRMS (EI) calcd for $C_{17}H_{20}O$ (M^+) m/z 240.1514, found 240.1514.

(*R*)-1-Cyclohexenyl-5-(2,5-dimethoxyphenyl)-4-pentyn-1-ol (3d).

Following the procedure described for the synthesis of **3a**, alcohol **3d** was prepared from **2d** as pale yellow semi-solid in 81% yield. The observed enantiomer ratio of 95.5% : 4.5% (91% *ee*) was determined by chiral HPLC. $[\alpha]^{22}_{D} = -12.9$ (*c* 0.605, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **3d**.[4]

(*R*)-1-Cyclopentenyl-5-phenyl-4-pentyn-1-ol (3e).

Following the procedure described for the synthesis of **3a**, alcohol **3e** was prepared from **2e** as a pale yellow liquid in 52% yield. The observed enantiomer ratio of 94.5% : 5.5% (89% *ee*) was determined by chiral GC. $[\alpha]^{23}_{D} = -11.5$ (*c* 1.70, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **3e**.[4]

(*R*)-5-(2,5-dimethoxyphenyl)-1-(6,6-dimethylcyclohexenyl)-4-pentyn-1-o1 (3f).

Following the procedure described for the synthesis of **3a** (with the exception that the reaction time at –78 °C was 72h instead of 40h), alcohol **3f** was prepared from **2f** as a viscous pale yellow liquid in 68% yield. The observed enantiomer ratio of 99.0% : 1.0% (98% *ee*) was determined by

chiral HPLC. $[\alpha]^{23}_D$ = +4.6 (*c* 0.980, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **3f**.[5]

(*S*)-2,3,3a,4,6,7-Hexahydroazulen-5(1*H*)-one (4a).

General procedure for the microwave-assisted cyclization/Claisen rearrangement:

Alcohol **3a** (213 mg, 1.42 mmol) was transferred to a 10 mL flame dried microwave vial along with anhydrous phenetole (1.5 mL) followed by the addition of 152 μl of MeLi in Et_2O (1.4 M, 0.213 mmol). The solution was heated at 210 °C for 60 min in the microwave oven. The phenetole solvent was then removed under reduced pressure and the residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to give ketone **4a** as a pale yellow oil (132 mg, 62%). The observed enantiomer ratio of 92.3% : 7.7% (85% *ee*) was determined by chiral GC. $[\alpha]^{22}_D$ = +79.8 (*c* 0.705, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **4a**.[4]

***(S)*-3,4,4a,5,7,8-hexahydro-1*H*-benzo[7]annulen-6(2*H*)-one (4b).**

Following the procedure described for the synthesis of **4a**, ketone **4b** was synthesized from alcohol **3b** as a pale yellow oil in 77% yield. The observed enantiomer ratio of 93.5% : 6.5% (87% *ee*) was determined by chiral GC. $[\alpha]^{23}_D$ = –7.1 (*c* 0.280, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **4b**.[4]

(4a*S*,5*R*)-5-phenyl-3,4,4a,5,7,8-hexahydro-1*H*-benzo[7]annulen-6(2*H*)-one (4c).

Following the procedure described for the synthesis of **4a**, ketone **4c** was synthesized from alcohol **3c** as a white solid in 78% yield (92:8 mixture of diastereomers). The observed enantiomer ratio (purified major diastereomer) of 92.5% : 7.5% (85% *ee*) was determined by chiral HPLC. $[\alpha]^{21}_D$ = +73.9 (*c* 0.655, $CHCl_3$). Mp. 75.5 – 77.0 °C. IR (neat) 3088, 3029, 2928, 2854, 1713, 1601, 1496, 1449, 1337, 1105, 739, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.30 (m, 4H), 7.27-7.24 (m, 1H), 5.59 (dd, *J*=8.54 Hz, *J*=4.64 Hz, 1H), 4.36 (d, *J*=10.7 Hz, 1H), 2.86-2.77 (m, 1H), 2.72-2.60 (m, 2H), 2.49-2.42 (m, 1H), 2.21-2.17 (m, 1H), 2.13-2.06 (m, 1H), 1.99-1.91 (m, 1H), 1.80-1.75 (m, 1H), 1.70-1.65 (m, 1H), 1.58-1.53 (m, 1H), 1.31-1.24 (m, 2H), 1.15-1.06 (m 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.4, 144.3, 137.7, 129.0, 128.2, 127.0,

[5] X. Li, T. V. Ovaska, *Org. Lett.* **2007**, *9*, 3837-3840.

119.7, 58.7, 48.0, 45.4, 39.1, 34.0, 29.1, 26.7, 20.7; HRMS (EI) calcd for $C_{17}H_{20}O$ (M^+) m/z 240.1514, found 240.1512.

(4a*S*,5*R*)-5-(2,5-dimethoxyphenyl)-3,4,4a,5,7,8-hexahydro-1*H*-benzo[7]annulen-6(2*H*)-one (4d).

Following the procedure described for the synthesis of **4a**, ketone **4d** was synthesized from alcohol **3d** as a pale yellow solid in 82% yield (77:23 mixture of diastereomers). The observed enantiomer ratio (purified major diastereomer) of 94.5% : 5.5% (89% *ee*) was determined by chiral HPLC. $[\alpha]^{22}_D$ = +39.6 (*c* 0.555, $CHCl_3$). Mp. 94.5–96.5 °C. The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **4d**.[4]

(3a*S*,4*R*)-4-Phenyl-2,3,3a,4,6,7-hexahydroazulen-5(1*H*)-one (4e).

Following the procedure described for the synthesis of **4a**, ketone **4e** was synthesized from alcohol **3e** as a pale yellow oil in 76% yield (92:8 mixture of diastereomers). The observed enantiomer ratio (purified major diastereomer) of 92.0% : 8.0% (84% *ee*) was determined by chiral HPLC. $[\alpha]^{23}_D$ = +14.8 (*c* 0.602 in $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **4e**.[4]

(*4aS, 5R,*)-5-(2,5-dimethoxyphenyl)-1,1-dimethyl-3,4,4a,5,7,8-hexahydro-*1H*-benzo[7]-annulen-6(*2H*)-one (4f).

Following the procedure described for the synthesis of **4a**, ketone **4f** was synthesized from alcohol **3f** as a viscous pale yellow oil in 79% yield (87:13 mixture of diastereomers). The observed enantiomer ratio (purified major diastereomer) of 97.5% : 2.5% (95% *ee*) was determined by chiral HPLC. $[\alpha]^{23}_D$ = +48.9 (*c* 2.24 in $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **4f**.[5]

(4a*S*,5*R*,7*S*)-5-(2,5-dimethoxyphenyl)-1,1,7-trimethyl-3,4,4a,5,7,8-hexahydro-1*H*-benzo[7]annulen-6(2*H*)-one (5).

To a solution of ketone **4f** (534 mg, 1.62 mmol) in 31 mL THF was added LiHMDS (1.0 M in THF, 1.94 mL, 1.94 mmol) at –78 °C and the resulting mixture was stirred for 30 min at this temperature. Methyl iodide (690 mg, 4.86 mmol) was added and the mixture was subsequently stirred at –60 °C for 3 h. A solution of aqueous NH_4Cl was then added to quench the reaction

and the resulting mixture was allowed to warm to room temperature. The THF solvent was removed under reduced pressure and the residue was diluted with Et_2O (100 mL). The layers were then separated and the ethereal layer was washed with brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure gave the crude product, which was purified by flash column chromatography (10% EtOAc in hexanes) to afford ketone **5** as a viscous colorless oil (474 mg, 85%). The observed enantiomeric excess (97% *ee*) was determined by chiral HPLC. $[\alpha]^{23}_D$ = +71.4 (*c* 0.620, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **5**.[5]

2-((*4aS, 5R, 7S*)- 1,1,7-trimethyl-6-oxo-2,3,4,4a,5,6,7,8-octahydro-1H-benzo[7]annulen-5-yl)cyclohexa-2,5-diene-1,4-dione (6).

To a solution of ketone **5** (466 mg, 1.36 mmol) in 13.5 mL CH_3CN and 6.8 mL H_2O was added cerium ammonium nitrate (1.87 g, 3.40 mmol) at room temperature. The resulting mixture was stirred for 45 min, then diluted with diethyl ether (100 mL) and H_2O (60 mL). The aqueous layer was then extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (15% EtOAc in hexane) to give quinone **6** as a yellow oil (397 mg, 93%). $[\alpha]^{22}_D$ = +93 (*c* 1.01, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical to those previously reported for racemic **6**.[5]

Tetracyclic frondosin B analogue (7).

Quinone **6** (197 mg, 0.630 mmol) was dissolved in $CHCl_3$ (11 mL) and the solution was degassed with nitrogen for 10 min. A catalytic amount of 10% Pd/C (56 mg) was then added and the resulting mixture was stirred rapidly under an atmosphere of H_2 (balloon) at room temperature for 10 min. The solution was then sparged with nitrogen for 5 min and diluted with 45 mL of diethyl ether. The solution was filtered through a short pad of Celite and concentrated under reduced pressure to afford the crude phenol, which was dissolved in CH_2Cl_2 (30 mL). Upon cooling to 0 °C, $BF_3{\cdot}Et_2O$ (1 M, 0.595 mL, 0.595 mmol) was added dropwise and the resulting mixture was stirred for 5 min. Saturated aqueous $NaHCO_3$ solution (6 mL) was then added to quench the reaction. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by

column chromatography (10% EtOAc in hexane) to give phenol **7** as a pale yellow oil (140 mg, 75%, two steps). $[\alpha]^{23}_{D} = -196$ (*c* 0.410, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra were identical to those previously reported for racemic **7**.[5]

(–)-Frondosin B

To a solution of **7** (39 mg, 0.132 mmol) in 10 mL benzene was added a catalytic amount of *p*-toluenesulfonic acid monohydrate (4.0 mg, 0.021 mmol) and the resulting mixture was heated at reflux for 5 h. The solvent was then removed under reduced pressure and the crude residue was purified by column chromatography using a Combiflash chromatography system (gradient run: 3-10% EtOAc in hexane) to give frondosin B (27 mg, 68%). $[\alpha]^{21}_{D} = -17.3$ (*c* 0.178, MeOH). The ^{1}H and ^{13}C NMR spectra were identical to those previously reported for racemic frondosin B.[5]

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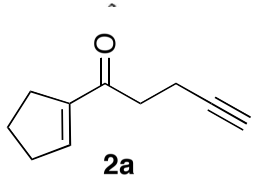
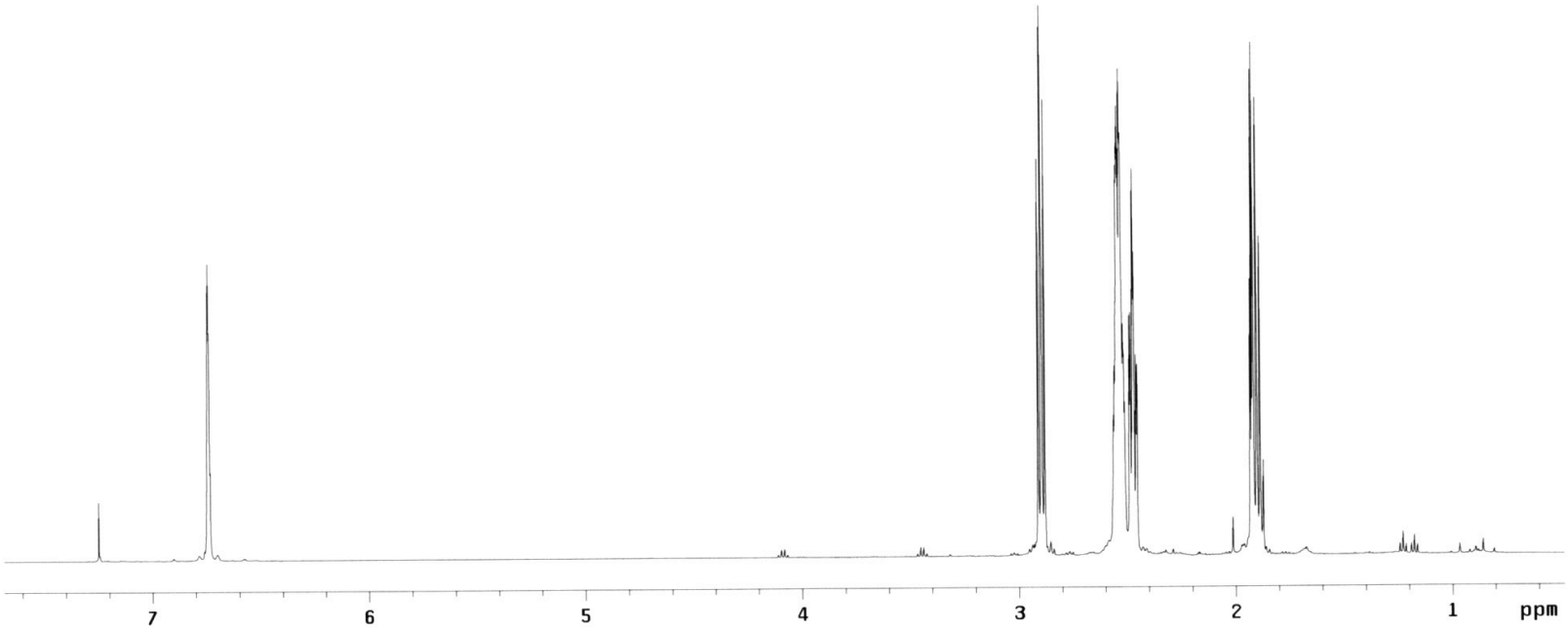


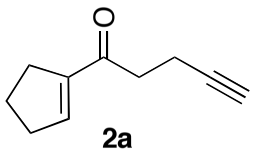
2a



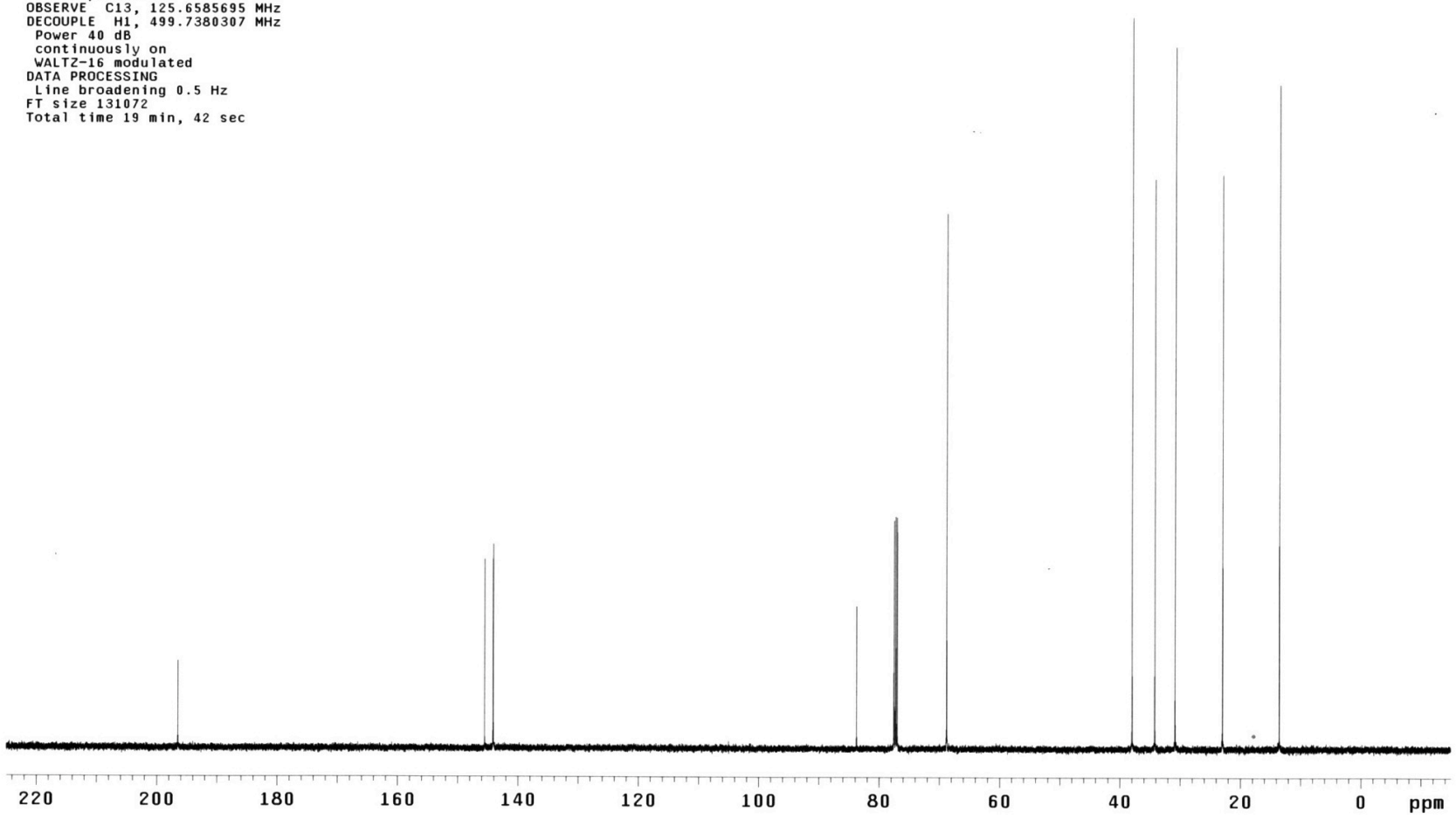
Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.03.13_06
File : /home/TVOlab/vnmrsys/data/tvo/s_tvo0730c_20080730/Carbon_01
Sample id : s_tvo0730c/20080730_001
Sample : tvo0730c

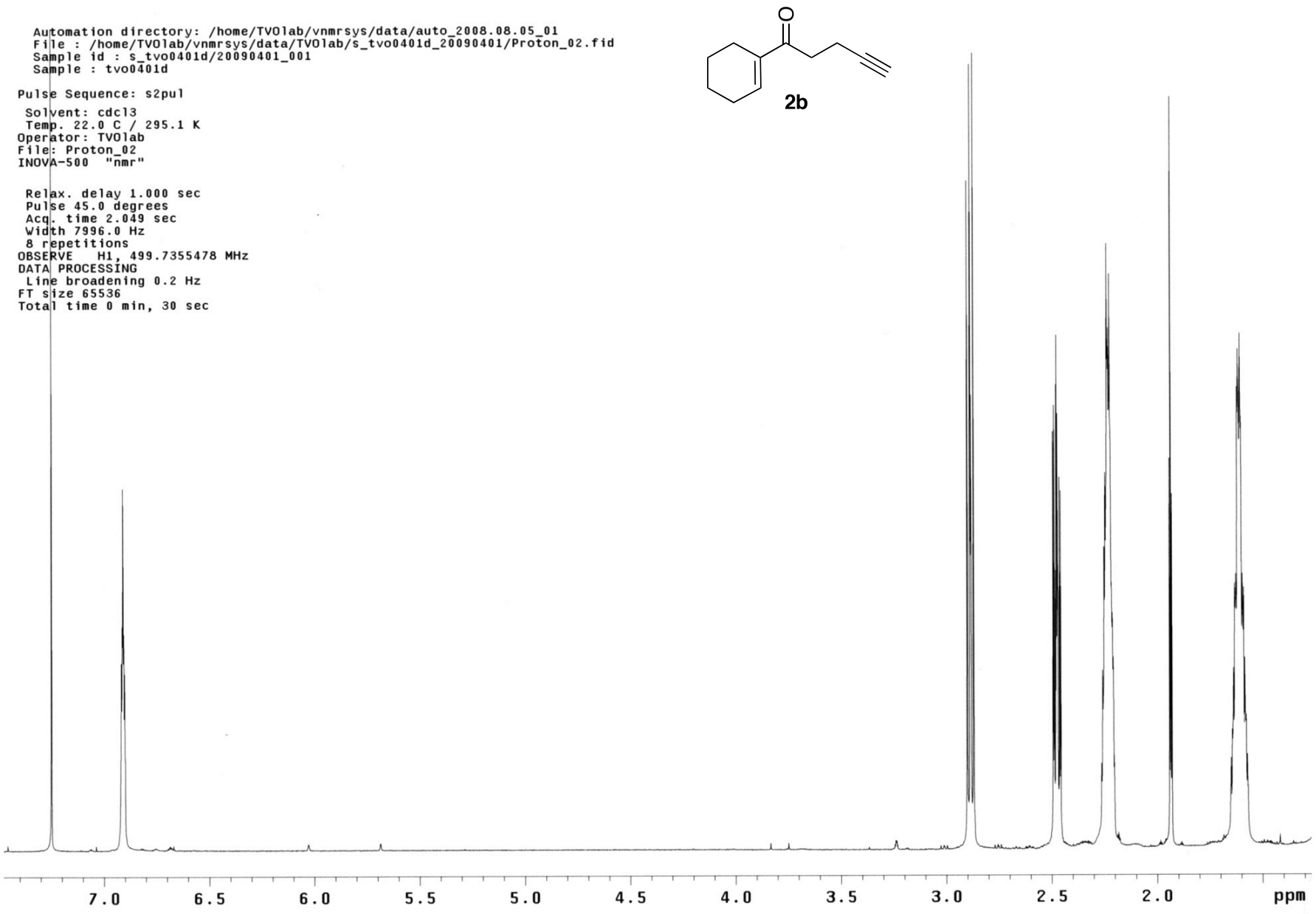
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: tvo
File: Carbon_01
INOVA-500 "nmr"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
512 repetitions
OBSERVE C13, 125.6585695 MHz
DECOUPLE H1, 499.7380307 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 42 sec



2a

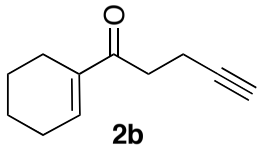



Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
File : /home/TVOlab/vnmrsys/data/TVOlab/s_tvo0401d_20090401/Proton_02.fid
Sample id : s_tvo0401d/20090401_001
Sample : tvo0401d
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Operator: TVOlab
File: Proton_02
INOVA-500 "nmr"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 7996.0 Hz
8 repetitions
OBSERVE H1, 499.7355478 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec
2b
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

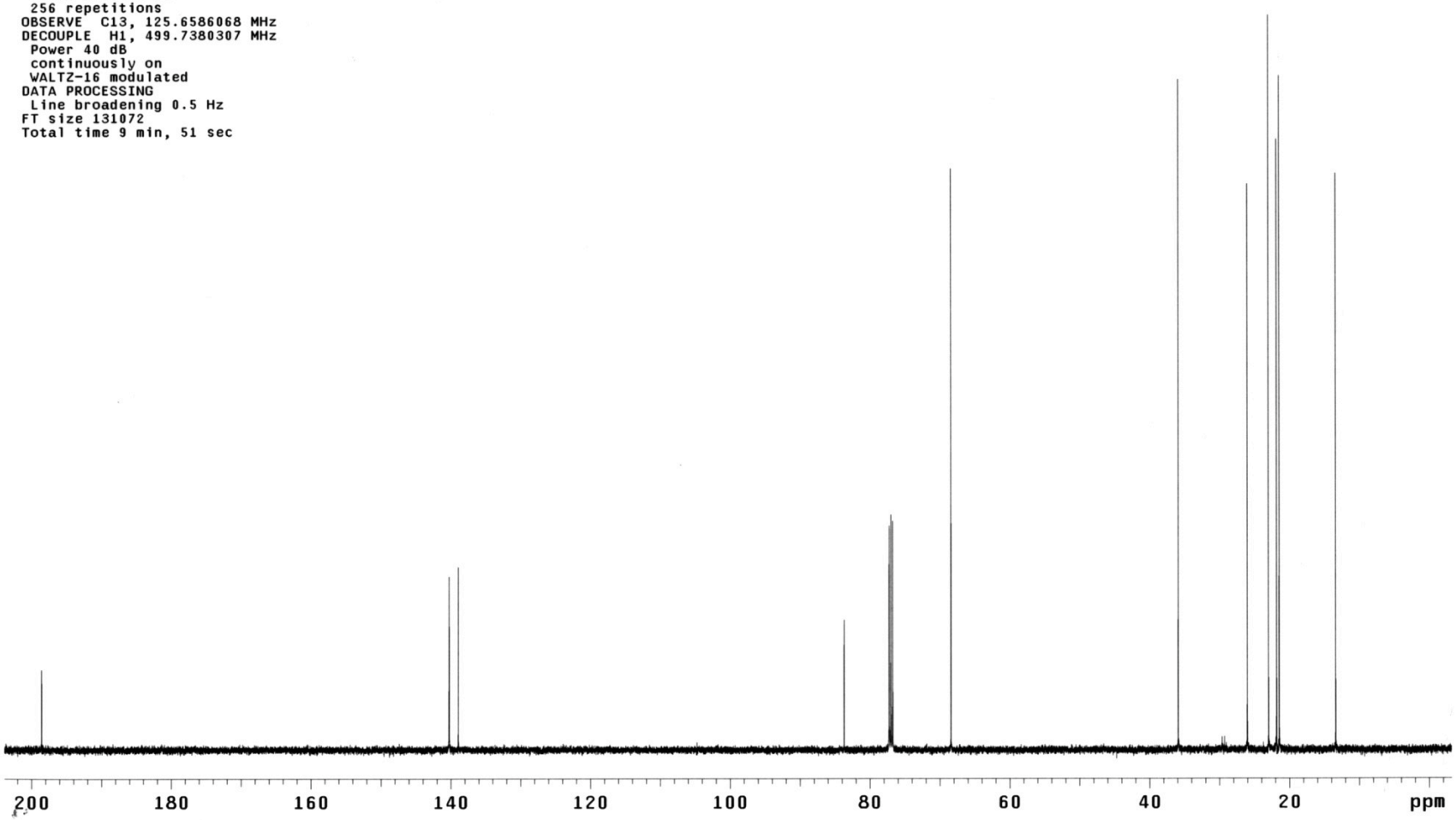
Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
File : /home/TVOlab/vnmrsys/data/TVOlab/s_tvo040109d_20090401/Carbon_01.fid
Sample id : s_tvo040109d/20090401_001
Sample : tvo040109d

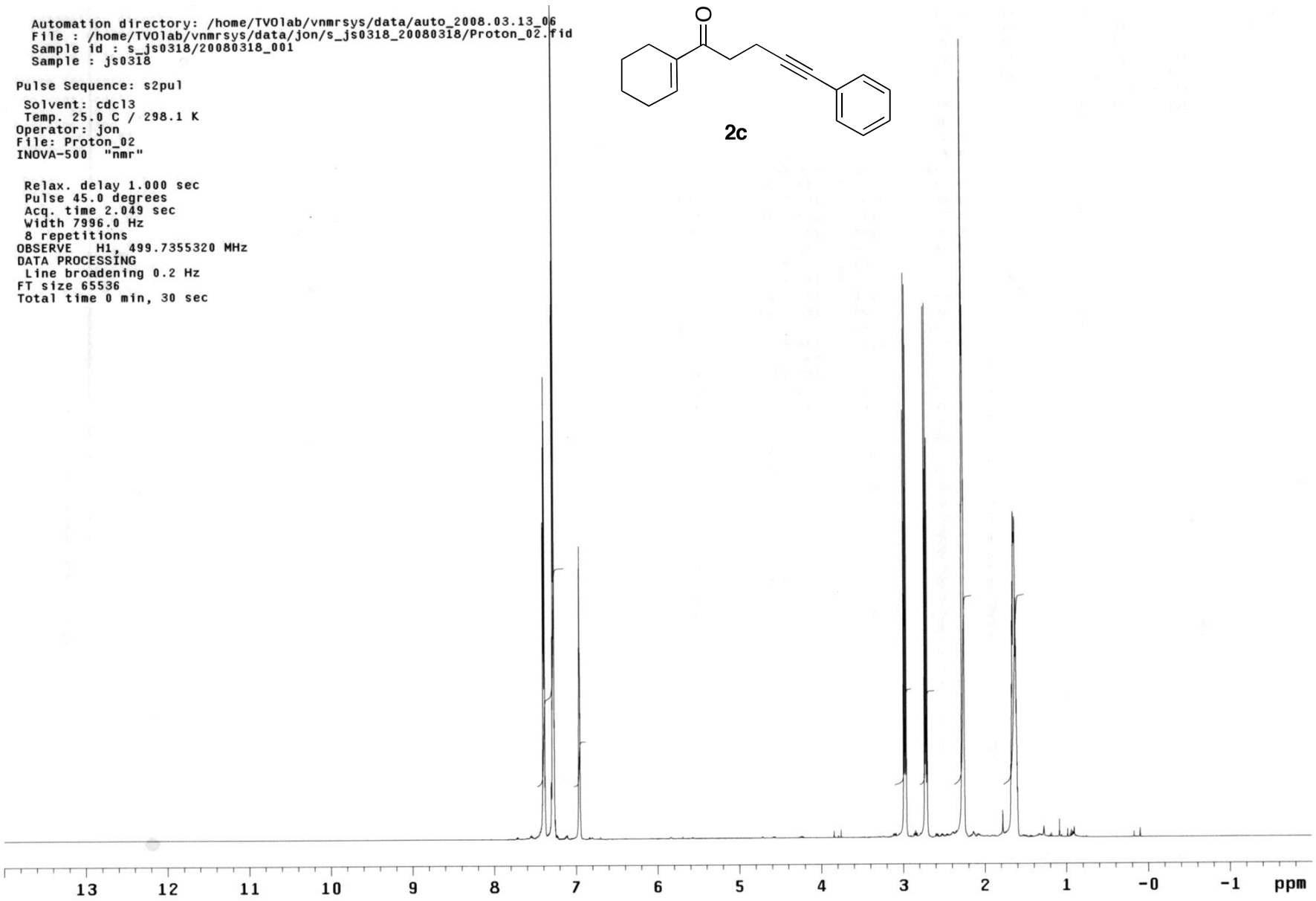
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Operator: TVOlab
File: Carbon_01
INOVA-500 "nmr"

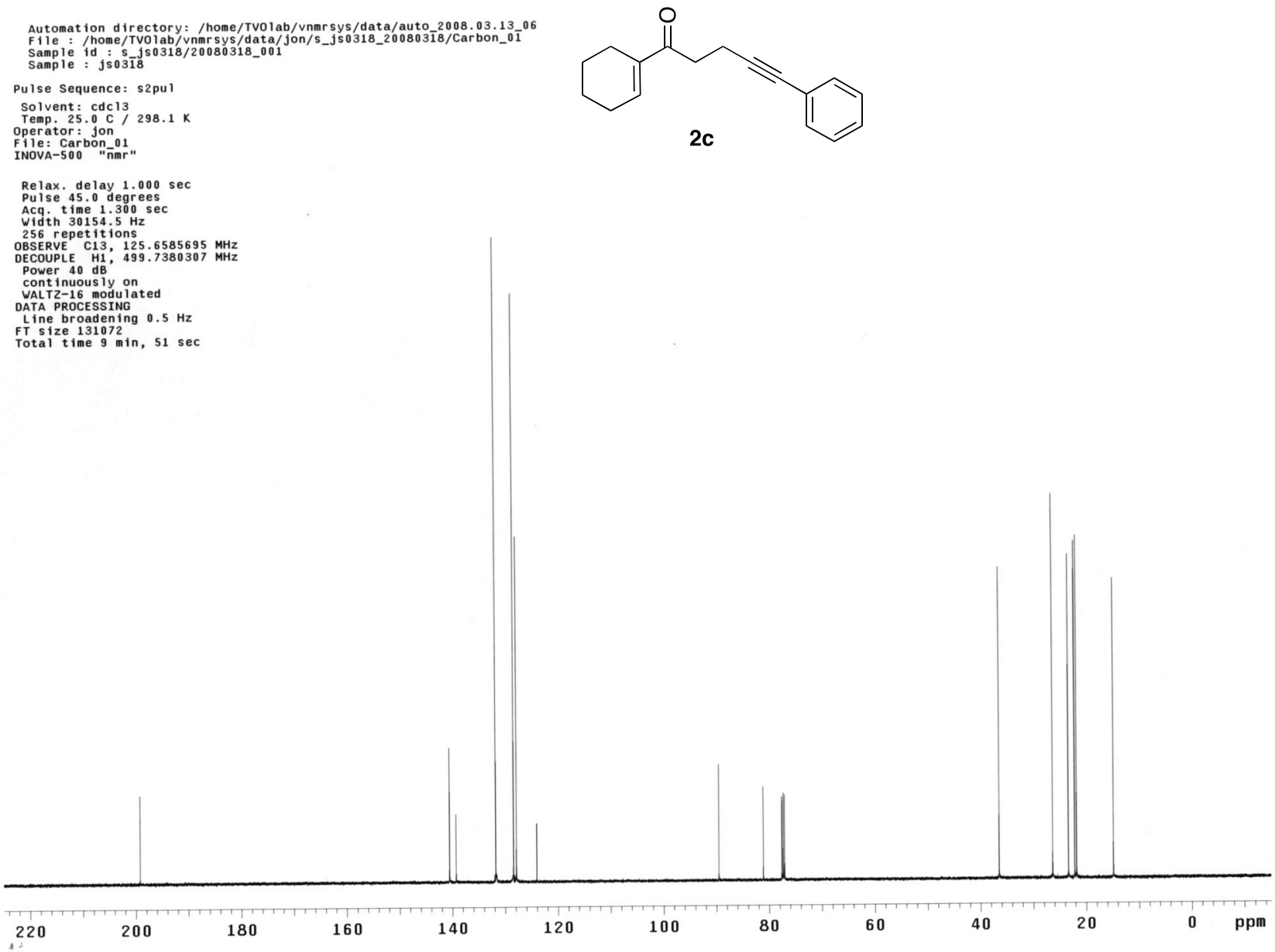
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
256 repetitions
OBSERVE C13, 125.6586068 MHz
DECOUPLE H1, 499.7380307 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 9 min, 51 sec

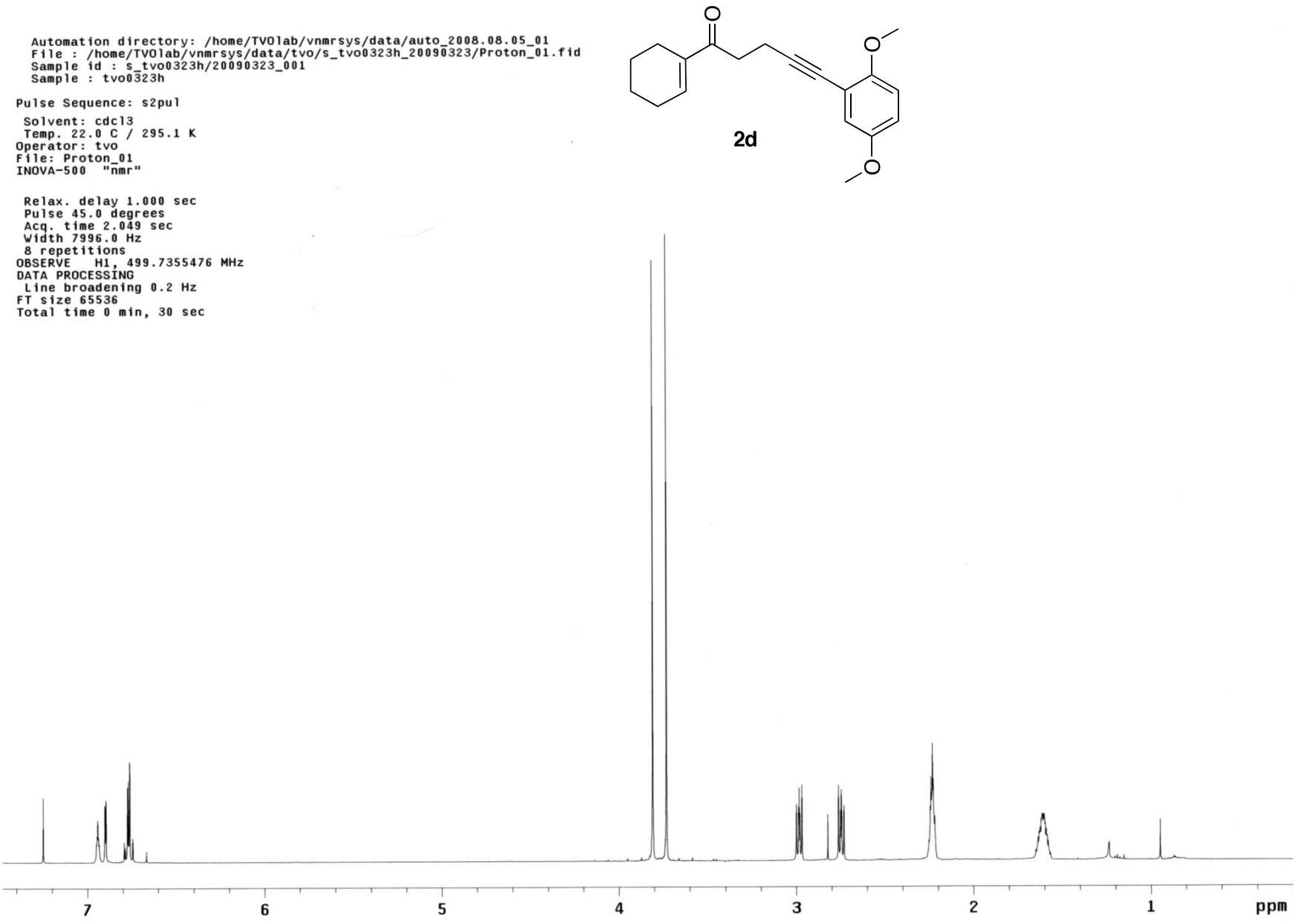


2b




Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.03.13_06
File : /home/TVOlab/vnmrsys/data/jon/s_js0318_20080318/Proton_02.fid
Sample id : s_js0318/20080318_001
Sample : js0318
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: jon
File: Proton_02
INOVA-500 "nmr"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 7996.0 Hz
8 repetitions
OBSERVE H1, 499.7355320 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec
2c
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm


Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.03.13_06
File : /home/TVOlab/vnmrsys/data/jon/s_js0318_20080318/Carbon_01
Sample id : s_js0318/20080318_001
Sample : js0318
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: jon
File: Carbon_01
INOVA-500 "nmr"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
256 repetitions
OBSERVE C13, 125.6585695 MHz
DECOUPLE H1, 499.7380307 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 9 min, 51 sec
O
2c
220
200
180
160
140
120
100
80
60
40
20
0
ppm

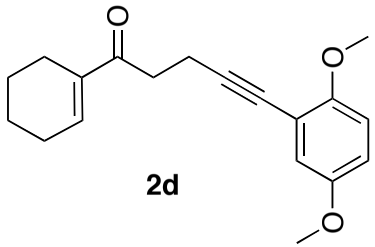

Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
File : /home/TVOlab/vnmrsys/data/tvo/s_tvo0323h_20090323/Proton_01.fid
Sample id : s_tvo0323h/20090323_001
Sample : tvo0323h
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Operator: tvo
File: Proton_01
INOVA-500 "nmr"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 7996.0 Hz
8 repetitions
OBSERVE H1, 499.7355476 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec
2d
7
6
5
4
3
2
1
ppm

Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
File : /home/TVOlab/vnmrsys/data/tvo/s_tvo0323c_20090323/Carbon_01.fid
Sample id : s_tvo0323c/20090323_002
Sample : tvo0323c

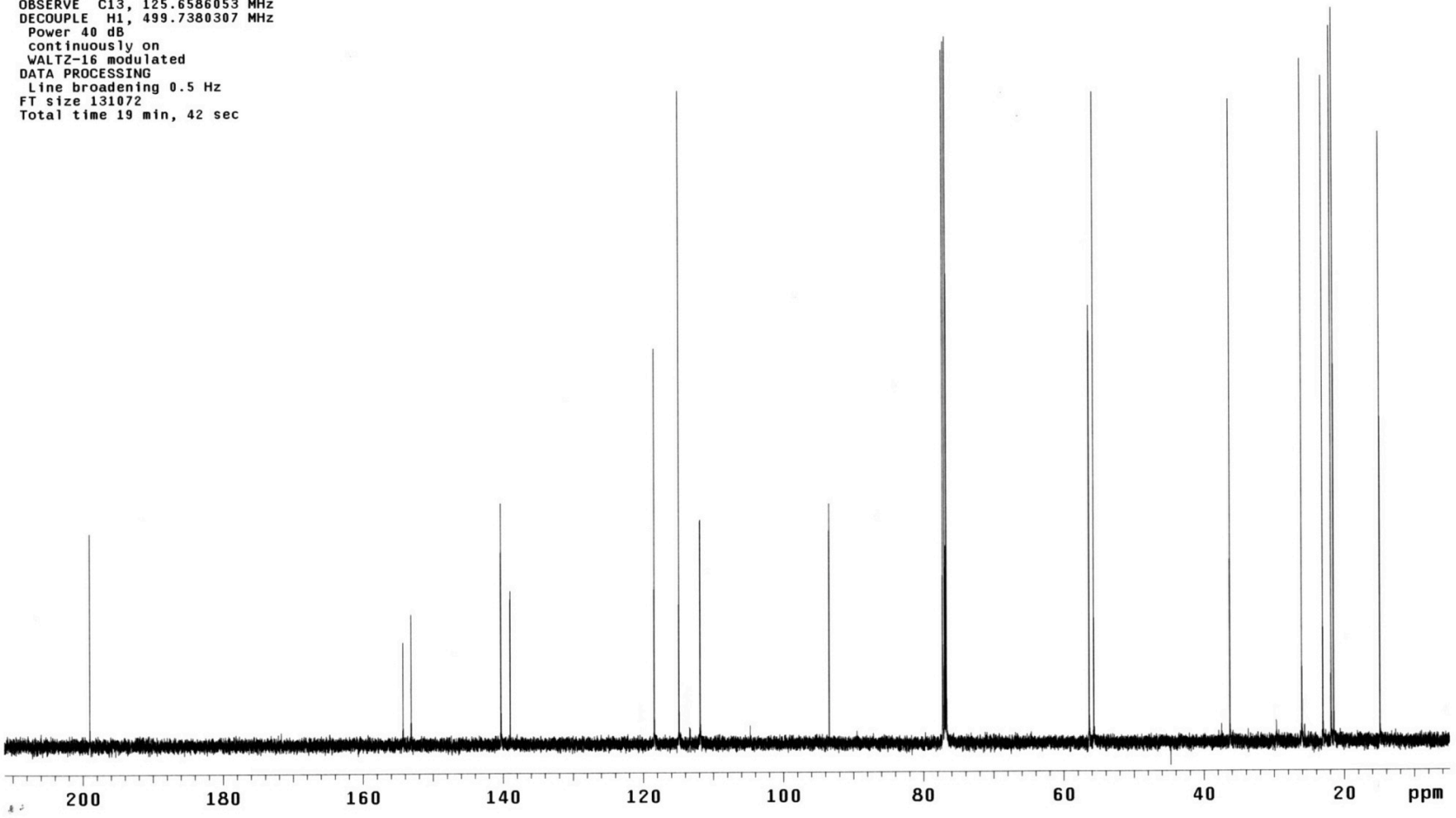
Pulse Sequence: s2pul

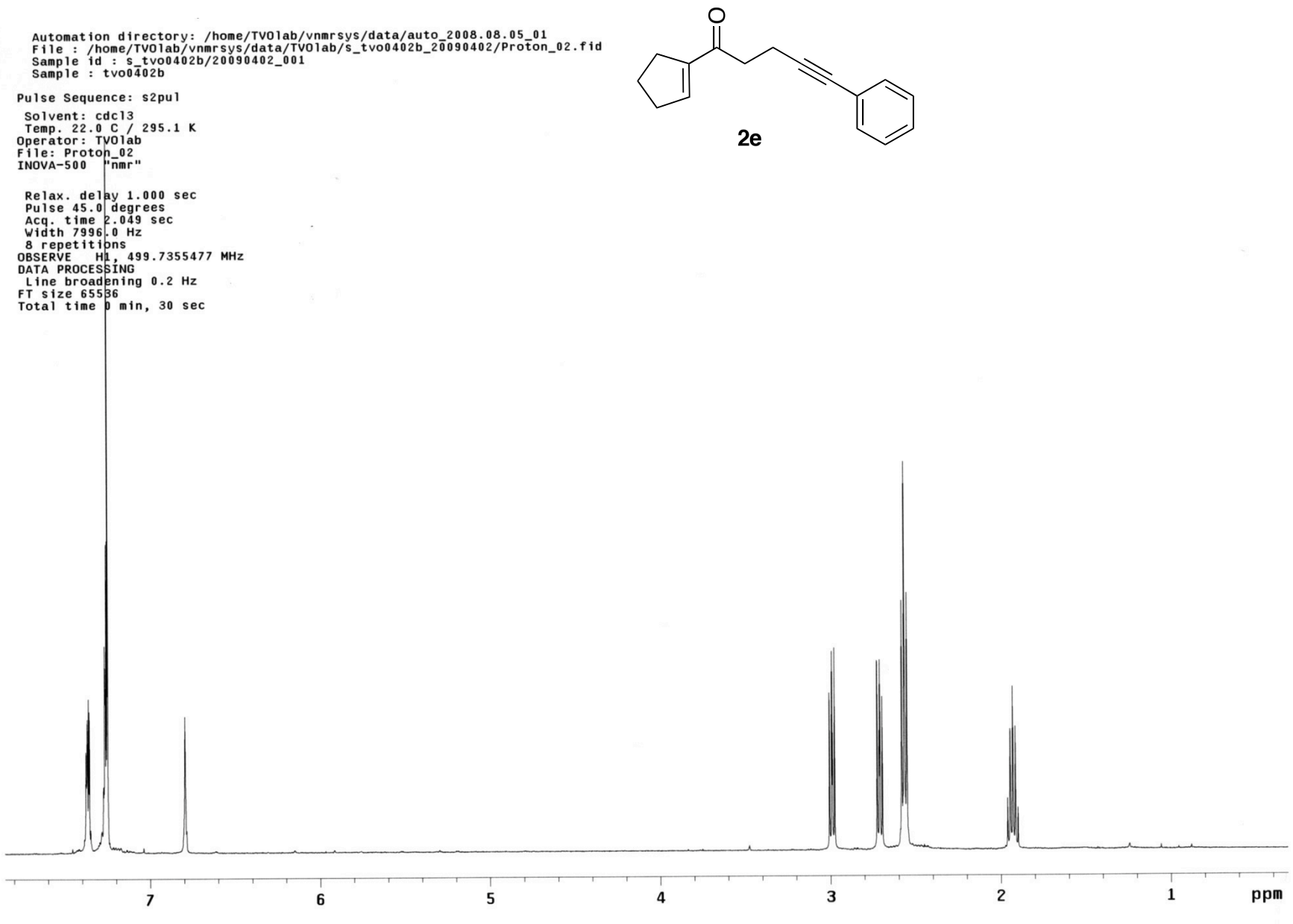
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Operator: tvo
File: Carbon_01
INOVA-500 "nmr"

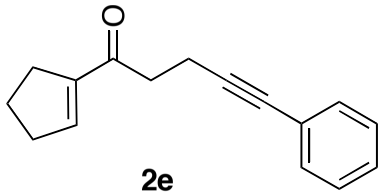
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
512 repetitions
OBSERVE C13, 125.6586053 MHz
DECOUPLE H1, 499.7380307 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 19 min, 42 sec



2d

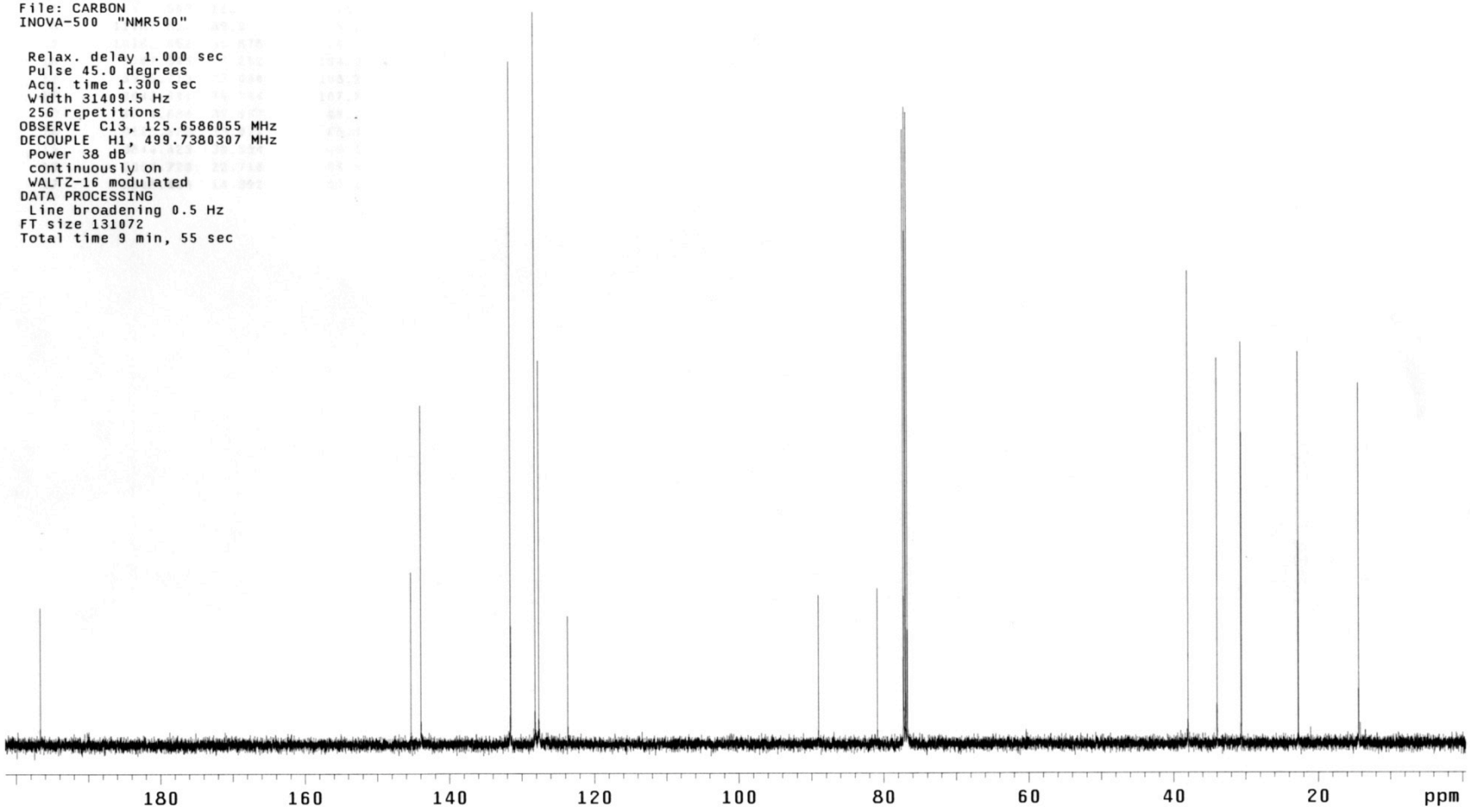



Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
File : /home/TVOlab/vnmrsys/data/TVOlab/s_tvo0402b_20090402/Proton_02.fid
Sample id : s_tvo0402b/20090402_001
Sample : tvo0402b
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Operator: TVOlab
File: Proton_02
INOVA-500 "nmr"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 7996.0 Hz
8 repetitions
OBSERVE H1, 499.7355477 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec
2e
7
6
5
4
3
2
1
ppm



2e

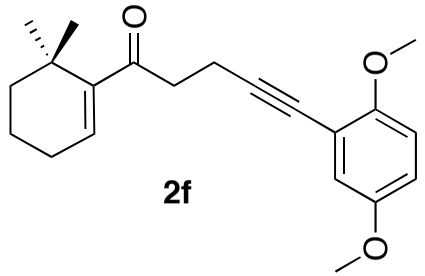
```
Archive directory: /export/home/TVOlab/vnmrsys/data
Sample directory: jas010808a_08Jan2008

Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 23.0 C / 296.1 K
User:  1-14-87
File: CARBON
INOVA-500  "NMR500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 31409.5 Hz
 256 repetitions
OBSERVE  C13, 125.6586055 MHz
DECOUPLE  H1, 499.7380307 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 131072
Total time 9 min, 55 sec
```



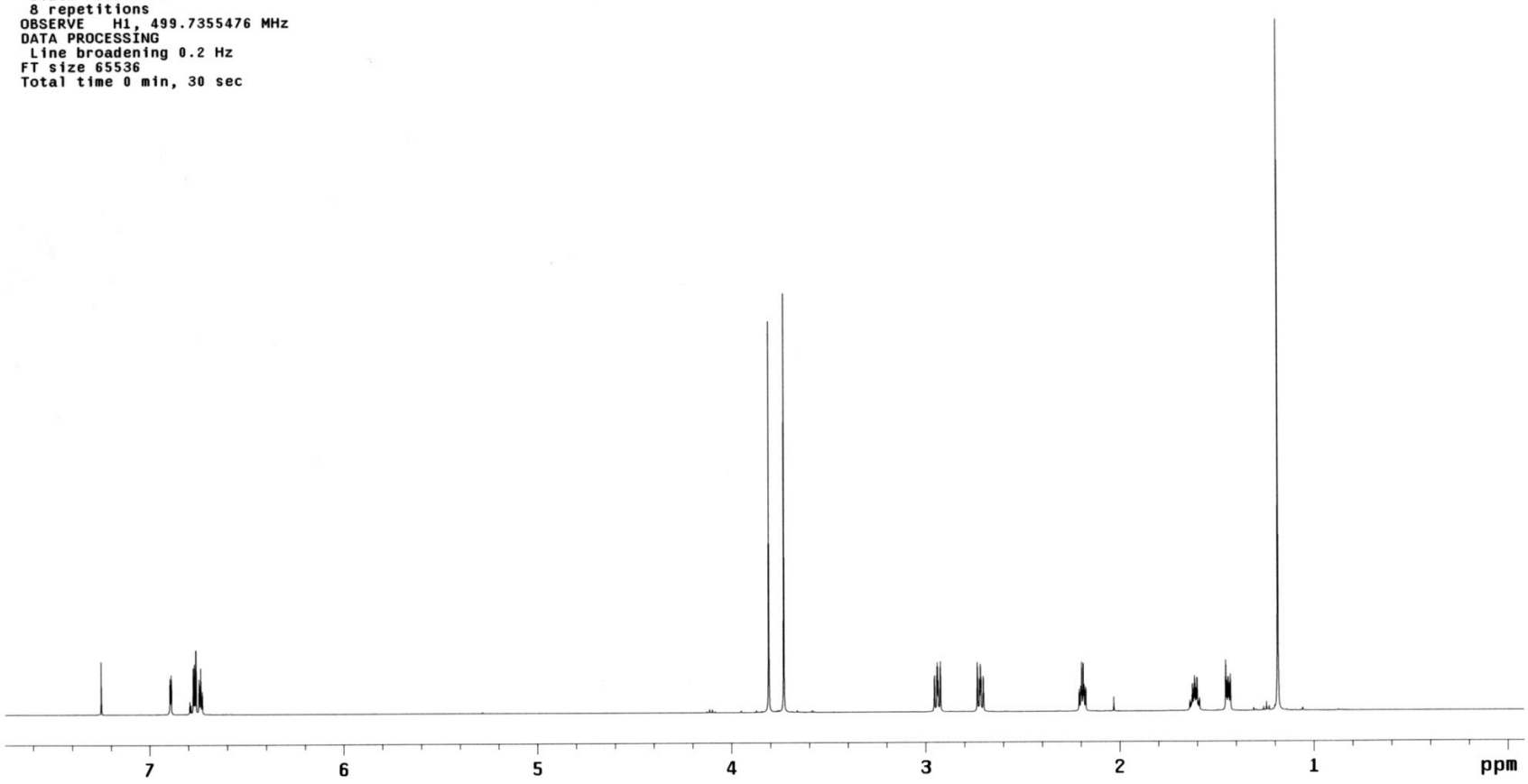
Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
File : /home/TVOlab/vnmrsys/data/TVOlab/s_tvo0320_20090320/Proton_02.fid
Sample id : s_tvo0320/20090320_001
Sample : tvo0320

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Operator: TVOlab
File: Proton_02
INOVA-500 "nmr"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 7996.0 Hz
8 repetitions
OBSERVE H1, 499.7355476 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec



2f

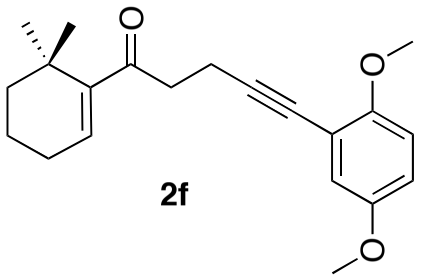


Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
File : /home/TVOlab/vnmrsys/data/TVOlab/s_tvo0320_20090320/Carbon_01.fid
Sample id : s_tvo0320/20090320_002
Sample : tvo0320

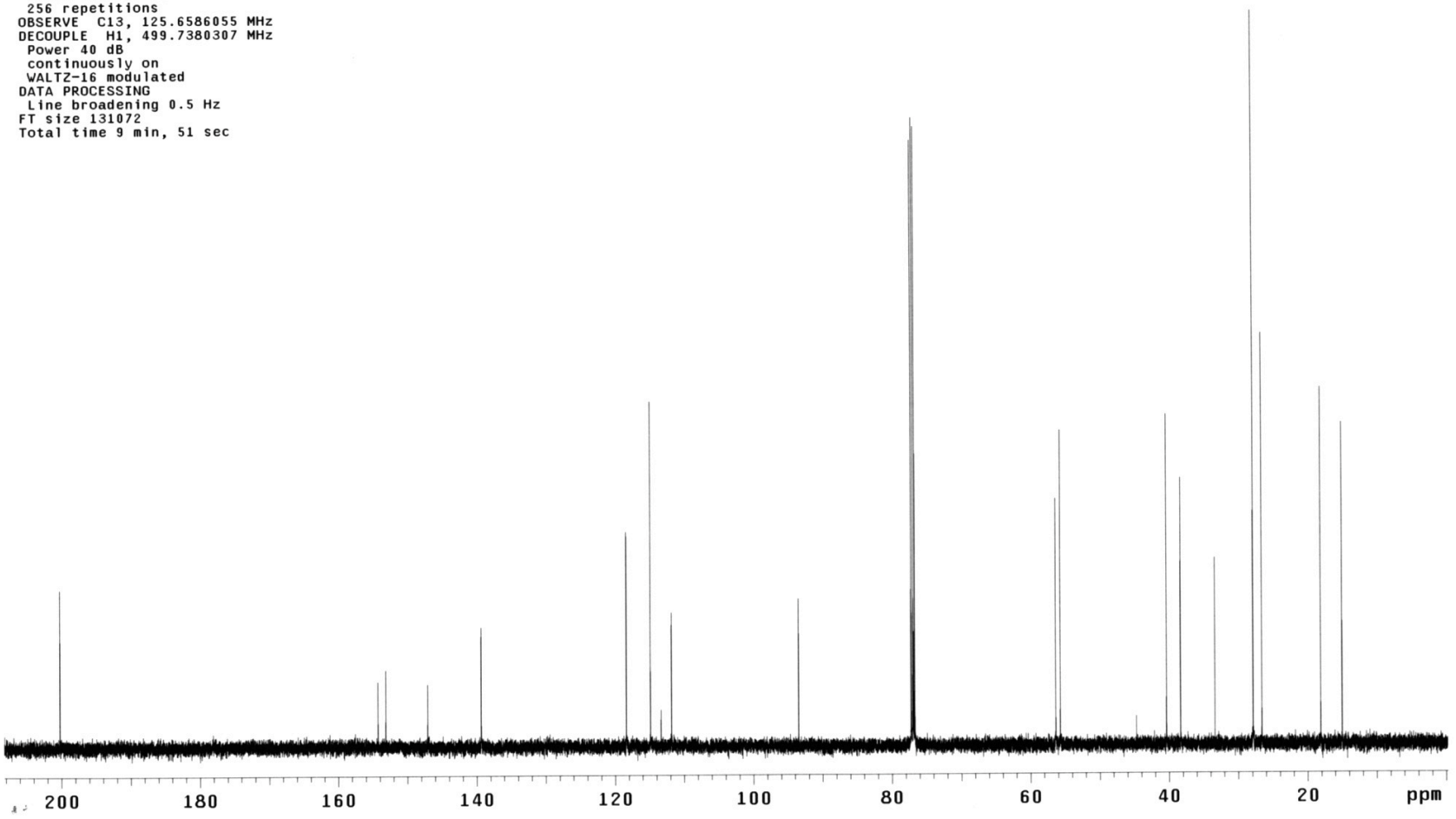
Pulse Sequence: s2pul

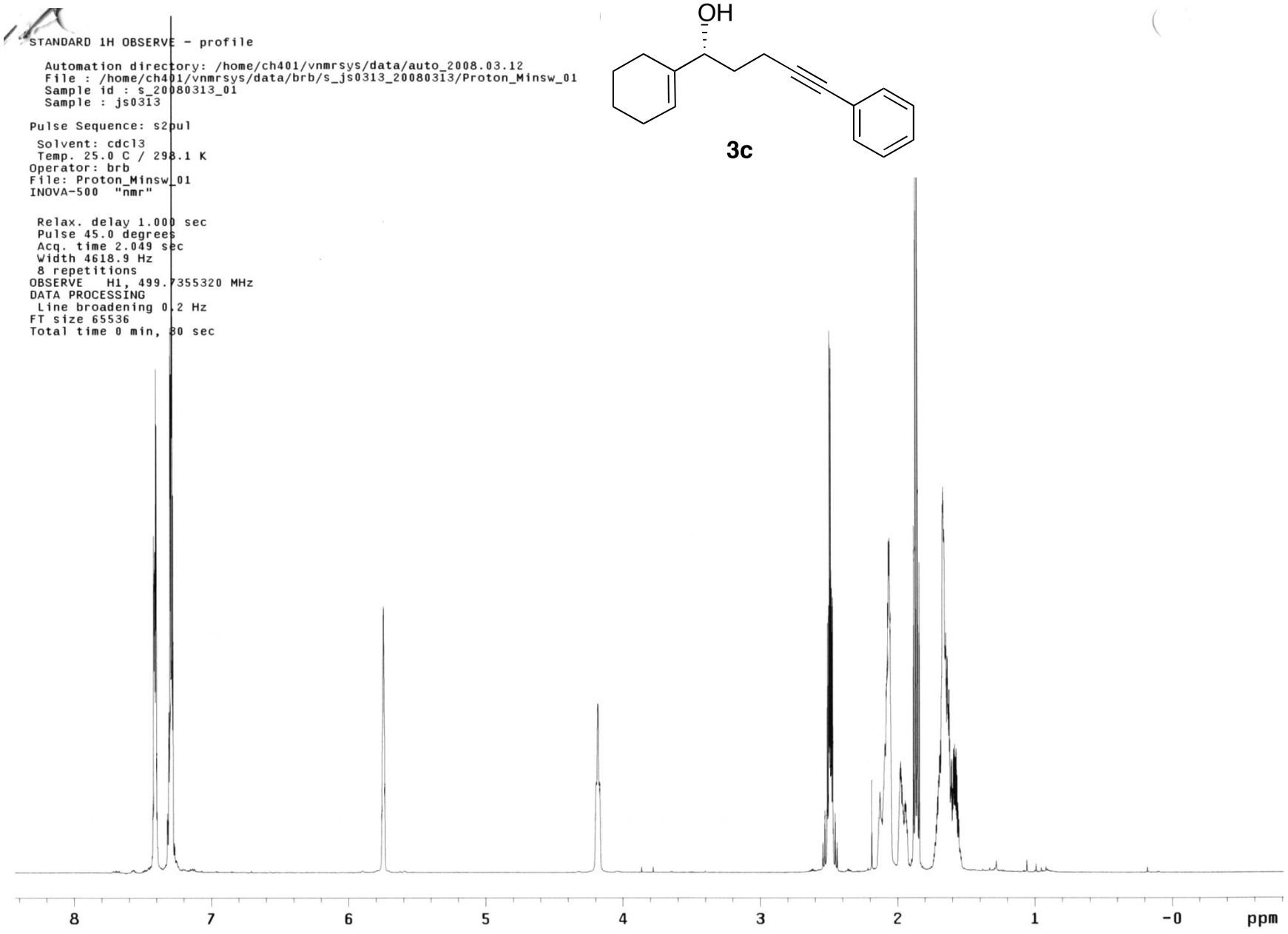
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Operator: TVOlab
File: Carbon_01
INOVA-500 "nmr"

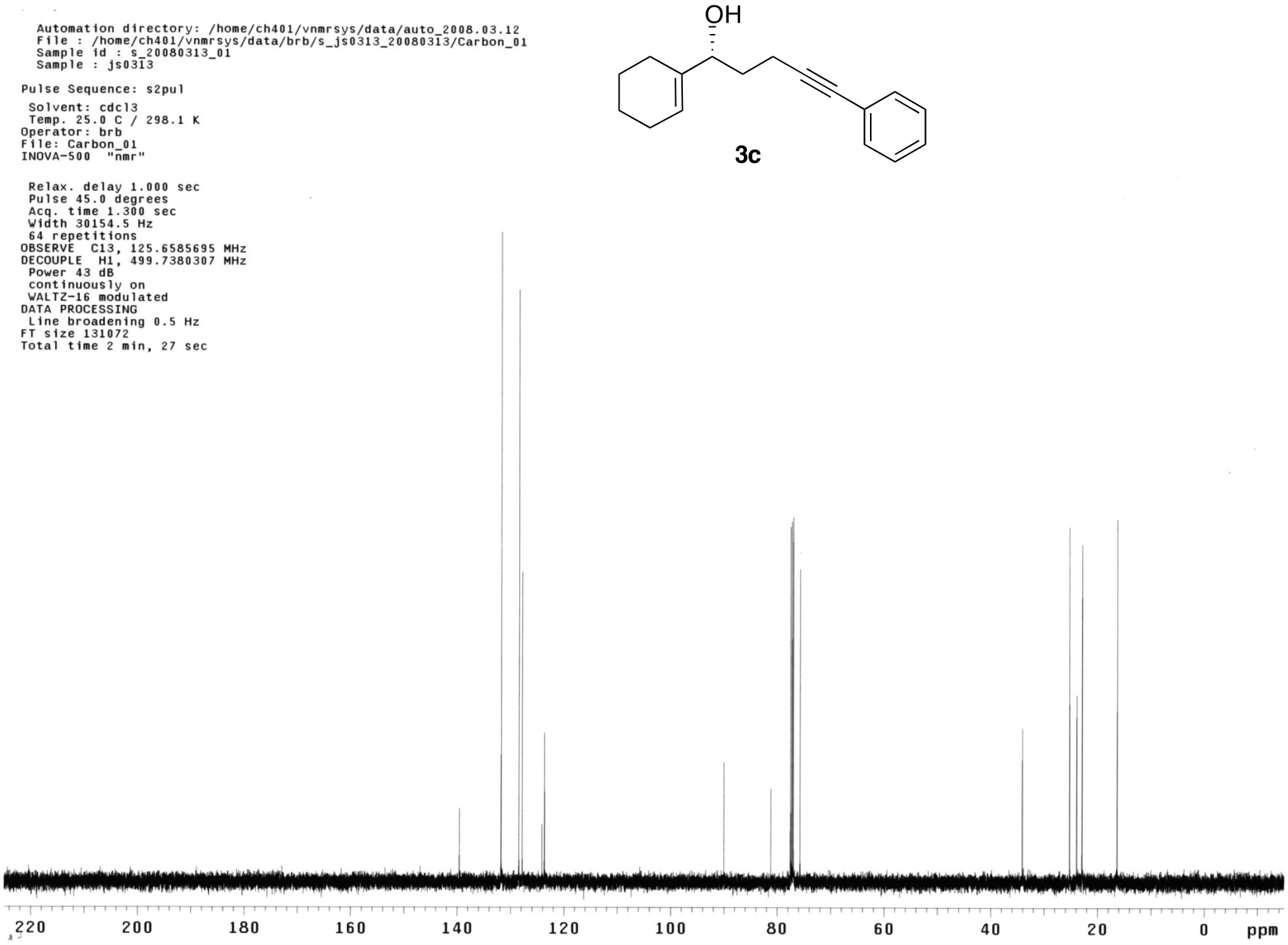
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
256 repetitions
OBSERVE C13, 125.6586055 MHz
DECOUPLE H1, 499.7380307 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 9 min, 51 sec



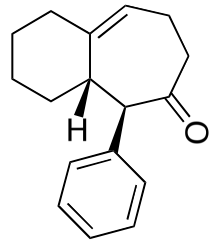
2f



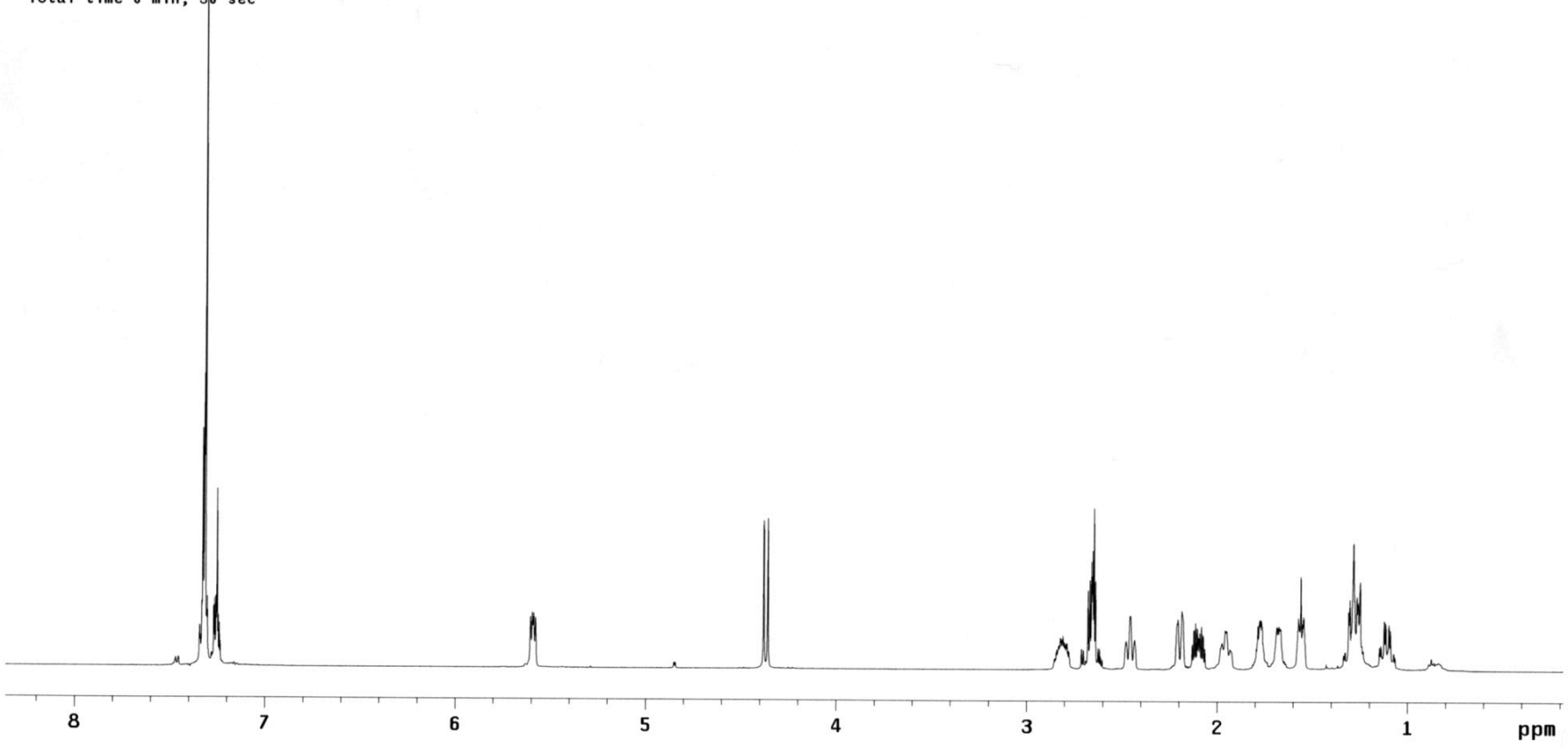

STANDARD 1H OBSERVE - profile
Automation directory: /home/ch401/vnmrsys/data/auto_2008.03.12
File : /home/ch401/vnmrsys/data/brb/s_js0313_20080313/Proton_Minsw_01
Sample id : s_20080313_01
Sample : js0313
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: brb
File: Proton_Minsw_01
INOVA-500 "nmr"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 4618.9 Hz
8 repetitions
OBSERVE H1, 499.7355320 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec
OH
3c
8
7
6
5
4
3
2
1
-0
ppm


Automation directory: /home/ch401/vnmrsys/data/auto_2008.03.12
File : /home/ch401/vnmrsys/data/brb/s_js0313_20080313/Carbon_01
Sample id : s_20080313_01
Sample : js0313
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: brb
File: Carbon_01
INOVA-500 "nmr"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
64 repetitions
OBSERVE C13, 125.6585695 MHz
DECOUPLE H1, 499.7380307 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 2 min, 27 sec
OH
3c
220
200
180
160
140
120
100
80
60
40
20
0
ppm

```
  Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
  File : /home/TVOlab/vnmrsys/data/bibi/s_bibizh_01-16_20090116/Proton_02.fid
  Sample id : s_bibizh_01-16/20090116_001
  Sample : bibizh_01-16

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: bibi
File: Proton_02
INOVA-500  "nmr"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 7996.0 Hz
 8 repetitions
OBSERVE   H1, 499.7355471 MHz
DATA PROCESSING
 Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 30 sec
```



4c

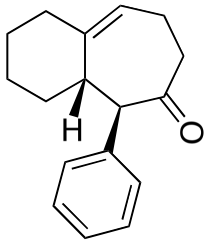


Automation directory: /home/TVOlab/vnmrsys/data/auto_2008.08.05_01
File : /home/TVOlab/vnmrsys/data/bibi/s_bibizh_01-16_20090116/Carbon_01.fid
Sample id : s_bibizh_01-16/20090116_002
Sample : bibizh_01-16

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: bibi
File: Carbon_01
INOVA-500 "nmr"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
256 repetitions
OBSERVE C13, 125.6586052 MHz
DECOUPLE H1, 499.7380307 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 9 min, 51 sec



4c