Access to harmonine, a chemical weapon of the ladybird beetles

Satish Chandra Philkhana, Prabhu Dhasaiyan, B. L. V. Prasad* and D. Srinivasa Reddy*

CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411008, India.

*Corresponding author:

Dr. D. Srinivasa Reddy

CSIR-National Chemical Laboratory,

Division of Organic Chemistry,

Dr. Homi Bhabha Road, Pune 411008, Maharashtra, India.

E-mail: ds.reddy@ncl.res.in

Tel. +91 20 25902445

Fax. +91 20 25902629

Electronic Supplementary Information

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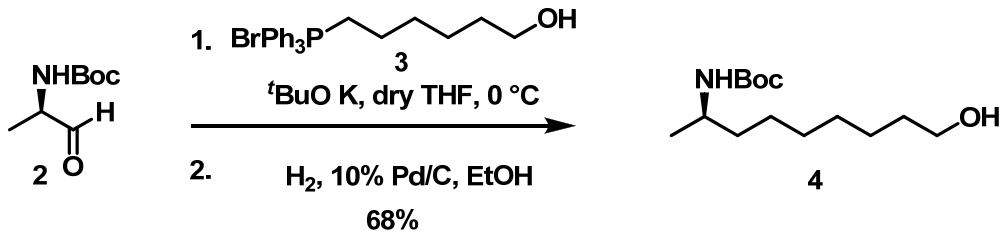
General:

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus *via* rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, or Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *para*-anisaldehyde, 2,4-DNP stain, $KMnO_4$, Ninhydrin solution followed by heating on a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz, or 500 MHz spectrometer. Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to $CDCl_3$ and CD_3OD using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS (ESI): *M/Z* (ESI) were recorded on ORBITRAP mass analyser (Thermo Scientific, Q Exactive). Mass spectra were measured with ESI ionization in MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using ChemDraw. Optical rotation values were recorded on P-2000 polarimeter at 589 nm. UV–Visible absorption spectra of nanoparticle dispersions were measured using a Jasco UV – Visible spectrophotometer (V-570 model). An aliquot of dispersed nanoparticle solutions was used for the measurement. The X-ray diffraction patterns of the samples were recorded by using X-Pert Pro PANalytical instrument. The nanoparticle solutions was drop coasted on a cleaned dustless glass slide and are air dried. By using Cu-Kα (1.54 Å) radiation, diffractogram were recorded within the range of 10°- 90°. TEM images were obtained on a FEI, TECHNAI G2 20 S - TWIN instrument operated at an accelerated voltage of 300 kV with a lattice resolution of 0.14 nm and point image resolution of 0.24 nm. A small volume of (~10μL) the dispersed nanoparticles was drop casted on a carbon coated copper grid (200 mesh size) and the excess solution was removed by dustless tissue paper. It was allowed to dry overnight at room temperature. The particle size distribution was determined using Gattan software (Pleasanton,

CA, USA). For the size distribution analysis 300 particles from figure 2C (in manuscript) were counted.

Experimental Data for Compounds

(*R*)-*tert*-butyl 9-hydroxynonan-2-ylcarbamate (4):

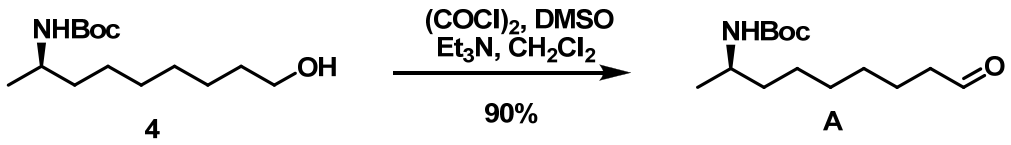


To an ice cooled solution of compound **3**[2] (6.0 g, 13.81 mmol) in dry THF (60 mL) was added solid potassium tertiary butoxide (1.28 g, 11.42 mmol) portion wise and stirred at same temperature for 20 min, which was followed by addition of N-Boc alaninal **2**[1] (1.80 g, 10.39 mmol) in dry THF drop wise and stirred at same temperature for 1 hour. After the reaction mixture was allowed to stir for another 4 hours and then quenched with saturated aqueous NH_4Cl (40 mL). The resulting solution was extracted with EtOAc (3 × 30 mL) and the combined organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give crude residue. Silica gel flash column chromatography (using 40% EtOAc : petroleum ether) of the residue obtained above afforded the unsaturated alcohol **3a** (1.80 g, 68%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 - 5.36 (m, 1 H), 5.24 - 5.19 (m, 1 H), 4.49 (br s, 2 H), 3.61 (dt, *J* = 2.1, 6.5 Hz, 2 H), 2.12 - 2.10 (m, 3 H), 1.48 - 1.55 (m, 2 H), 1.50 - 1.45 (m, 4 H), 1.44 - 1.41 (m, 9 H), 1.15 (t, 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 132.2, 131.0, 79.3, 62.9, 44.0, 32.6, 29.2, 28.5, 28.5, 28.4, 27.4, 25.3, 22.2; IR υ_{max}(film): cm^{-1} 3333, 1682, 1515, 1246, 1046, 1028; HRMS (ESI)**:** *m/z* calculated for $C_{14}H_{27}NO_3$ $[M+Na]^+$ 280.1883 found 280.1884.

To a solution of the above unsaturated alcohol (1.80 g, 10.39 mmol) in EtOAc (25 mL) was added 5% Pd/C (20 mg) and the mixture was stirred under hydrogen balloon pressure at room temperature for 1 hour. The catalyst was filtered off and the filtrate obtained was concentrated *in vacuo* to afford **4** (1.70 g, 99%) as colorless oil: $[\alpha]_D^{25}$ = + 0.67 (*c* = 1.2,

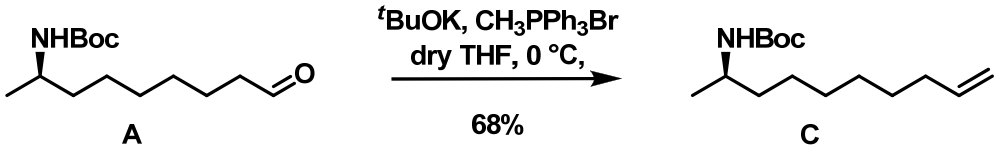
$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (br s, 1 H), 3.62 (t, *J* = 6.6 Hz, 2 H), 1.67 - 1.52 (m, 6 H), 1.52 - 1.47 (m, 9 H), 1.40 - 1.29 (m, 8 H), 1.07 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 78.9, 62.9, 46.5, 37.3, 32.7, 29.4, 29.3, 28.4 (2C), 28.3, 25.9, 25.6, 21.3; IR υ_{max}(film): cm^{-1} 3339, 2974, 2929, 2856, 1682, 1521, 1453, 1390, 1365, 1247, 1092; HRMS (ESI): *m/z* calculated for $C_{14}H_{29}NO_3$ $[M+Na]^+$ 282.2040 found 282.2039.

(*R*)-*tert*-Butyl 9-oxononan-2-ylcarbamate (A):



A stirred solution of oxalyl chloride (2.30 mL, 28.22 mmol) in 8.0 mL of CH_2Cl_2, under nitrogen, was cooled to −78 °C, treated drop wise over 15 min with DMSO (3.0 mL, 28.22 mmol) and stirred at −78 °C for 20 min. Then the reaction mixture was treated over 7 min with alcohol **4** (3.80 g, 21.71 mmol) dissolved in 10 mL of CH_2Cl_2 and was allowed to warm to − 20 °C during 2.5 hours. It was further kept at this temperature for 1.5 hours, re-cooled to −78 °C and treated with Et_3N (15 mL) during 5 min. This mixture was warmed to ambient temperature during 30 min, diluted with CH_2Cl_2, washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give 3.40 g (90%) of **A.** The aldehyde **A** was always freshly prepared and immediately forwarded for next step due to its unstable nature: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (t, *J* = 6.4 Hz, 1 H), 4.38 (br s, 1 H), 3.58 (br s, 1 H), 2.42 - 2.38 (m, 1 H), 2.33 - 2.13 (m, 1 H), 1.60 - 1.54 (m, 2 H), 1.40 (br s, 9 H), 1.28 - 1.21 (m, 8 H), 1.06 (d, *J* = 6.4 Hz, 3 H); IR υ_{max}(film): cm^{-1} 3354, 2930, 1700, 1520, 1456, 1365, 1248.

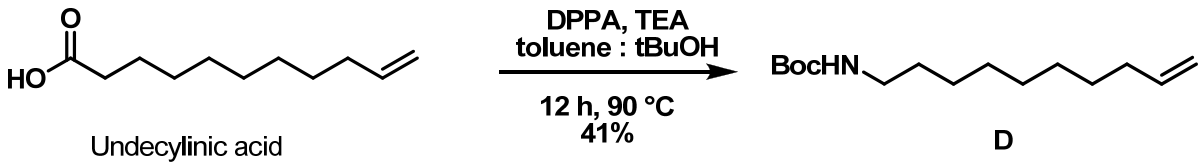
(*R*)-*tert*-Butyl dec-9-en-2-ylcarbamate (C):



To an ice cooled solution of methyltriphenylphosphonium bromide (7.22 g, 20.23 mmol) was added potassium tertiary butoxide (1.98 g, 17.68 mmol) portion wise, upon which the solution turns to bright yellow. The resulting reaction mixture was stirred at same

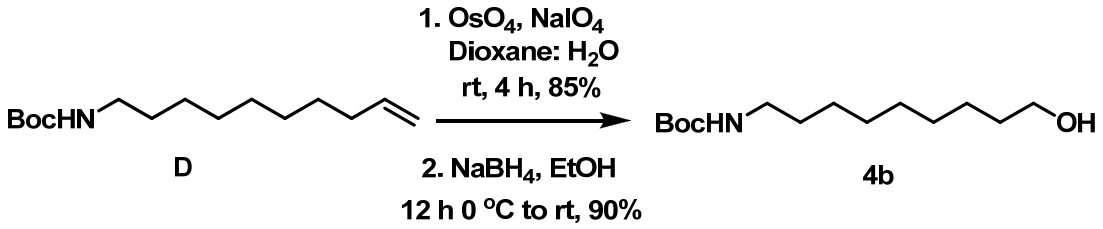
temperature for 20 min and then, a solution of freshly prepared **A** (1.30 g, 5.05 mmol) in THF was added drop wise over a period of 15 min. The same temperature was maintained for another 30 min before warming to room temperature and stirring it for further 4 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. Silica gel flash column chromatography (5% EtOAc : petroleum ether) of the residue obtained afforded the olefin **C** (0.90 g, 68%) as colorless oil: $[\alpha]_D^{25}$ = + 0.12 (*c* = 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 - 5.78 (m, 1 H), 5.01 - 4.92 (m, 2 H), 4.31 (br s, 1 H), 3.62 (br s, 1 H), 2.06 - 2.02 (m, 2 H), 1.44 (s, 9 H), 1.37 - 1.29 (m, 10 H), 1.10 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 139.2, 114.2, 78.9, 46.5, 37.4, 33.8, 29.4, 29.1, 28.8, 28.4 (3C), 26.0, 21.3; IR υ_{max}(film): cm^{-1} 3345, 2927, 1687, 1505, 1389, 1364, 1245, 1086; HRMS (ESI): *m/z* calculated for $C_{15}H_{29}O_2N$ $[M+Na]^+$ 278.2091, found 278.2092.

tert-Butyl dec-9-enylcarbamate (D)[3,4]:



This compound was prepared by following known procedures.[3,4] A stirred solution of the undecylinic acid (10.0 g, 54.30 mmol), diphenylphosphoryl azide (15 mL, 70.65 mmol) and triethylamine (18 mL, 135.70 mmol) in 1:1 *tert*-butyl alcohol (100 mL), toluene (100 mL) was refluxed for 18 hours. The reaction mixture was cooled, and the solvent was removed under reduced pressure to obtain crude residue, which was re-dissolved in EtOAc (20 mL) and washed successively with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, and then concentrated *in vacuo* to give crude residue. Silica gel flash column chromatography of the residue using 5% EtOAc: petroleum ether, afforded *N*-Boc amine **D** (5.80 g, 41%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 - 5.74 (m,1 H), 4.99 - 4.89 (m, 2 H), 4.59 (br s, 1 H), 3.07 (m, 2 H), 2.03 - 1.98 (m, 2 H), 1.41 (br s, 10 H), 1.34 - 1.31 (m, 2 H), 1.26 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 139.0, 114.1, 78.8, 40.5, 33.7, 30.0, 29.3, 29.1, 28.9, 28.8 (3C), 28.3, 26.7; IR υ_{max}(film): cm^{-1} 3354, 2925, 1690, 1640, 1507; HRMS (ESI): *m/z* calculated for $C_{15}H_{29}O_2N$ $[M+Na]^+$ 278.2091, found 278.2090.

tert-butyl 9-hydroxynonylcarbamate (4b):

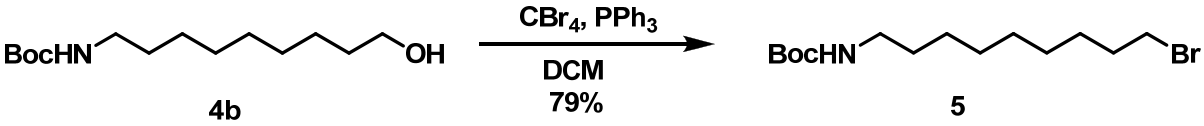


To a solution of alkene **D** (1.50 g, 5.88 mmol) in an 4:1 dioxane: water mixture (30 mL) were added a 2.5% solution of OsO_4 in ^tBuOH (3.0 mL , 0.294 mmol). After a period of 10 min, sodium meta-periodate (5.0 g, 23.52 mmol) was added and the resulting white mixture was stirred at room temperature for 5 hours, followed by addition of saturated aqueous $NaHSO_3$ and further stirred for another 30 min. The dioxane was removed under reduced pressure, brine was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Silica gel flash column chromatography of the residue using 25% EtOAc: petroleum ether, afforded aldehyde **4a** (1.29 g, 85%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.70-9.68 (m, 1 H), 4.64 (br s, 1 H), 3.03 - 3.02 (m, 2 H), 2.33 - 2.38 (m, 2 H), 1.54 - 1.56 (m, 2 H), 1.37 (br s, 10 H), 1.24 (br s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 156.0, 78.9, 43.9, 40.6, 30.0, 29.3, 29.1(2C), 28.4 (3C), 26.7, 22.0; IR υ_{max}(film): cm^{-1} 3362, 2855, 1694, 1516, 1390, 1247, 1167; HRMS (ESI): *m/z* calculated for $C_{14}H_{27}O_3N$ $[M+Na]^+$ 280.1883, found 280.1883.

To a solution of above aldehyde (1.20 g. 4.66 mmol) in EtOH (10 mL), was added $NaBH_4$ (0.21 g, 5.67 mmol) portion wise at −10 °C. After stirring for 5 min at the same temperature, the reaction was warmed to room temperature and continued stirring for 6 hours. Then reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel flash column chromatography using 40% EtOAc : petroleum ether afforded alcohol **4b** (1.10 g, 90%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (br s, 1 H), 3.55 (t, J = 8 Hz, 2 H), 3.04 - 3.03 (m, 2 H), 2.49 - 2.47 (m, 1 H), 1.53 - 1.46 (m, 2 H), 1.38 (s, 12 H), 1.24 - 1.18 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 78.8, 62.6, 40.4, 32.6, 29.9, 29.3, 29.2, 29.0, 28.3(3C), 26.6, 25.6; IR

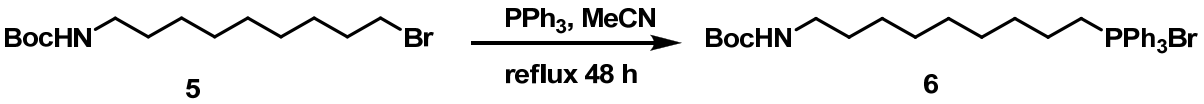
υ_{max}(film): cm^{-1} 3353, 1687, 1524, 1455, 1390; HRMS (ESI): *m/z* calculated for $C_{14}H_{29}O_3N$ $[M+Na]^+$ 282.2040, found 282.2042.

tert-Butyl 9-bromononylcarbamate (5):

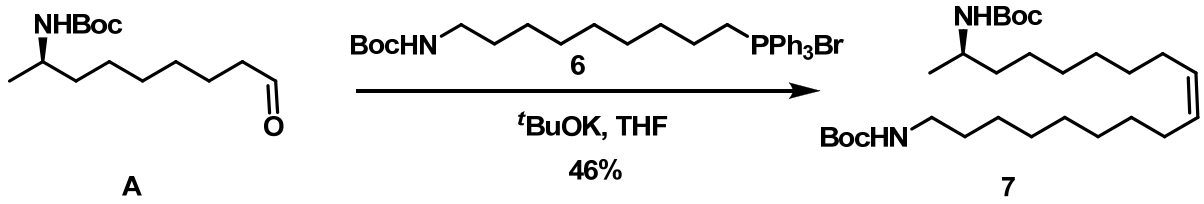


To a solution of alcohol **4a** (1.00 g, 3.89 mmol) in dry CH_2Cl_2 (20mL), was added triphenyl phosphine (1.52 g, 5.83 mmol) at 0 ^oC. After stirring for 5 min at same temperature, carbon tetrabromide (2.57 g, 7.78 mmol) was added portion wise and the reaction mixtre was allowed to stir for 3 more hours at 0 ^oC. The reaction mixture was concentrated *in vacuo* and the crude residue obtained was purified by silica gel flash column chromatography using 10% EtOAc : petroleum ether to afford compound **5** (0.98 g, 79%) as white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (br s, 1 H), 3.39 (t, *J* = 6.8 Hz, 2 H), 3.08 (q, *J* = 6.3 Hz, 2 H), 1.87 - 1.79 (m, 2 H), 1.38 (br s, 12 H), 1.28 - 1.24 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 79.0, 40.6, 34.0, 32.8, 30.0, 29.3, 29.2, 28.7, 28.4(3C), 28.1, 26.7; IR υ_{max}(film): cm^{-1} 3375, 2928, 1685, 1507, 1467; HRMS (ESI): *m/z* calculated for $C_{14}H_{28}O_2N$ $[M+Na]^+$ 344.1196, found 344.1201.

(*R,Z*)-*tert*-Butyl octadec-9-ene-1,17-diyldicarbamate (7):

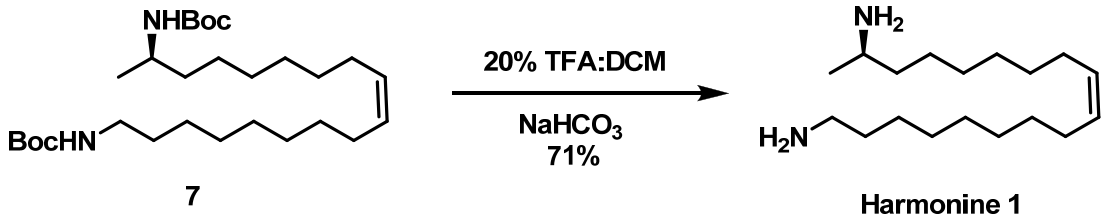


To a solution of **5** (1.20 g, 3.72 mmol) in dry acetonitrile (25 mL), was added triphenyl phosphine (1.20 g, 4.47 mmol) and heated under reflux for 36 hours. The resulting reaction mixture was concentrated *in vacuo* to give crude phosphonium salt, which was subjected to repeated washings with hexanes to obtain **6** as white solid. This salt obtained was used further without any extensive characterization. The same reaction was also performed under microwave conditions with similar results, in which the reaction mixture taken in 5ml MeCN and irradiated in microwave instrument (Monowave 300, Anton paar) for 1 hour at 140 ^oC.



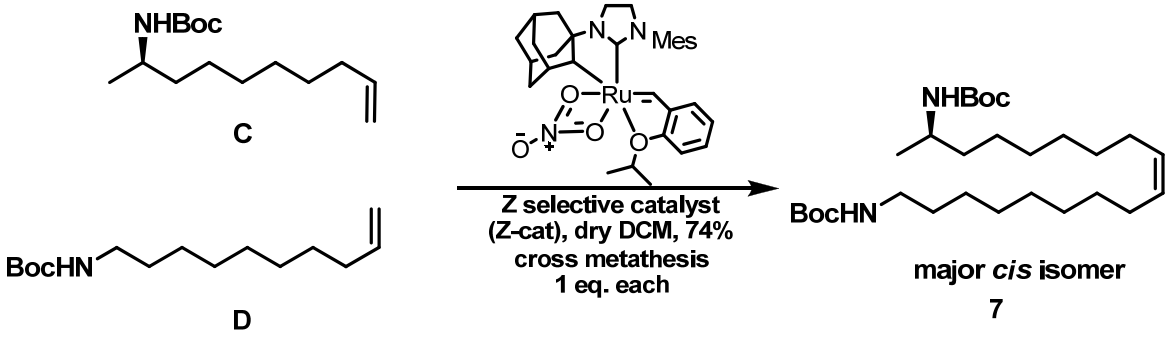
Compound **6** (0.50 g, 0.85 mmol) was taken in a clean dry round bottom flask and solid potassium tertiary butoxide (0.10 g, 0.85 mmol) was added to it. The reaction mixture was cooled to 0 ^{o}C and freshly distilled dry THF was added, which instantaneously gave deep red/orange color indicating the formation of ylide. The reaction mixture was stirred at same temperature for 5 min and then aldehyde **A** (0.13 g, 0.51 mmol), dissolved in dry THF, was added slowly and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred further for 2 hours before quenching it with saturated aqueous NH_4Cl solution and extracting with EtOAc (3 x 3 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel flash column chromatography of the residue obtained, using 10% EtOAc: petroleum ether, afforded compound **7** (0.112 g, 46%) as a colorless oil: $[\alpha]_D^{26}$ = + 0.82 (*c* = 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (t, *J* = 4.8 Hz, 2 H), 4.57 (br s, 1 H), 4.35 (br s, 1 H), 3.60 (br s, 1 H), 3.09 - 3.07 (m, 2 H), 1.99 - 1.96 (m, 4 H), 1.46 - 1.38 (m, 22 H), 1.27 (br s, 18 H), 1.08 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.3, 129.8, 129.8, 78.9, 78.8, 46.4, 40.6, 37.3, 30. 0, 29.7, 29.6, 29.4, 29.2, 29.2, 29.1, 28.4(6C), 28.3, 27.1(2C), 26.8, 25.9, 21.2; IR υ_{max}(film): cm^{-1} 3683, 3449, 2980, 2930, 1707, 1505; HRMS (ESI): *m/z* calculated for $C_{28}H_{54}O_4N_2$ $[M+Na]^+$ 505.3976, found 505.3977.

(R,Z)-octadec-9-ene-1,17-diamine (1): Harmonine



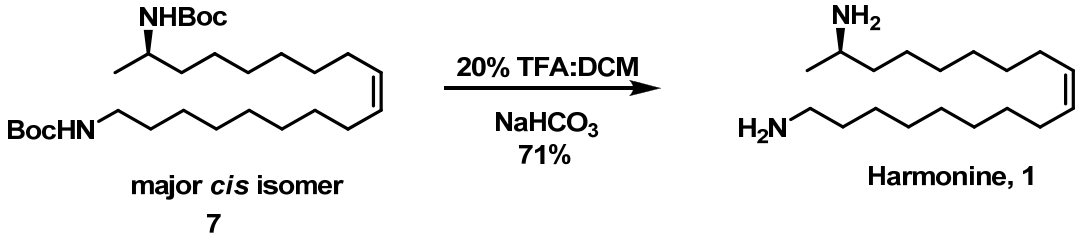
To a solution of **7** (0.10 g, 0.23 mmol) in CH_2Cl_2 (5.0 mL), was added trifluroacetic acid (1.0 mL) at 0 ^oC and stirred for 4 hours at room temperature. The resulting reaction mixture was concentrated *in vacuo* and neutralized with saturated aqueous sodium bicarbonate until the solution becomes basic (pH = 9-10). The aqueous layer was extracted with dichloromethane (3 x 3mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford harmonine **1** (41 mg, 71%) as a green oil: $[\alpha]_D^{26}$ = −1.75 (*c* = 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 5.35 (t, *J* = 4.5 Hz, 2 H), 2.88-2.85 (m, 1 H), 2.68 - 2.65 (m, 2 H), 2.02 - 2.00 (m, 4 H), 1.40 - 1.30 (m, 26 H), 1.05 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 129.8, 46.9, 42.1, 39.9, 33.5, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 29.2, 27.1(2C), 26.8, 26.4, 23.7; HRMS (ESI): *m/z* calculated for $C_{18}H_{38}N_2$ $[M+H]^+$ 283.3108, found 283.3101.

(*R,Z*)-*tert*-Butyl octadec-9-ene-1,17-diyldicarbamate (7): Using *Z*-selective catalyst[6]



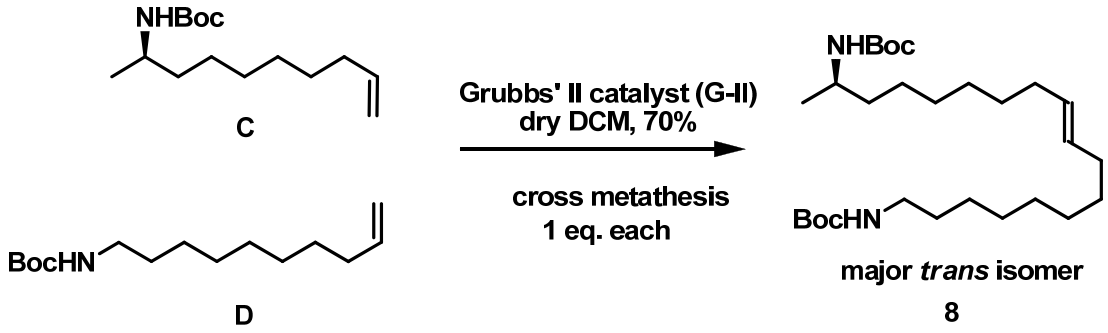
To a degassed solution of *Z*-selective catalyst (Aldrich product code: 771082) (10 mol%, 12.4 mg, 0.1 mmol) in dry CH_2Cl_2 (4.0 mL), equipped with a reflux condenser and syringe pump, was added a solution of compounds **C** (50 mg, 0.196 mmol) and **D** (50 mg, 0.196 mmol) dissolved in degassed CH_2Cl_2 (3.0 mL), over a period of 2 hours at a rate of 2.0 mL per hour at 45 ºC. The heating was continued at 45 ºC for another 10 hours, before concentrating the reaction mixture under reduced pressure to obtain a crude mixture, which was separated by silica gel column chromatography using 10% EtOAc : petroleum ether to afford the desired cross metathesis product (*R,Z)-tert*-butyl octadec-9-ene-1,17-diyldicarbamate **7** (70 mg, 74%) as major isomer (>90% desired *cis* isomer). The spectral data obtained is identical to that obtained *via* Wittig reaction.

Harmonine (1): Using *Z*-selective catalyst



To a solution of **7** (0.10 g, 0.207 mmol) in CH_2Cl_2 (4.0 mL), was added trifluroacetic acid (0.8 mL) and resulting reaction mixture was stirred for 4 hours at room temperature. Then reaction mixture was concentrated *in vacuo* and neutralized with saturated aqueous sodium bicarbonate until the solution becomes basic (pH = 9-10). The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 to afford the natural product harmonine **1** (42 mg, 71%) as a liquid. The spectral data obtained is identical to the harmonine obtained *via* Wittig reaction.

(*R,E*)-*tert*-Butyl octadec-9-ene-1,17-diyldicarbamate (8): using Grubbs' II catalyst

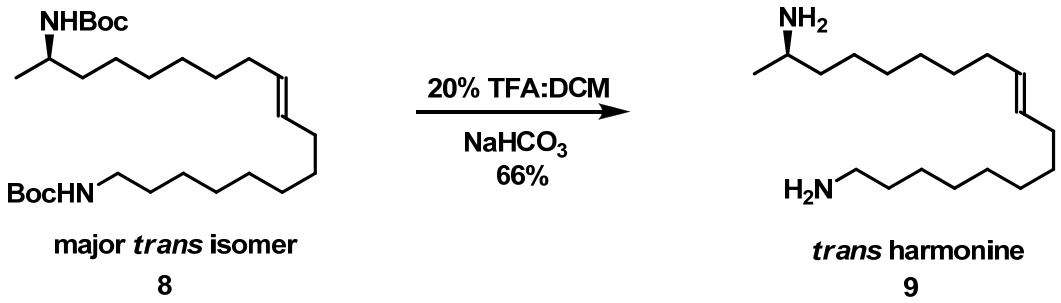


To a degassed solution of Grubbs' II generation catalyst (8 mol%, 20 mg, 0.024 mmol) in dry CH_2Cl_2 (5.0 mL), equipped with a reflux condenser and syringe pump, was added a solution of compounds **C** (77 mg, 0.30 mmol) and **D** (77 mg, 0.30 mmol) dissolved in degassed CH_2Cl_2 (3.0 mL), over a period of 2 hours at a rate of 2 mL per hour at 45 ºC. The heating was continued for another 10 hours before concentrating the reaction mixture under reduced pressure to obtain crude mixture, which was separated by silica gel column chromatography using 10% EtOAc : petroleum ether to afford the desired cross metathesis product (*R,E*)-*tert*-butyl octadec-9-ene-1,17-diyldicarbamate **8**$^{\#}$ (103 mg, 70%) as major compound (>90%): ^{1}H

NMR (400 MHz, $CDCl_3$) δ 5.34 (m, 2 H), 4.59 (br s, 1 H), 4.37 (br s, 1 H), 3.59 (br s, 1 H), 3.08 - 3.06 (m, 2 H), 1.93 - 1.92 (m, 4 H), 1.41 - 1.34 (m, 22 H), 1.27 (br s, 18 H), 1.07 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.4, 130.3, 130.3, 78.9, 78.8, 46.4, 40.5, 37.2, 32.4, 32.4, 30.0, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.3(6C), 27.1, 26.7, 26.0, 21.2; IR υ_{max}(film): cm^{-1} 3683, 3020, 2928, 2855, 1687, 1525; HRMS (ESI): *m/z* calculated for $C_{28}H_{54}O_4N_2$ $[M+Na]^+$ 505.3976, found 505.3976.

The NMR spectra show presence of ~5% of other compound which could be *cis* isomer.

(*R,E*)-octadec-9-ene-1,17-diamine : *trans*-harmonine (9)

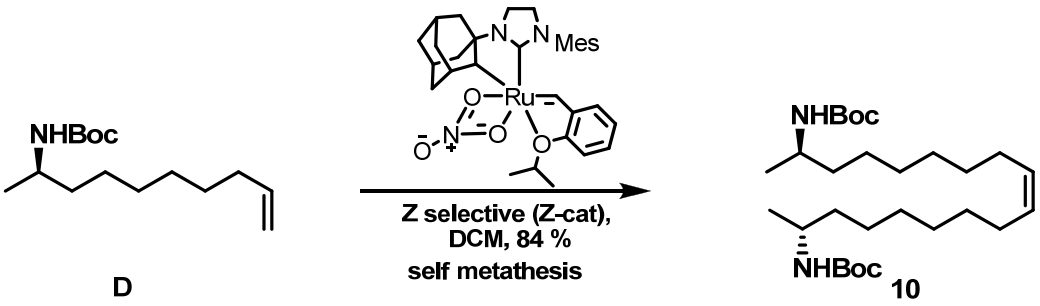


major *trans* isomer
8

trans harmonine
9

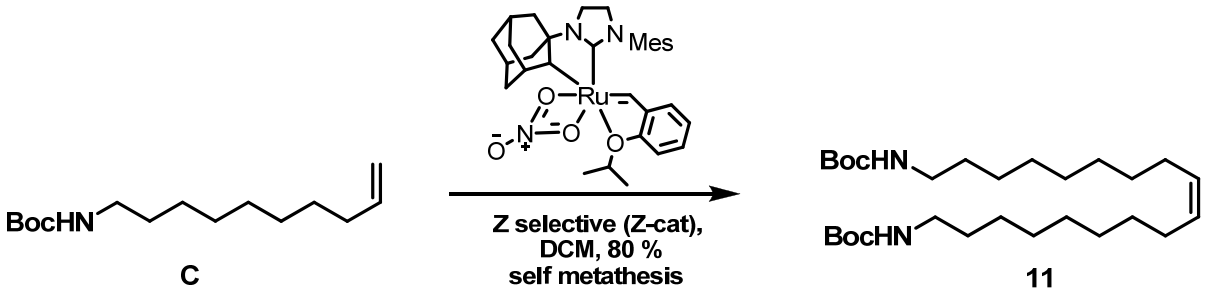
To a solution of **8** (90 mg, 0.186 mmol) in CH_2Cl_2 (5.0 mL), was added trifluroacetic acid (1.0 mL) and resulting reaction mixture was stirred for 4 hours at room temperature. The reaction mixture was then concentrated *in vacuo* and neutralized with saturated aqueous sodium bicarbonate until the solution becomes basic (pH = 9-10). The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 to afford *trans* harmonine **9** (35 mg, 66%, light yellow oil). ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (br s, 2 H), 2.86 - 2.85 (m, 1 H), 2.67 (t, *J* = 6.9 Hz, 2 H), 2.01 - 1.96 (m, 4 H), 1.49 (br s, 4 H), 1.43-1.41 (m, 2 H) 1.28 (br s, 20 H), 1.03 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.2, 130.2, 46.9, 42.1, 40.1, 33.7, 32.5 (2C), 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 29.1, 26.8, 26.4, 23.9; IR υ_{max}(film): cm^{-1} 3672, 1665, 1582, 1463, 1216; HRMS (ESI): *m/z* calculated for $C_{18}H_{38}N_2$ $[M+H]^+$ 283.3099, found 283.3108.

tert-Butyl (2*R*,17*R,Z*)-octadec-9-ene-2,17-diyldicarbamate (10):



To a degassed solution of **D** (55 mg, 0.215 mmol) in dry CH_2Cl_2 (4.0 mL) in a 10 mL round bottomed flask fixed with a reflux condenser was added *Z*-selective Grubbs' catalyst (Aldrich product code: 771082) (10 mol%, 13 mg, 0.021 mmol) and was heated to 55 ºC for 12 hours. The reaction mixture was concentrated under reduced pressure and the crude mixture was separated by silica gel column chromatography using 15% EtOAc : petroleum ether to afford compound **10** (44 mg, 84%) as colorless liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.34 (t, *J* = 4.7 Hz, 2 H), 4.30 (br s, 2 H), 3.62 (br s, 2 H), 2.02-1.99 (m, 4 H), 1.44 (br s, 18 H), 1.29 - 1.26 (m, 20 H), 1.10 (d, *J* = 8 Hz, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.4 (2C), 129.8 (2C), 78.9 (2C), 46.6 (2C), 37.4 (2C), 29.7 (2C), 29.4 (2C), 29.2 (2C), 28.5 (6C), 27.2 (2C), 26.0 (2C), 21.3 (2C); IR υ_{max}(film): cm^{-1} 3028, 2932, 2856, 1710, 1503, 1352, 1356, 1210.

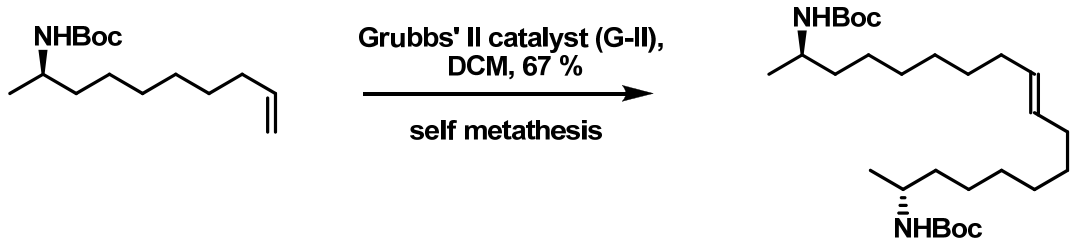
(*Z*)-*tert*-Butyl octadec-9-ene-1,18-diyldicarbamate (11):



To a degassed solution of **C** (70 mg, 0.274 mmol) in dry CH_2Cl_2 (4.0 mL) in a 10 mL round bottomed flask fixed with a reflux condenser was added *Z*-selective catalyst (Aldrich product code: 771082) (10 mol%, 17 mg, 0.027 mmol) and heated to 45 ºC for 12 hours. The reaction mixture was concentrated under reduced pressure and the crude mixture was separated by

silica gel column chromatography using 15% EtOAc : petroleum ether to afford compound **11** (53 mg, 80%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.34 (t, *J* = 4.6 Hz, 2 H), 4.53 (br s, 2 H), 3.09-3.11 (m, 4 H), 2.02 - 1.98 (m, 4 H), 1.44 (br s, 24 H), 1.28 (br s, 18 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.9 (2C), 129.8 (2C), 79.0 (2C), 40.6 (2C), 30.1 (2C), 29.7 (2C), 29.4 (2C), 29.3 (2C), 29.2 (2C), 28.4 (6C), 27.2 (2C), 26.8 (2C); IR υ_{max}(film): cm^{-1} 3445, 3020, 2856, 1702, 1508, 1442, 1216; HRMS (ESI): *m/z* calculated for $C_{28}H_{54}O_4N_2$ $[M+Na]^+$505.3976, found 505.3979.

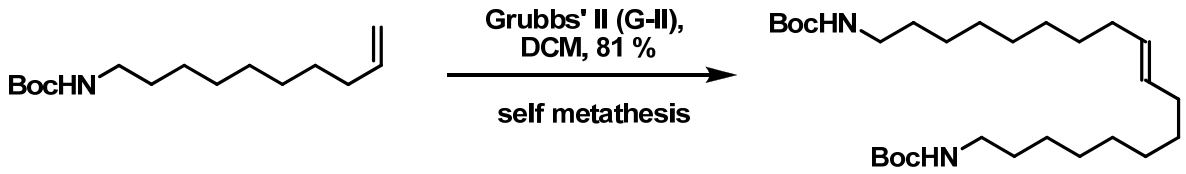
tert-Butyl (*2R,17R,E*)-octadec-9-ene-2,17-diyldicarbamate (12):



D **12**

To a degassed solution of **D** (30 mg, 0.117 mmol) in dry CH_2Cl_2 (5.0 mL) in a 10 mL round bottomed flask fixed with a reflux condenser was added Grubbs' II generation catalyst (5 mol%, 5.0 mg, 0.0058mmol) and heated to 55 ºC for 12 hours. The reaction mixture was concentrated under reduced pressure and the crude mixture was separated by silica gel column chromatography using 15% EtOAc : petroleum ether to afford compound **12** (19 mg, 67%) as colorless liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.39 (m, 2 H), 4.33 (br s, 2 H), 3.64 (br s, 2 H), 1.98 - 1.97 (m, 4 H), 1.46 (br s, 20 H), 1.34 - 1.28 (m, 18 H), 1.12 (d, *J* = 8 Hz, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.4 (2C), 130.4 (2C), 79.0 (2C), 46.6 (2C), 37.4 (2C), 32.6 (2C), 29.7 (2C), 29.5 (2C), 29.2 (2C), 28.5 (6C), 26.1 (2C), 21.3 (2C); IR υ_{max}(film): cm^{-1} 3020, 2932, 2856, 1705, 1503, 1367, 1216; HRMS (ESI): *m/z* calculated for $C_{28}H_{54}O_4N_2$ $[M+Na]^+$ 505.3976, found 505.3978.

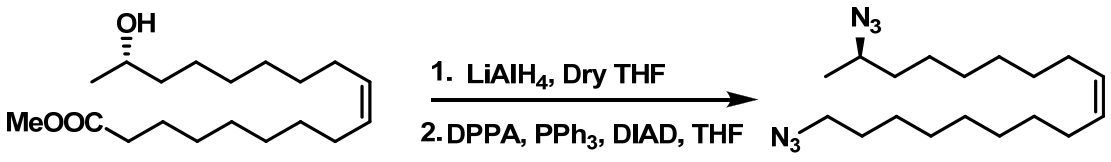
(*E*)-*tert*-Butyl octadec-9-ene-1,18-diyldicarbamate (13):



C **13**

To a degassed solution of **C** (30 mg, 0.117mmol) in dry CH_2Cl_2 (5.0 mL) in a 10 mL round bottomed flask fixed with a reflux condenser was added Grubbs' II generation catalyst (5 mol%, 5.0 mg, 0.0058 mmol) and heated to 55 ºC for 12 hours. The reaction mixture was concentrated under reduced pressure and the crude mixture was separated by silica gel column chromatography using 15% EtOAc : petroleum ether to afford product **13** (23 mg, 81%) as white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.37 - 5.34 (m, 2 H), 4.53 (br s, 2 H), 3.12 - 3.07 (m, 4 H), 2.01 - 1.95 (m, 4 H), 1.44 (br s, 24 H), 1.28 - 1.26 (m, 18 H); ^{13}C NMR (50MHz, $CDCl_3$) δ = 156.4 (2C), 130.4(2C), 79.1 (2C), 40.7 (2C), 32.6 (2C), 30.1 (2C), 29.7 (2C), 29.6 (2C), 29.5 (2C), 29.1(2C), 28.5 (6C), 26.9 (2C); IR υ_{max}(film): cm^{-1} 3445, 3018, 2856, 1708, 1508, 1456, 1393,1169; HRMS (ESI): *m/z* calculated for $C_{28}H_{54}O_4N_2$ $[M+Na]^+$ 505.3976, found 505.3979.

(*R,Z*)-1,17-diazidooctadec-9-ene (15):

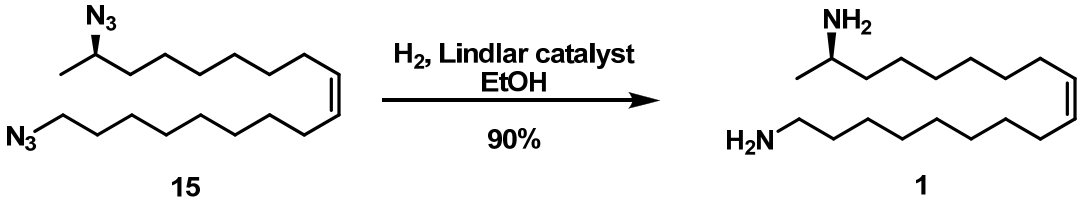


14 **15**

A stirred solution of lithium aluminium hydride (10 mg, 0.25 mmol) in 5.0 mL of dry THF, under argon, was cooled to 0 °C and treated drop wise over 15 min with a solution of ester **14**[4] (63 mg, 0.20 mmol) in dry THF. The resulting reaction mixture was warmed to room temperature during 30 min, stirred for another 8 hours, and then re-cooled to 0 ^{o}C and quenched simultaneously with saturated aqueous sodium sulphate and EtOAc until all of the turbidity is lost. The reaction mixture was then filtered through a pad of celite, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to obtain diol which was used as such for azide displacement reaction without any further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 - 5.33 (m, 2 H), 3.77 - 3.76 (m, 1 H), 3.59 (t, *J* = 6.6 Hz, 2 H), 2.64 (br s, 2 H), 2.04 - 1.97 (m, 4 H), 1.56 - 1.51 (m, 2 H), 1.30 (br s, 20 H), 1.17 (d, *J* = 6.1 Hz, 3 H).

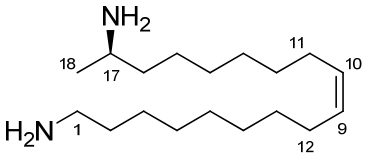
A solution of crude diol (0.20 mmol) in anhydrous THF (3.0 mL) was cooled to 0 ^{o}C, and triphenylphosphine (3.35 g, 12.80 mmol) was added at once. After 5 min of stirring, add this solution to previously cooled solution of DIAD (0.157 g, 0.80 mmol) and DPPA (0.166 g, 0.13 mL, 0.6 mmol) in dry THF (4 mL), at 0 ^{o}C. Then the ice bath was removed, and the resulting mixture was stirred at room temperature for 16 hours. Volatiles were evaporated *in vacuo*, and the residue was dissolved in EtOAc and subsequently washed with water and brine solution. Silica gel flash column chromatography using 3% EtOAc: petroleum ether afforded the diazide **15** (50 mg, 74 % for two steps) as colorless oil: $[\alpha]_D^{26} = -18.23$ (*c* = 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 - 5.34 (m, 2 H), 3.43 - 3.41 (m, 1 H), 3.26 (t, *J* = 7.0 Hz, 2 H), 2.03 - 2.02 (m, 4 H), 1.62 - 1.59 (m, 2 H), 1.43 - 1.28 (m, 20 H), 1.25 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 129.8, 58.0, 51.5, 36.2, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.1, 28.8, 27.2, 27.1, 26.7, 26.1, 19.5; IR υ_{max}(film): cm^{-1} 3019, 2930, 2856, 2100, 1729, 1465, 1216.

Harmonine (1)[5]: from diazide



15 **1**

To a degassed solution of diazide **15** (43 mg, 0.128 mmol) in ethanol was added commercially available Lindlar catalyst (10 mg) and subjected to hydrogenation under balloon pressure for 1 hour. The reaction mixture was filtered through the celite pad, washed with ethanol/ EtOAc and the filtrate was then concentrated *in vacuo* to obtain harmonine **1** (33 mg, 90%): $[\alpha]_D^{26.9} = -3.44$ (*c* = 1.62, C_6H_6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (t, *J* = 4.8 Hz, 2 H), 2.87 - 2.83 (m, 1 H), 2.67 (t, *J* = 6.9 Hz, 2 H), 2.01 - 1.94 (m, 4 H), 1.44 - 1.40 (m, 2 H), 1.29 (br s, 24 H), 1.05 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 129.8, 46.9, 42.2, 40.1, 33.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.2, 29.2, 27.1(2C), 26.8, 26.4, 23.7; HRMS (ESI): *m/z* calculated for $C_{18}H_{38}N_2$ $[M+H]^+$ 283.3108, found 283.3109.



Chemical Formula: $C_{18}H_{38}N_2$
Molecular Weight: 282.5077

Comparision table of harmonine synthesized and reported

Literature values#		**Obtained values**	
1H	**13 C**	**1H**	**13 C**
5.30-5.40 (2H, m, H-9, H-10)	130 (C-9, C-10),	5.35 (t, *J* = 4.5 Hz, 2 H)	129.9, 129.8
2.82-2.90 (1H, m, H-17)	46.5(C-17),	2.88-2.85 (m, 1 H)	46.9
2.67 (2H, t, *J = 7.0 Hz, H-1)*	41.5 (C-1),	2.68 - 2.65 (m, 2 H)	42.1
1.95 - 2.05 (4H, m, H-8, H-11)	28-30 (alkyl chain)	2.02 - 2.00 (m, 4 H)	39.9, 33.5*, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 29.2, 26.8, 26.4,
1.11-1.40 (22H, br s, alkyl chain)	27.0 (C-8, C-11),	1.40 - 1.30 (m, 26 H)	27.1(2C)
1.04 (3H, d, *J = 7.0 Hz,*H-18)	23.0 (C-18)	1.05 (d, *J* = 6.4 Hz, 3 H)	23.7
		38 H	**18 C**
$[\alpha]_D^{23} = -3.95$ (c = 1.04, $\mathbf{C_6H_6}$)		$[\alpha]_D^{26} = -1.75$ (*c* = 0.6, $\mathbf{CHCl_3}$) $[\alpha]_D^{26.9} = -3.44$ (*c* = 1.62, $\mathbf{C_6H_6}$)	

N. Alam, I. S. Choi, K-S. Song, J. Hong, C. O. Lee and J. H. Jung, *Bull. Kor. Chem. Soc.*, 2002**, 23**, 497–499

*The peaks at 39.9 and 33.5 corresponds to C2 and C16 carbons

Preparation of gold-nanoparticles of Harmonine:

Harmonine capped gold nanoparticles were prepared by following the previously reported procedures with slight modifications.[7 -9] In a 50 mL Round bottom flask, 0.025 gm of DDAB (didodecyldimethylammonium bromide) was added to 2.5 mL of toluene (dry). To that 1.5 mg of $AuCl_3$ (2 x 10^{-3}M) was added under vigorous stirring conditions leading to the formation of an orange coloured solution. An aqueous solution of $NaBH_4$ (40 - 50 µL, 9.4 M) was added drop wise to this orange coloured solution. The stirring was allowed to proceed for 1 - 2 h to ensure complete reduction. The reduction of Au^{+3} ions to AuNPs containing Au^0 was confirmed by the appearance of wine red colour.

To the wine red solution, harmonine (14 mg) was added in such a way that the metal to ligand molar ratio was 1:10. After 2 hours, 7.5 mL of absolute EtOH was added to this solution to separate the unreacted ligand, DDAB and other side products from the harmonine coated nanoparticles. The residual EtOH was removed under reduced pressure. The black

colour precipitate was redispersed again in 3 mL of toluene (dry). The so obtained nanoparticles were subjected to further characterization like UV - Vis, XRD, and TEM.

Harmonine Biological Profile[11] :

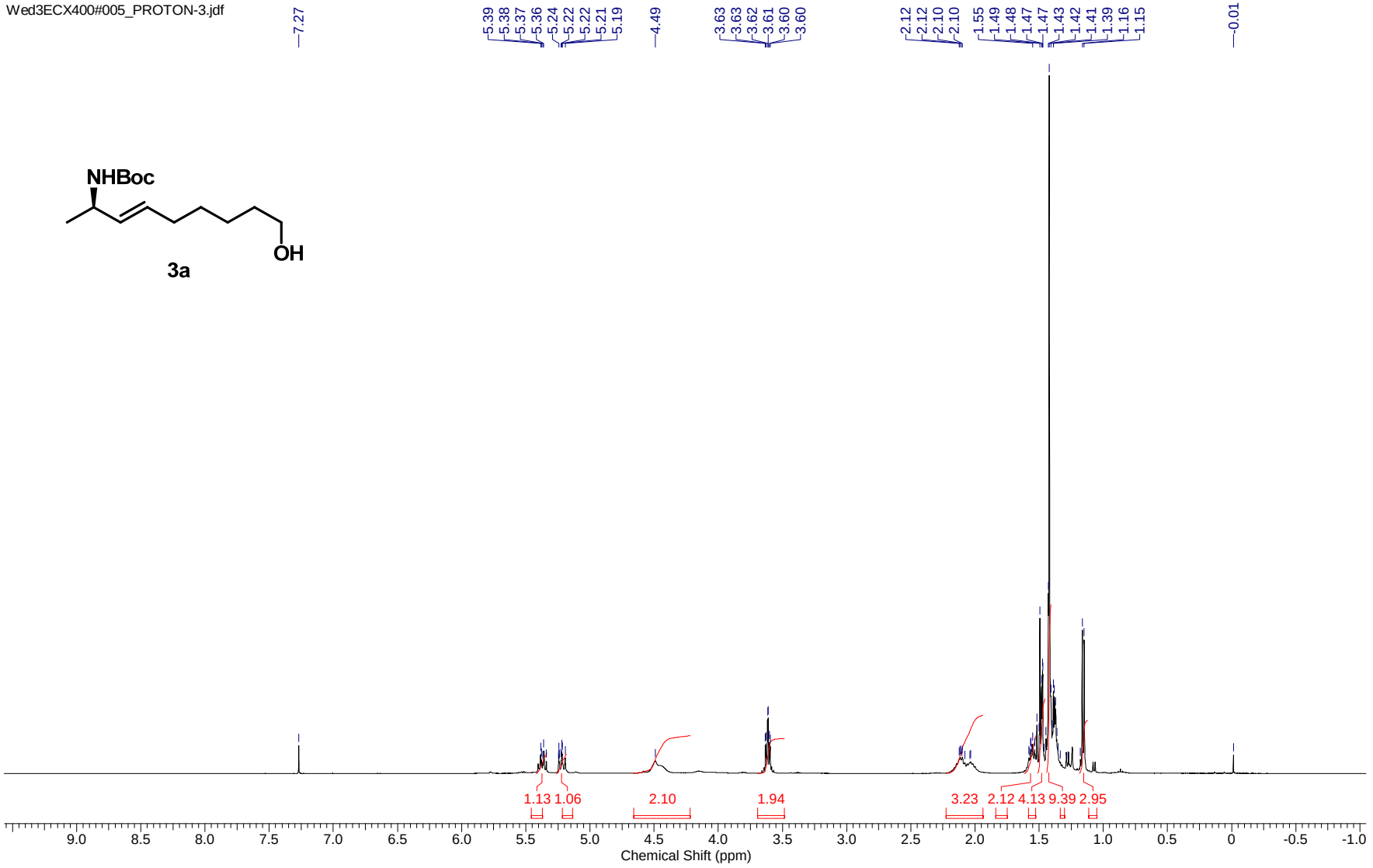
1. Antibacterial activities: (selected MIC values for *MTb* $H37_{RV}$: 44 μM; *E.Coli*: 89 μM; *Bacillus subtilis*: 44 μM; *Staphylococcus aureus*: 89 μM),
2. Antimalarial activities: (*Plasmodium falciparum* 3D7: 4.8 μM; Dd2: 7.6 μM)
3. Anticancer activities: (selected ED_{50} values for cell lines A549: 3.04 μg/mL; SK-OV-3: 2.86 μg/mL; SK-MEL-2: 2.87 μg/mL; XF498: 1.03; HCT15: 1.10 μg/mL).

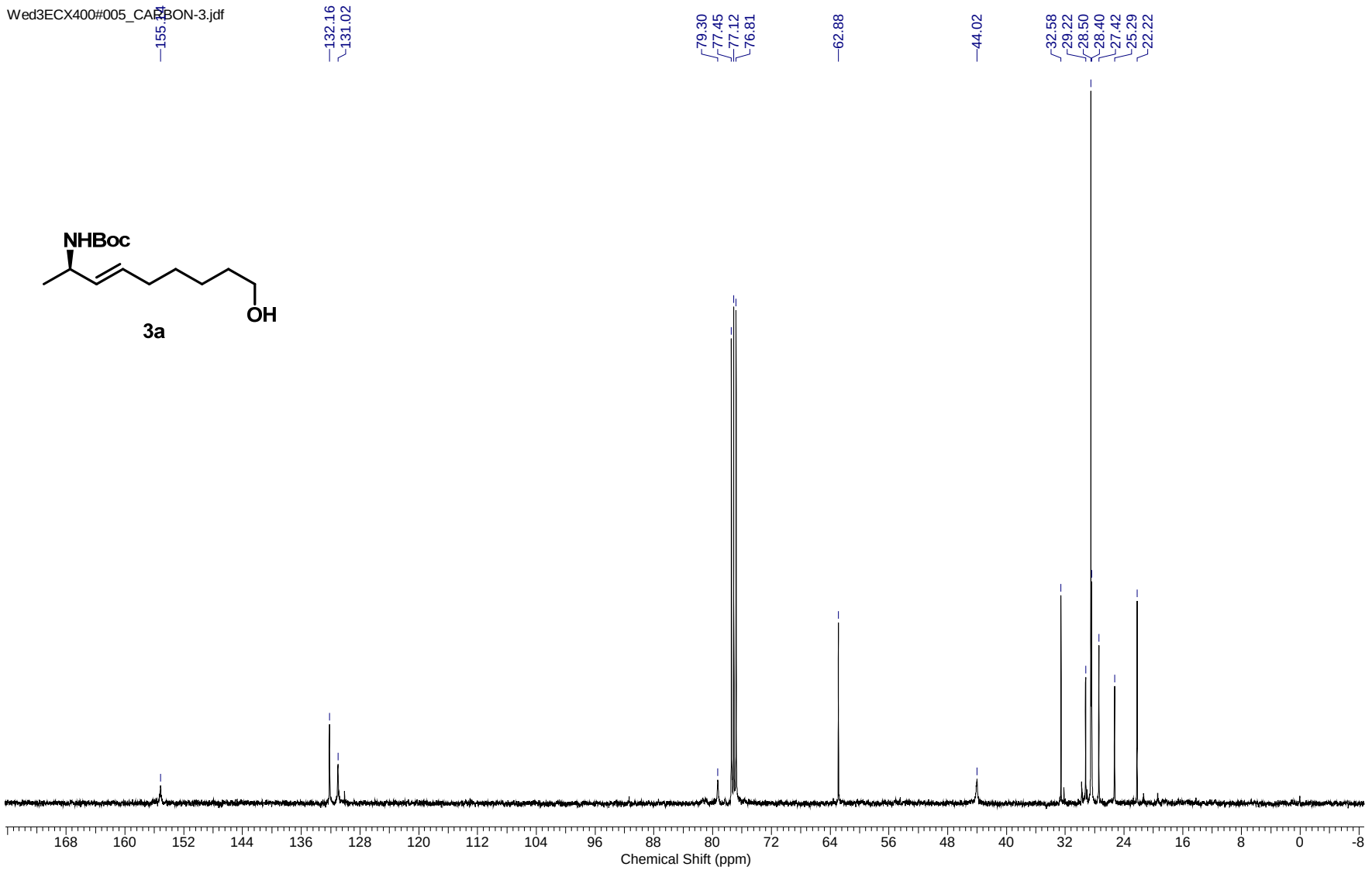
References :

1. For compound **2**: C. Jahns, T. Hoffmann, S. Müller, K. Gerth, P. Washausen, G. Höfle, H. Reichenbach, M. Kalesse and R. Müller, *Angew. Chem. Int. Ed.*, 2012, **51**, 5239 –5243.
2. For compound **3**: a) J. M. Chong, M. A. Heuft and P. Rabbat, *J. Org. Chem.*, 2000, **65**, 5837–5838; (b) J. E. Stumpel, D. Liu, D. J. Broer and A. P. H. J. Schenning, *Chem. Eur. J.*, 2013**, 19**, 10922–10927; c) M. Novak, A. Ebel, T. Meyer-Friedrichsen, A. Jedaa,; B. F. Vieweg, G. Yang, K. Voitchovsky, F. Stellacci, E. Spiecker, A. Hirsch and M. Halik, *Nano Lett.*, 2011, **11**, 156–159; d) M. Culcasi, G. Casano, C. Lucchesi, A. Mercier, J-L. Clément, V. Pique, L. Michelet, A. Krieger-Liszkay, M. Robin and S. Pietri, *J. Med. Chem.*, 2013, **56** , 2487–2499.
3. For compound **D**: A. D. Jones, D. W. Knight and D. E. Hibbs, *J. Chem. Soc., Perkin Trans.*, 2001**, 1**, 1182-1203.
4. J. A. Zerkowski and D. K. Y. Solaiman, *J. Am. Oil Chem. Soc.*, 2006, **83**, 621-628.
5. M. F. Braconier, J. C. Braekman and D. Daloze, *Bull. Soc. Chim. Belg.*, 1985, **94**, 605-613.
6. (a) M. B. Herbert, V. M. Marx, R. L. Pederson and R. H. Grubbs, *Angew. Chem. Int. Ed.*, 2013, **52**, 310–314; (b) B. L. Quigleya and R. H. Grubbs, *Chem. Sci.*, 2014, **5**, 501-506.
7. P. Sahu and B. L. V. Prasad, *Chem. Phys. Lett.*, 2012, **525-526**, 101-104.
8. B. L. V. Prasad, S. Stoeva, C. M. Sorensen and K. J. Klabunde, *Langmuir* **2002**, *18*, 7515 - 7520.

9. D. S. Sidhaye and B. L. V. Prasad, *New J. Chem*., **2011**, *35*, 755 –763.
10. P. Mulvaney, *Langmuir*, 1996, **12**, 788-80.
11. (a) M. F. Braconier, J. C. Braekman, D. Daloze and J. M. Pasteels, *Experientia*, 1985, **41**, 519-520; (b) N. Alam, I. S. Choi, K-S. Song, J. Hong, C. O. Lee and J. H. Jung, *Bull. Kor. Chem. Soc.*, 2002**, 23**, 497–499; (c) L. Sologub, A. Kuehn, S. Kern, J. Przyborski, R. Schillig and G. Pradel, *Cell. Microbiol.*, 2011**, 13**, 897–912; (d) C. R. Rohrich, C. J. Ngwa, J. Wiesner, H. Schmidtberg, T. Degenkolb, C. Kollewe, R. Fischer, G. Pradel and A. Vilcinskas, *Biol. Lett.*, 2012**, 8**, 308–311; (e) T. L. Galvan, S. Kells and W. D. Hutchison, *J. Agric. Food Chem.*, 2008, **56**, 1065–1071.

COPIES OF ^{1}H AND ^{13}C SPECTRA

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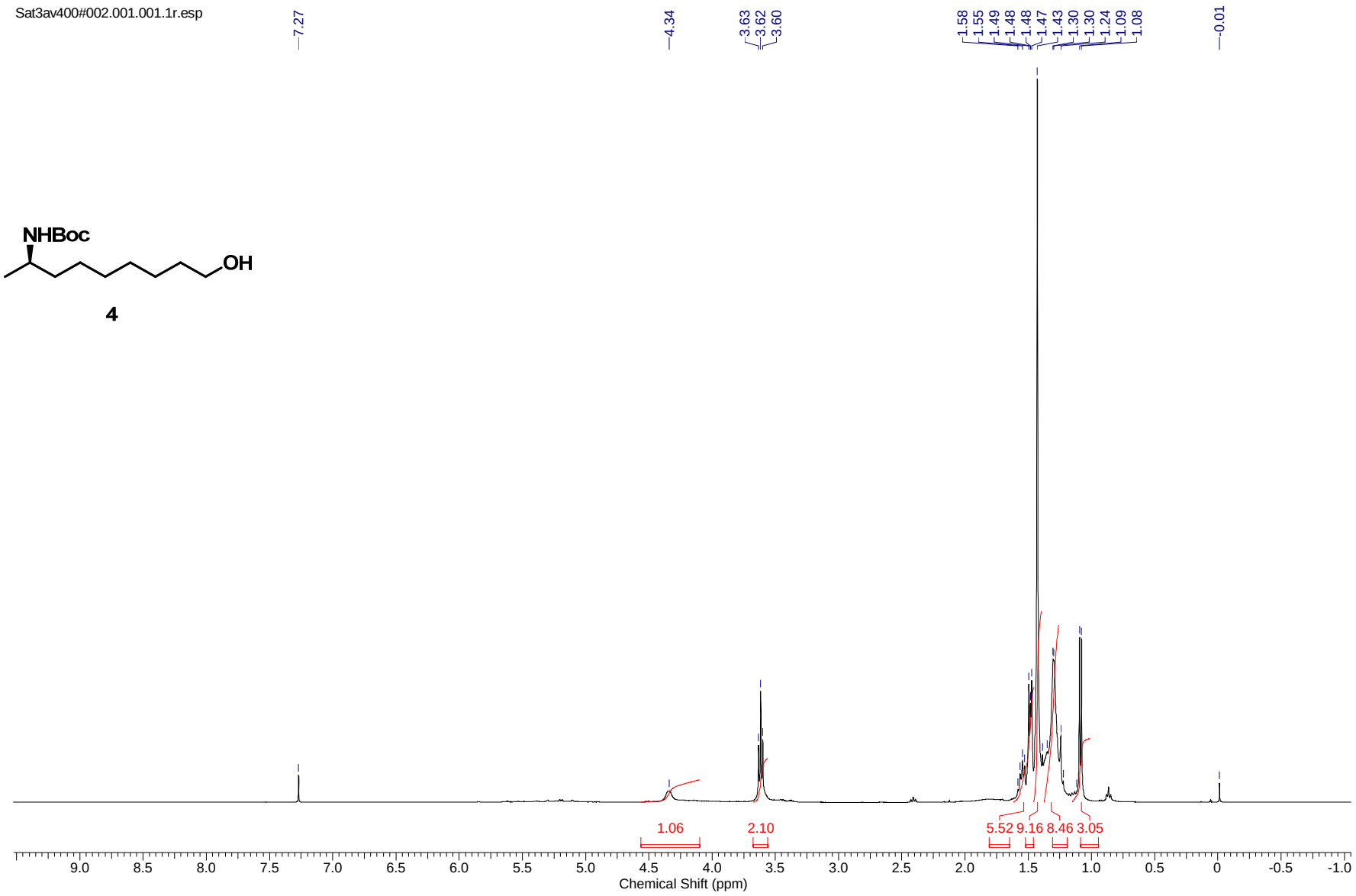
Chemical Shift (ppm)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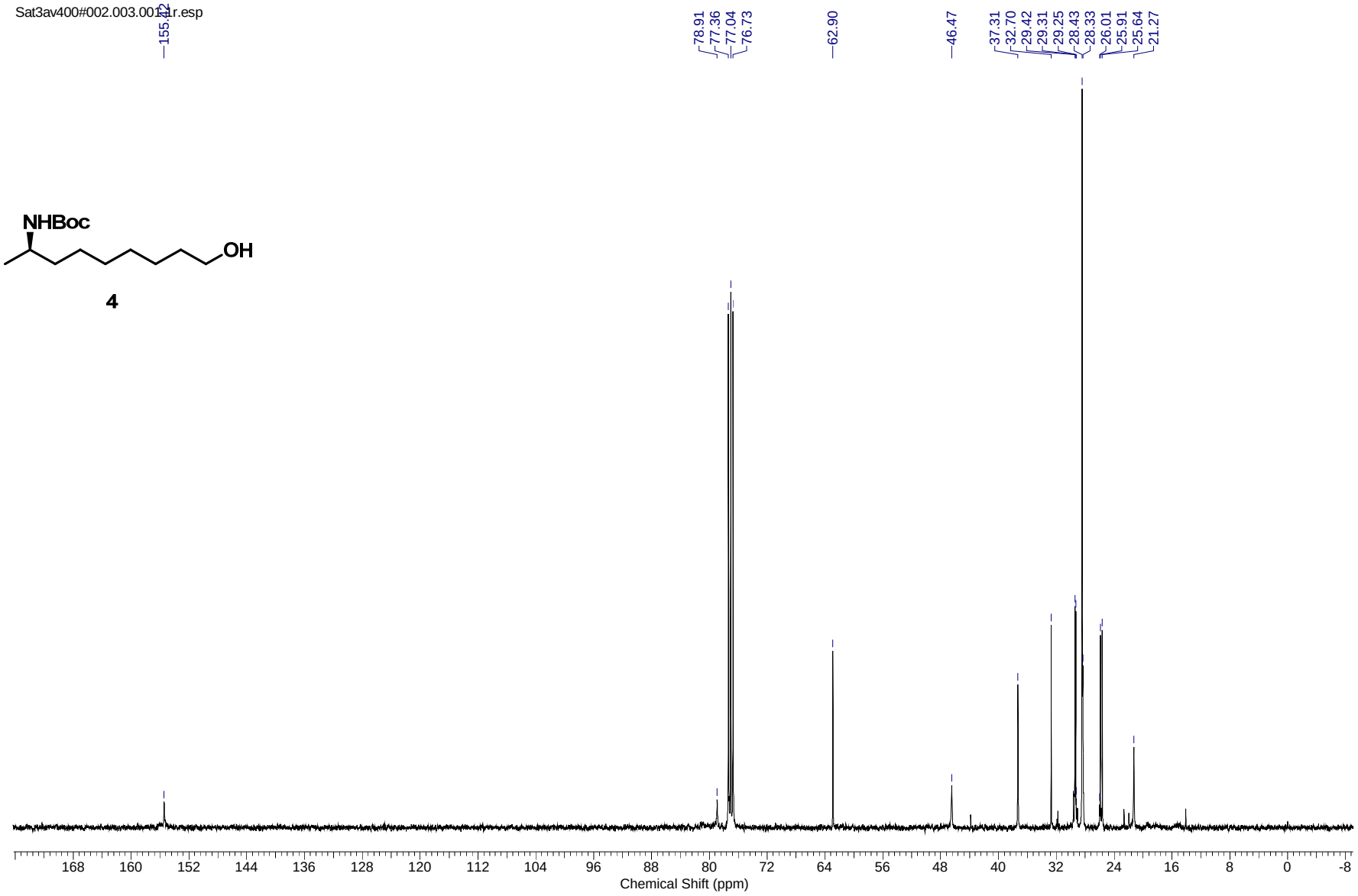
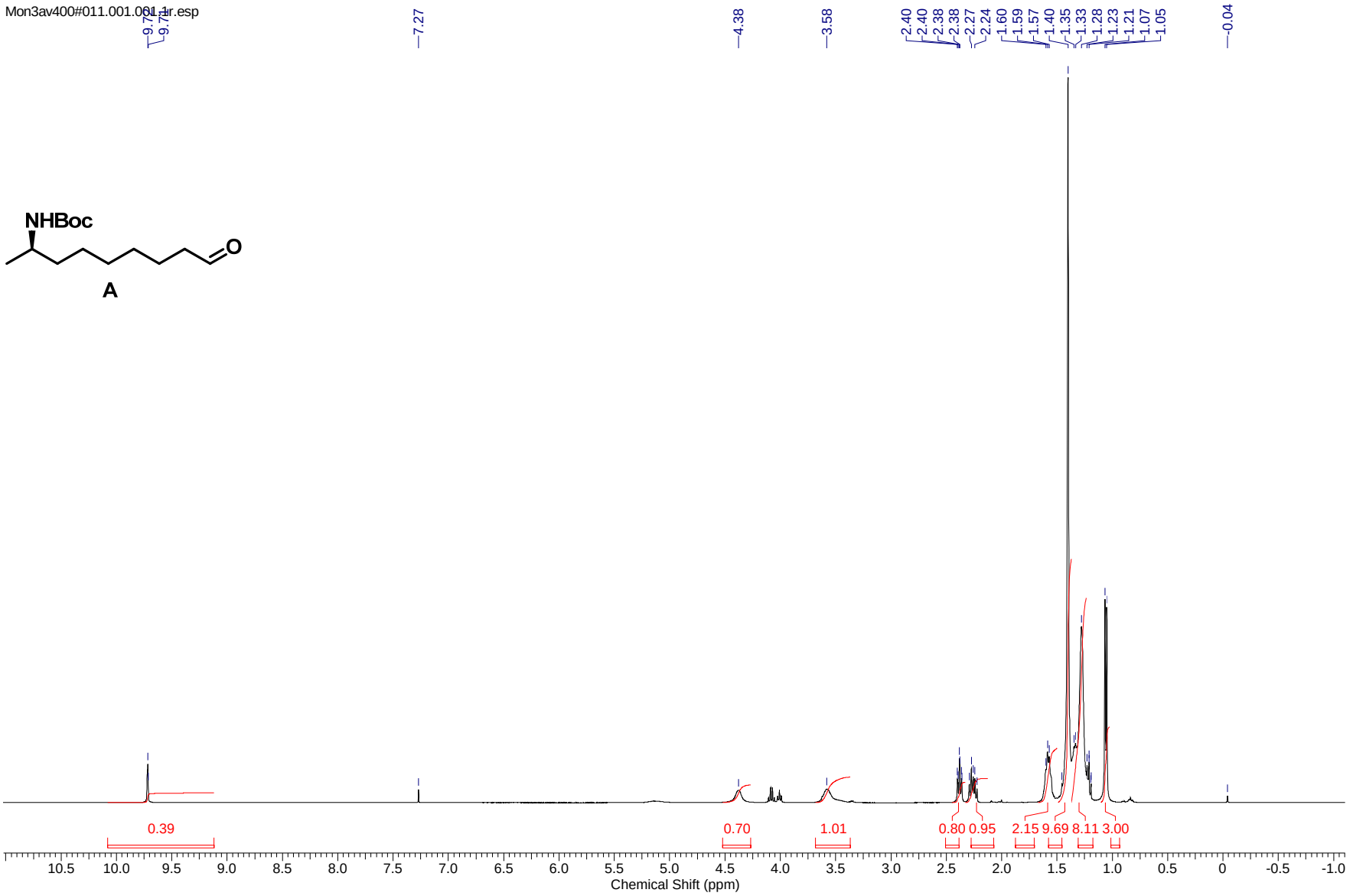
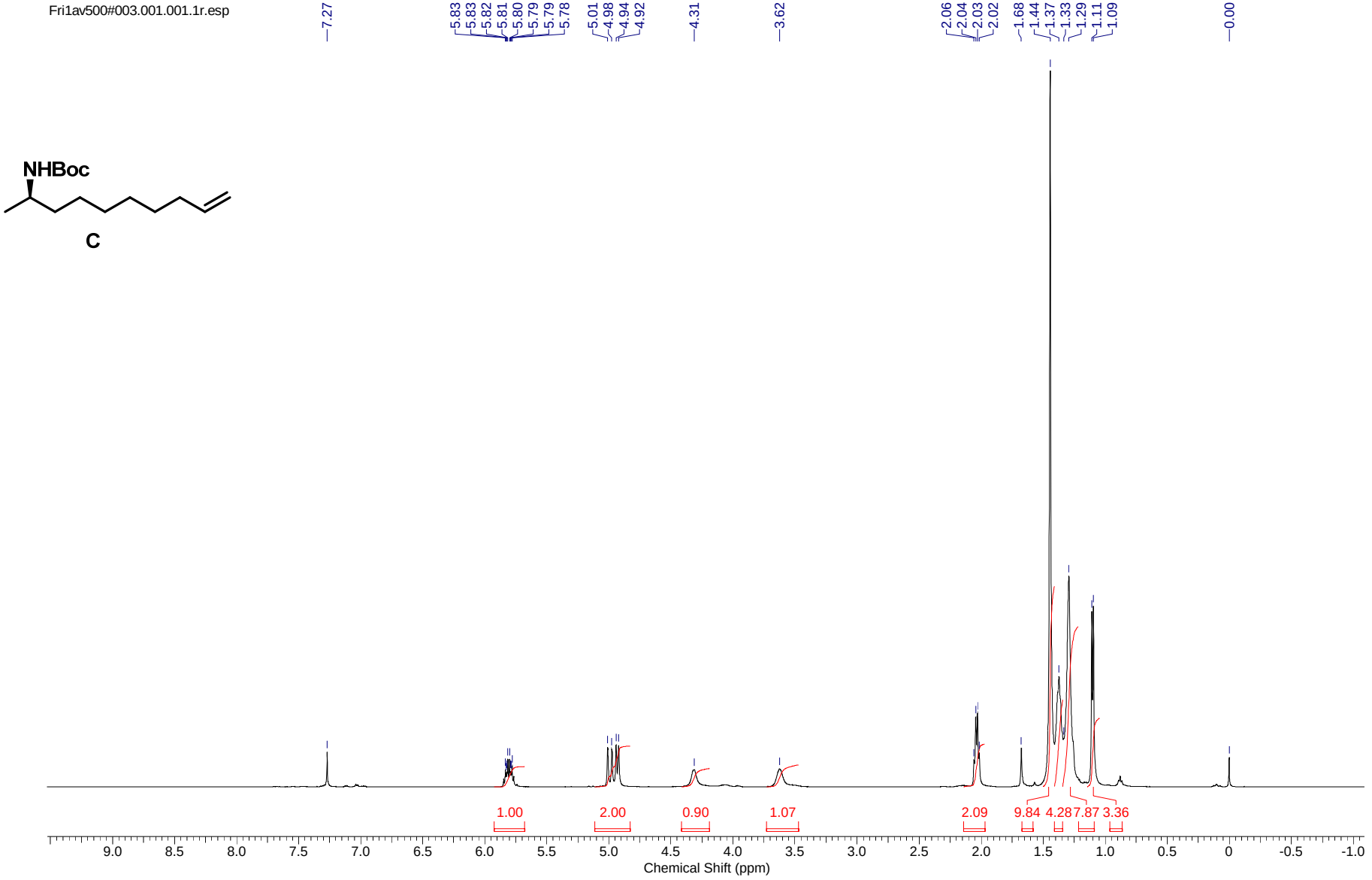
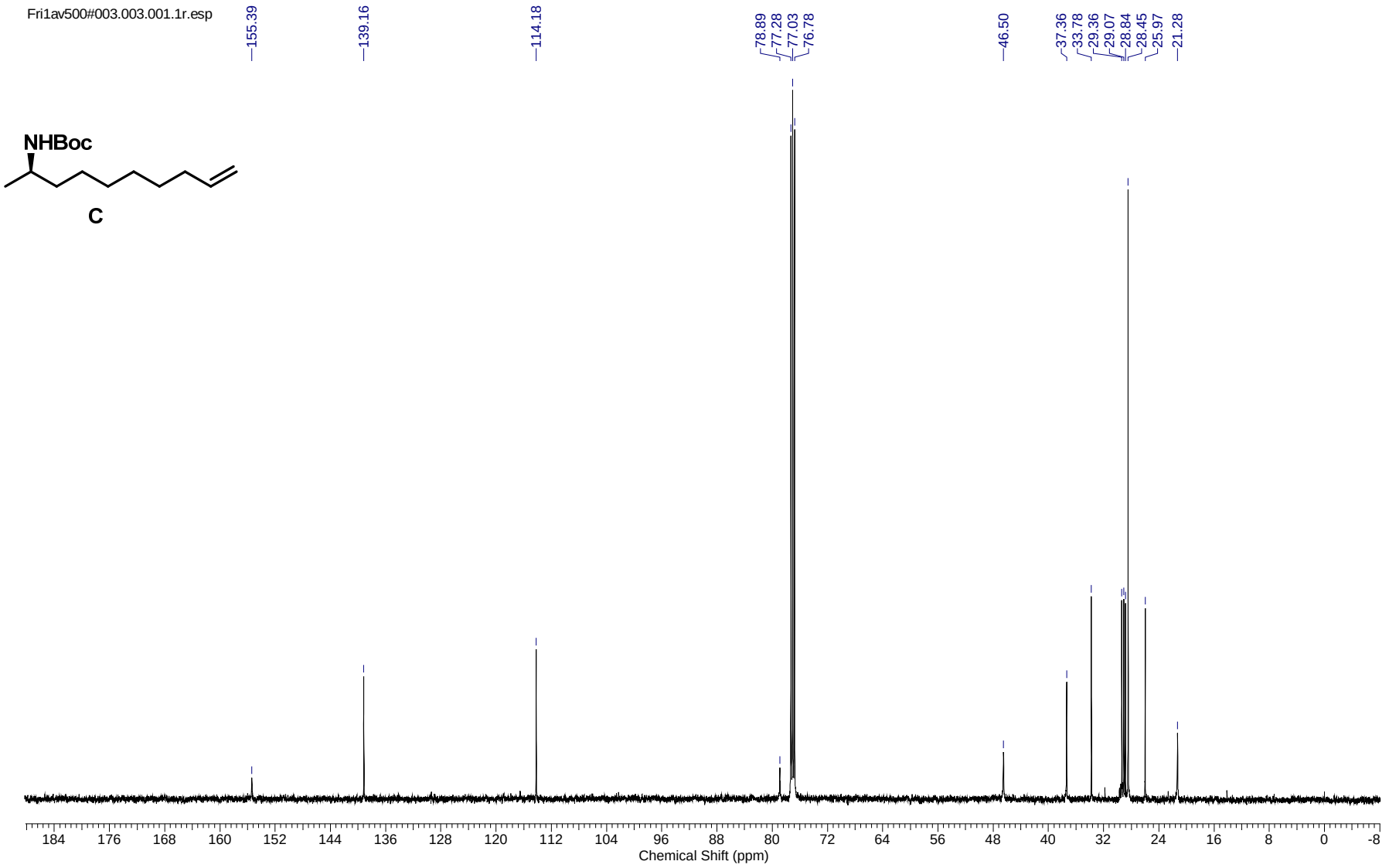
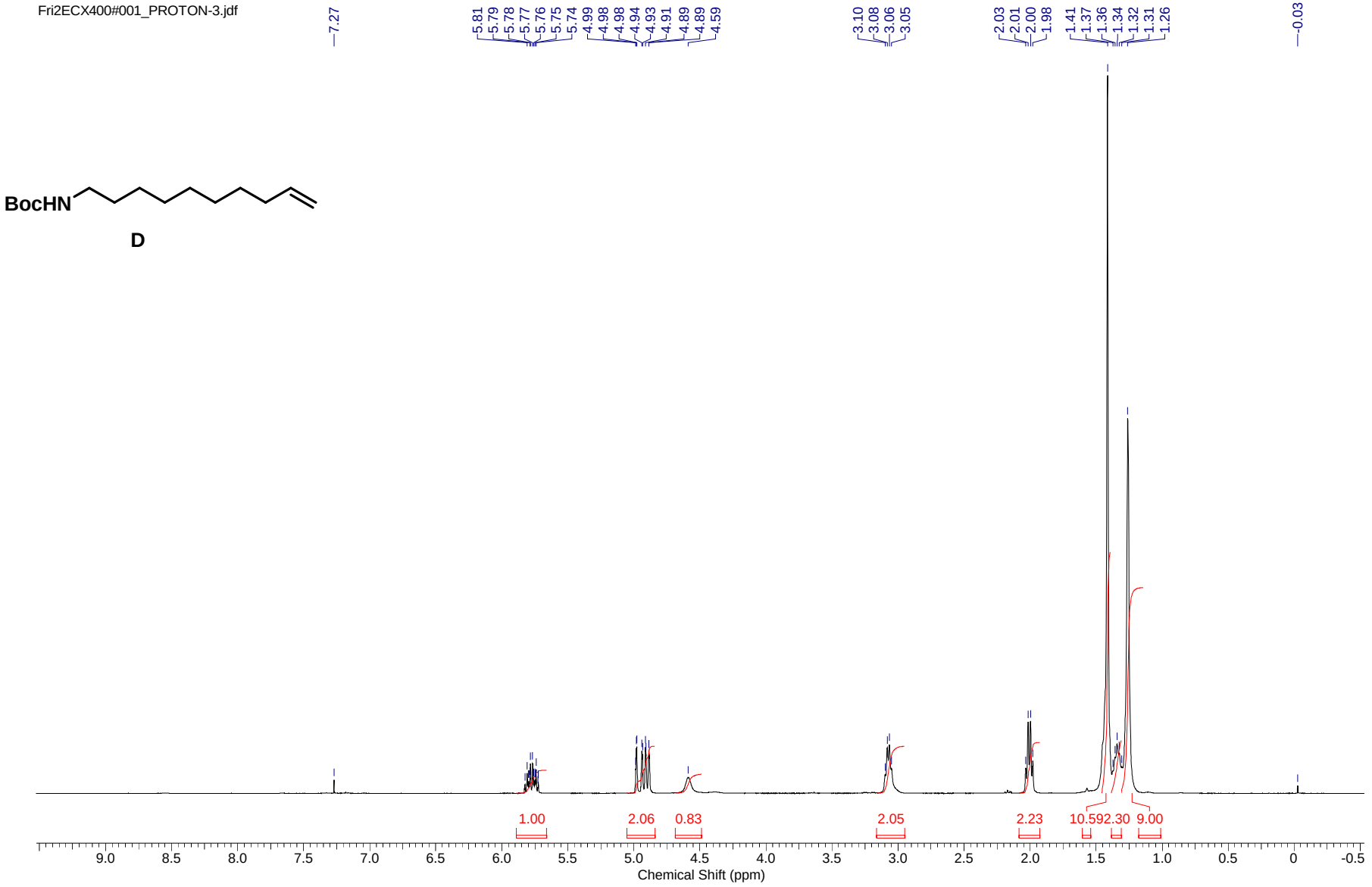
Chemical Shift (ppm)

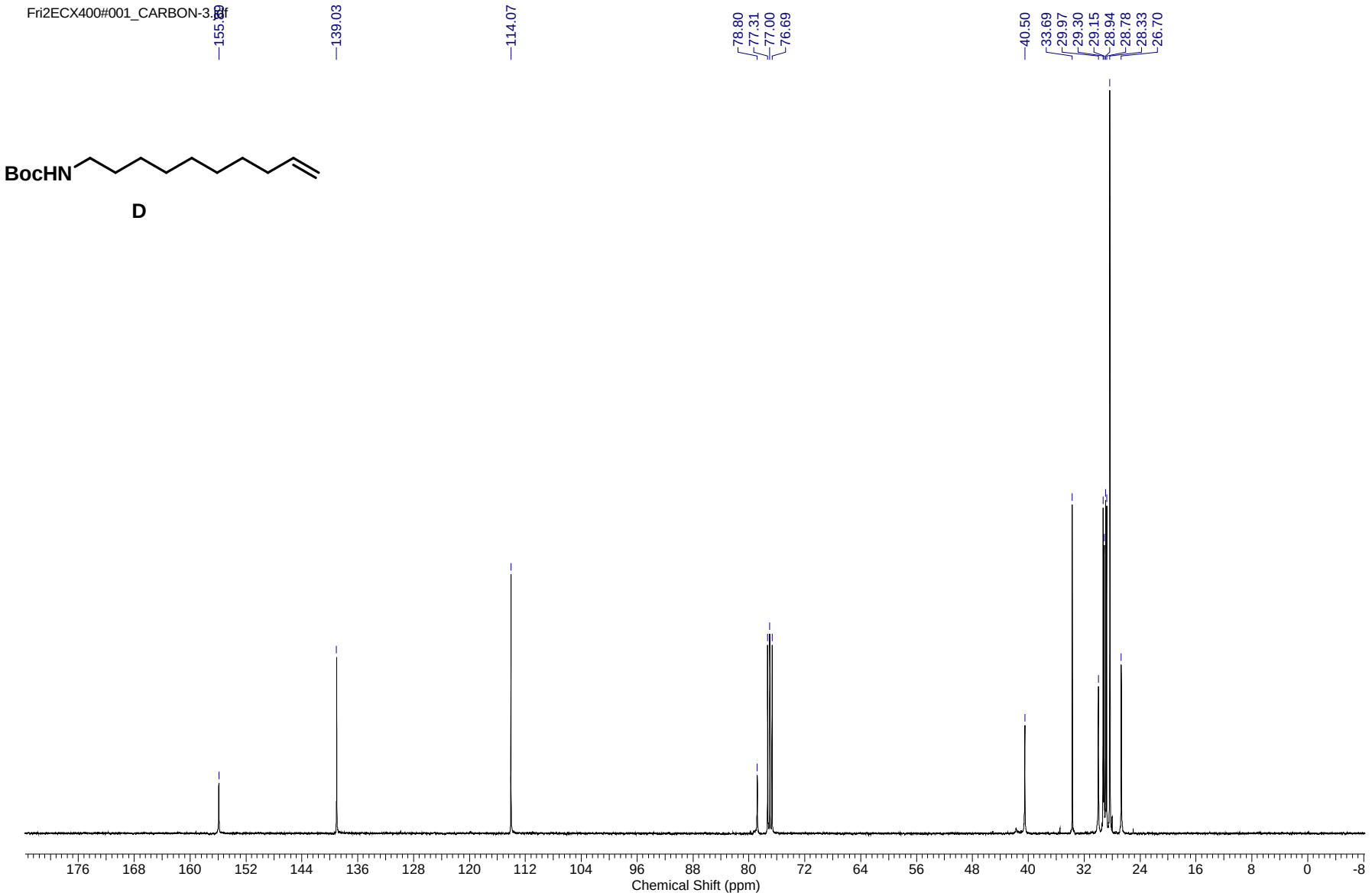

Sat3av400#002.003.001.1r.esp
155.42
78.91
77.36
77.04
76.73
62.90
46.47
37.31
32.70
29.42
29.31
29.25
28.43
28.33
26.01
25.91
25.64
21.27
NHBoc
OH
4
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8
Chemical Shift (ppm)

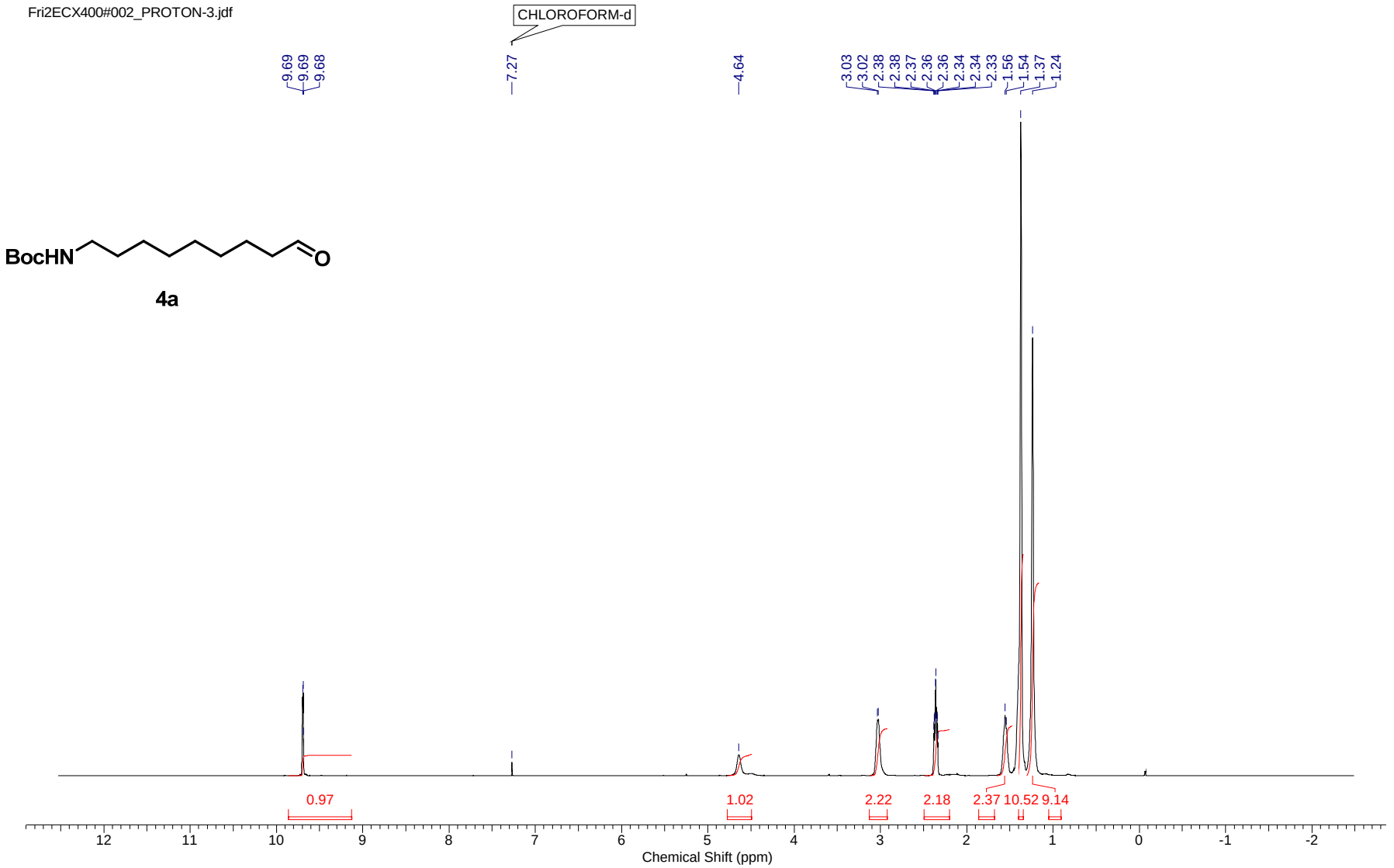

Mon3av400#011.001.001.1r.esp
9.76
9.76
7.27
4.38
3.58
2.40
2.40
2.38
2.38
2.27
2.24
1.60
1.59
1.57
1.40
1.35
1.33
1.28
1.23
1.21
1.07
1.05
0.04
NHBoc
O
A
0.39
0.70
1.01
0.80
0.95
2.15
9.69
8.11
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
Chemical Shift (ppm)

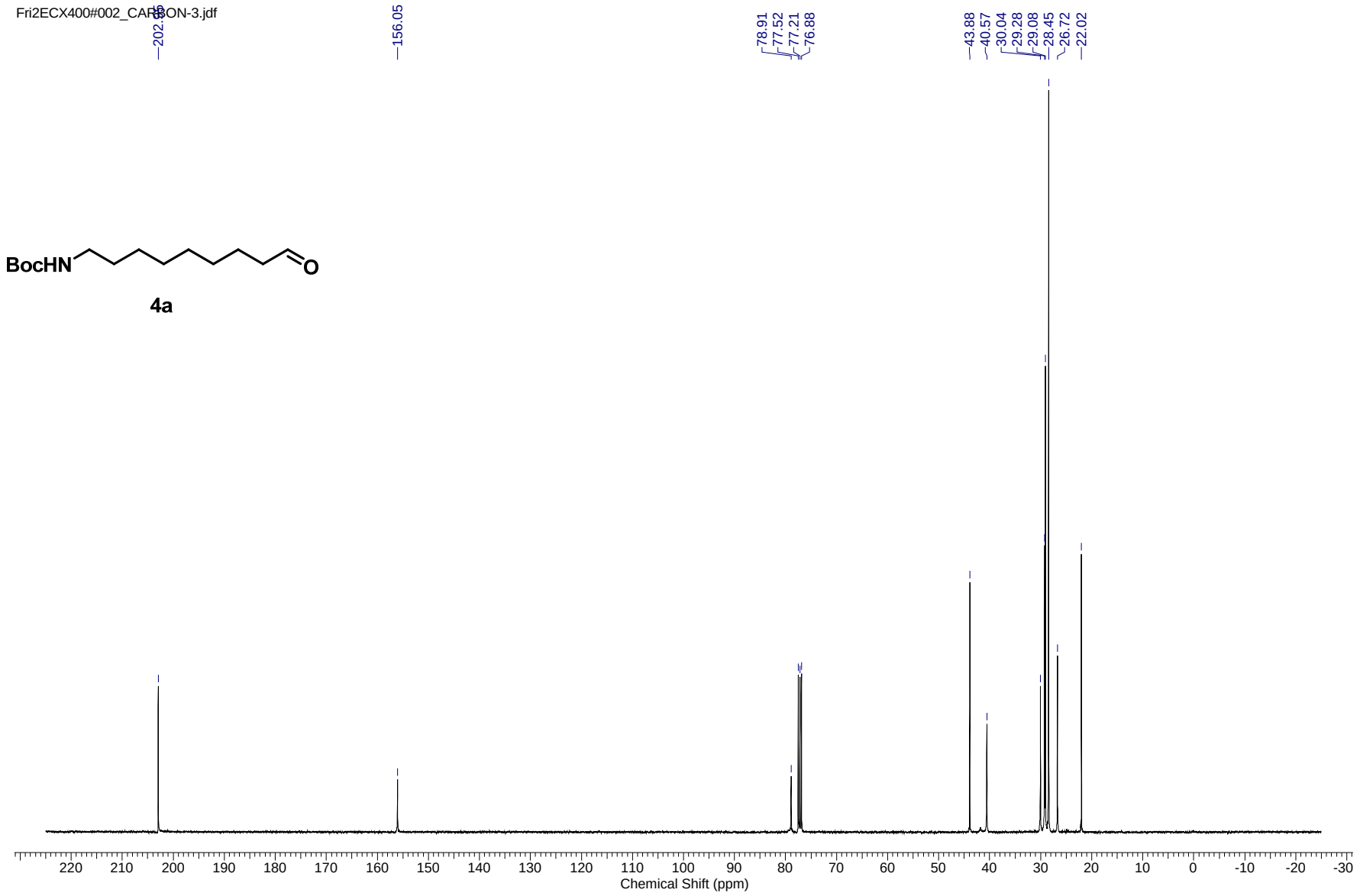

Fri1av500#003.001.001.1r.esp
7.27
5.83
5.83
5.82
5.81
5.80
5.79
5.79
5.78
5.01
4.98
4.94
4.92
4.31
3.62
2.06
2.04
2.03
2.02
1.68
1.44
1.37
1.33
1.29
1.11
1.09
0.00
NHBoc
C
1.00
2.00
0.90
1.07
2.09
9.84
4.28
7.87
3.36
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
Chemical Shift (ppm)

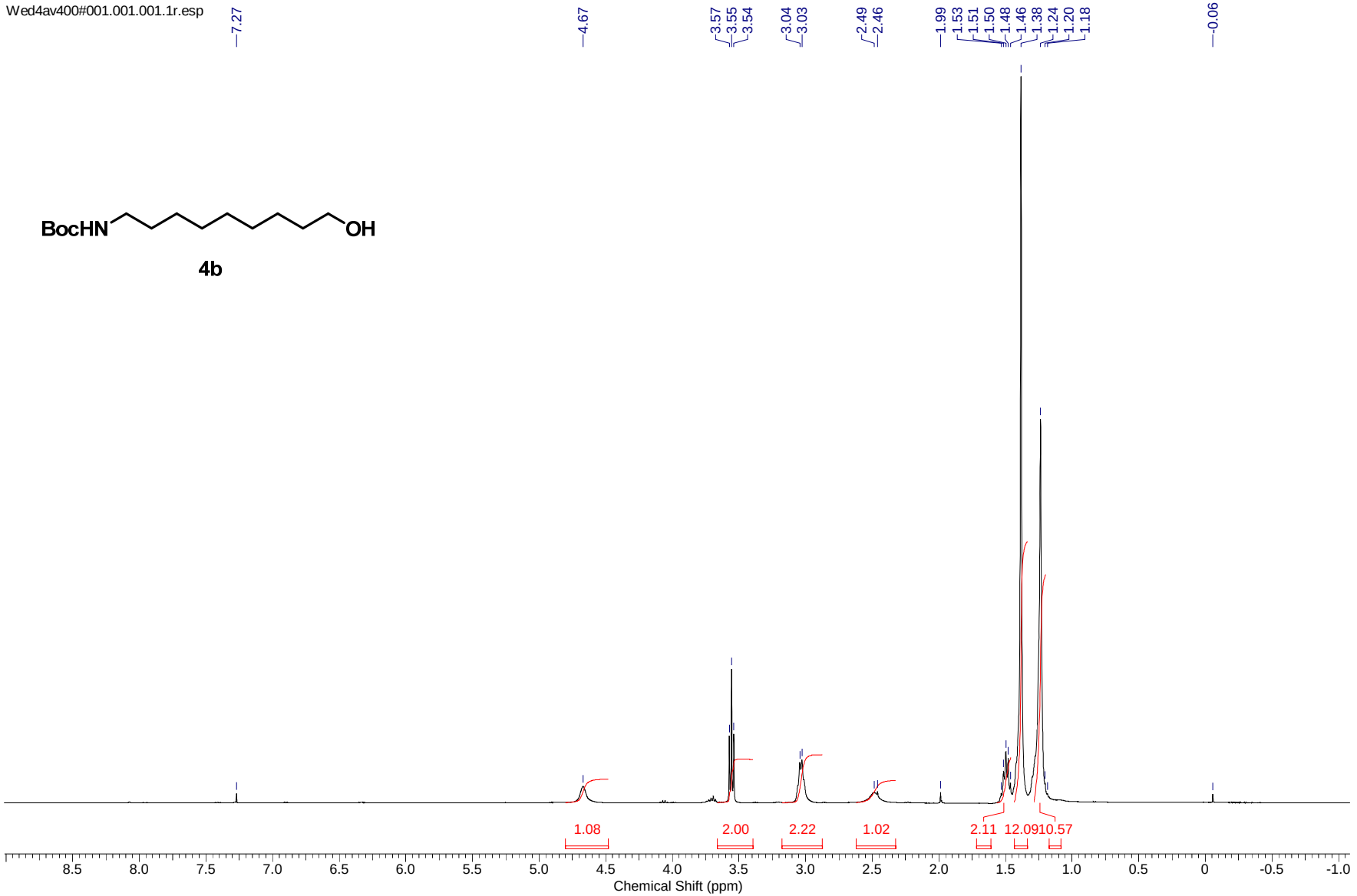

Fri1av500#003.003.001.1r.esp
155.39
139.16
114.18
78.89
77.28
77.03
76.78
46.50
37.36
33.78
29.36
29.07
28.84
28.45
25.97
21.28
NHBoc
C
184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8
Chemical Shift (ppm)

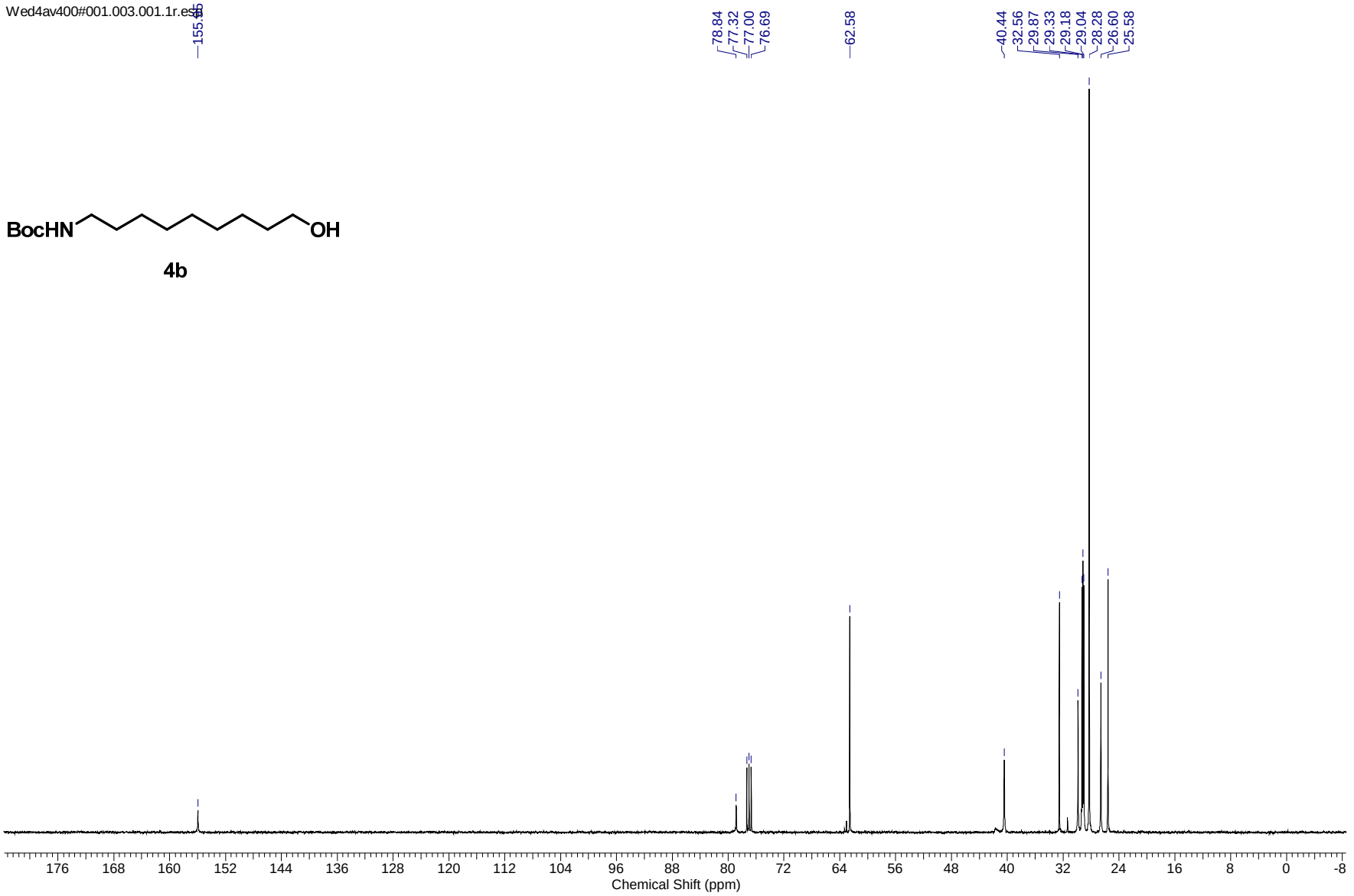

Fri2ECX400#001_PROTON-3.jdf
7.27
5.81
5.79
5.78
5.77
5.76
5.75
5.74
4.99
4.98
4.98
4.94
4.93
4.91
4.89
4.89
4.59
3.10
3.08
3.06
3.05
2.03
2.01
2.00
1.98
1.41
1.37
1.36
1.34
1.32
1.31
1.26
0.03
BocHN
D
1.00
2.06
0.83
2.05
2.23
10.59
2.30
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


Fri2ECX400#001_CARBON-3.fid
155.89
139.03
114.07
78.80
77.31
77.00
76.69
40.50
33.69
29.97
29.30
29.15
28.94
28.78
28.33
26.70
BocHN
D
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8
Chemical Shift (ppm)

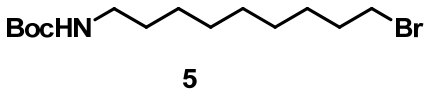

Fri2ECX400#002_PROTON-3.jdf
CHLOROFORM-d
9.69
9.69
9.68
7.27
4.64
3.03
3.02
2.38
2.38
2.37
2.36
2.36
2.34
2.34
2.33
1.56
1.54
1.37
1.24
BocHN
O
4a
0.97
1.02
2.22
2.18
2.37
10.52
9.14
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)


Fri2ECX400#002_CARBON-3.jdf
202.83
156.05
78.91
77.52
77.21
76.88
43.88
40.57
30.04
29.28
29.08
28.45
26.72
22.02
BocHN
O
4a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)

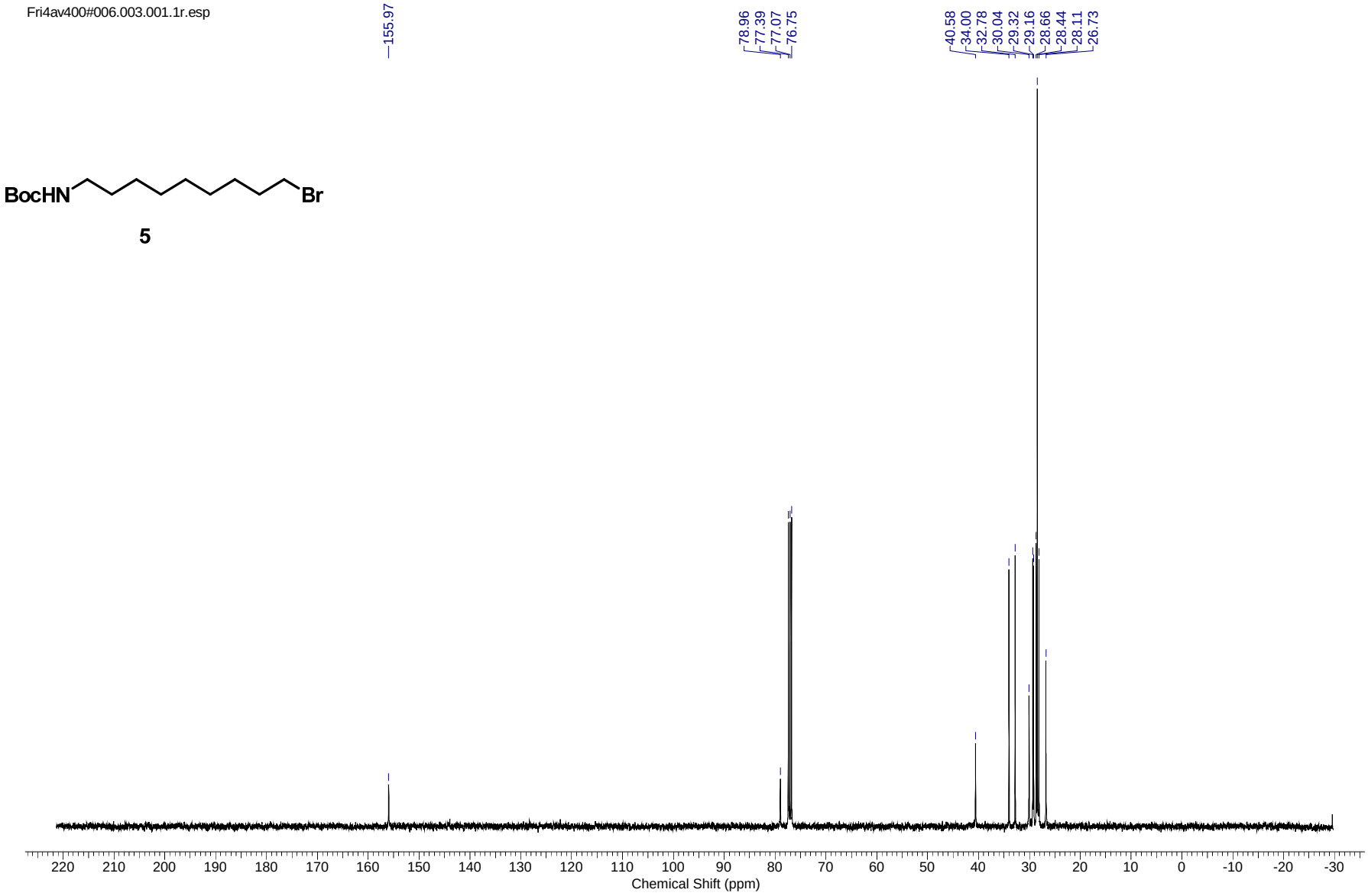

Wed4av400#001.001.001.1r.esp
7.27
4.67
3.57
3.55
3.54
3.04
3.03
2.49
2.46
1.99
1.53
1.51
1.50
1.48
1.46
1.38
1.24
1.20
1.18
0.06
BocHN
OH
4b
1.08
2.00
2.22
1.02
2.11
12.09
10.57
Chemical Shift (ppm)


Wed4av400#001.003.001.1r.esp
155.95
78.84
77.32
77.00
76.69
62.58
40.44
32.56
29.87
29.33
29.18
29.04
28.28
26.60
25.58
BocHN
OH
4b
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8
Chemical Shift (ppm)

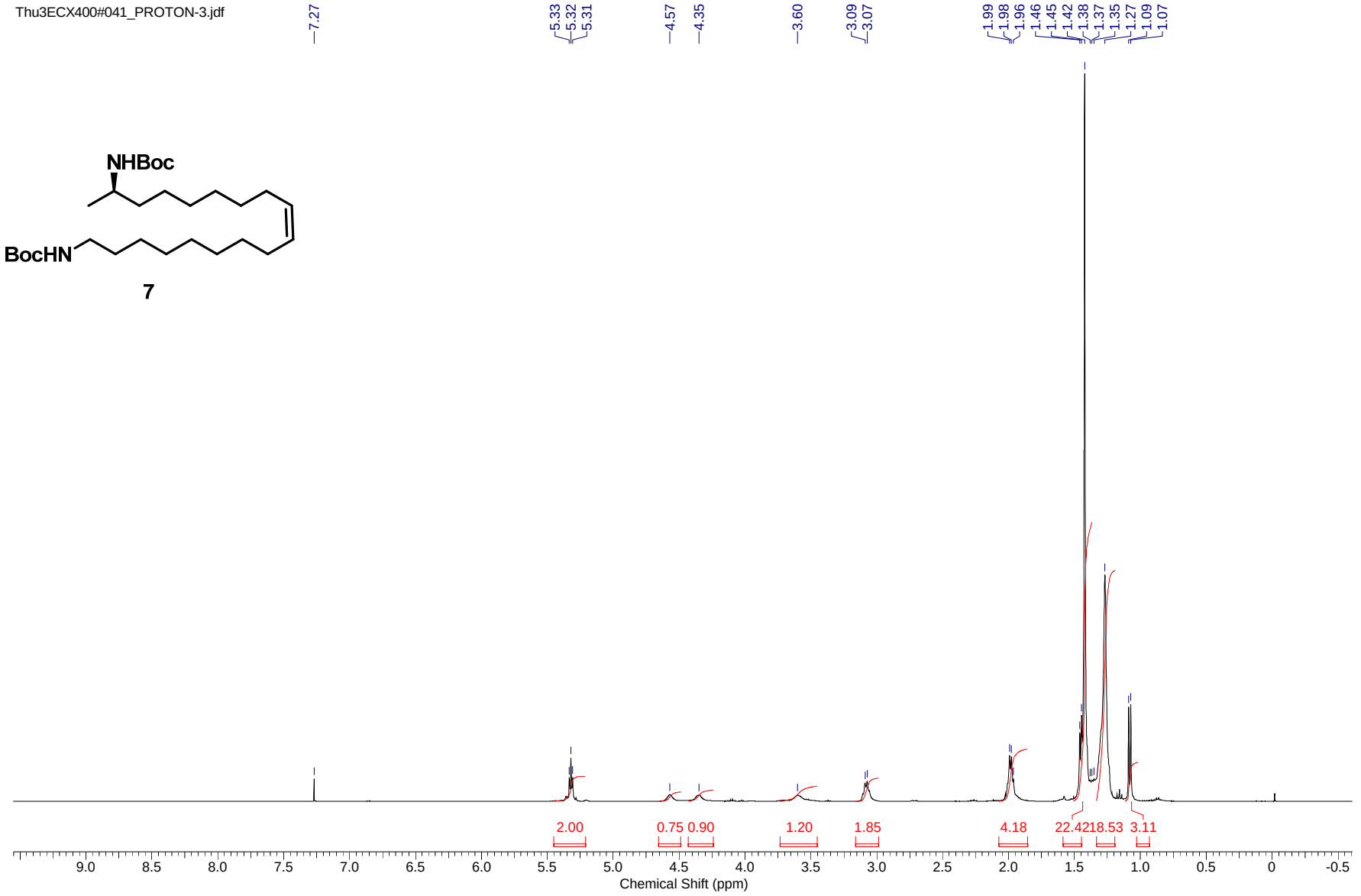
Fri4av400#006.001.001.1r.esp



5

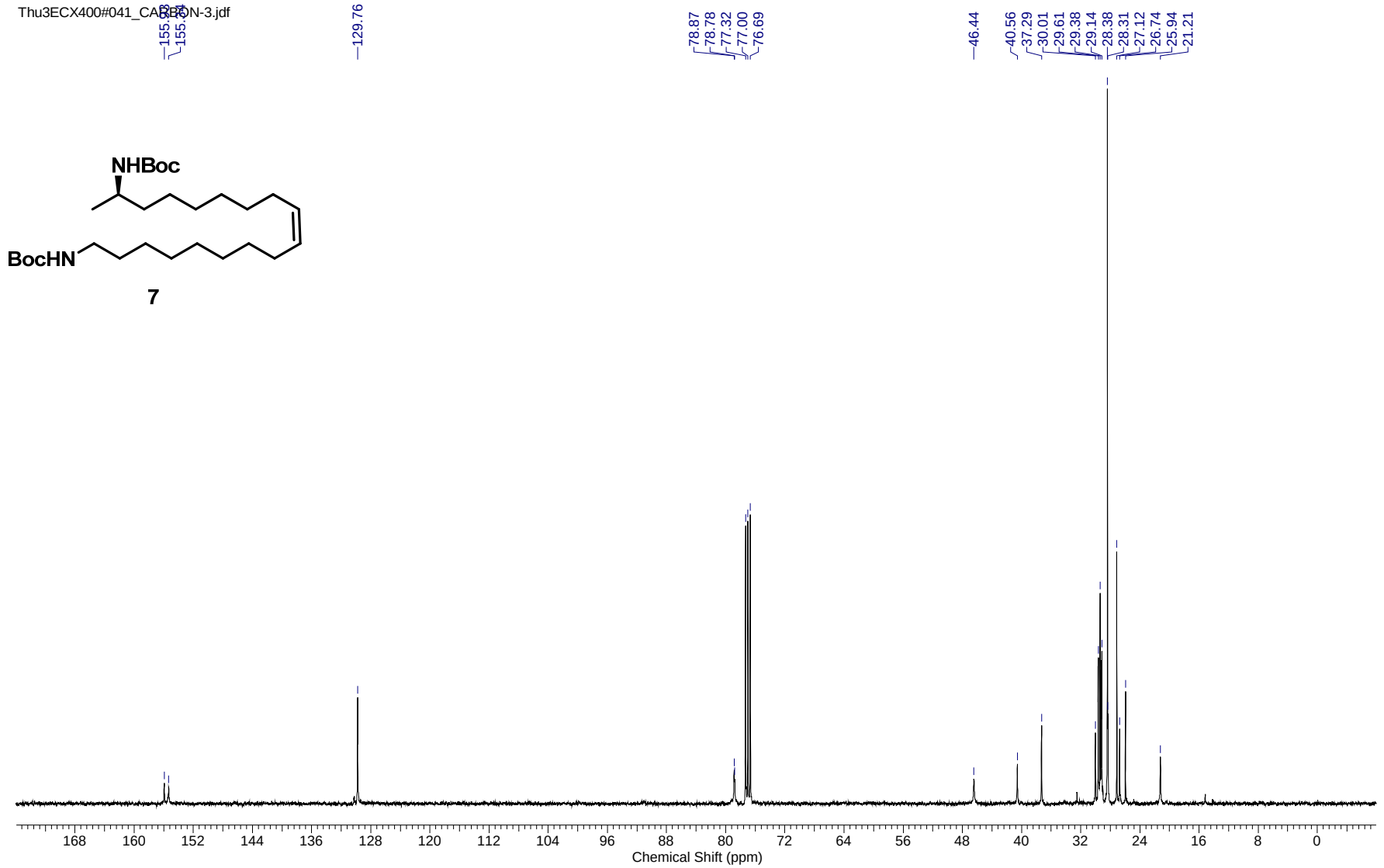

Fri4av400#006.003.001.1r.esp
155.97
78.96
77.39
77.07
76.75
40.58
34.00
32.78
30.04
29.32
29.16
28.66
28.44
28.11
26.73
BocHN
Br
5
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)

Wittig reaction (Approach 1)

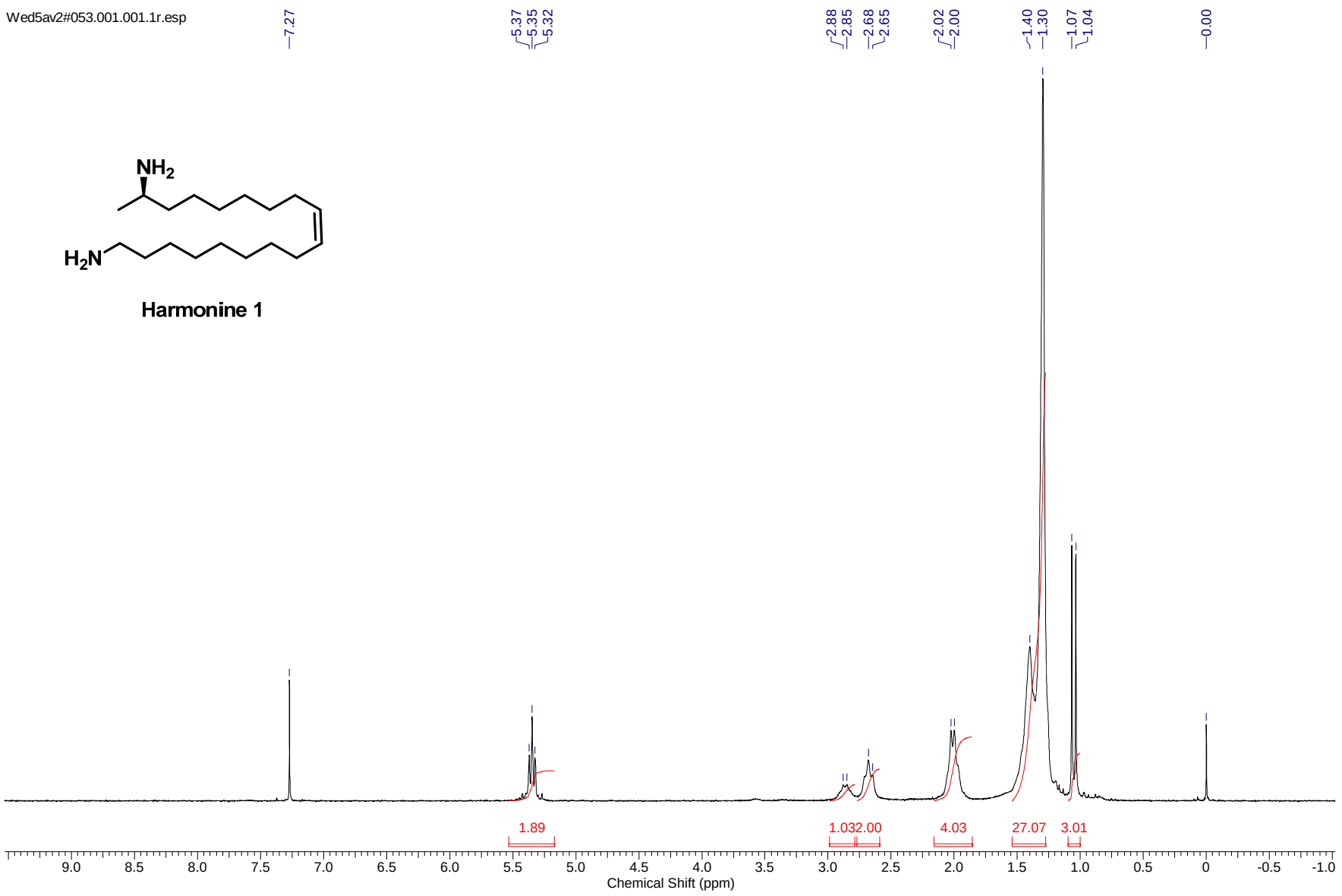


7

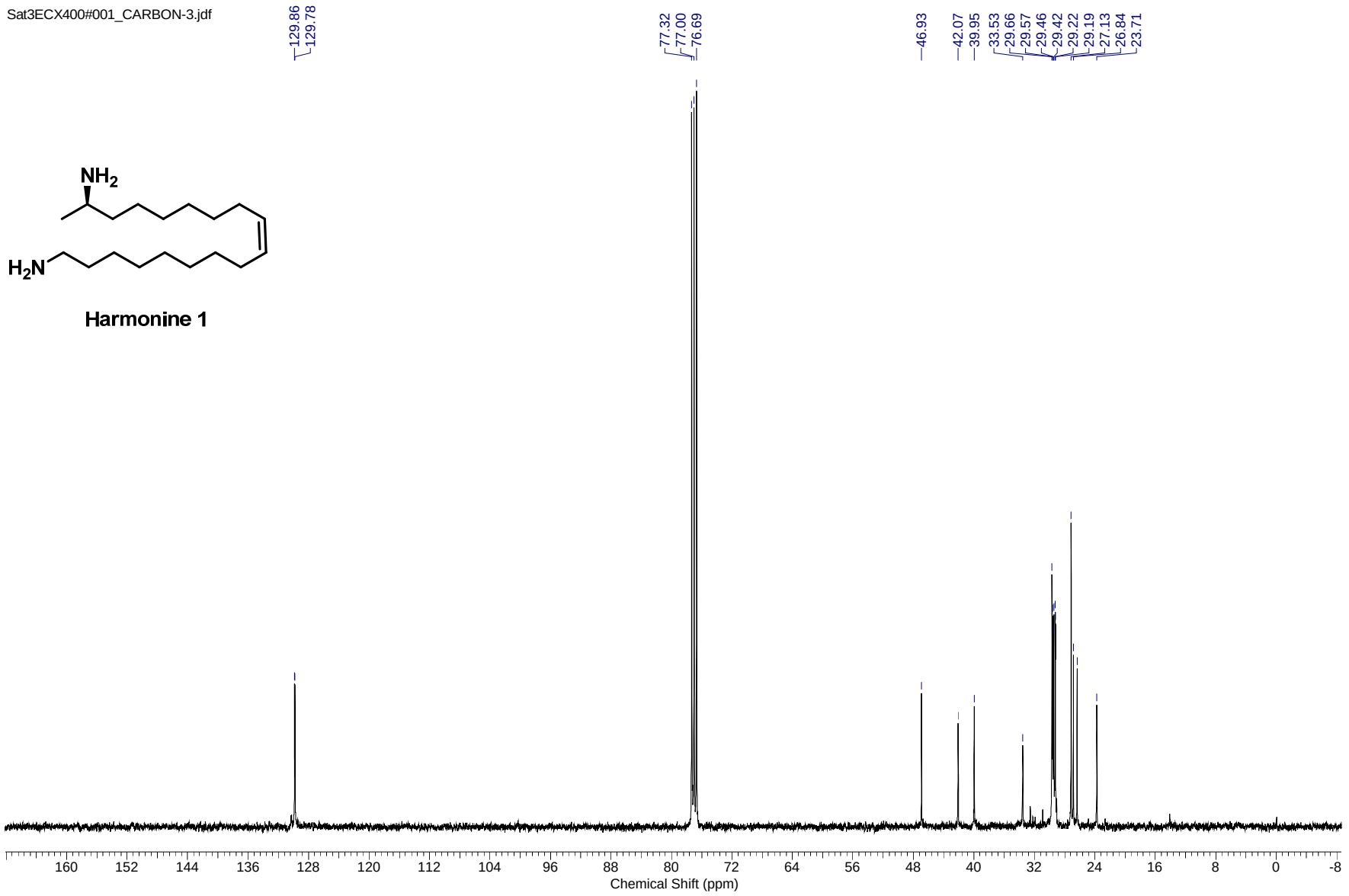
Wittig reaction (Approach 1)



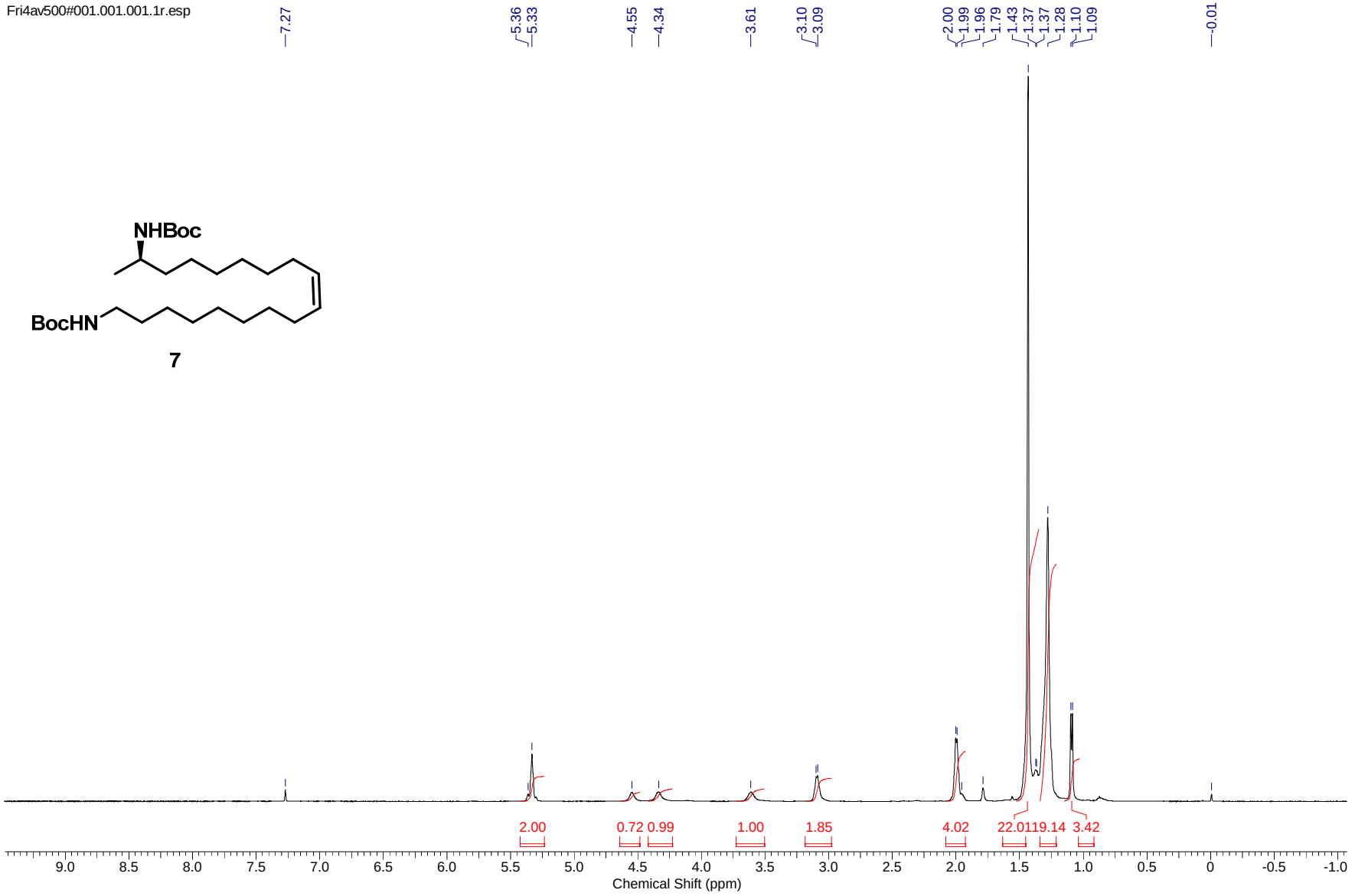
Wittig reaction (Approach 1)



Wittig reaction (Approach 1)

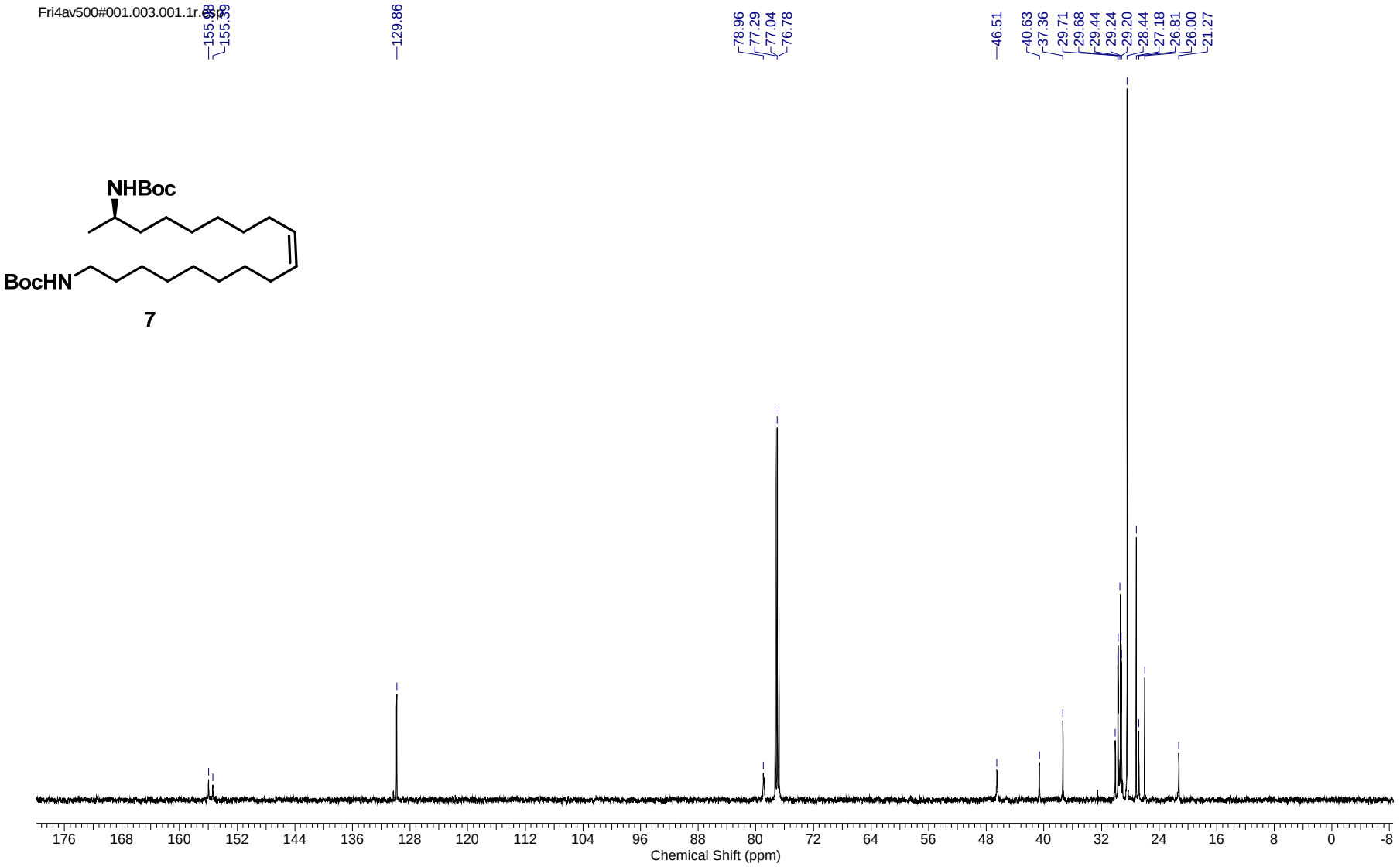


Z-Selective cross metathesis (Approach 2)

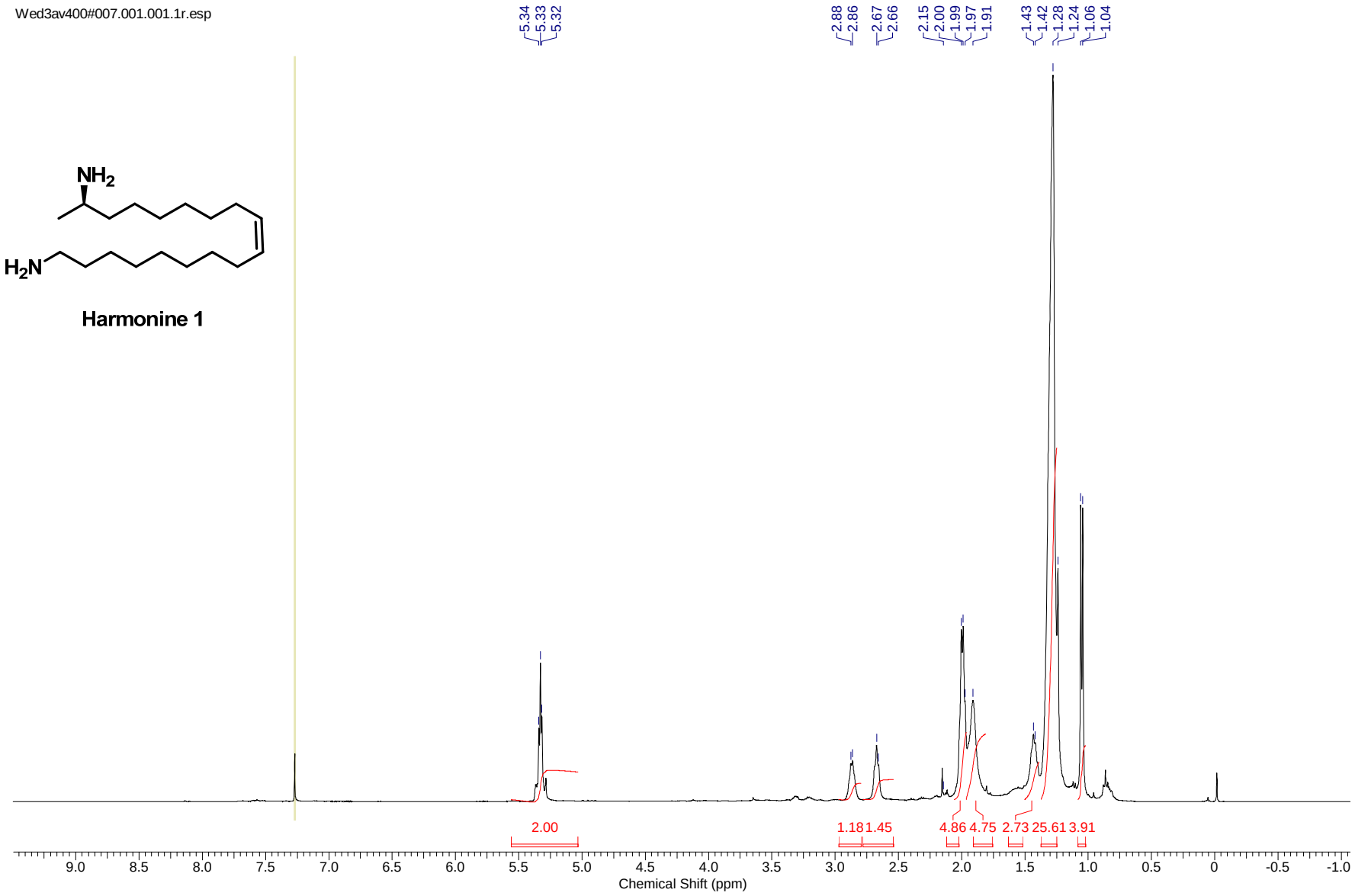


7

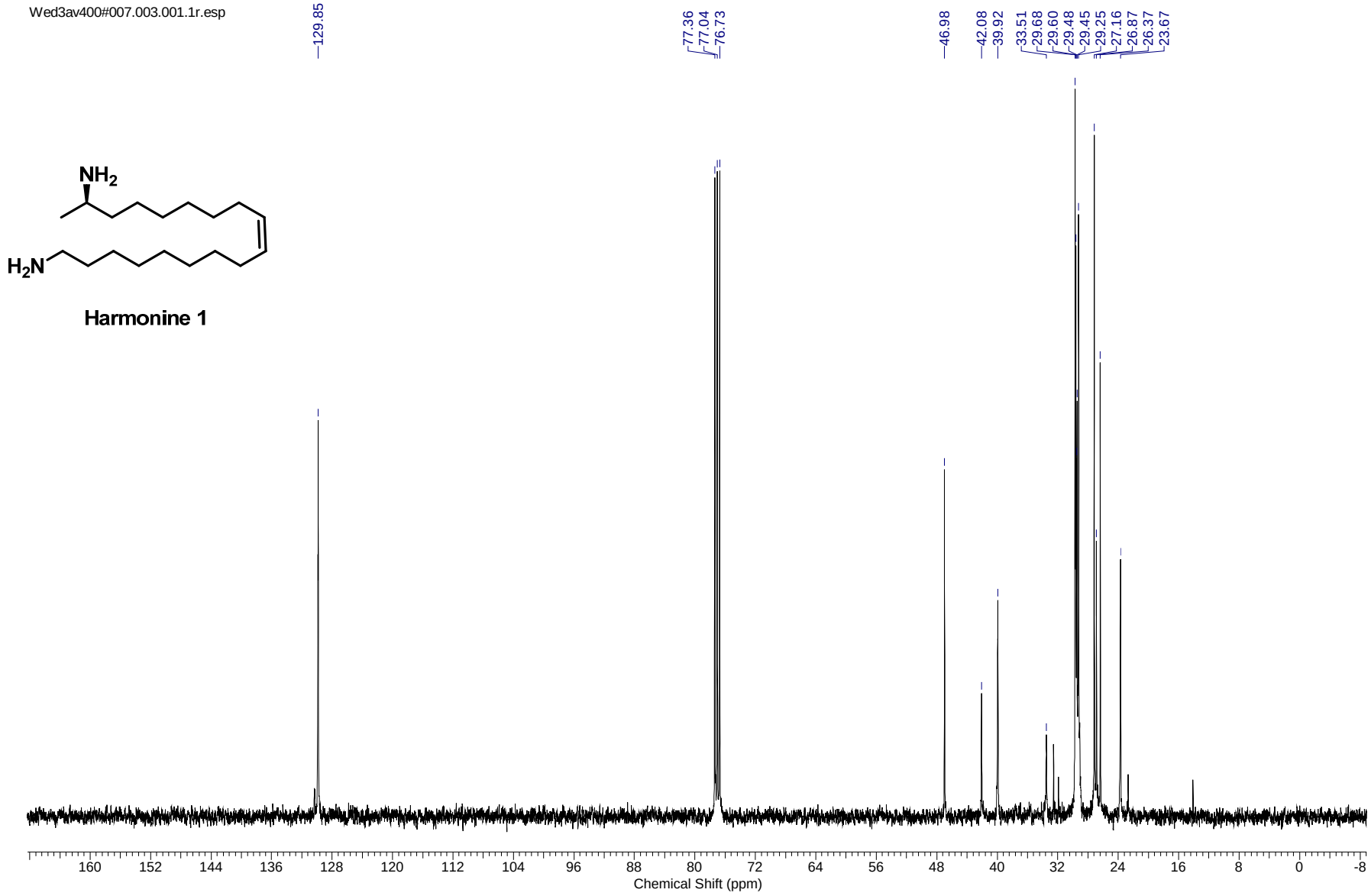
Z-Selective cross metathesis (Approach 2)



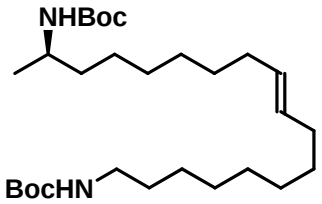
Z-Selective cross metathesis (Approach 2)



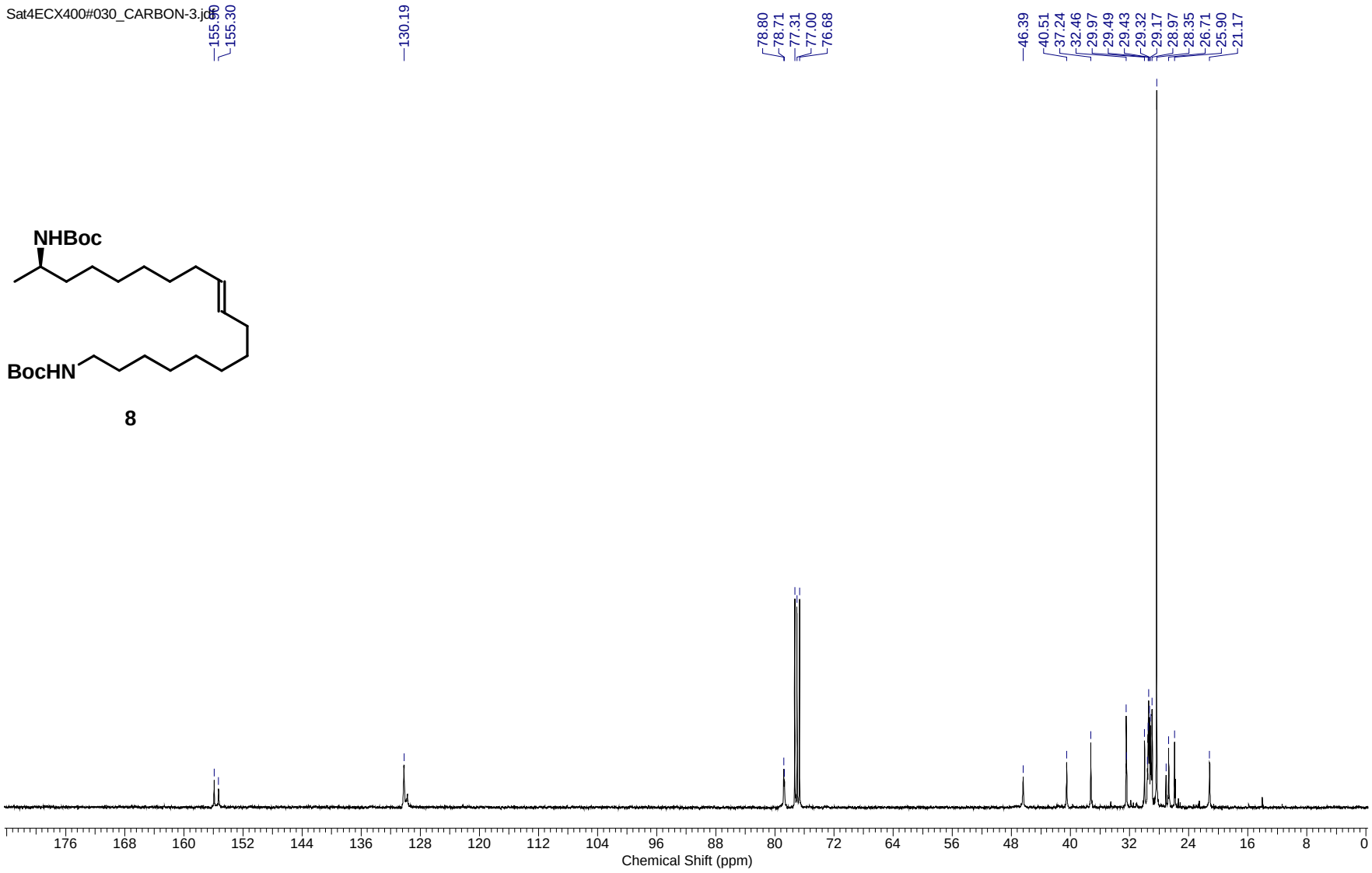
Z-Selective cross metathesis (Approach 2)



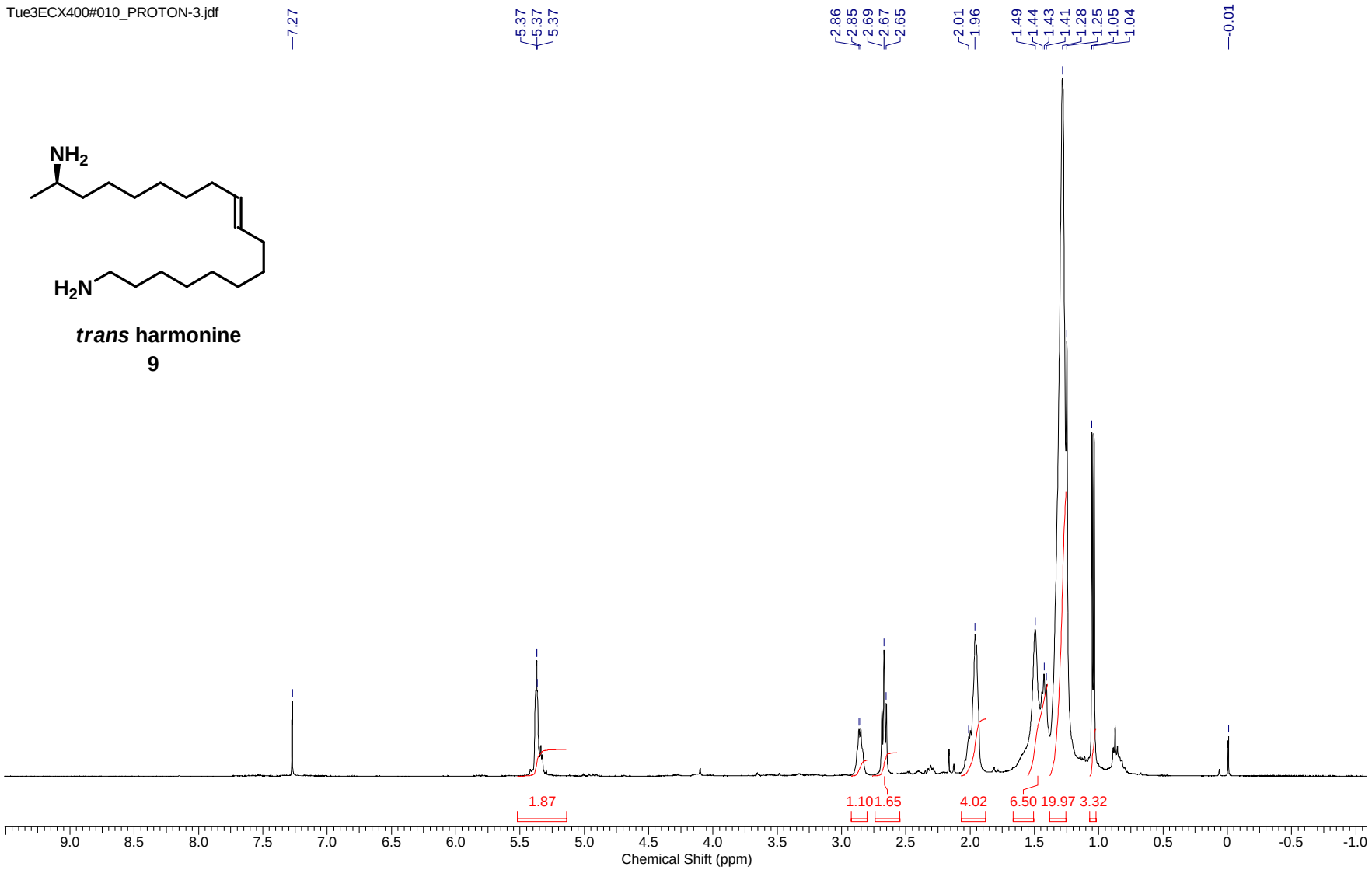
Sat4ECX400#030_PROTON-3.jdf

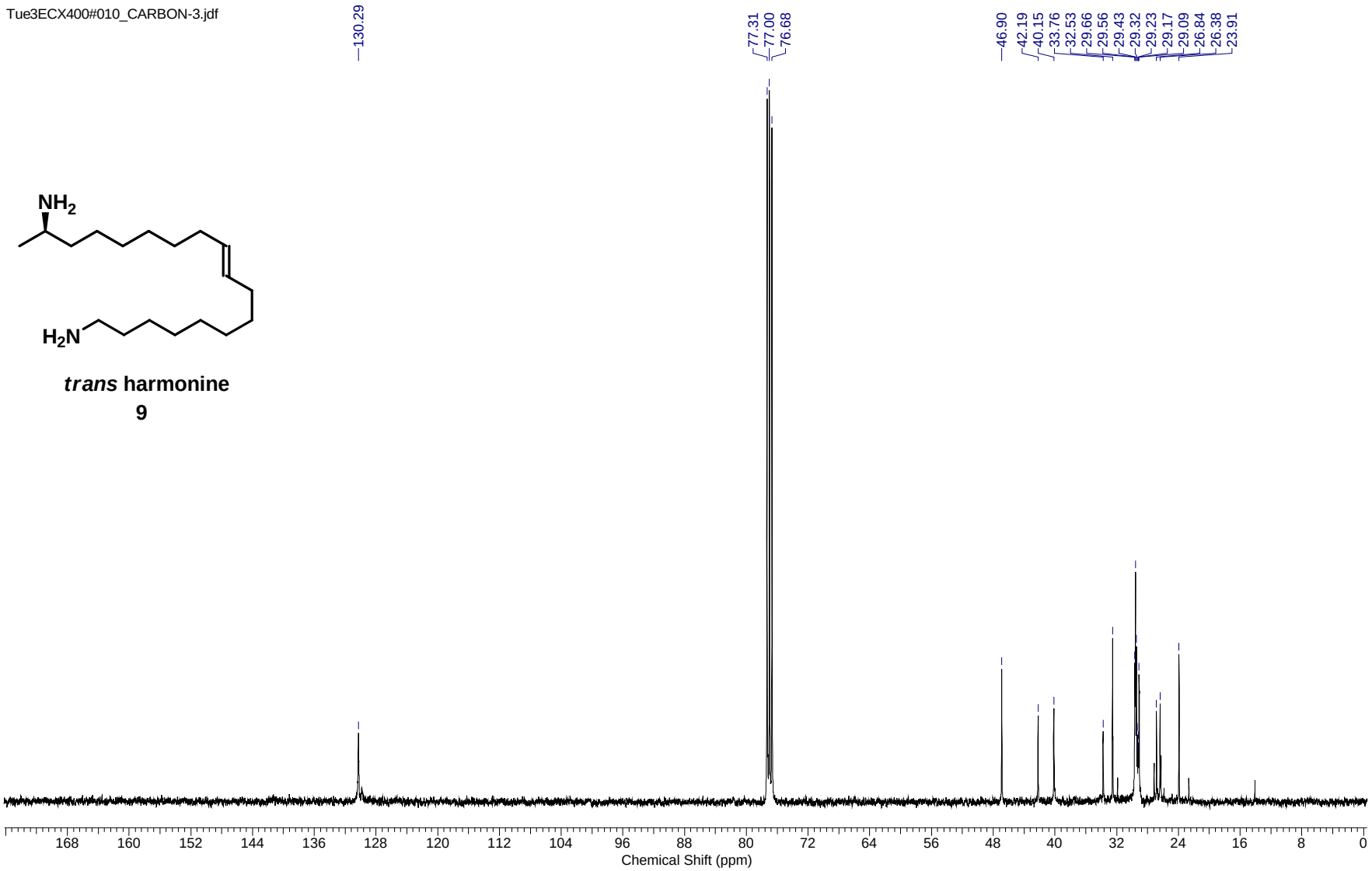


8


Sat4ECX400#030_CARBON-3.jdf
155.60
155.30
130.19
78.80
78.71
77.31
77.00
76.68
46.39
40.51
37.24
32.46
29.97
29.49
29.43
29.32
29.17
28.97
28.35
26.71
25.90
21.17
NHBoc
BocHN
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

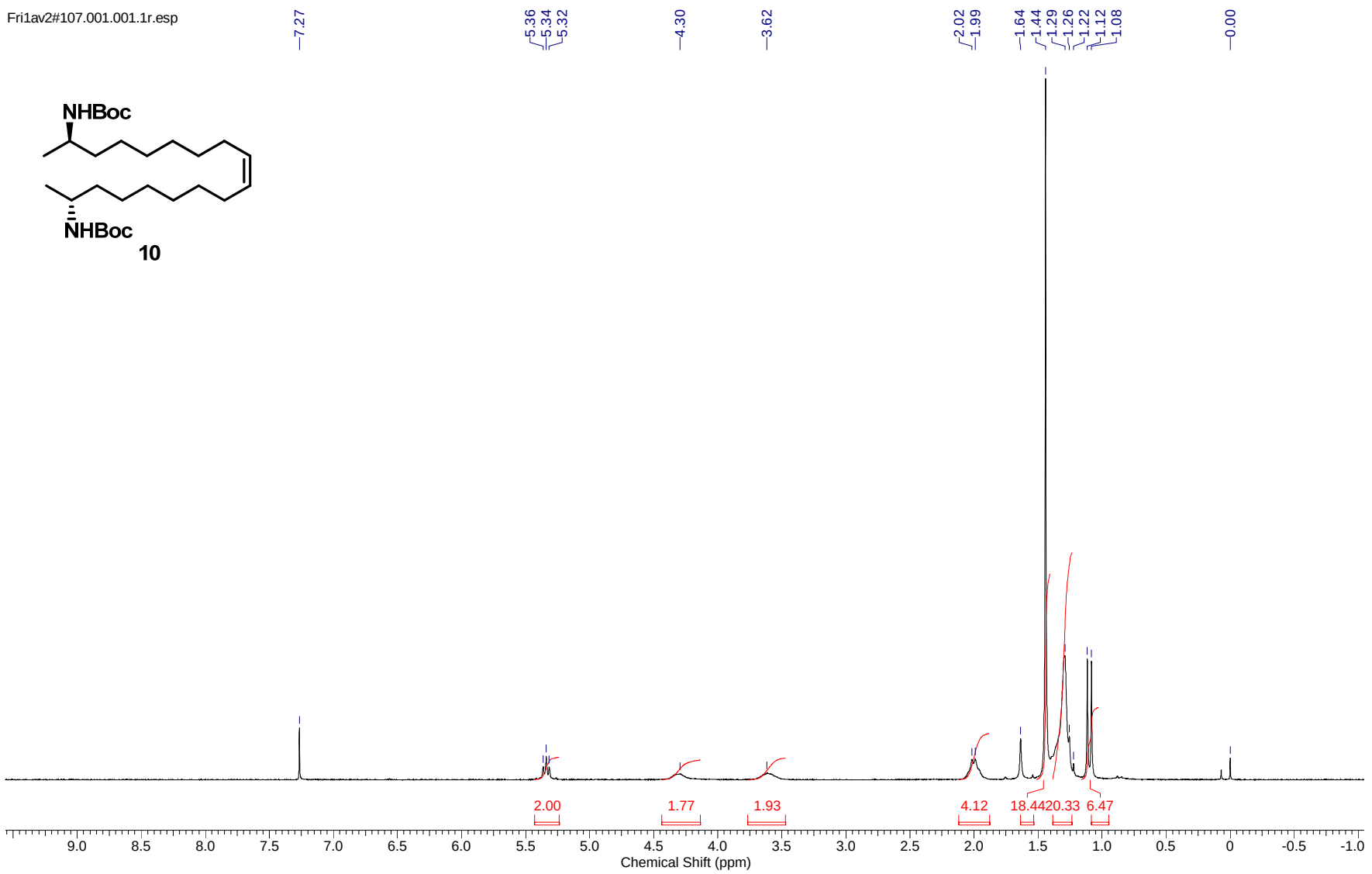
8

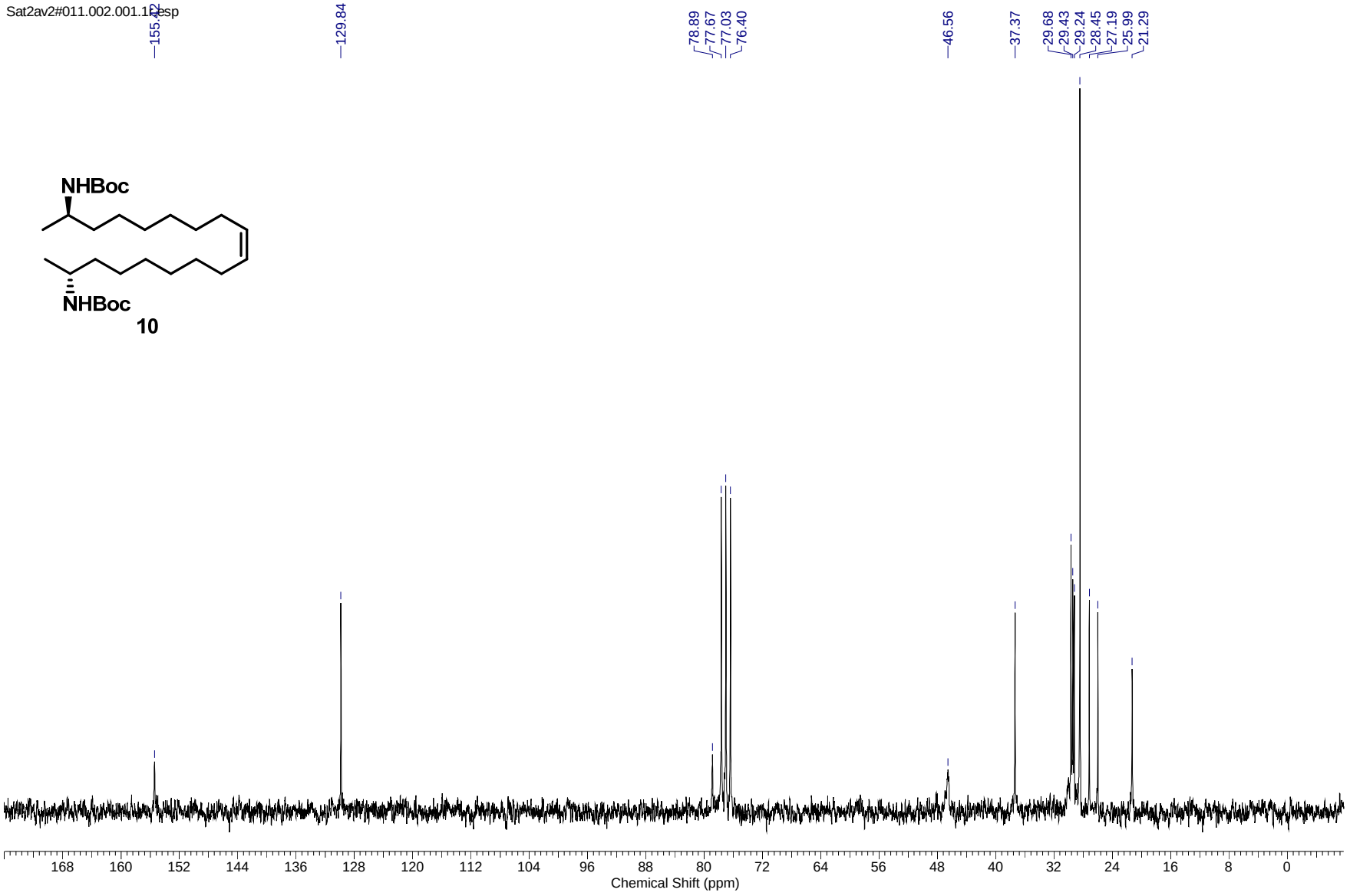

Tue3ECX400#010_PROTON-3.jdf
7.27
5.37
5.37
5.37
2.86
2.85
2.69
2.67
2.65
2.01
1.96
1.49
1.44
1.43
1.41
1.28
1.25
1.05
1.04
0.01
NH2
H2N
trans harmonine
9
1.87
1.10
1.65
4.02
6.50
19.97
3.32
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
Chemical Shift (ppm)

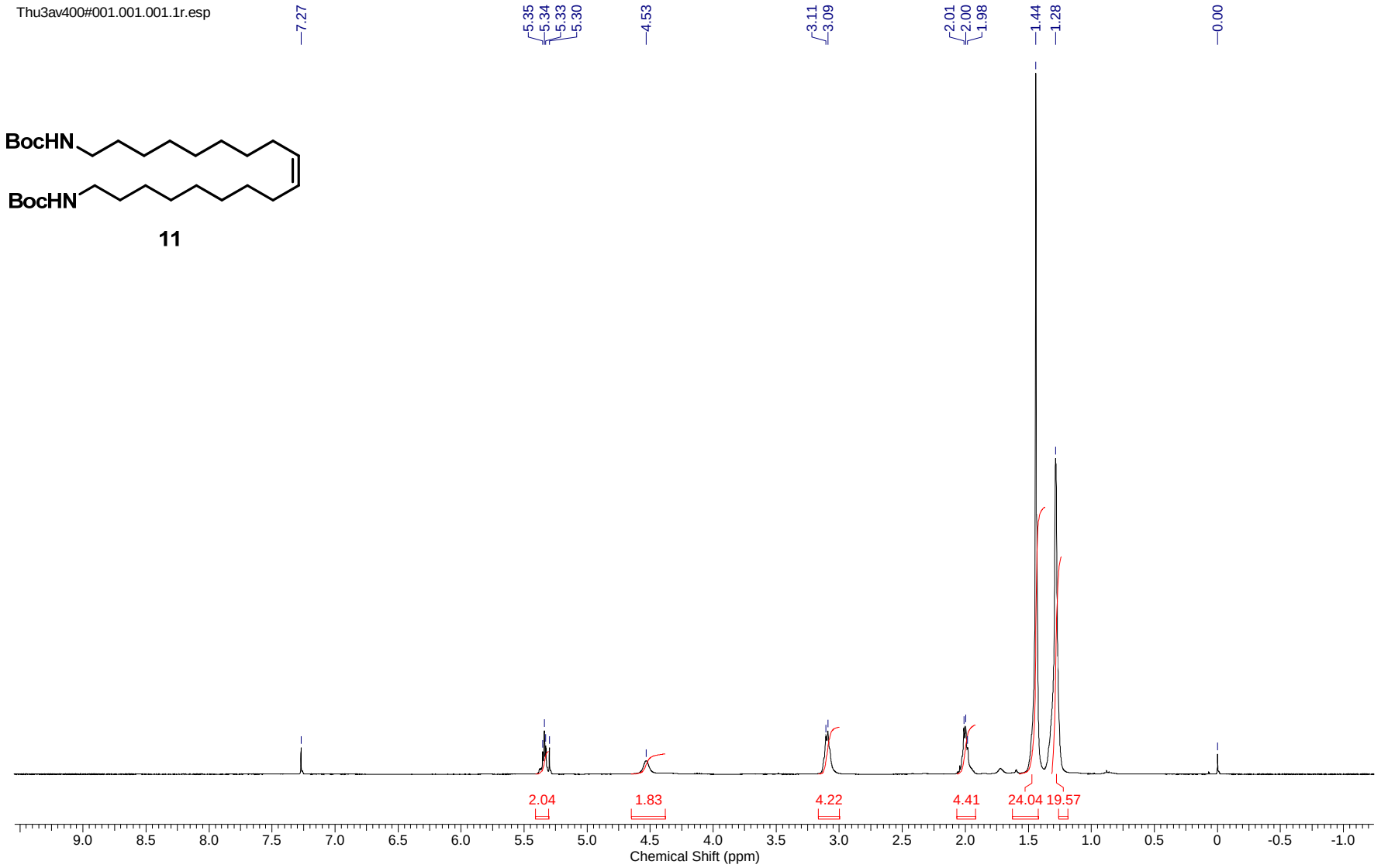


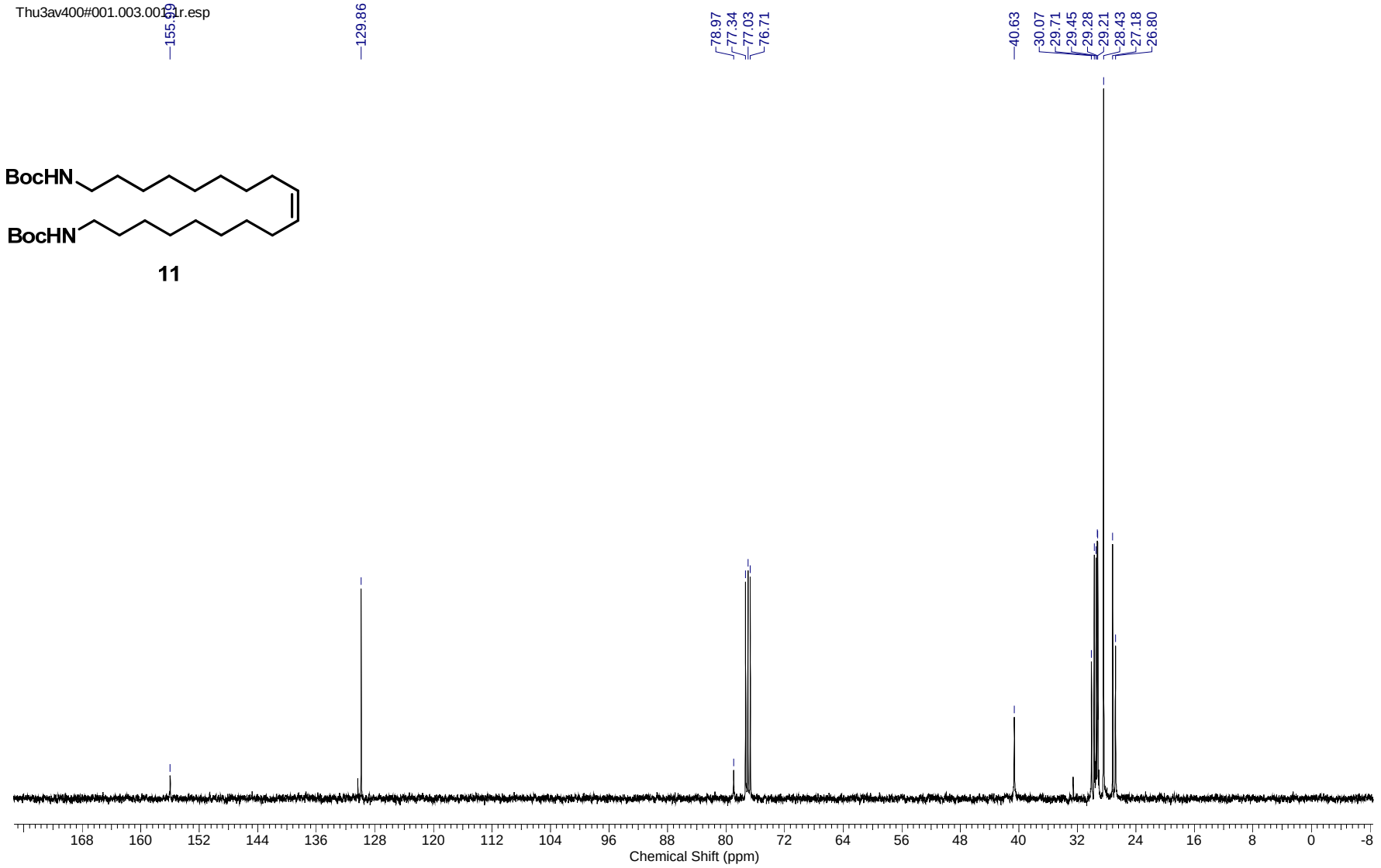
***trans* harmonine**

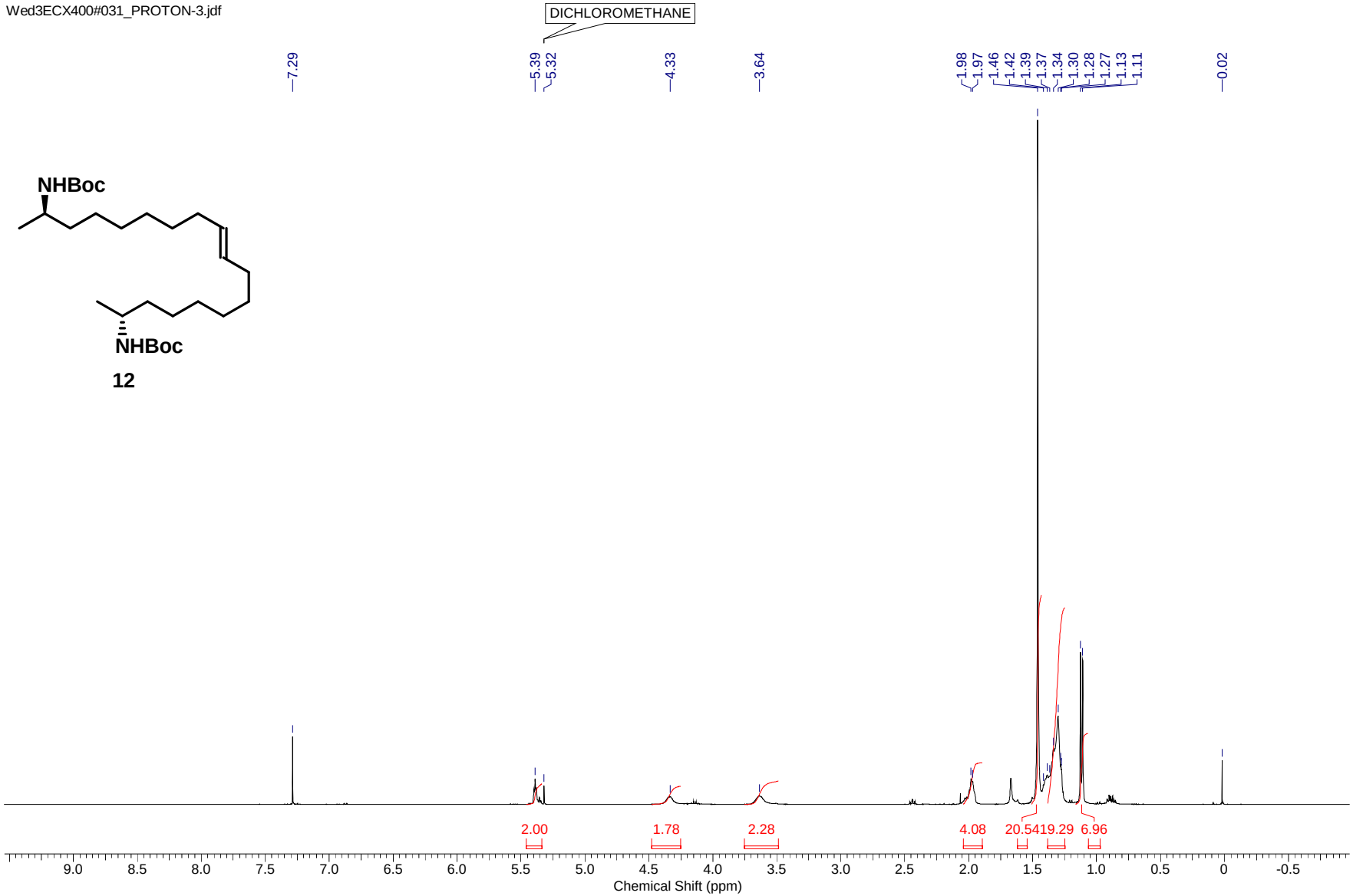
9

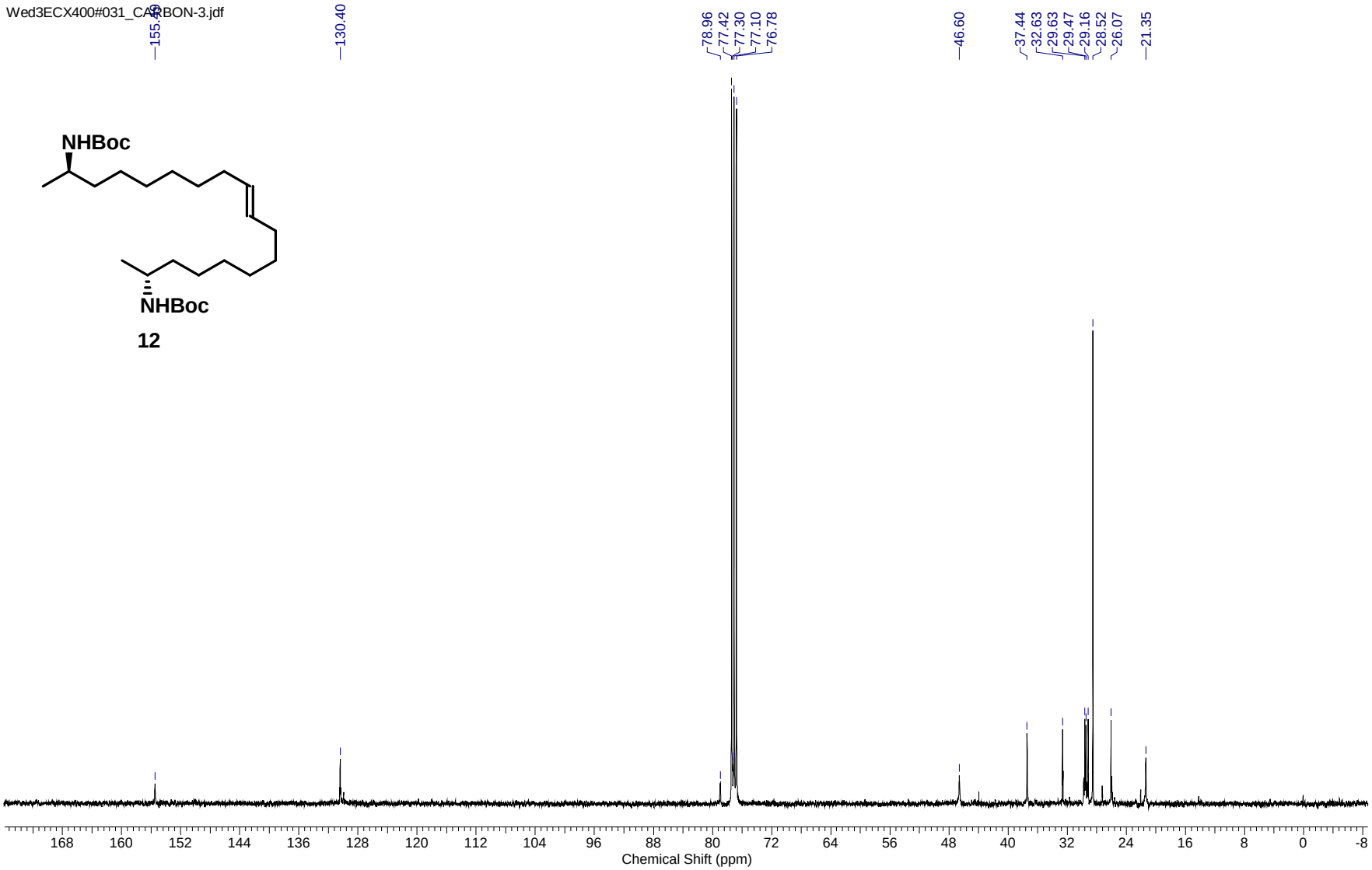

Fri1av2#107.001.001.1r.esp
7.27
5.36
5.34
5.32
4.30
3.62
2.02
1.99
1.64
1.44
1.29
1.26
1.22
1.12
1.08
0.00
NHBoc
NHBoc
10
2.00
1.77
1.93
4.12
18.44
20.33
6.47
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
Chemical Shift (ppm)

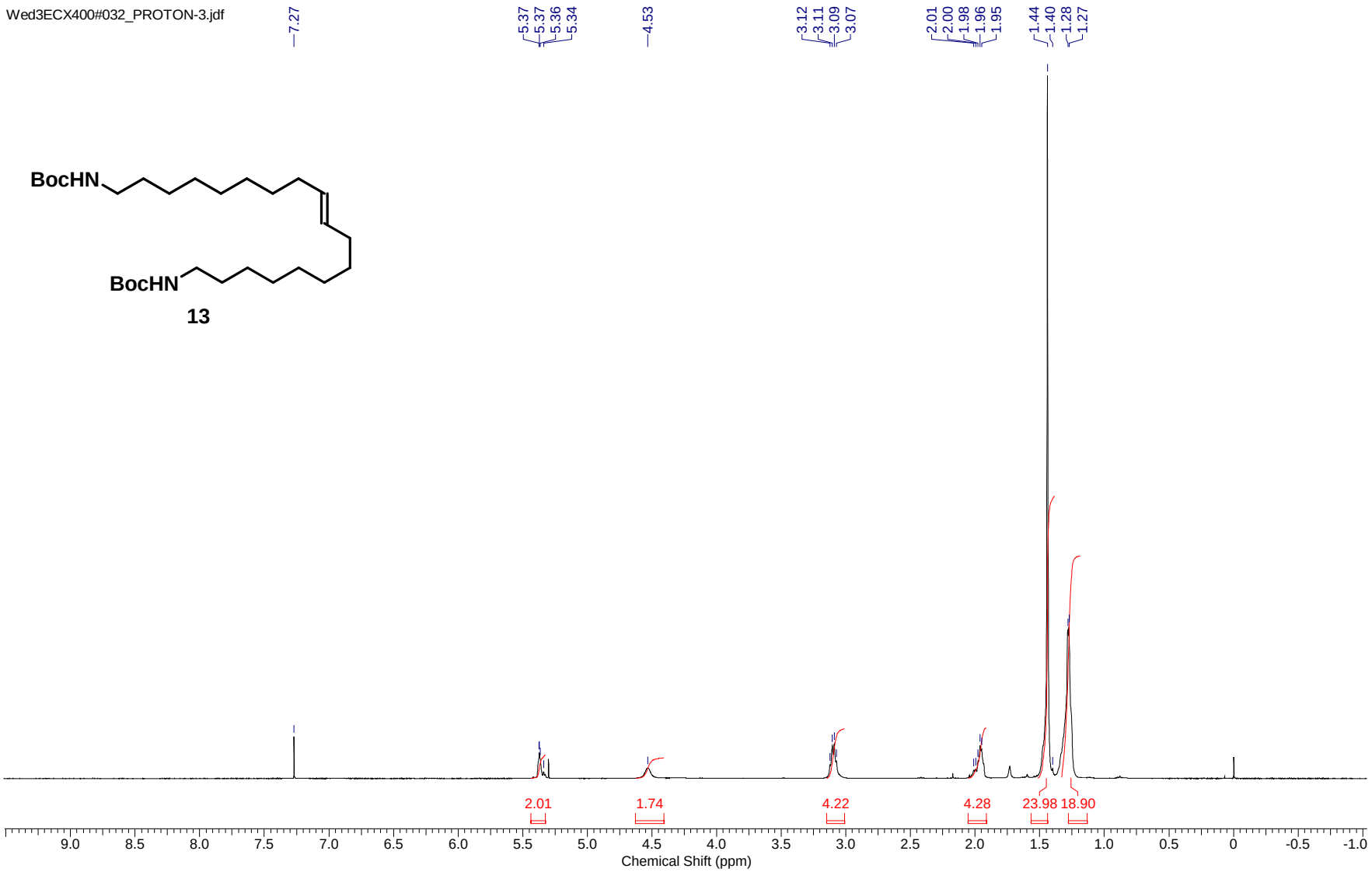

Sat2av2#011.002.001.1r.esp
155.42
129.84
78.89
77.67
77.03
76.40
46.56
37.37
29.68
29.43
29.24
28.45
27.19
25.99
21.29
NHBoc
NHBoc
10
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

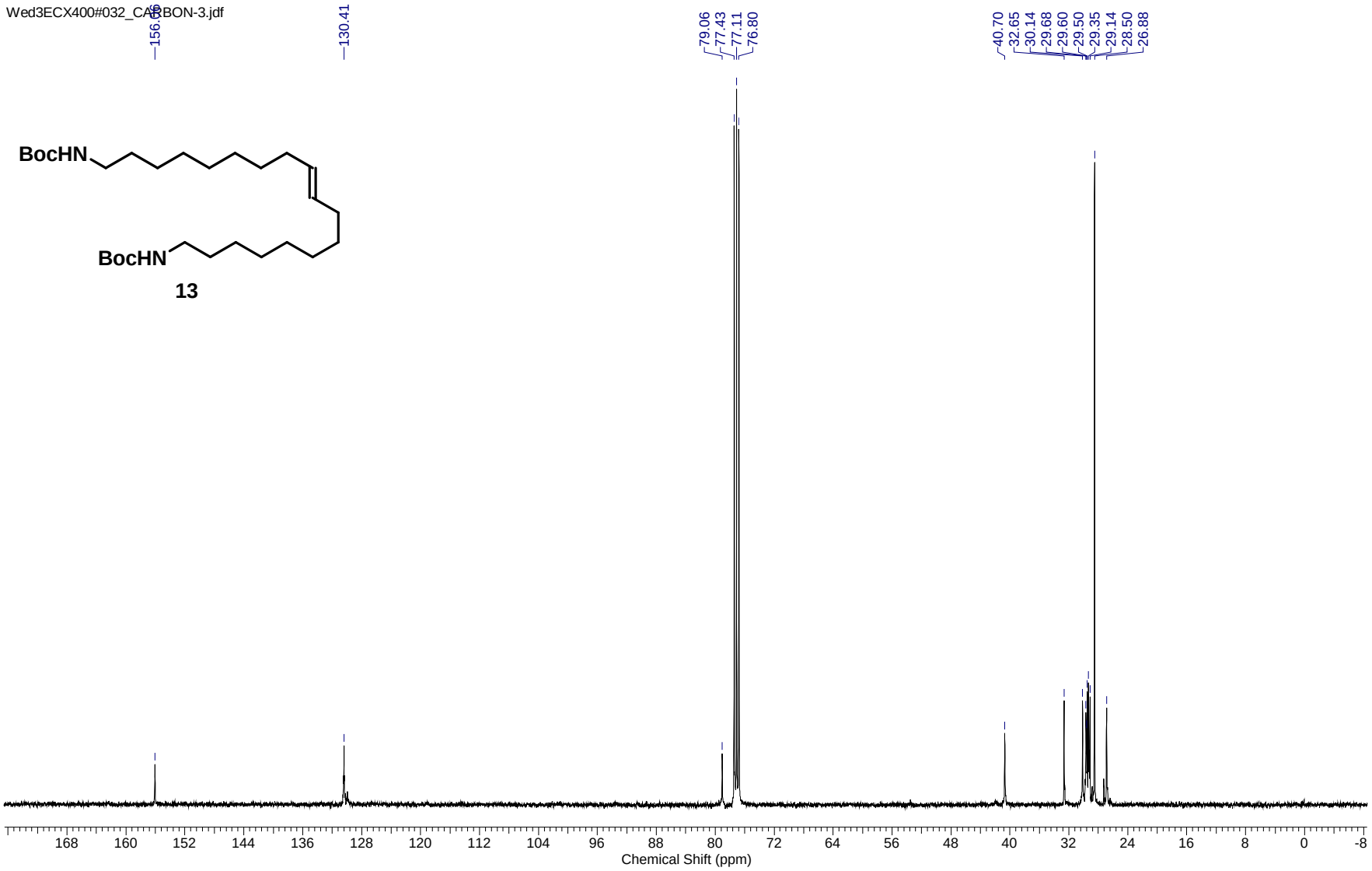

Thu3av400#001.001.001.1r.esp
7.27
5.35
5.34
5.33
5.30
4.53
3.11
3.09
2.01
2.00
1.98
1.44
1.28
0.00
BocHN
BocHN
11
2.04
1.83
4.22
4.41
24.04
19.57
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
Chemical Shift (ppm)

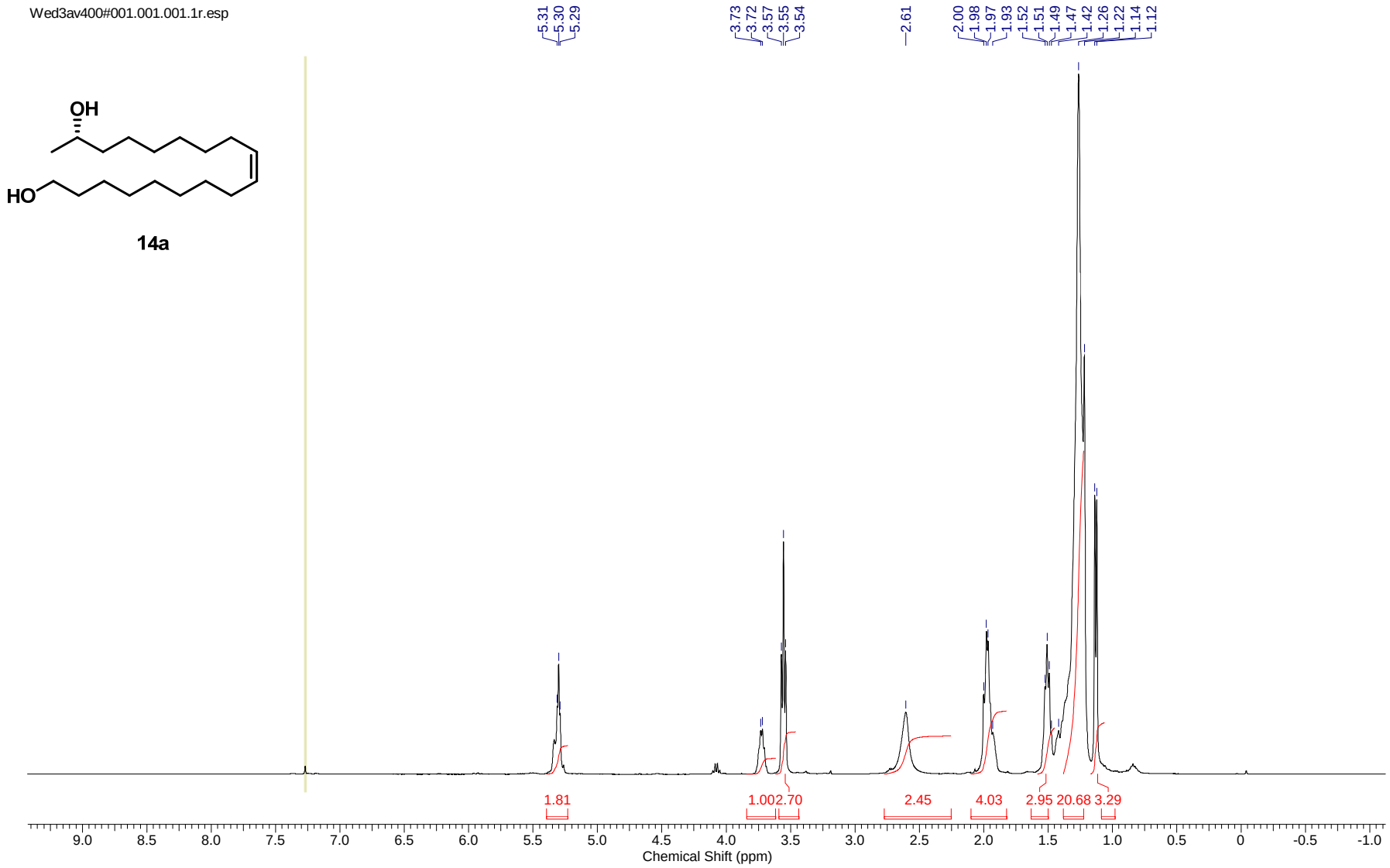

Thu3av400#001.003.001.1r.esp
155.39
129.86
78.97
77.34
77.03
76.71
40.63
30.07
29.71
29.45
29.28
29.21
28.43
27.18
26.80
BocHN
BocHN
11
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8
Chemical Shift (ppm)

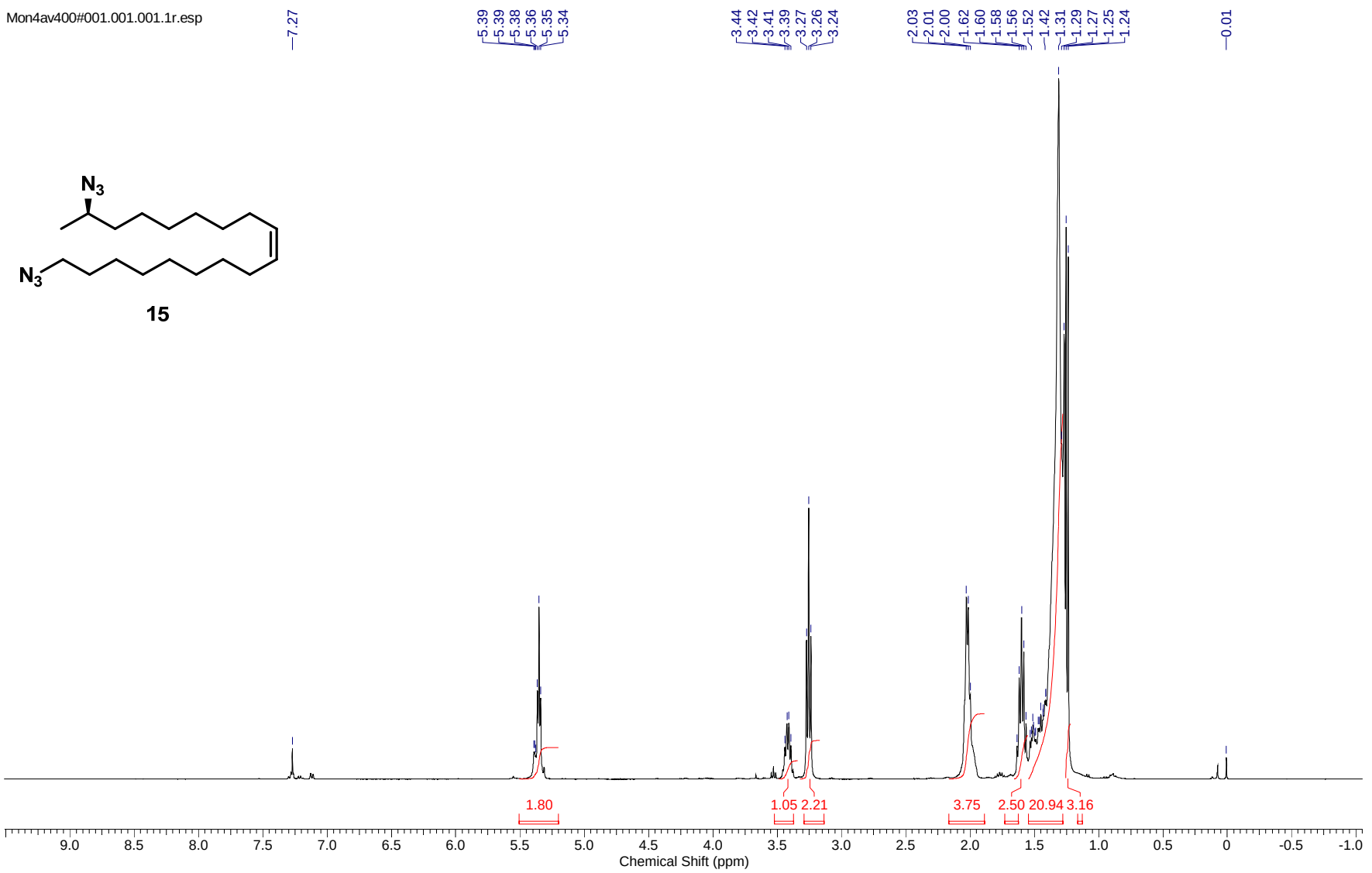

Wed3ECX400#031_PROTON-3.jdf
DICHLOROMETHANE
7.29
5.39
5.32
4.33
3.64
1.98
1.97
1.46
1.42
1.39
1.37
1.34
1.30
1.28
1.27
1.13
1.11
0.02
NHBoc
NHBoc
12
2.00
1.78
2.28
4.08
20.54
19.29
6.96
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


Wed3ECX400#031_CARBON-3.jdf
155.49
130.40
78.96
77.42
77.30
77.10
76.78
46.60
37.44
32.63
29.63
29.47
29.16
28.52
26.07
21.35
NHBoc
NHBoc
12
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8
Chemical Shift (ppm)

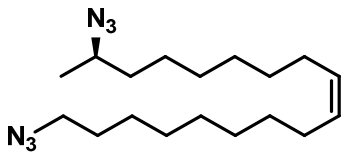

Wed3ECX400#032_PROTON-3.jdf
7.27
5.37
5.37
5.36
5.34
4.53
3.12
3.11
3.09
3.07
2.01
2.00
1.98
1.96
1.95
1.44
1.40
1.28
1.27
BocHN
BocHN
13
2.01
1.74
4.22
4.28
23.98
18.90
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
-1.0
Chemical Shift (ppm)


Wed3ECX400#032_CARBON-3.jdf
156.66
130.41
79.06
77.43
77.11
76.80
40.70
32.65
30.14
29.68
29.60
29.50
29.35
29.14
28.50
26.88
BocHN
BocHN
13
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8
Chemical Shift (ppm)


Wed3av400#001.001.001.1r.esp
5.31
5.30
5.29
3.73
3.72
3.57
3.55
3.54
2.61
2.00
1.98
1.97
1.93
1.52
1.51
1.49
1.47
1.42
1.26
1.22
1.14
1.12
OH
HO
14a
1.81
1.00
2.70
2.45
4.03
2.95
20.68
3.29
9.0
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
1.0
0.5
0
-0.5
-1.0
Chemical Shift (ppm)


Mon4av400#001.001.001.1r.esp
7.27
5.39
5.39
5.38
5.36
5.35
5.34
3.44
3.42
3.41
3.39
3.27
3.26
3.24
2.03
2.01
2.00
1.62
1.60
1.58
1.56
1.52
1.42
1.31
1.29
1.27
1.25
1.24
0.01
N3
N3
15
1.80
1.05
2.21
3.75
2.50
20.94
3.16
9.0
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
1.0
0.5
0
-0.5
-1.0
Chemical Shift (ppm)

Mon3av400#002.003.001.1r.esp



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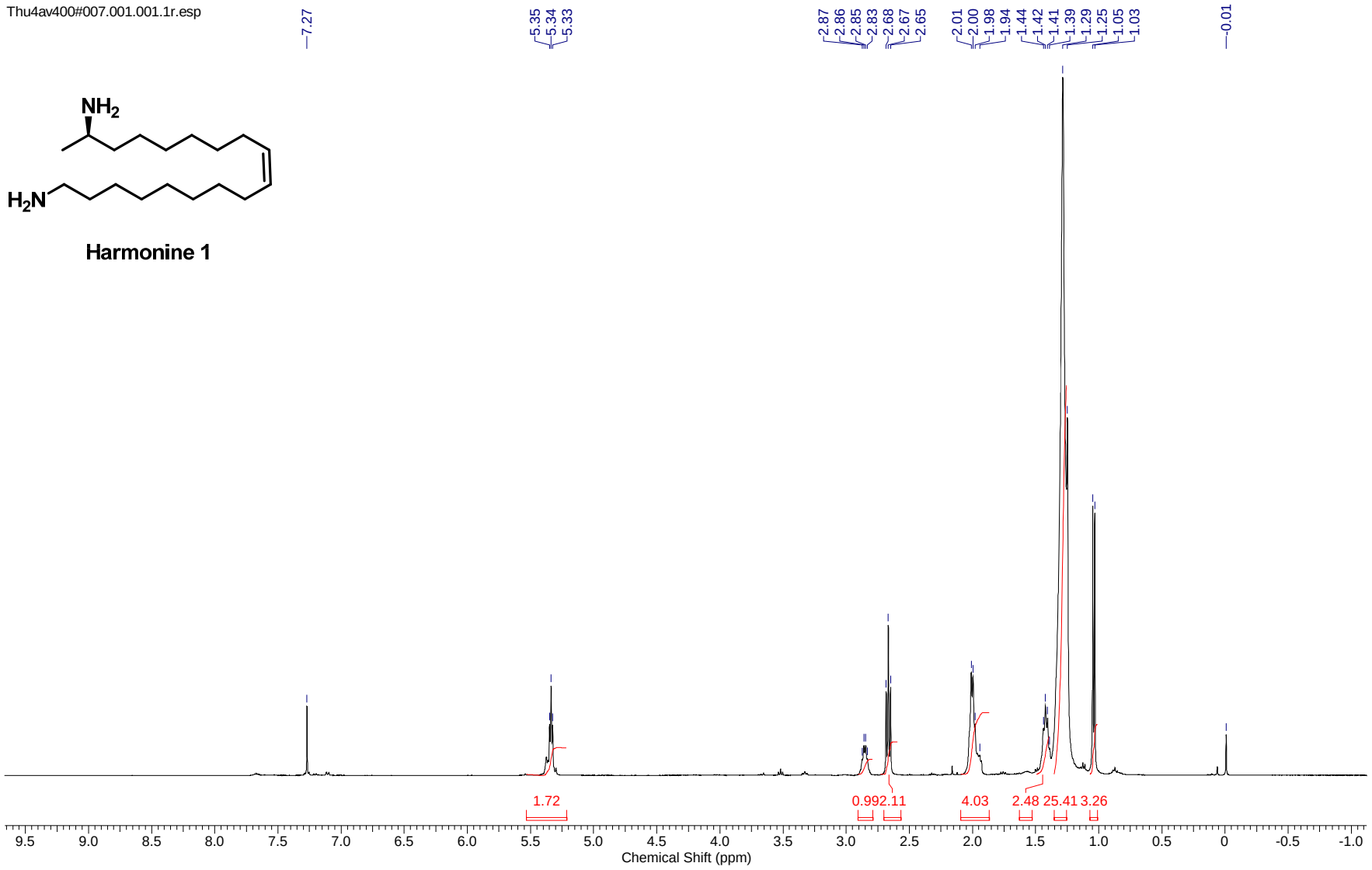
From sophorolipids (Approach 3)



From sophorolipids (Approach 3)