CONCISE TOTAL SYNTHESES OF Δ^{12}-PROSTAGLANDIN J NATURAL PRODUCTS USING STEREORETENTIVE METATHESIS

Thesis by

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To mom and dad.

ACKNOWLEDGEMENTS

I can still remember the rainy day when I walked on San Pasqual Walk five years ago during my first visit to Caltech. At that time, I never expected I would meet so many wonderful people with their help and support at this campus.

It was a winter morning when I had a casual talk with Professor Bob Grubbs in his office. He was so warm and welcoming and happily approved me to join his lab. This is Bob, who gives people unconditional support no matter who they are, or where they come from, to help them grow. This warm support makes me feel grateful every day at Caltech, and the warmth will be continued in the future. I'm also thankful to my co-advisor, Professor Brian Stoltz. I learned to be a synthetic chemist, from small details in weekly subgroups, to big ideas during conversation with him. Having both advisors was a unique experience. They both let me pursue my ideas and solve problems independently, and provided me great resources from both groups. I benefited not only from their guidance, but also from their wisdom. They are the advisors of my thesis, but also advisors in my life.

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I also value the amazing teaching experiences I've had, especially in Ch5a. Although I had to sacrifice Mondays and Fridays and put lots of effort in, I felt an incomparable achievement at the moment when I passed the torch to the students, who can confidently synthesize a small molecule like steroids after taking this class.

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Hsi Lai Temple has a great Chinese community. Every time I went there it's like my second hometown. From meditation and Buddhism classes, I learned to be more calm and not to be attached to the transient emotions.

Thanks to my mom and dad. They never put high expectations on me, but always think about me from thousands of miles away. I'm grateful to their unconditional love and support that can never be paid back.

ABSTRACT

Prostaglandins are an important class of naturally occurring molecules which have multifaceted biological functions and widespread medical applications. Chapter 1 discusses the development of concise syntheses of four Δ^{12}-Prostaglandin J natural products, enabled by convergent stereoretentive cross-metathesis by Ru-based metathesis catalyst. Exceptional control of alkene geometry was achieved through stereoretention. Short syntheses (7–8 steps in longest linear sequences) were realized in a modular approach. An improved route using enzymatic resolution to obtain enantiopure 15d-PGJ_2 was also discussed.

Chapter 2 discusses a mild palladium-catalyzed aerobic intramolecular aminoacetoxylation method. Pyrrolidine and indoline derivatives were synthesized using molecular oxygen as oxidant mediated by catalytic NO_x species, which acts as an electron transfer mediator to access high-valent palladium intermediate as the presumed active oxidant.

Chapter 3 presents a new, robust synthesis of *gem*-dialkyl acyclic diene monomers with low-cost. Telechelic *gem*-dialkyl polyethylenes can be made by the metathesis polymerization of the *gem*-dialkyl acyclic diene monomers, followed by hydrogenation. These polymers feature low glass transition temperature and can be used as elastomers in the synthesis of polyurethanes and other block polymers.

PUBLISHED CONTENT AND CONTRIBUTIONS

Li, J.; Grubbs, R. H.; Stoltz, B. M. Palladium-Catalyzed Aerobic Intramolecular Aminoacetoxylation of Alkenes Enabled by Catalytic Nitrate. *Org. Lett*. **2016**, *18*, 5449–5451. doi: 10.1021/acs.orglett.6b02722.

J. L. led project design, experimental work, data acquisition and analysis, and manuscript preparation.

Li, J.; Ahmed, T. S.; Xu, C.; Stoltz, B. M.; Grubbs, R. H. Concise Syntheses of Δ^{12}-Prostaglandin J Natural Products via Stereoretentive Metathesis. *J. Am. Chem. Soc.* **2019**, *141*, 154–158. doi: 10.1021/jacs.8b12816.

J. L. led project design, experimental work, data acquisition and analysis, and manuscript preparation.

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NOMENCLATURE

$[\alpha]_D$	specific rotation at wavelength of sodium D line
°C	degrees Celsius
Å	Ångstrom
Ac	acetyl
Acac	acetylacetonate
AcOH	acetic acid
ADH	alcohol dehydrogenase
Adm	adamantyl
ALB	aluminum-lanthanum-BINOL complex
All	allyl
An	anisole
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1-binaphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bis(oxazoline)
bp	boiling point
br	broad

Bu	butyl
Bz	benzoyl
c	concentration for specific rotation measurements (g/100 mL)
ca.	about (Latin circa)
calc'd	calculated
cat	catalytic
CDI	1,1'-carbonyldiimidazole
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethyl-cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DIBAL	diisobutylaluminum hydride
DIC	*N,N'*-Diisopropylcarbodiimide
DIFLUORPHOS	5,5'-Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole

DIPEA	*N,N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N, N*′-Dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide
dr	diastereomeric ratio
DTBM	di-*t*-butyl-methoxy
E	trans (entgegen) olefin geometry
e.g.	for example (Latin exempli gratia)
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI+	electron impact
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
FAB	fast atom bombardment
Fu	furanyl

g	gram(s)
G2	Grubbs catalyst 2nd generation
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)
HG-II	Hoveyda-Grubbs catalyst 2nd generation
hmim	2-methylimidazole
HMBC	heteronuclear multiple bond correlation
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide (HMPT)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	hertz
$h\nu$	light
i-	*iso*-
i-Pr	isopropyl
i.e.	that is (Latin id est)
IBX	2-iodoxybenzoic acid
IL-6	interleukin 6
IPA	isopropanol, 2-propanol
Ipc	diisopinocampheyl
IR	infrared (spectroscopy)
J	coupling constant
K	Kelvin(s) (absolute temperature)
kcal	kilocalorie
KP_i	potassium phosphate

L	liter; ligand
L*	chiral ligand
LDA	lithium diisopropylamide
LG	leaving group
lit.	literature value
LSB	lanthanum-sodium-BINOL
m	multiplet; milli
m	meta
M	metal; molar; molecular ion; Mega
m-CPBA	*meta*-chloroperoxybenzoic acid
m/z	mass to charge ratio
Me	methyl
mg	milligram(s)
min	minute(s)
MM	mixed method
MOC	methoxycarbonyl
mol	mole(s)
MOP	2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
n	nano
N	normal
n-	*normal*-
NADP	nicotinamide adenine dinucleotide phosphate
Naph	naphthyl

NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
Pd/C	palladium on carbon
pen	pentyl
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline
Pin	2,3-dimethylbutane-2,3-diol (pinacol)
Piv	trimethylacetyl, pivaloyl
p*Ka*	p*K* for association of an acid
pmdba	bis(4-methoxybenzylidene)acetone
PMP	*para*-methoxy phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Proton sponge	1,8-bis(dimethylamino)naphthalene
Py	pyridine
q	quartet
R	generic for any atom or functional group
RCM	ring-closing metathesis
Ref.	reference
R_f	retention factor

RRCM	relay ring-closing metathesis
s	singlet
s-	*sec*-
sat.	saturated
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SFC	supercritical fluid chromatography
Solv	solvent
t	triplet
t-	*tert*-
T-Hydro	70% TBHP in water
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBD	1,3,4-triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine

TMS	trimethylsilyl
TMP	tetramethylpiperidine
TOF	time-of-flight
Tol	tolyl
t_R	retention time
TRAP	2,2"-bis[1 -(diphenylphosphino)ethyl]-1,1"-biferrocene
TRIS	tris(hydroxymethyl)aminomethane
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
v/v	volume to volume
Val	valine
w	weak
w/v	weight to volume
X	anionic ligand or halide
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
λ	wavelength
μ	micro
Z	cis (zusammen) olefin geometry

CHAPTER 1

Concise Total Syntheses of Δ^{12}-Prostaglandin J Natural Products Via Stereoretentive Metathesis[†]

ABSTRACT

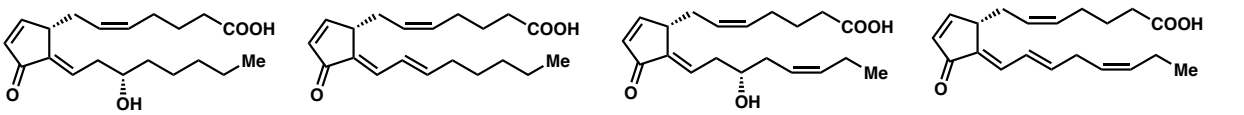
Δ^{12}-Prostaglandin J family is a type of secondary metabolite isolated in cell culture, and is recently discovered to have potent anticancer activity. Concise syntheses of four Δ^{12}-Prostaglandin J natural products (7–8 steps in the longest linear sequences) are developed, enabled by convergent stereoretentive cross-metathesis by Ru-based metathesis catalyst. Exceptional control of alkene geometry was achieved through stereoretention.

1.1 INTRODUCTION

Prostaglandins are an important class of naturally occurring molecules that are found in mammalian tissues and exhibit a broad range of biological functions and widespread medical applications.[1] The recently discovered Δ^{12}-prostaglandin J family (**1**–**4**, Figure 1.1.1) features a unique cross-conjugated dienone motif and has multifaceted biological properties that are uniquely different from other components of the PG family and have appealing anti-cancer activity.[2]

[†] Adapted with permission from Li, J.; Ahmed, T. S.; Xu, C.; Stoltz, B. M.; Grubbs, R. H. "Concise Syntheses of Δ^{12}-Prostaglandin J Natural Products via Stereoretentive Metathesis", *J. Am. Chem. Soc.,* **2019***, 141,* 154–158

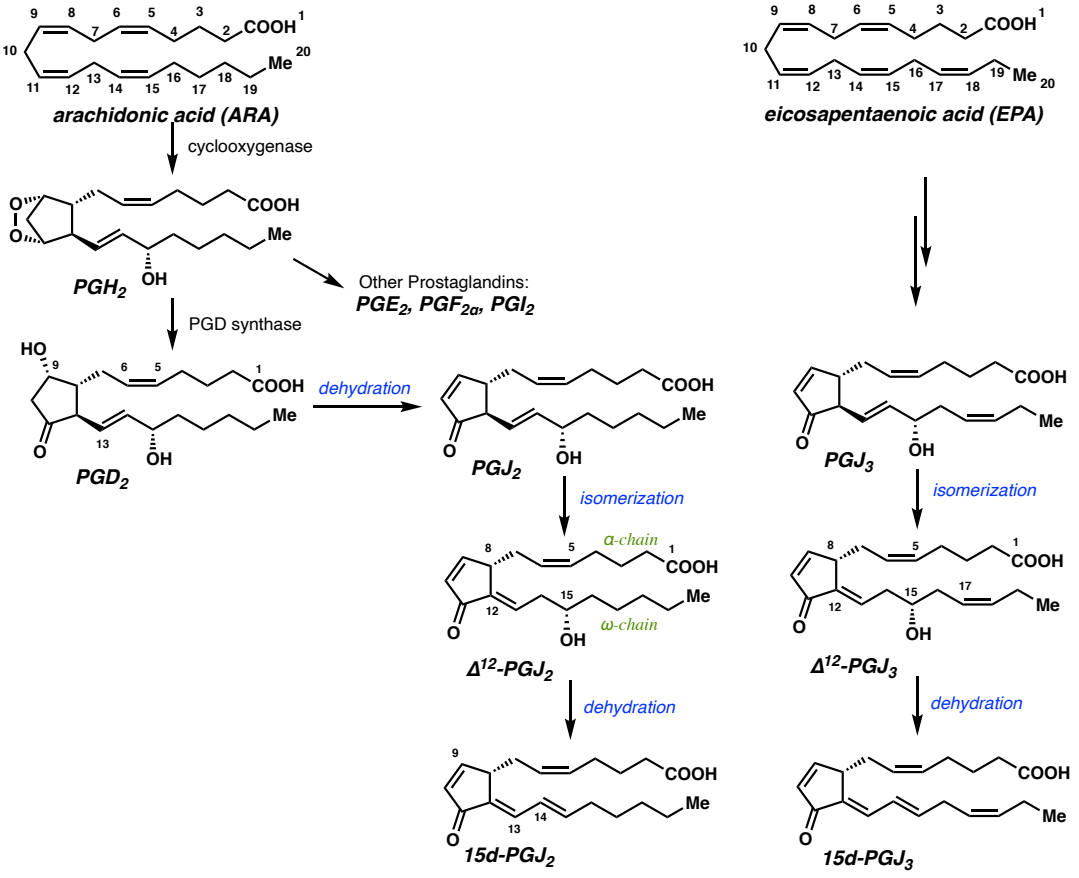
Figure 1.1.1. Structures of Δ[12] Prostaglandin J Natural Products



Δ[12]-prostaglandin J$_2$ (1) (Δ[12]-PGJ$_2$) ***15-deoxy-Δ[12,14]-prostaglandin J$_2$ (2) (15d-PGJ$_2$)*** ***Δ[12]-prostaglandin J$_3$ (3) (Δ[12]-PGJ$_3$)*** ***15-deoxy-Δ[12,14]-prostaglandin J$_3$ (4) (15d-PGJ$_3$)***

The proposed biosynthetic pathway to Δ[12]-prostaglandin J family is shown in Figure 1.1.2. Arachidonic acid (ARA) is released from membrane phospholipids, and then is converted by cyclooxygenase (COX; also known as PGH synthase) to PGH_2. This pivotal intermediate is converted enzymatically to a variety of biologically active prostaglandins, including PGD_2 , PGE_2, $PGF_{2\alpha}$, and PGI_2. PGD_2 can spontaneously undergo non-enzymatic dehydration and isomerization

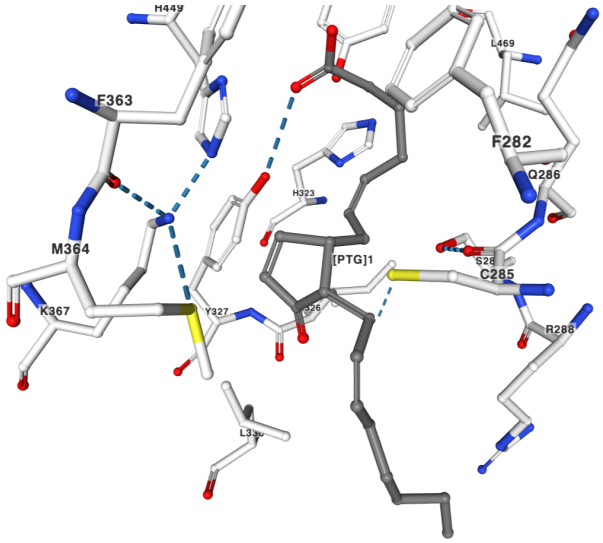
Figure 1.1.2. Biosynthesis of Δ[12] Prostaglandin J Natural Products



to form Δ^{12}-PGJ_2.[3] Further dehydration by loss of the 15-hydroxyl group results in the formation of 15d-PGJ_2. A similar biosynthetic pathway was known to account for the formation of Δ^{12}-PGJ_3 from the ω-3 eicosapentaenoic acid (EPA, Figure 1.1.2).[4]

15d-PGJ_2 is the most well-studied cyclopentenone prostaglandin and is reported to exert its effects on cells by binding the peroxisome proliferator activated receptor. It was demonstrated for the first time in 1995 that 15d-PGJ_2 is an endogenous ligand for PPAR-γ.[5] 15d-PGJ_2 up-regulates the expression, transcriptional activity, and DNA binding activity of PPAR-γ, and many of other cellular events mediated by 15d-PGJ_2 have been shown to be PPAR-γ-dependent.[6] PPARs are a family of ligand-activated nuclear transcription factors, which modulate gene expression through binding to specific DNA sequences, termed PPAR response elements (PPREs) in the enhancer regions. PPARs play an important role in physiological processes such as adipogenesis, glucose metabolism, and macrophage function, and also in regulation of cancer cell proliferation, survival, apoptosis, and tumor growth.[7] Crystallography data showed that 15d-PGJ_2 is the natural high affinity ligand to PPAR-γ and can form a covalent bond with cysteine C285 through a Michael addition (Figure 1.1.3) at C13. Furthermore, the carboxyl group of 15d-PGJ_2 is required for the formation of a hydrogen bond with Y327 residue.[8]

Figure 1.1.3. 15d-PGJ_2 Bind to PPAR-γ [9]



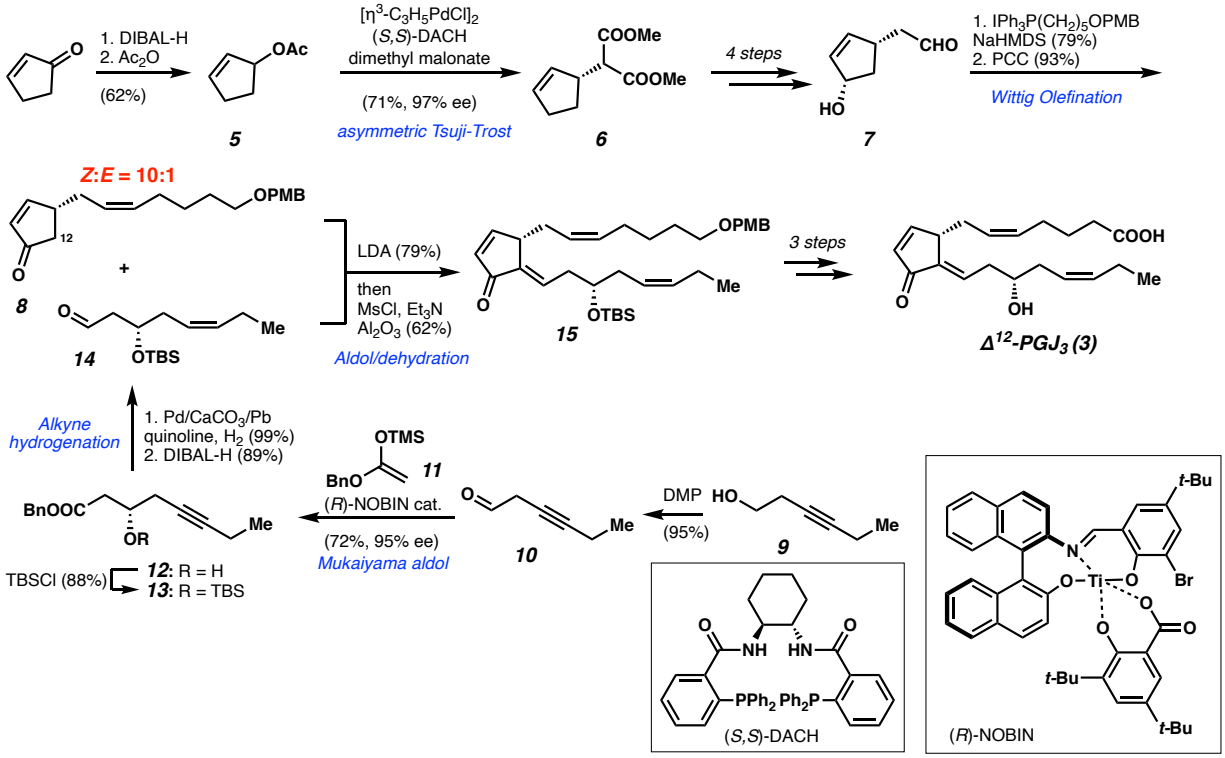
Δ^{12}-PGJ_3 (**3**) was recently identified in 2011 to have activity against leukemia stem cells with high potency, without adverse activity against the normal cells.[4] The interest in cancer stem cells (CSCs) is due to their inherent resistance against conventional chemotherapies which allow for relapse and metastasis. Δ^{12}-PGJ_3 showed impressive in vitro potency and selectivity of against chronic myelogenous leukemia (CML) stem cells (IC_{50} = 12 nm), and exceptional ability to effectively cure this form of leukemia in a mouse model. Studies of its stability, bioavailability, and hypersensitivity make Δ^{12}-PGJ_3 a lead compound for further investigation in search of new therapies for the treatment of acute and chronic myelogenous leukemia (AML and CML).[10]

1.2 PRIOR SYNTHETIC EFFORTS

Efforts directed toward the synthesis of various prostaglandins has had a profound effect on the development of new strategies and tactics employed in the field of synthetic chemistry, emanating from the seminal studies of Corey beginning in the 1960's.[11] Elegant contribution to the total synthesis of Δ^{12}-PGJ_3 (**3**) was reported by Nicolaou and co-workers in 2014 (Scheme

1.2.1).[12] The synthesis of cyclopentenone fragment **8** began with the preparation of racemic acetate by reduction of commercially available 2-cyclopentenone followed by acetylation. The C8 stereocenter was introduced by asymmetric Tsuji–Trost allylic alkylation of racemic acetate **5** with dimethyl malonate in the presence of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.5 mol%) and (*S,S*)-DACH-phenyl Trost ligand (1.5 mol%). The enantio-enriched dimethyl ester **6** was obtained in 71% yield and 97% ee. Upon a 4-step process, aldehyde **7** can undergo Wittig reaction with 2.5 equivalents of $IPh_3P(CH_2)_5OPMB$ in the presence of NaHMDS at –78 ºC, furnished the desired *Z*-alkene in high yield (79%) and good *Z*-selectivity (*Z*/*E* ≥ 10:1), which was converted to enone fragment **8** by PCC oxidation. To construct the ω-chain aldehyde, Mukaiyama aldol reaction with hex-3-ynal (**10**) and TMS-protected acetal **11**, in the presence of (*R*)-NOBIN catalyst developed by Carreira and co-workers[13] could afford homopropargylic alcohol **12** in 72% yield and 95% ee. Protection of the

Scheme 1.2.1. Nicolaou's 1st Generation Synthesis of Δ^{12} Prostaglandin J_3

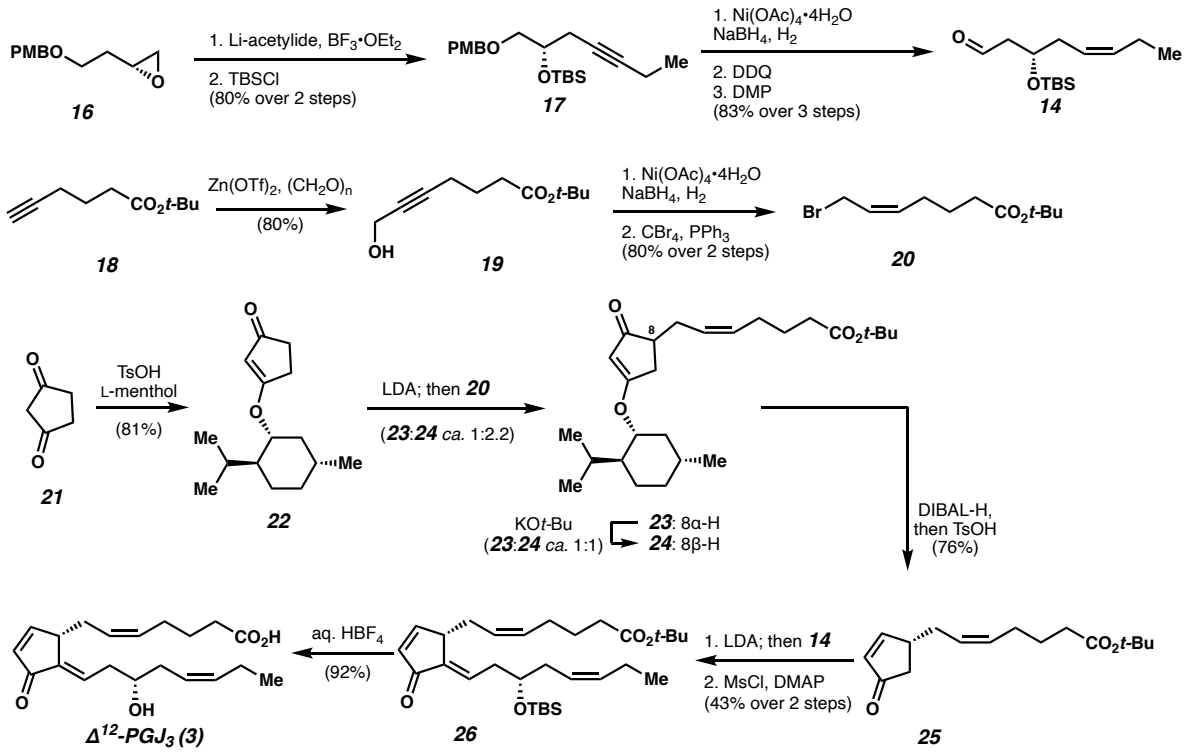


secondary alcohol with TBS group, semi-hydrogenation of the alkyne (H_2, Lindlar catalyst, quinoline) followed by DIBAL-H reduction provided ω-chain aldehyde **14** as the only geometrical isomer. At this stage, regioselective deprotonation of cyclopentenone **8** at the C12 position was achieved with LDA at –78 ºC, then ω-chain aldehyde **14** was added, and the aldol product was generated (79%) as a pair of C13 epimers (*ca.* 3:1 d.r.). Treatment of the aldol product with a mixture of MsCl and Et_3N gave the corresponding mesylate, which did not undergo β-elimination even with excess amount of Et_3N. By adding activated commercial neutral alumina, the cross-conjugated dienone intermediate **15** can be formed when while leaving the OTBS group intact. Δ^{12}-PGJ_3 (**3**) can be prepared in three additional steps.

In 2016, Nicolaou and co-workers reported a streamlined synthesis of Δ^{12}-PGJ_3 (Scheme 1.2.2).[14] The synthesis commenced with the preparation of ω-chain aldehyde **14** in a modified route. Ring-opening of chiral epoxide **16** with lithium acetylide under Lewis acidic conditions, and TBS protection of secondary alcohol formed **17**. Reduction of alkyne in **17** with nickel acetate furnished the desired *Z*-alkene. Deprotection of the primary alcohol with DDQ, followed by DMP oxidation furnished the ω-chain aldehyde **14**. The α-chain fragment was prepared from terminal alkyne **18**, which was alkylated with formaldehyde to produce propargyl alcohol **19**. Then, the alkyne was reduced to the *Z*-alkene in the same conditions with nickel acetate. The allylic alcohol was subjected to Appel conditions to provide allylic bromide **20**. Chiral induction of C8 was achieved by introducing L-menthol to cyclopentanedione **21** to form the vinyl ether **22**. Alkylation of **22** with allyl bromide **20** formed two diastereomers (**23**:**24** *ca.* 1:2.2) favored the β-H at C8 position. The undesired diastereomer **23** could be epimerized to **24** when subjected to KO*t*-Bu, which resulted in 1:1 ratio of two epimers. DIBAL-H reduction and hydrolysis elaborated enone **25**, which can undergo aldol reaction with ω-chain aldehyde **14** in the presence of LDA. MsCl

and excess amount of DMAP can eliminate the secondary alcohol of aldol product to form intermediate **26**. Global deprotection under aqueous HBF_4 gave Δ^{12}-PGJ_3 (**3**) in excellent yield (92%, Scheme 1.2.2). A number of Δ^{12}-PGJ_3 analogues were also accessible via this streamlined route by Nicolaou and co-workers in 2016, which enabled a comprehensive structural-activity relationship (SAR) study of their anti-cancer activities.[15]

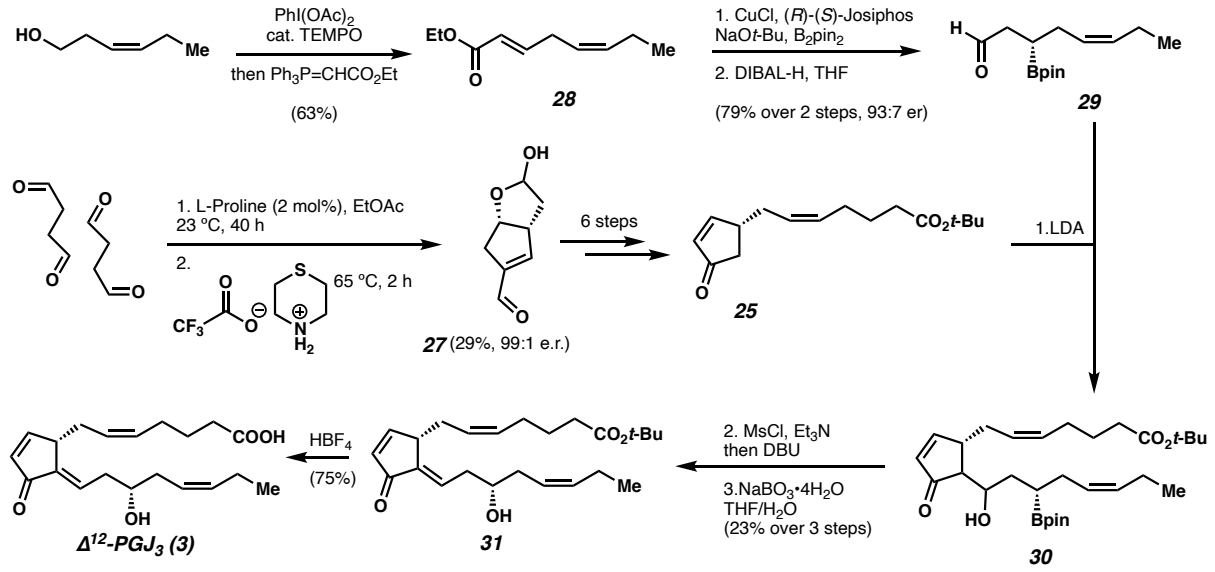
Scheme 1.2.2. Nicolaou's 2nd Generation Synthesis of Δ^{12} Prostaglandin J_3



In 2018, the Aggarwal group reported a synthesis of Δ^{12}-PGJ_3 features an L-Proline catalyzed homodimerization of succinaldehyde to form a key intermediate **27** in high enantioselectivity (99:1 e.r., Scheme 1.2.3).[16] Upon a six-step process, **27** was converted into the previously reported enone fragment **25**. The ω-chain aldehyde was prepared from asymmetric conjugate addition of α,β-unsaturated ester **28** with B_2pin_2, followed by reduction with DIBAL-H

in good yield and enantioselectivity (79% over 2 steps, 93:7 e.r.). Similar to the previous approaches by Nicolaou and co-workers, an aldol reaction was performed with enone fragment **25** and aldehyde **29** in the presence of 2.0 equivalent of LDA. Then the crude reaction mixture from the aldol reaction was treated with MsCl and Et_3N to give the corresponding mesylate, and subsequent elimination upon reaction with DBU produced exclusively the *E*-configured elimination product. Subsequent oxidation with $NaBO_3 \bullet 4H_2O$ gave the late stage intermediate **31**. Finally, treatment of **31** with aqueous HBF_4 gave Δ^{12}-PGJ_3 (**3**) in 75 % yield.

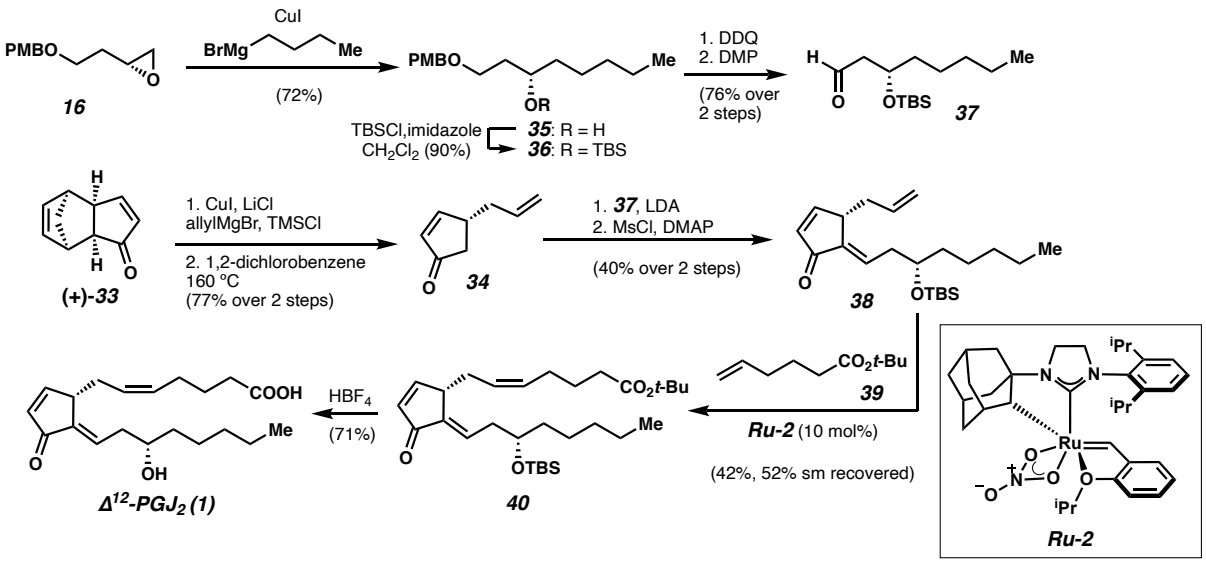
Scheme 1.2.3. Aggarwal's Synthesis of Δ^{12} Prostaglandin J_3



Synthetic efforts toward Δ^{12}-PGJ_2 and 15d-PGJ_2 compounds began in 2003, with a number of syntheses reported through various approaches.[17] In 2019, the synthesis of Δ^{12}-PGJ_2 was enabled by a concise approach using *Z*-selective cross-metathesis by Nicolaou and co-workers (Scheme 1.2.4).[18] Stereoselective conjugate addition of enantiomerically pure enone **(+)-33** with the allyl cuprate reagent generated from allyl magnesium bromide, CuI and LiCl in the presence of TMSCl, followed by thermally induced retro-Diels−Alder reaction, furnished the

enantiopure intermediate **34** in 77% yield over the two steps. Chiral epoxide **16** was reacted with *n*-BuMgBr in the presence of CuI to form the secondary alcohol **35** (72% yield). Protection of **35** with TBS group furnished the TBS-ether **36** (90% yield). Removal of the PMB group of **36** with DDQ followed by oxidation with DMP elaborated the ω-chain aldehyde **37** in 76% over 2 steps. Then the dienone intermediate **38** was obtained by aldol reaction of **34** and aldehyde **37** with LDA, followed by the treatment with MsCl and DMAP. Subjecting **38** with to an excess amount of *tert*-butyl ester **39** with 10 mol% loading of *Z*-selective metathesis catalyst **Ru-2**, furnished the protected Δ^{12}-PGJ_2 derivative **40** in 42% yield (>95:5 *Z*/*E*, 52% recovered starting material **38**, 90% yield based on recovered enone **38**), which was exposed to aqueous HBF_4 to reveal Δ^{12}-PGJ_2 (**1**) in 71% yield. This work presented a shorter synthetic sequence to Δ^{12}-PGJ_2 and its analogs, and the dimeric, trimeric, and tetrameric macrocyclic lactones consisting of Δ^{12}-PGJ_2 units were prepared for the biological evaluation of those compounds.

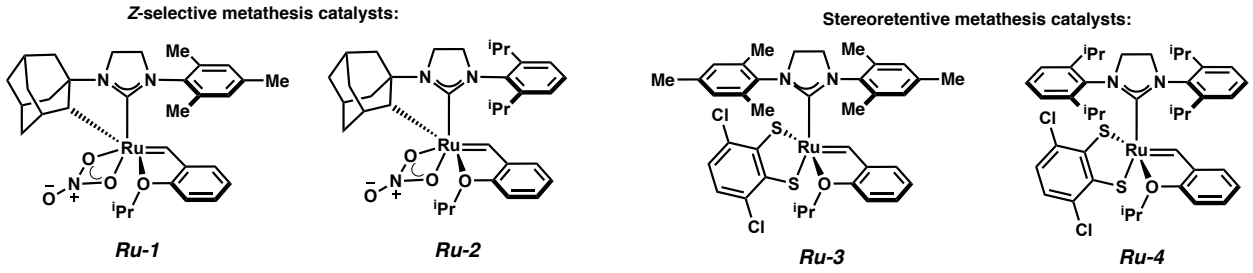
Scheme 1.2.4. Nicolaou's Synthesis of Δ^{12} Prostaglandin J_2



1.3 INTRODUCTION OF STEREORETENTIVE METATHESIS

Olefin cross-metathesis is a convergent method for building C–C double bonds in natural product syntheses.[19] Most importantly, conventional metathesis catalysts typically gave imperfect control of alkene geometry. Previous syntheses relied on the semi-hydrogenation of alkynes or Wittig reactions, requiring multi-step functional group manipulation with concomitant waste generation. From a strategic perspective, chemoselectivity among multiple alkenes has also been another concern, especially in the later stages. Stereo- and chemoselective metathesis catalysts are in demand to realize a convergent synthesis from simple alkene building blocks. However, it has seldom been applied in the previous syntheses of Δ^{12}-PGJ family.

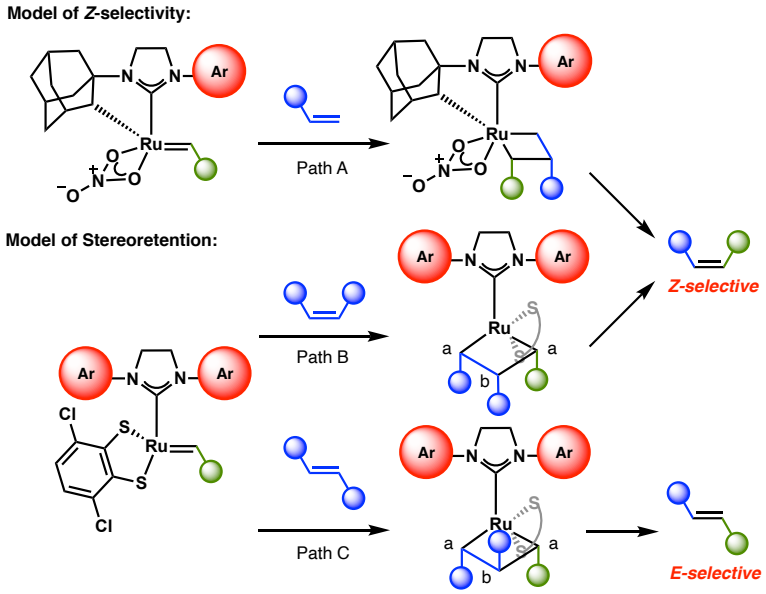
Figure 1.3.1. Structures of Z-selective and Stereoretentive Metathesis Catalysts



A series of cyclometallated ruthenium-based catalysts (e.g. **Ru-1**, **Ru-2**, Figure 1.3.1) were recently developed by Grubbs and co-workers, which enable *Z*-selective metathesis through a favored *syn*-metallacyclobutane intermediate (Figure 1.3.2, Path A).[20] More recently, catechodithiolate-based catalyst **Ru-3** and its dithiolate variants were developed by Hoveyda group and showed high *Z*-selectivity in ring-opening metathesis polymerizations, ring-opening cross-metathesis, and cross-metathesis with *Z*-olefins.[21] In fact, high kinetic *E*-selectivity in cross-metathesis with *E*-starting materials was also observed with **Ru-3**, the sIPr analogue **Ru-4**, and other less bulky fast-initiating analogues developed by Materia, Inc. and the Grubbs group, that defined these catalysts as stereoretentive.[22] The origin of the stereoretention was attributed to the

formation of a side-bound metallacyclobutane intermediate, of which the α-substituents are forced down to minimize steric interactions with the bulky N-aryl groups of the NHC. As a result, when starting with *Z*-alkenes, the α-substituent points down to generate *Z*-alkene products (Figure 1.3.2, Path B). When starting with *E*-alkenes, however, the β-substituent has to point up into the open space between two N-aryl groups, leading to the generation of *E*-alkene products, albeit with slower rates (Figure 1.3.2, Path C). Cross-metathesis between two terminal alkenes is not possible with stereoretentive metathesis catalysts, however, because the intermediate methylidene species are unstable and lead to catalyst decomposition. A methylene capping strategy was recently reported as a remedy to this problem, enabling the cross-metathesis of two terminal alkenes.[23] Despite the unique properties of these stereoretentive catalysts, to date, limited synthetic evaluation has been conducted with Ru-based stereoretentive catalysts,[24] as well as with Mo, W-based catalysts.[25] Total synthesis of the olefin-enriched Δ[12]-prostaglandin J natural products **1**–**4** sets a perfect test ground to evaluate the reactivity, chemoselectivity, and functional group compatibility of these newly developed metathesis catalysts.

Figure 1.3.2. Models of Z-and E-selectivity

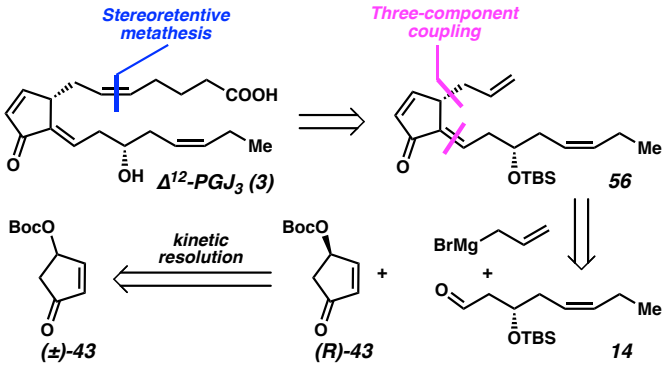


1.4 RESULTS AND DISCUSSIONS

1.4.1 Total Synthesis of Δ^{12}-PGJ$_2$, 15d-PGJ$_2$, Δ^{12}-PGJ$_3$, and 15d-PGJ$_3$

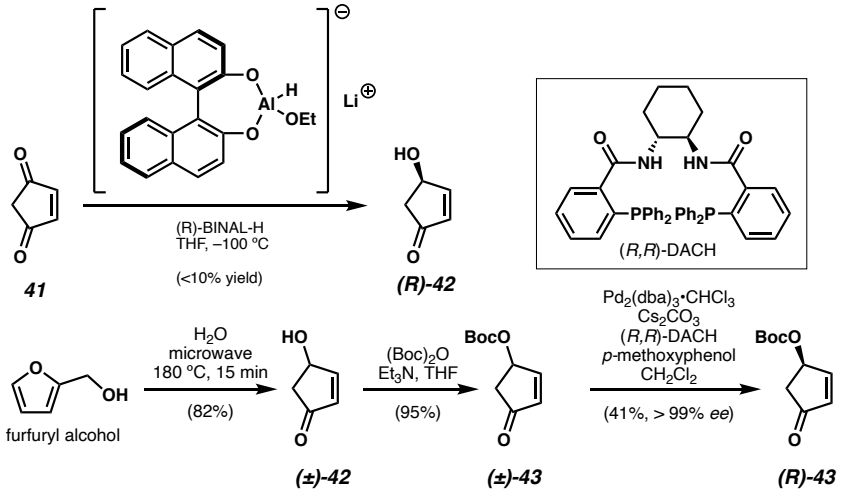
Retrosynthetically, Δ^{12}-PGJ$_3$ (**3**) for example can be simplified into a truncated prostaglandin structure **56** by use of stereoretentive metathesis (Scheme 1.4.1). A three-component coupling strategy[26] can be applied toward the synthesis of **56**, using a relatively simple and commercially available allyl Grignard reagent, ω-chain aldehyde **14**, and a chiral cyclopentenone **(*R*)-43**. The O-Boc group of **(*R*)-43** can be used as a traceless stereoinductive group to set the C8 stereocenter and give the desired enone moiety.[27]

Scheme 1.4.1. Retrosynthetic Analysis



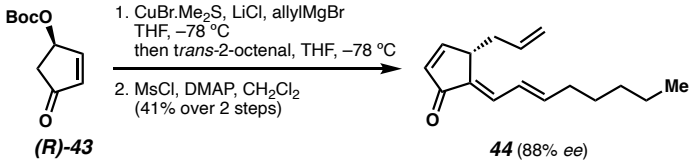
To construct chiral 4-hydroxyl-cyclopentenone **(*R*)-42**, asymmetric reduction with (*R*)-BINAL-H reagent developed by Noyori and co-workers[28] was firstly investigated. However, this reaction resulted in low yield of the alcohol product **(*R*)-42**, and required tedious cryogenic conditions. Alternatively, Boc-protected chiral cyclopentenone **(*R*)-43** was prepared from furfuryl alcohol in a three-step process. Kinetic resolution in the presence of Pd$_2$(dba)$_3$ and (*R,R*)-DACH phenyl Trost ligand furnished the enantiopure product **(*R*)-43** (99% ee) in 2.0 gram scale (Scheme 1.4.2).[29]

Scheme 1.4.2. Synthesis of ***(R)-43***



Then, CuBr•Me_2S and LiCl facilitated the diastereoselective conjugate addition of the allyl magnesium bromide. The enolate formed can then be trapped by the subsequently added commercially available *trans*-2-octenal, and the O-Boc group was eliminated in the course of the aldol reaction to form the desired cyclopentenone motif. The enal functionality of the aldehyde was well tolerated in the aldol step. Elimination with MsCl and DMAP favored 12*E*-product **44** as the major product in reasonable yield (41% over 2 steps, Scheme 1.4.3).

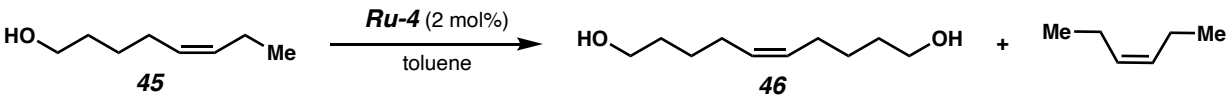
Scheme 1.4.3. Synthesis of ***44*** *by Three-component Coupling*



Stereoretentive metathesis was then evaluated on **44**. Since **44** cannot react with another terminal alkene using stereoretentive metathesis catalysts, we considered a symmetric *Z*-alkene **46** as the coupling partner, which could also be made by homodimerization of readily available **45** through stereoretentive metathesis. However, the homodimerization reaction only gave 50% conversion in the ambient pressure because of the thermodynamic equilibrium (Table 1.4.1, entry 1), and vacuum can be applied to remove the *cis*-3-hexene (b.p. 66–68 ºC) from the reaction

mixture. Performing the reaction under static vacuum gave 62% conversion, in which conditions *cis*-3-hexene still cannot be effectively removed (Table 1.4.1, entry 2). Decreasing the pressure will result in higher conversion (Table 1.4.1, entry 3–5), and using high boiling solvent such as toluene could ensure full conversion. With 1 mol% loading of **Ru-4** as the catalyst, 98% conversion could be achieved by applying dynamic vacuum to remove the by-product, *cis*-3-hexene (Table 1.4.1, entry 6). Next, **44** with an additional 5 mol% catalyst **Ru-4** were added into the reaction mixture, and the alcohol product **47** could be isolated in 95% yield in high Z-selectivity (>99% *Z*). This result established the efficacy of an efficient one-pot, stereoretentive homodimerization/cross-metathesis strategy to build the C5 *Z*-alkene. In contrast, synthesis of PGE_2 and $PGF_{2\alpha}$ using stereoretentive metathesis catalyst **Ru-3** required a large excess of gaseous butene and more complicated operations in the previously reported methylene capping strategy. The full conversion of first homodimerization step is necessary to avoid the formation of byproducts such as **48**. Under standard cross-metathesis conditions with alcohol **45**, the major

Table 1.4.1. Optimization of Homodimerization Reaction



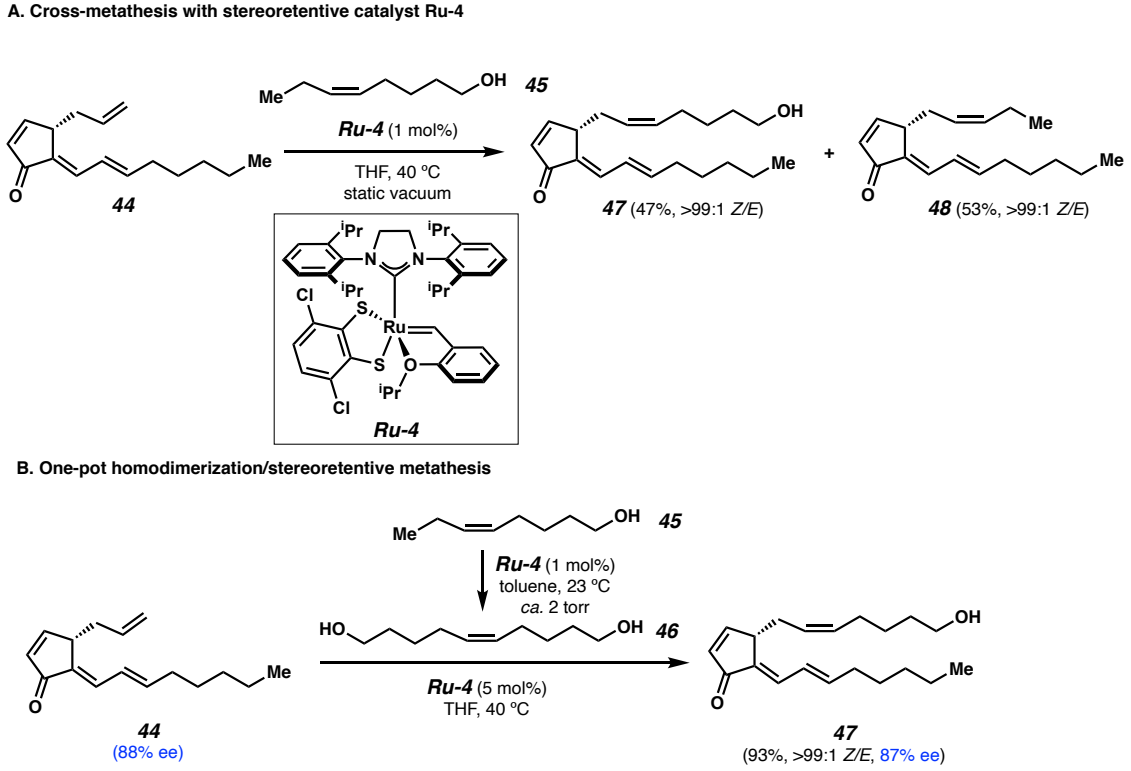
Entry	starting material	solvent	temperature	pressure	conversion[a]	yield
1	0.1 mmol	THF	23 ºC	760 torr	50%	25%
2	0.1 mmol	toluene	40 ºC	static vacuum[c]	62%	31%
3	0.1 mmol	toluene	40 ºC	dynamic vacuum[d] 107 torr	60%	30%
4	0.1 mmol	toluene	40 ºC	dynamic vacuum[d] 45 torr	90%	45%
5	6 mmol	toluene	40 ºC	dynamic vacuum[d] 45 torr	96%	48%
6[b]	6 mmol	toluene	23 ºC	dynamic vacuum[e] (*ca.* 2 torr)	>98%	49%

[a] Conversion was measured by GC analysis
[b] 1 mol% of catalyst was added
[c] Static vacuum was applied after one freeze-pump-thaw cycle of the reaction mixture in the Schlenk tube.
[d] Dynamic vacuum was performed by attaching the Schlenk tube to a vacuum regulator.
[e] The Schlenk tube was directly connected to high vacuum.

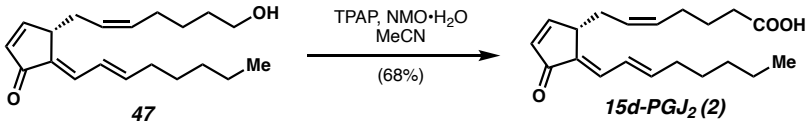
product is **48** from the reaction with propylidene (Scheme 1.4.4), which is hard to be converted further into the desired product **47** by a second cross-metathesis with alcohol **45**, unless dynamic vacuum is applied to effectively remove *cis*-3-hexene from the reaction system.

The C14 *E*-alkene tolerated the reaction, consistent with the much slower reaction of *E*-alkenes with **Ru-4** as seen previously.[22] The enantiopurity of intermediates **44** and **47** was also assessed. Three-component coupling product **44** proceeded with a small loss in enantiopurity (88% ee) from **(*R*)-43** (>99% ee), but the metathesis product **47** was obtained without significant erosion of enantiopurity (87% ee, Scheme 1.4.4). This result demonstrates that stereoretentive metathesis with catalyst **Ru-4** also retained the stereochemistry of the C8 stereocenter. Finally, Ley oxidation[30] of **47** with TPAP and NMO•H_2O gave 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (**2**) in 68% yield (Scheme 1.4.5).

*Scheme 1.4.4. Stereoretentive Metathesis with **44***

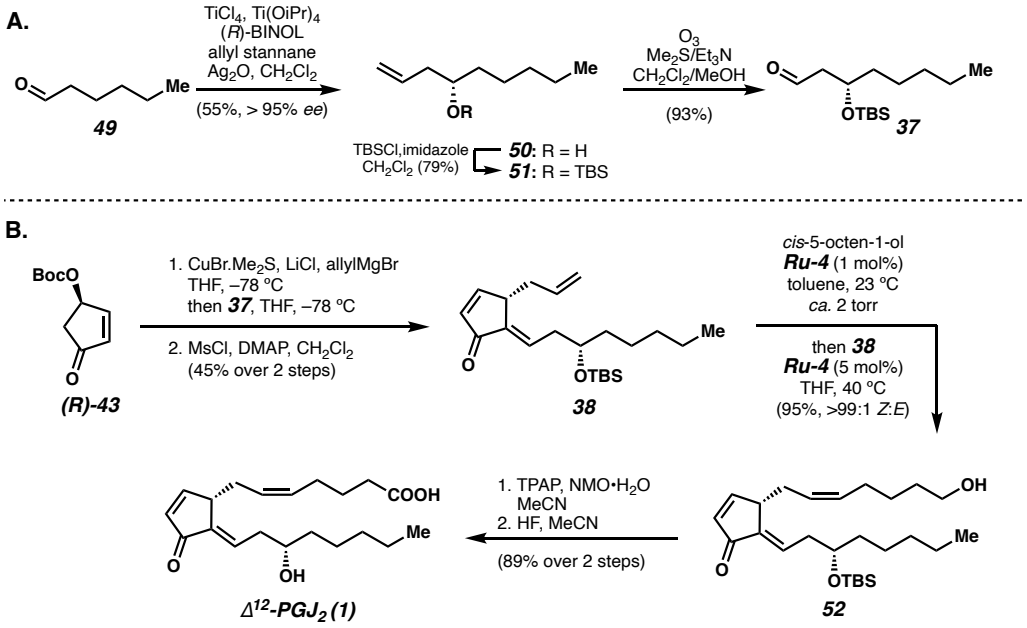


SCHEME 1.4.5. Completion of Synthesis of 15d-PGJ$_2$



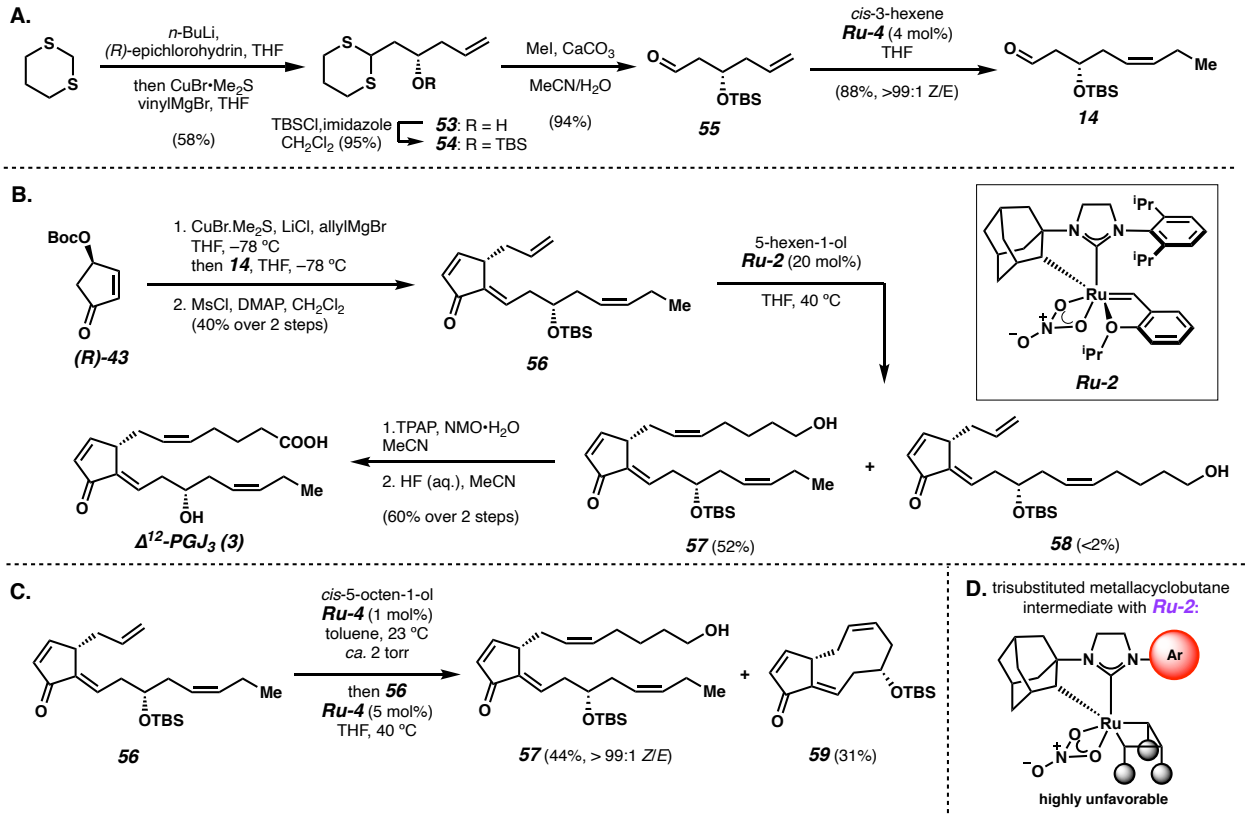
To synthesize Δ^{12}-PGJ$_2$, the ω-chain aldehyde **37** was firstly prepared from 5-hexenal (**49**) through asymmetric Keck allylation,[31] TBS protection, and ozonolysis (Scheme 1.4.6). With all the starting materials in hand, the same three-component coupling sequence was performed to obtain **38** in good yield (45% over 2 steps). **38** was then subjected to the standard one-pot stereoretentive homodimerization/cross-metathesis conditions, and alcohol **52** was obtained in excellent yield (95% yield, Scheme 1.4.6) with high *Z*-selectivity (>99% *Z*). Ley oxidation and deprotection of the TBS group of **52** in aqueous HF furnished the natural product Δ^{12}-PGJ$_2$ (**1**) in 89% yield over the last two steps.

Scheme 1.4.6. Synthesis of Δ^{12}-PGJ$_2$



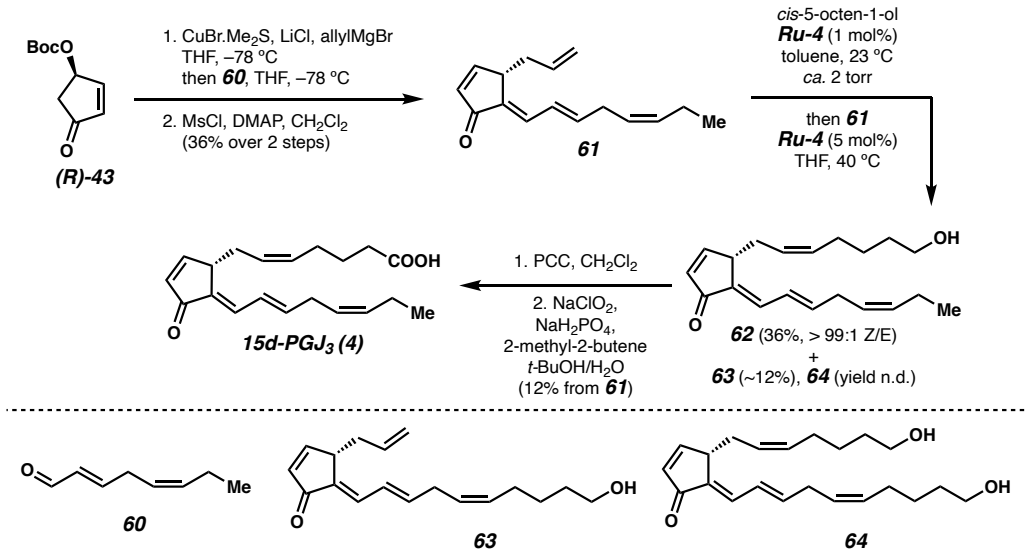
Synthesis of Δ^{12}-PGJ$_3$ (**3**) began with the preparation of the ω-chain aldehyde **14**. We envisioned the *Z*-alkene in **14** could also be generated from stereoretentive metathesis. First, we obtained chiral alcohol **53** through a reported chiral pool strategy with (*R*)-epichlorohydrin as the starting material (Scheme 1.4.7A).[32] TBS protection of the alcohol and subsequent removal of the 1,3-dithiol gave aldehyde **55**. Stereoretentive metathesis of **55** with an excess amount of *cis*-3-hexene using catalyst **Ru-4** (4 mol%) afforded ω-chain aldehyde **14** in good yield (88%) with high *Z*-selectivity (>99% *Z*). The short synthesis of aldehyde **14** proved that a broad range of functional groups, including aldehydes, can be tolerated without protecting group manipulations using stereoretentive catalysts. Then, **56** was synthesized through the standard three-component coupling sequence from **(*R*)-43** (40% yield over 2 steps, Scheme 1.4.7B).

Scheme 1.4.7. Synthesis of Δ^{12}-PGJ$_3$



Surprisingly, fast ring-closing metathesis (RCM) with **Ru-4** yielded **59** as a by-product (31% yield) bearing an unusual 9-membered ring, and the desired alcohol product **57** was obtained in only 44% yield (Scheme 1.4.7C). Alternatively, we chose to use cyclometallated catalyst **Ru-2** to circumvent the crossover of alkene reactivity. Because tri-substituted metallacyclobutane intermediates are highly unfavorable with this cyclometallated catalyst, this pathway can be easily avoided (Scheme 1.4.7D).[33] Chemoselective cross-metathesis of 5-hexen-1-ol with the allyl group of **56** furnished the desired product **57** in good yield (52%) with a trace amount of by-product **58** (less than 2%, Scheme 1.4.7B). The RCM product **59** was not observed under these conditions. The side-reaction of C17 internal *Z*-alkene could be attributed to ethylene produced or the residual ruthenium methylidene species in the solution. Then, Ley oxidation of **57** and deprotection of the TBS group with aqueous HF provided Δ^{12}-prostaglandin J_3 (**3**) in 8 linear steps.

Scheme 1.4.8. Synthesis of 15d-PGJ$_3$



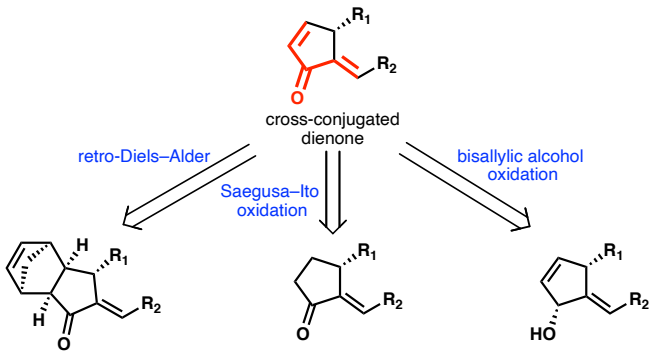
Finally, in the synthesis of 15d-PGJ$_3$ (**4**), crossover of metathesis reactivity between the allyl group and the C17 *Z*-alkene of **61** could also be expected. Standard stereoretentive metathesis conditions with **Ru-4** provided desired product **62** in 36% yield and by-products **63** and **64**

(Scheme 1.4.8). Compared to Δ^{12}-PGJ_3 (**3**) synthesis, where the steric bulk of the OTBS group may be beneficial to achieving good chemoselectivity, **61** has no such steric hindrance. However, no RCM of **61** was observed, possibly due to the ring strain of RCM product. Though **62** could not be separated from **63**, the mixture was subjected to PCC oxidation and Pinnick oxidation conditions, allowing us to isolate 15-deoxy-$\Delta^{12,14}$-prostaglandin J_3 (**4**) (12% yield from **61**).

1.4.2 Improved Synthesis of Enantiopure 15d-PGJ_2

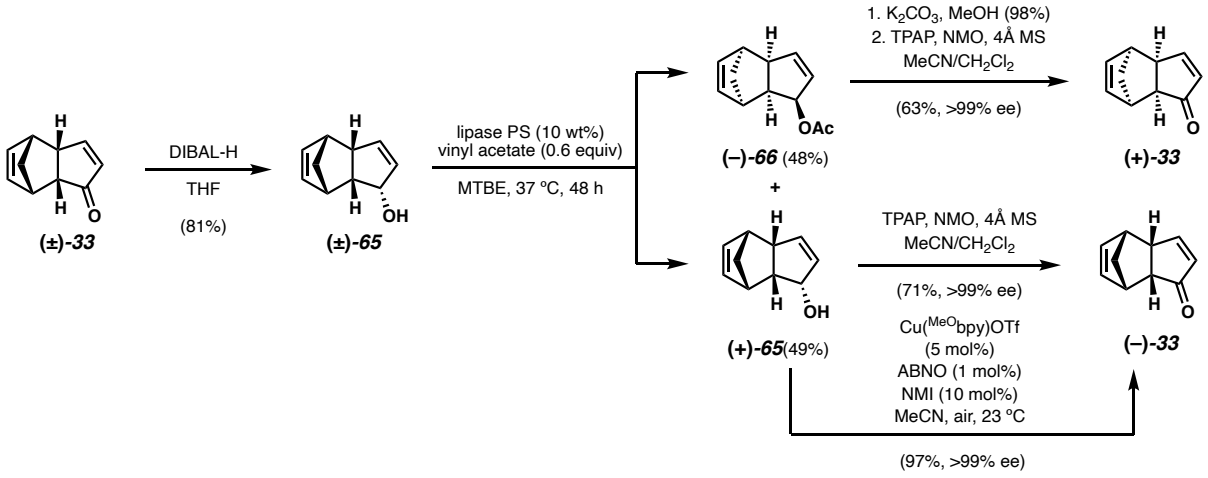
In the previous synthesis, erosion of enantioselectivity was observed in compound **44** after three-component coupling reaction (Scheme 1.4.3, 88% ee), due to the racemization of the relative acidic C8 stereocenter in the reactive 2-alkylidene cyclopentenone moiety. Previous approaches toward these types of cross-conjugated dienone prostaglandins utilized masked forms of this structural motif, and the enone was unmasked in the final step of the syntheses. For example, through retro-Diels–Alder reaction,[34] Saegusa–Ito oxidation,[17g] bisallylic alcohol oxidation[17b] (Scheme 1.4.9). We hypothesize that racemization could be attenuated in the masked enone motif above. Retro-Diels-Alder reaction is an appealing approach since the 3-oxodicyclopentadiene starting material is readily available, which was also utilized in Nicolaou's recent synthesis of Δ^{12}-PGJ_2 (Scheme 1.2.4).[18] The C8 stereocenter was introduced by stereoselective conjugate addition of enantiomerically pure enone **(+)-33** with allyl magnesium bromide, CuI and LiCl in the presence of TMSCl. Then, it was directly unmasked with thermally induced retro-Diels−Alder reaction, furnished enantiopure intermediate **34** in 77% yield over the two steps. We proposed that this unmasking step could be performed after the three-component coupling step, to have a better strategic efficiency and avoid the relatively volatile intermediate **34**.

Scheme 1.4.9. Reported Synthetic Strategies to Cross-Conjugated Dienone



Several approaches have been reported to access chiral 3-oxodicyclopentadiene moiety, including enzymatic resolution by lipase,[35] and keto reductases,[36] Co-catalyzed asymmetric intermolecular Pauson−Khand reaction (PKR) of norbornadiene and alkynes,[37] and kinetic resolution via Cu-catalyzed 1,3-dipolar cycloaddition reactions.[38] Lipase-mediated enzymatic resolution was performed to synthesize enantiomerically pure **33**, since racemic *endo*-3-oxodicyclopentadiene **(±)-33** can be readily obtained through one-pot allylic photooxidation of dicyclopentadiene catalyzed by tetraphenylporphyrin (TPP).[39] Then, the *endo*-alcohol **(±)-65** was obtained from DIBAL-H reduction in excellent yield. Kinetic resolution was successfully performed on 4.0 gram scale when **(±)-65** was treated with vinyl acetate (0.6 equivalent) in *tert*-butyl methyl ether in the presence of commercially available lipase PS-on-celite (10% w/w of the substrate). The *endo*-acetate **(–)-66** was isolated in 48% yield, leaving the *endo*-alcohol **(+)-65** in 49% yield after 48 h at 37 ºC. The *endo*-acetate **(–)-66** was treated with 1 equivalent of K_2CO_3 in methanol, which liberated the *endo*-alcohol **(–)-65**. Both enantiopure **(+)-** and **(–)-65** can be obtained (>99% ee) by oxidation of *endo*-alcohol enantiomers by TPAP and NMO, in the presence of 4 Å molecular sieves in CH_2Cl_2/MeCN.[40] Alternatively, **(+)-65** could also be oxidized in the reaction conditions reported by Stahl and coworkers,[41] which resulted in higher yield to obtain **(–)-33** (97% yield, Scheme 1.4.10).

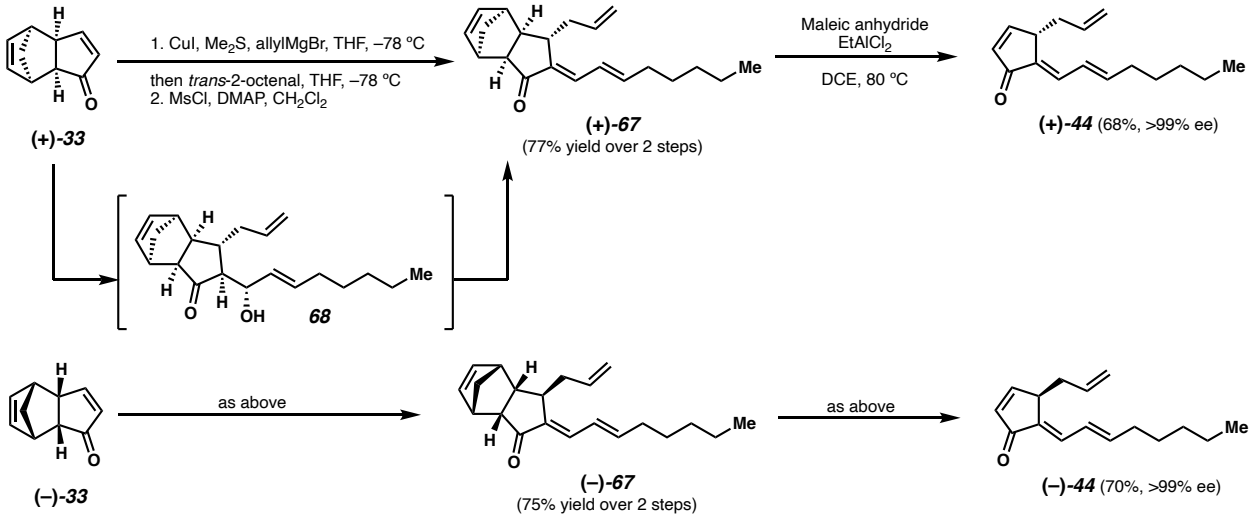
Scheme 1.4.10. Enzymatic Resolution



In previous reports by Nicolaou and others,[12,14,16,18] aldol reaction in the presence of LDA usually resulted in moderate yield (30–40%), although the first deprotonation step is selective at cyclopentenone to form the enolate. In our improved route, the overall yields were largely improved in the three-component coupling step. In the presence of CuI and Me_2S, allyl Gringard reagent firstly can form allyl cuprate, which undergoes regio- and stereoselective conjugate addition to the enone to form an enolate. Then, the resulting enolate can be trapped by the subsequent addition of an aldehyde, which could ensure the full conversion of starting material and reduce the by-product formation that occurred in previously reported aldol reactions with LDA. The reaction gave a mixture of aldol diastereomers, with adduct **68** identified as the major diastereomer, indicating an *anti*-aldol process. After elimination with MsCl and excess amount of DMAP, the mixture of diastereomers can be converted to the thermodynamically favored *E*-alkene in good yield (77% yield for **(+)-67**, 75% yield for **(–)-67**). Then, both enantiomers of **44** can be readily obtained in high enantioselectivity (>99% ee, Scheme 1.4.11), by Lewis acid-catalyzed retro-Diels-Alder reaction developed by Grieco,[42] using $EtAlCl_2$ and stoichiometric amount of maleic anhydride at a lower temperature (80 ºC) than the thermally induced conditions (> 160 ºC). In the previous synthesis with **(*R*)-43**, racemization was observed because the C8 position is

adjacent to enone and C8-H presents certain acidity, which is prone to racemize in the presence of base. However, when the enone was masked with the cyclopentadiene motif, the proton in the corresponding stereocenter is less prone to deprotonation. In addition, this reaction sequence was performed on a larger scale (1.6 gram starting material), and enantio-enriched enone **(+)-33** was used as the limiting reagent. Excess amount of **(*R*)-43** was required in the previous report of three-component coupling reactions because the O-Boc group is labile and **(*R*)-43** was converted to undesired by-products, and the reaction scale was limited (up to 200 mg starting material).

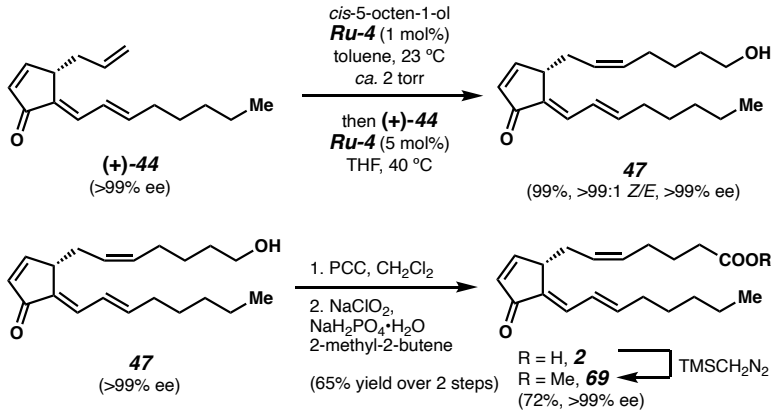
Scheme 1.4.11. Stereodivergent Three-component Coupling



Finally, **(+)-44** was carried on to the one-pot homodimerization/steroretentive metathesis reaction, and the primary alcohol product **47** was obtained in 99% yield and >99% ee with high *Z*-selectivity (>99:1 *Z*/*E*, Scheme 1.4.12). Then, oxidation of **47** with PCC, and then Pinnick oxidation gave rise to the enantiopure 15d-PGJ_2 (**2**) in 41.0 mg scale (65% yield over 2 steps). The enantiopurity was confirmed by synthesizing the methyl ester derivative of **2** with (trimethylsilyl)diazomethane, which **69** was obtained in 72% yield and 99% ee. This route presents a robust and scalable strategy to synthesize 15d-PGJ_2 and the enantioselectivity was

retained throughout the synthesis. In principle, this strategy can be applied to the synthesis of other Δ^{12}-PGJ analogs to obtain those compounds with high enantiopurity for biological studies.

Scheme 1.4.12. Synthesis of Enantiopure 15d-PGJ$_2$



1.5 CONCLUSIONS

In conclusion, a concise and convergent synthesis of four Δ^{12}-prostaglandin J natural products in shorter sequences (7–8 steps in the longest linear sequences) was developed, empowered by stereoretentive and stereoselective metathesis. Furthermore, the reactivity, chemoselectivity, and functional group compatibility of stereoretentive metathesis was evaluated. This study should inspire further practical applications of stereoselective metathesis, such as a facile one-pot stereoretentive homodimerization/cross-metathesis strategy to introduce *Z*-alkenes with excellent geometric control. An improved synthesis was also developed starting with enzymatic resolution of 3-oxodicyclopendadiene. Racemization can be avoided in the three-component coupling step using the chiral 3-oxodicyclopendadiene starting material and enantiopure 15d-PGJ$_2$ (>99% ee) was obtained. The modularity and expediency of this chemistry opens the synthesis of other prostaglandins and analogues to enable SAR studies in cancer treatment. With the well-defined kinetically *Z*/*E*-selective catalysts that have been developed to overcome the inherent thermodynamic preference of alkene product geometry, olefin metathesis can play a pivotal role in the synthesis design.

1.6 EXPERIMENTAL METHODS AND ANALYTICAL DATA

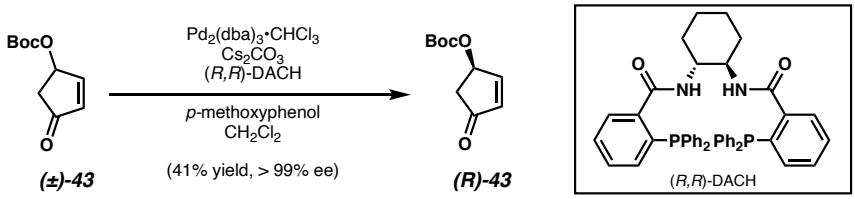
1.6.1 Materials and Methods

Unless noted in the specific procedure, reactions were performed in flame-dried glassware under argon atmosphere. All metathesis reactions were carried out under air-free conditions in dry glassware in a Vacuum Atmospheres Glovebox filled with N_2. General solvents were purified by passing through solvent purification columns. Commercially available substrates were used as received. All solvents and substrates were sparged with Ar before bringing into the glovebox and filtered over basic alumina (Brockmann I) prior to use. Reaction progress was monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralcel (IC) column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 210 nm. GC conversion data was obtained using an HP-5 capillary column with an Agilent 6850 FID gas chromatograph. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 spectrometer (500 MHz and 126 MHz, respectively), a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively), or a Varian Mercury 300 spectrometer (300 MHz and 75 MHz, respectively) and are reported in terms of chemical shift relative to residual $CHCl_3$ (δ 7.26 and δ 77.16 ppm, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration).

Abbreviations are used as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = complex multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using neat samples on ATR diamond, and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra HRMS were acquired from the Caltech Mass Spectral Facility using fast-atom bombardment (FAB+), electrospray ionization (TOF ES+) or electron impact (EI+). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

1.6.2 Experimental Procedures

Preparation of enone *(R)*-43:



Under argon atmosphere, a 500 mL flask was charged with **(±)-43** (prepared through procedures by Reiser and co-workers[27]) (5.02 g, 25.4 mmol, 2.0 equiv) in CH_2Cl_2 (100 mL), *p*-methoxyphenol (1.57 g, 12.7 mmol, 1.0 equiv) and Cs_2CO_3 (1.22 g, 3.75 mmol, 0.296 equiv) was added and the solution was cooled to 0 ºC. In another 100 mL flask, $Pd_2(dba)_3$•$CHCl_3$ (131 mg, 0.127 mmol, 0.01 equiv) and ligand (*R,R*)-DACH (306 mg, 0.44 mmol, 0.035 equiv) in CH_2Cl_2 (50 mL) was stirred until the initially purple solution turned yellow brown (4–5 min), and the catalyst solution was transferred to the 500 mL flask through a cannula. The solvent was removed under reduced pressure after 2.5 h stirring at 0 ºC. The residue was purified by flash chromatography (hexanes/EtOAc 9:1 to 6:1) to give ***(R)*-43** (2.06 g, 41%, > 99% ee confirmed by chiral SFC analysis).

TLC (4:1 hexanes/EtOAc): R_f= 0.4 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.32 (dd, *J* = 5.7, 1.3 Hz, 1H), 5.70 (dtd, *J* = 6.2, 2.3, 1.3 Hz, 1H), 2.82 (dd, *J* = 18.7, 6.4 Hz, 1H), 2.39 (dd, *J* = 18.7, 2.3 Hz, 1H), 1.49 (s, 9H).

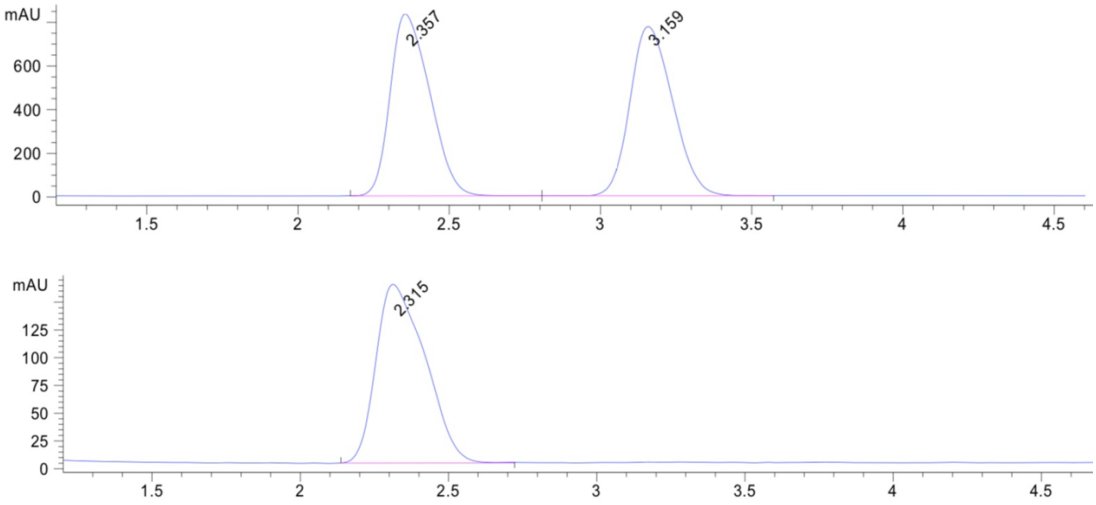
^{13}C NMR (101 MHz, $CDCl_3$): δ 204.7, 158.7, 152.8, 137.2, 83.4, 74.3, 41.1, 27.8.

FTIR (ATR): 2981, 2937, 1722, 1591, 1475, 1459, 1395, 1369, 1334, 1272, 1253, 1152, 1104, 994, 840, 791 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{10}H_{15}O_4$ $[M+H]^+$ 199.0965, found: 199.0986.

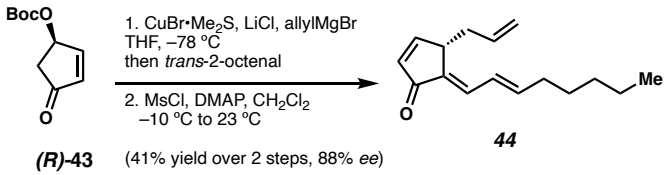
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$: +78.7° (c = 1.0, $CHCl_3$).

SFC Conditions: 3% IPA, 4.0 mL/min, Chiralcel IC column, λ = 210 nm, t_R (min): major = 2.36, minor = 3.16



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.315	BB	0.1948	1860.09827	161.00098	100.0000

Preparation of 44:



A 25 mL flask was flame dried and charged with CuBr•Me_2S (195 mg, 0.95 mmol, 3.0 equiv) and LiCl (42 mg, 1 mmol, 3.2 equiv) in a nitrogen-filled glove box. The flask was sealed with septum and brought out of glove box, and was heated under vacuum to remove residue water. Anhydrous THF (10 mL) was added, and the solution was vigorously stirred for 10 minute at 23 ºC until a yellow homogeneous solution was formed. At –78ºC, allylmagnesium bromide (0.9 mL, 1.0 M solution in THF, 0.9 mmol, 2.8 equiv) was added slowly. The reaction mixture was stirred at –78 ºC for 1 hour and a solution of ***(R)*-43** (188 mg, 0.95 mmol, 3.0 equiv) in THF (1 mL) was added slowly. After 30 minutes stirring at the same temperature, a solution of *trans*-2-octenal (40 mg, 0.32 mmol, 1.0 equiv) in THF (1 mL) was added slowly. The reaction was stirred for additional 2 hours at –78 ºC before a solution of saturated NH_4Cl and NH_3•H_2O (10 mL, 9:1 NH_4Cl/NH_3•H_2O) was added. The biphasic solution was vigorously stirred until a homogeneous dark blue solution was formed in aqueous phase. The phases were separated and the organic phase was washed with 10 mL saturated NH_4Cl solution. The combined aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and was concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 15:1) to give a mixture of diasteromers of the aldol products (57 mg, 0.23 mmol).

In a 25 mL flask, the crude aldol product was dissolved in CH_2Cl_2 (6 mL) and cooled to –10 ºC. DMAP (421 mg, 3.45 mmol, 15.0 equiv) and MsCl (53 μL, 0.69 mmol, 3.0 equiv) was added sequentially. The reaction mixture was slowly warmed to 23 ºC and stirred for 2 h before diluted

with 10 mL EtOAc and washed with 1 M HCl (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and was concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 15:1) to give **44** (30 mg, 41% yield over 2 steps, 88% ee by chiral HPLC analysis) as a colorless liquid.

TLC (4:1 hexanes/EtOAc): R_f = 0.56 (UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.95 (dt, *J* = 10.7, 1.2 Hz, 1H), 6.35 (dd, *J* = 6.0, 1.8 Hz, 1H), 6.33 – 6.15 (m, 2H), 5.81 – 5.64 (m, 1H), 5.11 – 5.01 (m, 2H), 3.60 (ddq, *J* = 8.5, 4.1, 1.9 Hz, 1H), 2.73 – 2.58 (m, 1H), 2.24 (dddd, *J* = 13.4, 9.7, 6.8, 1.5 Hz, 3H), 1.54 – 1.37 (m, 2H), 1.38 – 1.22 (m, 4H), 0.89 (t, 3H, *J* = 6.9 Hz).

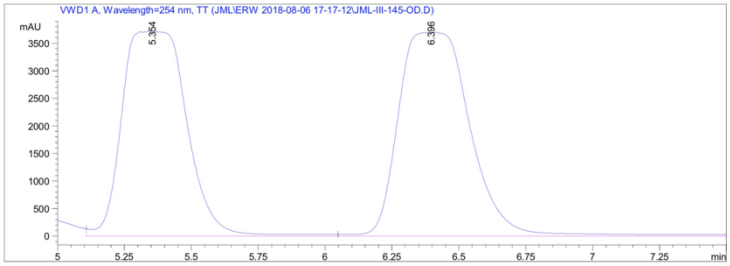
^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 160.6, 147.1, 135.4, 134.9, 134.3, 131.8, 125.7, 117.8, 43.2, 37.4, 33.6, 31.5, 28.6, 22.6, 14.1.

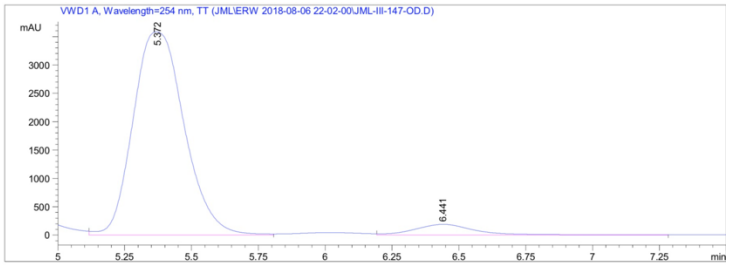
FTIR (ATR): 2954, 2928, 2859, 1699, 1642, 1581, 1458, 1344, 1194, 994, 918, 829, 734 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{16}H_{21}O$ $[M+H-H_2]^+$ 229.1586, found: 229.1581.

$[\alpha]_D^{23}$: +65.4° (c = 1.0, $CHCl_3$).

HPLC Conditions: 10% IPA, 1.0 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 5.37, minor = 6.44

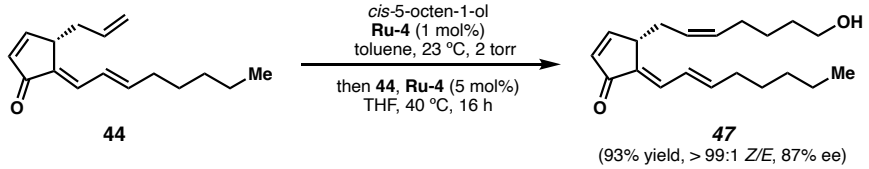




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.372	VV	0.2135	4.77187e4	3584.78198	93.8133
2	6.441	VV	0.2467	3146.90283	188.99858	6.1867

Preparation of 47:

A. One-pot homodimerization/stereoretentive metathesis method



In a nitrogen-filled glovebox, *cis*-5-octen-1-ol (113 mg, 0.88 mmol, 8.0 equiv) was dissolved in toluene (1 mL) in a 50 mL Schlenk flask and a solution of catalyst **Ru-4** (7.5 mg, 8.8 μmol, 1 mol%) in THF (0.6 mL) was added. The Schlenk flask was sealed and brought out of the glovebox, and then connected to high vacuum. The valve was gradually opened (*Caution: open slowly and stir well to avoid splashing*). After 15 minutes stirring, the flask was refilled with argon and sealed, and was brought back into the glovebox. The residue was diluted with THF (0.5 mL), and an aliquot was taken for GC analysis (conversion of homodimerization step was >98% by GC analysis). A solution of **44** (25 mg, 0.11 mmol, 1.0 equiv) in THF (0.5 mL) was added into the Schlenk flask and an additional portion of catalyst **Ru-4** (4.6 mg, 5.5 μmol, 5 mol%) solution in THF (0.2 mL) was added. The Schlenk flask was sealed and brought out of glovebox. The reaction was stirred for 24 h at 40 ºC before a few drops of ethyl vinyl ether were added. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 2:1) to give **47** (31 mg, 93%, >99:1 *Z/E*, 87% ee by chiral HPLC analysis).

TLC (4:1 hexanes/EtOAc): R_f = 0.2 (UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.95 (dt, *J* = 11.0, 1.3 Hz, 1H), 6.35 (dd, *J* = 6.0, 1.8 Hz, 1H), 6.34 – 6.19 (m, 2H), 5.52 – 5.44 (m, 1H), 5.38 – 5.30 (m, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 3.60 – 3.55 (m, 1H), 2.60 (dddd, *J* = 14.0, 6.2, 4.3, 1.4 Hz, 1H), 2.30 (dtd, *J* = 14.4, 8.6, 1.2 Hz, 1H), 2.25 – 2.17 (m, 2H), 2.01 (qd, *J* = 7.3, 1.4 Hz, 2H), 1.59 – 1.49 (m, 2H), 1.48 – 1.37 (m, 5H), 1.34 – 1.29 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H).

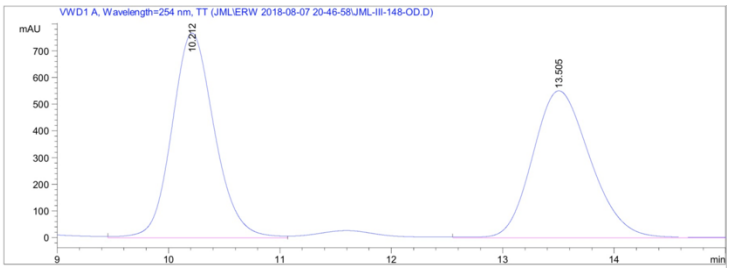
^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 160.9, 147.0, 135.4, 135.3, 132.6, 131.8, 125.8, 125.3, 62.9, 43.7, 33.6, 32.5, 31.5, 30.9, 28.6, 27.2, 25.8, 22.6, 14.2.

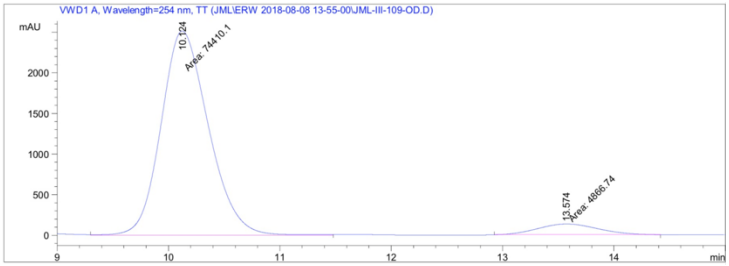
FTIR (ATR): 3445, 2960, 2930, 2862, 1690, 1629, 1580, 1447, 1264, 1207, 1054, 979, 732 cm^{-1}.

HRMS (TOF, ES+, m/z): calc'd for $C_{20}H_{31}O_2$ $[M+H]^+$ 303.2319, found: 303.2320.

$[\alpha]_D^{23}$: +115.8° (c = 0.5, $CHCl_3$).

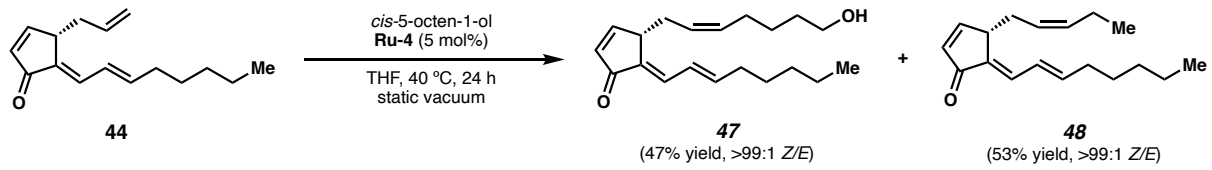
HPLC Conditions: 10% IPA, 1.0 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 10.12, minor = 13.57



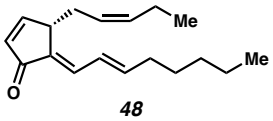


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.124	MM	0.4934	7.44101e4	2513.44019	93.8611
2	13.574	MM	0.6177	4866.74170	131.31406	6.1389

B. Cross-metathesis method



In a nitrogen-filled glovebox, **44** (49 mg, 0.21 mmol, 1.0 equiv) and *cis*-5-octen-1-ol (205 mg, 1.6 mmol, 7.6 equiv) was dissolved in THF (0.5 mL) in a 1-dram vial, and the solution was transferred to a 50 mL Schlenk flask. A solution of catalyst **Ru-4** (8.5 mg, 10 μmol, 5 mol%) in THF (0.5 mL) was added. The Schlenk flask was sealed and brought out of the glovebox, and freeze-pump-thaw for one time to keep it under static vacuum. The reaction was stirred for 16 h at 40 ºC before quenched with a few drops of ethyl vinyl ether. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 10:1 to 2:1) to give **47** (29 mg, 53%, >99:1 *Z/E*) and **48** (30 mg, 47%, >99:1 *Z/E*) as two major products.



48

TLC (4:1 hexanes/EtOAc): R_f= 0.6 (UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (ddd, *J* = 5.9, 2.6, 1.0 Hz, 1H), 6.95 (dt, *J* = 11.2, 1.2 Hz, 1H), 6.39 – 6.17 (m, 3H), 5.53 – 5.43 (m, 1H), 5.34 – 5.24 (m, 1H), 3.56 (ddq, *J* = 8.6, 4.1, 2.0 Hz, 1H), 2.70 – 2.47 (m, 1H), 2.34 – 2.17 (m, 3H), 1.99 (pd, *J* = 7.5, 1.6 Hz, 2H), 1.46 (p, *J* = 7.3 Hz, 2H), 1.31 (tt, *J* = 5.6, 2.8 Hz, 4H), 0.93 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H).

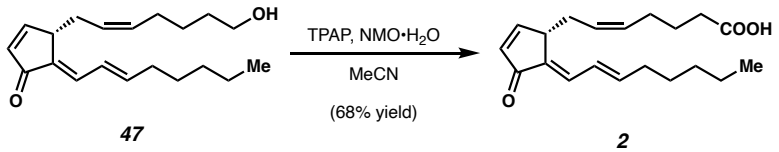
^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 160.9, 146.8, 135.4, 134.6, 131.7, 125.8, 124.3, 43.8, 33.6, 31.5, 30.8, 28.6, 22.6, 20.8, 14.3, 14.1.

FTIR (ATR): 2959, 2927, 2856, 2360, 1693, 1632, 1579, 1459, 1376, 1337, 1294, 1203, 1100, 1069, 1020, 976, 923, 867, 834, 805, 728, 668 cm^{-1}.

HRMS (TOF, ES+, m/z): calc'd for $C_{20}H_{31}O_2$ $[M+H]^+$ 259.2056, found: 259.2207.

$[\alpha]_D^{23}$**:** +210.8° (c = 1.0, $CHCl_3$).

Preparation of 15-deoxy-Δ^{12,14}-prostaglandin J$_2$ (2):



47 *2*

To a stirred solution of **47** (14 mg, 0.046 mmol, 1.0 equiv) in MeCN (0.5 mL) was added NMO•H_2O (65 mg, 0.46 mmol, 10.0 equiv). Tetrapropylammonium perruthenate (1.7 mg, 4.6 μmol, 0.1 equiv) was added until NMO•H_2O was fully dissolved and the reaction was stirred at 23 ºC for 3 hours. The reaction mixture was stirred for 3 hours and the solvent was removed *in vacuo*. The residue was loaded onto a silica gel column, flushed with CH_2Cl_2 then CH_2Cl_2/MeOH (20:1). 15-deoxy-Δ^{12,14}-prostaglandin J_2 (**2**) was obtained as a colorless oil (10 mg, 68% yield).

TLC (100% EtOAc): R_f= 0.70 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.95 (d, *J* = 11.0 Hz, 1H), 6.38 – 6.35 (m, 1H), 6.33 – 6.20 (m, 2H), 5.50 – 5.33 (m, 2H), 3.59 (ddd, *J* = 8.4, 4.1, 2.2 Hz, 1H), 2.59 (m, 1H), 2.36 – 2.19 (m, 5H), 2.05 (q, *J* = 7.3 Hz, 2H), 1.68 (quint, *J* = 7.5 Hz, 2H), 1.50 – 1.41 (m, 2H), 1.34 – 1.28 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 177.9, 160.8, 147.2, 135.5, 135.1, 131.9, 131.5, 126.2, 125.8, 43.6, 33.6, 33.2, 31.6, 30.8, 28.6, 26.7, 24.6, 22.6, 14.2.

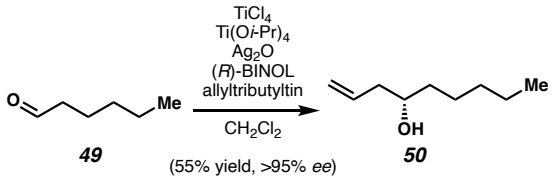
FTIR (ATR): 2960, 2928, 2850, 1708, 1692, 1629, 1456, 1265, 1207, 978, 734, 703 cm^{-1}.

HRMS (TOF, ES+, m/z): calc'd for $C_{20}H_{29}O_3$ $[M+H]^+$ 317.2111, found: 317.2127.

$[\alpha]_D^{23}$**:** +106.2° (c = 0.2, $CHCl_3$).

Spectral data (^{1}H NMR, ^{13}C NMR, HRMS) matched with the published data.[17b,d,g,h]

Preparation of (*S*)-non-1-en-4-ol (50):



Following the procedure by Yadav and co-workers[43], to a stirred solution of $TiCl_4$ (1.0 M solution in CH_2Cl_2, 2.5 mL, 2.5 mmol) in CH_2Cl_2 (50 mL) was added dried Ti(O*i*-Pr)$_4$ (2.24 mL,7.5 mmol) at 0 °C under argon. The solution was warmed to 23 ºC and stirred for 1 h, then Ag_2O (1.15 g, 5.0 mmol) was added, and the mixture was stirred for 5 h with the exclusion of direct light by aluminum foil. The reaction mixture was diluted with CH_2Cl_2 (80 mL) and (*R*)-binaphthol (2.86 g, 10 mmol) was added at 23 ºC. After 2 h, the reaction mixture was cooled to –15 °C and hexanal (5.0 g, 50 mmol) and allyltributyltin (17 mL, 55 mmol) was added sequentially, then the reaction mixture was warmed to 0 °C. After 8 h, saturated $NaHCO_3$ (50 mL) was added. The aqueous phase was extracted with diethyl ether (2 × 250 mL). The combined organic phases were washed with brine (1 × 200 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (SiO_2, 15:1 hexanes/EtOAc) afforded compound **50** as a colorless oil (3.94 g, 55% yield, > 95% ee by Mosher-ester analysis).

TLC (10:1 hexanes/EtOAc): R_f= 0.22 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (dddd, *J* = 17.6, 9.4, 7.8, 6.5 Hz, 1H), 5.17 – 5.03 (m, 2H), 3.62 (dtd, *J* = 8.0, 4.0, 2.4 Hz, 1H), 2.28 (dddt, *J* = 13.7, 6.8, 4.3, 1.3 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.74 (d, *J* = 3.6 Hz, 1H), 1.50 – 1.35 (m, 3H), 1.35 – 1.21 (m, 5H), 0.87 (t, *J* = 6.8 Hz, 3H).

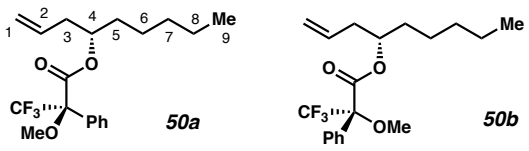
^{13}C NMR (101 MHz, $CDCl_3$): δ 135.1, 118.1, 70.8, 42.0, 36.9, 32.0, 25.5, 22.7, 14.1.

FTIR (ATR): 3355, 3077, 2956, 2929, 2859, 1641, 1467, 1435, 1378, 1124, 1027, 994, 911, 865, 725 cm^{-1}.

HRMS (EI+, m/z): calc'd for $C_9H_{18}O$ $[M]^+$ 142.1352, found: 142.1372.

$[\alpha]_D^{23}$**:** –7.2° (c = 1.0, $CHCl_3$).

Mosher-ester analysis of **50**:



To a stirred solution of **50** (21 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) in a 4 mL vial was added pyridine (0.1 mL, 1.24 mmol, 8.0 equiv) and *(S)*-(+)-Mosher chloride (100 mg, 0.40 mmol, 2.7 equiv) at 25 °C. After stirring for 2 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and saturated NH_4Cl solution (3 mL) was added. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were concentrated after drying over magnesium sulfate. (*R*)-MTPA ester **50a** was obtained through column chromatography (SiO_2, 20:1 hexanes/EtOAc) as a colorless oil (50 mg, 94 %).

Compound **50b** was prepared in the same manner and on the same scale as above using *(R)*-(−)-Mosher chloride. (*S*)-MTPA ester **50b** was obtained through column chromatography (SiO_2, hexanes/EtOAc, 20:1) as a colorless oil (51 mg, 96 %).

(*R*)-MTPA ester **50a**:

TLC (10:1 hexanes/EtOAc): R_f= 0.57 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.50 (m, 2H), 7.43 – 7.31 (m, 3H), 5.73 – 5.56 (m, 1H), 5.14 (dq, *J* = 7.2, 5.7 Hz, 1H), 5.06 – 4.98 (m, 2H), 3.55 (q, *J* = 1.3 Hz, 3H), 2.35 (dddd, *J* = 6.2, 5.0, 2.5, 1.3 Hz, 2H), 1.71 – 1.54 (m, 2H), 1.39 – 1.22 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 133.0, 132.5, 129.7, 128.4, 127.6, 123.5 (q, *J* = 288.6 Hz), 118.4, 84.7 (q, *J* = 27.5 Hz), 76.7, 55.6, 38.2, 33.4, 31.6, 25.0, 22.6, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ –71.3.

FTIR (ATR): 2955, 2934, 2861, 1743, 1643, 1612, 1506, 1451, 1258, 1166, 1121, 1081, 1020, 993, 912, 823, 764, 732, 716, 696, 648 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{19}H_{26}O_3F_3$ $[M+H]^+$ 359.1829, found: 359.1839.

(*S*)-MTPA ester **50b**:

TLC (10:1 hexanes/EtOAc): R_f = 0.57 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.52 (m, 2H), 7.43 – 7.34 (m, 3H), 5.76 (ddt, *J* = 16.1, 10.4, 7.0 Hz, 1H), 5.16 (dt, *J* = 10.8, 5.2 Hz, 1H), 5.13 – 5.08 (m, 2H), 3.56 (q, *J* = 1.3 Hz, 3H), 2.42 (ddt, *J* = 7.3, 6.1, 1.3 Hz, 2H), 1.65 – 1.49 (m, 2H), 1.27 – 1.10 (m, 6H), 0.84 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 133.4, 132.6, 129.6, 128.4, 127.5, 123.5 (q, *J* = 288.6 Hz), 118.5, 84.6 (q, *J* = 27.5 Hz), 76.7, 55.7, 38.5, 33.3, 31.6, 24.6, 22.6, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ –71.3.

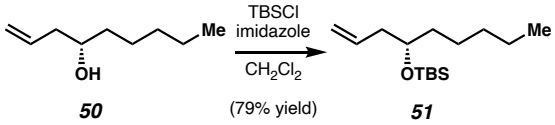
FTIR (ATR): 2960, 2934, 2861, 1742, 1643, 1498, 1451, 1257, 1167, 1121, 1081, 1019, 992, 912, 824, 764, 732, 717, 696, 648 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{19}H_{26}O_3F_3$ $[M+H]^+$ 359.1829, found: 359.1845.

Table 1.6.1. Comparison of ^{1}H NMR Data for (R)- and (S)-MTPA Esters

Proton	***(S)*-MTPA ester 50b**	***(R)*-MTPA ester 50a**	**Δδ: *(S)-(R)***
1	5.01	5.11	0.1
2	5.64	5.76	0.12
3	2.35	2.42	0.07
4	5.14	5.16	0.02
5	1.62	1.57	–0.05
6-8	1.28	1.20	–0.08
9	0.88	0.84	–0.04

Preparation of 51:



To a stirred solution of **50** (2.0 g, 14 mmol) in CH_2Cl_2 (60 mL) was added imidazole (2.86 g, 42 mmol, 3.0 equiv) and TBSCl (4.22 g, 28 mmol, 2.0 equiv). Saturated NH_4Cl solution (50 mL) was added after stirring overnight. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, 20:1 hexanes/EtOAc) gave **51** as a colorless oil (2.85 g, 79% yield).

TLC (10:1 hexanes/EtOAc): R_f= 0.85 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.5, 10.4, 7.1 Hz, 1H), 5.08 – 4.99 (m, 2H), 3.68 (quint, *J* = 5.7 Hz, 1H), 2.21 (dddt, *J* = 6.8, 5.3, 3.9, 1.3 Hz, 2H), 1.48 – 1.22 (m, 8H), 0.94 – 0.85 (m, 12H), 0.05 (s, 3H), 0.05 (s, 3H).

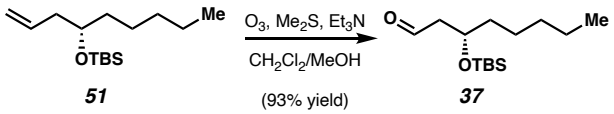
^{13}C NMR (101 MHz, $CDCl_3$): δ 135.7, 116.7, 72.2, 42.1, 37.0, 32.2, 26.1, 25.2, 22.8, 18.3, 14.2, –4.2, –4.4.

FTIR (ATR): 2956, 2929, 2857, 1641, 1472, 1463, 1361, 1255, 1127, 1049, 1005, 939, 910, 834, 807, 772, 664 cm^{-1}.

HRMS (EI+, m/z): calc'd for $C_{15}H_{31}OSi$ $[M+H-H_2]^+$ 255.2138, found: 255.2174.

$[\alpha]_D^{23}$: –15.7° (c = 1.0, $CHCl_3$).

Preparation of aldehyde 37:



To a stirred solution of **51** (1.6 g, 6.25 mmol) in CH_2Cl_2 (30 mL) and MeOH (30 mL) was bubbled with O_3 through a gas dispersion tube. When the color of the solution turned blue, dimethyl sulfide (13.2 mL) and triethylamine (1.2 mL) was added. The solution was stirred overnight and was concentrated under reduced pressure. Column chromatography (SiO_2, 20:1 hexenes/EtOAc) afforded **37** as a colorless oil (1.5 g, 93%)

TLC (4:1 hexanes/EtOAc): R_f= 0.77 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (td, *J* = 2.6, 0.7 Hz, 1H), 4.17 (quint, *J* = 5.8 Hz, 1H), 2.51 (ddd, *J* = 5.7, 2.6, 0.7 Hz, 2H), 1.56 – 1.41 (m, 2H), 1.37 – 1.22 (m, 6H), 0.96 – 0.83 (m, 12H), 0.07 (s, 3H), 0.05 (s, 3H).

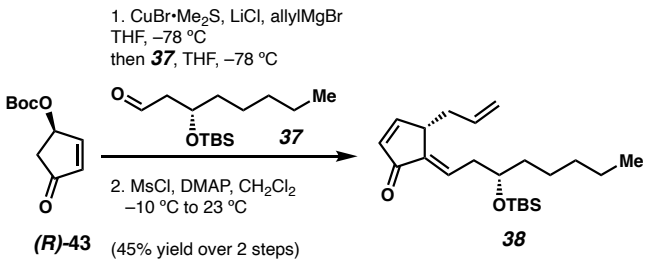
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.7, 68.4, 51.0, 38.0, 31.9, 25.9, 25.0, 22.7, 18.1, 14.2, –4.3, –4.5.

FTIR (ATR): 2956, 2929, 2857, 1713, 1472, 1361, 1253, 1096, 1050, 1005, 939, 834, 810, 774 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{14}H_{31}O_2Si$ $[M+H]^+$ 259.2088, found: 259.2088.

$[\alpha]_D^{23}$: –3.0° (c = 1.0, $CHCl_3$).

Preparation of 38:



A 25 mL flask was flame dried and charged with CuBr•Me_2S (144 mg, 0.70 mmol, 2.8 equiv) and LiCl (32 mg, 0.75 mmol, 3.0 equiv) in a nitrogen-filled glove box. The flask was sealed with septum and brought out of glove box, and was heated under vacuum to remove residue water. Anhydrous THF (5 mL) was added, and the solution was vigorously stirred for 10 minutes at 23 ºC until a yellow solution was formed. At –78 ºC, allylmagnesium bromide (0.68 mL, 1.0 M solution in THF, 0.68 mmol, 2.7 equiv) was added slowly. The reaction mixture was stirred at –78 ºC for 1 hour and a solution of ***(R)*-43** (149 mg, 0.75 mmol, 3.0 equiv) in THF (1 mL) was added slowly. After 30 minutes stirring at the same temperature, a solution of **37** (65 mg, 0.25 mmol, 1.0 equiv) in THF (1 mL) was added slowly. The reaction was stirred for an additional 2 hours at –78 ºC before a solution of saturated NH_4Cl and NH_3•H_2O (10 mL, 9:1 NH_4Cl/NH_3•H_2O) was added. The biphasic solution was vigorously stirred until a homogeneous dark blue solution was formed in aqueous phase. The phases were separated and the organic phase was washed with 10 mL saturated NH_4Cl solution. The combined aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 18:1) to give a mixture of diasteromers of the aldol product (82 mg, 0.22 mmol).

In a 25 mL flask, the crude aldol product was dissolved in CH_2Cl_2 (6 mL) and cooled to –10 ºC. DMAP (403 mg, 3.3 mmol, 15.0 equiv) and MsCl (51 μL, 0.66 mmol, 3.0 equiv) were added

sequentially. The reaction mixture was slowly warmed to 23 ºC and was stirred for 12 h before diluted with 10 mL EtOAc and washed with 1 M HCl (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give **38** (41 mg, 45% yield over 2 steps) as colorless liquid.

TLC (9:1 hexanes/EtOAc): R_f= 0.25 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.60 (ddt, *J* = 8.3, 7.0, 1.3 Hz, 1H), 6.33 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.79 – 5.65 (m, 1H), 5.11 – 5.01 (m, 2H), 3.83 (quint, *J* = 5.8 Hz, 1H), 3.50 (ddq, *J* = 8.4, 4.0, 2.0 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.51 – 2.31 (m, 2H), 2.18 (dddt, *J* = 14.3, 9.0, 7.9, 1.1 Hz, 1H), 1.53 – 1.11 (m, 8H), 0.96 – 0.79 (m, 12H), 0.05 (s, 3H), 0.05 (s, 3H).

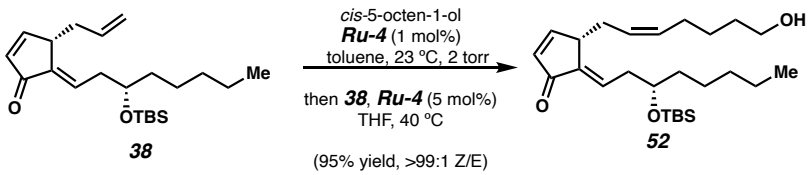
^{13}C NMR (101 MHz, $CDCl_3$): δ 196.5, 161.4, 138.5, 135.1, 134.3, 132.8, 117.8, 71.7, 43.1, 37.4, 37.1, 32.0, 26.0, 25.1, 22.8, 18.2, 14.2, –4.2, –4.5.

FTIR (ATR): 2955, 2928, 2856, 1705, 1656, 1582, 1472, 1360, 1252, 1207, 1127, 1050, 1005, 915, 863, 834, 806, 773, 726, 663 cm^{-1}.

HRMS (TOF, ES+, m/z): calc'd for $C_{22}H_{39}O_2Si$ $[M+H]^+$ 363.2714, found: 363.2711.

$[\alpha]_D^{23}$**:** +85.3° (c = 1.0, $CHCl_3$).

Preparation of 52:



In a nitrogen-filled glovebox, *cis*-5-octen-1-ol (150 mg, 1.17 mmol, 8.0 equiv) was dissolved in toluene (2 mL) in a 50 mL Schlenk flask, and a solution of catalyst **Ru-4** (9.9 mg, 11.7 μmol, 1 mol%) in THF (0.7 mL) was added. The Schlenk flask was sealed and brought out of the glovebox, and then connected to high vacuum. The valve was gradually opened (*Caution: open slowly and stir well to avoid splashing*). After 15 minutes stirring, the flask was refilled with argon and sealed, and was brought back into the glovebox. The residue was diluted with THF (0.5 mL), and an aliquot was taken for GC analysis (conversion of homodimerization step was >98% by GC analysis). A solution of **38** (53 mg, 0.146 mmol, 1.0 equiv) in THF (0.5 mL) was added into the Schlenk flask and an additional portion of catalyst **Ru-4** (6.2 mg, 7.3 μmol, 5 mol%) solution in THF (0.3 mL) was added. The Schlenk flask was sealed and brought out of glovebox. The reaction was stirred for 24 h at 40 ºC before a few drops of ethyl vinyl ether were added. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 2:1) to give **52** (60 mg, 95%, >99:1 *Z/E*).

TLC (3:1 hexanes/EtOAc): R_f= 0.23 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.59 (ddt, *J* = 8.3, 7.0, 1.3 Hz, 1H), 6.33 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.49 (dddt, *J* = 8.6, 7.2, 5.5, 1.5 Hz, 1H), 5.35 (dtt, *J* = 11.0, 8.4, 1.6 Hz, 1H), 3.84 (quint, *J* = 5.9 Hz, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 3.46 (ddt, *J* = 11.0, 4.2, 2.2 Hz, 1H), 2.63 (dddd, *J* = 13.8, 6.5, 4.2, 1.5 Hz, 1H), 2.50 – 2.34 (m, 2H), 2.17 (dddd, *J* = 14.5, 9.4, 8.0, 1.3 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.60 – 1.51 (m, 2H), 1.47 – 1.34 (m, 6H), 1.32 – 1.19 (m, 5H), 0.95 – 0.81 (m, 12H), 0.05 (s, 3H), 0.05 (s, 3H).

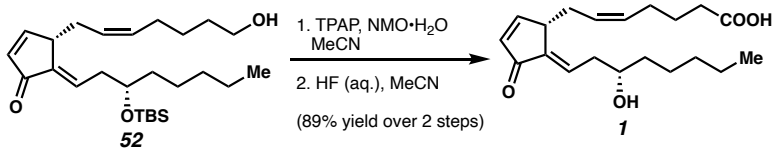
^{13}C NMR (101 MHz, $CDCl_3$): δ 196.5, 161.8, 138.8, 135.0, 132.7, 132.5, 125.4, 71.7, 62.9, 43.6, 37.5, 37.5, 32.5, 32.0, 30.7, 27.2, 26.0, 25.8, 25.1, 22.8, 18.2, 14.2, –4.2, –4.5.

FTIR (ATR): 3443, 2956, 2928, 2856, 1703, 1652, 1580, 1472, 1360, 1251, 1206, 1127, 1048, 1005, 975, 866, 834, 806, 773, 726, 664 cm^{-1}.

HRMS (TOF, ES+, m/z): calc'd for $C_{26}H_{47}O_3Si$ $[M+H]^+$ 435.3289, found: 435.3298.

$[\alpha]_D^{23}$**:** +83.5° (c = 1.0, $CHCl_3$).

Preparation of Δ[12]-prostaglandin J_2 (1):



To a stirred solution of **52** (26 mg, 0.06 mmol, 1.0 equiv) in MeCN (0.3 mL) was added NMO•H_2O (81 mg, 6 mmol, 10.0 equiv). Tetrapropylammonium perruthenate (2.1 mg, 6 μmol, 0.1 equiv) was added until NMO•H_2O was fully dissolved, and the reaction was stirred at 23 ºC for 3 hours. The solution was diluted with Et_2O (5 mL), passed through a short pad of silica gel, concentrated, and subjected to the next reaction without further purification.

The residue was dissolved in MeCN (1.0 mL) and cooled to 0 ºC. A solution of hydrofluoric acid (48 wt. % in H_2O, 0.2 mL) in MeCN (0.4 mL) was added dropwisely. The solution was stirred in the same temperature for 30 min before saturated $NaHCO_3$ solution (1.5 mL) and brine (1.5 mL) were added. The aqueous phase was extracted with EtOAc (5 × 5 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated (*not to dryness*). The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) to give **1** (18 mg, 89% over 2 steps) as a colorless liquid.

TLC (20:1 CH_2Cl_2/MeOH): R_f= 0.14 (UV).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.58 (ddt, *J* = 8.4, 7.2, 1.3 Hz, 1H), 6.36 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.54 – 5.38 (m, 2H), 3.86 (dtt, *J* = 7.9, 6.4, 4.0 Hz, 1H), 3.47 (ddt, *J* = 9.5, 4.0, 2.1 Hz, 1H), 2.78 – 2.68 (m, 1H), 2.57 (dt, *J* = 14.8, 6.8 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.40 – 2.33 (m, 2H), 2.20 – 2.02 (m, 3H), 1.77 – 1.64 (m, 2H), 1.61 – 1.41 (m, 3H), 1.40 – 1.24 (m, 5H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 196.6, 177.3, 162.0, 139.8, 135.0, 131.8, 131.7, 126.2, 71.5, 43.9, 37.3, 36.7, 33.1, 31.9, 30.6, 26.6, 25.4, 24.6, 22.8, 14.2.

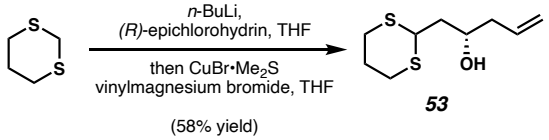
FTIR (ATR): 3445, 2960, 2929, 2858, 1699, 1646, 1579, 1463, 1406, 1265, 1237, 1135, 1084, 1033, 842, 810, 734, 702 cm^{-1}.

HRMS (TOF, ES+, m/z): calc'd for $C_{20}H_{31}O_4$ $[M+H]^+$ 335.2217, found: 335.2223.

$[\alpha]_D^{23}$**:** +99.5° (c = 0.2, $CHCl_3$).

Spectral data (^{1}H NMR, ^{13}C NMR, HRMS) matched with the published data.[17e]

Preparation of 53:



Procedures are same as Dai and co-workers.[32] 1,3-dithiane (1.2 g, 10 mmol, 1.0 equiv) was dissolved in THF (15 mL) and cooled to –78 ºC. *n*-BuLi (2.5 M solution in hexanes, 4.4 mL, 11 mmol, 1.1 equiv) was added and the solution was stirred at the same temperature for 15 min, then warmed up to –20 °C and stirred for 1 h. The reaction mixture was cooled down to –78 °C and *(R)*-epichlorohydrin (1.1 mL, 14 mmol, 1.4 equiv) was added dropwisely. The reaction mixture was stirred at –78 °C for 1 h, then slowly warmed to 23 ºC and stirred overnight and then cooled

to –40 ºC. In another flame-dried flask, vinyl magnesium bromide (28 mL, 1.0 M in THF, 28 mmol, 2.8 equiv) was added to a stirred solution of CuBr•Me_2S (124 mg, 0.6 mmol, 0.06 equiv) in THF (20 mL), and the resulting solution was transferred into the reaction mixture through a cannula at –40 ºC. The reaction mixture was slowly warmed to 23 ºC and stirred overnight before 1 M HCl (50 mL) was added. The biphasic mixture was extracted with EtOAc (3 × 50 mL). The combined organic extract was washed with brine, dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc = 9:1) to afford **53** (1.20 g, 58% yield) as colorless liquid.

TLC (4:1 hexanes/EtOAc): R_f= 0.27 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 – 5.72 (m, 1H), 5.14 (m, 2H), 4.26 (dd, *J* = 7.8, 6.6 Hz, 1H), 4.02 – 3.94 (m, 1H), 2.96 – 2.78 (m, 4H), 2.33 – 2.24 (m, 1H), 2.24 – 2.16 (m, 1H), 2.16 – 2.06 (m, 1H), 2.01 (d, *J* = 4.2 Hz, 1H), 1.95 – 1.82 (m, 3H).

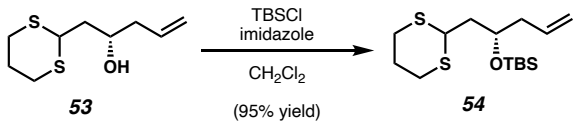
^{13}C NMR (101 MHz, $CDCl_3$): δ 134.2, 118.7, 67.6, 44.3, 42.2, 42.1, 30.5, 30.2, 26.0.

FTIR (ATR): 3413, 3073, 2930, 2900, 2851, 2827, 1640, 1422, 1275, 1242, 1172, 1123, 1062, 1027, 993, 908, 866, 770, 664 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_9H_{16}OS_2$ $[M]^+$ 204.0637, found: 204.0657.

$[\alpha]_D^{23}$: +22.2° (c = 1.0, $CHCl_3$).

Preparation of 54:



To a stirred solution of **53** (0.70 g, 3.43 mmol) in CH_2Cl_2 (20 mL) was added imidazole (0.70 g, 10.29 mmol, 3.0 equiv) and TBSCl (1.03 g, 6.86 mmol, 2.0 equiv). Saturated NH_4Cl solution (20 mL) was added after stirring overnight. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, 20:1 hexanes/EtOAc) gave **54** as a colorless oil (1.04 g, 95% yield).

TLC (10:1 hexanes/EtOAc): R_f = 0.54 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 – 5.71 (m, 1H), 5.07 – 5.00 (m, 2H), 4.08 (dd, *J* = 7.8, 6.9 Hz, 1H), 4.00 (qd, *J* = 6.2, 4.9 Hz, 1H), 2.92 – 2.75 (m, 4H), 2.23 (dtt, *J* = 7.5, 5.1, 1.3 Hz, 2H), 2.09 (dddt, *J* = 10.6, 5.0, 4.2, 2.8 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.83 – 1.78 (m, 2H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

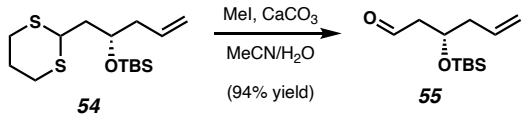
^{13}C NMR (101 MHz, $CDCl_3$): δ 134.3, 117.6, 68.1, 44.1, 42.3, 42.3, 30.7, 30.1, 26.2, 26.0, 18.2, –4.3, –4.5.

FTIR (ATR): 2952, 2928, 2896, 2855, 1640, 1472, 1423, 1360, 1254, 1185, 1070, 1004, 940, 915, 834, 808, 773, 666 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{15}H_{31}OS_2Si$ $[M+H]^+$ 319.1580, found: 319.1583.

$[\alpha]_D^{23}$: +41.1° (c = 1.0, $CHCl_3$).

Preparation of aldehyde 55:



54 ***55***

To a solution of **54** (636 mg, 2 mmol, 1.0 equiv) in MeCN/H_2O (20 mL, 9:1) was added $CaCO_3$ (1.0 g, 10 mmol, 5.0 equiv) and MeI (1.87 mL, 30 mmol, 15.0 equiv). The reaction mixture was stirred at 50 ºC for 6 h, then diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 20:1 hexanes/EtOAc) to afford **55** (430 mg, 94%) as a colorless liquid.

TLC (10:1 hexanes/EtOAc): R_f= 0.45 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (td, *J* = 2.4, 0.8 Hz, 1H), 5.78 (ddt, *J* = 16.5, 10.8, 7.2 Hz, 1H), 5.12 – 5.03 (m, 2H), 4.26 (quint, *J* = 5.9 Hz, 1H), 2.55 – 2.52 (m, 2H), 2.30 (ddt, *J* = 7.1, 6.0, 1.2 Hz, 2H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

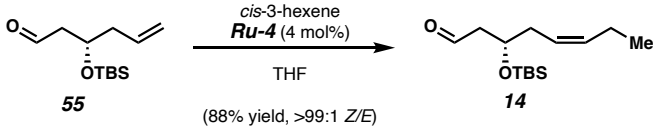
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3, 133.9, 118.3, 67.9, 50.5, 42.5, 25.9, 18.1, –4.2, –4.7.

FTIR (ATR): 2955, 2929, 2890, 2857, 1726, 1641, 1472, 1361, 1254, 1098, 1041, 1005, 915, 834, 810, 774, 680 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{12}H_{25}O_2Si$ $[M+H]^+$ 229.1618, found: 229.1629.

$[\alpha]_D^{23}$**:** +22.0° (c = 1.0, $CHCl_3$).

Preparation of aldehyde 14:



In a nitrogen-filled glovebox, **55** (146 mg, 0.64 mmol, 1 equiv) and *cis*-3-hexene (215 mg, 2.56 mmol, 4 equiv) were weighed into a 4 mL vial. A solution of catalyst **Ru-4** (22 mg, 25.6 μmol, 4 mol%) in THF (1.5 mL) was transferred into the vial. The reaction mixture was stirred for 1 h at 23 ºC. An aliquot was taken for GC analysis to monitor the conversion. Then the vial was brought out of the glovebox, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 20:1) to afford **14** (145 mg, 88%) as a colorless liquid.

TLC (10:1 hexanes/EtOAc): R_f= 0.45 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (t, *J* = 2.4 Hz, 1H), 5.54 – 5.41 (m, 1H), 5.32 (dtt, *J* = 10.8, 7.5, 1.6 Hz, 1H), 4.22 (dq, *J* = 7.1, 5.7 Hz, 1H), 2.51 (dd, *J* = 5.8, 2.4 Hz, 2H), 2.38 – 2.17 (m, 2H), 2.10 – 1.92 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

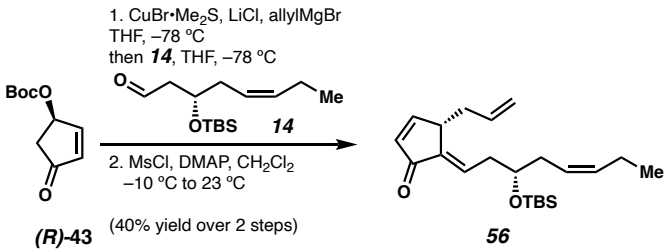
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4, 134.8, 123.7, 68.3, 50.6, 35.7, 25.9, 20.9, 18.1, 14.3, –4.2, –4.7.

FTIR (ATR): 2957, 2930, 2890, 2857, 1726, 1472, 1361, 1253, 1096, 1005, 938, 834, 811, 774, 680 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{14}H_{27}O_2Si$ $[M+H-H_2]^+$ 255.1774, found: 255.1780.

$[\alpha]_D^{23}$**:** +22.0° (c = 0.4, C_6H_6).

Preparation of 56:



A 25 mL flask was flame dried and charged with CuBr•Me_2S (142 mg, 0.69 mmol, 3.0 equiv) and LiCl (31 mg, 0.74 mmol, 3.2 equiv) in a nitrogen-filled glove box. The flask was sealed with a septum and brought out of the glove box, and heated under vacuum to remove residue water. Anhydrous THF (5 mL) was added, and the solution was vigorously stirred for 10 minute at 23 ºC until a yellow solution was formed. At –78ºC, allylmagnesium bromide (0.65 mL, 1.0 M solution in THF, 0.65 mmol, 2.8 equiv) was added slowly. The reaction mixture was stirred at –78 ºC for 1 hour and a solution of ***(R)*-43** (137 mg, 0.69 mmol, 3.0 equiv) in THF (1 mL) was added slowly. After 30 minutes stirring at the same temperature, a solution of **14** (59 mg, 0.23 mmol, 1.0 equiv) in THF (1 mL) was added slowly. The reaction was stirred for an additional 2 hours at –78 ºC before a solution of saturated NH_4Cl and NH_3•H_2O (10 mL, 9:1 NH_4Cl/NH_3•H_2O) was added. The biphasic solution was vigorously stirred until a homogeneous dark blue solution was formed in the aqueous phase. The phases were separated and the organic phase was washed with 10 mL saturated NH_4Cl solution. The combined aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 18:1) to give a mixture of diasteromers of the aldol products (50 mg, 0.13 mmol).

In a 25 mL flask, the crude aldol product was dissolved in CH_2Cl_2 (5 mL) and cooled to –10 ºC. DMAP (242 mg, 2.0 mmol, 15.0 equiv) and MsCl (31 μL, 0.4 mmol, 3.0 equiv) was added sequentially. The reaction mixture was slowly warmed to 23 ºC and was stirred for 12 h before diluted with 10 mL EtOAc and washed with 1 M HCl (5 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give **56** (33 mg, 40% yield over 2 steps) as a colorless liquid.

TLC (4:1 hexenes/EtOAc): R_f= 0.67 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (ddd, *J* = 6.1, 2.6, 1.0 Hz, 1H), 6.61 (ddt, *J* = 9.0, 8.0, 1.3 Hz, 1H), 6.33 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.79 – 5.64 (m, 1H), 5.52 – 5.41 (m, 1H), 5.42 – 5.30 (m, 1H), 5.10 – 5.01 (m, 2H), 3.88 (quint, *J* = 6.0 Hz, 1H), 3.48 (ddd, *J* = 8.8, 4.0, 2.0 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.46 – 2.38 (m, 2H), 2.30 – 2.11 (m, 3H), 2.05 – 1.95 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.4, 161.4, 138.6, 135.1, 134.4, 134.1, 132.7, 124.4, 117.7, 71.7, 43.1, 37.1, 36.9, 35.3, 26.0, 20.9, 18.2, 14.3, –4.4, –4.4.

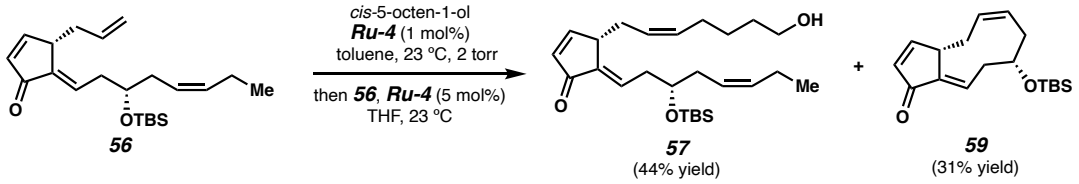
FTIR (ATR): 2957, 2929, 2894, 2856, 1706, 1657, 1582, 1472, 1366, 1253, 1148, 1083, 1005, 966, 915, 835, 808, 775 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{22}H_{37}O_2Si$ $[M+H]^+$ 361.2557, found: 361.2576.

$[\alpha]_D^{23}$: +122.3° (c = 1.0, $CHCl_3$).

Preparation of 57:

A. Stereoretentive metathesis using Ru-4:



In a nitrogen-filled glovebox, *cis*-5-octen-1-ol (72 mg, 0.55 mmol, 6.7 equiv) was dissolved in toluene (1 mL) in a 50 mL Schlenk flask and a solution of catalyst **Ru-4** (4.7 mg, 5.6 μmol, 1 mol%) in THF (0.6 mL) was added. The Schlenk flask was sealed and brought out of the glovebox, and then connected to high vacuum. The valve was gradually opened (*Caution: open slowly and stir well to avoid splashing*). After 15 minutes stirring, the flask was refilled with argon and sealed, and was brought back into the glovebox. The residue was diluted with 0.5 mL THF, and an aliquot was taken for GC analysis (conversion of homodimerization step was >98% by GC analysis). A solution of **56** (30 mg, 0.083 mmol, 1 equiv) in 0.5 mL THF was added into the Schlenk flask and an additional 0.4 mL of catalyst solution with **Ru-4** (2.9 mg, 3.5 μmol, 5 mol%) was added. The Schlenk flask was sealed and brought out of glovebox. The reaction was stirred for 12 h at 23 ºC before a few drops of ethyl vinyl ether were added. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 10:1 to 2:1). **57** (16 mg, 44%) and **59** (8 mg, 31%) was isolated as two products.

Compound **57**:

TLC (2:1 hexanes/EtOAc): R_f= 0.28 (UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (ddd, *J* = 6.0, 2.7, 1.0 Hz, 1H), 6.60 (ddt, *J* = 8.2, 7.0, 1.3 Hz, 1H), 6.32 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.53 – 5.43 (m, 2H), 5.41 – 5.31 (m, 2H), 3.89 (quint, *J* = 6.1 Hz, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 3.45 (ddq, *J* = 8.4, 4.3, 2.2 Hz, 1H), 2.68 – 2.55 (m, 1H), 2.43 (ddd, *J* = 7.7, 6.4, 2.3 Hz, 2H), 2.29 – 2.11 (m, 3H), 2.08 – 1.91 (m, 4H), 1.62 – 1.51 (m, 2H), 1.48 – 1.36 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 161.8, 138.9, 135.0, 134.2, 132.7, 132.5, 125.5, 124.4, 71.7, 62.9, 43.6, 37.0, 35.3, 32.5, 30.8, 27.2, 26.0, 25.9, 20.9, 18.2, 14.3, –4.4, –4.4.

FTIR (ATR): 3429, 2956, 2928, 2856, 2361, 2327, 1702, 1652, 1580, 1472, 1360, 1251, 1213, 1066, 1005, 968, 834, 807, 774, 721, 668 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{26}H_{45}O_3Si$ $[M+H]^+$ 433.3132, found: 433.3121.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$**:** +136.3° (c = 1.0, C_6H_6).

Compound **59**:

TLC (2:1 hexanes/EtOAc): R_f= 0.6 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (ddd, *J* = 5.9, 2.8, 1.0 Hz, 1H), 6.80 (ddt, *J* = 10.8, 8.8, 1.3 Hz, 1H), 6.31 (dd, *J* = 5.9, 1.7 Hz, 1H), 5.76 (q, *J* = 9.1 Hz, 1H), 5.61 (dddd, *J* = 11.9, 10.7, 5.2, 1.2 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.27 (d, *J* = 9.6 Hz, 1H), 2.38 (dd, *J* = 9.5, 3.0 Hz, 2H), 2.24 (q, *J* = 11.6 Hz, 2H), 2.17 – 1.95 (m, 2H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H).

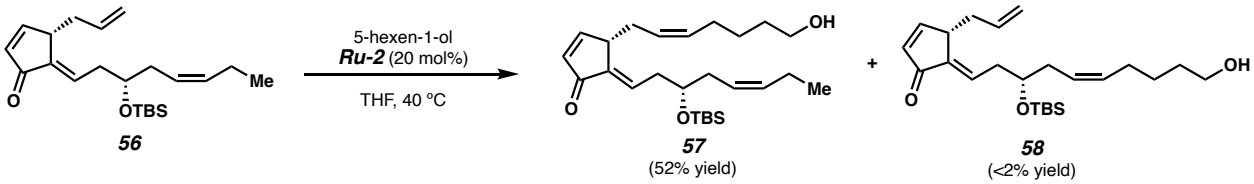
^{13}C NMR (101 MHz, $CDCl_3$): δ 196.4, 162.3, 141.3, 134.0, 132.4, 130.6, 129.6, 73.1, 44.2, 34.7, 34.5, 32.6, 26.0, 18.3, –4.6, –4.7.

FTIR (ATR): 2952, 2926, 2886, 2855, 2359, 2339, 1705, 1654, 1586, 1471, 1369, 1251, 1190, 1077, 1039, 997, 980, 938, 855, 835, 808, 790, 774, 727, 668 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{18}H_{29}O_2Si$ $[M+H]^+$ 305.1931, found: 305.1942.

$[\alpha]_D^{23}$**:** –27.8° (c = 0.8, $CHCl_3$)

B. *Z*-selective cross-metathesis using Ru-2:

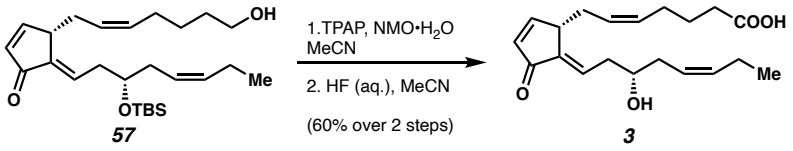


In a nitrogen-filled glovebox, **56** (64 mg, 0.18 mmol, 1.0 equiv) and 5-hexen-1-ol (142 mg, 1.42 mmol, 8.0 equiv) were weighed into a 4 mL vial. THF (0.3 mL) was added to dissolve the mixture. Catalyst **Ru-2** (24 mg, 20 mol%) was dissolved in THF (0.4 mL) and 0.1 mL of this catalyst solution was transferred into the vial. The vial was sealed with a 14/20 septum and brought out of the glovebox. The reaction was stirred at 40 ºC with a stream of argon (saturated with anhydrous THF) bubbling through a needle. A portion of the catalyst solution (0.1 mL) was added into the vial in each 1 hour. After all the catalyst was added, the reaction mixture was continued to stir for 4 h with argon bubbling. A few drops of ethyl vinyl ether were added, and the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 2:1) to afford **57** (40 mg, 52%) as a colorless liquid. Compund **58** was the proposed by-product (molar ratio of **57**:**58** was 32:1 as determined by crude NMR analysis).

Compound **57**: Characterization data were in agreement with previously obtained data.

Compound **58**: Characterization data not available due to the difficulty in separation; mass data was obtained by LC-MS (TOF, ES+, m/z): calc'd for $C_{24}H_{41}O_3Si$ $[M+H]^+$ 405.2819, found: 405.2801.

Preparation of Δ[12]-prostaglandin J$_3$ (3):



To a stirred solution of **57** (21.6 mg, 0.05 mmol, 1.0 equiv) in MeCN (0.5 mL) was added NMO•H_2O (67.5 mg, 0.5 mmol, 10.0 equiv). Tetrapropylammonium perruthenate (1.8 mg, 5 μmol, 0.1 equiv) was added until NMO•H_2O was fully dissolved and the reaction was stirred at 23 ºC for 3 hours. The solution was diluted with Et_2O (5 mL), passed through a short pad of silica gel, concentrated, and subjected to the next reaction without further purification.

The residue was dissolved in MeCN (1.0 mL) and cooled to 0 ºC. A solution of hydrofluoric acid (48 wt. % in H_2O, 0.2 mL) in MeCN (0.4 mL) was added dropwisely. The solution was stirred in the same temperature for 30 min before saturated $NaHCO_3$ solution (1.5 mL) and brine (1.5 mL) were added. The aqueous phase was extracted with EtOAc (5 × 5 mL). The combined organic phase was dried over magnesium sulfate, filtered, and concentrated (*not to dryness*). The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) and through Biotage® SNAP Ultra C18 column (H_2O/MeOH) to give **3** (10 mg, 60% over 2 steps) as a colorless liquid.

TLC (100% EtOAc): R_f= 0.55 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.57 (ddt, *J* = 8.4, 7.0, 1.2 Hz, 1H), 6.36 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.69 – 5.60 (m, 1H), 5.60 – 5.45 (m, 2H), 5.45 – 5.35 (m, 1H), 3.91 (quint, *J* = 6.8 Hz, 1H), 3.50 – 3.44 (m, 1H), 2.75 (ddd, *J* = 13.9, 6.9, 4.4 Hz, 1H), 2.68 – 2.58

(m, 1H), 2.49 (ddd, *J* = 15.2, 8.4, 7.0 Hz, 1H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.33 – 2.28 (m, 2H), 2.20 – 1.98 (m, 5H), 1.68 (quint, *J* = 7.0 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.4, 175.8, 161.8, 139.9, 136.4, 135.1, 131.7, 131.2, 126.3, 123.6, 71.1, 44.0, 36.3, 34.5, 32.9, 30.7, 26.6, 24.7, 20.9, 14.4.

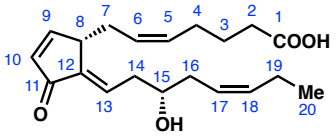
FTIR (ATR): 3449, 3010, 2956, 2919, 2850, 1728, 1703, 1650, 1579, 1455, 1375, 1222, 1182, 1046, 959, 838, 809, 721 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{20}H_{29}O_4$ $[M+H]^+$ 333.2060, found: 333.2060.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$**:** +122.6° (c = 0.5, C_6H_6).

Spectral data (^{1}H NMR, ^{13}C NMR, HRMS) matched with the published data.[12,14,16] Comparisons of ^{1}H NMR data of natural and synthetic Δ^{12}-prostaglandin J_3 (3) are listed in Table 1.6.2.

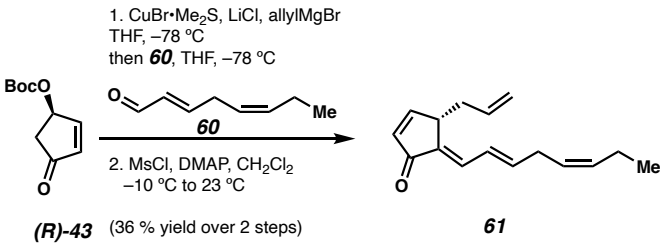
Table 1.6.2. Comparison of ^{1}H NMR Data for Δ^{12}-prostaglandin J_3 (3)



Δ[12] -PGJ$_3$ (3)

Proton Number	**Natural Δ^{12}-PGJ$_3$ ^{1}H NMR**[12] 600 MHz, $CDCl_3$ ^{1}H [δ, multi, *J* (Hz)]	**This Work, Synthetic Δ^{12}-PGJ$_3$ ^{1}H NMR** 400 MHz, $CDCl_3$ ^{1}H [δ, multi, *J* (Hz)]
1	n.d.	
2	2.35 (t, *J* = 7.0 Hz)	2.36 (t, *J* = 6.8 Hz)
3	hidden	1.78 – 1.66 (m)
4	2.02 (m)	2.20 – 2.10 (m)
5	5.42 (m)	5.60 – 5.51 (m)
6	hidden	5.51 – 5.45 (m)
7α	2.64 (m)	2.75 (ddd, *J* = 13.9, 6.9, 4.4 Hz)
7β	2.08 (m)	2.20 – 2.10 (m)
8	3.47 (ddd, *J* = 10.0, 4.0, 2.0 Hz)	3.50 – 3.44 (m)
9	7.56 (ddd, *J* = 6.0, 2.0, 1.0 Hz)	7.58 (ddd, *J* = 6.0, 2.6, 1.0 Hz)
10	6.35 (dd, *J* = 6.0, 2.0 Hz)	6.36 (dd, *J* = 6.0, 1.8 Hz)
11	n.d.	
12	n.d.	
13	6.58 (m)	6.57 (ddt, *J* = 8.4, 7.0, 1.2 Hz)
14α	2.55 (dt, *J* = 15.0, 7.0 Hz)	2.68 – 2.57 (m)
14β	2.47 (ddd, *J* = 15.0, 8.0, 6.0 Hz)	2.49 (ddd, *J* = 15.2, 8.4, 7.0 Hz)
15	3.88 (quint, *J* = 6.0 Hz)	3.91 (quint, *J* = 6.8 Hz)
16	2.28 (m)	2.33 – 2.28 (m)
17	hidden	5.45 – 5.35 (m)
18	5.51 (m)	5.69 – 5.60 (m)
19α	2.00 (m)	2.10 – 1.98 (m)
19β	1.98 (m)	2.10 – 1.98 (m)
20	0.96 (t, *J* = 7.0 Hz)	0.96 (t, *J* = 7.5 Hz)

Preparation of 61:



A 25 mL flask was flame dried and charged with CuBr•Me_2S (195 mg, 0.95 mmol, 1.9 equiv) and LiCl (42 mg, 1.0 mmol, 2.0 equiv) in a nitrogen-filled glove box. The flask was sealed with septum and brought out of glove box, and was heated under vacuum to remove residue water. Anhydrous THF (10 mL) was added, and the solution was vigorously stirred for 10 minute at 23 ºC until a yellow homogeneous solution was formed. At –78ºC, allyl magnesium bromide (0.9 mL, 1.0 M solution in THF, 0.9 mmol, 1.8 equiv) was added slowly. The reaction mixture was stirred at –78 ºC for 1 hour and a solution of ***(R)*-43** (198 mg, 1.0 mmol, 2.0 equiv) in THF (1 mL) was added slowly. After 30 minutes of stirring at the same temperature, a solution of known compound **60** (prepared according to Honda and co-workers[44]) (62 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was added slowly. The reaction was stirred for an additional 2 hours at –78 ºC before a solution of saturated NH_4Cl and $NH_3•H_2O$ (10 mL, 9:1 $NH_4Cl/NH_3•H_2O$) was added. The biphasic solution was vigorously stirred until a homogeneous dark blue solution formed in aqueous phase. The phases were separated and the organic phase was washed with 10 mL saturated NH_4Cl solution. The combined aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 15:1) to give a mixture of diasteromers of the aldol products (51 mg, 0.21 mmol).

In a 25 mL flask, the crude aldol product was dissolved in CH_2Cl_2 (6 mL) and cooled to –10 ºC. DMAP (384 mg, 3.15 mmol, 15.0 equiv) and MsCl (49 μL, 0.63 mmol, 3.0 equiv) was added sequentially. The reaction mixture was slowly warmed to 23 ºC and was stirred for 2 h before diluted with 10 mL EtOAc and washed with 1 M HCl (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc 15:1) to give **61** (41 mg, 36% yield over 2 steps) as a colorless liquid.

TLC (4:1 hexanes/EtOAc): R_f= 0.56 (UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (ddd, *J* = 5.9, 2.6, 1.0 Hz, 1H), 7.03 – 6.90 (m, 1H), 6.36 (dd, *J* = 6.1, 1.8 Hz, 1H), 6.34 – 6.29 (m, 1H), 6.21 (dt, *J* = 15.1, 6.3 Hz, 1H), 5.79 – 5.66 (m, 1H), 5.54 (dtt, *J* = 10.2, 7.2, 1.5 Hz, 1H), 5.37 (dtt, *J* = 10.5, 7.3, 1.6 Hz, 1H), 5.10 – 5.02 (m, 2H), 3.60 (ddq, *J* = 8.5, 4.0, 1.9 Hz, 1H), 3.00 – 2.95 (m, 2H), 2.65 (dddt, *J* = 13.7, 6.8, 4.2, 1.4 Hz, 1H), 2.25 (dddt, *J* = 14.2, 8.8, 7.7, 1.1 Hz, 1H), 2.07 (dquint, *J* = 7.5, 1.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 160.7, 144.5, 135.4, 135.4, 134.2, 134.1, 131.6, 125.8, 124.6, 117.9, 43.3, 37.4, 31.2, 20.7, 14.3.

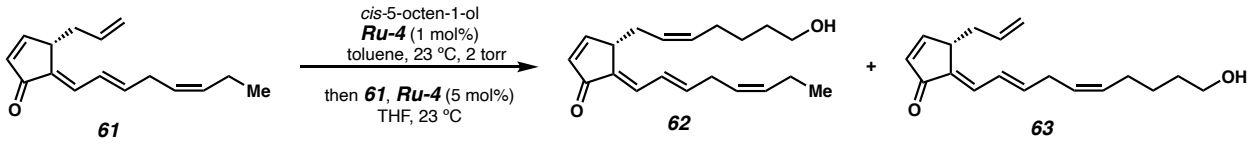
FTIR (ATR): 3011, 2963, 2931, 2874, 2361, 2335, 1692, 1629, 1579, 1440, 1339, 1280, 1207, 1100, 989, 915, 872, 839, 729, 668 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{16}H_{21}O$ $[M+H]^+$ 229.1587, found: 229.1588.

$[\alpha]_D^{23}$: +117.7° (c = 0.5, $CHCl_3$).

Preparation of 62:

A. Stereoretentive metathesis using Ru-4:



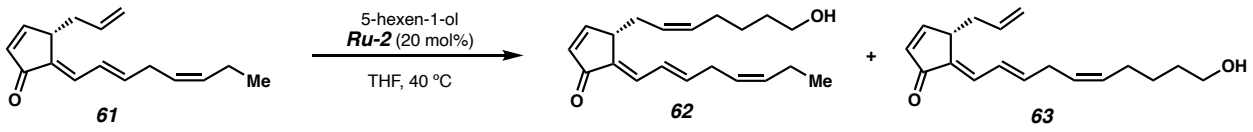
In a nitrogen-filled glovebox, *cis*-5-octen-1-ol (205 mg, 1.6 mmol, 8.0 equiv) was dissolved in toluene (1 mL) in a 50 mL Schlenk flask and a solution of catalyst **Ru-4** (13.6 mg, 16 μmol, 1 mol%) in THF (0.6 mL) was added. The Schlenk flask was sealed and brought out of the glovebox, and then connected to high vacuum. The valve was gradually opened (*Caution: open slowly and stir well to avoid splashing*). After 15 minutes stirring, the flask was refilled with argon and sealed, and was brought back into the glovebox. The residue was diluted with 0.5 mL THF, and an aliquot was taken for GC analysis (conversion of homodimerization step was >98% by GC analysis). A solution of **61** (46 mg, 0.2 mmol, 1.0 equiv) in 0.5 mL THF was added into the Schlenk flask and an additional 0.4 mL of catalyst solution with **Ru-4** (8.5 mg, 10 μmol, 5 mol%) was added. The Schlenk flask was sealed and brought out of glovebox. The reaction was stirred for 12 h at 23 ºC before a few drops of ethyl vinyl ether were added. The solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 2:1). Compounds **62** (22 mg, 36%) and **63** were separated as a mixture (28 mg, molar ratio of **62**:**63** was 3:1 as determined by crude NMR analysis).

Compound **62**: Characterization data not available due to the difficulty in separation.

Mass data was obtained by LC-MS (TOF, ES+, m/z): calc'd for $C_{20}H_{29}O_2$ $[M+H]^+$ 301.2162, found: 301.2080.

Compound **63**: Characterization data not available due to the difficulty in separation, mass data was obtained by LC-MS (TOF, ES+, m/z): calc'd for $C_{18}H_{25}O_2$ $[M+H]^+$ 273.1849, found: 273.1759.

B. *Z*-selective cross-metathesis using Ru-2:

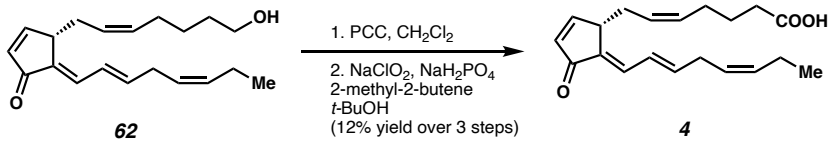


In a nitrogen-filled glovebox, **61** (23 mg, 0.1 mmol, 1.0 equiv) and 5-hexen-1-ol (80 mg, 0.8 mmol, 8.0 equiv) were weighed into a 4 mL vial. THF (0.1 mL) was added to dissolve the mixture. Catalyst **Ru-2** (13.6 mg, 20 mol%) was dissolved in THF (0.4 mL) and 0.1 mL of this catalyst solution was transferred into the vial. The vial was sealed with a 14/20 septum and brought out of the glovebox. The reaction was stirred at 40 ºC with a stream of argon (saturated with anhydrous THF) bubbling through a needle. A portion of the catalyst solution (0.1 mL) was added into the vial in each 1 hour. After all the catalyst was added, the reaction mixture was continued to stir for 2 h with argon bubbling. A few drops of ethyl vinyl ether was added, and the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc 2:1). Compounds **62** (9.2 mg, 31%) and **63** were separated as a mixture (12 mg, molar ratio of **62**:**63** was 3:1 as determined by crude NMR analysis).

Compound **62**: Characterization data not available due to the difficulty in separation. Mass data was obtained by LC-MS (TOF, ES+, m/z): calc'd for $C_{20}H_{29}O_2$ $[M+H]^+$ 301.2162, found: 301.2166.

Compound **63**: Characterization data not available due to the difficulty in separation, mass data was obtained by LC-MS (TOF, ES+, m/z): calc'd for $C_{18}H_{25}O_2$ $[M+H]^+$ 273.1849, found: 273.1855.

Preparation of 15-deoxy-Δ[12,14]-prostaglandin J_3 (4):



Pyridinium chlorochromate (22 mg, 0.1 mmol, 3.0 equiv) was added to a solution of **62** (mixed with by-product **63**) (10 mg, 0.033 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 23 ºC. The reaction was monitored by TLC and was diluted with Et_2O (3 mL) after stirring for 3 h. The resulting solution was filtered through a short pad of silica gel, and was subjected to the next step without further purification.

The residue was dissolved in *t*-BuOH (0.5 mL) at 23 ºC, and 2-methyl-2-butene (35 µL, 0.33 mmol, 10 equiv), a solution of $NaH_2PO_4 \bullet H_2O$ (6.9 mg, 0.05 mmol, 1.5 equiv) in H_2O (0.12 mL) and a solution of $NaClO_2$ (80 %, 5.6 mg, 0.05 mmol, 1.5 equiv) in H_2O (0.12 mL) was added sequentially. After stirring at 23 ºC for 30 minutes, the reaction mixture was diluted with a solution of $NaH_2PO_4 \bullet H_2O$ (108 mg) in H_2O (2 mL) and extracted with EtOAc (5 × 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) and purification through Biotage® SNAP Ultra C18 column (H_2O/MeOH) afforded pure compound **4** (4 mg, 0.013 mmol, 12% yield from **61**) as a colorless oil.

TLC (10:1 CH_2Cl_2/MeOH): R_f= 0.44 (UV).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (ddd, *J* = 6.1, 2.6, 1.0 Hz, 1H), 6.96 (d, *J* = 11.5 Hz, 1H), 6.42 – 6.31 (m, 2H), 6.22 (dt, *J* = 14.9, 6.3 Hz, 1H), 5.57 – 5.51 (m, 1H), 5.50 – 5.43 (m, 1H), 5.37 (dtt, *J* = 10.1, 6.8, 1.7 Hz, 2H), 3.64 – 3.55 (m, 1H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.60 (dt, *J* = 12.3, 5.9 Hz, 1H), 2.43 – 2.25 (m, 3H), 2.12 – 2.00 (m, 4H), 1.69 (quint, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 176.6, 160.9, 144.5, 135.5, 135.5, 134.2, 131.6, 131.5, 126.1, 125.8, 124.6, 43.6, 33.0, 31.2, 30.9, 26.7, 24.6, 20.7, 14.3.

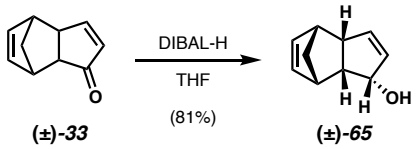
FTIR (ATR): 3010, 2960, 2926, 2874, 2854, 1710, 1693, 1626, 1578, 1512, 1455, 1208, 1154, 1087, 1024, 977, 817, 728 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{20}H_{27}O_3$ $[M+H]^+$ 315.1955, found: 315.1968.

$[\alpha]_D^{23}$**:** +129.6° (c = 0.07, C_6H_6).

Spectral data (^{1}H NMR, ^{13}C NMR, HRMS) matched with the published data.[15]

Preparation of (±)-65:



(±)-*33* (±)-*65*

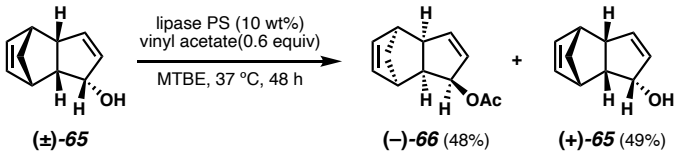
Racemic enone **(±)-33** was obtained from photooxygenation of dicyclopentadiene catalyzed by tetraphenylporphyrin (TPP) according to Mihelich-Eickhoff's procedure.[39] In a 500 mL round bottom flask, **(±)-33** (13.2 g, 8.9 mmol) was dissolved in anhydrous toluene (150 mL) under argon atmosphere. The solution was cooled to –78 ºC, and a solution of DIBAL-H (1.0 M solution in toluene, 13.4 mL, 13.4 mmol, 1.5 equiv) was added dropwisely. After 1.5 h, MeOH (50 mL) was added (dropwisely at beginning to avoid splashing). The reaction mixture was warmed to ambient

temperature and poured into a saturated Na-K tartrate solution (150 mL) and the biphasic solution was stirred overnight. The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (SiO_2, 10:1 to 4:1 hexanes/EtOAc) afforded compound **(±)-65** as a white solid (10.9 g, 81% yield).

TLC (4:1 hexanes/EtOAc): R_f= 0.3 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 5.7, 2.6 Hz, 1H), 5.81 (dd, *J* = 5.7, 3.2 Hz, 1H), 5.59 (s, 2H), 4.67 (t, *J* = 9.0 Hz, 1H), 3.29 (dd, *J* = 7.6, 4.1 Hz, 1H), 2.99 – 2.87 (m, 3H), 1.51 (ddt, *J* = 46.0, 8.0, 1.6 Hz, 2H), 1.23 (d, *J* = 9.6 Hz, 1H)

Enzymatic Kinetic resolution:



In a 250 mL round bottom flask, **(±)-65** (4.8 g, 32.4 mmol) was dissolved in MTBE (100 mL, 0.33M), and vinyl acetate (1.78 mL, 0.6 equiv) was added via syringe. Lipase PS (10% on celite, 480 mg, 10 wt%) was added to the flask. The flask was sealed with septum and kept under argon atmosphere, and placed in 37 ºC oil bath. After 48 h, the reaction mixture was filtered through celite and concentrated. Column chromatography (SiO_2, 10:1to 4:1 hexanes/EtOAc) afforded white solids **(–)-66** (2.93 g, 48% yield) and **(+)-65** (2.36 g, 49% yield).

(–)-66:

TLC (10:1 hexanes/EtOAc): R_f= 0.68 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 5.7, 2.9 Hz, 1H), 5.76 (dd, *J* = 5.6, 3.1 Hz, 1H), 5.70 (dt, *J* = 5.8, 2.0 Hz, 1H), 5.55 (dt, *J* = 5.8, 1.9 Hz, 1H), 5.44 (dq, *J* = 9.0, 1.7 Hz, 1H), 3.28 (ddt, *J* = 7.6, 3.5, 1.7 Hz, 1H), 3.08 (ddd, *J* = 8.9, 7.7, 4.1 Hz, 1H), 2.89 (ddp, *J* = 4.3, 2.9, 1.3 Hz, 1H), 2.76 (s, 1H), 2.07 (s, 3H), 1.46 (ddt, *J* = 39.3, 8.2, 1.7 Hz, 2H).

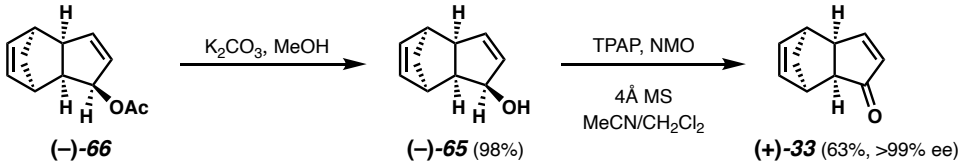
(+)-65:

TLC (10:1 hexanes/EtOAc): R_f= 0.28 ($KMnO_4$).

^{1}H NMR spectrum data matches **(±)-65**

$[\alpha]_D^{23}$: +117.9° (c = 1.0, $CHCl_3$).

Preparation of (+)-33:



To a stirred solution of **(–)-66** (2.8 g, 14.7 mmol) in MeOH (50 mL) was added K_2CO_3 (2.03 g, 1 equiv). The solution was stirred for 12 h and concentrated, then dissolved in water (30 mL) and extracted by Et_2O (30 mL). Column chromatography (SiO_2, 4:1 hexenes/EtOAc) afforded **(–)-65** as a white solid (2.04 g, 98%). Spectrum data matches **(±)-65**.

$[\alpha]_D^{23}$: –138.1° (c = 1.0, $CHCl_3$).

A 100 mL round bottom flask containing 4Å molecular sieves (9.0 g) was flame dried under vacuum. After the flask cooled down to room temperature, **(–)-65** (2.01 g, 13.6 mmol), NMO (3.19

g, 27.2 mmol, 2 equiv) was added and dissolved in MeCN (3 mL) and CH_2Cl_2 (27 mL). TPAP (150 mg, 0.42 mmol, 0.03 equiv) and the reaction was stirred under argon for 1 hour, and the reaction progress was monitored by GC. The reaction mixture was filtered over celite and concentrated. Column chromatography (SiO_2, 4:1 hexenes/EtOAc) afforded **(+)-33** as a white solid (1.24 g, 63%). NMR spectrum data matches **(±)-33**.

TLC (4:1 hexanes/EtOAc): R_f= 0.35 (UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 5.7, 2.6 Hz, 1H), 5.95 (ddd, *J* = 7.8, 5.6, 2.3 Hz, 2H), 5.78 (dd, *J* = 5.7, 3.0 Hz, 1H), 3.42 (dddd, *J* = 5.6, 4.2, 2.6, 1.6 Hz, 1H), 3.22 (dt, *J* = 4.1, 1.8 Hz, 1H), 2.97 (ddt, *J* = 4.2, 2.7, 1.4 Hz, 1H), 2.80 (t, *J* = 5.1 Hz, 1H), 1.78 – 1.60 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.9, 164.7, 137.1, 132.7, 52.9, 50.4, 48.4, 45.1, 44.2.

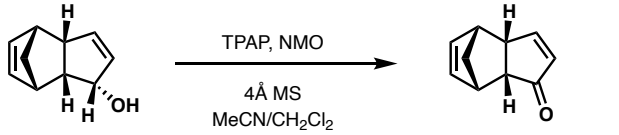
FTIR (ATR): 2990. 2972, 1683, 1576, 1347, 1333, 1294, 1251, 1224, 1194, 1178, 1120, 1091, 1018, 959, 853, 817, 784, 739, 721, 652 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{10}H_{11}O$ $[M+H]^+$ 147.0810, found: 147.0809.

$[\alpha]_D^{23}$: +136.6° (c = 1.0, $CHCl_3$).

Preparation of enone (–)-33:

A. Oxidation using TPAP, NMO:

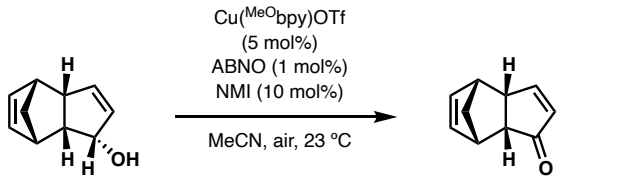


(+)-*65* **(–)-*33*** (71%, >99% ee)

A 100 mL round bottom flask containing 4Å molecular sieves (9.0 g) was flame dried under vacuum. After the flask cooled down to room temperature, **(+)-65** (2.00 g, 13.5 mmol), NMO (3.16 g, 27 mmol, 2 equiv) was added and dissolved in MeCN (3 mL) and CH_2Cl_2 (27 mL). TPAP (142

mg, 0.41 mmol, 0.03 equiv) was addedand the reaction was stirred under argon for 1 hour, and the reaction progress was monitored by GC. The reaction mixture was filtered over celite and concentrated. Column chromatography (SiO_2, 4:1 hexenes/EtOAc) afforded **(–)-33** as a white solid (1.41 g, 71%).

B. Oxidation using Stahl's conditions:



(+)-*65* **(–)-*33*** (97%, >99% ee)

An oven-dried, 200 mL round-bottomed flask was charged with alcohol **(+)-65** (2.01 g, 13.6 mmol, 1.0 equiv) and anhydrous MeCN (100 mL). The solution was vigorously stirred (>700 rpm) open to air while being treated with MeObpy (147 mg, 0.68 mmol, 0.05 equiv), $Cu(MeCN)_4OTf$ (256 mg, 0.68 mmol, 0.05 equiv), ABNO (0.04 M in MeCN, 3.4 mL, 135.6 μmol, 0.01 equiv), and then NMI (110 μL, 1.36 mmol, 0.10 equiv) via microsyringe. The resulting brick-red reaction mixture was vigorously stirred exposed to air at ambient temperature until the reaction mixture turned a blue-green in an hour, at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was diluted with Et_2O (50 mL), and filtered through Celite, washing with 50% EtOAc/hexanes. The filtrate was concentrated *in vacuo* and the crude residue was directly purified by flash chromatography (SiO_2, 4:1 hexenes/EtOAc) to afford **(–)-33** (1.92 g, 97% yield) as a white solid.

TLC (4:1 hexanes/EtOAc): R_f= 0.35 (UV).

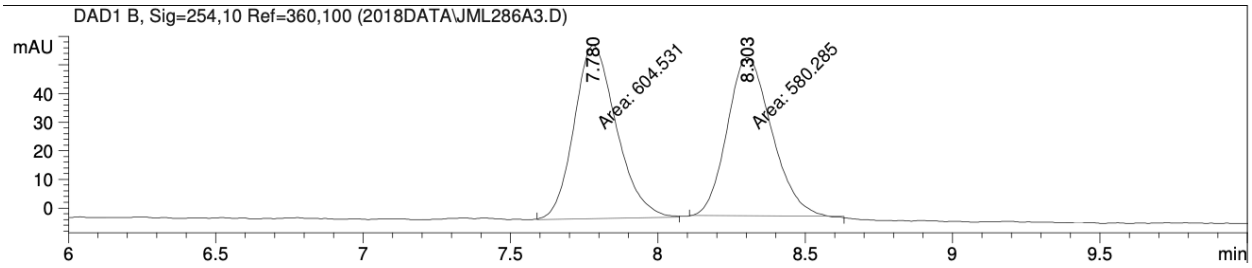
^{1}H NMR spectrum data matches **(+)-33**

$[\alpha]_D^{23}$: –121.9° (c = 1.0, $CHCl_3$).

HPLC Conditions:

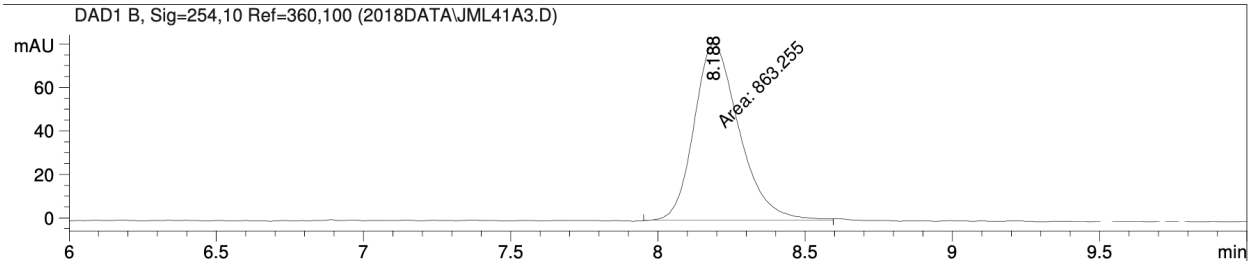
5% IPA, 1.0 mL/min, Chiralcel OJ-H column, λ = 254 nm, t_R (min) = 7.78, 8.30

(±)-33:



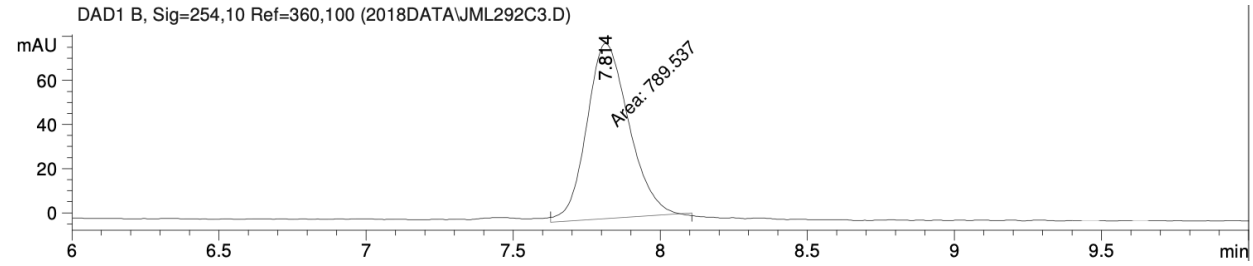
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.780	MM	0.1661	604.53131	60.67163	51.0232
2	8.303	MM	0.1745	580.28510	55.43233	48.9768

(+)-33:



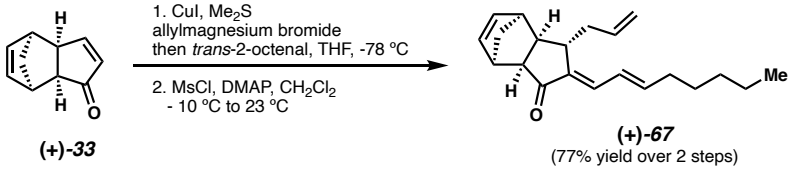
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.188	MM	0.1770	863.25543	81.28345	100.0000

(–)-33:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.814	MM	0.1656	789.53735	79.48574	100.0000

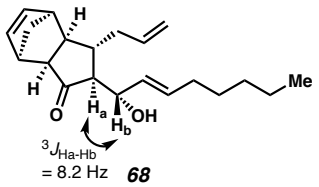
Preparation of (+)-67:



(+)-*33* **(+)-*67***
(77% yield over 2 steps)

A 250 mL flask was charged with CuI (2.56 g, 13.44 mmol, 1.2 equiv) and flame dried under vacuum. After cooling to room temperature, anhydrous THF (100 mL) and Me_2S (5 mL) was added, and the solution was vigorously stirred for 5 minutes at room temperature until a yellow homogeneous solution was formed. At –78ºC, allylmagnesium bromide (12.3 mL, 1.0 M solution in THF, 12.3 mmol, 1.1 equiv) was added slowly. The reaction mixture was stirred at –78 ºC for 1 hour and a solution of **(+)-33** (1.637 g, 11.2 mmol, 1.0 equiv) in THF (5 mL) was added slowly. After 30 minutes stirring at the same temperature, a solution of *trans*-2-octenal (2.826 g, 22.4 mmol, 2.0 equiv) in THF (3 mL) was added slowly. The reaction was stirred for additional 1 hour at –78 ºC, and a solution of saturated NH_4Cl and $NH_3•H_2O$ (100 mL, 9:1 $NH_4Cl/NH_3•H_2O$) was added. The biphasic solution was warmed to room temperature and was vigorously stirred until a homogeneous dark blue solution was formed in the aqueous phase. The phases were separated and the organic phase was washed with 20 mL saturated NH_4Cl solution. The combined aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and was concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 15:1) to give a mixture of diastereomers of the aldol products (3.6g).

A portion of reaction mixture was taken out and the major diastereomer **68** was isolated as follow:



68

TLC (4:1 hexanes/EtOAc): R_f= 0.33 (*p*-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (dd, *J* = 5.7, 2.9 Hz, 1H), 6.10 (dd, *J* = 5.8, 3.0 Hz, 1H), 5.80 (dddd, *J* = 15.7, 11.0, 8.1, 6.1 Hz, 1H), 5.63 (dt, *J* = 15.3, 6.7 Hz, 1H), 5.30 (ddt, *J* = 15.3, 8.0, 1.6 Hz, 1H), 5.13 – 5.06 (m, 2H), 4.18 (d, *J* = 1.9 Hz, 1H), 4.04 (td, *J* = 8.2, 1.9 Hz, 1H), 3.19 (ddt, *J* = 4.5, 3.0, 1.4 Hz, 1H), 3.09 (ddd, *J* = 10.2, 4.7, 2.4 Hz, 1H), 2.98 (tt, *J* = 2.9, 1.6 Hz, 1H), 2.64 (ddd, *J* = 9.9, 5.6, 4.1 Hz, 1H), 2.40 (dddd, *J* = 13.3, 5.5, 3.8, 1.7 Hz, 1H), 2.12 – 1.97 (m, 4H), 1.57 (dt, *J* = 8.4, 1.8 Hz, 1H), 1.51 – 1.42 (m, 2H), 1.41 – 1.22 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 135.8, 134.0, 129.8, 117.2, 73.1, 61.8, 56.6, 52.5, 47.2, 45.9, 45.5, 40.9, 40.4, 32.3, 31.6, 28.8, 22.6, 14.1. (Carbonyl peak not observed below 219 ppm)

FTIR (ATR): 3465, 3073, 2957, 2925, 2857, 1709, 1640, 1600, 1439, 1413, 1338, 1249, 1224, 1090, 973, 911, 836, 733 cm^{-1}.

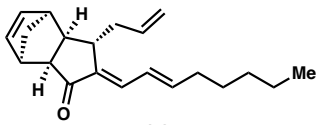
HRMS (FAB+, m/z): calc'd for $C_{21}H_{29}O_2$ $[M+H-H_2]^+$ 313.2168, found: 313.2158.

$[\alpha]_D^{23}$**:** +28.1° (c = 1.0, $CHCl_3$).

Kobayashi et al. established that for compounds **68** (*anti*-aldols) $^3J_{Ha\text{-}Hb}$ is in the range of 8.4 to 9.7 Hz, while for the corresponding *syn*-aldols $^3J_{Ha\text{-}Hb}$ is around 3 Hz.[45]

Without further separation, the crude aldol product was dissolved in CH_2Cl_2 (200 mL) and cooled to 0 ºC. DMAP (20.5 g, 168 mmol, 15.0 equiv) and MsCl (2.6 mL, 33.6 mmol, 3.0 equiv) was added sequentially. The reaction mixture was slowly warmed to room temperature and stirred for 16 h before washed with 1 M HCl (100 mL). The aqueous phase was extracted with EtOAc (3 ×

100 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to give **(+)-67** (2.55 g, 77% yield over 2 steps) as a yellow liquid.



(+)-*67*

TLC (10:1 hexanes/EtOAc): R_f= 0.48 (UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 10.7, 2.1 Hz, 1H), 6.20 – 6.04 (m, 2H), 5.97 (qd, *J* = 5.6, 2.7 Hz, 2H), 5.79 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.14 – 5.05 (m, 2H), 3.24 (tq, *J* = 2.8, 1.4 Hz, 1H), 3.01 (dp, *J* = 4.4, 1.4 Hz, 1H), 2.97 (dd, *J* = 8.6, 4.8 Hz, 1H), 2.64 – 2.56 (m, 2H), 2.35 – 2.26 (m, 1H), 2.22 – 2.07 (m, 3H), 1.49 – 1.37 (m, 4H), 1.35 – 1.23 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H).

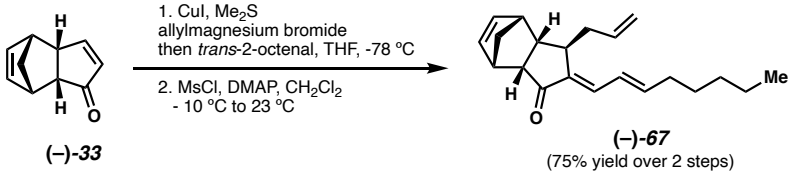
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8, 146.8, 141.1, 136.1, 136.0, 133.5, 132.7, 126.3, 117.1, 54.0, 51.5, 47.4, 47.2, 43.7, 41.2, 40.3, 33.5, 31.4, 28.5, 22.5, 14.0.

FTIR (ATR): 3062, 2957, 2928, 2858, 1701, 1625, 1600, 1438, 1341, 1293, 1202, 1178, 1122, 973, 912, 727, 698 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{21}H_{29}O$ $[M+H]^+$ 297.2218, found: 297.2214.

$[\alpha]_D^{23}$: +150.4° (c = 1.0, $CHCl_3$).

Preparation of (–)-67:



(–)-*33* **(–)-*67***
(75% yield over 2 steps)

A 250 mL flask was charged with CuI (571 mg, 3 mmol, 1.2 equiv) and flame dried under vacuum. After cooling to room temperature, anhydrous THF (25 mL) and Me_2S (1 mL) was added, and the solution was vigorously stirred for 5 minutes at room temperature until a yellow homogeneous solution was formed. At –78ºC, allylmagnesium bromide (2.75 mL, 1.0 M solution in THF, 2.75 mmol, 1.1 equiv) was added slowly. The reaction mixture was stirred at –78 ºC for 1 hour and a solution of **(–)-33** (365 mg, 2.5 mmol, 1.0 equiv) in THF (2 mL) was added slowly. After 30 minutes stirring at the same temperature, a solution of *trans*-2-octenal (631 mg, 5.0 mmol, 2.0 equiv) in THF (1 mL) was added slowly. The reaction was stirred for additional 1 hour at –78 ºC, and a solution of saturated NH_4Cl and $NH_3•H_2O$ (25 mL, 9:1 $NH_4Cl/NH_3•H_2O$) was added. The biphasic solution was warmed to room temperature and vigorously stirred until a homogeneous dark blue solution was formed in the aqueous phase. The phases were separated and the organic phase was washed with 10 mL saturated NH_4Cl solution. The combined aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and was concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 15:1) to give a mixture of diasteromers of the aldol products (790 mg).

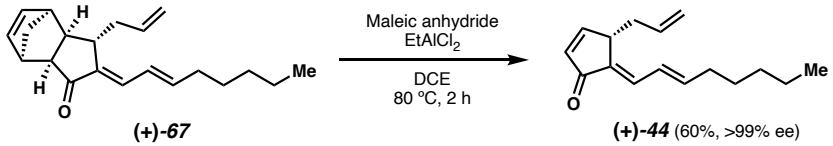
Without further separation, the crude aldol product was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 ºC. DMAP (4.58 g, 37.5 mmol, 15.0 equiv) and MsCl (0.58 mL, 7.5 mmol, 3.0 equiv) was added sequentially. The reaction mixture was slowly warmed to room temperature and stirred for

16 h before being washed with 1 M HCl (40 mL). The aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic phase was dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to give **(–)-67** (559 mg, 75% yield over 2 steps) as a yellow liquid.

Characterization data matches **(+)-67**.

$[\alpha]_D^{23}$**:** –193.4° (c = 1.0, $CHCl_3$).

Preparation of (+)-44:



(+)-*67* **(+)-*44*** (60%, >99% ee)

In a 100 mL round bottom flask, **(+)-67** (1.64 g, 5.54 mmol, 1.0 equiv) was dissolved in DCE (50 mL) and maleic anhydride (5.4 g, 55.4 mmol, 10.0 equiv) and $EtAlCl_2$ (6.0 mL, 1.0 M solution in hexanes, 6.0 mmol, 1.1 equiv) were added sequentially. A reflux condenser was attached and the reaction mixture was warmed to reflux under argon. After 2 hours, the reaction mixture was cooled down, concentrated, and directly loaded on silica gel. Purification by flash chromatography (hexanes/EtOAc 15:1) afforded **(+)-44** (760 mg, 60% yield, >99% ee by chiral HPLC analysis) as a colorless liquid.

TLC (4:1 hexanes/EtOAc): R_f= 0.56 (UV).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.95 (dt, *J* = 10.7, 1.2 Hz, 1H), 6.35 (dd, *J* = 6.0, 1.8 Hz, 1H), 6.33 – 6.15 (m, 2H), 5.81 – 5.64 (m, 1H), 5.11 – 5.01 (m, 2H), 3.60 (ddq, *J* = 8.5, 4.1, 1.9 Hz, 1H), 2.73 – 2.58 (m, 1H), 2.24 (dddd, *J* = 13.4, 9.7, 6.8, 1.5 Hz, 3H), 1.54 – 1.37 (m, 2H), 1.38 – 1.22 (m, 4H), 0.96 – 0.84 (t, 3H, *J* = 6.9 Hz).

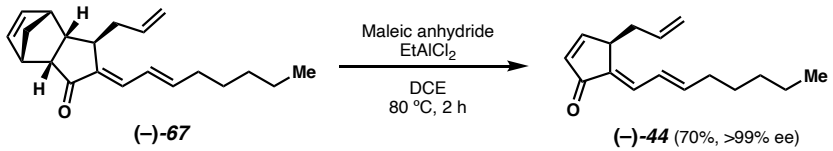
^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 160.6, 147.1, 135.4, 134.9, 134.3, 131.8, 125.7, 117.8, 43.2, 37.4, 33.6, 31.5, 28.6, 22.6, 14.1.

FTIR (ATR): 2956, 2926, 2856, 1692, 1631, 1580, 1440, 1338, 1280, 1207, 1102, 977, 915, 871, 839, 801, 753, 730, 666 cm^{-1}.

HRMS (FAB+, m/z): calc'd for $C_{16}H_{21}O$ $[M+H-H_2]^+$ 229.1586, found: 229.1581.

$[\alpha]_D^{23}$**:** +150.4° (c = 1.0, $CHCl_3$).

Preparation of (–)-44:



(–)-*67* **(–)-*44*** (70%, >99% ee)

In a 50 mL round bottom flask, **(–)-67** (667 mg, 2.25 mmol, 1.0 equiv) was dissolved in DCE (20 mL) and maleic anhydride (2.2 g, 22.5 mmol, 10.0 equiv) and $EtAlCl_2$ (2.5 mL, 1.0 M solution in hexanes, 2.5 mmol, 1.1 equiv) were added sequentially. A reflux condenser was attached and the reaction mixture was warmed to reflux under argon. After 2 hours, the reaction mixture was cooled down, concentrated, and directly loaded on silica gel. Purification by flash chromatography (hexanes/EtOAc 15:1) afforded **(–)-44** (361 mg, 70% yield, >99% ee by chiral HPLC analysis) as a colorless liquid.

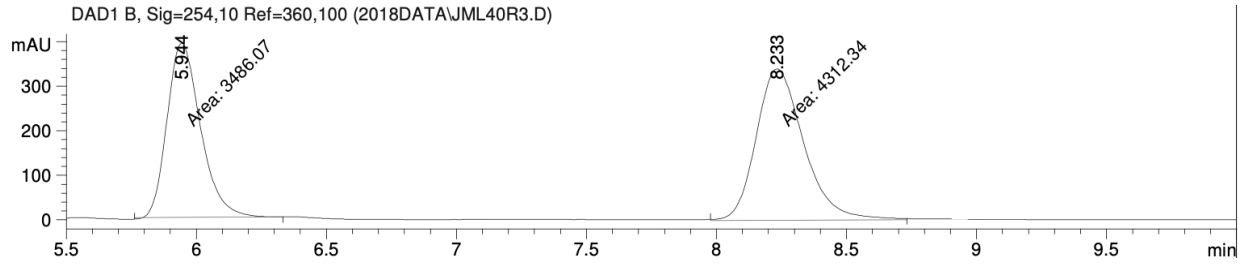
Characterization data matches **(+)-44.**

$[\alpha]_D^{23}$**:** –122.9° (c = 1.0, $CHCl_3$).

HPLC Conditions:

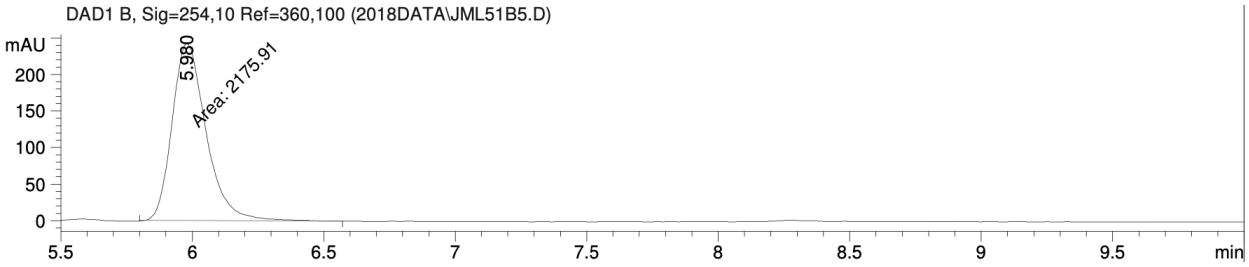
5% IPA, 1.0 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min) = 5.94, 8.23

(±)-44:



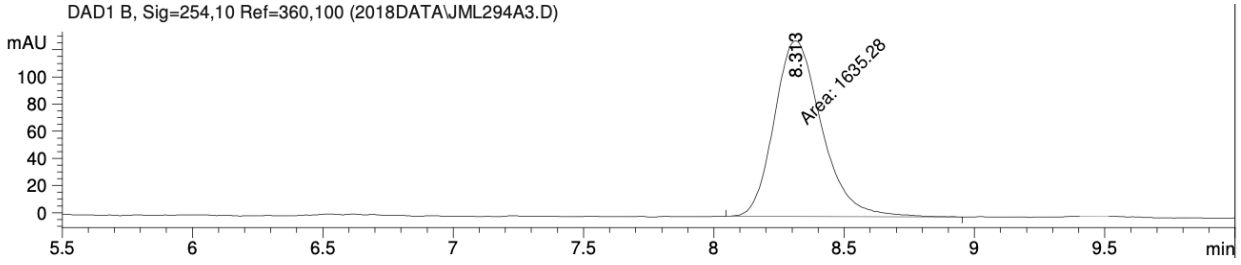
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.944	MM	0.1483	3486.06592	391.88913	44.7023
2	8.233	MM	0.2116	4312.34229	339.61151	55.2977

(+)-44:



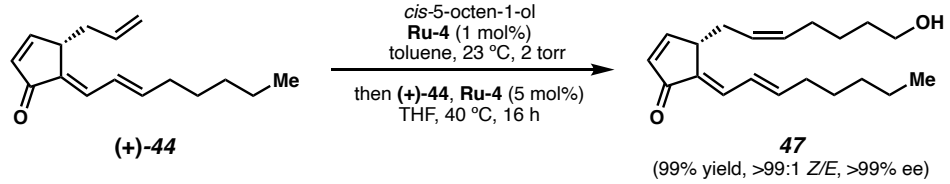
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.980	MM	0.1496	2175.91162	242.38094	100.0000

(–)-44:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.313	MM	0.2104	1635.28137	129.50676	100.0000

Preparation of 47:



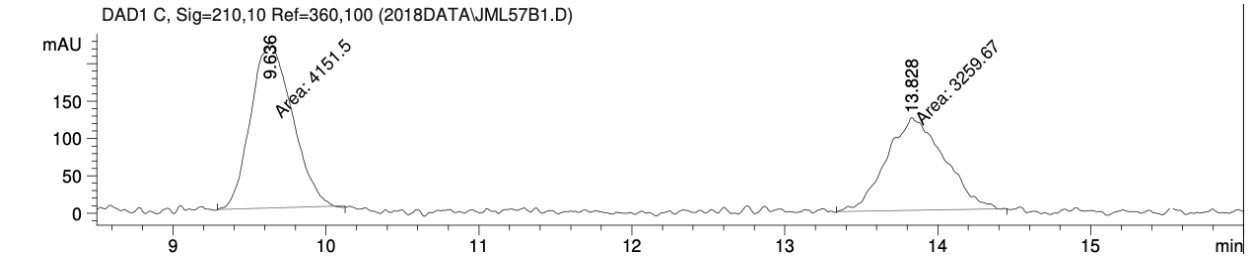
In a nitrogen-filled glovebox, *cis*-5-octen-1-ol (205 mg, 1.6 mmol, 8.0 equiv) was dissolved in toluene (2 mL) in a 50 mL Schlenk flask and a solution of catalyst **Ru-4** (13.5 mg, 16 μmol, 1 mol%) in THF (0.8 mL) was added. The Schlenk flask was sealed and brought out of the glovebox, and then connected to high vacuum. The valve was gradually opened (*Caution: open slowly and stir well to avoid splashing*). After 15 minutes stirring, the flask was refilled with argon and sealed, and was brought back into the glovebox. The residue was diluted with THF (0.5 mL), and an aliquot was taken for GC analysis (conversion of homodimerization step was >98% by GC analysis). A solution of **(+)-44** (46 mg, 0.2 mmol, 1.0 equiv) in THF (0.5 mL) was added into the Schlenk flask and an additional portion of catalyst **Ru-4** (8.5 mg, 10 μmol, 5 mol%) solution in THF (0.5 mL) was added. The Schlenk flask was sealed and brought out of glovebox. The reaction was stirred for 16 h at 40 ºC before quenched with a few drops of ethyl vinyl ether. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 2:1) to give **47** (60 mg, 99%, >99:1 *Z/E*, >99% ee by chiral HPLC analysis).

Spectral data (^{1}H NMR, ^{13}C NMR, HRMS, IR) matched with the published data.[46]

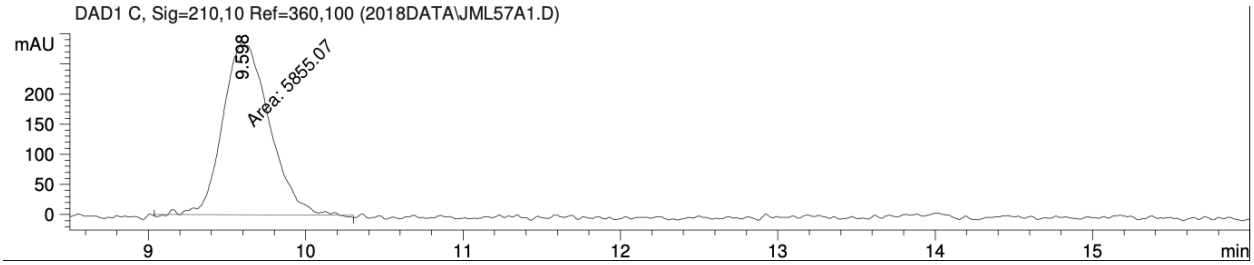
$[\alpha]_D^{23}$**:** +142.6° (c = 0.5, $CHCl_3$).

HPLC Conditions:

10% IPA, 1.0 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 9.64, minor = 13.83

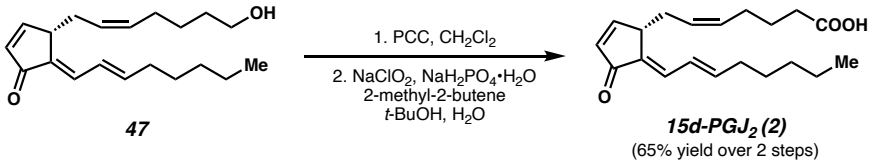


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.636	MM	0.3123	4151.50049	221.52171	56.0168
2	13.828	MM	0.4364	3259.67114	124.48434	43.9832



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.598	MM	0.3410	5855.06543	286.15173	100.0000

Preparation of 15-deoxy-Δ[12,14]-prostaglandin J_2 (2):



47 ***15d-PGJ$_2$ (2)***
(65% yield over 2 steps)

Pyridinium chlorochromate (129 mg, 0.6 mmol, 3.0 equiv) was added to a solution of **47** (60 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at room temperature. The reaction progress was monitored by TLC and diluted with Et_2O (2 mL) after stirring for 1 h. The resulting solution was filtered

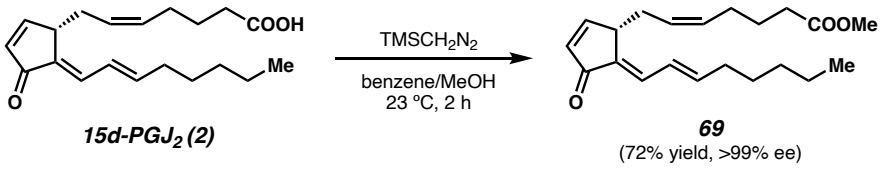
through a short pad of celite, and was concentrated and subjected to the next step without further purification.

The residue was dissolved in *t*-BuOH (3 mL) at room temperature, and 2-methyl-2-butene (210 µL, 2.0 mmol, 10 equiv), a solution of $NaH_2PO_4 \bullet H_2O$ (41.4 mg, 0.3 mmol, 1.5 equiv) in H_2O (0.72 mL) and a solution of $NaClO_2$ (80 %, 33.6 mg, 0.3 mmol, 1.5 equiv) in H_2O (0.72 mL) was added sequentially. After stirring at room temperature for 30 minutes, the reaction mixture was diluted with a solution of $NaH_2PO_4 \bullet H_2O$ (648 mg) in H_2O (12 mL) and extracted with EtOAc (5 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) afforded pure compound **2** (41 mg, 65% yield over 2 steps) as a colorless oil.

Spectral data (^{1}H NMR, ^{13}C NMR, HRMS, IR) matched with the published data.[46]

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$**:** +154.4° (c = 1.0, $CHCl_3$).

Preparation of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 methyl ester(69):



15d-PGJ$_2$ (2) ***69***
(72% yield, >99% ee)

In a 1-dram vial, 15d-PGJ_2 (**2**) (8.0 mg, 25 µmol, 1.0 equiv) was dissolved in C_6H_6/MeOH (3:2, 0.75 mL) at 23 °C. A solution of trimethylsilyldiazomethane (20 µL, 2.0 M in hexanes, 40 µmol, 1.5 equiv) (yellow color persists). After stirring for 2 hours, the reaction mixture was concentrated

under vacuum. The residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc, 4:1) to give **69** (6.0 mg, 72% yield, >99% ee) as a colorless oil.

TLC (4:1 hexanes/EtOAc): R_f= 0.28 (UV).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (ddd, *J* = 6.0, 2.6, 1.0 Hz, 1H), 6.95 (dt, *J* = 11.0, 1.2 Hz, 1H), 6.37 – 6.17 (m, 3H), 5.50 – 5.31 (m, 2H), 3.66 (s, 3H), 3.57 (ddt, *J* = 8.7, 3.8, 2.0 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.33 – 2.18 (m, 5H), 2.03 (q, *J* = 7.3 Hz, 2H), 1.66 (p, *J* = 7.5 Hz, 2H), 1.46 (p, *J* = 7.2 Hz, 2H), 1.31 (ddt, *J* = 9.3, 5.3, 3.6 Hz, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 174.0, 160.8, 147.1, 135.5, 135.2, 131.8, 131.6, 126.1, 125.8, 51.7, 43.6, 33.6, 33.5, 31.6, 30.9, 28.6, 26.8, 24.8, 22.6, 14.1.

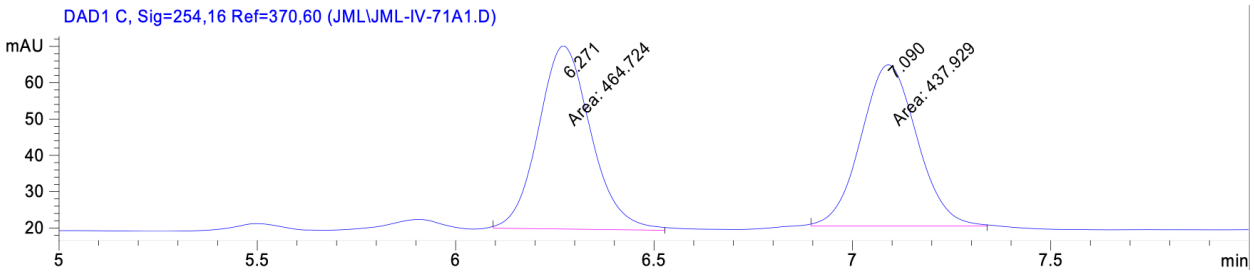
FTIR (ATR): 2953, 2927, 2856, 2360, 2342, 1736, 1694, 1632, 1579, 1436, 1364, 1205, 1090, 979, 836, 729, 668 cm^{-1}.

HRMS (TOF, ES+, m/z): calc'd for $C_{20}H_{29}O_3$ $[M+H]^+$ 331.2268, found: 331.2720.

$[\alpha]_D^{23}$: +72.1° (c = 0.2, $CHCl_3$).

SFC Conditions:

10% IPA, 4.0 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min)= 6.27, 7.09



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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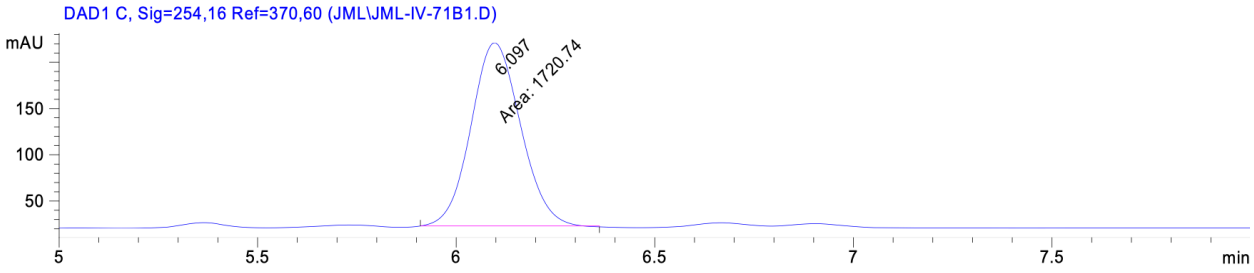
2	7.090	MM	0.1639	437.92932	44.52127	48.5158



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.097	MM	0.1443	1720.74133	198.71785	100.0000

1.7 NOTES AND REFERENCES

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9. Figure was adapted from RCSB Protein Data Bank website: https://www.rcsb.org/3d-view/2ZK1?preset=ligandInteraction&sele=PTG

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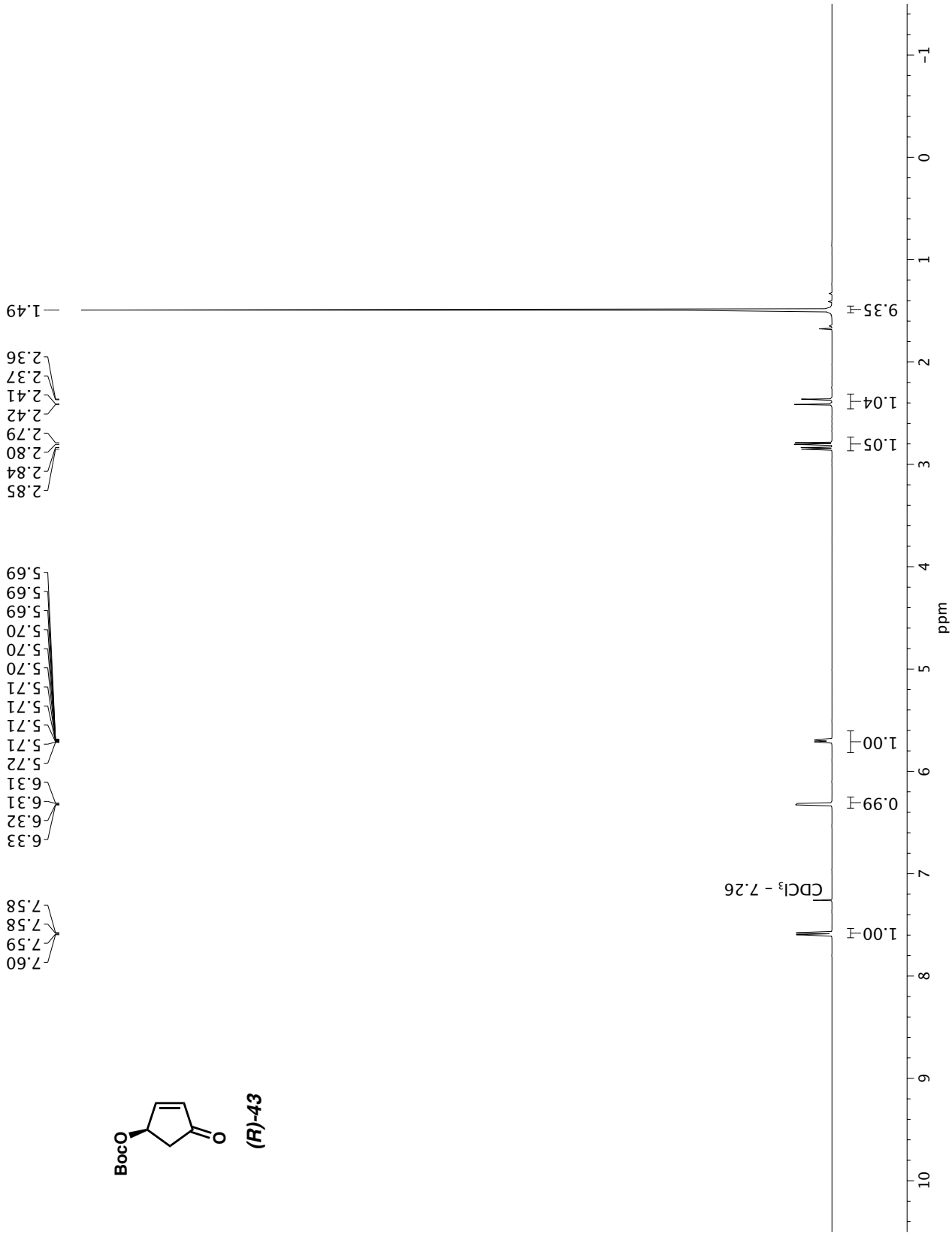
APPENDIX 1

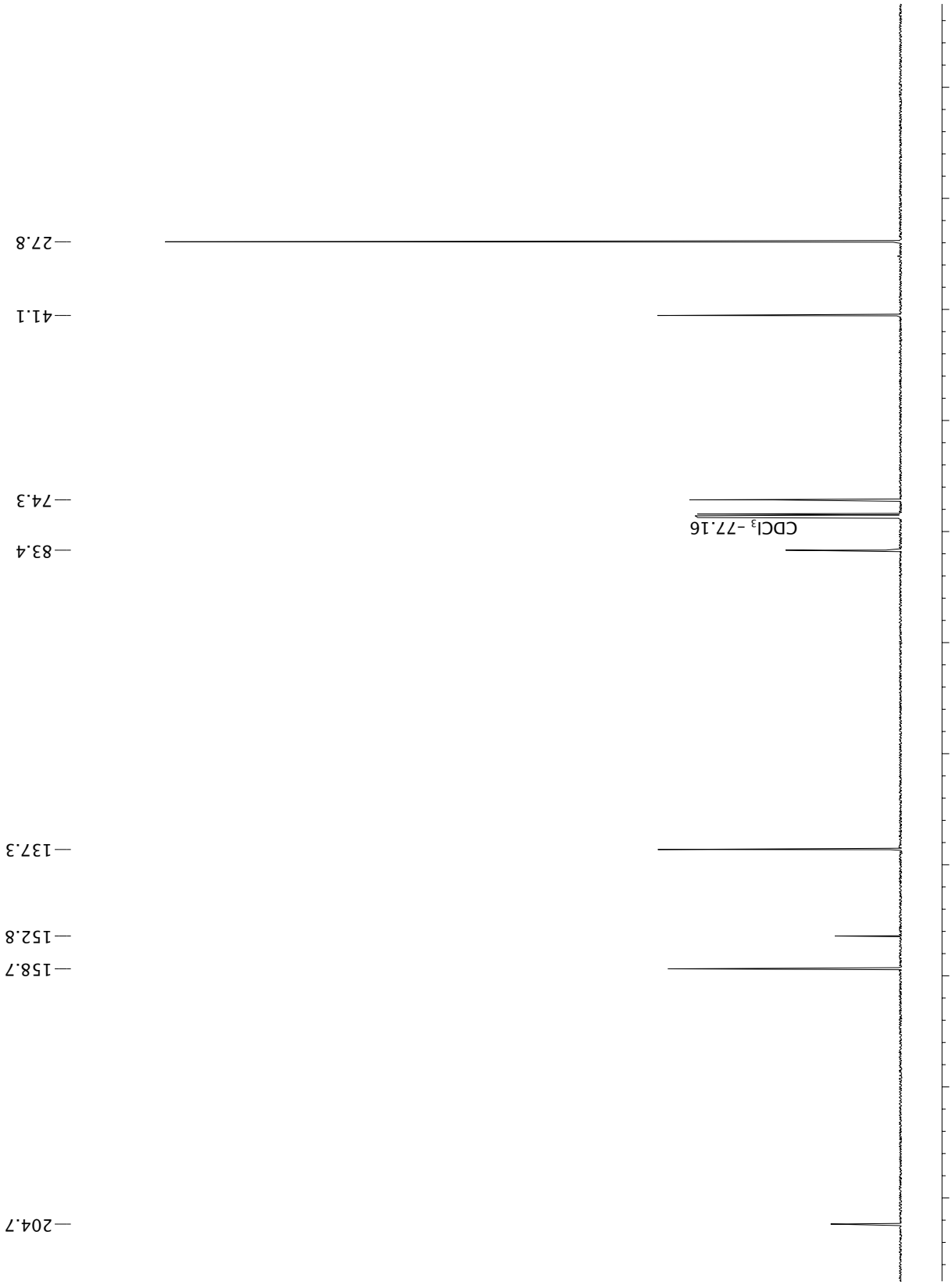
Spectra Relevant to Chapter 1:

Concise Total Syntheses of Δ^{12}-Prostaglandin J

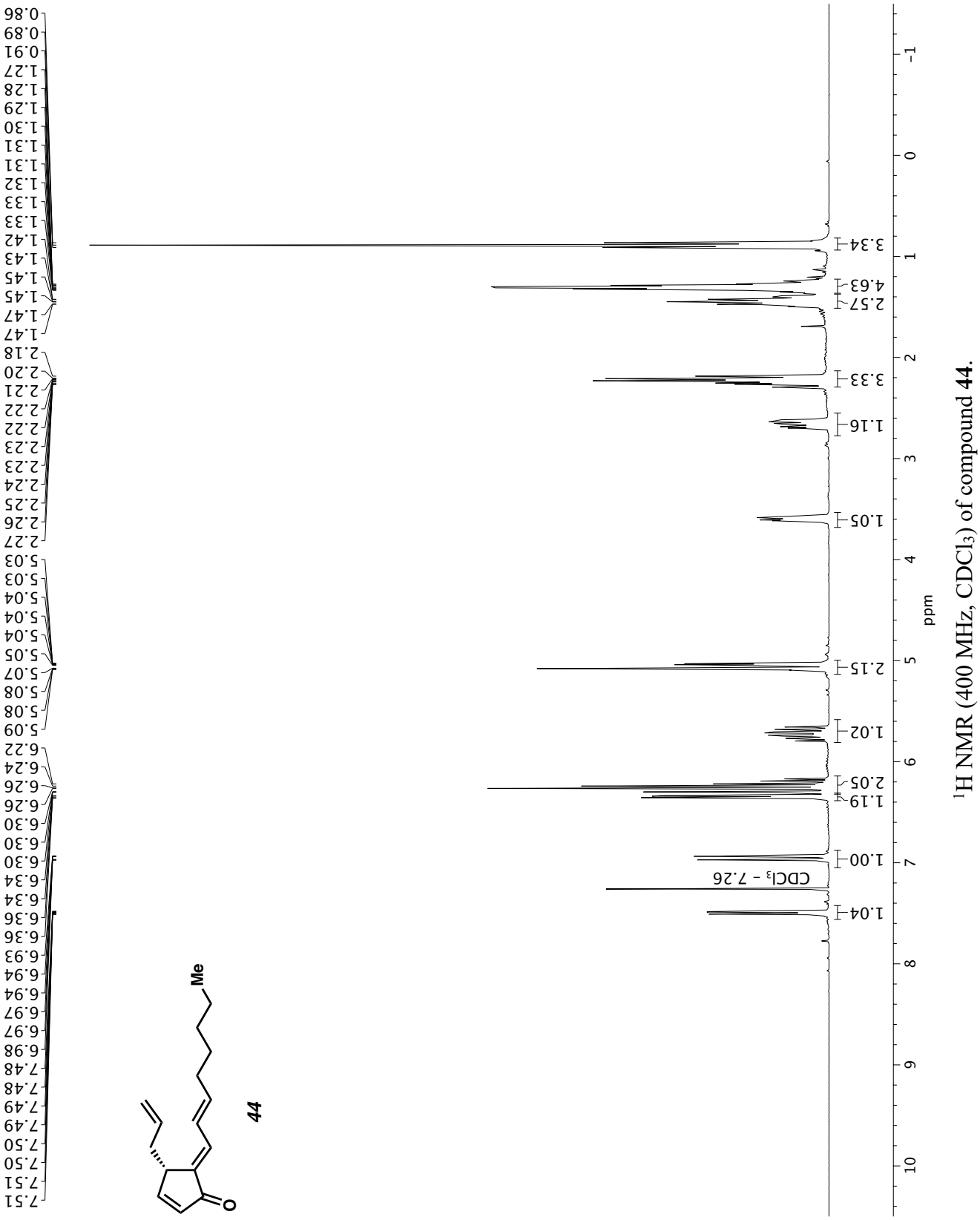
Natural Products Via Stereoretentive Metathesis



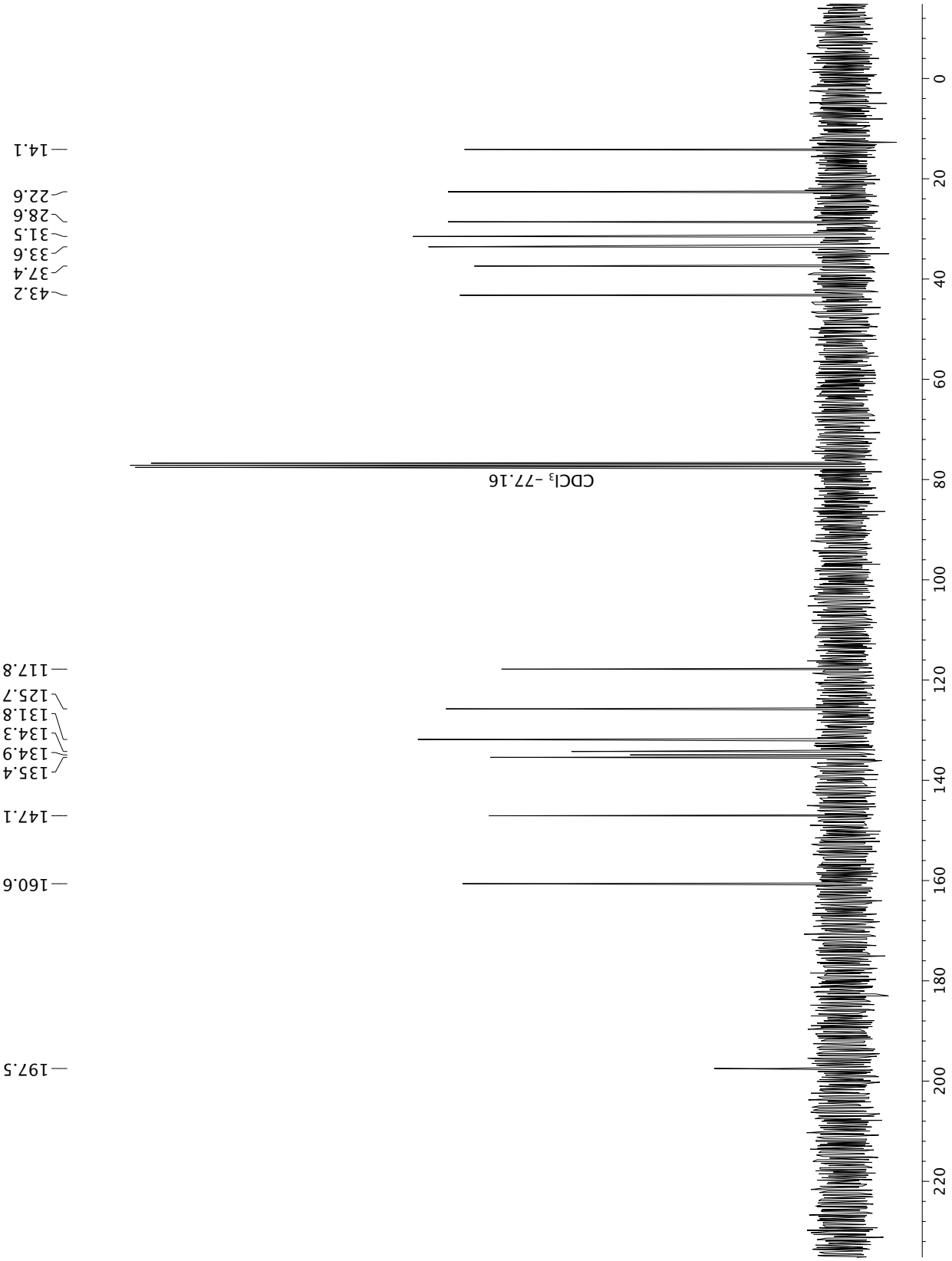
^{1}H NMR (400 MHz, $CDCl_3$) of compound ***(R)*-43**.



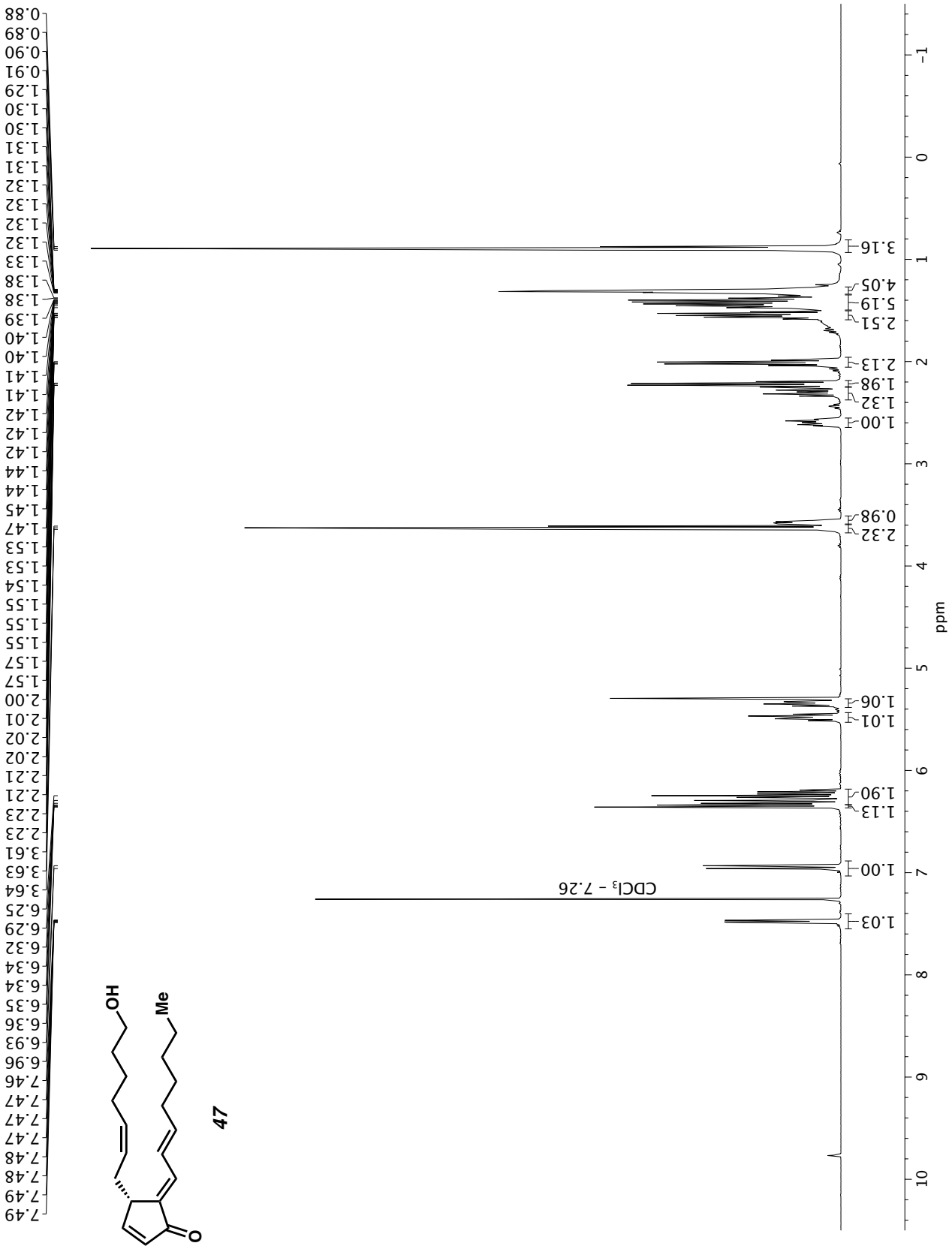
^{13}C NMR (101 MHz, $CDCl_3$) of compound ***(R)*-43**.



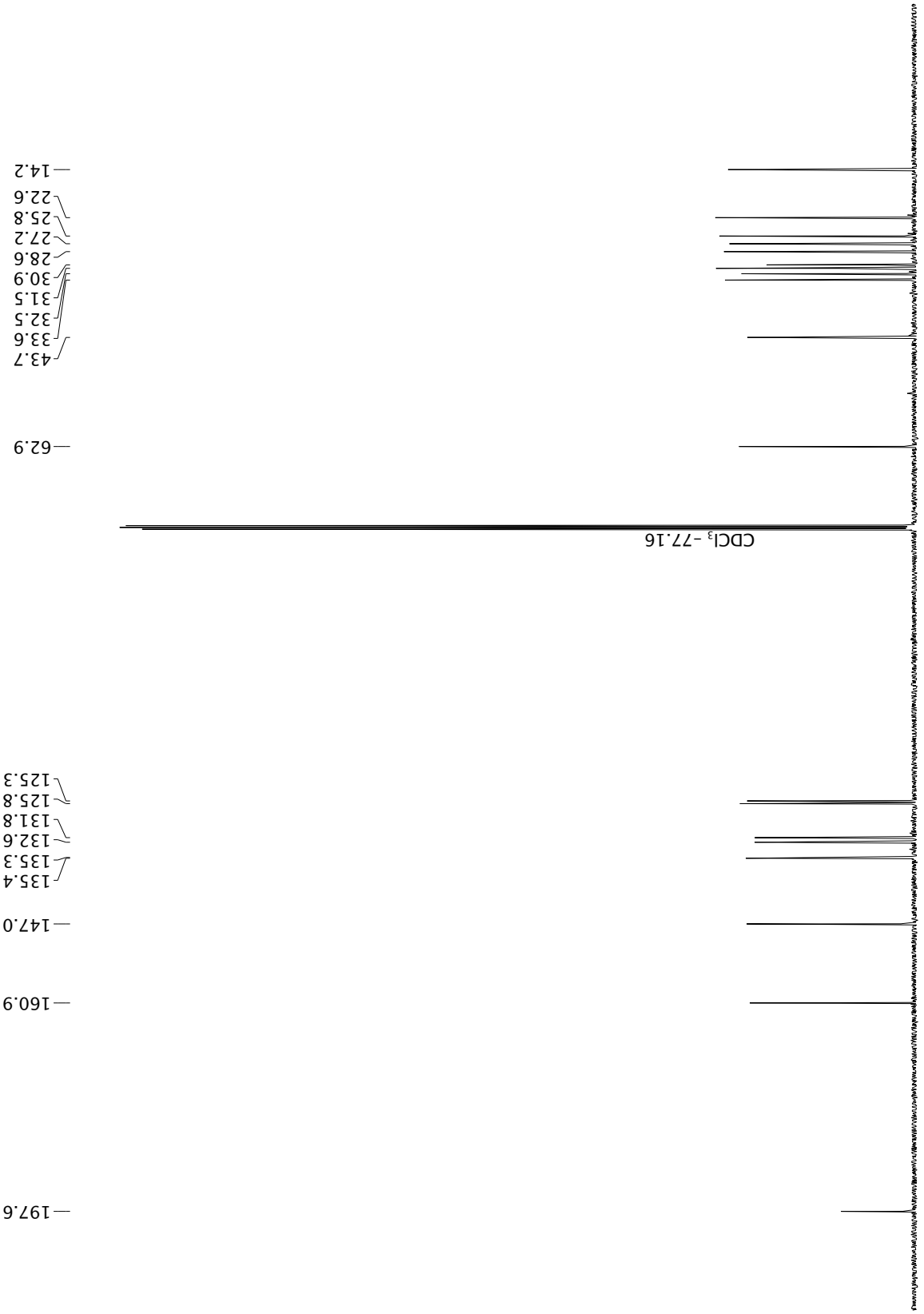
^{1}H NMR (400 MHz, $CDCl_3$) of compound **44**.



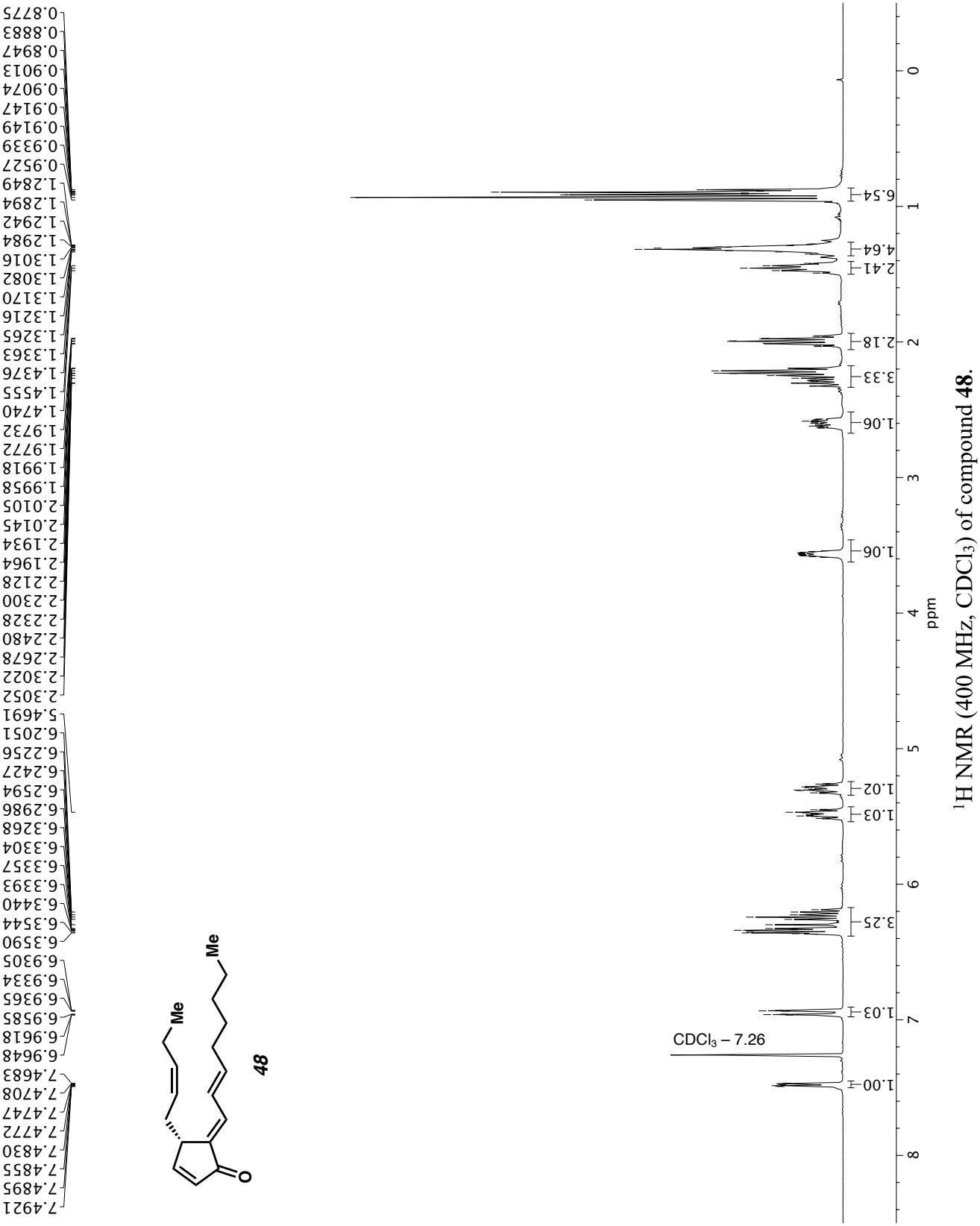
^{13}C NMR (101 MHz, $CDCl_3$) of compound **44**.



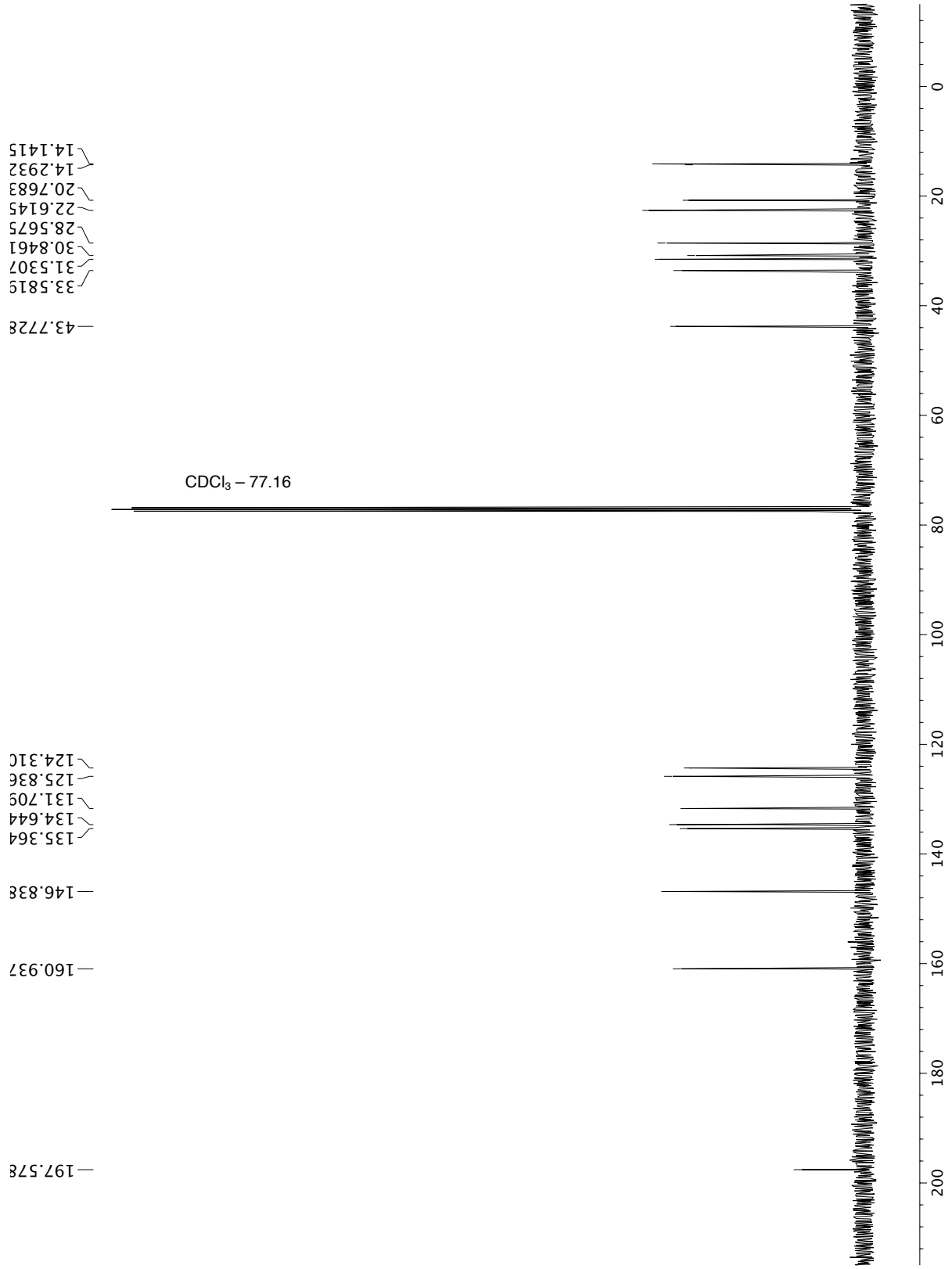
^{1}H NMR (400 MHz, $CDCl_3$) of compound **47**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **47**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **48**.



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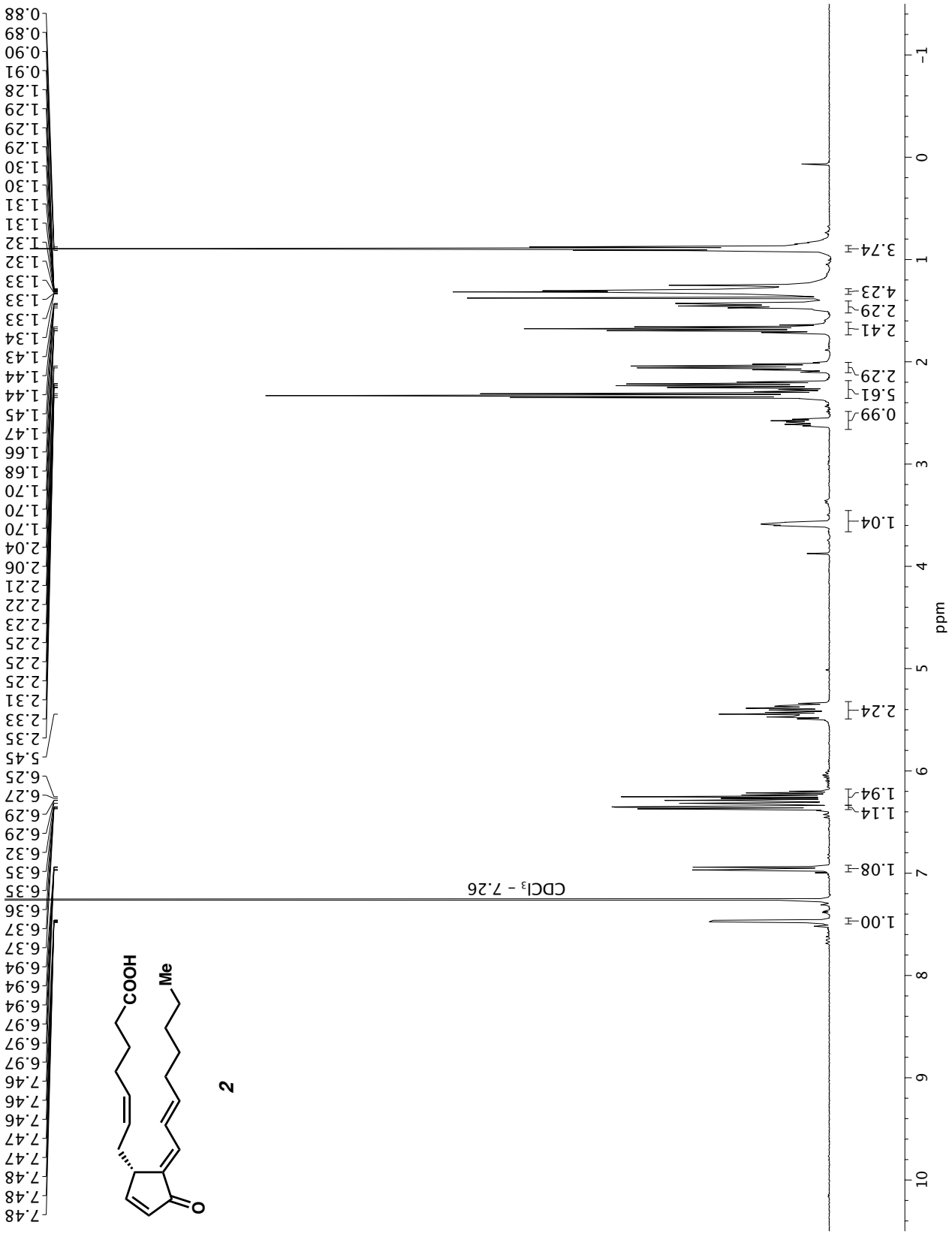
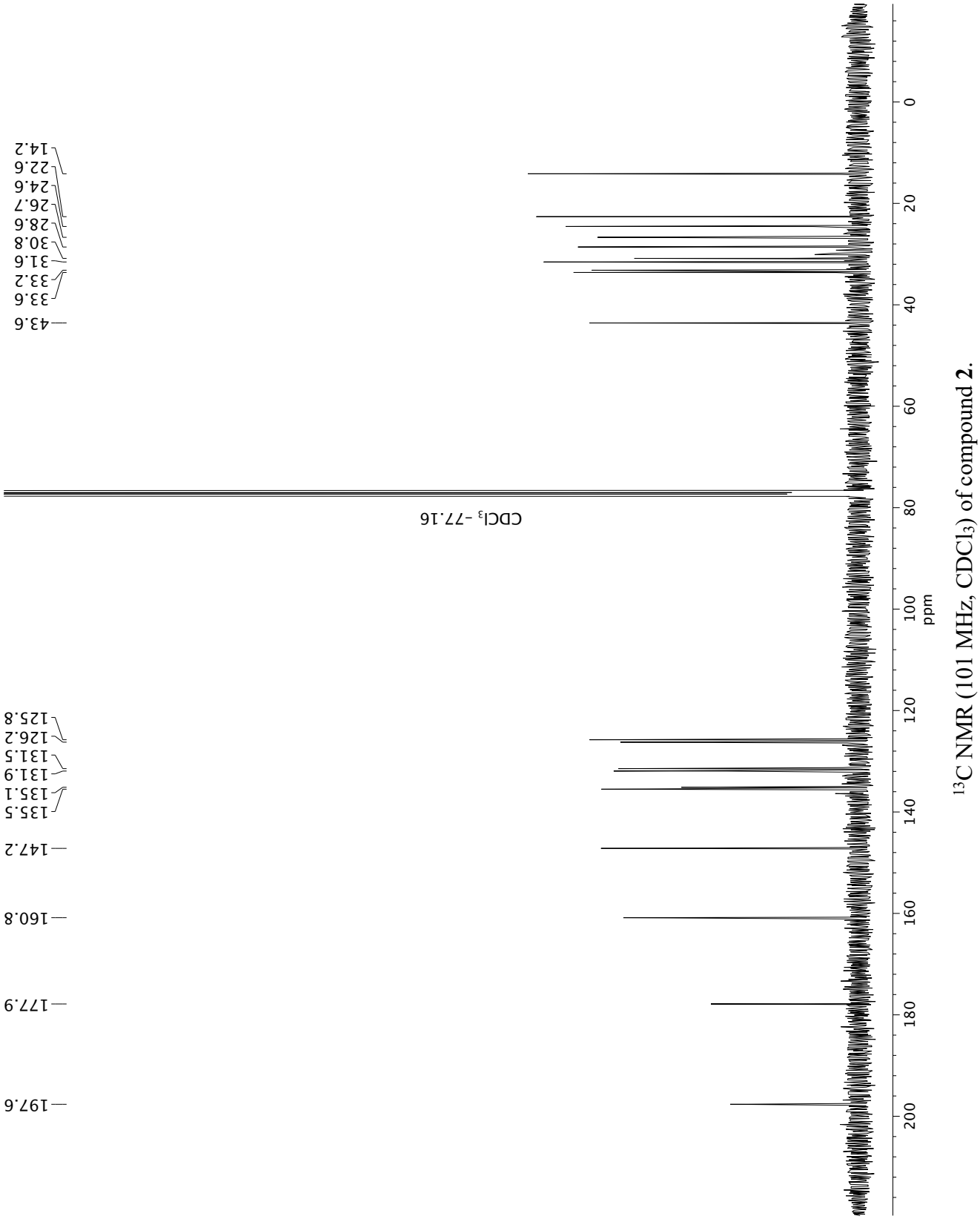


^{1}H NMR (400 MHz, $CDCl_3$) of compound **2**.



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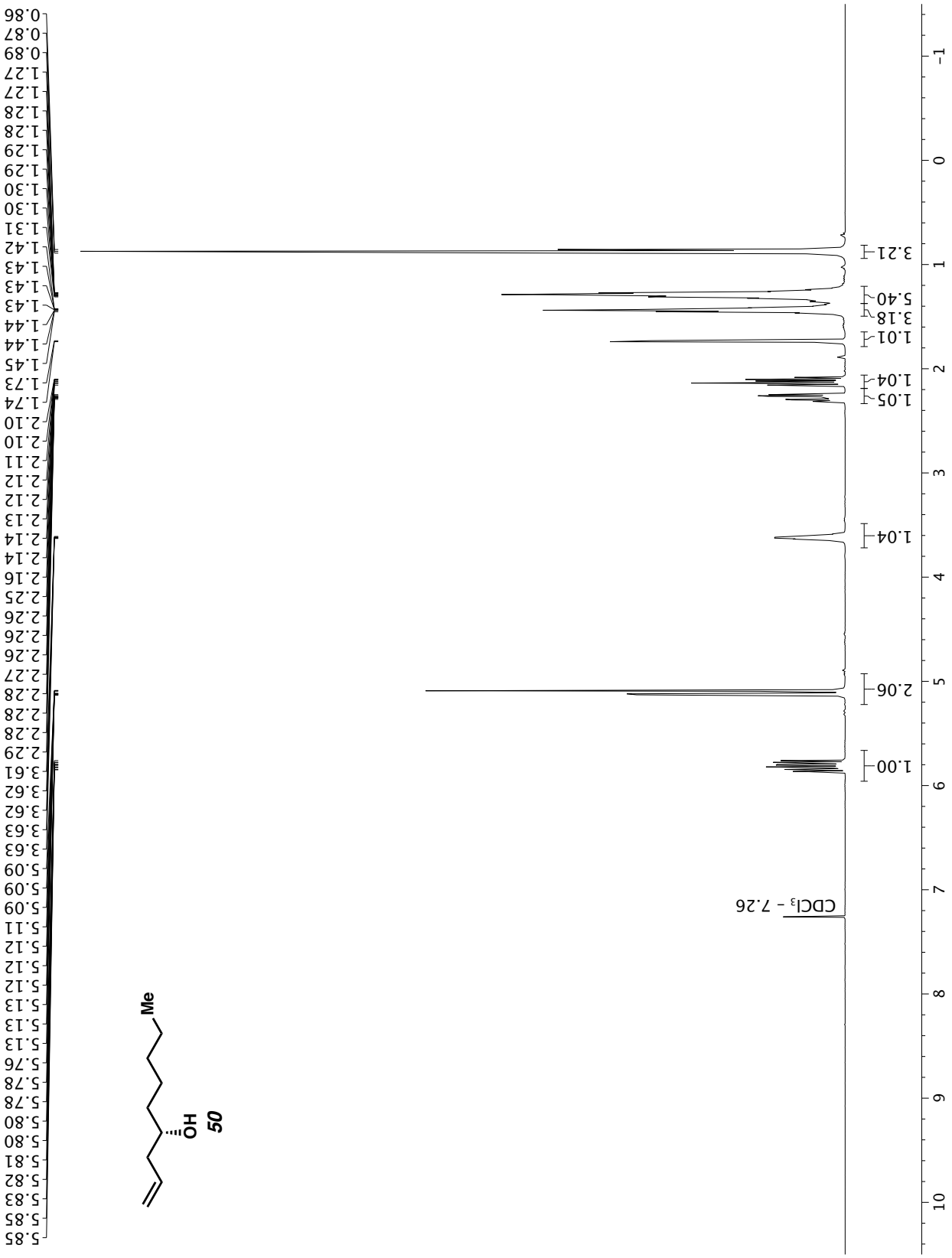

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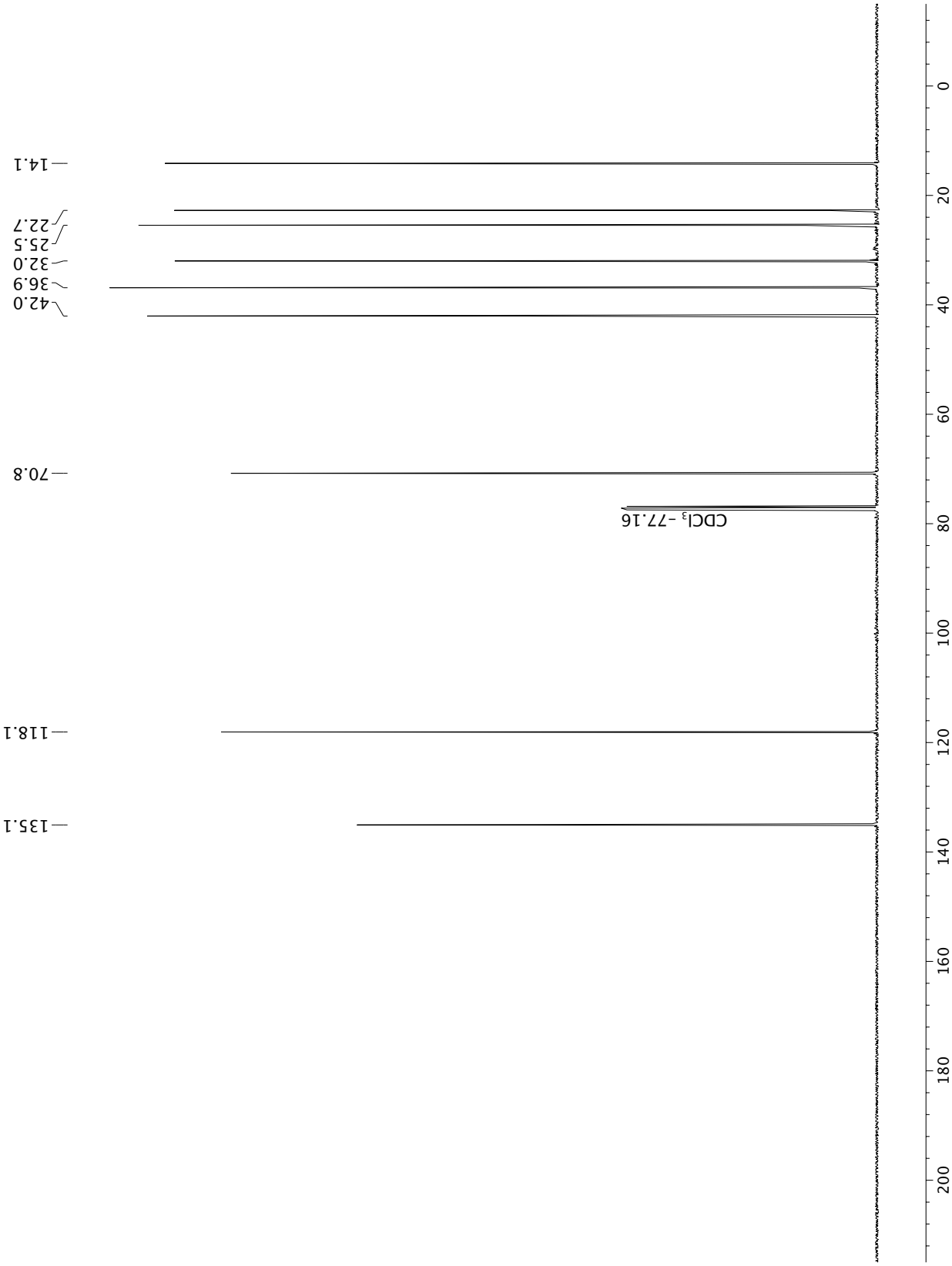

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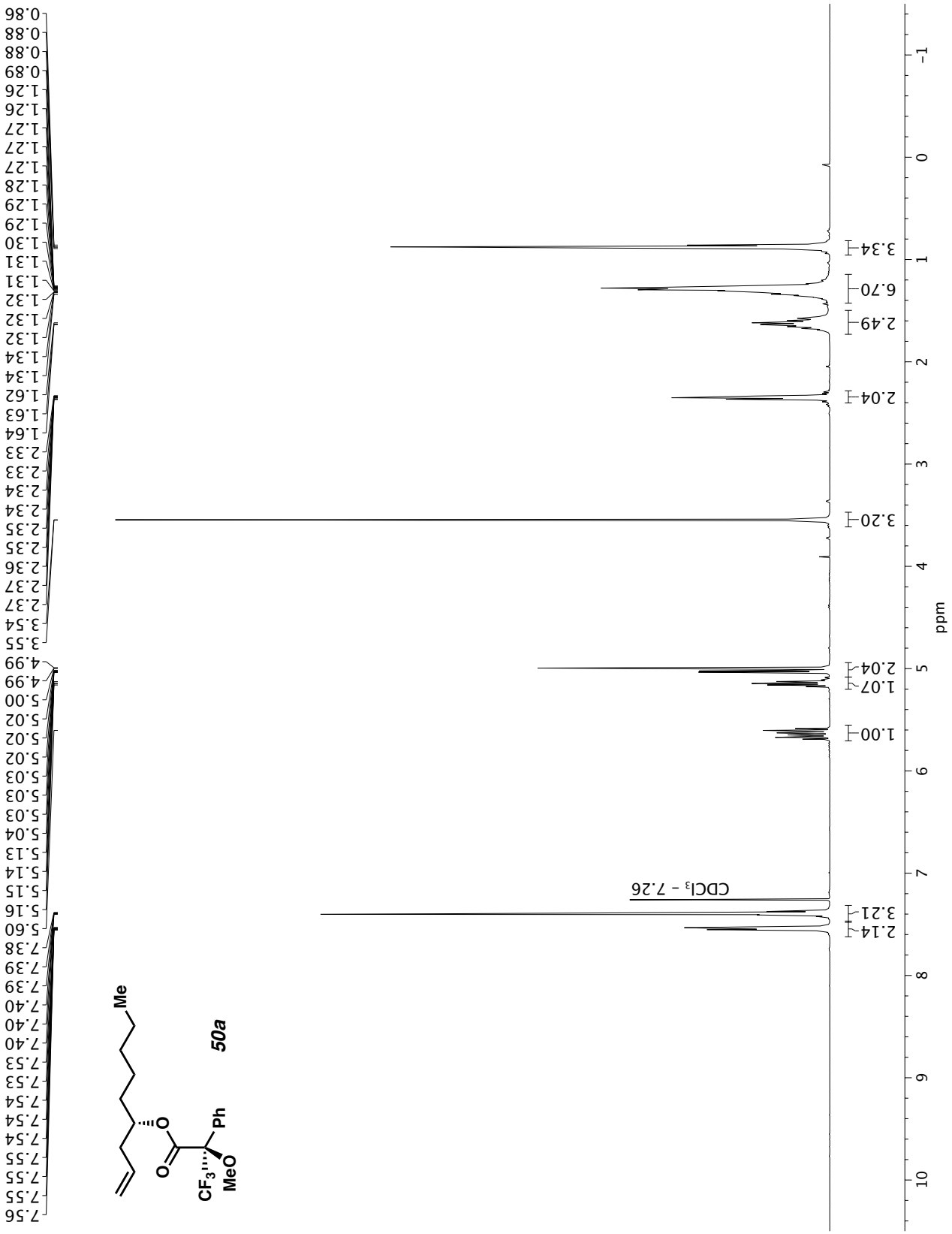
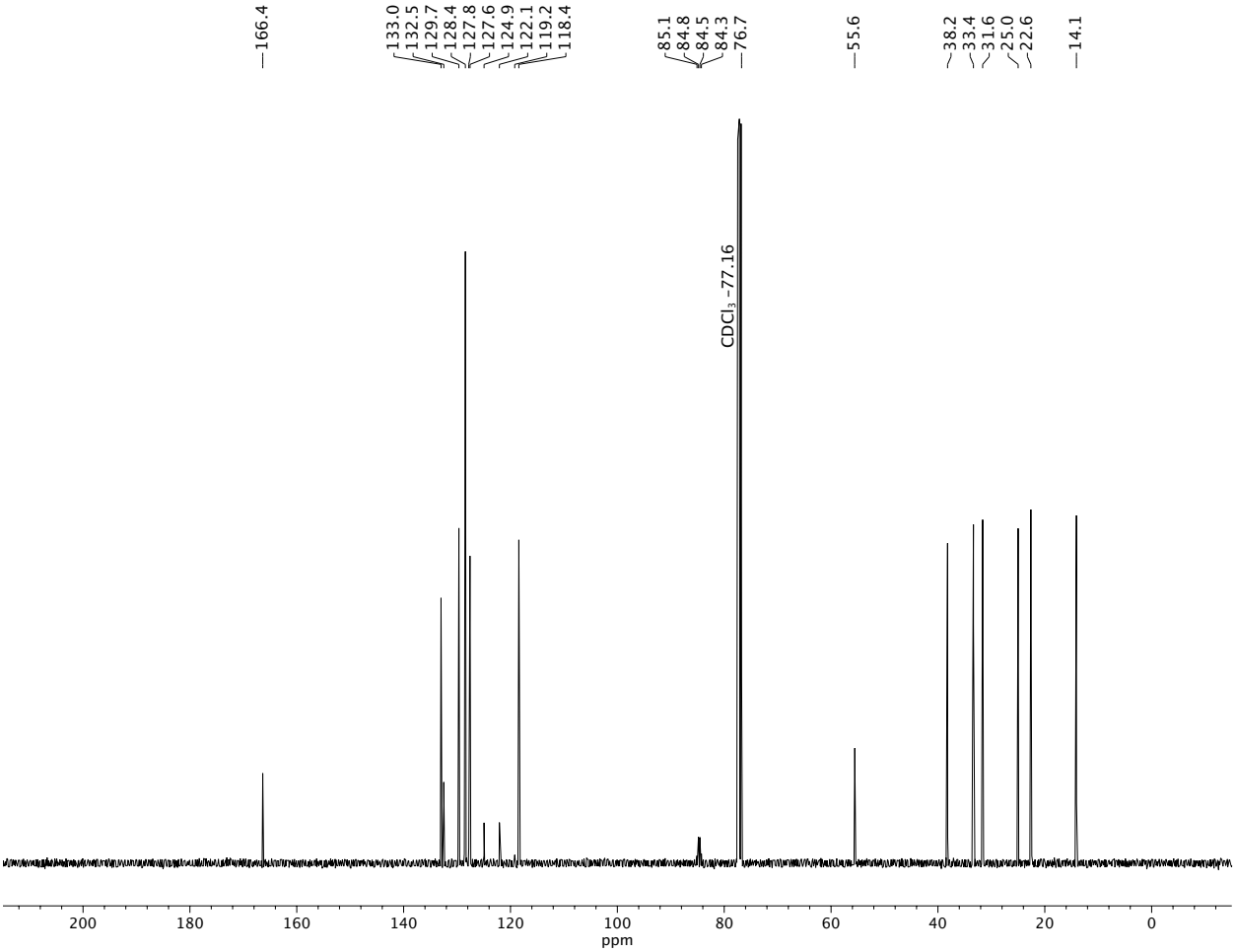
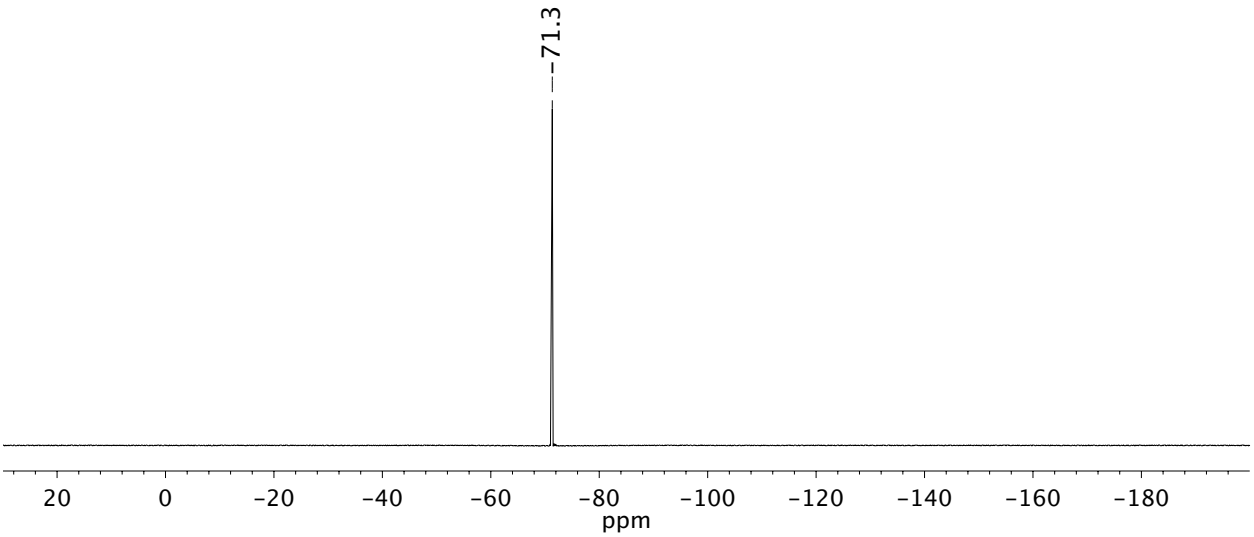


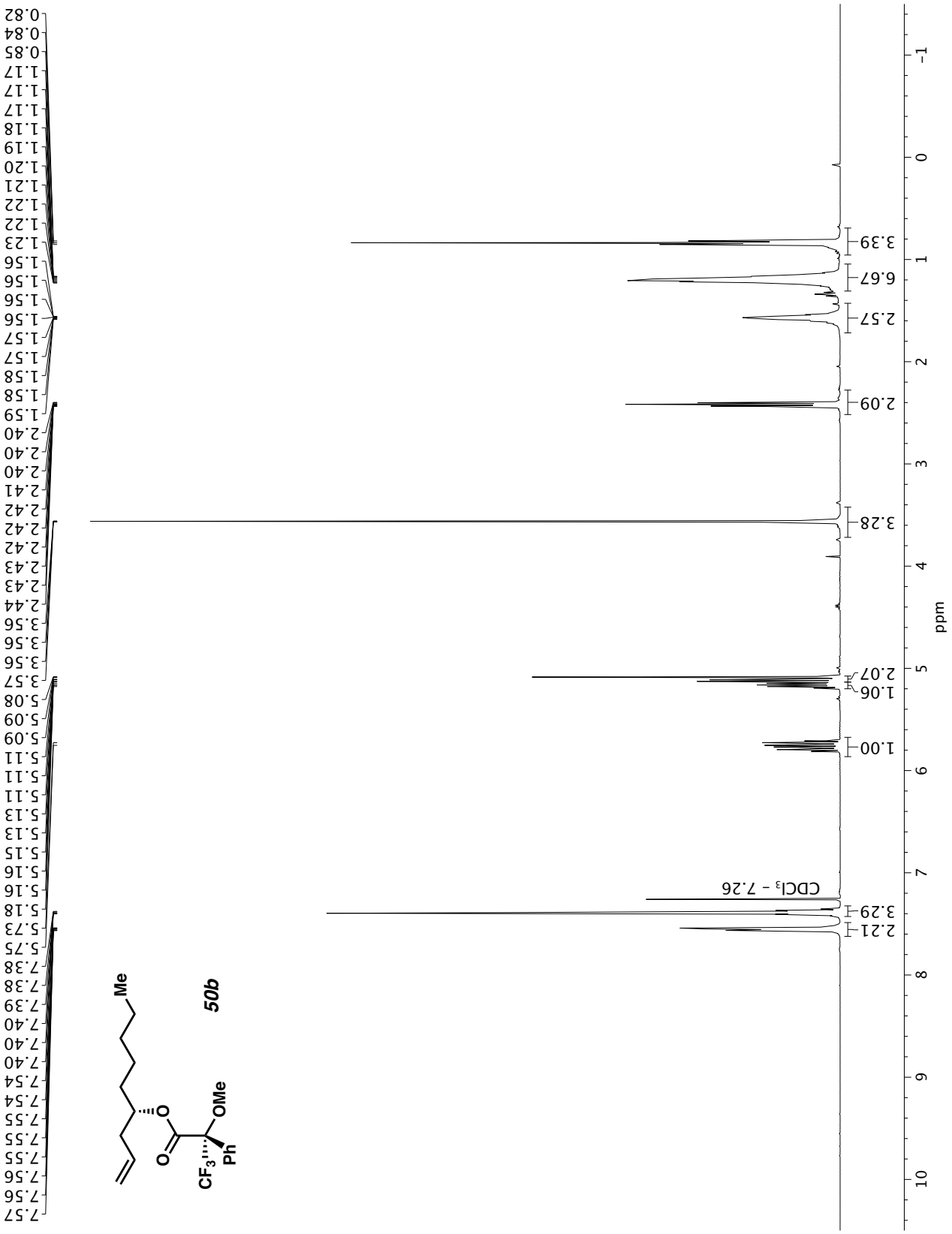
^{1}H NMR (400 MHz, $CDCl_3$) of compound **50a**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **50a**.



^{19}F NMR (282 MHz, $CDCl_3$) of compound **50a**.



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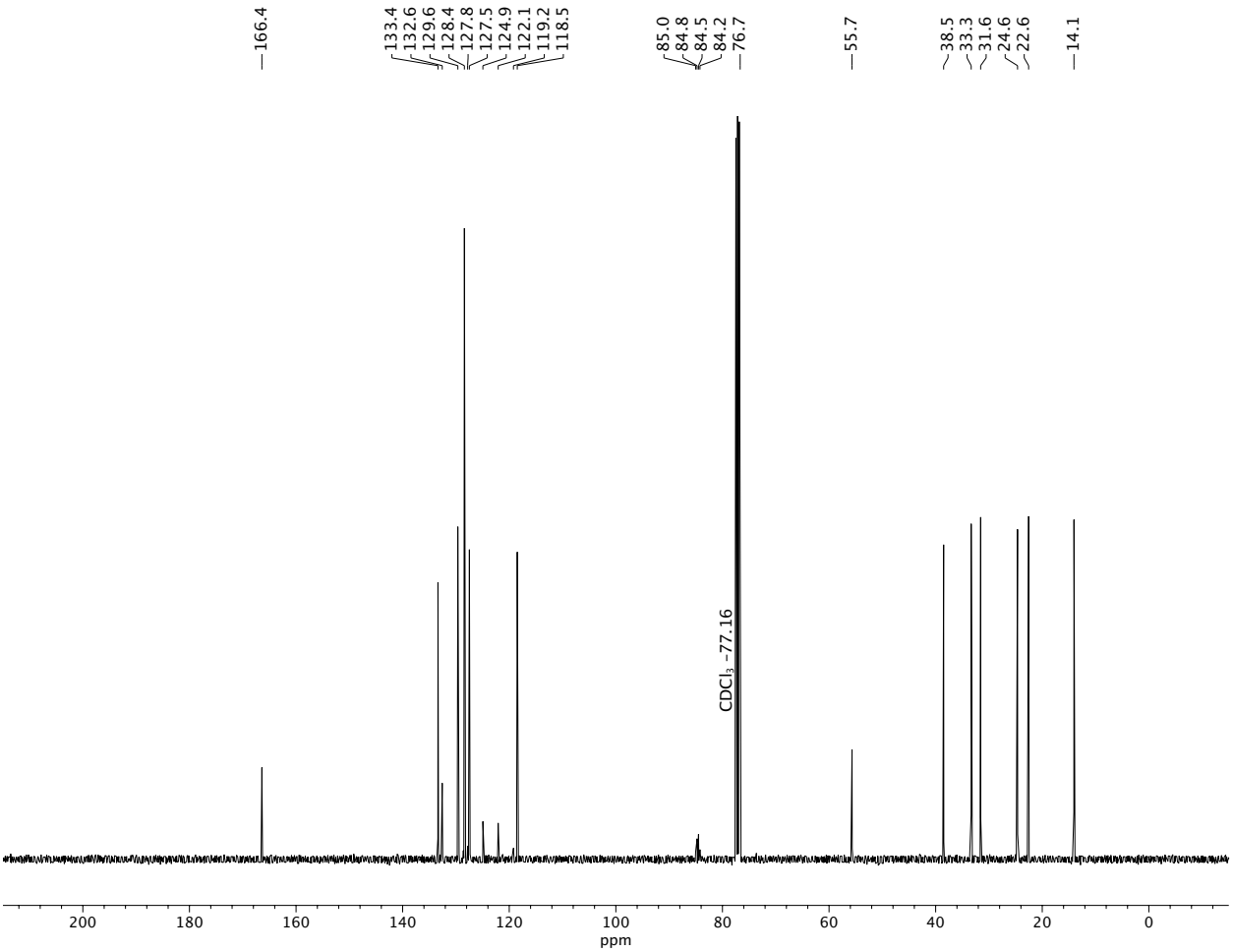
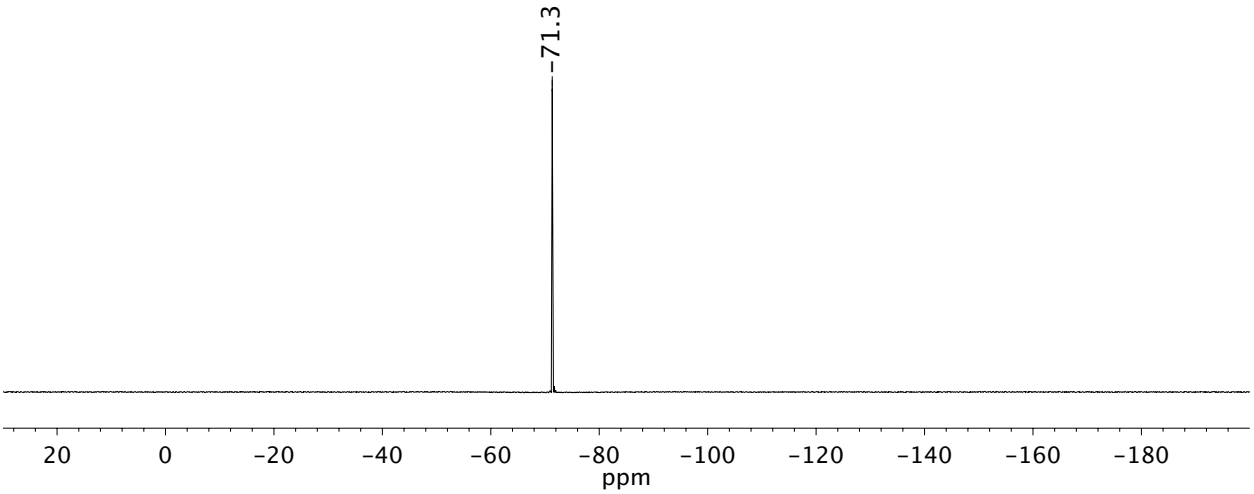
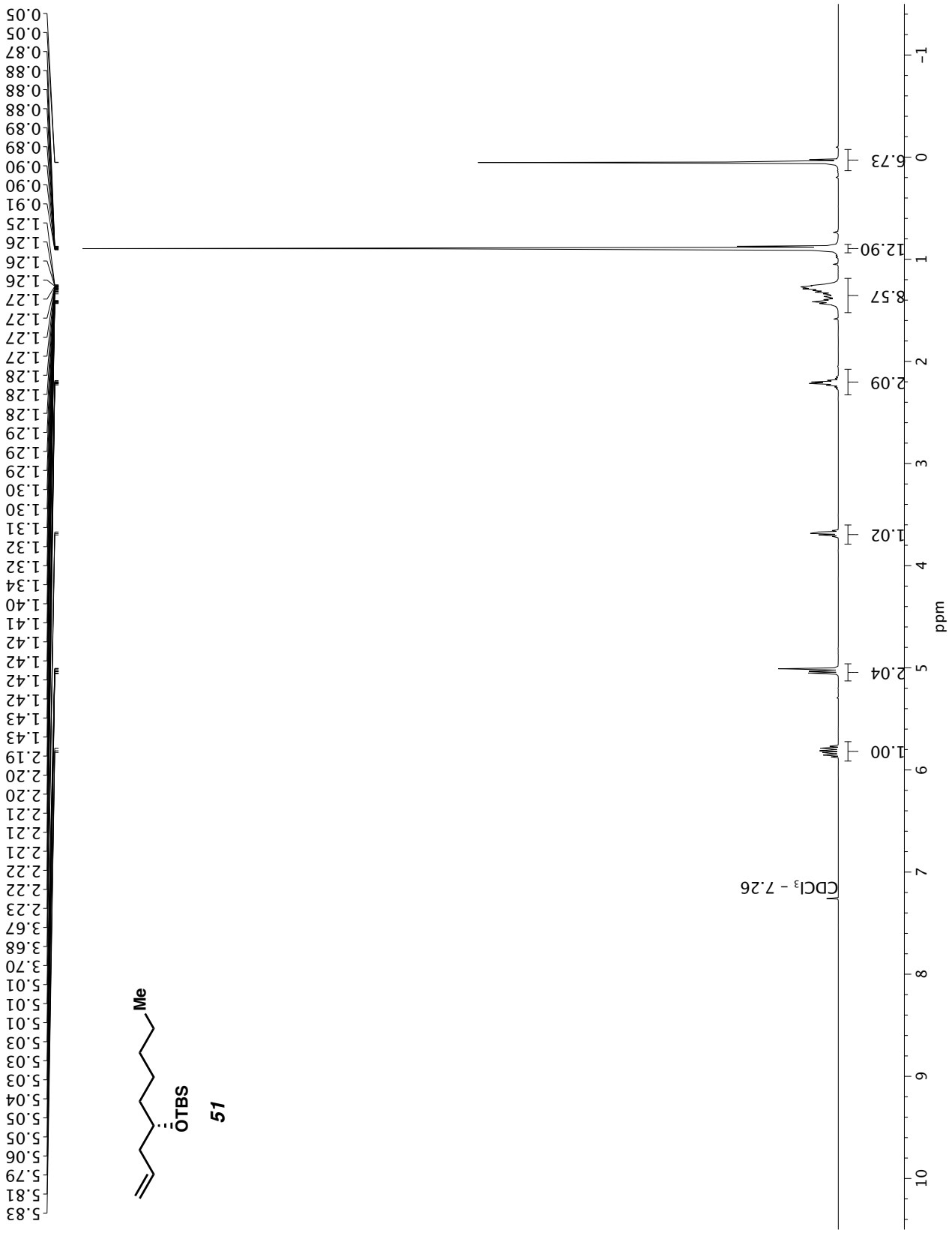


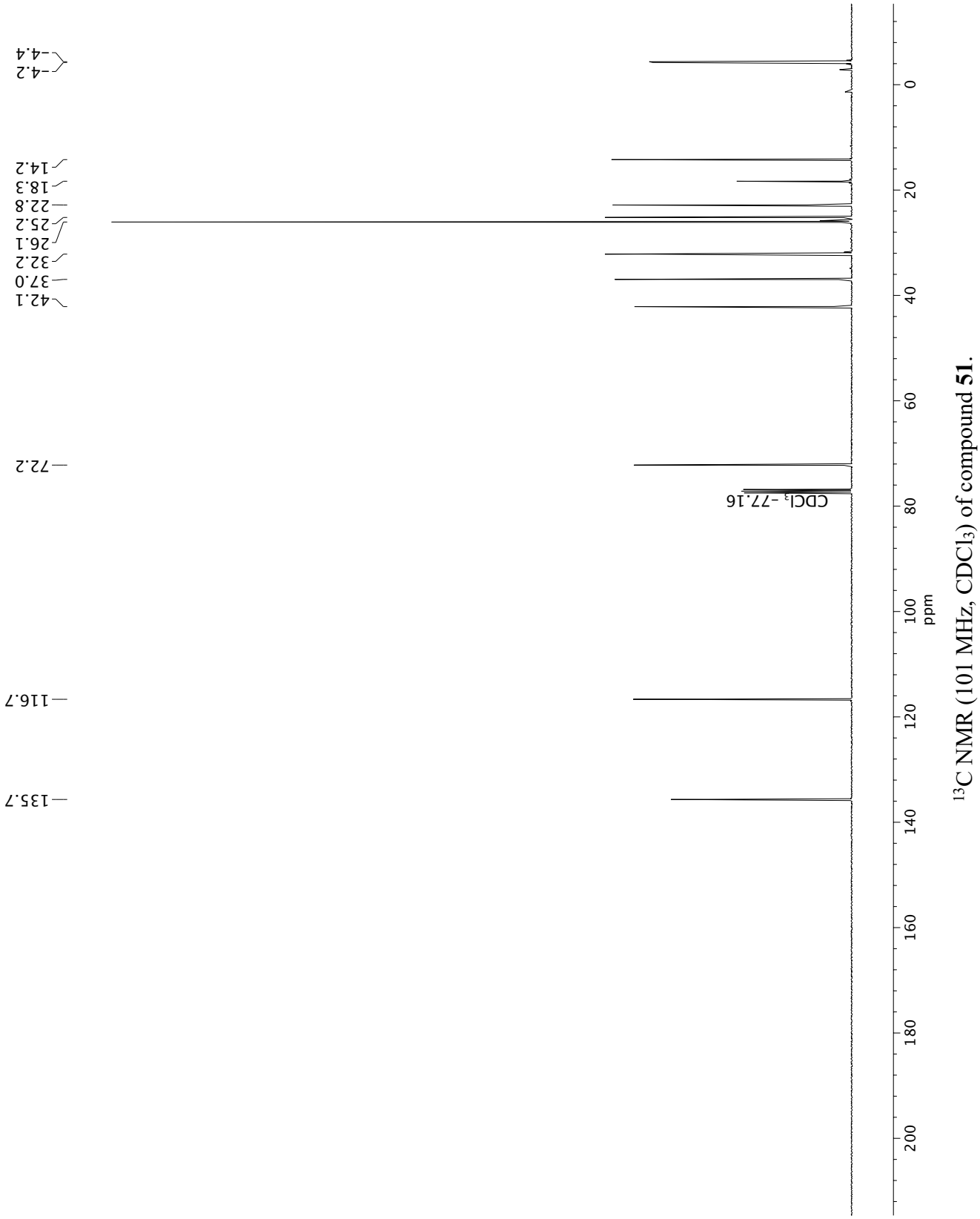
^{13}C NMR (101 MHz, $CDCl_3$) of compound **50b**.



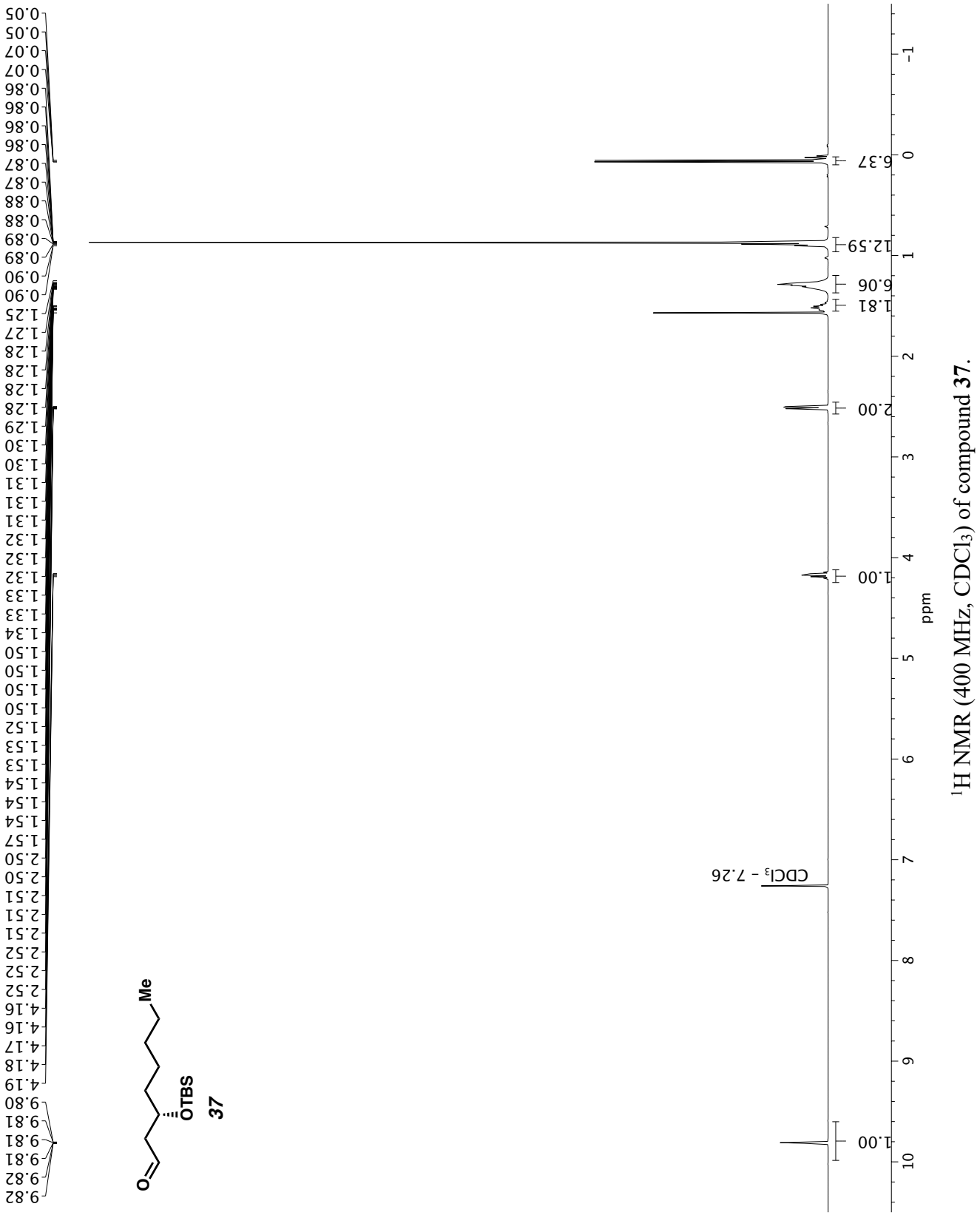
^{19}F NMR (282 MHz, $CDCl_3$) of compound **50b**.



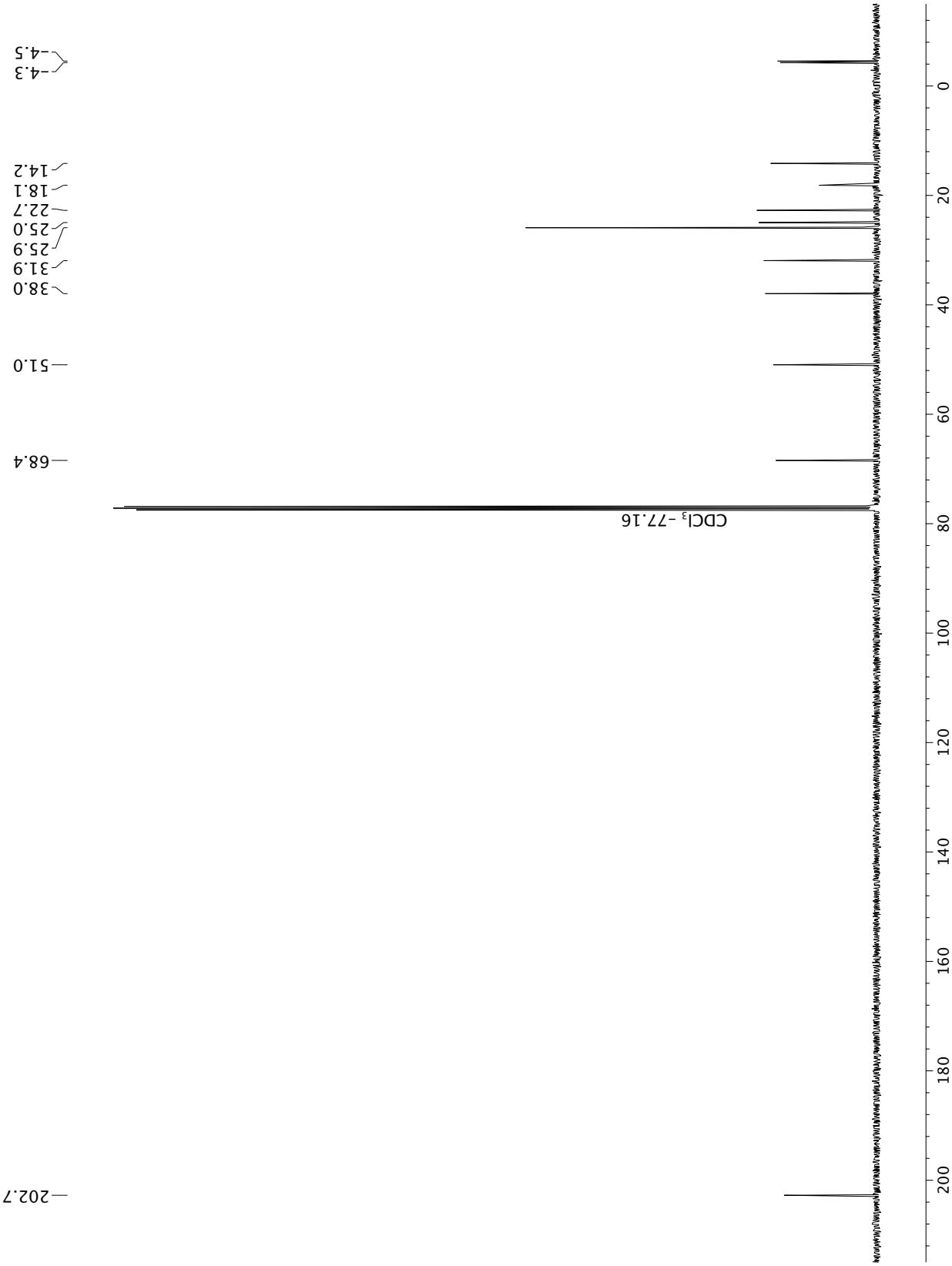
^{1}H NMR (400 MHz, $CDCl_3$) of compound **51**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **51**.

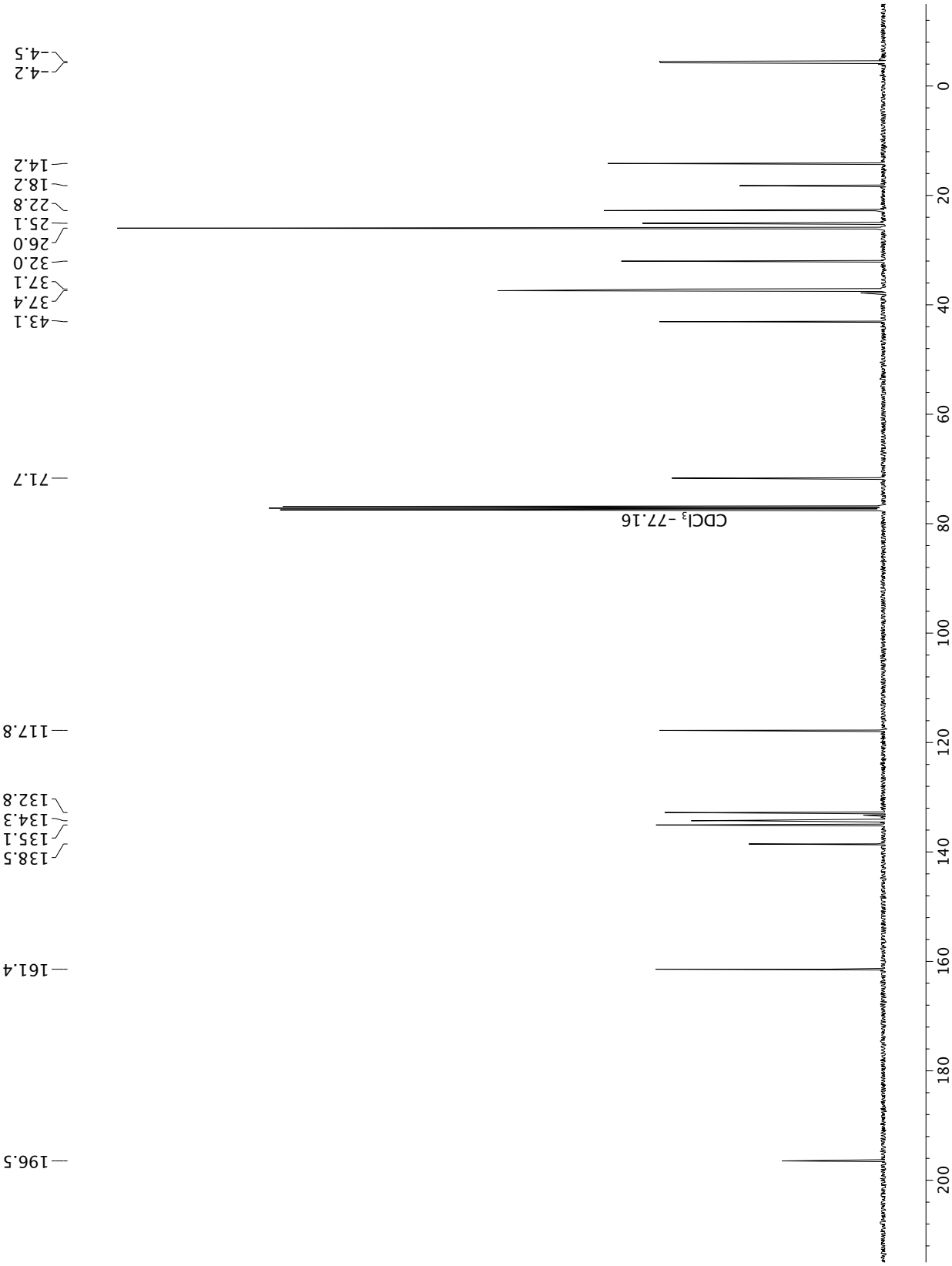


^{1}H NMR (400 MHz, $CDCl_3$) of compound **37**.

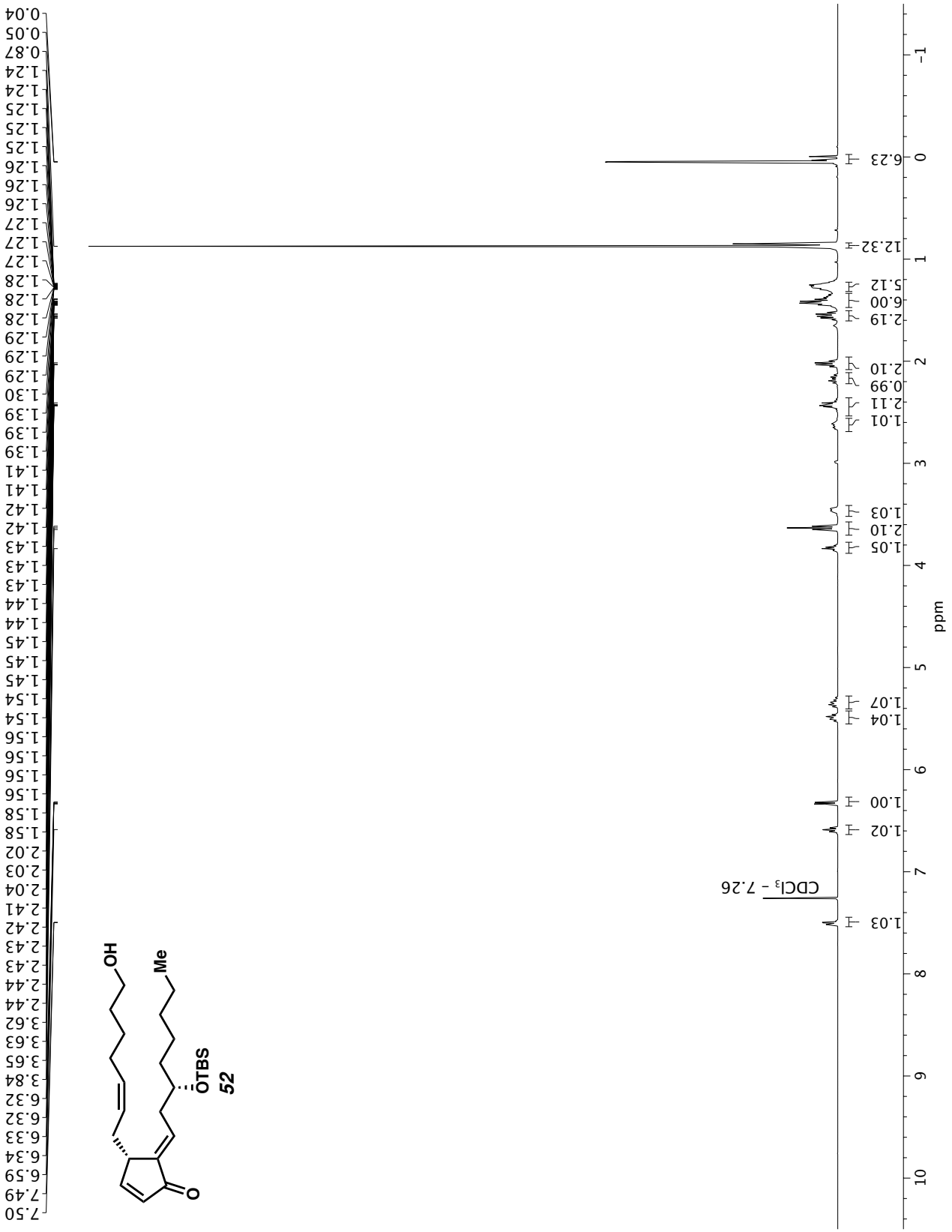


^{13}C NMR (101 MHz, $CDCl_3$) of compound **37**.

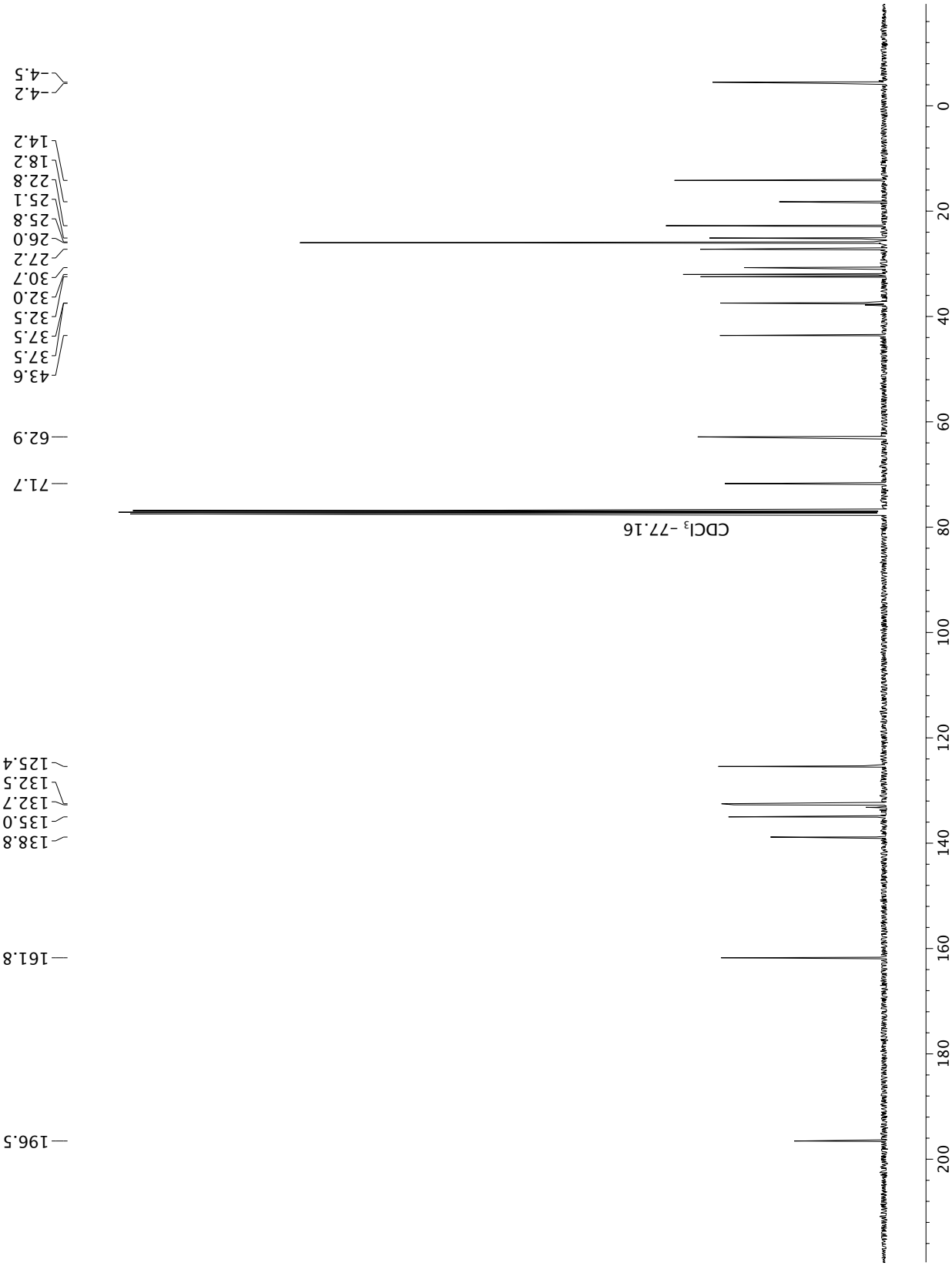
^{1}H NMR (400 MHz, $CDCl_3$) of compound **38**.



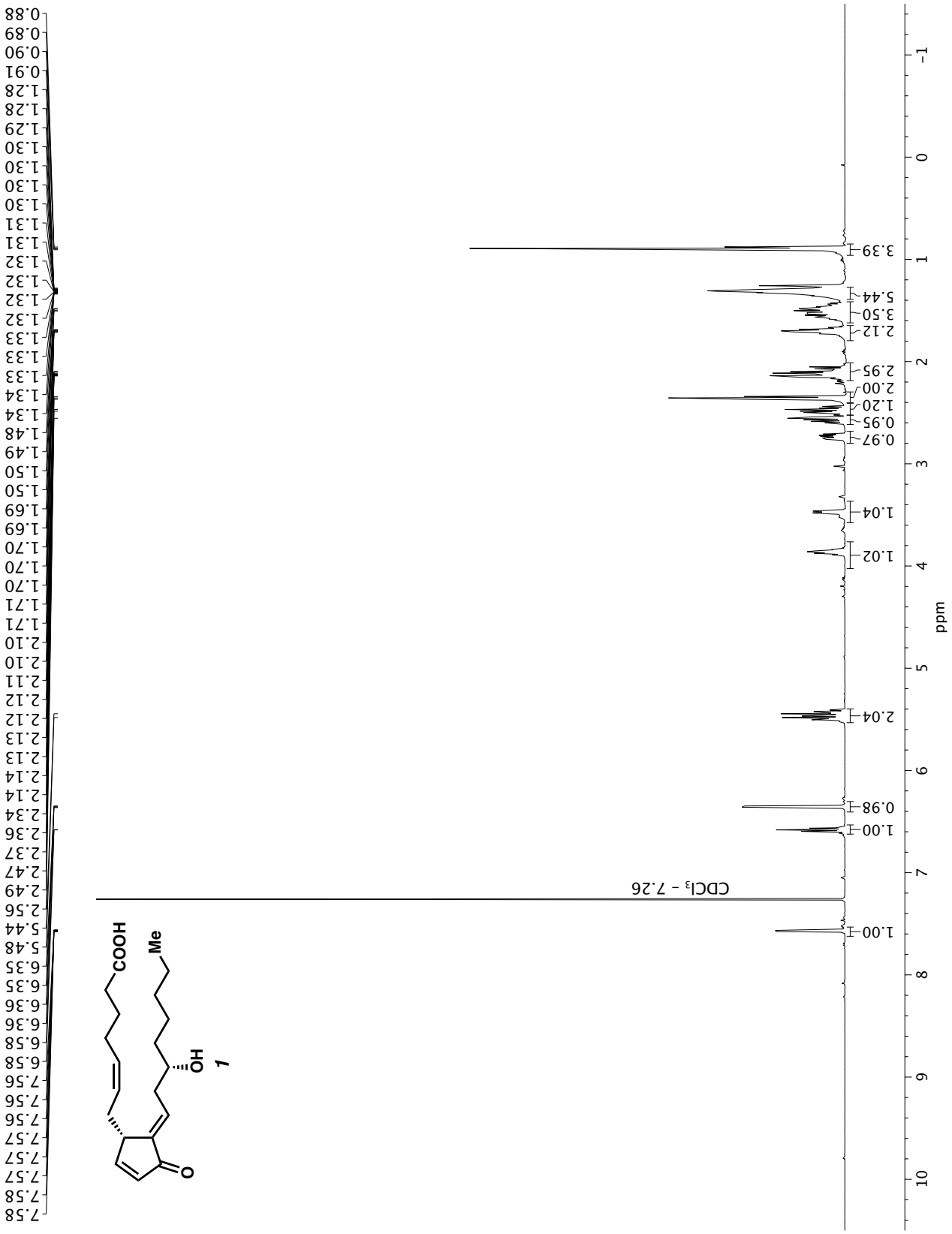
^{13}C NMR (101 MHz, $CDCl_3$) of compound **38**.



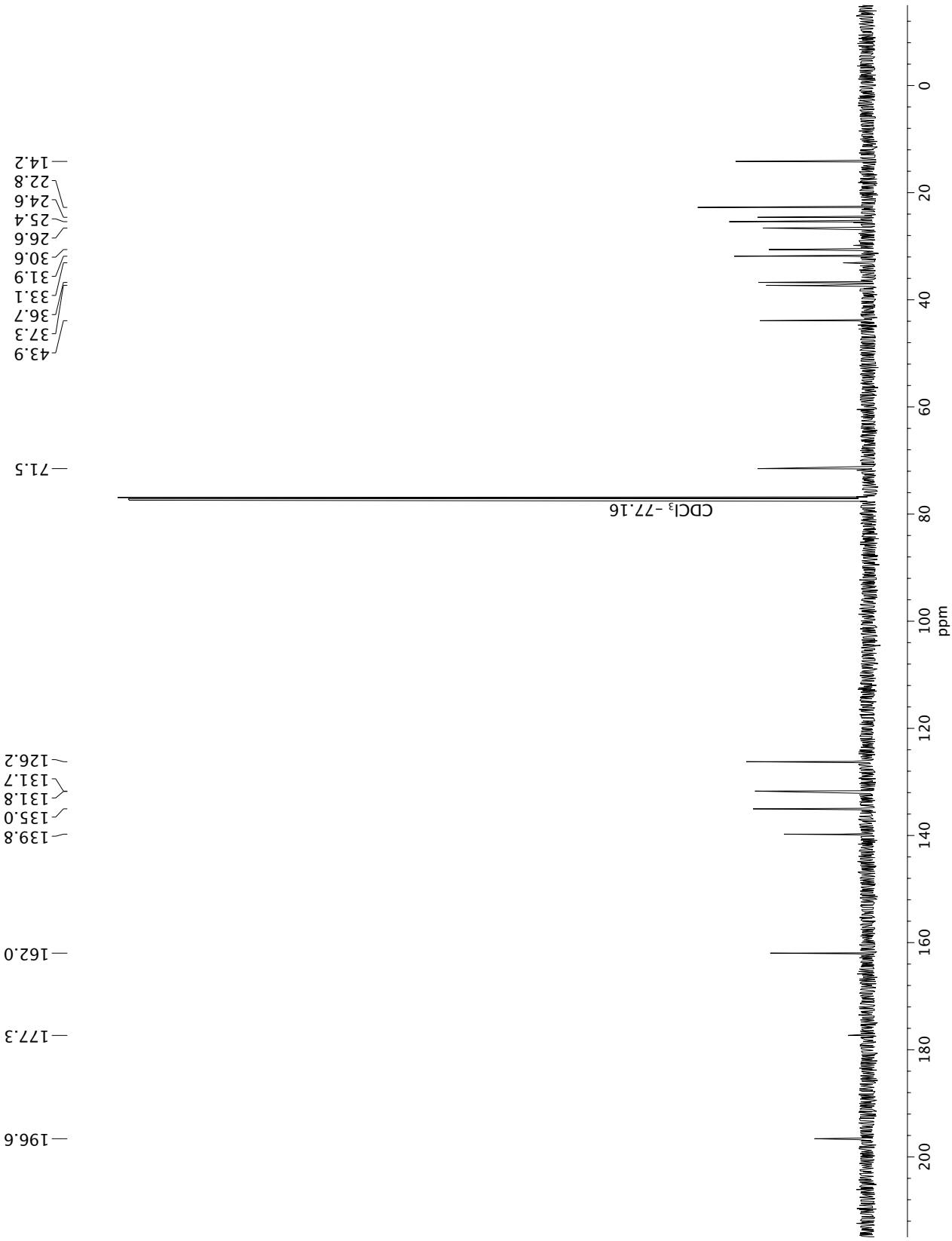
^{1}H NMR (400 MHz, $CDCl_3$) of compound **52**.



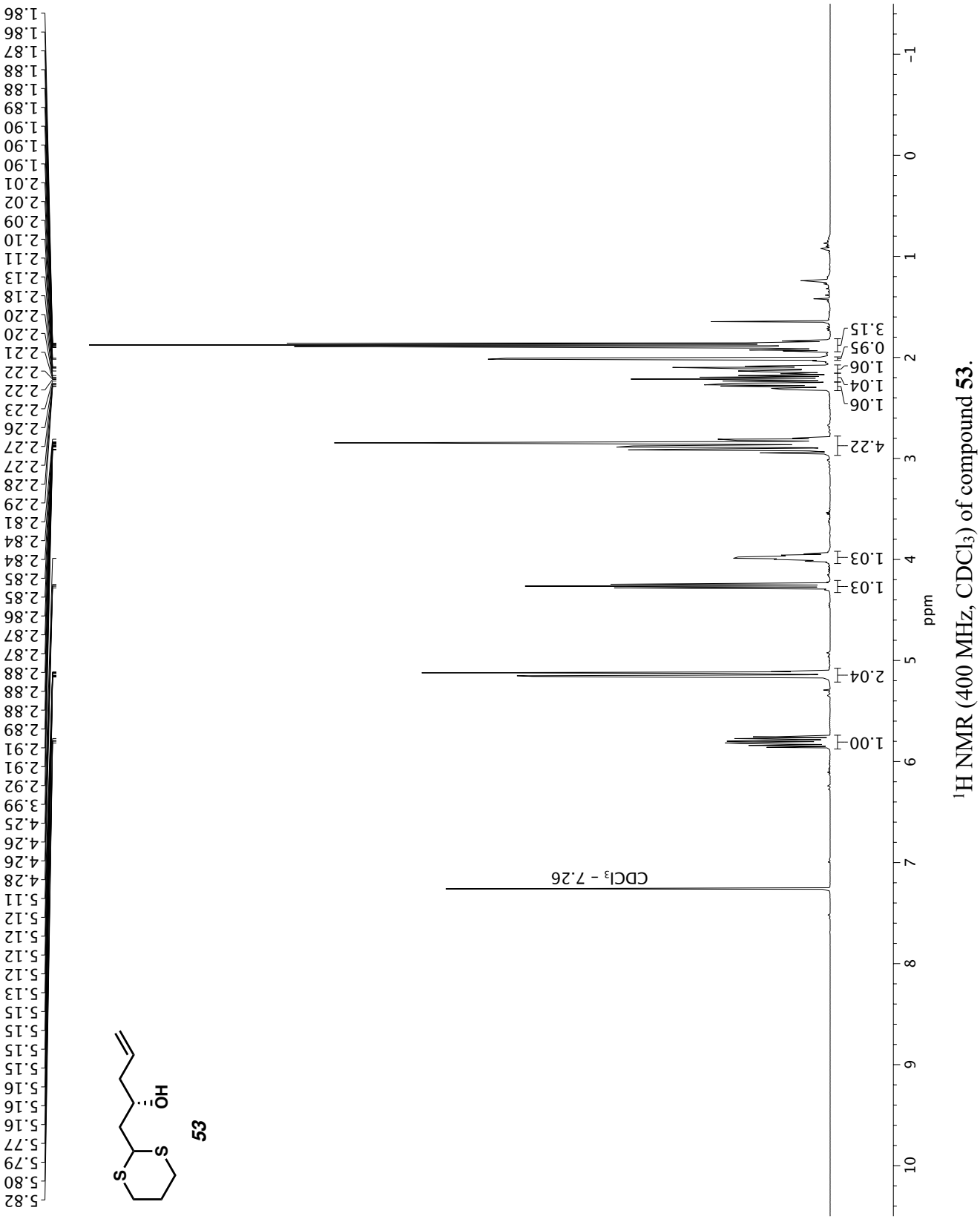
^{13}C NMR (101 MHz, $CDCl_3$) of compound **52**.



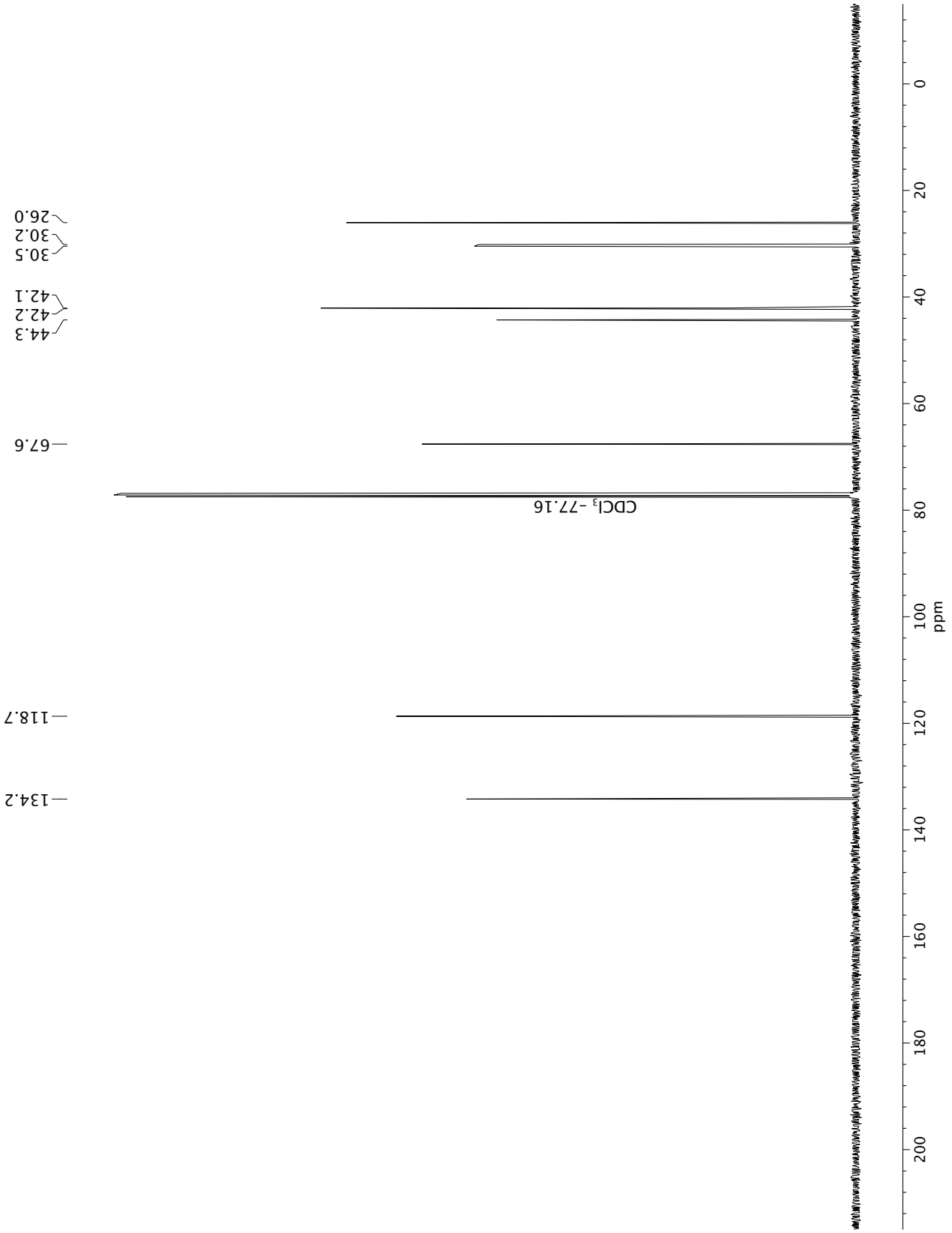
^{1}H NMR (500 MHz, $CDCl_3$) of compound **1**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **1**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **53**.



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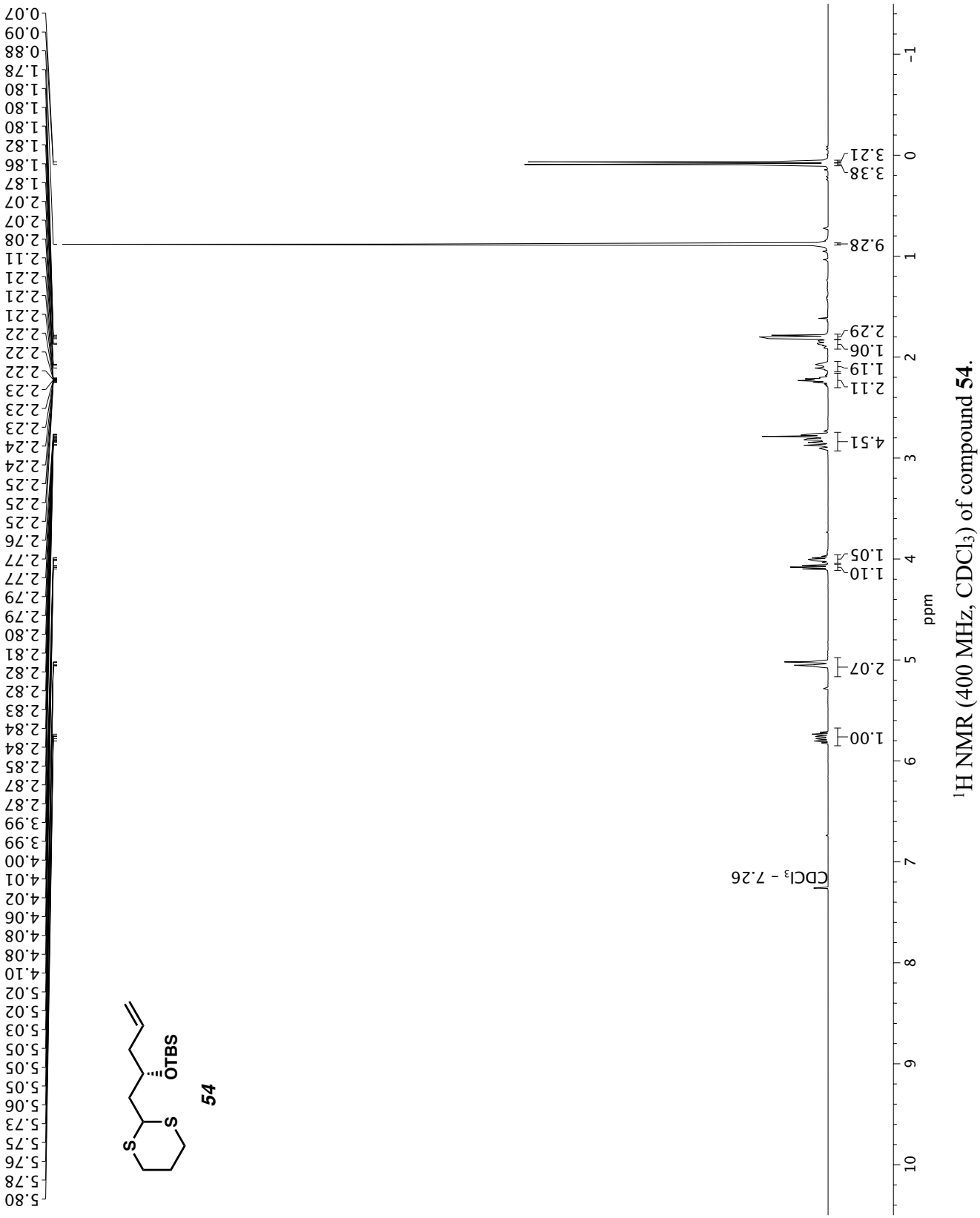
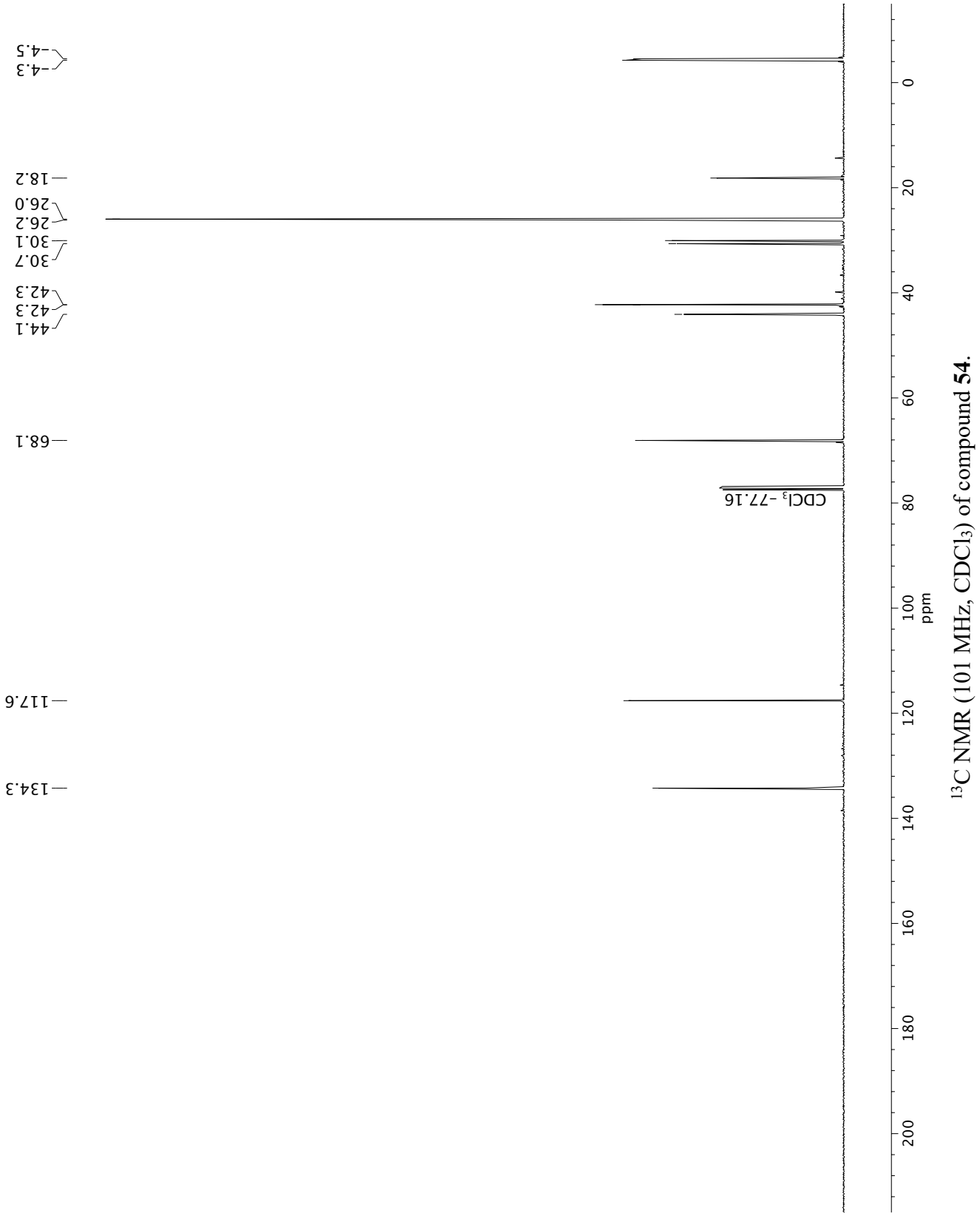
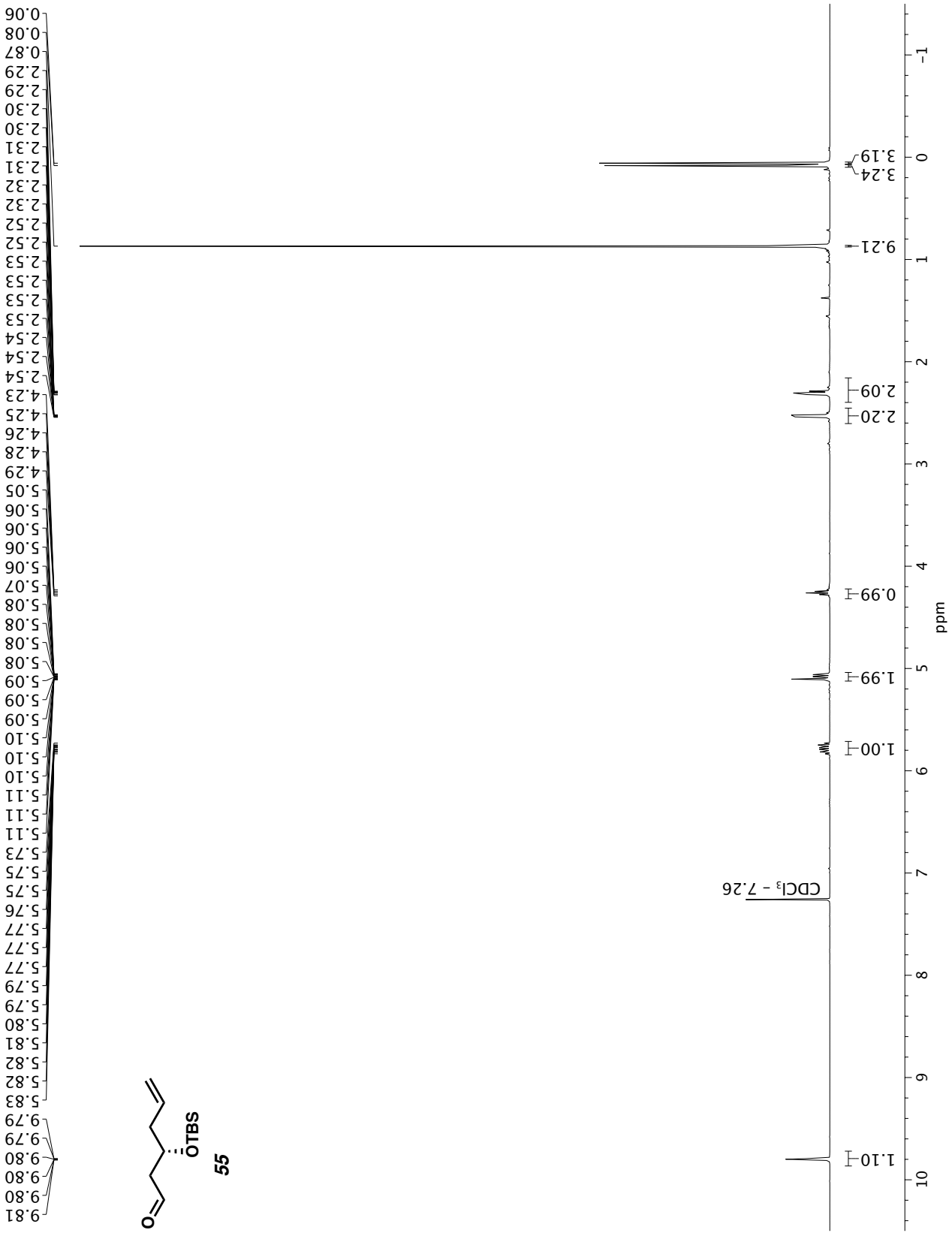


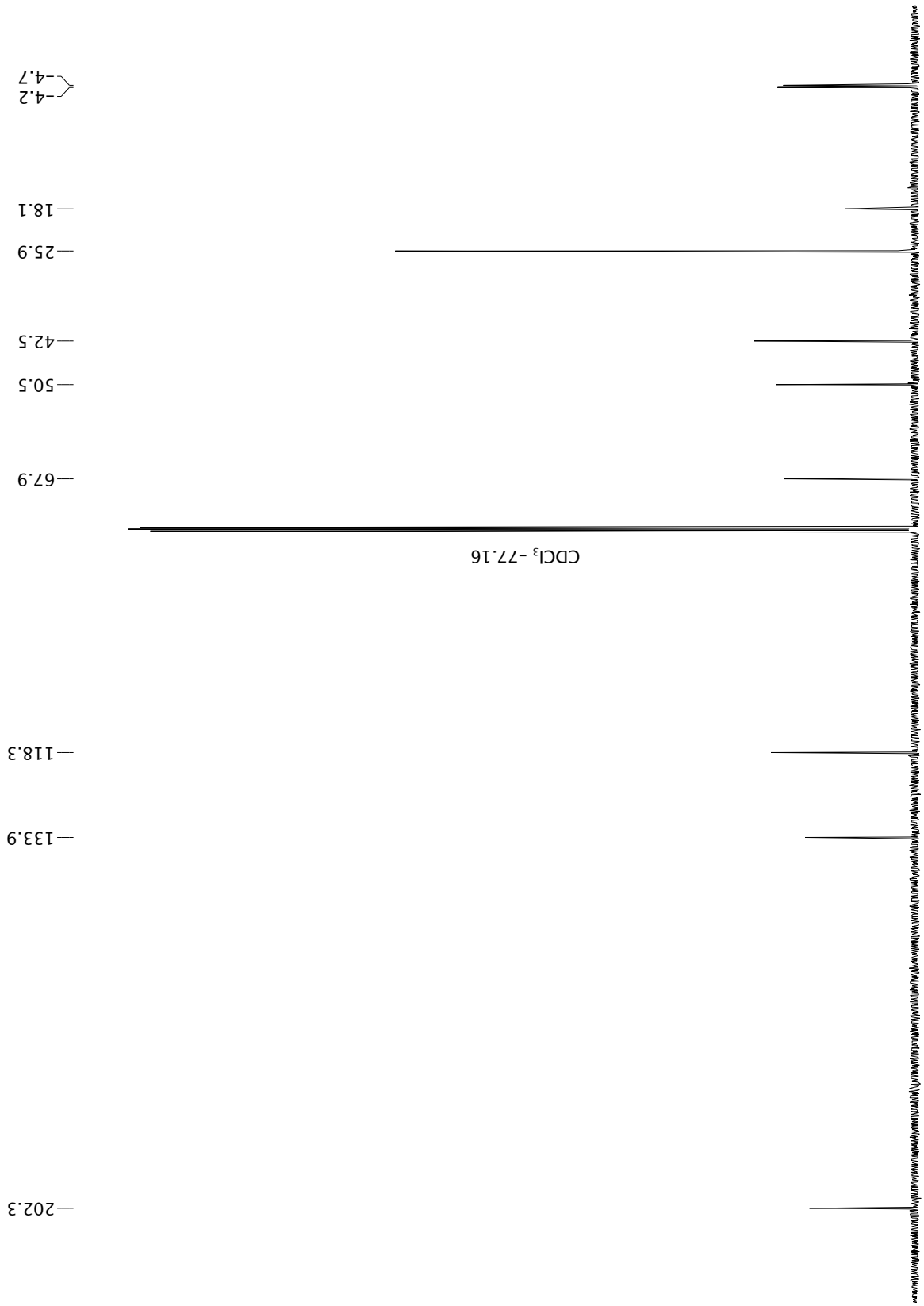
^{1}H NMR (400 MHz, $CDCl_3$) of compound **54**.



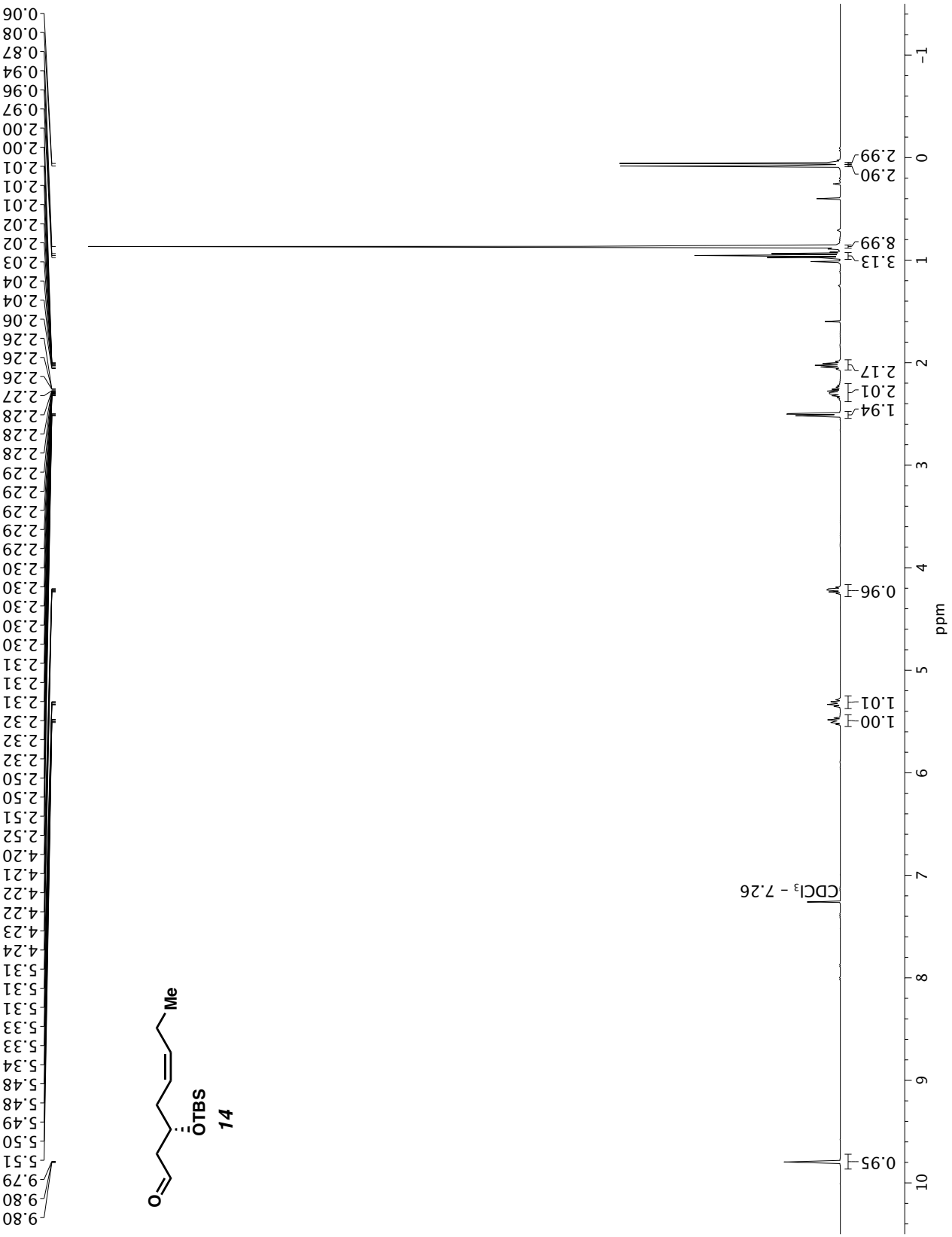
^{13}C NMR (101 MHz, $CDCl_3$) of compound **54**.



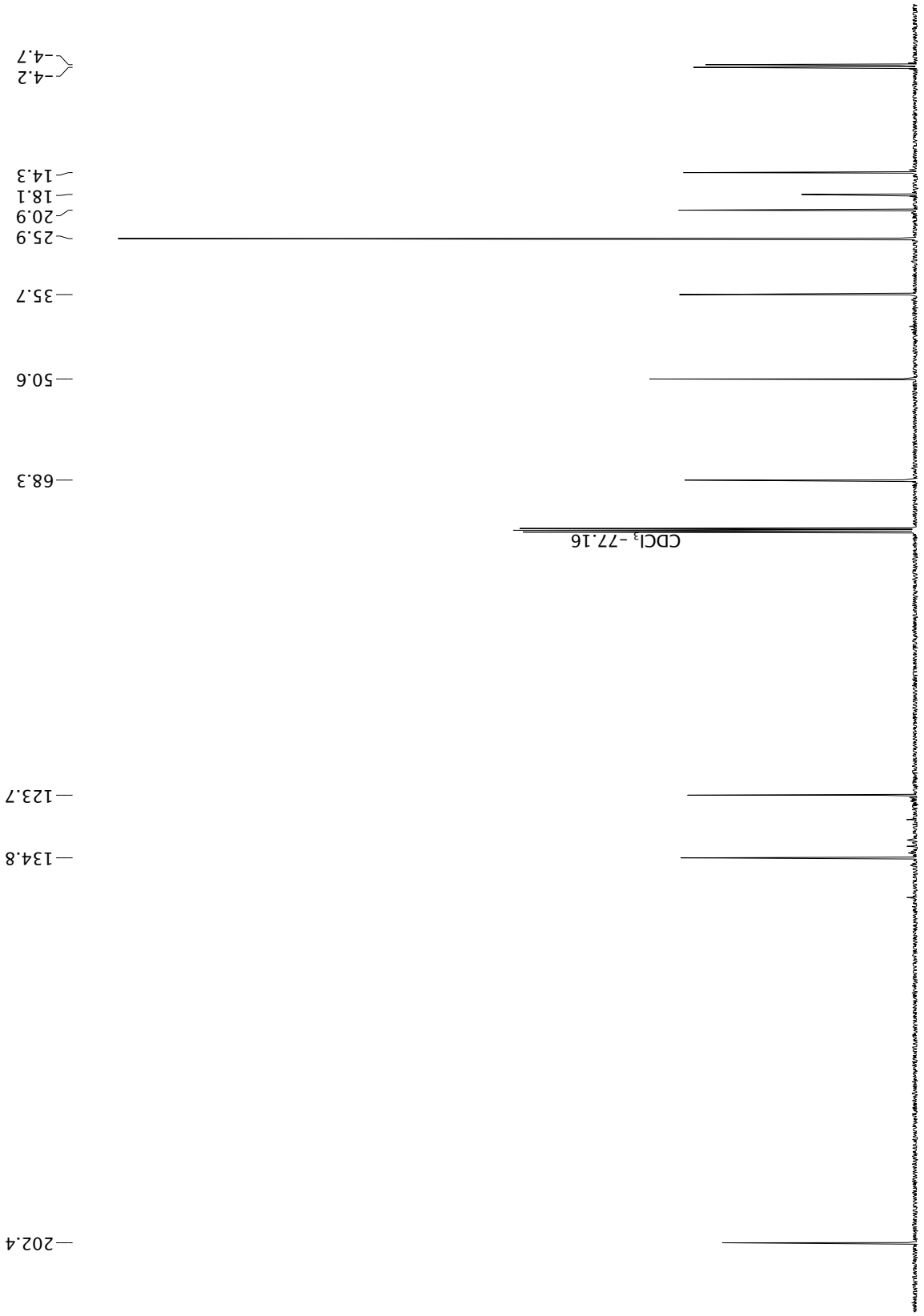
^{1}H NMR (400 MHz, $CDCl_3$) of compound **55**.



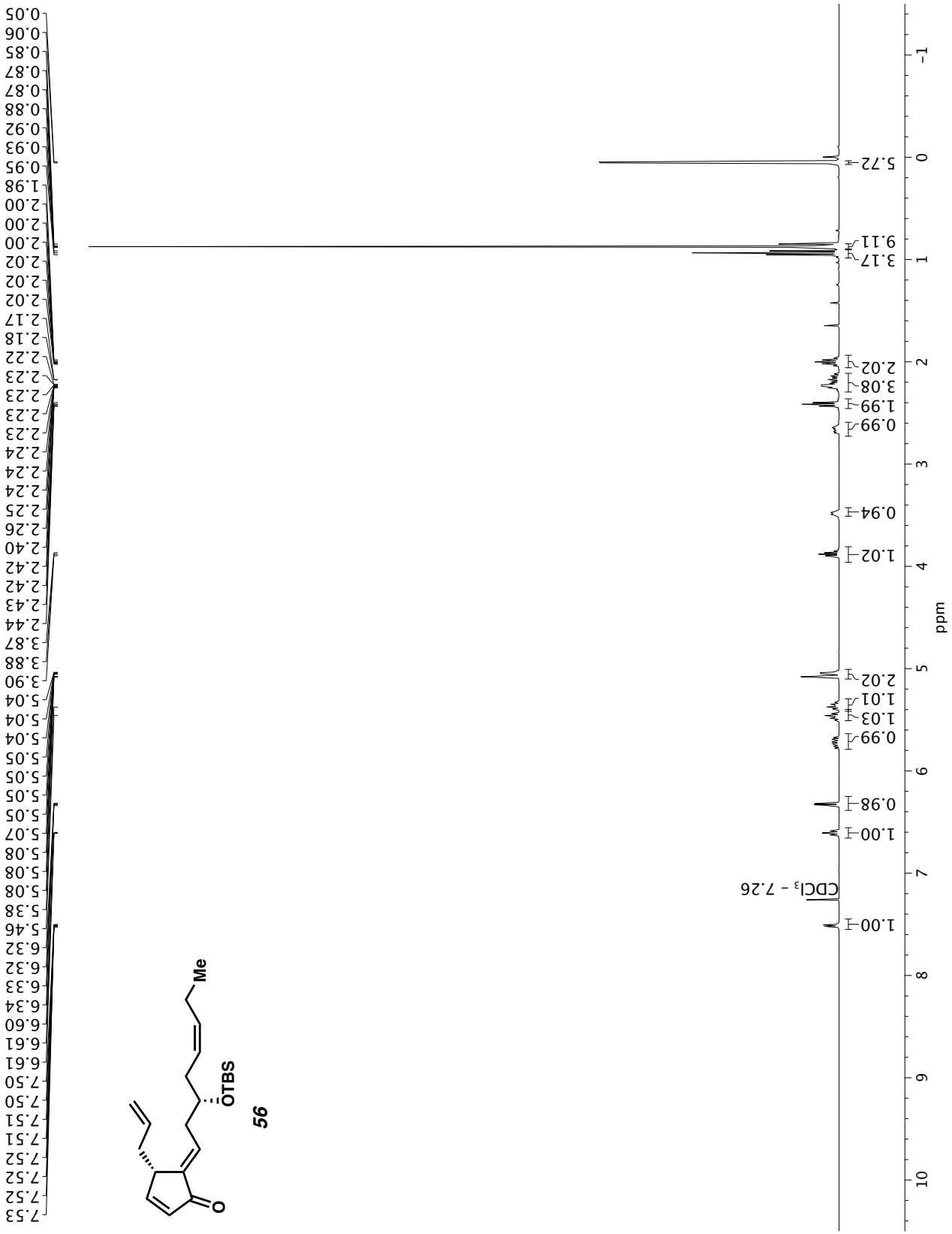
^{13}C NMR (101 MHz, $CDCl_3$) of compound **55**.



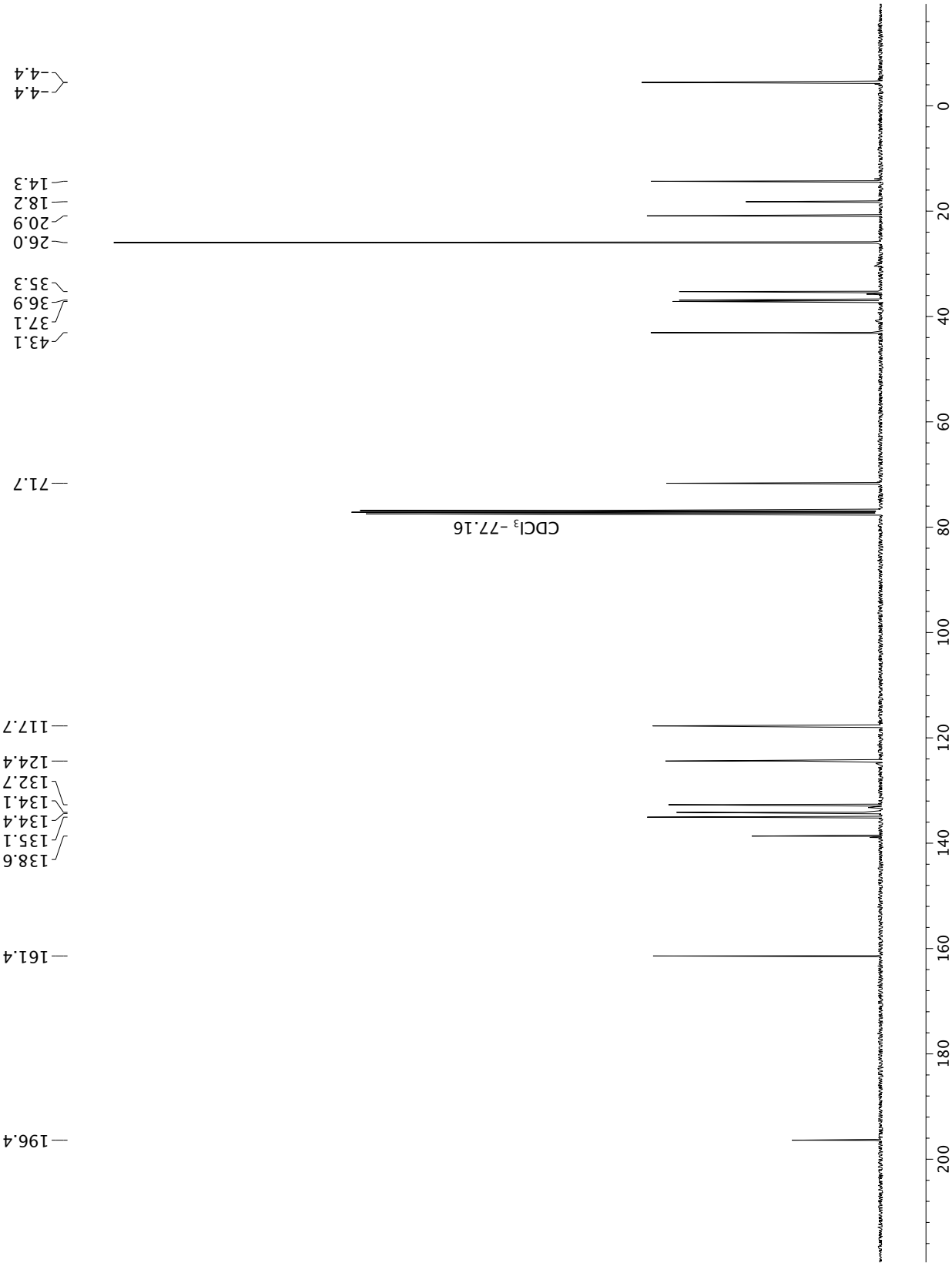
^{1}H NMR (400 MHz, $CDCl_3$) of compound **14**.



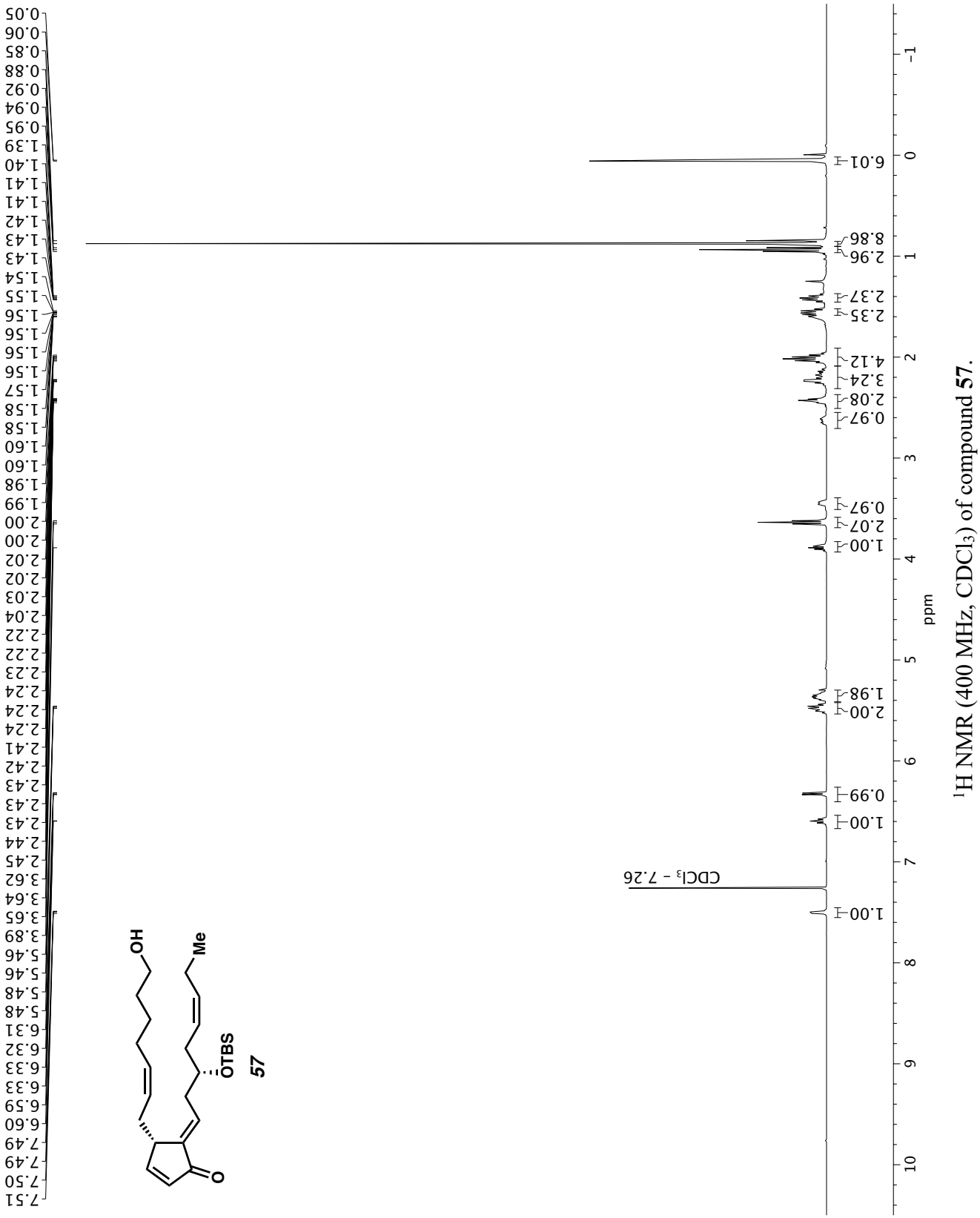
^{13}C NMR (101 MHz, $CDCl_3$) of compound **14**.



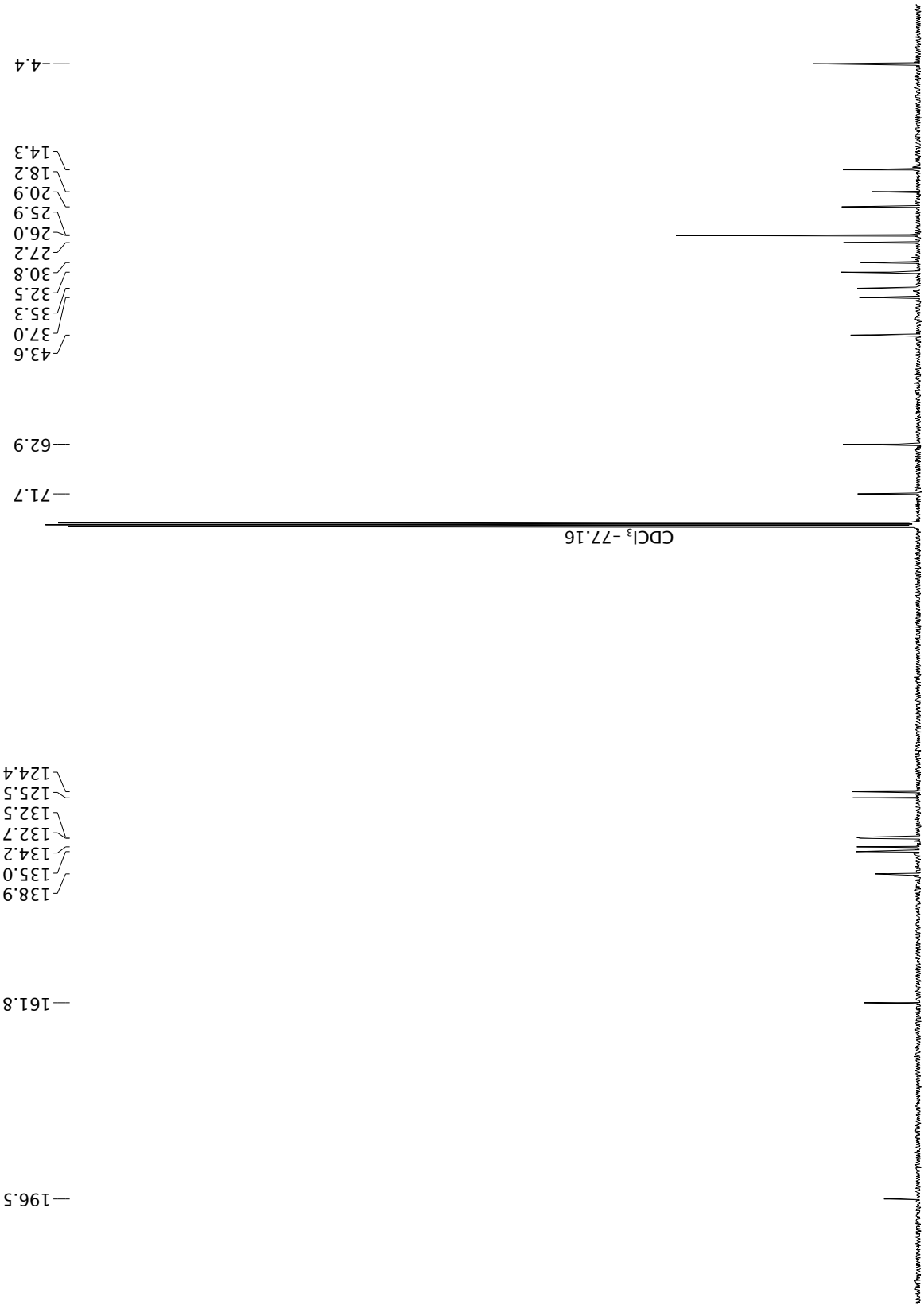
^{1}H NMR (400 MHz, $CDCl_3$) of compound **56**.



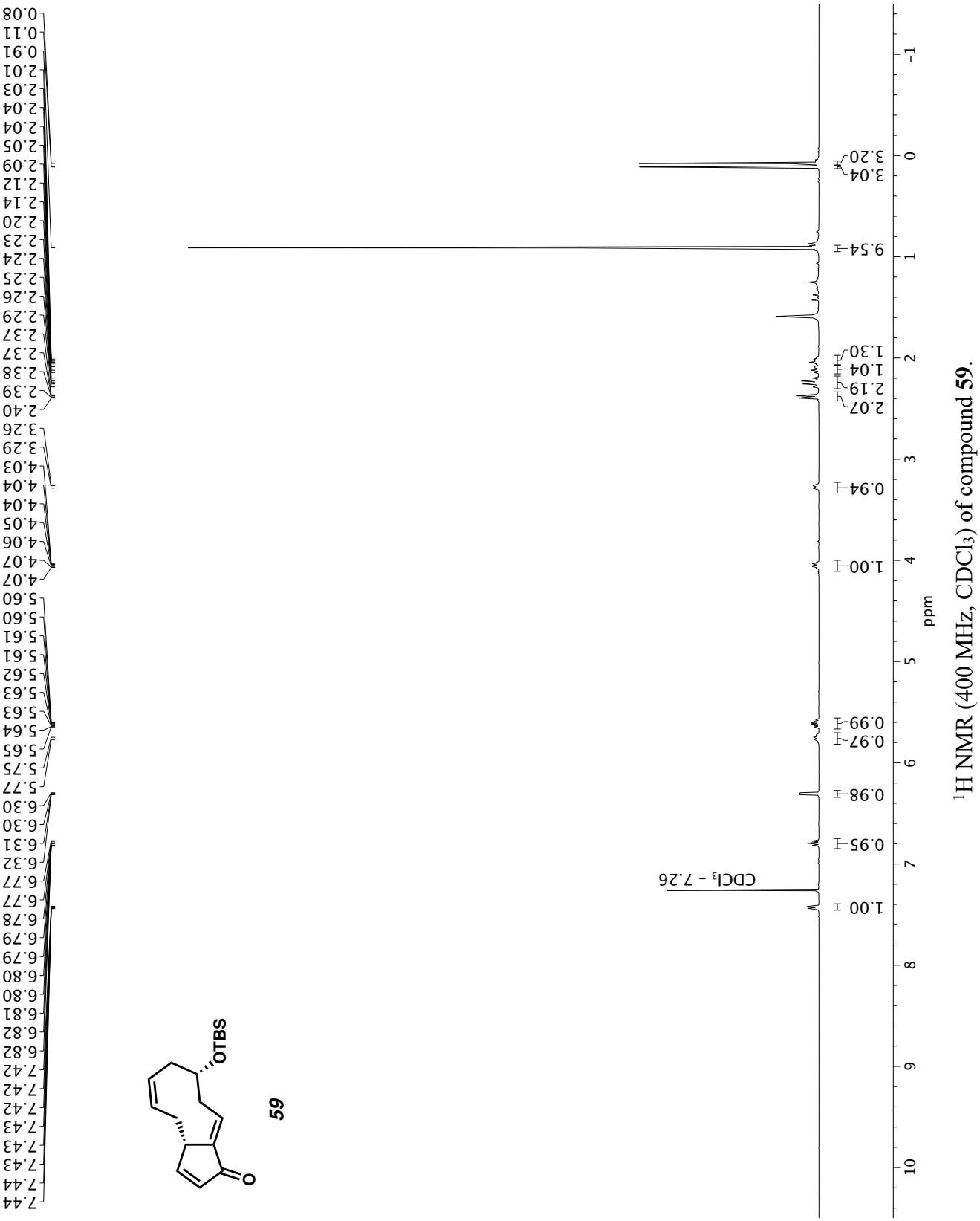
^{13}C NMR (101 MHz, $CDCl_3$) of compound **56**.



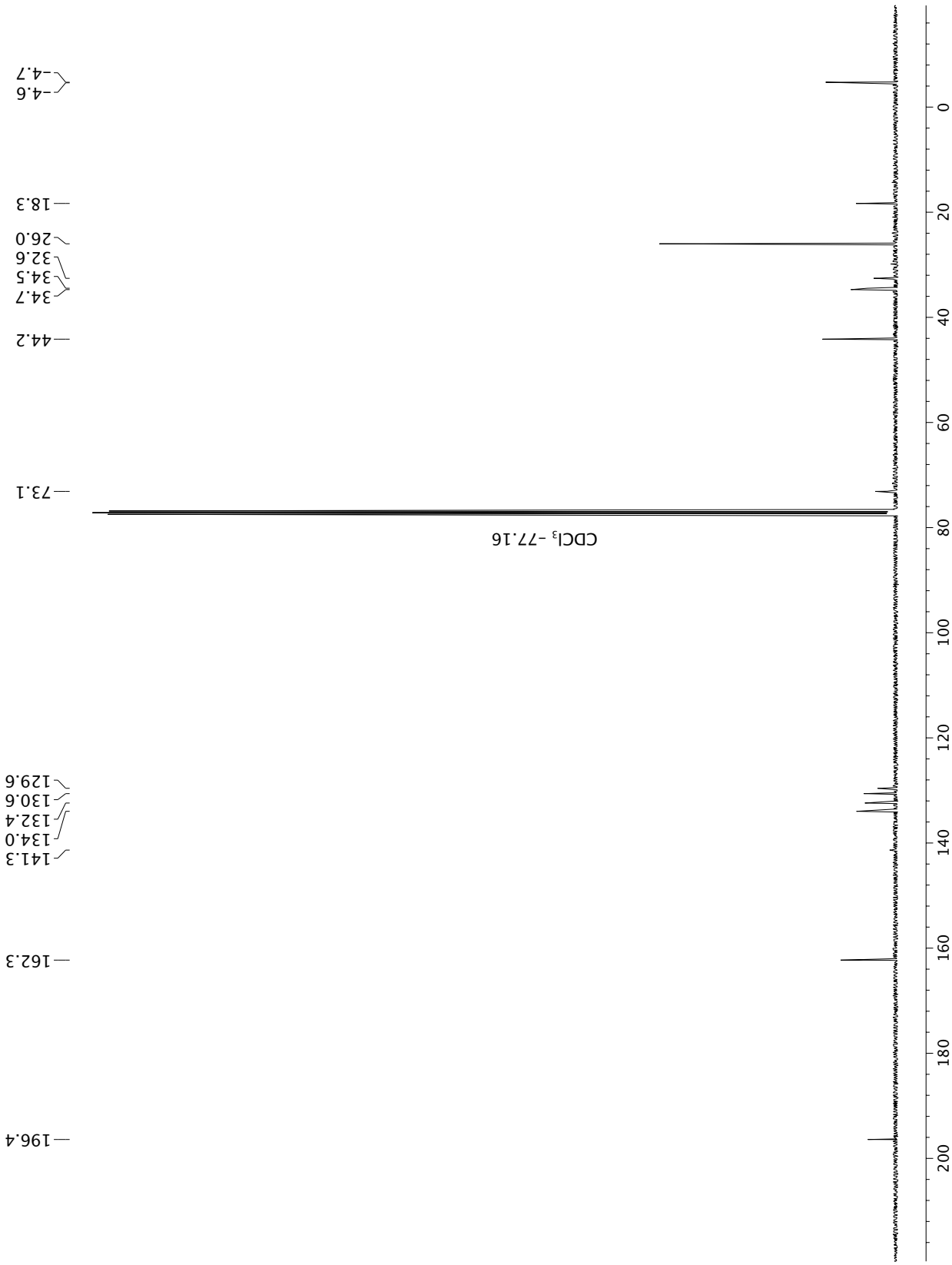
^{1}H NMR (400 MHz, $CDCl_3$) of compound **57**.



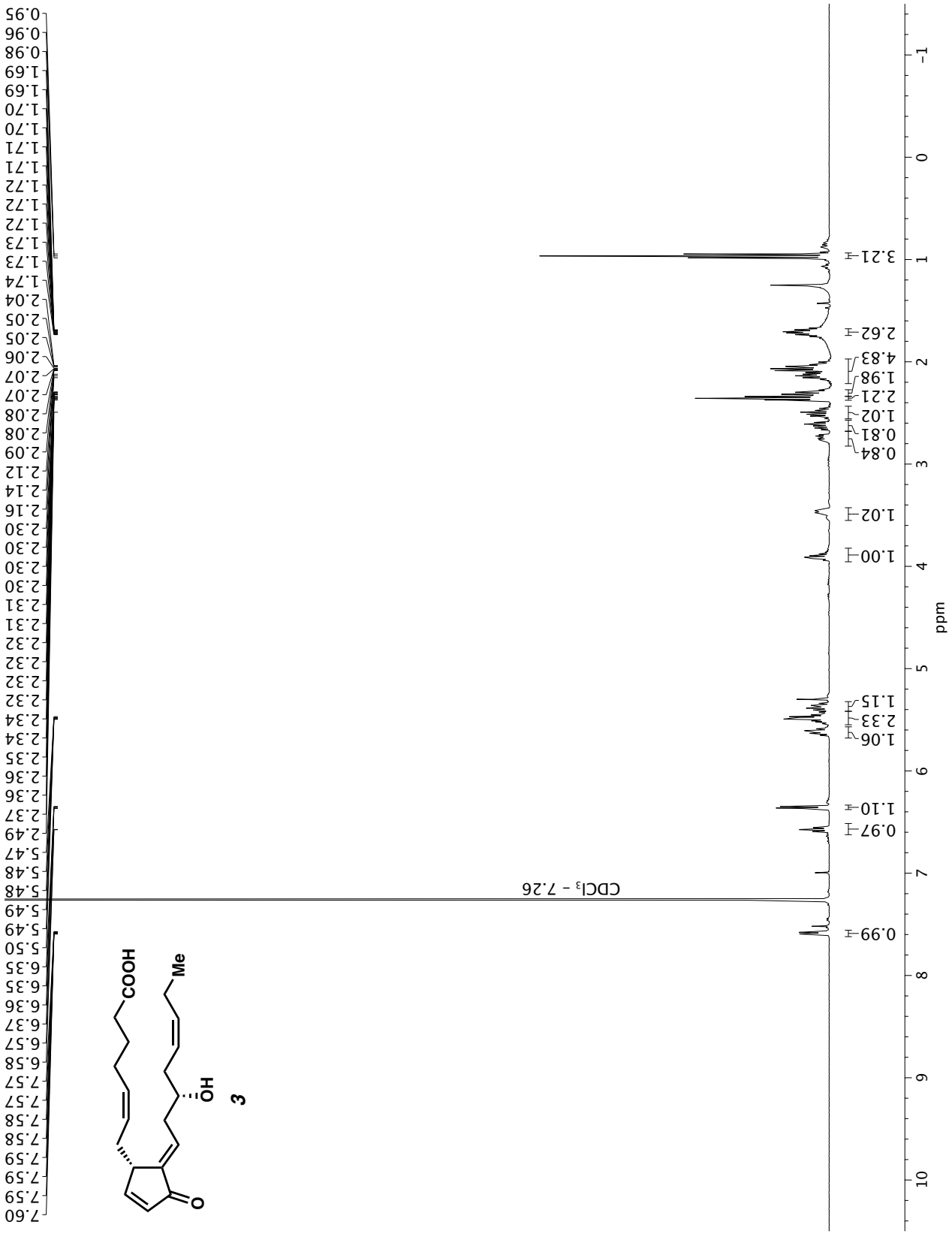
^{13}C NMR (101 MHz, $CDCl_3$) of compound **57**.



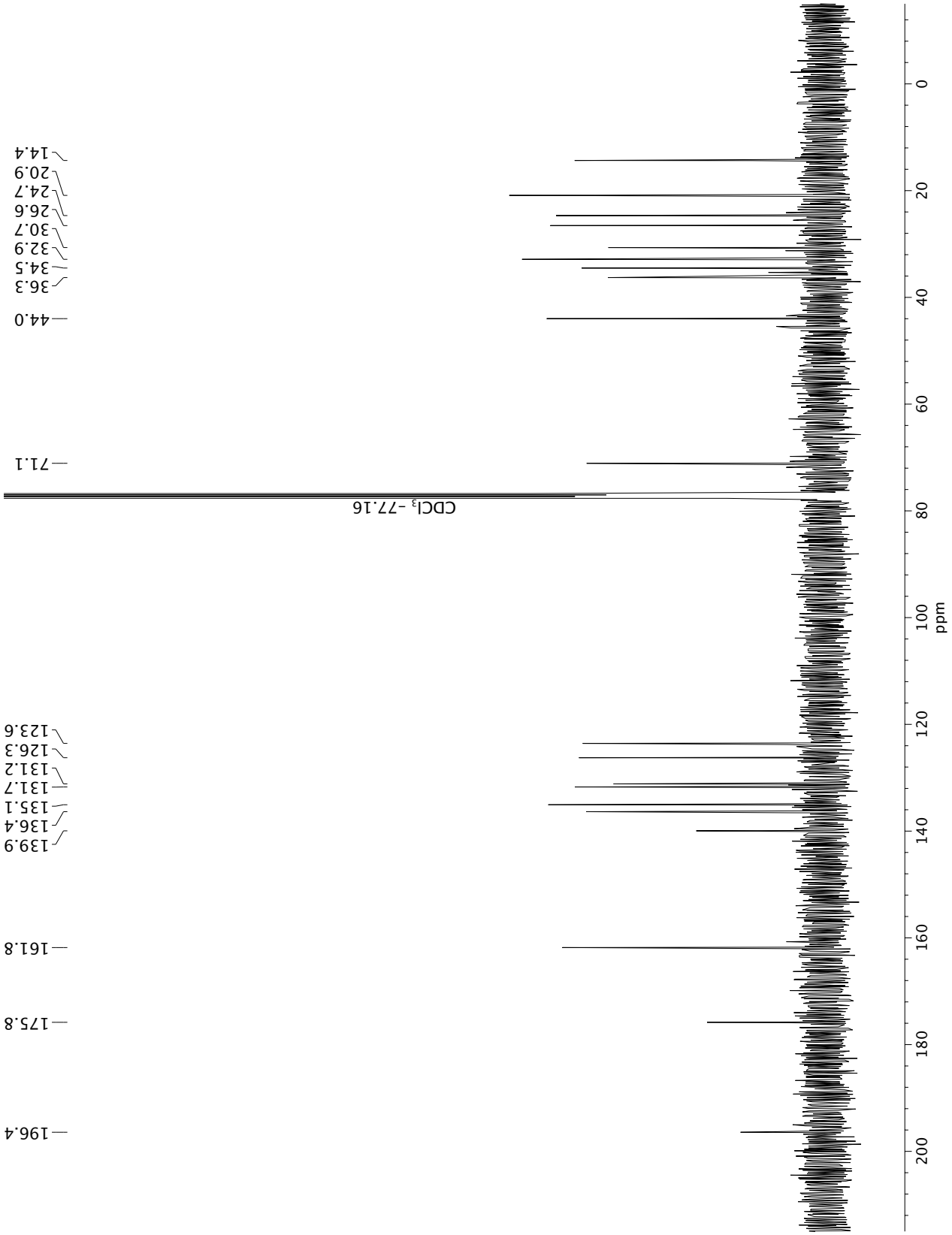
^{1}H NMR (400 MHz, $CDCl_3$) of compound **59**.



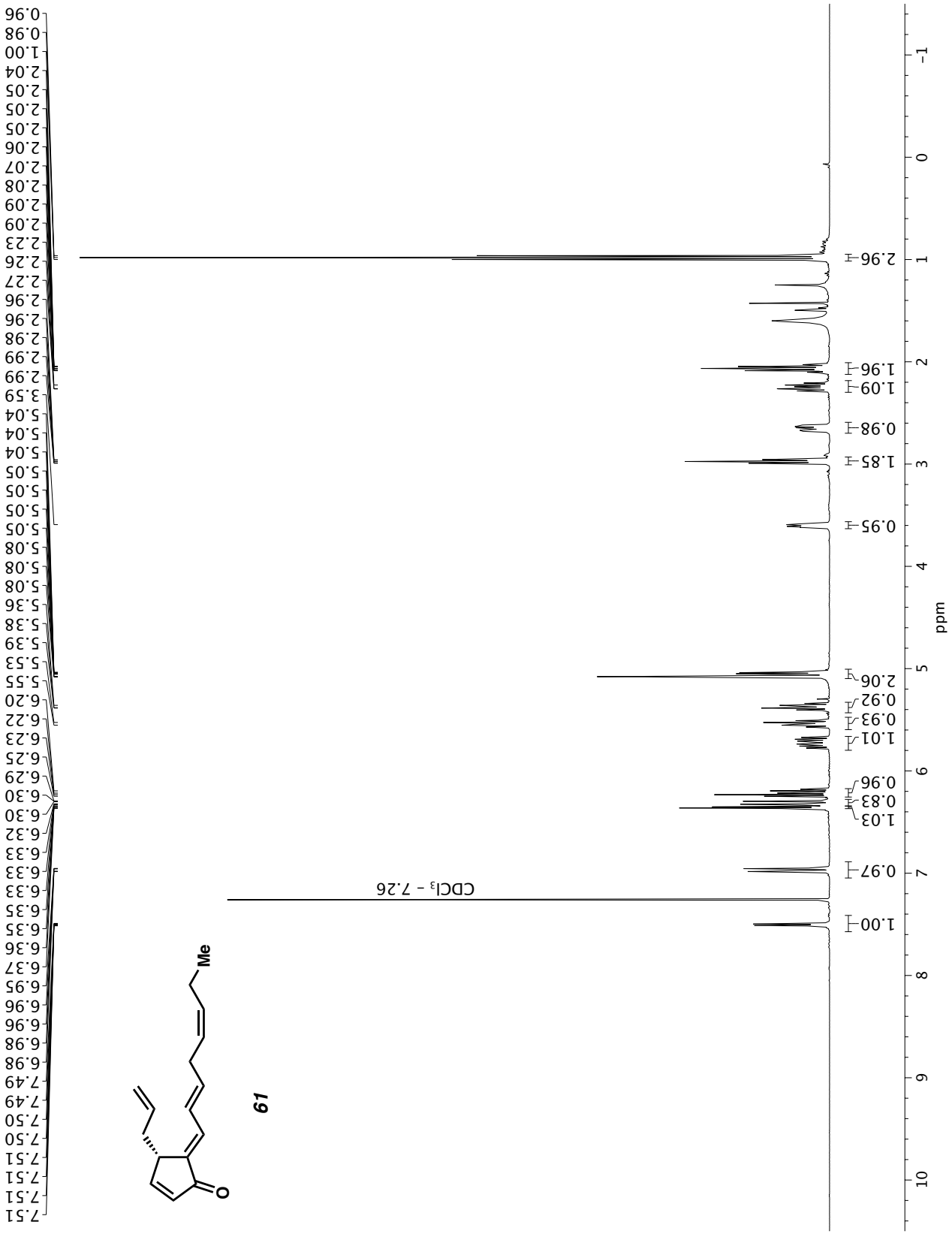
^{13}C NMR (101 MHz, $CDCl_3$) of compound **59**.



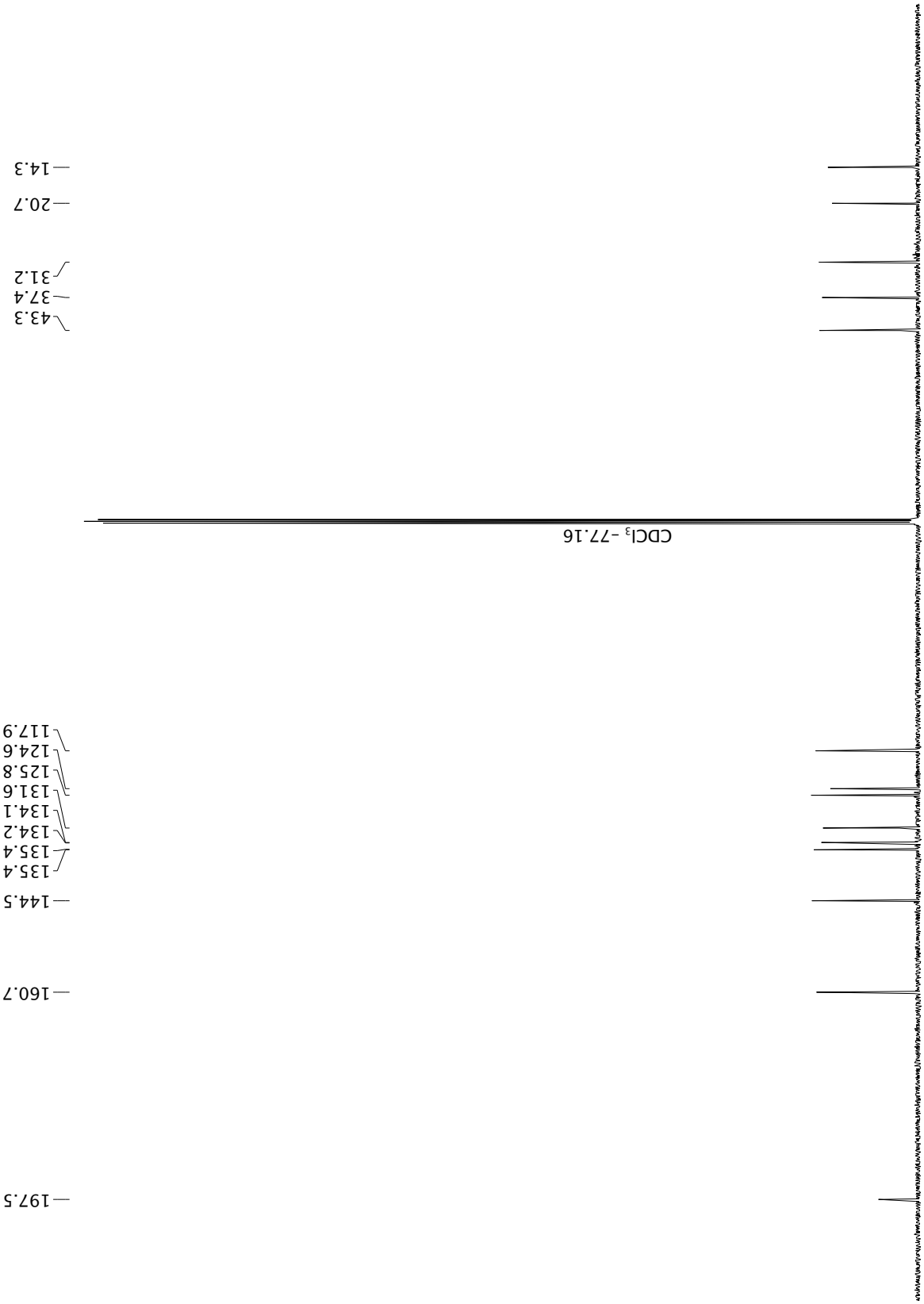
^{1}H NMR (400 MHz, $CDCl_3$) of compound **3**.



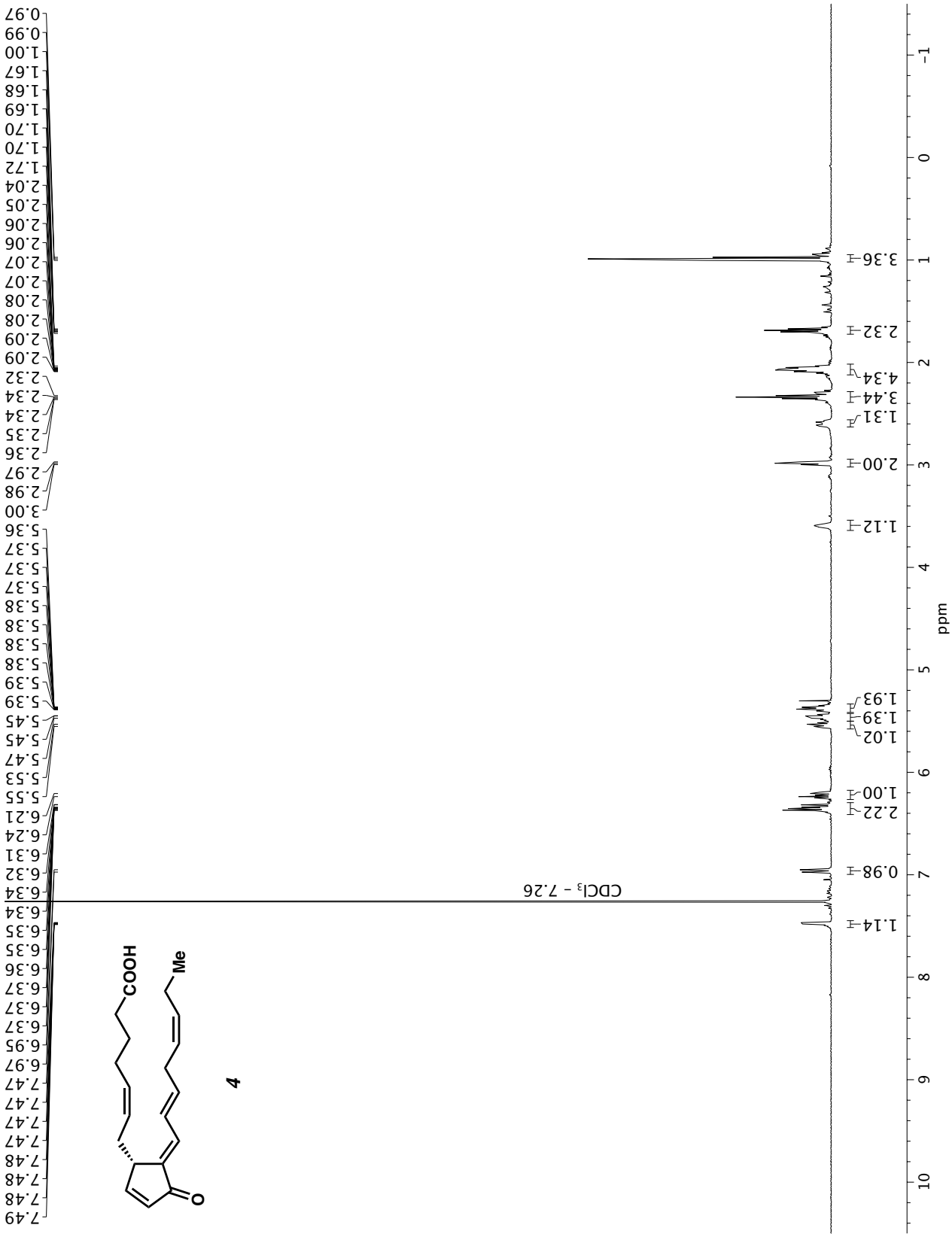
^{13}C NMR (101 MHz, $CDCl_3$) of compound **3**.



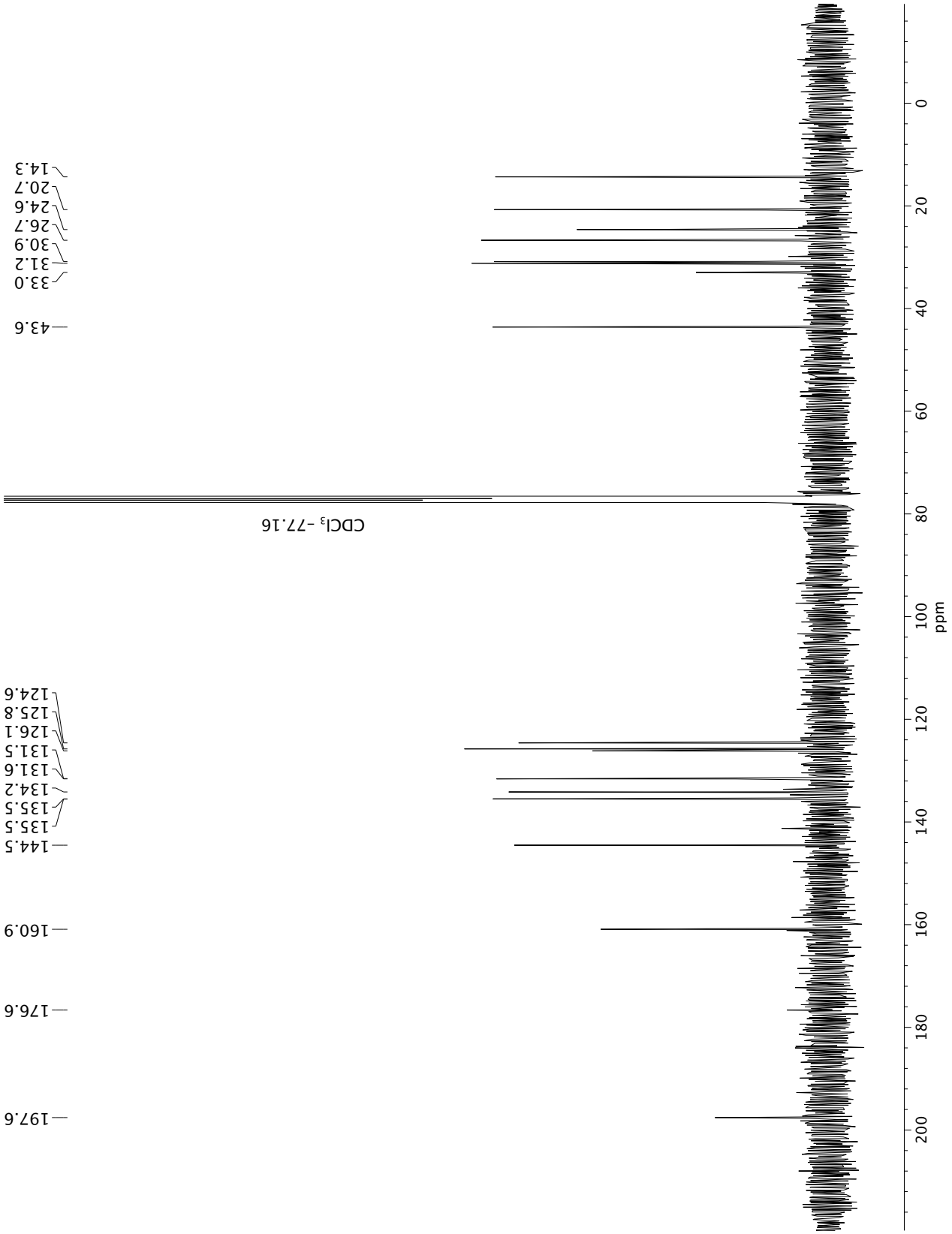
^{1}H NMR (400 MHz, $CDCl_3$) of compound **61**.



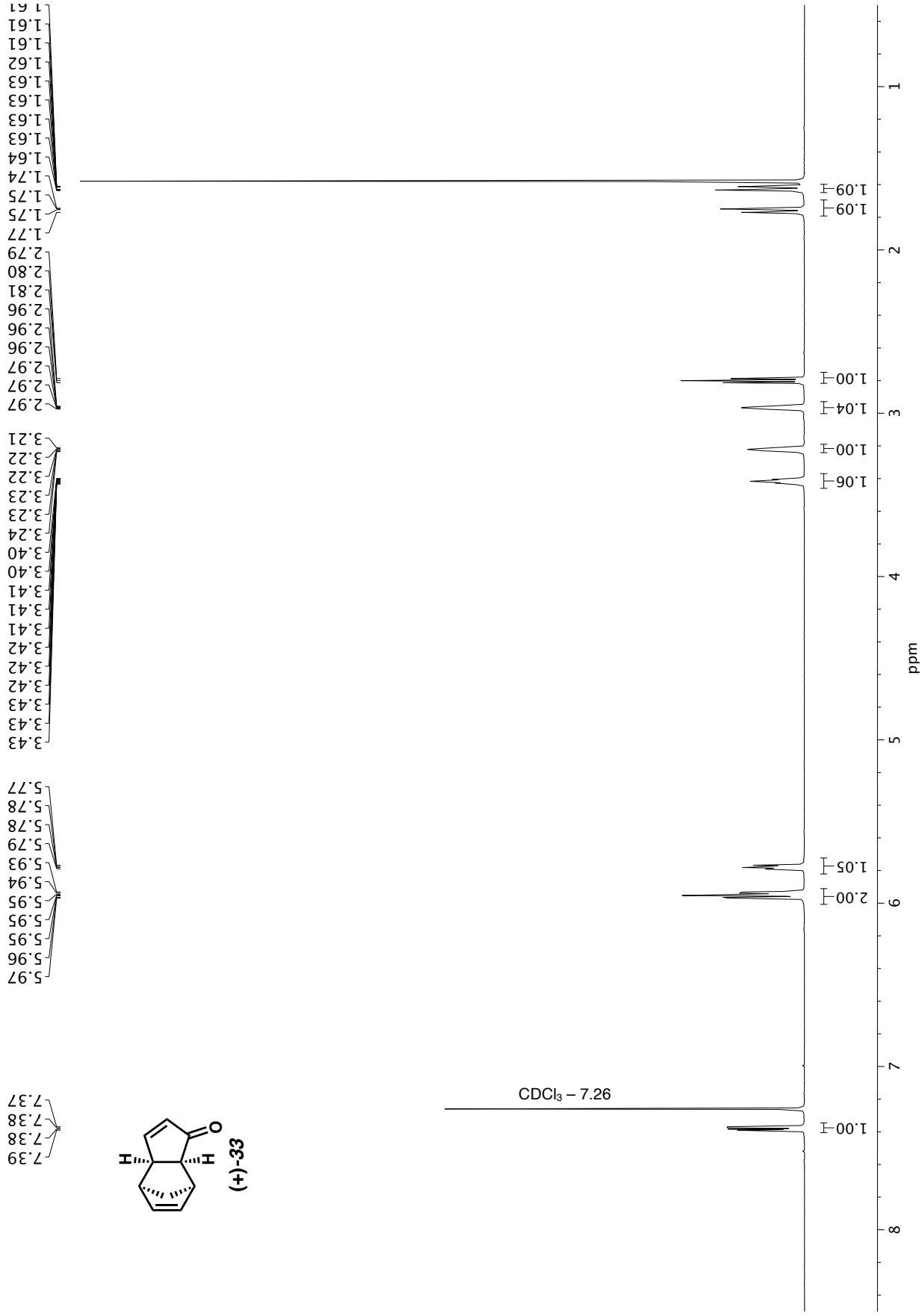
^{13}C NMR (101 MHz, $CDCl_3$) of compound **61**.



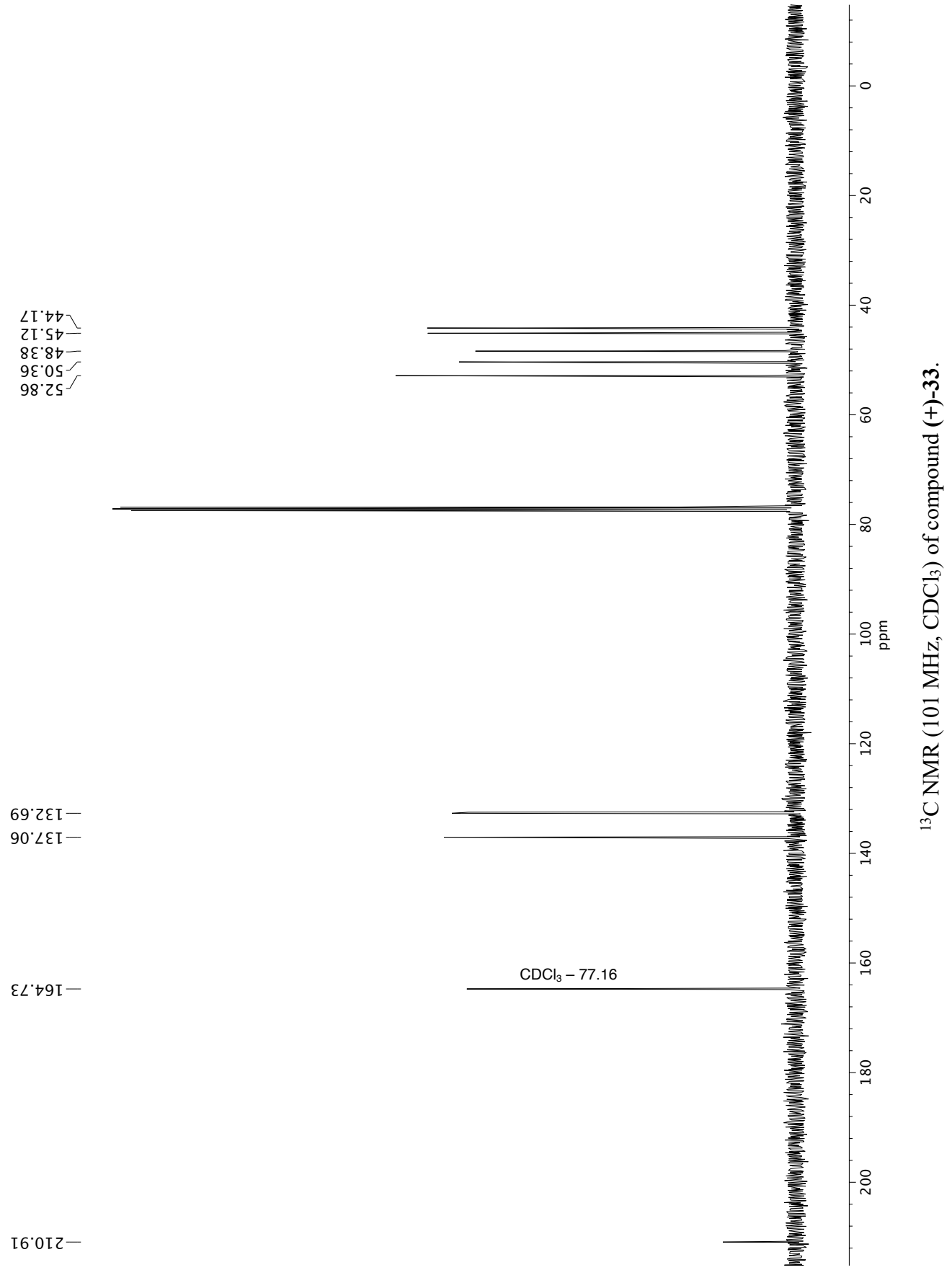
^{1}H NMR (400 MHz, $CDCl_3$) of compound **4**.



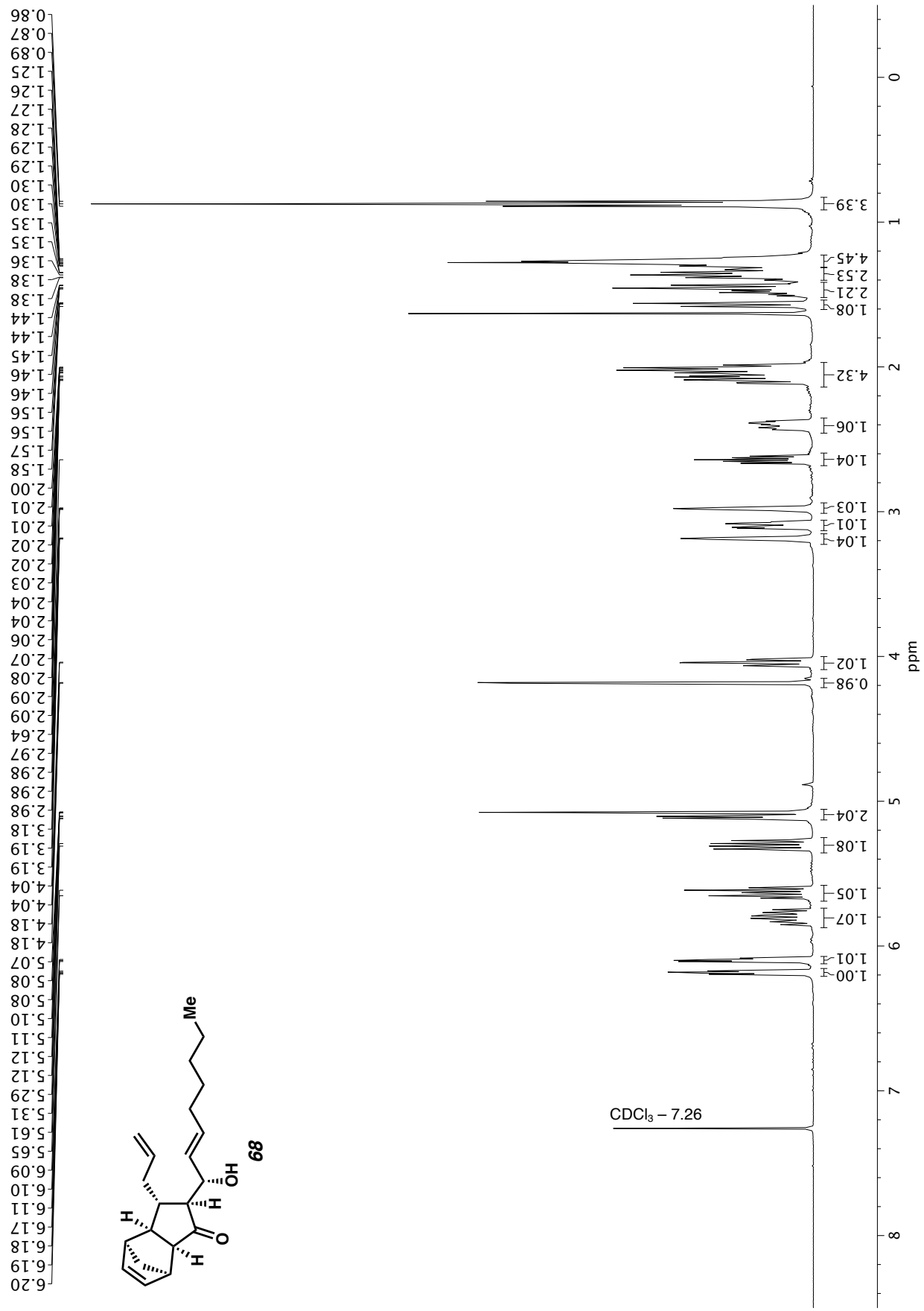
^{13}C NMR (101 MHz, $CDCl_3$) of compound **4**.



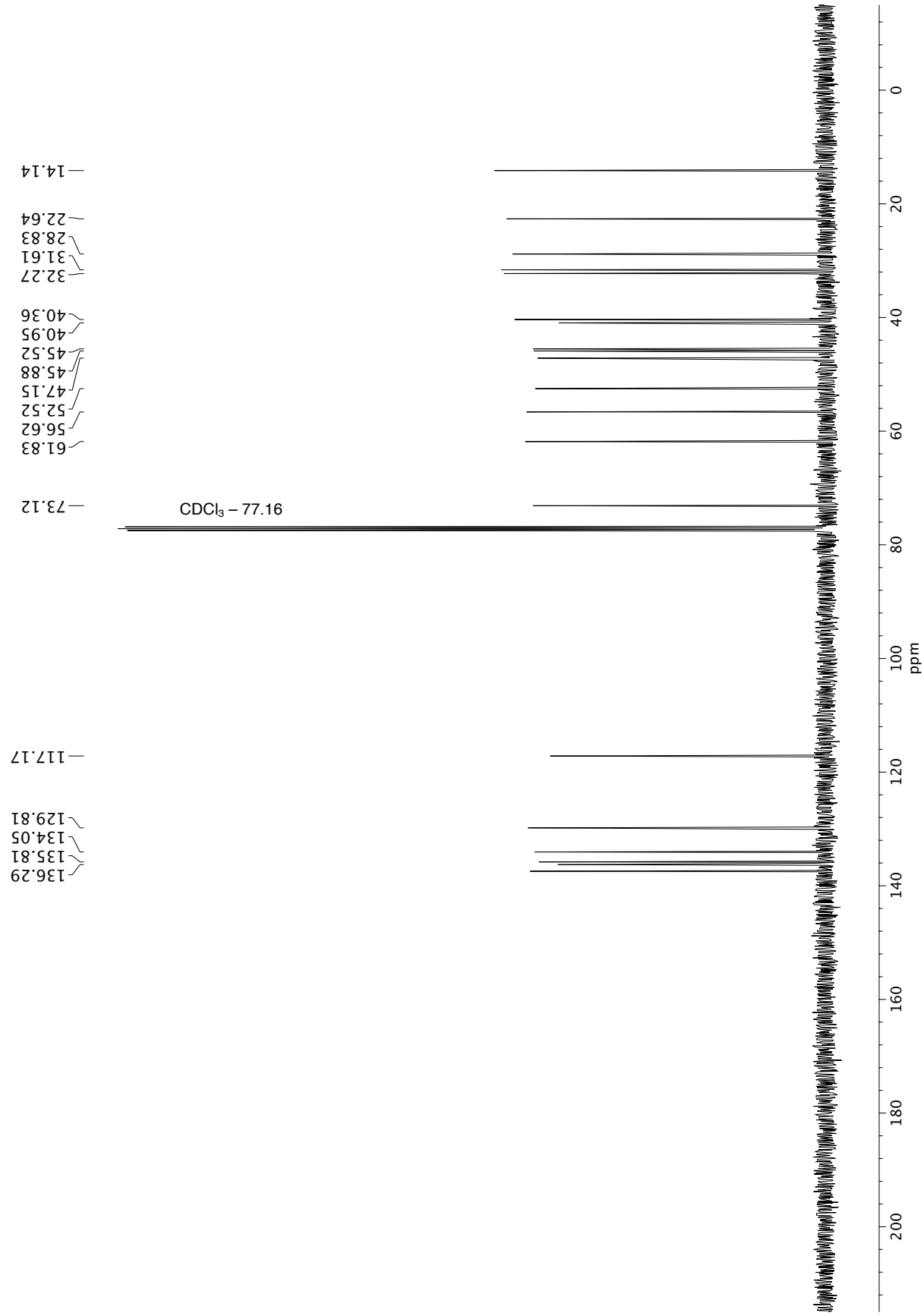
^{1}H NMR (400 MHz, $CDCl_3$) of compound **(+)-33**.



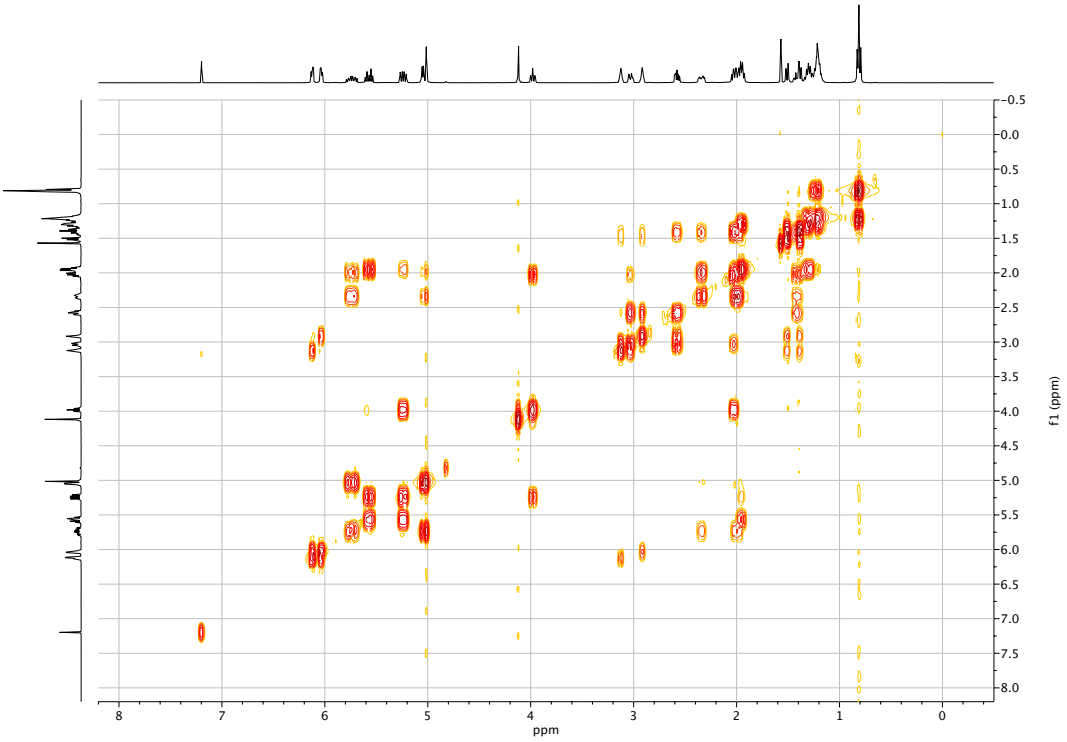
^{13}C NMR (101 MHz, $CDCl_3$) of compound **(+)-33**.



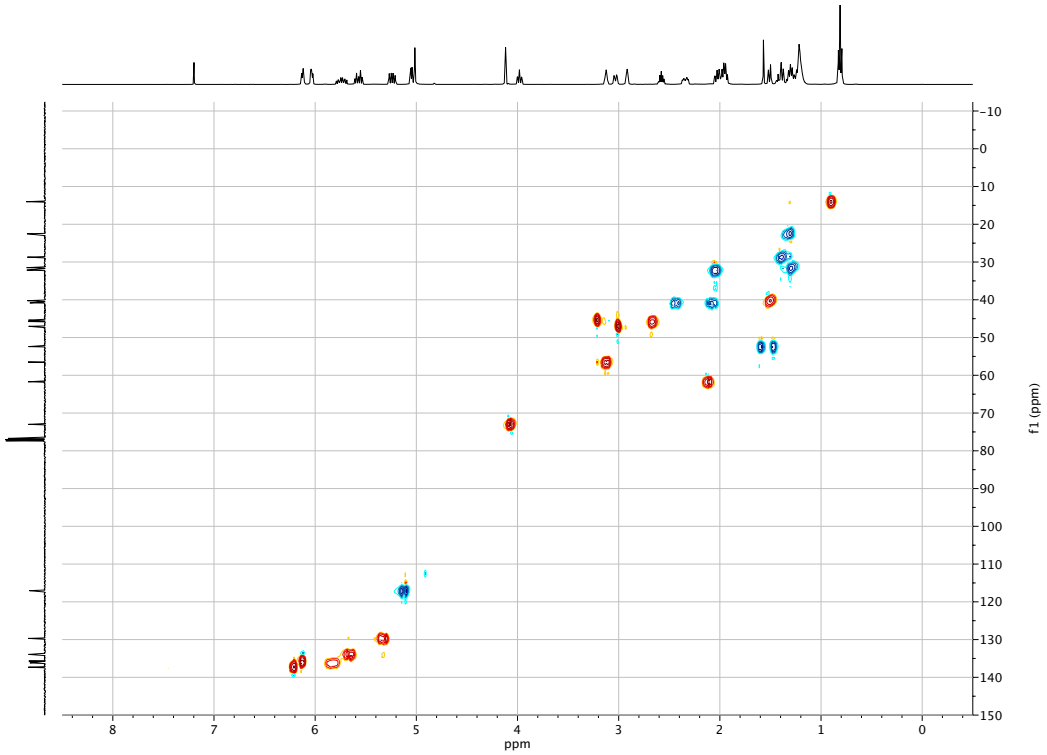
^{1}H NMR (400 MHz, $CDCl_3$) of compound **68**.



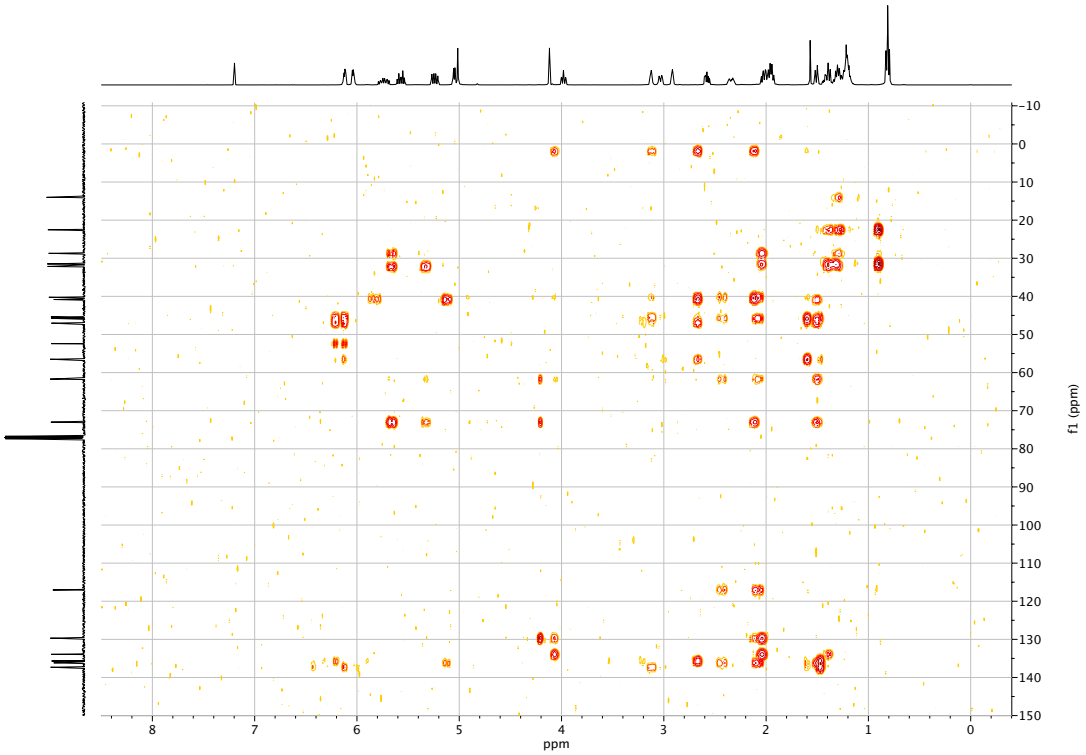
^{13}C NMR (101 MHz, $CDCl_3$) of compound **68**.



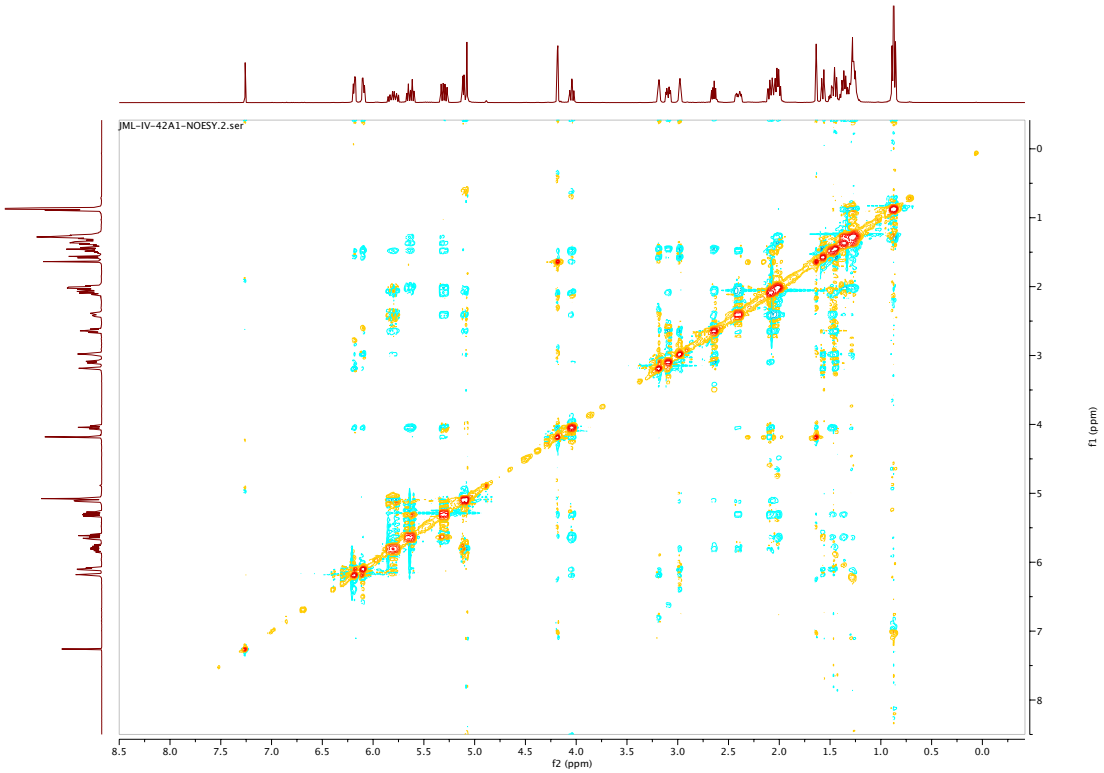
$^{1}H–^{1}H$ COSY NMR (400 MHz, $CDCl_3$) of compound **68**.



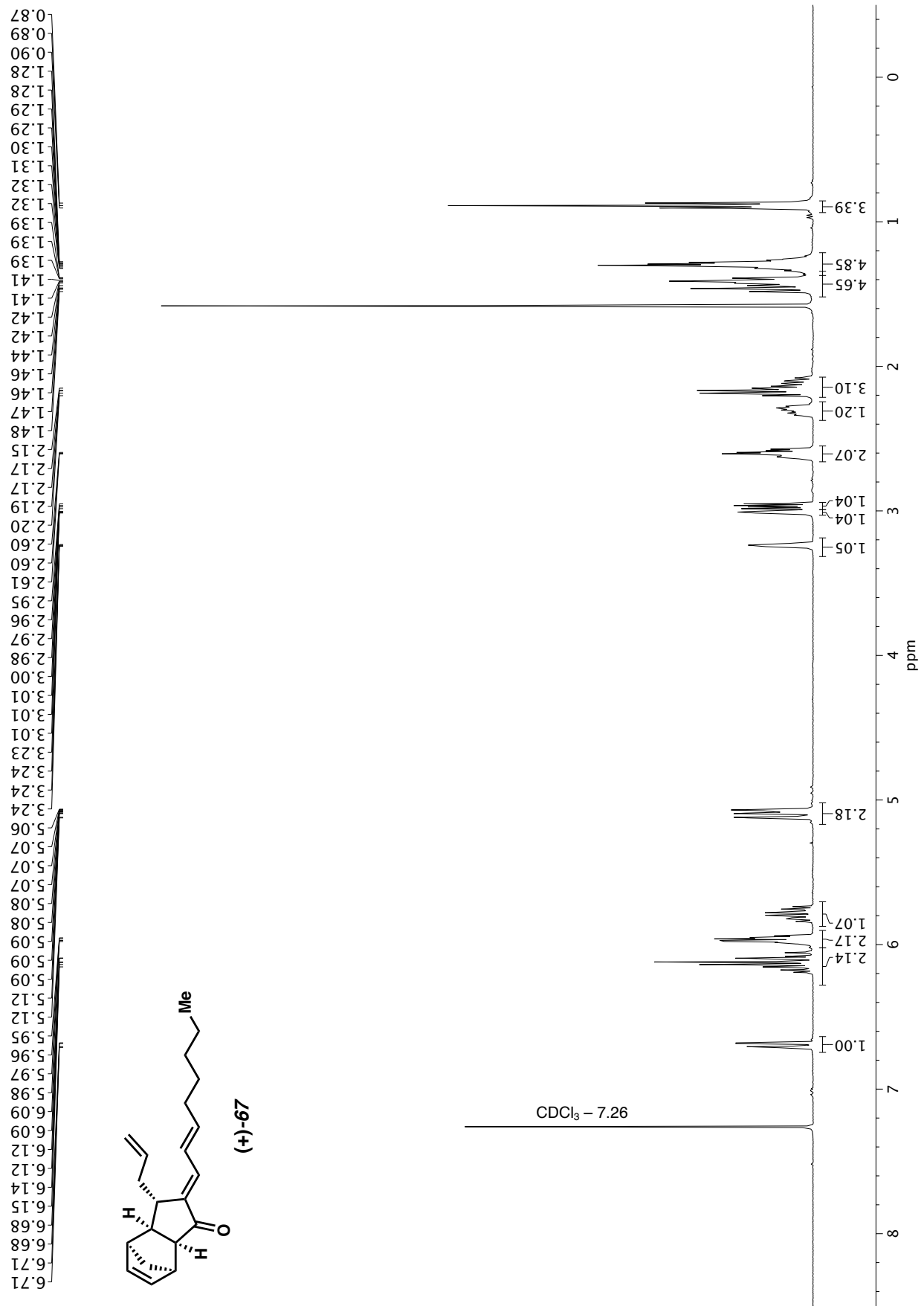
$^{1}H–^{13}C$ HSQC NMR (400 MHz, $CDCl_3$) of compound **68**.



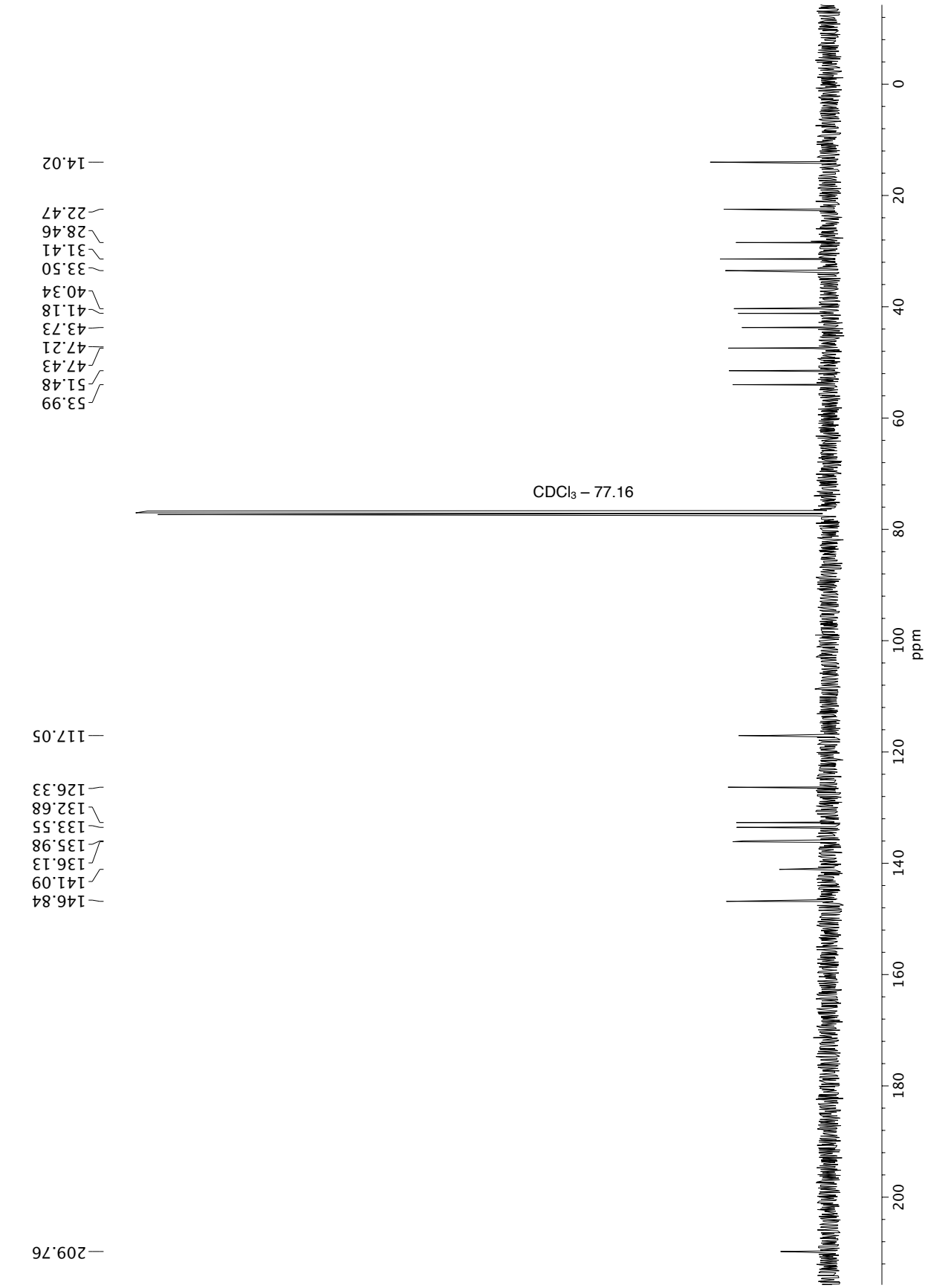
^{1}H–^{13}C HMBC NMR (400 MHz, $CDCl_3$) of compound **68**.



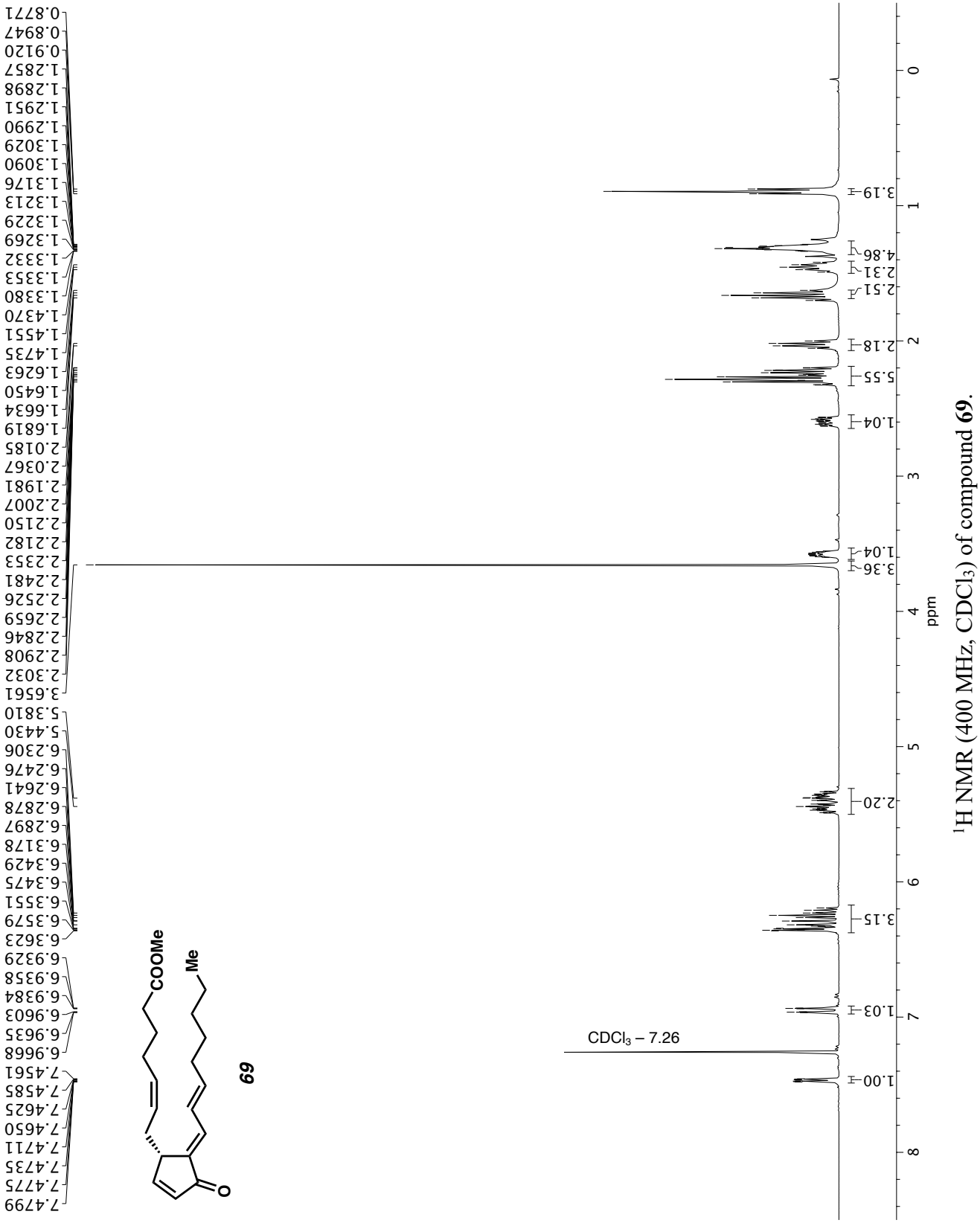
NOESY NMR (400 MHz, $CDCl_3$) of compound **68**.



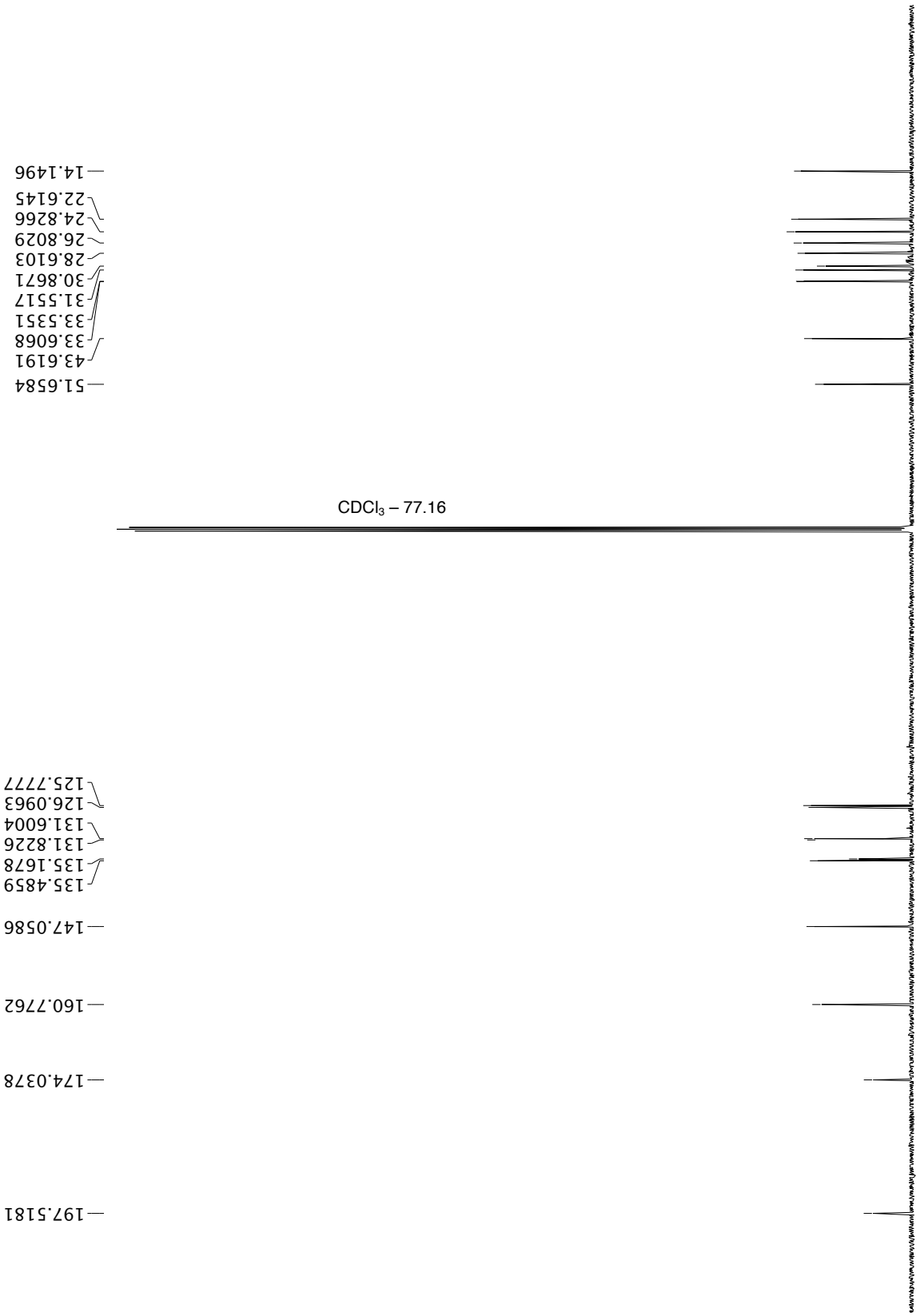
^{1}H NMR (400 MHz, $CDCl_3$) of compound **(+)-67**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **(+)-67**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **69**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **69**.

CHAPTER 2

Palladium-Catalyzed Aerobic Intramolecular Aminoacetoxylation of Alkenes Enabled by Catalytic Nitrate[†]

ABSTRACT

Palladium-catalyzed aminoacetoxylation of alkenes has been applied as an efficient strategy in the synthesis of nitrogen-containing heterocycles. The aminoacetoxylation products are generated from the reductive elimination of high-valent palladium intermediates and stoichiometric amount of strong oxidants are typically required to oxidize Pd(II) intermediates. A mild aerobic intramolecular aminoacetoxylation method for the synthesis of pyrrolidine and indoline derivatives was achieved using molecular oxygen as oxidant. A catalytic NO_x species acts as an electron transfer mediator to access a high-valent palladium intermediate as the presumed active oxidant.

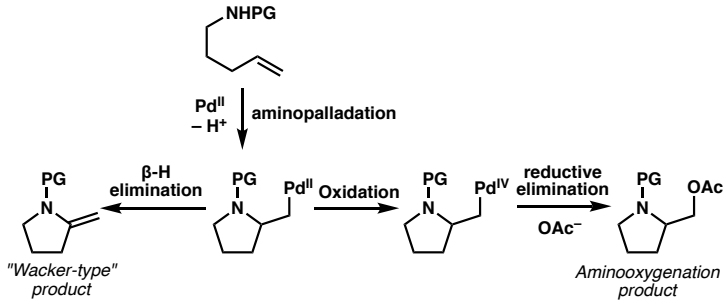
2.1 INTRODUCTION

Numerous alkene difunctionalization reactions enabled by palladium catalysts have been developed as efficient transformations for the construction of useful organic building blocks.[1] For example, palladium-catalyzed amination of alkenes has been applied as a new strategy to

[†] Adapted with permission from Li, J.; Grubbs, R. H.; Stoltz, B. M. Palladium-Catalyzed Aerobic Intramolecular Aminoacetoxylation of Alkenes Enabled by Catalytic Nitrate. *Org. Lett.* **2016**, *18*, 5449–5451.

synthesize nitrogen-containing heterocycles.[2] Arising from a key aminopalladation step, an alkylpalladium(II) intermediate can undergo versatile pathways to generate different structural motifs (Scheme 2.1.1).[2a] From the mechanistic view, to realize the aminooxygenation of alkene, a rapid β-hydride elimination process[3] should be avoided after forming the aminopalladation intermediate in the initial step. Oxidation of aminopalladation intermediate could form a Pd(IV) intermediate, which could readily undergo reductive elimination to obtain the difunctionalization product (Scheme 2.1.1). So, the key determinant to get the aminooxygenation product is the competition between two pathways, which relies on various reaction conditions, especially the choice of oxidants.[4]

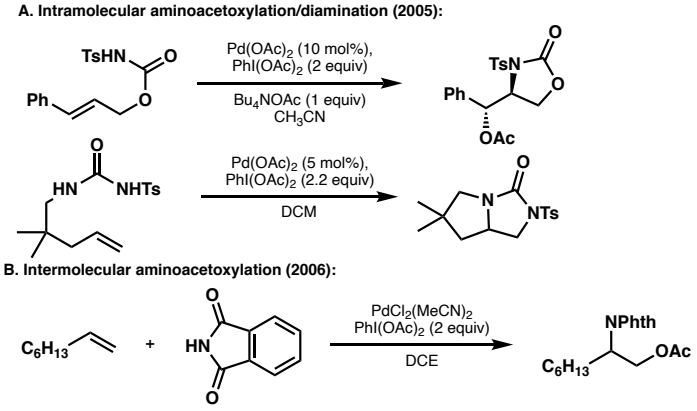
Scheme 2.1.1. Aminopalladation and Subsequent Transformations



In the past decade, aminooxygenation has been achieved by oxidizing the alkylpalladium(II) intermediate into high-valent palladium (Pd^{IV} or Pd^{III}) followed by C–O bond-forming reductive elimination. However, a stoichiometric amount of a strong oxidant, such as $PhI(OAc)_2$ or NFSI, is typically required to access the high-valent palladium intermediate. $PhI(OAc)_2$ is widely applied as a strong oxidant to generate the Pd(IV) intermediate to realize alkene difunctionalization and other reactions such as C–H functionalization, which have been reported by Sorensen[5], Stahl,[6] Sanford,[7] Muñiz,[8] Dong,[9] and Liu and co-workers[10]. For example, in Sorensen's pioneer study in 2005, N-tosyl carbamates can be obtained as diamination products from internal or terminal alkenes (Scheme 2.1.2A).[6] In this method, palladium acetate was applied as catalyst, which can

be oxidized to Pd(IV) species in the presence of 2 equivalents of $PhI(OAc)_2$. Muñiz and co-workers in the same year achieved the aminoacetoxylation in similar conditions (Scheme 2.1.2A).[9a] Liu, Stahl, and co-workers also developed various aminooxygen reactions using $PhI(OAc)_2$ as oxidant, and one impressive example is the intermolecular aminoacetoxylation by reacting terminal alkenes with phthalimide, to obtain protected amino alcohol products (Scheme 2.1.2B).[11]

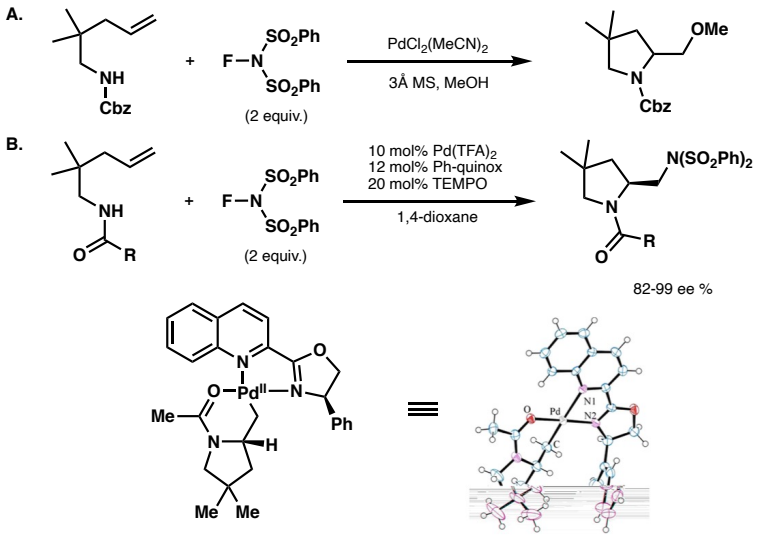
Scheme 2.1.2. Examples of Alkene Difunctionalization Using $PhI(OAc)_2$



Another approach to generate high-valent palladium intermediate is to use N-Fluorobenzenesulfonimide (NFSI) as oxidant, and several palladium-catalyzed alkene difunctionalization examples has been reported by Michael group. NFSI, a bystanding F^+ oxidant,[11] is strong enough to oxidize Pd(II) to Pd(IV), thus facilitate the difunctionalization reaction happening through reductive elimination. Such as the example shown in Scheme 2.1.2A, where 2 equivalents of NFSI were used to convert the Cbz-protected amino alkene into the pyrrolidine product catalyzed by $PdCl_2(MeCN)_2$, and the vicinal position is attached with methoxy group which is from the methanol solvent (Scheme 2.1.3A).[12]

An enantioselective diamination reaction was developed in 2013. In the highly oxidative conditions in the presence of NFSI, most phosphine ligands that can be successfully used in many enantioselective processes, are incompatible in such conditions and subjected to be oxidized. So, introduction of chiral elements becomes very challenging. In this example, Ph-quinox was used as a chiral ligands and 82-98 % ee can be achieved (Scheme 2.1.3B).[13] The key Pd(II) intermediate was isolated and the absolute structure was unambiguously determined by X-ray crystallography. This work shows very promising result that the challenging difunctionalization of alkene could be achieved by ligand design that could tolerate oxidative conditions, and new types of chiral ligands are anticipated by further research in this field.

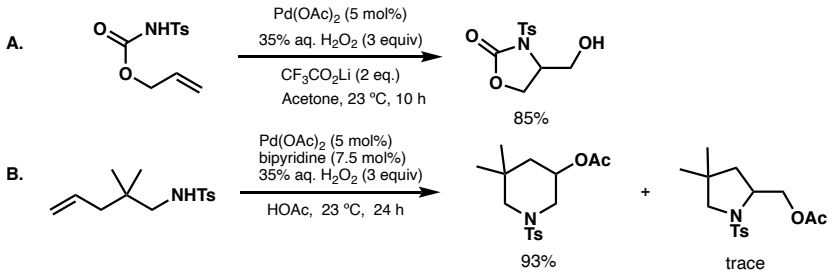
Scheme 2.1.3. Examples of Alkene Difunctionalization Using NFSI



However, stoichiometric amount of wasteful high-energy oxidants, such as $PhI(OAc)_2$, are typically required to access high-valent palladium centers and large quantities of by-products are generated. Recently, milder conditions have also been developed using H_2O_2 as an environmentally tractable and inexpensive oxidant. In 2014, the Liu group first reported a

palladium-catalyzed aminohydroxylation reaction with 3 equivalents of H_2O_2 as oxidant. Alkene tethered with N-tosyl carbamates can be converted to the aminohydroxylation product with a free hydroxyl group in high yield at room temperate (Scheme 2.1.4A).[14] In 2015, another example showed the ability of hydrogen peroxide of oxidizing Pd(II) to achieve aminoacetoxylation reaction with similar aminoalkene substrates as previous examples.[15] However, in this report, a six-membered piperidine derivative was formed as the major product over five-membered ring product, which is ascribed to the kinetic difference of 5-*exo* and 6-*endo* attack as they suggested. Bis-nitrogen ligands are very suitable to this reaction because they were proved to potentially suppress β-H elimination of palladium complex.[16]

Scheme 2.1.4. Examples of Alkene Difunctionalization by Using H_2O_2

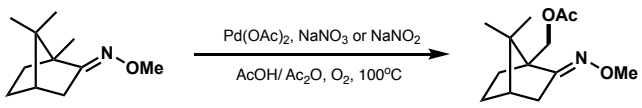


2.2 PALLADIUM-CATALYZED AEROBIC TRANSFORMATIONS

H_2O_2 was utilized as an environmentally tractable and inexpensive oxidant, but aerobic conditions are still in high demand from a sustainable perspective. A classic and well-studied example of a palladium-catalyzed aerobic homogeneous transformation is the Wacker process. This transformation was developed in the 1950s using O_2 as the terminal oxidant in combination with a Cu salt as a redox co-catalyst to facilite the reoxidation of Pd^0 to Pd^{II}.[17] In contrast, reports of alkene difunctionalizations under aerobic conditions are rare, presumably because the oxidation

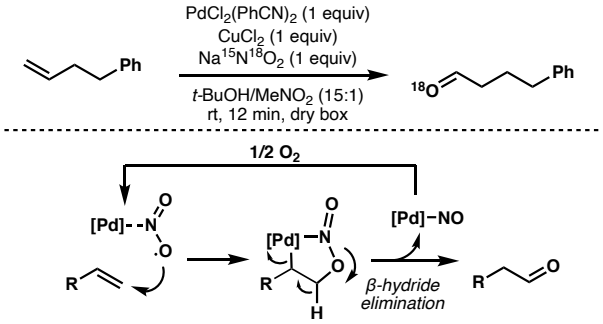
of the intermediate alkylpalladium(II) species using O_2 as the sole oxidant is kinetically challenging;[18] hence, care must be taken to avoid facile β-hydride elimination immediately (Scheme 2.1.1). Recently, NO_x species have been shown to be effective electron transfer mediators capable of facilitating the aerobic oxidation of alkylpalladium(II) intermediates to their high-valent counterparts.[19] Sanford and co-workers reported that nitrate/nitrite could serve as a redox co-catalyst in the aerobic acetoxylation of unactivated C(sp^3)–H bonds via C–O bond reductive elimination of a high-valent palladacycle directed by oxime ether or pyridine-type directing groups (Scheme 2.2.1).[20] $Pd(OAc)_2$ was used as a catalyst, with $NaNO_3$ as a co-catalyst, under 1 atm O_2 as the terminal oxidant. $NaNO_2$ can also play a similar activating role though the reactivity was lower than $NaNO_3$.

Scheme 2.2.1. Aerobic Palladium-catalyzed C(sp^3)–H Acetoxylation with NO_x Co-catalyst



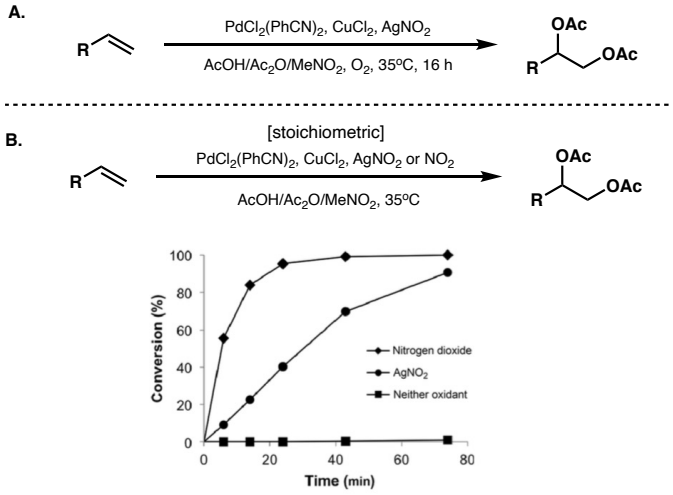
Grubbs and co-workers recently reported a nitrite-modified Wacker oxidation that shows anti-Markovnikov selectivity.[21] In the presence of nitrite from $AgNO_2$, aldehyde was obtained as the major product, which is catalyst-controlled. A [Pd]-NO_2 complex was proposed to be formed *in situ* and nitrite could be a donor of oxygen to form a [Pd]-NO complex, which could be re-oxidized by O_2 (Scheme 2.2.2). The oxygen atom in aldehyde product was proved to be donated from nitrite by ^{18}O-labeled study.

Scheme 2.2.2. Nitrite-modified Aldehyde-selective Wacker Oxidation



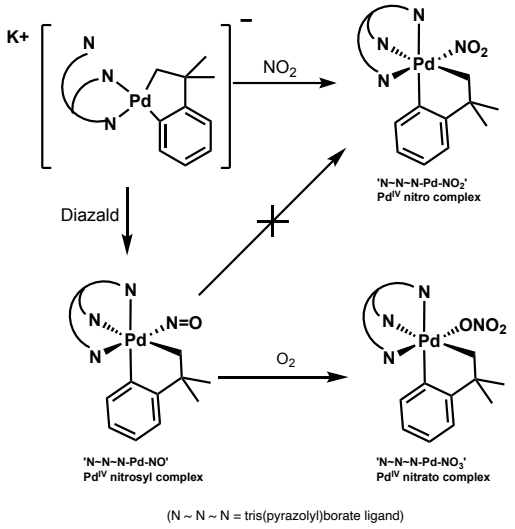
Very recently, the Grubbs group reported a palladium-catalyzed aerobic alkene diacetoxylation method mediated by a catalytic amount of silver nitrite. By simply changing the solvent from *t*-BuOH to AcOH, along with other slightly variations of reaction conditions, diacetoxylation of unbiased terminal alkenes was achieved by Grubbs and co-workers in 2014 (Scheme 2.2.3A).[22] NO_2 was released *in situ* in these acidic conditions, and served as an ETM to oxidize Pd(II) to higher oxidation states such as Pd(III) or Pd(IV), which was suggested by the mechanistic studies by reacting with NO_2 gas in the reaction conditions (Scheme 2.2.3B).

Scheme 2.2.3. Diacetoxylation of Unbiased Terminal Alkenes



However, the ligand sets coordinating with Pd were not defined in those methods, and palladium-nitrite ligands could be present as suggested by previous studies. The possible formation of [Pd]-NO_x complexes is supported by previous work by Cámpora, Palma, and co-workers.[23] A [Pd]-NO complex was synthesized by the reaction of an *in situ* generated anionic Pd(II) salt with diazald (N-nitroso-N-methyl-*p*-toluenesulfonamide). Oxidation of [Pd]-NO complex with O_2 in toluene gave [Pd]-NO_3 complex. Although no direct evidence was gained for [Pd]-NO_2 being formed as an intermediate in the reaction, its independent synthesis was accomplished by treating Pd(II) starting material with NO_2 (Scheme 2.2.4). This study suggests the redox conversions of [Pd]-NO_x complexes in the presence of O_2, which may provide some mechanistic evidences to the aerobic transformations mediated by Pd/NO_x catalysts.

Scheme 2.2.4. Evidence of [Pd]-NO_x Complexes



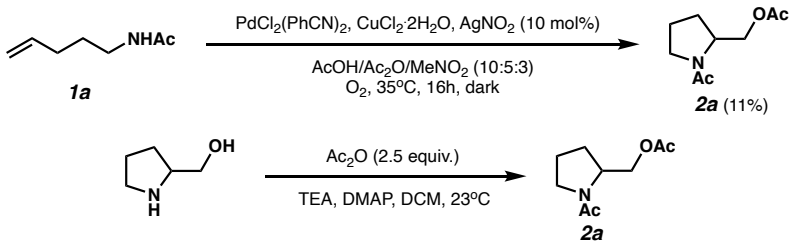
Based on the literature precedent of those aerobic transformations, we reasoned that a palladium-catalyzed aerobic aminooxygenation reaction might be possible using this electron transfer mediator strategy, as NO_x species could be a kinetically suitable mediator in the aerobic oxidation of the alkylpalladium(II) intermediate formed after aminopalladation. This aerobic

reaction can be an environmentally tractable alternative to current methods using wasteful high energy oxidants.

2.3 OPTIMIZATION OF PALLADIUM-CATALYZED AMINOOXYGENATION REACTIONS

We started our investigation by subjecting acetyl-protected aminoalkene substrate **1a** to our previously published intermolecular diacetoxylation reaction conditions. 11% of cyclized product **2a** was obtained, which is identical to the authentic product sample directly synthesized from pyrrolidin-2-ylmethanol.

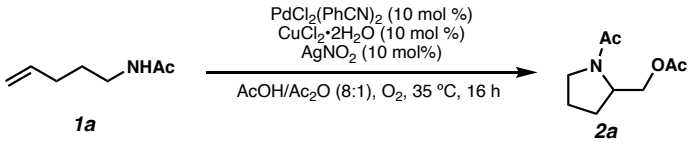
Scheme 2.3.1. Initial Trial and Synthesis of Authentic Product Sample



At the initial point of optimization, a control experiment was conducted to verify if all components are required for the conversion. We were delighted to find that removing nitromethane from the reaction system could boost the yield to 50% as measured by GC analysis (Table 2.3.1). However, AcOH and Ac_2O are both necessary for the transformation. In the solvent screen and solvent/co-solvent ratio experiments, the yield obtained in AcOH/Ac_2O was significantly above other solvents/Ac_2O tested, and removal of Ac_2O co-solvent dropped the yield. The role of the Ac_2O was not discussed in previous diacetoxylation conditions, but similar to Sanford's C–H acetoxylation example[19], it can potentially serve to sequester H_2O in the reaction conditions. In another set of reactions shown in Table 2.3.2, both $AgNO_2$ and the O_2 atmosphere are proved to be necessary for the product formation. Although the role of Cu still remains elusive, it could potentially make the reaction more efficient, because less product could still be obtained

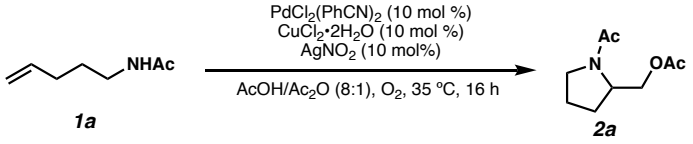
in 34% yield without $CuCl_2$ (Table 2.3.2, entry 3). Methyl ketone was the major byproduct, which was generated from the competing β-hydride elimination pathway. Possible alkene isomerization products were also detected.

Table 2.3.1. Initial Control Experiment of Solvent



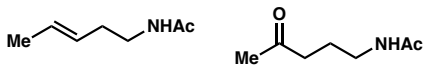
entry	conditions	conversion (%)	yield (%)[a]
1	no change	99	11
2	no Ac_2O	96	1
3	no AcOH, Ac_2O	99	1
4	no $MeNO_2$	100	50

Table 2.3.2. Initial Control Experiment of Catalysts



entry	conditions	conversion (%)	yield (%)[a]
1	no change	100	50
2	no $AgNO_2$	99	0
3	no $CuCl_2$	97	34
4	no $CuCl_2$, $AgNO_2$	86	0
5	no O_2	15	2

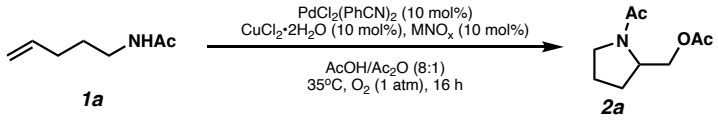
Observed by-products:



Next, different source of nitrates/nitrites were tested. To our delight, most of metal nitrates/nitrites and alkyl nitrites have shown decent reactivity, including very cheap source of sodium nitrate, sodium nitrite and *iso*-butylnitrite, the cheapest commercially available alkyl nitrite. Among them, cupric nitrate gave the highest yield of product (56%, Table 2.3.3 Entry 6). So, it was used as the optimized source of NO_x in the following optimization experiment, and a third

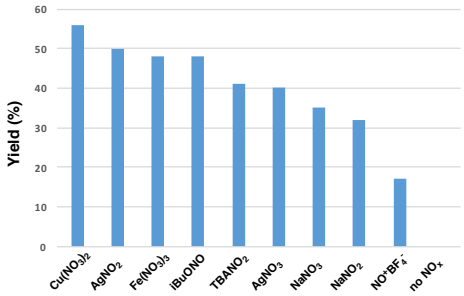
catalyst component $CuCl_2$ was not required anymore. Furthermore, reactions could be performed without shielding from light because light-sensitive silver nitrite was replaced.

Table 2.3.3. Nitrate/nitrite Sources Screening



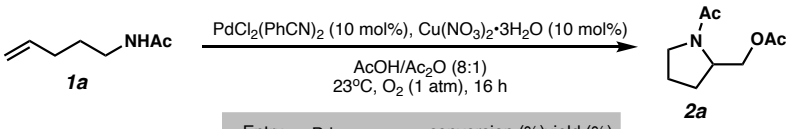
Entry	MNO_x	yield (%)
1	$AgNO_2$	50
2	$NaNO_2$	32
3*	$TBANO_2$	41
4	iBuONO	48
5	$NaNO_3$	35
6	**$Cu(NO_3)_2$**	**56**
7	$Fe(NO_3)_3$	48
8	$AgNO_3$	40
9	$NO^+BF_4^-$	17
10	no MNOx	0

*$TBANO_2$ = tetrabutylammonium nitrite



A series of Pd(II) sources with different counterions were tested. It was found that chloride ion gave the highest yield (Table 2.3.4, Entry 6) over the other counterions commonly used in palladium-catalyzed reactions. Additionally, reaction could be performed at room temperature to get higher yield. The following screening of ligands showed distinct results among different ligands (Table 2.3.5). Only benzonitrile, triphenylphosphine, and norbornadiene ligands showed decent yield, but other ligands tested showed no conversion, including the previously used bipyridine and di(2-pyridyl) ketone ligands in Liu's aminooxygenation example.[16]

Table 2.3.4. Palladium Counterions Screen

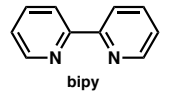


Entry	Pd sources	conversion (%)	yield (%)
1	$Pd(OAc)_2$	48	10
2	$Pd(TFA)_2$	73	17
3	$Pd(PhCN)_2Br_2$	100	54
4	$Pd(MeCN)_4(BF_4)_2$	37	14
5	$Pd(PhCN)_2Cl_2$	100	56
6*	$Pd(PhCN)_2Cl_2$	100	62

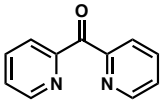
*Entry 6 was conducted in 23°C

Table 2.3.5. Ligand Screen

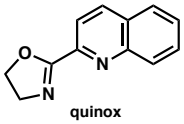
Entry	Pd sources	conversion (%)	yield (%)
1	**$Pd(PhCN)_2Cl_2$**	100	66
2	**$Pd(PPh_3)_2Cl_2$**	100	63
3	$Pd(nbd)Cl_2$	100	66
4	$Pd(COD)Cl_2$	9	0
5	$Pd(bipy)Cl_2$	0	0
6	$Pd(dppe)Cl_2$	0	0
7	$Pd(quinox)Cl_2$	0	0
8	$PdCl_2$, bipy	0	0
9	$PdCl_2$, dpk	0	0
10	$PdCl_2$	100	20



bipy



dpk

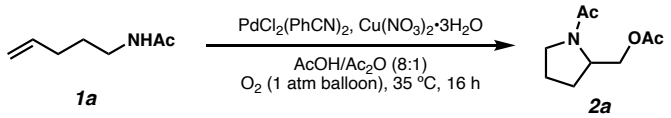


quinox

After the determination of best catalysts, the loading and ratio of those two catalysts were studied. When decreasing the loading of Pd and Cu catalysts from 10 mol % to 5 mol%, acceptable yield of 51% could still be obtained, and there was no significant increase of yield when increasing the loading of $Cu(NO_3)_2$ while keeping $PdCl_2(MeCN)_2$ as 5 mol%. However, when the loading of $Cu(NO_3)_2$ was lower than $PdCl_2(MeCN)_2$, decreased yield was obtained (Table 2.3.6 Entry 4). Similar result can be obtained by controlling Pd/Cu/nitrite ratio by adding $PdCl_2(MeCN)_2$, $CuCl_2$ and $AgNO_2$, that the optimal ratio of Pd/Cu/nitrite was 1:1:2 (Table 2.3.6, Entry 6), which suggested that a sufficient amount of nitrite/nitrate was required to get high catalytic turnover. Keeping the loading of $PdCl_2(PhCN)_2$ and $Cu(NO_3)_2$ as 5 mol%, further screening was conducted by tuning the solvent ratio, concentration, reaction time, temperature, and additives. For additives,

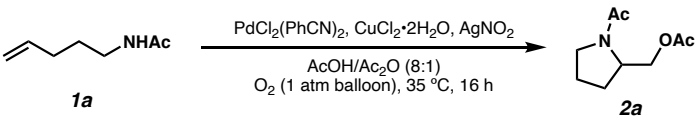
common acidic and basic additives, including the previous effective trifluoroacetate salts in Liu's work[15] have been tried, but none of them showed increased yield.

Table 2.3.6. Studies of Catalyst Loading and Ratio



1a ***2a***

entry	$PdCl_2(PhCN)_2$ (mol%)	$Cu(NO_3)_2 \cdot 3H_2O$ (mol%)	yield (%)[a]
1	5	5	51
2	5	7.5	52
3	5	10	52
4	10	5	17

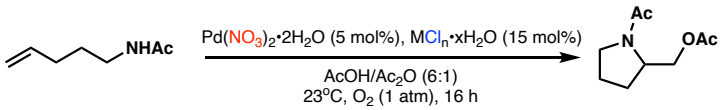


1a ***2a***

entry	$PdCl_2(PhCN)_2$ (mol%)	$CuCl_2 \cdot 2H_2O$ (mol%)	$AgNO_2$ (mol%)	yield (%)[a]
5	5	5	5	26
6	5	5	10	52

By switching the counterions between Pd and Cu, we found that the combination of $Pd(NO_3)_2 \cdot 2H_2O$ and $CuCl_2 \cdot 2H_2O$ also gave similar yield. Surprisingly, by replacing $CuCl_2$ into some simple chloride salts, such as sodium chloride or zinc chloride, decent yield could still be obtained, which suggests that Cu may not be necessary in this reaction (Table 2.3.7). But chloride anion was very important in this reaction, since low yield was obtained if adding no chloride in the reaction conditions. However, the reactions using $Pd(NO_3)_2$ as catalyst were less reproducible, and $Pd(NO_3)_2$ is a more expensive source of palladium.

Table 2.3.7. Reaction Conditions Using $Pd(NO_3)_2$ as Catalyst without Cu Salts



Entry	Cl^- source	yield(%)
1	$CuCl_2$	48
2	LiCl	55
3	NaCl	60
4	KCl	54
5	$ZnCl_2$	64
6	NBu_4Cl	5
7	$Cu(NO_3)_2$	11
8	no Cl^-	10

2.4 SUBSTRATE SCOPE

Next, we evaluated substrate scope and functional group tolerance under our optimized conditions. First, several linear aliphatic acetyl-protected amino alkenes were tested in the optimized conditions (Scheme 2.4.1). The *gem*-diphenyl substrate **1b** has been tried and gave a higher yield of 75%, which was expected to have the Thorpe-Ingold effect that could facilitate the cyclization processes. And *gem*-dibenzyl substrate also gave the corresponding pyrrolidine product **2c** in 83% yield. Different amine protecting groups were also tested at the initial stage. However, acetyl group is the best among different amine protecting groups that have been tested (Table 2.4.1, Entry 1).

Scheme 2.4.1. Optimized Reaction Conditions

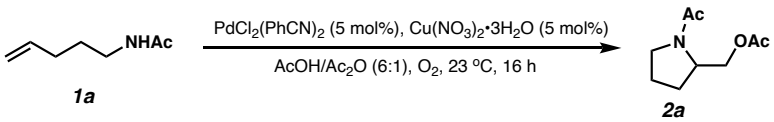
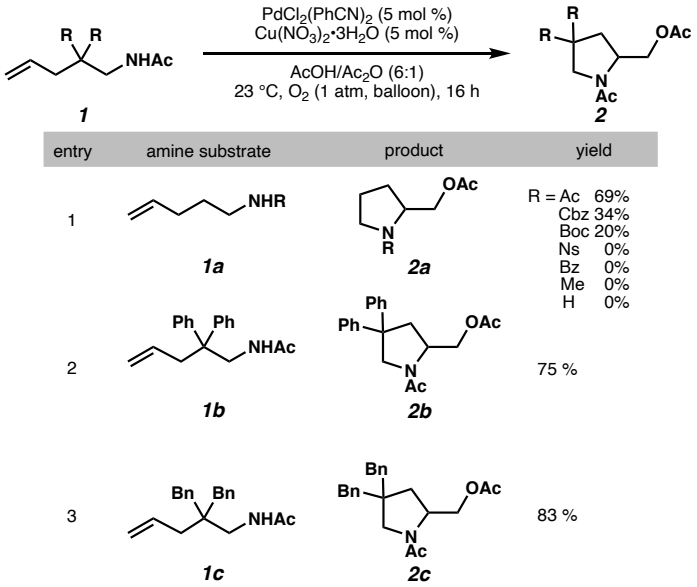
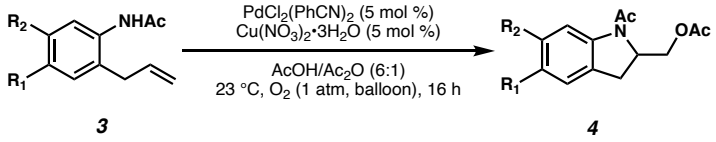


Table 2.4.1. Reactions with Aliphatic Amino Alkenes



Acetyl-protected aromatic amine substrates have been tried and we were delighted to find 87% yield could be obtained from *o*-allyl aniline substrate **3a**. Based on the good result obtained from *o*-allyl aniline substrate, we tested a series of *o*-allylaniline derivatives, obtaining a variety of indoline derivatives **4b-i** in moderate to excellent yields (Table 2.4.2, 30-95% yield). A variety of substituents and functional groups were well tolerated, including fluoro, chloro, methyl ester, and trifluoromethyl groups. A lesser extent nitro, and cyano groups gave lower yields due to the electronic effect. Notably, we also tested the reaction under air and product **4a** can also be obtained in good yield (Table 2.4.2, entry 2; 80% yield).

Table 2.4.2. Reactions with Aromatic Substrates

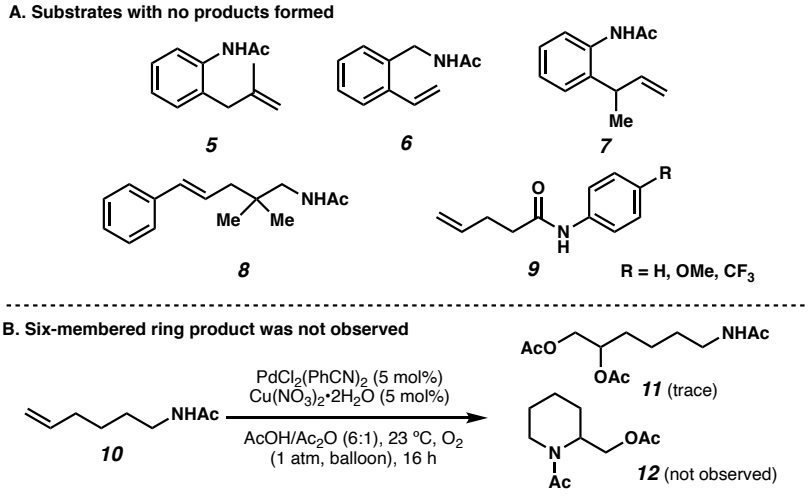


3 ***4***

entry	product	R_1	R_2	yield (%)[b]
1	***4a***	H	H	87
2[c]	***4a***	H	H	80
3	***4b***	Me	H	89
4	***4c***	H	Me	95
5	***4d***	F	H	88
6	***4e***	Cl	H	80
7	***4f***	COOMe	H	65
8	***4g***	CF_3	H	58
9	***4h***	NO_2	H	30
10	***4i***	CN	H	32

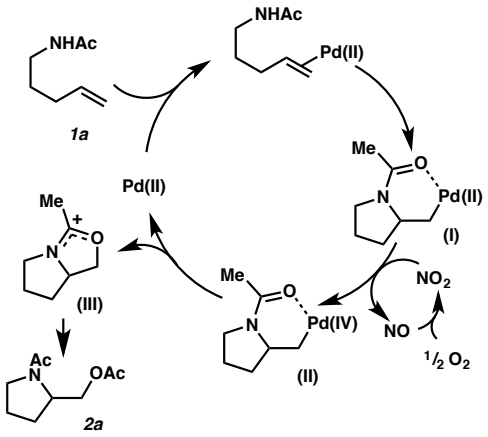
Efforts have been made to investigate whether this method can be applied to other types of substrates, but the substrates shown in Scheme 2.4.2 showed no reactivity. For example, alternation of the substrate structure gave no product, such as 2,2-disubstituted alkene **5**, *o*-vinyl benzylamine substrates **6**, and *o*-allylaniline with allylic substitution **7** (Scheme 2.4.2A), which may be ascribed to the steric bulk at the 2- or 3- positions of alkenes. Internal olefins are also synthesized but the reactivity was much lower, that trace amount of product can be detected by LC-MS from the reaction with substrate **8**. A series of amide **9** were also synthesized, which would expect the similar electronic property to the well-reacted *o*-allylaniline substrates **3**. However, those substrates with different amide acidity all showed no reactivity. Six-membered ring product **12** was not observed in the standard condition with substrate **10**. However, the diacetoxylation product **11** was observed in trace amount (Scheme 2.4.2B). In all, this method is very restricted to *o*-allylaniline and other linear terminal alkenes. The current reaction conditions are under optimized to be applied to a broader range of substrates.

Scheme 2.4.2. Substrates with Low Reactivity



Based on our observations and previous mechanistic studies, we propose the catalytic cycle shown in Scheme 2.4.3. Aminopalladation of the substrate **1a** likely forms Pd(II) intermediate **I**, which can be oxidized to high-valent palladium intermediate **II** by an NO_x species (possibly be NO_2) and molecular oxygen acts as the terminal oxidant. We envision that high-valent palladium intermediate **II** can then undergo the C–O bond-forming reductive elimination to release a cationic intermediate **III**, which forms the aminoacetoxylation product **2a** upon acetolysis. The source of additional oxygen atoms in the product is not verified, but a previous ^{18}O labeling study showed that the oxygen came from the AcOH solvent. Although the role of copper still remains elusive, the presence of copper is clearly advantageous as a decrease in yield was observed when no source of Cu was added.[24]

Scheme 2.4.3. Proposed Mechanism



2.5 CONCLUSIONS

In summary, this chapter presented a mild, aerobic intramolecular aminoacetoxylation method, which provides another example that catalytic nitrite/nitrate is capable of mediating the aerobic oxidation from Pd(II) to high-valent Pd(IV) intermediate after aminopalladation process, forming the desired aminoacetoxylation products in good to high yield (30-95%) from a variety of substrates. However, the amine protecting group is currently restricted to acetyl group. Internal olefins and steric hindered terminal olefins always showed low reactivity. Continuous efforts will be on the optimization of reaction conditions to fit in a larger range of substrates including the currently unreactive internal olefins. In addition, it would be worth introducing chiral ligands which may influence the stereoselectivity in the initial aminopalladation step and form the pyrrolidine or indolines with high enantioselectivity. Ongoing mechanistic studies, including a full stereochemical analysis, of this unique catalytic system would be beneficial to the development of novel stereoselective methods. Finally, in today's renaissance of NO_x redox chemistry, we anticipate efficient utilization of the oxidation potential of O_2 will enable access to even more environmentally benign processes rather than consuming other high-energy/high-cost stoichiometric oxidants.

2.6 EXPERIMENTAL METHODS AND ANALYTICAL DATA

2.6.1 Materials and Methods

Commercial reagents and metal salts were obtained from Sigma-Aldrich, TCI, Combi-Blocks, Alfa Aesar and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 MHz, Varian 400 MHz, or a Varian 300 MHz spectrometer. High-resolution mass spectra were provided by the California Institute of Technology Mass Spectrometry Facility, using JEOL JMS-600H High Resolution Mass Spectrometer. Gas chromatography data was obtained using an Agilent 6850 FID gas chromatograph equipped with a HP-5 (5%-phenyl)-methylpolysiloxane capillary column (Agilent). Response factors relative to the internal standard tridecane were collected for the substrate N-(pent-4-en-1-yl)acetamide (**1a**), and the product (1-acetylpyrrolidin-2-yl)methyl acetate (**2a**) following literature procedures.[25]

2.6.2 Experimental Procedures

General procedure A for isolation scale (0.5 mmol) aminoacetoxylation of alkenes:

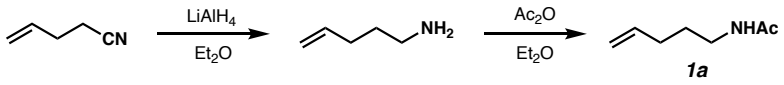
$PdCl_2(PhCN)_2$ (0.025 mmol, 9.6 mg), $Cu(NO_3)_2 \cdot 3H_2O$ (0.025 mmol, 6.0 mg) and alkene substrate (0.5 mmol) were weighed into a 50 mL flame-dried round bottom flask (14/20 neck) with a stir bar. The flask was sparged with oxygen (1 atm) from an oxygen balloon, through a vacuum adapter (14/20). AcOH (9.0 mL) and Ac_2O (1.5 mL) were premixed in a separated vial and sparged with oxygen (through needle and oxygen balloon) for 2 minutes. The oxygenated solvent mixture was then transferred into the flask *via* syringe. The reaction was then allowed to stir at 23 °C for 16 h under an atmosphere of oxygen (1 atm balloon). The solvent was removed

under reduced pressure. Dichloromethane (20 mL) was then added and the resulting mixture was washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with dichloromethane (2 × 20 mL) and the combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was purified by silica gel chromatography.

General procedure B for analytical scale (0.2 mmol) aminoacetoxylation of 1a:

$PdCl_2(PhCN)_2$ (0.01 mmol, 3.8 mg), $Cu(NO_3)_2 \cdot 3H_2O$ (0.01 mmol, 2.4 mg) and alkene substrate (0.5 mmol) were weighed into a 2-dram screw-cap vial charged with a stir bar. The vial was sparged with oxygen (1 atm balloon) for 45 seconds. AcOH (3.6 mL), Ac_2O (0.6 mL) and tridecane (0.00246 mmol, 6 μL) were subsequently added *via* syringe. The solution was saturated with oxygen by an additional 45 seconds of sparging. The reaction was then allowed to stir at 23 °C for 16 h under an atmosphere of oxygen (balloon). Next, an aliquot (*ca.* 0.2 mL) was injected into a 2 mL vial containing an estimated 1 mL of premixed EtOAc/pyridine solution (3:1) to quench the reaction. The resulting solution was subjected to GC analysis to determine yield.

Substrate Synthesis and Characterization Data

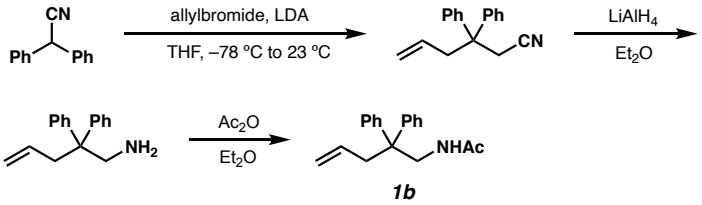


N-(pent-4-en-1-yl)acetamide (1a): Prepared according to the literature procedure from 4-pentenitrile[26] as a colorless oil (1.34 g, 52% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (bs, 1H), 5.73 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.10 – 4.82 (m, 2H), 3.17 (td, *J* = 7.3, 5.8 Hz, 2H), 2.02 (m, 2H), 1.91 (s, 3H), 1.54 (ddd, *J* = 14.7, 7.9, 6.8 Hz, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 137.7, 115.0, 39.1, 31.0, 28.6, 23.1;

HRMS (FAB+) *m/z* calc'd for $C_7H_{14}NO$ $[M+H]^+$: 128.1075, found: 128.1077.



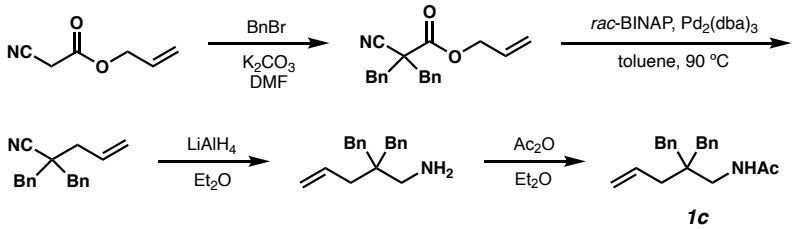
1b

N-(2,2-diphenylpent-4-enyl)acetamide (1b): Synthesized according to literature procedure[27] as a white solid (3.03 g, 54% yield over 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.2, 7.0 Hz, 4H), 7.28 – 7.24 (m, 2H), 7.22 – 7.19 (m, 4H), 5.45 (ddt, *J* = 16.7, 10.4, 7.1 Hz, 1H), 5.06 (bs, 1H), 5.03 – 4.96 (m, 2H), 3.99 (d, *J* = 5.8 Hz, 2H), 2.87 (dt, *J* = 7.2, 1.2 Hz, 2H), 1.87 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 145.2, 133.6, 128.3, 128.0, 126.6, 118.7, 50.2, 46.0, 42.1, 23.4;

HRMS (FAB+) *m/z* calc'd for $C_{19}H_{22}NO$ $[M+H]^+$: 280.1701, found 280.1702.



1c

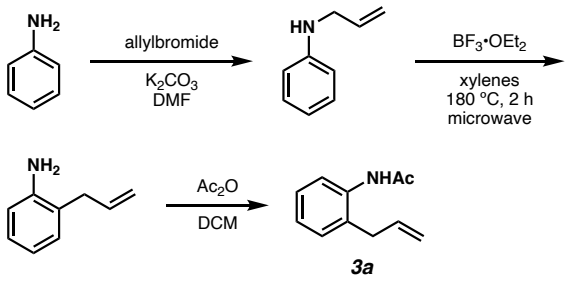
N-(2,2-dibenzylpent-4-en-1-yl)acetamide (1c): 2,2-dibenzyl-4-pentenenitrile could be prepared from allyl 2-cyanoacetate according to the literature procedure[28] as a colorless liquid (1.13 g, 72% yield). Then, $LiAlH_4$ (0.9 g, 23 mmol) was weighed into a flame-dried flask, and the flask was exchanged with vacuum/argon 3 times. 100 mL Et_2O was added to flask through cannula transfer. 2,2-dibenzyl-4-pentenenitrile (1.13 g, 4.3 mmol) was dissolved into 10 mL Et_2O and added *via* syringe. The reaction was stirred overnight and quenched with water and 1M NaOH solution. After the grey color of suspension turned white completely, the reaction mixture was filtered through celite. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* without purification. Then the crude 2,2-dibenzylpent-4-en-1-amine was dissolved into 50 mL Et_2O and acetic anhydride (1.2 mL, 12.9 mmol) was added. After 3 h, the reaction mixture was washed with saturate $NaHCO_3$ solution (20 mL), and then the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were concentrated *in vacuo* and purified by silica gel chromatography (50% EtOAc in hexanes). Product **1c** was obtained as a colorless oil (976 mg, 74% yield over last two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.30 – 7.25 (m, 2H), 7.23 – 7.20 (m, 4H), 6.01 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.24 – 5.13 (m, 2H), 5.02 (bs, 1H), 3.27 (d, J = 5.9 Hz, 2H), 2.76 – 2.66 (m, 4H), 2.16 (dt, J = 7.2, 1.4 Hz, 2H), 1.74 (s, 3H);

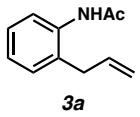
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 137.8, 134.5, 130.6, 128.3, 126.6, 118.8, 45.7, 43.4, 41.4, 39.4, 23.3 (one quaternary carbon signal unresolved);

HRMS (FAB+) *m/z* calc'd for $C_{21}H_{26}NO$ $[M+H]^+$: 308.2014, found 308.2013.

General procedure C: synthesis of *o*-allylaniline derivatives 3a, 3b, 3d, 3e



N-allylanilines can be prepared from the literature procedure.[29] In a 5 mL microwave tube, a solution of N-allylaniline (665 mg, 5 mmol) in 4 mL xylenes was added boron trifluoride etherate (0.7 mL, 5,5 mmol) under an argon atmosphere. Then the microwave tubes was sealed and heated to 180 °C in the microwave reactor for 2 h. After cooling down to room temperature, the reaction mixture was poured into 2 M NaOH solution (10 mL), and extracted with EtOAc (10 mL × 2). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The crude *o*-allylaniline was dissolved in DCM (30 mL) and acetic anhydride (1.4 mL, 15 mmol) was added dropwise. After reacting 2 h in room temperature, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (30% EtOAc in hexanes).

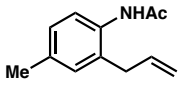


N-(2-allylphenyl)acetamide (3a): Prepared according to General Procedure C as a white solid (257 mg, 44% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.3, 4.0 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.20 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.00 (ddt, *J* = 16.6, 11.4, 6.2 Hz, 1H), 5.25 – 5.08 (m, 2H), 3.41 (d, *J* = 6.0, 2H), 2.17 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 136.4, 136.0, 130.2, 130.0, 127.5, 125.4, 123.9, 116.6, 37.0, 24.3;

HRMS (FAB+) *m/z* calc'd for $C_{11}H_{14}NO$ $[M+H]^+$: 176.1075, found: 176.1083.



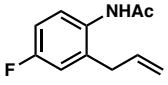
3b

N-(2-allyl-4-methylphenyl)acetamide (3b): Prepared according to General Procedure C from the corresponding N-allyl-4-methylaniline as a white solid (342 mg, 36% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.18 (bs, 1H), 7.08 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 5.98 (ddt, *J* = 16.5, 10.1, 6.1 Hz, 1H), 5.23 – 5.07 (m, 2H), 3.36 (dd, *J* = 6.2, 1.8 Hz, 2H), 2.33 (s, 3H), 2.16 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 136.5, 135.2, 133.3, 130.8, 130.3, 128.0, 124.2, 116.3, 36.9, 24.2, 20.9;

HRMS (FAB+) *m/z* calc'd for $C_{12}H_{16}NO$ $[M+H]^+$: 190.1232, found 190.1233.



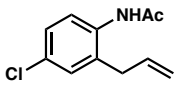
3d

***N*-(2-allyl-4-fluorophenyl)acetamide (3d):** Prepared according to General Procedure C from the corresponding N-allyl-4-fluoroaniline as a white solid (425 mg, 44% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.9, 5.4 Hz, 1H), 7.12 (bs, 1H), 6.97 (td, *J* = 8.4, 3.0 Hz, 1H), 6.93 (dd, *J* = 9.1, 3.0 Hz, 1H), 5.97 (ddt, *J* = 17.2, 10.1, 6.1 Hz, 1H), 5.26 – 5.08 (m, 2H), 3.37 (dt, *J* = 6.1, 1.7 Hz, 2H), 2.18 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 160.1 (d, *J* = 244.7 Hz), 135.5, 133.2 (d, *J* = 7.4 Hz), 131.7 (d, *J* = 2.6 Hz), 126.1 (d, *J* = 8.4 Hz), 117.1, 116.7 (d, *J* = 22.8 Hz), 114.0 (d, *J* = 22.1 Hz), 36.7, 24.1;

HRMS (FAB+) *m/z* calc'd for $C_{11}H_{13}NOF$ $[M+H]^+$: 194.0981, found 194.0977.



3e

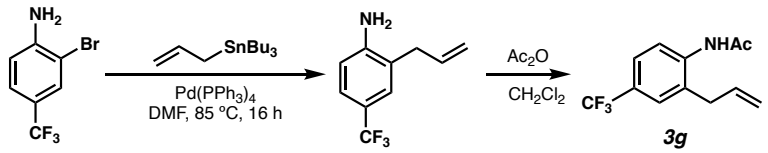
***N*-(2-allyl-4-chlorophenyl)acetamide (3e):** Prepared according to General Procedure C from the corresponding N-allyl-4-chloroaniline as a white solid (442 mg, 42% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.73 (m, 1H), 7.28 (bs, 1H), 7.25 – 7.22 (m, 1H), 7.18 (m, 1H), 6.00 – 5.90 (m, 1H), 5.26 – 5.09 (m, 2H), 3.36 (dt, *J* = 6.4, 1.9 Hz, 2H), 2.16 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 135.4, 134.6, 131.7, 130.3, 130.0, 127.4, 125.0, 117.2, 36.6, 24.3;

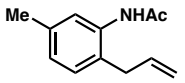
HRMS (FAB+) *m/z* calc'd for $C_{11}H_{13}NOCl$ $[M+H]^+$: 210.0686, found 210.0683.

General procedure D: synthesis of *o*-allyl aniline derivatives[30]



3g

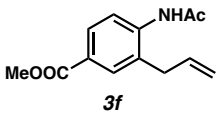
4-Amino-3-bromobenzotrifluoride (960 mg, 4 mmol) dissolved in dry DMF (10 mL) was added allyltributyltin (1.50 mL, 4.8 mmol) under argon at room temperature. $Pd(PPh_3)_4$ (457 mg, 0.39 mmol) was then added and the reaction mixture was stirred at 85 °C for 16 h. The reaction mixture was then cooled down to room temperature and diluted with water (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography gave 2-allyl-4-(trifluoromethyl)aniline (685 mg, 85% yield) as yellow oil. Then 2-allyl-4-(trifluoromethyl)aniline was dissolved in DCM (30 mL) and acetic anhydride (1.0 mL, 10.2 mmol) was added dropwise. After reacting 2 h in room temperature, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (30% EtOAc in hexanes).



3c

N-(2-allyl-5-methylphenyl)acetamide (3c): Prepared according to General Procedure D from the corresponding 2-bromo-5-methylaniline as a white solid (605 mg, 80% yield over 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (m, 1H), 7.23 (bs, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.96 – 6.94 (m, 1H), 5.98 (ddt, J = 16.5, 10.1, 6.1 Hz, 1H), 5.21 – 5.07 (m, 2H), 3.36 (dt, J = 6.3, 1.7 Hz, 2H), 2.35 (s, 3H), 2.16 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 137.2, 136.7, 135.8, 130.0, 127.1, 126.2, 124.5, 116.3, 36.6, 24.3, 21.2; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{16}NO$ $[M+H]^+$: 190.1232, found 190.1237.



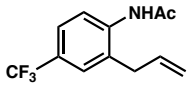
3f

Methyl 4-acetamido-3-allylbenzoate (3f): Prepared according to General Procedure D from the corresponding methyl 4-amino-3-bromobenzoate as a white solid (451 mg, 48% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.09 (m, 1H), 7.95 – 7.91 (m, 1H), 7.87 (bs, 1H), 7.57 – 7.50 (m, 1H), 5.97 (tdt, *J* = 11.1, 10.1, 6.0 Hz, 1H), 5.28 – 5.10 (m, 2H), 3.90 (s, 3H), 3.45 – 3.43 (m, 2H), 2.17 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 166.7, 140.6, 135.6, 131.7, 129.2, 128.1, 126.0, 121.9, 117.3, 52.1, 36.9, 24.6;

HRMS (FAB+) *m/z* calc'd for $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1130, found 234.1122.



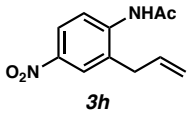
3g

N-(2-allyl-4-(trifluoromethyl)phenyl)acetamide (3g): Prepared according to General Procedure D as a white solid (583 mg, 60% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.51 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 5.97 (ddt, *J* = 17.3, 10.1, 6.1 Hz, 1H), 5.29 – 5.12 (m, 2H), 3.44 (dt, *J* = 6.1, 1.7 Hz, 2H), 2.18 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 139.3, 135.2, 129.4, 127.1 (q, *J* = 4.2 Hz), 126.7 (q, *J* = 32.6 Hz), 124.6 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272 Hz), 122.9, 117.6, 36.7, 24.4;

HRMS (FAB+) *m/z* calc'd for $C_{12}H_{13}NOF_3$ $[M+H]^+$: 244.0949, found 244.0952.



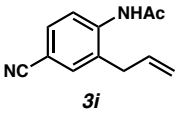
3h

N-(2-allyl-4-nitrophenyl)acetamide (3h): Prepared according to General Procedure D from the corresponding 2-bromo-4-nitroaniline as a white solid (183 mg, 21% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.1 Hz, 1H), 8.16 (dd, *J* = 9.0, 2.7 Hz, 1H), 8.10 (d, *J* = 2.7 Hz, 1H), 7.57 (bs, 1H), 6.00 (ddt, *J* = 16.5, 10.1, 6.1 Hz, 1H), 5.42 – 5.08 (m, 2H), 3.51 (dt, *J* = 6.1, 1.8 Hz, 2H), 2.22 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 143.6, 142.3, 134.5, 128.4, 125.6, 123.5, 121.6, 118.3, 36.8, 24.8;

HRMS (FAB+) *m/z* calc'd for $C_{11}H_{13}N_2O_3$ $[M+H]^+$: 221.0926, found 221.0919.



3i

***N*-(2-allyl-4-cyanophenyl)acetamide (3i):** Prepared according to General Procedure D from the corresponding 4-amino-3-bromobenzonitrile as a white solid (460 mg, 58% yield over 2 steps).

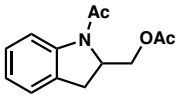
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.5 Hz, 1H), 7.56 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.51 (bs, 1H), 7.48 (d, *J* = 1.9 Hz, 1H), 5.97 (ddt, *J* = 16.8, 10.1, 6.1 Hz, 1H), 5.40 – 5.03 (m, 2H), 3.43 (dt, *J* = 6.1, 1.8 Hz, 2H), 2.20 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 140.5, 134.7, 133.9, 131.8, 128.9, 122.4, 118.8, 118.1, 107.6, 36.5, 24.7;

HRMS (FAB+) *m/z* calc'd for $C_{12}H_{13}N_2O$ $[M+H]^+$: 201.1028, found 201.1022.

Product characterization

Mixture of rotamer may occur in most products. A representative VT-NMR experiment was conducted on the product **4a**. At 75 °C in DMSO solvent, only one rotamer is predominantly appeared in ^{1}H NMR and the characterization data is shown below.



4a

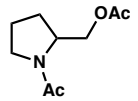
(1-acetylindolin-2-yl)methyl acetate (4a): Prepared according to the general procedure A to provide **4a** (102 mg, 87% yield) as a colorless oil. When the reaction was conducted under air (Table 3, entry 2), an air balloon was used instead of an oxygen balloon, which provided **4a** (94 mg, 80% yield) as a colorless oil.

^{1}H NMR (400 MHz, DMSO, 75 °C) δ 7.77 (bs, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.82 – 4.74 (m, 1H), 4.08 (d, *J* = 5.7 Hz, 2H), 3.33 (dd, *J* = 16.3, 9.2 Hz, 1H), 2.83 (d, *J* = 16.3 Hz, 1H), 2.26 (s, 3H), 1.87 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 170.7, 168.7, 141.9, 129.7, 127.7, 124.8, 124.2, 118.1, 64.9, 58.5, 32.1, 23.4, 20.7;

HRMS (FAB+) *m/z* calc'd for $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1130, found 234.1127.

For ^{1}H and ^{13}C NMR characterization of the rest of compounds, chemical shifts of only the major rotamer are reported. In ^{1}H and ^{13}C NMR spectra of products, only the major rotamer peaks are integrated.



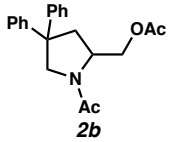
2a

(1-acetylpyrrolidin-2-yl)methyl acetate (2a) : Prepared according to the general procedure A to provide **2a** (64 mg, 69% yield) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from the major rotamer δ 4.32 (tt, *J* = 7.4, 3.7 Hz, 1H), 4.15 (dd, *J* = 10.8, 3.9 Hz, 1H) 4.09 (dd, *J* = 10.8, 6.8 Hz, 1H), 3.50 – 3.37 (m, 2H), 2.03 (s, 3H), 2.03 (s, 3H) (two overlapped singlets), 1.96 – 1.88 (m, 3H) 1.86 – 1.81 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 169.7, 63.8, 55.2, 47.9, 27.5, 24.0, 21.9, 20.9;

HRMS (FAB+) *m/z* calc'd for $C_9H_{16}NO_3$ $[M+H]^+$: 186.1130, found 186.1134.



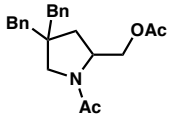
2b

(1-acetyl-4,4-diphenylpyrrolidin-2-yl)methyl acetate (2b): Prepared according to the general procedure A to provide **2b** (126 mg, 75% yield) as a white solid.

^{1}H NMR (500 MHz, DMSO, 23 °C) mixture of rotamers, chemical shifts reported are from major rotamer δ 7.46 – 7.43 (m, 2H), 7.38 – 7.35 (m, 2H), 7.33 – 7.28 (m, 4H), 7.19 (ddt, *J* = 9.0, 7.9, 1.4 Hz, 2H), 4.68 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.23 (dd, *J* = 10.6, 3.5 Hz, 1H), 4.06 (dd, *J* = 10.6, 6.3 Hz, 1H), 3.92 (dd, *J* = 10.0, 6.7, 1H), 3.82 (d, *J* = 11.2 Hz, 1H), 3.12 (ddd, *J* = 13.0, 7.1, 1.9 Hz, 1H), 2.30 (dd, *J* = 13.0, 9.2 Hz, 1H), 2.03 (s, 3H), 2.00 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 169.3, 145.2, 144.6, 128.8, 128.7, 126.8, 126.8, 126.6, 126.2, 64.1, 58.5, 55.0, 53.2, 40.1, 23.1, 20.9;

HRMS (FAB+) *m/z* calc'd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1756, found 338.1757.



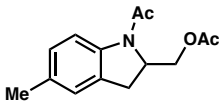
2c

(1-acetyl-4,4-dibenzylpyrrolidin-2-yl)methyl acetate (2c): Prepared according to the general procedure A to provide **2c** (152 mg, 83% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 7.38 – 7.22 (m, 6H), 7.19 – 7.09 (m, 4H), 4.33 (dd, *J* = 11.1, 4.1 Hz, 1H), 4.29 – 4.20 (m, 1H), 4.17 (dd, *J* = 11.1, 2.5 Hz, 1H), 3.31 (dd, *J* = 10.5, 1.6 Hz, 1H), 3.18 (d, *J* = 10.5 Hz, 1H), 2.80 (s, 2H), 2.69 (s, 2H), 2.03 (s, 3H), 1.93 – 1.89 (m, 1H), 1.79 (dd, *J* = 13.1, 9.1 Hz, 1H), 1.72 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 169.3, 137.5, 137.1, 130.8, 130.3, 128.4, 128.3, 126.9, 126.6, 63.6, 55.0, 54.6, 45.7, 43.9, 41.8, 35.0, 23.2, 20.6;

HRMS (FAB+) *m/z* calc'd for $C_{23}H_{28}NO_3$ $[M+H]^+$: 366.2069, found 366.2053.



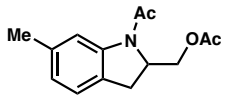
4b

(1-acetyl-5-methylindolin-2-yl)methyl acetate (4b): Prepared according to the general procedure A to provide **4b** (110 mg, 89% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.01 (m, 2H), 4.61 (m, 1H), 4.25 – 4.08 (m, 2H), 3.35 (dd, *J* = 16.1, 8.8 Hz, 1H), 2.83 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 2.06 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 168.4, 139.6, 133.8, 129.8, 128.1, 125.4, 117.8, 64.8, 58.6, 32.0, 23.3, 21.0, 20.8;

HRMS (FAB+) *m/z* calc'd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1287, found 248.1280.



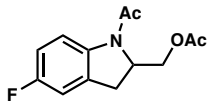
4c

(1-acetyl-6-methylindolin-2-yl)methyl acetate (4c): Prepared according to the general procedure A to provide **4c** (118 mg, 95% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 7.95 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 4.60 (m, 1H), 4.19 (dd, *J* = 11.8, 6.2 Hz, 2H), 3.31 (dd, *J* = 16.1, 8.8 Hz, 1H), 2.81 (d, *J* = 15.9 Hz, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 2.04 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 168.6, 142.0, 137.6, 126.8, 124.9, 124.4, 118.8, 64.8, 58.8, 31.7, 23.4, 21.6, 20.7;

HRMS (FAB+) *m/z* calc'd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1287, found 248.1280.



4d

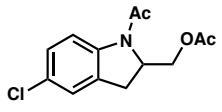
(1-acetyl-5-fluoroindolin-2-yl)methyl acetate (4d). Prepared according to the general procedure A to provide **4d** (110 mg, 88% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 8.05 (dd, *J* = 8.4, 4.9 Hz, 1H), 6.97 – 6.83 (m, 2H), 4.63 (m, 1H), 4.20 (dd, *J* = 11.2, 5.9 Hz, 2H), 3.37 (dd, *J* = 16.4, 8.9 Hz, 1H), 2.86 (d, *J* = 16.3 Hz, 1H), 2.34 (s, 3H), 2.03 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 168.4, 159.5 (d, *J* = 243.0 Hz), 134.2 (d, *J* = 2.7 Hz),

131.8 (d, *J* = 8.5 Hz), 121.7 (d, *J* = 7.8 Hz), 115.5 (d, *J* = 22.3 Hz), 112.0 (d, *J* = 24.8 Hz), 64.7, 58.8, 32.0, 23.1, 20.7;

HRMS (FAB+) *m/z* calc'd for $C_{13}H_{15}NO_3F$ $[M+H]^+$: 252.1036, found 252.1037.



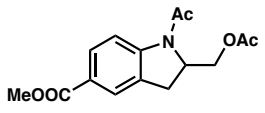
4e

(1-acetyl-5-chloroindolin-2-yl)methyl acetate (4e). Prepared according to the general procedure A to provide **4e** (107 mg, 80% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.18 – 7.15 (m, 2H), 4.63 (m, 1H), 4.19 (dd, *J* = 11.4, 5.8 Hz, 2H), 3.35 (dd, *J* = 16.4, 8.9 Hz, 1H), 2.86 (d, *J* = 16.3 Hz, 1H), 2.35 (s, 3H), 2.03 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 168.7, 140.7, 131.7, 129.0, 127.6, 124.9, 118.9, 64.7, 58.7, 31.9, 23.2, 20.7;

HRMS (FAB+) *m/z* calc'd for $C_{13}H_{15}NO_3Cl$ $[M+H]^+$: 268.0740, found 268.0738.



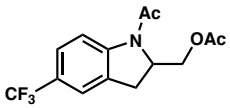
4f

methyl 2-(acetoxymethyl)-1-acetylindoline-5-carboxylate (4f). Prepared according to the general procedure A to provide **4f** (95 mg, 65% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 8.13 (s, 1H), 7.93 – 7.90 (m, 1H), 7.86 (s, 1H), 4.67 (m, 1H), 4.18 (m, 2H), 3.88 (s, 3H), 3.37 (m, 1H), 2.92 (d, *J* = 16.1 Hz, 1H), 2.39 (s, 3H), 2.00 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 169.0, 166.6, 146.0, 130.1, 126.2, 125.8, 117.2, 114.0, 64.7, 58.9, 52.0, 31.8, 23.5, 20.6;

HRMS (FAB+) *m/z* calc'd for $C_{15}H_{18}NO_5$ $[M+H]^+$: 292.1185, found 292.1183.



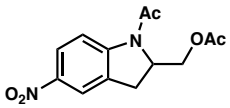
4g

(1-acetyl-5-(trifluoromethyl)indolin-2-yl)methyl acetate (4g). Prepared according to the general procedure A to provide **4g** (88 mg, 58% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 8.21 (s, 1H), 7.58 – 7.39 (m, 2H), 4.69 (m, *J* = 8.5 Hz, 1H), 4.23 (m, 2H), 3.41 (m, 1H), 2.96 (d, *J* = 16.3 Hz, 1H), 2.41 (s, 3H), 2.04 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 169.0, 144.8, 130.5, 125.4, 123.1, 121.8, 117.7, 64.6, 58.8, 31.9, 23.4, 20.6 (C–F coupling constants unresolved and one quaternary carbon signal unresolved);

HRMS (FAB+) *m/z* calc'd for $C_{14}H_{15}NO_3F_3$ $[M+H]^+$: 302.1004, found 302.1011.



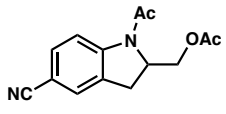
4h

(1-acetyl-5-nitroindolin-2-yl)methyl acetate (4h). Prepared according to the general procedure A to provide **4h** (41 mg, 30% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 8.24 (s, 1H), 8.17 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.09 (m, 1H), 4.78 (s, 1H), 4.24 (dd, *J* = 11.8, 5.1 Hz, 2H), 3.46 (dd, *J* = 16.5, 9.2 Hz, 1H), 3.03 (d, *J* = 16.5 Hz, 1H), 2.44 (s, 3H), 2.02 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 169.2, 147.4, 143.9, 124.7, 120.6, 117.3, 64.6, 59.2, 31.6, 23.5, 20.6 (one quaternary carbon signal unresolved);

HRMS (FAB+) *m/z* calc'd for $C_{13}H_{15}N_2O_5$ $[M+H]^+$: 279.0981, found 279.0975.



4i

(1-acetyl-5-cyanoindolin-2-yl)methyl acetate (4i). Prepared according to the general procedure A to provide **4i** (41 mg, 32% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers, chemical shifts reported are from major rotamer δ 8.22 (s, 1H), 7.59 – 7.52 (m, 1H), 7.48 (s, 1H), 4.71 (m, 1H), 4.22 (d, J = 9.1 Hz, 2H), 3.42 (d, J = 15.1 Hz, 1H), 2.97 (d, J = 16.4 Hz, 1H), 2.41 (s, 3H), 2.02 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 169.2, 145.8, 132.8, 128.4, 119.0, 118.1, 107.0, 64.6, 58.7, 31.7, 23.6, 20.6 (one quaternary carbon signal unresolved);

HRMS (FAB+) *m/z* calc'd for $C_{14}H_{15}N_2O_3$ $[M+H]^+$: 259.1083, found 259.1089.

2.7 NOTES AND REFERENCES

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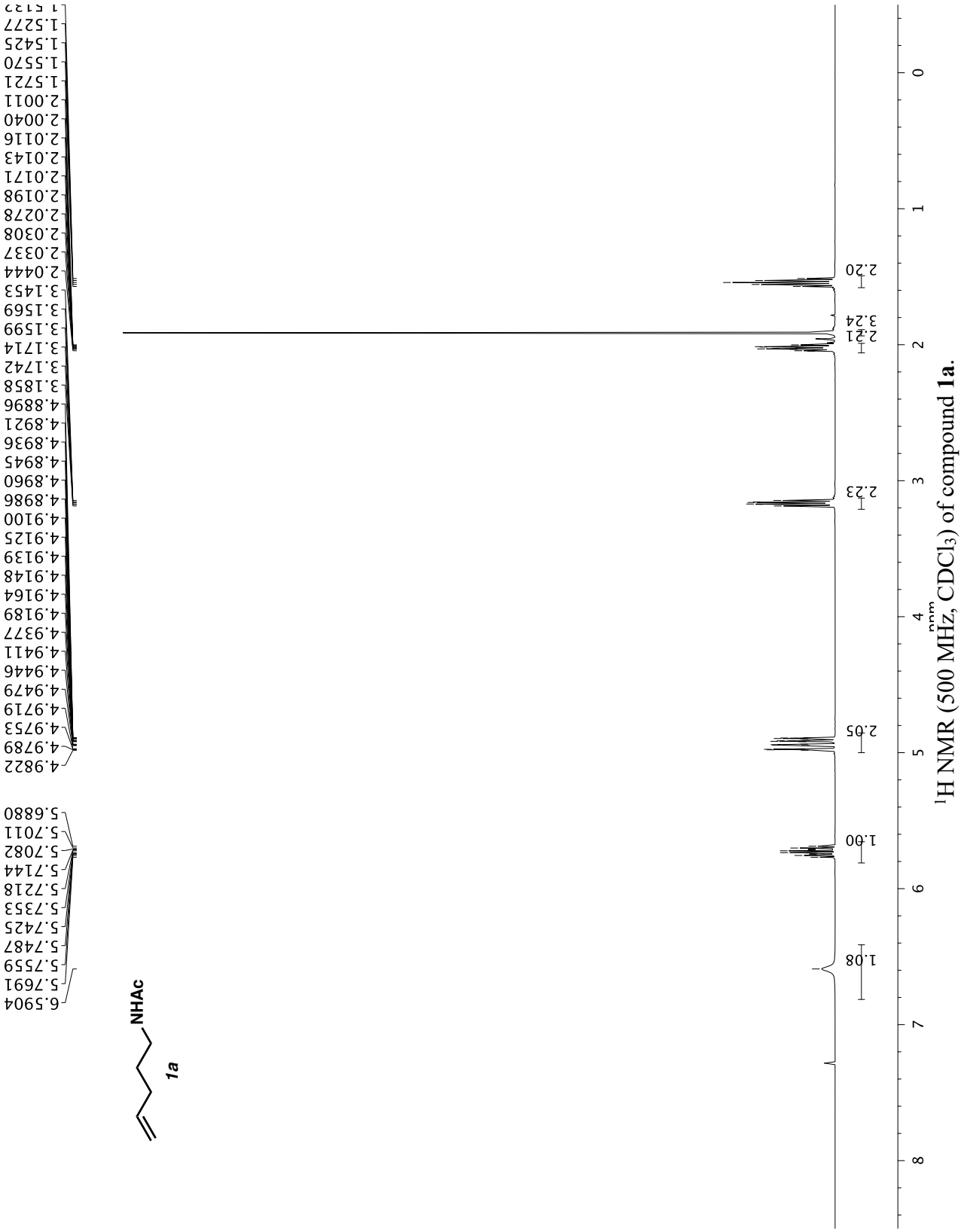
APPENDIX 2

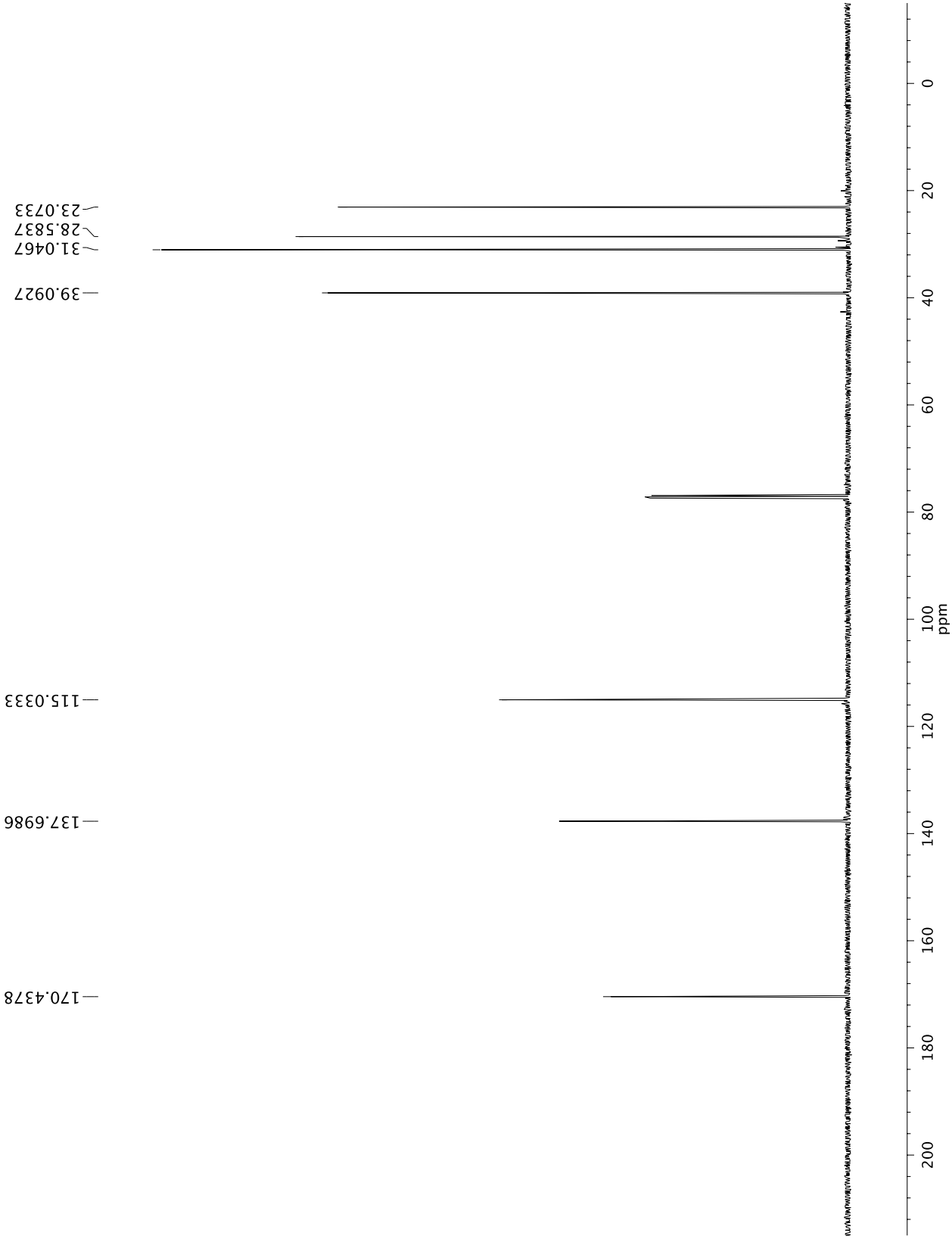
Spectra Relevant to Chapter 2:

Palladium-Catalyzed Aerobic Intramolecular

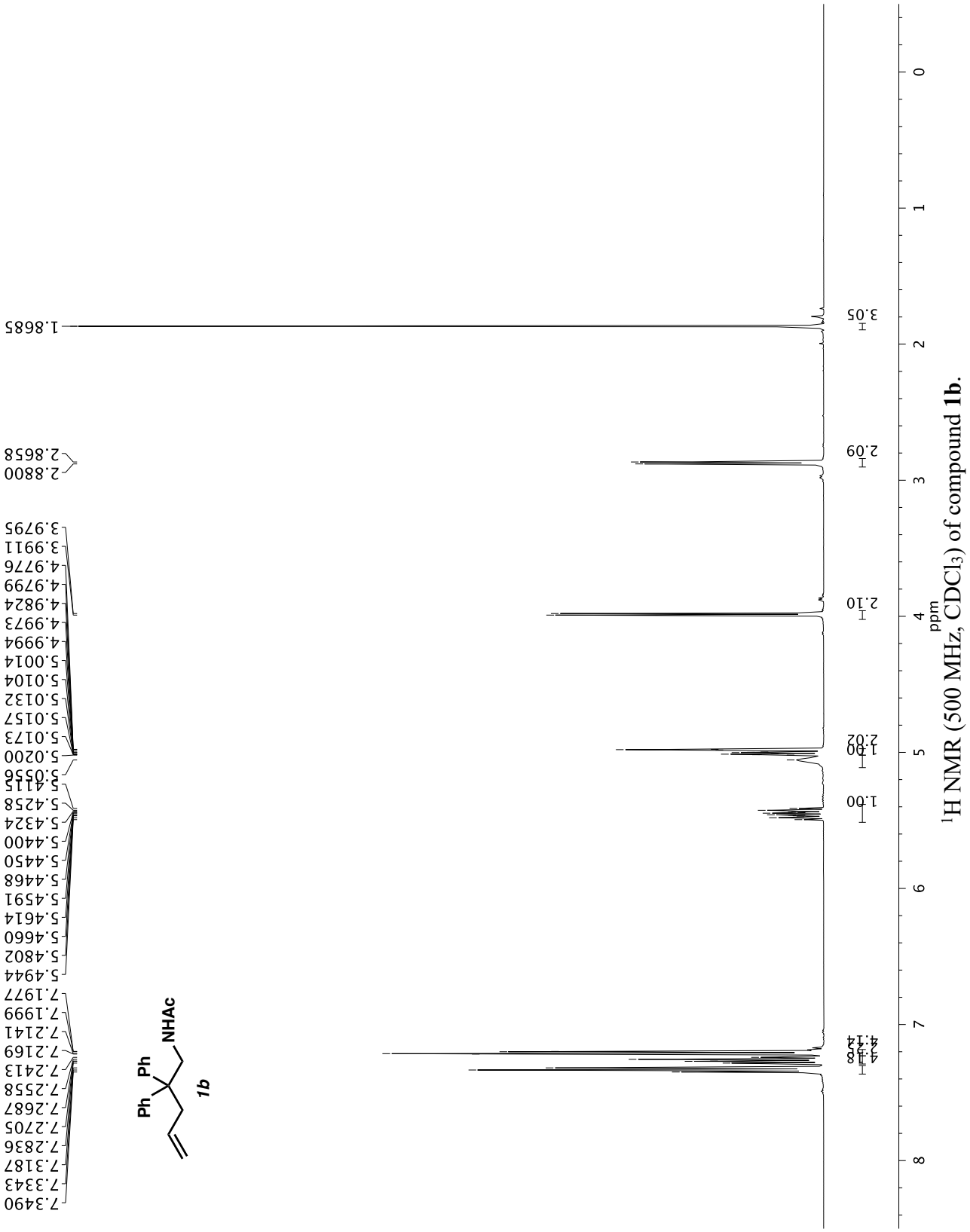
Aminoacetoxylation of Alkenes Enabled by Catalytic Nitrate



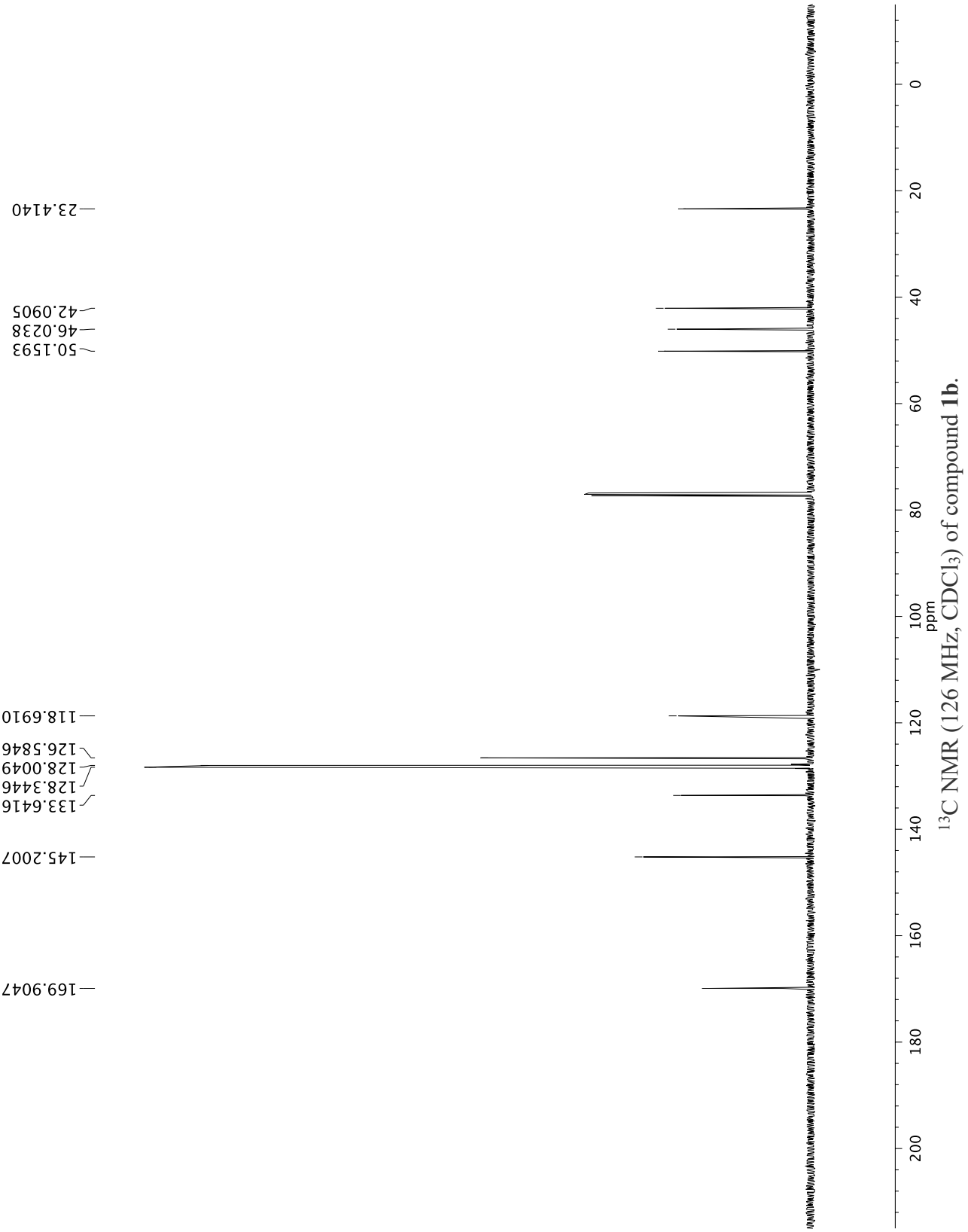
^{1}H NMR (500 MHz, $CDCl_3$) of compound **1a**.



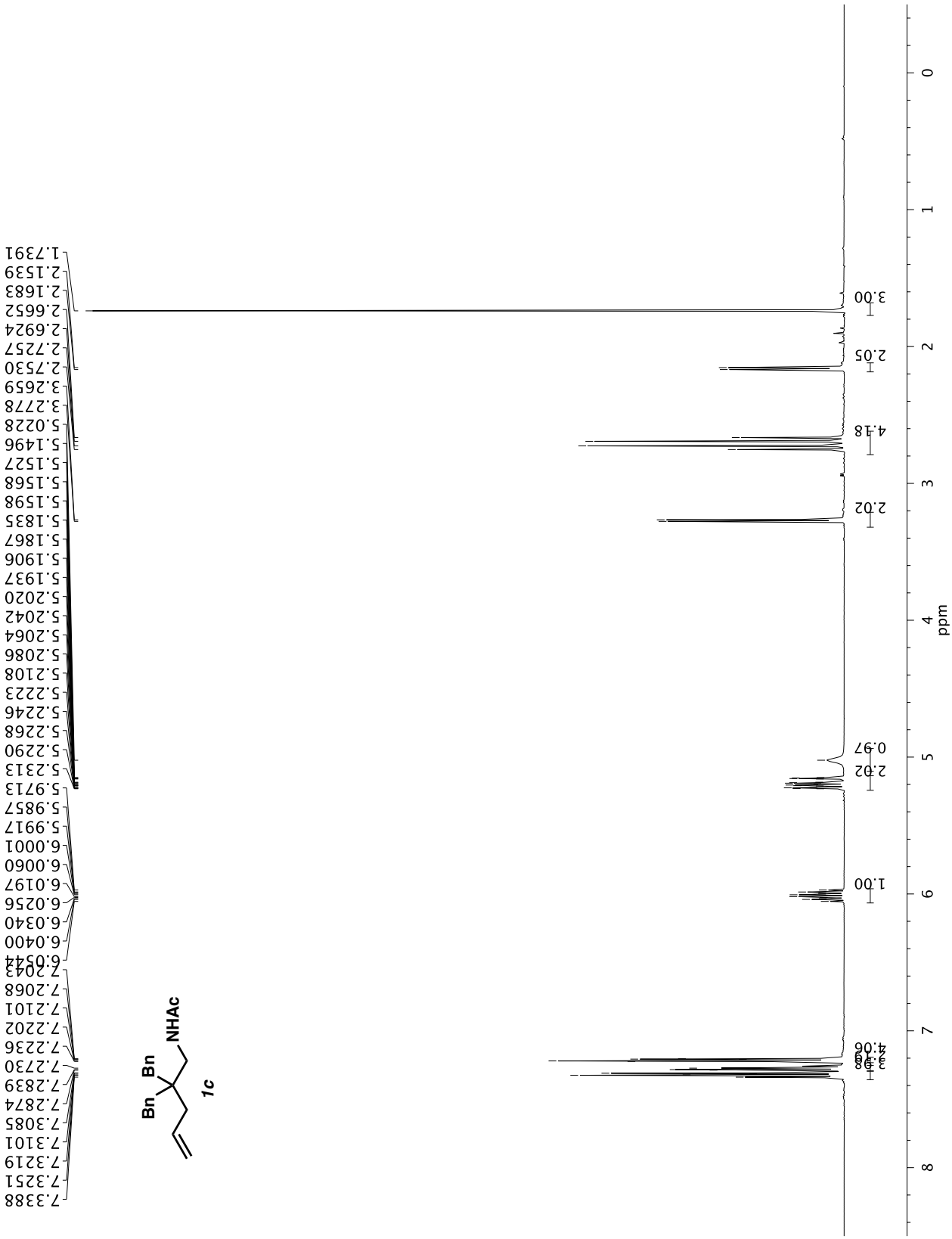
^{13}C NMR (126 MHz, $CDCl_3$) of compound **1a**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **1b**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **1b**.



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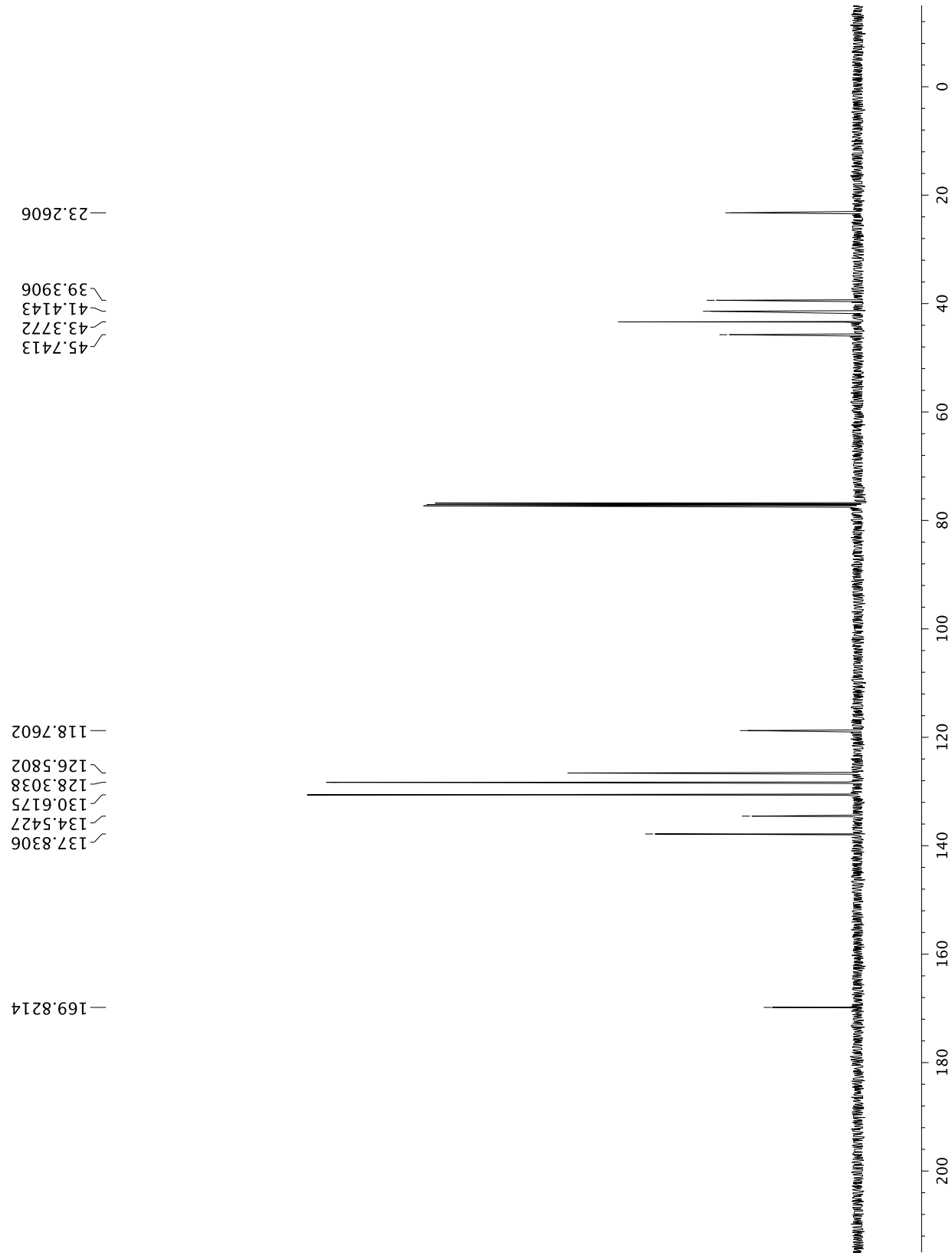
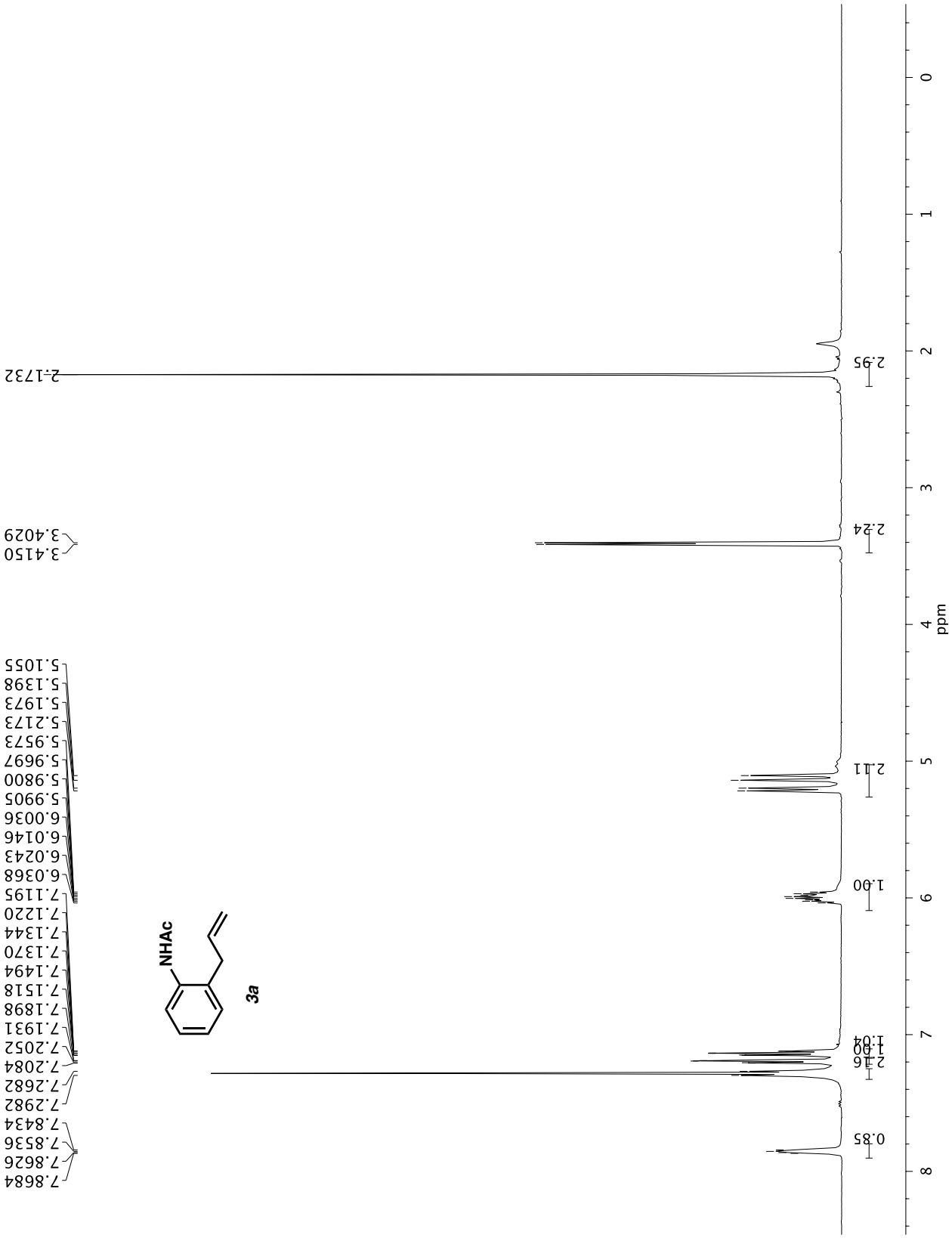
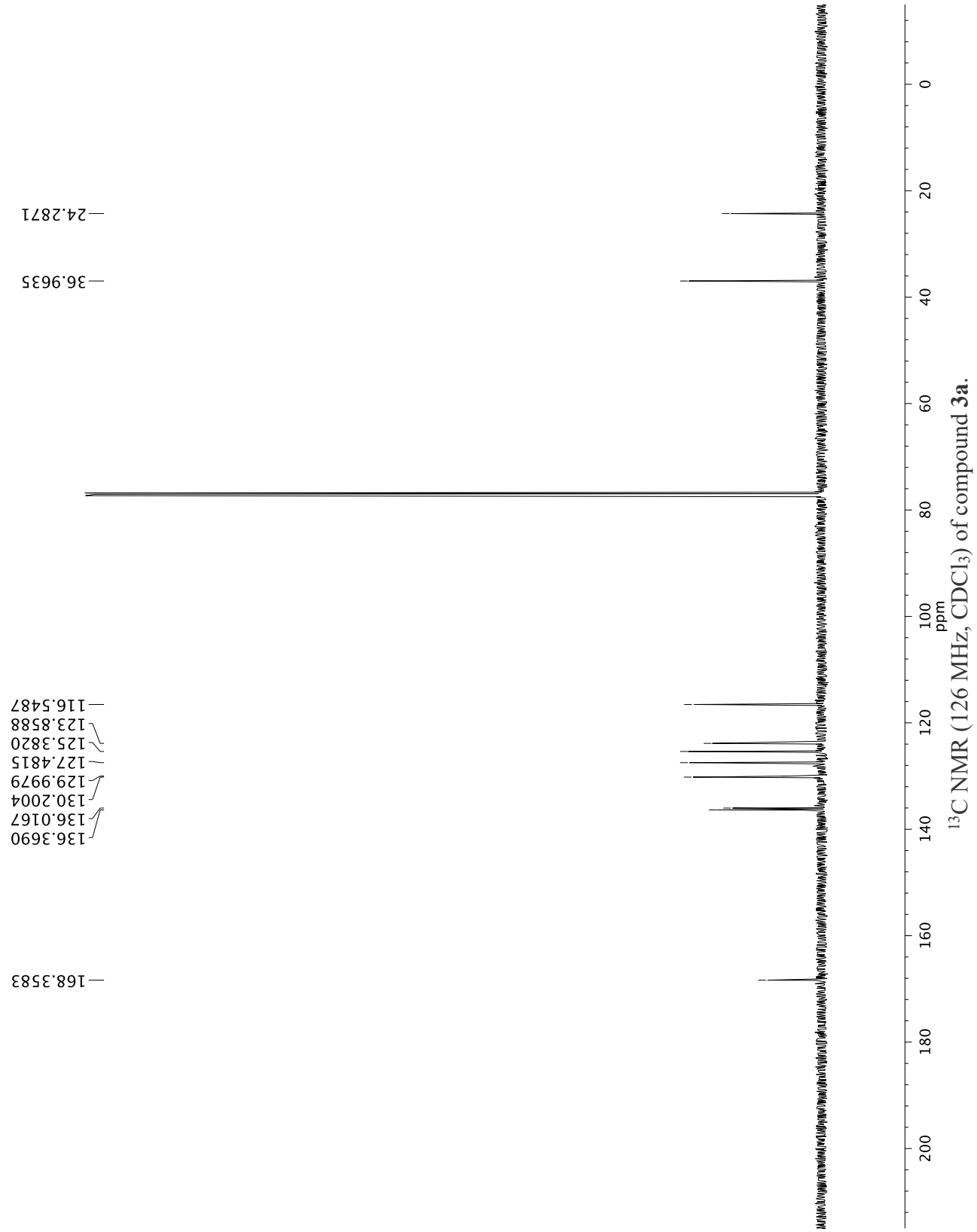


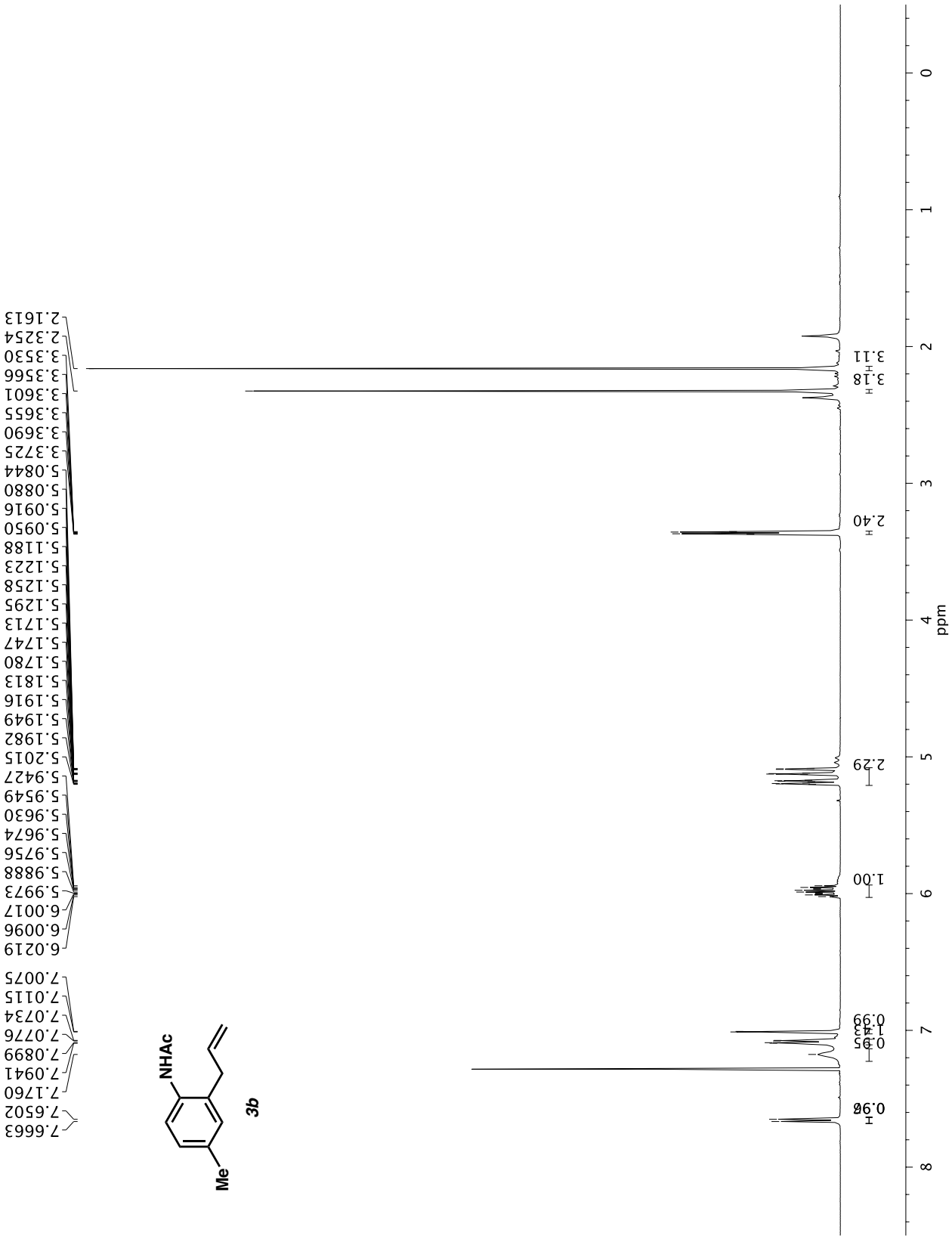
^{13}C NMR (126 MHz, $CDCl_3$) of compound **1c**.



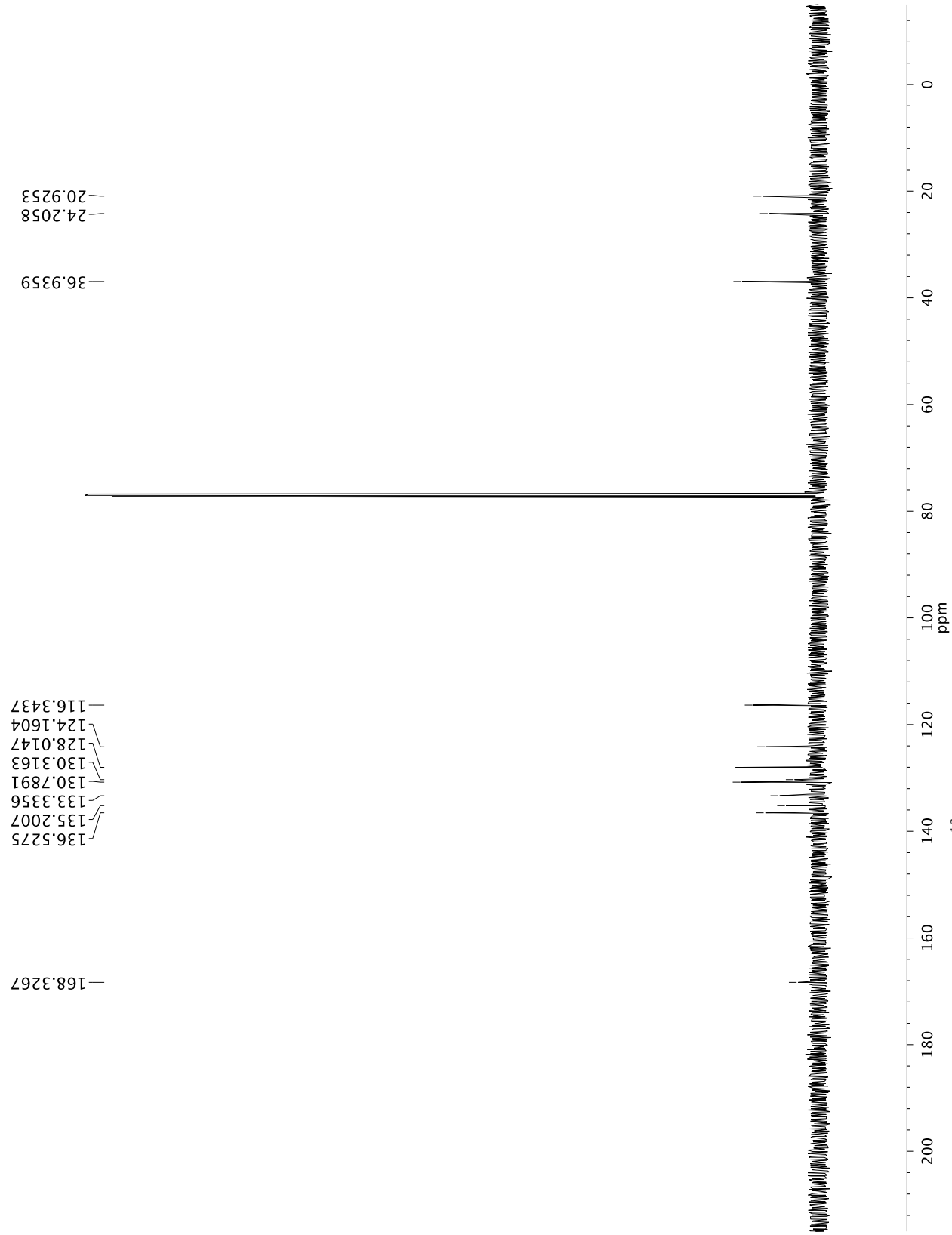
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3a**.



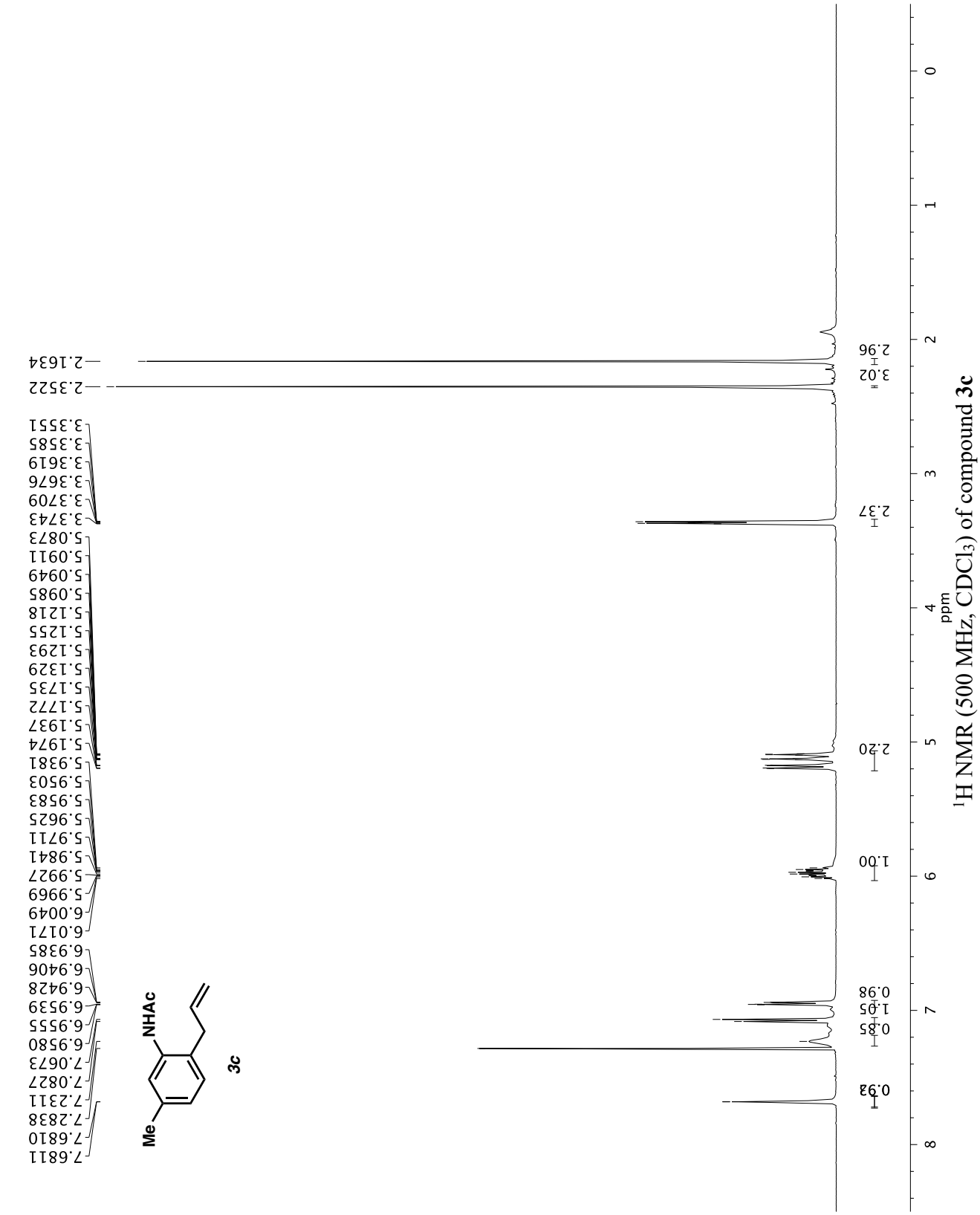
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3a**.



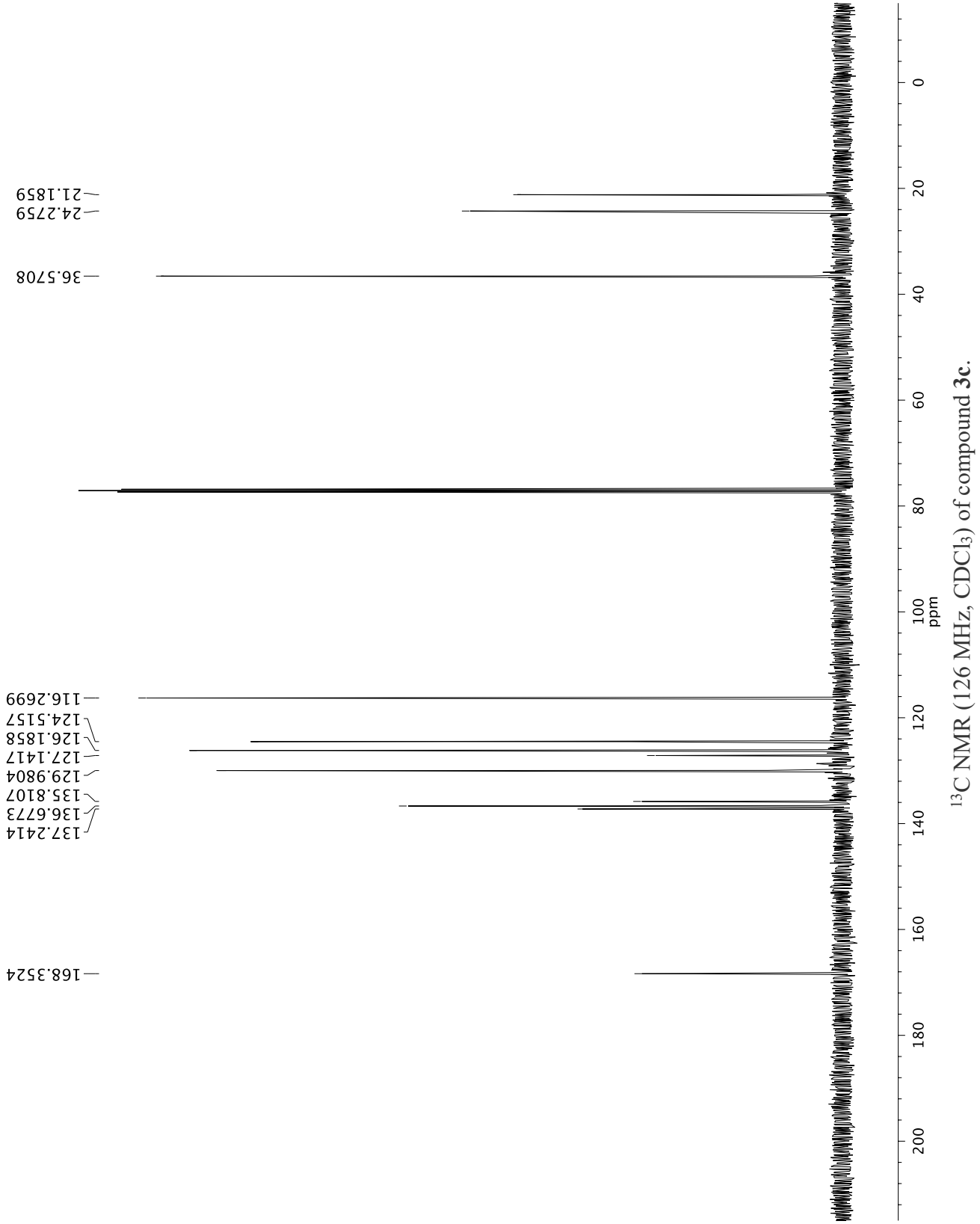
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3b**.



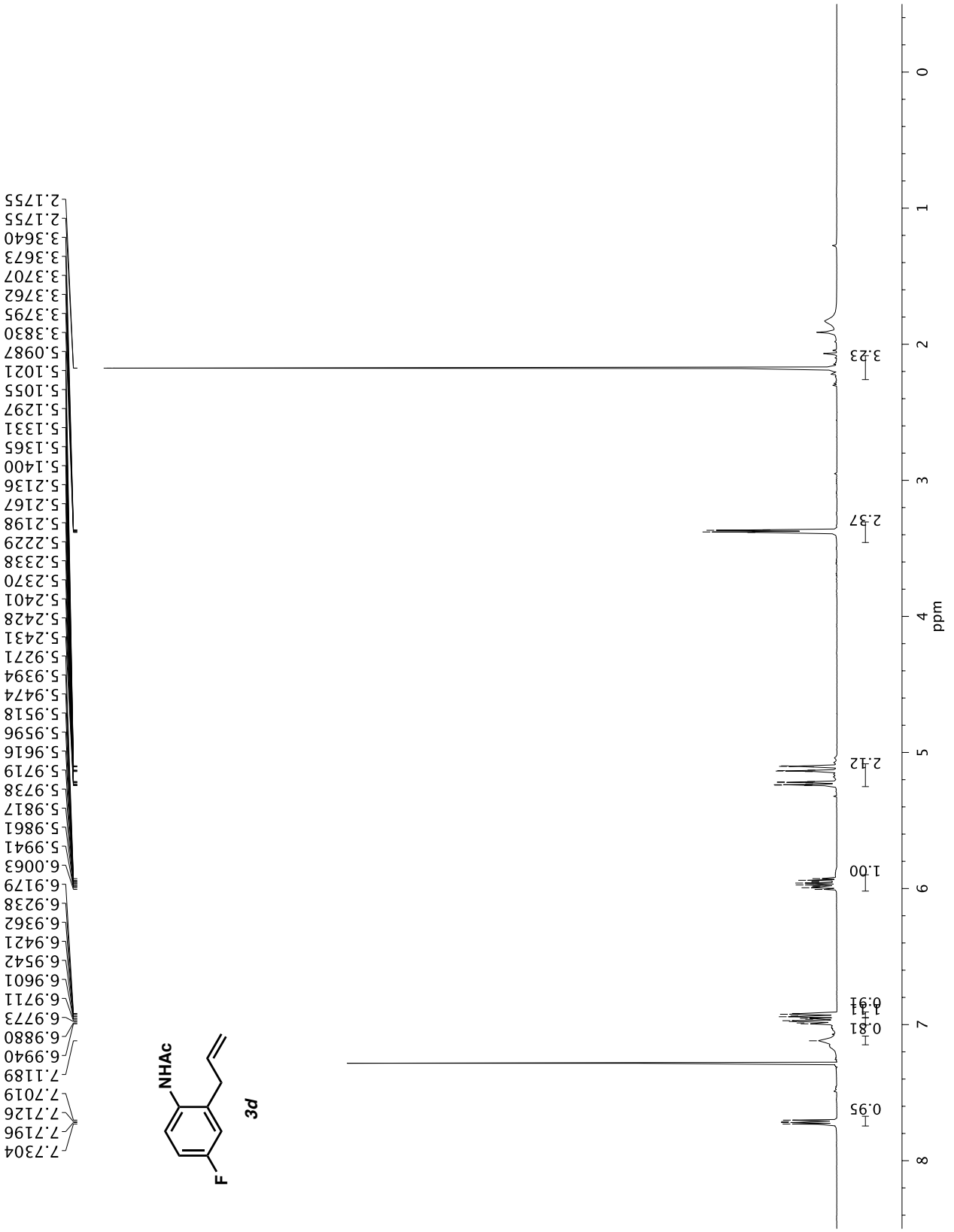
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3b**.



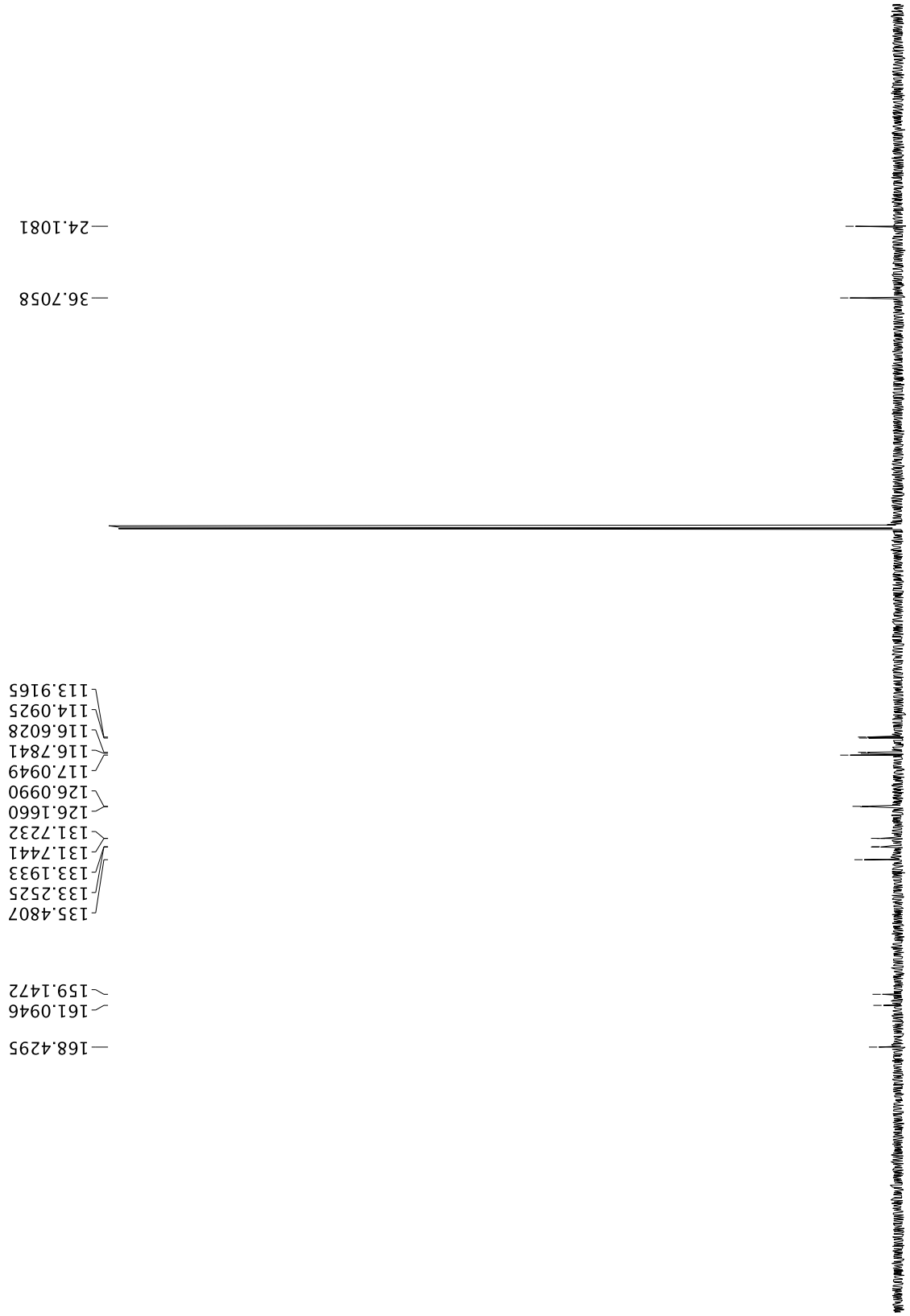
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3c**



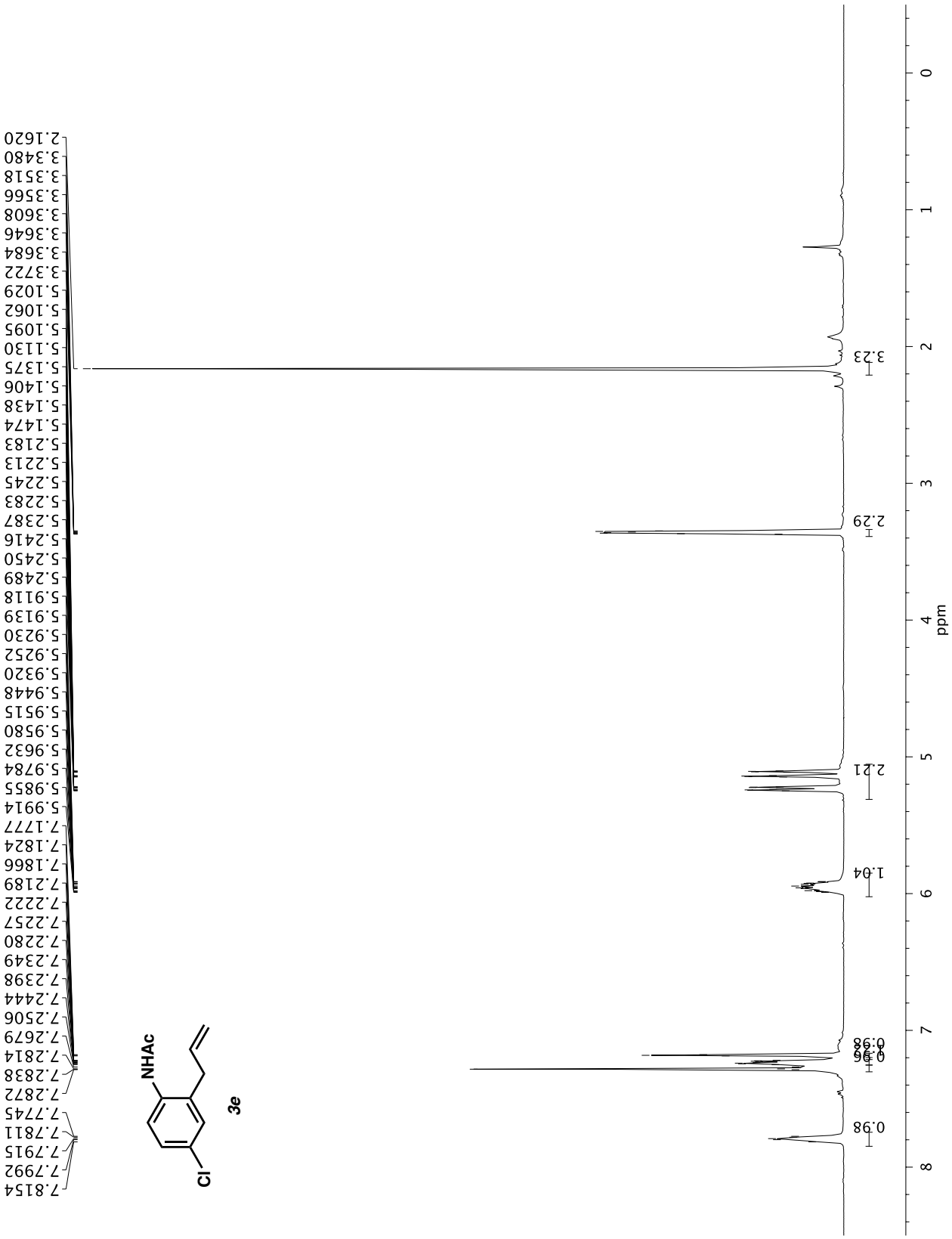
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3c**.



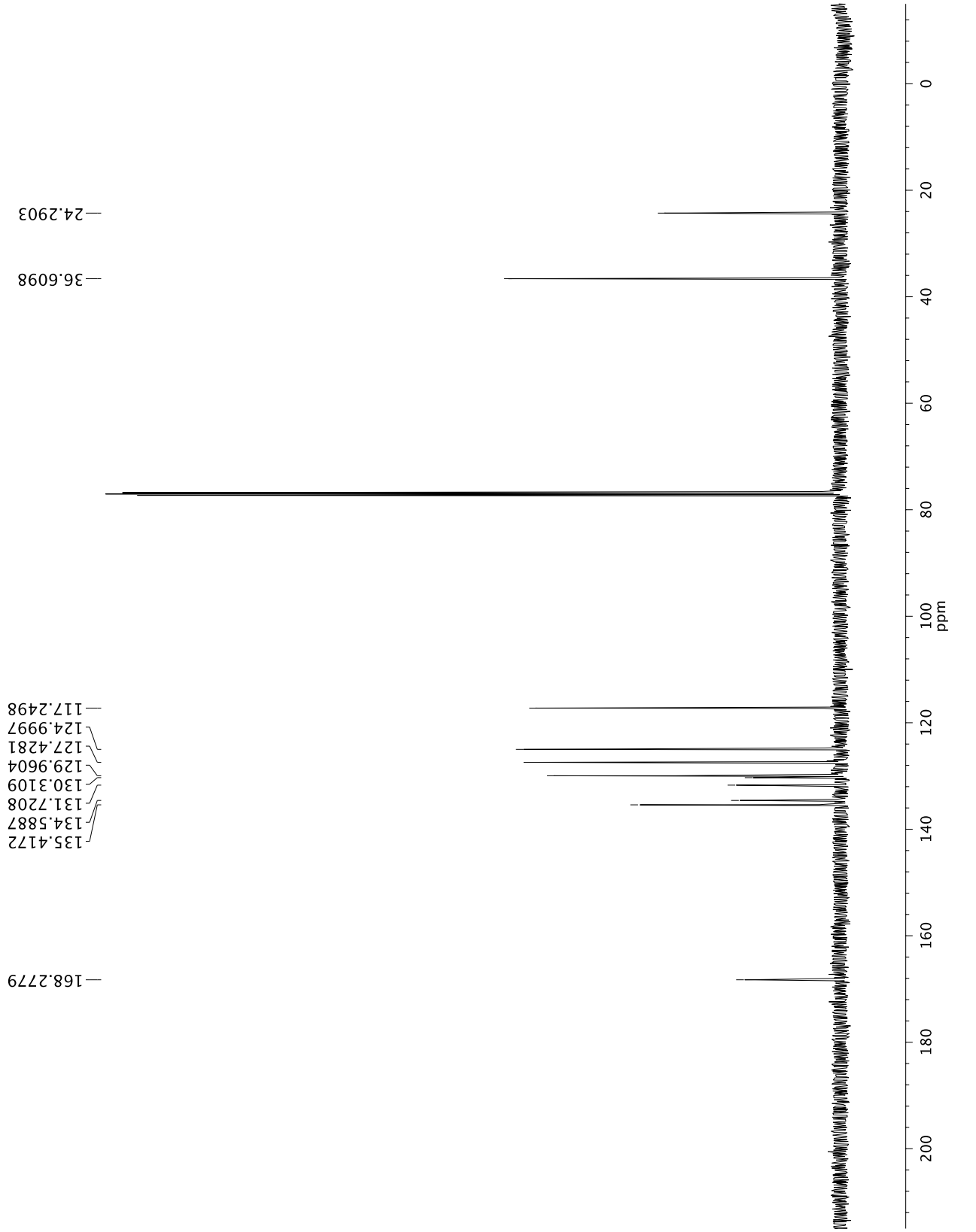
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3d**.



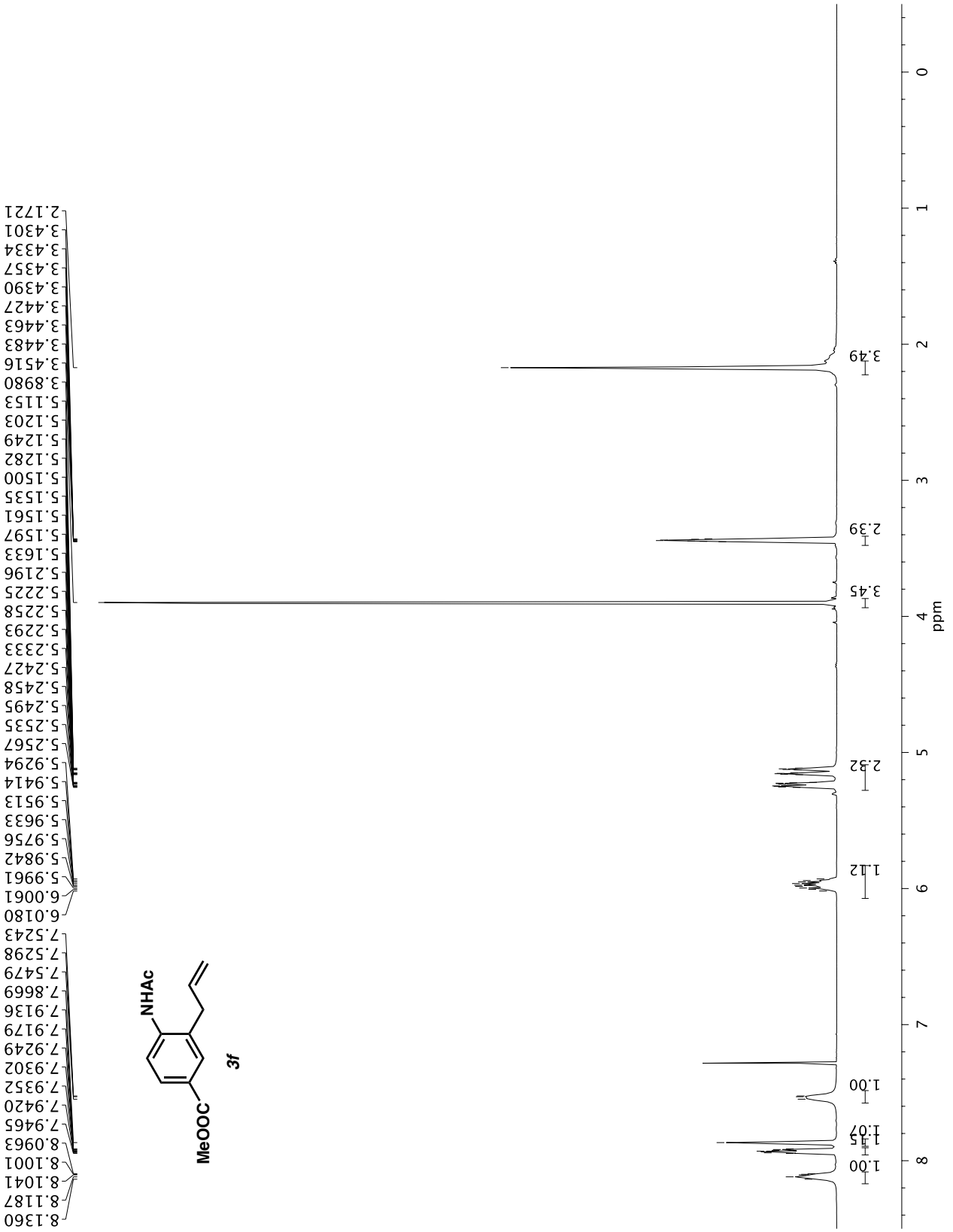
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3d**.



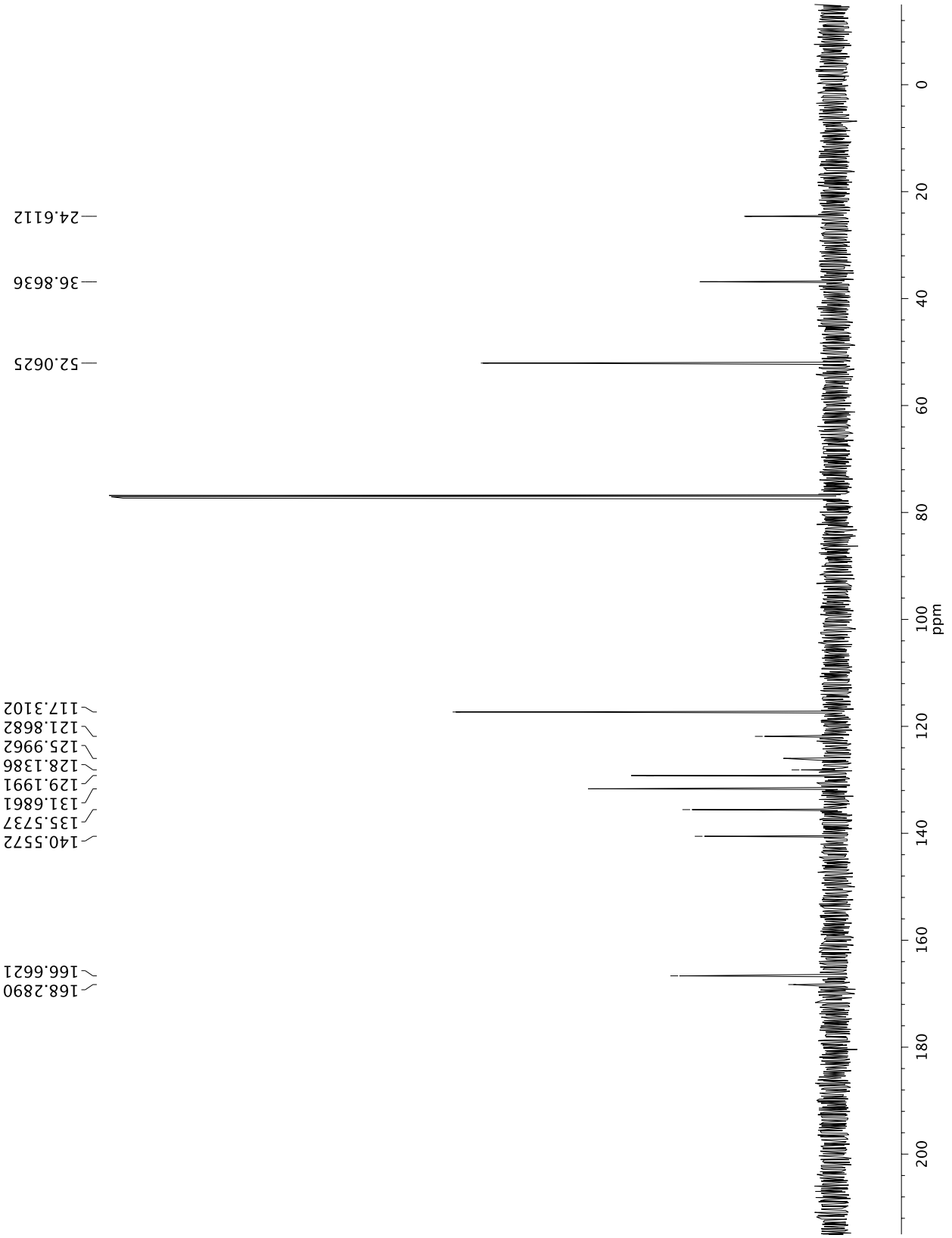
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3e**.



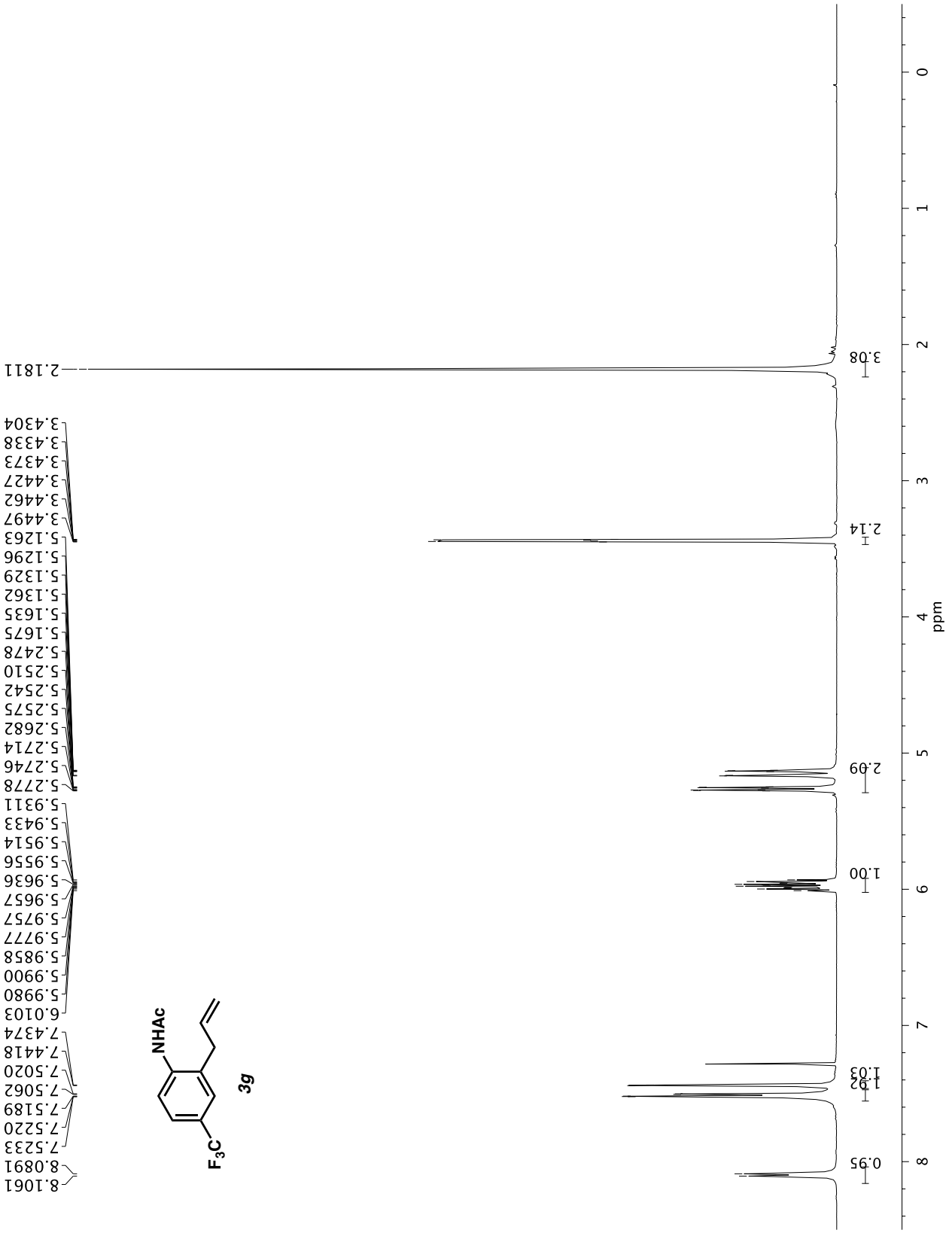
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3e**.



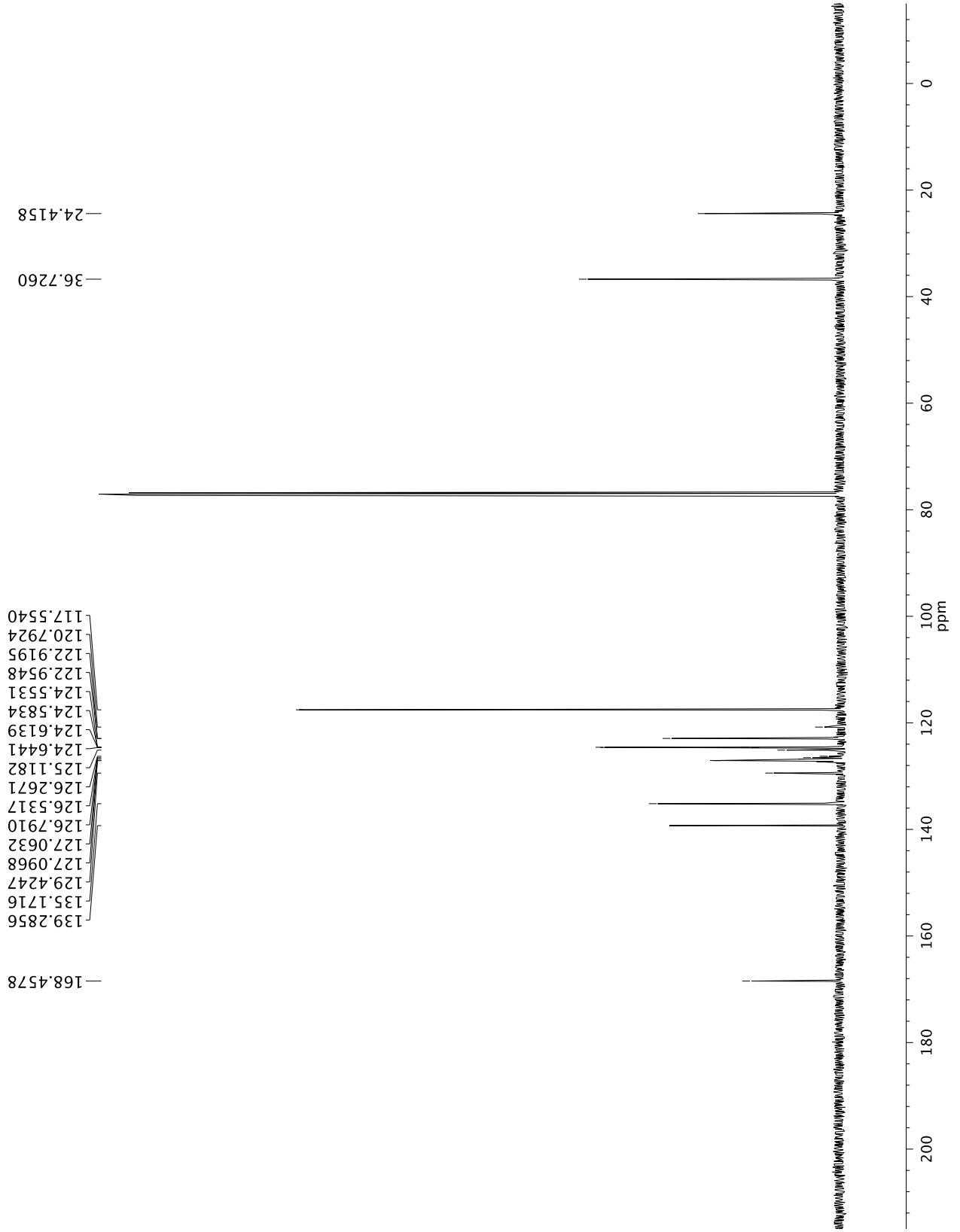
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3f**.



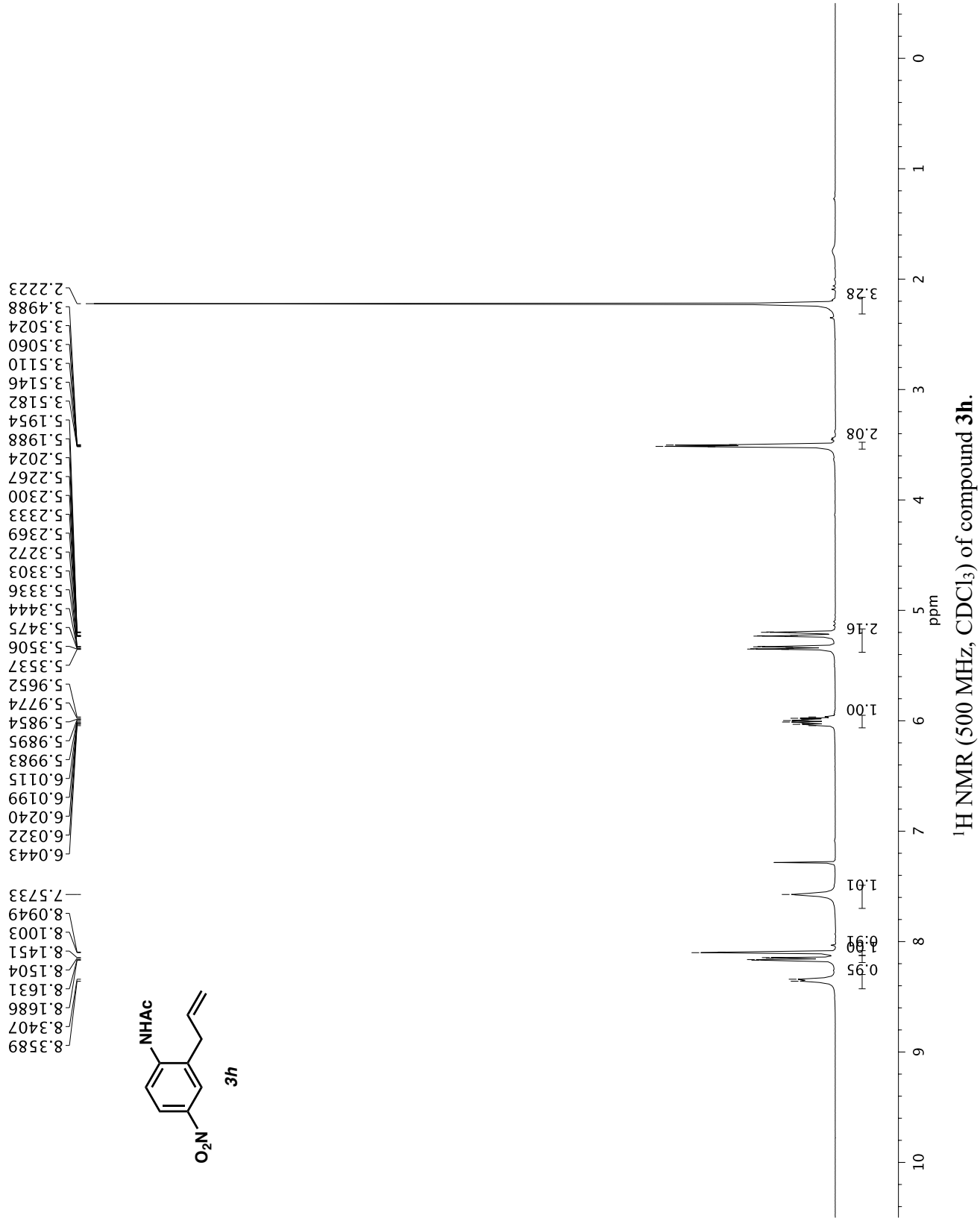
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3f**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **3g**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **3g**.



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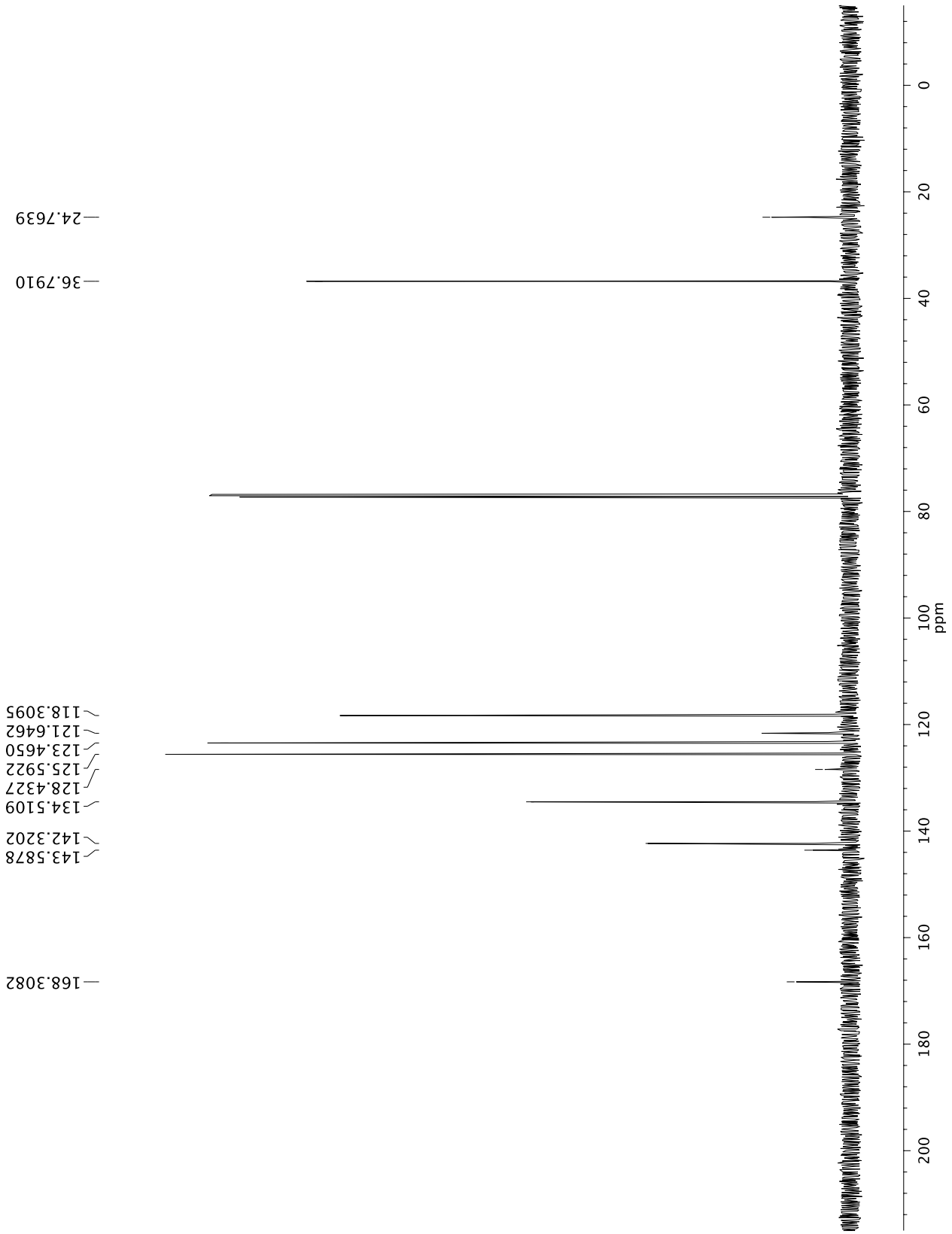

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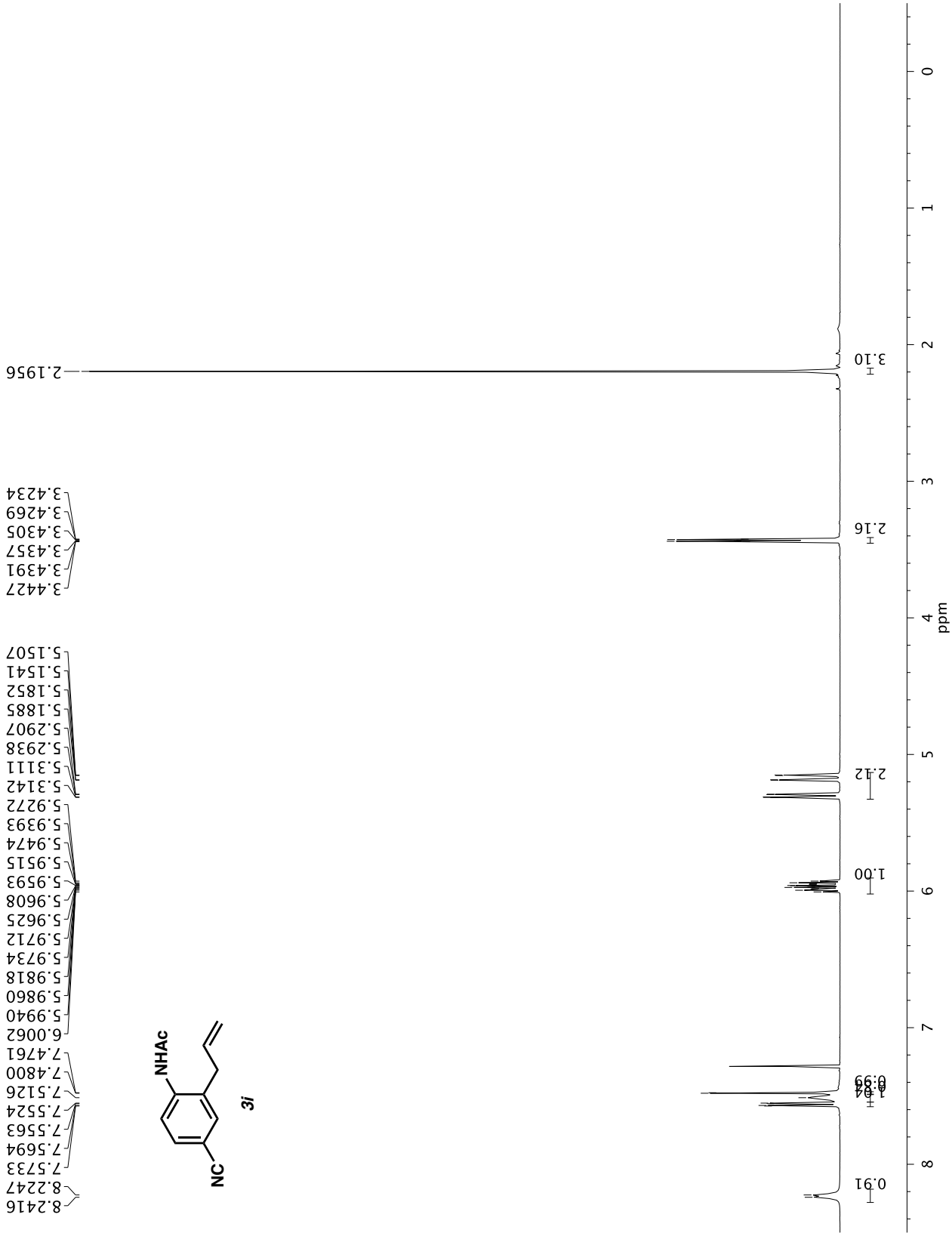
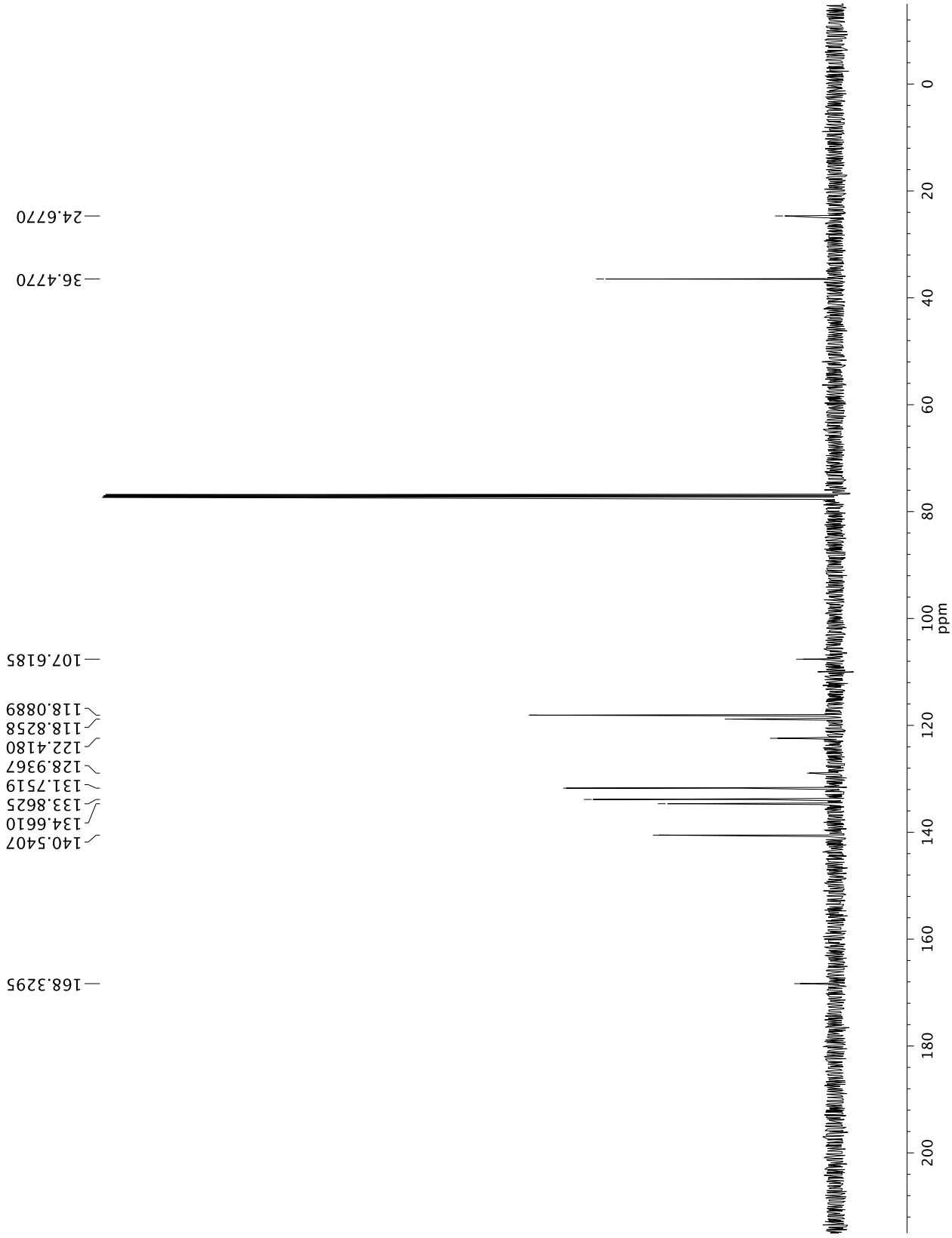


^{1}H NMR (500 MHz, $CDCl_3$) of compound **3i**.



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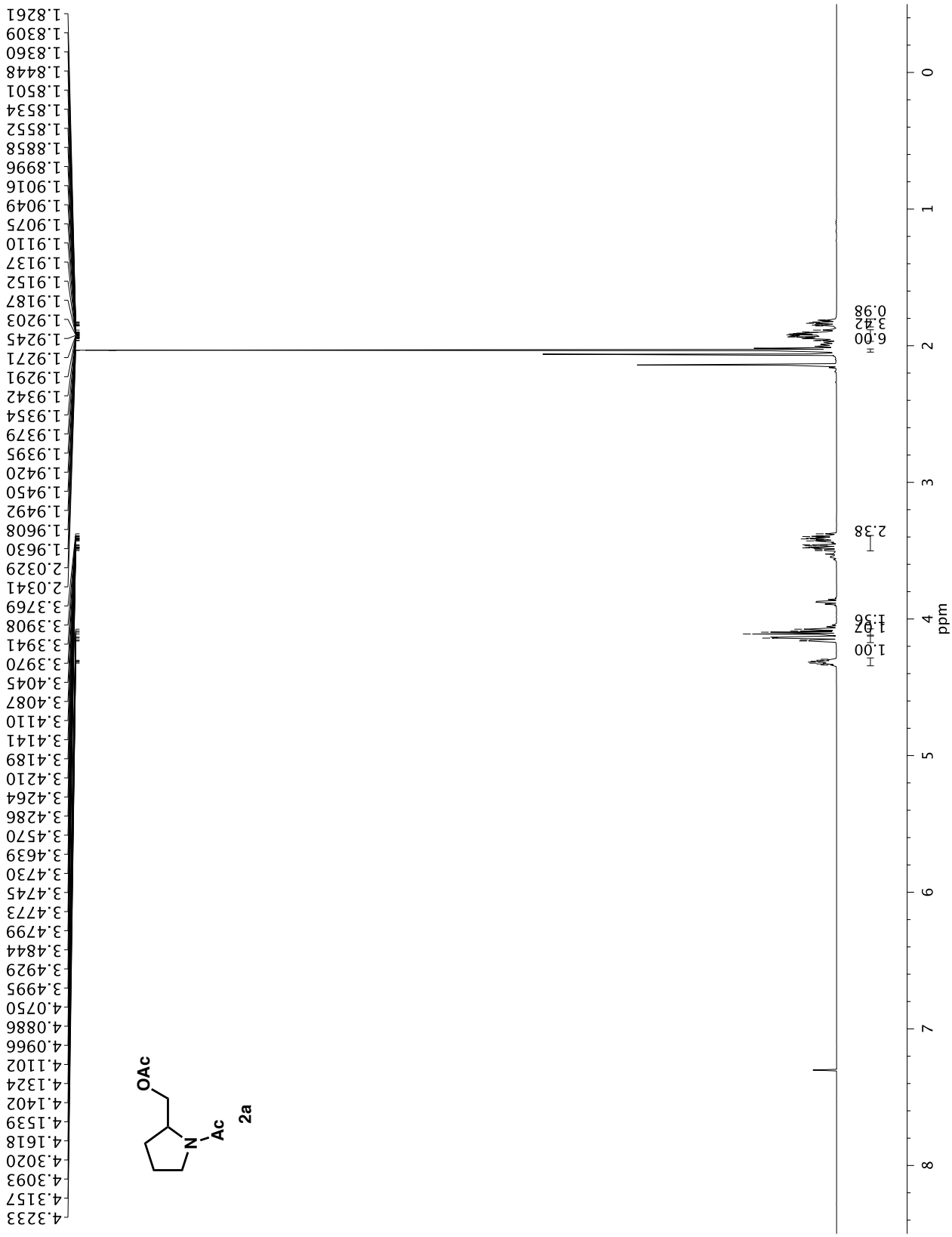

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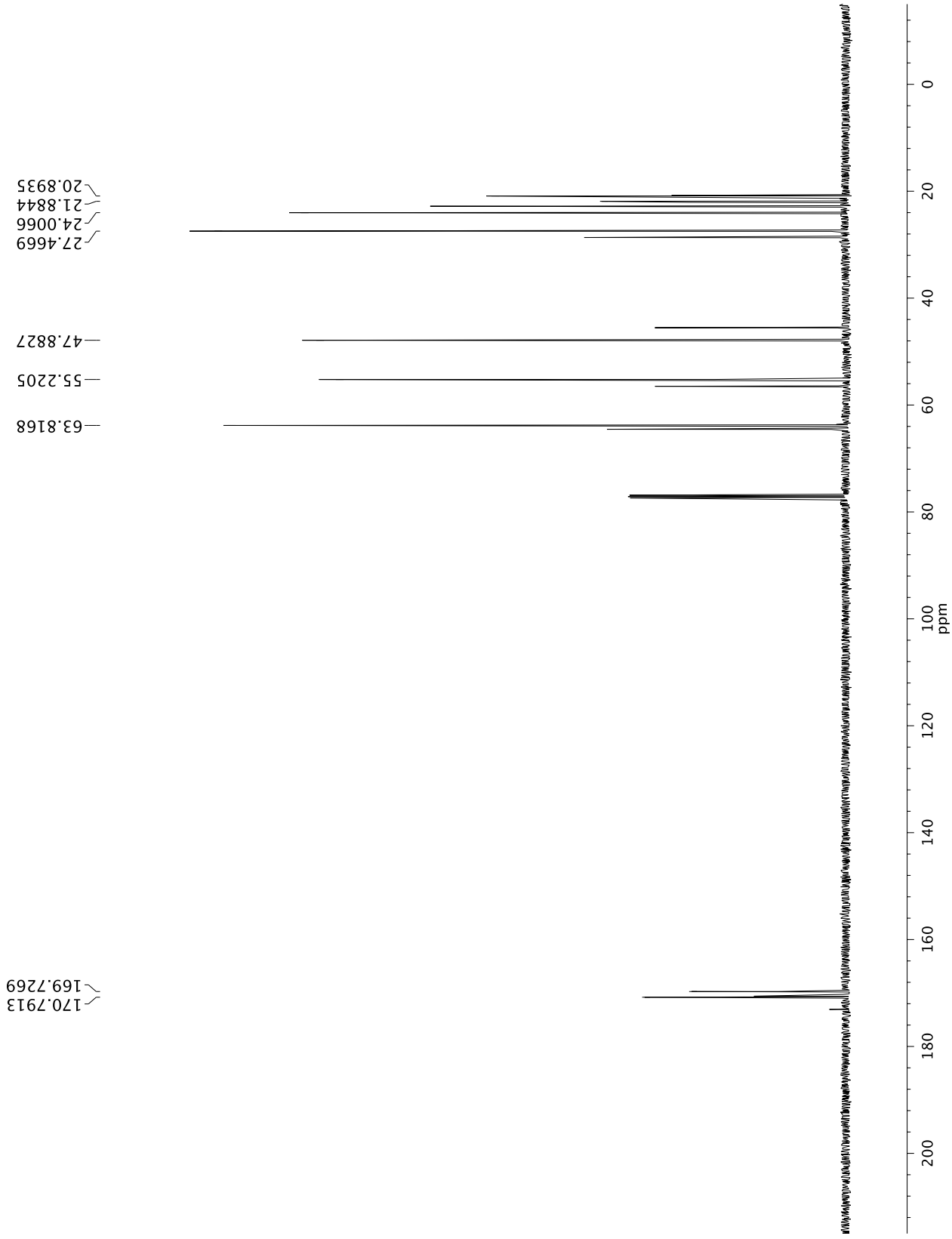
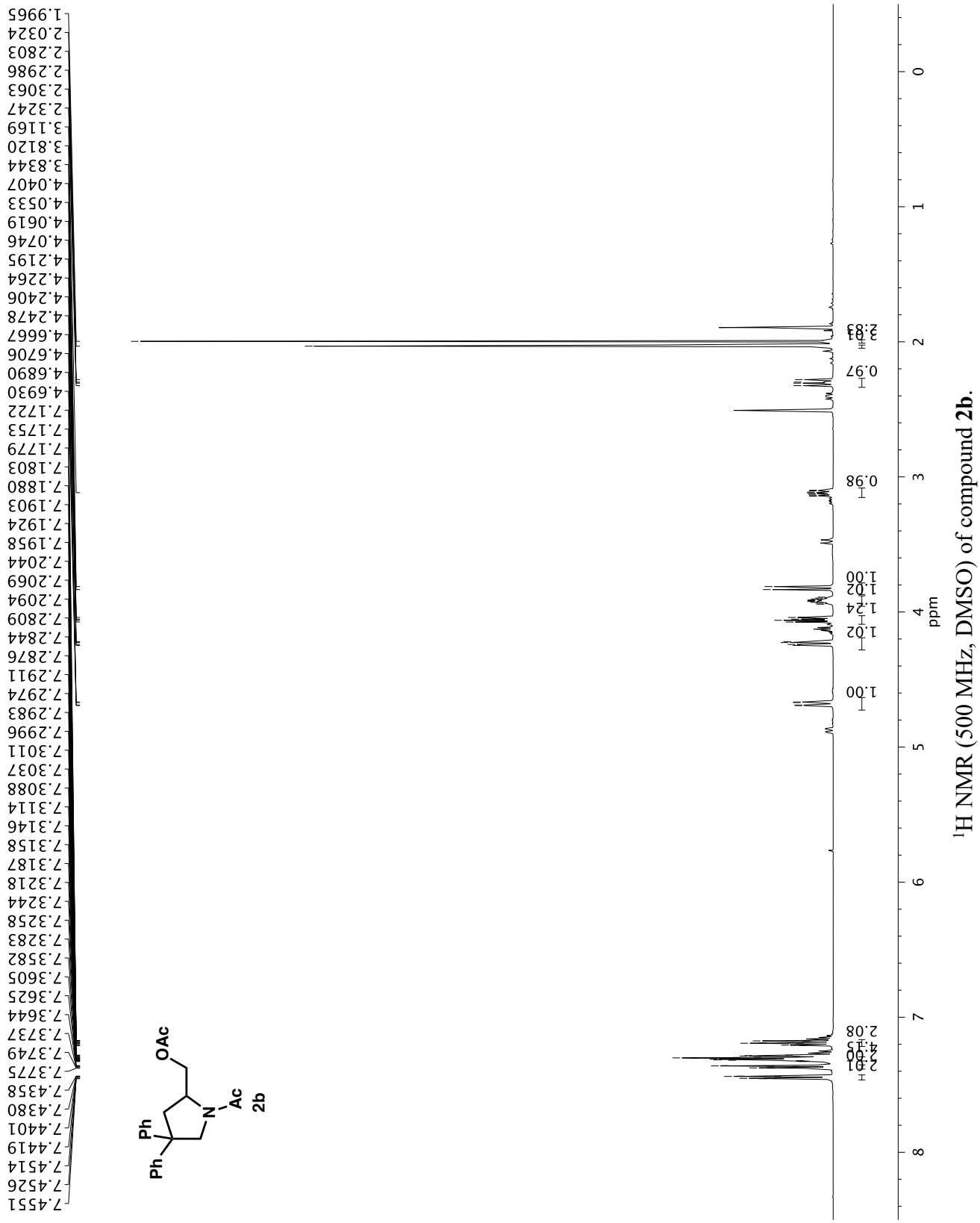
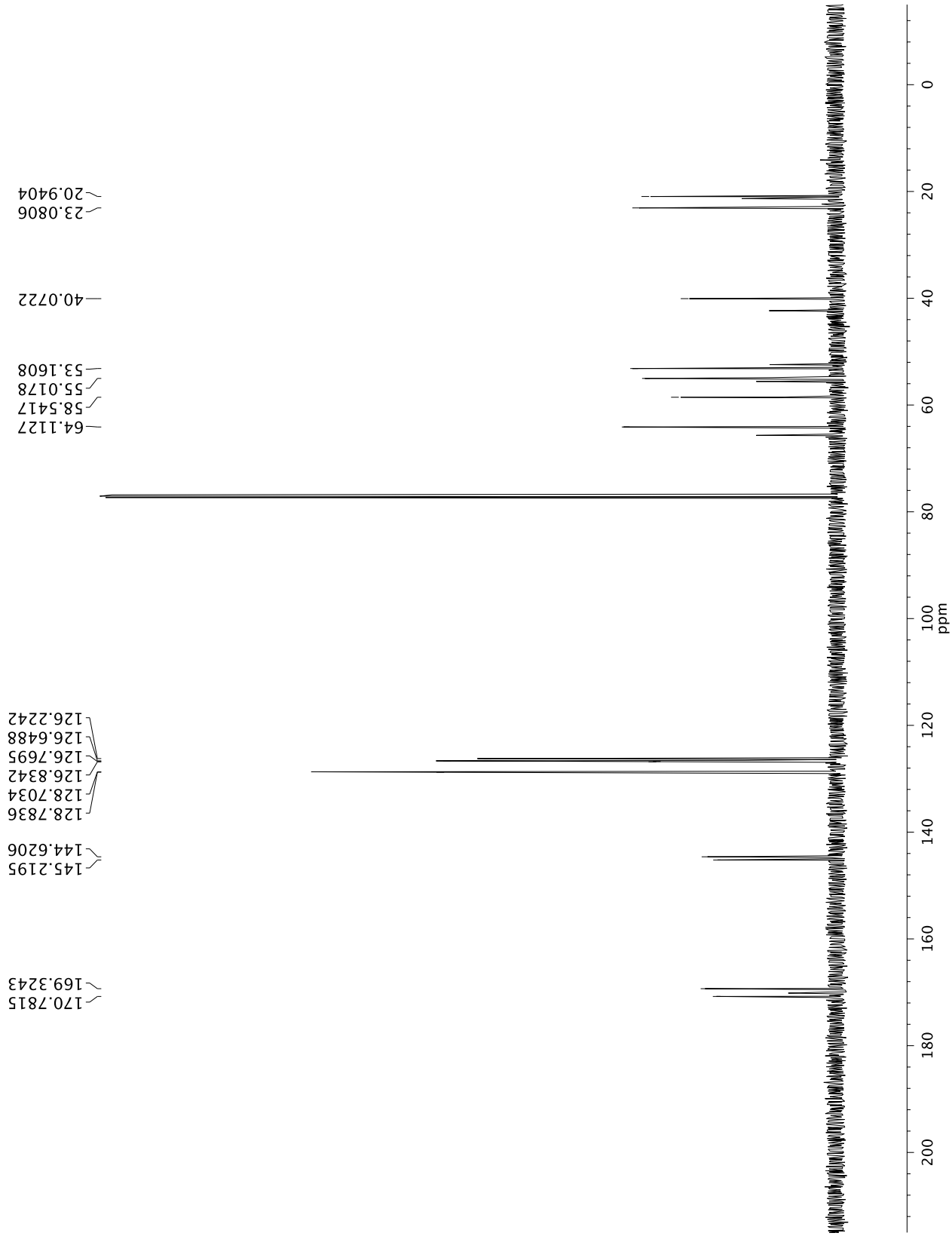


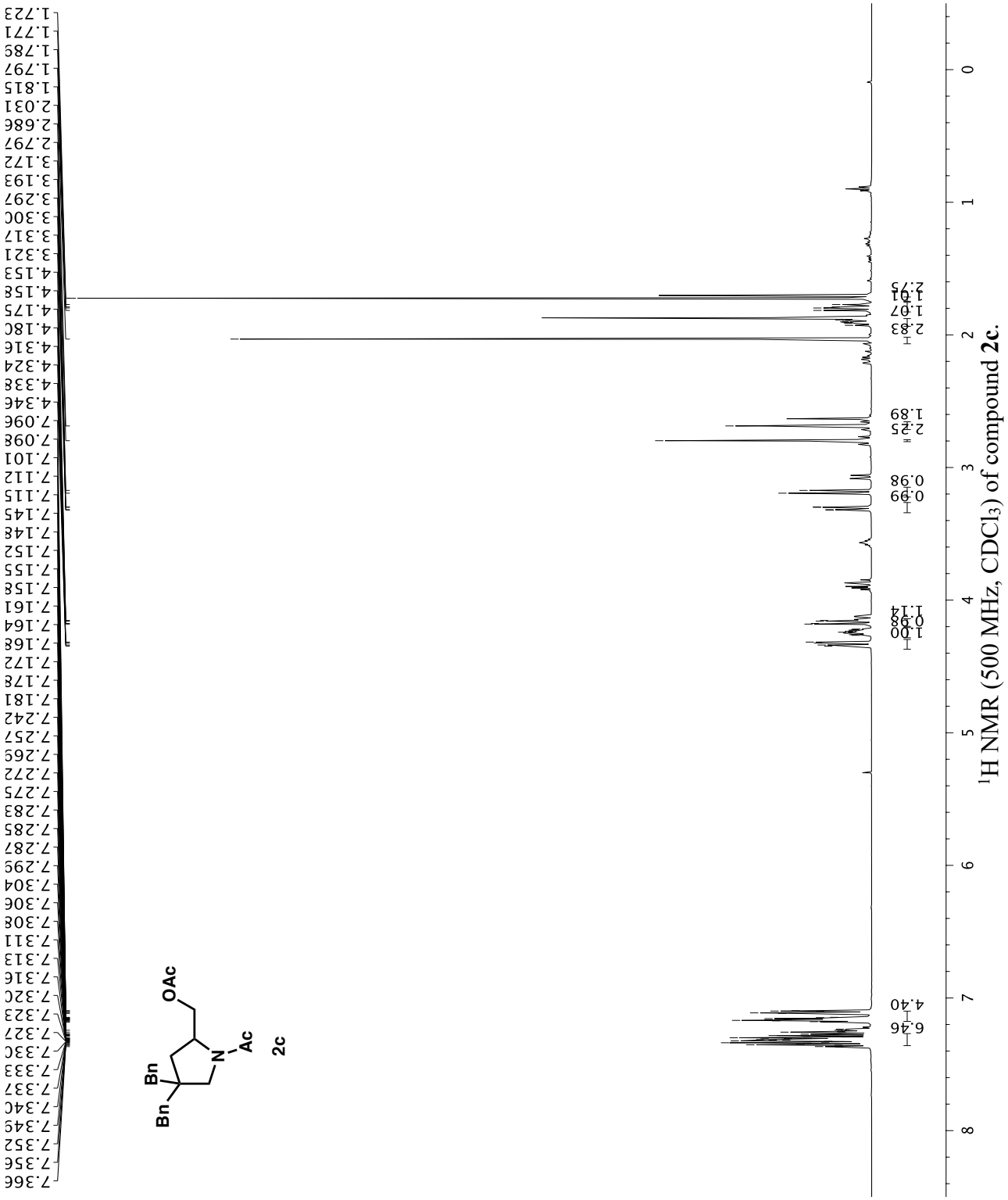
^{13}C NMR (126 MHz, $CDCl_3$) of compound **2a**.



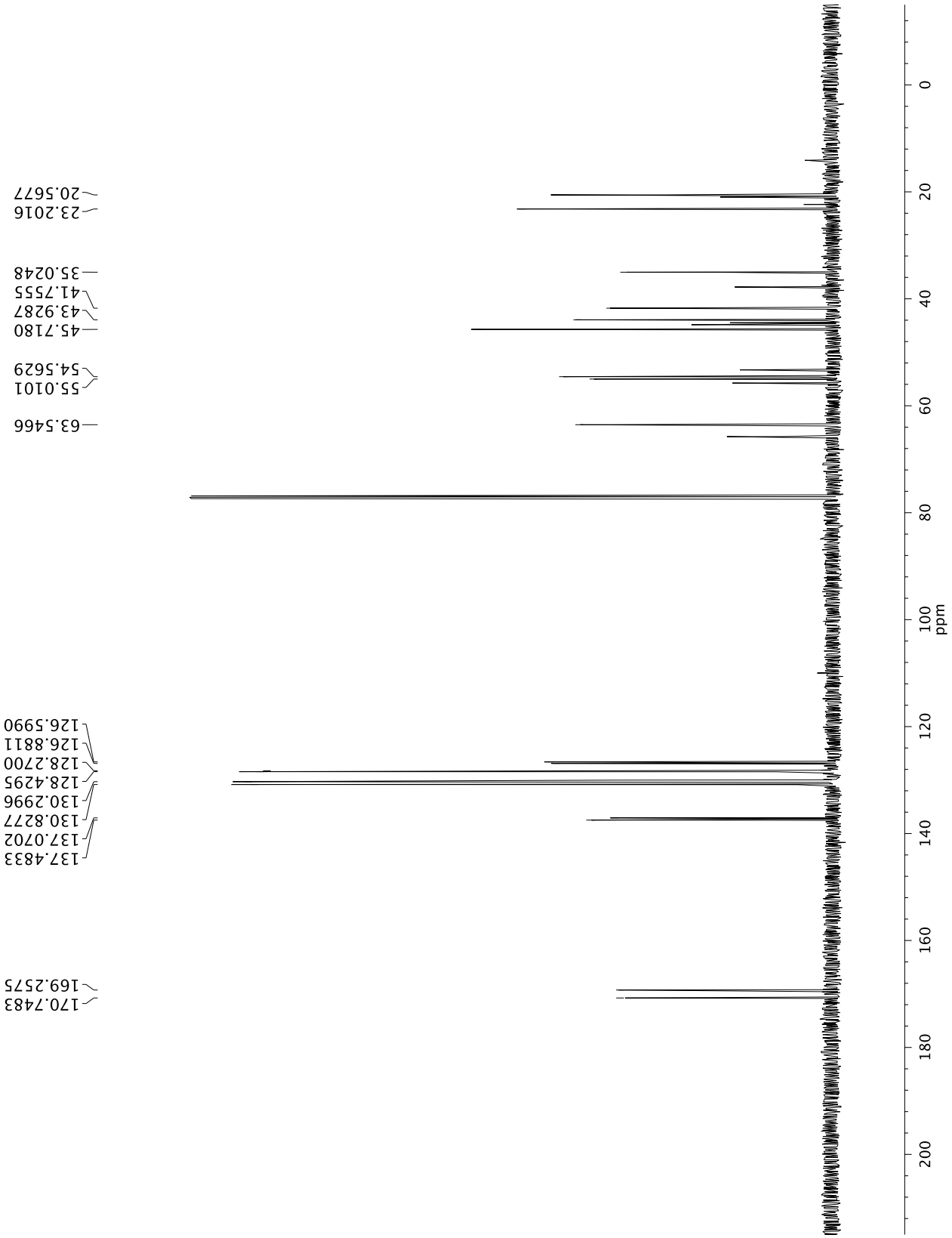
^{1}H NMR (500 MHz, DMSO) of compound **2b**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **2b**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **2c**.



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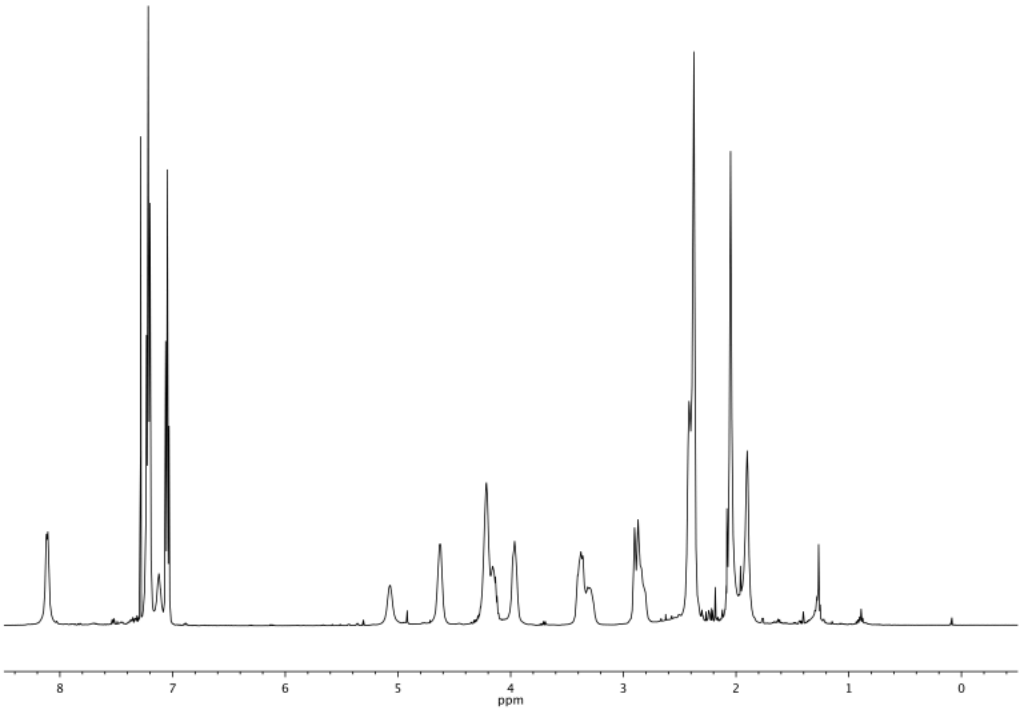
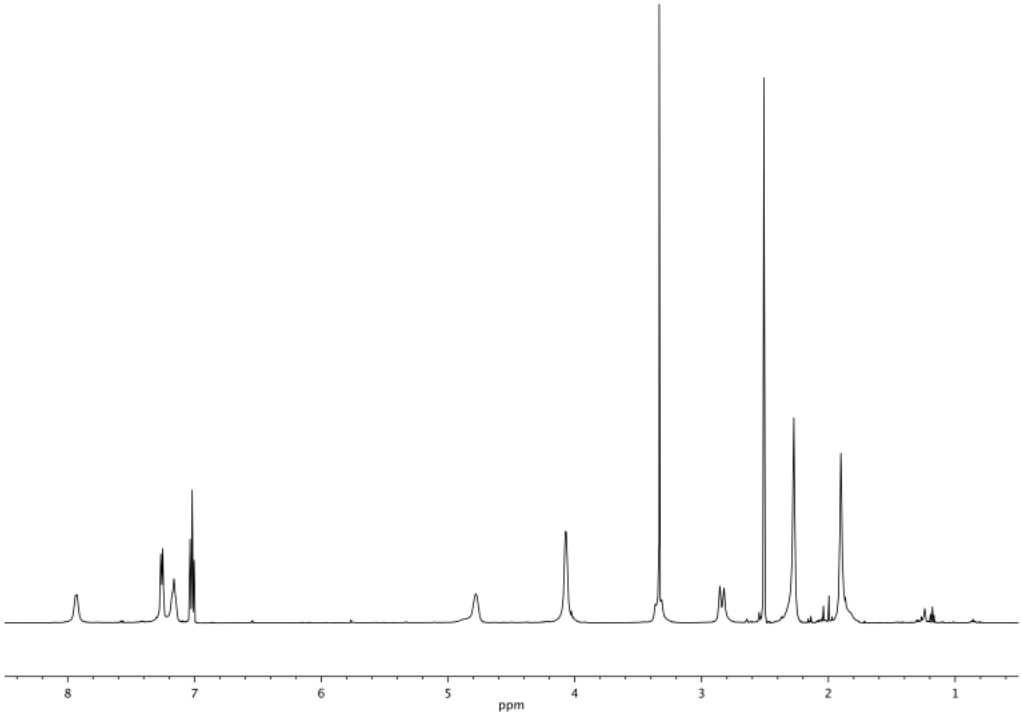
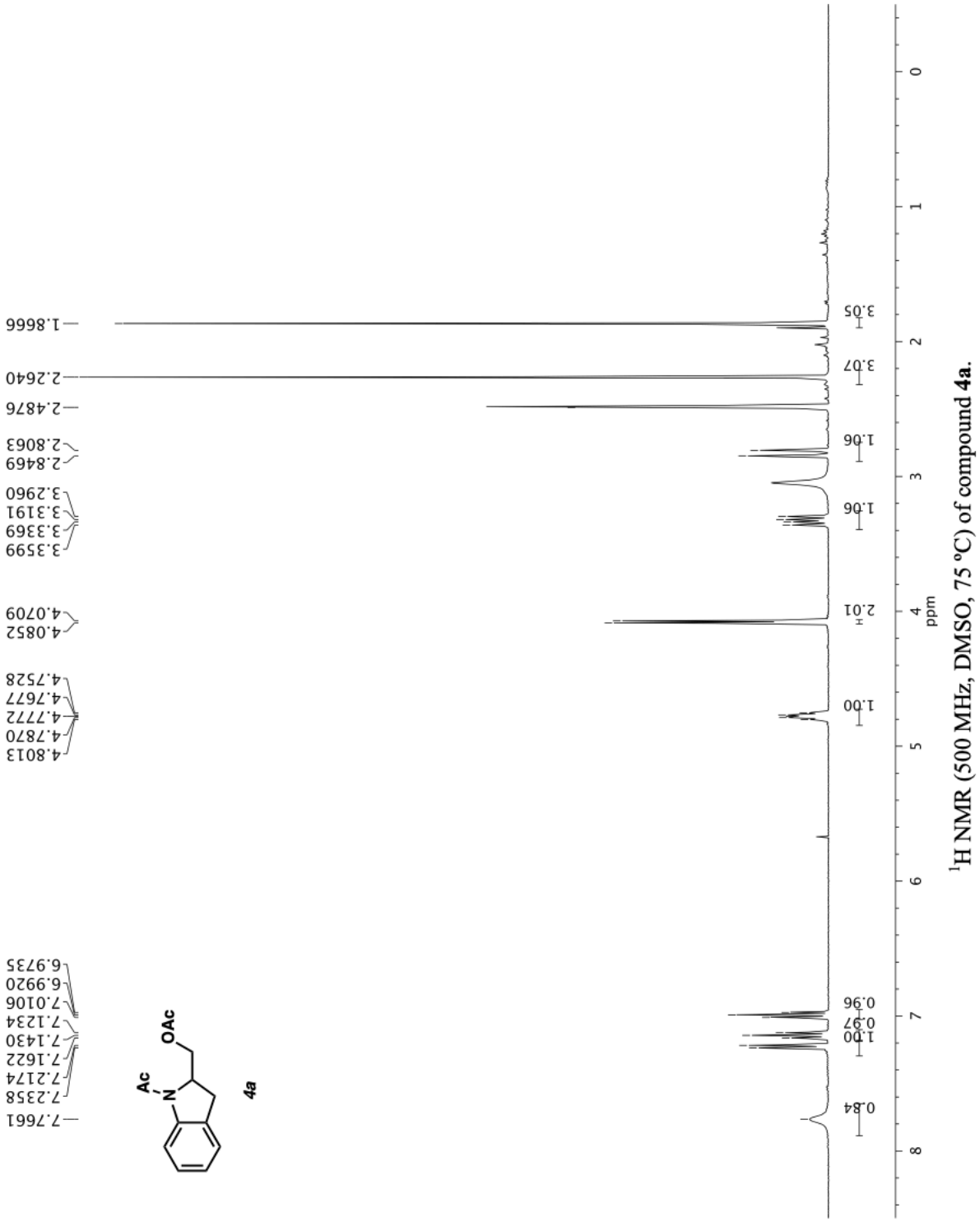


^{1}H NMR (500 MHz, $CDCl_3$, 23 ºC) of compound **4a**.



^{1}H NMR (500 MHz, DMSO, 23 ºC) of compound **4a**.



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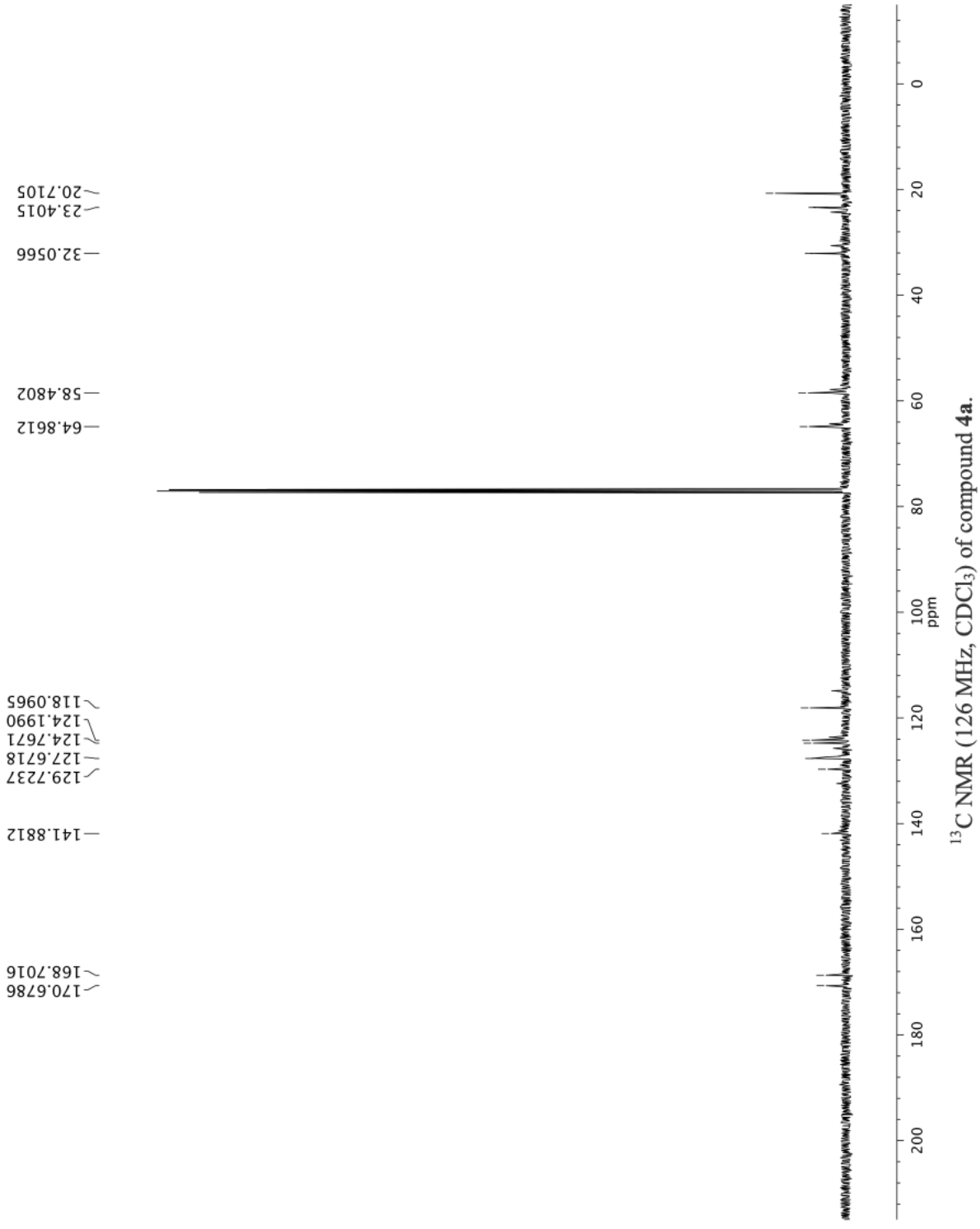
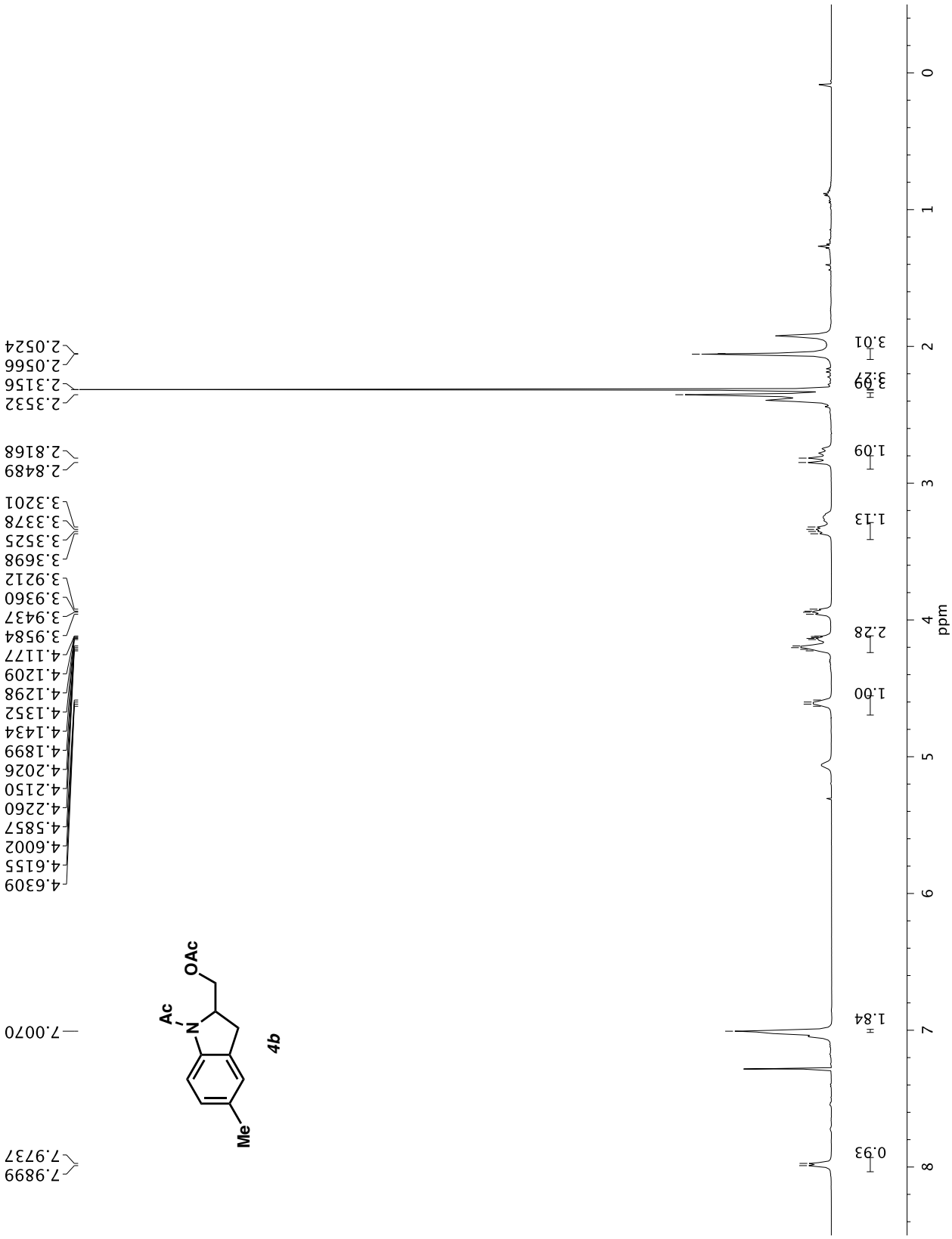
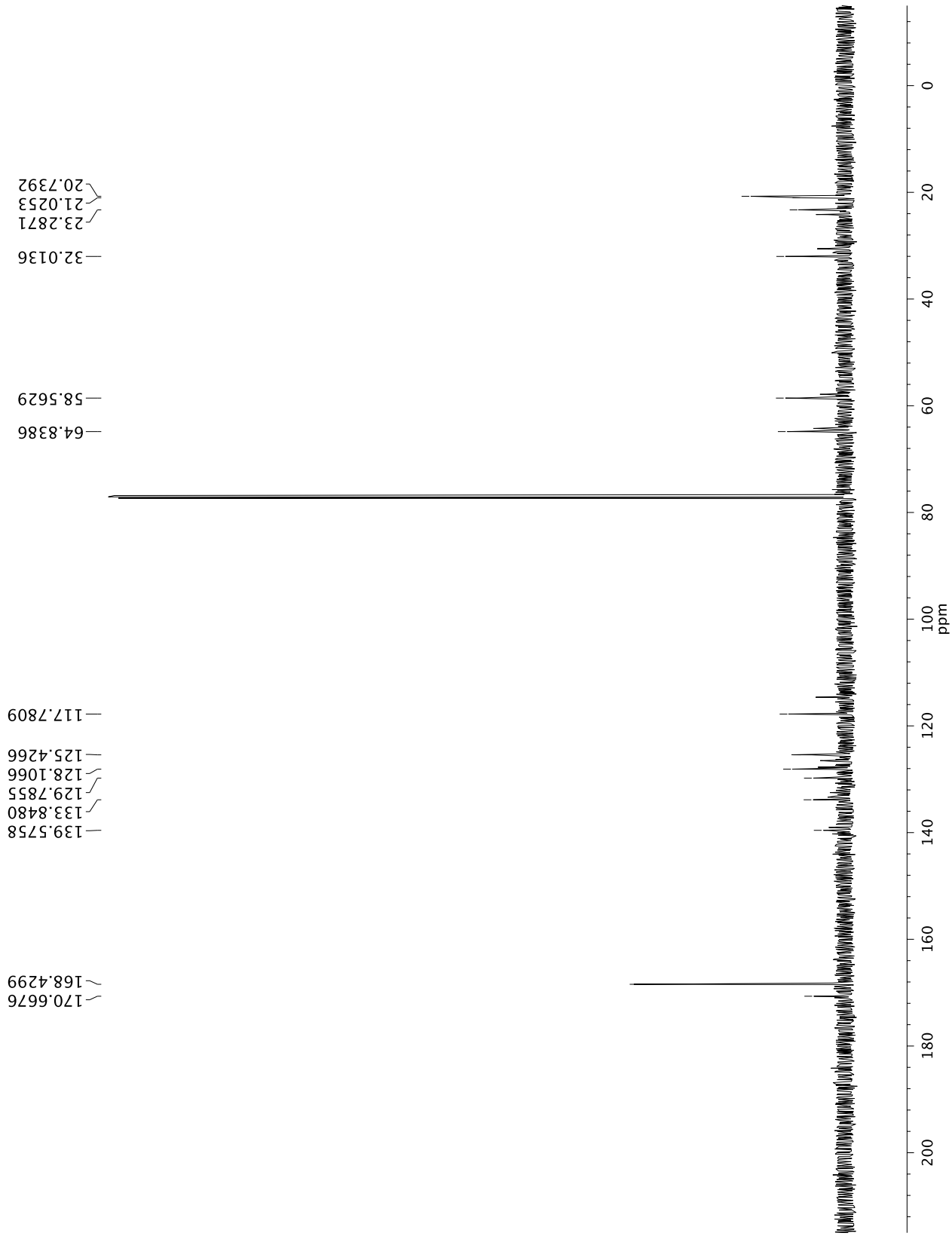


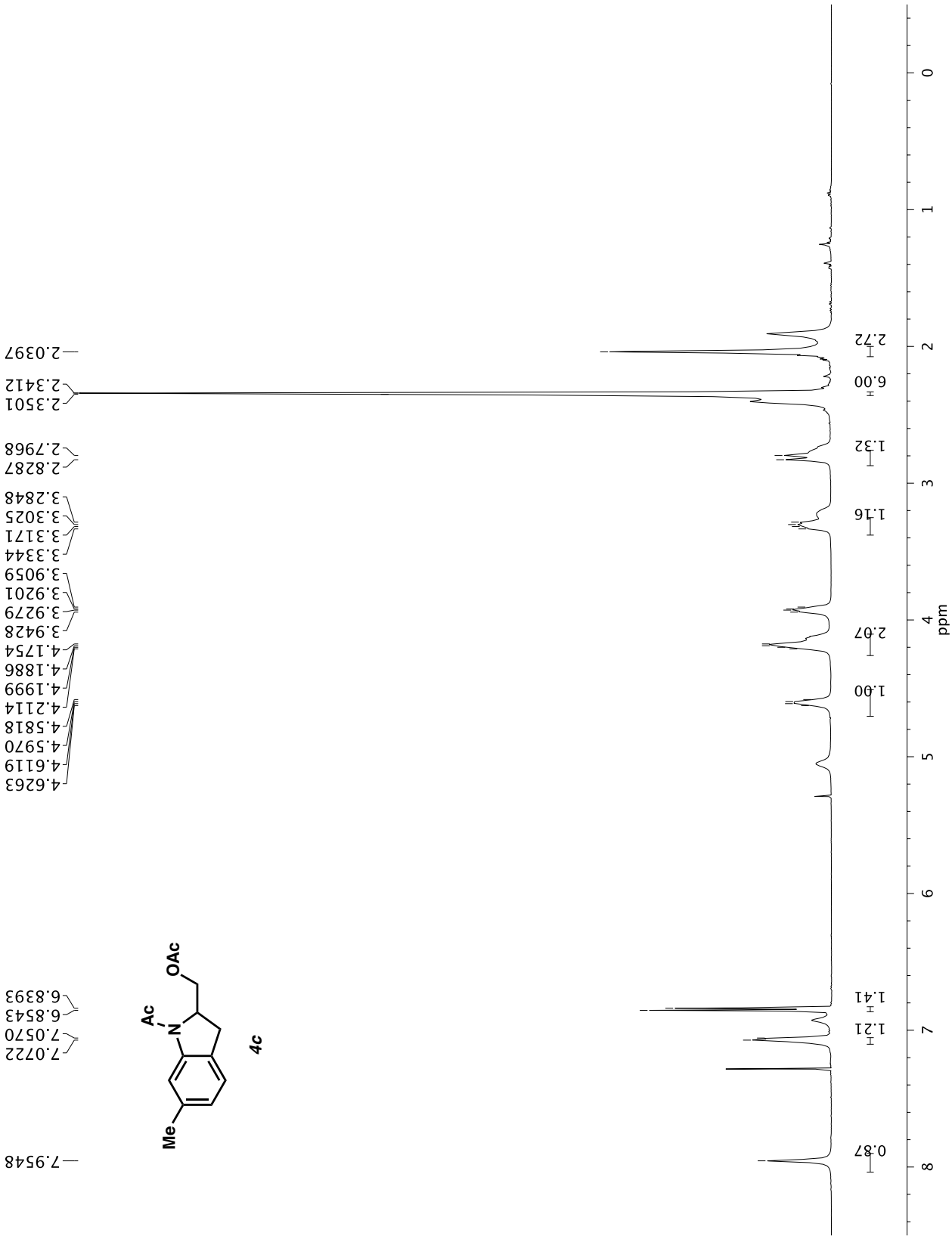
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4a**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **4b**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **4b**.



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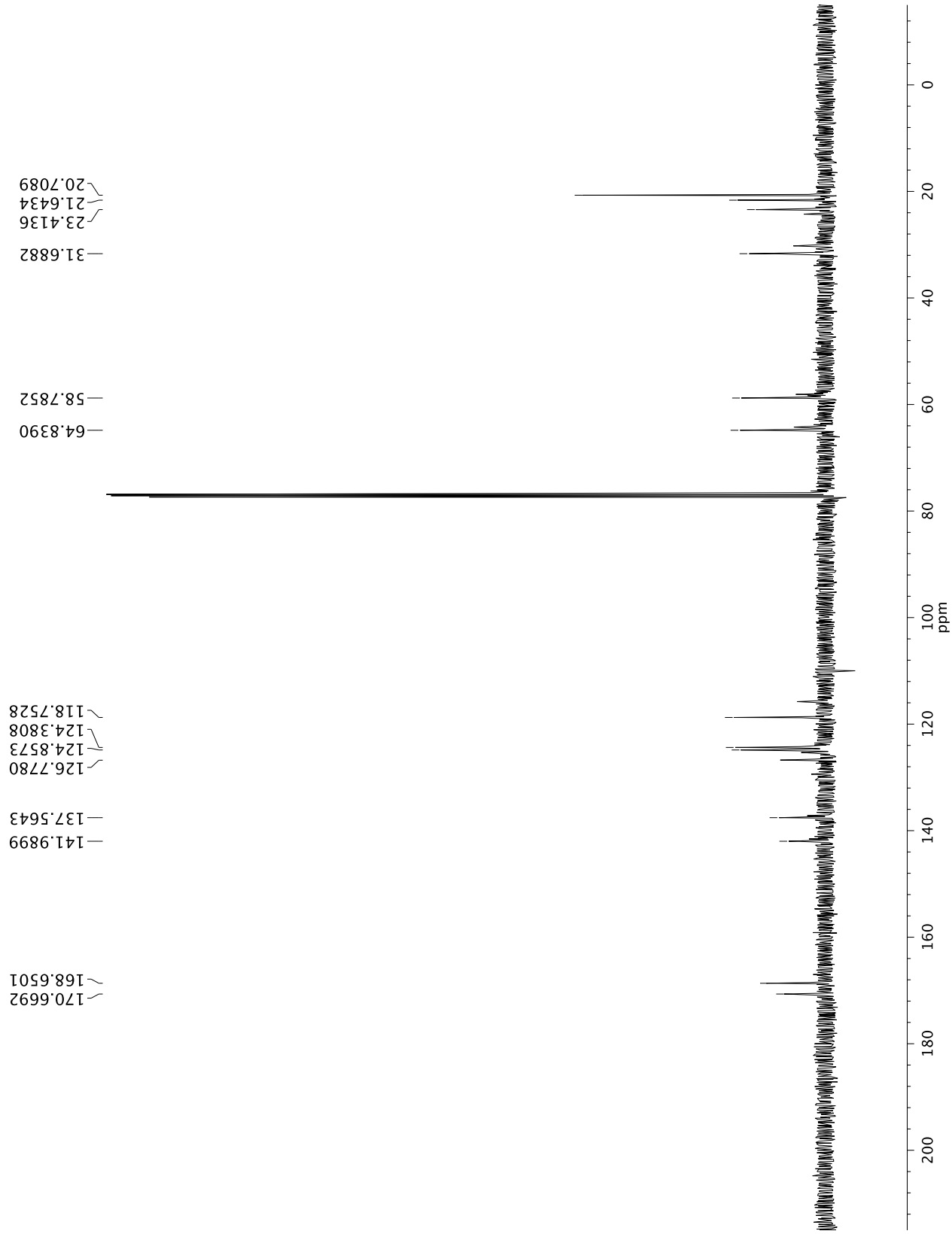
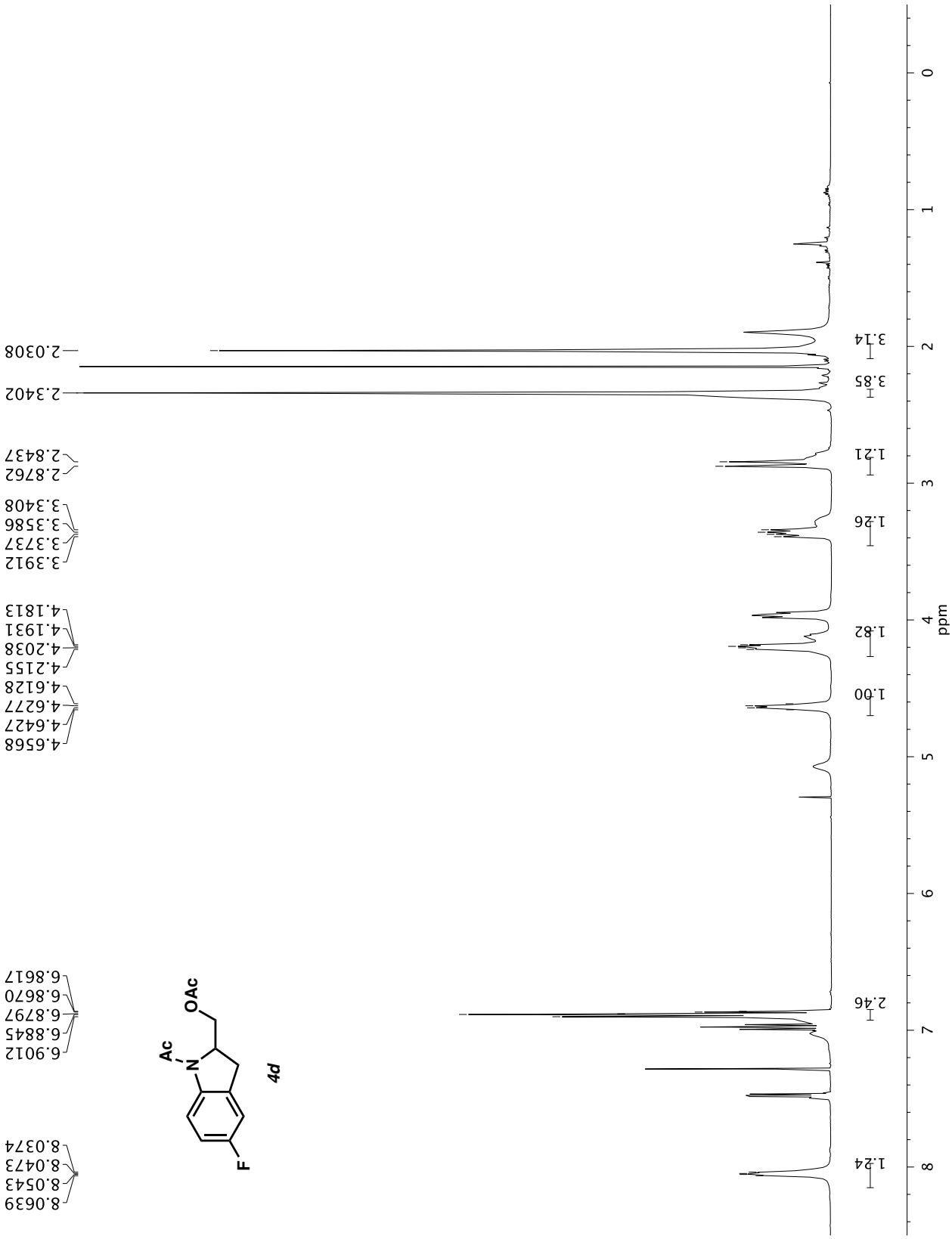
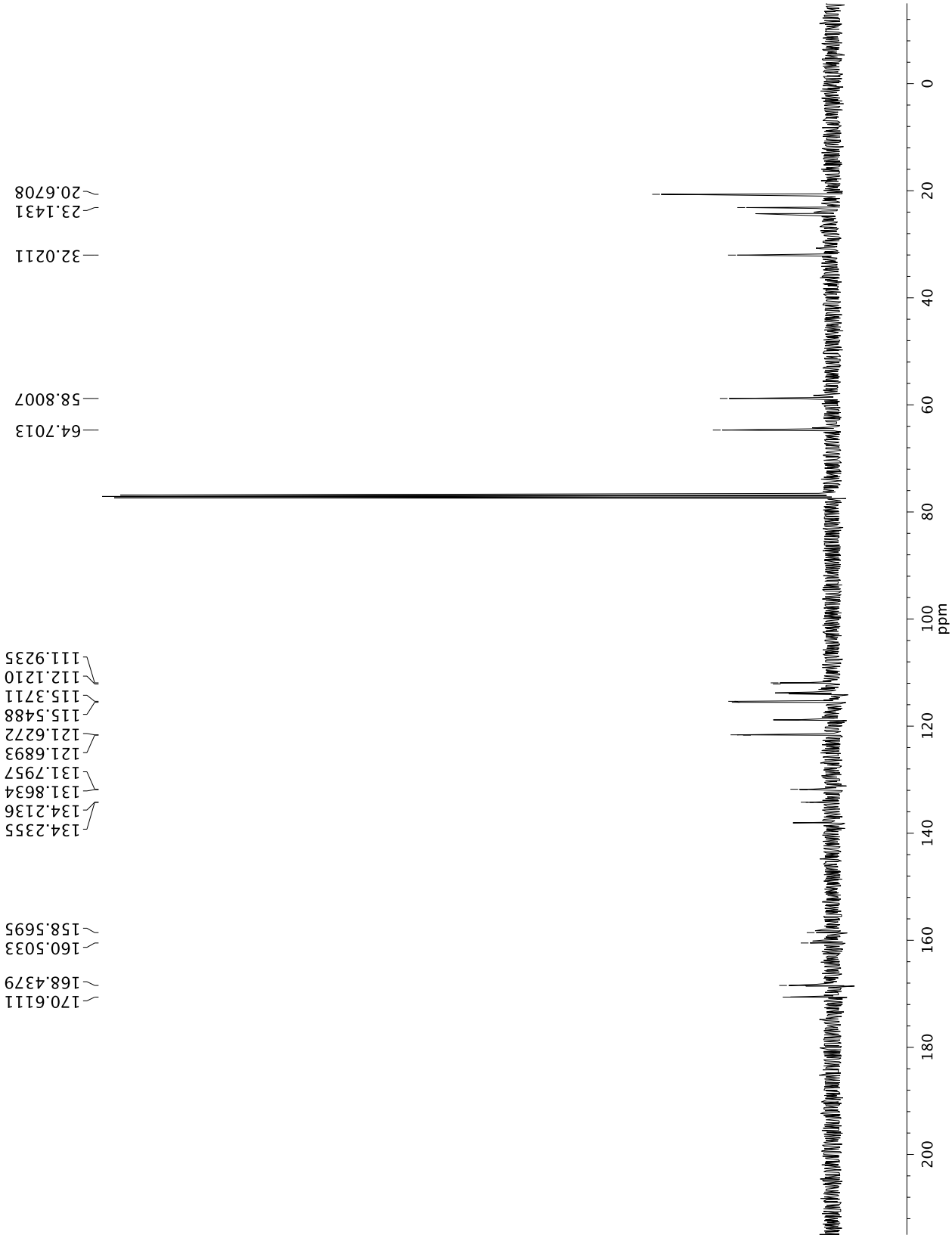


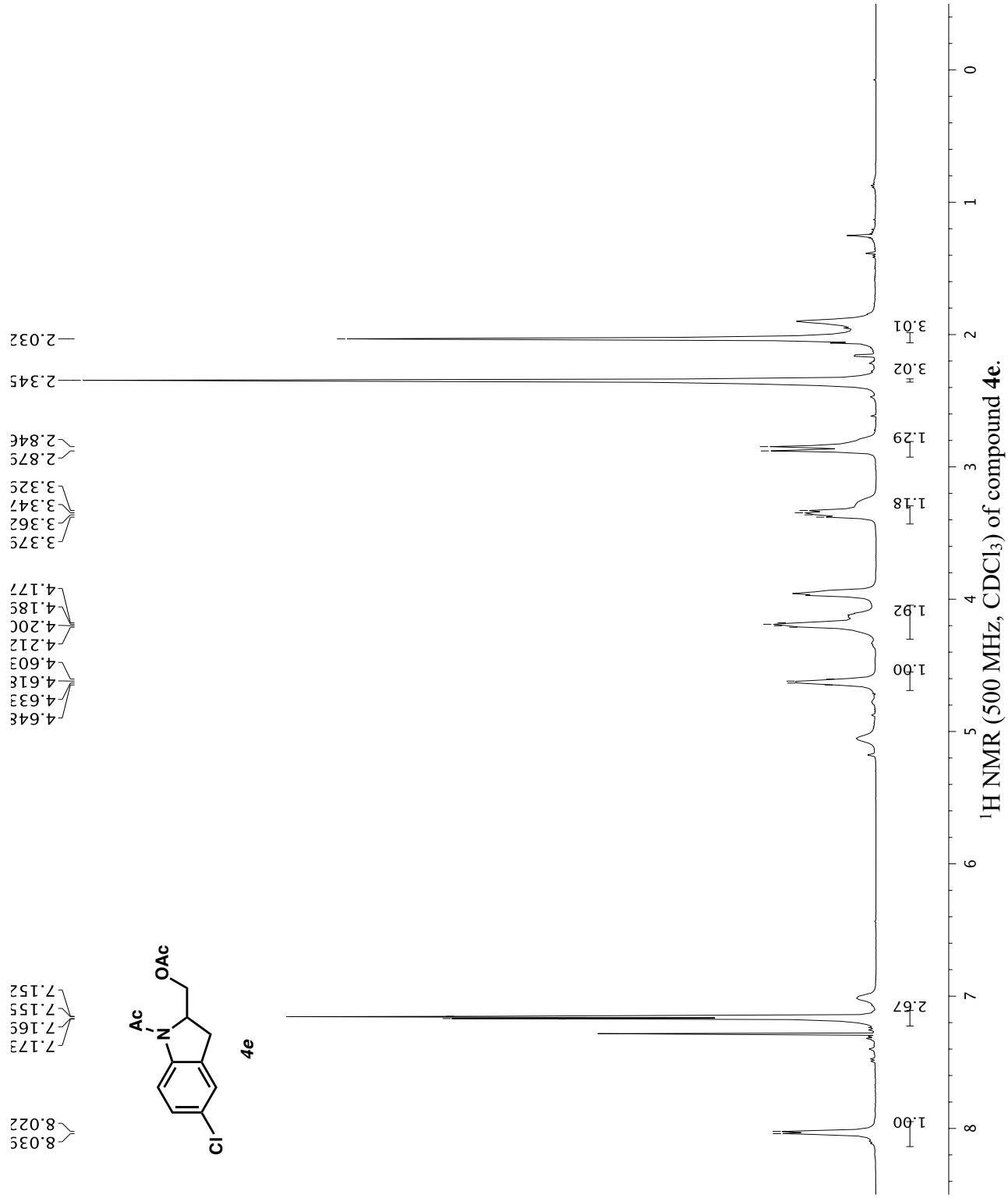
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4c**.



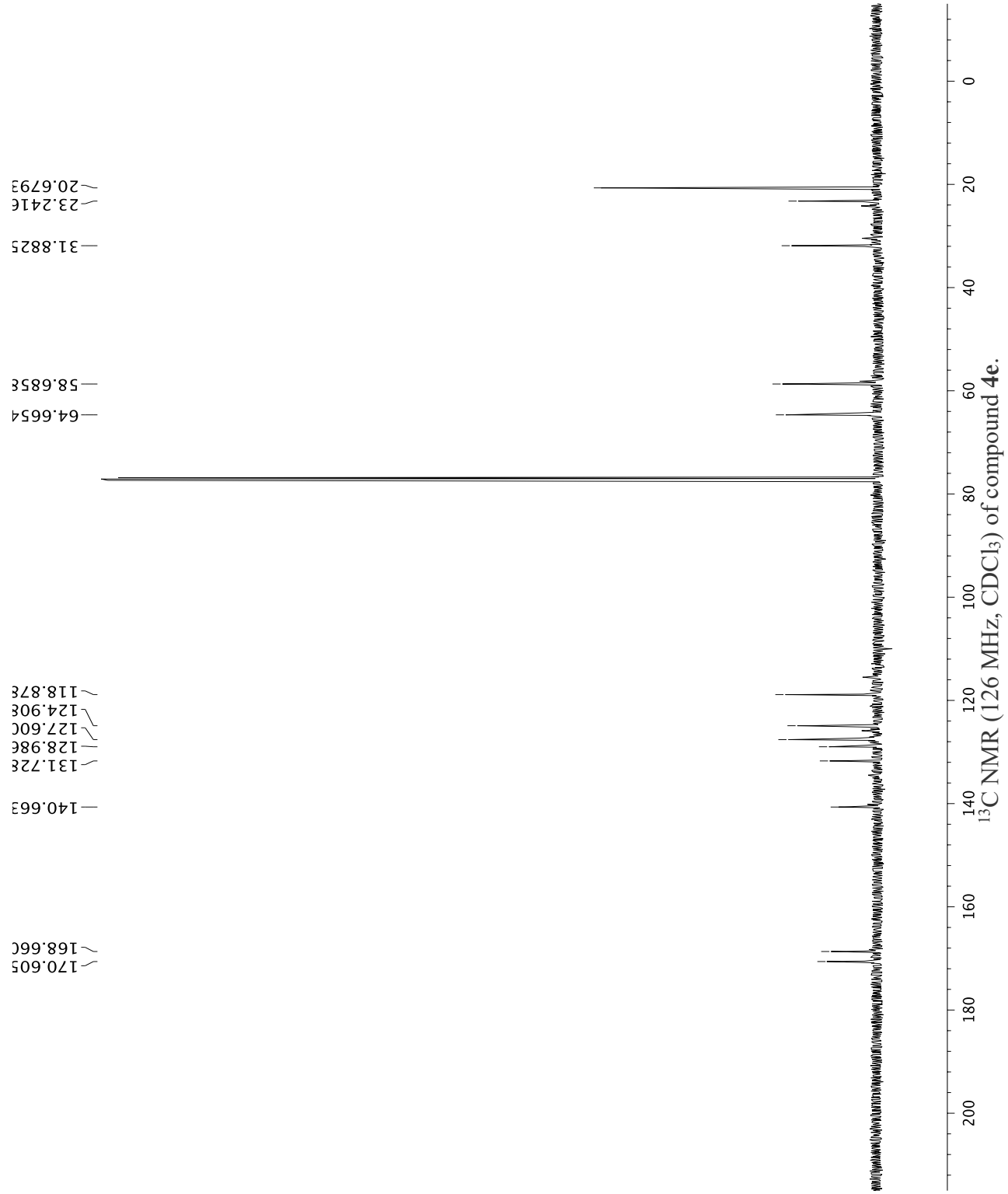
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4d**.



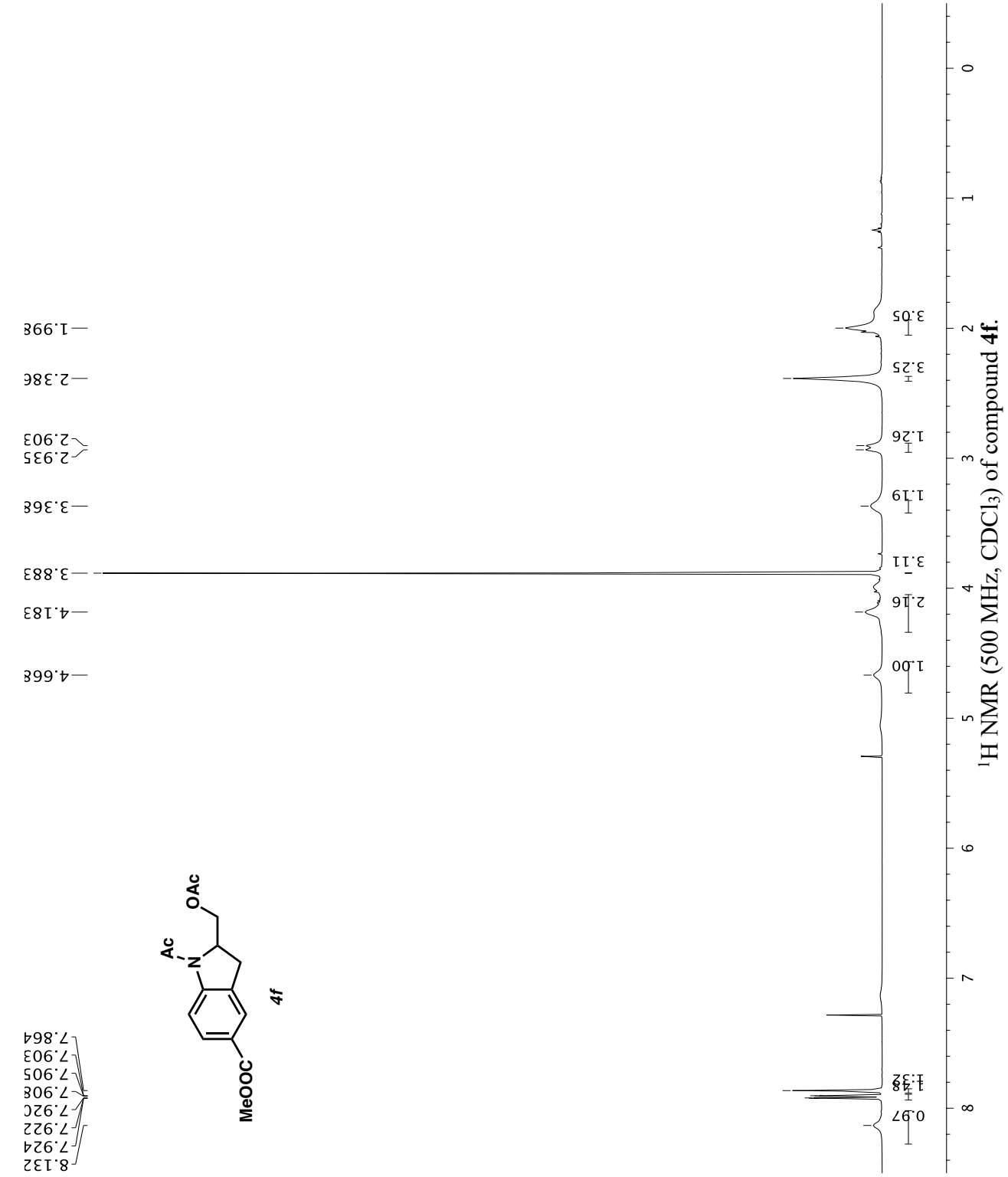
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4d**.



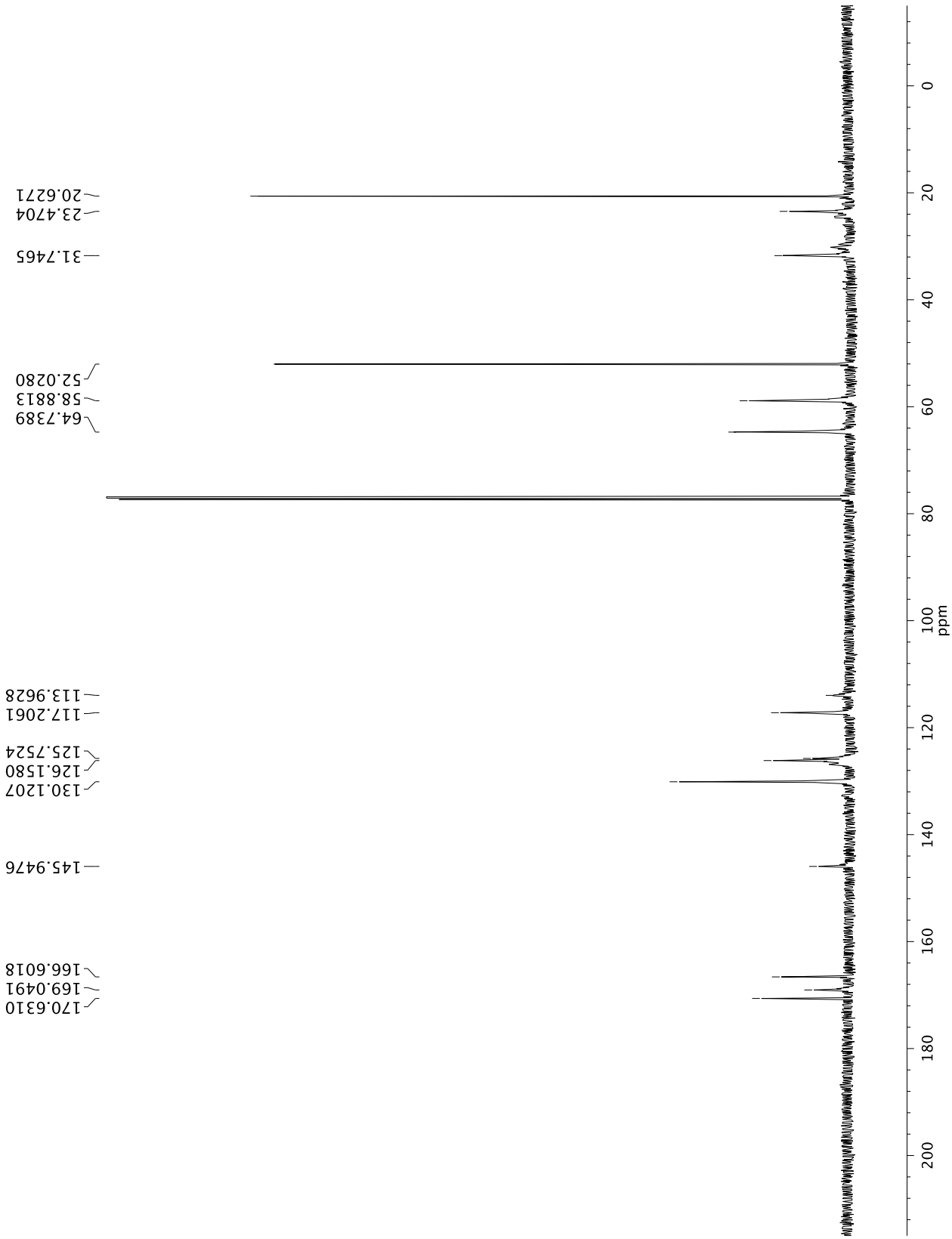
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4e**.



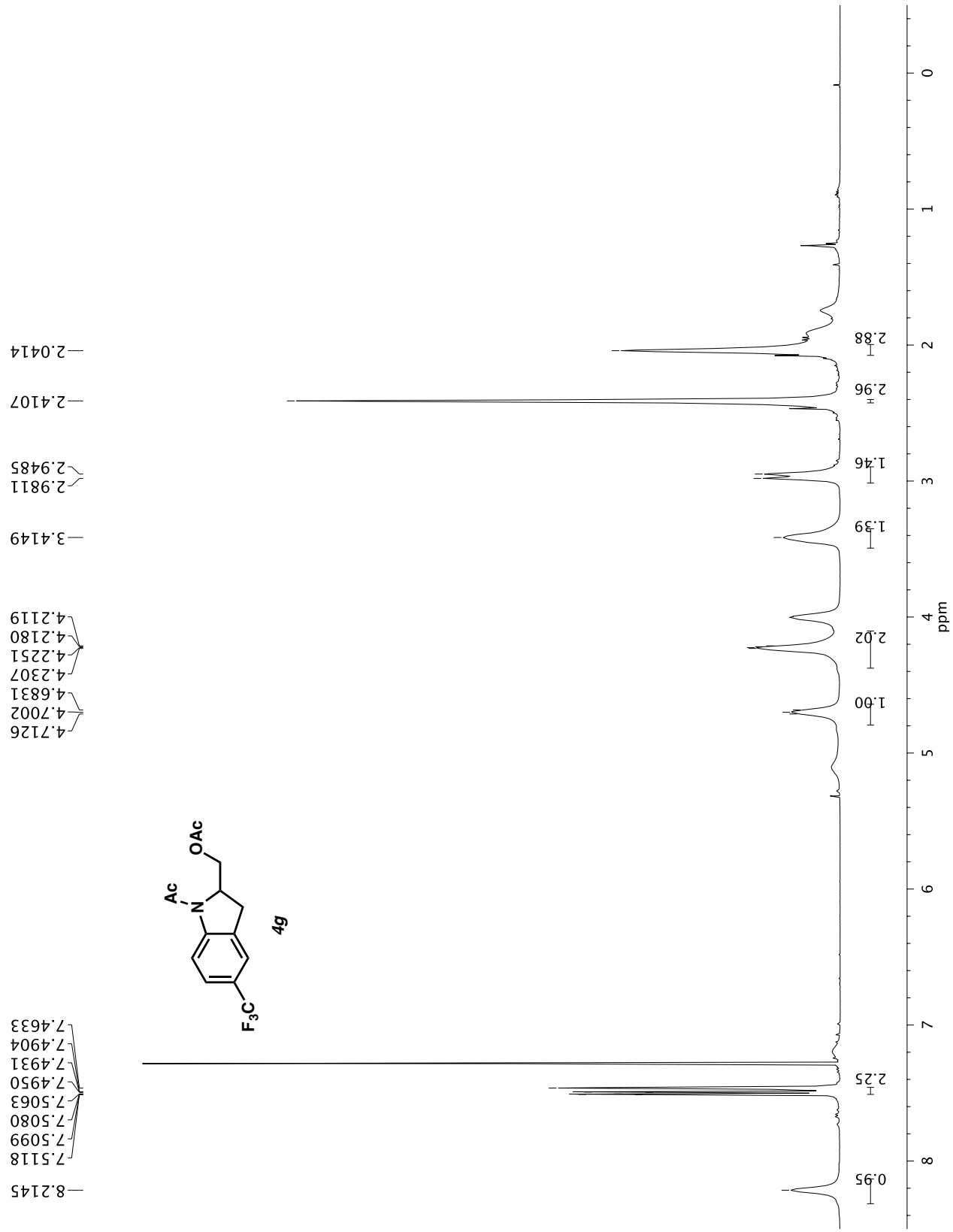
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4e**.



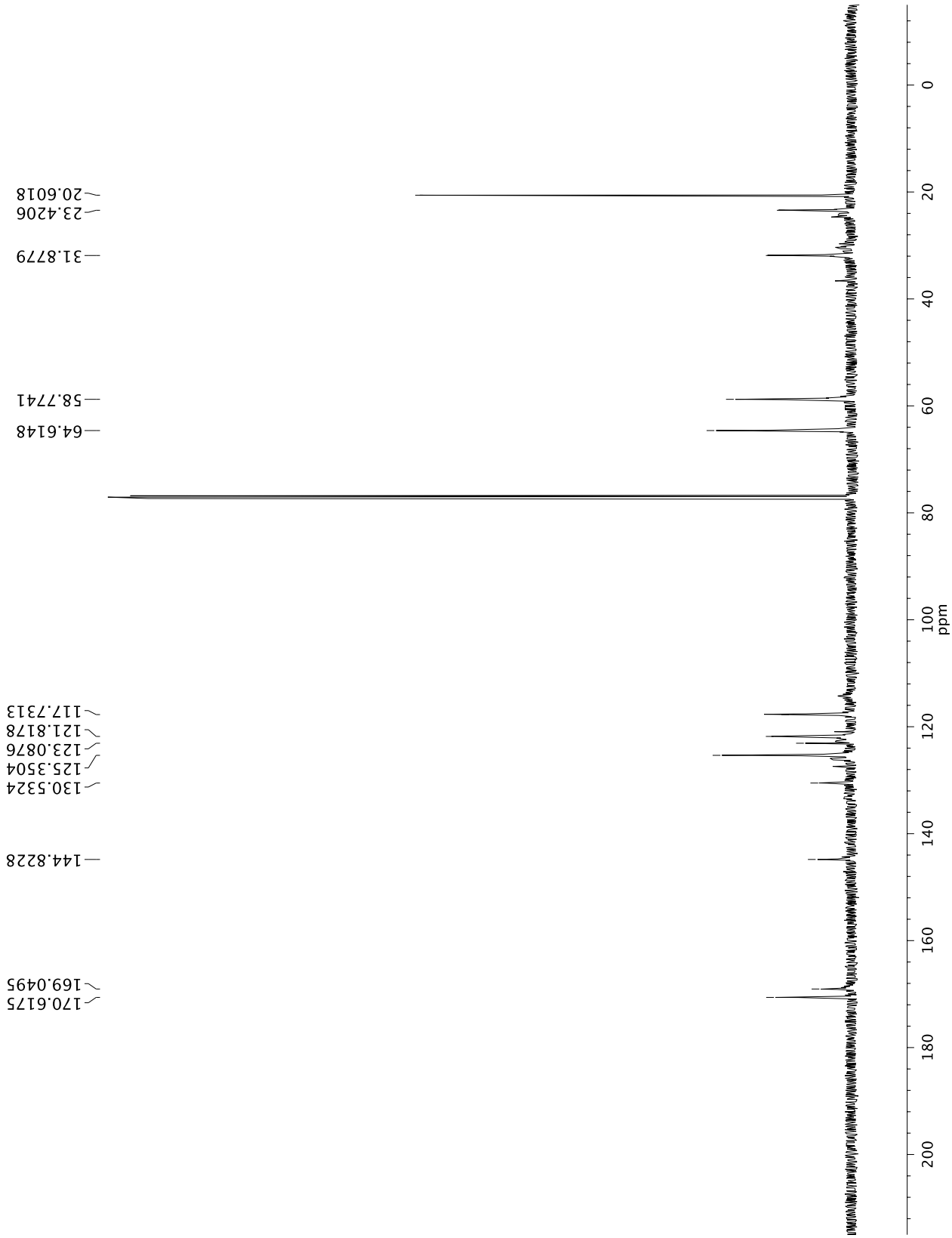
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4f**.



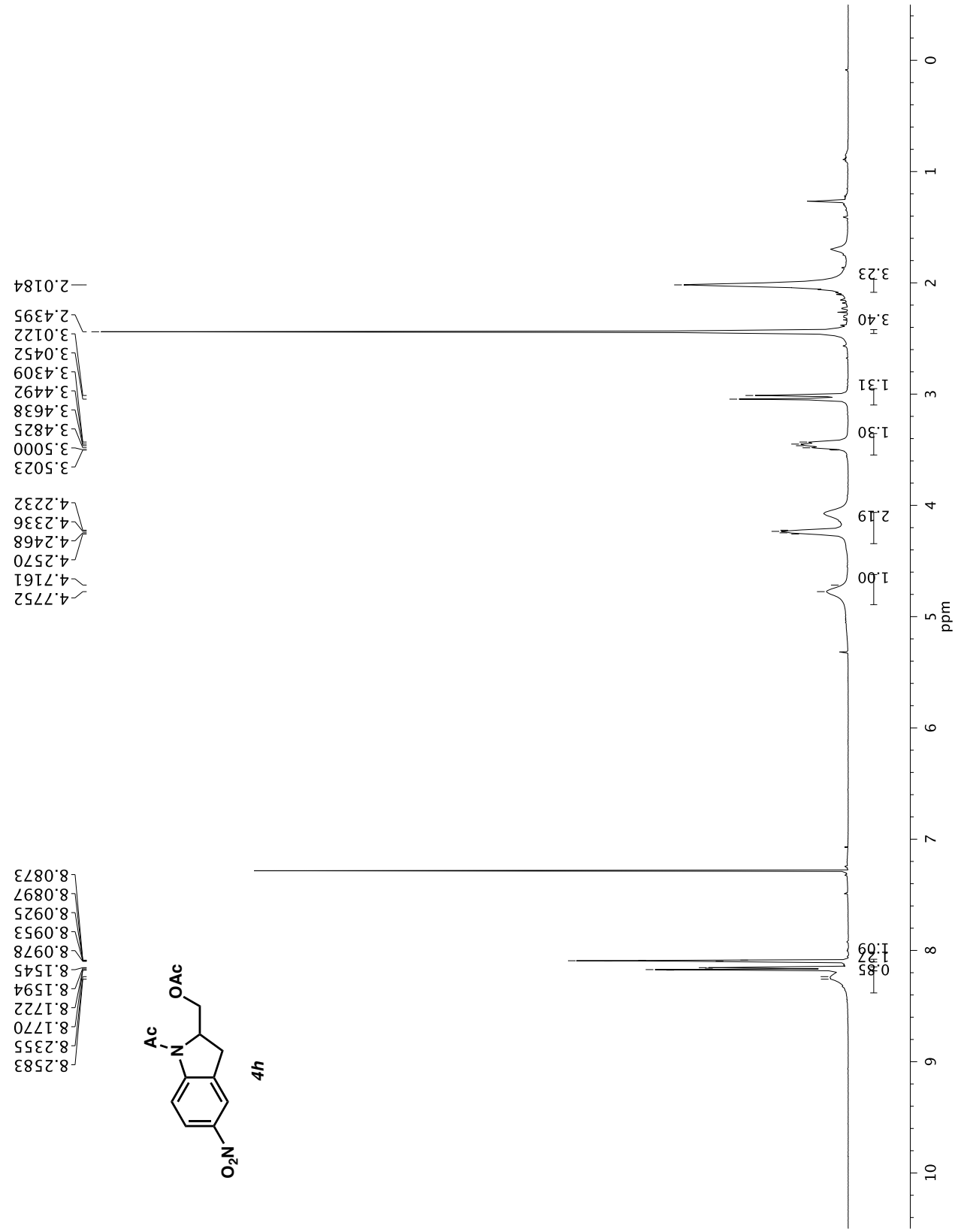
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4f**.

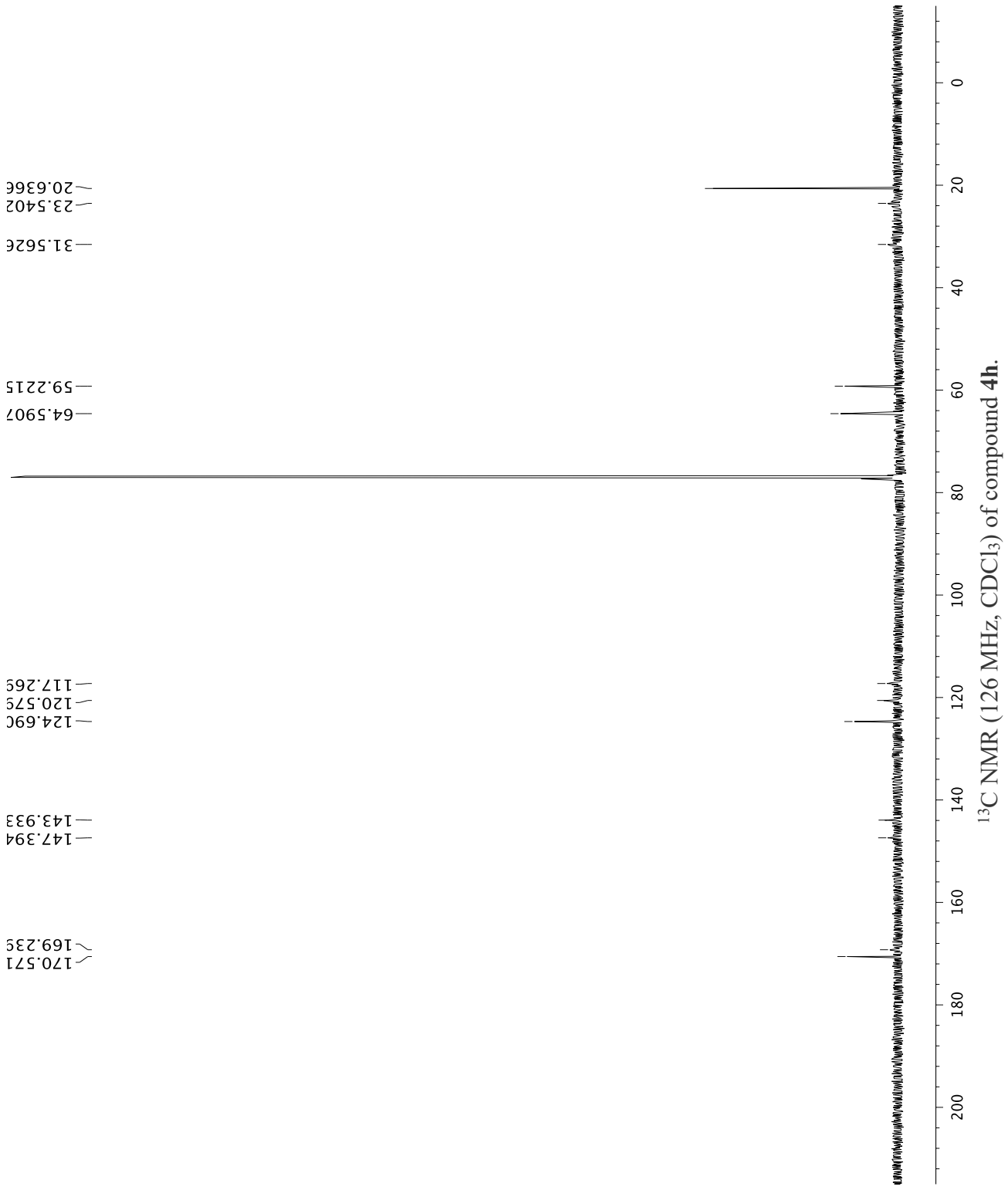


^{1}H NMR (500 MHz, $CDCl_3$) of compound **4g**.



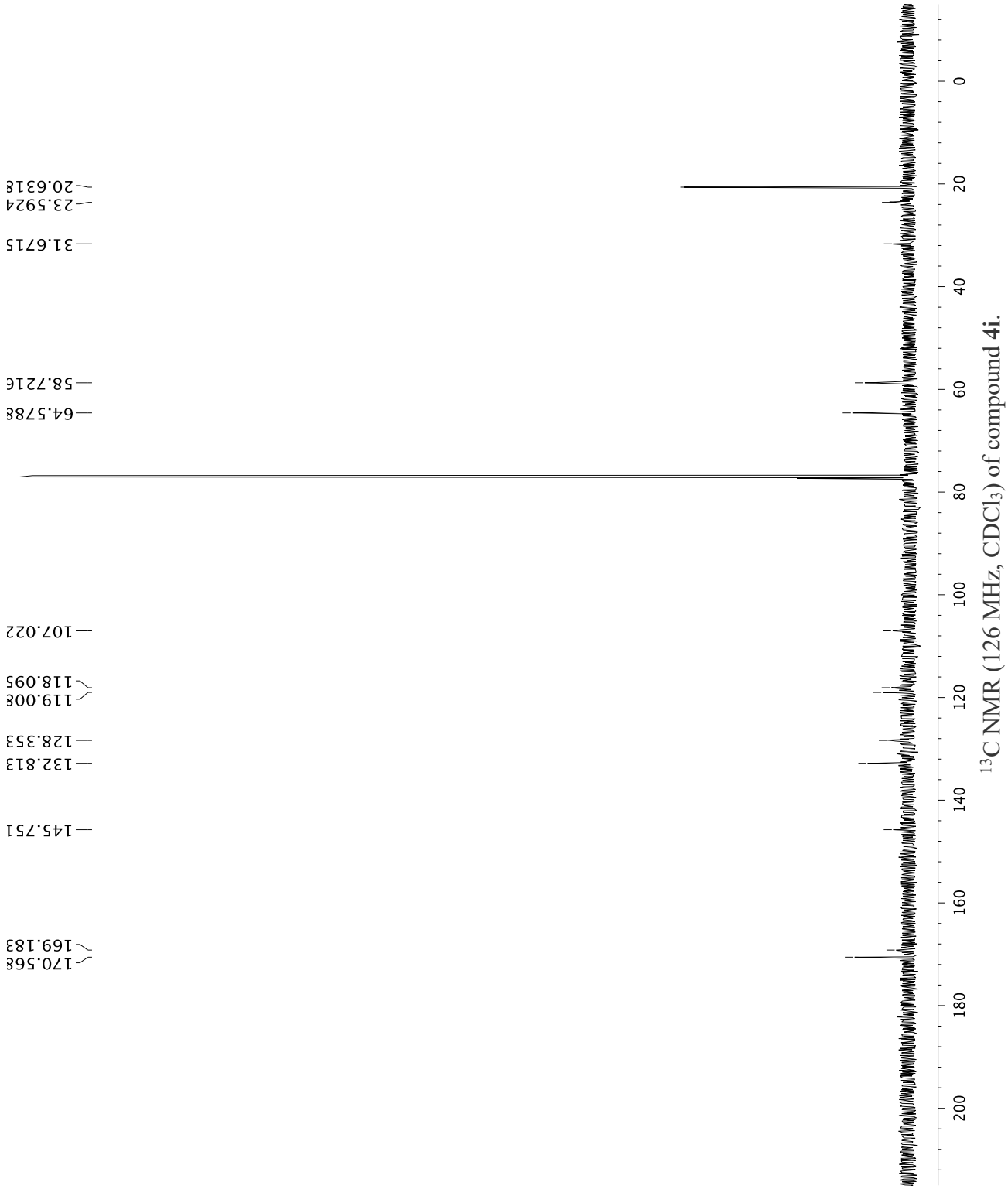
^{13}C NMR (126 MHz, $CDCl_3$) of compound **4g**.


8.2583
8.2355
8.1770
8.1722
8.1594
8.1545
8.0978
8.0953
8.0925
8.0897
8.0873
4.7752
4.7161
4.2570
4.2468
4.2336
4.2232
3.5023
3.5000
3.4825
3.4638
3.4492
3.4309
3.0452
3.0122
2.4395
2.0184
0.85
1.27
1.09
1.00
2.19
1.30
1.31
3.40
3.23
Ac
OAc
N
O_2N
4h
ppm
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4h**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **4h**.

^{1}H NMR (500 MHz, $CDCl_3$) of compound **4i**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **4i**.

CHAPTER 3

A Convenient Synthesis of Geminal-Dialkyl Dienes for Olefin Metathesis Polymerization

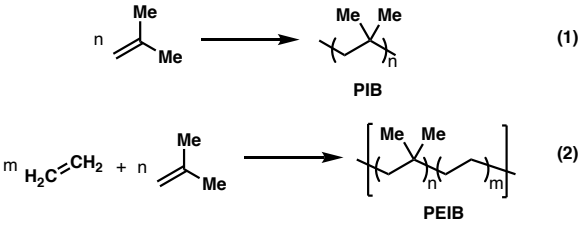
ABSTRACT

A new, robust synthesis of *gem*-dialkyl acyclic diene monomers has been developed. This route is scalable and flexible, allowing for the production of a wide range of diene monomers of different lengths and different *gem*-dialkyl substitution. The metathesis polymerization of these monomers and the hydrogenation of the resulting polyolefins leads to telechelic *gem*-dialkyl polyethylenes, which can be used as elastomers in the synthesis of polyurethanes and other block polymers.

3.1 INTRODUCTION

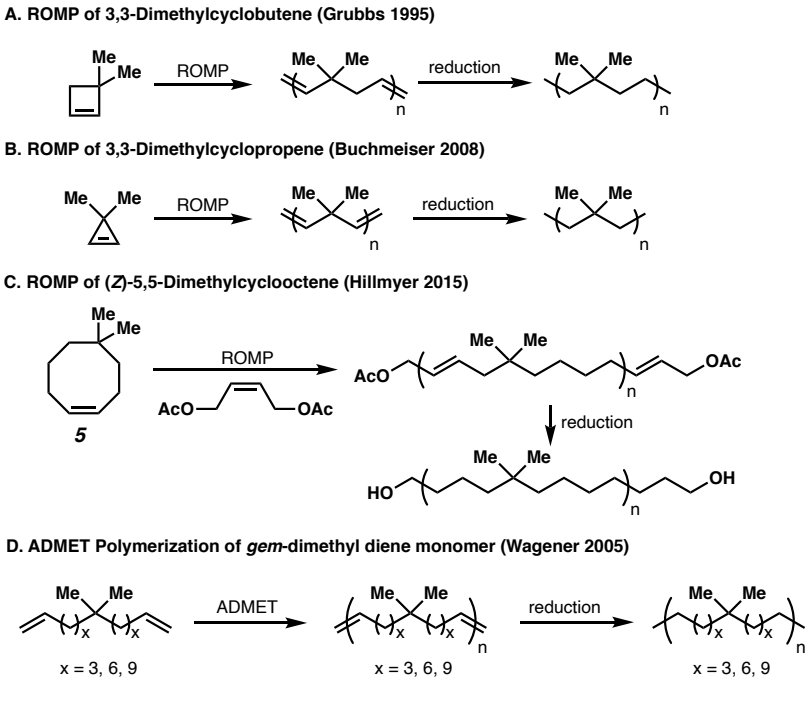
Poly(isobutylene) (PIB, Scheme 3.1.1, equation 1) is a homopolymer of isobutylene that has a number of unique properties, among them being low permeability, and excellent chemical compatibility and oxidative stability. PIB is particularly useful as a component of elastomeric polyurethanes as these properties provide superior performance over other polyester and polyether based materials. Poly(ethylene)-*co*-isobutylene (PEIB, Scheme 3.1.1, equation 2) is a copolymer of ethylene and isobutylene that has shown promise as an alternative to PIB, especially telechelic PEIB. The *gem*-dimethyl groups along the polymer backbone act as defects to interfere with the crystallization of the polymer, and so amorphous material with low glass transition temperature can be produced that is especially attractive for use in thermoplastic polyurethanes.

Scheme 3.1.1. Poly(isobutylene) and Poly(ethylene)-co-isobutylene



PEIB and its analogues have been difficult to produce due to the different reactivities of ethylene and isobutylene. Nevertheless, there are numerous examples of its synthesis using metallocene catalysts,[1] Lewis acid catalysts,[2] and olefin metathesis catalysts. Ring opening metathesis polymerization (ROMP) is well-suited for the production of these types of polymers, and it has been used by Grubbs (Scheme 3.1.2A),[3] Buchmeiser (Scheme 3.1.2B),[4] and the Hillmyer group (Scheme 3.1.2C) [5] to access PEIB and its related derivatives.

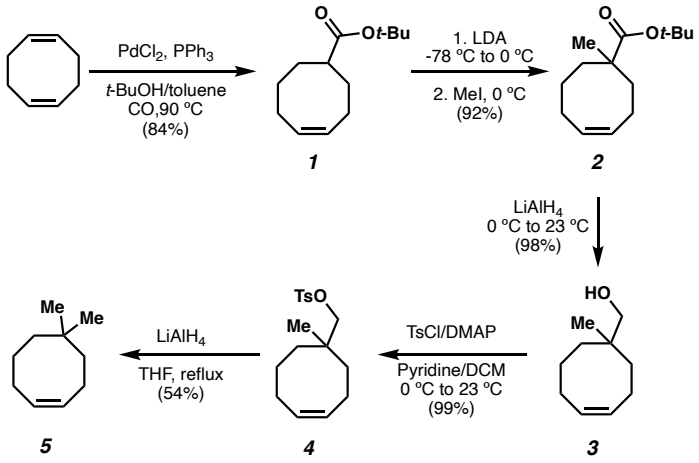
Scheme 3.1.2. PEIB Synthesis by Olefin Metathesis Polymerization



Linear polyolefins with precisely spaced *gem*-dimethyl groups, analogous to PEIB, have been synthesized using Acyclic Diene Metathesis (ADMET) polymerization, as first reported by Schwendeman and Wagener (Scheme 3.1.2D).[6,7] They showed that a higher frequency of *gem*-dimethyl groups in the polymer backbone led to amorphous polymers.[6] These "liquid rubbers" were incorporated into telechelic diols using Ru catalysis. Telechelic PEIB has also been synthesized using ring-opening metathesis polymerization (ROMP) from (*Z*)-5,5-dimethylcyclooct-1-ene (**5**)[5] and *cis*-1,4-diacetoxy-2-butene to afford polyolefins of different molecular weights (Scheme 3.1.2C). Hydrogenation of these polymers afforded the telechelic PEIB, which has been used in PEIB-polyurethane (PU) thermoplastic elastomers, which perform exceptionally well for biomedical applications.[8] Due to the amorphous PEIB component, the oxidative, hydrolytic, thermal stability, and the barrier properties of these copolymers are much improved than conventional PUs containing polyesters and polyethers as soft segments.[9]

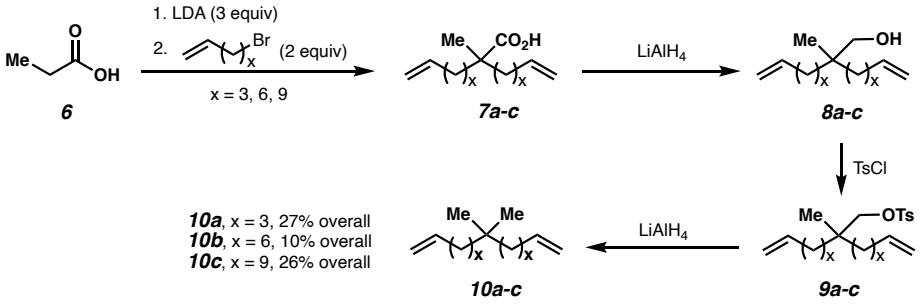
The synthesis of any polymer is predicated on the synthetic accessibility of the constituent monomers, which may be challenging to produce. For *gem*-dialkyl containing monomers, several different routes have previously been developed. Hillmyer and co-workers synthesized (*Z*)-5,5-dimethylcyclooct-1-ene (**5**) in five steps.[5] Starting from inexpensive 1,5-cyclooctadiene (1,5-COD), the *tert*-butyl ester **1** was prepared through Pd-catalyzed alkoxycarbonylation in 84% yield. Methylation with LDA and iodomethane gave α-methyl *tert*-butyl ester **2** in 92% yield. Then **2** was reduced to the primary alcohol **3** by $LiAlH_4$, and the alcohol was removed by tosylation and the subsequent reduction by $LiAlH_4$, which gave the monomer **5** in 54% yield (Scheme 3.1.3).

Scheme 3.1.3. Synthesis of 5,5-gem-dimethyl Cyclooctene by Hillmyer



As an alternative to ROMP, acyclic diene metathesis (ADMET) polymerization has also been used to prepare *gem*-dimethyl containing polymers. To prepare the monomer for ADMET polymerization, the Wagener group developed a synthetic route to diene monomers with different number of methylene units between the *gem*-dimethyl branch point and the terminal alkenes.[6] Propionic acid was treated with LDA, and alkylated by the addition of two equivalents of an alkenyl bromide to form the carboxylic acid intermediate (**7a-c**). Reduction of carboxylic acid with $LiAlH_4$ generates the primary alcohol (**8a-c**), which is deoxygenated through tosylation and reduction with $LiAlH_4$ to give the requisite symmetrical *gem*-dimethyl substituted diene monomers possessing 3, 6, and 9 methylene "spacer" units (**10a-c**, Scheme 3.1.4).

Scheme 3.1.4. Synthesis of Gem-dimethyl Diene Monomer by Wagener

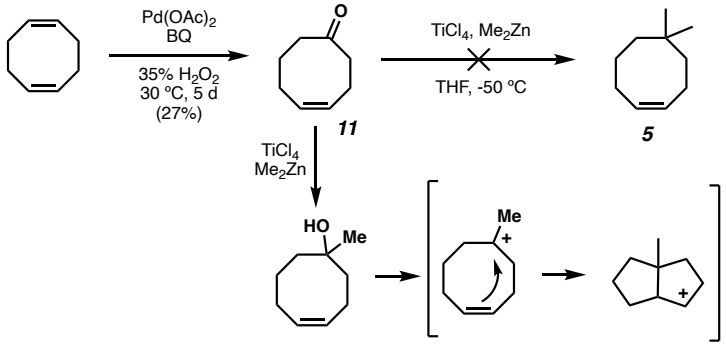


However, these routes to this type of *gem*-dimethyl substituted diene monomers required long synthetic sequences and wasteful materials. Due to the need of large quantities of these monomers (kilogram scale) in biomedical device development, we aimed to optimize a synthetic route from inexpensive sources, with fewer steps and operations. In this work, we have developed a new synthetic route to *gem*-dialkyl diene monomers for ADMET polymerization using the Claisen condensation of an unsaturated ester as the key step. This approach offers several benefits in terms of cost and scalability as well as synthetic flexibility. In particular, the unsaturated ester can be sourced from seed oils enabling a biorenewable route to these polymers. Telechelic polymers with different *gem*-dialkyl substituted diene monomers were prepared using Ru-catalyzed olefin metathesis, and the desired thermal properties (low glass transition temperature) has been accomplished.

3.2 DEVELOPMENT OF SYNTHETIC ROUTES TO *GEM*-DIALKYL DIENES

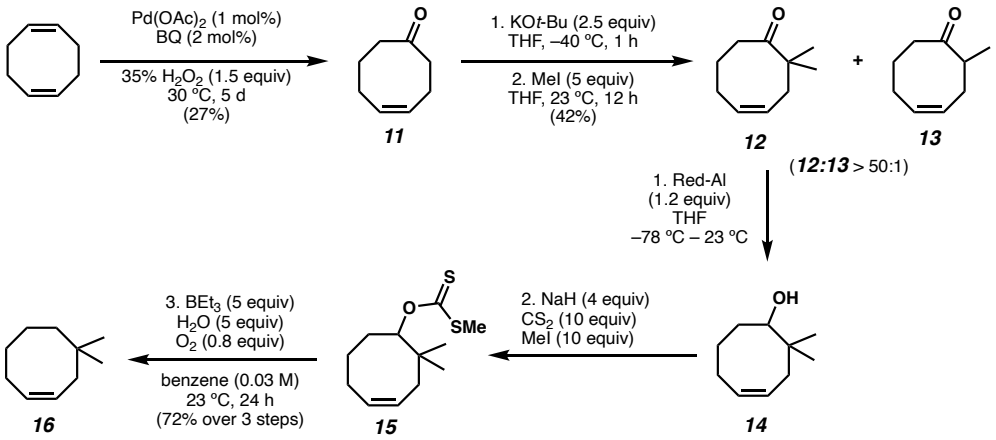
In Hillmyer's synthesis of *gem*-dimethyl cyclooctene monomers, the major disadvantage is the use of wasteful amount of tosyl chloride and dangerous $LiAlH_4$ reductant in order to remove the oxygen atom to furnish the all-carbon structure. Our initial proposal is to directly oxidize 1,5-COD to the ketone **11** in modified Wacker oxidation conditions with hydrogen peroxide as oxidant. *Geminal*-dimethylation through *in situ* formed $TiMe_2Cl_2$ reagent was reported by Reetz and co-workers in 1980,[10] and has been applied in the syntheses of a variety of *gem*-dimethyl containing molecules.[11] However, when the ketone **11** was subjected to the reaction conditions, a complex mixture of products was formed; the desired product **5** was never observed. We reasoned a fast transannular reaction caused the disappearance of alkenes after this reaction (Scheme 3.2.1).

*Scheme 3.2.1. Gem-dimethylation of Ketone **11**.*



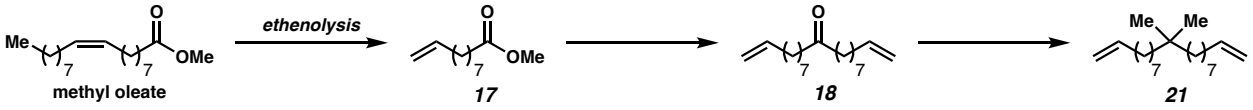
After several attempts to convert the ketone **11** with various approaches, we found that α-methylation with 2.5 equivalents KO*t*-Bu and 5 equivalents iodomethane gave the α,α-*gem*-dimethyl ketone **12** as the major product (dimethyl product **12**:monomethyl product **13** > 50:1), which was used as a precursor to the *gem*-dimethyl cyclooctene monomer upon deoxygenation. Ketone **12** was first reduced to the secondary alcohol **14** by Red-Al, then the alcohol was converted to xanthate **15**. Treatment of the crude xanthate **15** with BEt_3, H_2O and O_2 bubbling according to a radical deoxygenation conditions developed by Wood and co-workers,[12] finally provided the (*Z*)-4,4-dimethylcyclooct-1-ene (**16**, Scheme 3.2.2). However, this route still requires 5 steps to synthesize the *gem*-dimethyl cyclooctene monomer from 1,5-COD, and the scaling up of those reactions could be challenging.

*Scheme 3.2.2. Synthesis of Gem-dimethylcyclooctene Monomer **16***



In light of these synthetic difficulties, we decided to focus on the preparation of linear diene monomers instead of cyclooctene-based monomers. We were initially drawn to the Claisen condensation as a key step. The Claisen condensation reaction has been an important synthetic reaction for more than 100 years.[13] The β-ketoester intermediate from the Claisen condensation can be transformed into a symmetric linear ketone by hydrolysis and decarboxylation, and so the use of unsaturated esters provides linear dienes containing ketone groups, which are versatile intermediates upon further synthetic manipulations. Watson and Wagener used this transformation to synthesize diene monomers *en route* to ethylene/CO copolymers.[14] These long chain ketones provided a convenient starting point for our synthesis. Importantly, established ethenolysis chemistry can provide methyl 9-decenoate (**17**) from methyl oleate from plant oils,[15] providing an opportunity for a biorenewable synthesis of the ketone **18**, which can be used to synthesize the subsequent *gem*-dimethyl containing diene monomers such as **21** (Scheme 3.2.3).

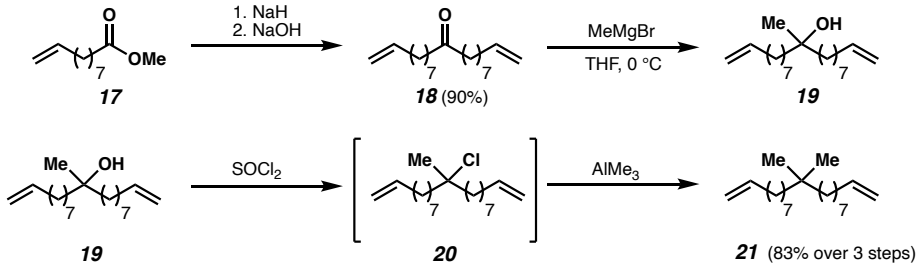
Scheme 3.2.3. Claisen Condensation Route



There are several reports of the direct transformation of ketones to the *gem*-dimethyl moiety. Unfortunately, $TiCl_2Me_2$,[16] $AlMe_3$,[17] and $AlMe_3$ in the presence of Me_3SiOTf[18] were all unsuccessful for the direct transformation of **18** to the desired monomer **21**. Instead, either olefin polymerization by $TiCl_2Me_2$ or the addition of a methyl nucleophile to the ketone by $AlMe_3$ was observed. The two methyl groups were installed sequentially: the first by a Grignard addition to **18**, and the second by S_N1 reaction of a subsequent tertiary alkyl halide with a nucleophilic alkylating reagent (Scheme 3.2.4). Precedent for the use of both alkyl zinc[10] and alkyl aluminum[19] nucleophiles to accomplish this transformation prompted us to explore these options. The addition of methylmagnesiumbromide to **18** proceeded in high yield and the resulting tertiary alcohol (**19**)

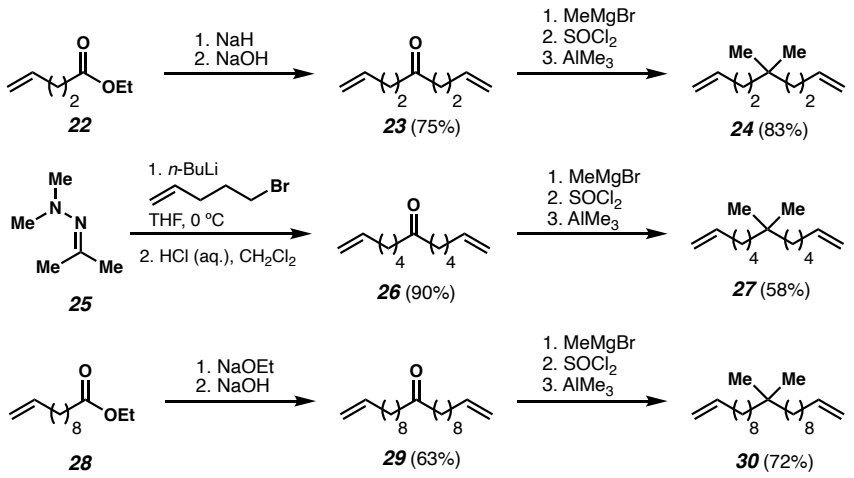
was easily transformed into the tertiary chloride **20** using $SOCl_2$. Substitution of **20** using $AlMe_3$ completed the sequence. The transformation of tertiary alcohol **19** to **21** can be achieved in a single pot procedure.[20] Me_2Zn was also a viable nucleophile, but $AlMe_3$ gave higher yields and is more economically viable.

*Scheme 3.2.4. Synthesis of Gem-dimethyl Diene Monomer **21***



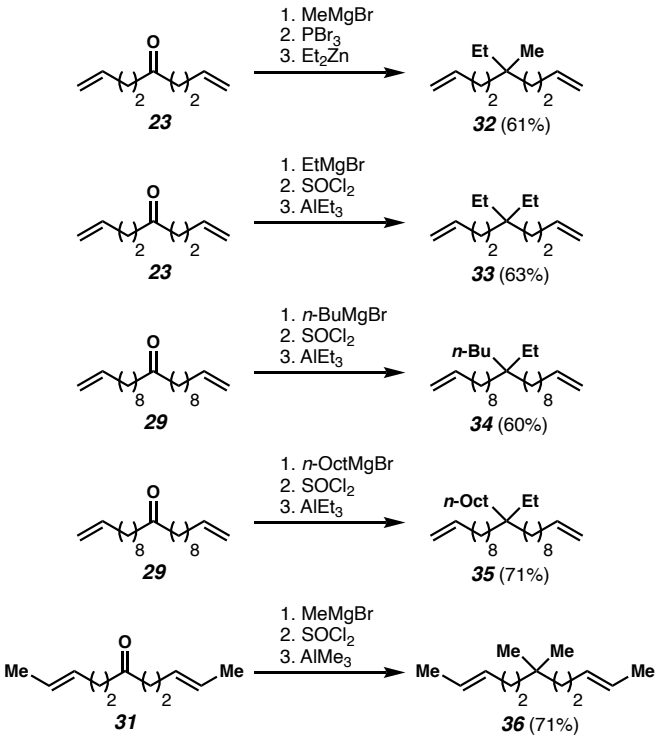
Following this success, several other linear diene monomers were prepared from ketones of varying lengths. Ethyl pent-4-enoate (**22**) was easily converted to nona-1,8-dien-5-one (**23**)[21] and the subsequent 9-carbon *gem*-dimethyl monomer **24**. Alkylation of acetone dimethylhydrazone **25** with 5-bromo-1-pentene provided the medium length ketone **26** in good yield (Scheme 3.2.5), which was readily transformed into the 13-carbon monomer **27** in 58% yield over three steps. Longer linear diene monomers were also synthesized from long chain unsaturated esters. Ethyl 10-undecenoate **28**, a precursor to Nylon,[22] was readily transformed into the ketone **29**, which was used to make the 21-carbon monomer **30** (Scheme 3.2.5).

Scheme 3.2.5. The Synthesis of Gem-dimethyl Diene Monomers with Different Lengths



The *gem*-dialkyl groups can easily be varied by using different Grignard and alkylzinc reagents or alkylaluminum reagents to provide both homo- and heterodialkyl substitution, as demonstrated by the preparation of **32**, **33**, **34**, and **35** (Scheme 3.2.6). This route tolerates both terminal and internal olefins with no detectable olefin isomerization, as demonstrated by the synthesis of **36** from **31**.

Scheme 3.2.6. Diene Monomers with Varying Alkyl Substitutions

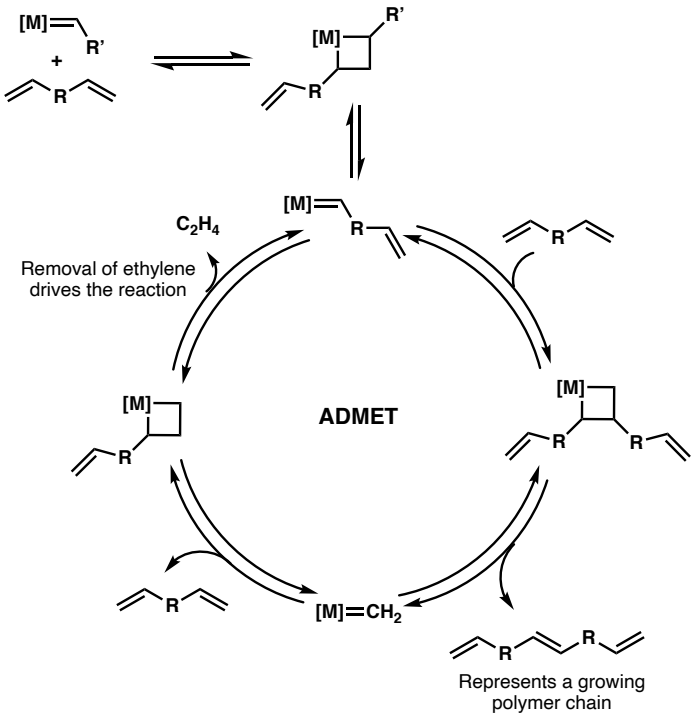


3.3 ADMET POLYMERIZATION OF *GEM*-DIALKYL DIENES

The two major types of metathesis polymerizations include ROMP and ADMET polymerization. ROMP is a chain-growth polymerization, whereas ADMET is a step-growth polymerization. The mechanism for ADMET polymerization is shown in Scheme 3.3.1. The olefin initially reacts with the metal alkylidene to form a metallacyclobutane intermediate by reversible [2+2] cycloaddition. Subsequent cycloreversion gives the growing polymer and a new alkylidene species, which undergoes further coordination, cycloaddition and cycloreversion. The productive pathway in ADMET polymerization of terminal olefins features the generation of the methylidene carbene catalyst and the condensate (e.g. ethylene). Note that each step in the mechanism is completely reversible. Therefore, the constant removal of condensate from the reaction mixture

is required to drive the equilibrium towards chain growth. ADMET polymerization was firstly observed in the late 1980s by Wagener and Lindmark-Hamburg[23] while studying the condensation of unconjugated α,ω-dienes with the $WCl_6/EtAlCl_2$ catalyst system. The development of well-defined ruthenium-based catalyst allowed ADMET to become a feasible and useful method of polymerization.[24]

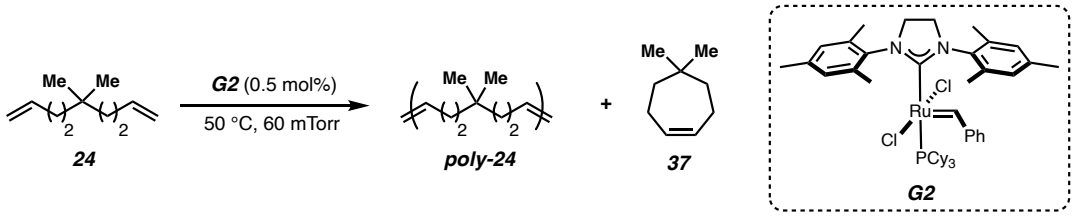
Scheme 3.3.1. Mechanism of ADMET Polymerization



The ADMET polymerization[25] of **21**, **24**, **27**, and **30** using the 2nd generation Ru catalyst (**G2**) produced the desired polyolefins with targeted molecular weights of 2000 g/mol. The polymerization of **24** was complicated by the formation of both polyolefin **poly-24** and the 7-membered cyclic olefin **37** (Scheme 3.3.2). ADMET polymerization is well-known to produce cyclic oligomers[26] as the reaction proceeds, but the *gem*-dimethyl substitution results in a pronounced Thorpe-Ingold effect[27] that favors cyclization. The cyclic olefin **37** also possesses low ring-strain, and did not fully incorporate into the growing polymer chain; prolonged reaction times (up to 5 days) did not result in full consumption of **37** (equilibrium ratios of ~3:1 **poly-24**:**37** were

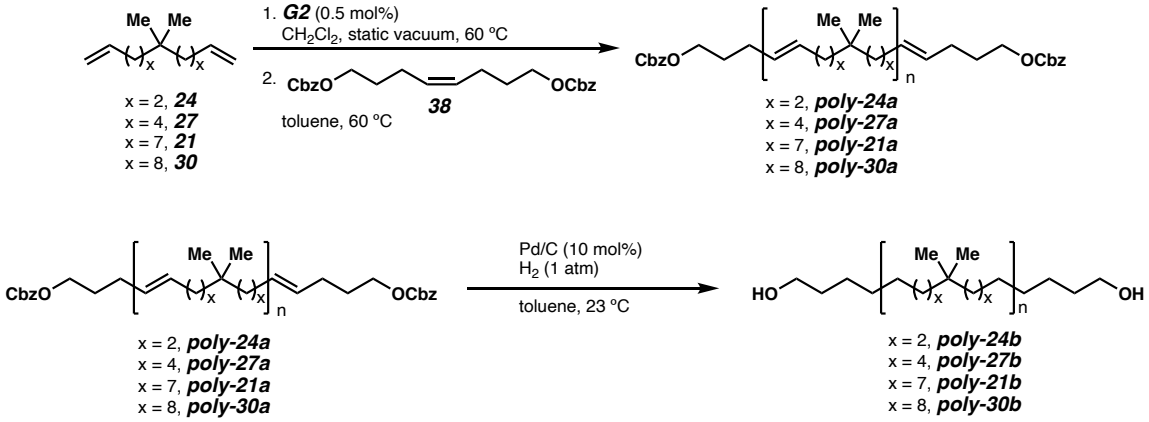
observed, in both the ADMET polymerization of **24** and **36**). However, once the desired molecular weight is achieved, **37** can easily be removed *in vacuo* and recycled in a subsequent ring-opening polymerization. The ROMP of **37** afforded the same distribution of **poly-24** and **37** as was achieved in the ADMET of **24**.

*Scheme 3.3.2. ADMET Polymerization of Short Chain Monomer **24***



The longer diene monomers (**21**, **27** and **30**) did not suffer from the competing ring-closing metathesis and readily polymerized using **G2** under static vacuum.[30] We used the "polymerization/depolymerization" method developed by Wagener[7] to produce the target telechelic diols. The chain transfer agent (CTA) **38** was added to the polyolefin mixture after sufficient reaction time to cleave the longer polyolefins and install the protected telechelic endgroups. Hydrogenation of the unsaturated polymers was accomplished using Pd/C under H_2 and the resulting telechelic PEIB derivatives were isolated in high yield after filtration and concentration *in vacuo* (Scheme 3.3.3).

Scheme 3.3.3. Synthesis of Gem-dimethyl Substituted Telechelic Polymers



Differential scanning calorimetry (DSC) was used to determine the effects of substitution and molecular weight on the thermal behavior for the series of polymers (see DSC traces in Figure 3.5.1). The measured T_g values (Table 3.3.1) were in agreement with those for the PEIB analogues prepared by both Wagener[6,7] and Hillmyer[5], and a higher density of substitution (e.g. **poly-24b**) resulted in amorphous materials without melting points. Polymers derived from the longer monomers **21** and **30** displayed broad, multimodal melting points indicating the semicrystalline nature of the longer saturated segments of the polymer, as described by Wagener.[7]

Table 3.3.1. Molecular Weight, Polydistribution, and Thermal Properties of Telechelic Polymers

Polymer	M_n[a]	**PDI**[b]	T_g	T_m
Poly-21b	4200	1.4	No T_g observed	–50 – 8 °C[c]
Poly-24b	2200	1.4	–60 °C	–[d]
Poly-27b	2000	1.5	–60 °C	–[d]
Poly-30b-1	3100	1.5	–50 °C	–24 – 0 °C[c]
Poly-30b-2	6300	1.1	–60 °C	–14 – 10 °C[c]
Poly-30b-3	17200	1.5	–26 °C	–12 – 50 °C[c]
Poly-30b-4	28700	1.7	–30 °C	30 °C
Poly-32b	3200	1.1	–52 °C	–[d]
Poly-34b	6800	1.4	–59 °C	–18 °C[c]

[a] Determined by ^{1}H NMR [b] PDI = M_w/M_n (determined by GPC) [c] broad melting point [d] no melting point observed

3.4 CONCLUSIONS

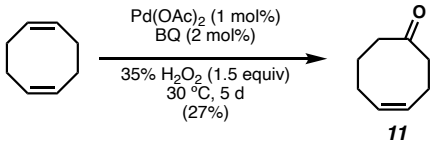
We have described a new synthetic route to *gem*-dialkyl diene monomers for ADMET polymerization. This route enables the use of unsaturated fatty acid esters as a raw material source, offers several benefits in terms of cost and scalability as well as synthetic flexibility. Several different diene monomers have been prepared and polymerized using Ru-catalyzed ADMET polymerization to access short (M_n ~2–7 kDa) amorphous telechelic polymers. These telechelic polymers are desirable as the soft segment of polyurethane elastomers for biomedical applications, and this work demonstrates a cost-effective and convenient route for their preparation.

3.5 EXPERIMENTAL METHODS AND ANALYTICAL DATA

3.5.1 Materials and Methods

Unless otherwise stated, all reactions were performed under argon atmosphere using oven dried glassware. Anhydrous solvents were dried using activated alumina and stored in Schlenk flasks over activated 3 Å molecular sieves. All reagents were purchased from commercial suppliers and used as received. NMR spectra were collected using Varian 500 or 600 MHz spectrometers or a Bruker 400 MHz spectrometer. Mass spectrometry was performed at the Caltech Mass spectrometry facility. Differential Scanning Calorimetry was performed using a Mettler Toledo DSC 3+ Star System. Ethyl-(*E*)-hex-4-enoate,[28] and nona-1,8-dien-5-one[21] were synthesized according to literature precedent.

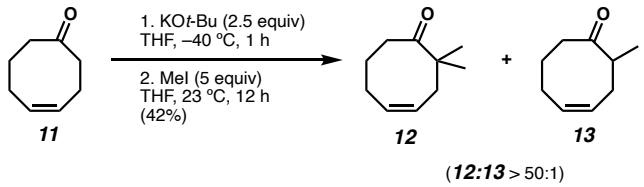
3.5.2 Experimental Procedures



11

(*Z*)-cyclooct-4-en-1-one (11): According to a known procedure,[29] to a solution of hydrogen peroxide (35% in water, 5 mL, 60 mmol) was added to a mixture of palladium acetate (90 mg, 0.4 mmol), benzoquinone (87 mg, 0.8 mmol) and 1,5-cyclooctadiene (5.4 mL, 40 mmol). The mixture was stirred for 5 days at 30° C. The mixture was poured into Et_2O (100 mL) and water was added (100 mL) then the mixture was slowly basified with 1M NaOH solution while cooling with ice. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were twice washed with 1M NaOH and dried over Na_2SO_4. Distillation under reduced pressure afforded ketone **11** (1.36 g, 27% yield) as a colorless oil.

Spectral data matched those reported in the literature.[30]



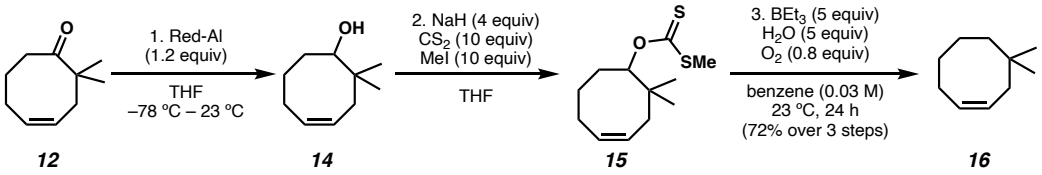
(*Z*)-2,2-dimethylcyclooct-4-en-1-one (12): To a stirred solution of KO*t*-Bu (5.61 g, 2.5 equiv) in THF (100 mL) was added ketone **11** (2.48 g, 20.0 mmol) in THF (20 mL). The solution was stirred for 1 hour at –40 ºC, and MeI (6.3 mL, 5.0 equiv) was added. The reaction mixture was slowly warmed to 23 ºC and stirring was continues for 20 hours. Water (50 mL) was then added and the aqueous phase was extracted by Et_2O (3 × 50 mL). GC analysis showed > 50:1 ratio of products **12** and **13**, and pure compound **12** can be isolated by column chromatography (SiO_2, 10:1 pentane/Et_2O) as a colorless liquid (1.29 g, 42%).

TLC (10:1 pentane/Et_2O): R_f= 0.4 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 – 5.56 (m, 1H), 2.45 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.25 (d, *J* = 7.2 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.64 – 1.54 (m, 1H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.5, 131.9, 129.2, 52.6, 37.8, 36.5, 27.3, 26.3, 23.7.

HRMS (FAB+, m/z): calc'd for $C_{10}H_{17}O$ $[M+H]^+$ 153.1279, found: 153.1276.



(*Z*)-4,4-dimethylcyclooct-1-ene (16): Ketone **12** (2.10 g, 13.8 mmol) in THF (50 mL) was added to a solution of Red-Al (16.6 mmol, 1.2 equiv) in THF (40 mL) dropwise at –78 °C under argon atmosphere. After stirring at the same temperature for 3 hours, the solution was quenched with 0.1 M HCl (100 mL), and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (50 mL) and brine

(50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a plug of silica with Et_2O wash. The crude alcohol product **14** was obtained as a colorless oil (2.23 g), which was used in the next step without further purification.

To a suspension of NaH (60% in mineral oil, 2.24 g, 96 mmol, 4.0 equiv) in THF (100 mL) at 0 °C was added alcohol **14** (2.23 g, 14 mmol, 1.0 equiv) in THF (20 mL). The mixture was stirred for 30 min, at which point CS_2 (8.4 mL, 140 mmol, 10.0 equiv) was added. The mixture was stirred for an additional 30 min, at which point iodomethane (8.7 mL, 140 mmol, 10.0 equiv) was added. The reaction mixture was allowed to warm to room temperature for 3 hours before being quenched with MeOH (50 mL) and evaporated *in vacuo*. The residue was dissolved in EtOAc (100 mL), washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. Column chromatography (SiO_2, hexanes) afforded crude xanthate **15** (4.42 g) as a yellow oil.

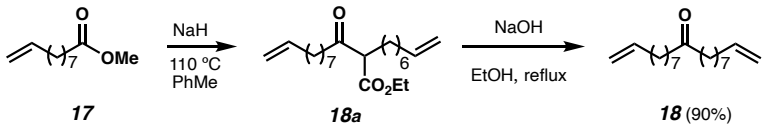
Then, methyl xanthate **15** (733 mg, 3 mmol, 1.0 equiv) was dissolved in a flame-dried 500 mL flask with benzene (100 mL), combined with H_2O (0.27 mL, 15 mmol, 5.0 equiv) and allowed to stir for 1 h. Argon gas was then bubbled through the solution for a period of 1 h, after which, a solution of BEt_3 (1.0 M in THF, 15 mL, 15 mmol, 5.0 equiv) was added via syringe pump over 1 h. On completion of BEt_3 addition, dry oxygen (54 mL, 2.4 mmol O_2, 0.8 equiv) was introduced via syringe pump at a rate of 1.2 ml/hr through a stainless steel cannula positioned beneath the reaction surface. Upon completion of air addition, hydrogen peroxide (30 % in water, 50 mL) and sodium hydroxide (3.0 M in water, 50 mL) were introduced simultaneously into the reaction mixture (*Caution*: reaction is exothermic). After stirring for 10 min, the solution was diluted with brine (100 mL), and the aqueous layer was extracted with EtOAc (3 × 100 mL). Combined organic portions were dried over anhydrous sodium sulfate, filtered, and concentrated. Distillation under reduced pressure afforded **16** as a colorless oil (297 mg, 72%).

TLC (pentane): R_f= 0.9 ($KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 – 5.48 (m, 2H), 2.17 – 2.04 (m, 2H), 1.92 (d, *J* = 8.2 Hz, 2H), 1.49 (dd, *J* = 6.0, 3.2 Hz, 4H), 1.33 – 1.23 (m, 2H), 0.89 (s, 6H).

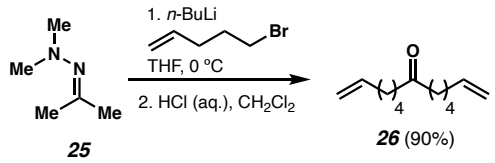
^{13}C NMR (126 MHz, $CDCl_3$) δ 131.4, 128.9, 39.7, 37.5, 36.1, 30.3, 29.0, 26.8, 23.5.

HRMS (EI+, m/z): calc'd for $C_{10}H_{18}$ $[M]^{+\bullet}$ 138.1409, found: 138.1408.



Nonadeca-1,18-dien-10-one (18): A 100 mL three-necked round bottom flask was fitted with a dropping funnel and two ground glass stoppers and charged with a magnetic stirbar, NaH (60 wt% in mineral oil, 3.7 g, 92 mmol, 1.2 equiv), and toluene (25 mL). This suspension was heated to 100 °C and a solution of methyl 9-decenoate (14.3 g, 80 mmol, 1 equiv) in toluene (10 mL) was added dropwise over the course of 30 min. The reaction mixture was then heated to 110 °C with stirring for 24 h, cooled to ambient temperature and quenched by the slow addition of MeOH. The solvent was removed *in vacuo* and the residue was suspended in EtOH (50 mL) and water (25 mL). NaOH (1.6 g, 1.0 equiv) was added and the reaction mixture was heated to reflux for 2 h. After cooling to ambient temperature, the reaction mixture was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with water (3 × 50 mL), brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Crystallization with MeOH afforded **18** as a white solid (10.2 g, 90% yield over two steps)

Spectral data matched those reported in the literature.[31]

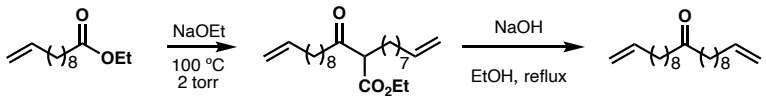


Trideca-1,12-dien-7-one (26): To a stirred solution of hydrazone **25** (4.0 g, 40 mmol, 1.0 equiv) in THF (80 mL) was added *n*-butyl lithium solution (16.8 mL, 2.5 M solution in hexanes, 42 mmol, 1.05 equiv). After stirring 30 minutes at 0 ºC, 5-bromo-1-pentene (4.8 mL, 40 mmol, 1.0 equiv) was added and the reaction mixture was stirred for 1 hour at 23 ºC. Then the reaction mixture was cooled to 0 ºC again and *n*-butyl lithium solution (16.8 mL, 2.5 M solution in hexanes, 42 mmol, 1.05 equiv) was added. After stirring 30 minutes at 0 ºC, 5-bromo-1-pentene (4.8 mL, 40 mmol, 1.0 equiv) was added again and the reaction mixture was stirred for 2 hours at 23 ºC before quenched by saturated NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction mixture was dissolved in CH_2Cl_2 (40 mL), and HCl solution (16 mL, 3.0 M) was added. After 12 h, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases are washed with saturated $NaHCO_3$ solution (100 mL). Column chromatography (SiO_2, 10:1 hexanes/EtOAc) gave **26** as a colorless oil (7.0 g, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 2H), 4.94 – 4.77 (m, 4H), 2.32 – 2.23 (m, 4H), 1.97 – 1.88 (m, 4H), 1.46 (dt, *J* = 15.2, 7.3 Hz, 4H), 1.30 – 1.20 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.2, 138.5, 114.6, 42.6, 33.6, 28.5, 23.3.

HRMS (EI+, m/z): calc'd for $C_{13}H_{22}O$ $[M]^{+\bullet}$ 194.1671, found: 194.1646.

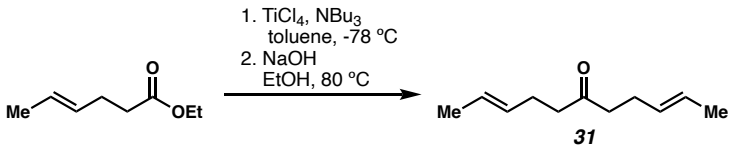


Henicosa-1,20-dien-11-one (29): A 500 mL flamed-dried round bottom flask charged with ethyl 10-undecenoate (21.0 g, 100 mmol, 1.0 equiv) and sodium ethoxide (3.4 g, 50 mmol, 0.5 equiv) was equipped with a reflux condenser and a vacuum adapter. The reaction was stirred at 100 ºC under a dynamic vacuum (2 torr) for 12 hours to remove the ethanol produced. After the reaction was cooled to 23 ºC, the crude β-keto ester **29a** was dissolved in ethanol (50 mL) and 2 M NaOH solution (20 mL, 1.0 equiv) was added. The reaction mixture was warmed to reflux for 2 hours and cooled to 23 ºC. A white solid precipitated and was collected by filtration and recrystallized from refluxing methanol, to give ketone **29** as a white solid (7.47 g, 63% yield over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 2H), 4.97 – 4.82 (m, 4H), 2.31 (t, *J* = 7.5 Hz, 4H), 2.01 – 1.91 (m, 4H), 1.49 (q, *J* = 7.0 Hz, 4H), 1.34 – 1.25 (m, 4H), 1.24 – 1.17 (m, 16H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.7, 139.2, 114.2, 42.8, 33.8, 29.4, 29.3, 29.3, 29.1, 28.9, 23.9.

HRMS (EI+, m/z): calc'd for $C_{21}H_{38}O$ $[M]^{+\bullet}$ 306.2923, found: 306.2927.



An oven-dried 500 mL three-necked round bottom flask was equipped with a magnetic stirbar and fitted with two rubber septa and a ground glass flow adaptor to introduce inert atmosphere. This flask was charged with (*E*)-hex-4-enoate (20 g, 140 mmol) and NBu_3 (17 mL,

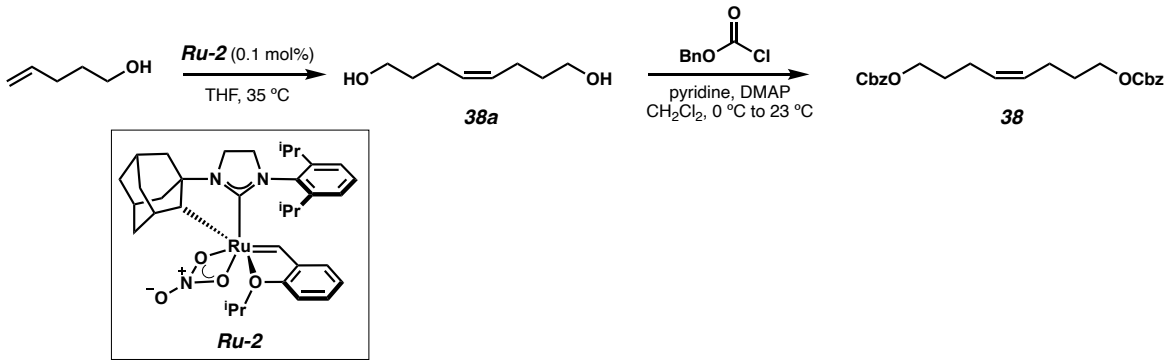
140 mmol) via syringe. Anhydrous toluene (350 mL) was added by cannula, and the reaction mixture was cooled to –78 °C. $TiCl_4$ (18.4 mL, 168 mmol) was added dropwise via syringe over twenty minutes, causing the reaction mixture to become deep red in color. The reaction mixture was stirred with warming to ambient temperature for 10 h, and saturated aqueous $NaHCO_3$ was carefully added to quench the reaction. The organic layer was separated, the aqueous layer was extracted with Et_2O (3 × 25 mL), and the combined organic layers were washed with water (20 mL), brine (2 × 20 mL), dried over $MgSO_4$, and concentrated to a clear, yellow oil.

The yellow oil was dissolved in EtOH (200 mL) and water (50 mL) and NaOH pellets were added (3 g). The reaction mixture was heated to 85 °C and monitored by TLC (5% Et_2O in hexanes) until the starting material was fully consumed. The reaction mixture was concentrated and extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with water (3 × 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The product **31** was purified by column chromatography (SiO_2, 5% Et_2O in hexanes) to yield a clear, pale yellow oil (11 g, 60 mmol, 85 %)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.49 – 5.34 (m, 4H), 2.43 (t, J = 7.4 Hz, 4H), 2.28 – 2.19 (m, 4H), 1.65 – 1.59 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.4, 129.7, 126.0, 42.8, 26.9, 18.0.

HRMS (EI+) calc'd for $C_{11}H_{18}O$ $[M]^{+\bullet}$ 166.1358; found 166.1346



(*Z*)-dibenzyl oct-4-ene-1,8-diyl bis(carbonate) (**38**): In a nitrogen-filled glovebox, 4-penten-1-ol (1.72 g, 20 mmol) was dissolved in 6 mL THF in a 20 mL vial equipped with a stir bar, and **Ru-2** (13.5 mg, 0.1 mol%) was added. The vial was placed on a 35 ºC stir plate without capping and stirring was continued for 4 hours. At that time the reaction progress was monitored by GC analysis to ensure full conversion, and the vial was brought outside the glovebox and the reaction mixture was quenched with a few drops of ethyl vinyl ether. Column chromatography (SiO_2, 2:1 hexanes/EtOAc) gave **38a** as a colorless oil (1.06 g, 74% yield).

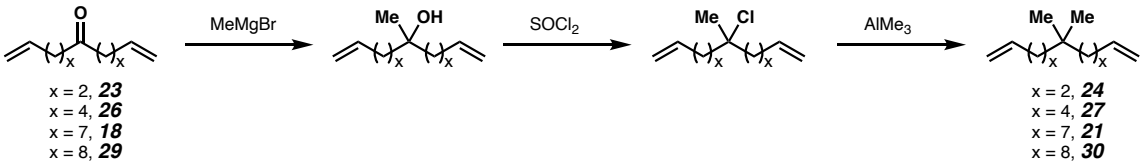
To the diol **38a** (1.06 g, 7.35 mmol, 1.0 equiv) in 30 mL CH_2Cl_2 , pyridine (3.0 mL, 36.75 mmol, 5.0 equiv) and DMAP (180 mg, 1.47 mmol, 0.2 equiv) was added sequentially at 0 ºC. Then benzyl chloroformate (4.2 mL, 29.4 mmol, 4.0 equiv) was added dropwisely. The mixture was left to stir at 23 ºC for overnight before it was quenched with 1 M HCl (30 mL). The aqueous phase was extracted by Et_2O three times. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (SiO_2, 9:1 hexanes/EtOAc) gave **38** as a colorless oil (2.52 g, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 10H), 5.38 (ddd, *J* = 5.6, 4.4, 1.1 Hz, 2H), 5.15 (s, 4H), 4.13 (t, *J* = 6.6 Hz, 4H), 2.18 – 2.03 (m, 4H), 1.72 (dq, *J* = 8.2, 6.7 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 135.4, 129.5, 128.7, 128.6, 128.5, 69.6, 67.7, 28.6, 23.4.

HRMS (FAB+, m/z): calc'd for $C_{24}H_{29}O_6$ $[M+H]^+$ 413.1964, found: 413.1961.

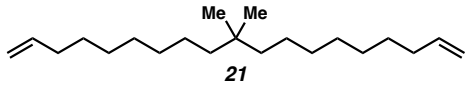
General Procedure A for *gem*-dimethylation of ketones:



In a flame-dried round-bottom flask, ketone (1.0 equiv) was dissolved in THF and the reaction mixture was cooled to 0 ºC. Methylmagnesium bromide solution (3.0 M solution in diethyl ether, 1.5 equiv) was added dropwise, and the reaction mixture was slowly warmed to 23 ºC. After 1 hour, the reaction mixture was cooled to 0 ºC, and quenched by saturated NH_4Cl solution. The aqueous phase was extracted with Et_2O twice, dried over anhydrous $MgSO_4$, filtered over a short silica plug, and concentrated under reduced pressure.

The crude tertiary alcohol was transferred into a Schlenk flask (with one side arm fitted with a glass stopcock) with dry CH_2Cl_2. The residual solvent was removed by connecting the side arm to vacuum. The flask was back-filled with argon and cooled to 0 ºC, and then $SOCl_2$ (2.5 equiv) was added slowly. A minimal amount of CH_2Cl_2 can be added to aid with stirring. The reaction mixture was stirred at 0 ºC for 1 hour, and the reaction progress can be monitored by TLC (using Al_2O_3 plate). The side arm of the Schlenk flask was reconnected to vacuum and excess $SOCl_2$ was removed at 0 ºC. Then the crude tertiary chloride product was dissolved in CH_2Cl_2 (0.3 M) and the reaction mixture was cooled to –78 ºC. Trimethylaluminum (2.0 M solution in hexanes, 2.0 equiv) was added dropwise. The reaction mixture was slowly warmed to 23 ºC and stirred for 4

hours and then quenched with aqueous HCl solution (1.0 M) at 0 ºC. The aqueous layer was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The *gem*-dimethylation products were purified by column chromatography (SiO_2, 100% hexanes) or distillation.



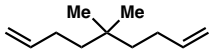
21

10,10-dimethylnonadeca-1,18-diene (**21**): Prepared according to General Procedure A from ketone **18** (10.2 g, 37 mmol) as a colorless liquid (9.1 g, 83% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 2H), 5.00 (dq, *J* = 17.1, 1.7 Hz, 2H), 4.93 (ddt, *J* = 10.2, 2.4, 1.2 Hz, 2H), 2.07 – 2.00 (m, 4H), 1.42 – 1.09 (m, 24H), 0.81 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 114.1, 42.0, 33.8, 32.6, 30.6, 29.6, 29.2, 29.0, 27.3, 24.0.

HRMS (EI+, m/z): calc'd for $C_{21}H_{40}$ $[M]^{+\bullet}$ 292.3130, found: 292.3144.



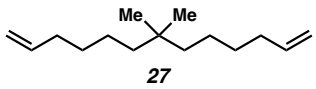
24

5,5-dimethylnona-1,8-diene (**24**): Prepared according to General Procedure A from ketone **23** (25 g, 181 mmol) as a colorless liquid (13 g, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 2H), 4.99 (dq, *J* = 17.1, 1.7 Hz, 2H), 4.94 – 4.86 (m, 2H), 2.02 – 1.93 (m, 4H), 1.30 – 1.22 (m, 4H), 0.86 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.80, 113.77, 41.06, 32.65, 28.58, 27.08.

HRMS (EI+, m/z): calc'd for $C_{11}H_{20}$ $[M]^{+\bullet}$ 152.1565, found: 152.1561.



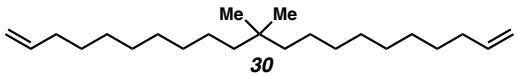
27

7,7-dimethyltrideca-1,12-diene (**27**): Prepared according to General Procedure A from ketone **26** (1.94 g, 10 mmol) as a colorless liquid (1.2 g, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 2H), 4.98 – 4.81 (m, 4H), 2.03 – 1.94 (m, 4H), 1.32 – 1.23 (m, 4H), 1.19 – 1.05 (m, 8H), 0.75 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 114.1, 41.8, 33.9, 32.7, 29.9, 27.3, 23.5.

HRMS (EI+, m/z): calc'd for $C_{15}H_{28}$ $[M]^{+\bullet}$ 208.2191, found: 208.2177.



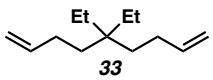
30

11,11-dimethylhenicosa-1,20-diene (**30**): Prepared according to General Procedure A from ketone **29** (7.47 g, 24.4 mmol) as a colorless liquid (5.66 g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 2H), 5.08 – 4.89 (m, 4H), 2.14 – 2.00 (m, 4H), 1.40 (q, *J* = 6.9 Hz, 4H), 1.35 – 1.12 (m, 24H), 0.84 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 114.2, 42.1, 34.0, 32.7, 30.8, 29.8, 29.7, 29.3, 29.1, 27.5, 24.2.

HRMS (EI+, m/z): calc'd for $C_{23}H_{44}$ $[M]^{+\bullet}$ 320.3443, found: 320.3425.



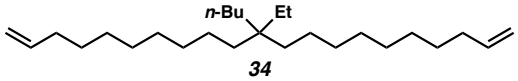
33

5,5-diethylnona-1,8-diene (**33**): Prepared according to modified General Procedure A from ketone **23** (276 mg, 2.0 mmol), EtMgBr, and $AlEt_3$ to afford **33** as a clear, colorless oil (230 mg, 63% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 2H), 5.00 (dq, *J* = 17.1, 1.6 Hz, 2H), 4.91 (ddt, *J* = 10.0, 2.3, 1.2 Hz, 2H), 1.96 – 1.87 (m, 4H), 1.26 – 1.19 (m, 8H), 0.75 (t, *J* = 7.5, 1.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 113.9, 37.3, 34.9, 28.0, 27.7, 7.6.

HRMS (EI+) calc'd for $C_{13}H_{24}$ $[M]^{+\bullet}$ 180.1878; found 180.1894.



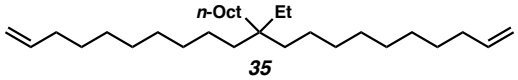
34

11-butyl-11-ethylhenicosa-1,20-diene (**34**): Prepared according to modified General Procedure A from ketone **29** (918 mg, 3 mmol) with *n*-butylmagnesium chloride solution (2.0 M solution in diethyl ether, 1.5 equiv) and triethylaluminum (2.0 equiv). **34** was obtained as a colorless liquid (680 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 2H), 4.96 – 4.82 (m, 4H), 2.01 – 1.92 (m, 4H), 1.35 – 1.25 (m, 4H), 1.25 – 1.11 (m, 24H), 1.07 – 0.99 (m, 8H), 0.82 (td, *J* = 7.2, 2.0 Hz, 3H), 0.64 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 114.2, 37.5, 37.1, 36.2, 35.9, 33.9, 33.9, 33.5, 30.8, 30.3, 29.8, 29.7, 29.7, 29.3, 29.1, 28.7, 26.8, 25.4, 23.8, 23.3, 23.1, 14.4, 14.4, 7.7.

HRMS (EI+, m/z): calc'd for $C_{27}H_{52}$ $[M]^{+\bullet}$ 376.4069, found: 376.4120.



35

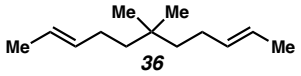
11-ethyl-11-octylhenicosa-1,20-diene (**35**): Prepared according to modified General Procedure A from ketone **29** (153 mg, 0.5 mmol) with *n*-octylmagnesium chloride solution (2.0 M solution in

THF, 1.5 equiv) and triethylaluminum (2.0 equiv). **35** was obtained as a colorless liquid (154 mg, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 2H), 4.99 – 4.80 (m, 4H), 2.04 – 1.90 (m, 4H), 1.34 – 1.26 (m, 4H), 1.25 – 1.10 (m, 34H), 1.05 – 1.00 (m, 6H), 0.83 – 0.78 (m, 3H), 0.64 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 114.2, 37.5, 37.2, 36.2, 34.0, 33.8, 32.1, 30.8, 30.8, 30.5, 30.3, 30.3, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.3, 29.1, 28.7, 26.8, 23.1, 22.9, 14.3, 7.7.

HRMS (EI+, m/z): calc'd for $C_{31}H_{60}$ $[M]^{+\bullet}$ 432.4695, found: 432.4714.



36

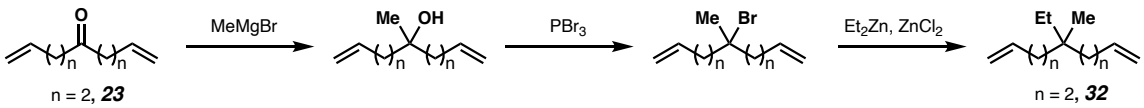
(2*E*,9*E*)-6,6-dimethylundeca-2,9-diene (36): Prepared according to general procedure A from ketone **31** (258 mg, 1.6 mmol) as a colorless liquid (230 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 – 5.39 (m, 4H), 1.96 – 1.89 (m, 4H), 1.66 (dt, *J* = 4.8, 1.3 Hz, 6H), 1.27 – 1.21 (m, 4H), 0.86 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 132.3, 124.2, 41.8, 32.6, 27.3, 27.1, 18.0.

HRMS (EI+) calc'd for $C_{13}H_{24}$ $[M]^{+\bullet}$ 180.1878; found 180.1865.

General Procedure B for *gem*-dialkylation of ketones:

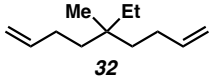


n = 2, ***23*** n = 2, ***32***

In a flame-dried round-bottom flask, ketone (1.0 equiv) was dissolved in THF and the reaction mixture was cooled to 0 ºC. Methylmagnesium bromide solution (3.0 M solution in diethyl ether, 1.5 equiv) was added dropwise, and the reaction mixture was slowly warmed to 23 ºC. After 1 hour, the reaction mixture was cooled to 0 ºC, and quenched by saturated NH_4Cl solution. The aqueous phase was extracted with Et_2O twice, dried over anhydrous $MgSO_4$, filtered over a short silica plug, and concentrated under reduced pressure.

A 100 mL round bottom flask equipped with a magnetic stirbar was charged with the tertiary alcohol (1.0 equiv) and dissolved in anhydrous CH_2Cl_2 (1 M). This solution was cooled to 0 °C and PBr_3 (0.35 equiv) was added dropwise. The reaction mixture was stirred for 2 h at 0 °C, and then concentrated *in vacuo*. The flask was fitted with a short path distillation head and the residue was distilled under vacuum to afford the tertiary bromide as a clear, colorless oil.

A 250 mL round bottom flask equipped with a magnetic stirbar was charged with $ZnCl_2$ (0.1 equiv) and the tertiary bromide (1 equiv) and dissolved in anhydrous CH_2Cl_2 (0.5 M). This solution was cooled to –40 °C and the dialkylzinc reagent (1.0 equiv) was added dropwise via syringe. The reaction mixture was stirred with warming to ambient temperature for 12 h, and then quenched by the dropwise addition of MeOH. The reaction mixture was washed with 1 M HCl, the organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The product was purified by distillation.



32

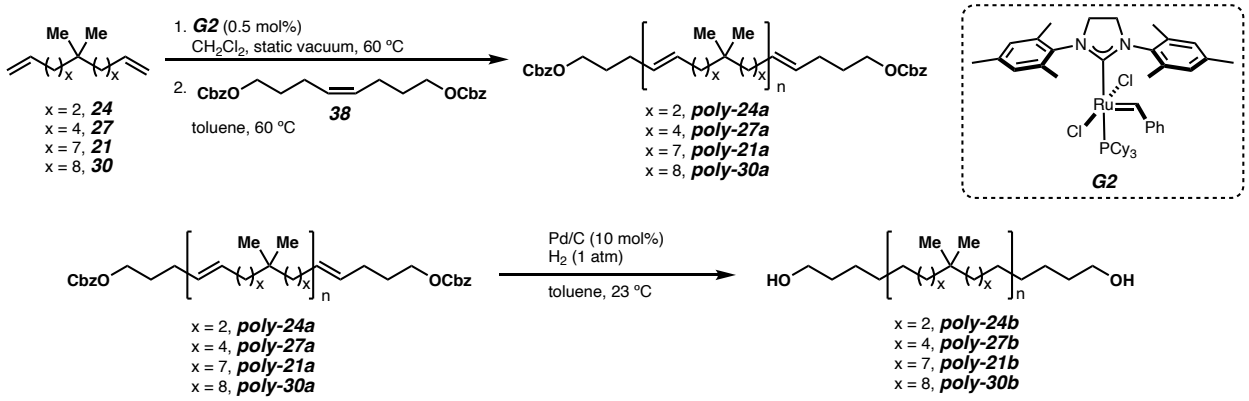
5-ethyl-5-methylnona-1,8-diene (32): Prepared according to general procedure B from ketone **23** (5.86 g, 42.5 mmol) and Et_2Zn to afford **32** as a clear, colorless oil (4.3 g, 61% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 2H), 4.97 (dt, *J* = 17.0, 1.8 Hz, 2H), 4.92 – 4.86 (m, 2H), 1.96 – 1.88 (m, 4H), 1.27 – 1.18 (overlapping m, 6H), 0.79 (s, 3H), 0.76 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 113.7, 38.1, 34.9, 31.4, 28.1, 24.4, 7.9.

HRMS (EI+) calc'd for $C_{12}H_{22}$ $[M]^{+\bullet}$ 166.1722; found 166.1700.

General Procedure C for ADMET Polymerization:



In a nitrogen-filled glovebox, monomer **30** (320 mg, 1 mmol) in 0.5 mL CH_2Cl_2 was transferred into a 50 mL Schlenk flask equipped with a stir bar, followed by Grubbs 2nd Generation Catalyst (4.2 mg, 0.5 mol%) in 0.5 mL CH_2Cl_2. The Schlenk tube was sealed and removed from the glovebox and placed under static vacuum after one freeze-pump-thaw cycle. Then the Schlenk flask was placed in to a 60 ºC oil bath for 12 hours. The valve was opened to dynamic vacuum and stirring was continued for 2 hours until the mixture turned viscous and became difficult to stir.

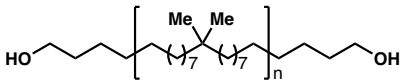
The Schlenk tube was sealed and taken into the glovebox where the CTA **38** (20.6 mg, 0.05 mmol, 20:1 monomer: CTA ratio) in 2 mL toluene was added. The Schlenk tube was removed from the glovebox and the side arm was flame dried under vacuum and backfilled three times with argon. Then the Schlenk tube was opened to the argon line and placed in a 60 °C oil bath for 72 h. The reaction mixture was transferred into a flame-dried round bottom flask and the solvent was removed under reduced pressure to obtain crude polymer **poly-30a**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.14 (m, 5H), 5.47 – 5.32 (m, 11H), 5.16 (s, 1H), 4.21 – 4.10 (m, 1H), 2.08 – 1.91 (m, 21H), 1.46 – 1.06 (m, 131H), 0.82 (s, 29H). ^{1}H NMR determined n = 22, M_n = 6800. GPC data: M_n = 5400; PDI (M_w/M_n) = 1.2.

The crude polymer **poly-30a** was dissolved in toluene (10 mL) and 10% palladium on carbon (100 mg, 0.1 equiv) was added in a round-bottom flask with a stir bar. The flask was sealed with a septum and back-filled with argon for three times, and then back-filled with H_2 using a balloon. The reaction was allowed to stir at 23 °C for 24 hours under an atmosphere of hydrogen (1 atm H_2 balloon). After that time the reaction mixture was filtered through a short pad of Celite (*caution: Palladium on carbon is highly flammable and the palladium waste must be collected separately and covered with water*). The filtered solution was concentrated upon heating under high vacuum to obtain the hydroxyl telechelic polymer **poly-30b** (286 mg, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (t, *J* = 6.6 Hz, 1H), 1.39 – 1.10 (m, 210H), 0.82 (s, 32H). ^{1}H NMR determined n = 21, M_n = 6300. GPC data: M_n = 7600; PDI (M_w/M_n) = 1.1.

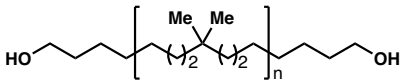
Table 3.5.1. Summary of Telechelic Polymer Samples Prepared.

Polymer	Monomer/CTA ratio	Yield (%)	n	M_n(NMR)(Da)
poly-21b	10:1	95	15	4200
poly-24b	22:1	55	16	2200
poly-27b	12:1	99	10	2000
poly-30b-1	8:1	99	10	3100
poly-30b-2	20:1	97	21	6300
poly-30b-3	50:1	96	58	17200
poly-30b-4	100:1	89	97	28700
poly-32b	22:1	56	22	3200
poly-34b	20:1	95	19	6800



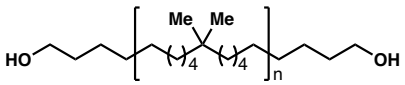
poly-21b

Telechelic polymer poly-21b: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.57 (t, *J* = 6.6 Hz, 1H), 1.62 – 1.48 (m, 7H), 1.32 – 1.00 (m, 122H), 0.74 (s, 22H). ^{1}H NMR determined n = 15, M_n = 4200. GPC data: M_n =2800; PDI (M_w/M_n) = 1.44.



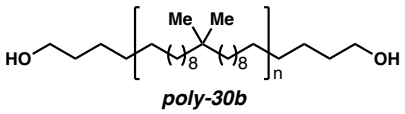
poly-24b

Telechelic polymer poly-24b: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.7 Hz, 1H), 1.59 – 1.52 (m, 1H), 1.36 – 1.04 (m, 46H), 0.80 (s, 20H).^{1}H NMR determined n = 16, M_n = 2200. GPC data: M_n =4000; PDI (M_w/M_n) = 1.4.



poly-27b

Telechelic polymer poly-27b: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.65 (t, *J* = 6.6 Hz, 1H), 1.43 – 1.09 (m, 58H), 0.82 (s, 13H).^{1}H NMR determined n = 10, M_n = 2000. GPC data: M_n = 3800; PDI (M_w/M_n) = 1.5.



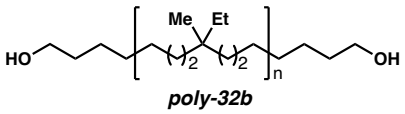
poly-30b

poly-30b-1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (dt, *J* = 6.5, 4.8 Hz, 1H), 1.41 – 1.17 (m, 94H), 0.82 (s, 15H). ^{1}H NMR determined n = 10, M_n = 3100.

poly-30b-2: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (t, *J* = 6.6 Hz, 1H), 1.34 – 1.11 (m, 208H), 0.82 (s, 32H). ^{1}H NMR determined n = 21, M_n = 6300.

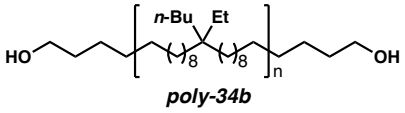
poly-30b-3: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (dt, *J* = 6.7, 5.6 Hz, 1H), 1.32 – 1.12 (m, 571H), 0.82 (s, 88H). ^{1}H NMR determined n = 58, M_n = 17200.

poly-30b-4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (dt, *J* = 6.6, 5.5 Hz, 1H), 1.35 – 1.11 (m, 943H), 0.82 (s, 146H). ^{1}H NMR determined n = 97, M_n = 28700.



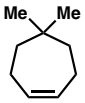
poly-32b

Telechelic polymer poly-32b: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.7 Hz, 1H), 1.55 (q, *J* = 6.9 Hz, 2H), 1.38 – 1.05 (m, 83H), 0.78 – 0.68 (m, 34H). ^{1}H NMR determined n = 22, M_n = 3200. GPC data: M_n =6800; PDI (M_w/M_n) = 1.1.



poly-34b

poly-34b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (q, *J* = 6.4 Hz, 1H), 1.34 – 1.19 (m, 265H), 1.14 – 1.09 (m, 56H), 0.92 – 0.87 (m, 29H), 0.72 (t, *J* = 7.5 Hz, 14H). ^{1}H NMR determined n = 19, M_n = 6800.



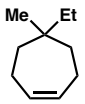
37

5,5-dimethylcyclohept-1-ene (37): After the polymerization of **24**, the cyclic olefin was removed by vacuum distillation from the reaction mixture (23 °C, 100 mTorr).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (ddd, *J* = 3.8, 2.9, 0.8 Hz, 2H), 2.06 – 1.94 (m, 4H), 1.40 – 1.32 (m, 4H), 0.87 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5, 40.3, 33.7, 29.3, 24.4.

HRMS (EI+, m/z) calc'd for C_9H_{16} $[M]^{+\bullet}$ 124.1252, found: 124.1264.



39

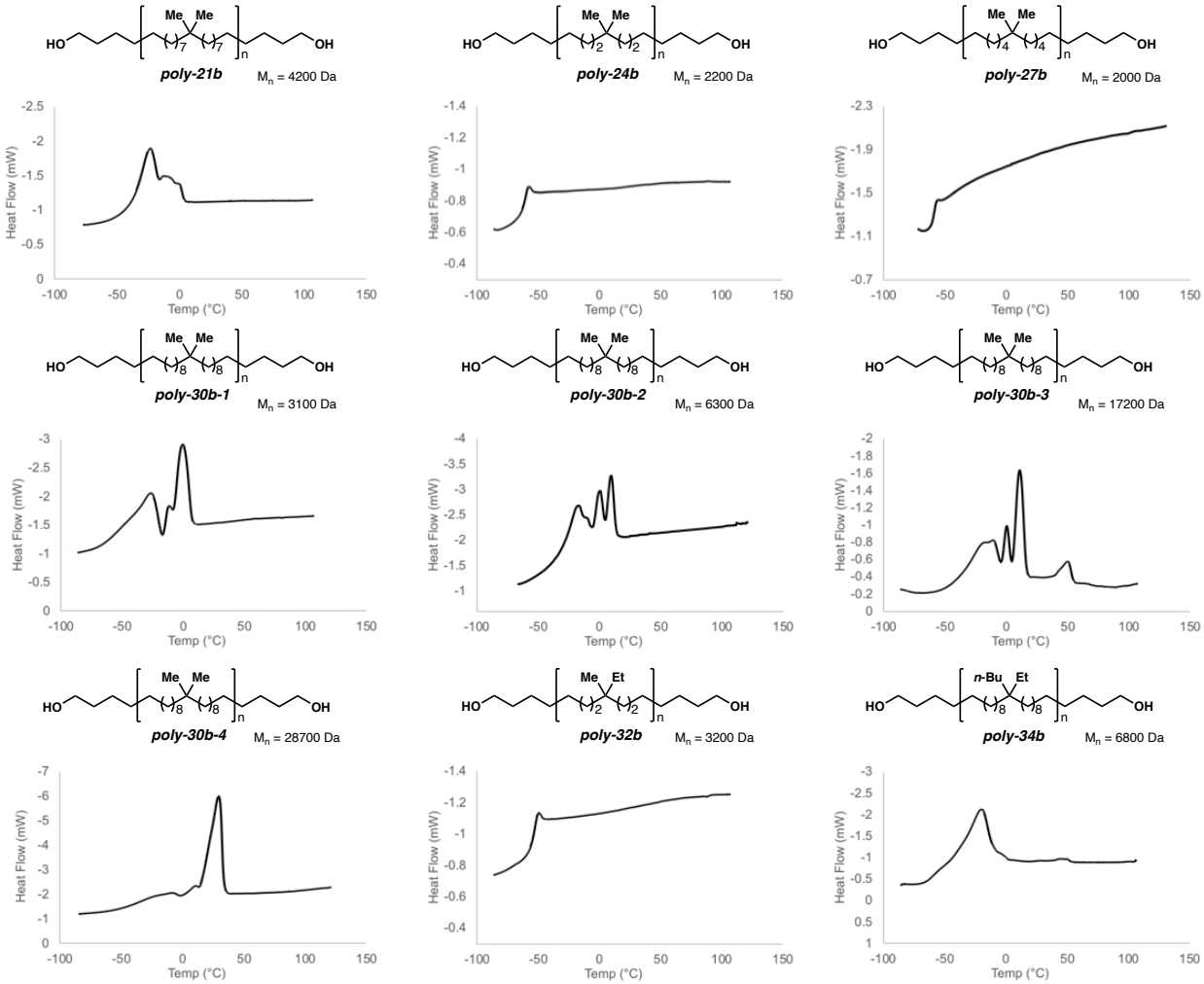
5-ethyl-5-methylcyclohept-1-ene (39): After the polymerization of **32**, the cyclic olefin was removed by vacuum distillation from the reaction mixture (23 °C, 100 mTorr).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.63 (t, *J* = 3.2 Hz, 2H), 2.09 – 2.01 (m, 4H), 1.49 – 1.33 (m, 4H), 1.29 (q, *J* = 7.5 Hz, 2H), 0.83 (s, 3H), 0.80 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.4, 38.3, 35.9, 33.6, 25.2, 24.1, 8.1.

HRMS (EI+, m/z) calc'd for $C_{10}H_{18}$ $[M]^{+\bullet}$ 138.1409, found: 138.1413.

Figure 3.5.1. DSC Traces for Different Gem*-dimethyl Polymer Samples*



3.6 NOTES AND REFERENCES

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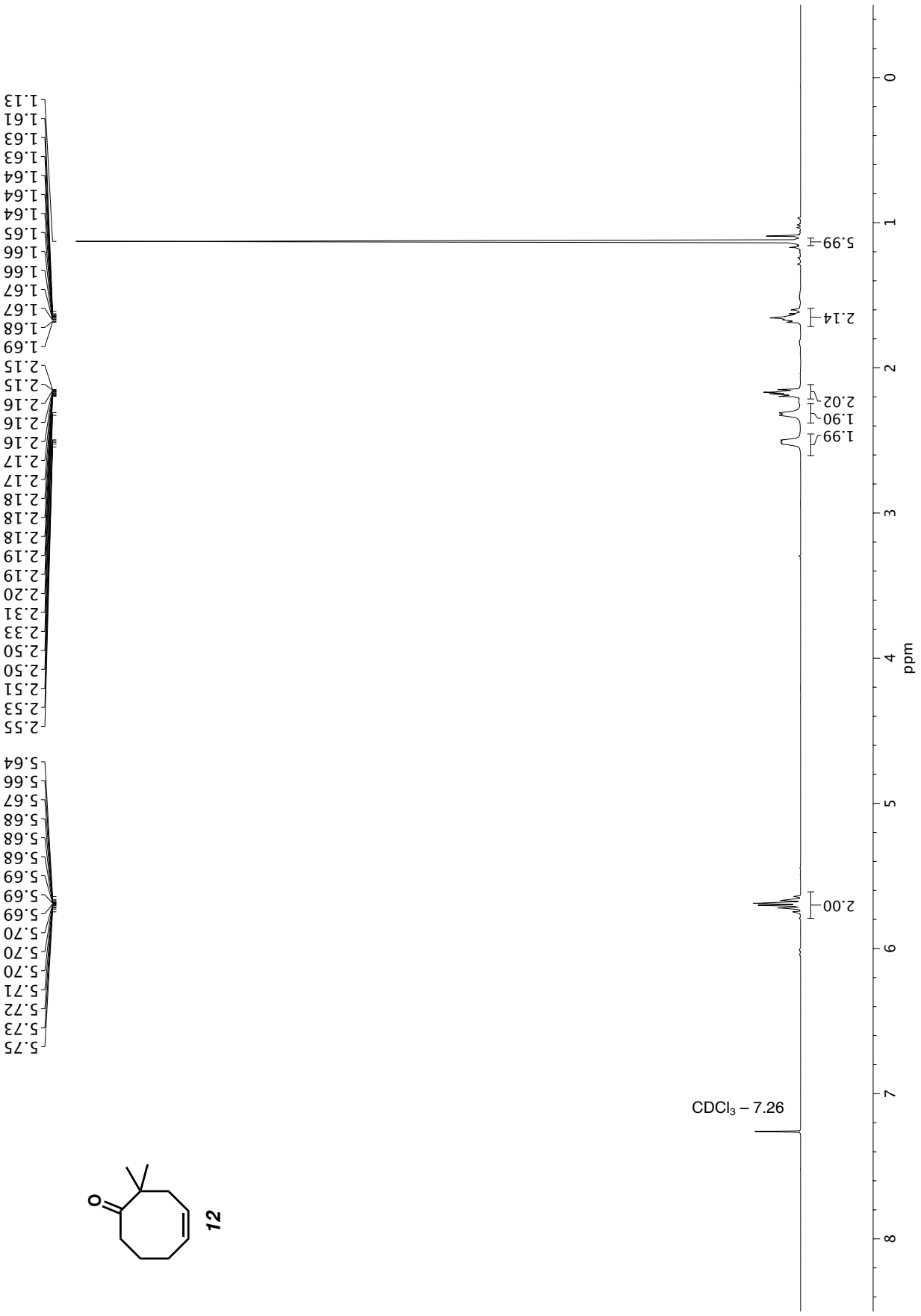
APPENDIX 3

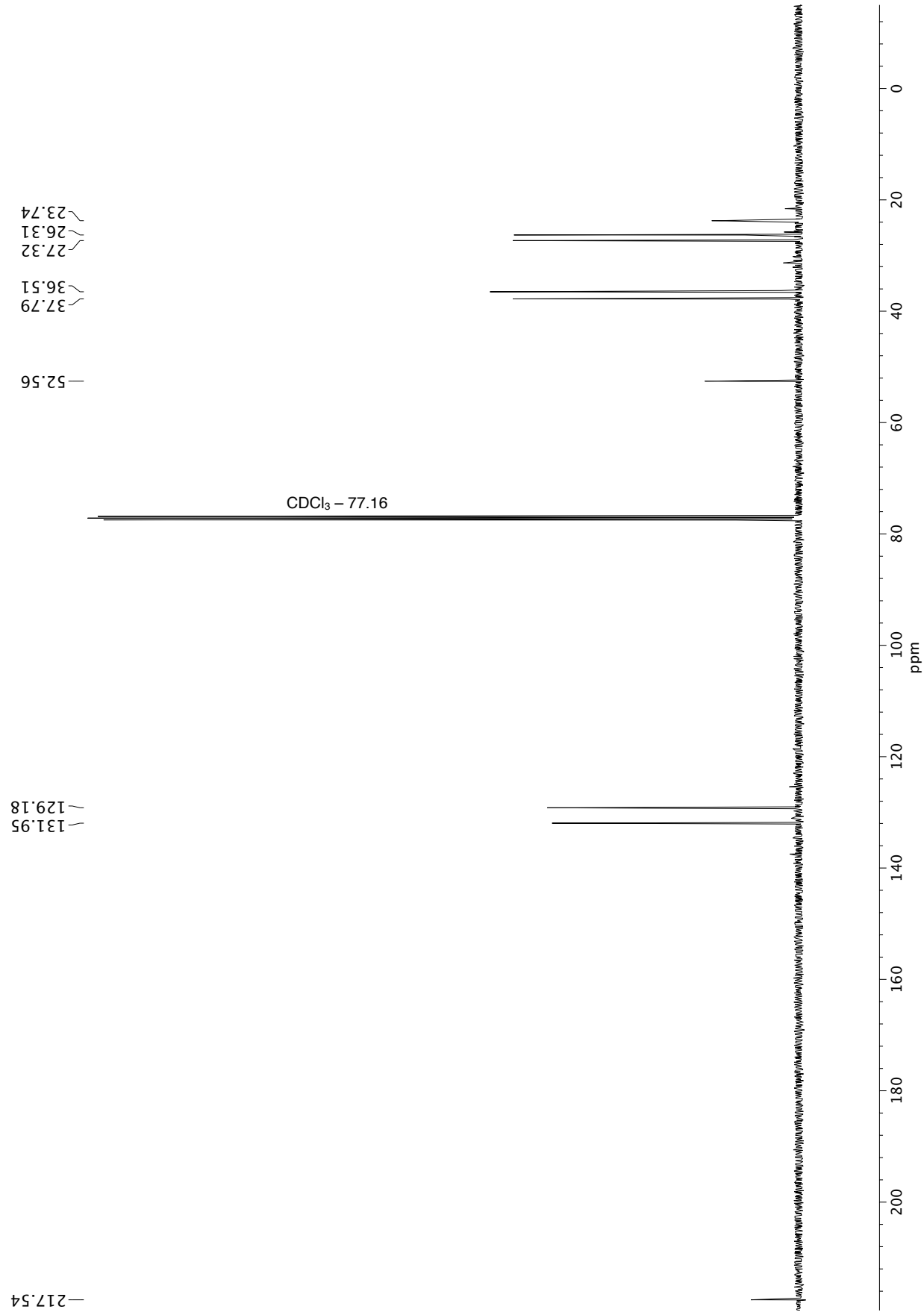
Spectra Relevant to Chapter 3:

A Convenient Synthesis of Geminal-Dialkyl Dienes

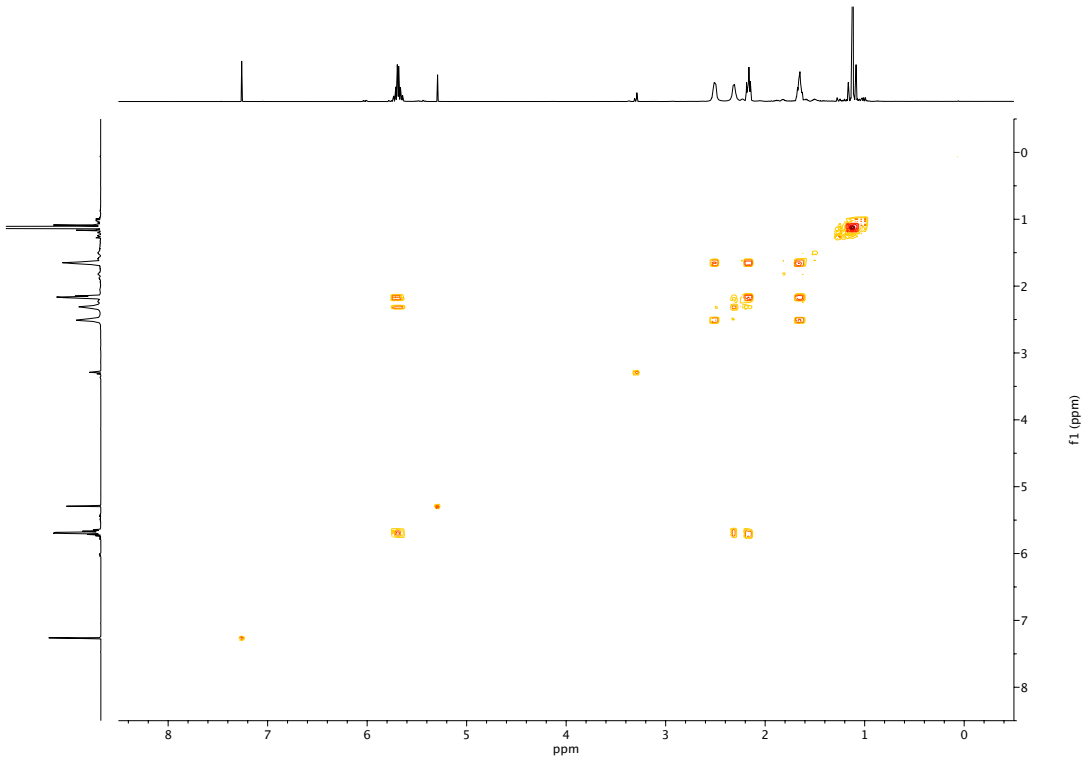
for Olefin Metathesis Polymerization



^{1}H NMR (400 MHz, $CDCl_3$) of compound **12**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **12**.



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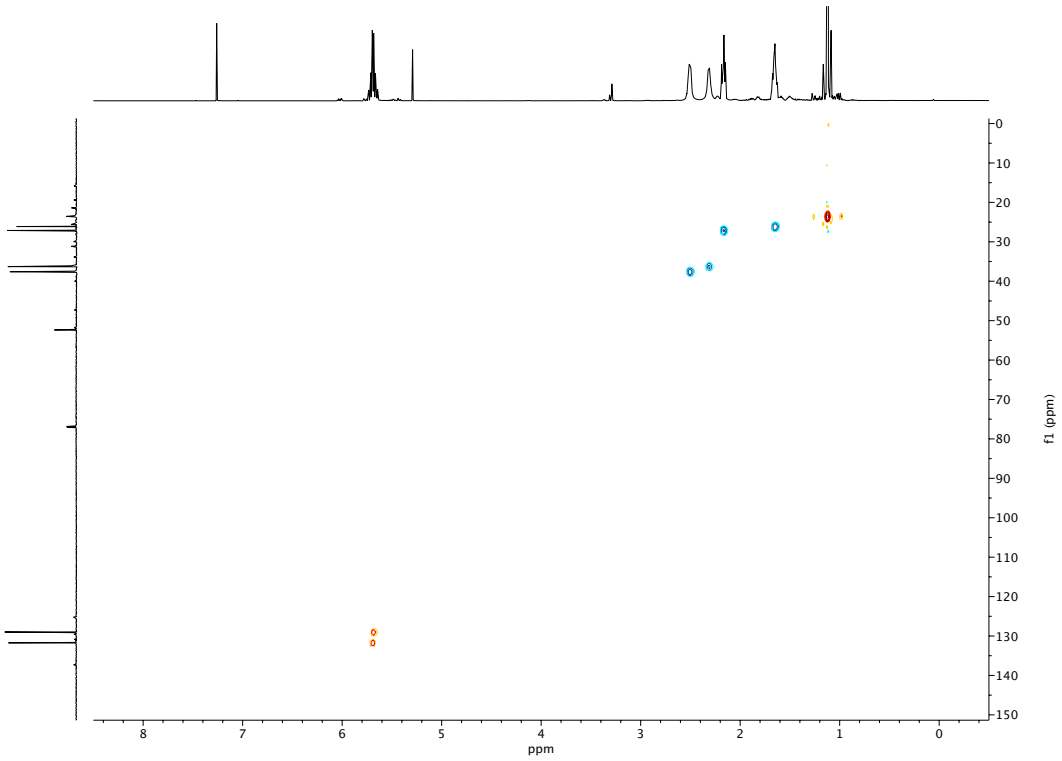

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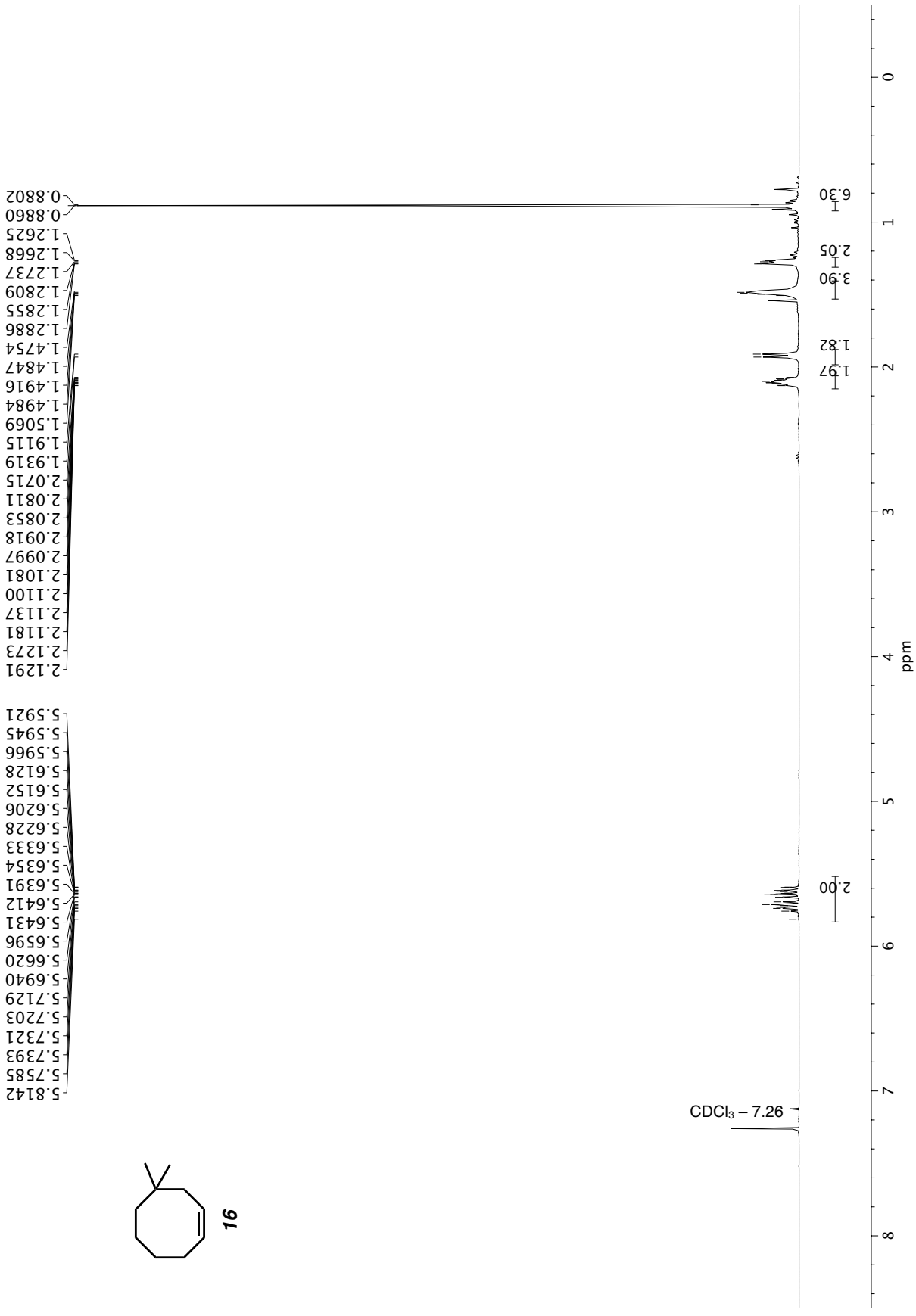

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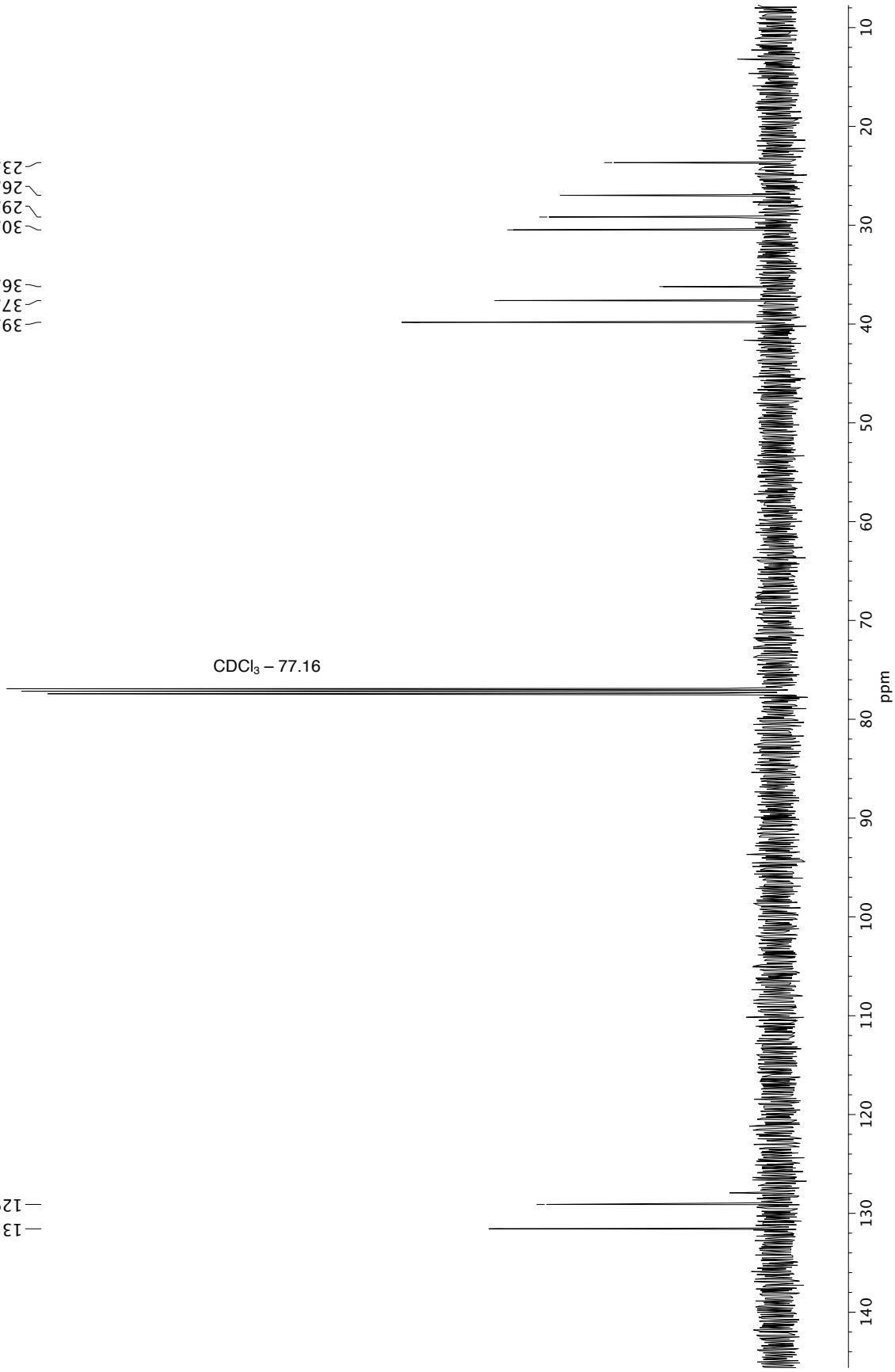
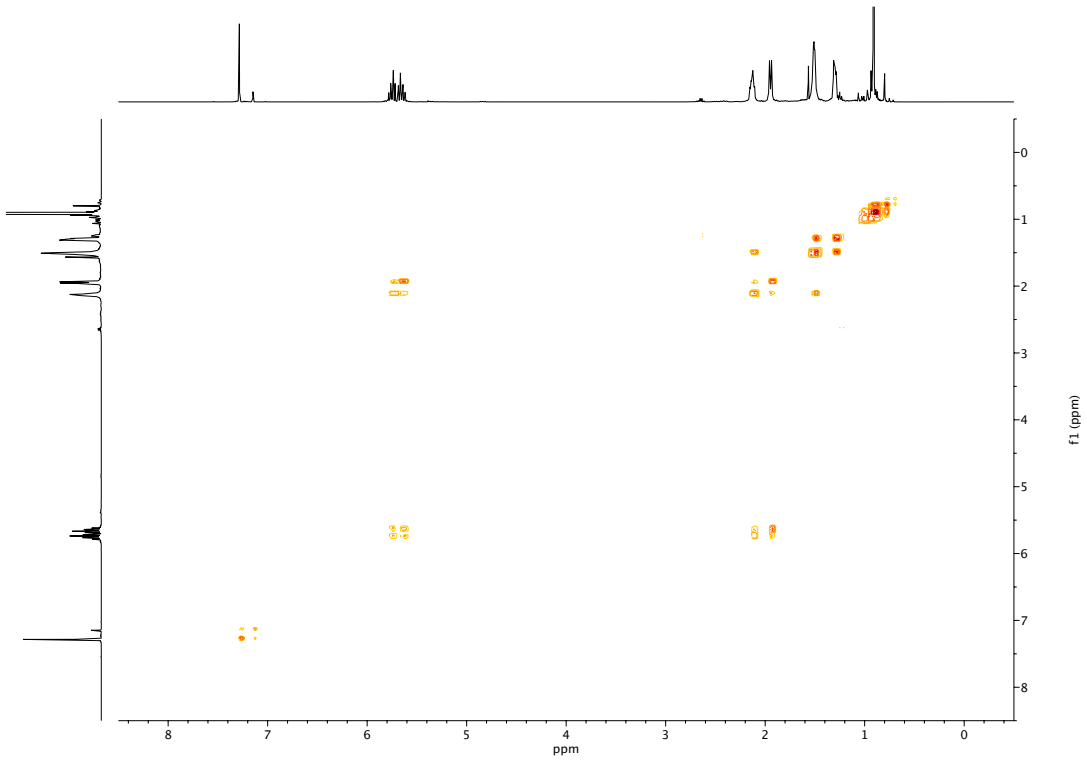
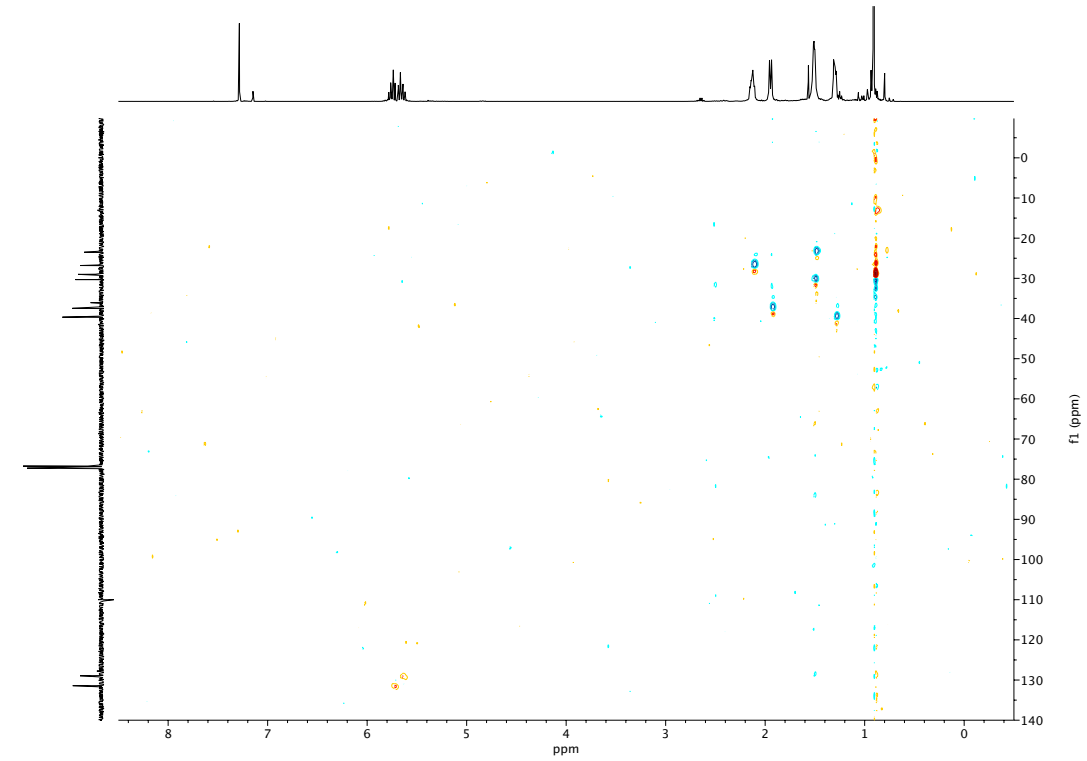


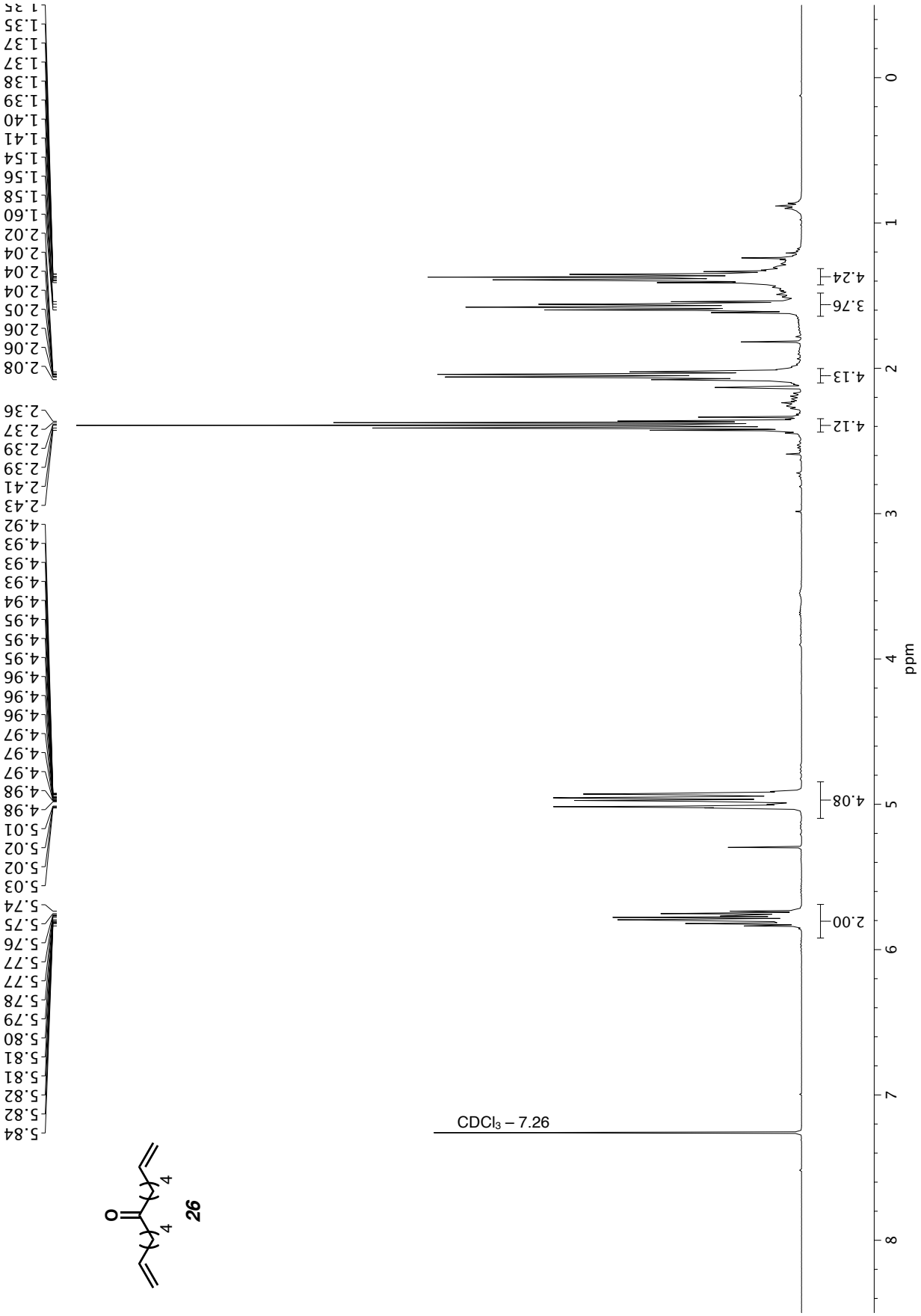
^{13}C NMR (101 MHz, $CDCl_3$) of compound **16**.



$^{1}H–^{1}H$ COSY NMR (400 MHz, $CDCl_3$) of compound **16**.



$^{1}H–^{13}C$ HSQC NMR (400 MHz, $CDCl_3$) of compound **16**.



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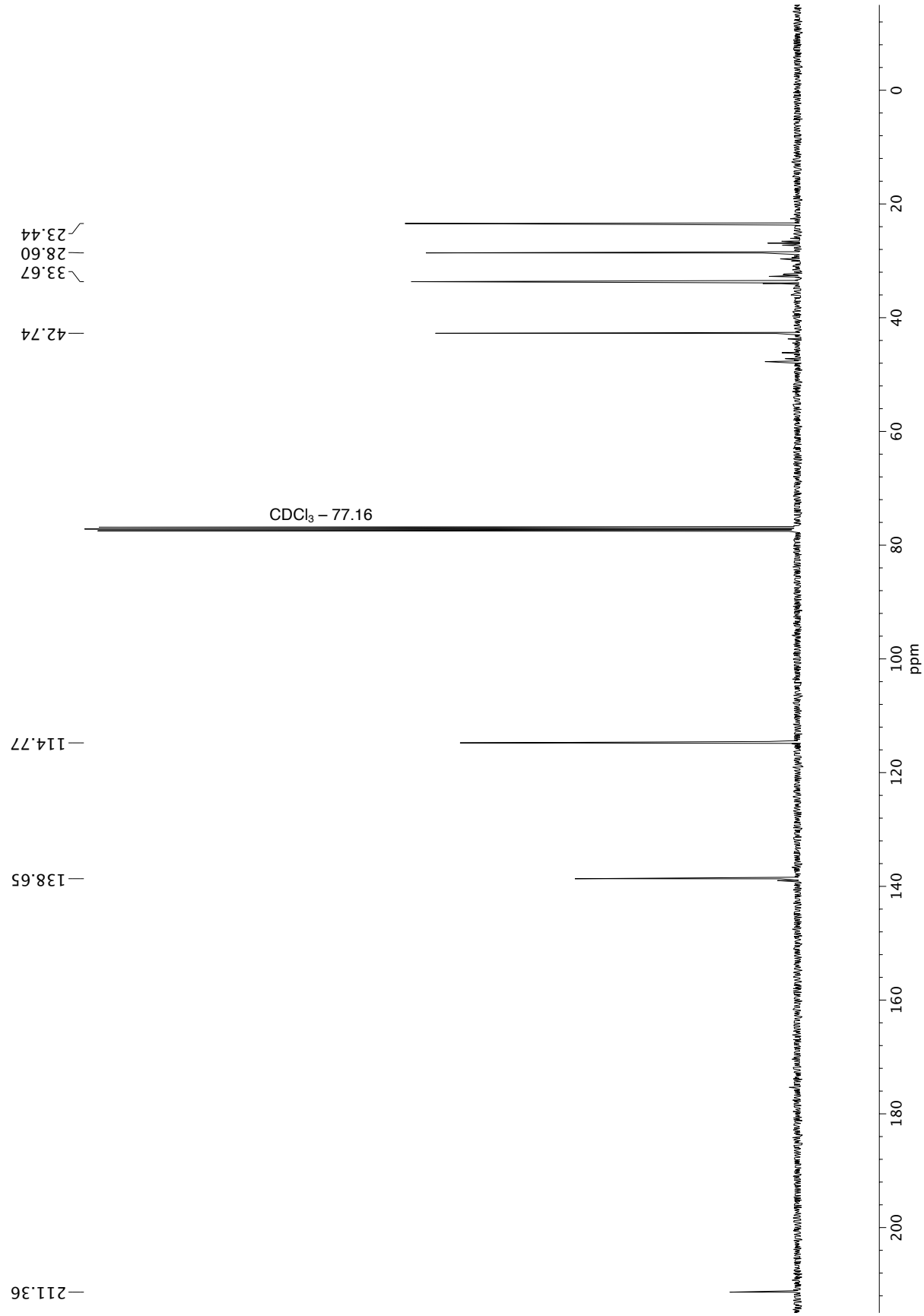
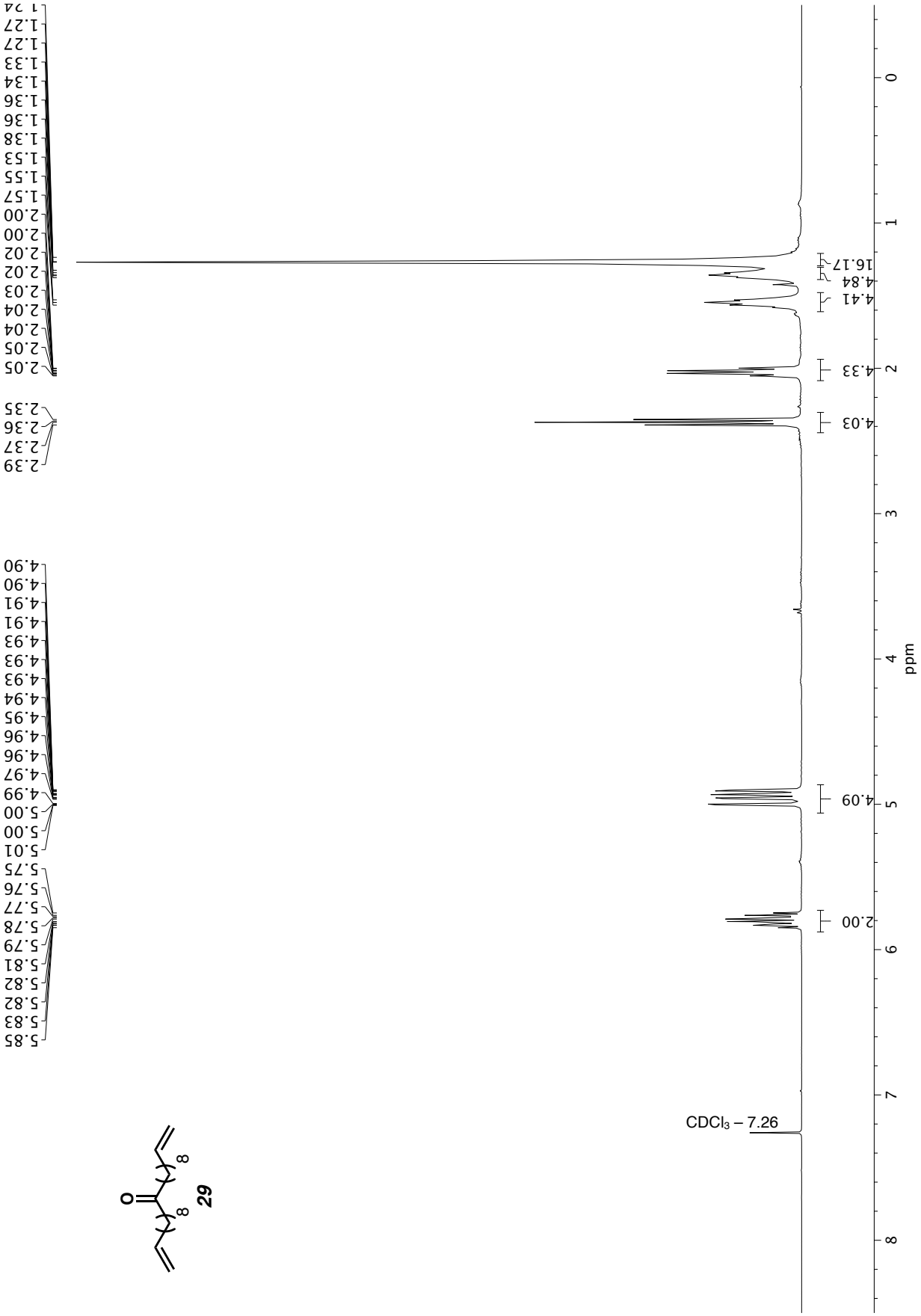


^{13}C NMR (101 MHz, $CDCl_3$) of compound **26**.



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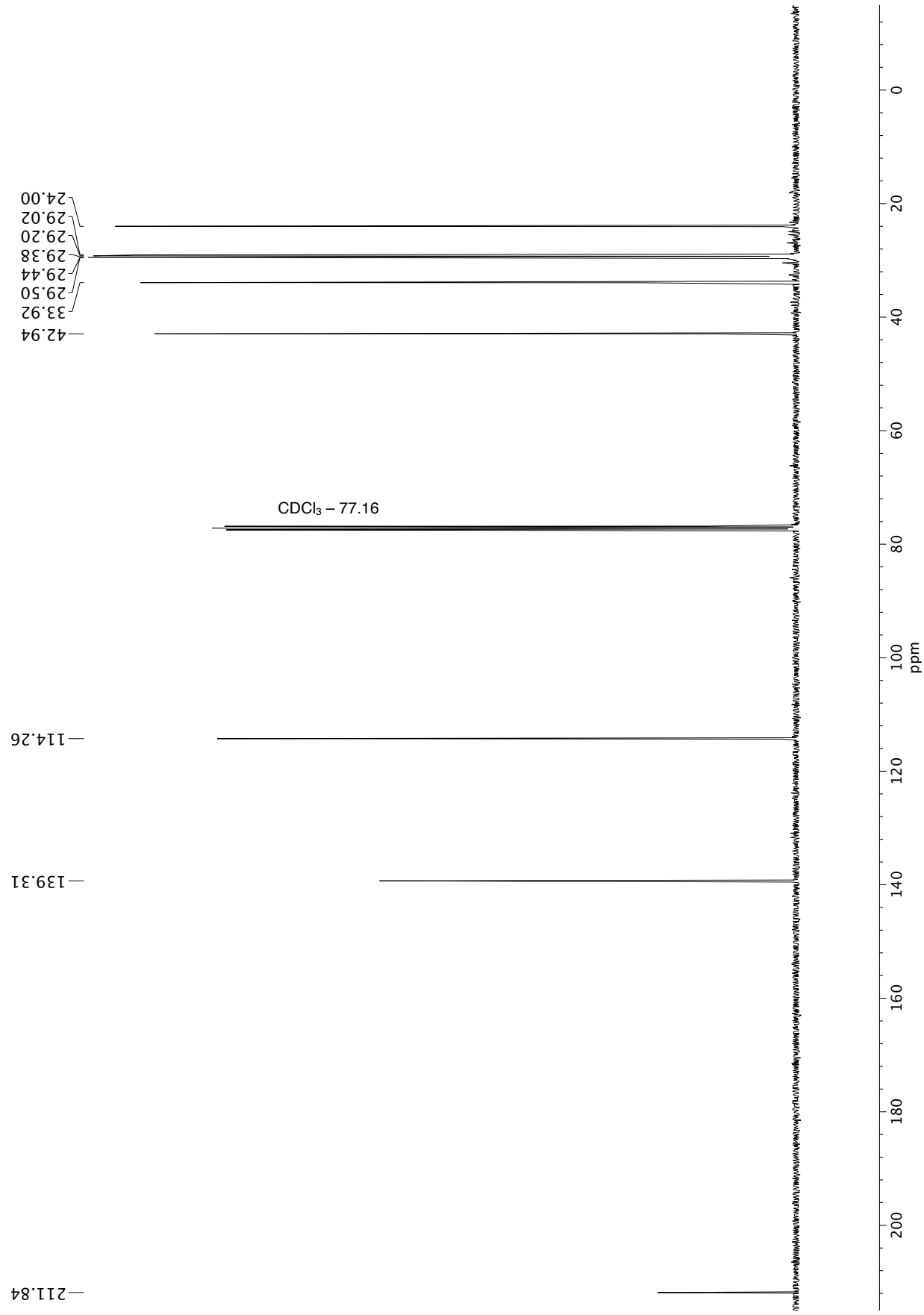

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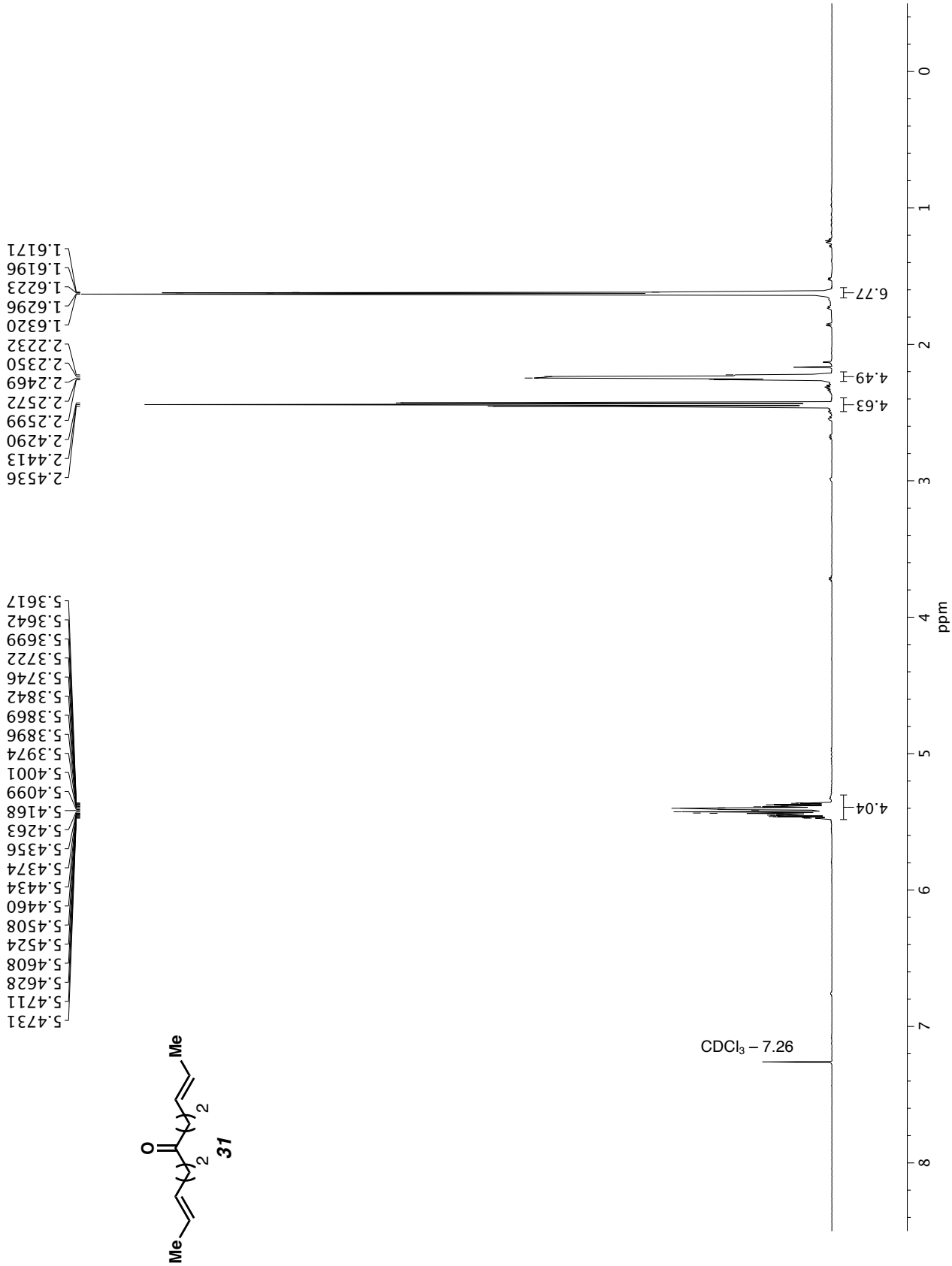
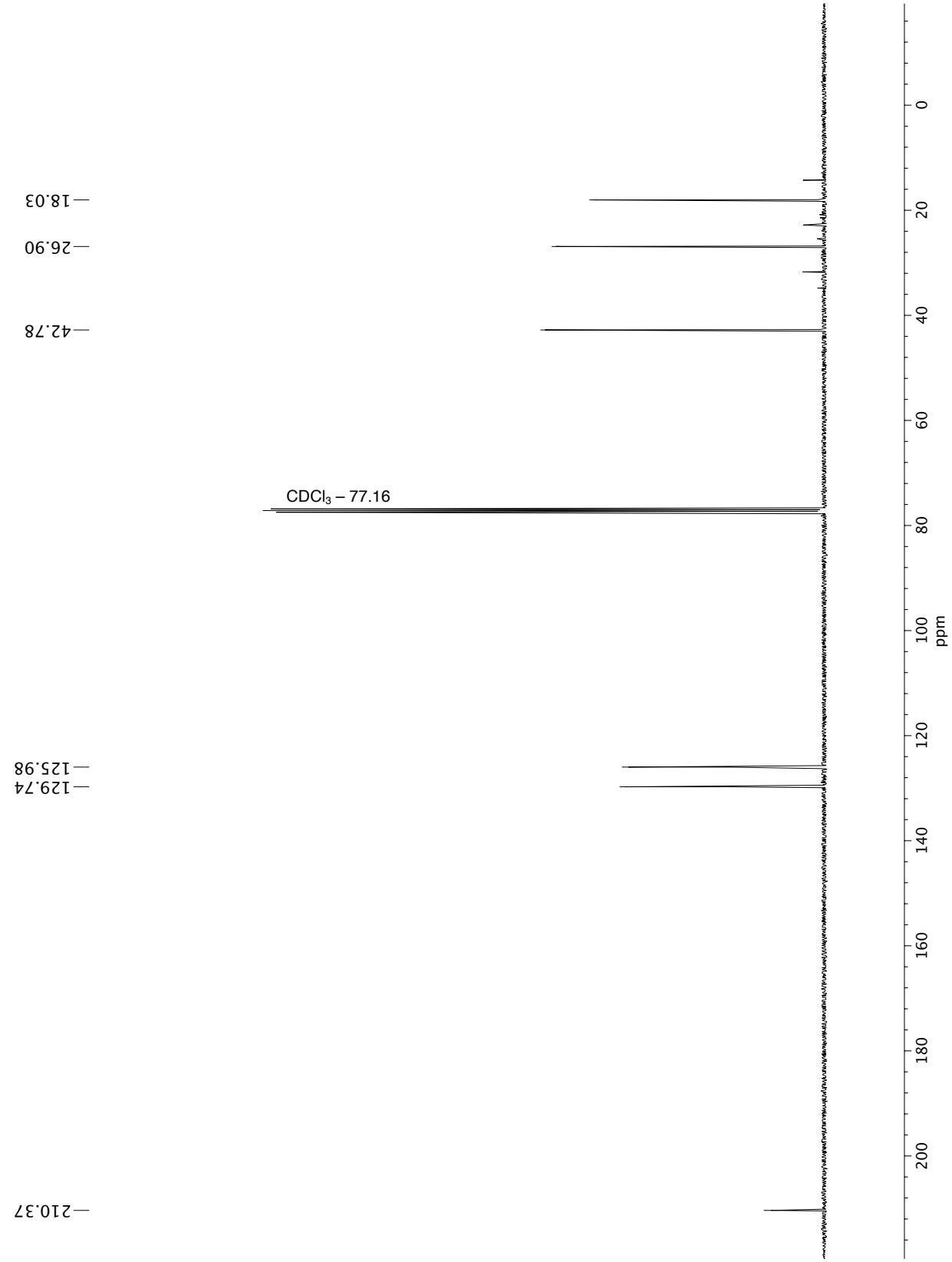


^{1}H NMR (600 MHz, $CDCl_3$) of compound **31**.



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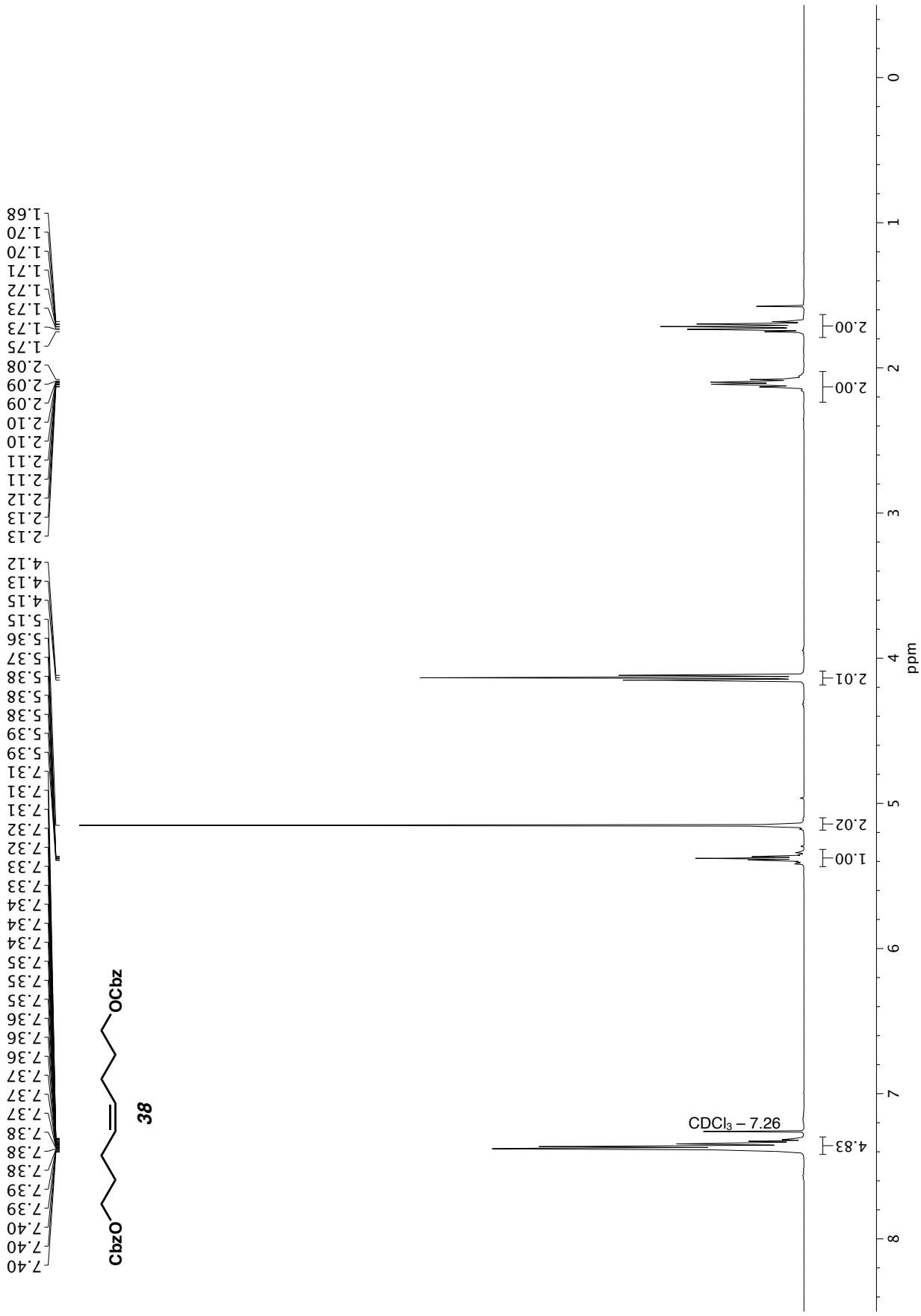
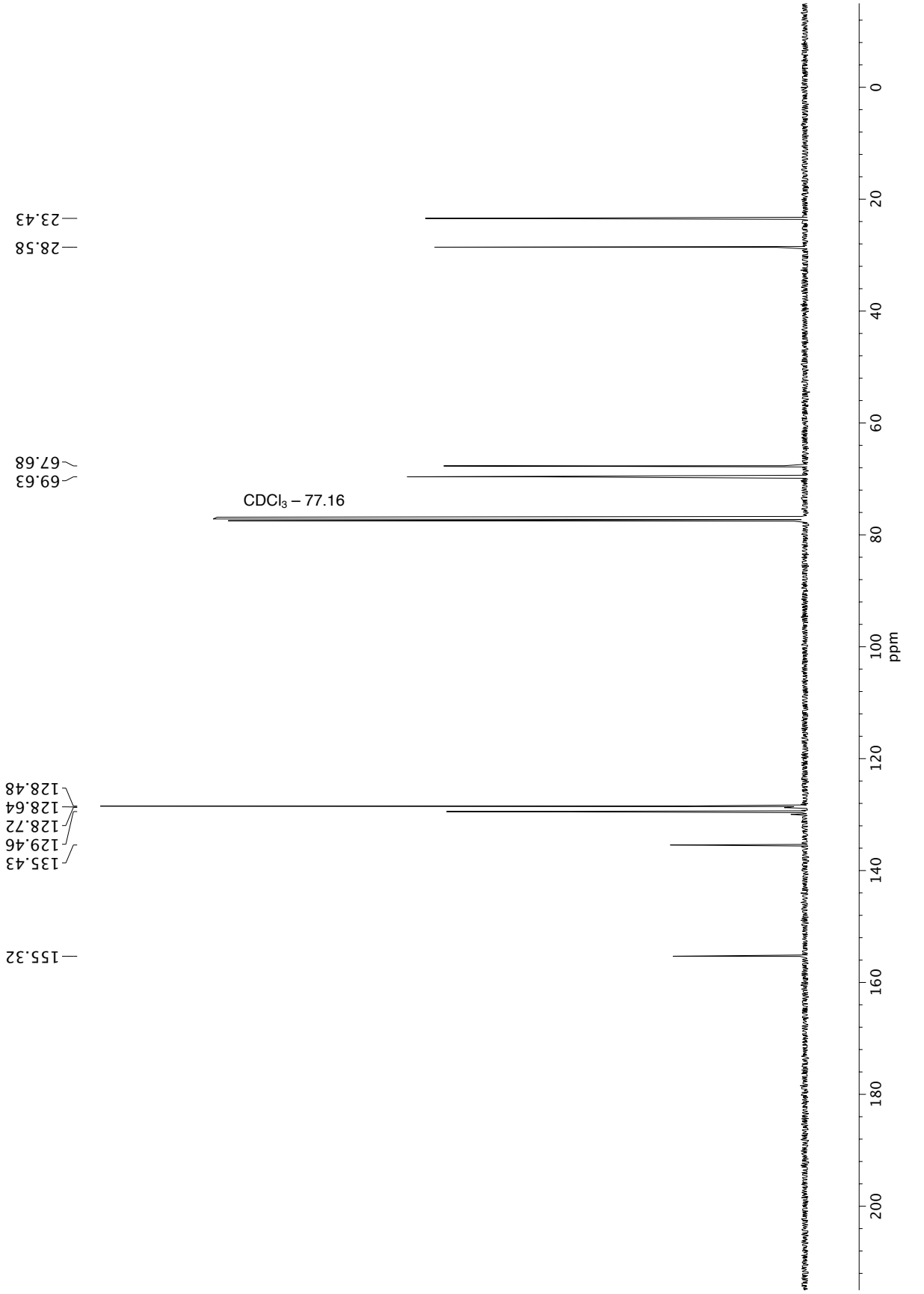
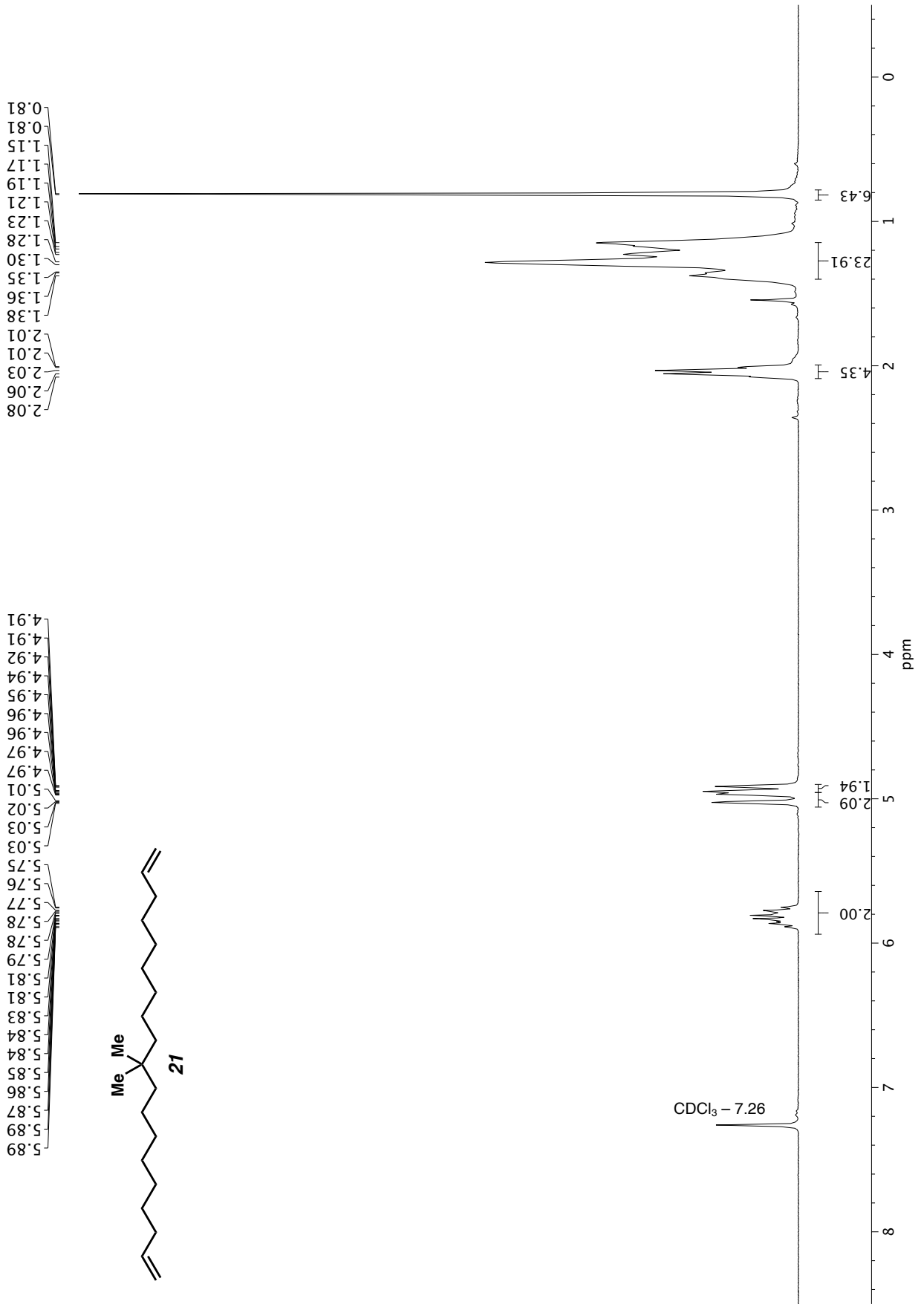


^{1}H NMR (600 MHz, $CDCl_3$) of compound **38**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **38**.



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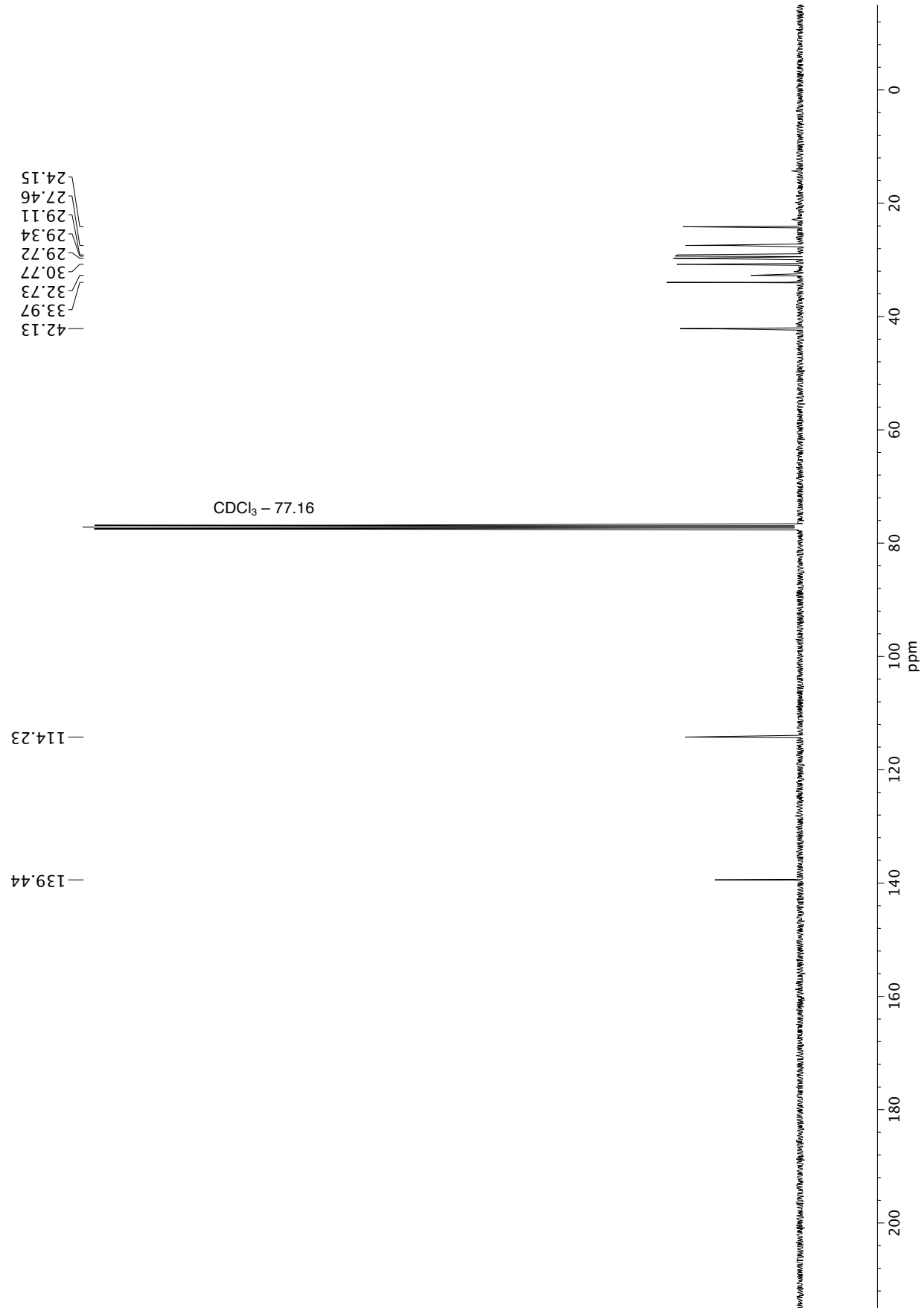
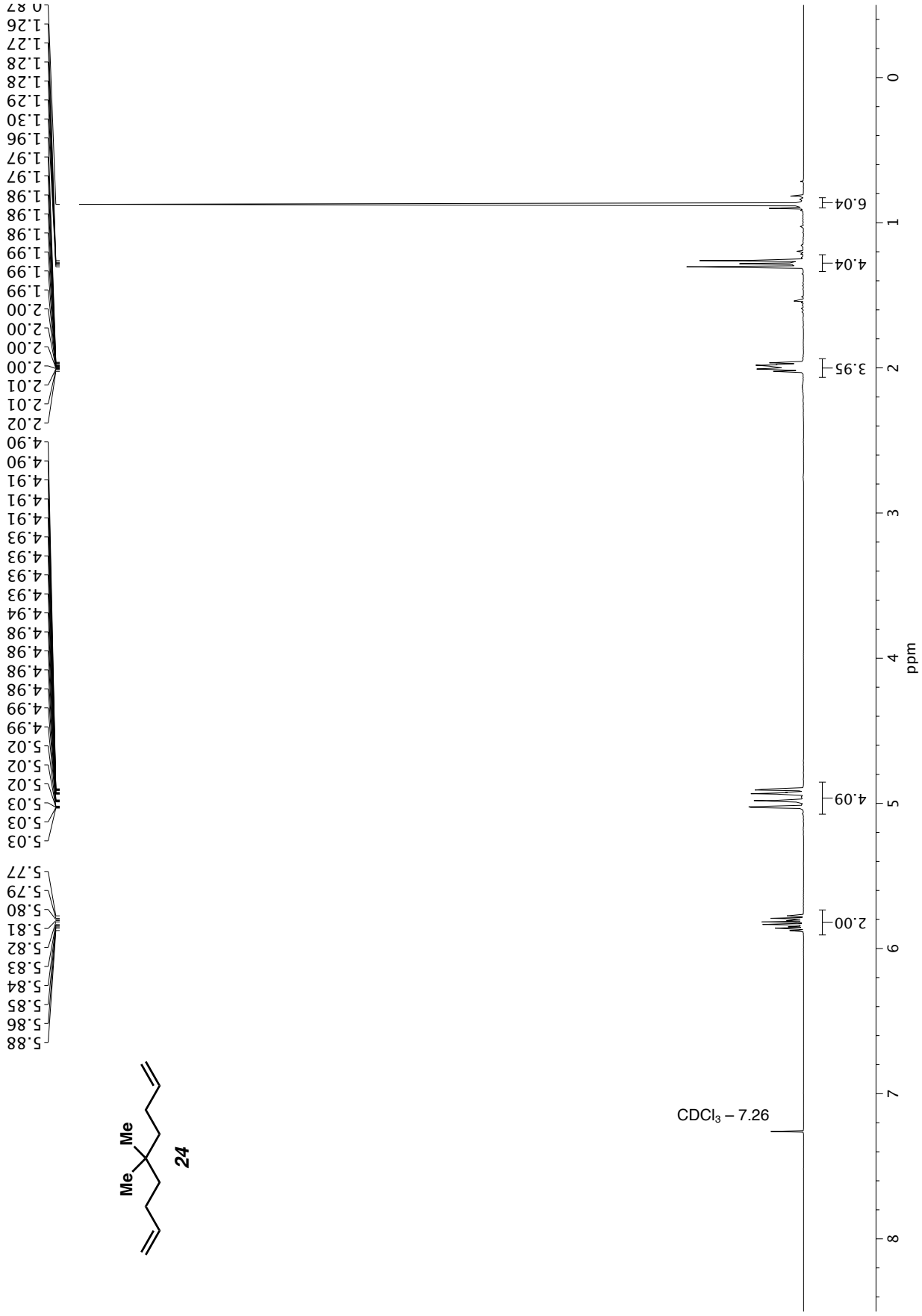
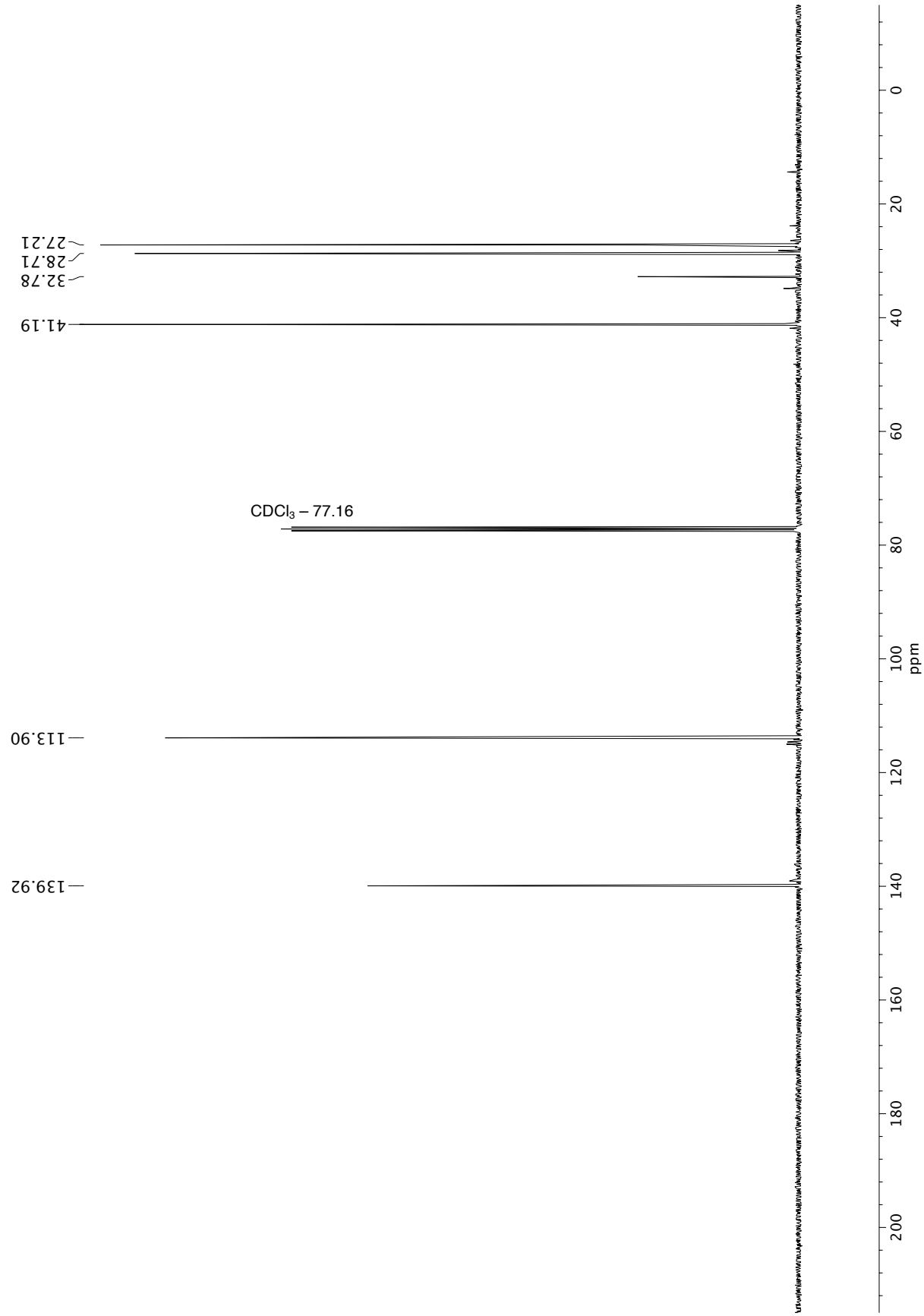


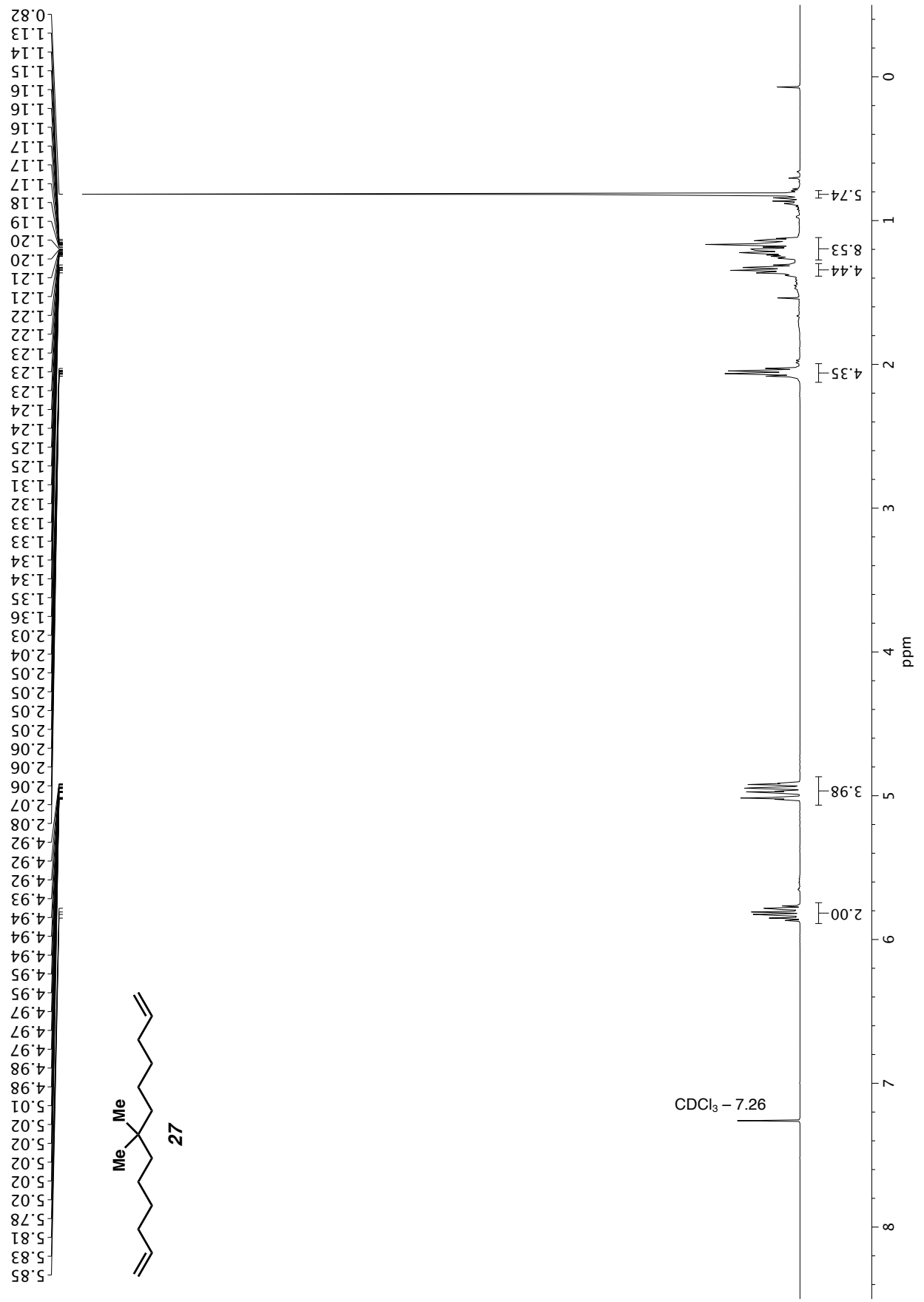
^{13}C NMR (101 MHz, $CDCl_3$) of compound **21**.



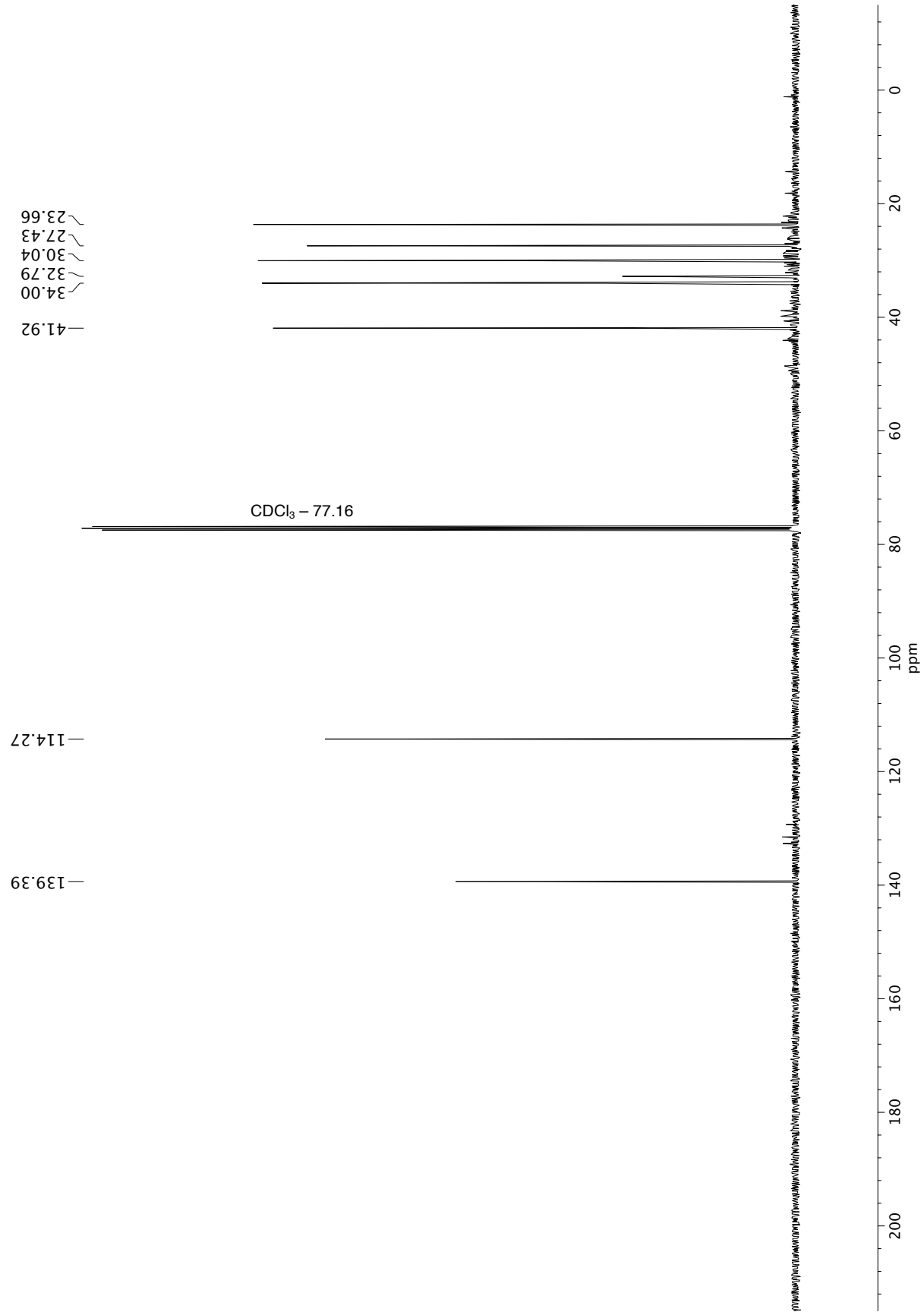
^{1}H NMR (400 MHz, $CDCl_3$) of compound **24**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **24**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **27**.



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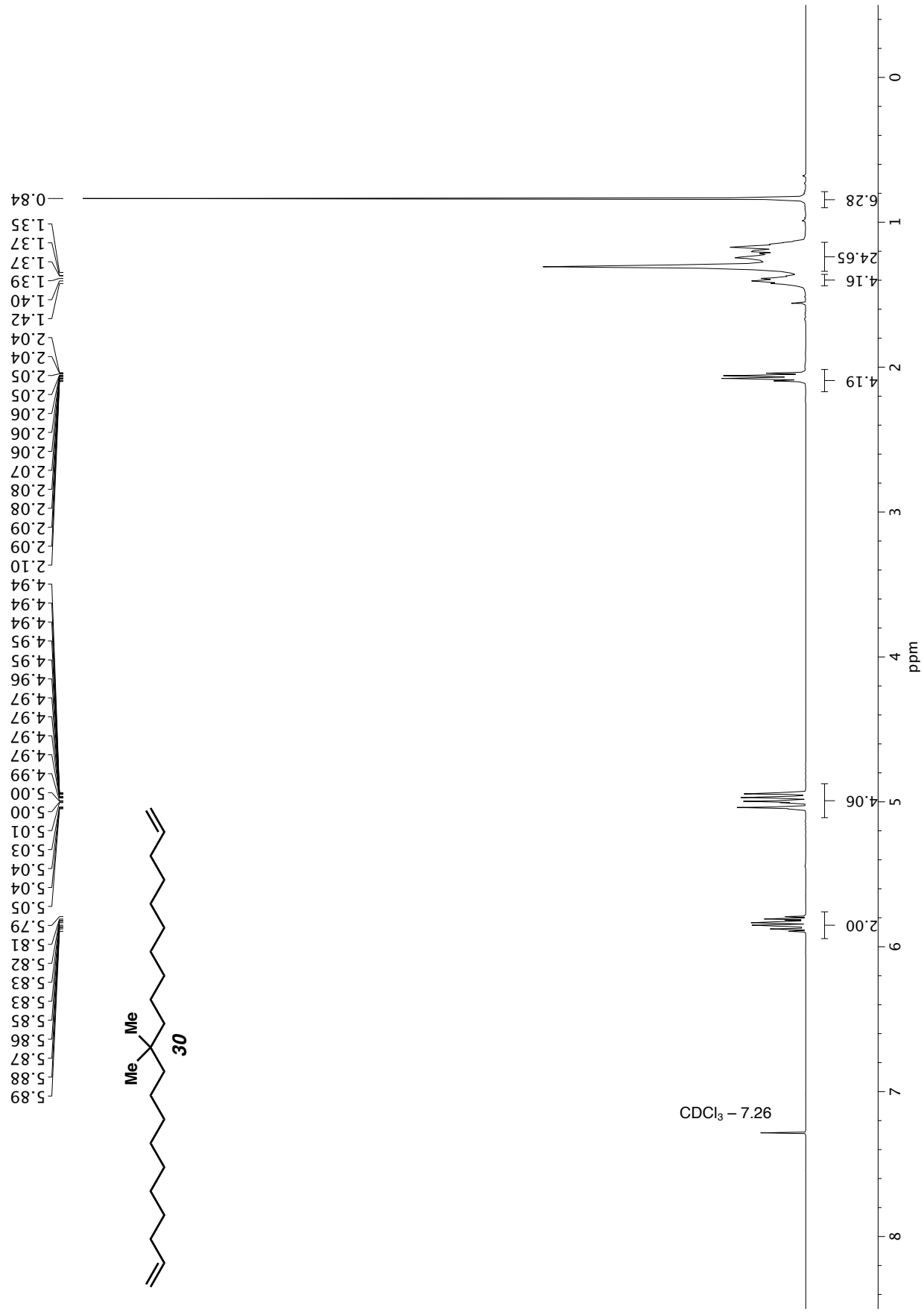

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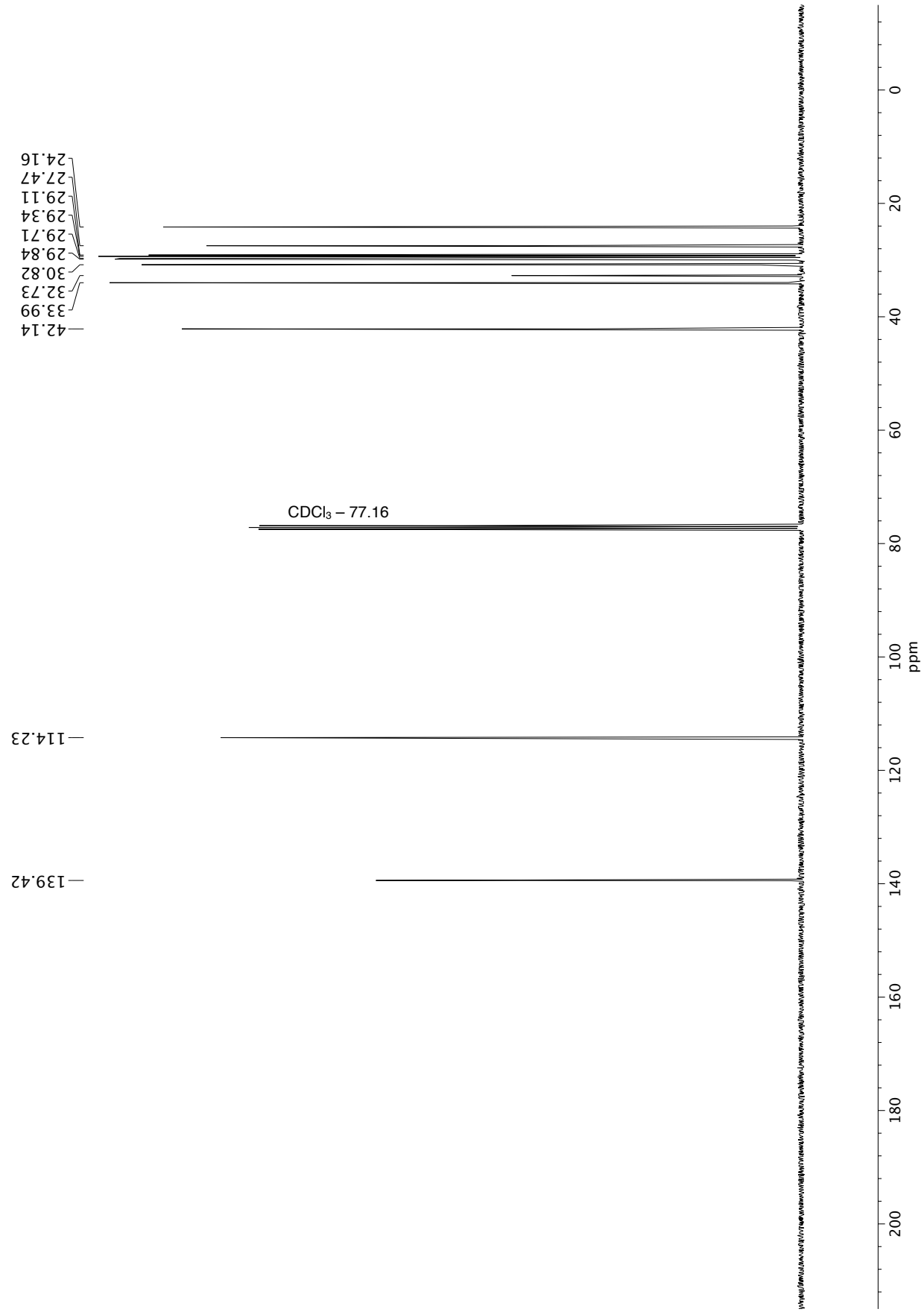

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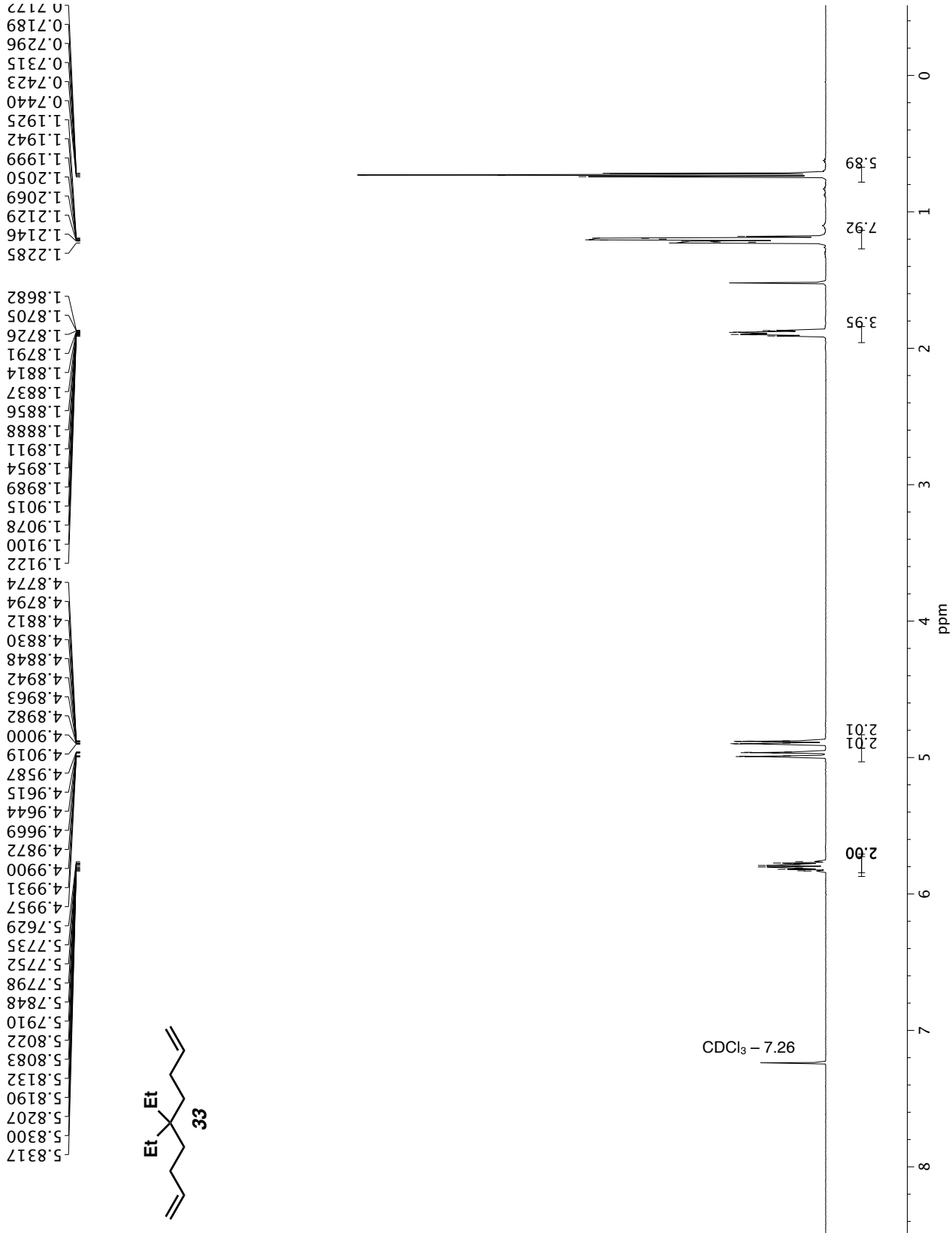

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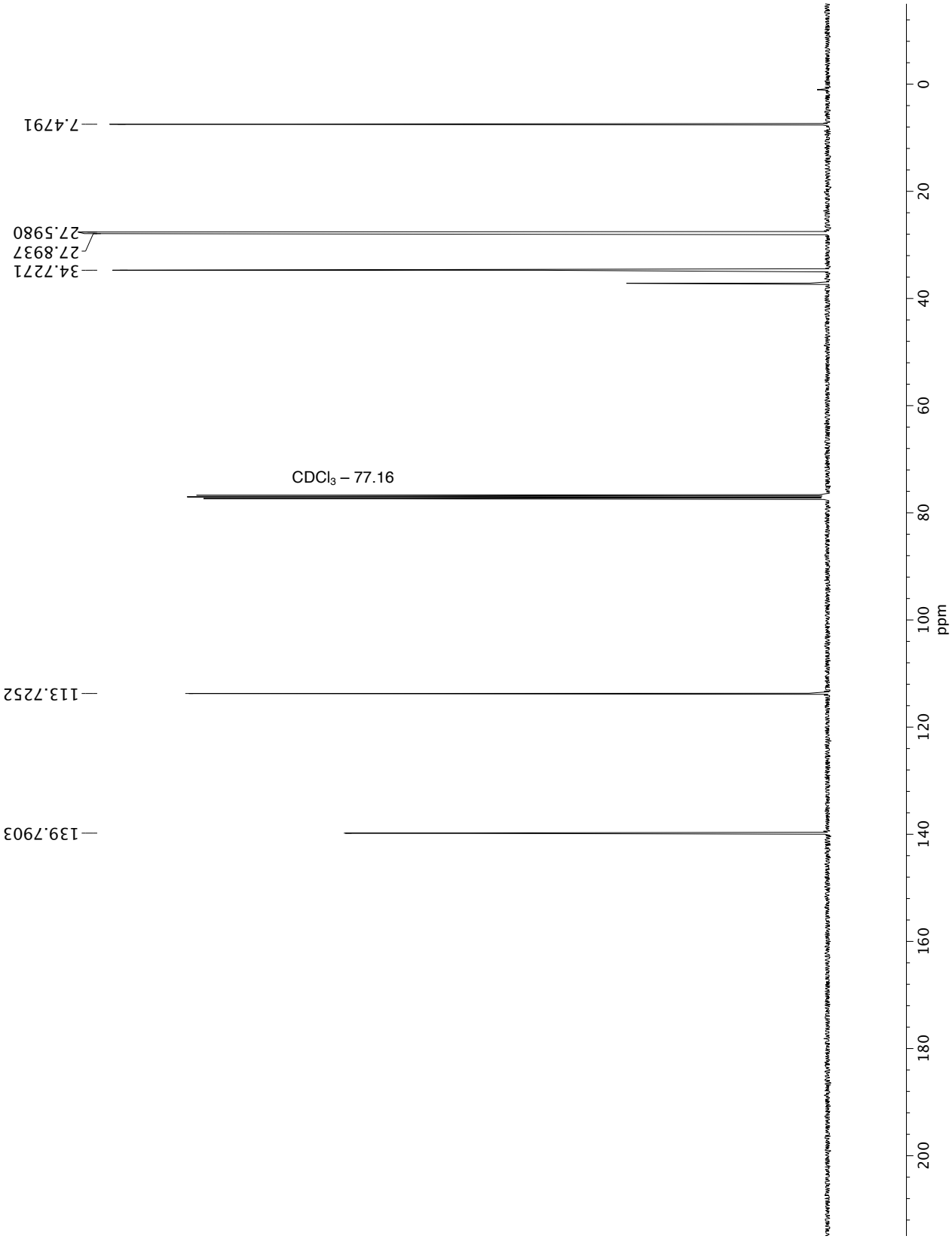

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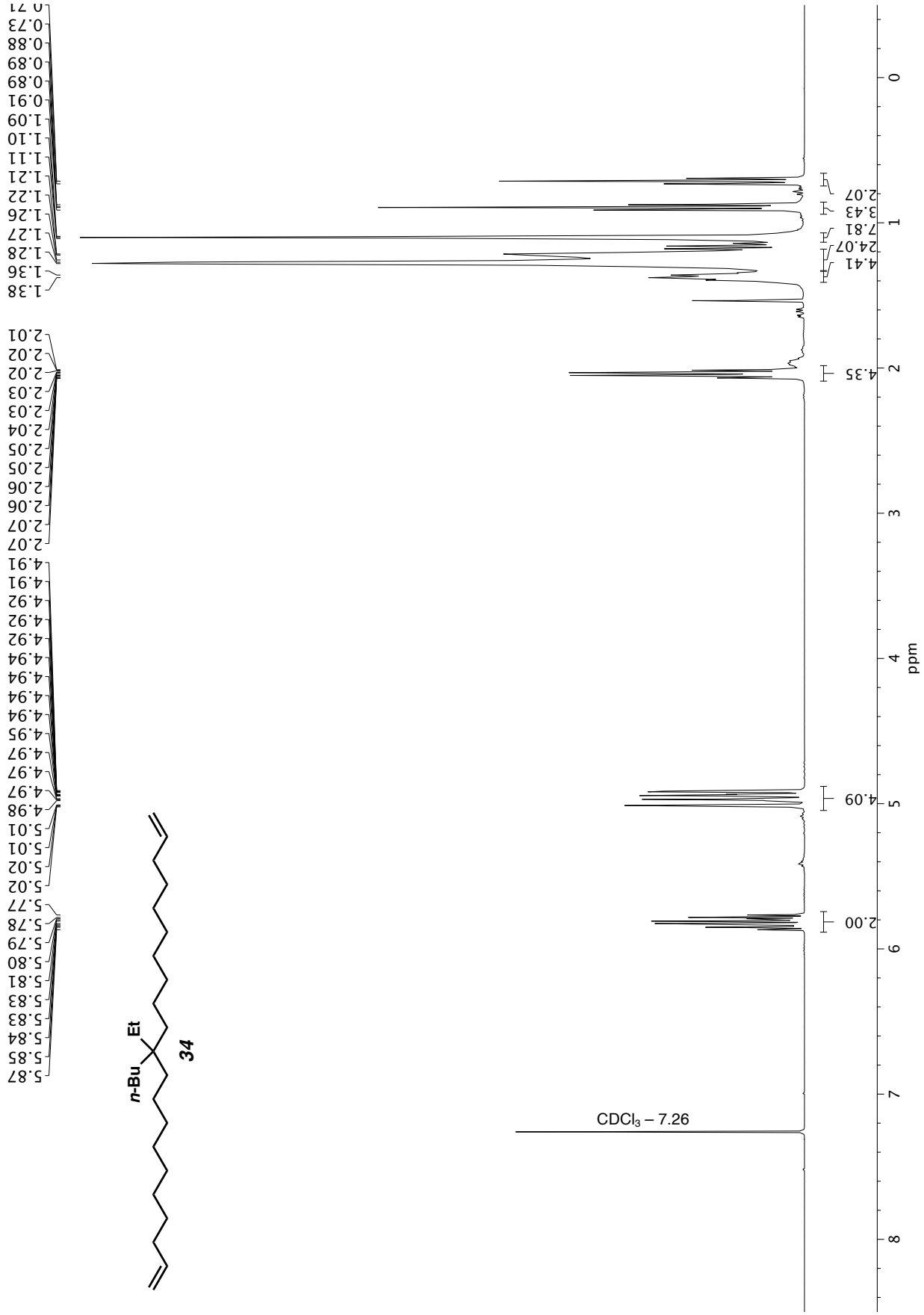

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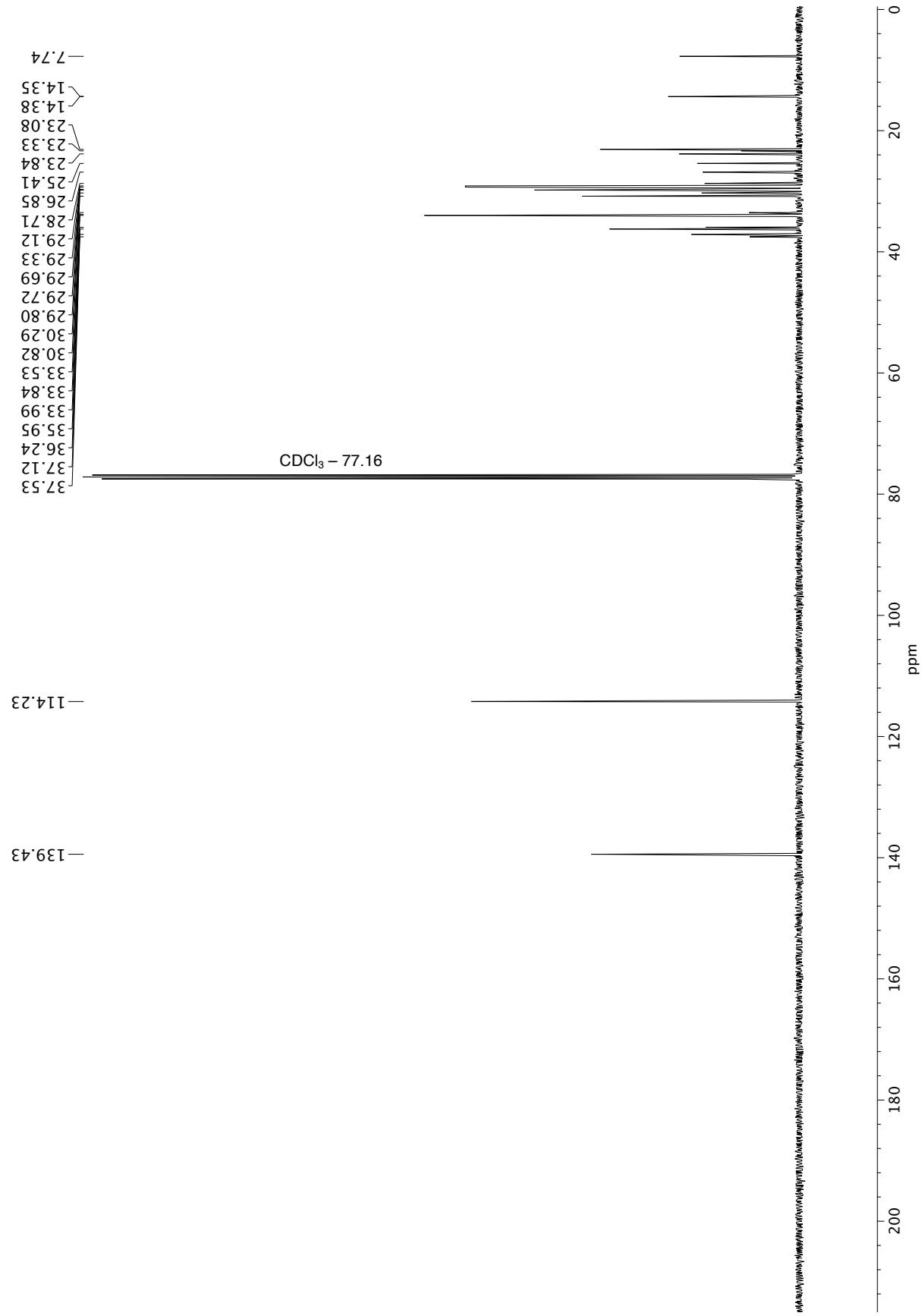

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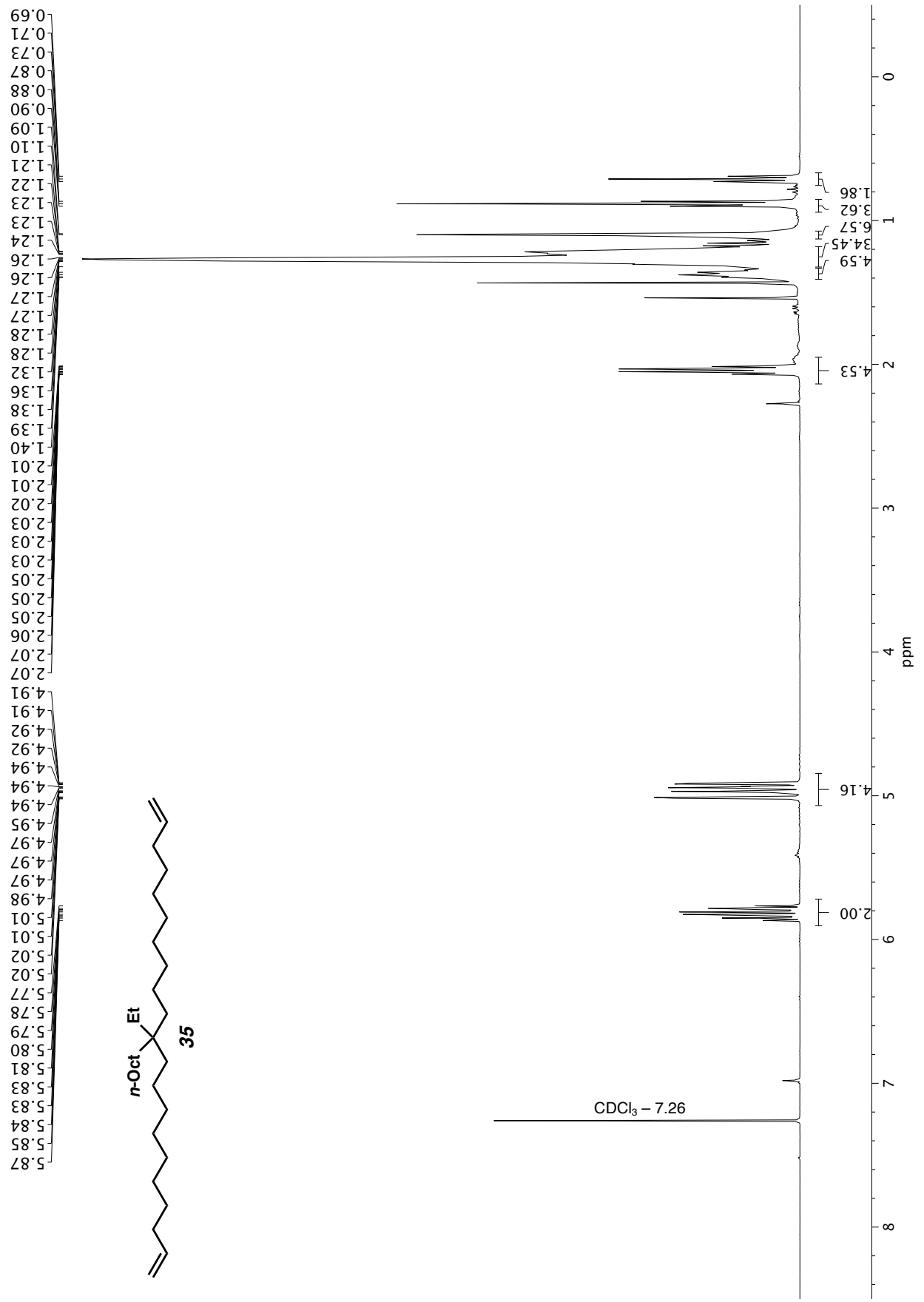
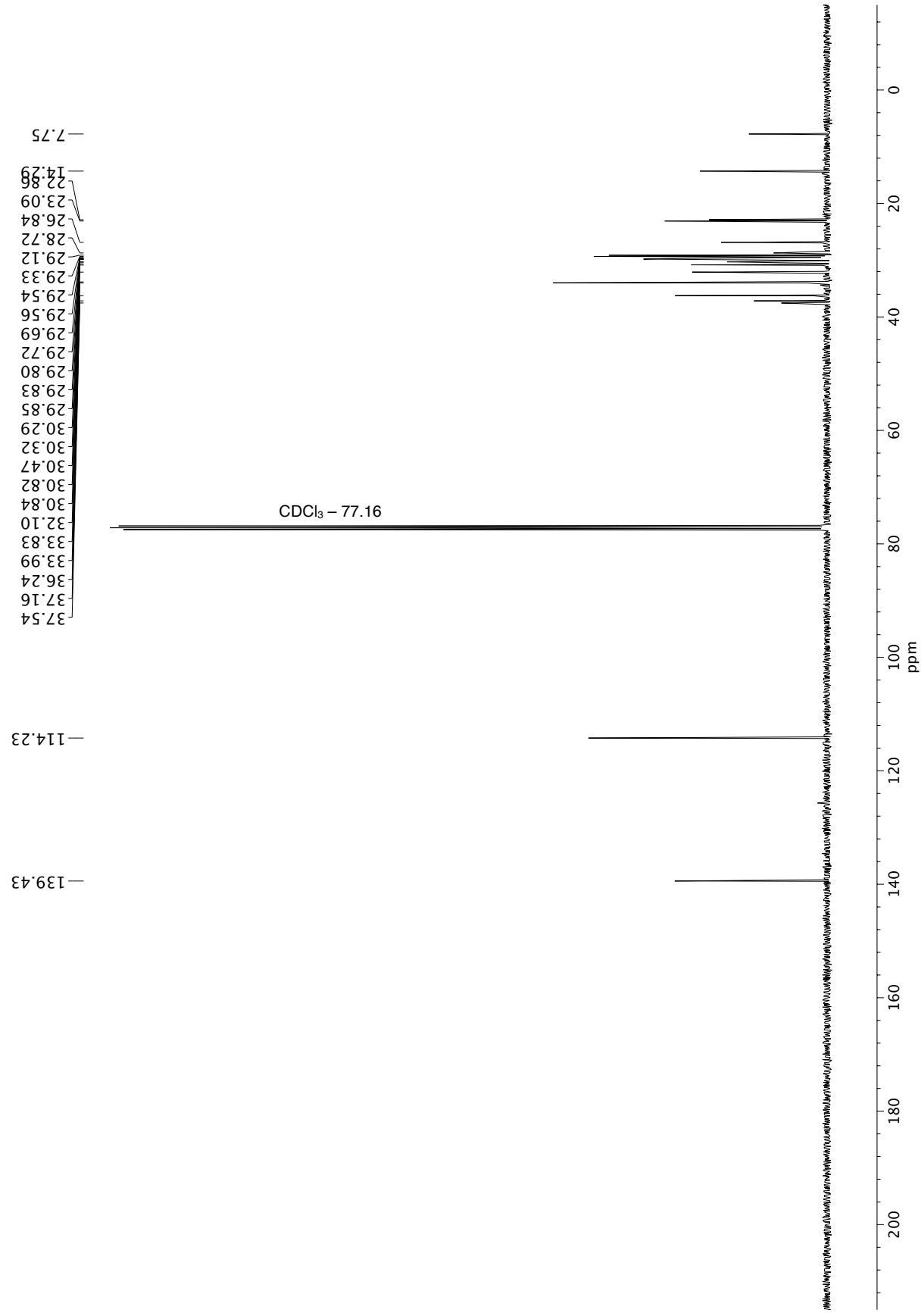


^{1}H NMR (400 MHz, $CDCl_3$) of compound **35**.



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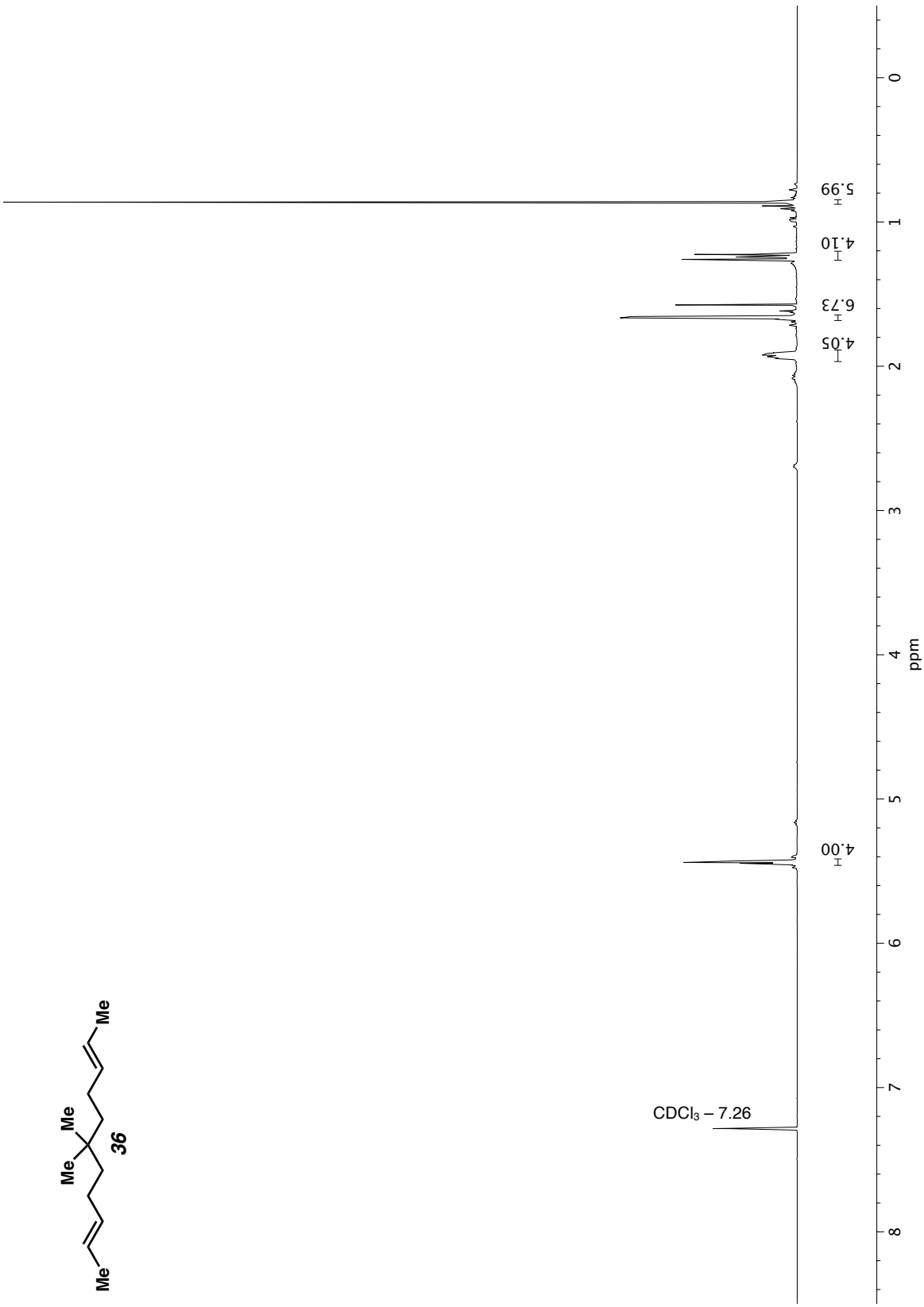

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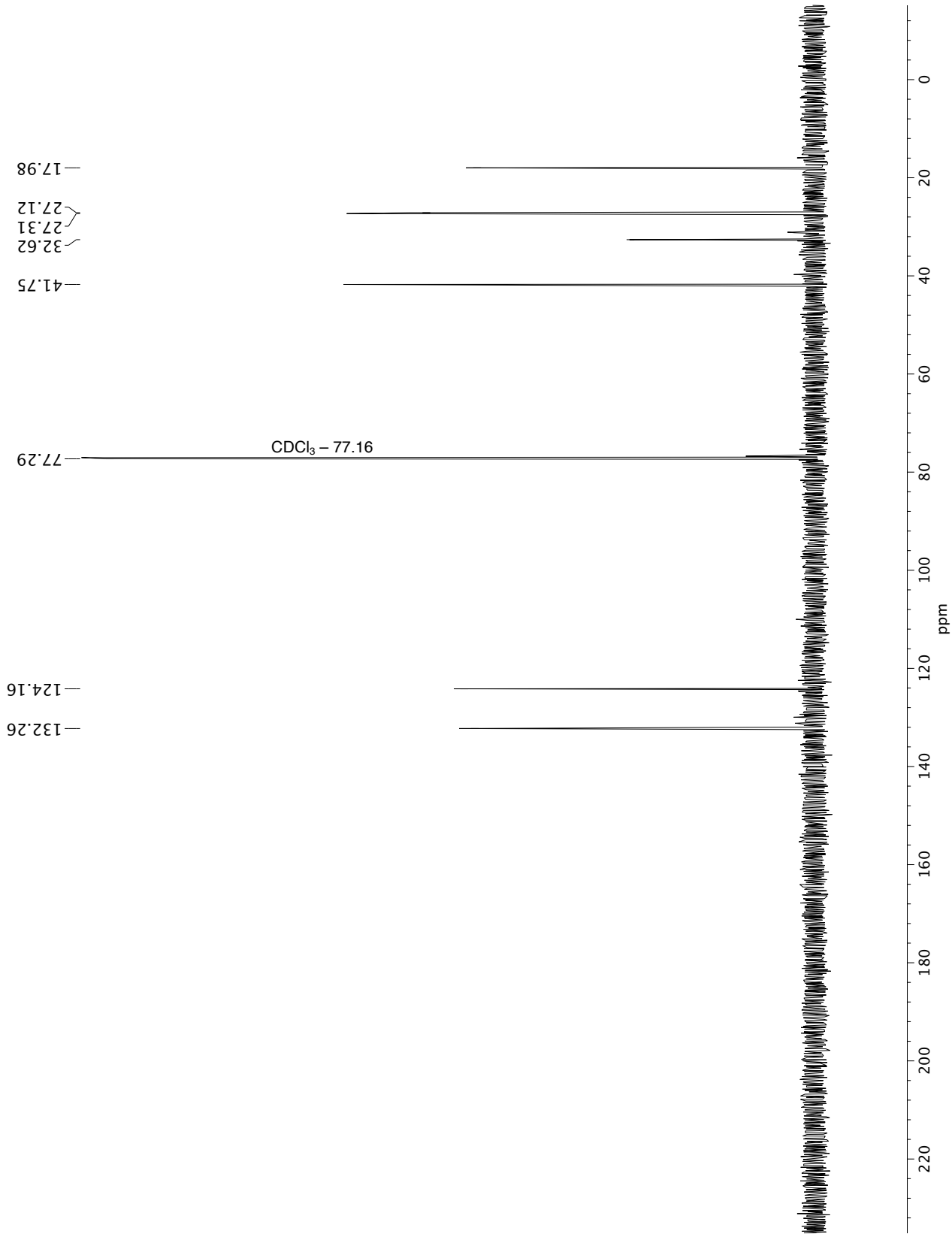

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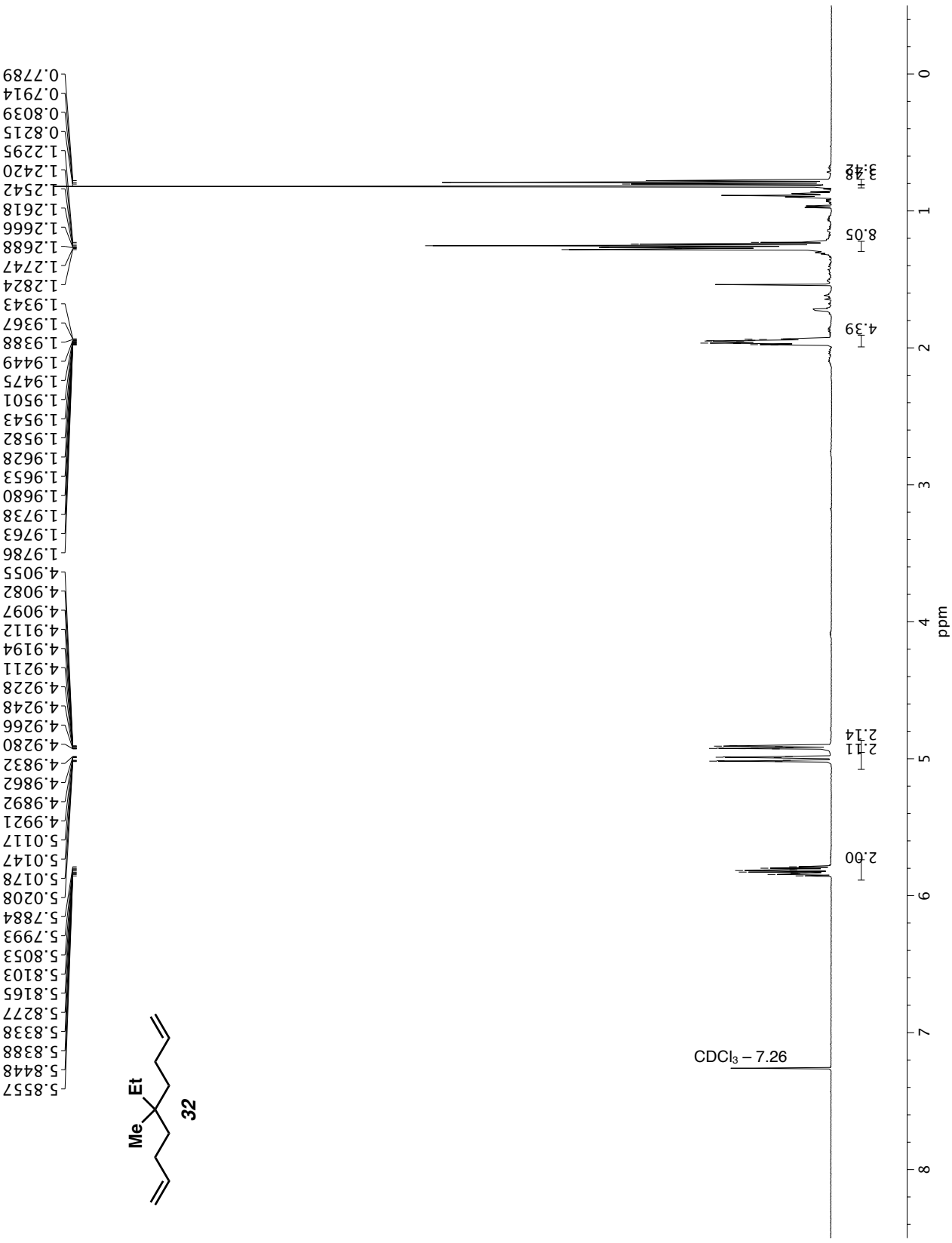

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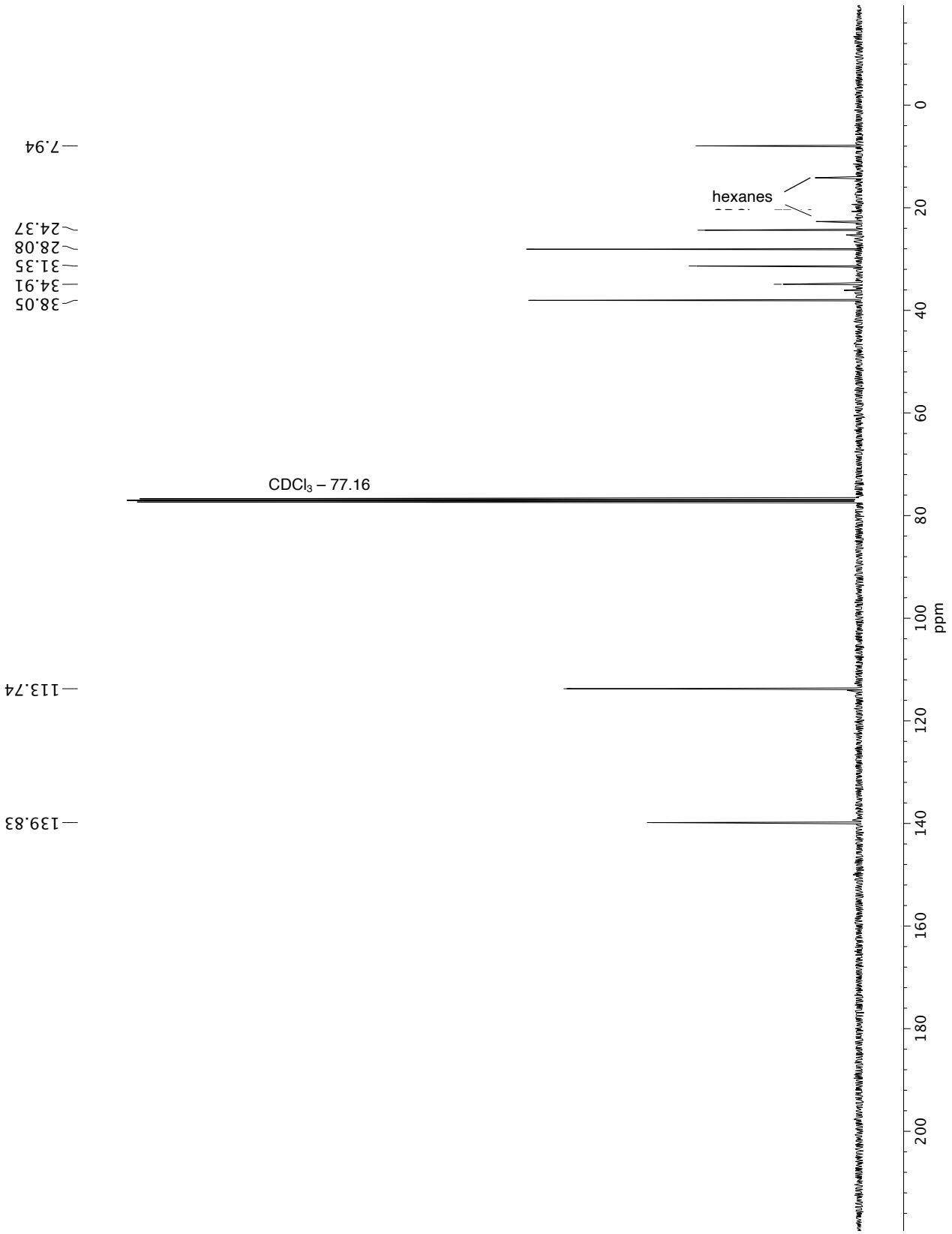

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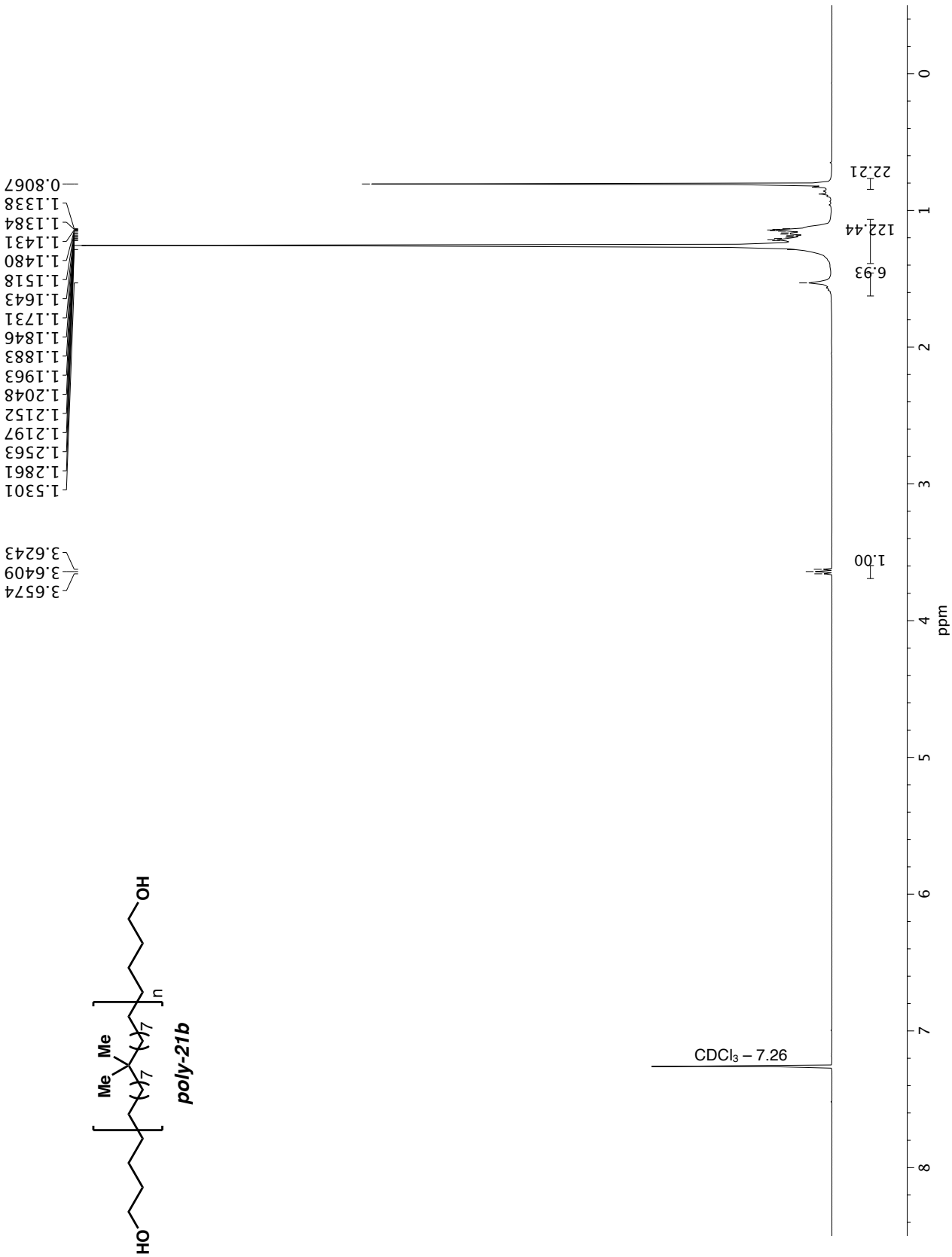

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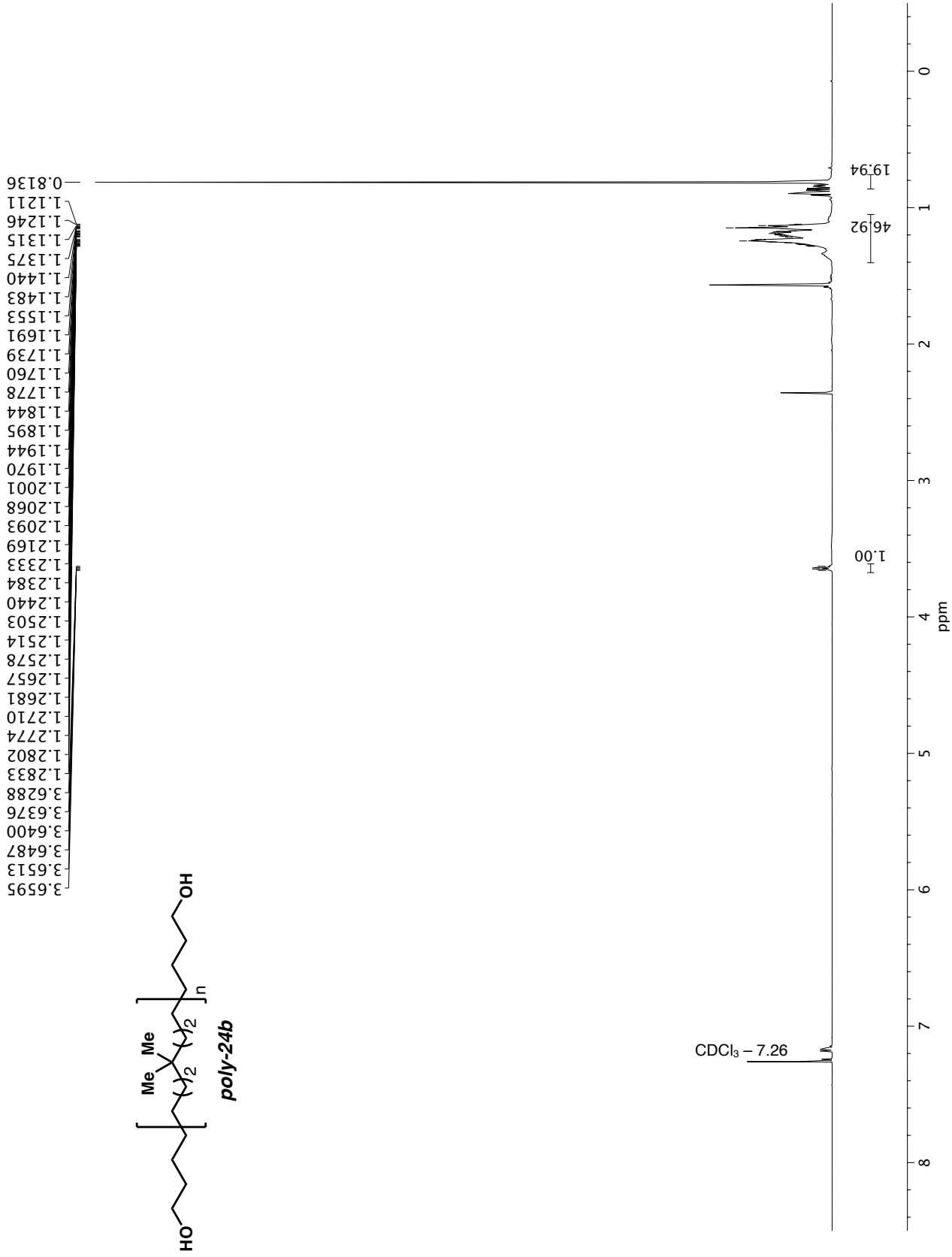

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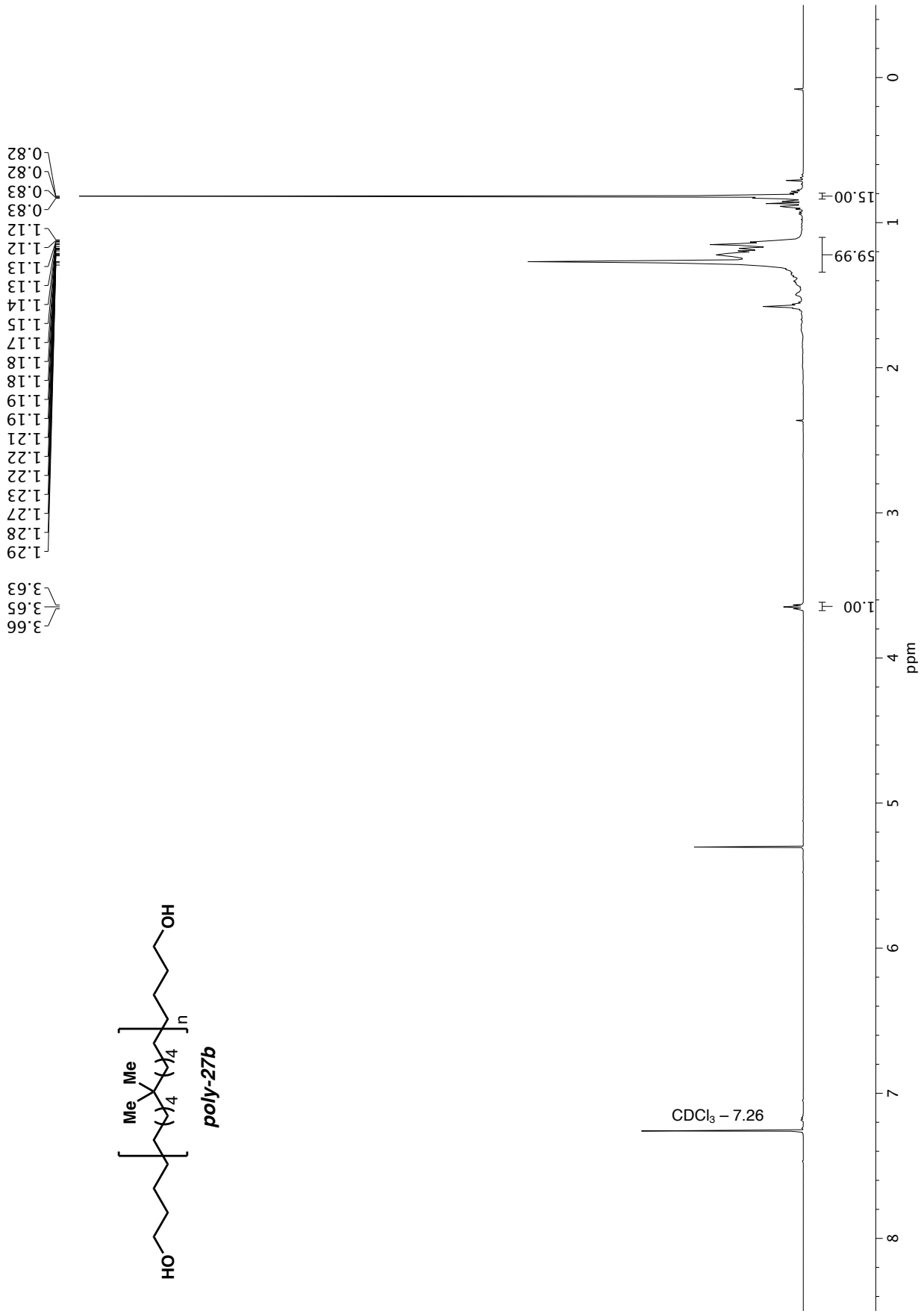

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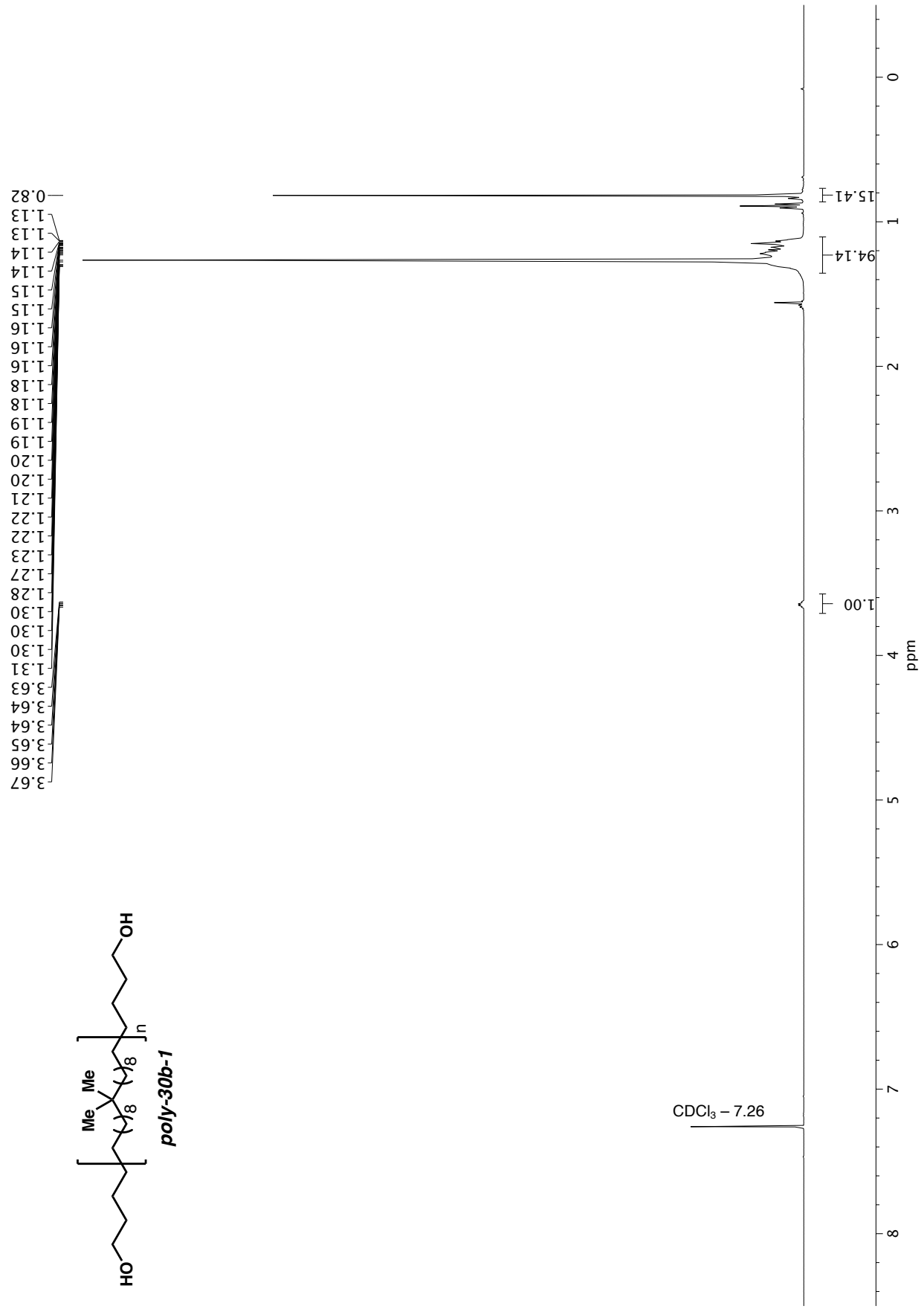
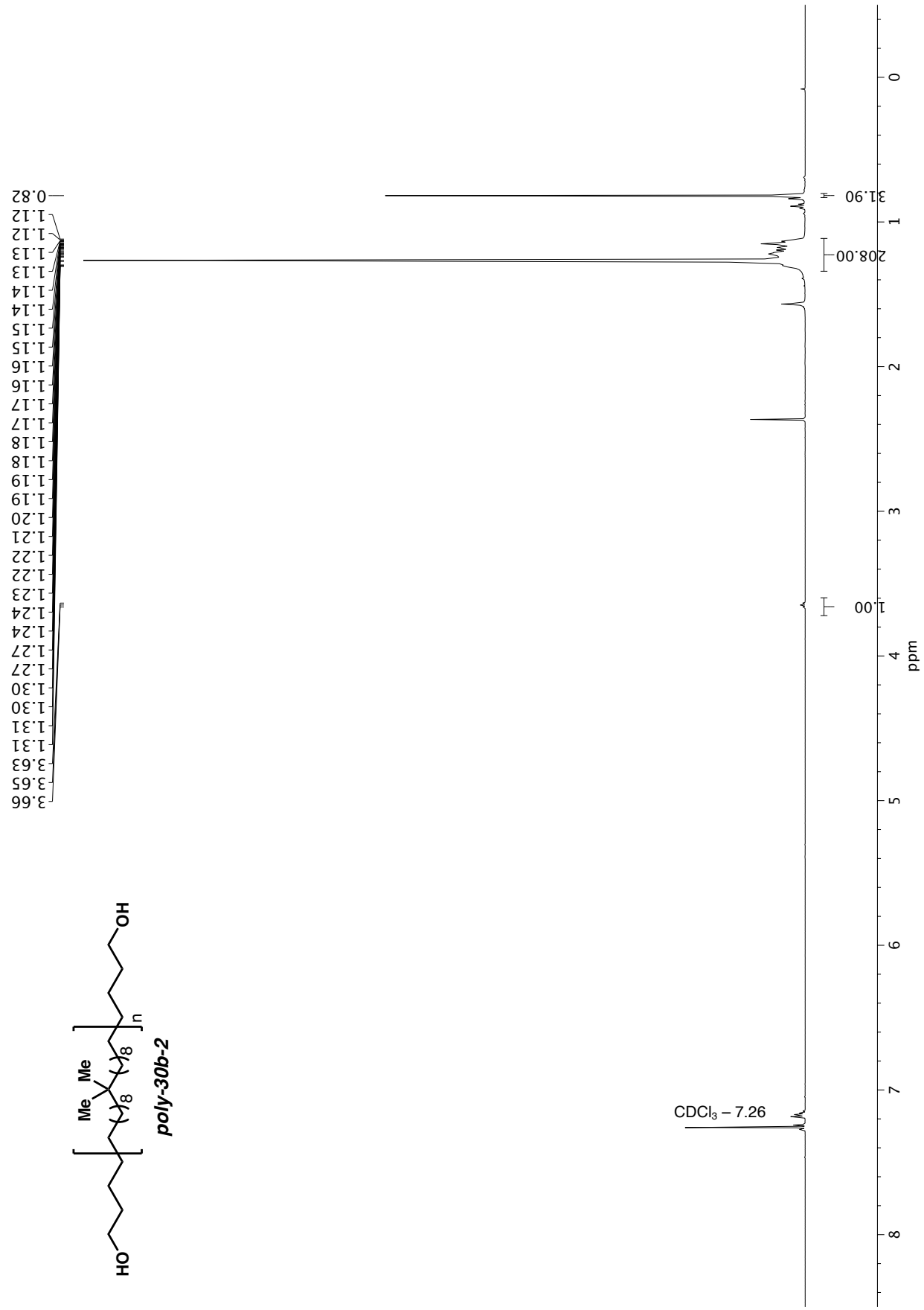
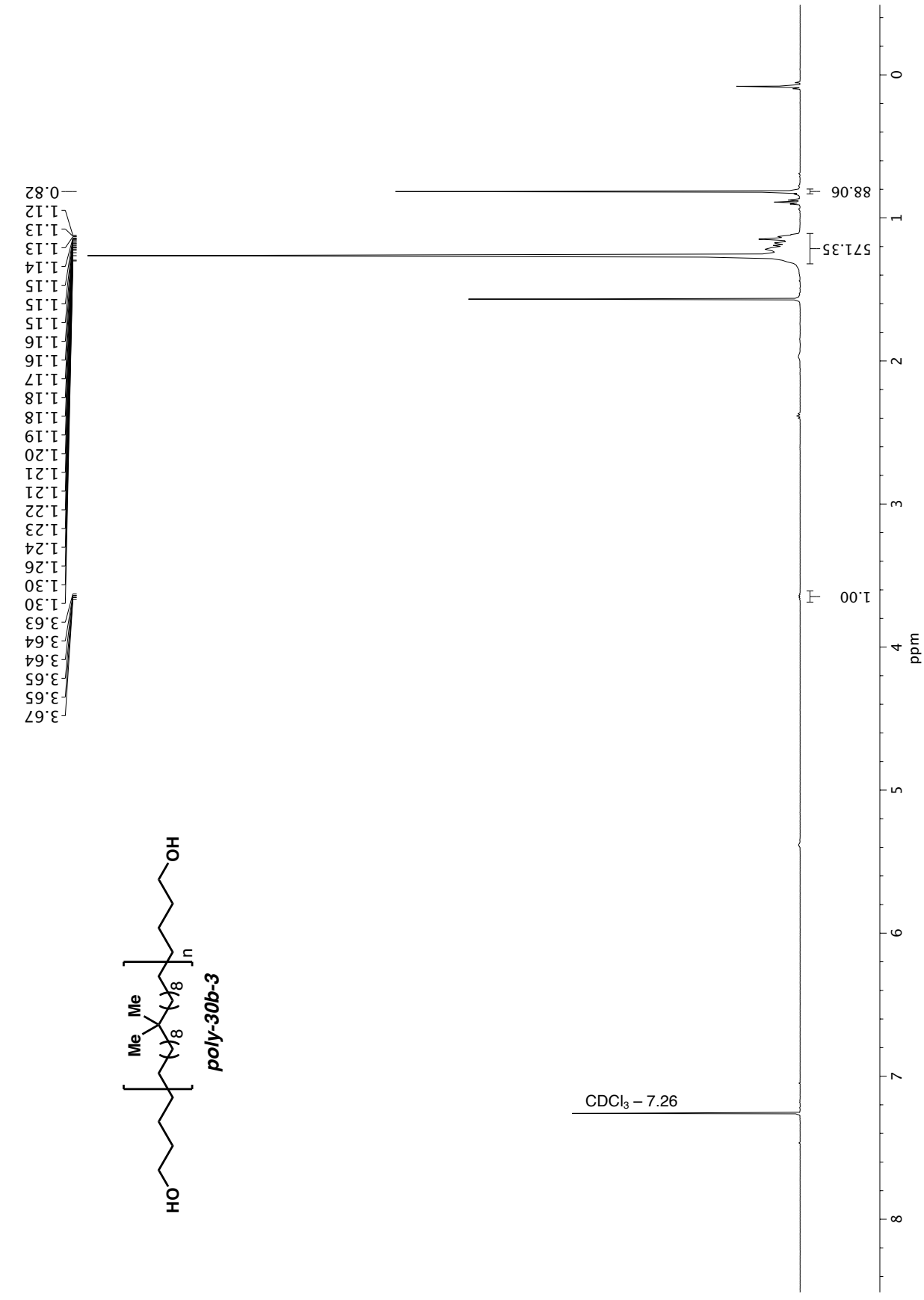


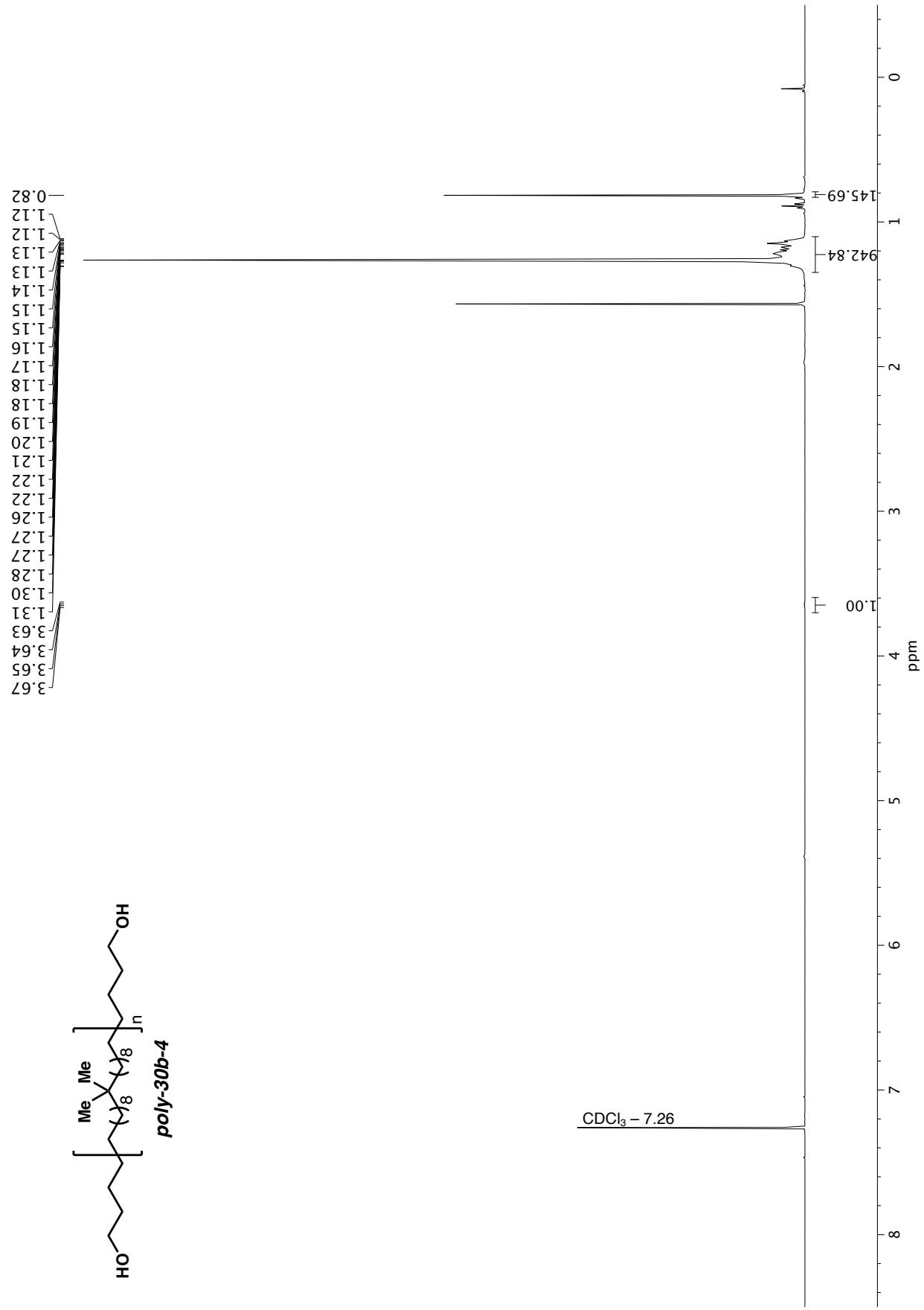
^{1}H NMR (500 MHz, $CDCl_3$) of compound **poly-30b-1**.



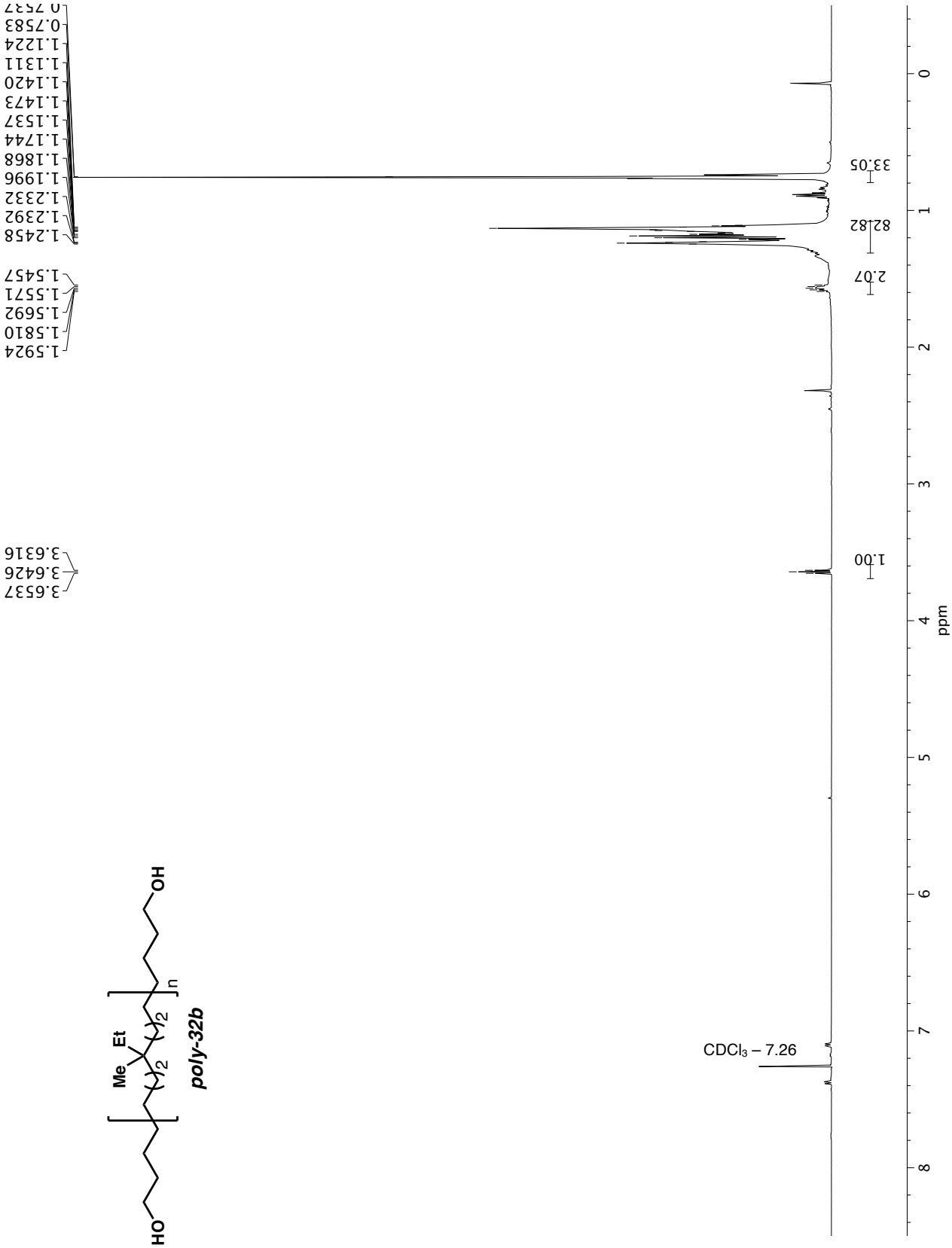
^{1}H NMR (500 MHz, $CDCl_3$) of compound **poly-30b-2**.



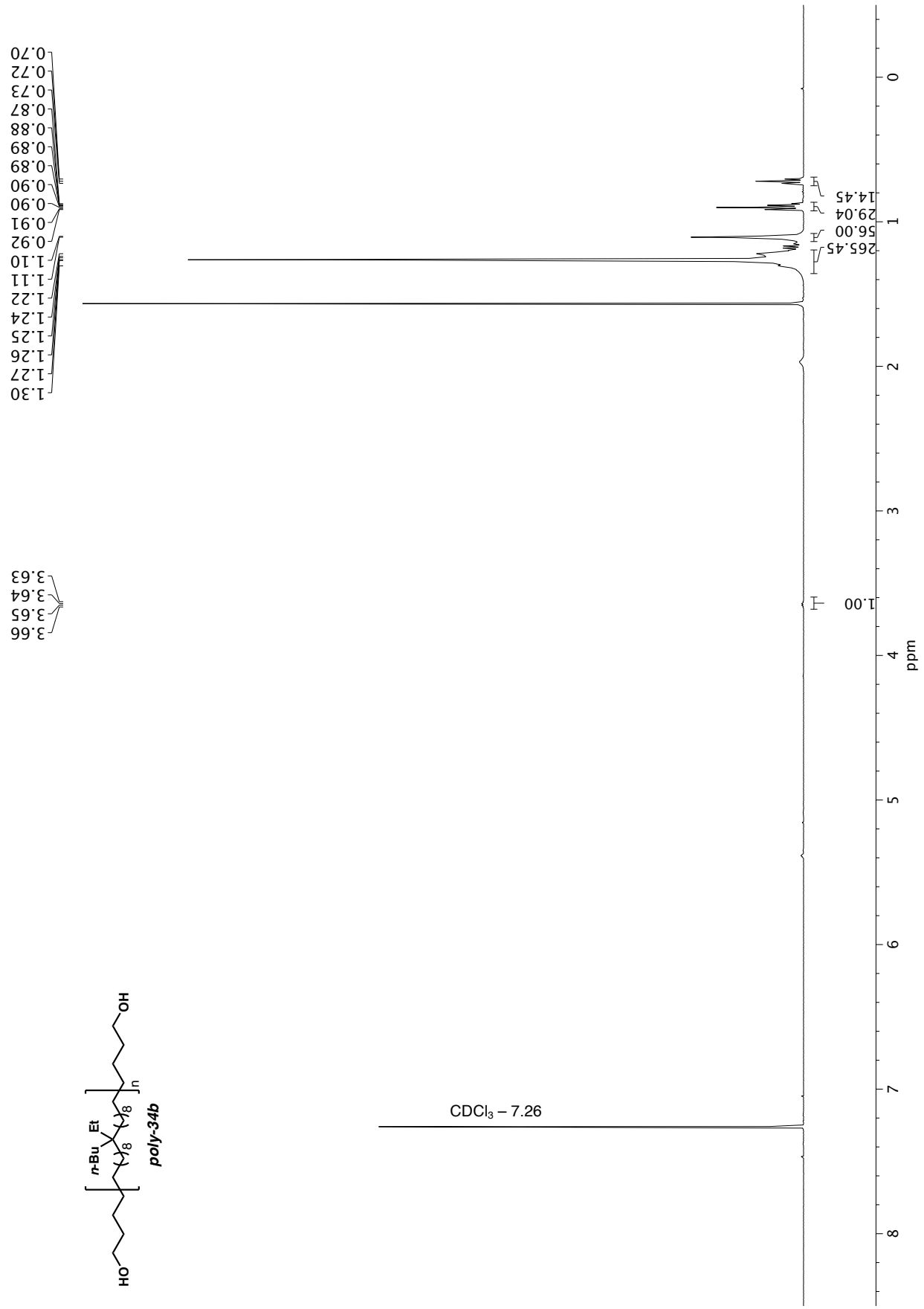
^{1}H NMR (500 MHz, $CDCl_3$) of compound **poly-30b-3**.



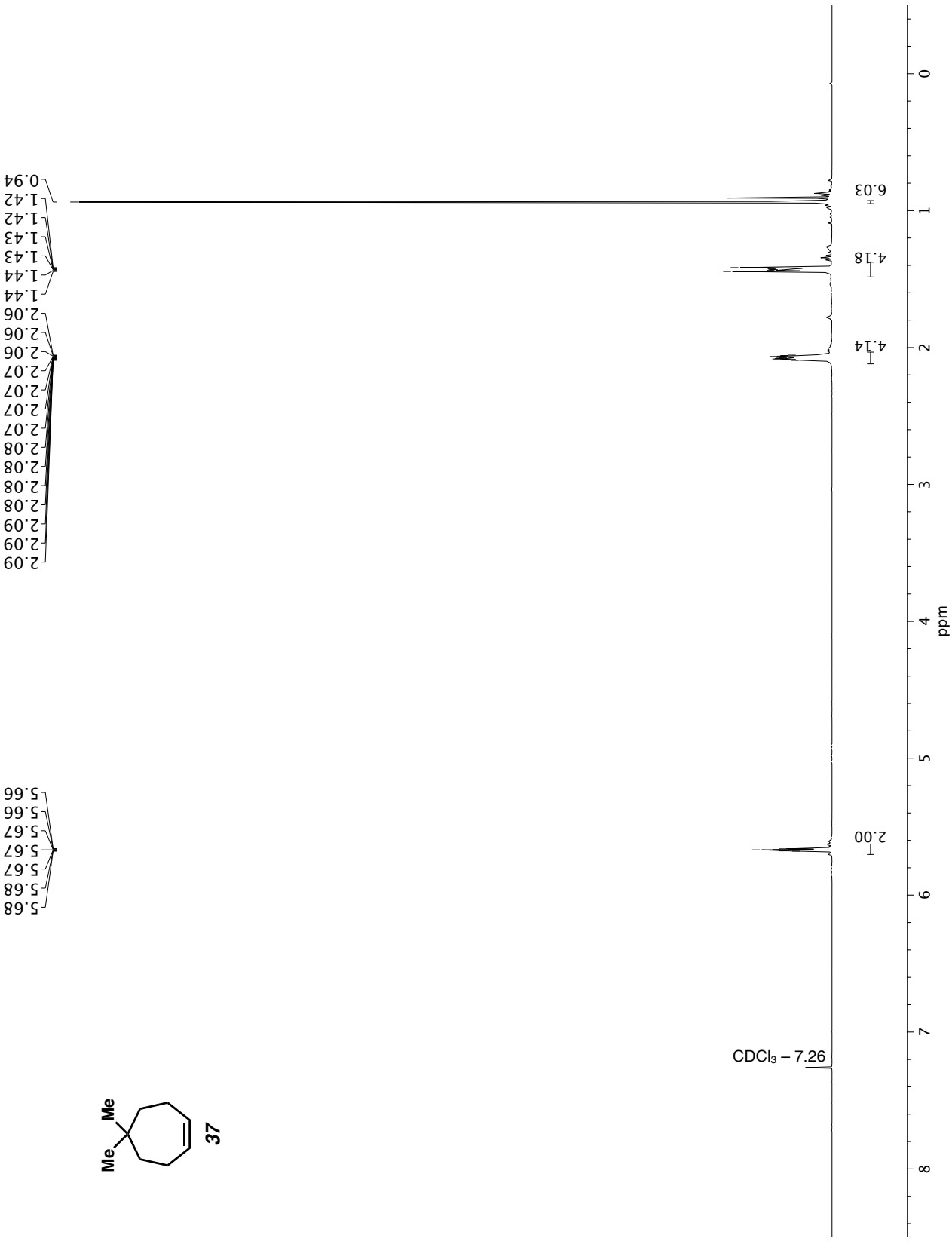
^{1}H NMR (500 MHz, $CDCl_3$) of compound **poly-30b-4**.



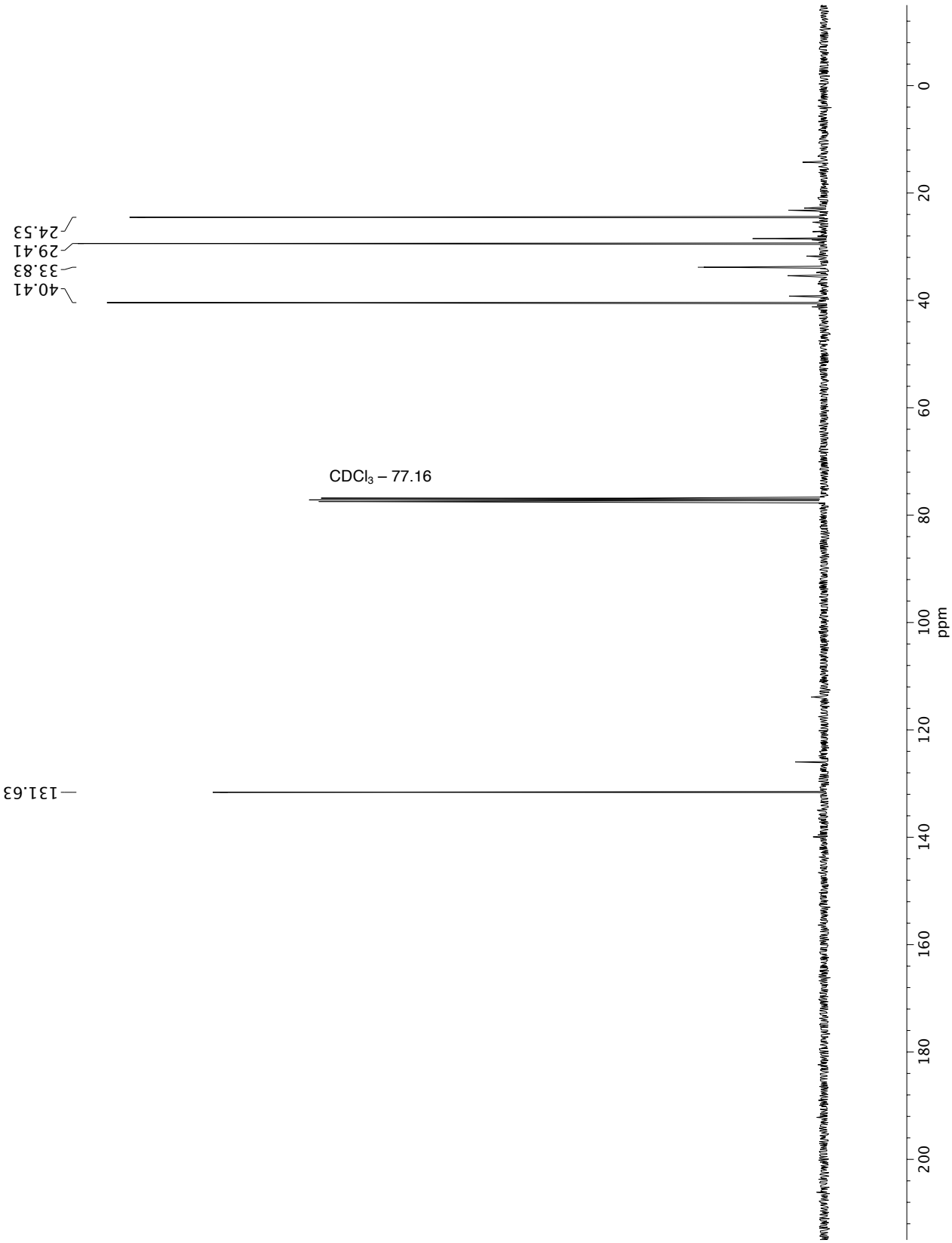
^{1}H NMR (500 MHz, $CDCl_3$) of compound **poly-32b**.



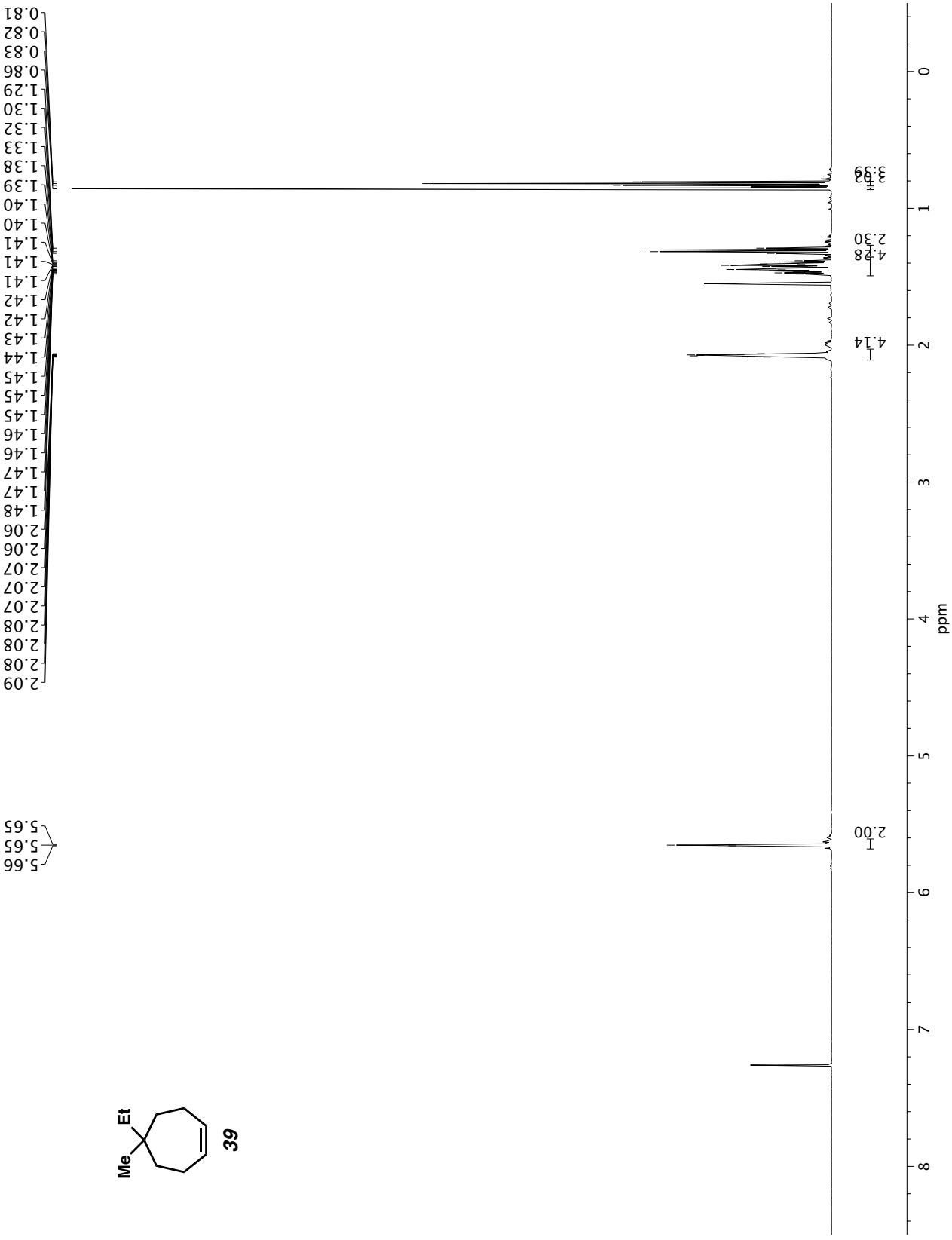
^{1}H NMR (500 MHz, $CDCl_3$) of compound **poly-34b**.



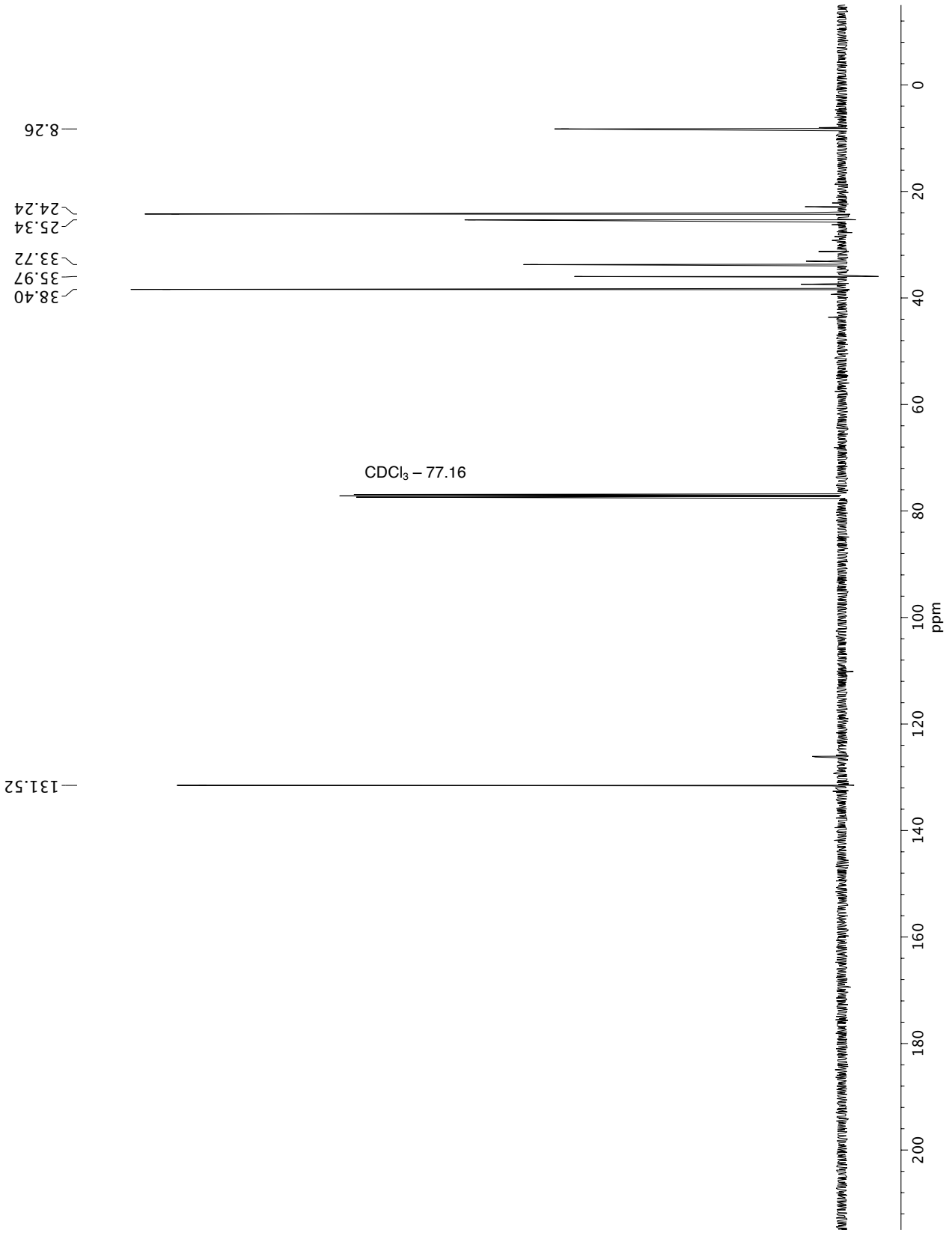
^{1}H NMR (400 MHz, $CDCl_3$) of compound **37**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **37**.



^{1}H NMR (600 MHz, $CDCl_3$) of compound **39**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **39**.

ABOUT THE AUTHOR

Jiaming Li was born in Urumqi, Xinjiang, China on November 28th, 1991 to Yongfu Li and Jiange Tan. Jiaming was raised in Urumqi and hadn't been to other provinces until he was 12, but he was always curious about the outside world. Jiaming was interested in many subjects including science, geography, and history. In high school, he spent most of the summers studying for the Chemistry Olympiad, and learned college level chemistry with his chemistry teacher Manli Jing.

In 2010, Jiaming was admitted to Zhejiang University and spent 4 years in Hangzhou, Zhejiang. Fascinated by the teaching by Prof. Xiaogang Peng in Physical Chemistry and Prof. Ping Lu in Organic Chemistry, Jiaming changed his major from engineering to chemistry. In his sophomore year, he joined Prof. Ping Lu's lab and worked on the synthesis of florescent sensors.

In the summer of 2013, Jiaming had a chance to study abroad and spent two months in Prof. Xi Chen's lab at UC Davis. During his time there, he synthesized a number of oligosaccharides using enzymes. It was a great experience for Jiaming to be immersed in chemical biology research, after taking biochemistry and molecular biology courses. This experience confirmed his goal to apply for graduate school in the U.S.

After obtaining Bachelor's degree in 2014, Jiaming moved to Pasadena, California to pursue his doctoral studies at the California Institute of Technology with Professor Robert Grubbs and Brian Stoltz. His doctoral research focused on the total synthesis of prostaglandins using newly developed olefin metathesis catalysts. Upon completion of his doctoral research in November, 2019, Jiaming will be a postdoc researcher in Prof. Brian Liau's lab at Harvard University.