A GENERAL APPROACH TO MEDIUM RING AZABICYCLES, TOTAL

SYNTHESIS OF CREMASTRINE, AND TOTAL SYNTHESIS OF

GRANDISINE D

By

Kristopher Neil Hahn

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Approved:

Craig W. Lindsley

Ned A. Porter

To Heather, My Parents, My Brother

and Sisters, and Hurley

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LIST OF ABBREVIATIONS

AIBN	2,2'-azobisisobutryonitrile
Ac	acetyl
AcOH	acetic acid
9-BBN	9-borabicyclo [3.3.1]nonane
BINOL	1,1'-bi-2-napthol
$BF_3 \cdot OEt_2$	boro trifluoride diethyl ether
Bn	benzyl
BnBr	benzyl bromide
Boc	*t*-Butyloxycarbonyl
BOM	benzyloxymethyl
BQ	1,4-benzoquinone
Bz	benzoyl
^{o}C	degrees Celsius
cat.	catalytic
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane

CH$_3$CN	acetonitrile
conc	concentration
CSA	10-camphorsulfonic acid
Cs$_2$CO$_3$	cesium carbonate
CYP450	cytochrome P450
δ	chemical shift in ppm
d	doublet
DBU	1, 8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublet
ddd	doublet of doublet of doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBALH	diisobutylaluminium hydride
DIEA	*N,N* diisopropylethylamine
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N, N*-dimethylformamide

DMPK	Drug Metabolism/Pharmacokinetics
DMSO	dimethyl sulfoxide
dt	doublet of triplet
eq.	equivalent
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
GPCR	G-protein coupled receptor
h	hour
HCl	hydrogen chloride
hERG	human ether-a-go-go related gene
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
IC_{50}	half maximal inhibitory concentration
Ipc	isopinocamphyl

K$_2$CO$_3$	potassium carbonate
KHMDS	potassium hexamethyldisilazide
L	liter(s)
LDA	lithium diisopropylamide
LIDBB	4,4'-di-tert-butyl-biphenyllithium
LiAlH4	lithium aluminum hydride
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MeI	iodomethane
MeOH	methanol
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
NaOH	sodium hydroxide
NCS	*N*-chlorosuccinimide

NMO	*N*-methylmorpholine N-oxide
Np	2-naphthyl
Ph	phenyl
Pd/C	palladium on carbon
PMB	4-methoxybenzyl
Ph	phenyl
ppm	parts per million
py	pyridine
Rh$_2$(OAc)$_4$	dirhodium acetate
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic acid
UV	ultraviolet

CHAPTER I

A NEW METHODOLGY TO ACCESS MEDIUM-RING AZABICYCLIC RING SYSTEMS: SYNTHESIS OF INDOLIZIDINE, PYRROLO[1,2-A]AZEPINE, PYRROLO[1,2-A] AZOCINE AZABICYCLES AND SYNTHESIS OF RELEVANT AZABICYCLIC LACTAMS

1.1. Introduction

The azabicyclic ring system is a common structural subunit present in numerous alkaloid natural products and serves as an important scaffold in biologically active and pharmaceutically significant compounds. Pyrrolizidine, indolizidine, pyrrolo[1,2-*a*]azepine, and pyrrolo[1,2-*a*]azocine are common examples of the azabicyclic ring system (Figure 1.1). Due to the importance of this ring system, we felt it warranted our attention to develop a rapid a versatile approach to access this ring system. Additionally, azabicyclic lactams are also a prevalent motif in a variety of natural products and biologically relevant compounds. A slight modification to the approach of generating azabicyclic ring systems that could be applied to synthesizing azabicyclic lactams would be desired. [1,2,3,4]
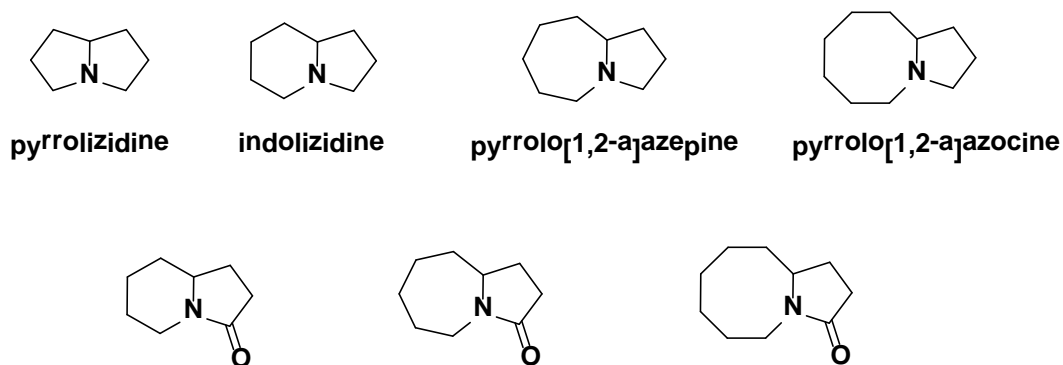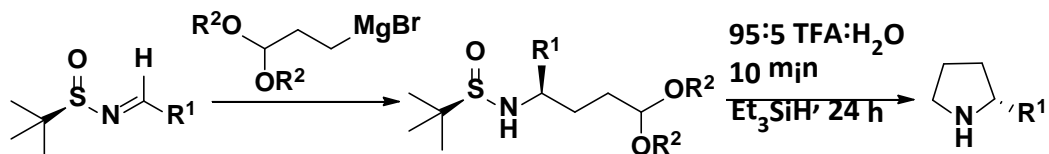

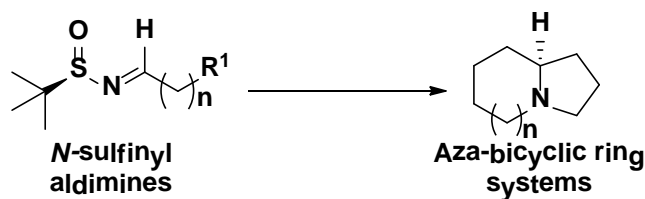**Figure 1.1** Azabicyclic ring systems and azabicyclic lactams

1.2. Background to Synthetic Approach

Magnesium or indium mediated enantioselective additions into sulfinyl aldimines, work pioneered by Ellman and coworkers in 2009 was the initial inspiration for our route to azabicyclic ring systems. As seen in Scheme 1.1, Ellman's work involves the addition of Grignard additions of an alkyl bromide bearing a latent aldehyde moiety into chiral *N*-sulfinyl aldimines. This enantioselective addition is dictated by the chirality of the *t*-butylsulfinamide allowing for the generation of new alkyl group stereocenters. A 95:5 trifluoroacetic acid:water mixture allows for deprotection of latent aldehyde and the *N*-sulfinyl substituent which undergoes an intramolecular reductive amination to form the imine, whereupon the addition of triethylsilane as a hydride source, gives the chiral 2-substituted pyrrolidine.[5]

Scheme 1.1 Ellman's approach to chiral 2-substituted pyrrolidines

Our group envisioned taking Ellman's work further and accessing diverse azabicyclic ring systems. Starting with more functionalized *N*-sulfinyl aldimines, through a number of functional group transformations and manipulations, we could enantioselectively generate, depending chirality of the *tert*-butylsulfinyl, indolizidine, pyrrolo[1,2-*a*]azepine, and pyrrolo[1,2-*a*]azocine azabicyclic ring systems and the relevant azabicyclic lactams (Scheme 1.2).[6]

N-sulfinyl aldimines

Aza-bicyclic ring systems

Scheme 1.2 Enantioenriched azabicyclic rings via chiral sulfinamides.

1.3. Synthesis of Indolizidine Ring System

The protocol we envision to generate a diverse array of azabicyclic ring systems involves a protocol of an asymmetric Grignard or indium mediated allylation, *N*-alkylation, ring closing metathesis (RCM), and finally an intramolecular reductive amination, or cyclization, to generate the desired enantiopure azabicycle.

The strategy began with commercially available aldehyde **1.1** which was condensed with chiral *tert*-butylsulfinamine **1.2** and copper sulfate to generate (R)-*N*-sulfinylaldimine **1.3** in 91% yield (Scheme 1.3). Next, a stereoselective indium-mediated addition of allyl bromide in a saturated aqueous sodium bromide solution into *N*-sulfinylaldimine **1.3** generates a new chiral stereocenter in the allylated **1.4** product in 87% yield. The diastereomeric ratio (d.r.) for this reaction was greater than 19:1 of the desired stereoisomer, which could separated through normal phase flash column chromatography, and the d.r. verified through either HPLC or proton NMR comparison. This secondary amine was then alkylated using allyl bromide and lithium hexamethyldisilazide (LHMDS) as the base to generate the dialkene product **1.5** in 80% yield. This was then refluxed with Grubbs 2nd generation catalyst in CH_2Cl_2 to undergo a ring closing metathesis reaction to form the unsaturated piperadine derivative **1.6** in 84% yield. The alkene was then subjected to a palladium catalyzed reductive hydrogenation to

generate the saturated six-member ring. Next, the crude material from the previous reaction is subjected to a global deprotection of the sulfinyl and the acetal to expose the amine and aldehyde. This spontaneously undergoes a reductive amination the form the imine, whereupon treatment with polymer supported triacetoxyborohydride in dichloroethane generates the enantiopure indolizidine product **1.7** in 81% yield from intermediate **1.6**, which happens to be the natural product (+)-coniceine.
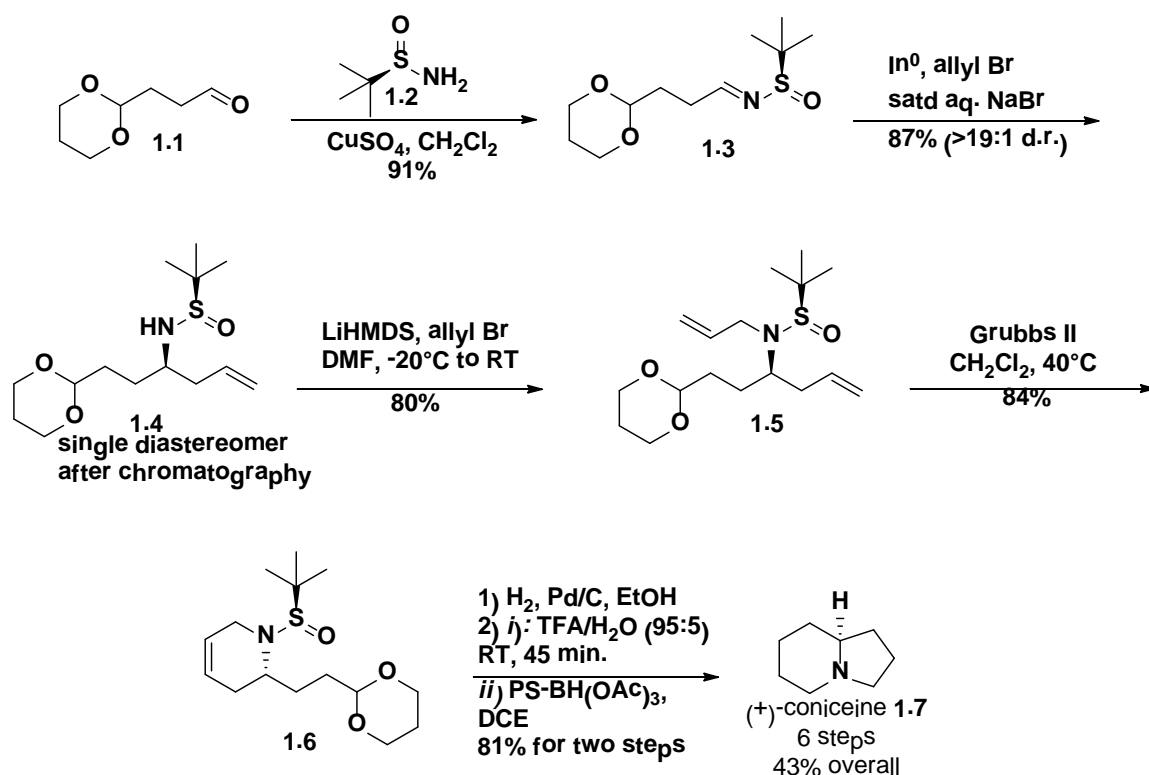
**Scheme 1.3** Synthetic route generate the indolizidine azabicycle

The (+) or (-) enantiomer of the indolizidine azabicycle can be rapidly generated depending on the chirality of the sulfinamide starting material used. Indolizidine **1.7**

could be accessed in 6 steps with an overall yield of 43% starting from commercially available materials.

1.4. Synthesis of Pyrrolo[1,2-a]azepine

Next, we sought to synthesize the pyrrolo[1,2-*a*]azepine using similar key reactions of an asymmetric addition into a chiral *N*-sulfinyl aldimine, a ring closing metathesis reaction catalyzed by a Grubbs 2nd generation catalyst, and finally a global deprotection/reductive amination to generate the '5,7' azabicyclic ring system.

The synthetic route for this azabicyclic adduct begins with a condensation between aldehyde **1.8** and the chiral *tert*-butylsulfinamide **1.2** with Ti(OEt)$_4$ to remove water from the reaction which generates *N*-sulfinylaldimine **1.9** (Scheme 1.4). An enatioselective addition a Grignard reagent **1.10** into *N*-sulfinylaldimine **1.9**, where the addition is directed by the existing chirality of the starting material substrate, forms the *N*-sulfinylamine **1.11** in excellent yield and a d.r. of more than 9:1. Next, alkylation with allyl bromide, and LHMDS as the base, gives the *bis*-alkene product **1.12** in 80% yield where the diastereomers can be separated from the previous Grignard addition by normal phase column chromatography.
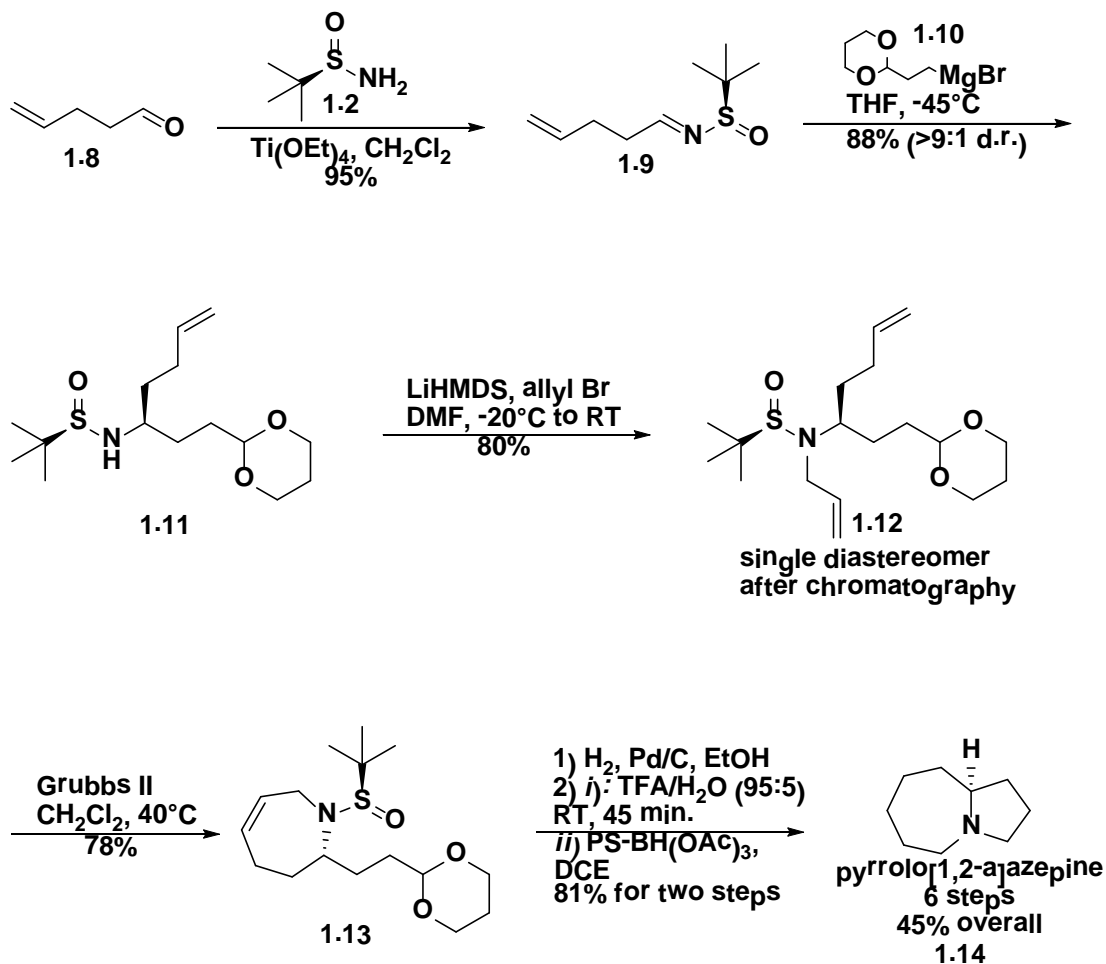
Scheme 1.4 Synthetic route to the azabicycle pyrrolo[1,2-*a*]azepine

With dialkene **1.12** in hand, we then subjected it to a ring closing metathesis reaction to form the unsaturated 7-membered ring **1.13** in 78% yield by refluxing in dichloromethane for 1 hour. Next, a reductive hydrogenation with palladium on carbon and hydrogen gas at room temperature in methanol gives the fully saturated 7 membered ring. From here it was one more step of a global deprotection of the sulfinyl and acetal with a 95:5 trifluoroacetic acid:water mixture to expose the amine and aldehyde, respectively. This intermediate than undergoes an intramolecular reductive amination whereupon treatment with polymer-supported triacetoxyborohydride gives the desired

pyrrolo[1,2-*a*]azepine **1.14** in 81% yield over two step, from the Grubbs cross metathesis reaction. Overall, the pyrrolo[1,2-*a*]azepine ring systems was generated from commercially available starting materials in 6 steps and 45% overall yield.

1.5.   Synthesis of Pyrrolo[1,2-a]azocine

The next ring system we sought to synthesize was the pyrrolo[1,2-*a*]azocine azabicyclic compound. Again, the robust and versatile methodology used to generate the indolizidine and pyrrolo[1,2-*a*]azepine is used make the pyrrolo[1,2-*a*]azocine desired scaffold. The route again uses key reactions of an asymmetric addition into a chiral *N*-sulfinyl aldimine, a ring closing metathesis reaction catalyzed by a Grubbs 2nd generation catalyst, and finally a global deprotection/reductive amination to generate the '5,8' azabicyclic ring system.

This strategy begins with commercially available aldehyde **1.15** which was condensed with chiral *tert*-butylsulfinamine **1.2** and copper sulfate to generate (*R*)-*N*-sulfinylaldimine **1.16** in 91% yield (Scheme 1.5). Next, a stereoselective indium-mediated addition of allyl bromide in a saturated aqueous sodium bromide solution into *N*-sulfinylaldimine **1.16** generates a new chiral stereocenter in the allylated **1.17** product in 87% yield. The diastereomeric ratio (d.r.) for this reaction was greater than 19:1 of the desired stereoisomer, which could separated through normal phase flash column chromatography, and the d.r. verified through either HPLC or proton NMR comparison. From here alkylation with 5-bromo-1-pentene, and again LHMDS as a base, generates the *bis*-alkene product **1.18** in 85% yield.
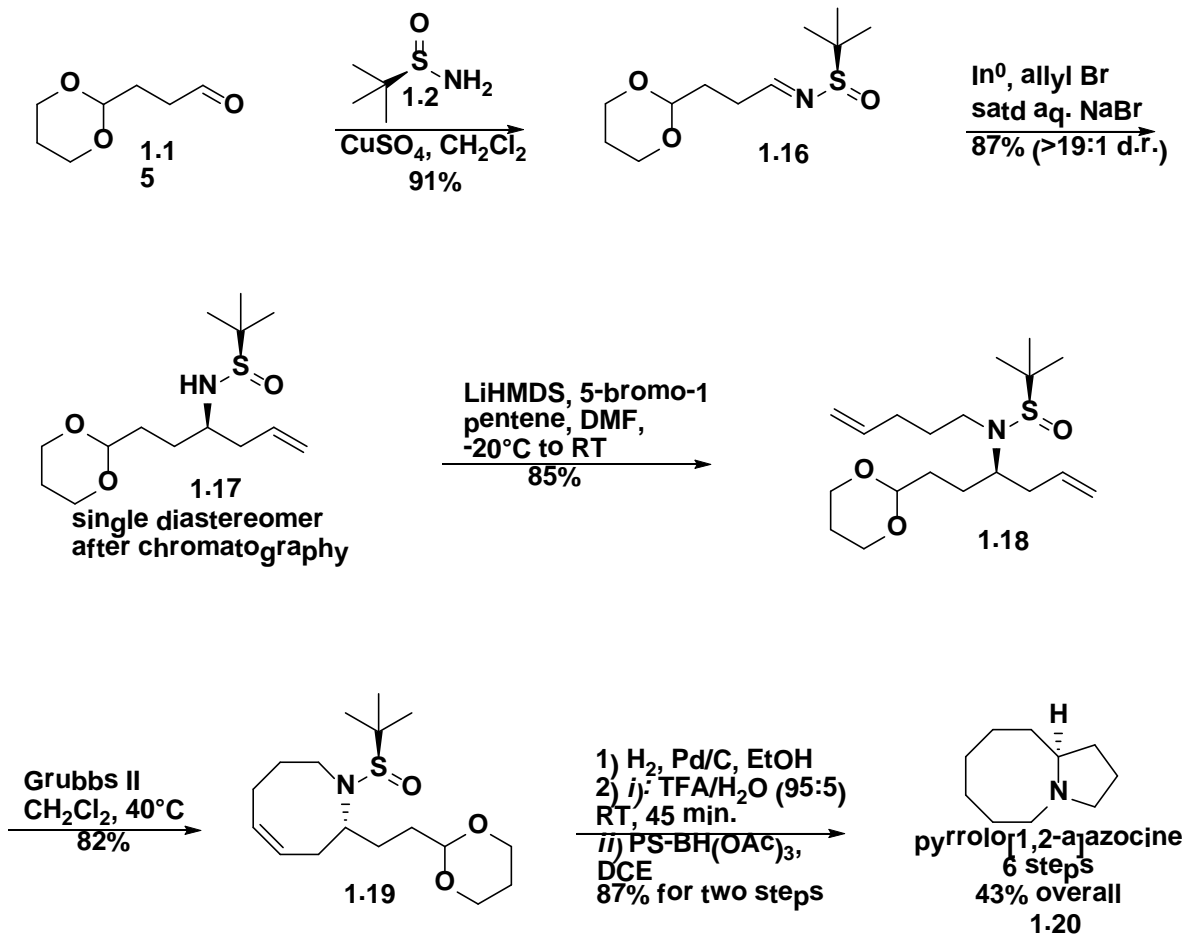
Scheme 1.5 Synthetic route to the azabicycle pyrrolo[1,2-*a*]azocine

Next, a ring closing metathesis reaction of *bis*-alkene **1.18** with Grubbs 2nd generation catalyst generates the unsaturated 8-membered ring **1.19** by refluxing in dichloromethane in 82% yield. The unsaturated 8-membered ring is saturated using palladium on carbon and hydrogen in ethanol to undergo a reductive hydrogenation to give the fully saturated 8-membered ring system. From here it was one more step of a global deprotection of the sulfinyl and acetal with a 95:5 trifluoroacetic acid:water mixture to expose the amine and aldehyde, respectively. This intermediate than undergoes an intramolecular reductive amination to give the imine intermediate

whereupon treatment with polymer-supported triacetoxyborohydride gives the desired pyrrolo[1,2-*a*]azocine **1.20** in 87% yield over two steps, from the Grubbs cross metathesis reaction. Overall, the pyrrolo[1,2-*a*]azocine ring systems was generated from commercially available starting materials in 6 steps and 43% overall yield.

1.6.   Synthesis of Azabicyclic Lactams

Using a slight variation of the approach to generate the indolizidine, pyrrolo[1,2-*a*]azocine, and pyrrolo[1,2-*a*]azocine azabicyclic ring systems, we can rapidly and efficiently form diverse azabicyclic lactams. This is another motif commonly found in a range of natural products and also pharmaceutically relevant compounds. The approach used to synthesize these compounds is also highly convergent where a deviation in one of the final steps allows for easy access to a variety of azabicyclic lactams.

The synthetic route (Scheme 1.6) begins with a condensation between aldehyde **1.21** and *tert*-butylsulfinamide **1.25** in dichloromethane with copper sulfate to remove water from the system to generate the chiral *N*-sulfinylaldimine **1.22** in 91% yield. From here, we use a similar enatioselective indium-mediated addition of allyl bromide in saturated aqueous sodium bromide to generate a new stereocenter in the olefin product **1.23** in 88% yield and greater than 9:1 d.r.. The two diastereomers can be easily separated by normal phase column chromatography to give the desired compound. Next, deprotection of the *N*-sulfinyl aldimine with 6N HCl in 1,4-dioxane exposed the primary amine that, after concentration *in vacuo*, is then treated with sodium carbonate to undergo

a lactamization between the amine and the methyl ester to give chiral γ-lactam **1.24** in excellent yield of 97% over the two steps.
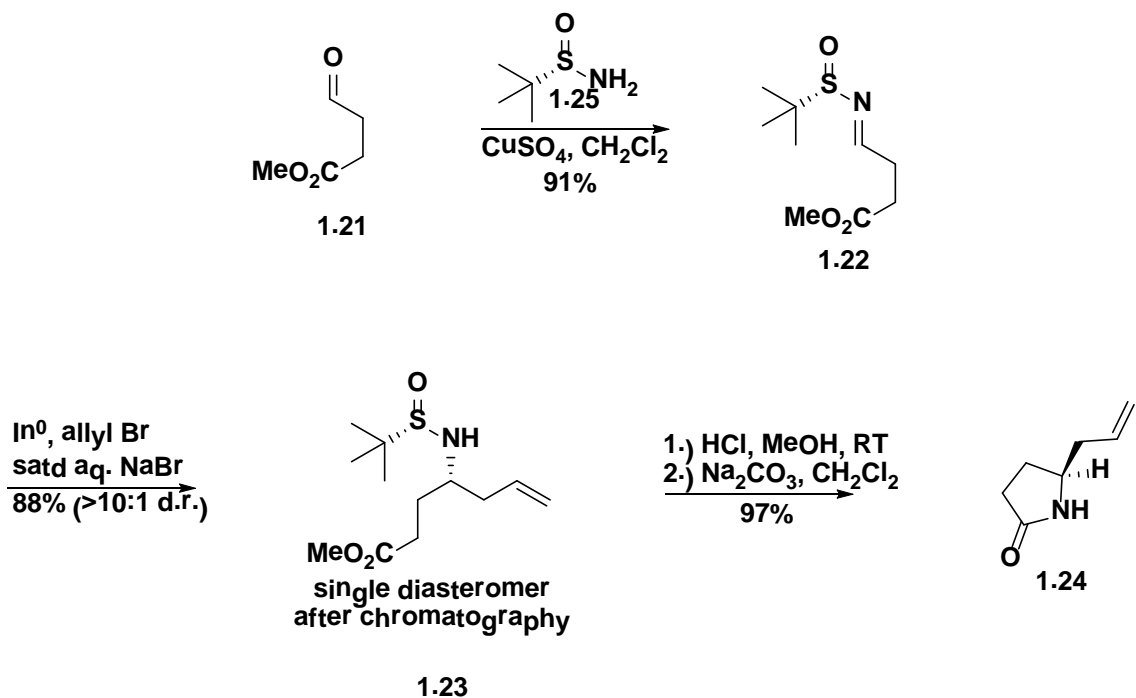
Scheme 1.6 Synthetic route to the chiral γ-lactam

From this point in the synthetic scheme, the next step is alkylation of the secondary amide. Depending upon the alkylating reagent, the desired azabicyclic lactam can be accessed rather efficiently and in a rapid manner. The "5,6" azabicyclic lactam can be formed treatment with LHMDS followed by allyl bromide to alkylate to the tertiary amide. This can then be subjected to a ring closing metathesis reaction using Grubbs 2nd generation catalyst to give the unsaturated 6 membered ring in 87% yield over 2 steps.
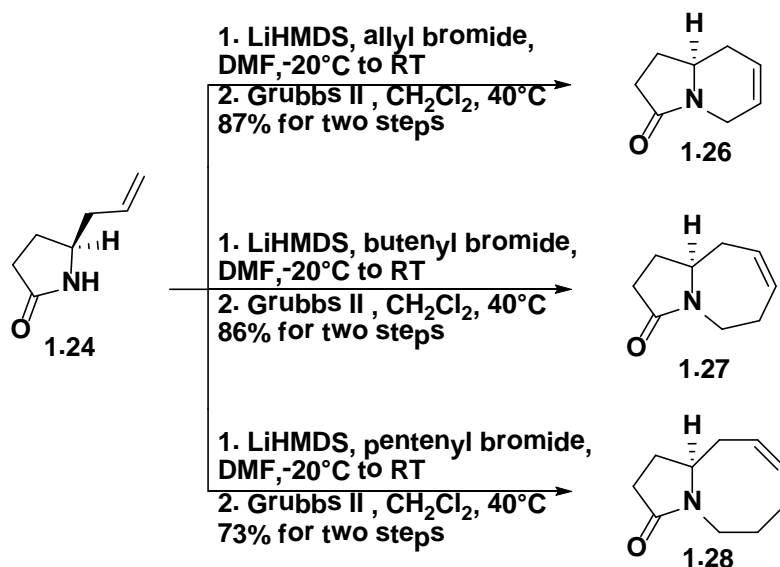
Scheme 1.7 Formation of enatiopure γ-azabicyclic lactam

The "5,7" azabicyclic lactam can be formed in a similar manner by treatment with LHMDS followed by butenyl bromide to alkylate to the tertiary amide. This can then be subjected to a ring closing metathesis reaction using Grubbs 2nd generation catalyst to give the unsaturated 7 membered ring in 86% yield over 2 steps. The "5,8" azabicyclic lactam can be formed again the same manner by treatment with LHMDS followed by 5-bromo-1-butene to alkylate to the tertiary amide. This can then be subjected to a ring closing metathesis reaction using Grubbs 2nd generation catalyst to give the unsaturated 8- membered ring in 73% yield over 2 steps. The alkene in all of the azabicyclic lactams can then be used as a functional handle to further diverse and functionalize to access a wide array of compounds.[7]

With this methodology of accessing azabicyclic clearly demonstrated to be successful, we next sought to apply this to the indolizidine containing natural product grandisine D and the pyrrolizidine containing natural product cremastrine.

1.7 Experimental Section

Flame-dried (under vacuum) glassware was used for all reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. All polymer-supported reagents were purchased from Biotage, Inc. Thin layer chromatography (TLC) was performed on glass-backed silica gel. Visualization was accomplished with UV light, and/or the use of anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hot-plate. Chromatography on silica gel was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies. IR spectra were recorded as thin films and are reported in wavenumbers (cm^{-1}). ^{1}H & ^{13}C NMR spectra were recorded on Bruker DRX-400 (400 MHz) or Bruker AV-NMR (600 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26, δ 77.0 (CDCl$_3$) and DMSO-d_6 2.50 ppm, 39.51 ppm for ^{1}H, ^{13}C respectively). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, br = broad, m = multiplet), coupling constant (Hz), integration. Optical rotations were measured on a JASCO P-2000 digital polarimeter. Concentration (c) in g/100 ml and solvent are given in parentheses. Low resolution mass spectra (LCMS) were obtained on an Agilent 1200 LCMS with electrospray ionization. A Micromass Q-Tof API-US mass spectrometer was used to acquire high-resolution mass spectrometry (HRMS) data. The value Δ is the error in the measurement (in ppm) given by the equation $\Delta = [(M_E - M_T)/ M_T] \times 10^6$, where M_E is the experimental mass and M_T is the theoretical mass. The HRMS results were obtained with ES as the ion source and leucine enkephalin as the reference.

(*R*)-2-methyl-*N*-(pent-4-en-1-ylidene)propane-2-sulfinamide (1.9).

4-pentenal (11.89 mmol, 0.5 g) was dissolved in THF (40 mL) and Ti(OEt)$_4$ (23.79 mmol, 2 eq.) was added followed by (*R*)-(+)-2-methyl-2-propanesulfinamide (2.0 mmol, 1.0 eq.). The mixture was stirred at rt for 5 h. The reaction is then quenched by addition of an equal volume of sat. NaHCO$_3$. The resulting mixture is filtered through a pad of Celite® and the filter cake rinsed washed with EtOAc. The filtrate was extracted with EtOAc (3 x 40 mL), the combined organic layer was washed with water, brine and dried over magnesium sulfate. Concentration *in vacuo* gave the crude aldimine which was purified by flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product 2.11 g (95%) as a colorless oil: $[\alpha]_D^{20} = +276.3$ (*c* = 1.00, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 8.08 (t, *J* = 4.4 Hz, 1H), 5.83 (m, 1H), 5.05 (m, 2H), 2.62 (m, 2H), 2.40 (q, *J* = 6.8, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 168.7, 136.6, 115.7, 56.4, 35.2, 29.2, 22.2; HRMS (TOF, ES+) C$_9$H$_{18}$NOS [M+H]$^+$ calc'd 188.1131, found 188.1130.
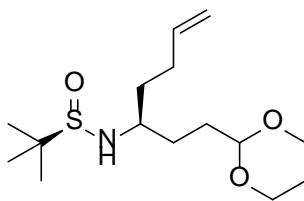
(*R*)-*N*-((*S*)-1-(1,3-dioxan-2-yl)hept-6-en-3-yl)-2-methylpropane-2-sulfinamide (1.11).

Magnesium turnings (4.99 g, 205.2 mmol) were flame dried with catalytic amount of Iodine in 500 mL reaction flask. 70 mL of THF was added, followed by dropwise addition of 2-(2-Bromoethyl)-1,3-dioxane (6.94 mL, 51.3 mmol). The reaction mixture was periodically cooled in a rt water bath to prevent refluxing. After addition of the 2-(2-bromoethyl)-1,3-dioxane solution was complete, the reaction mixture was stirred for 1 h. The solution was then transferred to a different flask and was cooled to −78 ∘C. Upon cooling, precipitate was observed and to the solid *N-tert*-Butanesulfinyl imine (1.63 g, 10.26 mmol) in 20 mL THF was added dropwise to the Grignard solution, the solution was stirred for overnight at −48 ∘C and then warmed to rt. The reaction mixture was quenched with sat NH_4Cl and extracted with EtOAc (3 x 40 mL). The organic layer was dried over sodium sulfate. Concentration *in vacuo* gave crude product as >9:1 dr, which was then purified by flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the product 2.74 g (88%) as a pale yellow oil: $[\alpha]_D^{20}$ = +55.1 (*c* = 1.00, $CHCl_3$); ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.80 (m, 1H), 5.05 (dd, *J* = 8.7, 17.2 Hz, 1H), 4.97 (dd, *J* = 8.4 Hz, 1H), 4.51 (t, *J* = 4.4 Hz, 1H), 4.07 (dd, *J* = 10.8, 5.2 Hz, 2H), 3.75 (dt, *J* = 12.4, 2.0 Hz, 2H), 3.23 (m, 1H), 3.05 (d, *J* = 6.8 Hz, 1H), 2.15 (q, *J* = 7.6, 2H), 2.07 (m, 1H), 1.56-1.75 (m, 6H), 1.54 (m, 1H), 1.33 (d, *J* = 13.6 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 137.9, 115.1, 101.9, 101.8, 66.8, 58.7, 56.2, 55.7, 36.9, 35.4, 31.2, 29.8, 29.7, 25.7, 25.6, 22.6; HRMS (TOF, ES+) $C_{15}H_{30}NO_3S$ $[M+H]^+$ calc'd 304.1946, found 304.1945.
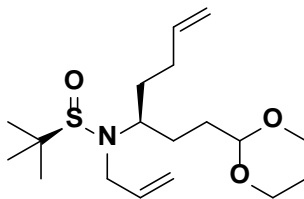
(*R*)-*N*-((*S*)-1-(1,3-dioxan-2-yl)hept-6-en-3-yl)-N-allyl-2-methylpropane-2-sulfinamide (1.12).

To a solution of (303 mg, 1 mmol) in DMF (2.8 mL) at -20 ^{o}C was added 1 M LiHMDS in THF (1.76 mL, 1.76 mmol) dropwise. The mixture was stirred for 20 mins and allyl bromide (0.43 mL, 5 mmol) was added. After stirring for 2 h, the reaction was quenched with sat. NH$_4$Cl, extracted with EtOAc (3 x 10 mL). The organic layer was washed with water, brine and dried over Na$_2$SO$_4$. Concentration *in vacuo* gave the residue which was then purified by automated flash chromatography (4:1 Hex/EtOAc) to yield the product 274.4 mg (80%) as a pale yellow oil: $[\alpha]_D^{20}$ = -40.5 (*c* = 1.00, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.71-5.89 (m, 2H), 5.15 (m, 2H), 4.98 (m, 2H), 4.49 (t, *J* = 5.2 Hz, 1H), 4.08 (dd, *J* = 11.6, 4.4 Hz, 2H), 3.95 (dd, *J* = 16.4, 5.2 Hz, 1H), 3.73 (t, *J* = 12.4 Hz, 2H), 3.11 (dd, *J* = 16.4, 7.2 Hz, 2H), 2.93 (m, 1H), 2.17 (m, 1H), 2.05 (m, 2H), 1.87 (m, 1H), 1.70 (m, 1H), 1.62 (m, 4H), 1.32 (d, *J* = 13.6 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 137.9, 136.1, 117.4, 114.8, 101.9, 66.8, 57.8, 45.1, 33.0, 32.8, 30.7, 27.6, 25.7, 23.6; HRMS (TOF, ES+) C$_{18}$H$_{34}$NO$_3$S [M+H]$^+$ calc'd 344.2259, found 344.2260.
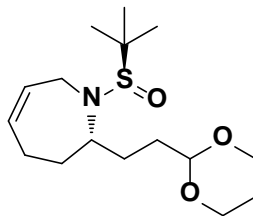
(*S*)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((*R*)-*tert*-butylsulfinyl)-2,3,4,7-tetrahydro-1H-azepine (1.13).

To a solution of (195.7 mg, 0.57 mmol) in CH_2Cl_2 (60 mL) was added 2nd Gen. Grubbs (24.2 mg, 0.028 mmol). The mixture was refluxed for 1 h and concentrated. The resulting crude product was purified by automated flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product 140.2 mg (78%) as yellow oil: $[\alpha]_D^{20} = +27.5$ ($c = 0.55$, $CHCl_3$);

^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.71 (m, 1H), 5.62 (m, 1H), 4.54 (t, $J = 4.8$ Hz, 1H), 4.11 (dd, $J = 7.4, 4.8$ Hz, 2H), 3.64-3.88 (m, 4H), 3.52 (m, 1H), 2.28 (m, 2H), 2.05 (m, 2H), 1.86 (m, 1H), 1.58-1.73 (m, 4H), 1.33 (q, $J = 13.6$ Hz, 1H), 1.2 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 131.1, 128.8, 102.1, 66.8, 60.8, 58.4, 42.3, 32.3, 32.2, 27.6, 25.7, 25.0, 23.5; HRMS (TOF, ES+) $C_{16}H_{30}NO_3S$ [M+H]$^+$ calc'd 316.1946, found 316.1946.
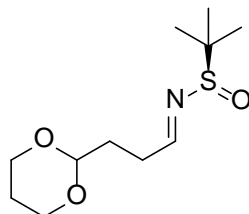
(*R*)-*N*-(3-(1,3-dioxan-2-yl)propylidene)-2-methylpropane-2-sulfinamide (1.3).

To a solution of 3-(1,3-dioxan-2-yl)propanal (2.1 g, 14.6 mmol) in CH_2Cl_2 (100 mL) was added (R)-2-methylpropane-2-sulfinamide (2.12 g, 17.5 mmol) and $CuSO_4$ (7.0 g, 43.8 mmol). The reaction mixture was stirred at rt overnight. The mixture was filtered through a through celite pad and washed with CH_2Cl_2. Concentration *in vacuo* gave the crude product which was purified by automated flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product 1.91 g (91%) as yellow oil: $[\alpha]_D^{20}$ = -208.8 (*c* = 0.86, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$)

δ (ppm): 8.11 (t, *J* = 4.0 Hz, 1H), 4.62 (t, *J* = 4.8 Hz, 1H), 4.10 (dd, *J* = 6.0, 4.8 Hz, 2H), 3.76 (m, 2H), 2.64 (sextet, *J* = 4.0 Hz, 2H), 2.07 (m, 1H), 1.93 (m, 2H), 1.32 (dm, *J* = 13.8 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 169.1, 101.0, 67.0, 56.7, 30.8, 30.7, 25.8, 22.5; HRMS (TOF, ES+) $C_{11}H_{22}NO_3S$ $[M+H]^+$ calc'd 248.1320, found 248.1319.
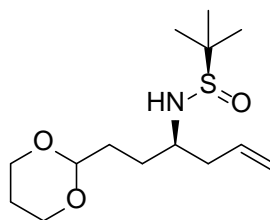
(R)-N-((R)-1-(1,3-dioxan-2-yl)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide (1.4).

In-Mediated allylation were done according to procedures published by Lin and co-workers. To a reaction flask containing (1.1 g, 4.45 mmol) and indium powder (2.05 g, 17.8 mmol) was added saturated aqueous NaBr solution (90 mL) followed by the allyl bromide (1.54 mL, 17.8 mmol). The resulting suspension stirred at rt overnight. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and filtered through a pad of celite. The aqueous layer was extracted with EtOAc (3x), dried over Na_2SO_4,

filtered, concentrated *in vacuo* to give the crude product as >19:1 *dr*, which was then purified by flash chromatography (1:1 Hex/EtOAc) to yield the allylation product 1.12 g (87%) as a pale yellow oil: $[\alpha]_D^{20}$ = -46.4 (*c* = 1.79, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.77 (m, 1H), 5.16 (d, *J* = 4 Hz, 1H), 5.13 (s, 1H), 4.51 (t, *J* = 4.5 Hz, 1H), 4.08 (dd, *J* = 5.0, 6.3 Hz, 2H), 3.74 (dt, *J* = 10, 2.2 Hz, 2H), 3.30 (m, 1H), 3.23 (d, *J* = 6.5 Hz, 1H), 2.37 (m, 2H), 2.05 (m, 1H), 1.63 (m, 3H), 1.33 (br, *J* = 14 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 133.9, 119.0, 101.9, 66.8, 55.8, 55.0, 40.5, 31.3, 29.2, 25.7, 22.6; HRMS (TOF, ES+) C$_{14}$H$_{28}$NO$_3$S [M+H]$^+$ calc'd 290.1790, found 290.1790.

General Procedure for *N*-alkylation:

To a solution of sulfinamide (1 equiv), in DMF at -20 °C was added LiHMDS (1 M, 1.0 equiv) and the mixture was stirred for 20 mins. Bromide (1.5 equiv.) was then added slowly to the mixture and the reaction was stirred for 3 hrs at rt. The reaction was quenched with saturated NH$_4$Cl solution and extracted with EtOAc (3x). The combined organic extracts were washed with water and the dried over Na$_2$SO$_4$. Filtration and concentration afforded the crude product, which was purified by flash chromatography (4:1 Hex/EtOAc).
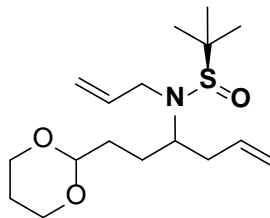
(*R*)-*N*-((*R*)-1-(1,3-dioxan-2-yl)hex-5-en-3-yl)-N-allyl-2-methylpropane-2-sulfinamide

(**1.5**). The product was prepared according to the general procedure using allyl bromide. The reaction was run on a 1 mmol scale, to afford the product as a off white gum (263.2 mg, 80%): $[\alpha]_D^{20}$ = +40.1 (*c* = 1.11, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.82 (m, 2H), 5.03-5.21 (m, 4H), 4.49 (t, *J* = 4.8 Hz, 1H), 4.07 (dd, *J* = 6.8, 4.8 Hz, 2H), 3.94 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.74 (t, *J* = 12.0 Hz, 2H), 3.20 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.09 (q, *J* = 6.8 Hz, 1H), 2.24-2.41 (m, 2H), 2.34 (t, *J* = 6.2 Hz, 1H), 1.83 (m, 1H), 1.65-1.73 (m, 2H), 1.62 (m, 1H), 1.33 (d, *J* = 13.6 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 136.5, 135.9, 117.4, 117.1, 102.2, 67.0, 58.2, 45.2, 39.1, 33.0, 27.6, 25.9, 23.9; HRMS (TOF, ES+) C$_{17}$H$_{32}$NO$_3$S [M+H]$^+$ calc'd 330.2103, found 330.2104.
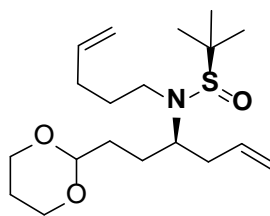
(*R*)-*N*-((*R*)-1-(1,3-dioxan-2-yl)hex-5-en-3-yl)-2-methyl-*N*-(pent-4-en-1-yl)propane-2-sulfinamide (**1.12**).

The product was prepared according to the general procedure using 5-bromopent-1-ene. The reaction was run on a 1 mmol scale, to afford the product as yellow oil (303.4 mg, 85 $\alpha]_D^{20}$ = +39.7 (*c* = 0.91, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.79 (m, 2H),

5.03 (m, 4H), 4.51 (t, J = 4.8 Hz, 1H), 4.07 (dd, J = 6.8, 4.8 Hz, 2H), 3.94 (dt, J = 12.0,

2.4 Hz, 2H), 3.23 (m, 1H), 3.06 (q, J = 6.4 Hz, 1H), 2.56 (m, 1H), 2.33 (m, 2H), 2.07 (m,

3H), 1.59-1.86 (m, 6H), 1.32 (d, J = 13.6 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100.6 MHz,

CDCl$_3$) δ (ppm): 137.8, 136.0, 117.1, 115.14, 102.3, 67.0, 66.9, 57.9, 42.8, 39.2, 33.1,

31.6, 29.6, 28.0, 24.0; HRMS (TOF, ES+) C$_{19}$H$_{36}$NO$_3$S [M+H]$^+$ calc'd 358.2416, found

358.2416.
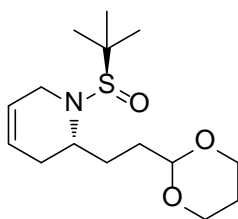
(R)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((R)-*tert*-butylsulfinyl)-1,2,3,6-tetrahydropyridine (1.6).

To a solution of (200 mg, 0.61 mmol) in CH$_2$Cl$_2$ (65 mL) was added 2nd Gen. Grubbs

(25.9 mg, 0.030 mmol). The mixture was refluxed for 1 h and concentrated. The resulting

crude product was purified by automated flash chromatography (4:1 to 1:1 Hex/EtOAc)

to yield the desired product 154.2 mg (84%) as off white solid: $[\alpha]_D^{20}$ = +20.7 (c = 1.05,

CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.69 (m, 2H), 4.53 (t, J = 5.2 Hz, 1H),

4.10 (dd, J = 7.6, 4.0 Hz, 2H), 3.85 (m, 1H), 3.76 (tt, J = 12.0, 2.8 Hz, 2H), 3.29-3.40 (m,

2H), 2.55 (m, 1H), 2.01-2.13 (m, 1H), 1.85-1.91 (m, 2H), 1.70-1.79 (m, 1H), 1.57-1.66

(m, 2H), 1.34 (d, J = 13.6 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm):

125.26, 123.57, 102.17, 67.00, 58.62, 56.90, 36.46, 32.86, 28.16, 26.88, 25.85, 23.49;

HRMS (TOF, ES+) C$_{15}$H$_{28}$NO$_3$S [M+H]$^+$ calc'd 302.1790, found 302.1788.
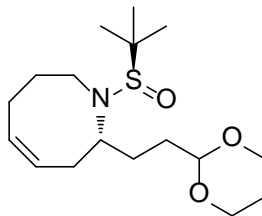
(*R*)-8-(2-(1,3-dioxan-2-yl)ethyl)-1-((*R*)-*tert*-butylsulfinyl)-1,2,3,4,7,8-

hexahydroazocine (1.19). To a solution of **1.18** (217.8 mg, 0.61 mmol) in CH_2Cl_2 (65

mL) was added 2nd Gen. Grubbs (25.9 mg, 0.030 mmol). The mixture was refluxed for 1

h and concentrated. The resulting crude product was purified by automated flash

chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product 178.6 mg (82%) as

off white solid: $[\alpha]_D^{20}$ = +24.6 (*c* = 1.16, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$) δ

(ppm): 5.75 (m, 2H), 4.52 (t, *J* = 4.4 Hz, 1H), 4.09 (m, 2H), 3.75 (m, 3H), 3.19 (m, 2H),

2.3-2.4 (m, 2H), 2.15-2.2 (m, 1H), 1.98-2.1 (m, 2H), 1.53-1.8 (m, 5H), 1.45 (m, 1H), 1.30

(d, *J* = 13.6 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 132.3, 127.6,

102.5, 67.0, 66.9, 58.2, 45.8, 32.7, 31.2, 30.9, 27.4, 25.9, 24.0, 23.9; HRMS (TOF, ES+)

$C_{17}H_{32}NO_3S$ $[M+H]^+$ calc'd 330.2103, found 330.2104.

General Procedure for Alkene-Reduction.

To a solution of sulfinamide (0.43 mmol) in EtOH (7 mL) was added Pd/C (45.6 mg,

0.43 mmol). The reaction mixture was purged and back filled with H_2 gas. The mixture

was stirred at rt overnight. The mixture was filtered through celite pad and washed with

CH_2Cl_2. Concentration *in vacuo* gave the crude product which was used without

purification.
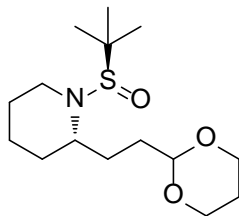
(*R*)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((*R*)-tert-butylsulfinyl)piperidine:

$[\alpha]_D^{20}$ = -3.06 (*c* = 1.00, CHCl$_3$); ^{1}HNMR (400.1 MHz, CDCl$_3$) δ (ppm): 4.52 (t, *J* = 5.2 Hz, 1H), 4.09 (dd, *J* = 6.4, 4.4 Hz, 2H), 3.75 (t, *J* = 11.6 Hz, 2H), 3.19-3.26 (m, 2H), 3.04 (m, 1H), 2.02-2.12 (m, 1H), 1.77-1.92 (m, 3H), 1.46-1.72 (m, 7H), 1.34 (d, *J* = 13.6 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 102.3, 67.1, 59.2, 58.5, 40.7, 32.7, 29.0, 26.3, 25.9, 25.7, 23.7, 19.6; HRMS (TOF, ES+) C$_{15}$H$_{30}$NO$_3$S [M+H]$^+$ calc'd 304.1946, found 304.1946.
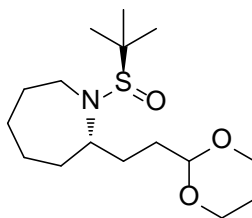
(*S*)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((*R*)-*tert*-butylsulfinyl)azepane:

$[\alpha]_D^{20}$ = -1.7 (*c* = 0.33, CHCl$_3$); ^{1}HNMR (400.1 MHz, CDCl$_3$) δ (ppm): 4.52 (t, *J* = 5.2 Hz, 1H), 4.10 (dd, J = 6.8, 4.8 Hz, 2H), 3.75 (t, *J* = 12.0 Hz, 2H), 3.48 (q, *J* = 6.0 Hz, 1H), 3.37 (m, 1H), 3.08 (m, 1H), 2.05 (m, 1H), 1.82-1.89 (m, 2H), 1.77 (m, 1H), 1.45-1.65 (m, 9H), 1.33 (d, *J* = 13.6 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ

(ppm): 101.5, 66.3, 60.8, 57.7, 42.3, 33.3, 32.1, 29.7, 27.6, 27.1, 25.3, 23.9, 23.5; HRMS (TOF, ES+) $C_{16}H_{32}NO_3S$ $[M+H]^+$ calc'd 318.2103, found 318.2101.
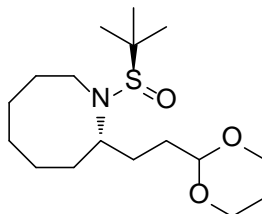
(R)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((R)-tert-butylsulfinyl)azocane:

$[\alpha]_D^{20}$ = -16.9 (c = 0.34, CHCl$_3$); ^{1}HNMR (400.1 MHz, CDCl$_3$) δ (ppm): 4.51 (t, J = 5.2 Hz, 1H), 4.08 (m, 2H), 3.75 (tt, J = 12.0, 2.4 Hz, 2H), 3.31-3.38 (m, 2H), 3.14-3.25 (m, 2H), 2.01-2.12 (m, 1H), 1.81-1.89 (m, 2H), 1.57-1.74 (m, 8H), 1.52 (m, 1H), 1.30-1.44 (m, 3H), 1.2 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 102.3, 67.0, 59.7, 58.6, 43.5, 33.1, 32.8, 29.2, 28.9, 28.6, 25.9, 25.0, 24.1, 22.9; HRMS (TOF, ES+) $C_{17}H_{34}NO_3S$ $[M+H]^+$ calc'd 332.2259, found 332.2257.

General Procedure for Ring Closure.

To the crude product cooled to 0 °C was added 5 ml of 95:5 TFA/H$_2$O, after stirring at rt for 1 h the mixture was concentrated in vacuo to remove the TFA /H$_2$O solvent. The residue was dissolved in DCE and PS-NaBH(OAc)$_3$ (0.5 g, 1.08 mmol) was added and placed on a shaker overnight. The beads were filterd off and the solvent was concentrated *in vacuo* to give the crude azabicyclic product. Purification by flash chromatography gave the desired azabicylic ring product.
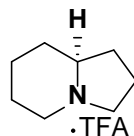
(S)-octahydroindolizine

(S)-octahydroindolizine (1.7).

Flash chromatography (9:1:0.5 CH_2Cl_2/MeOH/NH$_3$) yield the product 10.1 mg (81% over 2-steps) as a yellow oil: $[\alpha]_D^{20}$ = + 1.9 (c = 1.14, EtOH); ^{1}H NMR (400.1 MHz, MeOD) δ (ppm): 4.44 (dt, J= 2, 4 Hz, 1H), 3.61, m, 1H), 3.37 (m, 1H), 3.12 (m, 1H), 2.98 (t, J= 12.6 Hz, 1H), 2.04 (m, 1H), 1.89-1.39 (m, 9H); ^{13}C NMR (100.6 MHz, MeOD) δ (ppm): 62.2, 58.2, 45.9, 31.8, 29.8, 28.9, 23.5, 23.1; HRMS (TOF, ES+) $C_8H_{16}N$ [M+H]$^+$ calc'd 126.1277, found 126.1276.
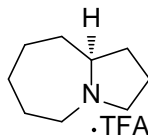
(S)-octahydro-1H-pyrrolo[1,2-a]azepine (1.14).

Flash chromatography (9:1:0.5 CH_2Cl_2/MeOH/NH$_3$) yield the product 11.9 mg (86% over 2-steps) as off white solid: $[\alpha]_D^{23}$ = +0.6 (c = + 1.55, EtOH); ^{1}H NMR (400.1 MHz, MeOD) δ (ppm): 4.57 (s, 1H), 3.60 (m, 2H), 3.23 (m, 1H), 3.17 (m, 1H), 2.05-1.59 (m, 12H); ^{13}C NMR (100.6 MHz, MeOD) δ (ppm): 62.21, 60.41, 46.51, 32.29, 31.83, 29.46, 27.57, 26.13, 25.74; HRMS (TOF, ES+) $C_{14}H_{18}O_4$ [M+H]$^+$ calc'd 140.1439, found 140.1439.
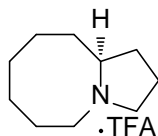
(S)-decahydropyrrolo[1,2-a]azocine (1.20).

Flash chromatography (9:1:0.5 CH₂Cl₂/MeOH/NH₃) yield the product 13.3 mg (87% over 2-steps) as off white solid: $[\alpha]_D^{20}$ = + 1.1 (c = 1.85, EtOH); ¹H NMR (400.1 MHz, MeOD) δ (ppm): 3.62 (m, 2H), 3.34 (m, 1H), 3.18 (m, 2H), 1.6-2.0 (m, 14H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 60.7, 57.4, 44.2, 30.8, 28.1, 27.9, 24.6, 24.1, 24.0, 23.2; HRMS (TOF, ES+) C₁₀H₂₀N [M+H]⁺ calc'd 154.1596, found 154.1594.
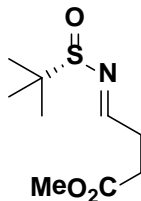
(S)-methyl 4-((tert-butylsulfinyl)imino)butanoate (1.22).

To a solution of methyl 4-oxobutanoate (10 g, 86.2 mmol) in CH₂Cl₂ (500 mL) was added (S)-2-methylpropane-2-sulfinamide (12.9 g, 106.2 mmol) and CuSO₄ (54.7 g, 344.0 mmol). The reaction mixture was stirred at rt overnight. The mixture was filtered through a pad of celite and washed with CH₂Cl₂. Concentration *in vacuo* gave the crude product which was purified by automated flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product 17.9 g (95%) as yellow oil: $[\alpha]_D^{20}$ = +178.1 (c = 1.67, CHCl₃); ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 8.13 (t, J = 2.8 Hz, 1H), 3.68 (s, 3H),

2.82-2.94 (m, 2H), 2.70-2.82 (m, 1H), 2.59-2.67 (m, 1H), 1.17 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 172.4, 167.3, 56.9, 51.9, 31.2, 29.2, 22.4; HRMS (TOF, ES+) C$_9$H$_{18}$NO$_3$S [M+H]$^+$ calc'd 220.1007, found 220.1007.
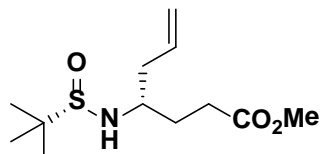
(*S*)-methyl-4-((*S*)-1,1-dimethylethylsulfinamido)hept-6-enoate (1.23).

In-Mediated allylation were done according to procedures previously shown. The reaction was run on a 50 mmol scale, to afford the crude product as >19:1 *dr*, which was then purified by flash chromatography (1:1 Hex/EtOAc) to yield the allylation product 11.5 g (88%) as yellow oil: $[\alpha]_D^{20}$ = +45.7 (*c* = 0.95, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.78 (m, 1H), 5.15 (m, 2H), 3.67 (s, 3H), 3.40 (m, 1H), 3.22 (d, *J*= 7.2 Hz, 1H), 2.40 (m, 3H), 1.90 (m, 1H), 1.75 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 173.9, 133.6, 119.6, 56.1, 55.1, 51.9, 40.1, 30.5, 30.1, 22.8; HRMS (TOF, ES+) C$_{12}$H$_{24}$NO$_3$S [M+H]$^+$ calc'd 262.1477, found 262.1476.
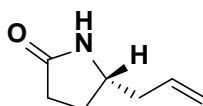
(*S*)-5-allylpyrrolidin-2-one (1.24).

To a solution of compound **1.23** (2.61 g, 10 mmol) in methanol (100 mL) was added 10 mL of 12 N HCl aqueous solution at room temperature. The resultant mixture was then stirred at rt for 2 h. After concentrated, the residue was dissolved in 150 mL

CH_2Cl_2 and 200 mL of saturated aqueous Na_2CO_3 was added. After overnight, the mixture is extracted with CH_2Cl_2; combined organic extracts were washed with water and brine and dried over Na_2SO_4. Filtration and concentration afforded the crude product, which was purified by flash chromatography (1:1 Hex/EtOAc) to yield the desired product 1.21 g (97%) as brown oil: $[\alpha]_D^{20}$ = +2.5 (c = 1.16, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm); 6.43 (br s, 1H), 5.74 (m, 1H), 5.11 (d, J = 12.7 Hz, 2H), 3.70 (q, J = 6.5 Hz, 1H), 2.32 (m, 2H), 2.22 (m, 3H), 1.76 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 173.4, 153.5, 146.9, 130.5, 125.5, 125.2, 116.6, 113.9, 111.9, 60.6, 55.7, 34.1, 28.6, 14.2; HRMS (TOF, ES+) $C_7H_{12}NO$ [M+H]$^+$ calc'd 126.0919, found 126.0921.

General Procedure for lactam *N*-alkylation:

To a solution of lactam (1 equiv), in DMF at 0 ^{o}C was added NaH (1.02 equiv) and the mixture was stirred for 10 mins and additional 10 mins at rt. At 0 ^{o}C bromide (1.5 equiv.) was then added slowly to the mixture and the reaction was warmed to rt and stirred for 2 hrs. The reaction was quenched with water and extracted with EtOAc (3x). The combined organic extract was the dried over Na_2SO_4. Filtration and concentration afforded the crude product, which was purified by flash chromatography (1:1 Hex/EtOAc).
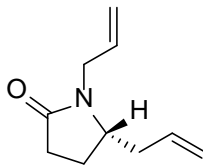
(*S*)-1,5-diallylpyrrolidin-2-one.

The product was prepared according to the general procedure using allyl bromide. The reaction was run on a 5 mmol scale, to afford the product as a light brown oil (800.3 mg, 97%): $[\alpha]_D^{20}$ = -21.4 (*c* = 0.44, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.70 (m, 2H), 5.17 (m, 4H), 4.33 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.67 (septet, *J* = 4.0 Hz, 1H), 3.55 (dd, *J* = 7.2 Hz, 1H), 2.8-2.47 (m, 3H), 2.05-2.23 (m, 2H), 1.77 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 175.03, 132.93, 132.89, 56.79, 43.25, 37.48, 30.18, 23.43; HRMS (TOF, ES+) C$_{10}$H$_{15}$NO [M+H]$^+$ calc'd 166.1228, found 166.1223.
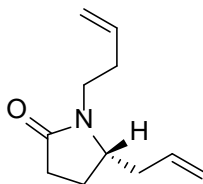
(*S*)-5-allyl-1-(but-3-en-1-yl)pyrrolidin-2-one.

The product was prepared according to the general procedure using 4-bromobut-1-ene. The reaction was run on a 5 mmol scale, to afford the product as colorless oil (868.2 mg, 97%): $[\alpha]_D^{20}$ = -26.3 (*c* = 0.73, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.66-5.82 (m, 2H), 5.03-5.18 (m, 4H), 3.66-3.80 (m, 2H), 2.97 (m, 1H), 2.18-2.57 (m, 7H), 1.69-1.78 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 175.3, 135.3, 132.9, 118.9,

117.0, 57.0, 39.7, 37.6, 31.9, 30.3, 23.6; HRMS (TOF, ES+) $C_{11}H_{18}NO$ [M+H]$^+$ calc'd 180.1388, found 180.1387.
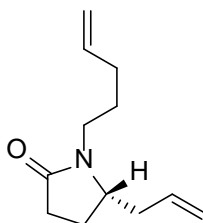
(*S*)-5-allyl-1-(pent-4-en-1-yl)pyrrolidin-2-one.

The product was prepared according to the general procedure using 5-bromopent-1-ene. The reaction was run on a 5 mmol scale, to afford the product as colorless oil (916.8 mg, 95%): $[\alpha]_D^{20}$ = -25.3 (*c* = 0.84, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.65-5.86 (m, 2H), 4.97-5.17 (m, 4H), 3.61-3.69 (m, 2H), 2.93 (m, 1H), 2.22-2.44 (m, 3H), 2.10-2.20 (m, 1H), 2.07 (m, 3H), 1.55-1.79 (m, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 175.2, 137.8, 132.9, 118.9, 115.3, 57.0, 40.0, 37.7, 31.3, 30.3, 26.7, 23.6; HRMS (TOF, ES+) $C_{12}H_{19}NO$ [M+H]$^+$ calc'd 194.2931, found 194.2929.

General Procedure for ring closing metathesis of *N*-alkyl lactam:

To a solution of N-alkyl-lactam (1 equiv), in CH$_2$Cl$_2$ was added 2nd Gen. Grubbs (0.05 equiv). The mixture was refluxed for 1 – 2 h and concentrated. The resulting crude

product was purified by automated flash chromatography (1:1 Hex/EtOAc) to yield the desired product.
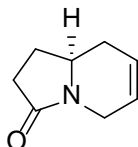
(*S*)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (1.26).

The product was prepared according to the general procedure. The reaction was run on a 3 mmol scale, to afford the product as a brown oil (316.5 mg, 77%): $[\alpha]_D^{20}$ = -27.3 (*c* = 0.62, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.78 (m, 1H), 5.69 (m, 1H), 4.24 (dd, *J* = 16.0, 2.5 Hz, 1H), 3.55 (m, 2H), 2.25-2.42 (m, 4H), 1.99 (m, 2H), 1.68 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 174.4, 124.3, 123.6, 53.1, 40.5, 32.6, 30.1, 25.7; HRMS (TOF, ES+) C$_8$H$_{12}$NO [M+H]$^+$ calc'd 138.0919, found 138.0916.
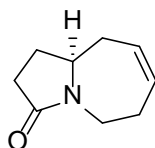
(*S*)-5,6,9,9a-tetrahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one (1.27).

The product was prepared according to the general procedure. The reaction was run on a 3 mmol scale, to afford the product as colorless oil (339.8 mg, 75%): $[\alpha]_D^{20}$ = -22.3 (*c* = 0.52, CHCl$_3$); ^{1}H NMR (400.1 MHz, MeOD) δ (ppm): 5.89 (m,1H), 5.80 (m, 1H), 3.81 (m, 2H), 3.08 (dt, *J* = 1.6, 8 Hz, 1H), 2.4-2.2 (m, 7H), 1.66 (m, 1H); ^{13}C NMR (100.6

MHz, CDCl$_3$) δ (ppm):176.89, 132.37, 129.76, 60.49, 42.61, 36.90, 31.34, 28.61, 26.48;

HRMS (TOF, ES+) C$_9$H$_{14}$NO [M+H]$^+$ calc'd 152.1119, found 152.1116.
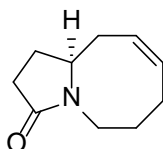
(S)-1,2,6,7,10,10a-hexahydropyrrolo[1,2-a]azocin-3(5H)-one (1.28).

The product was prepared according to the general procedure. The reaction was run on a 3 mmol scale, to afford the product as colorless oil (252.5 mg, 51%): [α]$_D^{20}$ = -20.8 (c = 0.42, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.81 (m, 1H), 5.71 (m, 1H), 3.81 (dt, J = 13.6, 4.0 Hz, 1H), 3.58 (septet, J = 4.8 Hz, 1H), 2.74 (m, 1H), 2.34-2.45 (m, 2H), 2.21-2.32 (m, 2H), 2.11-2.20 (m, 2H), 1.97-2.10 (m, 2H), 1.64-1.76 (m, 1H), 1.48-1.52 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 175.9, 133.4, 125.8, 61.6, 42.9, 33.1, 30.5, 26.9, 24.6, 24.5; HRMS (TOF, ES+) C$_{10}$H$_{16}$NO [M+H]$^+$ calc'd 166.1232, found 166.1233.

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CHAPTER II

TOTAL SYNTHESIS OF THE PYRROLIZIDINE CONTAINING NATURAL PRODUCT CREMASTRINE AND AN UNNATURAL ANALOGUE AND BIOLOGICAL EVALUATION AGAINST THE MUSCARINIC ACETYLCHOLINE RECEPTORS

2.1 Introduction

The azabicyclic ring system is a common structural subunit present in numerous alkaloid natural products and serves as an important scaffold in biologically active and pharmaceutically significant compounds.[1,2,3,4] Pyrrolizidine, indolizidine, pyrrolo[1,2-a]azepine, and pyrrolo[1,2-a]azocine are common examples of the azabicyclic ring system (Figure 2.1). Due to the importance of this ring system, much attention from the scientific community has been given to the synthesis of the azabicyclic skeleton. As previously shown, our lab has developed a robust and versatile methodology to access a variety of azabicyclic ring systems and azabicyclic lactams. The first total synthesis of cremastrine, a pyrrolizidine containing alkaloid, will highlight the usefulness and versatility of our methodology.

pyrrolizidine   indolizidine   pyrrolo[1,2-a]azepine   pyrrolo[1,2-a]azocine
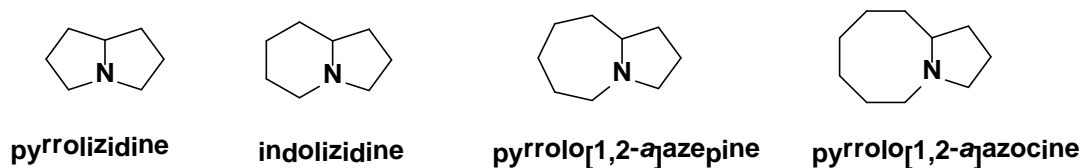
Figure 2.1 Azabicyclic Ring Systems

2.2 Approach to Azabicyclic Ring Systems Via Chiral Sulfinamides

Inspired by Ellman's synthesis of chiral 2-substituted pyrrolidines that proceeds with high yields and diastereoselectivity (Scheme 2.1)[5], we have developed a protocol to afford enantiopure azabicyclic ring systems.
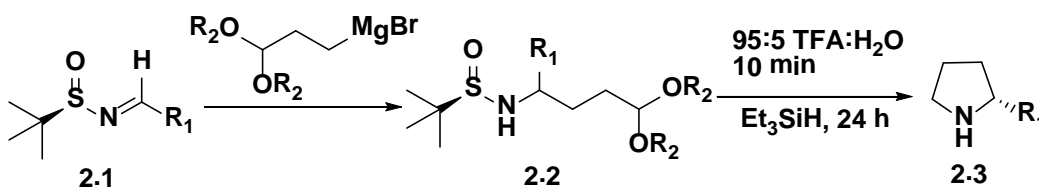
Scheme 2.1 Synthesis of Chiral 2-Substituted Pyrrolidines

Beginning with Ellman's chiral *N*-sulfinylaldimine, an asymmetric Grignard addition or Indium-mediated allylation, *N*-alkylation, ring closing metathesis (RCM), and finally an intramolecular reductive amination or cyclization, reliably and efficiently produces enatiopure azabicyclic ring systems. This approach is outlined in Scheme 2.2. This methodology has been applied to the synthesis cremastrine, a pyrrolizidine alkaloid with reported activity against the muscarinic M_3 receptor.
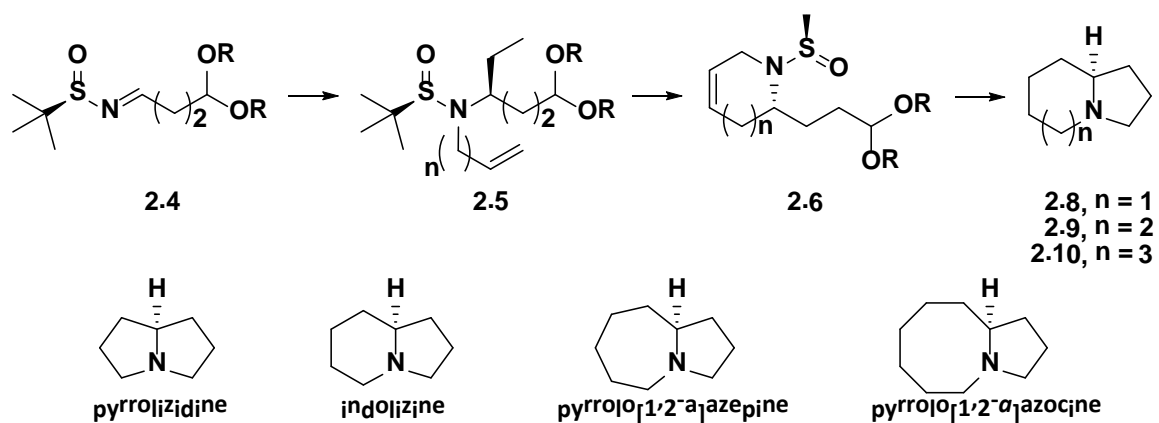
Scheme 2.2 Enantioenriched Azabicyclic Rings Via Chiral Sulfinamides

2.3 Background of Cremastrine

Cremastrine, a pyrrolizidine alkaloid containing a C9 α-hydroxy ester (seen in Figure 2.2), was isolated from an ethanol extract of the Japanese tuber *Cremastra appendiculata* in 2005 by Ikeda and coworkers. This plant is widely used in traditional medicine in Japan and China for treatment of burns, frostbite, skin irritations, and snakebites. In an effort to investigate the biological properties of this herbal remedy, bioassay-guided chromatography resulted in the isolation of the pyrrolizidine natural product, cremastrine.[6]
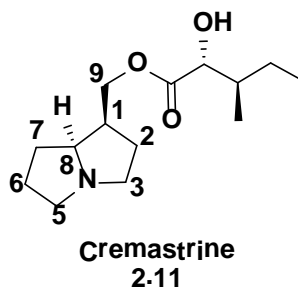
Figure 2.2 Cremastrine

Cremastrine was tested for activity against the muscarinic receptors where it demonstrated notable inhibitory activity at the M_3 receptor. Table 2.1 summarizes inhibition activities of cremastrine against all known muscarinic subtypes.[6] The muscarinic acetylcholine receptor belongs to the G-protein coupled receptor super family and to date, five different subtypes have been individually cloned. The receptor can be activated by acetylcholine and muscarine, and in turn, its activation can be blocked by atropine. M_2 and M_4 receptor subtypes are coupled to the G_i family of G-proteins, whereas M_1, M_3, and M_5 receptor subtypes couple to G_q family. Activation of the M_3 receptor is responsible for the increase of phosphatidyl inositol hydrolysis and calcium mobilization from the extracellular environment to the intracellular environment. The M_3 receptor is involved in a number of essential biological functions including neurotransmitter release, thermoregulation, smooth muscle contractions, gland secretion, cardiovascular activity, and meiosis. Due to its wide range of functions throughout the body, development of a highly selective agonist or antagonist could have a number of therapeutic applications. Such a ligand could be utilized in the treatment of irritable bowel syndrome, chronic obstructive pulmonary disease, and urinary tract disorders. To date, there is no highly selective agonist or antagonist of the M_3 receptor. [7]

Muscarinic Receptor	K_i (nM)
M_1	505
M_2	>5517
M_3	126
M_4	498
M_5	1220

Table 2.1 K_i Values of Cremastrine to Muscarinic Receptors, M_{1-5}

Tropanes are an example of alkaloid compounds that act as muscarinic acetylcholine receptor antagonists.[8] A number of biologically active nortropanes are shown Figure 2.3. Topologically, similarities exist between cremastrine and this scaffold, including a tertiary amine, a small aza-ring functionality, and an ester linkage from the aza-cyclic skeleton.
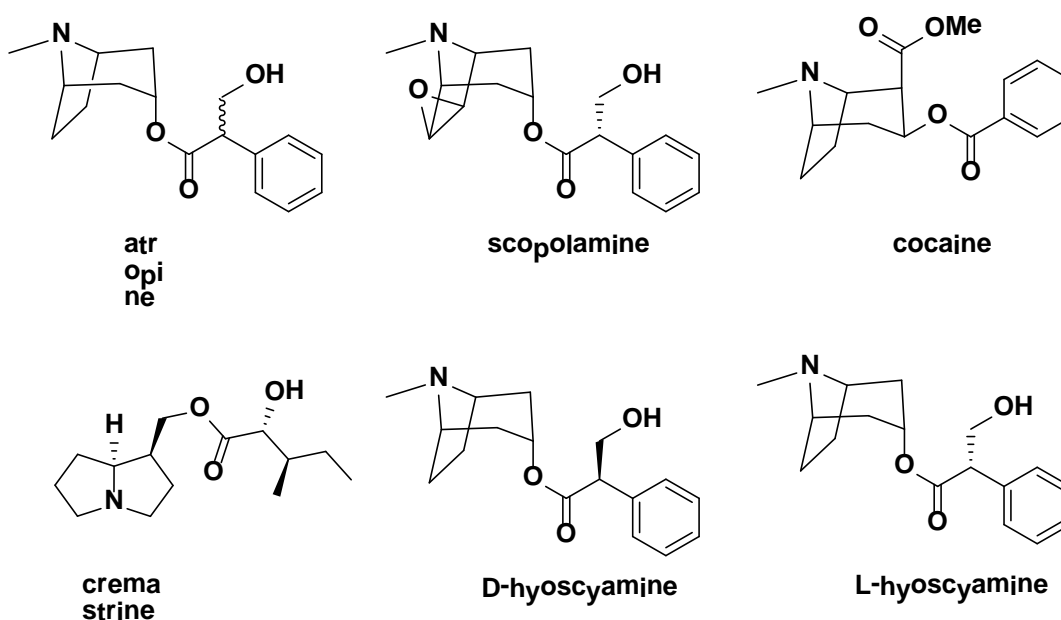
Figure 2.3 Topological Similarities Between Cremastrine and Tropane Derivatives

2.4 Other Approaches to the Pyrrolizidine Core

Due to the unique biological properties and promising applications of pyrrolizidine natural products, a variety of synthetic routes have been devised to access the pyrrolizidine core structure of a variety of natural products.[9] Two synthetic routes stand out in the literature: the total synthesis of epohelmin B by Fürstner and coworkers[9c] and the total synthesis of (-)-trachelanthamidine by Ishibashi and coworkers[9d].

Fürstner's approach (seen in scheme 2.3) uses an azonia-Cope rearrangement to set the chiral amine stereocenter with excellent optical purity and a nosyl deprotection/transannular-epoxide-opening cascade to access the pyrrolizidine core of the natural product.[9c] Azonia-Cope rearrangement methodology by Kobayashi and coworkers allowed for the transformation of aldehyde **2.12** to chiral homoallylic amine. This proceeded through a [3,3]-sigmatropic rearrangement to form homoallylic amine **2.13** after hydrolytic workup. A number of synthetic steps later they arrived at azacyclooctene derivative **2.16,** which upon treatment with mercaptoacetic acid initiates a transannular-epoixde-opening cascade reaction by exposing the secondary amine and spontaneously opening the oxirane to provide pyrrolizidine derivative **2.17.** One more synthetic transformation afforded the pyrrolizidine natural product, epohelmin B **2.18**, in 28% yield in 11 steps from commercially available starting materials.
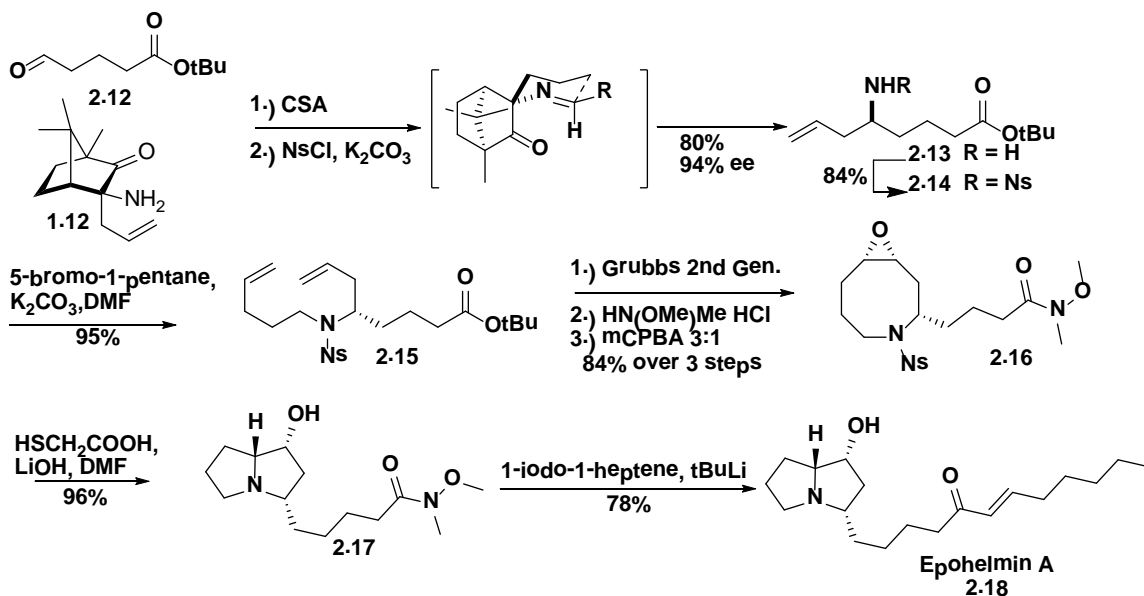
Scheme 2.3 Total Synthesis of Epohelmin B

Ishibashi and coworkers synthesized (-)-trachelanthamidine through a key single electron transfer step using 1,4-dimethylpiperazine to access the substituted pyrrolizidine ring (Scheme 2.4). Compound **2.21**, 2-(2-acetoxyethenyl)-*N*-(trichloroacetyl)pyrrolidine, was accessed from proline after a number of synthetic steps. Refluxing this trichloroacetyl in 1,4-dimethylpiperazine allowed for a radical cyclization reaction to furnish the pyrrolizidine core. This radical cyclization proceeds through a single electron transfer reaction from 1,4-dimethylpiperazine to eliminate a chloride anion and provide a radical intermediate. This radical species can then undergo an intramolecular termination step to form the substituted pyrrolizidine core as a single stereoisomer. Elucidation of the mechanism of this single electron transfer reaction is currently being explored by Ishibashi and coworkers. With pyrrolizidine **2.22**, two more synthetic transformations yielded (-)-trachelanthamidine **2.23** in 13% yield over 9 steps.[9d]
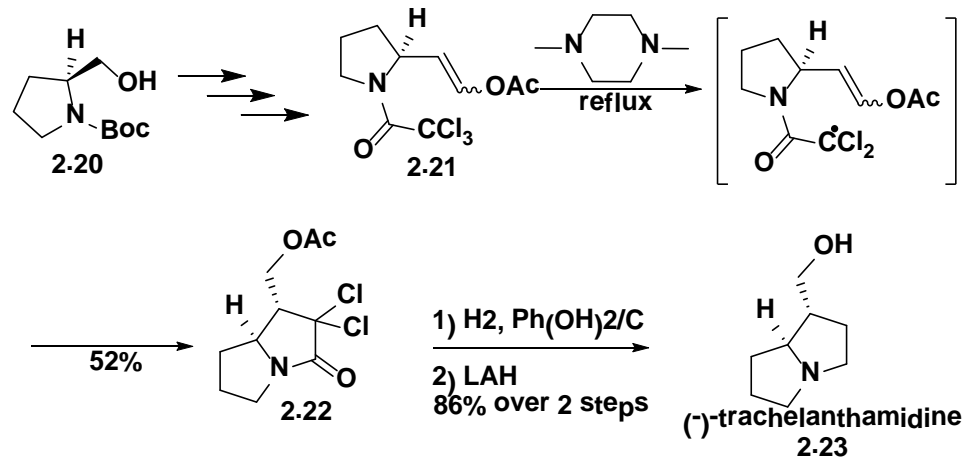
Scheme 2.4 Total synthesis of (-)-Trachelanthamidine

2.5 Total Synthesis of Cremastrine

Our retrosynthetic analysis sought to incorporate methodology developed in the Lindsley laboratory that allows for rapid and efficient access to the azabicyclic ring structure. Scheme 2.5 outlines our retrosynthesis of cremastrine **2.11**. An initial disconnection at the C9 ester linkage yields α-hydroxy carboxylic acid **2.24** and C9 hydroxy pyrrolizidine **2.23** where, in the synthetic direction, cremastrine can be accessed through a carbodiimide coupling of the alcohol and carboxylic acid. The pyrrolizidine core **2.23** could be accessed through pyrrolidine derivative **2.25** which is prepared from sulfinamide **2.26** after several steps. The chiral sulfinamide is constructed through an indium mediated addition of aldimine **2.27** and (*E*)-bromobutene derivative **2.28**. The *tert*-butyldimethylsilyl (TBS) protected α-hydroxy carboxylic acid can be accessed from the amino acid, D-isoleucine **2.29.**
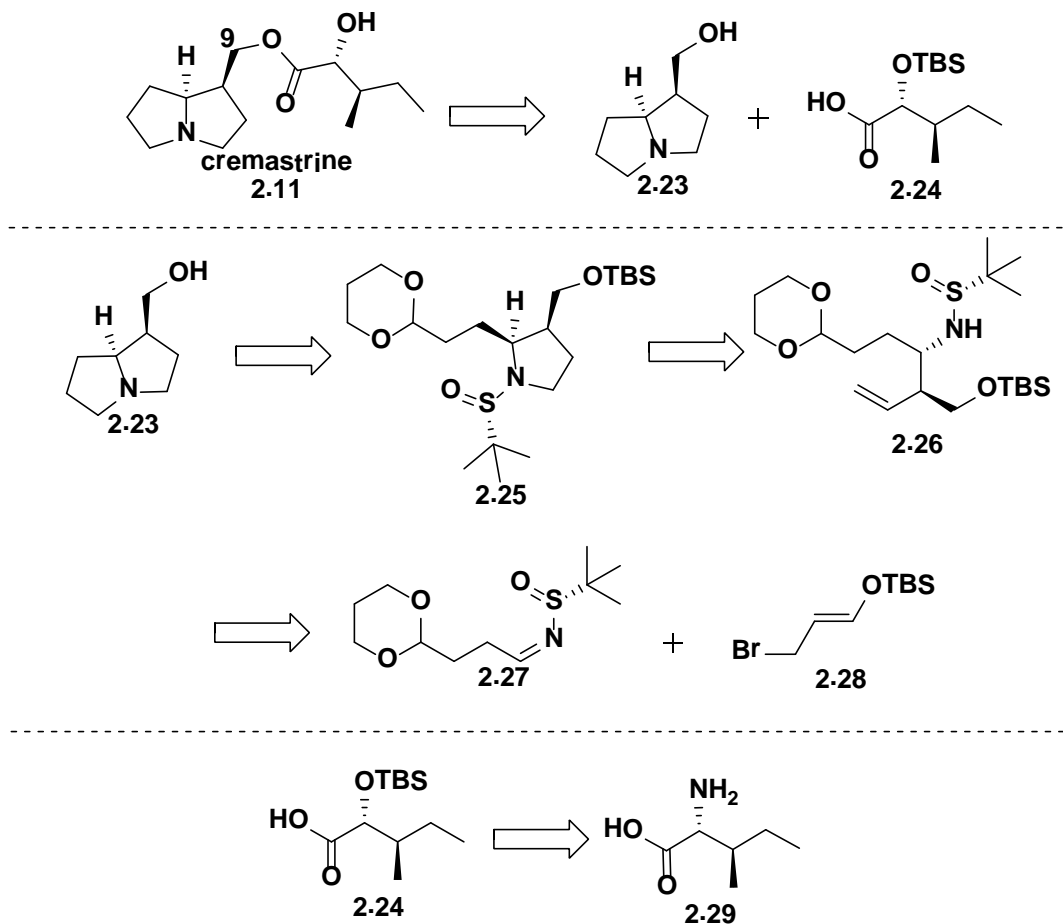
Scheme 2.5 Retrosynthesis of Cremastrine

Construction of TBS protected α-hydroxy carboxylic acid is outline in Scheme 1.6 below. Conversion of D-isoleucine **2.30** to α-hydroxy carboxylic acid **2.31** was accomplished using a procedure that converts the amino acid to the α-hydroxy acid with retention of stereochemistry. Treatment of the amino acid with aqueous nitrous acid leads to diazotization of the α amine stereocenter followed by hydrolysis to furnish the enatiopure α-hydroxy acid **2.31**.[10] Treatment of acid **2.31** with excess *tert-*

butyldimethylsilyl chloride, followed by basic hydrolysis, gives compound **2.32** in 65% yield over 3 steps.[11]
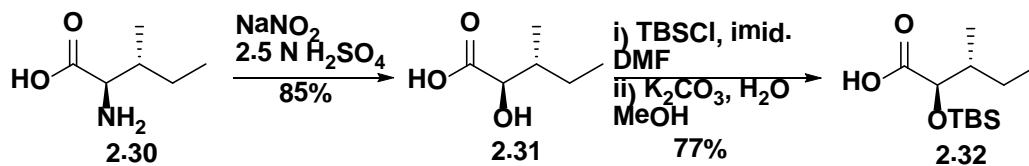
Scheme 2.6 Synthesis of α-Hydroxy Carboxylic Acid **2.32**

For the generation of the pyrrolizidine core (see Scheme 2.7), we initially began with acetal **2.32**. Displacement of the bromide with sodium cyanide yielded the nitrile which was reduced to the aldehyde **2.34** using diisobutylaluminium hydride.[12] Another approach to aldehyde **2.34,** which did not generate cyanide waste, began with 4-pentenal (**2.33**). Conversion of aldehyde **2.33** to the acetal, followed by oxidative cleavage with ozone and dimethyl sulfide, generated aldehyde **2.34**. A condensation of commercially available (*R*)-*tert*-butanesulfinamide and aldehyde **2.34** gives chiral aldimine **2.35**.
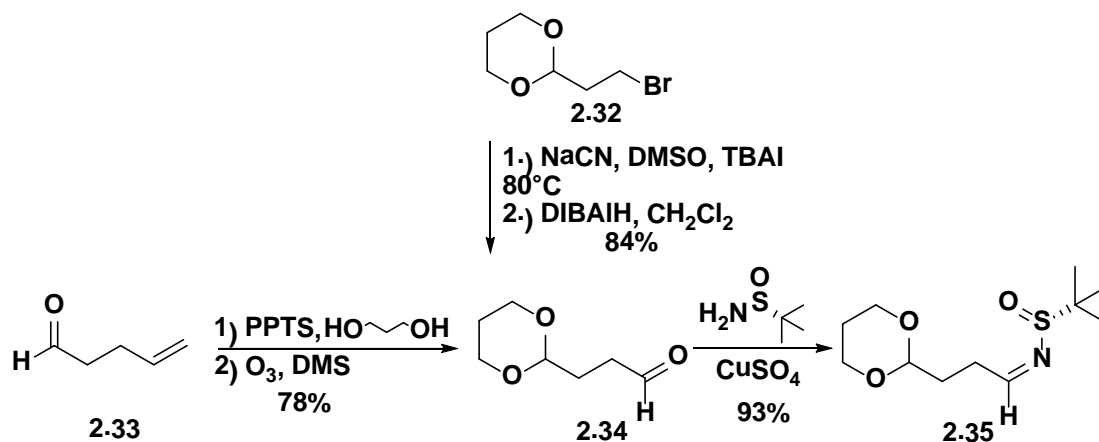
Scheme 2.7 Synthesis of *N*-sulfinylaldimine **2.35**

From aldimine **2.35**, we next sought to install two stereocenters through an indium mediated allylation using a variety of bromides. These results are outlined in Scheme 2.8. Utilizing bromo-ester **2.36** and **2.37** gave the desired homoallylic sulfinamide **2.41** and **2.42** in 50-55% conversions, respectively. These results were promising as revealed by the bromo-esters. Using free alcohol **2.40** led to lower conversion and diastereoselectivity, while no reaction occurred when PMB-ether **2.39** was used. An increase of the reaction conversion to product and moderate diastereoselectivity was observed when TBS-ether **2.38** was used (>85% conversion, >4:1 *d.r.*) (Scheme 2.8).
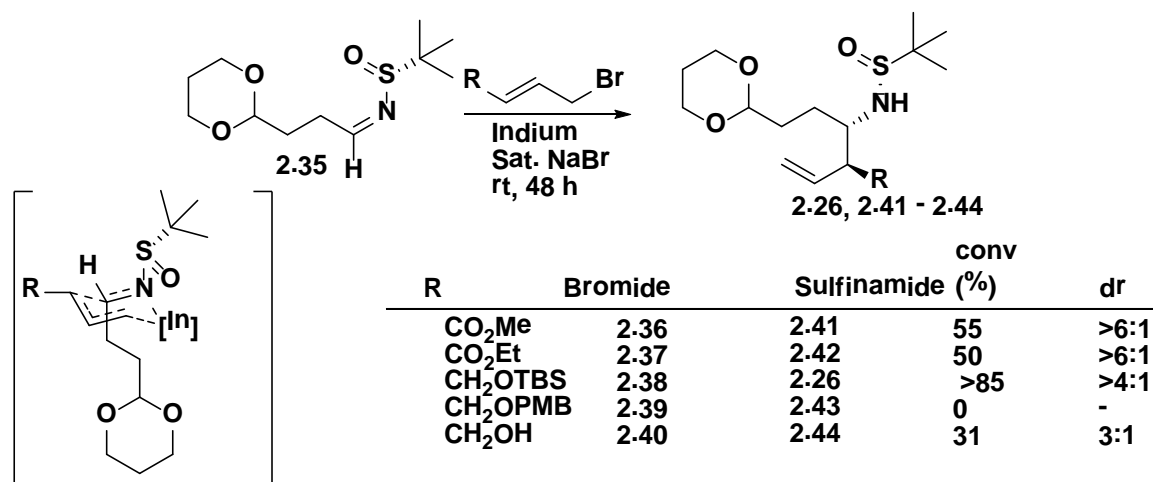
Scheme 2.8 Indium-Mediated Allylation Aldimine **2.35**

R	Bromide	Sulfinamide	conv (%)	dr
CO$_2$Me	2.36	2.41	55	>6:1
CO$_2$Et	2.37	2.42	50	>6:1
CH$_2$OTBS	2.38	2.26	>85	>4:1
CH$_2$OPMB	2.39	2.43	0	-
CH$_2$OH	2.40	2.44	31	3:1

The *syn*-configuration was assigned according to literature precedent and the six-membered chair Zimmerman-Traxler transition state model.[13] These reactions were all performed at 0.05 mmol scale of **2.35.** Surprisingly, upon scaling up the synthesis (even at 0.25 mmol scale of **2.35**) only 20% conversion to the desired product was observed. After surveying a variety of reaction conditions, we found that pre-mixing by stirring and sonication of the indium metal and bromide before adding the aldimine was crucial to deliver homoallylic sulfinamide **2.26** with yields consistent to the small-scale reactions.

With sulfinamide **2.26** in hand, next we sought to access the pyrrolizidine core structure **2.23**. Scheme 2.9 below outlines the synthetic approach. Hydroboration-oxidation of the terminal olefin of **2.26** furnished primary alcohol **2.45** in excellent yield. Initial attempts to form the substituted pyrrolidine ring system involved mesylation of the alcohol and displacement in a 5-*exo*-tet cyclization fashion. This was unfortunately unsuccessful, but under Mitsunobu conditions, we successfully obtained substituted

pyrrolidine **2.25**. NOESY-NMR data confirms the *syn*-stereochemical relationship of the two chiral centers on the pyrrolidine ring. From here, TBAF deprotection of the *tert*-butyldimethylsilyl ether gave primary alcohol **2.46**. Deprotection of the acetal and the sulfinyl exposed the aldehyde and amine, respectively. This was theorized to undergo an intramolecular condensation to form the imine, upon which an addition of a reducing agent would produce **2.23**, the pyrrolizidine core structure. A screening of conditions outlined in Scheme 1.9 resulted in no formation of any desired product. These conditions were based around work by Ellman and coworker's[5] and by the Lindsley laboratory.[14]
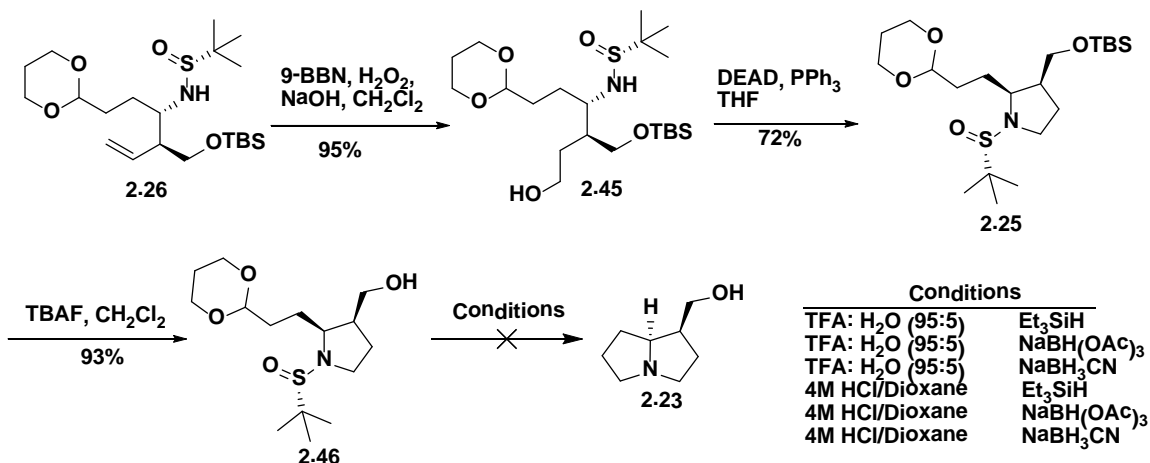
Scheme 2.9 Attempted Formation of the Pyrrolizidine Core Structure

We believe that the free alcohol underwent undesired side reactions that prevented the formation of **2.23** from substituted pyrrolidine **2.46**. The formation of the ester side chain of cremastrine would remove this alcohol from the ring closing reaction. Thus, we next sought to form the ester linkage through a carbodiimide coupling of primary alcohol **2.46** and carboxylic acid **2.24**. Scheme 2.10 outlines this approach. A 1-

ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC·HCl) mediated coupling between acid **2.24** and alcohol **2.46** gave ester **2.47** in excellent yield. Upon screening the same set of conditions previously used for the attempted transformation of **2.46** to **2.23**, the best deprotection/reductive amination conditions were found to be TFA:H$_2$O (95:5) followed by triethylsilane as the reducing agent. Global deprotection of **2.47** allowed for intramolecular condensation to the imine pyrrolizidine **2.48**, then reductive amination with triethyl silane furnished the natural product cremastrine **2.11** in 80% yield from ester **2.47**.
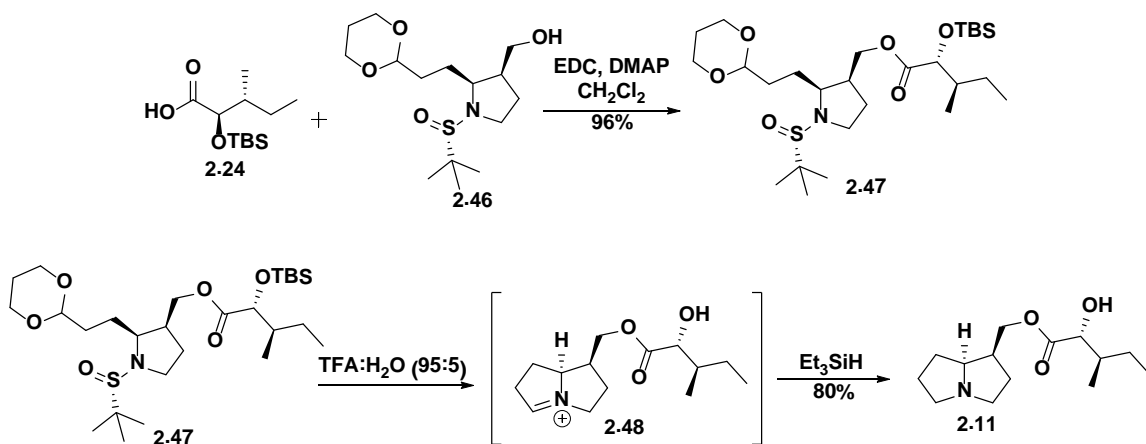
Scheme 2.10 Completion of the synthesis of cremastrine

Employing conditions developed in the Lindsley laboratory to access azabicyclic scaffolds, the total synthesis of cremastrine was completed. Starting from commercially available aldehyde **2.34**, cremastrine was synthesized in a longest linear sequence of 7 steps (9 steps overall) with a 31% overall yield. Additionally, an unnatural analogue, benzylated at the α-hydroxy ester linkage was generated from primary alcohol **2.46** using

similar chemistry to access cremastrine. Scheme 2.11 outlines the chemistry to this unnatural analogue
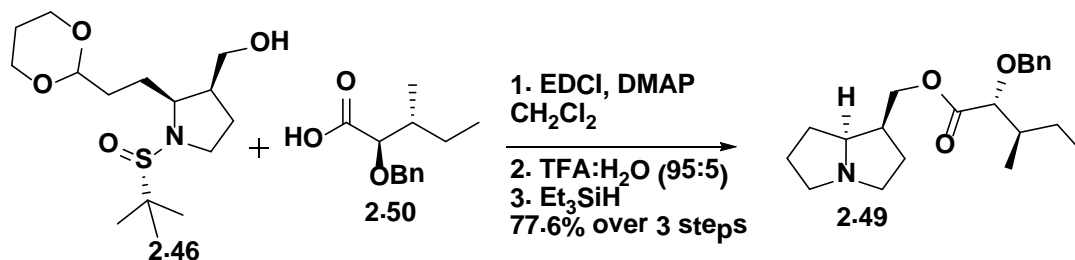
Scheme 2.11 Synthetic Route to an Unnatural Analogue of Cremastrine

Cremastrine was reported to display modest selectivity for the binding the the muscarininc acetylcholine receptor subtype 3 (2 to 20 fold), were upon evaluation by our lab of the natural and unnatural analogue against muscarinic acetylcholine receptor subtype 1-5 (M_1-M_5) in a functional assay to determine if the modest M_3 selectivity reported by Ikeda would translate into selective M_3 functional antagonist activity. It was shown that cremastrine was a *pan*-mAChR functional antagonist, which moderately inhibited M_1-M_5 (M_1 IC_{50} = 2.8 µM, M_2 IC_{50} = >10 µM, M_3 IC_{50} >10 µM, M_4 IC_{50} = >10 µM, M_5 IC_{50} = 4.0 µM). There was a clear preference for M_1 and M_5 and very weak activity at the M_3, contrary data to that of the isolation paper. Thus, it can be concluded that cremastrine is not a selective M_3 antagonist. The unnatural analog of cremastrine was more potent than the natural cremastrine (M_1 IC_{50} = 1.9 µM, M_2 IC_{50} = >10 µM, M_3 IC_{50} =5 µM, M_4 IC_{50} = 5.2 µM, M_5 IC_{50} = 2.0 µM), but is still a *pan*-mAChR antagonist.

2.6 Cremastrine Experimentals

All reagents were purchased from Sigma-Aldrich Corp., TCI America, FCH Group Reagents for Synthesis, and Alfa Aesar and were used without purification. Analytical thin-layer chromatography (TLC) was performed on 250 μm silica gel plates from Sorbent Technologies. Visualization was accomplished via UV light, and/or the use of iodine on silica and potassium permanganate solution followed by application of heat. Chromatography was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies or Silica RediSep Rf flash columns on a CombiFlash Rf automated flash chromatography system. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 (400 MHz) instrument or a Bruker AV-400 (500 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.00 (CDCl$_3$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet br = broad, dd=doublet of doublets, dq=doublet of quartets, td = triplet of doublets, pd = pentet of doublets, m = multiplet), coupling constant (Hz), integration. Low resolution mass spectra (LCMS) were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra (HRMS) were recorded on a Waters Qtof-API-US plus Acquity system with ES as the ion source. Analytical high pressure liquid chromatography (HPLC) was performed on an Agilent 1200 analytical LCMS with UV detection at 214 nm and 254 nm along with ELSD detection. Optical rotations were acquired on a Jasco P-2000 polarimeter at 23 ^{o}C and 589nm. The specific rotations were calculated according to the equation $[\alpha]_D^{23} = \frac{100\alpha}{l \, x \, c}$ where l is the path length in decimeters and c is the concentration in g/100mL.
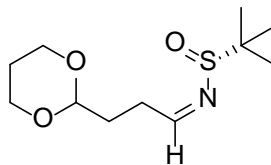
(*R*)-*N*-(3-(1,3-dioxan-2-yl)propylidene)-2-methylpropane-2-sulfinamide (2.35).

To a solution of 3-(1,3-dioxan-2-yl)propanal (2.1 g, 14.6 mmol) in CH_2Cl_2 (100 mL) was added (*R*)-2-methylpropane-2-sulfinamide (2.12 g, 17.5 mmol) and $CuSO_4$ (7.0 g, 43.8 mmol). The reaction mixture was stirred at rt overnight. The mixture was filtered through a through celite pad and washed with CH_2Cl_2. Concentration *in vacuo* gave the crude product which was purified by automated flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product (3.35 g, 93%) as yellow oil: $[\alpha]D^{20}$ = -208.8 (*c* = 0.86, CHCl3); 1H NMR (400.1 MHz, CDCl3) δ (ppm): 7.98 (t, *J* = 4.10 Hz, 7.36 Hz, 1H), 4.50 (t, *J* = 4.8 Hz, 1H), 3.97 (dd, *J* = 6.0, 4.8 Hz, 2H), 3.62 (dt, J = 2.25 Hz, 12.60 Hz, 2H), 2.52 (dt, *J* = 4.0 Hz, 2H), 1.93 (m, 1H), 1.81 (m, 2H), 1.23 (dm, *J* = 13.8 Hz, 1H), 1.07 (s, 9H); 13C NMR (100.6 MHz, CDCl3) δ (ppm): 168.69, 100.58, 66.57, 56.28, 30.40, 30.28, 25.45, 22.05; HRMS (TOF, ES+) $C_{11}H_{22}NO_3S$ [M+H]$_+$ calc'd 248.1320, found 248.1319.
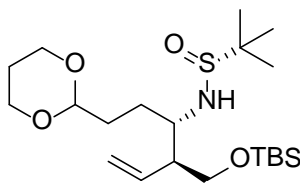
(R)-N-((3S,4S)-4-((((tert-butyldimethylsilyl)oxy)methyl)-1-(1,3-dioxan-2-yl)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide (2.26).

To a solution of (E)-((4-bromobut-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (10.28 g, 38.739 mmol) dissolved in a 9.3:10 solution of NaBr and H_2O (14 g:15 mL) was added indium powder (4.431 g, 38.739 mmol). This solution was stirred vigorously for 1 hour followed by sonication for another 1hr, upon which (R)-N-((3S,4S)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1-(1,3-dioxan-2-yl)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide was added. This solution stirred at rt for 48 hours, quenched with sat. $NaHCO_3$ and filtered through a bed of celite. Phases were separated and the aqueous phase was extracted with CH_2Cl_2. All organic layers were combined, washed with H_2O, dried my $MgSO_4$, filtered, and concentrated *in vacuo*. Crude product was purified by flash column chromatography (7:3 Hexanes:EtOAc) to give the desired product (3.57 g, 85 % yield, 4:1). $[\alpha]D^{20}$ = -23.2 (*c* = 1.0, CHCl3); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.74 – 5.61 (m, 1H), 5.26 – 5.07 (m, 2H), 4.47 (t, *J* = 4.89, 1H), 4.09 – 4.04 (m, 2H), 3.80 – 3.62 (m, 5H), 3.45 – 3.37 (m, 1H), 2.71 – 2.63 (m, 1H), 2.11 – 1.99 (m, 1H), 1.89 – 1.51 (m, 4H), 1.33 – 1.29 (d, *J* = 15, 1H), 1.17 (s, 9H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 135.0, 119.8, 102.1, 66.8, 64.2, 58.0, 56.0, 51.5 31.8, 26.2, 25.8, 25.7, 22.8, 18.2, -5.3, -5.4; HRMS (TOF, ES+) $C_{21}H_{43}NO_4SSi$ [M+H]$^+$ calc'd 434.2760, found 434.2762.
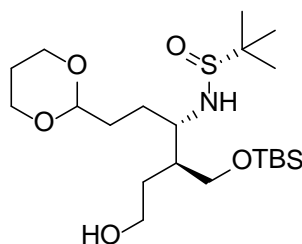
(R)-N-((3S,4S)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1-(1,3-dioxan-2-yl)-6-hydroxyhexan-3-yl)-2-methylpropane-2-sulfinamide (2.45).

To a solution of (870 mg, 2.007 mmol) in 0.25 mL anhydrous THF at 0°C was added 9-BBN (6 mL of 0.5M in THF). Stir for 4 hours at 0°C. Upon full consumption of starting material (TLC or LCMS), an excess of 30% H_2O_2:15% NaOH (1:1) (40ml total) was added slowly at 0°C. Stir for 16 hours and quench reaction with H_2O, extract 4X with EtOAc (15 mL ea), dried with $MgSO_4$, and filter through a bed of celite. Concentration *in vacuo* gave the crude product which was purified by flash chromatography (19:1 CH_2Cl_2:MeOH to 9:1 CH_2Cl_2:MeOH). To yield desired alcohol as a colorless oil (887mg, 98% yield). $[\alpha]D^{20}$ = -14.167 (c = 0.99, CHCl3); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 4.5 (t, J = 4.75, 1H), 4.28 (d, J = 8.86, 1H), 4.09 – 4.05 (m, 2H), 3.79 – 3.64 – (m, 4H), 3.57 – 3.53 (dd, J = 5.89, 1H), 3.22 (m, 1H), 2.09 – 2.00 (m, 2H), 1.89 – 1.81 (m, 1H), 1.77 – 1.71 (m, 1H), 1.61 – 1.42 (m, 5H), 1.32 (d, J = 13.2, 1H), 1.19 (s 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm):102.0, 66.8, 64.8, 61.5, 59.2, 56.0, 42.6, 32.3, 30.8, 27.7, 25.9, 25.7, 22.9, 18.3, -5.43, -5.46; HRMS (TOF, ES+) $C_{21}H_{46}NO_5SSi$ [M+H]$^+$ calc'd 452.2866, found 452. 2869.
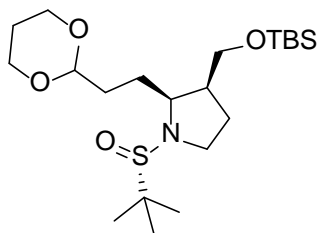
(2S,3S)-2-(2-(1,3-dioxan-2-yl)ethyl)-3-(((tert-butyldimethylsilyl)oxy)methyl)-1-((S)-tert-butylsulfinyl)pyrrolidine (2.25).

To a solution of (1.47 g, 3.26 mmol) in 32 mL THF at 0°C was added 1.9 mL of diethylazodicarboxylate (40% in toluene) (4.234 mmol) followed by triphenylphosphine (1.11 g 4.234 mmol). Reaction was monitored by TLC and stirred for 3 hours. Quench with 32 mL H_2O and separate the organic and aqueous layer. Aqueous was extracted 3 times with EtOAc (15 mL ea) and all organic layers were combined. Organic layer was dried with $MgSO_4$, filtered through a bed of celite, and concentrated *in vacuo*. Crude product was purified by column chromatography (100% CH_2Cl_2 to 10:1 CH_2Cl_2:MeOH) to give the desired compound as a colorless oil (1.02 g, 72%).). $[\alpha]D^{20}$ = -35.3 (*c* = 1.12, $CHCl_3$); ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm) = 4.49 (t, J = 5.02 Hz, 1H), 4.07 (dd, J = 5.05, 2H), 3.73 (m, 2H), 3.62 (m, 1H), 3.52 (m, 1H), 3.43 (m, 2H), 2.72 (m, 1H), 2.02 (m, 2H), 1.90 (m, 1H), 1.61 (m, 5H), 1.32 (d, J = 13 Hz, 1H), 1.18 (s, 9H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 102.10, 68.20, 66.83, 63.93, 57.36, 45.32, 40.46, 31.33, 30.23, 28.83, 25.88, 25.75, 23.99, 18.18, -5.4,0-5.45; HRMS (TOF, ES+) $C_{21}H_{43}NO_4SSi$ $[M+H]^+$ calc'd 434.2760, found 434.2761.
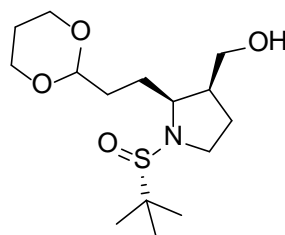
((2S,3S)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((S)-tert-butylsulfinyl)pyrrolidin-3-yl)methanol (2.46).

To a solution of (1.02 g, 2.35 mmol) in 25 mL THF at 0°C was added 3.0 mL of a 1.0 M solution of tetrabutylammonium fluoride dropwise. Allow to warm to RT and stir for 6 hours. Quench with 25 mL H_2O and extract 3 times with EtOAc (25 mL ea). Combine organic layers, dry with $MgSO_4$, and filter through a bed of celite. Concentrate *in vacuo* and purify crude material by flash column chromatography (100% CH_2Cl_2 to 10:1 CH_2Cl_2:MeOH) to give desired alcohol as a white solid (699 mg, 93% yield).). $[\alpha]D^{20}$ = -55.0 (c = 1.21, $CHCl_3$); ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm) = 4.48 (t, J = 5.15 Hz, 1H), 4.03 (dd, J = 4.85 Hz, 2H), 3.73 – 3.5 (m, 6 H), 2.79 (m, 1H), 2.28 (m, 1H), 2.0 (m, 1H), 1.88 (m, 1H), 1.68 (m, 2H), 1.55 – 1.44 (m, 3H), 1.29 (d, J = 9.2, 1H), 1.14 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) = 101.97, 68.01, 66.77, 61.37, 57.75, 44.52, 39.33, 32.10, 27.76, 25.63, 24.38, 24.03; HRMS (TOF, ES+) $C_{15}H_{29}NO_4S$ $[M+H]^+$ calc'd 320.1896, found 320.1896.
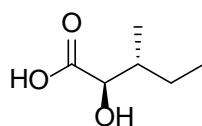
(2R,3R)-2-hydroxy-3-methylpentanoic acid (2.31).

A solution of D-isoleucine (1.311 g, 10.00 mmol) was dissolved in 40 mL of 0.5M H_2SO_4 and cooled to 0°C. Sodium nitrite was next dissolved in 13.5 mL H_2O and slowly added to the reaction flask. This solution stirred at 0°C for 3 hours and then at rt for 24 hours. Extract 3 times with diethyl ether (50 mL ea), organic layers were combined, and then washed once with brine and once with H_2O (15 mL ea). The organic phase was dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give a viscous oil. Recrystallization

with hexane-ether produced carboxylic acid (1.13 g, 8.5 mmol).). $[\alpha]D^{20}$ = -18.0 (c = 0.75, CHCl3); ^{1}H NMR (400.1 MHz, D_2O) δ (ppm) = 4.18 (d, J = 3.5 Hz, 1H), 1.86 (m, 1H), 1.48 – 1.38 (m, 1H), 1.29 – 1.18 (m, 1H), 0.98 (d, J = 7.3 Hz, 3H), 0.90 (t, J =7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 179.1, 74.5, 38.6, 23.8, 15.0, 11.6; HRMS (TOF, ES+) $C_6H_{12}O_3Na$ [M+H]$^+$ calc'd 155.0684, found 155.0683.
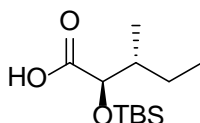
(2R,3R)-2-((tert-butyldimethylsilyl)oxy)-3-methylpentanoic acid (2.32).

To a cooled to 0°C solution of 1.25 (750 mg, 5.68 mmol) and imidazole (1.16 g, 17.03 mmol) in anhydrous DMF was added *tert*-butyldimethylsilyl chloride (2.14 g, 14.19 mmol). Reaction flask was removed from the ice bath and stirred at RT for 16 hours. The reaction was quenched with 100 mL H_2O, extracted 3 times with diethyl ether (50 mL ea), organic layers were combined, and washed with brine and water (50 mL ea). Organic layer was dried with $MgSO_4$, filtered through a bed of celite, and concentrate *in vacuo*. Crude was redissolved in 50 mL of MeOH and cooled to 0°C with an ice bath. K_2CO_3 (2 g, 138.025 mmol) was dissolved in 15 mL H_2O and slowly added to reaction flask. Reaction stirred for 4 hours at RT and subsequently concentrated *in vacuo*. Redissolve in 20 mL H_2O and acidify to pH=4 with 10% citric acid. Reaction was extracted 3 times with diethyl ether (40 mL ea), dry with Na_2SO_4, filtered through celite, and concentrated *in vacuo*. Crude oil was purified by column chromatography (5:1 hexanes: EtOAc) to give desired carboxylic acid (1.01 g, 4.37 mmol). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm)

= 4.14 (d, J = 4 Hz, 1 H), 1.8 (m, 1H), 1.5 (m, 1H), 1.27 (m, 1H), 0.97 – 0.83 (m, 16H), 0.1 (s, 6H). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 177.90, 76.68, 39.77, 25.64, 24.12, 18.10, 15.10, 11.70, -5.06, -5.19. HRMS (TOF, ES+) C$_6$H$_{26}$O$_3$SiNa [M+H]$^+$ calc'd 269.1549, found 269.1548.
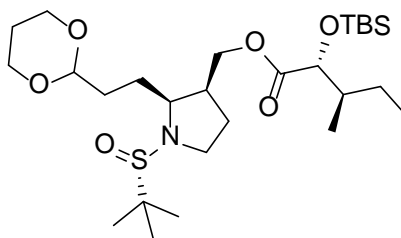
(2R,3R)-((2S,3S)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((S)-tert-butylsulfinyl)pyrrolidin-3-yl)methyl-2-((tert-butyldimethylsilyl)oxy)-3-methylpentanoate (2.47).

To a solution of alcohol (103 mg, 0.322 mmol) and acid (87 mg, 0.355 mmol) in 3.5 mL CH$_2$Cl$_2$ at 0°C was added 1 crystal of 4-dimethylaminopyridine followed by 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (135.8 mg, 0.71 mmol). Reaction was allowed to warm to rt. Reaction was stirred to 2 hours, quenched with H$_2$O, and extracted 3 times with diethyl ether (5 mL ea). Combine organic layers, dry with MgSO$_4$, and filter through a bed of celite. Concentrate *in vacuo* and purify crude material by flash column chromatography (50:1 CH$_2$Cl$_2$:MeOH to 10:1 CH$_2$Cl$_2$:MeOH) to give desired ester **1.42** as a light yellow solid (169 mg, 96% yield).). [α]D^{20} = -26.0 (*c* = 1.00, CHCl3);). ^{1}H NMR (400.1 MHz, CDCl3) δ (ppm) = 4.48 (t, J = 5.15 Hz, 1H), 4.11 – 4.04 (m, 4H), 4.00 (d, J=5.43, 1H), 3.76 – 3.69 (m, 3H), 3.64 (q, J=8.5, 1H), 3.43 (m, 1H), 2.84 – 2.74 (m, 2H), 2.47 (q, J = 5.1, 1H), 2.16 (q, J = 3.9, 1H), 2.11 – 1.94 (m, 2H), 1.82

– 1.71 (m, 2H), 1.69 (s, 1H), 1.66 – 1.41 (m, 5H), 1.32 (d, J = 13 Hz, 1H), 1.88 (s, 9H), 0.90 (s, 9H), 0.89 (d, J = 7.3 Hz, 3H), 0.86 (t, J=7.6 Hz, 3H). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm):173.45, 101.78, 76.33, 68.22, 67.80, 66.77, 57.83, 40.77, 39.39, 38.95, 32.11, 28.07, 25.64, 24.58, 23.99, 23.92, 23.88, 18.16, 15.38, 11.41, -5.00, -5.46. HRMS (TOF, ES+) C$_{27}$H$_{53}$NO$_6$SSi [M+H]$^+$ calc'd 548.3441, found 548.3445.
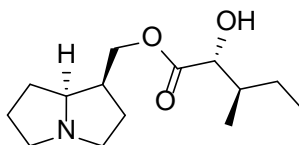
(2R,3R)-((1S,7aS)-hexahydro-1H-pyrrolizin-1-yl)methyl-2-hydroxy-3-methylpentanoate (2.11).

A solution of ester **15** (50 mg, 0.0914 mmol) in 2 mL of 95:5 trifluoroacetic acid:H$_2$O was stirred for 1 hr at room temperature then 0.19 mL of triethyl silane was added. This solution was stirred over night and concentrated *in vacuo* to give a crude, yellow oil. This was dissolved in 1 mL DMSO and purified by reverse phase chromatography (2% to 45% H$_2$O(0.1%TFA):AcCN) to give (19 mg, 80% yield) as a colorless oil. [α]D^{20} = -15.2 (c = 0.97, CHCl3) ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm) = 6.87 (m, 1H), 4.49 (d, J = 5.2, 1H), 4.33 (m, 1H), 4.20 (m, 1H), 4.18 (m, 1H), 3.55 (m, 1H), 3.49 (t, J = 7 Hz 1H), 2.88 (m, 1H), 2.8 (m, 1H), 2.65 (dt, J = 8.1, 1H), 1.99 (m, 1H), 1.90 – 1.80 (br m, 4H), 1.72 (m, 2H), 1.59 (m, 1H), 1.42 (m, 1H), 1.1 (d, J = 4 Hz, 3H), 0.99 (t, J = 7 Hz, 3H). ^{13}C NMR (100.6 MHz, pyr-d5) δ (ppm): 174.6, 75.6, 68.1, 63.1, 55.38, 53.27, 39.9, 39.46, 26.64, 26.2, 25.93, 24.78, 15.81, 11.75; HRMS (TOF, ES+) C$_{14}$H$_{26}$NO$_3$ [M+H]$^+$ calc'd 256.1913, found 256. 1911.
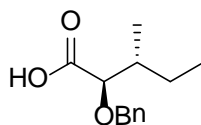
(2R,3R)-2-(benzyloxy)-3-methylpentanoic acid (2.50)

To a solution of carboxylic acid (180 mg, 1.347 mmol) in 13.8 mL of methanol was added 1 mL of trimethylsilyldiazomethane (2 M solution in diethyl ether) at 0°C. Allow to warm to rt and concentrate *in vacuo* to give a light yellow crude oil. The crude oil was then redissolved in 5 mL of CH_2Cl_2 followed by an addition of benzyl bromide (0.2 mL, 1.684 mmol) then silver oxide (390.2 mg, 1.684 mmol). Reaction was stirred over night, filtered through a pad of celite, washed with CH_2Cl_2, and concentrated *in vacuo* to yield crude benzyl ether. Crude was redissolved in 5 mL of methanol followed and cooled to 0°C. Next, 5 mL of a 0.28 M solution of potassium hydroxide was added dropwise and stirred for 1 hr. Aqueous solution was washed with ethyl acetate (2X, 5 mL ea), aqueous was acidified to PH=3, and aqueous was partitioned with diethyl ether (3X, 10 mL ea). All organic layers were combined, dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (8:1 to 4:1 hexanes: ethyl acetate) to give of carboxylic acid (201 mg, 70%). $[\alpha]D^{20}$ = -29.2 (*c* = 1.12, CHCl3) ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm) = 7.27 – 7.30 (m, 5H), 4.74 (d, *J* = 11.3 Hz, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 3.85 (d, *J* = 5.18 Hz, 1 H), 3.19 (m, 1H), 1.59 (m, 1H), 1.32 (m, 1H), 0.99 (d, *J* = 6.45 Hz, 3H) 0.90 (t *J* = 7.45, 3H) ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 177.55, 137.16, 128.40, 128.03, 127.97, 82.10, 72.88, 37.91, 24.48, 15.25, 11.40; HRMS (TOF, ES+) $C_{13}H_{17}O_3Na$ [M+H]$^+$ calc'd 244.1111, found 244.1113.
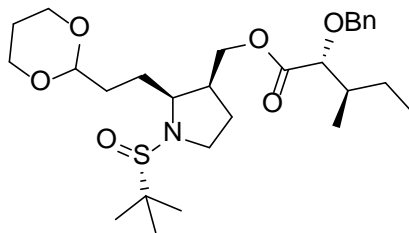
(2R,3R)-((2S,3S)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((S)-tert-butylsulfinyl)pyrrolidin-3-yl)methyl 2-(benzyloxy)-3-methylpentanoate (2.51)

To a solution of alcohol (81.23 mg, 0.2545 mmol) and (2R,3R)-2-(benzyloxy)-3-methylpentanoic acid (59.4 mg, 0.2676 mmol) in 3.5 mL CH_2Cl_2 at 0°C was added 1 crystal of 4-dimethylaminopyridine followed by 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (194.65 mg, 1.018 mmol). Reaction was allowed to warm to rt. Reaction was stirred to 2 hours, quenched with H_2O, and extracted 3 times with diethyl ether (5 mL ea). Combine organic layers, dry with $MgSO_4$, and filter through a bed of celite. Concentrate *in vacuo* and purify crude material by flash column chromatography (50:1 CH_2Cl_2:MeOH to 10:1 CH_2Cl_2:MeOH) to give desired ester as a light yellow solid (125 mg, 95% yield). $[\alpha]D^{20}$ = -4.1 (c = 1.00, CHCl3) ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm) = 7.35 – 7.27 (m, 5H), 4.67 (d, J = 11.89 Hz, 1H), 4.50 (1H, J = 4.89 Hz, 1H), 4.36 (d, J = 11.89 Hz, 1H), 4.21 – 4.04 (m, 5H), 3.75 – 3.61 (m, 5H), 2.83 (m, 1H), 2.49 (pentet, J = 7.23 Hz, 1H), 2.1 – 1.55 (m, 10H) 1.15 (s, 9H), 0.91 (d, J = 6.84 Hz, 3H), 0.86 (t, J = 7.67 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 172.44, 137.51, 128.24, 127.88, 127.69, 101.71, 82.41, 72.41, 67.72, 66.75, 63.28, 57.82, 40.71, 38.97, 37.90, 32.09, 28.04, 25.63, 24.62, 24.59, 23.98, 15.16, 11.19; HRMS (TOF, ES+) $C_{28}H_{45}NO_6S$ [M+H]$^+$ calc'd 524.3001, found 524.2999.
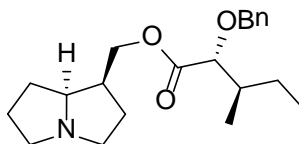
(2R,3R)-((1S,7aS)-hexahydro-1H-pyrrolizin-1-yl)methyl2-(benzyloxy)-3

methylpentanoate (2.49).

A solution of ester (50 mg, 0.0914 mmol) in 2 mL of 95:5 trifluoroacetic acid:H_2O was stirred for 1 hr at room temperature then 0.19 mL of triethyl silane was added. This solution was stirred over night and concentrated *in vacuo* to give a crude, yellow oil. This was dissolved in 1 mL DMSO and purified by reverse phase chromatography (2% to 45% H_2O(0.1%TFA):AcCN) to give (19 mg, 80% yield) as a colorless oil. $[\alpha]D^{20} = (c = 1.12,$ CHCl3) ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm) = 7.33 (m, 5H), 4.66 (d, J = 11.49, 1H), 4.38 (d, J = 11.50, 1H) 4.15 (dt, J = 11.26, 4.89 Hz, 2H), 3.74 (d, J = 5.65 Hz, 1H), 3.67 (m, 1H), 3.46 (m, 1H), 3.11 – 2.92 (m, 3H), 2.41 (sextet, J = 6.77 Hz, 1H), 2.01 (m, 1H), 1.88 – 1.78 (m, 3H), 1.58 (m, 2H), 1.25 (m, 3H), 0.91 (d, J =6.77 Hz, 3H), 0.87 (t, J = 7.91, 3H);); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 172.44, 137.48, 128.37, 127.86, 82.65, 72.53, 64.69, 62.72, 61.18, 44.29, 41.49, 38.00, 31.30, 29.68, 28.75, 28.05, 24.71, 15.17, 11.28; HRMS (TOF, ES+) C$_{21}$H$_{31}$NO$_3$ [M+H]$^+$ calc'd 346.2382, found 346.2381.
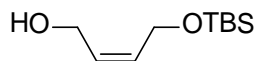
(Z)-4-((tert-butyldimethylsilyl)oxy)but-2-en-1-ol

To a solution of (Z)-but-2-ene-1,4-diol (30 g, 340.5 mmol) in 150 mL of anhydrous DMF was added imidazole (34.77 g, 510.7 mmol) and stirred for 30 min. Next tert-

butyldimethylsilyl chloride (51.32 g, 340.5 mmol) was added in 3 portions. Reaction was stirred for 1 hr and then quenched with 300 ml H_2O and extracted 3X with ether (100 ml ea). Organic was washed with brine (100 ml) and water (100 ml), dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography (3:1 hexane: EtOAc) to give 85.8 g, 95% yield. ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm) = 5.69 (m, 2H), 4.25 (dd, *J* = 4.97 Hz, 2H), 4.19 (d, *J* = 4.97 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100.6 MHz,CDCl$_3$) δ (ppm) = 134.35, 125.80, 58.90, 26.54, 25.81, 18.16, -5.30; HRMS (TOF, ES+) $C_{10}H_{22}O_2Si$ [M+H]$^+$ calc'd 203.3701, found 203.3702
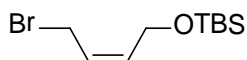
(Z)-((4-bromobut-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (2.28)

To a solution of N-bromosuccinimide (28.66 g, 161.027 mmol) and dimethyl sulfide (12.387 g, 199.37 mmol) in 400 ml anhydrous CH_2Cl_2 at -78°C was added (Z)-4-((tert-butyldimethylsilyl)oxy)but-2-en-1-ol (15.5 g, 76.679 mmol) at a slow rate. Reaction was allowed to warm to rt and stirred for 1.5 hrs. Quench withed a brine solution (400 ml), extracted diethyl ether (3X, 150 ml ea), dried with Na_2SO_4, filtered, concentrated *in vacuo*, and purified via flash column chromatography (6:1 Hexanes: EtOAc) to give 16.96 g of desired compound. ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm) = 5.74 (m, 2H), 4.32 (dd, *J* = 1.34 Hz, 2H), 4.02 (d, *J* = 8.11 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H) HRMS (TOF, ES+) $C_{10}H_{22}O_2Si$ [M+H]$^+$ calc'd 266.2642, found 266.2699.

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TOTAL SYNTHESIS OF THE INDOLIZIDINE CONTAINING NATURAL PRODUCT GRANDISINE D AND AN UNNATURAL ANALOGUE

3.1 Introduction

As previously shown, the methodology developed in our lab to generate azabicyclic ring systems and azabicyclic lactams can be quiet robust, versatile, and useful. This was clearly demonstrated during the rapid synthesis of cremastrine and an unnatural analogue in the previous chapters. To further highlight our technology to access highly functionalized azabicyclic ring systems, we next focused our attention towards the class of natural products known as the grandisines as seen in Figure 3.1. We focused our attention on grandisine D due to the fact that at the onset of the project only one synthetic effort existed and our route allowed for many possible derivatives to be made around the indolizidine scaffold similar to that of grandisine D.

grandisine A (3.1)   grandisine B (3.2)   grandisine C (3.3) : R = OH
                                            grandisine F (3.4) : R = NH₂

grandisine D (3.4)   grandisine E (3.5)   grandisine G (3.6)
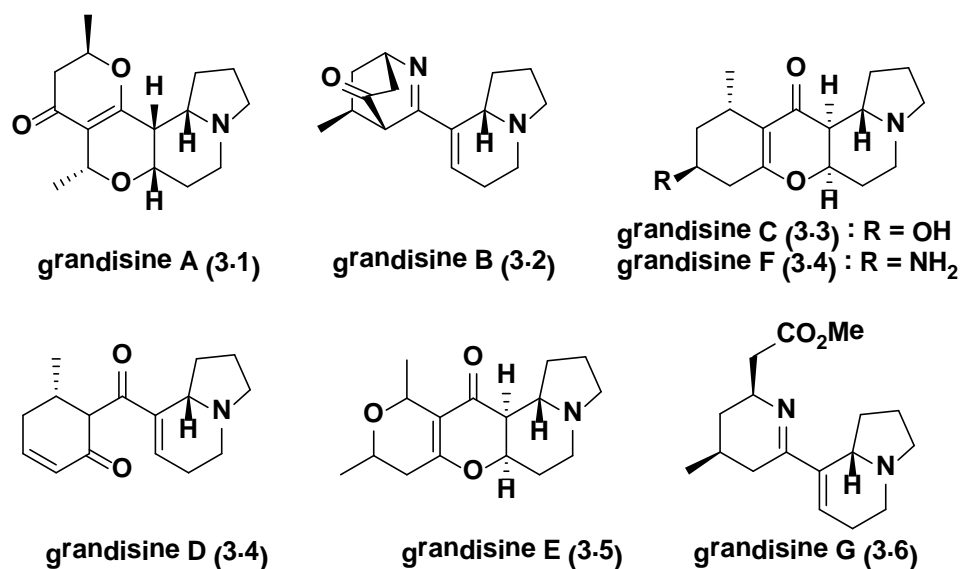
Figure 3.1 Grandisine A-G

3.2 Grandisine D Background

The grandisine alkaloids were isolated by Carroll and coworkers from the Australian rainforest tree *Elaeocarpus grandis* and all displayed selective human δ-opioid receptor affinity. Selective activation of the human δ-opioid receptor is an attractive feature due to the possibility to develop new analgesics with more potent and selective activity to the human δ-opioid receptor. The first synthetic effort to make grandisine D was accomplished by Tamura and co-workers in 2009 in 18 steps (12.5% overall yield) employing a Brønsted acid mediated Morita-Bayis-Hillman ring-closure reaction as the key step; however, two steps in their synthetic endeavors suffered from poor stereocontrol. The summation of their synthetic efforts is summarized in Scheme 3.1, where treatment of aldehyde **3.7** with the Brønsted acid, triflic acid, and dimethyl sulfide

in acetonitrile generates indolizidone **3.8**, where after a number of synthetic transformations, the Tamura laboratory was able to generate grandisine D.
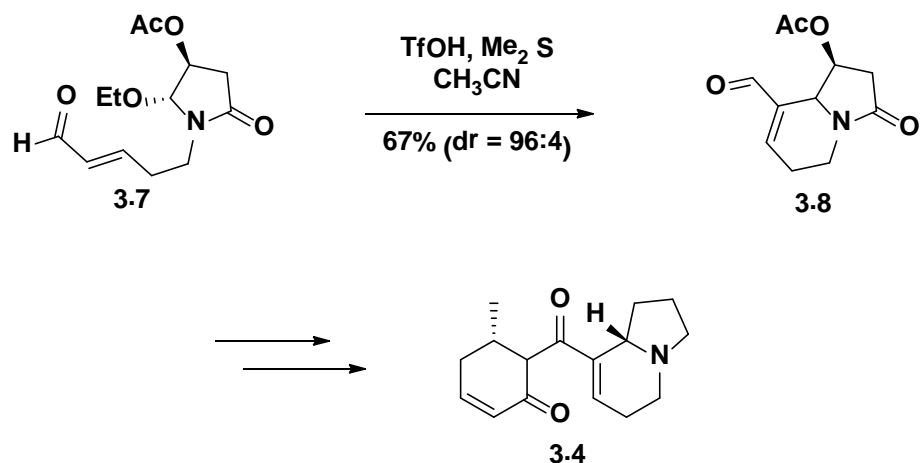
Scheme 3.1 Tamura and coworkers synthesis of grandisine D

During the Lindsley laboratories progress towards synthesizing grandisine D, an additional synthesis of grandisine D was accomplished by Taylor and coworkers in 2011 with a key step to generate the azabicyclic motif of an alkyne-acetal cyclization procedure to access the indolizidine core. The synthetic efforts by Taylor and coworkers generated grandisine D in 13 steps and 10% overall yield starting from the previously synthesized structure of *N*-Boc-prolinol **3.9** (Scheme 3.2). The key synthetic transformation of their efforts centered around an alkyne-acetal cyclization of late stage intermediate thioalkyne **3.10** where upon heating in a solution of formic, clean cyclization occurred giving them a single enatiomer of thioester **3.11**. A number of synthetic transformations later and they are able to access grandisine D. Interestingly, they were also able to prove that grandisine B is perhaps just an artifact of the isolation

procedure by stirring grandisine D in 35% aqueous ammonia to generate grandisine B in 72% yield.
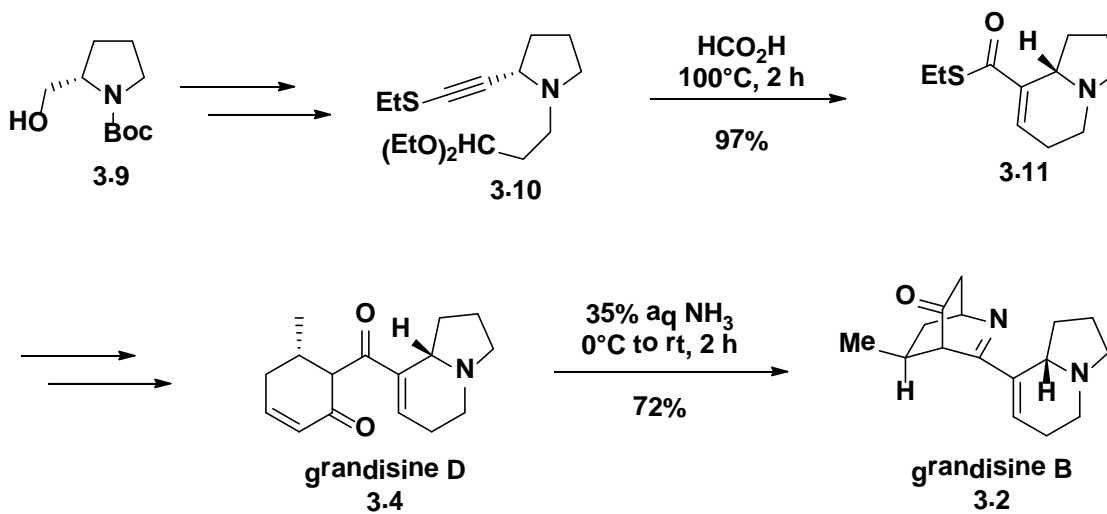
Scheme 3.2 Highlights of Taylor and coworkers synthesis of grandisine D and

grandisine B

Using the previously described technology developed by the Lindsley laboratory of rapidly and efficiently generating diverse azabicyclic ring systems, we achieved a vast improvement on the synthesis of grandisine D in both the number of steps and the overall yield.

3.3 Total Synthesis of Grandisine D

Our retrosynthetic analysis sought to incorporate methodology developed in the Lindsley laboratory that allows for rapid and efficient access to the azabicyclic ring structure. Scheme 3.5 outlines our retrosynthesis of grandisine D **3.4.** Grandisine D can

come about through an aldol between aldehyde **3.13** and chiral ketone **3.12** where the α,β-unsaturated aldehyde **3.13** can be generated from the technology developed in the Lindsley laboratory of synthesizing azabicyclic ring systems as previously shown.
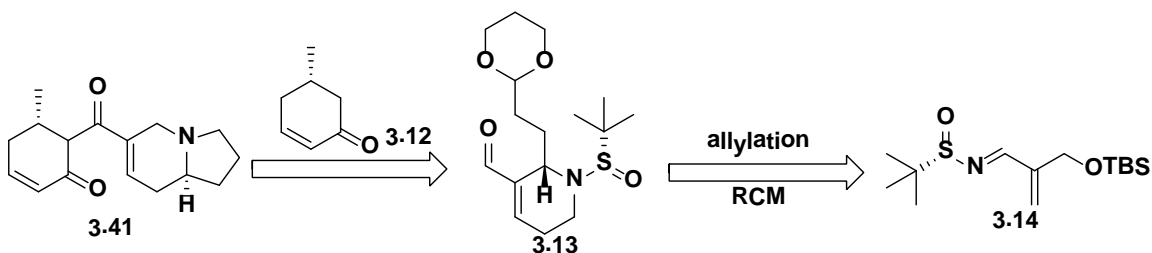
Scheme 3.3 Retrosynthesis of Grandisine D

Starting with commercially available diol **3.15**, monosilylation to the TBS ether followed by allylic oxidation to the α,β-unsaturated aldehyde **3.16** in 86% yield over two steps. The aldehyde in **3.16** is subsequently condensed with *tert*-butylsulfinamide **3.17**, with Ti(OEt)$_4$ to remove water from the reaction, which generates the α,β-unsaturated *N*-sulfinylaldimine **3.14** in 87% yield. Next, an enantioselective addition of the Grignard reagent **3.18** furnishes terminal alkene **3.19** in 79% yield and a greater than 10:1 d.r.. The new stereocenter in this molecule is again determined by the existing chirality of the *tert*-butylsulfinylamine which directs the addition into the aldimine.
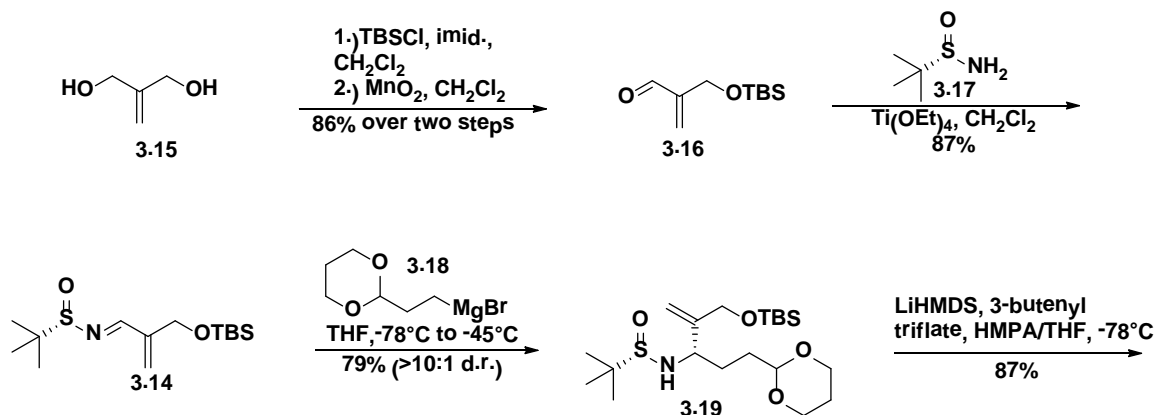
Scheme 3.4 Synthetic route to grandisine D

The remainder of the route is outlined in Scheme 3.4. **3.19** is alkylated using with 3-butenyl triflate with LHMDS as the base at -78°C to generate the dialkene product **3.20** is excellent yield. The diastereomers are separated at this point with normal phase silica gel flash column chromatography. Dialkene **3.20** is then subjected to a ring closing metathesis reaction using Grubbs 2nd generation catalyst and refluxing in dichloromethane to form the unsaturated 6-membered ring **3.21**. The primary silyl ether is converted to allylic primary alcohol **3.22** using TBAF in THF which proceeds forward in 87% yield. Allylic oxidation using MnO_2 in dichloromethane garnishes the α,β-unsaturated aldehyde **3.13** in quantitative yield. Next, a stereoselective dibutylboron triflate mediated aldol between aldehyde **3.13** and chiral α,β-unsaturated ketone **3.12** generates the racemic mixture of the secondary alcohol. The alcohol is oxidized to ketone **3.33** using a modified Moffatt oxidation with trifluoroacetic anhydride and DMSO with triethylamine in dichloromethane at -78°C in 77% yield over two steps. The final step in the synthetic scheme involves a global deprotection of the sulfinyl and acetal to the amine

and aldehyde, respectively. This intermediate than undergoes an intramolecular reductive

amination where concentration *in vacuo* of the imine and addition of polymer supported

triacetoxyborohydride gives the natural product grandisine D **3.4** in 47% yield.
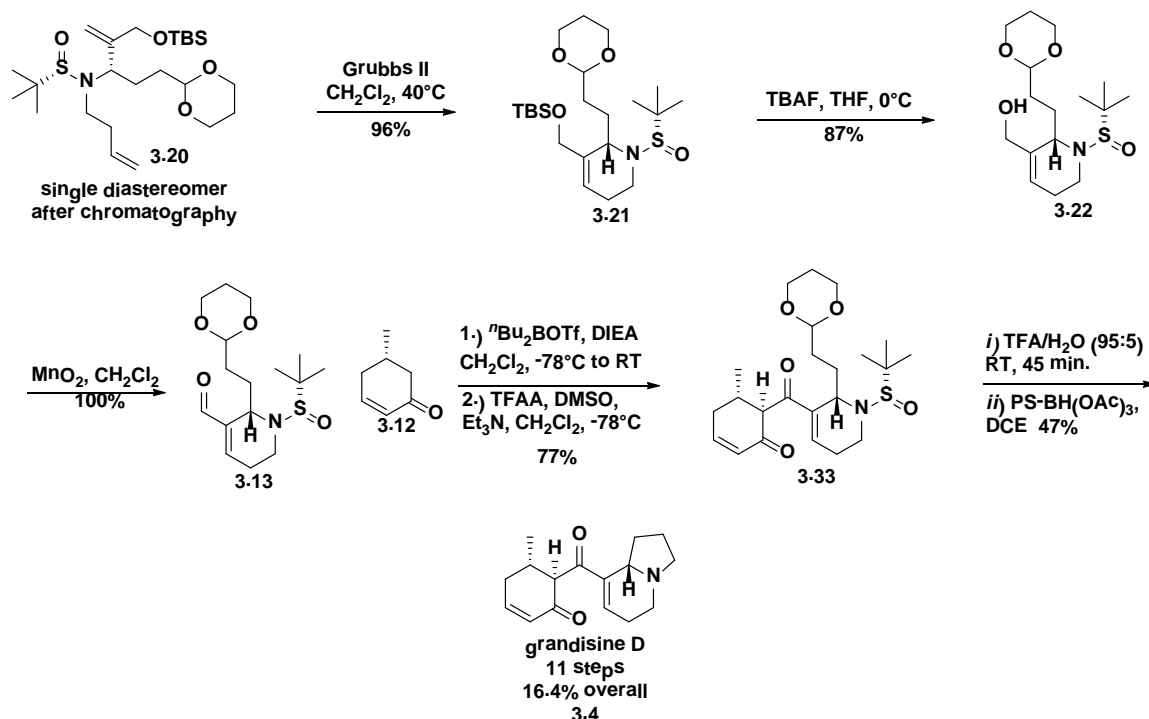
Scheme 3.5 Synthetic Route to Grandisine D (*continued*)

The entire route, starting from commercially available diol **3.15**, was

accomplished in 11 steps and 16.4% overall yield. Compared to the previous efforts by,

Tamura and co-workers in 2009 in 18 steps (12.5% overall yield) and Taylor and

coworkers in 13 steps (10% overall yield), our approach is fewer steps and a significantly

higher overall yield. Synthesizing grandisine D has again allowed for the clear

demonstration of the versatility and usefulness of forming azabicyclic ring containing

natural products and biologically active compounds using our technology. Outlined in

Scheme 3.5, is an example of an additional demonstration of the versatility of our azabicyclic technology used to generate a completely new unnatural analogue of grandisine. Further derivatives around the indolizidine ring of grandisine D are being generated and a screening for a new and potentially more potent and selective activator of the human δ-opioid receptor will be generated.
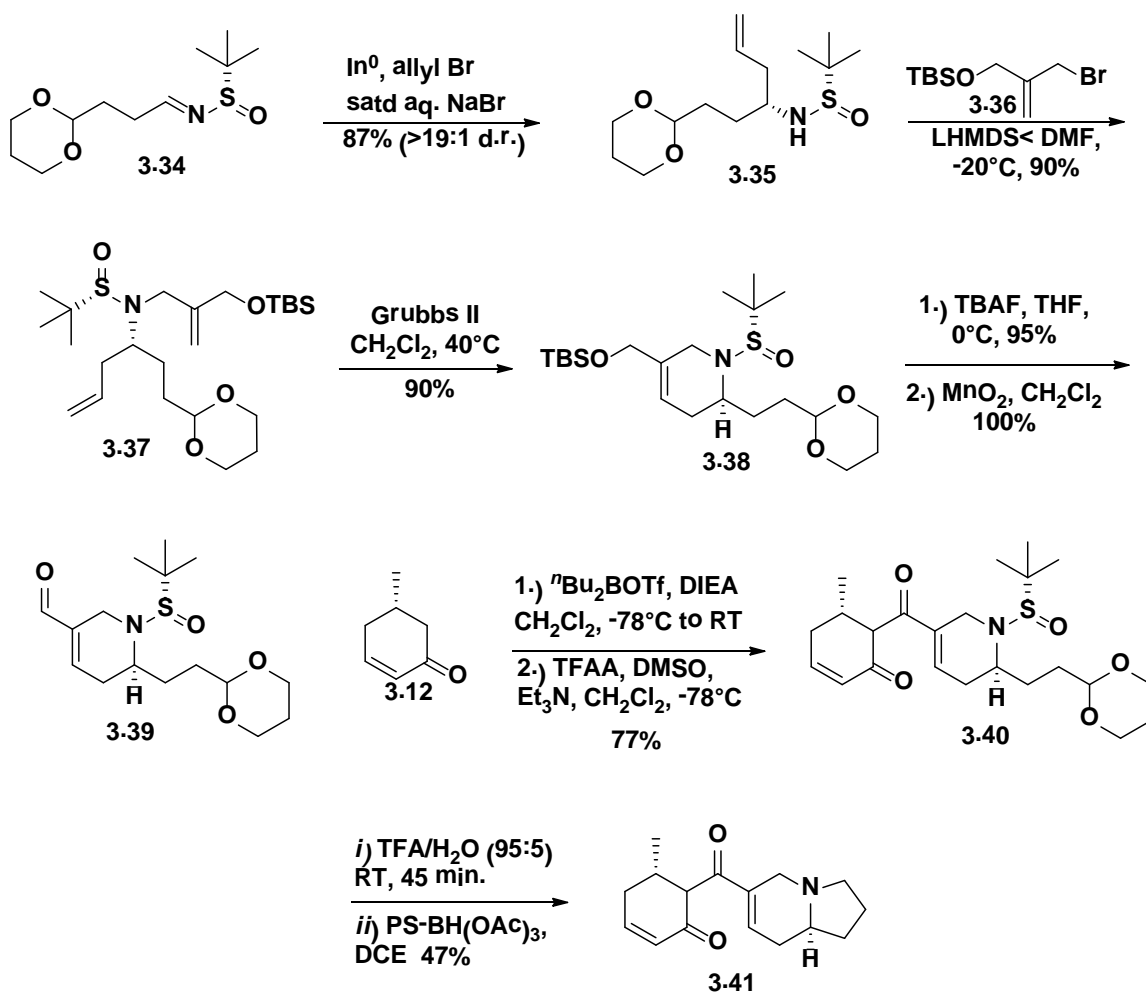
Scheme 3.6 Synthesis of an Unnatural Analogue of Grandisine D

3.7 Experimental Section

Flame-dried (under vacuum) glassware was used for all reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. All polymer-supported reagents were purchased from Biotage, Inc. Thin layer chromatography (TLC) was performed on glass-backed silica gel. Visualization was accomplished with UV light, and/or the use of anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hot-plate. Chromatography on silica gel was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies. IR spectra were recorded as thin films and are reported in wavenumbers (cm^{-1}). ^{1}H & ^{13}C NMR spectra were recorded on Bruker DRX-400 (400 MHz) or Bruker AV-NMR (600 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26, δ 77.0 (CDCl$_3$) and DMSO-d_6 2.50 ppm, 39.51 ppm for ^{1}H, ^{13}C respectively). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, br = broad, m = multiplet), coupling constant (Hz), integration. Optical rotations were measured on a JASCO P-2000 digital polarimeter. Concentration (c) in g/100 ml and solvent are given in parentheses. Low resolution mass spectra (LCMS) were obtained on an Agilent 1200 LCMS with electrospray ionization. A Micromass Q-Tof API-US mass spectrometer was used to acquire high-resolution mass spectrometry (HRMS) data. The value $\varDelta$ is the error in the measurement (in ppm) given by the equation $\varDelta = [(M_E - M_T)/ M_T] \times 10^6$, where M_E is the experimental mass and M_T is the theoretical mass. The HRMS results were obtained with ES as the ion source and leucine enkephalin as the reference.

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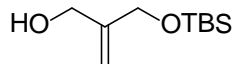
2-((((tert-butyldimethylsilyl)oxy)methyl)prop-2-en-1-ol.

To a flame-dried flask was added 350mL dry THF, followed by addition of NaH (2.74g, 113.5 mmol). To this solution at 0°C was added 2-methylenepropane-1,3-diol (10g, 113.5 mmol) drop wise. Mixture was then brought to room temperature and stirred for 45 min. *Tert*-butyldimethylsilyl chloride (17.11g, 113.5 mmol) was added in one batch and stirring was continued for an additional 50 min. until complete by TLC. Reaction quenched with H_2O, and extracted 3 times with ethyl acetate, washed with brine, dried with anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (4:1 to 1:1 Hex/EtOAc) yielded the product in 20.66 g (89%) as a clear oil: ^{1}H NMR (400.1 MHz, CDCl3) δ (ppm): 5.08 (d, J= 7.4 Hz, 2H), 4.25 (s, 2H), 4.17 (d, J= 6 Hz, 2H), 1.92 (t, J= 6 Hz, 1H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100.6 MHz, CDCl3) δ (ppm): 147.35, 111.08, 65.07, 64.67, 25.78, 18.21, -5.52; HRMS (TOF, ES+) $C_{10}H_{23}O_2Si$ [M+H]+ calc'd 203.1467, found 203.1466.

O⫽⟍⟍OTBS
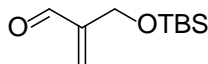
2-((((*tert*-butyldimethylsilyl)oxy)methyl)acrylaldehyde (3.16).

In a flame dried flask, alcohol (13.687g, 67.63 mmol) was dissolved in 200 mL DCM. While stirring, MnO_2(29.4g, 338 mmol) was added in two batches. Mixture was then stirred for 6 hours, until reaction was determined complete by TLC. Solution was filtered

through celite, concentrated *in vacuo*, and purified by flash chromatography (4:1 Hex/EtOAc) to yield product in 12.71g (89%) as clear oil. : ^{1}H NMR (400.1 MHz, CDCl3) δ (ppm): 9.62 (s, 1H), 6.52 (s, 1H) 6.11 (s, 1H), 4.40 (s, 2H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100.6 MHz, CDCl3) δ (ppm): 193.86, 149.74, 133.05, 59.79, 26.06, 18.52, -5.28; HRMS (TOF, ES+) $C_{10}H_{21}O_2Si$ [M+H]+ calc'd 201.1311, found 201.1312.
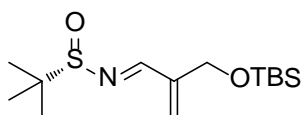
(*R*)-N-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)allylidene)-2-methylpropane-2-sulfinamide (3.14).

To a solution of aldehyde (9.00g, 45 mmol) in 400mL DCM was added (R)-2-methylpropane-2-sulfinamide (6.54g, 54 mmol) and $CuSO_4$ (14.00g, 90 mmol). Solution stirred at room temperature for 16 hours. Mixture filtered through a pad of celite, with DCM as an eluent. Solution was then concentrated *in vacuo* and purified by column chromatography (4:1 Hex/EtOAc) to yield product in 10.75 g (79%). $[\alpha]_D^{20} = 27.276$ (*c*= 0.01, MeOH); ^{1}H NMR (400.1 MHz, CDCl3) δ (ppm): 8.26 (s, 1H), 6.13 (s, 1H), 5.82 (s, 1H), 4.48 (dt, J=16, 7 Hz, 2H), 1.20 (s, 9H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}**C** NMR (100.6 MHz, CDCl3) δ (ppm): 163.32, 145.25, 127.42, 61.08, 57.62, 26.09, 22.70, 18.57, -5.23; HRMS (TOF, ES+) $C_{14}H_{30}O_2SiS$ [M+H]+ calc'd 304.1767, found 304.1765.
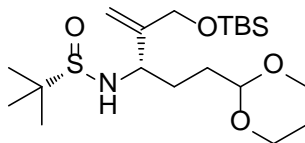
(*S*)-*N*-((*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(1,3-dioxan-2-yl)pent-1-en-3-yl)-2-methylpropane-2-sulfinamide (3.19).

In a flame dried flask under Argon gas was added (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide (19.8 mL, 0.5M in THF)to 30 mL THF. Mixture was then cooled to -78° C, and aldimine (1.00g, 3.3 mmol) was added drop wise as a solution in 20 mL THF. Reaction was then warmed to -48° C and stirred 16 hours. Reaction was quenched with NH_4Cl and brought to room temperature. Extracted 3 times with ethyl acetate, organic layers combined and dried with Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (1:1 Hex/EtOAc) to afford product in 1.13 g (80%) as a clear oil: $[\alpha]_D^{20}$ = 1.596 (*c*= 0.01, MeOH); ^{1}H NMR (400.1 MHz, CDCl3) δ (ppm): 5.30 (s, 1H), 5.20 (s, 1H), 5.07 (s, 1H), 4.50 (t, J= 5 Hz, 1H), 4.22 (q, J= 13.5, 18.7 Hz, 2H), 4.07 (dd, J= 5, 7 Hz, 2H), 3.76 (m, 3H), 3.70 (d, J= 7 Hz, 1H), 2.04 (m, 1H), 1.70 (m, 3H), 1.31 (br d, J= 13.6 Hz, 1H), 1.20 (s, 9H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100.6 MHz, CDCl3) δ (ppm): 148.66, 112.74, 102.12, 67.08, 64.75, 59.33, 56.00, 31.81, 29.48, 26.14, 26.01, 22.92, 18.55, -5.20; HRMS (TOF, ES+) $C_{20}H_{42}O_4SiS$ [M+H]+ calc'd 420.2604, found 420.2603.
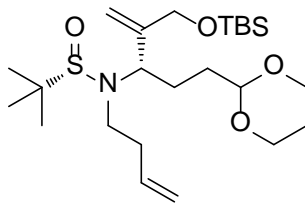
(S)-N-(but-3-en-1-yl)-N-((S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(1,3-dioxan-2-yl)pent-1-en-3-yl)-2-methylpropane-2-sulfinamide (3.20)

To a solution of sulfinamide (100 mg, 0.24 mmol) in 3 mL THF at -78 $^{\circ}$C was added HMPA (83 µL, 0.48 mmol) and ^{n}BuLi (94 µL, 2.5 M, 0.48 mmol). The mixture was stirred for 30 mins and a pre-cooled solution of but-3-enyl-trifluoromethanesulfonate (60 mg, 0.29 mmol) in 1 mL THF was then added slowly to the mixture. The mixture was stirred at -78 $^{\circ}$C for 30 mins. The reaction was quenched with water and extracted with EtOAc (3x). The combined organic extracts were washed with brine and dried over Na_2SO_4. Filtration and concentration afforded the crude product, which was purified by flash chromatography (1:1 Hex/EtOAc) to afford the product as a pale yellow oil (56 mg, 87% yield brsm): $[\alpha]_D^{20}$ = -2.53 (c = 1.00, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.67-5.77 (m, 1H), 5.32 (brd, J = 1.2 Hz,1H), 5.13 (s, 1H), 5.03 (dd, J = 17.2, 1.6 Hz, 1H), 5.02 (d, J = 10.0 Hz, 1H), 4.52 (t, J = 4.8 Hz, 1H), 4.05-4.08 (m, 4H), 3.72 (dt, J = 12.0, 2.4 Hz, 2H), 3.56 (dd, J = 10.8, 4.4 Hz, 1H), 3.29 (m, 1H), 2.58 (m, 1H), 2.38 (m, 1H), 2.25 (m, 1H), 1.95-2.23 (m, 3H), 1.67 (m, 1H), 1.50 (m, 1H), 1.32 (dm, J = 13.8 Hz, 1H), 1.14 (s, 9H), 0.89 (s, 9H), 0.05 (d, J = 8.0 Hz, 6H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 145.6, 135.3, 116.6, 112.9, 102.2, 67.0, 65.0, 61.7, 57.6, 42.2, 34.3, 32.8, 26.0, 25.9, 24.9, 23.7, 18.4, -5.1, -5.2; HRMS (TOF, ES+) $C_{24}H_{48}NO_4SiS$ [M+H]$^+$ calc'd 474.3073, found 474.3074.
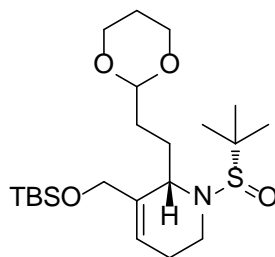
(*S*)-6-(2-(1,3-dioxan-2-yl)ethyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-((*S*)-tert-butylsulfinyl)-1,2,3,6-tetrahydropyridine (3.21)

To a solution of (1.2 g, 2.54 mmol) in CH_2Cl_2 (271 mL) was added 2nd Gen. Grubbs (107.7 mg, 0.127 mmol). The mixture was refluxed for 1 h and concentrated. The resulting crude product was purified by automated flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product 1.005 g (89%) as yellow oil: $[\alpha]_D^{20} = +2.6$ (*c* = 1.81, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.75 (s, 1H), 4.49 (t, *J*= 4.8 Hz, 1 H), 4.09 (m, 4H), 3.73 (dt, *J*= 12.0, 2.4 Hz, 3H), 3.53 (dd, *J*= 14.0, 6.4 Hz, 3H), 3.12 (m, 1H), 2.45 (m, 1H), 2.05 (m, 1H), 1.87-1.79 (m, 1H), 1.78-1.69 (m, 2H), 1.66-1.58 (m, 2H), 1.32 (br d, *J*= 13.2 Hz, 1H), 1.20 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 139.0, 122.3, 102.3, 67.0, 65.6, 58.9, 58.8, 37.8, 32.3, 27.9, 26.1, 26.0, 25.9, 25.2, 23.8, 18.5, -5.1, -5.3; HRMS (TOF, ES+) C$_{22}$H$_{44}$NO$_4$SiS [M+H]$^+$ calc'd 446.2760, found 446.2762.
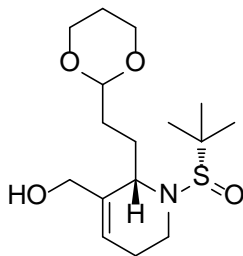
((*S*)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((*S*)-*tert*-butylsulfinyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (3.22)

To a solution of silyl ether (375 mg, 0.84 mmol) in THF (35 mL) under argon was added 1.0 M TBAF (1.3 mL, 1.26 mmol) dropwise at 0 ^{o}C. The mixture was warmed to rt and stirred for 2 h. The reaction was quenched with saturated NH$_4$Cl solution and extracted with EtOAc (3x). The combined organic extracts were washed with water and the dried over Na$_2$SO$_4$. Filtration and concentration afforded the crude product, which was purified by flash chromatography (9:1 CH$_2$Cl$_2$/MeOH) to afford the product as yellow oil (267 mg, 96%): $[\alpha]_D^{20}$ = +5.45 (*c* = 4.7, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.82 (br s, 1H), 4.52 (t, *J*= 4.8 Hz, 1H), 4.04 (m, 4H), 3.81 (br d, *J*= 7.2 Hz, 1H), 3.74 (dt, *J*= 2.4, 10 Hz, 2H), 3.57 (q, *J*= 7.2 Hz, 1H), 3.13 (m, 1H), 2.49 (m, 1H), 2.17 (m, 2H), 1.88 (m, 2H), 1.77 (m, 2H), 1.62 (m, 1H), 1.33 (d, *J*= 11 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 139.81, 124.20, 102.17, 67.05, 65.46, 59.43, 58.97, 37.43, 32.33, 27.80, 25.88, 25.23, 23.87; HRMS (TOF, ES+) C$_{16}$H$_{30}$NO$_4$S [M+H]$^+$ calc'd 332.1896, found 332.1898
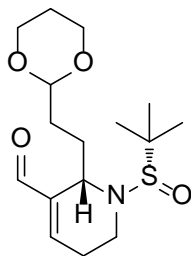
(S)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((S)-tert-butylsulfinyl)-1,2,5,6-tetrahydropyridine-3-carbaldehyde (3.13)

To a solution of alcohol (1.69 g, 5.11 mmol) in THF (300 mL) under argon was added MnO$_2$ (8.87 g, 102.1 mmol). The mixture was stirred at rt overnight. Filtration over celite and concentration afforded the pure product in 99% yield: $[\alpha]_D^{20}$ = +40.0 (c = 0.3, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 9.34 (s, 1H), 6.91 (t, J= 4 Hz, 1H), 4.51 (t, J= 4.4 Hz, 1H), 4.05 (m, 3H), 3.70 (m, 3H), 3.23 (m, 1H), 2.84 (m, 1H), 2.17 (dt, J= 5.2, 20 Hz, 1H), 2.04 (m, 1H), 1.7 (m, 4H), 1.32 (br d, J= 12.4 Hz, 1H), 1.20 (s, 9H) ; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 192.05, 150.64, 143.48, 102.11, 67.02, 59.36, 57.12, 36.48, 32.67, 28.57, 26.76, 25.88, 23.50; HRMS (TOF, ES+) C$_{16}$H$_{28}$NO$_4$S [M+H]$^+$ calc'd 330.1739, found 330.1741.
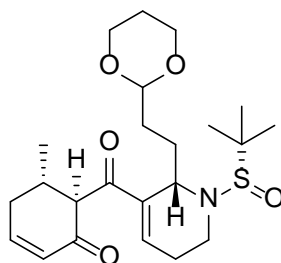
(5S,6R)-6-((S)-2-(2-(1,3-dioxan-2-yl)ethyl)-1-((S)-*tert*-butylsulfinyl)-1,2,5,6-tetrahydropyridine-3-carbonyl)-5-methylcyclohex-2-enone

To a solution of (*S*)-5-methylcyclohex-2-enone (43.5 mg, 0.395 mmol) in CH_2Cl_2 (2 mL) at -78 °C was added *N*-ethyl-*N*-isopropylamine (*i*Pr$_2$NEt) (0.103 mL, 0.592 mmol) and $^nBu_2BOTf$ (0.592 mL, 0.592 mmol). The mixture was stirred at 78 °C for 1 h. Aldehyde (86.6 mg, 0.263 mmol) dissolved in CH_2Cl_2 (2 mL) was added dropwise. The mixture was warm to rt and stir for 1.5 h. The reaction mixture was cool -78 °C and quenched with 0.1 mL each of MeOH and H_2O_2, diluted with $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with water and the dried over Na_2SO_4. Filtration and concentration afforded the crude product, which was used in the next step without purification.

To a stirred solution of DMSO (38 µL, 0.53 mmol) in CH_2Cl_2 (7 mL) at -78 ºC was added drop-wise trifluoroacetic anhydride (50 µL, 0.35 mmol). After stirring at -78 ºC for 30 mins, a pre-cooled solution of the crude alcohol dissolved in CH_2Cl_2 (4 mL). The reaction mixture was stirred at -78 ºC for 1 h, then Et$_3$N (0.18 mL, 1.32 mmol) was added drop-wise. The solution was further stirred at −78 ºC for a further 20 min, then warmed to rt and held for

1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (5x), dried over Na_2SO_4, filtered, concentrated *in vacuo* to give the crude product, which was then purified by flash chromatography (1:20 MeOH/EtOAc) to yield in 5:1 d.r., 88.4 mg (77% over 2-steps) as a pale yellow oil: $[\alpha]_D^{20}$ = +3.4 (*c* = 1.55, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 6.84 (m, 1H), 6.02 (d, *J*= 9.7 Hz, 1H), 5.91 (t, *J* = 3.8 Hz, 1H), 4.52 (m, 1H), 4.21 (m, 1H), 4.07 (m, 2H), 3.73 (m, 2H), 3.61 (m, 2H), 3.20 (m, 1H), 2.66 (m, 1H), 2.53 (m, 1H), 2.40 (m, 1H), 2.34 (m, 1H), 2.10-2.09 (m, 2H), 1.87-1.73 (m, 3H), 1.61 (m, 1H), 1.33 (d, *J*= 13.4

Hz, 1H), 1.20 (s, 9H), 1.08 (d, $J= 6.88$, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm):

200.98, 200.90, 147.6, 141.5, 128.9, 125.0, 102.2, 72.4, 67.3, 60.2, 59.2, 57.7, 36.34,

32.29, 30.95, 30.09, 27.97, 25.65, 23.53, 19.72 ; HRMS (TOF, ES+) C$_{23}$H$_{36}$NO$_5$S

[M+H]$^+$ calc'd 438.2371, found 438.2373.
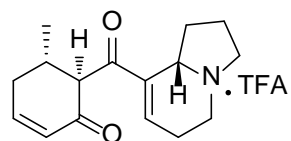
Grandisine D (3.4)

(43.7 mg, 0.1 mmol) was dissolved in 95:5 TFA : H2O to a final concentration of 0.1 M.

After stirring for 1.5 h, the mixture was concentrated in vacuo and the residue was

dissolved in DCE and PS-NaBH(OAc)$_3$ (0.5 g, 0.5 mmol) was added and placed on a

shaker for 2 h. The beads were filterd off and the solvent was concentrated *in vacuo* to

give the crude product. Purification by flash chromatography (28% NH$_3$-MeOH-AcOEt,

1:10:50) gave grandisine D as pale yellow oil (12.2 mg, 47%). To a solution of the

grandisine D (9 mg, 0.034 mmol) in DCM (1 mL) at 0 ℃ was added dropwise TFA (3.6

μL, 0.051 mmol). The solution was held at 0 ℃ for 30 min, then warmed to rt and held

for 1 h. The pale yellow solution was concentrated *in vacuo* to afford TFA salt of

grandisine D (12.1 mg, Quant.) as pale yellow oil; [α] $_D^{20}$ +68.8 (*c* 0.09, MeOH); ^{1}H

NMR (400.1 MHz, DMSO) δ (ppm): 10.47 (br s, 1H), 7.32 (bdd, $J = 4.0, 4.0$ Hz, 1H),

7.16 (ddd, $J = 10.0, 6.0, 2.4$ Hz, 1H), 5.94 (dd, $J = 10.0, 2.4$ Hz, 1H), 4.42 (dd, $J = 8.8,$

8.8 Hz, 1H), 4.36 (d, $J = 12.0$ Hz, 1H), 3.58-3.51 (m, 1H), 3.41-3.29 (m, 2H), 3.20-3.06

(m, 1H), 2.67-2.59 (m, 2H), 2.53-2.33 (m, 3H), 2.27-2.18 (m, 1H), 2.08-1.98 (m, 2H),

1.77-1.67 (m, 1H) 0.86 (d, J = 6.0 Hz, 3H); $^\delta$C (100 MHz, DMSO) 198.4, 196.9, 151.9, 140.0, 137.3, 128.3, 59.1, 58.0, 52.7, 43.0, 32.7, 32.3, 28.0, 22.4, 20.4, 19.1; HRMS (TOF, ES+) $C_{16}H_{22}NO_2$ [M+H]$^+$ calc'd 260.1651, found 260.1650.
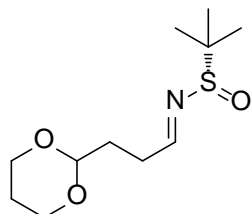
(S)-N-(3-(1,3-dioxan-2-yl)propylidene)-2-methylpropane-2-sulfinamide (3.34)

To a solution of 3-(1,3-dioxan-2-yl)propanal (10.1 g, 70.1 mmol) in CH_2Cl_2 (500 mL) was added (S)-2-methylpropane-2-sulfinamide (10.17 g, 84.1 mmol) and $CuSO_4$ (44.6 g, 280.4 mmol). The reaction mixture was stirred at rt overnight. The mixture was filtered through a through celite pad and washed with CH_2Cl_2. Concentration *in vacuo* gave the crude product which was purified by automated flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product 15.6 g (90%) as yellow oil: $[\alpha]_D^{20}$ = +209.3 (c = 0.86, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 8.11 (t, J = 4.0 Hz, 1H), 4.62 (t, J = 4.8 Hz, 1H), 4.10 (dd, J = 6.0, 4.8 Hz, 2H), 3.76 (m, 2H), 2.64 (sextet, J = 4.0 Hz, 2H), 2.07 (m, 1H), 1.93 (m, 2H), 1.32 (dm, J = 13.8 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 169.1, 101.0, 67.0, 56.7, 30.8, 30.7, 25.8, 22.5; HRMS (TOF, ES+) $C_{11}H_{22}NO_3S$ [M+H]$^+$ calc'd 248.1320, found 248.1319.
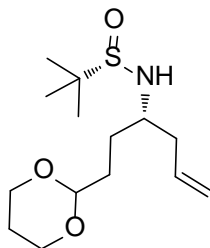
(*S*)-*N*-((*S*)-1-(1,3-dioxan-2-yl)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide (3.35)

In-Mediated allylation were done according to procedures published by Lin and co-workers. To a reaction flask containing sulfinimine (14.5 g, 58.7 mmol) and indium powder (27.0 g, 234.8 mmol) was added saturated aqueous NaBr solution (1174 mL, (1062.4 g of NaBr)) followed by the allyl bromide (36.8 mL, 234.8 mmol). The resulting suspension stirred at rt for 24 h. The reaction was quenched by the addition of saturated aqueous NaHCO$_3$ and filtered through a pad of celite. The aqueous layer was extracted with EtOAc (3x), dried over Na$_2$SO$_4$, filtered, concentrated *in vacuo* to give the crude product as >19:1 *dr*, which was then purified by flash chromatography (1:1 Hex/EtOAc) to yield the allylation product in 14.7 g (87%) as a pale yellow oil: $[\alpha]_D^{20}$ = +38.9 (*c* = 1.43, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.77 (m, 1H), 5.16 (d, *J* = 4 Hz, 1H), 5.13 (s, 1H), 4.51 (t, *J* = 4.5 Hz, 1H), 4.08 (dd, *J* = 5, 6.3 Hz, 2H), 3.74 (dt, *J* = 10, 2.2 Hz, 2H), 3.30 (m, 1H), 3.23 (d, *J* = 6.5 Hz, 1H), 2.37 (m, 2H), 2.05 (m, 1H), 1.63 (m, 3H), 1.33 (br, *J* = 14 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 133.9, 119.0, 101.9, 66.8, 55.8, 55.0, 40.5, 31.3, 29.2, 25.7, 22.6; HRMS (TOF, ES+) C$_{14}$H$_{28}$NO$_3$S [M+H]$^+$ calc'd 290.1790, found 290.1790.
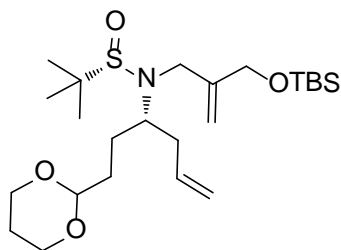
(*S*)-N-((*S*)-1-(1,3-dioxan-2-yl)hex-5-en-3-yl)-*N*-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)allyl)-2-methylpropane-2-sulfinamide (3.37)

To a solution of sulfinamide (1.4 g, 4.84 mmol) in 25 mL DMF at -20 °C was added LiHMDS (9.7 mL, 1 M in THF,) and the mixture was stirred for 20 mins at -20 °C and 20 mins at rt. The mixture was cooled back to -20 °C and (3.83 g, 14.83 mmol) was then added slowly to the mixture and the reaction was slowly. The mixture was stirred at -20 °C for 30 mins and rt overnight. The reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc (3x). The combined organic extracts were washed with water and the dried over Na₂SO₄. Filtration and concentration afforded the crude product, which was purified by flash chromatography (4:1 to 1:1 Hex/EtOAc) to afford the product as a pale yellow oil (2.06 g, 90%): $[\alpha]_D^{20}$ = -2.3 (*c* = 0.85, CHCl₃); ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 5.74-5.84 (m, 1H), 5.23 (s, 1H), 5.14 (s, 1H), 5.03 (m, 1H), 4.48 (t, *J* = 5.2 Hz, 1H), 4.05 (m, 4H), 3.94 (brd, *J* = 17.2 Hz, 1H), 3.72 (dt, *J* = 12.0, 2.4 Hz, 2H), 3.14 (d, *J* = 17.2 Hz, 1H), 2.96 (q, *J* = 7.2 Hz, 1H), 2.40 (dq, *J* = 28.2, 6.8 Hz, 2H), 1.89-2.09 (m, 2H), 1.61-1.80 (m, 3H), 1.32 (dm, *J* = 13.8 Hz, 1H), 1.29 (s, 9H), 1.19 (s, 9H), 0.06 (s, 6H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 145.2, 136.3, 117.2, 111.7, 102.2, 67.0, 66.9, 64.8, 62.6, 58.0, 53.6, 45.5, 39.5, 33.3, 27.3, 26.0, 25.9, 23.8, 18.5, -5.2, -5.3; HRMS (TOF, ES+) C₂₄H₄₈NO₄SiS [M+H]⁺ calc'd 474.3073, found 474.3076.
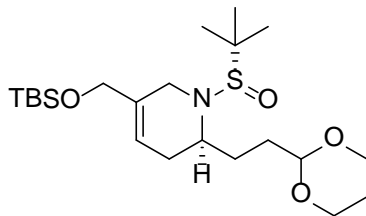
(*S*)-2-(2-(1,3-dioxan-2-yl)ethyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-((*S*)-*tert*-butylsulfinyl)-1,2,3,6-tetrahydropyridine (3.38).

To a solution of (1.0 g, 2.11 mmol) in CH_2Cl_2 (260 mL) was added 2nd Gen. Grubbs (89.5 mg, 0.106 mmol). The mixture was refluxed for 1 h and concentrated. The resulting crude product was purified by automated flash chromatography (4:1 to 1:1 Hex/EtOAc) to yield the desired product 0.845 g (90%) as yellow oil: $[\alpha]_D^{20}$ = -1.7 (*c* = 0.0181, $CHCl_3$); ^1H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 5.62 (d, *J*= 4.8 Hz, 1H), 4.51 (t, *J*= 4.8 Hz, 1 H), 4.09 (dd, *J*= 4, 7.6 Hz, 2H), 4.03 (d, *J*= 4 Hz, 1H), 3.73 (m, 3H), 3.34 (m, 2H), 2.52 (m, 1H), 2.06 (m, 1H), 1.89 (dd, *J*= 6, 12.4 Hz, 1H), 1.80 (m, 1H), 1.68 (m, 2H), 1.57 (m, 2H), 1.33 (br, d, *J*= 12.4 Hz, 1H), 1.16 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 135.3, 118.3, 102.3, 67.0, 65.5, 58.7, 56.8, 37.2, 32.9, 28.0, 27.0, 26.1, 25.9, 23.5, 18.5, -5.2; HRMS (TOF, ES+) $C_{22}H_{44}NO_4SiS$ [M+H]$^+$ calc'd 446.2760, found 446.2764.
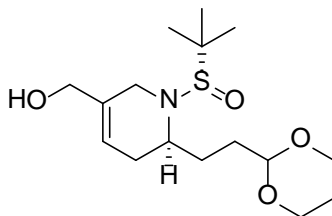
((*S*)-6-(2-(1,3-dioxan-2-yl)ethyl)-1-((*S*)-*tert*-butylsulfinyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol.

To a solution of (300 mg, 0.67 mmol) in THF (27 mL) under argon was added 1.0 M TBAF (1.01 mL, 1.01 mmol) dropwise at 0 $^{\circ}$C. The mixture was warmed to rt and stirred for 2 h. The reaction was quenched with saturated NH$_4$Cl solution and extracted with EtOAc (3x). The combined organic extracts were washed with water and the dried over Na$_2$SO$_4$. Filtration and concentration afforded the crude product, which was purified by flash chromatography (9:1 CH$_2$Cl$_2$/MeOH) to afford the product as yellow oil (210 mg, 95%): $[\alpha]_D^{20}$ = -116.1 (c = 4.7, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 5.64 (br d, J= 4.8 Hz, 1H), 4.49 (t, J= 4.8 Hz, 1H), 4.05 (dd, J= 11.6, 4.0 Hz, 2H), 3.91 (m, 3H), 3.71 (tt, J= 12.0, 3.6, Hz, 2H), 3.33 (m, 2H), 2.96 (br s, 1H), 2.52 (br d, J= 17.6 Hz, 1H), 2.04 (m, 1H), 1.87 (br dd, J= 17.6, 5.2, Hz, 1H), 1.79-1.68 (m, 2H), 1.59-1.49 (m, 2H), 1.31 (d, J= 12.4 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 135.7, 119.8, 101.9, 66.8, 65.2, 58.6, 56.9, 36.6, 32.6, 27.7, 26.8, 25.7, 23.3; HRMS (TOF, ES+) C$_{16}$H$_{30}$NO$_4$S [M+H]$^+$ calc'd 332.1896, found 332.1897.
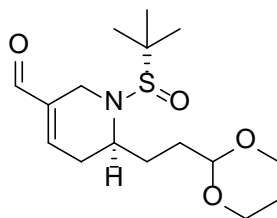
(S)-6-(2-(1,3-dioxan-2-yl)ethyl)-1-((S)-*tert*-butylsulfinyl)-1,2,5,6-tetrahydropyridine-3-carbaldehyde (3.39)

To a solution of alcohol (150 mg, 0.45 mmol) in THF (30 mL) under argon was added MnO$_2$ (796 mg, 9.16 mmol). The mixture was stirred at rt overnight. Filtration over celite and concentration afforded the pure product in Quant. yield: $[\alpha]_D^{20}$ = -8.1 (c = 1, MeOH);

^{1}H NMR (400.1 MHz, CDCl$_3$) δ (ppm): 9.34 (s, 1H), 6.91 (d, J= 5.2 Hz, 1H), 4.51 (t, J= 4.4 Hz, 1H), 4.12 (m, 3H), 3.72 (tt, J= 12.0, 2.8 Hz, 2H), 3.49 (m, 2H), 2.79 (dm, J= 3.2 Hz, 1H), 2.22 (ddd, J= 19.2, 6.0, 2.0 Hz, 1H), 2.06 (m, 1H), 1.75-1.51 (m, 4H), 1.32 (br d, J= 12.4 Hz, 1H), 1.18 (s, 9H) ; ^{13}C NMR (100.6 MHz, CDCl$_3$) δ (ppm): 191.9, 146.5, 138.7, 101.5, 66.7, 58.7, 56.6, 33.6, 32.3, 29.3, 26.8, 25.6, 23.2; HRMS (TOF, ES+) C$_{16}$H$_{28}$NO$_4$S [M+H]$^+$ calc'd 330.1739, found 330.1739.

(5S,6R)-6-((S)-6-(2-(1,3-dioxan-2-yl)ethyl)-1-((S)-$tert$-butylsulfinyl)-1,2,5,6-tetrahydropyridine-3-carbonyl)-5-methylcyclohex-2-enone (3.40)

To a solution of (S)-5-methylcyclohex-2-enone (43.5 mg, 0.395 mmol) in CH$_2$Cl$_2$ (2 mL) at -78 ^{o}C was added N-ethyl-N-isopropylpropylamine (iPr$_2$NEt) (0.103 mL, 0.592 mmol) and ^{n}Bu$_2$BOTf (0.592 mL, 0.592 mmol). The mixture was stirred at 78 ^{o}C for 1 h. Aldehyde (86.6 mg, 0.263 mmol) dissolved in CH$_2$Cl$_2$ (2 mL) was added dropwise. The mixture was warm to rt and stir for 1.5 h. The reaction mixture was cool -78 ^{o}C and quenched with 0.1 mL each of MeOH and H$_2$O$_2$, diluted with NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (3x). The combined organic extracts were washed with water and the dried over Na$_2$SO$_4$. Filtration and concentration afforded the crude product, which was used in the next step without purification.

To a stirred solution of DMSO (38 μL, 0.53 mmol) in CH$_2$Cl$_2$ (7 mL) at -78 ℃ was added drop-wise trifluoroacetic anhydride (50 μL, 0.35 mmol). After stirring at -78 ℃ for

30 mins, a pre-cooled solution of the crude alcohol dissolved in CH_2Cl_2 (4 mL). The reaction mixture was stirred at -78 ºC for 1 h, then Et_3N (0.18 mL, 1.32 mmol) was added dropwise. The solution was further stirred at −78 ºC for a further 20 min, then warmed to rt and held for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (5x), dried over Na_2SO_4, filtered, concentrated *in vacuo* to give the crude product, which was then purified by flash chromatography (1:20 MeOH/EtOAc) to yield the desired product **57**, 77.0 mg (67% over 2-steps) as a pale yellow oil: $[\alpha]_D^{20}$ = +3.6 (*c* = 0.27, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$) δ (ppm): 6.96 (m, 1H), 6.86 (br d, *J*= 5.2 Hz, 1H), 6.02 (d, *J*= 10 Hz, 1H), 4.51 (m, 1H), 4.08 (m, 3H), 3.82 (m, 1H), 3.72 (m, 3H), 3.53 (br d, *J*= 18.8 Hz, 1H), 3.39 (m, 1H), 2.77 (m, 1H), 2.67 (m, 1H), 2.56 (m, 1H), 2.09 (m, 3H), 1.75 (m, 1H), 1.59 (m, 2H), 1.32 (br d, *J*= 12.4 Hz, 1H), 1.16 (s, 9H), 0.99 (d, *J*= 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 197.73, 196.79, 149.98, 138.64, 129.34, 101.97, 67.00, 59.85, 58.91, 56.27, 34.79, 33.08, 32.90, 32.62, 29.04, 27.28, 25.88, 23.39, 22.86, 20.20; HRMS (TOF, ES+) $C_{23}H_{36}NO_5S$ [M+H]$^+$ calc'd 438.2371, found 438.2371.
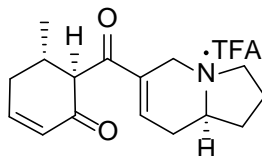
(5*S*,6*R*)-6-((*S*)-1,2,3,5,8,8a-hexahydroindolizine-6-carbonyl)-5-methylcyclohex-2-enone (3.41).

(40.7 mg, 0.093 mmol) was dissolved in 95: 5 (TFA: H_2O) to a final concentration of 0.1 M. After stirring for 1.5 h, the mixture was concentrated in vacuo and the residue was dissolved in DCE and PS-NaBH(OAc)$_3$ (0.5 g, 0.465 mmol) was added and placed on a shaker for 2 h. The beads were filterd off and the solvent was concentrated *in vacuo* to give the crude product. Purification by flash chromatography (28% NH$_3$-MeOH-AcOEt, 1:10:50) gave as pale yellow oil (11.8 mg, 49%). To a solution of (10 mg, 0.0386 mmol) in DCM (1 mL) at 0 ºC was added dropwise TFA (4.1 µL, 0.058 mmol). The solution was held at 0 ºC for 30 min, then warmed to rt and held for 1 h. The pale yellow solution was concentrated *in vacuo* to afford TFA salt of (13.7 mg, Quant.) as pale yellow oil; [α]$_D^{20}$ +2.1 (*c* 0.05, MeOH);

^{1}H NMR (600.1 MHz, DMSO) δ (ppm): 10.27 (br s, 1H), 7.33 (m, 1H), 7.15 (ddd, *J* = 10.2, 6.6, 2.4 Hz, 1H), 5.96 (dd, *J* = 10.2, 2.4 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.30 (d, *J* = 16.2 Hz, 1H), 3.80 (m, 1H), 3.74-3.68 (m, 1H), 3.30 (br s, 1H), 3.12-3.09 (m, 1H), 2.89 (dt, *J* = 19.8, 4.2, Hz, 1H), 2.55-2.44 (m, 3H), 2.32-2.27 (m, 1H), 2.32-2.27 (m, 1H), 2.24-2.19 (m, 1H), 2.06-1.99 (m, 1H), 1.97-1.91 (m, 1H), 1.64 (q, *J* = 10.2 Hz, 1H) 0.87 (d, *J* = 6.0 Hz, 3H); $^\delta$C (150.9 MHz, DMSO) 198.0, 196.8, 151.9, 140.9, 134.6, 128.4, 60.4, 59.5, 52.2, 47.8, 32.7, 32.6, 28.7, 27.6, 19.9, 19.2; HRMS (TOF, ES+) C$_{16}$H$_{22}$NO$_2$ [M+H]$^+$ calc'd 260.1651, found 260.1651.

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APPENDIX A1:

Spectra Relevant to Chapter I
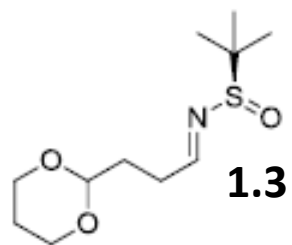
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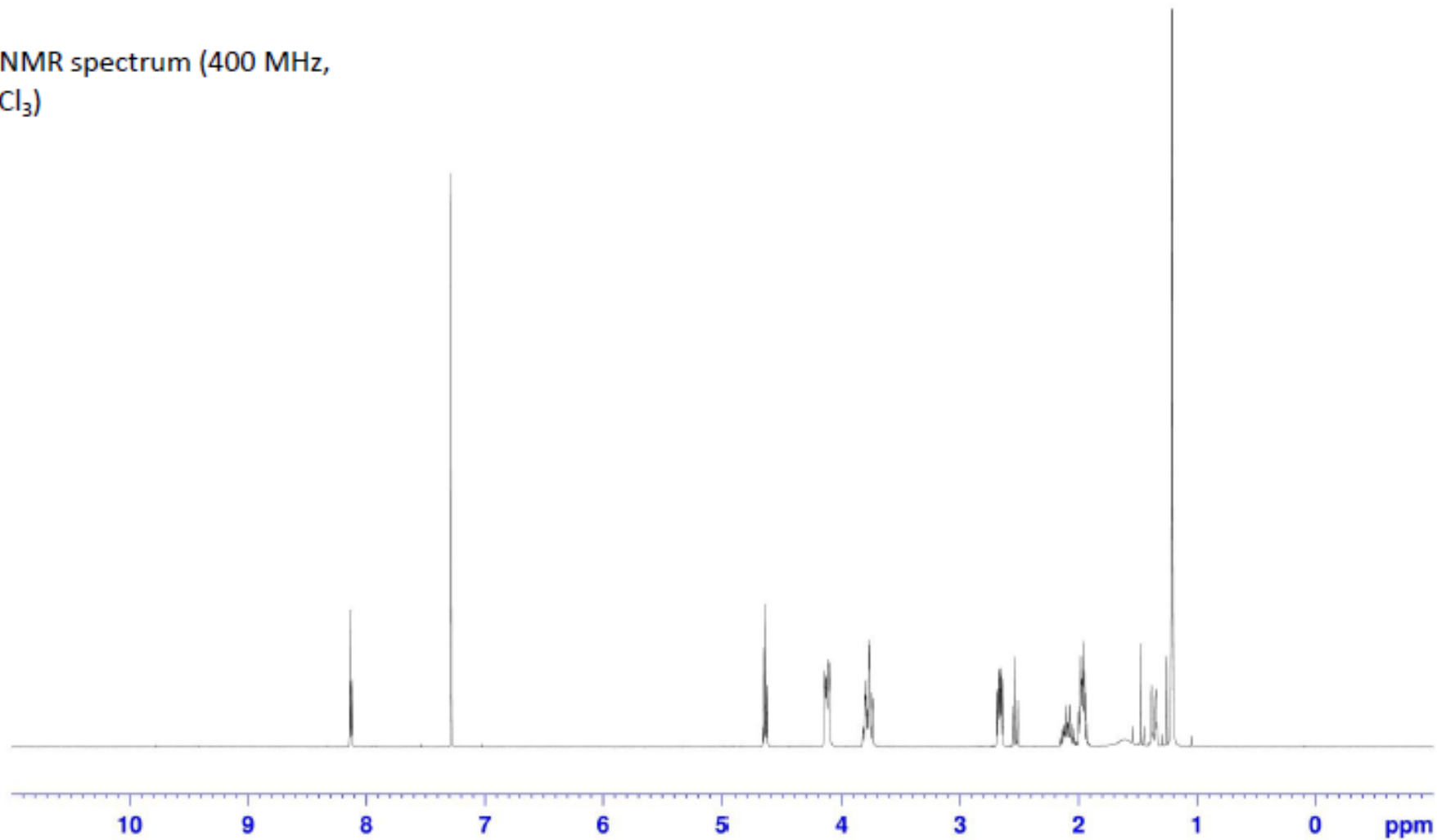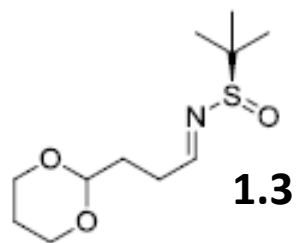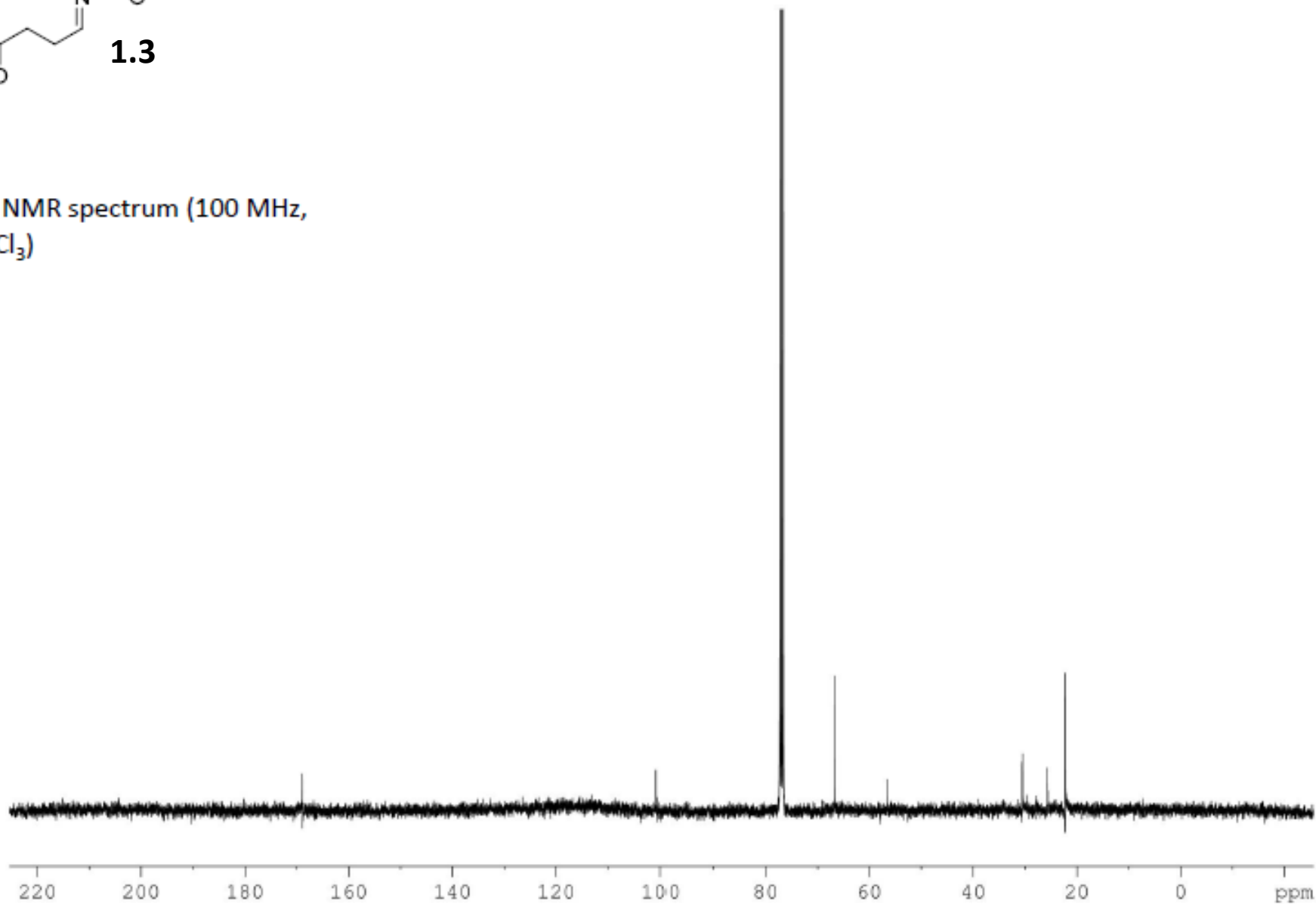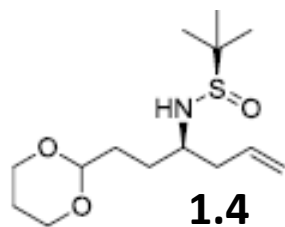
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1.3

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

1.4

¹H NMR spectrum (400 MHz, CDCl₃)

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

1.4

1.5

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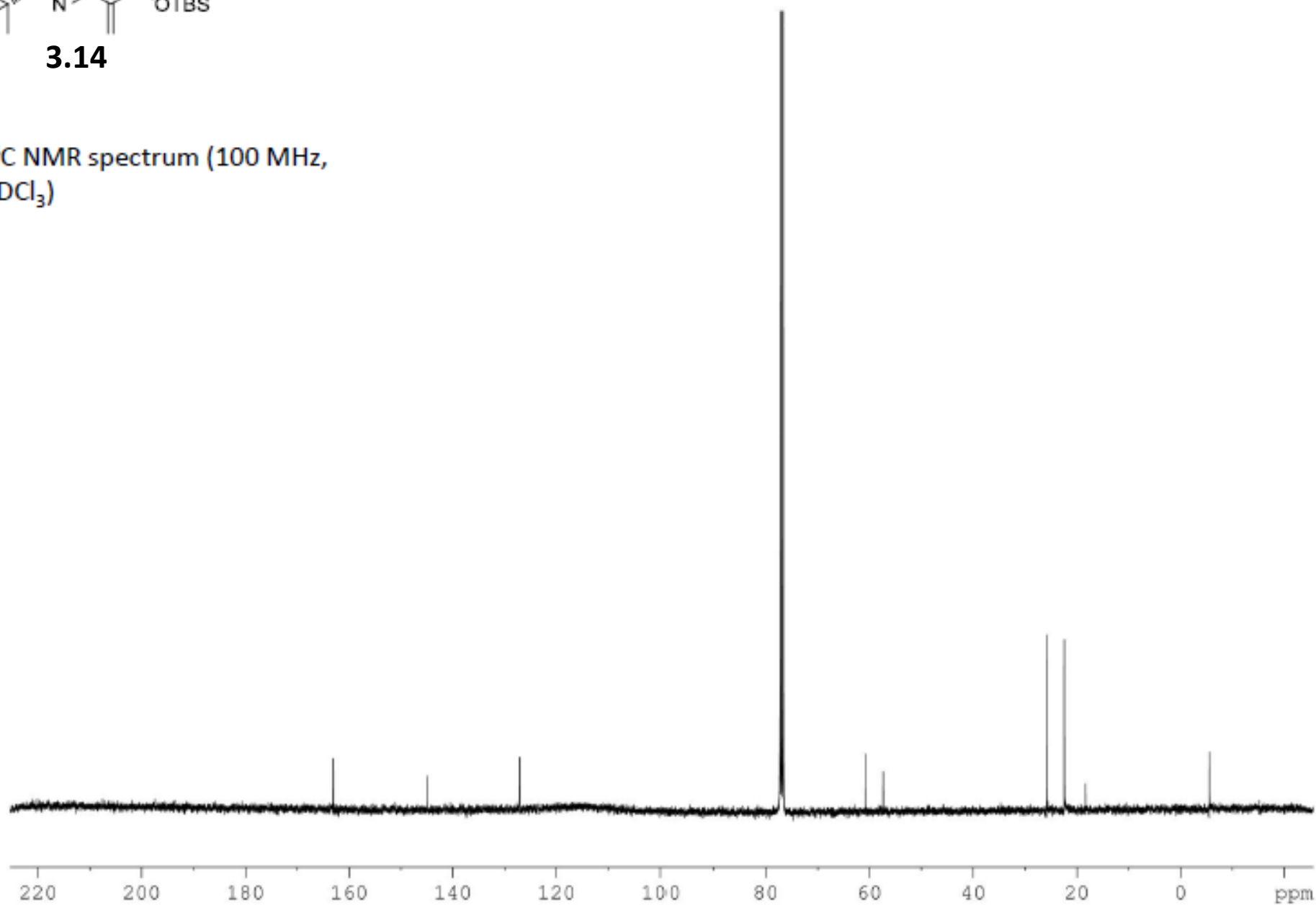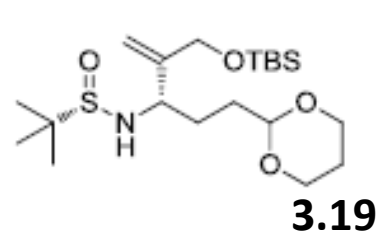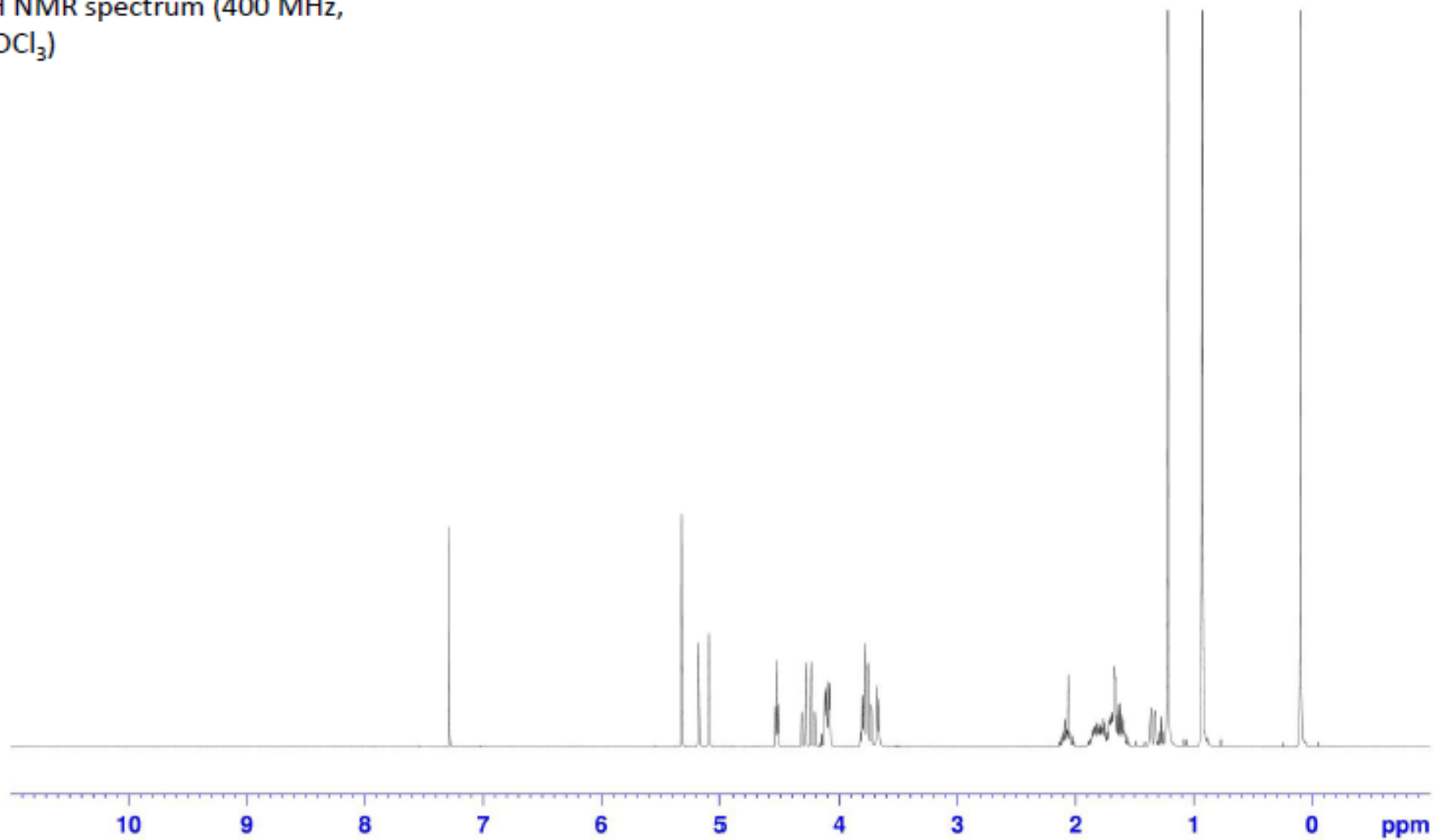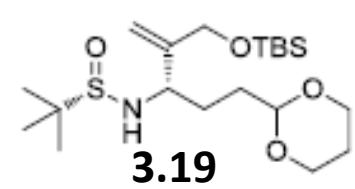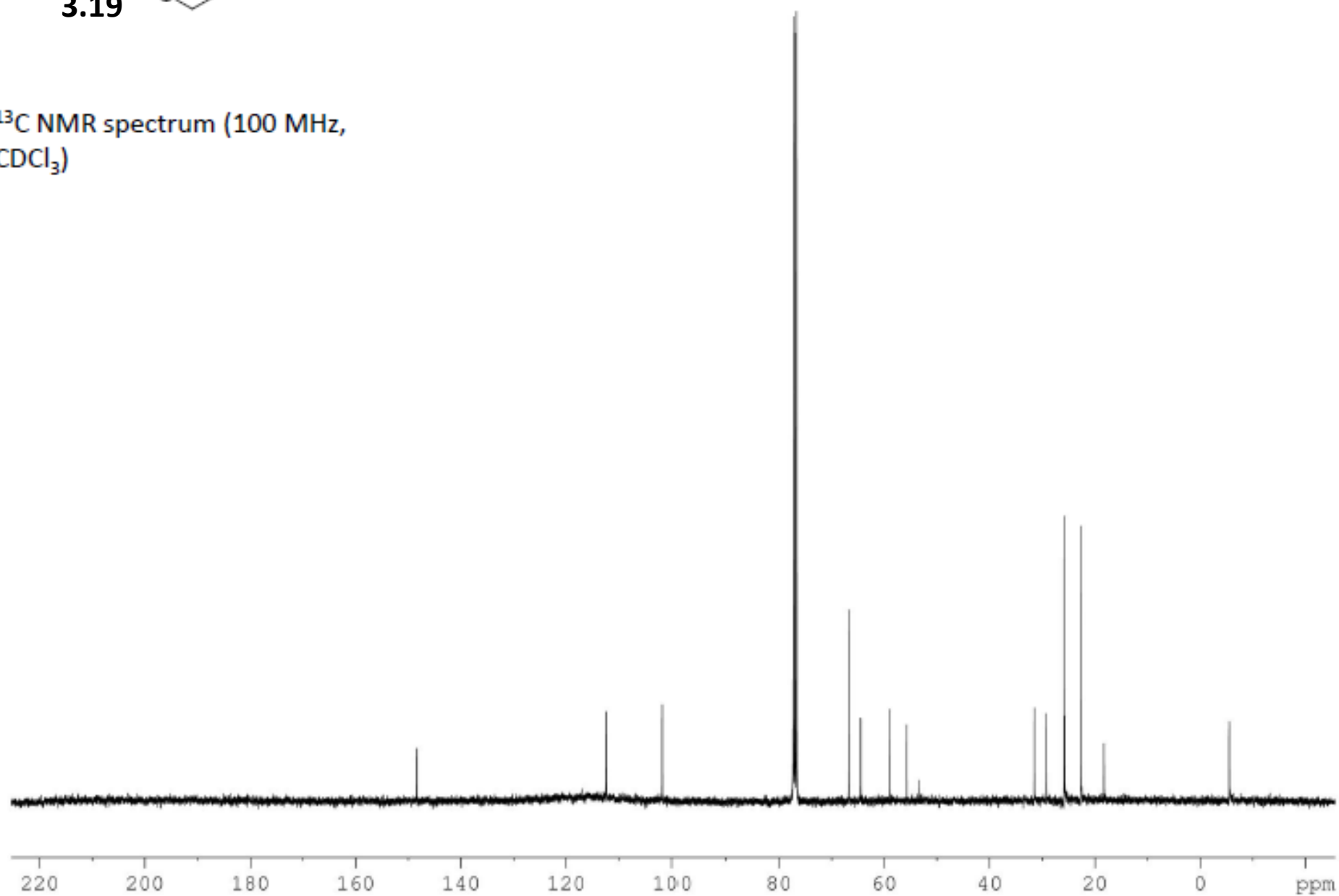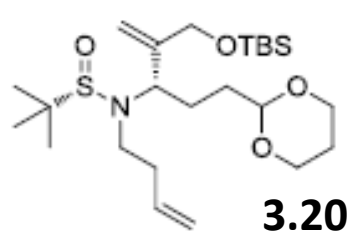
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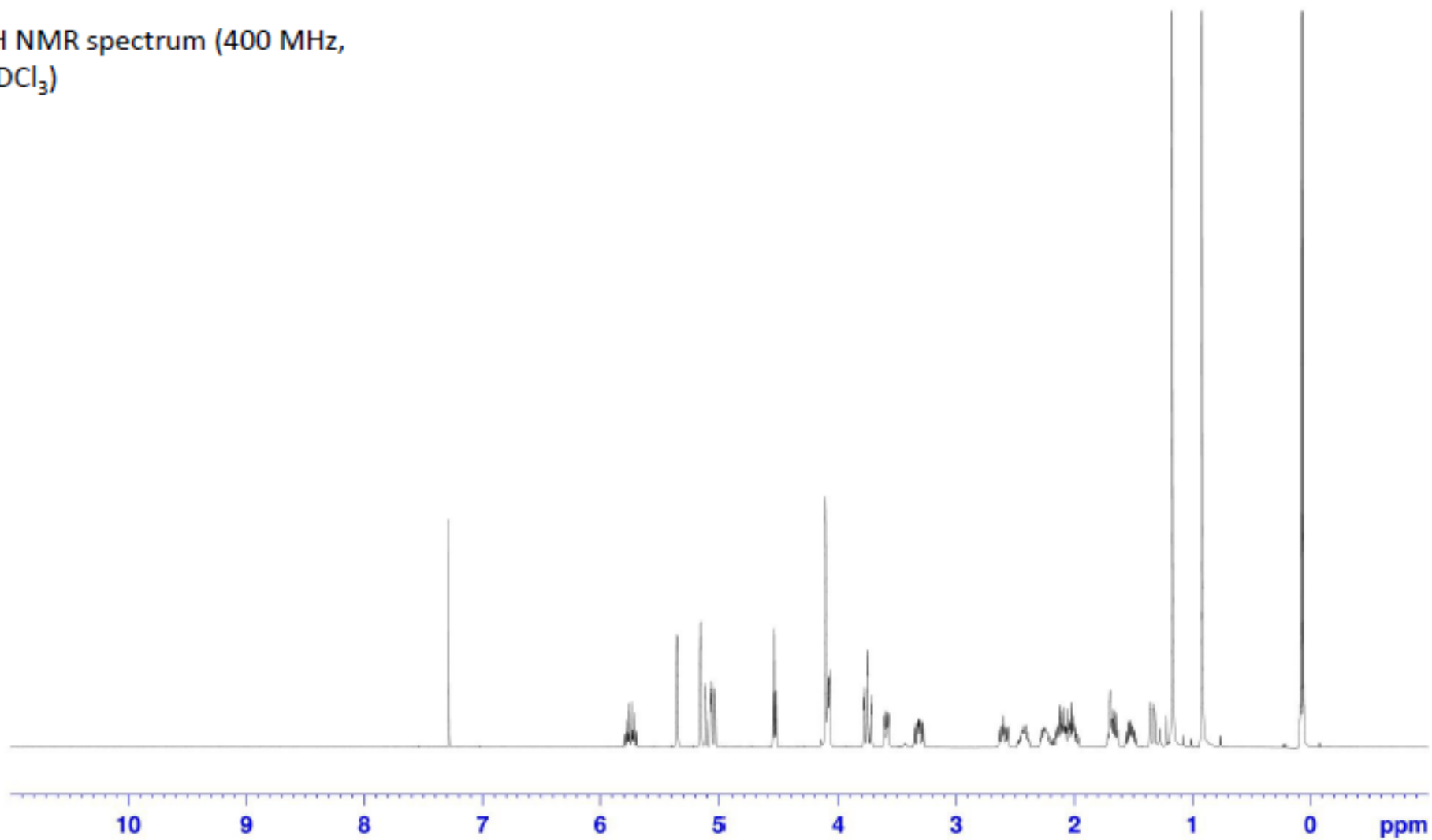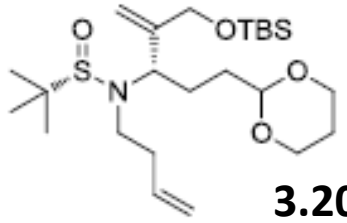
1.6

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1.6
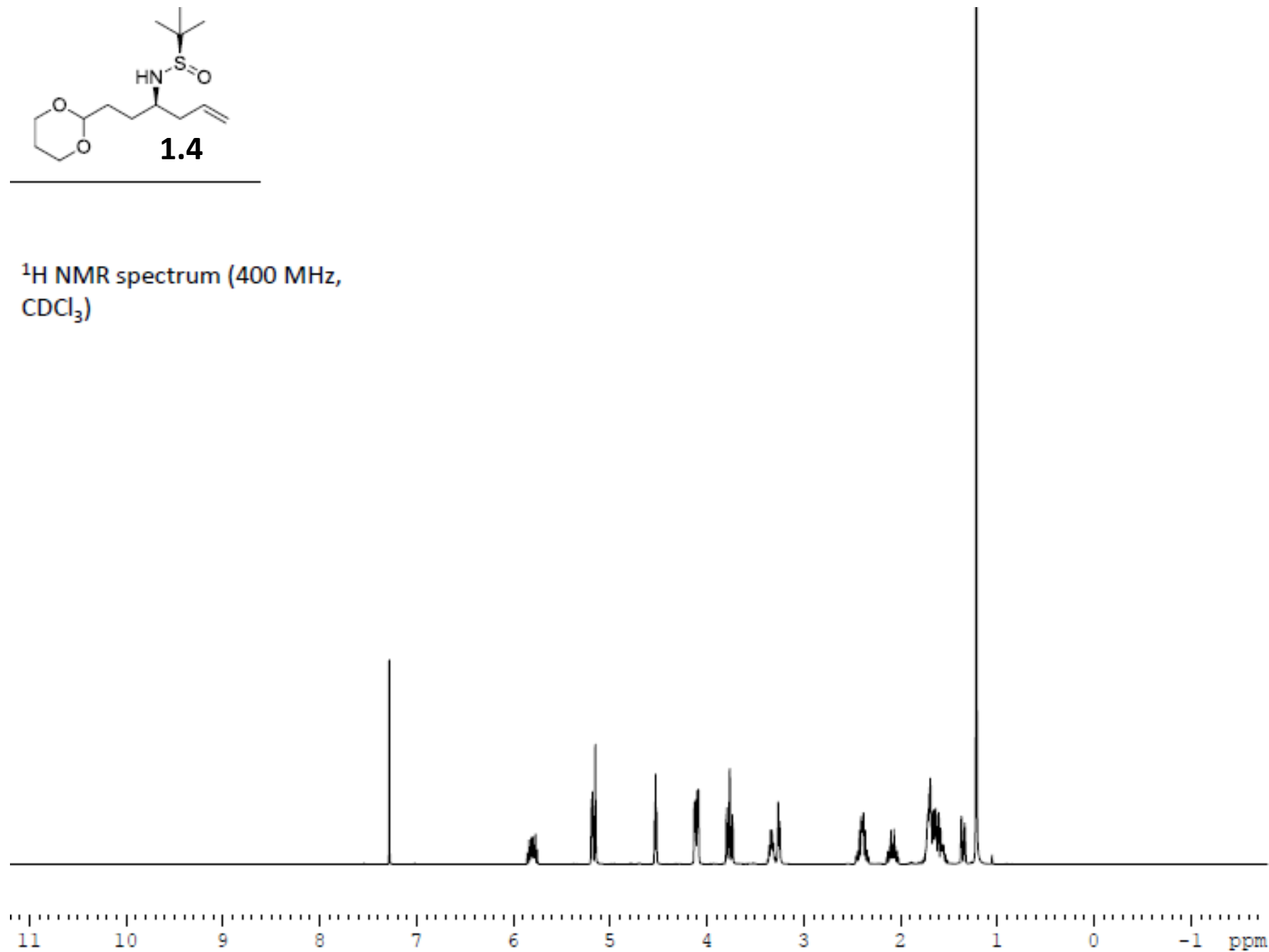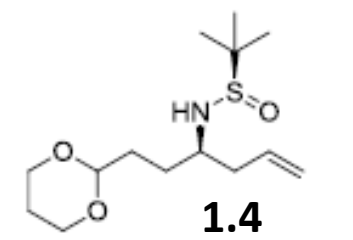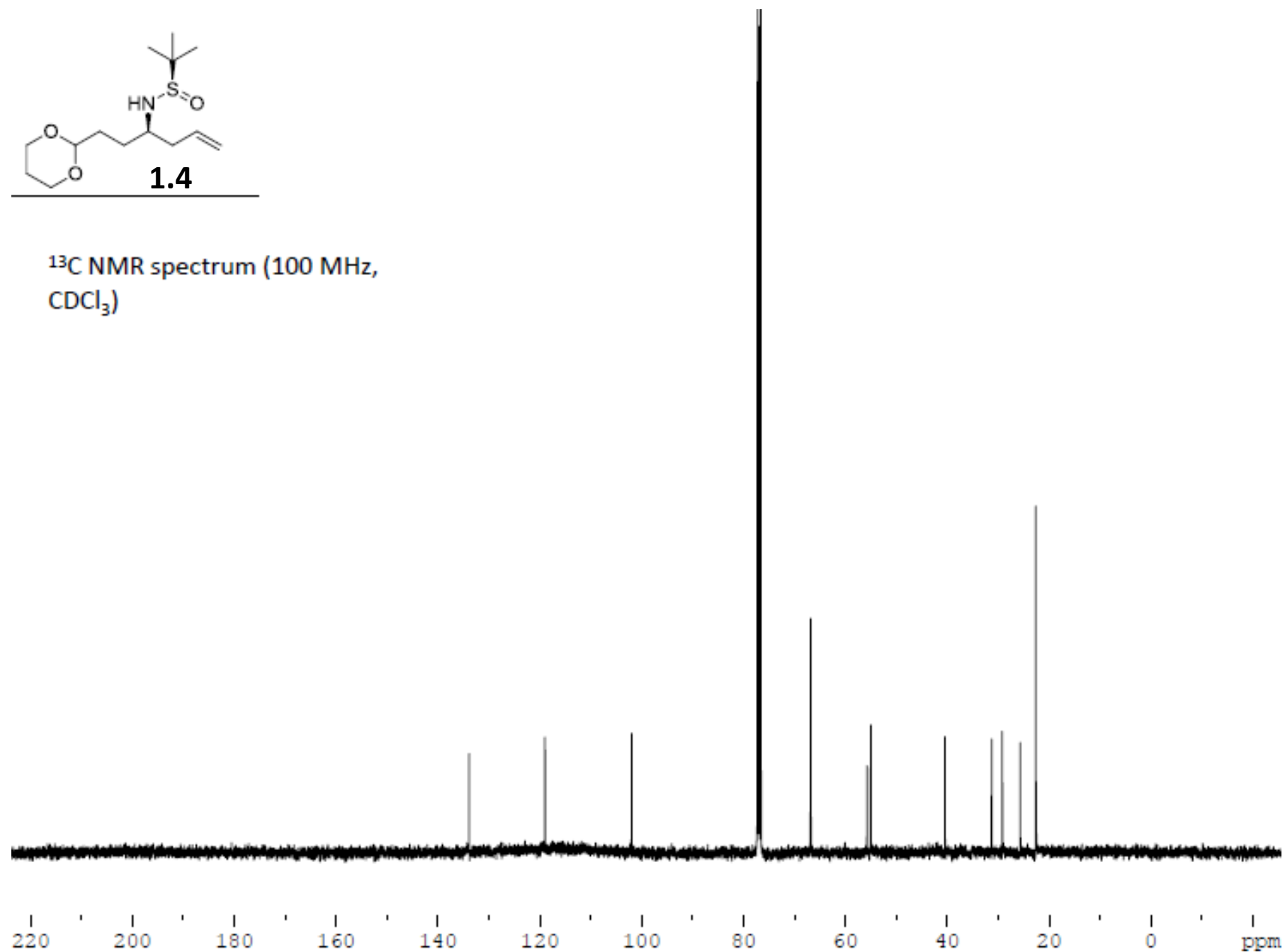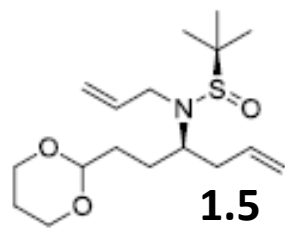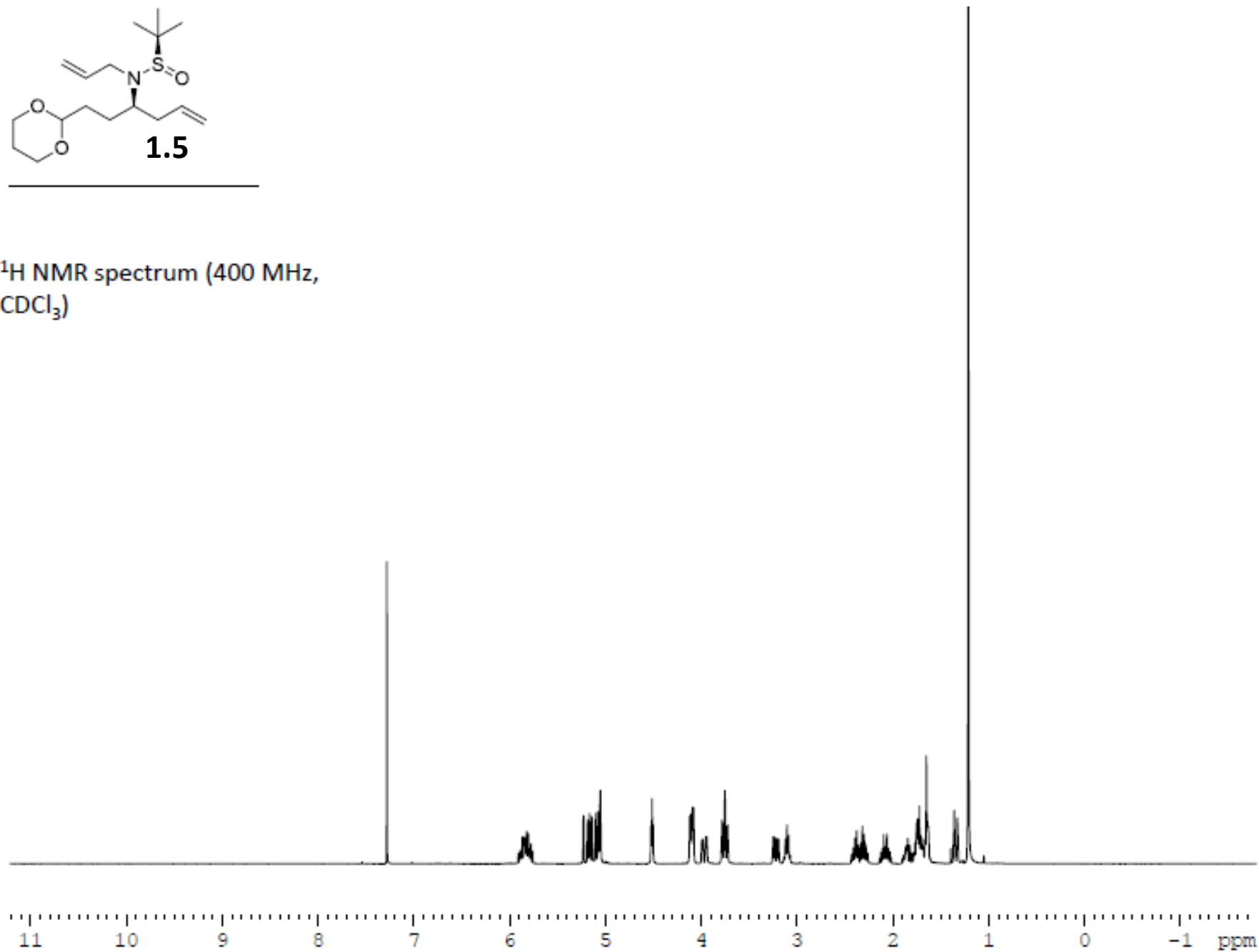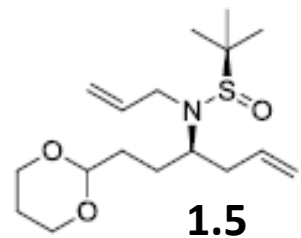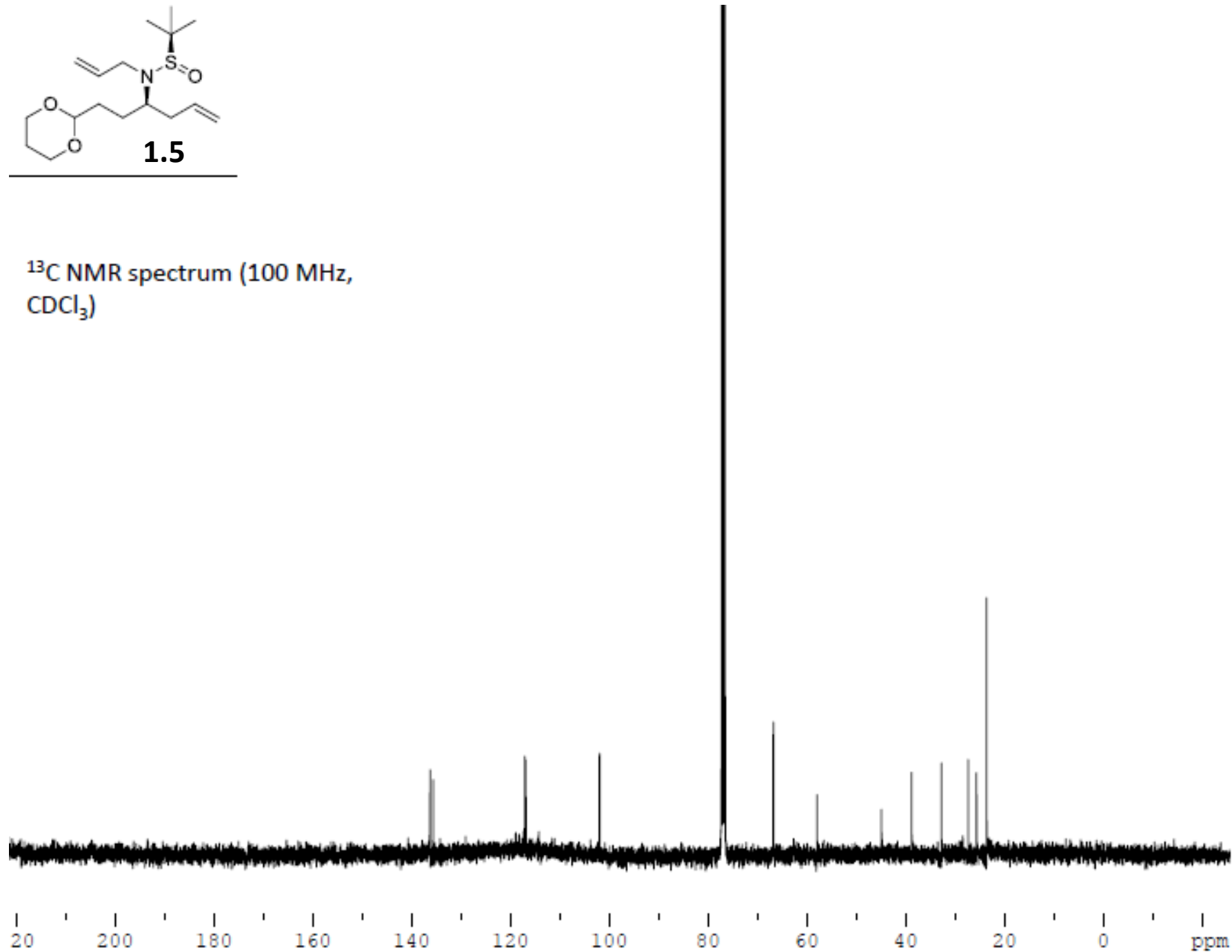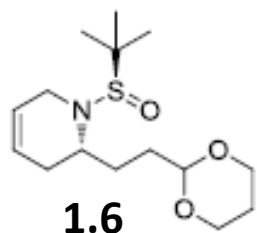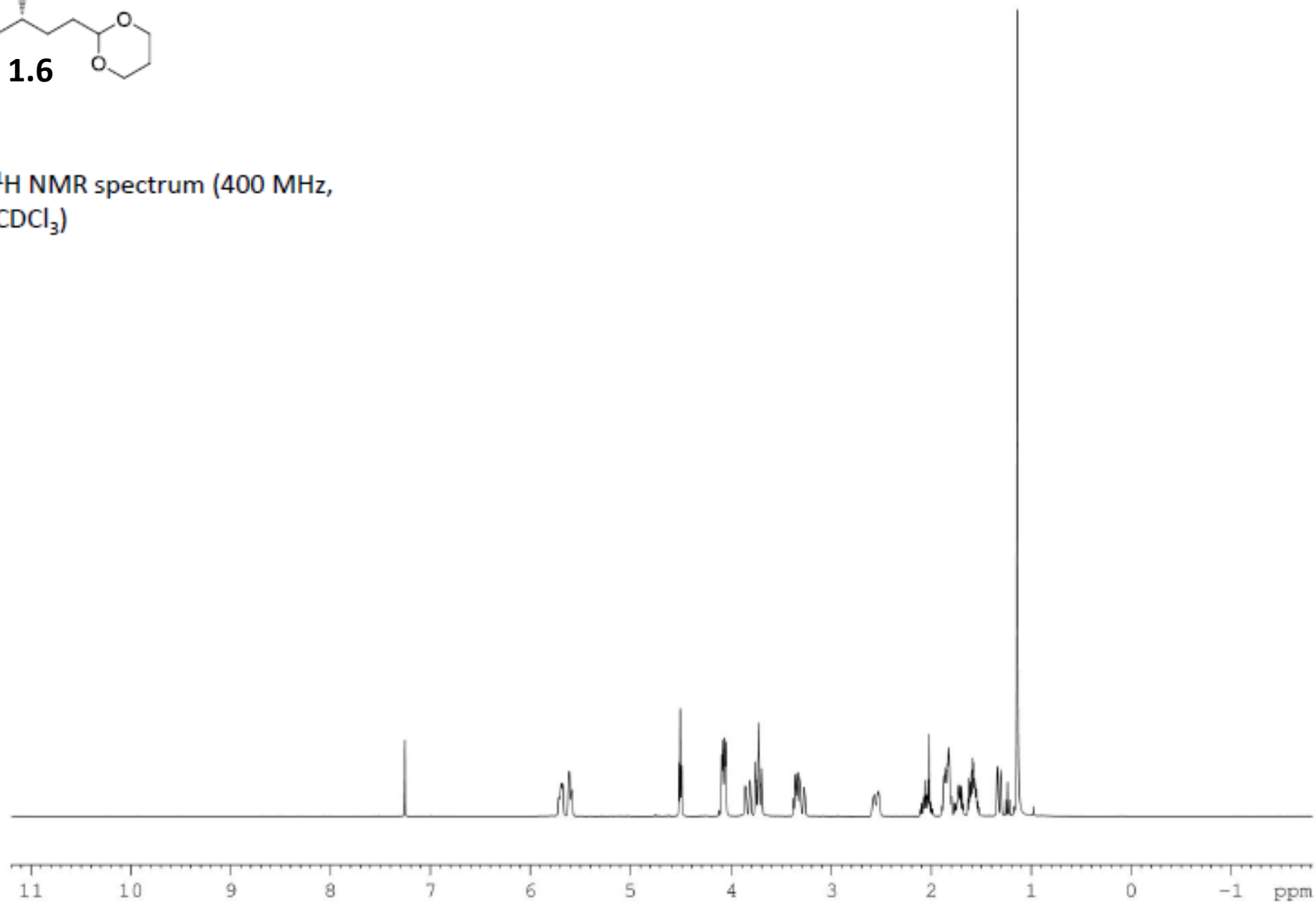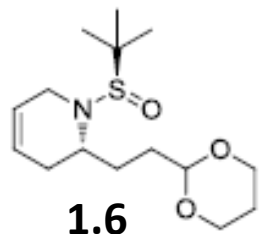
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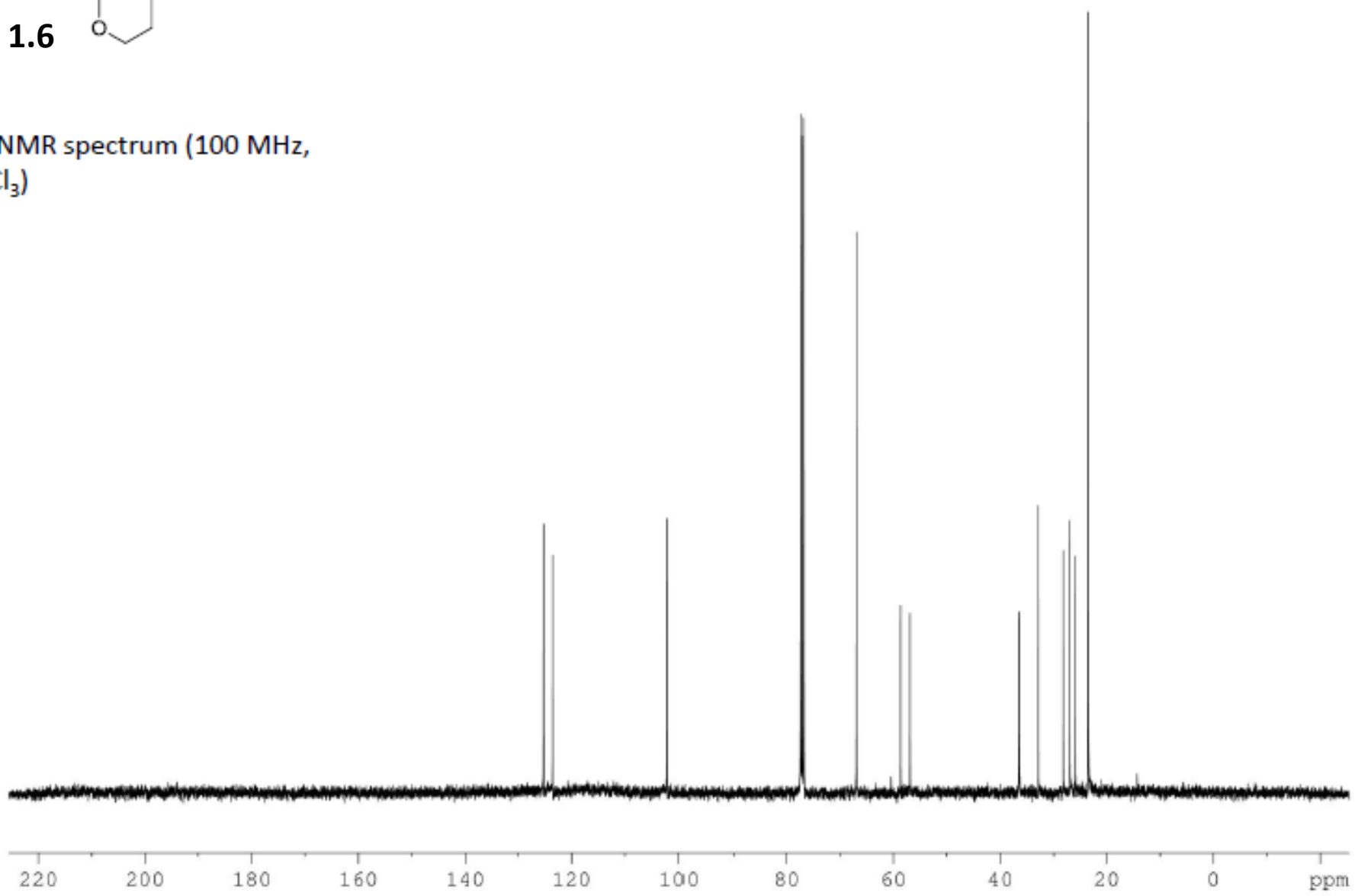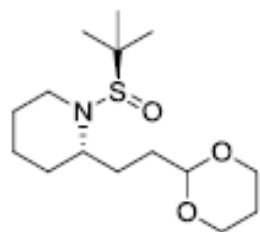
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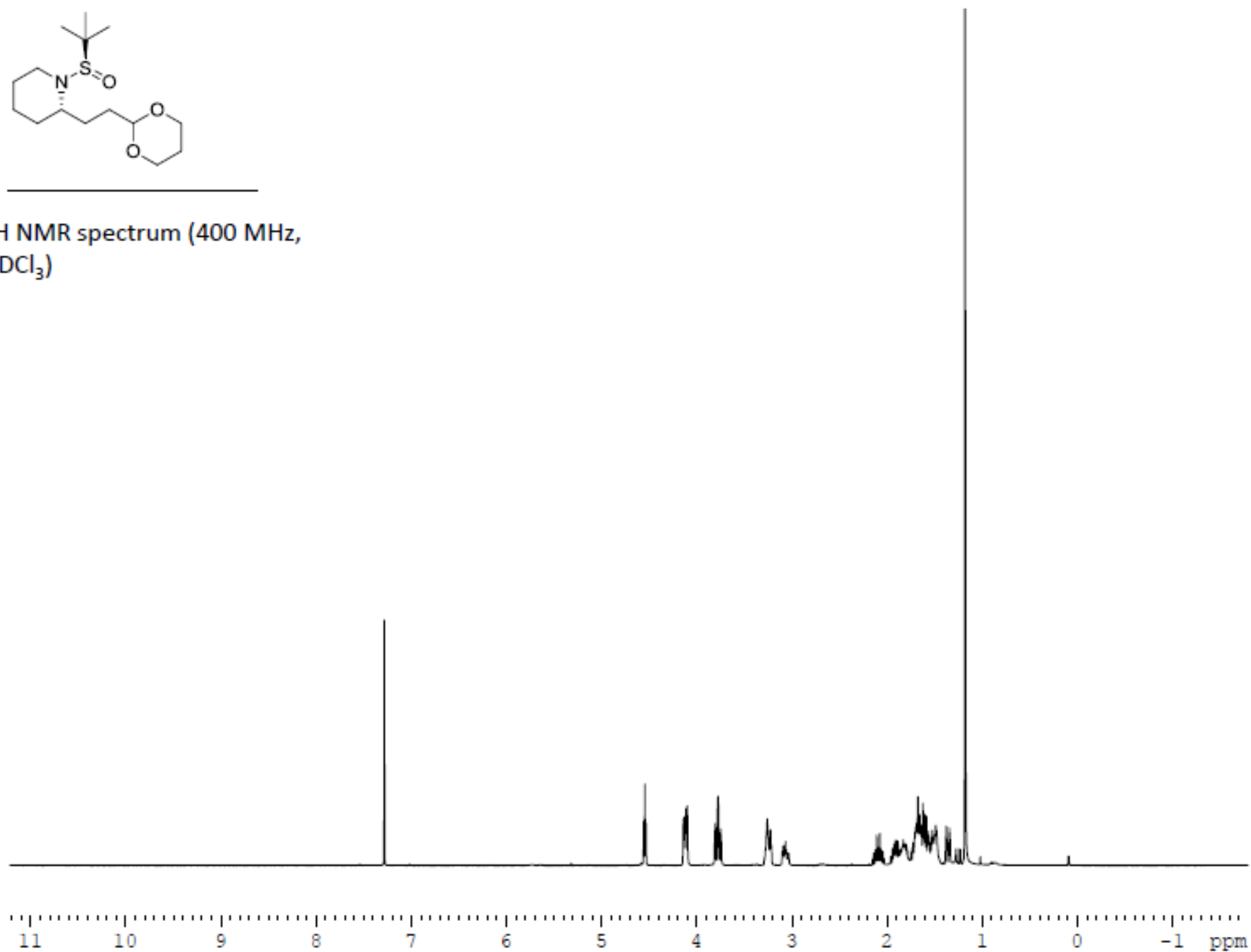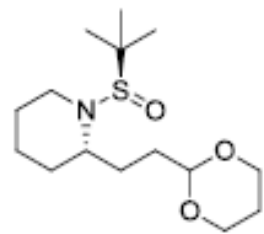
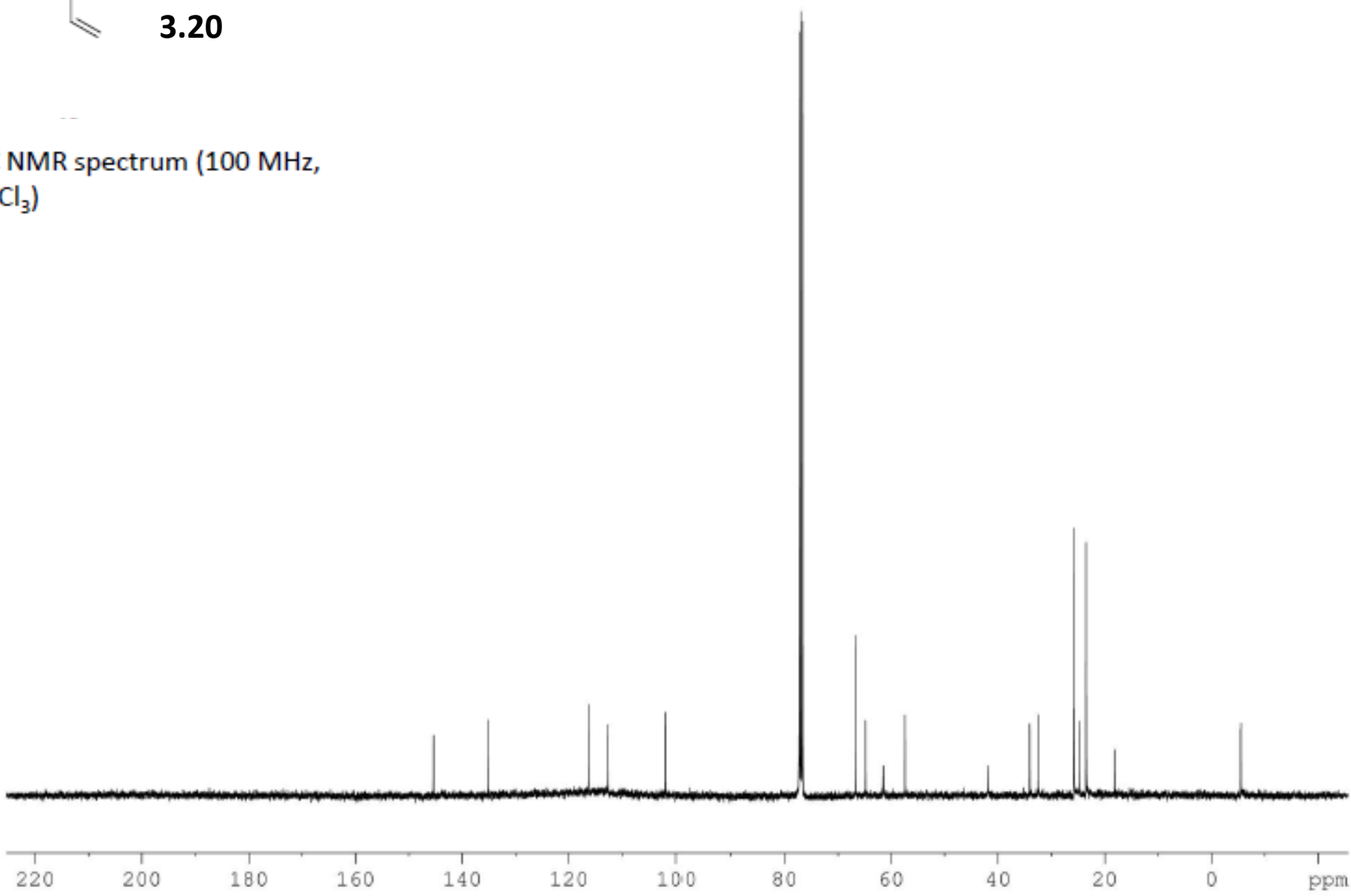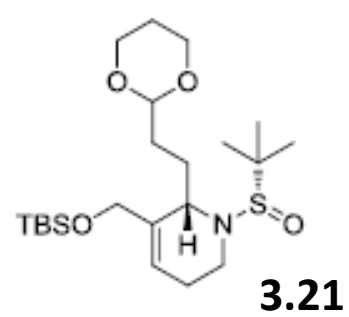^{13}C NMR spectrum (100 MHz, CDCl$_3$)

1.7

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1.7 ·TFA

^{13}C NMR spectrum (100 MHz, MeOD)

1.9

^{1}H NMR spectrum (400 MHz, CDCl$_3$)

¹³C NMR spectrum (100 MHz, CDCl₃)

1.9

1.11

^{1}H NMR spectrum (400 MHz, CDCl$_3$)
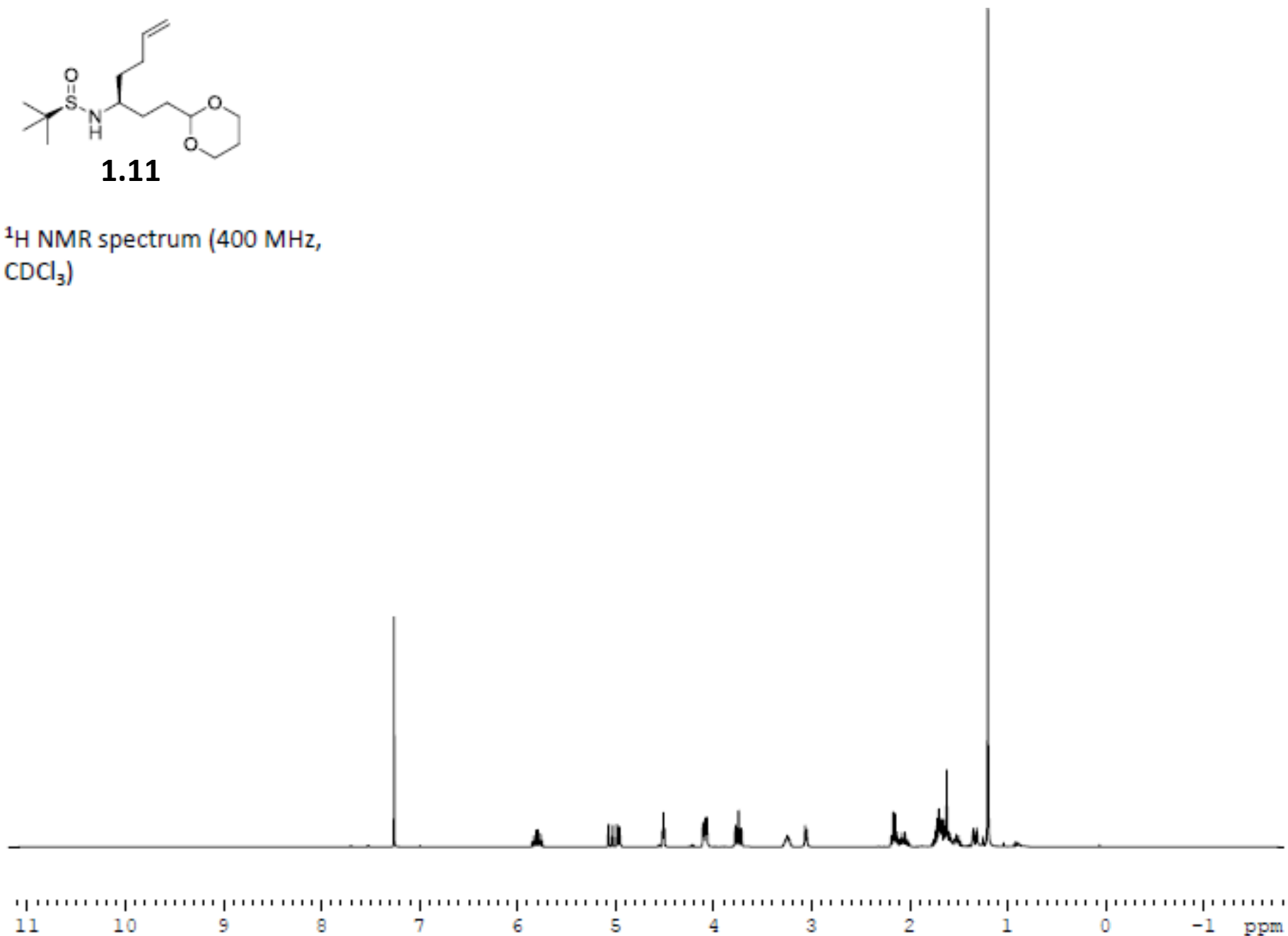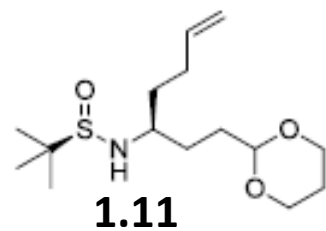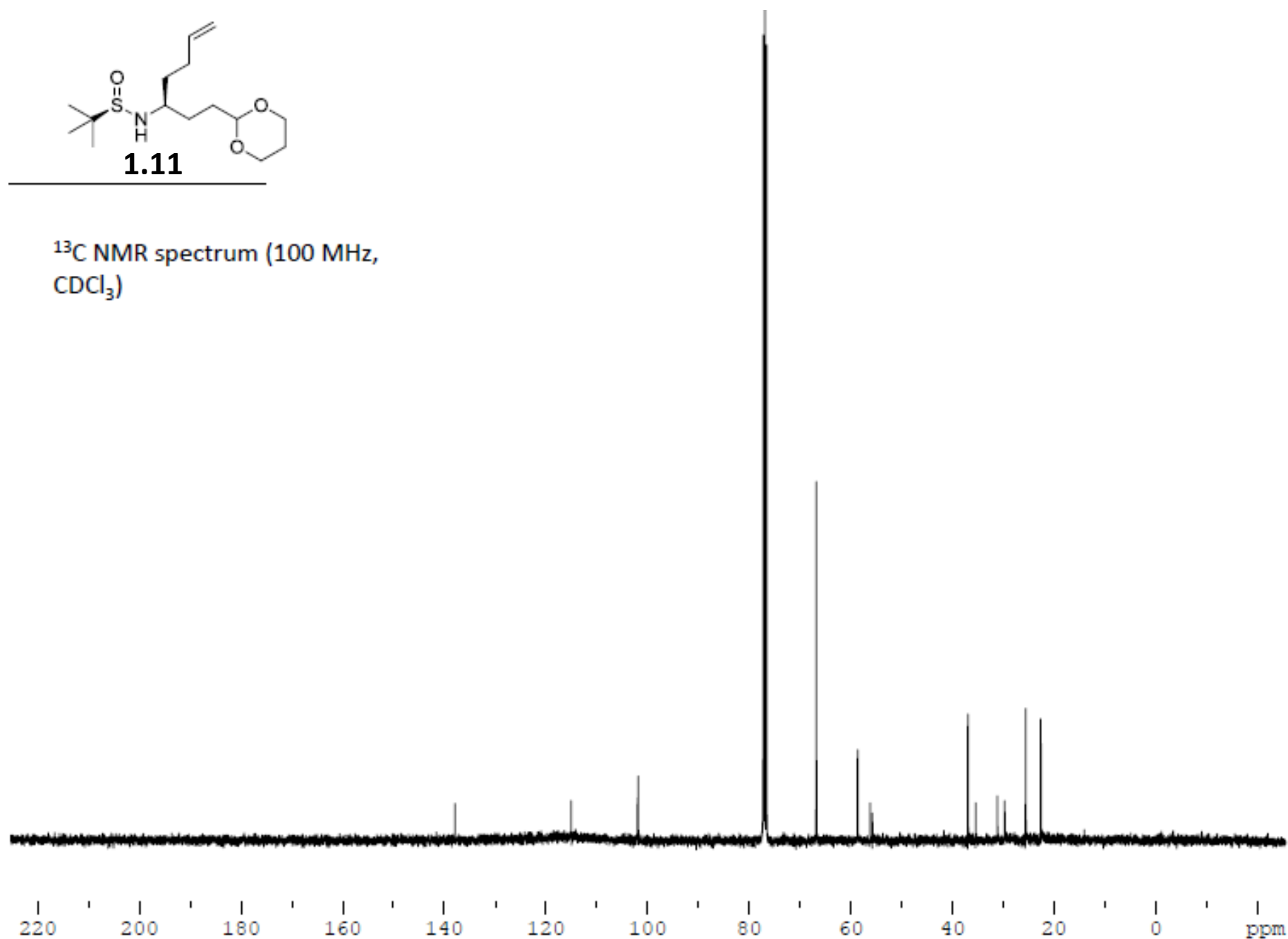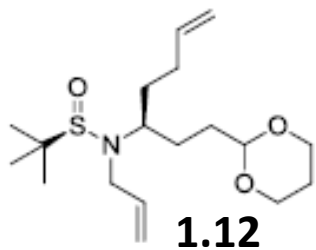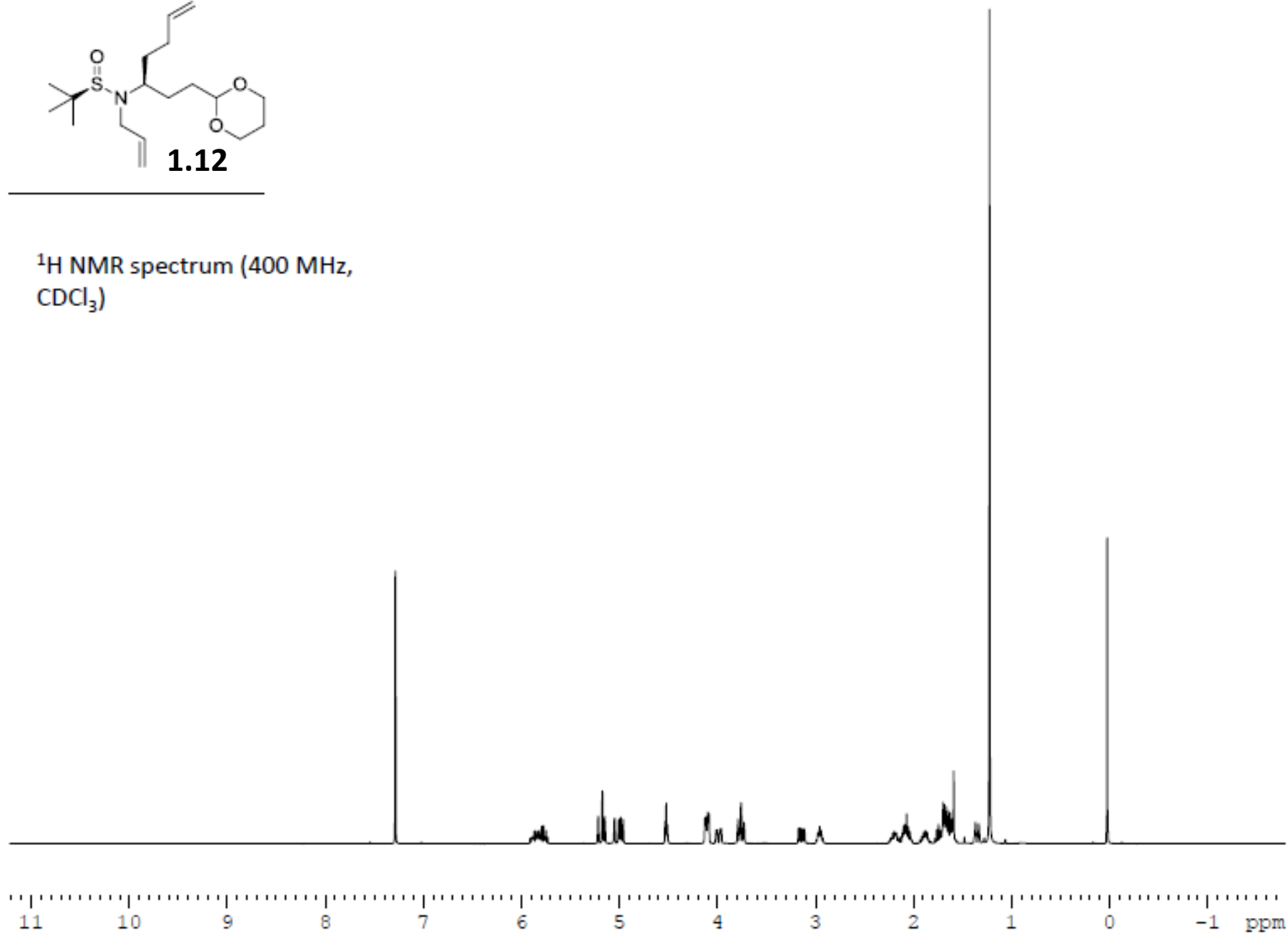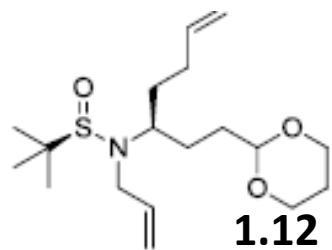
1.11

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

1.12

¹H NMR spectrum (400 MHz, CDCl₃)

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

1.13

^{1}H NMR spectrum (400 MHz, CDCl$_3$)

1.13

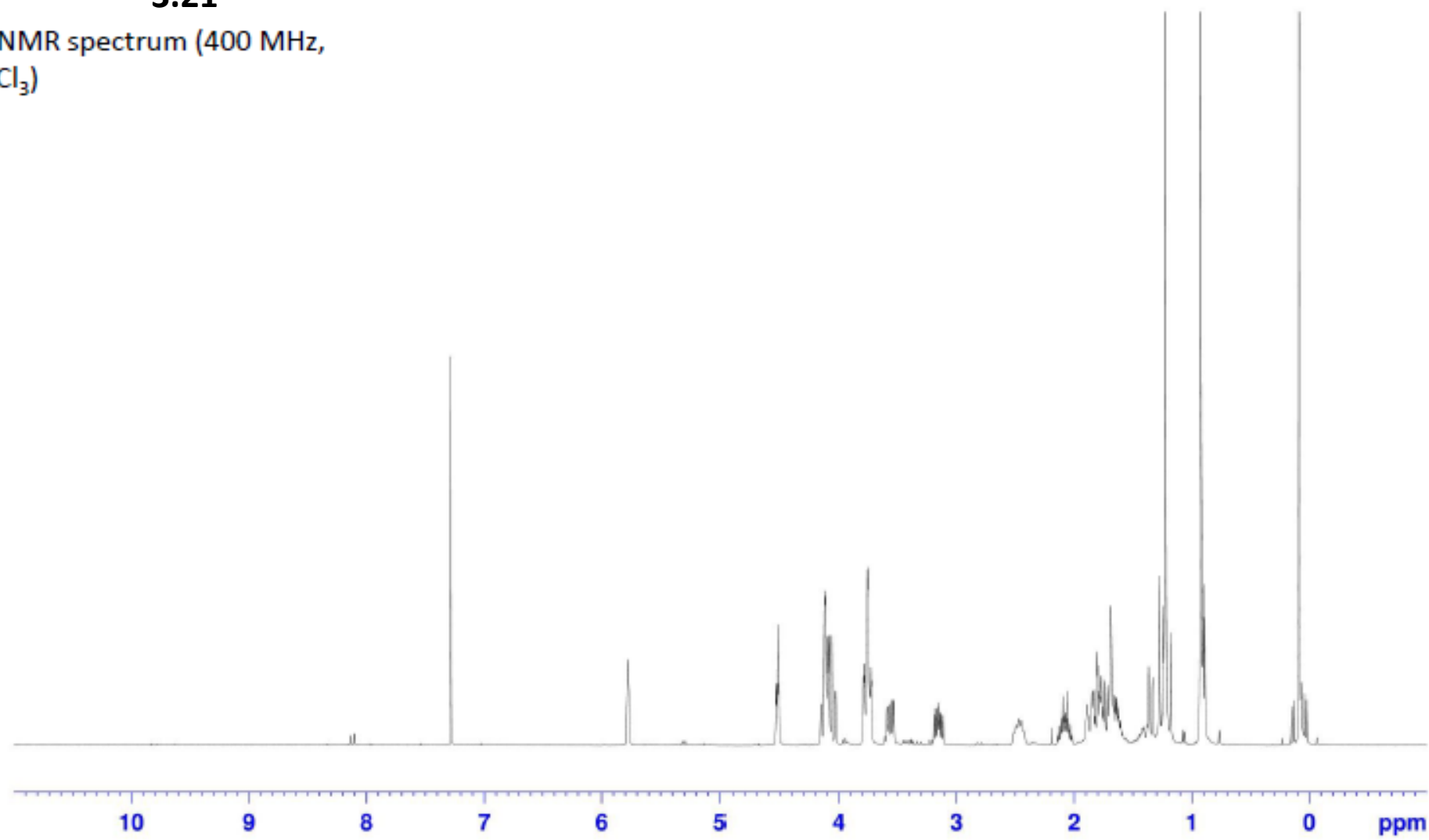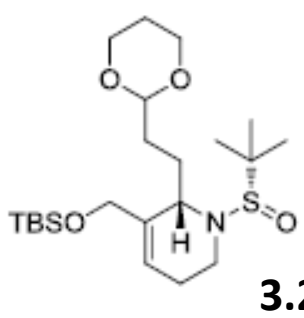^{13}C NMR spectrum (100 MHz, CDCl$_3$)
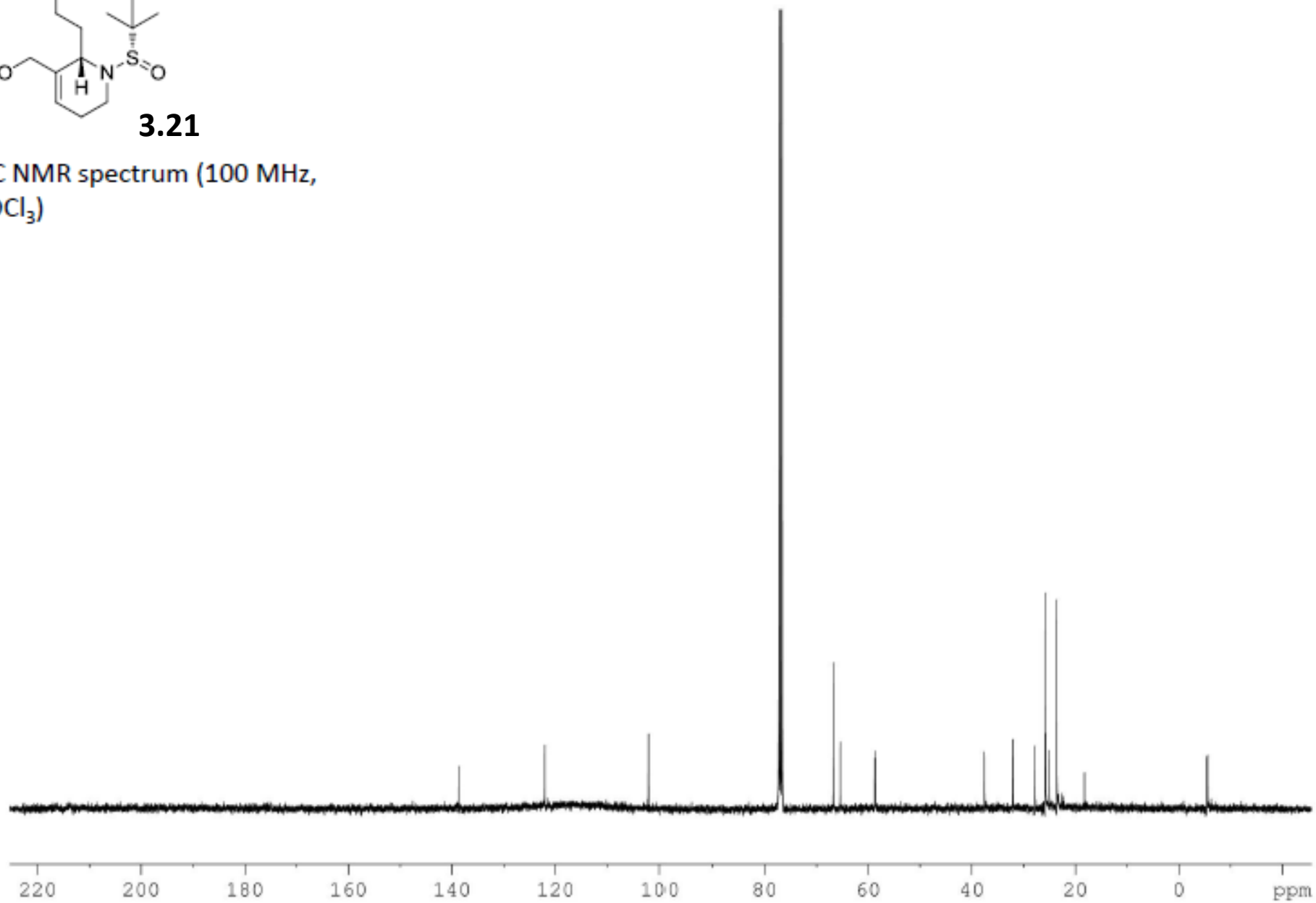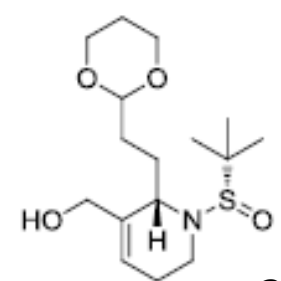
¹H NMR spectrum (400 MHz, CDCl₃)

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

1.14

¹H NMR spectrum (400 MHz, MeOD)

1.14 ·TFA

^{13}C NMR spectrum (100 MHz, MeOD)

1.18

¹H NMR spectrum (400 MHz, CDCl₃)

1.18

^{13}C NMR spectrum (100 MHz, CDCl$_3$)
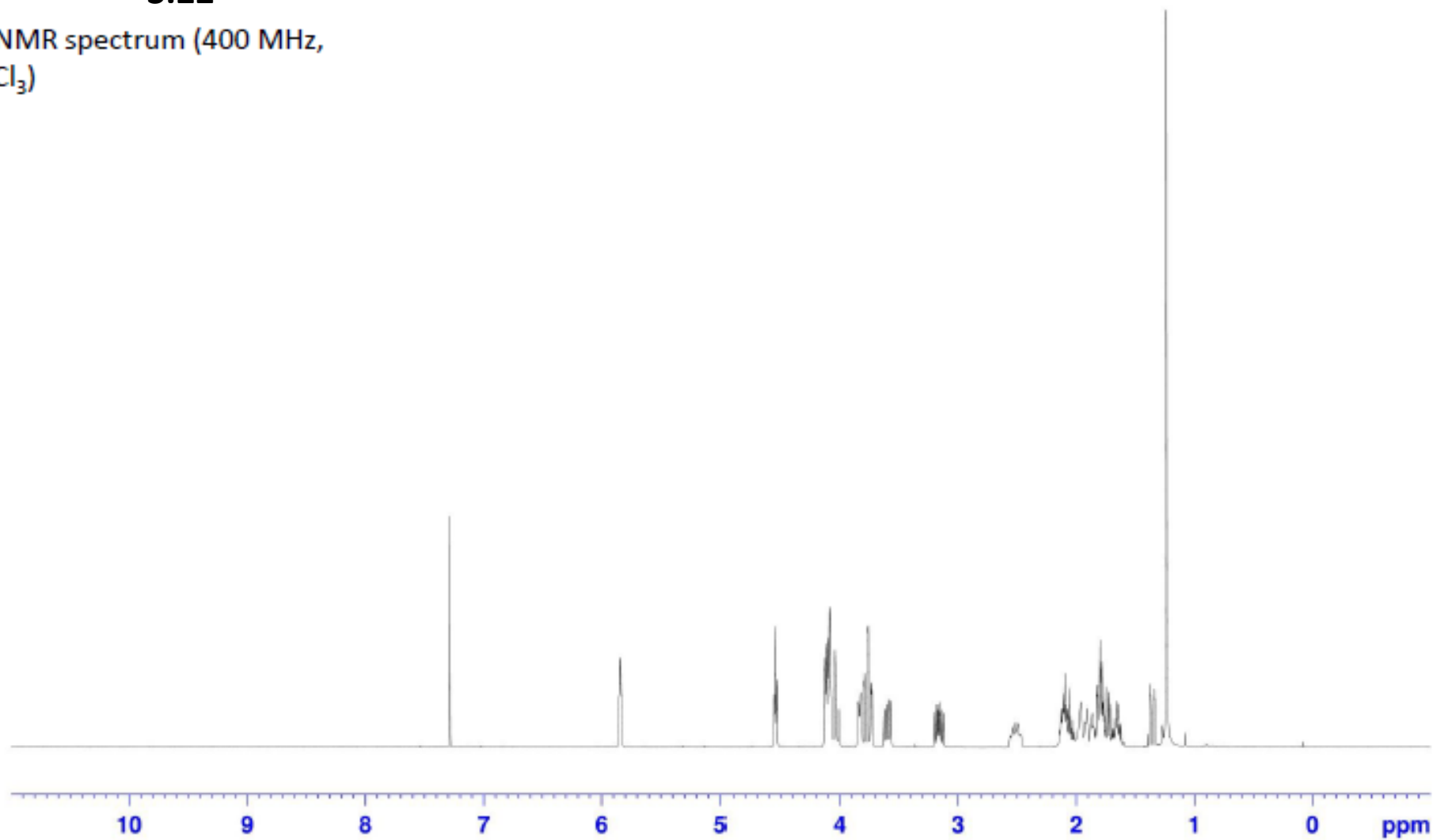
1.19

¹H NMR spectrum (400 MHz, CDCl₃)
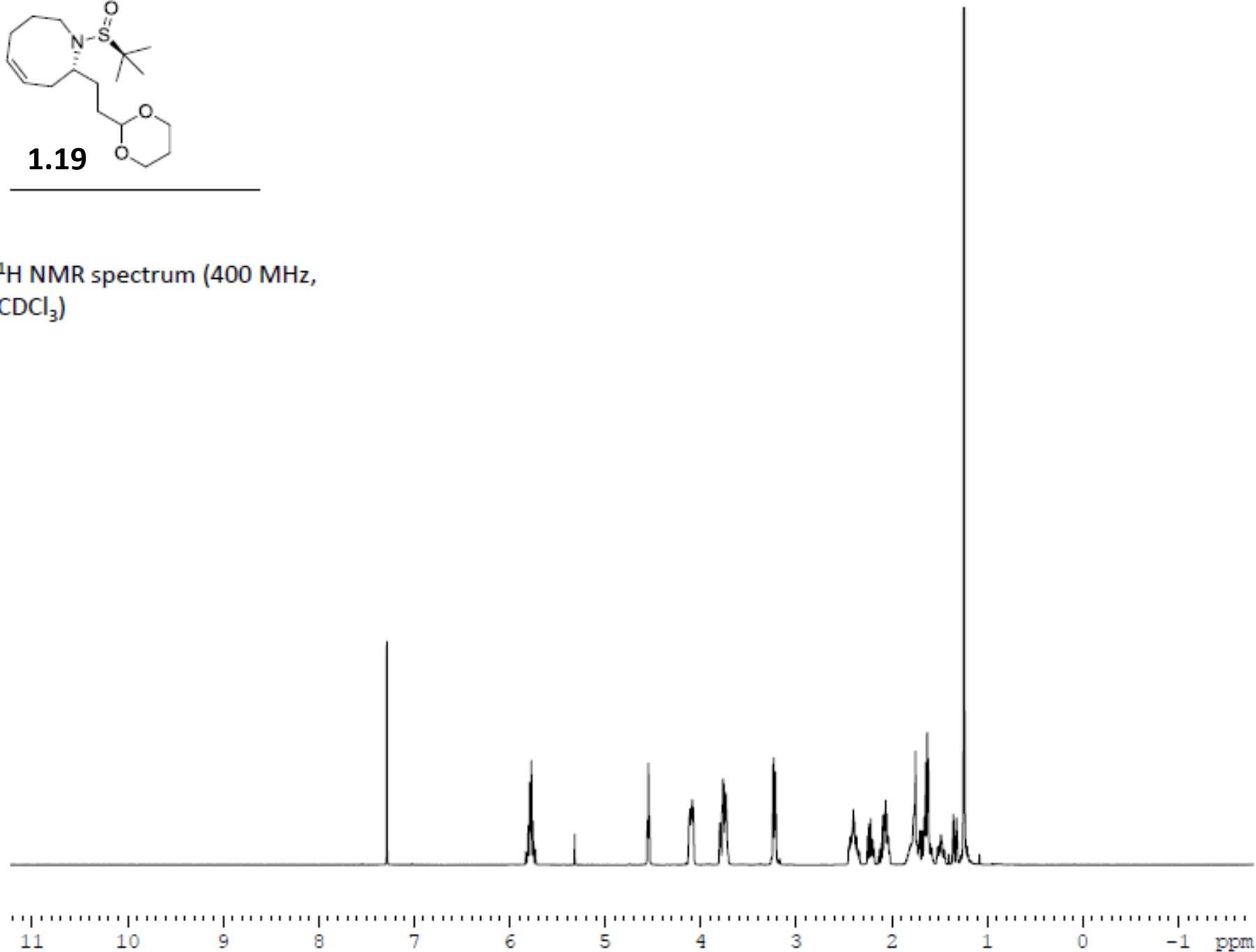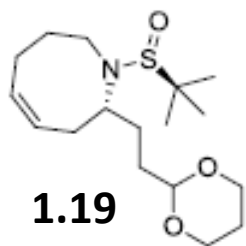
1.19

^{13}C NMR spectrum (100 MHz, CDCl$_3$)
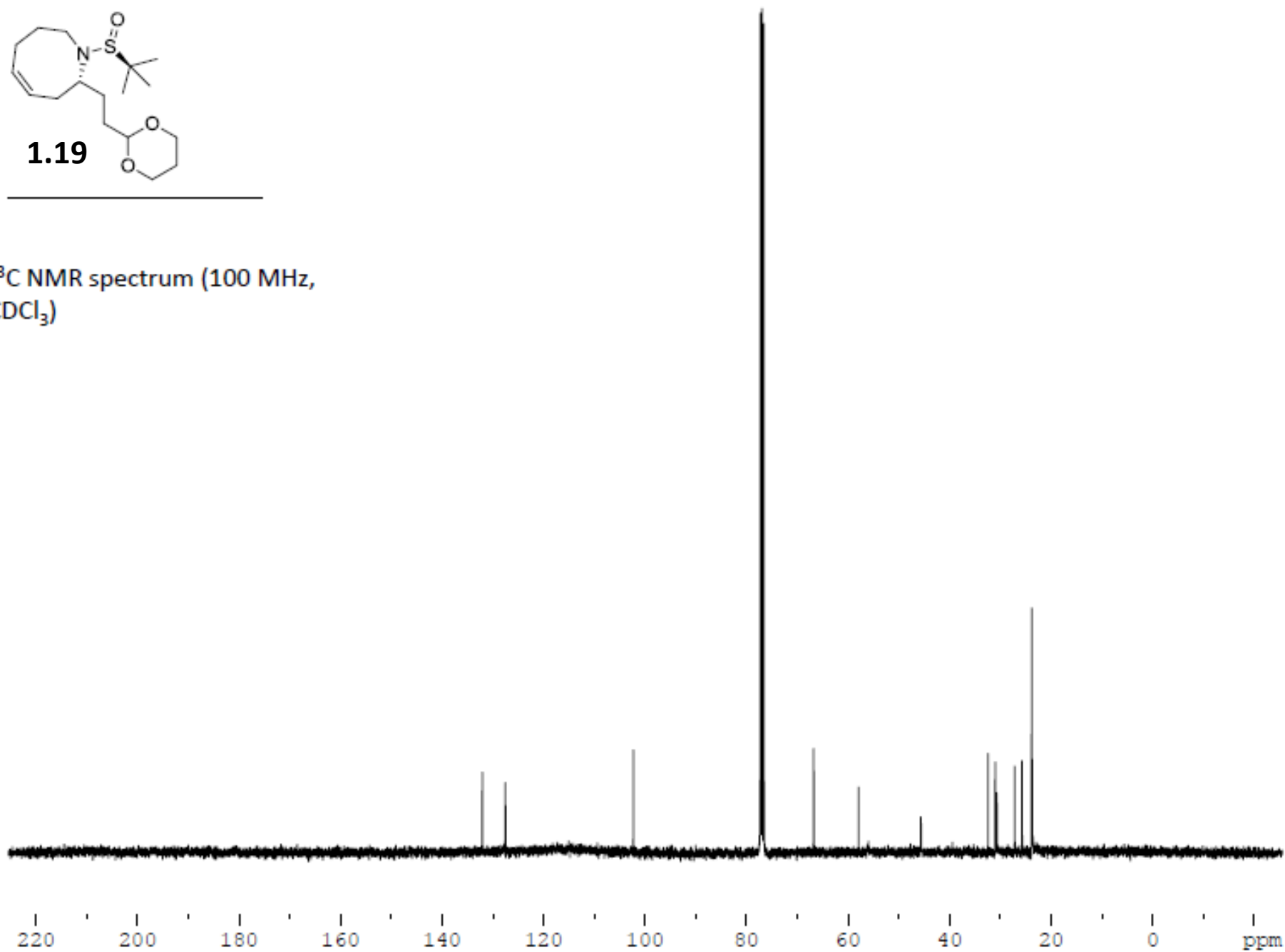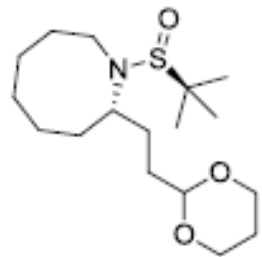
¹H NMR spectrum (400 MHz, CDCl₃)
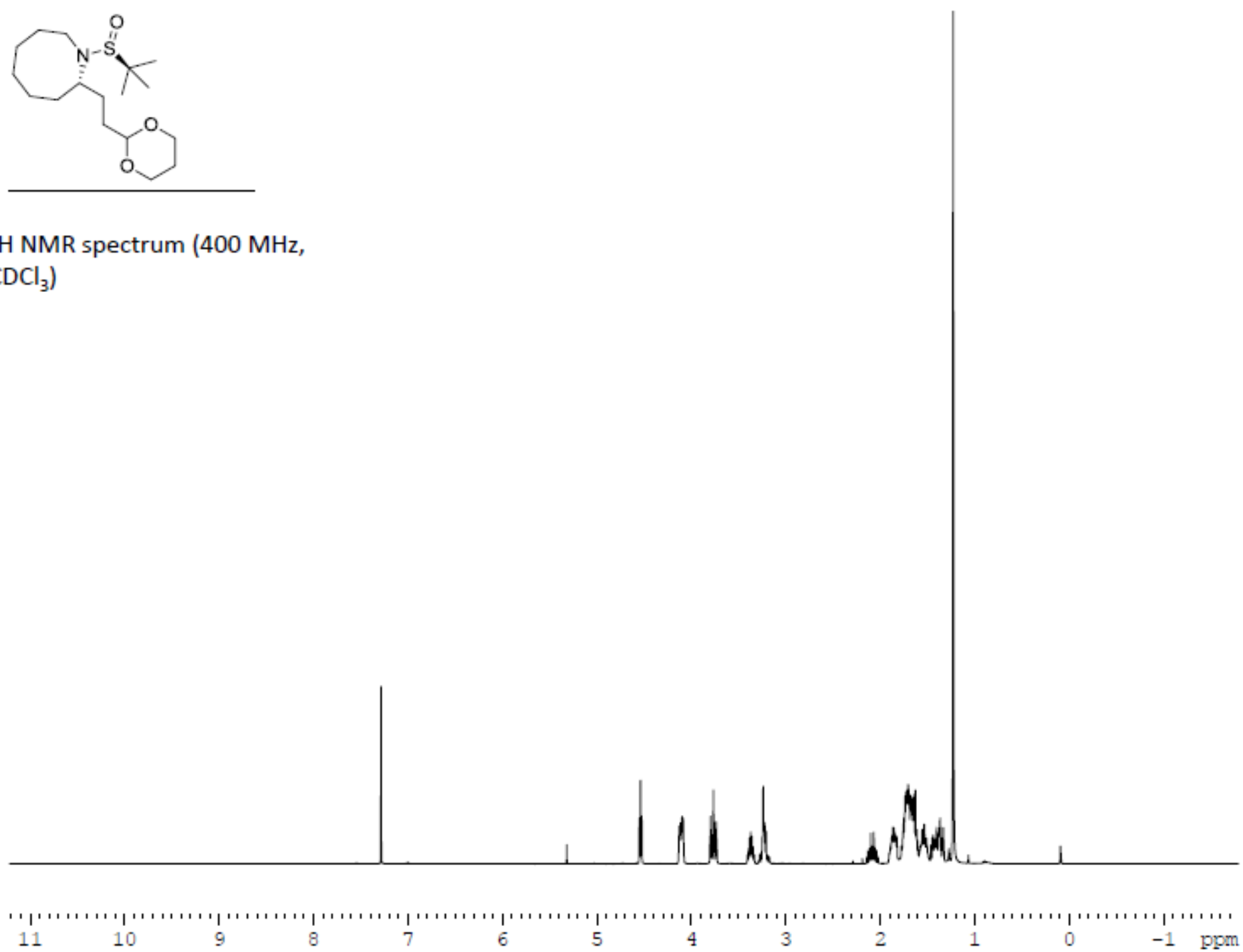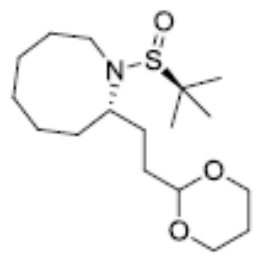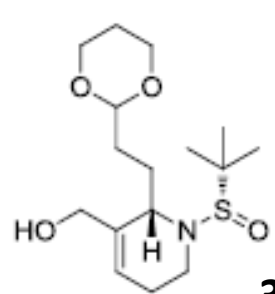
¹³C NMR spectrum (100 MHz, CDCl₃)
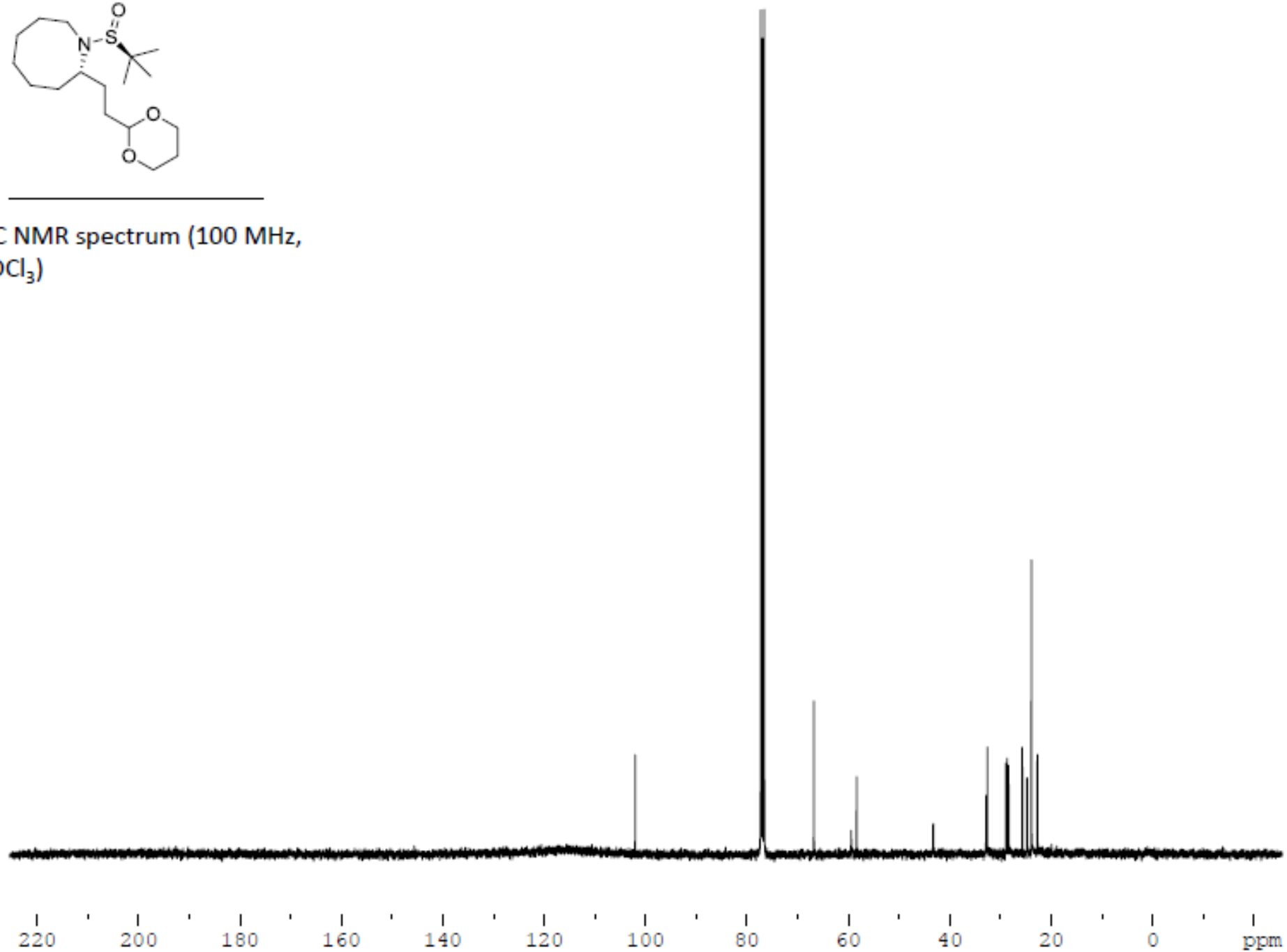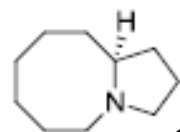
1.20

^{1}H NMR spectrum (400 MHz, MeOD)
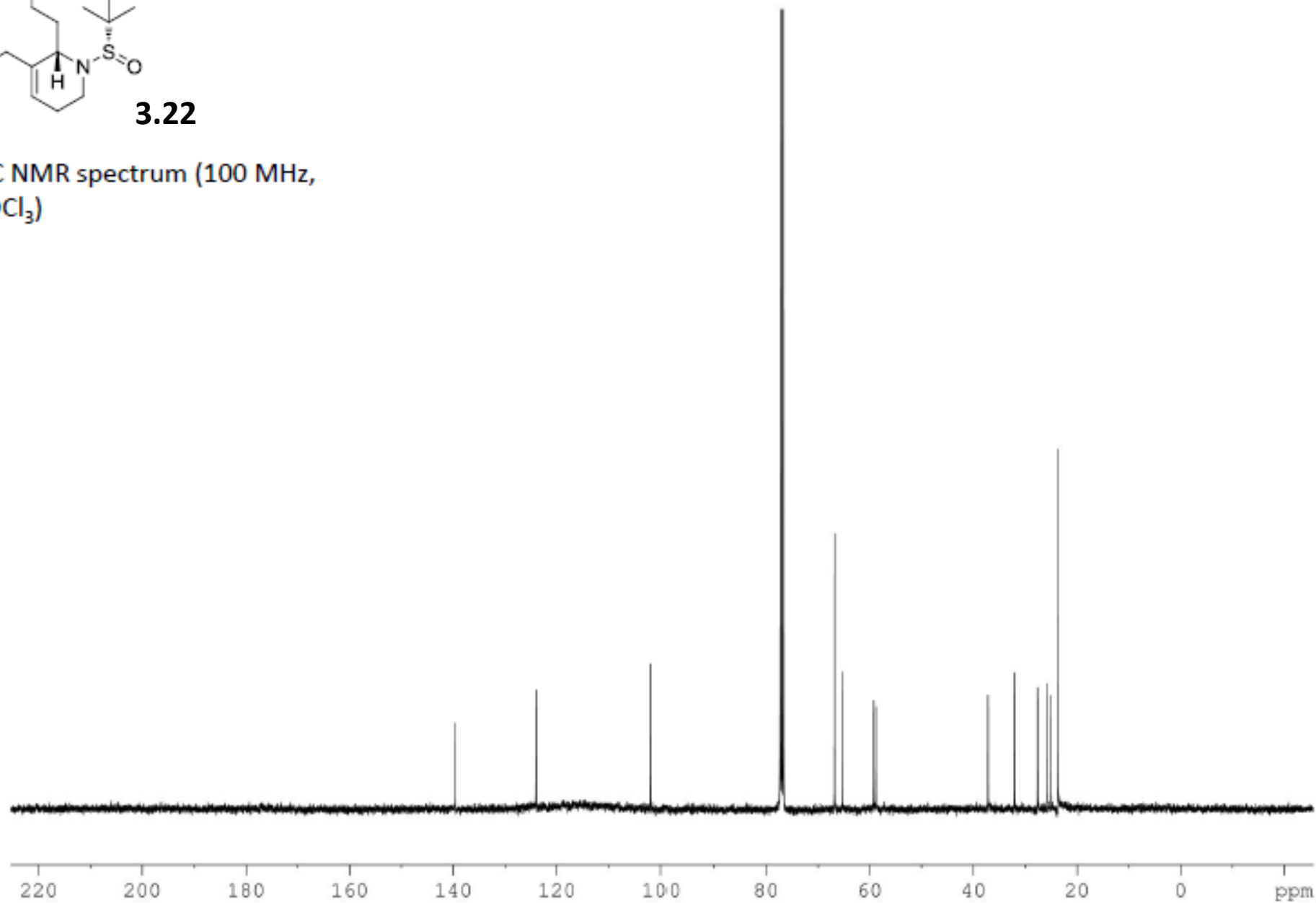
1.20
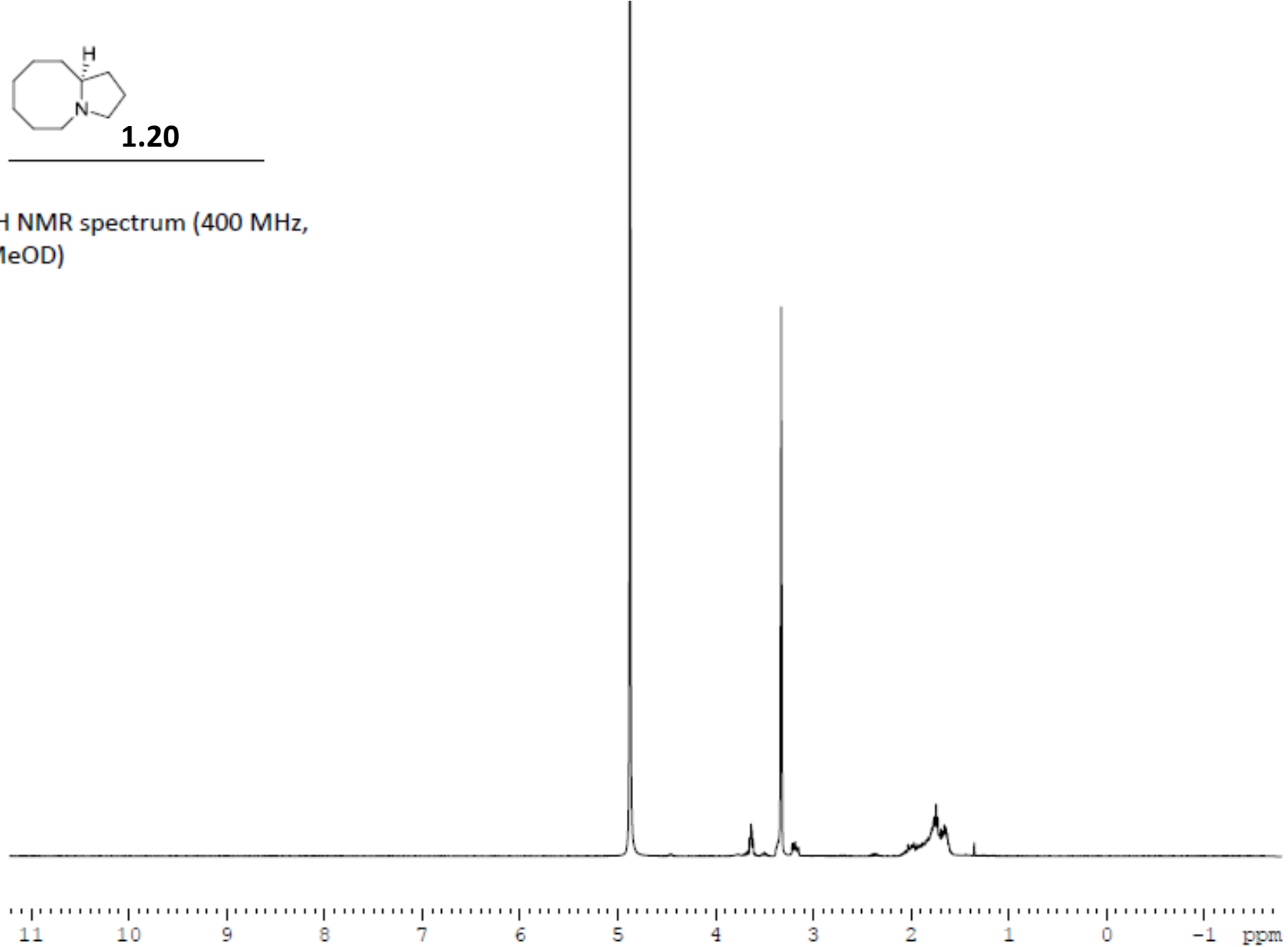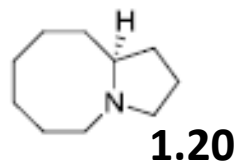
^{13}C NMR spectrum (100 MHz, MeOD)

¹H NMR spectrum (400 MHz, CDCl₃)

1.22

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

¹H NMR spectrum (400 MHz, CDCl₃)

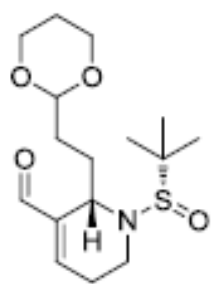^{13}C NMR spectrum (100 MHz, CDCl$_3$)

220   200   180   160   140   120   100   80   60   40   20   0   ppm
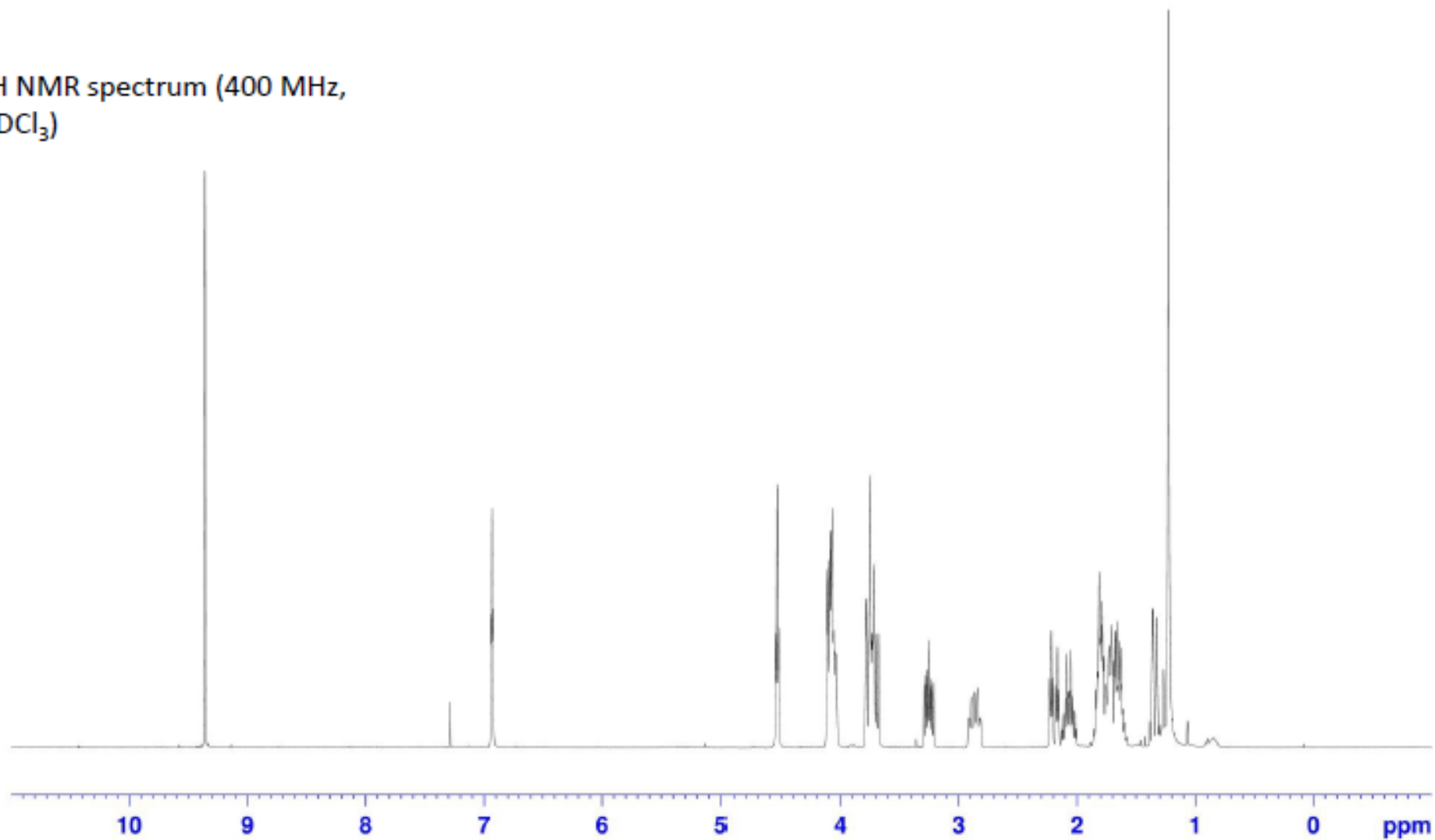
1.24

¹H NMR spectrum (400 MHz, CDCl₃)

1.24

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

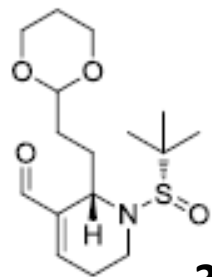¹H NMR spectrum (400 MHz, CDCl₃)

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

^{1}H NMR spectrum (400 MHz, CDCl$_3$)

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

¹H NMR spectrum (400 MHz, CDCl₃)

^{13}C NMR spectrum (100 MHz, CDCl$_3$)
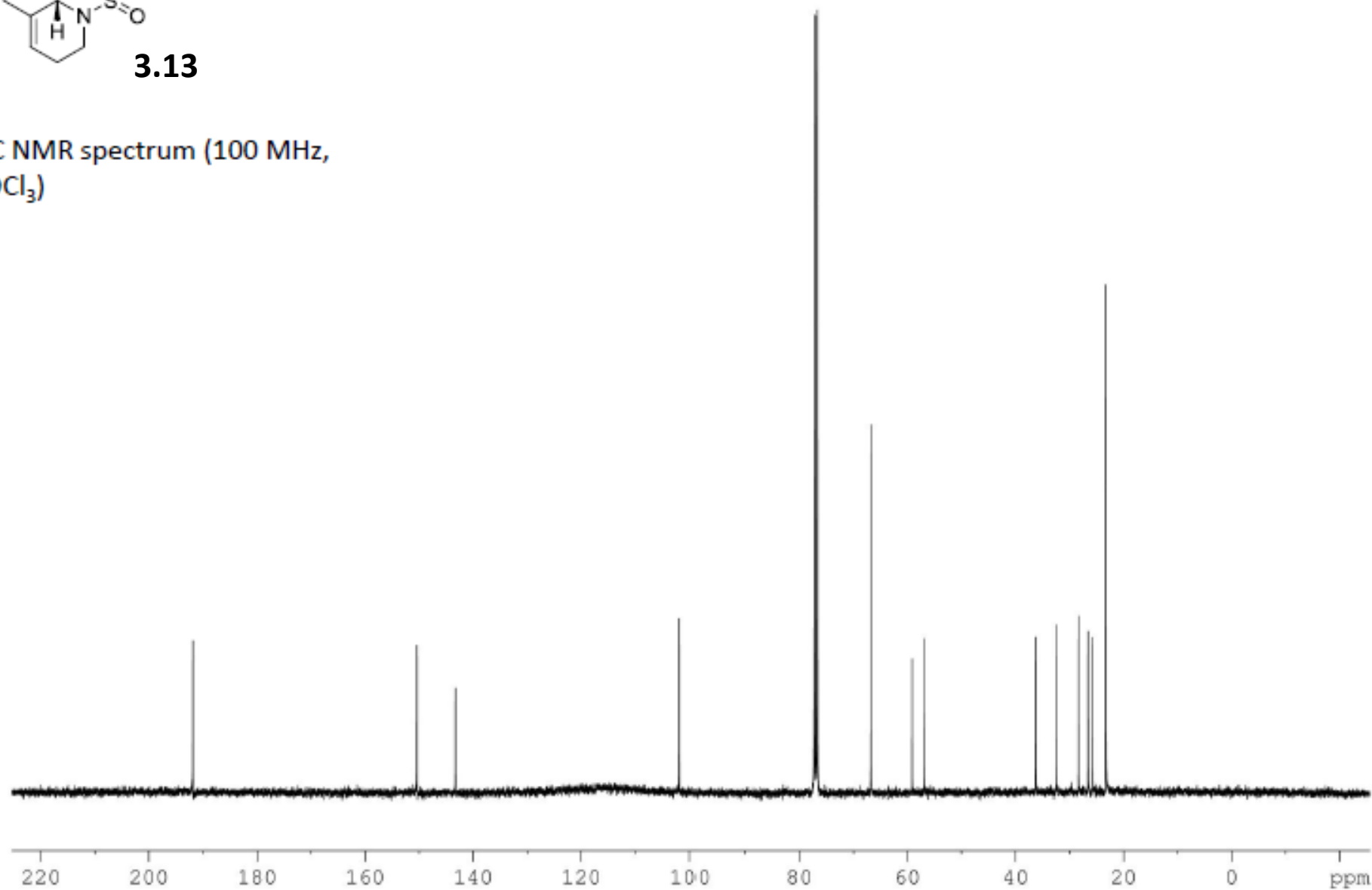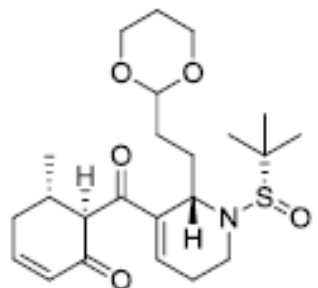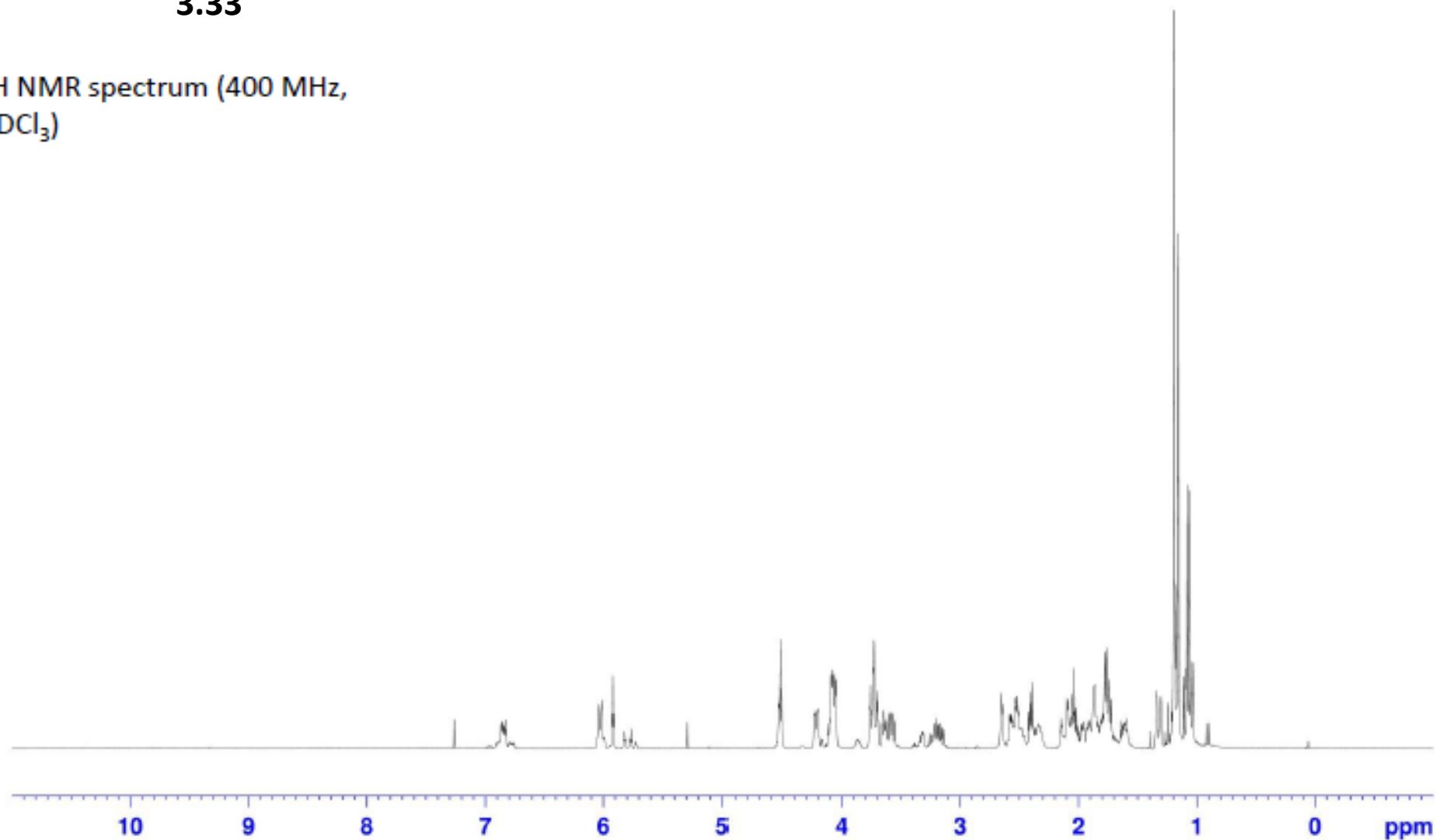
1.26

¹H NMR spectrum (400 MHz, CDCl₃)

1.26

¹³C NMR spectrum (100 MHz, CDCl₃)

1.27

¹H NMR spectrum (400 MHz, MeOD)

1.27
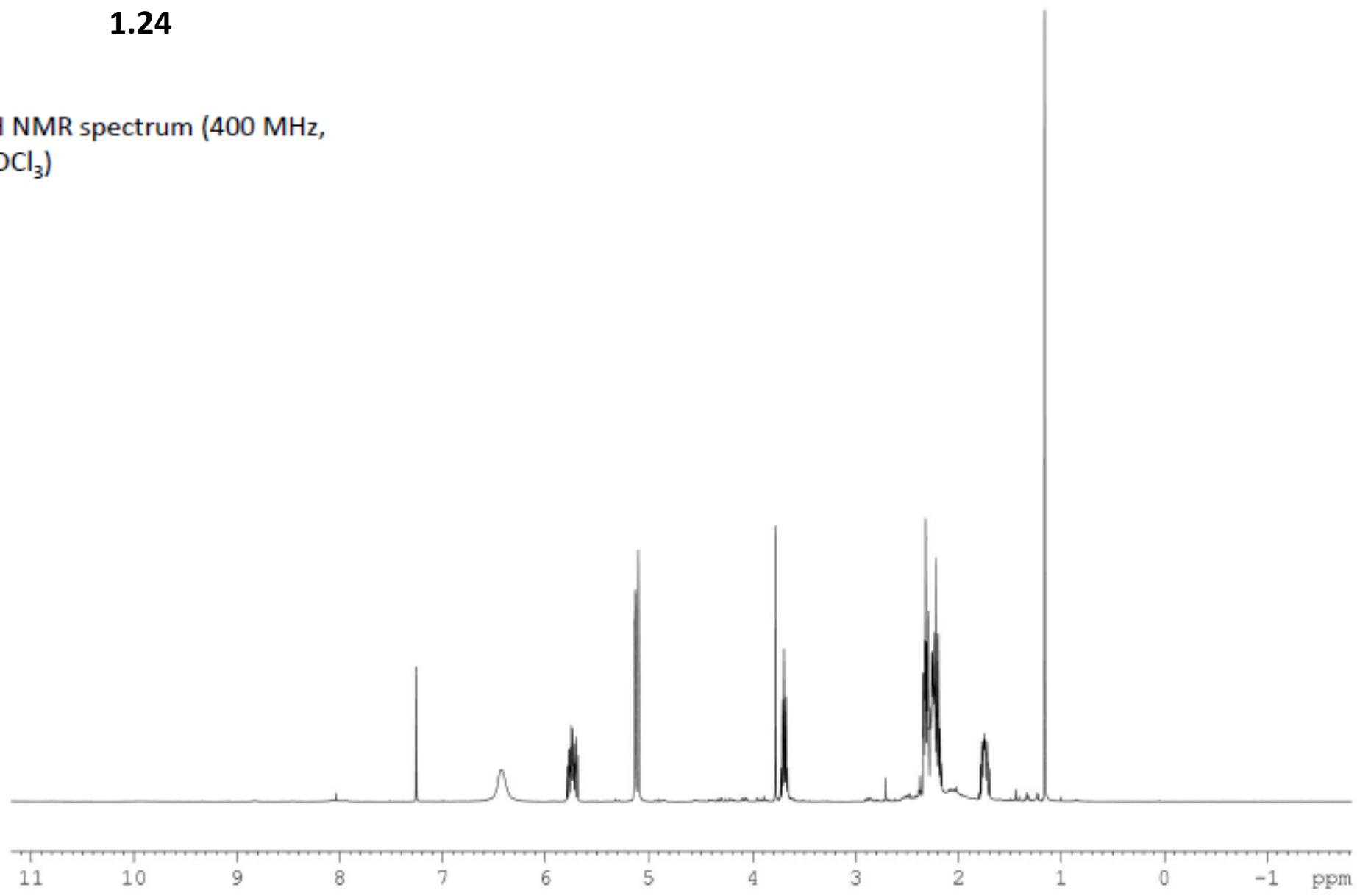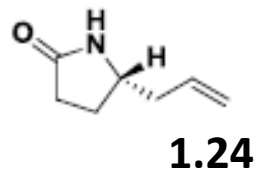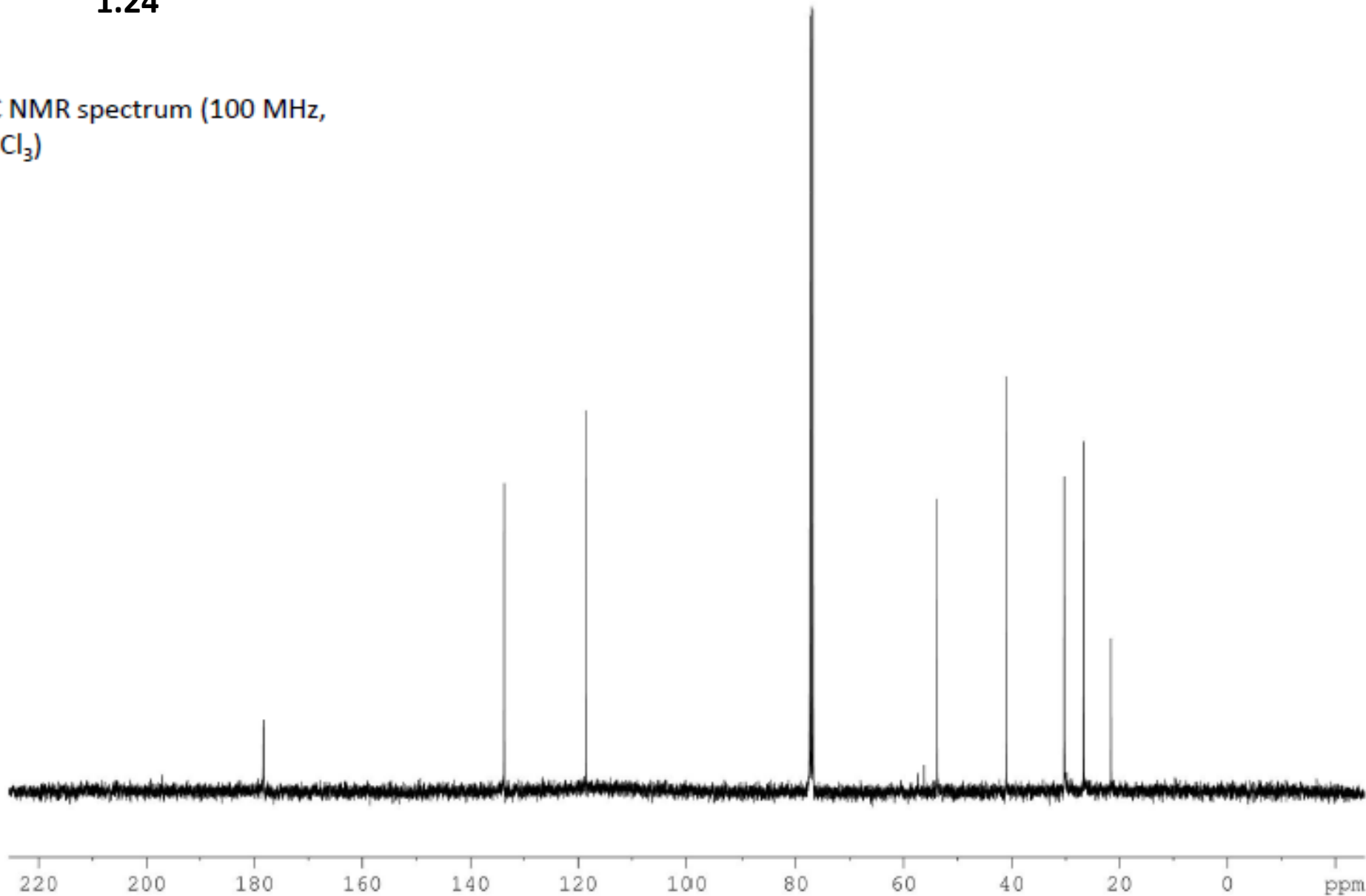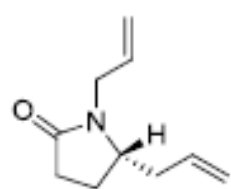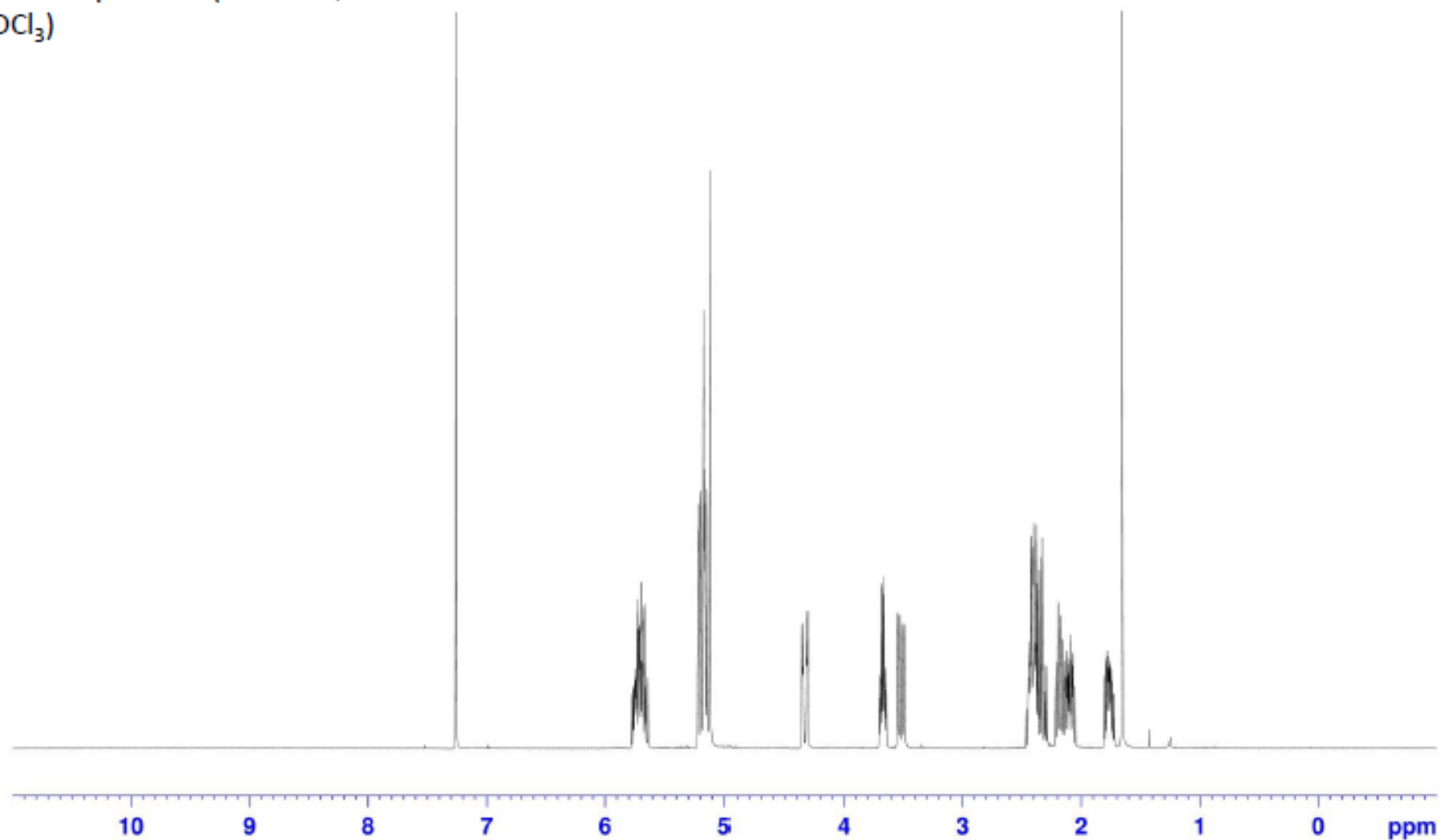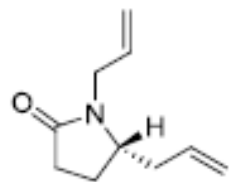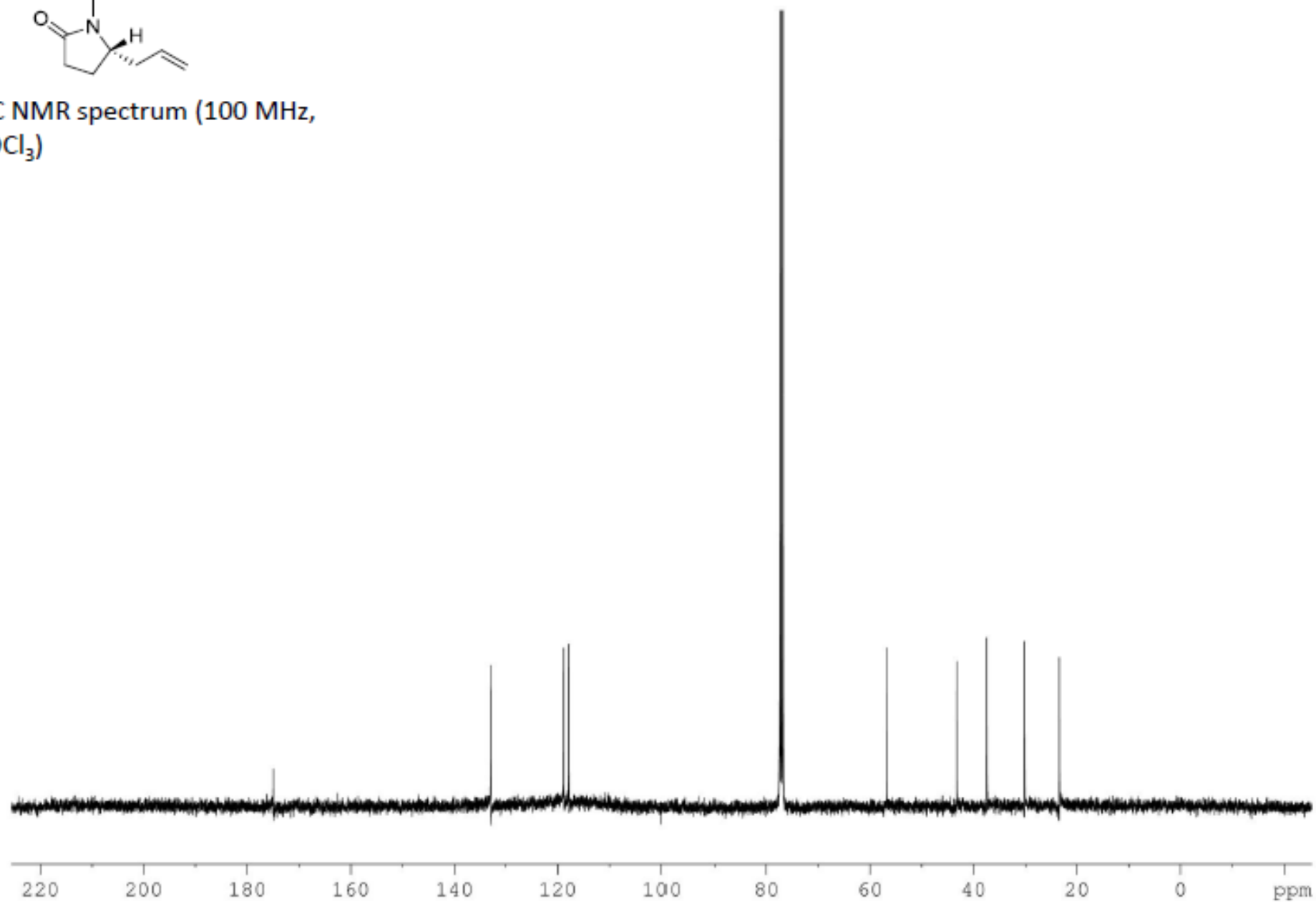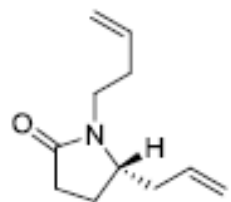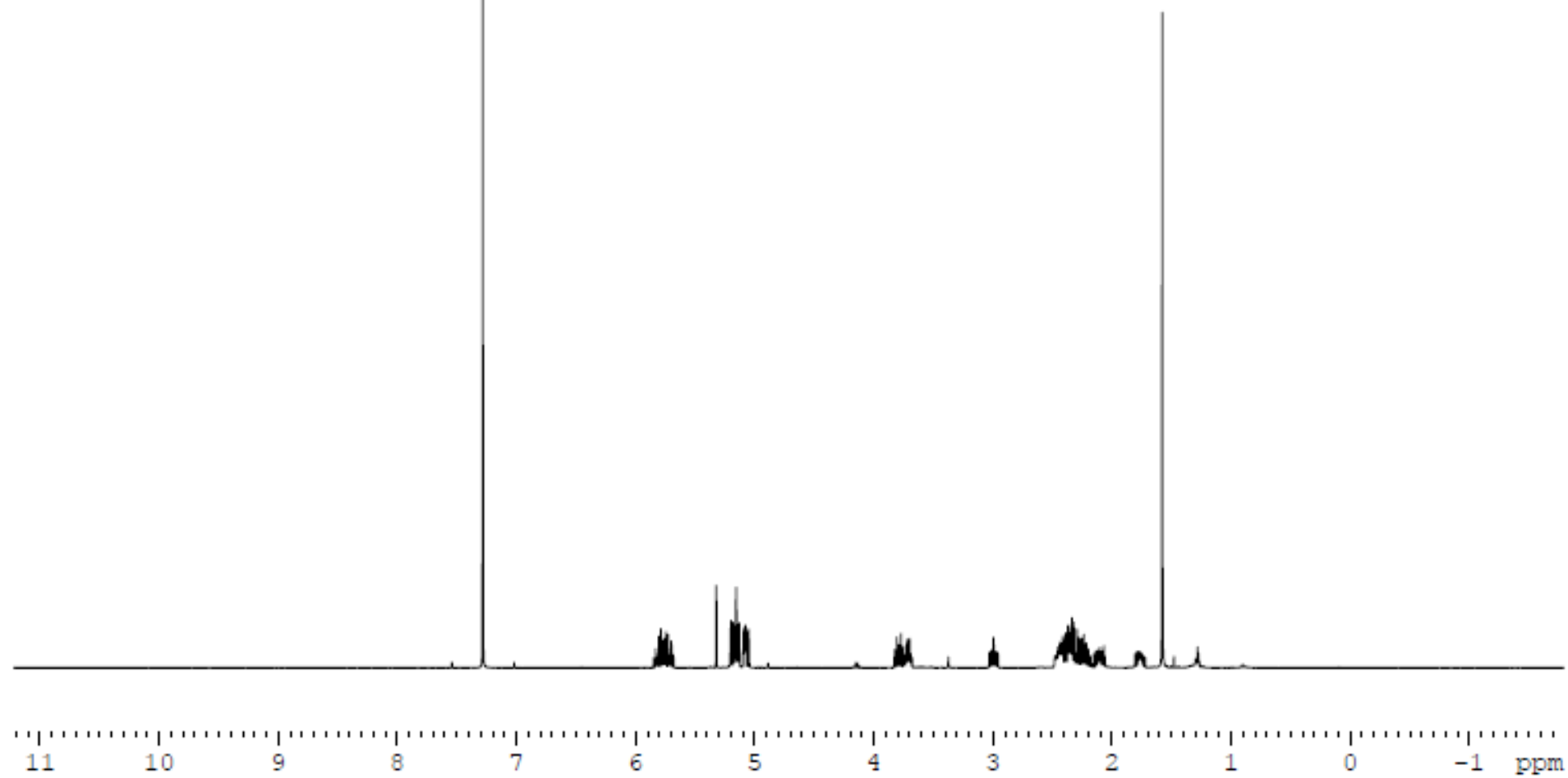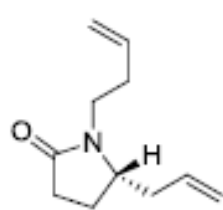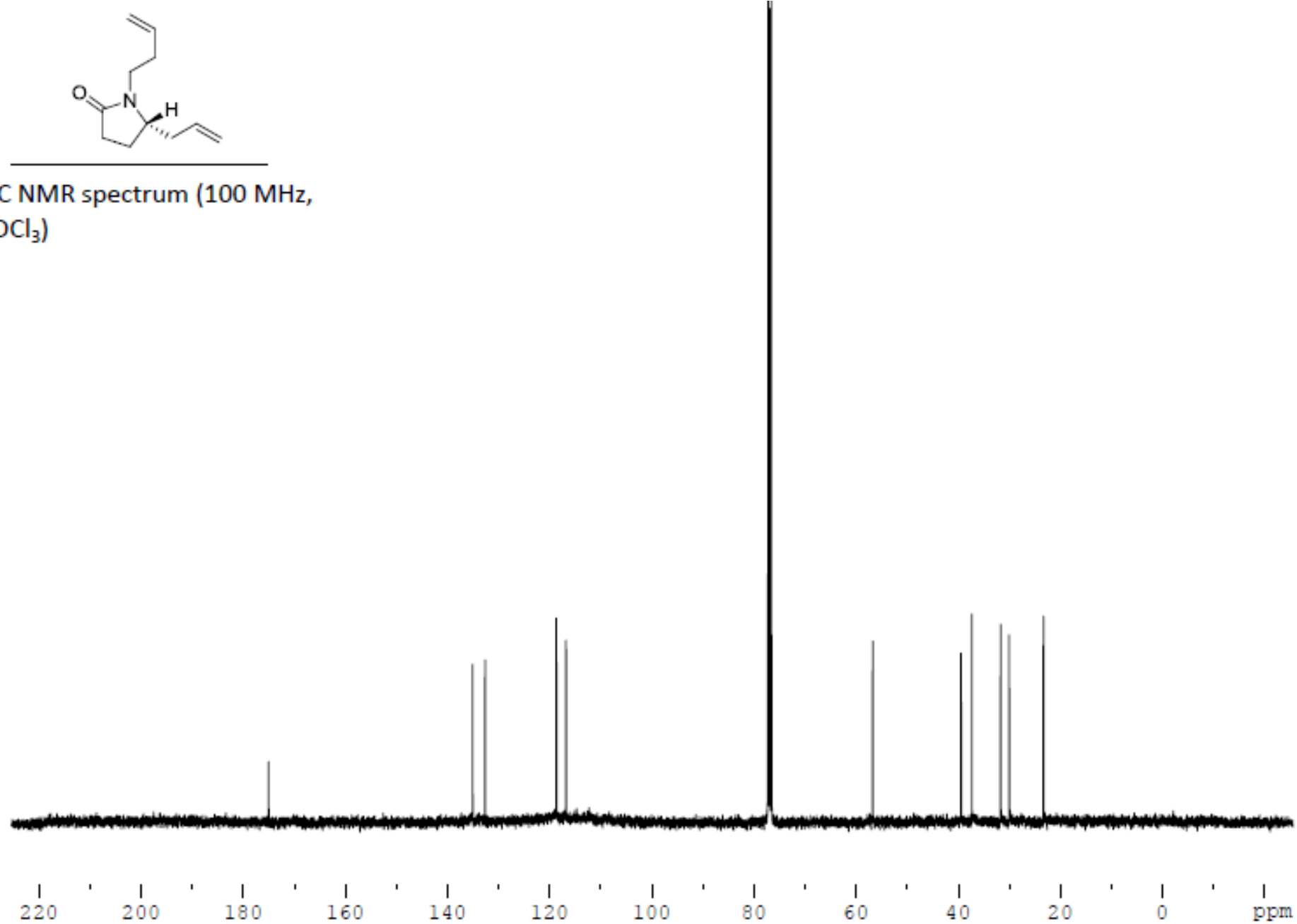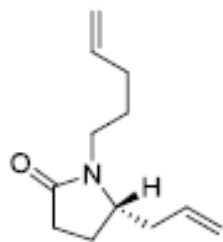
^{13}C NMR spectrum (100 MHz, MeOD)

1.28

^{1}H NMR spectrum (400 MHz, CDCl$_3$)

1.28
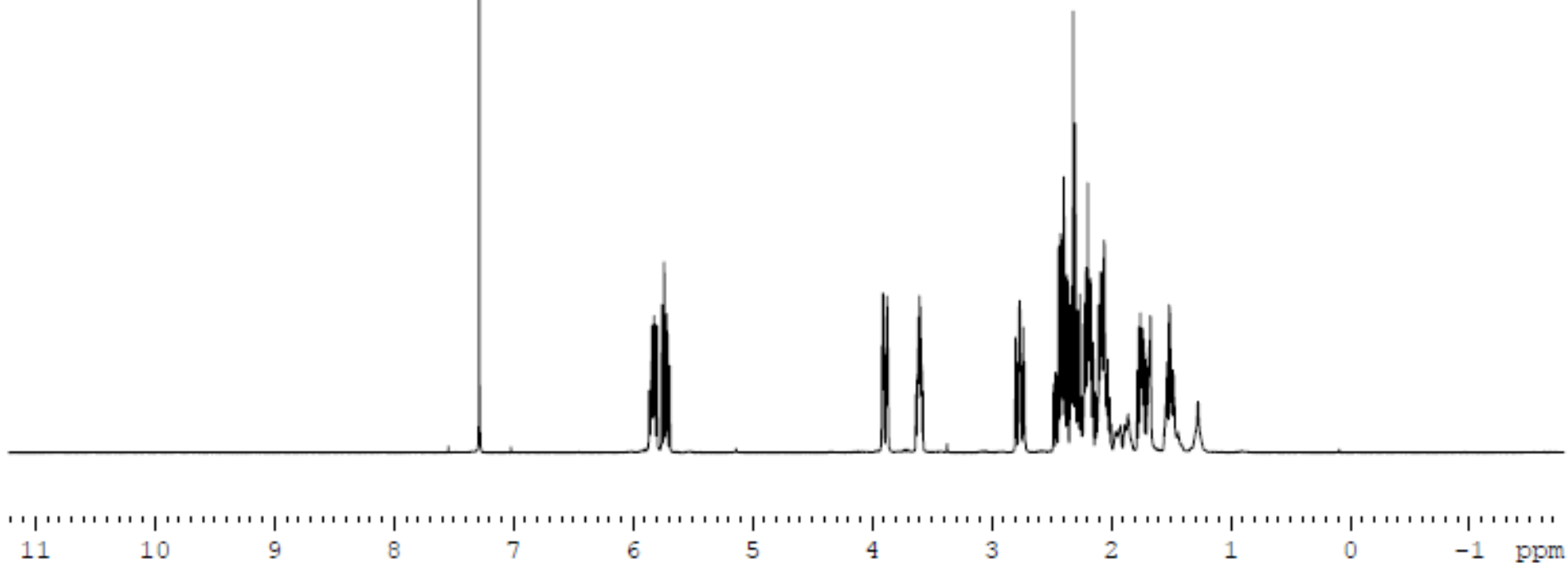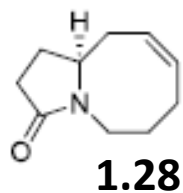
^{13}C NMR spectrum (100 MHz, CDCl$_3$)
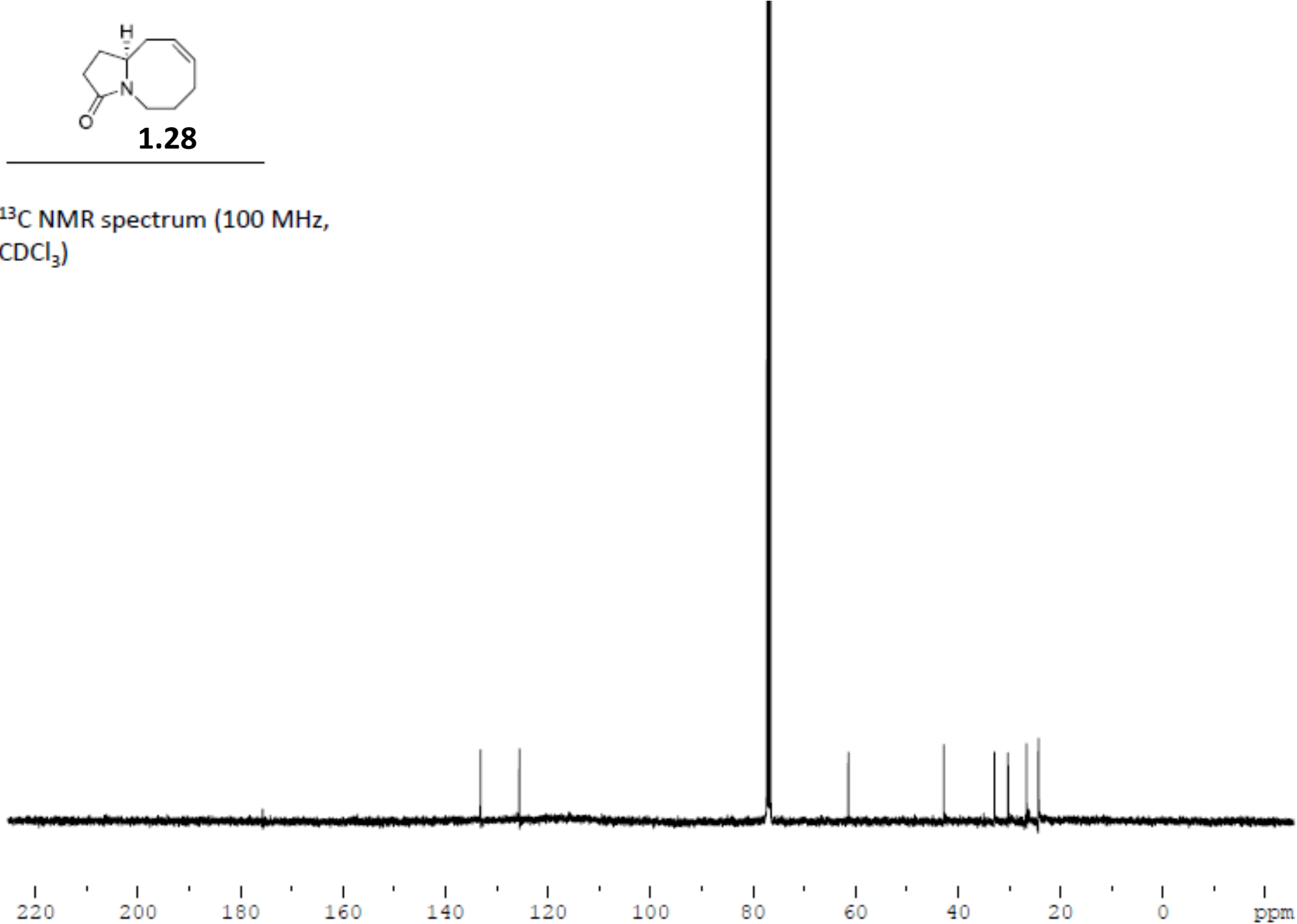
APPENDIX A2:

Spectra Relevant to Chapter II

2·35

2·26

2-26

2·45

2·25

2.46

2·46

2.47

2-47

2-31

11   10   9   8   7   6   5   4   3   2   1   0   −1 ppm

2-31

2·50

HO—⟋⟍═⟍—OTBS

11   10   9   8   7   6   5   4   3   2   1   0   ppm
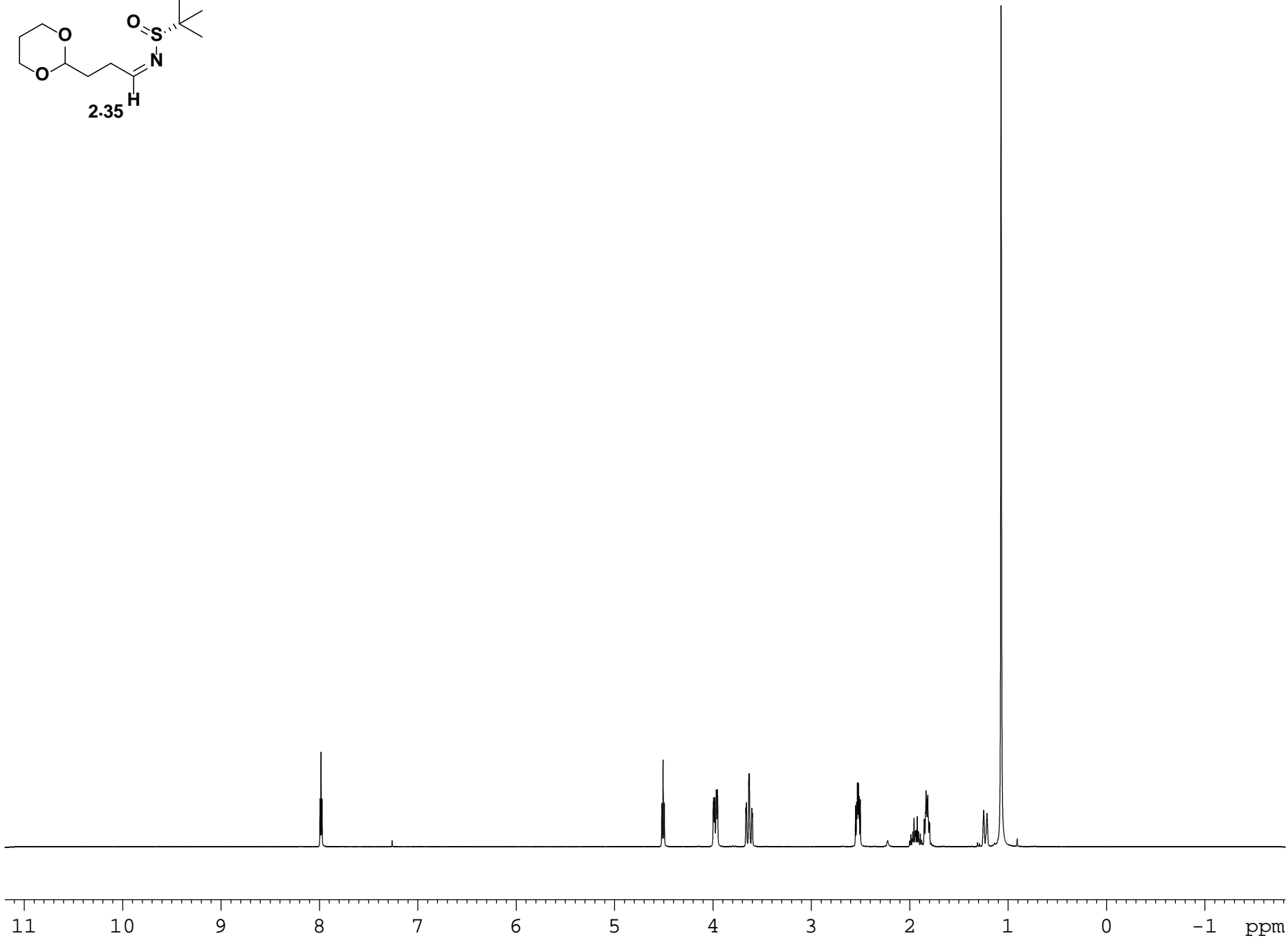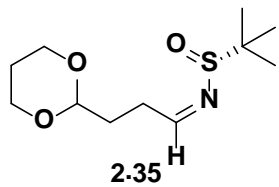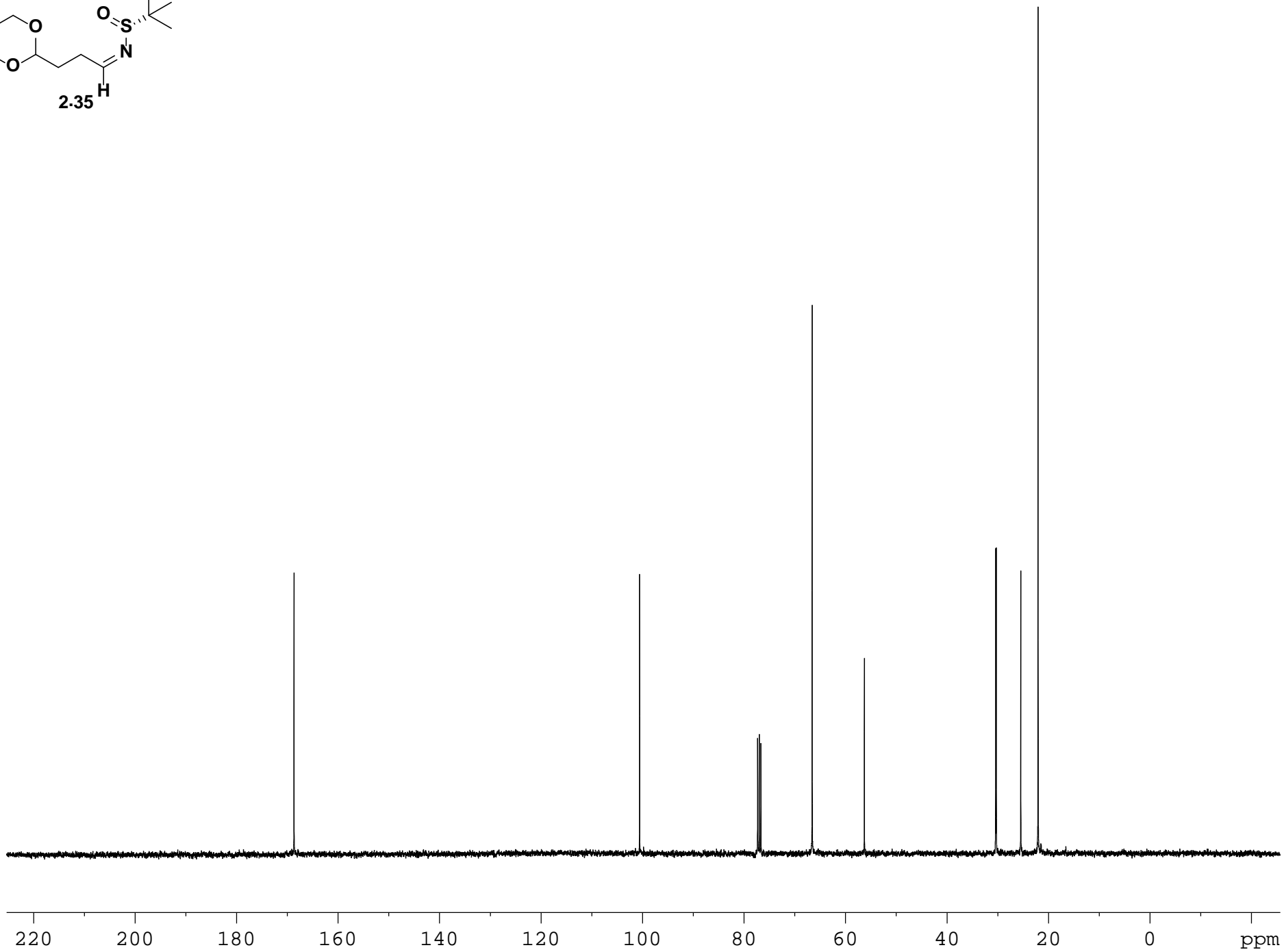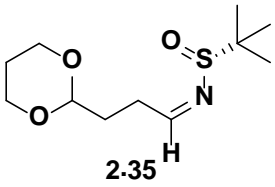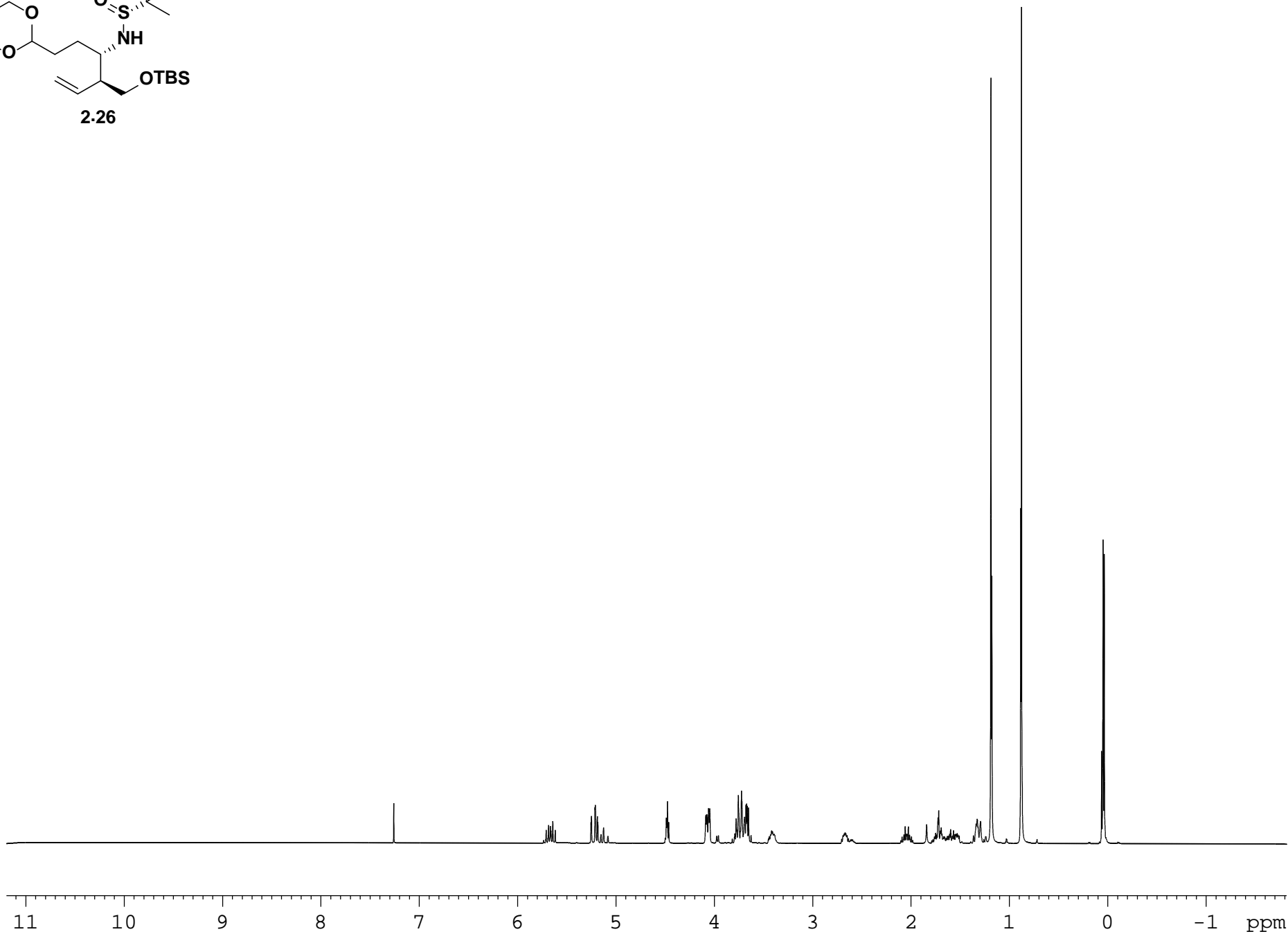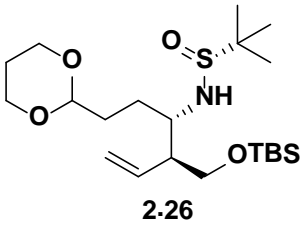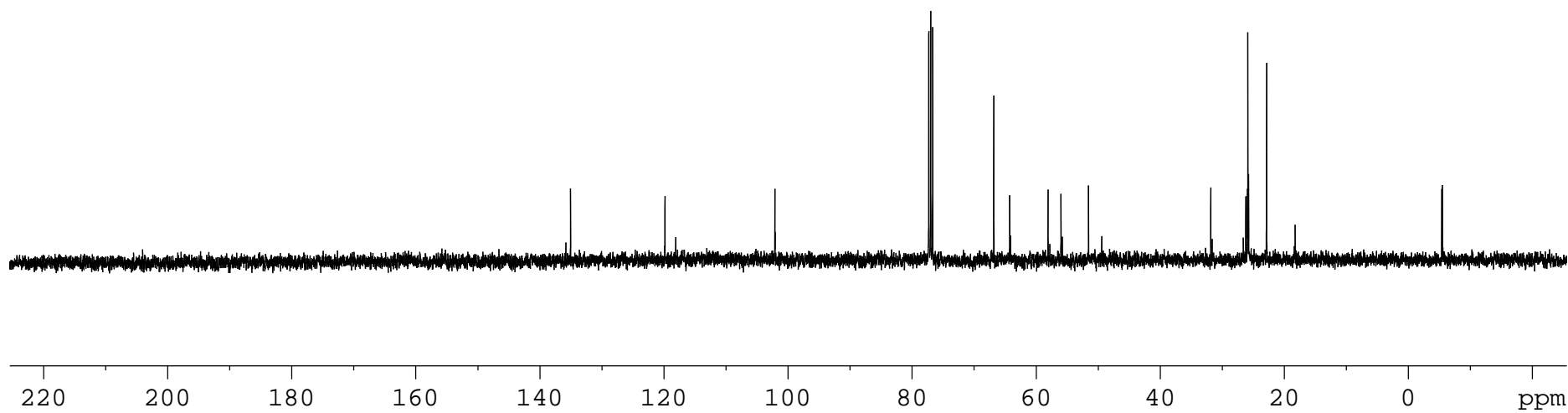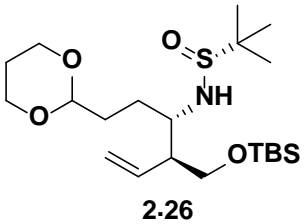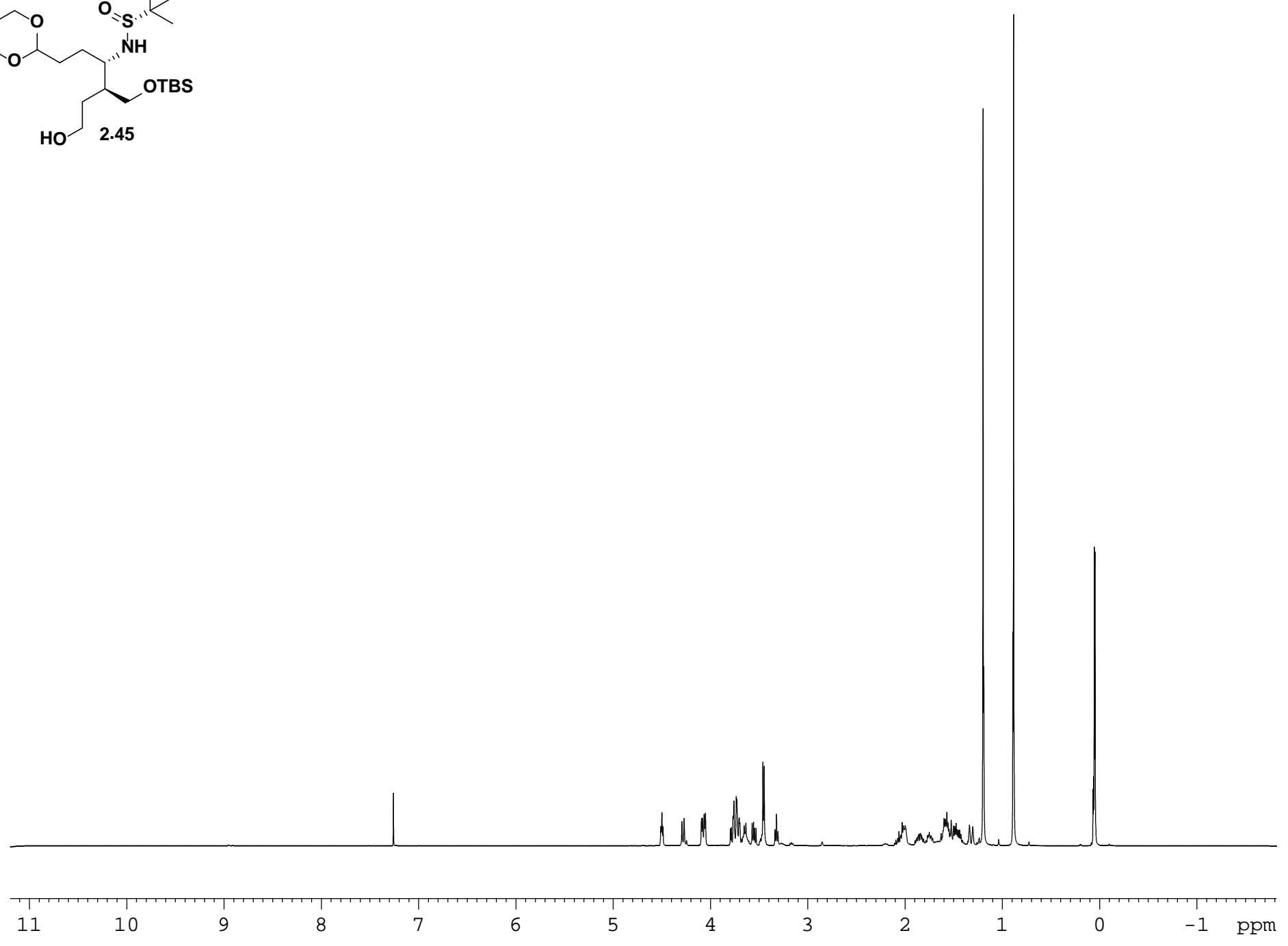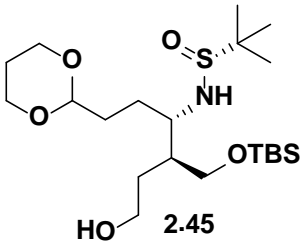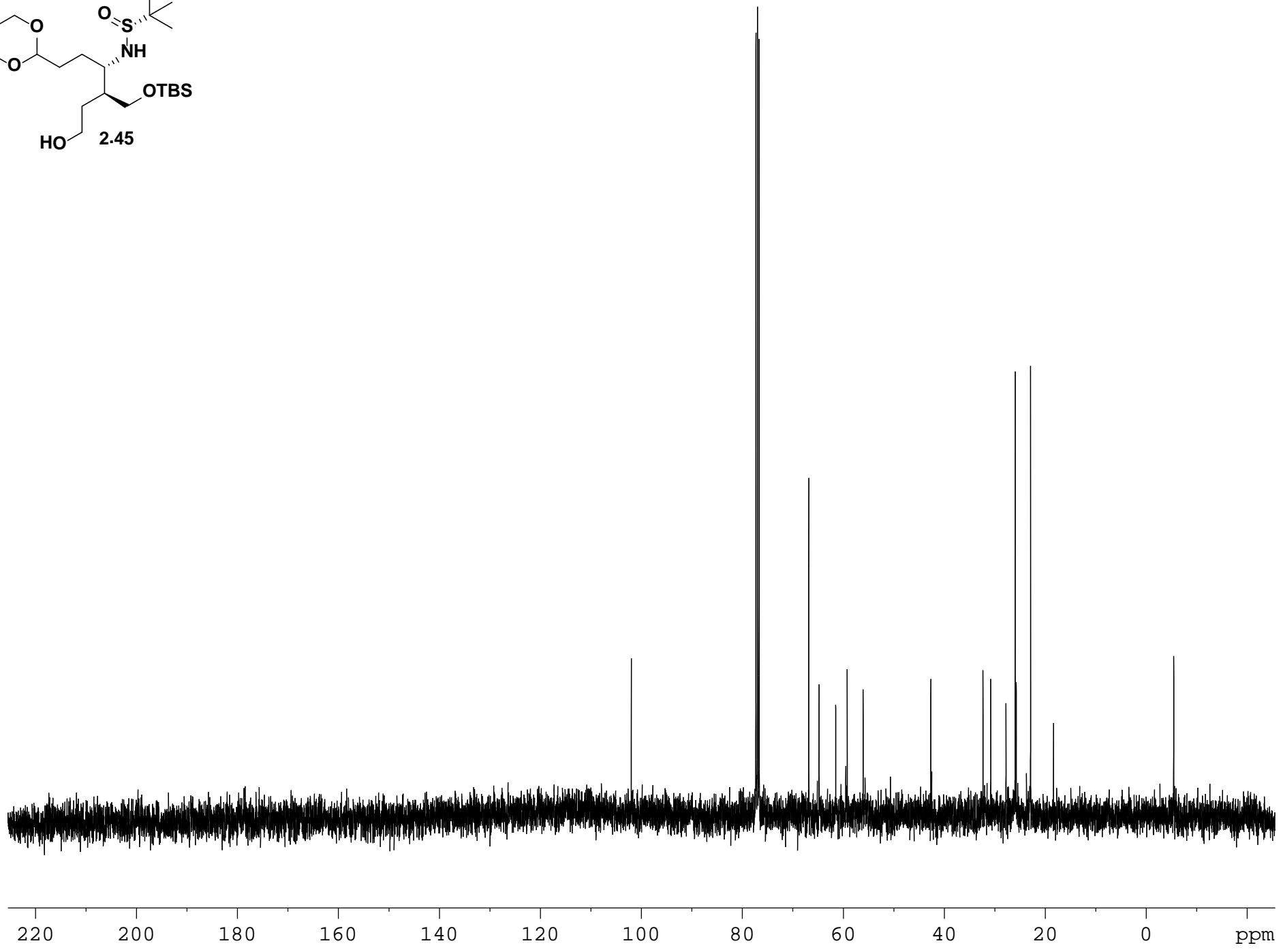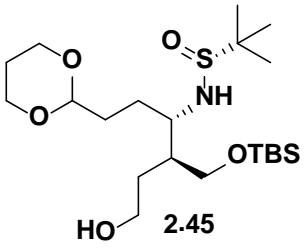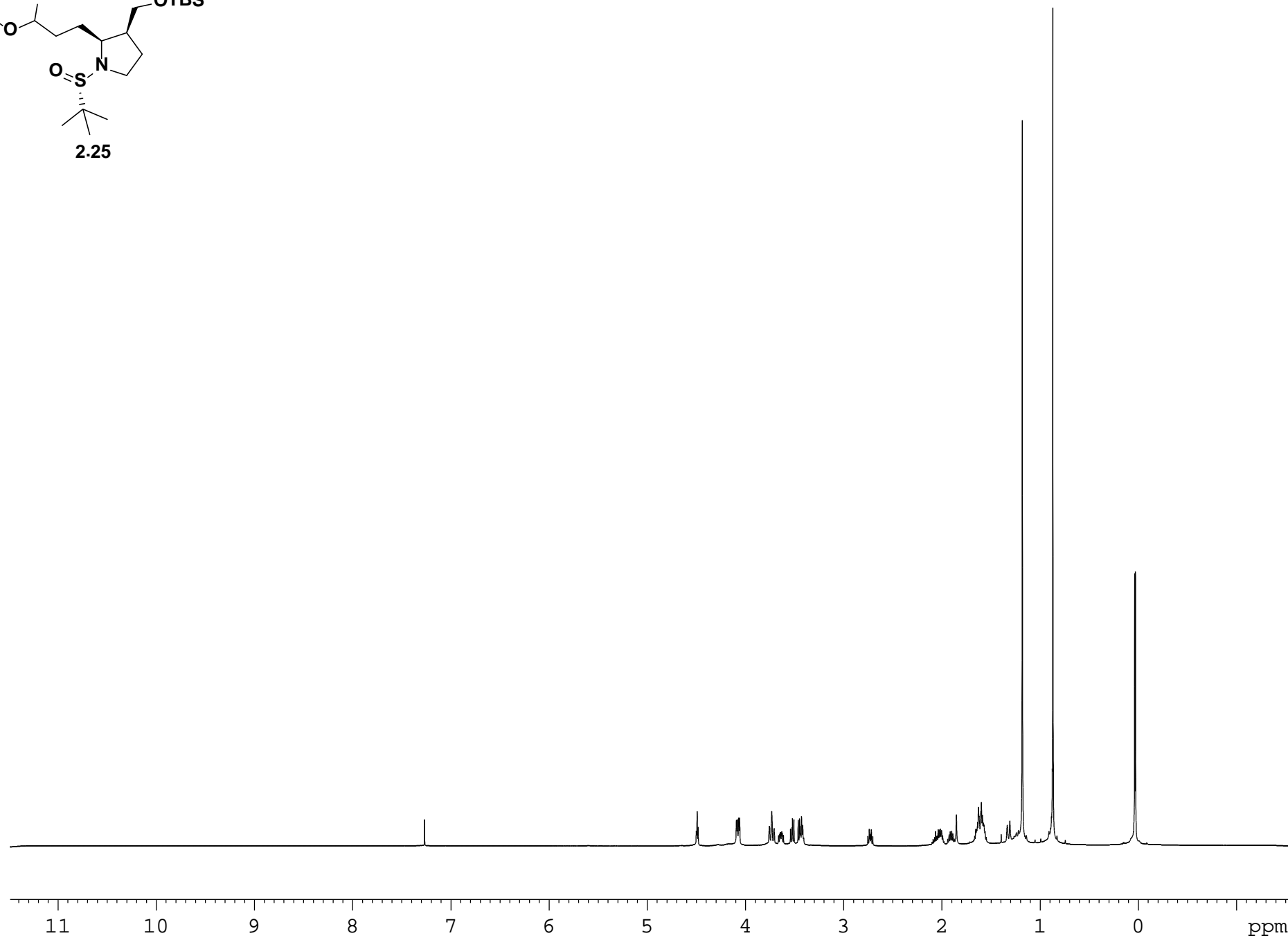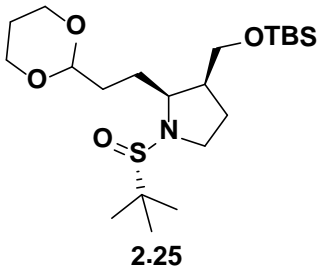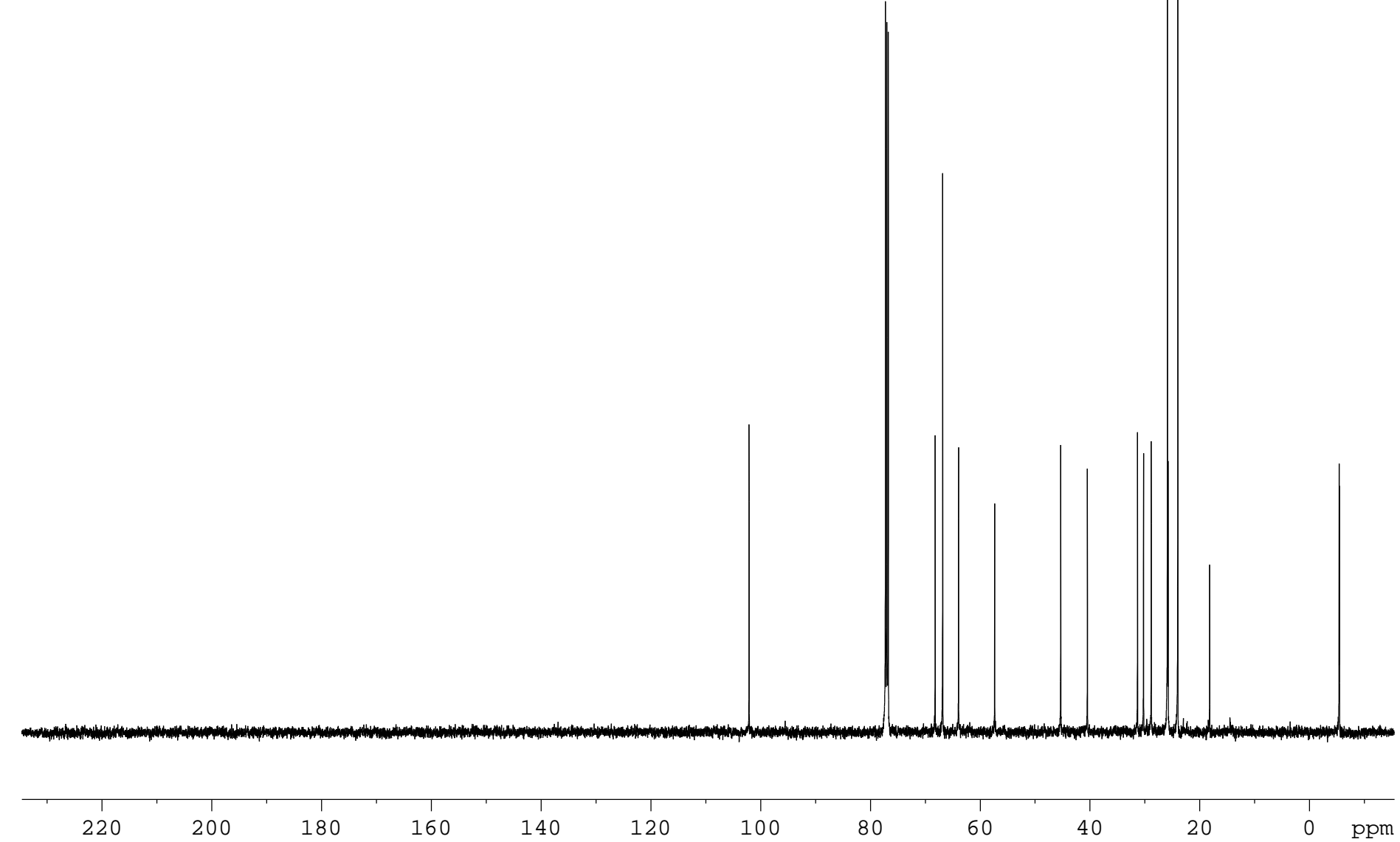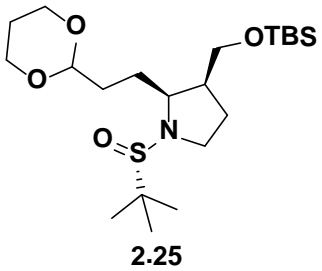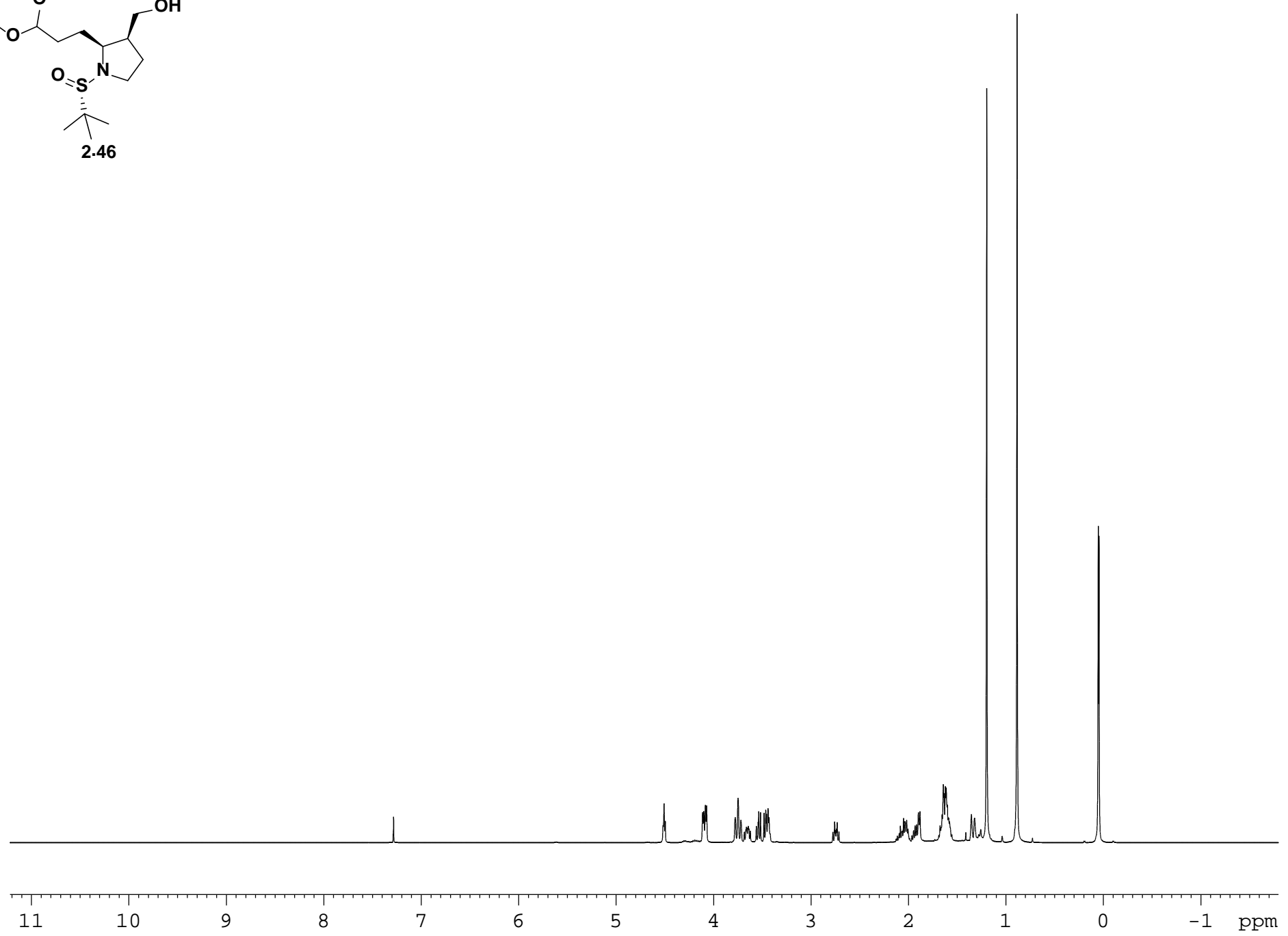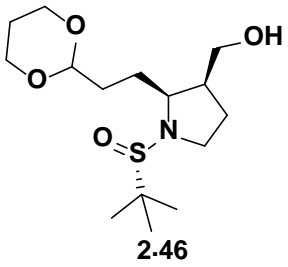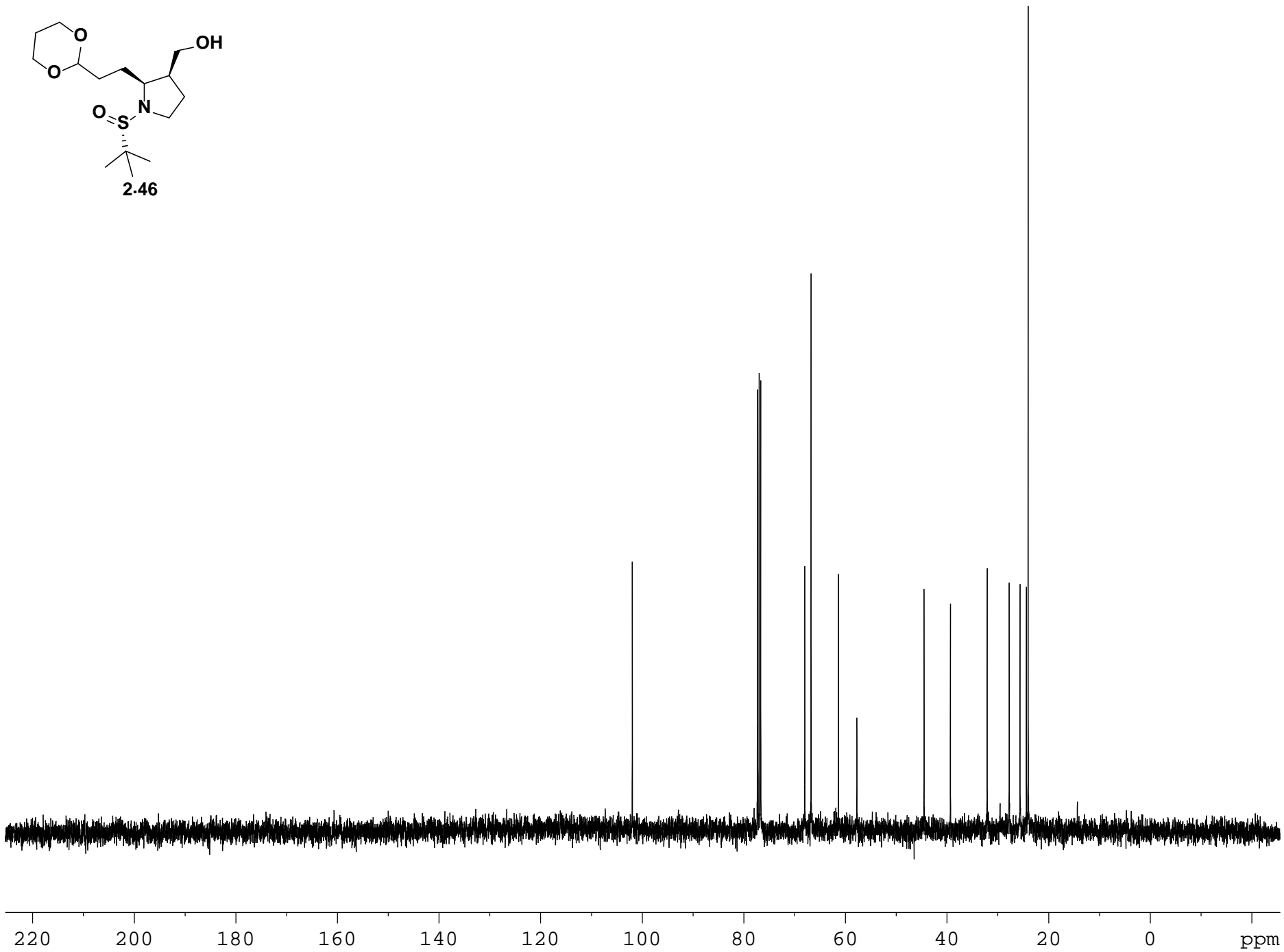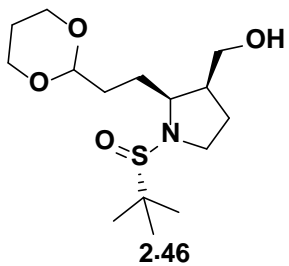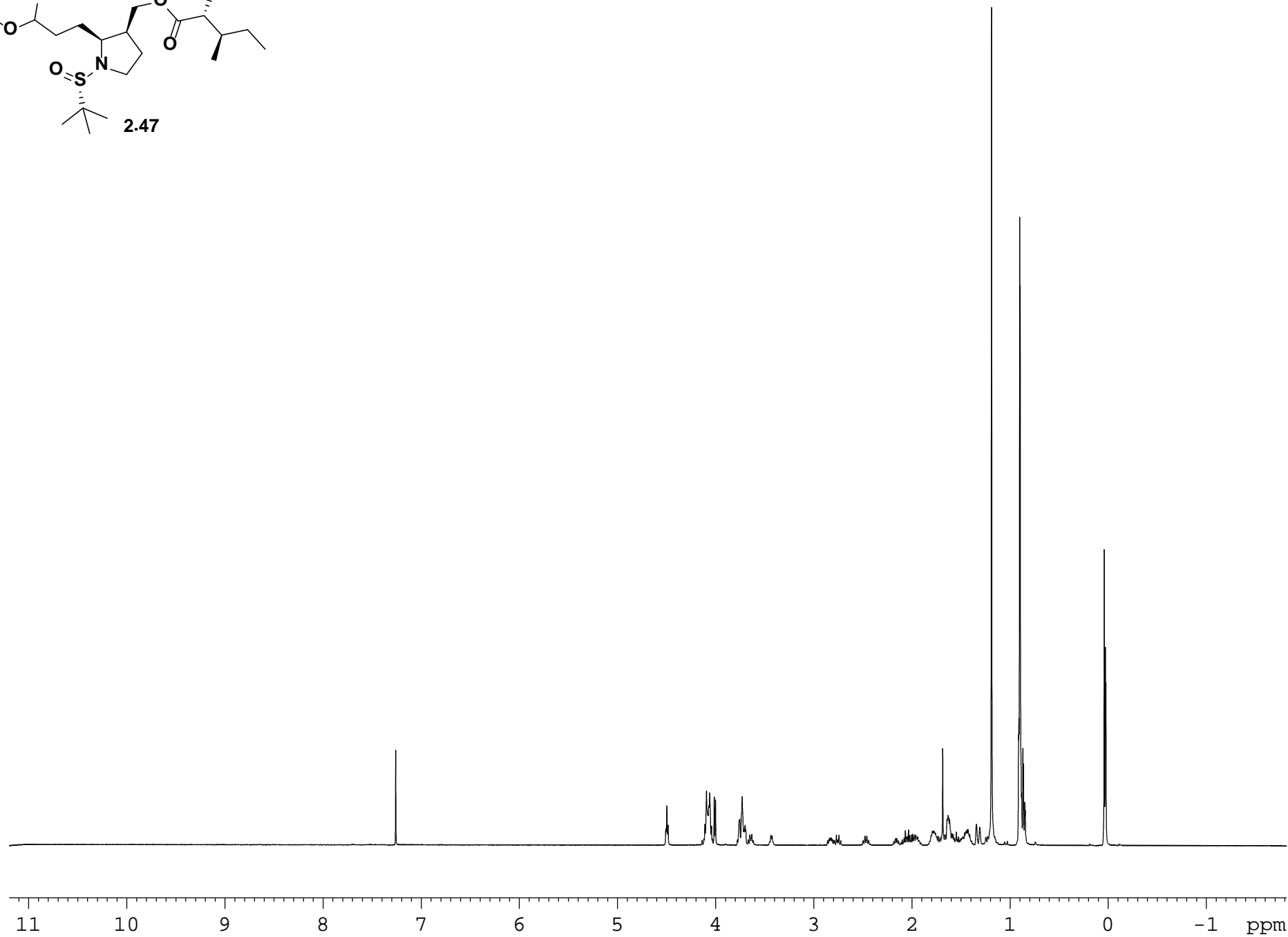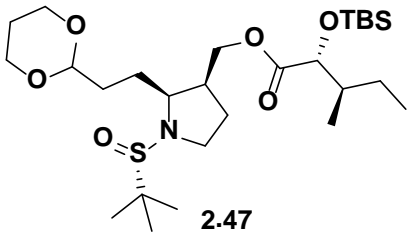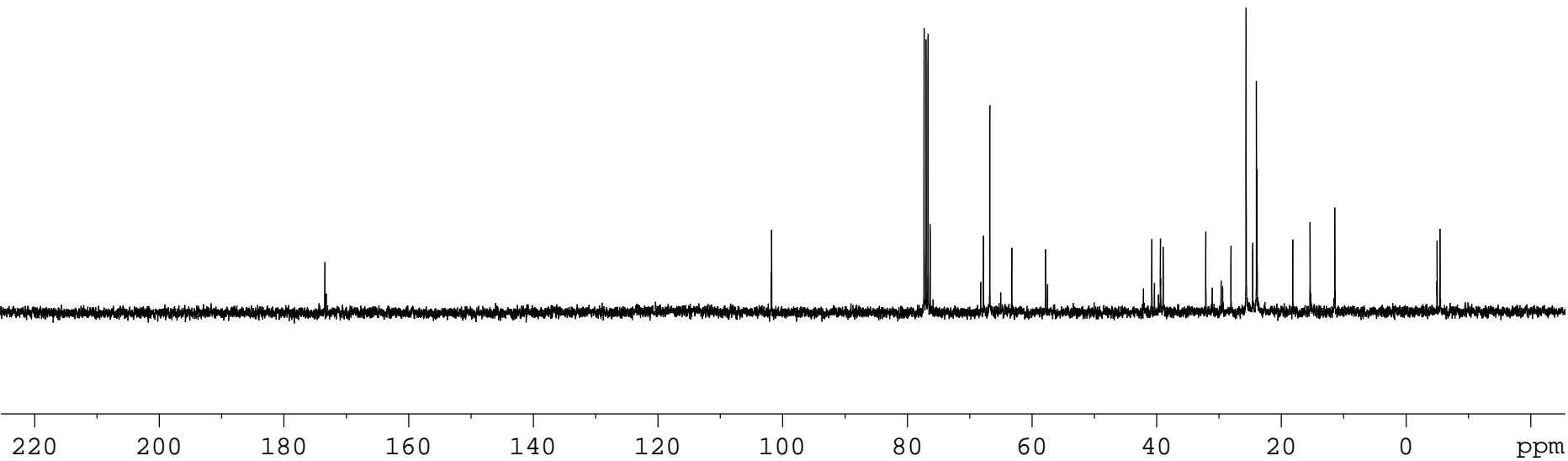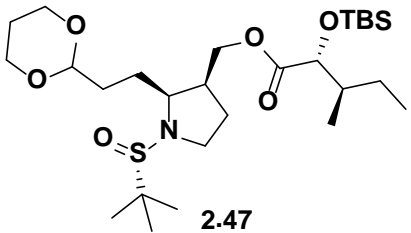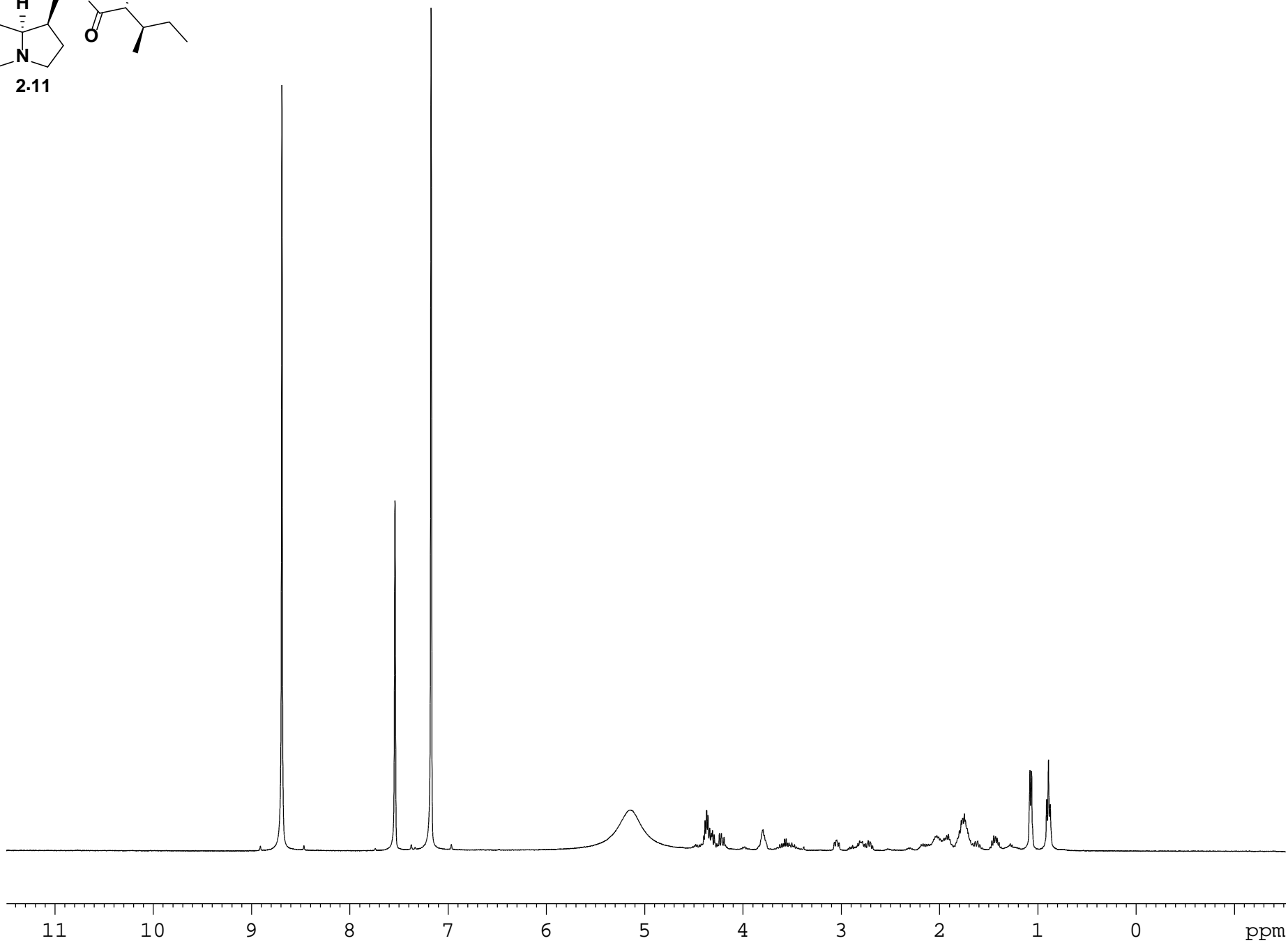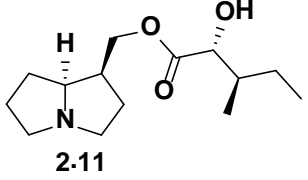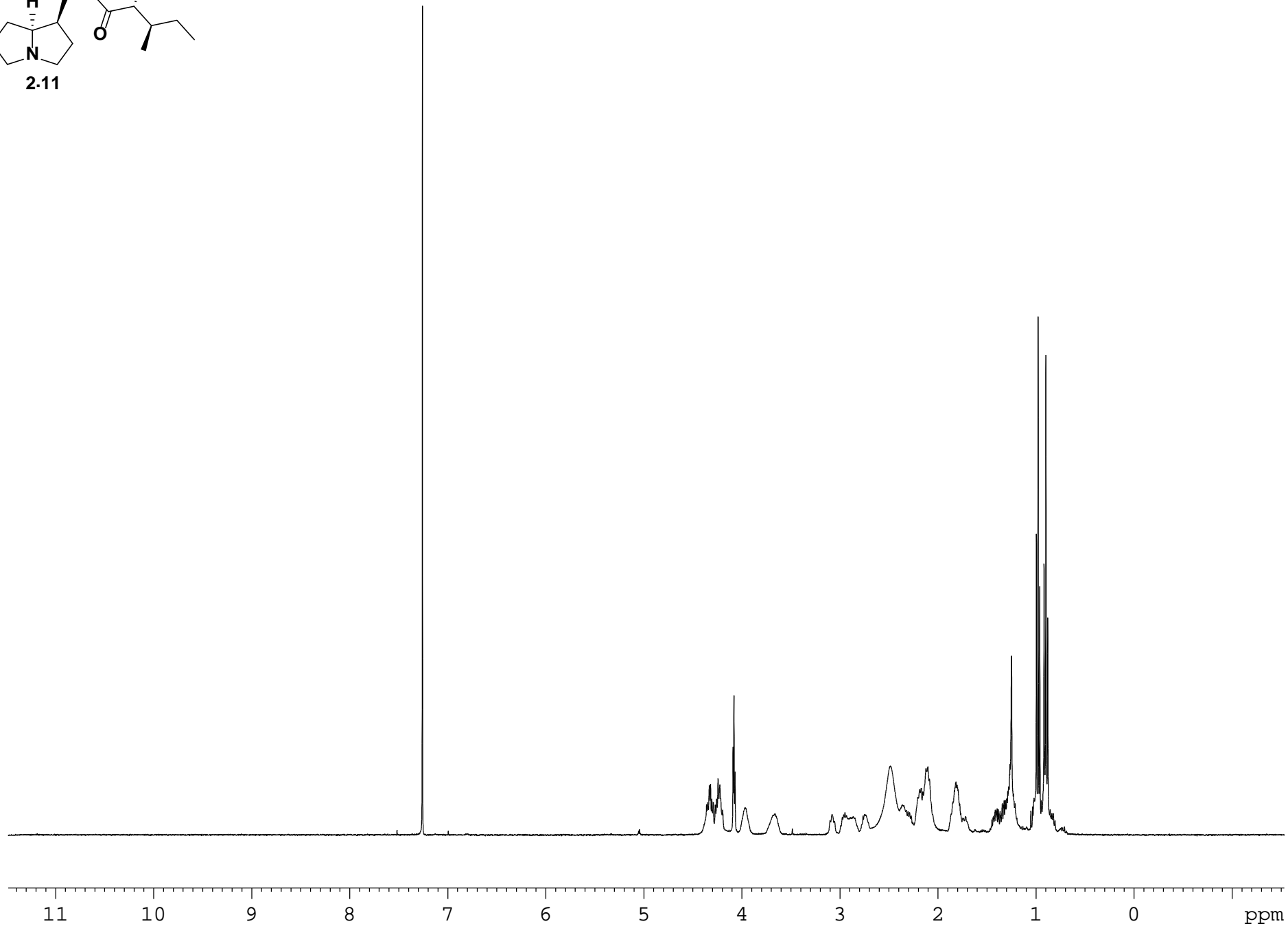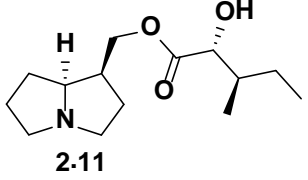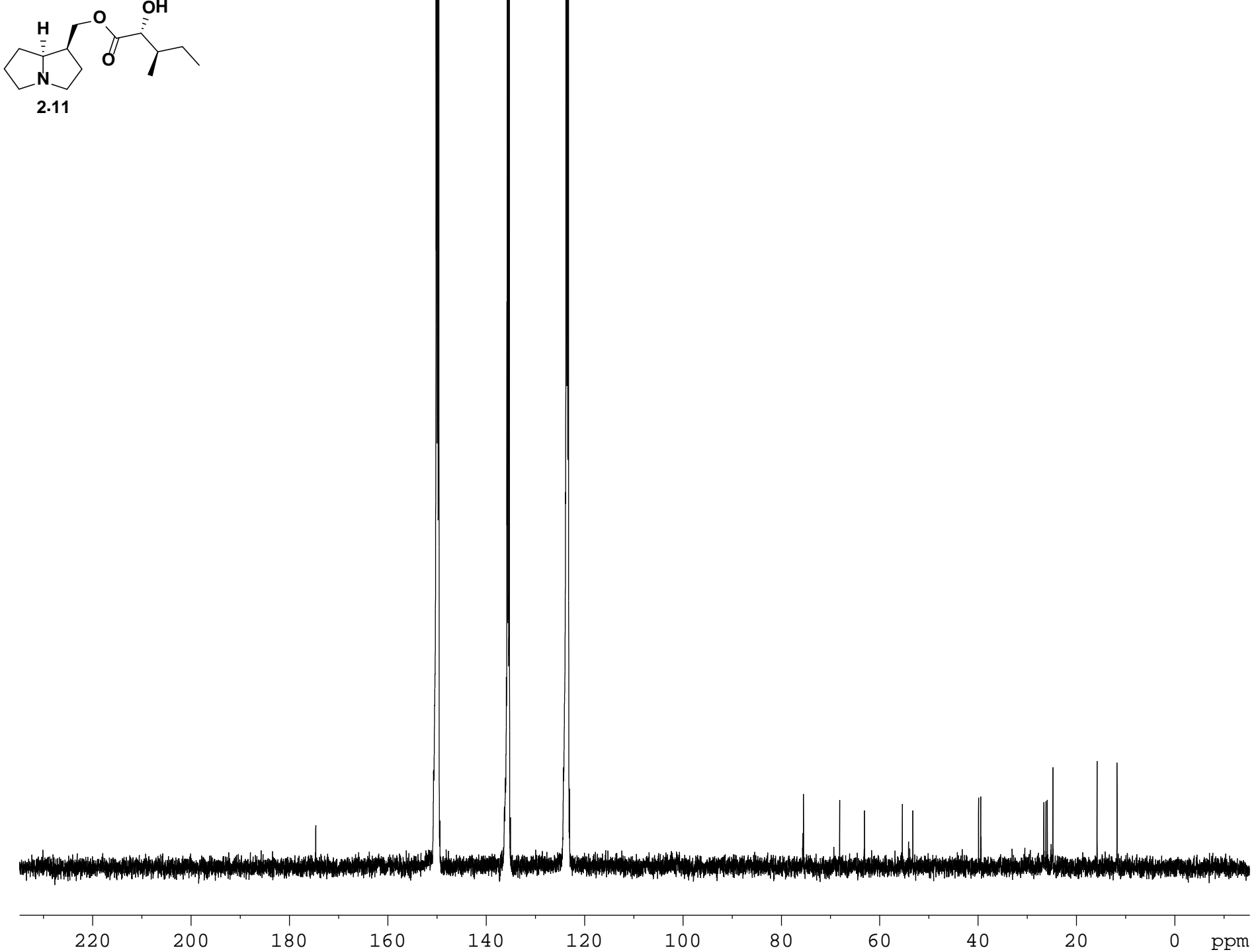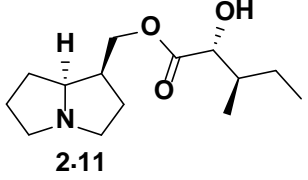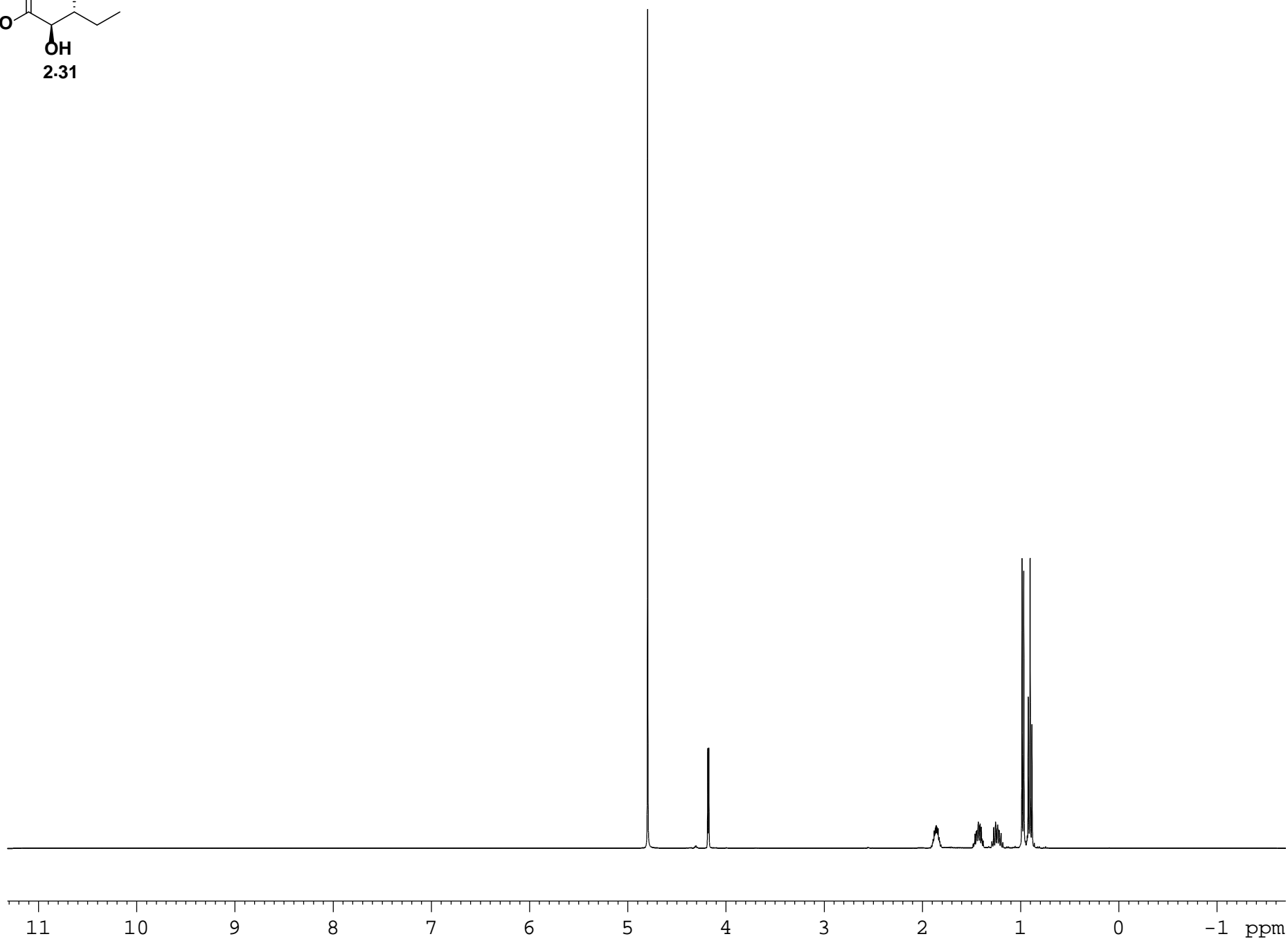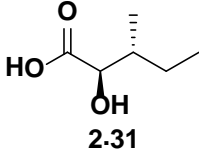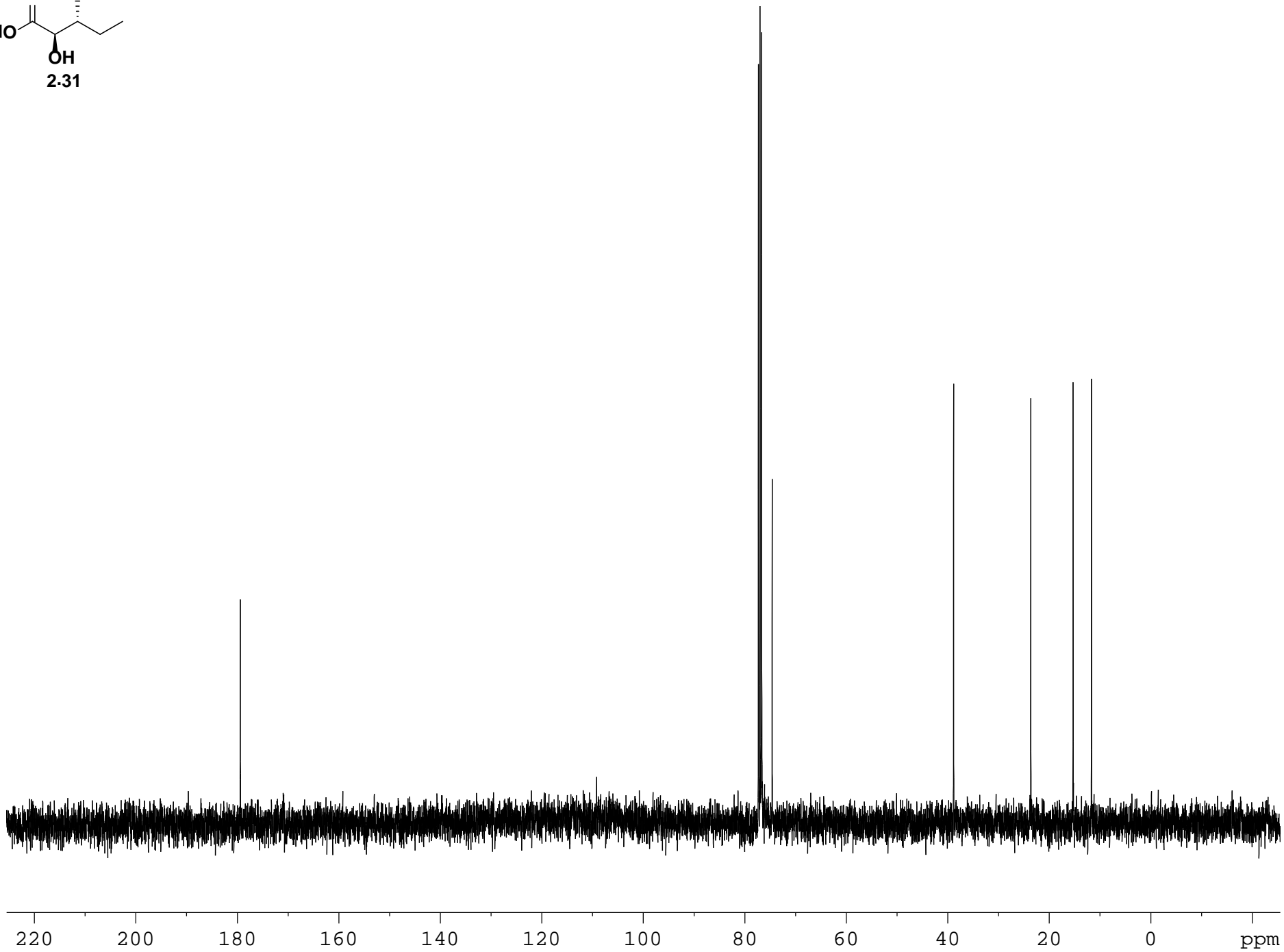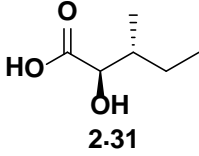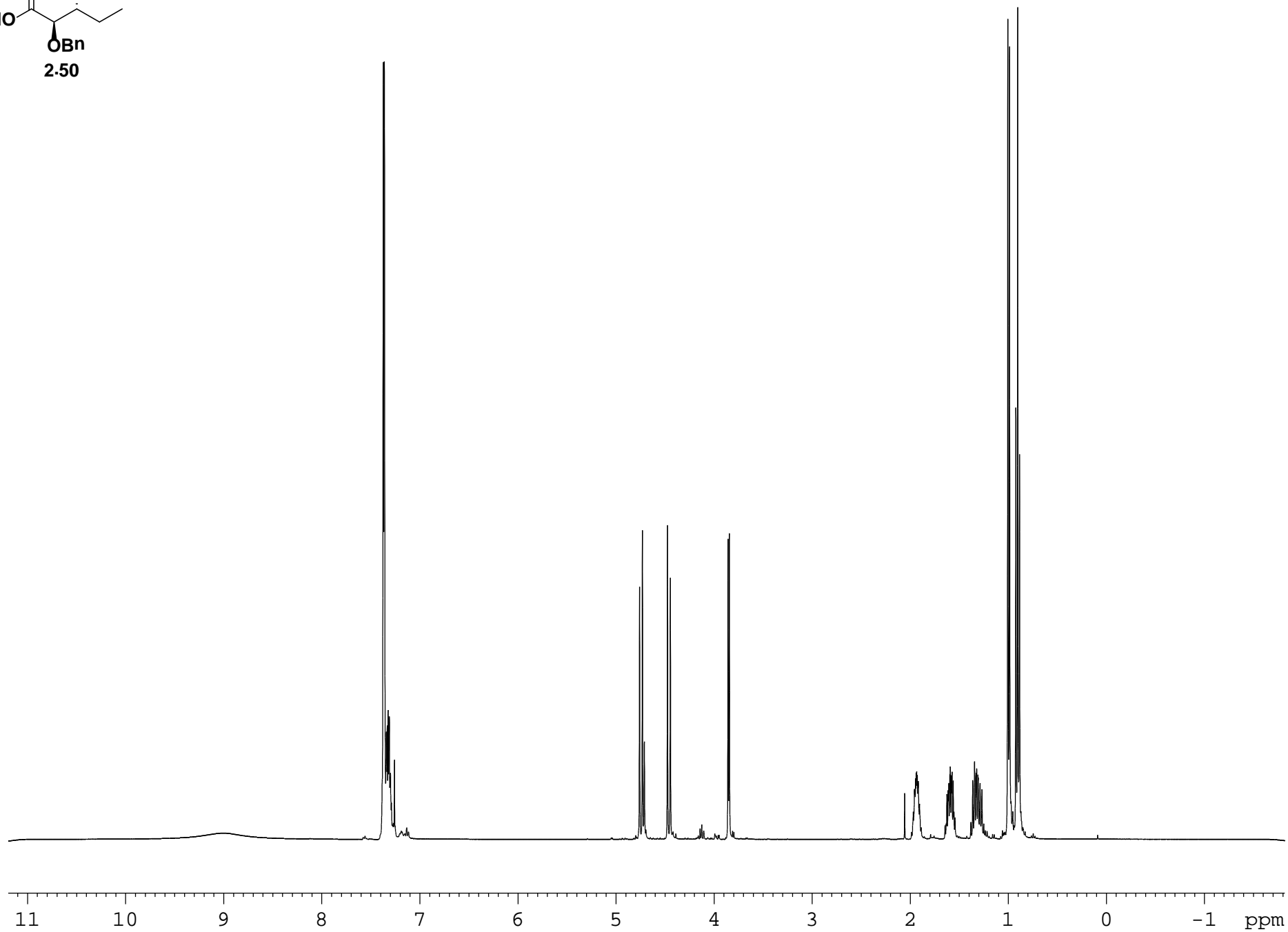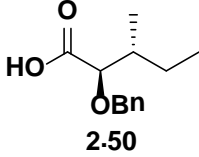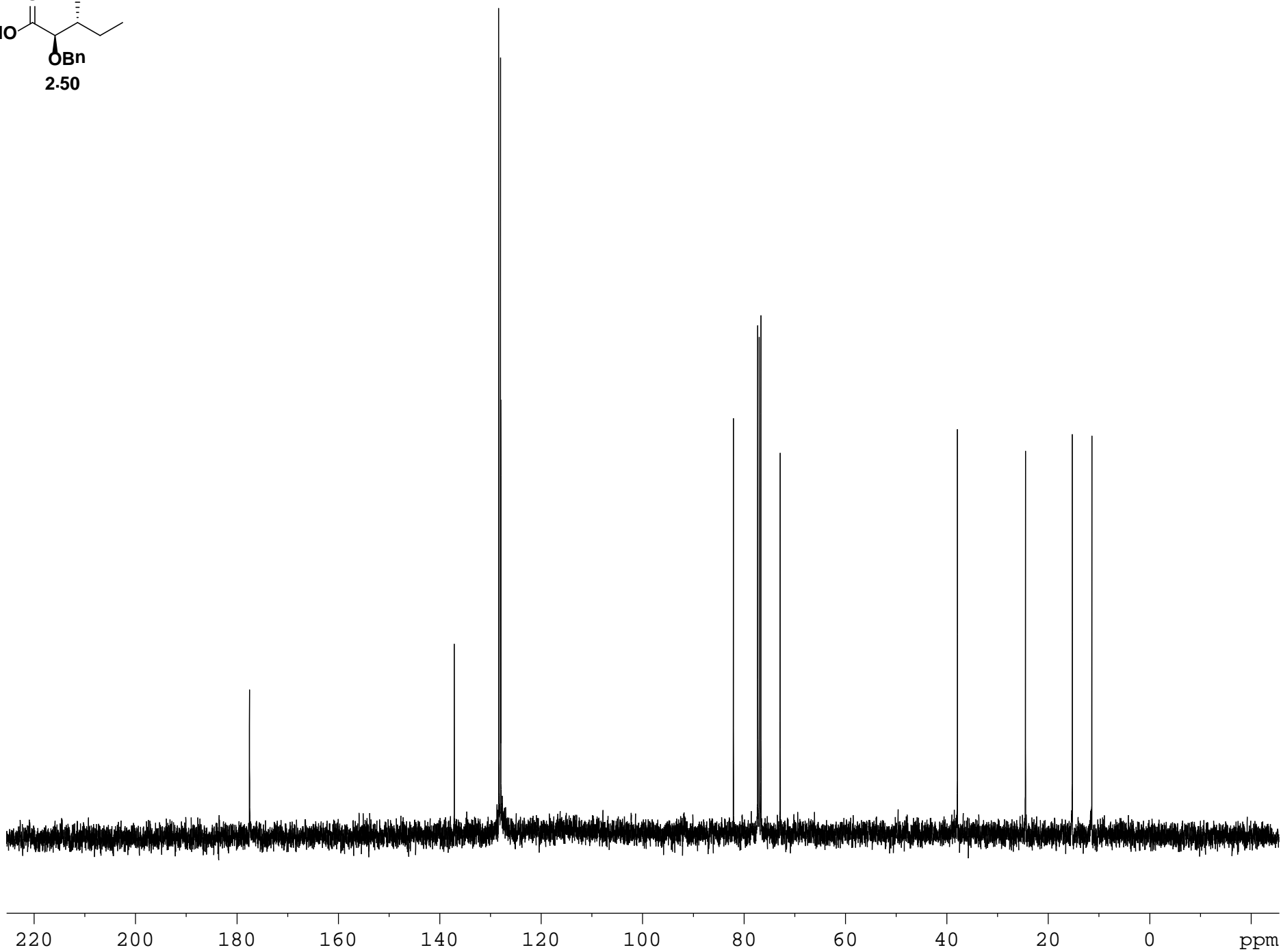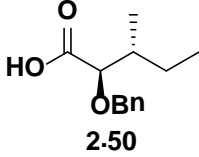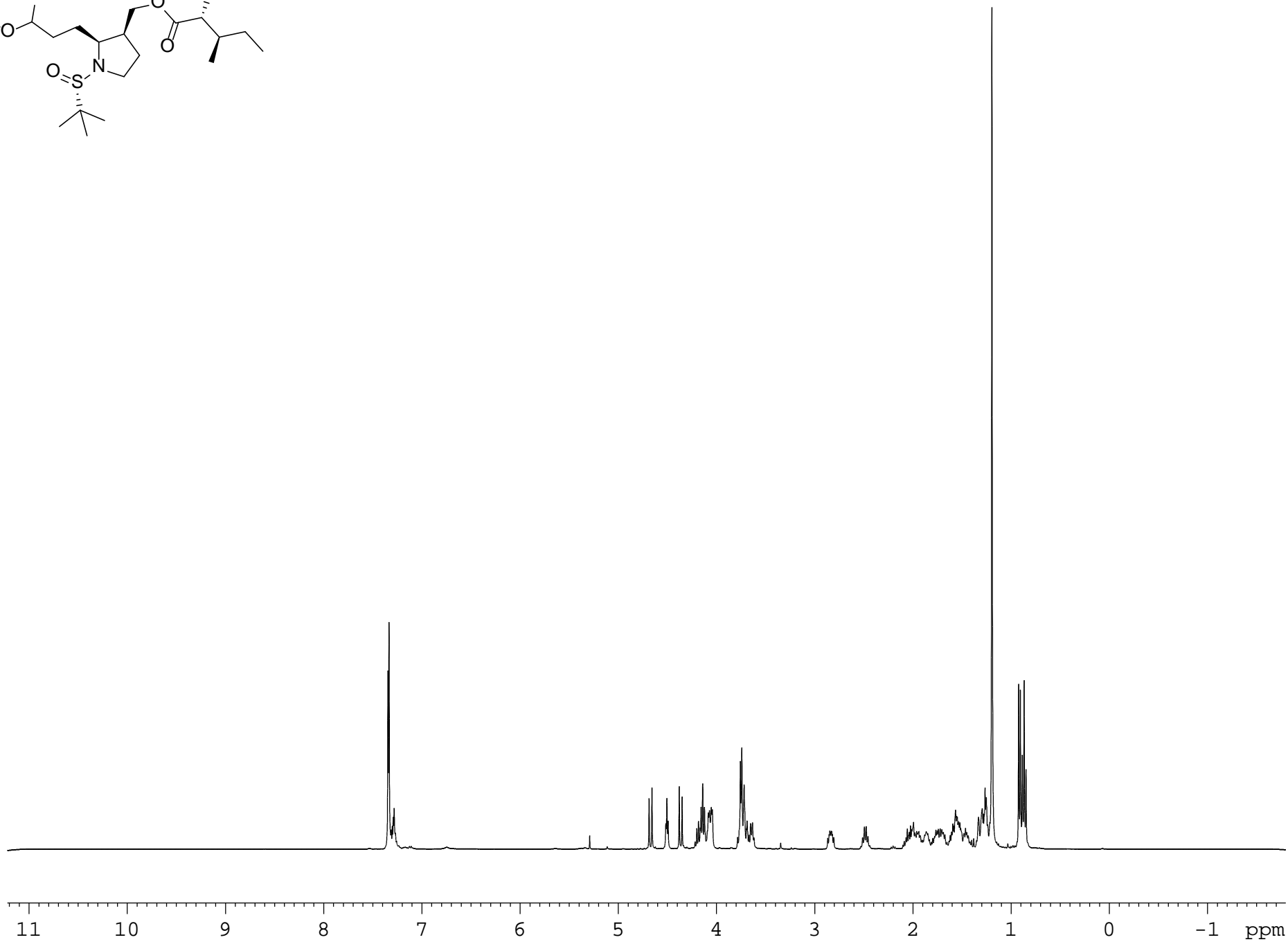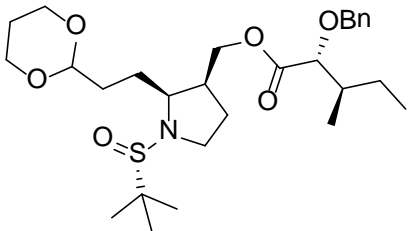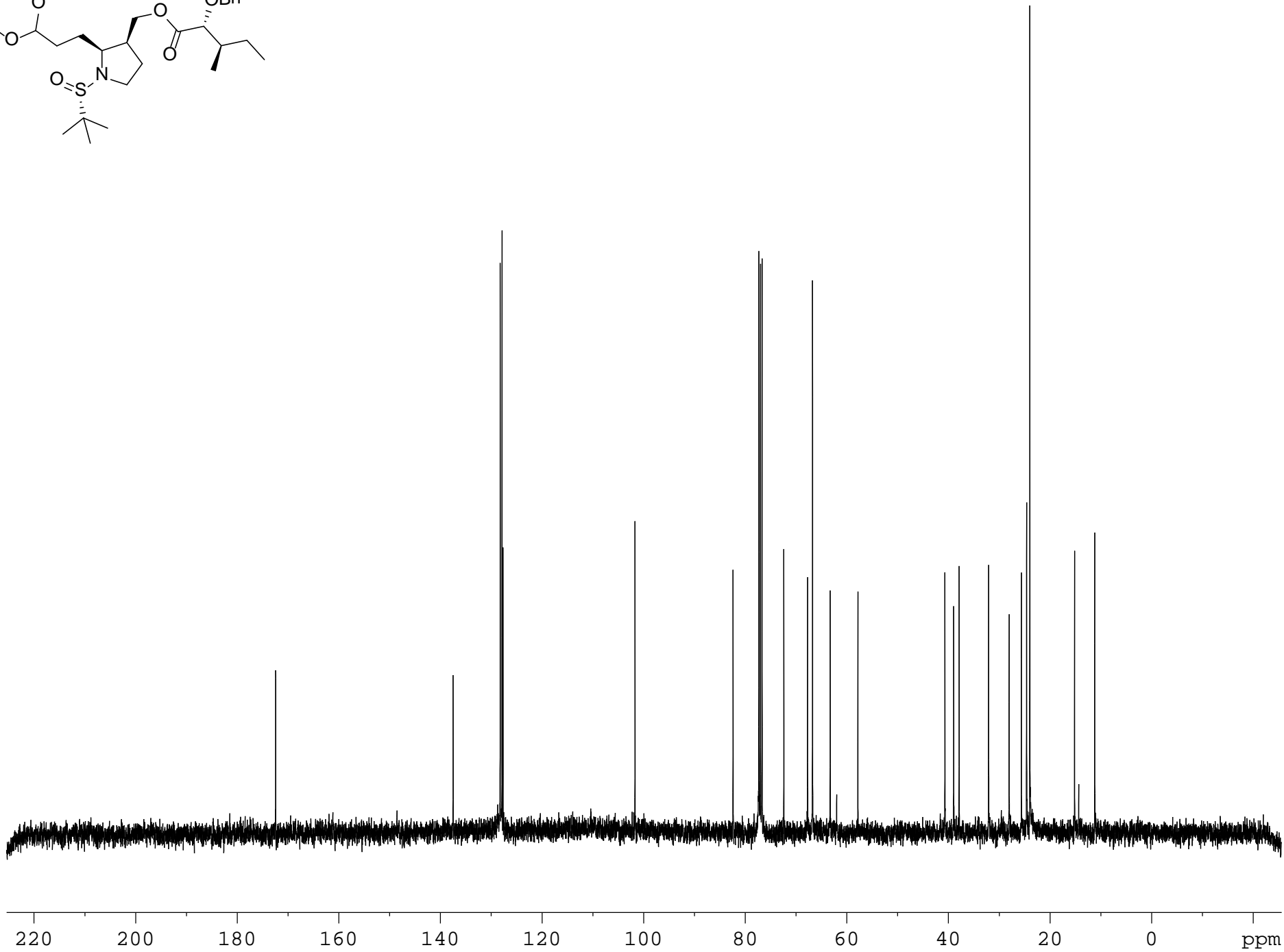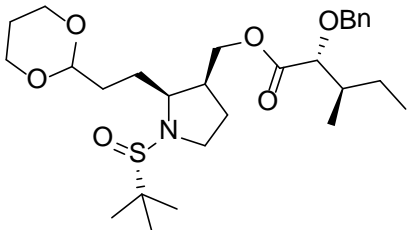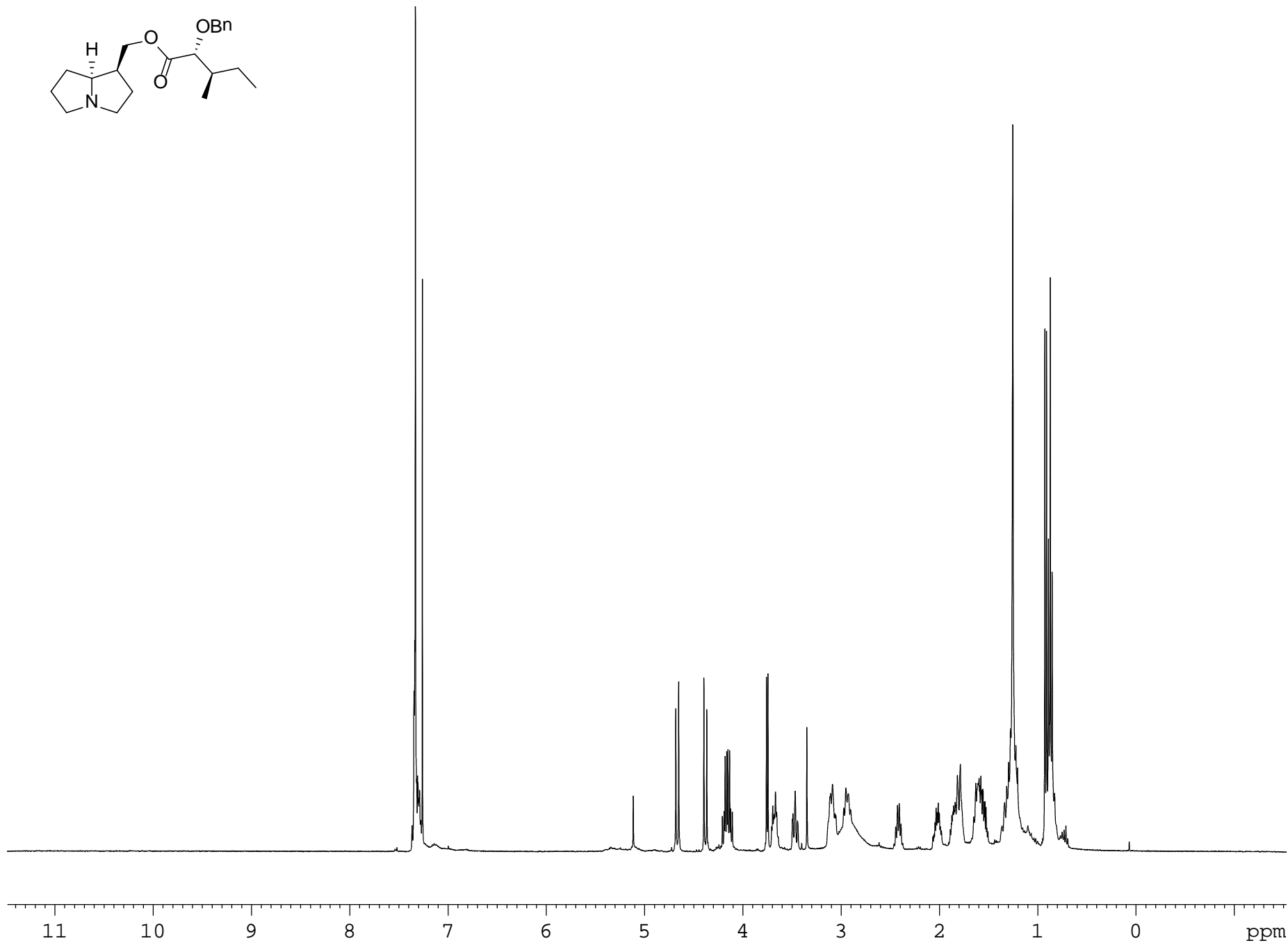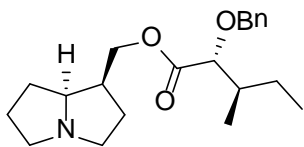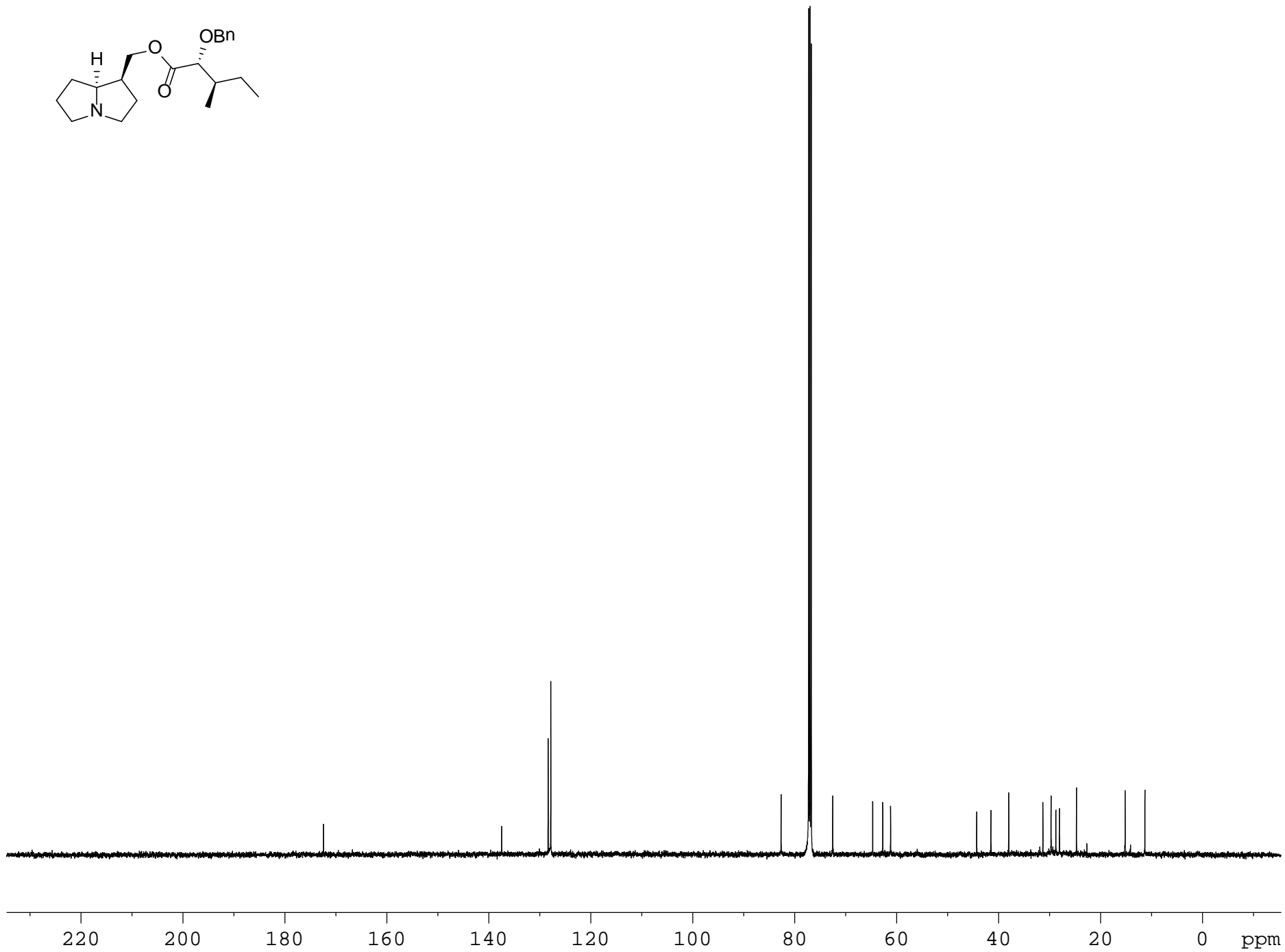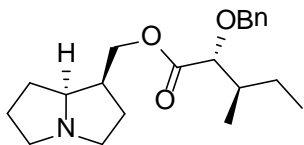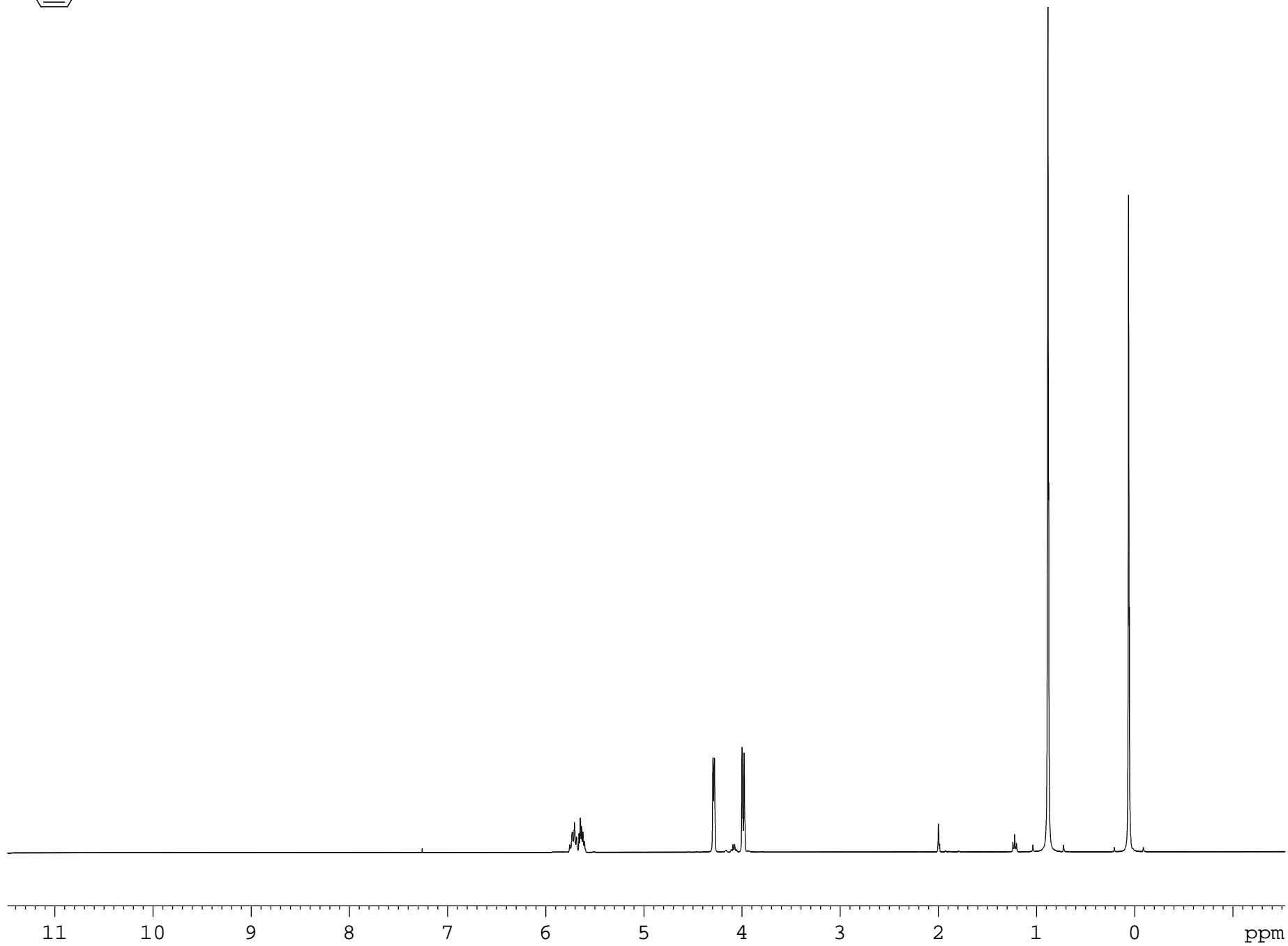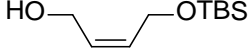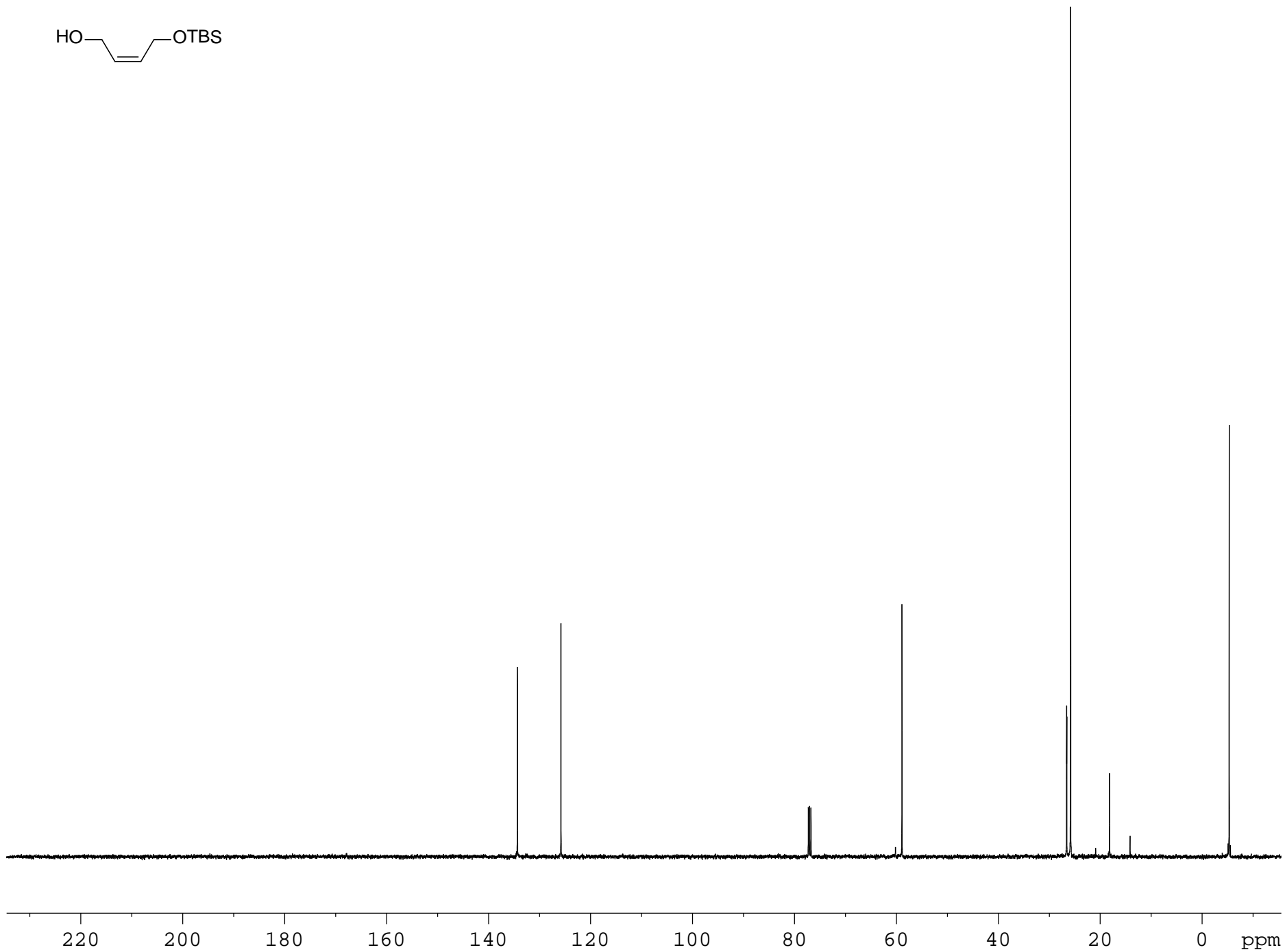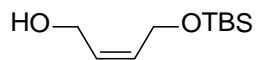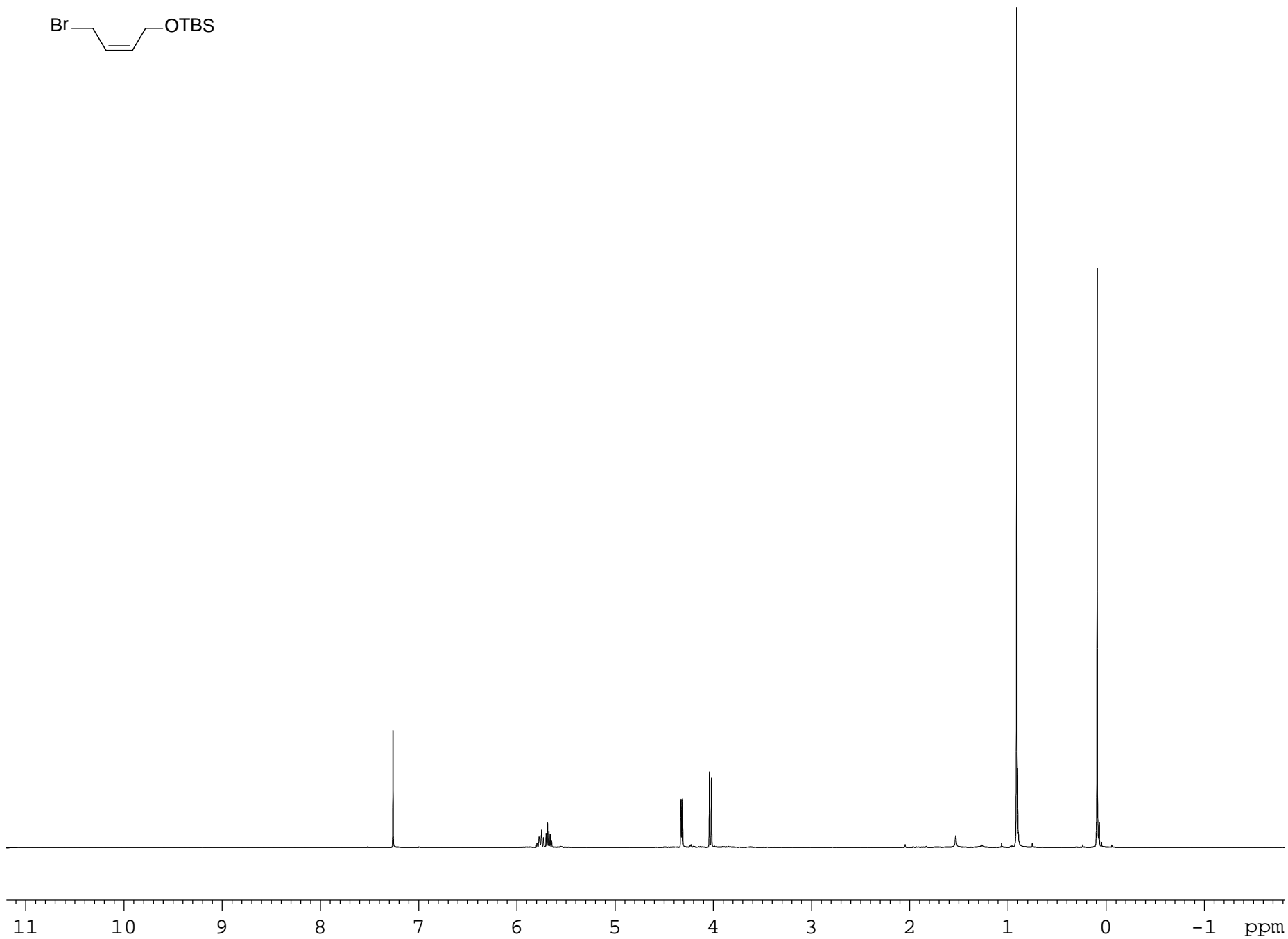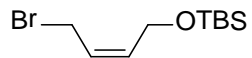
APPENDIX A3:

Spectra Relevant to Chapter III
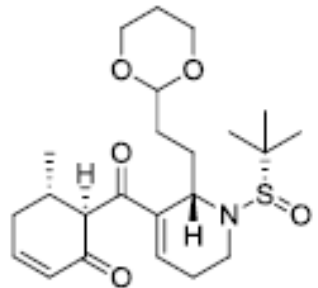
HO⤒OTBS
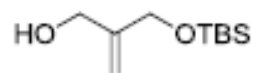
¹H NMR spectrum (400 MHz, CDCl₃)
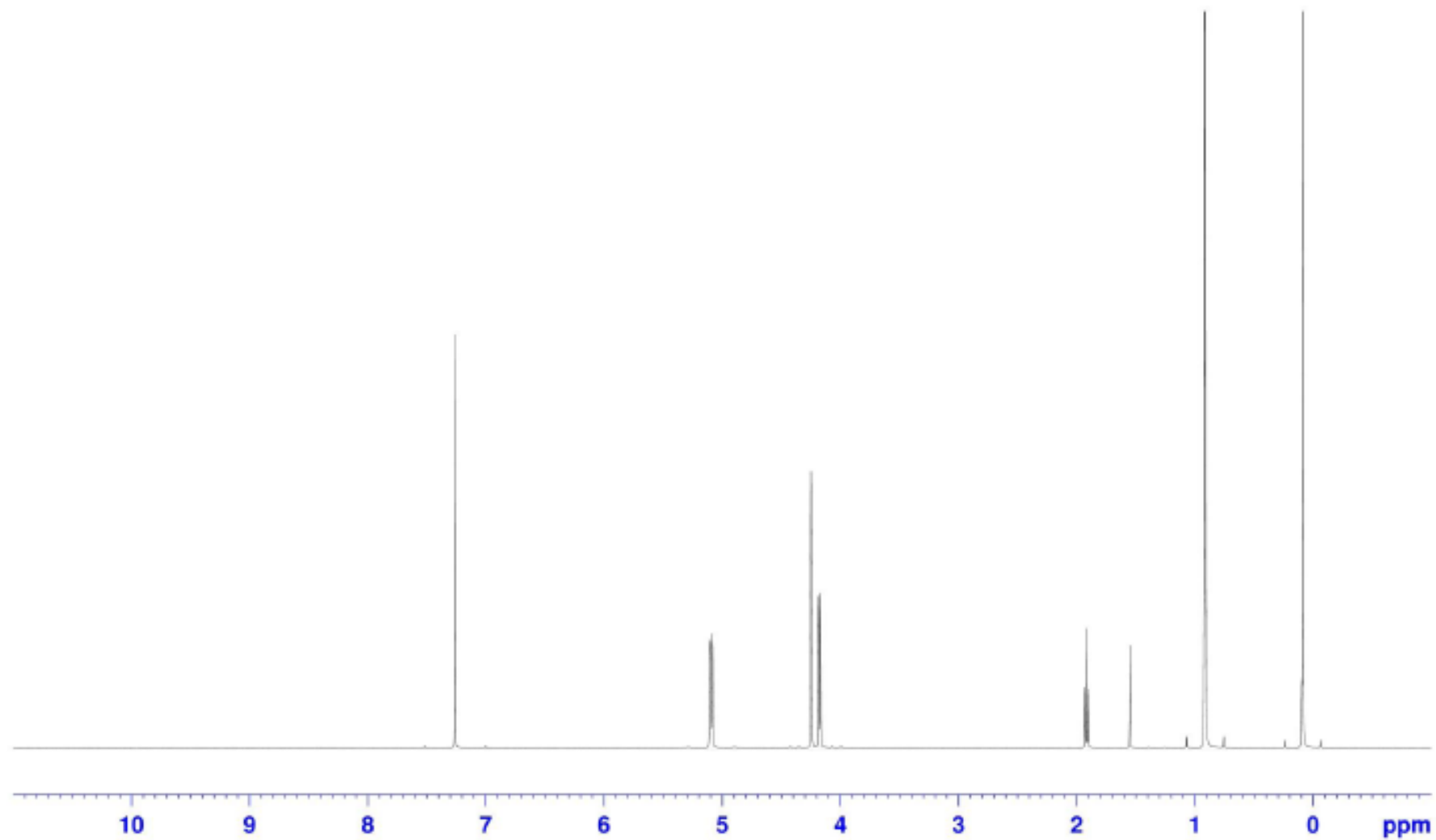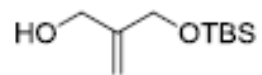
¹³C NMR spectrum (100 MHz, CDCl₃)

3.16

¹H NMR spectrum (400 MHz, CDCl₃)
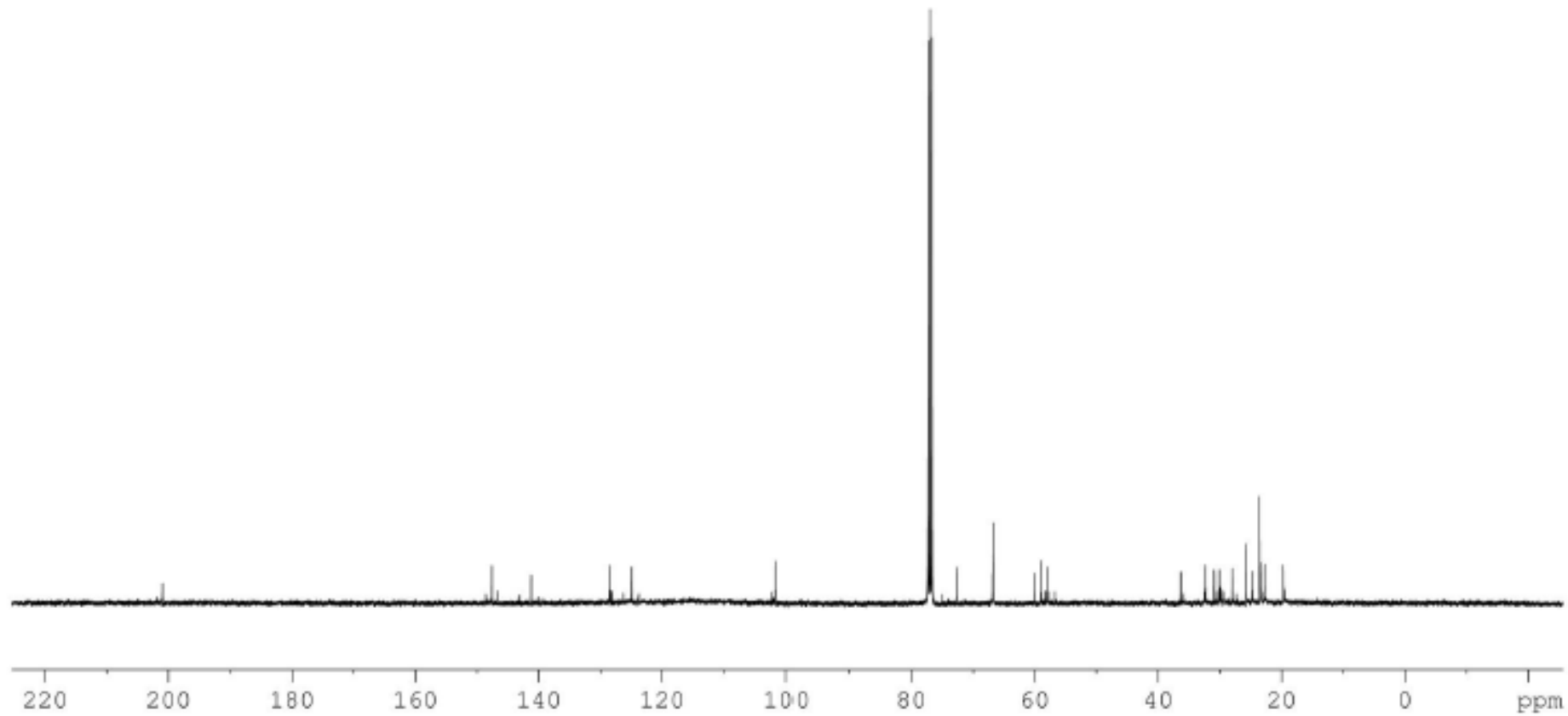
3.16

¹³C NMR spectrum (100 MHz, CDCl₃)

3.14
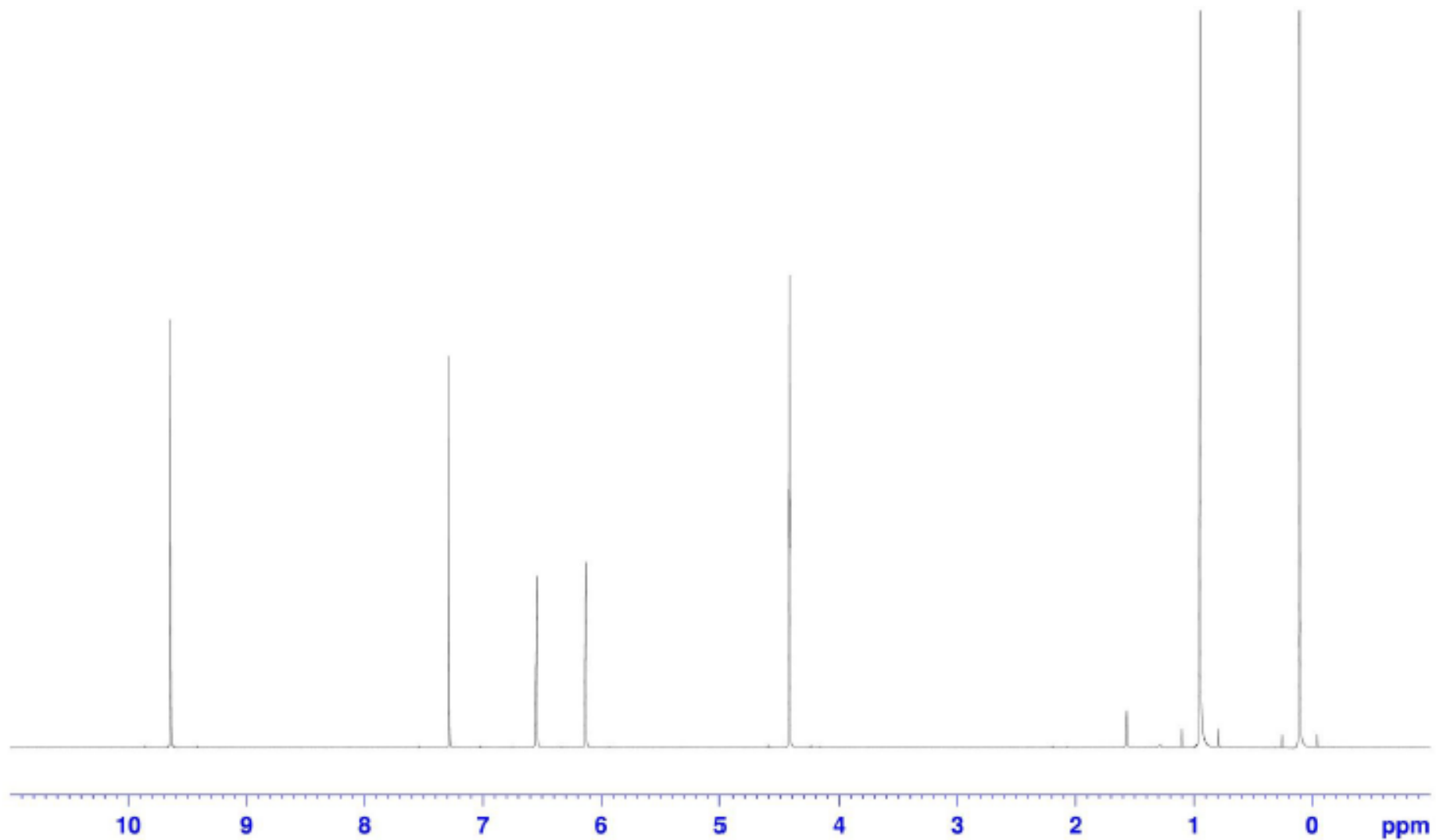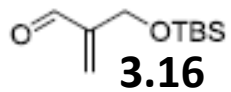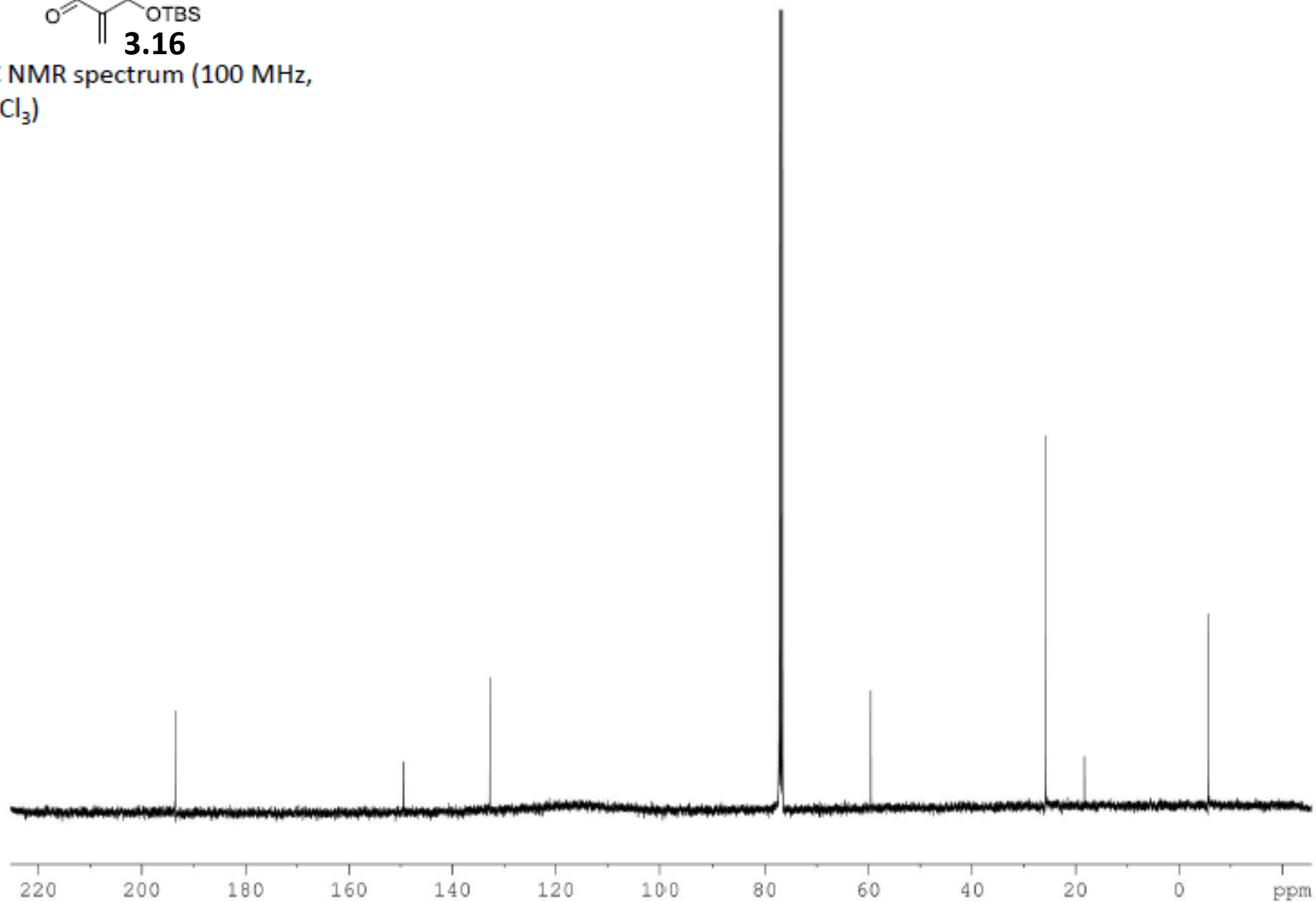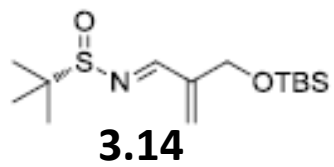
¹H NMR spectrum (400 MHz, CDCl₃)
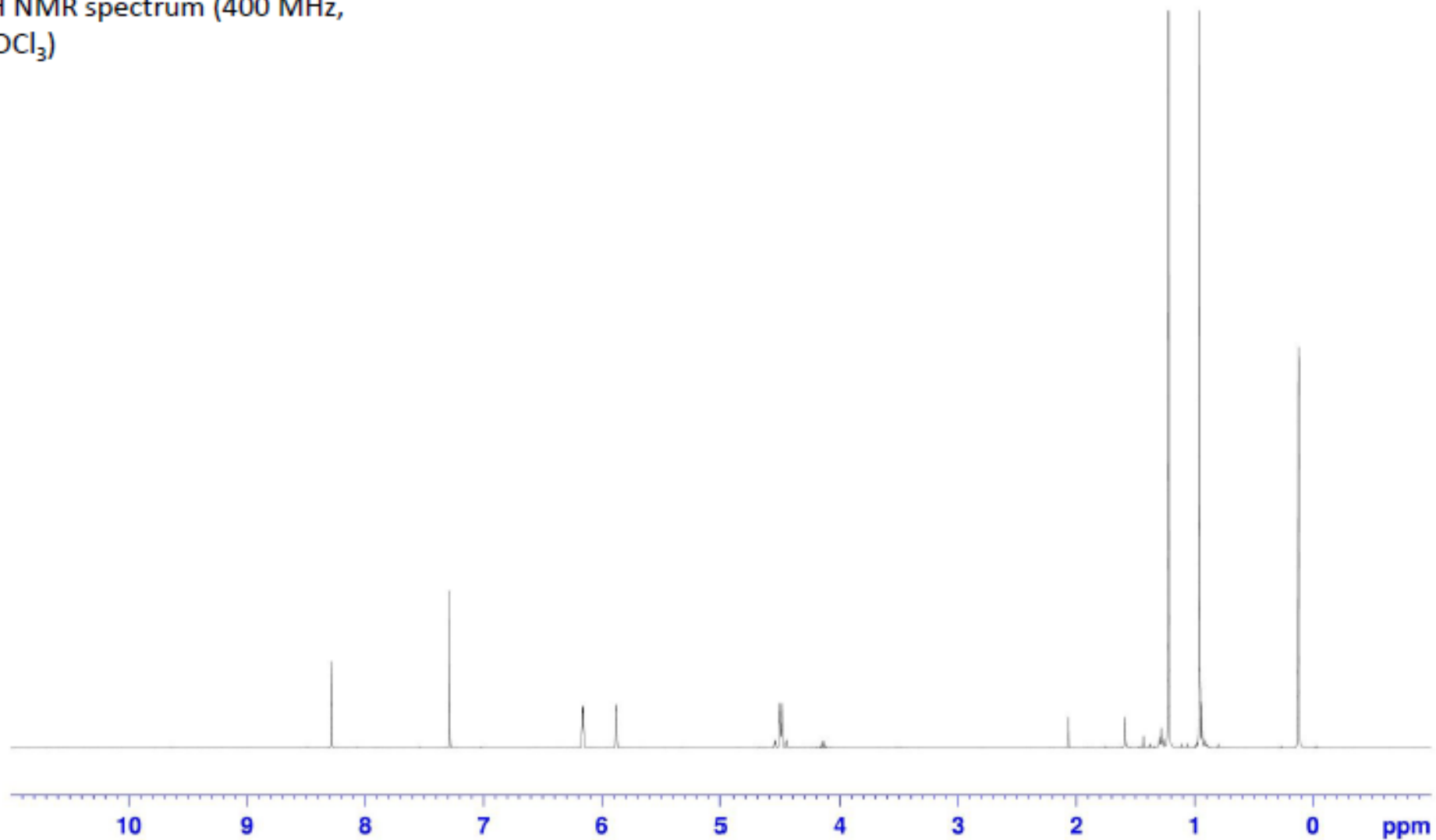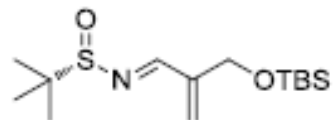
3.14

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

3.19

¹H NMR spectrum (400 MHz, CDCl₃)

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

3.19

3.20

¹H NMR spectrum (400 MHz, CDCl₃)

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

3.20

3.21

¹H NMR spectrum (400 MHz, CDCl₃)

3.21

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

3.22

¹H NMR spectrum (400 MHz, CDCl₃)

3.22

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

3.13

¹H NMR spectrum (400 MHz, CDCl₃)

3.13

¹³C NMR spectrum (100 MHz, CDCl₃)

3.33

¹H NMR spectrum (400 MHz, CDCl₃)

3.33

^{13}C NMR spectrum (100 MHz, CDCl$_3$)

3.4
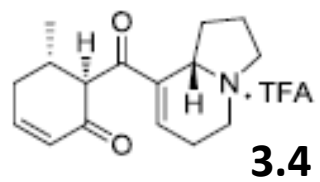
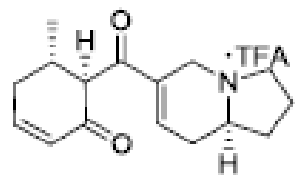¹H NMR spectrum (400 MHz,
DMSO)
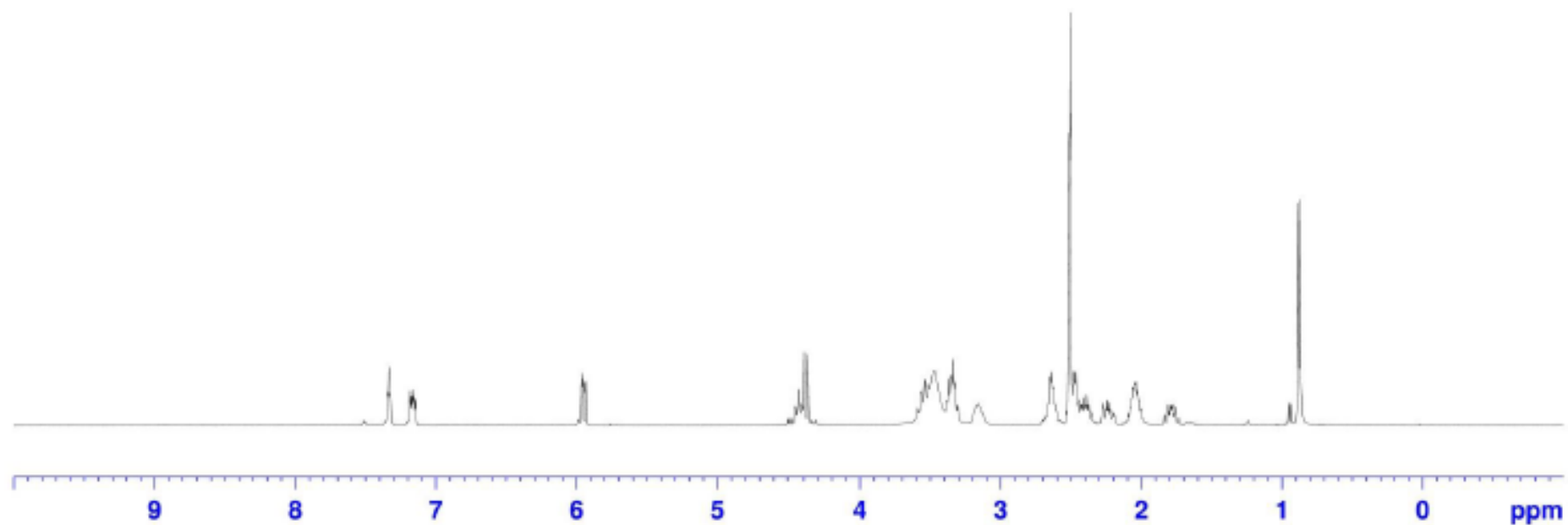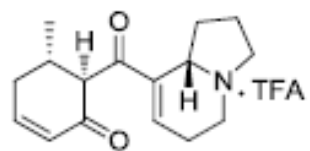
3.4

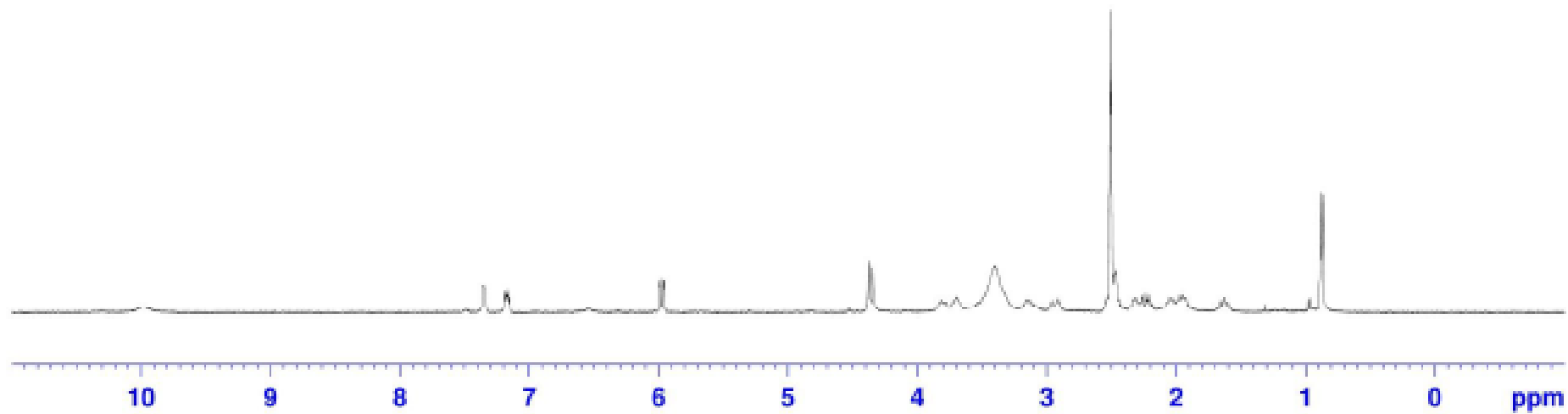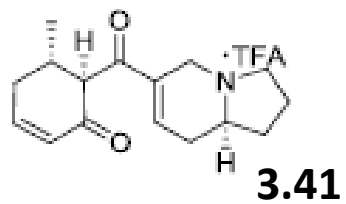¹³C NMR spectrum (100 MHz, DMSO)
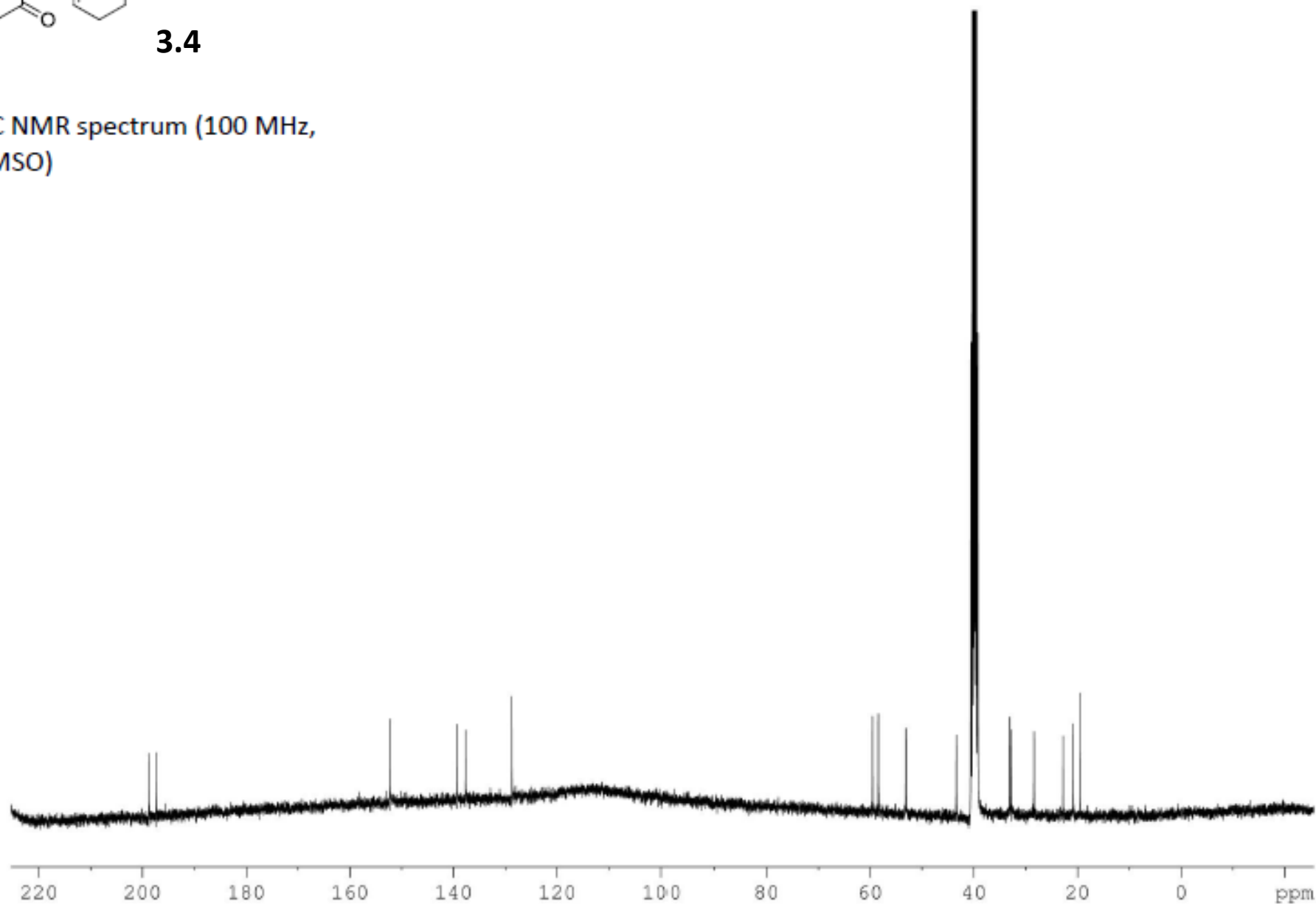
3.41

¹H NMR spectrum (600 MHz, DMSO)

3.41

^{13}C NMR spectrum (150.9 MHz, DMSO)