Electronic Supplementary Material (ESI) for ChemComm.

A Predictive Model for Additions to *N*-Alkyl Pyridiniums

Brian J. Knight, Zachary A. Tolchin, Joel M. Smith*

Department of Chemistry and Biochemistry, Florida State University, 95 Chieftan Way, Tallahassee, FL, 32306, USA

Corresponding Authors:

E-mail: jsmith17@fsu.edu

Table of Contents

General Experimental

All reactions were performed using flame-dried round-bottomed flasks or reaction vessels unless otherwise stated. Reactions were carried out under an inert atmosphere of nitrogen with dry solvents, unless otherwise stated. Dry benzene (PhH), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), dimethylformamide (DMF), 1,4-dioxane, methanol (MeOH), acetonitrile (MeCN), and tetrahydrofuran (THF) were obtained by passing the previously degassed solvents through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. NMR yields were compared to an internal standard of either trimethoxybenzene or dimethyl sulfone. Reactions were monitored by thin-layer chromatography carried out on Merck silica gel plates (glass-backed, 60G, F-254) or Sigma-Aldrich aluminum oxide plates (glass-backed, F-254). Basic silica plates were prepared by treating commercial silica gel plates with 50:1 hexanes:triethylamine followed by evaporation under reduced pressure. TLC plates were visualized using ultraviolet light and an appropriate developing agent. NMR spectra were recorded on a Bruker Avance III 400, 500, or 600 MHz NMR spectrometers and were calibrated using residual solvent as an internal reference (benzene-d_6: ^{1}H NMR δ = 7.16, ^{13}C NMR δ = 128.06; $CDCl_3$: ^{1}H NMR δ = 7.26, ^{13}C NMR δ = 77.16; CD_2Cl_2: ^{1}H δ = 5.32, ^{13}C NMR δ = 53.84; DMSO-d_6: ^{1}H δ = 2.50; methanol-d_4: ^{1}H δ = 3.31). ^{19}F NMR spectra were calibrated using 3-fluoropyridine as an internal reference (^{19}F NMR δ = –125.7).[1] The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and app = apparent. When analyzing dihydropyridine products, $CDCl_3$ was passed through a pad of K_2CO_3 prior to its use. Crude NMR spectra were analyzed to determine the ratio of dihydropyridine regioisomers. Unisolated regioisomers were assigned based on selected peaks in the crude ^{1}H NMR. Flash column chromatography was performed using VWR silica gel (irregular, 60 Å, 40-60 μm), prepared basic silica gel, or deactivated aluminum oxide (alumina, for chromatography, neutral, Brockman I, 50-200 μm, 60 Å). Basic silica gel was prepared by treating commercial silica gel with 50:1 hexanes:triethylamine followed by evaporation under reduced pressure. Deactivation of alumina to Brockman grade III alumina was accomplished by adding pure water (5% w/w) to solid aluminum oxide. The mixture was shaken and then allowed to sit and equilibrate overnight in a sealed container. Preparatory TLC was performed on Merck silica gel plates (glass-backed, 60G, F-254), basic silica plates, or Sigma-Aldrich aluminum oxide plates (glass-backed, F-254). High-resolution mass spectra (HRMS) were recorded on an Agilent 6230 TOF-MS spectrometer (DART). Reagents were purchased and used without further purification, unless

[1] Hartman, J. S.; Shoemaker, J. A. W.; Janzen, A. F.; Ragogna, P. J.; Szerminski, W. R. The Coordination Chemistry of (py)2BF2$^+$ and Related Difluoro Cations. *J. Fluorine Chem.* **2003**, *119*, 125–139.

otherwise stated. All reagents were purchased from the suppliers below. 2,2'-Azobis(2-methylpropionitrile) was recrystallized from methanol.

Acros Organics: 1,3-dithiane.

Alfa Aesar: acetyl chloride, 4-methoxybenzaldehyde, and sodium methoxide.

Cambridge Isotope Laboratories: chloroform-d_1, deuterium oxide, dichloromethane-d_2, dimethyl sulfoxide-d_6, and methanol-d_4.

EMD Chemicals: diethylamine.

Fisher Scientific: conc. ammonia hydroxide, conc. hydrochloric acid, magnesium metal, pyridine, sodium carbonate, and sodium chloride.

Matrix Scientific: methyl 5-chloronicotinate.

Macron Fine Chemicals: tert-butyl alcohol and sodium nitrite.

J. T. Baker Chemicals: conc. sulfuric acid and EDTA disodium salt dihydrate.

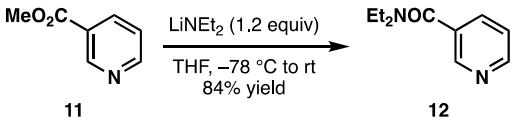
Oakwood Chemical: allyl bromide, 4-bromo-1-butene, 3-bromo-5-cyanopyridine, 2-(2-bromoethyl)-1,3-dioxane, 3-bromo-5-methylpyridine, 5-bromonicotinic acid, 5-bromo-3-pyridinemethanol, 3-bromo-1-(trimethylsilyl)-1-propyne, *tert*-butyldimethylchlorosilane, copper(I) chloride, 3,5-dibromopyridine, di-*tert*-butyldicarbonate, 4-(dimethylamino)pyridine, ethyl 2-bromobenzoate, isobutyl chloroformate, lithium aluminum hydride, magnesium sulfate, 3-methoxypyridine, methyl 5-methylnicotinate, methyl triflate, *N*-methylmorpholine, 3-methylpyridine, nicotinonitrile, phenethyl bromide, potassium carbonate, propargyl bromide solution (80% wt. in toluene), pyridine-3,5-dicarboxylic acid, 3-pyridinemethanol, sodium bicarbonate, sodium sulfate, thionyl chloride, tributyltin hydride, and trimethoxybenzene.

Sigma Aldrich: 2,2'-azobis(2-methylpropionitrile), *n*-butyllithium (2.5M in hexanes), 1,1'-carbonyldiimidazole, copper(I) cyanide, copper(I) iodide, copper(II) sulfate hexahydrate, *N*,*N*'-diethylenediamine, dimethyl sulfone, ethylamine solution (2M in THF), isopropenylmagnesium bromide (0.5 M in THF), imidazole, iodine, isopropylmagnesium chloride lithium chloride solution (1.3M in THF), lithium chloride, magnesium bromide, mercury(II) chloride, methyl formate, methyl nicotinate, phenylmagnesium chloride (2.0 M in THF), 1-propenylmagnesium bromide (0.5 M in THF), 1-propynylmagnesium bromide (0.5 M in THF), sodium iodide, 2,2,6,6-tetrapiperidinylmagnesium chloride lithium chloride solution (1.0 M in THF:toluene), trimethyl orthoformate, and vinylmagnesium bromide (1.0 M in THF).

Spectrum Chemicals: celite.

Synquest Laboratories: HF•pyridine.

Experimental Procedures and Characterization of Substrates



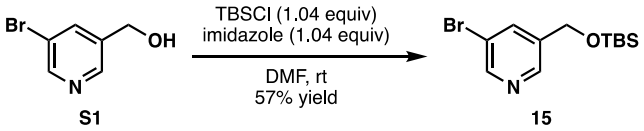
11 12

A solution of diethylamine (7.24 mL, 70.0 mmol) in THF (25 mL) cooled to –78 °C was charged with a solution of *n*-BuLi (24.8 mL, 2.42 M, 60 mmol) dropwise over 5 min. The solution stirred at –78 °C for 30 min and was then warmed to 0 °C and stirred for 20 min. The resulting lithium amide solution was cooled back to –78 °C. To a separate solution of methyl nicotinate (**11**, 6.86 g, 50.0 mmol) in THF (25 mL) cooled to –78 °C was added the above lithium amide solution via cannula over 5 min. The reaction mixture turned brown upon the addition. The mixture was removed from the cooling bath and warmed to rt. The reaction mixture was allowed to stir for 2 h and the color turned progressively darker. Upon completion of the reaction (as determined by TLC), a 1M HCl solution (200 mL) was added to the mixture and the product was extracted with EtOAc (10 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated via rotary evaporation. The crude mixture was purified by flash column chromatography (EtOAc eluent) to afford amide **12** (7.47 g, 84% yield). The characterization data for amide **12** was previously reported.[2]

Physical State: Dark amber oil.

$\boldsymbol{R_f}$ = 0.22 (EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68–8.62 (m, 2H), 8.65 (br s, 1H), 7.76 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.76 (dt, *J* = 7.8, 4.9 Hz, 1H), 3.56 (br s, 2H), 3.27 (br s, 2H), 1.26 (br s, 3H), 1.15 (br s, 3H).



S1 15

To a solution of alcohol **S1** (940 mg, 5.00 mmol) and imidazole (354 mg, 5.20 mmol) dissolved in DMF (25 mL) was added TBSCl (784 mg, 5.20 mmol) and the mixture was stirred at rt for 22 h. Upon disappearance of starting material (as determined by TLC), the mixture was diluted with Et_2O (20 mL). The organic layer was washed with H_2O (3 x 20 mL), a 10% aqueous LiCl solution (20 mL), and brine (20 mL).

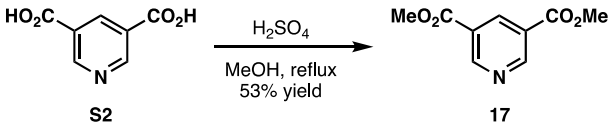
[2] Collin, H. P.; Reis, W. J.; Nielsen, D. U.; Lindhardt, A. T.; Valle, M. S.; Freitas, R. P.; Skrydstrup, T. COtab: Expedient and Safe Setup for Pd-Catalyzed Carbonylation Chemistry. *Org. Lett.* **2019**, *21*, 5775–5778.

The combined organic layers were dried over Na_2SO_4 and concentrated via rotary evaporation. The crude material was passed through a pad of silica (3:1 hexanes:EtOAc eluent) to afford silyl ether **15** (861 mg, 57% yield). The characterization data for silyl ether **15** was previously reported.[3]

Physical State: White solid.

R_f = 0.80 (3:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (500 MHz; $CDCl_3$) δ 8.56 (d, J = 2.2 Hz, 1H), 8.46 (d, J = 1.7 Hz, 1H), 7.82–7.80 (m, 1H), 4.74 (ABq, J_{AB} = 0.7 Hz, $\Delta\nu_{AB}$ = 1.0 Hz, 2H), 0.94 (s, 9H), 0.12 (s, 6H).



S2 17

A suspension of dicarboxylic acid **S2** (5.00 g, 29.9 mmol) in MeOH (100 mL) was slowly charged with conc. H_2SO_4 (2.0 mL), and the mixture was heated to reflux and stirred for 18 h. After the disappearance of the starting material (as determined by TLC), the reaction was carefully quenched with a sat. $NaHCO_3$ solution (30 mL) and the MeOH was removed via rotary evaporation. The product was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated via rotary evaporation. The crude material was purified via flash column chromatography (9:1 CH_2Cl_2:Et_2O eluent, silica) to obtain diester **17** (3.11 g, 53% yield).

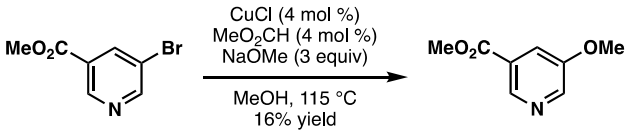
Physical State: Off-white solid.

R_f = 0.63 (9:1 CH_2Cl_2:Et_2O eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 9.36 (d, J = 2.1 Hz, 2H), 8.87 (t, J = 2.1 Hz, 1H), 3.99 (s, 6H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 165.0, 154.3, 138.1, 126.1, 52.8.

HRMS (DART): calc'd for $C_9H_{10}NO_4^+$ $[M+H]^+$ 196.0604; found 196.0606.



22 19

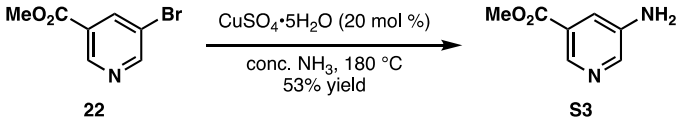
[3] Zhang, N.; Tomizawa, M.; Casida, J. E. Structural Features of Azidopyridinyl Neonicotinoid Probes Conferring High Affinity and Selectivity for Mammalian α4β2 and Drosophila Nicotinic Receptors *J. Med. Chem.* **2002**, *45*, 2832–2840.

A 15 mL flame-dried pressure vessel was charged with methyl 5-bromonicotinate (**22**, 1.50 g, 6.95 mmol), NaOMe (1.13 g, 20.9 mmol), CuCl (27.5 mg, 0.278 mmol), methyl formate (173 µL, 2.78 mmol), and MeOH (8.7 mL). The reaction vessel was flushed with nitrogen and sealed tightly with a Teflon screw-cap. The mixture was heated in a 115 ºC oil bath for 4 h. The reaction mixture was allowed to cool to rt and stirred open to air for 30 min. The MeOH was removed via rotary evaporation. To the crude mixture was added H_2O (10 mL) and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography (7:3 hexanes:EtOAc eluent, silica) to afford methyl ether **19** (190 mg, 16% yield). The characterization data for methyl ether **19** was previously reported.[4]

Physical State: Colorless oil.

$\boldsymbol{R_f}$ = 0.28 (7:3 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.83 (d, *J* = 1.7 Hz, 1H), 8.48 (d, *J* = 3.0 Hz, 1H), 7.79 (dd, *J* = 3.0, 1.7 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H).



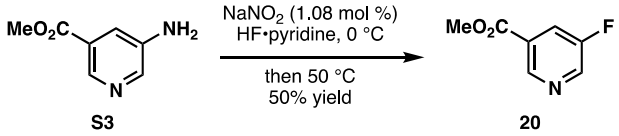
A 48 mL flame-dried pressure vessel was charged with 5-bromonicotinic acid (**22**, 4.04 g, 20.0 mmol) and $CuSO_4$•$5H_2O$ (1.00 g, 4.00 mmol), and the mixture was then dissolved in conc. aqueous ammonia (18 mL). The pressure vessel was flushed with nitrogen, tightly sealed with a Teflon screw cap, and then heated at 180 ºC for 24 h. The reaction mixture was concentrated via rotary evaporation and then suspended in MeOH (175 mL) and transferred to a round bottom flask. Acetyl chloride (10.0 mL, 140 mmol) and trimethyl orthoformate (30.0 mL, 174 mmol) were added to the flask and the mixture was heated to reflux for 48 h. The resulting mixture was concentrated via rotary evaporation and then charged with a solution of Na_2CO_3 (50 mL, 10% w/w). The product was extracted with CH_2Cl_2 (10 x 50 mL), and the combined extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated via rotary evaporation to afford analytically pure aniline **S3** (1.61 g, 53% yield).

Physical State: Light brown powder.

$\boldsymbol{R_f}$ = 0.16 (1:1 hexanes:EtOAc eluent, silica).

[4] Ma, C.; Zhao, C.-Q.; Xu, X.-T.; Li, Z.-M.; Wang, X.-Y.; Zhang, K.; and Mei, T.-S. Nickel-Catalyzed Carboxylation of Aryl and Heteroaryl Fluorosulfates Using Carbon Dioxide. *Org. Lett.* **2019**, *21*, 2464–2467.

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.62 (br s, 1H), 8.36 (br s, 1H), 7.61 (s, 1H), 3.93 (s, 3H).

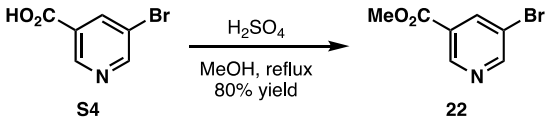


A plastic vial was charged with aminopyridine **S3** (913 mg, 6.00 mmol) and HF-pyridine (19 mL), and the mixture was cooled to 0 ºC. $NaNO_2$ (447 mg, 6.48 mmol) was added in one portion and the mixture was stirred at 0 °C for 30 min. The mixture was then heated to 50 ºC for 1 h and then quenched with an ice-cold sat. solution of $NaHCO_3$ (25 mL). The mixture was extracted with $CHCl_3$ (3 x 15 mL), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The crude material was purified by flash column chromatography (99:1 $CHCl_3$:MeOH eluent, silica) to afford pyridyl fluoride **20** (457 mg, 50% yield). The characterization data for pyridyl fluoride **20** was previously reported.[5]

Physical State: Yellow-orange solid.

***R*$_f$** = 0.37 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 9.04 (br s, 1H), 8.65 (d, *J* = 2.6 Hz, 1H), 8.00 (ddd, *J* = 8.6, 2.6, 1.7 Hz, 1H), 3.98 (s, 3H).



To a suspension of 5-bromonicotinic acid (**S4**, 20.0 g, 99.6 mmol) in MeOH (240 mL) was slowly added conc. H_2SO_4 (10 mL) and the resulting clear solution was heated to reflux for 36 h. After the disappearance of the starting material (as determined by TLC), the reaction was carefully quenched with a sat. $NaHCO_3$ solution (100 mL) and the MeOH was removed via rotary evaporation. The product was extracted with CH_2Cl_2 (4 x 30 mL), and the combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and concentrated via rotary evaporation to obtain a tan solid. The crude material was passed through a pad of silica (7:3 hexanes:EtOAc eluent) to afford ester **22** (17.1 g, 80% yield). The characterization data for ester **22** was previously reported.[6]

---

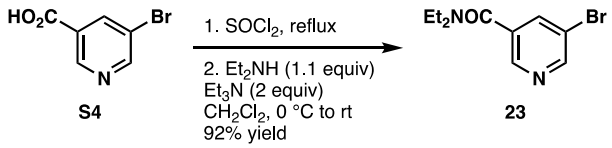
[5] Xing, B.; Ni, Chuanfa, N.; Hu, J. Hypervalent Iodine(III) Catalyzed Balz–Schiemann Fluorination under Mild Conditions. *Angew. Chem. Int. Ed.* **2018**, *57*, 9896–9900.

[6] Van Hemel, J.; Esmans, E. L.; Alderweireldt, F. C.; Dommisse, R. A.; De Groot, A.; Balzarini, J.; De Clercq, E. Synthesis and Biological Evaluation of Some Acyclic Pyridine C-Nucleosides. Part One.

Physical State: Off-white flaky solid.

R_f = 0.28 (9:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 9.13 (d, *J* = 1.7 Hz, 1H), 8.84 (d, *J* = 2.2 Hz, 1H), 8.44 (dd, *J* = 2.2, 1.7 Hz, 1H), 3.97 (s, 3H).



A suspension of 5-bromonicotinic acid (**S4**, 10.1 g, 50.0 mmol) in $SOCl_2$ (80 mL) was heated and stirred at reflux for 2 h. After the disappearance of the starting material (as determined by TLC), the reaction mixture was concentrated via rotary evaporation to afford a thick oil. The crude mixture was dissolved in CH_2Cl_2 (80 mL) and was cooled to 0 °C. The reaction mixture was charged with Et_3N (13.9 mL, 100 mmol) in one portion followed by the dropwise addition of diethylamine (5.69 mL, 55.0 mmol). The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to rt and stirred overnight. The reaction mixture was charged with a solution of sat. $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (1:1 hexanes:EtOAc eluent, silica) to afford amide **23** (11.9 g, 92% yield).

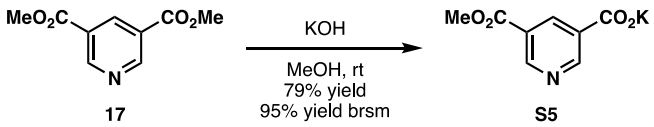
Physical State: Light amber oil.

R_f = 0.34 (1:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.53 (s, 1H), 7.86 (s, 1H), 3.52 (q, *J* = 6.3 Hz, 2H), 3.25 (q, *J* = 6.3 Hz, 2H), 1.24 (br s, 3H), 1.14 (br s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.9, 151.5, 145.2, 137.1, 134.4, 120.8, 43.6, 39.8, 14.4, 12.9.

HRMS (DART): calc'd for $C_{20}H_{27}Br_2N_4O_2^+$ $[2•M+H]^+$ 515.0495; found 515.0491.

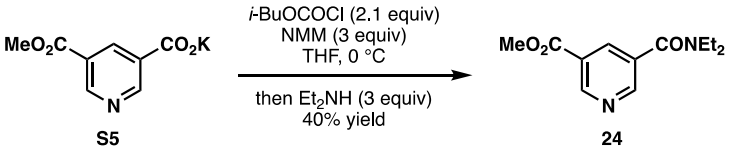


Diester **17** (1.50 g, 7.69 mmol) was added to a solution of KOH (453 mg, 8.07 mmol) in MeOH (77 mL), and the reaction mixture was stirred at rt for 24 h. The solution was extracted with Et_2O (3 x 20 mL), and the combined organic layers were concentrated to afford analytically pure diester **17** (260 mg). The aqueous layer was concentrated to afford analytically pure potassium nicotinate **S5** (1.32 g, 79% yield, 95% brsm).

Physical State: White solid.

R_f = 0.05 (9:1 $CHCl_3$:MeOH eluent, silica).

^{1}H NMR (400 MHz; DMSO-d_6) δ 9.11 (d, J = 2.0 Hz, 1H), 8.97 (d, J = 2.2 Hz, 1H), 8.57 (dd, J = 2.2, 2.0 Hz, 1H), 3.88 (s, 3H).



Potassium nicotinate **S5** (1.00 g, 4.59 mmol) and *N*-methylmorpholine (1.00 mL, 9.17 mmol) were dissolved in THF (35 mL) cooled to 0 ºC. The reaction vessel was charged with isobutyl chloroformate (0.650 mL, 5.05 mmol) and the mixture was stirred for 1 h at 0 ºC. After 1 h, the reaction mixture was charged with additional *N*-methylmorpholine (0.500 mL, 4.55 mmol) and then isobutyl chloroformate (0.300 mL, 2.31 mmol), and the mixture was allowed to stir for 1 h. Diethylamine (1.43 mL, 13.8 mmol) was added to the mixture and the reaction was allowed to stir at rt for another 10 h. The mixture was filtered through a glass fritted funnel, and the filtrate was concentrated via rotary evaporation to afford analytically pure amide **24** (432 mg, 40% yield).

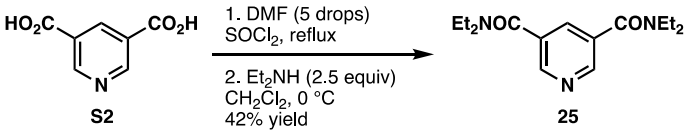
Physical State: Light yellow oil.

R_f = 0.35 (3:1 EtOAc:hexanes eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.24 (d, J = 2.0 Hz, 1H), 8.80 (d, J = 2.0 Hz, 1H), 8.32 (t, J = 2.0 Hz, 1H), 3.97 (s, 3H), 3.58 (q, J = 6.5 Hz, 2H), 3.25 (q, J = 6.5 Hz, 2H), 1.27 (t, J = 6.5 Hz, 3H), 1.15 (t, J = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.7, 165.3, 151.4, 151.0, 135.4, 132.9, 125.9, 52.8, 43.7, 39.9, 14.5, 13.0.

HRMS (DART): calc'd for $C_{24}H_{33}N_4O_6^+$ $[2•M+H]^+$ 473.2395; found 473.2428.

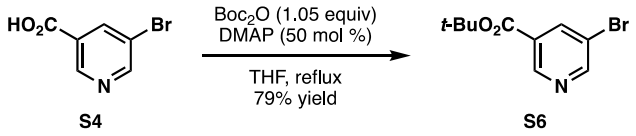


A stirring suspension of dicarboxylic acid **S2** (1.67 g, 10.0 mmol) in $SOCl_2$ (10.0 mL) at rt was added DMF (5 drops). The vessel was then equipped with a $CaCl_2$ drying tube. The mixture was refluxed for 3 h. Then, $SOCl_2$ was removed via rotary evaporation and the resulting yellow residue was dissolved in CH_2Cl_2 (10 mL). A separate solution of diethylamine (2.58 mL, 25.0 mmol) dissolved in CH_2Cl_2 (25 mL) was cooled to 0 ºC. The diacyl chloride solution was added dropwise to the diethylamine solution, ensuring that the temperature remained below 5 ºC. The resulting mixture was stirred at rt for 30 min resulting in a brown solution. The reaction was quenched with aqueous NaOH (20 mL, 1.0 M) followed by the addition of solid NaCl until the aqueous solution was near saturation. The solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (3:2 acetone:EtOAc eluent, silica) to afford diamide **25** (1.16 g, 42% yield). The characterization data for diamide **25** was previously reported.[7]

Physical State: White solid.

R_f = 0.32 (3:2 acetone:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 2.1 Hz, 2H), 7.74 (t, J = 2.1 Hz, 1H), 3.56 (q, J = 6.4 Hz, 4H), 3.27 (q, J = 6.4 Hz, 4H), 1.26 (t, J = 6.4 Hz, 6H), 1.15 (t, J = 6.4 Hz, 6H).



5-Bromonicotinic acid (**S4**, 4.04 g, 20.0 mmol), di-*tert*-butyldicarbonate (4.58 g, 21.0 mmol), and (4-dimethylamino)pyridine (1.22 g, 10.0 mmol) were dissolved in THF (100 mL) and heated and stirred at reflux for 1 h. The reaction mixture was concentrated under reduced pressure. To this mixture was added a sat. $NaHCO_3$ solution (30 mL) and this mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced

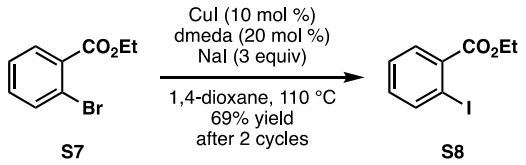
[7] Speelman, J. C.; Kellogg, R. M. Behavior of Pyridinium Salts Obtained from Derivatives of Pyridinedicarboxylic Acids in Basic Solutions. Addition of Hydroxide or Alkoxide to Form 1,2-Dihydropyridine Intermediates. *J. Org. Chem.* **1990**, 55, 2, 647–653.

pressure. The crude mixture was purified by flash column chromatography (9:1 hexanes:EtOAc eluent, silica) to afford *tert*-butyl ester **S6** (4.09 g, 79% yield). The characterization data for *tert*-butyl ester **S6** was previously reported.[8]

Physical State: White solid.

R_f = 0.36 (9:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (d, *J* = 1.8 Hz, 1H), 8.80 (d, *J* = 2.3 Hz, 1H), 8.36 (dd, *J* = 2.3, 1.8 Hz, 1H), 1.61 (s, 9H).



A 48 mL pressure vessel was charged with ethyl 2-bromobenzoate (**S7**, 3.18 mL, 20.0 mmol), CuI (381 mg, 2.00 mmol), and NaI (9.00 g, 60.0 mmol), then the vessel was placed under vacuum and backfilled with N_2. *N*,*N*'-dimethylethylenediamine (431 μL, 4.00 mmol) and 1,4-dioxane (40 mL) were added to the mixture, and the vessel was sealed tightly with a Teflon cap. The mixture was stirred and heated at 110 ºC for 18 h. The suspension was observed to turn greyish blue after 2 h. The reaction mixture cooled to rt and then added Celite (1.0 g). The resulting slurry was filtered through a plug of silica (Et_2O eluent) and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (9:1 hexanes:EtOAc eluent, silica) to afford a 9:1 mixture (5.24 g) of ethyl 2-iodobenzoate (**S8**) and ethyl 2-bromobenzoate (**S7**) as a colorless oil. The mixture (4.64 g, 15.4 mmol **S8** + 1.71 mmol **S7**) was resubjected to the reaction conditions, which afforded pure ethyl 2-iodobenzoate (**S8**, 3.78 g, 69% yield over 2 cycles) as a light amber oil. The characterization data for aryl iodide **S8** was previously reported.[9]

Physical State: Colorless oil.

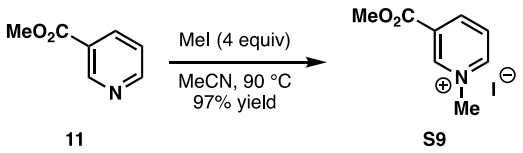
R_f = 0.36 (9:1 hexanes:Et_2O eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.40 (ddd, *J* = 7.8, 7.5, 1.2 Hz, 1H), 7.40 (ddd, *J* = 7.9, 7.5, 1.7 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (q, *J* = 7.1 Hz, 3H).

---

[8] Wright, S. W. Preparation of 2-, 4-, 5-, and 6-Aminonicotinic Acid tert-Butyl Esters. *J. Heterocyclic Chem.* **2012**, *49*, 442–445.

[9] Li, L.; Liu, W.; Zeng, H.; Mu, X.; Cosa, G.; Mi, Z.; Li, C.-J. Photo-Induced Metal-Catalyst-Free Aromatic Finkelstein Reaction. *J. Am. Chem. Soc.* **2015**, *137*, 8328-8331.



To a 15 mL pressure vessel was added pyridine **11** (1.37 g, 10.0 mmol), MeCN (3.3 mL), and MeI (2.49 mL, 40.0 mmol). The vessel was sealed with a Teflon cap and heated and stirred at 90 °C for 1 h. Upon completion, as determined by TLC, the mixture was concentrated under reduced pressure to afford a crude solid. The solid was washed with hexanes (3 x 2 mL). The resulting solid was dried under reduced pressure to afford methylpyridinium **S9** (2.70 g, 97% yield).

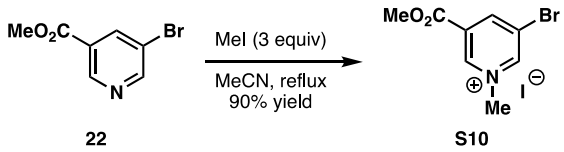
Physical State: Light yellow solid.

R_f = 0.09 (9:1 $CHCl_3$:MeOH eluent, silica).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.55 (s, 1H), 9.23 (d, J = 6.2 Hz, 1H), 8.96 (d, J = 8.1 Hz, 1H), 8.29 (dd, J = 8.1, 6.2 Hz, 1H), 4.45 (s, 3H), 3.98 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 162.1, 148.8, 146.6, 144.6, 129.1, 127.9, 53.5, 48.4, 39.5.

HRMS (DART): calc'd for $C_8H_{10}NO_2^+$ $[M]^+$ 152.0706; found 152.0705**.**



A flask was charged with methyl 5-bromonicotinate (**22**, 4.00 g, 18.6 mmol), MeCN (6.4 mL), and MeI (2.32 mL, 37.2 mmol). The mixture was heated and stirred at reflux for 24 h. At this point, additional MeI (1.16 mL, 18.6 mmol) was charged to the mixture and the reaction was heated and stirred at reflux for an addition 6 h. Upon completion as determined by TLC, the mixture was charged with EtOAc until there was no further precipitation. The resulting solid was isolated by filtration and the filter cake was washed with EtOAc (3 x 2 mL). The solid was dried under reduced pressure to afford methylpyridinium **S10** (6.02 g, 90% yield). The characterization data for methylpyridinium **S10** was previously reported.

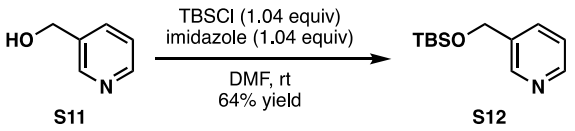
Physical State: Yellow crystalline solid.

R_f = 0.11 (9:1 $CHCl_3$:MeOH eluent, silica).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.63 (s, 1H), 9.59 (s, 1H), 9.19 (s, 1H), 4.39 (s, 3H), 3.98 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 161.4, 150.3, 146.9, 145.6, 129.9, 121.6, 53.7, 48.4.

HRMS (DART): calc'd for $C_8H_9BrNO_2^+$ $[M]^+$ 229.9811; found 229.9811**.**

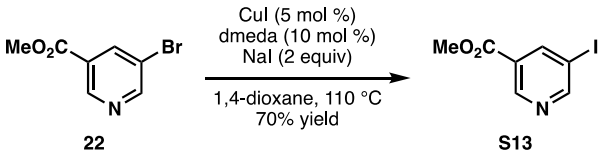


To a solution of alcohol **S11** (485 µL, 5.00 mmol) and imidazole (354 mg, 5.20 mmol) dissolved in DMF (25 mL) was added TBSCl (784 mg, 5.20 mmol), and the mixture was stirred at rt for 16 h. Upon disappearance of starting material (as determined by TLC), the mixture was diluted with Et_2O (20 mL), washed with H_2O (3 x 20 mL), a 10% aqueous LiCl solution (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was passed through a pad of silica (7:3 hexanes:EtOAc eluent) to afford silyl ether **S12** (716 mg, 64% yield). The characterization data for silyl ether **S12** was previously reported.[10]

Physical State: Colorless oil.

***R**$_f$* = 0.56 (7:3 hexanes:EtOAc eluent, silica).

^{1}H NMR (500 MHz; $CDCl_3$) δ 8.56 (s, 1H), 8.50 (d, *J* = 4.7 Hz, 1H), 7.67–7.64 (m, 1H), 7.27 (dd, *J* = 7.8, 4.7 Hz, 2H), 4.76 (s, 2H), 0.94 (s, 9H), 0.11 (s, 6H).



To a 15 mL flame-dried pressure vessel was added methyl 5-bromonicotinate (**22**, 645 mg, 3.00 mmol), CuI (28.6 mg, 0.150 mmol), and NaI (900 mg, 6.00 mmol), and then, the vessel was placed under vacuum and backfilled with N_2. *N*,*N*'-dimethylethylenediamine (32.3 µL, 0.300 mmol) and 1,4-dioxane (3.0 mL) were added, and the vessel was sealed tightly with a Teflon cap. The mixture was heated at 110 ºC for 24 h. The solution was observed to turn grey after 2 h and was brown after 24 h. The reaction mixture was cooled to rt and diluted with a 30% aqueous NH_3 solution (15 mL) and the blue mixture was poured into a solution of Na_2EDTA in H_2O (60 mL, 50 mg/mL) and stirred for 30 min. The resulting mixture was

[10] Xia, Q.; Wang, Q.; Yan, C.; Dong, J.; Song, H.; Li, L.; Liu, Y.; Wang, Q.; Liu, X.; Song, H. Merging Photoredox with Brønsted Acid Catalysis: The Cross-Dehydrogenative C–O Coupling for sp^3 C–H Bond Peroxidation. *Chem. Eur. J.* **2017**, *23*, 10871–10877.

extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with brine (25 mL), dried with $MgSO_4$, and concentrated via rotary evaporation. The crude material was passed through a pad of silica (1:1 hexanes:EtOAc eluent) to obtain pyridyl iodide **S13** (550 mg, 70% yield).

Physical State: Off-white solid.

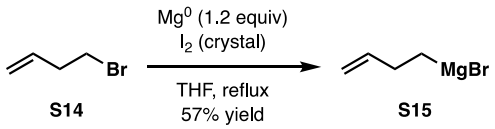
R_f = 0.28 (9:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (br s, 1H), 8.99 (br s, 1H), 8.26 (t, J = 2.0 Hz, 1H), 3.96 (t, 3H).

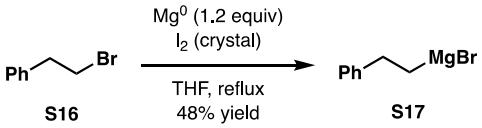
^{13}C NMR (126 MHz, $CDCl_3$): δ 164.6, 159.5, 149.3, 145.3, 127.7, 92.9, 52.9.

HRMS (DART): calc'd for $C_7H_7INO_2^+$ $[M+H]^+$ 263.9516; found 263.9532.

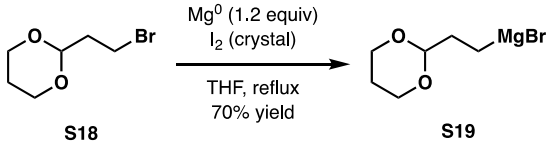
Procedures for the Preparation of Grignard Reagents



Magnesium turnings (583 mg, 24.0 mmol) were suspended in THF (10 mL) and the reaction mixture was charged with a crystal of iodine. The mixture was then heated and stirred at reflux until its color lightened. At this point, 4-bromo-1-butene (**S14**, 2.03 mL, 20.0 mmol) was added in 5 equal portions over the course of 1 h while the mixture continued to stir at reflux. The resulting amber suspension was heated at reflux for an additional hour. At this point, the reaction mixture was cooled to rt and the suspension was titrated with iodine and lithium chloride to indicate the formation of Grignard reagent **S15** (11.0 mL, 1.04 M, 57% yield).

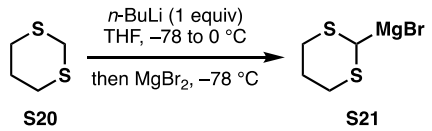


Magnesium turnings (123 mg, 5.06 mmol) were suspended in THF (2.1 mL) and the reaction mixture was charged with a crystal of iodine. The mixture was then heated at reflux until its color lightened. At this point, alkyl bromide **S16** (781 mg, 4.22 mmol) was added in 5 equal portions over the course of 1 h while the mixture continued to stir at reflux. The resulting amber suspension was heated at reflux for an additional hour. At this point, the reaction mixture was cooled to rt and the suspension was titrated with iodine and lithium chloride to indicate the formation of Grignard reagent **S17** (3.98 mL, 0.512 M, 48% yield).

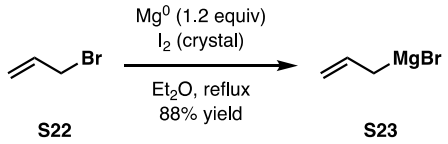


Magnesium turnings (1.02 g, 42 mmol) were suspended in THF (18 mL) and the reaction mixture was charged with a crystal of iodine. The mixture was then heated at reflux until its color lightened. At this point, alkyl bromide **S18** (4.77 mL, 35.0 mmol) was added in 5 equal portions over the course of 1 h while the mixture continued to stir at reflux. The resulting amber suspension was heated at reflux for an additional hour. At this point, the reaction mixture was cooled to rt and the suspension was titrated with iodine and

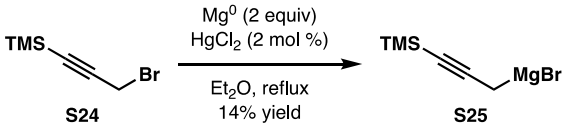
lithium chloride to indicate the formation of Grignard reagent **S19** (21.8 mL, 1.12 M, 70% yield). The Grignard reagent was diluted with additional THF to afford a 1.00 M solution.



A solution of *n*-BuLi (524 µL, 1.91 M in hexanes, 1.00 mmol) was added dropwise to a stirred suspension of 1,3-dithiane (**S20**, 120 mg, 1.00 mmol) in THF (1.0 mL) at –78 °C and stirred for 10 min. The solution was then warmed to 0 °C and stirred for 1 h. Over the course of the reaction a white precipitate developed. The suspension was then cooled to –78 °C and charged with $MgBr_2$ (184 mg, 1.00 mmol) in one portion. The suspension was warmed to 0 °C and stirred for 10 min. Transmetalation was assumed to be quantitative. Grignard reagent **S21** was used without titration.

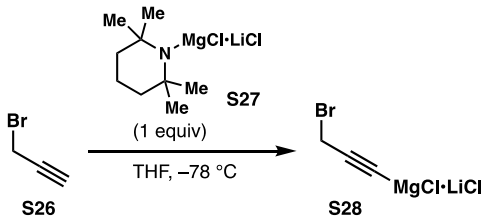


Magnesium turnings (146 mg, 6.00 mmol) were suspended in Et_2O (10 mL) and the reaction mixture was charged with a crystal of iodine. The mixture was then heated at reflux until its color lightened. At this point, allyl bromide (**S22**, 432 µL, 5.00 mmol) was added in 5 equal portions over the course of 1 h while the mixture continued to stir at reflux. The resulting dark suspension was heated at reflux for an additional hour. At this point, the reaction mixture was cooled to rt and the suspension was titrated with iodine and lithium chloride to indicate the formation of Grignard reagent **S23** (10.0 mL, 0.44 M, 88% yield).

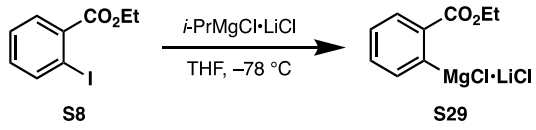


Magnesium turnings (243 mg, 10.0 mmol) and $HgCl_2$ (27.2 mg, 0.100 mmol) were suspended in Et_2O (4.2 mL) and the reaction mixture was charged with a crystal of iodine. The mixture was then heated at reflux until its color lightened. At this point, propargyl bromide **S24** (817 µL, 5.00 mmol) was added in 5 equal portions over the course of 1 h while the mixture continued to stir at reflux. The resulting dark suspension was heated at reflux for an additional hour. At this point, the reaction mixture was cooled to rt

and the suspension was titrated with iodine and lithium chloride to indicate the formation of Grignard reagent **S25** (5.81 mL, 0.24 M, 14% yield).

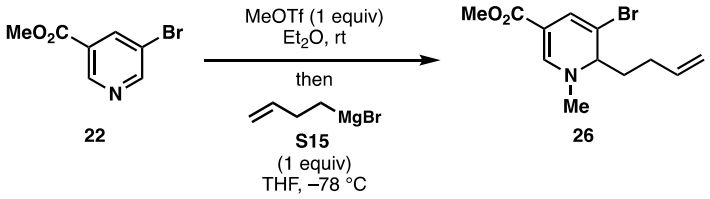


To a solution of propargyl bromide (**S26**, 123 µL, 80% wt/v in toluene, 1.00 mmol) in THF (1.0 mL) cooled to –78 °C was added TMPMgCl•LiCl (**S27**, 1.32 mL, 0.76 M, 1.00 mmol) dropwise over 5 min. The reaction mixture was stirred at –78 °C for 1 h and deprotonation was assumed to be quantitative. Grignard reagent **S28** was used without titration.



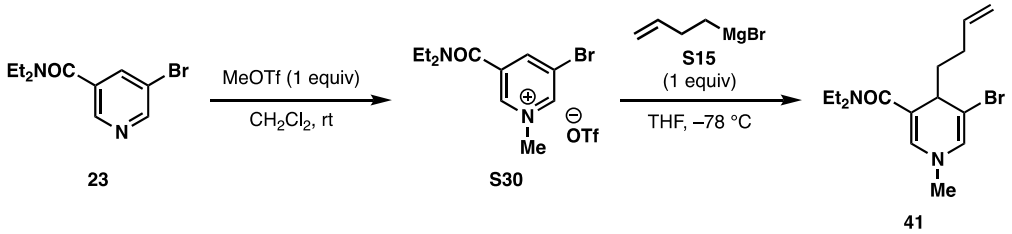
To a stirring solution of ethyl 2-iodobenzoate (**S8**, 615 mg, 2.22 mmol) in THF (2.0 mL) cooled to –78 °C was added *i*PrMgCl•LiCl (2.70 mL, 0.74 M, 2.00 mmol) dropwise over 5 min. The resulting suspension stirred at –78 °C for 5 min and turned yellow. The suspension was then warmed to –46 °C, which fully dissolved the Grignard reagent. This yellow solution was stirred at –40 °C for 1 h. At this point, the reaction mixture was titrated with *p*-anisaldehyde to indicate the formation of Grignard reagent **S29** (0.40 M).

General Procedure for the Methylation/Grignard Addition of Pyridines



General Procedure A

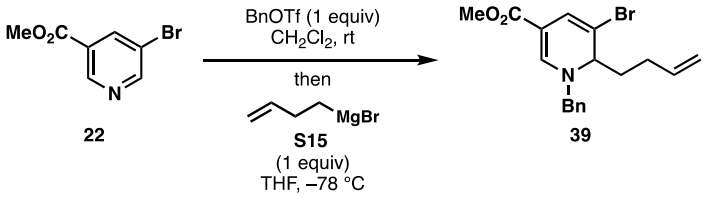
A 30 mL culture tube was charged with pyridine (1.00 mmol, 1.0 equiv) and Et_2O (1.0 mL, 1.0 M). The tube was placed in a rt water bath and was charged with MeOTf (110 µL, 1.00 mmol, 1.0 equiv) in a single portion. The reaction mixture was stirred until the starting material was consumed (determined by TLC). The reaction was typically completed within 1 h. The reaction mixture was then concentrated under reduced pressure. The reaction vessel was cooled to –78 °C, then the mixture was charged with THF (4 mL) taking care to wash the solids off the side of the culture tube's walls. The mixture was then charged with the Grignard reagent (1.00 mL, 1.0 M in THF, 1.0 equiv) dropwise over 5 min resulting in a 0.2 M solution. The mixture was allowed to stir for approx. 2 h or until the disappearance of the pyridinium by TLC (9:1 $CHCl_3$:MeOH, R_f = ~0.25). The reaction was then quenched with a sat. solution of $NaHCO_3$ (4 mL) and filtered through a small pad of celite. The resulting mixture was extracted with either Et_2O or EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to typically afford a yellow oil. When Grignard reagents were titrated to a molarity less than 1.0 M, less THF was used in the reaction to keep the total volume at 5.0 mL (0.2 M reaction).



General Procedure B

A 100 mL round bottom flask was charged with pyridine (3.00 mmol, 1.0 equiv) and CH_2Cl_2 (30 mL, 0.1 M). The flask was then charged with MeOTf (395 µL, 3.60 mmol, 1.2 equiv) in one portion and allowed to stir at rt for 2 h. In a scintillation vial, the solvent was removed via rotary evaporation and the resulting sticky residue was washed with hexanes (3 x 10 mL) and triturated with hexanes (10 mL) and was rapidly stirred (1000 rpm) at rt overnight. The hexane was removed, and the vial was placed under vacuum for 12

h to yield a clear sticky wax in quantitative yield. The resultant residue (1.00 mmol, 1.0 equiv) was added to a 30 mL culture tube and was dissolved in THF (4 mL) and cooled to –78 °C. Grignard reagent (1.00 mL, 1.0 M in THF, 1.0 equiv) was added dropwise over 5 min resulting in a 0.2 M solution. The mixture was allowed to stir until the disappearance of the pyridinium by TLC (9:1 $CHCl_3$:MeOH, R_f = ~0.25). The reaction was then quenched with a sat. solution of $NaHCO_3$ (4 mL) at –78 °C and the resulting suspension was filtered through a small pad of celite. The resulting mixture was extracted with either Et_2O or EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to typically afford a yellow oil.



General Procedure C

To a 30 mL vial in a rt water bath, a solution of BnBr (1.00 mmol, 1.0 equiv) and pyridine (1.00 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was charged with AgOTf (1.00 mmol, 1.0 equiv). The suspension stirred for 1h at rt. Upon completion as determined by TLC, the reaction mixture was concentrated under reduced pressure to afford a light purple solid. The reaction vessel was cooled to –78 °C, then the mixture was charged with THF (4 mL) taking care to wash the solids off the side of the culture tube's walls. The mixture was then charged with Grignard reagent (1.00 mL, 1.0 M in THF, 1.0 equiv) dropwise over 5 min resulting in a 0.2 M solution. The mixture was allowed to stir for 2 h. The disappearance of the pyridinium was observed by TLC (9:1 $CHCl_3$:MeOH, R_f = 0.50). The reaction was then quenched with a sat. solution of $NaHCO_3$ (4 mL) and filtered through a small pad of celite. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford an orange oil.

Optimization Details for Methylation/Grignard Addition of Pyridines

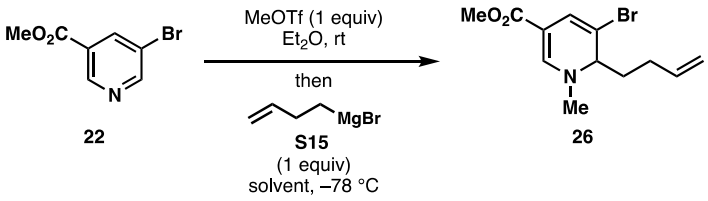


Table S1. Optimization for the addition of Grignard reagent **S15**.[a]

Entry	Reaction Time (h)	Solvent Ratio	Prod. Ratio (C4:C6)	Combined Yield
1	0.25 h	1.7:1 THF:Et_2O	1:7.7	82%
2	1 h	1.7:1 THF:Et_2O	1:9.4	91%
3	2 h	1.7:1 THF:Et_2O	1:10	89%
4	0.25 h	1.7:1 Et_2O:THF	1:2.9	79%
5	1 h	1.7:1 Et_2O:THF	1:3.1	77%
6	2 h	1.7:1 Et_2O:THF	1:2.9	88%
7	2 h	4:1 THF:Et_2O	1:7.0	80%
8	2 h	THF[b]	1:8.5	87%
9	2 h	1:4 THF:CH_2Cl_2[c]	1:2.5	89%

a) Unless otherwise noted, the reaction conditions were as follows: in a 30 mL test tube, pyridine **22** (1.00 mmol) was suspended in Et_2O (2.0 mL) and the mixture was placed under a N_2 atmosphere. The reaction vessel was placed in a rt water bath and the mixture was stirred lightly. MeOTf (1.0 equiv) was added dropwise to the mixture and the reaction was stirred for 1 h. After the disappearance of the starting material (determined by TLC), the thick, white mixture was cooled to –78 ºC and charged with THF (4.0 mL). THF and Et_2O were added to the reaction vessel to obtain the desired solvent ratio. The Grignard (1.0 equiv) was added dropwise to the mixture and the resulting yellow mixture was stirred for **X** h while ensuring continuous stirring. The reaction was then quenched with the addition of a sat. $NaHCO_3$ solution (4 mL) and the mixture was allowed to warm to rt NMR yields were determined by ^1H NMR analysis of unpurified reaction mixture using trimethoxybenzene as an internal standard.

b) Et_2O from the methylation step was removed under reduced pressure and THF (4 mL) was added before the addition of the Grignard solution in THF (1 mL).

c) Et_2O from the methylation step was removed under reduced pressure and CH_2Cl_2 (4 mL) was added before the addition of the Grignard solution in THF (1 mL).

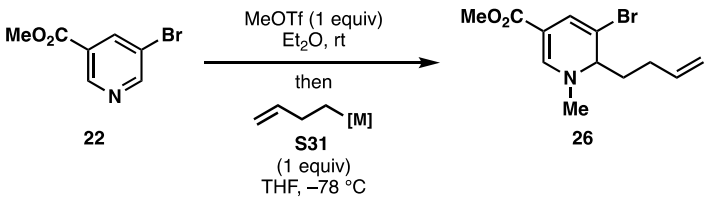


Table S2. Evaluation of different organometallic reagents.[a]

Entry	M	Prod. Ratio (C4:C6)	Combined Yield
1	Mg	1:8.5	87%
2	Zn[b]	1:1.5[b]	20%
3	Cu[c]	1.8:1[c]	58% (36% C4, 22% C6)[d]

a) Unless otherwise noted, the reaction conditions were as follows: in a 30 mL test tube, pyridine **22** (1.00 mmol) was suspended in Et_2O (1.0 mL) and the mixture was placed under a N_2 atmosphere. The reaction vessel was placed in a rt water bath and the mixture was stirred lightly. MeOTf (1.0 equiv) was added dropwise to the mixture and the reaction was stirred for 1 h. After the disappearance of the starting material (determined by TLC), the thick, white mixture was cooled to –78 ºC and charged with THF (4.0 mL). The Grignard reagent (1.0 equiv) was added dropwise to the mixture and the resulting yellow mixture was stirred for 2 hours while ensuring continuous stirring. The reaction was then quenched with the addition of a sat. $NaHCO_3$ solution (4 mL) and the mixture was allowed to warm to rt NMR yields were determined by ^1H NMR analysis of unpurified reaction mixture using trimethoxybenzene as an internal standard.

b) A zinc reagent was used and prepared from the Grignard reagent. To a 30 mL test tube containing a stirring solution of flame-dried LiCl (1mmol) in THF (1 M) at –78 °C, the Grignard reagent (1 equiv, 1.0 M) was added. The mixture stirred for 1 h. This zinc reagent was added by syringe to the methylpyridinium suspension at –78 °C bringing this mixture's volume to 5 mL. The reaction mixture stirred for 2 h at –78 °C and was then warmed to –40 °C and was stirred for 6 h. The reaction was quenched as in the general procedures.

c) A copper reagent was used and prepared from the Grignard reagent. To a 30 mL test tube containing a stirring suspension of oven-dried LiCl (2 mmol) and freshly prepared oven-dried CuCN (1 mmol) in THF (1 M) at –78 °C, the Grignard reagent (1 equiv, 1.0 M) was added. This reaction mixture stirred at –78 °C for 1 h. The methylpyridinium triflate was added as a solid powder to the suspension of organocopper reagent, and the reaction mixture was diluted to 5.0 mL. The reaction mixture stirred at –78 °C for 2 h. To quench the reaction, the mixture was poured into a saturated solution of ethylenediaminetetraacetic acid.

d) Isolated yields.

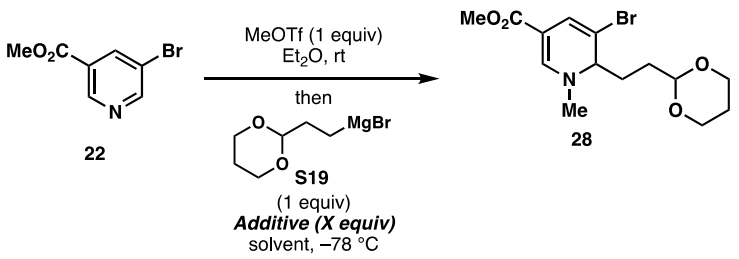


Table S3. Optimization for the addition of Grignard reagent **S19**.[a]

Entry	Additive (equiv)	Solvent Ratio	Prod. Ratio (C4:C6)	Combined Yield
1		1.7:1 THF:Et_2O	1:1.1	86%
2		1.7:1 THF:Et_2O	1:1.3	90%
3	LiCl (1.0)	1.7:1 THF:Et_2O	1:1.6	82%
4	DMF (10.0)	1.7:1 THF:Et_2O	1:1.7	30%
5		THF[b]	1:2.9	78%
6	HMPA (1.0)	1.7:1 THF:Et_2O	1:2.0	81%
7	DMPU (1.0)	1.7:1 THF:Et_2O	1:2.2	48%
8	TMEDA (1.0)	1.7:1 THF:Et_2O	1:2.1	81%
9	DME (1.0)	1.7:1 THF:Et_2O	1:1.3	82%
10	DMA (1.0)	1.7:1 THF:Et_2O	1:1.5	68%
11	HMPA (1.0)	THF[b]	1:1.4	35%
12	HMPA (10.0)	THF[b]	1:1.1	4%
13		4:1 THF:Et_2O	1:1.8	77%

a) Unless otherwise noted, the reaction conditions were as follows: in a 30 mL test tube, pyridine **22** (1.00 mmol) was suspended in Et_2O (1.0 mL) and the mixture was placed under a N_2 atmosphere. The reaction vessel was placed in a rt water bath and the mixture was stirred lightly. MeOTf (1.0 equiv) was added dropwise to the mixture and the reaction was stirred for 1 h. After the disappearance of the starting material (determined by TLC), the thick, white mixture was cooled to –78 ºC and charged with THF (4.0 mL). ***Additive***, THF, and Et_2O were added to the reaction vessel to obtain the tabulated amounts. The Grignard reagent (1.0 equiv) was added dropwise to the mixture and the resulting yellow mixture was stirred for 2 hours while ensuring continuous stirring. The reaction was then quenched with the addition of a sat. $NaHCO_3$ solution (4 mL) and the mixture was allowed to warm to rt NMR yields were determined by ^1H NMR analysis of unpurified reaction mixture using trimethoxybenzene as an internal standard.

b) Et_2O from the methylation step was removed under reduced pressure and THF (4 mL) was added before the addition of the Grignard solution in THF (1 mL).

Troubleshooting: Frequently Asked Questions

Question 1:

Does my source of MeOTf matter?

Answer:

We used commercial methyl triflate supplied by Oakwood Chemical. MeOTf from two additional sources was also used during the course of this study. Both resulted in inferior results (i.e. little to no dihydropyridine product was observed). This is presumed to be due to triflic acid as an impurity in these sources. Distillation of these MeOTf batches prior to use did increase the yield, but not substantially.

Question 2:

Can I use MeI to methylate pyridines?

Answer:

When methylpyridinium iodides are used in the Grignard addition reaction, the dihydropyridine products are observed in trace to poor yields.

Question 3:

Can I use MeI to methylate pyridines with an additive such as NaOTf to help solubilize the pyridinium?

Answer:

Yes, NaOTf (10 mol %) does help facilitate the reaction, but this results in poorer yields than when MeOTf as the methylating agent. Although we did not extensively investigate the effect of additives, NaOTf performed the best.

Question 4:

Why do amide-containing substrates require a separate methylating procedure?

Answer:

When amide-containing substrates were used in General Procedure A (alkylating in Et_2O), we observed diminished yields of dihydropyridines. We suspect that these conditions gave competitive alkylation of the amide vs. the pyridine. All four of the amide substrates surveyed gave quantitative alkylations in dichloromethane (General Procedure B).

Question 5:

When suspending the pyridinium salt in THF before the Grignard addition, does the reaction vessel have to be in a cooling bath?

Answer:

We found that small amount of residual MeOTf can rapidly polymerize THF at rt. This results in a gelatinous reaction mixture at –78 °C that has trouble stirring and significantly reduced yields of the dihydropyridine products. Cooling the reaction vessel to –78 °C before the addition of THF circumvents this issue.

Question 6:

Are there any indicative color changes during the addition of the Grignard reagent?

Answer:

We often observe that the reaction mixture changes to bright yellow upon the addition of the Grignard reagent. In multiple cases, the color did not change to bright yellow, it was either a different color or was a light yellow, and we obtained either a poor yield or the product was not observed. When the reaction mixture turned deep red, this typically resulted in a poor yield and significant decomposition. We used these color changes as quick diagnostic tests for the reaction's success.

Question 7:

How do you monitor Grignard addition reactions?

Answer:

We monitor reactions by TLC using standard silica plates and 9:1 $CHCl_3$:MeOH eluent. The resulting pyridiniums typically have R_f = ~0.25.

Question 7:

After quenching the reaction with a sat. solution of $NaHCO_3$, is it necessary to filter through celite?

Answer:

It is not necessary to filter through celite, but the removal of salts helps ease the work-up.

Question 8:

I obtained the dihydropyridine product, but the yield in not satisfactory for my purposes. What do you recommend I try to increase the isolated yield of the product?

Answer:

1. For relatively electron-rich pyridines, warming the reaction mixture was required to obtain satisfactory yields.

2. For pyridines lacking sensitive functional groups, increasing the Grignard reagent equivalency should help the yield.

3. The dihydropyridine may be light sensitive, try isolating and purifying in an environment with reduced lighting.

4. The dihydropyridine may oxidize fast, try isolating and purifying as fast as possible. Do not leave the dihydropyridine products out to ambient air.

5. The dihydropyridine products may be sensitive to silica, since silica is slightly acidic. Try using either basic silica or alumina.

Question 9:

Are the dihydropyridine products bench stable?

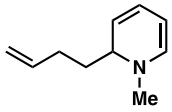
Answer:

It is presumed that all dihydropyridines isolated in this study potentially decompose upon standing at rt open to air. We have confirmed this with multiple examples. Most of the dihydropyrdines isolated in this study are stable for months when stored as solids in the fridge. More electron-rich dihydropyridines or those with aryl, alkenyl, and alkynyl substituents were stable when stored frozen in PhH.

Experimental Procedures and Characterization Data for Dihydropyridines

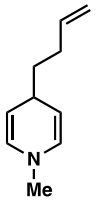
Compound 6a and 6b

The protocol of General Procedure A was followed on 1.00 mmol scale; however, the mixture was stirred at –78 °C for 2 h and then it was allowed to slowly warm to rt and it was stirred for another 4 h. The reaction did not go to completion as analyzed by TLC. The crude ^{1}H NMR indicates a 1.7:1 ratio of C2:C4 addition products (27% and 16% NMR yield, respectively). The resulting products are highly susceptible to oxidation and could not be isolated analytically pure. The crude mixture was analyzed by HRMS (DART): calc'd for $C_{10}H_{14}N^+$ $[M–H]^+$ 148.1121; found 148.1118.



6a

^{1}H NMR (400 MHz, CH_2Cl_2, selected peaks): δ 4.51 (ddd, J = 7.0, 5.5, 1.4 Hz, 1H), 3.95 (dt, J = 8.4, 4.5 Hz, 1H), 2.78 (s, 3H).

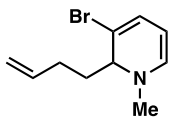


6b

^{1}H NMR (400 MHz, CH_2Cl_2, selected peaks): δ 4.31 (dd, *J* = 8.1, 3.7 Hz, 2H), 3.03–2.97 (m, 1H), 2.77 (s, 3H).

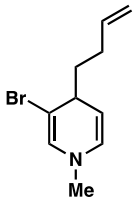
Compound S32a and S32b

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1.3:1 ratio of C2:C4 addition products (24% and 20% NMR yield, respectively). The resulting products are highly susceptible to oxidation and could not be isolated analytically pure. The crude mixture was analyzed by HRMS (DART): calc'd for $C_{10}H_{13}BrN^+$ $[M–H]^+$ 226.0226; found 226.0225.



S32a

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 6.21 (d, *J* = 6.2 Hz, 1H), 6.01 (d, *J* = 6.8 Hz, 1H), 4.50 (dd, J = 6.8, 6.2 Hz, 1H), 4.22 (t, J = 4.9 Hz, 1H), 2.85 (s, 3H).

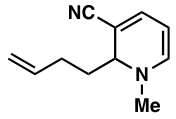


S32b

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 6.14 (d, *J* = 1.6 Hz, 1H), 4.31 (dd, *J* = 7.9, 4.1 Hz, 1H), 2.81 (s, 3H).

Compound S33a, S33b, and S36c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:1.6:6.3 ratio of C2:C4:C6 addition products (8%, 13%, 52% NMR yield, respectively). The products were purified by column chromatography (gradient 7:3→3:2 CH_2Cl_2:hexanes eluent, basic silica) to afford 19.9 mg (11% yield) of dihydropyridine **S33b** and 64.4 mg (39% yield) of dihydropyridine **S33c**. Dihydropyridine **S33a** was isolated but not in analytical purity despite repeated purification attempts.

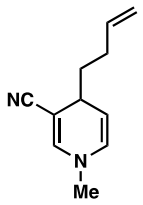


S33a

R_f = 0.32 (7:3 CH_2Cl_2:hexanes eluent, basic silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.67 (d, *J* = 6.4 Hz, 1H), 6.33 (d, *J* = 6.8 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.09 (dq, *J* = 17.0, 1.7 Hz, 1H), 5.01 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.77 (dd, *J* = 6.8, 6.4 Hz, 1H), 4.10 (t, *J* = 5.8 Hz, 1H), 3.01 (s, 3H), 2.24–2.18 (m, 2H), 1.87–1.78 (m, 1H), 1.66–1.57 (m, 1H).

HRMS (DART): calc'd for $C_{11}H_{13}N_2^+$ $[M–H]^+$ 173.1079; found 173.1060.

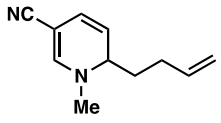


S33b

Physical State: Light yellow oil.

R_f = 0.46 (7:3 CH_2Cl_2:hexanes eluent, basic silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.51 (d, *J* = 1.6 Hz, 1H), 5.83 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.72 (dt, *J* = 8.1, 1.6 Hz, 1H), 5.04 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.95 (dq, *J* = 10.2 1.6 Hz, 1H), 4.63 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.26–3.18 (m, 1H), 2.94 (s, 3H), 2.22–2.05 (m, 2H), 1.66–1.51 (m, 2H).
^{13}C NMR (151 MHz; $CDCl_3$): δ 143.6, 138.5, 129.0, 121.6, 114.9, 105.7, 41.0, 37.3, 32.5, 29.9, 29.4.
HRMS (DART): calc'd for $C_{11}H_{13}N_2^+$ $[M–H]^+$ 173.1079; found 173.1060.

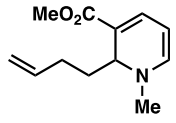


S33c

Physical State: Amber oil.
R_f = 0.53 (7:3 CH_2Cl_2:hexanes eluent, basic silica).
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (s, 1H), 5.91 (d, *J* = 9.8 Hz, 1H), 5.80 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.04 (dq, J = 16.9, 1.5 Hz, 1H), 4.99 (dq, J = 10.2, 1.5 Hz, 1H), 4.94 (dd, *J* = 9.8, 4.7 Hz, 1H), 4.11 (dt, J = 7.7, 4.7 Hz, 1H), 2.95 (s, 3H), 2.23–2.04 (m, 2H), 1.87–1.74 (m, 1H), 1.54–1.44 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 148.4, 137.7, 121.7, 121.6, 115.3, 112.9, 76.4, 58.3, 41.7, 32.8, 27.5.
HRMS (DART): calc'd for $C_{11}H_{13}N_2^+$ $[M–H]^+$ 173.1079; found 173.1060.

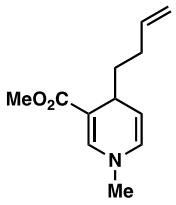
Compound 7a, 7b, and 7c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:1.6:8.9 ratio of C2:C4:C6 addition products (8%, 15%, and 73% respectively). The products were purified by flash column chromatography (gradient 9:1→4:1 hexanes:EtOAc, silica) to afford 129 mg (62% yield) of dihydropyridine **7c**.



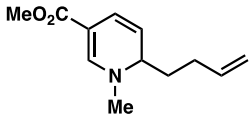
7a

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 7.13 (d, *J* = 6.6 Hz, 1H), 6.37 (d, *J* = 6.6 Hz, 1H), 4.52 (t, *J* = 6.2 Hz, 1H), 3.06 (s, 3H).



7b

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 7.11 (d, *J* = 1.6 Hz, 1H), 3.39 (dt, *J* = 6.9, 4.5 Hz, 1H), 3.00 (s, 3H).



7c

Physical State: Light amber oil.

R_f = 0.51 (7:3 hexanes:EtOAc eluent, silica).

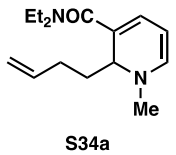
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (s, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.79 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.01 (dq, *J* = 17.0, 1.7 Hz, 1H), 4.95 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.92 (dd, *J* = 8.0, 3.4 Hz, 1H), 4.12 (dt, *J* = 5.6, 3.4 Hz, 1H), 3.66 (s, 3H), 2.98 (s, 3H), 2.20–2.04 (m, 2H), 1.83–1.74 (m, 1H), 1.51–1.43 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.1, 148.0, 138.1, 122.3, 115.0, 111.6, 96.4, 58.9, 50.7, 41.7, 33.0, 27.6.

HRMS (DART): calc'd for $C_{12}H_{16}NO_2^+$ $[M–H]^+$ 206.1176; found 206.1185.

Compound S34a and S34b

The protocol of General Procedure B was followed on 1.00 mmol scale; however, the mixture was stirred for 2 h at –78 ºC and then it was allowed to warm to rt and stirred for an additional 2.5 h. The crude ^{1}H NMR indicates a 2.8:1 ratio of C2:C4 addition products (68% and 24% NMR yield, respectively). The products were purified by flash column chromatography (7:3 hexanes:EtOAc eluent, alumina) to afford 61.9 mg (25% yield) of dihydropyridine **S34a** and 25.3 mg (10% yield) of dihydropyridine **S34b**. Consistently, dihydropyridines **S34a** and **S34b** afforded partial decomposition upon purification.

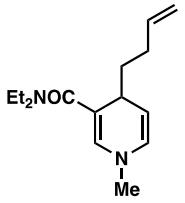


S34a

Physical State: Amber-yellow oil.

R_f = 0.54 (7:3 hexanes:EtOAc eluent, alumina).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.16–6.13 (m 2H), 5.78 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 4.98 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.92 (dq, *J* = 10.3, 1.6 Hz, 1H), 4.69 (t, *J* = 6.4 Hz, 1H), 4.46 (t, *J* = 6.1 Hz, 1H), 3.57–3.49 (m, 2H), 3.45–3.36 (m, 2H), 2.98 (s, 3H), 2.07–2.01 (m, 2H), 1.68–1.48 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 6H).
^{13}C NMR (151 MHz; $CDCl_3$): δ 172.1, 139.1, 138.6, 125.6, 114.79, 114.62, 92.4, 58.6, 41.9, 41.4, 31.3, 28.9, 13.7.
HRMS (DART): calc'd for $C_{15}H_{23}N_2O^+$ $[M–H]^+$ 247.1805; found 247.1799.

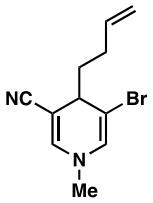


S34b

Physical State: Dark yellow oil.
R_f = 0.39 (7:3 hexanes:EtOAc eluent, alumina).
^{1}H NMR (400 MHz; $CDCl_3$) δ 6.08 (d, *J* = 1.4 Hz, 1H), 5.83–5.72 (m, 2H), 4.95 (dq, *J* = 17.3, 1.7 Hz, 1H), 4.87 (d, *J* = 10.2 Hz, 1H), 4.57 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.44–3.37 (m, 5H), 2.87 (s, 3H), 2.13–1.96 (m, 2H), 1.41–1.35 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 6H).
^{13}C NMR (151 MHz; $CDCl_3$): δ 172.6, 139.2, 133.3, 130.0, 114.2, 107.9, 103.6, 41.1, 40.7, 38.1, 33.7, 29.7, 13.7.
HRMS (DART): calc'd for $C_{15}H_{23}N_2O^+$ $[M–H]^+$ 247.1805; found 247.1806.

Compound S35b and S35c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:4.7 ratio of C4:C6 addition products (15% and 65% NMR yield, respectively). The products were purified by flash column chromatography (7:3 hexanes:CH_2Cl_2 eluent, basic silica) to afford 14.8 mg (6% yield) of dihydropyridine **S35b** and 135 mg (54% yield) of dihydropyridine **S35c**.



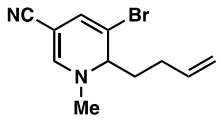
S35b

Physical State: Light amber oil.
R_f = 0.25 (7:3 hexanes:CH_2Cl_2 eluent, basic silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.54 (d, *J* = 1.3 Hz, 1H), 6.16 (d, *J* = 1.3 Hz, 1H), 5.87 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.07 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.97 (dq, *J* = 10.3, 1.6 Hz, 1H), 3.57 (t, *J* = 4.1 Hz, 1H), 2.99 (s, 3H), 2.20–2.11 (m, 2H), 1.87–1.76 (m, 1H), 1.71–1.61 (m, 1H).

^{13}C NMR (101 MHz; $CDCl_3$): δ 142.4, 138.1, 130.4, 120.1, 115.0, 103.7, 81.0, 40.97, 40.80, 32.8, 28.8.

HRMS (DART): calc'd for $C_{11}H_{15}BrNO^+$ $[M–H]^+$ 251.0178; found 251.0186.



S35c

Physical State: Beige solid.

R_f = 0.17 (7:3 hexanes:CH_2Cl_2 eluent, basic silica).

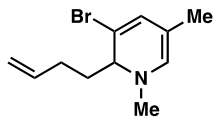
^{1}H NMR (500 MHz; $CDCl_3$) δ 6.78 (s, 1H), 6.27 (s, 1H), 5.82 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.07 (dd, *J* = 16.9, 1.2 Hz, 1H), 5.01 (d, *J* = 10.3 Hz, 1H), 4.33 (t, *J* = 4.2 Hz, 1H), 2.98 (s, 3H), 2.32–2.10 (m, 2H), 1.89–1.72 (m, 2H).

^{13}C NMR (126 MHz; $CDCl_3$): δ 147.1, 137.3, 124.1, 120.1, 115.5, 104.3, 77.1, 65.1, 42.0, 30.1, 27.8.

HRMS (DART): calc'd for $C_{11}H_{12}BrN_2^+$ $[M–H]^+$ 251.0178; found 251.0191.

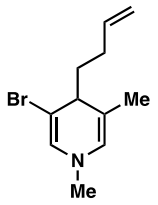
Compound S36a, S36b, and S37b

The protocol of General Procedure A was followed on 1.00 mmol scale; however, the mixture was stirred at –78 °C for 2 h and then it was warmed to –40 ºC and stirred for an additional 2 h. The reaction was then allowed to warm to rt for 2 h, for a total of 6 h of reaction time. The reaction did not go to completion as analyzed by TLC. The crude ^{1}H NMR indicates a 1:12 ratio of C2:C4 addition products (5% and 58% NMR yield, respectively). The product was purified by flash column chromatography (19:1 hexanes:Et_2O eluent, silica) to afford 49.7 mg (<21% yield) of partially pure dihydropyridine **S36b**. This product was unable to be isolated in analytical purity. Upon standing, dihydropyridine **S36b** oxidizes to pyridinium **S37b**. A mixture of dihydropyridine **S36b** and pyridinium **S37b** was purified by flash column chromatography (9:1 $CHCl_3$:MeOH eluent, silica) to afford an analytical sample of pyridinium **S37b**.



S36a

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 4.04 (t, *J* = 5.2 Hz, 1H).



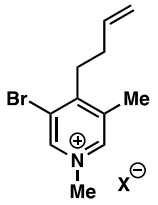
S36b

Physical State: Amber oil.

R_f = 0.71 (9:1 hexanes:EtOAc, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (s, 1H), 5.61 (s, 1H), 5.87 (ddt, J = 17.1, 10.1, 6.6 Hz, 1H), 5.00 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.91 (dq, *J* = 10.1, 1.7 Hz, 1H), 3.34 (br s, 1H), 2.78 (s, 3H), 2.10–1.89 (m, 2H), 1.78–1.67 (m, 1H), 1.54 (s, 3H), 1.57–1.46 (m, 1H).

HRMS (DART): calc'd for $C_{11}H_{15}BrNO^+$ $[M–H]^+$ 240.0382; found 240.0393.



S37b

Physical State: Brown solid.

R_f = 0.11 (9:1 $CHCl_3$:MeOH eluent, silica).

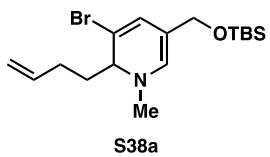
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 9.69 (s, 1H), 5.82–5.69 (m, 1H), 5.04–4.95 (m, 2H), 4.64 (s, 3H), 3.00–2.90 (m, 2H), 2.53 (s, 3H), 2.27–2.17 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.3, 144.8, 144.7, 138.3, 135.1, 124.5, 117.1, 47.8, 32.6, 30.9, 17.6.

HRMS (DART): calc'd for $C_{11}H_{15}BrNO^+$ $[M–H]^+$ 240.0382; found 240.0400.

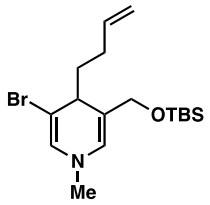
Compound S38a and S38b

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:3.6 ratio of C2:C4 addition products (15% and 55% NMR yield, respectively). The mixture was purified by flash column chromatography (19:1 hexanes:Et_2O eluent, alumina) to afford 141 mg (38% yield) of dihydropyridine **S38b**.



S38a

^{1}H NMR (400 MHz; CD_2Cl_2, selected peaks) δ 6.28 (s, 1H), 5.98 (s, 1H), 4.19 (t, J = 4.9 Hz, 1H), 0.94 (s, 9H), 0.12 (s, 6H).



S38b

Physical State: Brown oil.

R_f = 0.62 (19:1 hexanes:Et_2O eluent, alumina).

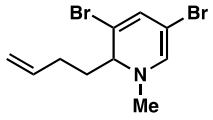
^{1}H NMR (400 MHz; $CDCl_3$) δ 6.17 (d, J = 1.4 Hz, 1H), 5.93–5.83 (m, 2H), 5.01 (dq, J = 17.1, 1.9 Hz, 1H), 4.92 (ddt, J = 10.0, 1.9, 1.1 Hz, 1H), 3.99 (ABq, J_{AB} = 12.5 Hz, $\Delta\nu_{AB}$ = 30.8 Hz, 2H), 3.50 (t, J = 3.6 Hz, 1H), 2.84 (s, 3H), 2.12–1.97 (m, 2H), 1.79–1.71 (m, 1H), 1.56–1.47 (m, 1H), 0.90 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (126 MHz; $CDCl_3$): δ 139.5, 132.7, 128.2, 114.0, 110.3, 99.3, 64.3, 42.1, 40.4, 30.5, 28.9, 26.1, 18.6, –5.12, –5.14.

HRMS (DART): calc'd for $C_{17}H_{29}BrNOSi^+$ $[M–H]^+$ 370.1196; found 370.1163.

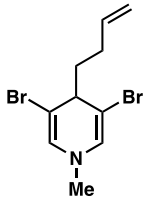
Compound S39a and S39b

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:2.8 ratio of C2:C4 addition products (24% and 66% NMR yield, respectively). The crude filtrate was dried with Na_2SO_4 instead of $MgSO_4$. The products were purified by flash column chromatography (hexanes eluent, alumina) to afford 94.8 mg (31% yield) of dihydropyridine **S39b**.



S39a

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 6.26 (d, J = 1.0 Hz, 1H), 4.06 (t, J = 5.2 Hz, 1H), 2.86 (s, 3H).



S39b

Physical State: Dark amber oil.

R_f = 0.34 (hexanes eluent, alumina).

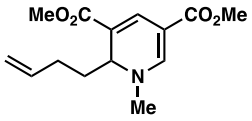
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (s, 2H), 5.90 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.06 (ddt, 17.0, 2.1, 1.6 *J* = Hz, 1H), 4.95 (ddt, 10.2, 2.1, 1.2 *J* = Hz, 1H), 3.71 (t, *J* = 3.6 Hz), 2.85 (s, 3H), 2.11–2.03 (m, 2H), 1.80–1.73 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.0, 132.0, 114.4, 97.3, 48.3, 40.3, 30.2, 28.5.

HRMS (DART): calc'd for $C_{10}H_{12}Br_2N^+$ $[M–H]^+$ 303.9331; found 303.9345.

Compound S40a and S40b

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 5.9:1 ratio of C2:C4 addition products (85% and 7% NMR yield, respectively). The products were purified by flash column chromatography (19:1 CH_2Cl_2:Et_2O eluent, silica) to afford 220 mg (83% yield) of dihydropyridine **S40a** and 15.9 mg (6% yield) of dihydropyridine **S40b**.



S40a

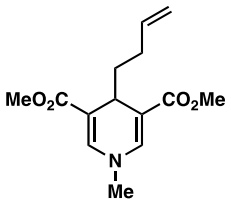
Physical State: Yellow solid.

R_f = 0.48 (19:1 CH_2Cl_2:Et_2O eluent, silica).

^{1}H NMR (600 MHz; $CDCl_3$) δ 7.64 (s, 1H), 7.51 (s, 1H), 5.76 (ddt, *J* = 16.9, 10.4, 6.5 Hz, 1H), 5.00 (dd, *J* = 16.9, 1.5 Hz, 1H), 4.94 (d, *J* = 10.4 Hz, 1H), 4.60 (t, *J* = 5.1 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.19 (s, 3H), 2.15–1.99 (m, 2H), 1.74–1.61 (m, 2H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 166.7, 166.4, 150.5, 137.8, 133.6, 115.1, 109.0, 98.1, 58.1, 51.5, 51.1, 42.9, 31.9, 28.2.

HRMS (DART): calc'd for $C_{14}H_{18}NO_4^+$ $[M–H]^+$ 264.1230; found 264.1221.



S40b

Physical State: Light yellow oil.

R_f = 0.52 (19:1 CH_2Cl_2:Et_2O eluent, silica).

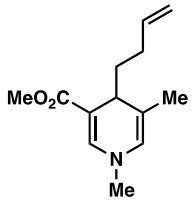
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.11 (s, 2H), 5.78 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 4.96 (ddt, *J* = 16.9, 2.0, 1.6 Hz, 1H), 4.88 (ddt, *J* = 10.3, 2.0, 1.6 Hz, 1H), 3.91 (t, *J* = 4.9 Hz, 1H), 3.73 (s, 6H), 3.16 (s, 3H), 1.98–1.92 (m, 2H), 1.51–1.46 (m, 2H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 167.8, 140.1, 139.3, 114.1, 107.0, 51.4, 41.6, 35.4, 30.4, 28.9.

HRMS (DART): calc'd for $C_{14}H_{18}NO_4^+$ $[M–H]^+$ 264.1230; found 264.1221.

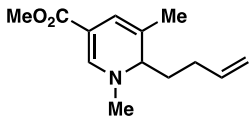
Compound S41b and S41c

The protocol of General Procedure A was followed on 1.00 mmol scale; however, the mixture was stirred at –78 °C for 3 h. The crude ^{1}H NMR indicates a 1:16 ratio of C4:C6 addition products (5% and 78% NMR yield, respectively). The product was purified by flash column chromatography (4:1 hexanes:EtOAc eluent, silica) to afford 156 mg (70% yield) of dihydropyridine **S41c**.



S41b

^{1}H NMR (400 MHz; $CDCl_3$, selected peaks) δ 7.14 (d, *J* = 1.4 Hz, 1H), 5.66 (t, *J* = 1.4 Hz, 1H), 3.40 (t, *J* = 4.0 Hz, 1H).



S41c

Physical State: Orange oil.

R_f = 0.27 (4:1 hexanes:EtOAc eluent, silica).

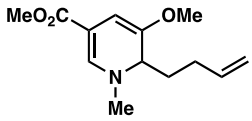
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.22 (s, 1H), 6.20 (s, 1H), 5.80 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.00 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.94 (br d, *J* = 10.3, 1.6 Hz, 1H), 4.05 (t, *J* = 3.8 Hz, 1H), 3.66 (s, 3H), 2.98 (s, 3H), 2.22–2.14 (m, 1H), 2.11–2.01 (m, 1H), 1.76–1.58 (m, 5H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 167.2, 146.0, 138.3, 119.1, 118.4, 114.8, 96.8, 63.3, 50.7, 41.7, 29.8, 27.9, 20.7.

HRMS (DART): calc'd for $C_{13}H_{18}NO_2^+$ $[M–H]^+$ 220.1332; found 220.1336.

Compound S42c

The protocol of General Procedure A was followed on 1.00 mmol scale; however, the mixture was stirred for 12 h at –78 ºC then warmed to –40 ºC and stirred for an additional 11 h. The reaction did not go to completion as analyzed by TLC. The crude ^{1}H NMR indicates a >20:1 ratio of **S42c** to other regioisomers. The product was purified by flash column chromatography (7:3 hexanes:EtOAc eluent, silica) to afford 109 mg (46% yield) of dihydropyridine **S42c**.



S42c

Physical State: Amber Oil.

R_f = 0.50 (7:3 hexanes:EtOAc eluent, silica).

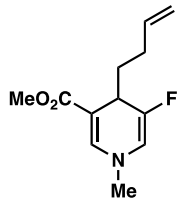
^{1}H NMR (600 MHz; $CDCl_3$) δ 7.11 (s, 1H), 5.79 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.56 (s, 1H), 4.99 (dq, *J* = 17.0, 1.7 Hz, 1H), 4.93 (dq, *J* = 10.3, 1.7 Hz, 1H), 4.10 (t, *J* = 4.3 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 2.98 (s, 3H), 2.14–1.99 (m, 2H), 1.73–1.67 (m, 2H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 167.4, 145.1, 142.3, 138.3, 114.7, 95.7, 91.5, 60.8, 55.1, 50.8, 41.1, 29.9, 27.9.

HRMS (DART): calc'd for $C_{13}H_{18}BrNO_3^+$ $[M–H]^+$ 236.1281; found 236.1295.

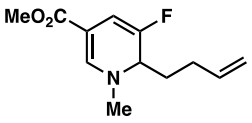
Compound S43b and S43c

The protocol of General Procedure A was followed on 1.00 mmol scale; however, the mixture was stirred at –78 °C for 3 h. The crude ^{1}H NMR indicates a 1:16 ratio of C4:C6 addition products. The products were purified by flash column chromatography (9:1 hexanes:EtOAc→4:1 hexanes:EtOAc eluent, silica) to afford 163 mg (72% yield) of dihydropyridine **S43c**.



S43b

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 7.09 (s, 1H).



S43c

Physical State: Amber oil.

R_f = 0.22 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.15 (s, 1H), 6.10 (d, *J* = 13.4 Hz, 1H), 5.80 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.03 (dq, *J* = 17.0, 1.7 Hz, 1H), 4.97 (ddt, *J* = 10.3, 3.1, 1.7 Hz, 1H), 4.37 (dt, *J* = 7.9, 3.1 Hz, 1H), 3.67 (s, 3H), 3.00 (s, 3H), 2.25–2.04 (m, 2H), 1.83–1.66 (m, 2H).

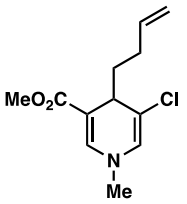
^{13}C NMR (101 MHz; $CDCl_3$): δ 166.6 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 147.7 (d, $^1J_{C\text{-}F}$ = 257.5 Hz), 144.3, 137.6, 115.3, 100.6 (d, $^2J_{C\text{-}F}$ = 17.9 Hz), 93.4 (d, $^3J_{C\text{-}F}$ = 7.0 Hz), 59.4 (d, $^2J_{C\text{-}F}$ = 33.0 Hz) 51.0, 41.1 (d $^4J_{C\text{-}F}$ = 1.4 Hz), 29.7 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 27.5.

^{19}F NMR (376 MHz; $CDCl_3$): δ –123.5.

HRMS (DART): calc'd for $C_{12}H_{15}FNO_2^+$ $[M–H]^+$ 224.1081; found 224.1085.

Compound S44b and S44c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:9.6 ratio of C4:C6 addition products. The products were purified by flash column chromatography (7:3 hexanes:EtOAc eluent, silica) to afford 12.2 mg (5% yield) of dihydropyridine **S43b** and 122.9 mg (51% yield) of dihydropyridine **S44c**.



S44b

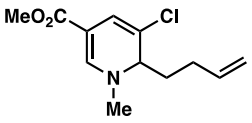
Physical State: Yellow oil.

R_f = 0.41 (7:3 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.10 (d, *J* = 1.4 Hz, 1H), 6.06 (d, *J* = 1.4 Hz, 1H), 5.83 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.00 (dq, *J* = 17.0, 1.7 Hz, 1H), 4.91 (ddt, *J* = 10.4, 2.3, 1.7 Hz, 1H), 3.71 (t, *J* = 4.1 Hz, 1H), 3.69 (s, 3H), 3.02 (s, 3H), 2.05–2.00 (m, 2H), 1.74–1.58 (m, 2H).

^{13}C NMR (101 MHz; $CDCl_3$): δ 168.0, 140.9, 139.1, 127.5, 115.6, 114.2, 99.9, 92.1, 51.2, 41.0, 39.0, 32.2, 29.1.

HRMS (DART): calc'd for $C_{12}H_{15}ClNO_2^+$ $[M–H]^+$ 240.0786; found 240.0800.



S44c

Physical State: Brown oil.

R_f = 0.66 (7:3 hexanes:EtOAc eluent, silica).

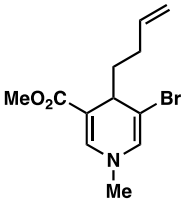
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.25 (s, 1H), 6.57 (s, 1H), 5.80 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.02 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.96 (dq, *J* = 10.3, 1.6 Hz, 1H), 4.27 (t, *J* = 4.1 Hz, 1H), 3.66 (s, 3H), 3.00 (s, 3H), 2.28–2.19 (m, 1H), 2.13–2.04 (m, 1H), 1.88–1.70 (m, 2H).

^{13}C NMR (101 MHz; $CDCl_3$): δ 166.2, 146.1, 137.7, 121.3, 115.2, 114.7, 96.2, 64.1, 50.9, 41.7, 29.7, 27.6.

HRMS (DART): calc'd for $C_{12}H_{15}ClNO_2^+$ $[M–H]^+$ 240.0786; found 240.0802.

Compound 26b and 26c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:8.5 ratio of C4:C6 addition products (9% and 78% NMR yield, respectively). The products were purified by flash column chromatography (4:1 hexanes:EtOAc eluent, silica) to afford 35.7 mg (12% yield) of dihydropyridine **26b** and 225 mg (78% yield) of dihydropyridine **26c**.



26b

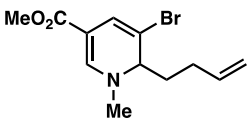
Physical State: Grey solid.

R_f = 0.41 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, *J* = 1.5 Hz, 1H), 6.19 (d, *J* = 1.5 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.00 (ddt, *J* = 17.1, 2.1, 1.4, 1H), 4.91 (ddt, *J* = 10.2, 2.1, 1.4, 1H), 3.78 (t, *J* = 4.1 Hz, 1H), 3.69 (s, 3H), 3.02 (s, 3H), 2.06–1.99 (m, 2H), 1.73–1.56 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.9, 140.9, 139.1, 130.3, 114.2, 105.1, 99.4, 51.2, 41.0, 40.2, 32.5, 28.9.

HRMS (DART): calc'd for $C_{12}H_{15}BrNO_2^+$ $[M–H]^+$ 284.0281; found 284.0301.



26c

Physical State: Brown solid.

R_f = 0.20 (4:1 hexanes:EtOAc eluent, silica).

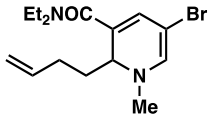
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.29 (s, 1H), 6.79 (s, 1H), 5.82 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1H), 5.04 (ddt, *J* = 17.0, 1.6, 1.5 Hz, 1H), 4.98 (ddt, *J* = 10.3, 1.5, 1.3 Hz, 1H), 4.36 (t, *J* = 4.1 Hz, 1H), 3.68 (s, 3H), 3.01 (s, 3H), 2.32–2.23 (m, 1H), 2.16–2.06 (m, 1H), 1.92–1.84 (m, 1H), 1.80–1.71 (m, 1H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 166.0, 146.4, 137.7, 125.4, 115.2, 103.8, 97.1, 65.4, 50.9, 41.9, 30.1, 27.6.

HRMS (DART): calc'd for $C_{12}H_{15}BrNO_2^+$ $[M–H]^+$ 284.0281; found 284.0293.

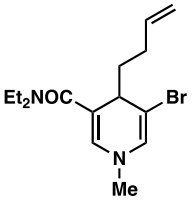
Compound 41a, 41b, and 41c

The protocol of General Procedure B was followed on 1.00 mmol scale; however, the reaction was stirred at –78 °C for 3 h. The crude ^{1}H NMR indicates a 1.4:5.8:1 ratio of C2:C4:C6 addition products (17%, 55%, and 12% NMR yield, respectively). The product was purified by flash column chromatography (1:1 hexanes:EtOAc, silica) to afford 110 mg (34% yield) of dihydropyridine **41b**. Consistently, dihydropyridines **41b** afforded partial decomposition upon purification.



41a

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 6.32 (d, *J* = 1.1 Hz, 1H), 6.15 (d, *J* = 1.1 Hz, 1H), 4.37 (t, *J* = 6.4 Hz, 1H), 2.99 (s, 3H).



41b

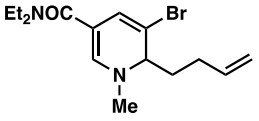
Physical State: Amber oil.

R_f = 0.41 (1:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (d, *J* = 1.4 Hz, 1H), 6.13 (d, *J* = 1.4 Hz, 1H), 5.83 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.00 (dq, J = 16.9, 1.7 Hz, 1H), 4.92 (ddt, J = 10.2, 2.3, 1.3 Hz, 1H), 3.78 (dd, *J* = 5.3, 3.6 Hz, 1H), 3.49–3.373 (m, 4H), 2.92 (s, 3H), 2.13–2.04 (m, 2H), 1.76–1.66 (m, 1H), 1.48–1.37 (m, 1H), 1.15 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.1, 138.8, 132.2, 131.2, 114.3, 106.5, 101.1, 42.1, 41.0, 40.6, 33.6, 29.4, 13.6.

HRMS (DART): calc'd for $C_{15}H_{22}BrN_2O^+$ $[M–H]^+$ 325.0910; found 325.0909.

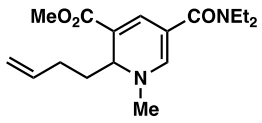


41c

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 6.90 (s, 1H), 6.45 (d, *J* = 1.0 Hz, 1H), 4.29 (t, *J* = 4.5 Hz, 1H), 2.98 (s, 3H).

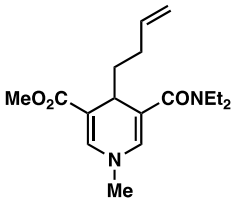
Compound S45a, S45b, and S45c

The protocol of General Procedure B was followed on 1.00 mmol scale; however, the mixture was stirred at –78 °C for 3 h and it was then warmed to rt and allowed to stir for an additional hour. The crude ^{1}H NMR indicates a 1:4.5:6.8 ratio of C2:C4:C6 addition products (5%, 22%, and 35% NMR yield, respectively). The products were purified by flash column chromatography (7:3 hexanes:EtOAc→7:3 CH_2Cl_2:EtOAc eluent, silica) to afford 84.3 mg (28% yield) of dihydropyridine **S45b** and 108 mg (35% yield) of dihydropyridine **S45c**.



S45a

^{1}H NMR (400 MHz; $CDCl_3$, selected peaks) δ 7.33 (s, 1H), 7.32 (s, 1H), 4.59 (t, *J* = 5.7 Hz, 1H).



S45b

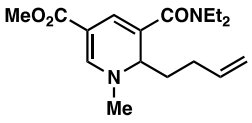
Physical State: Light yellow oil.

***R*$_f$** = 0.47 (7:3 CH_2Cl_2:EtOAc eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.13 (d, *J* = 1.2 Hz, 1H), 6.18 (d, *J* = 1.2 Hz, 1H), 5.76 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 4.95 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.87 (dq, *J* = 10.4, 1.6 Hz, 1H), 3.71–3.68 (m, 4H), 3.48–3.32 (m, *J* = 7.5 Hz, 4H), 3.09 (s, 3H), 2.01 (q, *J* = 7.6 Hz, 2H), 1.58–1.49 (m, 1H), 1.41–1.32 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 171.2, 168.2, 140.9, 139.0, 130.8, 115.1, 114.2, 102.7, 51.2, 41.3, 36.4, 33.3, 29.5, 13.6.

HRMS (DART): calc'd for $C_{34}H_{51}N_4O_6^+$ [2•M–H]$^+$ 611.3803; found 611.3855.



S45c

Physical State: Amber oil.

R_f = 0.38 (7:3 CH_2Cl_2:EtOAc eluent, silica).

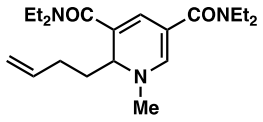
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.38 (s, 1H), 6.70 (s, 1H), 5.75 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.02–4.93 (m, 2H), 4.66 (t, *J* = 5.3 Hz, 1H), 3.70 (s, 3H), 3.57–3.39 (m, 4H), 3.13 (s, 3H), 2.12–1.95 (m, 2H), 1.78–1.68 (m, 1H), 1.54–1.46 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 170.7, 166.9, 148.2, 137.6, 124.1, 115.41, 115.24, 96.4, 59.4, 50.9, 42.5, 41.5, 32.2, 28.2, 13.6.

HRMS (DART): calc'd for $C_{34}H_{51}N_4O_6^+$ [2•M–H]$^+$ 611.3803; found 611.3847.

Compound S46a and S46b

The protocol of General Procedure B was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1.9:1 ratio of C2:C4 addition products (63% and 33% NMR yield, respectively). The products were purified by flash column chromatography (99:1 CH_2Cl_2:EtOH→19:1 CH_2Cl_2:EtOH eluent, silica) to afford 205.3 mg (59% yield) of dihydropyridine **S46a** and 54.9 mg (16% yield) of dihydropyridine **S46b**.



S46a

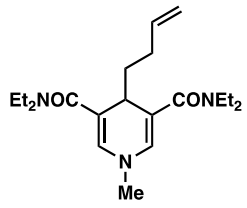
Physical State: Bright yellow oil.

R_f = 0.35 (99:1 CH_2Cl_2:EtOH eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.01 (s, 1H), 6.44 (s, 1H), 5.78 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.00 (dd, *J* = 17.0, 1.4 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 4.48 (t, *J* = 5.8 Hz, 1H), 3.49–3.33 (m, 8H), 3.10 (s, 3H), 2.12–2.03 (m, 2H), 1.75–1.54 (m, 2H), 1.16 (q, *J* = 7.3 Hz, 12H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 170.9, 170.2, 144.6, 138.0, 125.4, 115.1, 113.6, 101.3, 59.3, 42.4, 41.6, 41.37, 41.35, 31.9, 28.9, 13.79, 13.70.

HRMS (DART): calc'd for $C_{40}H_{65}BrN_6O_4^+$ [M–H]$^+$ 693.5062; found 693.5078.



S46b

Physical State: Light yellow oil.

R_f = 0.28 (99:1 CH_2Cl_2:EtOH eluent, silica).

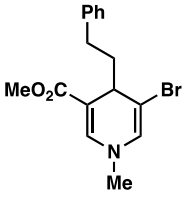
^{1}H NMR (400 MHz; $CDCl_3$) δ 6.21 (s, 2H), 5.74 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 4.96 (br dd, *J* = 17.0, 1.6 Hz, 1H), 4.87 (d, *J* = 10.3 Hz, 1H), 3.69 (t, *J* = 5.9 Hz, 1H), 3.52–3.38 (m, 8H), 3.02 (s, 3H), 2.02 (q, *J* = 7.6 Hz, 2H), 1.43–1.37 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 12H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 172.0, 138.8, 131.9, 114.4, 110.7, 41.13, 41.07, 37.2, 36.0, 29.9, 13.7.

HRMS (DART): calc'd for $C_{40}H_{65}BrN_6O_4^+$ $[M–H]^+$ 693.5062; found 693.5073.

Compound 27b and 27c

The protocol of General Procedure A was followed on 1.84 mmol scale. The crude ^{1}H NMR indicates a 1:11 ratio of C4:C6 addition products. The products were purified by column chromatography (4:1 hexanes:EtOAc, silica) to afford 49.1 mg (8% yield) of dihydropyridine **27b** and 538 mg (87% yield) of dihydropyridine **27c**.



27b

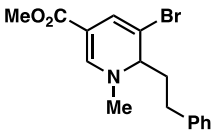
Physical State: Colorless oil.

R_f = 0.35 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.23 (m, 2H), 7.20–7.13 (m, 4H), 6.23 (d, *J* = 1.4 Hz, 1H), 3.86 (t, *J* = 4.0 Hz, 1H), 3.70 (s, 3H), 3.04 (s, 3H), 3.26–3.52 (m, 2H), 1.99–1.82 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.9, 142.8, 141.0, 130.4, 128.6, 128.3, 125.7, 105.3, 99.5, 51.3, 41.0, 40.5, 35.0, 31.0.

HRMS (DART): calc'd for $C_{16}H_{17}BrNO_2^+$ $[M–H]^+$ 334.0437; found 334.0450.



27c

Physical State: Orange solid.

R_f = 0.25 (4:1 hexanes:EtOAc eluent, silica).

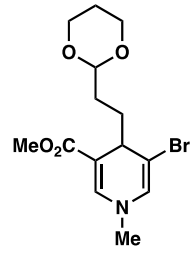
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.26 (m, 3H), 7.22–7.16 (m, 3H), 6.85 (s, *J* = 1.0 Hz, 1H), 4.43 (t, *J* = 3.9 Hz, 1H), 3.69 (s, 3H), 2.99 (s, 3H), 2.90–2.80 (m, 1H), 2.72–2.61 (m, 1H), 2.16–2.06 (m, 1H), 2.04–2.93 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.1, 146.6, 141.5, 128.6, 128.5, 126.1, 125.7, 104.1, 97.1, 65.6, 51.0, 41.8, 32.7, 29.7.

HRMS (DART): calc'd for $C_{16}H_{17}BrNO_2^+$ $[M–H]^+$ 334.0437; found 334.0454.

Compound 28b, 28c, and S47c

The protocol of General Procedure A was followed on 1 mmol scale. The crude ^{1}H NMR indicates a 1:2.6 of C4:C6 addition products. The products were purified by flash column chromatography (gradient 4:1→7:3→3:2→1:1 hexanes:EtOAc, silica) to afford 74.1 mg (23% yield) of dihydropyridine **28b** and 203.9 mg (59% yield) of dihydropyridine **28c**. Upon standing, dihydropyridine **28c** oxidizes to pyridinium **S47c**. A mixture of dihydropyridine **28c** and pyridinium **S47c** was purified by flash column chromatography (4:1 EtOAc:MeOH eluent, silica) to afford pyridinium **S47c**. Single crystals of pyridinium **S47c** were grown by slow evaporation of a saturated EtOAc solution.



28b

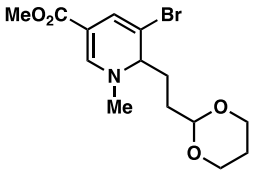
Physical State: Amber oil.

R_f = 0.44 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 1.4 Hz, 1H), 6.17 (d, *J* = 1.4 Hz, 1H), 4.52–4.48 (m, 1H), 4.11–4.04 (m, 2H), 3.81–3.77 (m, 1H), 3.77–3.69 (m, 2H), 3.66 (s, 3H), 2.97 (s, 3H), 2.13–1.99 (m, 1H), 1.74–1.52 (m, 4H), 1.35–1.28 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.7, 141.0, 130.4, 104.7, 99.0, 67.05, 67.04, 51.2, 41.0, 40.0, 30.2, 27.5, 26.0.

HRMS (DART): calc'd for $C_{14}H_{19}BrNO_4^+$ $[M–H]^+$ 344.0492; found 345.0495.



28c

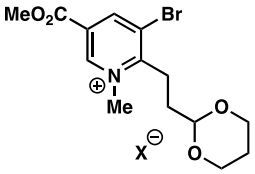
Physical State: Amber oil.

R_f = 0.31 (1:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.28 (s, 1H), 6.73 (d, J = 1.2 Hz, 1H), 4.54–4.50 (m, 1H), 4.41–4.38 (m, 1H), 4.06–4.01 (m, 2H), 3.75–3.69 (m, 2H), 3.61 (s, 3H), 2.98 (s, 3H), 2.04–1.93 (m, 1H), 1.88–1.69 (m, 4H), 1.66–1.56 (m, 1H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ 166.0, 147.0, 126.0, 104.3, 102.2, 97.0, 65.8, 51.0, 42.1, 29.4, 26.4, 25.4.

HRMS (DART): calc'd for $C_{14}H_{19}BrNO_4^+$ $[M–H]^+$ 344.0492; found 345.0500.



S47C

Physical State: Beige solid.

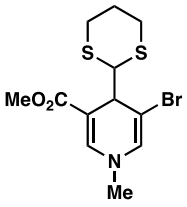
R_f = 0.15 (4:1 EtOAc:MeOH eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.85 (s, 1H), 4.87 (s, 3H), 4.70 (t, J = 3.7 Hz, 1H), 4.01–3.95 (m, 5H), 3.75–3.67 (m, 2H), 3.56–3.48 (m, 2H), 2.11–2.04 (m, 2H), 2.04–1.94 (m, 2H).

HRMS (DART): calc'd for $C_{14}H_{19}BrNO_4^+$ $[M–H]^+$ 344.0492; found 345.0493.

Compound 29b and 29c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:1.1 ratio of C4:C6 addition products. The products were purified by flash column chromatography (7:3 hexanes:EtOAc, silica) to afford 29.6 mg (8% yield) of dihydropyridine **29b** and 36.1 mg (10% yield) of dihydropyridine **29c**.



29b

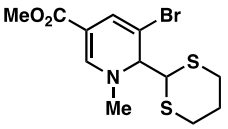
Physical State: Amber oil.

R_f = 0.12 (7:3 hexanes:EtOAc eluent, silica).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.39 (s, 1H), 4.16 (ABq, J_{AB} = 4.1 Hz, $\Delta\nu_{AB}$ = 17.6 Hz, 2H), 3.72 (s, 3H), 3.11 (s, 3H), 2.88–2.78 (m, 4H), 2.09–2.01 (m, 1H), 1.90–1.79 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.5, 141.0, 131.9, 98.5, 87.6, 55.6, 51.4, 45.8, 41.2, 31.6, 31.0, 26.1.

HRMS (DART): calc'd for $C_{12}H_{15}BrNO_2S_2^+$ $[M–H]^+$ 347.9722; found 347.9727.



29c

Physical State: Yellow film.

R_f = 0.20 (7:3 hexanes:EtOAc eluent, silica).

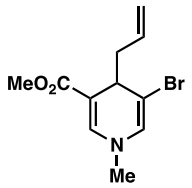
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (s, 1H), 6.89 (s, 1H), 4.40 (ABq, J_{AB} = 3.9 Hz, $\Delta\nu_{AB}$ = 32.6 Hz, 2H), 3.67 (s, 3H), 3.26 (s, 3H), 2.93–2.81 (m, 4H), 2.13–2.05 (m, 1H), 1.92–1.82 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 125.7, 145.3, 126.4, 99.8, 99.4, 69.5, 51.8, 51.1, 44.8, 31.1, 30.1, 25.7.

HRMS (DART): calc'd for $C_{12}H_{15}BrNO_2S_2^+$ $[M–H]^+$ 347.9722; found 347.9738.

Compound 30b and 30c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:3.9 ratio of C4:C6 addition products. The products were purified by flash column chromatography (4:1 hexanes:EtOAc, silica) to afford 22.1 mg (8% yield) of dihydropyridine **30b** and 44.1 mg (16% yield) of dihydropyridine **30c**. Dihydropyridines **30b** and **30c** both decompose rapidly upon standing under ambient conditions.



30b

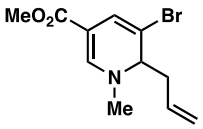
Physical State: Yellow oil.

R_f = 0.39 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 1.35 Hz, 1H), 6.17 (d, *J* = 1.5 Hz, 1H), 5.82–5.70 (m, 1H), 5.07–4.98 (m, 2H), 3.81 (t, *J* = 4.1 Hz, 1H), 3.69 (s, 3H), 2.99 (s, 3H), 2.42–2.26 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.6, 140.7, 134.6, 130.1, 117.4, 104.7, 99.0, 51.0, 40.8, 40.5, 37.6.

HRMS (DART): calc'd for $C_{11}H_{13}BrNO_2^+$ $[M–H]^+$ 270.0124; found 270.0139.



30c

Physical State: Yellow oil that rapidly turns green.

R_f = 0.28 (4:1 hexanes:EtOAc eluent, silica).

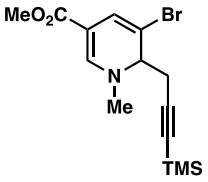
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 6.76 (s, 1H), 5.89 (ddt, J = 14.8, 10.0, 7.4 Hz, 1H), 5.15 (d, *J* = 14.8 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.33 (t, *J* = 4.4 Hz, 1H), 3.66 (s, 3H), 3.00 (s, 3H), 2.58–2.48 (m, 1H), 2.44–2.35 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 146.1, 132.4, 125.3, 119.1, 103.4, 97.2, 65.8, 50.8, 41.9, 35.5.

HRMS (DART): calc'd for $C_{11}H_{13}BrNO_2^+$ $[M–H]^+$ 270.0124; found 270.0139.

Compound 31c and S48c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicated a complex mixture; and therefore, the crude ratio of products could not be determined. However, dihydropyridine **31c** is the major isomer in the crude ^{1}H NMR. The product was purified by flash column chromatography (7:3 hexanes:Et_2O eluent, silica) to afford 56.7 mg (17% yield) of a 9:1 mixture of dihydropyridine **31c** and dihydropyridine **S48c**, respectively. Dihydropyridine **31c** decomposes rapidly upon standing under ambient conditions.



31c

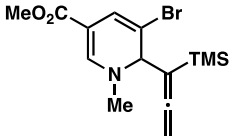
Physical State: Dark amber film.

R_f = 0.27 (7:3 hexanes:Et_2O eluent, silica).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 1H), 6.79 (d, *J* = 1.1 Hz, 1H), 4.38 (ddd, J = 6.8, 3.6, 1.1 Hz, 1H), 3.67 (s, 3H), 3.21 (s, 3H), 2.64 (dd, *J* = 17.4, 6.8 Hz, 1H), 2.52 (dd, *J* = 17.4, 3.6 Hz, 1H), 0.11 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$, peaks of major and minor isomers): δ 212.1, 165.8, 145.5, 125.6, 124.9, 103.0, 101.8, 98.6, 96.4, 87.8, 70.4, 70.0, 65.7, 43.1, 41.9, 22.7, –0.14, –0.21.

HRMS (DART): calc'd for $C_{14}H_{19}BrNO_2Si^+$ $[M–H]^+$ 340.0363; found 340.0368.

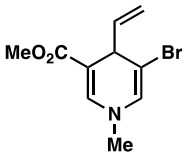


S48c

^{1}H NMR (500 MHz, $CDCl_3$, selected peaks): δ 7.25 (d, *J* = 1.1 Hz, 1H), 6.72 (d, *J* = 1.1 Hz, 1H), 4.97 (s, 1H), 4.51 (ABq, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 19.9 Hz, 2H), 2.89 (s, 3H), 0.15 (s, 9H).

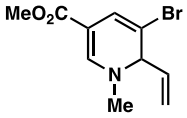
Compound 32b and 32c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:10 ratio of C4:C6 addition products. The product was purified by flash column chromatography (4:1 hexanes:EtOAc eluent, silica) to afford 150 mg (58% yield) of dihydropyridine **32c**. This product was unstable and decomposes upon standing under ambient conditions. Efforts were made to keep the product under an inert atmosphere whenever possible, and it is required to work expeditiously to isolate pure material in good yield.



32b

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 7.09 (d, J = 1.5 Hz, 1H), 6.55 (d, *J* = 1.4 Hz, 1H).



32c

Physical State: Amber oil that darkens rapidly.

R_f = 0.21 (4:1 hexanes:EtOAc eluent, silica).

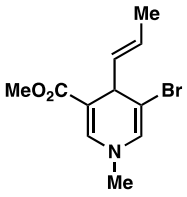
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (s, 1H), 6.72 (s, 1H), 5.80 (ddd, *J* = 17.1, 9.9, 8.0 Hz, 1H), 5.25 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 9.9 Hz, 1H), 4.51 (d, J = 8.0 Hz, 1H), 3.65 (s, 3H), 2.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 145.5, 132.2, 124.3, 118.7, 104.0, 96.7, 68.9, 50.9, 41.4.

HRMS (DART): calc'd for $C_{10}H_{11}BrNO_2^+$ $[M–H]^+$ 255.9968; found 255.9970.

Compound 33b and 33c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:2.2 ratio of C4:C6 addition products. The product was purified by flash column chromatography (4:1 hexanes:EtOAc, silica) to afford 64.0 mg (23% yield) of dihydropyridine **33b** and 146 mg (54% yield) dihydropyridine **33c**.



33b

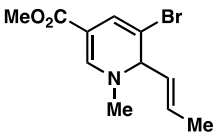
Physical State: Orange solid.

R_f = 0.42 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 1.5 Hz, 1H), 6.56 (dd, *J* = 1.5, 1.3 Hz, 1H), 4.94 (app s, 1H), 4.88–4.86 (m, 1H), 4.74–4.72 (m, 1H), 3.69 (s, 3H), 2.94 (s, 3H), 1.77 (d, *J* = 1.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.2, 143.4, 141.7, 112.8, 108.8, 82.7, 63.0, 51.5, 41.5, 17.7.

HRMS (DART): calc'd for $C_{11}H_{15}BrNO_2^+$ $[M+H]^+$ 272.0267; found 272.0260.



33c

Physical State: Yellow solid.

R_f = 0.25 (4:1 hexanes:EtOAc eluent, silica).

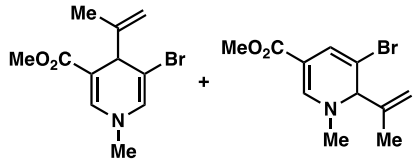
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 6.83 (s, 1H), 4.98 (s, 1H), 4.94 (q, *J* = 1.3 Hz, 1H), 4.68 (s, 1H), 3.70 (s, 3H), 2.85 (s, 3H), 1.76 (d, J = 1.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 146.3, 140.1, 125.3, 116.1, 105.1, 95.7, 72.9, 50.9, 41.3, 16.1.

HRMS (DART): calc'd for $C_{11}H_{15}BrNO_2^+$ $[M+H]^+$ 272.0267; found 272.0260.

Compound 34b and 34c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:1 ratio of C4:C6 addition products. The product was purified by flash column chromatography (4:1 hexanes:EtOAc, silica) to afford 183 mg (68% yield) of a 1:1 mixture of dihydropyridine **34b** and dihydropyridine **34c**.



1:1 34b:34c

Physical State: Amber oil.

R_f = 0.42 (4:1 hexanes:EtOAc eluent, silica).

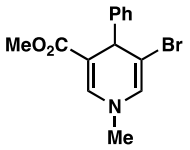
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.23 (s, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 5.76–5.67 (m, 2H), 5.52–5.43 (m, 2H), 4.96 (d, *J* = 9.9 Hz, 1H), 4.45 (d, *J* = 8.4 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 2.91 (s, 3H), 2.89 (s, 3H), 1.76 (d, *J* = 7 Hz, 3H), 1.76 (d, *J* = 7 Hz, 3H), 1.73 (d, *J* = 6.6 Hz, 3H), 1.73 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.11, 166.10, 145.7, 145.5, 130.5, 129.2, 125.9, 125.7, 124.03, 123.95, 105.3, 105.0, 96.5, 96.1, 68.4, 62.0, 50.9, 41.3, 41.1, 17.6, 13.3.

HRMS (DART): calc'd for $C_{11}H_{13}BrNO_2^+$ $[M–H]^+$ 270.0124; found 270.0128.

Compound 35b and 35c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:1.3 ratio of C4:C6 addition products. The product was purified by flash column chromatography (gradient 4:1→3:2 hexanes:EtOAc eluent, silica) to afford 92.2 mg (30% yield) of dihydropyridine **35b** and 104 mg (34% yield) of dihydropyridine **35c**.



35b

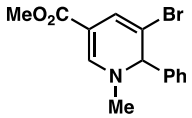
Physical State: Amber oil.

R_f = 0.33 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.35 (m, 6H), 6.89 (d, *J* = 1.0 Hz, 1H), 5.11 (s, 1H), 3.72 (s, 3H), 2.82 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.1, 145.5, 139.2, 128.9, 128.3, 127.7, 123.9, 106.9, 95.9, 70.3, 51.0, 41.7.

HRMS (DART): calc'd for $C_{14}H_{14}BrNO_2^+$ $[M–H]^+$ 306.0124; found 306.0126.



35c

Physical State: Yellow solid.

R_f = 0.24 (9:1 hexanes:EtOAc eluent, silica).

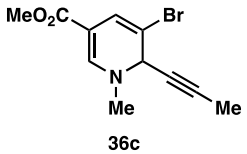
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.41 (m, 2H), 7.35–7.27 (m, 3 H), 7.20 (d, *J* = 1.3 Hz, 1H), 6.60 (t, *J* = 1.3 Hz, 1H), 5.43 (app s, 1H), 3.65 (s, 3H), 2.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.1, 143.2, 140.8, 136.6, 128.8, 128.5, 127.0, 111.5, 82.4, 61.2, 51.6, 41.6.

HRMS (DART): calc'd for $C_{14}H_{14}BrNO_2^+$ $[M–H]^+$ 306.0124; found 306.0126.

Compound 36c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates >20:1 ratio of **36c** to other isomers. The product was purified by flash column chromatography (4:1 hexanes:EtOAc, silica) to afford 203 mg (75% yield) of dihydropyridine **36c**.



36c

Physical State: Light yellow solid.

R_f = 0.27 (4:1 hexanes:EtOAc eluent, silica).

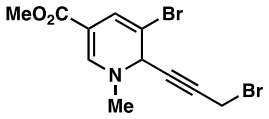
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 6.76 (s, 1H), 4.89 (q, J = 2.0 Hz, 1H), 3.67 (s, 3H), 3.04 (s, 3H), 1.85 (d, J = 2.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 165.9, 144.9, 124.4, 102.7, 97.6, 82.6, 74.5, 57.6, 51.0, 41.4, 3.8.

HRMS (DART): calc'd for $C_{11}H_{13}BrNO_2^+$ $[M+H]^+$ 270.0124; found 270.0099.

Compound 37c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates >20:1 ratio of **37c** to other isomers. The product was purified by flash column chromatography (4:1 hexanes:EtOAc eluent, silica) to afford 154.1 mg (44% yield) of dihydropyridine **37c**.



37c

Physical State: Dark brown solid.

R_f = 0.22 (4:1 hexanes:EtOAc eluent, silica).

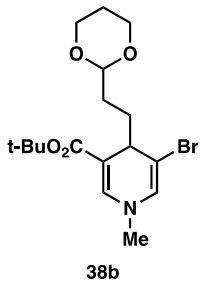
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (s, 1H), 6.79 (s, 1H), 5.01 (s, 1H), 3.92 (app t, 2H), 3.69 (s, 3H), 3.05 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.7, 144.8, 125.1, 101.4, 98.0, 81.4, 81.3, 57.7, 51.2, 41.6, 13.8.

HRMS (DART): calc'd for $C_{11}H_{10}Br_2NO_2^+$ $[M–H]^+$ 345.9079; found 345.9086.

Compound 38b and 38c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:1.5 ratio of C4:C6 addition products. The products were purified by column chromatography (4:1 hexanes:EtOAc eluent, silica) to afford 94.2 mg (24% yield) of dihydropyridine **38b** and 140 mg (36% yield) of dihydropyridine **38c**.



38b

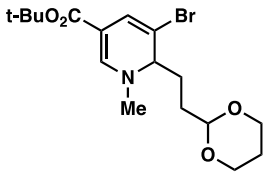
Physical State: Yellow oil.

R_f = 0.41 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.00 (s, 1H), 6.16 (s, 1H), 4.50 (t, J = 4.6 Hz, 1H), 4.12–4.05 (m, 2H), 3.78–3.70 (m, 3H), 2.96 (s, 3H), 2.11–2.02 (m, 1H), 1.72–1.64 (m, 1H), 1.64–1.54 (m, 4H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.8, 140.2, 130.5, 104.5, 102.9, 101.1, 79.5, 67.01, 67.00, 40.9, 40.2, 30.4, 28.5, 27.6, 26.0.

HRMS (DART): calc'd for $C_{17}H_{25}BrNO_4^+$ $[M–H]^+$ 386.0961; found 386.0974.



38c

Physical State: Yellow oil.

R_f = 0.29 (4:1 hexanes:EtOAc eluent, silica).

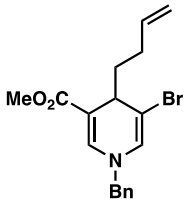
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 1H), 6.70 (s, 1H), 4.53 (dd, J = 5.5, 3.9 Hz, 1H), 4.35 (t, J = 3.8 Hz, 1H), 4.10–4.04 (m, 3H), 3.77–3.70 (m, 2H), 2.96 (s, 3H), 2.11–1.98 (m, 2H), 1.88–1.75 (m, 3H), 1.70–1.63 (m, 1H), 1.43 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.1, 145.9, 126.0, 102.0, 98.5, 79.0, 67.0, 65.4, 41.8, 29.1, 25.9, 25.1.

HRMS (DART): calc'd for $C_{17}H_{25}BrNO_4^+$ $[M–H]^+$ 386.0961; found 386.0970.

Compound 39b and 39c

The protocol of General Procedure C was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a 1:2.2 ratio of C4:C6 addition products (22% and 48% NMR yield, respectively). The products were purified by flash column chromatography (9:2 hexanes:EtOAc eluent, silica) to afford 71.9 mg (20% yield) of dihydropyridine **39b** and 169 mg (47% yield) of dihydropyridine **39c**.



39b

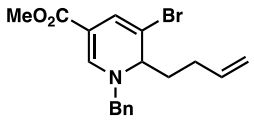
Physical State: Colorless oil.

R_f = 0.38 (9:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.29 (m, 3H), 7.27 (d, J = 1.4 Hz, 1H), 7.22–7.18 (m, 2H), 6.23 (d, J = 1.4 Hz, 1H), 5.83 (ddt, J = 16.9, 10.2, 6.5 Hz, 1H), 4.99 (dq, J = 16.9, 1.5 Hz, 1H), 4.92 (ddd, J = 10.2, 3.3, 1.5 Hz, 1H), 4.35 (s, 2H), 3.82 (t, J = 4.0 Hz, 1H), 3.70 (s, 3H), 2.06–1.98 (m, 2H), 1.77–1.58 (m, 2).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.8, 140.5, 139.0, 136.5, 129.4, 129.1, 128.4, 127.3, 114.3, 105.7, 100.2, 57.8, 51.3, 40.5, 32.5, 28.9.

HRMS (DART): calc'd for $C_{18}H_{19}BrNO_2^+$ $[M–H]^+$ 360.0594; found 360.0591.



39c

Physical State: Colorless oil.

R_f = 0.28 9:1 (hexanes:EtOAc eluent, silica).

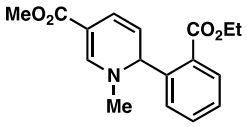
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.44 (br s, 1H), 7.41–7.31 (m, 3H), 7.26–7.21 (m, 2H), 6.82 (d, *J* = 1.0 Hz, 1H), 5.80 (ddt, J = 16.9, 10.2, 6.5 Hz, 1H), 5.04 (dq, J = 16.9, 1.4 Hz, 1H), 4.98 (dt, J = 10.2, 1.4 Hz, 1H), 4.39 (s, 2H), 4.29 (t, J = 4.4 Hz, 1H), 3.69 (s, 3H), 2.35–2.23 (m, 1H), 2.23–2.11 (m, 1H), 1.88–1.68).

^{13}C NMR (151 MHz; $CDCl_3$): δ 166.1, 145.9, 137.7, 135.5, 129.3, 128.5, 127.5, 125.4, 115.3, 104.3, 98.4, 63.0, 58.3, 51.1, 30.6, 27.9.

HRMS (DART): calc'd for $C_{18}H_{19}BrNO_2^+$ $[M–H]^+$ 360.0594; found 360.0591.

Compound 40c

The protocol of General Procedure A was followed on 1.00 mmol scale. The crude ^{1}H NMR indicates a >20:1 ratio of **40c** to other regioisomers. The product was purified by flash column chromatography (3:2 hexanes:EtOAc eluent, silica) to afford 35.2 mg (12% yield) of dihydropyridine **40c**.



40c

Physical State: Yellow oil.

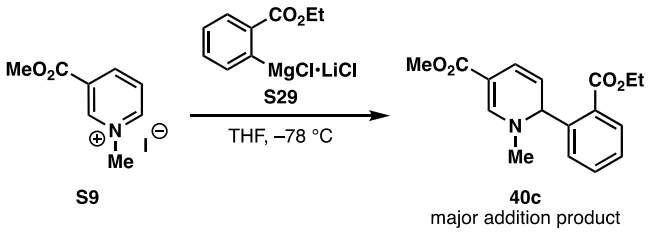
R_f = 0.40 (3:2 hexanes:EtOAc eluent, silica).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 9.6, 1.6 Hz, 1H), 7.76 (dd, *J* = 9.6, 1.6 Hz, 1H), 7.55 (dt, *J* = 9.6, 1.6, 1H), 7.46 (app s, 1H), 7.33 (dt, *J* = 9.6, 1.6 Hz, 1H), 6.35 (dt, *J* = 10.0, 1.4 Hz, 1H), 6.09 (d, *J* = 4.0 Hz, 1H), 5.20 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.41–4.32 (m, 2H), 3.70 (s, 3H), 2.82 (s, 3H), 1.40 (t, *J* = 8.9 Hz, 3H).

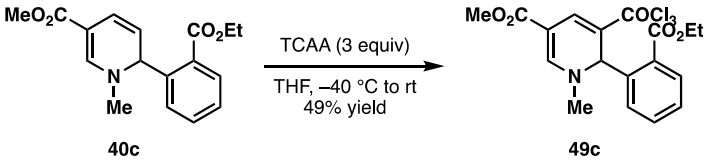
^{13}C NMR (126 MHz, $CDCl_3$): δ 167.2, 167.1, 148.0, 144.2, 133.3, 130.3, 128.7, 127.7, 127.5, 119.9, 114.4, 95.4, 61.4, 60.1, 50.8, 42.1, 14.4.

HRMS (DART): calc'd for $C_{17}H_{18}NO_4^+$ $[M–H]^+$ 300.1230; found 300.1238.

Additional Experiments



A 30 ml test tube charged with methylpyridinium **S9** (137 mg, 1.00 mmol) and THF (3.2 mL) was cooled to –78 °C. To the suspension was added Grignard reagent **S29** (1.84 mL, 0.54 M in THF, 1.0 mmol) dropwise over 5 min resulting in a 0.2 M solution. The mixture stirred for 2 h. The reaction was then quenched with a sat. solution of $NaHCO_3$ (4 mL) and filtered through a small pad of celite. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford a yellow oil. Analysis of the crude material by ^1H NMR indicated that dihydropyridine **40c** was the major addition product.

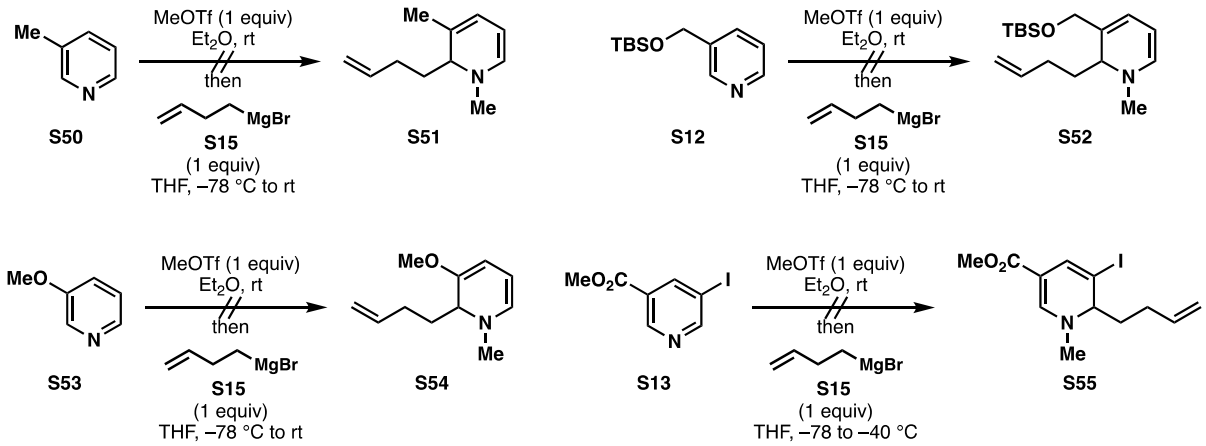


A test tube containing a mixture of dihydropyridine **40c** (17.8 mg, 59.1 μmol) in THF (0.59 mL) cooled to –40 °C was charged with TCAA (32.4 μL, 0.177 mmol) in one portion. The mixture was stirred at –40 °C for 5 min and then warmed to rt and stirred for 1.5 h. The reaction was then quenched with a sat. solution of Na_2CO_3 (2.0 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (4:1 hexanes:EtOAc eluent, silica) to afford dihydropyridine **S49c** (12.5 mg, 49% yield) as a bright yellow-orange film. The characterization data for dihydropyridine **S49c** was previously reported.[11]

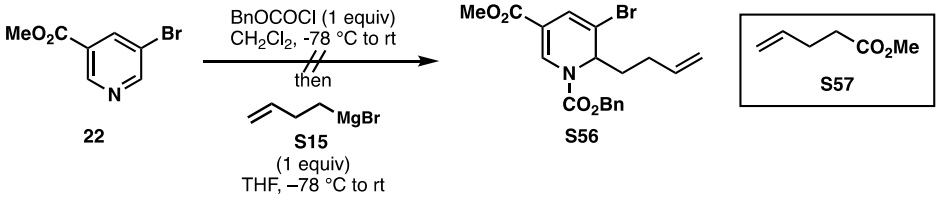
R_f = 0.31 (4:1 hexanes:EtOAc eluent, silica).

[11] Bennasar, M.-L.; Roca, T.; Monerris, M.; Juan, C.; Bosch, J. Synthesis of 4-Functionalized Aryl-3,5-diacyl-1,4-dihydropyridines. *Tetrahedron* **2002**, 58, 8099–8106.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 1.2 Hz, 1H), 7.84-7.78 (m, 2H), 7.76 (app s, 1H), 7.49 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.34 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.76 (s, 1H), 4.60-4.38 (m, 2H), 3.79 (s, 3H), 3.19 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H).

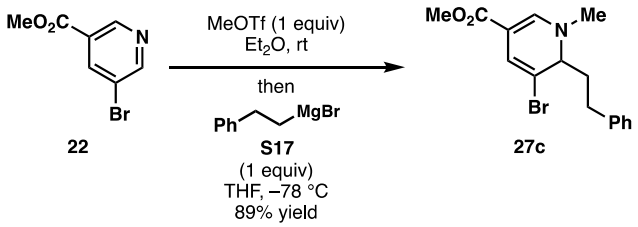


Substrates **S50**, **S12**, **S53**, and **S13** all failed to produce dihydropyridine products when subjected to the standard reaction conditions.



Using pyridine **22**, an acylation/Grignard addition procedure failed to afford dihydropyridine **S56** after numerous attempts and conditions. Similar results were observed when using either MeOCOCl or BnOCOCl. We do observe ester **S57** in some crude reaction mixtures. We were unable to obtain conclusive evidence for the formation of the acylpyridinium, and are therefore unsure if the Grignard reagent adds into the chloroformate or the 1-acylpyridinium.

Experimental Procedures and Characterization Data for the Synthesis of Insecticide 3

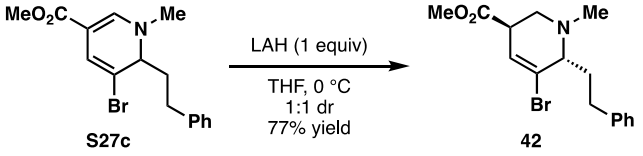


A 100 mL round-bottom flask was charged with pyridine **22** (2.16 g, 10.00 mmol) and Et_2O (10 mL). The vessel was placed in a rt water bath and was charged with MeOTf (1.13 mL, 10.0 mmol) dropwise. The reaction mixture was stirred until the starting material was consumed, as determined by TLC. The reaction was completed within 1 h. The reaction mixture was then concentrated under reduced pressure. The reaction vessel was cooled to –78 °C, then the mixture was charged with THF (40 mL) taking care to wash the solids off the sides of the flask. The mixture was then charged with a phenylmagnesium bromide solution (**S17**, 10.0 mL, 1.0 M in THF) dropwise over 5 min resulting in a 0.2 M solution. The mixture was allowed to stir for 2 h. The mixture was quenched upon the disappearance of the pyridinium by TLC (9:1 $CHCl_3$:MeOH, R_f = 0.26). The reaction was then quenched with a sat. solution of $NaHCO_3$ (40 mL) and filtered through a small pad of celite. The resulting mixture was charged with water (40 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were then washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford an orange oil. The crude mixture was purified by flash column chromatography (4:1 hexanes:EtOAc eluent, silica) to afford dihydropyridine **27c** (3.00 g, 89% yield). The characterization data for dihydropyridine **27c** is reported above (page 51).

Physical State: Orange solid.

R_f = 0.25 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.26 (m, 3H), 7.22–7.16 (m, 3H), 6.85 (s, J = 1.0 Hz, 1H), 4.43 (t, J = 3.9 Hz, 1H), 3.69 (s, 3H), 2.99 (s, 3H), 2.90–2.80 (m, 1H), 2.72–2.61 (m, 1H), 2.16–2.06 (m, 1H), 2.04–2.93 (m, 1H).



To a stirring suspension of dihydropyridine **27c** (1.01 g, 3.00 mmol) in THF (20 mL) at 0 °C was added LAH (114 mg, 3.00 mmol) in 4 portions over 10 min. The reaction mixture was stirred at 0 °C for 45 min. Upon completion by TLC, the mixture was cooled to –78 °C and was then charged with EtOAc (10 mL) dropwise. The mixture was stirred at 0 °C for 10 min and was then cooled to –78 °C. The mixture was then charged with a sat. Rochelle solution (10 mL) dropwise. The mixture was stirred at 0 °C for 10 min and then it was stirred at rt for an additional 10 min. To the mixture was charged with water (40 mL) and the product was extracted with EtOAc (3 x 40 mL). The combined organic layers washed with brine (20 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (4:1 hexanes:EtOAc eluent, silica) to afford tetrahydropyridine **42** (776 mg, 77% yield) as a 1:1 mixture of diastereomers.

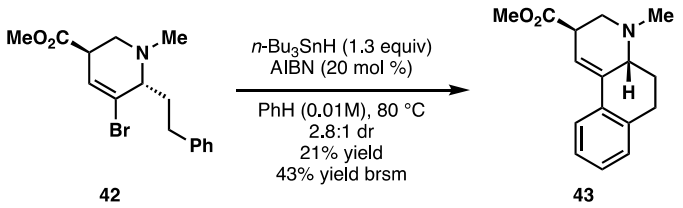
Physical State: Light yellow oil.

R_f = 0.34 (4:1 hexanes:EtOAc eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.31–7.26 (m, 4H), 7.24–7.15 (m, 6H), 6.37 (d, *J* = 1.6 Hz, 1H), 6.24 (d, *J* = 3.1 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.48–3.40 (m, 1H), 3.28–3.16 (m, 3H), 3.02–2.90 (m, 3H), 2.90–2.76 (m, 2H), 2.72–2.60 (m, 3H), 2.48 (s, 3H), 2.44 (s, 3H), 2.20–1.95 (m, 3H), 1.91–1.79 (m, 1H).

^{13}C NMR (151 MHz; $CDCl_3$): δ 172.4, 172.1, 142.4, 142.1, 128.7, 128.6, 128.5, 128.4, 128.0, 127.0, 126.0, 125.88, 125.86, 124.7, 66.0, 65.7, 52.34, 52.26, 49.9, 46.6, 43.1, 42.4, 42.3, 39.7, 33.2, 32.5, 32.3, 30.8.

HRMS (DART): calc'd for $C_{16}H_{21}BrNO_2^+$ $[M+H]^+$ 338.0750; found 338.0761.



42 43

In a 300 mL Schlenk flask, a solution of vinyl bromide **42** (338 mg, 1.00 mmol), *n*-Bu_3SnH (350 µL, 1.30 mmol), and AIBN (32.8 mg, 200 µmol) in PhH (100 mL) was deoxygenated by subjecting the mixture to 3 freeze-pump-thaw cycles. The solution was then placed under a N_2 environment and was then stirred and heated at reflux for 24 h. After this period of time, the mixture was concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (4:1 hexanes:EtOAc → EtOAc eluent, silica) to afford tetrahydropyridine **42** (347 mg) and tricycle **43** (108 mg, 21% yield, 43% yield brsm) as a 2.8:1 mixture of diastereomers.

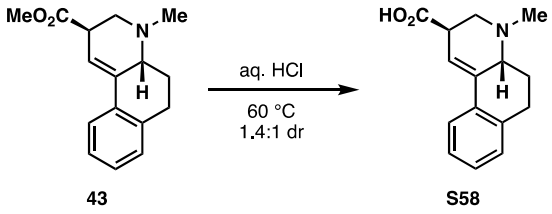
Physical State: Colorless oil.

R_f = 0.43 (EtOAc eluent, silica).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.64–7.60 (m, 1H), 7.59–7.55 (m, 0.33H), 7.21–7.14 (m, 2.66H), 7.12–7.07 (m, 1.33), 6.40 (br s, 1H), 6.38 (d, *J* = 5.5 Hz, 0.33H), 3.76 (s, 3H), 3.72 (s, 0.99H), 3.70–3.63 (m, 1H), 3.35 (d, *J* = 11.3 Hz, 0.33H), 3.22 (dd, *J* = 11.4, 5.6 Hz, 1H), 3.22–3.16 (m, 0.33H), 2.96–2.87 (m, 2.66H), 2.81 (d, *J* = 12.6 Hz, 1H), 2.75 (d, *J* = 12.7 Hz, 0.33H), 2.59–2.50 (m, 1.33H), 2.52 (s, 3H), 2.48 (s, 0.99H), 2.45–2.37 (m, 1.33H), 1.65–1.53 (m, 1.33H).

^{13}C NMR (126 MHz; $CDCl_3$): δ 173.5, 172.9, 137.9, 137.3, 136.1, 135.9, 133.7, 133.3, 129.0, 128.9, 127.72, 127.67, 126.3, 126.2, 124.7, 124.6, 116.0, 115.4, 62.9, 62.7, 54.1, 53.2, 52.24, 52.18, 43.5, 43.2, 42.3, 41.7, 28.80, 28.78, 28.51, 28.47.

HRMS (DART): calc'd for $C_{16}H_{20}NO_2^+$ $[M+H]^+$ 258.1489; found 258.1488.



43 **S58**

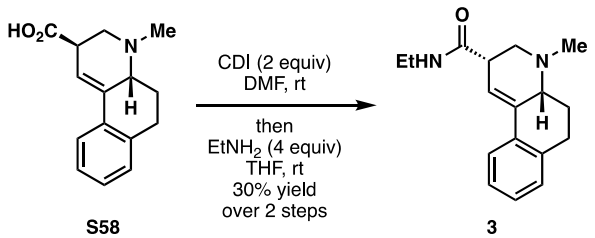
In a scintillation vial sealed with a Teflon screw cap, tricycle **43** (35.7 mg, 139 μmol) dissolved in a 2.7 M HCl solution (1.3 mL) was heated and stirred at 60 °C for 1 h. Upon completion as determined by TLC, the mixture was concentrated under reduced pressure affording a colorless film. The resulting material was charged with a solution of 1M NaOH until the solution shifted to pH 6. The solution was purified by flash column chromatography (4:1 MeCN:H_2O, silica) to afford acid **S58** (28.7 mg) as a 1.4:1 mixture of diastereomers.

Physical State: White powder.

R_f = 0.28 (4:1 MeCN:H_2O eluent, silica).

^{1}H NMR (400 MHz; D_2O, selected peaks) δ 7.65–7.57 (m, 1.7H), 7.31–7.21 (m, 3.4H), 7.19–7.12 (m, 1.7H), 6.50 (d, *J* = 5.0 Hz, 0.7H), 6.53 (s, 1H), 3.10 (s, 2.1H), 3.08 (s, 3H).

HRMS (DART): calc'd for $C_{15}H_{18}NO_2^+$ $[M+H]^+$ 244.1332; found 244.1331.



S58 **3**

A 9 mL tube containing a stirring solution of acid **S58** (20.0 mg) in DMF (0.82 mL) was charged with CDI (26.7 mg, 164 μmol) in one portion. The mixture stirred at rt for 1.5 h and was then charged with a solution of $EtNH_2$ (123 μL, 2 M in THF, 247 μmol). The reaction mixture stirred at rt for 1 h. Upon completion as determined by TLC, the mixture was charged with a sat. solution of $NaHCO_3$ (2 mL). The product was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude mixture was purified by column chromatography to afford amide **3** (7.8 mg, 30% yield over 2 steps) as a single diastereomer.

Physical State: Colorless film.

R_f = 0.19 (97:3 CH_2Cl_2:MeOH, silica).

^{1}H NMR (400 MHz; benzene-d_6) δ 7.55 (br s, 1H), 7.34 (d, J = 7.4 Hz, 1H), 7.04 (dt, J = 7.2, 1.1 Hz, 1H), 6.98 (dt, J = 7.2, 1.1 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.38 (d, J = 6.0 Hz, 1H), 3.30–3.19 (m, 2H), 3.13–3.06 (m, 1H), 2.71 (d, J = 11.6 Hz, 1H), 2.58–2.52 (m, 2H), 2.34 (dq, J = 12.1, 2.5 Hz, 1H), 2.09 (dd, J = 11.6, 4.0 Hz, 1H), 2.03–1.96 (m, 1H), 1.98 (s, 3H), 1.37–1.20 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H).

^{13}C NMR (126 MHz; benzene-d_6): δ 172.9, 137.3, 135.7, 133.8, 128.9, 128.4, 126.6, 125.1, 118.2, 62.5, 54.2, 45.0, 42.7, 34.2, 29.0, 28.7, 15.2.

HRMS (DART): calc'd for $C_{17}H_{23}N_2O^+$ $[M+H]^+$ 271.1805; found 271.1823.

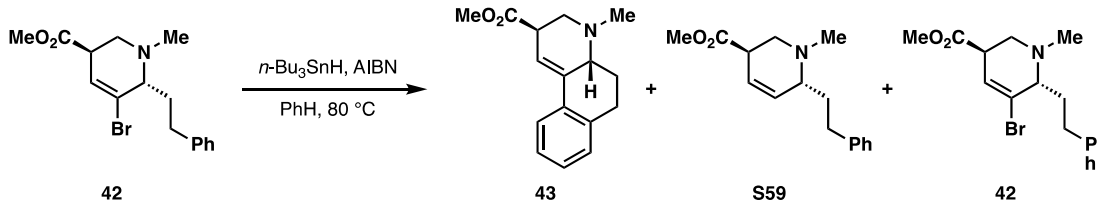


Table S4. Radical annulation optimization affording tricycle **43**.[a]

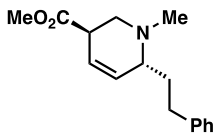
Entry	*n*-Bu_3SnH (equiv)	AIBN (mol %)	Conc. (M)	Hours	% Yield 43:S59:42
1	1.30	20	0.1	24	9:13:5
2	1.30	20	0.03	24	13:0:46
3	1.30	20	0.01	24	23:0:44
4	1.30	20	0.01	48	13:0:53
5[c]	1.30	20	0.01	48	13:0:61
6	1.30	40	0.01	24	17:0:50
7	2.60	20	0.01	24	25:0:37
8[d]	1.95	30	0.01	48	9:0:15

a) In a 100 mL Schlenk flask, a solution of vinyl bromide **42** (67.4 mg, 0.200 mmol), *n*-Bu_3SnH (69.9 µL, 0.260 mmol), and AIBN (6.6 mg, 40.0 µmol) in PhH (2.0 mL) was deoxygenated by subjecting the mixture to 3 freeze-pump-thaw cycles. The solution was then placed under a N_2 environment and was then stirred and heated at reflux for 24 h. After this period of time, the mixture was concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (4:1 hexanes:EtOAc → EtOAc eluent, silica).

b) The reaction was performed with 1.00 mmol of **42**, instead of 0.200 mmol.

c) A solution of *n*-Bu_3SnH (70 µL, 0.260 mmol, 1.3 equiv) and AIBN (6.6 mg, 40.0 µmol, 20 mol %) were dissolved in PhH (10.0 mL) and added by syringe-pump to a refluxing and stirring solution of **42** (67.4 mg, 0.200 mmol) in PhH (10 mL) over the course of 11 h. The mixture stirred and refluxed for 48 h.

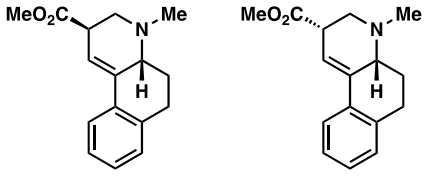
d) The reaction was initially charged with *n*-Bu_3SnH (70 µL, 0.260 mmol, 1.3 equiv) and AIBN (6.6 mg, 40.0 µmol, 20 mol %). After 1 d of heating and stirring at reflux, additional *n*-Bu_3SnH (35.0 µL, 0.130 mmol, 0.65 equiv) was added to the reaction. The reaction stirred at reflux for an additional day.



S59
1:1 dr

^{1}H NMR (400 MHz, $CDCl_3$, selected peaks): δ 5.96-5.88 (m, 2H), 5.80-5.71 (m, 2H), 3.71 (app s, 6H), 2.38 (s, 3H), 2.37 (s, 3H).

HRMS (DART): calc'd for $C_{16}H_{22}NO_2^+$ $[M+H]^+$ 260.1645; found 260.1658.

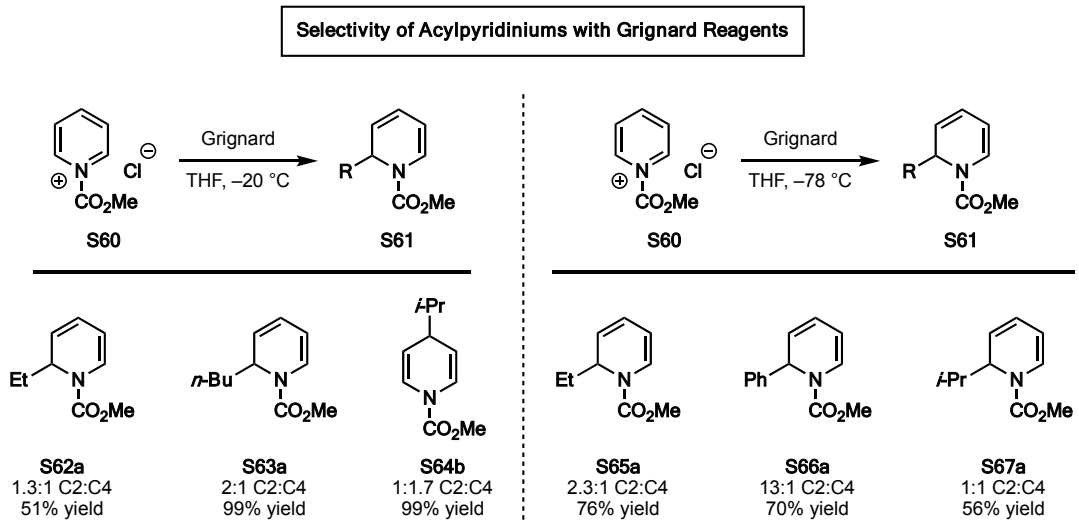


β-43 α-43

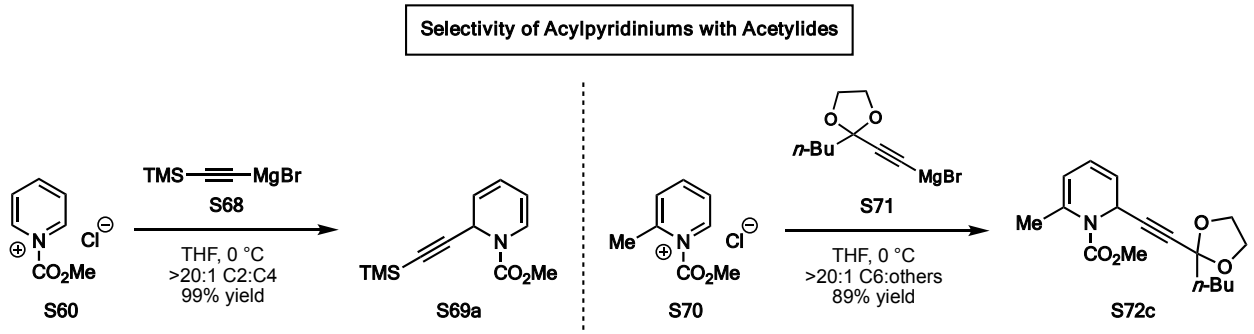
Table S5. Despyrrole methyl lysergates **β-43** and **α-43** ^{1}H NMR spectra comparison.

	Literature Sample (*J. Chem. Soc. Perkin Trans. I* 1984, 2911–2917)	**This Work**
β-43	7.64 (m, 1H)	7.64–7.60 (m, 1H)
	6.42 (br s, 1H)	6.40 (br s, 1H)
	3.78 (s, 3H)	3.76 (s, 3H)
	3.66 (m, 1H)	3.70–3.63 (m, 1H)
	3.22 (br dd, J = 11.5, 6 Hz, 1H)	3.22 (dd, J = 11.4, 5.6 Hz, 1H)
	2.80 (dq, J = 12, 3 Hz, 1H)	2.81 (d, J = 12.6 Hz, 1H)
	2.53 (s, 3H)	2.52 (s, 3H)
α-43	7.59 (m, 1H)	7.59–7.55 (m, 1H)
	6.39 (br d, J = 5 Hz, 1H)	6.38 (d, J = 5.5 Hz, 1H)
	3.74 (s, 3H)	3.72 (s, 3H)
	3.37 (br d, J = 12 Hz, 1H)	3.35 (d, J = 11.3 Hz, 1H)
	3.21 (m, 1H)	3.22–3.16 (m, 1H)
	2.77 (br d, J = 13 Hz, 1H)	2.75 (d, J = 12.7 Hz, 1H)
	2.50 (s, 3H)	2.48 (s, 3H)

Literature Examples of Grignard Additions into Acyl- and Alkylpyridiniums



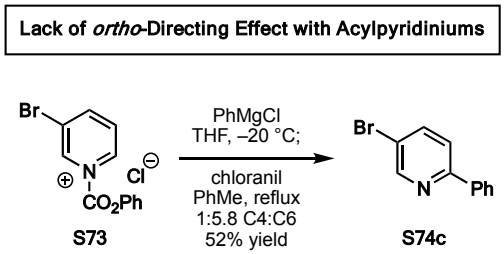
Alkyl and aryl Grignard nucleophiles favor the C2/C6 position of 1-acylpyridiniums.[12,13] Larger nucleophiles can erode this selectivity. This preference may be a result of a guiding effect by the acyl group.



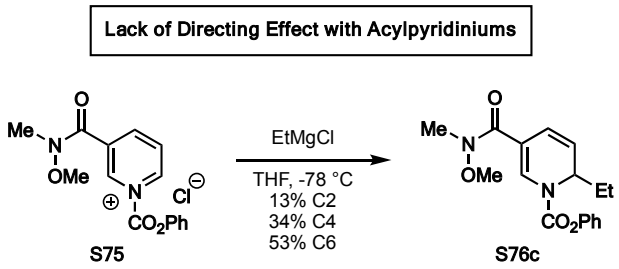
Acetylide Grignard nucleophiles strongly favor the C2/C6 position, often producing a single regioisomer.[12,14] This selectivity is likely due matching of the hard nucleophile with the harder positions of the 1-acylpyridinium.

---

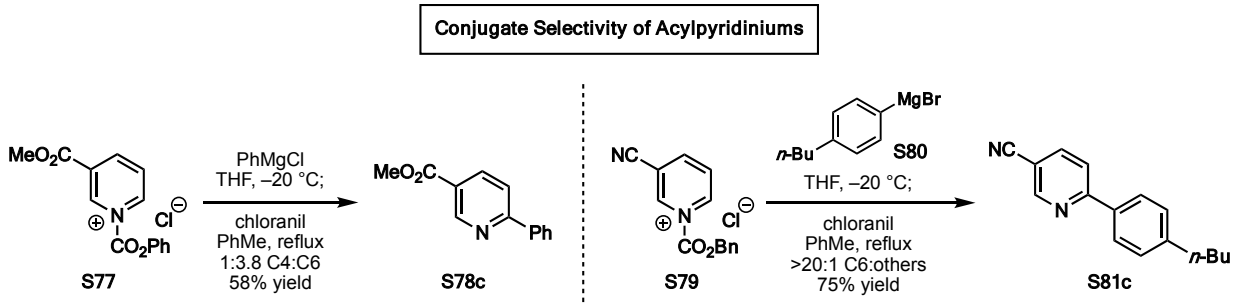
[12] Yamaguchi, R.; Nakazono, Y.; Kawanisi, M. On the Regioselectivity of the Reaction of *N*-Methoxycarbonylpyridinium Chloride with Grignard Reagents: Highly Regioselective Synthesis of 2-Substituted *N*-Methoxycarbonyl-1,2-dihydropyridines. *Tetrahedron Lett.* **1983**, *24*, 1801–1804.
[13] Comins, D. L.; Abdullah, A. H. Regioselective Addition of Grignard Reagents to 1-Acylpyridinium Salts. A Convenient Method for the Synthesis of 4-Alkyl(aryl)pyridines. *J. Org. Chem.* **1982**, *47*, 4315–4319.
[14] Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. An Efficient Regio- and Stereoselective Synthesis of (±)-Monomorine I via the Highly Regioselective α-Alkynylation of a 1-Acylpyridinium Salt. *J. Org.*



There are few examples of Grignard additions into the 1-acylpyridinium of 3-bromopyridine.[15] These examples lacked a significant *ortho*-directing effect by the bromide substituent. Instead, the major isomer was the C6 addition product. This may indicate a steric effect by the bromide that outweighs any potential *ortho*-directing effect.



We found one example of a Grignard addition into a 1-acylpyridinium with a Weinreb amide substituent.[16] This example lacked a significant directing effect by the amide substituent. Instead, the major isomer was the C6 addition product. This too may indicate a steric effect by the amide that outweighs any potential directing effect.

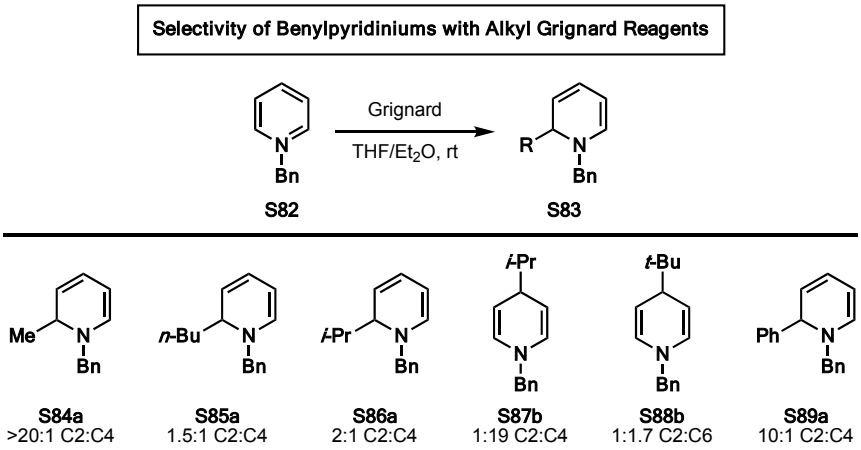


Chem. **1987**, *52*, 2094–2096.

[15] Comins, D. L.; Mantlo, N. B. Regioselective Arylation of 3-Bromopyridine. *J. Heterocyclic. Chem.* 1983, 20, 1239–1243.

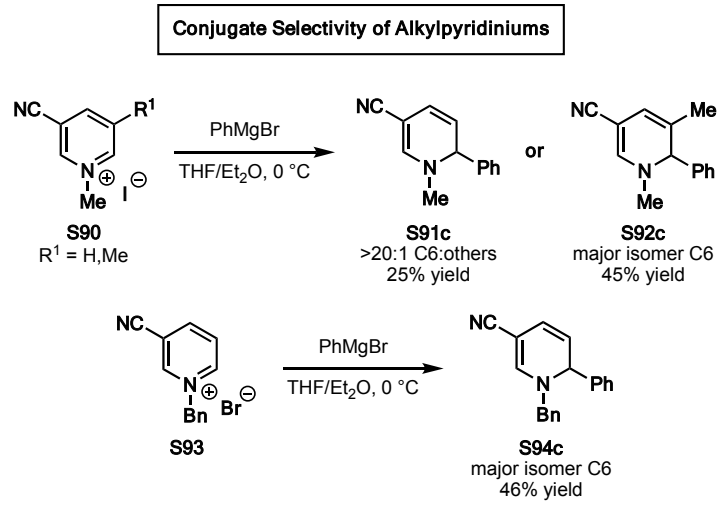
[16] Wallace, D. J.; Gibb, A. D.; Cottrell, I. F.; Kennedy, D. J.; Brands, K. M. J.; Dolling, U. H. Observation on the DDQ Oxidation of 1-Acyldihydropyridines – A Synthetic Application. *Synthesis* **2001**, 1784–1789.

Additions of Grignard reagents into 1-Acylpyridiniums derived from nicotinates[17] and nicotinitrile[18] have been studied. There may be a *para*-directing effect by π-EWGs, but this is not conclusive based on the available data. This is because the 2/6-position of pyridines is generally favored, and substitution at the 3-position tends to result in a strong preference for Grignard addition at the 6-position.

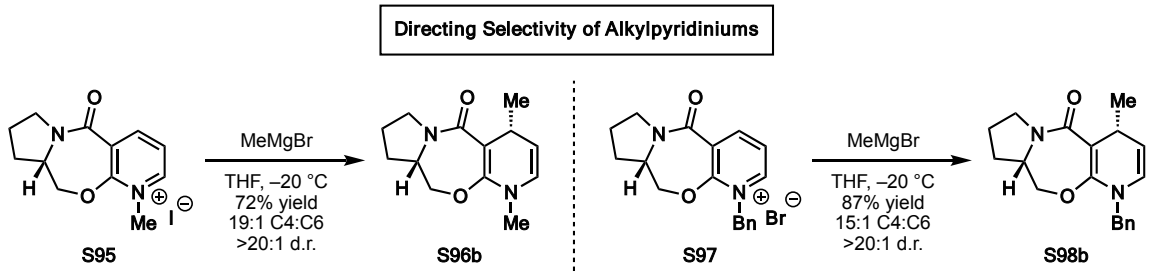


The innate selectivity of 1-benzylpyridinium with alkyl Grignard reagents has been studied.[19] Generally, C2 is slightly favored, but this selectivity can be eroded or reversed with larger nucleophiles. However, the reactivity trend has some anomalous results, such as the lower selectivity for *t*-Bu Grignard compared to *i*-Pr Grignard reagents.

[17] Comins, D. L.; Stroud, E. D.; Herrick, J. J. Regioselective Addition of Grignard Reagents to the 1-Phenoxycarbonyl Salts of Alkyl Nicotinates. *Heterocycles* **1984**, *22*, 151–157.
[18] Chia, W.-L.; Lu, R.-S. Facile Synthesis of a Series of Liquid Crystalline 2-(4'-Alkylphenyl)5-cyanopyridines. U.S. Patent US 2008/0146813 A1, Jun. 19, 2008.
[19] Holm, T. Mechanism of the Grignard Addition Reaction. XV. The Reaction of Grignard Reagents with Benzylpyridinium Chloride. *Acta Chemica Scandinavica.* **1991**, *45*, 276–279.

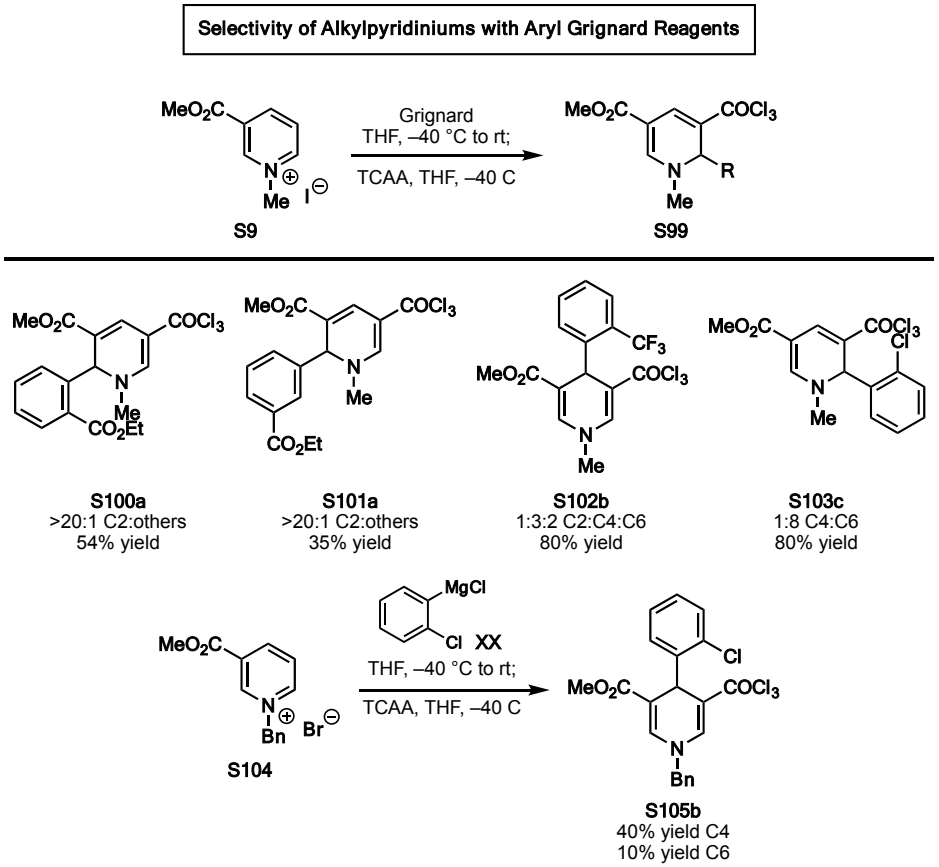


Conjugate selectivity has been previously observed with Grignard reagents and alkylpyridiniums.[20] Shown above is a Grignard addition at the 6-position of an alkylpyridinium with a nitrile at the 3-position, a *para* directing group.



An amide directing effect has been observed previously.[21] Shown above are examples of alkylpyridiniums with amide substitution at the 3-position strongly preferencing Grignard addition to the 4-position.

[20] Lyle, R. E.; White, E., V. The Reaction of Organometallic Reagents with Pyridinium Ions. *J. Org. Chem.* **1971**, *36*, 772–777.
[21] Schultz, A. G.; Flood, L. Regio-and Stereoselective Control in the Addition of Grignard Reagents to the Pyridine Ring System. *J. Org. Chem.* **1986**, *51*, 838–841.



The addition of aryl Grignard reagents into alkylpyridiniums of methyl nicotinate has been previously studied; however, no explanation was given for the observed reactivity trends.[11] This study reports aryl Grignard reagents adding selectively to the C2, C4, and C6 position of this electrophile.

Crystallographic Data for Pyridinium S47c

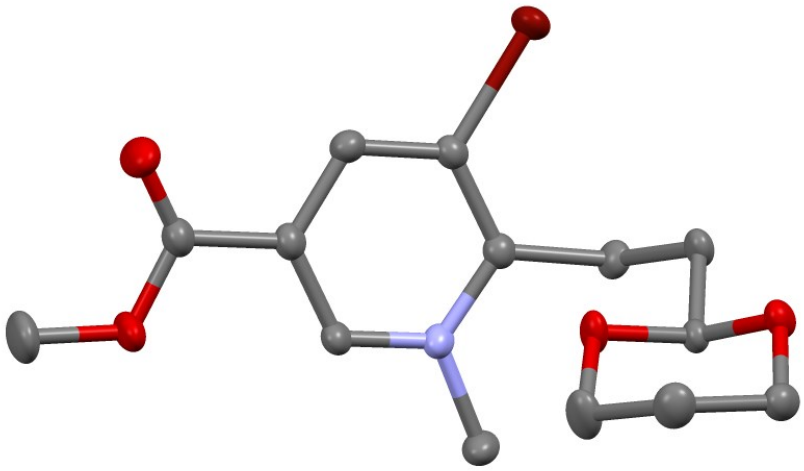


Figure S1. Solid-state structure of pyridinium **S47c** at 50% thermal ellipsoid. Hydrogen atoms and the counter ion have been omitted for clarity. C, N, O, and Br atoms are depicted as gray, blue, red, and dark red ellipsoids, respectively.

Table S6. Crystal data and structure refinement for BK-2_sx (pyridinium **S47c**).

Identification code	BK-2_sx
Empirical formula	$C_{28}H_{38}Br_3N_2O_8$
Formula weight	770.33
Temperature/K	150.00(10)
Crystal system	triclinic
Space group	P–1
a/Å	10.89440(10)
b/Å	13.39160(10)
c/Å	14.63390(10)
α/°	113.1790(10)
β/°	99.6000(10)
γ/°	103.8560(10)
Volume/Å^3	1822.22(3)
Z	2
ρ_{calc}g/cm^3	1.404
μ/mm^{-1}	4.469
F(000)	778.0
Crystal size/mm^3	0.304 × 0.202 × 0.166
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.872 to 155.786
Index ranges	$-13 \leq h \leq 13$, $-16 \leq k \leq 16$, $-18 \leq l \leq 12$
Reflections collected	39990
Independent reflections	7684 [R_{int} = 0.0643, R_{sigma} = 0.0394]
Data/restraints/parameters	7684/0/374
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0422, wR_2 = 0.1210
Final R indexes [all data]	R_1 = 0.0438, wR_2 = 0.1226
Largest diff. peak/hole / e Å^{-3}	0.84/–1.14

Table S7. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for BK-2_sx (pyridinium **S47c**). U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
Br1	–2244.8(3)	827.2(3)	459.0(2)	25.84(9)
O5	–6611.0(19)	1149.7(18)	1637.3(15)	23.4(4)
O6	–4541.5(18)	1610.1(18)	2751.4(15)	22.9(4)
O7	732(2)	1019(2)	3944.9(18)	36.6(5)
O8	787(2)	2641(2)	5257.8(16)	32.5(5)
N1	–1870(2)	3214.0(19)	3405.9(18)	20.7(4)
C1	–1735(3)	1732(2)	1913(2)	19.4(5)
C2	–861(3)	1487(2)	2526(2)	21.4(5)
C3	–502(3)	2137(2)	3596(2)	21.2(5)
C4	414(3)	1863(3)	4274(2)	24.9(6)
C5	1613(4)	2407(4)	5985(3)	45.6(9)
C6	–1007(3)	3006(2)	4022(2)	20.0(5)
C7	–2271(2)	2596(2)	2352(2)	19.1(5)
C8	–2336(3)	4181(3)	3928(2)	27.3(6)
C9	–3265(3)	2849(2)	1702(2)	21.4(5)
C10	–4677(3)	1969(3)	1284(2)	22.3(5)
C11	–5314(2)	1939(2)	2120(2)	18.4(5)
C12	–5077(3)	1572(3)	3573(2)	31.3(7)
C13	–6502(3)	775(3)	3132(3)	30.3(6)
C14	–7270(3)	1104(3)	2400(2)	25.5(6)
Br2	7723.6(3)	809.5(2)	5318.7(2)	23.75(9)
O1	3475.1(19)	1158.9(18)	6732.0(14)	23.0(4)
O2	5607.5(19)	1769.2(18)	7810.3(15)	23.5(4)
O3	10735(2)	1131(2)	8840.2(17)	32.6(5)
O4	10681(2)	2709.1(19)	10153.1(16)	32.1(5)
N2	8204(2)	3346.6(19)	8212.4(18)	20.2(4)

C15	8276(2)	1786(2)	6761.1(19)	18.6(5)
C16	9154(3)	1569(2)	7396(2)	21.2(5)
C17	9524(3)	2246(2)	8463(2)	19.8(5)
C18	10396(3)	1963(2)	9162(2)	22.8(5)
C19	11478(4)	2474(4)	10895(3)	45.0(9)
C20	9055(3)	3151(2)	8858(2)	20.3(5)
C21	7790(3)	4363(2)	8692(2)	27.2(6)
C22	7746(3)	2660(2)	7171(2)	18.9(5)
C23	6650(3)	2808(2)	6516(2)	20.0(5)
C24	5296(3)	1891(2)	6221(2)	21.3(5)
C25	4757(2)	1983(2)	7129.4(19)	18.3(5)
C26	5155(3)	1856(3)	8703(2)	33.5(7)
C27	3757(3)	1024(3)	8351(2)	30.4(6)
C28	2895(3)	1219(3)	7561(2)	25.6(6)
Br3	9360.0(4)	4991.8(3)	6770.2(3)	39.47(11)

Table S8. Anisotropic displacement parameters ($Å^2 \times 10^3$) for BK-2_sx (pyridinium **S47c**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	29.51(16)	31.10(16)	15.78(14)	8.08(12)	7.05(11)	12.40(12)
O5	17.3(9)	29.5(10)	18.1(9)	8.5(8)	1.9(7)	5.2(8)
O6	18.4(9)	34.7(11)	21.1(9)	18.5(8)	3.6(7)	9.5(8)
O7	43.6(13)	36.6(12)	30.4(11)	11.0(10)	5.1(10)	26.0(11)
O8	35.4(11)	35.7(12)	19.7(10)	6.4(9)	–3.4(8)	19.1(10)
N1	16.5(10)	17.6(10)	22.2(11)	5.4(9)	1.7(8)	5.3(8)
C1	17.3(11)	19.8(12)	17.7(12)	7.2(10)	3.8(9)	3.9(9)
C2	20.2(12)	20.7(12)	22.2(13)	7.5(10)	7.3(10)	8.2(10)
C3	17.0(11)	22.1(12)	20.5(12)	8.2(10)	2.3(10)	4.6(10)
C4	20.8(12)	28.5(14)	22.0(13)	9.7(11)	2.5(10)	8.3(11)
C5	42.7(19)	60(2)	30.1(17)	17.7(16)	–4.3(14)	26.1(18)
C6	16.9(11)	19.6(12)	17.6(12)	4.8(10)	1.3(9)	4.8(10)
C7	16.7(11)	18.3(12)	20.2(12)	8.5(10)	4.2(9)	3.5(9)
C8	25.1(13)	23.1(13)	26.6(14)	4.0(11)	3.8(11)	11.3(11)
C9	22.7(12)	23.7(13)	24.1(13)	15.3(11)	6.7(10)	10.8(10)
C10	20.0(12)	31.3(14)	16.5(12)	12.2(11)	3.1(10)	9.3(11)
C11	16.6(11)	21.7(12)	16.3(11)	8.4(10)	2.1(9)	7.6(10)
C12	26.2(14)	50.6(19)	24.4(14)	25.4(14)	7.0(11)	11.0(13)
C13	28.5(15)	38.5(16)	31.9(15)	22.2(13)	13.3(12)	11.0(13)
C14	19.8(12)	29.4(14)	24.2(13)	9.5(11)	6.5(10)	7.6(11)
Br2	26.11(15)	26.44(15)	14.66(14)	6.59(11)	3.96(11)	8.13(12)
O1	18.0(9)	27.8(10)	15.7(8)	7.1(7)	1.9(7)	2.2(7)
O2	19.8(9)	35.4(11)	18.1(9)	15.6(8)	3.3(7)	9.6(8)
O3	36.5(12)	31.3(11)	25.8(10)	7.6(9)	0.9(9)	19.2(10)
O4	37.5(12)	31.0(11)	18.4(10)	4.2(8)	–5.9(8)	17.7(9)
N2	21.3(10)	14.2(10)	19.0(11)	4.6(8)	0.5(8)	4.7(8)
C15	17.3(11)	18.3(11)	14.6(11)	5.9(9)	1.0(9)	2.1(9)

C16	19.1(12)	17.9(12)	23.5(13)	7.3(10)	4.9(10)	5.8(10)
C17	16.3(11)	18.0(12)	19.0(12)	6.5(10)	–1.0(9)	3.0(9)
C18	19.7(12)	21.6(13)	22.6(13)	7.9(10)	–0.1(10)	7.4(10)
C19	47(2)	54(2)	26.8(16)	13.8(15)	–8.1(14)	25.2(18)
C20	18.6(12)	15.5(11)	18.4(12)	4.1(9)	–2.8(9)	3.3(9)
C21	30.9(14)	18.9(12)	24.5(13)	3.0(10)	0.0(11)	13.6(11)
C22	18.4(11)	16.5(11)	17.7(12)	8.0(10)	1.2(9)	1.5(9)
C23	20.0(12)	21.2(12)	18.5(12)	10.5(10)	2.0(9)	6.3(10)
C24	19.0(12)	28.1(13)	13.7(11)	10.0(10)	0.2(9)	4.8(10)
C25	17.2(11)	21.5(12)	14.6(11)	8.2(9)	1.0(9)	6.6(10)
C26	30.8(15)	55(2)	20.1(13)	22.8(14)	7.8(12)	14.2(14)
C27	29.9(15)	42.5(17)	25.9(14)	20.7(13)	11.7(12)	12.8(13)
C28	24.4(13)	29.8(14)	21.8(13)	10.4(11)	9.1(11)	8.7(11)
Br3	39.86(19)	37.68(19)	26.32(17)	10.26(14)	8.52(14)	–3.24(15)

Table S9. Bond lengths for BK-2_sx (pyridinium **S47c**).

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Br1	C1	1.886(3)	Br2	C15	1.885(3)
O5	C11	1.406(3)	O1	C25	1.411(3)
O5	C14	1.437(3)	O1	C28	1.443(3)
O6	C11	1.413(3)	O2	C25	1.407(3)
O6	C12	1.434(3)	O2	C26	1.444(3)
O7	C4	1.202(4)	O3	C18	1.201(4)
O8	C4	1.321(4)	O4	C18	1.326(4)
O8	C5	1.456(4)	O4	C19	1.455(4)
N1	C6	1.347(4)	N2	C20	1.356(3)
N1	C7	1.361(4)	N2	C21	1.482(3)
N1	C8	1.478(3)	N2	C22	1.357(3)
C1	C2	1.385(4)	C15	C16	1.384(4)
C1	C7	1.399(4)	C15	C22	1.395(4)
C2	C3	1.387(4)	C16	C17	1.386(4)
C3	C4	1.498(4)	C17	C18	1.500(3)
C3	C6	1.376(4)	C17	C20	1.381(4)
C7	C9	1.509(3)	C22	C23	1.505(3)
C9	C10	1.543(4)	C23	C24	1.540(4)
C10	C11	1.513(4)	C24	C25	1.514(4)
C12	C13	1.515(4)	C26	C27	1.517(5)
C13	C14	1.513(4)	C27	C28	1.510(4)

Table S10. Bond angles for BK-2_sx (pyridinium **S47c**).

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C11	O5	C14	110.7(2)	C25	O1	C28	110.6(2)
C11	O6	C12	111.4(2)	C25	O2	C26	111.2(2)
C4	O8	C5	115.6(3)	C18	O4	C19	115.5(2)
C6	N1	C7	122.4(2)	C20	N2	C21	117.0(2)
C6	N1	C8	116.7(2)	C20	N2	C22	122.5(2)
C7	N1	C8	121.0(2)	C22	N2	C21	120.4(2)
C2	C1	Br1	118.2(2)	C16	C15	Br2	118.2(2)
C2	C1	C7	121.4(2)	C16	C15	C22	121.5(2)
C7	C1	Br1	120.38(19)	C22	C15	Br2	120.19(19)
C1	C2	C3	118.3(2)	C15	C16	C17	118.9(2)
C2	C3	C4	119.1(2)	C16	C17	C18	119.3(2)
C6	C3	C2	119.9(2)	C20	C17	C16	119.2(2)
C6	C3	C4	121.0(2)	C20	C17	C18	121.5(2)
O7	C4	O8	125.3(3)	O3	C18	O4	125.8(3)
O7	C4	C3	122.9(3)	O3	C18	C17	122.6(3)
O8	C4	C3	111.7(2)	O4	C18	C17	111.6(2)
N1	C6	C3	120.4(2)	N2	C20	C17	120.3(2)
N1	C7	C1	117.6(2)	N2	C22	C15	117.3(2)
N1	C7	C9	120.1(2)	N2	C22	C23	120.1(2)
C1	C7	C9	122.4(2)	C15	C22	C23	122.6(2)
C7	C9	C10	114.2(2)	C22	C23	C24	112.8(2)
C11	C10	C9	114.2(2)	C25	C24	C23	114.3(2)
O5	C11	O6	111.6(2)	O1	C25	C24	107.9(2)
O5	C11	C10	108.5(2)	O2	C25	O1	111.2(2)
O6	C11	C10	108.0(2)	O2	C25	C24	108.4(2)
O6	C12	C13	110.4(2)	O2	C26	C27	109.9(2)
C14	C13	C12	109.5(2)	C28	C27	C26	109.2(3)
O5	C14	C13	110.2(2)	O1	C28	C27	110.1(2)

Table S11. Torsion angles for BK-2_sx (pyridinium **S47c**).

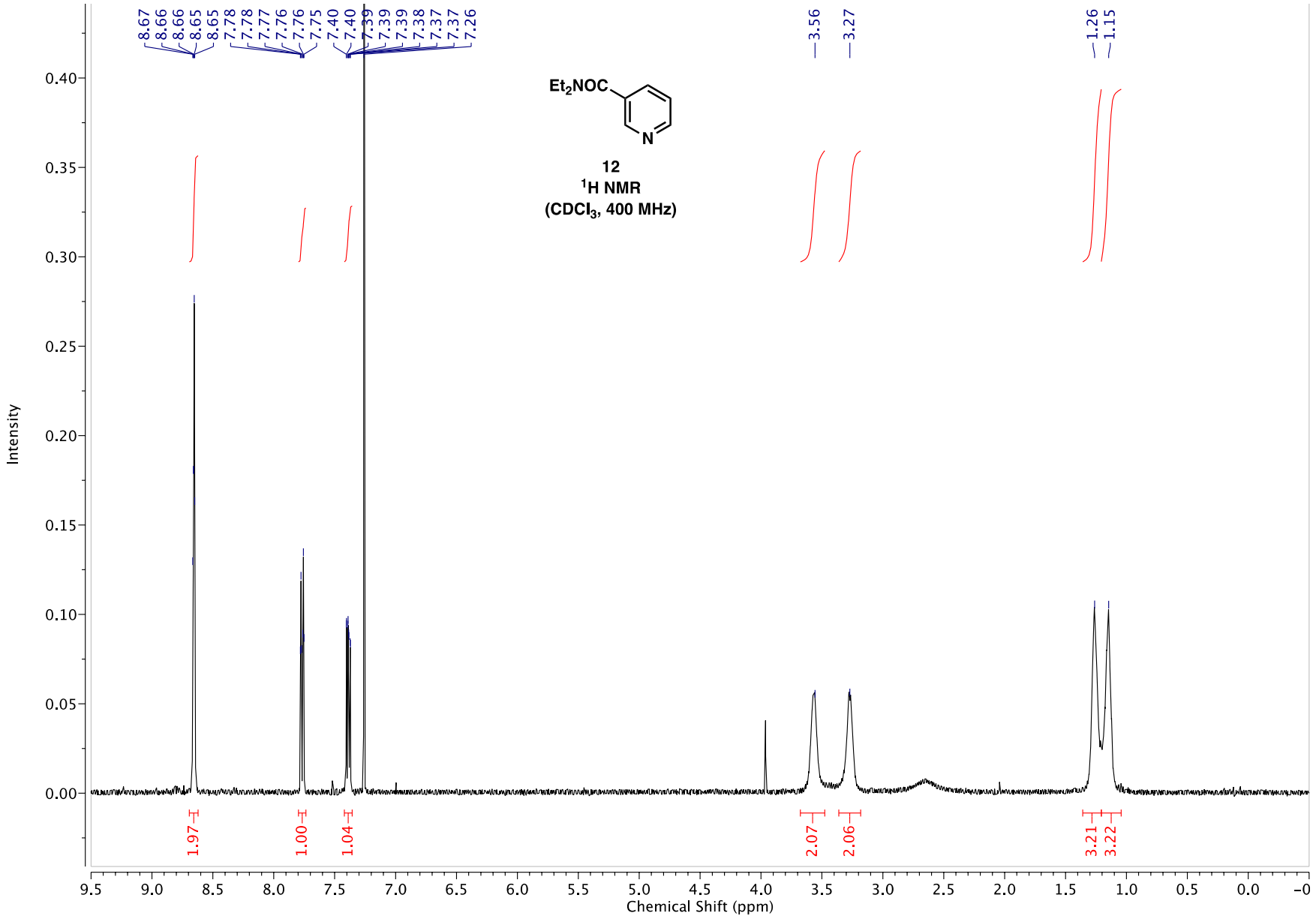
A	B	C	D	Angle/°	A	B	C	D	Angle/°
Br1	C1	C2	C3	–178.8(2)	Br2	C15	C16	C17	–177.1(2)
Br1	C1	C7	N1	179.53(18)	Br2	C15	C22	N2	–178.73(18)
Br1	C1	C7	C9	–0.1(3)	Br2	C15	C22	C23	5.1(3)
O6	C12	C13	C14	–51.6(4)	O2	C26	C27	C28	–52.6(4)
N1	C7	C9	C10	–103.1(3)	N2	C22	C23	C24	–101.8(3)
C1	C2	C3	C4	178.3(2)	C15	C16	C17	C18	175.5(2)
C1	C2	C3	C6	–0.5(4)	C15	C16	C17	C20	–3.0(4)
C1	C7	C9	C10	76.5(3)	C15	C22	C23	C24	74.2(3)
C2	C1	C7	N1	2.0(4)	C16	C15	C22	N2	4.9(4)
C2	C1	C7	C9	–177.6(2)	C16	C15	C22	C23	–171.2(2)
C2	C3	C4	O7	–9.2(4)	C16	C17	C18	O3	–4.1(4)
C2	C3	C4	O8	172.2(3)	C16	C17	C18	O4	178.5(3)
C2	C3	C6	N1	1.4(4)	C16	C17	C20	N2	2.5(4)
C4	C3	C6	N1	–177.4(3)	C18	C17	C20	N2	–176.0(2)
C5	O8	C4	O7	–2.3(5)	C19	O4	C18	O3	0.1(5)
C5	O8	C4	C3	176.2(3)	C19	O4	C18	C17	177.5(3)
C6	N1	C7	C1	–1.1(4)	C20	N2	C22	C15	–5.6(4)
C6	N1	C7	C9	178.6(2)	C20	N2	C22	C23	170.6(2)
C6	C3	C4	O7	169.6(3)	C20	C17	C18	O3	174.4(3)
C6	C3	C4	O8	–9.0(4)	C20	C17	C18	O4	–3.0(4)
C7	N1	C6	C3	–0.6(4)	C21	N2	C20	C17	–177.5(3)
C7	C1	C2	C3	–1.2(4)	C21	N2	C22	C15	173.9(2)
C7	C9	C10	C11	64.1(3)	C21	N2	C22	C23	–9.8(4)
C8	N1	C6	C3	–178.6(2)	C22	N2	C20	C17	2.0(4)
C8	N1	C7	C1	176.8(2)	C22	C15	C16	C17	–0.7(4)
C8	N1	C7	C9	–3.5(4)	C22	C23	C24	C25	67.4(3)
C9	C10	C11	O5	177.1(2)	C23	C24	C25	O1	175.1(2)
C9	C10	C11	O6	–61.7(3)	C23	C24	C25	O2	–64.4(3)

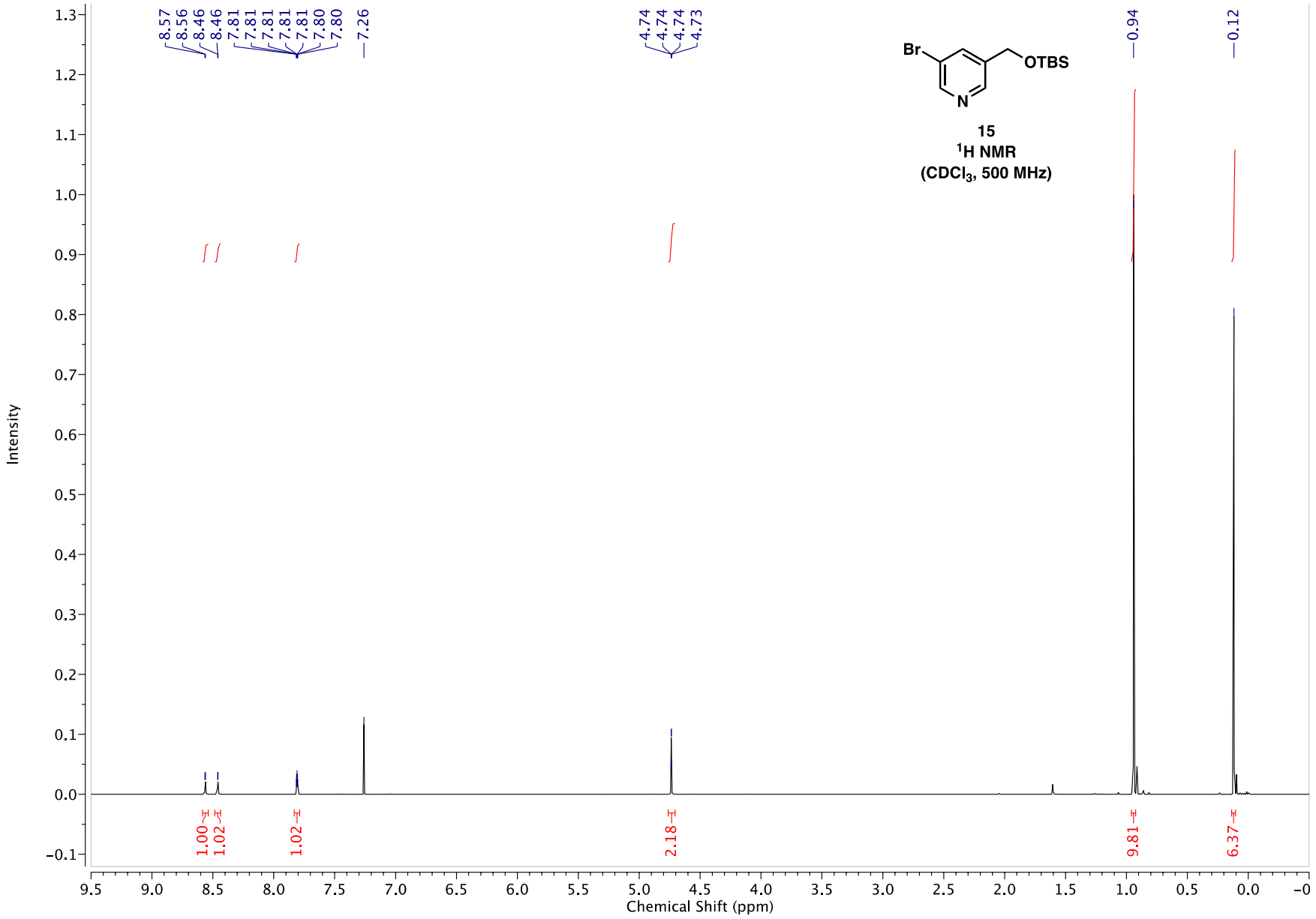
C11	O5	C14	C13	–57.8(3)	C25	O1	C28	C27	–58.1(3)
C11	O6	C12	C13	55.9(3)	C25	O2	C26	C27	57.2(3)
C12	O6	C11	O5	–61.3(3)	C26	O2	C25	O1	–62.2(3)
C12	O6	C11	C10	179.5(2)	C26	O2	C25	C24	179.4(2)
C12	C13	C14	O5	52.6(3)	C26	C27	C28	O1	53.3(3)
C14	O5	C11	O6	62.1(3)	C28	O1	C25	O2	62.4(3)
C14	O5	C11	C10	–179.0(2)	C28	O1	C25	C24	–178.9(2)

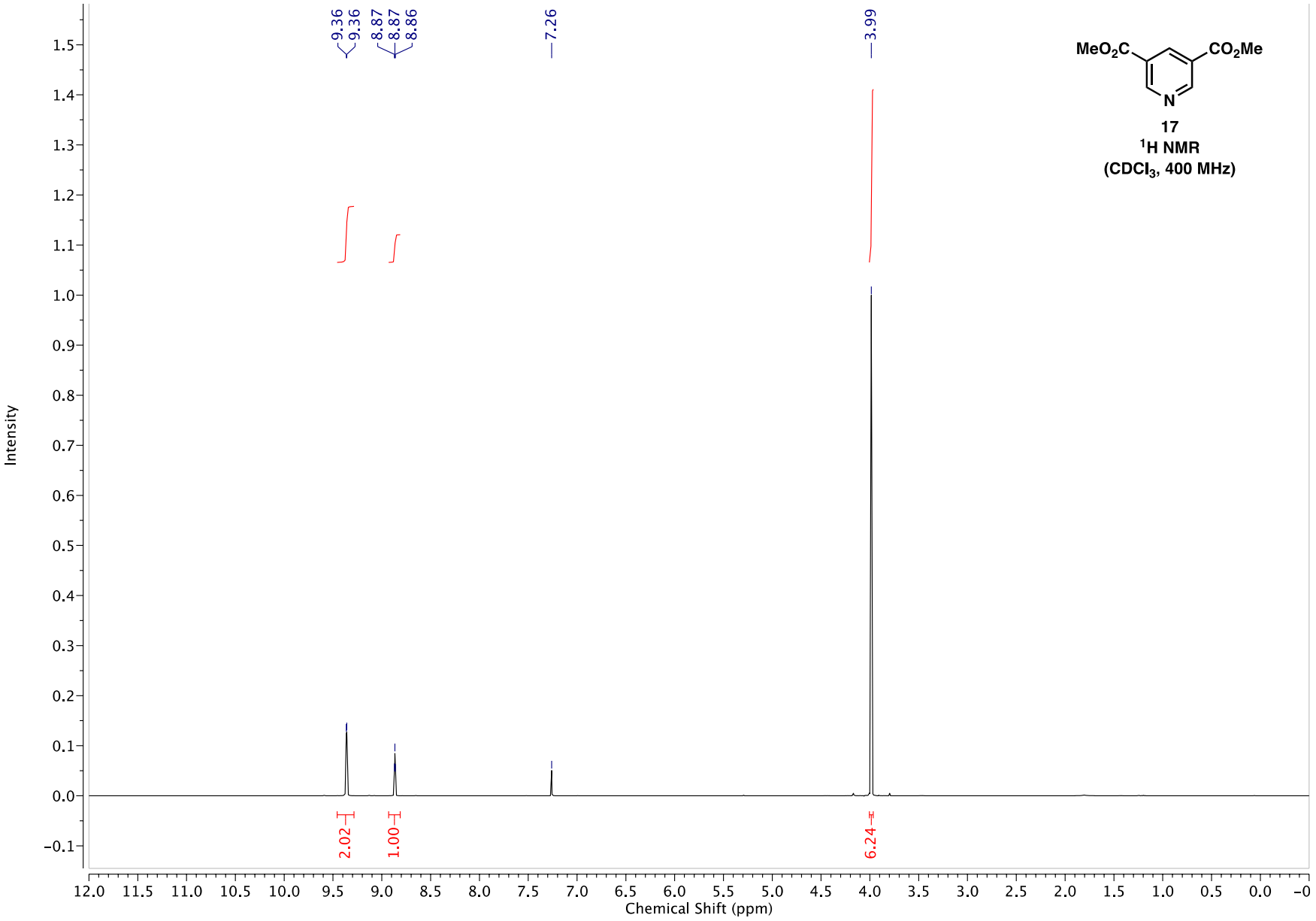
Table S12. Hydrogen atom coordinates (Å×10^4) and isotropic displacement parameters (Å^2×10^3) for BK-2_sx (pyridinium **S47c**).

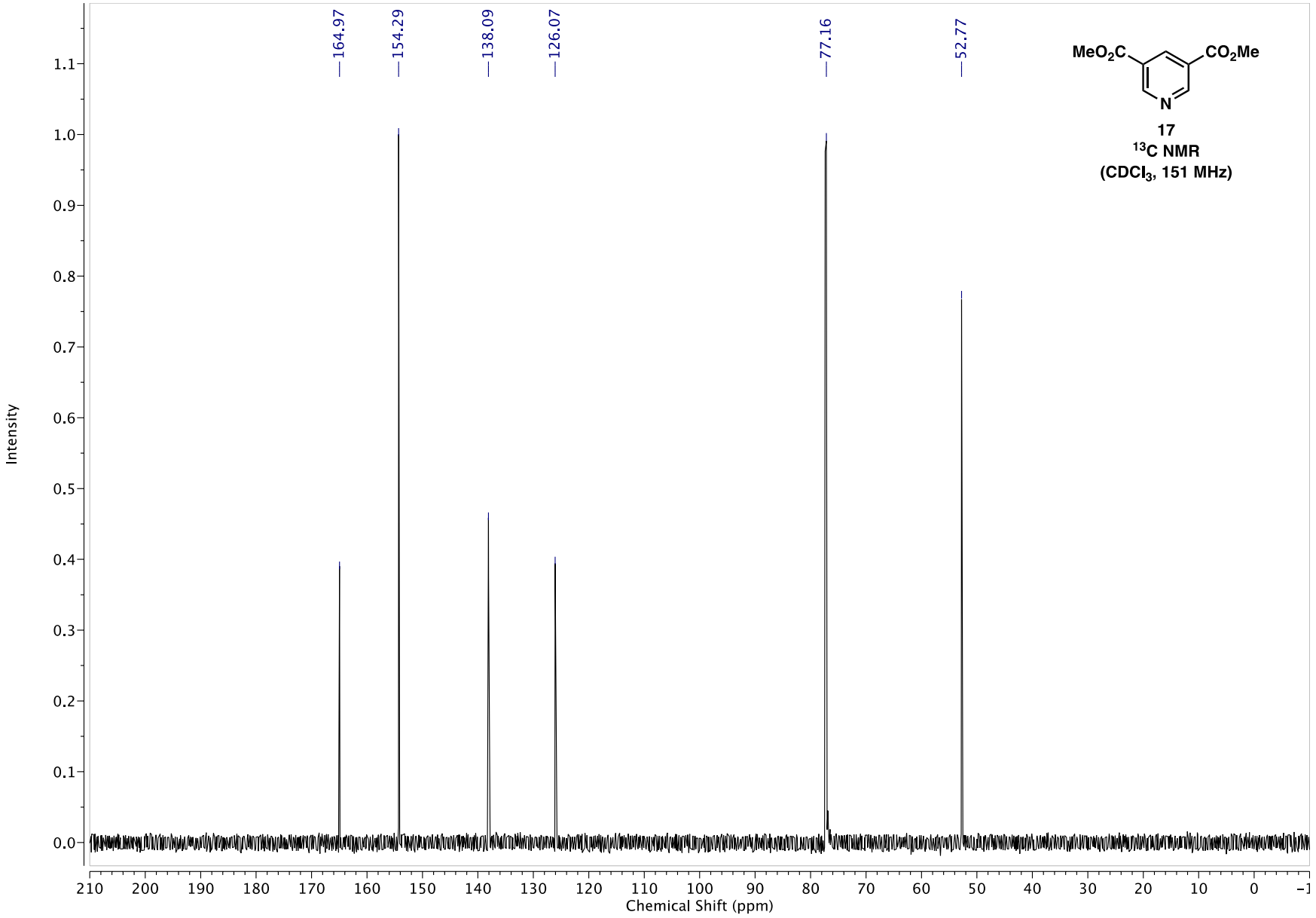
Atom	*x*	*y*	*z*	U(eq)
H2	–514.58	888.82	2220.9	26
H5A	1168.54	1637.49	5908.82	68
H5B	1761.1	2985.67	6697.3	68
H5C	2463.41	2439.46	5839.72	68
H6	–745.51	3461.69	4754.46	24
H8A	–2014.87	4791.55	3729.36	41
H8B	–1997.07	4486.33	4683.5	41
H8C	–3304.61	3906.16	3718.97	41
H9A	–2960.88	2866.64	1105.62	26
H9B	–3291.96	3625.35	2126.22	26
H10A	–5238.19	2154.79	811.82	27
H10B	–4646.77	1191.01	869.28	27
H11	–5337.54	2724	2551.84	22
H12A	–5028.86	2357.25	4050.06	38
H12B	–4547.61	1293.73	3975.59	38
H13A	–6540.22	–33.47	2753.31	36
H13B	–6900.58	836.79	3704.24	36
H14A	–8172.41	530.38	2048.01	31
H14B	–7347.96	1866.74	2800.01	31
H16	9498.7	965.06	7106.11	25
H19A	11085.38	1669.48	10752.53	68
H19B	11507.17	2986.03	11602.03	68
H19C	12376.89	2609.66	10831.47	68
H20	9329.83	3638.95	9585.68	24
H21A	8097.75	4912.48	8423.35	41
H21B	8175.74	4734.29	9447.92	41
H21C	6824.14	4114.92	8520.22	41
H23A	6863.96	2764.01	5872.68	24

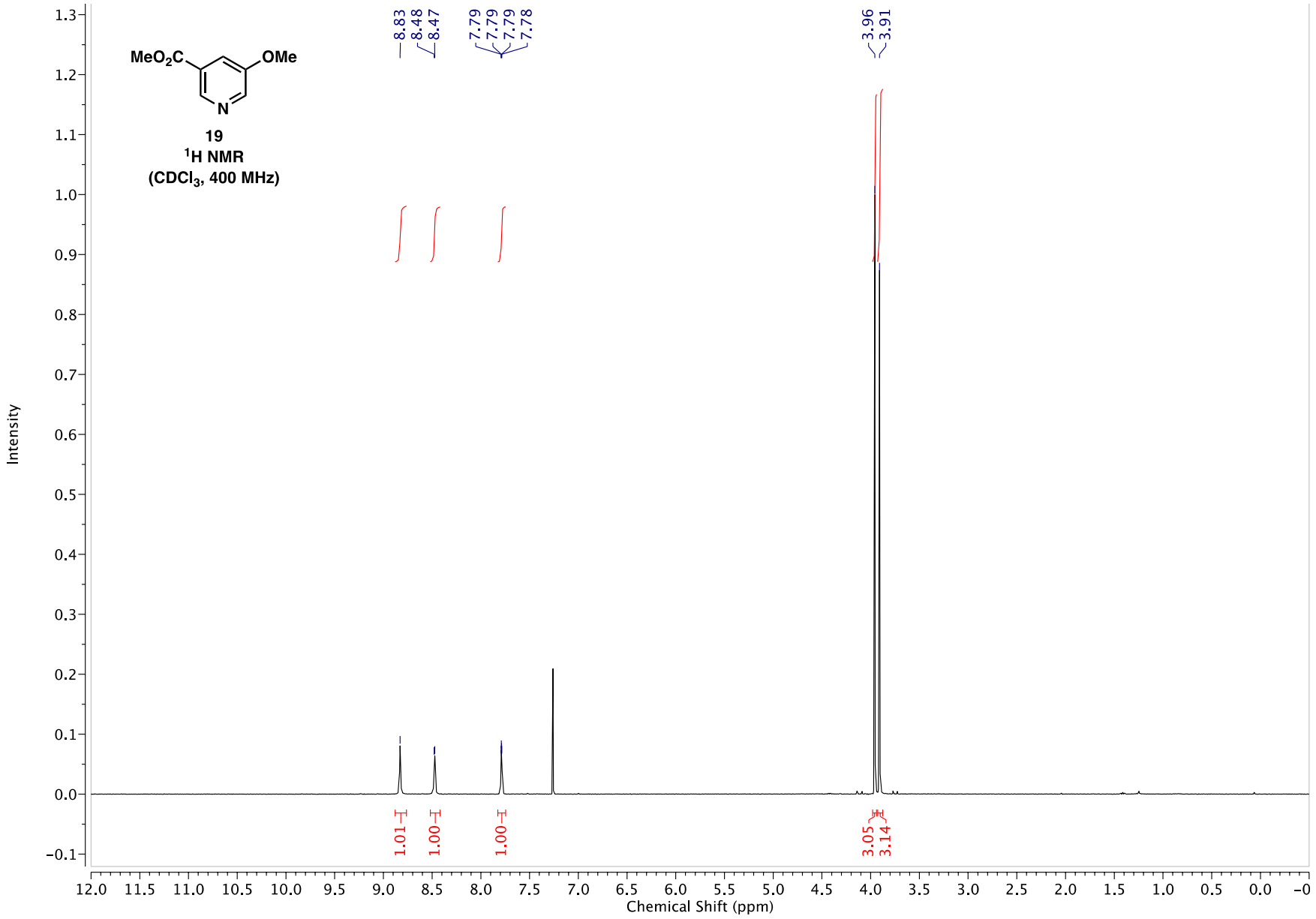
H23B	6595.75	3583.48	6902.51	24
H24A	4652.75	1958.88	5703.59	26
H24B	5375.28	1117.11	5885.87	26
H25	4713.39	2774.9	7500.17	22
H26A	5176.74	2654.21	9109.25	40
H26B	5749.3	1672.44	9156.16	40
H27A	3755.42	219.87	8037.63	36
H27B	3408.02	1149.95	8954.59	36
H28A	2004.64	625.4	7272.51	31
H28B	2797.07	1985.15	7901.58	31

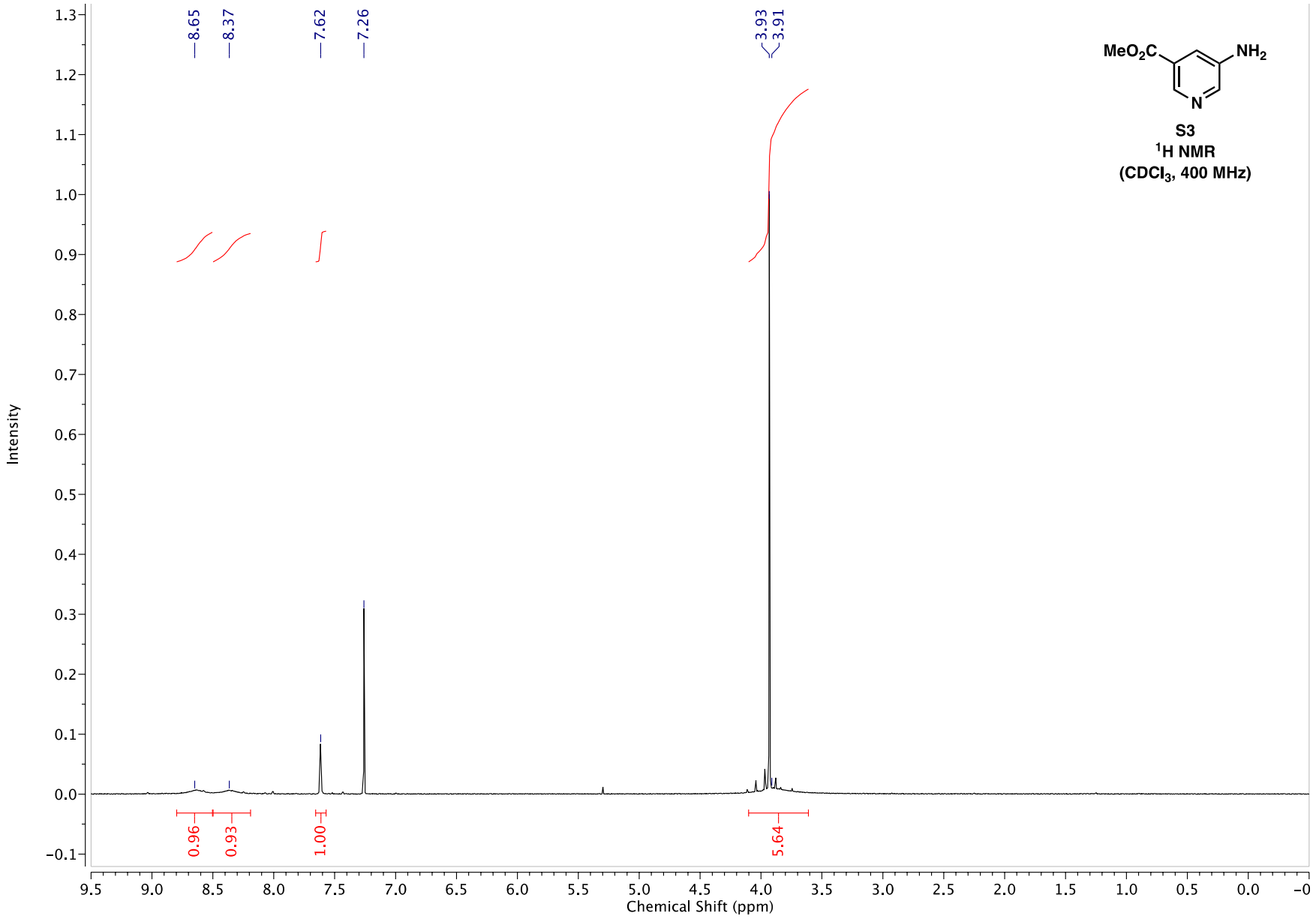

8.67
8.66
8.66
8.65
8.65
7.78
7.78
7.77
7.76
7.76
7.75
7.40
7.40
7.39
7.39
7.39
7.38
7.37
7.37
7.26
3.56
3.27
1.26
1.15
Et2NOC
N
12
1H NMR
(CDCl3, 400 MHz)
Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
1.97
1.00
1.04
2.07
2.06
3.21
3.22
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

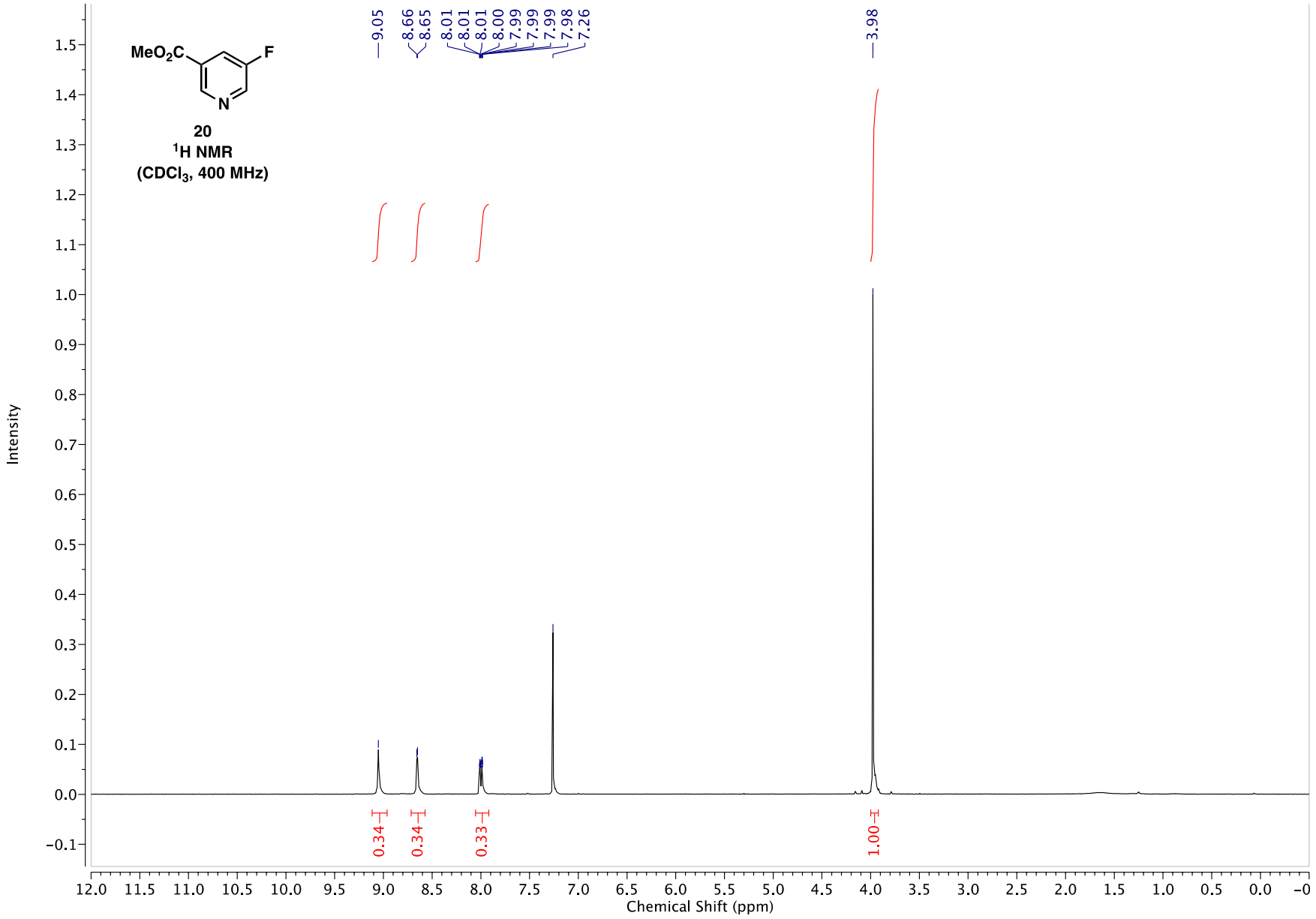

8.57
8.56
8.46
8.46
7.81
7.81
7.81
7.81
7.80
7.80
7.26
4.74
4.74
4.74
4.73
0.94
0.12
Br
OTBS
N
15
1H NMR
(CDCl3, 500 MHz)
Intensity
Chemical Shift (ppm)
1.00
1.02
1.02
2.18
9.81
6.37

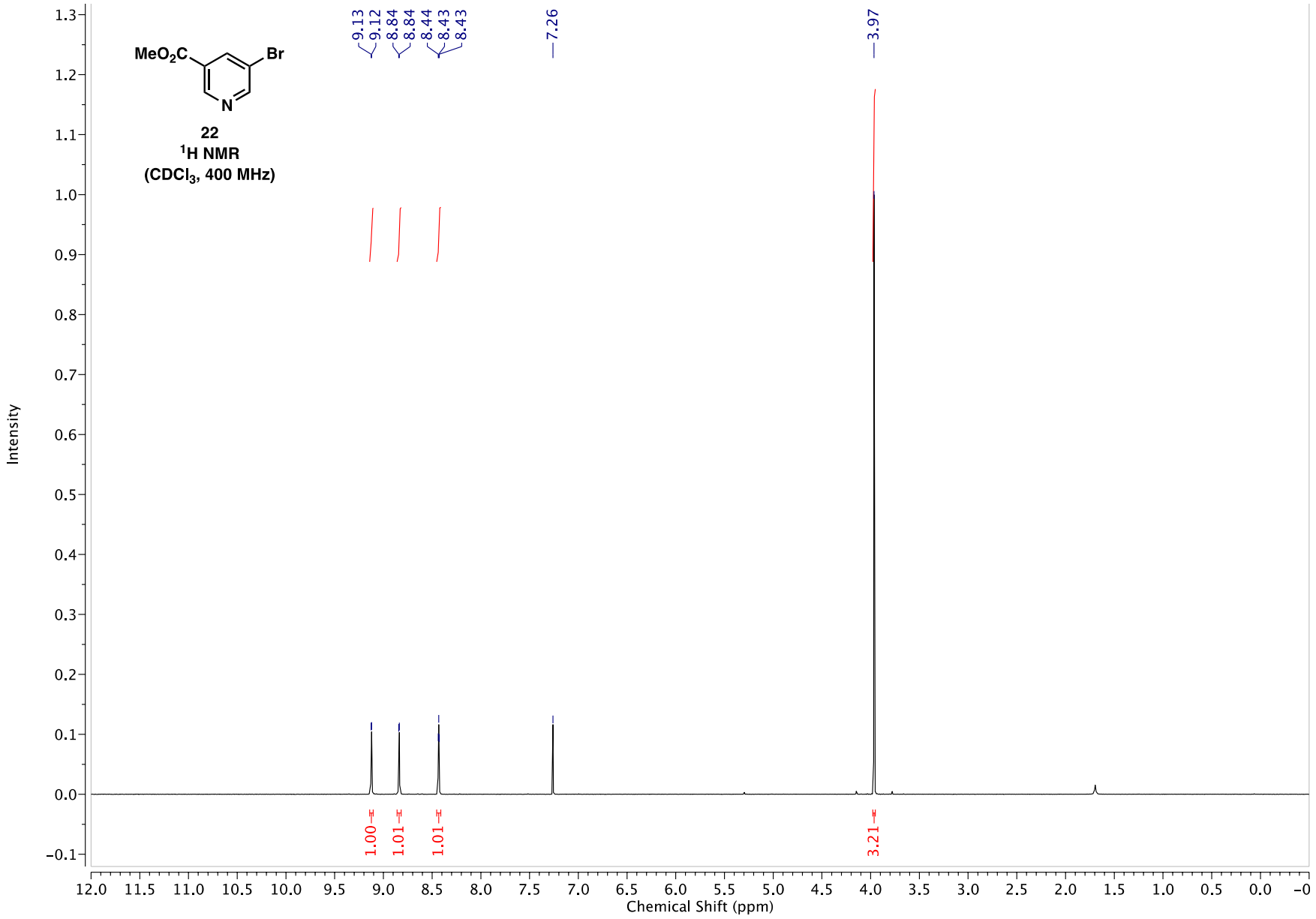

9.36
9.36
8.87
8.87
8.86
7.26
3.99
MeO2C
CO2Me
N
17
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
2.02
1.00
6.24

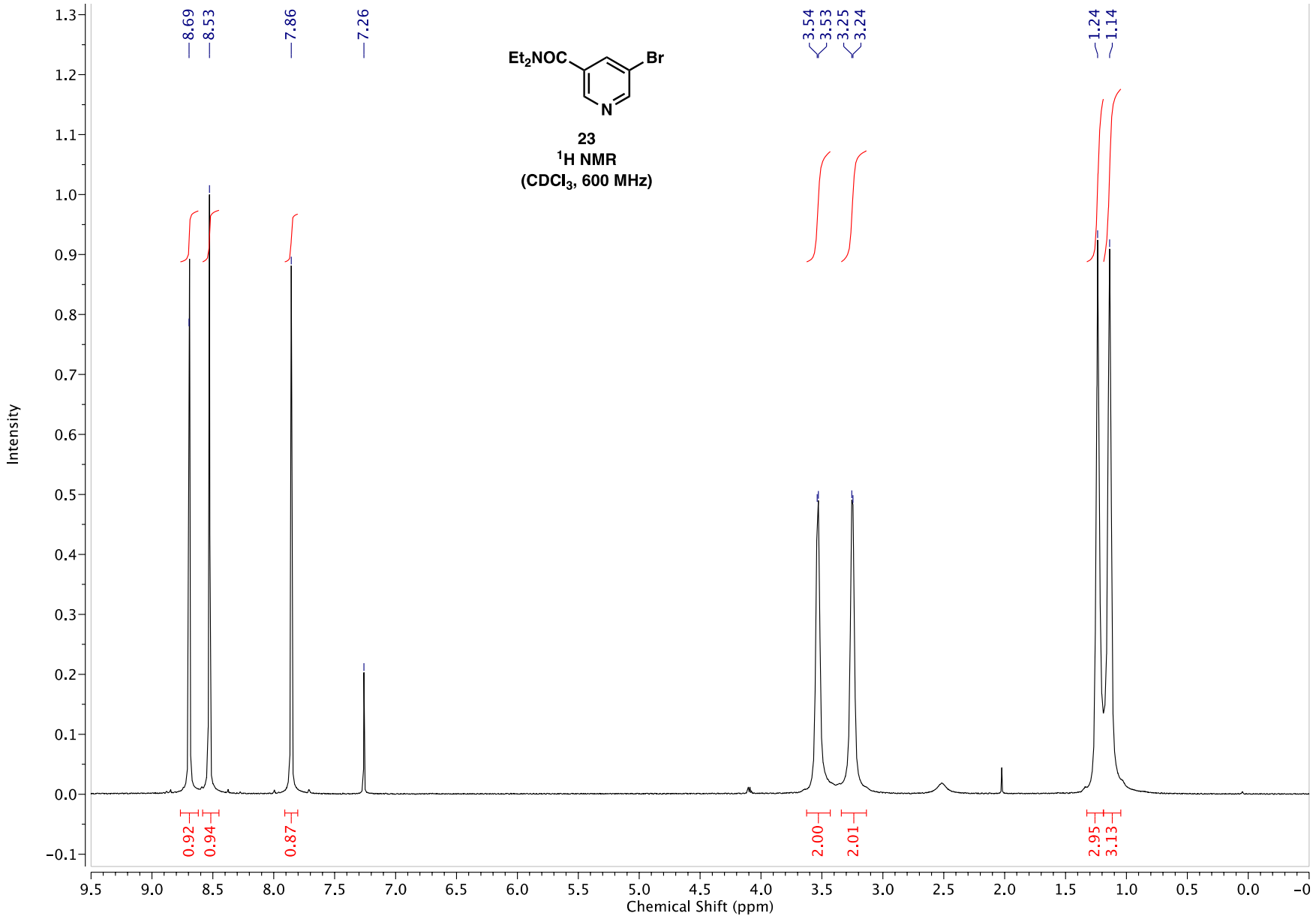

164.97
154.29
138.09
126.07
77.16
52.77
MeO2C
CO2Me
N
17
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

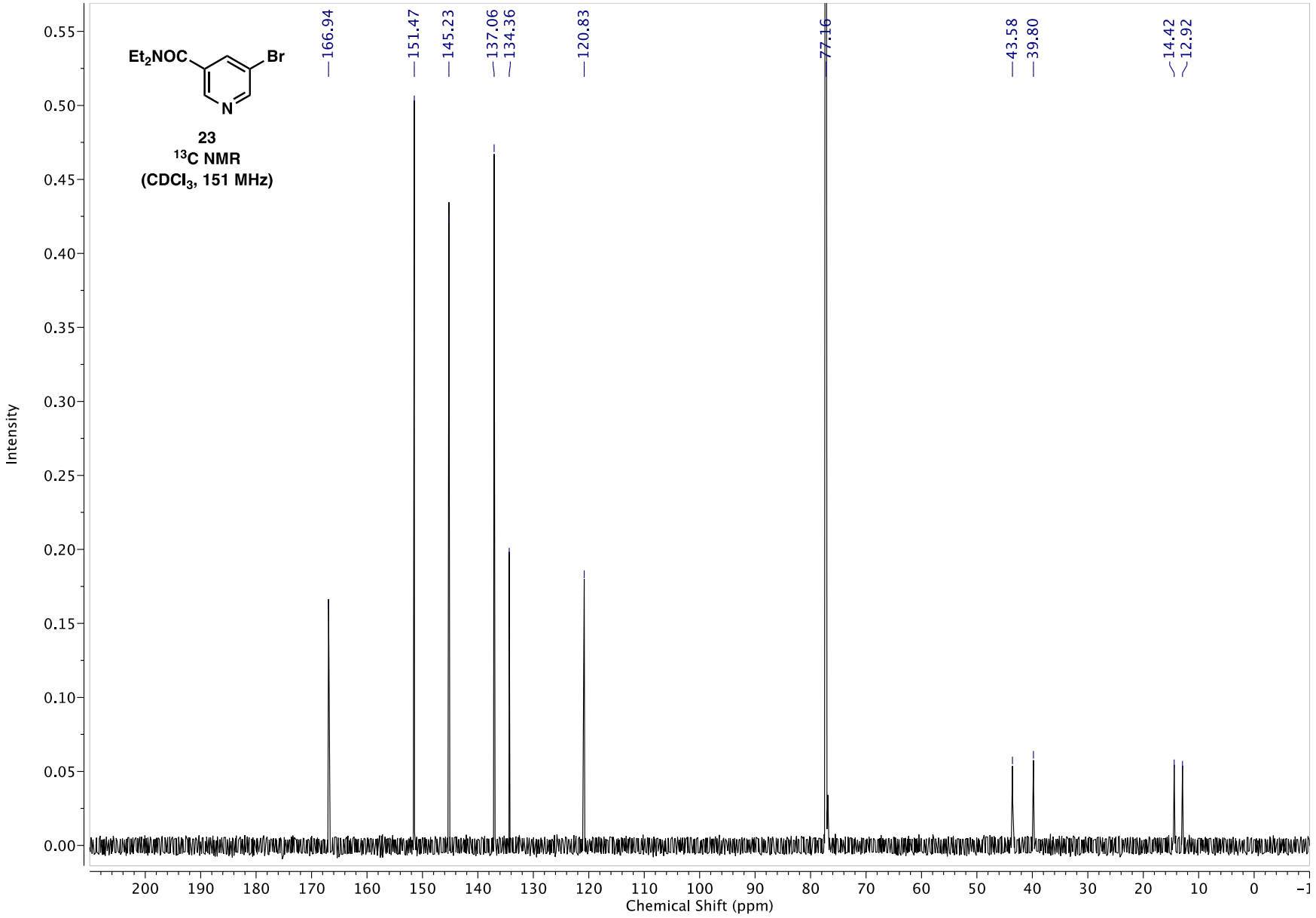

MeO2C
OMe
N
19
1H NMR
(CDCl3, 400 MHz)
8.83
8.48
8.47
7.79
7.79
7.79
7.78
3.96
3.91
1.01
1.00
1.00
3.05
3.14
Intensity
Chemical Shift (ppm)

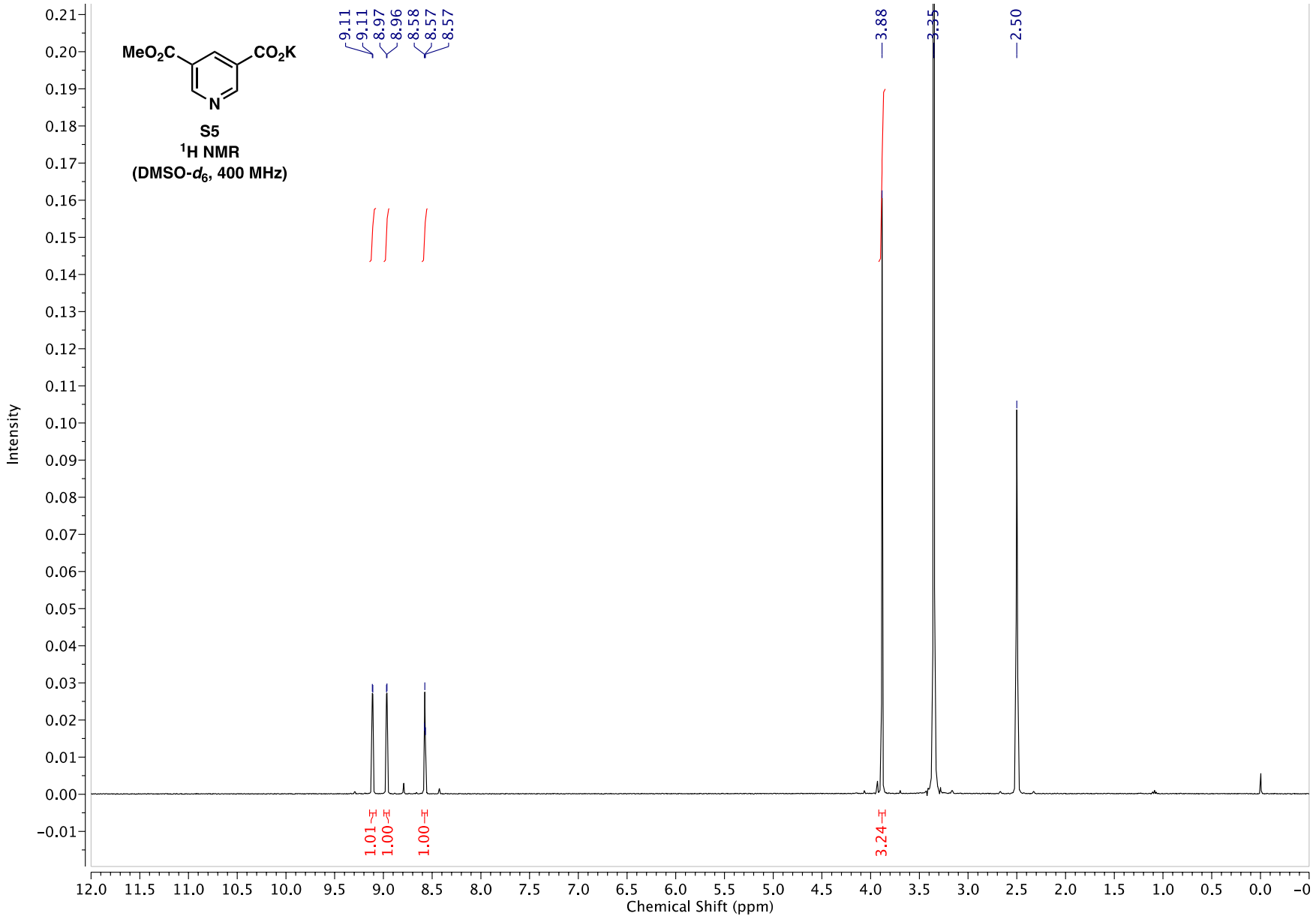

8.65
8.37
7.62
7.26
3.93
3.91
MeO2C
NH2
N
S3
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
0.96
0.93
1.00
5.64

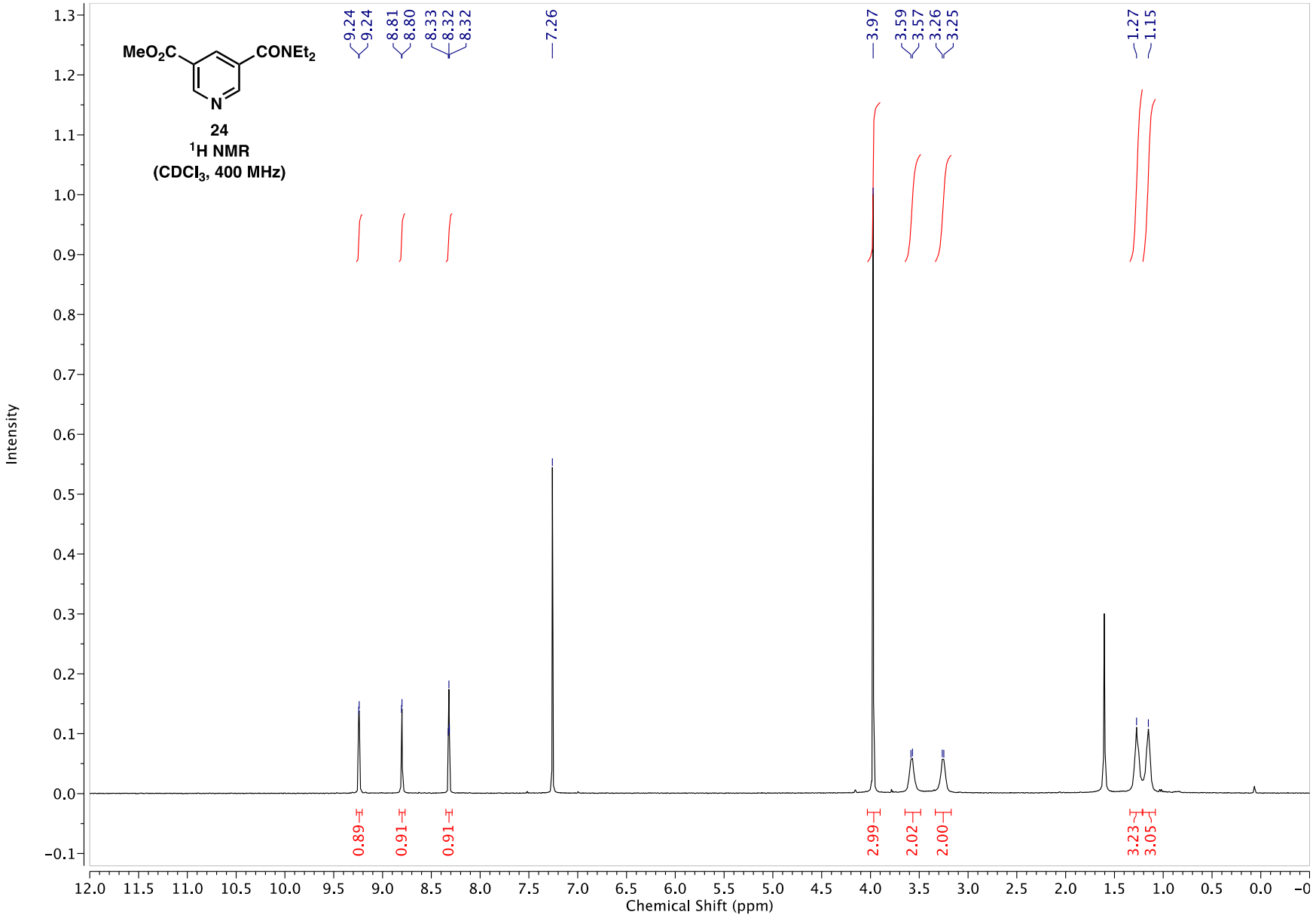

MeO2C
F
N
20
1H NMR
(CDCl3, 400 MHz)
9.05
8.66
8.65
8.01
8.01
8.01
8.00
7.99
7.99
7.99
7.98
7.26
3.98
0.34
0.34
0.33
1.00
Intensity
Chemical Shift (ppm)

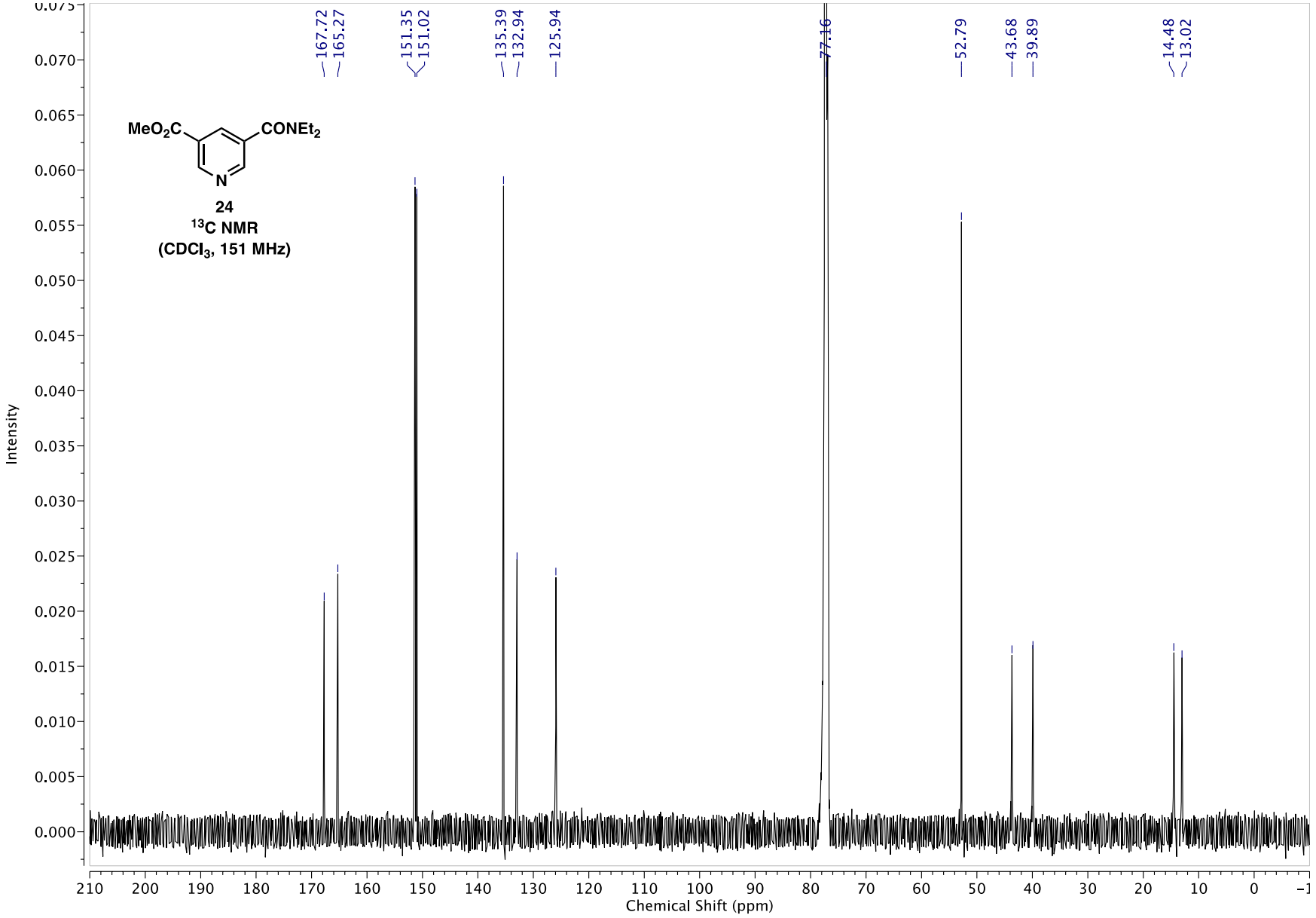

MeO2C
Br
N
22
1H NMR
(CDCl3, 400 MHz)
9.13
9.12
8.84
8.84
8.44
8.43
8.43
7.26
3.97
1.00
1.01
1.01
3.21
Intensity
Chemical Shift (ppm)

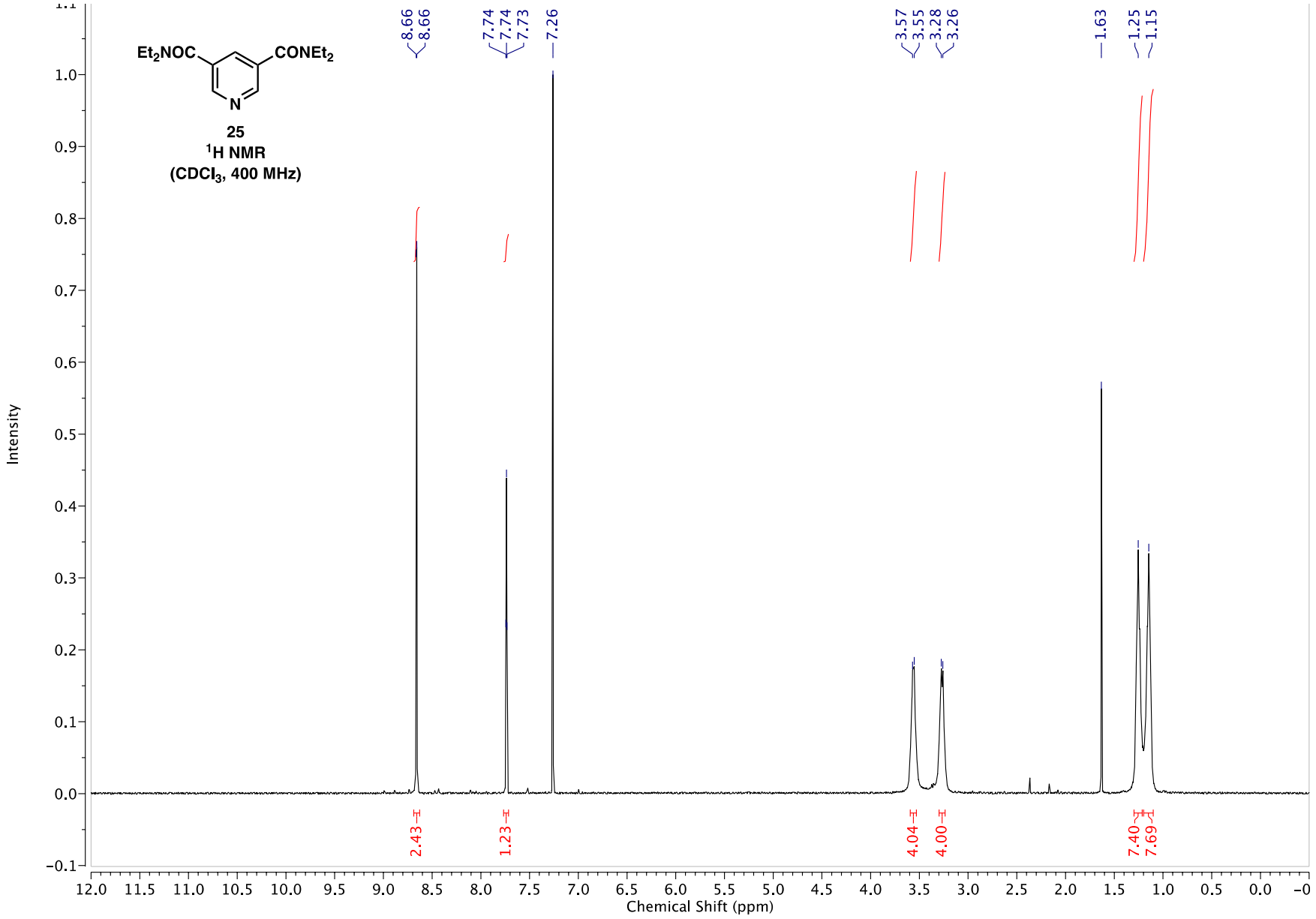

8.69
8.53
7.86
7.26
3.54
3.53
3.25
3.24
1.24
1.14
Et2NOC
Br
N
23
1H NMR
(CDCl3, 600 MHz)
Intensity
Chemical Shift (ppm)
0.92
0.94
0.87
2.00
2.01
2.95
3.13

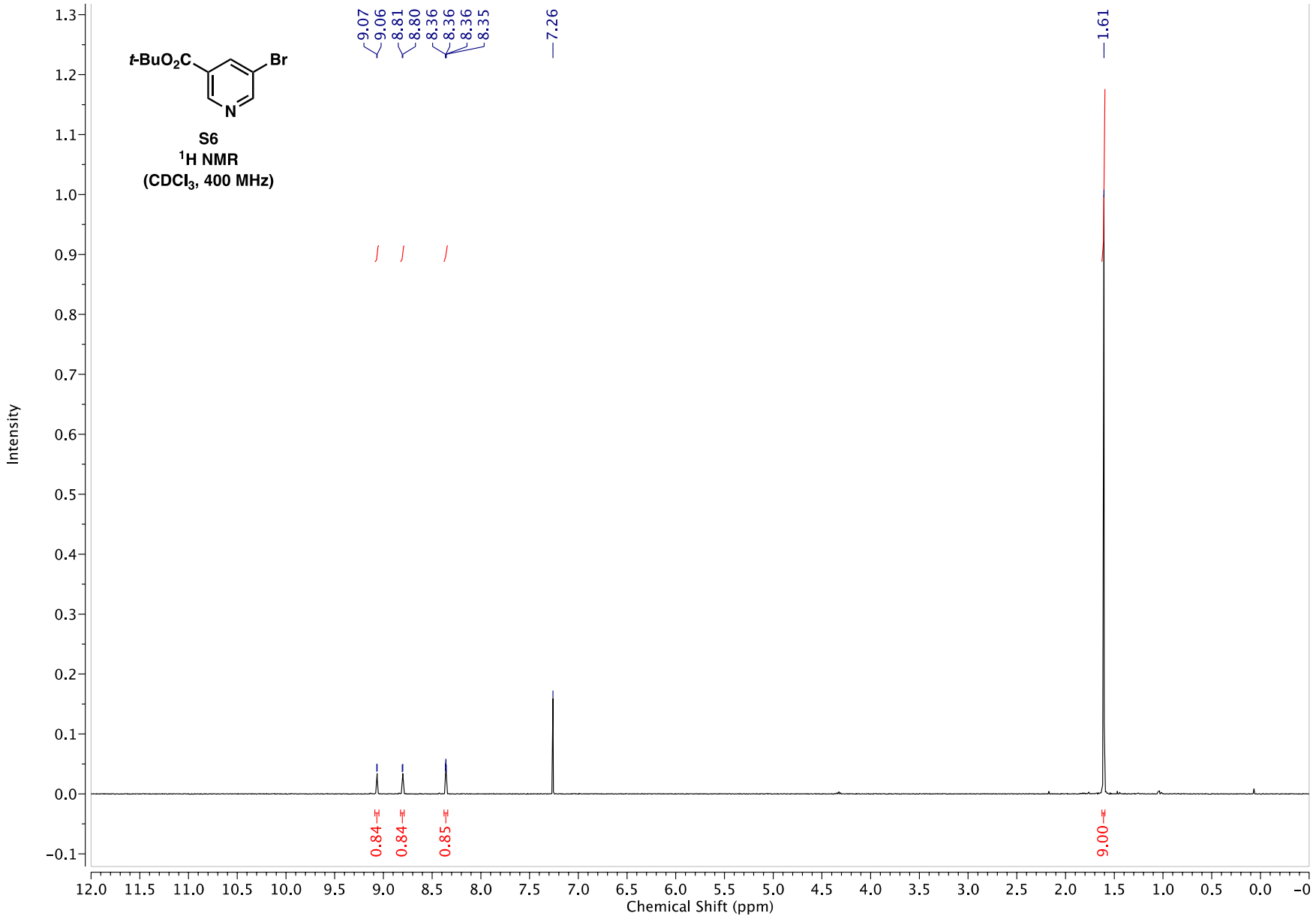

Et2NOC
Br
N
23
13C NMR
(CDCl3, 151 MHz)
166.94
151.47
145.23
137.06
134.36
120.83
77.16
43.58
39.80
14.42
12.92
Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

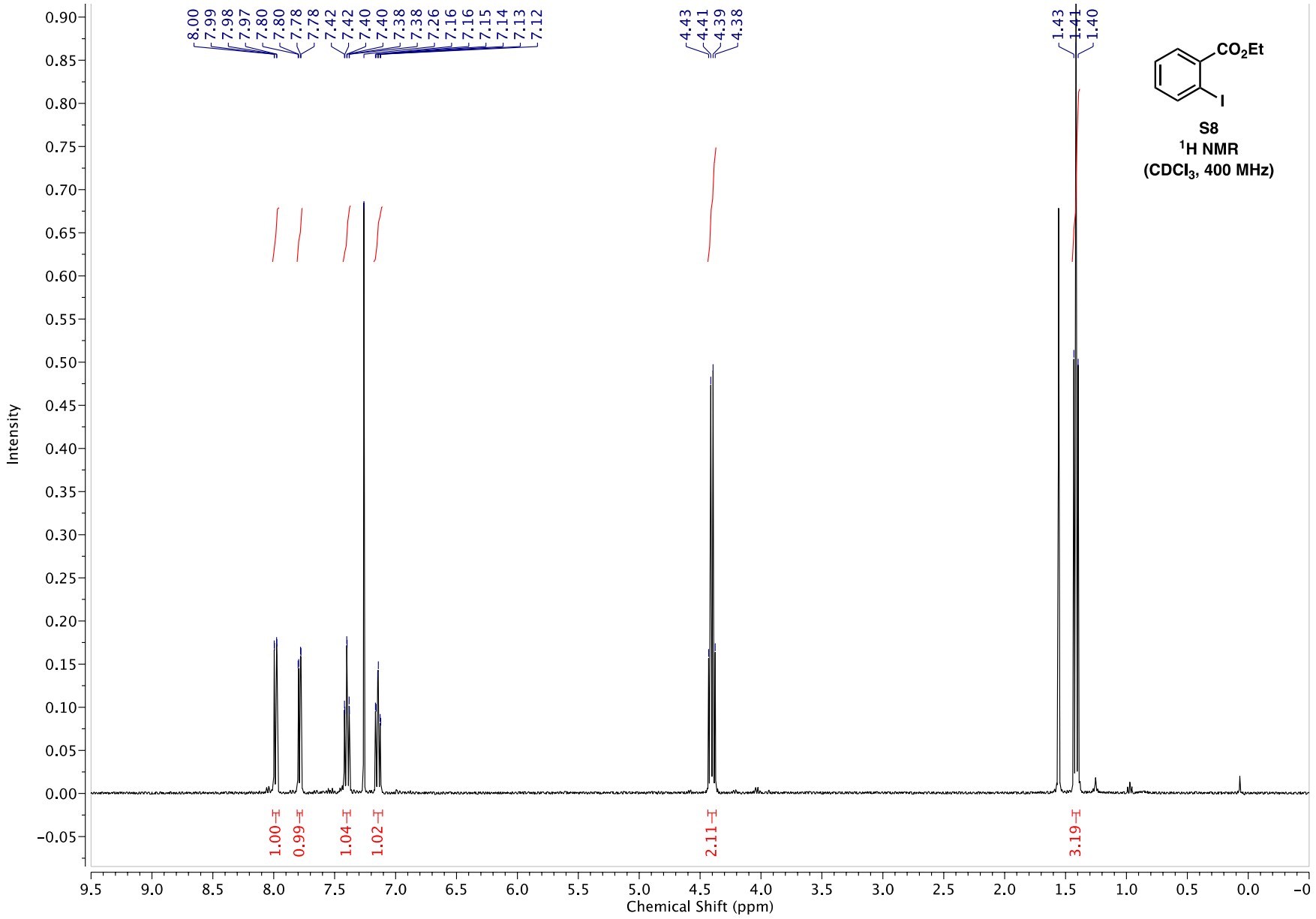

MeO2C
CO2K
N
S5
1H NMR
(DMSO-d6, 400 MHz)
9.11
9.11
8.97
8.96
8.58
8.57
8.57
3.88
3.35
2.50
1.01
1.00
1.00
3.24
Intensity
Chemical Shift (ppm)

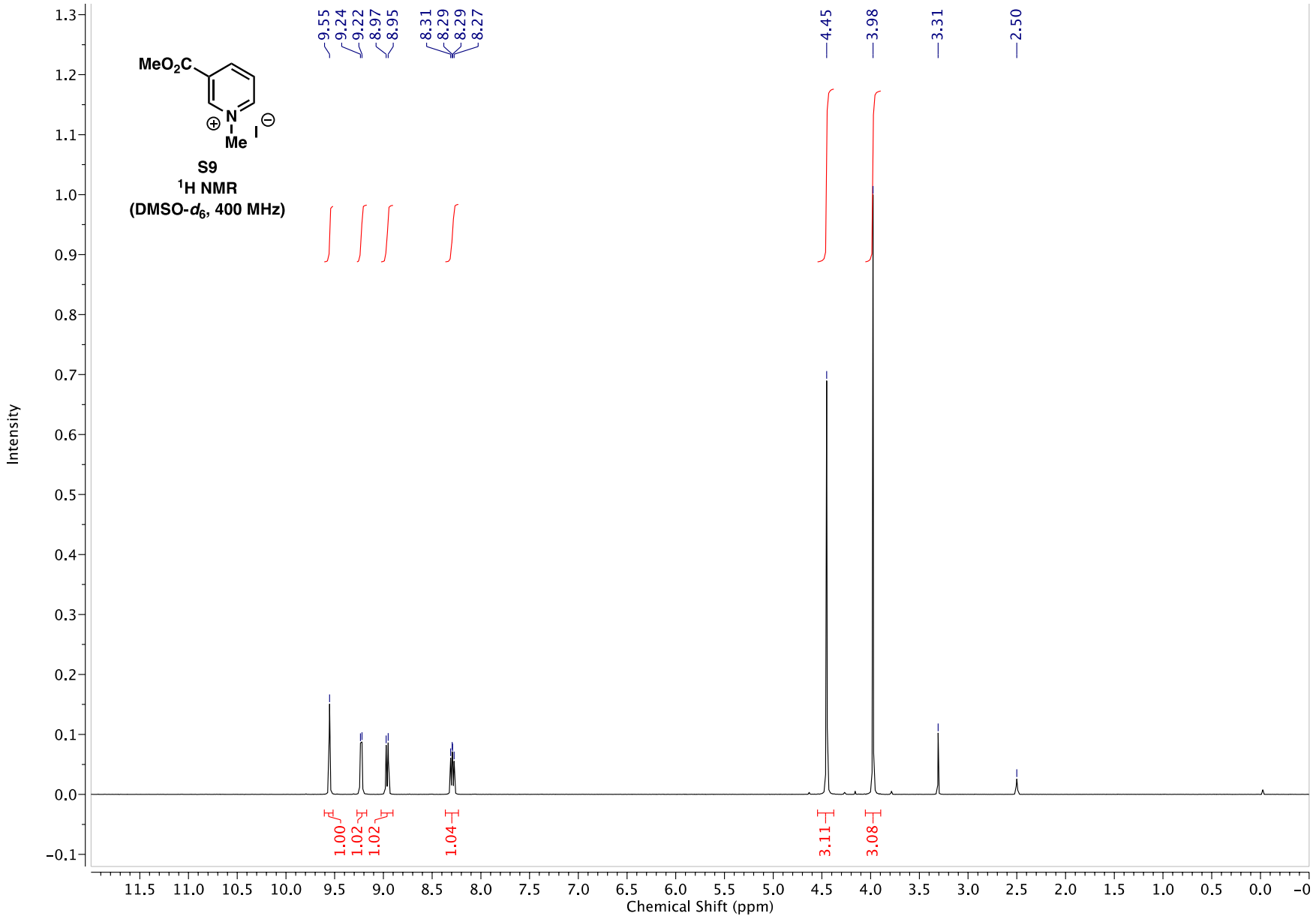

MeO2C
CONEt2
N
24
1H NMR
(CDCl3, 400 MHz)
9.24
9.24
8.81
8.80
8.33
8.32
8.32
7.26
3.97
3.59
3.57
3.26
3.25
1.27
1.15
0.89
0.91
0.91
2.99
2.02
2.00
3.23
3.05
Intensity
Chemical Shift (ppm)

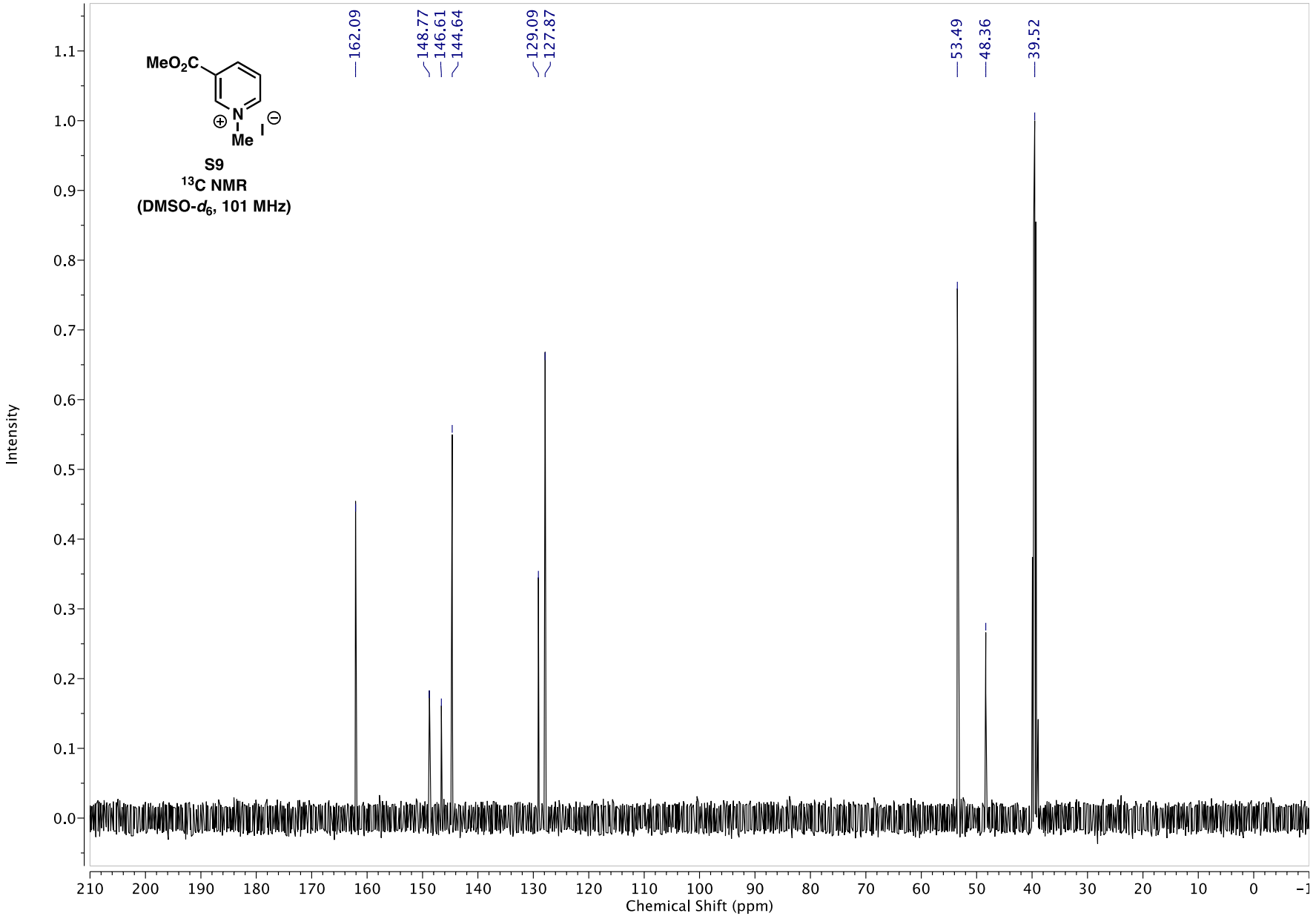

167.72
165.27
151.35
151.02
135.39
132.94
125.94
77.16
52.79
43.68
39.89
14.48
13.02
MeO2C
CONEt2
N
24
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

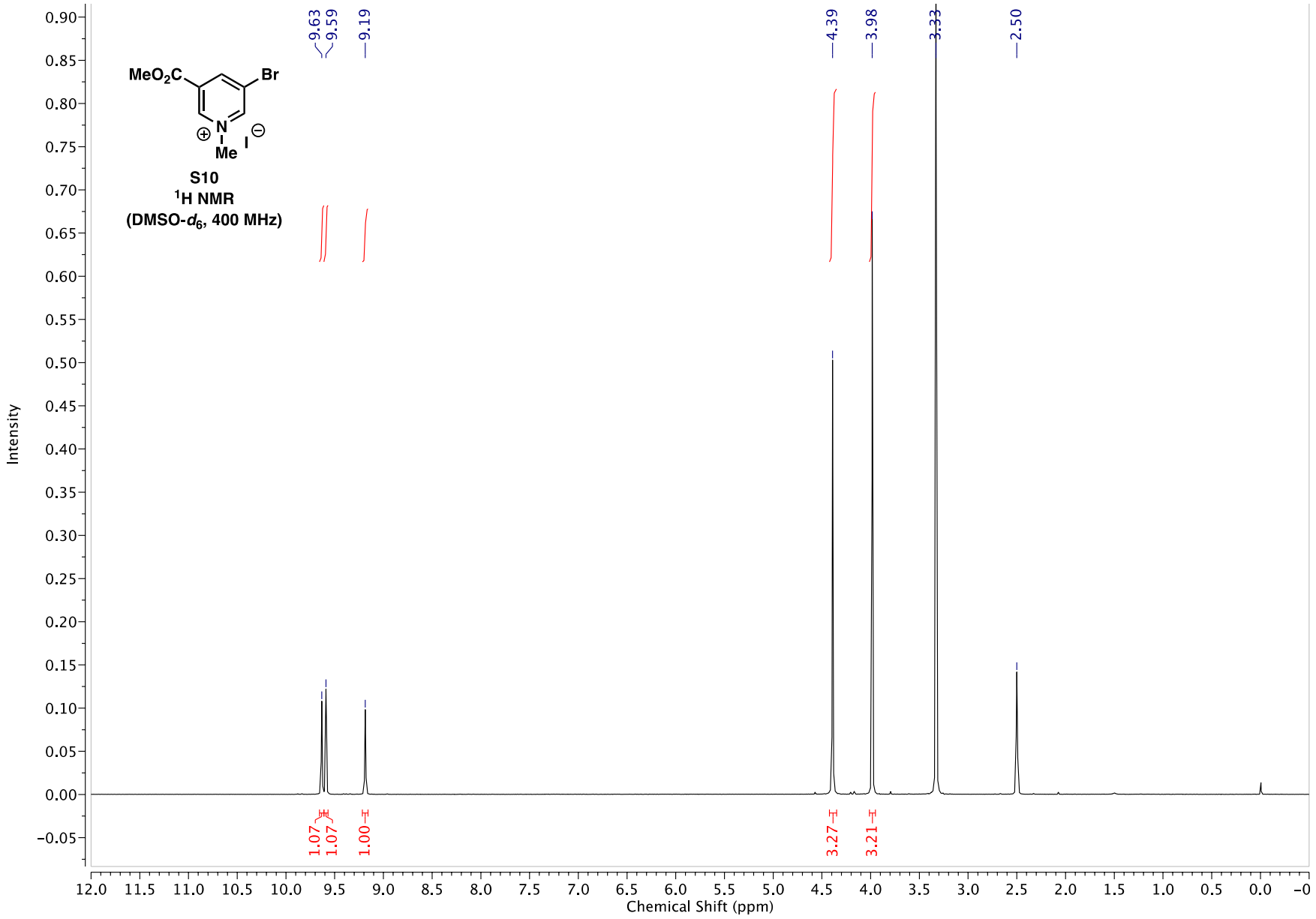

Et2NOC
CONEt2
N
25
1H NMR
(CDCl3, 400 MHz)
8.66
8.66
7.74
7.74
7.73
7.26
3.57
3.55
3.28
3.26
1.63
1.25
1.15
2.43
1.23
4.04
4.00
7.40
7.69
Intensity
Chemical Shift (ppm)

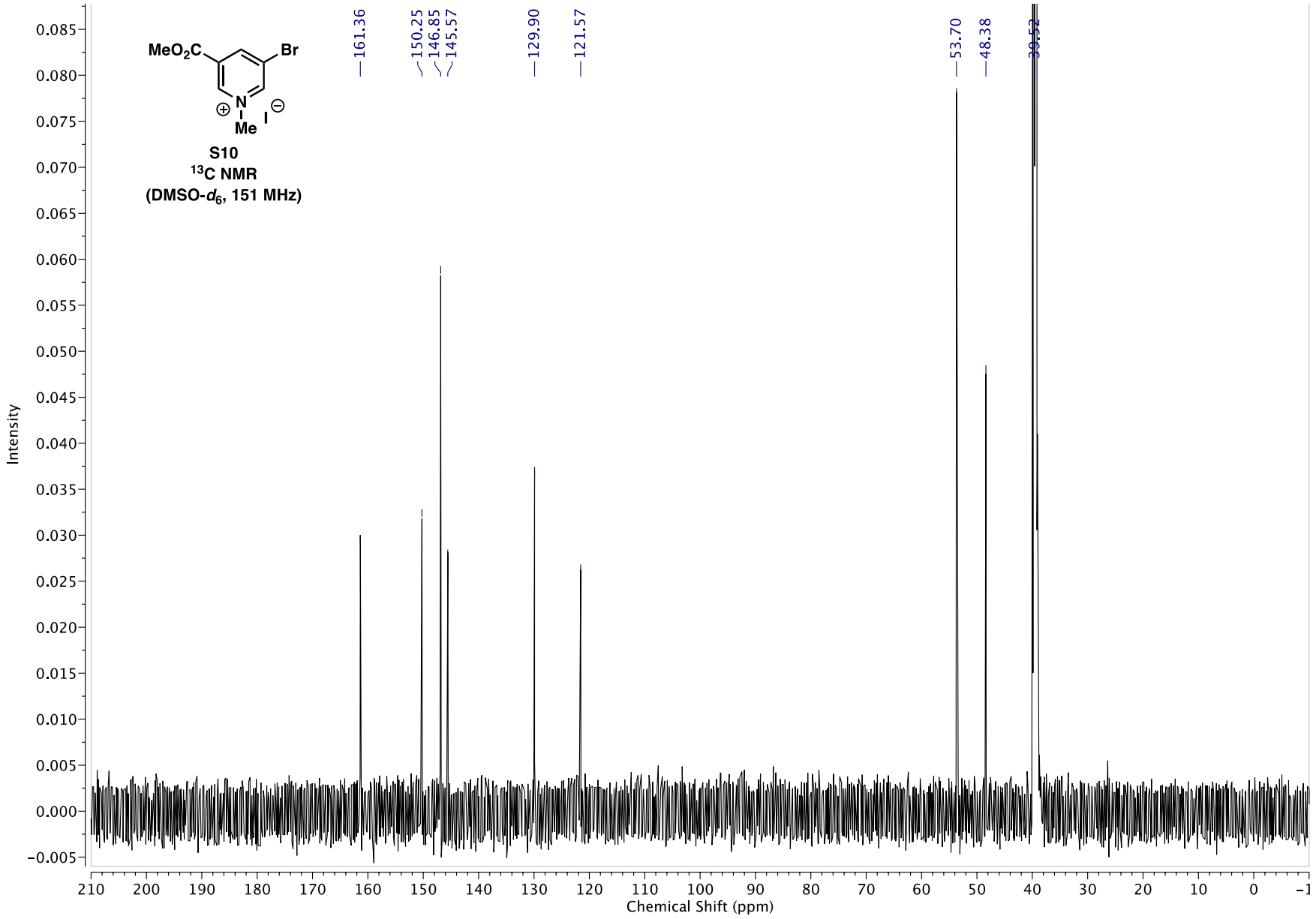

t-BuO2C
Br
N
S6
1H NMR
(CDCl3, 400 MHz)
9.07
9.06
8.81
8.80
8.36
8.36
8.36
8.35
7.26
1.61
0.84
0.84
0.85
9.00
Intensity
Chemical Shift (ppm)

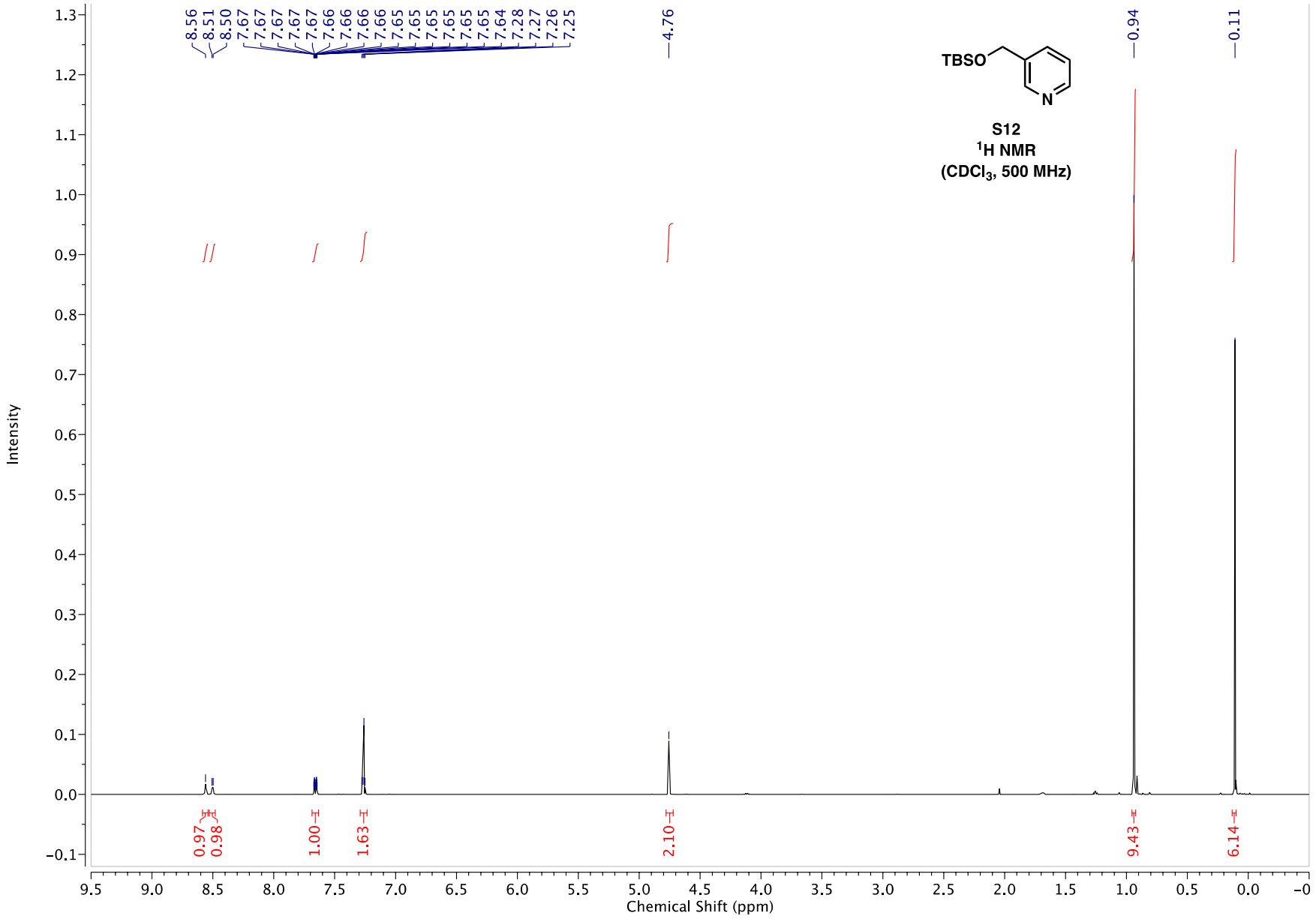

8.00
7.99
7.98
7.97
7.80
7.80
7.78
7.78
7.42
7.42
7.40
7.40
7.38
7.38
7.26
7.16
7.16
7.15
7.14
7.13
7.12
4.43
4.41
4.39
4.38
1.43
1.41
1.40
CO2Et
I
S8
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
1.00
0.99
1.04
1.02
2.11
3.19

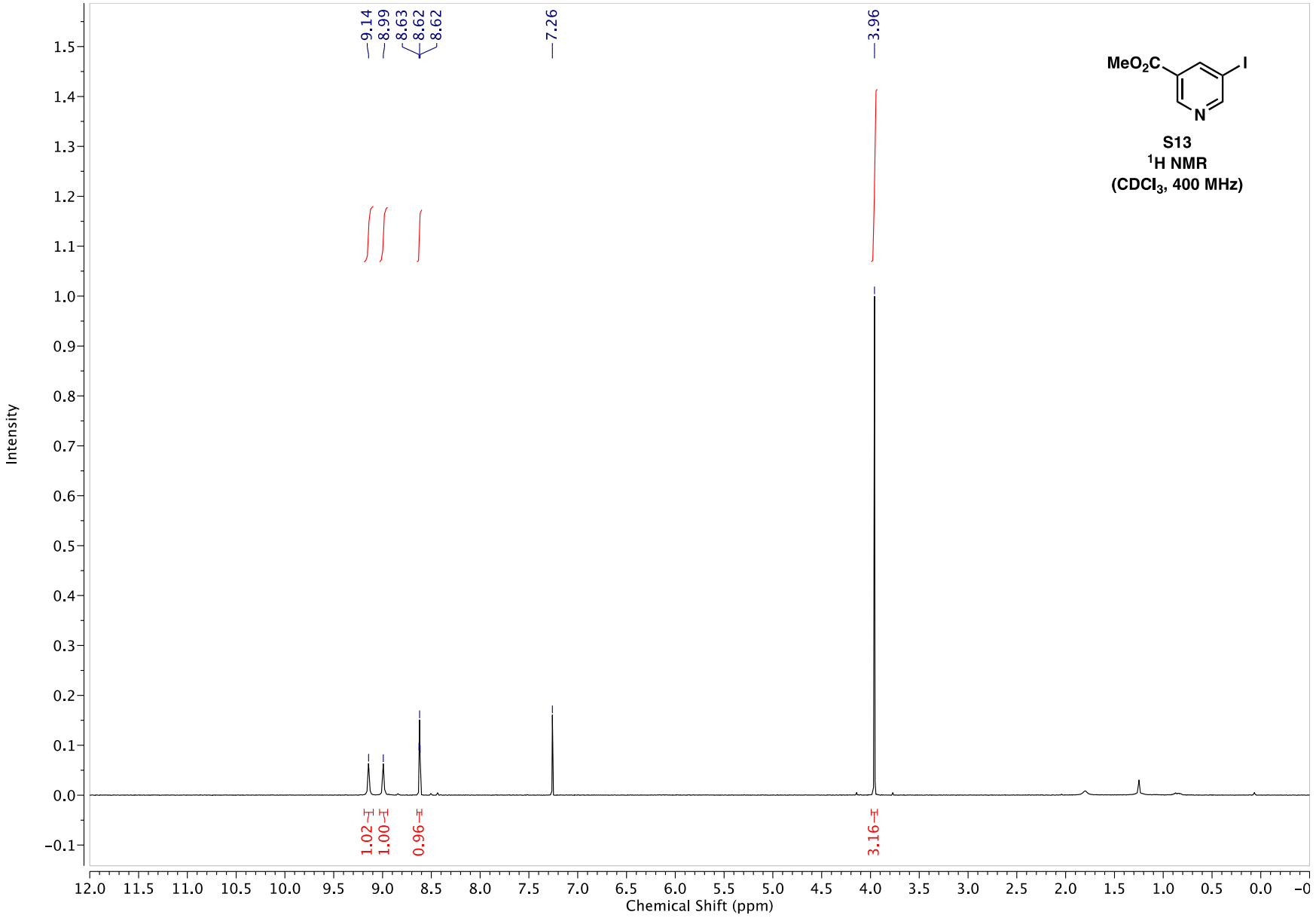

MeO2C
N
Me
I
S9
1H NMR
(DMSO-d6, 400 MHz)
9.55
9.24
9.22
8.97
8.95
8.31
8.29
8.29
8.27
4.45
3.98
3.31
2.50
1.00
1.02
1.02
1.04
3.11
3.08
Intensity
Chemical Shift (ppm)

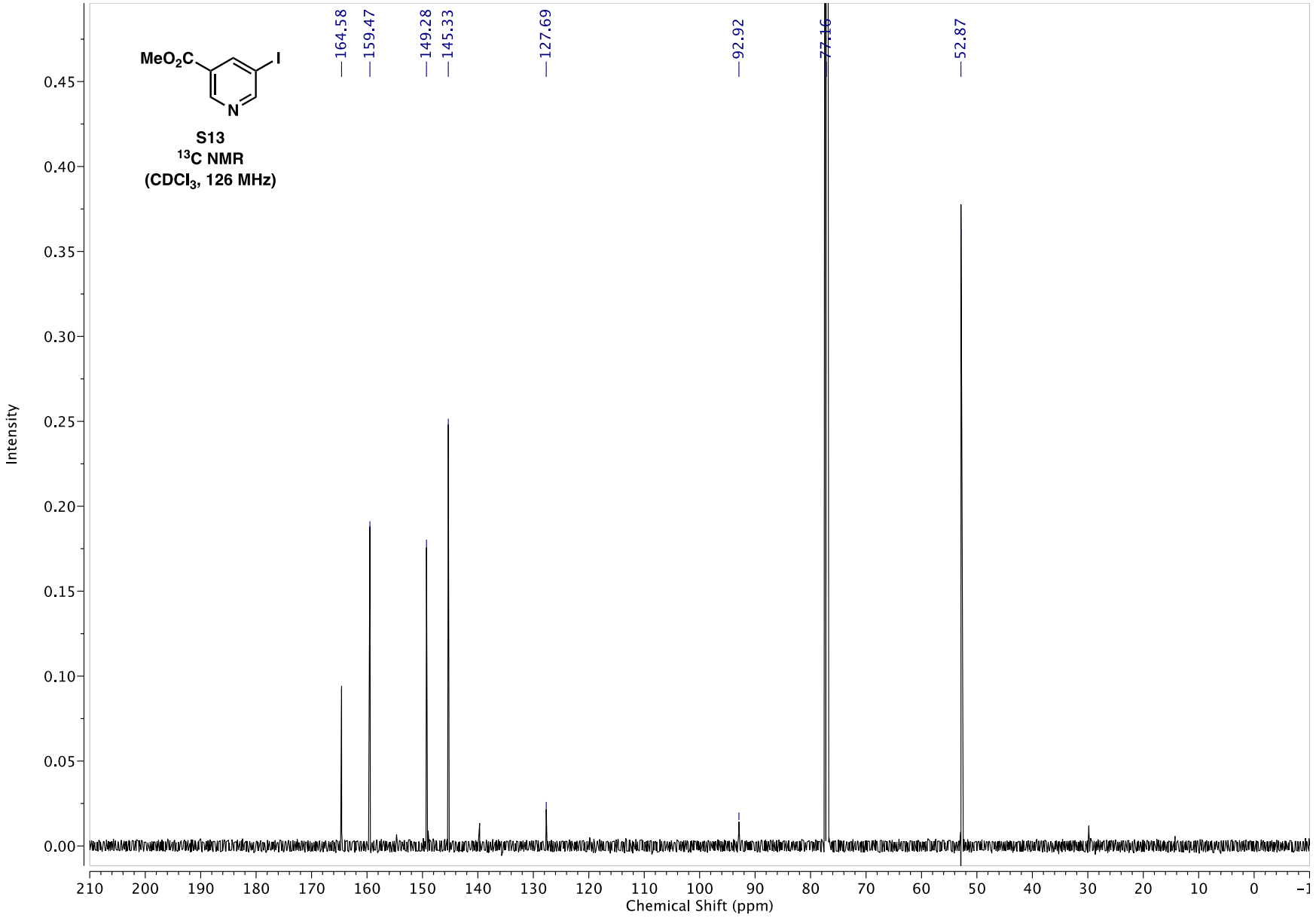

MeO2C
N
Me
I
S9
13C NMR
(DMSO-d6, 101 MHz)
162.09
148.77
146.61
144.64
129.09
127.87
53.49
48.36
39.52
Intensity
Chemical Shift (ppm)

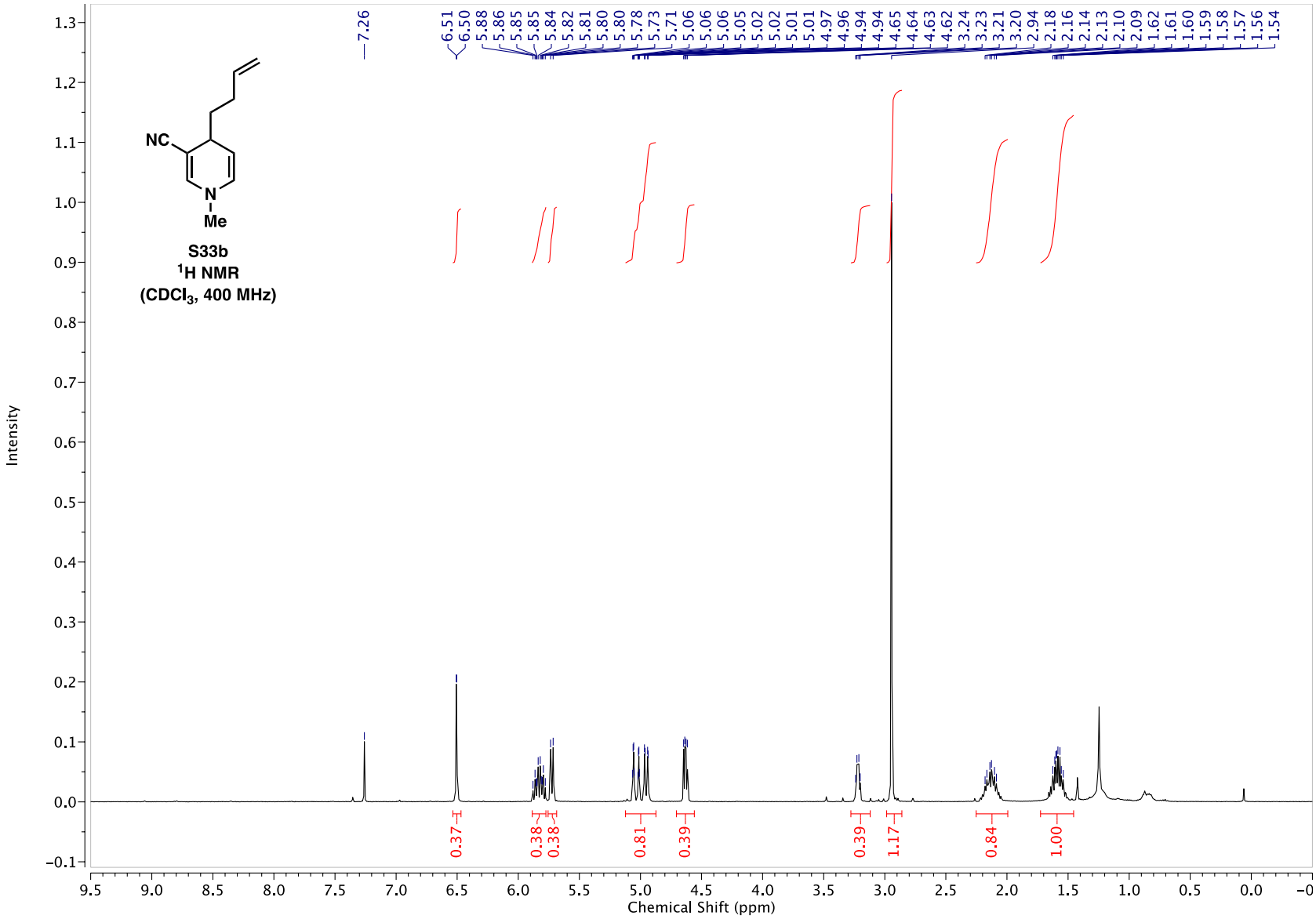

MeO2C
Br
N
Me
I
S10
1H NMR
(DMSO-d6, 400 MHz)
9.63
9.59
9.19
4.39
3.98
3.33
2.50
1.07
1.07
1.00
3.27
3.21
Intensity
Chemical Shift (ppm)

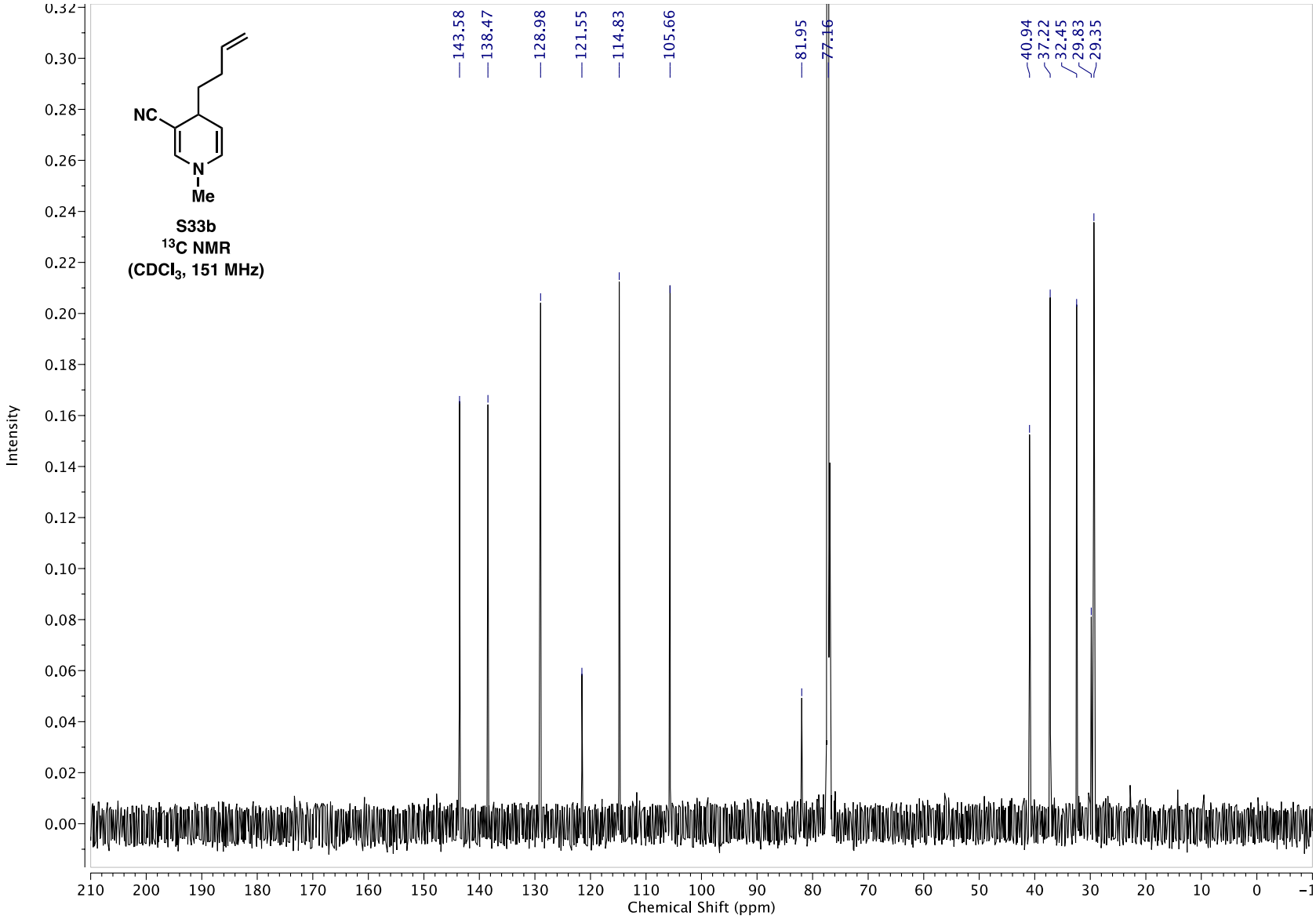

MeO2C
Br
N
Me
I
S10
13C NMR
(DMSO-d6, 151 MHz)
161.36
150.25
146.85
145.57
129.90
121.57
53.70
48.38
39.52
Intensity
Chemical Shift (ppm)

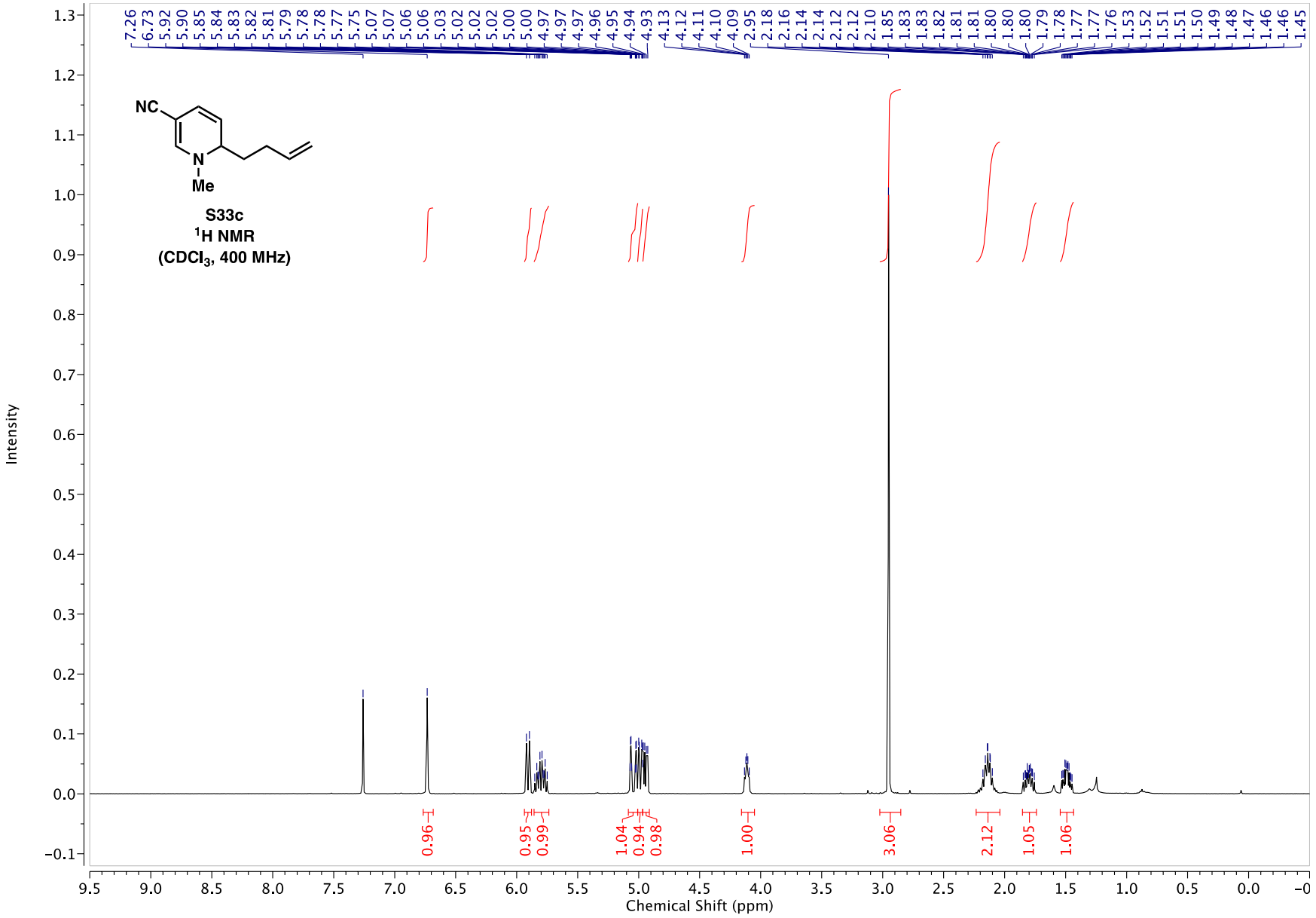

8.56
8.51
8.50
7.67
7.67
7.67
7.67
7.67
7.66
7.66
7.66
7.66
7.65
7.65
7.65
7.65
7.65
7.65
7.64
7.28
7.27
7.26
7.25
4.76
0.94
0.11
TBSO
N
S12
1H NMR
(CDCl3, 500 MHz)
Intensity
Chemical Shift (ppm)
0.97
0.98
1.00
1.63
2.10
9.43
6.14

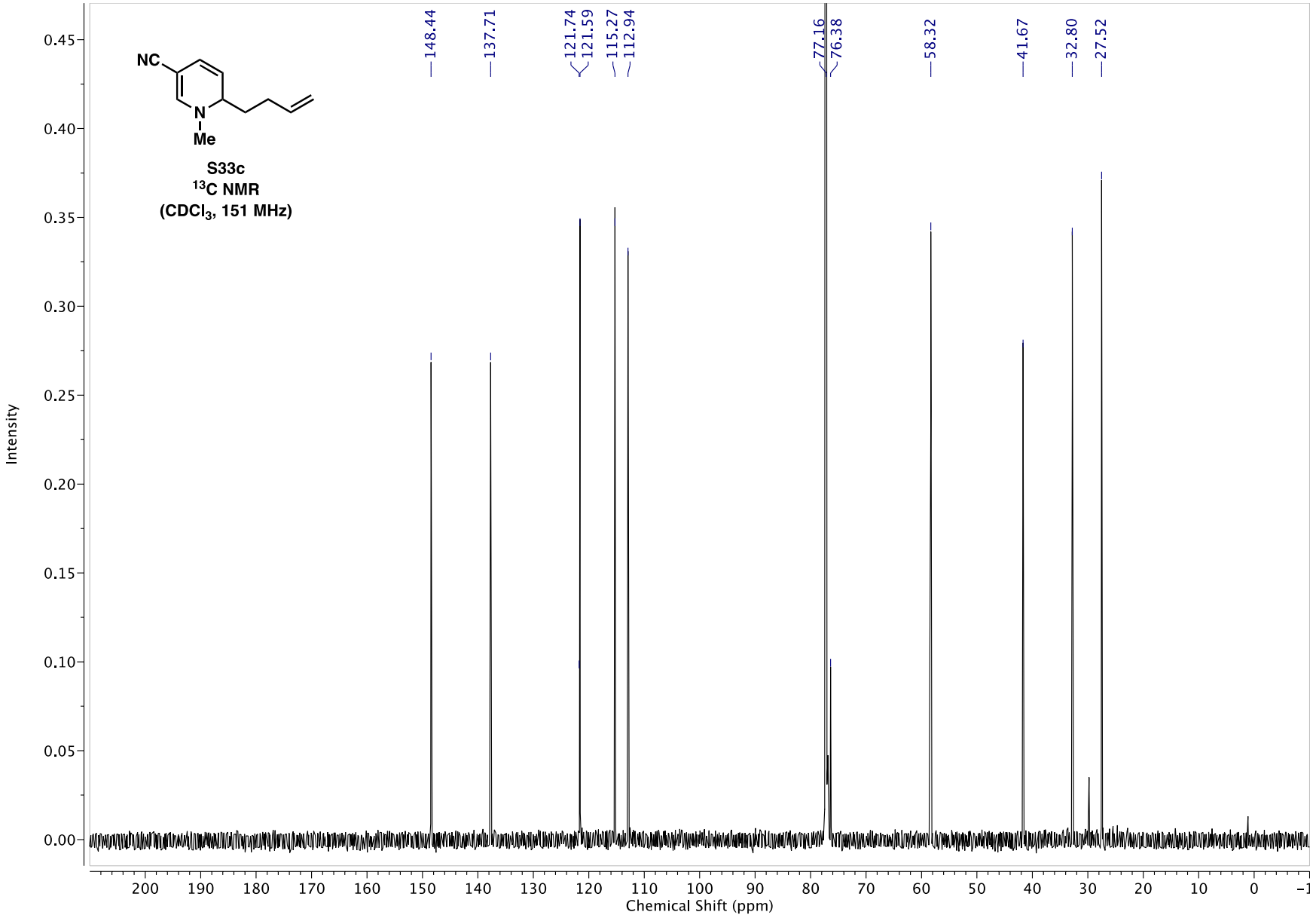

9.14
8.99
8.63
8.62
8.62
7.26
3.96
MeO2C
I
N
S13
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
1.02
1.00
0.96
3.16

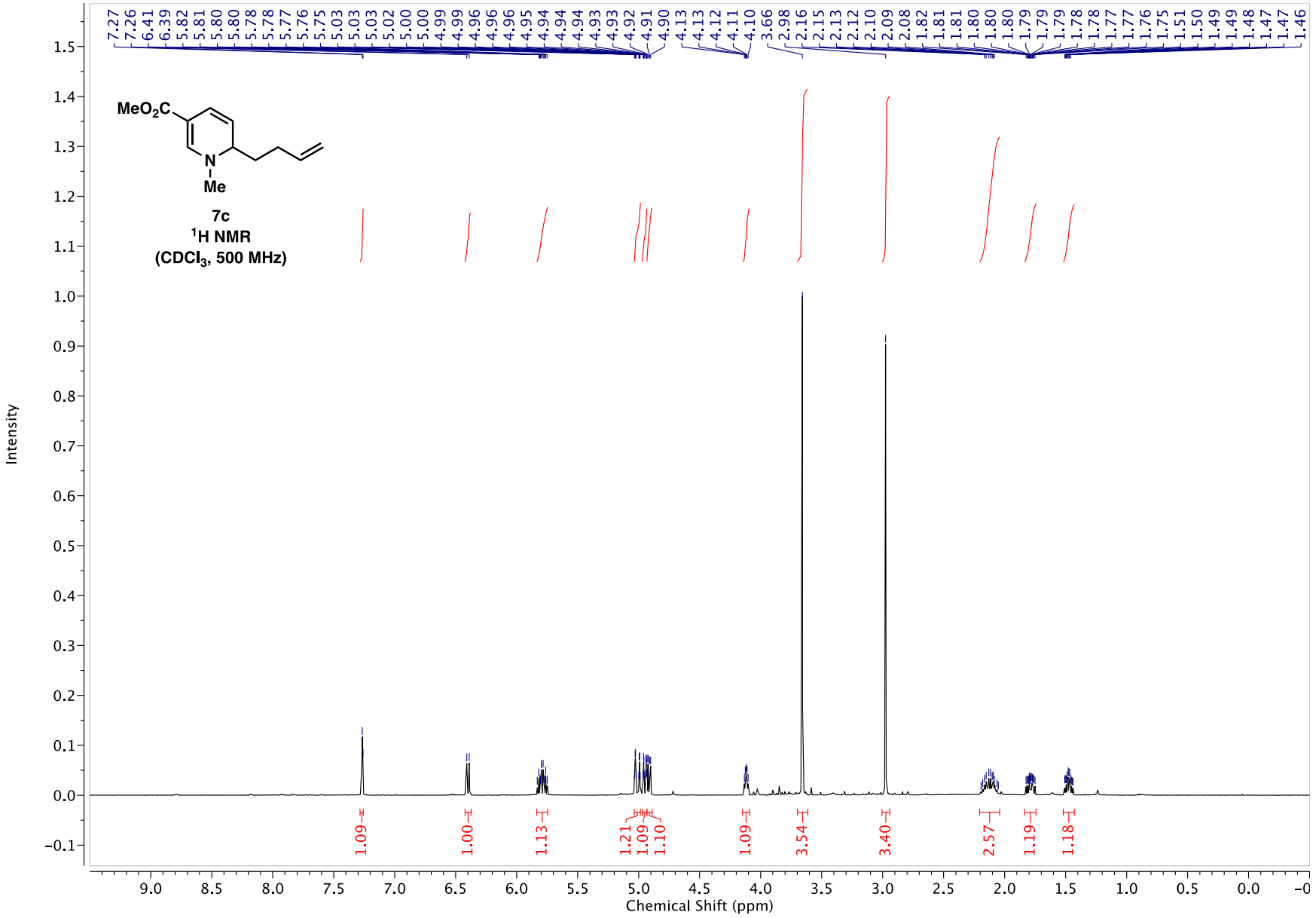

MeO2C
I
N
S13
13C NMR
(CDCl3, 126 MHz)
164.58
159.47
149.28
145.33
127.69
92.92
77.16
52.87
Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

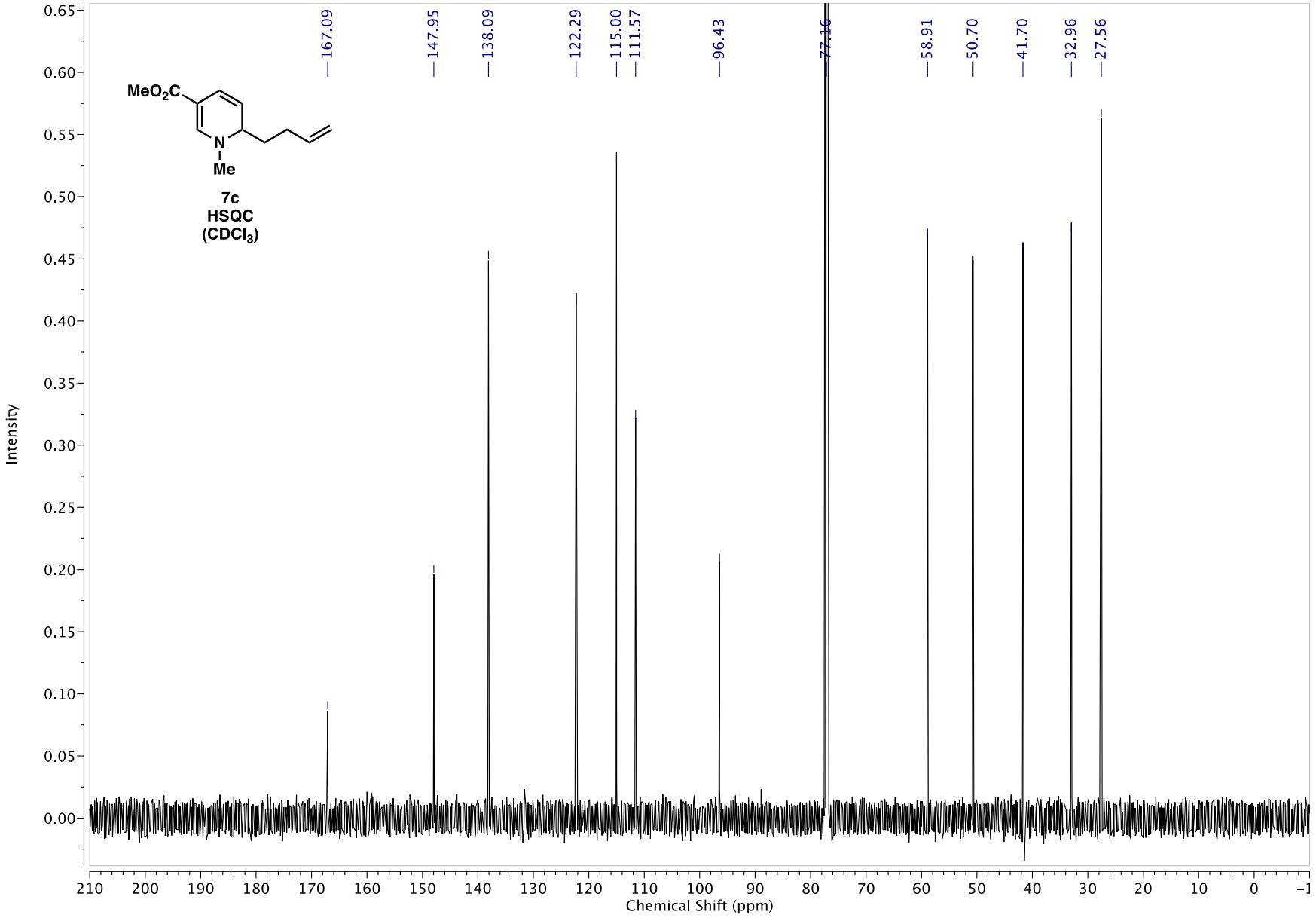

NC
N
Me
S33b
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
7.26
6.51
6.50
5.88
5.86
5.85
5.85
5.84
5.82
5.81
5.80
5.80
5.78
5.73
5.71
5.06
5.06
5.06
5.05
5.02
5.02
5.01
5.01
4.97
4.96
4.94
4.94
4.65
4.64
4.63
4.62
3.24
3.23
3.21
3.20
2.94
2.18
2.16
2.14
2.13
2.10
2.09
1.62
1.61
1.60
1.59
1.58
1.57
1.56
1.54
0.37
0.38
0.38
0.81
0.39
0.39
1.17
0.84
1.00

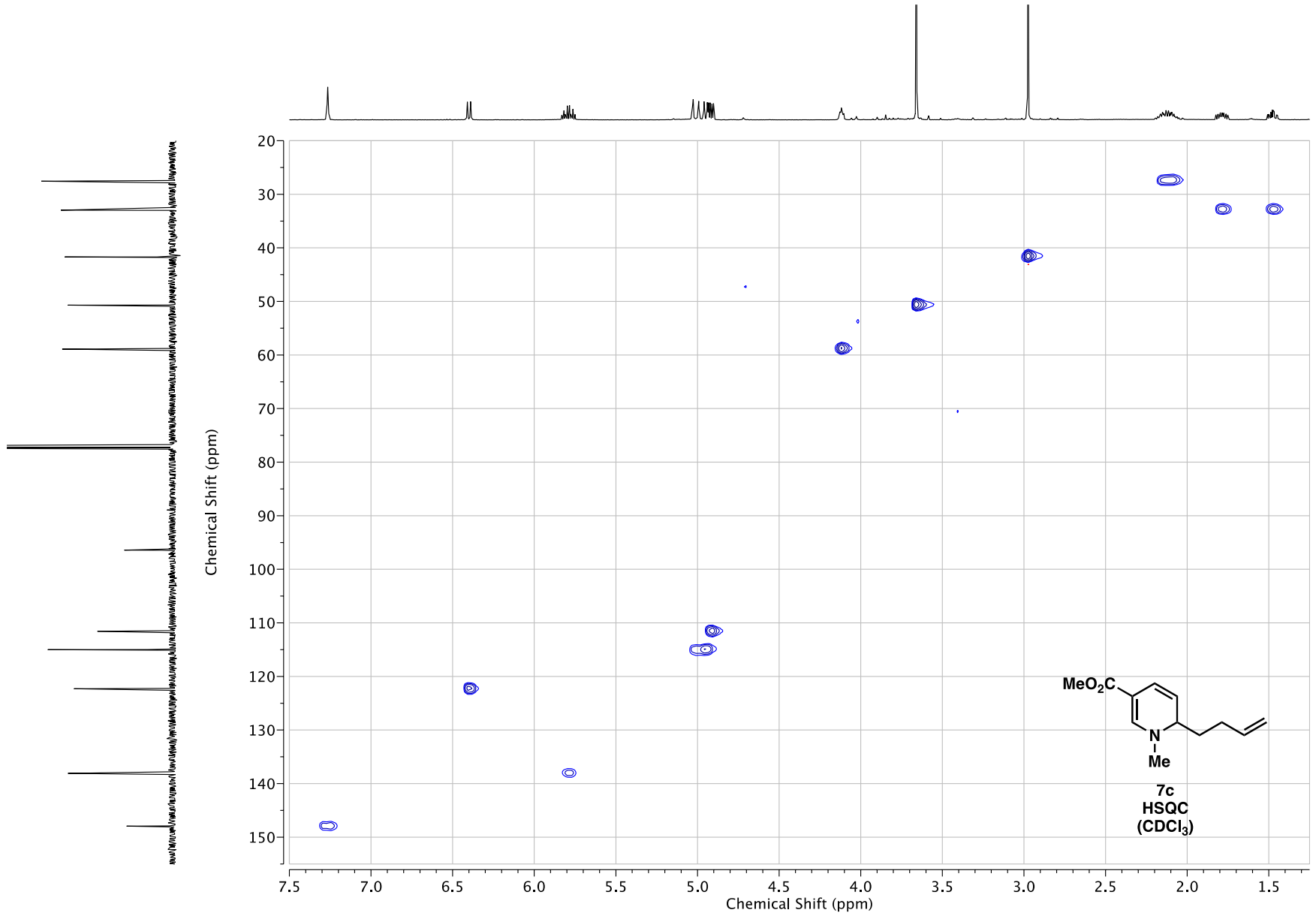

NC
N
Me
S33b
13C NMR
(CDCl3, 151 MHz)
143.58
138.47
128.98
121.55
114.83
105.66
81.95
77.16
40.94
37.22
32.45
29.83
29.35
Intensity
Chemical Shift (ppm)

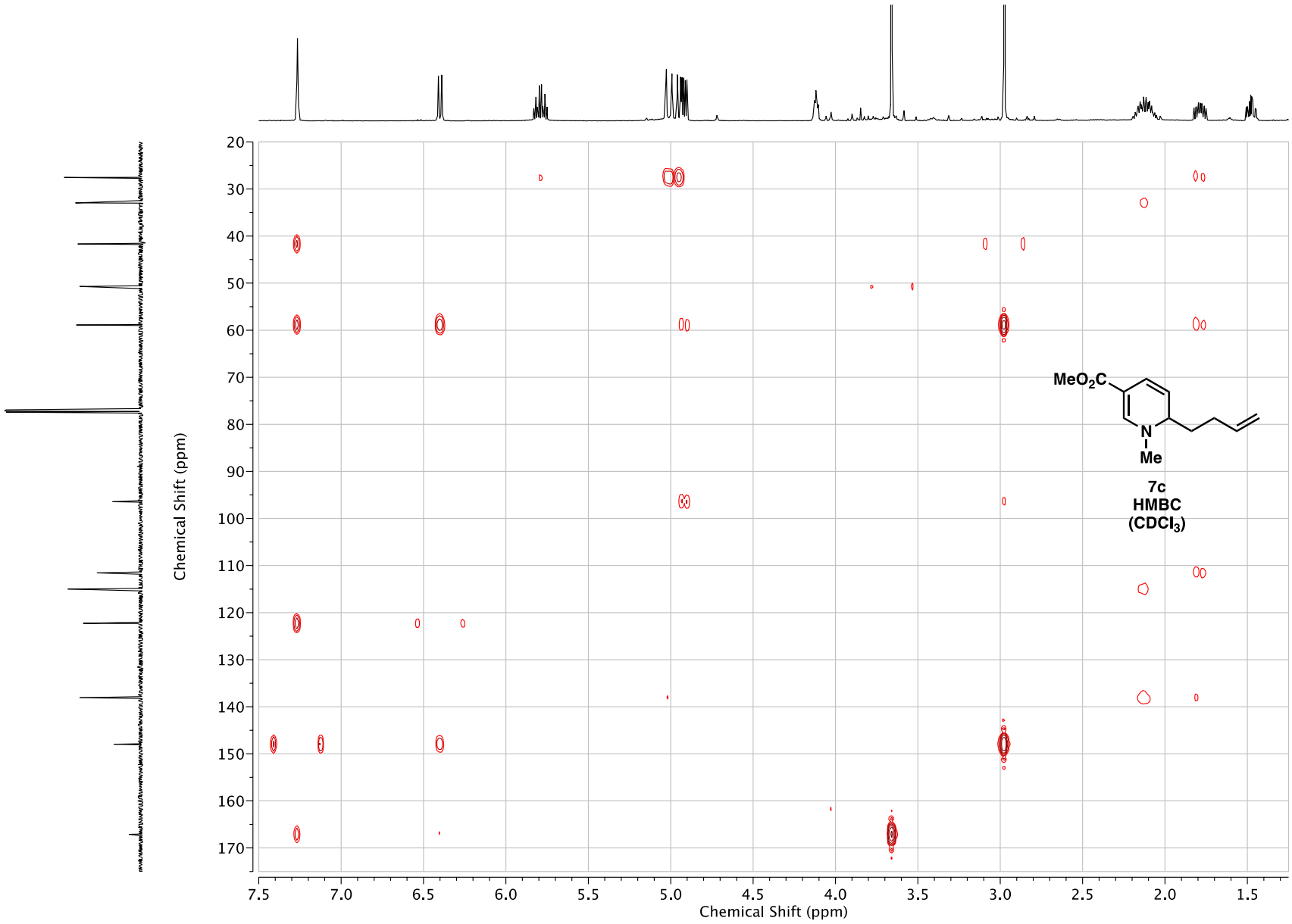

NC
N
Me
S33c
^{1}H NMR
($CDCl_3$, 400 MHz)
Intensity
Chemical Shift (ppm)
0.96
0.95
0.99
1.04
0.94
0.98
1.00
3.06
2.12
1.05
1.06

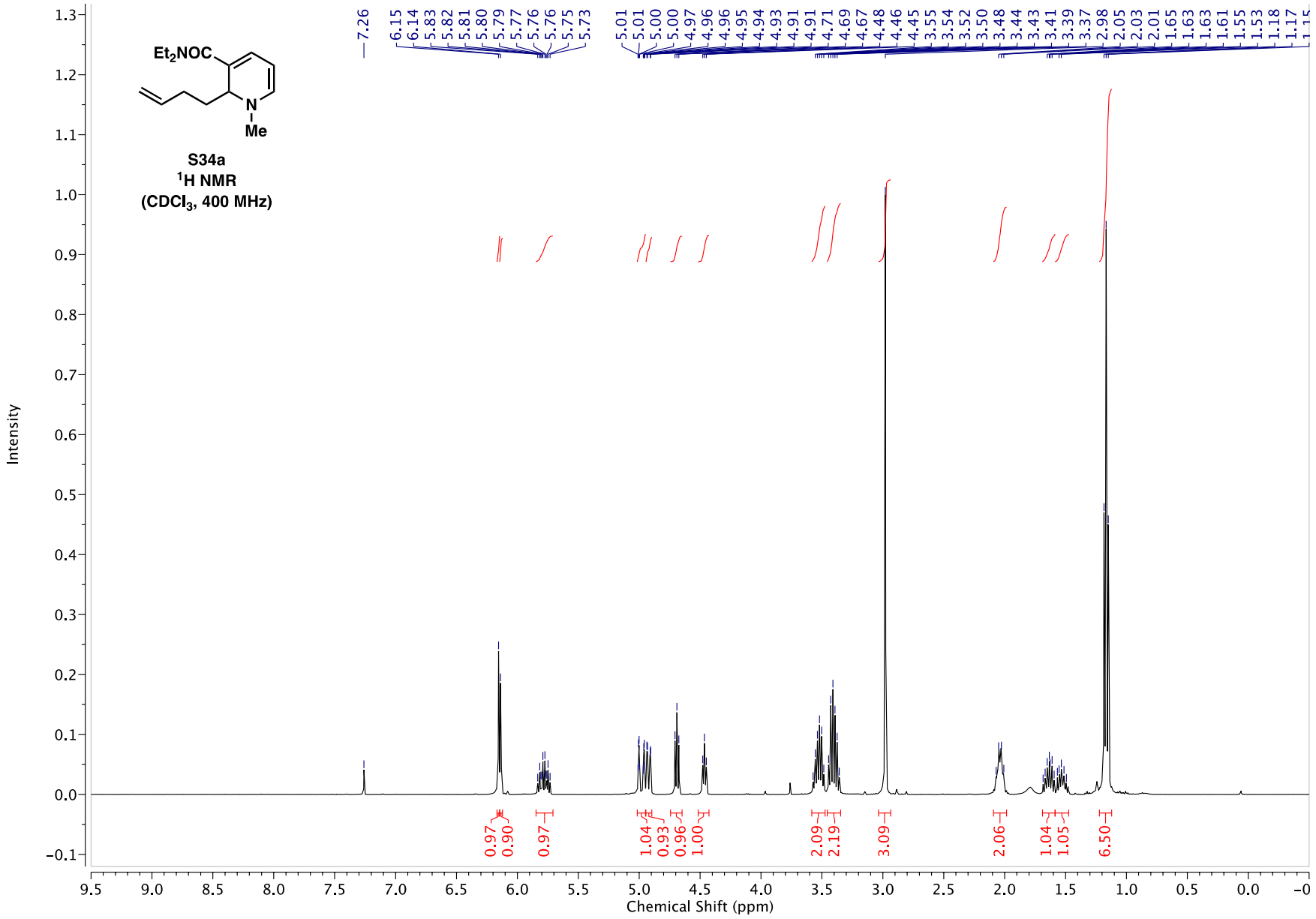

NC
N
Me
S33c
13C NMR
(CDCl3, 151 MHz)
148.44
137.71
121.74
121.59
115.27
112.94
77.16
76.38
58.32
41.67
32.80
27.52
Intensity
Chemical Shift (ppm)

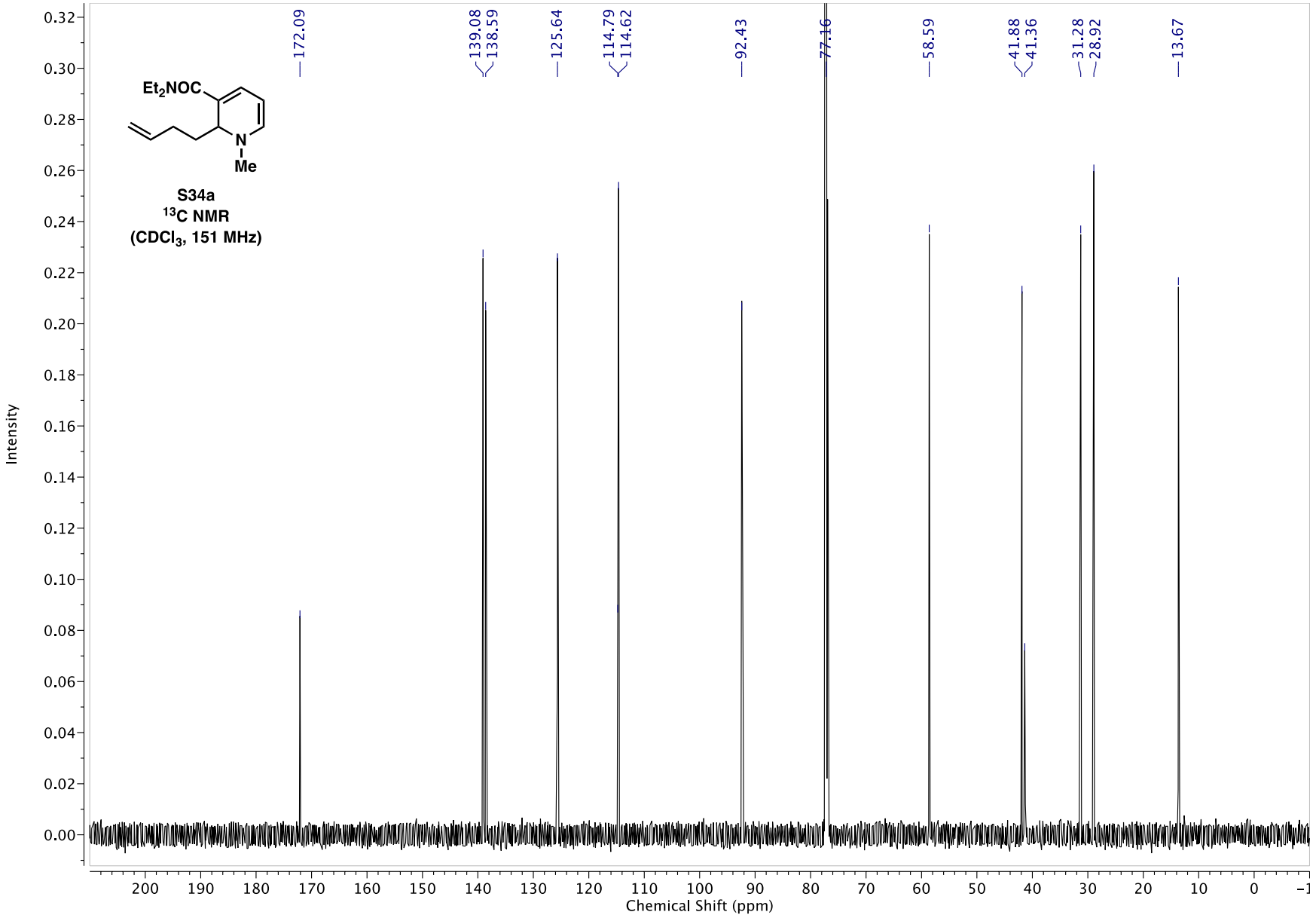

7.27 7.26 6.41 6.39 5.82 5.81 5.80 5.80 5.78 5.78 5.77 5.76 5.75 5.03 5.03 5.03 5.02 5.00 5.00 4.99 4.99 4.96 4.96 4.96 4.95 4.94 4.94 4.94 4.93 4.93 4.92 4.91 4.90 4.13 4.13 4.12 4.11 4.10 3.66 2.98 2.16 2.15 2.13 2.12 2.10 2.09 2.08 1.82 1.81 1.81 1.80 1.80 1.80 1.79 1.79 1.79 1.78 1.78 1.77 1.77 1.76 1.75 1.51 1.50 1.49 1.49 1.48 1.47 1.47 1.46
MeO2C
N
Me
7c
1H NMR
(CDCl3, 500 MHz)
Intensity
1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0 -0.1
1.09 1.00 1.13 1.21 1.09 1.10 1.09 3.54 3.40 2.57 1.19 1.18
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 -0
Chemical Shift (ppm)

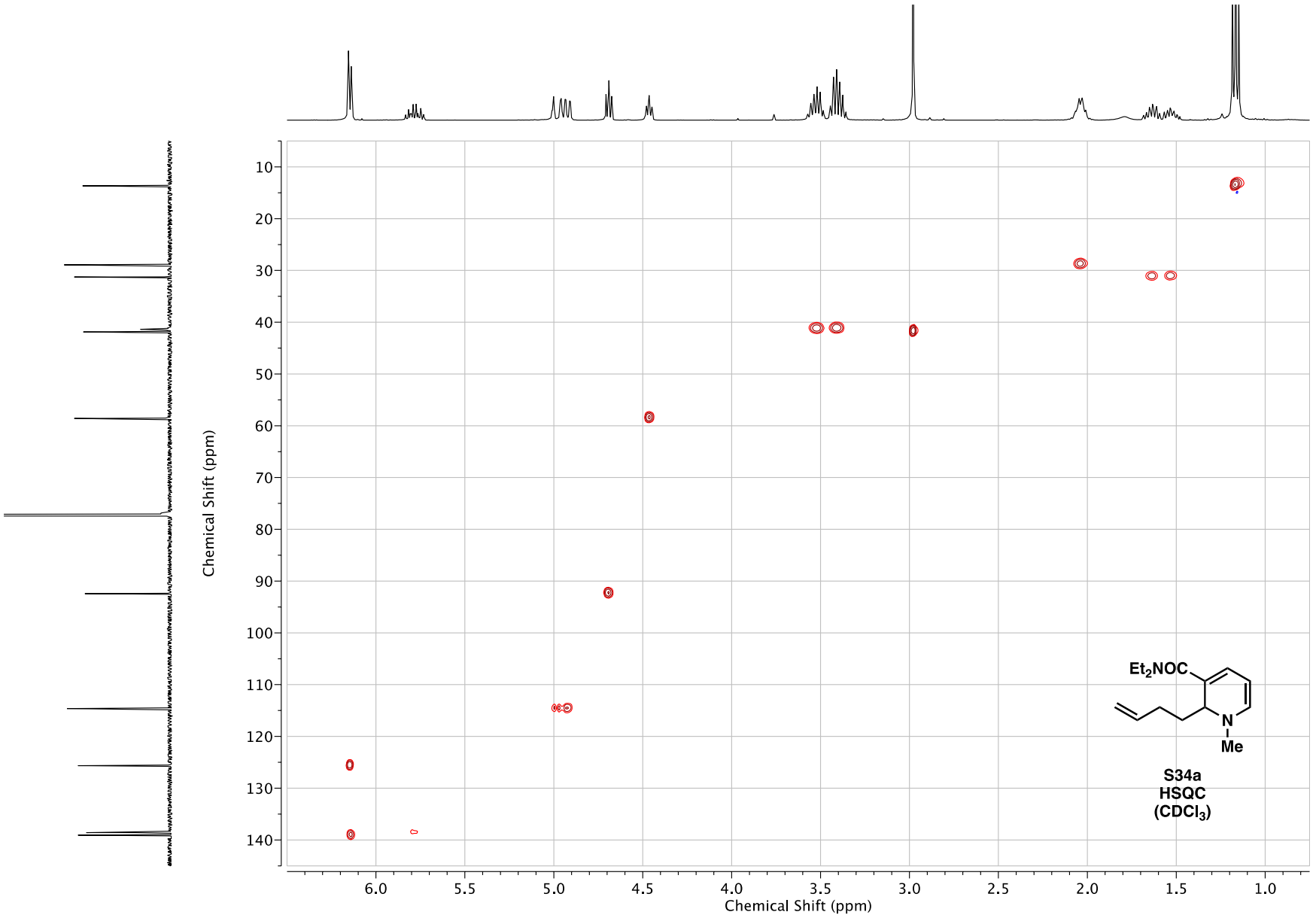

MeO2C
N
Me
7c
HSQC
(CDCl3)
167.09
147.95
138.09
122.29
115.00
111.57
96.43
77.16
58.91
50.70
41.70
32.96
27.56
Intensity
Chemical Shift (ppm)

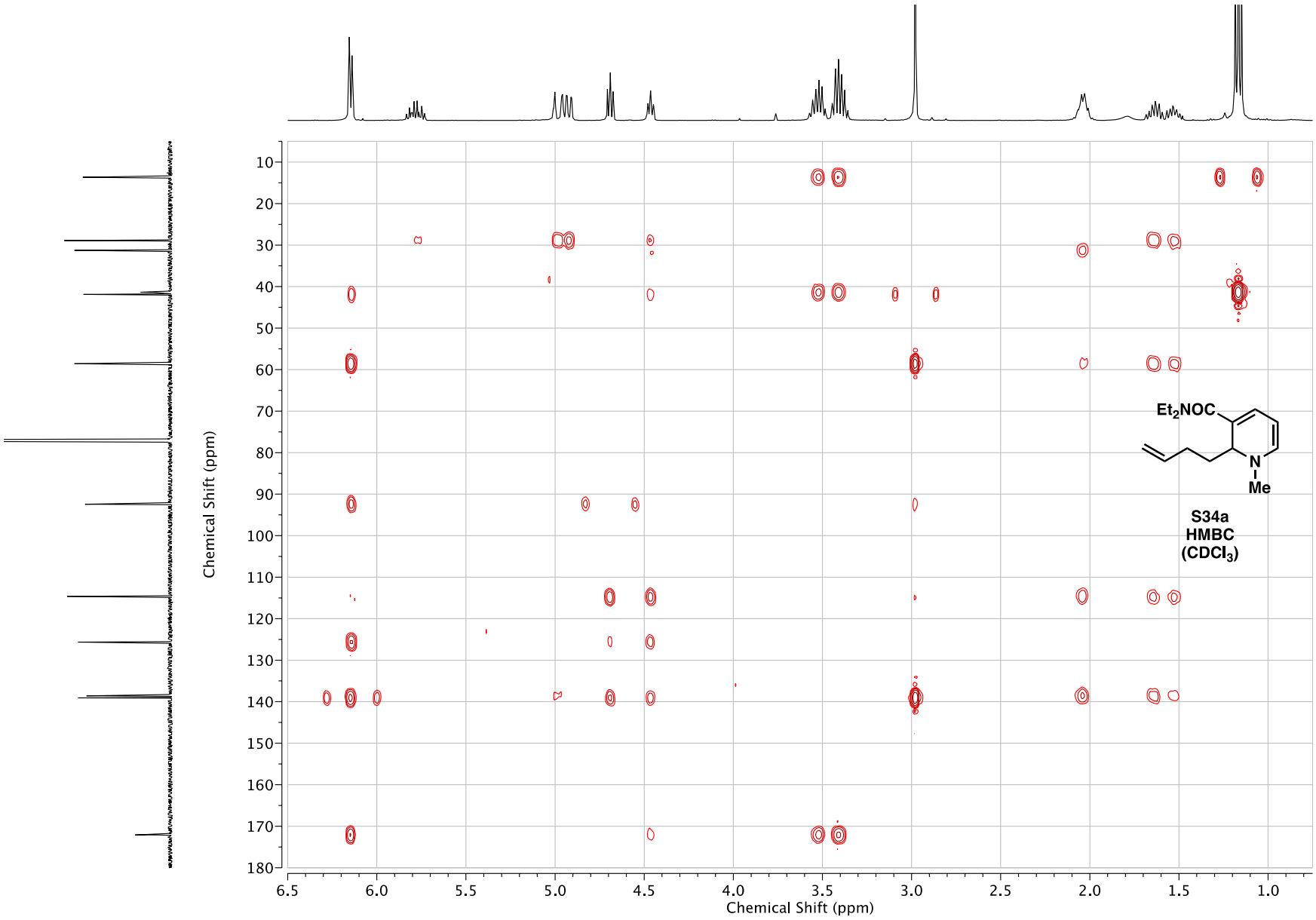

Chemical Shift (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)
MeO2C
N
Me
7c
HSQC
(CDCl3)

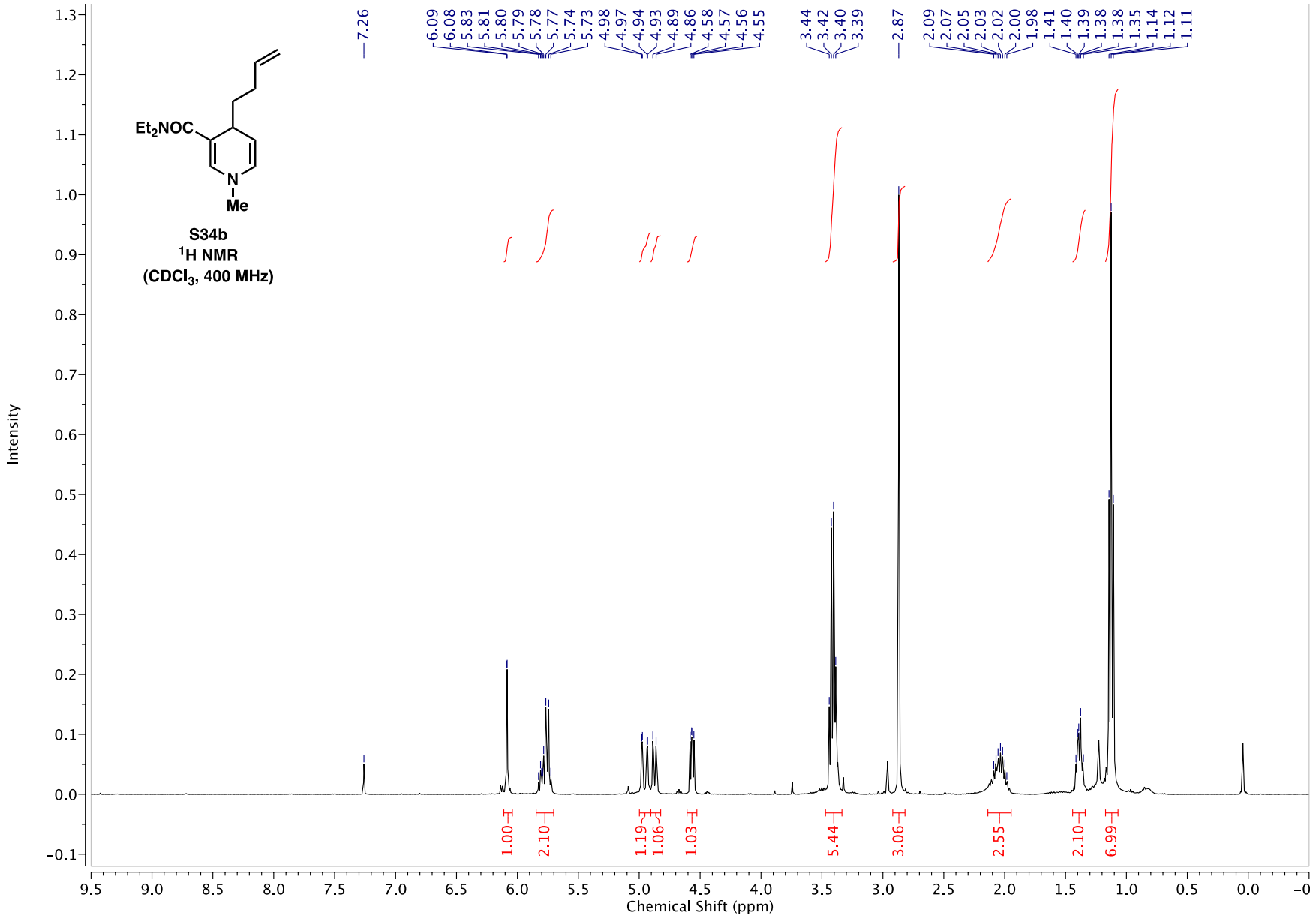

Chemical Shift (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)
MeO2C
N
Me
7c
HMBC
(CDCl3)

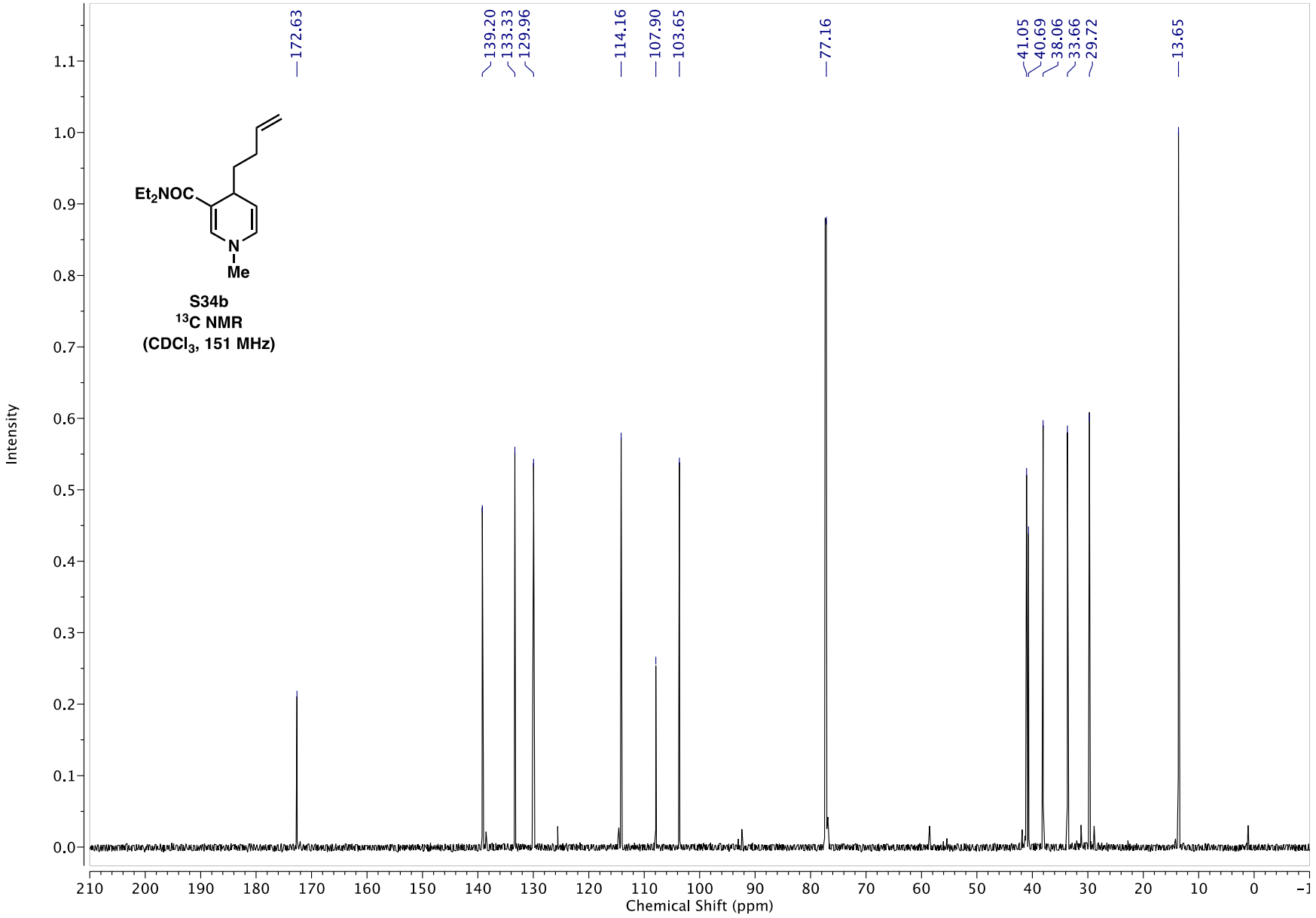

Et2NOC
N
Me
S34a
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)

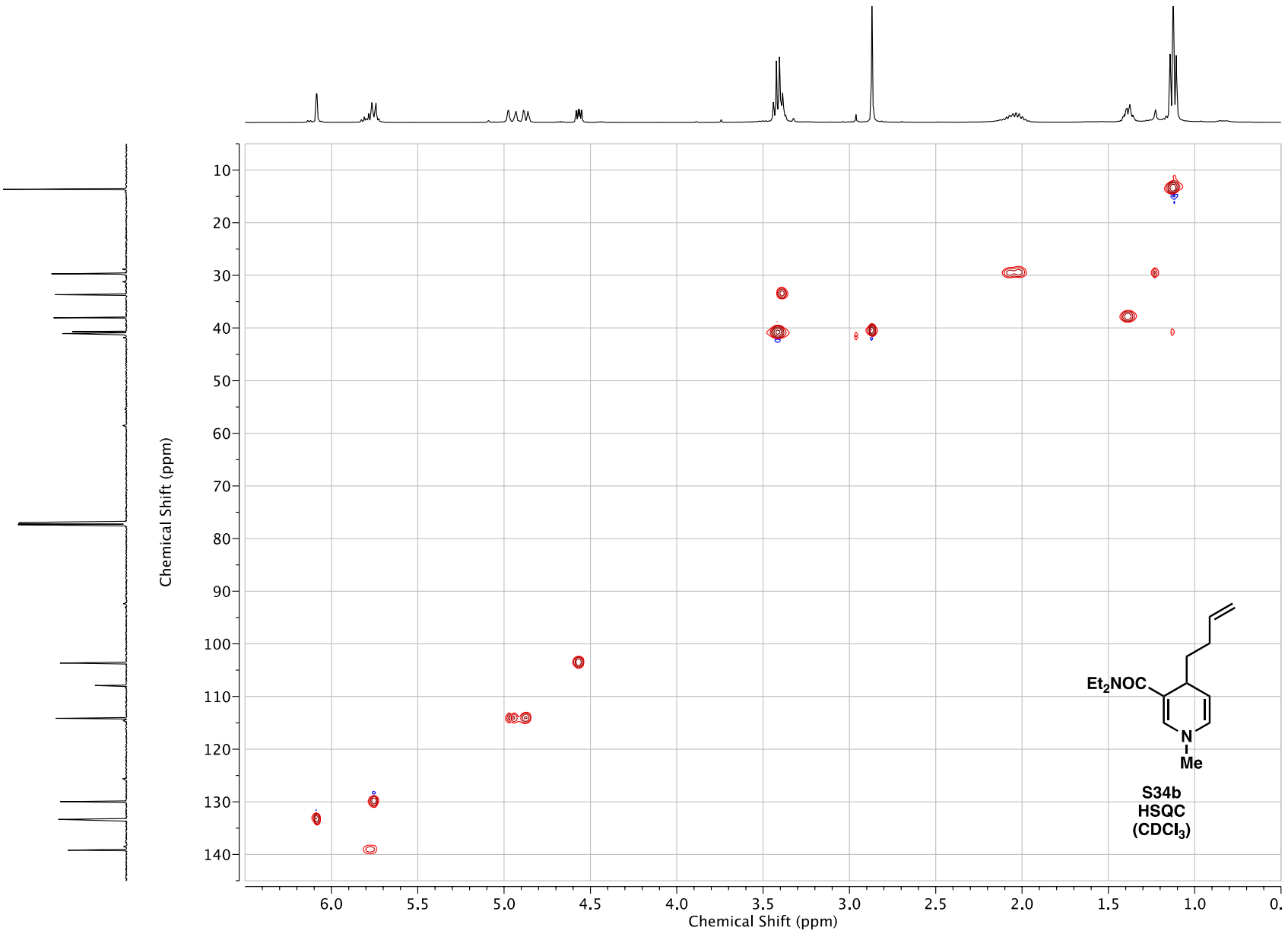

Et2NOC
N
Me
S34a
13C NMR
(CDCl3, 151 MHz)
172.09
139.08
138.59
125.64
114.79
114.62
92.43
77.16
58.59
41.88
41.36
31.28
28.92
13.67
Intensity
Chemical Shift (ppm)

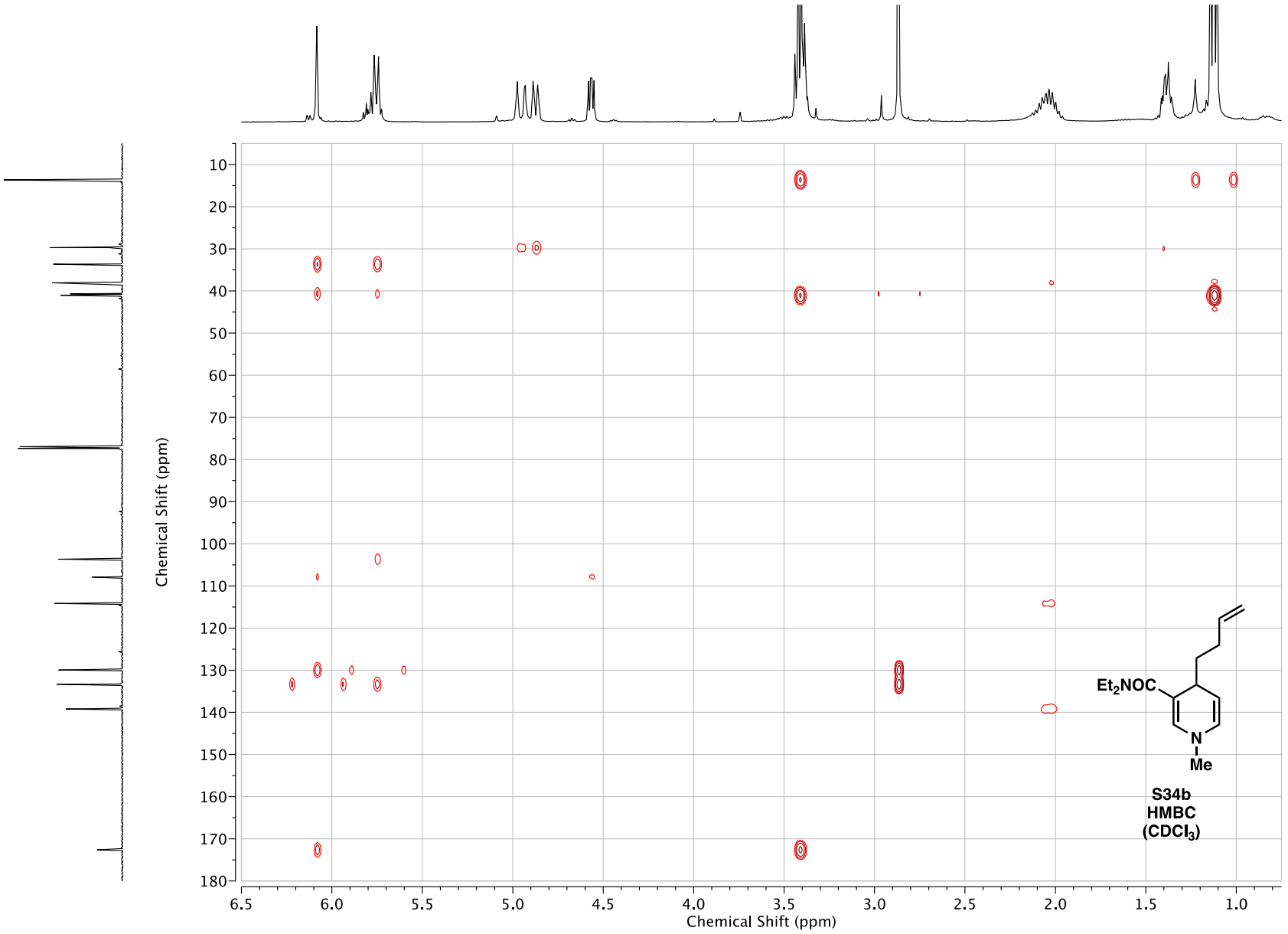

Chemical Shift (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)
Et2NOC
N
Me
S34a
HSQC
(CDCl3)

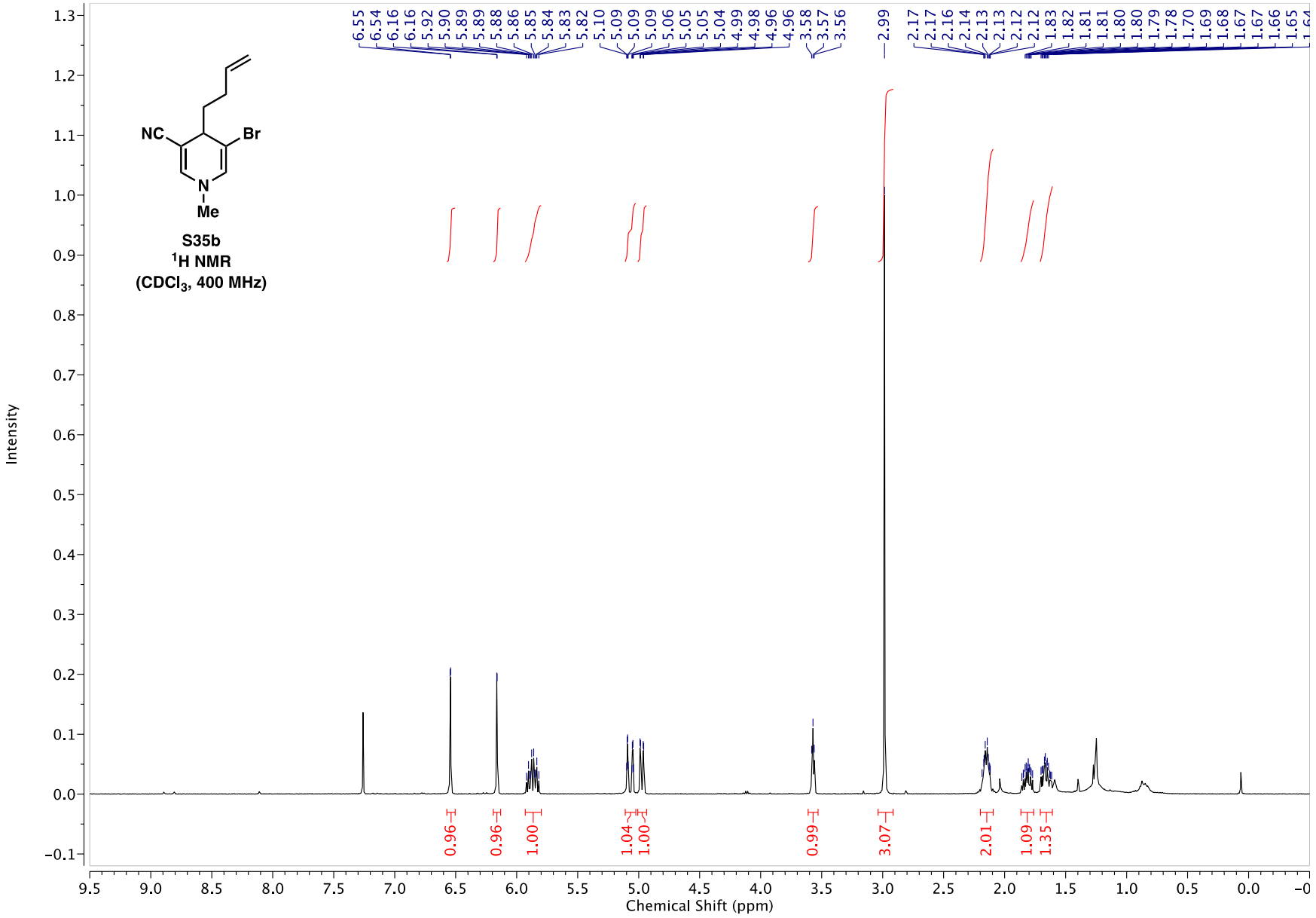

Chemical Shift (ppm)
Chemical Shift (ppm)
Et2NOC
N
Me
S34a
HMBC
(CDCl3)

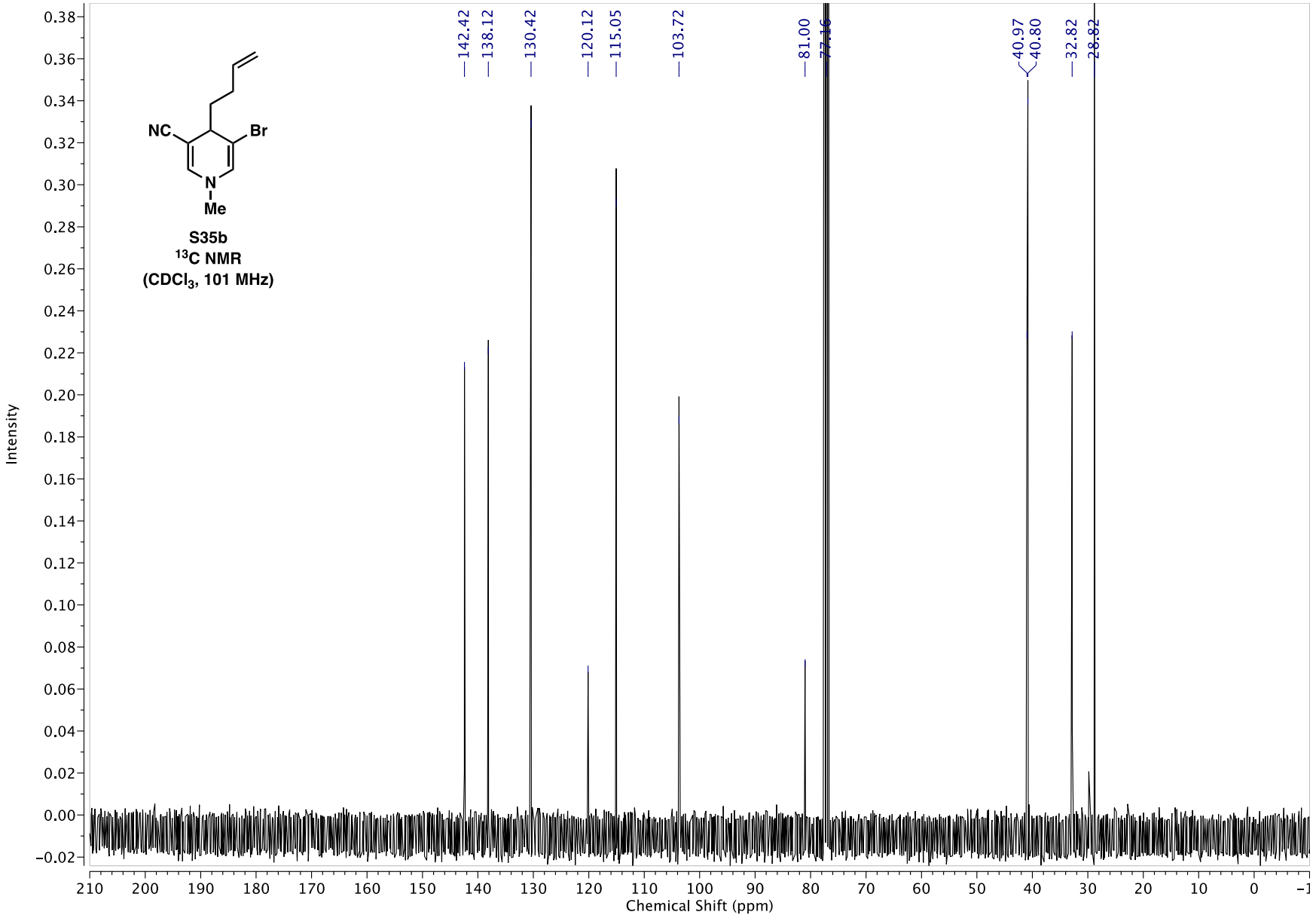

Et2NOC
N
Me
S34b
1H NMR
(CDCl3, 400 MHz)
7.26
6.09
6.08
5.83
5.81
5.80
5.79
5.78
5.77
5.74
5.73
4.98
4.97
4.94
4.93
4.89
4.86
4.58
4.57
4.56
4.55
3.44
3.42
3.40
3.39
2.87
2.09
2.07
2.05
2.03
2.02
2.00
1.98
1.41
1.40
1.39
1.38
1.38
1.35
1.14
1.12
1.11
1.00
2.10
1.19
1.06
1.03
5.44
3.06
2.55
2.10
6.99
Intensity
Chemical Shift (ppm)

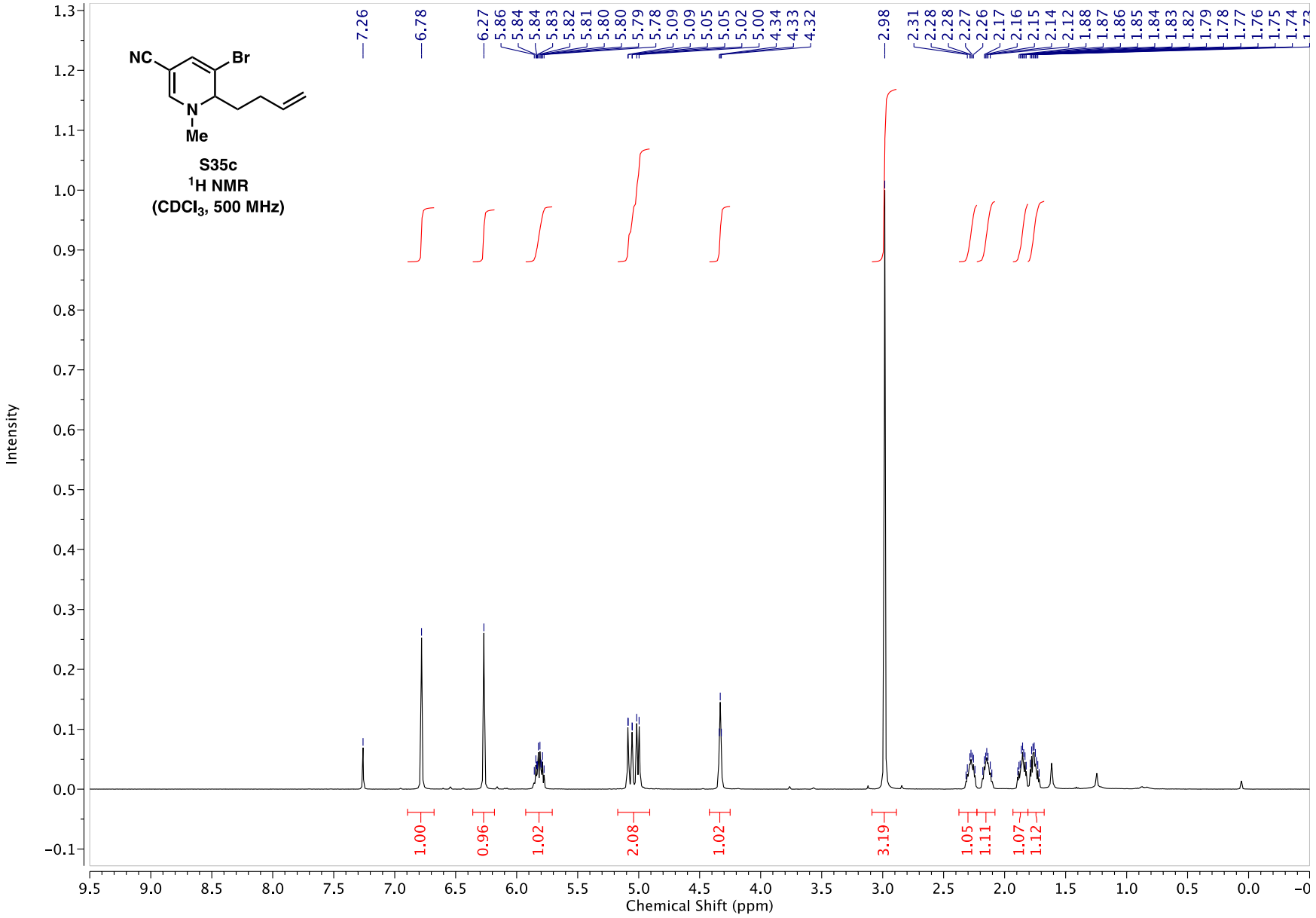

172.63
139.20
133.33
129.96
114.16
107.90
103.65
77.16
41.05
40.69
38.06
33.66
29.72
13.65
Et2NOC
N
Me
S34b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

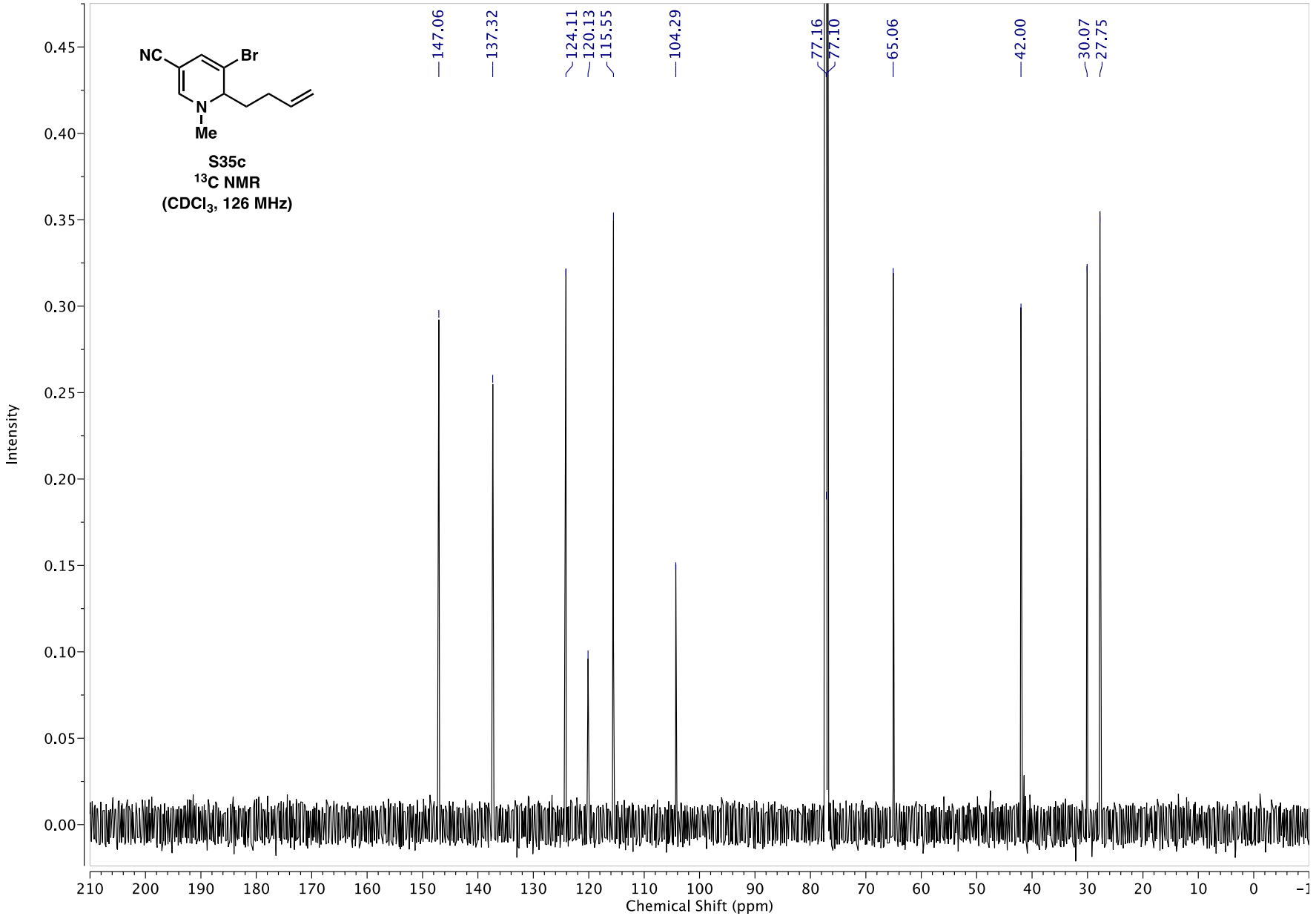

Chemical Shift (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.
Chemical Shift (ppm)
Et2NOC
N
Me
S34b
HSQC
(CDCl3)

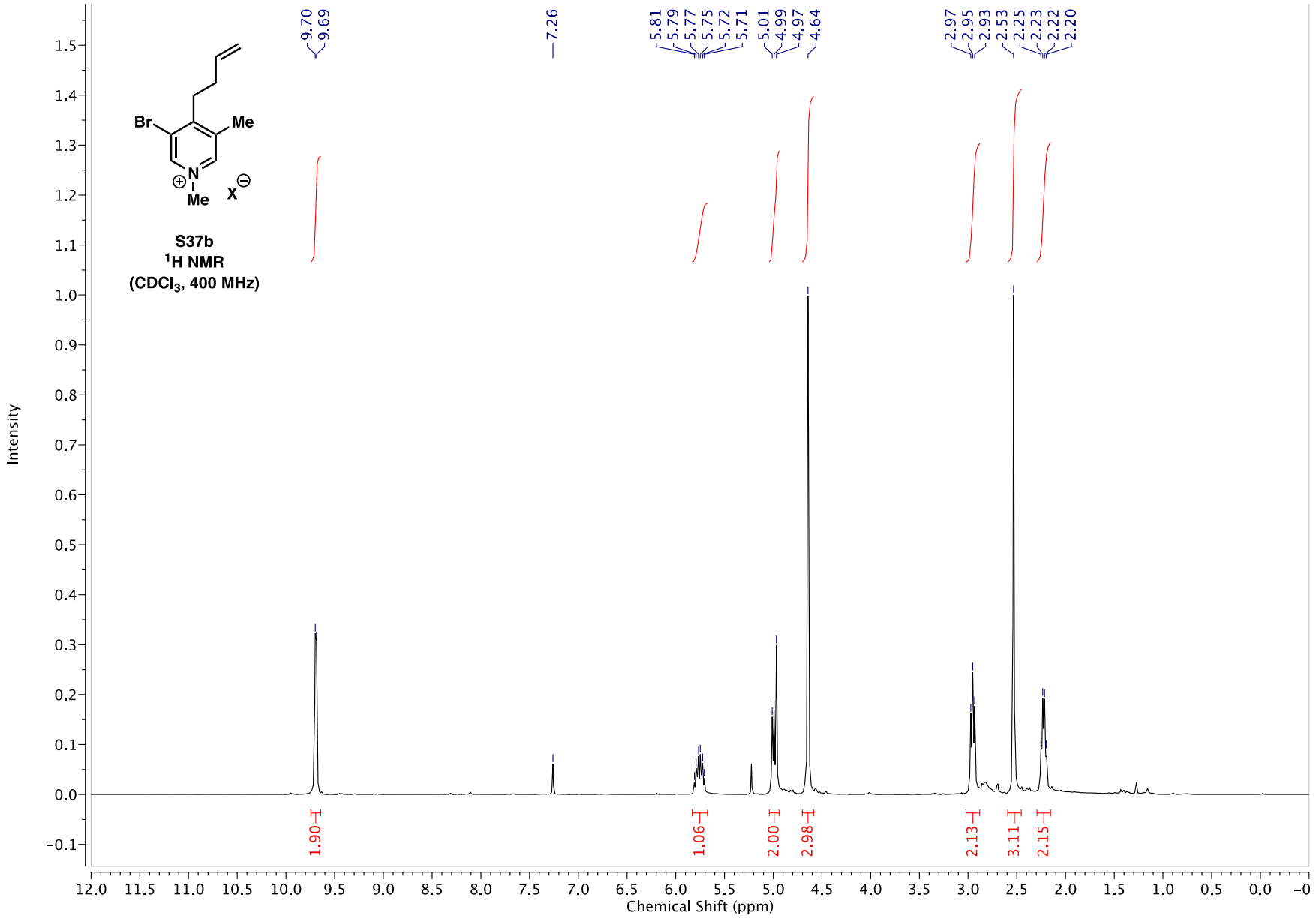

Chemical Shift (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)
Et2NOC
N
Me
S34b
HMBC
(CDCl3)

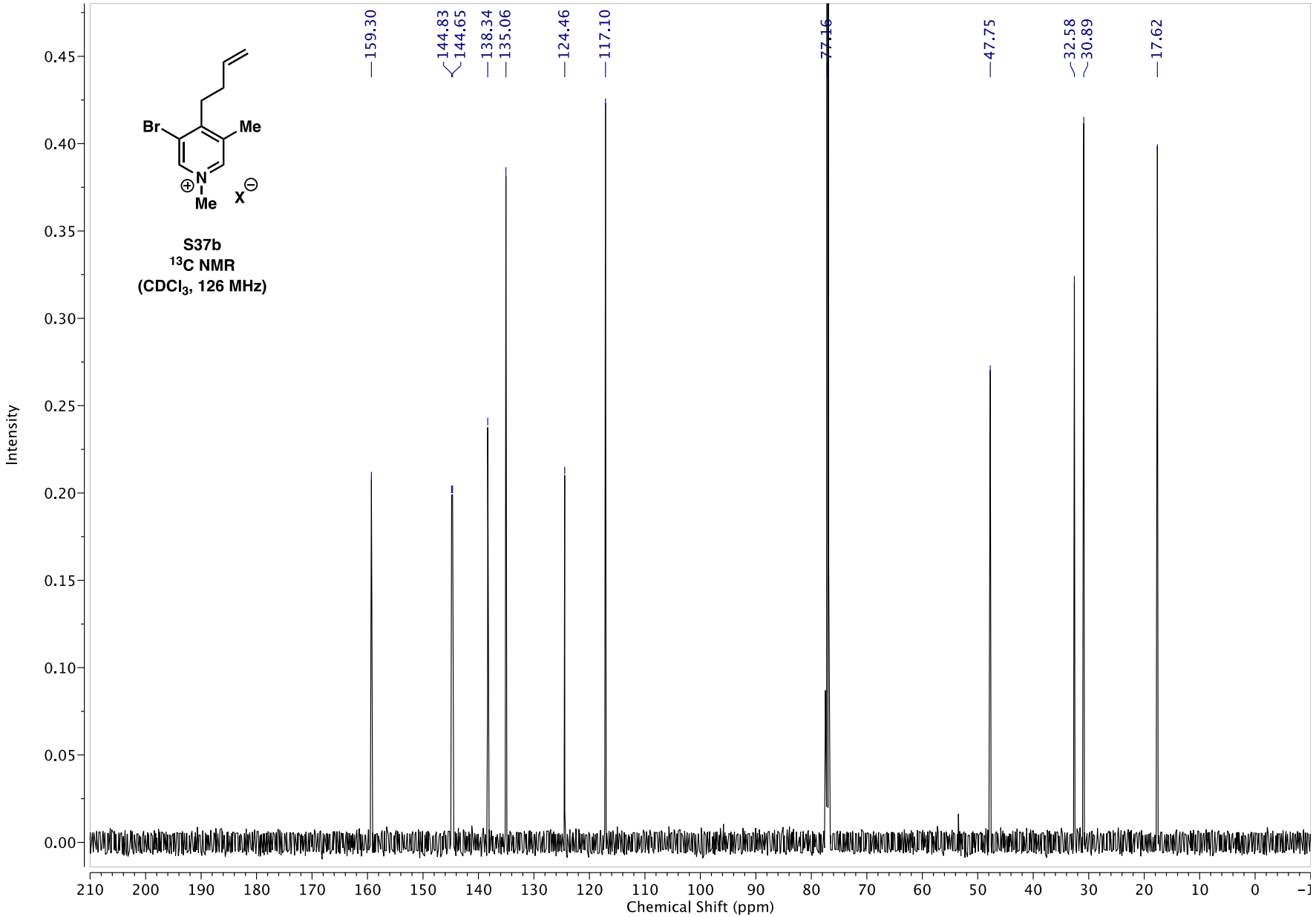

NC
Br
N
Me
S35b
^{1}H NMR
($CDCl_3$, 400 MHz)
Intensity
Chemical Shift (ppm)
0.96
0.96
1.00
1.04
1.00
0.99
3.07
2.01
1.09
1.35

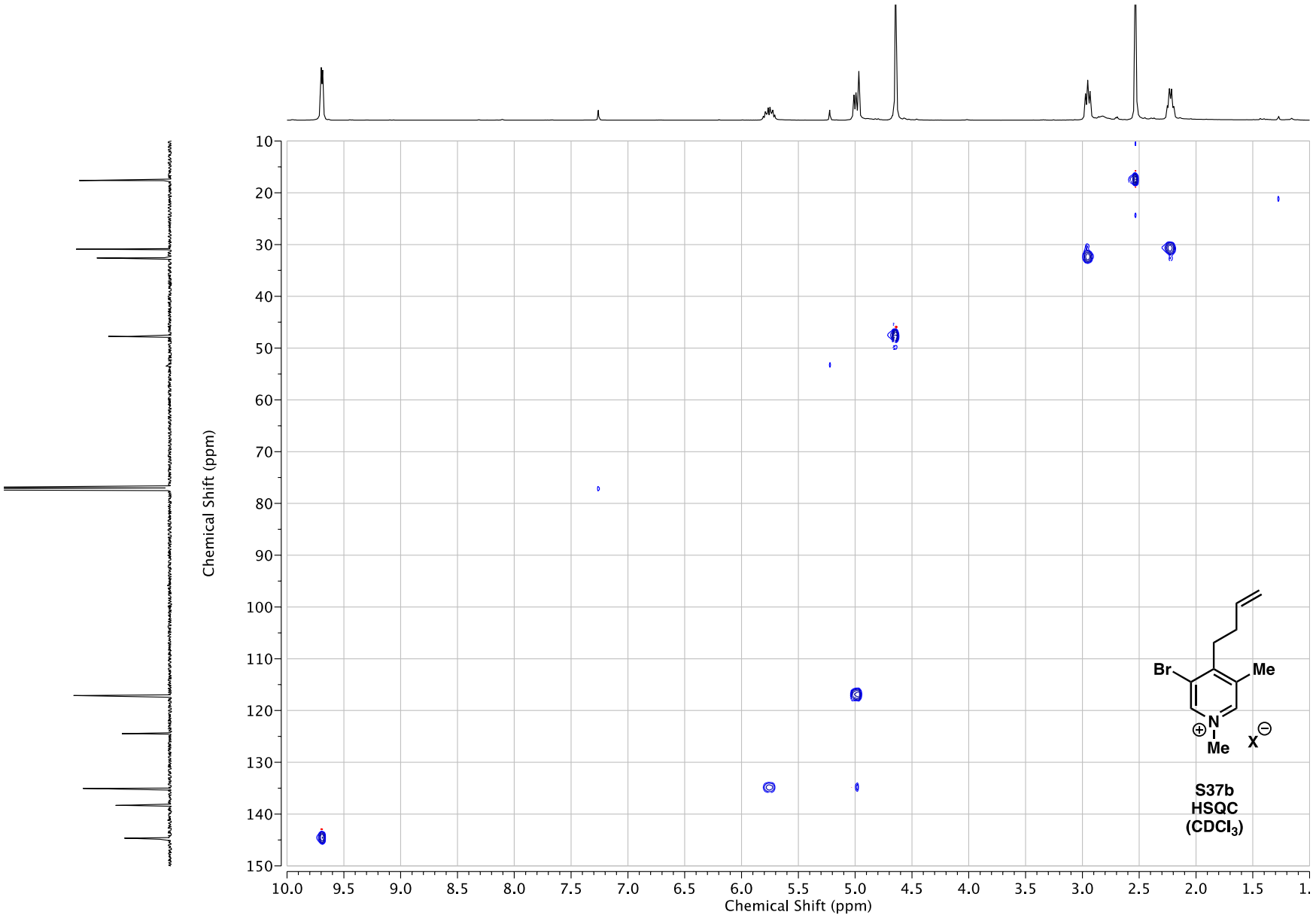

NC
Br
N
Me
S35b
13C NMR
(CDCl3, 101 MHz)
142.42
138.12
130.42
120.12
115.05
103.72
81.00
77.16
40.97
40.80
32.82
28.82
Intensity
Chemical Shift (ppm)

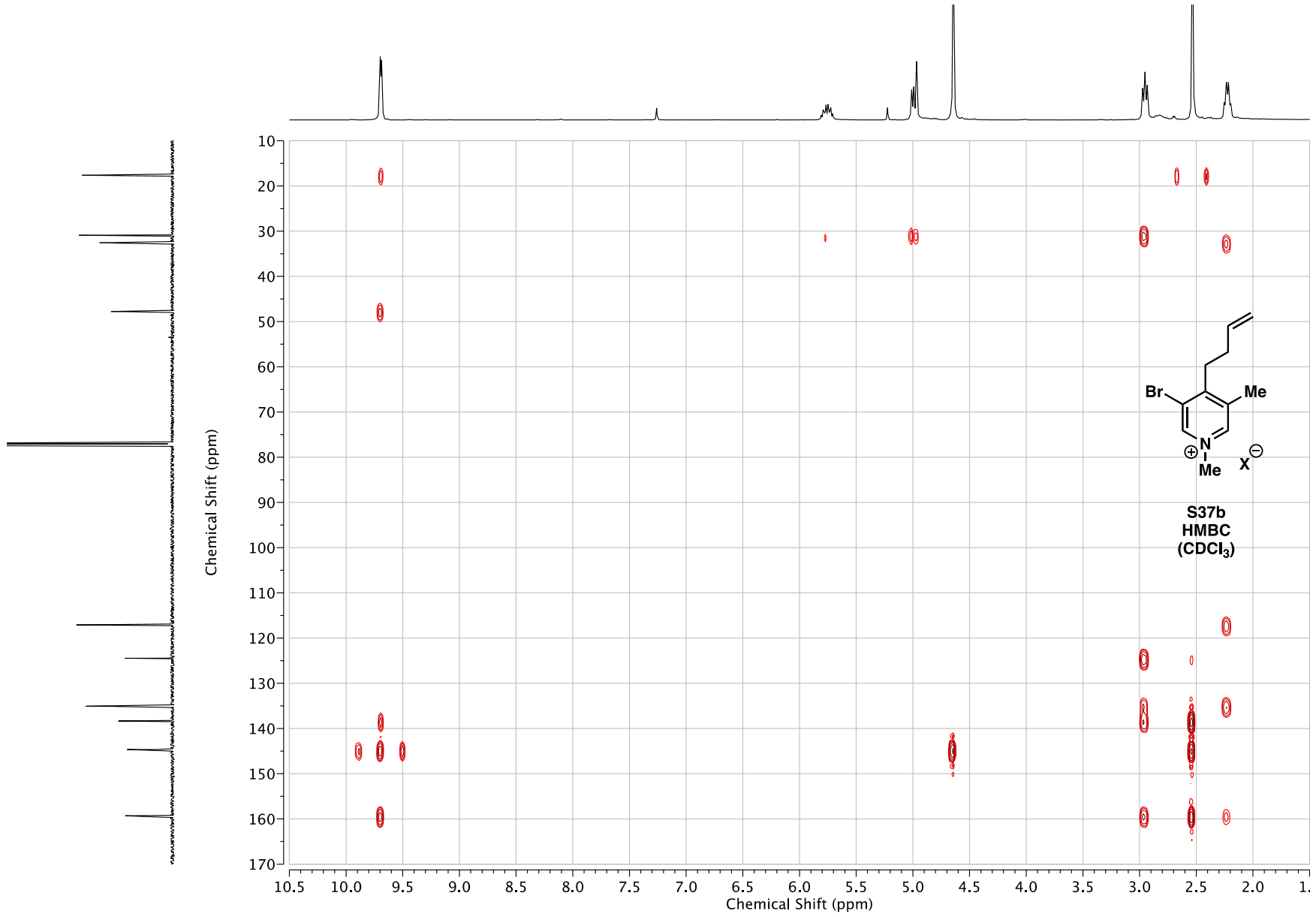

NC
Br
N
Me
S35c
^{1}H NMR
($CDCl_3$, 500 MHz)
Intensity
Chemical Shift (ppm)
1.00
0.96
1.02
2.08
1.02
3.19
1.05
1.11
1.07
1.12

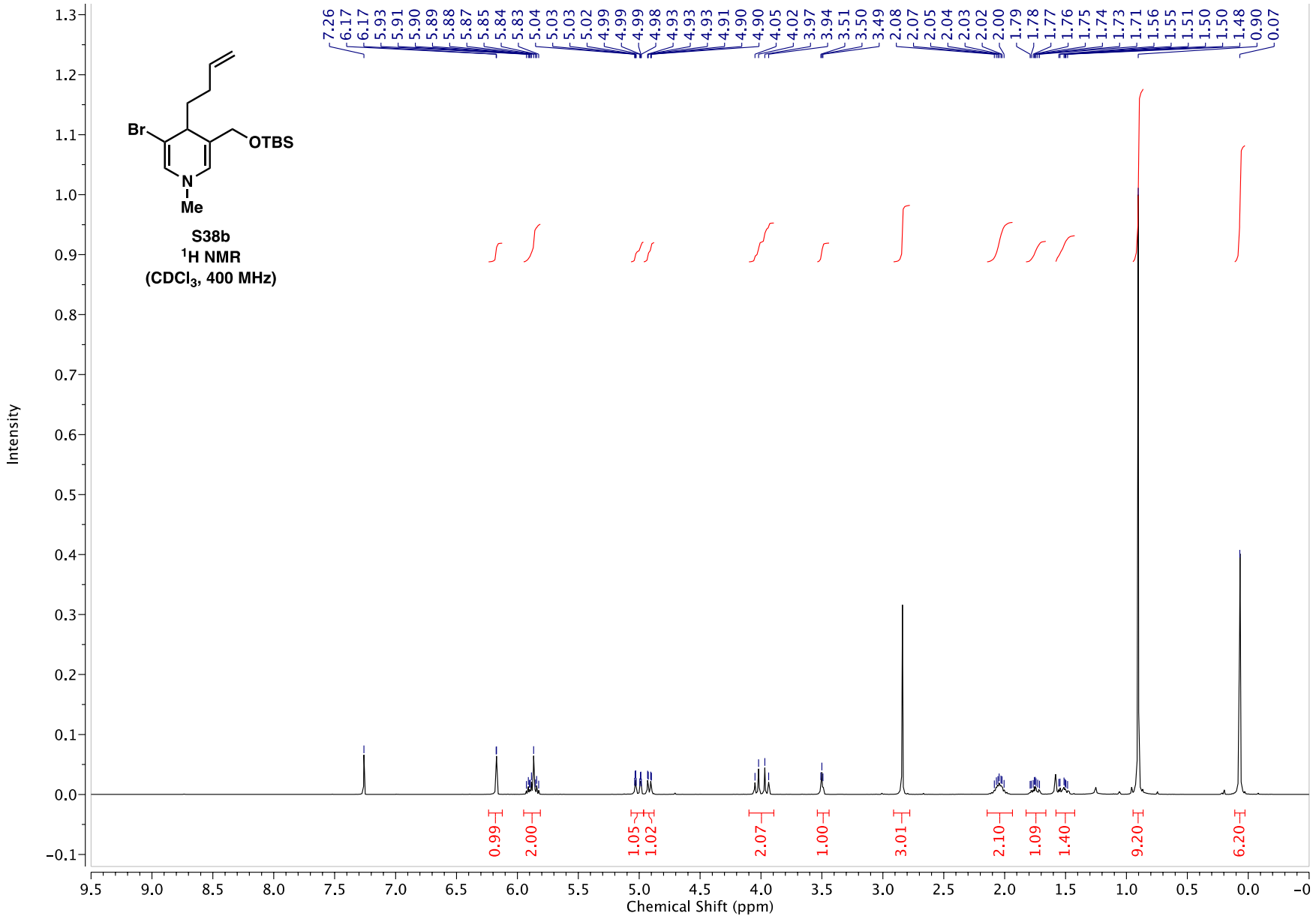

NC
Br
N
Me
S35c
13C NMR
(CDCl3, 126 MHz)
147.06
137.32
124.11
120.13
115.55
104.29
77.16
77.10
65.06
42.00
30.07
27.75
Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

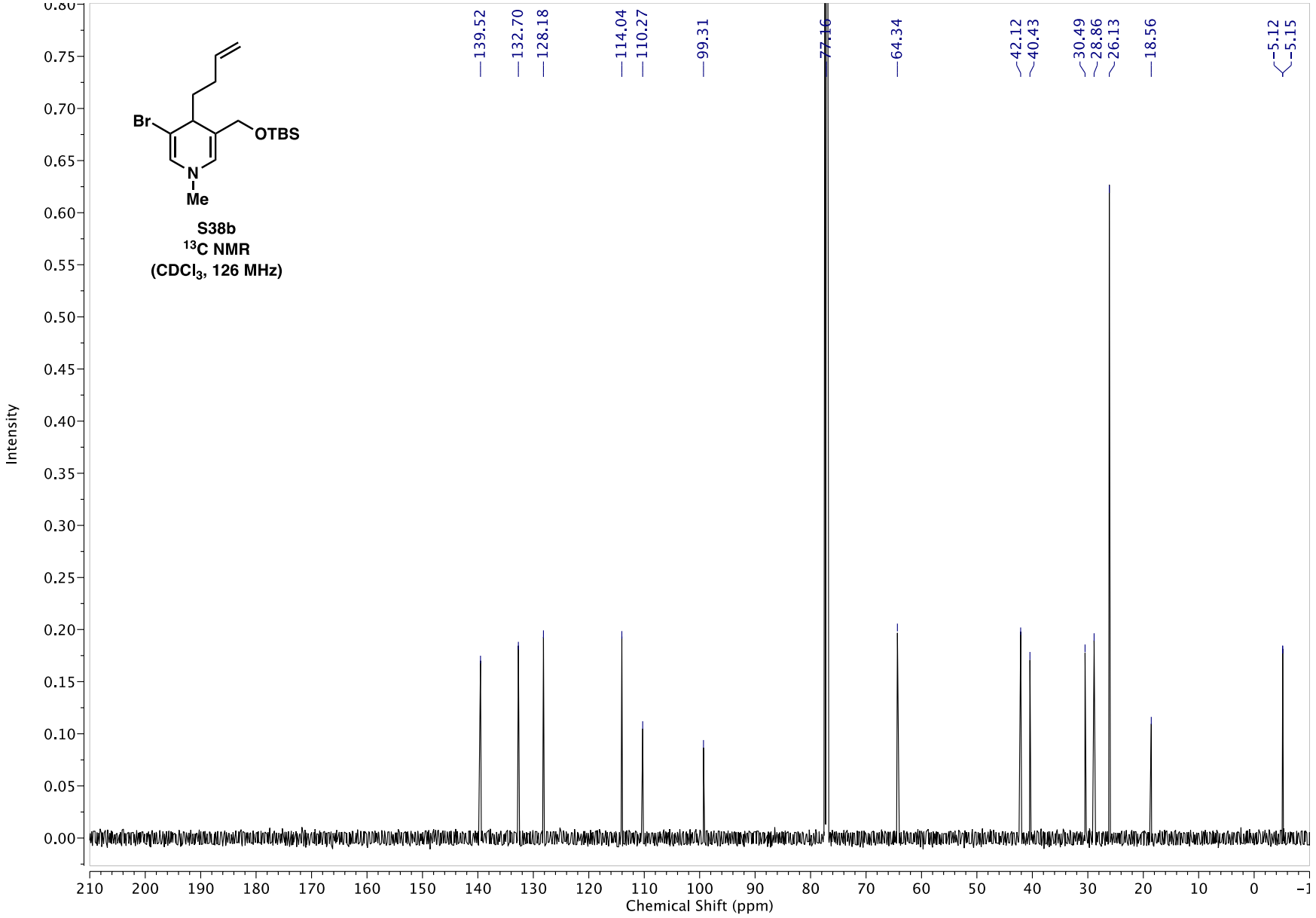

9.70
9.69
7.26
5.81
5.79
5.77
5.75
5.72
5.71
5.01
4.99
4.97
4.64
2.97
2.95
2.93
2.53
2.25
2.23
2.22
2.20
Br
Me
N
Me
X
S37b
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
1.90
1.06
2.00
2.98
2.13
3.11
2.15

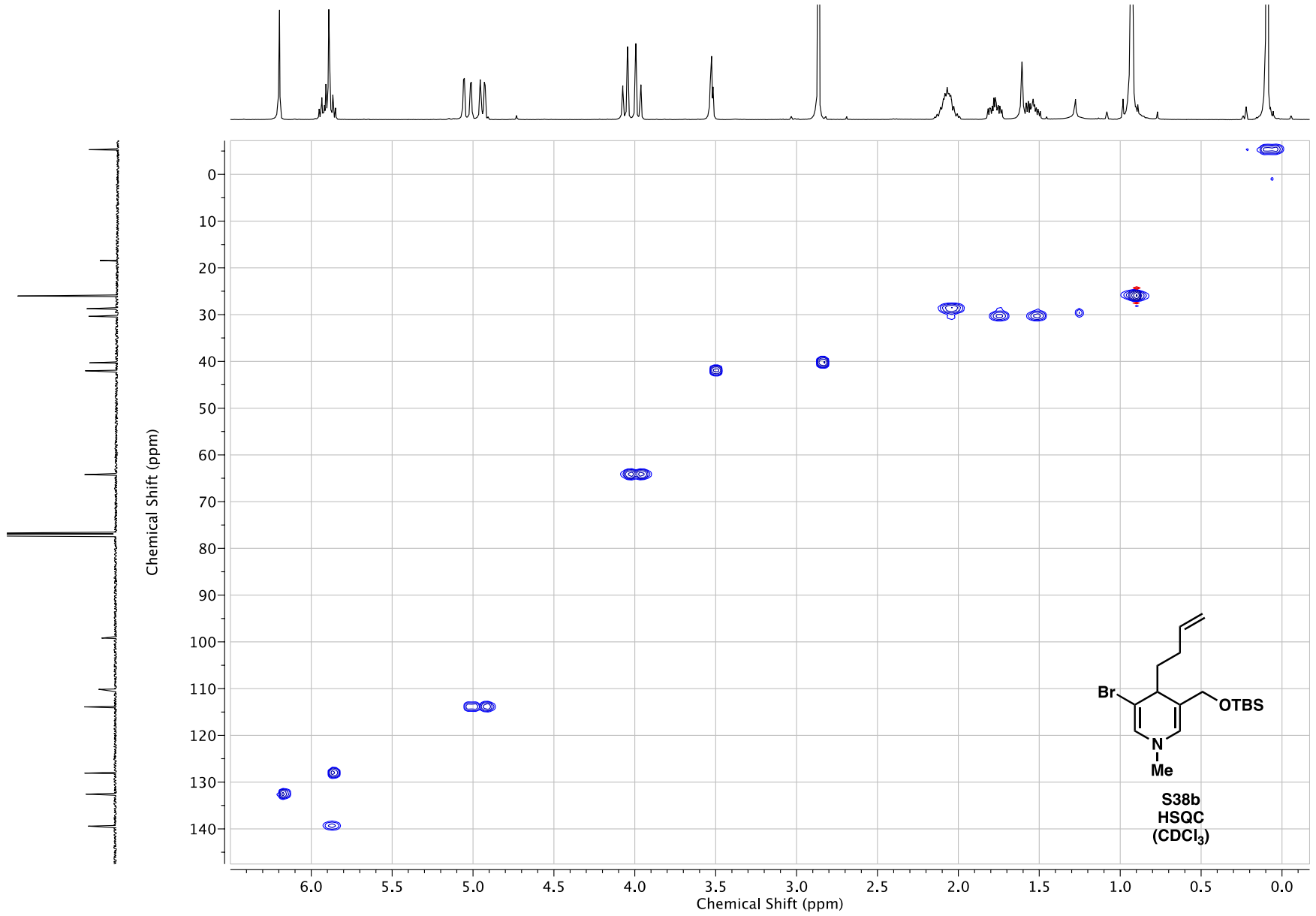

159.30
144.83
144.65
138.34
135.06
124.46
117.10
77.16
47.75
32.58
30.89
17.62
Br
Me
N
Me
X
S37b
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

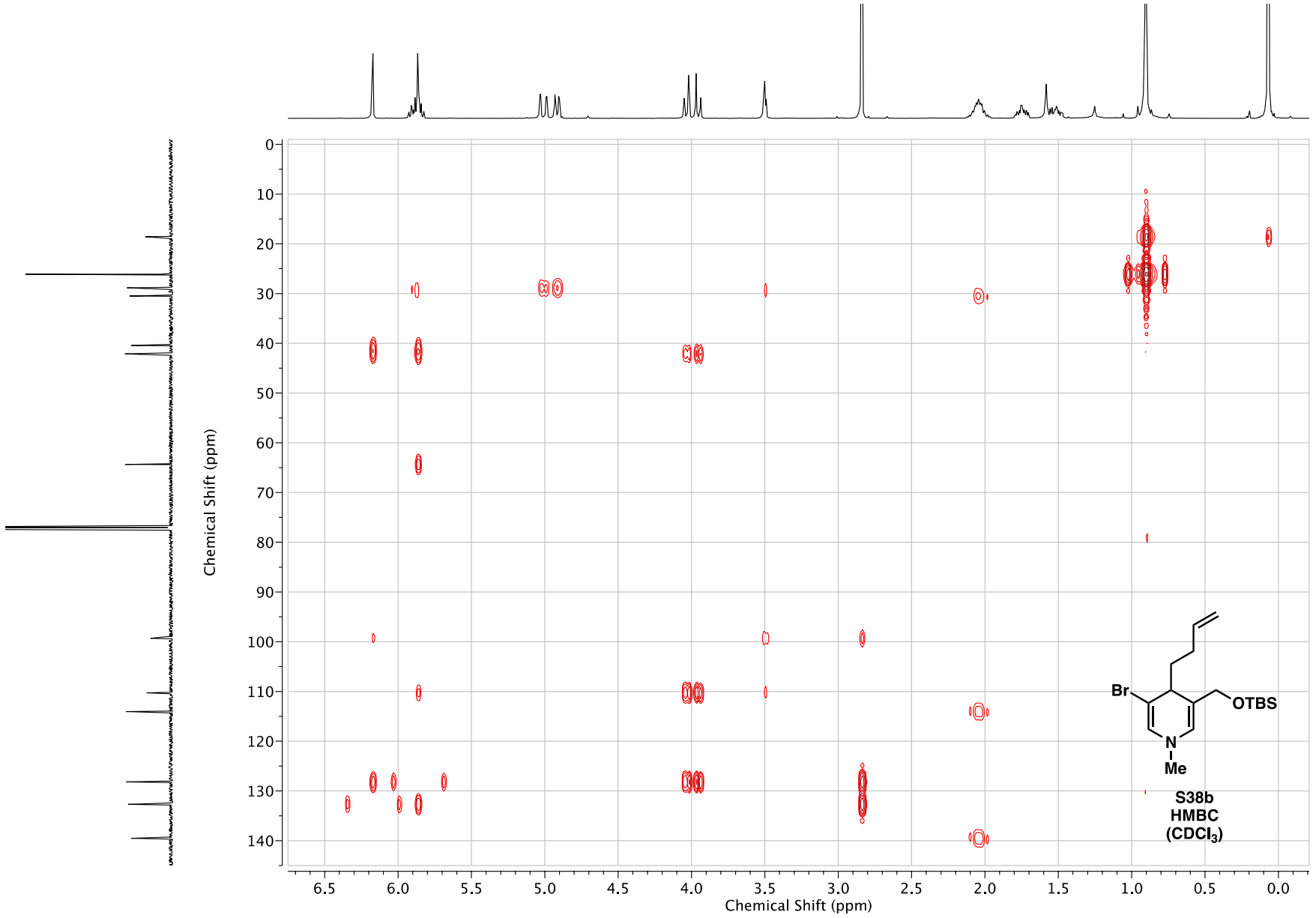

Chemical Shift (ppm)
Chemical Shift (ppm)
Br
Me
N
Me
X
S37b
HSQC
(CDCl3)

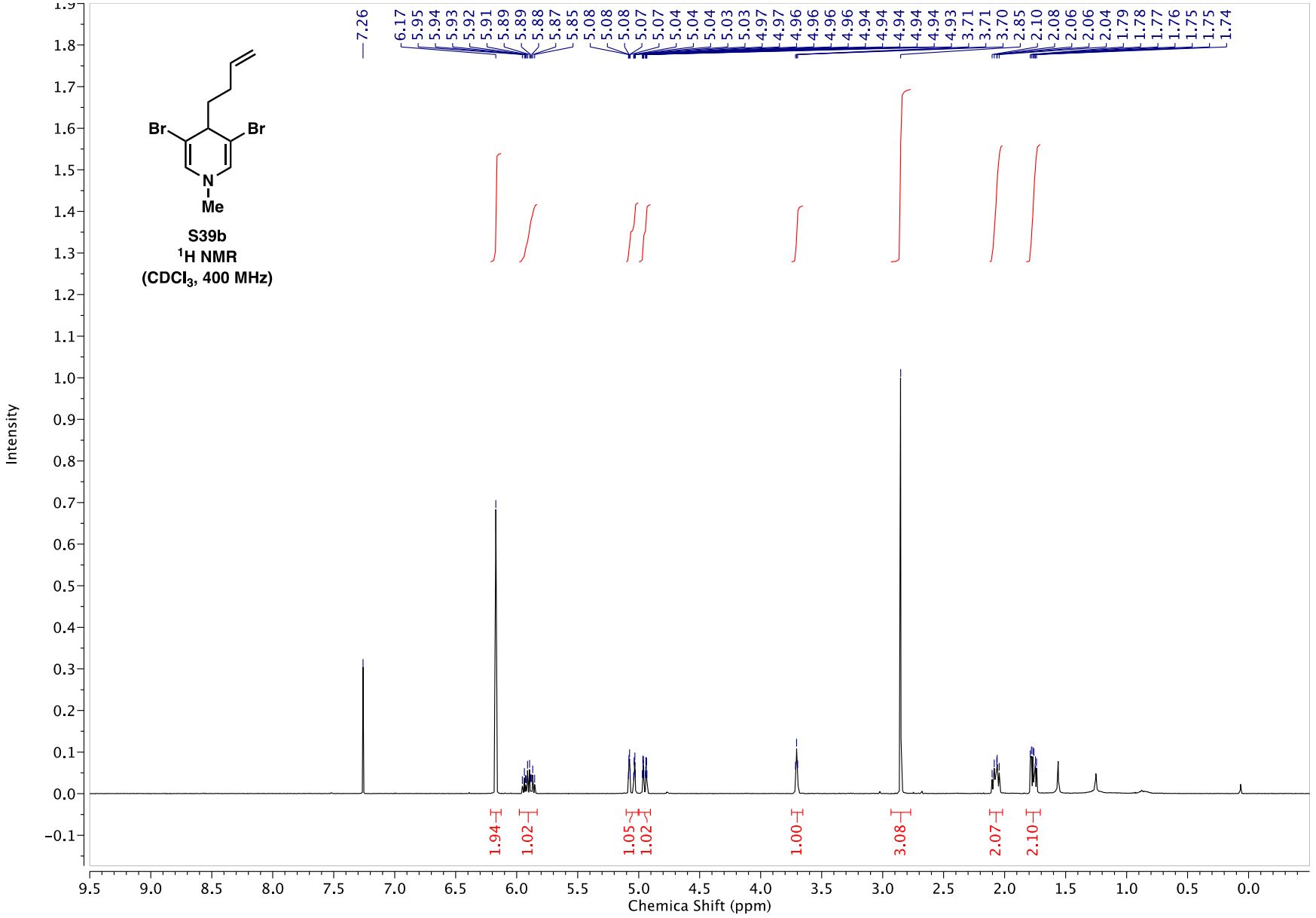

Chemical Shift (ppm)
Chemical Shift (ppm)
Br
Me
N
Me
X
S37b
HMBC
(CDCl3)

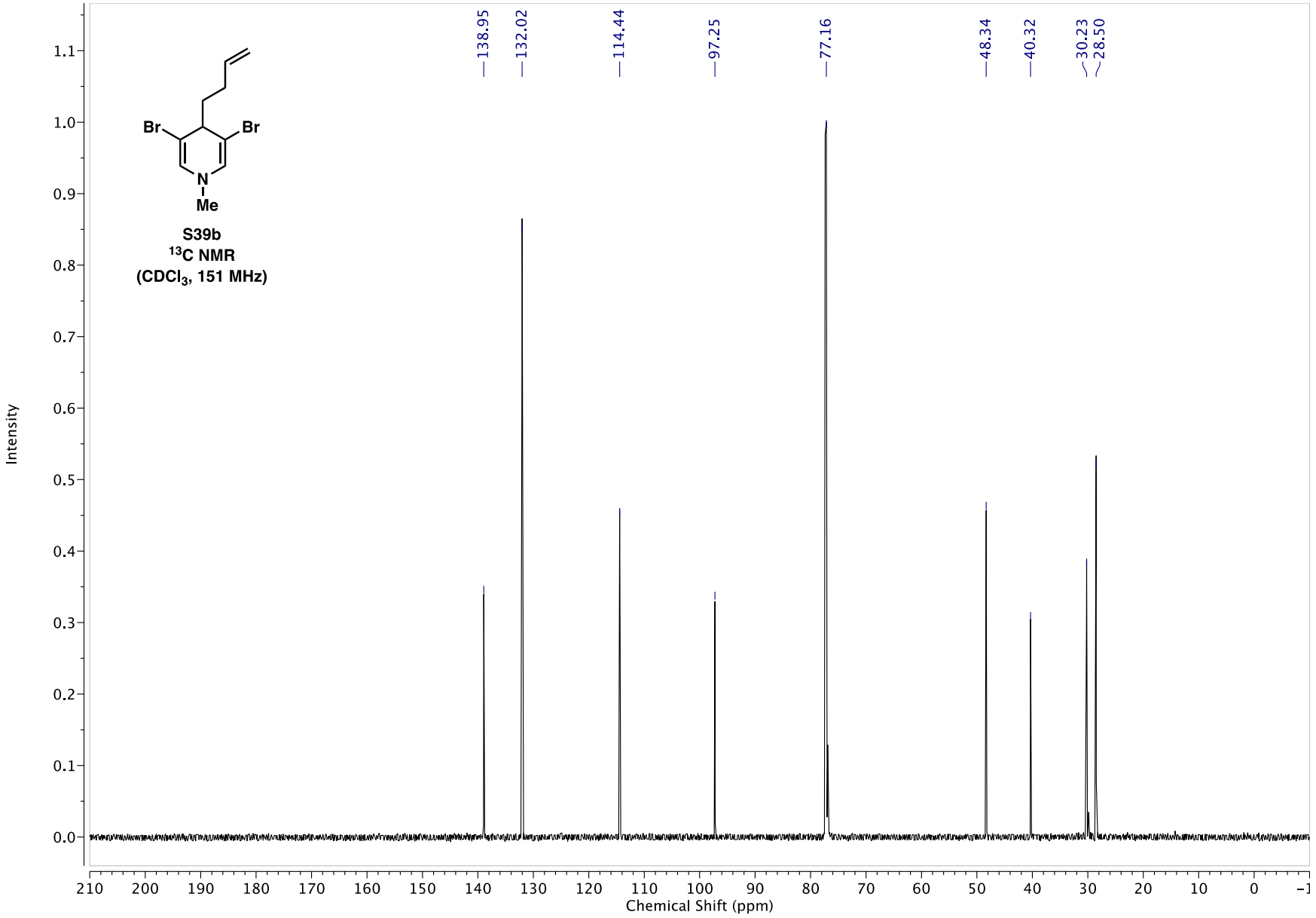

Br
OTBS
N
Me
S38b
^{1}H NMR
($CDCl_3$, 400 MHz)
Intensity
Chemical Shift (ppm)

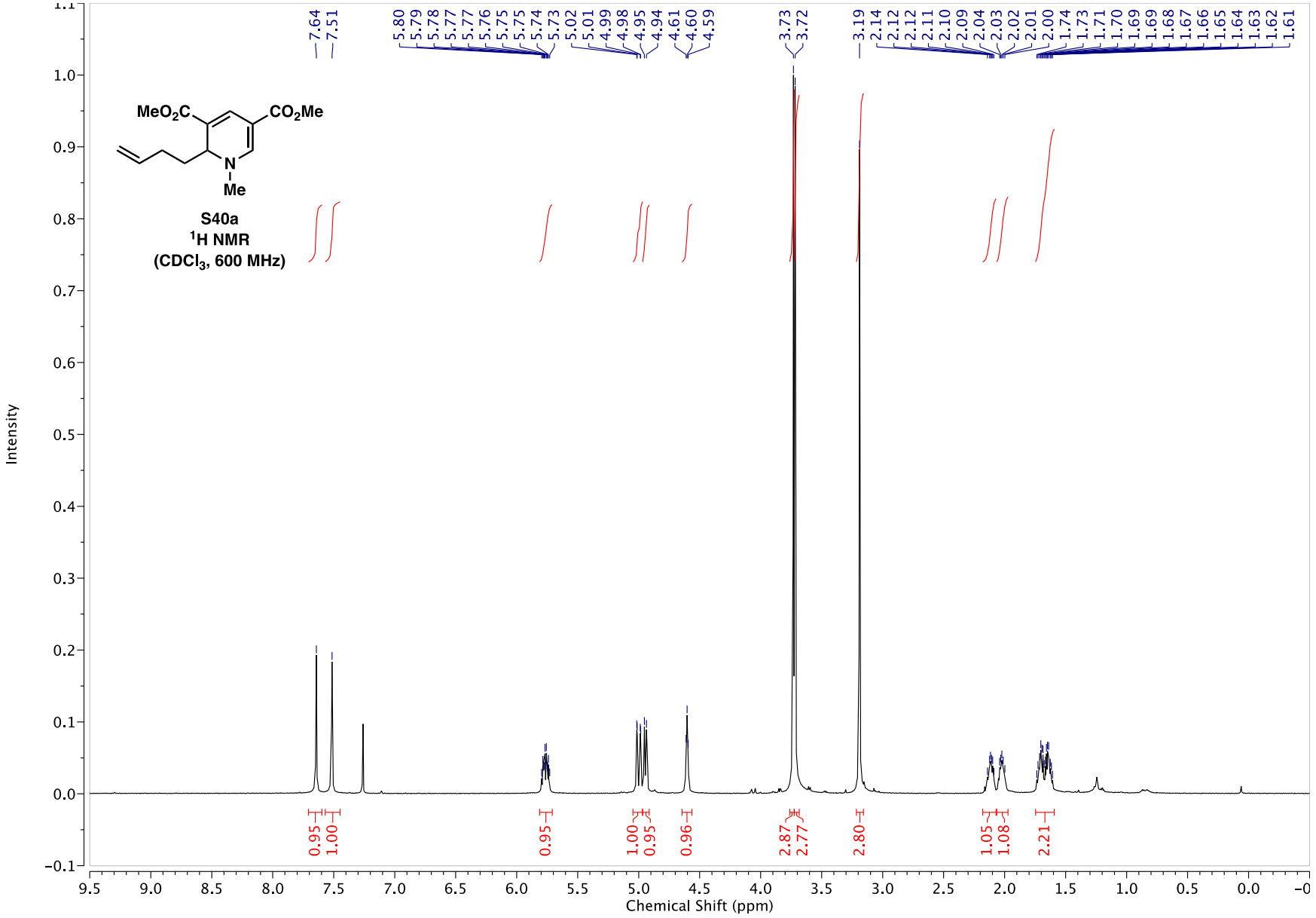

Br
OTBS
N
Me
S38b
13C NMR
(CDCl3, 126 MHz)
139.52
132.70
128.18
114.04
110.27
99.31
77.16
64.34
42.12
40.43
30.49
28.86
26.13
18.56
-5.12
-5.15
Intensity
Chemical Shift (ppm)

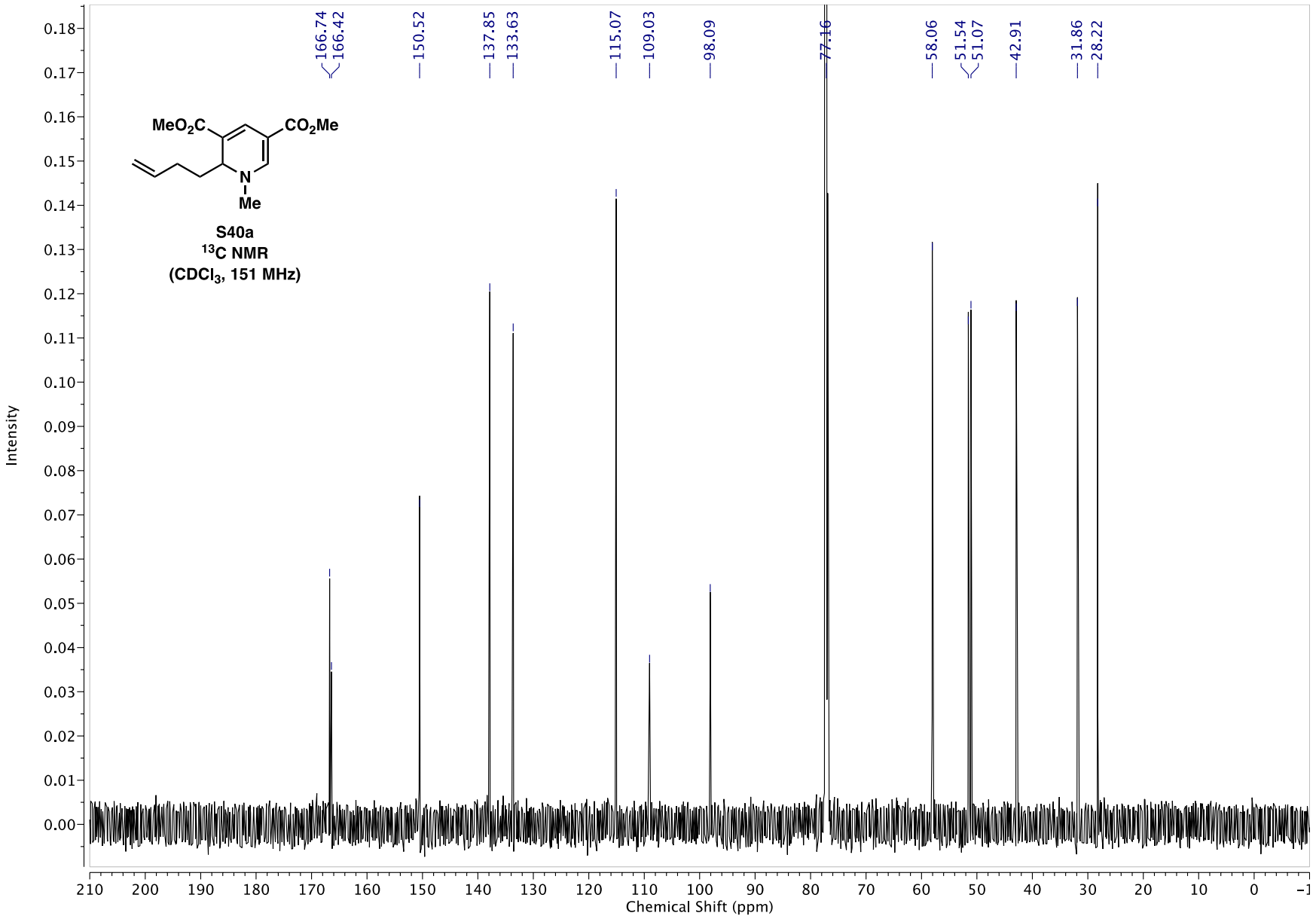

Chemical Shift (ppm)
Chemical Shift (ppm)
Br
OTBS
N
Me
S38b
HSQC
(CDCl3)

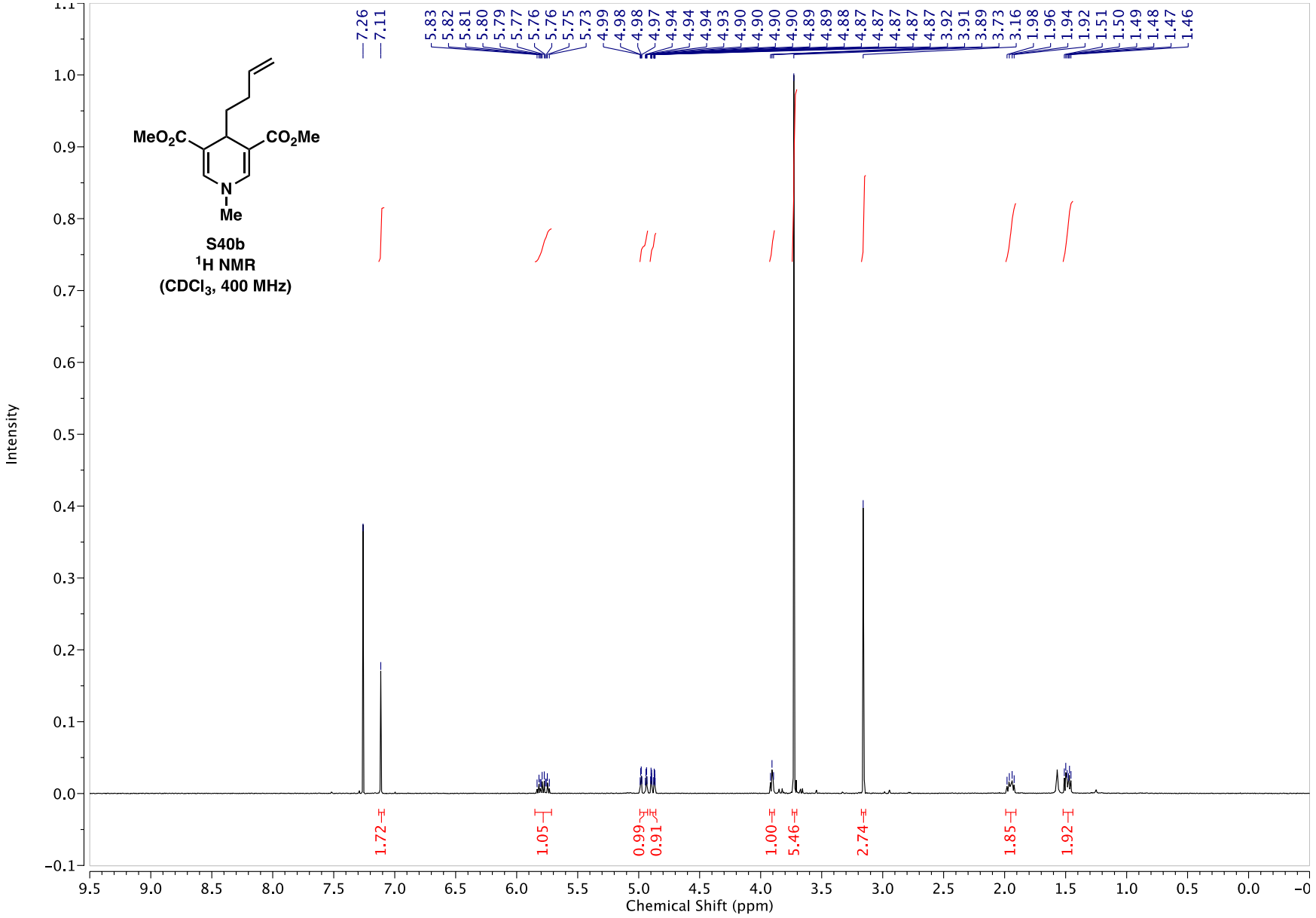

Chemical Shift (ppm)
Chemical Shift (ppm)
Br
OTBS
N
Me
S38b
HMBC
(CDCl3)

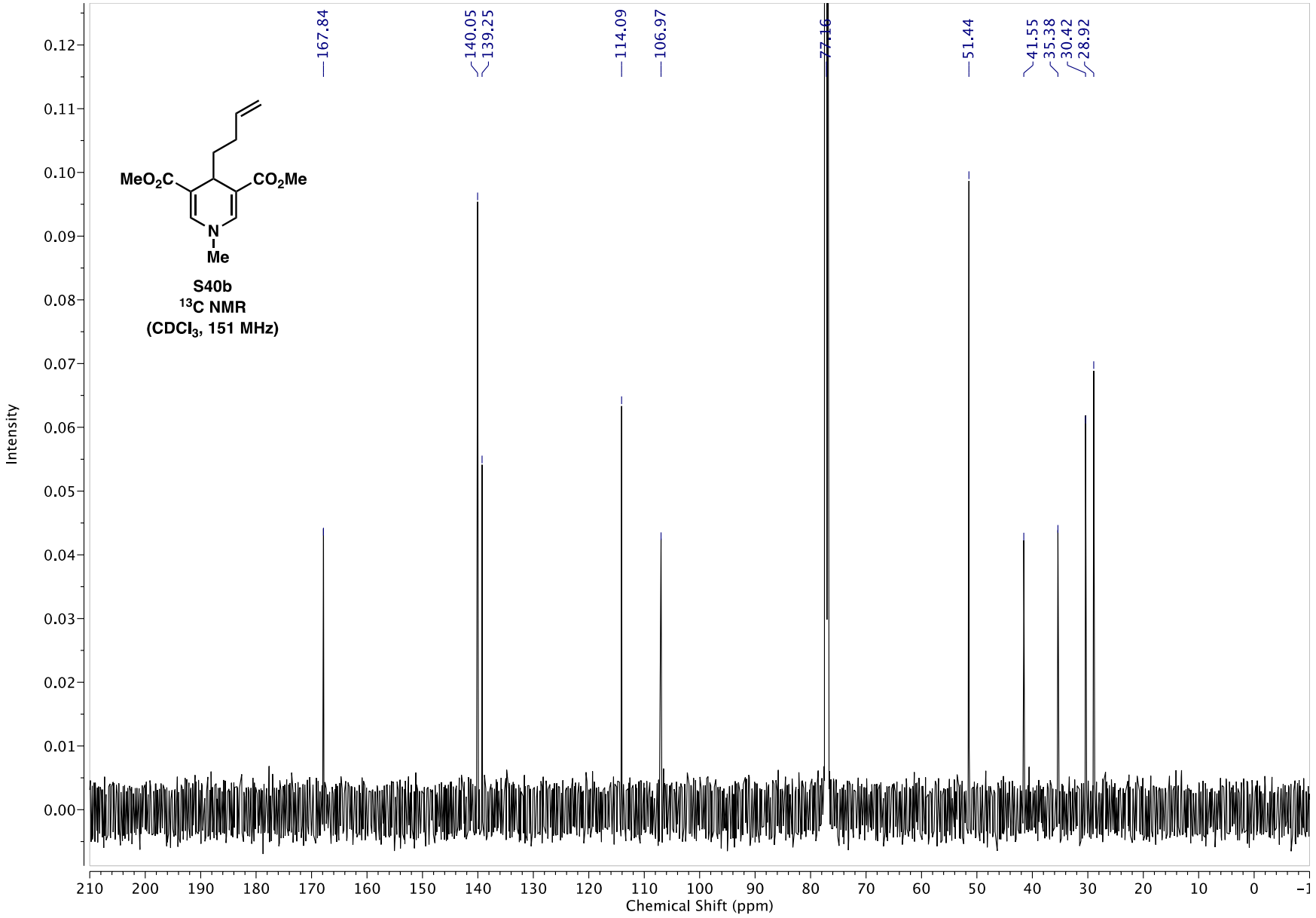

Br
Br
N
Me
S39b
1H NMR
(CDCl3, 400 MHz)
7.26
6.17
5.95
5.94
5.93
5.92
5.91
5.89
5.89
5.88
5.87
5.85
5.08
5.08
5.08
5.07
5.07
5.04
5.04
5.04
5.03
5.03
4.97
4.97
4.96
4.96
4.96
4.96
4.94
4.94
4.94
4.94
4.94
4.93
3.71
3.71
3.70
2.85
2.10
2.08
2.06
2.06
2.04
1.79
1.78
1.77
1.76
1.75
1.75
1.74
1.94
1.02
1.05
1.02
1.00
3.08
2.07
2.10
Intensity
Chemica Shift (ppm)

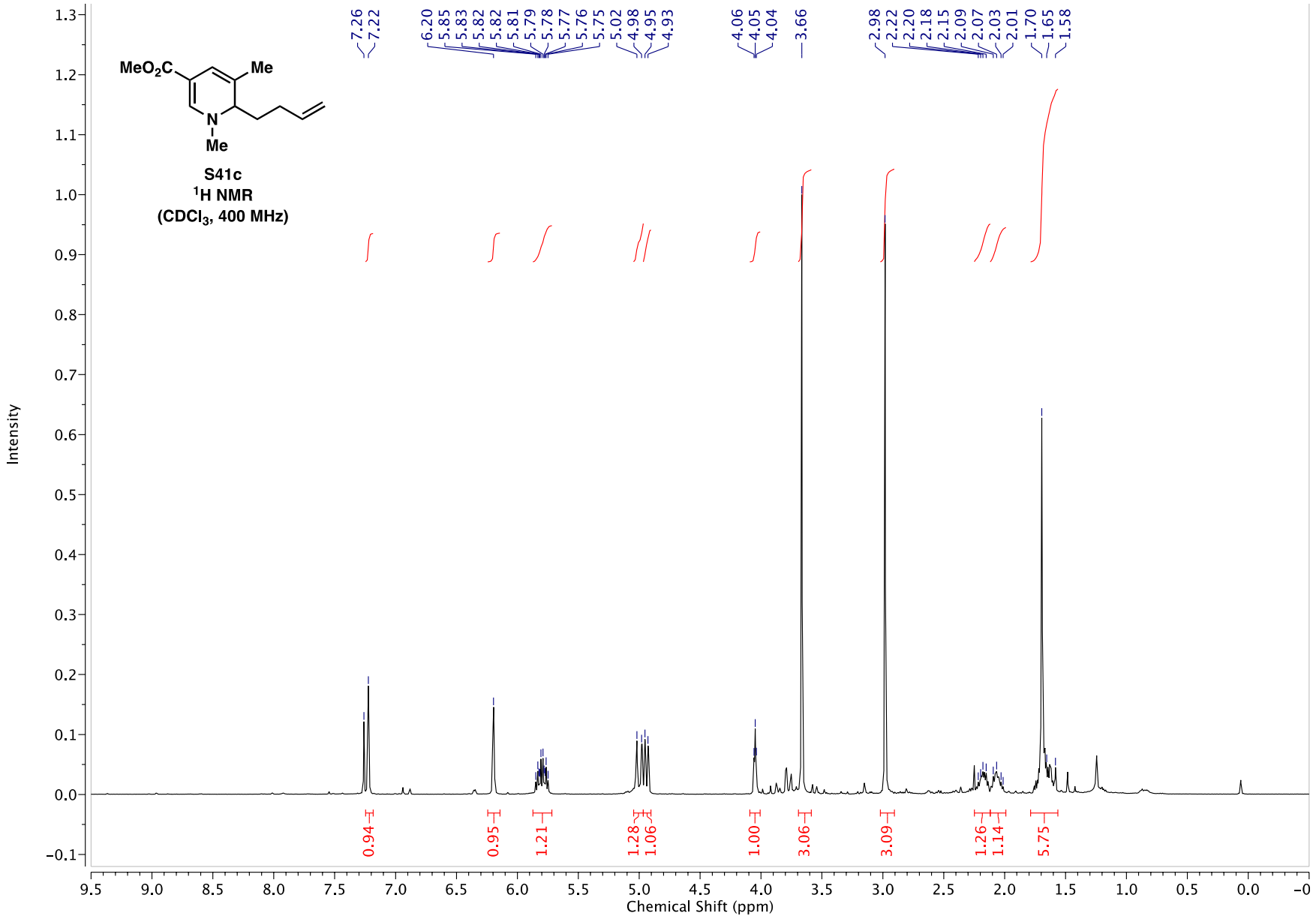

138.95
132.02
114.44
97.25
77.16
48.34
40.32
30.23
28.50
Br
Br
N
Me
S39b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

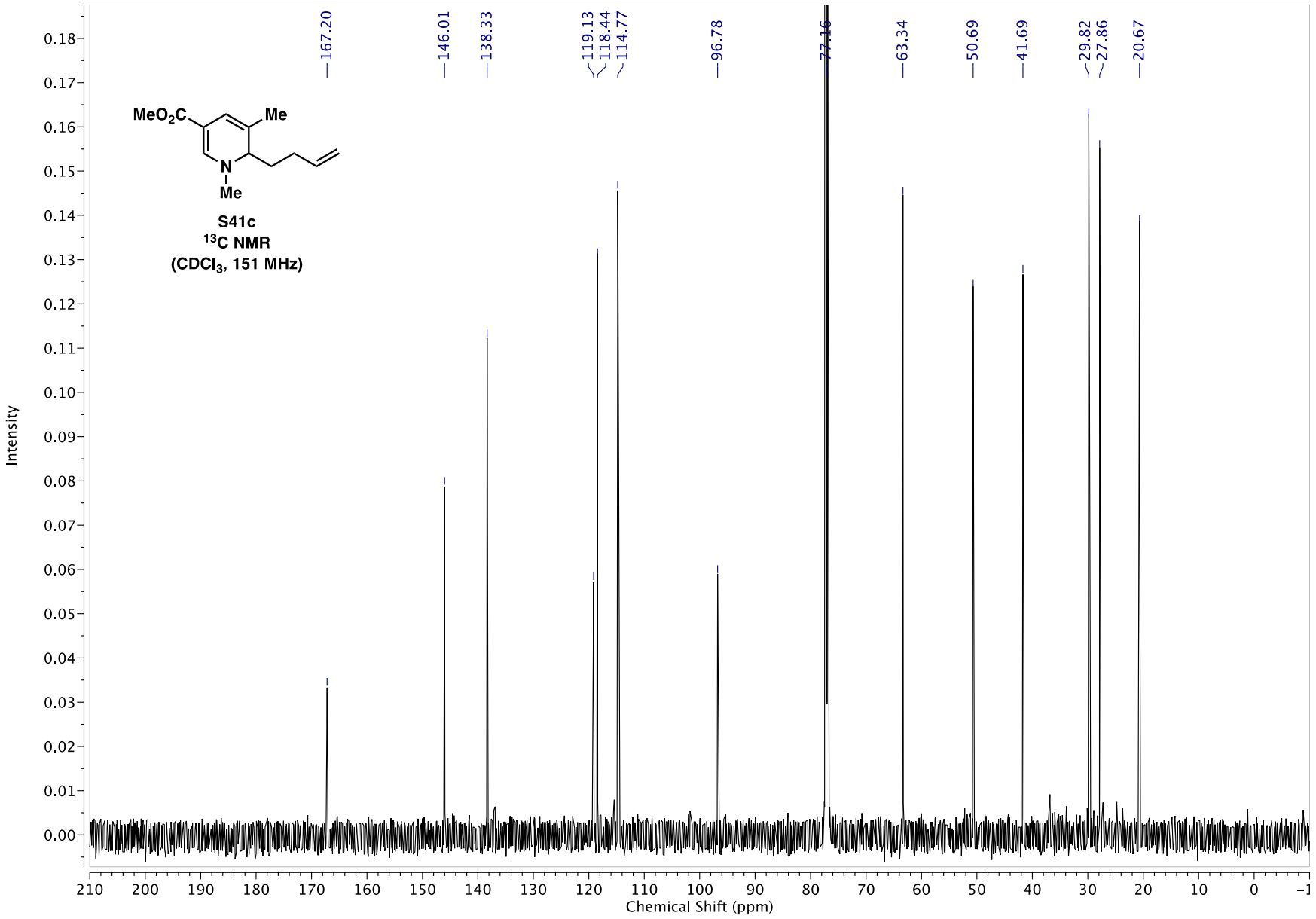

MeO2C
CO2Me
N
Me
S40a
1H NMR
(CDCl3, 600 MHz)
Intensity
Chemical Shift (ppm)

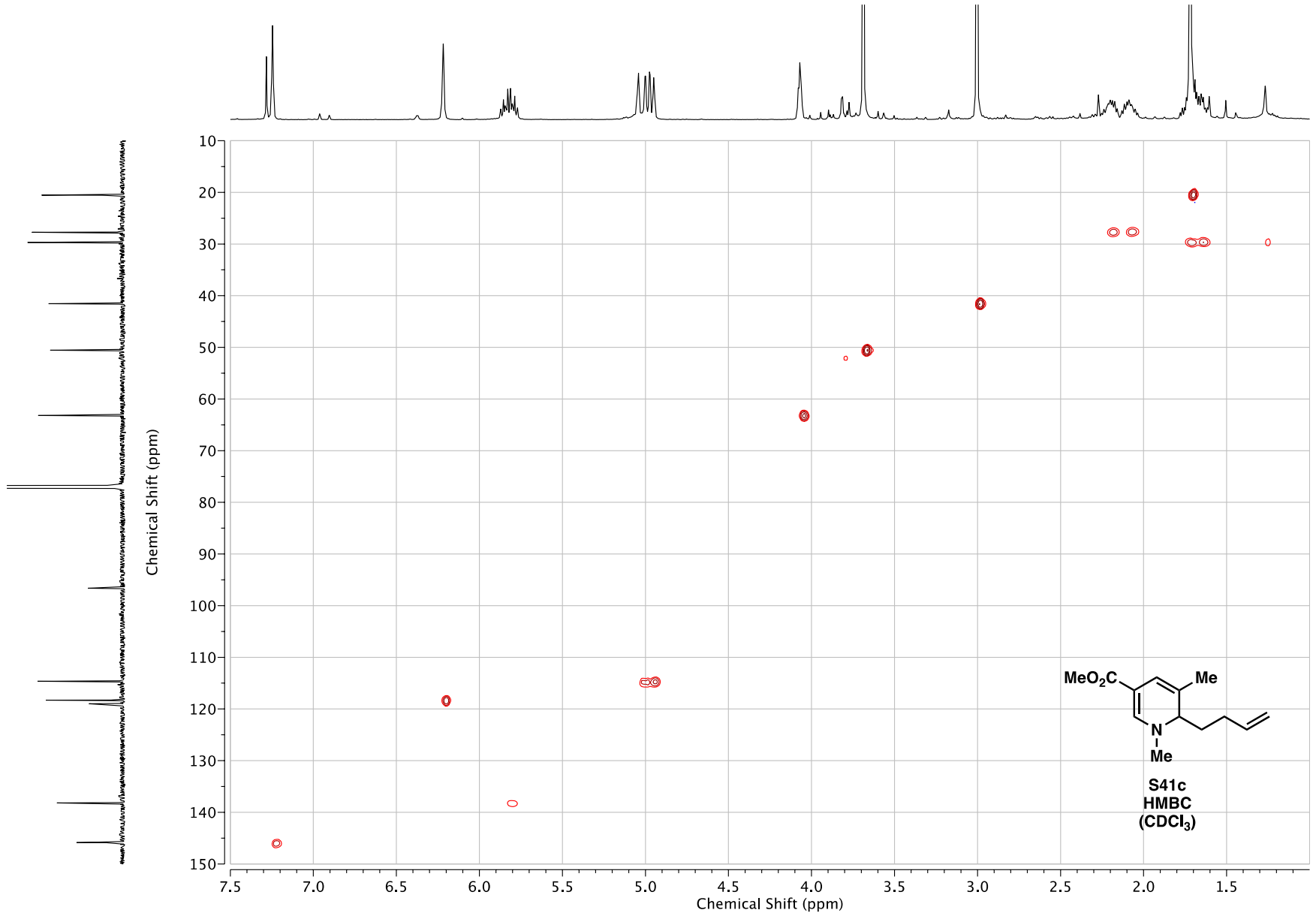

166.74
166.42
150.52
137.85
133.63
115.07
109.03
98.09
77.16
58.06
51.54
51.07
42.91
31.86
28.22
MeO2C
CO2Me
N
Me
S40a
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

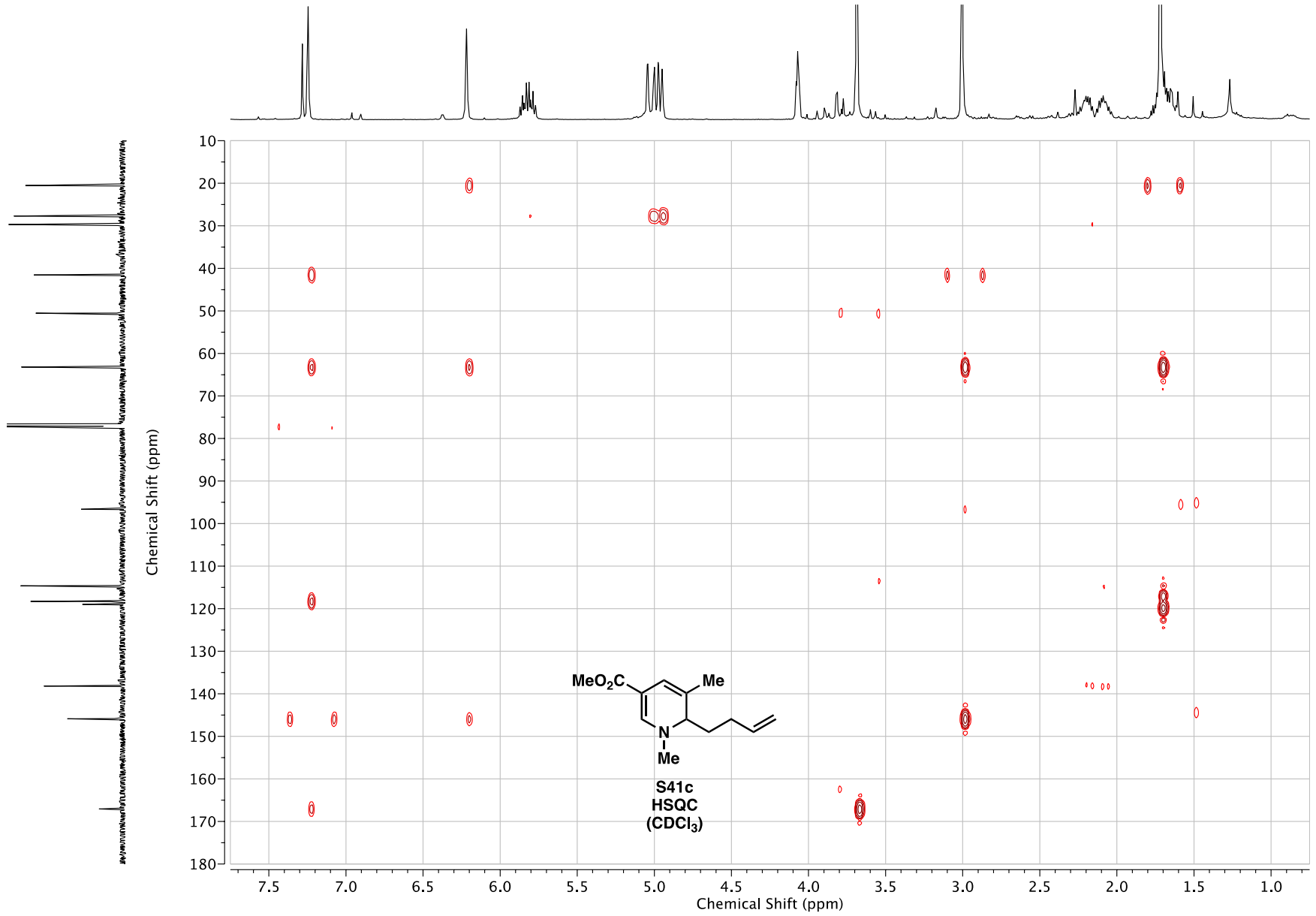

7.26
7.11
5.83
5.82
5.81
5.80
5.79
5.77
5.76
5.76
5.75
5.73
4.99
4.98
4.98
4.97
4.94
4.94
4.94
4.93
4.90
4.90
4.90
4.90
4.89
4.89
4.88
4.87
4.87
4.87
4.87
4.87
3.92
3.91
3.89
3.73
3.16
1.98
1.96
1.94
1.92
1.51
1.50
1.49
1.48
1.47
1.46
MeO2C
CO2Me
N
Me
S40b
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
1.72
1.05
0.99
0.91
1.00
5.46
2.74
1.85
1.92

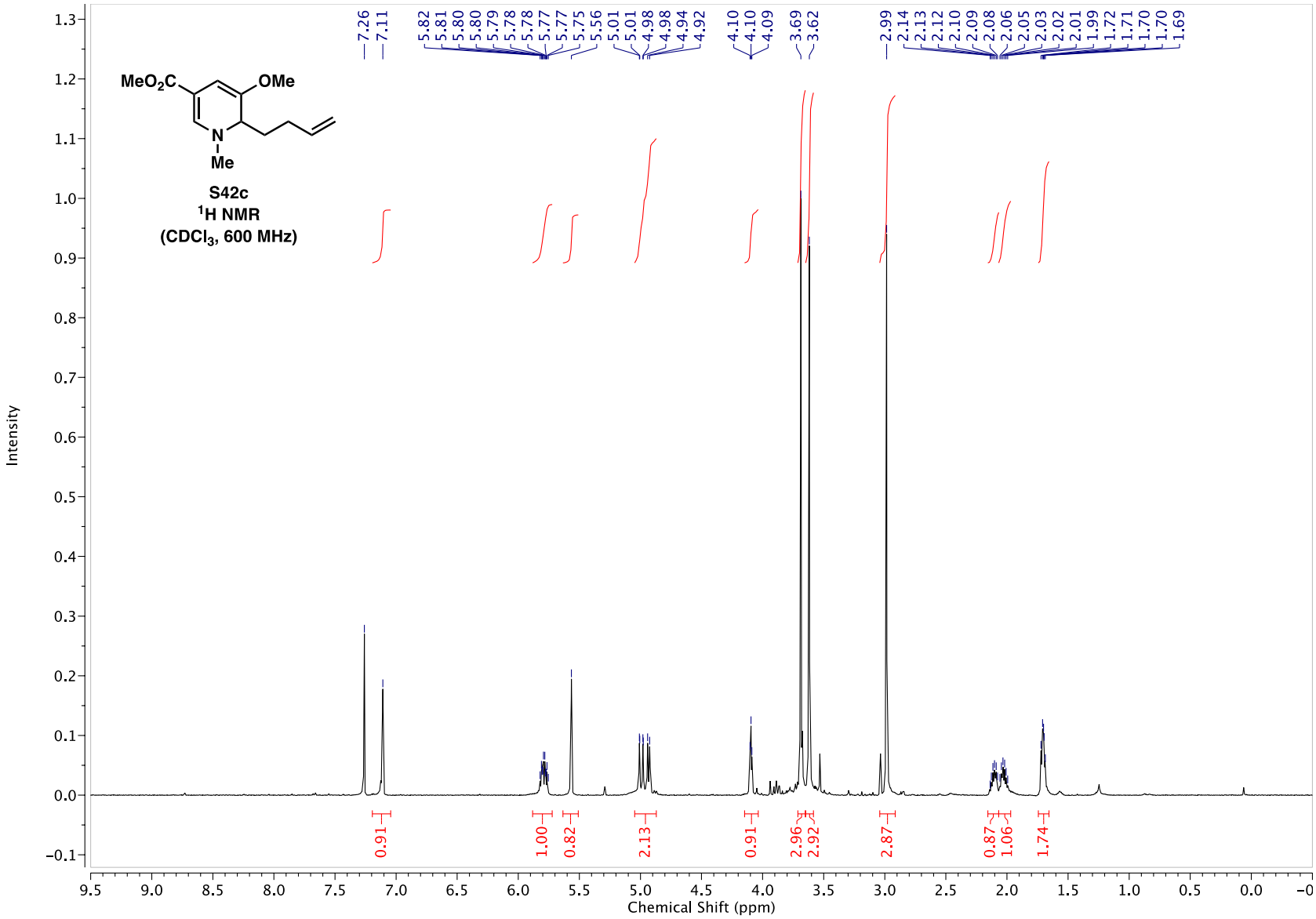

167.84
140.05
139.25
114.09
106.97
77.16
51.44
41.55
35.38
30.42
28.92
MeO2C
CO2Me
N
Me
S40b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

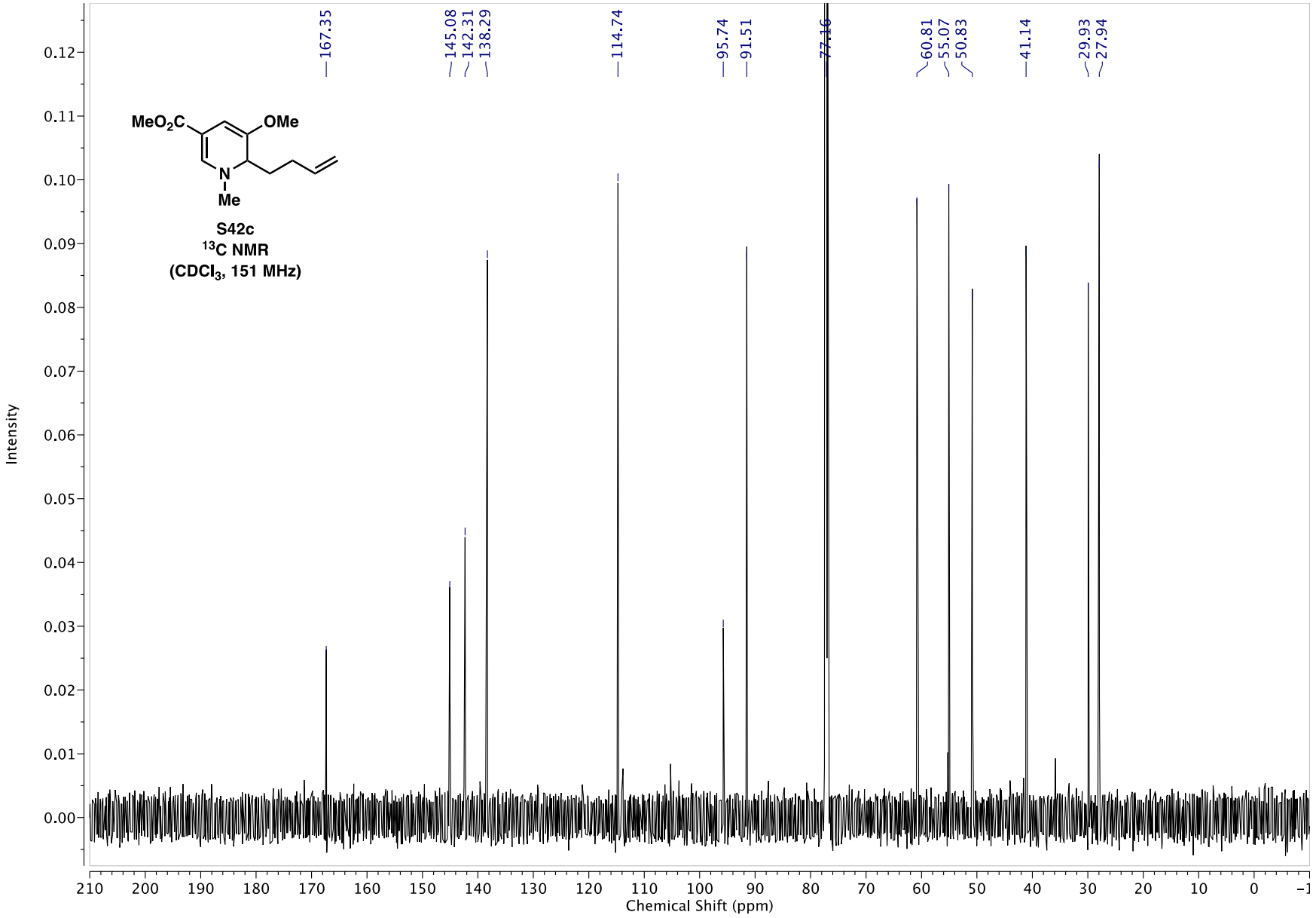

MeO2C
Me
N
Me
S41c
1H NMR
(CDCl3, 400 MHz)
7.26
7.22
6.20
5.85
5.83
5.82
5.82
5.81
5.79
5.78
5.77
5.76
5.75
5.02
4.98
4.95
4.93
4.06
4.05
4.04
3.66
2.98
2.22
2.20
2.18
2.15
2.09
2.07
2.03
2.01
1.70
1.65
1.58
0.94
0.95
1.21
1.28
1.06
1.00
3.06
3.09
1.26
1.14
5.75
Intensity
Chemical Shift (ppm)

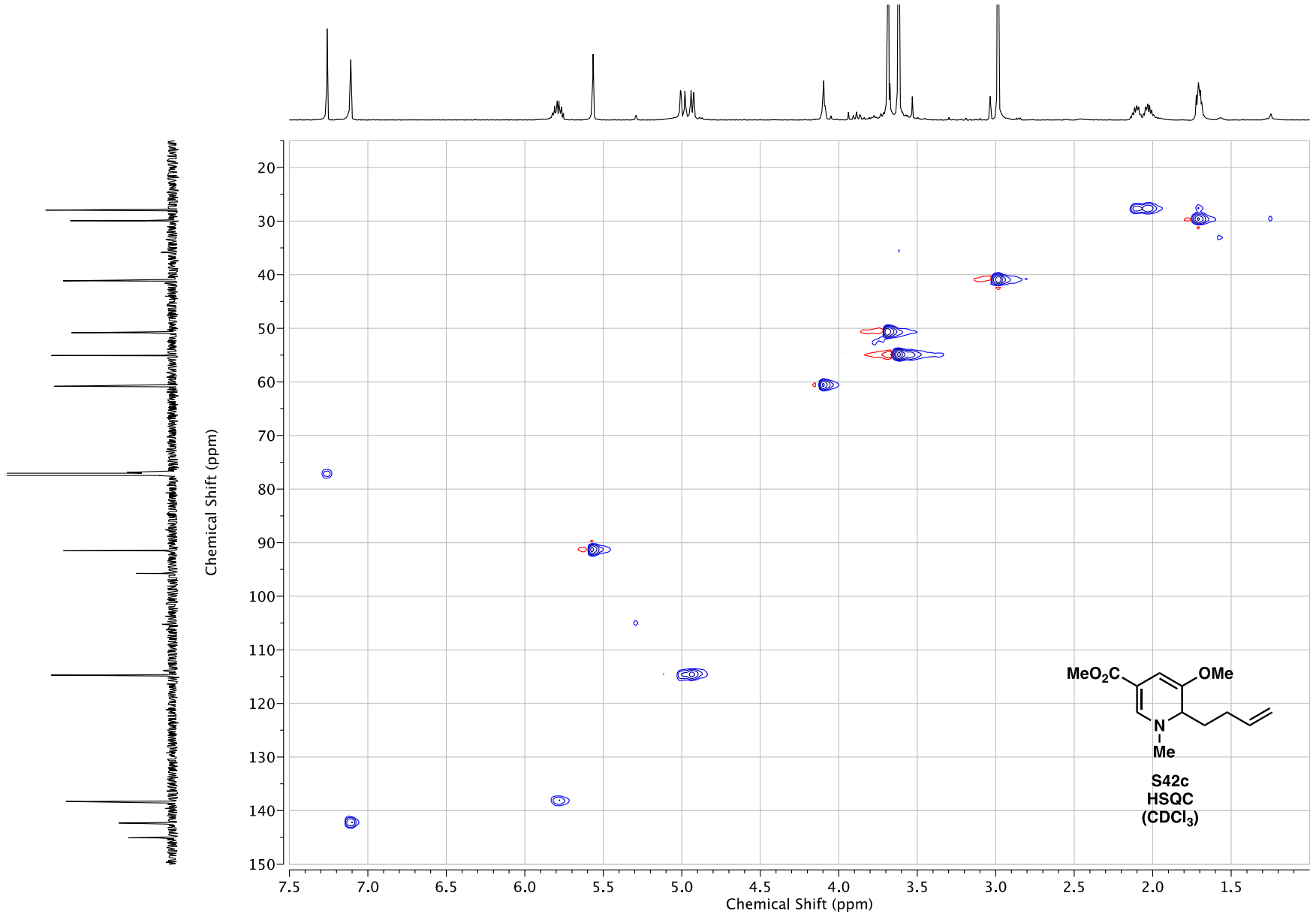

167.20
146.01
138.33
119.13
118.44
114.77
96.78
77.16
63.34
50.69
41.69
29.82
27.86
20.67
MeO2C
Me
N
Me
S41c
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

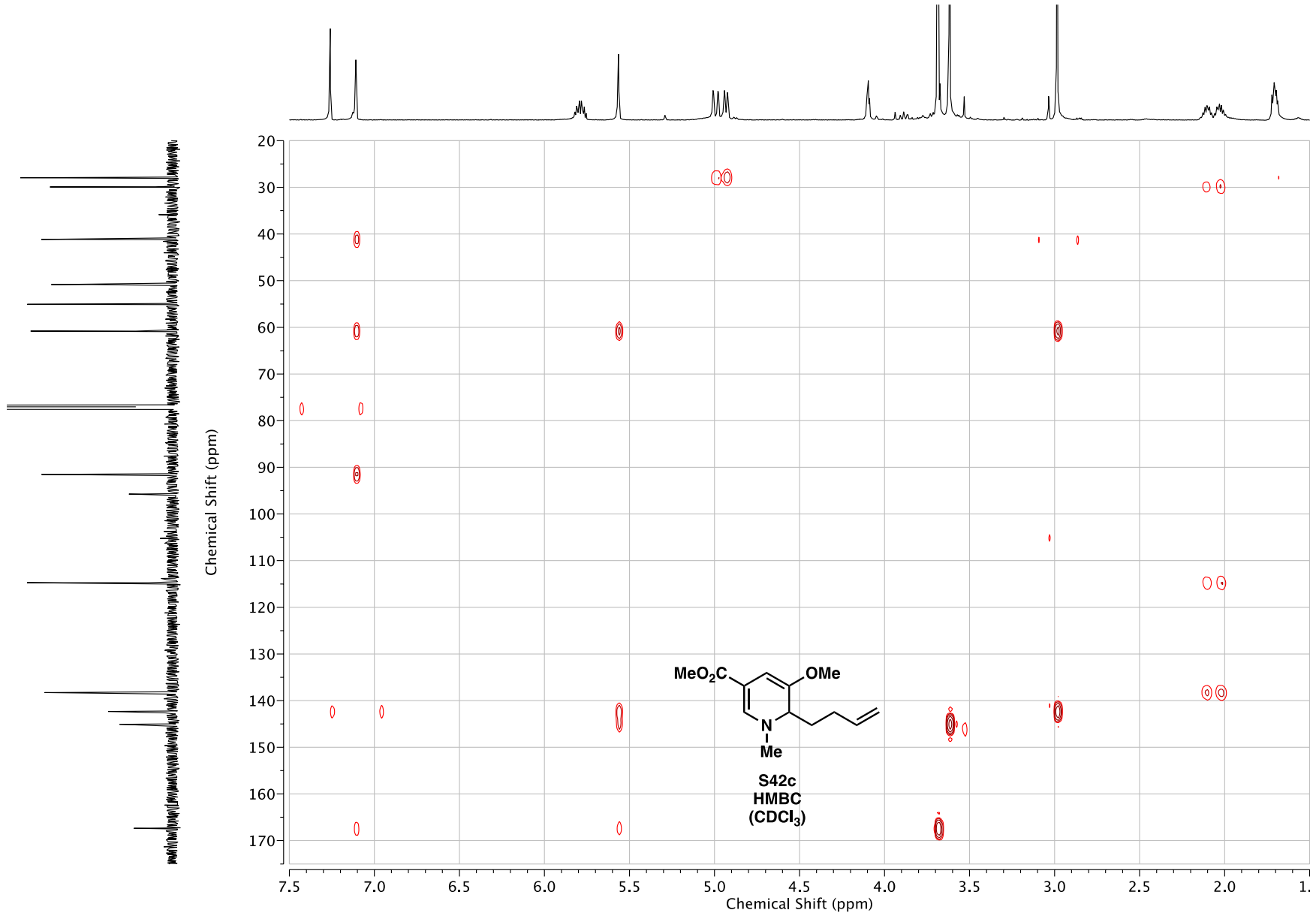

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Me
N
Me
S41c
HMBC
(CDCl3)

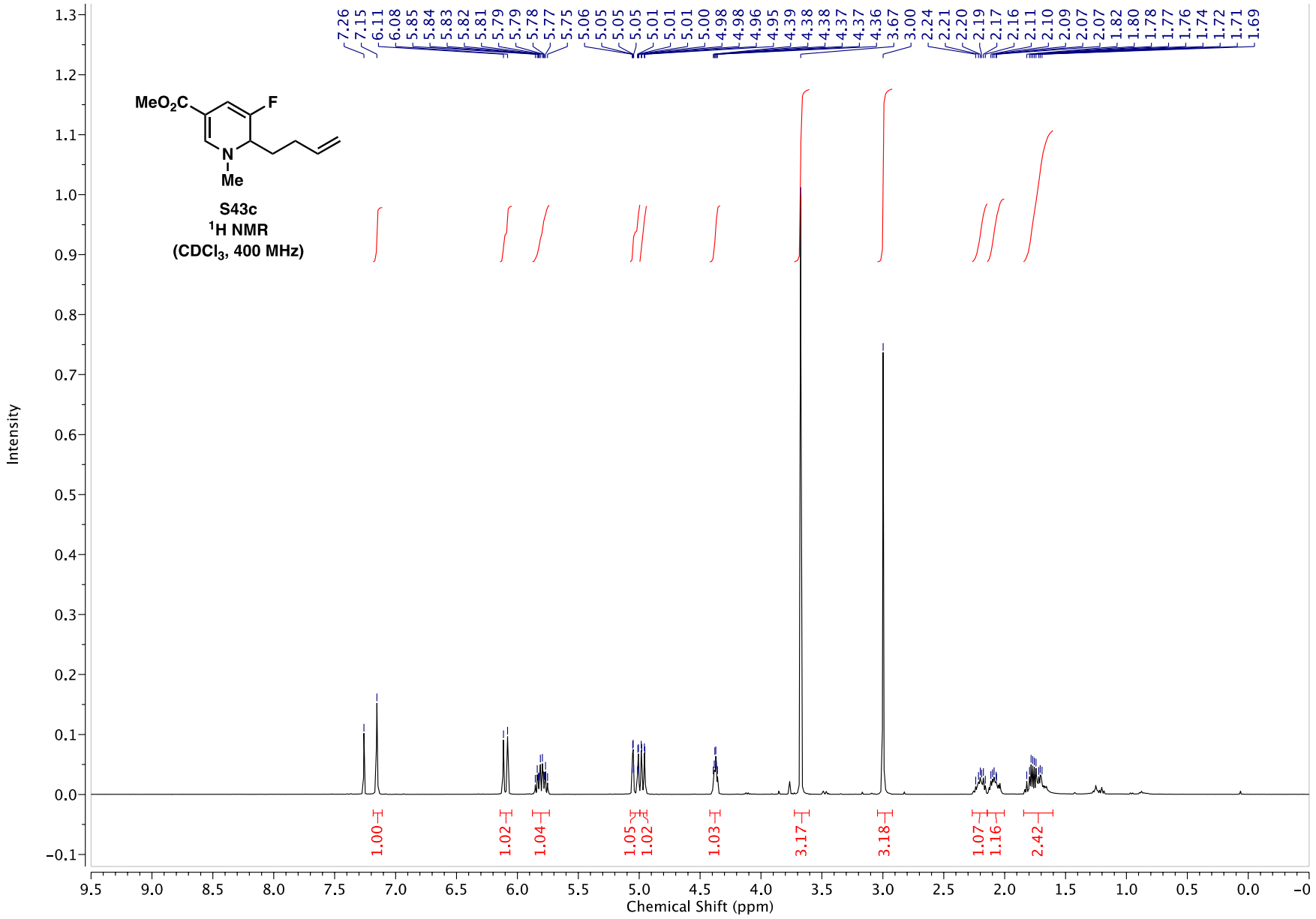

MeO2C
Me
N
Me
S41c
HSQC
(CDCl3)
Chemical Shift (ppm)
Chemical Shift (ppm)

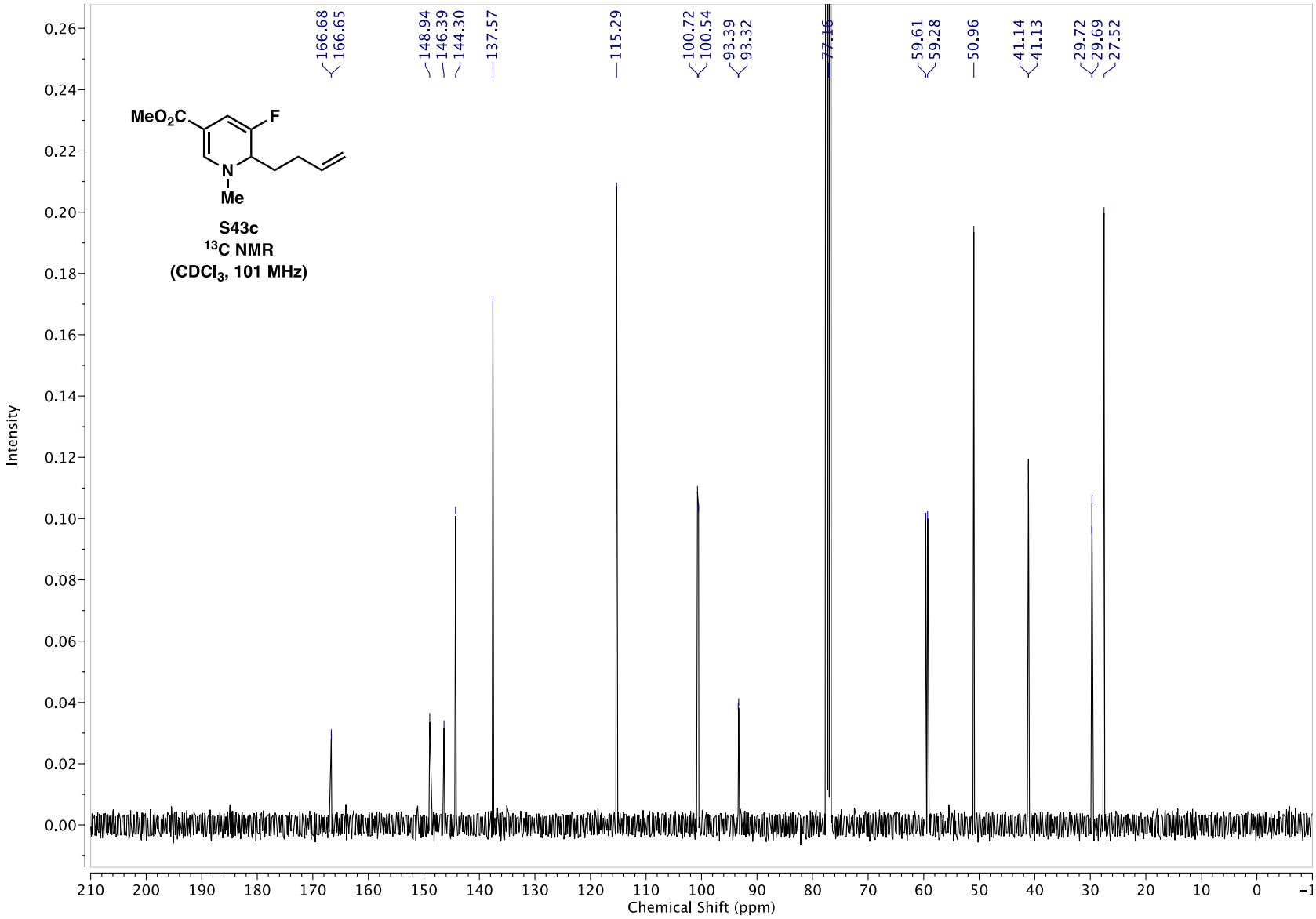

MeO2C
OMe
N
Me
S42c
1H NMR
(CDCl3, 600 MHz)
Intensity
Chemical Shift (ppm)
7.26
7.11
5.82
5.81
5.80
5.80
5.79
5.78
5.78
5.77
5.77
5.75
5.56
5.01
5.01
4.98
4.98
4.94
4.92
4.10
4.10
4.09
3.69
3.62
2.99
2.14
2.13
2.12
2.10
2.09
2.08
2.06
2.05
2.03
2.02
2.01
1.99
1.72
1.71
1.70
1.70
1.69
0.91
1.00
0.82
2.13
0.91
2.96
2.92
2.87
0.87
1.06
1.74

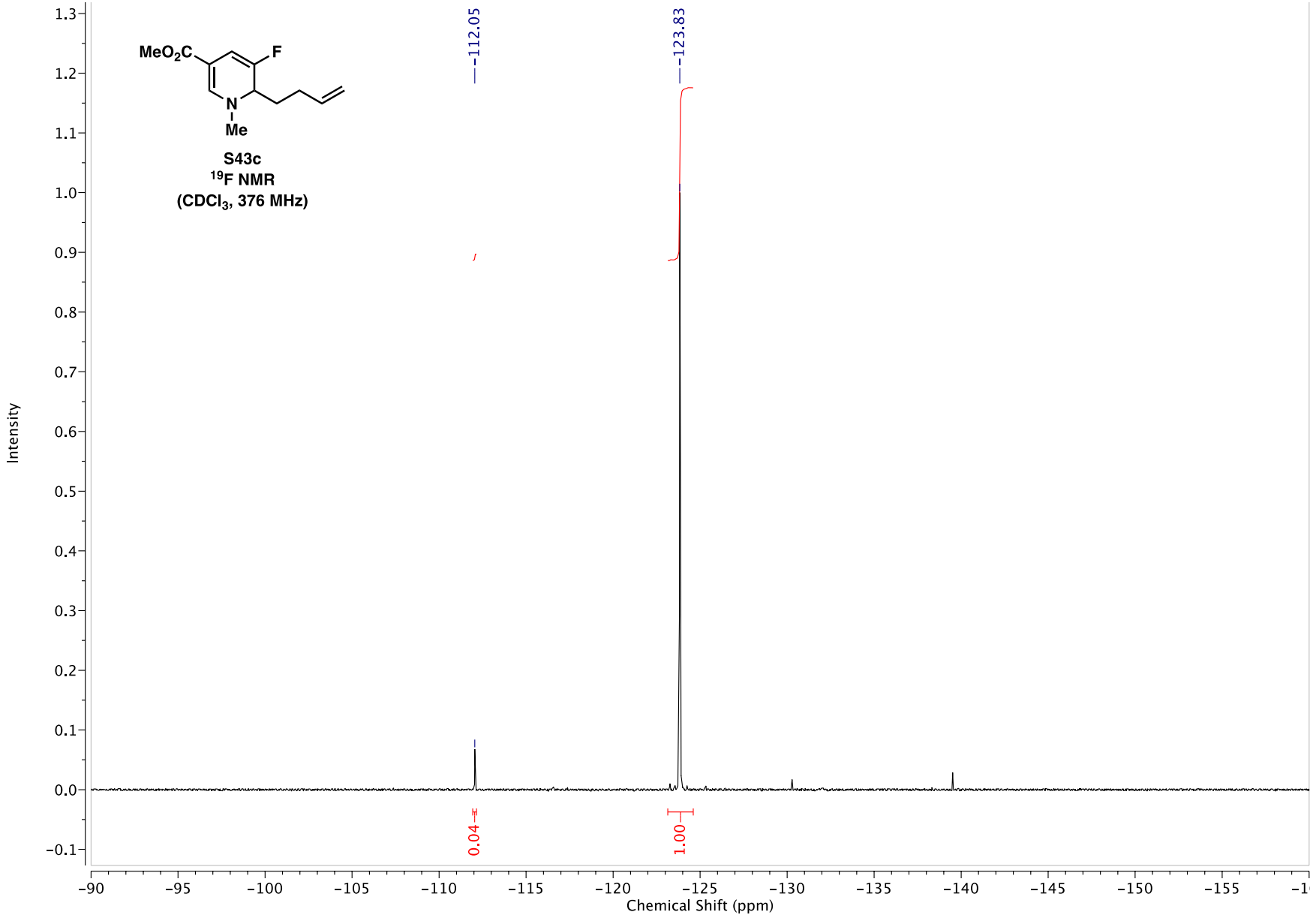

167.35
145.08
142.31
138.29
114.74
95.74
91.51
77.16
60.81
55.07
50.83
41.14
29.93
27.94
MeO2C
OMe
N
Me
S42c
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

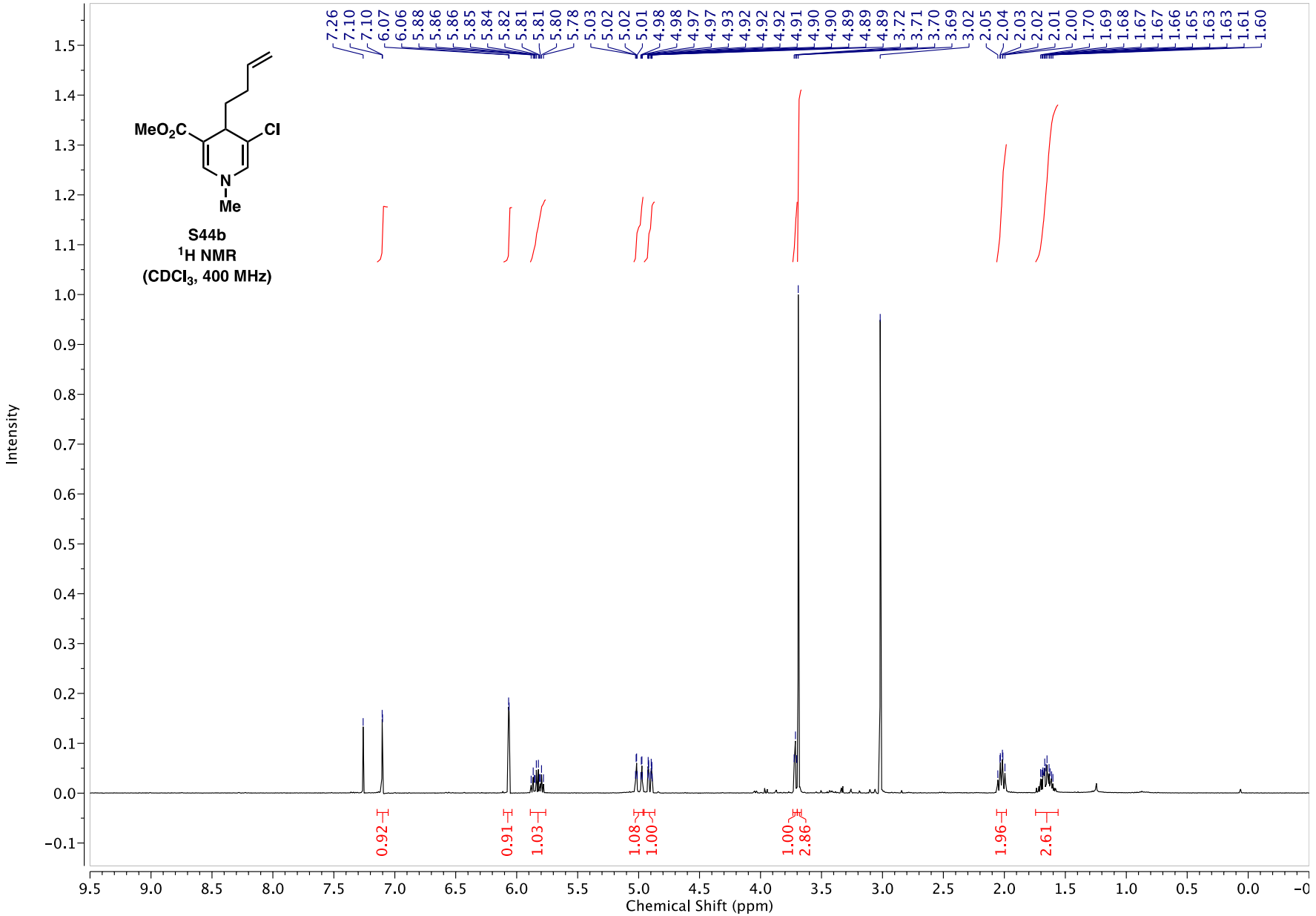

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
OMe
N
Me
S42c
HSQC
(CDCl3)

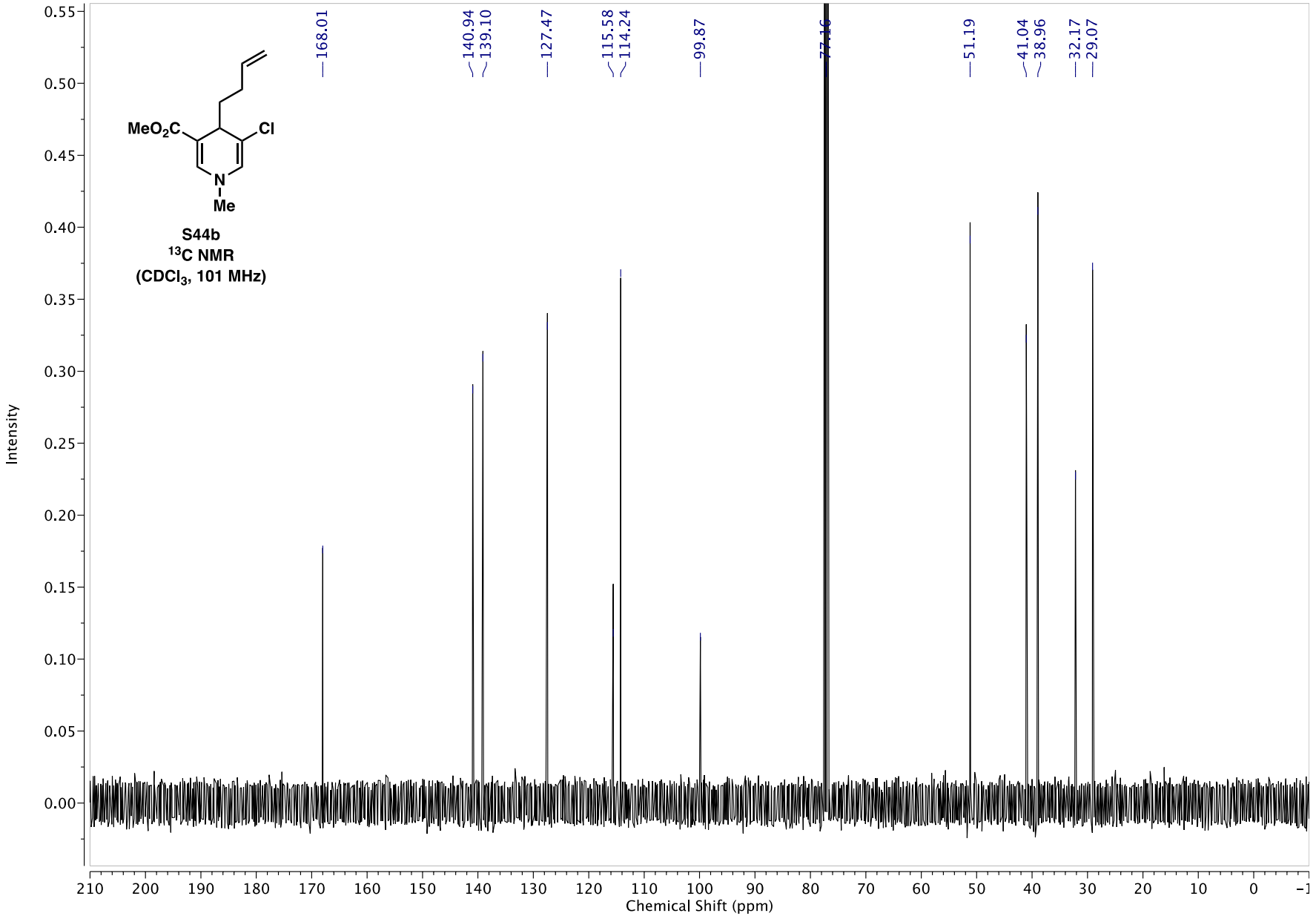

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
OMe
N
Me
S42c
HMBC
(CDCl3)

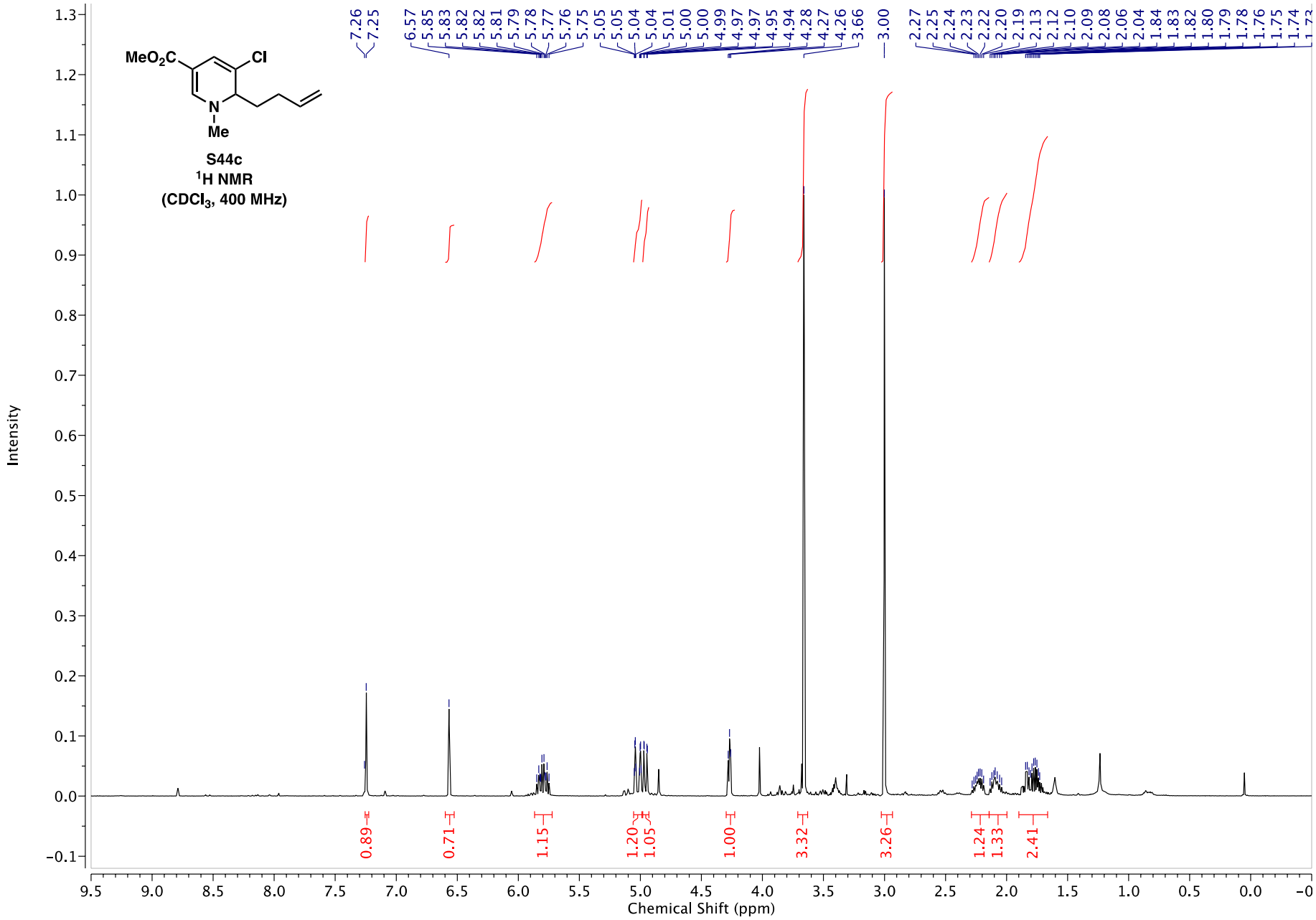

MeO2C
F
N
Me
S43c
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
7.26 7.15 6.11 6.08 5.85 5.84 5.83 5.82 5.81 5.79 5.79 5.78 5.77 5.75 5.06 5.05 5.05 5.05 5.01 5.01 5.01 5.00 4.98 4.98 4.96 4.95 4.39 4.38 4.38 4.37 4.37 4.36 3.67 3.00 2.24 2.21 2.20 2.19 2.17 2.16 2.11 2.10 2.09 2.07 2.07 1.82 1.80 1.78 1.77 1.76 1.74 1.72 1.71 1.69
1.00
1.02
1.04
1.05
1.02
1.03
3.17
3.18
1.07
1.16
2.42

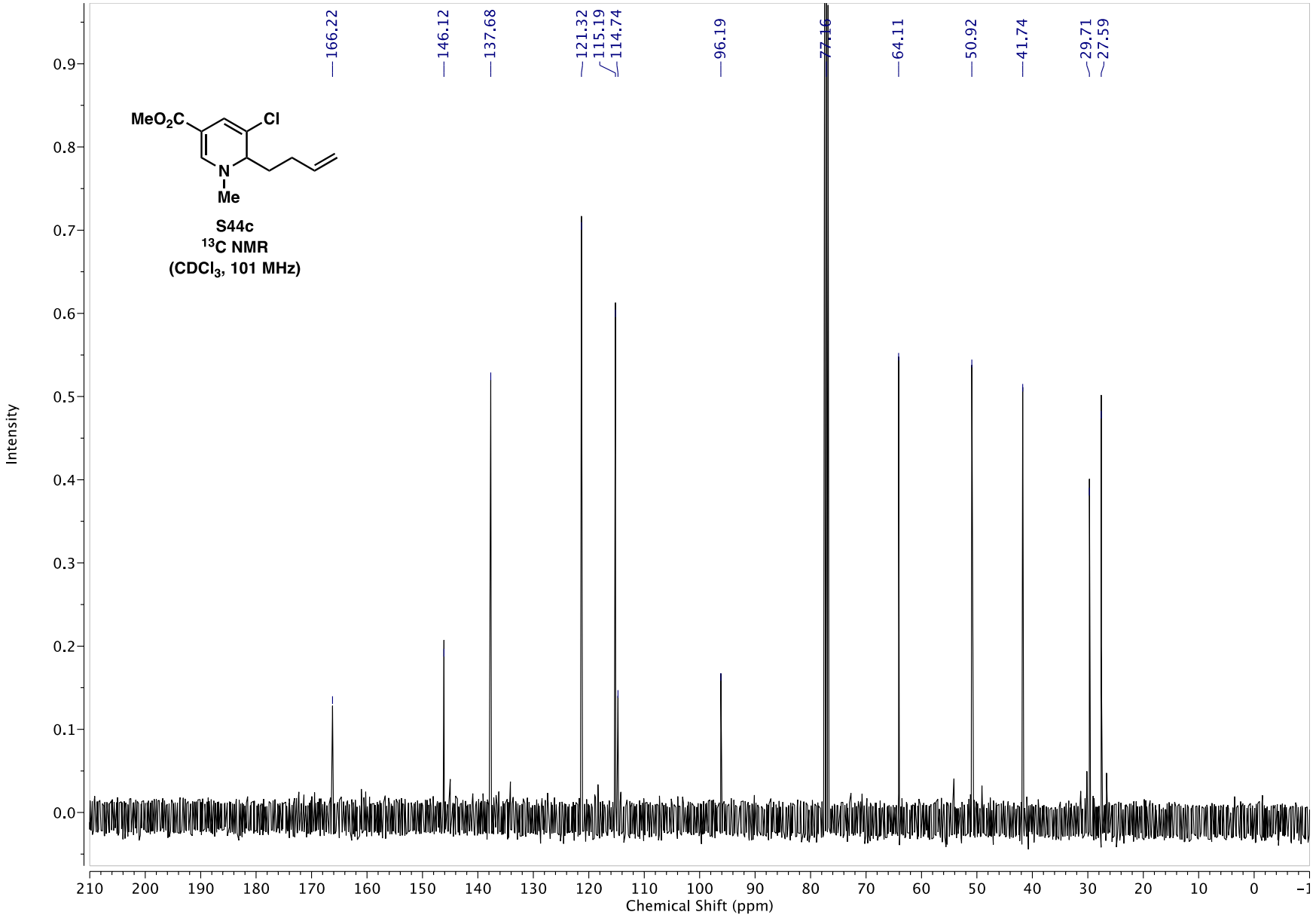

166.68
166.65
148.94
146.39
144.30
137.57
115.29
100.72
100.54
93.39
93.32
77.16
59.61
59.28
50.96
41.14
41.13
29.72
29.69
27.52
MeO2C
F
N
Me
S43c
13C NMR
(CDCl3, 101 MHz)
Intensity
Chemical Shift (ppm)

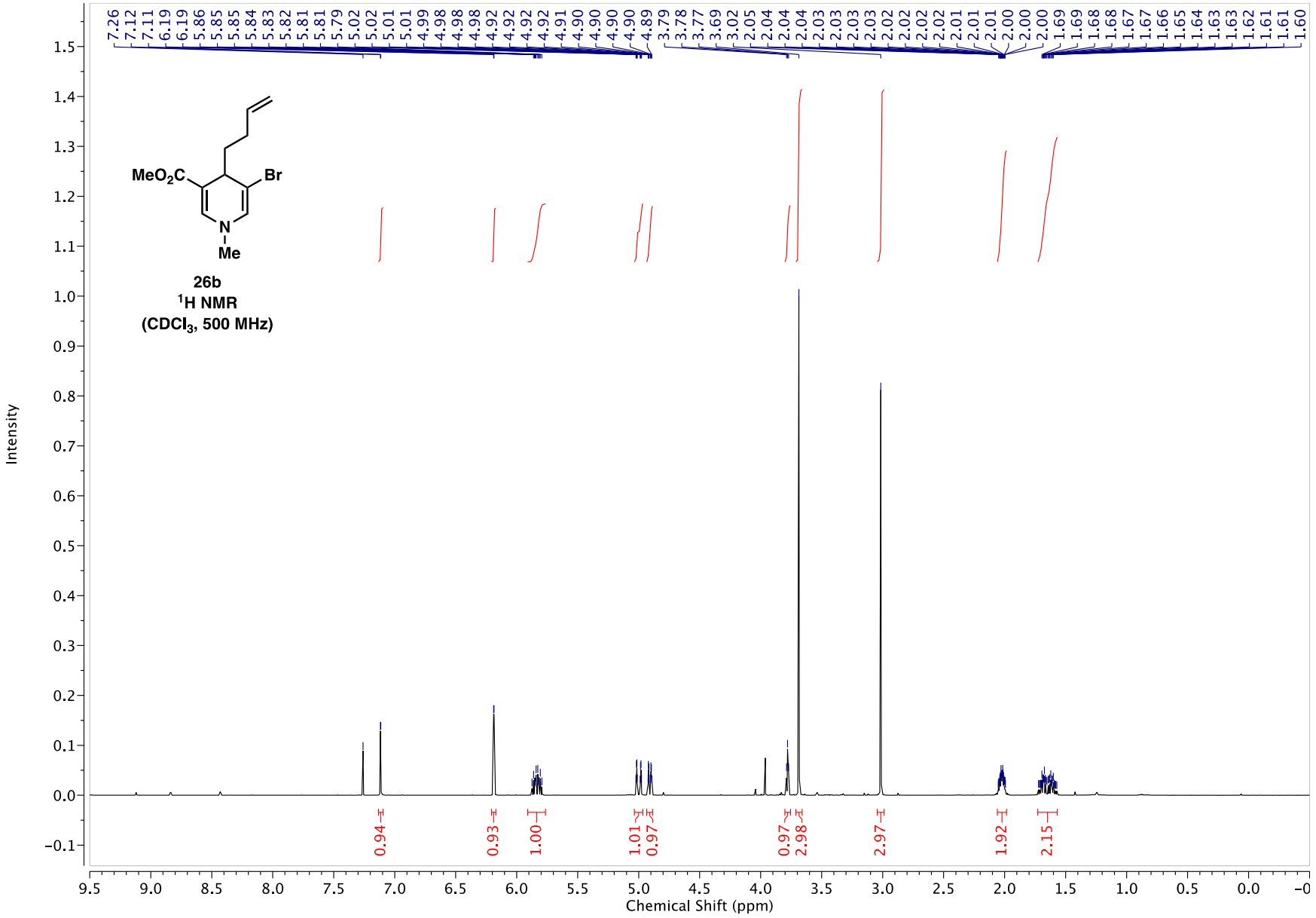

MeO2C
F
N
Me
S43c
19F NMR
(CDCl3, 376 MHz)
-112.05
-123.83
0.04
1.00
Intensity
Chemical Shift (ppm)

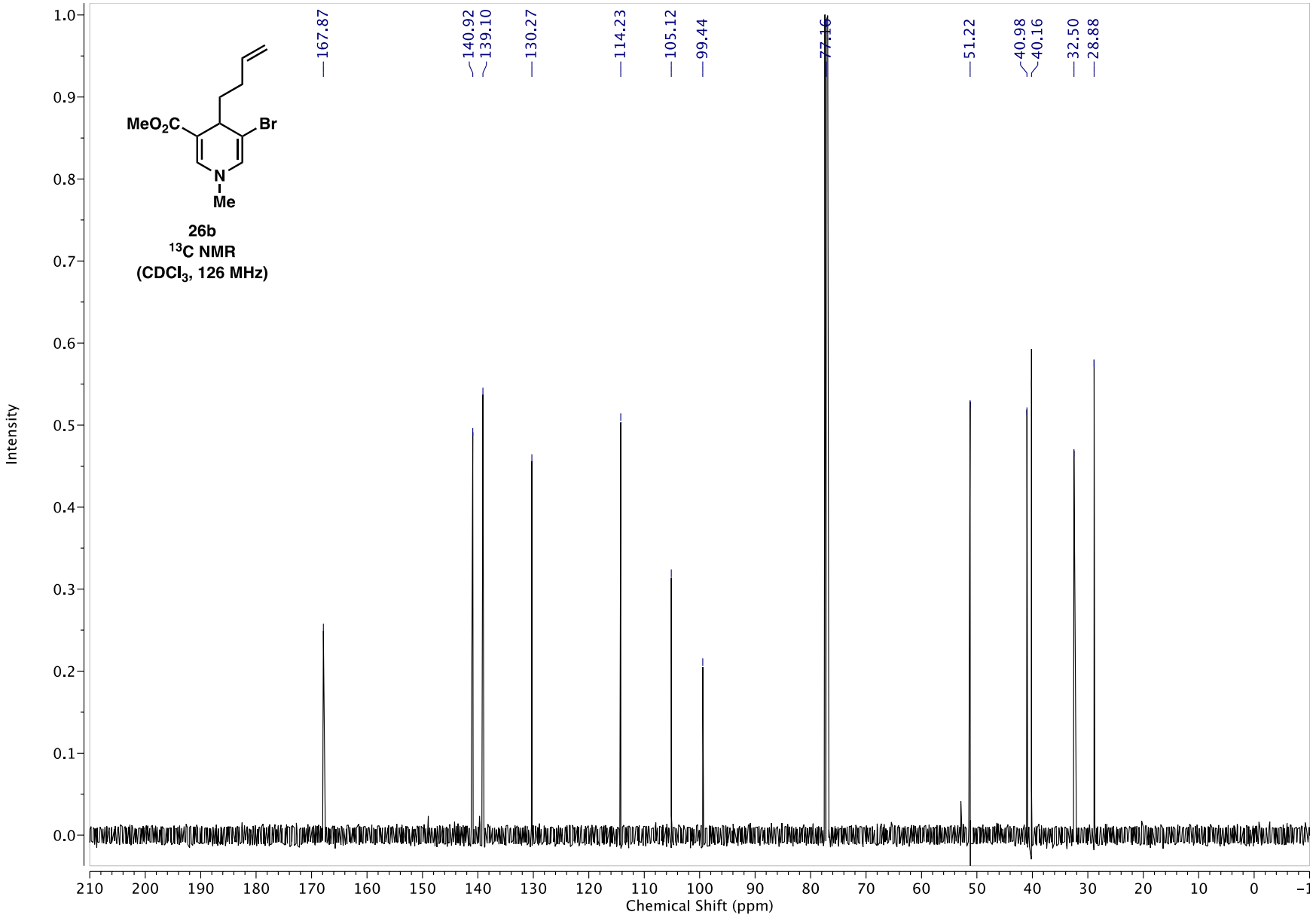

MeO2C
Cl
N
Me
S44b
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
0.92
0.91
1.03
1.08
1.00
1.00
2.86
1.96
2.61

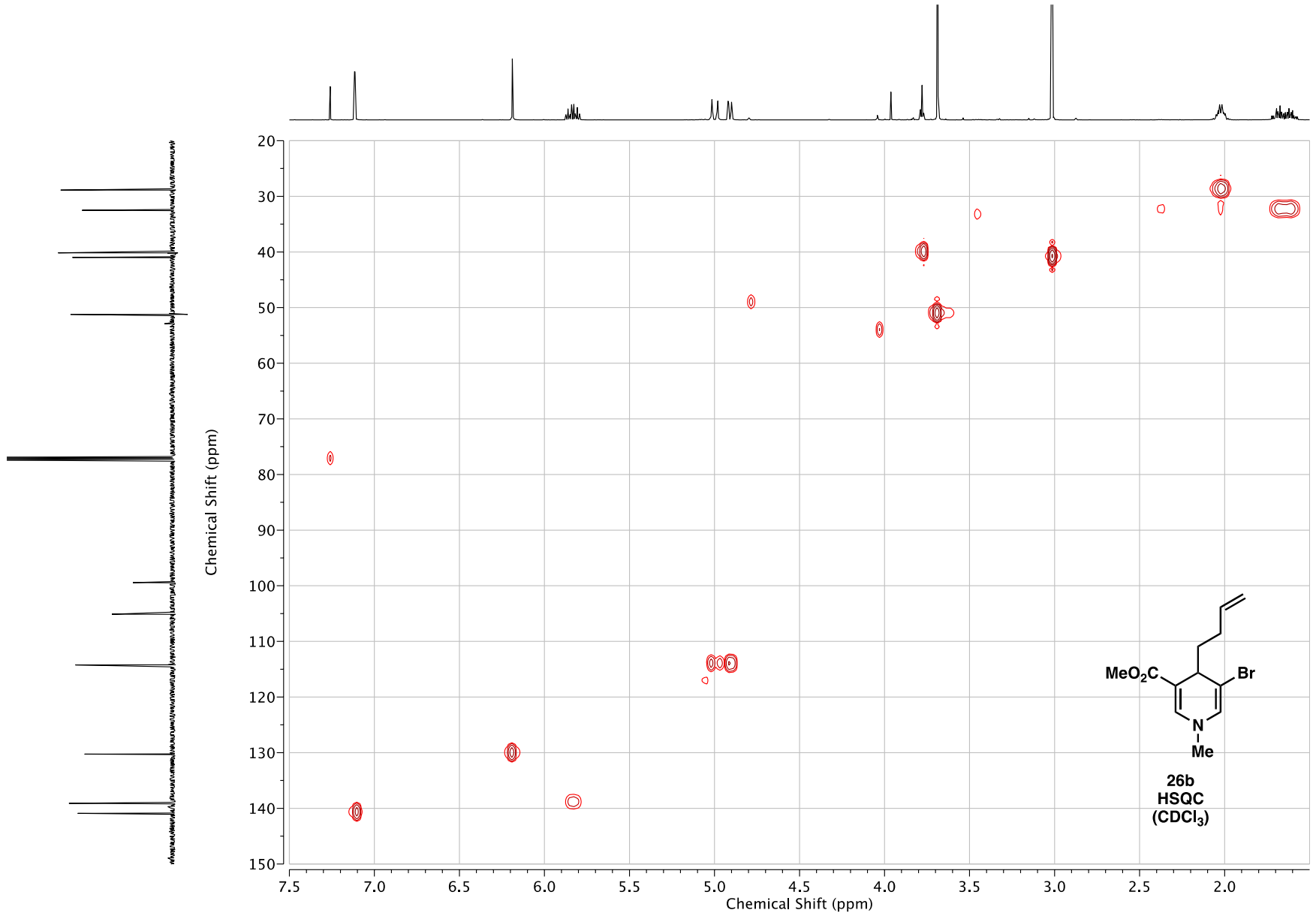

168.01
140.94
139.10
127.47
115.58
114.24
99.87
77.16
51.19
41.04
38.96
32.17
29.07
MeO2C
Cl
N
Me
S44b
13C NMR
(CDCl3, 101 MHz)
Intensity
Chemical Shift (ppm)

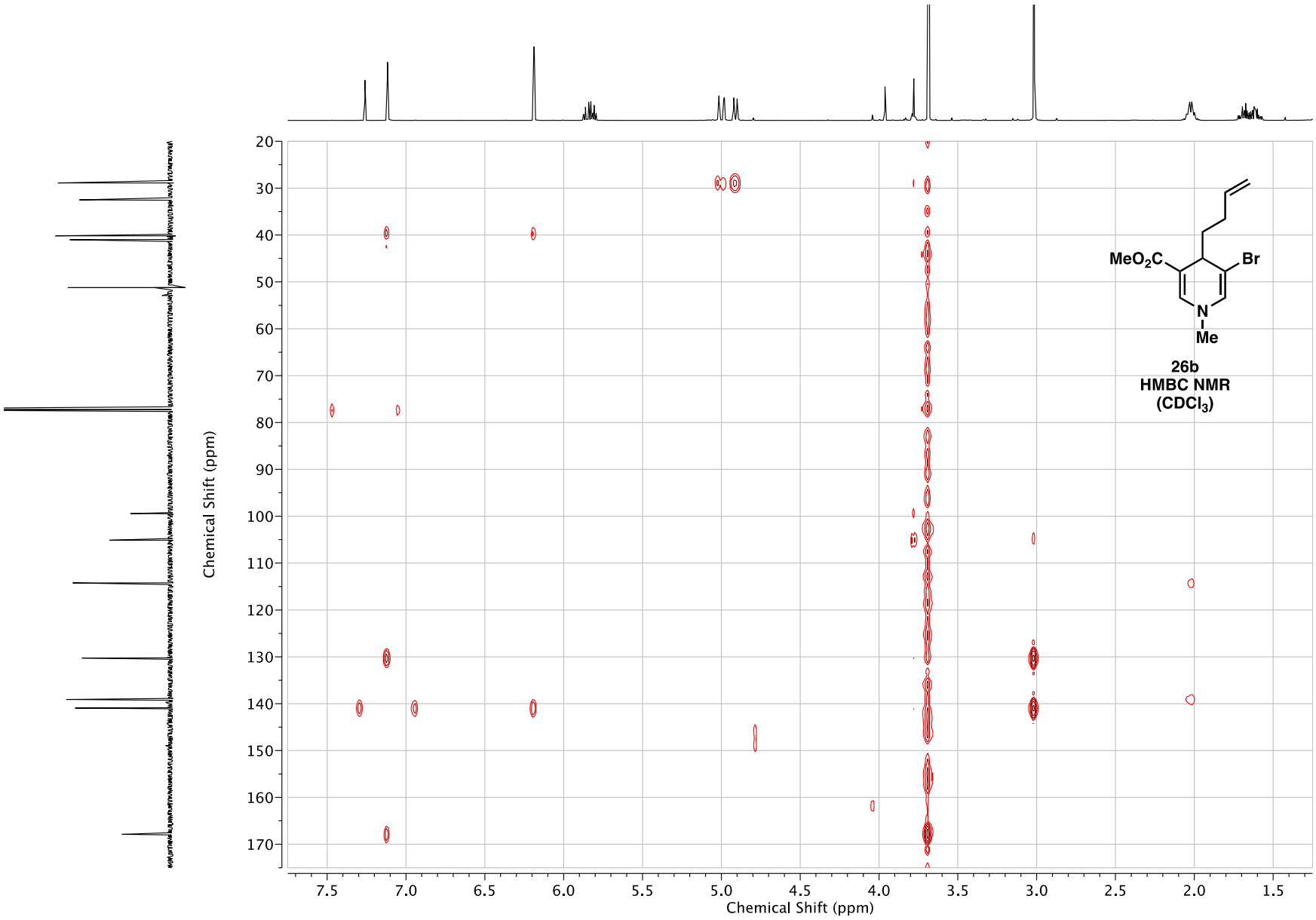

MeO2C
Cl
N
Me
S44c
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
0.89
0.71
1.15
1.20
1.05
1.00
3.32
3.26
1.24
1.33
2.41

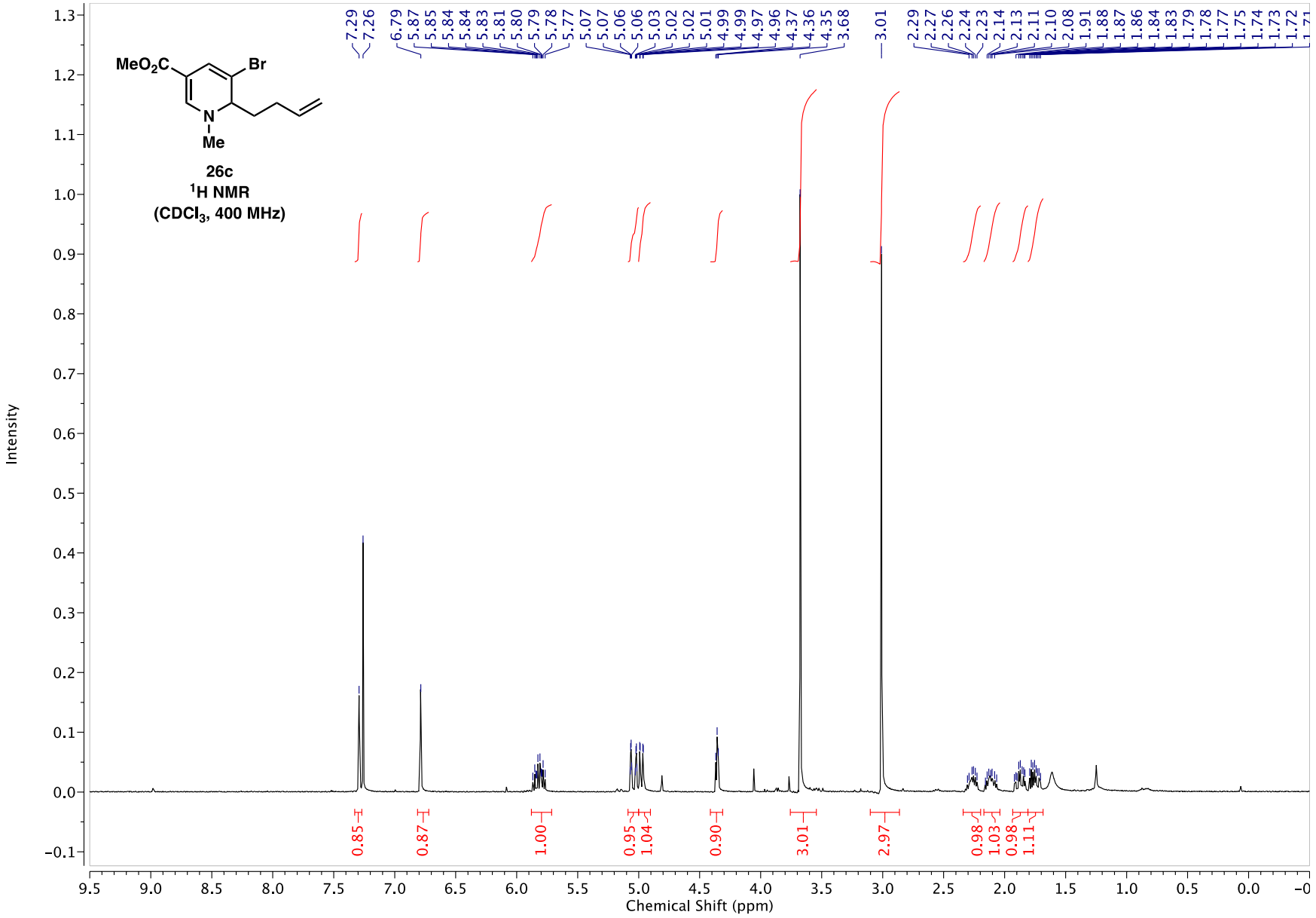

166.22
146.12
137.68
121.32
115.19
114.74
96.19
77.16
64.11
50.92
41.74
29.71
27.59
MeO2C
Cl
N
Me
S44c
13C NMR
(CDCl3, 101 MHz)
Intensity
Chemical Shift (ppm)

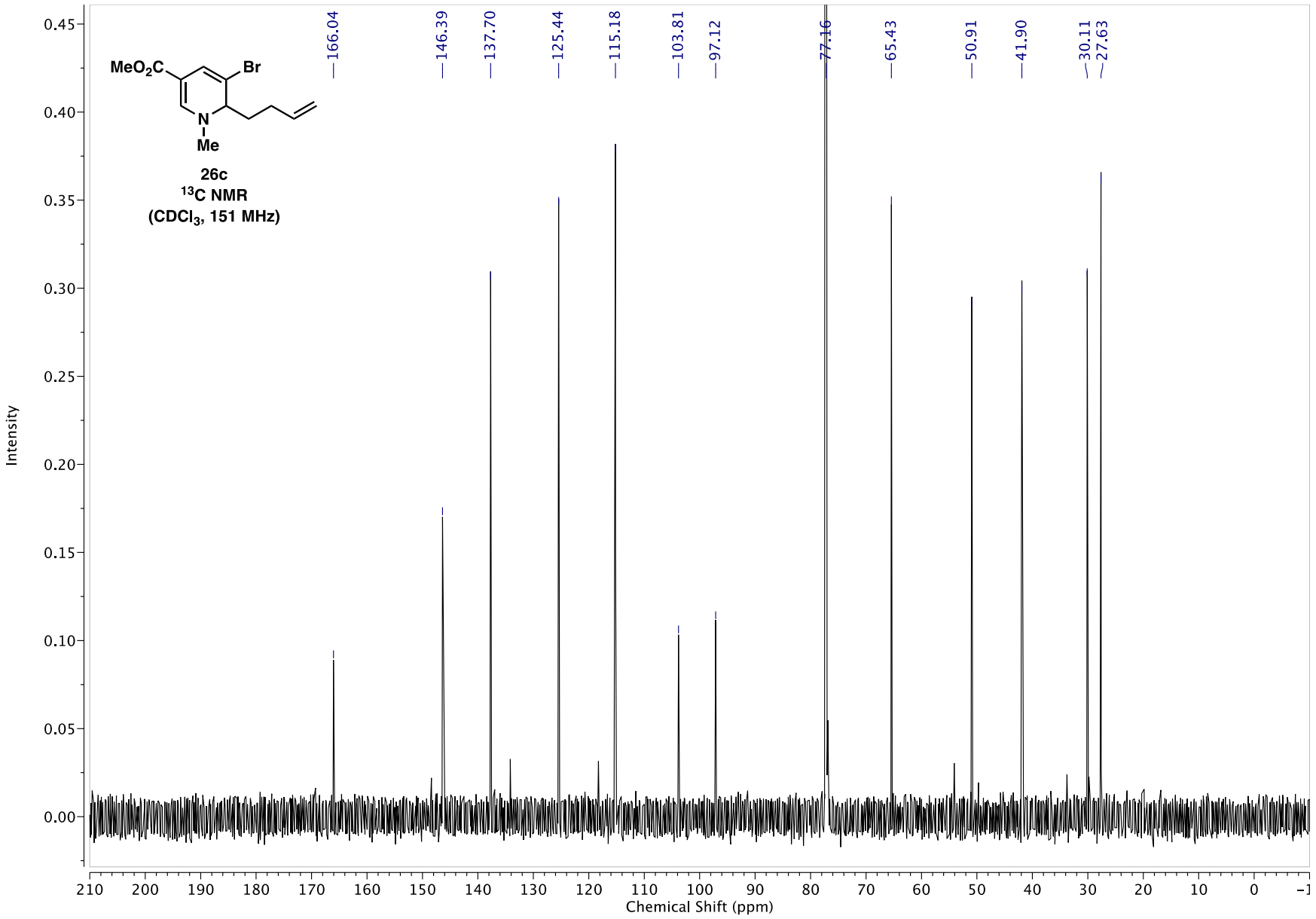

MeO2C
Br
N
Me
26b
1H NMR
(CDCl3, 500 MHz)
Intensity
Chemical Shift (ppm)
0.94
0.93
1.00
1.01
0.97
0.97
2.98
2.97
1.92
2.15

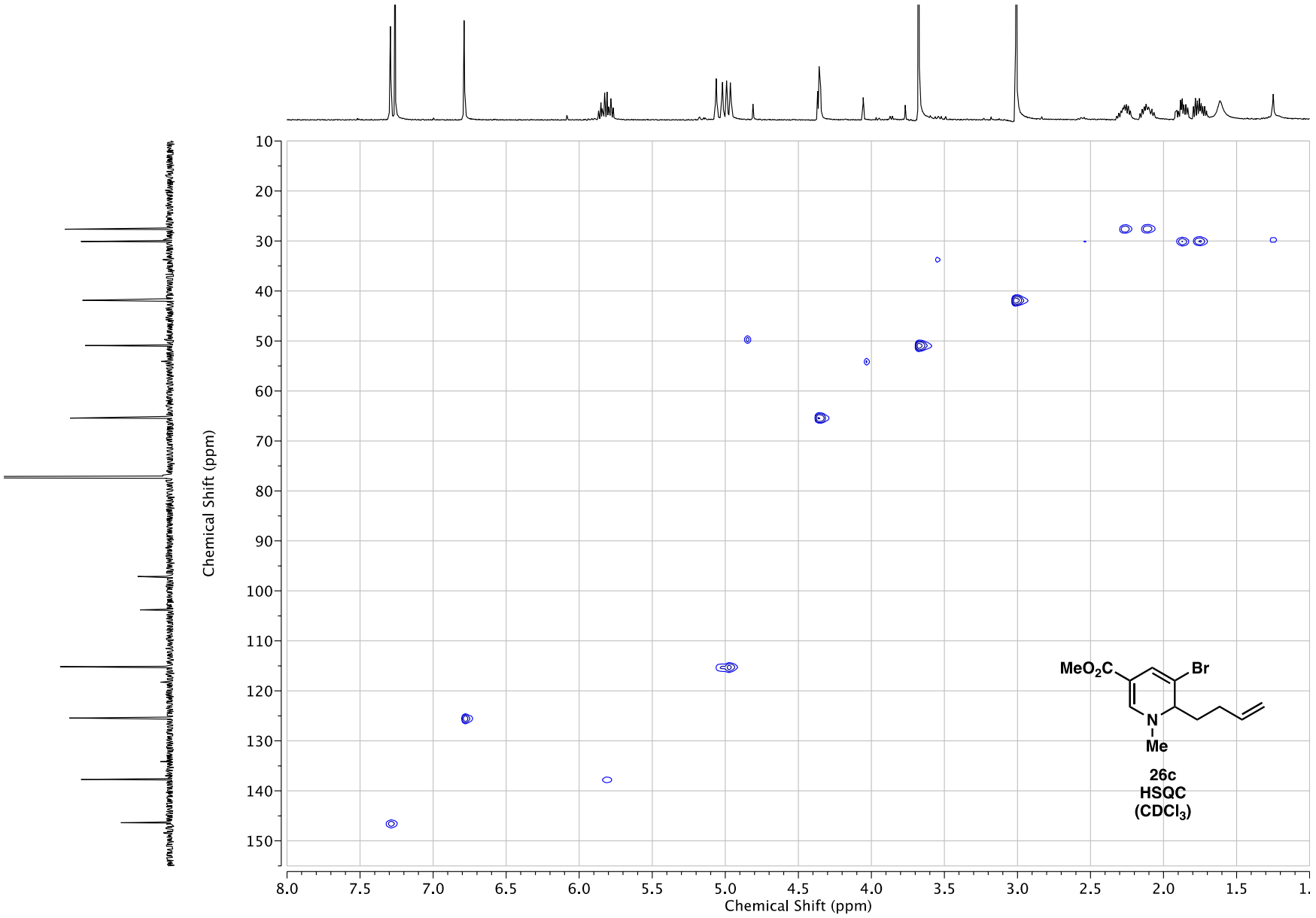

167.87
140.92
139.10
130.27
114.23
105.12
99.44
77.16
51.22
40.98
40.16
32.50
28.88
MeO2C
Br
N
Me
26b
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

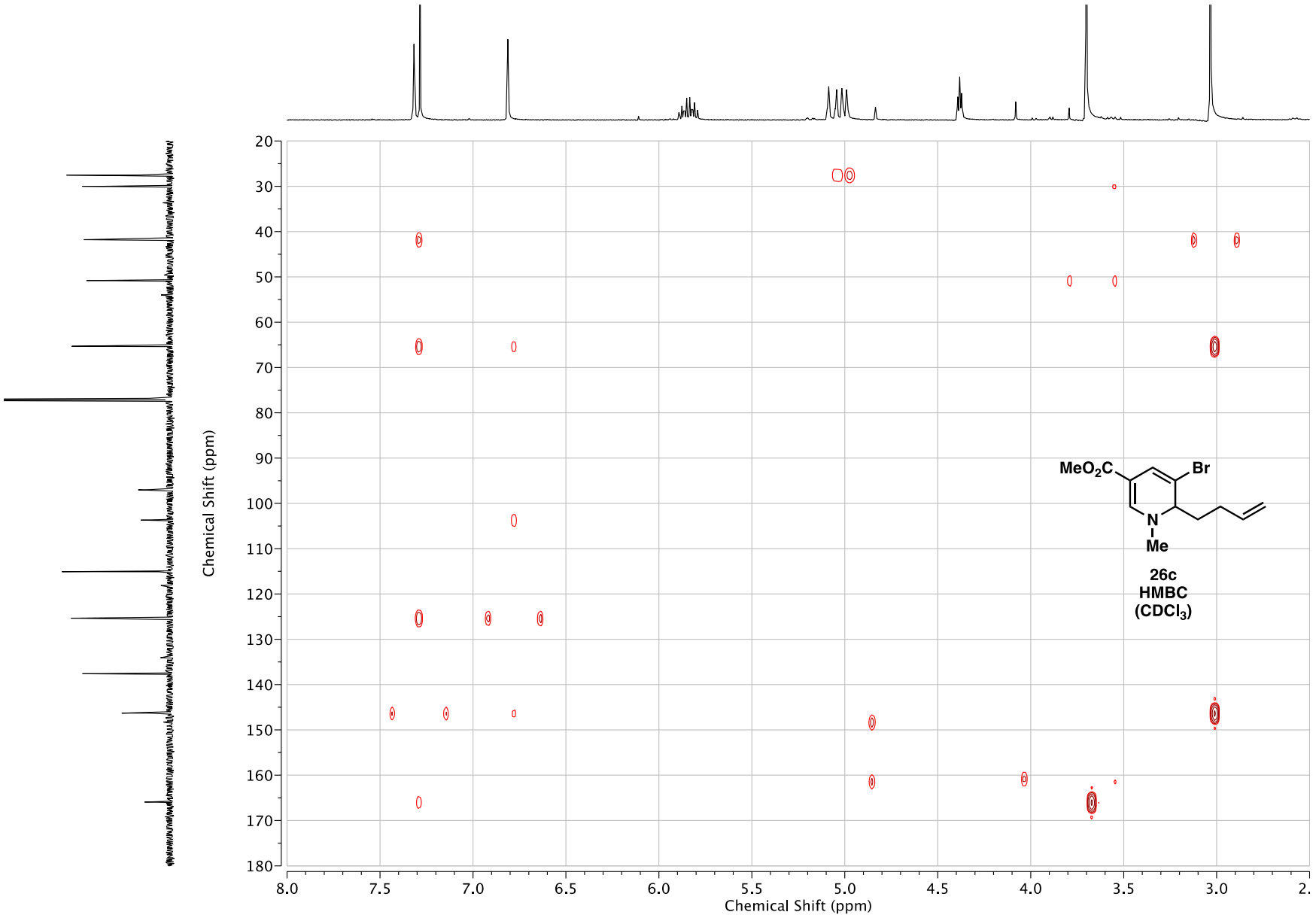

Chemical Shift (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)
MeO2C
Br
N
Me
26b
HSQC
(CDCl3)

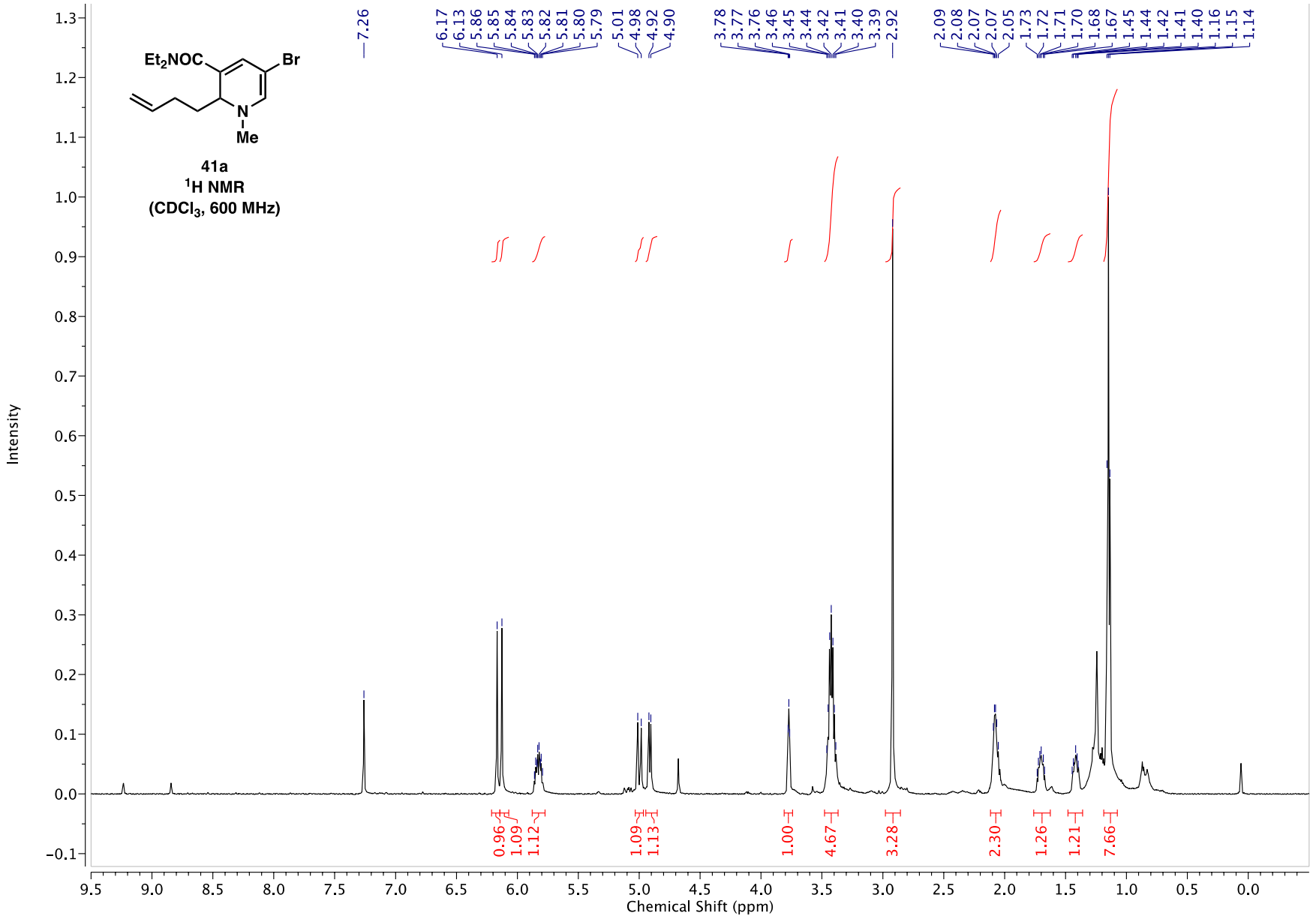

Chemical Shift (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)
MeO2C
Br
N
Me
26b
HMBC NMR
(CDCl3)

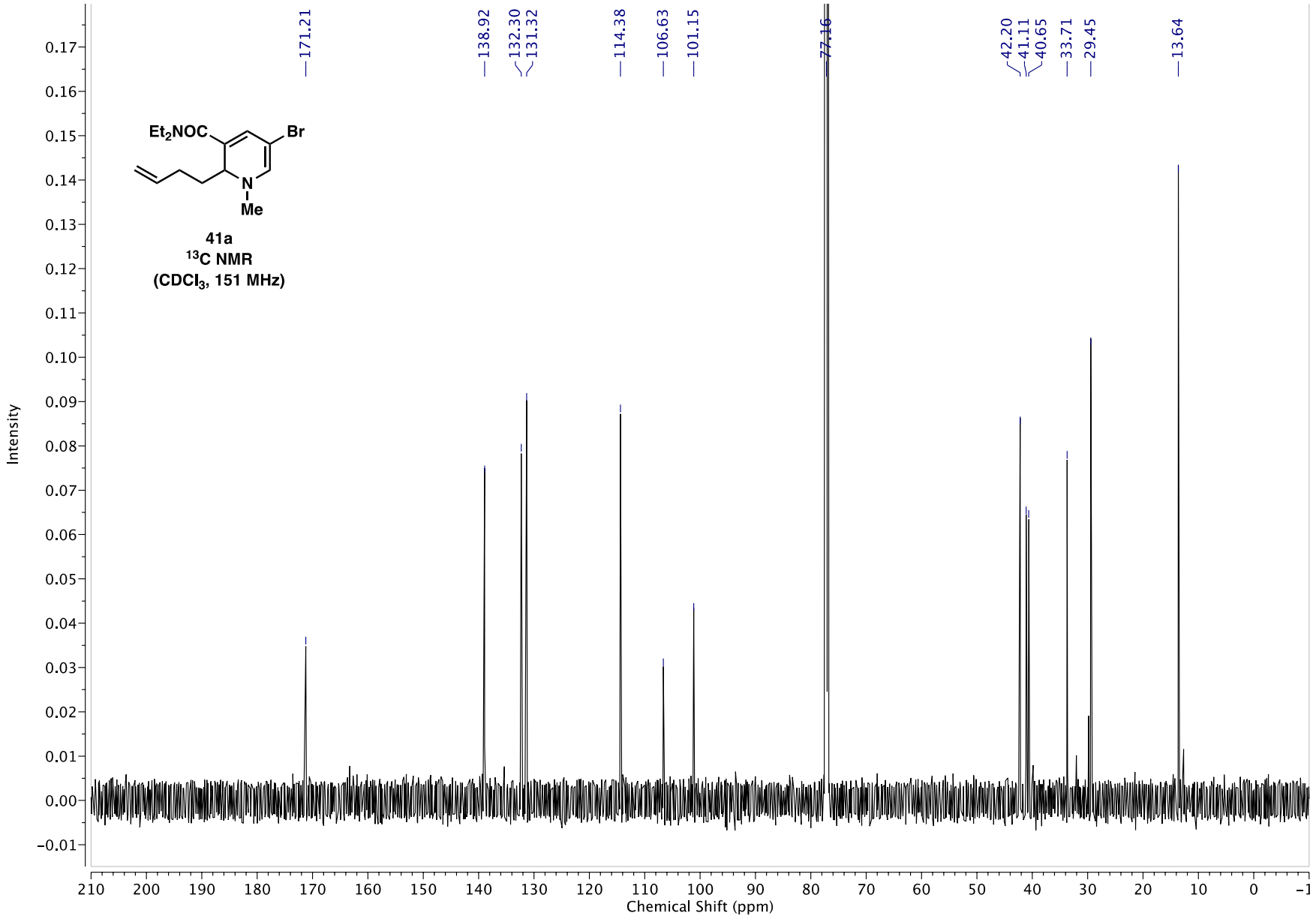

MeO2C
Br
N
Me
26c
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
7.29
7.26
6.79
5.87
5.85
5.84
5.84
5.83
5.81
5.80
5.79
5.78
5.77
5.07
5.07
5.06
5.06
5.03
5.02
5.02
5.01
4.99
4.99
4.97
4.96
4.37
4.36
4.35
3.68
3.01
2.29
2.27
2.26
2.24
2.23
2.14
2.13
2.11
2.10
2.08
1.91
1.88
1.87
1.86
1.84
1.83
1.79
1.78
1.77
1.75
1.74
1.73
1.72
0.85
0.87
1.00
0.95
1.04
0.90
3.01
2.97
0.98
1.03
0.98
1.11

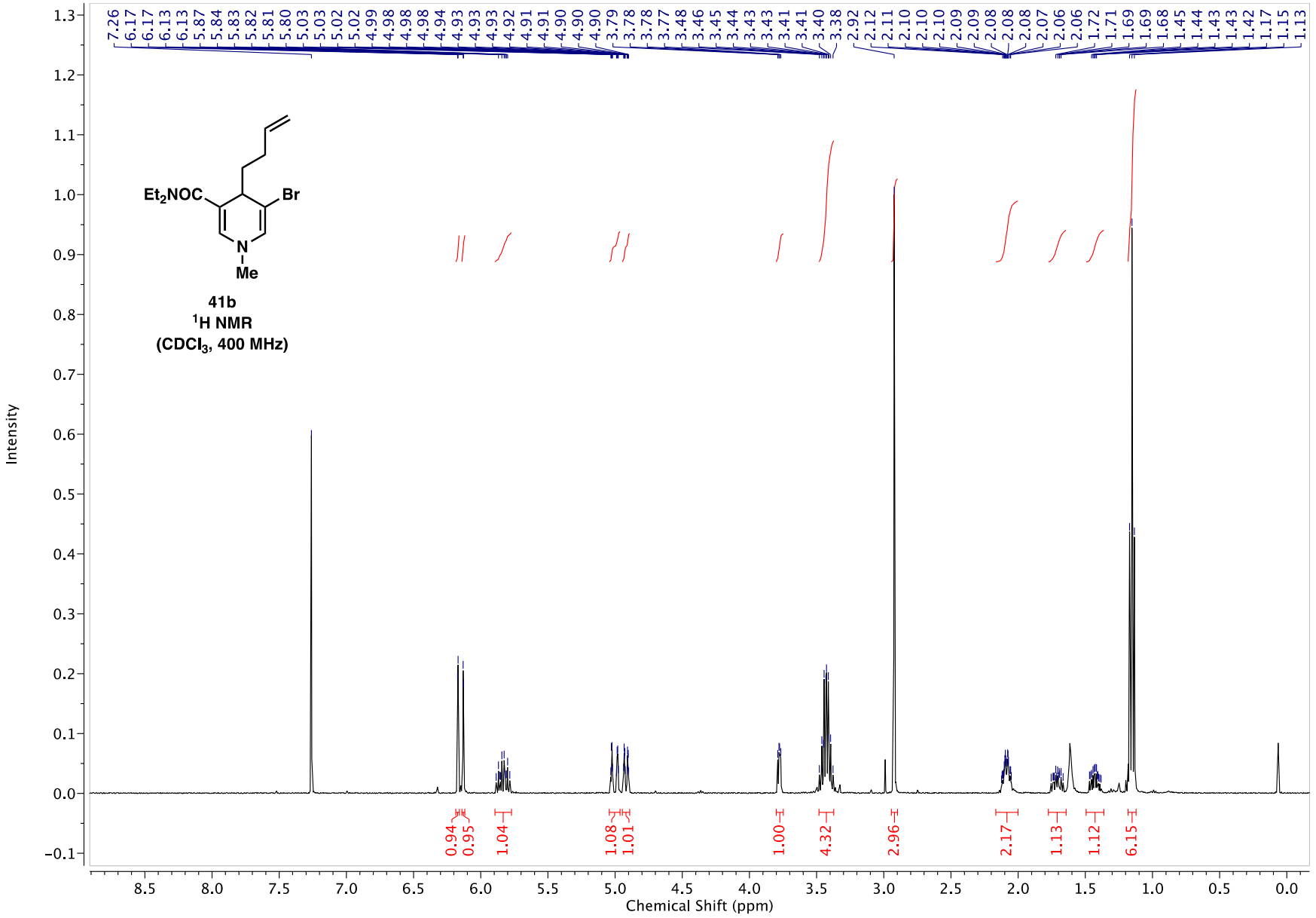

MeO2C
Br
N
Me
26c
13C NMR
(CDCl3, 151 MHz)
166.04
146.39
137.70
125.44
115.18
103.81
97.12
77.16
65.43
50.91
41.90
30.11
27.63
Intensity
Chemical Shift (ppm)

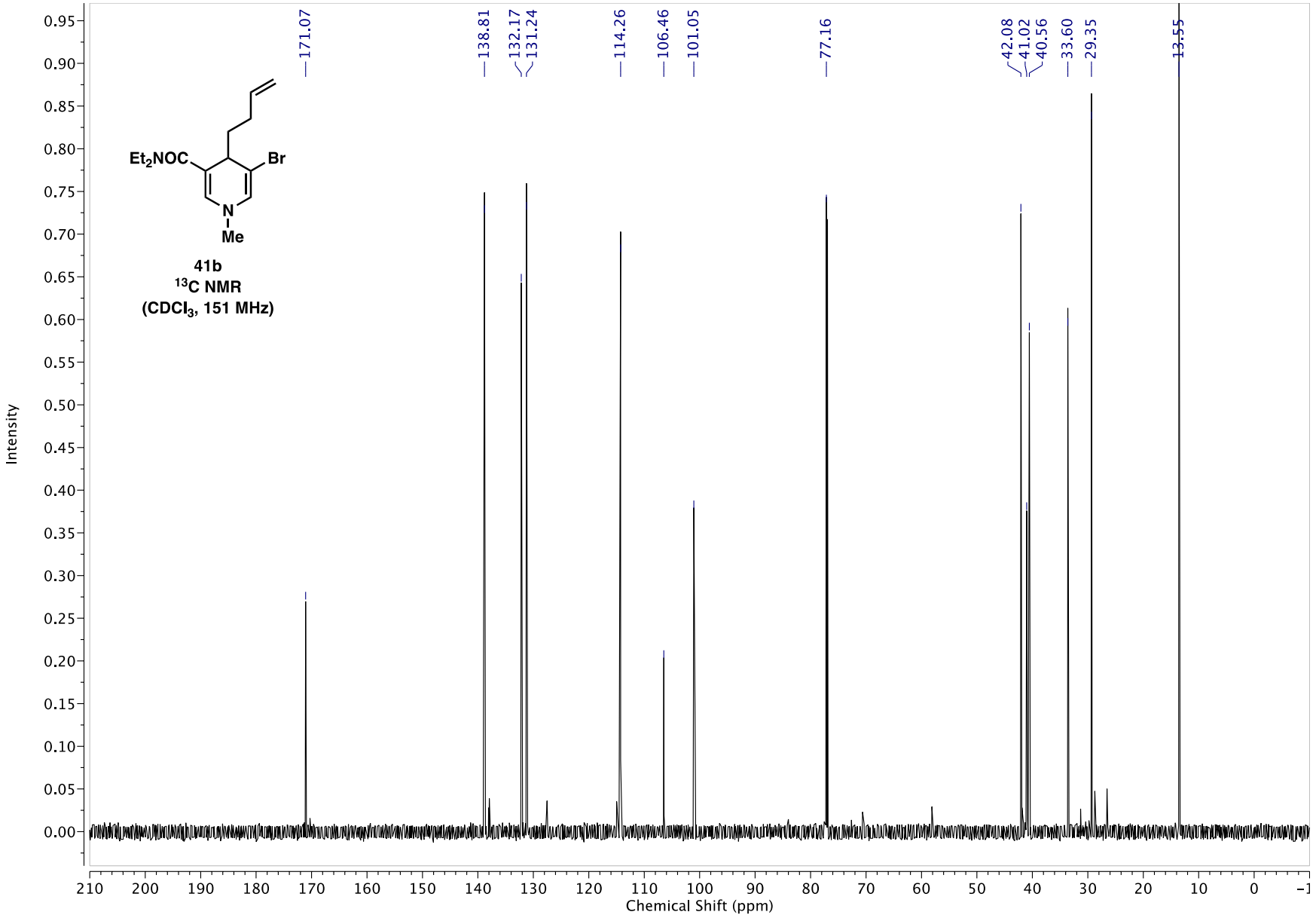

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
26c
HSQC
(CDCl3)

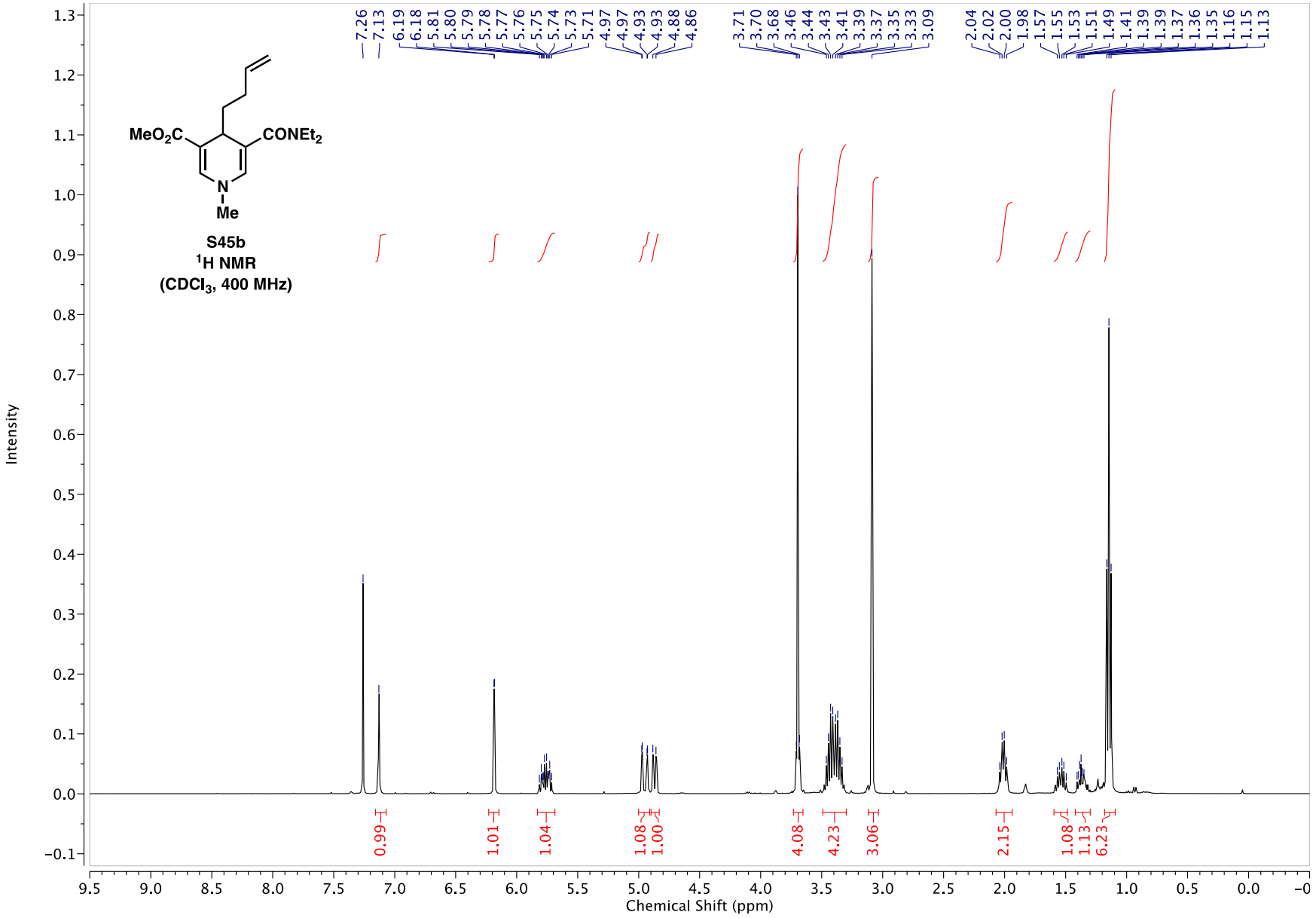

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
26c
HMBC
(CDCl3)

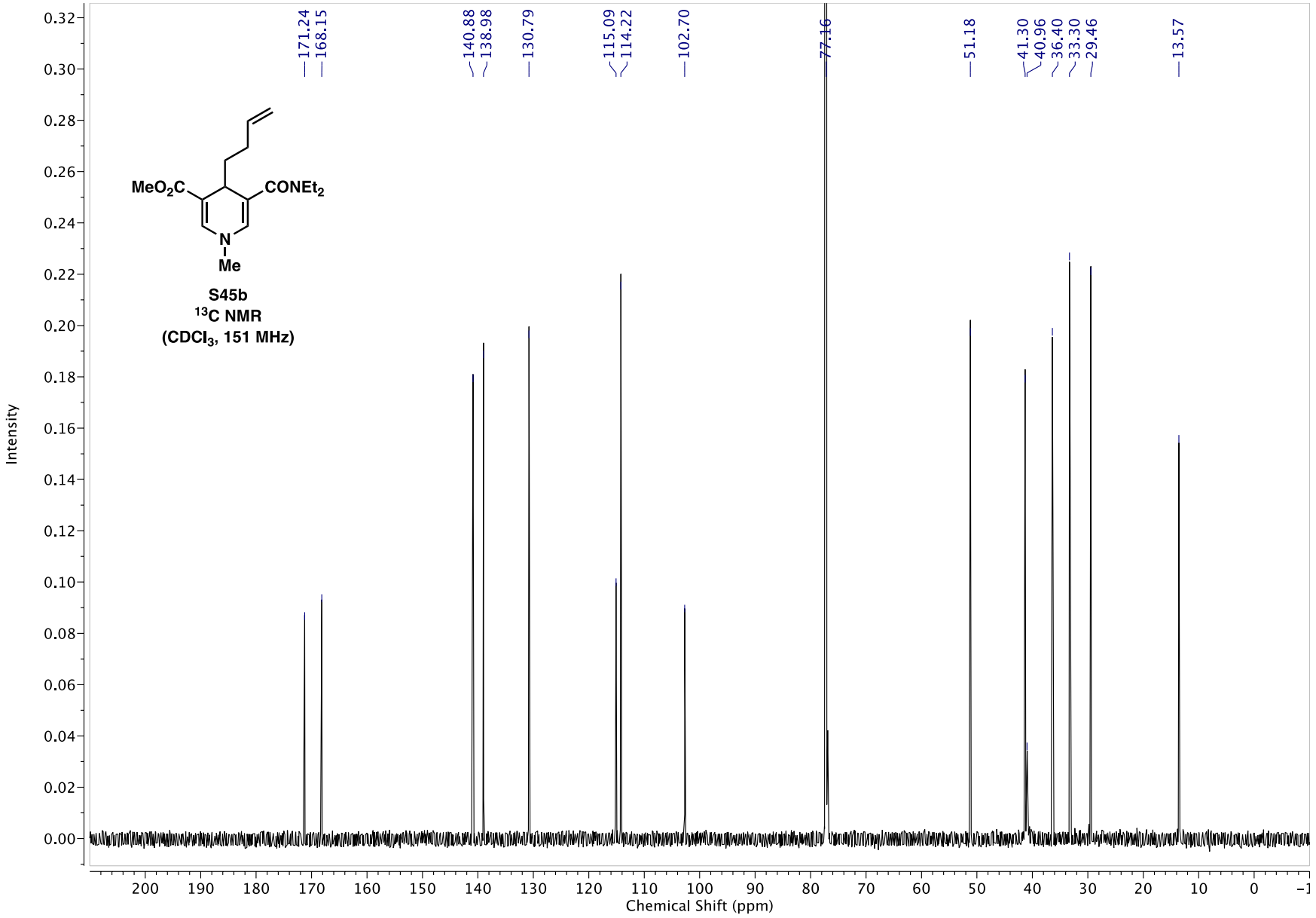

Et2NOC
Br
N
Me
41a
1H NMR
(CDCl3, 600 MHz)
Intensity
Chemical Shift (ppm)
7.26
6.17
6.13
5.86
5.85
5.84
5.83
5.82
5.81
5.80
5.79
5.01
4.98
4.92
4.90
3.78
3.77
3.76
3.46
3.45
3.44
3.42
3.41
3.40
3.39
2.92
2.09
2.08
2.07
2.07
2.05
1.73
1.72
1.71
1.70
1.68
1.67
1.45
1.44
1.42
1.41
1.40
1.16
1.15
1.14
0.96
1.09
1.12
1.09
1.13
1.00
4.67
3.28
2.30
1.26
1.21
7.66

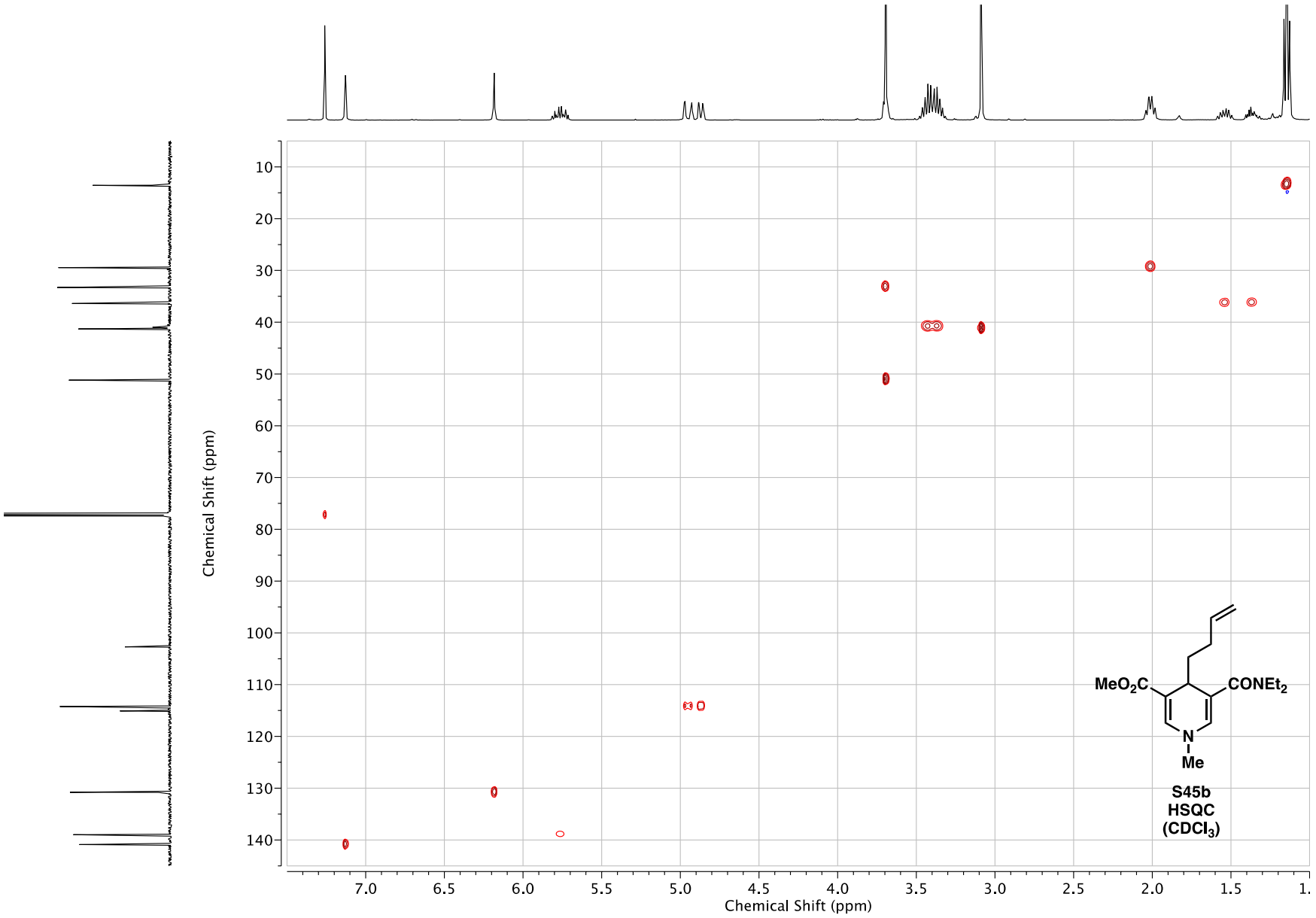

171.21
138.92
132.30
131.32
114.38
106.63
101.15
77.16
42.20
41.11
40.65
33.71
29.45
13.64
Et2NOC
Br
N
Me
41a
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

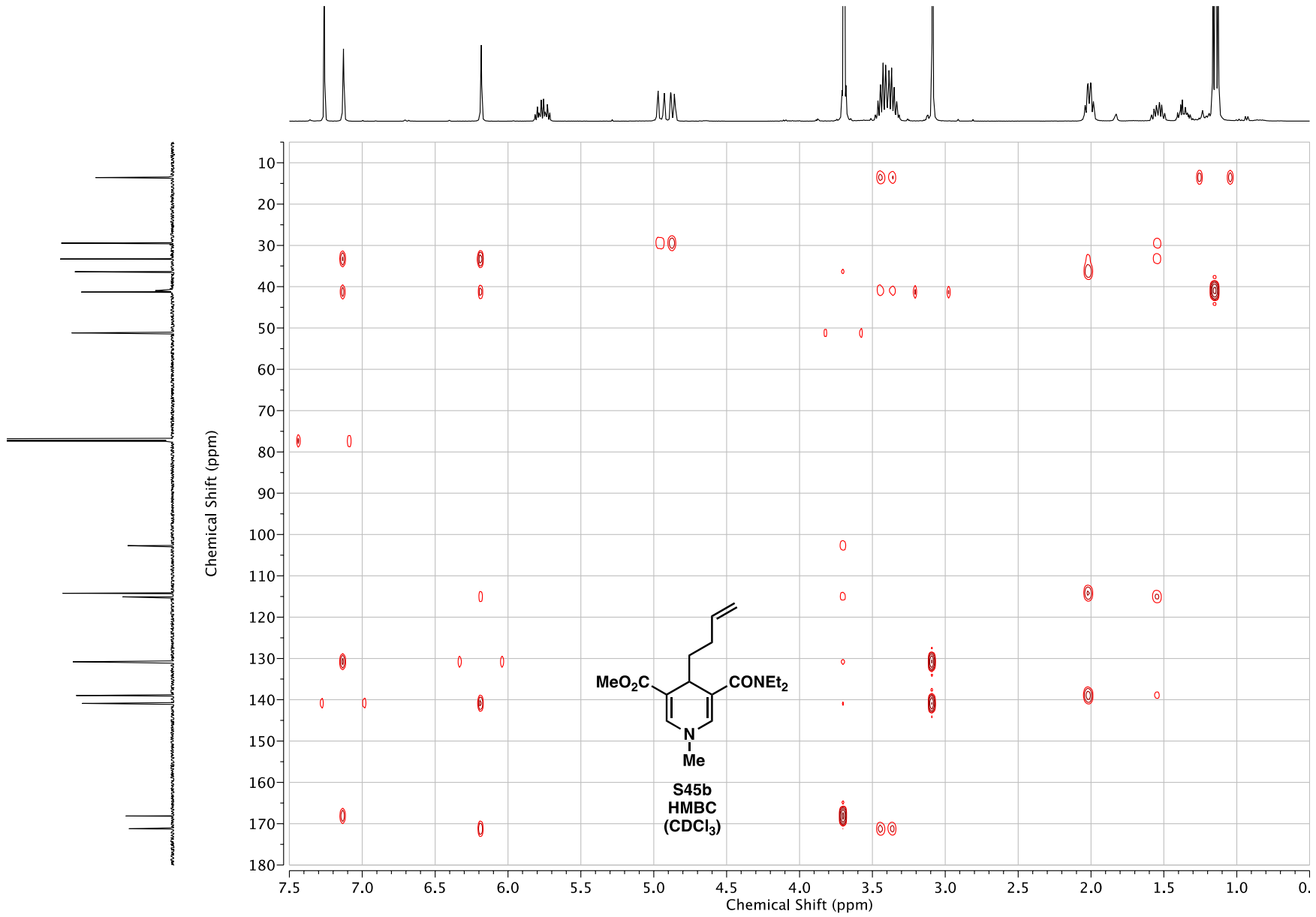

41b
1H NMR
(CDCl3, 400 MHz)
Et2NOC
Br
N
Me
Intensity
Chemical Shift (ppm)

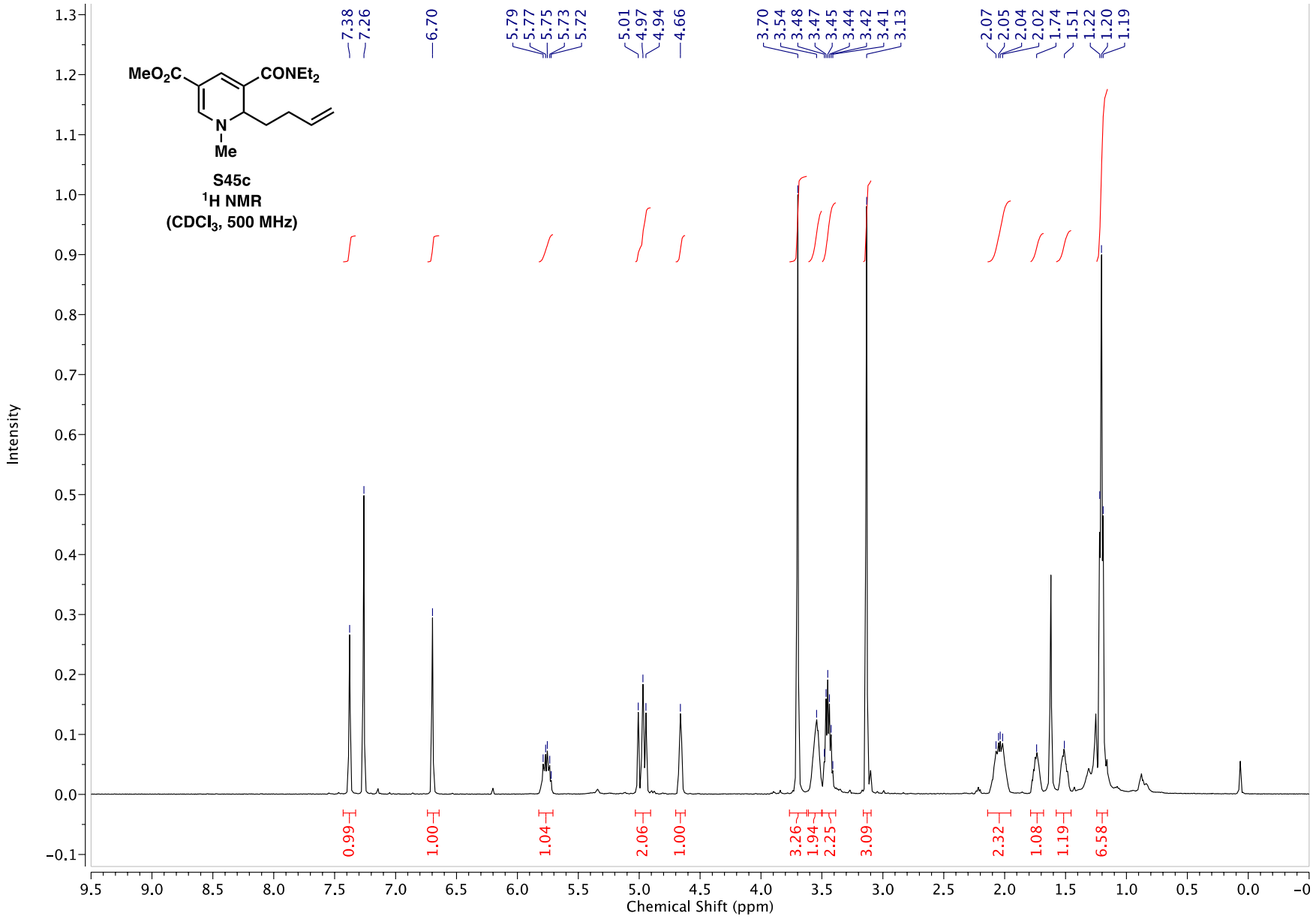

171.07
138.81
132.17
131.24
114.26
106.46
101.05
77.16
42.08
41.02
40.56
33.60
29.35
13.55
Et2NOC
Br
N
Me
41b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

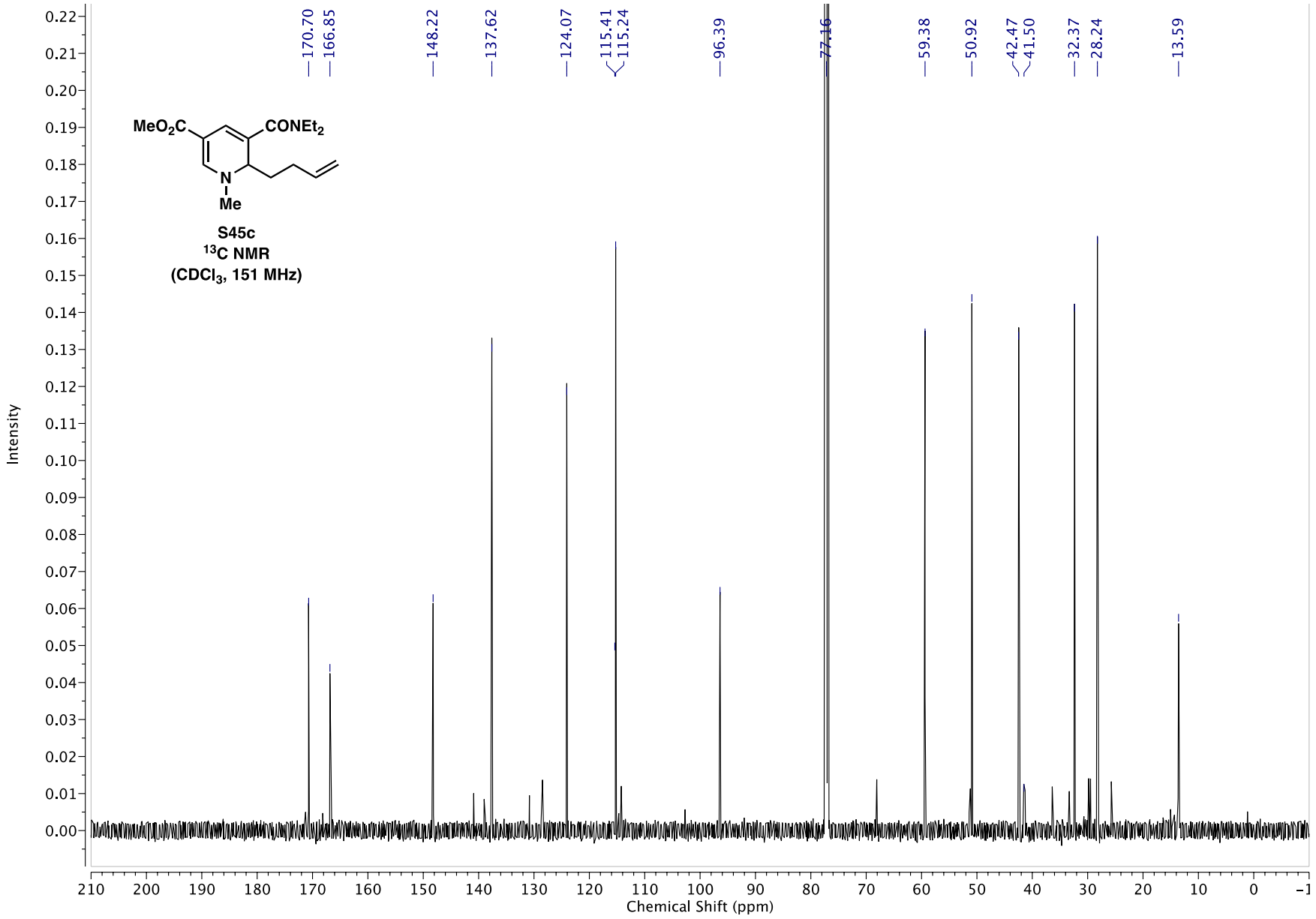

MeO2C
CONEt2
N
Me
S45b
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
7.26
7.13
6.19
6.18
5.81
5.80
5.79
5.78
5.77
5.76
5.75
5.74
5.73
5.71
4.97
4.97
4.93
4.93
4.88
4.86
3.71
3.70
3.68
3.46
3.44
3.43
3.41
3.39
3.37
3.35
3.33
3.09
2.04
2.02
2.00
1.98
1.57
1.55
1.53
1.51
1.49
1.41
1.39
1.39
1.37
1.36
1.35
1.16
1.15
1.13
0.99
1.01
1.04
1.08
1.00
4.08
4.23
3.06
2.15
1.08
1.13
6.23

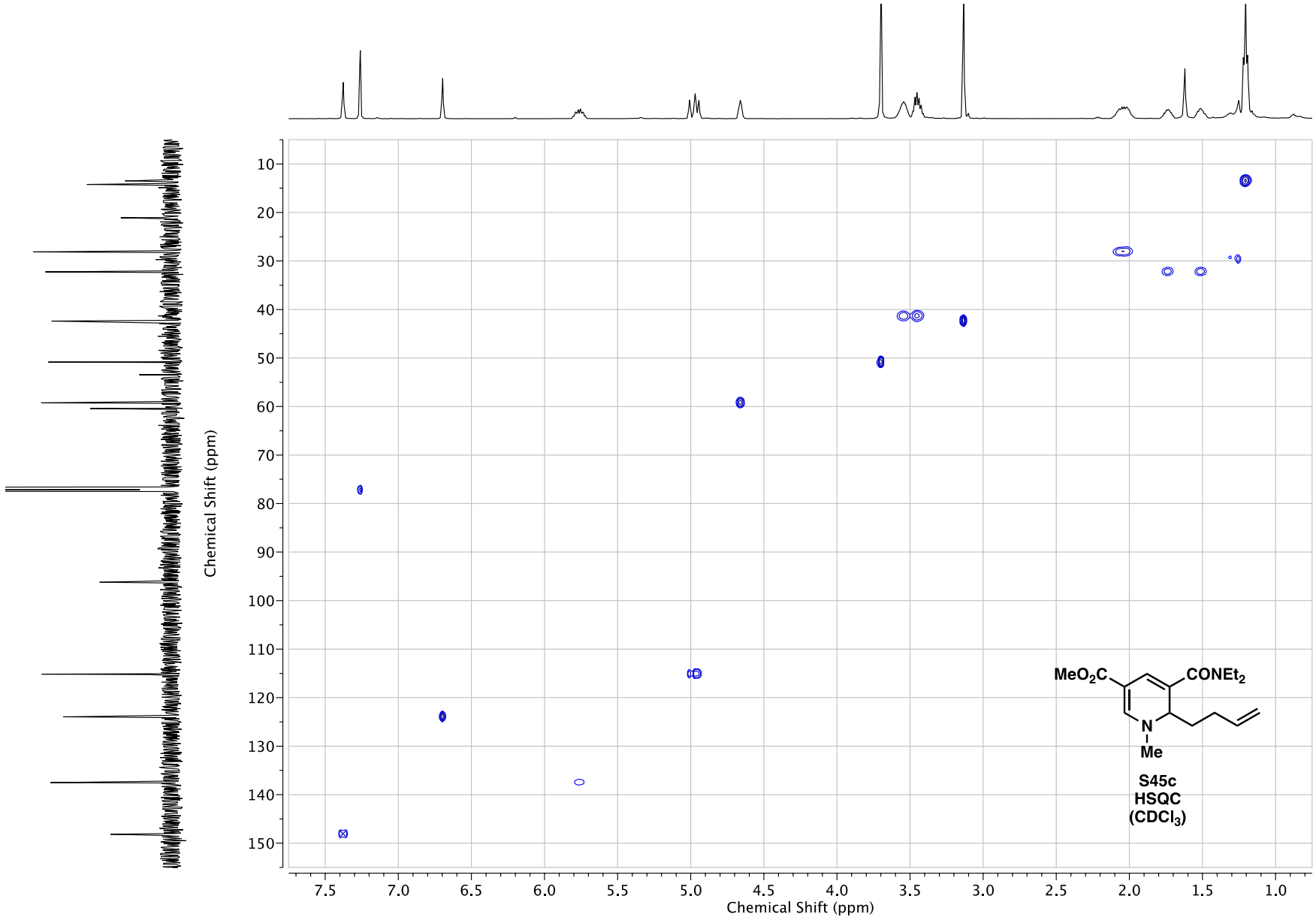

171.24
168.15
140.88
138.98
130.79
115.09
114.22
102.70
77.16
51.18
41.30
40.96
36.40
33.30
29.46
13.57
MeO2C
CONEt2
N
Me
S45b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

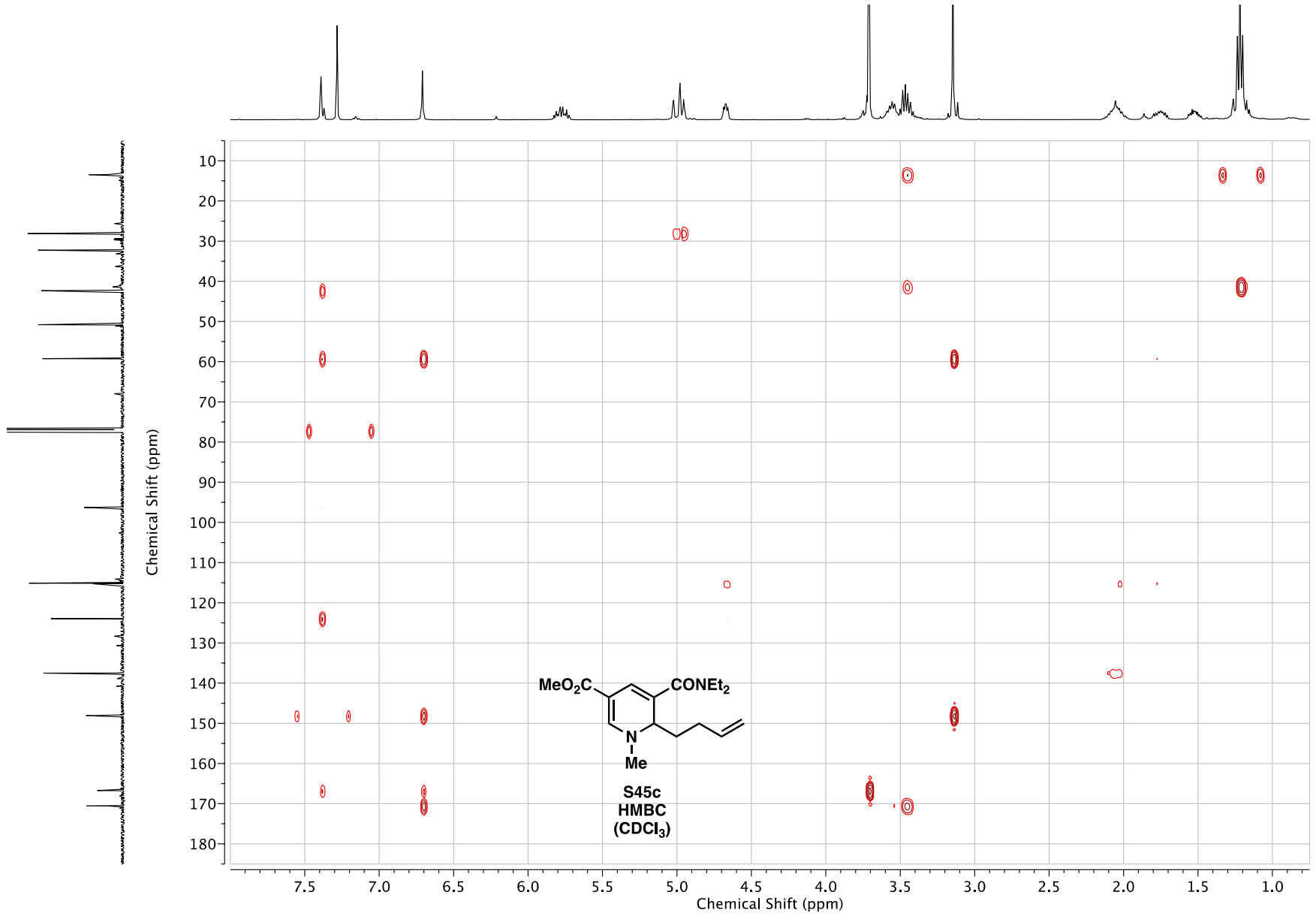

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
CONEt2
N
Me
S45b
HSQC
(CDCl3)

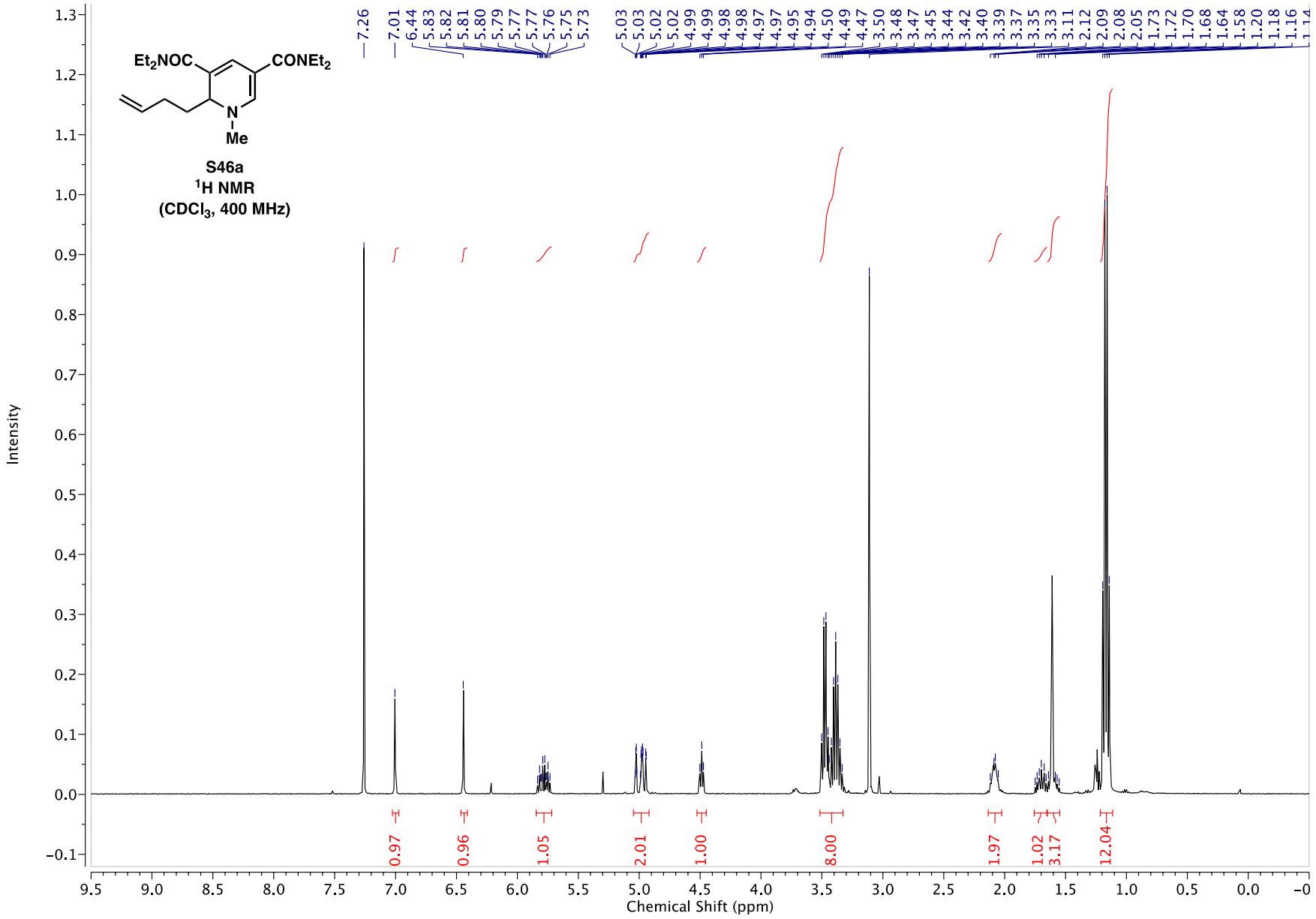

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
CONEt2
N
Me
S45b
HMBC
(CDCl3)

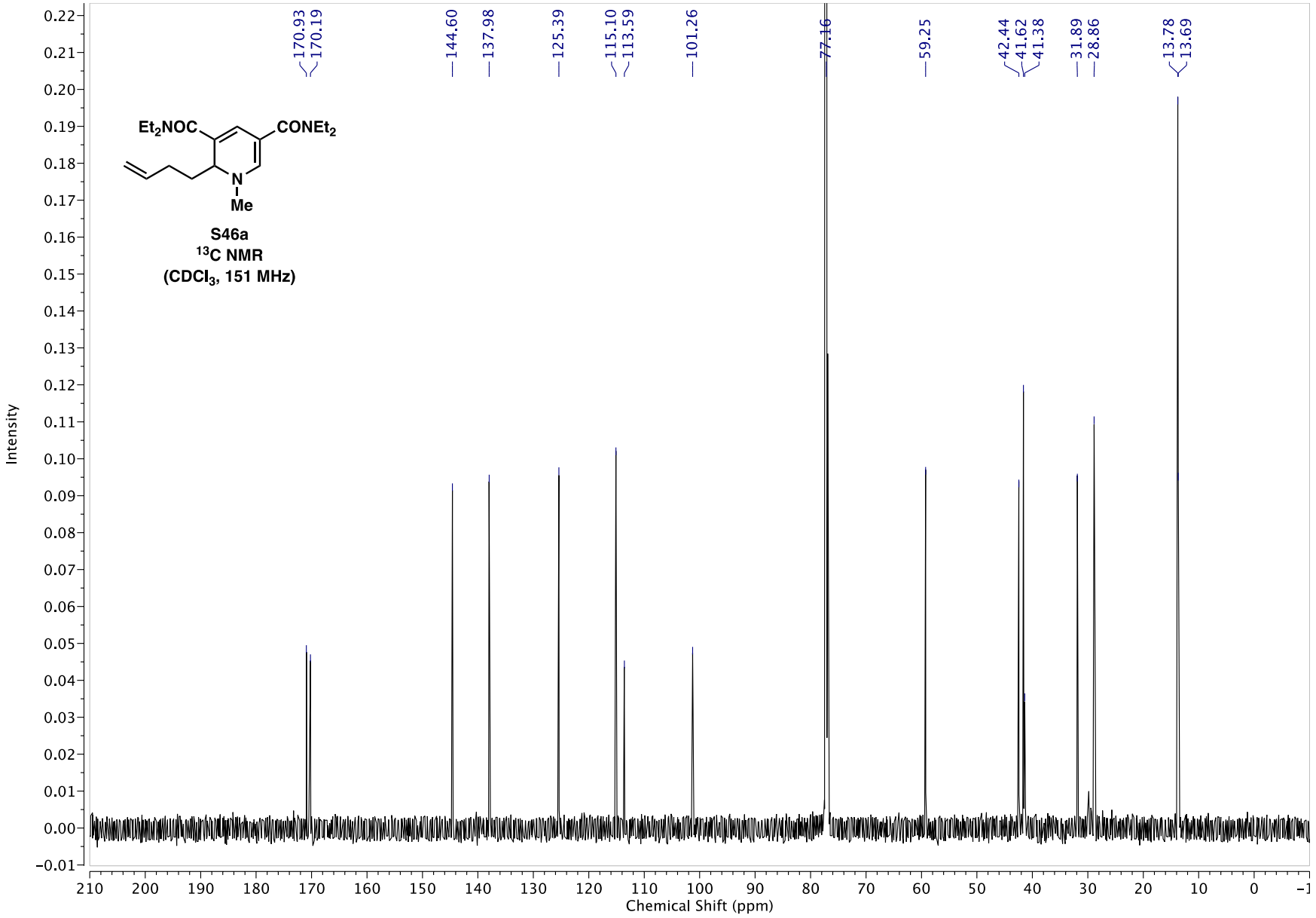

MeO2C
CONEt2
N
Me
S45c
1H NMR
(CDCl3, 500 MHz)
7.38
7.26
6.70
5.79
5.77
5.75
5.73
5.72
5.01
4.97
4.94
4.66
3.70
3.54
3.48
3.47
3.45
3.44
3.42
3.41
3.13
2.07
2.05
2.04
2.02
1.74
1.51
1.22
1.20
1.19
0.99
1.00
1.04
2.06
1.00
3.26
1.94
2.25
3.09
2.32
1.08
1.19
6.58
Intensity
Chemical Shift (ppm)

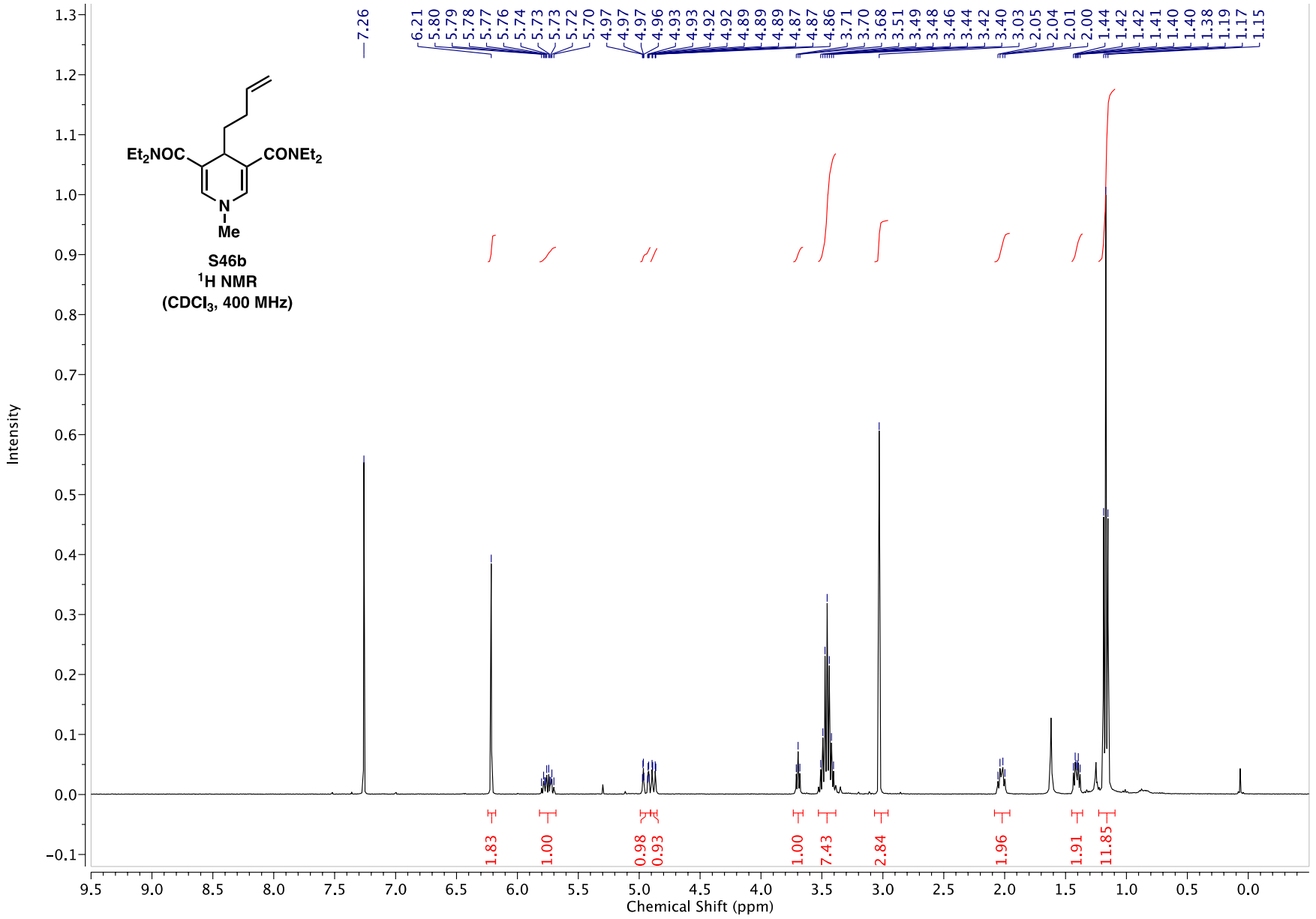

170.70
166.85
148.22
137.62
124.07
115.41
115.24
96.39
77.16
59.38
50.92
42.47
41.50
32.37
28.24
13.59
MeO2C
CONEt2
N
Me
S45c
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

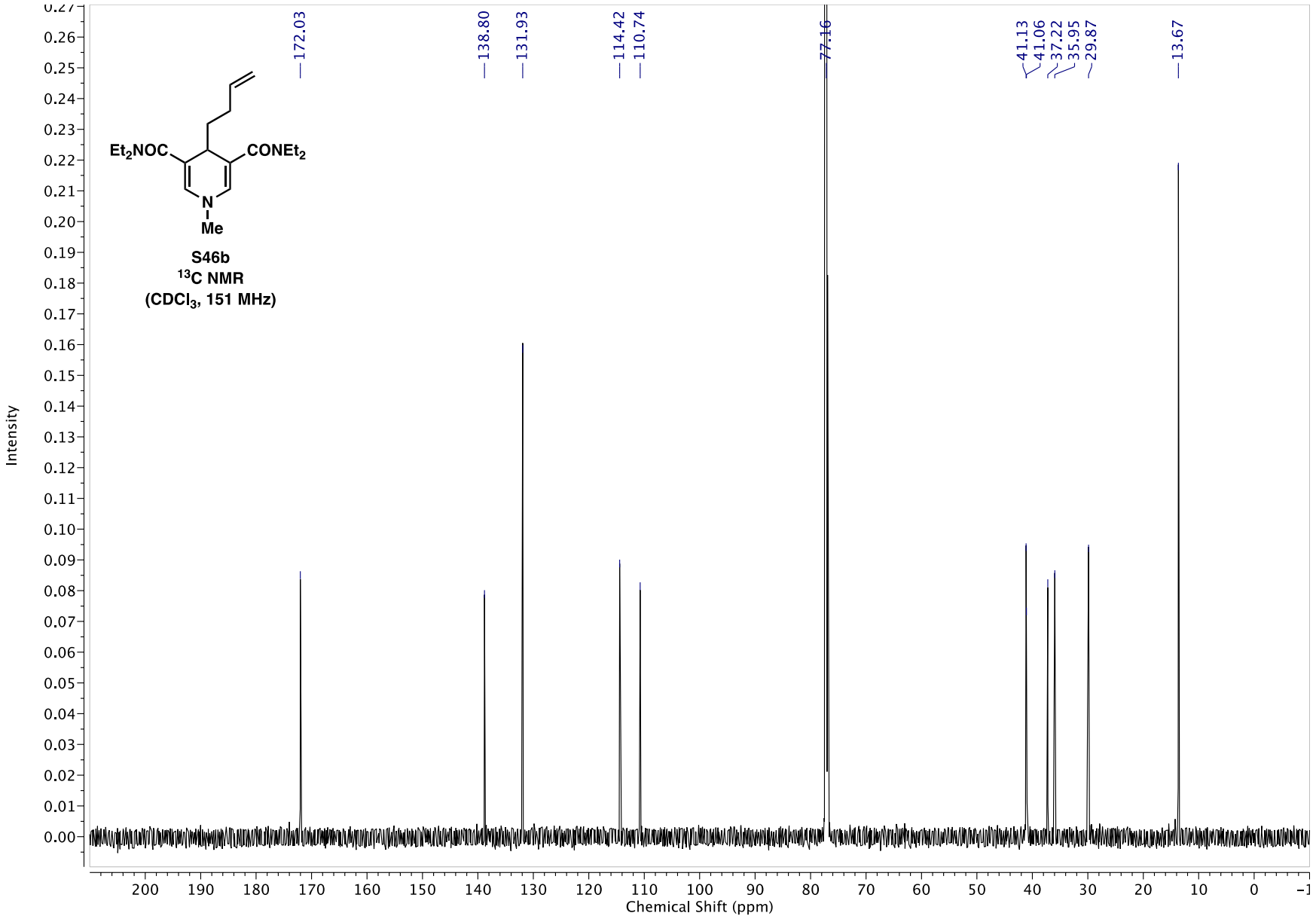

Chemical Shift (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)
MeO2C
CONEt2
N
Me
S45c
HSQC
(CDCl3)

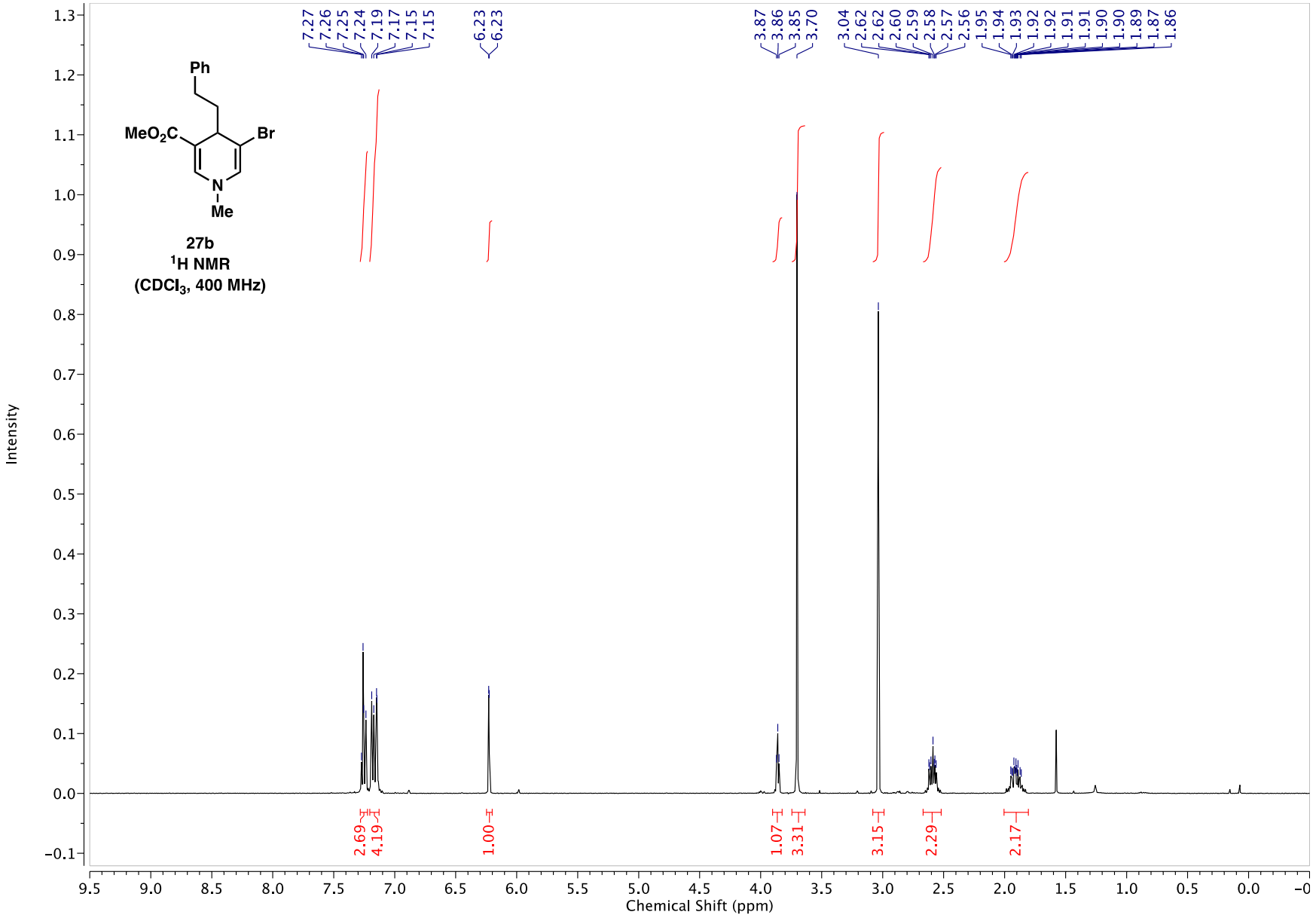

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
CONEt2
N
Me
S45c
HMBC
(CDCl3)

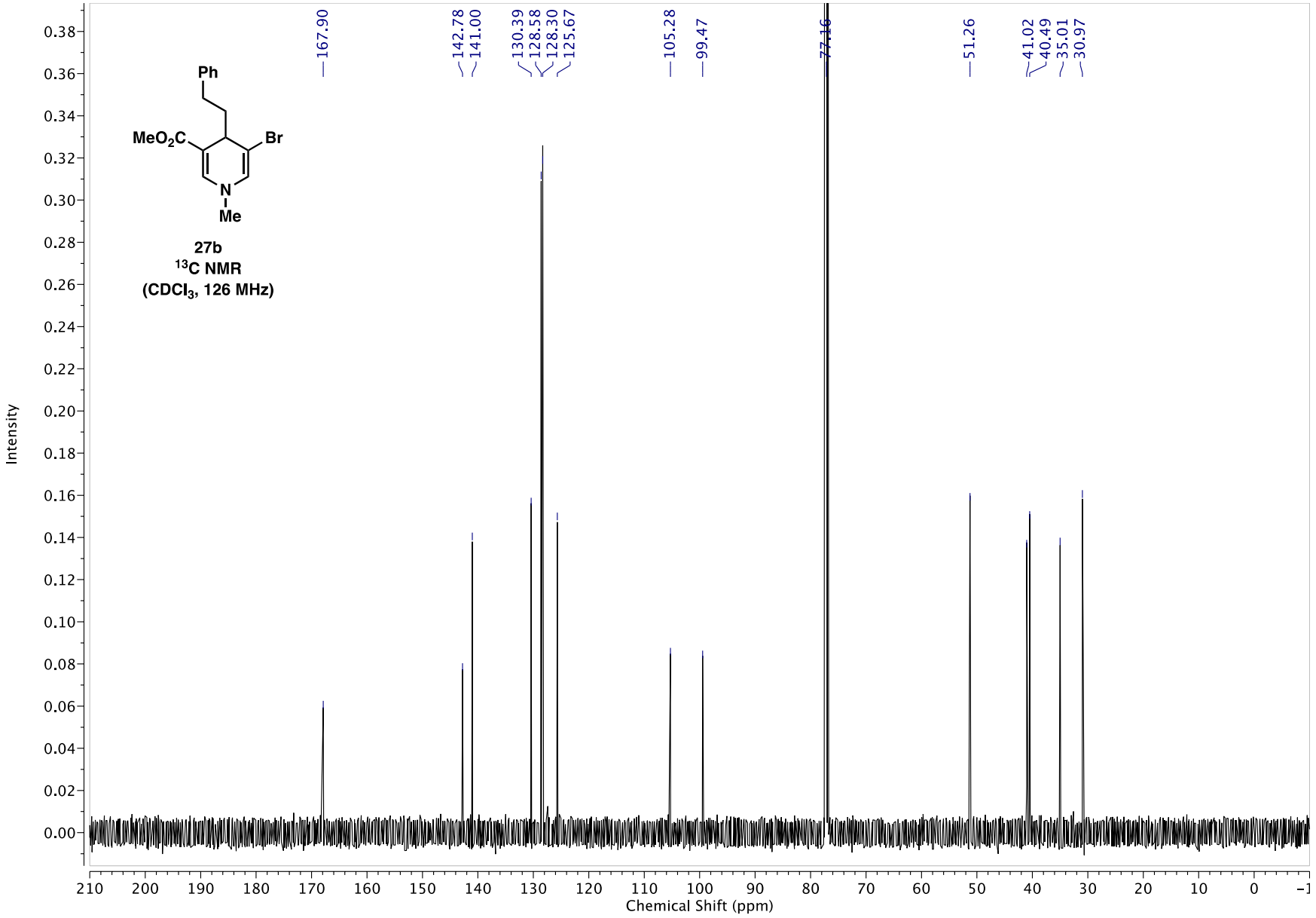

Et2NOC
CONEt2
N
Me
S46a
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
0.97
0.96
1.05
2.01
1.00
8.00
1.97
1.02
3.17
12.04

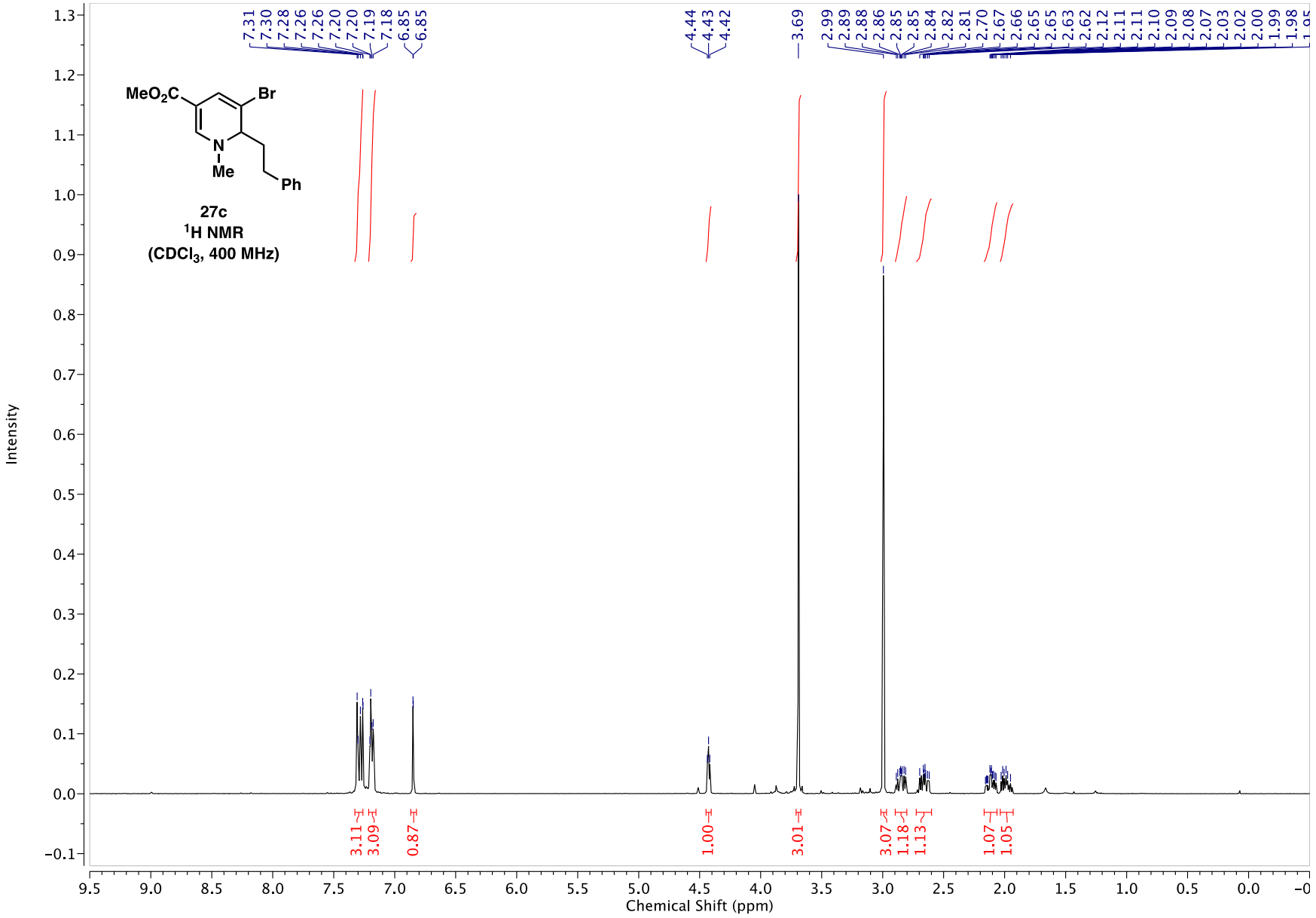

170.93
170.19
144.60
137.98
125.39
115.10
113.59
101.26
77.16
59.25
42.44
41.62
41.38
31.89
28.86
13.78
13.69
Et2NOC
CONEt2
N
Me
S46a
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

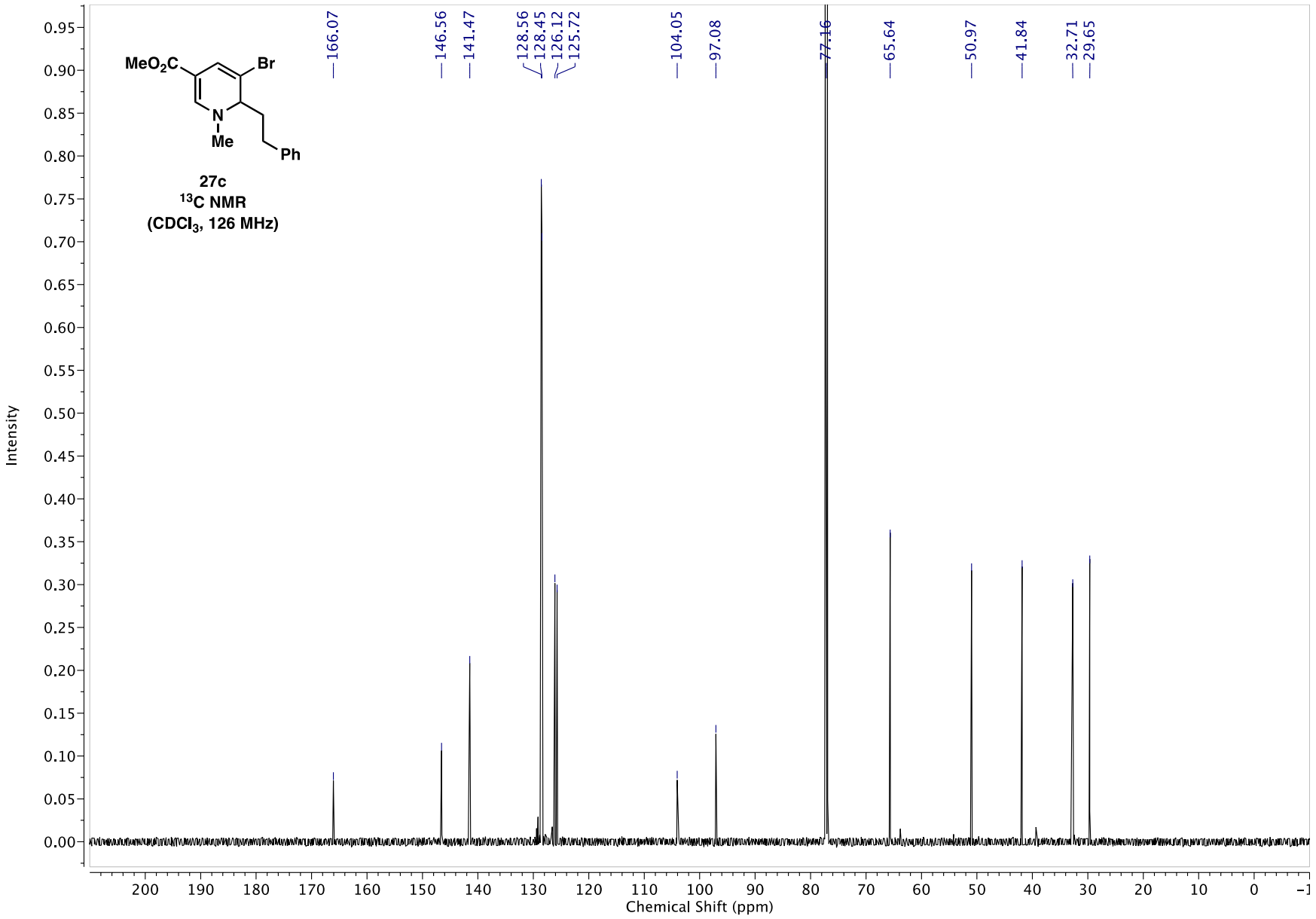

Et2NOC
CONEt2
N
Me
S46b
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
7.26
6.21
5.80
5.79
5.78
5.77
5.76
5.74
5.73
5.73
5.72
5.70
4.97
4.97
4.96
4.93
4.93
4.92
4.92
4.89
4.89
4.89
4.87
4.87
4.86
3.71
3.70
3.68
3.51
3.49
3.48
3.46
3.44
3.42
3.40
3.03
2.05
2.04
2.01
2.00
1.44
1.42
1.42
1.41
1.40
1.40
1.38
1.19
1.17
1.15
1.83
1.00
0.98
0.93
1.00
7.43
2.84
1.96
1.91
11.85

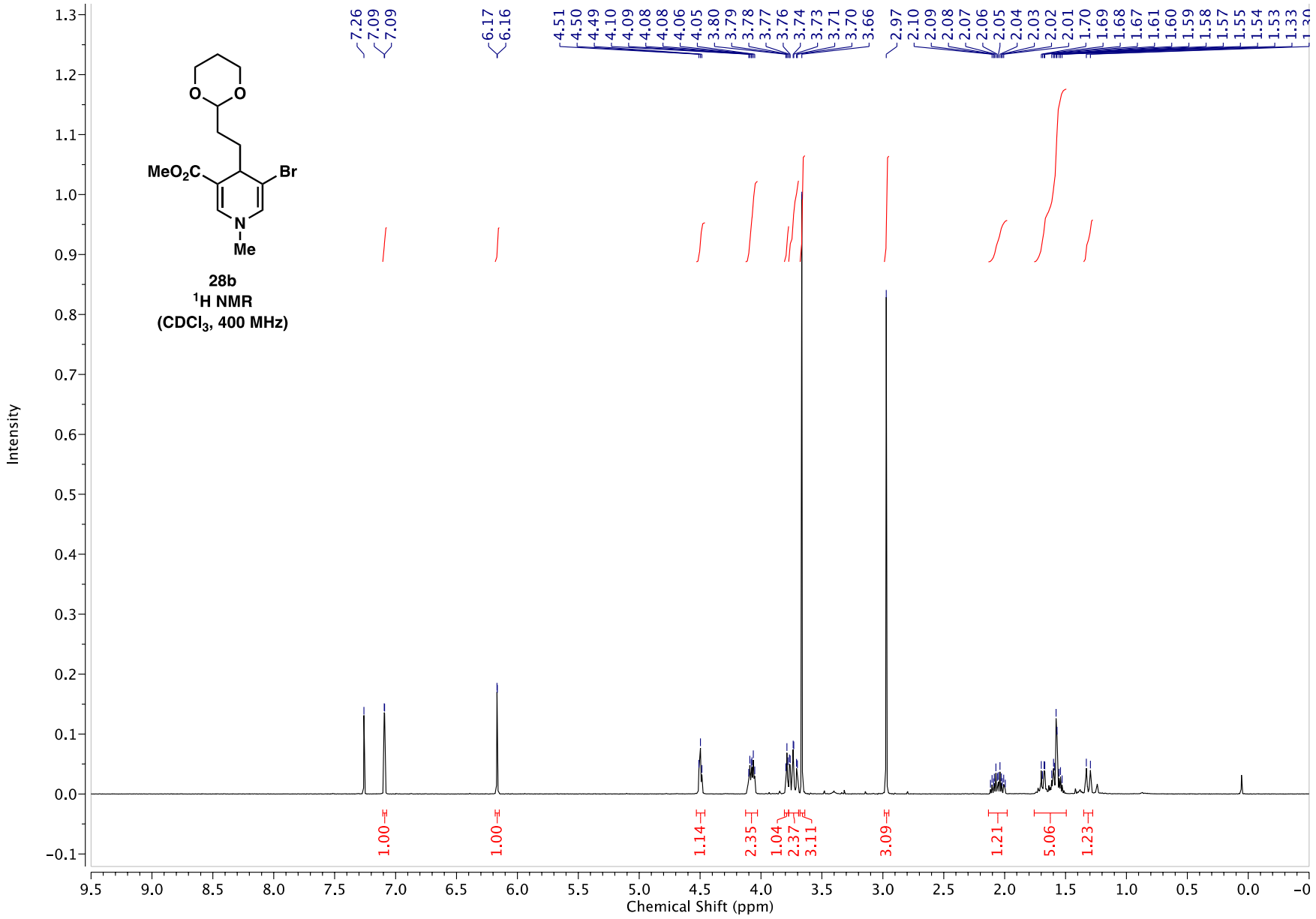

172.03
138.80
131.93
114.42
110.74
77.16
41.13
41.06
37.22
35.95
29.87
13.67
Et2NOC
CONEt2
N
Me
S46b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

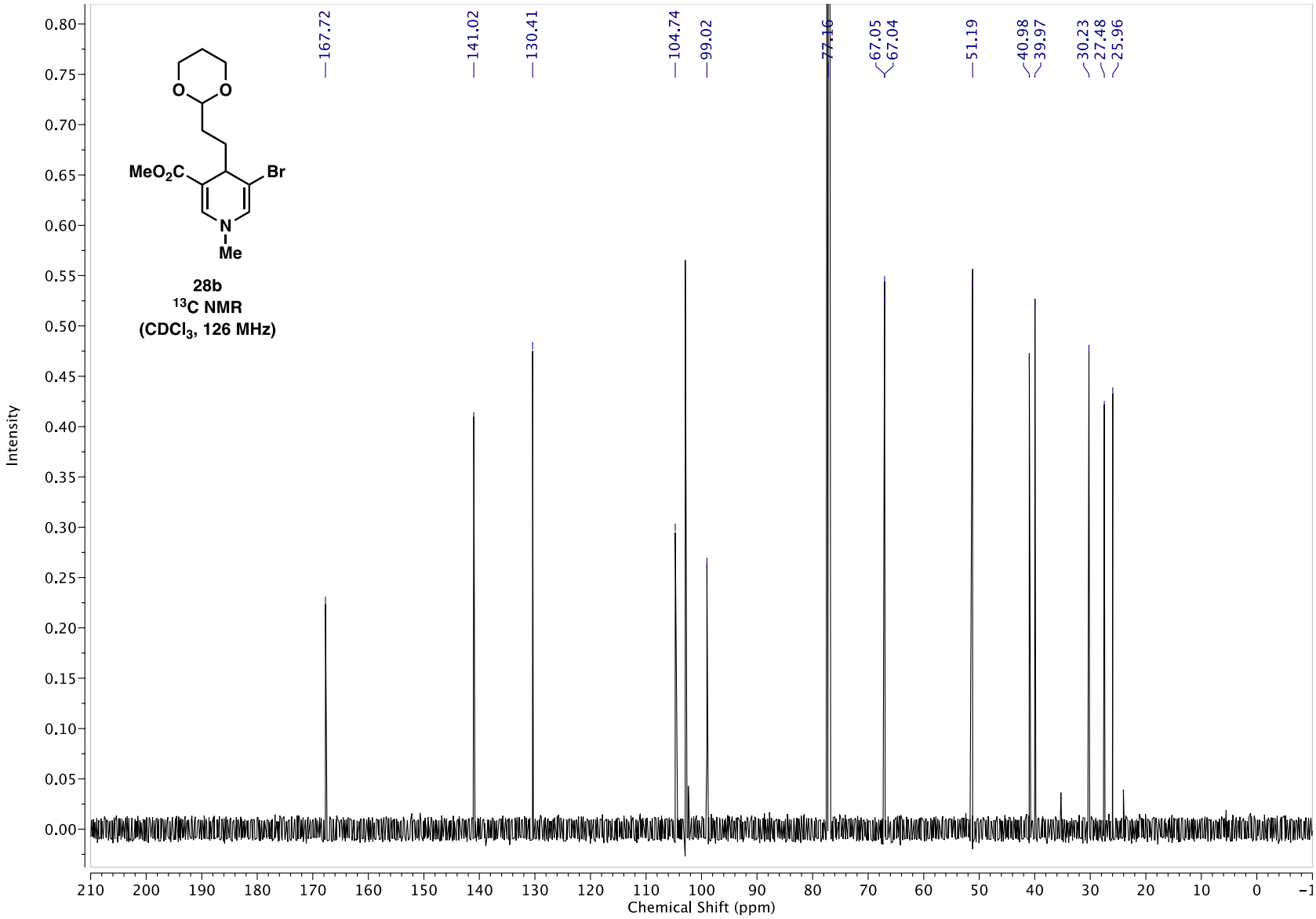

Ph
MeO2C
Br
N
Me
27b
1H NMR
(CDCl3, 400 MHz)
7.27
7.26
7.25
7.24
7.19
7.17
7.15
7.15
6.23
6.23
3.87
3.86
3.85
3.70
3.04
2.62
2.62
2.60
2.59
2.58
2.57
2.56
1.95
1.94
1.93
1.92
1.92
1.91
1.91
1.90
1.90
1.89
1.87
1.86
2.69
4.19
1.00
1.07
3.31
3.15
2.29
2.17
Intensity
Chemical Shift (ppm)

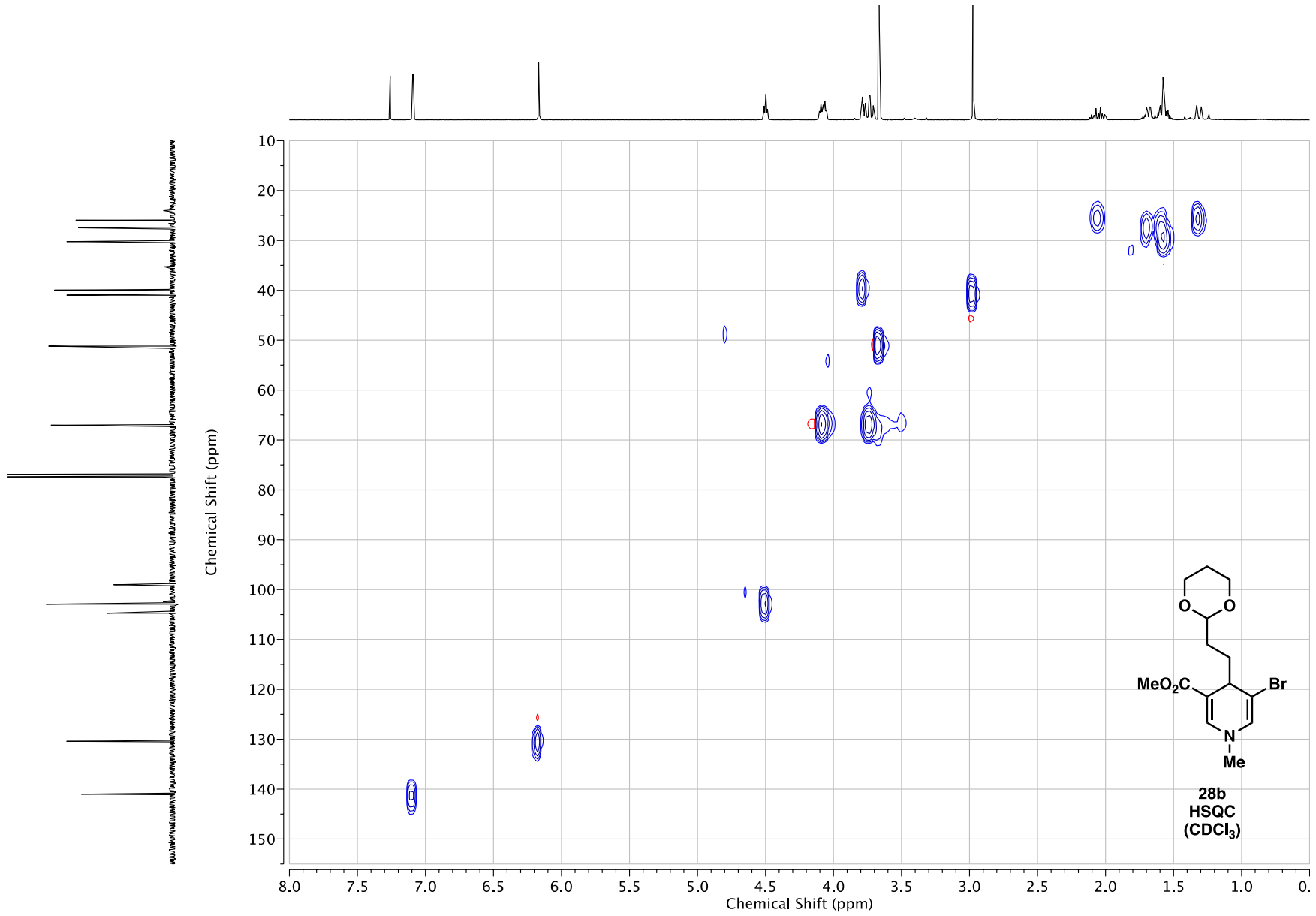

167.90
142.78
141.00
130.39
128.58
128.30
125.67
105.28
99.47
77.16
51.26
41.02
40.49
35.01
30.97
Ph
MeO2C
Br
N
Me
27b
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

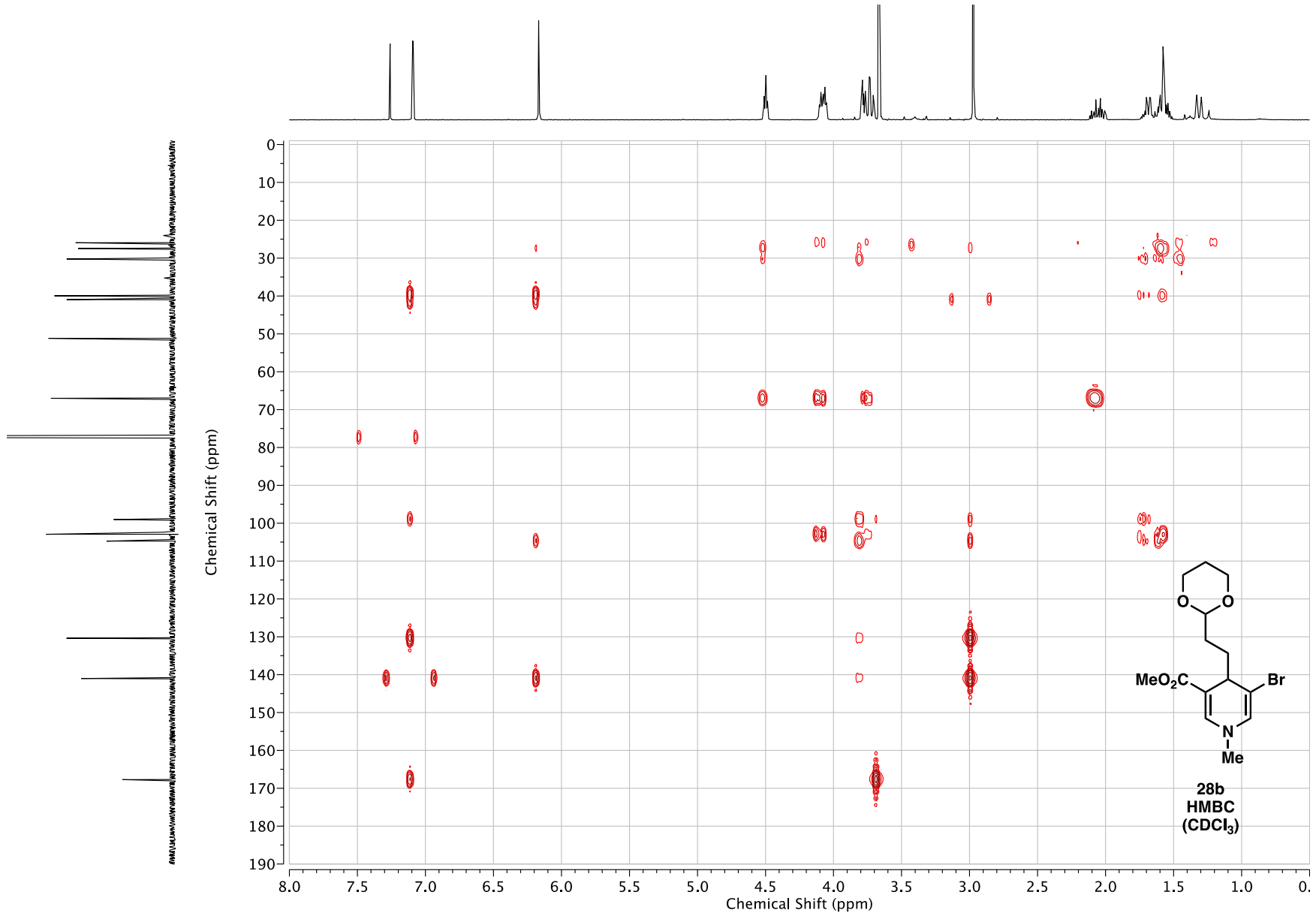

MeO2C
Br
N
Me
Ph
27c
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)

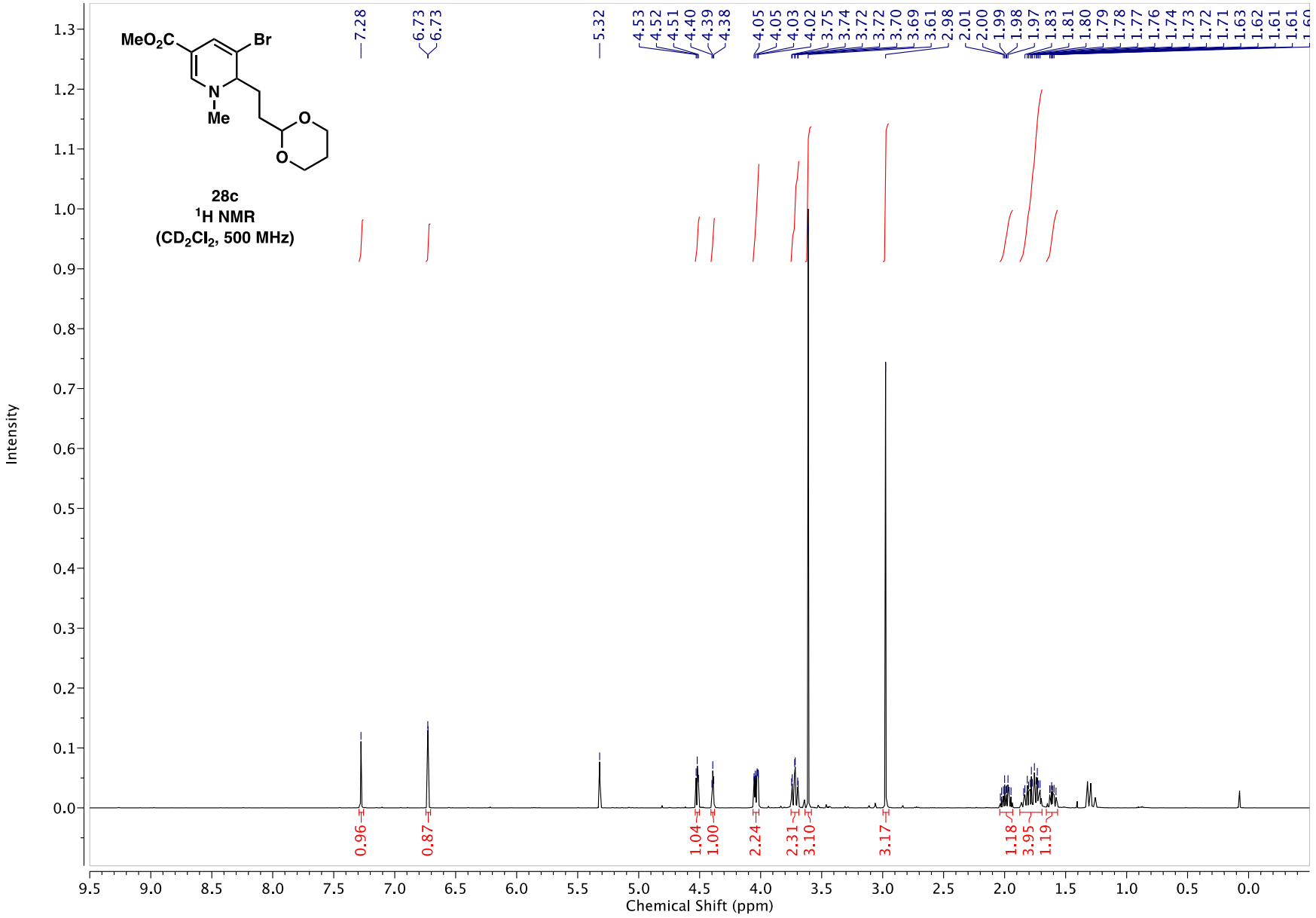

MeO2C
Br
N
Me
Ph
27c
13C NMR
(CDCl3, 126 MHz)
166.07
146.56
141.47
128.56
128.45
126.12
125.72
104.05
97.08
77.16
65.64
50.97
41.84
32.71
29.65
Intensity
Chemical Shift (ppm)

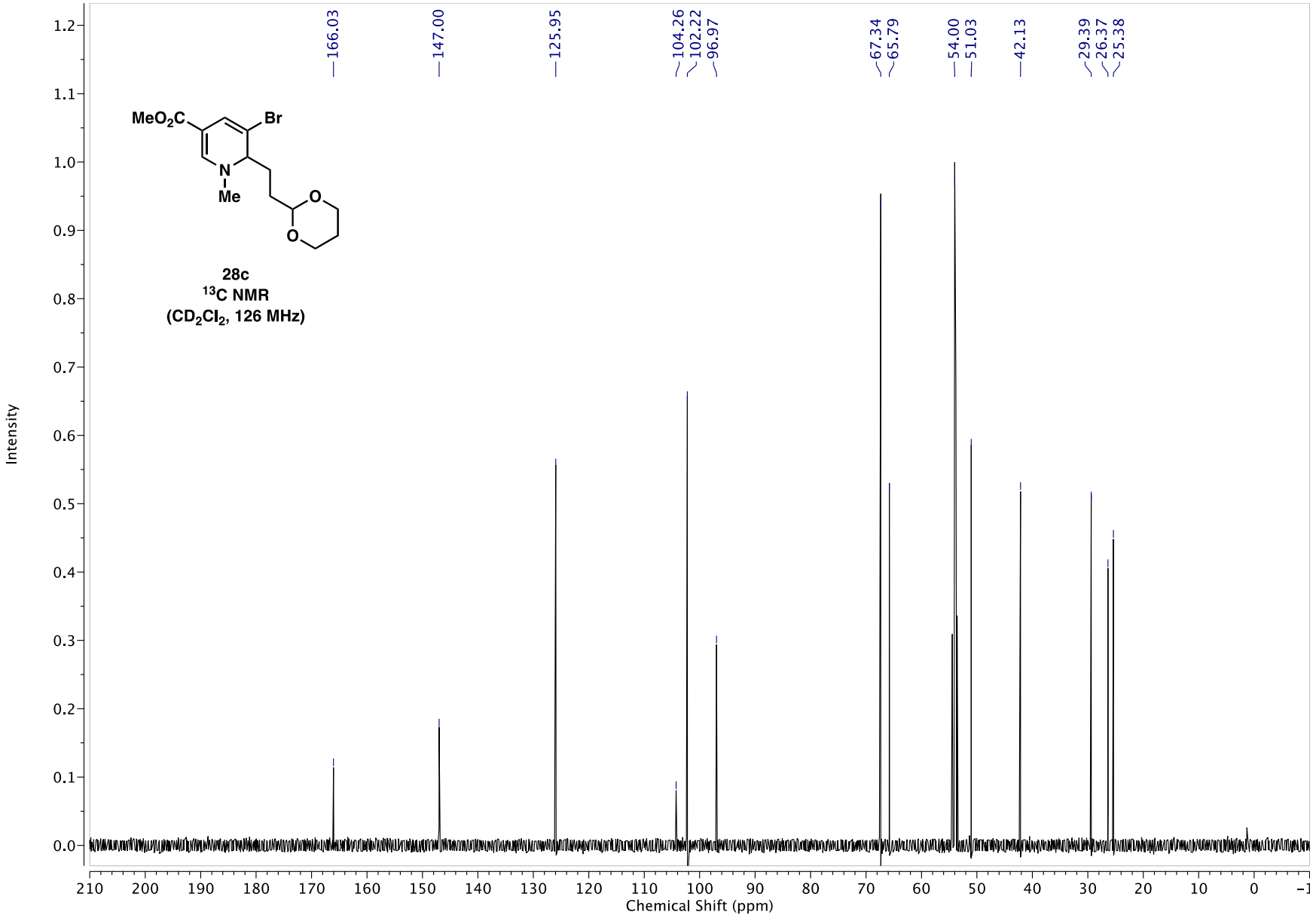

28b
1H NMR
(CDCl3, 400 MHz)
MeO2C
Br
N
Me
Intensity
Chemical Shift (ppm)
7.26
7.09
7.09
6.17
6.16
4.51
4.50
4.49
4.10
4.09
4.08
4.08
4.06
4.05
3.80
3.79
3.78
3.77
3.76
3.74
3.73
3.71
3.70
3.66
2.97
2.10
2.09
2.08
2.07
2.06
2.05
2.04
2.03
2.02
2.01
1.70
1.69
1.68
1.67
1.61
1.60
1.59
1.58
1.57
1.55
1.54
1.53
1.33
1.00
1.00
1.14
2.35
1.04
2.37
3.11
3.09
1.21
5.06
1.23

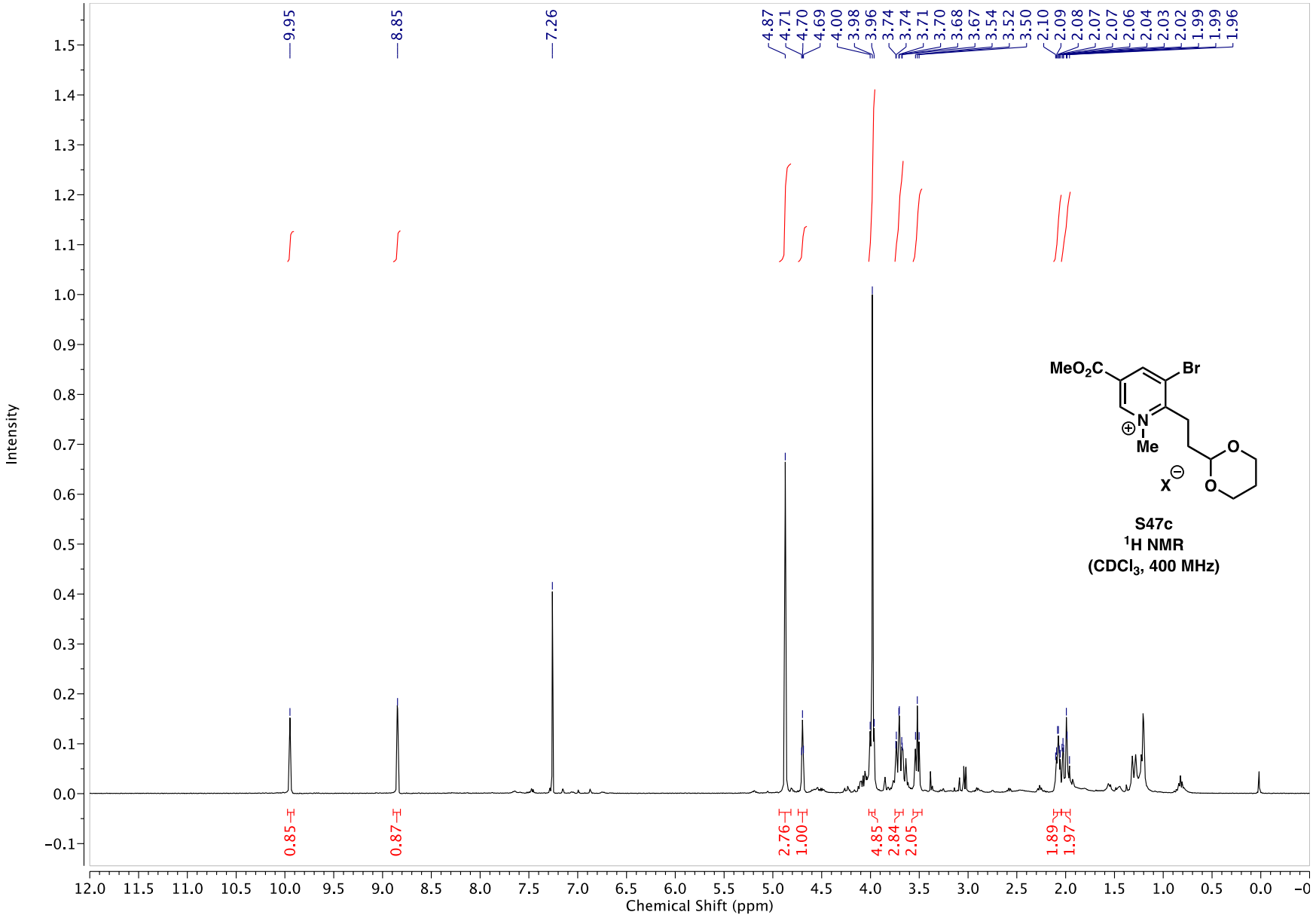

167.72
141.02
130.41
104.74
99.02
77.16
67.05
67.04
51.19
40.98
39.97
30.23
27.48
25.96
MeO2C
Br
N
Me
28b
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

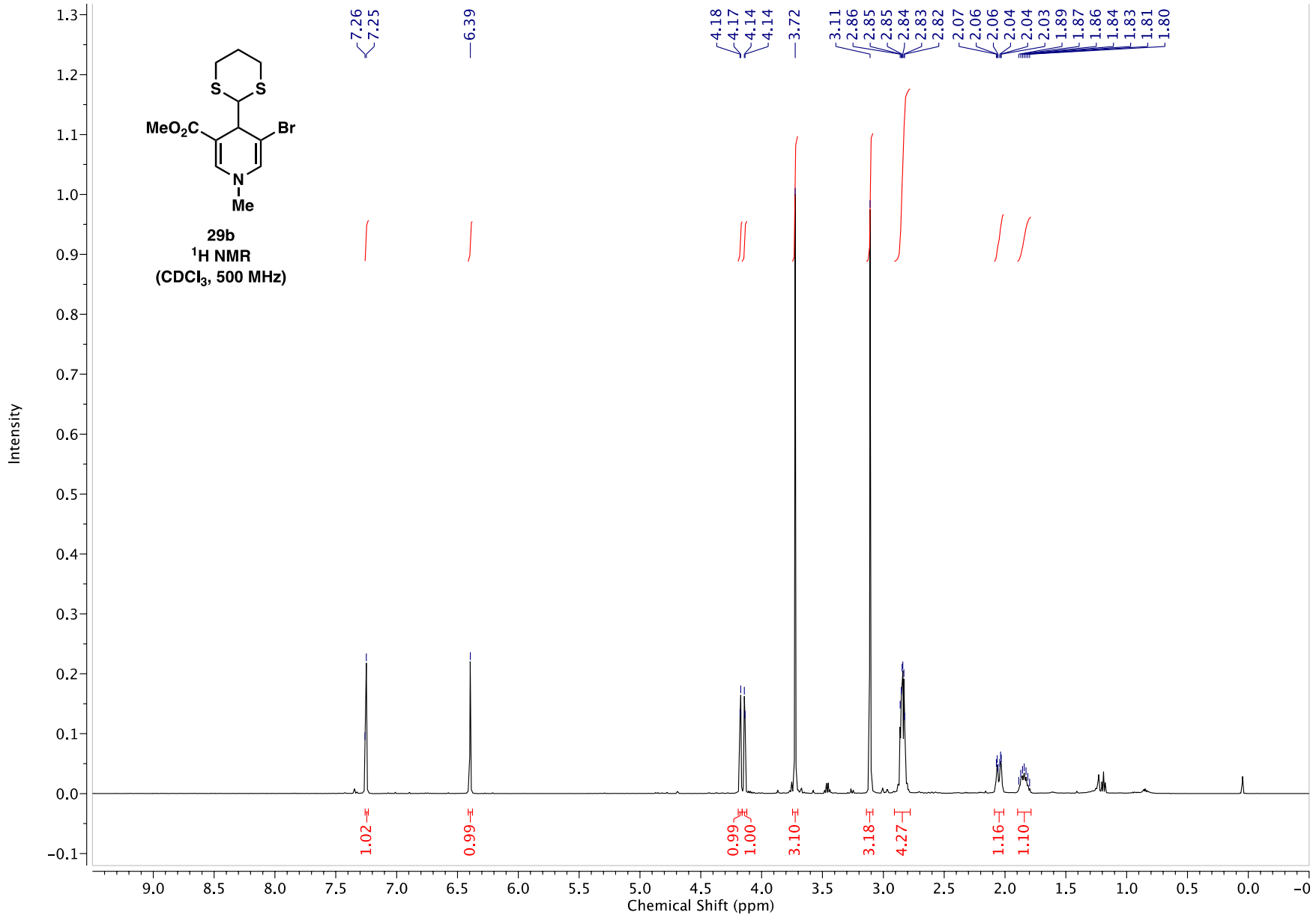

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
28b
HSQC
(CDCl3)

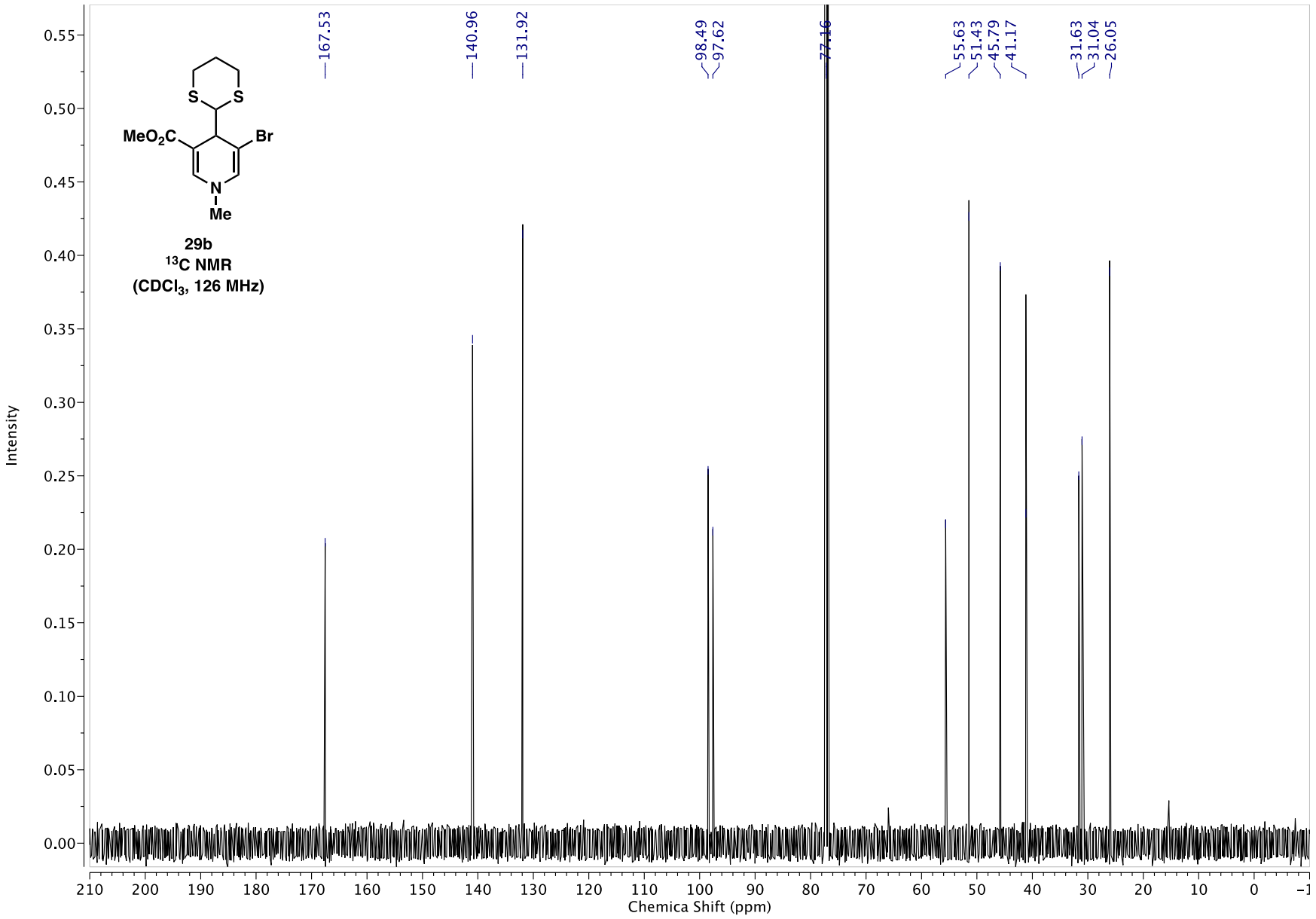

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
28b
HMBC
(CDCl3)

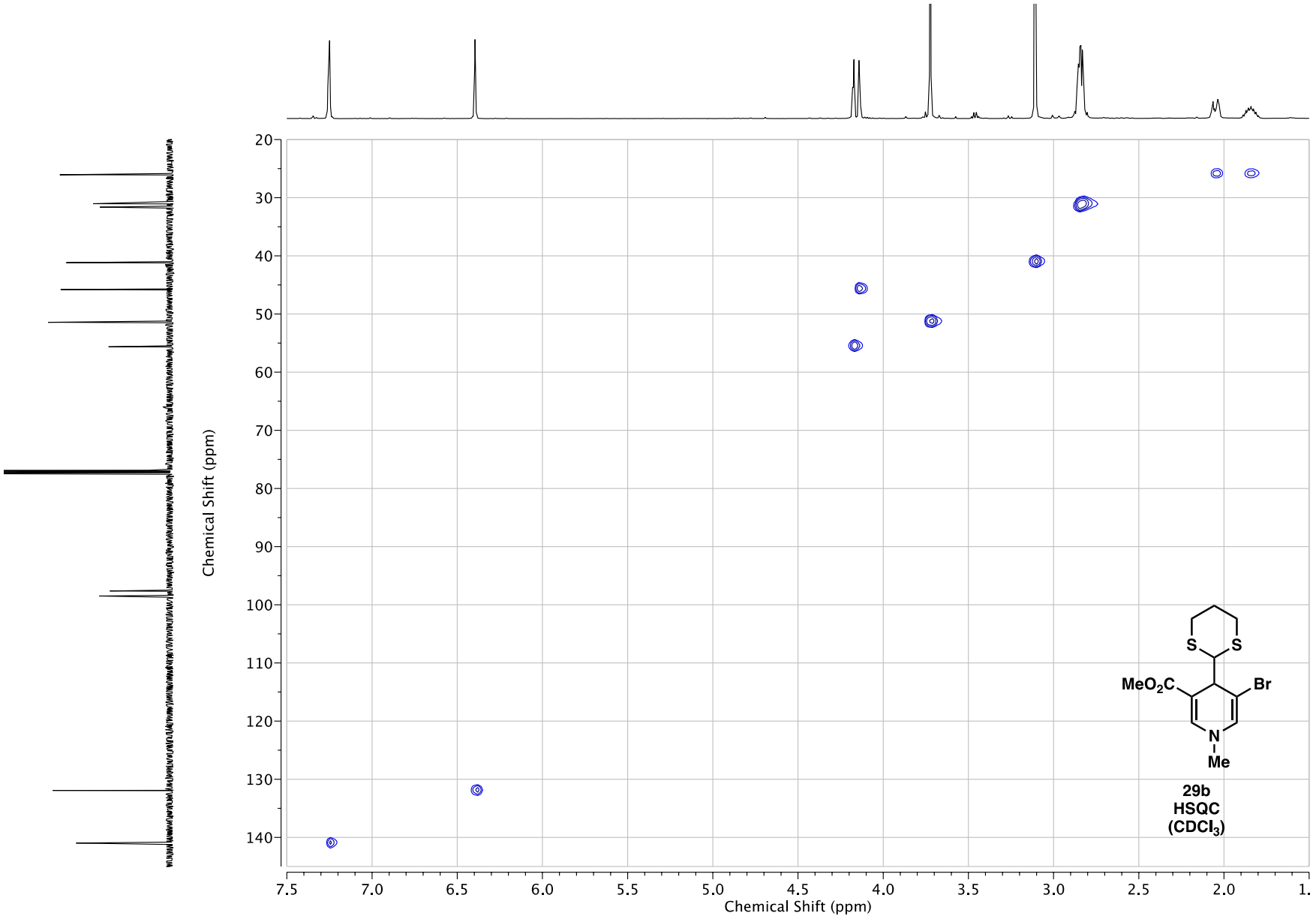

MeO2C
Br
N
Me
O
O
28c
1H NMR
(CD2Cl2, 500 MHz)
7.28
6.73
6.73
5.32
4.53
4.52
4.51
4.40
4.39
4.38
4.05
4.05
4.03
4.02
3.75
3.74
3.72
3.72
3.70
3.69
3.61
2.98
2.01
2.00
1.99
1.98
1.97
1.83
1.81
1.80
1.79
1.78
1.77
1.76
1.74
1.73
1.72
1.71
1.63
1.62
1.61
1.61
0.96
0.87
1.04
1.00
2.24
2.31
3.10
3.17
1.18
3.95
1.19
Intensity
Chemical Shift (ppm)

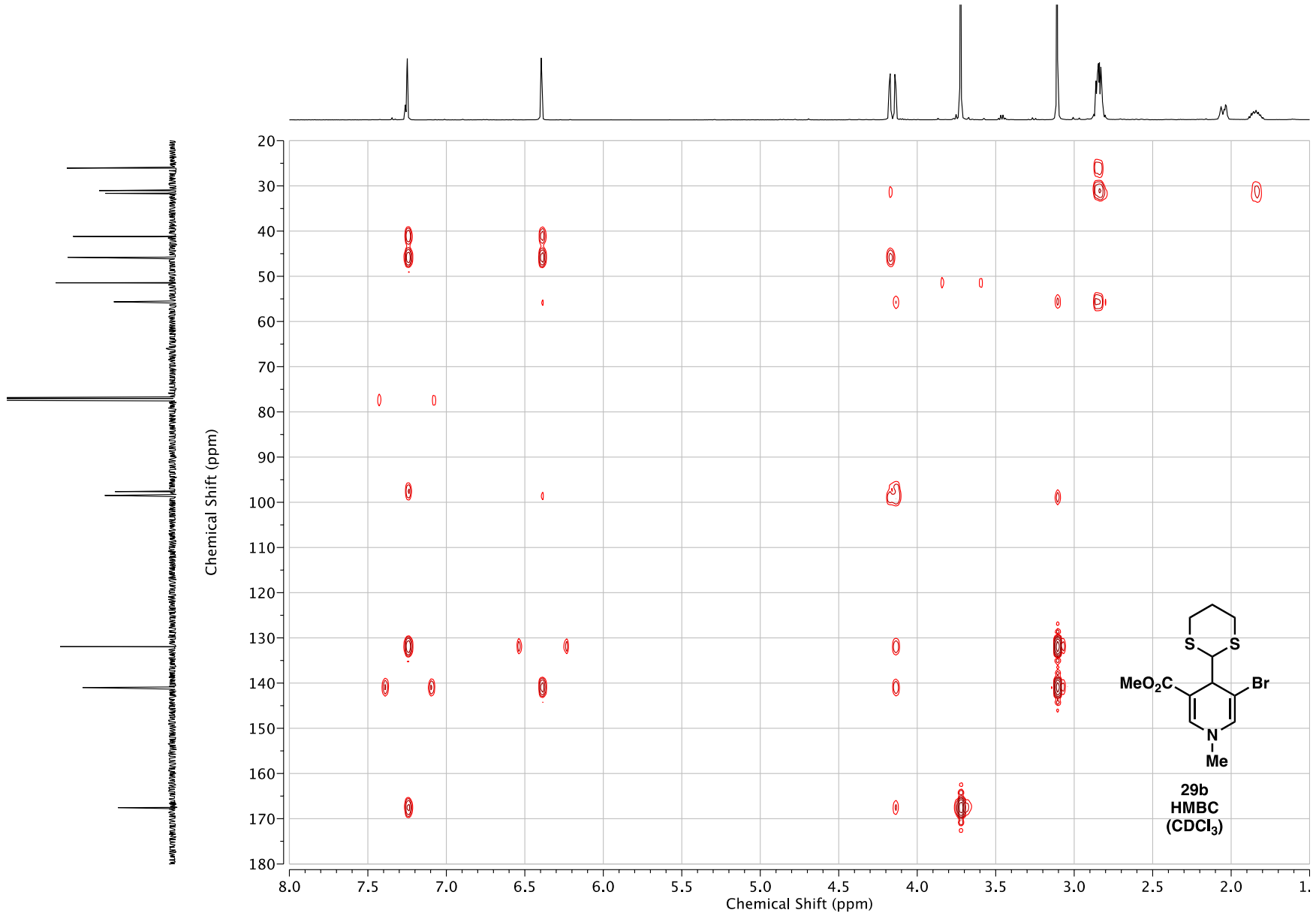

166.03
147.00
125.95
104.26
102.22
96.97
67.34
65.79
54.00
51.03
42.13
29.39
26.37
25.38
MeO2C
Br
N
Me
O
O
28c
13C NMR
(CD2Cl2, 126 MHz)
Intensity
Chemical Shift (ppm)

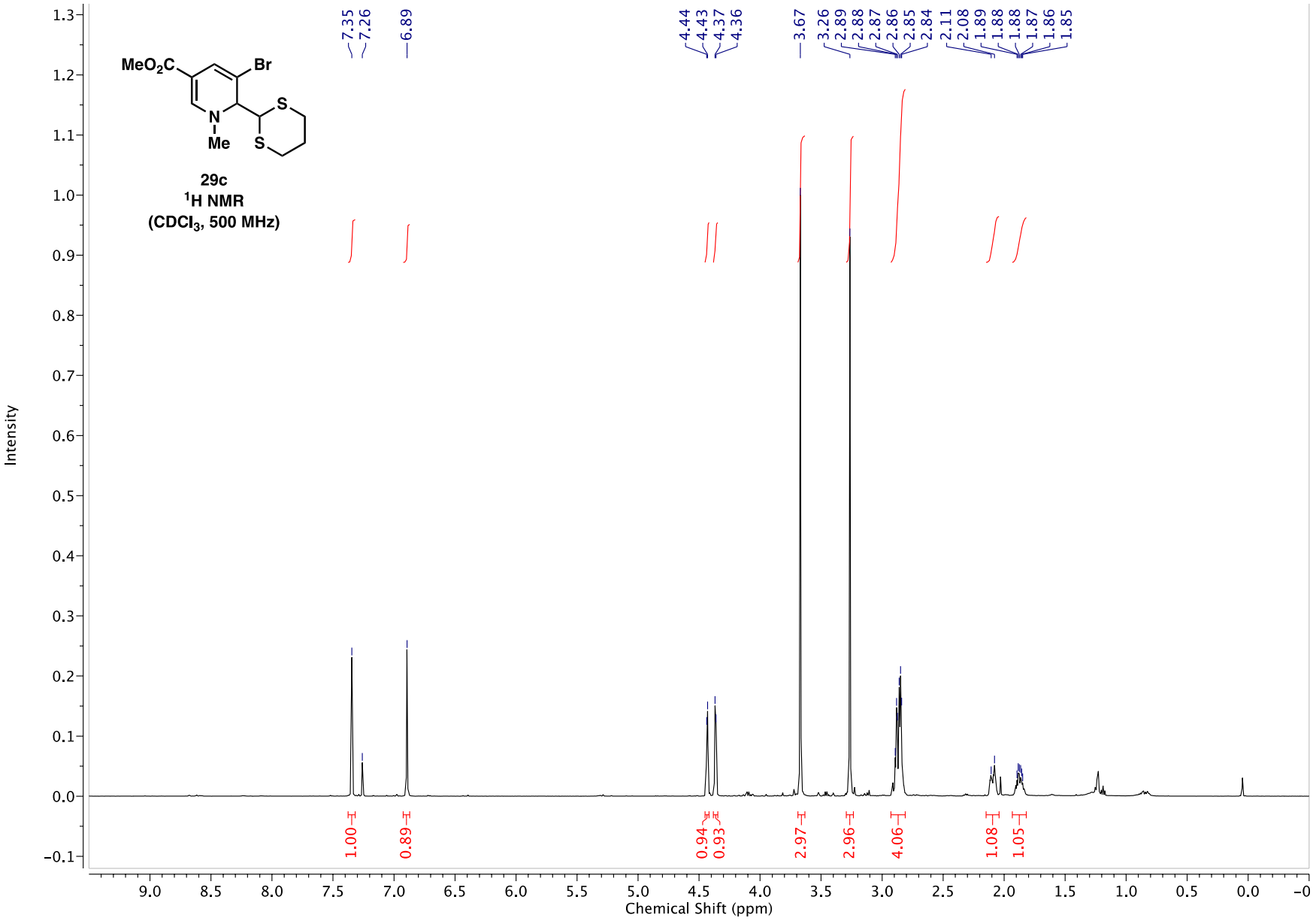

9.95
8.85
7.26
4.87
4.71
4.70
4.69
4.00
3.98
3.96
3.74
3.74
3.71
3.70
3.68
3.67
3.54
3.52
3.50
2.10
2.09
2.08
2.07
2.07
2.06
2.04
2.03
2.02
1.99
1.99
1.96
0.85
0.87
2.76
1.00
4.85
2.84
2.05
1.89
1.97
Intensity
Chemical Shift (ppm)
MeO2C
Br
N
Me
O
O
X
S47c
1H NMR
(CDCl3, 400 MHz)

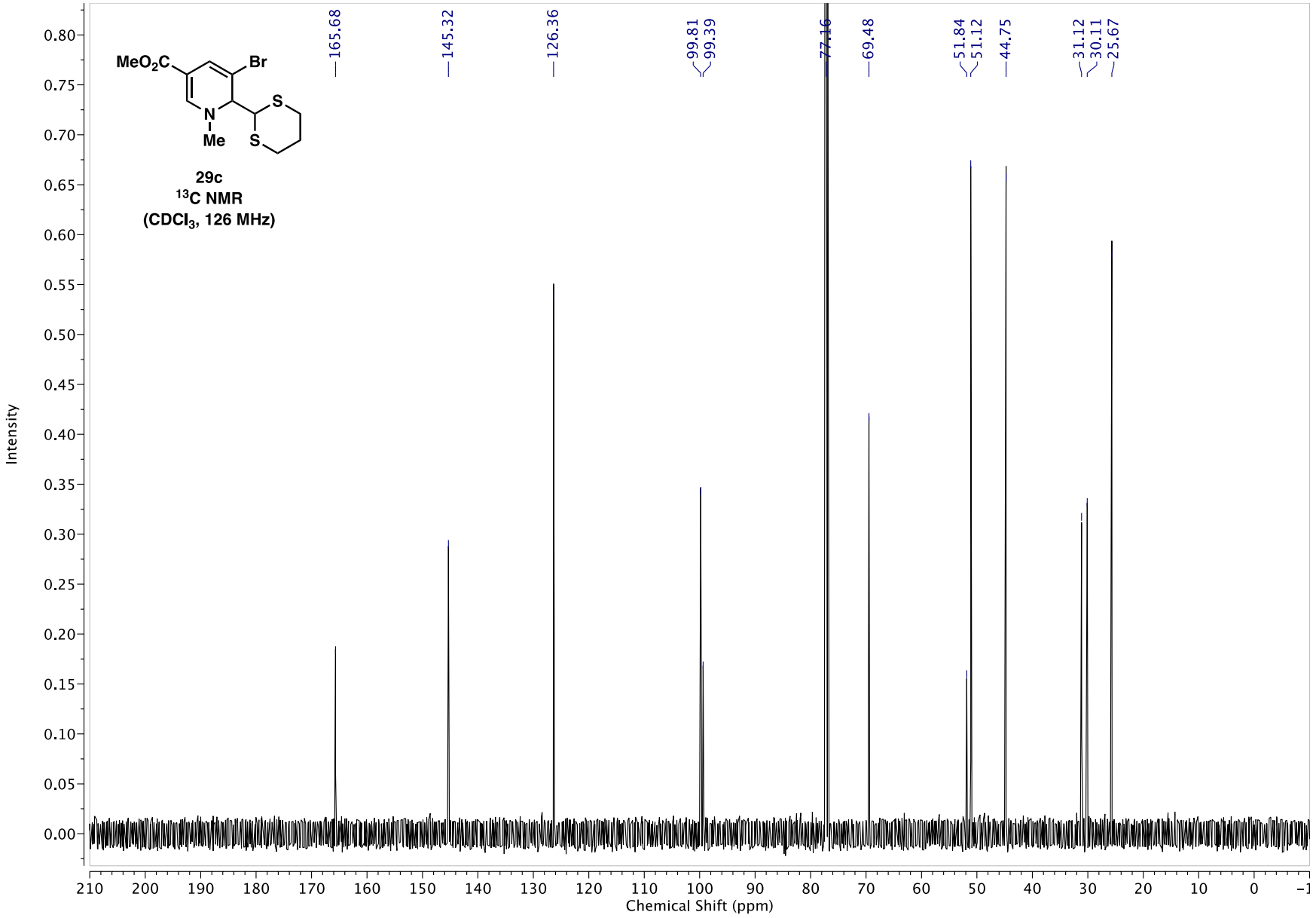

29b
1H NMR
(CDCl3, 500 MHz)
MeO2C
Br
S
S
N
Me
7.26
7.25
6.39
4.18
4.17
4.14
4.14
3.72
3.11
2.86
2.85
2.85
2.84
2.83
2.82
2.07
2.06
2.06
2.04
2.04
2.03
1.89
1.87
1.86
1.84
1.83
1.81
1.80
1.02
0.99
0.99
1.00
3.10
3.18
4.27
1.16
1.10
Intensity
Chemical Shift (ppm)

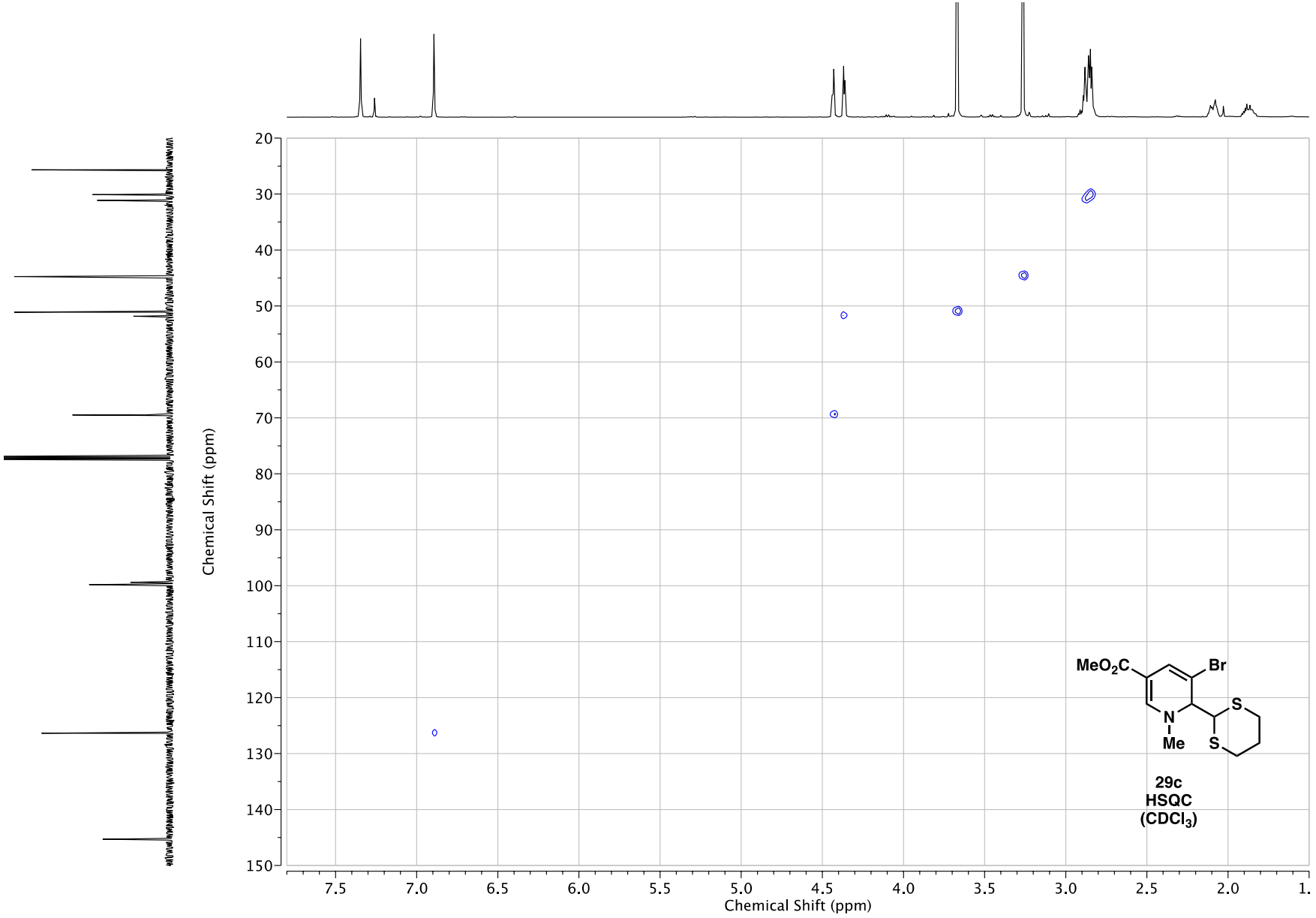

167.53
140.96
131.92
98.49
97.62
77.16
55.63
51.43
45.79
41.17
31.63
31.04
26.05
S
S
MeO2C
Br
N
Me
29b
13C NMR
(CDCl3, 126 MHz)
Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemica Shift (ppm)

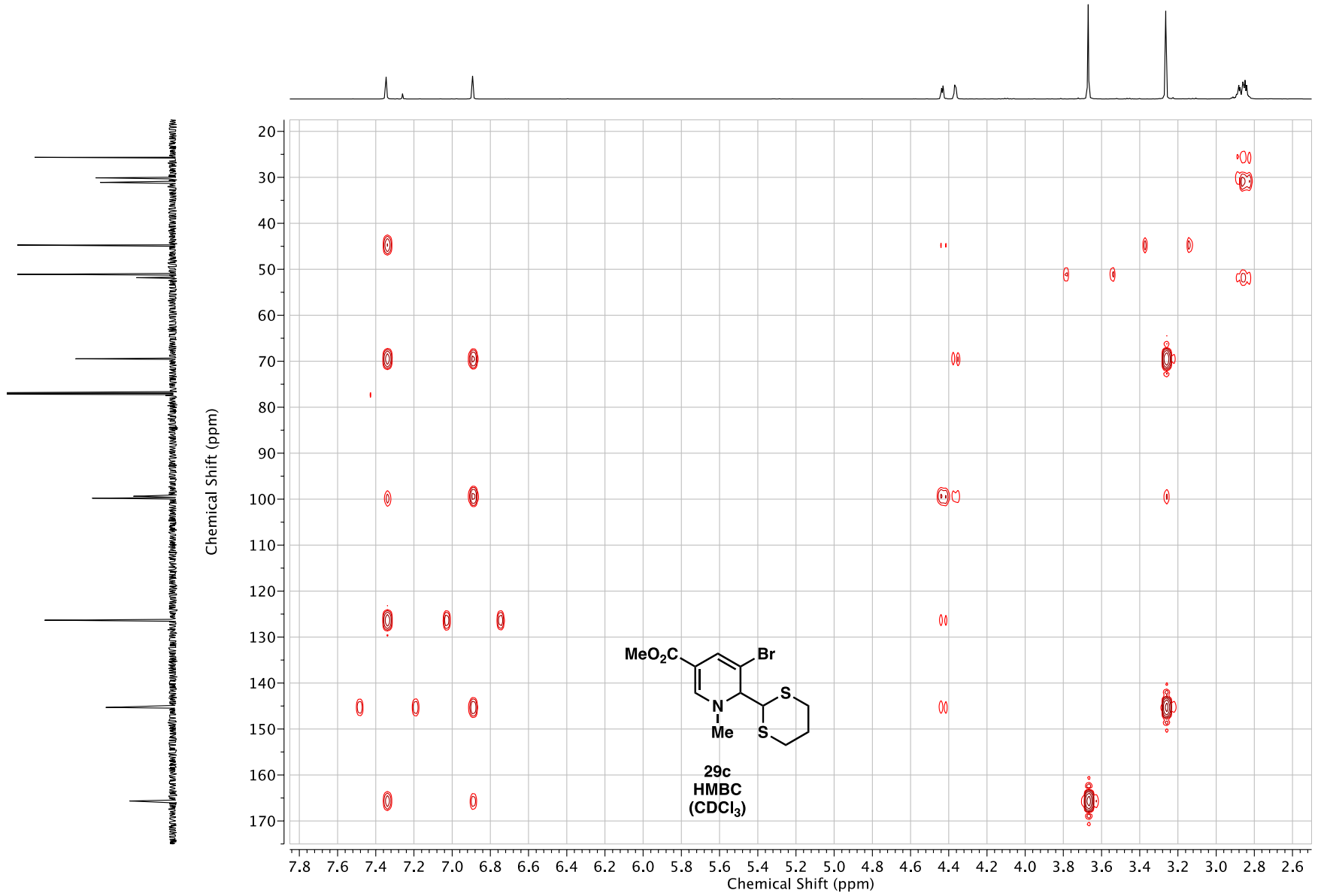

Chemical Shift (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.
Chemical Shift (ppm)
S
S
MeO2C
Br
N
Me
29b
HSQC
(CDCl3)

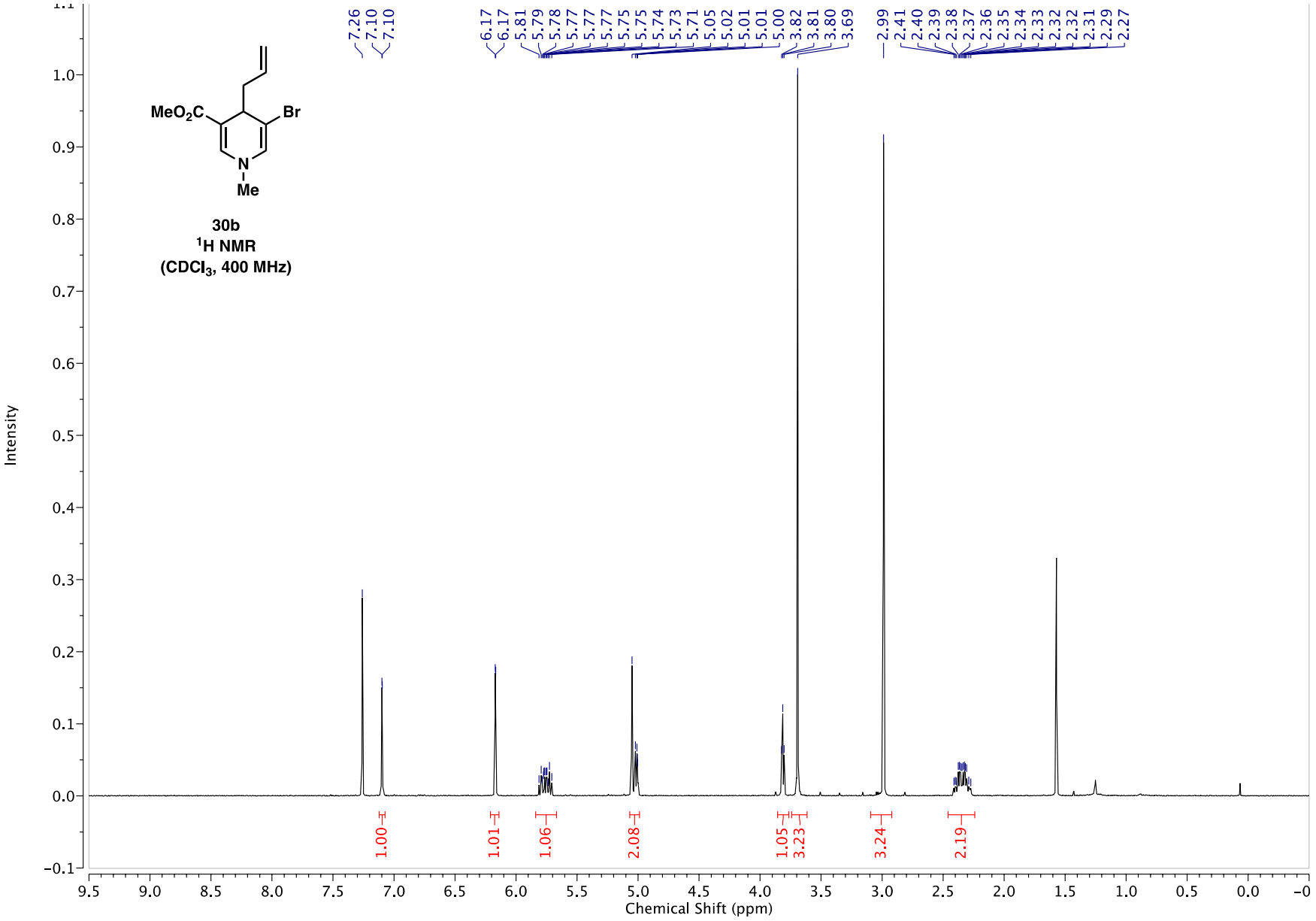

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
S
S
N
Me
29b
HMBC
(CDCl3)

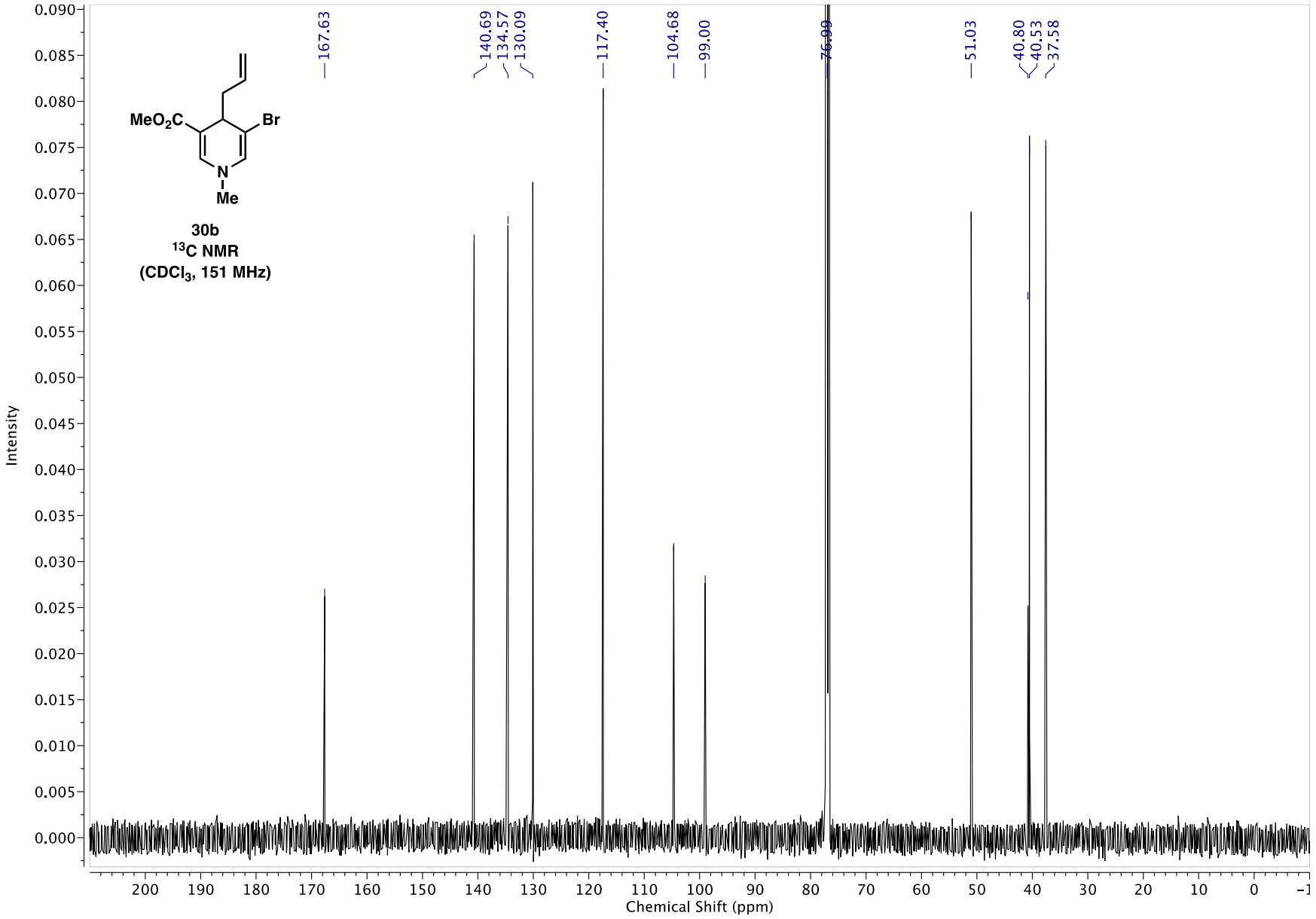

MeO2C
Br
N
Me
S
S
29c
1H NMR
(CDCl3, 500 MHz)
7.35
7.26
6.89
4.44
4.43
4.37
4.36
3.67
3.26
2.89
2.88
2.87
2.86
2.85
2.84
2.11
2.08
1.89
1.88
1.87
1.86
1.85
1.00
0.89
0.94
0.93
2.97
2.96
4.06
1.08
1.05
Intensity
Chemical Shift (ppm)

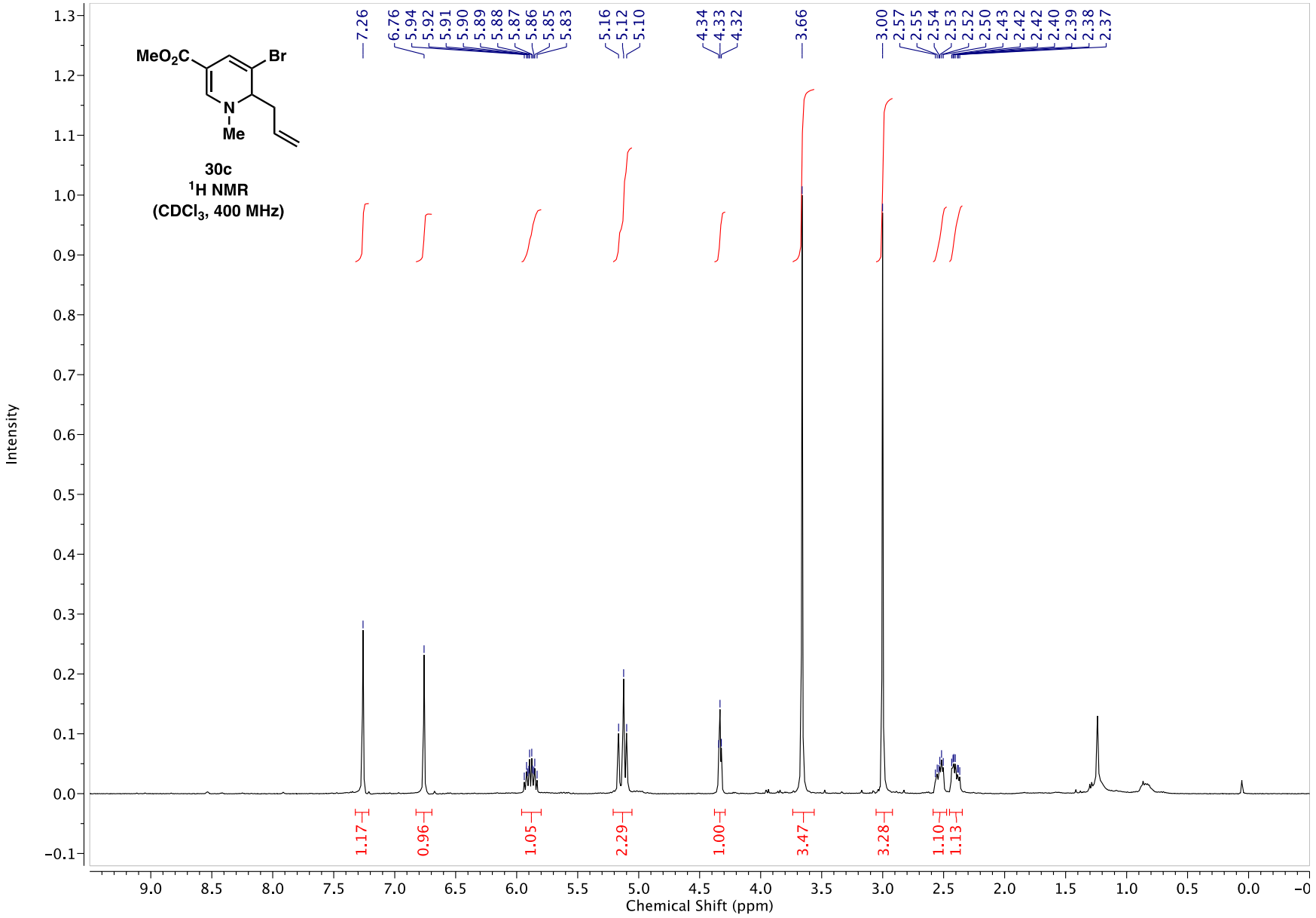

MeO2C
Br
N
Me
S
S
29c
13C NMR
(CDCl3, 126 MHz)
165.68
145.32
126.36
99.81
99.39
77.16
69.48
51.84
51.12
44.75
31.12
30.11
25.67
Intensity
Chemical Shift (ppm)

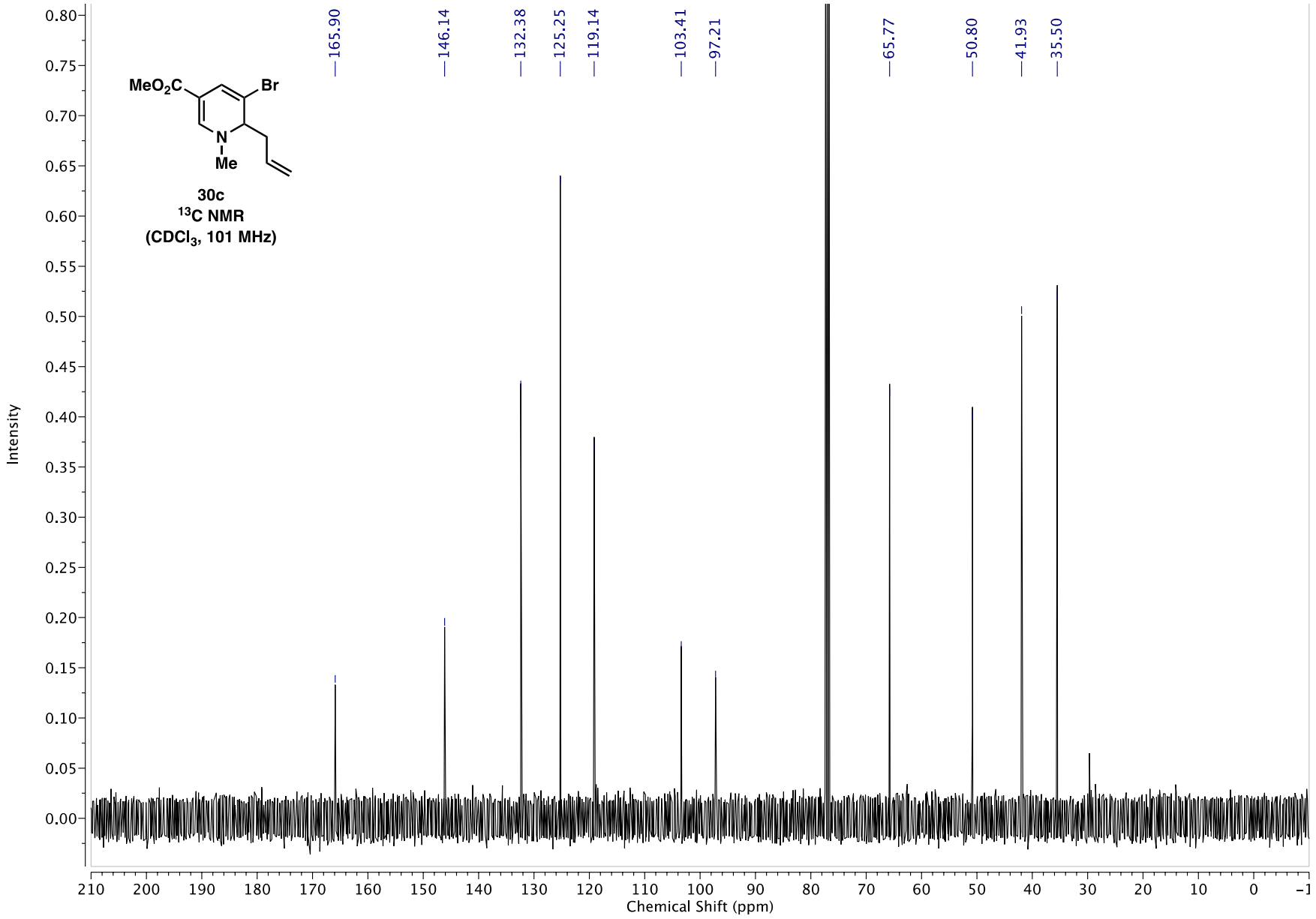

Chemical Shift (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.
Chemical Shift (ppm)
MeO2C
Br
N
Me
S
S
29c
HSQC
(CDCl3)

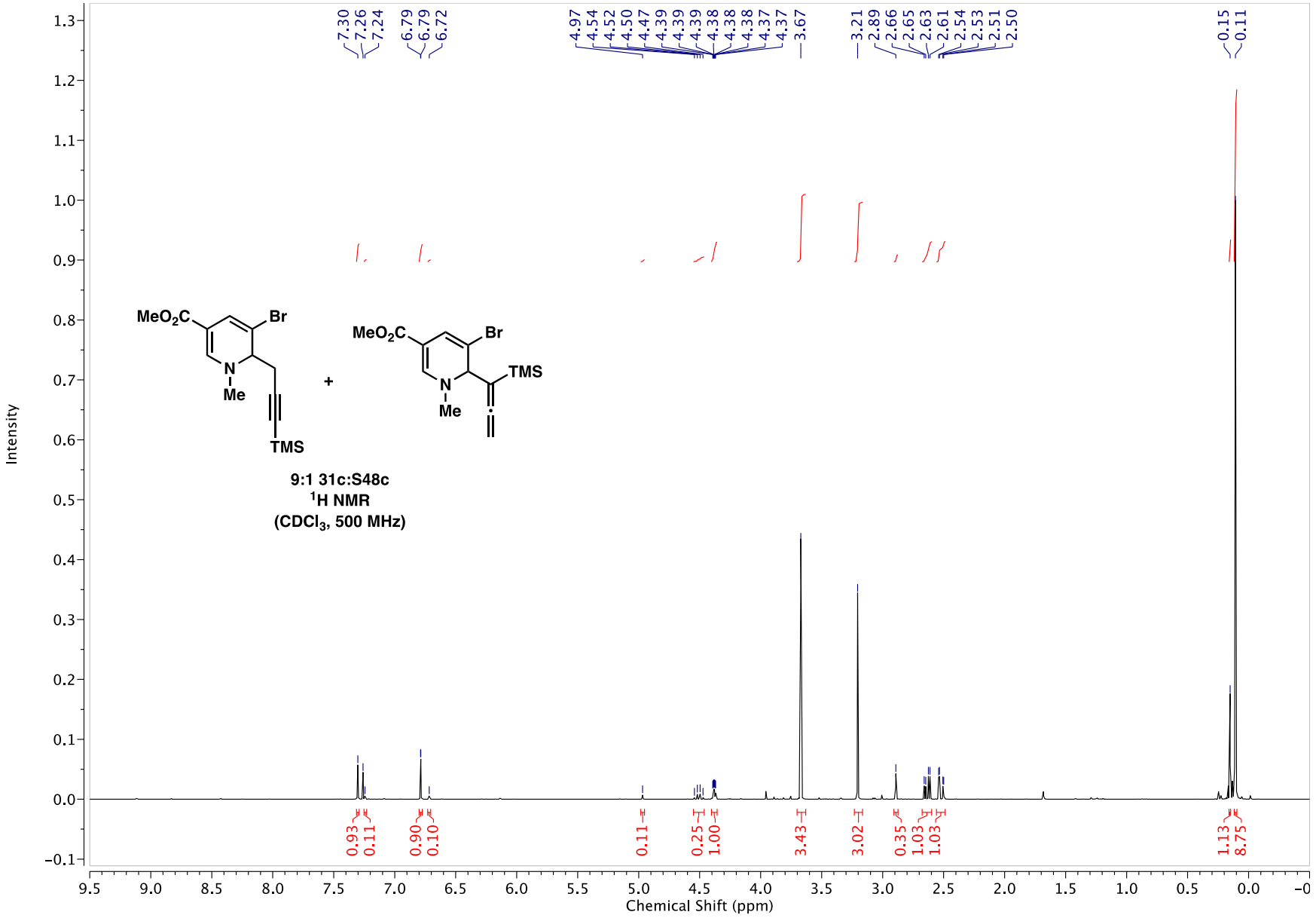

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
S
S
29c
HMBC
(CDCl3)

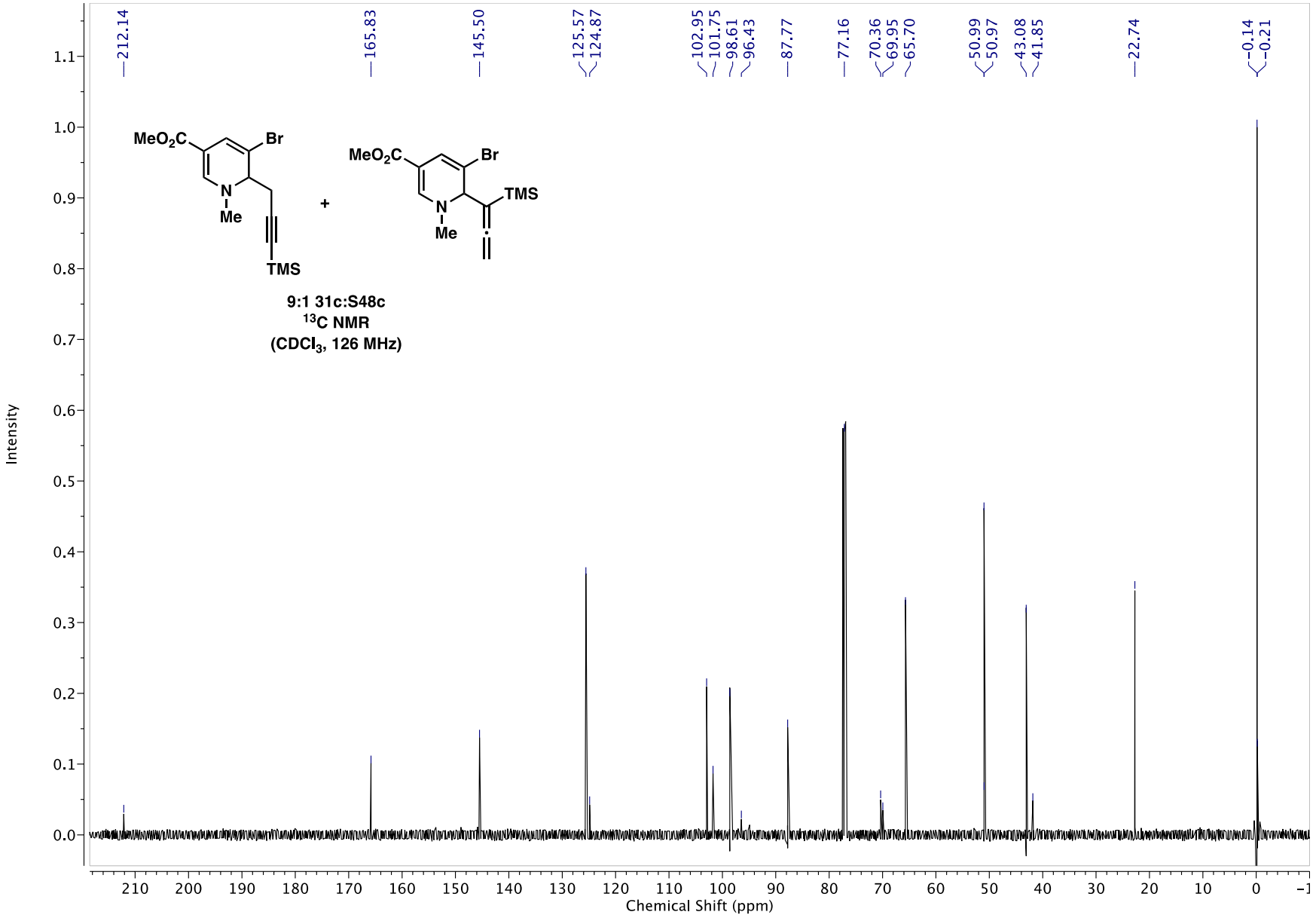

MeO2C
Br
N
Me
30b
1H NMR
(CDCl3, 400 MHz)
7.26
7.10
7.10
6.17
6.17
5.81
5.79
5.78
5.77
5.77
5.77
5.75
5.75
5.74
5.73
5.71
5.05
5.02
5.01
5.01
5.00
3.82
3.81
3.80
3.69
2.99
2.41
2.40
2.39
2.38
2.37
2.36
2.35
2.34
2.33
2.32
2.32
2.31
2.29
2.27
1.00
1.01
1.06
2.08
1.05
3.23
3.24
2.19
Intensity
Chemical Shift (ppm)

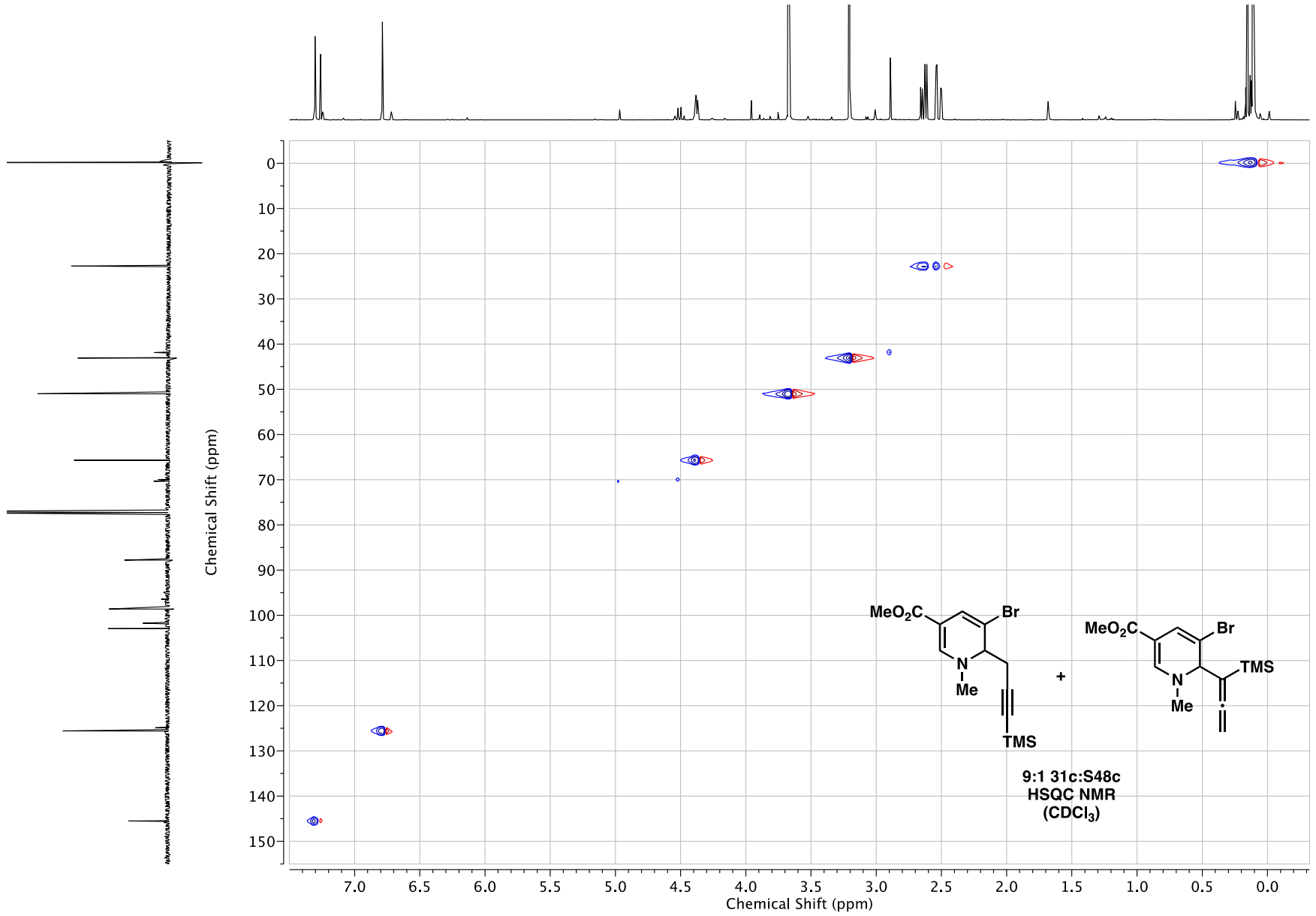

167.63
140.69
134.57
130.09
117.40
104.68
99.00
76.99
51.03
40.80
40.53
37.58
MeO2C
Br
N
Me
30b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

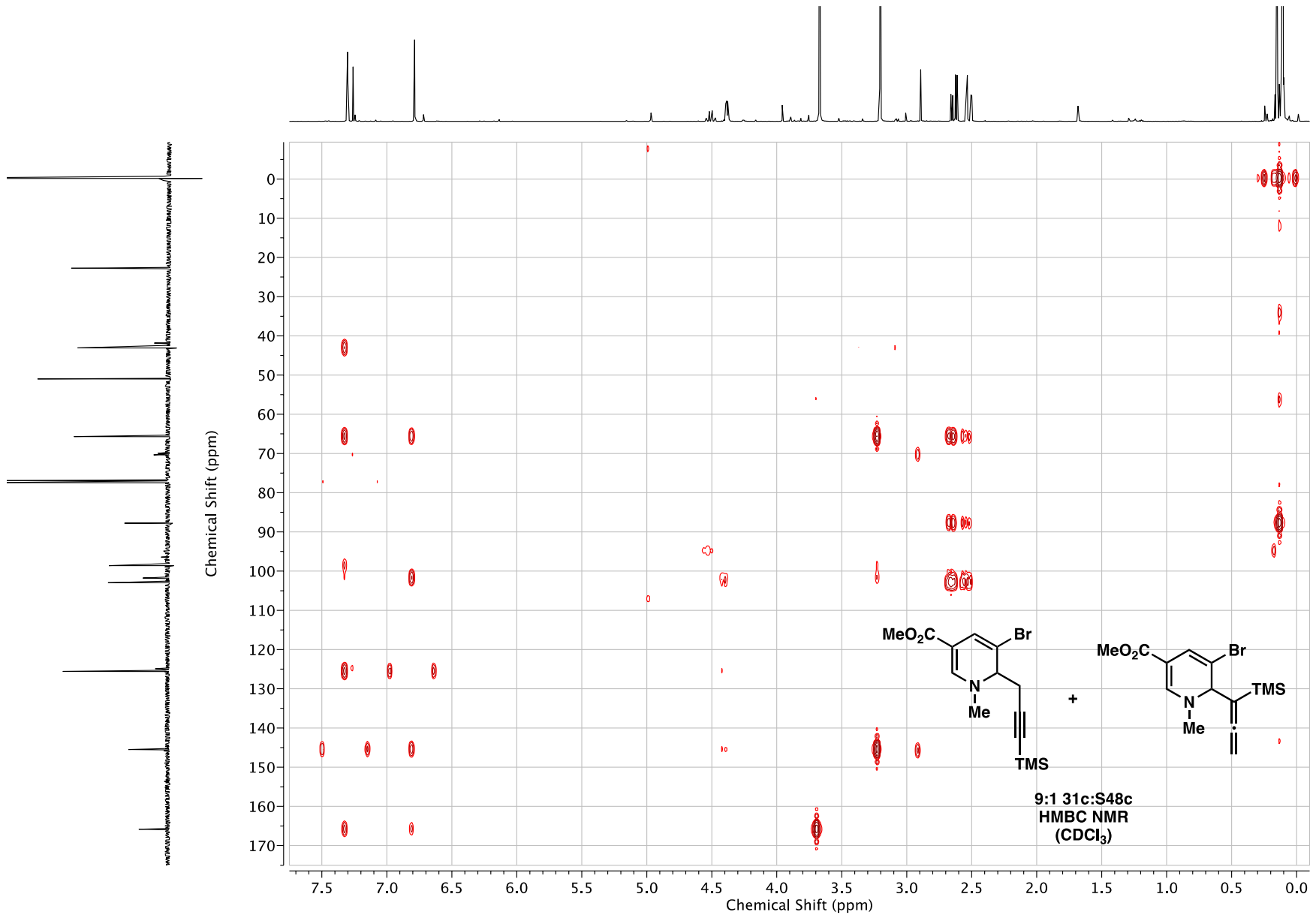

MeO2C
Br
N
Me
30c
1H NMR
(CDCl3, 400 MHz)
7.26
6.76
5.94
5.92
5.91
5.90
5.89
5.88
5.87
5.86
5.85
5.83
5.16
5.12
5.10
4.34
4.33
4.32
3.66
3.00
2.57
2.55
2.54
2.53
2.52
2.50
2.43
2.42
2.42
2.40
2.39
2.38
2.37
1.17
0.96
1.05
2.29
1.00
3.47
3.28
1.10
1.13
Intensity
Chemical Shift (ppm)

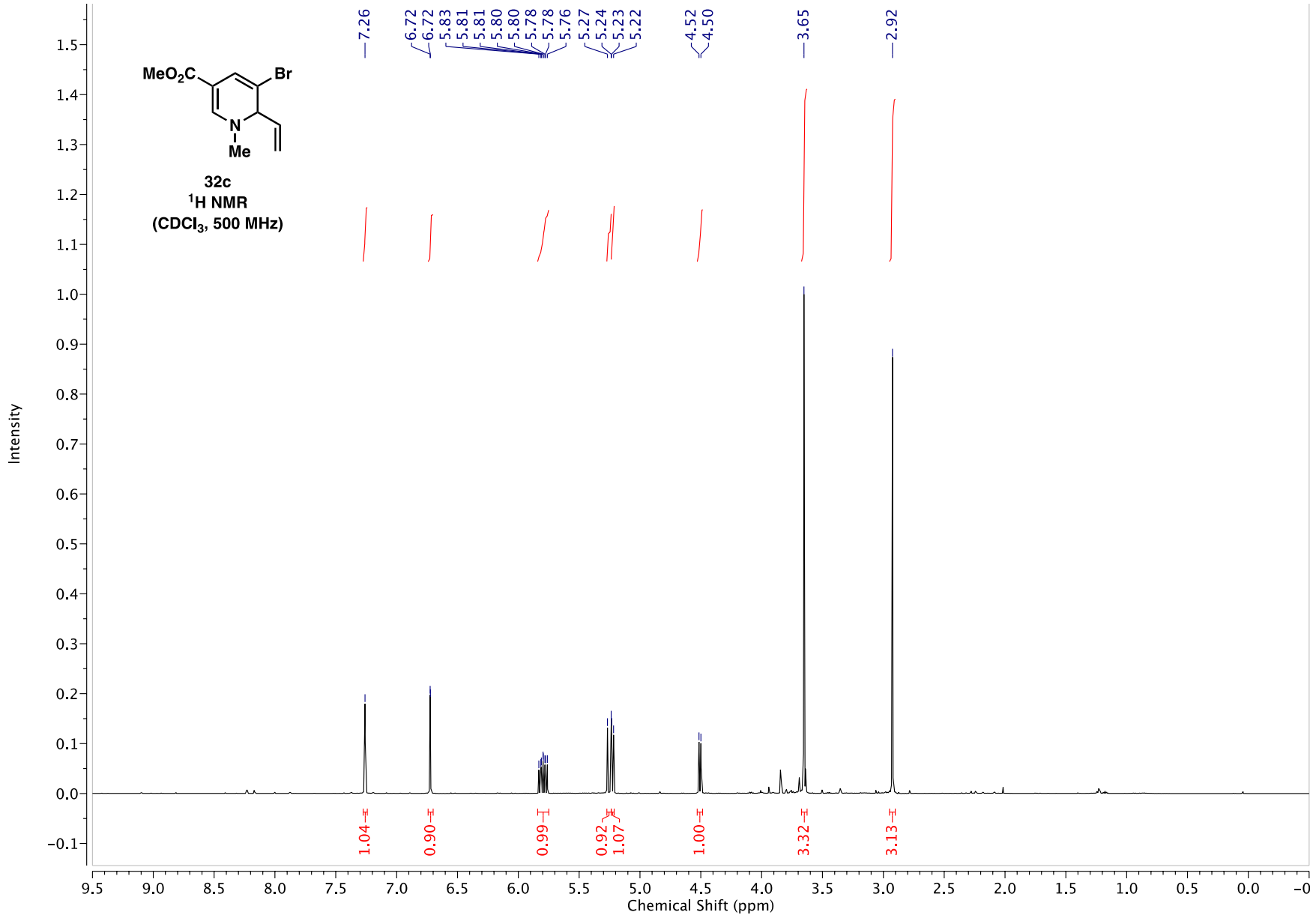

MeO2C
Br
N
Me
30c
13C NMR
(CDCl3, 101 MHz)
165.90
146.14
132.38
125.25
119.14
103.41
97.21
65.77
50.80
41.93
35.50
Intensity
Chemical Shift (ppm)

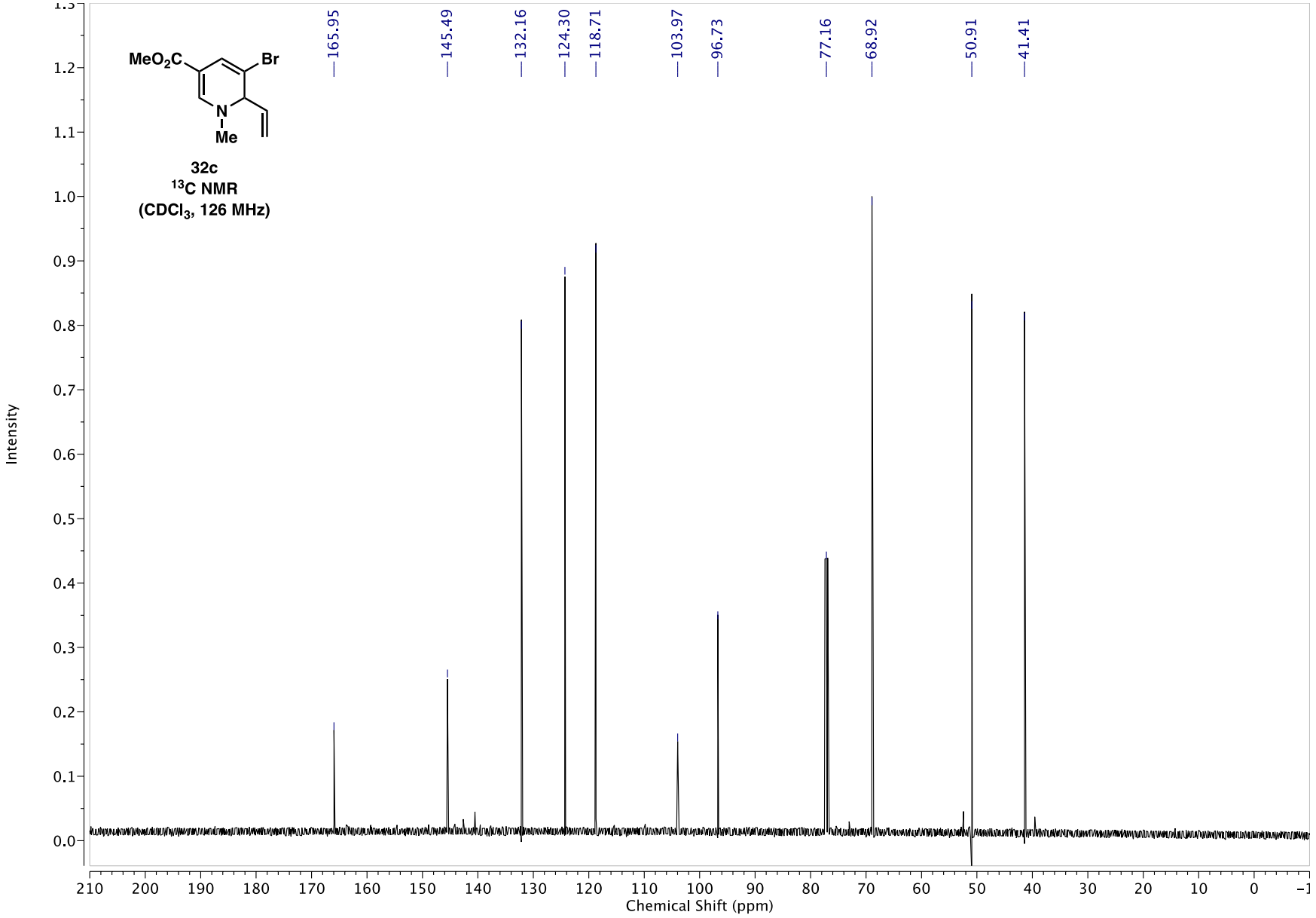

7.30
7.26
7.24
6.79
6.79
6.72
4.97
4.54
4.52
4.50
4.47
4.39
4.39
4.39
4.38
4.38
4.38
4.37
4.37
3.67
3.21
2.89
2.66
2.65
2.63
2.61
2.54
2.53
2.51
2.50
0.15
0.11
MeO2C
Br
N
Me
TMS
+
MeO2C
Br
TMS
N
Me
9:1 31c:S48c
1H NMR
(CDCl3, 500 MHz)
Intensity
Chemical Shift (ppm)
0.93
0.11
0.90
0.10
0.11
0.25
1.00
3.43
3.02
0.35
1.03
1.03
1.13
8.75

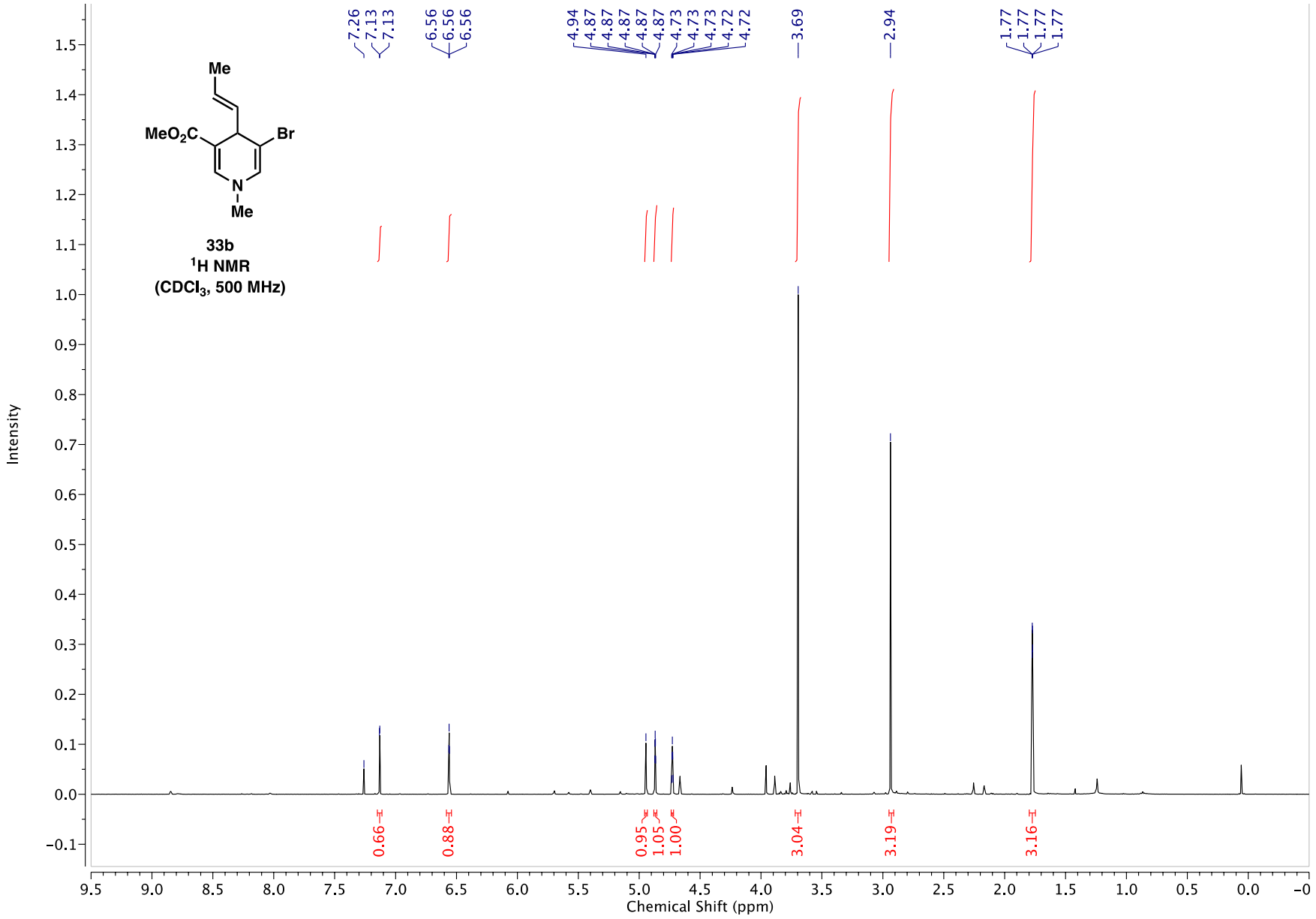

212.14
165.83
145.50
125.57
124.87
102.95
101.75
98.61
96.43
87.77
77.16
70.36
69.95
65.70
50.99
50.97
43.08
41.85
22.74
-0.14
-0.21
MeO2C
Br
N
Me
TMS
+
MeO2C
Br
TMS
N
Me
9:1 31c:S48c
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

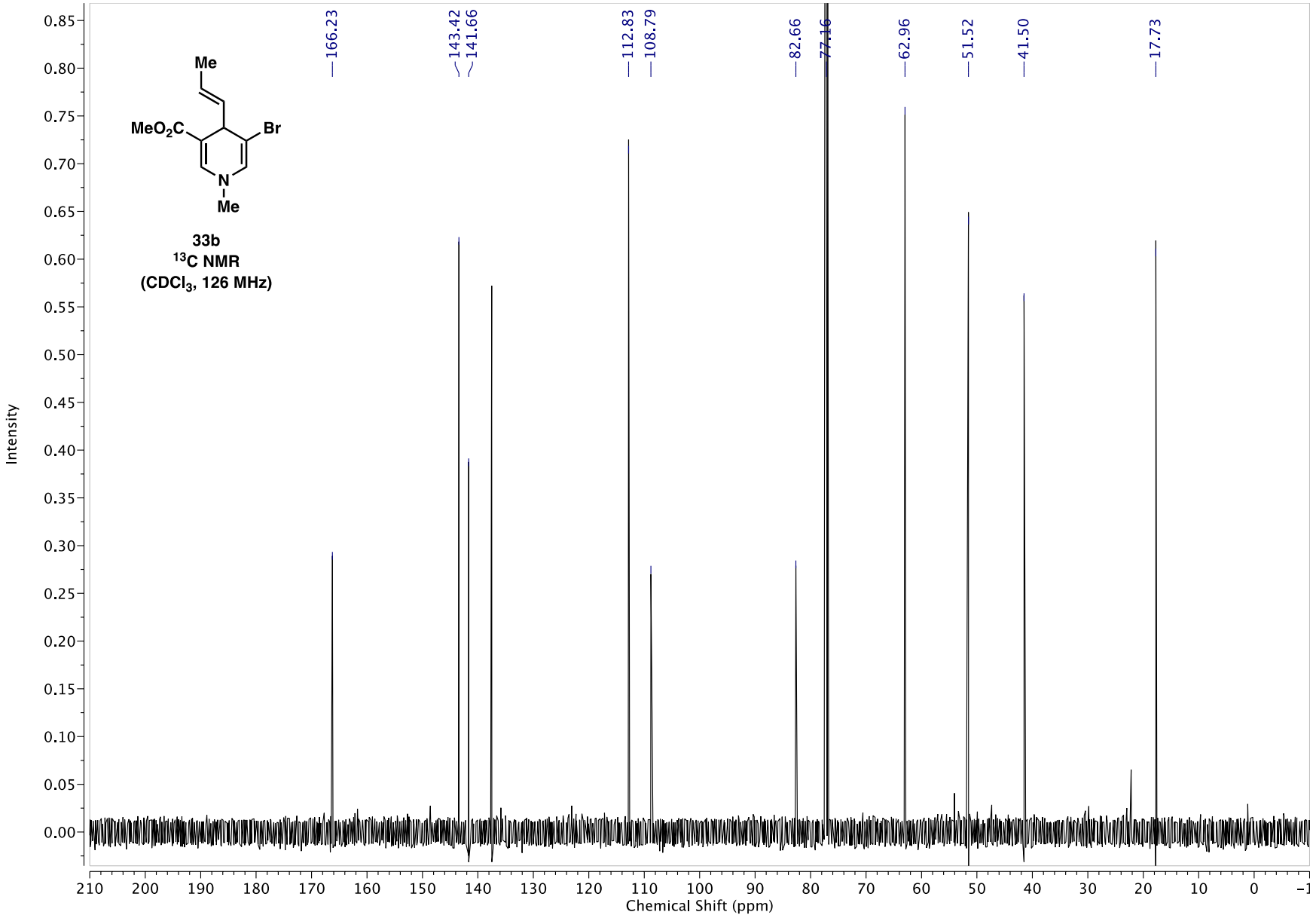

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
TMS
+
MeO2C
Br
TMS
N
Me
9:1 31c:S48c
HSQC NMR
(CDCl3)

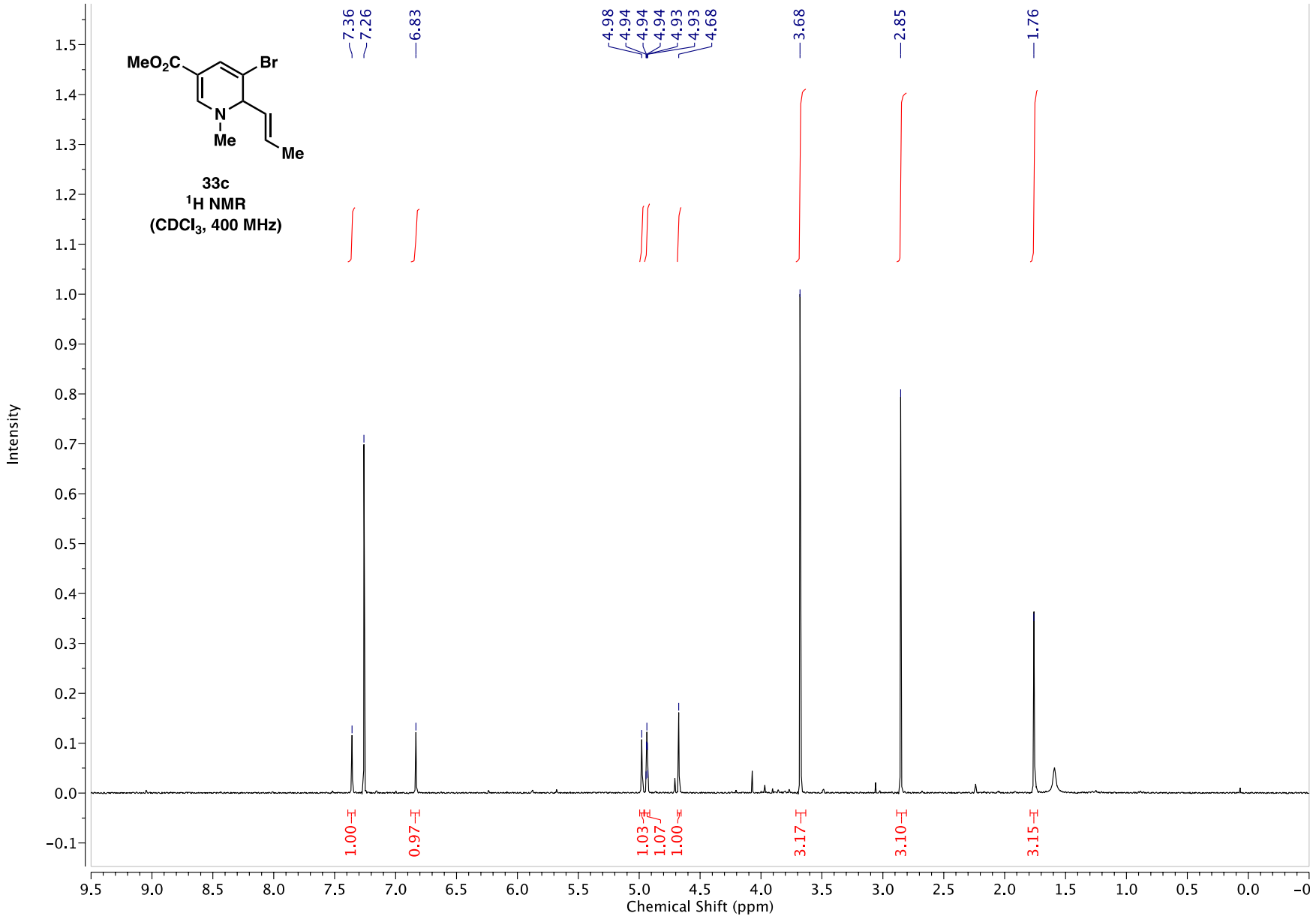

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
TMS
+
MeO2C
Br
TMS
N
Me
9:1 31c:S48c
HMBC NMR
(CDCl3)

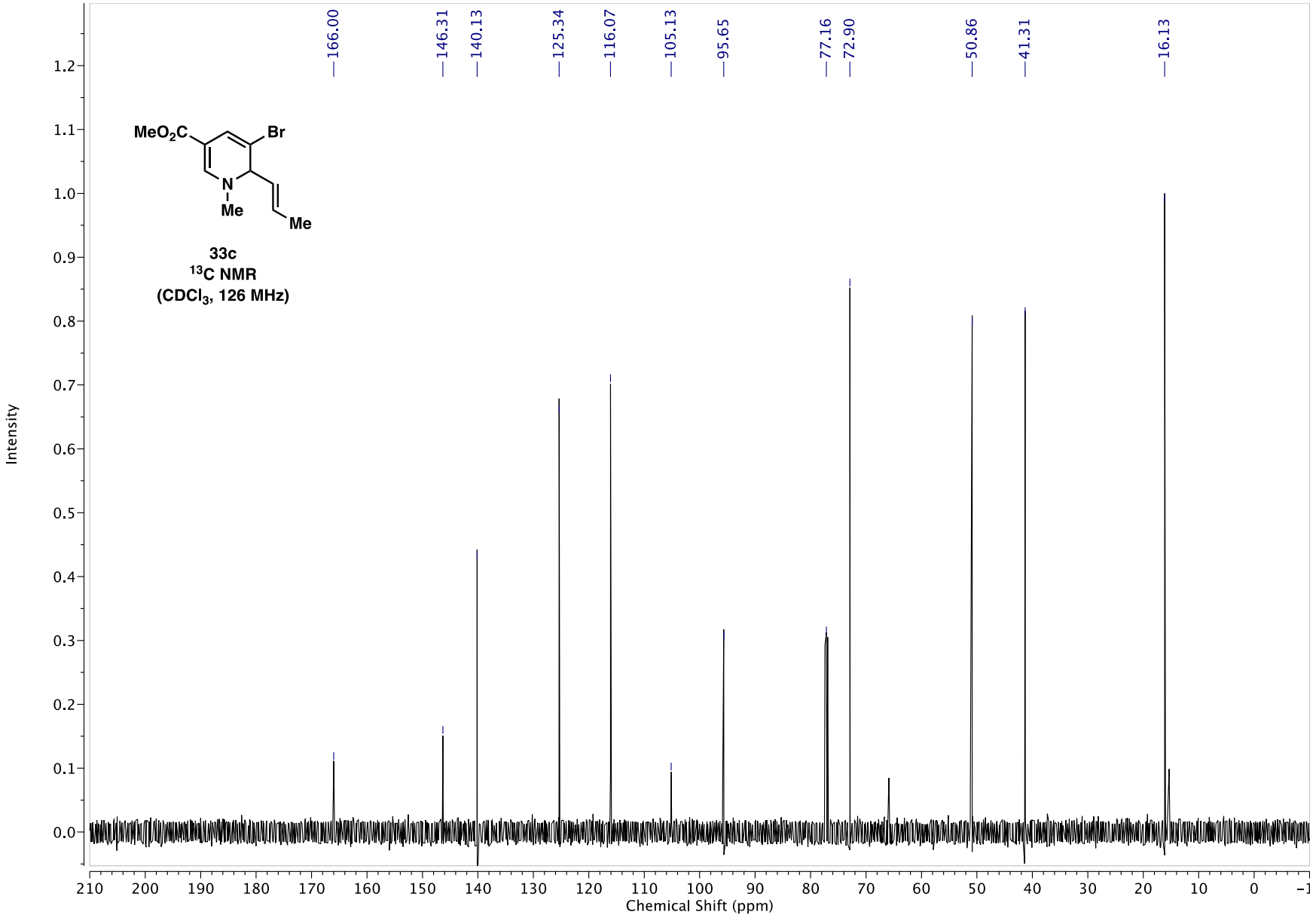

MeO2C
Br
N
Me
32c
1H NMR
(CDCl3, 500 MHz)
7.26
6.72
6.72
5.83
5.81
5.81
5.80
5.80
5.78
5.78
5.76
5.27
5.24
5.23
5.22
4.52
4.50
3.65
2.92
1.04
0.90
0.99
0.92
1.07
1.00
3.32
3.13
Intensity
Chemical Shift (ppm)

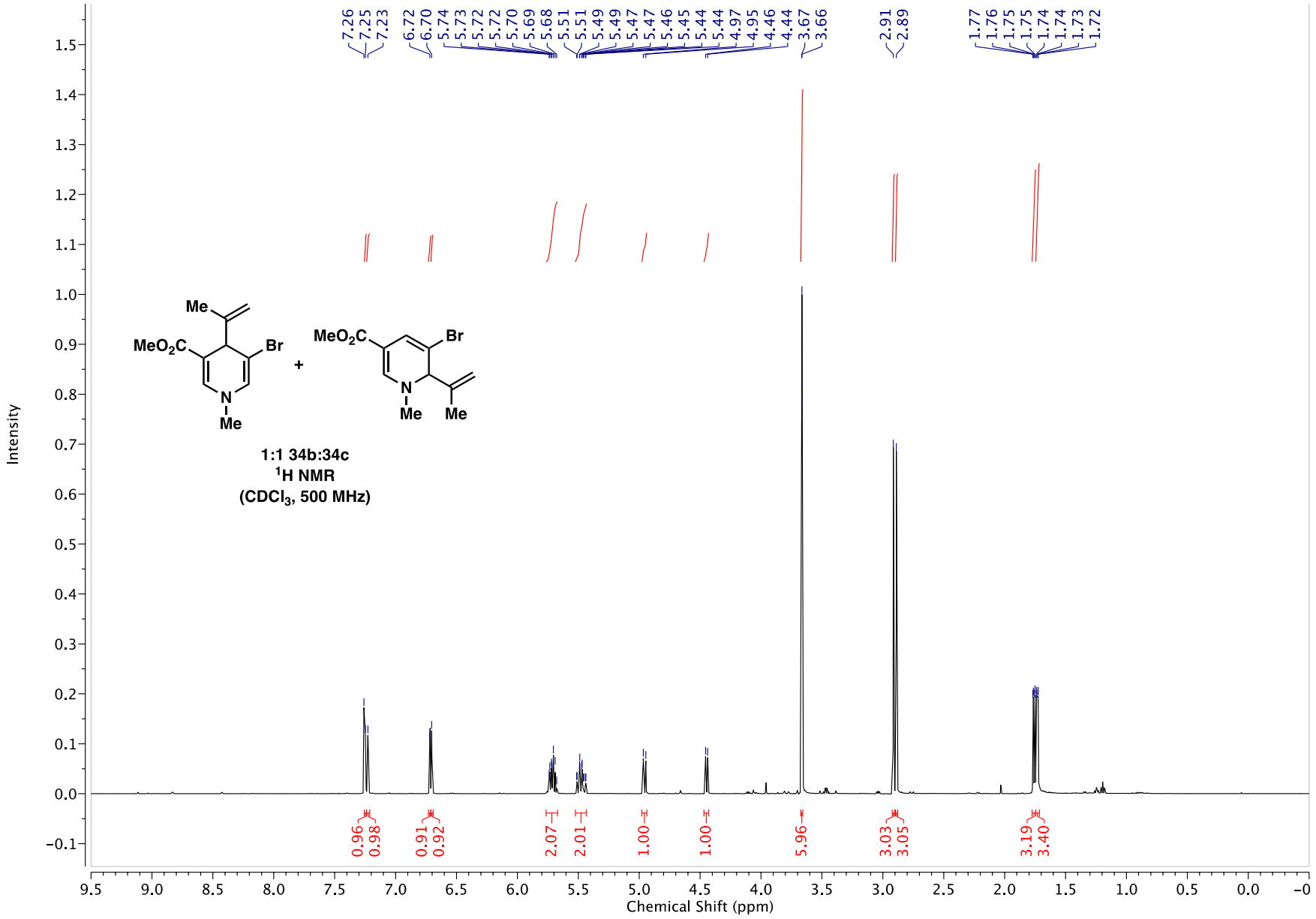

MeO2C
Br
N
Me
32c
13C NMR
(CDCl3, 126 MHz)
165.95
145.49
132.16
124.30
118.71
103.97
96.73
77.16
68.92
50.91
41.41
Intensity
Chemical Shift (ppm)

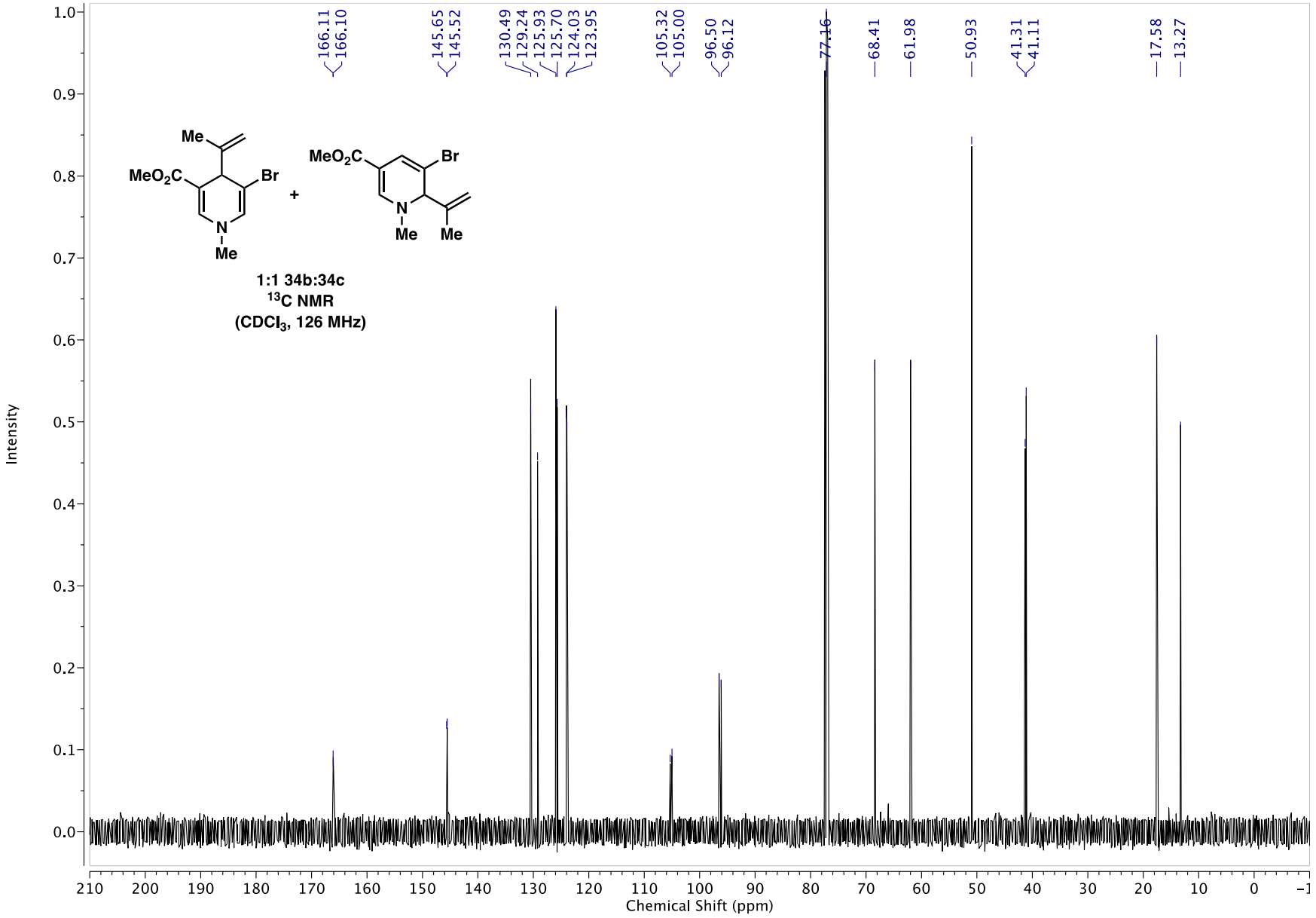

Me
MeO2C
Br
N
Me
33b
1H NMR
(CDCl3, 500 MHz)
7.26
7.13
7.13
6.56
6.56
6.56
4.94
4.87
4.87
4.87
4.87
4.73
4.73
4.73
4.72
4.72
3.69
2.94
1.77
1.77
1.77
1.77
0.66
0.88
0.95
1.05
1.00
3.04
3.19
3.16
Intensity
Chemical Shift (ppm)

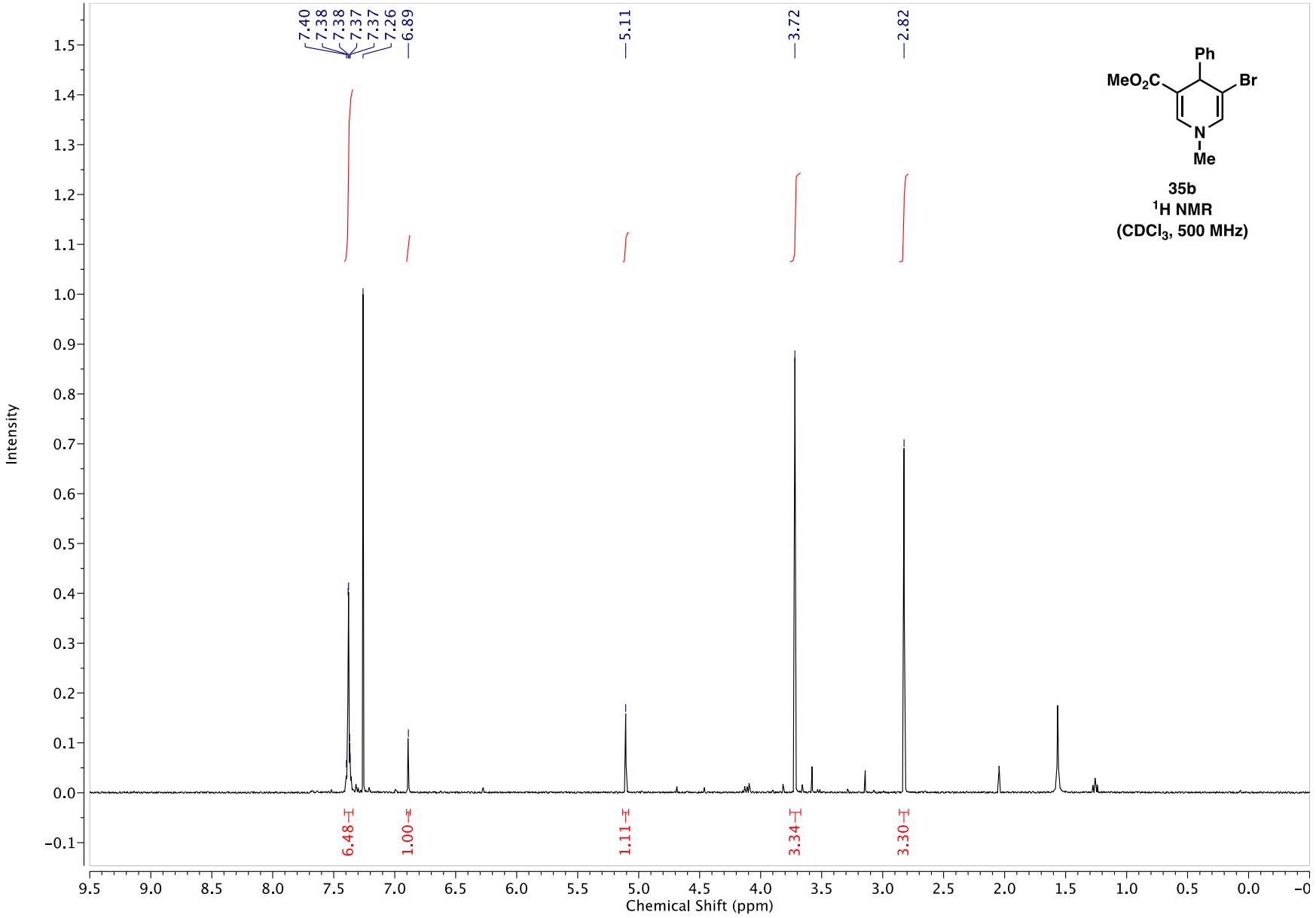

166.23
143.42
141.66
112.83
108.79
82.66
77.16
62.96
51.52
41.50
17.73
Me
MeO2C
Br
N
Me
33b
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

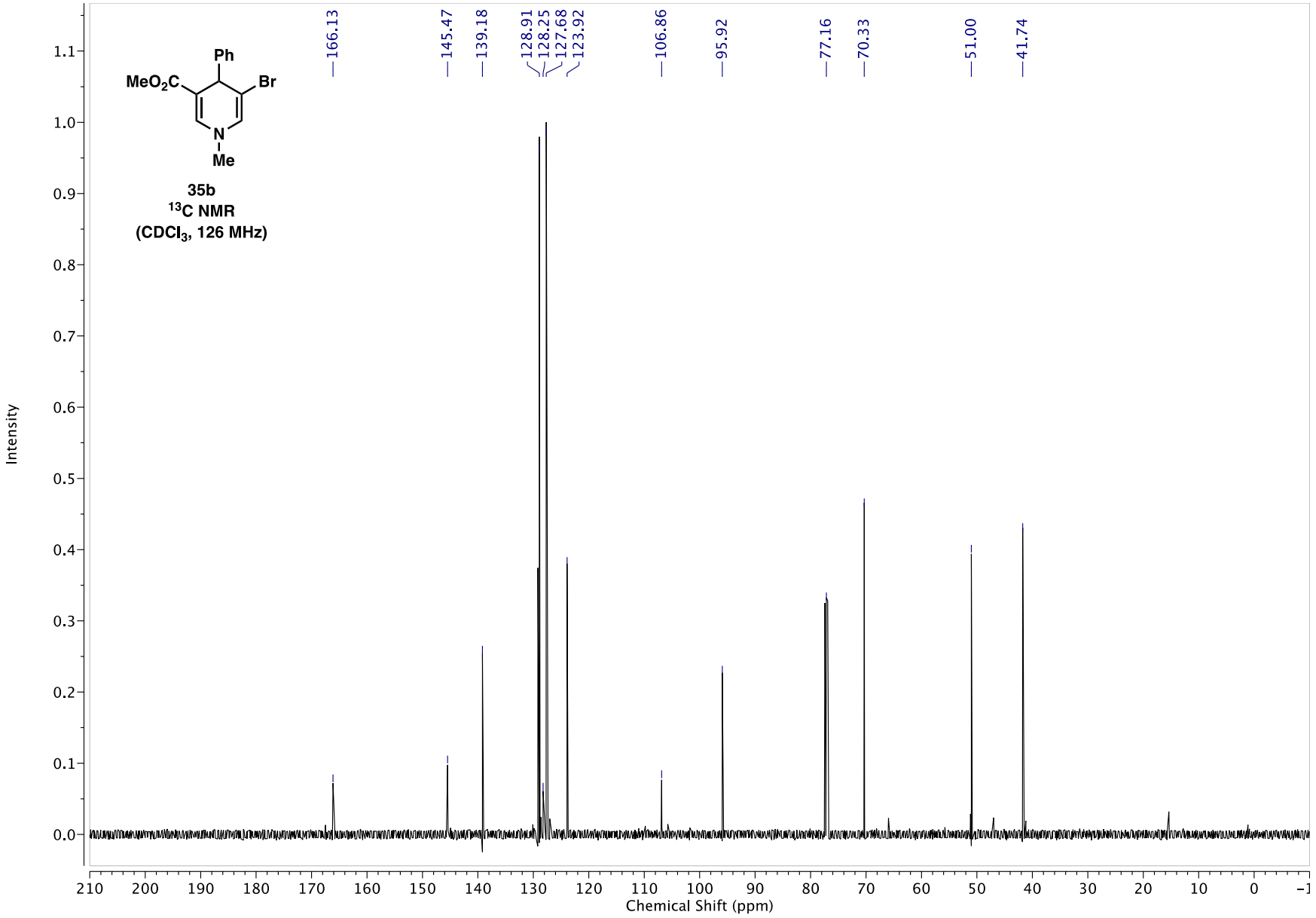

MeO2C
Br
N
Me
Me
33c
1H NMR
(CDCl3, 400 MHz)
7.36
7.26
6.83
4.98
4.94
4.94
4.94
4.93
4.93
4.68
3.68
2.85
1.76
1.00
0.97
1.03
1.07
1.00
3.17
3.10
3.15
Intensity
Chemical Shift (ppm)

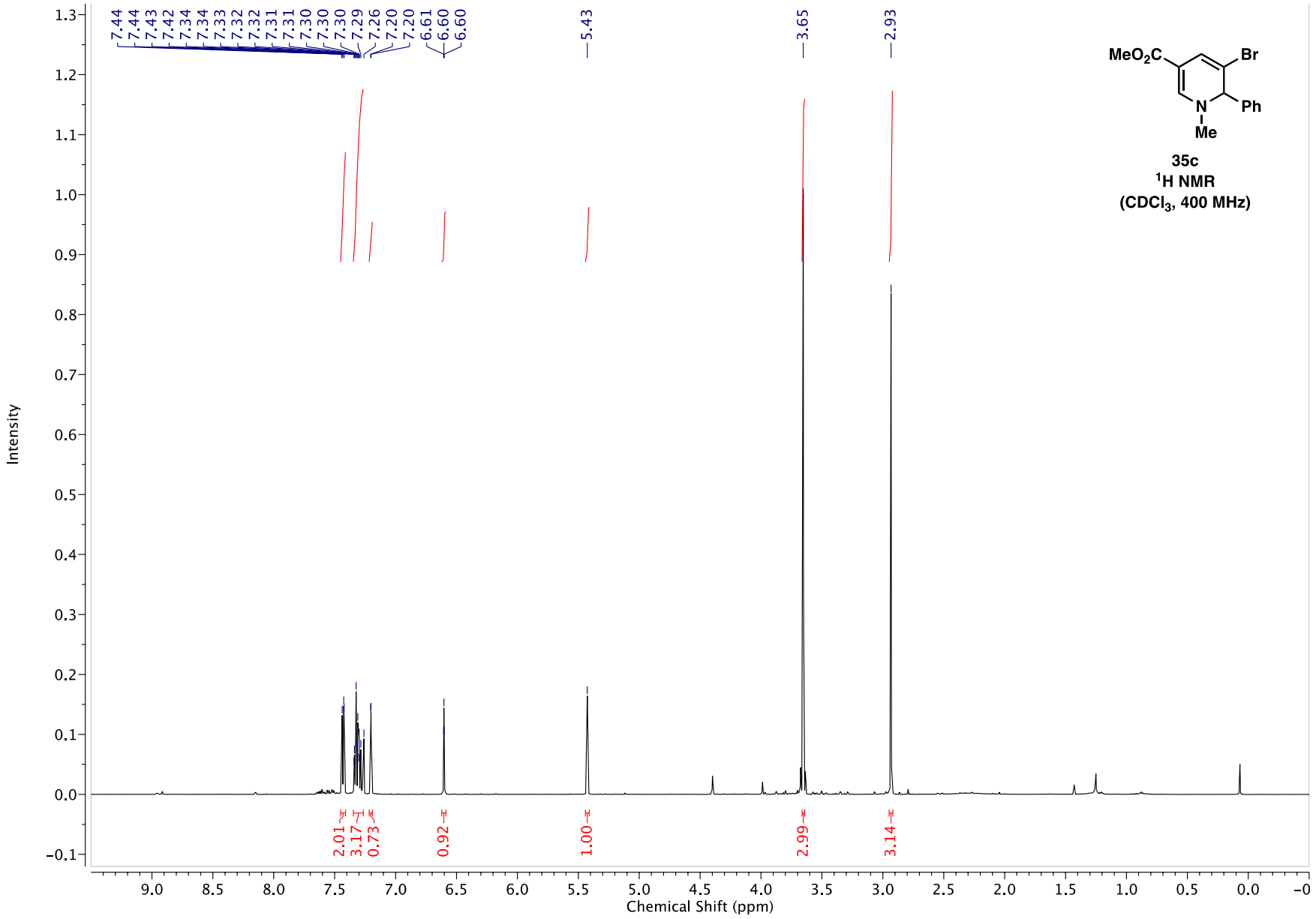

166.00
146.31
140.13
125.34
116.07
105.13
95.65
77.16
72.90
50.86
41.31
16.13
MeO2C
Br
N
Me
Me
33c
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

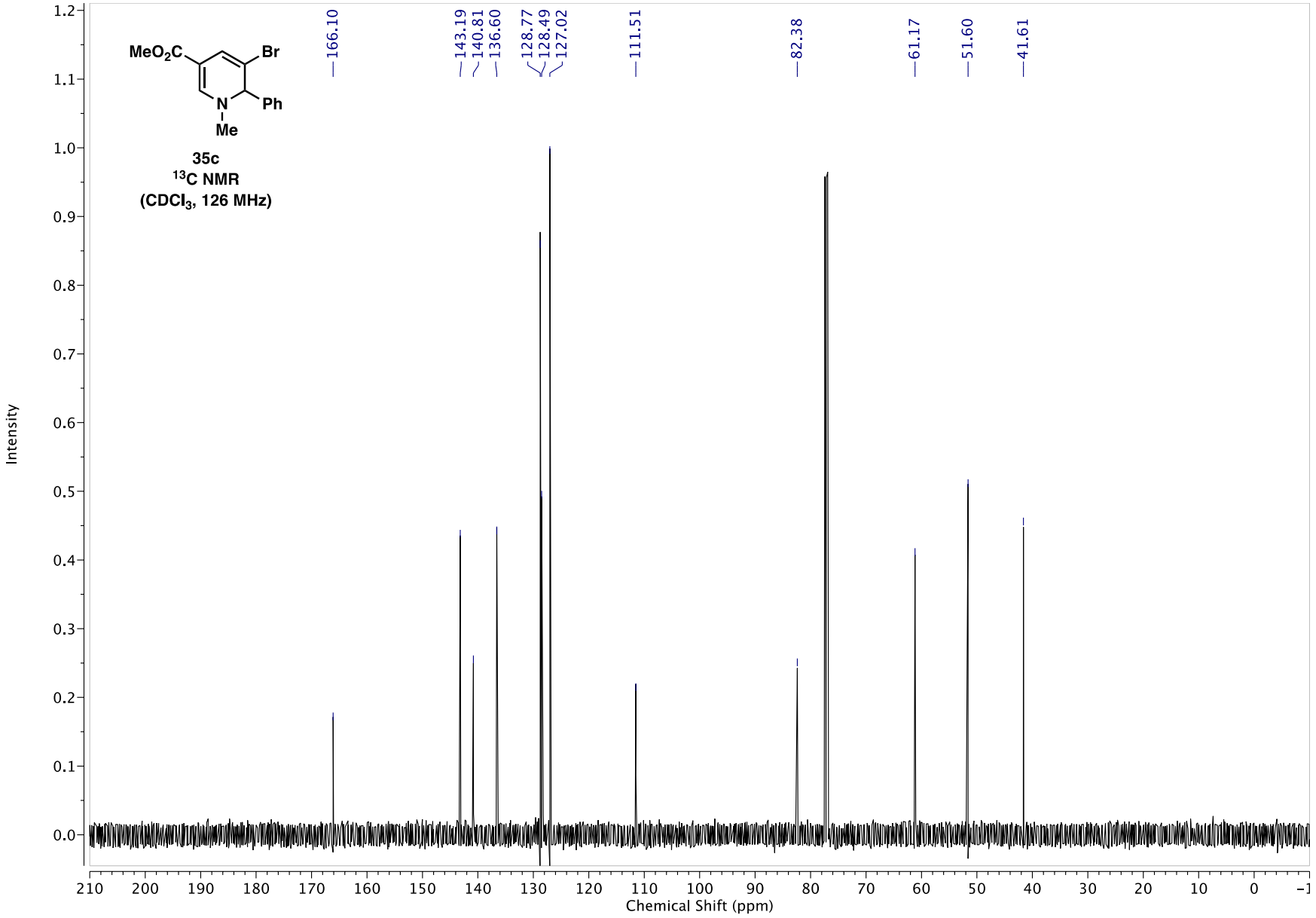

7.26
7.25
7.23
6.72
6.70
5.74
5.73
5.72
5.72
5.70
5.69
5.68
5.51
5.51
5.49
5.49
5.47
5.47
5.46
5.45
5.44
5.44
4.97
4.95
4.46
4.44
3.67
3.66
2.91
2.89
1.77
1.76
1.75
1.75
1.74
1.74
1.73
1.72
Me
MeO2C
Br
N
Me
+
MeO2C
Br
N
Me
Me
1:1 34b:34c
1H NMR
(CDCl3, 500 MHz)
Intensity
Chemical Shift (ppm)
0.96
0.98
0.91
0.92
2.07
2.01
1.00
1.00
5.96
3.03
3.05
3.19
3.40

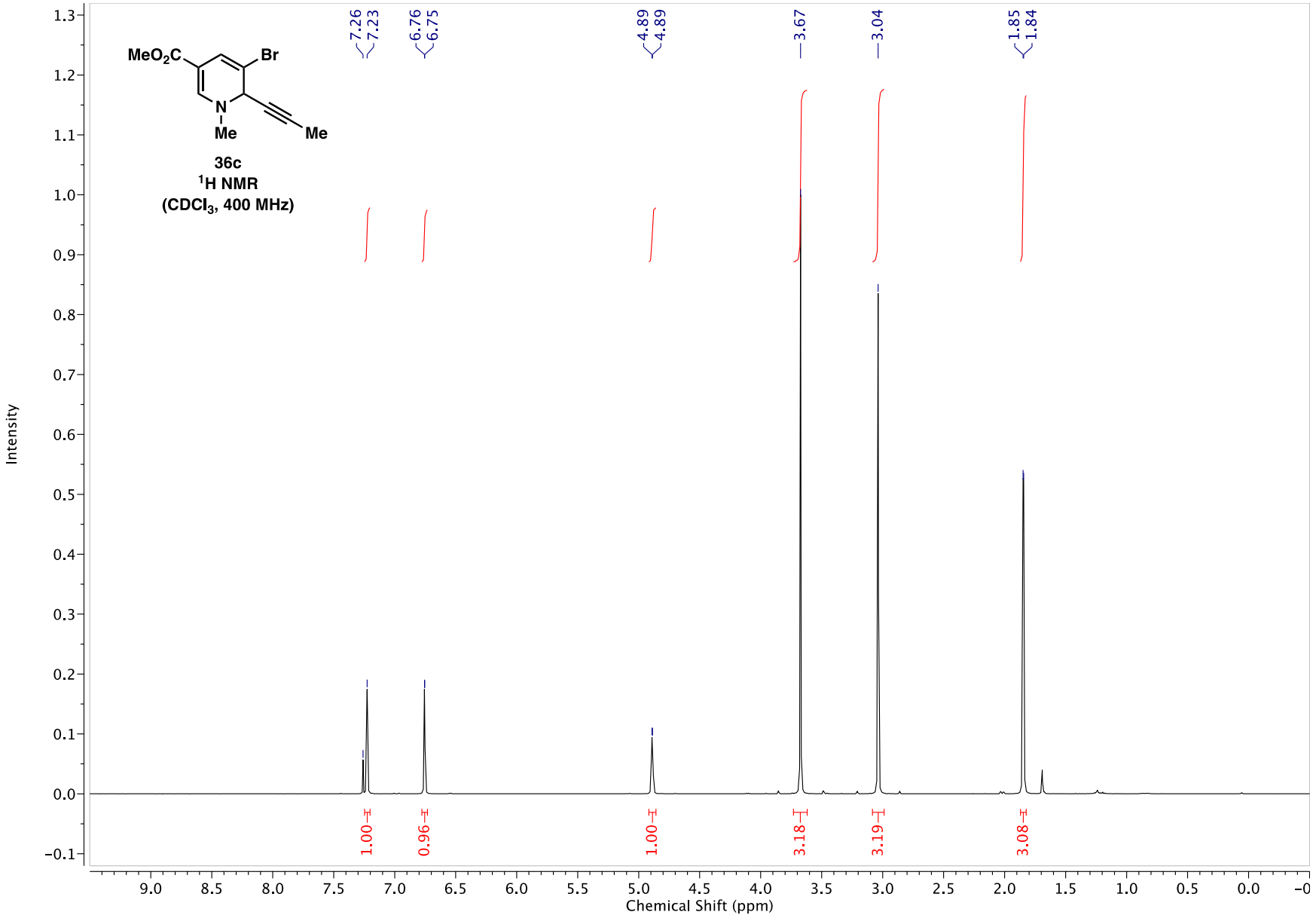

166.11
166.10
145.65
145.52
130.49
129.24
125.93
125.70
124.03
123.95
105.32
105.00
96.50
96.12
77.16
68.41
61.98
50.93
41.31
41.11
17.58
13.27
Me
MeO2C
Br
N
Me
+
MeO2C
Br
N
Me
Me
1:1 34b:34c
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

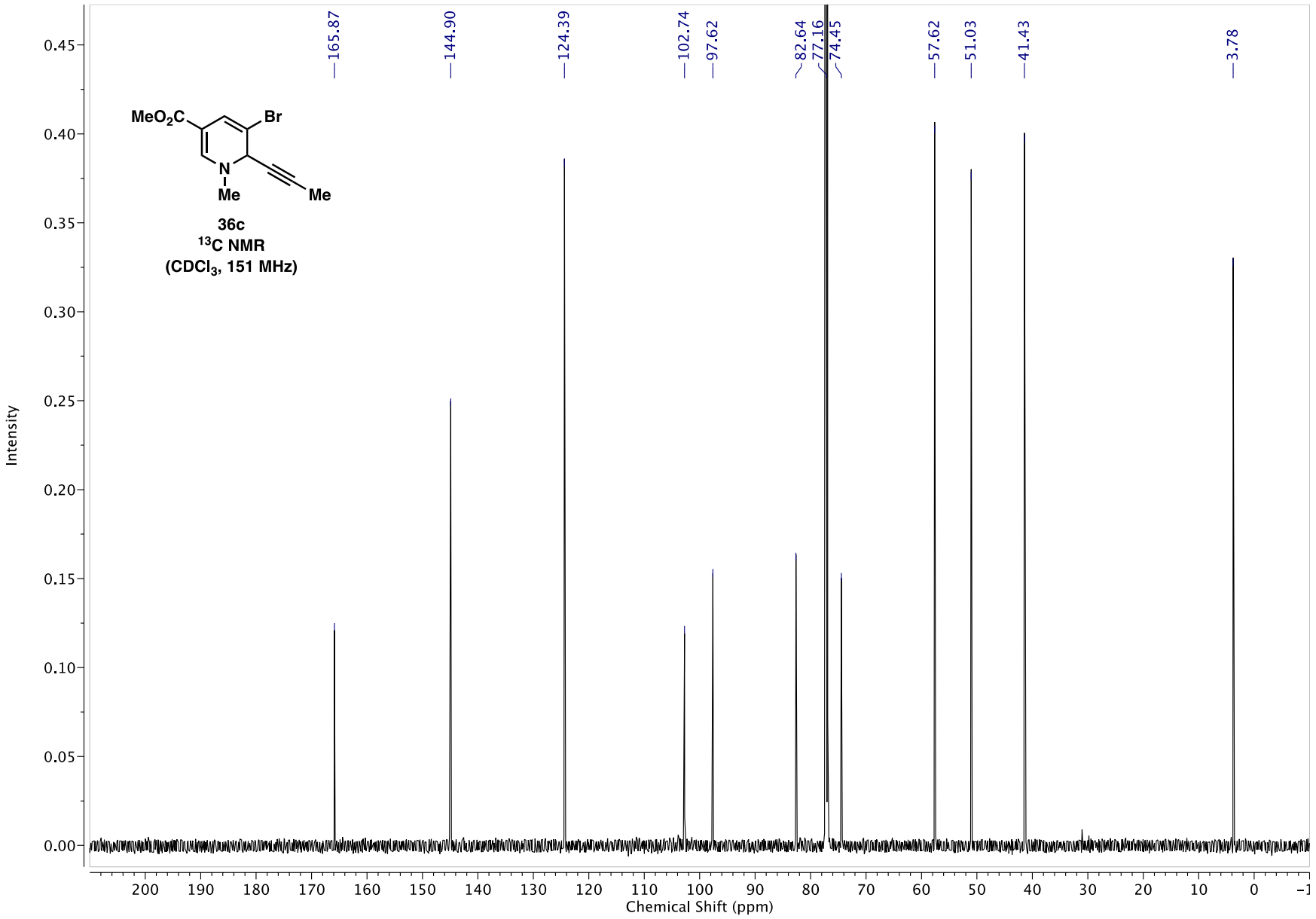

7.40
7.38
7.38
7.37
7.37
7.26
6.89
5.11
3.72
2.82
Ph
MeO2C
Br
N
Me
35b
1H NMR
(CDCl3, 500 MHz)
Intensity
Chemical Shift (ppm)
6.48
1.00
1.11
3.34
3.30

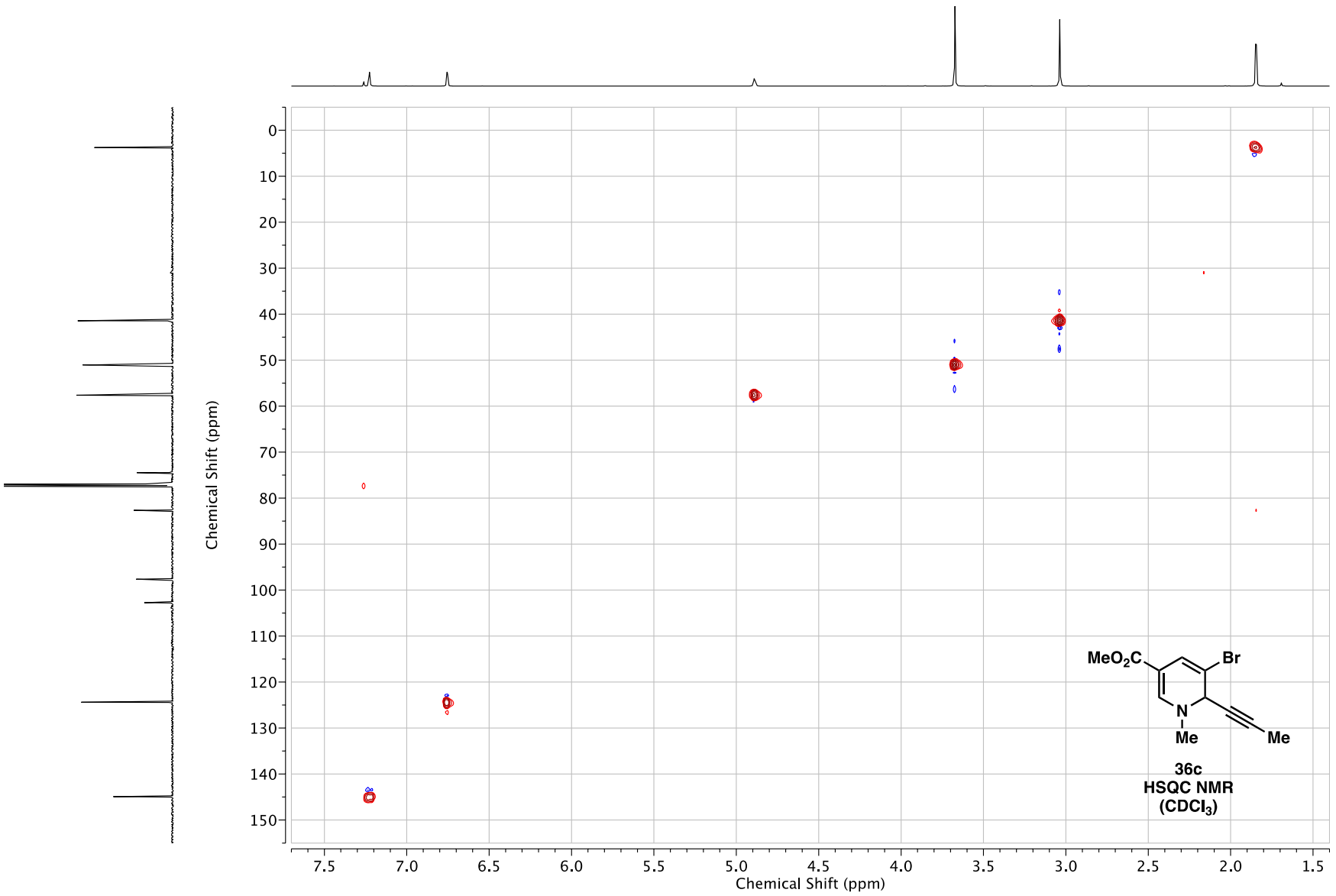

166.13
145.47
139.18
128.91
128.25
127.68
123.92
106.86
95.92
77.16
70.33
51.00
41.74
Ph
MeO2C
Br
N
Me
35b
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

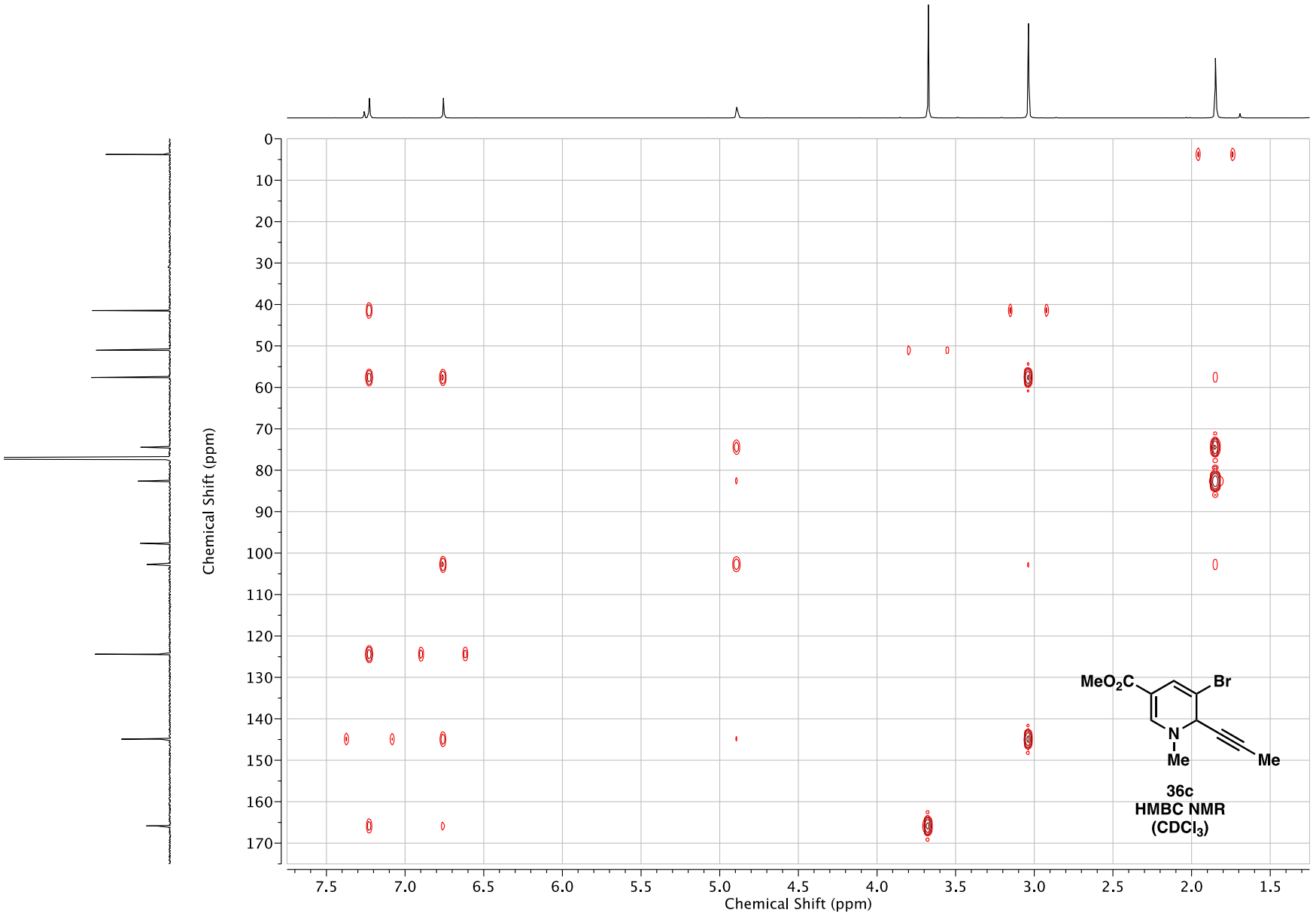

7.44
7.44
7.43
7.42
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.30
7.29
7.26
7.20
7.20
6.61
6.60
6.60
5.43
3.65
2.93
MeO2C
Br
N
Ph
Me
35c
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)
2.01
3.17
0.73
0.92
1.00
2.99
3.14

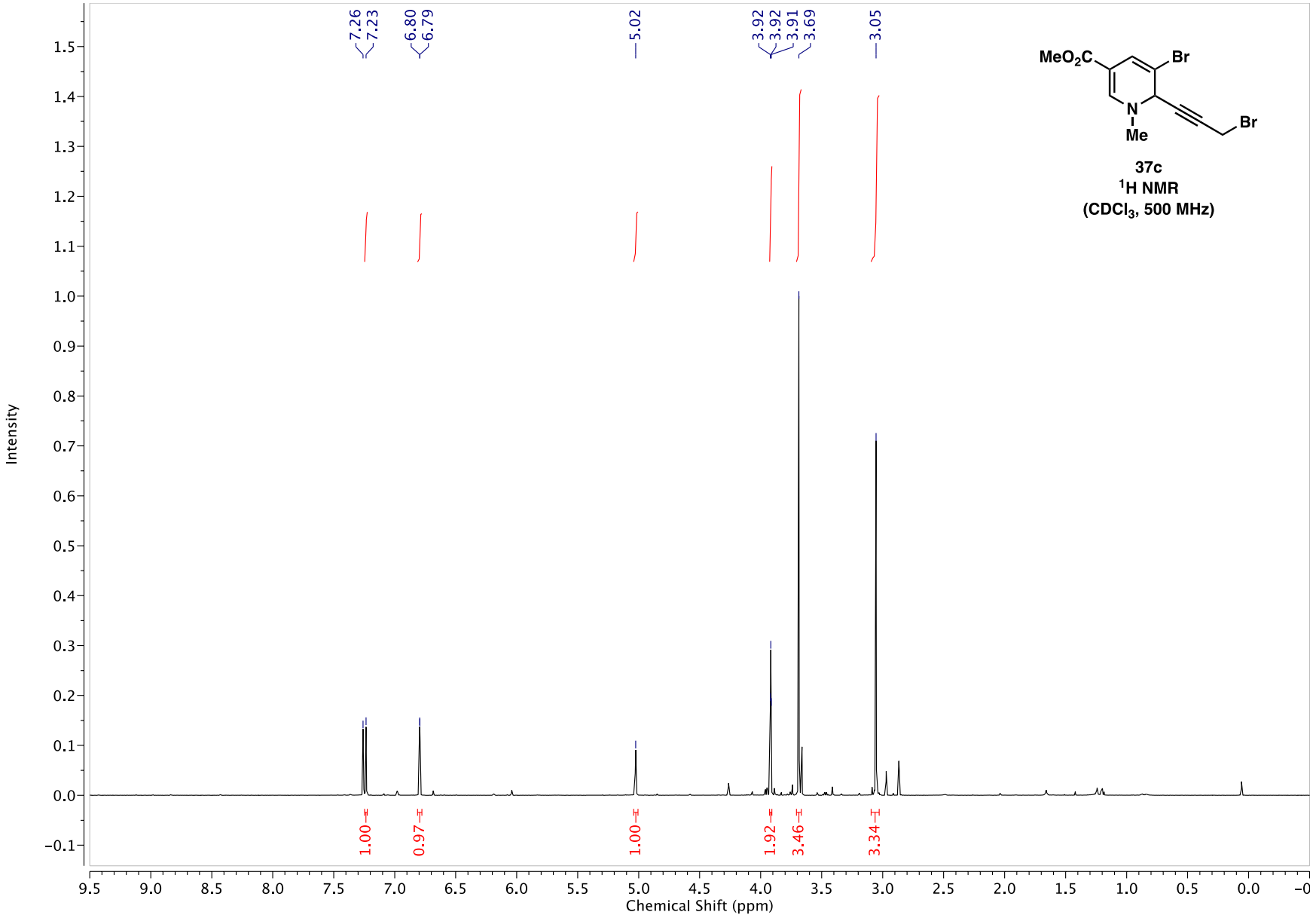

MeO2C
Br
N
Ph
Me
35c
13C NMR
(CDCl3, 126 MHz)
166.10
143.19
140.81
136.60
128.77
128.49
127.02
111.51
82.38
61.17
51.60
41.61
Intensity
Chemical Shift (ppm)

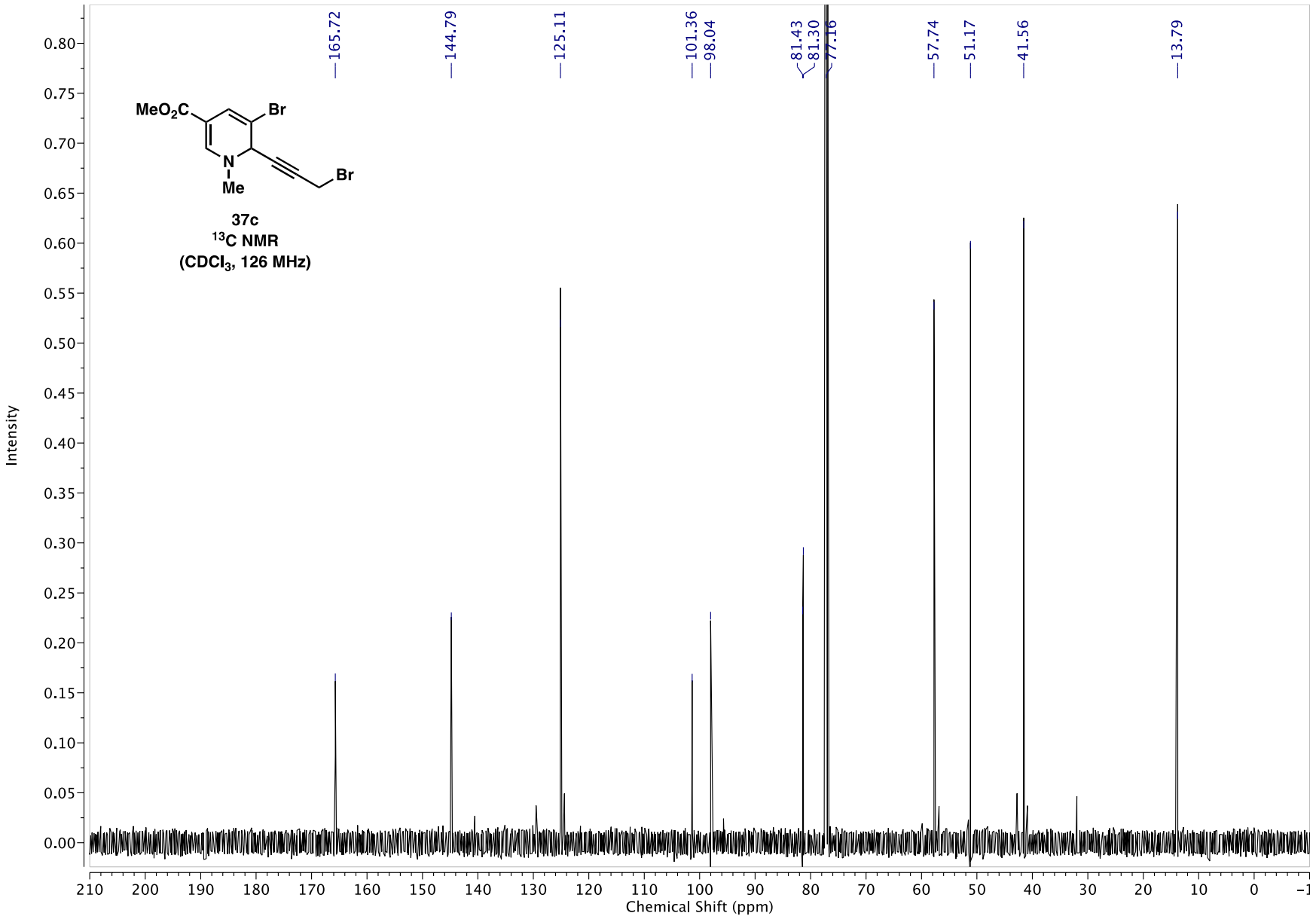

MeO2C
Br
N
Me
Me
36c
1H NMR
(CDCl3, 400 MHz)
7.26
7.23
6.76
6.75
4.89
4.89
3.67
3.04
1.85
1.84
1.00
0.96
1.00
3.18
3.19
3.08
Intensity
Chemical Shift (ppm)

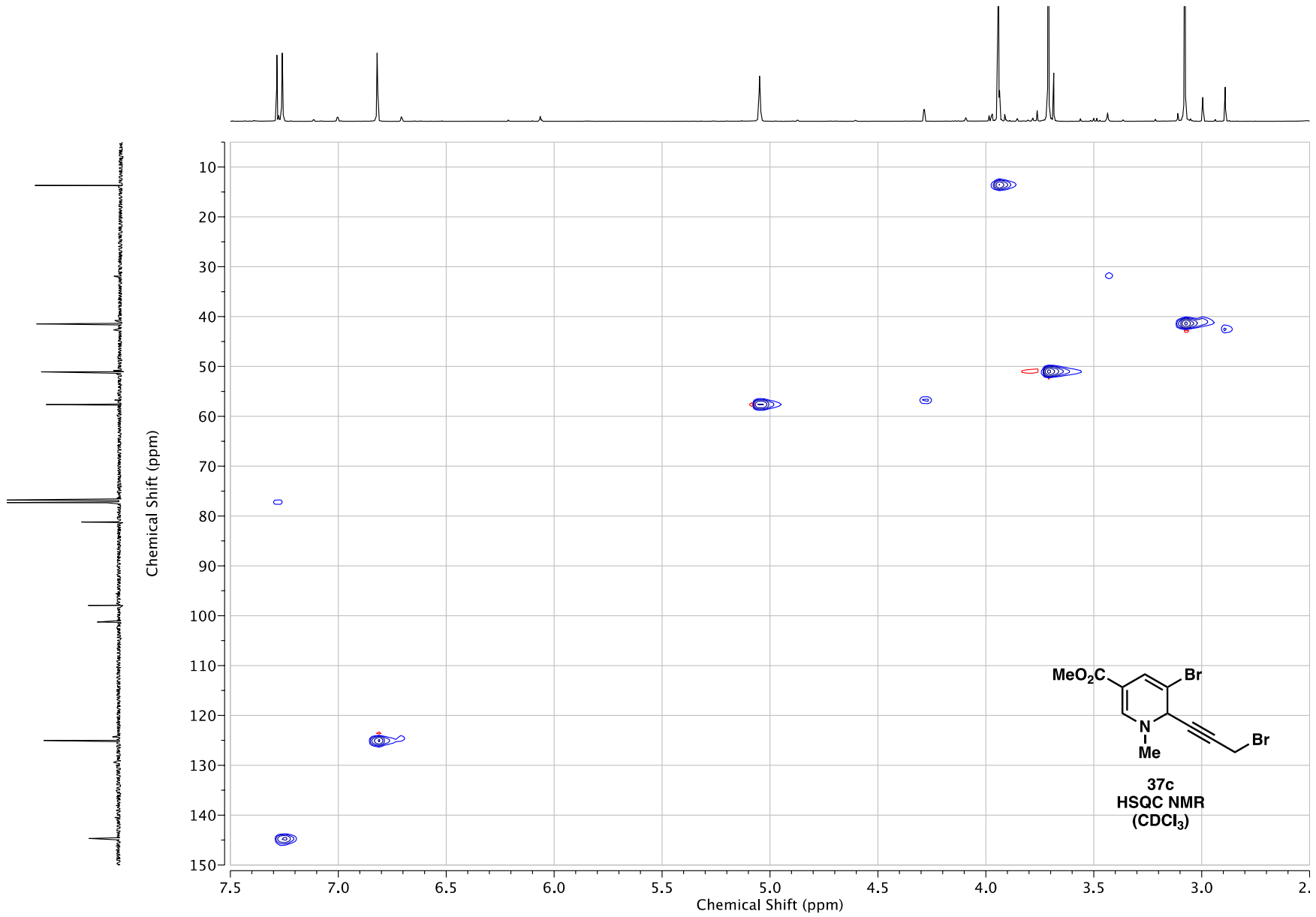

165.87
144.90
124.39
102.74
97.62
82.64
77.16
74.45
57.62
51.03
41.43
3.78
MeO2C
Br
N
Me
Me
36c
13C NMR
(CDCl3, 151 MHz)
Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

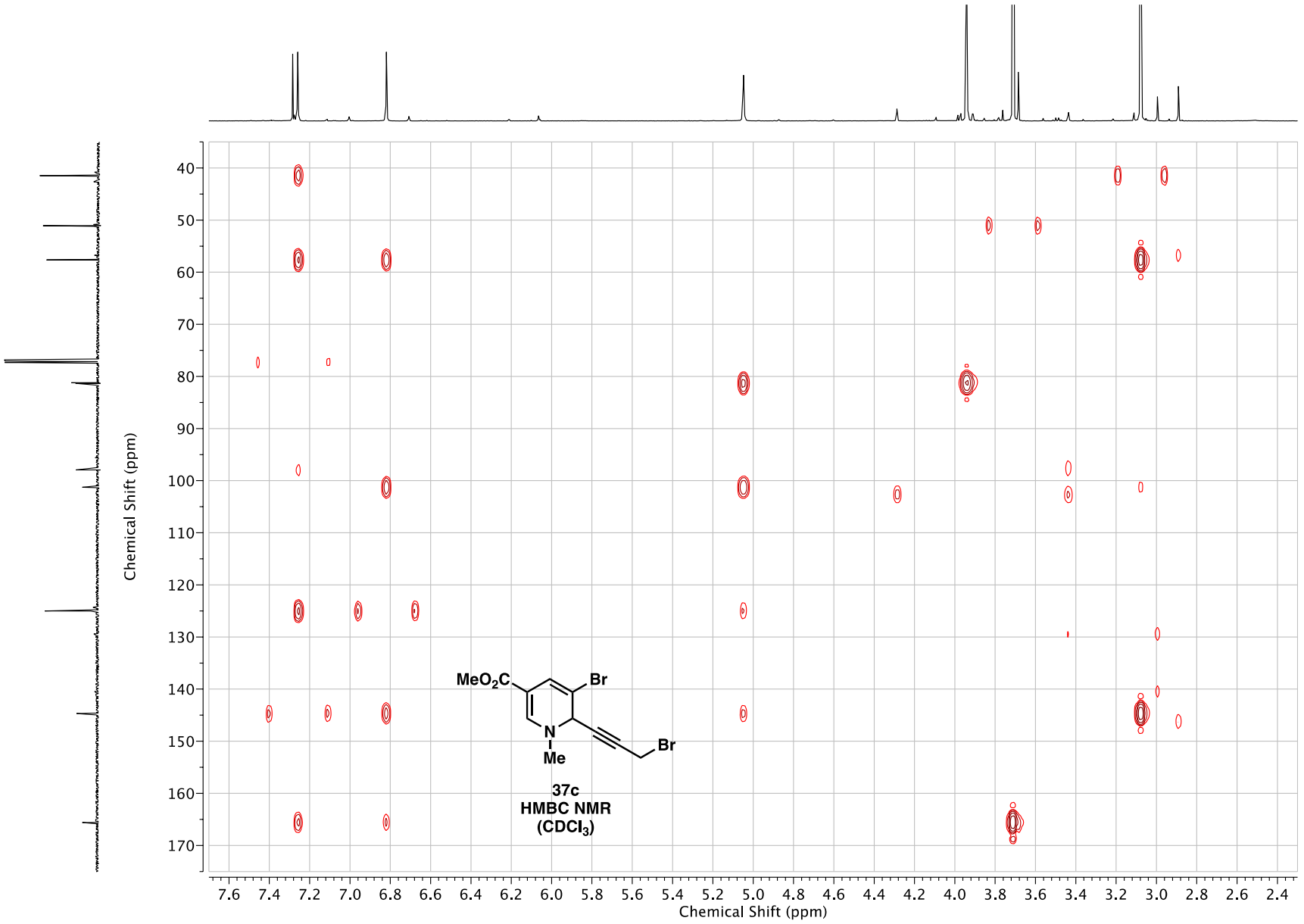

Chemical Shift (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)
MeO2C
Br
N
Me
Me
36c
HSQC NMR
(CDCl3)

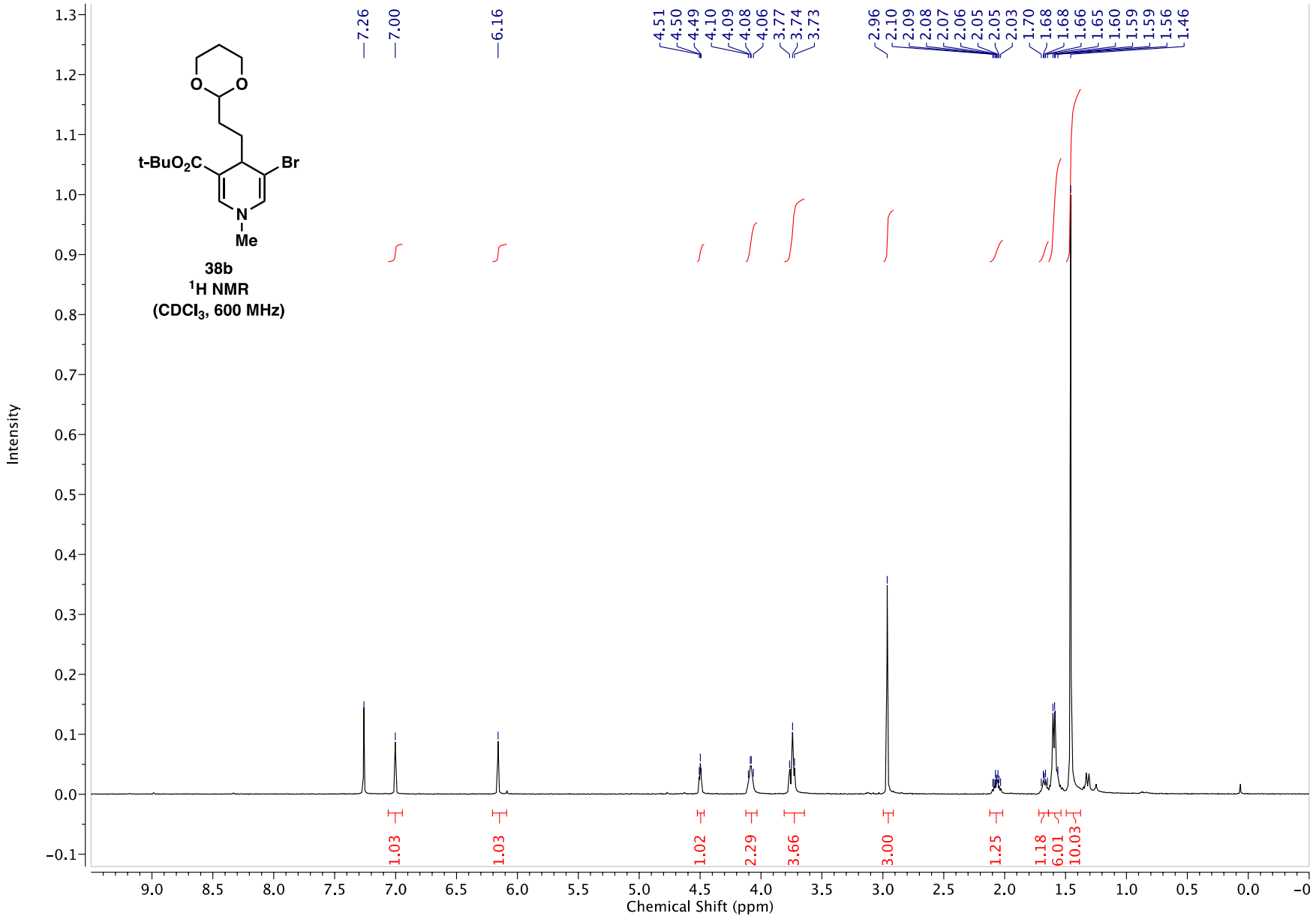

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
Me
36c
HMBC NMR
(CDCl3)

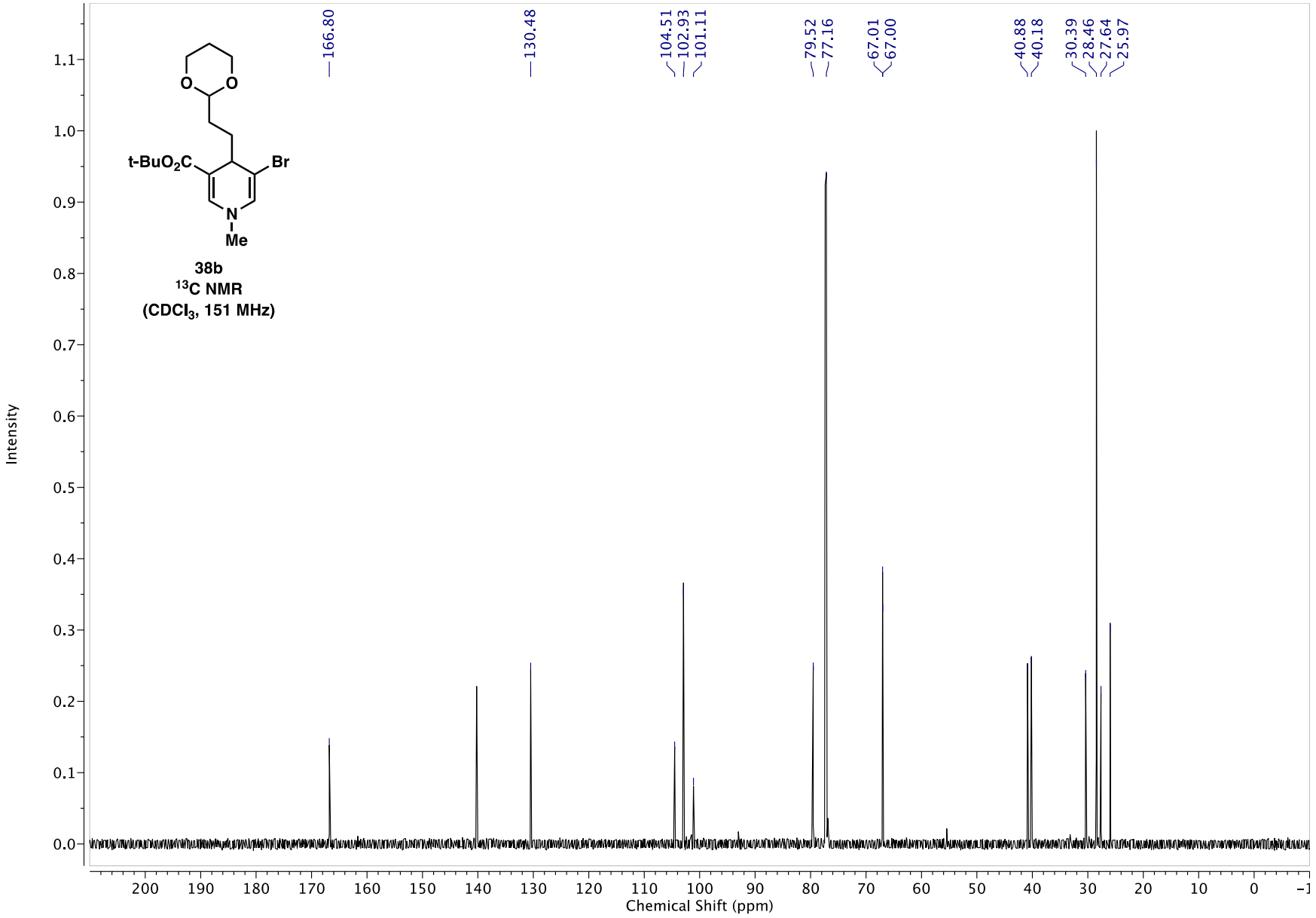

7.26
7.23
6.80
6.79
5.02
3.92
3.92
3.91
3.69
3.05
MeO2C
Br
N
Me
Br
37c
1H NMR
(CDCl3, 500 MHz)
Intensity
1.00
0.97
1.00
1.92
3.46
3.34
Chemical Shift (ppm)

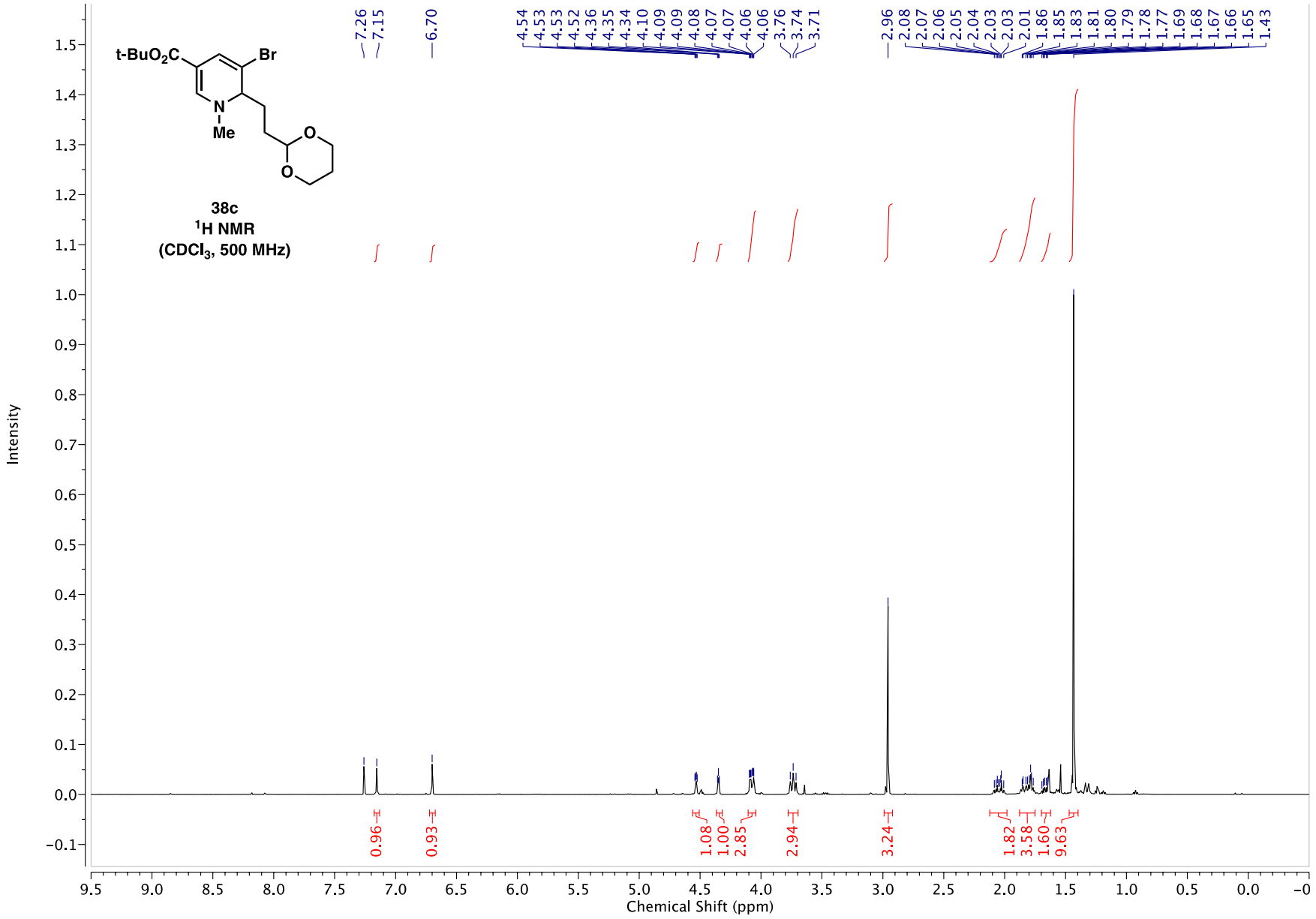

165.72
144.79
125.11
101.36
98.04
81.43
81.30
77.16
57.74
51.17
41.56
13.79
MeO2C
Br
N
Me
Br
37c
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

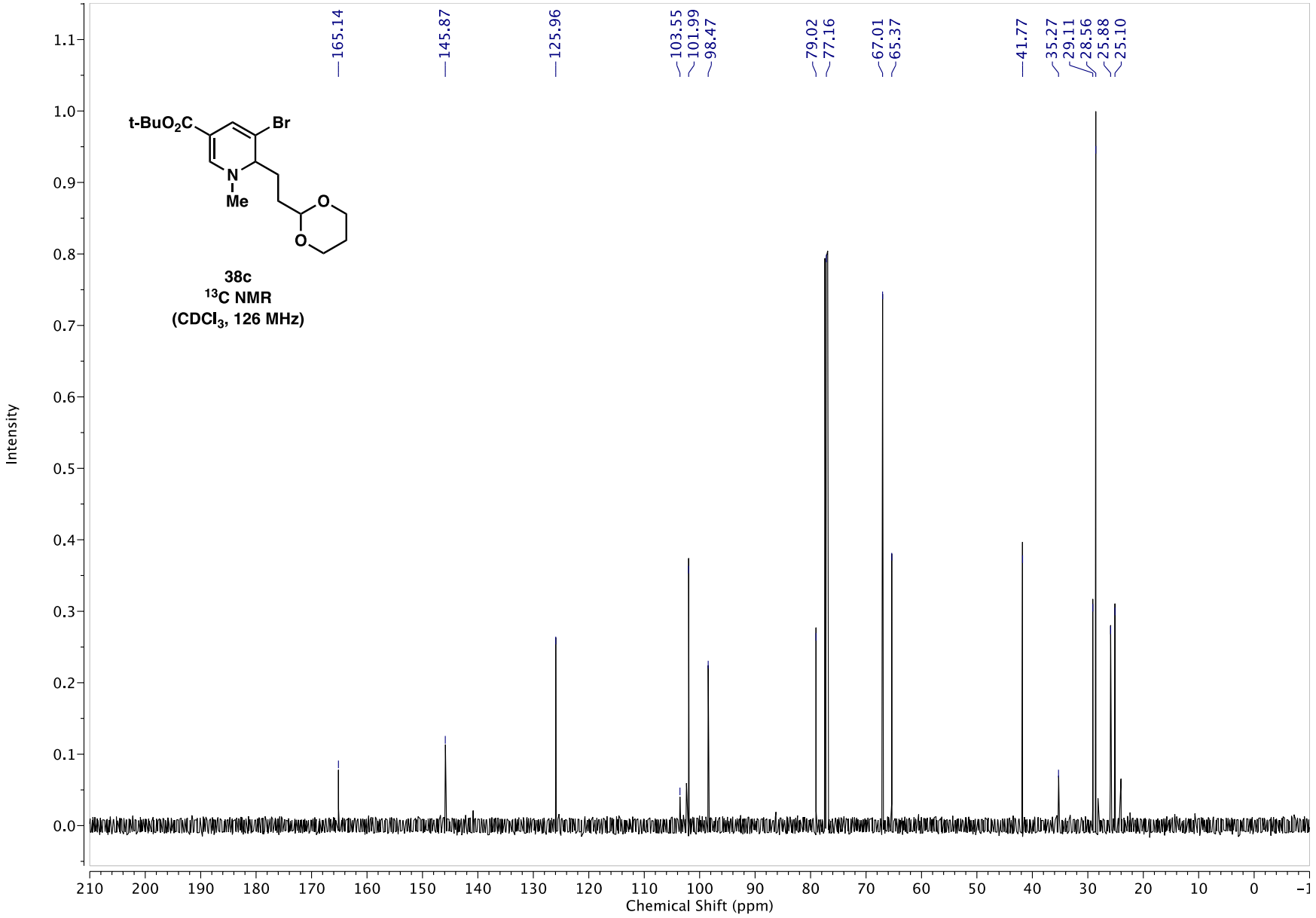

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
Br
37c
HSQC NMR
(CDCl3)

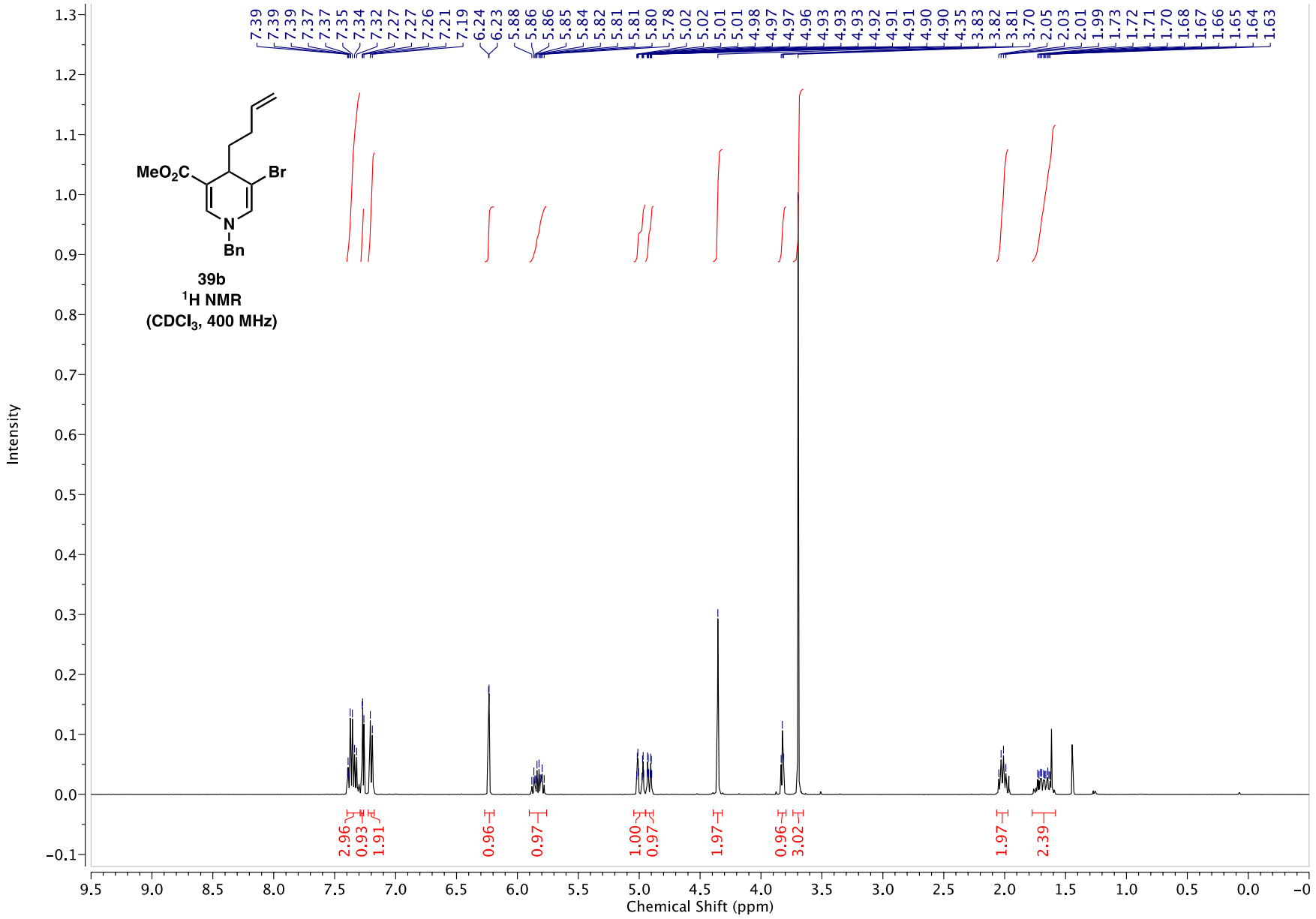

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
Br
N
Me
Br
37c
HMBC NMR
(CDCl3)

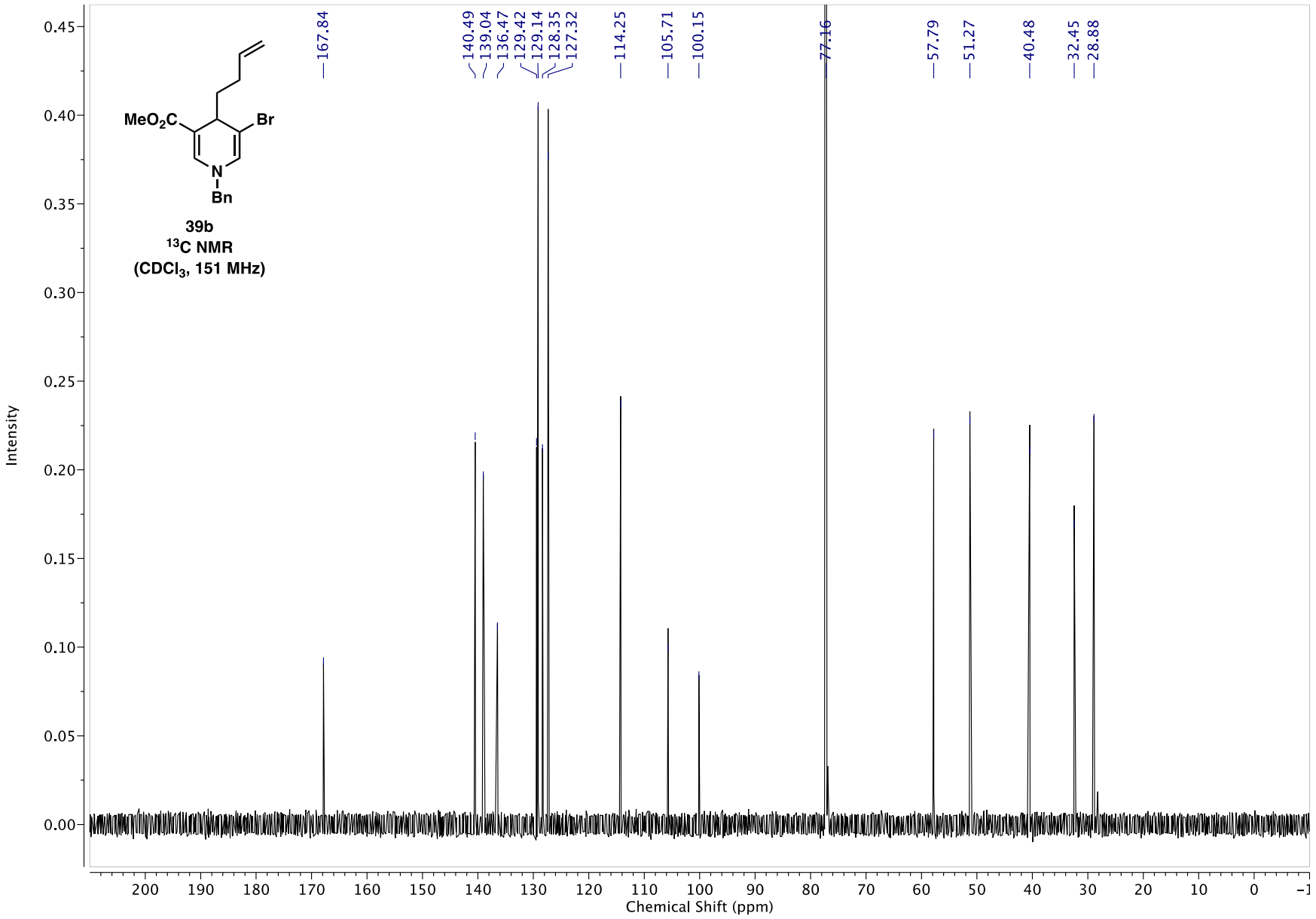

38b
1H NMR
(CDCl3, 600 MHz)
t-BuO2C
Br
N
Me
Intensity
Chemical Shift (ppm)
7.26
7.00
6.16
4.51
4.50
4.49
4.10
4.09
4.08
4.06
3.77
3.74
3.73
2.96
2.10
2.09
2.08
2.07
2.06
2.05
2.05
2.03
1.70
1.68
1.68
1.66
1.65
1.60
1.59
1.59
1.56
1.46
1.03
1.03
1.02
2.29
3.66
3.00
1.25
1.18
6.01
10.03

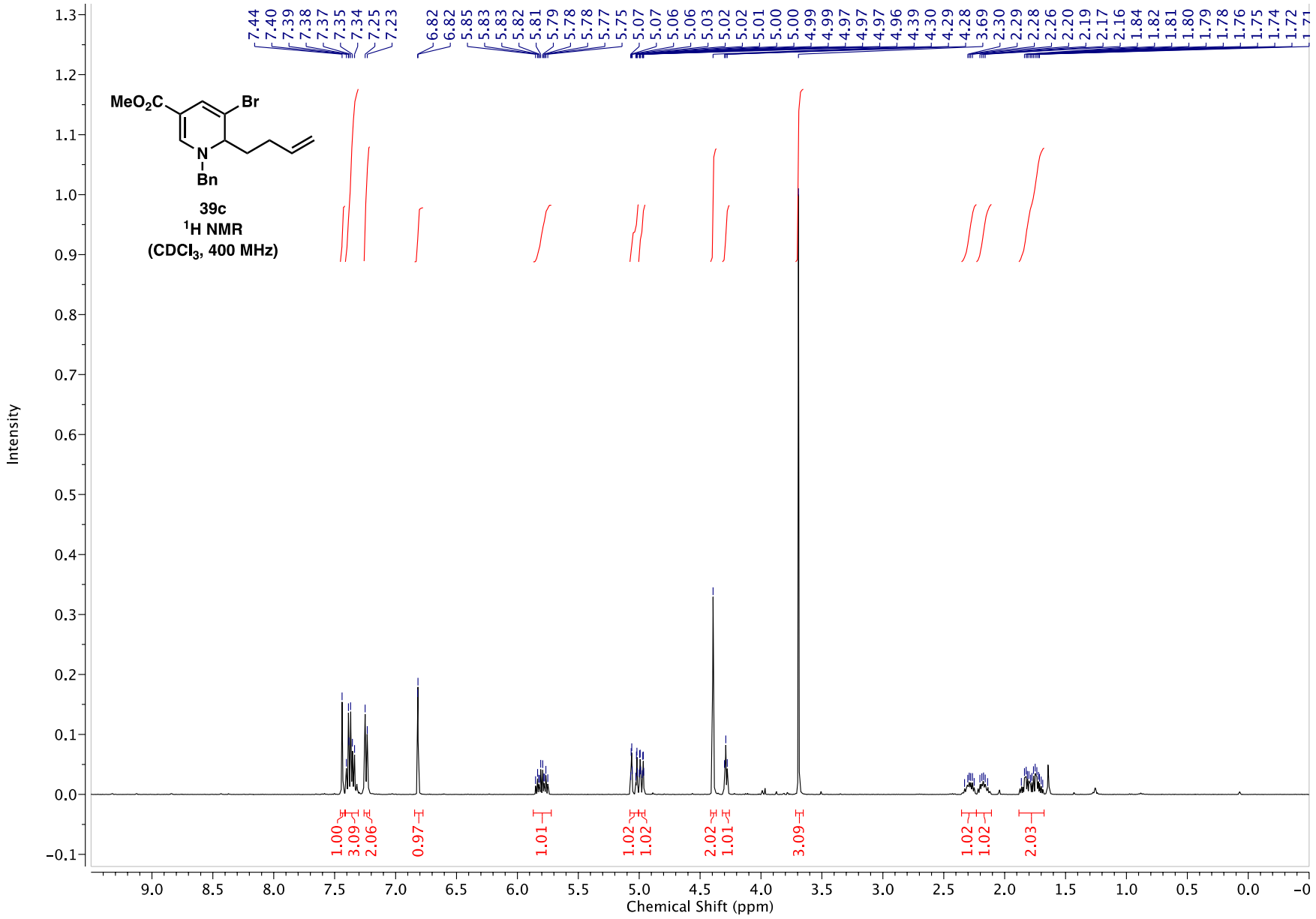

166.80
130.48
104.51
102.93
101.11
79.52
77.16
67.01
67.00
40.88
40.18
30.39
28.46
27.64
25.97
t-BuO2C
Br
N
Me
38b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

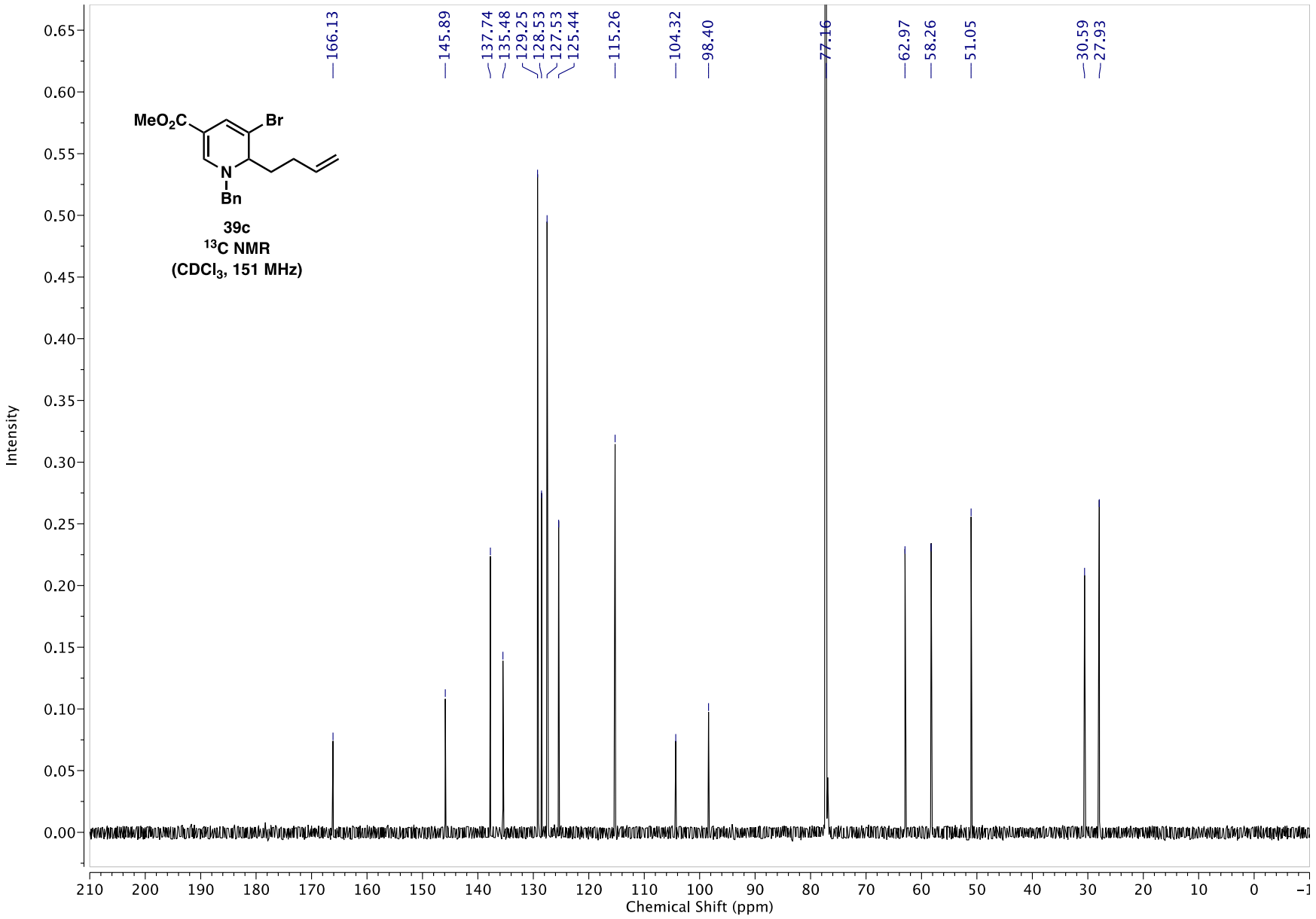

t-BuO2C
Br
N
Me
O
O
38c
1H NMR
(CDCl3, 500 MHz)
7.26
7.15
6.70
4.54
4.53
4.53
4.52
4.36
4.35
4.34
4.10
4.09
4.09
4.08
4.07
4.07
4.06
4.06
3.76
3.74
3.71
2.96
2.08
2.07
2.06
2.05
2.04
2.03
2.03
2.01
1.86
1.85
1.83
1.81
1.80
1.79
1.78
1.77
1.69
1.68
1.67
1.66
1.65
1.43
0.96
0.93
1.08
1.00
2.85
2.94
3.24
1.82
3.58
1.60
9.63
Intensity
Chemical Shift (ppm)

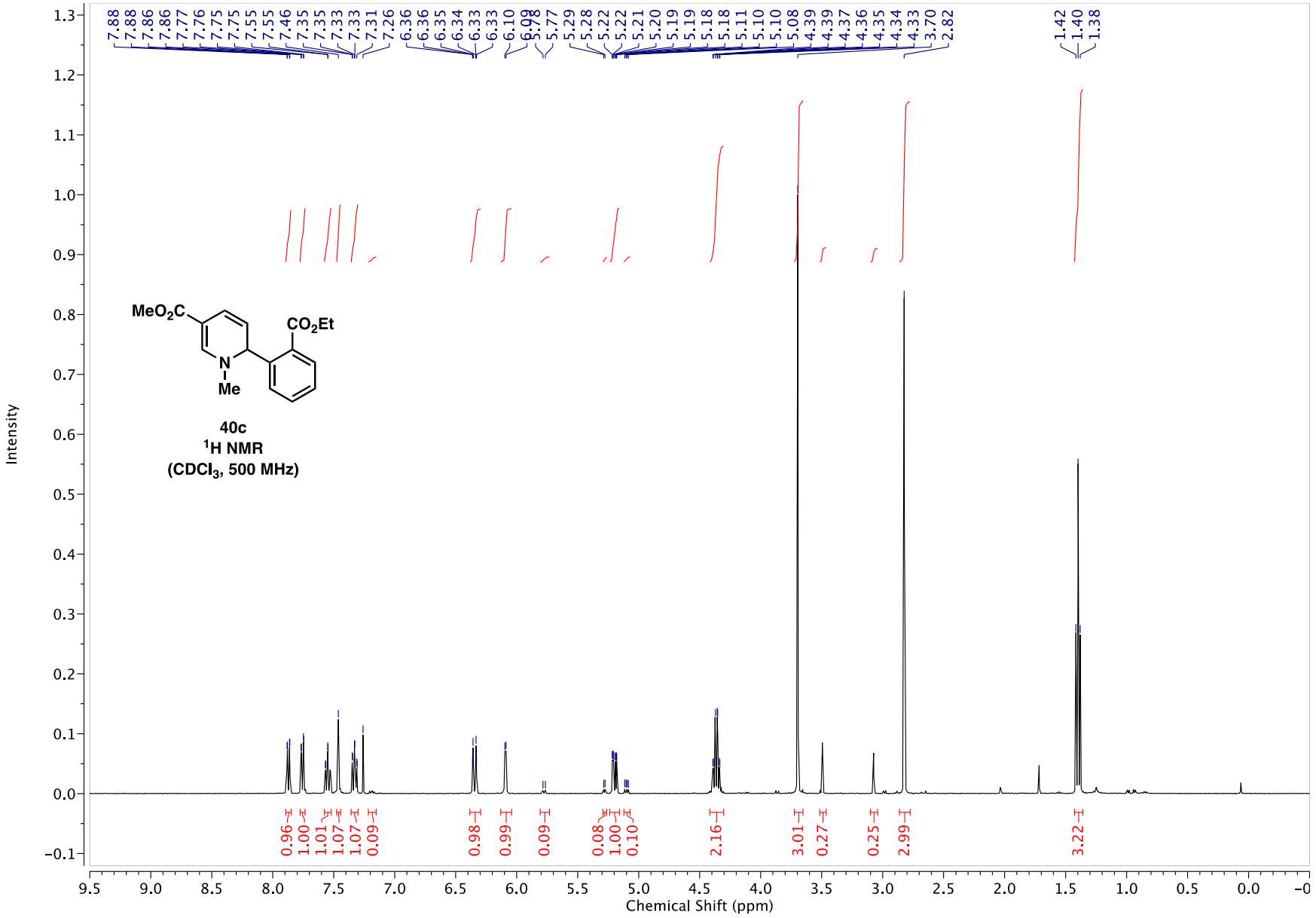

165.14
145.87
125.96
103.55
101.99
98.47
79.02
77.16
67.01
65.37
41.77
35.27
29.11
28.56
25.88
25.10
t-BuO2C
Br
N
Me
O
O
38c
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

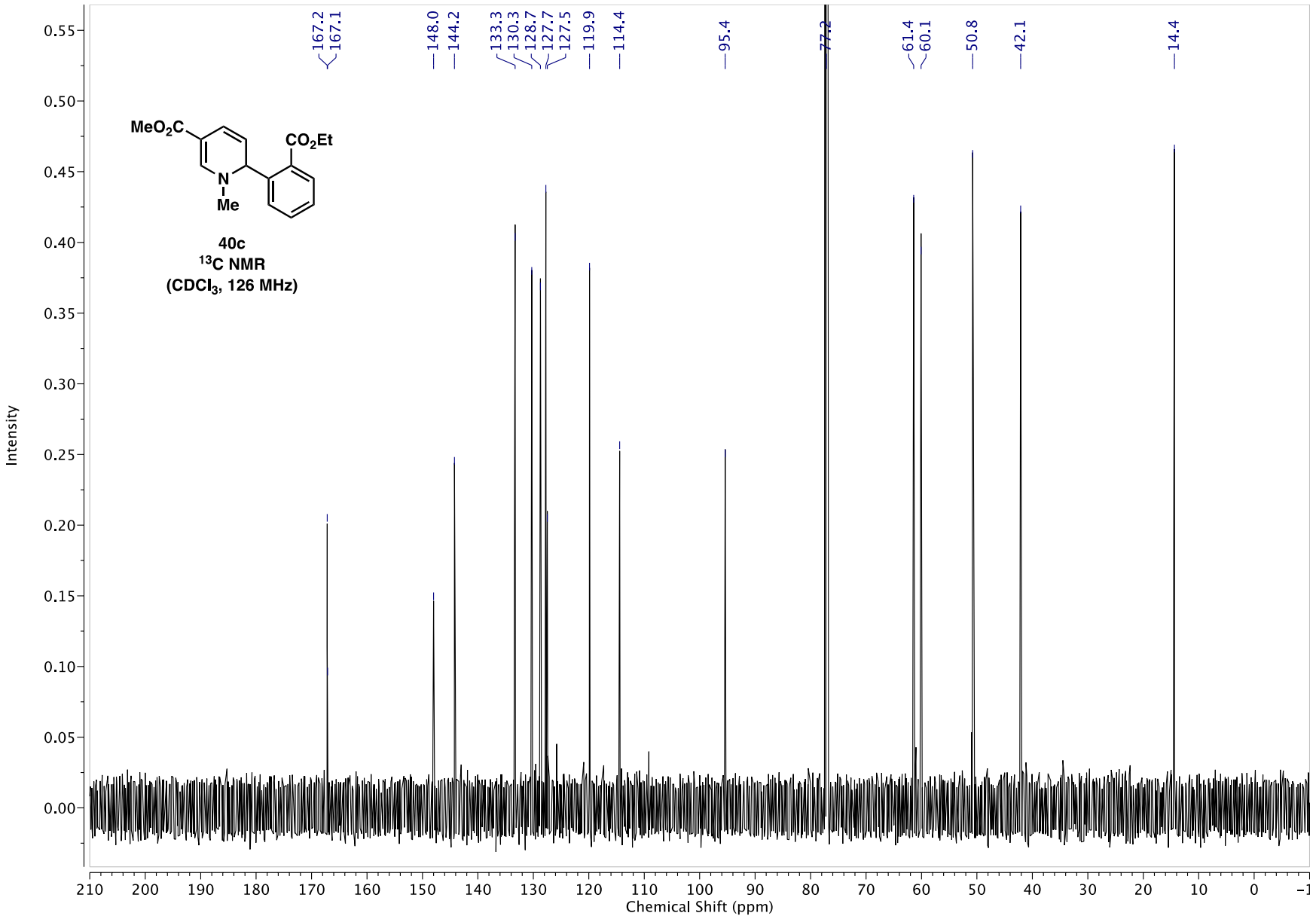

39b
1H NMR
(CDCl3, 400 MHz)
MeO2C
Br
N
Bn
Intensity
Chemical Shift (ppm)
2.96
0.93
1.91
0.96
0.97
1.00
0.97
1.97
0.96
3.02
1.97
2.39

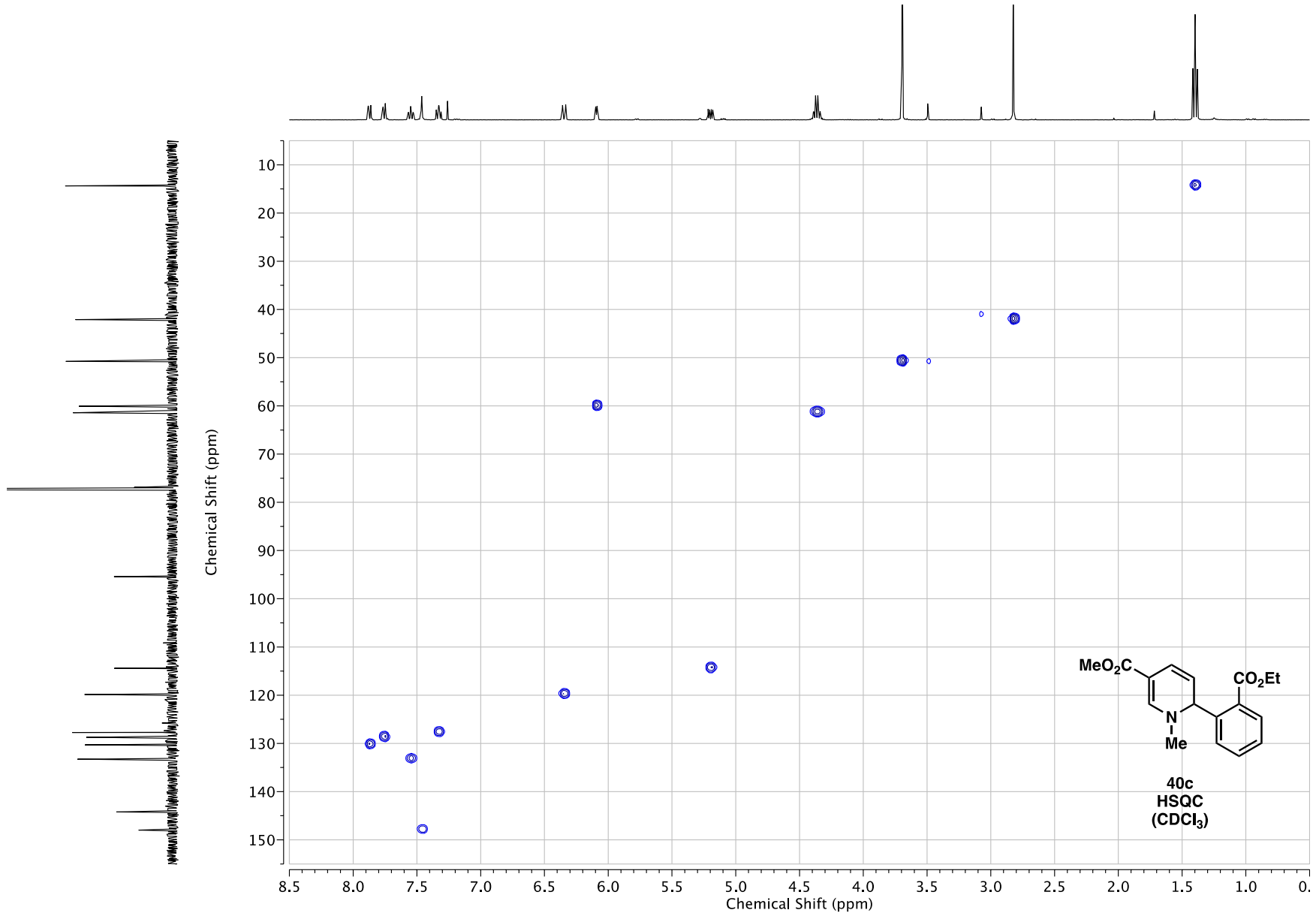

167.84
140.49
139.04
136.47
129.42
129.14
128.35
127.32
114.25
105.71
100.15
77.16
57.79
51.27
40.48
32.45
28.88
MeO2C
Br
N
Bn
39b
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

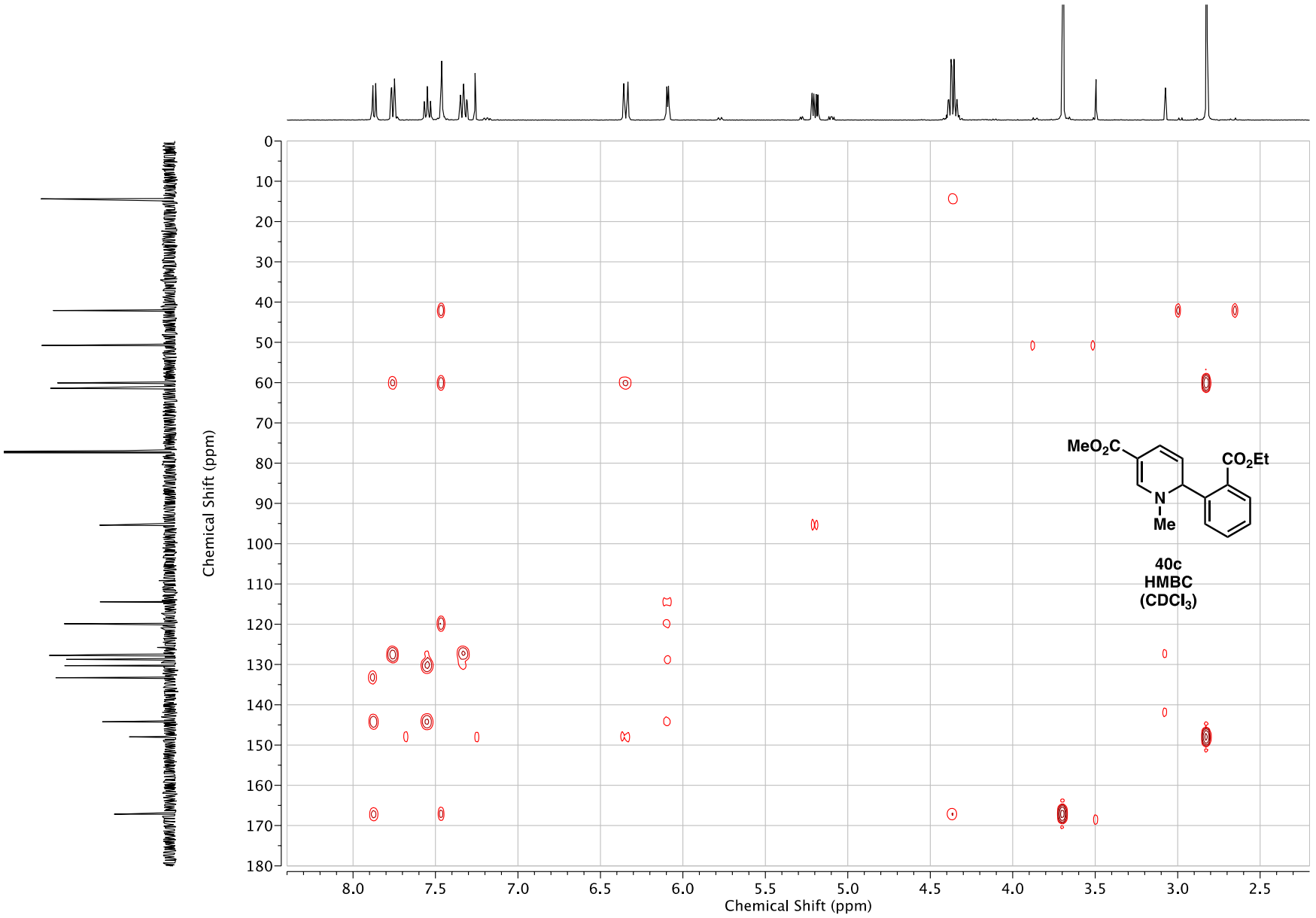

MeO2C
Br
N
Bn
39c
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)

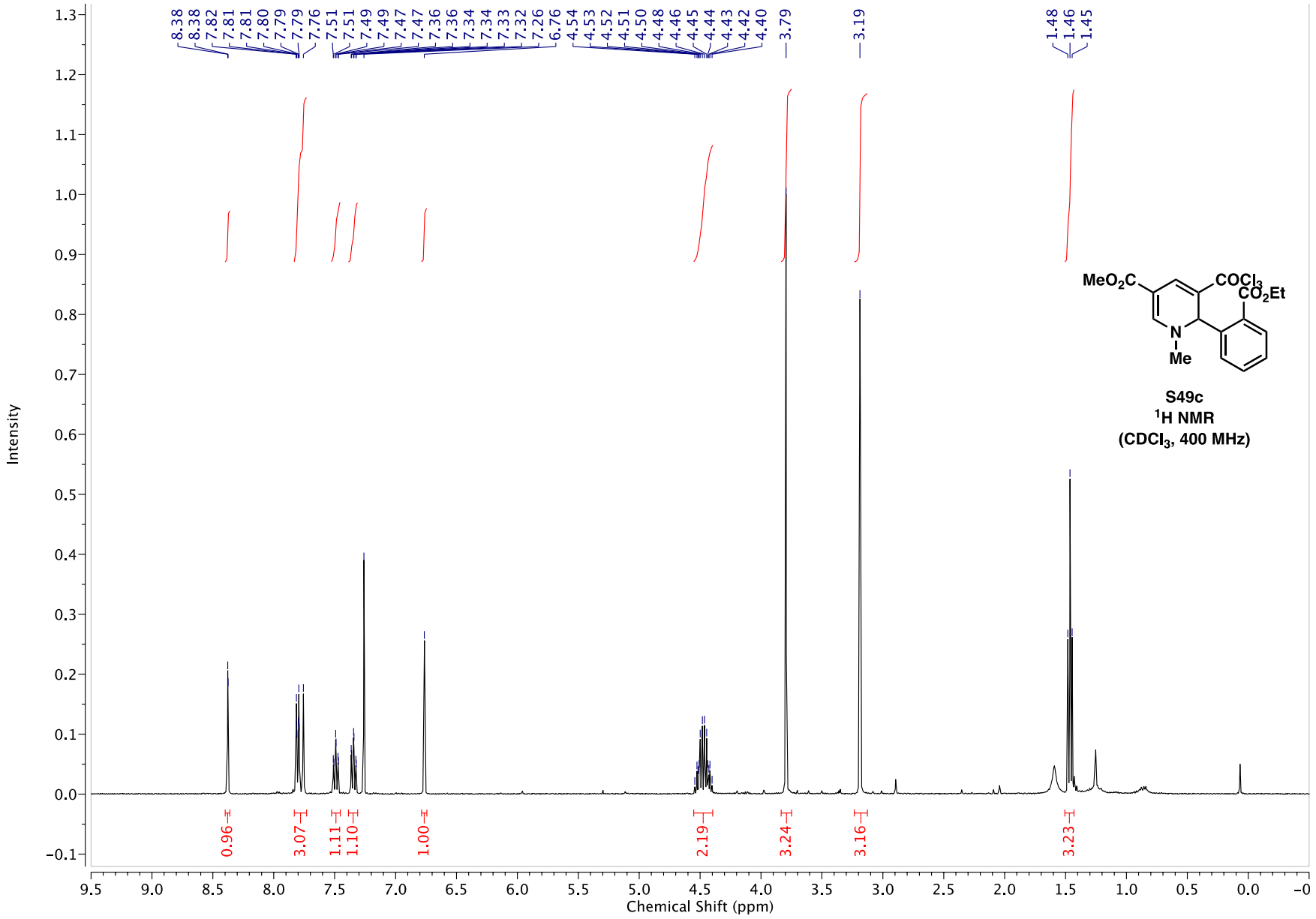

166.13
145.89
137.74
135.48
129.25
128.53
127.53
125.44
115.26
104.32
98.40
77.16
62.97
58.26
51.05
30.59
27.93
MeO2C
Br
N
Bn
39c
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

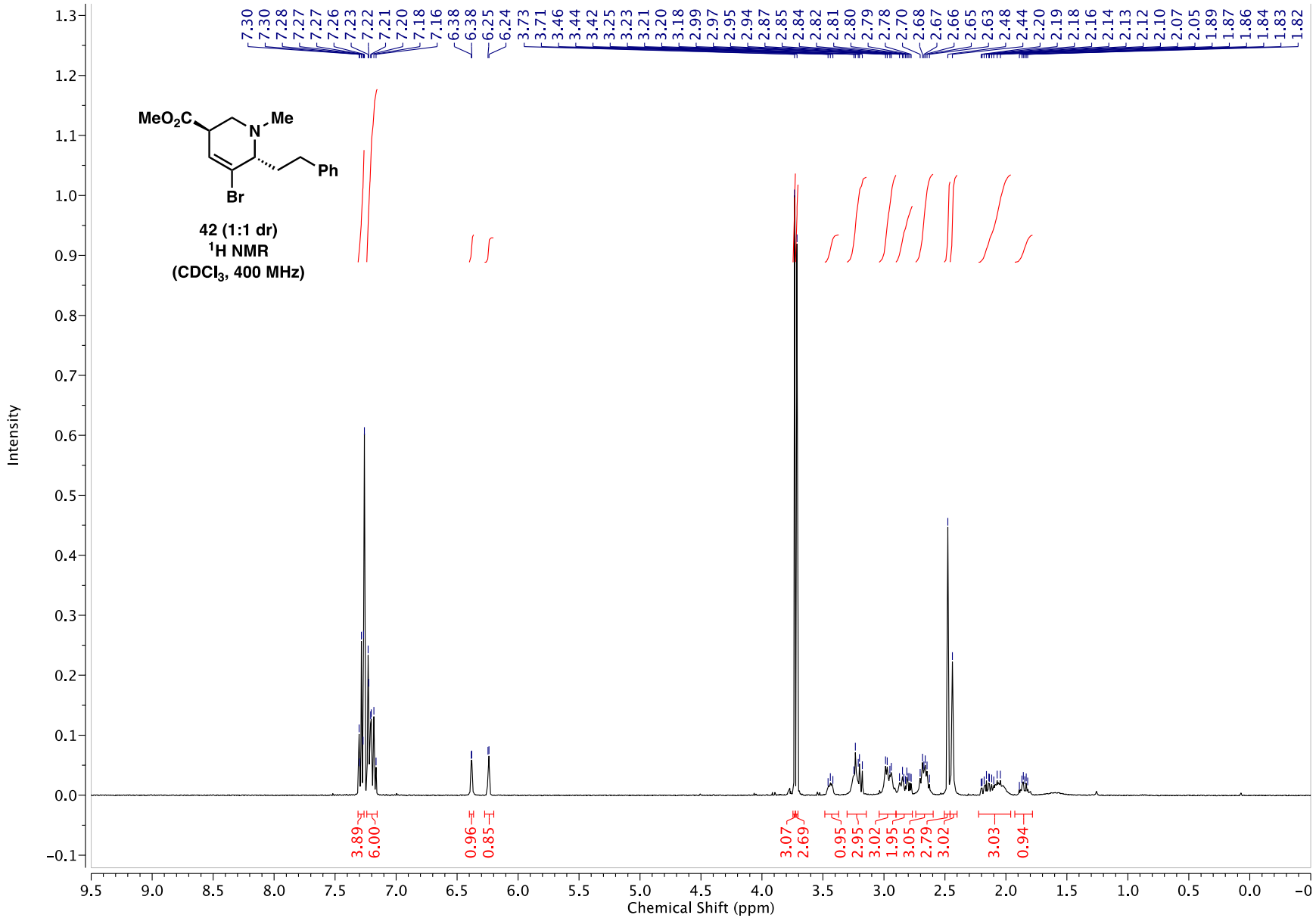

MeO2C
CO2Et
N
Me
40c
1H NMR
(CDCl3, 500 MHz)
Intensity
Chemical Shift (ppm)

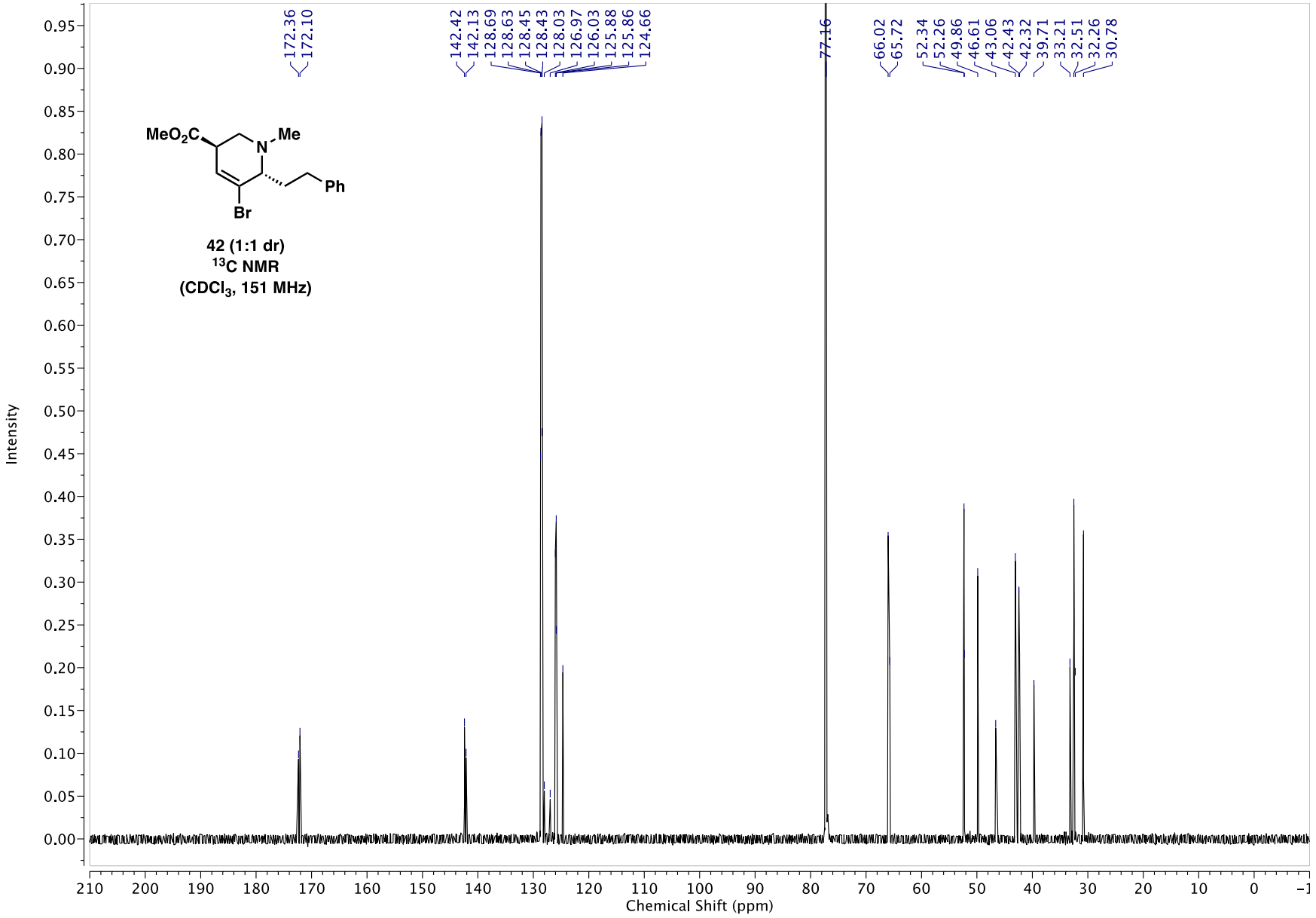

167.2
167.1
148.0
144.2
133.3
130.3
128.7
127.7
127.5
119.9
114.4
95.4
77.2
61.4
60.1
50.8
42.1
14.4
MeO2C
CO2Et
N
Me
40c
13C NMR
(CDCl3, 126 MHz)
Intensity
Chemical Shift (ppm)

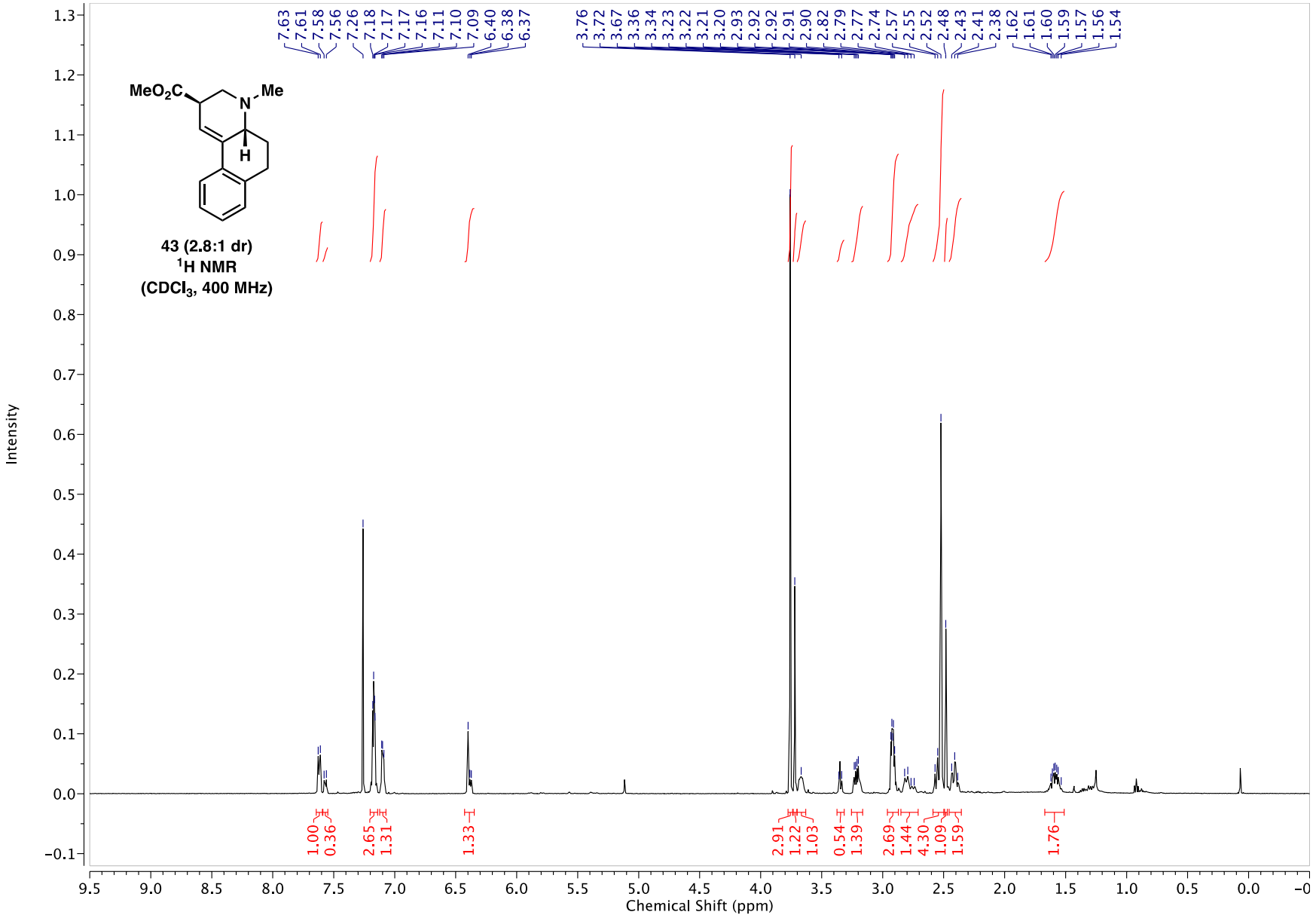

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
CO2Et
N
Me
40c
HSQC
(CDCl3)

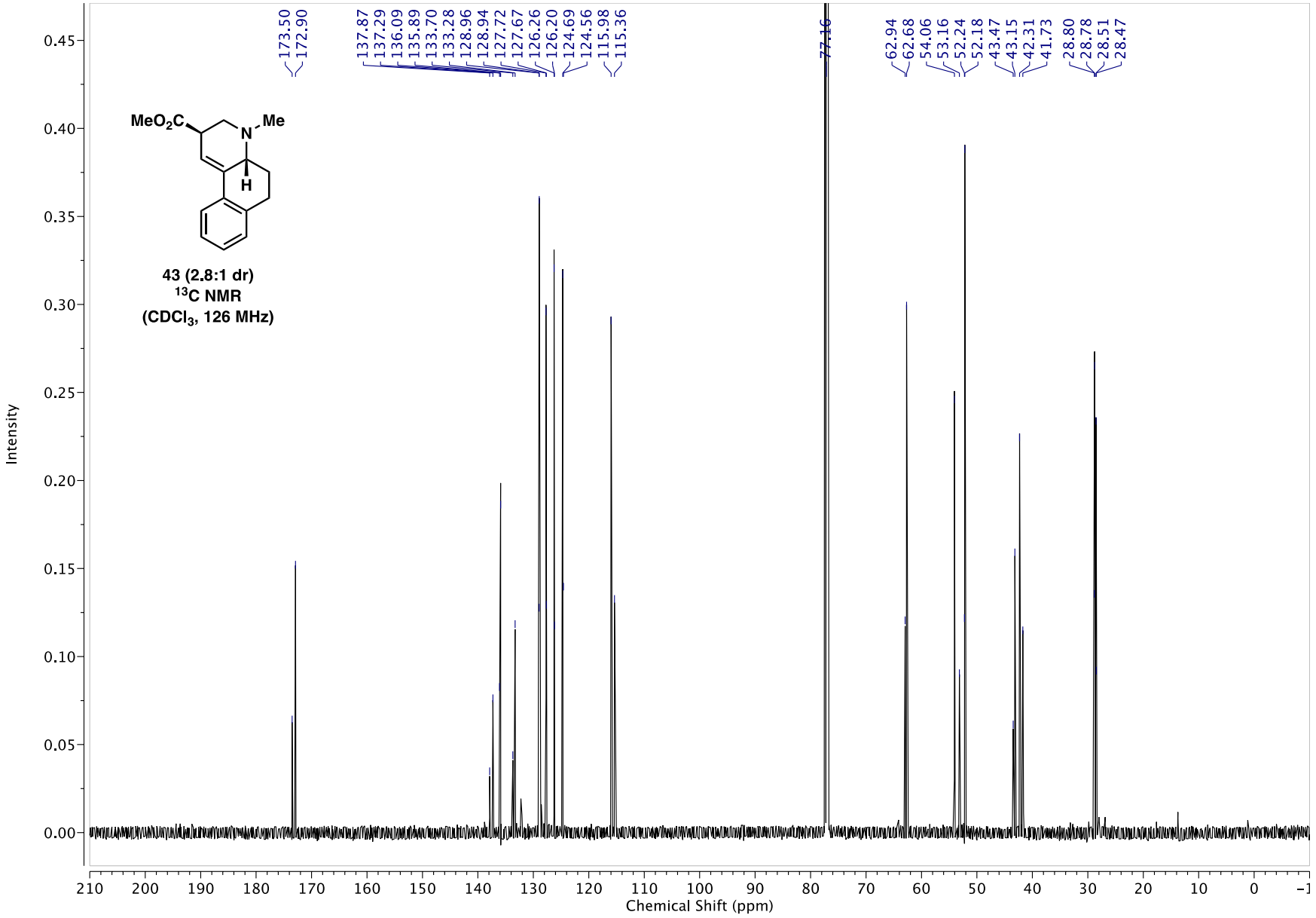

Chemical Shift (ppm)
Chemical Shift (ppm)
MeO2C
CO2Et
N
Me
40c
HMBC
(CDCl3)

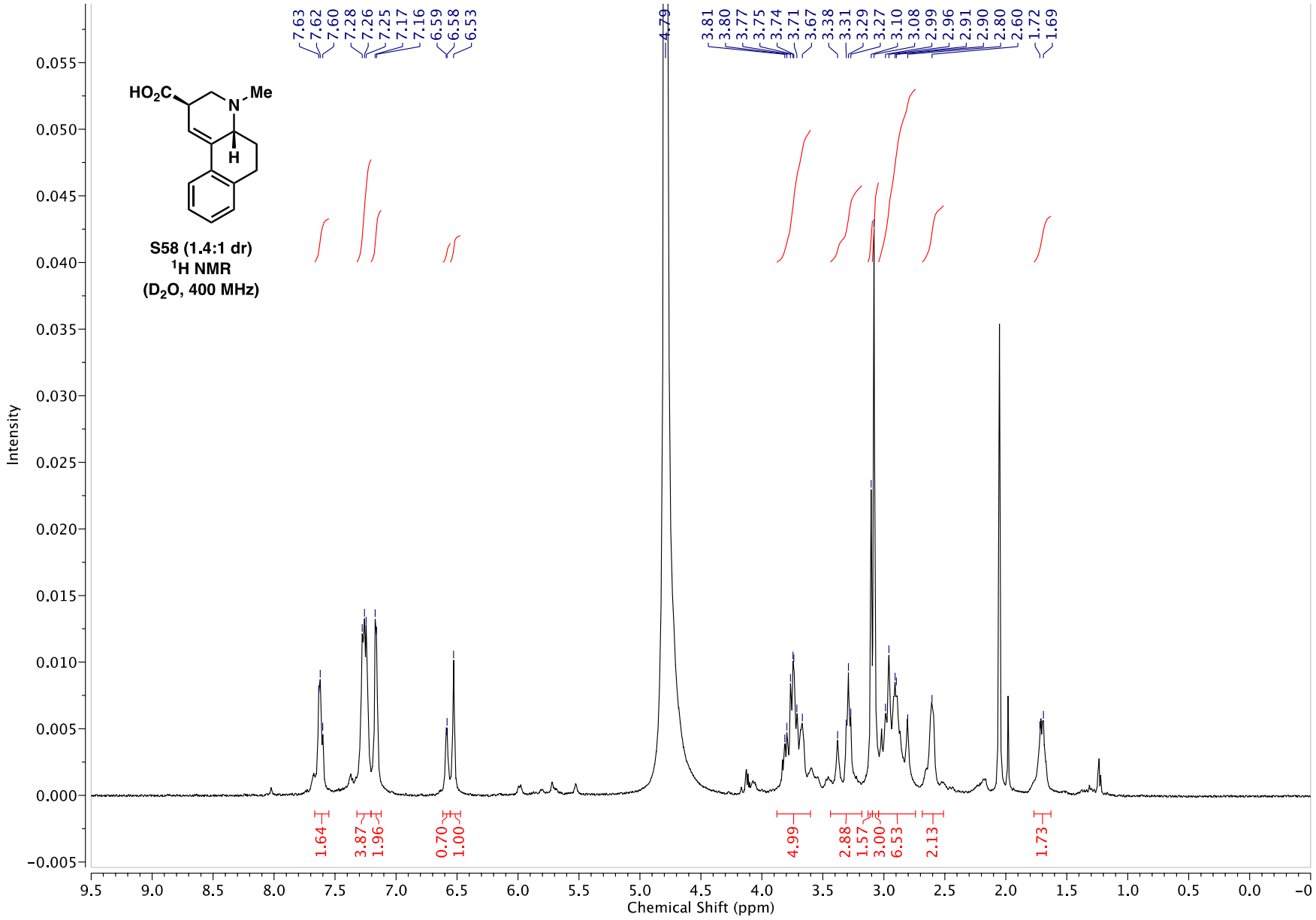

8.38
8.38
7.82
7.81
7.81
7.80
7.79
7.79
7.76
7.51
7.51
7.49
7.49
7.47
7.47
7.36
7.36
7.34
7.34
7.33
7.32
7.26
6.76
4.54
4.53
4.52
4.51
4.50
4.48
4.46
4.45
4.44
4.43
4.42
4.40
3.79
3.19
1.48
1.46
1.45
0.96
3.07
1.11
1.10
1.00
2.19
3.24
3.16
3.23
Intensity
Chemical Shift (ppm)
MeO2C
COCl3
CO2Et
N
Me
S49c
1H NMR
(CDCl3, 400 MHz)

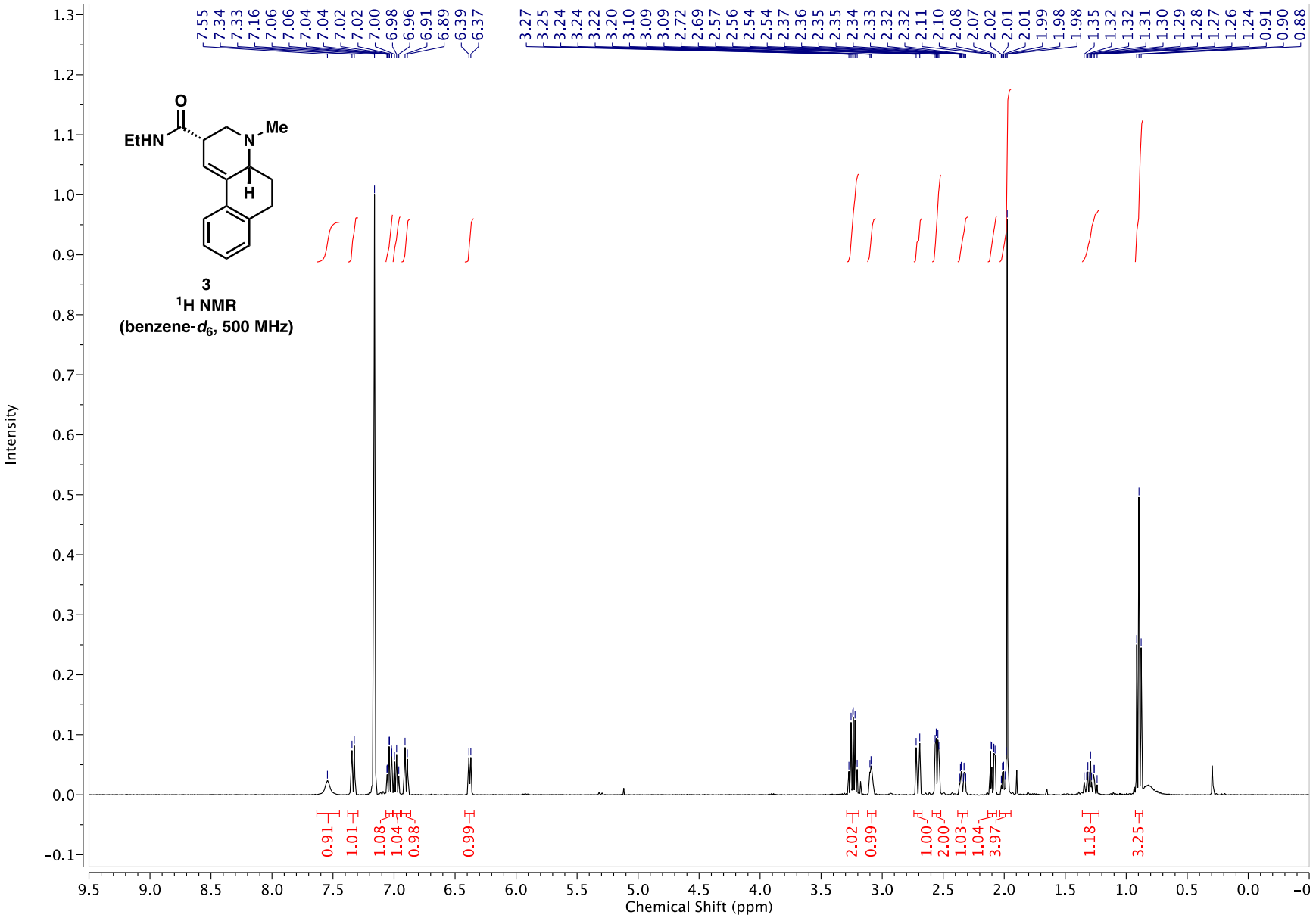

MeO2C
N
Me
Ph
Br
42 (1:1 dr)
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)

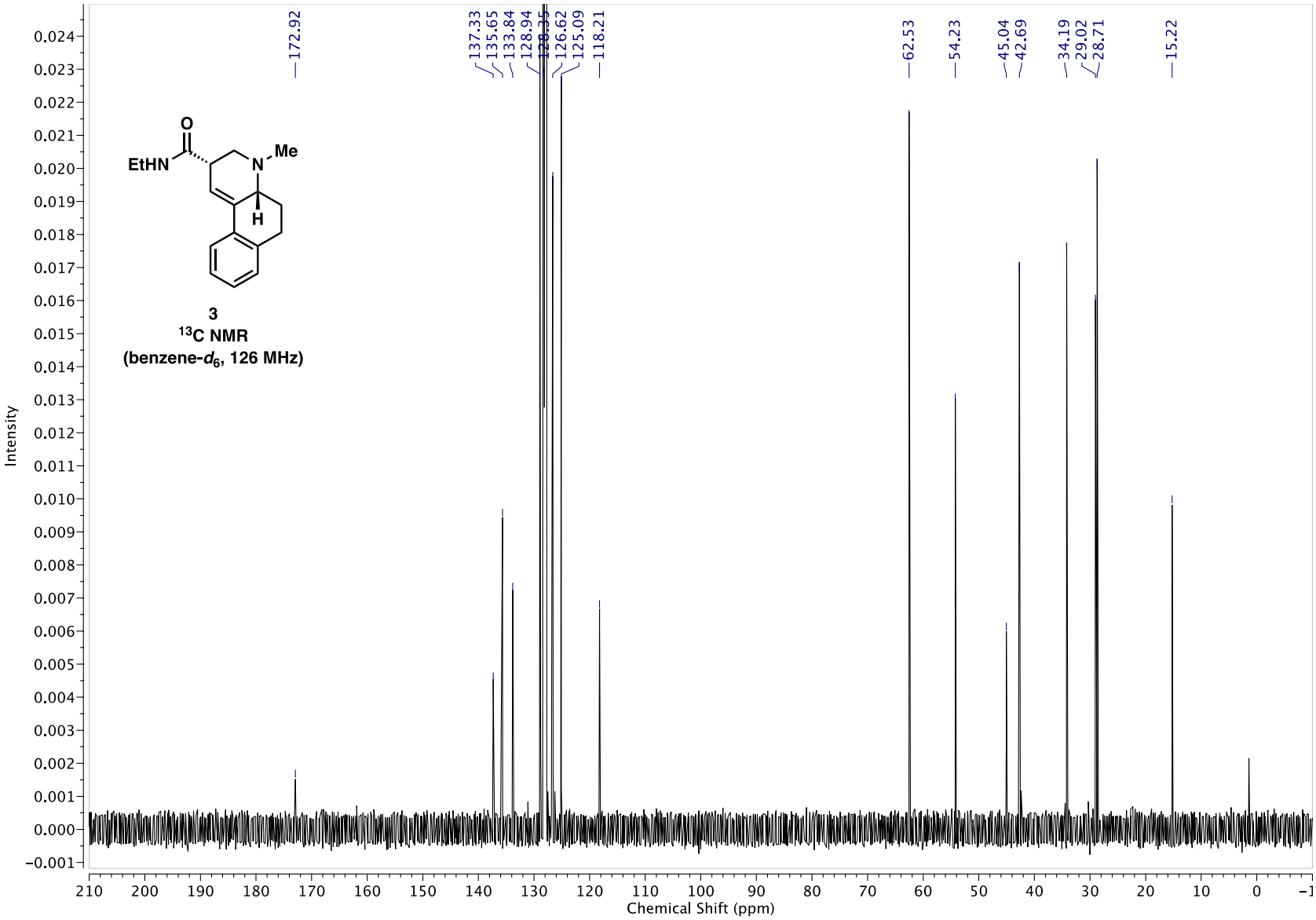

172.36
172.10
142.42
142.13
128.69
128.63
128.45
128.43
128.03
126.97
126.03
125.88
125.86
124.66
77.16
66.02
65.72
52.34
52.26
49.86
46.61
43.06
42.43
42.32
39.71
33.21
32.51
32.26
30.78
MeO2C
N
Me
Ph
Br
42 (1:1 dr)
13C NMR
(CDCl3, 151 MHz)
Intensity
Chemical Shift (ppm)

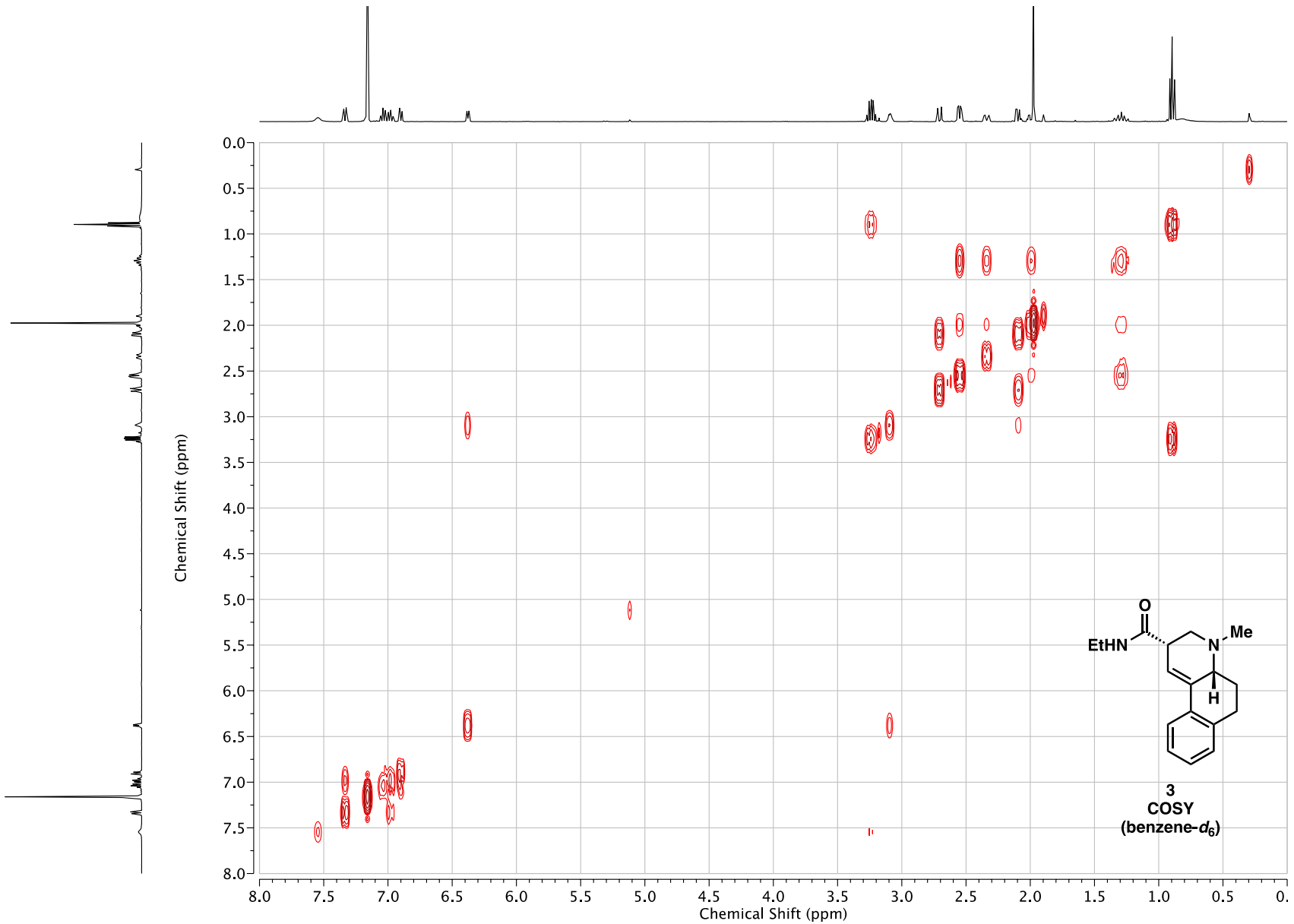

MeO2C
N
Me
H
43 (2.8:1 dr)
1H NMR
(CDCl3, 400 MHz)
Intensity
Chemical Shift (ppm)


173.50
172.90
137.87
137.29
136.09
135.89
133.70
133.28
128.96
128.94
127.72
127.67
126.26
126.20
124.69
124.56
115.98
115.36
77.16
62.94
62.68
54.06
53.16
52.24
52.18
43.47
43.15
42.31
41.73
28.80
28.78
28.51
28.47
MeO2C
N
Me
H
43 (2.8:1 dr)
13C NMR
(CDCl3, 126 MHz)
Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)


S58 (1.4:1 dr)
1H NMR
(D2O, 400 MHz)
HO2C
N
Me
H
7.63
7.62
7.60
7.28
7.26
7.25
7.17
7.16
6.59
6.58
6.53
4.79
3.81
3.80
3.77
3.75
3.74
3.71
3.67
3.38
3.31
3.29
3.27
3.10
3.08
2.99
2.96
2.91
2.90
2.80
2.60
1.72
1.69
1.64
3.87
1.96
0.70
1.00
4.99
2.88
1.57
3.00
6.53
2.13
1.73
Intensity
Chemical Shift (ppm)


7.55
7.34
7.33
7.16
7.06
7.06
7.04
7.04
7.02
7.02
7.00
6.98
6.96
6.91
6.89
6.39
6.37
3.27
3.25
3.24
3.24
3.22
3.20
3.10
3.09
3.09
2.72
2.69
2.57
2.56
2.54
2.54
2.37
2.36
2.35
2.35
2.34
2.33
2.32
2.32
2.11
2.10
2.08
2.07
2.02
2.01
2.01
1.99
1.98
1.98
1.35
1.32
1.32
1.31
1.30
1.29
1.28
1.27
1.26
1.24
0.91
0.90
0.88
O
EtHN
N
Me
H
3
1H NMR
(benzene-d6, 500 MHz)
Intensity
Chemical Shift (ppm)
0.91
1.01
1.08
1.04
0.98
0.99
2.02
0.99
1.00
2.00
1.03
1.04
3.97
1.18
3.25


172.92
137.33
135.65
133.84
128.94
128.35
126.62
125.09
118.21
62.53
54.23
45.04
42.69
34.19
29.02
28.71
15.22
O
EtHN
N
Me
H
3
13C NMR
(benzene-d6, 126 MHz)
Intensity
Chemical Shift (ppm)


Chemical Shift (ppm)
Chemical Shift (ppm)
O
EtHN
N
Me
H
3
COSY
(benzene-d_6)