STUDIES IN PALLADIUM-CATALYZED ALLYLIC ALKYLATION: ENANTIOSELECTIVE TOTAL SYNTHESES OF STRUCTURALLY DIVERSE ALKALOIDS

Thesis by

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To my parents,

They truly are the best.

ACKNOWLEGEMENTS

I can only hope that unlike my numerous over-the-top emails, the following expressions of sincere gratitude are actually read…

Where better to begin than with Professor Brian Stoltz. I actually didn't meet Brian before arriving at Caltech, largely due to a sudden shake-up in the lab's funding situation. In fact, my first conversation with Brian was under the auspices of us having a shared interest in playing the drums. Over the course of that fall term it became increasingly clear that I should join his group, and at the same time increasingly unclear whether that would be possible. After winning an NSF fellowship, I sent Brian an [unprofessionally celebratory] email and he responded by revealing he had forgotten that I had yet to *officially* join the group… classic stuff from both of us. I have come to know Brian and his family quite well over these years and I will certainly miss hearing about the mischief that Harry and Teddy get up to, as well as the teasing and ridicule that Erna so readily throws my way! Brian's willingness to integrate his family into the lab's activities and connect with his group members on a personal level is one of the many things that makes him such an outstanding boss. As much as I cringe at Brian's insistence on describing group members as brothers, sisters, aunts, and uncles, the Stoltz lab is nothing if not a family. Brian's intuition and seemingly endless recollection of chemical synthesis are certainly felt by everyone in the group. Yet it is his ability to place lofty expectations upon his students while simultaneously exuding patience and encouragement that sets him apart from his peers in our field. I am grateful for all the project advice, career guidance, subtext steeped in disappointment and frustration, casual conversation, and vote of confidence you have ever given me.

I'd also like to thank Professor Sarah Reisman for her support as my committee chair. First and foremost, I admire Sarah as a scientist – she is so damn intense about everything she does. She only goes after hard problems, and the creativity and brilliance in her lab's work is something I expect will continue for a very long time. Secondly, Sarah has always been very approachable. I've always felt comfortable coming to her to discuss chemistry or life after Caltech, and she's always felt comfortable zinging me about my personality flaws and affinity for sweatpants. It's been fun.

The other members of my committee, Professors Mark Davis and Bob Grubbs, have also enriched my experiences in graduate school. I have close friends in each of their groups, which has made me come to appreciate them as leaders and mentors. Since we all know them to be endlessly decorated scientists, I'd like to instead highlight how remarkably perceptive they both are. Since neither Mark nor Bob is my chair, and since they both are incredibly busy, I often felt self-conscious about annoying them whenever I had to schedule a meeting or get a form signed. What impressed me time and time again was how Mark and Bob would always manage to mention something from a previous interaction that I had assumed they'd forgotten, if they even noticed to begin with! This seemingly small gesture on their part goes a long way with the students, and I have come to realize that this is simply a byproduct of the culture that my committee members and their faculty colleagues have created. So thank you all for actively supporting an environment where professors treat students as peers.

Dr. Scott Virgil's value to the division cannot be overstated. His sincere interest in, and ability to contribute to *everybody's* project, is difficult to comprehend. I cannot say whether his intellect exceeds his generosity because I have yet to witness the limit of either.

It is only fitting, then, that his wife Silva is such a delightful person in her own right. I have enjoyed their lovely holiday parties, their hard work in supporting what my labmates and I do, and every unplanned encounter with them that brightened my day. The world could use more people like Scott and Silva.

I doubt anyone would ever consider pursuing a PhD without having learned from a series of nurturing and inspiring teachers. I would like to give a special thanks to Professors Harry Ensley, Scott Grayson, Brent Koplitz, Hank Ashbaugh, John Prindle, and Russell Schmehl at Tulane University for their teaching and encouragement. Professor Grayson gave me perhaps the single most useful, if not unsettling, piece of advice regarding grad school: "The easiest part of grad school is getting into grad school." I'd also like to thank Mr. Haywood Torrence, Mr. Mike Auerbach, Dr. Sherwood Williams, Mrs. Kathy Eagen, Mrs. Jennifer Bain-Takahashi, and Mrs. Jennifer Seavey. Ms. Heather Murphy saved my life when I was a senior in high school – shouts out to her.

I must also thank everyone on the administrative side of the division of Chemistry and Chemical Engineering. You all do a fantastic job of ensuring things run smoothly. Special thanks to Lynne Martinez, Agnes Tong, Elisa Brink, Joe Drew, Anne Penney, Paula Higdon, Alison Ross, and Amy Woodall-Ojeda. Caltech CCE also has world-class scientific facilities and resources, which would not be possible without the talents and commitment of Dr. Dave VanderVelde, Dr. Mona Shahgholi, Naseem Torian, Dr. Scott Virgil (bears repeating), Rick Gerhart, and Jeff Groseth.

My time in the Stoltz lab has left me with many irreplaceable friendships. The first of these was formed on my recruitment weekend when I had the pleasure of meeting Dr. Christopher Haley. Christopher's broad interests served to enrich my cultural sensibilities,

and our personality differences (and similarities) resulted in many memorable conversations, meals, and outings. I always admired his ability to identify subtle yet important questions following a seminar, and I have sought counsel from his superb chemical intuition on multiple occasions. I look forward to many more years of him impatiently telling me "Girl, _____."

Dr. Rob Craig[1] is also someone who for better or for worse has become one of my closest friends. Like me, Rob knew next to nothing about synthetic lab technique when he joined the group. As a third year student, he dutifully took first-year-me under his wing. While I never reached his level of experimental skill, he is the reason I don't suck at making molecules. I'm excited that he's going to be in the bay area when we begin our respective careers, and I can't wait to see him bring his synthetic prowess and unmatched work ethic to bear in the world of medicinal chemistry.

Dr. Jeff Holder, Dr. Corey Reeves, and Dr. Jonny Gordon were all highly encouraging and instructive co-workers who helped me get up to speed in the early days. Jeff's taste in professional sports teams is garbage, but despite this sad reality he is a super sharp guy and is someone I know I can count on to always be in my corner. I have always respected Corey for his unbending nature and his ability to not waste time. He also introduced me to Professor Brothers and Point Break, so, you know, ten thumbs up. I lack the verbal proficiency required to properly describe Jonny... he is a singularly unique individual whose unrelenting wit and surprising athleticism have contributed to several of my favorite memories during graduate school.

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1. Also known as: (a) Tiny. (b) Mr. Baby. (c) Rob Rohrs. (d) Captain Tiny Mr. Baby Jr., II.

I joined the lab with one other student – Katerina Korch. I have undoubtedly missed having you around the past couple years, but I am so excited to see the things you'll accomplish at Delaware and beyond. I consider myself very fortunate to be your friend and I wish you nothing but the best.

She is six feet tall, she snort-laughs, she kills her pets, and she can't do a single pullup. Her name is Samantha Shockley and she is the best frienemy I could ask for. Sam is also an incredibly hard worker, a gifted writer, a thoughtful chemist, and someone whose opinion means a great deal to me.[2] Dr. Eric Welin and Dr. J. Caleb Hethcox joined the group in my fourth year and immediately elevated the collective chemical knowledge, accountability, and overall collegial atmosphere within the Stoltz group. I have benefited so much from each of you, intellectually and otherwise. Shoshana Bachman was the first classmate I met before our first-year orientation. We've gone through many of the twists and turns of graduate school concurrent with one another, and have come to be good friends in the process.

I've had the good fortune of working directly with many talented and dedicated chemists over the past few years. Specifically, I'd like to thank Dr. Koji Chiyoda, Dr. Rob Craig, Dr. Etienne Donckele, Jun Kikuchi, Steven Loskot, Dr. Yoshitaka Numajiri, and Chris Reimann for allowing me to work alongside you on some exciting and challenging projects. Speaking of "working alongside," I must thank Elizabeth Goldstein for being an exceedingly kind and lenient hoodmate for the past three years.

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2. I regret putting this in writing.

I have overlapped with some fantastic graduate students over the past five years who I have yet to mention. Dr. Doug Duquette, Dr. Alex Goldberg, Dr. Allen Hong, Dr. Kelly Kim, Dr. Yiyang Liu, and Dr. Nick O'Connor are all people I truly look up to as mentors, and people I am thankful to call friends. To my younger labmates – especially Eric Alexy, Anthony Chen, Tyler Fulton, Steven Loskot, Fa Ngamnithiporn, Chris Reimann, David Schuman, and Austin Wright – the lab is in excellent hands moving forward, and I can't wait to read about all the kick-ass chemistry to come.

I'd like to thank Steven Loskot and Austin Wright in particular for being incredible partners for some of the least pleasant group jobs (Glovebox and Solvent System, respectively). You are both model labmates who take your responsibilities to the group seriously. I have always admired you two for your diligence and accountability, both in the context of these jobs and beyond.

Unsurprisingly, the Stoltz lab attracts outstanding postdocs and visiting scholars from all over the globe. In addition to those previously mentioned, I am particularly thankful to have learned from Dr. Max Klatte, Dr. Guillaume Lapointe, Dr. Marc Liniger, Dr. Wen-bo (Boger) Liu, Dr. Alex Marziale, Dr. Jared Moore, Dr. Gerit Pototschnig, Dr. Daisuke Saito, Lukas Hilpert, and Nina Vrielink.

I am forever indebted to the graduate students who preceded my time in the Stoltz lab, and whose intellectual contributions and tireless efforts have paved the way for my work and the work of my current labmates. I'm lucky to have met many of them and I'd especially like to thank Dr. Kevin Allan, Dr. Eric Ashley, Dr. Doug Behenna, Dr. Chris Gilmore, Professor Mike Krout, Professor Jeremy May, Professor JT Mohr, Professor Jenny Roizen, Dr. Pam Tadross, and Professor Uttam Tambar.

The last few years would be woefully incomplete without the experiences and friendships that I have come to love outside of the lab. Playing softball with my labmates every summer is something that always brought me great pride and enjoyment. Those seasons involved many ups and downs, but you all made our softball team special each and every year. To all my teammates who tolerated my obnoxious hypercompetitive self – thank you. To my friends on opposing teams who hated my obnoxious hypercompetitive self during those games – suck it, we're better than you.

To Trevor Del Castillo, Ben Matson, and Mark Nestbit – thanks for all the jams, pizza, Workaholics, beers, laughs, and of course long-term hospitality toward my drums. I should have made more time to play, but then we wouldn't be able to say things "not bad for five months off," or "still got it!"

One of the best decisions I've made, for many reasons, was to check out Crossfit Resistance. That gym has turned into my California family, and will be hard to leave behind when we move up to the bay. I was in worst shape of my life when I joined in the fall of 2014, and never could have predicted the things I can now do. Crossfit is a source of endless amusement for my friends who don't partake, but it has taught me a lot about setting goals, patience, humility, and discipline. It also helps me justify all the donuts and ice cream I eat. Gainz and food aside, the real MVPs of that experience are Alan and Joanna Jardeleza, Mike and Tina Enriquez, JB and Donna Banayad, Nabil Suleiman, Paolo Sison, Jorge Goytisolo, Brendan Kelly, Alberto Galvan, Mark and Kathy Labajo, Chris Guerra, Patrick Ng, Ara Keshishian, Stirling Dimitrius, Tony Lee, Ron Tien, and Roger Kennedy.

In my time as an RA, I worked with some unbelievably compassionate people. As much as I have loved my time at Caltech, not everyone is as fortunate. And there is a lot of

hard work that happens each and every day on this campus to provide support for every member of this community. Dr. Swarnima Manohar, Dr. Dorothy Pan, Dr. Corey Reeves, and Emily Wyatt are selfless and thoughtful people who did amazing work as RAs – work that so few people will ever know about. I've become especially close friends with Emily, and wish her the best in finishing up at Caltech and beyond. Nilza Santana-Castillo was my immediate supervisor for my final few months in that role, and she continues to serve the grad student community on a daily basis. The joke "does your back hurt from carrying the team?" was originally a reference to Larissa Charnsangavej, or at least that's what I've always assumed. Larissa is one of the most giving people on this planet, and it was so bittersweet to see her leave Caltech. Our team nearly fell apart in her absence, but I'm sure she has already changed the lives of countless people up at Berkeley. My two higher up bosses as an RA were Felicia Hunt and Dr. Kate McAnulty. The two of them are absolute all-stars who are rare examples of unconditional advocates for students at Caltech. Felicia and Kate love their jobs and their teams, and I consider myself extraordinarily lucky to have had a front-row seat to their invaluable contributions to our community. I will always be fiercely loyal to them both, because my thanks alone will never be enough.

The following Caltech friends[3] have helped make my time as a graduate student special: Julian Edwards, Dr. Brett McGuire, Dr. Mike Post, Matt Griffin, Dr. Kangway Chuang, Dr. Maddi Kieffer, Dr. Haoxuan Wang, Victor Mak, Lauren Chapman, Nick Cowper, Dr. Elliot Farney, Alice Wong, Dr. John Steeves, Dr. Nathaniel Kadunce, Kelvin Bates, Julie Hofstra, Dr. Zach Wickens, Dr. William Wolf, Paul Walton, Dr. Oliver

3. There is no order to this list, other than grouping people I associate with one another. I will try to roughly go lab by lab. I'm going to forget somebody. It's a bummer, but it's something we'll have to live with.

Shafaat, Dr. Garret Miyake, Crystal Chu, Dr. Dan Ziegler, Dr. Sue Zultanski, Dr. Wes Sattler, Dr. Aaron Sattler, Matt Davis, Adam Boynton, Joshua Buss, Nik Thompson, Jordan Beck, and Kelsey Poremba.

There is a very dear group of friends I must thank for their unconditional love and good will. I have known them so well for so long that neither my move across the country, nor the month-long stretches of zero communication due to the lonely abyss that is graduate research could jeopardize those relationships. I've known Jarel Cohen, James Cody, and Will Riedel since the summer before highschool and we have been emotionally inseparable ever since. Add in Connor Fleming, Hannah Catlow, and Ana Vucetic and you have quite simply the finest group of friends that I will never deserve. I'm not going to say anything more specific here for three reasons: 1) You all know *exactly* how I feel about you and how we got to this point, 2) *None* of you are ever going to read this, and 3) other people *might* read this and it's none of their goddamn business. It would be remiss of me to not point out how lucky I am to have become a part of your respective families, and vice versa. Much love to Dave and Pava Cohen, Sharon Williams, Doug Fleming and Laura Sardo, and the late Dr. Charles Riedel.

I also have wonderful family and friends, and would like to thank the following people for truly caring about me and supporting me throughout my life. Especially Rich Sibly, Doug and Jean Johnson, Bud and Nancy Langworthy, Bob and Sigrid Calandra, Scott Holtzmann and Joann Marshall, Nick and Julie Noyes, Dennis and JoAnne Simmonds, Casey Brown, John and Charlotte Sibly, Brett and Kim Seeger, David Centers, and families thereof.

To my sisters, Allison and Shelly, thank you for loving me despite the multitude of differences between us. The three of us are almost totally orthogonal in how we are wired yet we have always managed to be there for one another. Allison, I hope that you are able to read between the lines of my tough love to see how unbelievably proud I am of you and what you do. Shelly, we are almost on the complete opposite ends of the spectrum in how we prefer to communicate but I think about you and your incredible family every day. Korry, Bella, and Eva are enormously important to me as well – plus now that mom and dad live in New Orleans I can see you all every trip home!

If I had to choose the single best thing that has happened since I moved to the West coast, it is without a doubt the addition of Dao Chau Nguyen in my life. DC is thoughtful, intelligent, funny, prickly, beautiful, and quite simply perfect. Living together for the past year has been wonderful – starting and ending each day with her makes all the stuff in between so much easier. I love how we've integrated into one another's families, and I can't wait to move up North with you and Rumble.

Finally, I love my parents. So much. My adult life has insanely big shoes to fill because Pat and Jean worked their asses off to provide me with a rich and unforgettable childhood. The work they did overseas meant I got to spend all five years of elementary school living in the Philippines and Panamá. There are so many incredible places I would have never seen and people I would have never met were it not for my parents. Their careers were defined by doing dangerous and challenging work that by nature resulted in zero external attention or praise. Thus, my motivation to make meaningful contributions to modern medicine is directly inspired by my parents' values and demeanor. The hardest part about coming to Caltech was knowing that I would only see them 2–3 times per year. It is

literally painful to think about how much more time I wish I could have spent with them over these years. They are supportive to a fault, and have only ever wanted me to take the best possible steps forward. Somehow this summer I am moving farther away from them still! At least now they're retired and I'll have weekends free to host them as often as they'd like. Mom and Dad, I love you.

ABSTRACT

Presented herein are three projects, all unified by the use of palladium-catalyzed, enantioconvergent, decarboxylative allylic alkylations to synthesize stereochemically rich, nitrogen-containing small molecules. The ubiquity of nitrogen in biologically active natural products and pharmaceutical ingredients necessitates perpetual exploration and development of relevant small molecules. Highly robust palladium-catalyzed allylic alkylation reactions of non-stabilized enolates enable the construction of sterically encumbered all-carbon quaternary and tetrasubstituted tertiary stereocenters present within such targets.

The successful development of a novel substrate class for palladium-catalyzed allylic alkylation, namely dihydropyrido[1,2-*a*]indolones (DHPIs), has enabled divergent syntheses of multiple monoterpene indole alkaloids. By setting the C20 quaternary stereocenter present within these alkaloids at an early stage in the synthesis, the remaining stereocenters can be forged with exquisite levels of control. Critical to the success of this work was the identification of highly tunable and predictable cyclizations between an indole and a C2-tethered iminium moiety. Regiodivergent cyclizations were used to complete the first catalytic enantioselective total synthesis of (–)-goniomitine, along with efficient formal syntheses of (+)-aspidospermidine and (–)-quebrachamine. Stereodivergent cyclization strategies were then employed in total syntheses of (+)-limaspermidine and (+)-kopsihainanine A. Synthetic efforts toward the highly caged *Kopsia* alkaloids (–)-kopsinine, (–)-kopsinilam, and (–)-kopsifoline G are also discussed.

Lastly, the synthesis of challenging α-quaternary Mannich-type products was accomplished through a simple, elegant inversion of strategy. The chiral building blocks made available by this technology bear significant potential in the realm of medicinal chemistry. Furthermore, this work enabled rapid total syntheses of (–)-isonitramine and (+)-sibirinine.

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B.P.P. participated in project design, evaluated the reaction scope, completed the conversion of (–)-isonitramine to (+)-sibirinine, and participated in writing of the manuscript.

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B.P.P. lead project design, execution, and writing of the manuscript.

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B.P.P. participated in project design, evaluated the reaction scope, and lead the preparation of the manuscript.

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LIST OF ABBREVIATIONS

Å	Ångstrom
λ	wavelength
μ	micro
$[\alpha]_D$	specific rotation at wavelength of sodium D line
[H]	reduction
[O]	oxidation
°C	degrees Celsius
Ac	acetyl
AcOH	acetic acid
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
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
cf.	compare (Latin confer)
CI	chemical ionization
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DIBAL	diisobutylaluminum hydride
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
e.g.	for example (Latin exempli gratia)
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide

ee	enantiomeric excess
EI+	electron impact
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
h	hour(s)
$h\nu$	light
HMBC	heteronuclear multiple bond correlation
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
Hz	hertz
i.e.	that is (Latin id est)
IBX	2-iodoxybenzoic acid
IPA	isopropanol, 2-propanol
i-Pr	isopropyl
IR	infrared (spectroscopy)
IRC	intrinsic reaction coordinate
J	coupling constant
K	Kelvin(s) (absolute temperature)

kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L	liter; ligand
LDA	lithium diisopropylamide
lit.	literature value
m	multiplet; milli
m	meta
M	metal; molar; molecular ion
m/*z*	mass to charge ratio
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
MM	mixed method
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal
nbd	norbornadiene
NBS	*N*-bromosuccinimide
n-Bu	butyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Ns	2-nitrobenzenesulfonyl

Nu	nucleophile
o	ortho
p	para
PCC	pyridinium chlorochromate
Pd/C	palladium on carbon
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PHOX	phosphinooxazoline ligand
p*Ka*	p*K* for association of an acid
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTU	*n*-Propylthiouracil
Py	pyridine
q	quartet
R	generic for any atom or functional group
Ref.	reference
R_f	retention factor
s	singlet or strong or selectivity factor
sat.	saturated
SFC	supercritical fluid chromatography
sp	sparteine
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide

TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
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
TOF	time-of-flight
Tol	tolyl
t_R	retention time
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
v/*v*	volume to volume
w	weak
w/*v*	weight to volume
X	anionic ligand or halide

Chapter 1

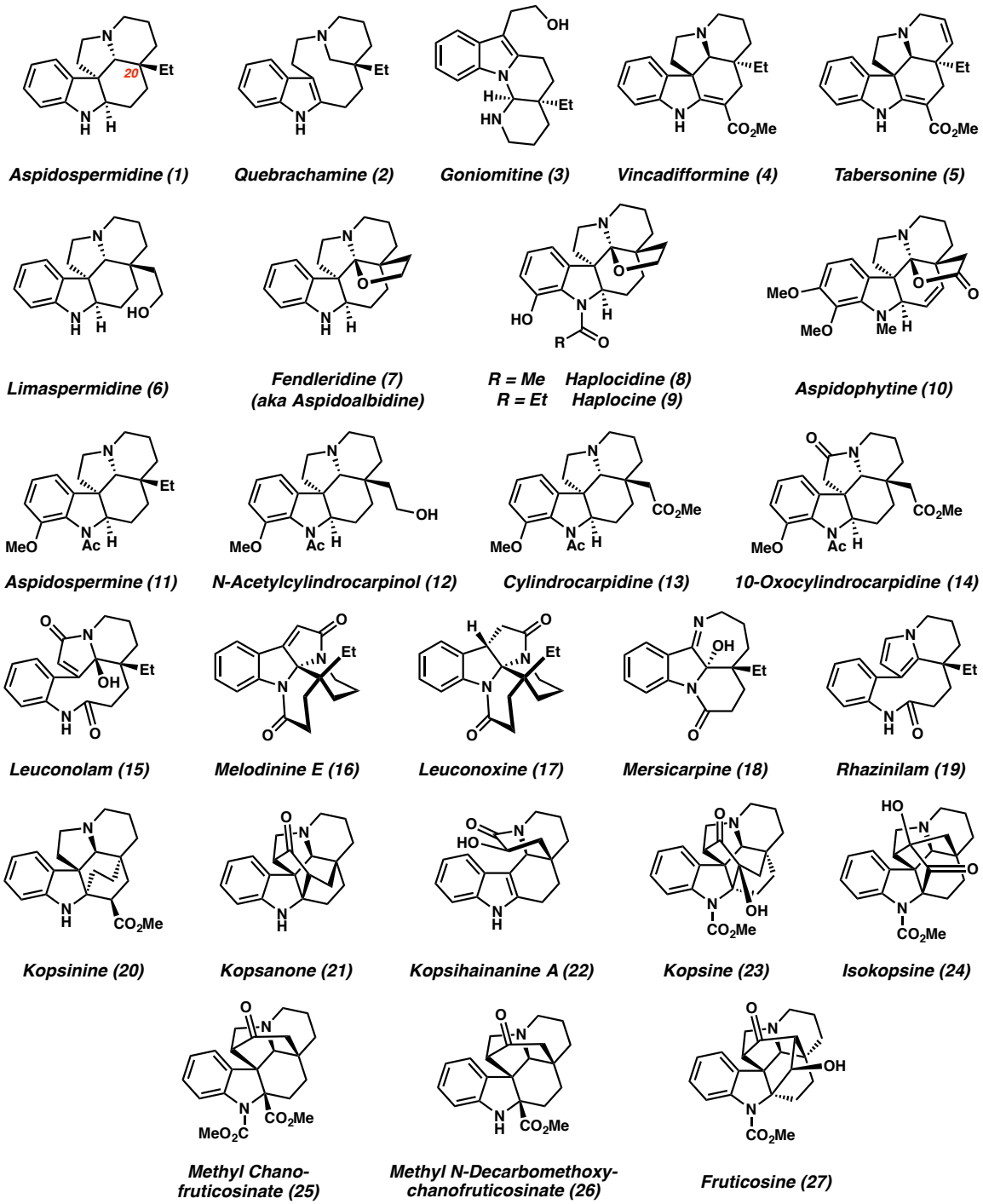
Enantioselective Palladium-Catalyzed Allylic Alkylation Reactions in the Synthesis of Aspidosperma and Structurally Related Monoterpene Indole Alkaloids

1.1 INTRODUCTION

The structural intricacies and biological activities of monoterpene indole alkaloids have rendered these compounds attractive targets for total synthesis over the course of more than half a century.[1] In particular, the structurally related *Aspidosperma* and *Kopsia* classes of alkaloids comprise some of the most frequently targeted structures in chemical synthesis (Figure 1.1.1). Consequently, numerous strategically unique total syntheses have been reported for various *Aspidosperma* and *Kopsia* family members. In the past five years, however, enantioselective Pd-catalyzed allylic alkylation reactions of prochiral enolates have become an increasingly popular tool to construct the stereogenic all-carbon quaternary center at C20,[2] which is a unifying feature of these classic targets (see **1**, Figure 1.1.1). Presented herein are completed enantioselective syntheses of *Aspidosperma* and *Kopsia* alkaloids that implement such a Pd-catalyzed allylic alkylation.

In order to establish a broader context within this field, we will briefly discuss other noteworthy unified strategies that have enabled successful syntheses of multiple monoterpene indole alkaloids from the *Aspidosperma* and/or *Kopsia* families. While some non-asymmetric syntheses of these compounds have undoubtedly made profound contributions to modern organic synthesis, we will only cover enantioselective syntheses in this review.

Figure 1.1.1. Representative Aspidosperma and Structurally Related Alkaloids



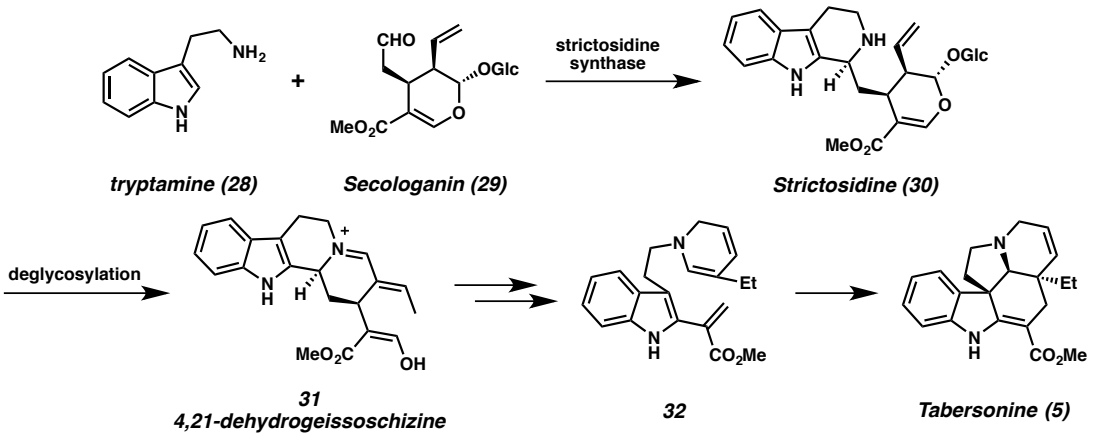
1.2 STRUCTURE, BIOSYNTHESIS, AND NOTEWORTHY BIOLOGICAL ACTIVITY OF ASPIDOSPERMA AND RELATED ALKALOIDS

The *Aspidosperma* alkaloids are unified through a largely conserved pentacyclic core that is most clearly visible in the non-functionalized namesake of the family, aspidospermidine (**1**, Figure 1.1.1).[3] Two notable structural outliers are the nine-membered ring-containing quebrachamine (**2**),[4] and the aminal-containing goniomitine (**3**).[5] Vincadifformine (**4**)[6] and tabersonine (**5**)[7] contain additional unsaturation within the pentacyclic core. Common oxygenation patterns include terminal alcohols (e.g., **6**),[8] *N,O*-ketals (e.g., **7**–**10**),[9,10] and oxygenation about the benzene fragment (e.g., **11**–**14**).[11–14] Leuconolam (**15**)[15] is related to *Aspidosperma* alkaloids through indoline oxidative cleavage, and can undergo subsequent ring closure to furnish various aminal-containing structures (e.g., **16** and **17**)[16,17] or additional rearrangement and fragmentation to give mersicarpine (**18**).[18] The pyrrole ring in rhazinilam (**19**)[19] is expected to originate from a biochemical oxidation pathway similar to that of leuconolam (**15**).[20] *Kopsia* alkaloids (e.g., **20**–**27**)[21–28] typically contain additional carbon-based rings, often resulting in highly caged structures.

The biosynthesis of all monoterpene indole alkaloids is believed to begin with an enzymatic Pictet–Spengler reaction[29] between tryptamine (**28**) and secologanin (**29**) to yield strictosidine (**30**, Scheme 1.2.1).[30] Subsequent deglycosylation and iminium condensation affords 4,21-dihydrogeissoschizine (**31**), which undergoes a series of skeletal rearrangements to arrive at dihydropyridine **32**. At this stage, it is envisioned that either a Diels–Alder cycloaddition, or a stepwise Michael addition/Friedel–Crafts

reaction/tautomerization cascade delivers tabersonine (**5**), thereby enabling general entry into alkaloids of the *Aspidosperma* type.[31]

Scheme 1.2.1. Proposed Biosynthetic Pathway of Aspidosperma Alkaloids



In addition to their stereochemically rich polycyclic scaffolds, several *Aspidosperma* and *Kopsia* alkaloids have demonstrated promising biological activity. Vincadifformine (**4**) displayed cytotoxicity in KB/VJ300 vincristine-resistant human oral epidermoid carcinoma cells.[32] Tabersonine (**5**) showed cytotoxicity toward HL-60 myeloid leukemia cells at low micromolar concentrations.[33] Rhazinilam (**19**) showed sub-micromolar toxicities in A549 human lung adenocarcinoma and HT29 human colon adenocarcinoma cell lines,[34a] but is perhaps best known for its remarkable in vitro inhibition of both microtubule assembly and disassembly.[34b,c]

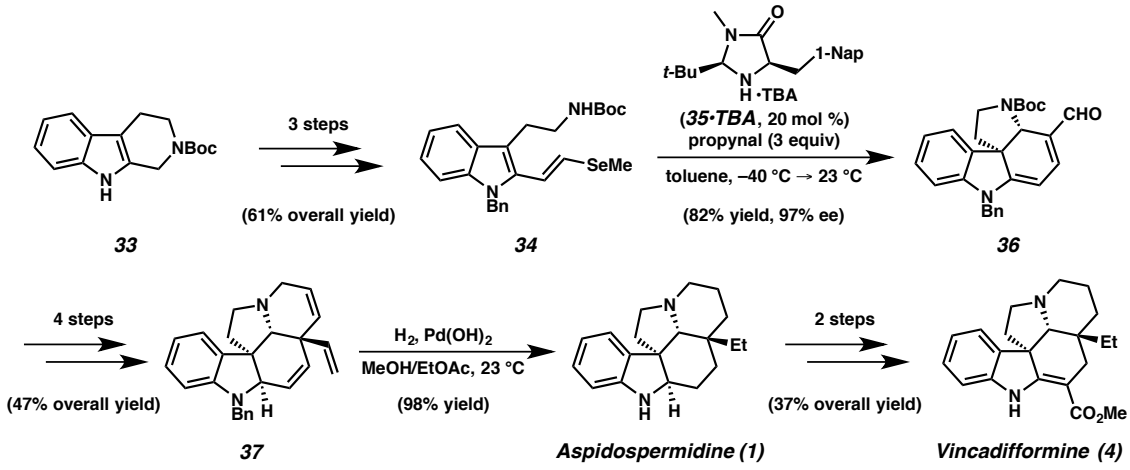
1.3 IMPORTANT UNIFIED STRATEGIES

The purpose of this section is not to recount every completed monoterpene indole alkaloid total synthesis.[35] Rather, a representative selection of synthetic strategies that have born access to multiple *Aspidosperma* and/or *Kopsia* family members will be highlighted to establish a broader context for this field.

1.3.1 MACMILLAN'S ORGANOCASCADE CATALYSIS

In 2011, MacMillan and co-workers demonstrated the power of their enantioselective organocascade catalysis[36] through the divergent total syntheses of (+)-aspidospermidine (**1**), (+)-vincadifformine (**4**), (–)-kopsinine (**20**), and (–)-kopsanone (**21**), along with the *Strychnos* alkaloids (–)-strychnine and (–)-akuammicine.[37] Treatment of vinyl selenide **34** with 20 mol % of imidizalidinone tribromoacetic acid salt **35•TBA** in the presence of propynal delivered spiroindoline **36** in high yield and excellent enantioselectivity (Scheme 1.3.1.1). A four step sequence including a Pd-catalyzed Heck cyclization gave triene **37**, which was globally reduced to arrive at (+)-aspidospermidine (**1**). Sequential Swern oxidation and C-acylation completed an enantioselective synthesis of (+)-vincadifformine (**4**).

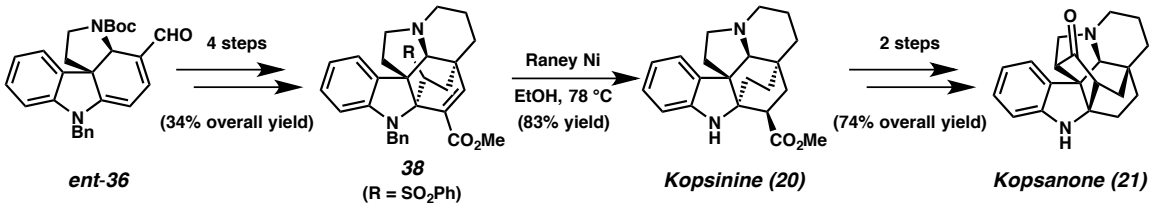
*Scheme 1.3.1.1. MacMillan's Enantioselective Organocascade Catalysis Toward (+)-Aspidospermidine (**1**) and (+)-Vincadifformine (**4**)*



In a similar fashion, the authors synthesized ***ent*-36**, which was swiftly converted to hexacyclic sulfone **38** (Scheme 1.3.1.2). Global reduction using Raney nickel furnished (–)-kopsinine (**20**), which was advanced to (–)-kopsanone (**21**) in a further two

steps. This unified approach from the MacMillan group stands out for its elegant and highly enantioselective organocascade reaction, along with thoughtful synthetic planning to enable multiple highly productive transformations.

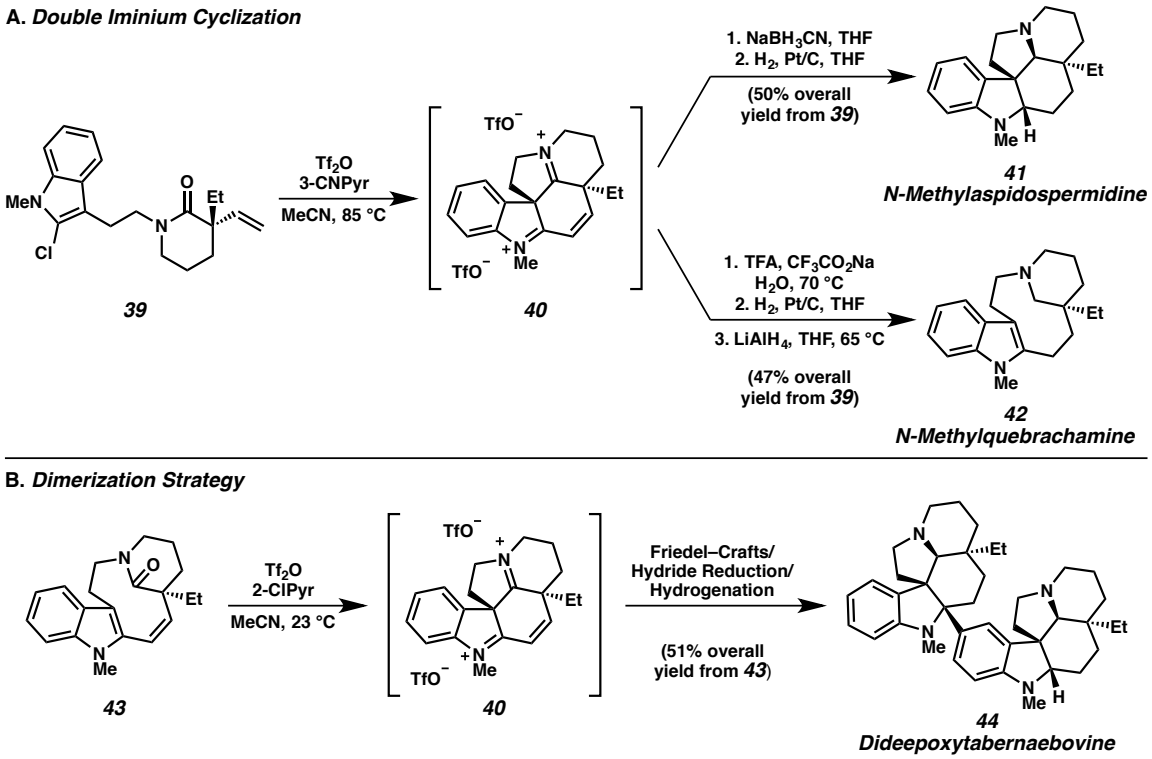
*Scheme 1.3.1.2. Divergent Synthetic Access to (–)-Kopsinine (**20**) and (–)-Kopsanone (**21**)*



1.3.2 MOVASSAGHI'S DIIMINIUM CYCLIZATIONS

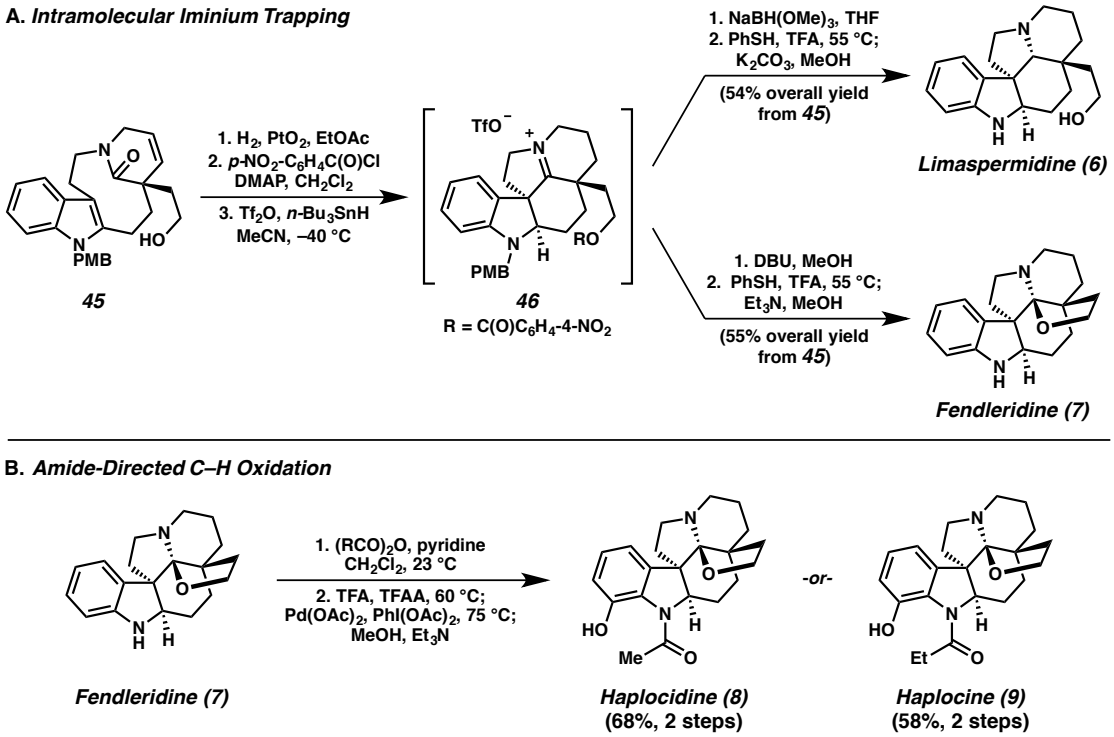
The Movassaghi group has leveraged their expertise in interrupted Bischler–Napieralski reactions[38] to synthesize versatile diiminium species en route to multiple *Aspidosperma* alkaloids.[39] In their first report, α-Quaternary δ-lactam **39**[40] was subjected to the combination of triflic anhydride and 3-cyanopyridine with heating to deliver diiminium **40** (Scheme 1.3.2.1A).[39a] Hydride reduction, followed by hydrogenation gave *N*-methylaspidospermidine (**41**)[41] in 50% overall yield from **39**. Alternatively, heating diiminium **40** in aqueous acid effected a Grob fragmentation, and subsequent hydrogenation and lactam reduction yielded *N*-methylquebrachamine (**42**)[42] in 47% overall yield from **39**. Critically, the authors found that nine-membered lactam **43** could be converted to diiminium **40** under milder conditions (Scheme 1.3.2.1B). A number of non-hydride nucleophiles could react preferentially at the C2 iminium of **40**, including a stereo- and regioselective Friedel–Crafts reaction that enabled an efficient synthesis of homodimeric dideepoxytabernaebovine (**44**).

Scheme 1.3.2.1. Movassaghi's First Generation Diiminium Cyclization Cascade



In a subsequent report, Movassaghi and co-workers employed a similarly mild transannular cylization in the total syntheses of additional monomeric and dimeric *Aspidosperma* alkaloids.[39b] Most recently, the Movassaghi group coupled their diiminium cyclization chemistry with amide-directed C–H oxidation to synthesize arene-oxidized *Aspidosperma* alkaloids.[39c] Nine-membered lactam **45**[43] was efficiently converted to pentacyclic iminium **46**, which could undergo hydride reduction and subsequent deprotection to deliver (+)-limaspermidine (**6**), or saponification and concomitant *N*,*O*-ketalization en route to fendleridine (**7**, Scheme 1.3.2.2A). Fendleridine (**7**) could then be smoothly acylated to provide a directing group for arene Pd-catalyzed C–H oxidation (Scheme. 1.3.2.2B). These late-stage oxidations enabled concise total syntheses of haplocidine (**8**) and haplocine (**9**), further demonstrating the broad utility of Movassaghi's diiminium cyclization strategy in the synthesis of *Aspidosperma* alkaloids.

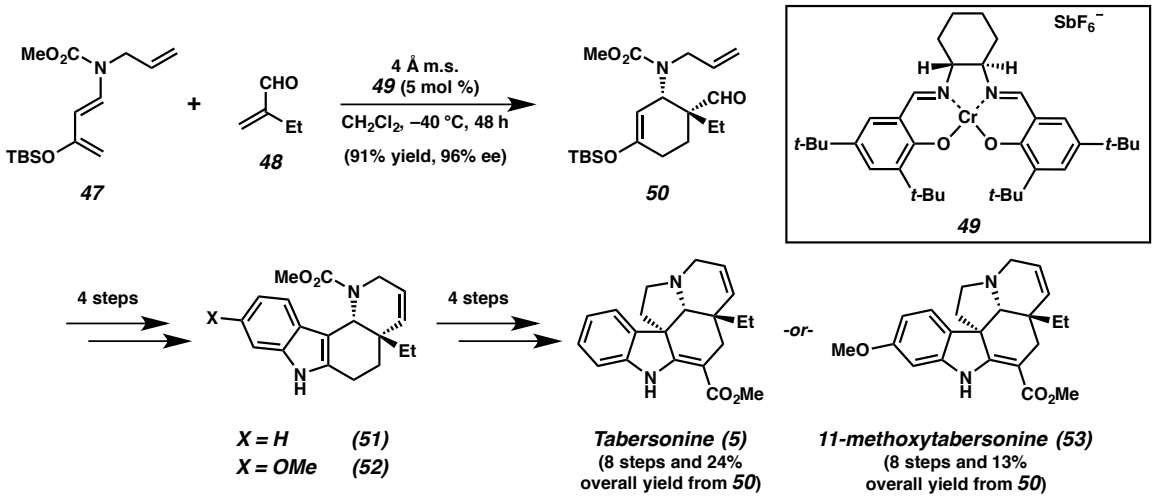
Scheme 1.3.2.2. Movassaghi's Synthesis of N,O-Ketal-Containing Alkaloids



1.3.3 RAWAL'S ENANTIOSELECTIVE DIELS–ALDER CYCLOADDTION

The Rawal group utilized an enantioselective Diels–Alder cycloaddition to complete highly streamlined and scalable syntheses of several family members.[44] Treatment of diene **47** with Cr(III)–Salen catalyst **49** in the presence of ethacrolein (**48**) and molecular sieves gave cyclohexene **50** in 91% yield and 96% enantiomeric excess (Scheme 1.3.3.1). The indole moiety was introduced using a regioselective *o*-nitroarylation followed by reductive cyclization. Rawal and co-workers took advantage of this relatively late-stage indole construction in the divergent syntheses of tabersonine (**5**) and 11-methoxytabersonine (**53**).[2,45] Furthermore, the authors diverted the penultimate intermediate from their synthesis of tabersonine (**5**) to complete additional total syntheses of aspidospermidine (**1**) and quebrachamine (**2**).

Scheme 1.3.3.1. Rawal's Cr(III)–Salen-Catalyzed Enantioselective Diels–Alder Reaction

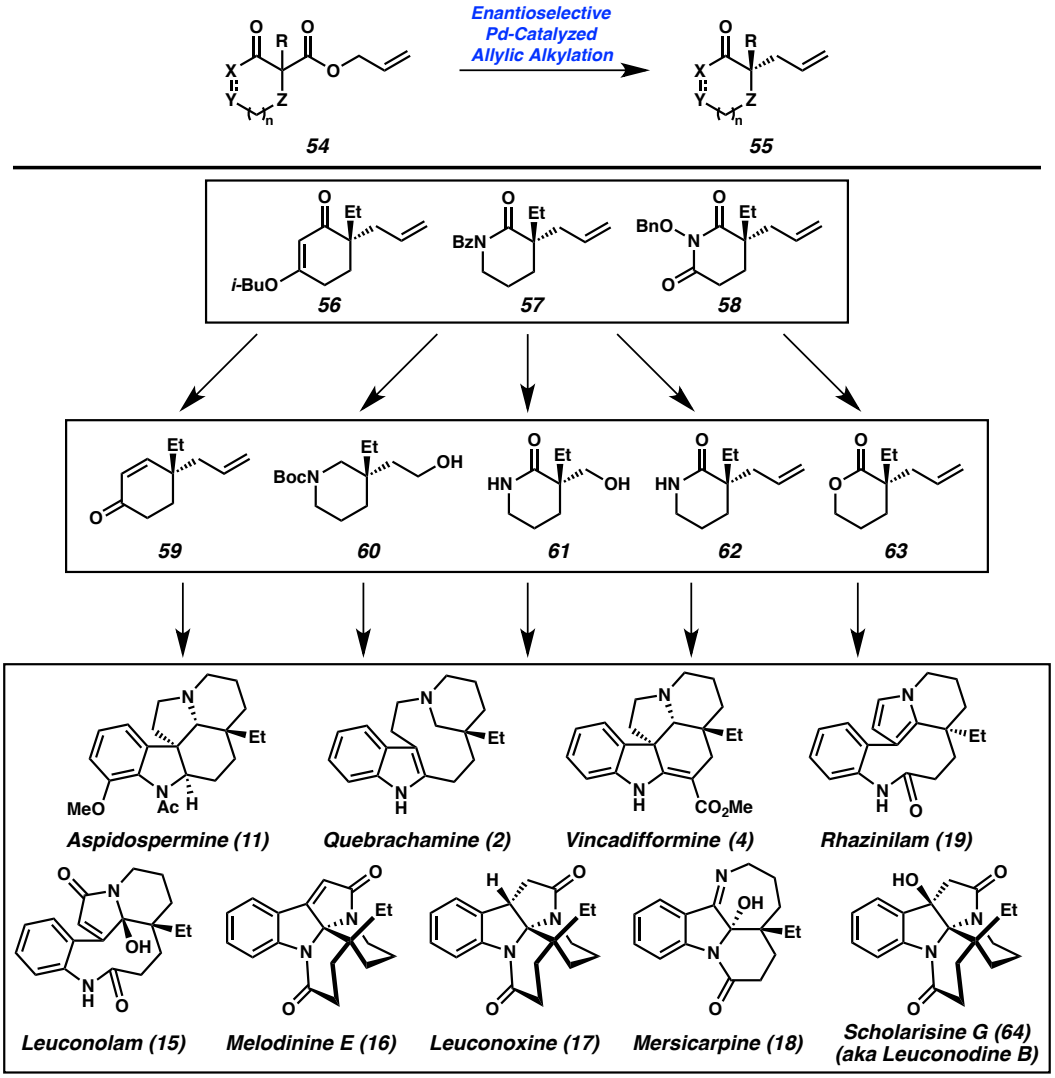


1.4 ENANTIOSELECTIVE Pd-CATALYZED ALLYLIC ALKYLATIONS IN ASPIDOSPERMA AND KOPSIA ALKALOID TOTAL SYNTHESIS

Among the many synthetic challenges facing chemists in pursuit of *Aspidosperma* and *Kopsia* alkaloids is the ubiquitous all-carbon quaternary stereocenter at C20. Since the mid 2000's, enantioselective Pd-catalyzed allylic alkylation reactions of non-stabilized enolates have enabled access to challenging stereogenic quaternary centers.[46,47] Using this approach, racemic β-oxoesters such as **54** can be swiftly converted to their corresponding α-quaternary product (**55**) in high yield and enantioselectivity. The allylic alkylation products (e.g., **56**–**58**) can be further elaborated to chiral building blocks (e.g., **59**–**63**) that previously required lengthy synthetic sequences to achieve high levels of enantiopurity (Scheme 1.4.1).[48]

Indeed, our lab has employed this methodology to construct monocyclic chiral building blocks possessing an all-carbon quaternary center in multiple rapid asymmetric formal syntheses of *Aspidosperma* alkaloids. Vinylogous ester **56** can be transformed into γ-quaternary enone **59** in straightforward fashion,[48] completing formal syntheses of (–)-aspidospermine (**11**) and (–)-quebrachamine (**2**).[49] α-Quaternary piperidin-2-one **57** provides access to heterocycles **60**–**62**,[46c,48] which constitute asymmetric formal syntheses of (–)-quebrachamine (**2**),[50] (–)-vincadifformine (**4**),[51] and (+)-rhazinilam (**19**),[52] respectively. Finally, imide **58** can be easily converted to lactone **63** over three steps,[53] thereby providing enantioselective access to (–)-leuconolam (**15**), (+)-melodinine E (**16**), (–)-leuconoxine (**17**), (–)-mersicarpine (**18**), and (–)scholarisine G (**64**, aka leuconodine B).[54]

Scheme 1.4.1. Pd-Catalyzed Allylic Alkylation Provides Facile Access to Important Chiral Building Blocks en Route to Aspidosperma Alkaloids

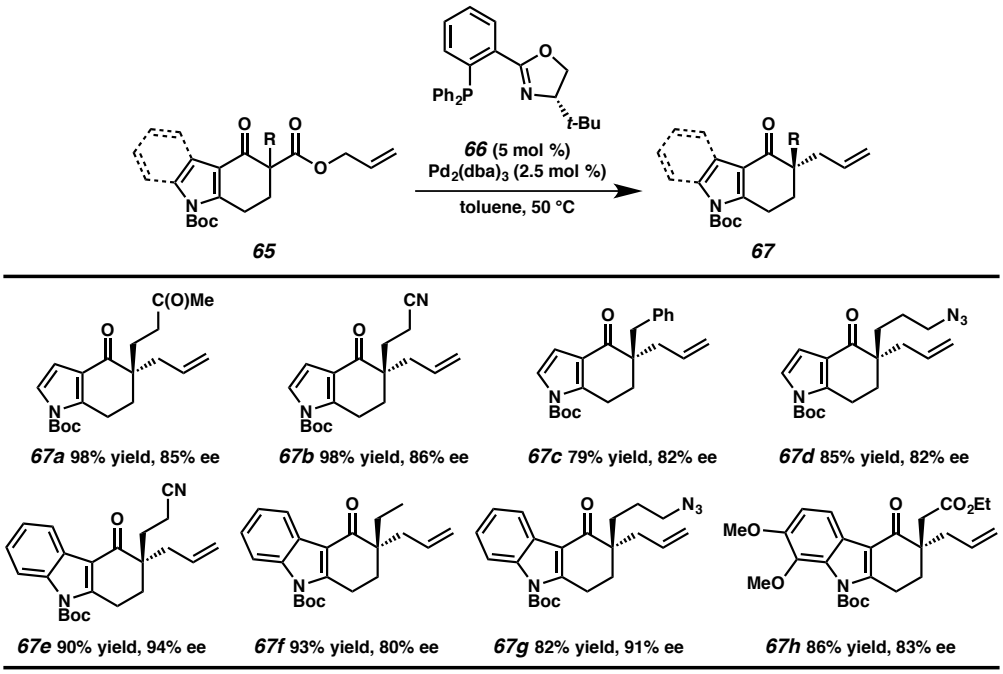


Recently, several groups have used Pd-catalyzed allylic alkylations to set the C20[2] all-carbon quaternary center in de novo enantioselective total syntheses. The stereochemical information at C20 can then be used to set the remaining stereocenters with high levels of selectivity. Most of the studies described herein utilize conditions developed by the Stoltz group for decarboxylative allylic alkylations, namely the combination of $Pd_2(dba)_3$ and a phosphinooxazoline (PHOX) ligand.[46a–c]

1.4.1 LUPTON'S FORMAL SYNTHESIS OF KOPSIHAINANINE A

In 2013, the Lupton group reported the enantioselective decarboxylative Pd-catalyzed allylic alkylation of Boc-protected indolone and carbazolone substrates (e.g., **65**, Table 1.4.1.1).[55] The authors found that the combination of $Pd_2(dba)_3$ (2.5 mol %) and (*S*)-*t*-BuPHOX (**66**, 5 mol %) in toluene at 50 °C delivered the α-quaternary products (e.g., **67a–h**) in 69–98% yield and 80–94% ee. Broad functional group tolerance was observed at the α-position, and one example (**67h**) illustrated the compatibility of an electronically differentiated indole fragment.

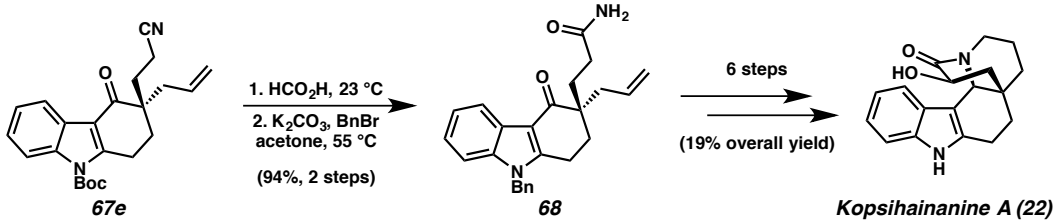
Table 1.4.1.1. Selected Examples from Lupton's Enantioselective Pd-Catalyzed Allylic Alkylations of Indolone and Carbazolone Substrates



Noting the clear resemblance between their α-quaternary carbazolone products (e.g., **67e–h**) and monoterpene indole alkaloids, the authors carried out a rapid enantioselective formal synthesis of (+)-kopsihainanine A (**22**). Nitrile **67e** was treated

with formic acid to effect hydration with concomitant Boc removal, and subsequent reprotection delivered *N*-benzyl carbazolone **68** (Scheme 1.4.1.1). *N*-benzyl carbazolone **68** was carried through six additional steps by She and co-workers in their synthesis of (±)-kopsihainanine A (**22**).[56]

*Scheme 1.4.1.1. Enantioselective Formal Synthesis of (+)-Kopsihainanine A (**22**)*

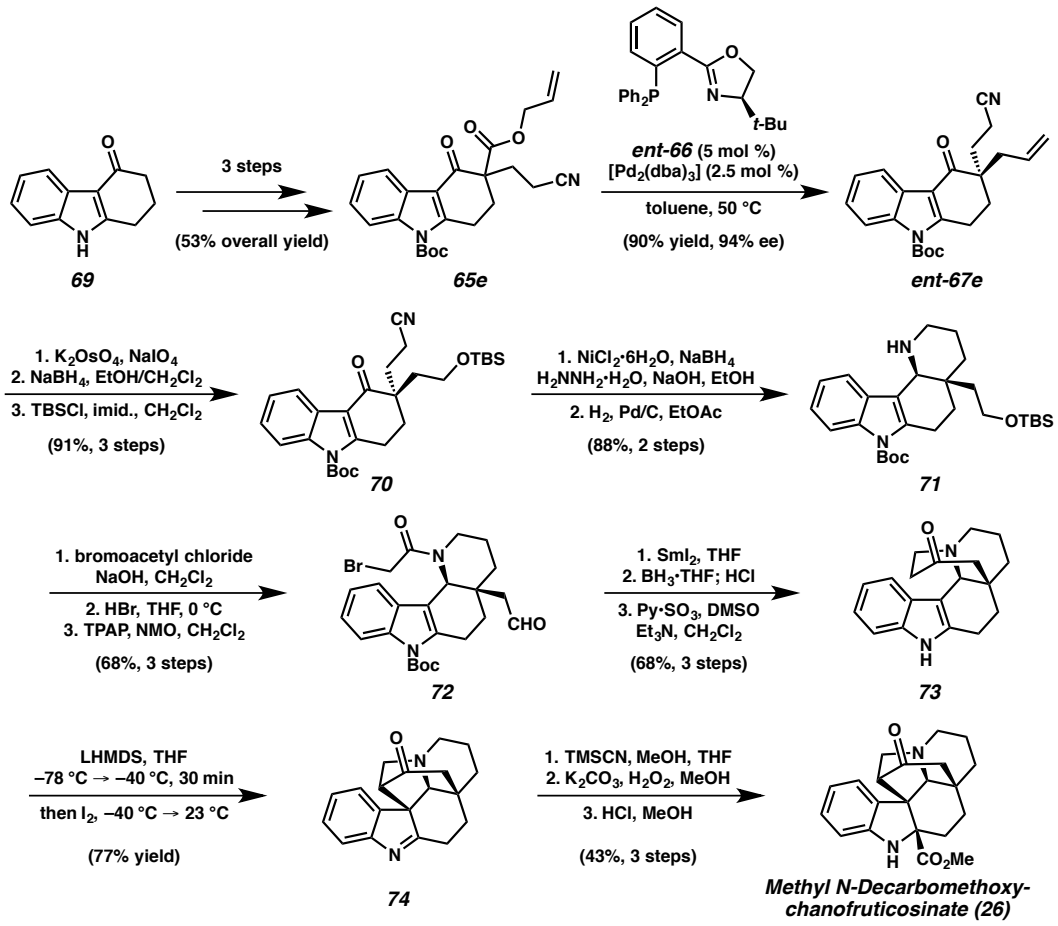


1.4.2 MA'S TOTAL SYNTHESIS OF METHYL N-DECARBOMETHOXYCHANOFRUTICOSINATE

Ma and co-workers devised an elegant total synthesis of (+)-methyl *N*-decarbomethoxychanofruticosinate (**26**) featuring an enantioselective Pd-catalyzed allylic alkylation of a carbazolone substrate and a late-stage intramolecular oxidative coupling reaction.[57] Beginning from commercially available carbazolone **69**, a four-step sequence including a Pd-catalyzed allylic alkylation using (*R*)-*t*-BuPHOX (***ent*-66**) delivered ***ent*-67e** (Scheme 1.4.2.1). Oxidative cleavage of the allyl fragment, reduction of the resulting aldehyde, and alcohol protection using TBSCl gave silyl ether **70**. Reductive cyclization using nickel boride, followed by imine hydrogenation, delivered tetracycle **71** with the requisite *trans*-fused octahydroquinoline subunit. Acylation of the secondary amine, followed by alcohol deprotection and subsequent oxidation, gave aldehyde **72**. An intramolecular Reformatsky-type reaction was mediated by SmI_2, and the resulting β-hydroxyamide was subjected to amide reduction and then alcohol oxidation to arrive at ketone **73**. Ketone **73** was deprotonated using LHMDS, and the resulting enolate

underwent smooth iodine-promoted oxidative coupling to give imine **74**.[58] Nucleophilic addition of cyanide, followed by hydration and subsequent esterification delivered the highly caged target, (+)-methyl *N*-decarbomethoxychanofruticosinate (**26**), in 19 steps and 5% overall yield from commercially available **69**.

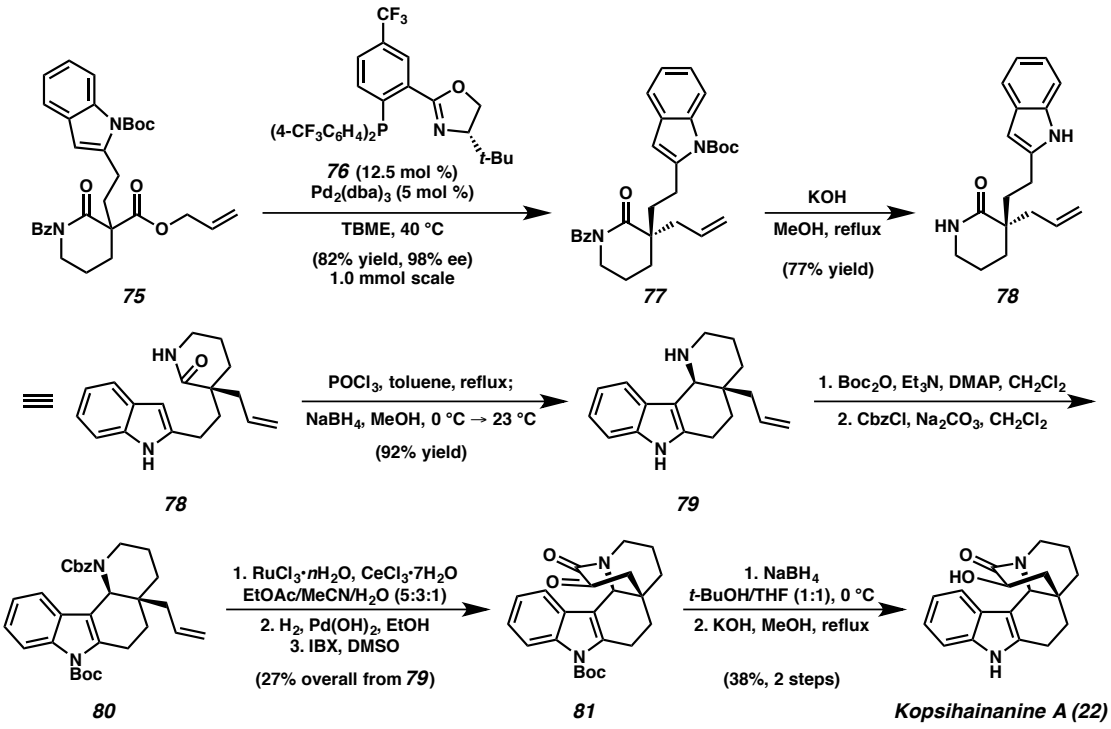
*Scheme 1.4.2.1. Ma's Total Synthesis of (+)-Methyl N-Decarbomethoxychanofruticosinate (**26**)*



1.4.3 MUKAI'S TOTAL SYNTHESIS OF KOPSIHAINANINE A

Mukai and co-workers exploited the exceptional enantioselectivities achieved through the asymmetric allylic alkylation of piperidin-2-ones[46c] in a highly enantioselective total synthesis of (+)-kopsihainanine A (**22**).[59] The addition of 1,3–Dicarbonyl **75**, available in five linear steps from indole, to a solution of $Pd_2(dba)_3$ (5 mol %) and electron deficient (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 12.5 mol %) in TBME at 40 °C delivered α-quaternary amide **77** in 82% yield and 98% ee on a one-mmol scale (Scheme 1.4.3.1). Following global deprotection, the key Bischler–Napieralski cyclization was performed to deliver tetracycle **79** in excellent yield as a single diastereomer bearing the desired *trans*-fused [6,6] subunit. A further seven steps were required to advance the Bischler–Napieralski product (**79**) to (+)-kopsihainanine A (**22**). Despite multiple protecting group and redox manipulations, Mukai and co-workers completed a total synthesis of (+)-kopsihainanine A (**22**) in 15 steps and 3% overall yield from indole.

*Scheme 1.4.3.1. Mukai's Total Synthesis of (+)-Kopsihainanine A (**22**)*

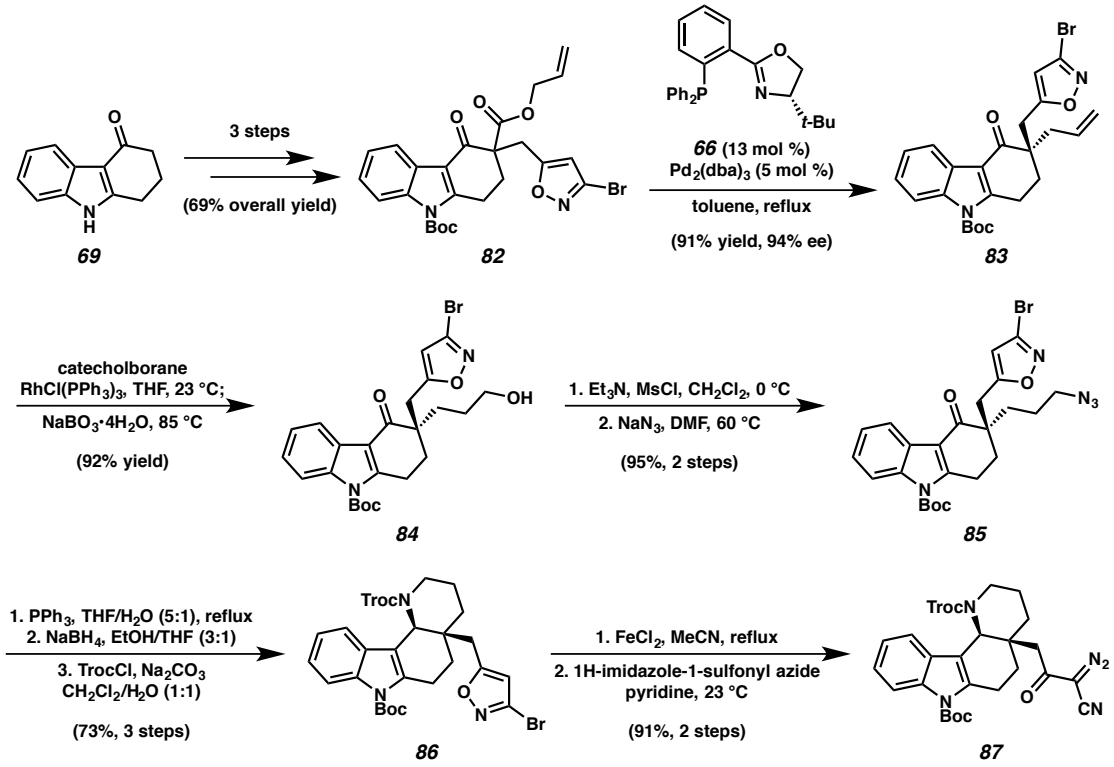


1.4.4 QIN'S TOTAL SYNTHESIS OF MULTIPLE KOPSIA ALKALOIDS

The most recent report in this field is a beautiful unified approach to multiple highly caged *Kopsia* alkaloids by Qin and co-workers.[60] Racemic carbazolone **82** underwent enantioconvergent Pd-catalyzed allylic alkylation using (*S*)-*t*-BuPHOX (**55**, 13 mol %) and $Pd_2(dba)_3$ (5 mol %) in refluxing toluene to deliver the α-quaternary product (**83**) in 91% and 94% ee (Scheme 1.4.4.1). Remarkably, the crucial heteroaryl bromide motif withstands this Pd(0)-catalyzed transformation, despite somewhat forcing conditions. The terminal alkene was transformed to a primary azide (**85**), which could undergo an aza-Wittig reaction and ensuing hydride reduction with high diastereoselectivity. Protection of the piperidine nitrogen with TrocCl then delivered tetracycle **86**. The authors masterfully unveiled a β-ketonitrile moiety through reductive N–O cleavage and concomitant bromide elimination. Diazo transfer proceeded smoothly

to give α-diazoketone **87**, which enabled the investigation of their key metal-catalyed intramolecular cyclopropanation.

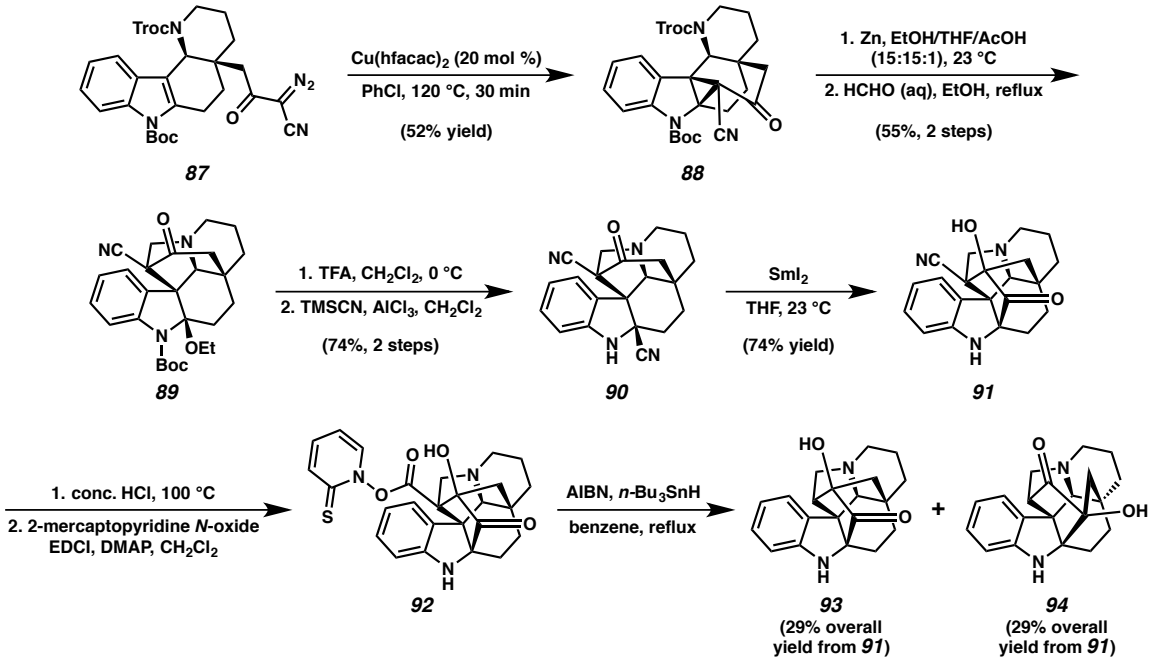
*Scheme 1.4.4.1. Synthesis of α-Diazoketone **87***



After screening various rhodium and copper catalysts, Qin and co-workers found that the use of 20 mol % $Cu(hfacac)_2$ in chlorobenzene at 120 °C resulted in a 52% yield of the desired cyclopropanated indoline **88** (Scheme 1.4.4.2). Troc removal and cyclopropane opening was accomplished with zinc dust, and an intramolecular Mannich reaction formed the pyrrolidine subunit to give hexacycle **89**. A three-step sequence of nitrogen deprotection, cyanation, and samarium-mediated acyloin condensation gave highly caged α-hydroxyketone **91**. Nitrile hydration and esterification with 2-mercaptopyridine *N*-oxide delivered **92**, which undergoes radical decarboxylation to give

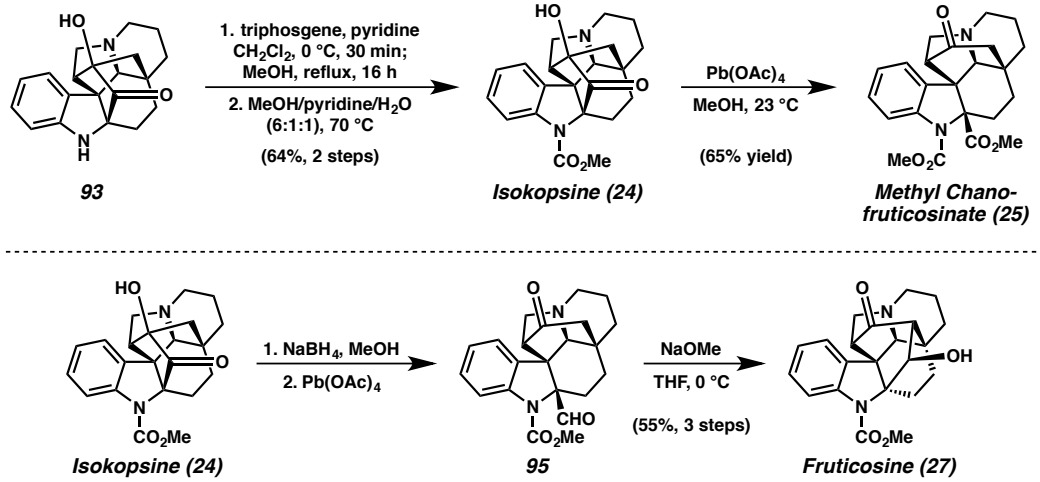
a mixture of **93** and **94**,[61] bearing the carbocyclic cores of (–)-isokopsine (**24**) and (–)-kopsine (**23**), respectively.

Scheme 1.4.4.2. Intramolecular Cyclopropanation and Elaboration to the Carbocyclic Cores of Caged Kopsia Alkaloids



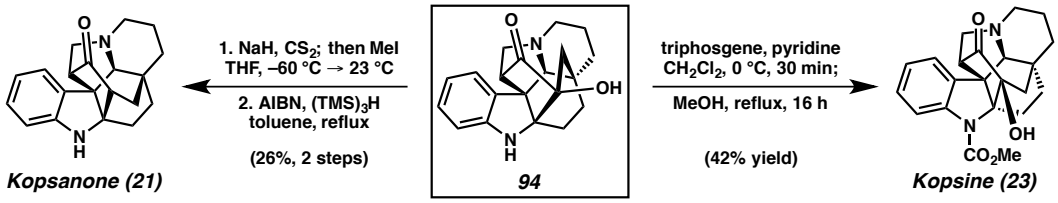
Heptacycle **93** was globally carbomethoxylated, and chemoselective carbonate cleavage occurred to give (–)-isokopsine (**24**, Scheme 1.4.4.3). C–C scission was achieved using $Pb(OAc)_4$ to furnish (+)-methyl chanofruticosinate (**25**). Furthermore, (–)-isokopsine (**24**) could be reduced with sodium borohydride, and the resulting diol cleaved by $Pb(OAc)_4$ to provide aldehyde **95**. Treatment of **95** with sodium methoxide in THF effected an intramolecular aldol condensation to give (–)-fruticosine (**27**).

*Scheme 1.4.4.3. Completion of (–)-Isokopsine (**24**), (+)-Methyl Chanofruticosinate (**25**), and (–)-Fruticosine (**27**)*



Lastly, the authors advanced heptacycle **94** to complete syntheses of (–)-kopsanone (**21**) and (–)-kopsine (**23**). The tertiary alcohol in **94** was converted to a xanthate ester, and ensuing radical deoxygenation gave (–)-kopsanone (**21**, Scheme 1.4.4.4, Left). Conversely, treatment of **94** with triphosgene followed by methanolysis gave (–)-kopsine (**23**, Scheme 1.4.4.4, Right).[62]

*Scheme 1.4.4.4. Completion of (–)-Kopsanone (**21**) and (+)-Kopsine (**23**)*

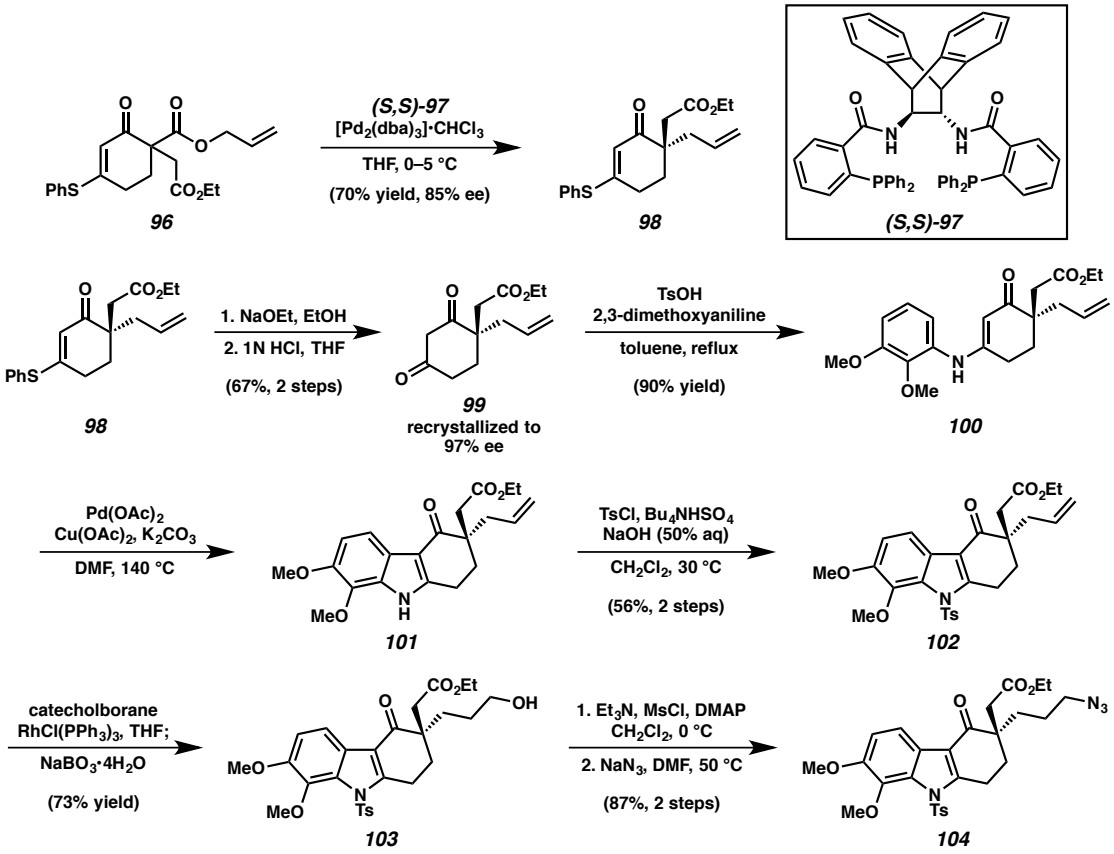


In summary, Qin and co-workers have designed and executed an impressive unified strategy toward several structurally daunting targets. Instrumental to their success were an enantioselective Pd-catalyzed allylic alkylation, the incorporation of a bromoisoxazole fragment as a masked β-ketonitrile, a copper-catalyzed intramolecular cyclopropanation, and several late-stage skeletal rearrangements.

1.4.5 QIU'S TOTAL SYNTHESIS OF (–)-ASPIDOPHYTINE

In 2013, Qiu and co-workers reported a stereocontrolled total synthesis of (–)-aspidophytine (**10**).[63] Enantioselective Pd-catalyzed allylic alkylation of β-ketoester **96** was accomplished using $[Pd_2(dba)_3]$•$CHCl_3$ and (*S*,*S*)-ANDEN-Phenyl Trost ligand (**97**) to give known vinylogous thioester **98** in 70% yield and 85% ee (Scheme 1.4.5.1).[64] A two-step hydrolysis protocol gave cyclohexane-1,3-dione **99**, which could be enriched to 97% ee through recrystallization. The dimethoxyindole fragment in (–)-aspidophytine (**10**) was constructed through an acid-catalyzed vinylogous amide formation followed by Pd-catalyzed oxidative cyclization. Subsequent *N*-tosylation under phase-transfer conditions gave α-quaternary carbazolone **102**. The allyl fragment in **102** was converted to a primary azide in straightforward fashion to arrive at carbazolone **104**.

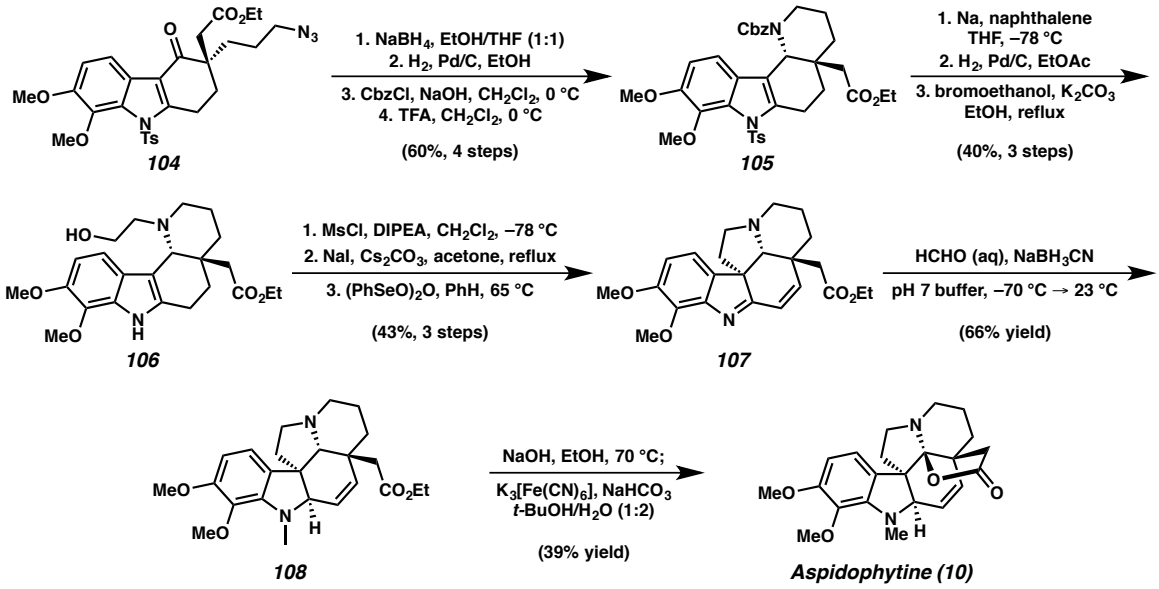
Scheme 1.4.5.1. Synthesis of α-Quaternary Carbazolone ***104***



The authors then expertly used the single stereocenter in **104** to build the three remaining rings and complete their synthesis of (–)-aspidophytine (**10**) in a stereoselective fashion (Scheme 1.4.5.2). A four-step sequence effected ketone and azide reduction along with amine protection and a Pictet–Spengler-type cyclization to deliver *cis*-fused tetracycle **105**. Global deprotection is followed by regioselective alkylation using 2-bromoethanol furnished aminoalcohol **106**. Pyrrolidine annulation and selenoxide elimination gave α,β-unsaturated imine **107**, which could undergo hydride reduction and reductive amination in the same pot to yield penultimate *N*-methyl indoline **108**. This intermediate was converted to (–)-aspidophytine (**10**) by adapting a two-step protocol reported by Corey.[65] While their synthesis required 20 steps and proceeded in 0.6%

overall yield from known α-quaternary vinylogous thioester **98**, Qiu and co-workers successfully assembled one of the most functionally elaborate members of the *Aspidosperma* family.

*Scheme 1.4.5.2. Qiu's Endgame for (–)-Aspidophytine (**10**)*

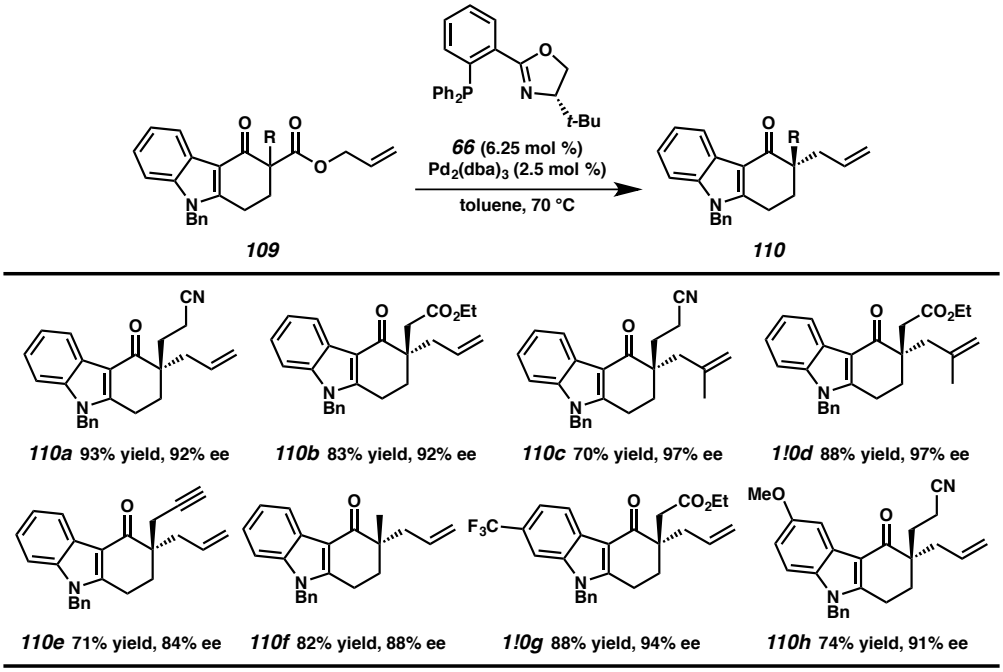


1.4.6 SHAO'S TOTAL SYNTHESES ENABLED BY ENANTIOENRICHED α-QUATERNARY CARBAZOLONES

In 2013, the Shao group began what has become a fruitful research program in the application of Pd-catalyzed allylic alkylation reactions of carbazolone substrates in the context of monoterpene alkaloid total synthesis. Their initial disclosure was published back-to-back with that of Lupton and co-workers,[55] and detailed the asymmetric allylic alkylation of *N*-benzyl carbazolone substrates (Table 1.4.6.1).[66] Using similar reaction conditions, a range of enantioenriched α-quaternary carbazolone products were obtained in 70–93% yield and 84–97% ee. Compounds bearing either nitrile or ester motifs performed well (e.g., **110a** and **110b**), and substitution at the 2-position of the allyl fragment resulted in high levels of enantioselectivity (e.g., **110c** and **110d**), as is often the

case in these allylic alkylations.[67] Simple alkyl substituents were also tolerated (e.g., **110e** and **110f**), and electronically differentiated arene fragments were compatible (e.g., **110g** and **110h**).

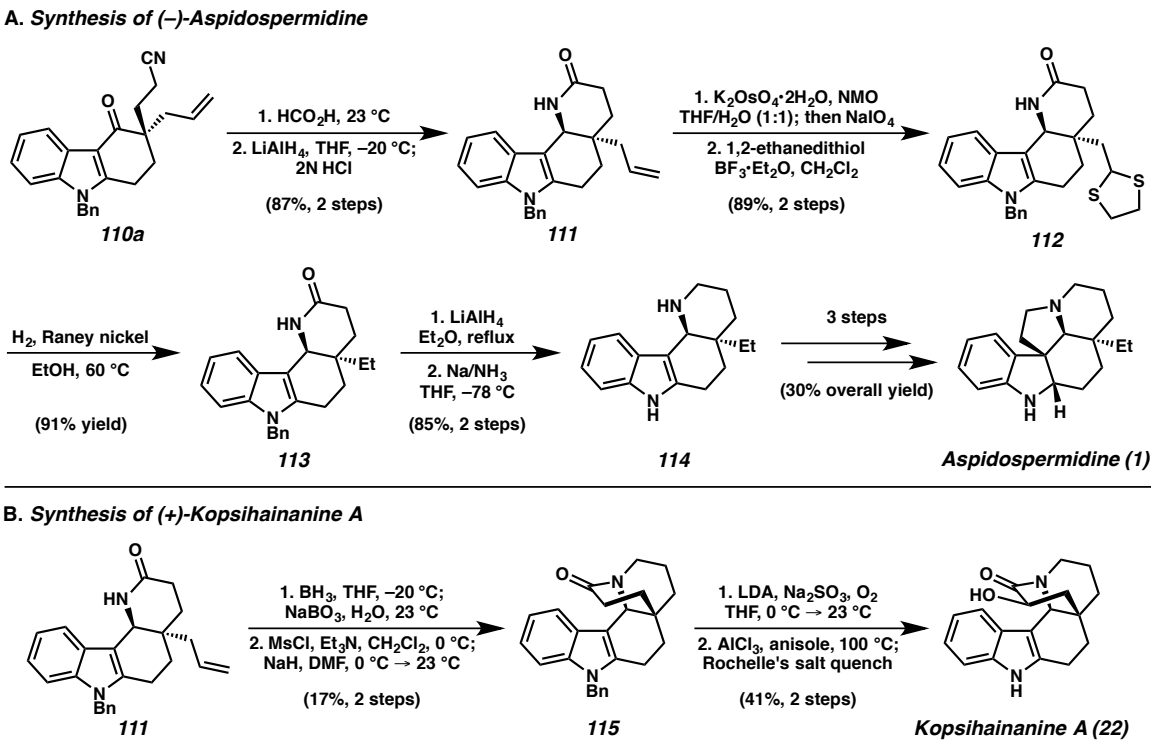
Table 1.4.6.1. Selected Examples from Shao's First Report on Enantioselective Pd-Catalyzed Allylic Alkylations of Carbazolone Substrates



Shao's first application of this chemistry was in the total syntheses of (–)-aspidospermidine (**1**) and (+)-kopsihainanine A (**22**). Beginning from α-quaternary carbazolone **110a**, hydration of the pendant nitrile followed by ketone reduction and acid-promoted cyclization gave lactam **111** (Scheme 1.4.6.1A). A three-step dehomologation protocol was used to convert **111** into tetracycle **113**, which bears the desired C20 ethyl substituent. Lactam reduction and debenzylation under dissolving metal conditions furnished **114**, which was converted to (–)-aspidospermidine (**1**) using a three-step sequence adapted from Heathcock and co-workers.[68] The authors found that lactam **111** could also serve as an intermediate toward (+)-kopsihainanine A (**22**, Scheme 1.4.6.1B).

Hydroboration/oxidation and base-promoted cyclization of the corresponding mesylate gave pentacycle **115**, which underwent α-hydroxylation and debenzylation to complete the first catalytic enantioselective synthesis of (+)-kopsihainanine (**22**) in short order, albeit in low yield.

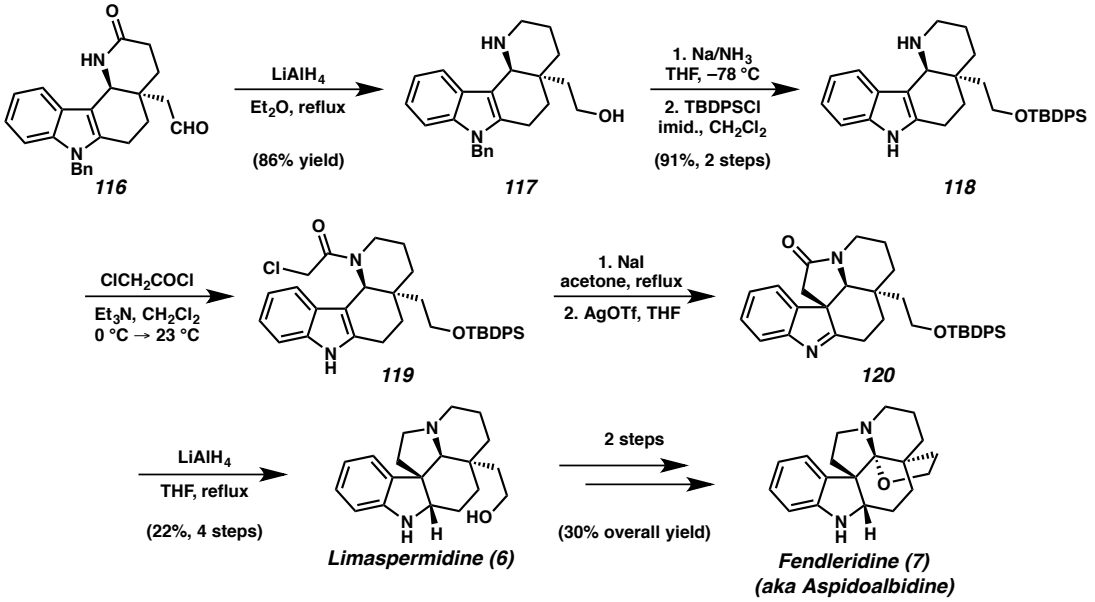
*Scheme 1.4.6.1. Shao's Divergent Syntheses of (–)-Aspidospermidine (**1**) and (+)-Kopsihainanine A (**22**)*



Later that same year, Shao and co-workers published an enantioselective total synthesis of (–)-limaspermidine (**6**).[69] Aldehyde **116**, which was an intermediate in their synthesis of (–)-aspidospermidine (**1**), was instead treated with excess $LiAlH_4$ in refluxing ether to give primary alcohol **117** (Scheme 1.4.6.2). Debenzylation and TBDPS-protection provided silyl ether **118**, which underwent regioselective acylation to deliver α-chloroamide **119**. Finkelstein displacement of the chloride and subsequent AgOTf-mediated annulation furnished pentacyclic imine **120**. Global hydride reduction

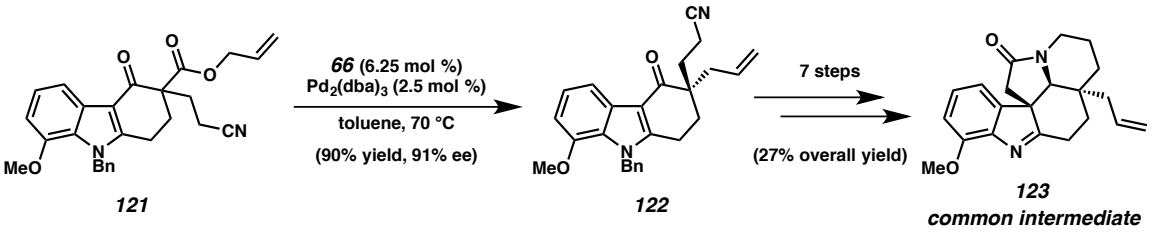
and desilylation completed their total synthesis of (–)-limaspermidine (**6**), which had previously been converted to (–)-acetylaspidoalbidine (**7**) in a further two steps by Banwell and co-workers.[70]

*Scheme 1.4.6.2. Shao's Total Synthesis of (–)-Limaspermidine (**6**) and Formal Synthesis of (–)-Acetylaspidoalbidine (**7**)*



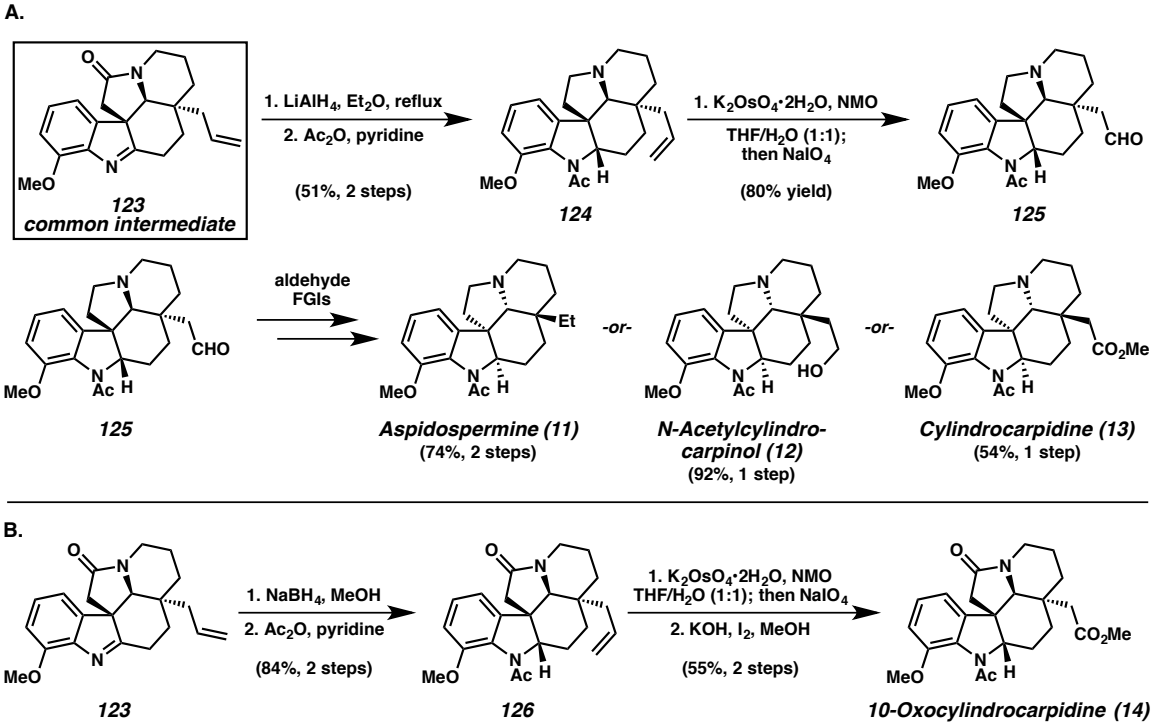
In a 2014 report, Shao and co-workers expanded their investigations to access alkaloids bearing oxygenation on the arene fragment.[71] Allylic alkylation precursor **121** was synthesized in five steps and 41% overall yield from commercially available materials. Using their previously optimized conditions, α-quaternary carbazolone **122** was obtained in 90% yield and 91% ee (Scheme 1.4.6.3). The authors then employed a familiar seven-step sequence to arrive at pentacyclic imine **123**, which served as a common intermediate in their divergent total syntheses of (+)-aspidospermine (**11**), (–)-*N*-acetylcylindrocarpinol (**12**), (+)-cylindrocarpidine (**13**), and (+)-10-oxocylindrocarpidine (**14**).

Scheme 1.4.6.3. Synthesis of Common Intermediate ***123***



Exhaustive hydride reduction, *N*-acylation, and oxidative cleavage of the terminal olefin gave aldehyde **125** (Scheme 1.4.6.4A). (+)-Aspidospermine (**11**), (–)-*N*-acetylcylindrocarpidine (**12**), and (+)-cylindrocarpidine (**13**) were each available from aldehyde **125** in 1–2 steps. Alternatively, chemoselective reduction of **123** using sodium borohydride left the pyrrolidin-2-one intact, which facilitated the first total synthesis of (–)-10-oxocylindrocarpidine (**14**, Scheme 1.4.6.4B).

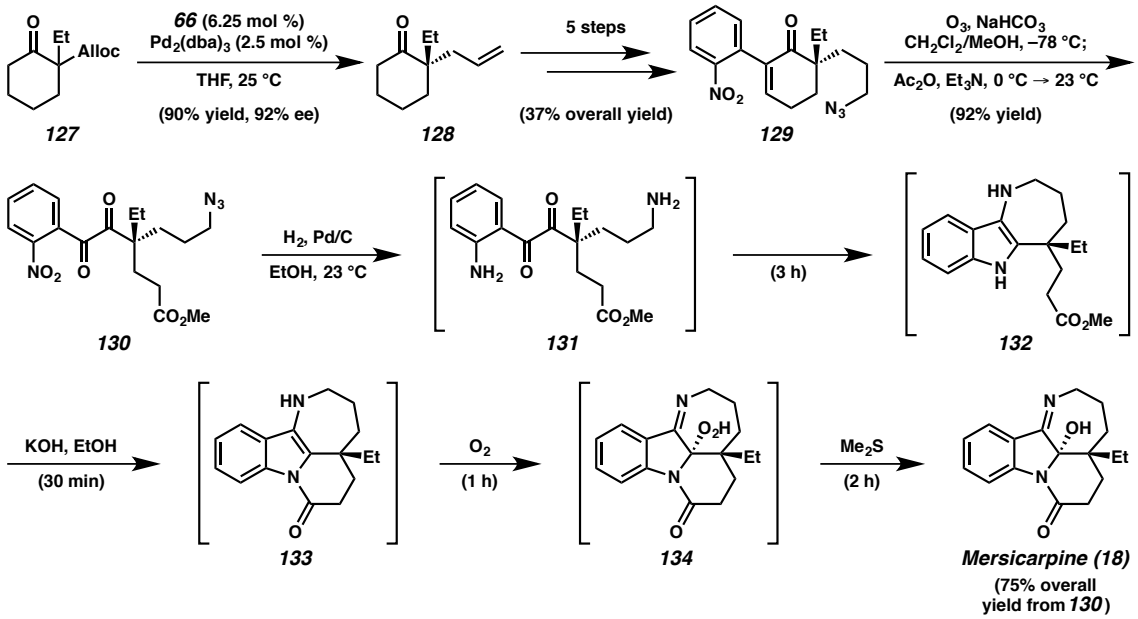
Scheme 1.4.6.4. Shao's Divergent Syntheses of C12-Methoxy Alkaloids ***11–14***



1.4.7 ZHU'S OXIDATION/REDUCTION/POLYCYCLIZATION CASCADES

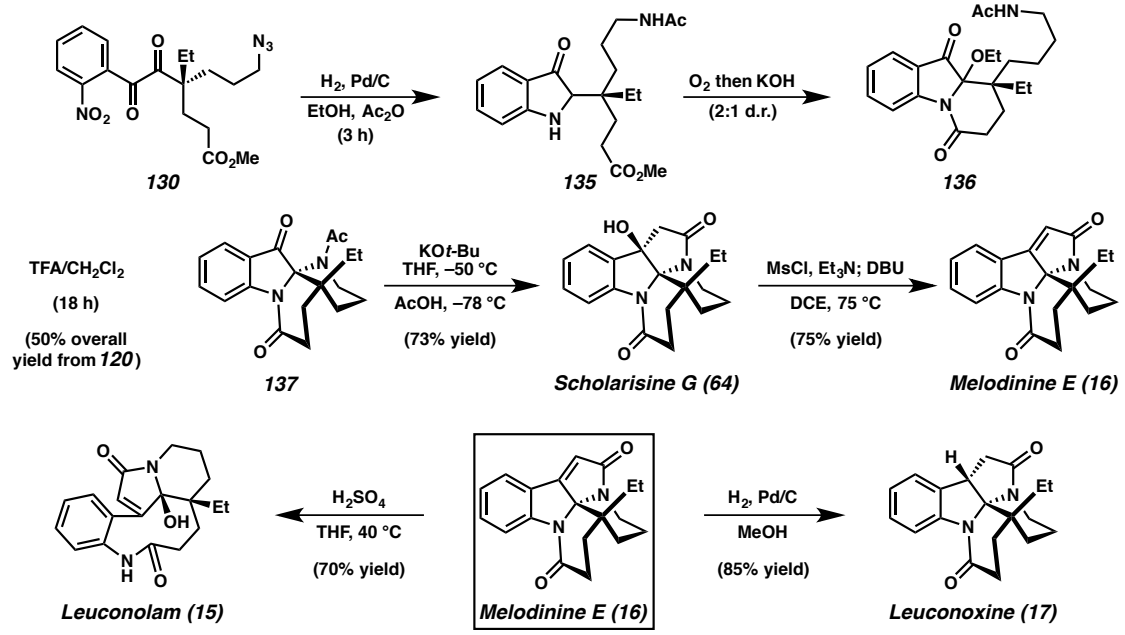
The laboratories of Jieping Zhu have combined Pd-catalyzed allylic alkylation with their domino oxidation/reduction/polycyclization cascades to complete enantioselective syntheses of a structurally unique subset of *Aspidosperma* alkaloids (e.g., **15**–**19**).[72] The known enantioselective Pd-catalyzed allylic alkylation of β-ketoester **127** proceeded smoothly to give α-quaternary ketone **128** in 90% yield and 92% ee (Scheme 1.4.7.1). The authors carried out a five-step sequence to introduce the azide and *o*-nitrophenyl substituents present in enone **129**. Ozonolysis of **129**, followed by treatment of the intermediate hydroperoxide with Ac_2O and Et_3N provided methyl ester **130**. Hydrogenation of **130** revealed the nascent aniline and primary amine in **131**, which cyclized regioselectively under the reaction conditions to give tricycle **132**. The addition of KOH effected lactamization, and sparging with oxygen provided the presumed hydroperoxide (**134**), which was reduced by dimethyl sulfide to deliver (–)-mersicarpine (**18**) in a remarkable 75% one-pot yield from azide **130**.

*Scheme 1.4.7.1. Zhu's Synthesis of (–)-Mersicarpine (**18**)*



Furthermore, the authors found that hydrogenation of azide **130** in the presence of acetic anhydride resulted in acetylation of the primary amine to give acetamide **135** (Scheme 1.4.7.2). Aerobic oxidation of the 3-oxindole moiety followed by the addition of KOH produced lactam **136**, which underwent acid-promoted cyclization to afford aminal **137**. An intramolecular aldol condensation completed a total synthesis of (–)-scholarisine G (**64**). The tertiary benzylic alcohol in (–)-scholarisine G (**64**) was smoothly dehydrated to give (+)-melodinine E (**16**), which could be further elaborated to (–)-leuconolam (**15**) and (–)-leuconoxine (**17**).[73]

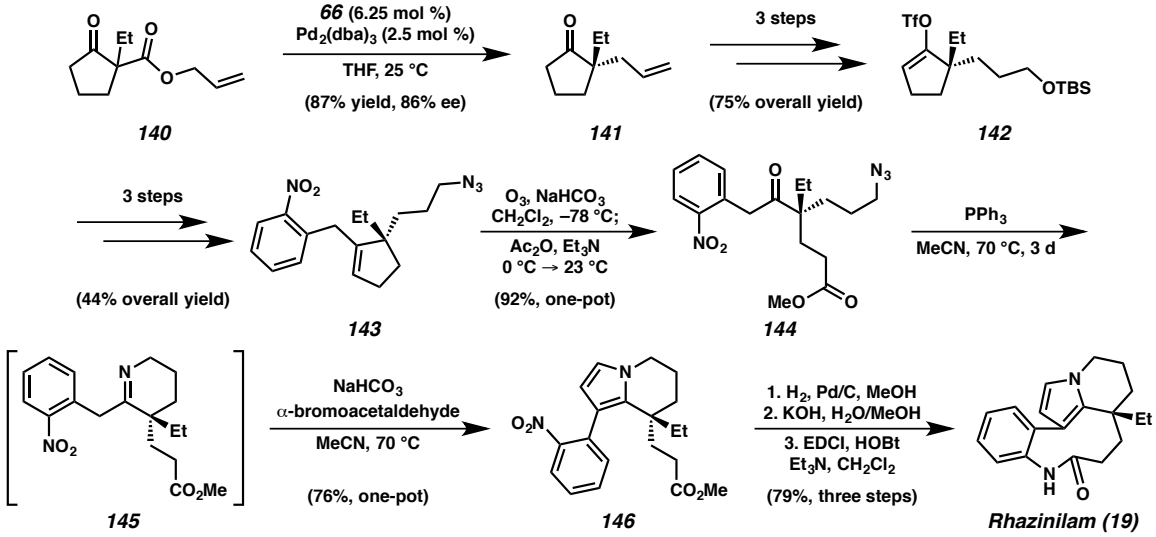
Scheme 1.4.7.2. Tailoring Primary Amine Nucleophilicity to Access Aminal-Containing Alkaloids



Following their successful elaboration of α-quaternary cyclohexanone **128** toward multiple alkaloids, Zhu and co-workers devised clever syntheses of (–)-rhazinilam (**19**), (–)-leucomidine B (**138**),[74] and (+)-leuconodine F (**139**)[75] beginning from five-membered β-ketoester **140** (Scheme 1.4.7.3). The known synthesis of α-quaternary cyclopentanone **141** proceeded in 87% yield and 86% ee under typical reaction conditions.[67,76] The authors conducted a three-step sequence to access cyclopentenyl triflate **142**, which was advanced through an additional three steps to give cyclopentene **143**. A familiar ozonolysis with an Ac_2O/Et_3N workup yielded methyl ester **144**, which could undergo smooth aza-Wittig cyclization to deliver imine **145**. While this imine intermediate could be isolated, the authors were pleased to find that pyrrole formation could occur in the same pot to afford tetrahydroindolizine **146**. This intermediate was converted to (–)-

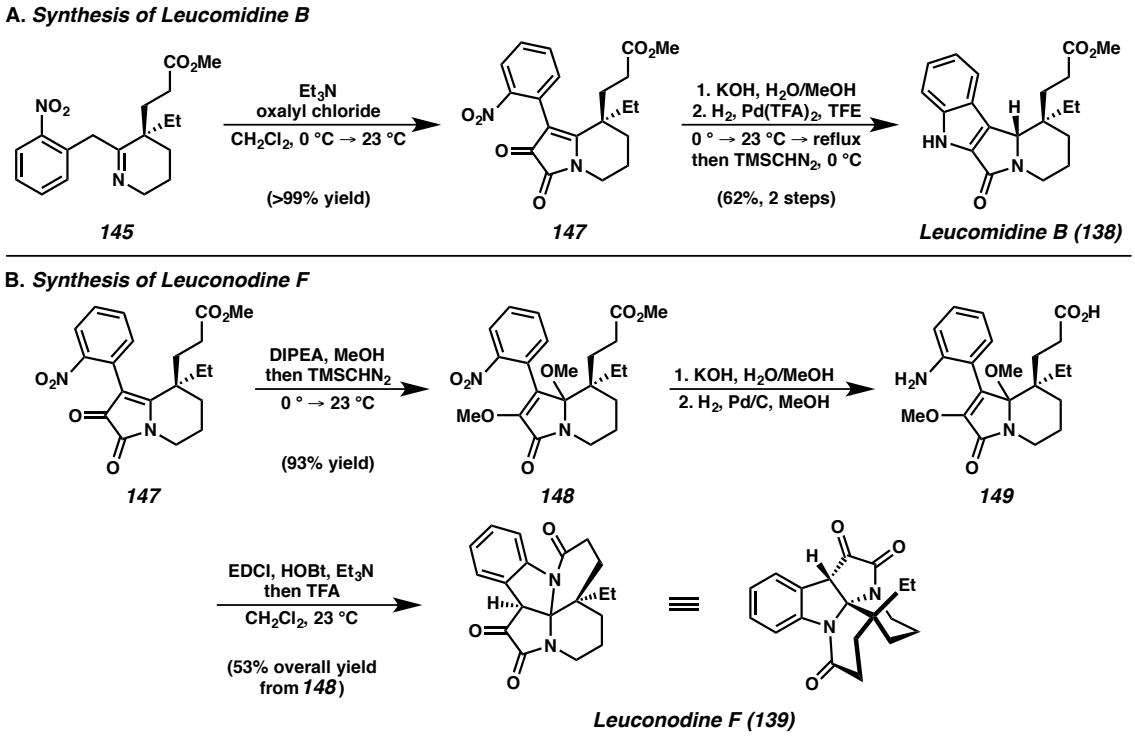
rhazinilam (**19**) using a well-precedented reduction/hydrolysis/macrolactamization sequence.

*Scheme 1.4.7.3. Zhu's Total Synthesis of (–)-Rhazinilam (**19**)*



Furthermore, Zhu and co-workers found that facile cyclocondensation could occur between imine **145** and oxalyl chloride to give dioxopyrrole **147** (Scheme 1.4.7.4A). Saponification of the methyl ester, followed by nitro reduction/indolization and remethylation delivered (–)-leucomidine B (**138**). It was discovered that saponification was required to achieve high levels of diastereoselectivity at the stereogenic aminomethine in the natural product. Alternatively, the ketone in **147** could be protected as the corresponding methyl enolether (**148**, Scheme 1.4.7.4B). This enabled regiodivergent aniline cyclization in their total synthesis of (+)-leuconodine F (**139**).

*Scheme 1.4.7.4. Zhu's Total Synthesis of (–)-Leucomidine B (**138**) and (+)-Leuconodine F (**139**)*



The Zhu group has elegantly leveraged the high enantioselectivities available in Pd-catalyzed allylic alkylations of cyclic substrates to prepare precursors for their reduction/oxidation/cyclization cascades. Critically, they have demonstrated the ability to tune participating functional groups for the controlled, divergent construction of multiple monoterpene indole alkaloid scaffolds.

1.5 CONCLUSION AND OUTLOOK

Monoterpene indole alkaloids of the *Aspidosperma* type have long inspired innovation in chemical synthesis. Over the past five years, several research groups have utilized enantioselective Pd-catalyzed allylic alkylations of prochiral enolates to synthesize a wide variety of structurally unique *Aspidosperma* and *Kopsia* alkaloids, further highlighting the widespread utility of these reactions. Critical to the success of these endeavors is the ability to construct multiple stereocenters in the respective targets with high diastereoselectivity by leveraging the all-carbon quaternary center formed in the Pd-catalyzed allylic alkylation event. Future studies to reduce the loadings of precious-metal catalysts, develop non-precious-metal-catalyzed allylic alkylation reactions, and the combine this reactivity with emerging synthetic methods will be of paramount importance in the advancement of chemical synthesis.

1.6 NOTES AND REFERENCES

1. For reviews, see: (a) Saxton, J. E. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, **1998**; *Vol. 51*, 1–197. (b) Kam, T.-S.; Lim, K.-H. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: Amsterdam, **2008**; *Vol. 66*, 1–111.
2. For a uniform numbering system of monoterpene indole alkaloids, see: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–510.
3. Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. *Tetrahedron Lett.* **1961**, *2*, 485–492.
4. Hesse, O. *Ber. Dtsch. Chem. Ges.* **1980**, *13*, 2308–2309.
5. Randriambola, L.; Quirion, J.-C. Kan-Fan, C.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 2123–2126.
6. Djerassi, C.; Budzikiewicz, H.; Wilson, J. M.; Gosset, J.; Le Men, J.; Janot, M.-M. *Tetrahedron Lett.* **1962**, *3*, 235–239.
7. Janot, M.-M.; Pourrat, H.; Le Men, J. *Bull. Soc. Chim. Fr.* **1954**, 707–708.
8. Medina, J. D.; Di Genova, L. *Planta Med.* **1979**, *37*, 165–167.
9. Burnell, R. H.; Medina, J. D.; Ayer, W. A. *Can. J. Chem.* **1966**, *44*, 28–31.
10. Cava, M. P.; Talapatra, S. K.; Nomura, K.; Weisbach, J. A.; Douglas, B.; Shoop, E. C. *Chem. Ind.* **1963**, 1242–1243.
11. Fraude, G. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 2189–2191.
12. Milborrow, B. V.; Djerassi, C. *J. Chem. Soc. C* **1969**, 417–424.
13. Djerassi, C.; Archer, A. A. P. G.; George, T.; Gilbert, B.; Shoolery, J. N.; Johnson, L. F. *Experientia* **1960**, *16*, 532–534.

14. Achenbach, H. *Tetrahedron Lett*. **1967**, *8*, 1793–1797.

15. Goh, S. H.; Wei, C.; Ali, A. R. M. *Tetrahedron Lett*. **1984**, *25*, 3484–3484.

16. Feng, T.; Cai, X.-H.; Liu, Y.-P.; Li, Y.; Wang, Y.-Y.; Luo, X.-D. *J. Nat. Prod*. **2010**, *73*, 22–26.

17. Abe, F.; Yamauchi, T. *Phytochemistry* **1994**, *35*, 169–171.

18. Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett*. **2004**, *45*, 5995–5998.

19. Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett*. **1972**, *13*, 909–912.

20. Goh, S. H.; Ali, A. R. M. *Tetrahedron Lett*. **1986**, *27*, 2501–2504.

21. Crow, W. D.; Michael, M. *Aust. J. Chem*. **1955**, *8*, 129–135.

22. (a) Kump, C.; Dugan, J. J.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 1237–1243. (b) Ferreira Filho, J. M.; Gilbert, B.; Kitagawa, M.; Paes Leme, L. A.; Durham, L. J. *J. Chem. Soc. C,* **1966**, 1260–1266.

23. Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem*. **2011**, *9*, 5334–5336.

24. Greshoff, M. *Ber. Dtsch. Chem. Ges*. **1890**, *23*, 3537–3550.

25. Govindachari, T. R.; Nagarajan, K.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 433–444.

26. Guggisberg, A.; Hesse, M.; Von Philipsborn, W.; Nagarajan, K.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 2321–2337.

27. Chen, W.-S.; Li, S.-H.; Kirfel, A.; Will, G.; Breitmaier, E. *Liebigs Ann. Chem*. **1981**, 1886–1892.

28. Battersby, A. R.; Gregory, H. *J. Chem. Soc*. **1963**, 22–32.

29. For a review, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.

30. O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547.

31. Detailed information regarding the enzymatic conversion of 4,21-dihydrogeissoschizine (**31**) to tabersonine (**5**) is currently unknown.

32. Lim, K.-H.; Hiraku, O.; Komiyama, K.; Koyano, T.; Hayashi, M.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1302–1307.

33. Feng, T.; Li, Y.; Liu, Y.-P.; Cai, X.-H.; Wang, Y.-Y.; Luo, X.-D. *Org. Lett.* **2010**, *12*, 968–971.

34. (a) Wu, Y.; Suehiro, M.; Kitajima, M.; Matsuzaki, T.; Hashimoto, S.; Nagoaka, M.; Zhang, R.; Takayama, H. *J. Nat. Prod.* **2009**, *72*, 204–209. (b) David, B.; Sévenet, T.; Morgat, M.; Guénard, D.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Motil. Cytoskeleton* **1994**, *28*, 317–326. (c) David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Païs, M.; Wright, M.; Guénard, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155–2158.

35. For reviews that are broader in scope, see: (a) Hájíček, J. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1681–1767. (b) Hájíček, J. *Collect. Czech. Chem. Commun.* **2007**, *72*, 821–898. (c) Hájíček, J. *Collect. Czech. Chem. Commun.* **2011**, *76*, 2023–2083. (d) Saxton, J. E. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, **1998**; *Vol. 50*, 343–376. (e) Lopchuk, J. M. in *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A., Eds.; Elsevier: Oxford, UK, **2011**; *Vol. 23*, 1–25.

36. Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.

37. Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188.

38. For leading references, see: (a) Medley, J. W.; Movassaghi, M. *Org. Lett.* **2013**, *15*, 3614–3617. (b) White, K. L.; Mewald, M.; Movassaghi, M. *J. Org. Chem.* **2015**, *80*, 7403–7411.

39. (a) Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4572–4576. (b) Mewald, M.; Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 11634–11639. (c) White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389.

40. An asymmetric alkylation using Myers' pseudoephenamine chiral auxiliary enabled a highly enantioselective convergent synthesis of lactam **39**. For the first disclosure of the pseudoephenamine chiral auxiliary, see: Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 4568–4571.

41. Walser, A.; Djerassi, C. *Helv. Chim. Acta.* **1965**, *48*, 391–404.

42. Mokrý, J.; Kompiš, I. *Chem. Zvesti* **1963**, *17*, 852–860.

43. Lactam **45** was prepared by an enzymatic resolution of the corresponding acetate.

44. Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641.

45. Pyuskyulev, B.; Kompis, I.; Ognyanov, I.; Spiteller, G. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1289–1294.

46. For leading references, see: (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927. (c) Behenna, D. C.; Liu, Y.;

Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. (e) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357.

47. Xu, J. Palladium Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Unstabilized Enolates: Scope, Mechanism and Synthetic Applications. Ph.D. Dissertation, Stanford University, Palo Alto, CA, 2008.

48. For a review on enantioselective formal syntheses of classic natural products via Pd-catalyzed allylic alkylation, see: Liu, Y.; Liniger, M.; McFadden, R. M.; Roizen, J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T.; Virgil, S. C.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2014**, *10*, 2501–2512.

49. Meyers and co-workers used enone **59** to intercept an advanced intermediate in Stork's syntheses of (±)-quebrachamine (**2**) and (±)-aspidospermine (**11**). For Meyers' formal syntheses, see: (a) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673–4676. For Stork's original syntheses of **2** and **11**, see: (b) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873.

50. Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431–4439.

51. Pandey, G.; Kumara, C. P. *Org. Lett.* **2011**, *13*, 4672–4675.

52. Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647–8651.

53. For the enantioselective formal syntheses of multiple alkaloid targets via lactone **63**, see: Li, Z.; Geng, Q.; Lv, Z.; Pritchett, B. P.; Baba, K.; Numajiri, Y.; Stoltz, B. M.; Liang, G. *Org. Chem. Front.* **2015**, *2*, 236–240.

54. Feng, T.; Cai, X.-H.; Zhao, P.-J.; Du, Z.-Z.; Li, W.-Q.; Luo, X.-D.; *Planta Med.* **2009**, *75*, 1537–1541.

55. Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116.

56. Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chem.–Eur. J.* **2012**, *18*, 6729–6732.

57. Yi, W.; Zhao, D.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12988–12991.

58. For pioneering studies in intramolecular oxidative couplings from the Ma group, see: Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228.

59. Mizutani, M.; Yasuda, S.; Mukai, C. *Chem. Commun.* **2014**, *50*, 5782–5785.

60. Leng, L.; Zhou, X.; Liao, Q.; Wang, F.; Song, H.; Zhang, D.; Liu, X.-Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 3703–3707.

61. A diol bearing the same carbon skeleton as **93** was also isolated in 9% overall yield from acyloin adduct **91**.

62. Constitutionally isomeric byproducts were isolated in the final steps of (–)-kopsanone (**21**) and (–)-kopsine (**23**), but have been omitted from this review for clarity.

63. Yang, R.; Qiu, F. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 6015–6018.

64. Trost and co-workers used (*R,R*)-**97** in 1,4-dioxane at 23 °C to synthesize **98**, presumably in the opposite enantiomeric series, in 82% yield and 90% ee. No explanation was given for the deviation from Trost's superior conditions. For the original report, see: Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112.

65. He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.

66. Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 4117–4121.

67. Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223.

68. Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642–2645.

69. Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444–11449.

70. Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621–5623.

71. Shen, X.-L.; Zhao, R.-R.; Mo, M.-J.; Peng, F.-Z.; Zhang, H.-B.; Shao, X.-H. *J. Org. Chem.* **2014**, *79*, 2473–2480.

72. Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127–19130.

73. In an ensuing full paper, the authors disclosed the conversion of (+)-melodinine E (**16**) to additional related alkaloids. For details, see: Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712–6724.

74. Motegi, M.; Nugroho, A. E.; Hirasawa, Y.; Arai, T.; Hadi, A. H. A.; Morita, H. *Tetrahedron Lett.* **2012**, *53*, 1227–1230.

75. For initial isolation of leuconodine F (**139**), which was originally named 6-oxoleuconoxine, see: (a) Lim, S.-H.; Sim, K.-M.; Abdullah, Z.; Hiraku, O.;

Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1380–1383. For subsequent isolation and renaming, see: (b) Low, Y.-Y.; Hong, F.-J.; Lim, K.-H.; Thomas, N. F.; Kam, T.-S. *J. Nat. Prod.* **2014**, *77*, 327–338.

76. Craig, R. A., II; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160–5163.

CHAPTER 2

Chemoselectivity in Indole-Iminium Cyclizations: Total Synthesis of (–)-Goniomitine and Formal Syntheses of (+)-Aspidospermidine and (–)-Quebrachamine†

2.1 INTRODUCTION, BACKGROUND, AND RETROSYNTHETIC ANALYSIS

Monoterpene indole alkaloids have been extensively studied by chemists and biologists alike due to their vast structural diversity and broad biological activity.[1] (–)-Goniomitine (**3**), isolated from the bark of *Gonioma malagasy*, is an *Aspidosperma* alkaloid with a unique octahydroindolo[1,2-*a*][1,8]naphthyridine core (Figure 2.1).[2] The key structural differences between goniomitine (**3**) and many *Aspidosperma* alkaloids (e.g., **1**, **2**, and **4**, Figure 2.1.1)[3] are the aminal functionality at C21 and the vestigial (2-hydroxy)ethyl moiety at C7.[4]

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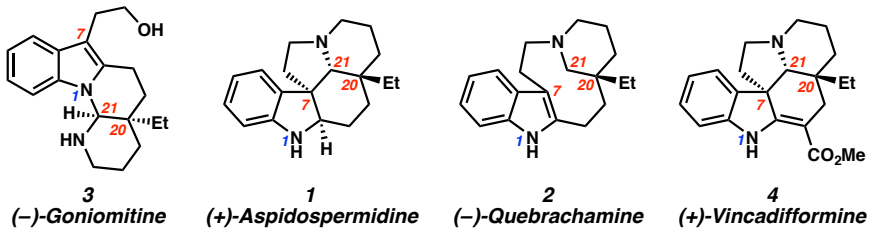
† This work was performed in collaboration with Dr. Yoshitaka Numajiri and Jun Kikuchi, both of whom are alumni of Stoltz group. Additionally, this research has been published and adapted with permission from Pritchett, B. P.; Kikuchi, J.; Numajiri, Y.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 13529–13532. Copyright 2016 Wiley-VCH.

Figure 2.1.1. Skeletally Diverse Aspidosperma Alkaloids



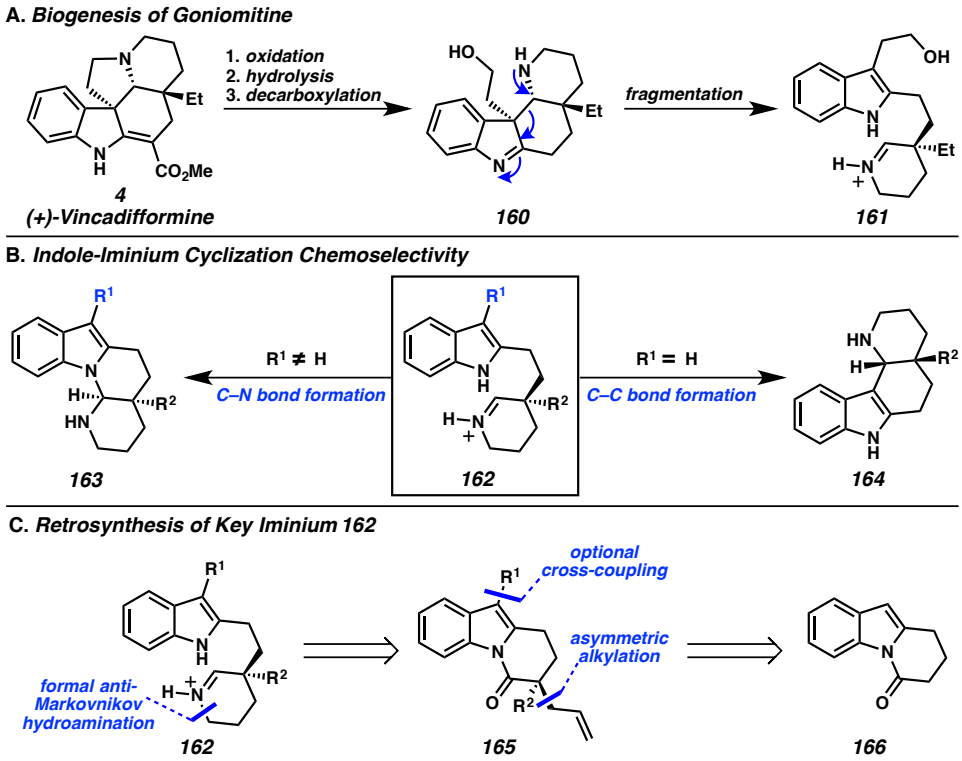
3 ***(–)-Goniomitine*** **1** ***(+)-Aspidospermidine*** **2** ***(–)-Quebrachamine*** **4** ***(+)-Vincadifformine***

Biosynthetically, these features are believed to arise from oxidative degradation of the tryptamine fragment in vincadifformine (**4**) to give **160**, which is poised to undergo retro-Mannich fragmentation to give iminium **161** (Scheme 2.1.1A). N1–C21 recombination of iminium **161** can then furnish goniomitine (**3**).[5] Cyclizations between an indole and a C2-tethered iminium moiety (e.g., **162**, Scheme 2.1.1B) are remarkably chemoselective. In the case of a C3-substituted indole fragment (e.g., **162**, $R^1 \neq H$), cyclization proceeds via C–N bond formation to furnish aminal-containing tetracycle **163**, as seen in previous syntheses of goniomitine (**3**).[5–7] Conversely, a C3-unsubstituted indole fragment (e.g., **162**, $R^1 = H$) undergoes C–C bond formation followed by rearomatization to arrive at alternative tetracycle **164**, a core that is present in numerous alkaloids (e.g., **1** and **4**).[8]

We anticipated that iminium intermediates such as **162** could be accessed in straightforward fashion from compounds containing a dihydropyrido[1,2-*a*]indolone (DHPI) core (Scheme 2.1.1C). Retrosynthetically, we envisioned that the propylamine fragment in **162** could arise from an anti-Markovnikov hydroamination of the allyl functionality in α-quaternary lactam **165**. Given our lab's long-standing interest in the asymmetric synthesis of all-carbon quaternary centers, we believed that we could employ our Pd-catalyzed allylic alkylation chemistry to construct the quaternary stereocenter at C20 in an enantioselective fashion.[9,10] We expected that a cross-coupling reaction could

enable optional substitution at the C3 position of the DHPI scaffold, thereby providing selective routes to tetracycles **163** and **164**. Therefore, development of this versatile substrate class in our Pd-catalyzed allylic alkylation chemistry would provide a powerful tool for divergent enantioselective syntheses of multiple *Aspidosperma* alkaloids.

Scheme 2.1.1. Biosynthetic Origin and Synthetic Versatility of Iminium ***162***



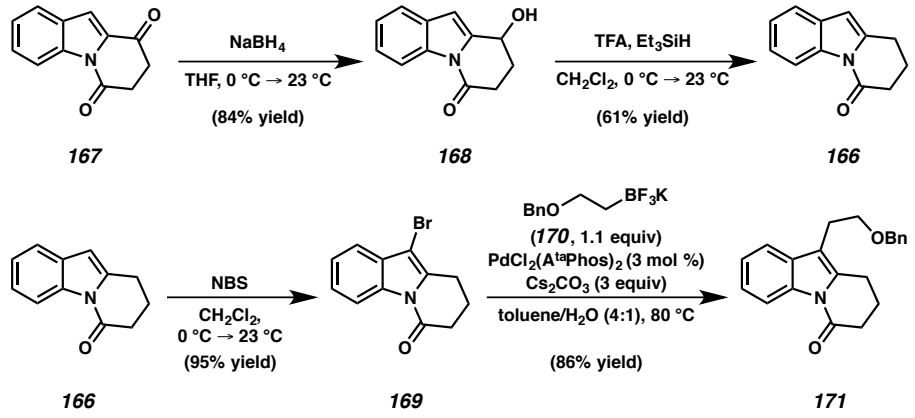
Due to its antiproliferative activity and unusual structure, several groups have targeted goniomitine (**3**) for total synthesis.[6,7] While modern approaches to this molecule have improved upon the seminal report by Takano and co-workers,[7a] a synthesis of goniomitine (**3**) that employs asymmetric catalysis to achieve stereocontrol has not yet been demonstrated. To date, asymmetric syntheses of goniomitine (**3**) have relied on either enzymatic resolutions or chiral pool materials.[7] Furthermore, in previous syntheses of goniomitine, unless the (2-hydroxy)ethyl moiety was incorporated using a tryptophol-

derived starting material, a multi-step sequence from an unsubstituted C7 position was required. We instead anticipated that a cross-coupling reaction between a C3-brominated DHPI and a suitable organometallic reagent would enable efficient access to the (2-hydroxy)ethyl fragment in the natural product. Realization of this synthetic plan would deliver the first catalytic enantioselective total synthesis of (–)-goniomitine (**3**).

2.2 PALLADIUM-CATALYZED ALLYLIC ALKYLATION REACTIONS OF DHPI SUBSTRATES

Our synthesis of (–)-goniomitine (**3**) commenced from known dicarbonyl **167**,[11] which underwent regioselective ketone reduction using sodium borohydride to give alcohol **168** in 84% yield (Scheme 2.2.1). Treatment of alcohol **168** with triethylsilane in the presence of trifluoroacetic acid afforded known *N*-acyl indole **166** in 61% yield.[12] Regioselective bromination occurred to give heteroaryl bromide **169** in 95% yield. Gratifyingly, treatment of **169** with potassium (2-benzyloxy)ethyl trifluoroborate (**170**) and catalytic $PdCl_2(A^{ta}Phos)_2$ afforded cross-coupled product **171** in 86% yield.[13,14] Facile C-acylation and C-alkylation of tricycles **166**, **169**, and **171** positioned us to investigate the heretofore untested asymmetric allylic alkylation of the dihydropyrido[1,2-*a*]indolone (DHPI) substrate class.

Scheme 2.2.1. Synthesis and Suzuki Cross-Coupling of a 3-Bromoindole Fragment[a]

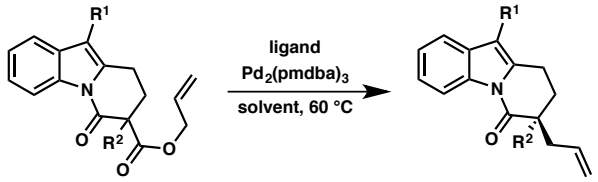


[a] A[ta]Phos = di-*tert*-butyl(4-dimethylamino)phenylphosphine

Exposure of (2-benzyloxy)ethyl-substituted DHPI **172a** to the catalyst derived from $Pd_2(pmdba)_3$ (10 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 25 mol %)[15] yielded the α-quaternary product **165a** in 38% yield and 89% enantiomeric excess (Table 2.2.1, Entry 1). Switching from toluene to TBME as solvent greatly improved the reaction rate and yield, albeit with a minor decrease in enantioselectivity (Entry 2). Previous studies by our group have revealed that electron-withdrawing substituents on the lactam nitrogen atom provide the best results in the allylic alkylation chemistry.[9b] As the enolate intermediate would be in cross-conjugation with the arene π-system, we postulated that a bromide at the C3 position could provide both a beneficial electronic effect and a handle for cross-coupling downstream. While there are numerous reports of aryl bromides withstanding the conditions of Pd-catalyzed allylic alkylation reactions, their strategic implementation for cross-coupling events following the allylic alkylation is comparatively limited.[16] Gratifyingly, brominated β-amidoester **172b** reacted to give the desired quaternary alkylated product **165b** (Entries 3 and 4), which in TBME was afforded in 83% yield and 96% ee with no observable interference from the C3 bromide (Entry 4). Given that the

successful inclusion of a C3–H substrate in our allylic alkylation chemistry would enable divergent construction of additional alkaloids (*vide infra*), we were pleased to find that β-amidoester **172c** could deliver α-quaternary lactam **165c** in 71% yield and 94% ee (Entry 6). Reaction of **172b** with electron-neutral (*S*)-*t*-BuPHOX (**66**)[17] as the ligand, in either toluene or TBME as solvent, resulted in diminished ee (Entries 7 and 8).

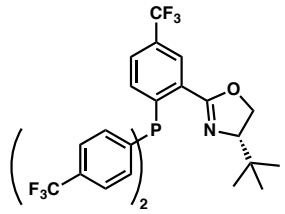
Table 2.2.1. Pd-Catalyzed Asymmetric Allylic Alkylation of DHPI Substrates[a]



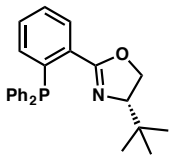
172 ***165***

entry	R^1 (*172* → *165*)	R^2	solvent	$Pd_2(pmdba)_3$ mol %	ligand (mol %)	time [h]	yield [%][b]	ee [%][c]
1	CH_2CH_2OBn (*172a* → *165a*)	Et	toluene	10	***76*** (25)	72	38	89
2	CH_2CH_2OBn (*172a* → *165a*)	Et	TBME	10	***76*** (25)	24	59	87
3	Br (*172b* → *165b*)	Et	toluene	5	***76*** (12.5)	24	21	93
4	Br (*172b* → *165b*)	Et	TBME	5	***76*** (12.5)	8	83	96
5	H (*172c* → *165c*)	Et	toluene	10	***76*** (25)	48	54	92
6	H (*172c* → *165c*)	Et	TBME	5	***76*** (12.5)	24	71	94
7[e]	Br (*172b* → *165b*)	Et	toluene	10	***66*** (25)	24	50	80
8[f]	Br (*172b* → *165b*)	Et	TBME	10	***66*** (25)	24	63	72

[a] Reactions were performed in stated solvent (0.033 M) at 60 °C.
[b] Isolated yield.
[c] Determined by chiral SFC analysis.
[d] pmdba = 4,4'-dimethoxydibenzylideneacetone
[e] Reaction performed at 40 °C
[f] Reaction performed at 35 °C



76
(S)-(CF3)3-t-BuPHOX

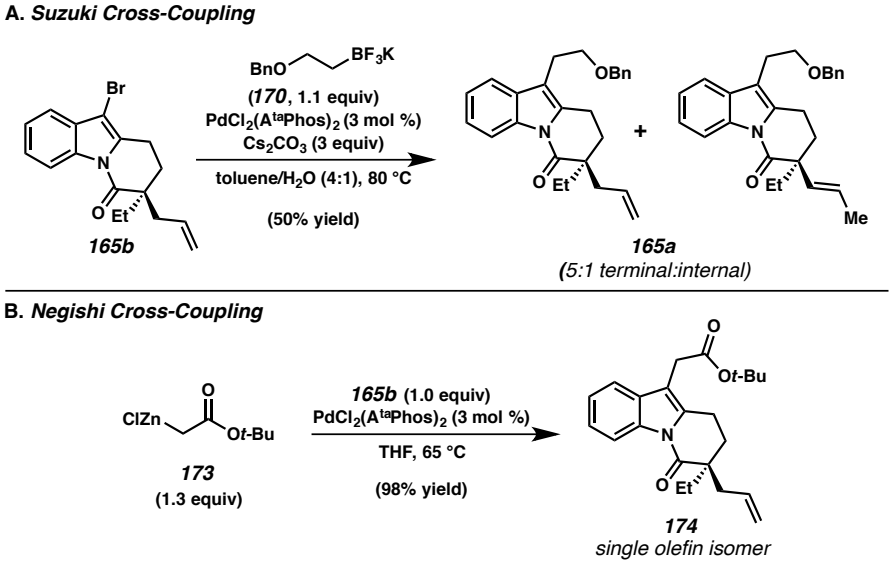


66
(S)-t-BuPHOX

2.3 CROSS-COUPLING OF 3-BROMO α-QUATERNARY DHPI 165b

We next turned our attention toward the cross-coupling of brominated α-quaternary lactam **165b** with a suitable hydroxyethyl surrogate. Unfortunately, we found that the Suzuki reaction between **165b** and trifluoroborate **170** could not be improved beyond a 50% yield of inseparable olefin isomers **165a** in a 5:1 ratio (Scheme 2.3.1A). We hypothesized that a Pd–H species was responsible for this undesired isomerization pathway, and sought to identify an alternative C_{sp^3} nucleophilic coupling partner that would not allow for facile β-hydride elimination. Recognizing that a reduction would ultimately be required to convert the amide present in **165b** to the aminal present in goniomitine (**3**), we decided to incorporate a substituent in a higher oxidation state via the cross-coupling, thereby allowing concomitant unveiling of the (2-hydroxy)ethyl moiety at a later stage. After investigating a multitude of Negishi conditions, we were thrilled to find that Reformatsky reagent **173** could be efficiently coupled with heteroaryl bromide **165b** using catalytic $PdCl_2(A^{ta}Phos)_2$ to deliver arylated product **174** in 98% yield without any detectable amount of undesired olefin isomers (Scheme 2.3.1B).[18]

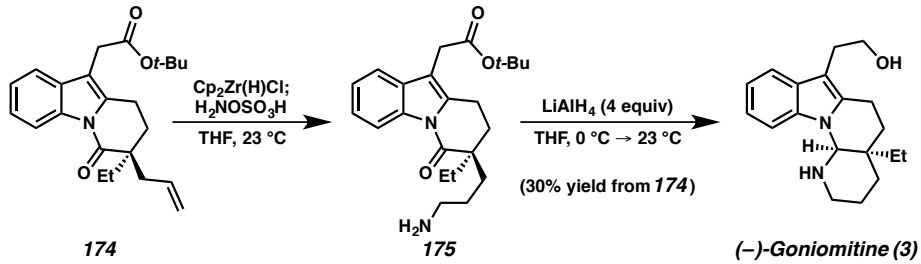
*Scheme 2.3.1. Cross-Coupling Reactivity of α-Quaternary DHPI **165b***



2.4 (–)-GONIOMITINE ENDGAME

With the requisite carbon–carbon bonds established, we began investigating methods to effect an anti-Markovnikov hydroamination of the terminal olefin of **174**. To this end, we employed a one-pot hydrozirconation/amination sequence reported by Hartwig and co-workers.[19] To our knowledge, this is the first implementation of Hartwig's hydrozirconation/amination protocol in the context of natural product synthesis. Following this formal hydroamination, we were pleased to find that complete reduction of the *tert*-butyl ester of **175** could be achieved alongside partial reduction of the amide carbonyl in one pot using a single reductant. In the event, primary amine **175** was subjected to $LiAlH_4$ in THF, followed by acidic workup, to afford (–)-goniomitine (**3**) in 30% yield from **174** (Scheme 2.4.1).

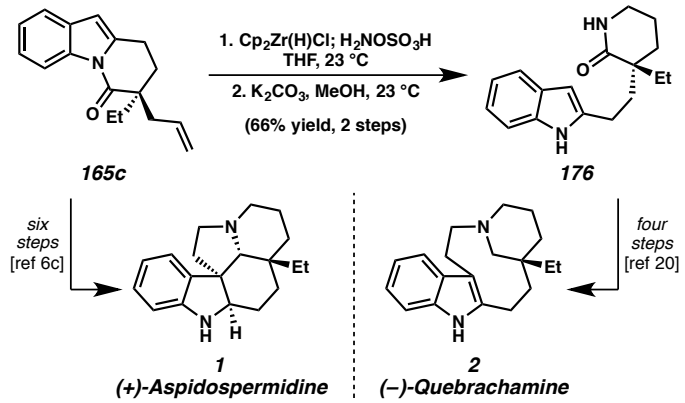
*Scheme 2.4.1. Completion of the Synthesis of (–)-Goniomitine (**3**)*



2.5 ASYMMETRIC FORMAL SYNTHESES OF (+)-ASPIDOSPERMIDINE AND (–)-QUEBRACHAMINE

Having completed the total synthesis of (–)-goniomitine (**3**), we sought to leverage the flexibility of the DHPI scaffold by exploiting the chemoselectivity in cyclizations of an indole with a C2-tethered iminium functionality (cf. Scheme 2.1.1B). Indeed, the synthesis of **165c** completes an enantioselective formal synthesis of (+)-aspidospermidine (**1**) (Scheme 2.5.1).[6c] Furthermore, treatment of **165c** with the aforementioned hydroamination conditions followed by a mild amide exchange furnishes free N–H α-quaternary δ-lactam **176** in 66% yield over two steps, constituting an asymmetric formal synthesis of (–)-quebrachamine (**2**).[20]

Scheme 2.5.1. Asymmetric Formal Syntheses of Other Aspidosperma Alkaloids



2.6 CONCLUSION

In summary, we have completed the first catalytic enantioselective total synthesis of (–)-goniomitine (**3**) in 11 steps and 8% overall yield from indole, or 7 steps and 17% overall yield from known DHPI **166**. The redox efficiency and freedom from protecting-group manipulations is a marked improvement from previous nonracemic syntheses, which deliver the target in 10–28 steps and 0.25–3.2% overall yield from commercial materials.[21] Rationally designed heteroaryl bromide **172b** underwent Pd-catalyzed allylic alkylation to deliver the α-quaternary product (**165b**) in 83% yield and 96% ee. The surprisingly robust C_{aryl}–Br bond served as a handle for a subsequent Negishi cross-coupling. The compatibility of aryl bromides in our allylic alkylation reactions, along with the identification of cross-coupling conditions that do not isomerize the allyl group, provide a powerful platform for the convergent synthesis of complex organic molecules. Additionally, by completing formal syntheses of (+)-aspidospermidine (**1**) and (–)-quebrachamine (**2**), we demonstrate the ability of the DHPI scaffold to provide divergent, enantioselective access to structurally diverse alkaloid frameworks.

2.7 EXPERIMENTAL SECTION

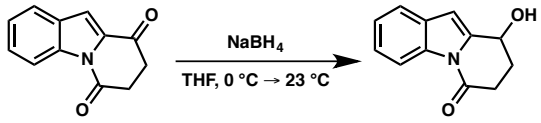
2.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[22] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, CAM, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. Melting points were measured with BÜCHI Melting Point B-545. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, br t = broad triplet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell, and are reported as $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Analytical SFC was

performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in mixed ionization mode (MM: ESI/APCI).

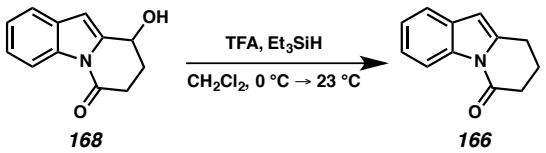
Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. NBS was purchased from Sigma Aldrich, recrystallized from H_2O, and stored in a –25 °C freezer. 2-*tert*-Butoxy-2-oxoethylzinc chloride (**173**, 0.5 M in Et_2O) was purchased from Rieke Metals and used within three days. Bis(cyclopentadienyl) zirconium chloride hydride was purchased from Strem Chemicals and stored at room temperature in a N_2-filled glovebox. Hydroxylamine-*O*-sulfonic acid was purchased from Sigma Aldrich and stored at –30°C in the glovebox freezer. $PdCl_2(A^{ta}Phos)_2$ was purchased from Sigma Aldrich and stored at ambient temperature in a dessicator. MeOH was distilled from magnesium methoxide immediately prior to use. (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**),[15] tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) $Pd_2(pmdba)_3$,[23] and allyl cyanoformate[24] were prepared by known methods.

2.7.2 EXPERIMENTAL PROCEDURES



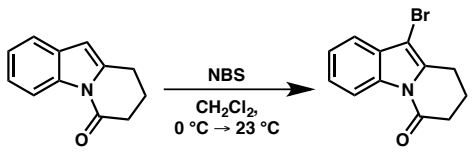
167 *168*

9-Hydroxy-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (168): To a solution of tricycle **167**[11] (5.92 g, 29.7 mmol, 1.00 equiv) in THF (300 mL) was added $NaBH_4$ (1.24 g, 32.8 mmol, 1.1 equiv) in two equal portions over 10 min at 0°C. The reaction mixture was allowed to warm to 23 °C over the course of 2 h at which point full consumption of starting material was observed by TLC analysis. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The biphasic mixture was poured into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and stripped onto silica gel. Flash column chromatography (SiO_2, 40% EtOAc in hexanes to 60% EtOAc in hexanes eluent) afforded alcohol **168** (5.03 g, 84% yield) as a tan amorphous solid: R_f = 0.45 (1:1 EtOAc:hexanes eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (dq, *J* = 8.2, 0.9 Hz, 1H), 7.53 (ddd, *J* = 7.7, 1.4, 0.8 Hz, 1H), 7.35 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.30–7.26 (m, 1H), 6.60 (t, *J* = 0.8 Hz, 1H), 5.12 (t, *J* = 4.5 Hz, 1H), 3.19–3.11 (m, 1H), 2.74 (dt, *J* = 17.5, 5.1 Hz, 1H), 2.28–2.22 (m, 2H), 1.96 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 139.8, 135.1, 129.2, 125.5, 124.3, 120.8, 116.8, 106.7, 62.6, 29.8, 29.6; IR (Neat Film, NaCl) 3396, 3059, 2960, 2934, 1704, 1597, 1473, 1453, 1372, 1358, 1321, 1178, 1086, 1052, 1022, 1006, 980, 942, 814, 754 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{12}H_{12}NO_2$ $[M+H]^+$: 202.0863, found 202.0862.



168 *166*

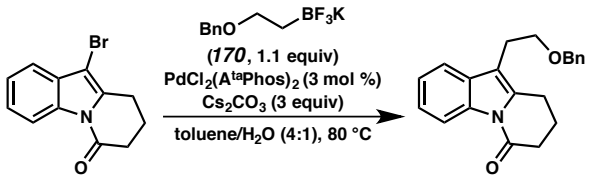
8,9-Dihydropyrido[1,2-*a*]indol-6(7*H*)-one (166): Two flasks were each charged with alcohol **168** (4.38 g, 21.8 mmol, 1.00 equiv), CH_2Cl_2 (220 mL), and Et_3SiH (7.6 g, 65.4 mmol, 3.0 equiv). Each flask was then cooled to 0 °C in an ice water bath. To each flask was then added TFA (14.9 g, 130.8 mmol, 6.0 equiv) over 15 min at 0°C. The solution turned to dark purple, and was allowed to warm to 23 °C over the course of 2 h, and then stirred at 23 °C for an additional 2 h. At this point, full consumption of starting material was observed by TLC analysis. The reaction was quenched by the careful addition of saturated aqueous $NaHCO_3$ at 0 °C until evolution of gas ceased. The two reaction mixtures were combined in a separatory funnel, and extracted with CH_2Cl_2 (3 x 500 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, 20% Et_2O in hexanes to 35% Et_2O in hexanes eluent) afforded heteroarene **166** (5.0 g, 61% yield) as a white solid: R_f = 0.25 (3:7 Et_2O:hexanes eluent); physical and spectroscopic data were consistent with those reported in the literature.[12]



166 *169*

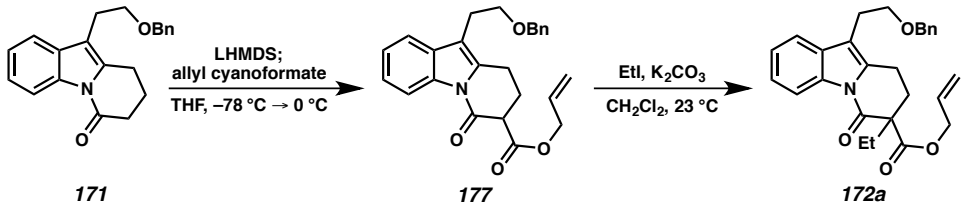
10-Bromo-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (169): To a solution of heteroarene **166** (910 mg, 4.91 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was charged NBS (900 mg, 5.05 mmol, 1.02 equiv) in three equal portions over 15 min at 0°C. After 10

min, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. Full consumption of starting material was complete within 20 minutes, as observed by TLC analysis. The crude reaction mixture was stripped onto silica gel and purified by flash column chromatography (SiO_2, 25% hexanes in CH_2Cl_2 eluent) to afford heteroaryl bromide **169** (1.24 g, 95% yield) as a white amorphous solid: R_f = 0.45 (3:1 CH_2Cl_2:hexanes eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46–8.42 (m, 1H), 7.49–7.44 (m, 1H), 7.38–7.31 (m, 2H), 2.99 (dd, *J* = 6.9, 5.8 Hz, 2H), 2.84–2.80 (m, 2H), 2.19–2.10 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 135.4, 134.0, 128.9, 125.5, 124.6, 118.5, 116.5, 96.7, 34.4, 22.8, 20.9; IR (Neat Film, NaCl) 3405, 3052, 2959, 2878, 2837, 1907, 1788, 1706, 1593, 1446, 1343, 1258, 1209, 1170, 1142, 1087, 1021, 982, 928, 908, 836, 799, 746, 650, 618 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{10}NOBr$ [M]$^+$: 262.9940, found 262.9936.



10-(2-(Benzyloxy)ethyl)-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (171): A 15 mL round bottom flask equipped with a magnetic stirring bar and a rubber septum was charged with heteroaryl bromide **169** (200 mg, 0.757 mmol, 1.0 equiv), potassium (2-benzyloxy)ethyltrifluoroborate (**170**, 200 mg, 0.826 mmol, 1.1 equiv), $PdCl_2(A^{ta}phos)_2$ (16 mg, 22.5 μmol, 0.03 equiv), and Cs_2CO_3 (740 mg, 2.27 mmol, 3.0 equiv). The flask was evacuated and backfilled with argon three times. Toluene (3.1 mL) and degassed water (0.7 mL) were added via syringe, and the flask was placed into a preheated 80 °C

oil bath with stirring. After stirring for 2 h, the biphasic reaction mixture was cooled to 23 °C, poured into water (15 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (25% Et_2O in hexanes) afforded heteroarene **171** (207 mg, 86% yield) as a light yellow oil: R_f = 0.3 (3:2 hexanes:Et_2O eluent); physical and spectroscopic data were consistent with those reported in the literature.[6e]



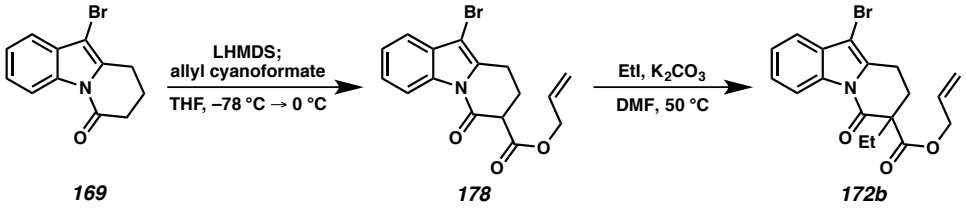
171 *177* *172a*

Allyl 10-(2-(benzyloxy)ethyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (177): A flame-dried round bottom flask was charged with LHMDS (282 mg, 1.69 mmol, 2.0 equiv) and a magnetic stirring bar in a N_2-filled glove box. The flask was sealed, removed from the glovebox, fitted with an argon line, and suspended in a dry ice/acetone bath. THF (4.5 mL) was added slowly to the flask and allowed to stir until the LHMDS had been completely dissolved. A solution of heteroarene **171** (270 mg, 0.845 mmol, 1.0 equiv) in THF (1.1 mL) was added dropwise, and the reaction was allowed to stir for 30 min at –78 °C. Allyl cyanoformate (112 mg, 1.01 mmol, 1.2 equiv) was then added dropwise, and the reaction was allowed to warm slowly to 0 °C over 4 h. Once the cooling bath temperature reached 0 °C, 100 mL of saturated aqueous NH_4Cl was then added slowly and the mixture stirred for 20 min before being extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash column

chromatography (SiO_2, 50% Et_2O in hexanes) to give tertiary β-amidoester **177** (256 mg, 75% yield) as a yellow oil: R_f = 0.3 (3:2 hexanes:Et_2O eluent); ^1H NMR (500 MHz, $CDCl_3$) δ 8.48–8.41 (m, 1H), 7.47–7.41 (m, 1H), 7.34–7.25 (m, 7H), 5.93 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.75–4.67 (m, 2H), 4.49 (s, 2H), 3.80 (dd, *J* = 8.1, 5.0 Hz, 1H), 3.68 (t, *J* = 6.9 Hz, 2H), 3.06 (ddd, *J* = 16.4, 7.9, 4.5 Hz, 1H), 2.95 (t, *J* = 6.9 Hz, 2H), 2.94–2.87 (m, 1H), 2.46 (dtd, *J* = 13.0, 8.4, 4.5 Hz, 1H), 2.29 (ddt, *J* = 13.0, 7.9, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 165.0, 138.4, 134.9, 133.6, 131.6, 130.5, 128.5, 127.73, 127.65, 124.6, 124.3, 119.1, 118.1, 116.7, 114.6, 73.2, 69.5, 66.4, 51.1, 25.02, 24.98, 20.0; IR (Neat Film, NaCl) 3062, 3032, 2941, 2857, 1737, 1697, 1622, 1454, 1376, 1307, 1258, 1171, 1128, 1094, 1020, 937, 803, 746, 698 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1856, found 404.1867.

Allyl 10-(2-(benzyloxy)ethyl)-7-ethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172a): To a solution of β-amidoester **177** (210 mg, 0.52 mmol, 1.0 equiv) in CH_2Cl_2 (3.5 mL) were added Cs_2CO_3 (678 mg, 2.08 mmol, 4.0 equiv) and EtI (0.25 mL, 3.12 mmol, 6.0 equiv) at 23 °C with stirring. After 18 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (10 mL) was added, followed by extraction with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (SiO_2, 25% Et_2O in hexanes) afforded quaternary β-amidoester **172a** (165 mg, 73% yield) as a faintly yellow oil: R_f = 0.33 (7:3 hexanes:Et_2O eluent); ^1H NMR (400 MHz, $CDCl_3$) δ 8.54–8.45 (m, 1H), 7.48–7.40 (m, 1H), 7.35–7.22 (m, 7H), 5.82 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.22 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.16 (dq, *J* = 10.5, 1.3

Hz, 1H), 4.64–4.59 (m, 2H), 4.50 (s, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 3.06 (dt, *J* = 16.8, 4.8 Hz, 1H), 2.99–2.81 (m, 3H), 2.46 (dt, *J* = 13.5, 4.8 Hz, 1H), 2.23–2.06 (m, 3H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 167.8, 138.4, 135.1, 133.9, 131.5, 130.7, 128.5, 127.7, 127.6, 124.4, 124.0, 118.8, 118.0, 116.9, 113.9, 73.2, 69.6, 66.2, 56.6, 28.9, 28.1, 24.9, 19.1, 9.4; IR (Neat Film, NaCl) 3028, 2938, 2857, 1734, 1701, 1620, 1457, 1370, 1328, 1310, 1225, 1189, 1098, 1020, 986, 935, 750, 697 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{27}H_{30}NO_4$ $[M+H]^+$: 432.2169, found 432.2177.



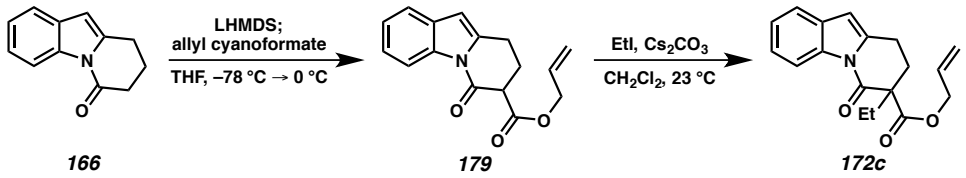
169 ***178*** ***172b***

Allyl 10-bromo-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (178): A flame-dried round bottom flask was charged with LHMDS (2.62 g, 1.69 mmol, 2.0 equiv) and a magnetic stirring bar in a N_2-filled glove box. The flask was sealed, removed from the glovebox, fitted with an argon line, and suspended in a dry ice/acetone bath. THF (48 mL) was added slowly to the flask and allowed to stir until the LHMDS had been completely dissolved. A solution of heteroaryl bromide **169** (2.07 g, 7.83 mmol, 1.0 equiv) in THF (4 mL) was added dropwise, and the reaction was allowed to stir for 30 min at –78 °C. Allyl cyanoformate (1.04 g, 9.36 mmol, 1.2 equiv) was then added dropwise, and the reaction was allowed to warm slowly to 0 °C over 4 h. Once the cooling bath temperature reached 0 °C, saturated aqueous NH_4Cl (200 mL) was then added slowly and the mixture stirred for 20 min before being extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (SiO_2, 10% EtOAc in

hexanes) afforded tertiary β-amidoester **178** (2.67 g, 98% yield) as clear colorless oil: R_f = 0.6 (3:1 hexanes:EtOAc eluent, orange by *p*-anisaldehyde stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46–8.41 (m, 1H), 7.50–7.44 (m, 1H), 7.39–7.33 (m, 2H), 5.93 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.76–4.67 (m, 2H), 3.85 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.08 (ddd, *J* = 16.9, 8.2, 4.8 Hz, 1H), 2.98 (ddd, *J* = 17.0, 7.9, 4.9 Hz, 1H), 2.59–2.50 (m, 1H), 2.37 (ddt, *J* = 13.4, 8.2, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 164.5, 134.3, 134.1, 131.4, 129.0, 125.8, 125.0, 119.2, 118.7, 116.6, 97.6, 66.6, 50.8, 24.5, 20.6; IR (Neat Film, NaCl) 3059, 2948, 2883, 1742, 1712, 1598, 1450, 1377, 1346, 1307, 1239, 1215, 1173, 1151, 1090, 1022, 986, 924, 753 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{15}NO_3Br$ $[M+H]^+$: 348.0230, found 348.0220.

Allyl 10-bromo-7-ethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172b): To a solution of β-amidoester **178** (166 mg, 0.476 mmol, 1.0 equiv) in DMF (1.6 mL) were added K_2CO_3 (263 mg, 1.9 mmol, 4.0 equiv) and EtI (0.08 mL, 0.95 mmol, 2.0 equiv). The reaction mixture was heated to 50 °C with stirring. After 5 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (5 mL) was added, followed by extraction with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (SiO_2, 10% Et_2O in hexanes) afforded quaternary β-amidoester **172b** (136 mg, 76% yield) as a clear colorless oil: R_f = 0.45 (17:3 hexanes:Et_2O eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51–8.46 (m, 1H), 7.49–7.44 (m, 1H), 7.39–7.32 (m, 2H), 5.84 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.25 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.69–4.60 (m, 2H), 3.12 (dt, *J* = 17.3, 4.6 Hz,

1H), 2.90 (ddd, J = 17.0, 11.7, 4.9 Hz, 1H), 2.53 (ddd, J = 13.6, 4.9, 4.3 Hz, 1H), 2.26–2.11 (m, 3H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 167.4, 134.5, 134.4, 131.3, 129.1, 125.6, 124.8, 119.0, 118.6, 116.7, 97.0, 66.4, 56.6, 28.5, 28.1, 19.9, 9.4; IR (Neat Film, NaCl) 3054, 2961, 2878, 1728, 1708, 1594, 1448, 1369, 1325, 1306, 1261, 1219, 1176, 1088, 1025, 920, 798, 748 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{19}NO_3Br$ $[M+H]^+$: 376.0543, found 376.0560.



Allyl 6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (179): A flame-dried round bottom flask was charged with LHMDS (1.8 g, 10.8 mmol, 2.0 equiv) and a magnetic stirring bar in a N_2-filled glove box. The flask was sealed, removed from the glovebox, fitted with an argon line, and suspended in a dry ice/acetone bath. THF (32 mL) was added slowly to the flask and allowed to stir until the LHMDS had been completely dissolved. A solution of heteroarene **166** (1.0 g, 5.4 mmol, 1.0 equiv) in THF (4 mL) was added dropwise, and the reaction was allowed to stir for 30 min at –78 °C. Allyl cyanoformate (720 mg, 6.48 mmol, 1.2 equiv) was then added dropwise, and the reaction mixture was allowed to warm slowly to 0 °C over 4 h. Once the cooling bath temperature reached 0 °C, saturated aqueous NH_4Cl (200 mL) was then added slowly and the mixture stirred for 20 min before being extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 15% acetone in hexanes) afforded tertiary β-amidoester **179** (1.32 g, 91% yield) as a faintly yellow oil which

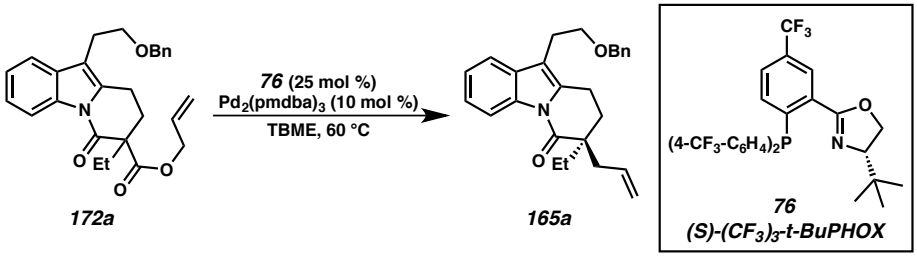
solidified to an off-white amorphous solid upon storage at –30 °C: R_f = 0.35 (4:1 hexanes:acetone eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45–8.42 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.24 (m, 2H), 6.36 (td, *J* = 1.4, 0.7 Hz, 1H), 5.93 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.77–4.67 (m, 2H), 3.83 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.11 (dddd, *J* = 16.4, 8.1, 4.5, 1.4 Hz, 1H), 2.98 (dddd, *J* = 16.4, 8.5, 4.6, 1.5 Hz, 1H), 2.55–2.46 (m, 1H), 2.38–2.29 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 165.2, 137.0, 135.1, 131.5, 129.9, 124.51, 124.48, 120.0, 119.1, 116.7, 105.8, 66.5, 51.1, 25.3, 21.8; IR (Neat Film, NaCl) 3085, 3051, 2946, 2850, 1732, 1690, 1577, 1454, 1381, 1356, 1301, 1213, 1177, 1148, 1021, 977, 932, 802, 742 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{16}NO_3$ $[M+H]^+$: 270.1130, found 270.1140.

Allyl 7-ethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172c): To a solution of β-amidoester **179** (790 mg, 2.93 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) were added Cs_2CO_3 (3.82 g, 11.73 mmol, 4.0 equiv) and EtI (1.41 mL, 17.6 mmol, 6.0 equiv) at 23 °C with stirring. After 18 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (100 mL) was added, followed by extraction with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (SiO_2, 15% Et_2O in hexanes) afforded quaternary β-amidoester **172c** (760 mg, 87% yield) as a faintly yellow oil: R_f = 0.3 (17:3 hexanes:Et_2O eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (ddt, *J* = 8.0, 1.3, 0.7 Hz, 1H), 7.48–7.43 (m, 1H), 7.33–7.23 (m, 2H), 6.31 (dt, *J* = 1.8, 0.9 Hz, 1H), 5.84 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.65 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.07 (dtd, *J* = 16.8, 4.8, 1.0 Hz, 1H), 2.98 (dddd, *J* = 16.7, 11.7, 4.7, 1.9 Hz, 1H), 2.47 (dt, *J* = 13.5, 4.6 Hz, 1H), 2.26–2.10

(m, 3H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 168.0, 137.3, 135.3, 131.4, 130.1, 124.27, 124.25, 119.9, 118.8, 116.8, 105.2, 66.2, 56.7, 29.2, 28.2, 20.8, 9.4; IR (Neat Film, NaCl) 3395, 3051, 2964, 2880, 1704, 1597, 1446, 1353, 1260, 1101, 1021, 877, 798, 746 cm^{-1}; HRMS (ESI/APCI) m/z calc'd for $C_{18}H_{20}NO_3$ [M+H]$^+$: 298.1438, found 298.1435.

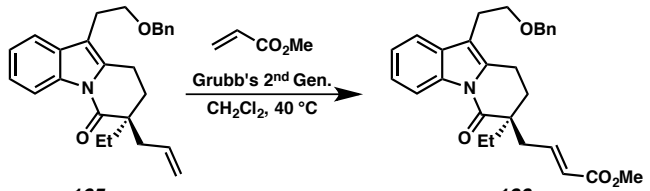
General Procedure A: Pd-Catalyzed Allylic Alkylation

Please note that the absolute configuration of **165a** and **165c** have been inferred from previous studies.[9] The absolute configuration of **165b** was assigned by conversion to (–)-goniomitine (**3**).



(*S*)-7-Allyl-10-(2-(benzyloxy)ethyl)-7-ethyl-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (165a): An oven-dried 20 mL scintillation vial was charged with $Pd_2(pmdba)_3$ (14 mg, 12.7 μmol, 0.1 equiv), (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 18.8 mg, 31.8 μmol, 0.25 equiv), and a magnetic stirring bar in a N_2-filled glove box. The vial was then charged with TBME (3.2 mL) and stirred at 23 °C for 30 minutes, generating a dark purple solution. To the preformed catalyst solution was added a solution of **172a** (55 mg, 0.127 mmol, 1.0 equiv) in TBME (0.64 mL). The vial was sealed, removed from the glovebox, and placed in a preheated 60 °C heating block with stirring. Full consumption of starting material was achieved after 24 h, as determined by TLC analysis. The crude reaction mixture was

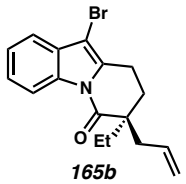
stripped onto silica gel, and purified by flash column chromatography (SiO_2, 5% Et_2O in hexanes) to afford α-quaternary lactam **165a** (29 mg, 59% yield) as a faintly yellow oil: R_f = 0.33 (17:3 hexanes:Et_2O eluent); 89% *ee*,[25] $[\alpha]_D^{25}$ –29.5 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.53–8.46 (m, 1H), 7.47–7.42 (m, 1H), 7.34–7.23 (m, 7H), 5.87–5.74 (m, 1H), 5.14–5.10 (m, 1H), 5.09 (s, 1H), 4.50 (s, 2H), 3.69 (t, *J* = 7.0 Hz, 2H), 3.00–2.93 (m, 4H), 2.62 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.38 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.00–1.93 (m, 2H), 1.84 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.72 (dq, *J* = 14.5, 7.4 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 138.5, 135.1, 134.4, 133.8, 130.7, 128.5, 127.71, 127.66, 124.1, 123.7, 118.8, 117.9, 116.8, 113.2, 73.2, 69.7, 46.6, 40.0, 28.6, 28.4, 24.9, 18.1, 8.5; IR (Neat Film, NaCl) 3066, 3032, 2930, 2856, 1694, 1619, 1455, 1366, 1309, 1260, 1189, 1100, 1073, 1020, 916, 801, 750, 696 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{26}H_{30}NO_2$ $[M+H]^+$: 388.2271, found 388.2269.



165a *180*

Methyl (*S*,*E*)-4-(10-(2-(benzyloxy)ethyl)-7-ethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-7-yl)but-2-enoate (180): To a solution of terminal olefin **165a** (11 mg, 28 μmol, 1.0 equiv) and methyl acrylate (25 mg, 280 μmol, 10 equiv) in CH_2Cl_2 (0.6 mL) was added Grubb's second generation catalyst (1.2 mg, 1.4 μmol, 0.05 equiv) at 23 °C. The reaction was sealed and placed in a preheated 40 °C heating block with stirring. After 3 h, complete consumption of starting material was observed by TLC analysis. Flash column chromatography (SiO_2, 35% Et_2O in hexanes) afforded α,β-unsaturated ester **180** (3.8

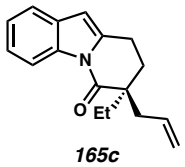
mg, 30% yield) as a clear colorless oil: R_f = 0.2 (7:3 hexanes:Et_2O eluent); 89% *ee*, $[\alpha]_D^{25}$ –64.4 (*c* 0.11, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.50–8.45 (m, 1H), 7.47–7.42 (m, 1H), 7.34–7.22 (m, 7H), 6.95 (ddd, *J* = 15.5, 8.2, 7.1 Hz, 1H), 5.94–5.89 (m, 1H), 4.50 (s, 2H), 3.71 (s, 3H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.00–2.92 (m, 4H), 2.79 (ddd, *J* = 14.2, 7.1, 1.6 Hz, 1H), 2.52 (ddd, *J* = 14.2, 8.3, 1.3 Hz, 1H), 1.96 (dd, *J* = 7.3, 6.0 Hz, 2H), 1.78 (qd, *J* = 7.4, 4.6 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 166.6, 144.6, 138.4, 135.0, 133.9, 130.7, 128.5, 127.73, 127.67, 124.6, 124.3, 123.9, 118.0, 116.8, 113.7, 73.2, 69.6, 51.7, 46.7, 38.0, 29.0, 28.4, 24.9, 18.1, 8.5; IR (Neat Film, NaCl) 3028, 2923, 2854, 1722, 1693, 1620, 1455, 1434, 1371, 1312, 1271, 1187, 1101, 1074, 1021, 751, 697 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{28}H_{31}NO_4$ $[M]^+$: 445.2248, found 445.2246; SFC conditions: 8% *i*-PrOH, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 40.93, minor = 44.73.



165b

(*S*)-7-Allyl-10-bromo-7-ethyl-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (165b): The reaction was conducted according to general procedure A. α-Quaternary β-amidoester **172b** (386 mg, 1.02 mmol, 1.0 equiv); $Pd_2(pmdba)_3$ (56 mg, 51 μmol, 0.05 equiv); (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 76 mg, 0.128 mmol, 0.125 equiv); TBME (31 mL). The reaction mixture was stirred for 8 h at 60 °C. Flash column chromatography (SiO_2, 40% CH_2Cl_2 in hexanes) afforded α-quaternary lactam **165b** (274 mg, 83% yield) as a clear colorless oil: R_f = 0.33 (2:1 hexanes:CH_2Cl_2 eluent); 96% *ee*, $[\alpha]_D^{25}$ –36.0 (*c* 1.26, $CHCl_3$); ^1H NMR

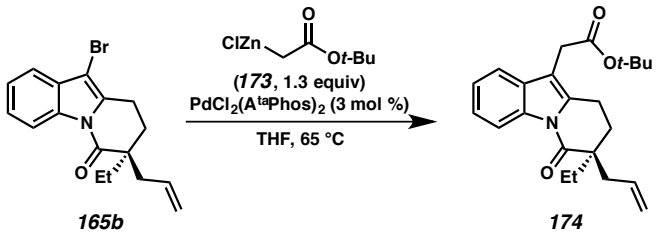
(500 MHz, $CDCl_3$) δ 8.50–8.47 (m, 1H), 7.49–7.45 (m, 1H), 7.37–7.31 (m, 2H), 5.81 (dddd, *J* = 16.6, 10.5, 7.7, 6.9 Hz, 1H), 5.16–5.14 (m, 1H), 5.12 (t, *J* = 1.2 Hz, 1H), 3.08–2.94 (m, 2H), 2.63 (ddt, *J* = 14.0, 7.0, 1.3 Hz, 1H), 2.40 (ddt, *J* = 14.0, 7.8, 1.1 Hz, 1H), 2.10–1.99 (m, 2H), 1.85 (dq, *J* = 14.0, 7.5 Hz, 1H), 1.81–1.69 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 135.0, 134.3, 133.4, 129.2, 125.3, 124.4, 119.1, 118.4, 116.7, 96.3, 46.7, 39.8, 28.4, 28.2, 18.9, 8.5; IR (Neat Film, NaCl) 3075, 2971, 2939, 1704, 1639, 1594, 1449, 1367, 1348, 1307, 1179, 1151, 1057, 1025, 922, 751 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{18}NOBr$ $[M]^+$: 331.0566, found 331.0566; SFC conditions: 2% MeOH, 3 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 11.87, minor = 11.11.



165c

(*S*)-7-Allyl-7-ethyl-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (165c): The reaction was conducted according to general procedure A. α-Quaternary β-amidoester **172c** (730 mg, 2.45 mmol, 1.0 equiv); $Pd_2(pmdba)_3$ (134 mg, 0.12 μmol, 0.05 equiv); (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 181 mg, 0.31 μmol, 0.125 equiv); TBME (74 mL). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 5% Et_2O in hexanes) afforded α-quaternary lactam **165c** (410 mg, 71% yield) as a clear colorless oil: R_f = 0.6 (17:3 hexanes:Et_2O eluent); 94% *ee*, $[\alpha]_D^{25}$ –69.7 (*c* 2.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.52–8.45 (m, 1H), 7.48–7.43 (m, 1H), 7.31–7.20 (m, 2H), 6.29 (td, *J* = 1.5, 0.8 Hz, 1H), 5.82 (dddd, *J* = 17.0, 10.2, 7.7, 6.9 Hz, 1H), 5.16–5.11 (m, 1H), 5.14–5.07 (m, 1H), 3.04 (tt, *J* = 6.3, 1.4 Hz, 2H), 2.64 (ddt, *J* = 14.0, 6.9, 1.3 Hz, 1H), 2.41 (ddt, *J* = 13.9,

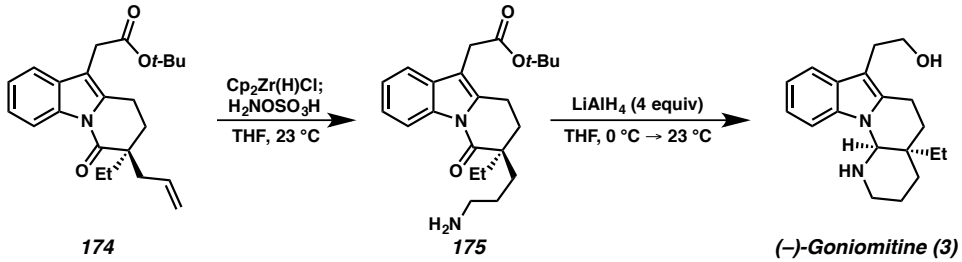
7.8, 1.1 Hz, 1H), 2.08–1.95 (m, 2H), 1.87 (dq, J = 13.9, 7.5 Hz, 1H), 1.83–1.68 (m, 1H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 137.9, 135.3, 133.7, 130.2, 124.0, 123.9, 119.8, 118.8, 116.7, 104.6, 46.7, 40.1, 28.9, 28.6, 19.8, 8.5; IR (Neat Film, NaCl) 3073, 2968, 2940, 2877, 1691, 1595, 1573, 1450, 1354, 1299, 1181, 1049, 1004, 911, 795, 743 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.1539, found 254.1534; SFC conditions: 2% MeOH, 3 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 11.08, minor = 10.06.



165b *174*

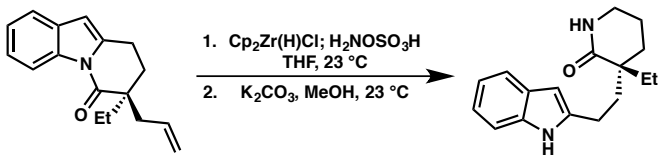
tert-Butyl (*S*)-2-(7-allyl-7-ethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)acetate (174): To an oven-dried 20 mL scintillation vial was charged heteroaryl bromide **165b** (188 mg, 0.565 mmol, 1.0 equiv), $PdCl_2(A^{ta}Phos)_2$ (12 mg, 17 μmol, 0.03 equiv), THF (4.2 mL), and a magnetic stirring bar in a N_2-filled glovebox. A commercially available (from Rieke Metals) solution of Reformatsky reagent **173** in Et_2O (1.47 mL, 0.5 M, 0.735 mmol, 1.3 equiv) was added dropwise. The reaction was sealed and placed in a preheated 65 °C heating block with stirring. After 3 h, full consumption of starting material was observed by TLC analysis. The solution was cooled to 23 °C and MeOH (ca. 1 mL) was added to quench any excess Reformatsky reagent. The crude reaction mixture was stripped onto silica gel and purified by flash column chromatography (SiO_2, 8% Et_2O in hexanes) to afford cross-coupled product **174** (204 mg, 98% yield) as a clear colorless oil: R_f = 0.25 (9:1 hexanes:Et_2O eluent); $[\alpha]_D^{25}$ –39.8

(*c* 0.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.49–8.47 (m, 1H), 7.50–7.47 (m, 1H), 7.31–7.25 (m, 2H), 5.82 (dddd, *J* = 17.1, 10.2, 7.7, 6.9 Hz, 1H), 5.13 (ddt, *J* = 9.5, 2.0, 1.2 Hz, 1H), 5.10 (q, *J* = 1.2 Hz, 1H), 3.54 (s, 2H), 3.07–2.95 (m, 2H), 2.63 (ddt, *J* = 14.0, 7.0, 1.3 Hz, 1H), 2.41 (ddt, *J* = 14.0, 7.7, 1.1 Hz, 1H), 2.07–1.96 (m, 2H), 1.91–1.80 (m, 1H), 1.79–1.70 (m, 1H), 1.43 (s, 9H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 170.2, 135.03, 134.96, 133.7, 130.3, 124.3, 123.8, 118.8, 118.2, 116.7, 109.9, 81.3, 46.6, 39.9, 31.6, 28.5, 28.4, 28.2, 18.1, 8.5; IR (Neat Film, NaCl) 3073, 2972, 2933, 1729, 1698, 1618, 1456, 1366, 1311, 1259, 1141, 1075, 1022, 917, 802, 752 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found 368.2210.



(–)-Goniomitine (3): An oven-dried scintillation vial was charged with α-quaternary lactam **174** (137 mg, 0.37 mmol, 1.0 equiv), THF (1.5 mL), and a magnetic stirring bar in a N_2-filled glovebox. To this solution was added bis(cyclopentadienyl) zirconium chloride hydride (115 mg, 0.445 mmol, 1.2 equiv), and the mixture was stirred at 23 °C until a yellow solution was observed (ca. 45 min). An additional portion of bis(cyclopentadienyl) zirconium chloride hydride (29 mg, 0.11 mmol, 0.3 equiv) was added and the reaction mixture was stirred for an additional 30 min. Hydroxylamine-O-sulfonic acid (71 mg, 0.63 mmol, 1.7 equiv) was added, the vial was sealed and removed from the glovebox, and stirring was resumed at 23 °C in a fume hood for an additional 30

min. The crude reaction mixture was loaded directly onto a short plug of silica gel and eluted with 10% MeOH in CH_2Cl_2 to deliver primary amine **175** (98 mg, R_f = 0.2, 9:1 CH_2Cl_2:MeOH eluent) as an orange foam. Semi-crude primary amine **175** was immediately dissolved in THF (5.1 mL) and cooled to 0 °C. A solution of $LiAlH_4$ (1.02 mL, 1.0 M in THF, 4.0 equiv) was added dropwise, and the reaction was stirred at 0 °C for 1 h. At this point, the cooling bath was removed and the reaction was stirred for an additional 6 h. The reaction was cooled to 0 °C and quenched by the careful addition of H_2O (5 mL) and AcOH (15 mL) and stirred for 6 hours. The solution was basified with 2N NaOH until pH > 12, and was extracted with EtOAc (3 x 100 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 3% MeOH in CH_2Cl_2 eluent) afforded (–)-goniomitine (**3**) (33 mg, 30% yield over two steps) as a faintly yellow oil: R_f = 0.45 (9:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ –67.1 (c 0.085, $CHCl_3$ (passed through basic alumina)); ^{1}H NMR (500 MHz, $CDCl_3$ (passed through basic alumina)) δ 7.51 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.29 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.14 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.79 (s, 1H), 3.83 (t, *J* = 6.5 Hz, 2H), 3.08–3.00 (m, 2H), 2.98–2.90 (m, 2H), 2.88–2.76 (m, 2H), 2.52 (td, *J* = 12.9, 6.6 Hz, 1H), 1.93–1.87 (m, 1H), 1.79–1.66 (m, 3H), 1.6 (dq, *J* = 15, 7.6 Hz, 1H), 1.55–1.45 (m, 3H), 1.21 (dq, *J* = 14.7, 7.3 Hz, 1H), 0.89 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 132.8, 129.2, 120.7, 119.7, 118.2, 108.4, 106.1, 71.7, 62.7, 45.8, 35.2, 34.2, 28.8, 27.8, 21.8, 21.7, 18.7, 7.2; IR (Neat Film, NaCl) 3288 (br), 3051, 2934, 2877, 2241, 1679, 1611, 1462, 1416, 1357, 1309, 1203, 1188, 1108, 1044, 1013, 908, 867, 737 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for C19H27N2O [M+H]+: 299.2118, found 299.2121.



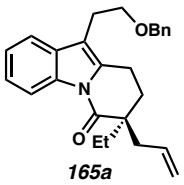
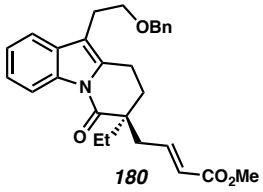
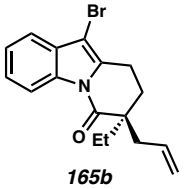
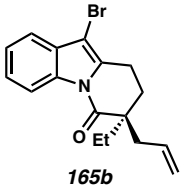
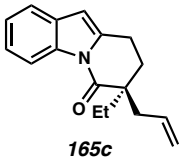
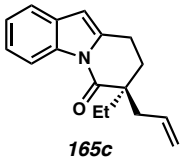
165c ***176***

(*R*)-3-(2-(1*H*-Indol-2-yl)ethyl)-3-ethylpiperidin-2-one (176): An oven-dried 1-dram vial was charged with α-quaternary lactam **165c** (40 mg, 0.16 mmol, 1.0 equiv), THF (0.8 mL), and a magnetic stirring bar in a N_2-filled glovebox. To this solution was added bis(cyclopentadienyl) zirconium chloride hydride (49 mg, 0.19 mmol, 1.2 equiv), and the mixture was stirred at 23 °C until a light yellow solution was observed (ca. 30 min). Hydroxylamine-*O*-sulfonic acid (29 mg, 0.25 mmol, 1.6 equiv) was added, the vial was sealed and removed from the glovebox, and stirring was resumed at 23 °C in a fume hood for an additional 30 min. The crude reaction mixture was loaded directly onto a short plug of silica gel and eluted with 10% MeOH in CH_2Cl_2 to deliver the intermediate primary amine (R_f = 0.2, 9:1 CH_2Cl_2:MeOH eluent). The semi-crude primary amine was immediately dissolved in MeOH (5.2 mL), then K_2CO_3 (65 mg, 0.47 mmol, 3.0 equiv) was added. The reaction was stirred at 23 °C for 1 h, at which point complete consumption of starting material was determined by TLC analysis. The reaction mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 x 75 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 40% acetone in hexanes) afforded free N–H lactam **176** (28 mg, 66% yield over two steps) as a white amorphous solid: R_f = 0.3 (3:2 hexanes:acetone eluent); $[\alpha]_D^{25}$ –32.7 (*c* 0.41, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.50 (ddt, *J* = 7.7, 1.4, 0.8 Hz, 1H), 7.29 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.09 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.07–7.02 (m, 1H), 6.21 (dd, *J* = 2.0, 0.9 Hz, 1H), 5.83 (br s, 1H), 3.32

(td, J = 5.7, 2.2 Hz, 2H), 2.90–2.82 (m, 1H), 2.69 (dddd, J = 14.7, 11.1, 4.6, 1.0 Hz, 1H), 2.13 (ddd, J = 13.6, 11.2, 4.5 Hz, 1H), 1.90–1.75 (m, 6H), 1.67–1.60 (m, 1H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 140.0, 136.2, 128.8, 121.0, 119.8, 119.5, 110.6, 99.3, 45.3, 42.9, 37.8, 31.3, 29.2, 23.9, 19.8, 8.6; IR (Neat Film, NaCl) 3285, 3252, 2971, 2952, 2868, 1643, 1588, 1486, 1456, 1421, 1351, 1328, 1287, 1216, 1104, 1010, 795, 735 cm^{-1}; HRMS (ESI/APCI) m/z calc'd for $C_{17}H_{23}N_2O$ $[M+H]^+$: 271.1805, found 271.1813.

2.7.3 DETERMINATION OF ENANTIOMERIC EXCESS

Table 2.7.3.1. Determination of Enantiomeric Excess of α-Quaternary DHPIs

entry	product	compound assayed	assay conditions	ee (%)
1	 ***165a***	 ***180***	**SFC: 8% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 40.93, minor 44.73**	**89**
2	 ***165b***	 ***165b***	**SFC: 2% MeOH, 3 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 11.87, minor 11.11**	**96**
3	 ***165c***	 ***165c***	**SFC: 2% MeOH, 3 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 11.08, minor 10.06**	**94**

2.7.4 COMPARISON OF SYNTHETIC (–)-GONIOMITINE TO PUBLISHED DATA

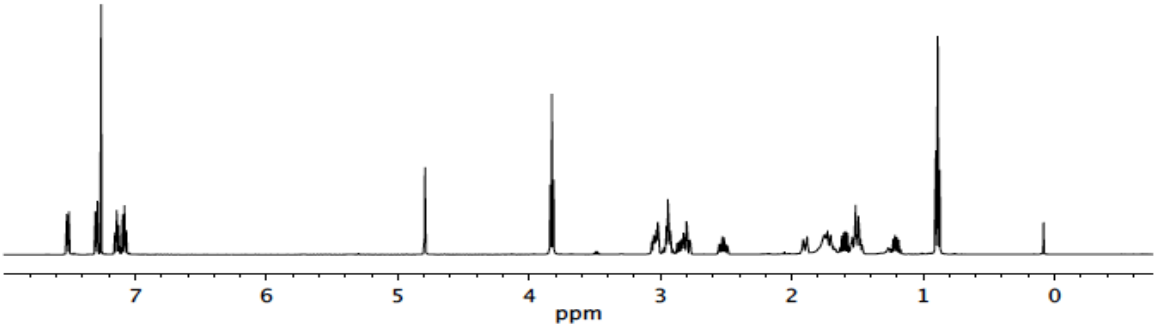
The optical rotation of our synthetic (–)-goniomitine (**3**), $[\alpha]_D^{25}$ –67.1 (*c* 0.085, $CHCl_3$ (passed through basic alumina)), differs from values previously reported in the literature: $[\alpha]_D^{25}$ –80 (*c* 0.9, $CHCl_3$),[2] $[\alpha]_D^{25}$ –87.1 (*c* 0.42, $CHCl_3$),[7a] $[\alpha]_D^{25}$ –78.1 (*c* 0.14, $CHCl_3$),[7b] $[\alpha]_D^{25}$ –80 (*c* 0.46, $CHCl_3$).[7c] We have also noted that some ^{13}CNMR resonances of the natural product vary depending on the $CDCl_3$ used to make the sample (*vide supra*). Since we obtained SFC traces of both *rac*- and (–)-**165b**, and since the quaternary center is not susceptible to racemization, we do not believe that this discrepancy indicates erosion of enantiopurity.

*Table 2.7.4.1. Comparison of Synthetic and Natural (–)-Goniomitine (**3**)*

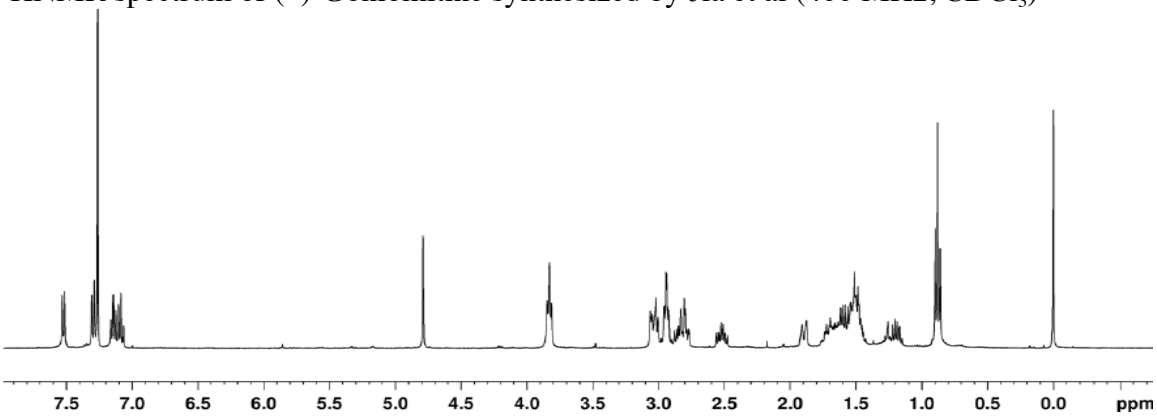
Synthetic (–)-Goniomitine ($CDCl_3$ directly from bottle)	**Synthetic (–)-Goniomitine** ($CDCl_3$ filtered through basic alumina)	**Natural (–)-Goniomitine**[2]
^{1}H NMR (500 MHz, $CDCl_3$)	*^{1}H NMR (500 MHz, $CDCl_3$)*	*^{1}H NMR (400 MHz, $CDCl_3$)*
4.80 (s, 1H)	4.79 (s, 1H)	4.86 (s, 1H)
3.83 (t, J = 6.4, 2H)	3.83 (t, J = 6.5, 2H)	3.81 (t, 2H)
2.93 (td, J = 6.5, 2.2 Hz, 2H)	2.94 (td, J = 6.6, 3.3 Hz, 2H)	3.0 (t, 2H)
1.57 (dt, J = 15.0, 7.5 Hz, 1H)	1.57 (dt, J = 15.0, 7.5 Hz, 1H)	1.56 (m, J = 7 Hz, 1H)
1.20 (dq, J = 14.7, 7.7 Hz, 1H)	1.21 (dq, J = 14.7, 7.3 Hz, 1H)	1.20 (m, J = 7 Hz, 1H)
0.87 (t, J = 7.6 Hz, 3H)	0.89 (t, J = 7.6 Hz, 3H)	0.86 (t, J = 7 Hz, 3H)
^{13}C NMR (126 MHz, $CDCl_3$)	*^{13}C NMR (126 MHz, $CDCl_3$)*	*^{13}C NMR ($CDCl_3$)*
135.4	135.5	135.4
132.6	132.8	132.6
129.3	129.2	129.3
120.9	120.7	120.8
120.1	119.7	119.9
118.2	118.2	118.1
108.7	108.4	108.7
107.4	106.1	106.8
70.6	71.7	71.1
62.5	62.7	62.6
44.9	45.8	45.4
35.3	35.2	35.3
33.6	34.2	33.8
28.7	28.8	28.7
27.7	27.8	27.8
21.7	21.8	21.8
20.3	21.7	20.8
18.5	18.7	18.5
7.2	7.2	7.3

*Figure 2.7.4.1. Comparison of ^{1}HNMR and ^{13}CNMR Spectra of Synthetic (–)-Goniomitine (**3**)*

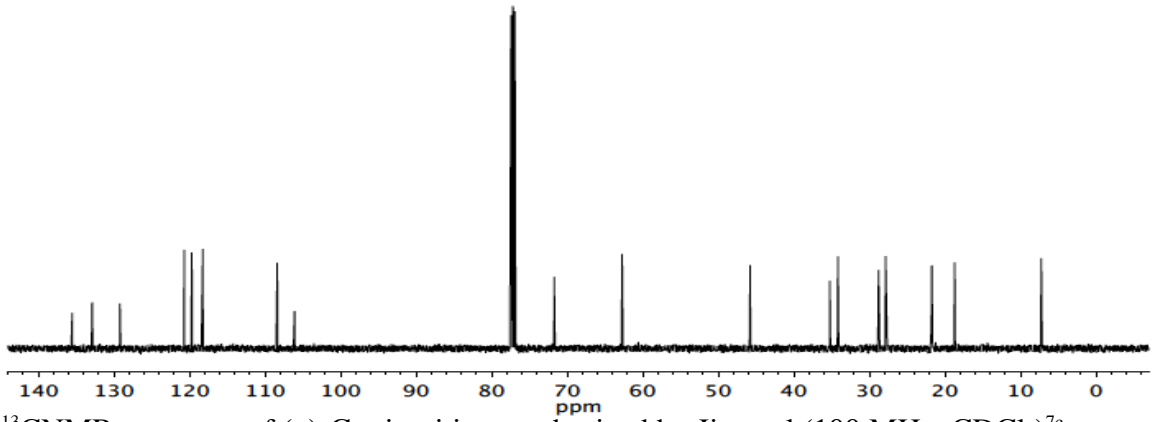
^{1}HNMR spectrum of our synthetic (–)-Goniomitine (500 MHz, $CDCl_3$)



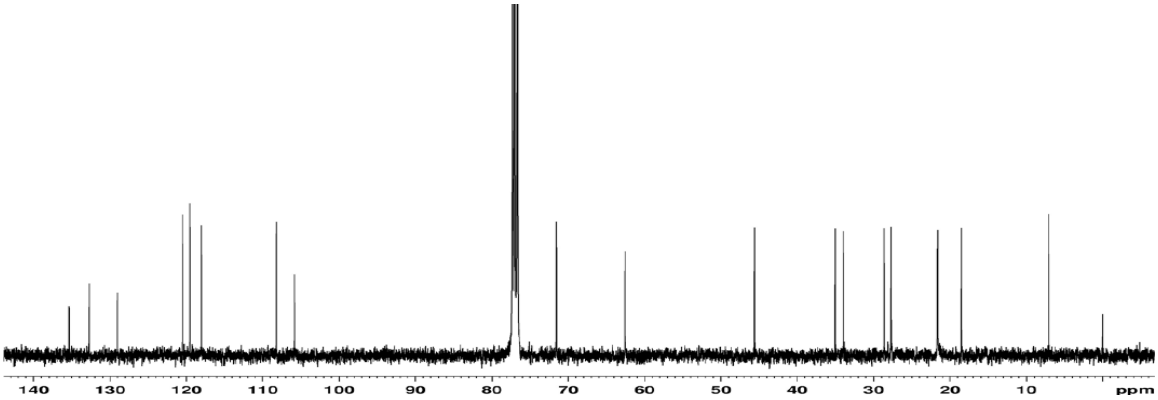
^{1}HNMR spectrum of (–)-Goniomitine synthesized by Jia et al (400 MHz, $CDCl_3$)[7c]



^{13}CNMR spectrum of our synthetic (–)-Goniomitine (126 MHz, $CDCl_3$)



^{13}CNMR spectrum of (–)-Goniomitine synthesized by Jia et al (100 MHz, $CDCl_3$)[7c]



2.8 NOTES AND REFERENCES

1. For reviews, see: (a) Saxton, J. E. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, **1998**; *Vol. 51*, 1–197. (b) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547.

2. For initial isolation of goniomitine (**3**) and proposed biosynthesis from vincadifformine (**4**), see: Randriambola, L.; Quirion, J.-C.; Kan-Fan, C.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 2123–2126.

3. (a) Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. *Tetrahedron Lett.* **1961**, *2*, 485–492. (b) Hesse, O. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2308–2309. (c) Djerassi, C.; Budzikiewicz, H.; Wilson, J. M.; Gosset, J.; Le Men, J.; Janot, M.-M. *Tetrahedron Lett.* **1962**, *3*, 235–239.

4. For a uniform numbering system of monoterpene indole alkaloids, see: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–510.

5. For a biomimetic semisynthesis of goniomitine (**3**) from vincadifformine (**4**), see: Lewin, G.; Bernadat, G.; Aubert, G.; Cresteil, T. *Tetrahedron* **2013**, *69*, 1622–1627.

6. For a total synthesis of (±)-goniomitine (**3**), as well as the evaluation of its antiproliferative activity, see: (a) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 5767–5770. For other nonenantioselective total syntheses, see: (b) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157–159. (c) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563–14572. (d) Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3272–3276. (e)

Zhou, B.; Du, J.; Yang, Y.; Li, Y. *Chem. Eur. J.* **2014**, *20*, 12768–12772. (f) Vellucci, J. K.; Beaudry, C. M. *Org. Lett.* **2015**, *17*, 4558–4560.

7. For asymmetric syntheses of goniomitine (**3**), see: (a) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1991**, 462–464. (b) Mizutani, M.; Inagaki, F.; Nakanishi, T.; Yanagihara, C.; Tamai, I.; Mukai, C. *Org. Lett.* **2011**, *13*, 1796–1799. (c) Zhou, S.; Jia, Y. *Org. Lett.* **2014**, *16*, 3416–3418. (d) Li, H.; Cheng, P.; Jiang, L.; Yang, J.-L.; Zu, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 2754–2757.

8. For selected examples of this type of cyclization (i.e., **162** → **164**), see: (a) Nicolaou, K. C.; Dalby, S. M.; Majumder, U. *J. Am. Chem. Soc.* **2008**, *130*, 14942–14943. (b) Chen, Z.; Zhou, S.; Jia, Y. *J. Org. Chem.* **2015**, *80*, 12545–12551. (c) Mizutani, M.; Yasuda, S.; Mukai, C. *Chem. Commun.,* **2014**, *50*, 5782–5785.

9. For examples of asymmetric allylic alkylation of nitrogen-containing substrates published by our group, see: (a) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223. (b) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133. (c) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179–183. (d) Numajiri, Y.; Jiménez-Osés, G.; Wang, B.; Houk,

K. N.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 1082–1085. (e) Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2015**, *137*, 1040–1043.

10. For asymmetric allylic alkylation of carbazolone substrates, see: (a) Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116. (b) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 4117–4121. (c) Leng, L.; Zhou, X.; Liao, Q.; Wang, F.; Song, H.; Zhang, D.; Liu, X.-Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 3703–3707.

11. Zhong, X.; Li, Y.; Han, F.-S. *Chem. Eur. J.* **2012**, *18*, 9784–9788.

12. For a single-step, albeit low-yielding synthesis of **166** from indole, see: Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990–12993.

13. For Suzuki cross-couplings of alkoxyethyl trifluoroborate reagents (e.g., **170**), see: Fleury-Brégeot, N.; Presset, M.; Beaumard, F.; Colombel, V.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2012**, *77*, 10399–10408.

14. A^{ta}Phos = (4-(dimethylamino)phenyl)di-*tert*-butyl phosphine. For its development, see: Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787–1789.

15. McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

16. For selected examples of Mizoroki–Heck and Suzuki cross-couplings, respectively, of allylic alkylation products, see: (a) Mingoia, F.; Vitale, M.;

Madec, D.; Prestat, G.; Poli, G. *Tetrahedron Lett.* **2008**, *49*, 760–763. (b) Zhuo, C.-X.; You, S.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 10056–10059.

17. Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

18. Multiple parameters were investigated for the Suzuki reaction, to no avail. Arylation using a Reformatsky reagent prepared in situ from *tert*-butyl bromoacetate proceeded in high yields using several palladium precatalysts, but as a 1:3–5:1 mixture of olefin isomers (terminal:internal). The reaction employing organozinc chloride **173**, purchased from Rieke Metals, and $PdCl_2(A^{ta}Phos)_2$ was singularly successful in this transformation.

19. Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909–8914.

20. Bajtos, B.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, *7*, 1072–1077.

21. Following the publication of this work, Zu and co-workers reported an enantioselective total synthesis of (–)-goniomitine (**3**) in five steps and 23% overall yield from 2-ethyl cyclopentanone ($160/10g from Bepharm, 2/27/17) using a chiral auxiliary-assisted Michael addition, see reference 7d.

22. Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

23. (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–256. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.

24. Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486–3487.

25. The enantiomeric excess of compound **165a** was difficult to discern using SFC analysis. Cross metathesis with methyl acrylate afforded **180**, which enabled reliable ee determination.

APPENDIX 1

A Fischer Indolization Approach Toward the Total Synthesis of (–)-Goniomitine †

A1.1 INITIAL RETROSYNTHETIC ANALYSIS

In our initial retrosynthetic analysis of (–)-goniomitine (**3**), we believed that late-stage redox manipulations and alcohol deprotection could furnish the natural product from lactam **165a** (Scheme A1.1.1). We expected the quaternary center in lactam **165a** could arise from the enantioselective Pd-catalyzed decarboxylative allylic alkylation of racemic β-amidoester **172a**. Importantly, we believed that enantioconvergent construction of the quaternary center would offer significant improvement over the comparatively poor stereocontrol featured in previous enantioselective syntheses of (–)-goniomitine (**3**).[1] Disconnection of the ethyl and alloc groups revealed key dihydropyrido[1,2-*a*]indolone (DHPI) **171**, which we anticipated could be accessed via the Fischer indolization of 1,3-cyclohexanedione **181**.

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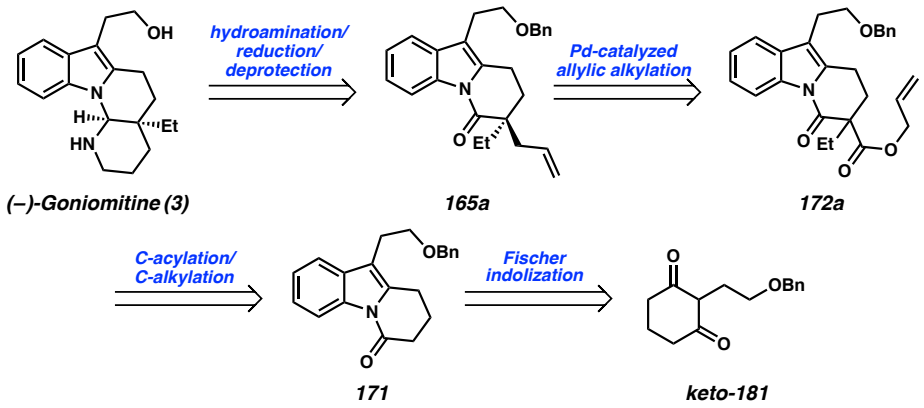
† This work was performed in collaboration with Dr. Yoshitaka Numajiri and Jun Kikuchi, both of whom are alumni of Stoltz group. Additionally, this research has been published and adapted with permission from Pritchett, B. P.; Kikuchi, J.; Numajiri, Y.; Stoltz, B. M. *Heterocycles* **2017**, *95*, 1245–1253.

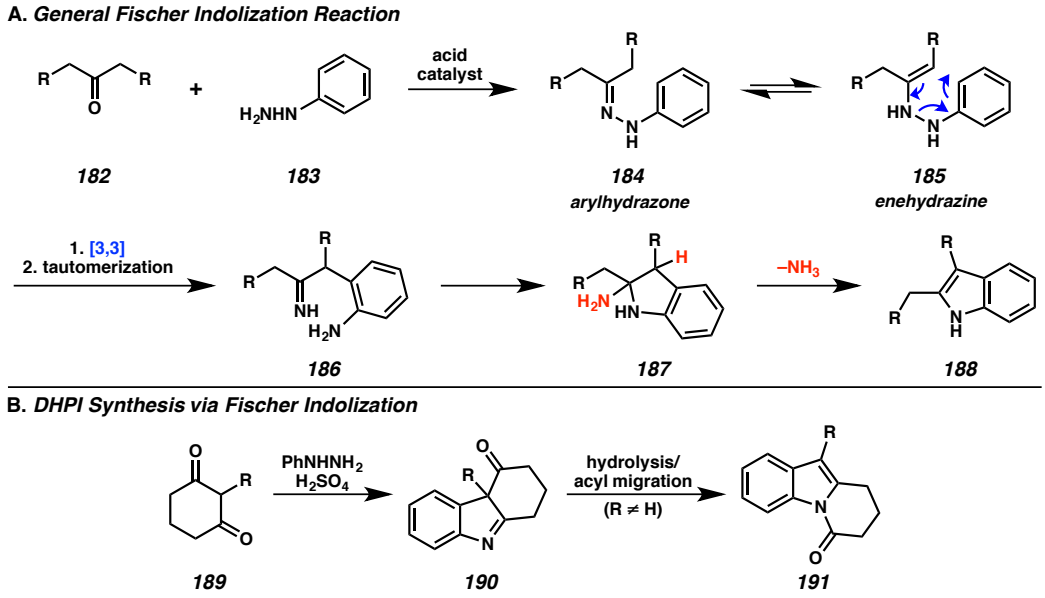
*Scheme A1.1.1. Initial Retrosynthesis of (–)-Goniomitine (**3**)*



A1.2 BRIEF INTRODUCTION TO THE FISCHER INDOLIZATION

The acid-promoted Fischer indolization reaction, first discovered in 1883, is one of the most robust and widely utilized methods for the synthesis of substituted indoles from carbonyl precursors.[2] Ketones (e.g., **182**) and aldehydes can be converted to the respective arylhydrazones (e.g., **184**) under either Brønsted or Lewis acidic conditions (Scheme A1.2.1A). The arylhydrazone intermediate (**184**) undergoes tautomerization to the corresponding enehydrazine (**185**), followed by a [3,3]-sigmatropic rearrangement and finally elimination of ammonia to deliver an indole product (**188**). This venerable transformation has seen widespread use in the realm of total synthesis,[3] and has been rendered enantioselective in an elegant desymmetrization reaction of *meso* cyclic ketones.[4] Of particular relevance to our synthetic plan toward (–)-goniomitine (**3**) was a report from Teuber and co-workers describing a Fischer indolization protocol for the synthesis of DHPI products (Scheme A1.2.1B).[5] They found that treatment of 2-substituted 1,3-cyclohexanediones (**189**) with phenylhydrazine and sulfuric acid first gives tricycle **190**, which undergoes sequential hydrolysis and *N*-acylation to furnish DHPI **191**.

Scheme A1.2.1. Relevant Fischer Indolization Reactions



A1.3 DHPI MODEL SYSTEM STUDIES

Our studies on the Pd-catalyzed allylic alkylation of the previously unexplored DHPI substrate class commenced with C3-methyl DHPI **193**, which is readily available from 2-methyl-1,3-cyclohexanedione (**192**, Scheme A1.3.1).[5] DHPI **193** was smoothly acylated using LHMDS and allyl cyanoformate. Subsequent site-selective alkylation with iodomethane delivered racemic β-amidoester **172d** in 77% overall yield from **193**. We found that subjecting **172d** to a solution of $Pd_2(pmdba)_3$ (5 mol%) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 12.5 mol%) in toluene at 60 °C resulted in minimal conversion, despite prolonged reaction times (Table A1.3.1, Entry 1). Full consumption of starting material was only achieved after switching from toluene to TBME as solvent, and raising the loading of $Pd_2(pmdba)_3$ and ligand to 10 mol% and 25 mol%, respectively (Entry 2). Under these conditions, we were able to isolate α-quaternary DHPI **165d** in 60% yield and 90% enantiomeric excess.

*Scheme A1.3.1. Synthesis of C3-Methyl α-Quaternary DHPI **165d***

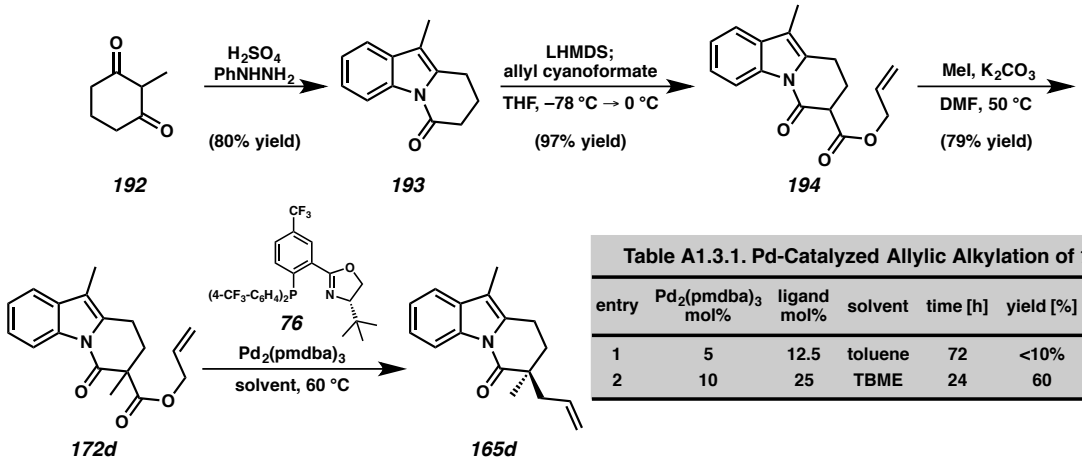


Table A1.3.1. Pd-Catalyzed Allylic Alkylation of *172d*

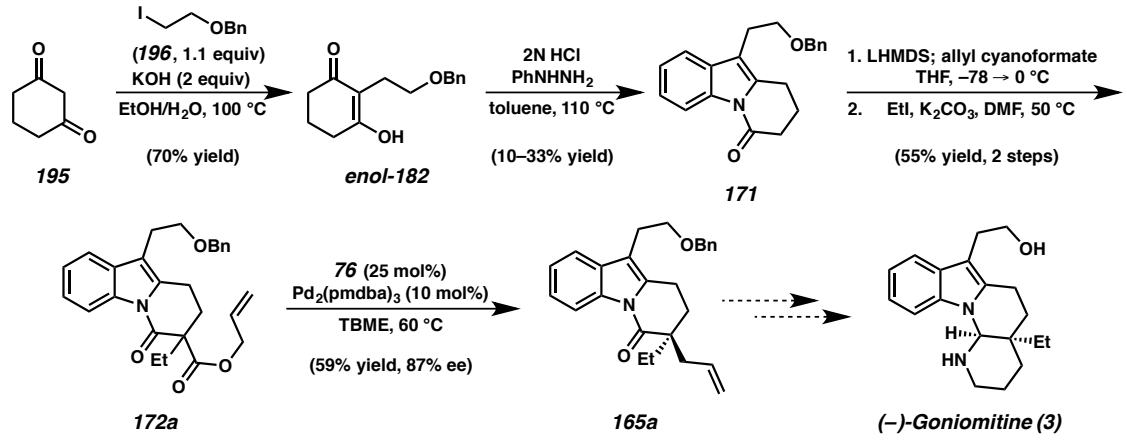
entry	$Pd_2(pmdba)_3$ mol%	ligand mol%	solvent	time [h]	yield [%]	ee [%]
1	5	12.5	toluene	72	<10%	90
2	10	25	TBME	24	60	90

A1.4 INTRACTABLE ROUTE TO (–)-GONIOMITINE

Regarding the total synthesis of (–)-goniomitine (**3**), our first challenge was to establish a regioselective C-alkylation of 1,3-cyclohexanedione (**195**) with (2-benzyloxy)ethyl iodide (**196**). Although Ma and co-workers previously reported this transformation, we were unsuccessful in our attempts to reproduce their work.[6] We discovered that slightly different conditions afforded the desired C-alkylated product **182** in 70% yield as the enol tautomer (Scheme A1.4.1). After investigating several conditions for the Fischer indolization reaction, it was discovered that subjecting ***enol*-182** to 2N HCl in refluxing toluene furnished key DHPI **171**, albeit in an unsatisfactory range of 10–33% yield. Nevertheless, we were able to synthesize β-amidoester **172a** from DHPI **171** in 55% yield over a two-step sequence analogous to that described above (cf. Schemes A1.3.1 and A1.4.1), which put us in position to test the allylic alkylation chemistry on the real system. Once again, we observed that TBME as solvent, along with high catalyst loading, was required to deliver α-quaternary allylic alkylation product **165a** in a disappointing 59% yield and 87% enantiomeric excess. We thus concluded that

C3-alkyl substituents on the indole core of DHPI substrates were detrimental for Pd-catalyzed decarboxylative allylic alkylation reactions.

*Scheme A1.4.1. Synthesis of α-Quaternary DHPI **165a** Toward (–)-Goniomitine (**3**)*



A1.5 CONCLUSION

To summarize, we employed a Fischer indolization protocol to synthesize a key tricyclic DHPI intermediate (**171**) toward (–)-goniomitine (**3**) in three steps from commercial materials. While this transformation failed to deliver the product in good yield, sufficient material was made available to study the Pd-catalyzed enantioselective allylic alkylation of the DHPI substrate class. As a result, we discovered a critical electronic effect at the C3 position of the indole moiety that led to a reevaluation of our strategy, and consequently the first catalytic enantioselective total synthesis of (–)-goniomitine (**3**).[7]

A1.6 EXPERIMENTAL SECTION

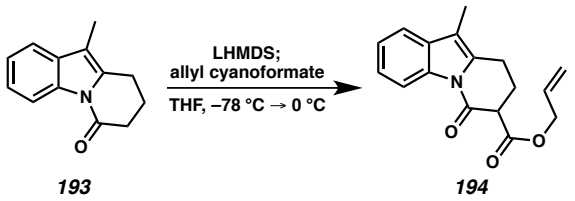
A1.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[8] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, CAM, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. Melting points were measured with BÜCHI Melting Point B-545. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, br t = broad triplet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralcel OB-H column (4.6 mm x 25 cm) obtained

from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in mixed ionization mode (MM: ESI/APCI).

Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Phenylhydrazine was purified by distillation and stored at –30 °C in a freezer. (2-Benzyloxy)ethyl iodide (**196**),[9] (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**),[10] tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) $Pd_2(pmdba)_3$,[11] and allyl cyanoformate[12] were prepared by known methods.

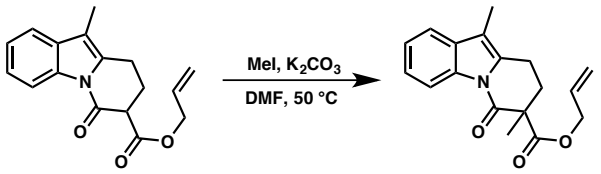
A1.6.2 EXPERIMENTAL PROCEDURES



193 *194*

Allyl 10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (194): A flame-dried round bottom flask was charged with LHMDS (670 mg, 4.0 mmol, 1.9 equiv) and a magnetic stirring bar in a N_2-filled glove box. The flask was sealed, removed from the glovebox, fitted with an argon line, and suspended in a dry ice/acetone bath. THF (11 mL) was added slowly to the flask and allowed to stir until the LHMDS had been completely dissolved. A solution of C3-methyl DHPI **193** (420 mg, 2.1 mmol, 1.0 equiv) in THF (2.5 mL) was added dropwise, and the reaction was allowed to stir for 30 min at –78 °C. Allyl cyanoformate (270 mg, 2.43 mmol, 1.15 equiv) was then added dropwise, and the reaction was allowed to warm slowly to 0 °C over 4 h. Once the cooling bath temperature reached 0 °C, 100 mL of saturated aqueous NH_4Cl was then added slowly and the mixture stirred for 20 min before being extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 15% acetone in hexanes) to give tertiary β-amidoester **194** (580 mg, 97% yield) as a faintly yellow oil: R_f = 0.41 (3:1 hexanes:acetone eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45–8.41 (m, 1H), 7.45–7.41 (m, 1H), 7.32–7.27 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.72 (dq, *J* = 5.7, 1.5 Hz, 2H), 3.82 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.04 (dddd, *J* = 16.4, 8.1, 4.7, 1.1 Hz, 1H), 2.90 (dddd, *J* = 16.3, 8.3, 4.7, 1.2 Hz, 1H), 2.55–2.45 (m,

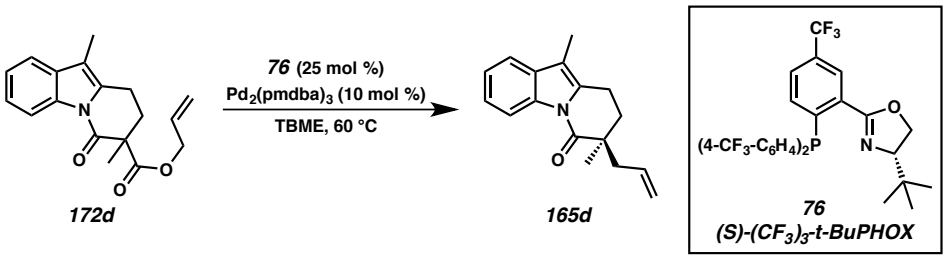
1H), 2.33 (ddt, *J* = 13.1, 8.0, 4.8 Hz, 1H), 2.19 (t, *J* = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 164.9, 134.8, 132.1, 131.6, 131.3, 124.6, 124.2, 119.0, 118.0, 116.6, 113.3, 66.4, 51.1, 25.0, 19.8, 8.6; IR (Neat Film, NaCl) 3050, 2943, 2359, 1741, 1698, 1627, 1459, 1396, 1383, 1370, 1338, 1308, 1269, 1246, 1220, 1172, 1156, 1128, 1104, 1028, 989, 750 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1281, found 284.1287.



194 ***172d***

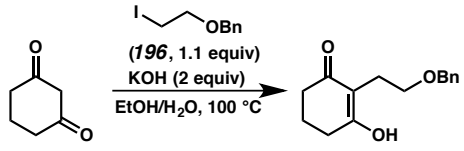
Allyl 7,10-dimethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172d): To a solution of β-amidoester **194** (107 mg, 0.38 mmol, 1.0 equiv) in DMF (1.2 mL) were added K_2CO_3 (61 mg, 0.45 mmol, 1.2 equiv) and MeI (28 μL, 0.45 mmol, 1.2 equiv). The reaction mixture was heated to 50 °C with stirring. After 5 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (10 mL) was added, followed by extraction with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (SiO_2, 15% acetone in hexanes) afforded quaternary β-amidoester **172d** (88 mg, 79% yield) as a clear colorless oil: R_f = 0.47 (3:1 hexanes:acetone eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49–8.44 (m, 1H), 7.45–7.41 (m, 1H), 7.33–7.27 (m, 2H), 5.84 (ddt, *J* = 17.2, 10.4, 5.5 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.64 (dq, *J* = 5.5, 1.5 Hz, 2H), 3.06–2.96 (m, 1H), 2.87 (dddd, *J* = 16.8, 11.0, 4.8, 1.4 Hz, 1H), 2.58 (ddd, *J* = 13.4, 5.4, 4.8 Hz, 1H), 2.18

(dd, J = 1.1, 0.7 Hz, 3H), 2.07 (ddd, J = 13.5, 11.0, 4.8 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 168.5, 135.0, 132.3, 131.5 (2C),[13] 124.5, 124.1, 118.7, 118.0, 116.7, 112.9, 66.3, 52.6, 32.9, 21.7, 19.1, 8.5; IR (Neat Film, NaCl) 2939, 1735, 1700, 1628, 1458, 1385, 1345, 1364, 1267, 1240, 1060, 971, 934, 752 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found 298.1435.



(*S*)-7-Allyl-7,10-dimethyl-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (165d): An oven-dried 20 mL scintillation vial was charged with $Pd_2(pmdba)_3$ (14 mg, 12.7 μmol, 0.1 equiv), (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 18.8 mg, 31.8 μmol, 0.25 equiv), and a magnetic stirring bar in a N_2-filled glove box. The vial was then charged with TBME (3.2 mL) and stirred at 23 °C for 30 min, generating a dark purple solution. To the preformed catalyst solution was added a solution of **172d** (55 mg, 0.127 mmol, 1.0 equiv) in TBME (0.64 mL). The vial was sealed, removed from the glovebox, and placed in a preheated 60 °C heating block with stirring. Full consumption of starting material was achieved after 24 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO_2, 30% CH_2Cl_2 in hexanes) to afford α-quaternary lactam **165d** (19.5 mg, 60% yield) as a clear colorless oil: R_f = 0.41 (1:1 hexanes:CH_2Cl_2 eluent); 90% ee, $[\alpha]_D^{25}$ –75.8 (*c* 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48–8.44 (m, 1H), 7.44–7.40 (m, 1H), 7.30–7.26 (m, 2H), 5.88–5.78 (m, 1H),

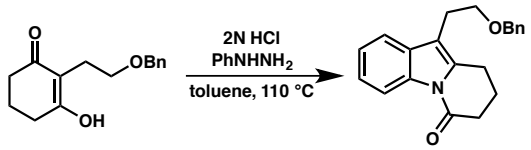
5.17–5.13 (m, 1H), 5.13–5.11 (m, 1H), 2.96 (dddt, J = 16.5, 8.0, 5.6, 1.3 Hz, 2H), 2.66–2.60 (m, 1H), 2.42 (ddt, J = 13.8, 7.7, 1.1 Hz, 1H), 2.18 (t, J = 1.0 Hz, 3H), 2.09 (ddd, J = 13.7, 8.5, 5.4 Hz, 1H), 1.87 (ddd, J = 13.5, 7.3, 5.2 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 134.9, 133.5, 133.0, 131.5, 124.2, 123.7, 119.0, 117.8, 116.6, 112.0, 43.1, 42.3, 31.7, 23.3, 18.3, 8.5; IR (Neat Film, NaCl) 3074, 2968, 2933, 2864, 1694, 1625, 1455, 1382, 1360, 1336, 1311, 1291, 1247, 1190, 1121, 1060, 1015, 999, 916, 803, 753 cm^{-1}; HRMS (ESI/APCI) m/z calc'd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.1539, found 254.1547; SFC conditions: 5% *i*-PrOH, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, τ_R (min): major = 7.55, minor = 5.97.



195 *enol-182*

2-(2-(Benzyloxy)ethyl)-3-hydroxycyclohex-2-en-1-one (*enol*-182): A flask was charged with a magnetic stirring bar, 1,3-cyclohexanedione (**195**, 336 mg, 3.0 mmol, 1.0 equiv), and KOH (170 mg, 3.0 mmol, 1.0 equiv). EtOH (1.3 mL) and H_2O (0.2 mL) were added at 23 °C with stirring, followed by (2-benzyloxy)ethyl iodide[9] (**196**, 870 mg, 3.3 mmol, 1.1 equiv). The flask was fitted with a reflux condenser, placed in an oil bath, and the reaction was heated to 110 °C with stirring. After 18 h, an additional portion of KOH (170 mg, 3.0 mmol, 1.0 equiv) was added and the reaction was stirred for 1 h at which point full consumption of starting material was determined by TLC analysis. The reaction mixture was then removed the oil bath and allowed to cool to 23 °C. The reaction mixture was poured onto EtOAc (50 mL) and washed with H_2O (2 x 25 mL). The combined aqueous layers were acidified to pH 2 using 1N HCl and were then extracted with EtOAc

(3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 45% EtOAc in hexanes) afforded ***enol*-182** (515 mg, 70% yield) as a colorless amorphous solid: R_f = 0.25 (1:1 hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.39–7.28 (m, 5H), 4.58 (s, 2H), 3.63–3.59 (m, 2H), 2.73–2.67 (m, 2H), 2.46 (t, *J* = 6.3 Hz, 2H), 2.34 (dd, *J* = 7.2, 6.1 Hz, 2H), 1.91 (dt, *J* = 12.6, 6.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 174.8, 136.6, 128.8, 128.4, 128.1, 114.1, 73.8, 72.1, 36.6, 29.5, 22.7, 20.7; IR (Neat Film, NaCl) 3059, 3029, 2934, 2867, 2664, 1574, 1453, 1372, 1266, 1191, 1095, 856, 735, 697 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329, found 247.1324.



***enol*-182** **171**

10-(2-(Benzyloxy)ethyl)-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (171): A flask was charged with a magnetic stirring bar, ***enol*-182** (370 mg, 1.5 mmol, 1.0 equiv), $PhNHNH_2$ (162 mg, 1.5 mmol, 1.0 equiv), and toluene (3 mL). Aqueous HCl (2N, 1.5 mL) was then added at 23 °C. The flask was fitted with a reflux condenser, placed in an oil bath, and the reaction was heated to 100 °C with stirring. After 24 h, the reaction mixture was cooled to 23 °C, diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded DHPI **171** (158 mg, 33% yield) as an orange oil: R_f = 0.3 (3:2 hexanes:Et_2O eluent); spectroscopic data were consistent with those reported in the literature.[14]

A1.7 NOTES AND REFERENCES

1. For asymmetric total syntheses of goniomitine (**3**), see: (a) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun*. **1991**, 462–464. (b) Mizutani, M.; Inagaki, F.; Nakanishi, T.; Yanagihara, C.; Tamai, I.; Mukai, C. *Org. Lett*. **2011**, *13*, 1796–1799. (c) Zhou, S.; Jia, Y. *Org. Lett*. **2014**, *16*, 3416–3418. (d) Li, H.; Cheng, P.; Jiang, L.; Yang, J.-L.; Zu, L. *Angew. Chem. Int. Ed*. **2017**, *56*, 2754–2757.

2. For seminal publications, see: (a) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 2241–2245. (b) Fischer, E.; Hess, O. *Ber*. **1884**, *17*, 559–568.

3. For selected applications of Fischer indolization reactions in total synthesis, see: (a) Bian, Z.; Marvin, C. C.; Pettersson, M.; Martin, S. F. *J. Am. Chem. Soc*. **2014**, *136*, 14184–14192. (b) Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett*. **2000**, *2*, 1625–1627.

4. Müller, S.; Webber, M. J.; List, B. *J. Am. Chem. Soc*. **2011**, *133*, 18534–18537.

5. Teuber, H.-J.; Worbs, E.; Cornelius, D. *Arch. Pharm*. **1982**, *315*, 388–396.

6. Moreover, the spectral data obtained for compound **182** do not match those previously reported. We believe that the ^{1}H NMR data reported by Ma and co-workers instead belong to the *O*-alkylated constitutional isomer. For details, see: Ma, D.; Tang, G.; Kozikowski, A. P. *Org. Lett*. **2002**, *4*, 2377–2380.

7. Pritchett, B. P.; Kikuchi, J.; Numajiri, Y.; Stoltz, B. M. *Angew. Chem. Int. Ed*. **2016**, *55*, 13529–13532.

8. Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

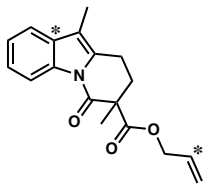
9. King, B. W. Lactam Derivatives as Inhibitors of Matrix Metalloproteinases and/or TNF-Alpha Converting Enzyme. US Patent 2004266751, December 30, 2004.

10. McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett*. **2010**, *51*, 5550–5554.

11. (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem*. **1974**, *65*, 253–256. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett*. **2004**, *6*, 4435–4438.

12. Childs, M. E.; Weber, W. P. *J. Org. Chem*. **1976**, *41*, 3486–3487.

13. For compound **172d**, HMBC correlations can be seen between protons on the allyl fragment and the ^{13}C resonance at 135.1 ppm. Additional HMBC correlations to this resonance can be seen from all aryl protons, as well as the C3-methyl protons. As such, we believe the overlapping ^{13}C resonances belong to the indicated carbons (see inset).



14. Zhou, B.; Du, J.; Yang, Y.; Li, Y. *Chem.–Eur. J*. **2014**, *20*, 12768–12772.

APPENDIX 2

Miscellaneous Studies Relevant to Chapter 2

A2.1 INTRODUCTION

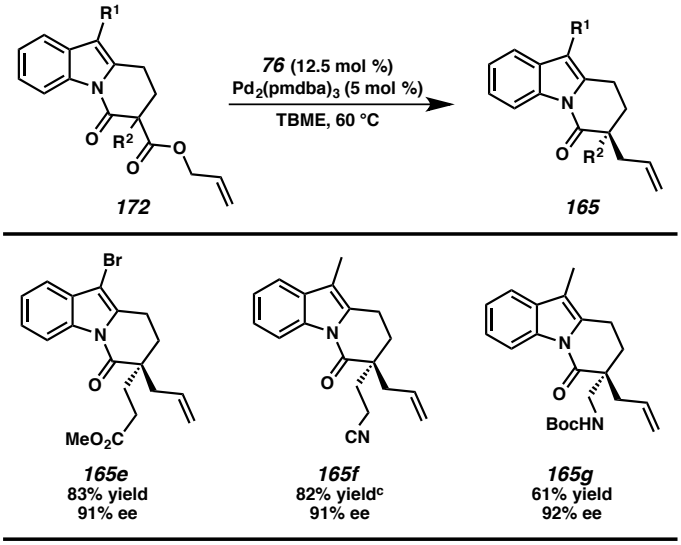
This section presents enantioenriched α-quaternary DHPIs that were not further advanced in the context of a planned total synthesis. Additional noteworthy reactions of DHPIs are also discussed.

A2.2 BRIEF SUBSTRATE SCOPE EXPLORATION

A series of β-amidoesters (**172e–g**) were subjected to the aforementioned optimized Pd-catalyzed decarboxylative allylic alkylation conditions to furnish the corresponding α-quaternary DHPI products (Table A2.2.1). Once again, a bromide at the C3 position of the indole nucleus was tolerated (e.g., **172e** → **165e**), but C3-alkyl groups (e.g., **172f** and **172g**) did not perform as well. While nitrile **165f** bearing a C3-methyl group was obtained in 82% yield and 91% ee, an elevated catalyst loading was required to achieve full conversion. Interestingly, α-quaternary Mannich adduct **172g**[1] reached full conversion using a typical catalyst loading, albeit with slightly diminished yield. It is possible that an α-substituent capable of coordinating to the palladium center (e.g., the

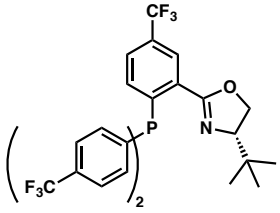
carbamate carbonyl in **172g**) is able to override the innate poor reactivity of C3-alkyl substrates.

Table A2.2.1. Pd-Catalyzed Allylic Alkylation of Additional DHPI Substrates[a,b]



165e	165f	165g
83% yield	82% yield[c]	61% yield
91% ee	91% ee	92% ee

[a] Reaction conditions for the Pd-catalyzed allylic alkylation: **172** (1 equiv), $Pd_2(pmdba)_3$ (5 mol %) and **76** (12.5 mol %) in TBME (0.033 M) at 60 °C.
[b] Enantiomeric excesses were determined by chiral SFC analysis.
[c] Reaction was performed using 10 mol % $Pd_2(pmdba)_3$ and 25 mol % **76**.



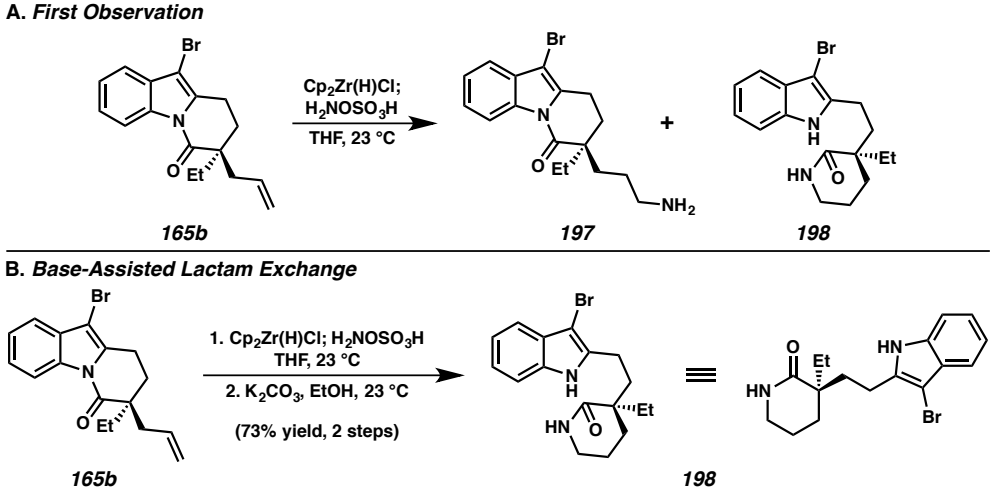
76
(S)-(CF3)3-t-BuPHOX

A2.3 DISCOVERY OF A FACILE LACTAM EXCHANGE PROCESS

Simultaneous to our efforts in avoiding olefin isomerization during the cross-coupling of α-quaternary DHPI **165b**, we investigated conditions for an anti-Markovnikov hydroamination of the allyl group. Upon exposure of DHPI **165b** to the hydrozirconation/amination protocol developed by Hartwig and co-workers,[2] we were surprised to co-isolate the desired primary amine **197** with a highly related byproduct in

an approximately 1:1 ratio (Scheme A2.3.1A). ^{1}HNMR analysis of this mixture indicated the presence of a free indole N–H bond, which led us to conclude that the primary amine in **197** had cyclized to give δ-lactam **198**. Noting the ease with which this process occurred, and the synthetic utility of the free N–H lactams (e.g., **176**, *vide supra*), we were pleased to discover that treatment of this mixture with potassium carbonate in ethanol smoothly converted all material to the translactamized product (**198**) in 73% yield over the two steps (Scheme A2.3.1B).

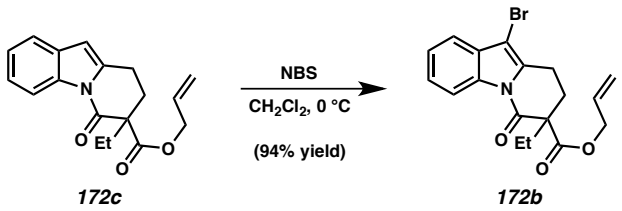
Scheme A2.3.1. Discovery of a Facile Lactam Exchange Reaction



A2.4 OPTIONAL DELAYED BROMINATION

In an effort to repurpose some material in our synthesis of (–)-goniomitine (**3**), we were pleased to find that bromination could be accomplished at a later point in the synthetic sequence. In the event, C3-unsubstituted DHPI **172c** was treated with NBS to afford C3-brominated DHPI **172b** in 94% yield (Scheme A2.4.1).

Scheme A2.4.1. Bromination at a Later Stage



A2.5 CONCLUSIONS

The enantioselective Pd-catalyzed decarboxylative allylic alkylation of DHPI substrates typically proceeds in good yield and high ee. An unusual substitution effect is observed at the C3 position of the indole nucleus. In the cases of a C3–H or C3–Br functionality, the substrates perform well. C3–alkyl substrates, however, typically require higher catalyst loadings to reach full conversion. The origin of this effect is unknown. The lactam carbonyl ^{13}CNMR shift for these compounds is not appreciably affected by the substituent at C3, therefore a simple enolate stabilization trend is not obviously at play. Interestingly, α-substituents capable of a Lewis basic interaction with the Pd(II) center appear to be able to override the poor reactivity of C3–alkyl substrates. Nevertheless, this substrate class affords access to structurally complex nitrogen-containing small molecules that could be of broad interest to the synthetic community.

A2.6 EXPERIMENTAL SECTION

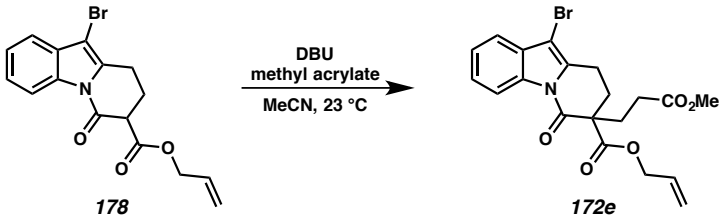
A2.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[3] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, CAM, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. Melting points were measured with BÜCHI Melting Point B-545. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively) or $CHDCl_2$ (δ 5.32 and δ 53.84, respectively). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, br t = broad triplet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing

Chiralcel (OB-H and OD-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in mixed ionization mode (MM: ESI/APCI).

Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. NBS was purchased from Sigma Aldrich, recrystallized from H_2O, and stored in a –25 °C freezer. Bis(cyclopentadienyl) zirconium chloride hydride was purchased from Strem Chemicals and stored at room temperature in a N_2-filled glovebox. Hydroxylamine-*O*-sulfonic acid was purchased from Sigma Aldrich and stored at –30°C in the glovebox freezer. (*S*)-$(CF_3)_3$-*t*-BuPHOX,[4] and tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) $[Pd_2(pmdba)_3]$[5] were prepared by known methods.

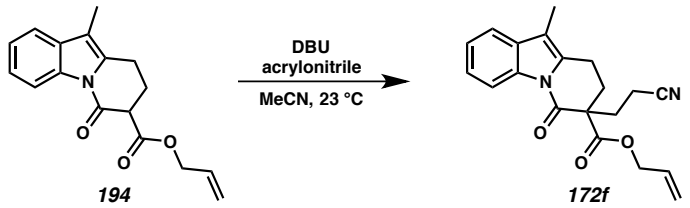
A2.6.2 EXPERIMENTAL PROCEDURES



178 *172e*

Allyl 10-bromo-7-(3-methoxy-3-oxopropyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172e): To a solution of β-amidoester **178** (395 mg, 1.13 mmol, 1.0 equiv) in MeCN (7.6 mL) were added methyl acrylate (0.2 mL, 2.22 mmol, 1.96 equiv) and DBU (9 μL, 59 μmol, 0.05 equiv) at 23 °C with stirring. After 8 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (100 mL) was added, followed by extraction with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, then dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 30% Et_2O in hexanes) afforded quaternary β-amidoester **172e** (444 mg, 90% yield) as a clear colorless oil: R_f = 0.35 (3:2 hexanes:Et_2O eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47–8.43 (m, 1H), 7.49–7.45 (m, 1H), 7.39–7.34 (m, 2H), 5.83 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.24 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.21 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.65 (dq, *J* = 5.7, 1.6 Hz, 2H), 3.67 (s, 3H), 3.12 (dt, *J* = 17.4, 4.8 Hz, 1H), 2.87 (ddd, *J* = 17.1, 11.4, 5.0 Hz, 1H), 2.71–2.64 (m, 1H), 2.58–2.46 (m, 2H), 2.46–2.41 (m, 2H), 2.16 (ddd, *J* = 13.6, 11.4, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 170.5, 167.0, 134.3, 134.0, 131.1, 129.2, 125.7, 124.9, 119.4, 118.7, 116.7, 97.4, 66.7, 55.6, 52.0, 29.90, 29.88, 29.80, 19.8; IR (Neat Film, NaCl) 2949, 1734, 1709, 1597, 1449, 1371, 1345, 1310, 1226, 1173, 1087, 1039, 922,

750 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{20}H_{21}NO_5Br$ $[M+H]^+$: 434.0598, found 434.0586.

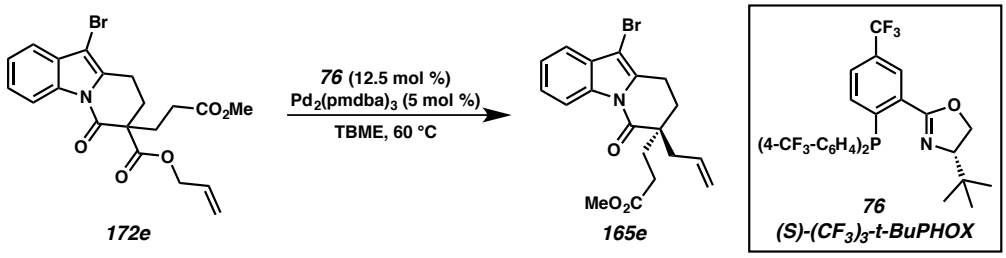


Allyl 7-(2-cyanoethyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172f): To a solution of β-amidoester **194** (73 mg, 0.26 mmol, 1.0 equiv) in MeCN (1.7 mL) were added acrylonitrile (34 μL, 0.52 mmol, 2.0 equiv) and DBU (6 μL, 39 μmol, 0.1 equiv) at 23 °C with stirring. After 4 h, starting material was completely consumed as determined by TLC analysis. The reaction mixture was diluted with ethyl acetate (20 mL). The resulting mixture was washed with 1N HCl, saturated aqueous sodium bicarbonate and brine, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded nitrile **172f** (55.6 mg, 64% yield) as a clear colorless oil: R_f = 0.32 (4:1 hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45–8.39 (m, 1H), 7.47–7.41 (m, 1H), 7.35–7.28 (m, 2H), 5.84 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.28–5.19 (m, 2H), 4.67 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.06 (dt, *J* = 16.8, 4.8 Hz, 1H), 2.89–2.77 (m, 2H), 2.64 (ddd, *J* = 17.0, 9.7, 6.0 Hz, 1H), 2.55 (dt, *J* = 13.4, 4.8 Hz, 1H), 2.50–2.38 (m, 2H), 2.21–2.13 (m, 1H), 2.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 166.6, 134.9, 131.5, 131.3, 131.0, 124.8, 124.5, 119.6, 119.4, 118.2, 116.7, 113.6, 66.8, 55.2, 31.2, 30.7, 18.8, 13.8, 8.6; IR (Neat Film, NaCl) 3051, 2940, 2862, 2248, 1734, 1696, 1627, 1458, 1384, 1369, 1338, 1316, 1227, 1185, 1137,

1090, 1057, 935, 752 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{21}N_2O_3$ $[M+H]^+$: 337.1552, found 337.1566.

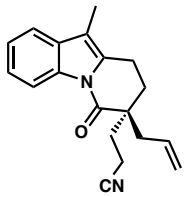
General Procedure A: Pd-Catalyzed Allylic Alkylation

Please note that the absolute configuration of **165e** and **165f** have been inferred from previous studies.[6]



Methyl (*R*)-3-(7-allyl-10-bromo-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-7-yl)propanoate (165e): A flame-dried 100 mL Schlenk flast was charged with $Pd_2(pmdba)_3$ (34 mg, 31 μmol, 0.05 equiv), (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 46 mg, 78 μmol, 0.125 equiv), and a magnetic stirring bar in a N_2-filled glove box. The flask was then charged with TBME (17 mL) and stirred at 23 °C for 30 minutes, generating a dark purple solution. To the preformed catalyst solution was added a solution of **172e** (270 mg, 0.622 mmol, 1.0 equiv) in TBME (1.8 mL, including washings). The flask was sealed, removed from the glovebox, and placed in a preheated 60 °C oil bath with stirring. Full consumption of starting material was achieved after 12 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO_2, 25% Et_2O in hexanes) to afford α-quaternary lactam **165e** (201 mg, 83% yield) as a faintly yellow oil: R_f = 0.38 (7:3 hexanes:Et_2O eluent); 91% ee, $[\alpha]_D^{25}$ –6.7 (*c* 1.54, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.47–8.42 (m, 1H),

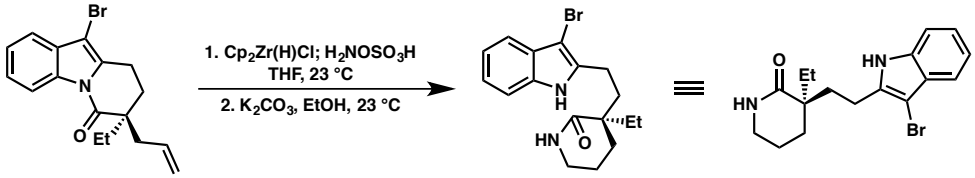
7.50–7.44 (m, 1H), 7.37–7.31 (m, 2H), 5.84–5.74 (m, 1H), 5.18 (q, J = 1.1 Hz, 1H), 5.17–5.14 (m, 1H), 3.64 (s, 3H), 3.03 (t, J = 6.7 Hz, 2H), 2.61 (ddt, J = 14.1, 7.1, 1.2 Hz, 1H), 2.53–2.37 (m, 3H), 2.18–2.05 (m, 3H), 2.05–1.97 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 172.3, 134.6, 134.3, 132.5, 129.2, 125.5, 124.6, 119.9, 118.5, 116.7, 96.8, 51.9, 45.8, 39.9, 30.3, 29.1, 28.9, 18.8; IR (Neat Film, NaCl) 3075, 2949, 2868, 1738, 1704, 1639, 1595, 1449, 1372, 1347, 1309, 1176, 1107, 1036, 996, 922, 835, 754 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{20}NO_3Br$ [M]$^+$: 389.0626, found 389.0632; SFC conditions: 10% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 9.17, minor = 7.99.



165f

(*R*)-3-(7-Allyl-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-7-yl)propanenitrile (165f): The reaction was conducted according to general procedure A. α-Quaternary β-amidoester **172f** (27 mg, 0.08 mmol, 1.0 equiv); $Pd_2(pmdba)_3$ (8.8 mg, 8 μmol, 0.1 equiv); (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 11.9 mg, 0.02 mmol, 0.25 equiv); TBME (2.4 mL). The reaction mixture was stirred for 9 h at 60 °C. Flash column chromatography (SiO_2, 33% Et_2O in hexanes) afforded nitrile **165f** (19.2 mg, 82% yield) as a clear colorless oil: R_f = 0.19 (7:3 hexanes:Et_2O eluent); 91% ee, $[\alpha]_D^{25}$ +20.7 (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46–8.38 (m, 1H), 7.43 (ddt, J = 6.6, 4.3, 2.1 Hz, 1H), 7.32–7.28 (m, 2H), 5.78 (ddt, J = 16.8, 10.2, 7.4 Hz, 1H), 5.23–5.16 (m, 2H), 3.02–2.97 (m, 2H), 2.60–2.50 (m, 2H), 2.49–2.42 (m, 2H), 2.32–2.23 (m, 1H), 2.18 (t, J = 1.1 Hz, 3H), 2.08–1.99 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 134.8, 131.9, 131.8,

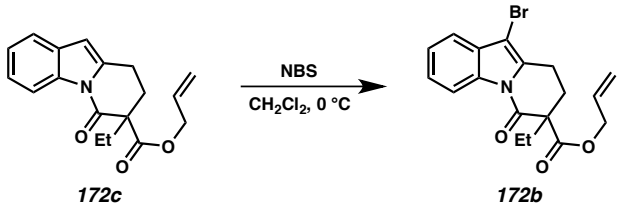
131.5, 124.6, 124.2, 120.3, 119.8, 118.1, 116.6, 113.1, 45.8, 39.7, 31.5, 29.1, 17.8, 12.8, 8.5; IR (Neat Film, NaCl) 3073, 2935, 2862, 2247, 1690, 1625, 1457, 1382, 1370, 1317, 1187, 1056, 920, 754 cm^{-1}; HRMS (ESI+) m/z calc'd for $C_{19}H_{21}N_2O$ $[M+H]^+$: 293.1654, found 293.1680; SFC conditions: 10% IPA, 3 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 8.29, minor = 7.35.



165b *198*

(*R*)-3-(2-(3-Bromo-1*H*-indol-2-yl)ethyl)-3-ethylpiperidin-2-one (198): An oven-dried scintillation vial was charged with α-quaternary DHPI **165b** (305 mg, 0.92 mmol, 1.0 equiv), THF (3.7 mL), and a magnetic stirring bar in a N_2-filled glovebox. To this solution was added bis(cyclopentadienyl) zirconium chloride hydride (284 mg, 1.1 mmol, 1.2 equiv), and the mixture was stirred at 23 °C until a light yellow solution was observed (ca. 30 min). Hydroxylamine-*O*-sulfonic acid (166 mg, 1.47 mmol, 1.6 equiv) was added, the vial was sealed and removed from the glovebox, and stirring was resumed at 23 °C in a fume hood for an additional 30 min. The crude reaction mixture was loaded directly onto a plug of silica gel and eluted (CH_2Cl_2: NH_3 (7N solution in MeOH) = 95:5) to deliver a mixture of the primary amine **197** and secondary lactam **198** (250 mg, ca. 1:1 ratio, 78% combined yield). A portion (190 mg, 0.54 mmol, 1.0 equiv) of this mixture was dissolved in EtOH (11 mL), then K_2CO_3 (225 mg, 1.63 mmol, 3.0 equiv) was added. The reaction was stirred at 23 °C for 1 h, at which point complete consumption of starting material was determined by TLC analysis. The reaction mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 x 75 mL). The combined

organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 40% acetone in hexanes) afforded free N–H lactam **198** (176 mg, 93% yield) as a white amorphous solid: R_f = 0.4 (3:2 hexanes:acetone eluent); $[\alpha]_D^{25}$ – 11.6 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.33 (br s, 1H), 7.44–7.40 (m, 1H), 7.29–7.26 (m, 1H), 7.15–7.08 (m, 2H), 6.10 (s, 1H), 3.30 (q, *J* = 4.4, 3.4 Hz, 2H), 2.98 (ddd, *J* = 14.4, 10.5, 6.1 Hz, 1H), 2.64 (ddd, *J* = 14.4, 10.4, 4.9 Hz, 1H), 2.07 (ddd, *J* = 13.7, 10.4, 4.9 Hz, 1H), 1.90–1.81 (m, 4H), 1.79–1.73 (m, 2H), 1.63 (dq, *J* = 14.8, 7.4 Hz, 1H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 177.4, 137.7, 135.4, 127.8, 122.3, 120.3, 118.3, 111.4, 89.0, 45.6, 43.1, 37.2, 31.6, 29.3, 22.5, 20.0, 8.6; IR (Neat Film, NaCl) 3290, 3221, 3183, 3058, 2961, 2935, 2874, 1640, 1615, 1454, 1333, 1297, 1228, 797, 742 , 671, 627 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{22}N_2OBr$ $[M+H]^+$: 349.0910, found 349.0909.



Allyl 10-bromo-7-ethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172b): To a solution of β-amidoester **172c** (218 mg, 0.73 mmol, 1.0 equiv) in CH_2Cl_2 (3.7 mL) at 0 °C was added NBS (138 mg, 0.76 mmol, 1.04 equiv) in three equal portions over 10 minutes. After 10 min, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. Full consumption of starting material was complete within 1 h, as observed by TLC analysis. The crude reaction mixture was stripped onto silica gel and purified by flash column chromatography (SiO_2, 60% CH_2Cl_2 in hexanes) to afford quaternary β-amidoester **172b** (259 mg, 94% yield) as a clear colorless oil.[7]

A2.7 NOTES AND REFERENCES

1. For convenience regarding the numbering of compounds, the experimental procedures and spectra for **172g** and **165g** are located in Chapter 4.

2. Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909–8914.

3. Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

4. McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

5. (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–256. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.

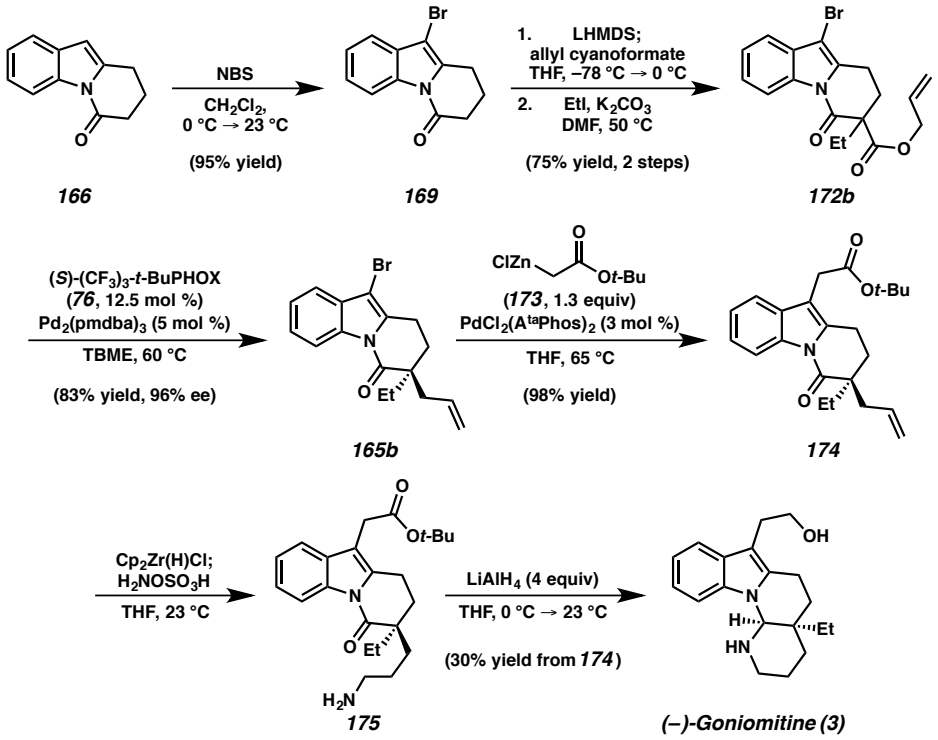
6. For examples of asymmetric allylic alkylation of nitrogen-containing substrates published by our group, see: (a) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223. (b) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133. (c) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179–183. (d) Numajiri, Y.; Jiménez-Osés, G.; Wang, B.; Houk, K. N.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 1082–1085. (e) Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2015**, *137*, 1040–1043.

7. The spectral data for **172b** matched those reported in Chapter 2.

APPENDIX 3

Synthetic Summary for Chapter 2: Chemoselectivity in Indole-Iminium Cyclizations: Total Synthesis of (–)-Goniomitine and Formal Syntheses of (+)-Aspidospermidine and (–)-Quebrachamine

*Scheme A3.1. Catalytic Enantioselective Total Synthesis of (–)-Goniomitine (**3**)*



*Scheme A3.2. Enantioselective Formal Syntheses of (+)-Aspidospermidine (**1**) and (–)-Quebrachamine (**2**)*

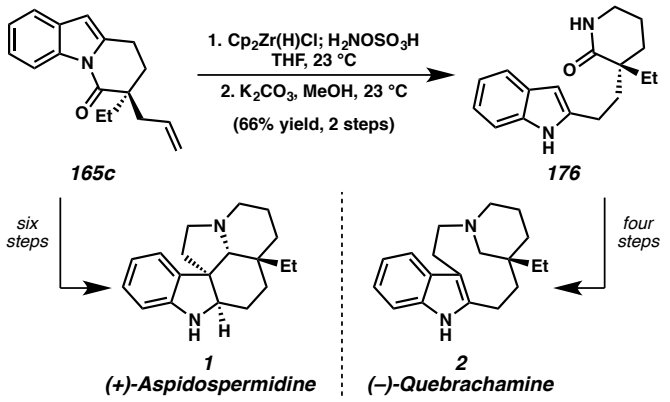
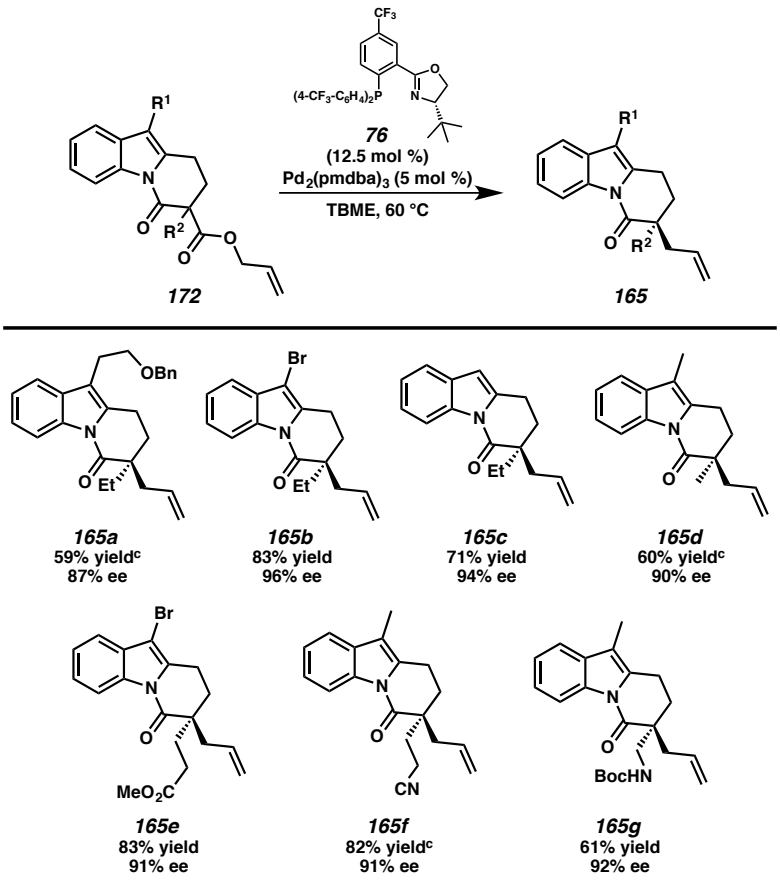


Table A3.1. Enantioselective Pd-Catalyzed Decarboxylative Allylic Alkylation of DHPI Substrates[a,b]



[a] Reaction conditions for the Pd-catalyzed allylic alkylation: **172** (1 equiv), $Pd_2(pmdba)_3$ (5 mol %) and **76** (12.5 mol %) in TBME (0.033 M) at 60 °C.
[b] Enantiomeric excesses were determined by chiral SFC analysis.
[c] Reaction was performed using 10 mol % $Pd_2(pmdba)_3$ and 25 mol % **76**.

APPENDIX 4

Spectra Relevant to Chapter 2:

Chemoselectivity in Indole-Iminium Cyclizations:

Total Synthesis of (–)-Goniomitine and Formal Syntheses of

(+)-Aspidospermidine and (–)-Quebrachamine

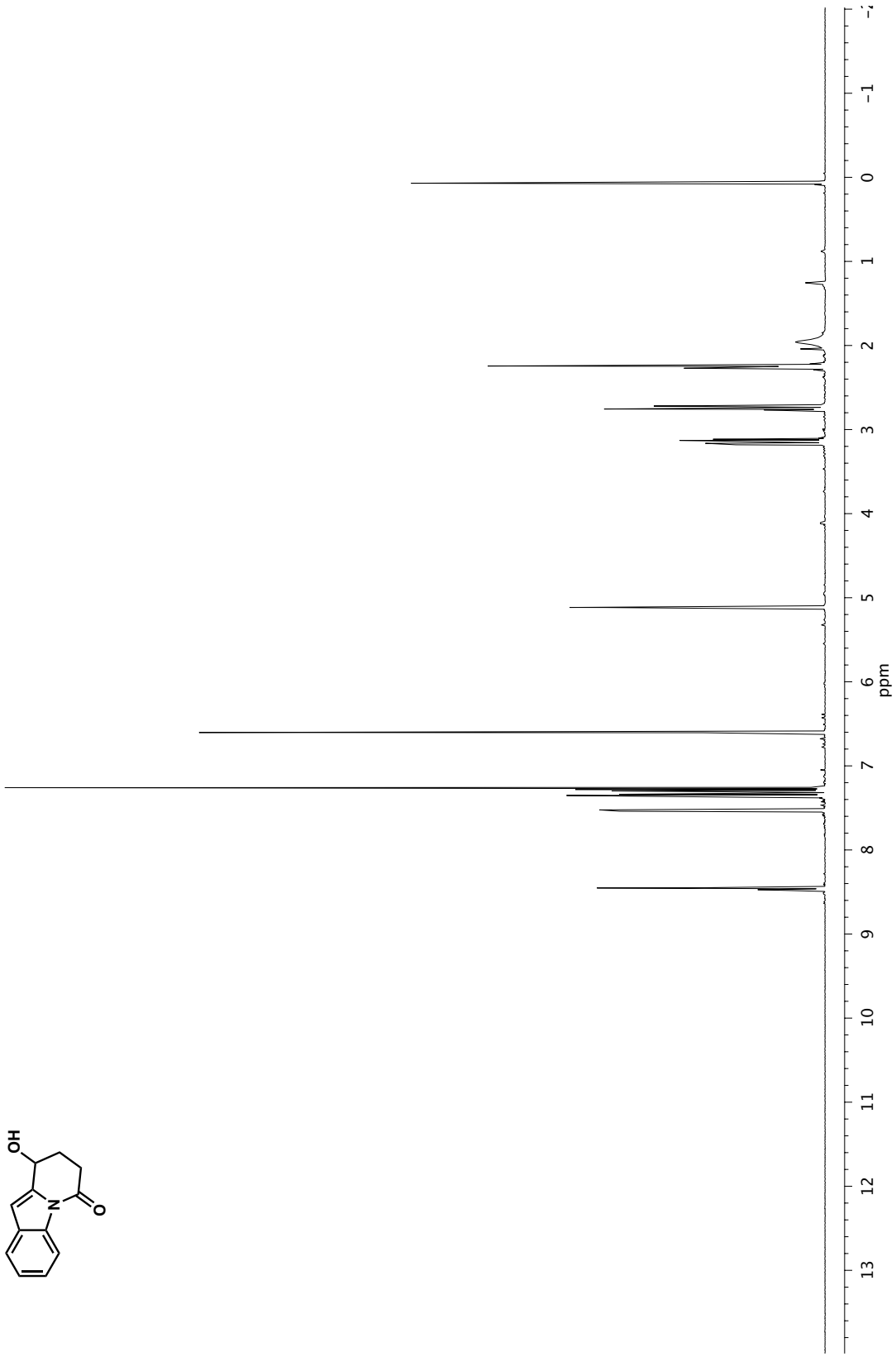


Figure A4.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **168**.

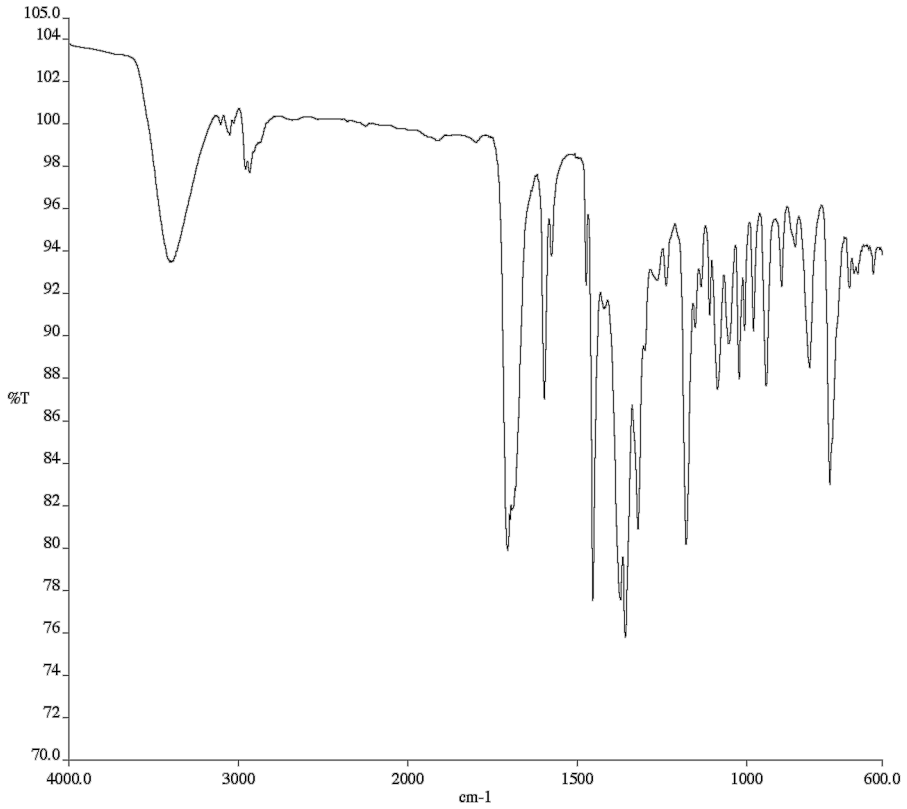


Figure A4.2. Infrared spectrum (Thin Film, NaCl) of compound **168.**

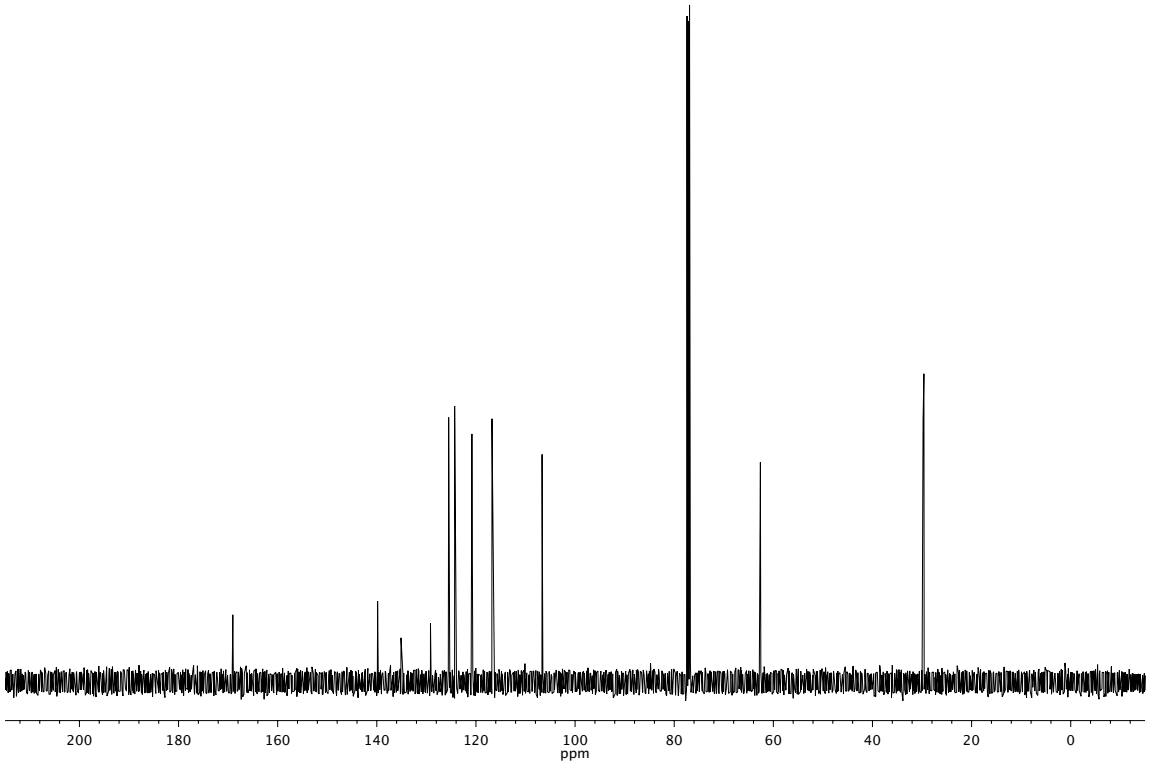


Figure A4.3. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **168**.

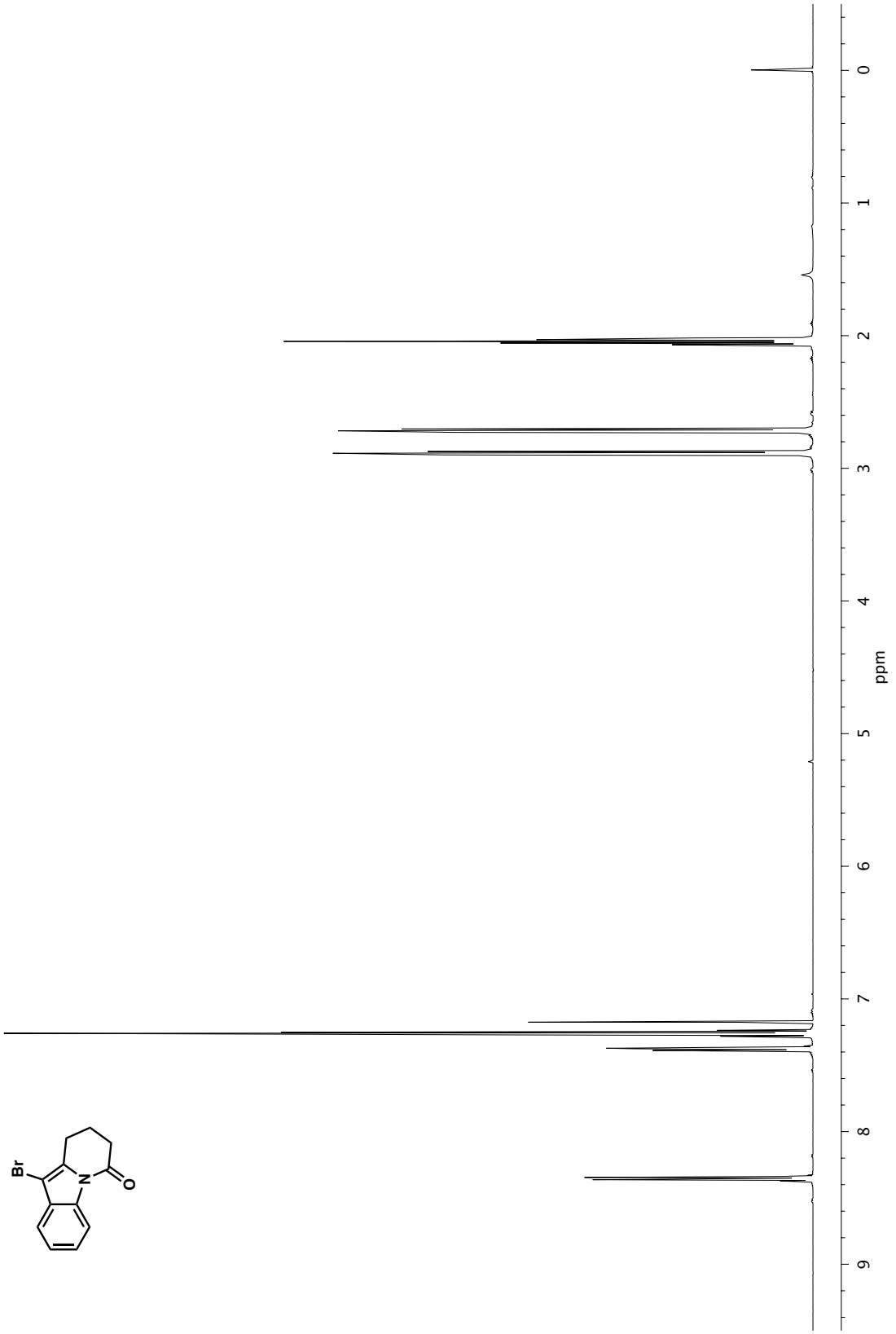


Figure A4.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **169**.

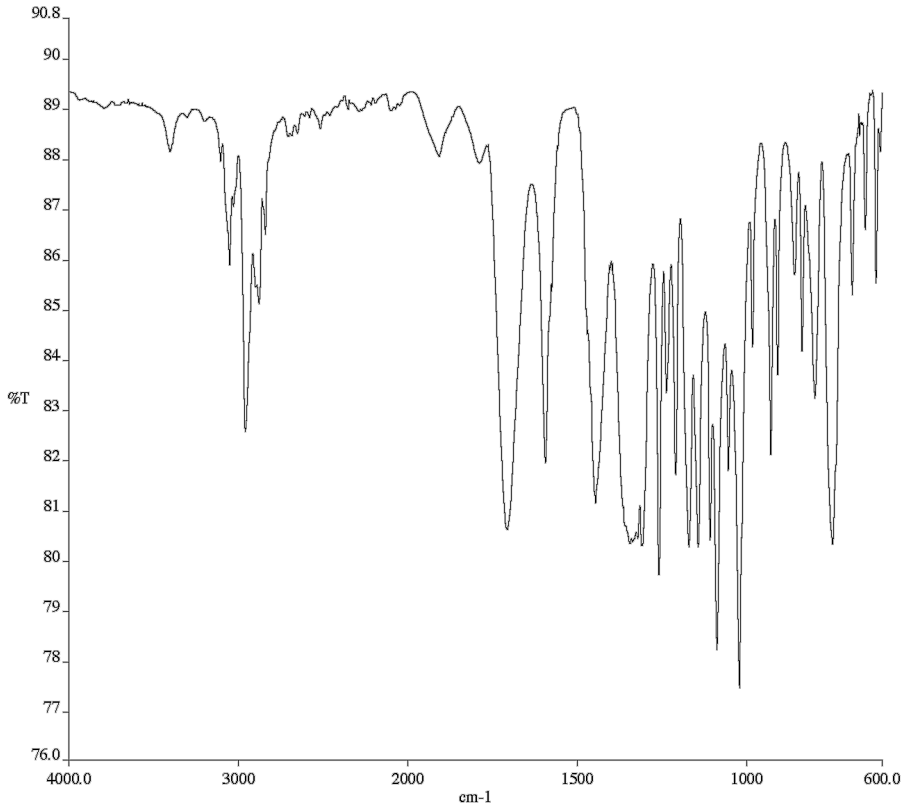


Figure A4.5. Infrared spectrum (Thin Film, NaCl) of compound **169.**

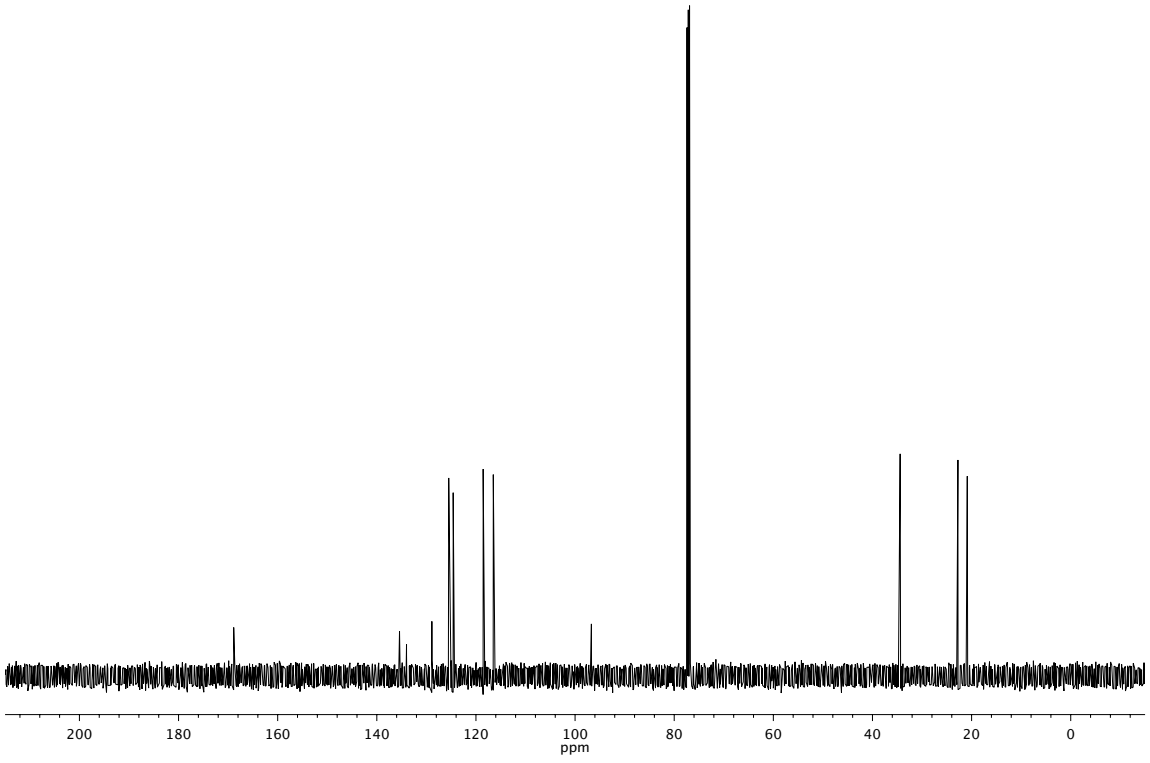


Figure A4.6. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **169**.

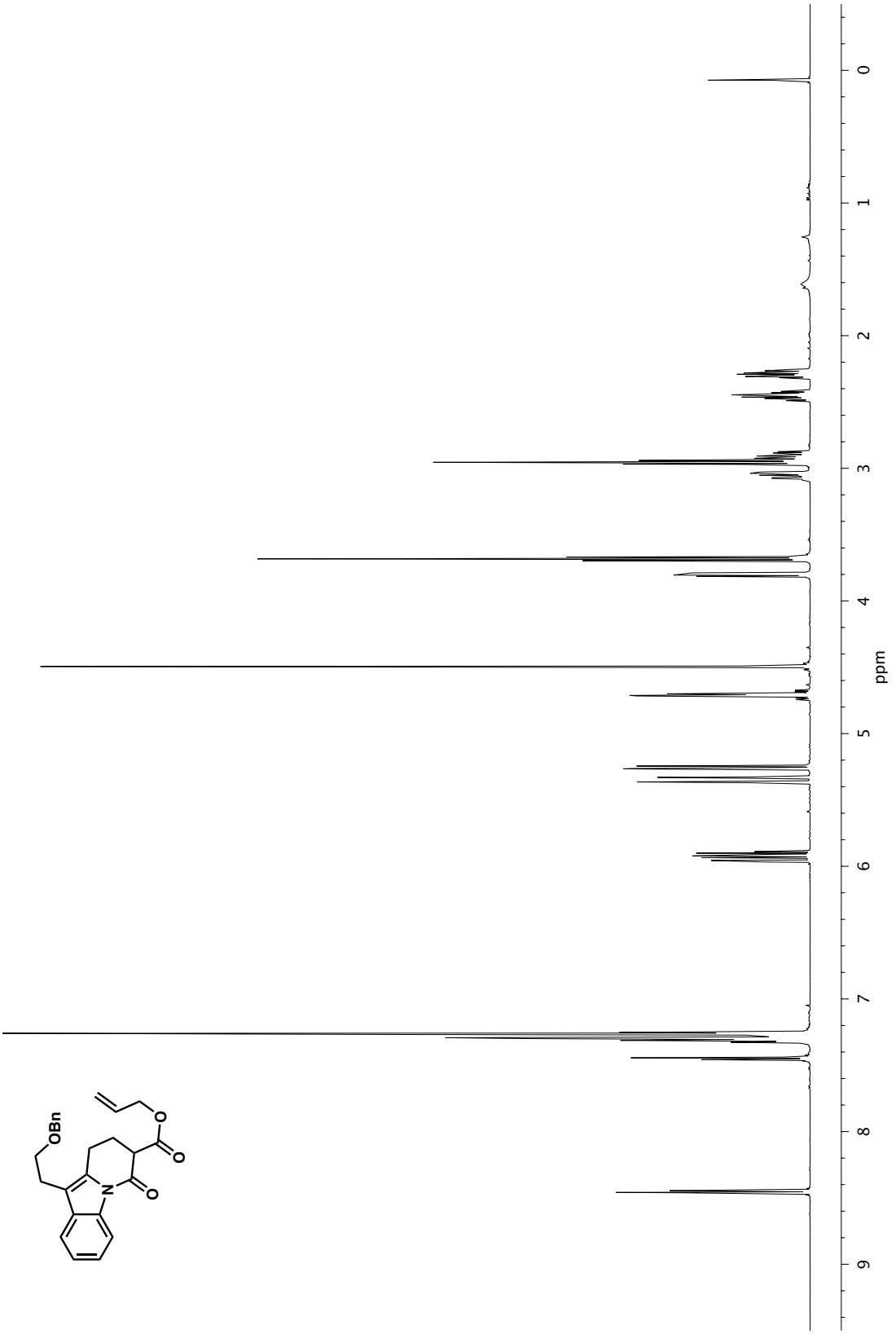


Figure A4.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **177**.

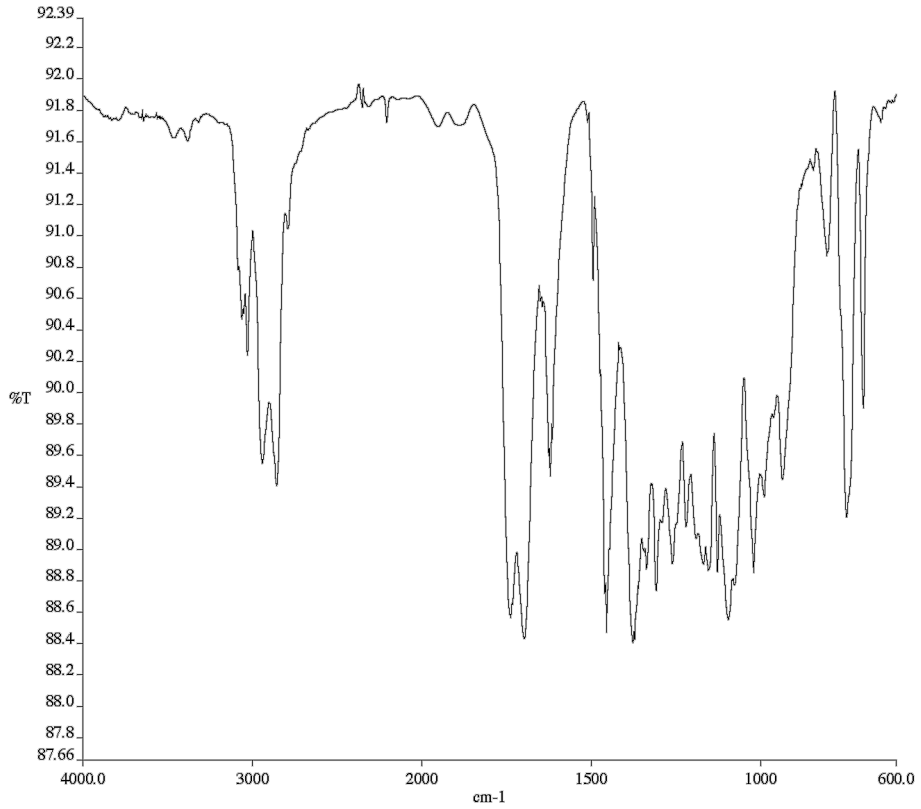


Figure A4.8. Infrared spectrum (Thin Film, NaCl) of compound **177.**

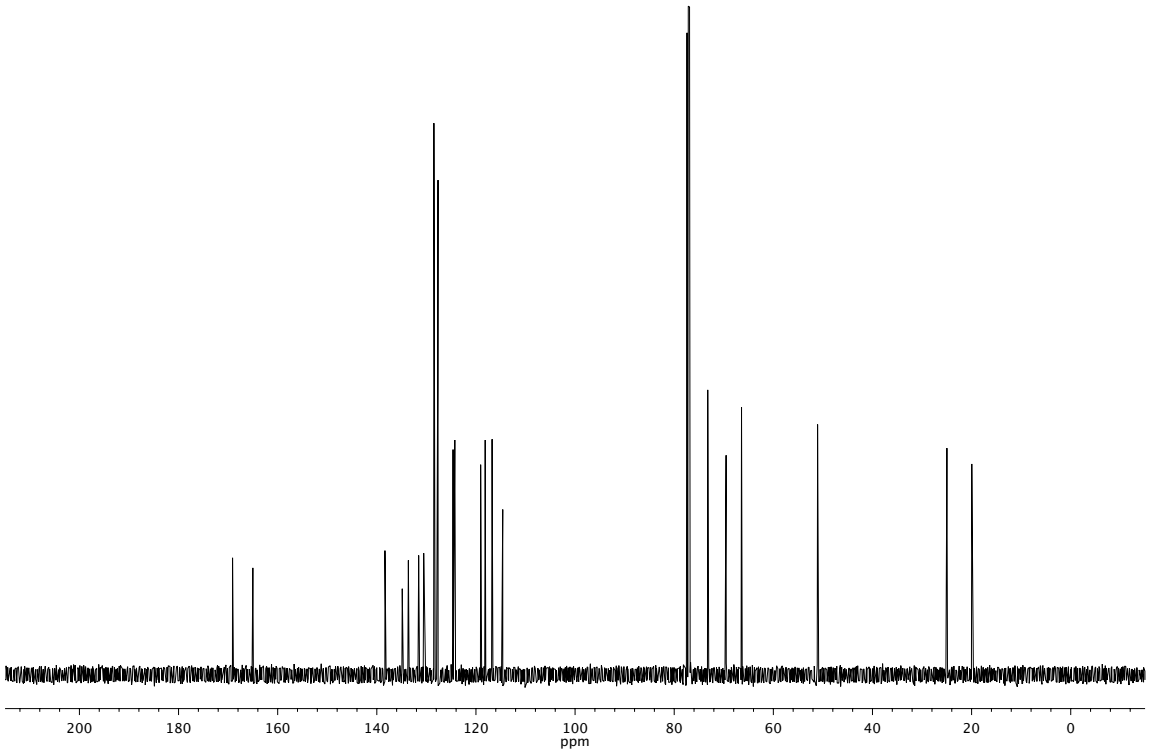


Figure A4.9. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **177**.

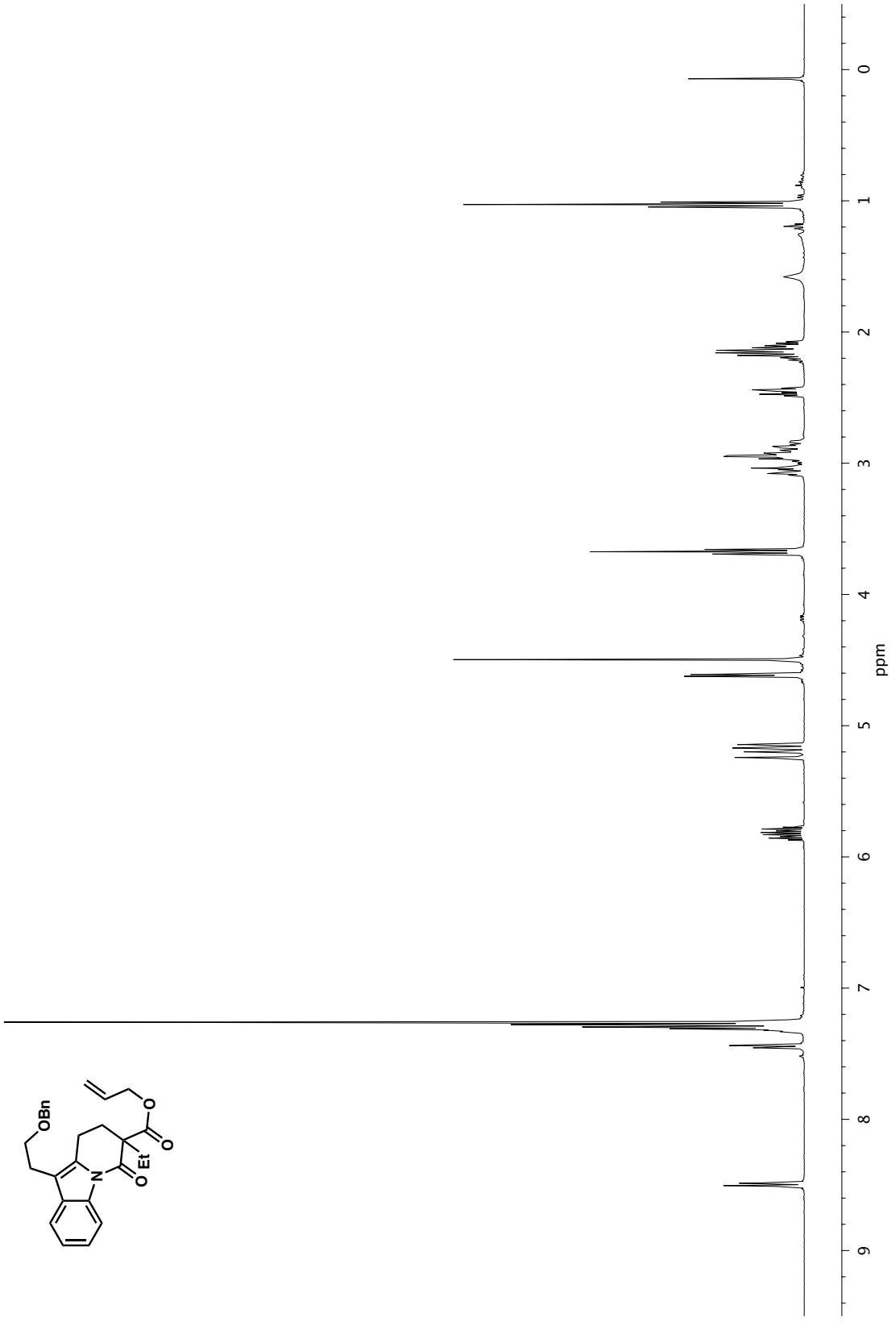


Figure A4.10. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **172a**.

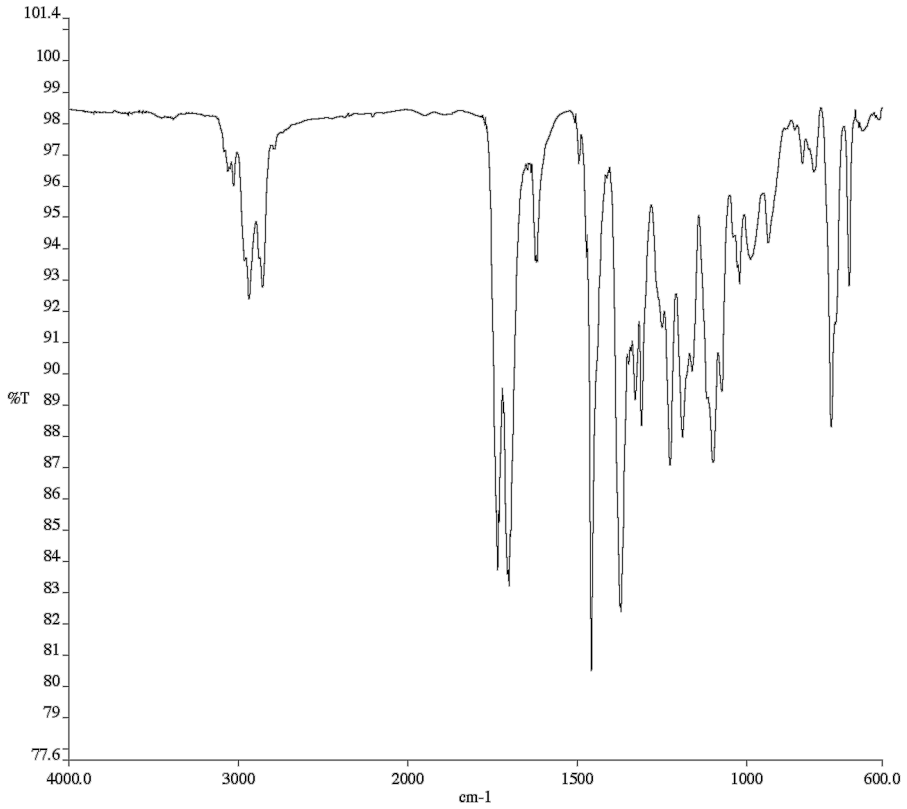


Figure A4.11. Infrared spectrum (Thin Film, NaCl) of compound **172a.**

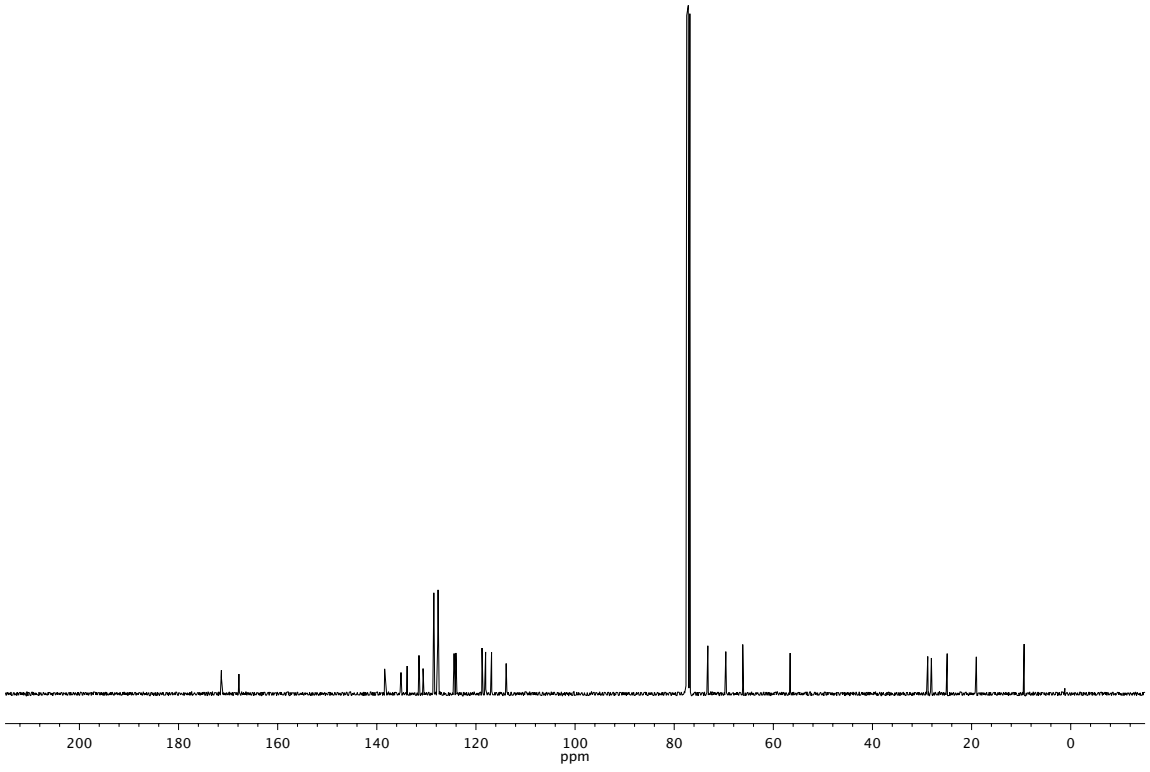


Figure A4.12. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **172a**.

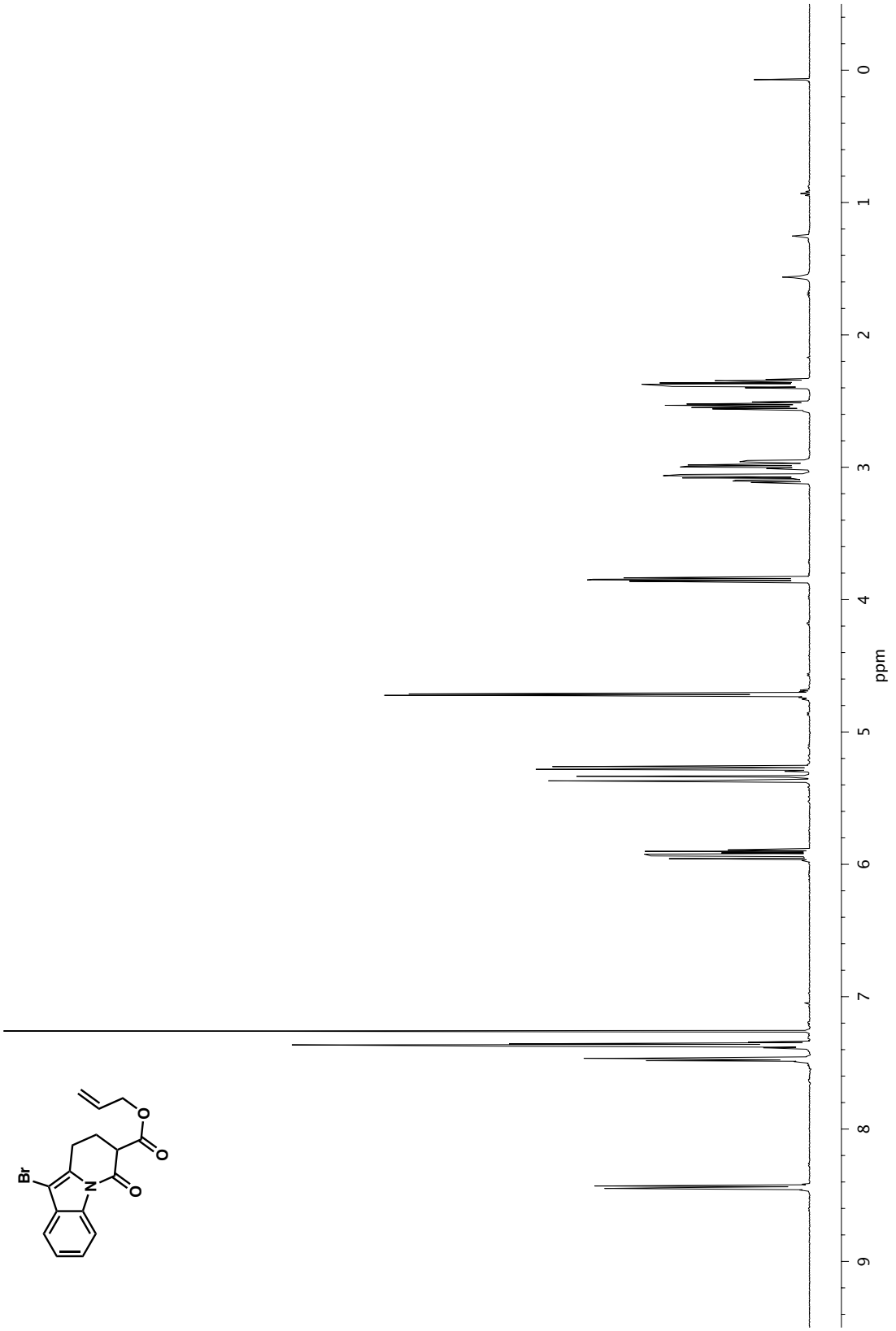


Figure A4.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **178**.

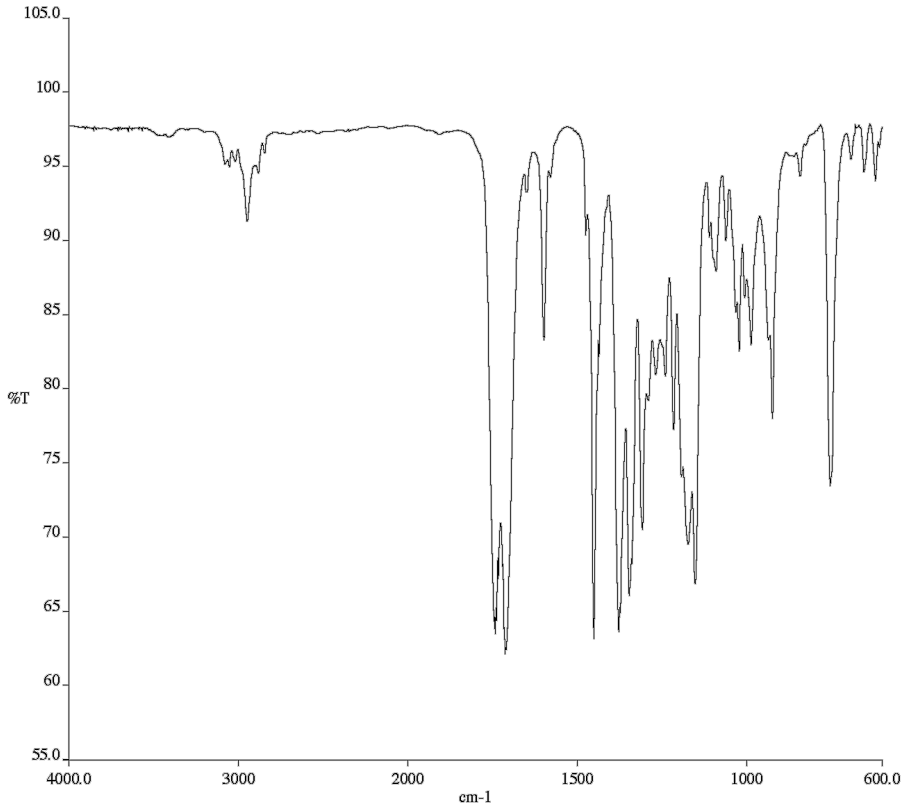


Figure A4.14. Infrared spectrum (Thin Film, NaCl) of compound **178.**

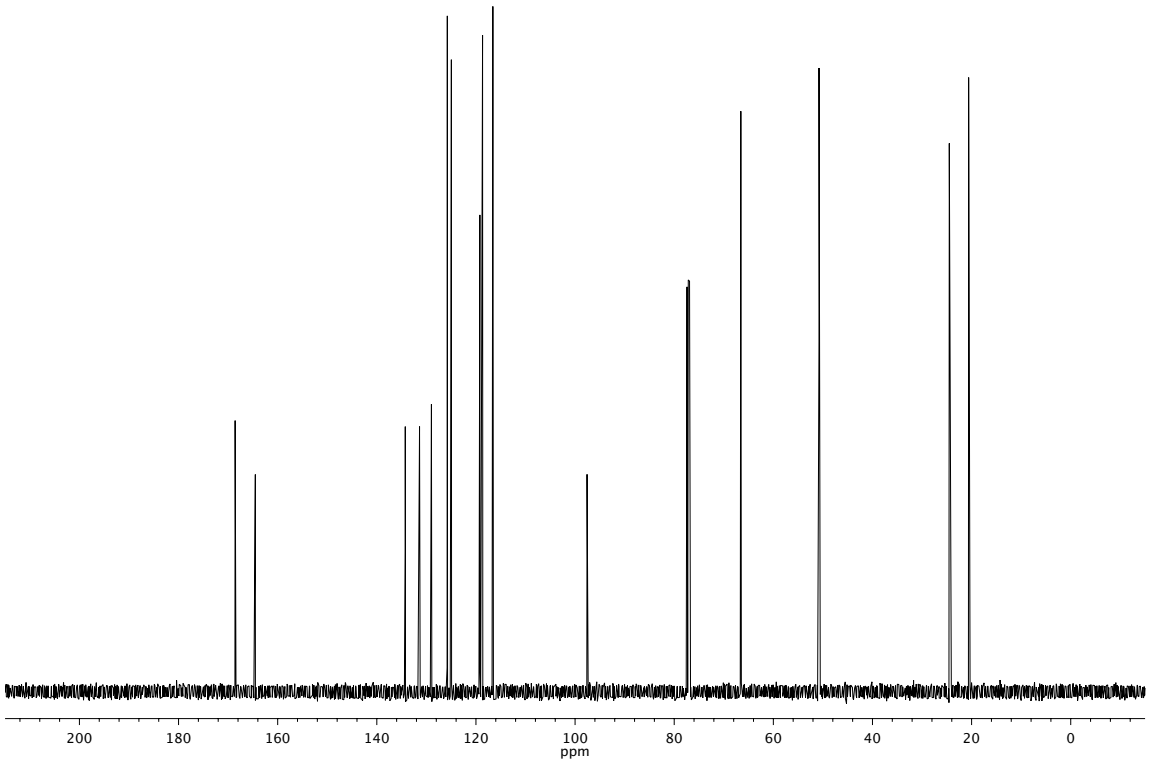


Figure A4.15. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **178**.

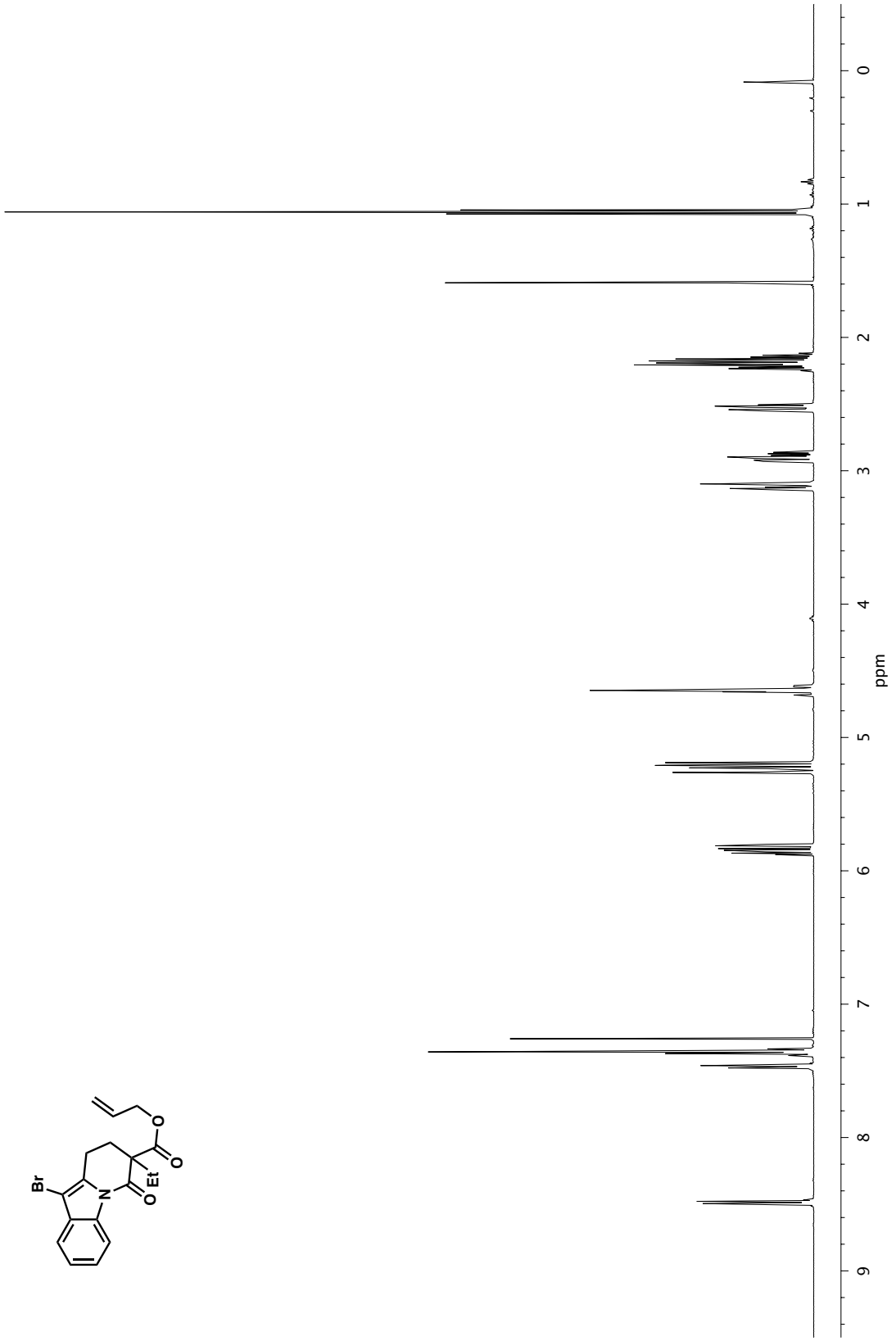


Figure A4.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172b**.

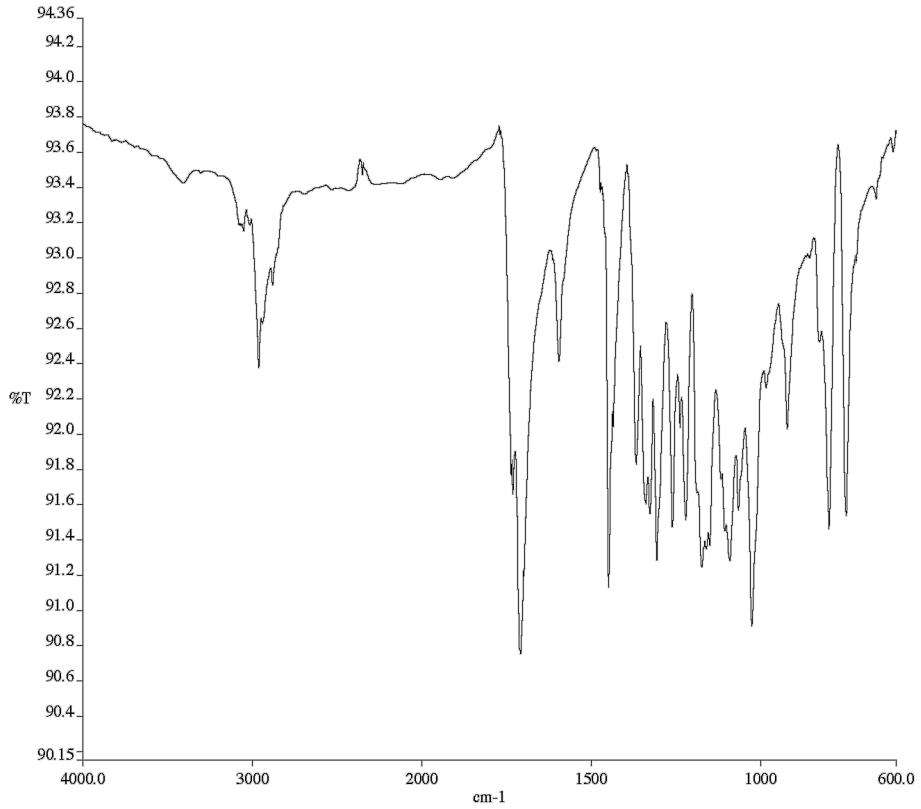


Figure A4.17. Infrared spectrum (Thin Film, NaCl) of compound **172b.**

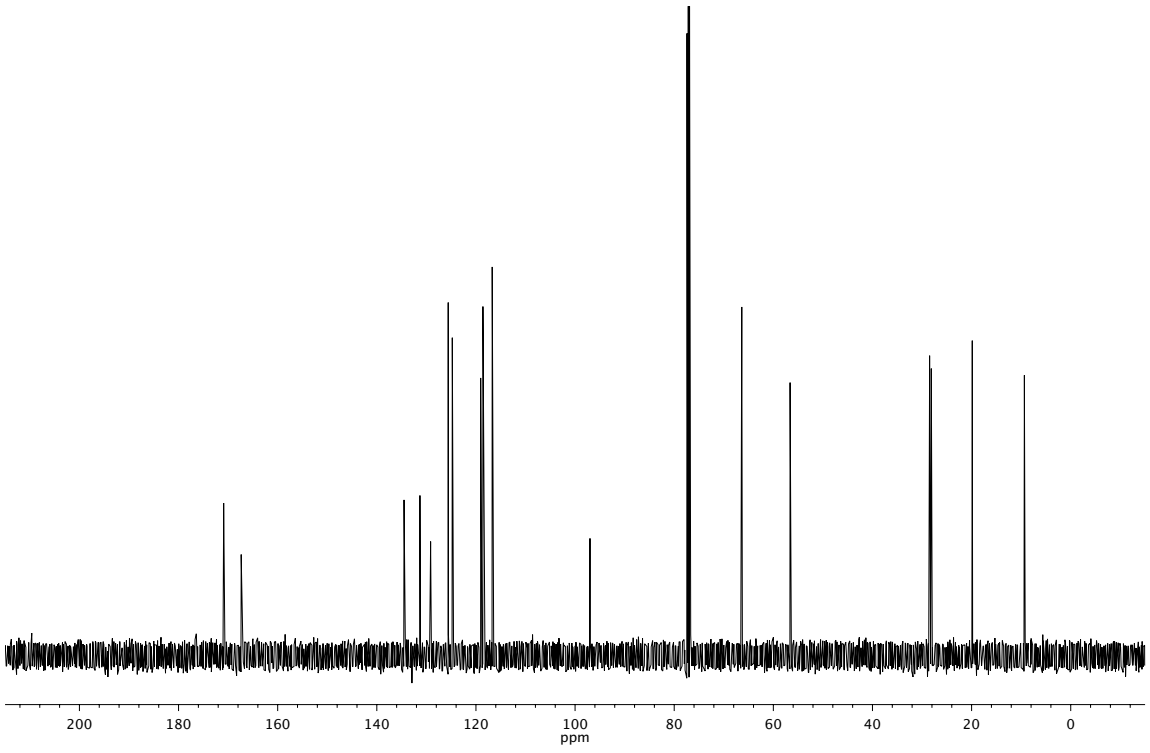


Figure A4.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172b**.

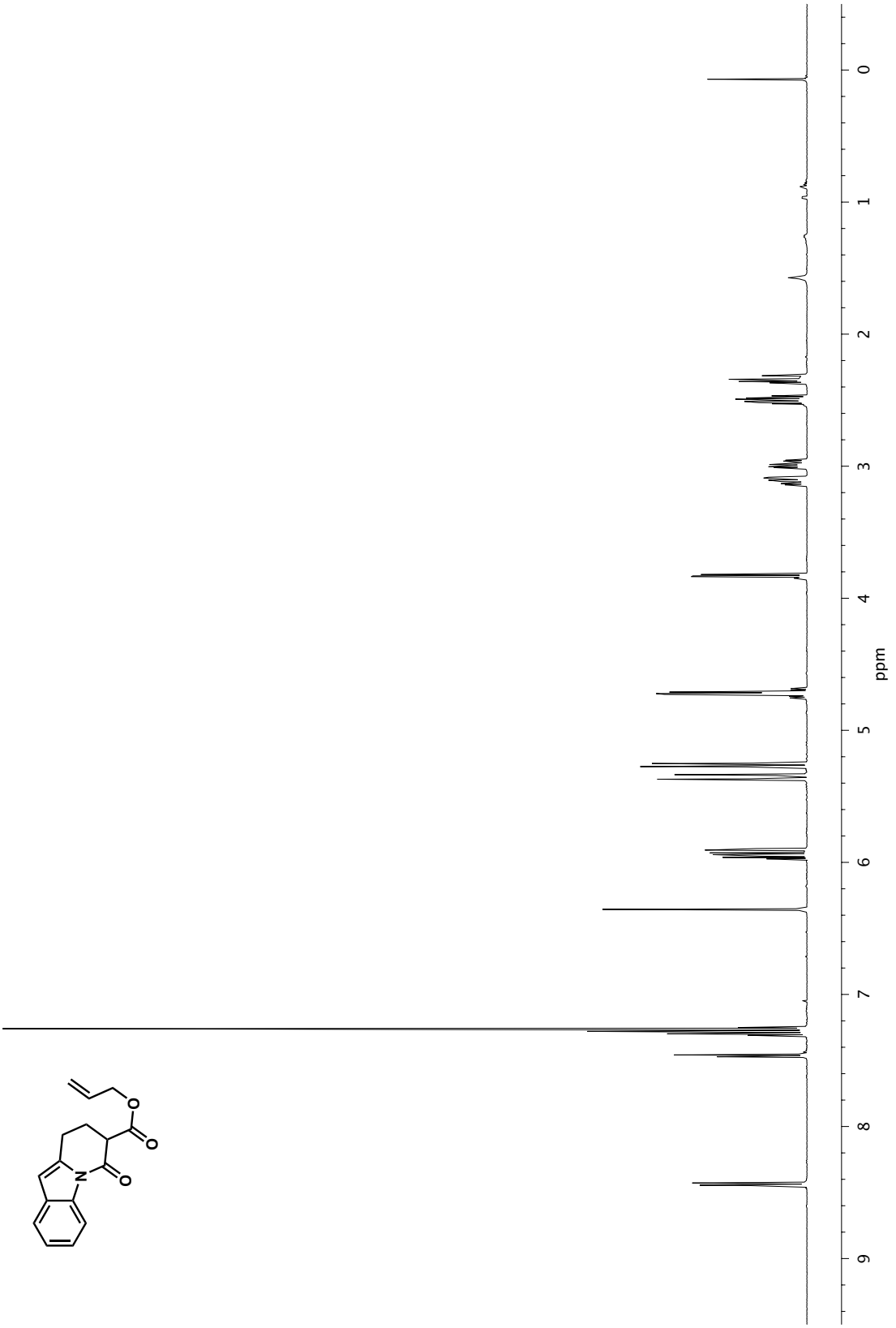


Figure A4.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **179**.

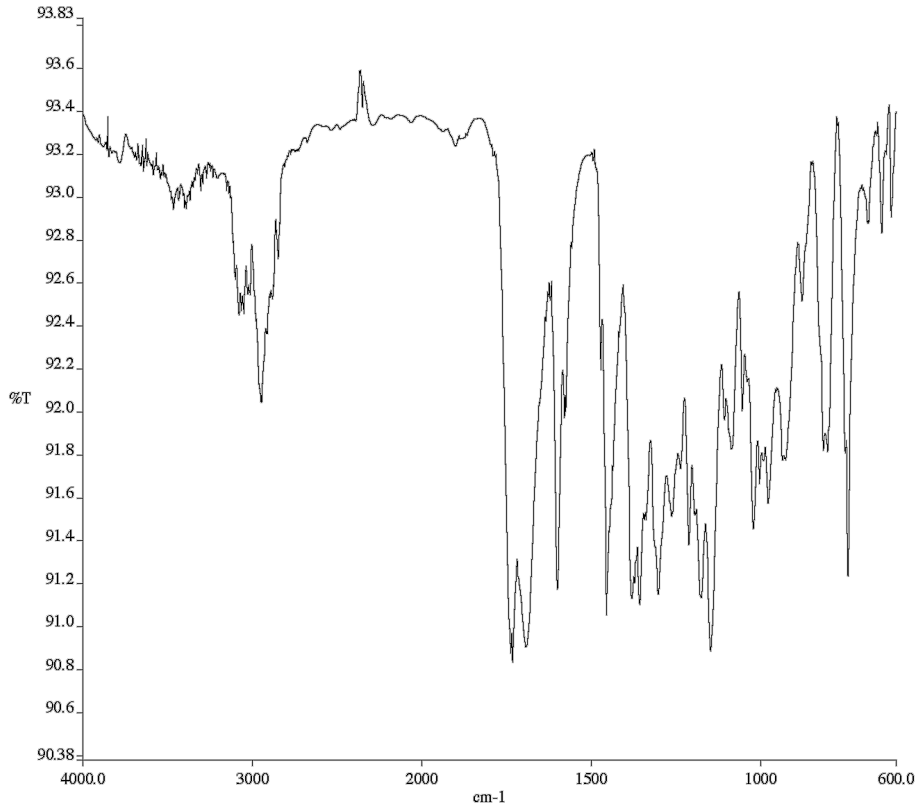


Figure A4.20. Infrared spectrum (Thin Film, NaCl) of compound **179.**

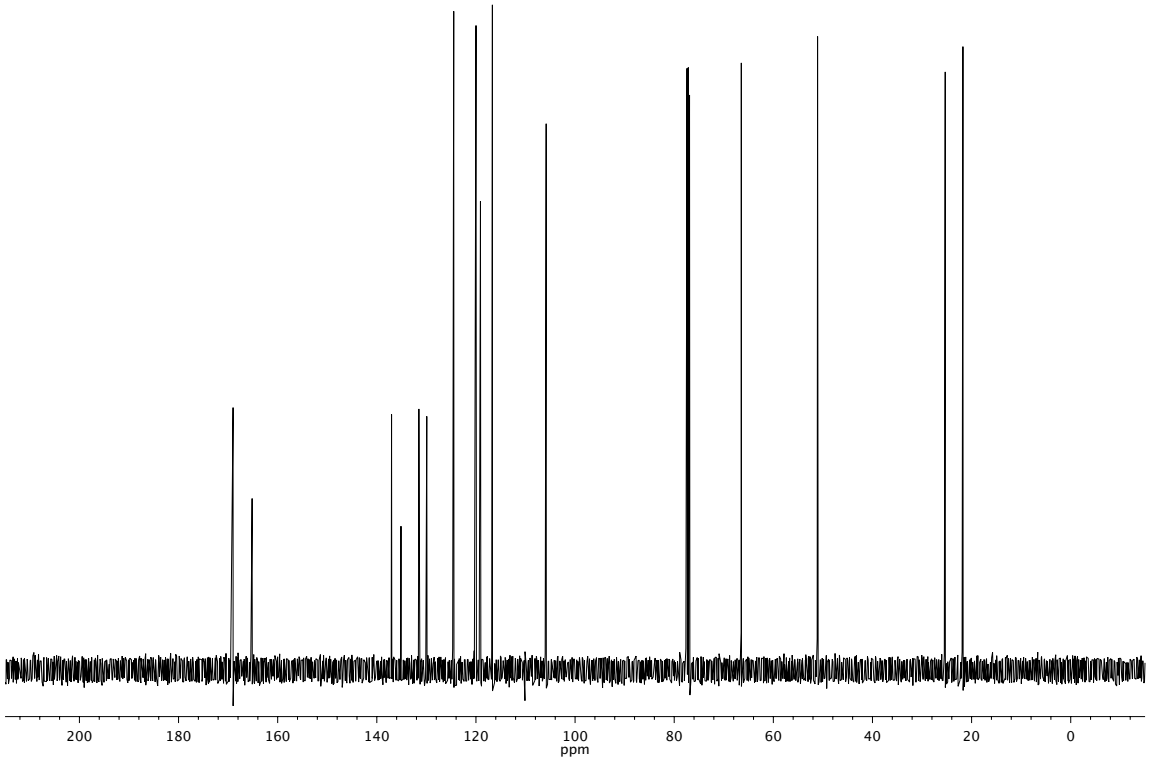


Figure A4.21. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **179**.

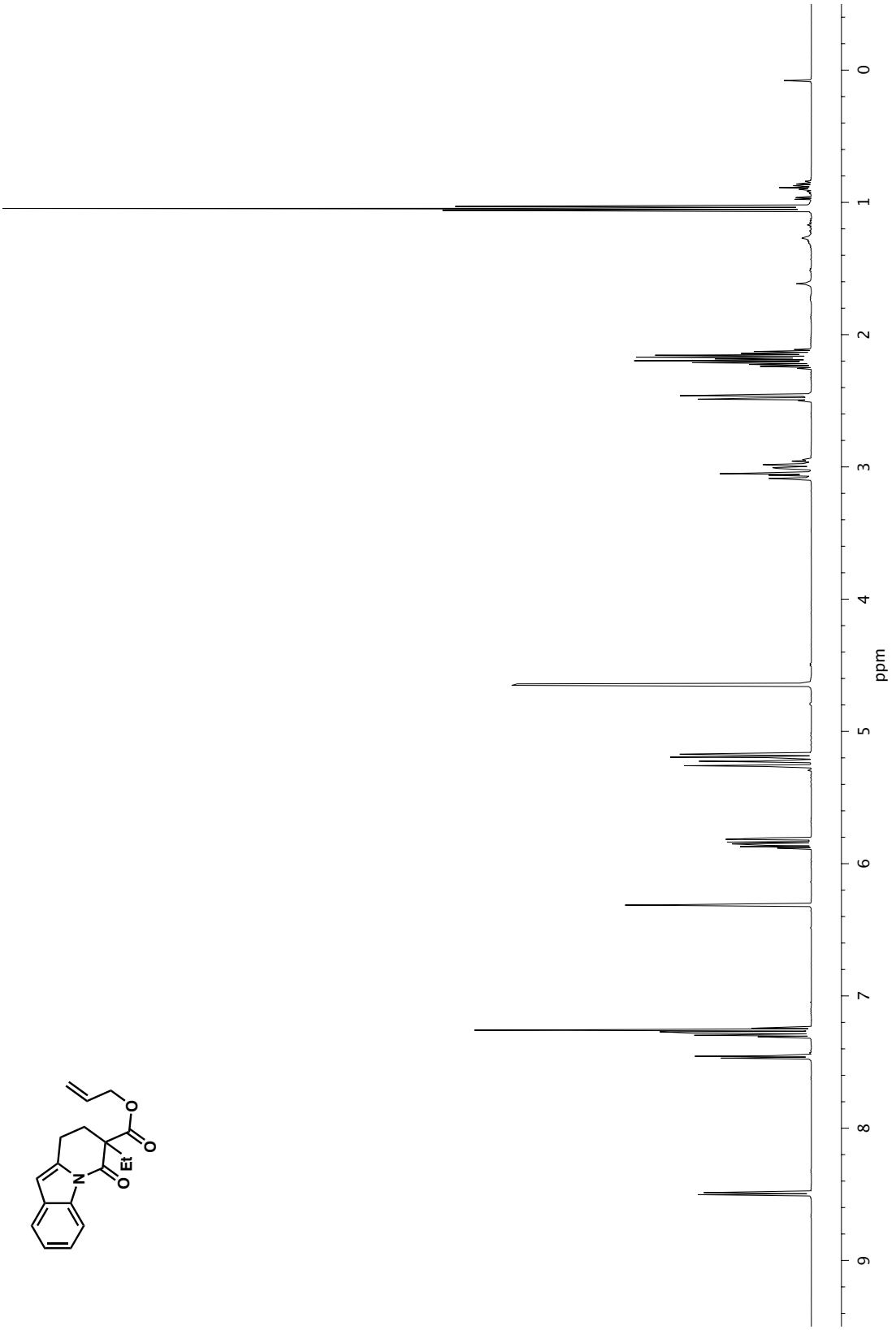


Figure A4.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172c**.

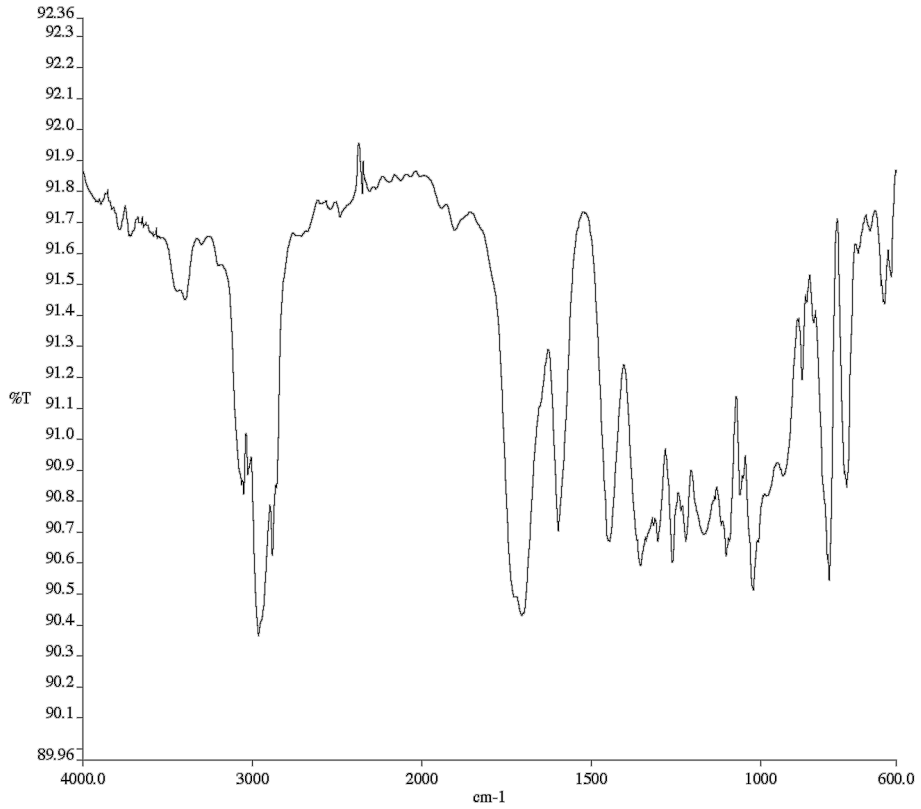


Figure A4.23. Infrared spectrum (Thin Film, NaCl) of compound **172c.**

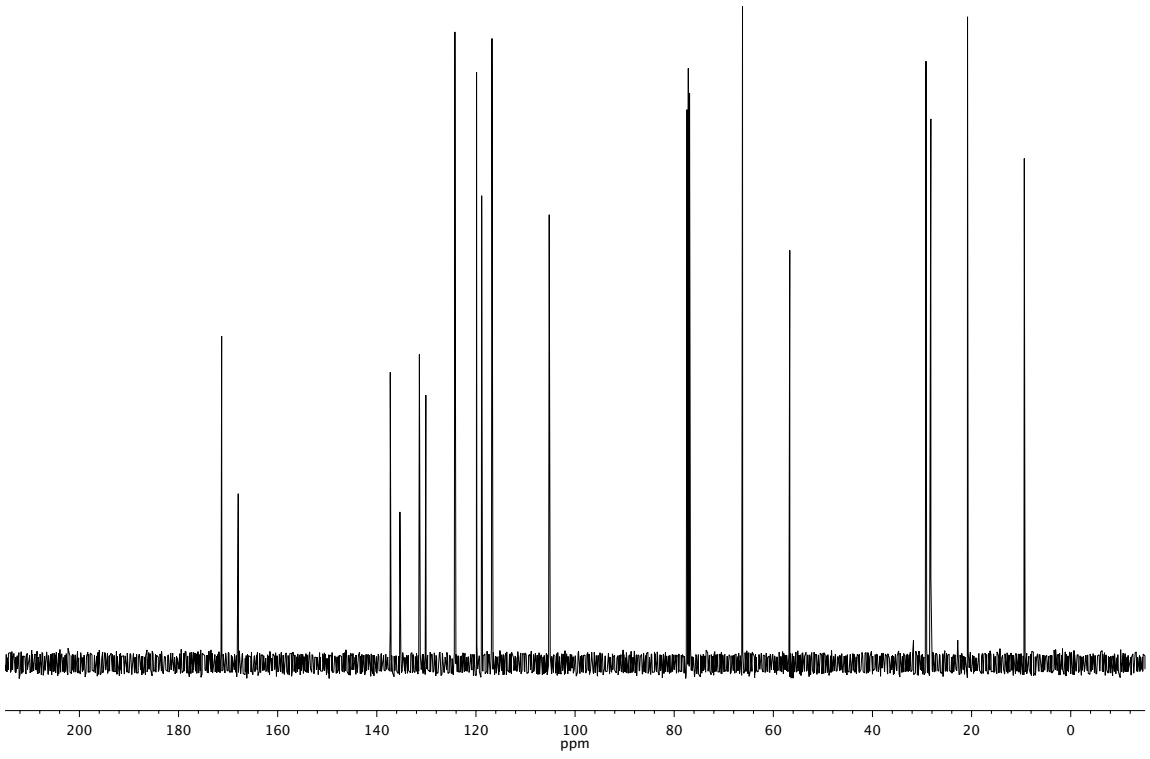


Figure A4.24. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172c**.

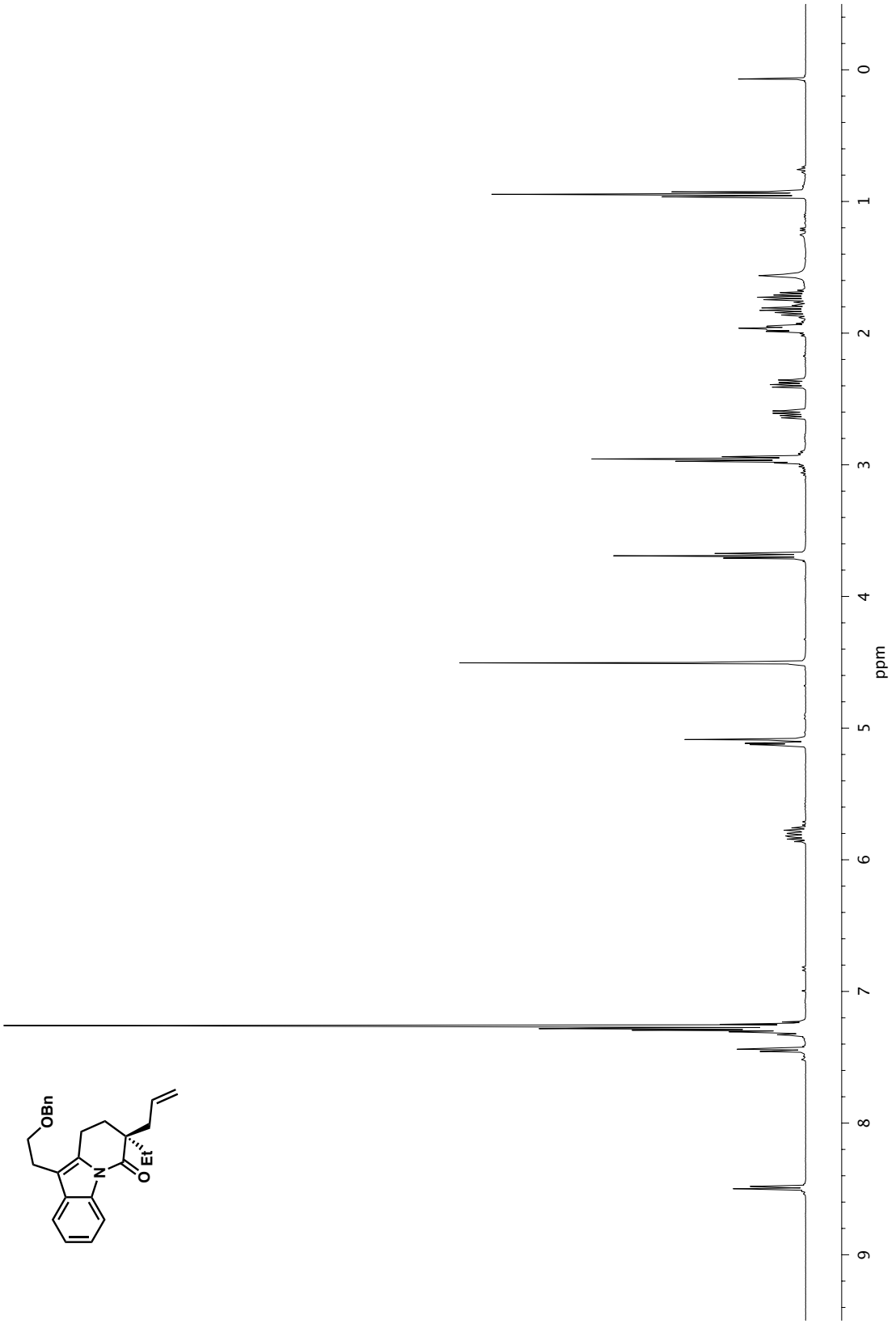


Figure A4.25. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **165a**.

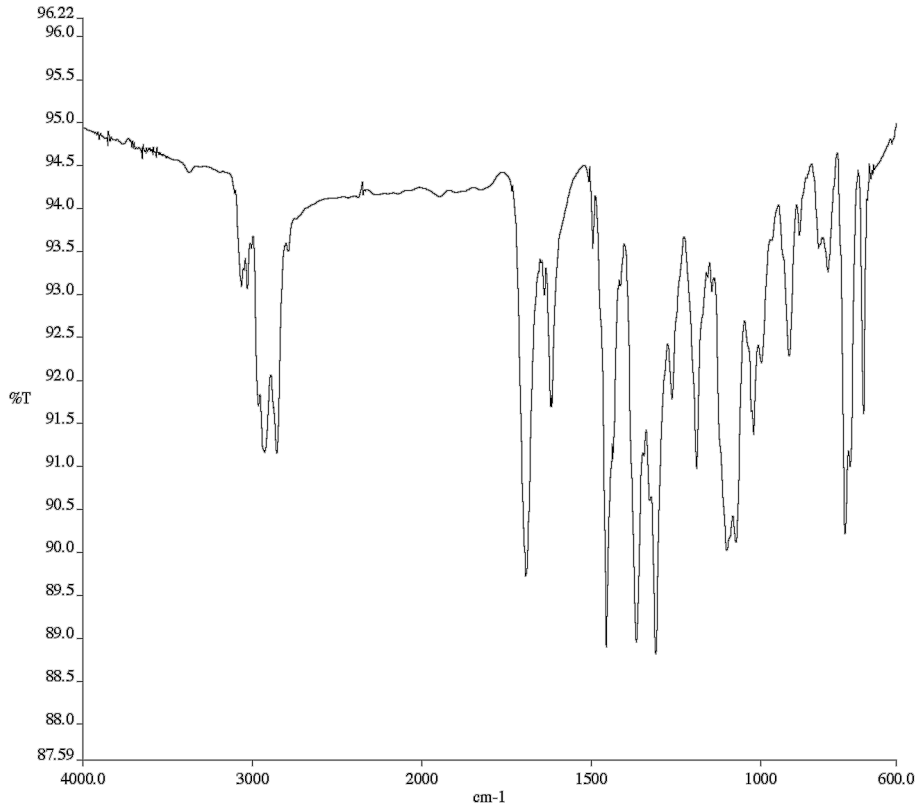


Figure A4.26. Infrared spectrum (Thin Film, NaCl) of compound **165a.**

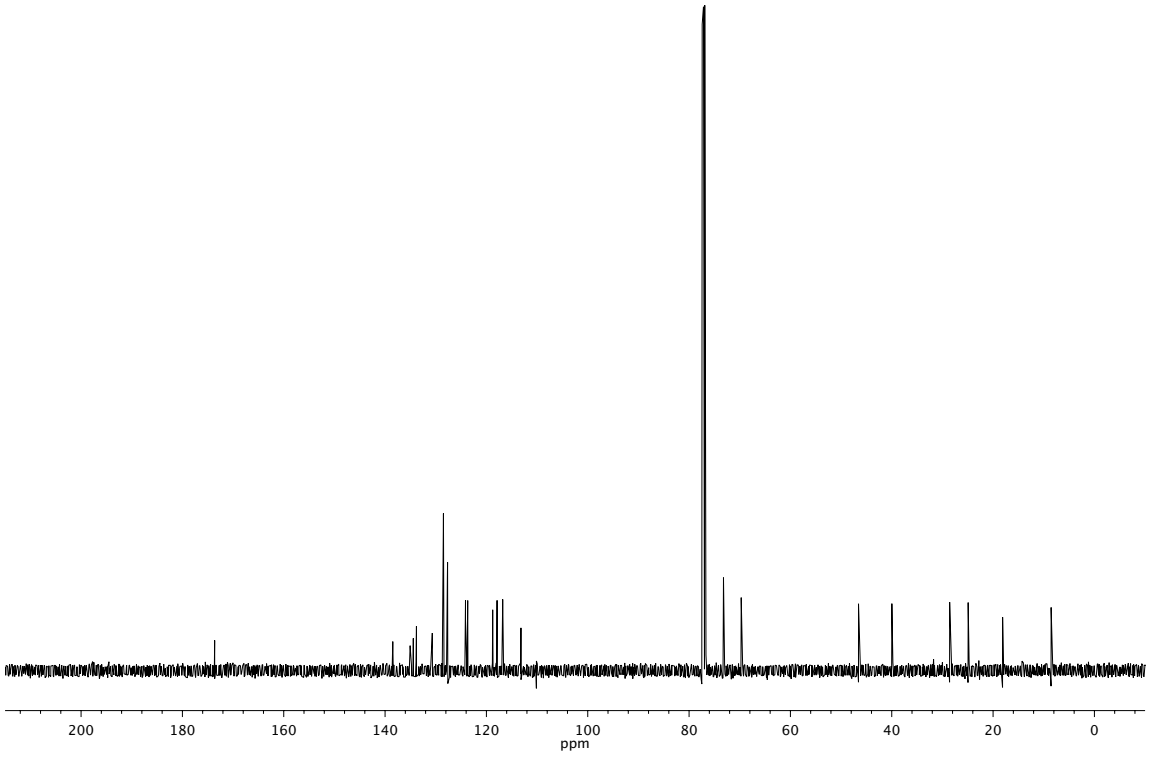


Figure A4.27. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165a**.

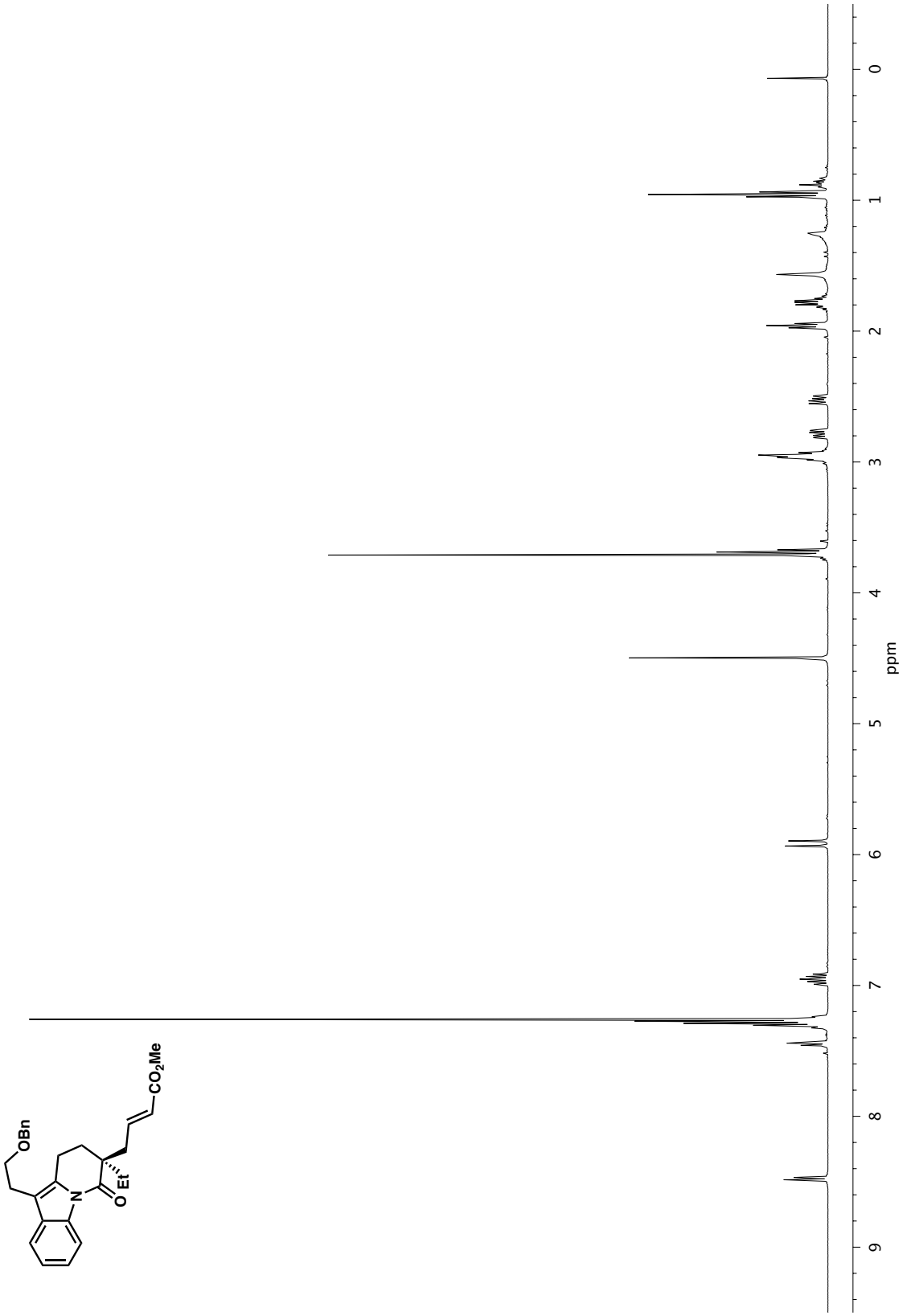


Figure A4.28. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **180**.

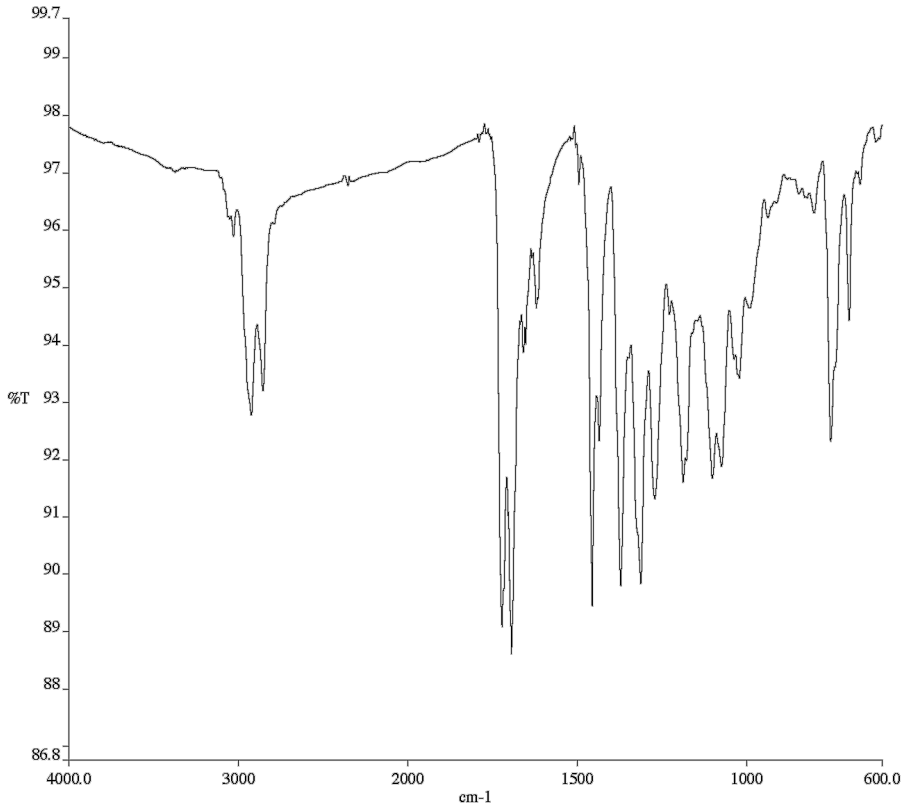


Figure A4.29. Infrared spectrum (Thin Film, NaCl) of compound **180.**

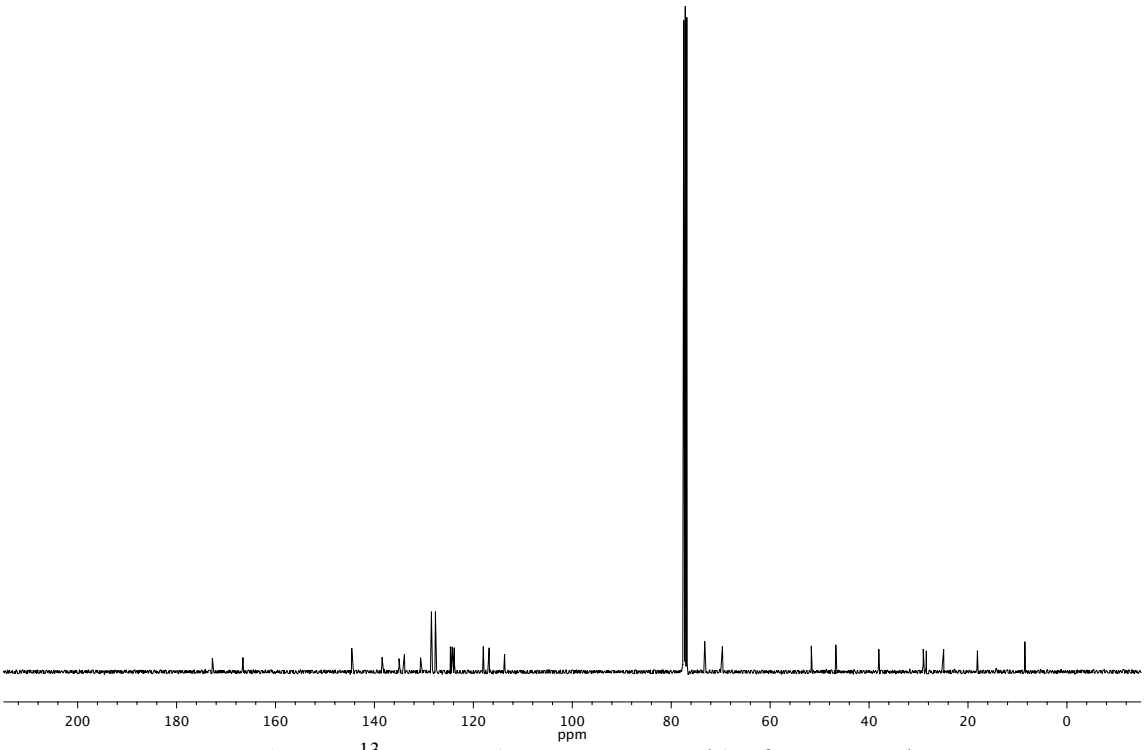


Figure A4.30. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **180**.

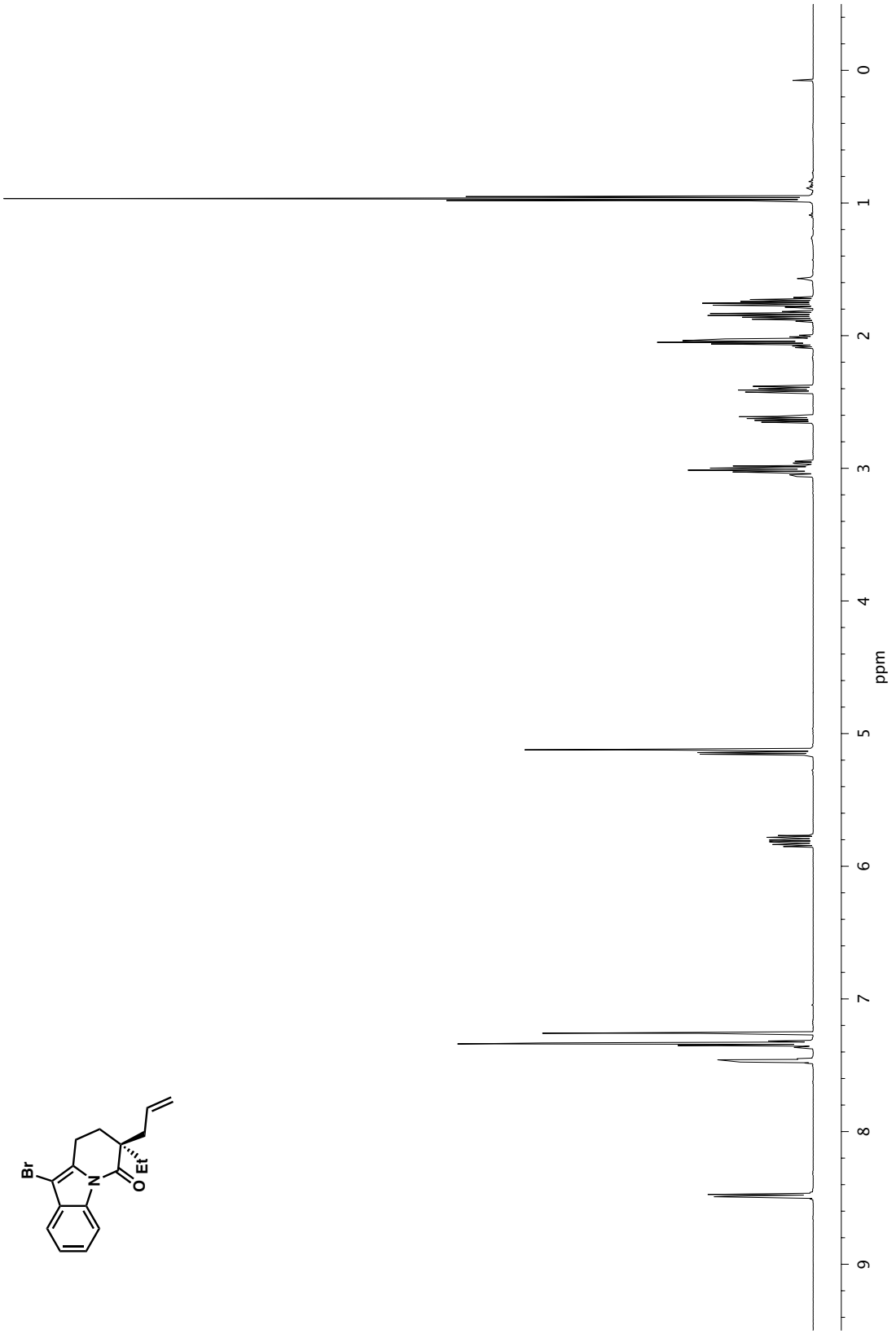


Figure A4.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165b**.

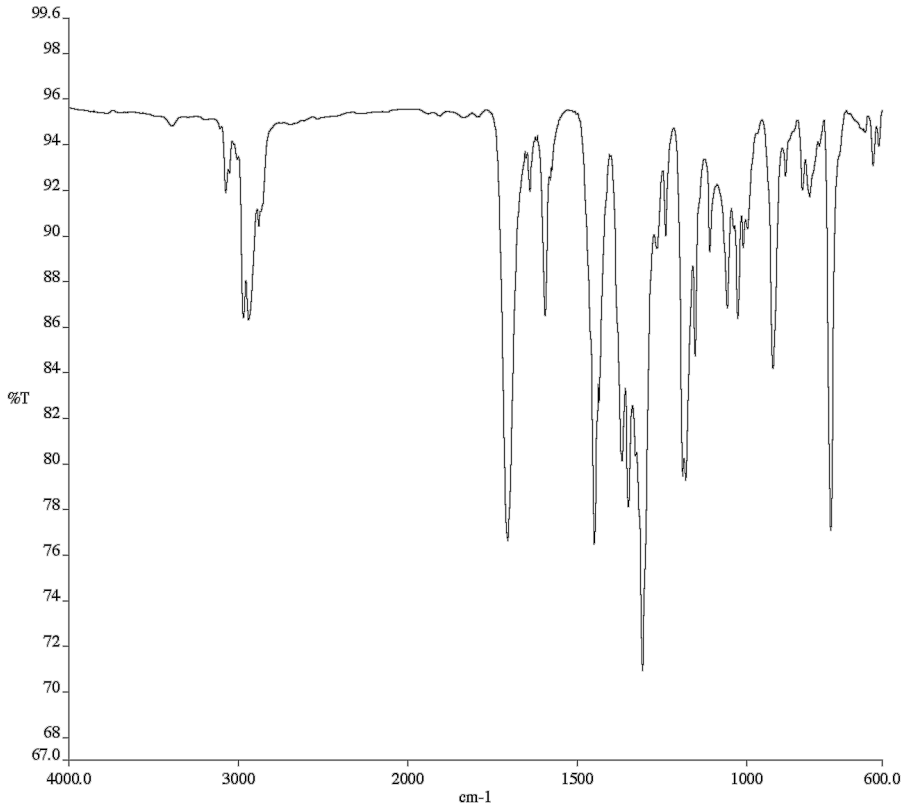


Figure A4.32. Infrared spectrum (Thin Film, NaCl) of compound **165b.**

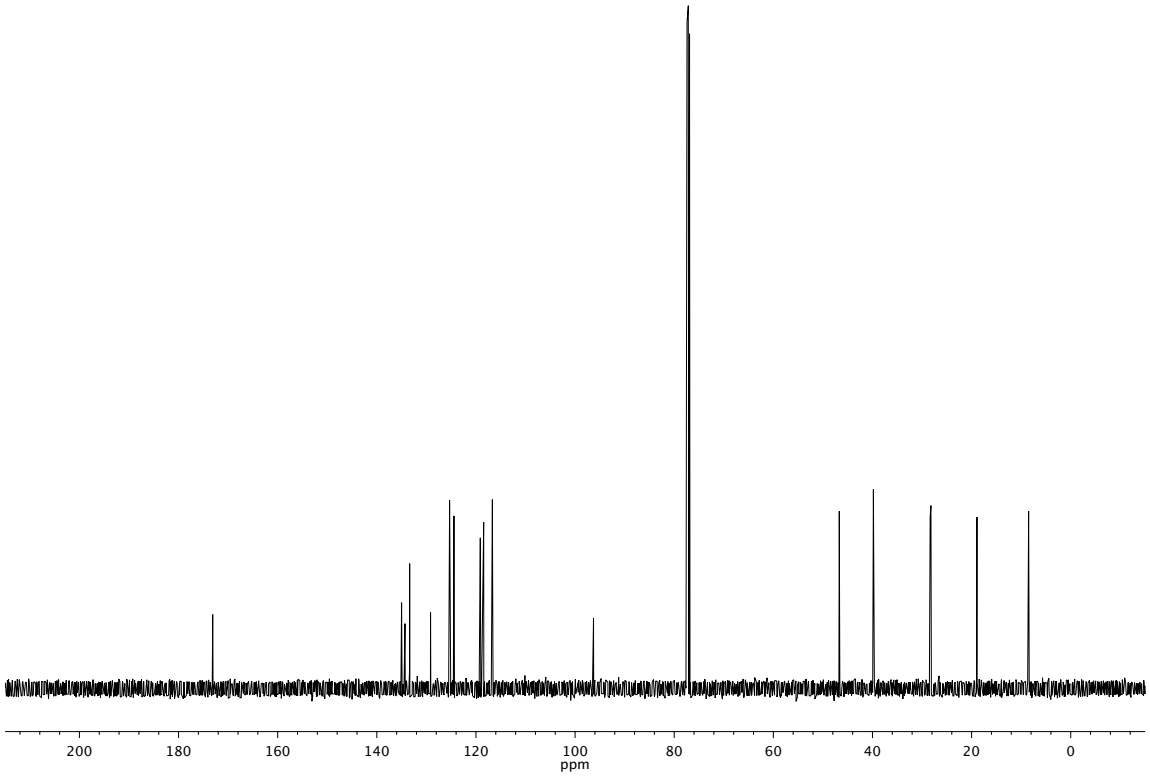


Figure A4.33. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165b**.

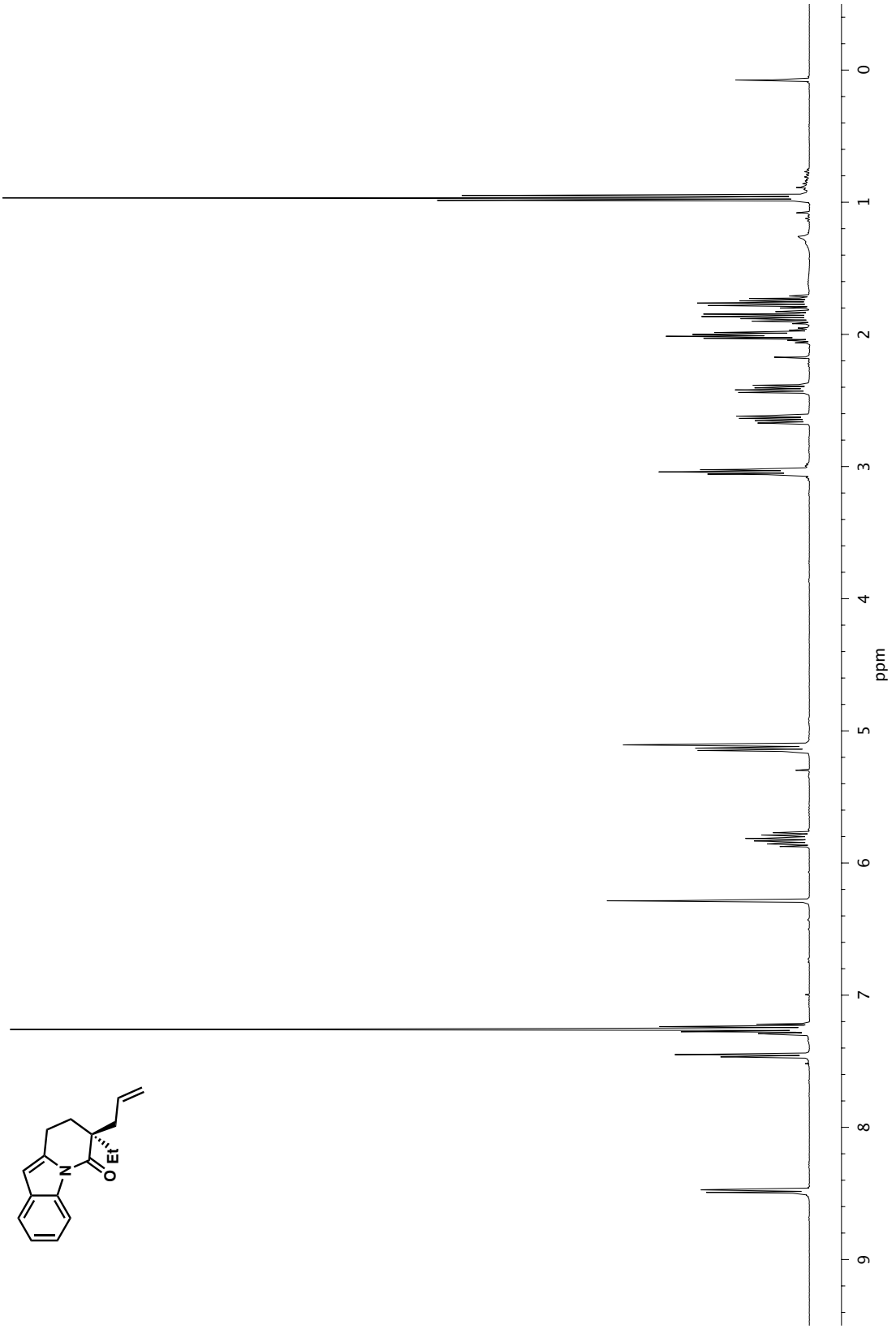


Figure A4.34. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **165c**.

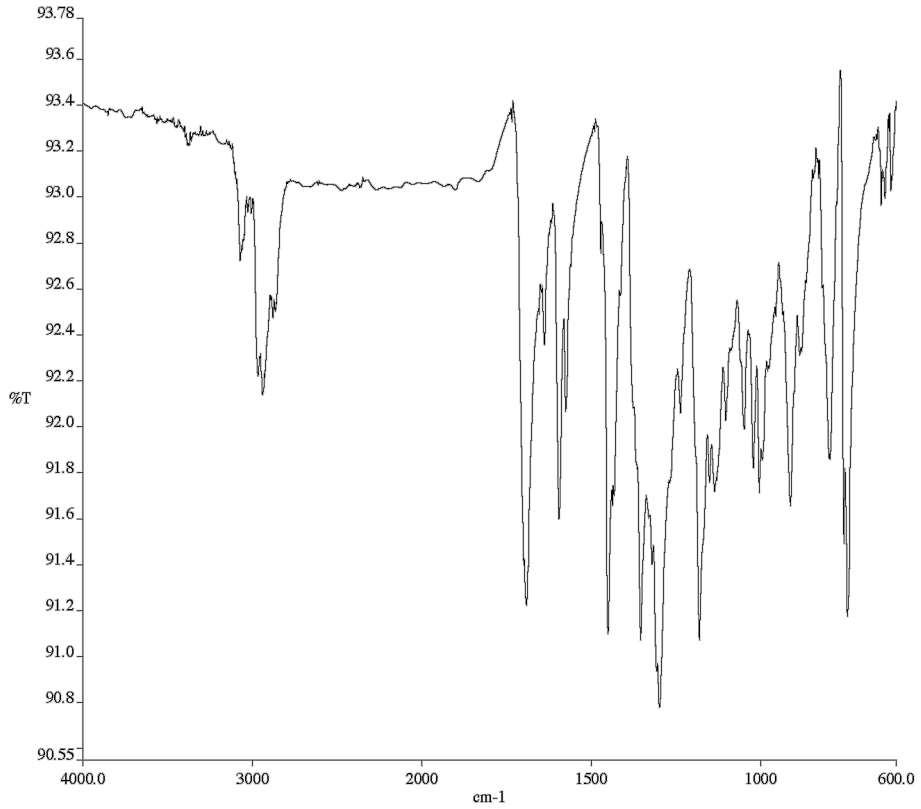


Figure A4.35. Infrared spectrum (Thin Film, NaCl) of compound **165c.**

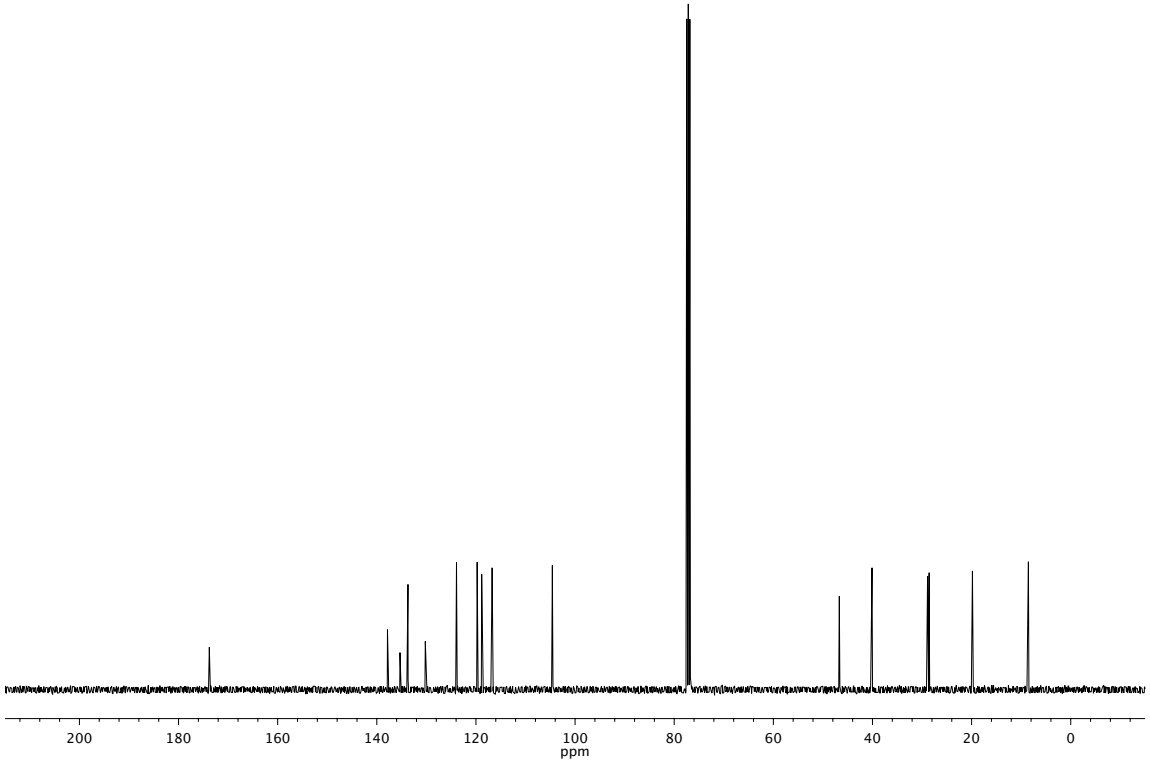


Figure A4.36. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **165c**.

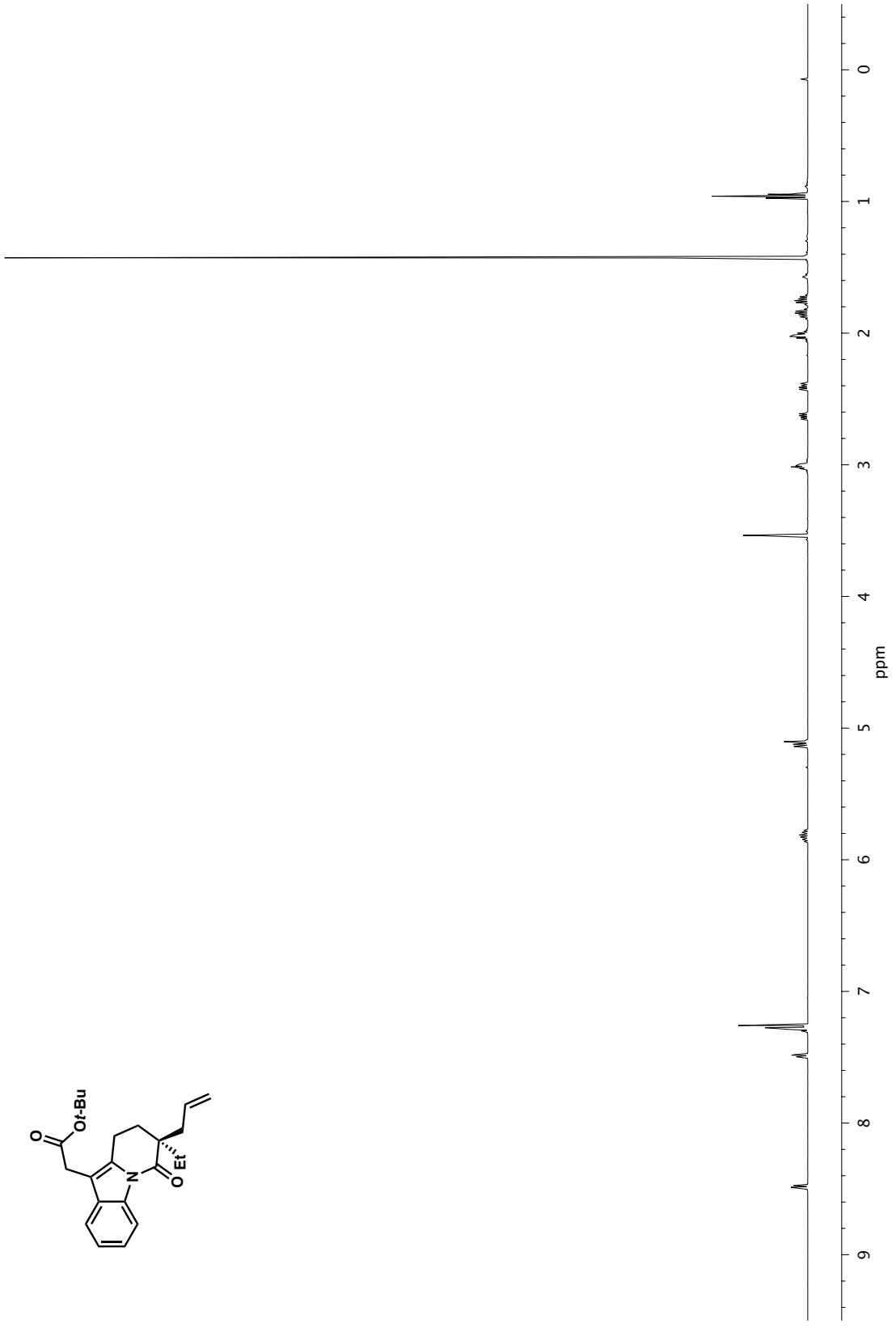


Figure A4.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **174**.

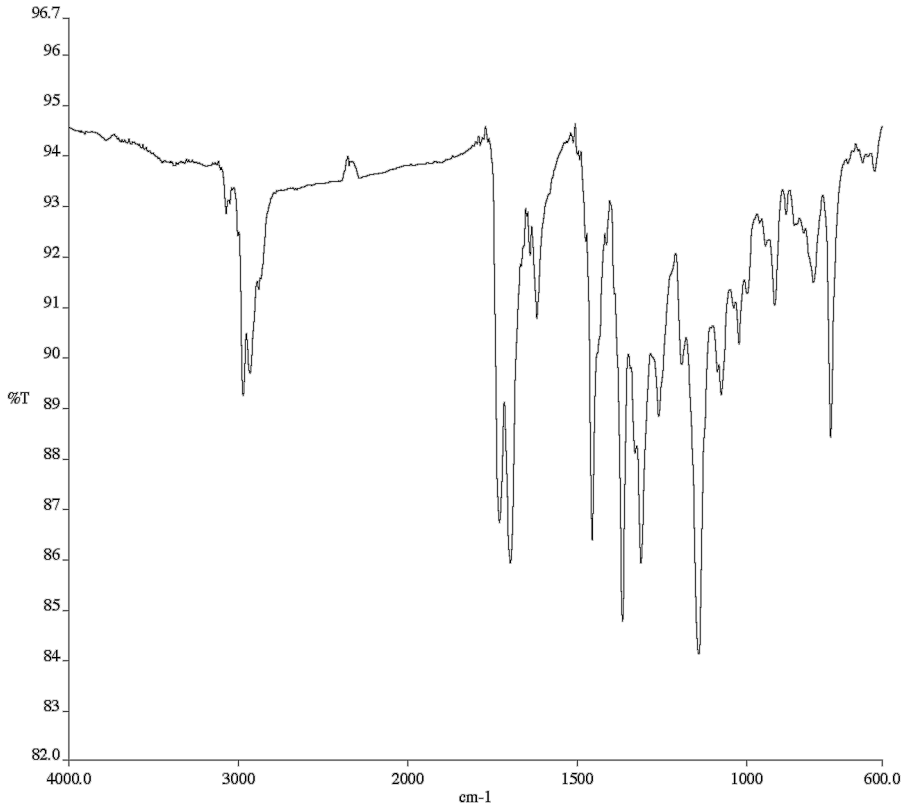


Figure A4.38. Infrared spectrum (Thin Film, NaCl) of compound **174.**

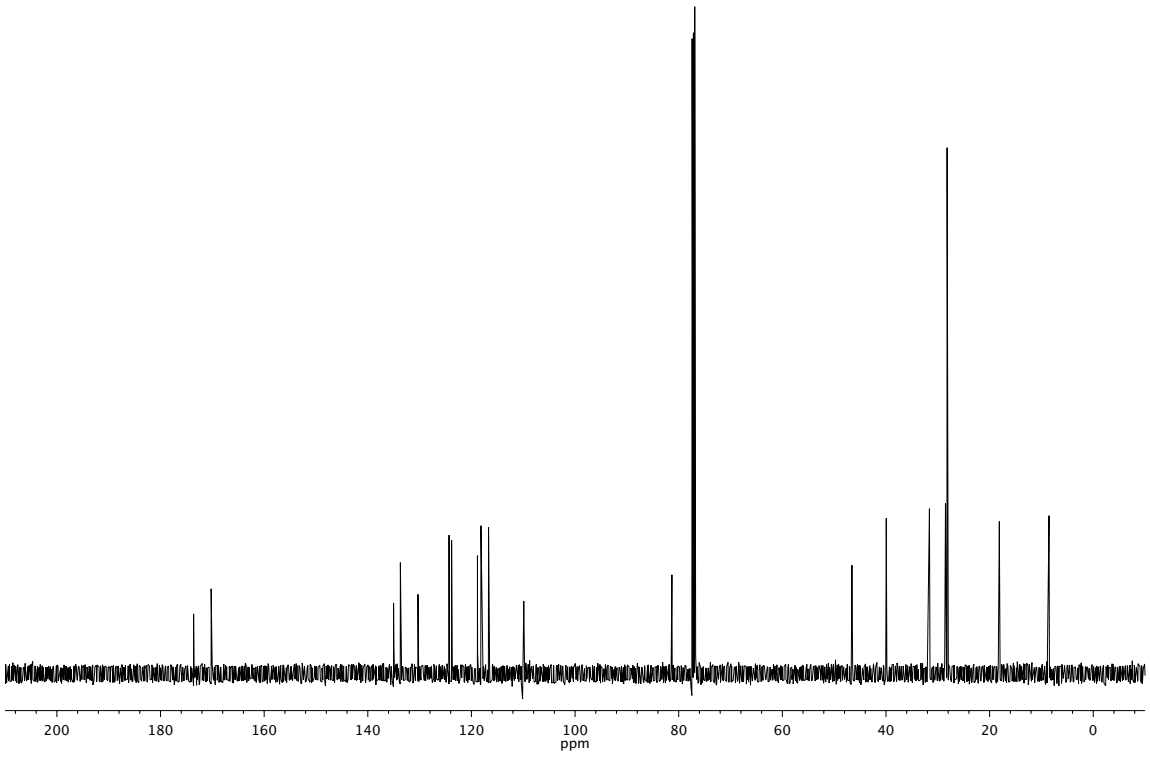


Figure A4.39. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **174**.

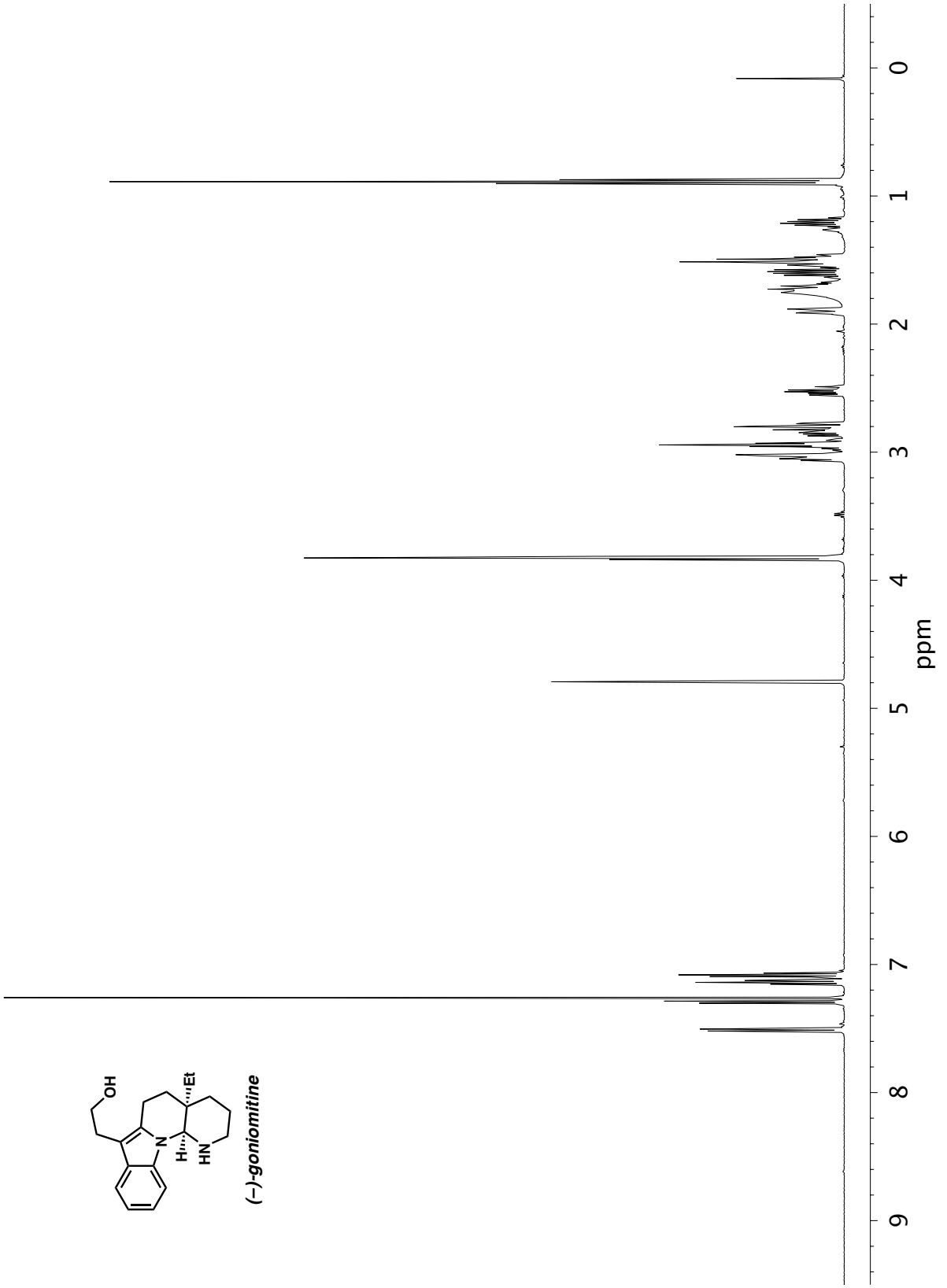


Figure A4.40. ^{1}H NMR (500 MHz, $CDCl_3$) of (–)-goniomitine (**3**).

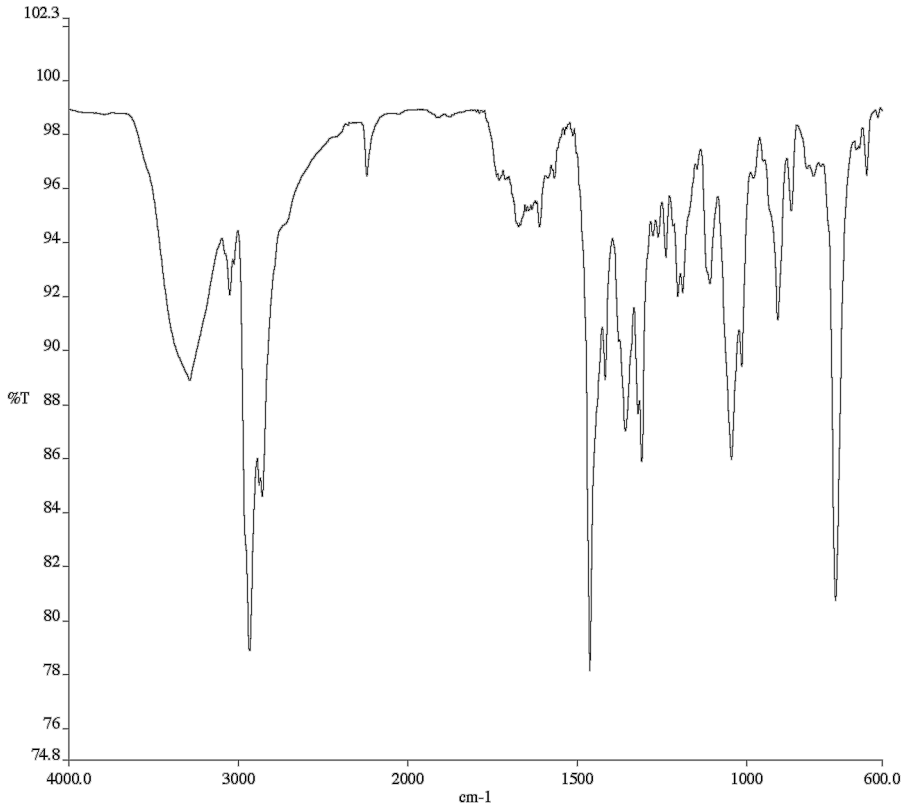


Figure A4.41. Infrared spectrum (Thin Film, NaCl) of (–)-goniomitine (**3**).

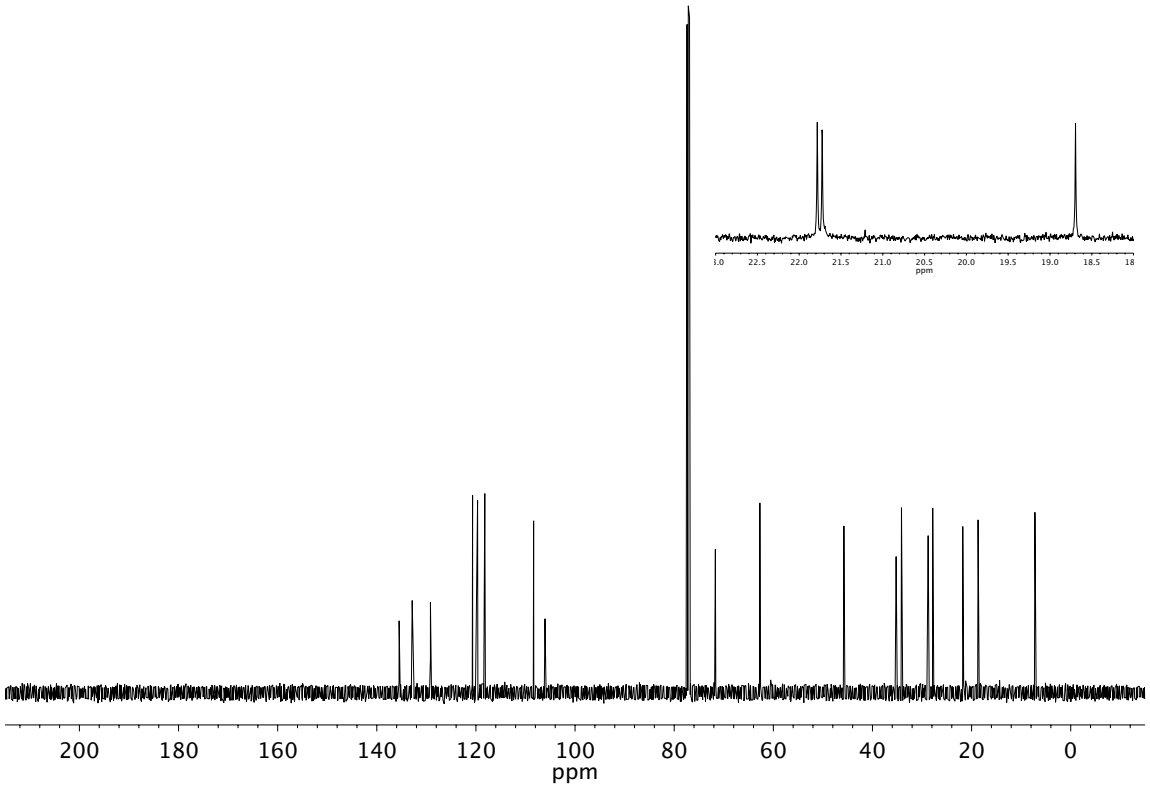


Figure A4.42. ^{13}C NMR (126 MHz, $CDCl_3$) of (–)-goniomitine (**3**).

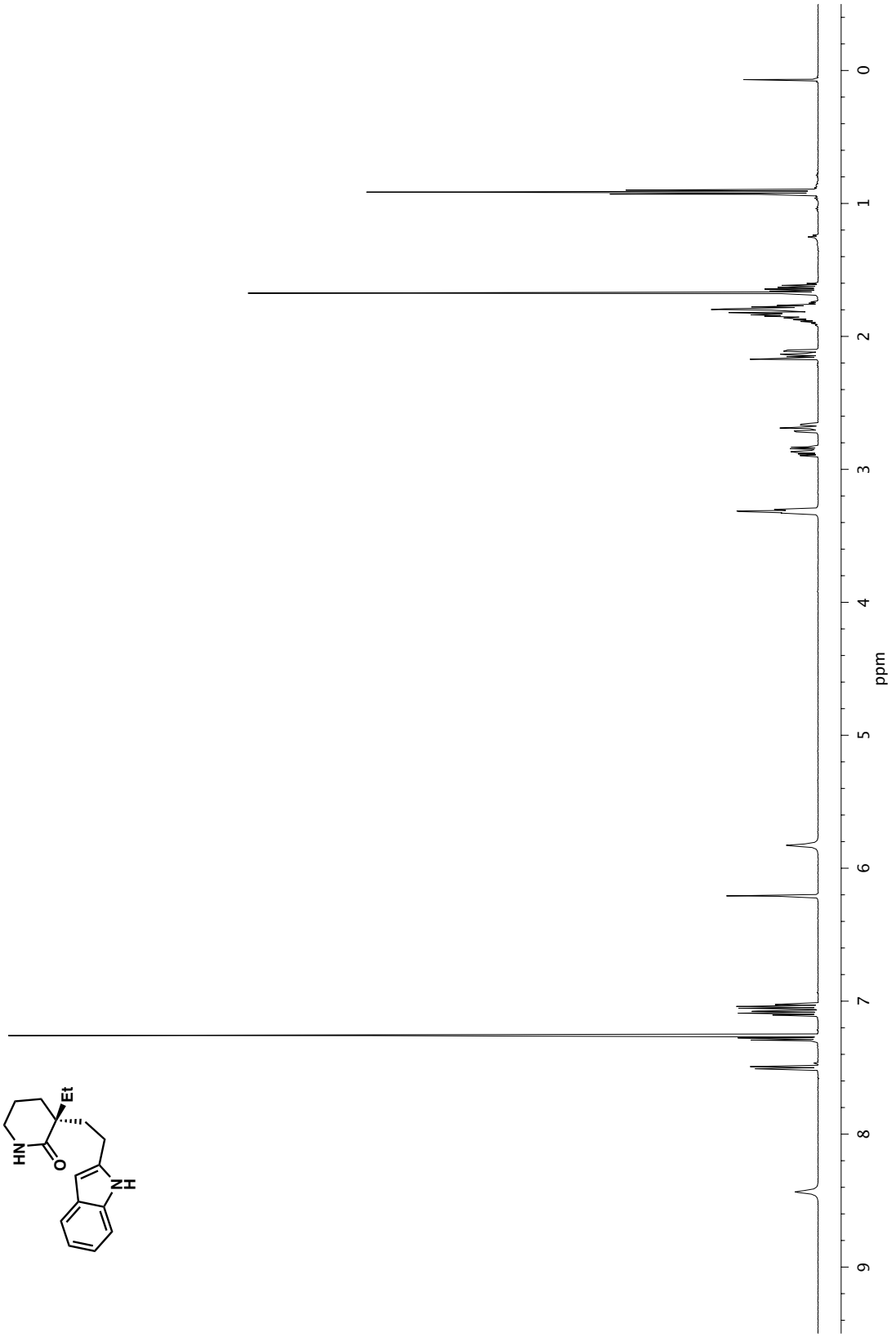


Figure A4.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compounds **176**.

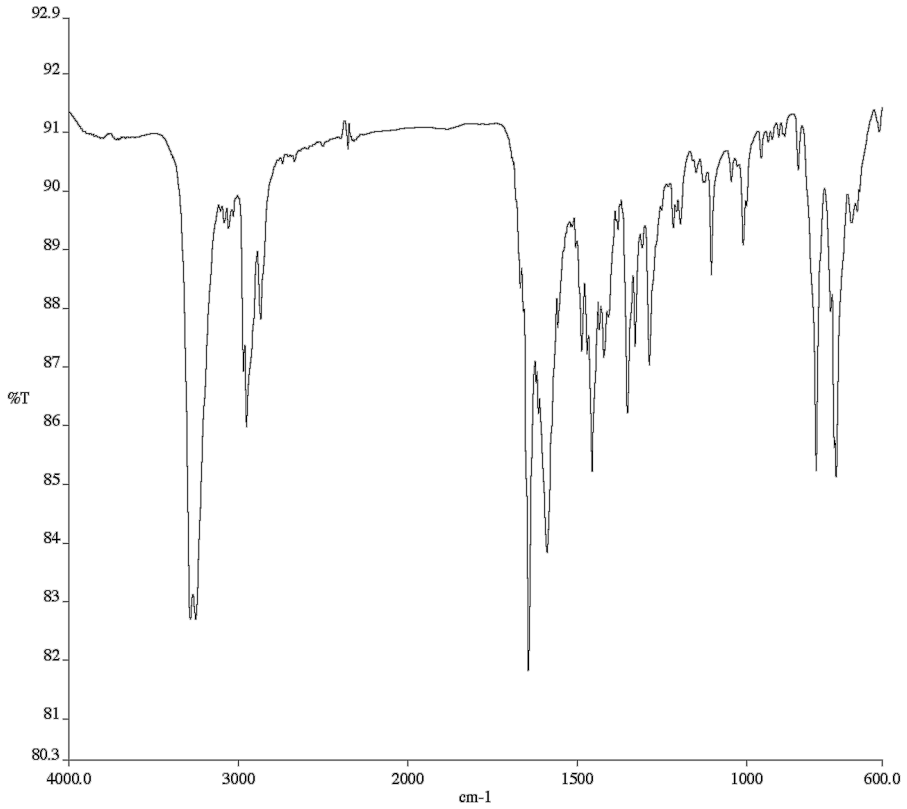


Figure A4.44. Infrared spectrum (Thin Film, NaCl) of compound **176.**

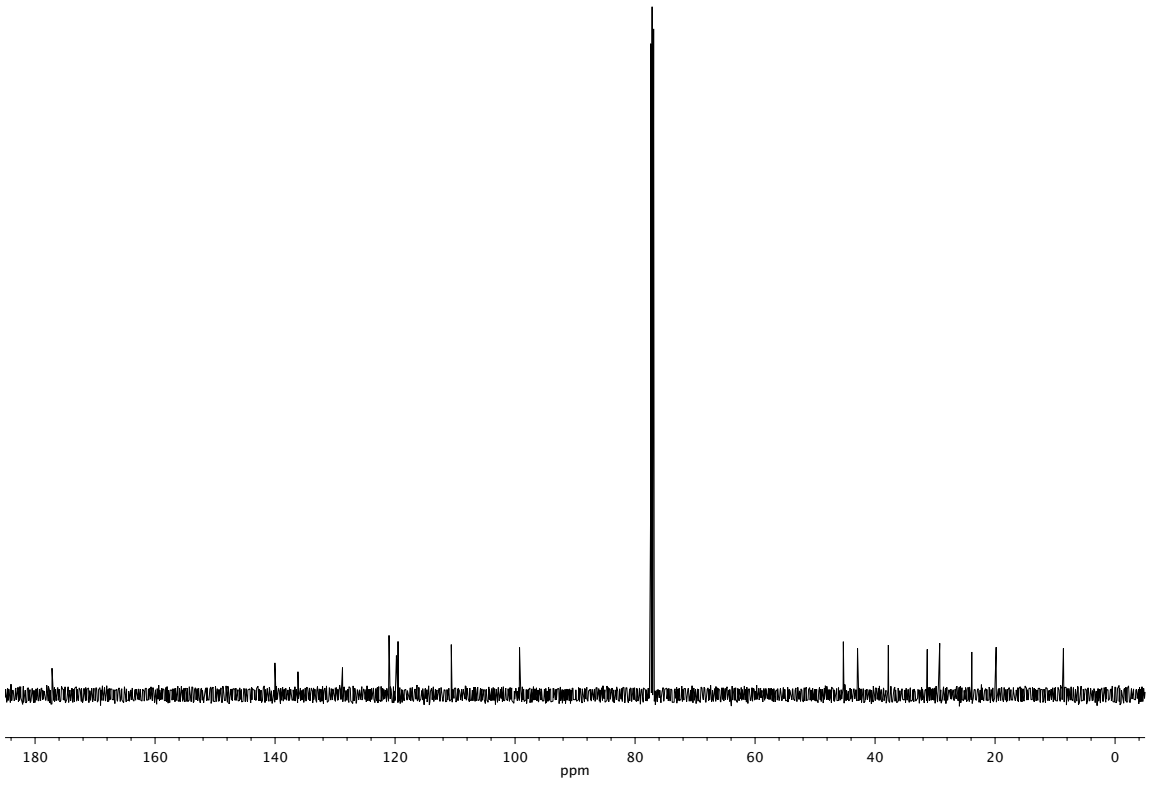


Figure A4.45. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **176**.

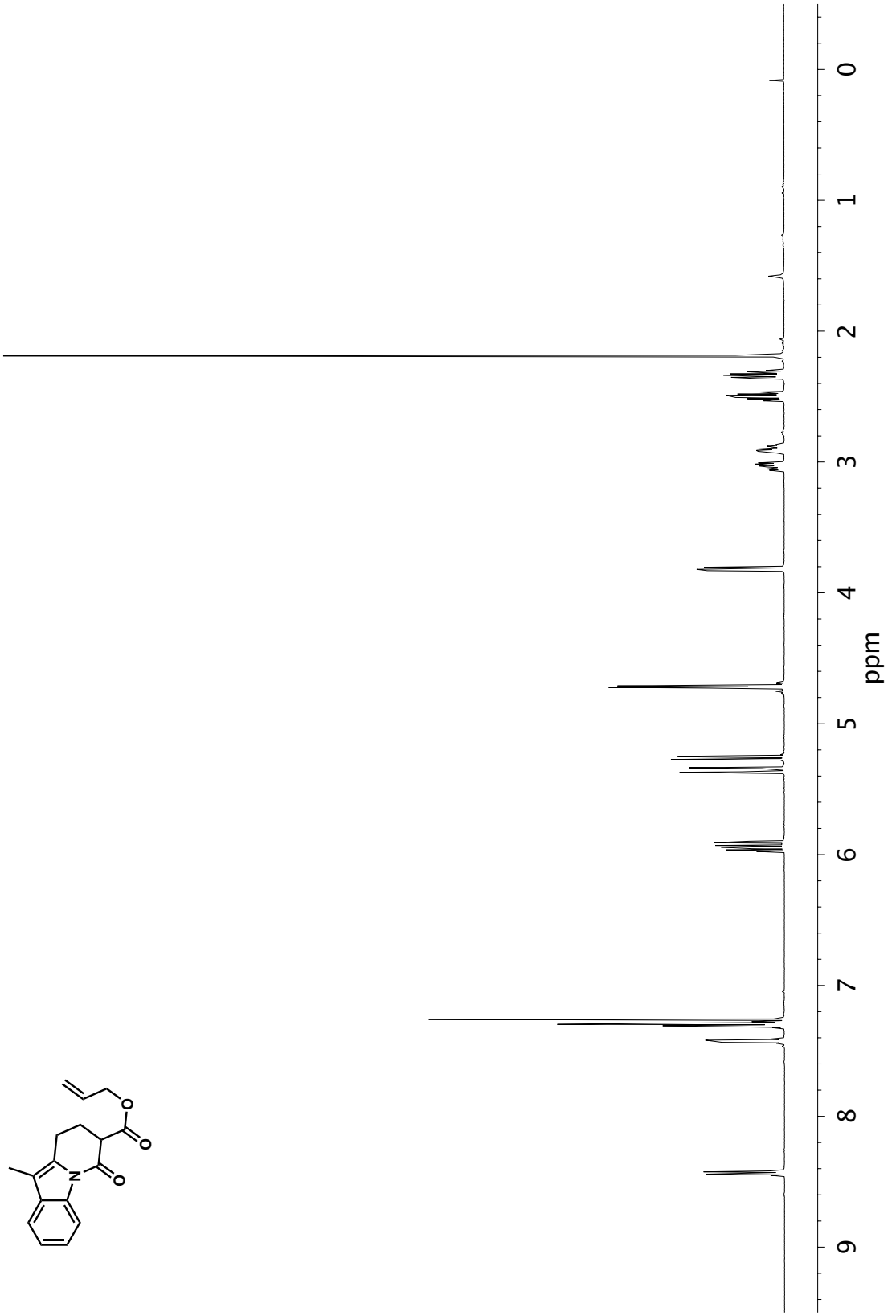


Figure A4.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **194**.

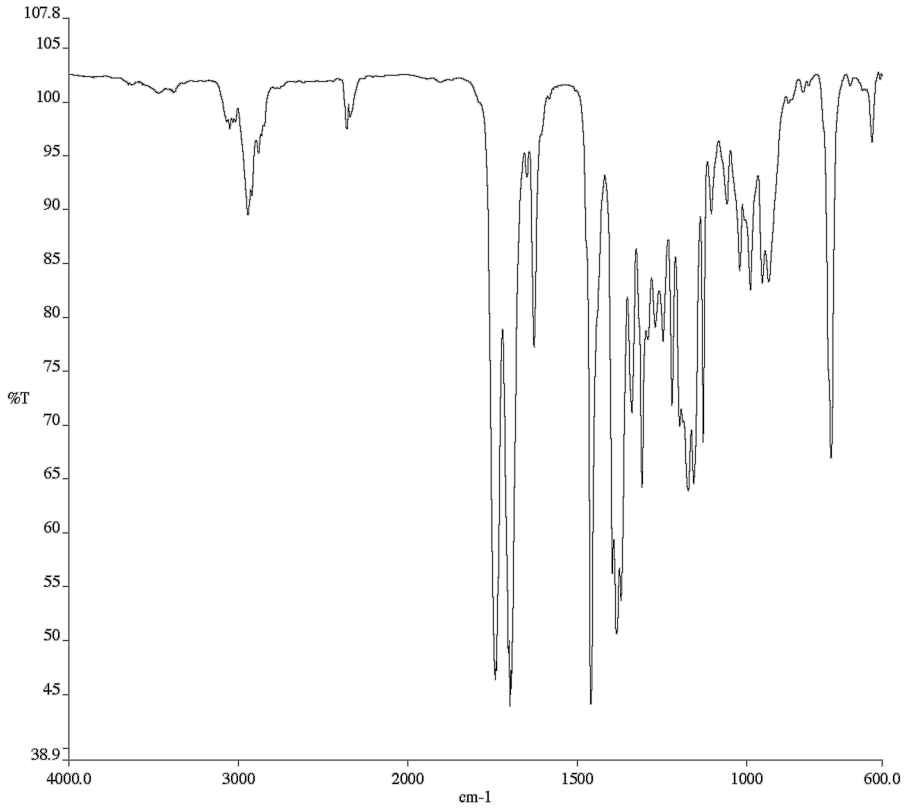


Figure A4.47. Infrared spectrum (Thin Film, NaCl) of compound **194.**

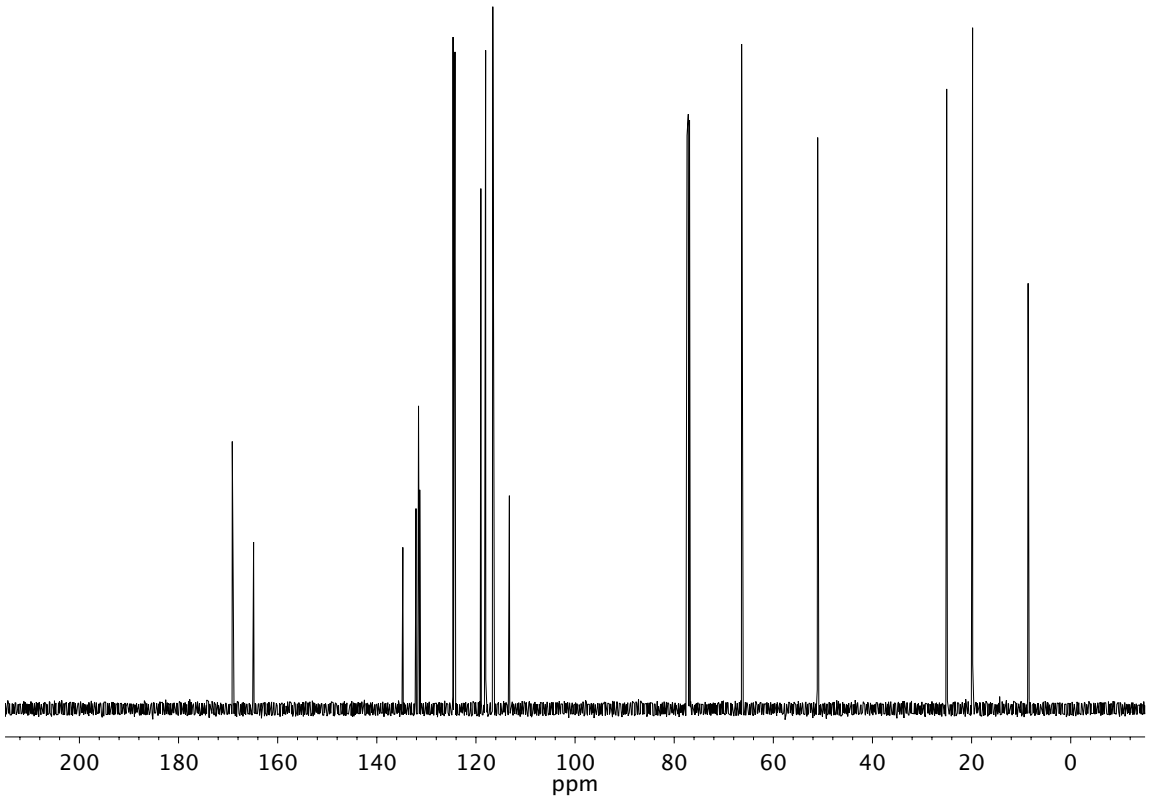


Figure A4.48. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **194**.

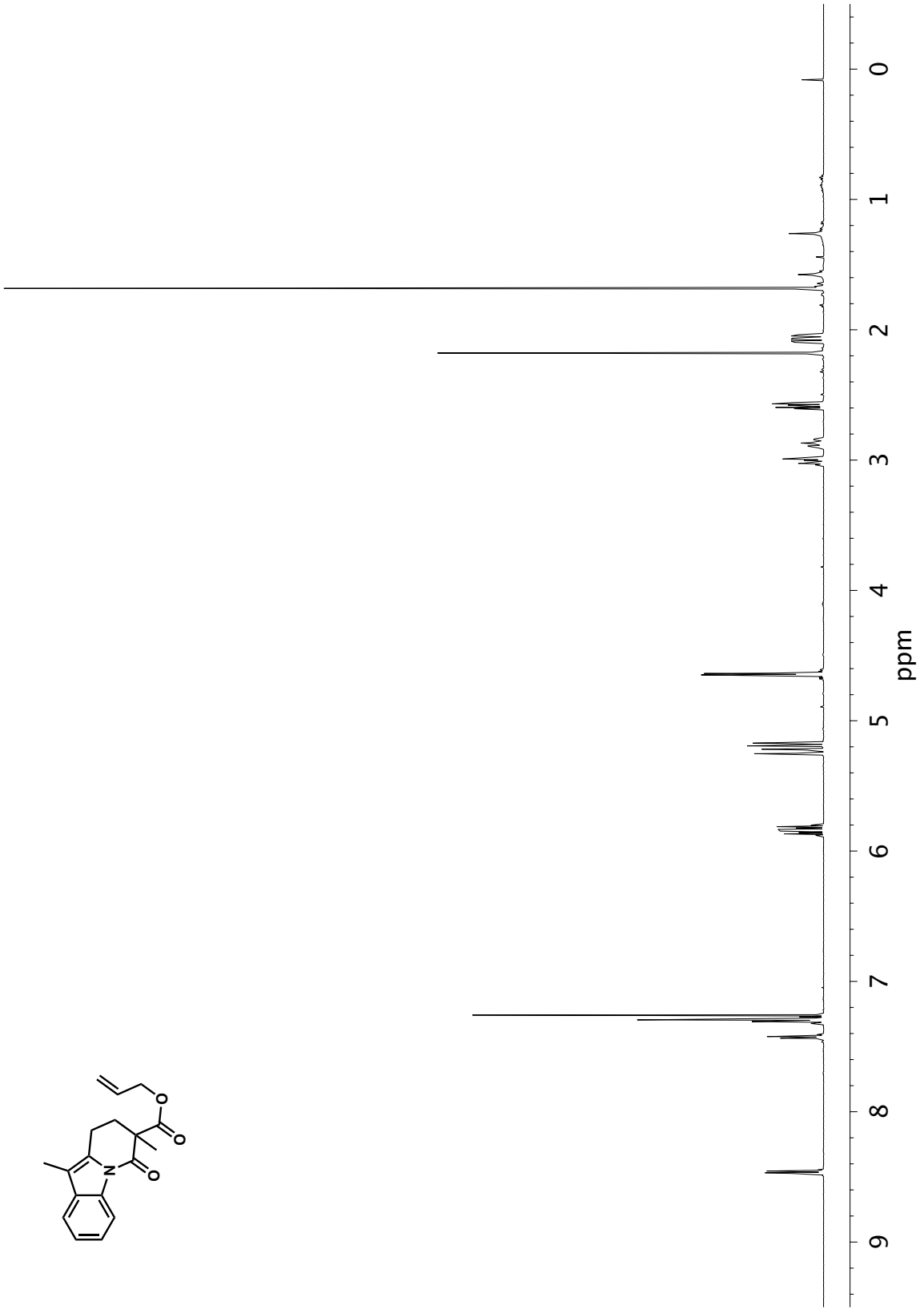


Figure A4.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172d**.

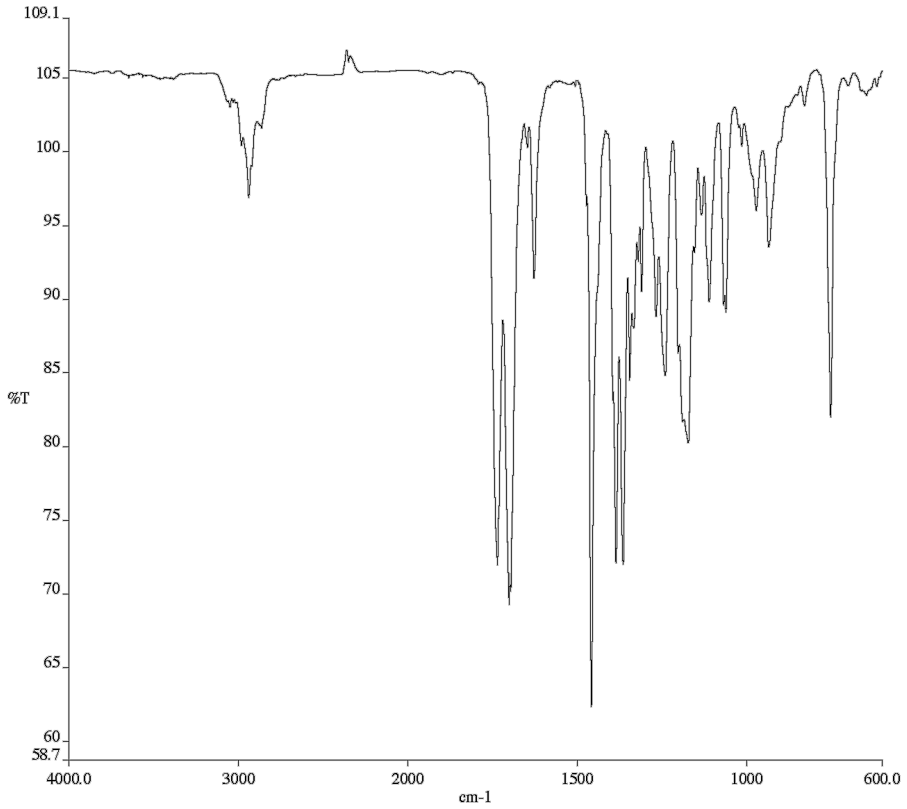


Figure A4.50. Infrared spectrum (Thin Film, NaCl) of compound **172d.**

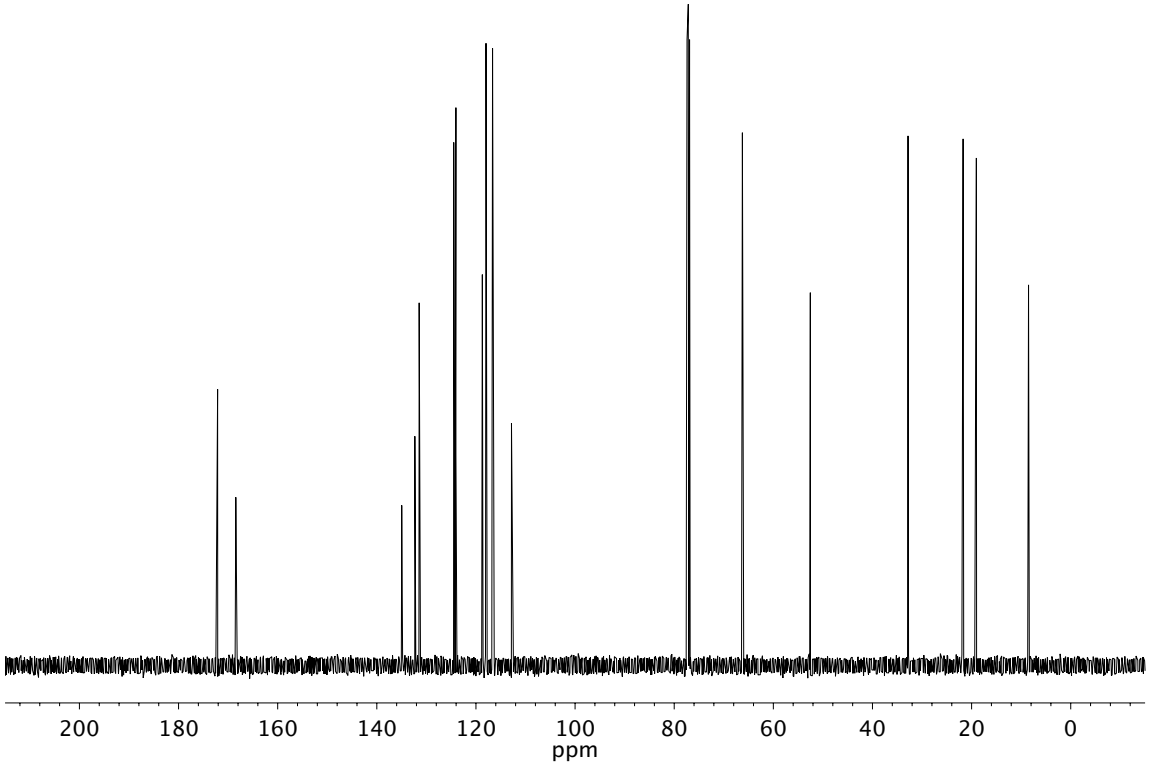


Figure A4.51. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172d**.

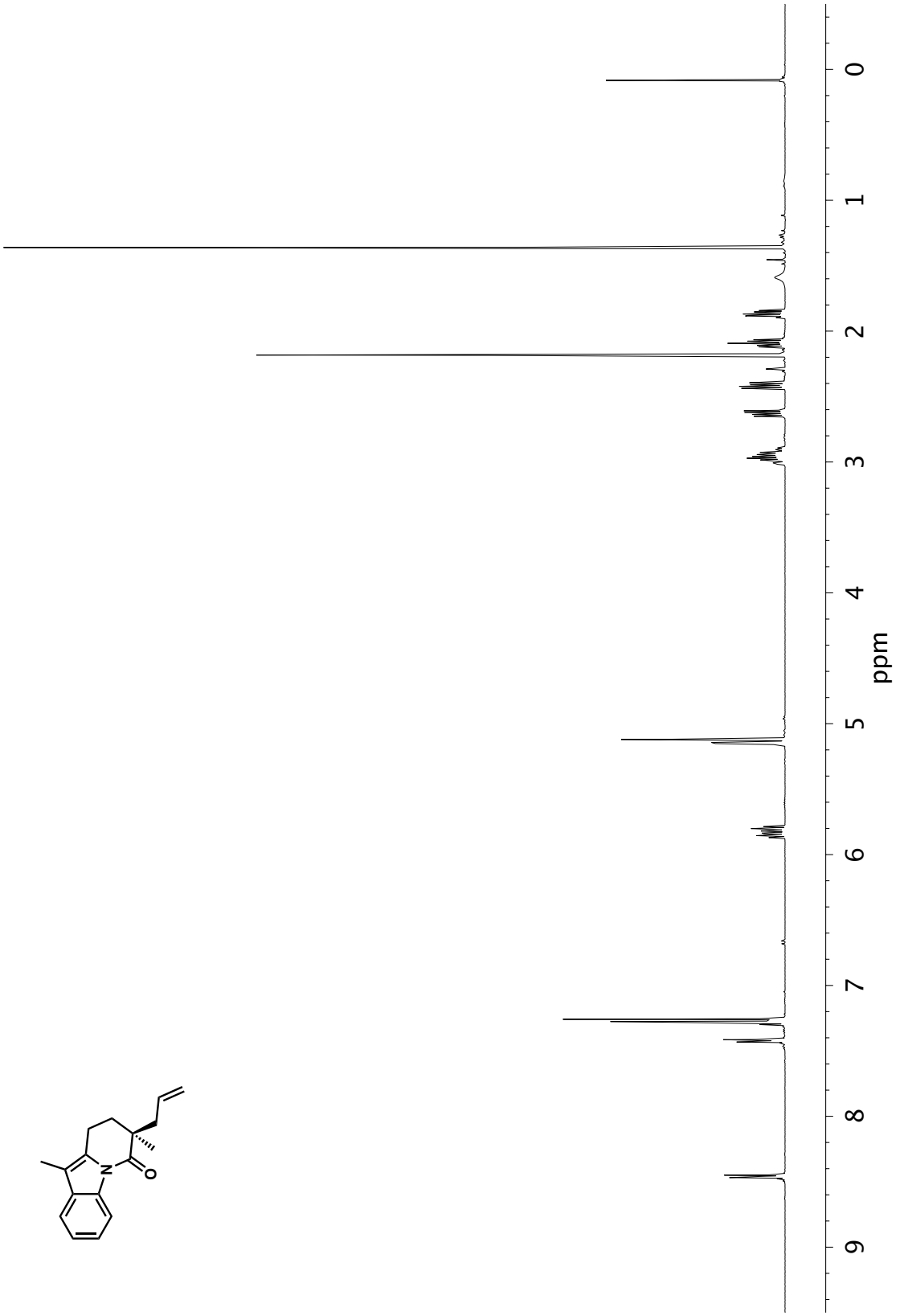


Figure A4.52. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165d**.

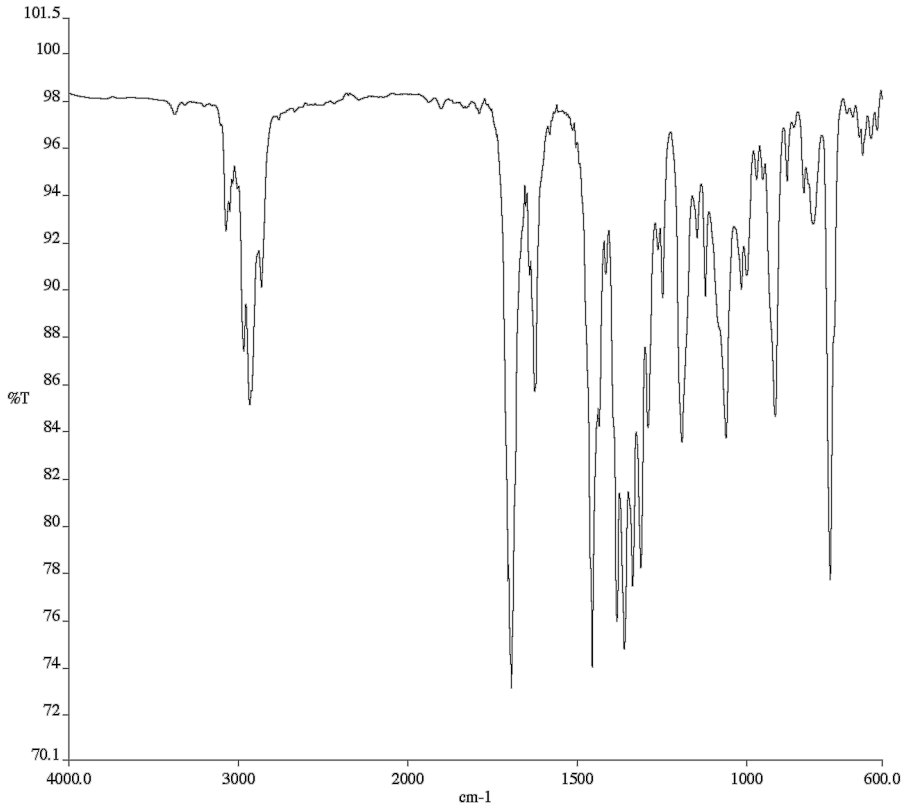


Figure A4.53. Infrared spectrum (Thin Film, NaCl) of compound **165d.**

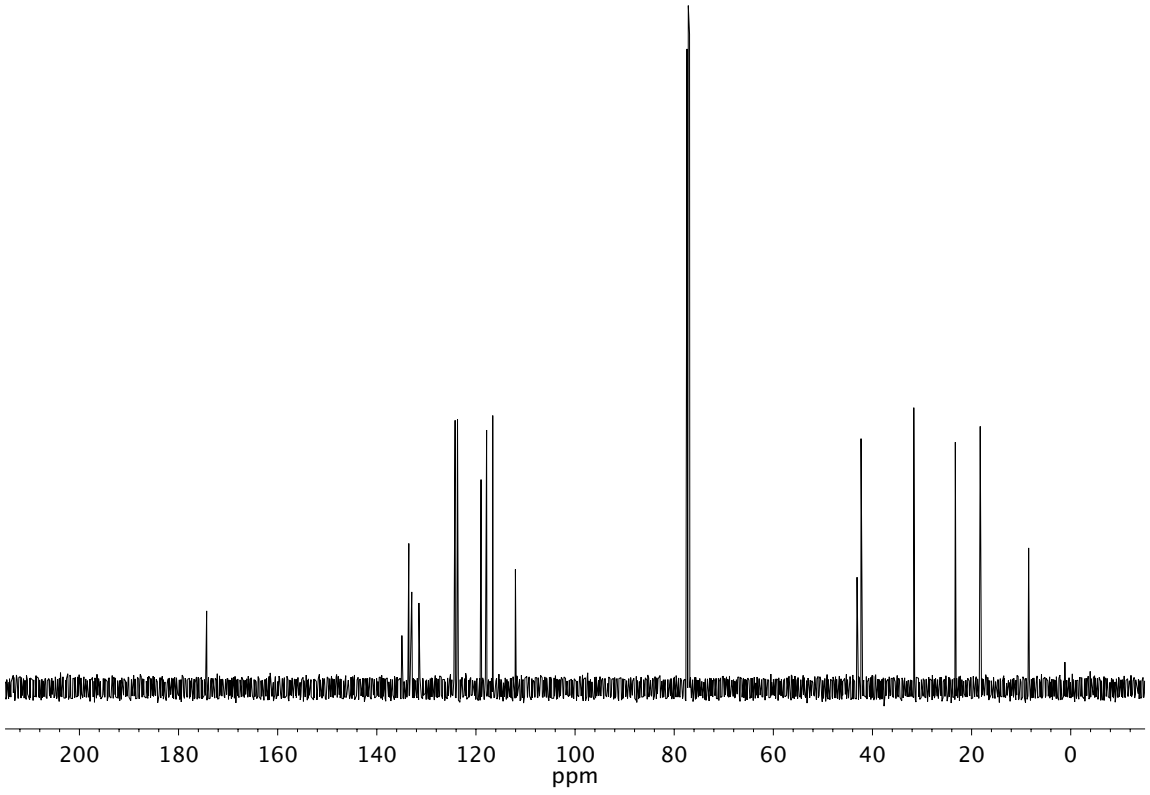


Figure A4.54. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165d**.

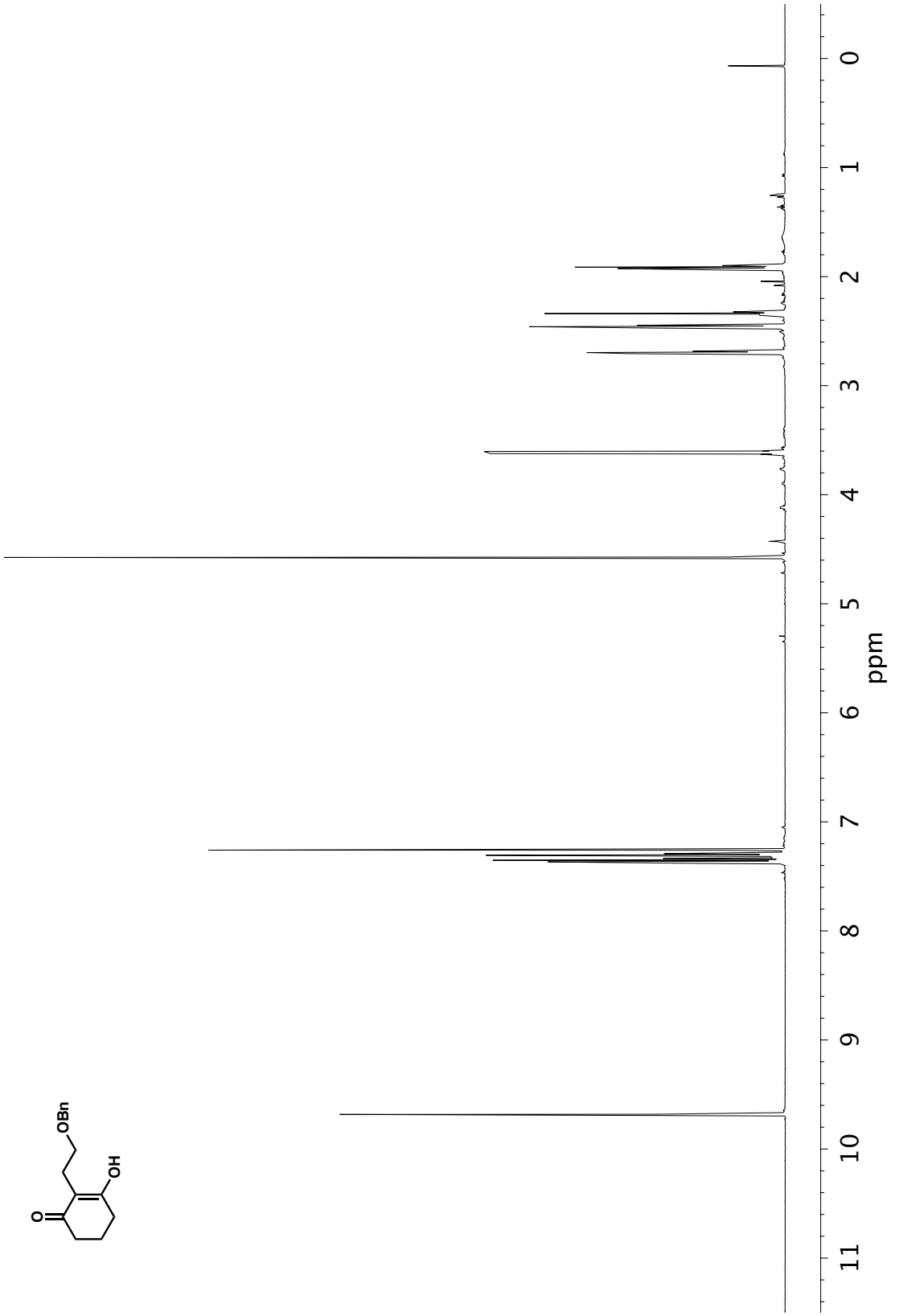


Figure A4.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound ***enol*-182**.

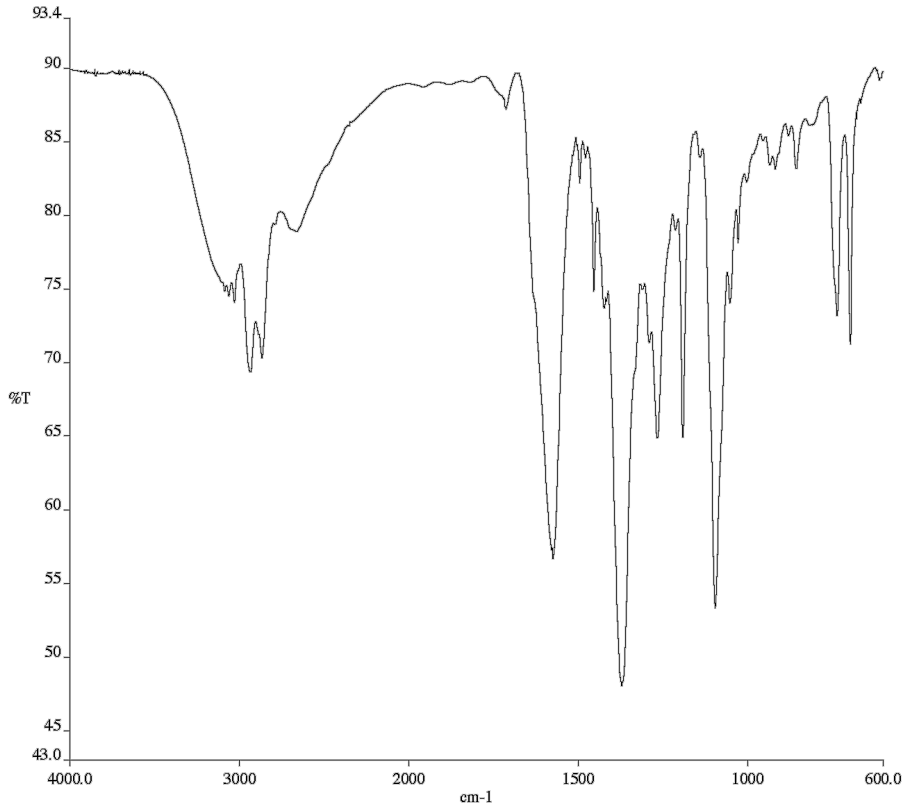


Figure A4.56. Infrared spectrum (Thin Film, NaCl) of compound ***enol*-182.**

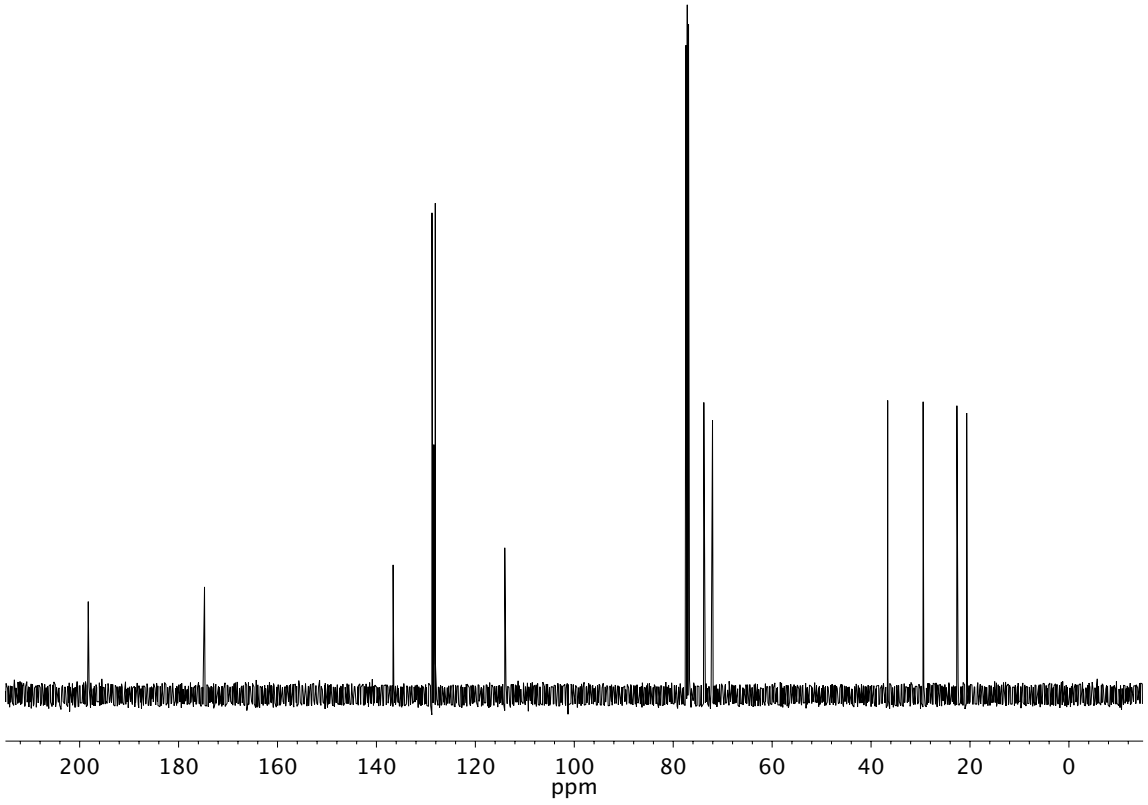


Figure A4.57. ^{13}C NMR (126 MHz, $CDCl_3$) of compound ***enol*-182**.

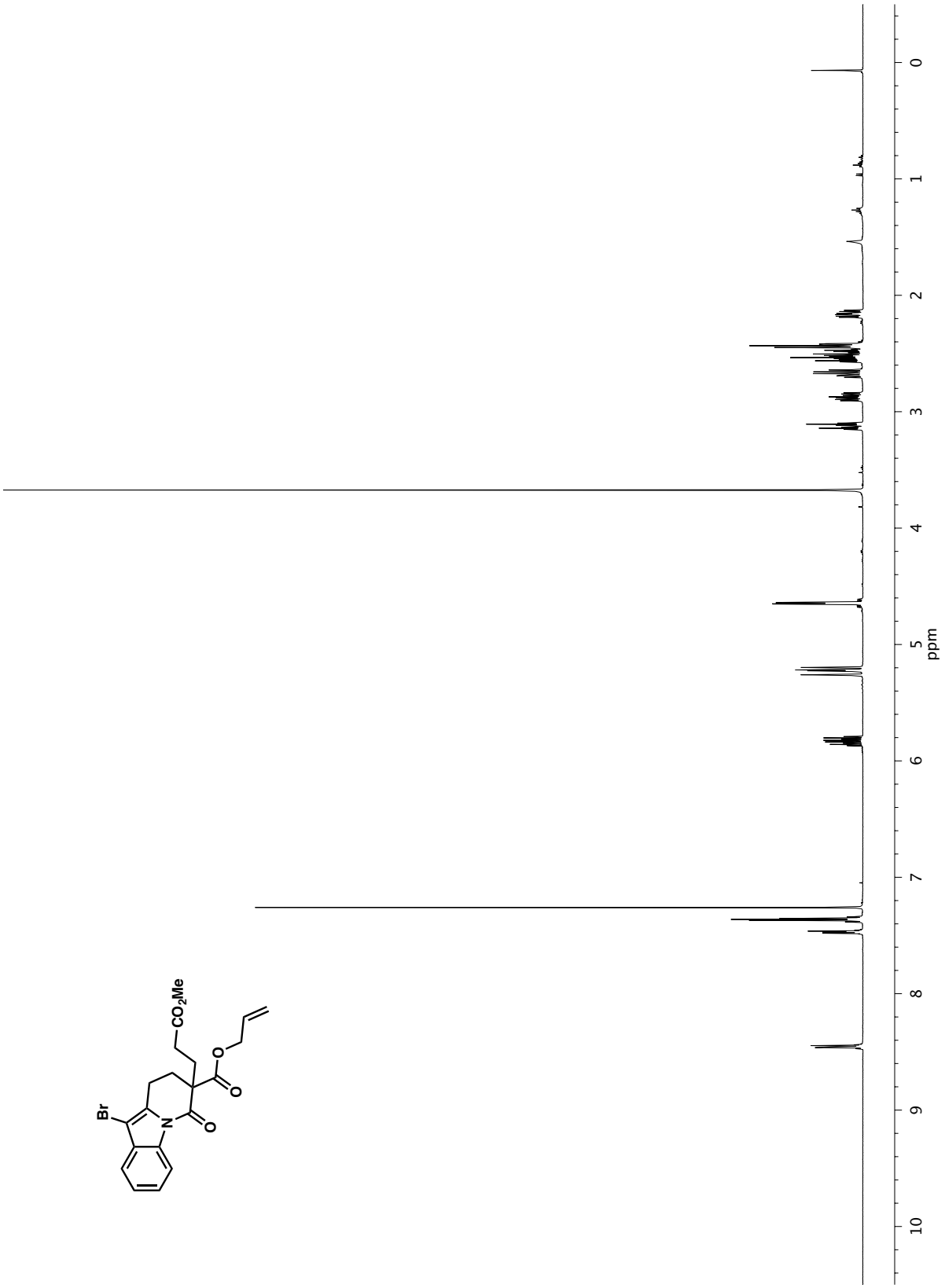


Figure A4.58. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172e**.

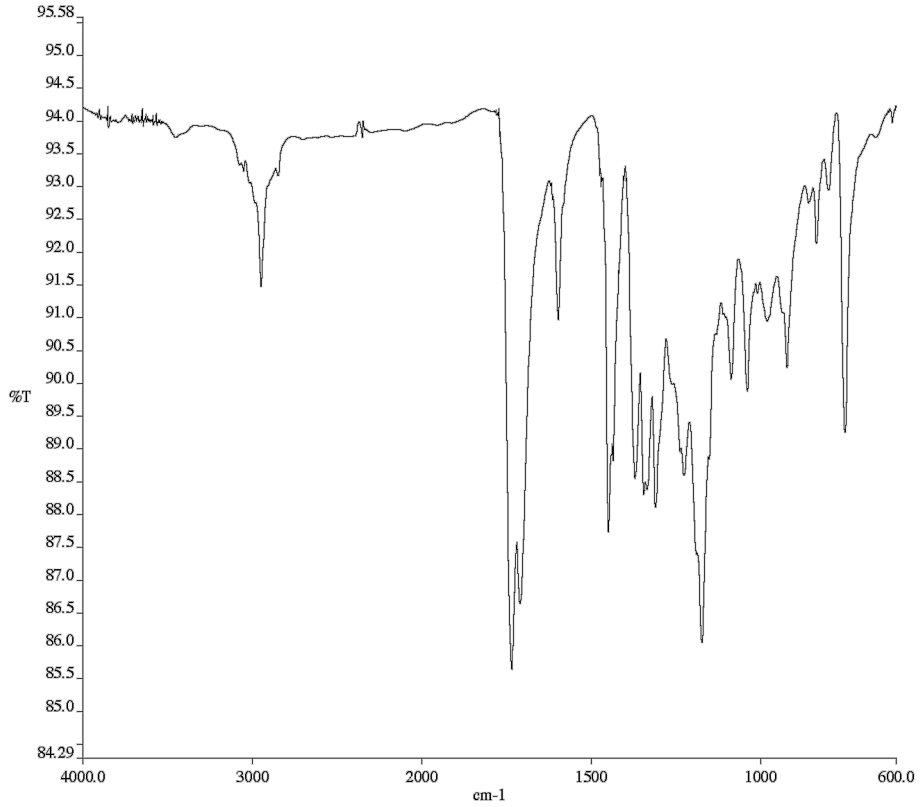


Figure A4.59. Infrared spectrum (Thin Film, NaCl) of compound **172e**.

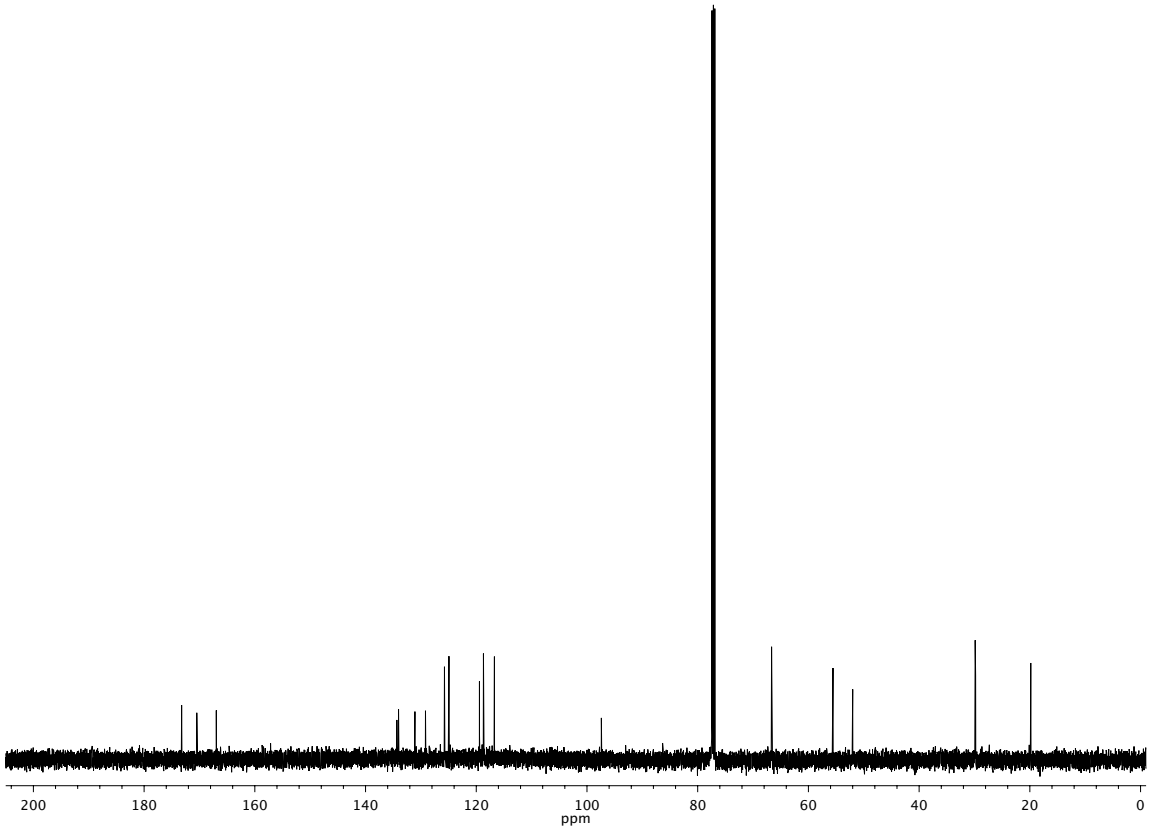


Figure A4.60. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172e**.

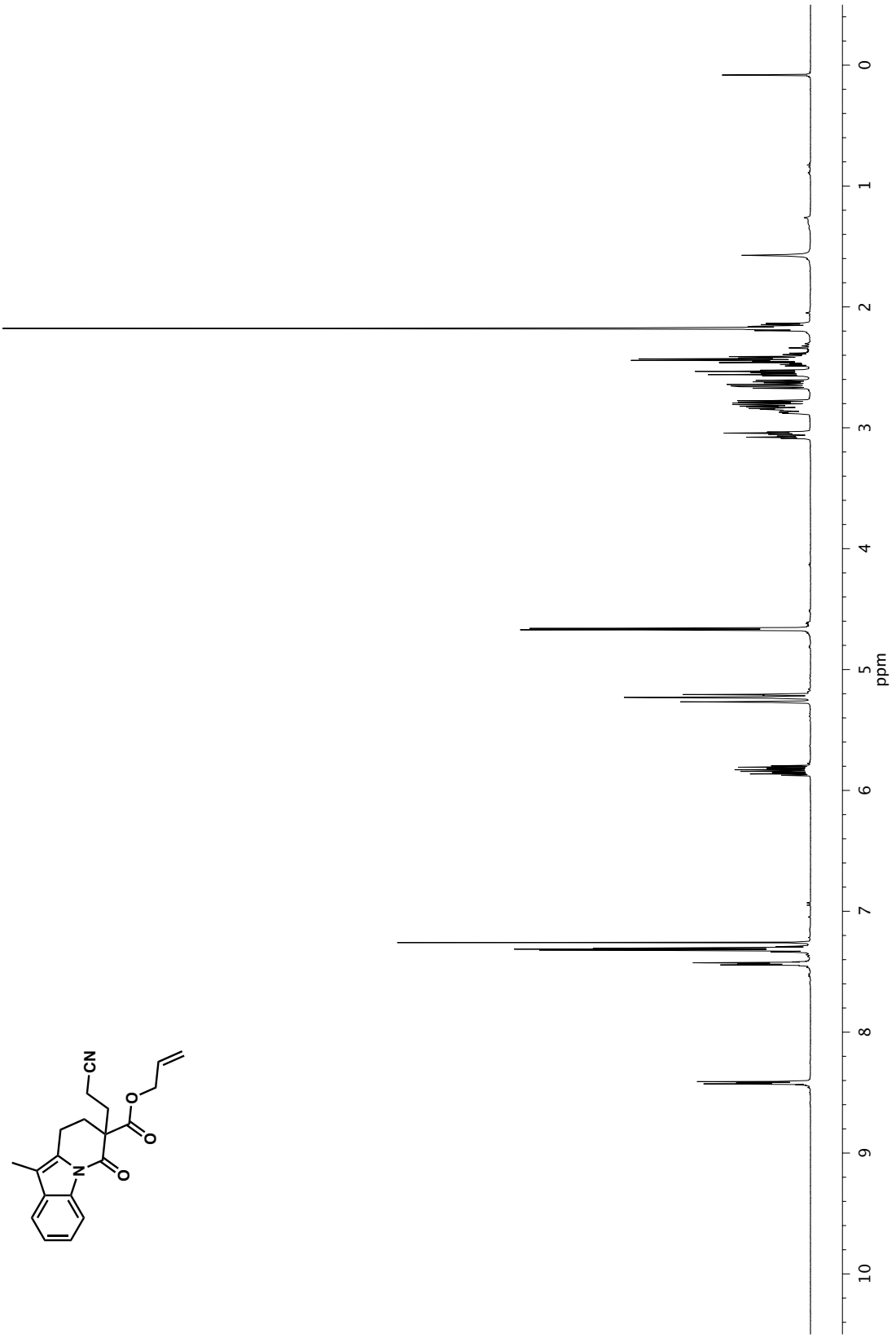


Figure A4.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172f**.

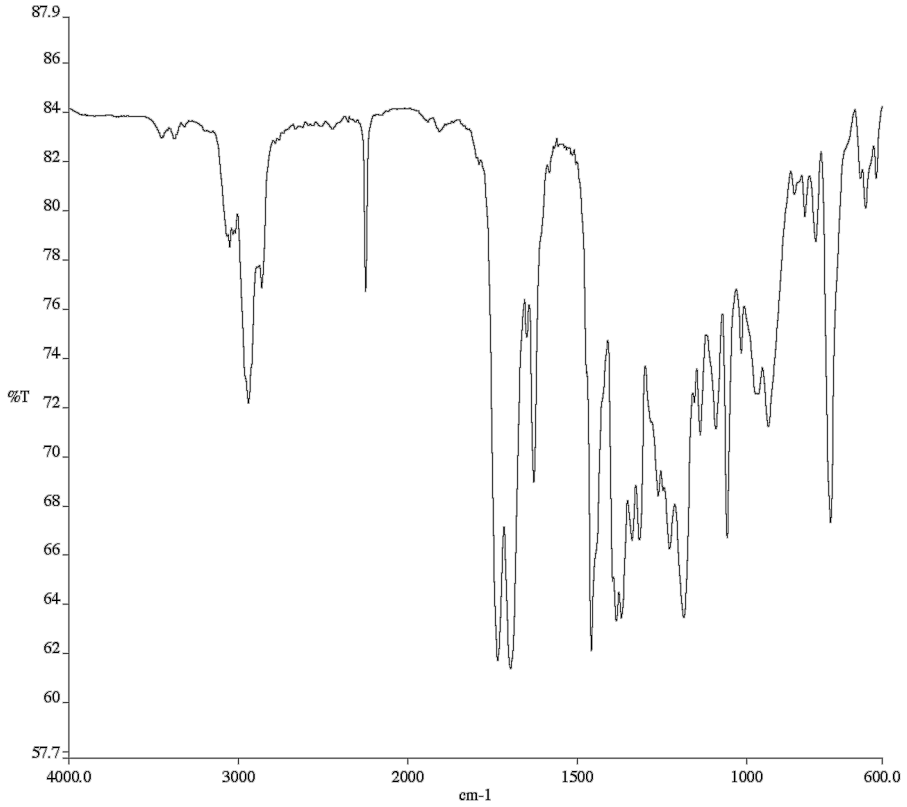


Figure A4.62. Infrared spectrum (Thin Film, NaCl) of compound **172f**.

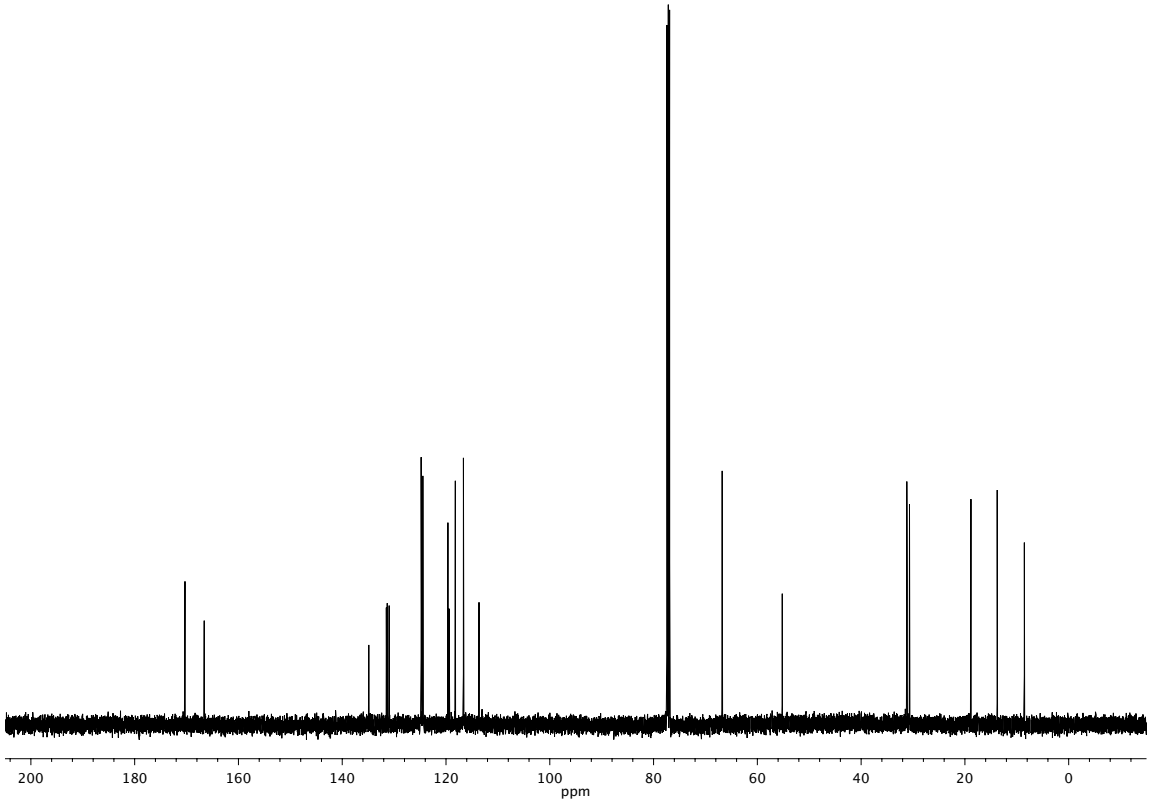


Figure A4.63. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172f**.

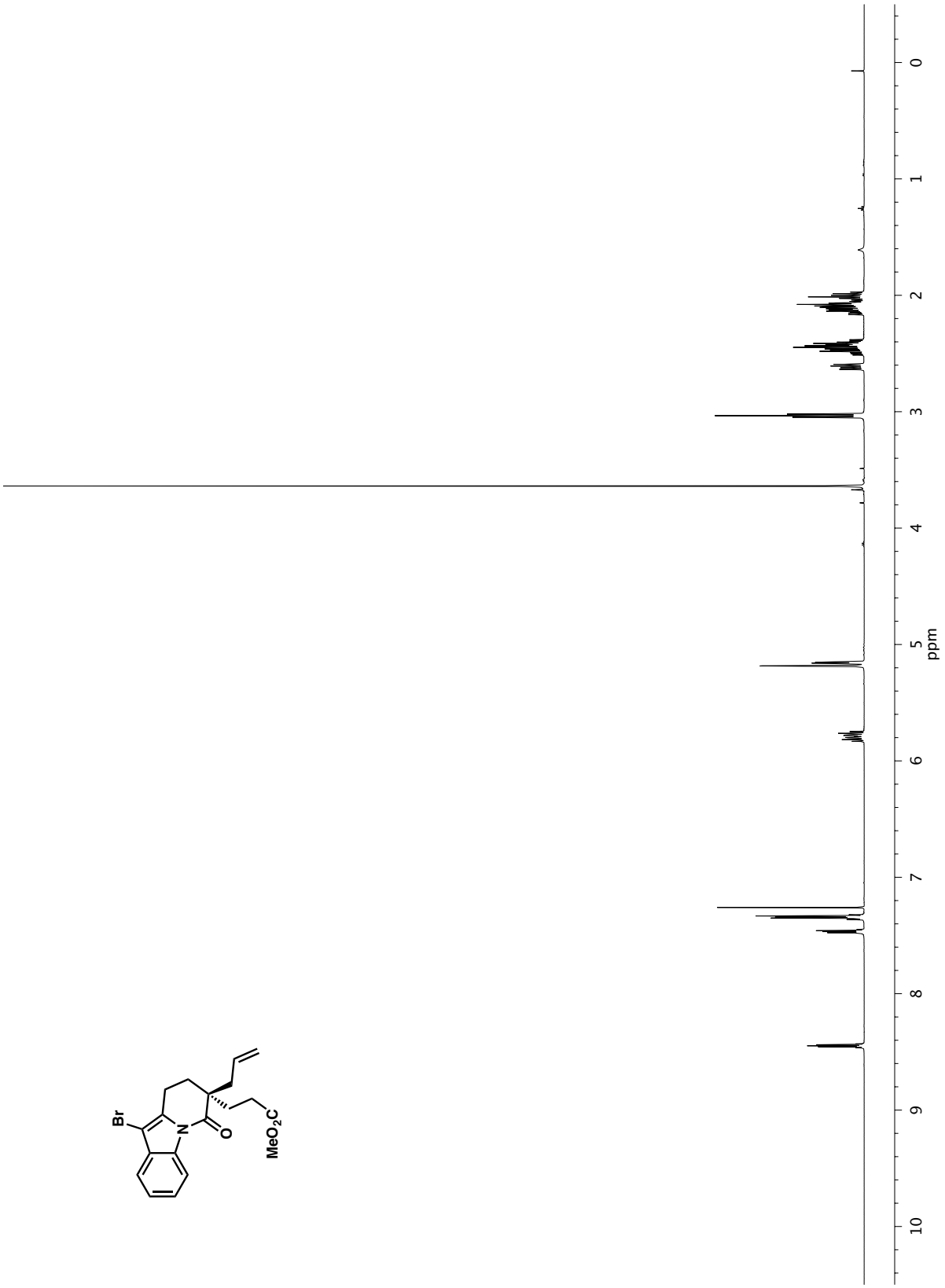


Figure A4.64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165e**.

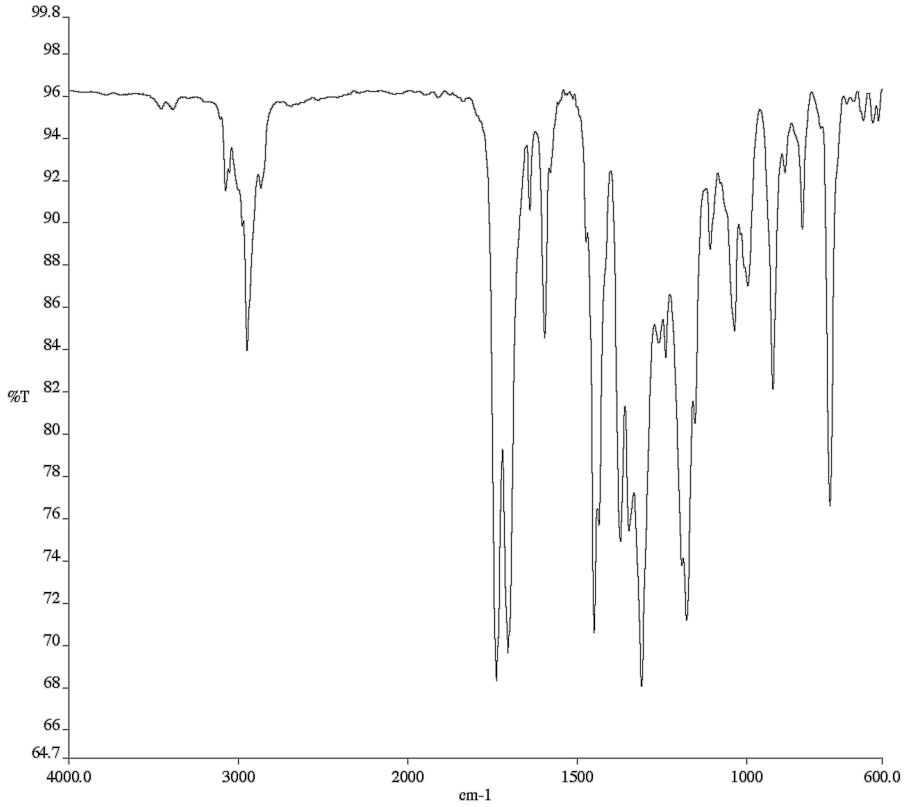


Figure A4.65. Infrared spectrum (Thin Film, NaCl) of compound **165e**.

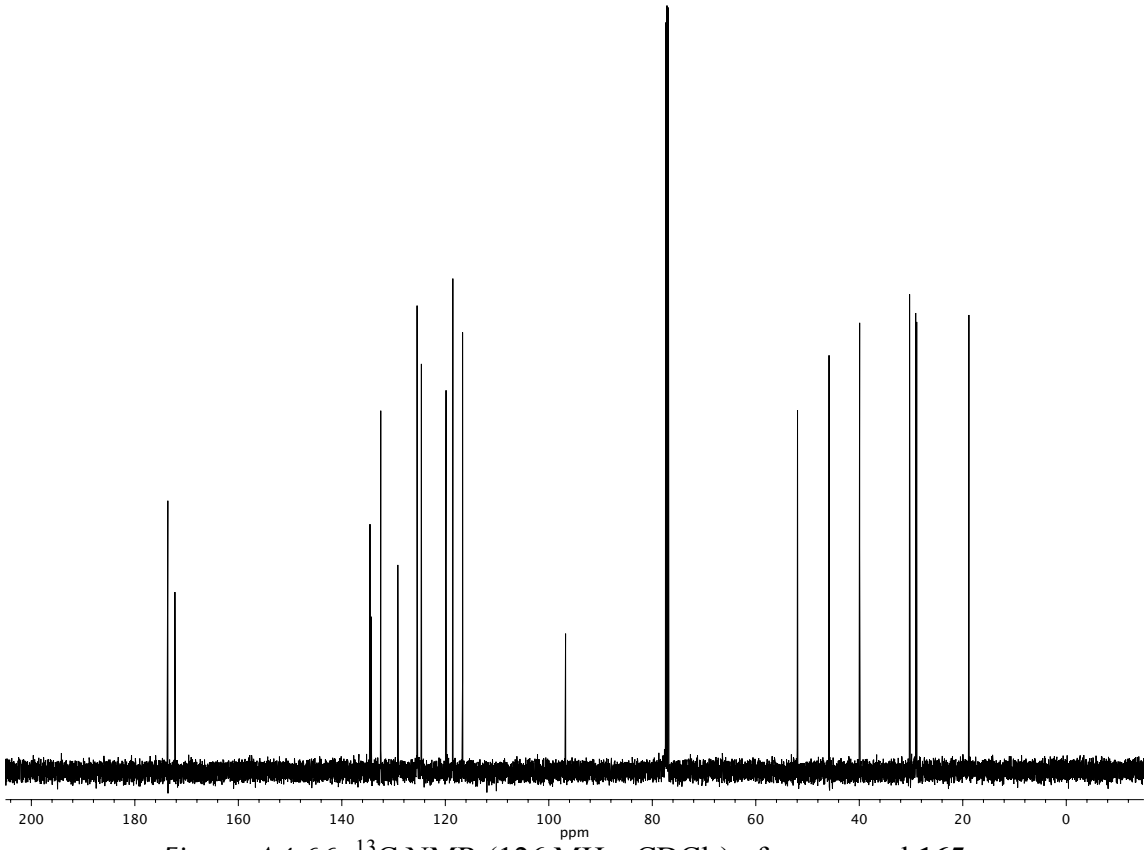


Figure A4.66. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165e**.

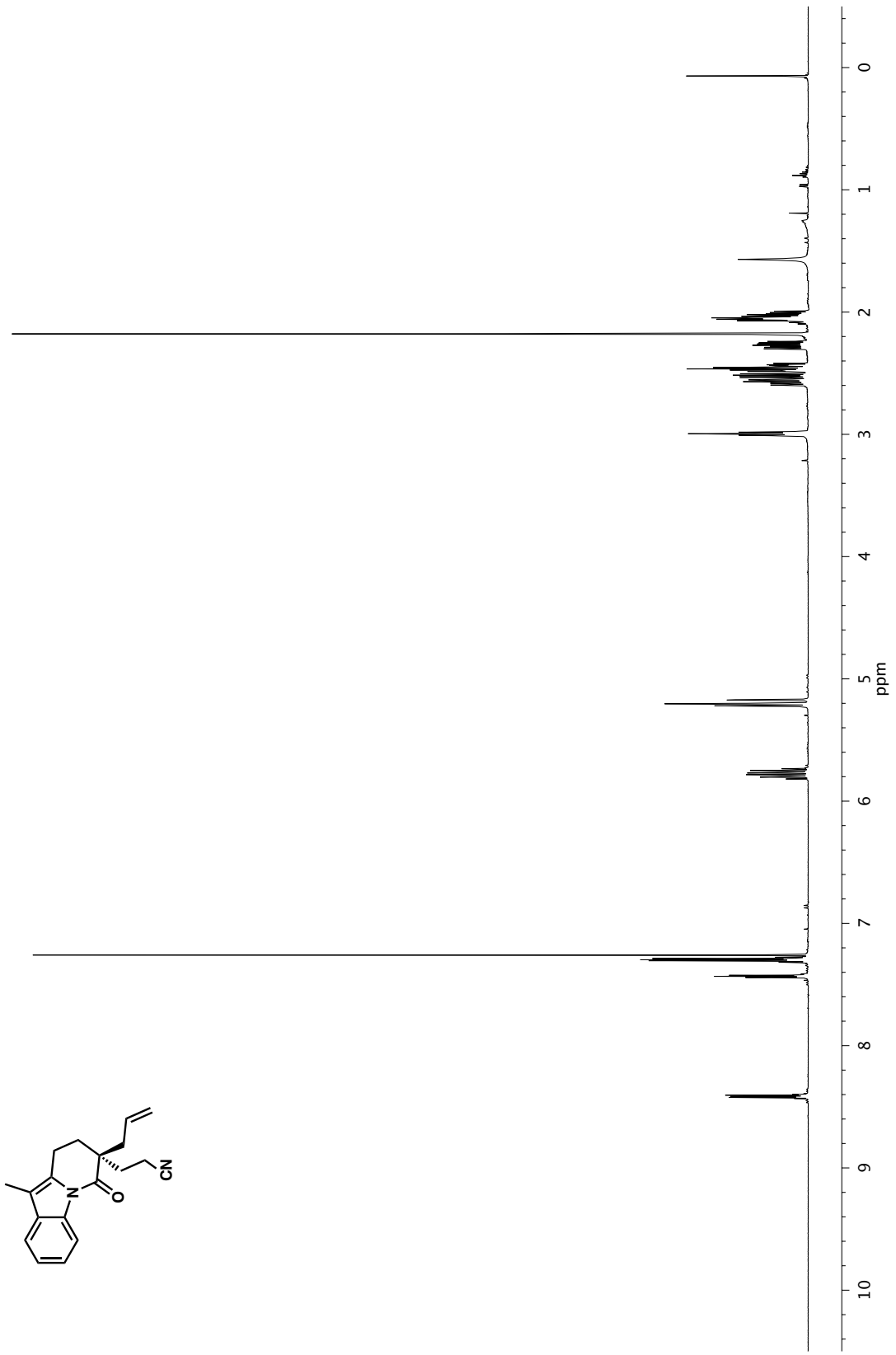


Figure A4.67. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165f**.

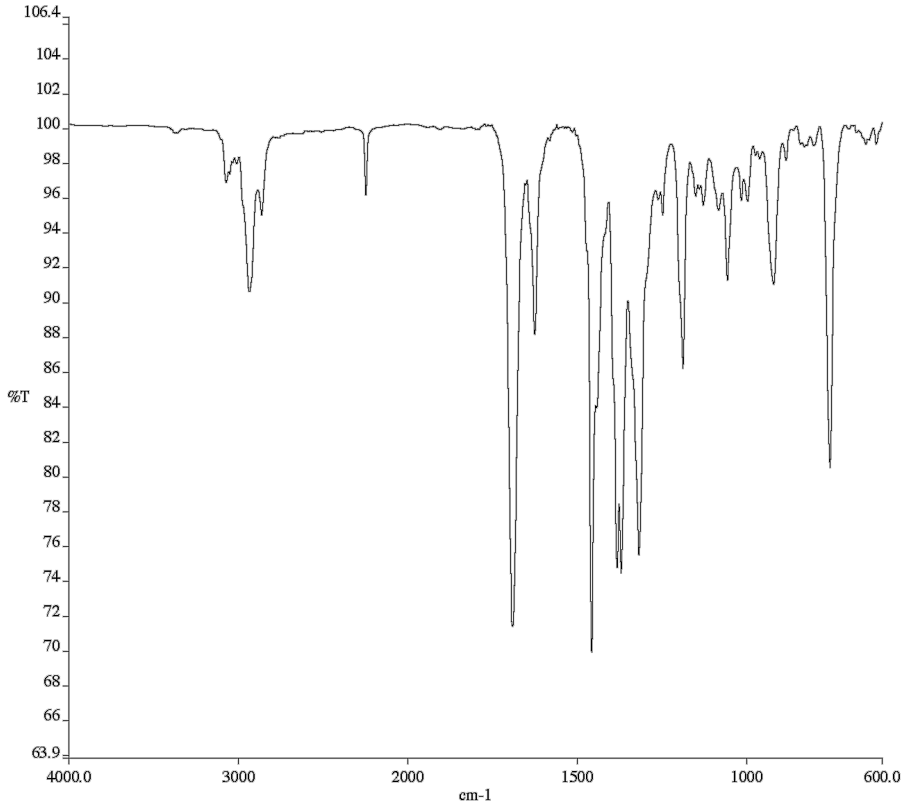


Figure A4.68. Infrared spectrum (Thin Film, NaCl) of compound **165f**.

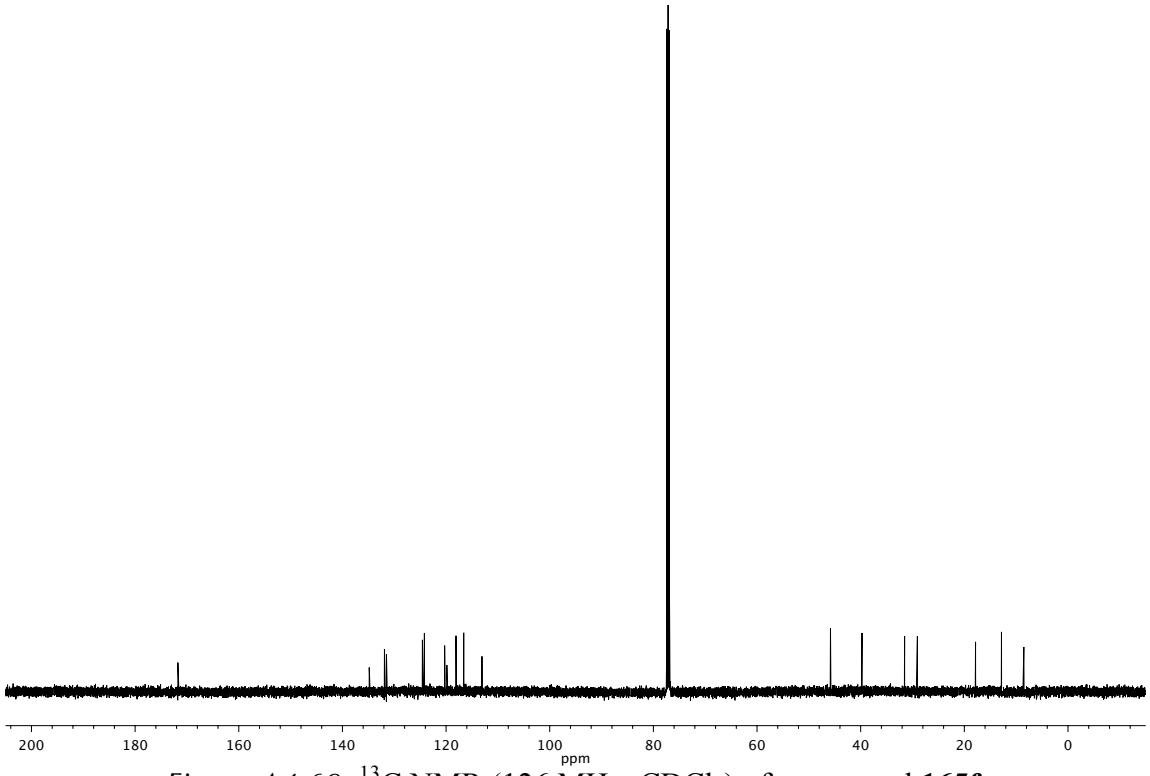


Figure A4.69. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165f**.

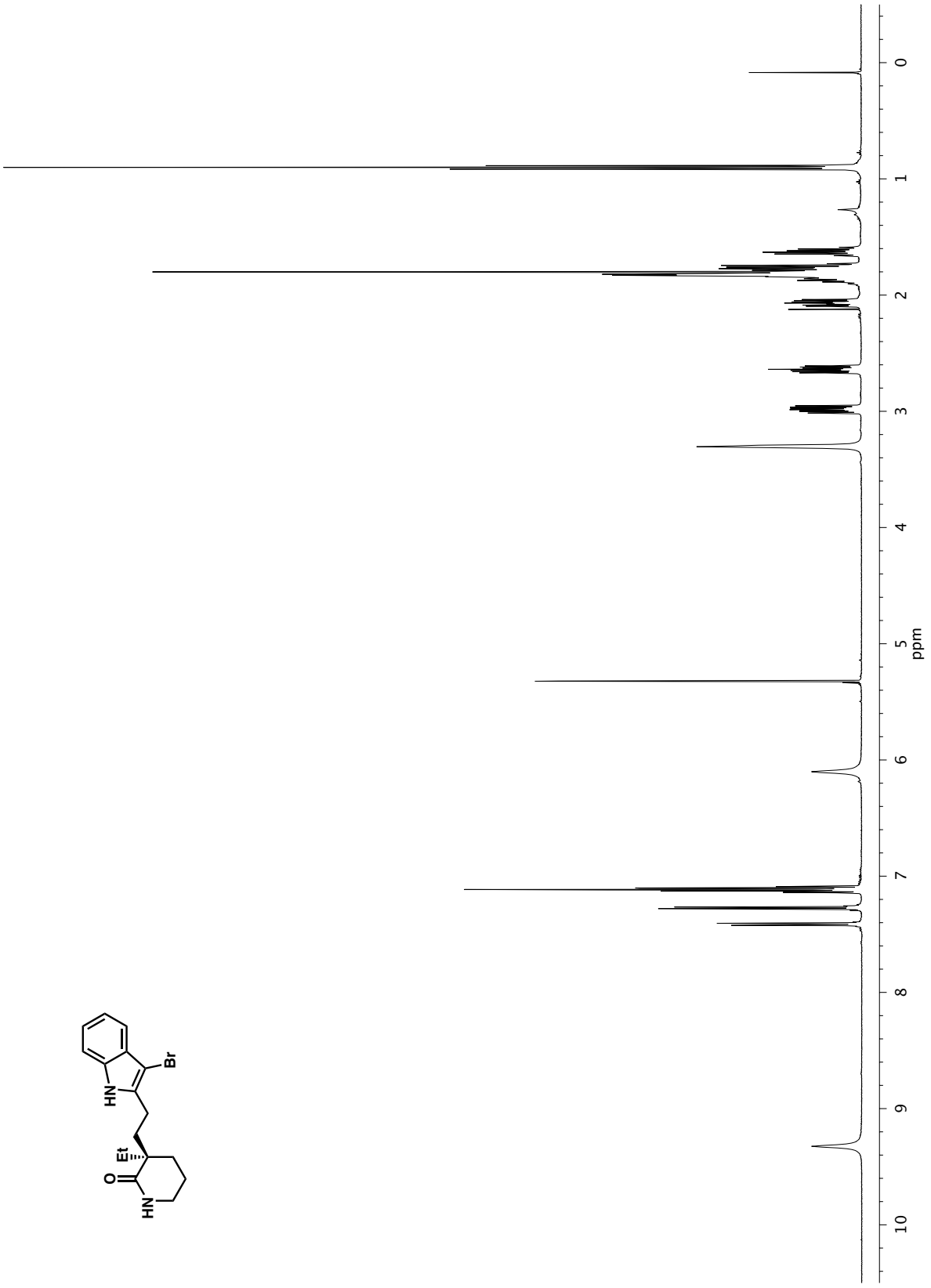


Figure A4.70. ^{1}H NMR (500 MHz, CD_2Cl_2) of compound **198**.

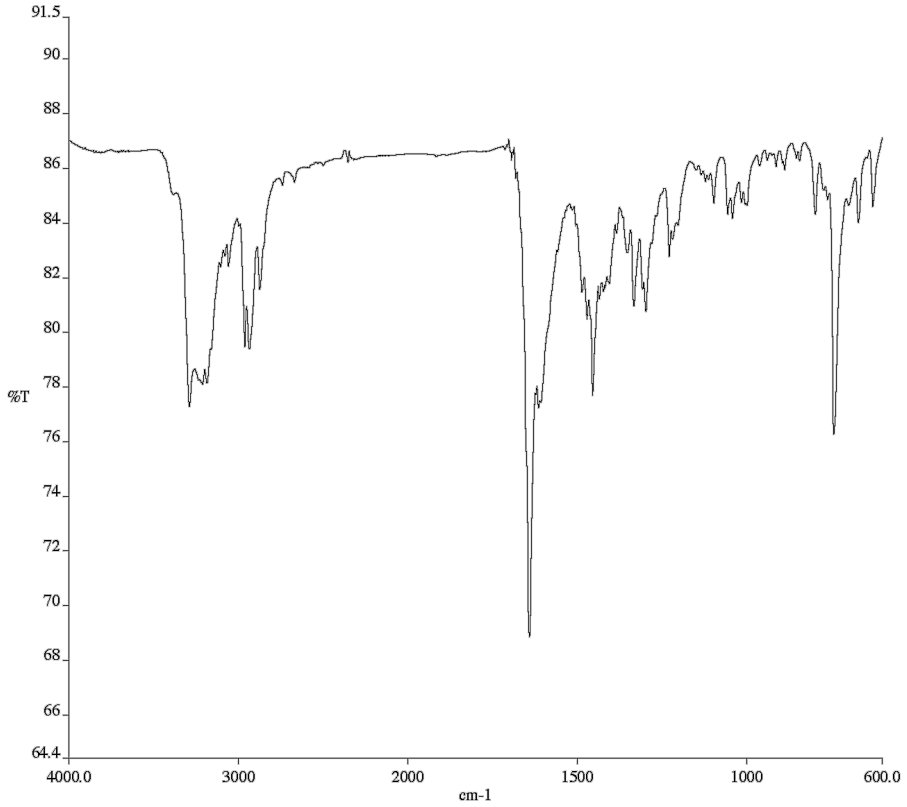


Figure A4.71. Infrared spectrum (Thin Film, NaCl) of compound **198**.

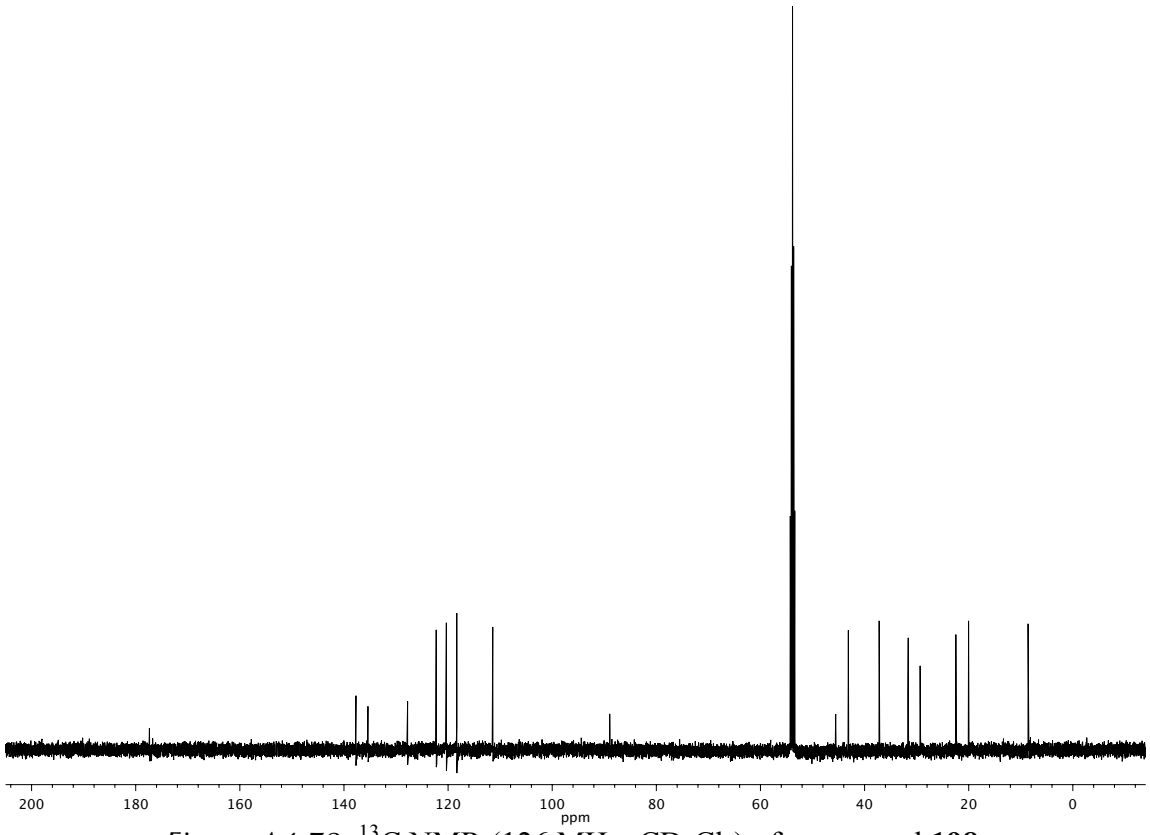


Figure A4.72. ^{13}C NMR (126 MHz, CD_2Cl_2) of compound **198**.

CHAPTER 3

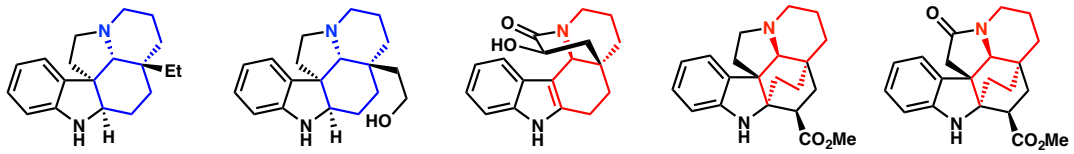
Stereoselectivity in Indole-Iminium Cyclizations: Total Synthesis of (+)-Limaspermidine, Formal Synthesis of (+)-Kopsihainanine A, and Progress Toward the Total Syntheses of (–)-Kopsinine and (–)-Kopsinilam[†]

3.1 INTRODUCTION AND SYNTHETIC DESIGN

Monoterpene indole alkaloids from the structurally related *Aspidosperma* and *Kopsia* families have attracted the attention of synthetic chemists for over the course of more than half a century due to their intricate polycyclic structures and broad biological activity.[1,2] One significant structural difference between these families is the ring fusion geometry of the octa- or decahydroquinoline moiety contained within the polycyclic core. *Aspidosperma* alkaloids typically possess a *cis*-fused azadecalin motif (e.g., **1** and **6**, blue highlight, Figure 3.1.1).[3] Conversely, members of the *Kopsia* family often contain a *trans*-fused azadecalin substructure (e.g., **22**, **20**, and **199**, red highlight, Figure 3.1.1).[4]

[†] This work was performed in collaboration with Dr. Etienne Donckele, a Postdoctoral scholar in the Stoltz group. A manuscript detailing the syntheses of (+)-Limaspermidine (**6**) and (+)-Kopsihainanine A (**22**) is currently in preparation.

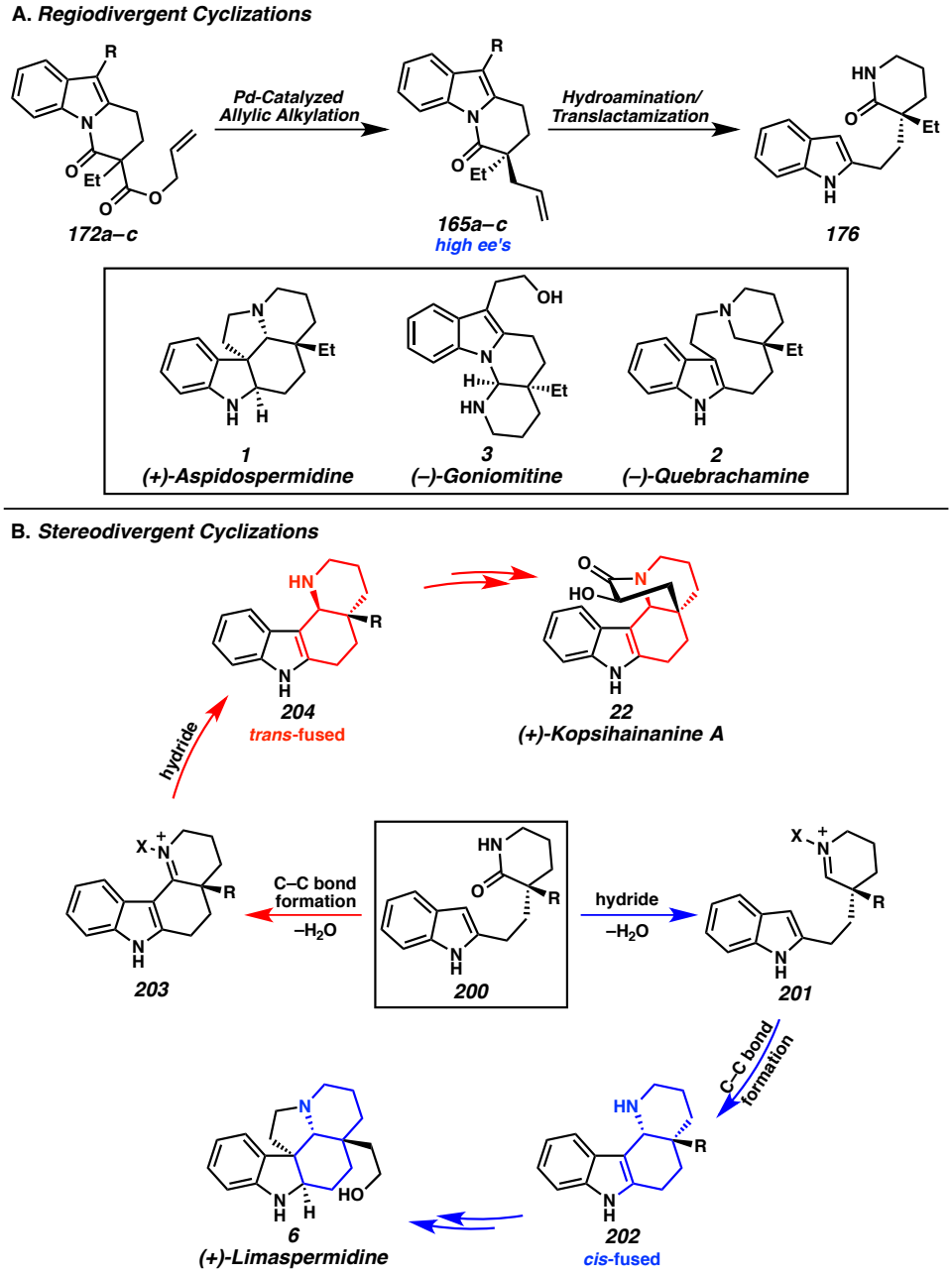
Figure 3.1.1. Representative Aspidosperma and Kopsia Alkaloids.



1 ***(+)-Aspidospermidine*** ***6*** ***(+)-Limaspermidine*** ***22*** ***(+)-Kopsihainanine A*** ***20*** ***(–)-Kopsinine*** ***199*** ***(–)-Kopsinilam***

We recently reported the enantioselective Pd-catalyzed allylic alkylation of dihydropyrido[1,2-*a*]indolone (DHPI) substrates.[5] The utility of the enantioenriched α-quaternary DHPI products was illustrated through *regiodivergent* indole-iminium cyclization pathways to access multiple *Aspidosperma* alkaloid frameworks (Scheme 3.1.1A). Given the high enantioselectivities and rapid accessibility of these chiral building blocks, we sought to further highlight the versatility of the DHPI substrate class by leveraging *stereodivergent* indole-iminium cyclizations toward additional monoterpene indole alkaloid targets (Scheme 3.1.1B).

Scheme 3.1.1. DHPIs as Precursors for Indole-Iminium Cyclizations.



We envisioned that δ-lactam **200**, available in two steps from the α-quaternary Pd-catalyzed allylic alkylation product (cf. Scheme 3.1.1A),[5] could undergo hydride reduction and subsequent dehydration to deliver C2-tethered iminium **201** (Scheme 3.1.1B, Blue Path). A Pictet–Spengler-type cyclization could then occur, with the indole

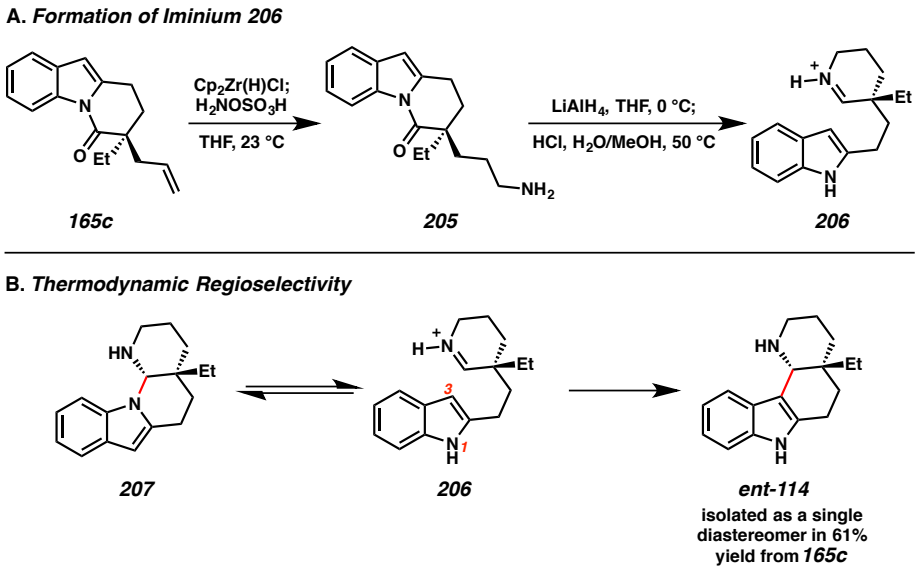
moiety approaching from the less hindered α-face, to yield tetracycle **202** bearing a *cis*-fused octahydroquinoline subunit. We anticipated that such an intermediate could be advanced to (+)-limaspermidine (**6**). Alternatively, by reversing the order of these events (i.e., C–C formation *then* C–H formation), a Bischler–Napieralski cyclization could furnish tetracyclic iminium **203**, and the ensuing hydride reduction would proceed from the less hindered α-face of the molecule to give the *trans*-fused octahydroquinoline subunit in tetracycle **204** (Scheme 3.1.1B, Red Path).[6] We expected that **204** could be carried on in a total synthesis of (+)-kopsihainanine A (**22**).

3.2 DEVELOPMENT OF STEREODIVERGENT CYCLIZATION STRATEGIES FROM A COMMON DHPI PRECURSOR

At the outset of our investigations, we aimed to verify whether the aforementioned stereodivergent cyclization strategies were viable using α-quaternary DHPI **165c** as a model system (Scheme 3.2.1). We were delighted to find that subjecting **165c** to formal anti-Markovnikov hydroamination conditions developed by Hartwig,[7] followed by addition of lithium aluminum hydride, and subsequent quenching with hydrochloric acid and methanol resulted in the formation of putative C2-tethered iminium **206** (Scheme 3.2.1A). The indole moiety is nucleophilic at N1 and C3, which gives rise to isomeric tetracycles bearing either a newly formed C–N or C–C bond (**207** and ***ent*-114**, respectively, Scheme 3.2.1B). C–N bond formation gives aminal **207**, which can revert to iminium **206** via hydrolysis. Alternatively, a Pictet–Spengler-type reaction forms a C–C bond with subsequent rearomatization to irreversibly furnish *cis*-fused

tetracycle ***ent*-114**. Remarkably, this one-pot sequence delivers ***ent*-114** in 61% yield as a single diastereomer without the need to exchange solvents or isolate any intermediates.

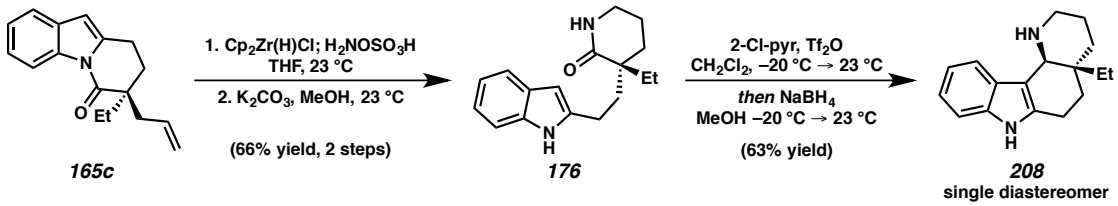
Scheme 3.2.1. One-Pot Synthesis of Cis-Fused Tetracycle ***ent-114*** *from α-Quaternary DHPI* ***165c****.*



Having successfully constructed the *cis*-fused octahydroquinoline moiety present in tetracycle ***ent*-114** using a one-pot hydroamination/reduction/Pictet–Spengler sequence, we next explored reaction conditions for a stereodivergent cyclization that would instead furnish a *trans*-fused octahydroquinoline system. As previously discussed, δ-lactam **176** is available in 66% yield over two steps from DHPI **165c** (Scheme 3.2.2). Amide activation proceeded smoothly in the presence of 2-chloropyridine and triflic anhydride, and subsequent reduction using sodium borohydride provided *trans*-fused tetracycle **208** as a single diastereomer in 63% yield. With the means to access both ring fusion geometries from the same Pd-catalyzed allylic alkylation products (i.e., α-

quaternary DHPIs), we embarked on the application of this stereodivergent strategy in the context of monoterpene indole alkaloid total synthesis.

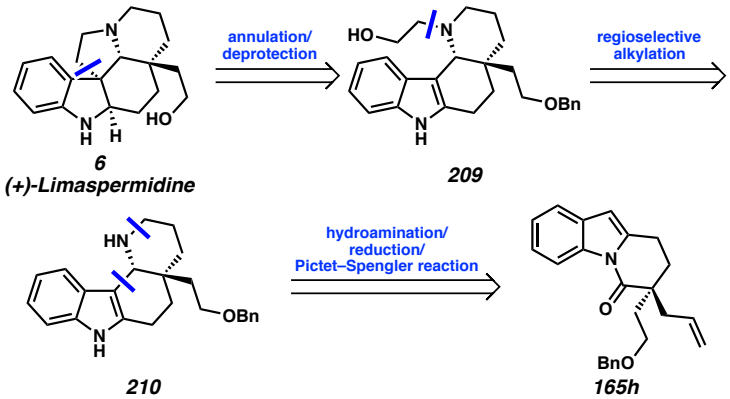
*Scheme 3.2.2. Synthesis of Trans-Fused Tetracycle **208** from α-Quaternary DHPI **165c**.*



3.3 RETROSYNTHETIC ANALYSIS OF (+)-LIMASPERMIDINE

Retrosynthetically, we believed (+)-limaspermidine (**6**) could be synthesized via late-stage annulation and alcohol deprotection of ethanolamine **209**, which in turn could arise from the regioselective alkylation of tetracycle **210** (Scheme 3.3.1). The *cis* ring fusion geometry of the azadecalin subunit in **210** would be controlled through a Pictet–Spengler-type cyclization following the anti-Markovnikov hydroamination and subsequent hydride reduction of α-quaternary DHPI **165h**.

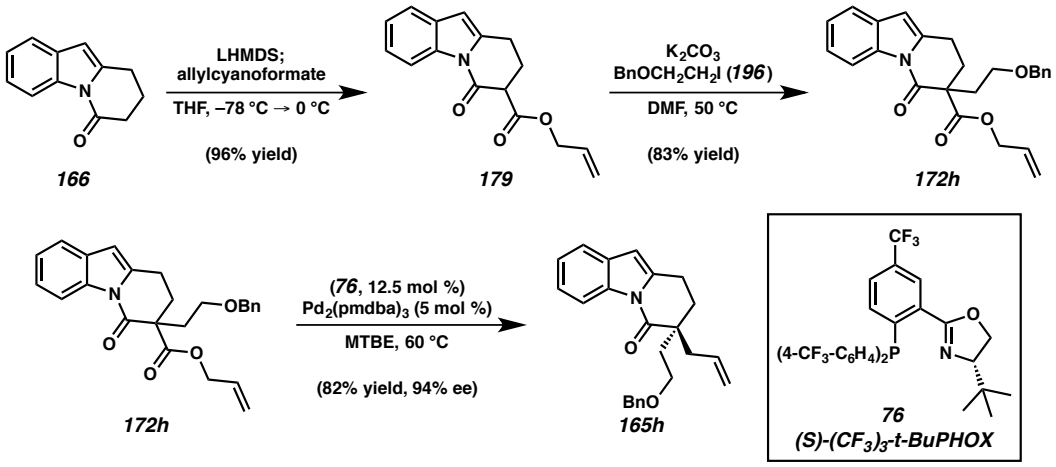
*Scheme 3.3.1. Retrosynthetic Analysis of (+)-Limaspermidine (**6**).*



3.4 TOTAL SYNTHESIS OF (+)-LIMASPERMIDINE

Our synthesis of (+)-limaspermidine (**6**) began from unsubstituted DHPI **166**, which is available in multi-gram quantities from indole (Scheme 3.4.1).[5] Straightforward C-acylation using allyl cyanoformate, followed by C-alkylation using (2-benzyloxy)ethyl iodide (**196**)[8] delivered β-amidoester **172h** in 80% yield over the two steps. Treatment of **172h** to a solution of $Pd_2(pmdba)_3$ (5 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 12.5 mol %) in TBME at 60 °C delivered α-quaternary DHPI **165h** in 82% yield and 94% ee.

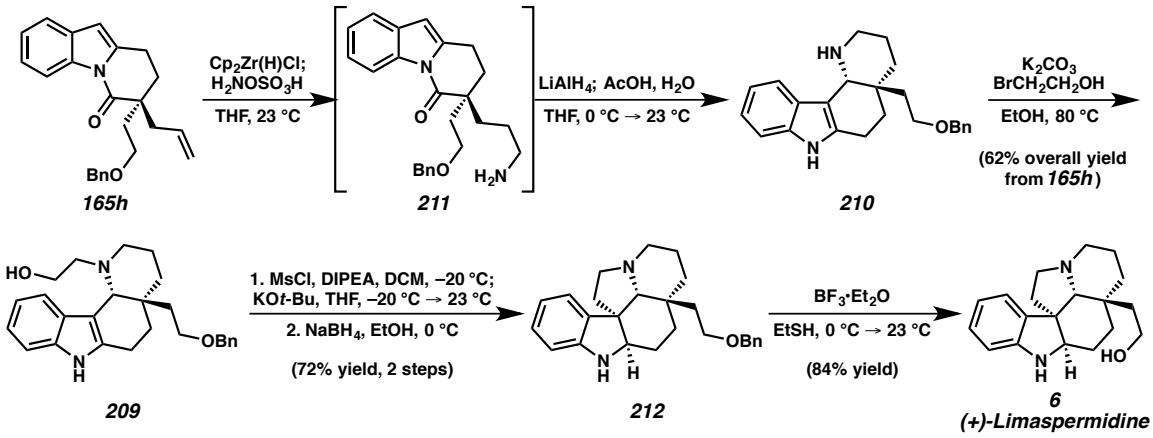
*Scheme 3.4.1. Synthesis of α-Quaternary DHPI **165h**.*



Anti-Markovnikov hydroamination was accomplished using the aforementioned hydrozirconation/amination protocol developed by Hartwig and co-workers (Scheme 3.4.2).[7] Upon complete formation of the intermediate primary amine (**211**), lithium aluminum hydride was added, followed by quenching with acetic acid and water to promote the desired indole-iminium cyclization. This one-pot sequence furnished *cis*-fused tetracycle **210** in 60% yield. Regioselective piperidine alkylation gave primary alcohol **209** in 83% yield (50% over two steps). Importantly, we found that tetracycle **210**

could be advanced without purification to afford ethanolamine **209** in an improved 62% yield over the two steps. Ethanolamine **209** was treated with methanesulfonyl chloride followed by potassium *tert*-butoxide to effect pyrrolidine annulation. Subsequent hydride reduction yielded *O*-benzyl limaspermidine (**212**), which succumbed to debenzylation using excess BF_3•Et_2O in ethanethiol as solvent to give (+)-limaspermidine (**6**) in 60% yield over the final three steps.[9]

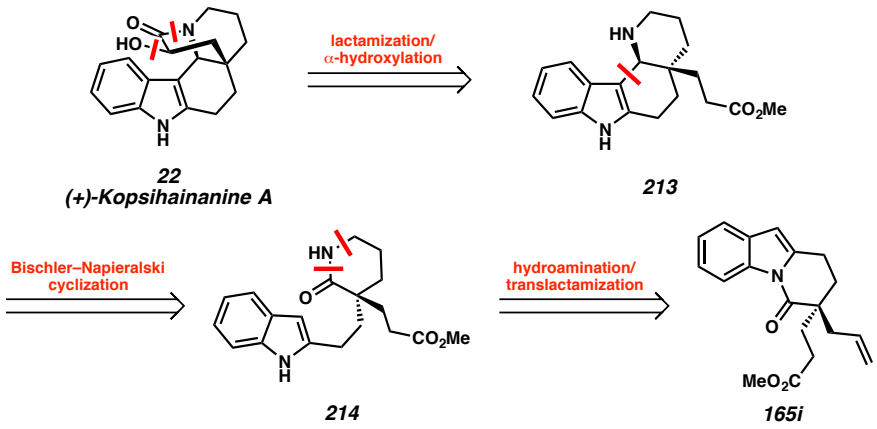
*Scheme 3.4.2. Completed Total Synthesis of (+)-Limaspermidine (**6**).*



3.5 RETROSYNTHETIC ANALYSIS OF (+)-KOPSIHAINANINE A

We imagined that an intramolecular lactamization and subsequent α-hydroxylation of tetracycle **213** could furnish (+)-kopsihainanine A (**22**, Scheme 3.5.1). The *trans*-fused octahydroquinoline subunit of **213** could be constructed through a Bischler–Napieralski cyclization of δ-lactam **214**,[6] which would in turn be synthesized from α-quaternary DHPI **165i** via anti-Markovnikov hydroamination and translactamization.

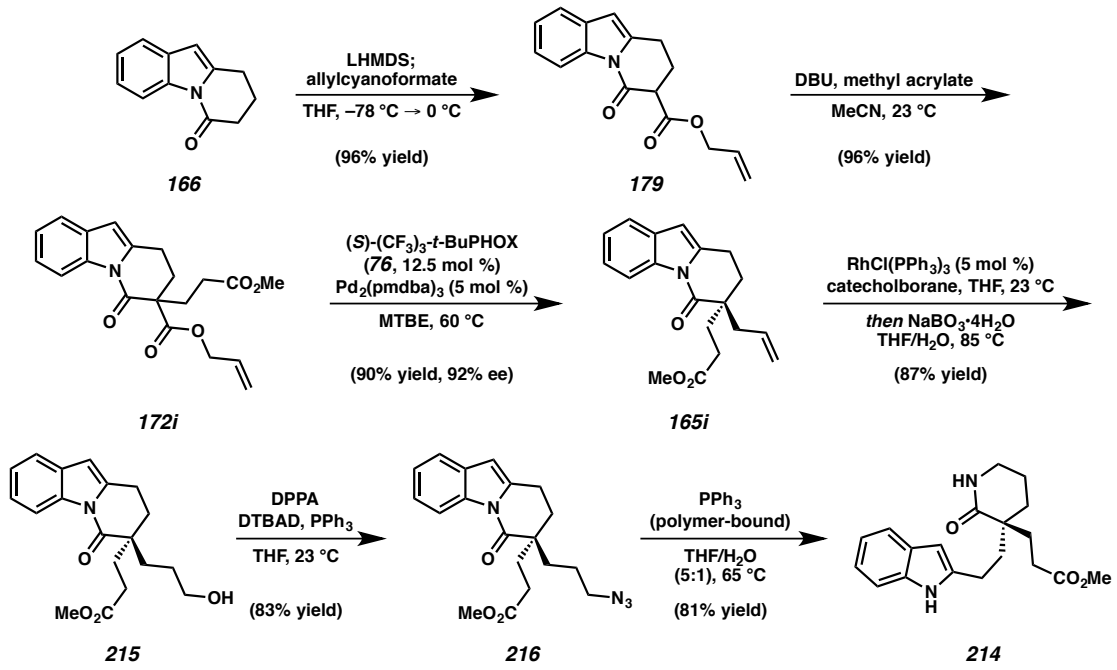
*Scheme 3.5.1. Retrosynthetic Analysis of (+)-Kopsihainanine A (**22**).*



3.6 FORMAL SYNTHESIS OF (+)-KOPSIHAINANINE A

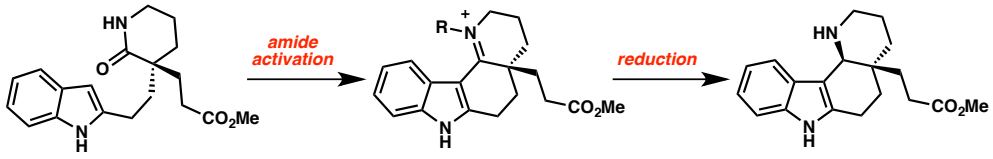
Beginning from the same tricyclic DHPI core (**166**), C-acylation followed by a Michael reaction using methyl acrylate furnished β–amidoester **172i** in 92% yield over the two steps (Scheme 3.6.1). Gratifyingly, subjecting **172i** to the aforementioned enantioselective Pd-catalyzed decarboxylative allylic alkylation conditions delivered α-quaternary DHPI **165i** in 90% yield and 92% ee. Unfortunately, we were unable to effect the desired one-pot hydrozirconation/amination protocol on this substrate. We observed over-reduction of the methyl ester upon treatment with Schwartz's reagent. Instead, we implemented a Rh-catalyzed hydroboration,[10] and subsequent Mitsunobu-type displacement to arrive at azide **216** in 72% yield over two steps. A Staudinger reaction using polymer-bound triphenylphosphine reduced the azide in **216** to the corresponding primary amine, and concomitant translactamization afforded δ-lactam **214** in 81% yield.

*Scheme 3.6.1. Synthesis of α-Quaternary δ-Lactam **214**.*



We next investigated the Bischler–Napieralski cyclization of **214** to access the *trans*-fused octahydroquinoline subunit present in many *Kopsia* alkaloids. To this end, δ-lactam **214** was exposed to $POCl_3$ in refluxing toluene to give tetracyclic iminium **217**, which could be reduced using sodium borohydride in methanol (Table 3.6.1, Entry 1). We observed an increased yield upon switching to the combination of triflic anhydride and 2-chloropyridine for amide activation (Entry 2). After optimization of stoichiometry and careful reaction timing, *trans*-fused tetracycle **213** could be synthesized in 84% yield (Entry 3).

*Table 3.6.1. Synthesis of Trans-Fused Tetracycle **213** en Route to Kopsia Alkaloids*[11]

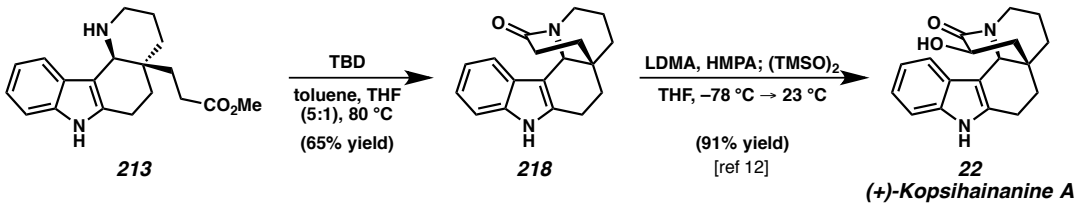


214 ***217*** ***213***

Entry	Activation Conditions	Activation Time	Reduction Conditions	Yield of ***213***
1	$POCl_3$ (1.5 equiv) toluene, 100 °C, 45 min	30 min at 100 °C	$NaBH_4$, MeOH 0 °C → 23 °C	50%
2	2-Cl-pyr (1.6 equiv) Tf_2O (1.4 equiv) CH_2Cl_2, –15 °C → 23 °C	45 min at –15 °C then 45 min out of bath	$NaBH_4$, MeOH –15 °C → 23 °C	65%
3	2-Cl-pyr (1.2 equiv) Tf_2O (1.1 equiv) CH_2Cl_2, –20 °C → 23 °C	15 min at –20 °C then 15 min out of bath	$NaBH_4$, MeOH –20 °C → 23 °C	84%

With *trans*-fused tetracycle **213** in hand, we sought to complete a highly efficient synthesis of (+)-kopsihainanine A (**22**). Several Brønsted bases and Lewis acids were screened for the lactamization of **213**, but we ultimately found that the bicyclic guanidine base, TBD, smoothly facilitated this transformation to deliver lactam **218** in 65% yield (Scheme 3.6.2). Compound **218** was previously shown to undergo α-hydroxylation via enolization using LDMA and trapping with $(TMSO)_2$ in Zhu's total synthesis of (±)-kopsihainanine A (**22**).[12] Thus, we have completed an asymmetric formal synthesis of the *Kopsia* alkaloid (+)-kopsihainanine A (**22**) in eight steps and 26% overall yield from the tricyclic DHPI core (**166**).

*Scheme 3.6.2. Enantioselective Formal Synthesis of (+)-Kopsihainanine A (**22**).*

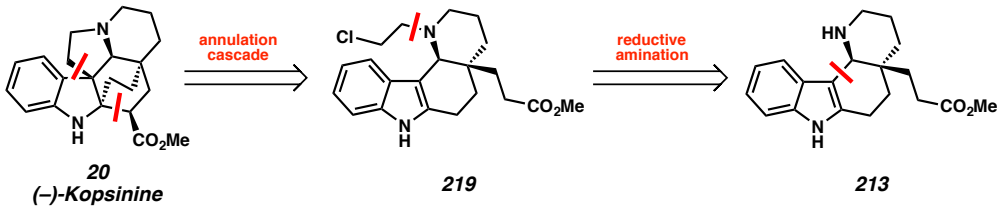


213 ***218*** ***22***
(+)-Kopsihainanine A

3.7 RETROSYNTHETIC ANALYSIS OF (–)-KOPSININE

We imagined that a base-promoted annulation cascade could forge the vicinal quaternary and tetrasubstituted tertiary stereocenters of the indoline moiety present in (–)-kopsinine (**20**, Scheme 3.7.1). Alkyl chloride **219** could arise from the reductive amination between chloroacetaldehyde and the piperidine nitrogen of tetracycle **213**, which we previously employed in our synthesis of (+)-kopsihainanine A (**22**).

*Scheme 3.7.1. Retrosynthetic Analysis of (–)-Kopsinine (**20**).*

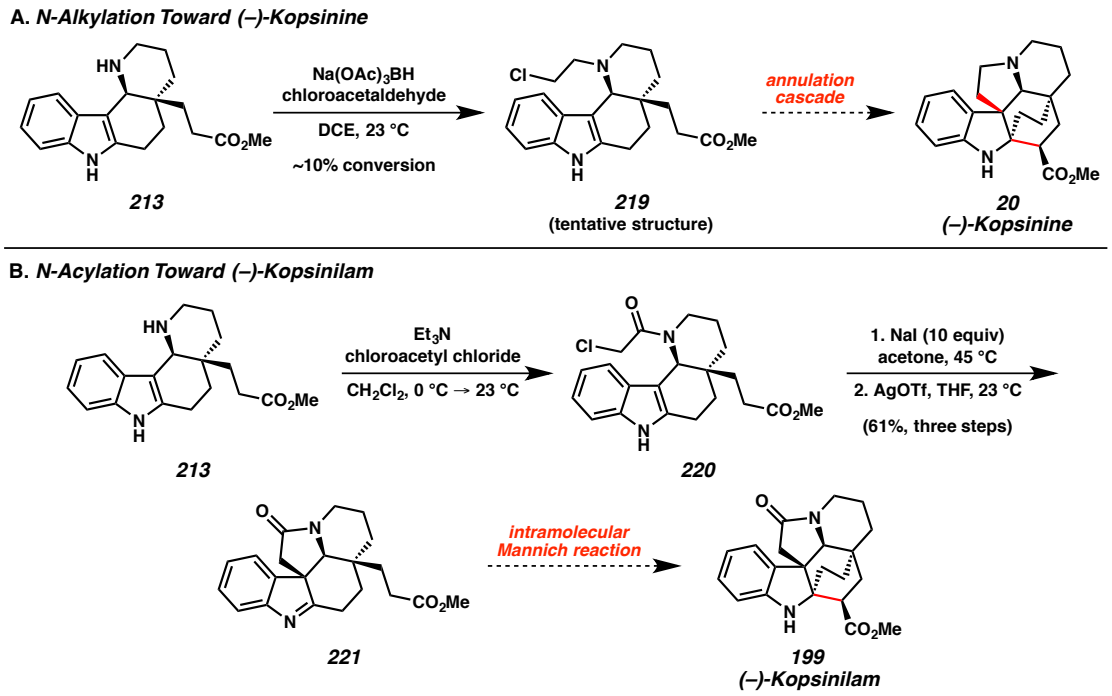


3.8 PROGRESS TOWARD THE TOTAL SYNTHESES OF (–)-KOPSININE AND (–)-KOPSINILAM

The reactivity of the piperidine nitrogen in **213** proved to be unexpectedly challenging (Scheme 3.8.1). Direct alkylations such as that used in our synthesis of ethanolamine **209** were unsuccessful (cf. Scheme 3.4.2).[13] Reductive amination using chloroacetaldehyde[14] and sodium triacetoxyborohydride resulted in minimal conversion of starting material, although the mass of the desired alkyl chloride **219** was observed by high resolution LCMS (Scheme 3.8.1A).[15] Despite this recalcitrant alkylation, we were optimistic that N-acylation would be facile. Fortunately, treatment of tetracycle **213** with chloroacetyl chloride and triethylamine gave α-chloroacetamide **220** (Scheme 3.8.1B). A Finkelstein reaction was effective for halide exchange, and an ensuing silver-mediated Friedel–Crafts-type annulation provided pentacyclic indolenine **221** in 61% yield over the

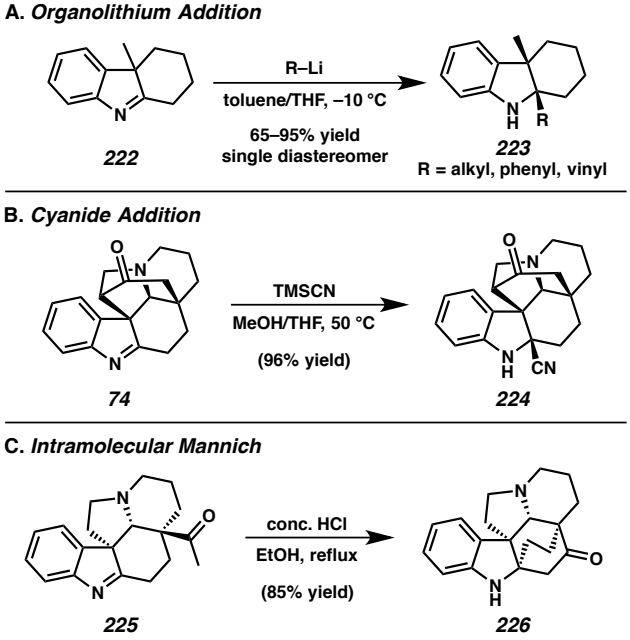
three steps. At this stage, all that remained was the final C–C bond that we planned to construct through an intramolecular Mannich reaction. Unfortunately, pentacycle **221** failed to undergo the desired C–C bond formation under either basic conditions (LDA in THF, LHMDS in THF, and NaOMe in MeOH), Lewis acidic conditions (TMSOTf in CH_2Cl_2), or Brønsted acidic conditions (HCl in MeOH, *p*-TsOH in CH_2Cl_2, and TFA in THF).

*Scheme 3.8.1. Endgame Studies Toward (–)-Kopsinine (**20**) and (–)-Kopsinilam (**199**).*



Carbon-based nucleophilic additions into imines of this type (e.g., **221**) are typically limited to either organolithium reagents[16] or cyanide (Scheme 3.8.2A and 3.8.2B, respectively).[17] To our knowledge, the lone example of enol addition is the acid-promoted cyclization of ketone **225** to give indoline **226** in 85% yield (Scheme 3.8.2C).[18]

Scheme 3.8.2. Relevant Additions of Carbon-Based Nucleophiles to Indolenines.



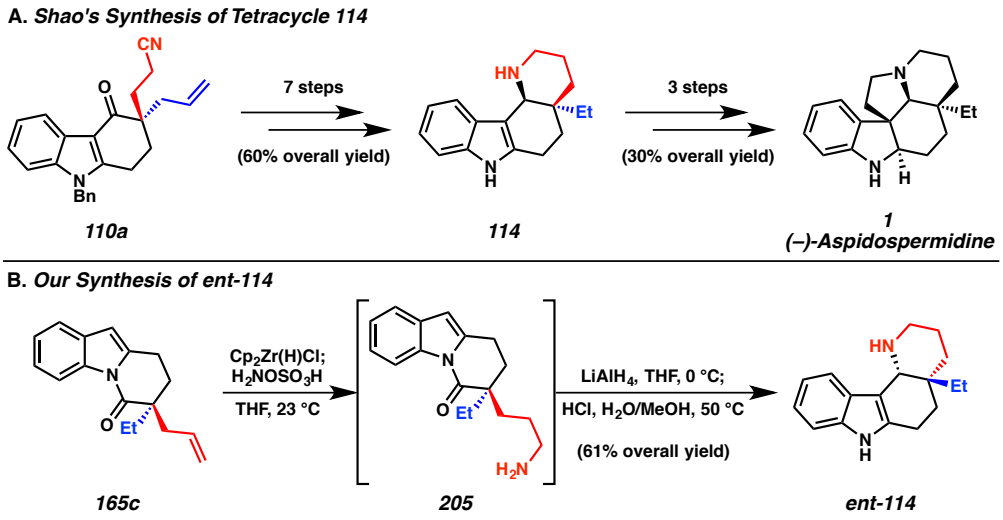
While enamine tautomerization of **221** is theoretically possible, we believe that the strain introduced into the resulting central cyclohexene ring would disfavor such a tautomerization. We hypothesize that the imine in **221** is not sufficiently electrophilic for straightforward enolate addition. Accordingly, either a radical addition or an imine activation that results in a formal positive charge at nitrogen is likely the most promising path forward.

3.9 COMPARISON OF SUBSTRATE CLASSES IN ENANTIOSELECTIVE Pd-CATALYZED ALLYLIC ALKYLATION FOR MONOTERPENE INDOLE ALKALOID TOTAL SYNTHESIS

The enantioselective Pd-catalyzed allylic alkylation of carbazolone substrates has garnered significant interest from the synthetic community over the past five years.[19] While these investigations have resulted in successful syntheses of numerous monoterpene indole alkaloids, we believe that the stereocontrolled cyclizations and

exocyclic C20 substituent variability afforded by α-quaternary DHPIs renders this substrate class highly valuable within the synthetic community. Perhaps the most direct comparison can be seen in Shao's total synthesis of (–)-aspidospermidine (**1**).[19d] Seven steps are required to convert their Pd-catalyzed allylic alkylation product, α-quaternary carbazolone **110a**, into *cis*-octahydroquinoline-containing tetracycle **114** (Scheme 3.9.1A). Conversely, our DHPI Pd-catalyzed allylic alkylation product (i.e., **165c**) is converted to the same tetracycle in one pot without any sacrifice in overall yield (Scheme 3.9.1B). The choice to convert the allyl group to a propylamine fragment enables high levels of exocyclic substituent flexibility at C20, which in turn requires less cumbersome downstream elaboration (e.g., obviating the tedious conversion of an allyl group to an ethyl group). Futhermore, the *N*-acyl moiety acts as a traceless protecting group for the indole nitrogen, thereby eliminating wasted time and materials for protection/deprotection steps.

Scheme 3.9.1. Comparative Synthetic Utility of Carbazolone and DHPI Pd-Catalyzed Allylic Alkylation Products.



3.10 CONCLUSIONS AND OUTLOOK

The combination of Pd-catalyzed allylic alkylations of dihydropyrido[1,2-*a*]indolone (DHPI) substrates with stereodivergent indole-iminium cyclization strategies is a powerful tool for the synthesis of *Aspidosperma* and *Kopsia* monoterpene indole alkaloids. The high enantioselectivities and synthetic flexibility conferred by the DHPI substrate class enabled rapid syntheses of (+)-limaspermidine (**6**) and (+)-kopsihainanine A (**22**). A highly advanced intermediate toward (–)-kopsinilam (**199**) was also synthesized, with only an intramolecular Mannich addition remaining to complete the synthesis.

The enantioselective construction of the C20 all-carbon quaternary center is leveraged to set the remaining stereocenters in these targets in a controlled and predictable fashion. The *N*-acyl moiety in the DHPI substrate class acts as a traceless protecting group for the indole nitrogen, which adds elegance and efficiency en route to complex tetracyclic alkaloid building blocks. The future of using α-quaternary DHPIs for the total synthesis of monoterpene indole alkaloids is indeed bright!

3.11 EXPERIMENTAL SECTION

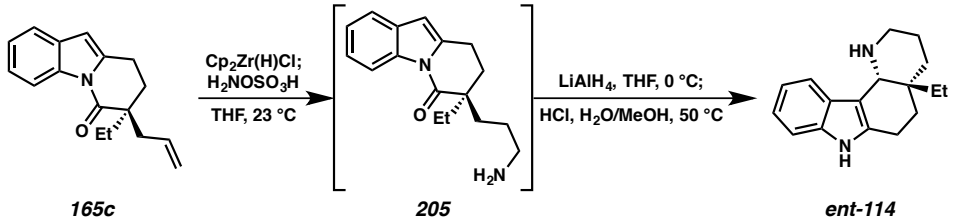
3.11.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[20] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, CAM, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. Melting points were measured with BÜCHI Melting Point B-545. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, br t = broad triplet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Analytical SFC was

performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H) or Chiralcel (OD-H)columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in mixed ionization mode (MM: ESI/APCI).

Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Bis(cyclopentadienyl) zirconium chloride hydride was purchased from Strem Chemicals and stored at room temperature in a N_2-filled glovebox. Hydroxylamine-*O*-sulfonic acid was purchased from Sigma Aldrich and stored at –30°C in the glovebox freezer. MeOH was distilled from magnesium methoxide immediately prior to use. (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**),[21] tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) $Pd_2(pmdba)_3$,[22] allyl cyanoformate,[23] and (2-benzyloxy)ethyl iodide (**196**)[24] were prepared by known methods.

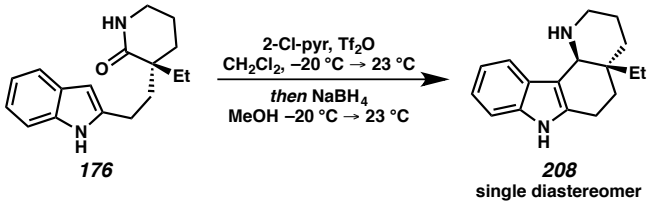
3.11.2 EXPERIMENTAL PROCEDURES



165c *205* *ent-114*

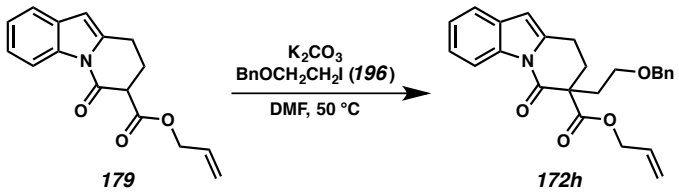
***Cis*-fused tetracycle *ent*-114**: An oven-dried scintillation vial was charged with α-quaternary DHPI **165c** (53 mg, 0.209 mmol, 1.0 equiv), THF (1.0 mL), and a magnetic stirring bar in a N_2-filled glovebox. To this solution was added bis(cyclopentadienyl) zirconium chloride hydride (65 mg, 0.252 mmol, 1.2 equiv), and the mixture was stirred at 23 °C for 30 min. A second portion of bis(cyclopentadienyl) zirconium chloride hydride (11 mg, 43 μmol, 0.2 equiv) was added, and the reaction mixture was stirred for an additional 30 min at which point a light yellow solution was observed. Hydroxylamine-*O*-sulfonic acid (38 mg, 0.336 mmol, 1.6 equiv) was added, the vial was sealed and removed from the glovebox, and stirring was resumed at 23 °C in a fume hood for an additional 10 min. The reaction mixture was cooled to 0 °C and $LiAlH_4$ (0.84 mL, 1.0 M in THF, 0.84 mmol, 4.0 equiv) was added over five minutes. The reaction was stirred at 0 °C for 15 minutes before careful quenching with H_2O (2 mL), then MeOH (8 mL) and 6N HCl (1 mL). The vial was sealed and placed in a pre-heated 50 °C heating block. After stirring at this temperature for one hour, the reaction mixture was cooled to ambient temperature and poured onto brine (50 mL) and EtOAc (50 mL). The solution was basified with 2N NaOH until pH > 12, and was then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 10% NH_3 (7N solution in MeOH), 45% EtOAc and

45% hexanes) afforded *cis*-fused tetracycle ***ent*-114** (32.7 mg, 61% yield) as a white amorphous solid: R_f = 0.59 (2:2:1 hexanes:EtOAc:NH_3 (7N solution in MeOH) eluent); ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.26–7.22 (m, 1H), 7.01 (td, *J* = 7.9, 7.5, 1.5 Hz, 1H), 6.96 (td, *J* = 7.4, 1.3 Hz, 1H), 3.71 (s, 1H), 3.05–2.97 (m, 1H), 2.83–2.68 (m, 3H), 2.42 (ddd, *J* = 13.7, 11.0, 7.3 Hz, 1H), 1.88–1.81 (m, 1H), 1.78–1.65 (m, 1H), 1.61–1.46 (m, 4H), 1.10 (dq, *J* = 14.5, 7.5 Hz, 1H), 0.87 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 138.1, 135.9, 128.4, 121.6, 119.7, 118.2, 111.5, 111.2, 57.5, 46.8, 35.8, 35.5, 30.7, 24.7, 22.7, 20.9, 7.9; IR (Neat Film, NaCl) 3193, 3052, 2927, 2855, 1678, 1622, 1571, 1461, 1430, 1200, 1183, 1134, 743 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{23}N_2$ $[M+H]^+$: 255.1856, found 255.1860.



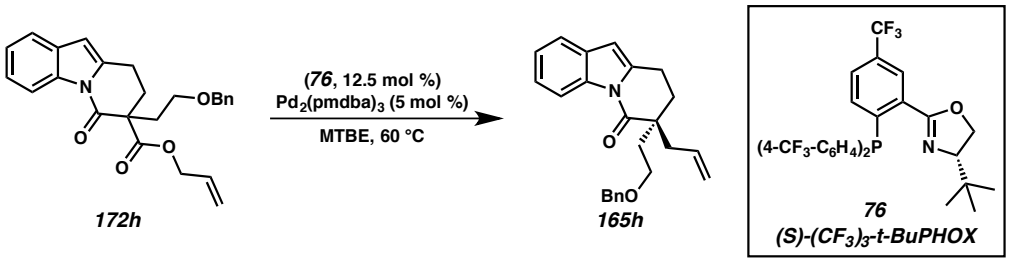
***Trans*-fused tetracycle 208**: To a solution of δ-lactam **176** (39 mg, 0.144 mmol, 1.0 equiv) in CH_2Cl_2 (4.8 mL) were added 2-chloropyridine (22 μL, 0.229 mmol, 1.6 equiv) and triflic anhydride (34 μL, 0.202 mmol, 1.4 equiv) at –20 °C (dry ice in H_2O/MeOH (7:3) bath). After 15 min, the reaction mixture was removed from the cooling bath and stirring continued for a further 15 min. At this time, the reaction mixture was cooled back to –20 °C and a solution of $NaBH_4$ (27 mg, 0.714 mmol, 5.0 equiv) in MeOH (5 mL) was added dropwise over a period of two minutes. The reaction was diluted with CH_2Cl_2 and quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The biphasic mixture was poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column

chromatography (SiO_2, 2% Et_3N in EtOAc) afforded *trans*-fused tetracycle **208** (23.2 mg, 63% yield) as a faintly pink amorphous solid: R_f = 0.22 (9:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +110.9 (*c* 0.34, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.70 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.32–7.27 (m, 1H), 7.05 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 6.99 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 4.19 (app t, *J* = 1.8 Hz, 1H), 3.47–3.37 (m, 1H), 3.09 (td, *J* = 13.3, 4.3 Hz, 1H), 2.84–2.66 (m, 2H), 1.99–1.82 (m, 3H), 1.73–1.64 (m, 1H), 1.61–1.45 (m, 2H), 1.43–1.17 (m, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 137.9, 136.2, 126.7, 121.7, 120.1, 119.2, 112.1, 106.1, 64.5, 47.1, 37.3, 32.1, 32.0, 20.7, 20.3, 17.7, 7.5; IR (Neat Film, NaCl) 3397, 3156, 3051, 2923, 2852, 1578, 1463, 1430, 1375, 1326, 1247, 1096, 875, 738 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{23}N_2$ $[M+H]^+$: 255.1856, found 255.1855.



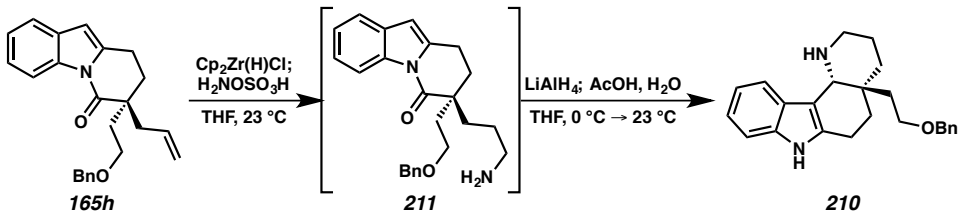
Allyl 7-(2-(benzyloxy)ethyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172h): To a solution of β-amidoester **179** (727 mg, 2.70 mmol, 1.0 equiv) in DMF (9 mL) were added K_2CO_3 (522 mg, 3.78 mmol, 1.4 equiv) and iodide **196**[8] (990 mg, 3.78 mmol, 1.4 equiv) at 23 °C with stirring. The reaction mixture was placed in a pre-heated 50 °C oil bath. After 4 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (50 mL) was added, followed by extraction with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated. Flash column chromatography (SiO_2, 25% Et_2O in hexanes) afforded quaternary β-amidoester **172h**

(903 mg, 83% yield) as a clear colorless oil: R_f = 0.32 (7:3 hexanes:Et_2O eluent); ^1H NMR (500 MHz, $CDCl_3$) δ 8.49–8.43 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.22 (m, 2H), 7.23–7.18 (m, 5H), 6.31 (dt, *J* = 1.8, 0.9 Hz, 1H), 5.81 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.21 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.16 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.64–4.56 (m, 2H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 3.74 (t, *J* = 6.3 Hz, 2H), 3.07 (dtd, *J* = 16.7, 4.7, 1.1 Hz, 1H), 2.96 (dddd, *J* = 16.6, 11.7, 4.6, 1.8 Hz, 1H), 2.59–2.49 (m, 2H), 2.41 (dt, *J* = 14.3, 6.1 Hz, 1H), 2.27 (ddd, *J* = 13.5, 11.8, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 167.9, 138.2, 137.2, 135.4, 131.4, 130.2, 128.4, 127.64, 127.62, 124.30, 124.28, 119.9, 118.9, 116.8, 105.3, 73.1, 66.8, 66.4, 55.3, 34.7, 30.3, 20.9; IR (Neat Film, NaCl) 3066, 3032, 2930, 2855, 1728, 1701, 1597, 1577, 1451, 1353, 1333, 1301, 1171, 1093, 1026, 973, 798, 733, 695 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1856, found 404.1865.



(*S*)-7-Allyl-7-(2-(benzyloxy)ethyl)-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (165h): A flame-dried 100 mL Schlenk Flask was charged with $Pd_2(pmdba)_3$ (56 mg, 51.1 μmol, 0.05 equiv), (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 77 mg, 0.13 mmol, 0.125 equiv), and a magnetic stirring bar in a N_2-filled glove box. The flask was then charged with TBME (28 mL) and stirred at 23 °C for 30 minutes, generating a dark purple solution. To the preformed catalyst solution was added a solution of **172h** (417 mg, 1.03 mmol, 1.0 equiv) in TBME (3 mL, including washings). The flask was sealed, removed from the glovebox, and

placed in a preheated 60 °C oil bath with stirring. Full consumption of starting material was achieved after 8 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO_2, 12% Et_2O → 25% Et_2O in hexanes) to afford α-quaternary DHPI **165h** (305 mg, 82% yield) as a faintly yellow oil: R_f = 0.5 (7:3 hexanes:Et_2O eluent); 94% *ee*, $[\alpha]_D^{25}$ +22.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49–8.46 (m, 1H), 7.49–7.46 (m, 1H), 7.30–7.25 (m, 2H), 7.25–7.20 (m, 5H), 6.30 (q, *J* = 1.3 Hz, 1H), 5.82 (ddt, *J* = 16.0, 11.2, 7.4 Hz, 1H), 5.15 (t, *J* = 1.1 Hz, 1H), 5.14–5.11 (m, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 3.69 (dt, *J* = 9.6, 6.9 Hz, 1H), 3.62 (ddd, *J* = 9.6, 7.2, 5.7 Hz, 1H), 3.05 (ddd, *J* = 7.5, 5.9, 1.3 Hz, 2H), 2.66 (ddt, *J* = 13.9, 7.0, 1.3 Hz, 1H), 2.49–2.42 (m, 1H), 2.29 (dt, *J* = 14.2, 7.1 Hz, 1H), 2.12–2.03 (m, 2H), 1.99 (ddd, *J* = 14.2, 6.9, 5.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 138.3, 137.7, 135.3, 133.2, 130.2, 128.4, 127.62, 127.59, 124.02. 123.96, 119.8, 119.3, 116.7, 104.7, 73.2, 66.7, 45.6, 40.9, 35.4, 29.5, 19.9; IR (Neat Film, NaCl) 3062, 3028, 2930, 2856, 1693, 1639, 1595, 1574, 1451, 1433, 1355, 1299, 1181, 1097, 1026, 1001, 915, 797, 733, 695 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{24}H_{26}NO_2$ $[M+H]^+$: 360.1958, found 360.1962; SFC conditions: 15% *i*-PrOH, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 8.83, minor = 9.71.

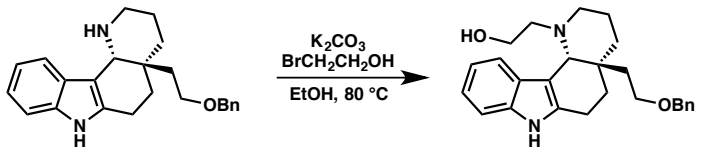


(4a*R*,11c*R*)-4a-(2-(Benzyloxy)ethyl)-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido[3,2-*c*]carbazole (210): A flame-dried round bottom flask was charged with α-quaternary DHPI **165h** (98 mg, 0.273 mmol, 1.0 equiv), THF (1.4 mL), and a magnetic stirring bar

in a N_2-filled glovebox. To this solution was added bis(cyclopentadienyl) zirconium chloride hydride (84 mg, 0.325 mmol, 1.2 equiv), and the mixture was stirred at 23 °C for 30 min. A second portion of bis(cyclopentadienyl) zirconium chloride hydride (14 mg, 54 μmol, 0.2 equiv) was added, and the reaction mixture was stirred for an additional 30 min at which point a brown solution was observed. Hydroxylamine-*O*-sulfonic acid (46 mg, 0.406 mmol, 1.5 equiv) was added, the vial was sealed and removed from the glovebox, and stirring was resumed at 23 °C in a fume hood for an additional 10 min. The reaction mixture was then cooled to 0 °C and $LiAlH_4$ (0.82 mL, 1.0 M in THF, 0.82 mmol, 3.0 equiv) was added over five minutes. The reaction was stirred at 0 °C for 15 minutes before careful quenching with H_2O (2.2 mL) and AcOH (6.6 mL). Stirring was continued at 23 °C for 12h, at which point complete equilibration to the desired Pictet–Spengler product **210** was observed by LCMS. The mixture was basified with 2N NaOH until pH > 12, and was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford crude *cis*-fused tetracycle **210** (96 mg), which was carried on without further purification.

An analytical sample of **210** was obtained after flash column chromatography (SiO_2, 2% Et_3N in EtOAc): off-white foam; R_f = 0.45 (19:1 EtOAc:Et_3N eluent); $[\alpha]_D^{25}$ – 23.1 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.35–7.24 (m, 6H), 7.14–7.01 (m, 2H), 4.45 (s, 2H), 3.75 (s, 1H), 3.61–3.54 (m, 2H), 3.01 (d, *J* = 12.2 Hz, 1H), 2.80–2.72 (m, 3H), 2.36 (app q, *J* = 10.2 Hz, 1H), 1.85–1.75 (m, 2H), 1.65–1.43 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 136.3, 134.1, 128.5, 127.60, 127.57, 127.5, 121.0, 119.3, 117.6, 112.1, 110.6, 73.0, 66.9, 56.7, 46.3, 36.7, 35.1, 34.4, 25.4, 22.8, 20.3; IR (Neat Film, NaCl) 3401, 3295, 3147, 3057, 3030,

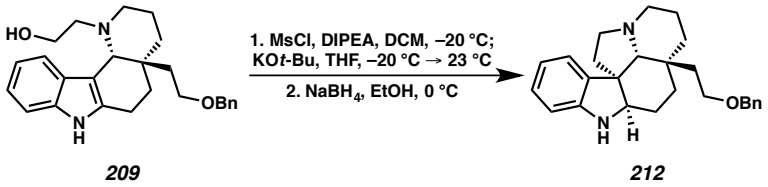
2926, 2854, 1622, 1588, 1495, 1466, 1452, 1364, 1328, 1101, 1028, 1011, 806, 739, 697 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{24}H_{29}N_2O$ $[M+H]^+$: 361.2274, found 361.2287.



210 ***209***

Ethanolamine 209: To a solution of crude *cis*-fused tetracycle **210** (96 mg, 0.266 mmol, 1.0 equiv) in EtOH (8.9 mL) were added 2-bromoethanol (0.15 mL, 2.11 mmol, 8.0 equiv), K_2CO_3 (295 mg, 2.11 mmol, 8.0 equiv) and a magnetic stirring bar. The suspension was heated to 80 °C and stirred for 4 h, at which point full consumption of starting material was observed by TLC analysis. The suspension was concentrated to dryness, partitioned between H_2O (75 mL) and EtOAc (75 mL), and extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1% Et_3N in EtOAc) gave ethanolamine **209** (68 mg, 62% yield in two steps from **165h**) as tan foam: R_f = 0.5 (19:1 EtOAc:Et_3N eluent); $[\alpha]_D^{25}$ +17.8 (*c* 1.28, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.42–7.38 (m, 1H), 7.32–7.28 (m, 2H), 7.27–7.22 (m, 4H), 7.12–7.05 (m, 2H), 4.40 (d, *J* = 11.9 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 3.56–3.42 (m, 3H), 3.24 (s, 1H), 3.17–3.07 (m, 3H), 2.87–2.72 (m, 3H), 2.26–2.17 (m, 2H), 1.89–1.74 (m, 2H), 1.66–1.51 (m, 3H), 1.48–1.41 (m, 1H), 1.30 (ddd, *J* = 14.1, 8.3, 5.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 136.2, 135.4, 129.9, 128.5, 127.62, 127.57, 121.1, 119.6, 117.8, 110.6, 110.5, 73.0, 67.0, 63.2, 58.0, 54.2, 52.3, 36.84, 36.82, 35.8, 25.2, 22.1, 20.5; IR (Neat Film, NaCl) 3406, 3212, 3178, 3107, 3060, 3031, 2943, 2871, 1619, 1584, 1496, 1452, 1366, 1329, 1305, 1246, 1187, 1104, 1075, 1038, 983, 903, 870, 741,

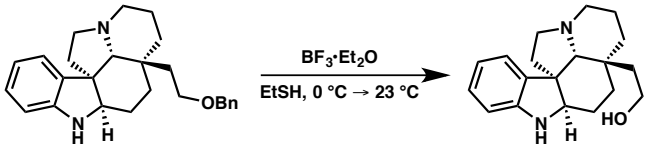
697 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{26}H_{33}N_2O_2$ $[M+H]^+$: 405.2537, found 405.2541.



209 ***212***

***O*-Benzyl Limaspermidine (212)**: To a solution of primary alcohol **209** (64 mg, 158 μmol, 1.0 equiv) and *N,N*-diisopropylethylamine (DIPEA, 36 μL, 206 μmol, 1.3 equiv) in CH_2Cl_2 (3.1 mL) was added methanesulfonyl chloride (MsCl, 12.5 μL, 161 μmol, 1.02 equiv) dropwise at –15 °C (ice/MeOH bath). After stirring at –15 °C for 45 min, KO*t*-Bu (0.79 mL, 0.5 M in THF, 0.395 mmol, 2.5 equiv) was added and the reaction mixture was allowed to warm to 0 °C over a period of 2 h. The reaction mixture was quenched with brine (25 mL), and extracted with EtOAc (5 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was dissolved in EtOH (4.8 mL) and the resulting solution cooled to 0 °C. $NaBH_4$ (30 mg, 0.79 mmol, 5.0 equiv) was added in three equal portions over 10 min. After stirring at 0 °C for 15 additional min, the reaction mixture was removed from the ice bath and stirring was continued for a further 3 h. Sodium citrate dihydrate (233 mg, 0.79 mmol, 5.0 equiv) and H_2O (5 mL) were added, and the mixture was stirred at 23 °C for 30 min. The reaction mixture was partitioned between H_2O (20 mL) and EtOAc (20 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 8% MeOH in CH_2Cl_2) gave *O*-benzyl limaspermidine (**212**, 44.6 mg, 73% yield) as faint yellow oil: R_f = 0. 22 (19:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +10.0 (*c* 0.44, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30

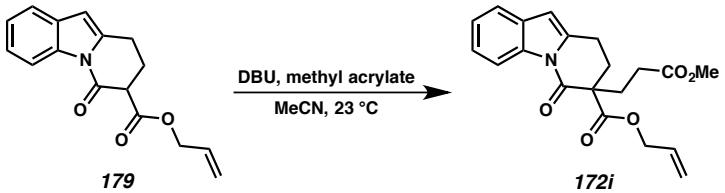
(dd, *J* = 8.0, 6.5 Hz, 2H), 7.27–7.23 (m, 1H), 7.22–7.19 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 7.02 (td, *J* = 7.6, 1.3 Hz, 1H), 6.74 (td, *J* = 7.3, 1.0 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.51 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.44 (ddd, *J* = 9.6, 8.1, 5.9 Hz, 1H), 3.40–3.35 (m, 1H), 3.15–3.10 (m, 1H), 3.05 (d, *J* = 11.0 Hz, 1H), 2.35–2.22 (m, 2H), 2.27 (s, 1H), 2.08–1.93 (m, 2H), 1.86 (ddd, *J* = 14.5, 8.3, 6.5 Hz, 1H), 1.80–1.70 (m, 1H), 1.66 (ddt, *J* = 13.0, 6.4, 3.1 Hz, 2H), 1.54–1.42 (m, 3H), 1.31–1.19 (m, 2H), 1.08–1.03 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 138.6, 135.4, 128.4, 127.7, 127.5, 127.4, 123.0, 119.4, 110.6, 72.8, 71.0, 66.2, 65.6, 53.9, 53.6, 53.0, 38.7, 36.9, 35.6, 35.5, 28.4, 24.4, 21.9; IR (Neat Film, NaCl) 3361, 3027, 2928, 2857, 2779, 2722, 1606, 1481, 1462, 1363, 1332, 1259, 1176, 1095, 1026, 740, 697 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{26}H_{33}N_2O$ $[M+H]^+$: 389.2587, found 389.2592.



XX ***6***
(+)-Limaspermidine

(+)-Limaspermidine (6): To a solution of *O*-benzyl limaspermidine (**212**, 21 mg, 54 μmol, 1.0 equiv) in EtSH (1.8 mL) was added BF_3•Et_2O (133 μL, 1.07 mmol, 20 equiv) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was transferred to a pre-heated 30 °C oil bath and stirred for an additional 4 h. After cooling to 23 °C and quenching with saturated aqueous $NHCO_3$ (5 mL) and H_2O (5 mL), the mixture was stirred for an additional 2 h, then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 8% MeOH in CH_2Cl_2) furnished (+)-limaspermidine (**6**, 13.5 mg,

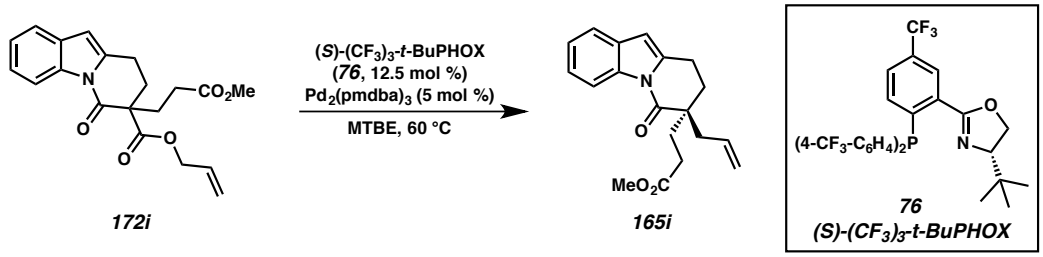
84% yield) as an off-white amorphous solid: R_f = 0. 27 (9:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +22.6 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.01 (td, *J* = 7.6, 1.3 Hz, 1H), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 3.63 (td, *J* = 10.0, 5.4 Hz, 1H), 3.58–3.48 (m, 2H), 3.16–3.10 (m, 1H), 3.04 (app dt, *J* = 10.9, 2.2 1H), 2.34–2.22 (m, 3H), 2.06 (td, *J* = 13.8, 3.5 Hz, 1H), 1.99 (ddd, *J* = 12.4, 10.9, 2.9 Hz, 1H), 1.81–1.67 (m, 3H), 1.65 (d, *J* = 13.5 Hz, 1H), 1.54–1.44 (m, 3H), 1.27 (td, *J* = 13.4, 4.6 Hz, 1H), 1.19 (ddd, *J* = 14.2, 9.3, 5.4 Hz, 1H), 1.04 (dd, *J* = 13.7, 3.8 Hz, 1H), 0.92 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 135.4, 127.5, 122.9, 119.3, 110.6, 70.8, 65.5, 58.8, 53.9, 53.6, 53.0, 40.6, 38.7, 35.62, 35.55, 28.4, 24.4, 21.9; IR (Neat Film, NaCl) 3308, 3149, 2930, 2858, 2816, 2793, 1607, 1466, 1320, 1256, 1216, 1166, 1041, 1015, 900, 749 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{27}N_2O$ $[M+H]^+$: 299.2118, found 299.2114.



179 ***172i***

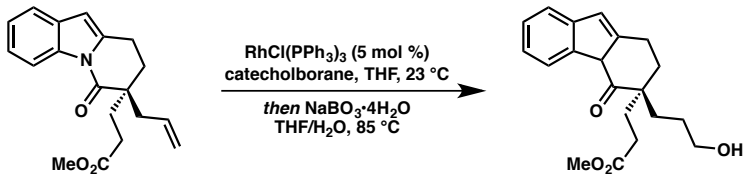
Allyl 7-(3-methoxy-3-oxopropyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172i): To a solution of β-amidoester **179** (530 mg, 1.96 mmol, 1.0 equiv) in MeCN (13.1 mL) were added methyl acrylate (0.36 mL, 3.92 mmol, 2.0 equiv) and DBU (15 μL, 98 μmol, 0.05 equiv) at 23 °C with stirring. After 90 min, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (100 mL) was added, followed by extraction with EtOAc (3 x 150 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), then dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 25% acetone in hexanes)

afforded quaternary β-amidoester **172i** (670 mg, 96% yield) as a light yellow oil: R_f = 0.33 (3:1 hexanes:acetone eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47–8.44 (m, 1H), 7.47–7.45 (m, 1H), 7.31–7.24 (m, 2H), 6.32 (dt, *J* = 1.7, 0.9 Hz, 1H), 5.83 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.65 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.67 (s, 3H), 3.09 (dtd, *J* = 16.8, 4.9, 1.1 Hz, 1H), 2.96 (dddd, *J* = 16.7, 11.5, 4.8, 1.8 Hz, 1H), 2.68 (ddd, *J* = 15.8, 9.3, 6.5 Hz, 1H), 2.55 – 2.47 (m, 2H), 2.44 (ddd, *J* = 10.7, 5.6, 3.9 Hz, 2H), 2.13 (ddd, *J* = 13.4, 11.4, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 170.9, 167.5, 136.8, 135.3, 131.2, 130.1, 124.44, 124.42, 120.0, 119.2, 116.8, 105.6, 66.5, 55.6, 52.0, 30.6, 30.0, 29.9, 20.8; IR (Neat Film, NaCl) 2951, 2854, 1738, 1704, 1600, 1577, 1455, 1375, 1357, 1315, 1227, 1176, 1087, 1034, 989, 935, 802, 755 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{20}H_{22}NO_5$ $[M+H]^+$: 356.1492, found 356.1498.



Methyl (*R*)-3-(7-allyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-7-yl)propanoate (165i): A flame-dried 250 mL Schlenk Flask was charged with $Pd_2(pmdba)_3$ (90 mg, 82.1 μmol, 0.05 equiv), (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 120 mg, 0.202 mmol, 0.125 equiv), and a magnetic stirring bar in a N_2-filled glove box. The flask was then charged with TBME (42 mL) and stirred at 23 °C for 30 minutes, generating a dark purple solution. To the preformed catalyst solution was added a solution of **172i** (580 mg, 1.63 mmol, 1.0 equiv) in TBME (7 mL, including washings). The flask was sealed, removed from the glovebox,

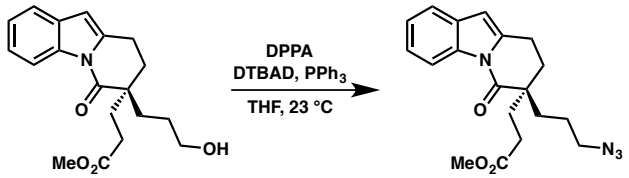
and placed in a preheated 60 °C oil bath with stirring. Full consumption of starting material was achieved after 12 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO_2, 25% Et_2O in hexanes) to afford α-quaternary DHPI **165i** (456 mg, 90% yield) as a yellow oil: R_f = 0.29 (7:3 hexanes:Et_2O eluent); 92% *ee*, $[\alpha]_D^{25}$ –4.2 (*c* 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47–8.43 (m, 1H), 7.47–7.44 (m, 1H), 7.29–7.22 (m, 2H), 6.30 (td, *J* = 1.4, 0.7 Hz, 1H), 5.85–5.75 (m, 1H), 5.18–5.16 (m, 1H), 5.15–5.14 (m, 1H), 3.64 (s, 3H), 3.07 (td, *J* = 6.7, 1.4 Hz, 2H), 2.63 (ddt, *J* = 14.1, 7.1, 1.2 Hz, 1H), 2.53–2.39 (m, 3H), 2.18–2.03 (m, 3H), 2.01–1.91 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 172.9, 137.4, 135.3, 132.8, 130.2, 124.14, 124.11, 119.9, 119.6, 116.7, 105.0, 51.9, 45.8, 40.2, 30.5, 29.6, 29.2, 19.7; IR (Neat Film, NaCl) 3459, 3376, 3077, 2948, 2865, 1731, 1694, 1639, 1597, 1575, 1452, 1358, 1310, 1258, 1176, 1101, 1031, 996, 920, 879, 800, 757, 644 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found 312.1584; SFC conditions: 7% *i*-PrOH, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 15.71, minor = 14.34.



165i ***215***

Primary alcohol 215: To a solution of DHPI **165i** (1.2 g, 3.85 mmol, 1.0 equiv) in THF (38 mL) were added $RhCl(PPh_3)_3$ (176 mg, 0.19 mmol, 0.05 equiv) and catecholborane (7.6 mL, 1.0 M in THF, 7.6 mmol, 2.0 equiv) sequentially at 23 °C. After stirring at 23 °C for 30 min, H_2O (10 mL) and $NaBO_3$•$4H_2O$ (2.9 g, 18.8 mmol, 5.0 equiv). The reaction mixture was transferred to a pre-heated 85 °C oil bath and stirred for 15 min.

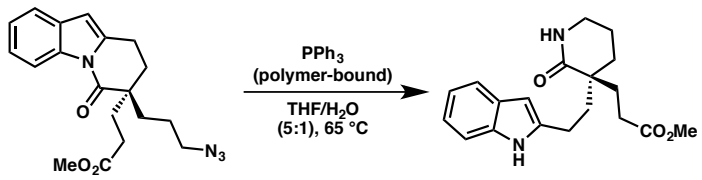
After cooling to 23 °C, the resulting suspension was filtered. The filter cake was washed with THF, and the filtrate was concentrated to dryness. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (40 mL), and the aqueous layer was extracted with CH_2Cl_2 (40 mL). The combined organic layers were washed with 1N aq. NaOH (3 x 40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 20% Et_2O in CH_2Cl_2) afforded alcohol **215** as a yellow oil (1.09 g, 86%): R_f = 0.21 (4:1 CH_2Cl_2:Et_2O eluent); $[\alpha]_D^{25}$ +10.9 (*c* 1.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44–8.41 (m, 1H), 7.47–7.44 (m, 1H), 7.29–7.21 (m, 2H), 6.29 (app q, *J* = 1.1 Hz, 1H), 3.66–3.61 (m, 2H), 3.64 (s, 3H), 3.07 (ddt, *J* = 7.2, 5.8, 1.3, 2H), 2.52–2.36 (m, 2H), 2.17–2.02 (m, 3H), 2.00–1.88 (m, 2H), 1.77–1.69 (m, 2H), 1.66–1.59 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 173.4, 137.3, 135.2, 130.2, 124.13, 124.10, 119.9, 116.7, 105.1, 62.8, 51.9, 45.6, 31.6, 30.6, 29.7, 29.2, 27.1, 19.7; IR (Neat Film, NaCl) 3449, 2948, 2869, 1736, 1695, 1598, 1575, 1454, 1379, 1356, 1335, 1311, 1181, 1056, 1024, 819, 802, 758 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1700, found 330.1705.



215 ***216***

Azide 216: To a solution of alcohol **215** (148 mg, 0.45 mmol, 1.0 equiv) in THF (2.3 mL) were added PPh_3 (147 mg, 0.56 mmol, 1.25 equiv), DPPA (0.11 mL, 0.52 mmol, 1.15 equiv), and DTBAD (129 mg, 0.56 mmol, 1.25 equiv) sequentially at 0 °C. After stirring for 15 min, the reaction mixture was removed from the cooling bath and stirred for an additional 30 min at 23 °C. 2N aq. HCl (1 mL) was added, the mixture was poured into

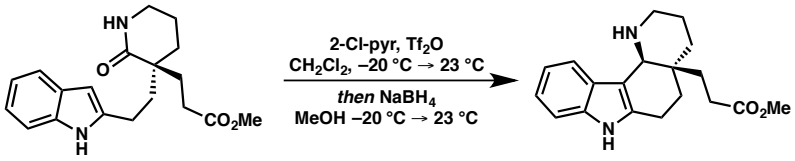
H_2O (20 mL), and was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 20% EtOAc in hexanes) afforded azide **216** as a yellow oil (132 mg, 83%): R_f = 0.33 (3:1 hexanes:EtOAc eluent); $[\alpha]_D^{25}$ –65.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45–8.41 (m, 1H), 7.49–7.43 (m, 1H), 7.31–7.21 (m, 2H), 6.31 (app q, *J* = 1.3 Hz, 1H), 3.65 (s, 3H), 3.32 (td, *J* = 6.4, 1.3 Hz, 2H), 3.09 (dddd, *J* = 7.2, 5.7, 4.4, 1.5 Hz, 2H), 2.50–2.37 (m, 2H), 2.18–2.06 (m, 2H), 2.06–1.96 (m, 2H), 1.95–1.84 (m, 1H), 1.77–1.61 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 172.8, 137.1, 135.3, 130.2, 124.23, 124.19, 119.9, 116.7, 105.2, 52.0, 51.8, 45.6, 32.7, 30.5, 29.8, 29.1, 23.7, 19.7; IR (Neat Film, NaCl) 2949, 2868, 2096, 1736, 1694, 1597, 1575, 1454, 1380, 1356, 1336, 1312, 1302, 1262, 1179, 1027, 1000, 819, 803, 758 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{23}N_4O_3$ $[M+H]^+$: 355.1765, found 355.1767.



216 ***214***

Methyl (*R*)-3-(3-(2-(1*H*-indol-2-yl)ethyl)-2-oxopiperidin-3-yl)propanoate (214): To a solution of azide **216** (700 mg, 1.97 mmol, 1.0 equiv) in THF (20 mL) and H_2O (4 mL) was added polymer-bound PPh_3 (1.31 g, ~3 mmol/g loading, 3.94 mmol, 2.0 equiv) in one portion. The reaction mixture was placed in a pre-heated oil bath and stirred at 65 °C for 4 h. After cooling to 23 °C, the reaction mixture filtered, washing with EtOAc, and the filtrate was concentrated to dryness. Flash column chromatography (SiO_2, 4% MeOH in CH_2Cl_2) afforded δ-lactam **214** as a light yellow foam (525 mg, 81%): R_f = 0.27 (19:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ –21.4 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37

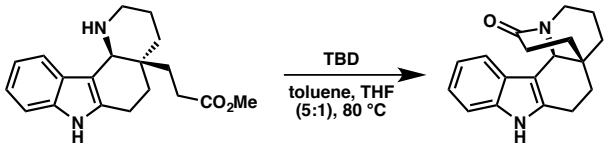
(br s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.30–7.27 (m, 1H), 7.10 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.04 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.21 (s, 1H), 5.85 (br s, 1H), 3.66 (s, 3H), 3.32 (td, *J* = 5.7, 2.1 Hz, 2H), 2.86 (ddd, *J* = 14.6, 11.1, 5.8 Hz, 1H), 2.69 (ddd, *J* = 15.0, 11.0, 4.5 Hz, 1H), 2.42 (h, *J* = 8.5 Hz, 2H), 2.16 (ddd, *J* = 13.7, 11.2, 4.6 Hz, 1H), 2.01 (t, *J* = 8.2 Hz, 2H), 1.91–1.80 (m, 4H), 1.77–1.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 174.1, 139.5, 136.2, 128.7, 121.1, 119.8, 119.5, 110.7, 99.4, 51.9, 44.3, 42.8, 37.5, 33.2, 30.2, 29.4, 23.6, 19.5; IR (Neat Film, NaCl) 3287, 3054, 2949, 2870, 1731, 1645, 1551, 1489, 1456, 1417, 1289, 1173, 1094, 1061, 1012, 910, 782, 748 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{25}N_2O_3$ $[M+H]^+$: 329.1860, found 329.1868.



214 ***213***

***Trans*-fused tetracycle 213**: To a solution of δ-lactam **214** (111 mg, 0.338 mmol, 1.0 equiv) in CH_2Cl_2 (8.4 mL) were added 2-chloropyridine (39 μL, 0.405 mmol, 1.2 equiv) and triflic anhydride (63 μL, 0.372 mmol, 1.1 equiv) at –20 °C (dry ice in H_2O/MeOH (7:3) bath). After 15 min, the reaction mixture was removed from the cooling bath and stirring continued for a further 15 min. At this time, the reaction mixture was cooled back to –20 °C and a solution of $NaBH_4$ (64 mg, 1.69 mmol, 5.0 equiv) in MeOH (8.4 mL) was added dropwise over a period of two minutes. The reaction was diluted with CH_2Cl_2 and quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The biphasic mixture was poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1% MeOH → 8% MeOH in CH_2Cl_2) afforded *trans*-fused

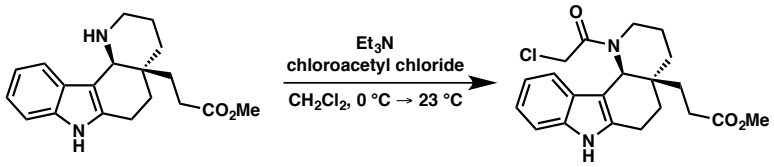
tetracycle **213** (89 mg, 84% yield) as a yellow foam: R_f = 0.22 (9:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +21.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.9 Hz, 1H), 7.82 (br s, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.07 (ddd, *J* = 8.1, 7.1, 1.4 Hz, 1H), 7.01 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 3.96 (app t, *J* = 2.0 Hz, 1H), 3.61 (s, 3H), 3.33–3.26 (m, 1H), 2.91 (td, *J* = 12.9, 3.8 Hz, 1H), 2.75 (dddd, *J* = 20.2, 11.8, 6.2, 3.1 Hz, 1H), 2.65 (ddt, *J* = 16.7, 6.4, 1.4 Hz, 1H), 2.30 (ddd, *J* = 14.8, 12.1, 5.5 Hz, 1H), 2.20 (ddd, *J* = 14.8, 11.9, 4.8 Hz, 1H), 1.98 (td, *J* = 13.4, 12.7, 5.3 Hz, 1H), 1.78–1.69 (m, 3H), 1.62–1.42 (m, 3H), 1.35–1.23 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 136.1, 133.1, 127.2, 120.9, 120.5, 119.2, 110.8, 110.4, 64.1, 51.8, 47.2, 35.5, 33.6, 32.0, 29.0, 22.5, 20.6, 20.3; IR (Neat Film, NaCl) 3395, 3177, 3054, 2926, 2856, 1731, 1619, 1579, 1465, 1435, 1317, 1250, 1198, 1174, 1142, 1109, 1014, 875, 856, 739, 693 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{25}N_2O_2$ $[M+H]^+$: 313.1911, found 313.1905.



213 ***218***

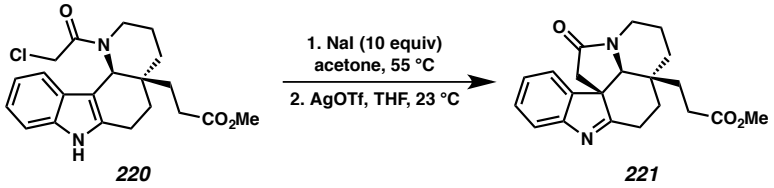
Pentacyclic lactam 218: In an N_2-filled glovebox, an oven-dried scintillation vial was charged with a magnetic stirring bar, *cis*-fused tetracycle **213** (56 mg, 0.179 mmol, 1.0 equiv), toluene (2.2 mL), THF (0.44 mL), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 25 mg, 0.179 mmol, 1.0 equiv) at 23 °C. The vial was sealed and removed from the glovebox and placed in a pre-heated 80 °C heating block. After stirring for 5 h at 80 °C, the reaction mixture was cooled to 23 °C stripped onto silica gel. Flash column chromatography (SiO_2, 2% MeOH in CH_2Cl_2) afforded lactam **218** (32.5 mg, 65% yield) as a white amorphous solid: R_f = 0.32 (19:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ –17.5 (*c* 0.38,

$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.72–7.67 (m, 1H), 7.26 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.02 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.41 (dd, *J* = 12.9, 5.6 Hz, 1H), 4.33 (app t, *J* = 2.0 Hz, 1H), 3.15 (td, *J* = 12.8, 3.3 Hz, 1H), 3.02 (dddd, *J* = 13.6, 11.1, 6.6, 3.2 Hz, 1H), 2.76 (ddt, *J* = 17.2, 5.8, 1.7 Hz, 1H), 2.11–2.04 (m, 2H), 2.01–1.83 (m, 4H), 1.73–1.67 (m, 2H), 1.59–1.48 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.1, 136.3, 133.2, 125.1, 121.9, 120.3, 119.8, 111.2, 110.4, 64.4, 53.8, 39.9, 37.0, 35.0, 34.6, 27.8, 22.5, 19.8; IR (Neat Film, NaCl) 3273, 3059, 2924, 2853, 1657, 1464, 1409, 1328, 1245, 1163, 1131, 1075, 910, 846, 804, 738 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{18}H_{21}N_2O$ $[M+H]^+$: 281.1648, found 281.1649.



213 ***220***

α-Chloroacetamide 220: To a solution of tetracycle **213** (140 mg, 0.45 mmol, 1.0 equiv) and Et_3N (102 μL, 0.73 mmol, 1.6 equiv) in CH_2Cl_2 (5 mL) was added chloroacetyl chloride (36 μL, 0.45 mmol, 1.0 equiv) dropwise at 0 °C. After stirring for 15 min at 0 °C, the reaction was quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to afford α-chloroacetamide **220** (170 mg, R_f = 0.41 in 9:1 CH_2Cl_2:MeOH eluent), which was immediately advanced without further purification.



220 ***221***

Indolenine 221: To a solution of crude α-chloroacetamide **220** (170 mg) in acetone (3 mL) was added sodium iodide (670 mg, 4.5 mmol, 10 equiv) at 23 °C. The reaction was heated to 55 °C for 2 h in the dark. After cooling to 23 °C, H_2O (5 mL) was added, and the mixture was extracted with EtOAc (3 x 5mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford an α-iodoacetamide intermediate, which was immediately advanced without further purification.

To a solution of the crude α-iodoacetamide in THF (6 mL) was added AgOTf (226 mg, 0.88 mmol, 2.0 equiv) at 23 °C. The flask was covered with aluminum foil and the mixture was stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was separated and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 2% MeOH in CH_2Cl_2) afforded indolenine **221** as a light yellow oil (96 mg, 61% yield): R_f = 0.39 (19:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +35.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.36 (td, *J* = 7.6, 1.2 Hz, 1H), 7.31 (ddd, *J* = 7.5, 1.2, 0.6 Hz, 1H), 7.19 (td, *J* = 7.5, 1.1 Hz, 1H), 4.31 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.71 (s, 3H), 3.19 (d, *J* = 17.0 Hz, 1H), 3.07–2.99 (m, 3H), 2.94 (s, 1H), 2.40 (dd, *J* = 17.0, 1.4 Hz, 1H), 2.31–2.26 (m, 3H), 1.99 (ddd, *J* = 13.9, 4.3, 2.9 Hz, 2H), 1.94–1.85 (m, 1H), 1.81 (ddd, *J* = 13.9, 4.8, 2.1 Hz, 1H), 1.62–1.54 (m, 1H), 1.23–1.13 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.6, 173.5, 172.0, 153.1, 146.0, 128.8, 126.4, 121.3, 120.5, 74.3, 57.1, 52.2, 40.1, 39.7, 39.3, 34.6,

33.4, 29.1, 28.5, 21.8, 19.2; IR (Neat Film, NaCl) 2948, 2865, 1736, 1690, 1565, 1460, 1423, 1260, 1196, 1062, 916, 869, 766, 730 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{21}H_{25}N_2O_3$ $[M+H]^+$: 353.1860, found 353.1852.

3.11.3 COMPARISON OF SYNTHETIC (+)-LIMASPERMIDINE TO PUBLISHED DATA

*Table 3.11.3.1. Comparison of Synthetic (+)-Limaspermidine (**6**) ^1H NMR Data.*

This Work	**Movassaghi's Report**[25]
^1H NMR (500 MHz, $CDCl_3$)	*^1H NMR (400 MHz, $CDCl_3$)*
7.08 (dd, *J* = 7.4, 1.2 Hz, 1H)	7.08 (d, *J* = 7.7 Hz, 1H)
7.01 (td, *J* = 7.6, 1.3 Hz, 1H)	7.01 (app td, *J* = 7.6, 1.3 Hz, 1H)
6.73 (td, *J* = 7.4, 1.0 Hz, 1H)	6.73 (app td, *J* = 7.4, 1.0 Hz, 1H)
6.64 (d, *J* = 7.7 Hz, 1H)	6.64 (d, *J* = 7.7 Hz, 1H)
3.63 (td, *J* = 10.0, 5.4 Hz, 1H)	3.63 (td, *J* = 10.0, 5.5 Hz, 1H)
3.58–3.48 (m, 2H)	3.58–3.47 (m, 2H)
3.16–3.10 (m, 1H)	3.17–3.08 (m, 1H)
3.04 (app dt, *J* = 10.9, 2.2 Hz, 1H)	3.05 (d, *J* = 11.1 Hz, 1H)
2.34–2.22 (m, 3H)	2.37–2.17 (m, 3H)
2.06 (td, *J* = 13.8, 3.5 Hz, 1H)	2.16–1.90 (m, 2H)
1.99 (ddd, *J* = 12.4, 10.9, 2.9 Hz, 1H)	
1.81–1.67 (m, 3H)	1.87–1.58 (m, 5H)
1.65 (d, *J* = 13.5 Hz, 1H)	
1.54–1.44 (m, 3H)	1.58–1.37 (m, 3H)
1.27 (td, *J* = 13.4, 4.6 Hz, 1H)	1.37–1.12 (m, 2H)
1.19 (ddd, *J* = 14.2, 9.3, 5.4 Hz, 1H)	
1.04 (dd, *J* = 13.7, 3.8 Hz, 1H)	1.03 (d, *J* = 13.7 Hz, 1H)
0.92 (br s, 1H)	0.89 (br s, 1H)

*Table 3.11.3.2. Comparison of Synthetic (+)-Limaspermidine (**6**) ^{13}C NMR Data.*

This Report	**Movassaghi's Report**[25]
^{13}C NMR (126 MHz, $CDCl_3$)	*^{13}C NMR (125 MHz, $CDCl_3$)*
149.6	149.6
135.4	135.4
127.5	127.5
122.9	122.9
119.3	119.3
110.6	110.6
70.8	70.8
65.5	65.5
58.8	58.8
53.9	53.9
53.6	53.6
53.0	53.0
40.6	40.7
38.7	38.7
35.62	35.6
35.55	35.6
28.4	28.4
24.4	24.5
21.9	21.9

3.12 NOTES AND REFERENCES

1. For reviews on *Aspidosperma* alkaloids, see: (a) Saxton, J. E. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, **1998**; *Vol. 51*, 1–197. (b) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547.

2. For a review on *Kopsia* alkaloids, see: Kam, T.-S.; Lim, K.-H. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier, New York, **2008**, *Vol. 66*, 1–111.

3. For isolation of (+)-aspidospermidine (**1**) and (+)-limaspermidine (**6**), respectively, see: (a) Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. *Tetrahedron Lett.* **1961**, *2*, 485–492. (b) Medina, J. D.; Di Genova, L. *Planta Med.* **1979**, *37*, 165–167.

4. For isolation of (+)-kopsihainanine A (**22**), (–)-kopsinine (**20**), and (–)-kopsinilam (**199**), respectively, see: (a) Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem.* **2011**, *9*, 5334–5336. (b) Crow, W. D.; Michael, M. *Aust. J. Chem.* **1955**, *8*, 129–135. (c) Kump, C.; Schmid, H. *Helv. Chim. Acta* **1962**, *45*, 1090–1050.

5. Pritchett, B. P.; Kikuchi, J.; Numajiri, Y.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 13529–13532.

6. For examples of similar Bischler–Napieralski cyclizations toward monoterpene indole alkaloids, albeit not from DHPI starting materials, see: (a) Nicolaou, K. C.; Dalby, S. M.; Majumder, U. *J. Am. Chem. Soc.* **2008**, *130*, 14942–14943. (b) Chen, Z.; Zhou, S.; Jia, Y. *J. Org. Chem.* **2015**, *80*, 12545–12551. (c) Mizutani, M.; Yasuda, S.; Mukai, C. *Chem. Commun.* **2014**, *50*, 5782–5785. (d) Medley, J.

W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4572–4576. (e) Mewald, M.; Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 11634–11639. (f) White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389.

7. Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909–8914.

8. For best results, (2-benzyloxy)ethyl iodide (**196**) should be stored in a freezer and used within two months of preparation.

9. Other debenzylation conditions such as Pd-catalyzed hydrogenolysis, Na-naphthalenide reduction, and BF_3•Et_2O in Me_2S were unsuccessful.

10. For seminal publications, see: (a) Männig, D.; Nöth, H. *Angew. Chem. Int. Ed.* **1985**, *24*, 878–879. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917–6918.

11. For Table 3.6.1 entry 1, a solvent swap was required following amide activation. For entries 2 and 3, a solution of $NaBH_4$ in MeOH was added directly to the reaction mixture at –15 °C. For details, see the experimental section.

12. Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102–15108.

13. Screening various combinations of base (Na_2CO_3, K_2CO_3, and Cs_2CO_3), solvent (acetone, MeOH, and MeCN), and electrophile (1-chloro-2-iodoethane, 2-bromoethanol, and TBS-protected 2-bromoethanol) resulted in no desired N-alkylation.

14. Chloroacetaldehyde was used as a 50% by weight solution in water. It is conceivable that the excess water present made iminium formation difficult.

15. We have yet to isolate alkyl chloride **219**.

16. In the case of organolithium additions, the authors propose a radical pathway based on EPR studies. For details, see: Rodríguez, J. G.; Urrutia, A. *Tetrahedron* **1998**, *54*, 15613–15618.

17. For an example, see: Wei, Y.; Zhao, D.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12988–12991.

18. Dufour, M.; Gramain, J.-C.; Husson, H.-P.; Sinibaldi, M.-E.; Troin, Y. *J. Org. Chem.* **1990**, *55*, 5483–5490, and references therein.

19. (a) Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4113–4116. (b) Yi, W.; Zhao, D.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12988–12991. (c) Leng, L.; Zhou, X.; Liao, Q.; Wang, F.; Song, H.; Zhang, D.; Liu, X.-Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 3703–3707. (d) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 4117–4121. (e) Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444–11449. (f) Shen, X.-L.; Zhao, R.-R.; Mo, M.-J.; Peng, F.-Z.; Zhang, H.-B.; Shao, X.-H. *J. Org. Chem.* **2014**, *79*, 2473–2480.

20. Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

21. McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

22. (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–256. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.

23. Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486–3487.

24. King, B. W. Lactam Derivatives as Inhibitors of Matrix Metalloproteinases and/or TNF-Alpha Converting Enzyme. US Patent 2004266751, December 30, 2004.

25. White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389.

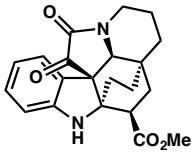
APPENDIX 5

Miscellaneous Studies Relevant to Chapter 3

A5.1 INTRODUCTION

This section presents alternative syntheses of intermediates from Chapter 3, along with an unoptimized synthesis of a highly advanced pentacyclic intermediate toward (–)-kopsifoline G (**227**, Figure A5.1.1).[1]

*Figure A5.1.1. Structure of (–)-Kopsifoline G (**227**)*



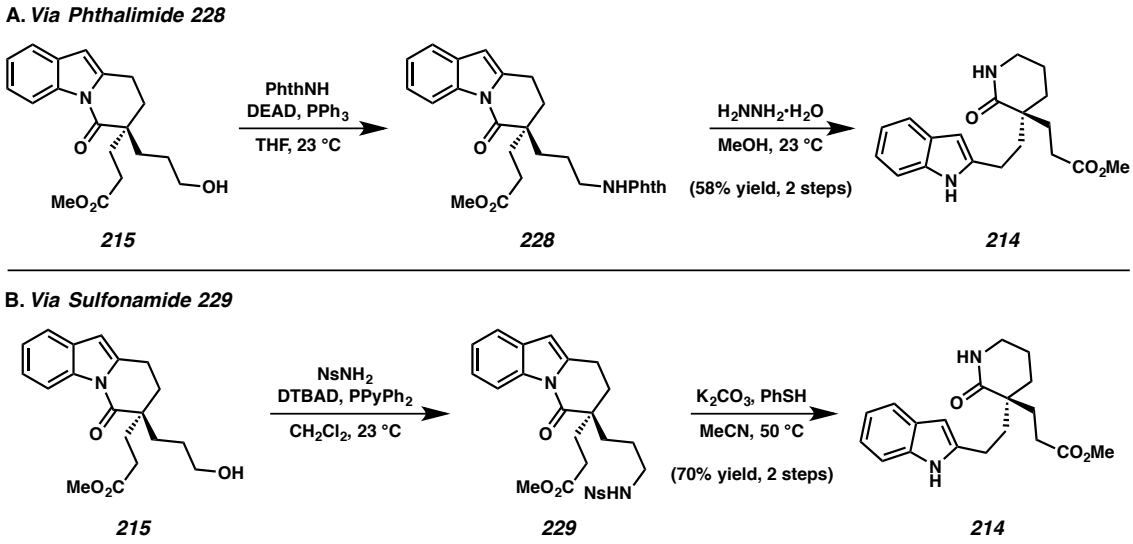
227
(–)-Kopsifoline G

A5.2 ALTERNATIVE ROUTES TO δ-LACTAM 214

Our initial synthesis of lactam **214** involved the Mitsunobu displacement of primary alcohol **215** with phthalimide to give **227** (Scheme A5.2.1A). Unfortunately, we found that despite multiple iterations of column chromatography, primary phthalimide **227** could not be rigorously purified. Hydrazinolysis of the impure material revealed the primary amine, and ensuing translactamization gave δ-lactam **214** in 58% yield over two steps Alternatively, Mitsunobu displacement of alcohol **215** with 2-

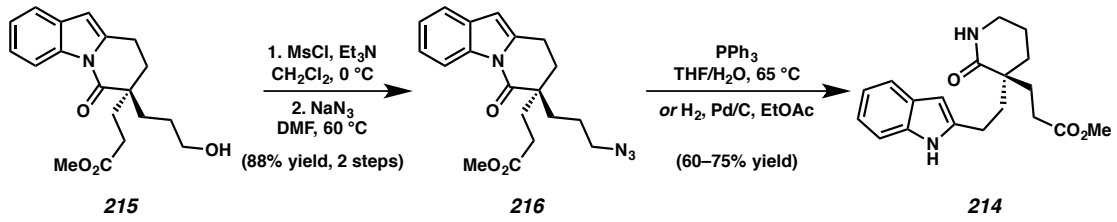
nitrobenzenesulfonamide gave sulfonamide **228** (Scheme A5.2.1B). Treatment of sulfonamide **228** with thiophenol effected amine deprotection and concomitant translactamization to arrive at **214** in 70% yield over two steps. We noticed that the thiol-promoted deprotection/cyclization failed to reach full conversion on larger scale, even at elevated temperatures. Given these complications, we decided to move forward with an azide as a masked primary amine.

*Scheme A5.2.1. Alternative Syntheses of Lactam **214***



A traditional mesylate formation/azide displacement protocol proceeded in 88% yield over two steps (Scheme A5.2.2). We examined several conditions for the reduction of azide **216**, including hydrogenation and Staudinger reactions, but the aforementioned use of polymer-bound PPh_3 proved synthetically superior in this context.

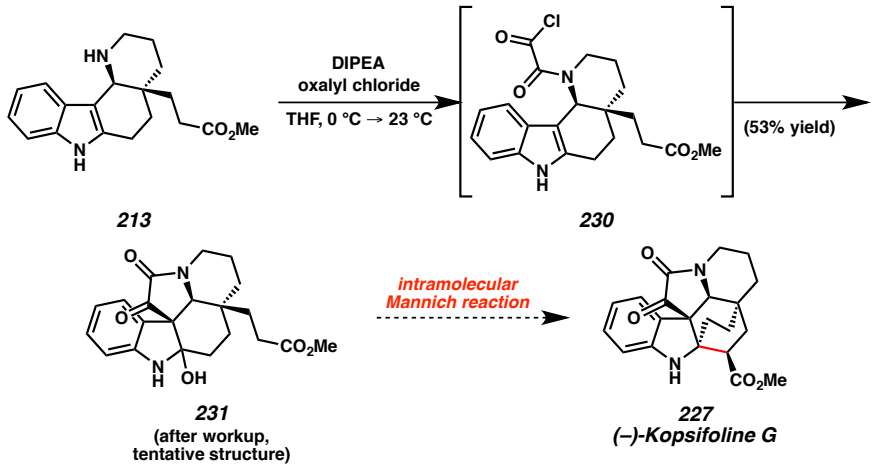
*Scheme A5.2.2. Alternative Synthesis and Reduction of Azide **216***



A5.3 ONE-POT ACYLATION/ANNULATION WITH OXALYL CHLORIDE

In our efforts to synthesize complex polycyclic *Kopsia* alkaloids (e.g., **227**), we found that N-acylation of tetracycle **213** could be achieved under mild conditions (*vide supra*). We thus postulated that **213** could react with oxalyl chloride to give an *N*-oxalyl piperidine intermediate (**230**), which would be poised to undergo a Friedel–Crafts-type acylation at C3 of the indole nucleus (Scheme A5.3.1). In the event, treatment of **213** with oxalyl chloride afforded what we believe to be hemiaminal **231** in 53% yield.[2]

*Scheme A5.3.1. A Pyrrolidine-Dione Annulation Toward (–)-Kopsifoline G (**227**)*



A5.4 CONCLUSIONS

Our investigations toward the enantioselective synthesis of complex *Kopsia* alkaloids revealed that the best method for introducing the piperidine nitrogen (N4)[3] found in these targets is via an azide. Furthermore, while multiple conditions successfully promote azide reduction with concomitant cyclization, the best reagent for this transformation proved to be polymer-bound PPh_3. Lastly, we found that tetracycle **213** could react with oxalyl chloride in an N-acylation/Friedel–Crafts acylation cascade to

give pyrrolidine-dione-containing **231**, which has been tentatively assigned by HRMS, IR, and 2D NMR data.

A5.5 EXPERIMENTAL SECTION

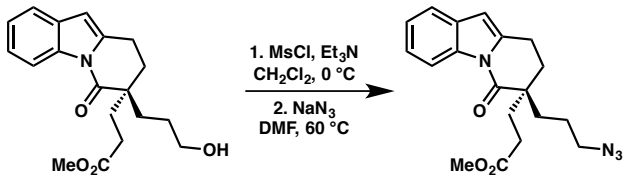
A5.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[4] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, CAM, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. Melting points were measured with BÜCHI Melting Point B-545. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, br t = broad triplet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment

(FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in mixed ionization mode (MM: ESI/APCI).

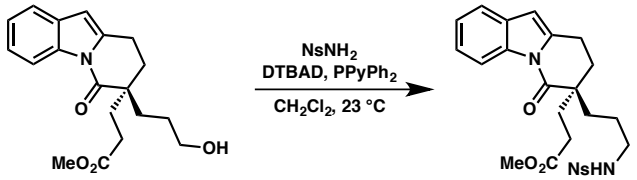
Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated.

A5.5.2 EXPERIMENTAL PROCEDURES



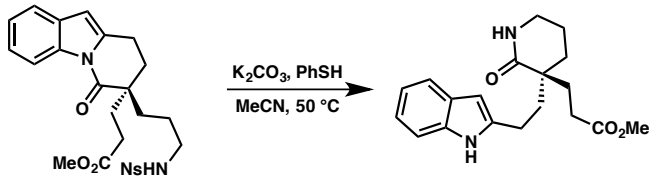
215 *216*

Azide 216: To a solution of alcohol **215** (1.1 g, 3.33 mmol, 1.0 equiv) and Et_3N (1.5 mL, 10.76 mmol, 3.2 equiv) in CH_2Cl_2 (24 mL) was added methanesulfonyl chloride (MsCl, 0.28 mL, 3.62 mmol, 1.09 equiv) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, then was quenched with sat. aq. $NaHCO_3$ (10 mL). After stirring for an additional 15 min, the aqueous layer was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was dissolved in DMF (24 mL), and NaN_3 (240 mg, 3.69 mmol, 1.1 equiv) was added. The suspension was stirred at 60 °C for 1h, at which point complete consumption of starting material was determine by TLC analysis. The reaction mixture was diluted with H_2O (20 mL), and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with H_2O (2×20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. Flash column chromatography (SiO_2, 20% EtOAc in hexanes) afforded azide **216** as a yellow oil (1.04 g, 88% over two steps): R_f = 0.33 (3:1 hexanes:EtOAc eluent). Physical and spectral data matched those reported in Chapter 3.



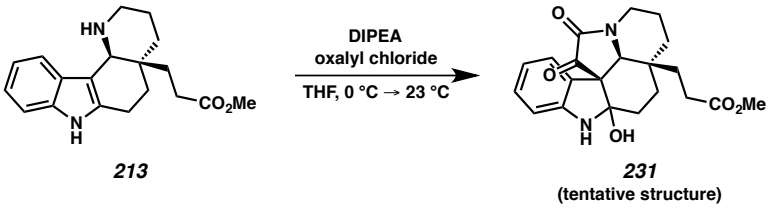
215 ***229***

Sulfonamide 229: To a solution of alcohol **215** (164 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) were added 2-nitrobenzenesulfonamide (306 mg, 1.5 mmol, 3.0 equiv), diphenyl-2-pyridylphosphine (263 mg, 1.0 mmol, 2.0 equiv) at 23 °C. Di-*tert*-butylazodicarboxylate (1 mL, 1.0 M in CH_2Cl_2, 2.0 equiv) was added over 30 min via syringe pump, and the resulting mixture was stirred at 23 °C for an additional 2 h. HCl (5 mL, 4.0 M in 1,4-dioxane) was added, and after stirring for 1 h, the reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with 4 M aq. HCl (2 x 20 mL). the organic layer was dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 20% EtOAc in hexanes) afforded sulfonamide **229** (216 mg, 85%) as a yellow foam: R_f = 0.29 (4:1 hexanes:EtOAc eluent); $[\alpha]_D^{25}$ –87.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39–8.34 (m, 1H), 8.07 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.66 (td, *J* = 7.6, 1.5 Hz, 1H), 7.60 (td, *J* = 7.7, 1.6 Hz, 1H), 7.48–7.44 (m, 1H), 7.28–7.24 (m, 2H), 6.30 (q, *J* = 1.2 Hz, 1H), 5.36 (t, *J* = 6.1 Hz, 1H), 3.64 (s, 3H), 3.14 (qd, *J* = 6.4, 1.6 Hz, 2H), 3.05 (tdd, *J* = 7.1, 5.4, 1.5 Hz, 2H), 2.37 (dt, *J* = 10.1, 6.6 Hz, 2H), 2.12–1.90 (m, 4H), 1.86–1.79 (m, 1H), 1.68–1.58 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 172.7, 148.1, 137.1, 135.2, 133.8, 133.7, 132.9, 131.1, 130.2, 125.5, 124.24, 124.20, 120.0, 116.7, 105.2, 52.0, 45.5, 44.2, 32.4, 30.5, 29.7, 29.0, 24.5, 19.6; IR (Neat Film, NaCl) 3332, 2949, 1731, 1692, 1596, 1539, 1453, 1440, 1357, 1341, 1312, 1166, 1078, 909, 853, 782, 759, 730, 654 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{25}H_{31}N_4O_7S$ $[M+NH_4]^+$: 531.1908, found 531.1915.

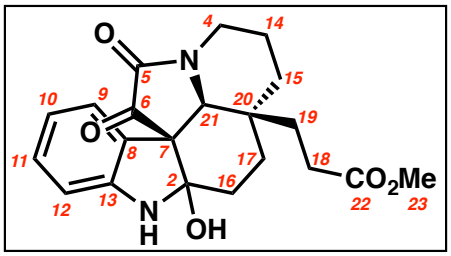


229 ***214***

Methyl (*R*)-3-(3-(2-(1*H*-indol-2-yl)ethyl)-2-oxopiperidin-3-yl)propanoate (214): To a solution of sulfonamide **229** (308 mg, 0.6 mmol, 1.0 equiv) in MeCN (10 mL) were added thiophenol (195 mg, 1.77 mmol, 3.0 equiv) and K_2CO_3 (325 mg, 2.4 mmol, 4.0 equiv) at 23 °C. The reaction mixture was placed in a pre-heated oil bath and stirred at 50 °C for 12 h. After cooling to 23 °C, the reaction mixture was concentrated to dryness. Flash column chromatography (SiO_2, 4% MeOH in CH_2Cl_2) afforded δ-lactam **214** as a light yellow foam (163 mg, 83%): R_f = 0.27 (19:1 CH_2Cl_2:MeOH eluent). Physical and spectral data matched those reported in Chapter 3.



213 ***231***
(tentative structure)



Hemiaminal 231: To a solution of tetracycle **213** (15 mg, 48 μmol, 1.0 equiv) in THF (1 mL) was added *N,N*-diisopropylethylamine (DIPEA, 14.4 μL, 106 μmol, 2.2 equiv) and oxalyl chloride (4.3 μL, 50 μmol, 1.05 equiv) at 0 °C. After 30 min, the reaction mixture was removed from the cooling bath and allowed to stir at 23 °C for an additional 2.5 h. At this time, full consumption of starting material was determined by TLC analysis.

Saturated aq. $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (SiO_2, 2% MeOH in CH_2Cl_2) afforded hemiaminal **231**[5] (9.8 mg, 53% yield) as a light orange amorphous solid: R_f = 0.3 (19:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +124.2 (*c* 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (td, *J* = 7.7, 1.2 Hz, 1H, C_{10}**H**), 7.03 (dd, *J* = 7.6, 0.7 Hz, 1H, C_9**H**), 6.78 (td, *J* = 7.5, 1.0 Hz, 1H, C_{11}**H**), 6.64 (ddd, *J* = 7.9, 1.0, 0.5 Hz, 1H, C_{12}**H**), 5.27 (s, 1H), 4.19 (dd, *J* = 13.4, 6.1 Hz, 1H, C_3**H**$_a$), 4.12 (s, 1H), 3.67 (s, 3H, C_{23}**H**$_3$), 3.65 (s, 1H, C_{21}**H**), 2.85–2.75 (m, 2H, C_{16}**H**$_a$, C_3**H**$_b$), 2.64 (dt, *J* = 19.5, 9.5 Hz, 1H, C_{21}**H**$_b$), 2.24 (ddd, *J* = 9.1, 6.4, 4.0 Hz, 2H, C_{18}**H**$_2$), 2.00 (ddd, *J* = 14.7, 9.5, 1.3 Hz, 1H,), 1.95–1.90 (m, 1H), 1.89–1.80 (m, 3H), 1.66–1.60 (m, 1H), 1.48–1.39 (m, 1H), 1.38–1.30 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.1 (**C**$_6$), 173.3 (**C**$_{22}$), 168.3 (**C**$_5$), 147.7 (**C**$_8$), 130.2 (**C**$_{10}$), 129.8 (**C**$_{13}$), 122.9 (**C**$_9$), 120.2 (**C**$_{11}$), 110.8 (**C**$_{12}$), 95.4 (**C**$_2$), 74.4 (**C**$_{21}$), 59.4 (**C**$_7$), 52.1 (**C**$_{23}$), 39.8 (**C**$_3$), 36.6 (**C**$_{20}$), 34.3 (**C**$_{16}$), 32.9, 28.9, 28.6 (**C**$_{18}$), 21.0 (**C**$_{19}$), 19.6; IR (Neat Film, NaCl) 3486, 3294, 3015, 2950, 2871, 1732, 1693, 1603, 1484, 1468, 1442, 1315, 1271, 1171, 1130, 1019, 752 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{21}H_{25}N_2O_5$ $[M+H]^+$: 385.1758, found 385.1752.

A5.6 NOTES AND REFERENCES

1. For the isolation of (–)-kopsifoline G (**227**), see: Chen, J.; Li, X.; Li, N.; Lu, J.; Xu, X.; Duan, H.; Qin, L. *Chem. Nat. Compd.* **2012**, *48*, 834–835.
2. This reaction has not been optimized. The structural assignment of **231** was tentatively assigned according to HRMS, IR and 2D NMR data. For details, see the experimental information. We cannot make a definitive claim regarding the stereochemistry of the hemiaminal.
3. For a uniform numbering system of monoterpene indole alkaloids, see: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–510.
4. Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
5. Some preliminary ^{1}H and ^{13}C assignments for compound **231** have been made. See the inset for numbering.

APPENDIX 6

Synthetic Summary for Chapter 3:

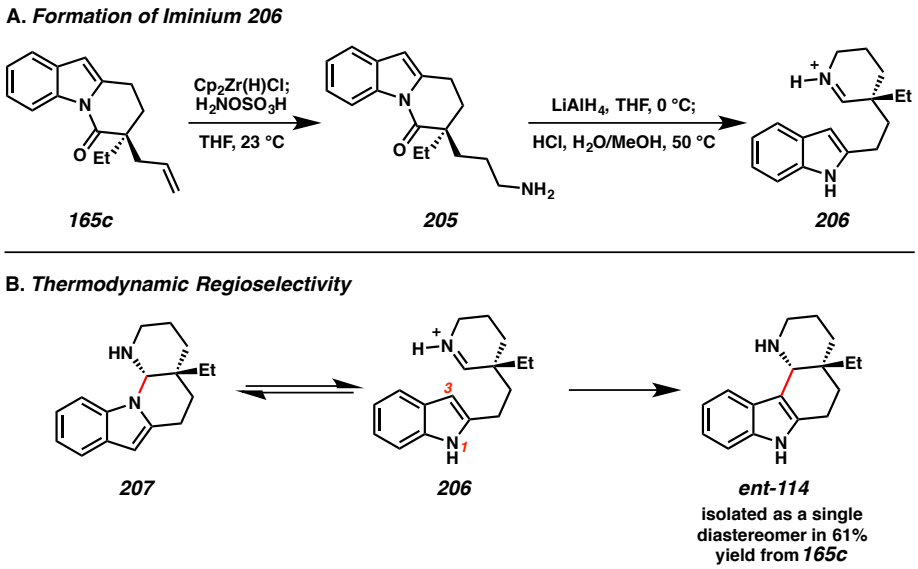
Stereoselectivity in Indole-Iminium Cyclizations:

Total Synthesis of (+)-Limaspermidine, Formal Synthesis of

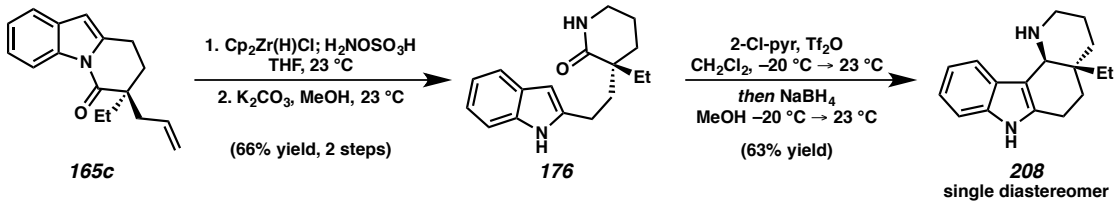
(+)-Kopsihainanine A, and Progress Toward the Total

Synthesis of (–)-Kopsinine and (–)-Kopsinilam

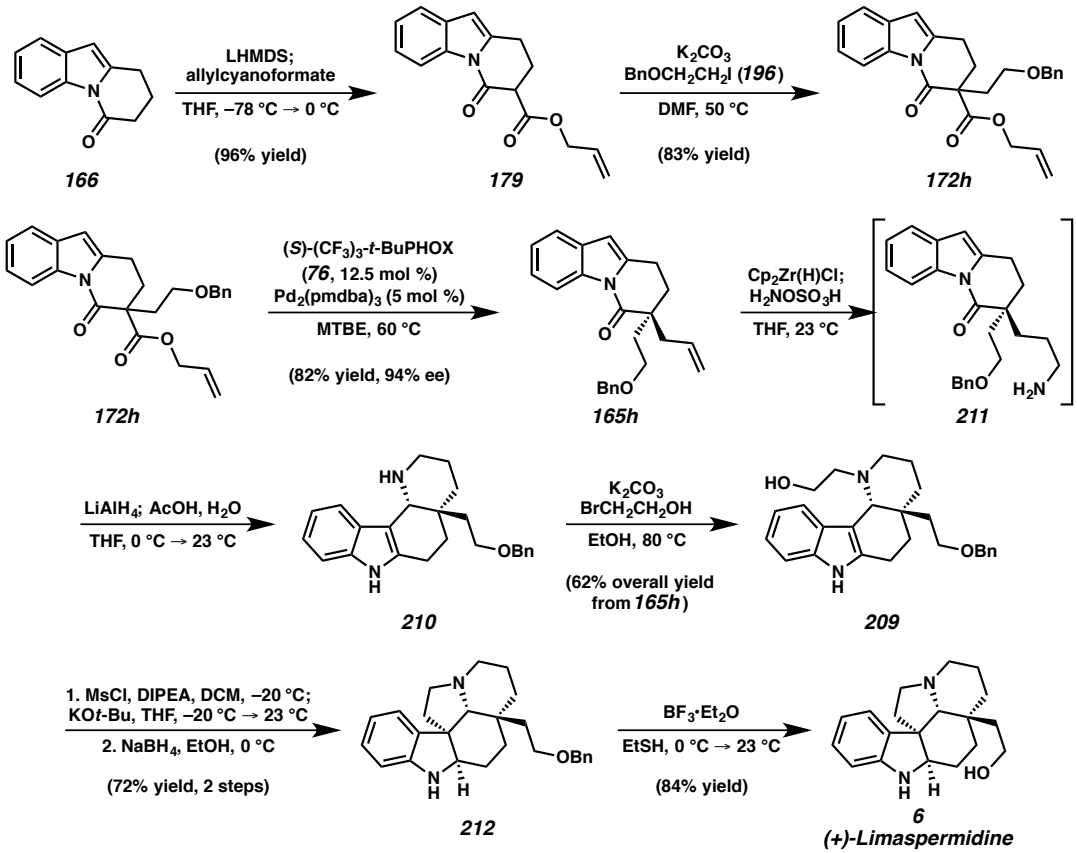
Scheme A6.1. Hydroamination/Reduction/Pictet–Spengler Cascade for the Synthesis of Cis-Fused Octahydroisoquinoline-Containing Building Blocks



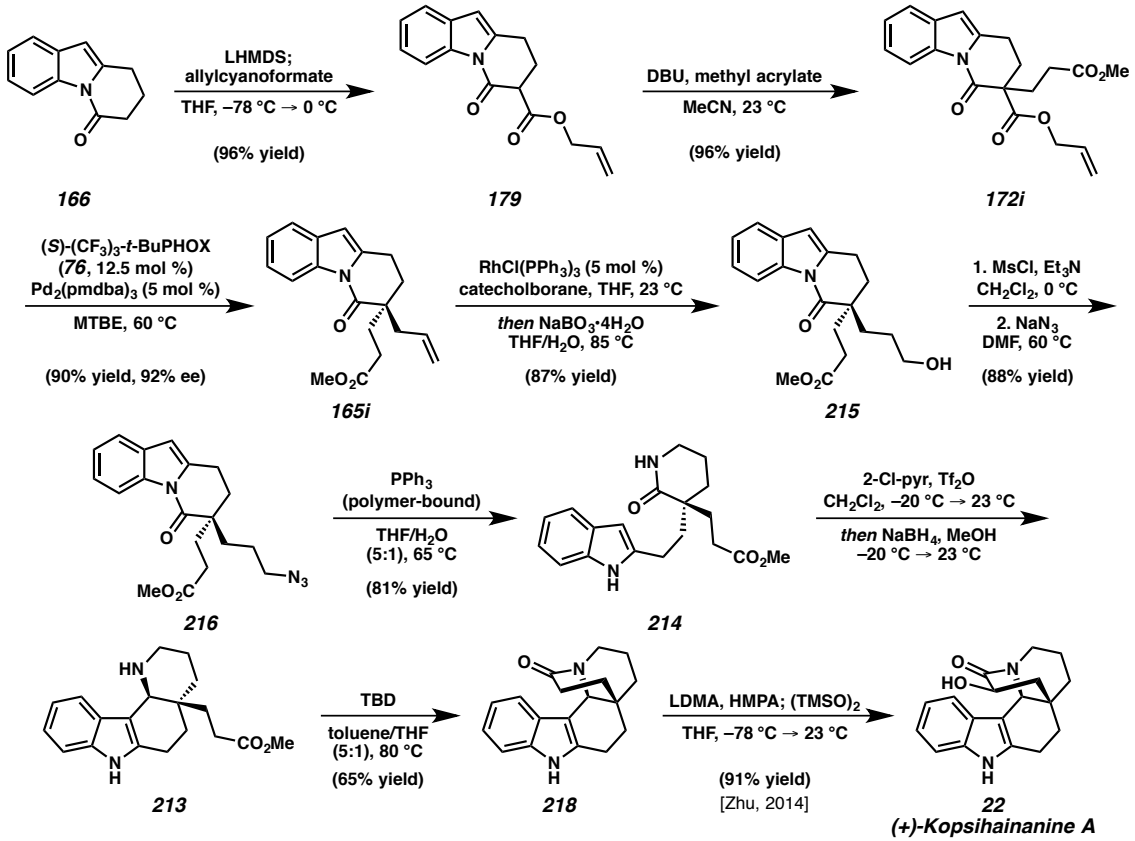
Scheme A6.2. Hydroamination/Translactamization/Bischler–Napieralski Sequence for the Synthesis of Trans-Fused Octahydroisoquinoline-Containing Building Blocks



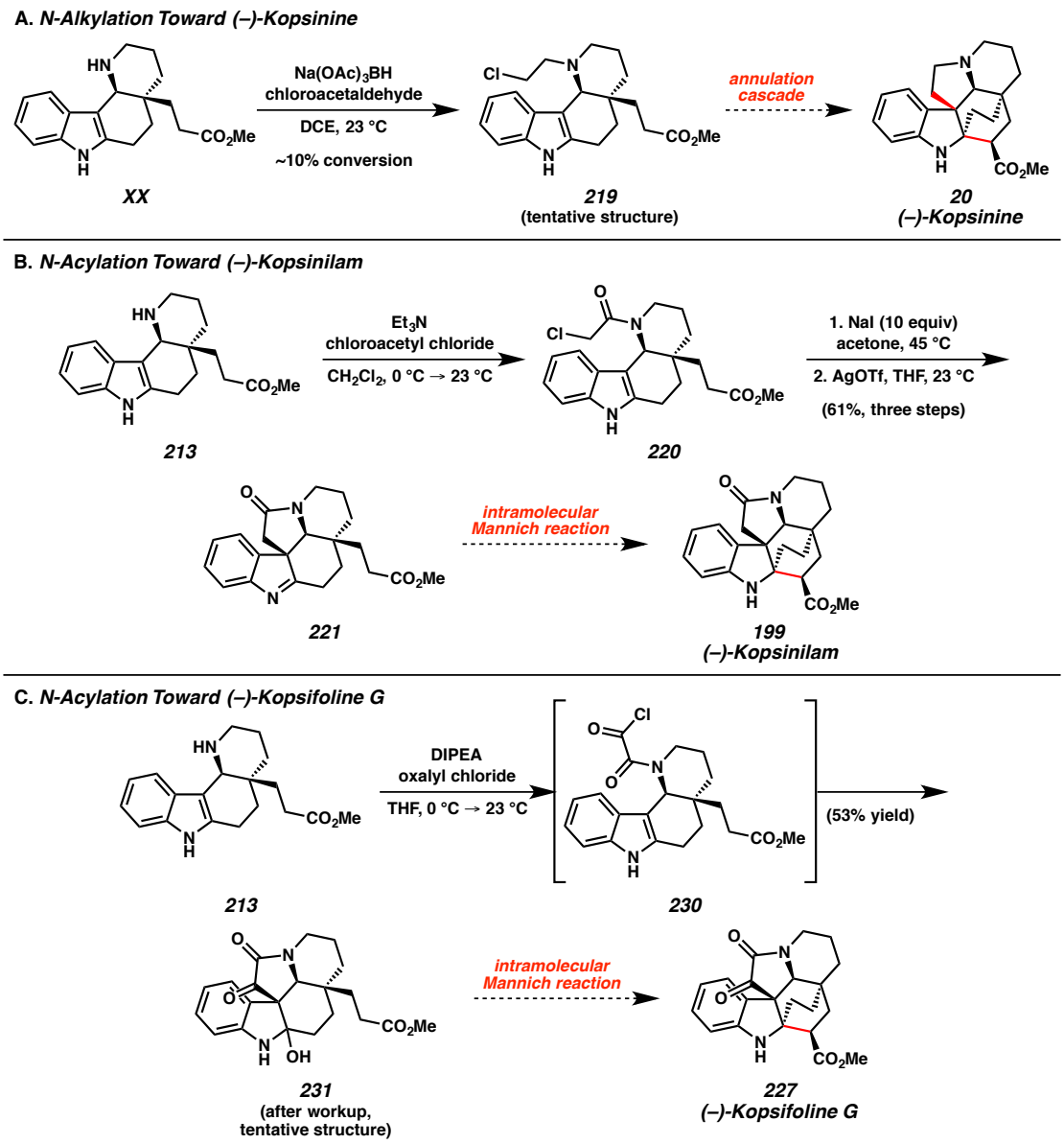
*Scheme A6.3. Catalytic Enantioselective Total Synthesis of (+)-Limaspermidine (**6**)*



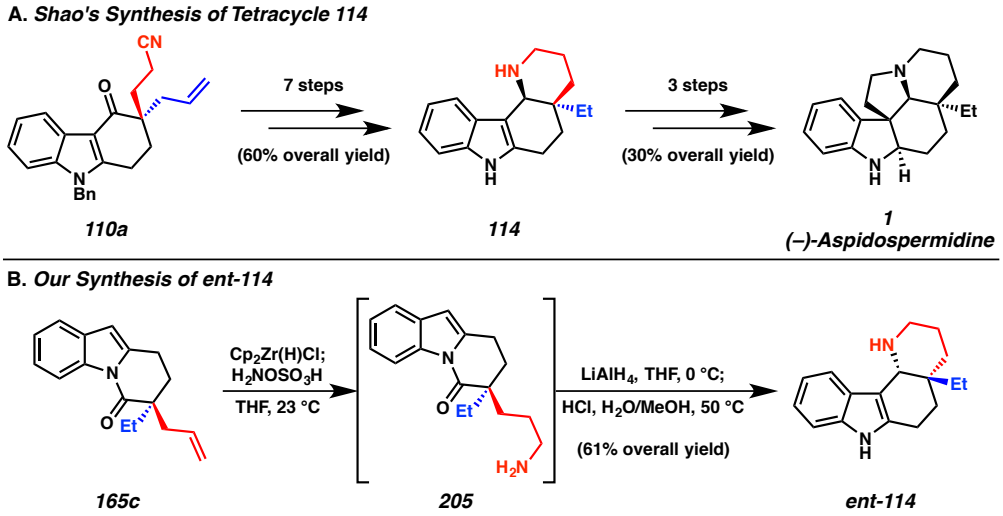
*Scheme A6.4. Catalytic Enantioselective Synthesis of (+)-Kopsihainanine A (**22**)*



*Scheme A6.5. Progress Toward the Total Syntheses of (–)-Kopsinine (**20**), (–)-Kopsinilam (**199**), and (–)-Kopsifoline G (**227**)*



Scheme A6.6. Comparative Synthetic Utility of Carbazolone and DHPI Pd-Catalyzed Allylic Alkylation Products.



APPENDIX 7

Spectra Relevant to Chapter 3:

Stereoselectivity in Indole-Iminium Cyclizations:

Total Synthesis of (+)-Limaspermidine, Formal Synthesis of

(+)-Kopsihainanine A, and Progress Toward the Total

Synthesis of (–)-Kopsinine and (–)-Kopsinilam

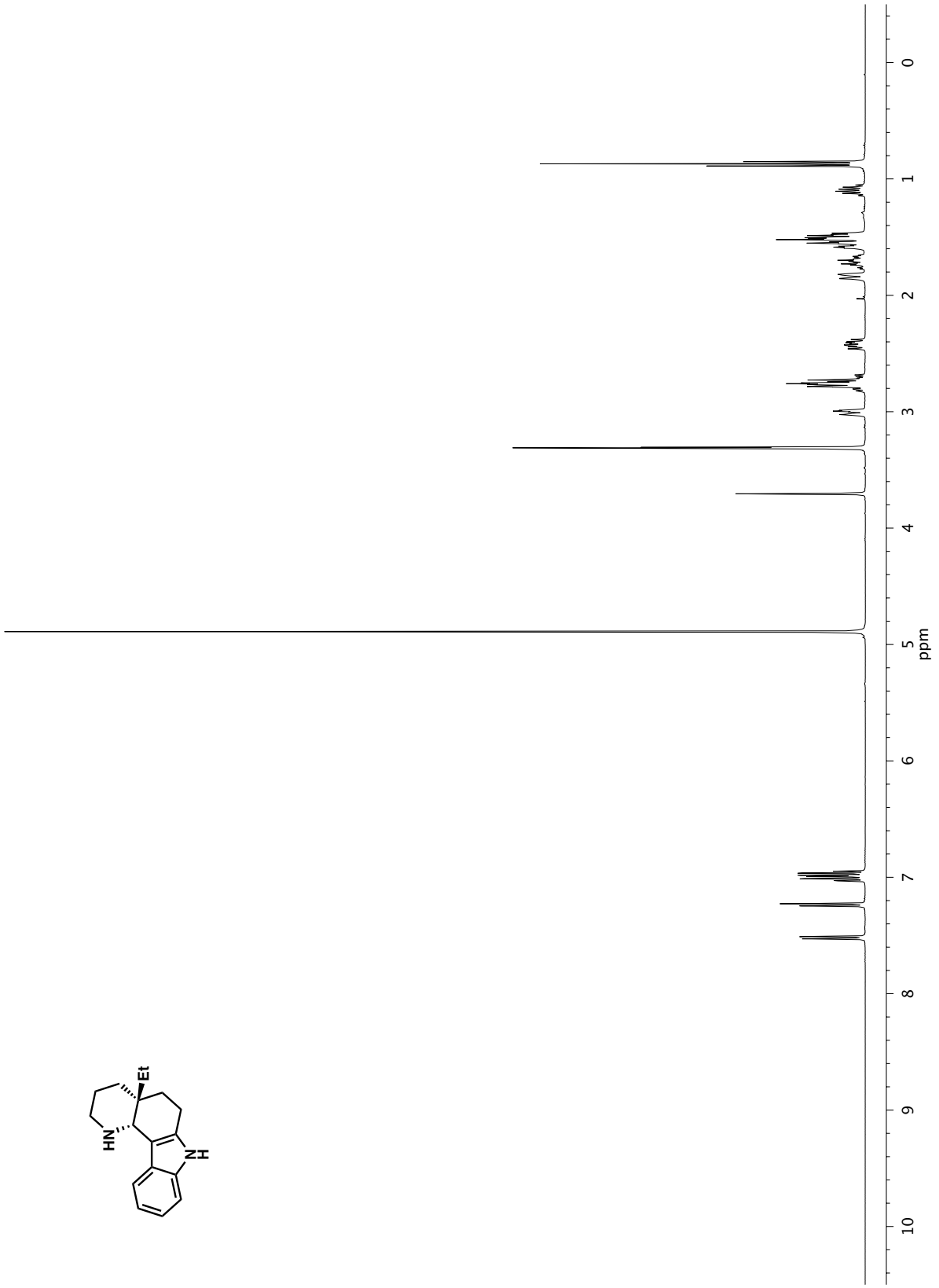


Figure A7.1. ^{1}H NMR (400 MHz, CD_3OD) of compound ***ent*-114**.

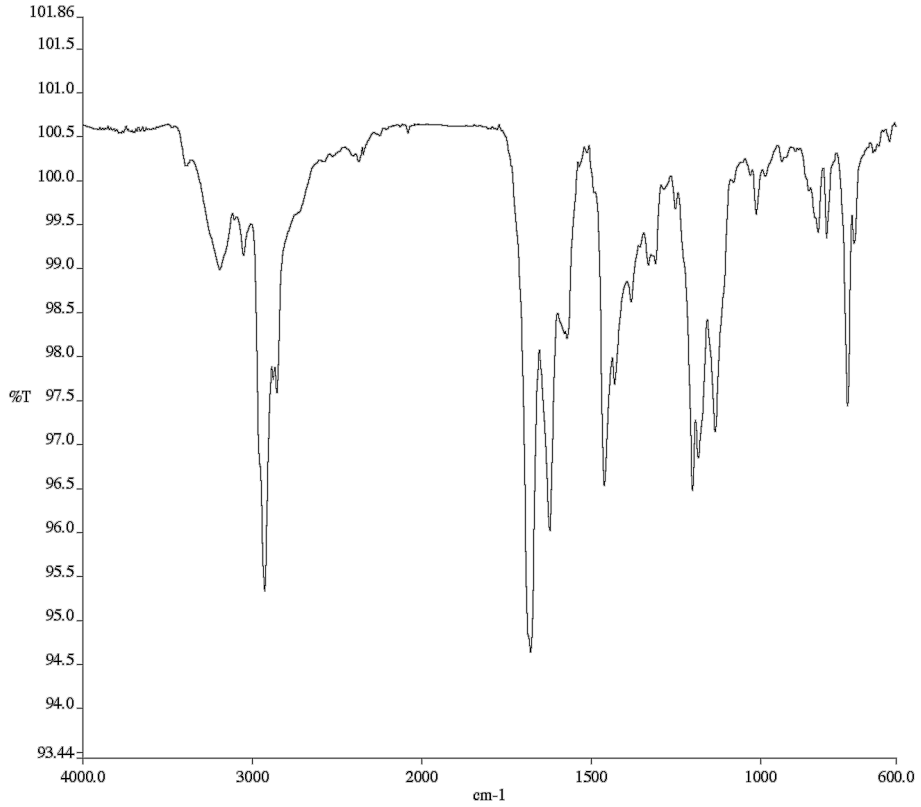


Figure A7.2. Infrared spectrum (Thin Film, NaCl) of compound ***ent*-114**.

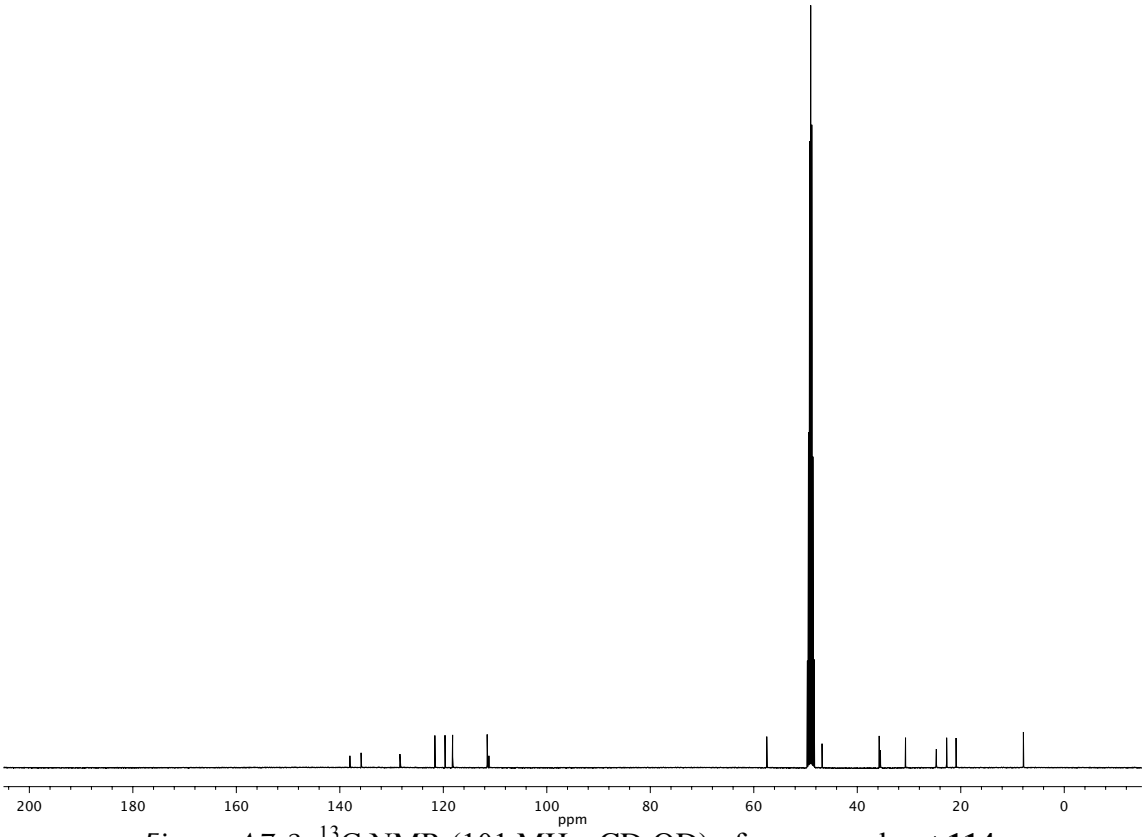


Figure A7.3. ^{13}C NMR (101 MHz, CD_3OD) of compound ***ent*-114**.

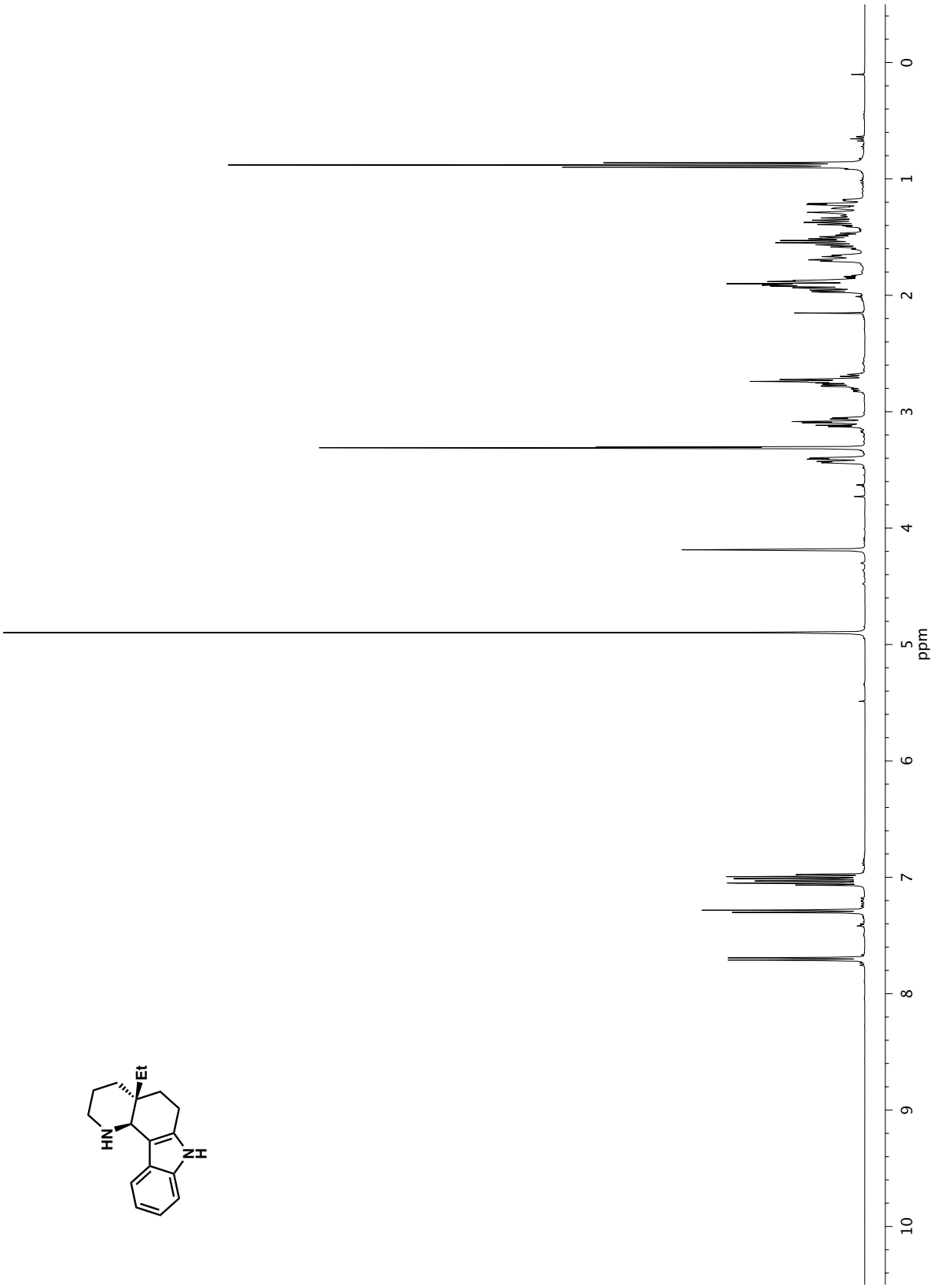


Figure A7.4. ^{1}H NMR (400 MHz, CD_3OD) of compound **208**.

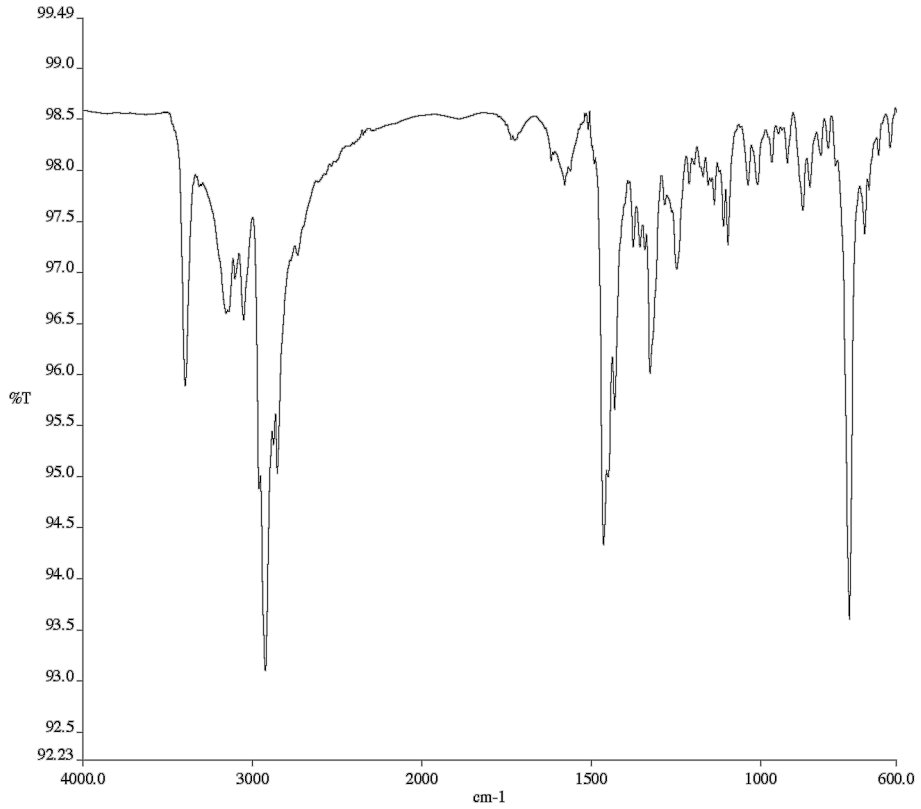


Figure A7.5. Infrared spectrum (Thin Film, NaCl) of compound **208**.

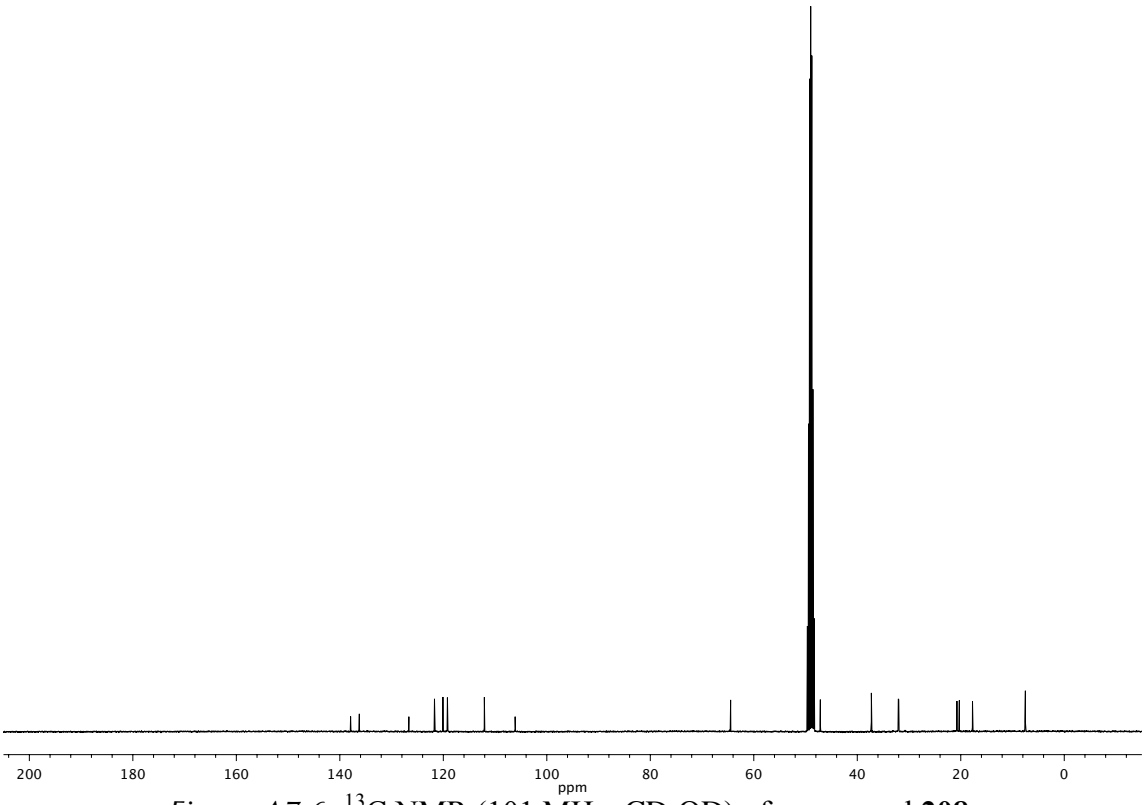


Figure A7.6. ^{13}C NMR (101 MHz, CD_3OD) of compound **208**.

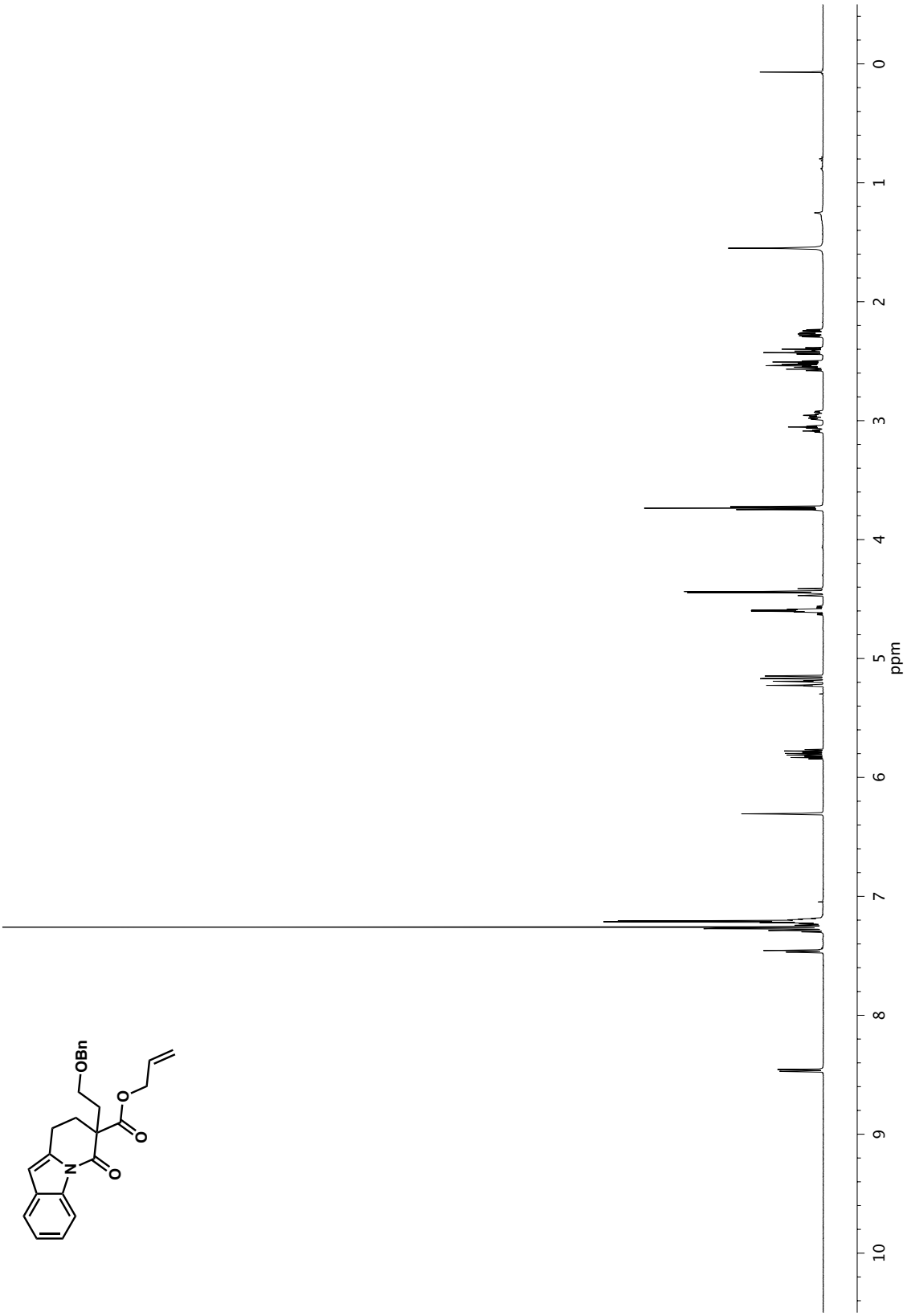


Figure A7.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172h**.

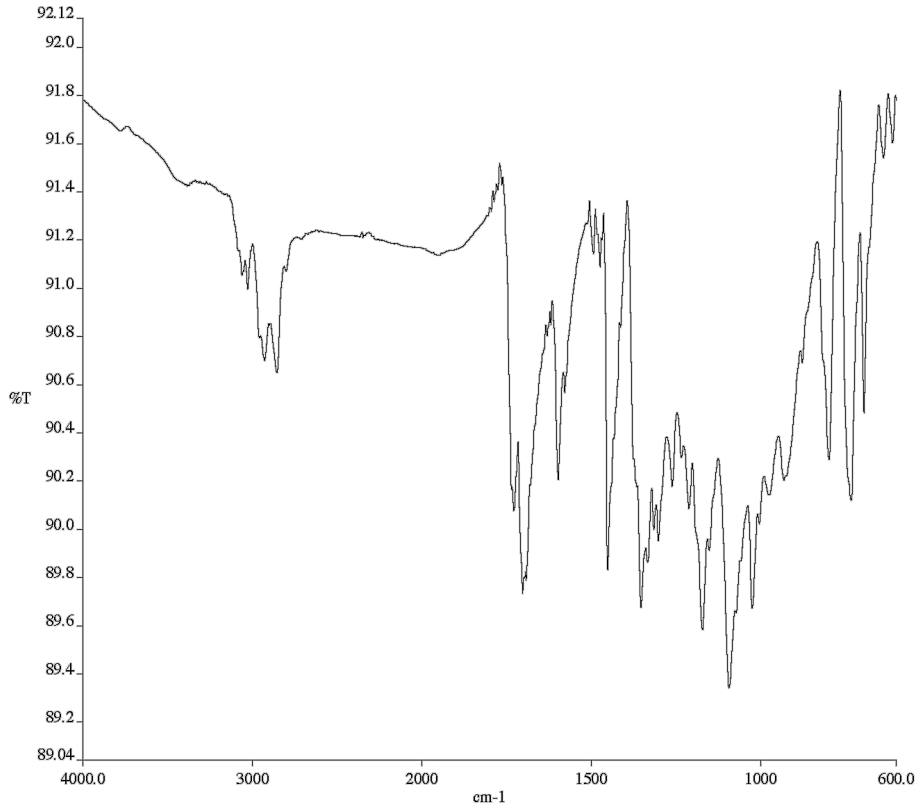


Figure A7.8. Infrared spectrum (Thin Film, NaCl) of compound **172h**.

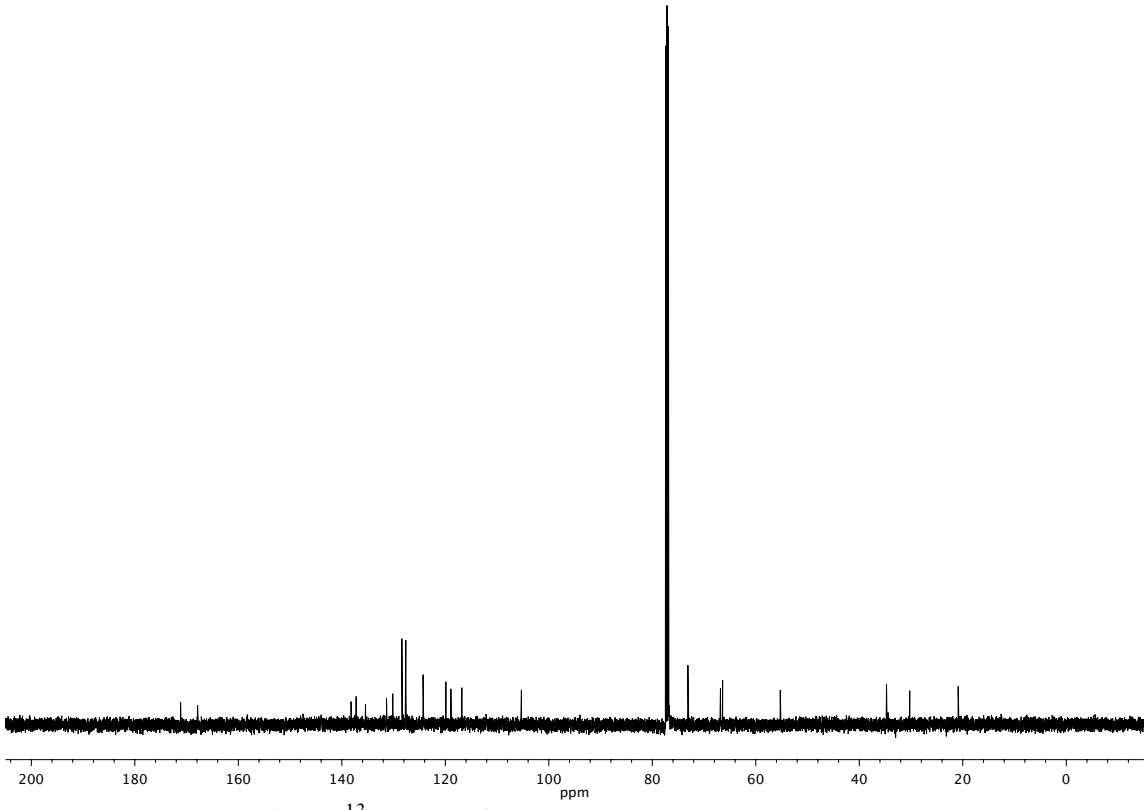


Figure A7.9. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172h**.

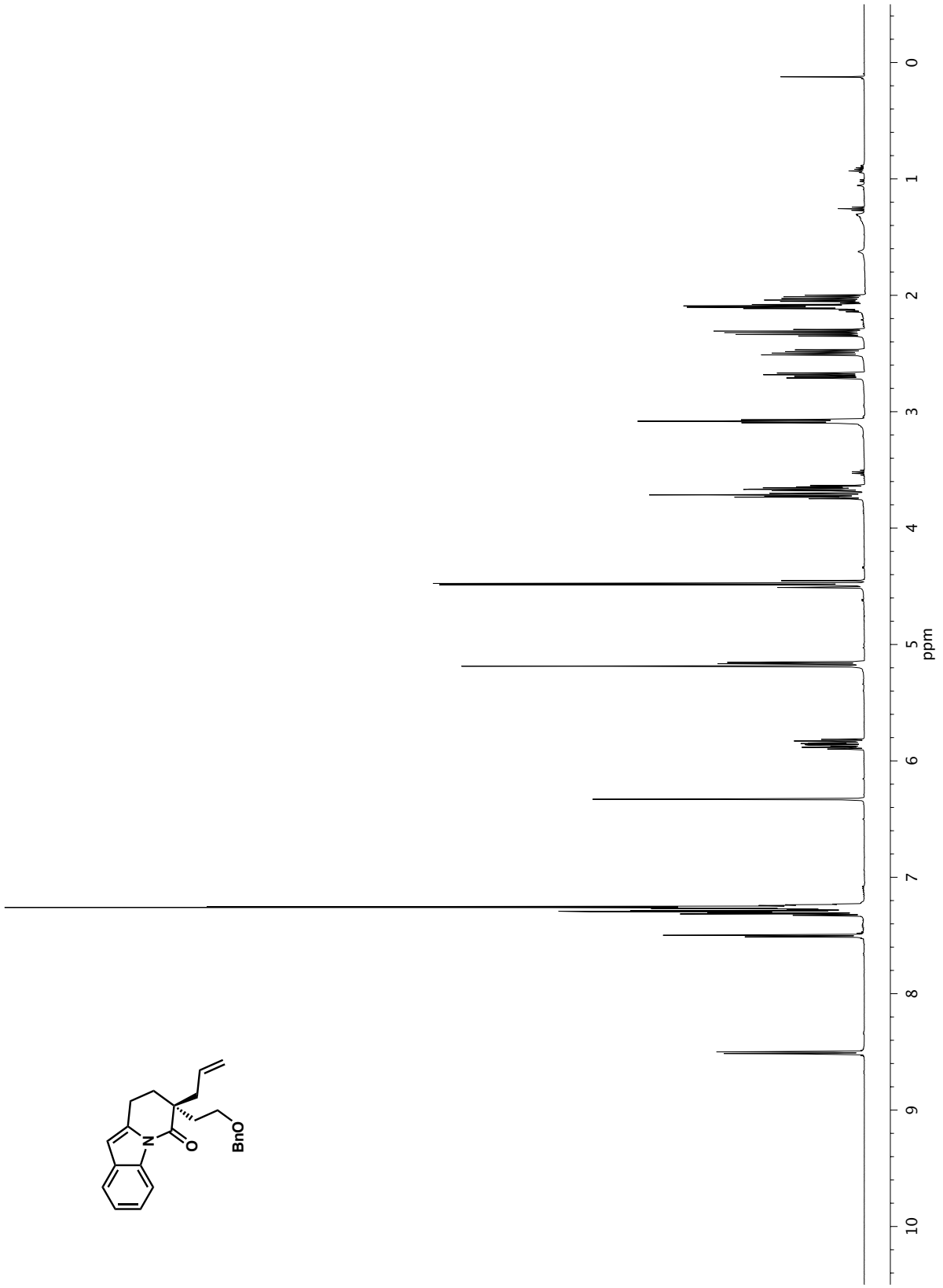


Figure A7.10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165h**.

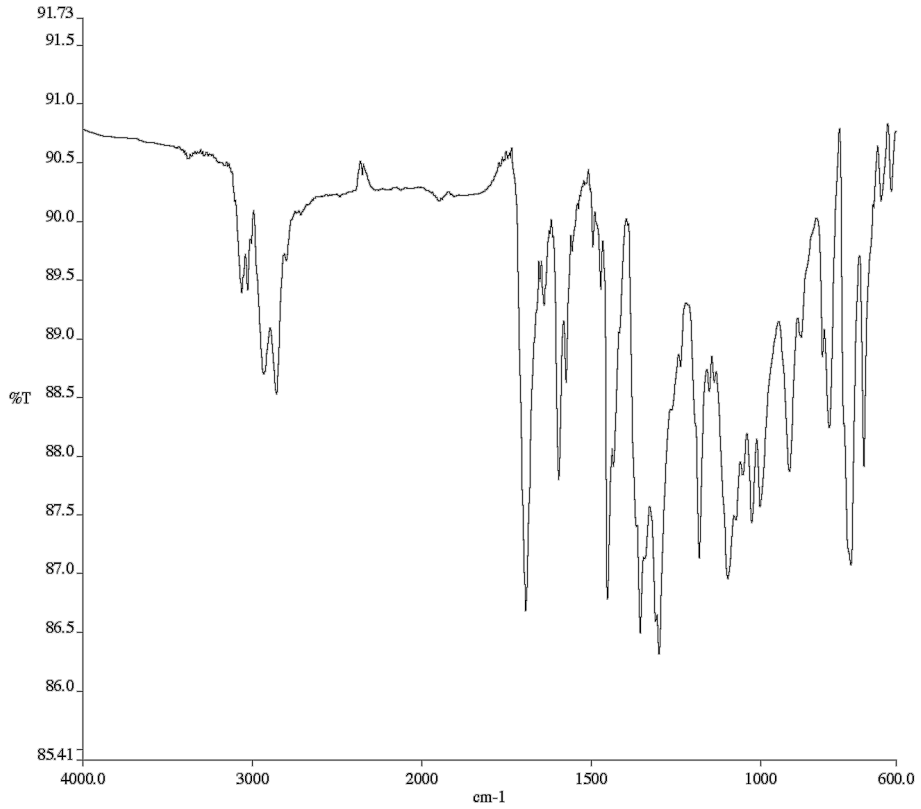


Figure A7.11. Infrared spectrum (Thin Film, NaCl) of compound **165h**.

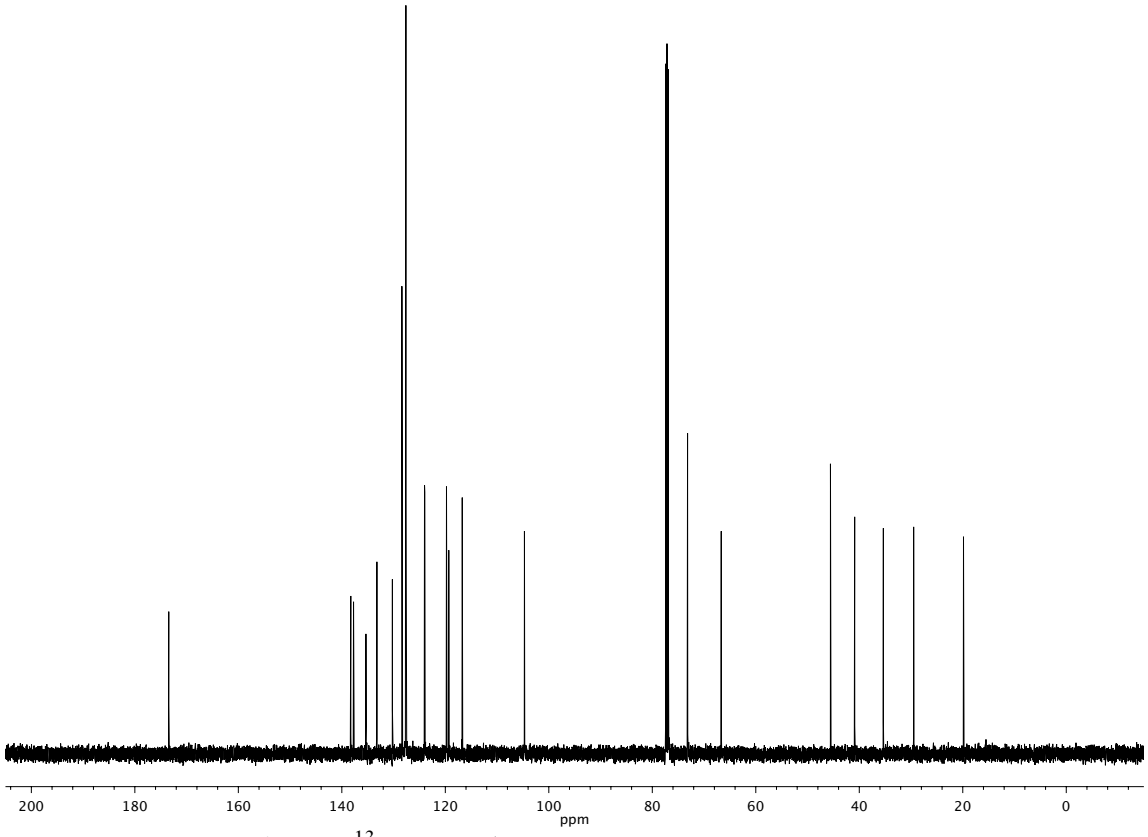


Figure A7.12. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165h**.

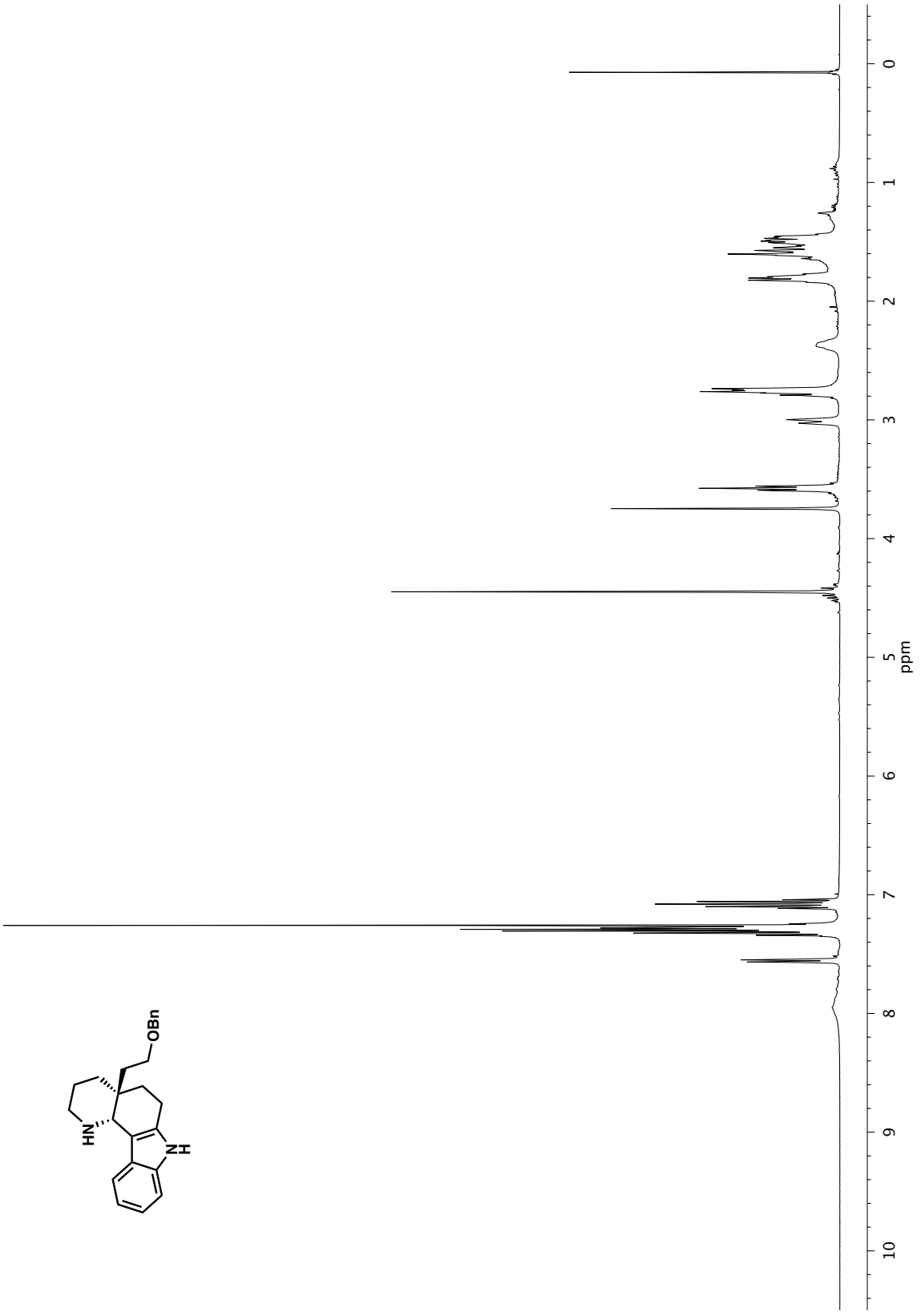


Figure A7.13. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **210**.

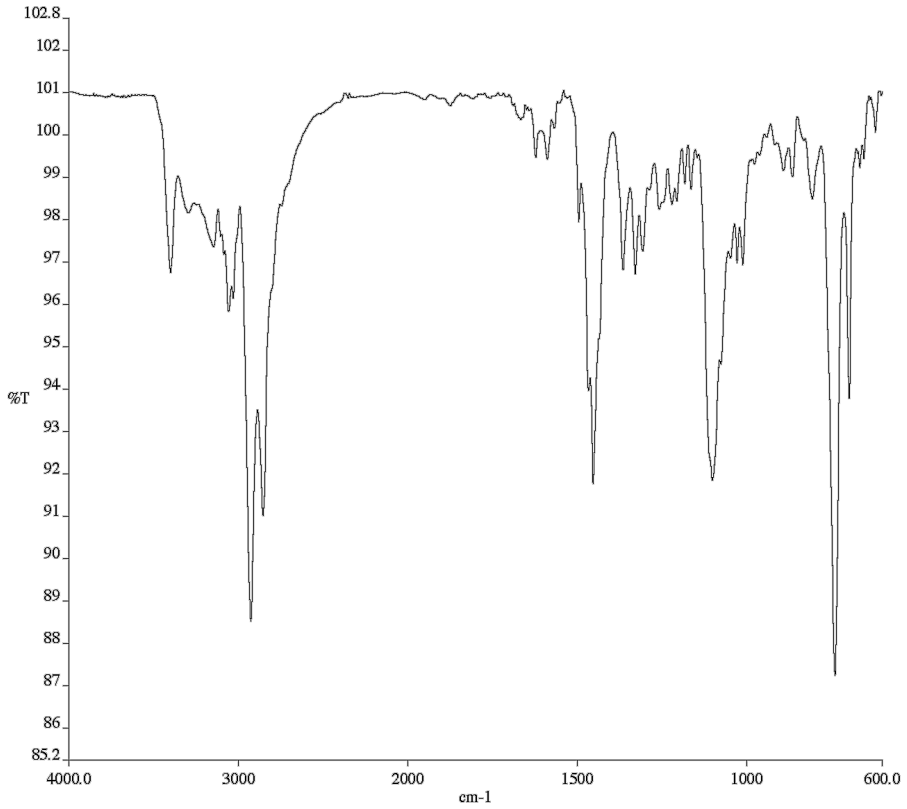


Figure A7.14. Infrared spectrum (Thin Film, NaCl) of compound **210**.

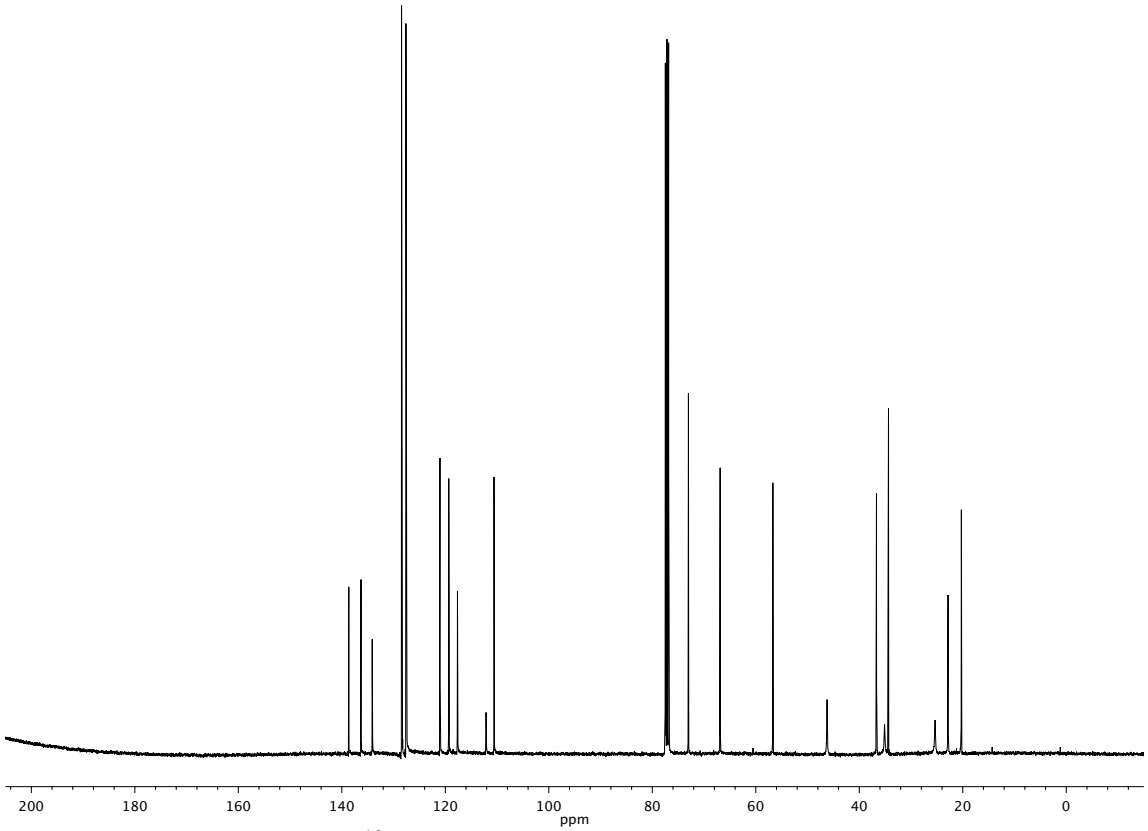


Figure A7.15. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **210**.

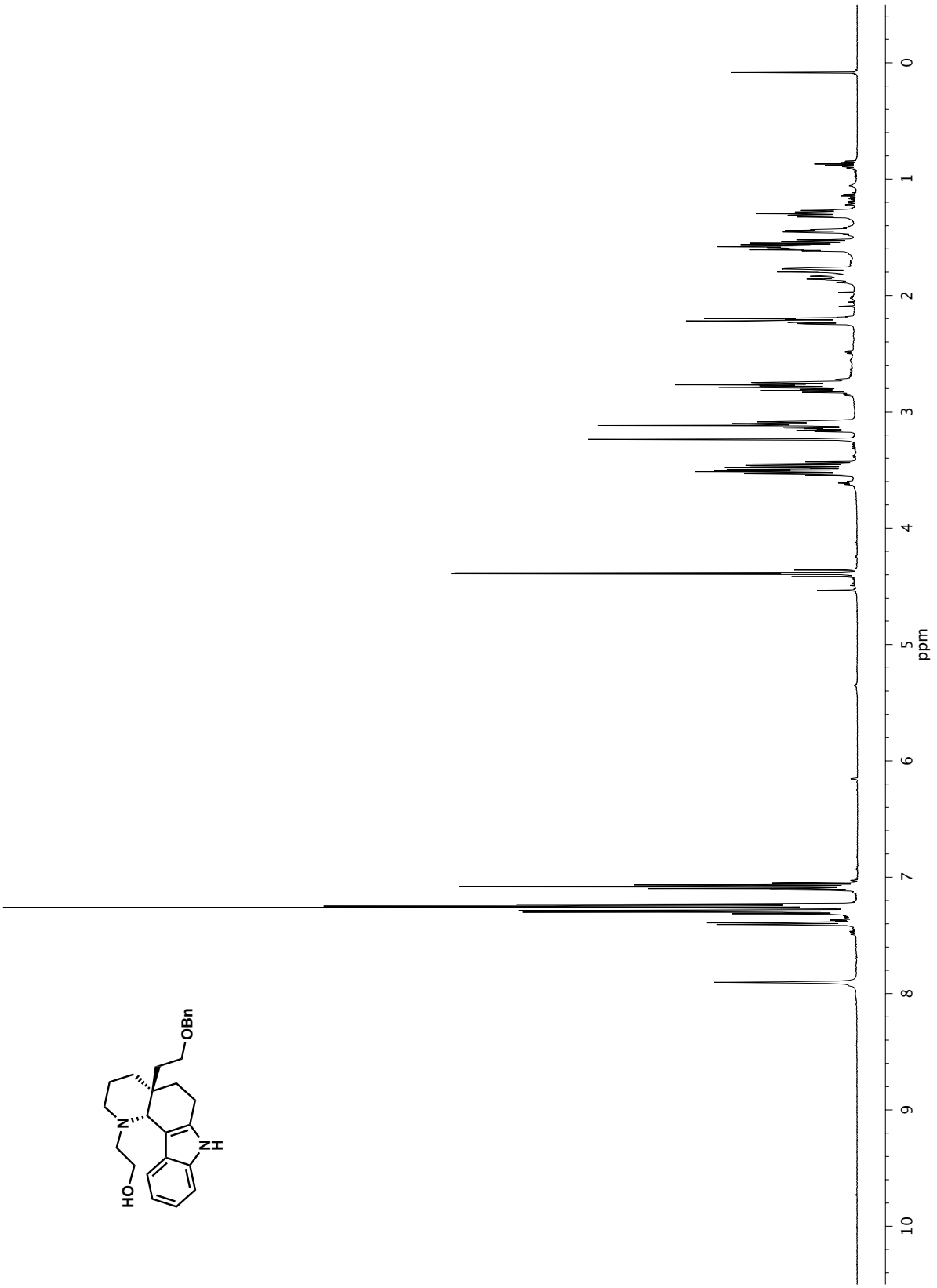


Figure A7.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **209**.

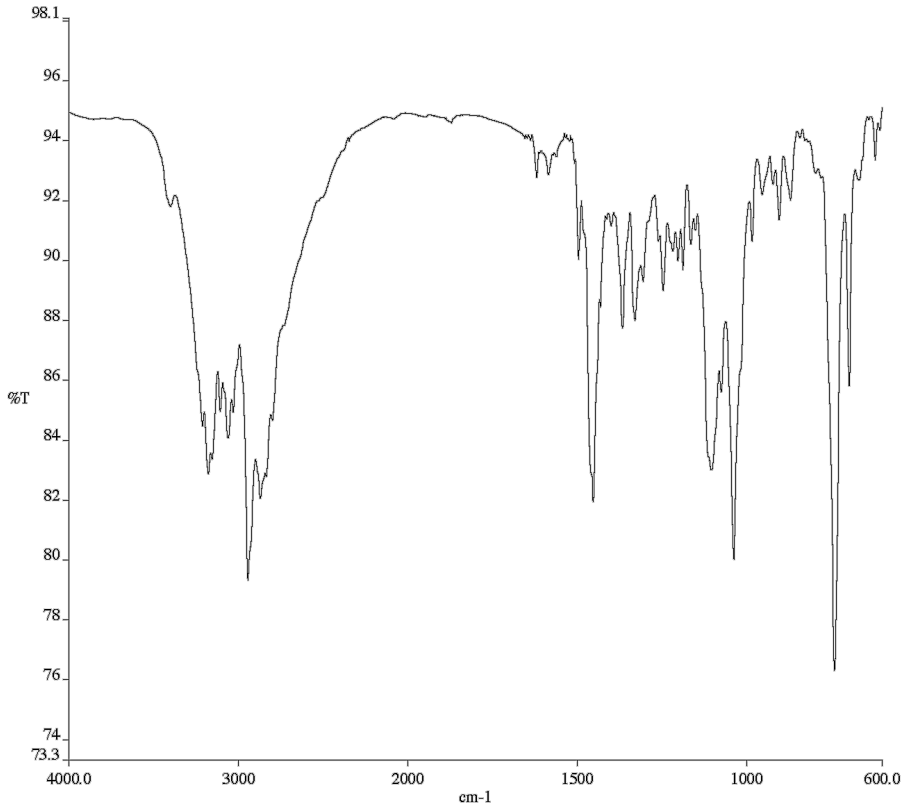


Figure A7.17. Infrared spectrum (Thin Film, NaCl) of compound **209**.

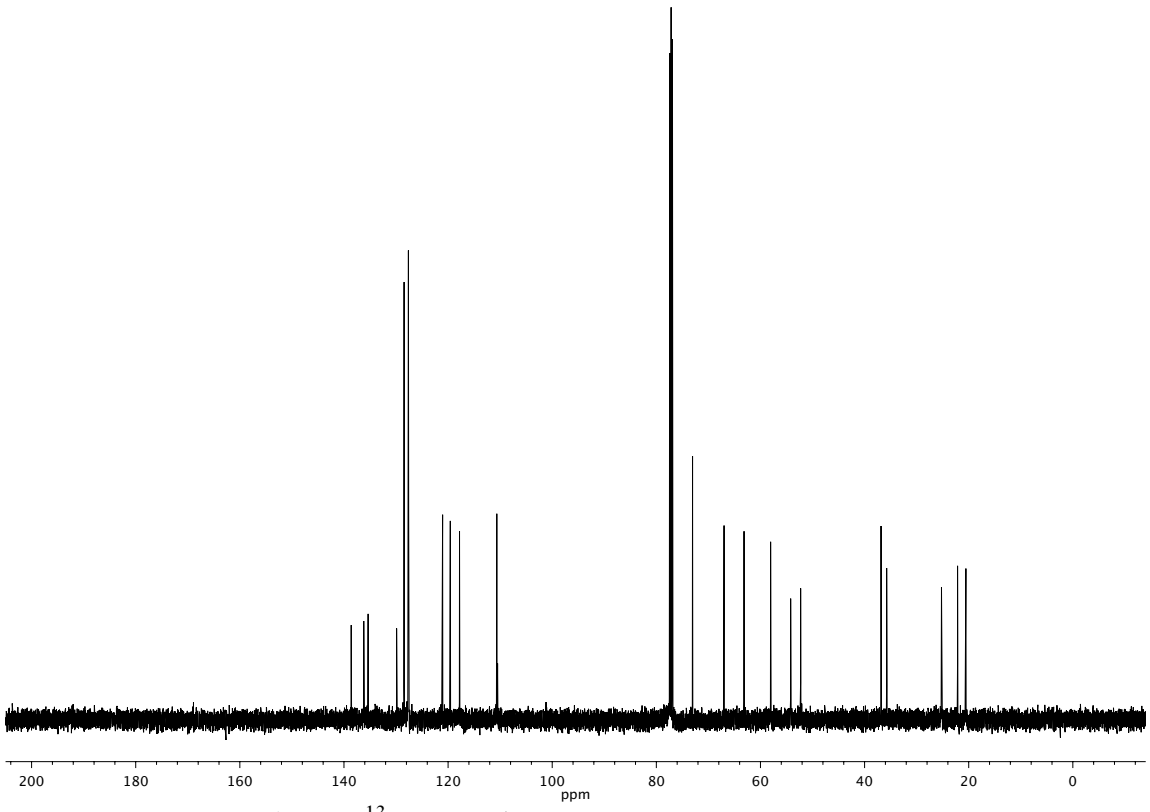


Figure A7.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **209**.

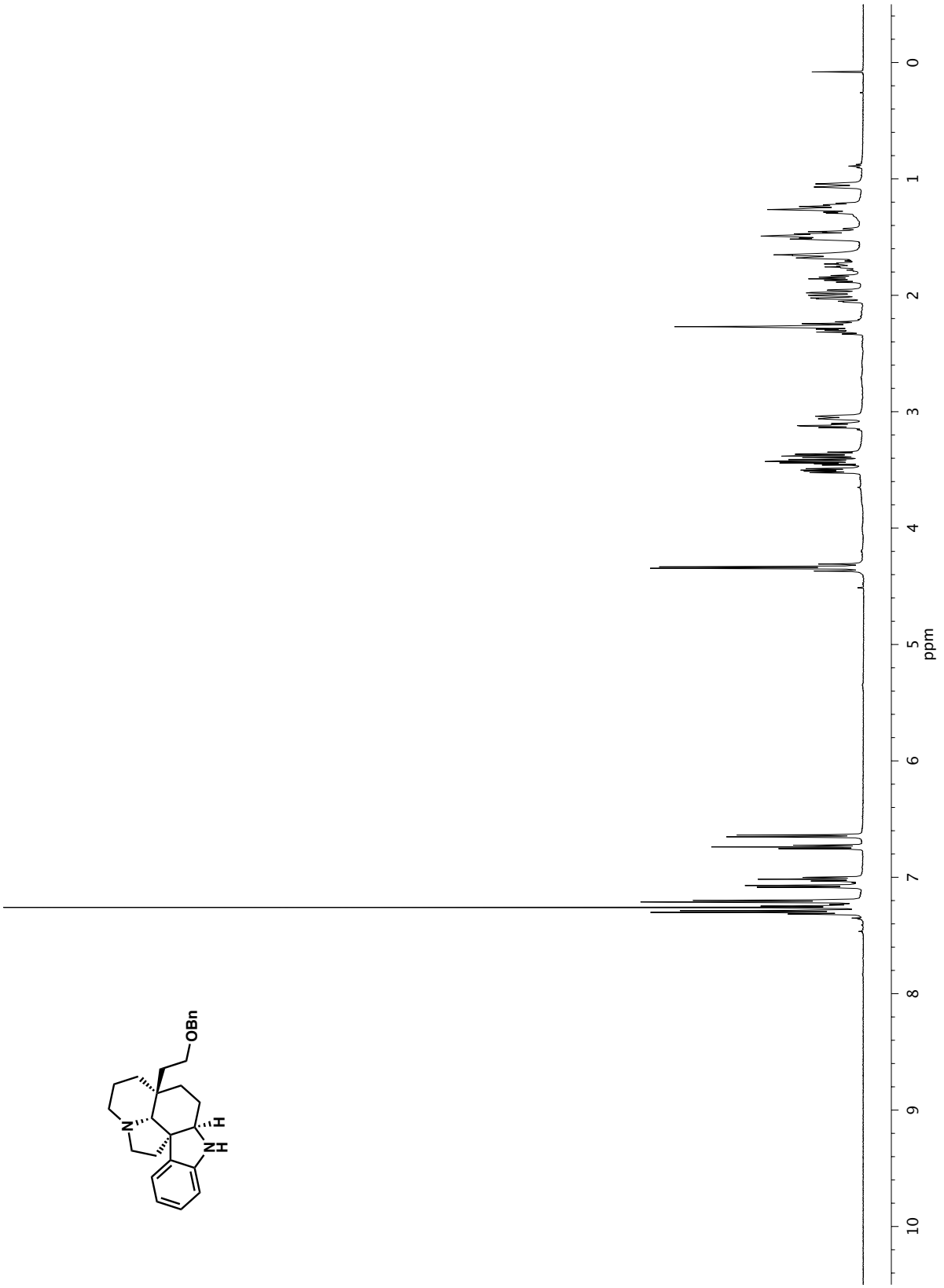


Figure A7.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **212**.

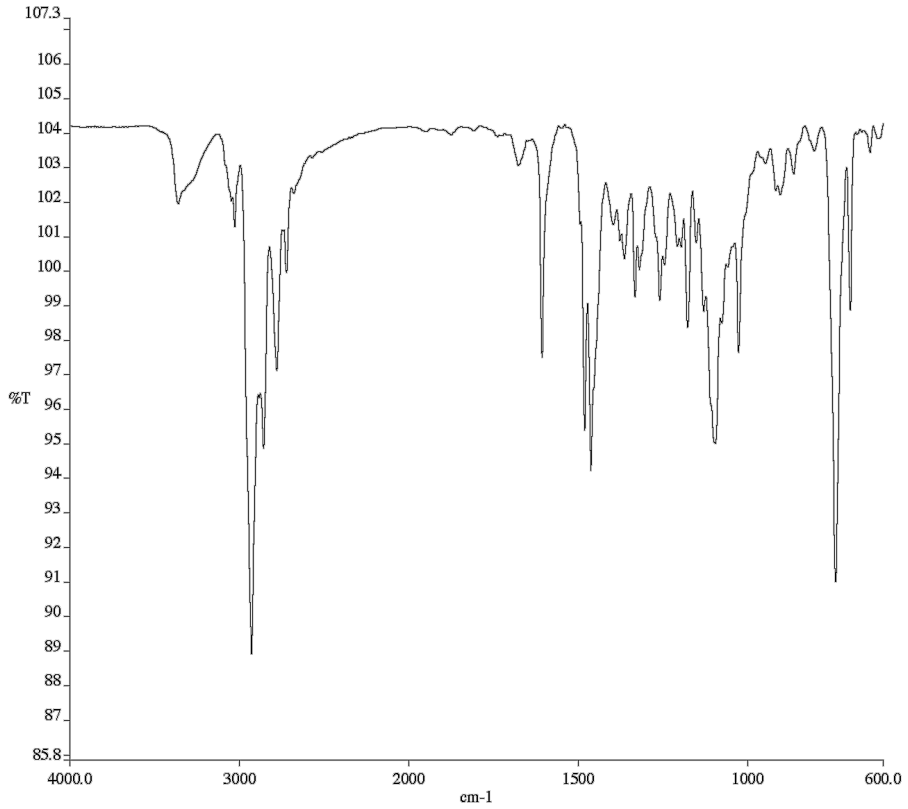


Figure A7.20. Infrared spectrum (Thin Film, NaCl) of compound **212**.

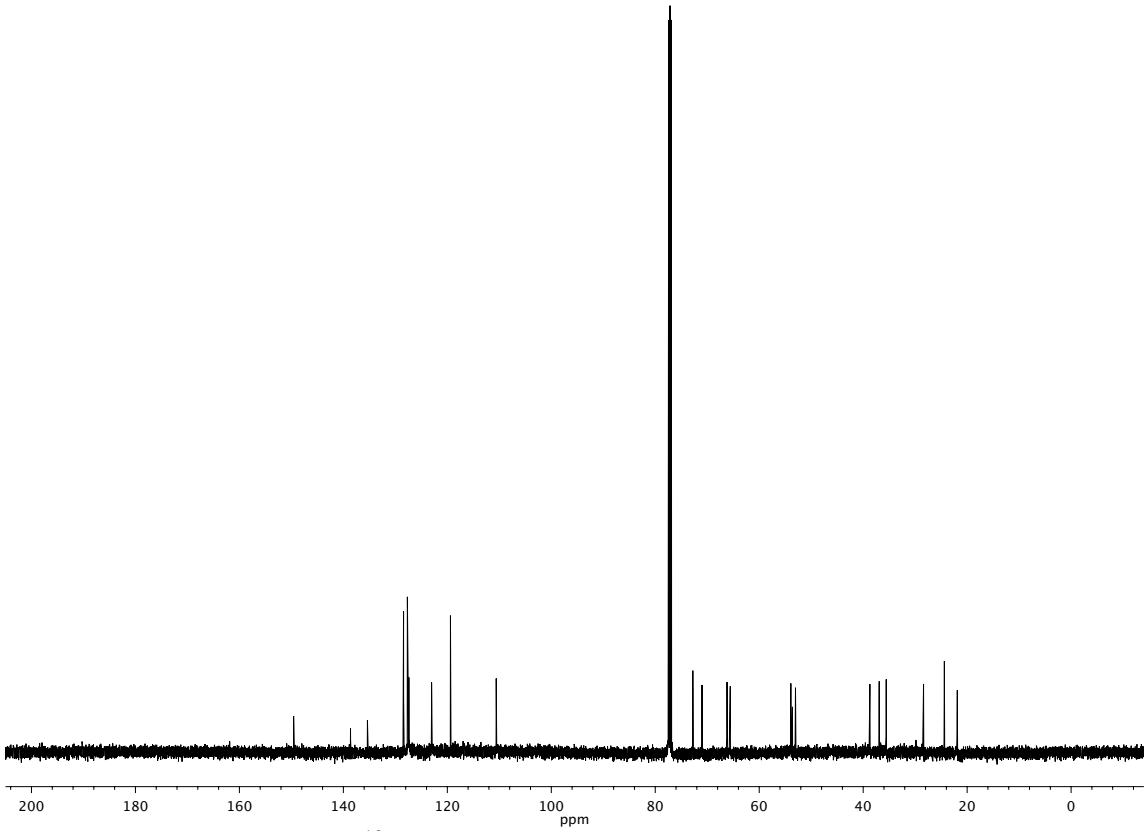


Figure A7.21. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **212**.

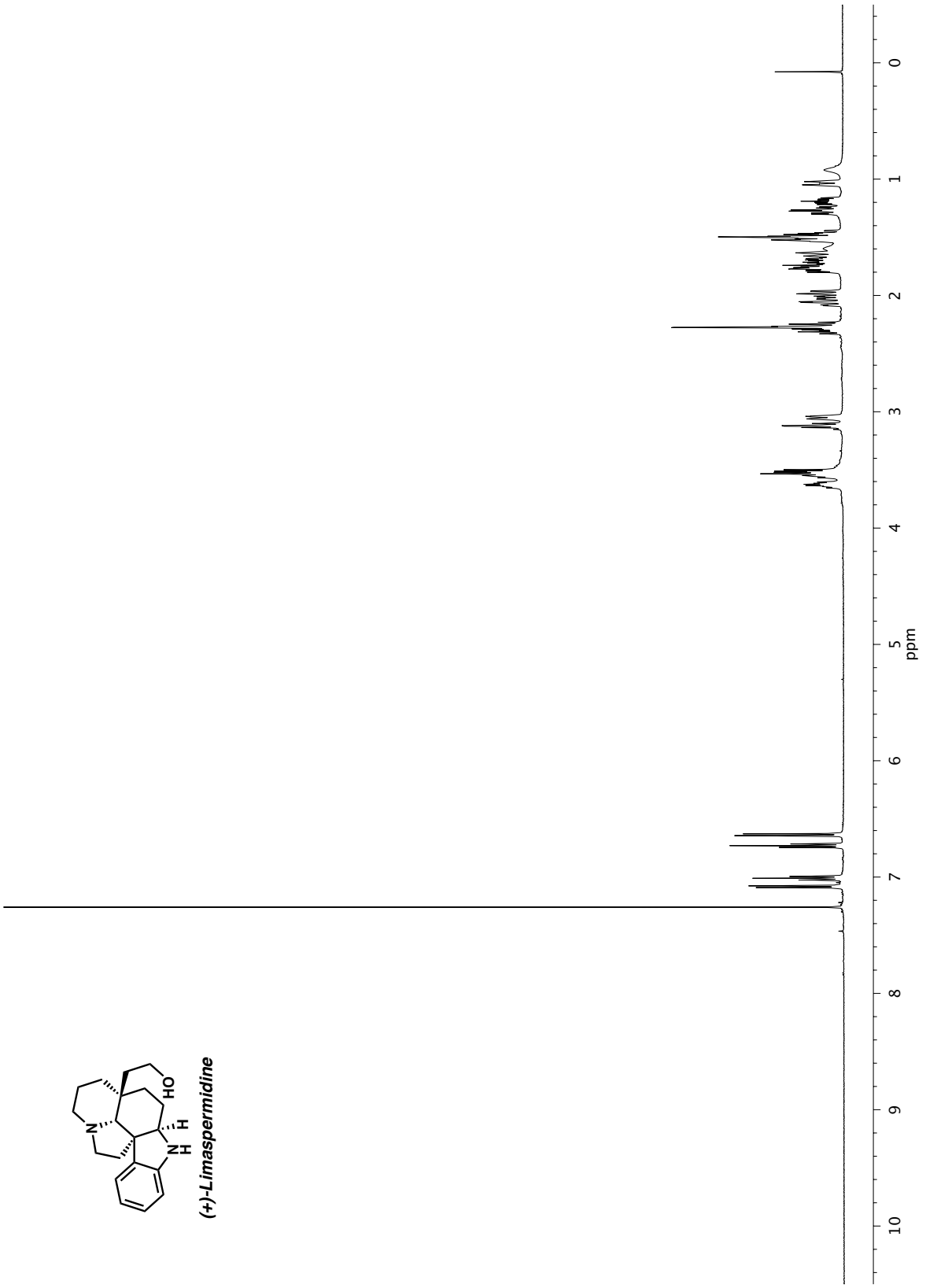


Figure A7.22. ^{1}H NMR (500 MHz, $CDCl_3$) of (+)-Limaspermidine (**6**).

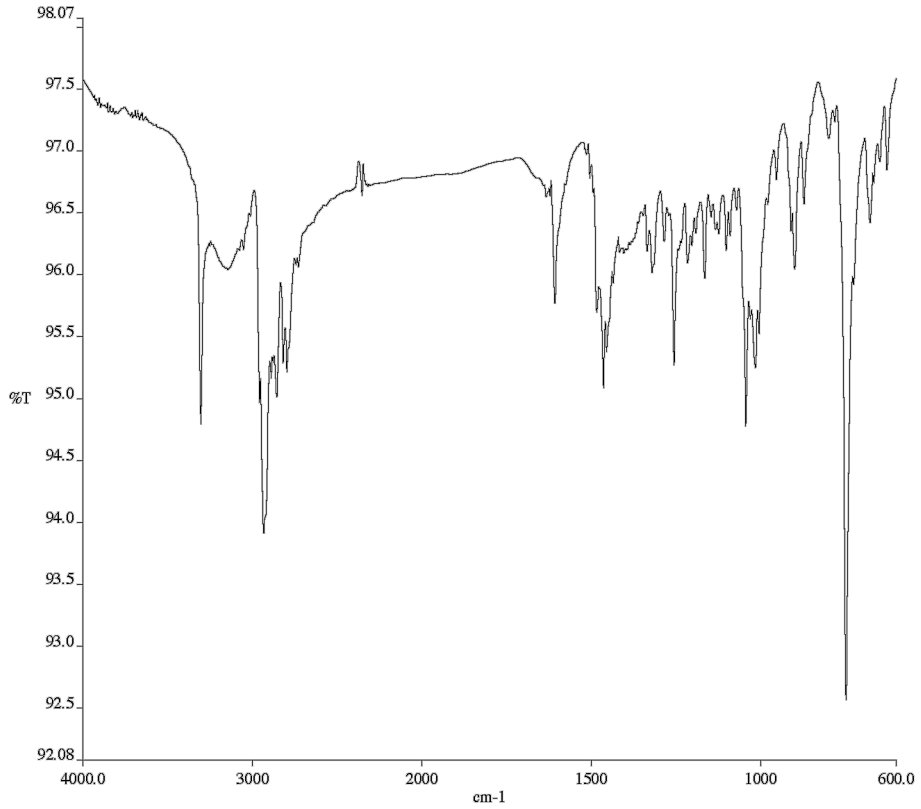


Figure A7.23. Infrared spectrum (Thin Film, NaCl) of (+)-Limaspermidine (**6**).

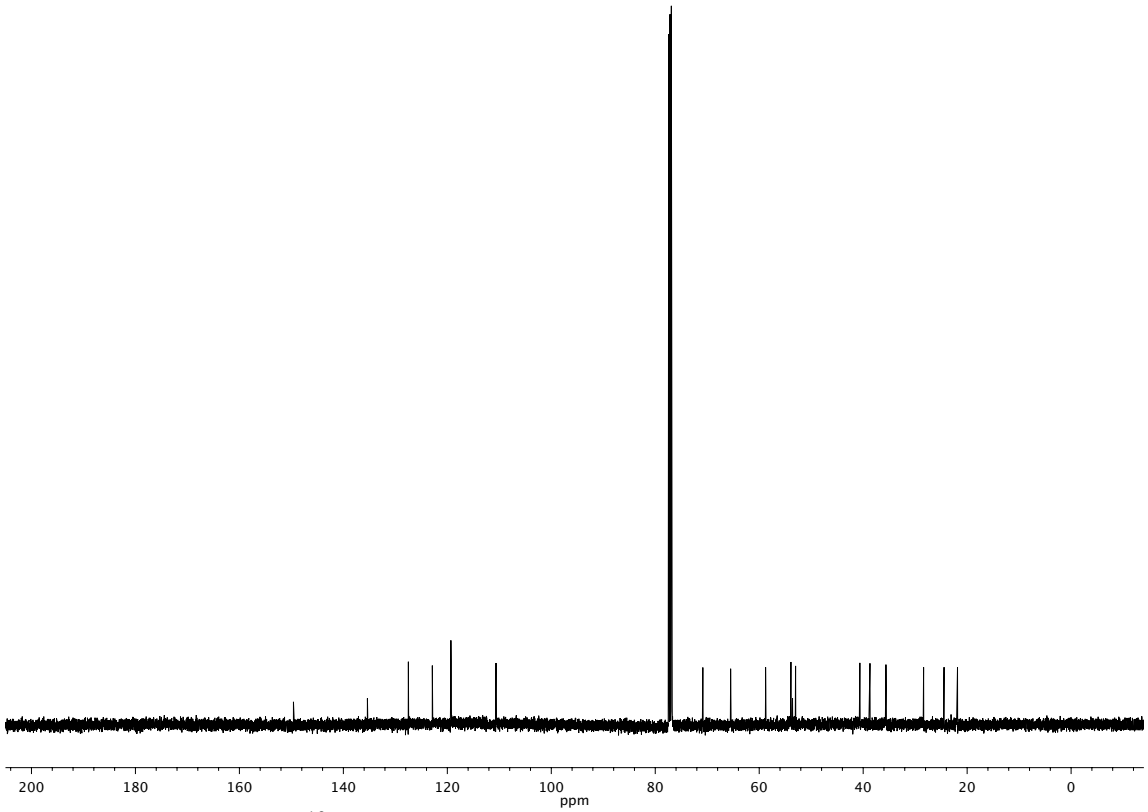


Figure A7.24. ^{13}C NMR (126 MHz, $CDCl_3$) of (+)-Limaspermidine (**6**).

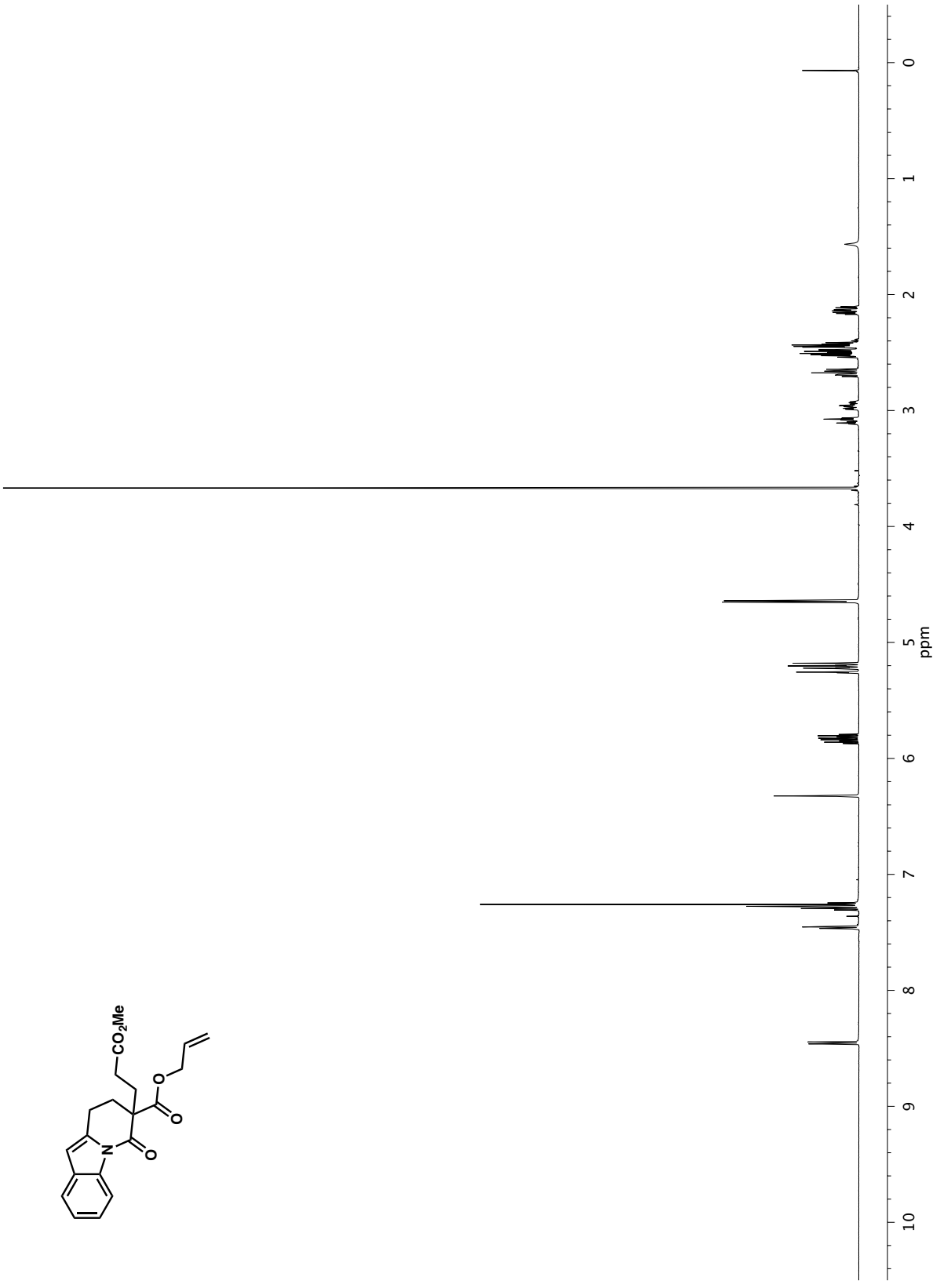


Figure A7.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172i**.

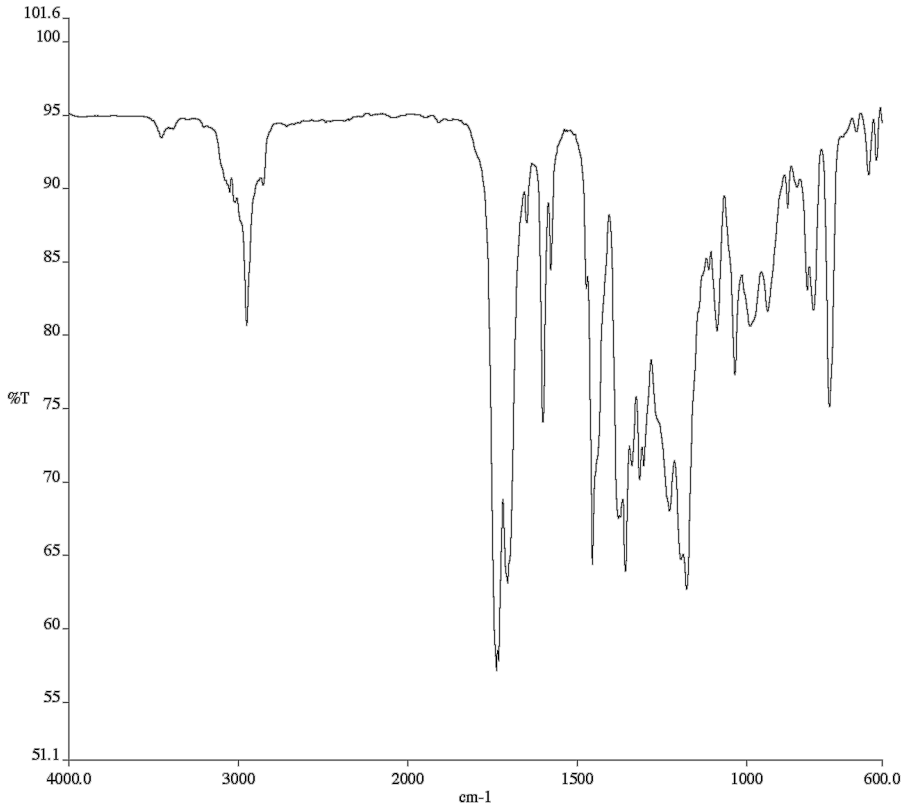


Figure A7.26. Infrared spectrum (Thin Film, NaCl) of compound **172i**.

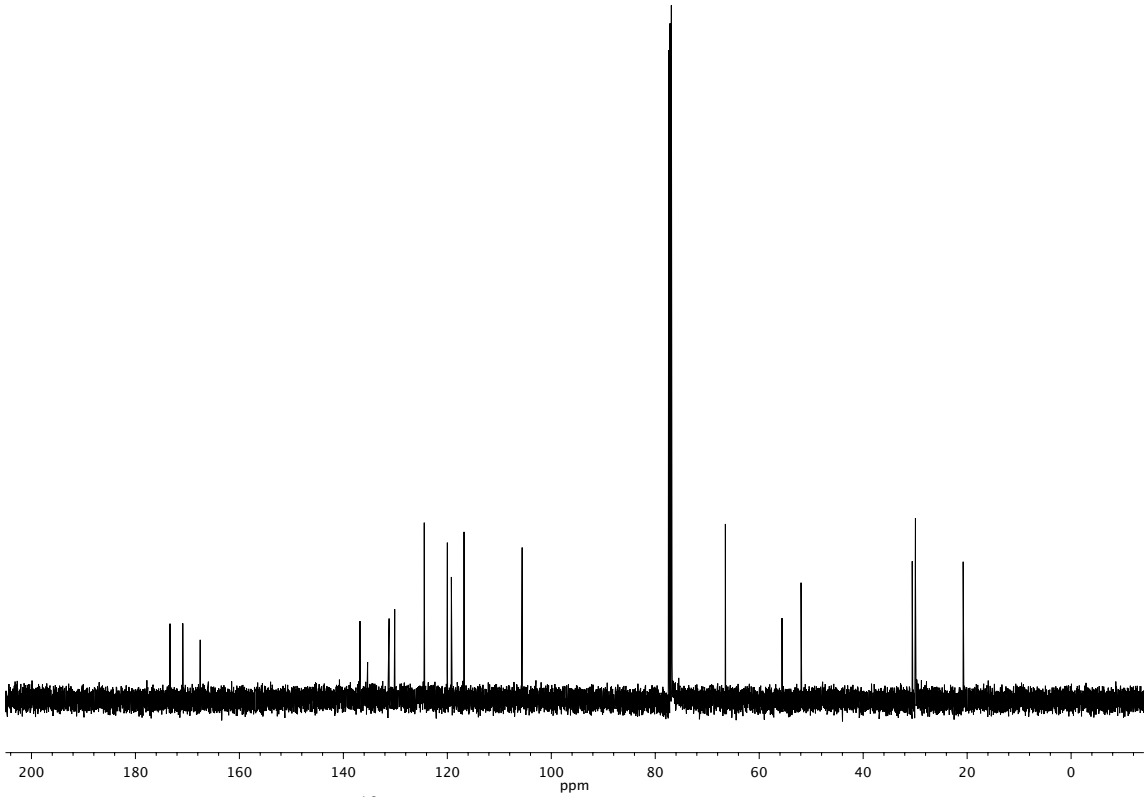


Figure A7.27. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172i**.

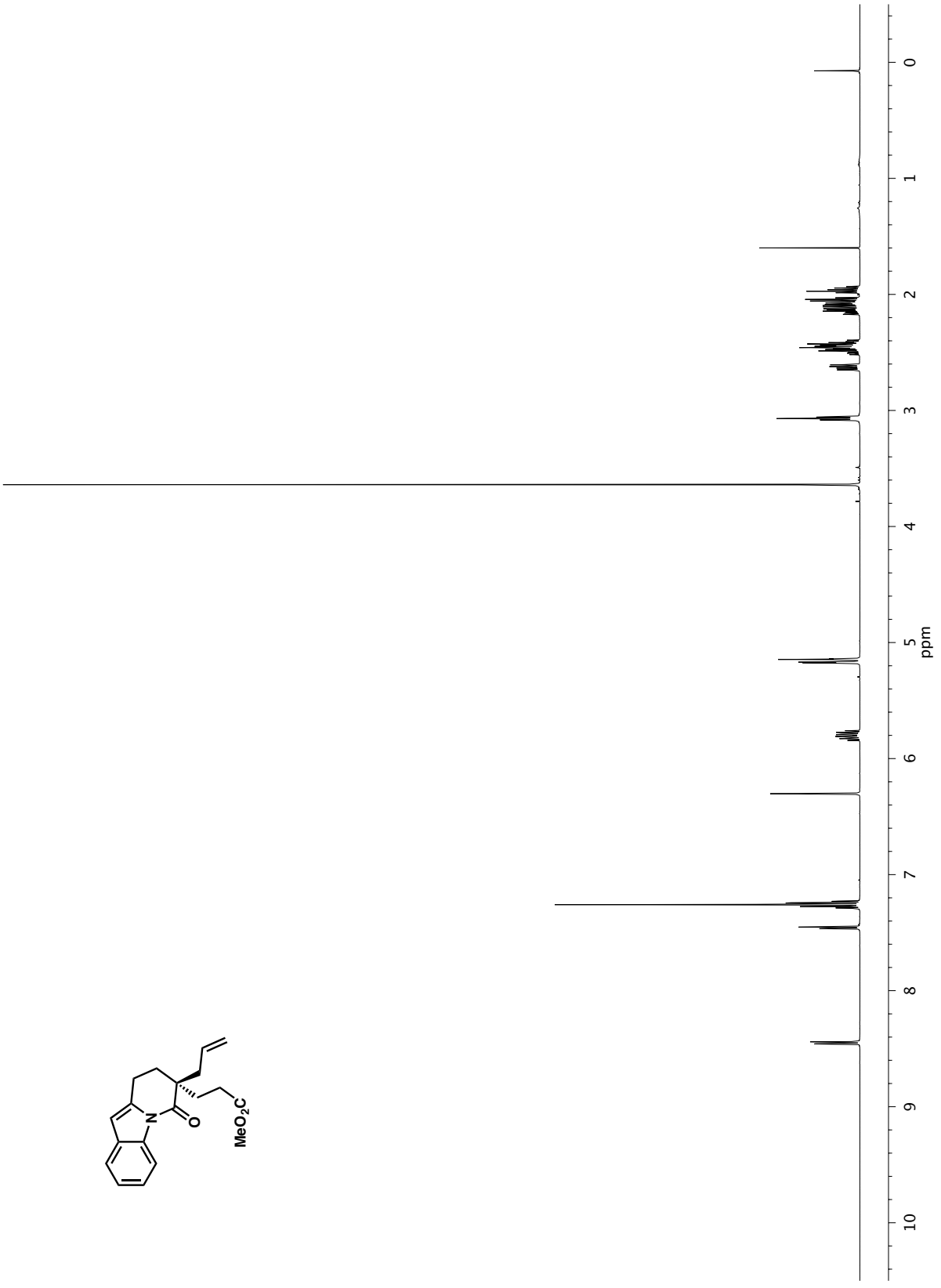


Figure A7.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165i**.

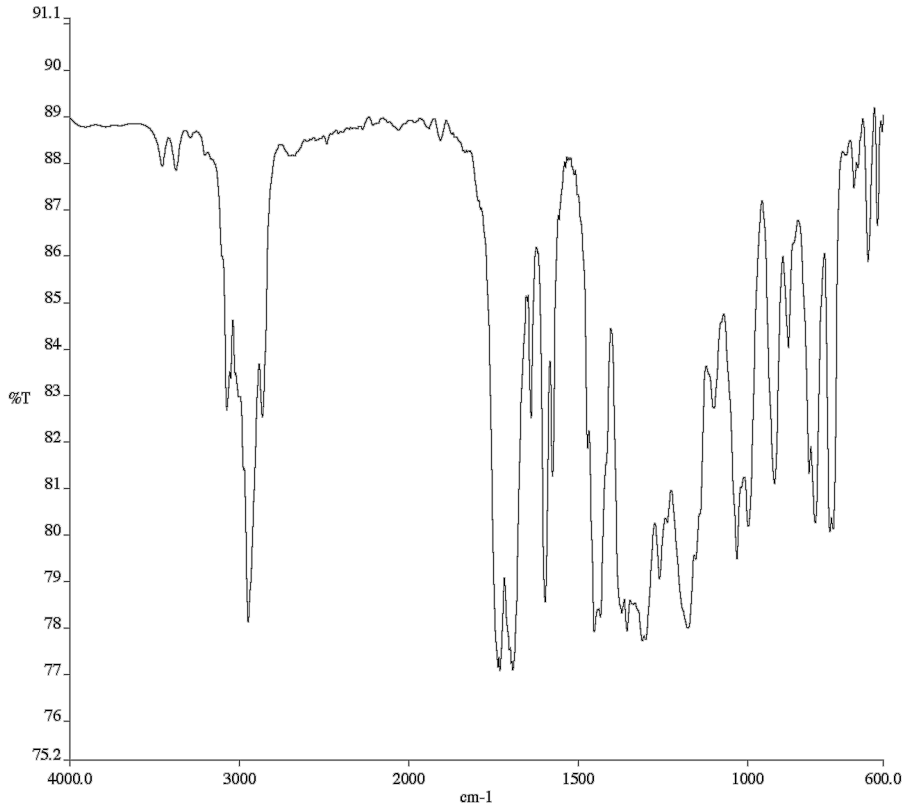


Figure A7.29. Infrared spectrum (Thin Film, NaCl) of compound **165i**.

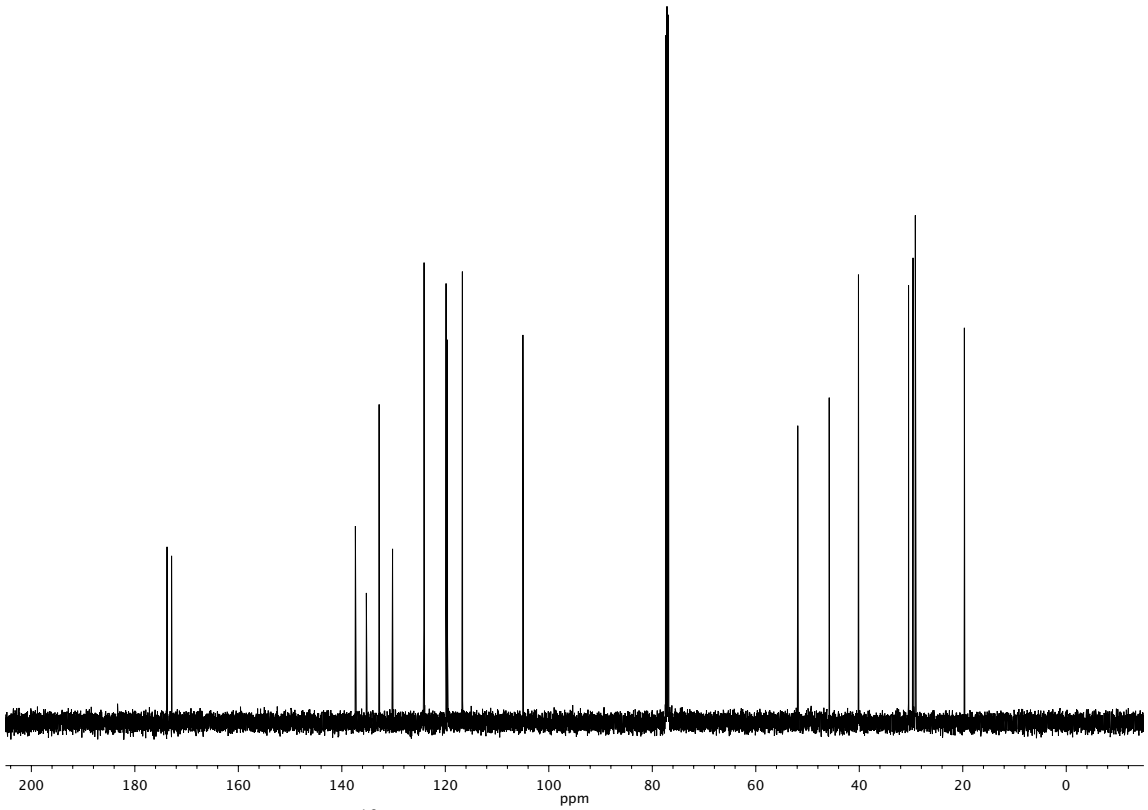


Figure A7.30. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165i**.

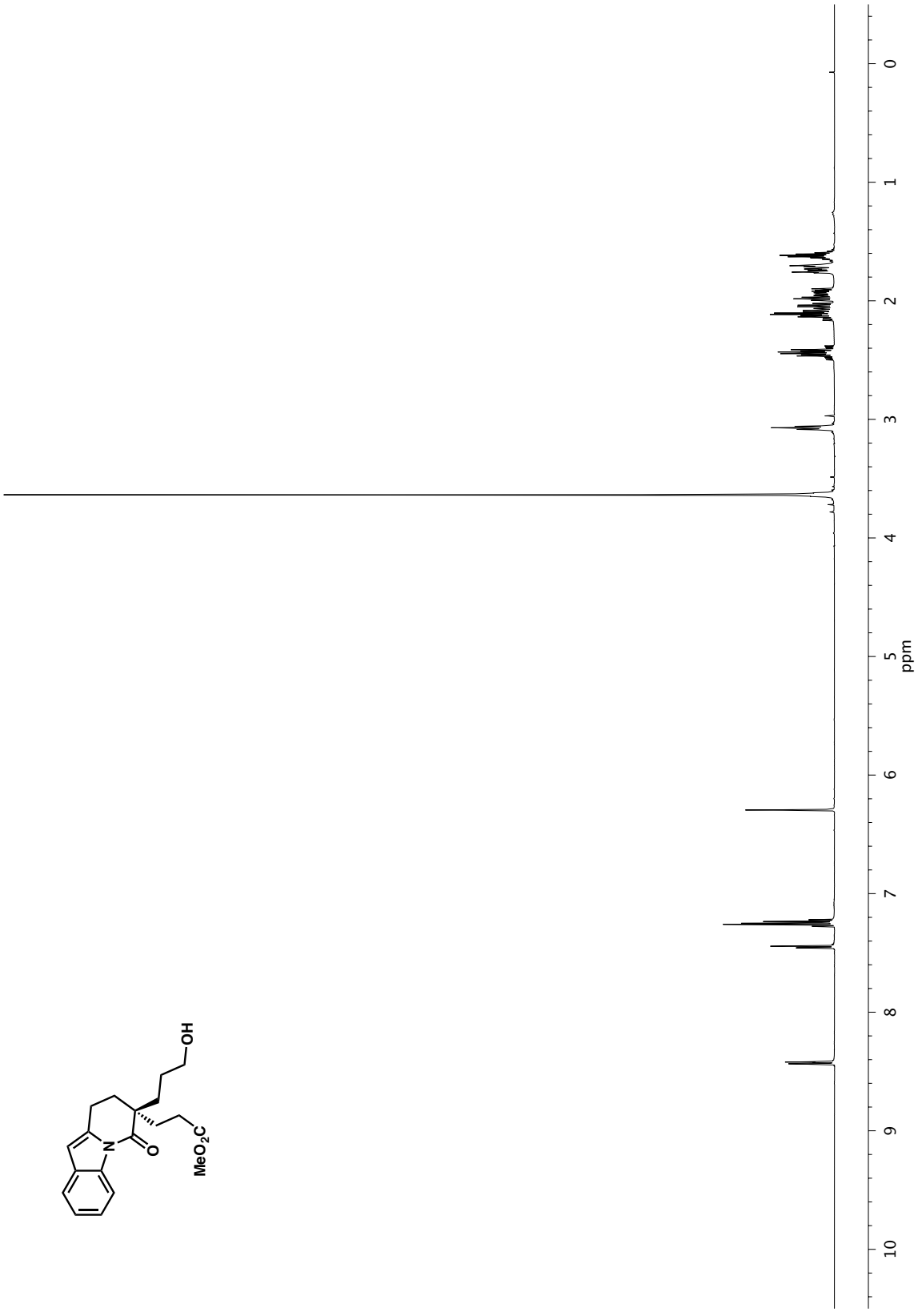


Figure A7.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **215**.

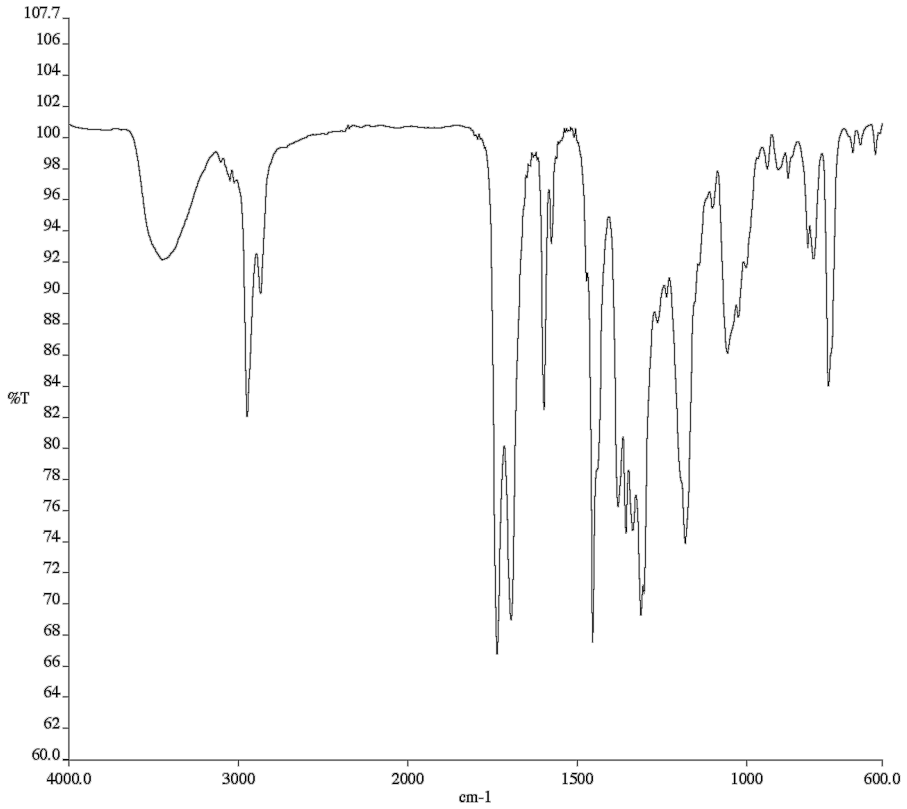


Figure A7.32. Infrared spectrum (Thin Film, NaCl) of compound **215**.

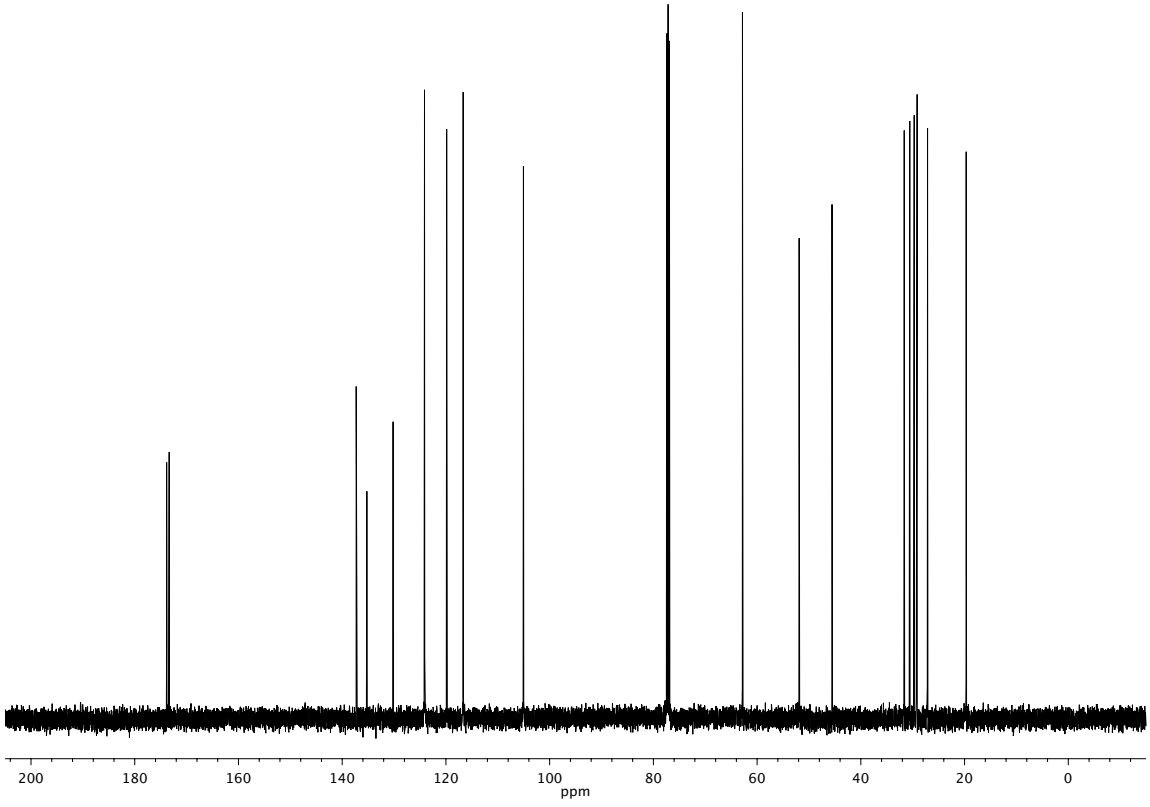


Figure A7.33. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **215**.

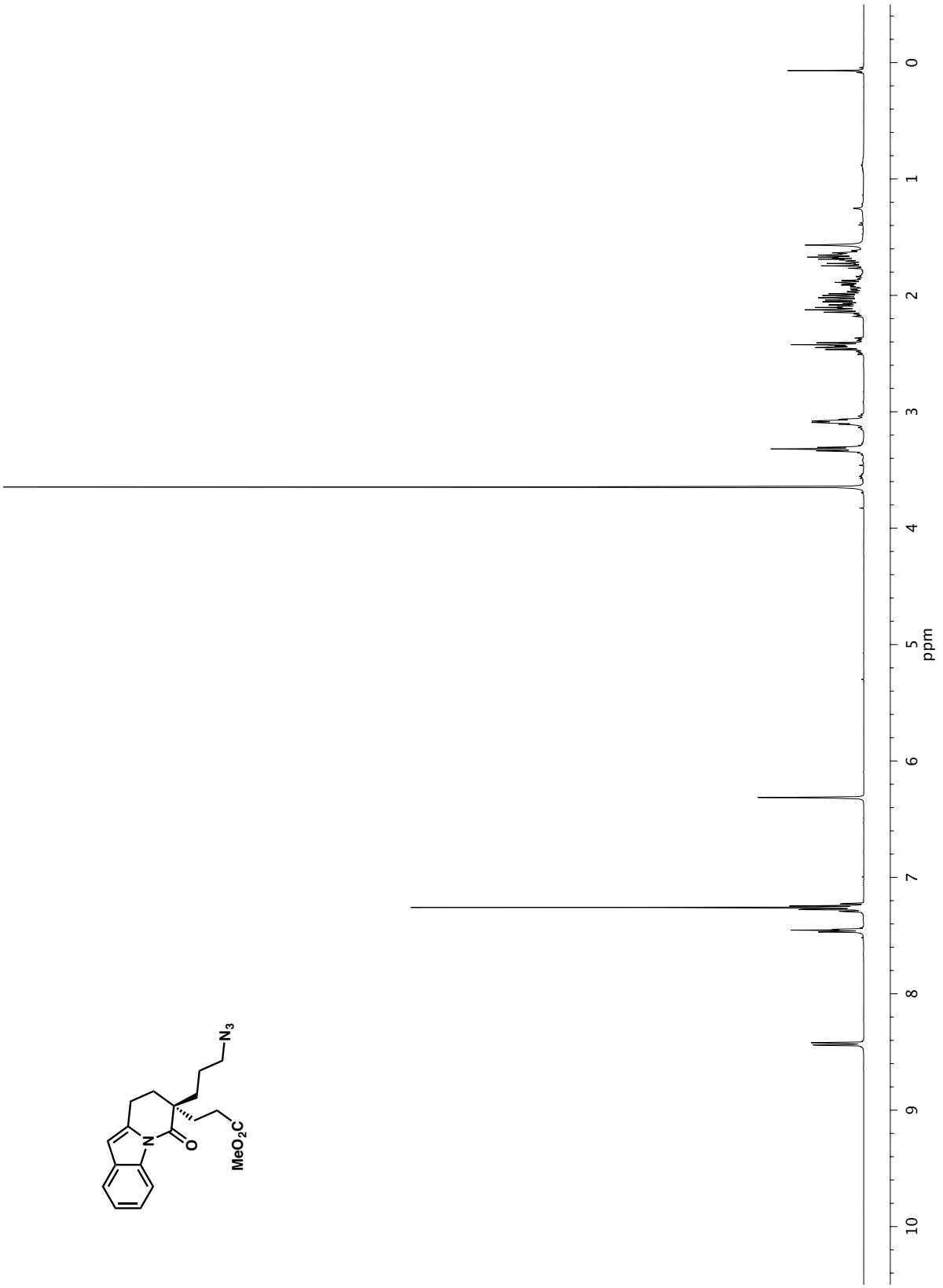


Figure A7.34. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **216**.

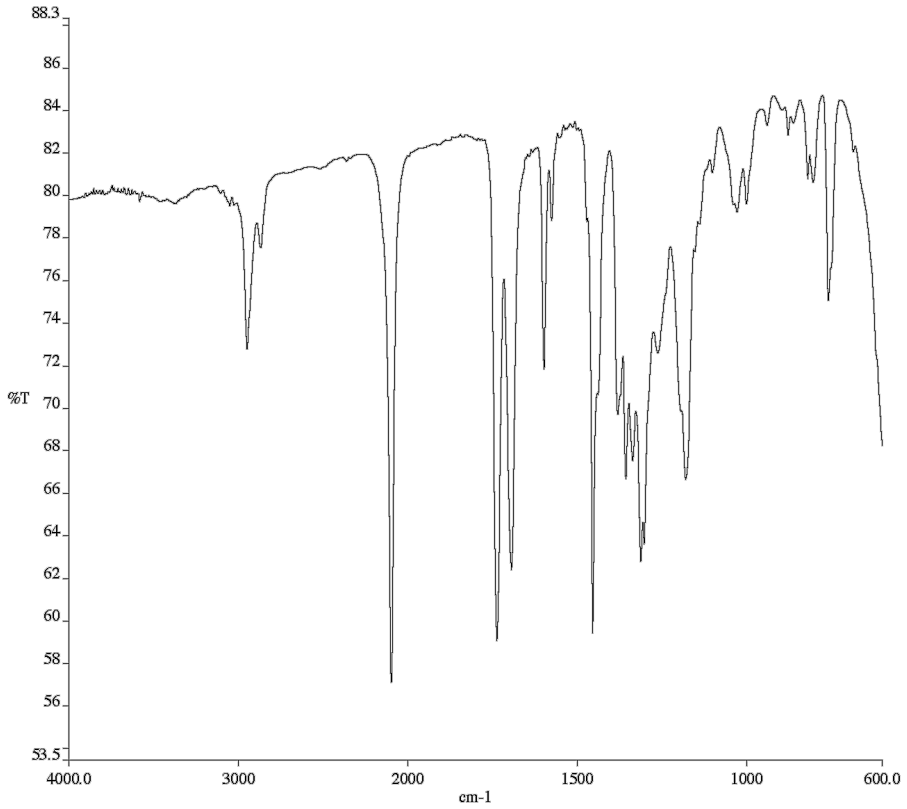


Figure A7.35. Infrared spectrum (Thin Film, NaCl) of compound **216**.

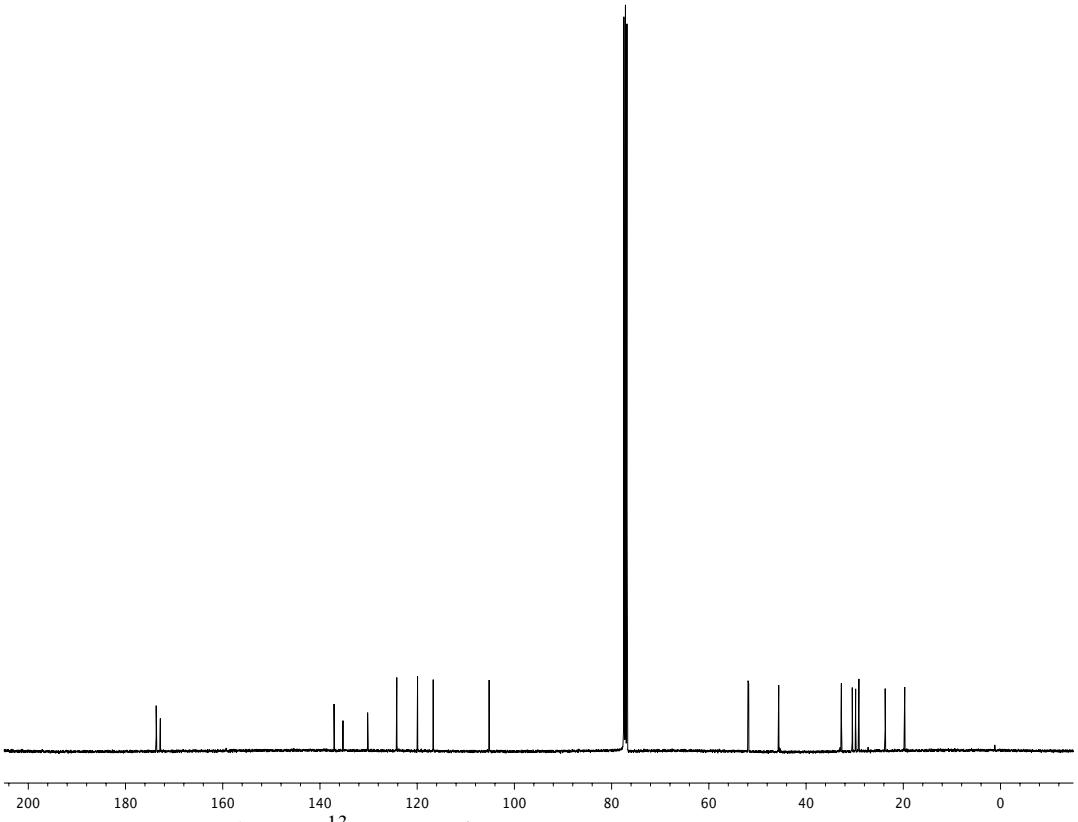


Figure A7.36. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **216**.

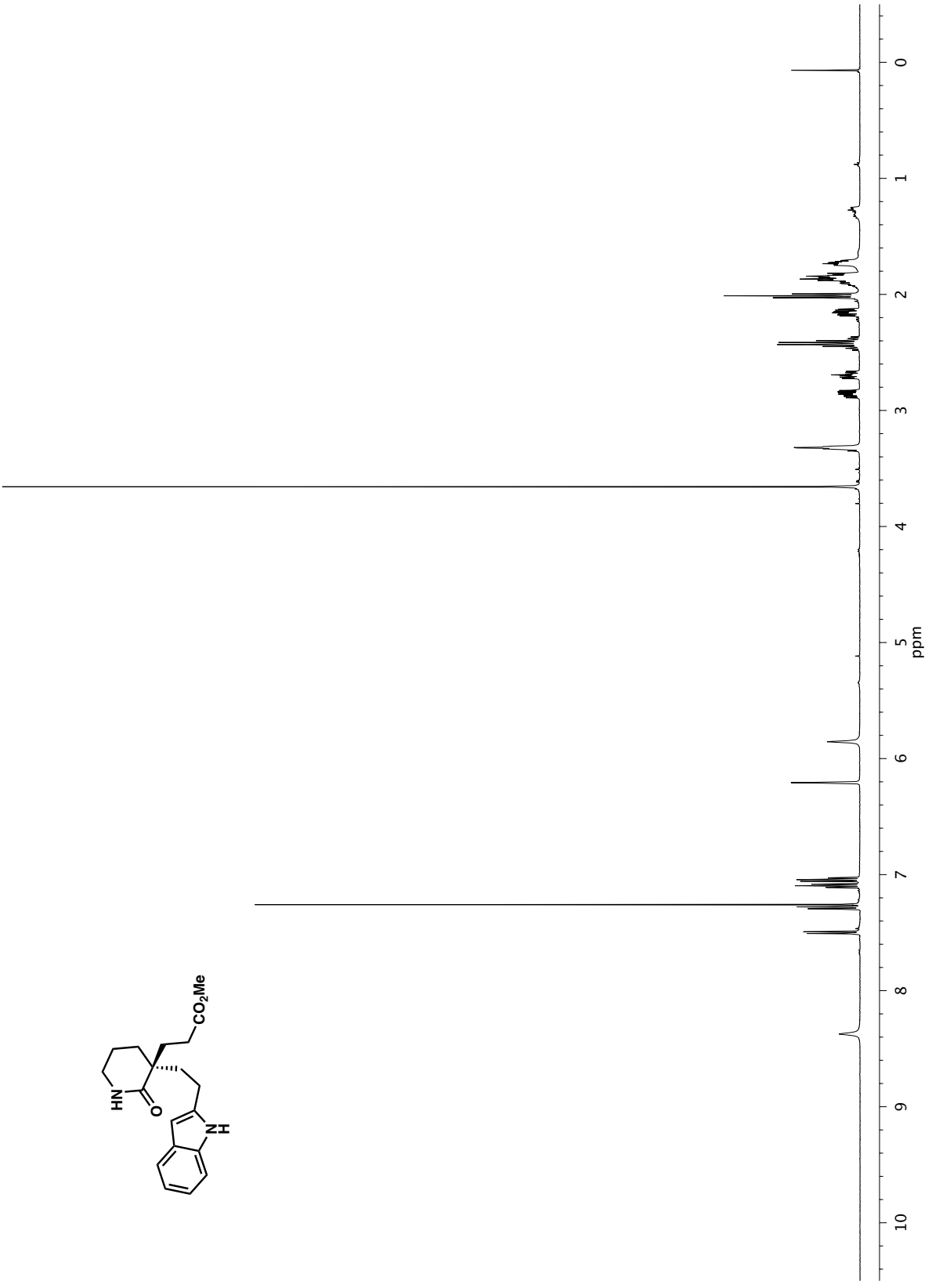


Figure A7.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **214**.

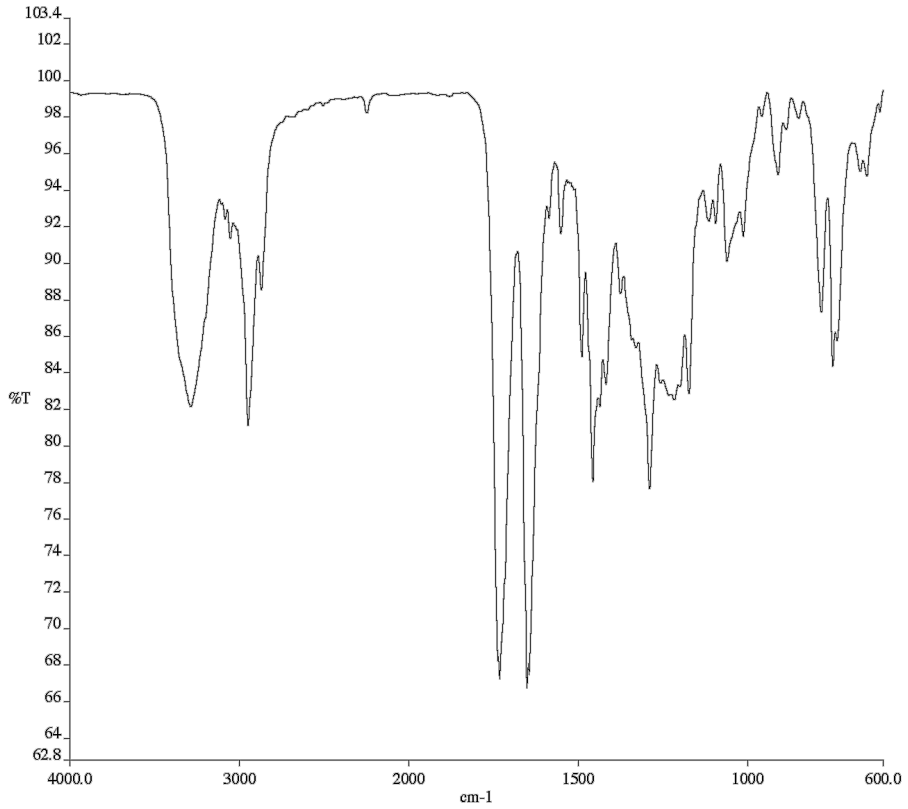


Figure A7.38. Infrared spectrum (Thin Film, NaCl) of compound **214**.

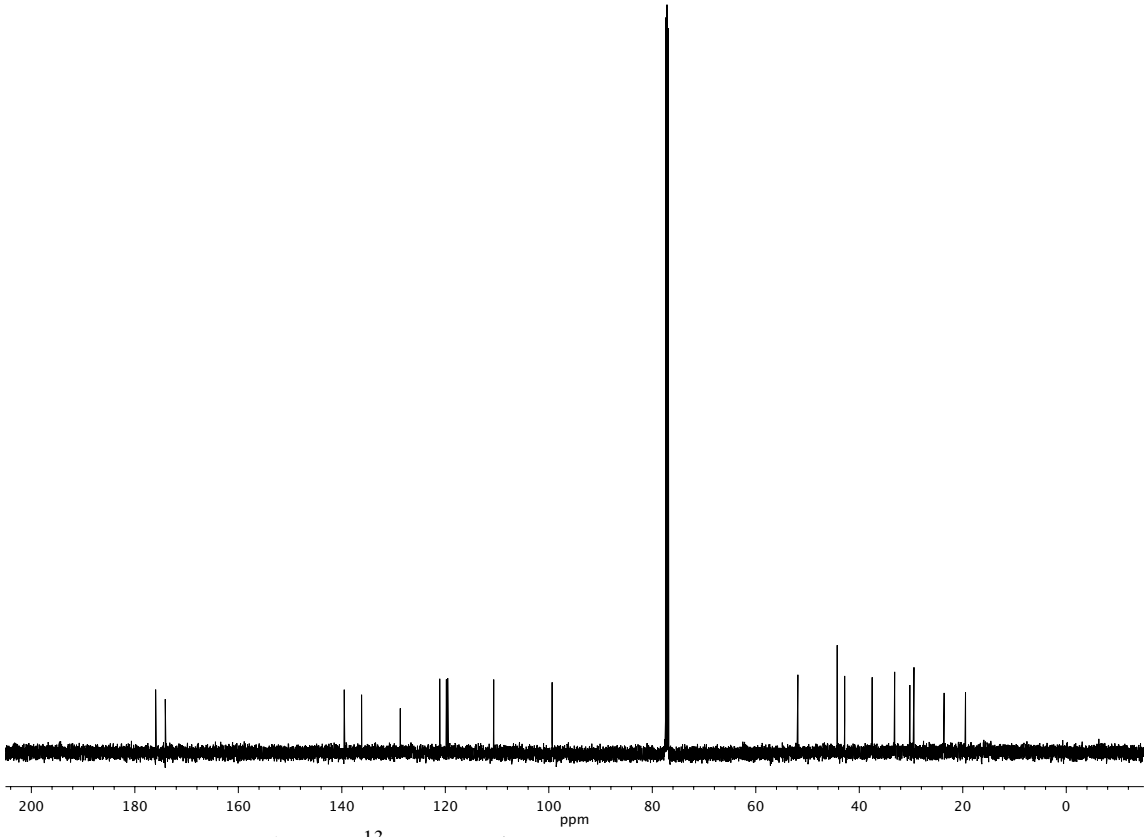


Figure A7.39. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **214**.

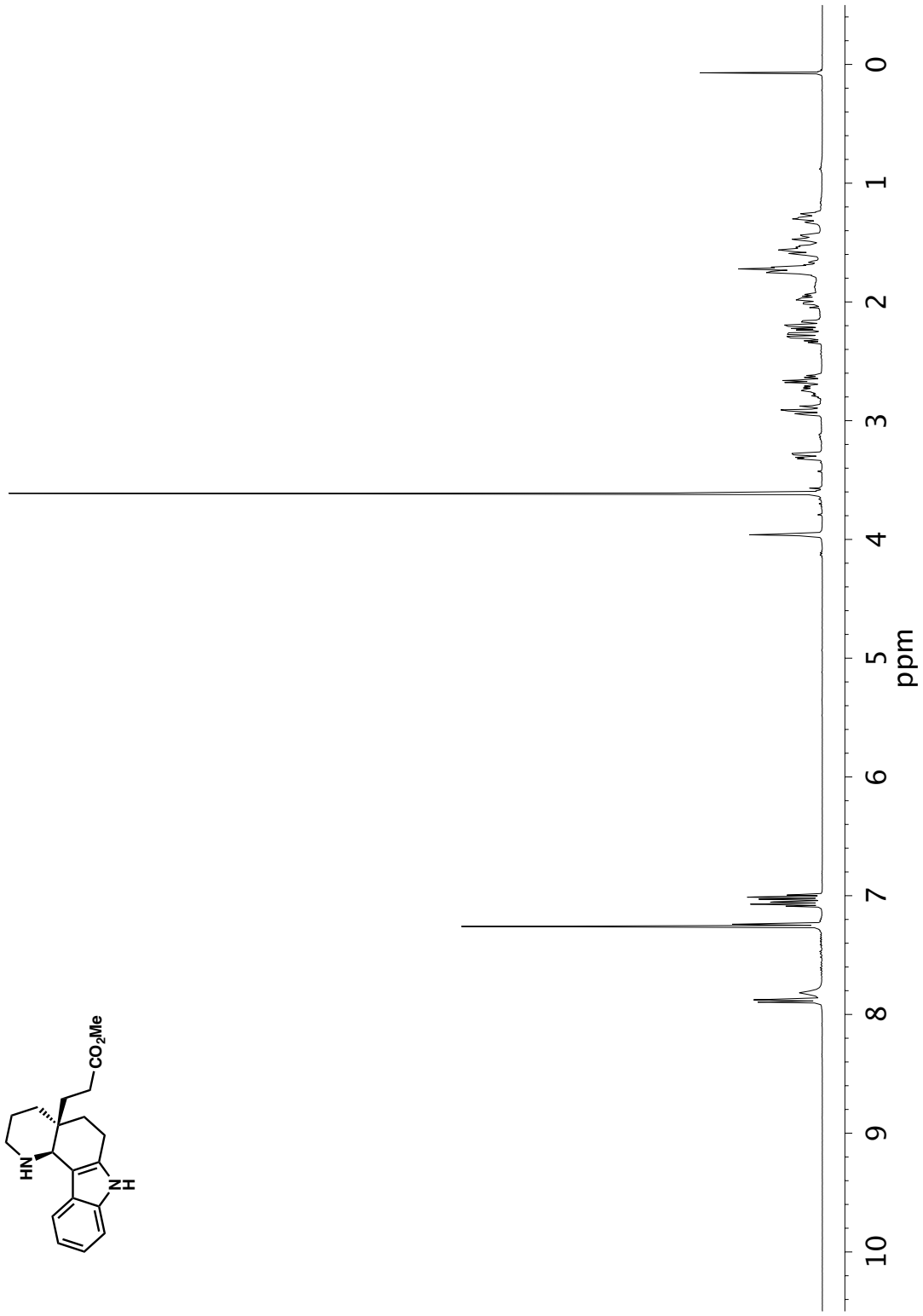


Figure A7.40. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **213**.

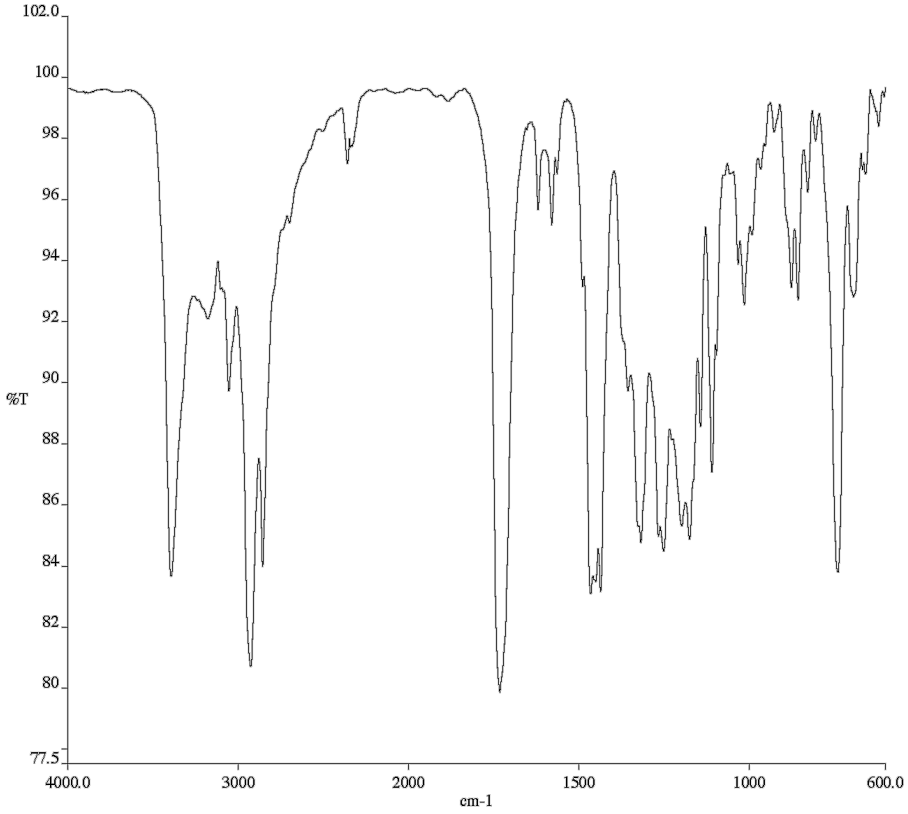


Figure A7.41. Infrared spectrum (Thin Film, NaCl) of compound **213**.

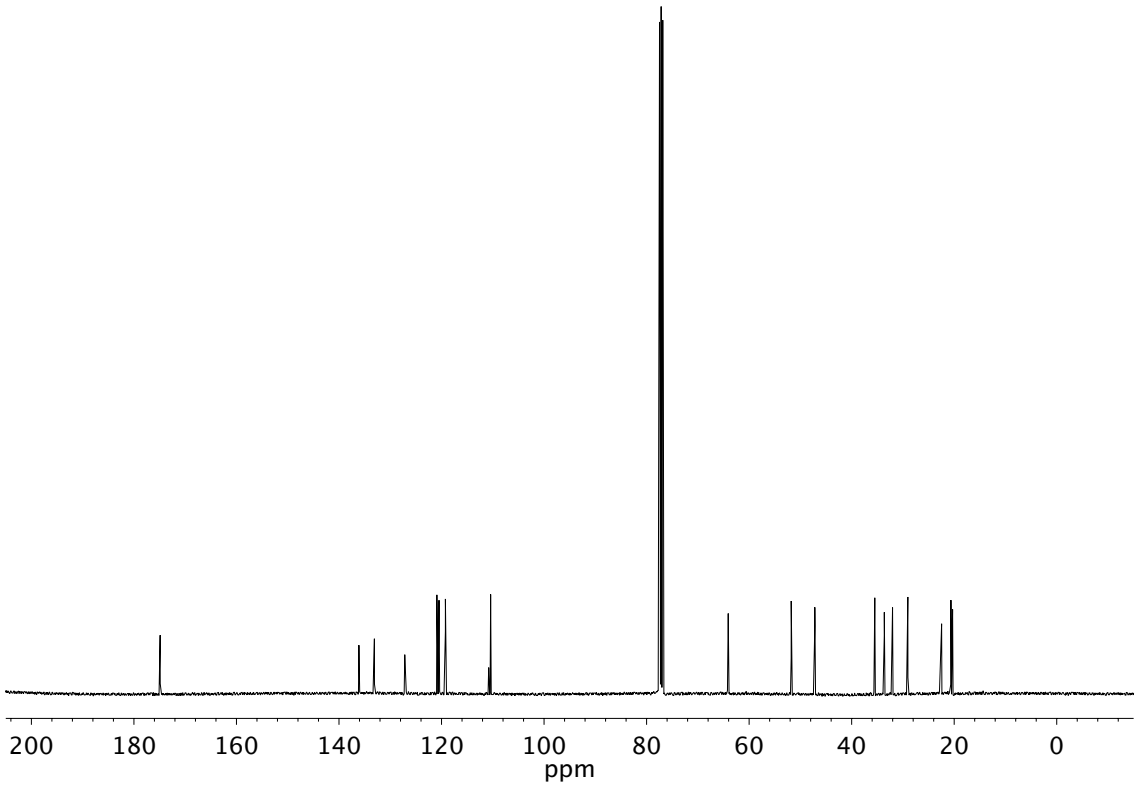


Figure A7.42. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **213**.

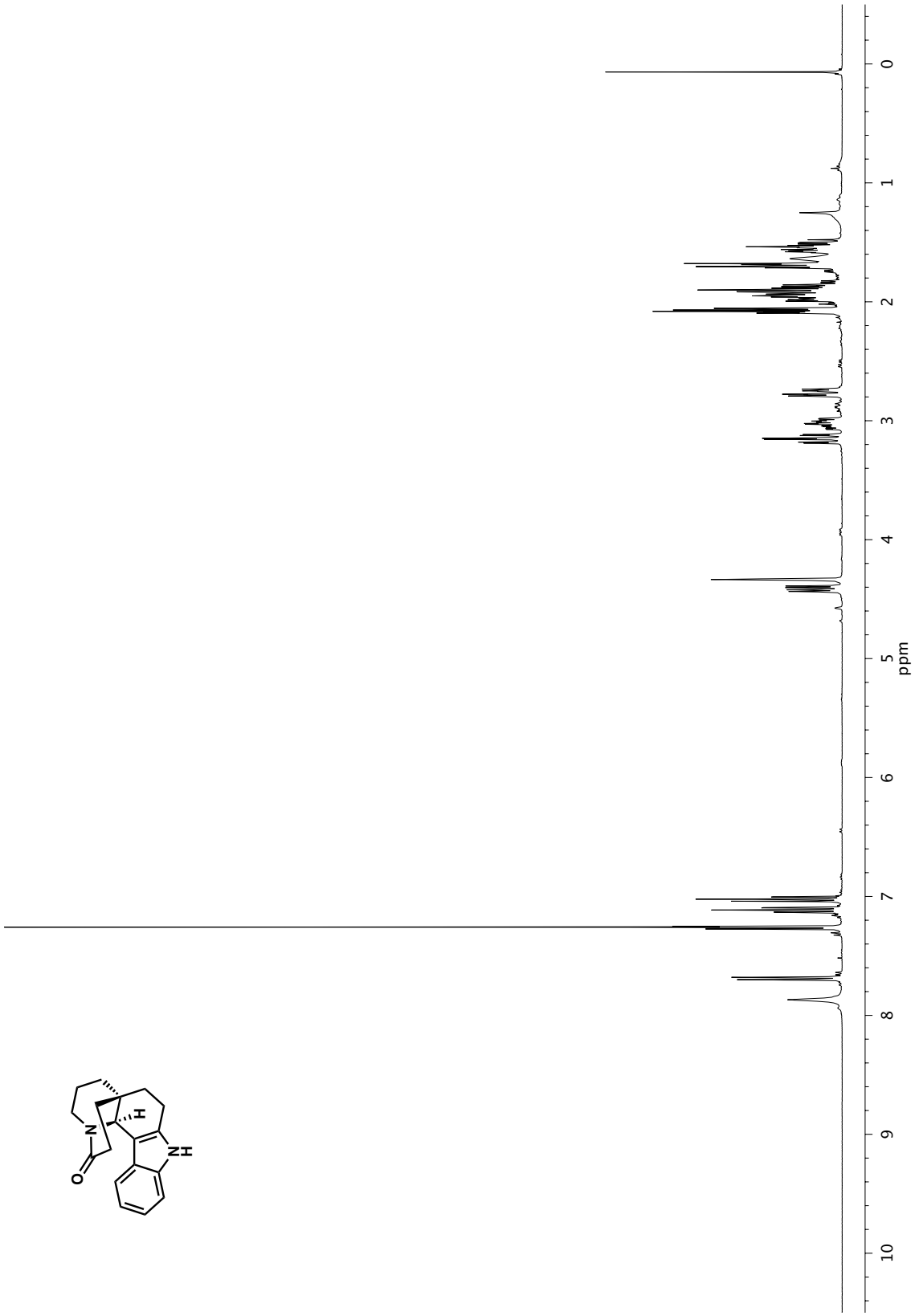


Figure A7.43. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **218**.

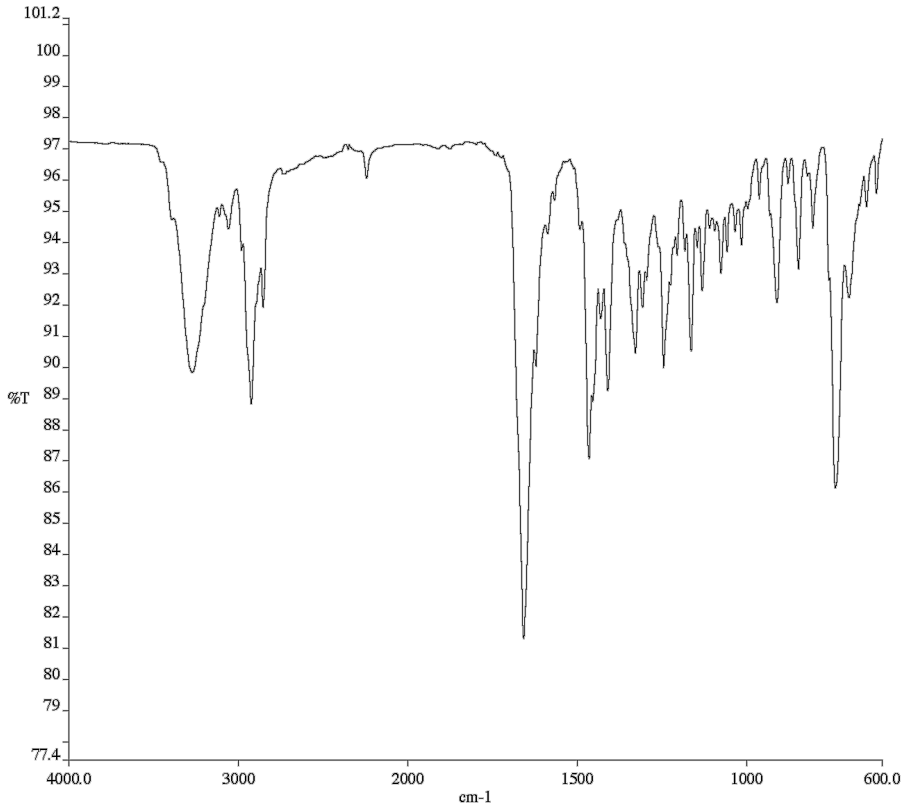


Figure A7.44. Infrared spectrum (Thin Film, NaCl) of compound **218**.

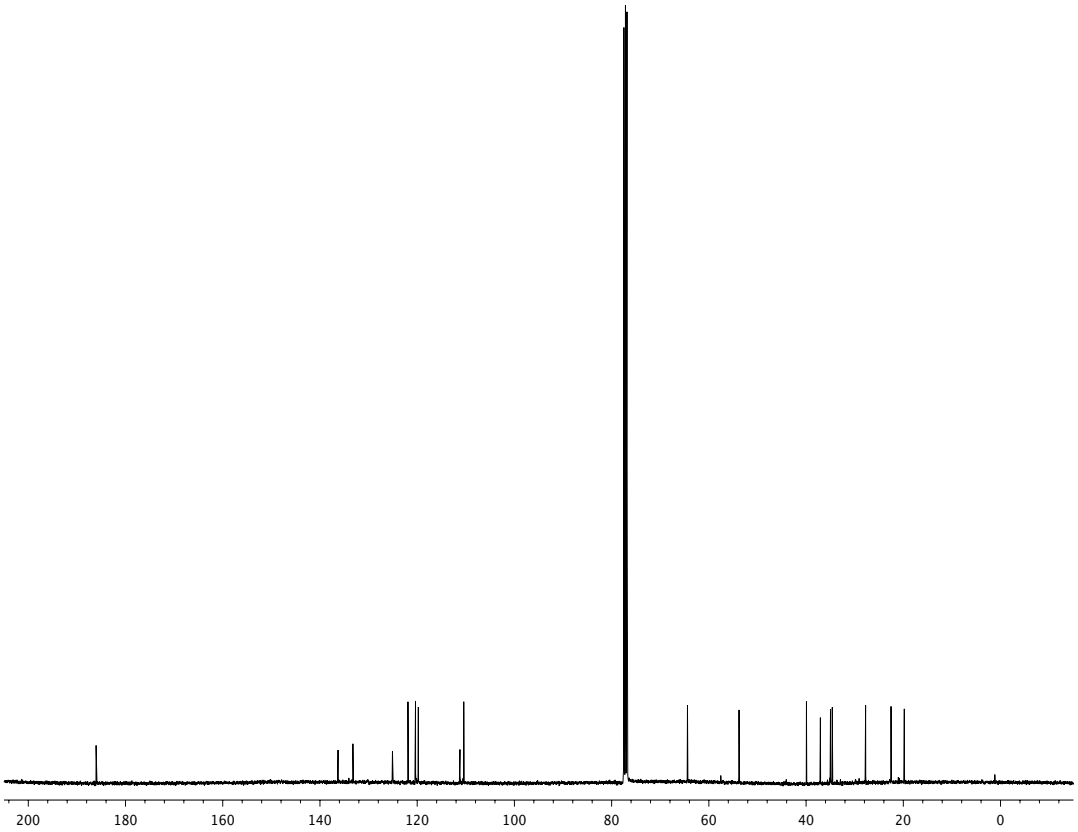


Figure A7.45. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **218**.

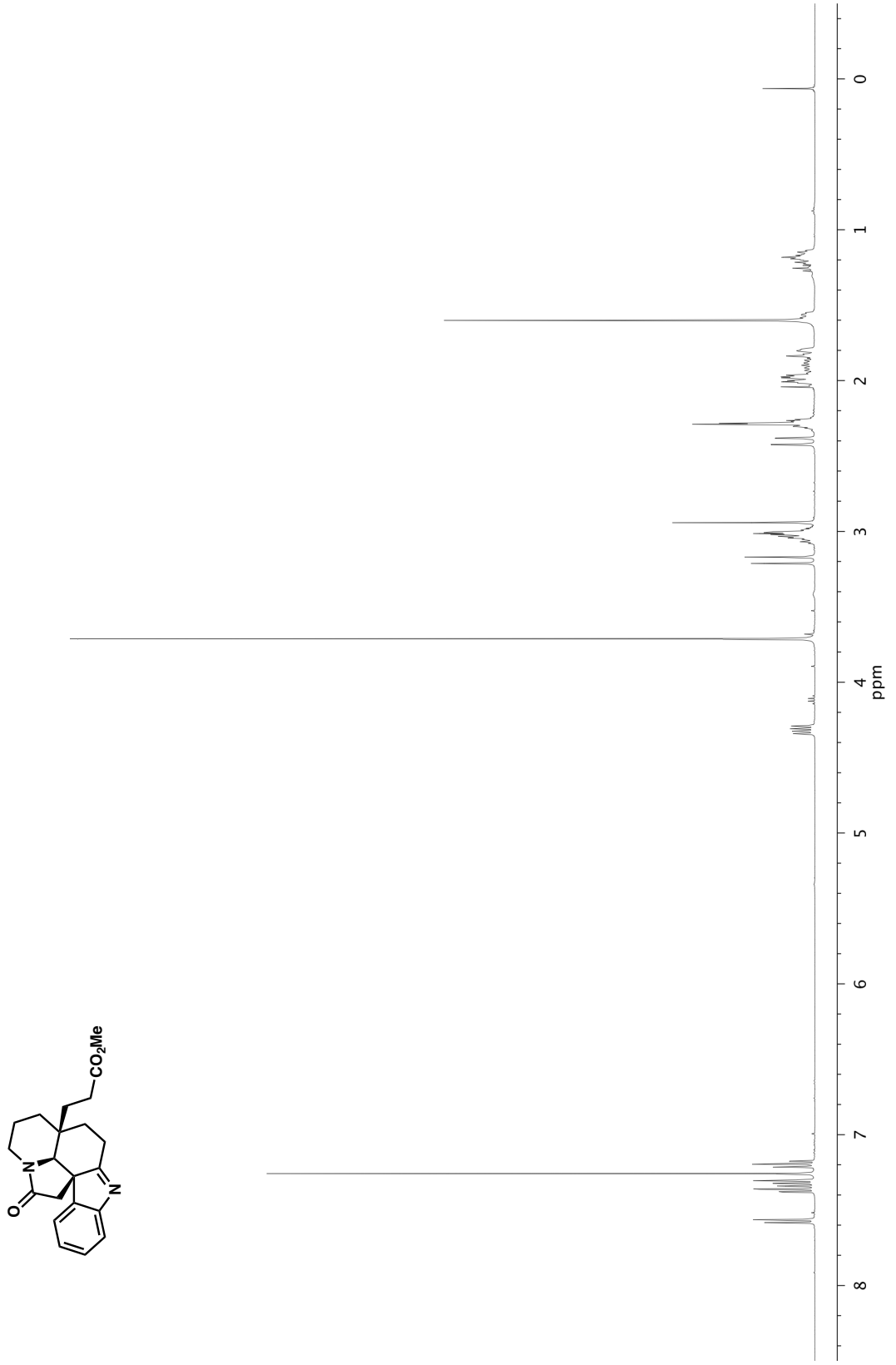


Figure A7.46. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **221**.

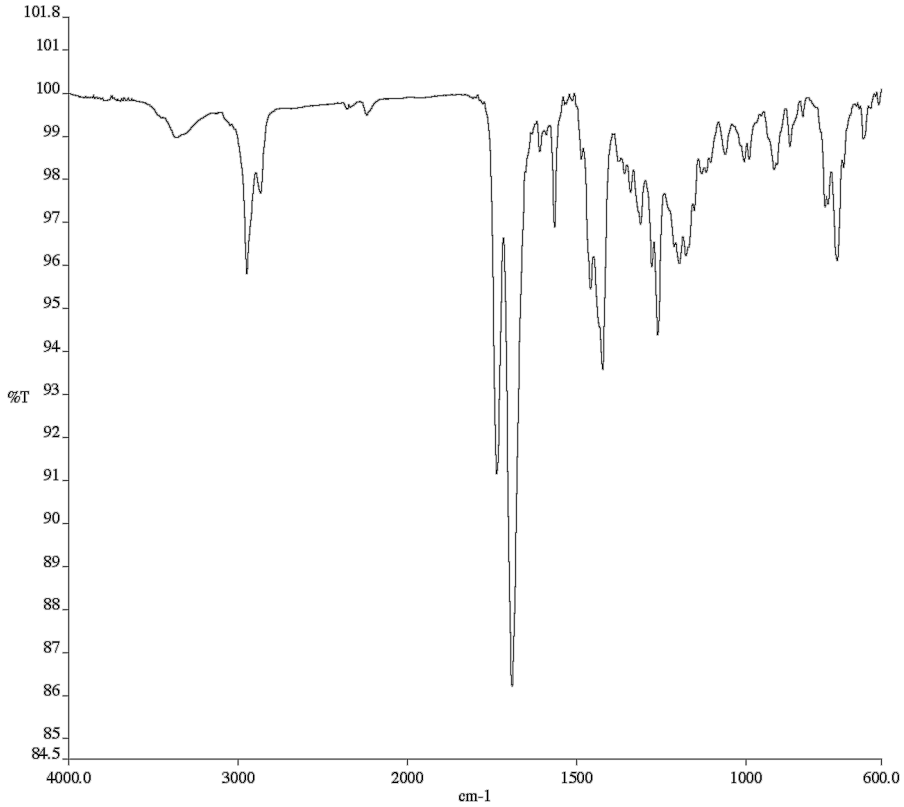


Figure A7.47. Infrared spectrum (Thin Film, NaCl) of compound **221**.

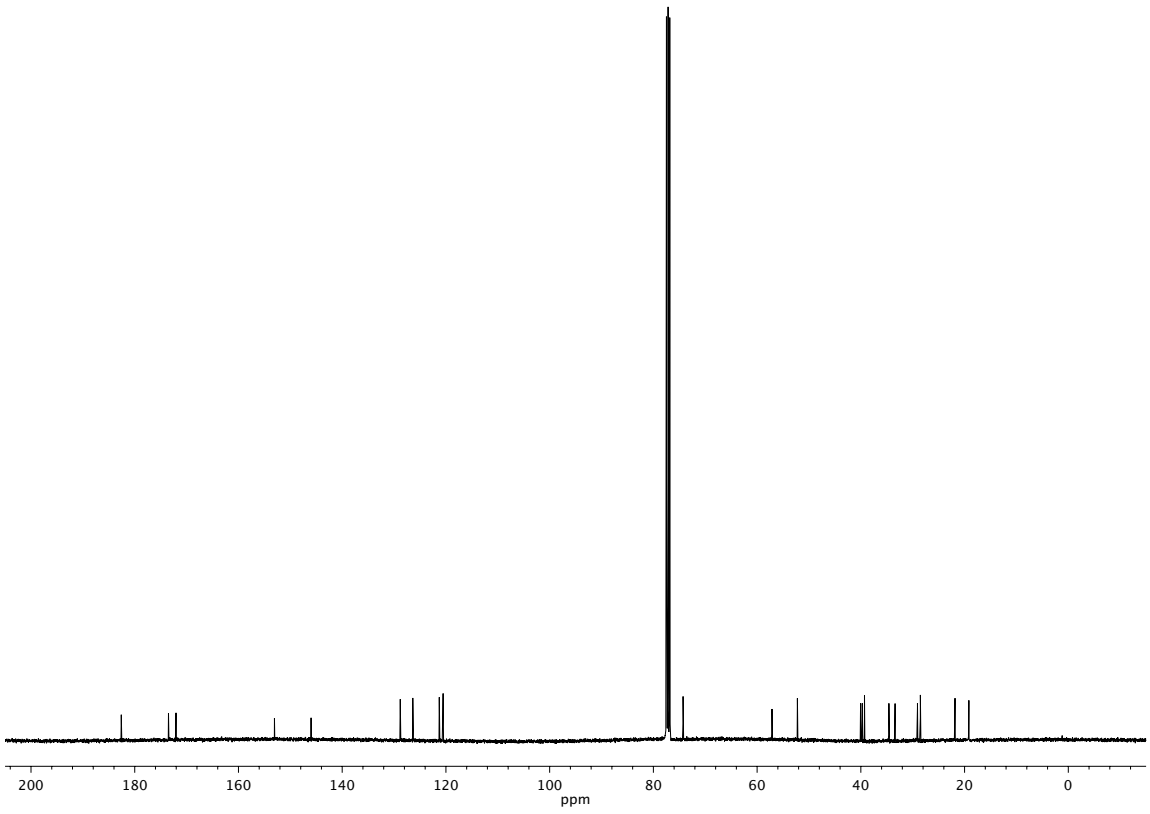


Figure A7.48. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **221**.

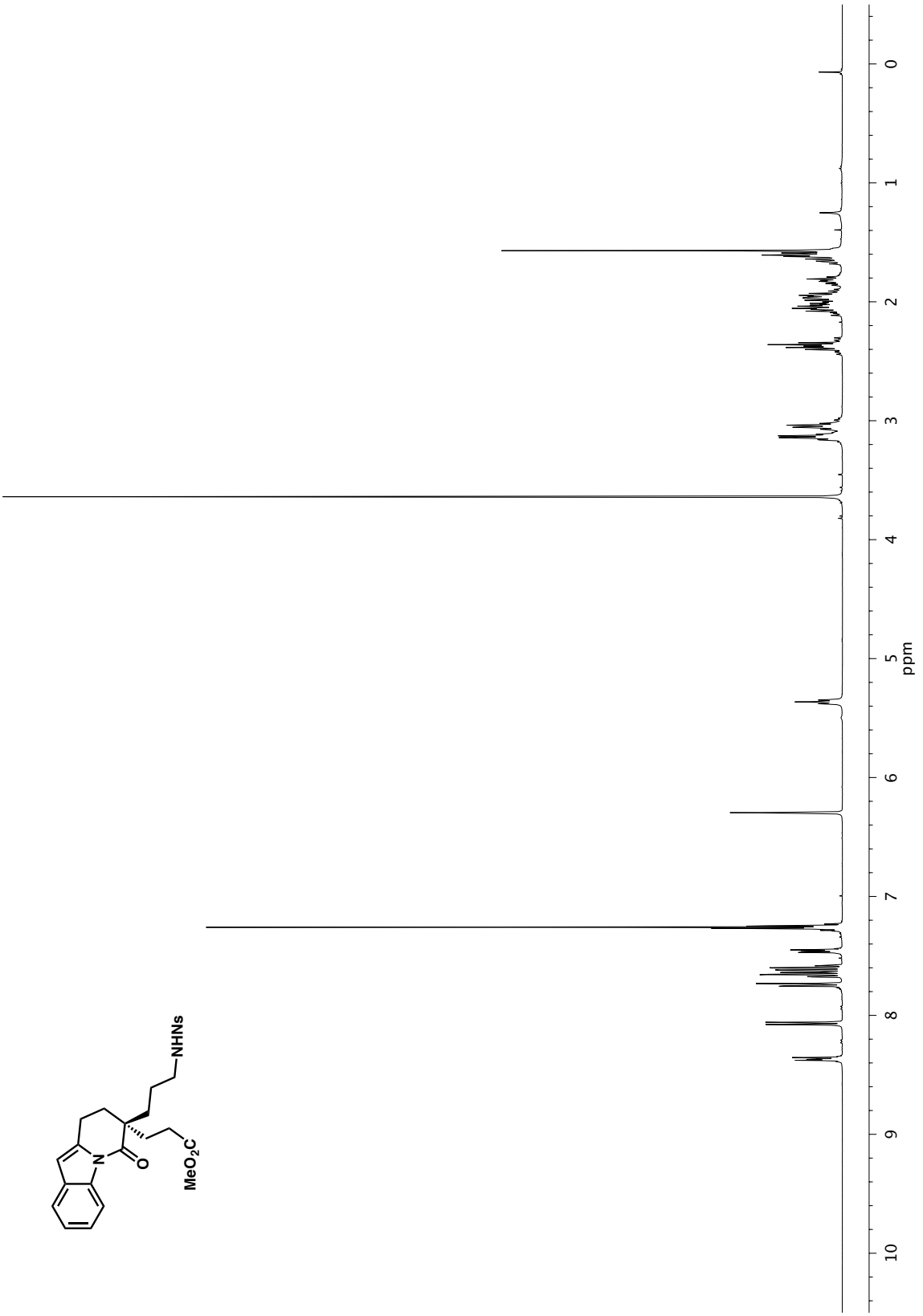


Figure A7.49. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **229**.

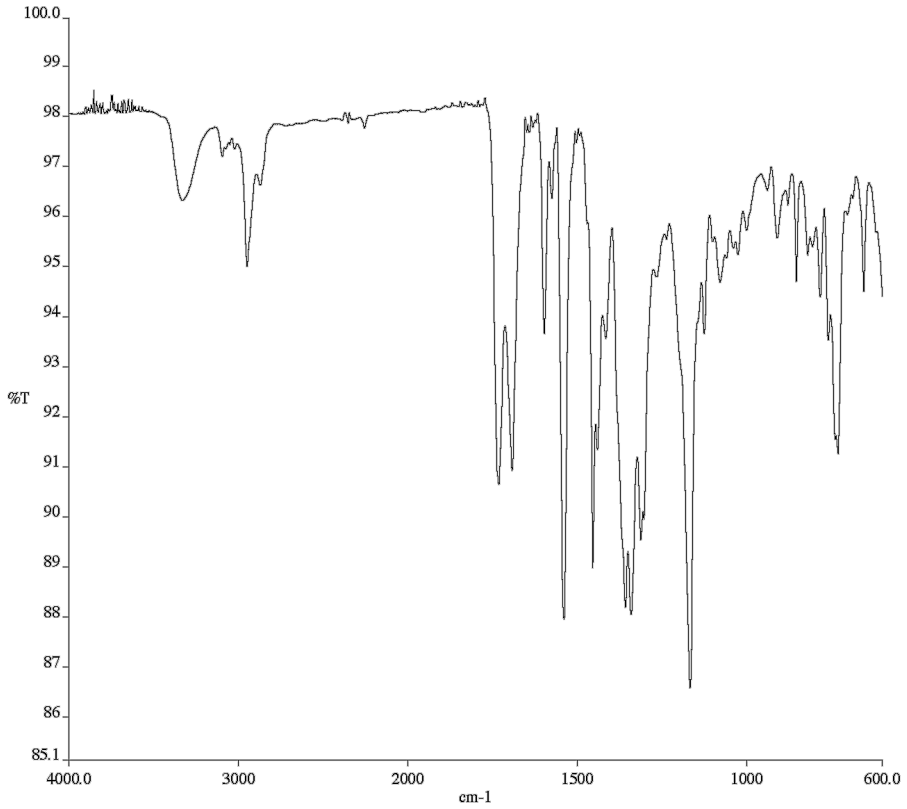


Figure A7.50. Infrared spectrum (Thin Film, NaCl) of compound **229**.

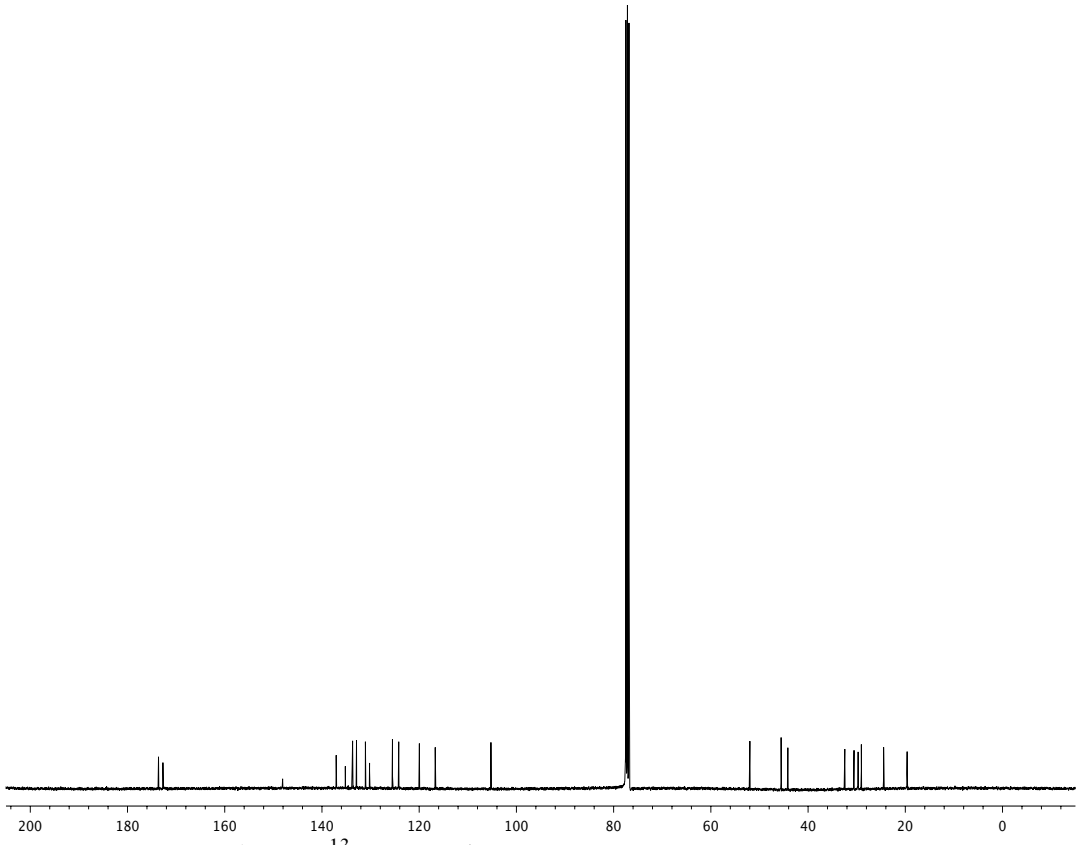


Figure A7.51. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **229**.

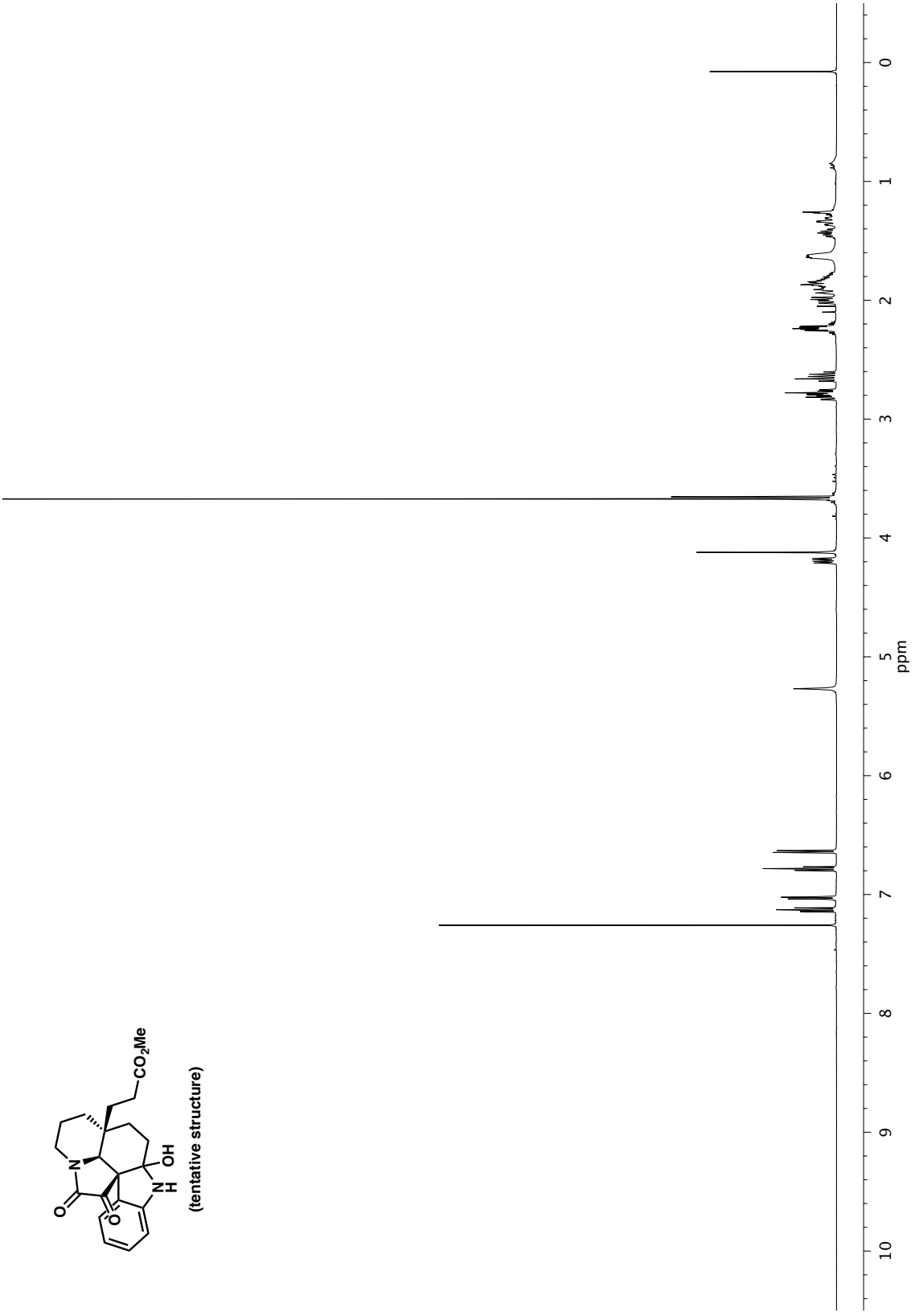


Figure A7.52. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **231**.

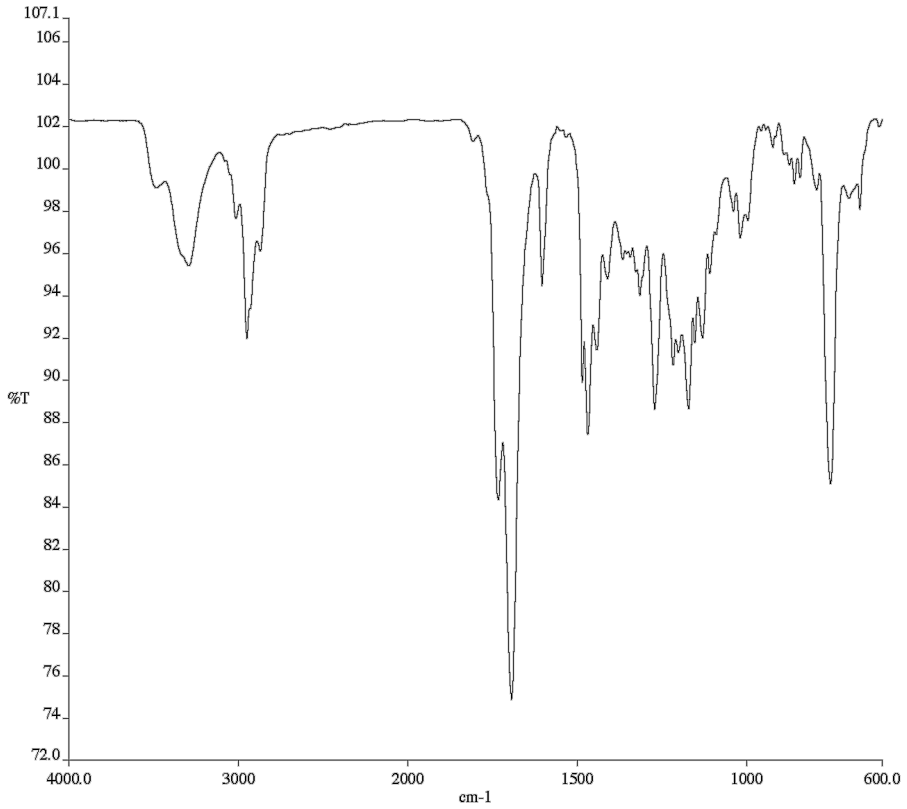


Figure A7.53. Infrared spectrum (Thin Film, NaCl) of compound **231**.

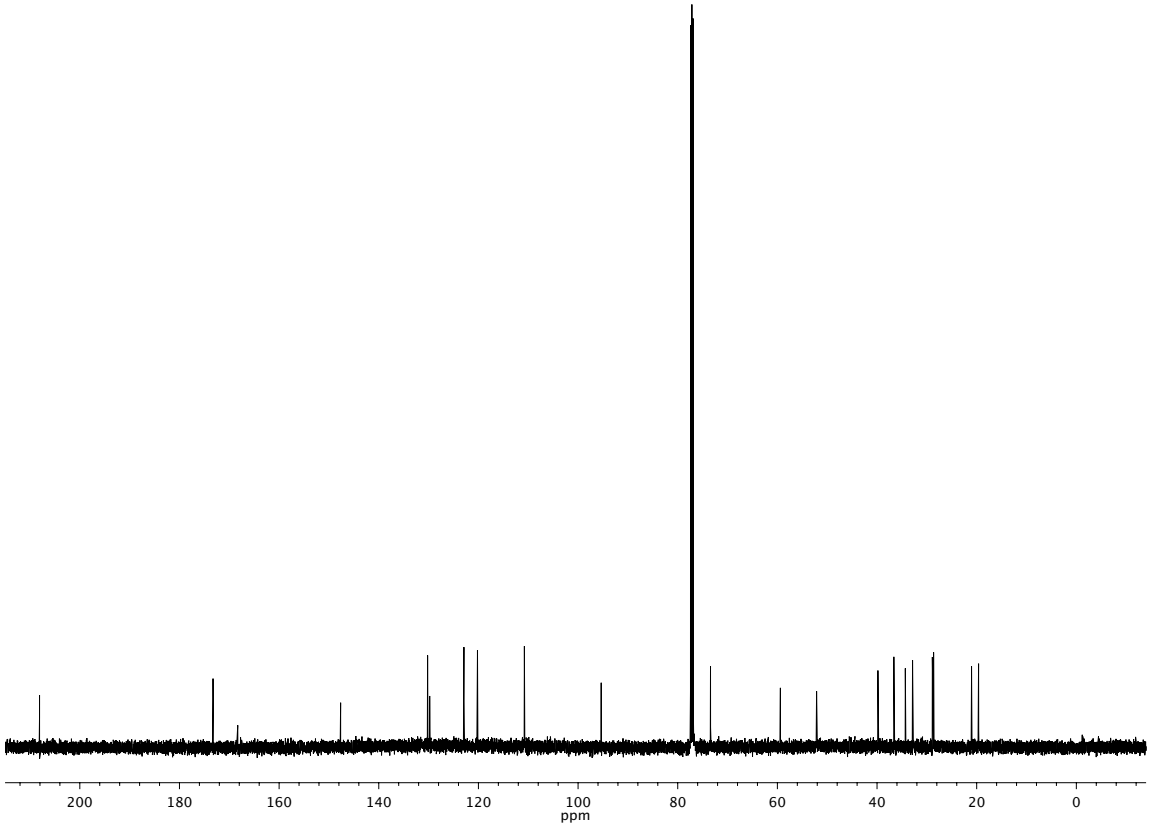


Figure A7.54. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **231**.

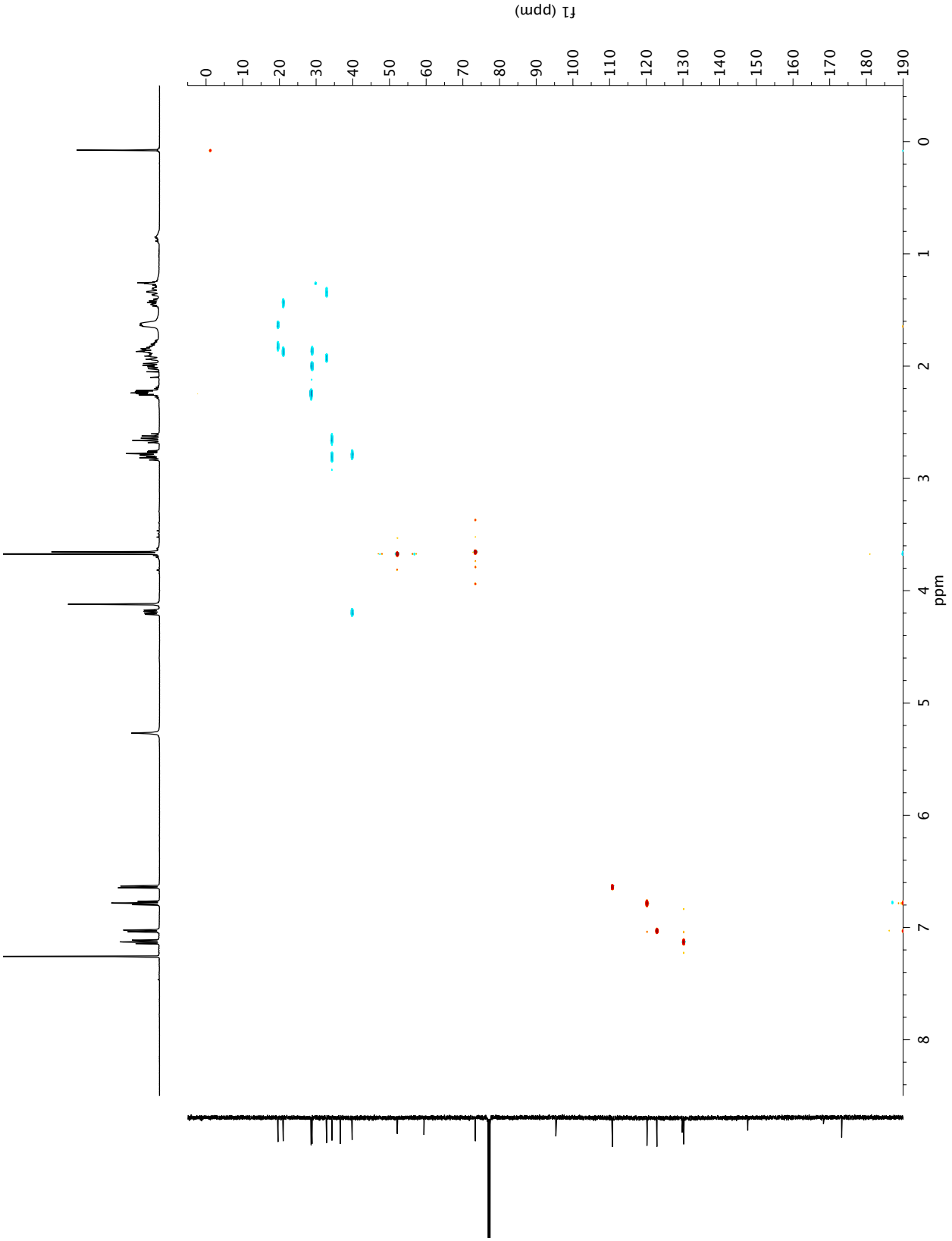


Figure A7.55. HSQC (500 MHz, $CDCl_3$) of compound **231**.

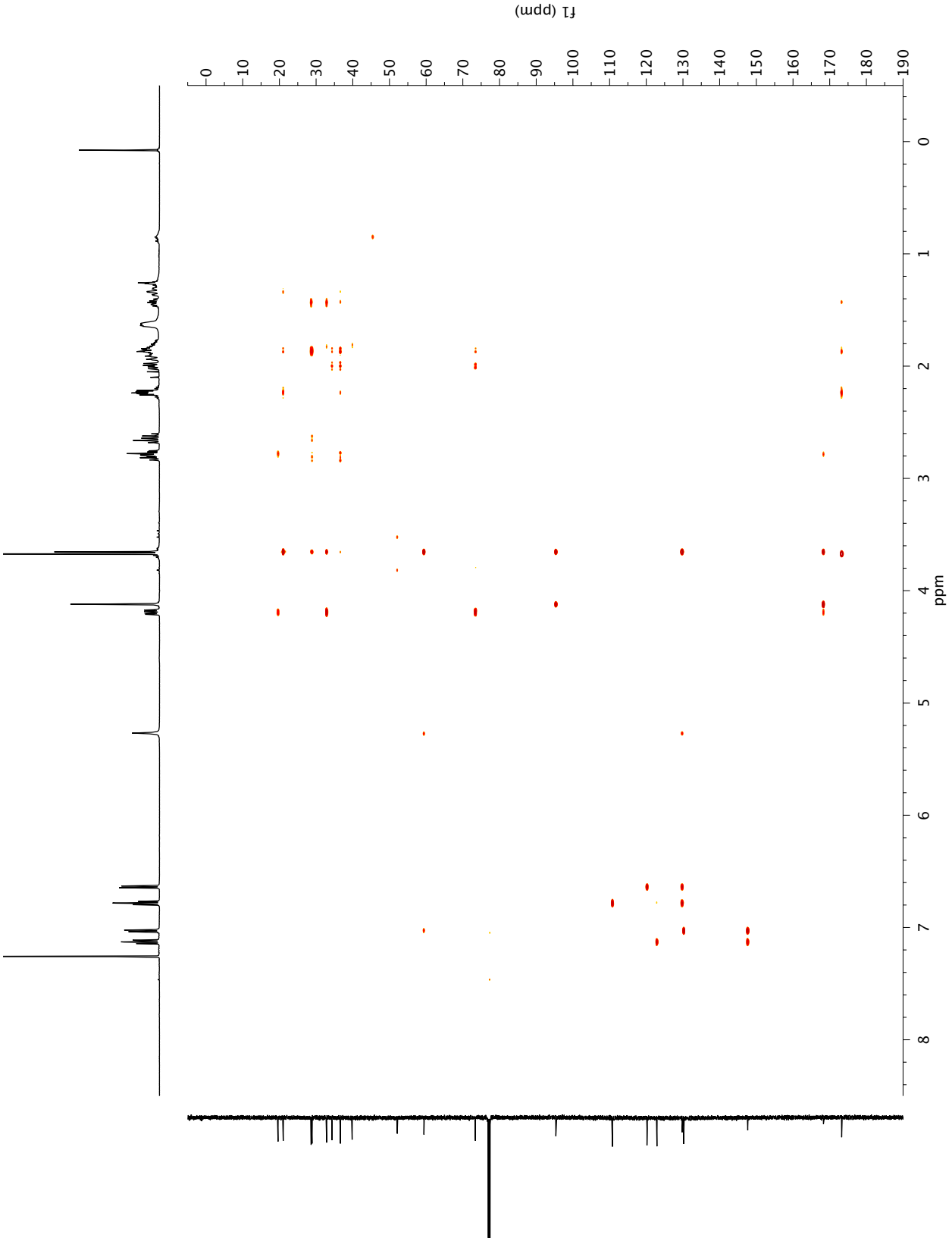


Figure A7.56. HMBC (500 MHz, $CDCl_3$) of compound **231**.

CHAPTER 4

Enantioselective Synthesis of α-Quaternary Mannich Adducts: Total Syntheses of (–)-Isonitramine and (+)-Sibirinine[†]

4.1 INTRODUCTION AND BACKGROUND

The Mannich reaction, first discovered in the early 20th century, is among the most robust reactions known to produce nitrogen-containing compounds. In a classic intermolecular Mannich reaction, an aldehyde, an amine and an α-acidic carbonyl compound react to form a β-amino carbonyl product.[1] Recent progress in this area, including modified imine donors and well-explored catalyst systems, has made available a wide variety of asymmetric α-functionalizations of carbonyl compounds.[2] To date, asymmetric Mannich-type reactions[3] and α-aminomethylation reactions[4] to establish α-stereogenic α-quaternary carbonyl compounds have been limited to 1,3-dicarbonyl nucleophiles (e.g., **232**, Scheme 4.1.1.A). To our knowledge, the lone exceptions are the

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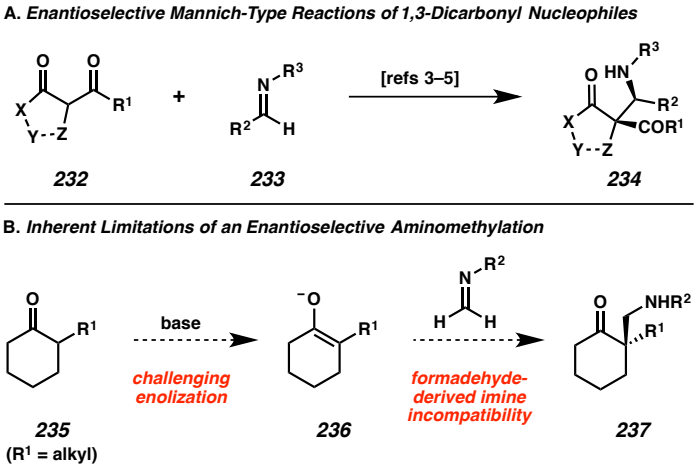
[†] This work was performed in collaboration with Dr. Yoshitaka Numajiri and Dr. Koji Chiyoda, both of whom are alumni of Stoltz group. Additionally, this work has been published and adapted with permission from Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2015**, *137*, 1040–1043.

proline-catalyzed Mannich-type reaction of α-branched aldehydes reported by Barbas and co-workers,[5] and Trost's zinc ProPhenol-catalyzed Mannich-type reaction of tetralone nucleophiles.[3e] However, these substrates only possess one enolizable position and in the latter example the resulting enolates are stabilized through conjugation with the arene π-system. Moreover, these reactions[3–5] require prochiral aldimine electrophiles derived from either glyoxalate esters (e.g., **233**, $R^2 = CO_2R$) or aryl aldehydes (e.g., **233**, R^2 = (hetero)aryl), which add an additional element of stereocontrol via the facial bias of the imine (Scheme 4.1.1.A).

The synthesis of enantioenriched α-quaternary Mannich adducts[6] derived from α-alkyl-substituted ketones (e.g., **235**, Scheme 4.1.1.B) is limited by three important considerations. First, there are two enolizable positions of similar pK_a, which will result in nonselective enolization. Second, it is unlikely that the equilibrating conditions required to access the thermodynamically preferred enolate (i.e., **236**) will be amenable to enantioselective addition into an aldimine electrophile. Finally, it is unclear whether non-prochiral formaldehyde-derived imines can be successfully implemented this transformation. To overcome these challenges, we envisioned a strategy wherein the alkylation, not the aminomethylation, would be the enantiodetermining step.

Scheme 4.1.1. Limitations of Existing Enantioselective Mannich-Type Reactions

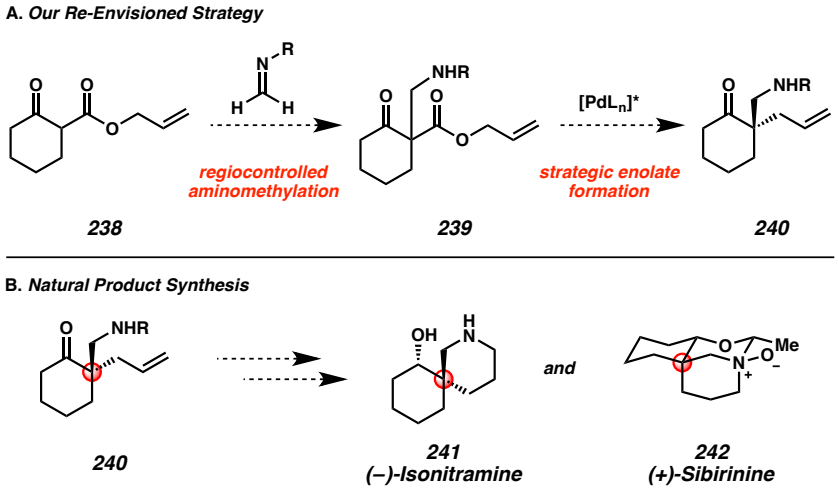


4.2 STRATEGIC PALLADIUM-CATALYZED ALLYLIC ALKYLATION

Over the course of the past decade, our group has demonstrated decarboxylative palladium-catalyzed asymmetric alkylation of β-ketoesters as a powerful tool to access quaternary centers with high enantioselectivities.[7] The extensive substrate scope and broad functional group compatibility of this transformation[8,9] encouraged further exploration of palladium catalysts in the synthesis of amine-containing substrates, thereby facilitating access to enantioenriched bioactive alkaloids or pharmaceutical candidates. We therefore sought to implement our well-studied, reliable alkylation chemistry in a simple yet powerful strategy for the synthesis of α-quaternary Mannich products in an enantioselective fashion (Scheme 4.2.1.A). Introduction of an aminomethyl group to β-ketoester **238** using classical Mannich chemistry would furnish β-aminoketone **239**. A palladium-catalyzed asymmetric allylic alkylation reaction would then afford the enantioenriched α-quaternary ketone product **240**. Compound **240** can be thought of as an α-aminomethylation product of the so-called "thermodynamic" enolate of compound **235**. We imagined that successful exploration of this inverted strategy

would enable rapid, stereocontrolled total syntheses of (–)-isonitramine and (+)-sibirinine (**241** and **242**, respectively, Scheme 4.2.1.B).[10–12]

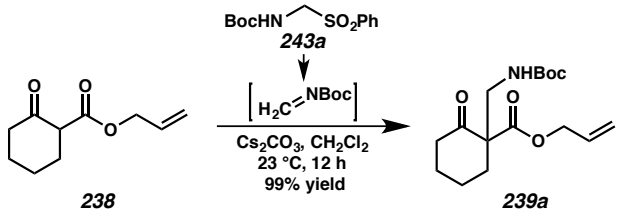
Scheme 4.2.1. α-Quaternary Mannich Adducts via Enantioselective Alkylation



4.3 NITROGEN PROTECTING GROUP EVALUATION

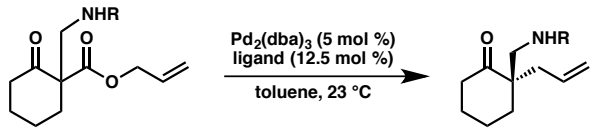
To introduce the aminomethyl moiety, we employed sulfonylmethyl carbamates (e.g., **243a**) as versatile and readily available imine precursors.[13] In the presence of Cs_2CO_3, the Boc-protected imine generated from **243a** reacted with β-ketoester **238**[14] to smoothly afford β-aminoketone **239a** (99% yield) at ambient temperature (Scheme 4.3.1). In a similar manner, we obtained other protected aminoketones (e.g., **239b–g**) in good to excellent yields.[15]

*Scheme 4.3.1. Synthesis of β-Ketoester **239a***

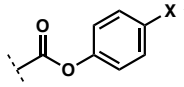


With β-ketoesters **239a–g** in hand, our investigation into this substrate class commenced in the context of palladium-catalyzed allylic alkylation (Table 4.3.1). We found that exposure of Boc-protected substrate **239a** to a the catalyst derived from $Pd_2(dba)_3$ (5 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 12.5 mol %)[16] in toluene at ambient temperature afforded the desired product **240a** in 94% yield and 86% ee (entry 1). Cbz-protected **239b** also gave excellent yield and ee (entry 3). It is important to note that we did not detect any *N*-alkylated side products, a result that highlights the mild nature of our reaction conditions.[17] Arylcarbamates **239c–e** gave slightly decreased enantioselectivities in the products (entries 4–6). Changing from carbamate to benzoyl or tosyl protecting groups resulted in poor enantioselectivity (entries 7 and 8, respectively), possibly due to their ability to coordinate to the catalyst and/or the enhanced acidity of the N–H proton. Alternatively, it is possible that a beneficial lewis-basic interaction between the nitrogen protecting group and the palladium(II) center is maximized when using carbamates. We found that the more electron-withdrawn ligand, **76**, gave higher enantioselectivity. In the case of (*S*)–*t*-BuPHOX (**66**),[18] we observed diminished ee (Table 4.3.1, entry 2).

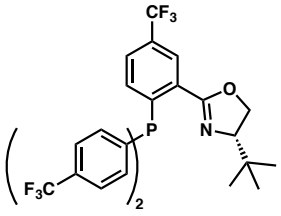
Table 4.3.1. Optimization of the Amine Protecting Group[a]



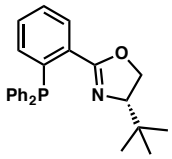
239 *240*

entry	R (*239* → *240*)	ligand	yield [%][b]	ee [%][c]
1	Boc (*239a* → *240a*)	*76*	94	86
2	Boc (*239a* → *240a*)	*76*	ND[d]	80
3	Cbz (*239b* → *240b*)	*76*	96	86
4	 X = OMe (*239c* → *240c*)	*76*	91	83
5	X = H (*239d* → *240d*)	*76*	90	77
6	X = F (*239e* → *240e*)	*76*	84	77
7	Bz (*239f* → *240f*)	*76*	ND[d]	56
8	Ts (*239g* → *240g*)	*76*	54	24

[a] Reaction performed with 0.2 mmol of **239**, 5 mol % of $Pd_2(dba)_3$ (dba = dibenzylideneacetone), 12.5 mol % of ligand in toluene (0.033 M) at 23 °C.
[b] Isolated yield.
[c] Determined by chiral SFC analysis. Absolute stereochemistry has been assigned by anology, except in entry 2, which was assigned by conversion into (–)-isonitramine (**241**).
[d] A yield was not determined.



76
(S)-(CF_3)$_3$-t-BuPHOX



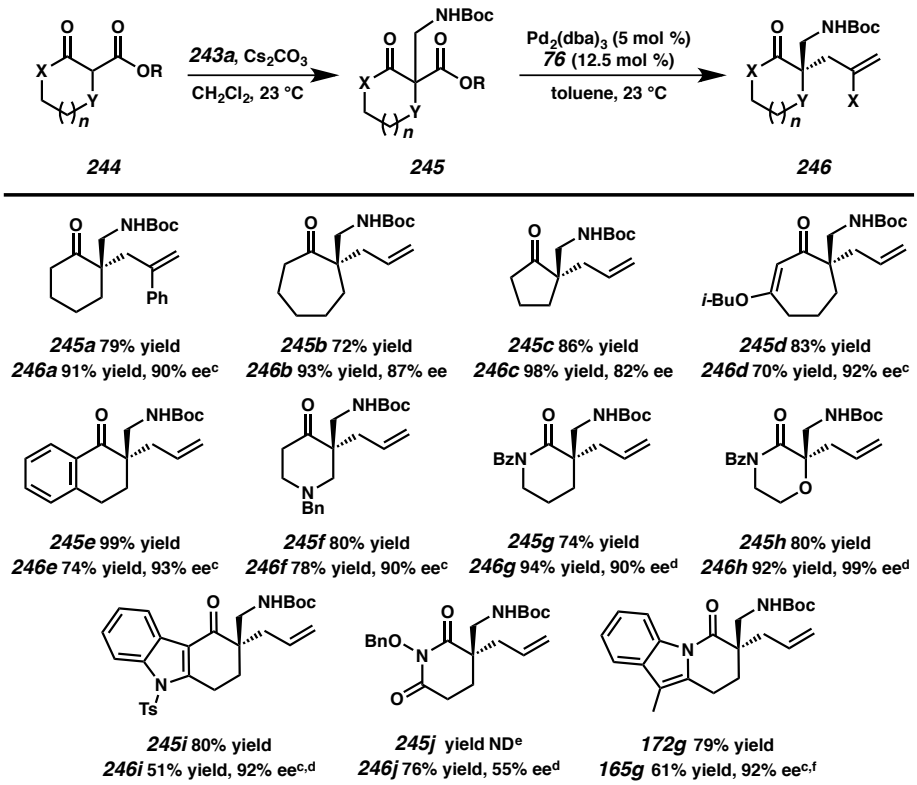
66
(S)-t-BuPHOX

4.4 β-OXOESTER SUBSTRATE SCOPE INVESTIGATION

We found that a broad range of ketones and amides (e.g., **245a–j**, and **172g**) can easily be converted into enantioenriched α-tetrasubstituted Mannich-type products (e.g., **246a–j**, and **165g**) with this two-step strategy (Table 4.4.1). For all substrates, the first step proceeded in good to excellent yields (51–98%). In the allylic alkylation, 2-phenyl-2-propenyl-substituted **246a** was obtained in high yield (91%) and excellent enantioselectivity (90% ee). Cycloheptanone **245b** proved to be a good substrate and the corresponding α-quaternary cycloheptanone **246b** was isolated in 93% yield and 87% ee,

while cyclopentanone **246c** was synthesized with slightly lower enantioselectivity (82% ee). Vinylogous ester **245d** and tetralone **245e** afforded α-quaternary vinylogous ester **246d** and tetralone **246e** in 70% yield and 92% ee, and 74% yield and 93% ee, respectively. Basic tertiary amines are tolerated by the reaction conditions, as 4-piperidinone **246f** was isolated in 78% yield and 90% ee. We were pleased to find that under slightly elevated reaction temperatures (40 °C), the desired lactam **246g**, morpholinone **246h**, and carbazolone **246i** were available in moderate to excellent yields (51–94%) and excellent enantioselectivities (90–99% ee). Unfortunately, imide **245j** performed poorly in this chemistry, to deliver the corresponding α-quaternary product (**246j**) in 76% yield but only 55% ee. C3-methyl DHPI **165g** was obtained in 61% yield and 92% ee.

*Table 4.4.1. Two-Step Enantioselective Synthesis of α-Aminomethyl Carbonyl Compounds (**246**) from β-Oxoesters (**244**)*[a,b]



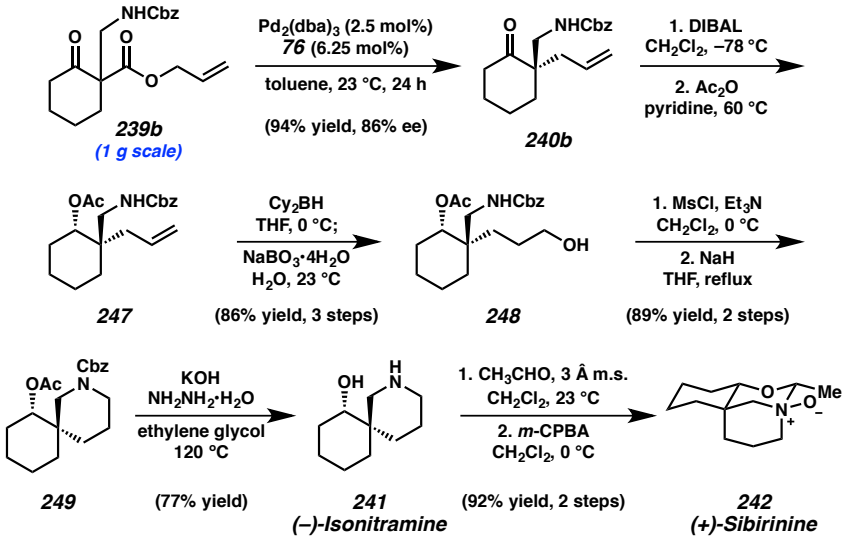
[a] Reaction conditions for the Pd-catalyzed allylic alkylation: **245** (1 equiv), $Pd_2(dba)_3$ (5 mol %) and **XX** (12.5 mol %) in toluene (0.033 M) at 23 °C for 12–48 h.
[b] Enantiomeric excesses were determined by chiral SFC analysis.
[c] $Pd_2(pmdba)_3$ (pmdba = bis(4-methoxybenzylidene)acetone) was used instead of $Pd_2(dba)_3$.
[d] Reactions were performed on **245g**, **245h**, and **245i** at 40 °C.
[e] A detailed synthetic procedure for compound **245j** was not found, therefore a yield cannot be claimed.
[f] Reaction was performed in TMBE (0.033 M) at 60 °C.

4.5 TOTAL SYNTHESES OF (–)-ISONITRAMINE AND (+)-SIBIRININE

In order to exhibit the utility of our method for generating interesting and useful chiral building blocks, total syntheses of (–)-isonitramine (**241**) and (+)-sibirinine (**242**) was carried out (Scheme 4.5.1). (–)-Isonitramine (**241**) is a spirocyclic alkaloid posessing an azaspiro[5.5]undecane core. (+)–Sibirinine (**242**) is a tricyclic alkaloid featuring an *N*,*O*-acetal, a tertiary amine *N*-oxide, and two pairs of vicinal stereocenters, including an all-carbon quaternary center. Asymmetric allylic alkylation using one gram of **239b** proceeded with one half of the typical catalyst loading without any loss of

enantioselectivity. Reduction of β-amino ketone **240b** with diisobutylaluminum hydride (DIBAL), followed by acetylation of the resulting alcohol, yielded carbamate **247** as a single diastereomer. Hydroboration of the terminal alkene in carbamate **247** provided primary alcohol **248** in 86% yield over 3 steps. Cyclization of the mesylate derived from primary alcohol **248** smoothly delivered spirocycle **249**. Simultaneous removal of the acetyl and Cbz groups using potassium hydroxide furnished (–)-isonitramine (**241**) in 77% yield. Treatment of (–)-isonitramine (**241**) with excess acetaldehyde yielded the desired *N,O*-acetal, which was smoothly *N*-oxidized by *m*-CPBA to give (+)-sibirinine (**242**) in 92% yield over two steps. Notably, conversion of (–)-isonitramine (**241**) to (+)-sibirinine (**242**) can be accomplished in one pot by forming the *N,O*-acetal intermediate under an oxygen atmosphere, albeit in diminished yield. Spectral data of (–)-**241** and (+)-**242** were in agreement with those previously reported.[11,12] Furthermore, our synthesis of (–)-isonitramine (**241**) confirms the absolute stereochemistry of **240b**.[11]

*Scheme 4.5.1. Total Syntheses of (–)-Isonitramine (**241**) and (+)-Sibirinine (**242**)*



4.6 CONCLUSION

In summary, we have developed an inverted approach to the synthesis of α-quaternary and -tetrasubstituted tertiary Mannich-type products by strategic enolate formation to give products in moderate to excellent yields and good to excellent enantiomeric excess. This chemistry tolerates a variety of ketone, amide, and vinylogous ester functionalities even in the presence of basic tertiary amines and relatively acidic N–H moieties. Multiple ring sizes, aromatic, and heteroaromatic scaffolds are also accessible via this strategy. Furthermore, this method enables the efficient construction of spirocyclic amine-containing scaffolds, as illustrated in our syntheses of the alkaloids (–)-isonitramine (**241**) and (+)-sibirinine (**242**). The first total synthesis of (+)-sibirinine (**242**) was accomplished in 11 steps and 36% overall yield from commercially available diallyl pimelate.

4.7 EXPERIMENTAL SECTION

4.7.1 MATERIALS AND METHODS

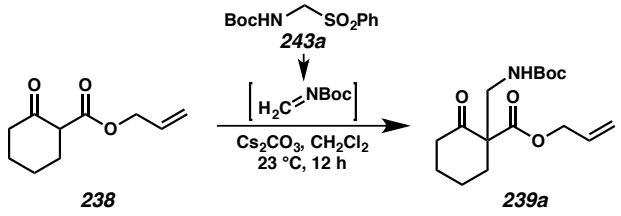
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[19] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. Melting points were measured with BÜCHI Melting Point B-545. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and a Varian Mercury 300 spectrometer (300 MHz and 76 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, br t = broad triplet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical

chromatography system utilizing Chiralpak (AD-H, AS-H) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI/APCI).

Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Et_3N and pyridine were distilled from calcium hydride prior to use. MeOH was distilled from magnesium methoxide immediately prior to use. (*S*)-*t*-BuPHOX,[18] (*S*)-$(CF_3)_3$-*t*-BuPHOX,[16] tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) $Pd_2(pmdba)_3$,[20] sulfonyl carbamates **243a–g**,[21] and 1,3-dicarbonyl compounds **238**,[14] **244a–h**[7,8b,8c] were prepared by known methods.

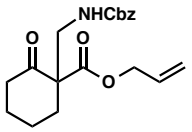
4.7.2 EXPERIMENTAL PROCEDURES

General Procedure A: α-Aminomethyl 1,3-dicarbonyl Substrate Synthesis

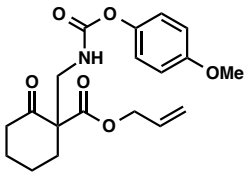


Allyl 1-(((*tert*-butoxycarbonyl)amino)methyl)-2-oxocyclohexane-1-carboxylate (239a): To a stirred solution of β-ketoester **238** (0.91 g, 5.0 mmol, 1 equiv) in CH_2Cl_2 (25 mL) was added sulfonylmethyl carbamate **243a** (1.63 g, 6.0 mmol, 1.2 equiv) in one portion at ambient temperature. After stirring for 5 min, Cs_2CO_3 (4.70 g, 12.5 mmol, 2.5 equiv) was added in one portion. After 12 h, full consumption of starting material was determined by TLC analysis. Saturated aqueous ammonium chloride was added slowly, and the biphasic mixture was stirred at ambient temperature for 20 min and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10% EtOAc in hexanes) afforded α-aminomethyl β-ketoester 2**39a** (1.55 g, 99% yield) as a faintly yellow oil. R_f = 0.55 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 16.5, 10.4, 5.8 Hz, 1H), 5.33 (m, 1H), 5.25 (m, 1H), 5.17 (m, 1H), 4.63 (m, 2H), 3.54 (dd, *J* = 13.9, 7.7 Hz, 1H), 3.40 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.59–2.41 (m, 3H), 1.99 (m, 1H), 1.81 (m, 1H), 1.73–1.51 (m, 3H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0, 171.0, 156.0, 131.6, 119.2, 79.4, 66.4, 62.4, 44.4, 40.9, 33.9, 28.5, 27.3, 22.2; IR (Neat Film, NaCl) 3461, 3404, 2976, 2939, 2867, 1713, 1501, 1452, 1366, 1247, 1229, 1168, 1141 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{26}NO_5$ $[M+H]^+$: 312.1811, found 312.1824.

Spectroscopic Data for 239b–g, 245a–j, and 172g

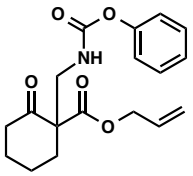


Allyl 1-(benzyloxycarbonylaminomethyl)-2-oxocyclohexane-1-carboxylate (239b): The reaction was conducted according to general procedure A. Ketoester **238** (1.66 g, 9.09 mmol); sulfonylmethyl carbamate **243b** (3.33 g, 10.9 mmol); Cs_2CO_3 (7.40 g, 22.7 mmol). The reaction mixture was stirred for 18 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **239b** (2.95 g, 8.54 mmol, 94% yield) as a colorless oil. R_f = 0.27 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.86 (ddt, *J* = 16.6, 10.5, 5.9 Hz, 1H), 5.41 (m, 1H), 5.32 (m, 1H), 5.23 (m, 1H), 5.11–5.01 (m, 2H), 4.63–4.52 (m, 2H), 3.62 (dd, *J* = 13.8, 7.7 Hz, 1H), 3.46 (dd, *J* = 13.8, 5.6 Hz, 1H), 2.59–2.42 (m, 3H), 2.00 (m, 1H), 1.81 (m, 1H), 1.72–1.53 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 170.7, 156.5, 136.6, 131.5, 128.6, 128.2, 128.1, 119.3, 66.8, 66.4, 62.2, 44.8, 40.9, 33.9, 27.2, 22.1; IR (Neat Film, NaCl) 3450, 3394, 2943, 1724, 1711, 1509, 1453, 1265 1219, 1141, 981 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{24}NO_5$ $[M+H]^+$: 346.1649, found 346.1634.

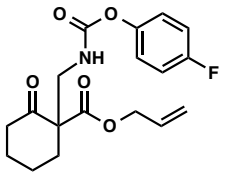


Allyl 1-((4-methoxyphenoxy)carbonylaminomethyl)-2-oxocyclohexane-1-carboxylate (239c): The reaction was conducted according to general procedure A. Ketoester **238** (182 mg, 1.00 mmol); sulfonylmethyl carbamate **243c** (386 mg, 1.20 mmol); Cs_2CO_3 (910 mg, 2.50 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester

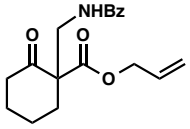
239c (265 mg, 0.733 mmol, 73% yield) as a colorless oil. R_f = 0.18 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01–6.97 (m, 2H), 6.88–6.82 (m, 2H), 5.91 (m, 1H), 5.67 (m, 1H), 5.34 (m, 1H), 5.26 (m, 1H), 4.67–4.64 (m, 2H), 3.78 (s, 3H), 3.67 (dd, *J* = 13.9, 7.7 Hz, 1H), 3.53 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.62–2.46 (m, 3H), 2.03 (m, 1H), 1.84 (m, 1H), 1.76–1.58 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9, 170.7, 157.0, 155.3, 144.7, 131.5, 122.4, 119.4, 114.4, 66.5, 62.2, 55.7, 45.0, 40.9, 34.0, 27.2, 22.1; IR (Neat Film, NaCl) 3377, 2943, 1742, 1732, 1709, 1498, 1201, 1055 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{24}NO_6$ $[M+H]^+$: 362.1598, found 362.1601.



Allyl 1-(phenoxycarbonylaminomethyl)-2-oxocyclohexane-1-carboxylate (239d): The reaction was conducted according to general procedure A. Ketoester **238** (182 mg, 1.00 mmol); sulfonylmethyl carbamate **243d** (350 mg, 1.20 mmol); Cs_2CO_3 (910 mg, 2.50 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **239d** (310 mg, 0.936 mmol, 94% yield) as a colorless oil. R_f = 0.25 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 2H), 7.18 (m, 1H), 7.12–7.05 (m, 2H), 5.92 (ddt, *J* = 17.3, 10.5, 5.9 Hz, 1H), 5.71 (m, 1H), 5.34 (m, 1H), 5.26 (m, 1H), 4.71–4.62 (m, 2H), 3.68 (dd, *J* = 13.9, 7.8 Hz, 1H), 3.53 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.64–2.47 (m, 3H), 2.04 (m, 1H), 1.84 (m, 1H), 1.77–1.58 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9, 170.7, 154.8, 151.1, 131.5, 129.3, 125.4, 121.6, 119.5, 66.5, 62.1, 45.0, 40.9, 34.0, 27.3, 22.1; IR (Neat Film, NaCl) 3377, 2943, 1745, 1728, 1709, 1514, 1489, 1202, 1143 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{22}NO_5$ $[M+H]^+$: 332.1492, found 332.1483.

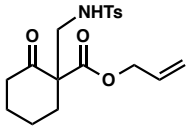


Allyl 1-((4-fluorophenoxy)carbonylaminomethyl)-2-oxocyclohexane-1-carboxylate (239e): The reaction was conducted according to general procedure A. Ketoester **238** (182 mg, 1.00 mmol); sulfonylmethyl carbamate **243e** (371 mg, 1.20 mmol); Cs_2CO_3 (910 mg, 2.50 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **239e** (278 mg, 0.796 mmol, 80% yield) as a colorless oil. R_f = 0.28 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08–6.98 (m, 4H), 5.91 (ddt, *J* = 17.2, 10.5, 5.9 Hz, 1H), 5.72 (m, 1H), 5.34 (m, 1H), 5.26 (m, 1H), 4.68–4.60 (m, 2H), 3.67 (dd, *J* = 13.9, 7.8 Hz, 1H), 3.52 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.64–2.46 (m, 3H), 2.04 (m, 1H), 1.83 (m, 1H), 1.76–1.57 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9, 170.7, 160.0 (*J* = 243 Hz), 154.8, 147.0 (*J* = 4 Hz), 131.4, 123.0 (*J* = 9 Hz), 119.5, 115.9 (*J* = 23 Hz), 66.6, 62.1, 45.1, 40.9, 34.0, 27.3, 22.1; IR (Neat Film, NaCl) 3377, 2944, 1746, 1732, 1711, 1497, 1219, 1193, 1147 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{21}FNO_5$ $[M+H]^+$: 350.1398, found 350.1392.



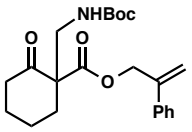
Allyl 1-(benzamidomethyl)-2-oxocyclohexane-1-carboxylate (239f): The reaction was conducted according to general procedure A. Ketoester **238** (182 mg, 1.00 mmol); sulfonylmethyl carbamate **243f** (413 mg, 1.50 mmol); Cs_2CO_3 (977 mg, 3.0 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **239f** (250 mg, 0.793 mmol, 79% yield)

as a white amorphous solid. R_f = 0.30 (40% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 2H), 7.49–7.44 (m, 1H), 7.42–7.36 (m, 2H), 6.96–6.87 (m, 1H), 5.83 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.27 (dq, *J* = 17.1, 1.4 Hz, 1H), 5.18 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.65–4.52 (m, 2H), 3.96 (dd, *J* = 13.6, 7.7 Hz, 1H), 3.65 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.61–2.49 (m, 3H), 2.05–1.97 (m, 1H), 1.87–1.81 (m, 1H), 1.75–1.58 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.5, 170.8, 167.4, 134.4, 131.6, 131.4, 128.6, 127.0, 119.5, 66.6, 62.2, 43.3, 40.9, 34.2, 27.2, 22.1; IR (Neat Film, NaCl) 3447, 3356, 3061, 3028, 2943, 2866, 1712, 1667, 1651, 1602, 1580, 1519, 1488, 1450, 1307, 1280, 1203, 1142 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found 316.1559.

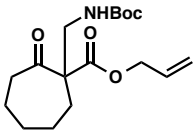


Allyl 1-(((4-methylphenyl)sulfonamido)methyl)-2-oxocyclohexane-1-carboxylate (239g): The reaction was conducted according to general procedure A. Ketoester **238** (182 mg, 1.00 mmol); sulfonylmethyl carbamate **243g** (488 mg, 1.50 mmol); Cs_2CO_3 (977 mg, 3.0 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 25% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **239g** (365 mg, 0.999 mmol, >99% yield) as a clear colorless oil. R_f = 0.25 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.69 (m, 2H), 7.30 (dd, *J* = 8.4, 1.0 Hz, 2H), 5.88 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.20 (dd, *J* = 8.3, 5.8 Hz, 1H), 4.61 (dt, *J* = 5.9, 1.3 Hz, 2H), 3.21 (dd, *J* = 12.5, 8.4 Hz, 1H), 3.06 (dd, *J* = 12.5, 5.8 Hz, 1H), 2.65–2.56 (m, 1H), 2.46–2.36 (m, 4H), 2.06–1.97 (m, 1H), 1.82–1.76 (m, 1H), 1.72–1.58 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0, 170.4, 143.6, 137.0, 131.4, 129.9, 127.1, 119.6, 66.6, 61.6, 47.2, 40.9,

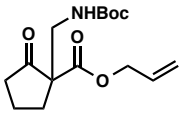
34.1, 27.0, 22.1, 21.7; IR (Neat Film, NaCl) 3289, 2942, 2867, 1728, 1709, 1451, 1335, 1206, 1163, 1092 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{24}NO_5S$ $[M+H]^+$: 366.1375, found 366.1367.



2-Phenylallyl 1-(((*tert*-butoxycarbonyl)amino)methyl)-2-oxocyclohexane-1-carboxylate (245a): The reaction was conducted according to general procedure A. Ketoester **244a** (311 mg, 1.2 mmol); sulfonylmethyl carbamate **243a** (392 mg, 1.44 mmol); Cs_2CO_3 (977 mg, 3.0 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **245a** (368 mg, 0.95 mmol, 79% yield) as a pale yellow oil. R_f = 0.5 (25% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2H), 7.36–7.32 (m, 2H), 7.31–7.27 (m, 1H), 5.53 (d, *J* = 0.9 Hz, 1H), 5.37 (q, *J* = 1.1 Hz, 1H), 5.1 (d, *J* = 13.0 Hz, 1H), 5.07 (t, *J* = 7.0 Hz, 1H), 5.01 (d, *J* = 13.0, 1H), 3.48 (dd, *J* = 13.9, 7.6 Hz, 1H), 3.35 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.38–2.27 (m, 2H), 2.26–2.18 (m, 1H), 1.81 (m, 1H), 1.69–1.63 (m, 1H), 1.60–1.50 (m, 1H), 1.49–1.41 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.7, 170.8, 155.0, 142.4, 137.9, 128.7, 128.3, 126.3, 116.3, 79.4, 66.9, 62.3, 44.3, 40.6, 33.7, 28.4, 27.2, 21.9; IR (Neat Film, NaCl) 3458, 3411, 2975, 2938, 2866, 1715, 1499, 1365, 1167, 1141 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{29}NO_5Na$ $[M+Na]^+$: 410.1938, found 410.1923.

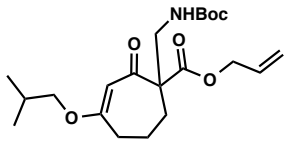


Allyl 1-(*t*-butoxycarbonylaminomethyl)-2-oxocycloheptane-1-carboxylate (245b): The reaction was conducted according to general procedure A. Ketoester **244b** (196 mg, 1.00 mmol); sulfonylmethyl carbamate **243a** (326 mg, 1.20 mmol); Cs_2CO_3 (815 mg, 2.50 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **245b** (234 mg, 0.719 mmol, 72% yield) as a colorless oil. R_f = 0.47 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.32 (m, 1H), 5.25 (m, 1H), 5.18 (m, 1H), 4.68–4.56 (m, 2H), 3.56 (dd, *J* = 14.0, 7.7 Hz, 1H), 3.50 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.68 (m, 1H), 2.56 (ddd, *J* = 13.0, 8.3, 3.3 Hz, 1H), 2.08 (m, 1H), 1.86–1.76 (m, 2H), 1.73–1.48 (m, 5H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.2, 171.7, 156.1, 131.7, 119.0, 79.4, 66.2, 63.9, 45.3, 42.7, 31.7, 30.1, 28.4, 25.7, 25.3; IR (Neat Film, NaCl) 3461, 2976, 2933, 1718, 1501, 1456, 1366, 1248m 1225, 1169 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{27}NO_5Na$ $[M+Na]^+$: 348.1781, found 348.1772.

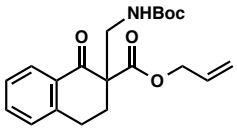


Allyl 1-(*t*-butoxycarbonylaminomethyl)-2-oxocyclopentane-1-carboxylate (245c): The reaction was conducted according to general procedure A. Ketoester **244c** (168 mg, 1.00 mmol); sulfonylmethyl carbamate **243a** (326 mg, 1.20 mmol); Cs_2CO_3 (815 mg, 2.50 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **245c** (255 mg, 0.858 mmol, 86% yield) as a colorless oil. R_f = 0.50 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.29 (m, 1H), 5.24 (m, 1H), 5.13

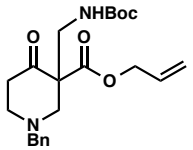
(m, 1H), 4.67–4.55 (m, 2H), 3.50 (dd, *J* = 14.0, 7.0 Hz 1H), 3.46 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.49–2.34 (m, 3H), 2.16–1.98 (m, 3H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.7, 171.3, 156.3, 131.5, 118.8, 79.7, 66.1, 61.5, 42.1, 38.2, 31.7, 28.4, 19.8; IR (Neat Film, NaCl) 3394, 2976, 1749, 1715, 1504, 1454, 1366, 1249, 1229, 1168, 966 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{15}H_{23}NO_5Na$ $[M+Na]^+$: 320.1468, found 320.1467.



Allyl 1-(((*tert*-butoxycarbonyl)amino)methyl)-4-isobutoxy-2-oxocyclohept-3-ene-1-carboxylate (245d): The reaction was conducted according to general procedure A. Ketoester **244d**[22] (100 mg, 0.375 mmol); sulfonylmethyl carbamate **243a** (122 mg, 0.45 mmol); Cs_2CO_3 (305 mg, 0.936 mmol). The reaction mixture was stirred for 10 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **245d** (123 mg, 0.311 mmol, 83% yield) as a clear oil. R_f = 0.5 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.38 (s, 1H), 5.29 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.27 (m, 1H), 5.21 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.63 (ddt, *J* = 13.2, 5.9, 1.4 Hz, 1H), 4.56 (ddt, *J* = 13.3, 5.8, 1.4 Hz, 1H), 3.64 (dd, *J* = 13.7, 7.8 Hz, 1H), 3.51–3.44 (m, 3H), 2.55 (ddd, *J* = 17.9, 10.0, 4.2 Hz, 1H), 2.44 (ddd, *J* = 17.8, 7.1, 3.8 Hz, 1H), 2.36 (m, 1H), 2.03–1.94 (m, 2H), 1.89–1.76 (m, 2H), 1.40 (s, 9H), 0.94 (dd, *J* = 6.7, 1.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 174.9, 172.1, 156.1, 131.7, 118.8, 105.3, 79.3, 74.9, 66.2, 63.9, 46.4, 34.2, 29.3, 28.5, 27.9, 21.3, 19.2; IR (Neat Film, NaCl) 3459, 3394, 3083, 2961, 2934, 2874, 1734, 1718, 1636, 1610, 1499, 1388, 1366, 1232, 1171 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{33}NO_6Na$ $[M+Na]^+$: 418.2200, found 418.2192.

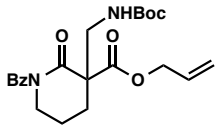


Allyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (245e): The reaction was conducted according to general procedure A. Ketoester **244e** (230.3 mg, 1.0 mmol); sulfonylmethyl carbamate **243a** (326 mg, 1.2 mmol); Cs_2CO_3 (815 mg, 2.5 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **245e** (395 mg, 0.999 mmol, >99% yield) as a pale yellow oil. R_f = 0.5 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.34–7.29 (m, 1H), 7.23 (dq, *J* = 7.8, 0.7 Hz, 1H), 5.86–5.76 (m, 1H), 5.33–5.27 (m, 1H), 5.22–5.14 (m, 2H), 4.61 (dt, *J* = 2.4, 1.4 Hz, 1H), 4.59 (dt, *J* = 2.4, 1.4 Hz, 1H), 3.79 (dd, *J* = 13.9, 7.9 Hz, 1H), 3.56 (dd, *J* = 13.9, 5.4 Hz, 1H), 3.10 (dt, *J* = 17.5, 5.4 Hz, 1H), 3.02 (ddd, *J* = 17.4, 9.4, 4.8 Hz, 1H), 2.57 (dt, *J* = 13.8, 5.3 Hz, 1H), 2.20 (ddd, *J* = 14.1, 9.5, 5.0 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.6, 171.0, 156.1, 143.4, 134.1, 131.9, 131.5, 129.0, 128.0, 127.0, 118.7, 79.5, 66.1, 59.4, 43.6, 29.3, 28.5, 25.8; IR (Neat Film, NaCl) 3454, 3395, 2977, 2934, 1731, 1717, 1683, 1601, 1505, 1456, 1366, 1235, 1170 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1811, found 360.1801.



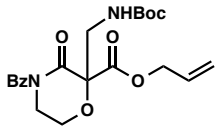
Allyl 1-benzyl-3-(((*tert*-butoxycarbonyl)amino)methyl)-4-oxopiperidine-3-carboxylate (245f): The reaction was conducted according to general procedure A. Ketoester **244f**[Error! Bookmark not defined.] (296 mg, 1.08 mmol); sulfonylmethyl carbamate **243a**

(353 mg, 1.296 mmol); Cs_2CO_3 (882 mg, 2.7 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **245f** (349 mg, 0.867 mmol, 80% yield) as a clear colorless oil. R_f = 0.45 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.20–7.12 (m, 4H), 7.11–7.05 (m, 1H), 5.71 (ddt, *J* = 16.5, 10.9, 5.7 Hz, 1H), 5.37 (t, *J* = 6.8 Hz, 1H), 5.09 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.94 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.47 (d, *J* = 5.8, 1.4 Hz, 2H), 3.63 (dd, *J* = 13.9, 6.0 Hz, 1H), 3.57 (dd, *J* = 13.9, 7.4 Hz, 1H), 3.23–3.20 (m, 1H), 3.19 (d, *J* = 13.5 Hz, 1H), 3.10 (d, *J* = 13.4 Hz, 1H), 2.65 (ddd, *J* = 14.3, 10.0, 6.7 Hz, 1H), 2.37–2.29 (m, 2H), 1.99 (d, *J* = 11.6, 1H), 1.93–1.87 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, C_6D_6) δ 205.9, 170.5, 155.9, 138.3, 132.2, 129.0, 128.7, 127.6, 118.4, 79.0, 66.1, 62.9, 61.9, 58.9, 53.1, 43.0, 40.3, 28.4; IR (Neat Film, NaCl) 3457, 2976, 2925, 2811, 1718, 1499, 1366, 1250, 1225, 1169 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{31}N_2O_5$ $[M+H]^+$: 403.2233, found 403.2238.

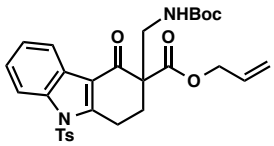


Allyl 1-benzoyl-3-(*tert*-butoxycarbonylaminomethyl)-2-oxopiperidine-3-carboxylate (245g): The reaction was conducted according to general procedure A. Amido ester **244g** (231 mg, 0.800 mmol); sulfonylmethyl carbamate **243a** (261 mg, 0.960 mmol); Cs_2CO_3 (652 mg, 2.00 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15→20% EtOAc in hexanes) afforded α-aminomethyl amido ester **245g** (245 mg, 0.588 mmol, 74% yield) as a colorless oil. R_f = 0.36 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.74 (m, 2H), 7.50 (m, 1H), 7.44–7.36 (m, 2H), 5.97 (ddt, *J* = 16.6, 10.4, 6.0 Hz, 1H), 5.40 (m, 1H), 5.33 (m, 1H), 5.15 (m, 1H),

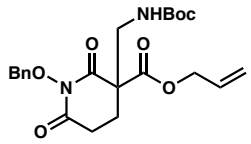
4.82–4.63 (m, 2H), 3.91–3.74 (m, 2H), 3.71 (dd, J = 13.9, 7.5 Hz, 1H), 3.50 (dd, J = 13.9, 5.9 Hz, 1H), 2.43 (m, 1H), 2.12–1.91 (m, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 172.2, 170.7, 156.1, 135.6, 132.1, 131.3, 128.3, 128.3, 119.9, 79.7, 66.8, 58.4, 46.8, 44.7, 29.1, 28.4, 20.0; IR (Neat Film, NaCl) 3446, 2976, 1714, 1684, 1500, 1449, 1391, 1366, 1271, 1249, 1164, 1141, 939 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{28}N_2O_6Na$ $[M+Na]^+$: 439.1840, found 439.1854.



Allyl 4-benzoyl-2-(*tert*-butoxycarbonylaminomethyl)-3-oxomorpholine-2-carboxylate (245h): The reaction was conducted according to general procedure A. Morpholinone **244h** (100 mg, 0.346 mmol); sulfonylmethyl carbamate **243a** (188 mg, 0.691 mmol); Cs_2CO_3 (338 mg, 1.04 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 20→25% EtOAc in hexanes) afforded α-aminomethyl morpholinone **245h** (132 mg, 0.315 mmol, 91% yield) as a colorless oil. R_f = 0.34 (10% EtOAc in toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.65 (m, 2H), 7.52 (m, 1H), 7.43–7.38 (m, 2H), 5.97 (m, 1H), 5.41 (m, 1H), 5.33 (m, 1H), 5.00 (brs, 1H), 4.76–4.73 (m, 2H), 4.30–4.17 (m, 2H), 4.05–3.90 (m, 2H), 3.87–3.72 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 167.7, 167.5, 155.8, 134.7, 132.5, 131.0, 128.5, 128.3, 119.9, 83.1, 79.9, 67.2, 62.1, 45.0, 44.8, 28.4; IR (Neat Film, NaCl) 3388, 2977, 2934, 1746, 1714, 1693, 1507, 1449, 1367, 1317, 1279, 1233, 1165, 1066, 944, 757, 727, 693 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{26}N_2O_7Na$ $[M+Na]^+$: 441.1632, found 441.1636.

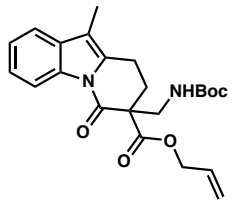


Allyl 3-(((*tert*-butoxycarbonyl)amino)methyl)-4-oxo-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate (245i): The reaction was conducted according to general procedure A. Ketoester **244i**[23] (400 mg, 0.994 mmol); sulfonylmethyl carbamate **243a** (307 mg, 1.13 mmol); Cs_2CO_3 (770 mg, 2.36 mmol). The reaction mixture was stirred for 24 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-ketoester **245i** (418 mg, 0.756 mmol, 80% yield) as a clear colorless oil. R_f = 0.33 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21–8.17 (m, 1H), 8.15–8.12 (m, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.38–7.31 (m, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.80 (m, 1H), 5.25–5.17 (m, 2H), 5.15 (m, 1H), 4.58 (dt, *J* = 5.8, 1.4 Hz, 2H), 3.74 (dd, *J* = 14.0, 7.7 Hz, 1H), 3.59 (m, 2H), 3.41 (ddd, *J* = 19.2, 8.3, 5.2 Hz, 1H), 2.67 (dt, *J* = 13.9, 5.4 Hz, 1H), 2.37 (s, 3H), 2.28 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.4, 170.6, 156.1, 150.7, 146.1, 136.2, 135.3, 131.5, 130.4, 126.9, 125.8, 125.7, 125.2, 121.9, 118.9, 117.1, 114.0, 79.6, 66.2, 59.3, 43.3, 29.2, 28.5, 22.1, 21.8; IR (Neat Film, NaCl) 3445, 3054, 2977, 2933, 2254, 1733, 1713, 1596, 1558, 1505, 1481, 1451, 1410, 1380, 1244, 1174, 1090 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{29}H_{33}N_2O_7S$ $[M+H]^+$: 553.2003, found 553.1994.



Allyl 1-(benzyloxy)-3-(((*tert*-butoxycarbonyl)amino)methyl)-2,6-dioxopiperidine-3-carboxylate (245j): A detailed preparative procedure for compound **245j** was not recorded. However, the physical and spectral data are as follows: clear colorless oil; R_f =

0.41 (40% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2H), 7.39–7.34 (m, 3H), 5.86 (ddt, J = 16.6, 10.4, 5.9 Hz, 1H), 5.33 (dq, J = 17.2, 1.4 Hz, 1H), 5.27 (dq, J = 10.4, 1.2 Hz, 1H), 5.12 (t, J = 7.0 Hz, 1H), 5.02–4.96 (m, 2H), 4.65 (dq, J = 6.0, 1.3 Hz, 2H), 3.77–3.63 (m, 2H), 2.87 (dt, J = 18.1, 4.7 Hz, 1H), 2.67 (ddd, J = 17.8, 11.9, 5.4 Hz, 1H), 2.26 (dt, J = 14.2, 4.9 Hz, 1H), 2.05–1.98 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 167.08, 167.05, 156.1, 133.8, 130.8, 130.1, 129.3, 128.6, 120.2, 80.1, 78.0, 67.1, 57.7, 43.8, 30.1, 28.4, 23.7; IR (Neat Film, NaCl) 3452, 3394, 2977, 2888, 1731, 1703, 1504, 1454, 1366, 1336, 1301, 1239, 1184, 976, 859, 751, 699 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{28}N_2O_7Na$ $[M+Na]^+$: 455.1789, found 455.1797.

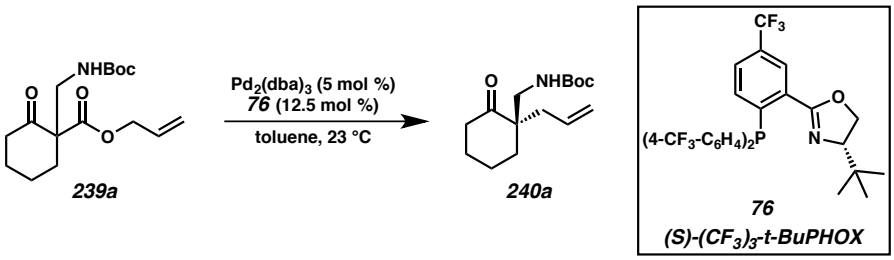


Allyl 7-(((*tert*-butoxycarbonyl)amino)methyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (172g): The reaction was conducted according to general procedure A. β-Amidoester **194** (98 mg, 0.346 mmol, 1.0 equiv); sulfonylmethyl carbamate **243a** (113 mg, 0.416 mmol, 1.2 equiv); Cs_2CO_3 (281 mg, 0.862 mmol, 2.5 equiv); CH_2Cl_2 (1.7 mL). The reaction mixture was stirred for 12 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded α-aminomethyl β-amidoester **172g** (113 mg, 79% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46–8.40 (m, 1H), 7.46–7.40 (m, 1H), 7.34–7.27 (m, 2H), 5.85 (ddt, J = 16.4, 10.9, 5.7 Hz, 1H), 5.36 (t, J = 6.8 Hz, 1H), 5.26 (d, J = 17.2 Hz, 1H), 5.21 (dq, J = 10.6, 1.3 Hz, 1H), 4.65 (dt, J = 5.7, 1.4 Hz, 2H), 3.91 (dd, J = 13.9, 7.4 Hz, 1H), 3.73 (dd, J = 13.9, 6.0 Hz, 1H), 3.13 (dt, J = 16.8, 4.9 Hz, 1H), 2.88–2.80 (m, 1H), 2.53 (dt, J = 13.6,

5.0 Hz, 1H), 2.23–2.15 (m, 1H), 2.17 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 167.3, 156.2, 134.9, 132.0, 131.6, 131.3, 124.6, 124.4, 119.2, 118.1, 116.6, 113.4, 79.7, 66.6, 58.2, 44.1, 28.5, 28.1, 18.7, 8.5; IR (Neat Film, NaCl) 3447, 2976, 2935, 1736, 1715, 1697, 1628, 1503, 1458, 1388, 1366, 1247, 1226, 1172, 1125, 1059, 962, 863, 752 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{28}N_2O_5Na$ $[M+Na]^+$: 435.1890, found 435.1889.

General Procedure B: Palladium-Catalyzed Allylic Alkylation

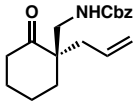
Please note that the absolute configuration of all products **240** and **246** has been inferred from previous studies,[Error! Bookmark not defined.] with the exception of **240b**, which was assigned by conversion to (–)-isonitramine (**241**). For isolated yields, see Tables 4.3.1 and 4.4.1. For GC, HPLC, or SFC conditions, as well as optical rotation data, please refer to Tables 4.7.4.1 and 4.7.4.2.



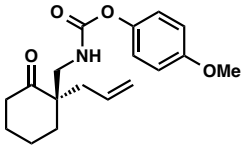
(*S*)-*Tert*-butyl ((1-allyl-2-oxocyclohexyl)methyl)carbamate (240a): In a nitrogen-filled glove box, [$Pd_2(dba)_3$] (9.2 mg, 0.010 mmol, 0.05 equiv) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**) (14.8 mg, 0.025 mmol, 0.125 equiv) were added to a 20 mL scintillation vial equipped with a magnetic stirring bar. The vial was then charged with toluene (4.1 mL) and stirred at 25 °C for 30 min, generating a yellow solution. To the preformed catalyst solution was added a solution of **239a** (62.3 mg, 0.20 mmol, 1 equiv) in toluene (2.0 mL). The vial was sealed and stirred at 25 °C until the full consumption of β-ketoester **239a** was observed by TLC analysis. The reaction mixture was concentrated *in vacuo*. Flash column chromatography (SiO_2, 2% EtOAc in CH_2Cl_2 eluent) afforded α-quaternary ketone **240a** (50.2 mg, 94% yield) as a colorless oil. 86% ee, $[\alpha]_D^{25}$ –25.5 (*c* 0.865, C_6H_6); R_f = 0.55 (5% EtOAc in DCM); ^{1}H NMR (400 MHz, C_6D_6) δ 5.64 (m, 1H), 5.05 (br t, *J* = 6.4 Hz, 1H), 4.94 (ddt, *J* = 10.1, 2.0, 1.0 Hz, 1H), 4.87 (dq, *J* = 17.0, 1.5 Hz, 1H), 3.30 (dd, *J* = 13.9, 7.2 Hz, 1H), 3.24 (dd, *J* = 13.9, 6.1 Hz, 1H), 2.15–2.08 (m, 2H), 2.01–1.91

(m, 2H), 1.44 (s, 9H), 1.41–1.30 (m, 2H), 1.25–1.12 (m, 2H); ^{13}C NMR (101 MHz, C_6D_6) δ 213.5, 156.2, 133.3, 118.5, 78.7, 53.1, 45.2, 39.1, 37.9, 33.7, 28.5, 27.1, 20.6; IR (Neat Film, NaCl) 3462, 3395, 2977, 2939, 2867, 1718, 1499, 1167 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{15}H_{25}NO_3Na$ $[M+Na]^+$: 290.1727, found 290.1718; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 7.65, minor = 8.46.

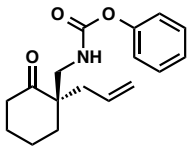
Spectroscopic Data for 240b–g, 246a–j, and 165g



(*S*)-Benzyl (1-allyl-2-oxocyclohexyl)methylcarbamate (240b): The reaction was conducted according to general procedure B. Ketoester **239b** (69.1 mg, 0.200 mmol). The reaction mixture was stirred at 23 ºC for 14 h. Flash column chromatography (SiO_2, 10→15% EtOAc in hexanes) afforded ketone **240b** (57.7 mg, 0.191 mmol, 96% yield) as a colorless oil. 86% ee, $[\alpha]_D^{25}$ –38.6 (*c* 1.20, $CHCl_3$); R_f = 0.44 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.25 (m, 5H), 5.67 (m, 1H), 5.21 (m, 1H), 5.16–5.00 (m, 4H), 3.34 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.24 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.54–2.20 (m, 4H), 1.99 (m, 1H), 1.81–1.60 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.5, 156.9, 136.7, 132.2, 128.6, 128.2, 128.1, 119.2, 66.8, 53.2, 45.4, 39.3, 38.0, 33.7, 27.2, 20.6.; IR (Neat Film, NaCl) 3351, 2937, 1722, 1702, 1510, 1454, 1234, 1134 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1756; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 8.12, minor = 9.06.

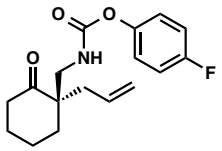


(*S*)-4-Methoxyphenyl (1-allyl-2-oxocyclohexyl)methylcarbamate (240c): The reaction was conducted according to general procedure B. Ketoester **239c** (72.3 mg, 0.200 mmol). The reaction mixture was stirred at 23 ºC for 24 h. Flash column chromatography (SiO_2, 15→20% EtOAc in hexanes) afforded ketone **240c** (57.6 mg, 0.181 mmol, 91% yield) as a colorless oil. 83% ee, $[\alpha]_D^{25}$ –29.3 (*c* 0.76, $CHCl_3$); R_f = 0.25 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05–6.97 (m, 2H), 6.90–6.81 (m, 2H), 5.70 (m, 1H), 5.49 (m, 1H), 5.18–5.09 (m, 2H), 3.78 (s, 3H), 3.40 (dd, *J* = 13.9, 6.0 Hz, 1H), 3.28 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.55–2.44 (m, 2H), 2.41–2.28 (m, 2H), 2.03 (m, 1H), 1.90–1.64 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.6, 157.0, 155.6, 144.8, 132.2, 122.5, 119.3, 114.4, 55.7, 53.2, 45.6, 39.4, 38.0, 33.8, 27.3, 20.6; IR (Neat Film, NaCl) 3345, 2937, 1740, 1700, 1501, 1201 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{24}NO_4$ $[M+H]^+$: 318.1700, found 318.1705; SFC conditions: 10% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): major = 9.47, minor = 11.13.

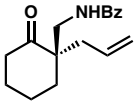


(*S*)-phenyl (1-allyl-2-oxocyclohexyl)methylcarbamate (240d): The reaction was conducted according to general procedure B. Ketoester **239d** (66.3 mg, 0.200 mmol). The reaction mixture was stirred at 23 ºC for 24 h. Flash column chromatography (SiO_2, 10→15% EtOAc in hexanes) afforded ketone **240d** (51.5 mg, 0.179 mmol, 90% yield) as a colorless oil. 77% ee, $[\alpha]_D^{25}$ –28.9 (*c* 0.40, $CHCl_3$); R_f = 0.29 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.7 Hz, 2H), 7.17 (m, 1H), 7.11 (d, *J* = 8.0 Hz,

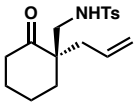
2H), 5.70 (m, 1H), 5.53 (m, 1H), 5.20–5.11 (m, 2H), 3.41 (dd, J = 14.0, 6.0 Hz, 1H), 3.29 (dd, J = 14.0, 7.2 Hz, 1H), 2.55–2.45 (m, 2H), 2.42–2.29 (m, 2H), 2.03 (m, 1H), 1.90–1.65 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.7, 155.1, 151.2, 132.1, 129.3, 125.3, 121.6, 119.4, 53.2, 45.6, 39.4, 38.0, 33.8, 27.3, 20.6; IR (Neat Film, NaCl) 3346, 2937, 1743, 1701, 1490, 1203 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1589; SFC conditions: 10% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): major = 6.53, minor = 8.13.



(*S*)-4-fluorophenyl (1-allyl-2-oxocyclohexyl)methylcarbamate (240e): The reaction was conducted according to general procedure B. Ketoester **239e** (69.9 mg, 0.200 mmol). The reaction mixture was stirred at 23 ºC for 24 h. Flash column chromatography (SiO_2, 10→15% EtOAc in hexanes) afforded ketone **240e** (51.4 mg, 0.168 mmol, 84% yield) as a colorless oil. 77% ee, $[\alpha]_D^{25}$ –27.4 (*c* 0.78, $CHCl_3$); R_f = 0.37 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10–6.97 (m, 4H), 5.69 (m, 1H), 5.54 (m, 1H), 5.17–5.10 (m, 2H), 3.40 (dd, J = 13.9, 6.0 Hz, 1H), 3.27 (dd, J = 13.9, 7.2 Hz, 1H), 2.55–2.45 (m, 2H), 2.41–2.29 (m, 2H), 2.04 (m, 1H), 1.91–1.63 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.7, 160.0 (J = 243 Hz), 155.1, 147.1 (J = 4 Hz), 132.1, 123.1 (J = 7 Hz), 119.4, 115.9 (J = 24 Hz), 53.2, 45.6, 39.4, 37.9, 33.8, 27.3, 20.6; IR (Neat Film, NaCl) 3347, 2938, 1742, 1699, 1498, 1192 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{21}FNO_3$ $[M+H]^+$: 306.1500, found 306.1493; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AS-H column, λ = 210 nm, t_R (min): major = 6.94, minor = 8.24.

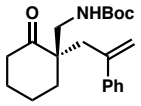


(*S*)-*N*-((1-allyl-2-oxocyclohexyl)methyl)benzamide (240f): The reaction was conducted according to general procedure B. Ketoester **239f** (19.1 mg, 0.60 mmol). The reaction mixture was stirred at 23 ºC for 20 h. Flash column chromatography (SiO_2, 10→15% EtOAc in hexanes) afforded ketone **240f** as a colorless oil. 56% ee, R_f = 0.23 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.49 (m, 1H), 7.45–7.40 (m, 2H), 6.78 (m, 1H), 5.66 (m, 1H), 5.15 (d, *J* = 1.2 Hz, 1H), 5.12 (m, 1H), 3.58 (dd, *J* = 13.8, 6.1 Hz, 1H), 3.55 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.56–2.47 (m, 2H), 2.40–2.32 (m, 2H), 2.03 (m, 1H), 1.92–1.79 (m, 2H), 1.77–1.61 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.6, 167.5, 134.7, 132.3, 131.6, 128.7, 127.0, 119.4, 53.5, 43.9, 39.5, 38.3, 34.1, 27.4, 20.6; IR (Neat Film, NaCl) 3439, 3338, 3070, 2936, 2864, 1693, 1668, 1649, 1535, 1515, 1486, 1454, 1286, 1127 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found 272.1638; SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.04, minor = 4.91.



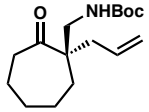
(*S*)-*N*-((1-Allyl-2-oxocyclohexyl)methyl)-4-methylbenzenesulfonamide (240g): The reaction was conducted according to general procedure B. Ketoester **239g** (74.0 mg, 0.202 mmol). The reaction mixture was stirred at 23 ºC for 20 h. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded ketone **240g** (35.3 mg, 0.109 mmol, 54% yield) as a yellow oil. 24% ee, R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (m, 2H), 7.30 (dd, *J* = 8.3, 0.9 Hz, 2H), 5.61 (dddd, *J* = 16.3, 10.8, 7.9, 6.9 Hz, 1H), 5.11–5.06 (m, 3H), 2.97 (dd, *J* = 12.6, 6.7 Hz, 1H), 2.70 (dd, *J* =

12.6, 7.5 Hz, 1H), 2.50–2.43 (m, 2H), 2.41 (s, 3H), 2.31–2.21 (m, 2H), 2.01 (m, 1H), 1.84–1.55 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.7, 143.4, 137.0, 131.5, 129.9, 127.0, 119.7, 52.5, 47.7, 39.2, 37.4, 33.4, 27.1, 21.6, 20.5; IR (Neat Film, NaCl) 3285, 3071, 2938, 2865, 1919, 1762, 1703, 1638, 1598, 1495, 1454, 1333, 1164, 1091 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{24}NO_3S$ $[M+H]^+$: 322.1471, found 322.1456; SFC conditions: 15% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 3.14, minor = 3.85.

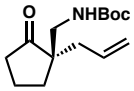


(*S*)-*tert*-Butyl ((2-oxo-1-(2-phenylallyl)cyclohexyl)methyl)carbamate (246a): The reaction was conducted according to general procedure B. Ketoester **245a** (110 mg, 0.284 mmol); $[Pd_2(pmdba)_3]$ (15.6 mg, 0.014 mmol, 0.05 equiv). The reaction mixture was stirred at 23 ºC for 24 h. Flash column chromatography (SiO_2, 20% acetone in hexanes) afforded ketone **246a** (88.7 mg, 0.258 mmol, 91% yield) as a yellow oil. 90% ee, $[\alpha]_D^{25}$ –30.9 (*c* 4.45, $CHCl_3$); R_f = 0.55 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 5.23 (d, *J* = 1.4 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.67 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.16 (dd, *J* = 14.0, 8.5 Hz, 1H), 3.09 (dd, *J* = 13.9, 4.7 Hz, 1H), 2.99 (d, *J* = 14.1 Hz, 1H), 2.71 (d, *J* = 14.1 Hz, 1H), 2.38 (ddd, *J* = 14.4, 10.8, 5.7 Hz, 1H), 2.30 (dt, *J* = 13.9, 4.8 Hz, 1H), 1.87 (dt, *J* = 15.3, 5.5 Hz, 1H), 1.77–1.60 (m, 5H), 1.38 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9, 156.3, 144.9, 142.7, 128.6, 127.7, 126.7, 118.3, 79.1, 54.0, 44.9, 39.8, 39.7, 34.4, 28.5, 27.2, 20.9; IR (Neat Film, NaCl) 3463, 3374, 2975, 2935, 2865, 1713, 1703, 1699, 1505, 1455, 1365, 1247, 1169 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{30}NO_3$ $[M+H]^+$: 344.2226, found 344.2236; SFC conditions:

15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 2.46, minor = 2.78.

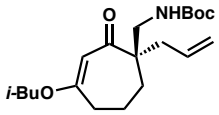


(*S*)-*tert*-Butyl (1-allyl-2-oxocycloheptyl)methylcarbamate (246b): The reaction was conducted according to general procedure B. Ketoester **245b** (97.6 mg, 0.300 mmol). The reaction mixture was stirred at 23 ºC for 20 h. Flash column chromatography (SiO_2, 10→15% EtOAc in hexanes) afforded ketone **246b** (78.7 mg, 0.280 mmol, 93% yield) as a pale yellow oil. 87% ee, $[\alpha]_D^{25}$ –22.7 (*c* 0.85, $CHCl_3$); R_f = 0.53 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 17.3, 10.4, 7.5 Hz, 1H), 5.12–5.03 (m, 2H), 4.93 (brs, 1H), 3.31–3.19 (m, 2H), 2.65–2.56 (m, 1H), 2.46 (ddd, *J* = 11.3, 8.8, 2.5 Hz, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 1.79–1.41 (m, 8H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 217.1, 156.2, 133.2, 118.8, 79.3, 54.8, 45.2, 41.1, 39.4, 33.3, 30.8, 28.5, 26.7, 24.7; IR (Neat Film, NaCl) 3372, 2930, 1716, 1698, 1503, 1365, 1247, 1117 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{28}NO_3$ $[M+H]^+$: 282.2064, found 282.2051; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.25, minor = 4.63.

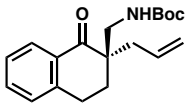


(*S*)-*tert*-Butyl (1-allyl-2-oxocyclopentyl)methylcarbamate (246c): The reaction was conducted according to general procedure B. Ketoester **245c** (59.5 mg, 0.200 mmol). The reaction mixture was stirred at 23 ºC for 20 h. Flash column chromatography (SiO_2, 10→15% EtOAc in hexanes) afforded ketone **246c** (50.0 mg, 0.196 mmol, 98% yield) as a colorless oil. 82% ee, $[\alpha]_D^{25}$ –12.8 (*c* 0.96, $CHCl_3$); R_f = 0.38 (25% EtOAc in hexanes);

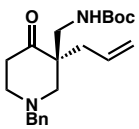
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 1H), 5.14–5.05 (m, 2H), 4.86 (brs, 1H), 3.25 (dd, *J* = 13.9, 6.9 Hz, 1H), 3.14 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.30–2.23 (m, 2H), 2.20–2.13 (m, 2H), 1.99–1.79 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 222.6, 156.3, 133.0, 119.1, 79.5, 52.5, 44.0, 38.4, 37.5, 31.1, 28.5, 18.8; IR (Neat Film, NaCl) 3360, 2975, 1713, 1510, 1365, 1248, 1166 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{14}H_{23}NO_3Na$ $[M+Na]^+$: 276.1570, found 276.1565; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 2.97, minor = 4.26.



(*S*)-*tert*-Butyl ((1-allyl-4-isobutoxy-2-oxocyclohept-3-en-1-yl)methyl)carbamate (246d): The reaction was conducted according to general procedure B. Ketoester **245d** (100 mg, 0.253 mmol); $[Pd_2(pmdba)_3]$ (13.9 mg, 0.012 mmol, 0.05 equiv). The reaction mixture was stirred at 23 ºC for 24 h. Flash column chromatography (SiO_2, 10% EtOAc in hexanes) afforded ketone **246d** (62.2 mg, 0.177 mmol, 70% yield) as a pale yellow oil. 92% ee, $[\alpha]_D^{25}$ –28.7 (*c* 0.65, $CHCl_3$); R_f = 0.6 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddt, *J* = 17.5, 10.3, 7.4 Hz, 1H), 5.28 (s, 1H), 5.10–5.03 (m, 3H), 3.53–3.44 (m, 2H), 3.33 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.18 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.55–2.42 (m, 2H), 2.37–2.28 (m, 2H), 1.98 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.94–1.87 (m, 1H), 1.81–1.72 (m, 3H), 1.41 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.8, 172.7, 156.4, 133.4, 118.8, 104.9, 79.1, 74.7, 55.5, 47.1, 41.3, 36.1, 31.6, 28.6, 28.0, 20.5, 19.3; IR (Neat Film, NaCl) 3373, 3075, 2972, 2931, 2868, 1716, 1694, 1504, 1393, 1366, 1249, 1166 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{34}NO_4$ $[M+H]^+$: 352.2488, found 352.2474; SFC conditions: 3% IPA, 2.5 mL/min, Chiralpak AS-H column, λ = 254 nm, t_R (min): major = 4.41, minor = 6.12.

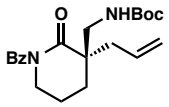


(*S*)-*tert*-Butyl ((2-allyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)carbamate (246e): The reaction was conducted according to general procedure B. Ketoester **245e** (81 mg, 0.225 mmol); $[Pd_2(pmdba)_3]$ (12.3 mg, 0.011 mmol, 0.05 equiv). The reaction mixture was stirred at 23 ºC for 24 h. Flash column chromatography (SiO_2, 10% EtOAc in hexanes) afforded ketone **246e** (52.2 mg, 0.167 mmol, 74% yield) as a pale yellow oil. 93% ee, $[\alpha]_D^{25}$ –1.3 (*c* 1.32, $CHCl_3$); R_f = 0.6 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 5.79 (m, 1H), 5.15–5.05 (m, 3H), 3.50 (dd, *J* = 13.9, 6.2 Hz, 1H), 3.29 (dd, *J* = 13.9, 6.9 Hz, 1H), 3.11 (ddd, *J* = 16.9, 11.1, 5.3 Hz, 1H), 2.94 (dt, *J* = 17.5, 4.6 Hz, 1H), 2.37 (dd, *J* = 14.2, 8.0 Hz, 1H), 2.28 (dd, *J* = 14.2, 6.8 Hz, 1H), 2.11 (ddd, *J* = 14.0, 11.1, 5.2 Hz, 1H), 2.03 (dt, *J* = 14.0, 4.7 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2, 156.4, 143.5, 133.7, 132.7, 131.6, 129.0, 127.9, 126.9, 119.2, 79.2, 49.3, 44.8, 36.6, 28.9, 28.5, 25.0; IR (Neat Film, NaCl) 3449, 3378, 3073, 2976, 2930, 1716, 1699, 1678, 1600, 1505, 1455, 1365, 1232, 1170 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1913, found 316.1920; SFC conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 2.48, minor = 2.80.



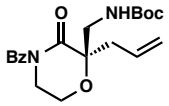
(*S*)-*tert*-Butyl ((3-allyl-1-benzyl-4-oxopiperidin-3-yl)methyl)carbamate (246f): The reaction was conducted according to general procedure B. Ketoester **245f** (115 mg, 0.286 mmol); $[Pd_2(pmdba)_3]$ (15.7 mg, 0.014 mmol, 0.05 equiv). The reaction mixture was

stirred at 23 ºC for 24 h. Flash column chromatography (SiO_2, 10% EtOAc in hexanes) afforded ketone **246f** (79.3 mg, 0.223 mmol, 78% yield) as a pale yellow oil. 90% ee, $[\alpha]_D^{25}$ –34.0 (*c* 1.58, $CHCl_3$); R_f = 0.55 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.61 (m, 1H), 5.07 (m, 1H), 5.04 (d, *J* = 1.1 Hz, 1H), 5.00 (m, 1H), 3.58 (d, *J* = 13.0 Hz, 1H), 3.53 (d, *J* = 13.0 Hz, 1H), 3.37 (dd, *J* = 14.0, 7.3 Hz, 1H), 3.19 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.84 (m, 1H), 2.69 (d, *J* = 11.6 Hz, 1H), 2.63–2.50 (m, 3H), 2.48–2.36 (m, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.8, 156.2, 138.3, 132.6, 129.0, 128.5, 127.4, 119.2, 79.3, 62.3, 59.7, 53.6, 53.1, 44.1, 39.5, 38.1, 28.5; IR (Neat Film, NaCl) 3452, 3373, 3063, 2976, 2929, 2807, 1713, 1638, 1504, 1453, 1391, 1365, 1248, 1170 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{31}N_2O_3$ $[M+H]^+$: 359.2335, found 359.2345; SFC conditions: 8% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.94, minor = 6.46.

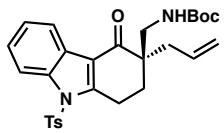


(*S*)-*tert*-Butyl ((3-allyl-1-benzoyl-2-oxopiperidin-3-yl)methyl)carbamate (246g): The reaction was conducted according to general procedure B. Amidoester **245g** (83.3 mg, 0.200 mmol). The reaction mixture was stirred at 40 ºC for 20 h. Flash column chromatography (SiO_2, 15→20% EtOAc in hexanes) afforded lactam **246g** (69.7 mg, 0.187 mmol, 94%) as a colorless oil. 90% ee, $[\alpha]_D^{25}$ +33.6 (*c* 1.05, $CHCl_3$); R_f = 0.29 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.46 (m, 3H), 7.44–7.37 (m, 2H), 5.78 (m, 1H), 5.24–5.15 (m, 2H), 4.96 (m, 1H), 3.84 (m, 1H), 3.73 (ddd, *J* = 12.7, 10.3, 4.3 Hz, 1H), 3.37 (dd, *J* = 13.8, 6.5 Hz, 1H), 3.22 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.60 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.48 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.12–1.93 (m, 3H), 1.82 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 175.4, 156.4, 136.3, 131.9,

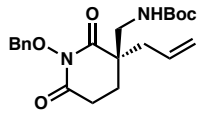
131.8, 128.4, 127.6, 120.1, 79.5, 48.8, 47.2, 46.0, 39.7, 28.8, 28.5, 19.3; IR (Neat Film, NaCl) 3373, 2975, 1693, 1678, 1502, 1390, 1365, 1272, 1248, 1167 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{28}N_2O_4Na$ $[M+Na]^+$: 395.1941, found 395.1954; SFC conditions: 10% MeOH, 3.0 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 2.64, minor = 3.12.



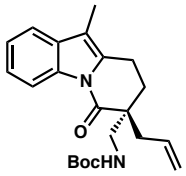
(*R*)-*tert*-Butyl ((2-allyl-4-benzoyl-3-oxomorpholin-2-yl)methyl)carbamate (246h): The reaction was conducted according to general procedure B. Morpholinone **245h** (33.0 mg, 0.079 mmol). The reaction mixture was stirred at 40 ºC for 12 h. Flash column chromatography (SiO_2, 15→20% EtOAc in hexanes) afforded morpholinone **246h** (27.3 mg, 0.073 mmol, 92%) as a colorless oil. 99% ee, $[\alpha]_D^{25}$ +10.8 (*c* 0.93, $CHCl_3$); R_f = 0.43 (33% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.57–7.48 (m, 3H), 7.43–7.38 (m, 2H), 5.89 (m, 1H), 5.23–5.17 (m, 2H), 4.88 (br s, 1H), 4.14–3.88 (m, 4H), 3.63 (m, 1H), 3.40 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.69 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.52 (dd, *J* = 14.3, 7.0 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 172.6, 155.9, 135.6, 132.1, 131.7, 128.3, 128.1, 119.9, 82.2, 79.9, 60.6, 46.0, 45.5, 40.0, 28.5; IR (Neat Film, NaCl) 3382, 2978, 1707, 1689, 1509, 1367, 1281, 1250, 1225, 1166, 1091 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{26}N_2O_5Na$ $[M+Na]^+$: 397.1734, found 397.1728; SFC conditions: 3% MeOH, 2.5 mL/min, Chiralpak AS-H column, λ = 254 nm, t_R (min): major = 4.06, minor = 4.62.



(*S*)-*tert*-Butyl ((3-allyl-4-oxo-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)methyl)carbamate (246i): The reaction was conducted according to general procedure B. Ketoester **245i** (100 mg, 0.181 mmol); $[Pd_2(pmdba)_3]$ (10.0 mg, 0.009 mmol, 0.05 equiv). The reaction mixture was stirred at 40 ºC for 48 h. Flash column chromatography (SiO_2, 10% EtOAc in hexanes) afforded ketone **246i** (46.9 mg, 0.091 mmol, 51% yield) as a white foam.[24] 92% ee, $[\alpha]_D^{25}$ –13.3 (*c* 0.28, C_6H_6); R_f = 0.45 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (m, 1H), 8.16 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.41–7.31 (m, 2H), 7.28 (m, 2H), 5.77 (m, 1H), 5.11 (m, 1H), 5.08 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.05 (br t, *J* = 6.7 Hz, 1H), 3.49 (dd, *J* = 13.9, 6.2 Hz, 1H), 3.44 (dt, *J* = 19.2, 4.8 Hz, 1H), 3.33–3.28 (m, 1H), 3.27 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.38 (s, 3H), 2.32–2.28 (m, 2H), 2.16–2.11 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 156.4, 150.1, 146.1, 136.4, 135.6, 132.9, 130.5, 126.8, 126.0, 125.6, 125.1, 121.9, 119.3, 116.6, 114.1, 79.4, 49.4, 44.6, 37.5, 29.5, 28.5, 21.8, 21.6; IR (Neat Film, NaCl) 3432, 3372, 3058, 2976, 2928, 1712, 1657, 1505, 1451, 1407, 1366, 1247, 1173 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{28}H_{33}N_2O_5S$ $[M+H]^+$: 509.2105, found 509.2094; SFC conditions: 15% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): major = 7.21, minor = 5.19.



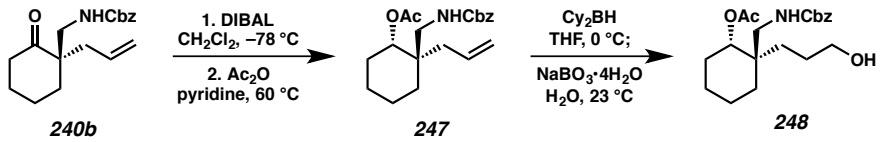
(*S*)-*tert*-Butyl-((3-allyl-1-(benzyloxy)-2,6-dioxopiperidin-3-yl)methyl)carbamate (246j): The reaction was conducted according to general procedure B. Imidoester **245j** (72 mg, 0.166 mmol, 1.0 equiv); $[Pd_2(pmdba)_3]$ (7.6 mg, 0.008 mmol, 0.05 equiv); ligand (**76**, 12.4 mg, 0.0208 mmol, 0.125 equiv); toluene (5.1 mL). The reaction mixture was stirred at 60 ºC for 24 h. Flash column chromatography (SiO_2, 30% EtOAc in hexanes) afforded imide **246j** (49 mg, 76% yield) as a clear colorless oil. 55% ee; R_f = 0.5 (40% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.39–7.36 (m, 3H), 5.66 (ddt, J = 17.3, 10.1, 7.4 Hz, 1H), 5.19–5.16 (m, 1H), 5.13 (dq, J = 16.9, 1.5 Hz, 1H), 5.04–4.97 (m, 2H), 4.82 (t, J = 6.6 Hz, 1H), 3.40 (dd, J = 14.1, 6.2 Hz, 1H), 3.31 (dd, J = 14.1, 7.3 Hz, 1H), 2.84–2.69 (m, 2H), 2.30 (d, J = 7.4 Hz, 2H), 1.89–1.76 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 167.8, 156.3, 133.8, 131.2, 130.3, 129.4, 128.6, 120.5, 80.0, 78.2, 48.3, 45.4, 38.2, 29.4, 28.5, 23.3; IR (Neat Film, NaCl) 3377, 3064, 3033, 2975, 2935, 2251, 1734, 1718, 1696, 1507, 1452, 1365, 1248, 1169, 973, 914, 750, 699 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{28}N_2O_5Na$ $[M+Na]^+$: 411.1890, found 411.1885; SFC conditions: 5% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): major = 3.74, minor = 3.01.



***tert*-Butyl (*S*)-((7-allyl-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-7-yl)methyl)carbamate (165g)**: The reaction was conducted according to general procedure B. α-Quaternary β-amidoester **172g** (37 mg, 0.09 mmol, 1.0 equiv);

$Pd_2(pmdba)_3$ (4.9 mg, 4.5 μmol, 0.05 equiv); (*S*)-$(CF_3)_3$-*t*-BuPHOX (**76**, 6.6 mg, 11.1 μmol, 0.125 equiv); TBME (2.7 mL). The reaction mixture was stirred for 12 h at 60 °C. Flash column chromatography (SiO_2, 30% Et_2O in hexanes) afforded α-quaternary DHPI **165g** (20 mg, 61% yield) as an off-white foam: R_f = 0.33 (7:3 hexanes:Et_2O eluent); 92% ee, $[\alpha]_D^{25}$ +40.1 (*c* 0.41, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45–8.39 (m, 1H), 7.46–7.41 (m, 1H), 7.32–7.27 (m, 2H), 5.83 (ddt, J = 16.7, 10.3, 7.4 Hz, 1H), 5.21–5.11 (m, 3H), 3.61 (dd, J = 13.9, 6.1 Hz, 1H), 3.42 (dd, J = 13.9, 7.1 Hz, 1H), 3.04 (dt, J = 16.8, 4.9 Hz, 1H), 2.94 (dddd, J = 18.4, 10.9, 6.2, 1.6 Hz, 1H), 2.50 (dt, J = 7.3, 1.2 Hz, 2H), 2.20–2.17 (m, 3H), 2.11–2.00 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 156.4, 134.8, 132.6, 132.1, 131.6, 124.4, 124.1, 119.8, 118.0, 116.5, 112.8, 79.5, 48.1, 45.4, 37.9, 28.5, 27.2, 17.8, 8.5; IR (Neat Film, NaCl) 3448, 3373, 3069, 2975, 2931, 2865, 1716, 1690, 1625, 1507, 1457, 1384, 1365, 1340, 1318, 1246, 1168, 1078, 916, 752 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{22}H_{29}N_2O_3$ $[M+H]^+$: 369.2178, found 369.2169; SFC conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 19.76, minor = 21.43.

Total Synthesis of (–)-Isonitramine (241) and (+)-Sibirinine (242)



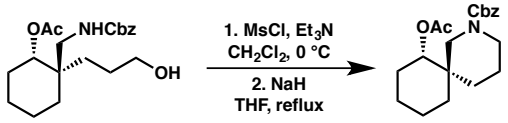
240b *247* *248*

Alcohol 248: To a solution of enantioenriched ketone **240b** (851 mg, 2.82 mmol) in CH_2Cl_2 (14.2 mL) was added DIBAL (6.21 mL, 1.0 M solution in CH_2Cl_2, 6.21 mmol, 2.20 equiv) dropwise at –78 ºC. After stirring at –78 ºC for 15 min, the reaction mixture was quenched with saturated aqueous Rochelle's salt (20 mL) and stirred at 23 °C for 2 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used for the next reaction without further purification.

To a solution of the crude secondary alcohol in Ac_2O (7.1 mL) was added pyridine (7.1 mL) at room temperature. After full consumption of the starting material was observed by TLC analysis, the reaction mixture was concentrated and azeotropically dried with toluene twice. The resulting residue was used in the next reaction without further purification.

To a flame-dried flask was added cyclohexene (1.43 mL, 14.1 mmol, 5.00 equiv), diethyl ether (10 mL), and BH_3•Me_2S (7.05 mL, 2.0 M solution in THF, 3.5 mmol, 1.24 equiv) at 0 ºC. The reaction mixture was stirred at 0 ºC for 3 h, then the solid was allowed to settle without stirring, and the supernatant was removed using a syringe. To the resulting solid was added THF (8.0 mL) and a solution of acetate **247** in THF (6.2 mL) at 0 ºC. After full consumption of acetate **247** by TLC analysis, the reaction mixture

was quenched with $NaBO_3$ (3.25 g, 21.2 mmol, 7.52 equiv) and H_2O (14 mL) and stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc, the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, 30→50% EtOAc in hexanes) afforded alcohol **248** (886 mg, 86% yield, over 3 steps) as a colorless oil. $[\alpha]_D^{25}$ +7.5 (*c* 0.95, $CHCl_3$); R_f = 0.33 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.35 (m, 1H), 5.14–5.02 (m, 2H), 4.77 (dd, *J* = 9.7, 4.5 Hz, 1H), 3.68–3.58 (m, 2H), 3.30 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.88 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.05 (s, 3H), 1.71–1.16 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 157.1, 136.7, 128.6, 128.3, 128.2, 75.3, 66.9, 63.5, 45.5, 40.9, 30.0, 26.9, 26.0, 25.3, 23.9, 21.4, 20.4; IR (Neat Film, NaCl) 3385, 2937, 2866, 1718, 1528, 1455, 1374, 1247, 1026 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{30}NO_5$ $[M+H]^+$: 364.2118, found 364.2109.

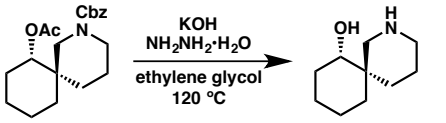


248 ***249***

Spirocycle 249: To a solution of primary alcohol **248** (865 mg, 2.38 mmol) in CH_2Cl_2 (12 mL) was added Et_3N (0.497 mL, 3.57 mmol, 1.50 equiv) and MsCl (0.203 mL, 2.63 mmol, 1.10 equiv) at 0 ºC. After full consumption of alcohol **248** was observed by TLC analysis, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (25 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated

under reduced pressure. The crude product was used in the next reaction without further purification.

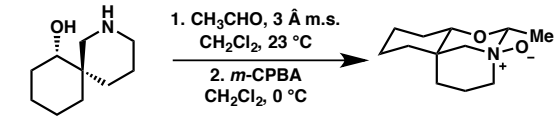
To a suspension of sodium hydride (114 mg, 60 wt% dispersion in mineral oil, 2.86 mmol) in THF (6 mL) was added a solution of the above methanesulfonate in THF (6 mL) at 0 ºC. The reaction mixture was stirred at reflux for 2 h. Upon cooling to 23 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and diluted with CH_2Cl_2 (20 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, 15% EtOAc in hexanes) afforded spirocycle **249** (732 mg, 89% yield, over 2 steps) as a colorless oil. $[\alpha]_D^{25}$ +46.8 (*c* 0.97, $CHCl_3$); R_f = 0.57 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 7.39–7.26 (m, 5H), 5.20–5.01 (m, 2H), 4.86–4.61 (m, 1H), 3.96–2.91 (m, 4H), 2.05 (s, 3H), 1.87–1.00 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 170.6, 155.7, 137.0, 128.6, 128.1, 128.0, 75.2 (74.3), 67.2, 51.4 (50.7), 44.8, 37.0 (36.9), 30.6 (29.1), 30.2, 26.5, 22.4 (21.8), 21.3, 20.8 (20.7), 20.6 (20.5); IR (Neat Film, NaCl) 2938, 2861, 1732, 1699, 1434, 1242 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{29}NO_4$ $[M+H]^+$: 346.2013, found 346.2016.



249 ***241 (–)-Isonitramine***

(–)-Isonitramine (241): To a solution of spirocycle **249** (712 mg, 2.06 mmol) in ethylene glycol (13 mL) was added KOH (3.00 g, 53.4 mmol, 25.92 equiv) and hydrazine hydrate (0.51 mL) at 23 °C. After stirring at 120 ºC for 1.5 h, the reaction mixture cooled to 23

°C and diluted with H_2O (100 mL). The aqueous phase was extracted with CH_2Cl_2 (200 mL) using a continuous liquid/liquid extractor and the organic phase was concentrated under reduced pressure. Flash column chromatography (SiO_2, $CHCl_3$:MeOH:NH_3(aq) = 46:50:4 eluent) afforded (–)-isonitramine (**241**) (270 mg, 77% yield) as a white solid. $[\alpha]_D^{25}$ –4.1 (*c* 0.96, $CHCl_3$); Lit: $[\alpha]_D^{20}$ –5.0 (*c* 2.1, $CHCl_3$)[11e]; R_f = 0.30 ($CHCl_3$:MeOH:NH_3 (aq) = 46:50:4); m.p. 86.9–88.8 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.04 (m, 1H), 2.94 (m, 1H), 2.60 (ddd, *J* = 11.3, 11.3, 3.4 Hz, 1H), 2.52 (d, *J* = 11.3 Hz, 1H), 2.24 (m, 1H), 2.06 (m, 1H), 1.78–1.14 (m, 8H), 1.06 (ddd, *J* = 13.3, 13.3, 5.5 Hz, 1H), 0.96 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.7, 61.0, 47.4, 36.9, 36.3, 29.9, 29.0, 24.4, 23.3, 20.4; IR (Neat Film, NaCl) 3292, 2929, 2858, 1539, 1457, 1419, 1282, 1064 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{10}H_{20}NO$ $[M+H]^+$: 170.1539, found 170.1541.



241 ***(–)-Isonitramine*** ***242*** ***(+)-Sibirinine***

(+)-Sibirinine (242): An oven-dried 1-dram vial was charged with a magnetic stirring bar, (–)-isonitramine (**241**, 20 mg, 0.118 mmol), oven-dried powdered 3 Å molecular sieves (40 mg), and CH_2Cl_2 (1.5 mL). To this stirring suspension was added acetaldehyde (0.133 mL, 2.36 mmol, 20.0 equiv). The vial was sealed with a teflon-lined cap, and the reaction was stirred at 23 °C for 30 h. The reaction mixture was then filtered through celite, washing with CH_2Cl_2. The filtrate was concentrated under reduced pressure to yield a pale yellow oil, which was used in the subsequent reaction without further purification.

The above crude hemiaminal was dissolved in CH_2Cl_2 (1.2 mL) and cooled to 0 °C (water/ice bath). To this stirring solution was added *m*-CPBA (29 mg, 0.13 mmol) in one portion. After 15 min, full consumption of starting material was observed by TLC analysis. The reaction mixture was filtered through celite, washing with CH_2Cl_2, and concentrated under reduced pressure. Flash column chromatography (SiO_2, CH_2Cl_2: NH_3 (7N solution in MeOH) = 92:8 eluent) afforded (+)-sibirinine (**242**) (22.9 mg, 92% yield, over 2 steps) as a colorless oil. $[\alpha]_D^{25}$ +10.3 (*c* 0.56, $CHCl_3$); R_f = 0.40 (CH_2Cl_2: NH_3 (7N solution in MeOH) = 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (qd, *J* = 5.8, 1.5 Hz, 1H), 3.73 (dd, *J* = 13.4, 7.1 Hz, 1H), 3.53 (ddd, *J* = 12.0, 4.1, 1.5 Hz, 1H), 3.21 (d, *J* = 12.2 Hz, 1H), 3.11 (dt, *J* = 12.2, 2.5 Hz, 1H), 3.03 (dddd, *J* = 14.7, 13.4, 5.5, 1.6 Hz, 1H), 2.45 (tdt, *J* = 14.4, 13.5, 5.9 Hz, 1H), 2.32 (dd, *J* = 14.1, 5.8 Hz, 1H), 1.87 (dtd, *J* = 13.1, 3.8, 1.7 Hz, 1H), 1.79 (dq, *J* = 12.3, 3.6 Hz, 1H), 1.65 (d, *J* = 5.8 Hz, 3H), 1.64–1.60 (m, 1H), 1.57–1.46 (m, 2H), 1.46 (dt, *J* = 13.0, 4.0 Hz, 1H), 1.41–1.31 (m, 2H), 1.23 (m, 1H), 1.17 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 102.2, 84.4, 77.8, 62.5, 38.2, 34.7, 27.0, 26.3, 24.7, 21.2, 19.6, 14.6; IR (Neat Film, NaCl) 2934, 2854, 1466, 1446, 1367, 1138, 1120, 1103, 961, 940 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{12}H_{22}NO_2$ $[M+H]^+$: 212.1645, found 212.1640.

4.7.3 DETERMINATION OF ENANTIOMERIC EXCESS

Table 4.7.3.1. Determination of Enantiomeric Excess and Optical Rotation – Part 1

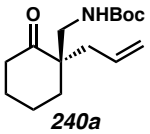
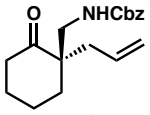
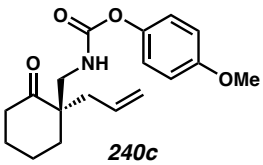
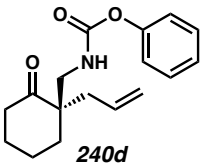
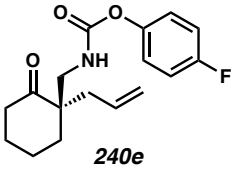
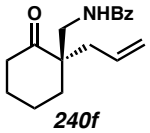
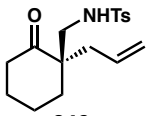
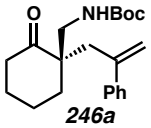
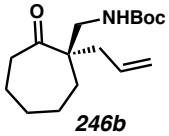
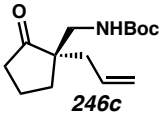
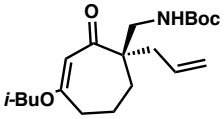
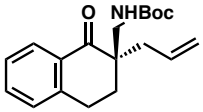
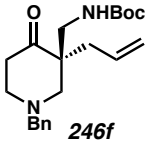
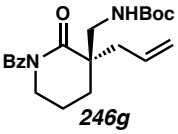
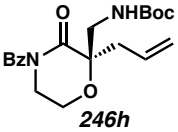
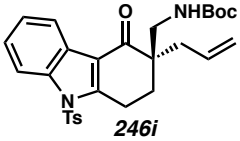
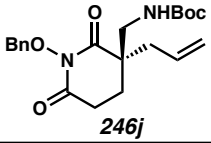
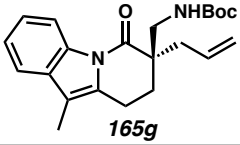
entry	compound	analytic conditions	ee (%)	polarimetry
1	 ***240a***	**SFC: 5% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 3.73, minor 4.30**	**86**	**$[\alpha]_D^{25}$ –25.5 (*c* 0.865, C_6H_6)**
2	 ***240b***	**SFC: 5% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 8.12, minor 9.06**	**86**	**$[\alpha]_D^{25}$ –38.6 (*c* 1.20, $CHCl_3$)**
3	 ***240c***	**SFC: 10% IPA, 2.5 mL/min Chiralcel OB-H, λ = 210 nm t_R (min): major 9.47, minor 11.13**	**83**	**$[\alpha]_D^{25}$ –29.3 (*c* 0.76, $CHCl_3$)**
4	 ***240d***	**SFC: 10% IPA, 2.5 mL/min Chiralcel OB-H, λ = 210 nm t_R (min): major 6.53, minor 8.13**	**77**	**$[\alpha]_D^{25}$ –28.9 (*c* 0.40, $CHCl_3$)**
5	 ***240e***	**SFC: 10% IPA, 2.5 mL/min Chiralpak AS-H, λ = 210 nm t_R (min): major 6.94, minor 8.24**	**77**	**$[\alpha]_D^{25}$ –27.4 (*c* 0.78, $CHCl_3$)**
6	 ***240f***	**SFC: 20% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 4.04, minor 4.91**	**56**	**Specific Rotation Not Determined**
7	 ***240g***	**SFC: 15% IPA, 2.5 mL/min Chiralcel OJ-H, λ = 210 nm t_R (min): major 3.14, minor 3.85**	**24**	**Specific Rotation Not Determined**

Table 4.7.3.2. Determination of Enantiomeric Excess and Optical Rotation – Part 2

entry	compound	analytic conditions	ee (%)	polarimetry
1	 ***246a***	SFC: 15% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 2.46, minor 2.78	90	$[\alpha]_D^{25}$ –30.87 (*c* 4.45, $CHCl_3$)
2	 ***246b***	SFC: 5% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 4.25, minor 4.63	87	$[\alpha]_D^{25}$ –22.7 (*c* 0.85, $CHCl_3$)
3	 ***246c***	SFC: 5% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 2.97, minor 4.26	82	$[\alpha]_D^{25}$ –12.8 (*c* 0.96, $CHCl_3$)
4	 ***246d***	SFC: 3% IPA, 2.5 mL/min Chiralpak AS-H, λ = 254 nm t_R (min): major 4.41, minor 6.12	92	$[\alpha]_D^{25}$ –28.7 (*c* 0.65, $CHCl_3$)
5	 ***246e***	SFC: 15% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 2.48, minor 2.80	93	$[\alpha]_D^{25}$ –1.3 (*c* 1.32, $CHCl_3$)
6	 ***246f***	SFC: 8% IPA, 2.5 mL/min Chiralpak AD-H, λ = 210 nm t_R (min): major 4.94, minor 6.46	90	$[\alpha]_D^{25}$ –34.0 (*c* 1.58, $CHCl_3$)
7	 ***246g***	SFC: 10% MeOH, 3.0 mL/min Chiralpak AD-H, λ = 254 nm t_R (min): major 2.64, minor 3.12	90	$[\alpha]_D^{25}$ +33.6 (*c* 1.05, $CHCl_3$)
8	 ***246h***	SFC: 3% MeOH, 2.5 mL/min Chiralpak AS-H, λ = 254 nm t_R (min): major 4.06, minor 4.62	99	$[\alpha]_D^{25}$ +10.8 (*c* 0.93, $CHCl_3$)
9	 ***246i***	SFC: 15% IPA, 2.5 mL/min Chiralcel OB-H, λ = 210 nm t_R (min): major 7.21, minor 5.19	92	$[\alpha]_D^{25}$ –13.3 (*c* 0.28, C_6H_6)
10	 ***246j***	SFC: 5% IPA, 2.5 mL/min Chiralcel OB-H, λ = 210 nm t_R (min): major 3.74, minor 3.01	55	ND
11	 ***165g***	SFC: 5% IPA, 2.5 mL/min Chiralcel OD-H, λ = 210 nm t_R (min): major 19.76, minor 21.43	92	$[\alpha]_D^{25}$ +40.1 (*c* 0.41, $CHCl_3$)

4.7.4 COMPARISON OF SYNTHETIC (+)-SIBIRININE TO PUBLISHED DATA

As detailed above, we found that hemiaminal formation and subsequent *N*-oxidation of (–)-isonitramine (**241**) furnished (+)-sibirinine (**242**). This finding is in contrast to a previous report, where (–)-sibirinine (**242**) was obtained in a similar sequence from (–)-isonitramine (**241**).[12] Given that the optical rotation of our synthesized (–)-isonitramine (**241**) matches those found in previously reported syntheses,[11] and that the optical rotation reported in the isolation paper of (–)-isonitramine[10] (**241**) has been refuted,[11e] the optical rotation values reported in the isolation of sibirinine[12] (**242**) should be regarded as incorrect.

Limited spectral data were available for sibirinine (**242**) in the isolation paper.[12] Full ^{13}C NMR, partial ^{1}H NMR, optical rotation, and HRMS data were reported. Comparisons between data obtained from the synthetic material and data available in the literature are detailed in the following table.

*Table 4.7.4.1. Comparison of Synthetic and Natural Sibirinine (**242**)*

Synthetic (+)-sibirinine	**Natural sibirinine**[12]
^{1}H NMR (500 MHz, $CDCl_3$)	*^{1}H NMR ($CDCl_3$)*
4.50 (qd, *J* = 5.8, 1.5 Hz, 1H)	4.58 (qd, *J* = 5.7, 1.2 Hz, 1H)
3.21 (d, *J* = 12.2 Hz, 1H)	3.31 (d, *J* = 12 Hz, 1H)
3.11 (dt, *J* = 12.2, 2.5 Hz, 1H)	3.17 (dd, *J* = 12, 2.3 Hz, 1H)
1.65 (d, *J* = 5.8 Hz, 3H)	1.65 (d, *J* = 5.7 Hz, 3H)
^{13}C NMR (126 MHz, $CDCl_3$)	*^{13}C NMR ($CDCl_3$)*
102.2	101.9
84.4	84.3
77.8	77.1
62.5	62.0
38.2	38.1
34.7	34.5
27.0	26.8
26.3	26.1
24.7	24.6
21.2	21.0
19.6	19.0
14.6	14.4

4.8 Notes and References

1. For selected reviews of Mannich reactions and references therein, see; (a) Kleinman, E. F. *in Comprehensive Organic Synthesis*, Vol. 2 (Eds.: Trost, B. M.; Flemming, I.; Heathcock, C. H.), Pergamon, Oxford, **1991**, chapter. 4.1. (b) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791–1837. (c) Tramontini, M. Syntesis 1973, 703–775. (d) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.

2. (a) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704. (b) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112.

3. For selected examples of asymmetric Mannich-type reactions to construct quaternary centers, see: (a) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525–1529. (b) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362–1364. (c) Xue, S.; Yu, S.; Deng, Y. H.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271–2274. (d) Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 56–57. (e) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003–2006. (f) Trost, B. M.; Saget, T.; Hung, C.-I. *J. Am. Chem. Soc.* **2016***, 138*, 3659–3662.

4. (a) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981–984. (b) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857–8867. (c) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528–6531. (d) Hamashima, Y.; Sasamoto, N.; Umebayashi, N.; Sodeoka, M. *Chem.-Asian J.* **2008**, *3*, 1443–1455.

5. Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507–2510.

6. For non-enantioselective reactions to provide α-aminomethyl α-quaternary ketones, see; (a) Danishefsky, S.; Prisbylla, M.; Lipisko, B. *Tetrahedron Lett.* **1980**, *21*, 805–808. (b) Matsumoto, K.; Hashimoto, S.; Otani, S.; Atnita, F.; Osugi, J. *Synthetic Commun.* **1984**, *14*, 585–590. (c) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226–7232.

7. Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927.

8. (a) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novak, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem.–Eur. J.* **2011**, *17*, 14199–14223. (b) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2012**, *4*, 130–133. (c) Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem.–Eur. J.* **2013**, *19*, 4414–4418. (d) Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6718–6721.

9. For related studies, see: (a) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248–7251. (b) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117–4121. (c) Gartshore, C. J.; Lupton, D. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 4113–4116. (d) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.*

2009, *131*, 18343–18357. (e) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109–3112.

10. For the isolation of (–)-isonitramine (**241**), see: Ibragimov, A. A.; Osmanov, Z.; Tashchodzhaev, B.; Abdullaev, N. D.; Yagudaev, M. R.; Yunusov, S. Y. *Khimiya Prir. Soedin.* **1981**, 623–629.

11. For selected total syntheses of isonitramine (**241**), see; (a) Deyine, A.; Poirier, J.-M.; Duhamel, L.; Duhamel, P. *Tetrahedron Lett.* **2005**, *46*, 2491–2493. (b) Francois, D.; Lallemand, M.-C.; Selkti, M.; Tomas, A.; Kunesch, N.; Husson, H.-P. *Angew. Chem., Int. Ed.* **1998**, *37*, 104–105. (c) Pandey, G.; Kumara, C. P.; Burugu, S. K.; Puranik, V. G. *Eur. J. Org. Chem.* **2011**, 7372–7377. (d) Park, Y.; Lee, Y. J.; Hong, S.; Lee, M.; Park, H.-G. *Org. Lett.* **2012**, *14*, 852–854. (e) Quirion, J.-C.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 3311–3314.

12. For the isolation of sibirinine (**242**), see: Ibragimov, A. A.; Abdullaev, N. D.; Osmanov, Z.; Yunusov, S. Y. *Khimiya Prir. Soedin.* **1987**, 685–689.

13. (a) Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2002**, *43*, 1079–1080. (b) Sikriwal, D.; Kant, R.; Maulik, P. R.; Dikshit, D. K. *Tetrahedron* **2010**, *66*, 6167–6173.

14. (a) Tsuji, J.; Nisar, M.; Shimizu, I.; Minami, I. *Synthesis* **1984**, 1009. (b) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 194–211.

15. See experimental section.

16. McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

17. In some cases, a free N–H functionality can act as a good nucleophile toward π-allylpalladium complexes. For examples, see: Tsuji, J. Palladium Reagents and Catalysts–New Perspectives for the 21st Century; John Wiley & Sons, Ltd.: 2004.

18. Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

19. Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

20. (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–256. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.

21. (a) Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2002**, *43*, 1079–1080. (b) Sikriwal, D.; Kant, R.; Maulik, P. R.; Dikshit, D. K. *Tetrahedron* **2010**, *66*, 6167–6173.

22. Hong, A. Y.; Bennett, N. B.; Krout, M. R.; Jensen, T.; Harned, A. M.; Stoltz, B. M. *Tetrahedron* **2011**, *67*, 10234–10248.

23. Gartshore, C. J.; Lupton, D. W. *Aust. J. Chem.* **2013**, *66*, 882–890.

24. α-Quaternary carbazolone **245i** decomposes in chloroform after approximately 30 minutes. The resulting impurity was not isolated or identified.

APPENDIX 8

Synthetic Summary for Chapter 4:

Enantioselective Synthesis of α-Quaternary Mannich Adducts:

Total Syntheses of (–)-Isonitramine and (+)-Sibirinine

Scheme A8.1. Synthesis and Application of α-Quaternary Mannich Adducts

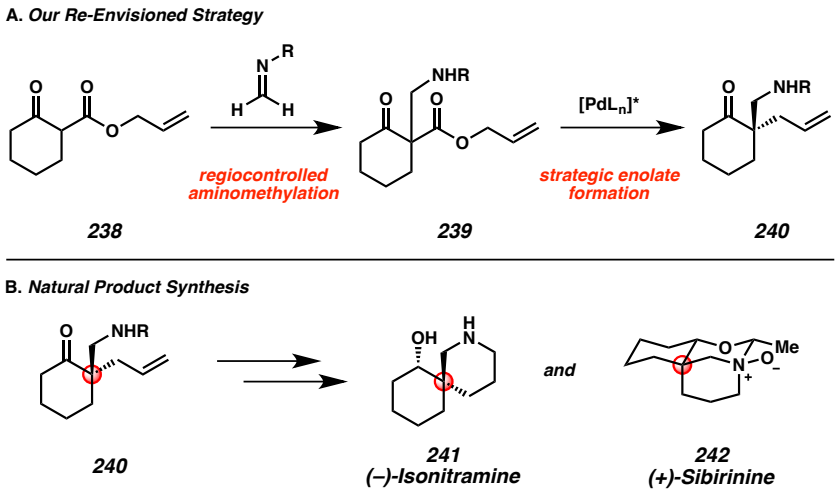
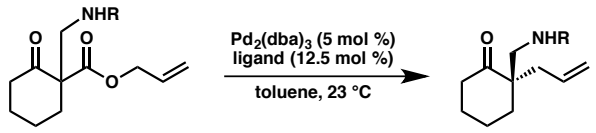
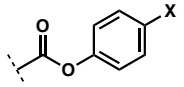


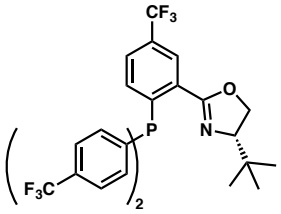
Table A8.1. Optimization of the Amine Protecting Group



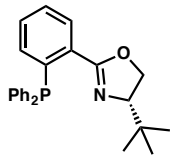
239 ***240***

entry	R (***239*** → ***240***)	ligand	yield [%][b]	ee [%][c]
1	Boc (***239a*** → ***240a***)	***76***	94	86
2	Boc (***239a*** → ***240a***)	***76***	ND[d]	80
3	Cbz (***239b*** → ***240b***)	***76***	96	86
4	 X = OMe (***239c*** → ***240c***)	***76***	91	83
5	X = H (***239d*** → ***240d***)	***76***	90	77
6	X = F (***239e*** → ***240e***)	***76***	84	77
7	Bz (***239f*** → ***240f***)	***76***	ND[d]	56
8	Ts (***239g*** → ***240g***)	***76***	54	24

[a] Reaction performed with 0.2 mmol of **239**, 5 mol % of $Pd_2(dba)_3$ (dba = dibenzylideneacetone), 12.5 mol % of ligand in toluene (0.033 M) at 23 °C.
[b] Isolated yield.
[c] Determined by chiral SFC analysis. Absolute stereochemistry has been assigned by anology, except in entry 2, which was assigned by conversion into (–)-isonitramine (**241**).
[d] A yield was not determined.

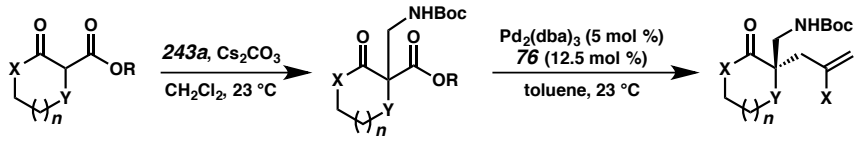


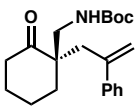
76
(S)-(CF$_3$)$_3$-t-BuPHOX



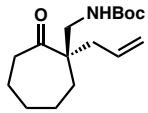
66
(S)-t-BuPHOX

*Table A8.2. Two-Step Enantioselective Synthesis of α-Aminomethyl Carbonyl Compounds (**246**) from β-Oxoesters (**244**)*

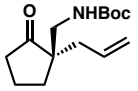




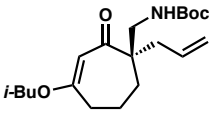
245a 79% yield
246a 91% yield, 90% ee[c]



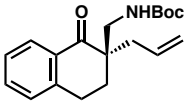
245b 72% yield
246b 93% yield, 87% ee



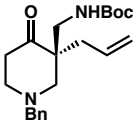
245c 86% yield
246c 98% yield, 82% ee



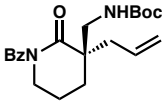
245d 83% yield
246d 70% yield, 92% ee[c]



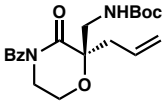
245e 99% yield
246e 74% yield, 93% ee[c]



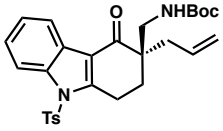
245f 80% yield
246f 78% yield, 90% ee[c]



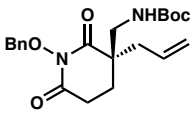
245g 74% yield
246g 94% yield, 90% ee[d]



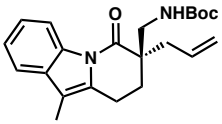
245h 80% yield
246h 92% yield, 99% ee[d]



245i 80% yield
246i 51% yield, 92% ee[c,d]



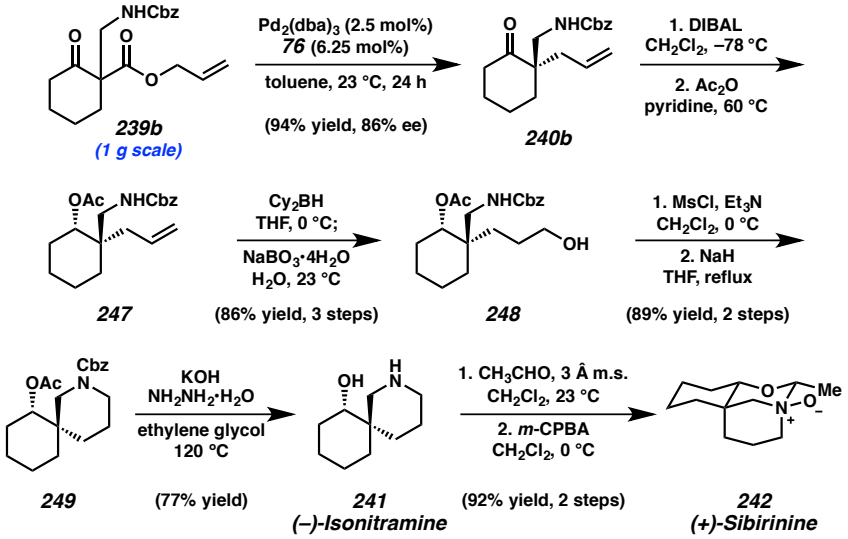
245j yield ND[e]
246j 76% yield, 55% ee[d]



172g 79% yield
165g 61% yield, 92% ee[c,f]

[a] Reaction conditions for the Pd-catalyzed allylic alkylation: **245** (1 equiv), $Pd_2(dba)_3$ (5 mol %) and **XX** (12.5 mol %) in toluene (0.033 M) at 23 °C for 12–48 h.
[b] Enantiomeric excesses were determined by chiral SFC analysis.
[c] $Pd_2(pmdba)_3$ (pmdba = bis(4-methoxybenzylidene)acetone) was used instead of $Pd_2(dba)_3$.
[d] Reactions were performed on **245g**, **245h**, and **245i** at 40 °C.
[e] A detailed synthetic procedure for compound **245j** was not found, therefore a yield cannot be claimed.
[f] Reaction was performed in TMBE (0.033 M) at 60 °C.

*Scheme A8.2. Total Syntheses of (–)-Isonitramine (**241**) and (+)-Sibirinine (**242**)*



APPENDIX 9

Spectra Relevant to Chapter 4:

Enantioselective Synthesis of α-Quaternary Mannich Adducts:

Total Syntheses of (–)-Isonitramine and (+)-Sibirinine

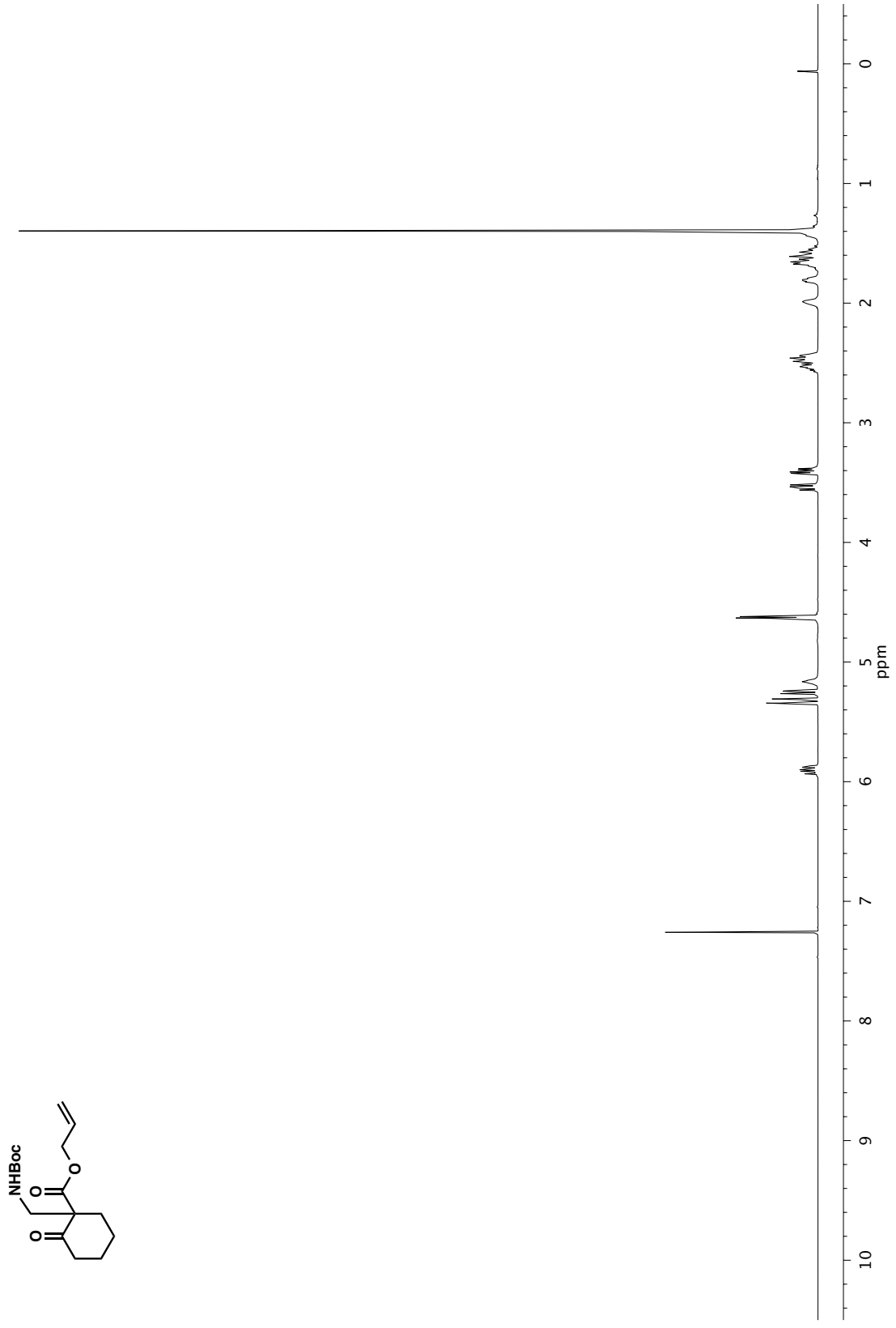


Figure A9.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **239a**.

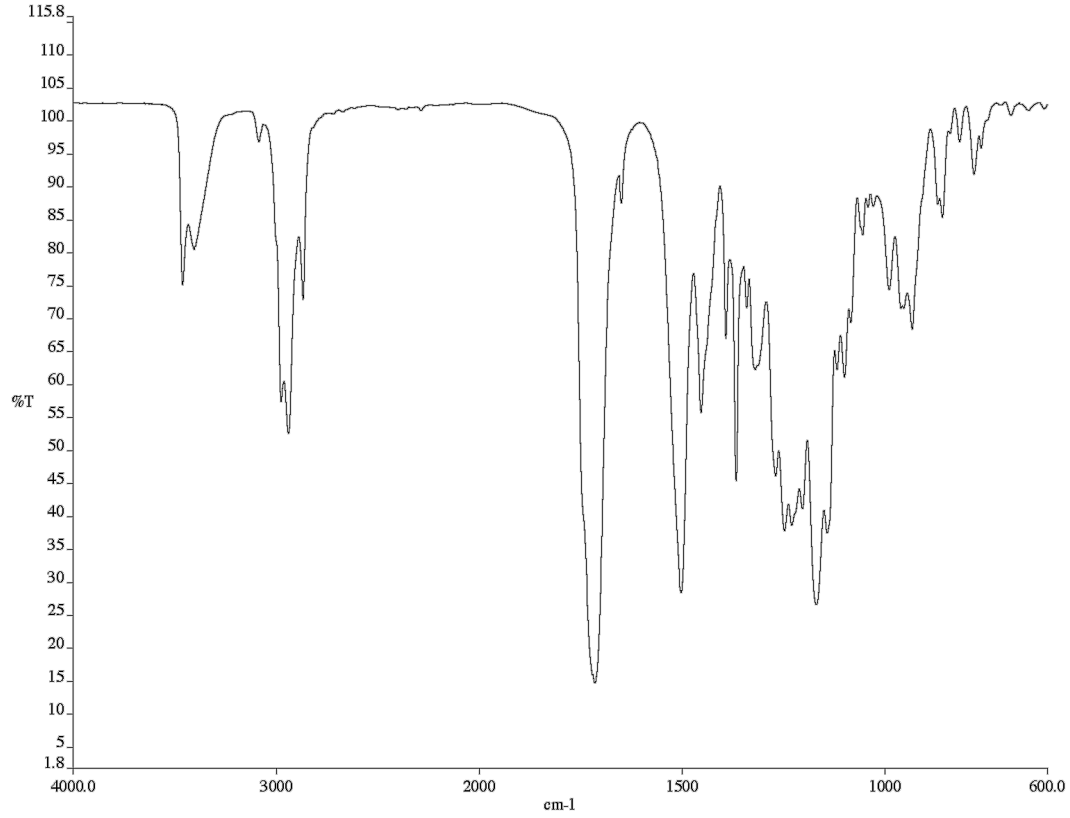


Figure A9.2. Infrared spectrum (Thin Film, NaCl) of compound **239a**.

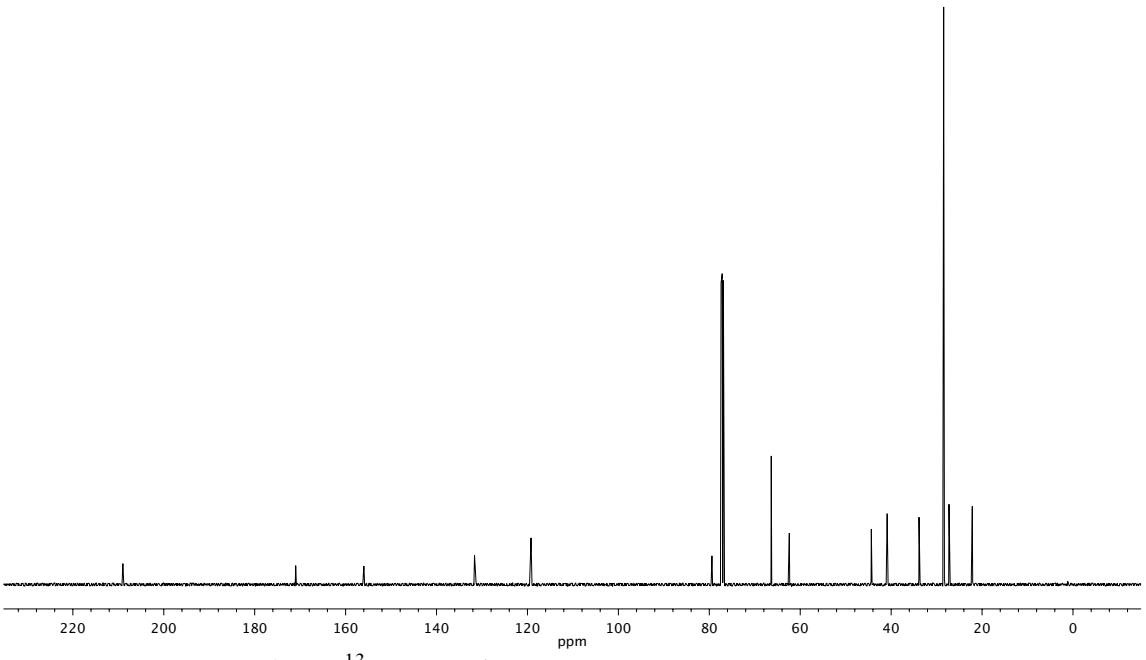


Figure A9.3. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **239a**.

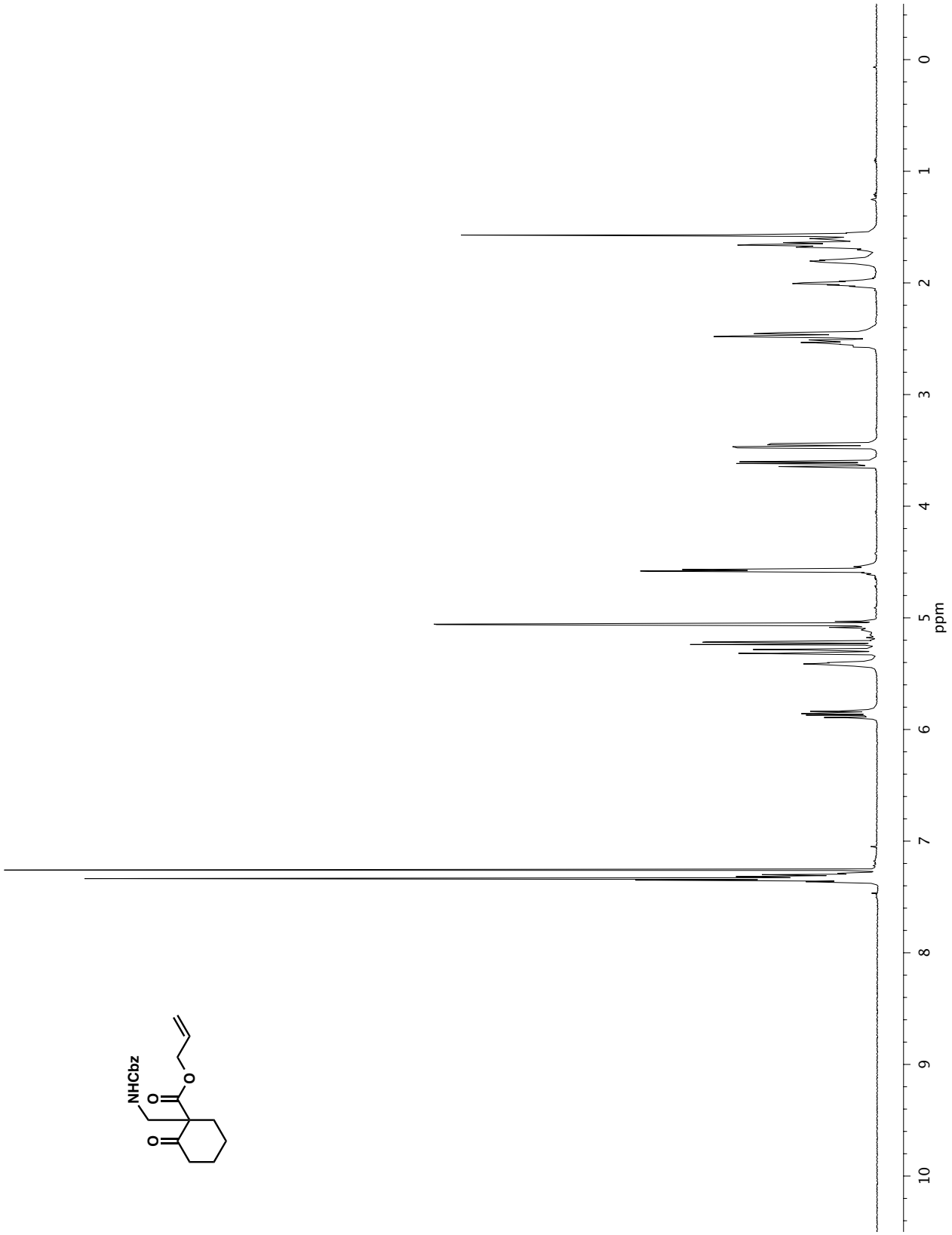


Figure A9.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **239b**.

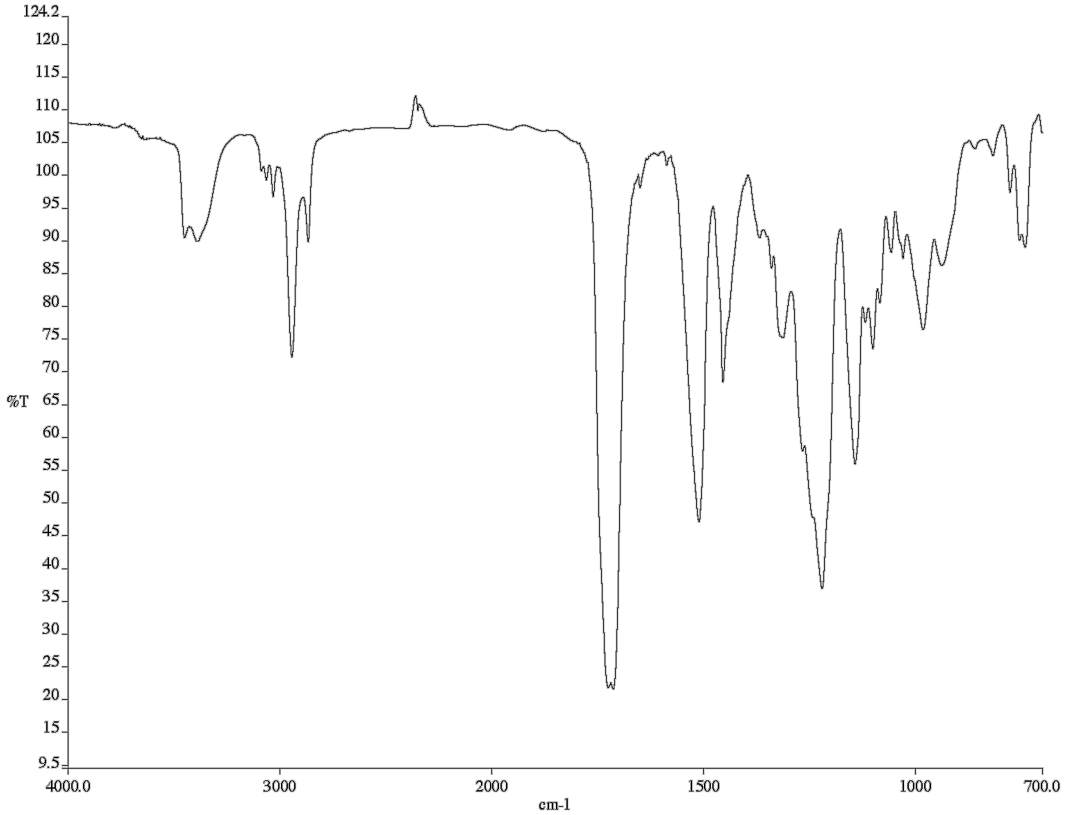


Figure A9.5. Infrared spectrum (Thin Film, NaCl) of compound **239b**.

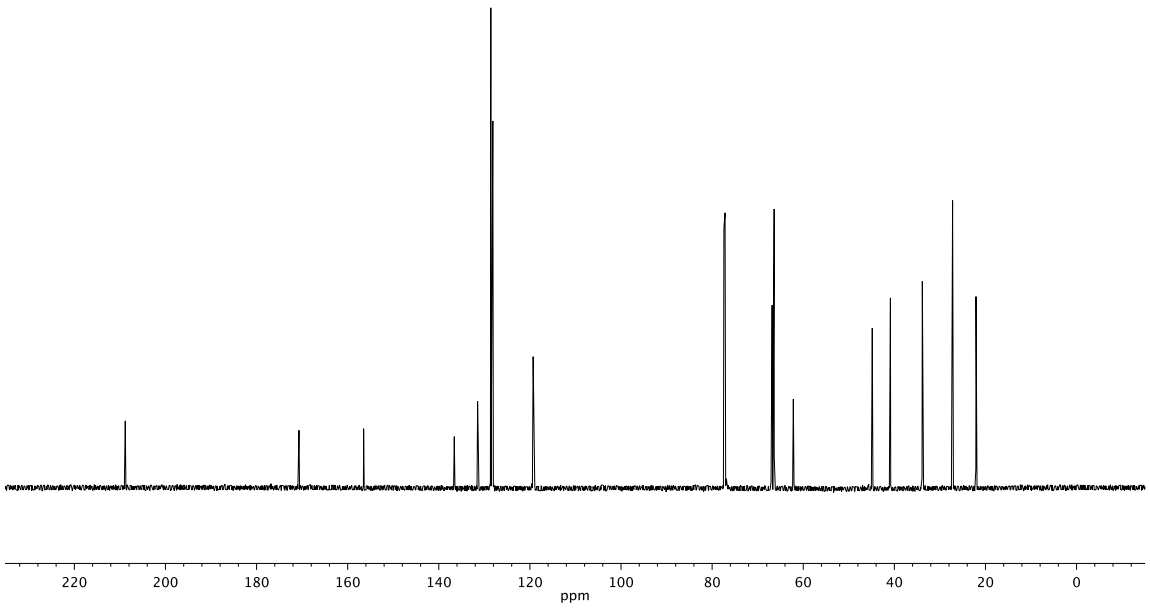


Figure A9.6. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **239b**.

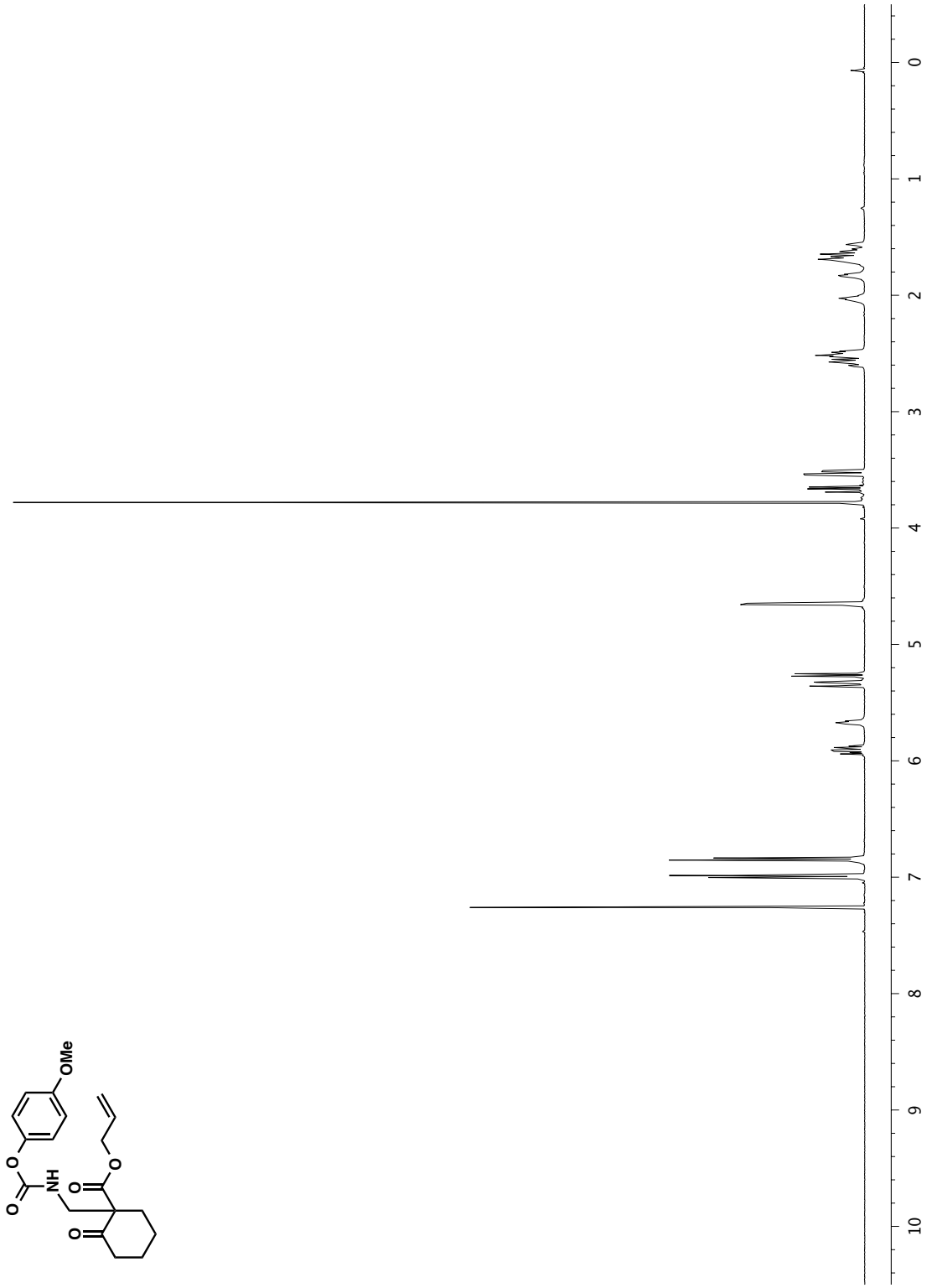


Figure A9.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **239c**.

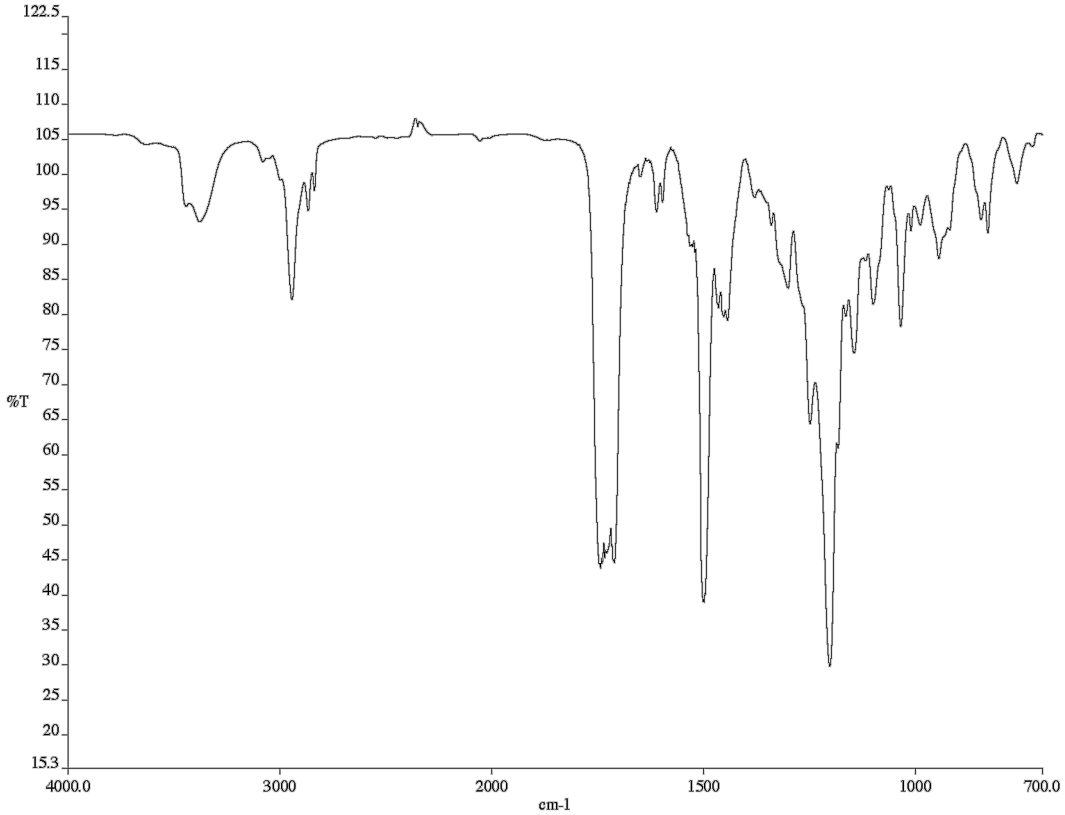


Figure A9.8. Infrared spectrum (Thin Film, NaCl) of compound **239c**.

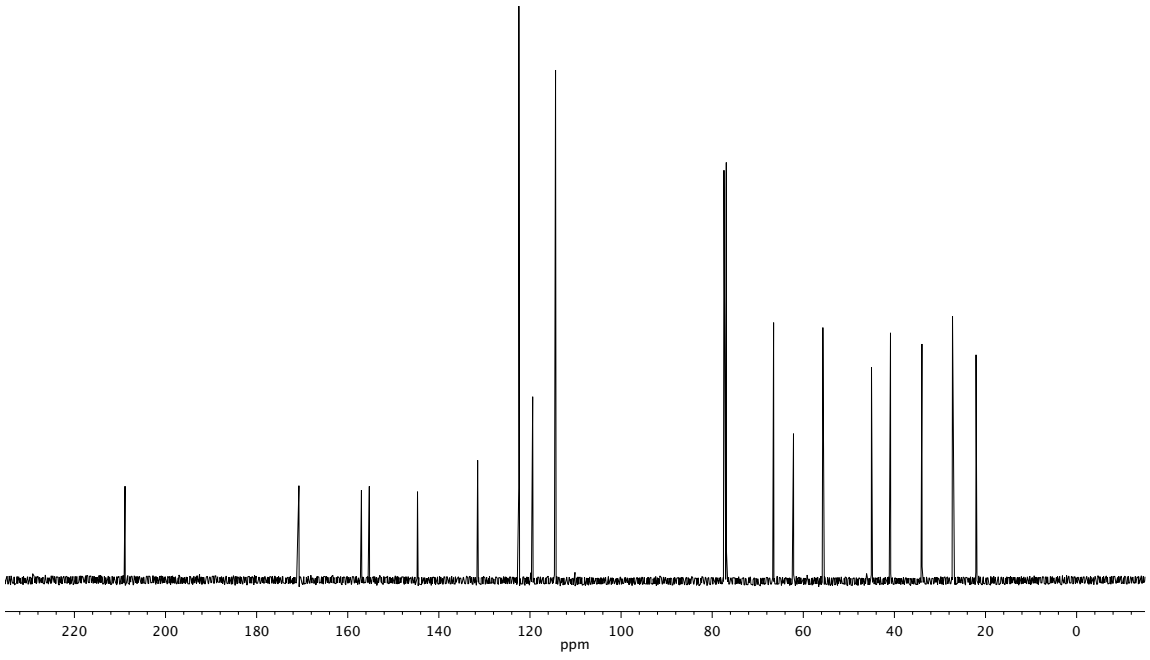


Figure A9.9. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **239c**.

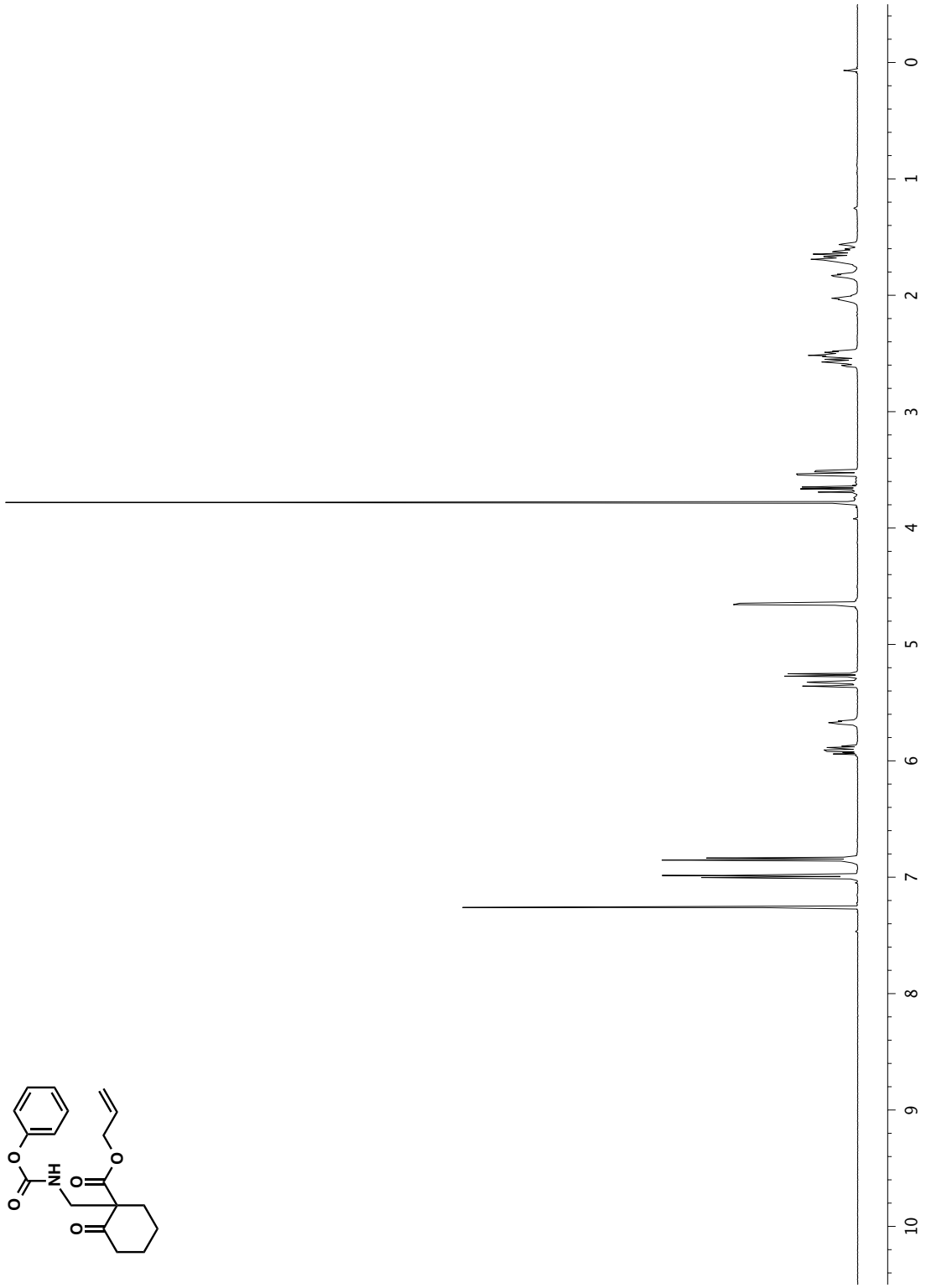


Figure A9.10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **239d**.

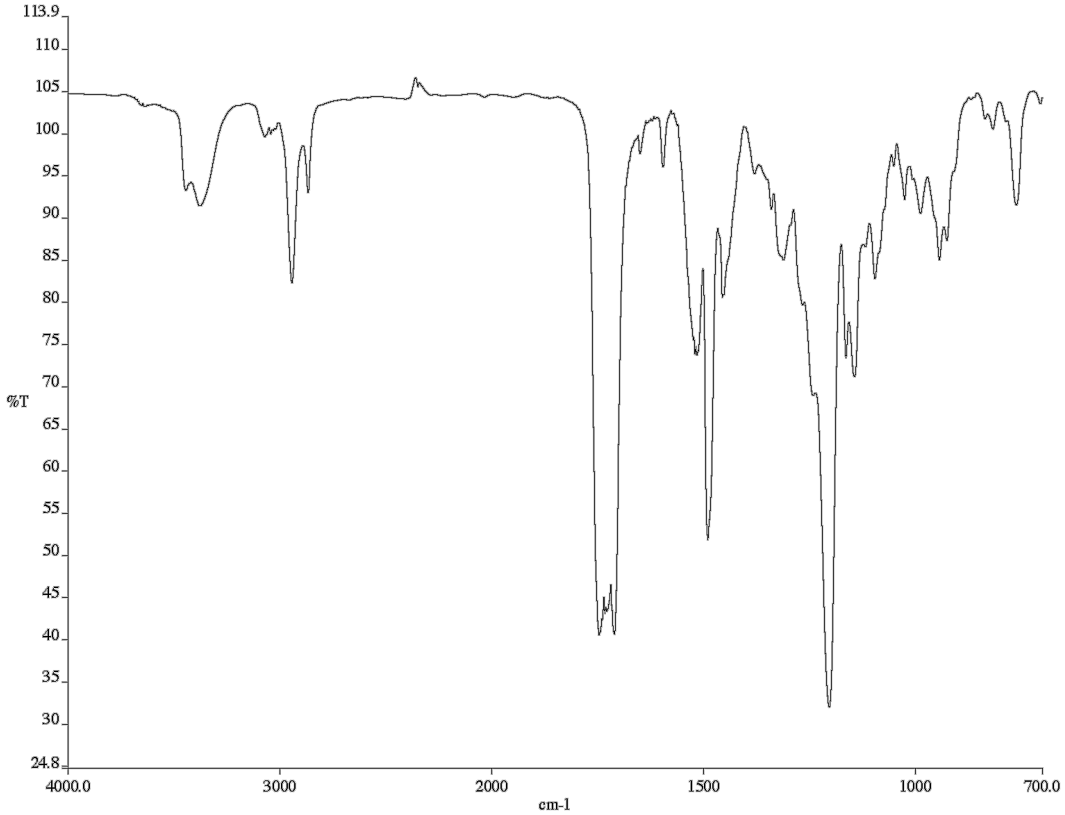


Figure A9.11. Infrared spectrum (Thin Film, NaCl) of compound **239d**.

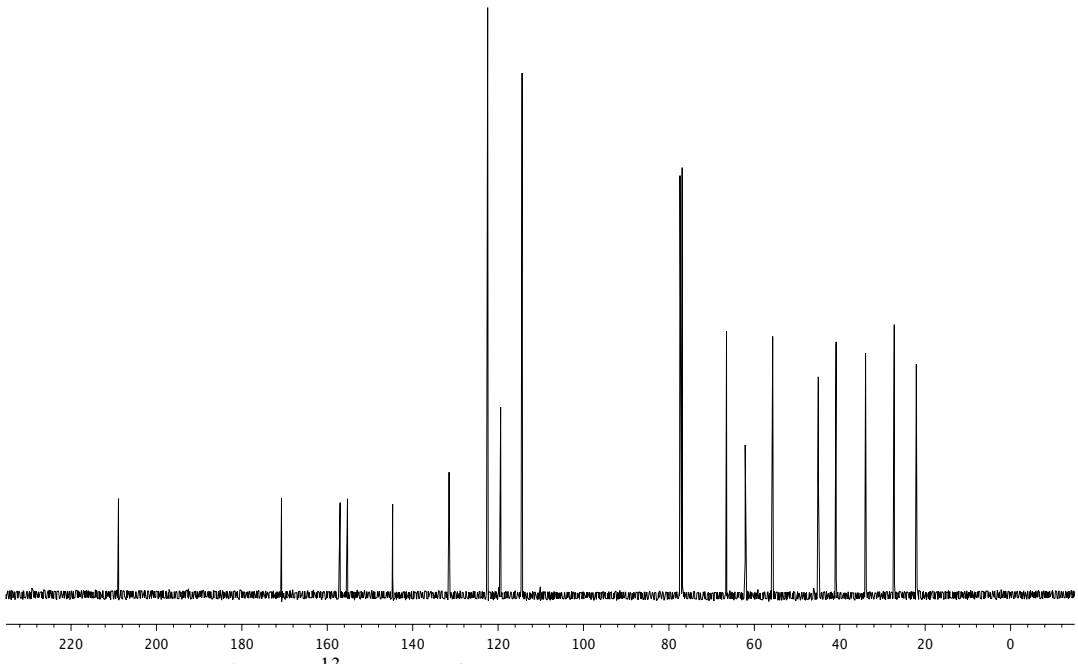


Figure A9.12. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **239d**.

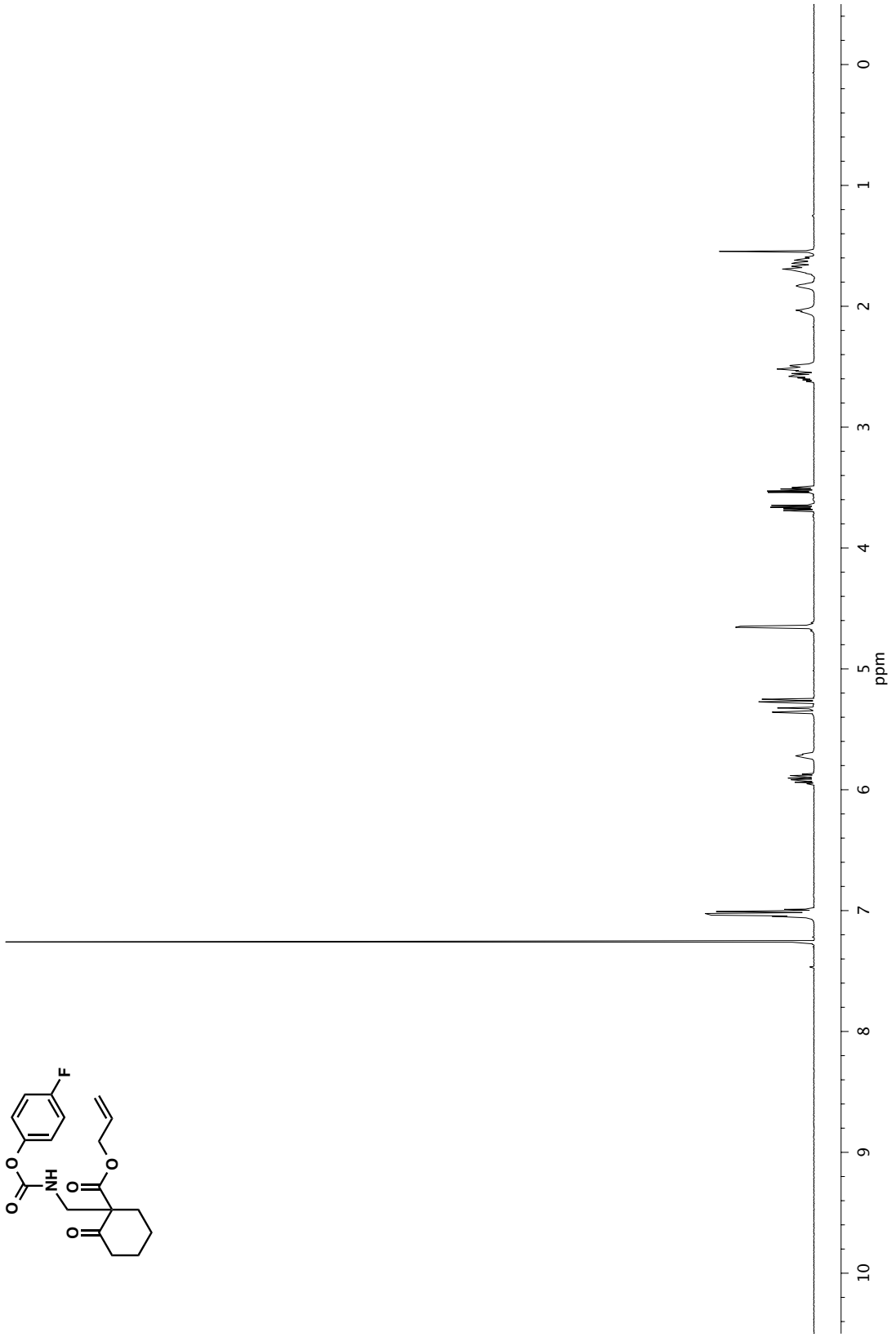


Figure A9.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **239e**.

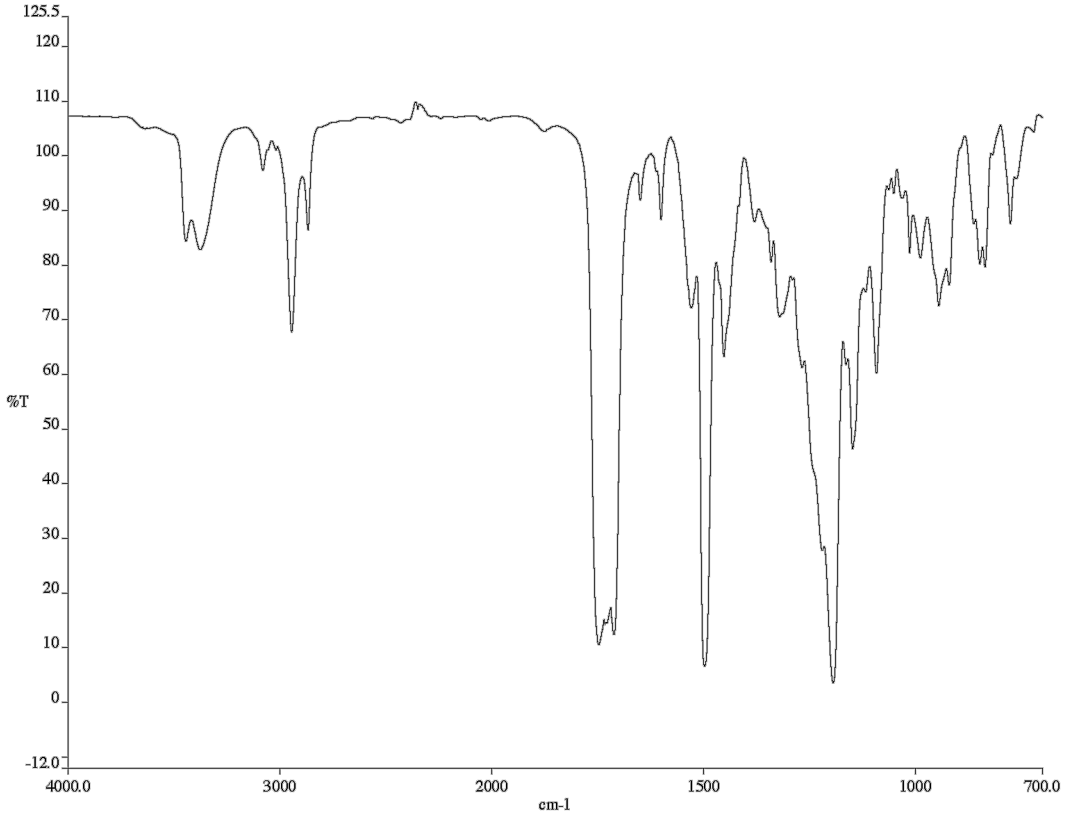


Figure A9.14. Infrared spectrum (Thin Film, NaCl) of compound **239e**.

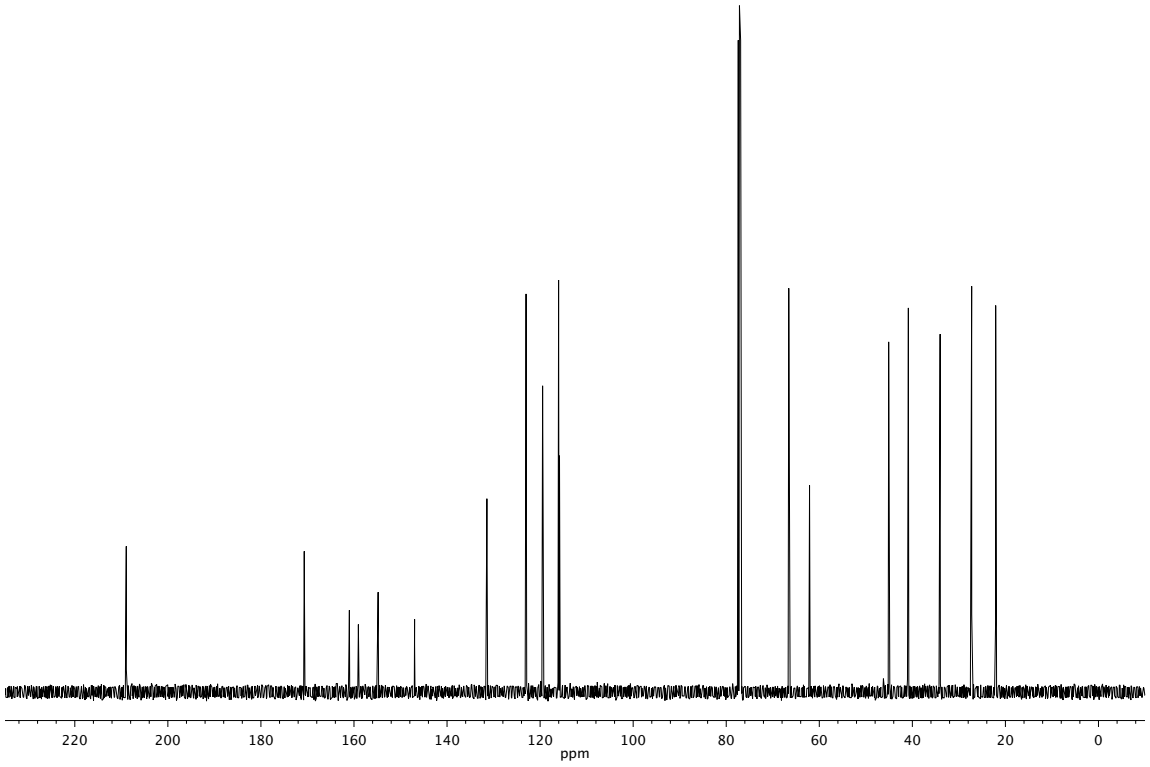


Figure A9.15. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **239e**.

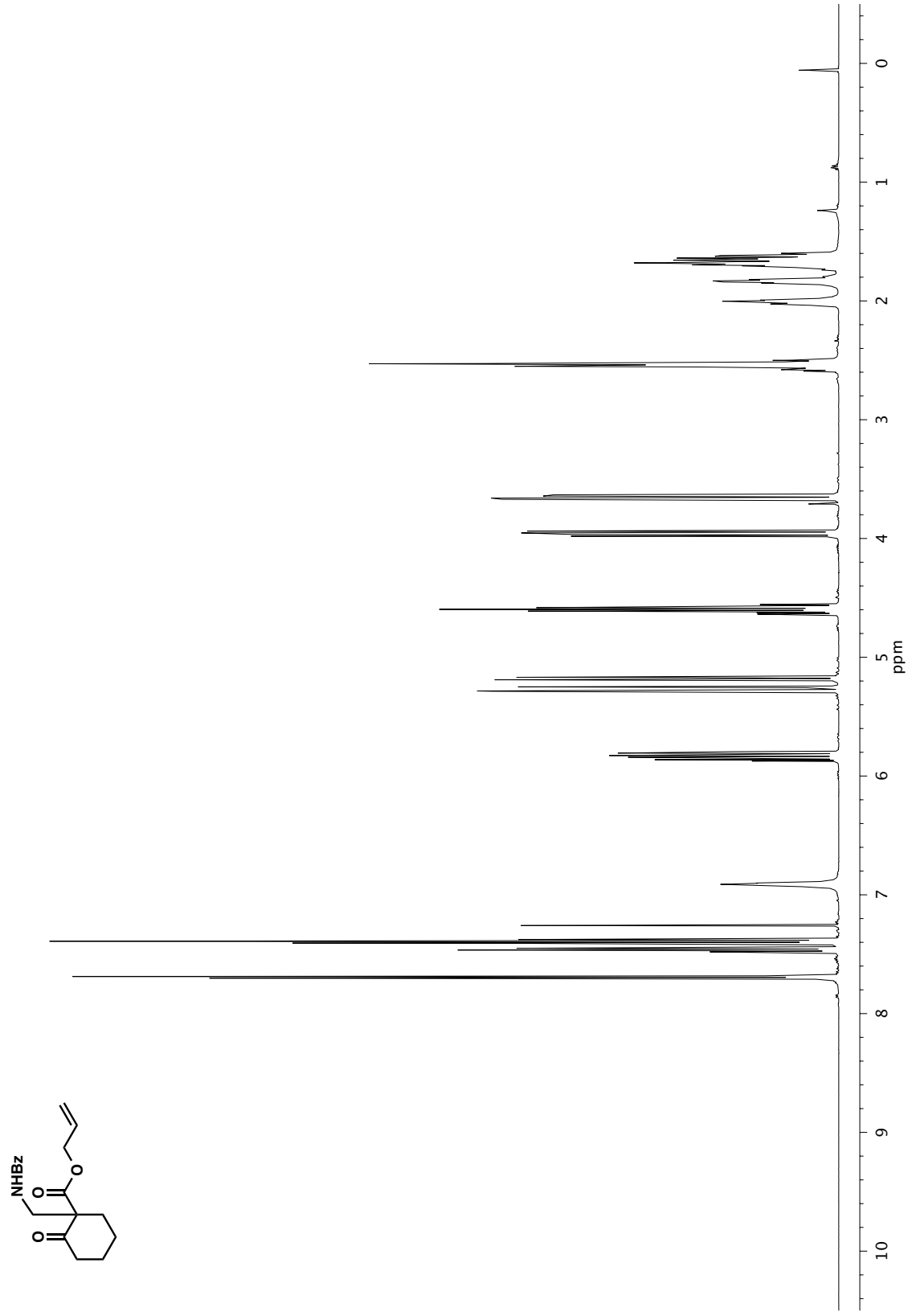


Figure A9.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **239f**.

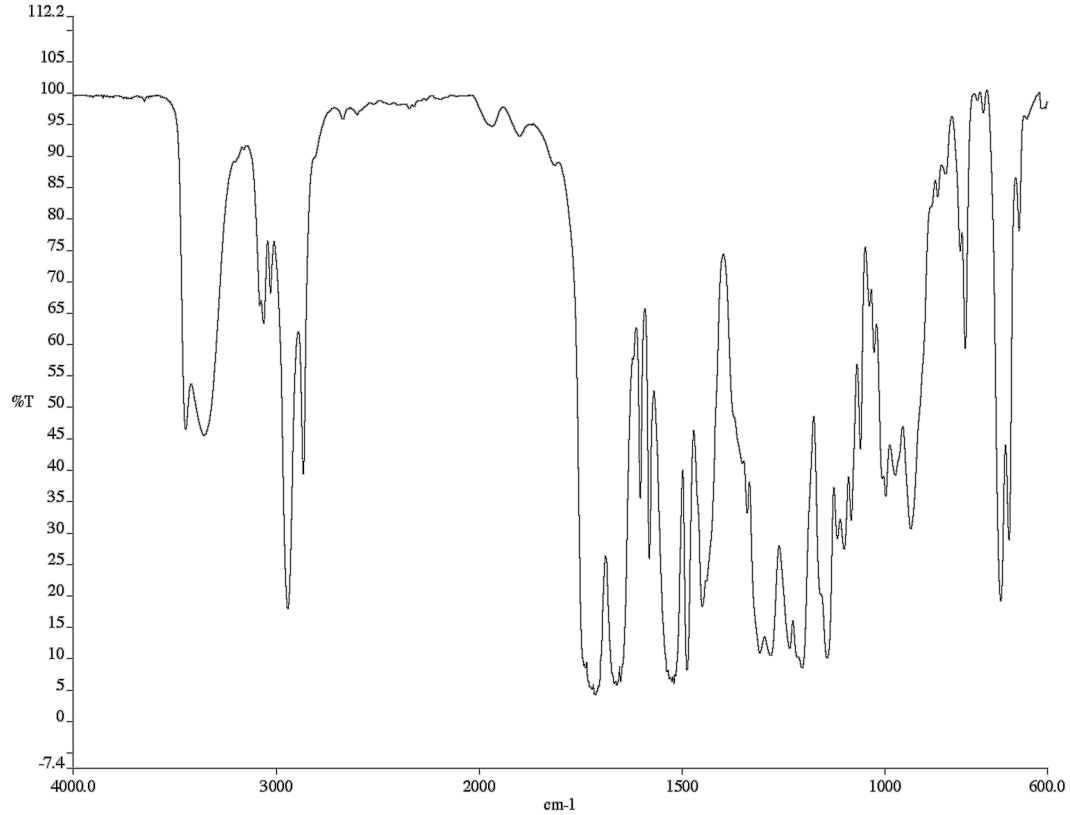


Figure A9.17. Infrared spectrum (Thin Film, NaCl) of compound **239f**.

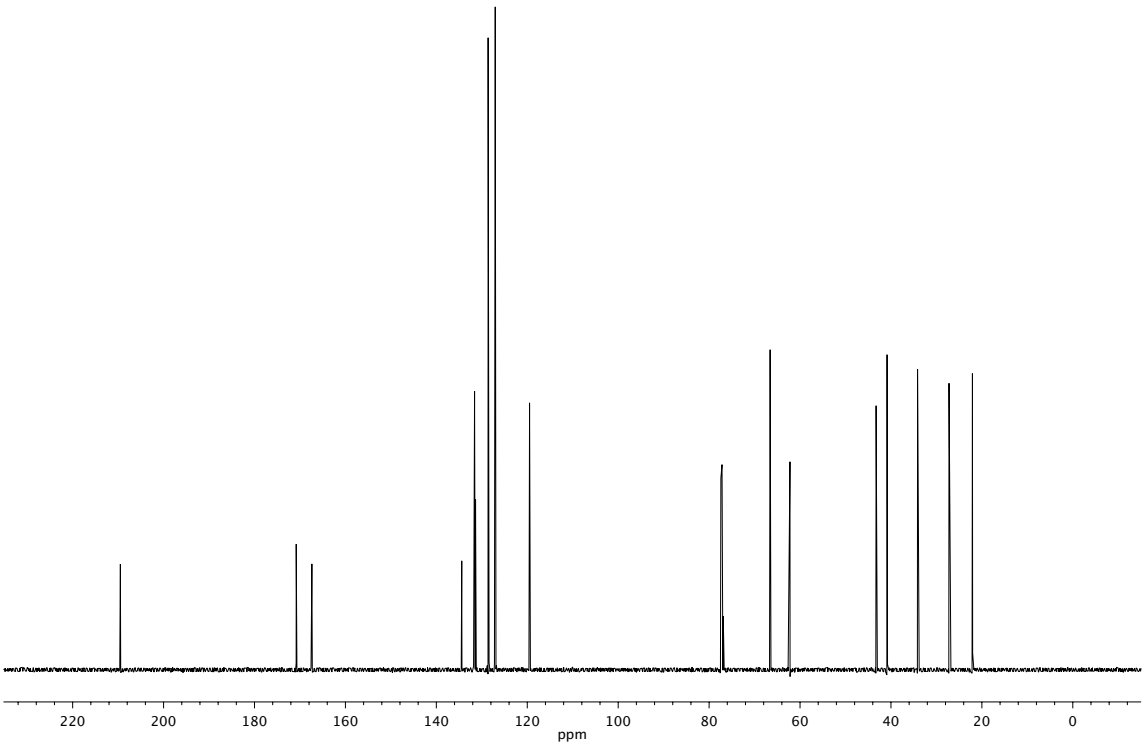


Figure A9.18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **239f**.

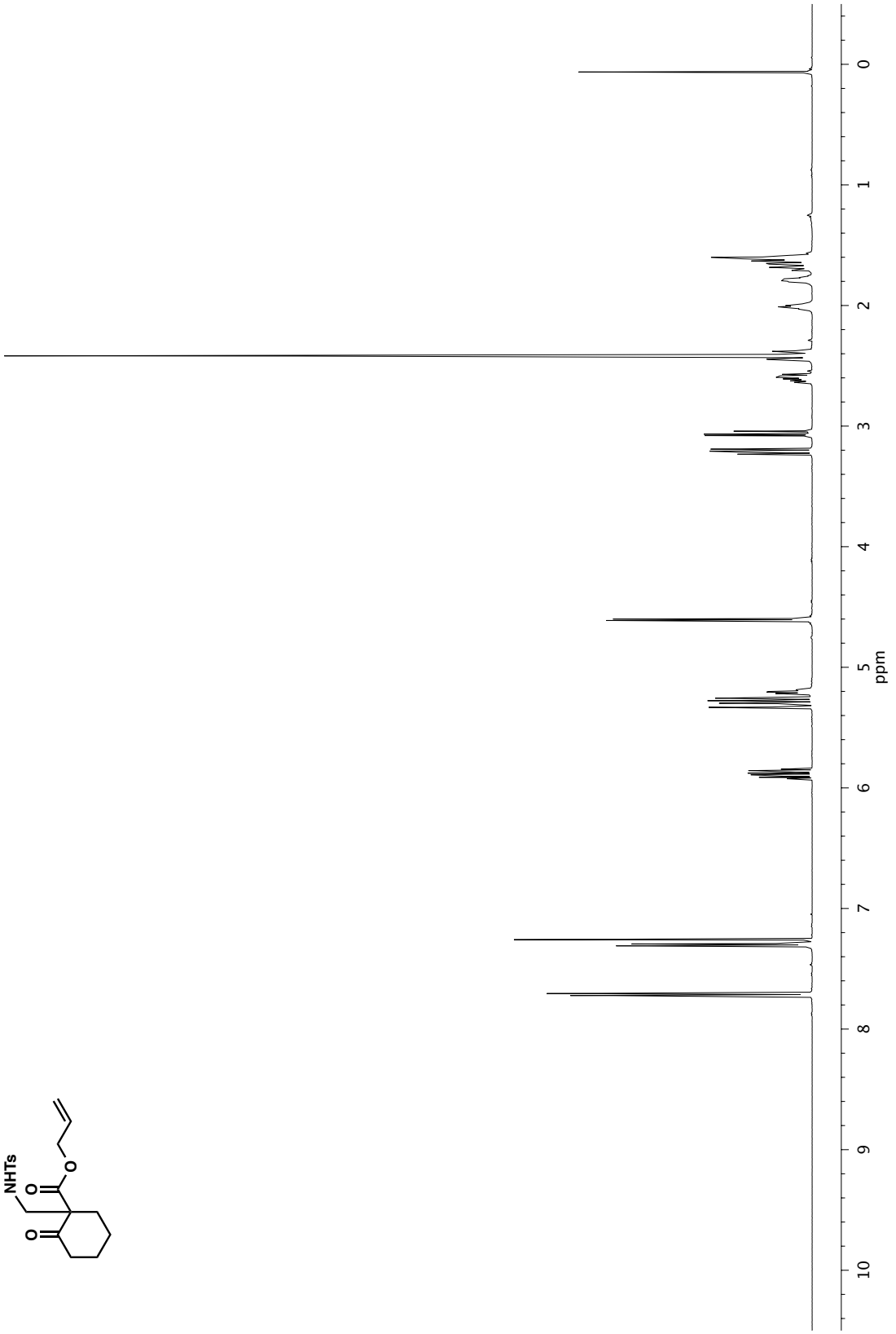


Figure A9.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **239g**.

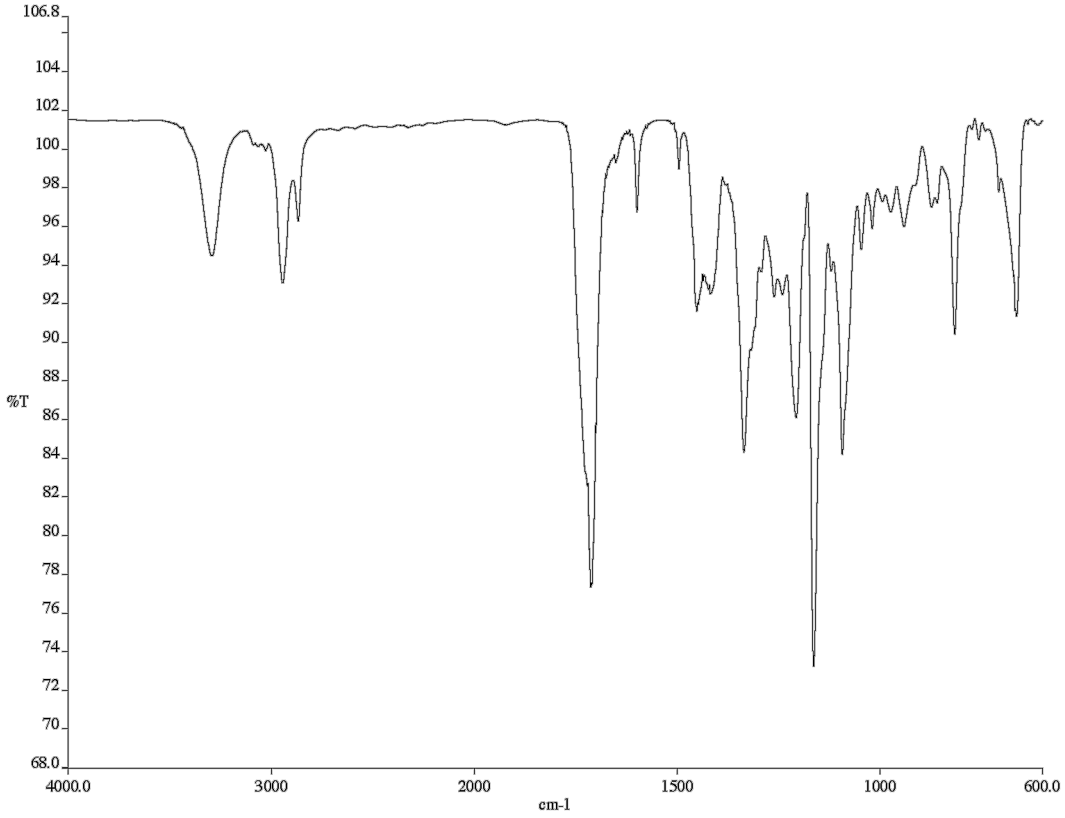


Figure A9.20. Infrared spectrum (Thin Film, NaCl) of compound **239g**.

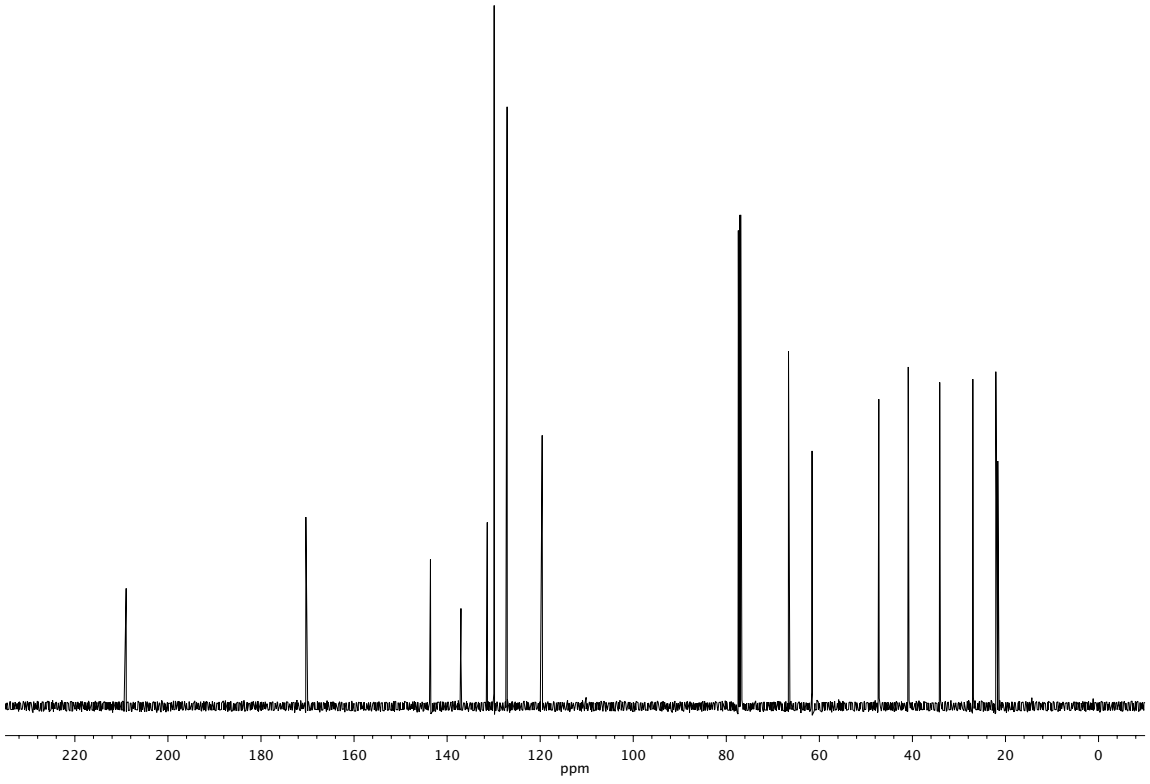


Figure A9.21. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **239g**.

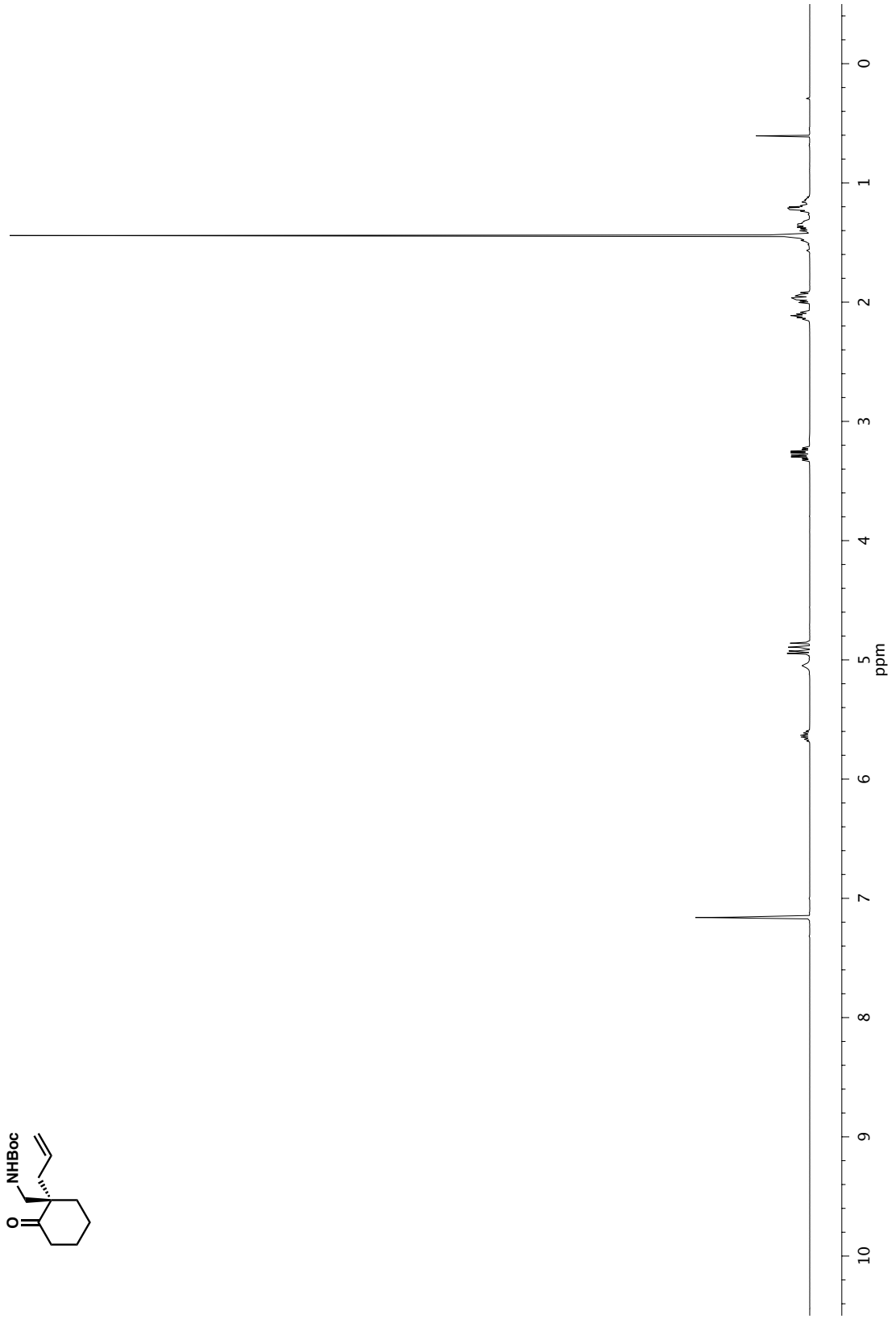


Figure A9.22. ^{1}H NMR (400 MHz, C_6D_6) of compound **240a**.

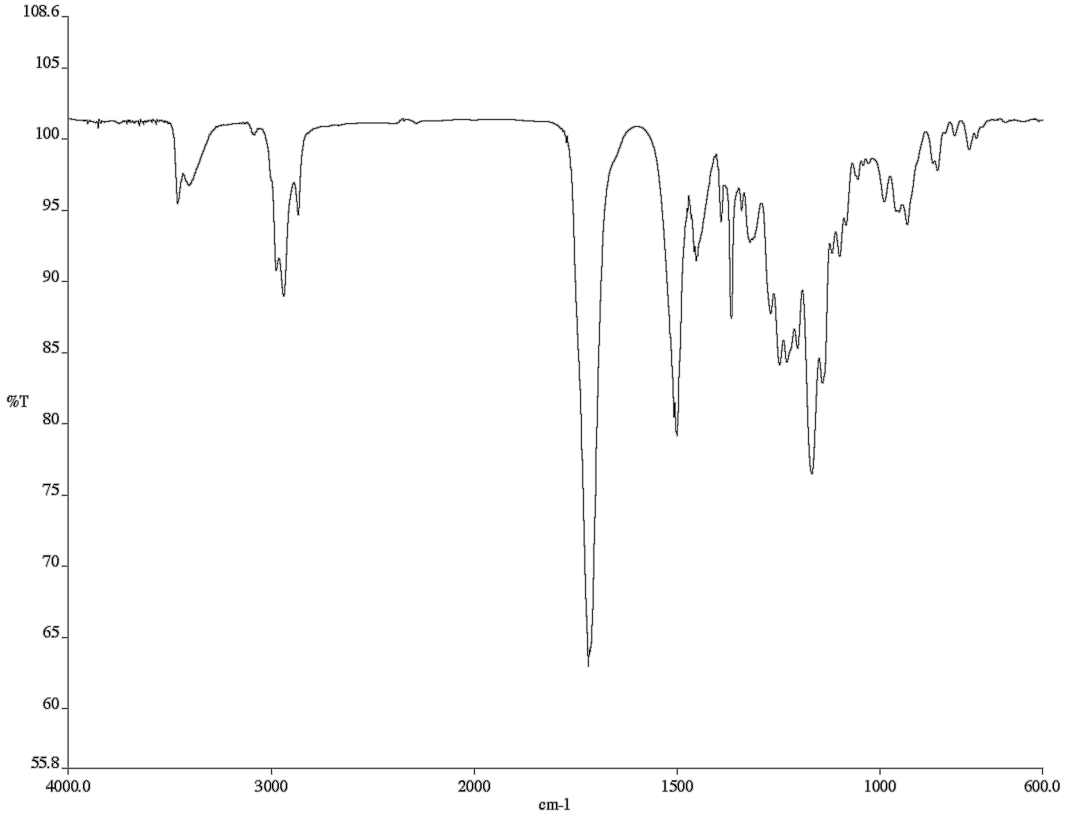


Figure A9.23. Infrared spectrum (Thin Film, NaCl) of compound **240a**.

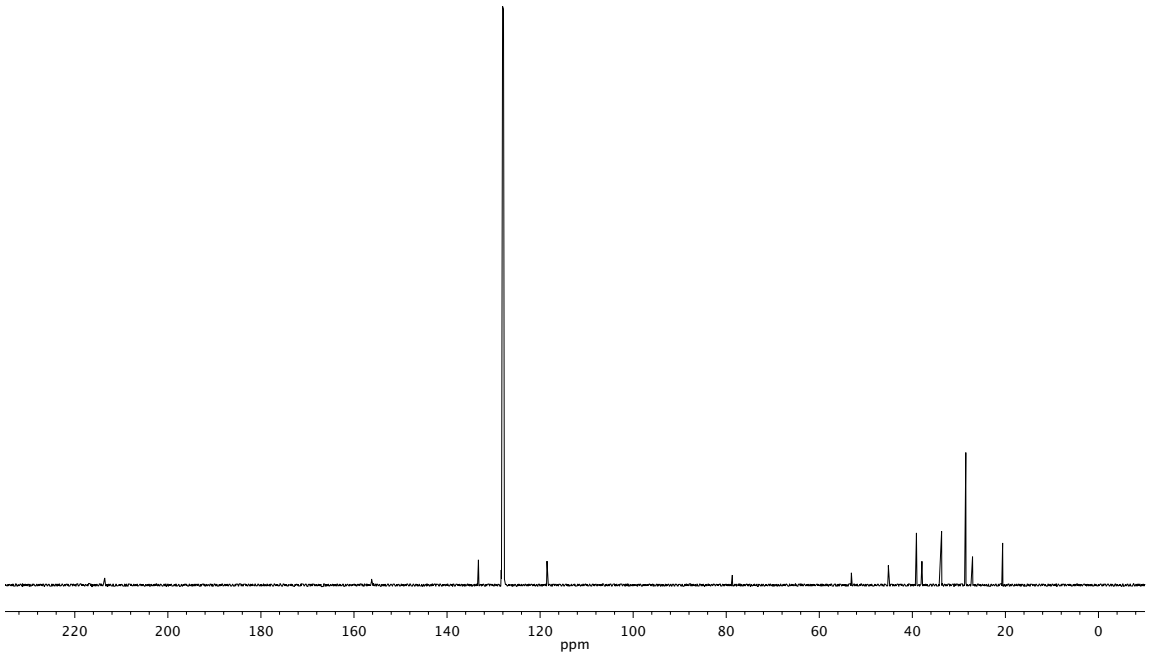


Figure A9.24. ^{13}C NMR (101 MHz, C_6D_6) of compound **240a**.

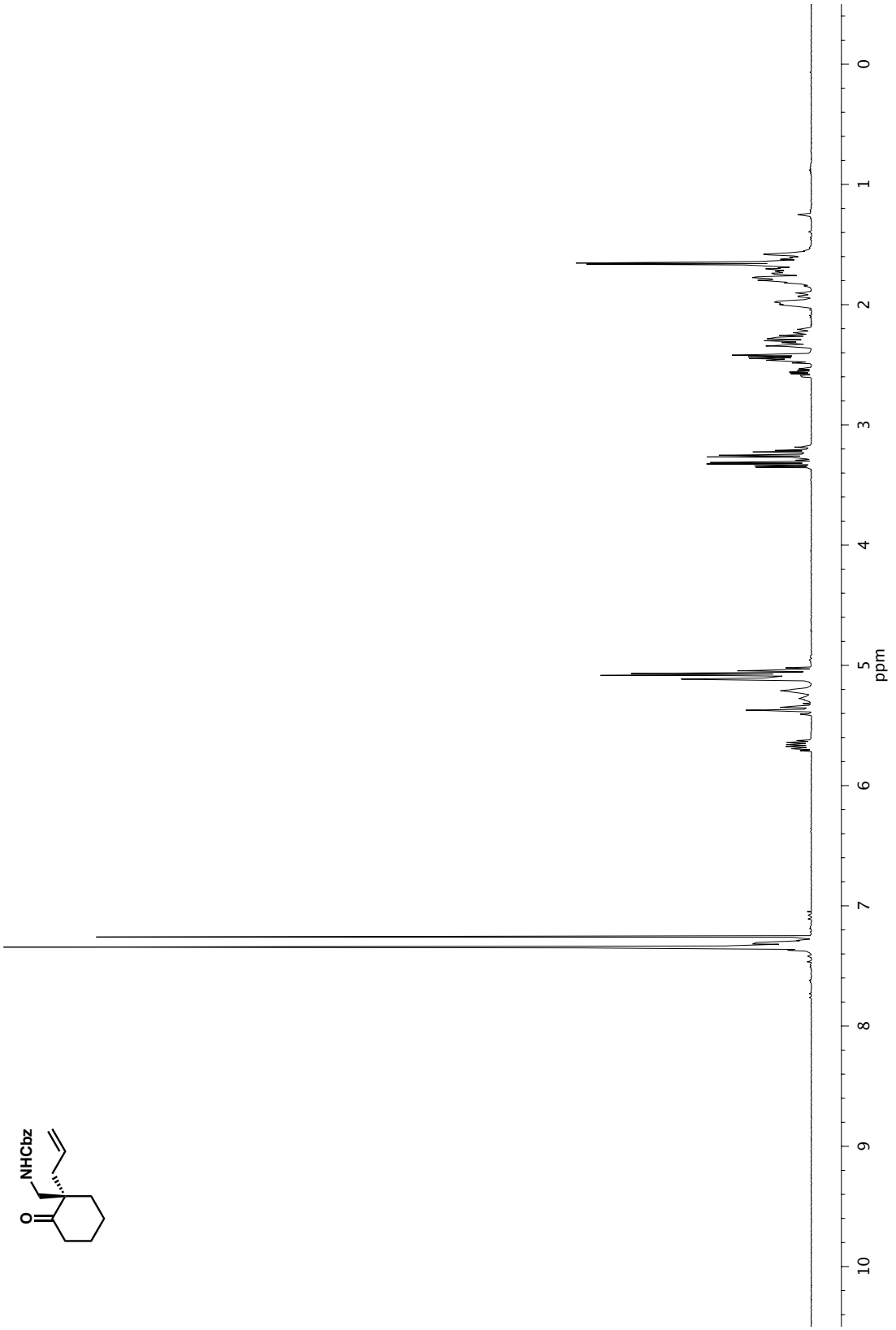


Figure A9.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **240b**.

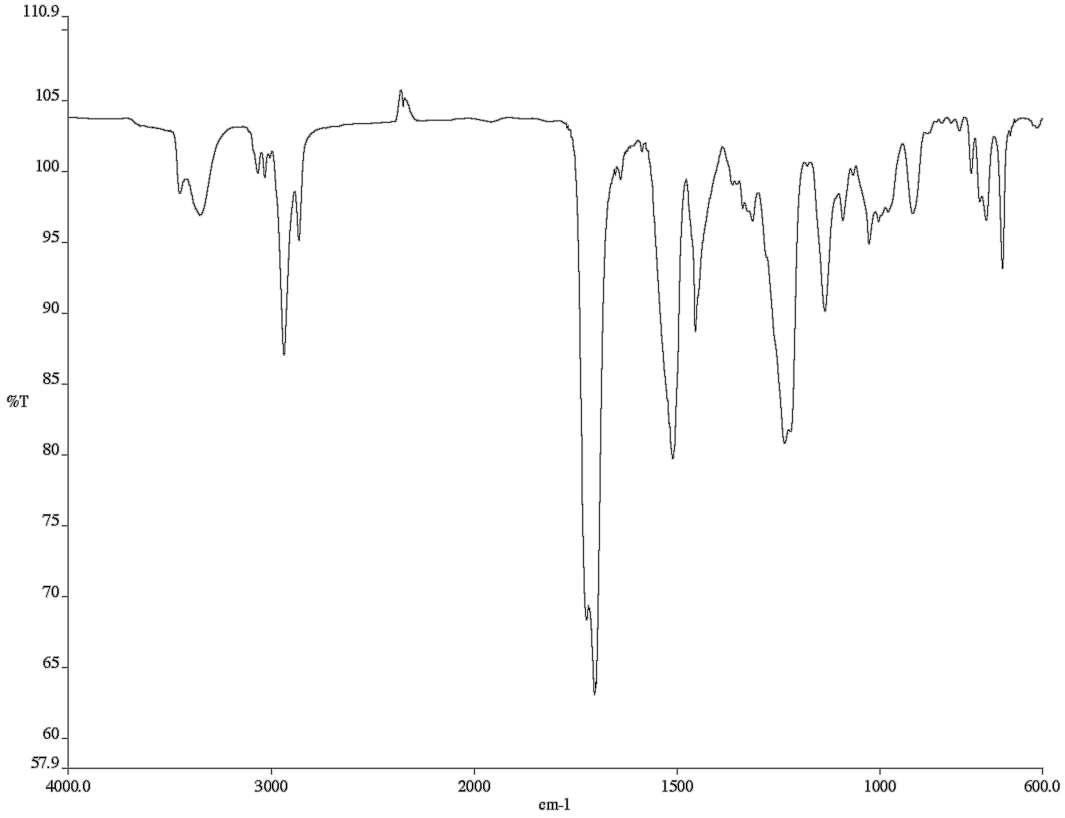


Figure A9.26. Infrared spectrum (Thin Film, NaCl) of compound **240b**.

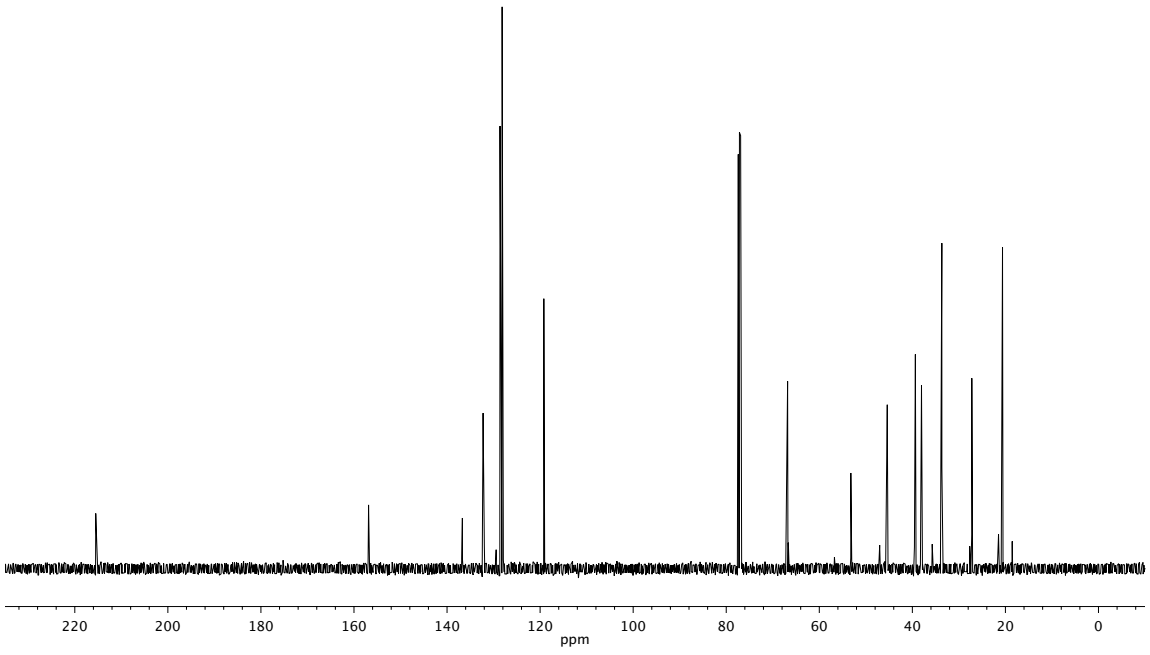


Figure A9.27. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **240b**.

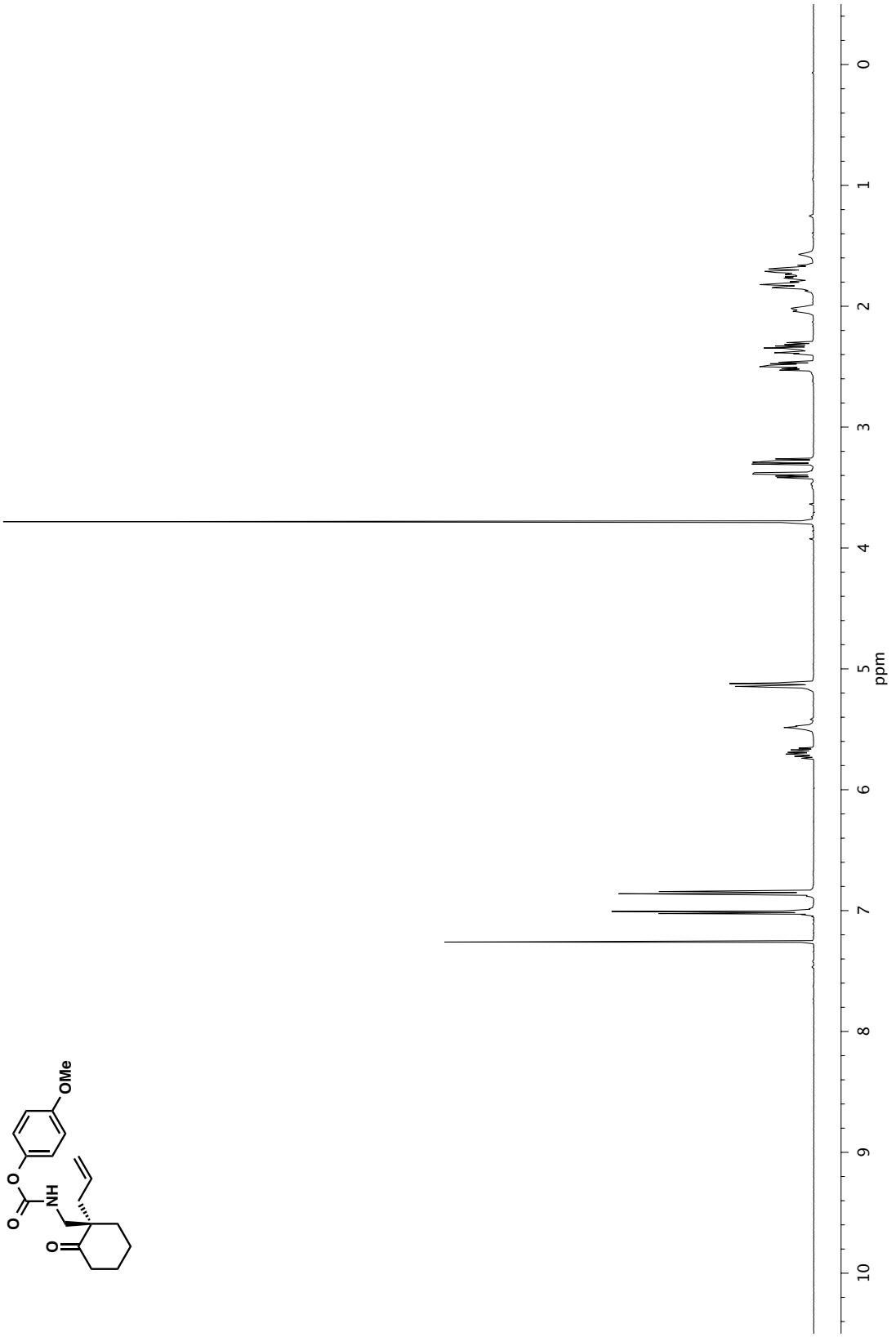


Figure A9.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **240c**.

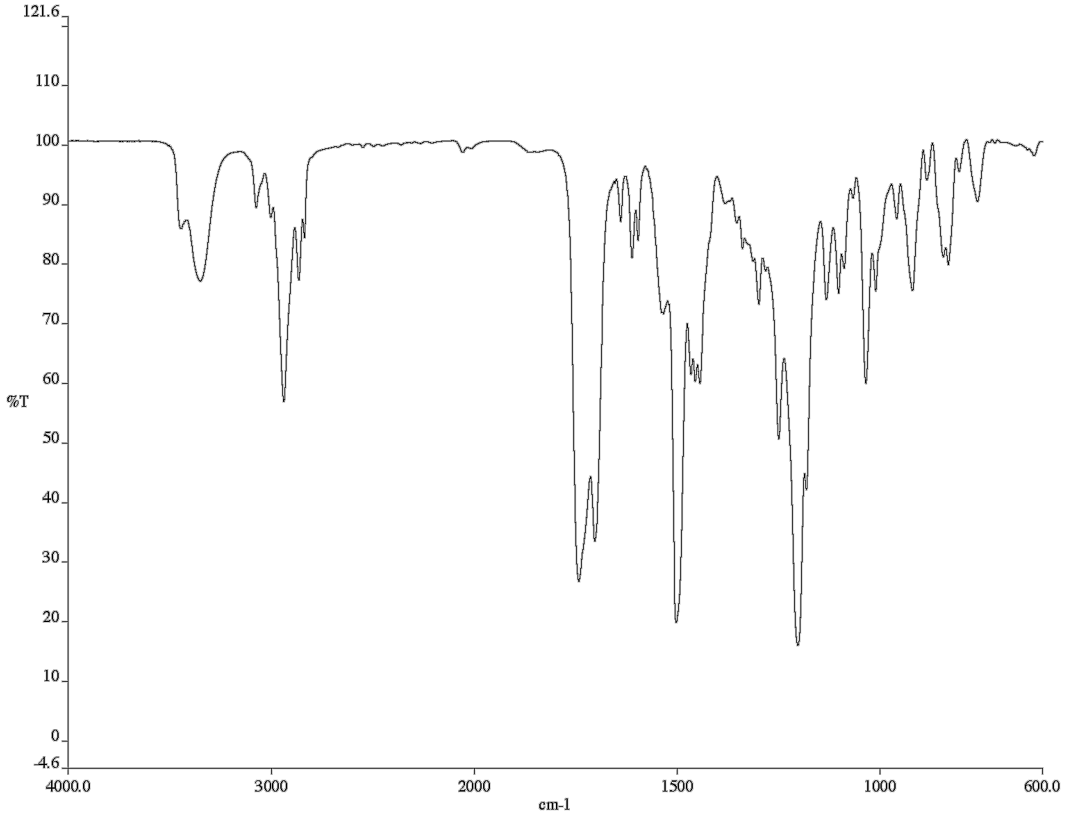


Figure A9.29. Infrared spectrum (Thin Film, NaCl) of compound **240c**.

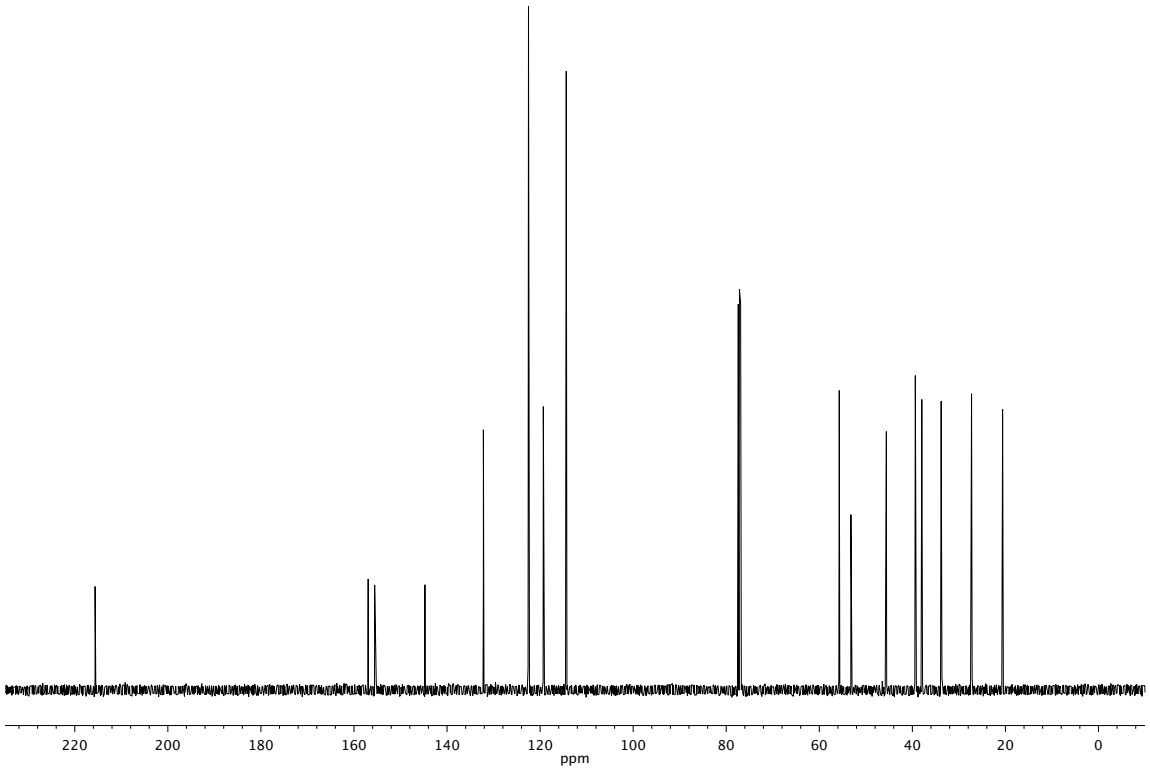


Figure A9.30. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **240c**.

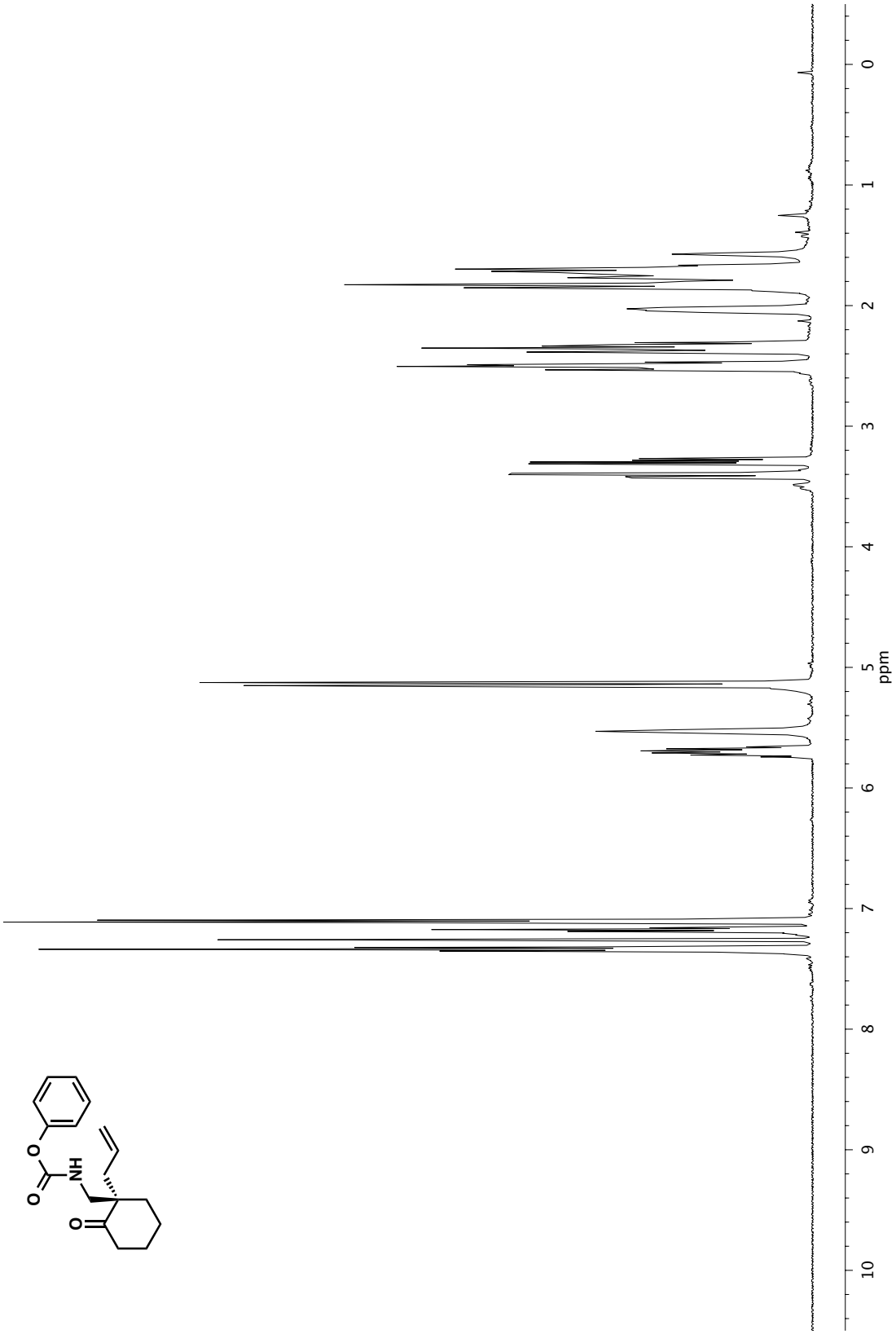


Figure A9.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **240d**.

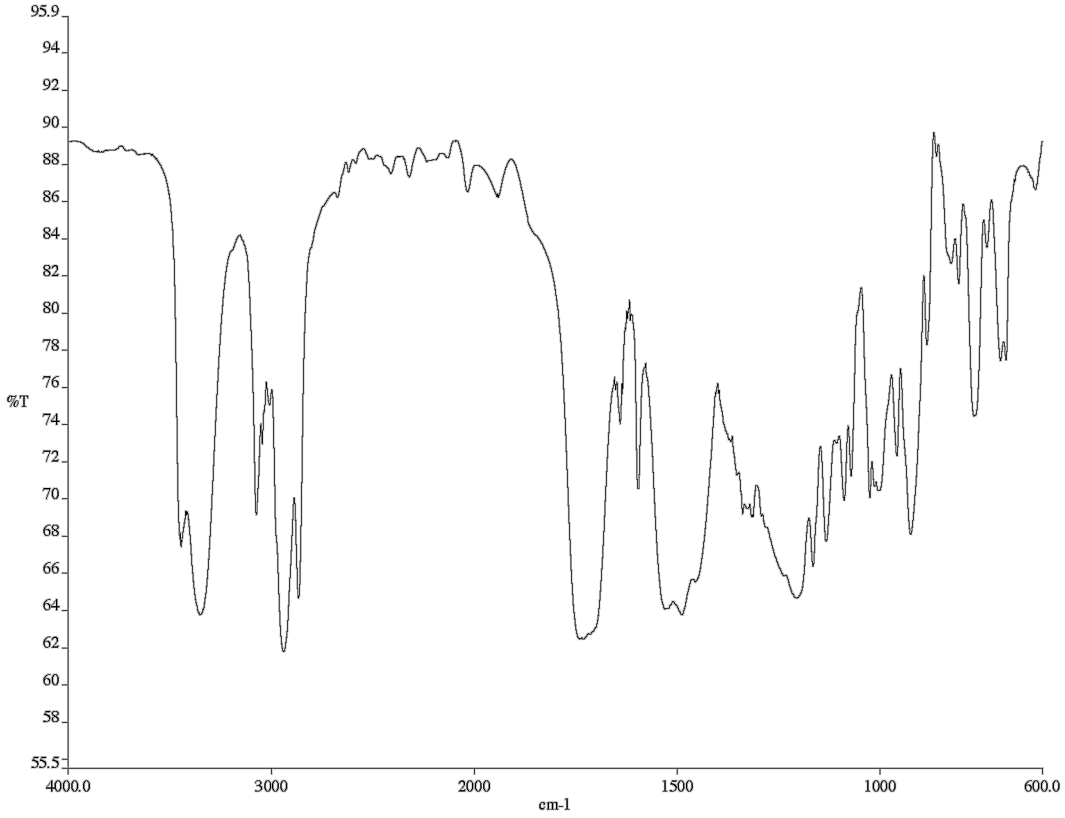


Figure A9.32. Infrared spectrum (Thin Film, NaCl) of compound **240d**.

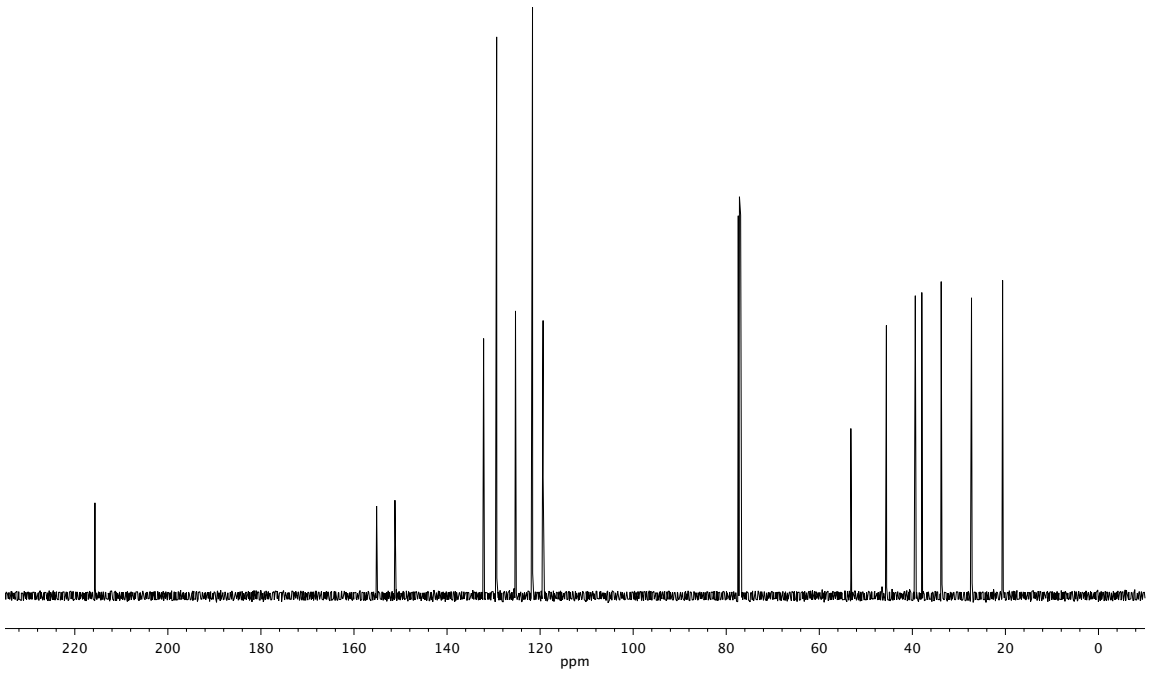


Figure A9.33. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **240d**.

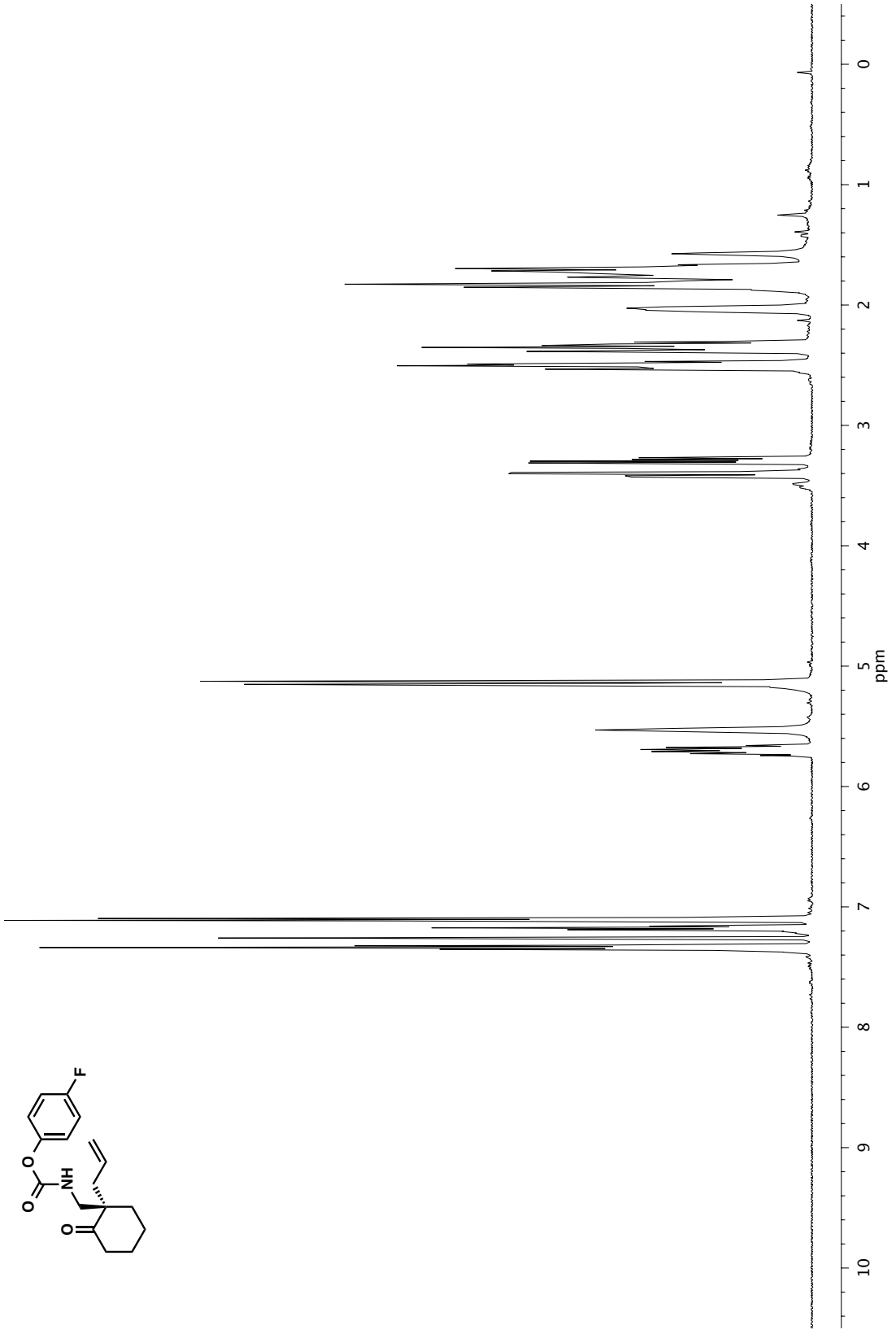


Figure A9.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **240e**.

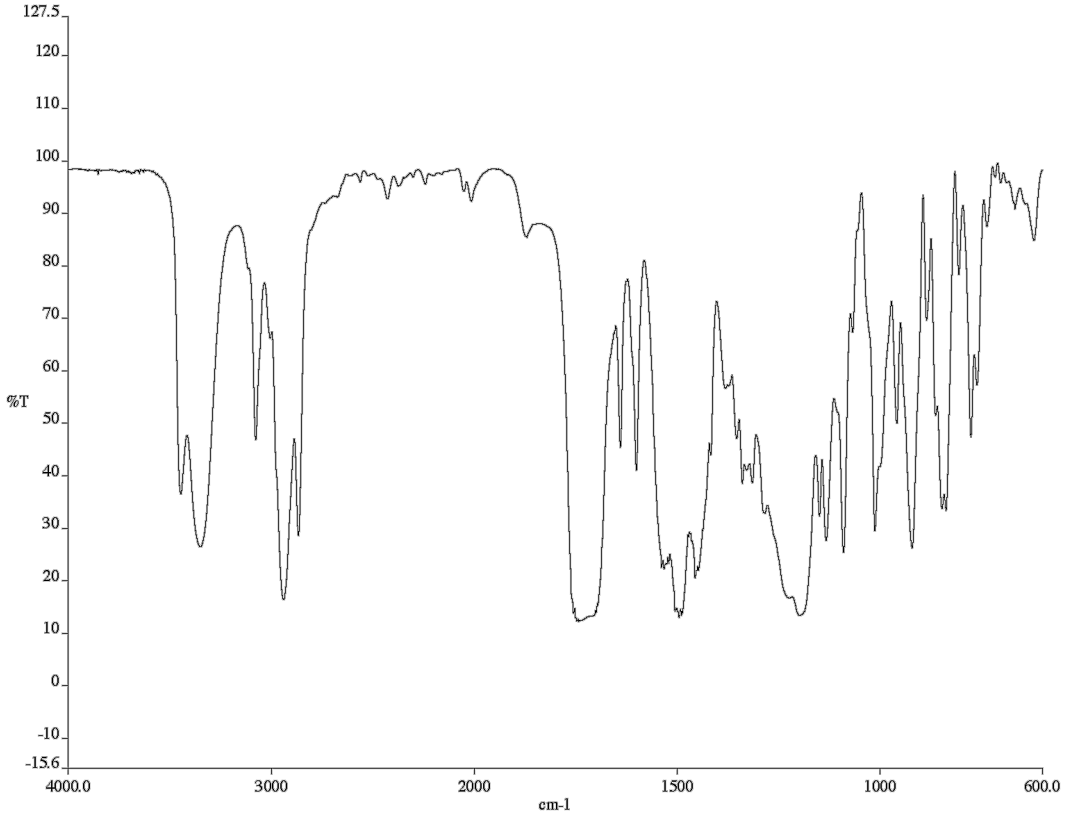


Figure A9.35. Infrared spectrum (Thin Film, NaCl) of compound **240e**.

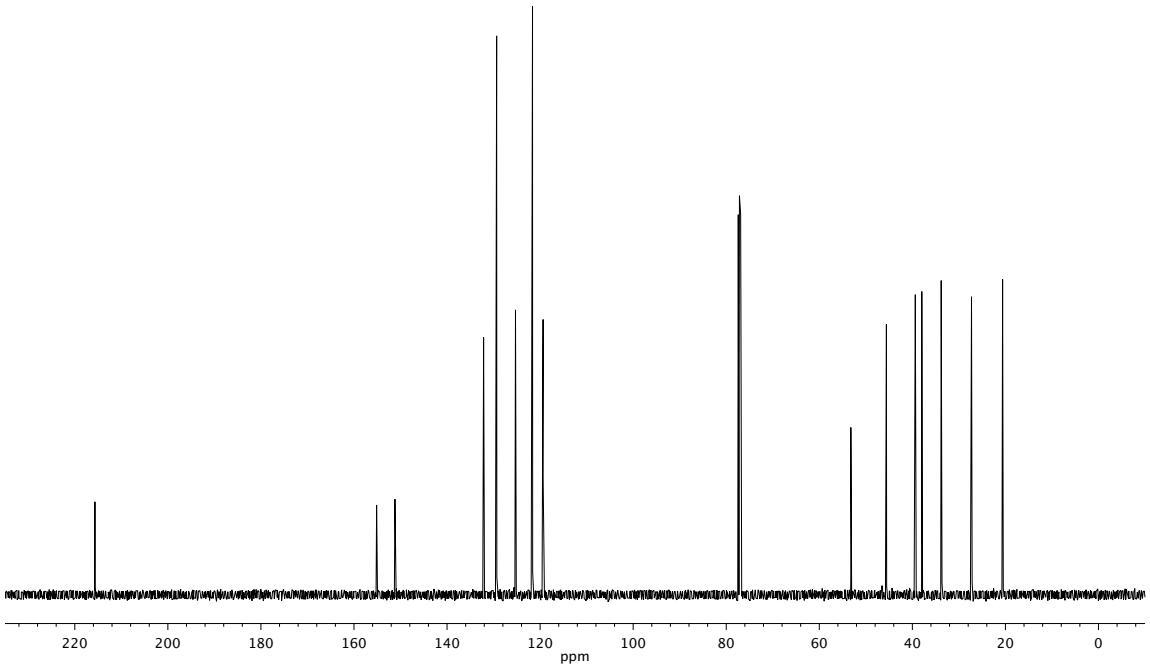


Figure A9.36. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **240e**.

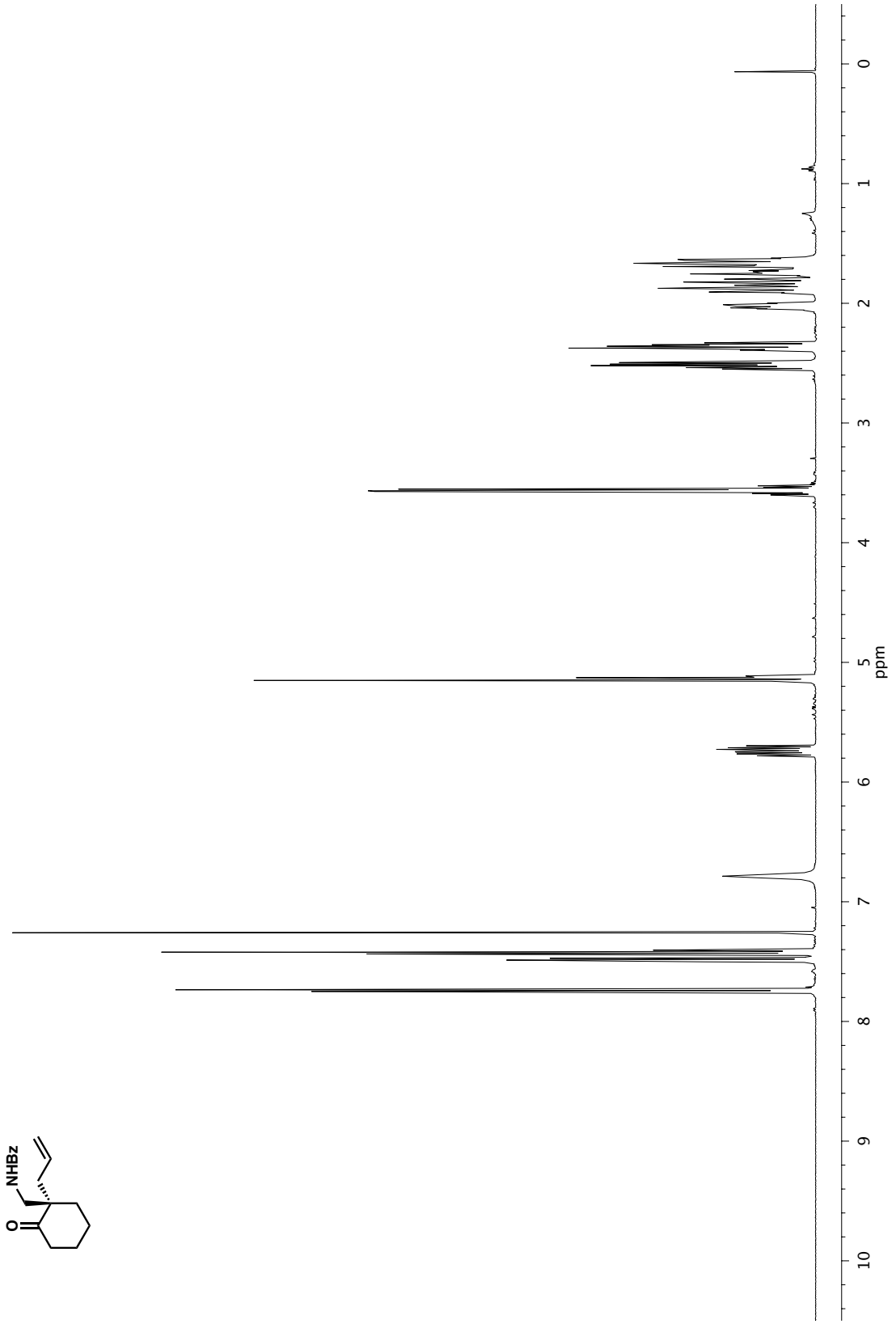


Figure A9.37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **240f**.

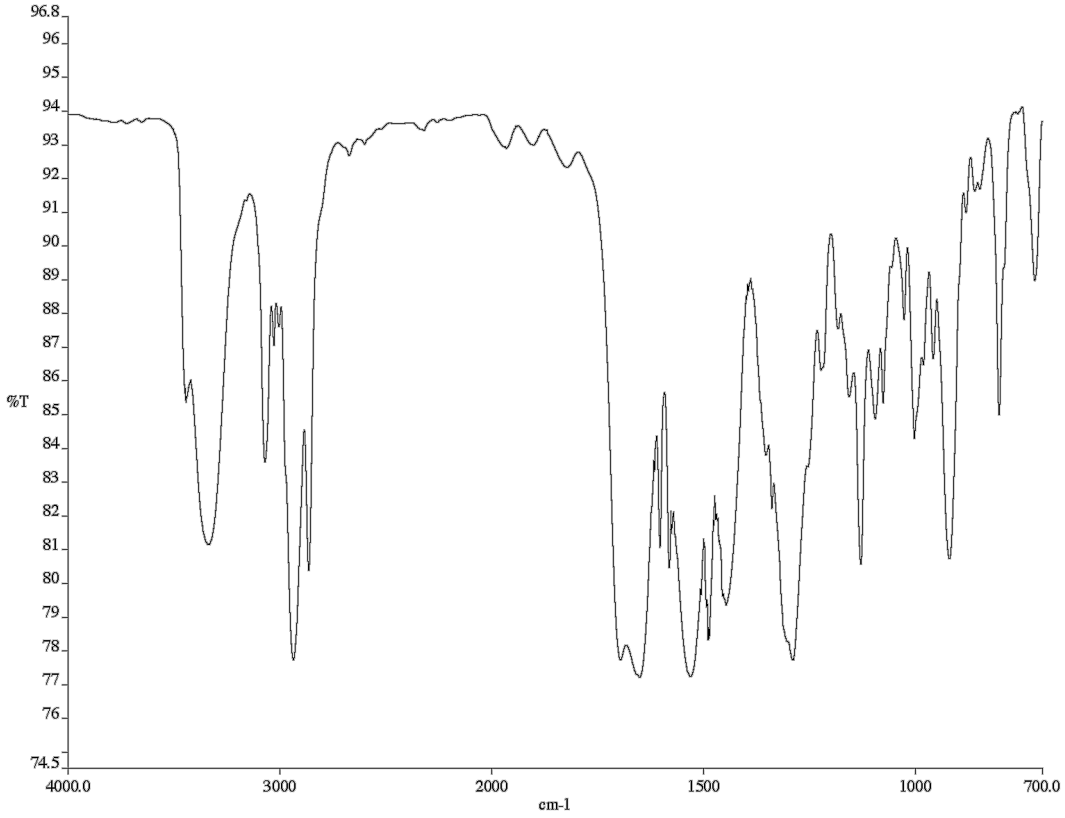


Figure A9.38. Infrared spectrum (Thin Film, NaCl) of compound **240f**.

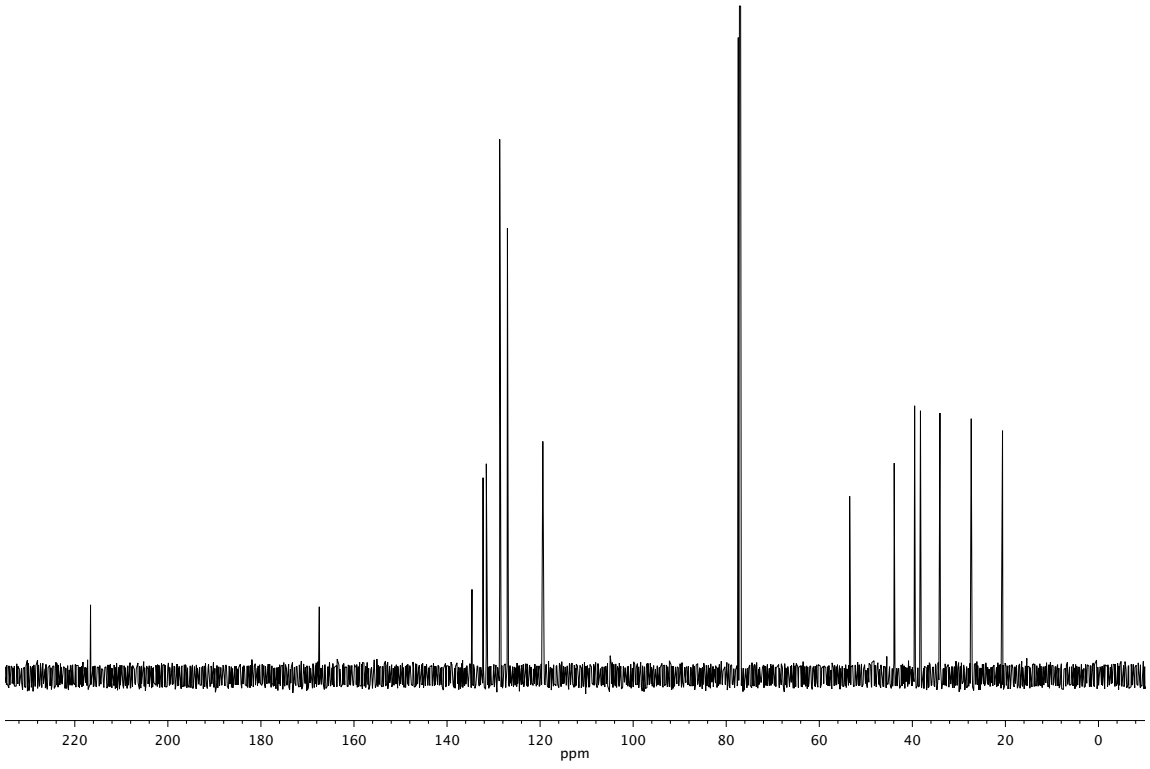


Figure A9.39. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **240f**.

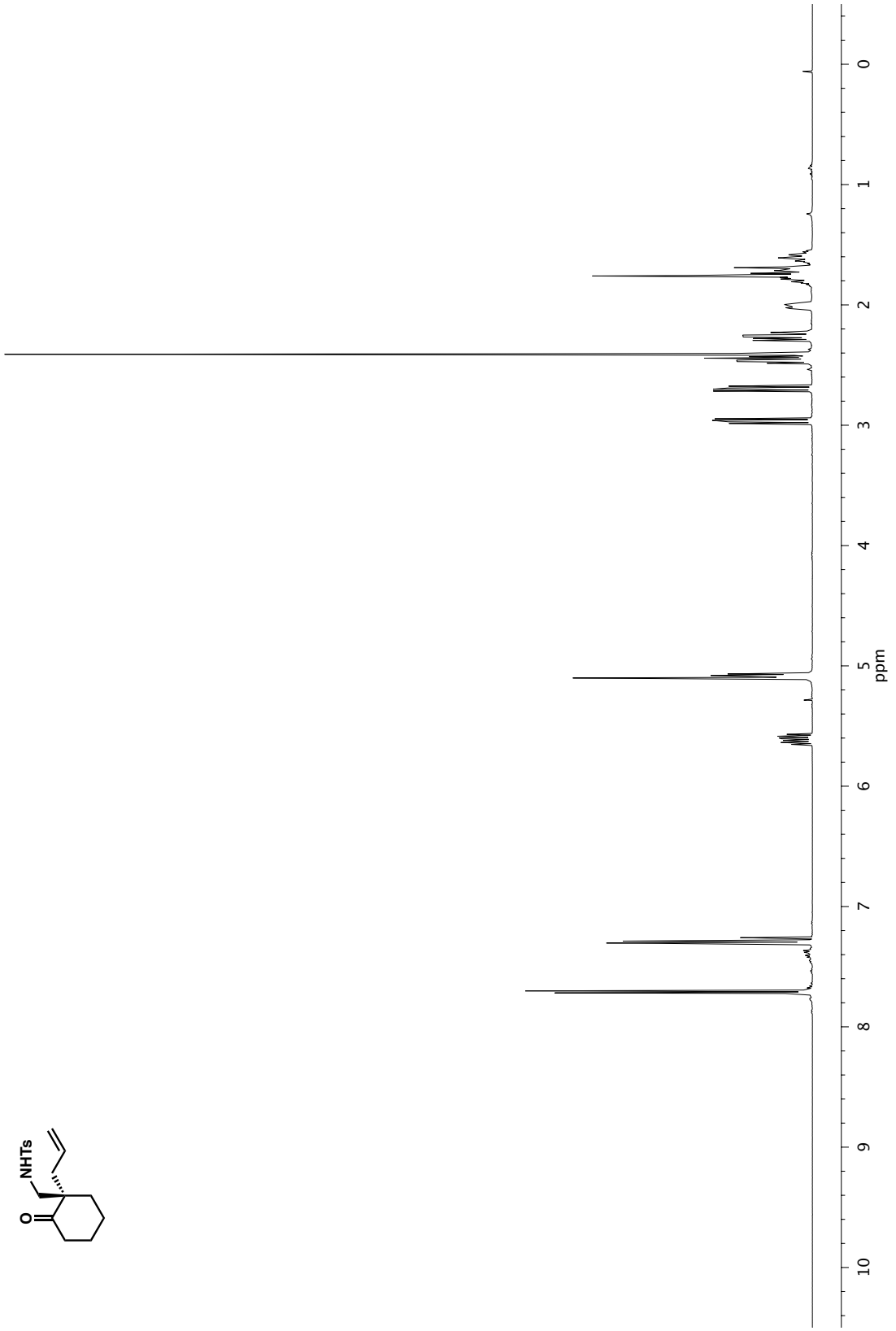


Figure A9.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **240g**.

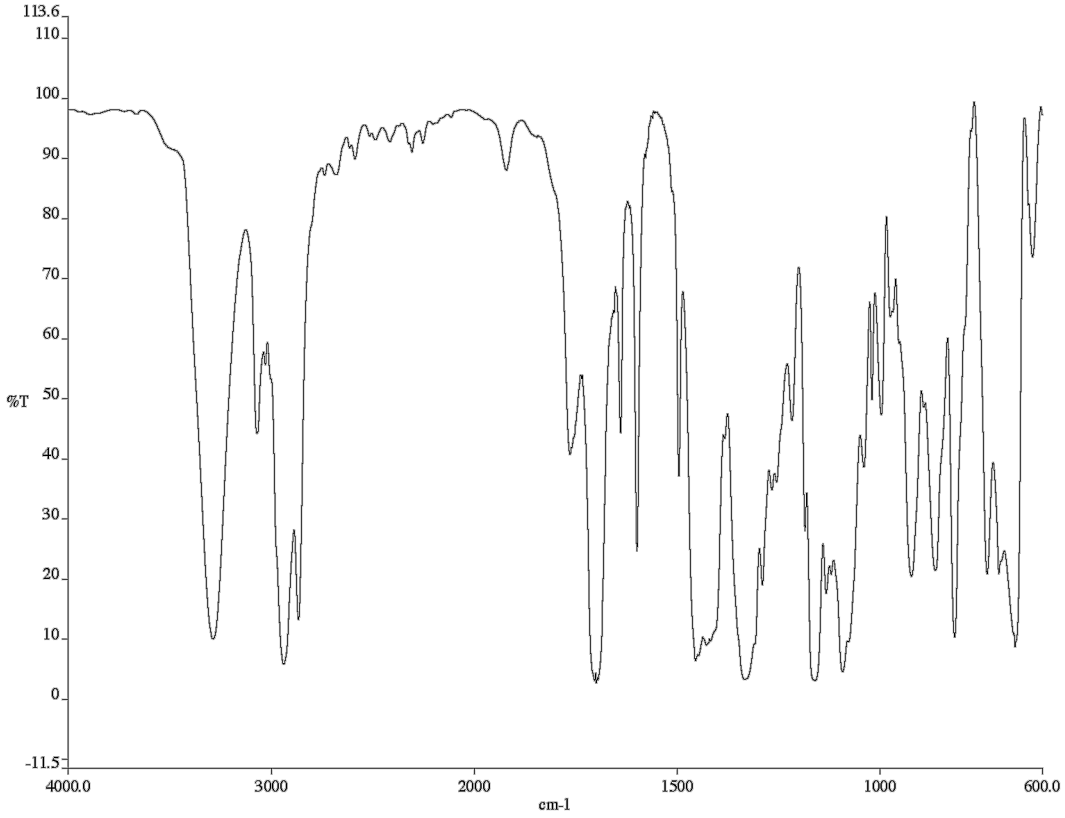


Figure A9.41. Infrared spectrum (Thin Film, NaCl) of compound **240g**.

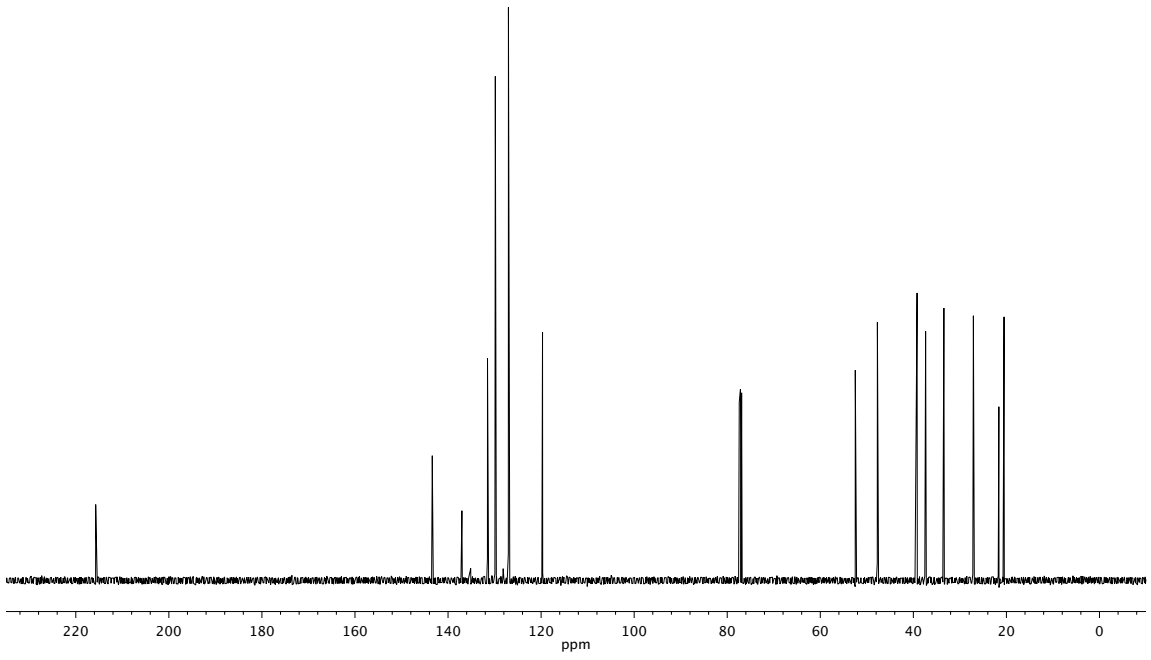


Figure A9.42. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **240g**.

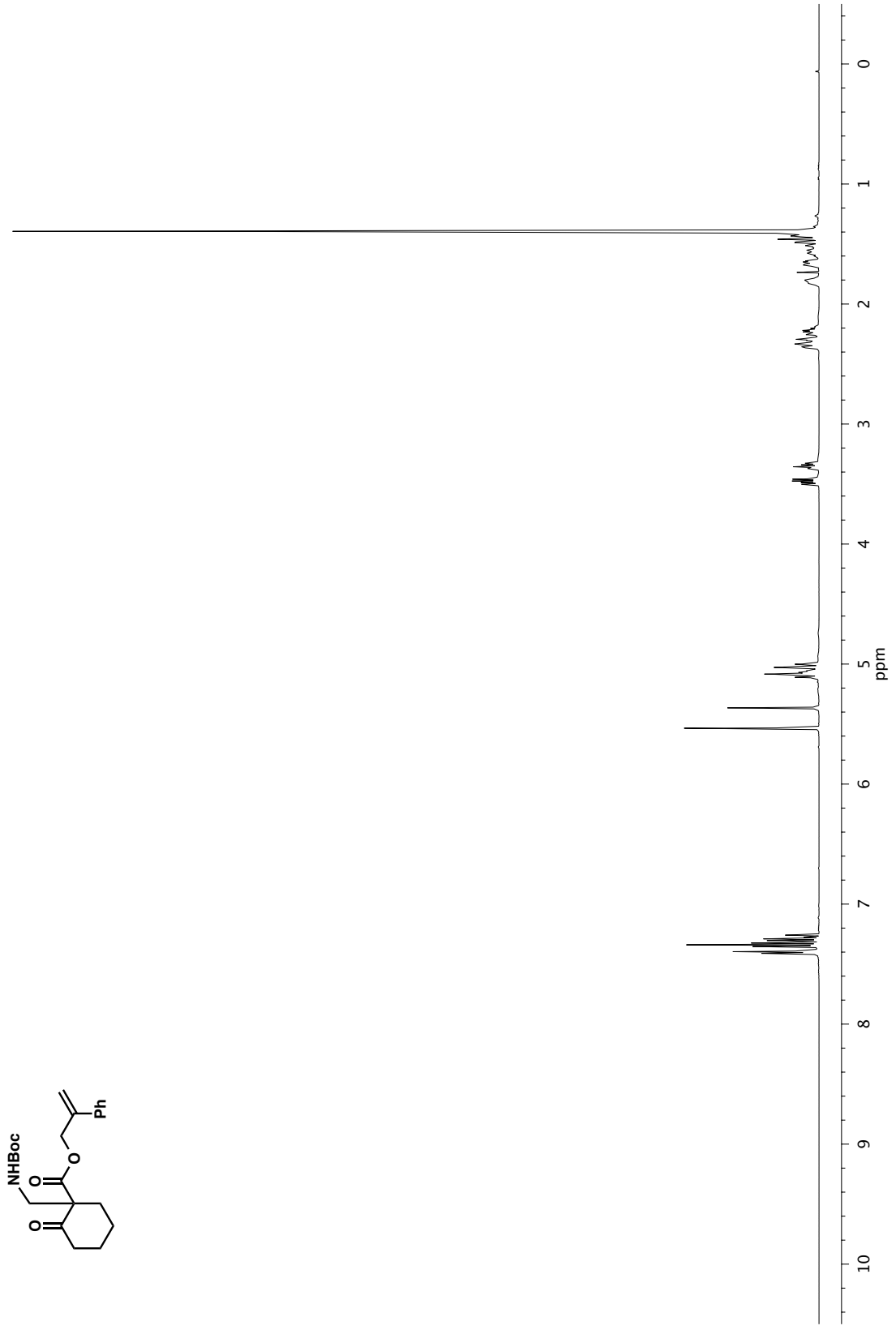


Figure A9.43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245a**.

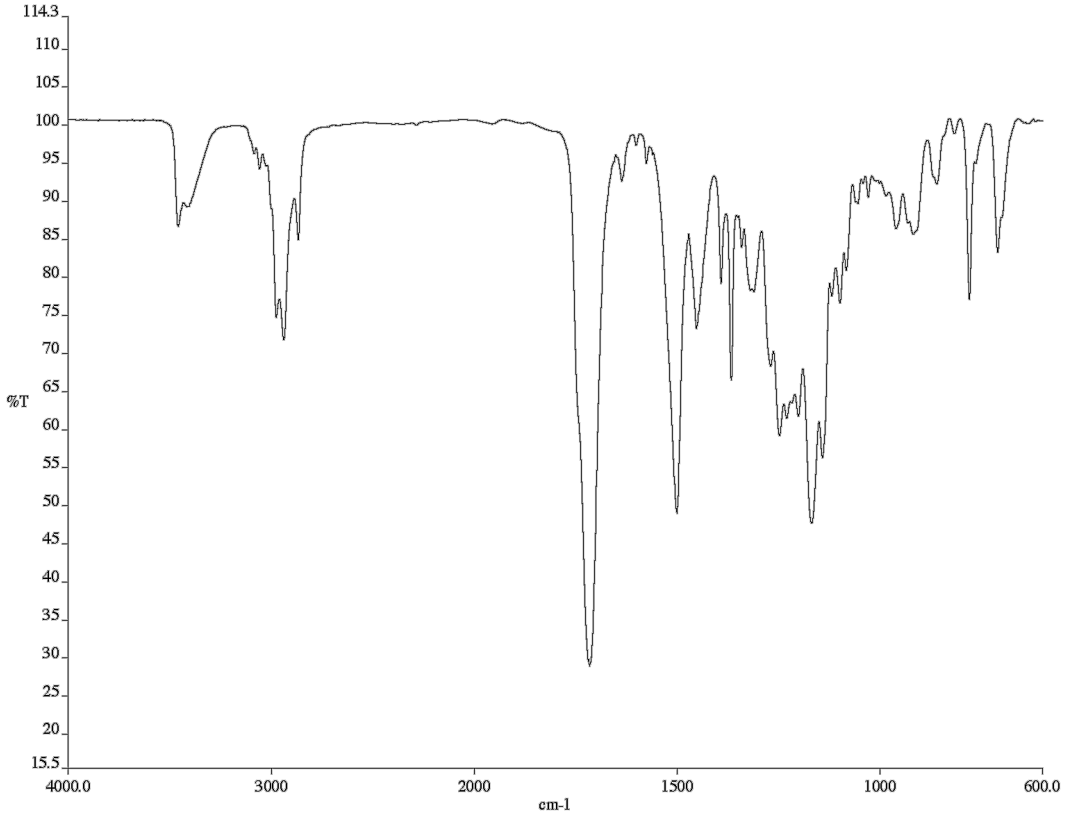


Figure A9.44. Infrared spectrum (Thin Film, NaCl) of compound **245a**.

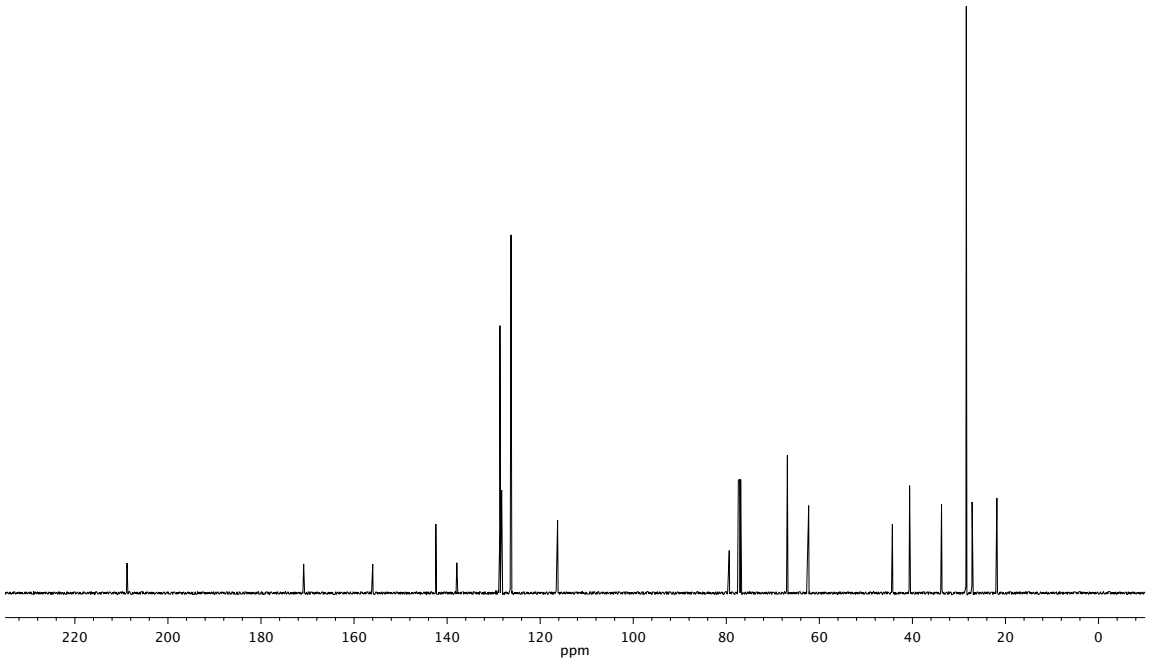


Figure A9.45. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245a**.

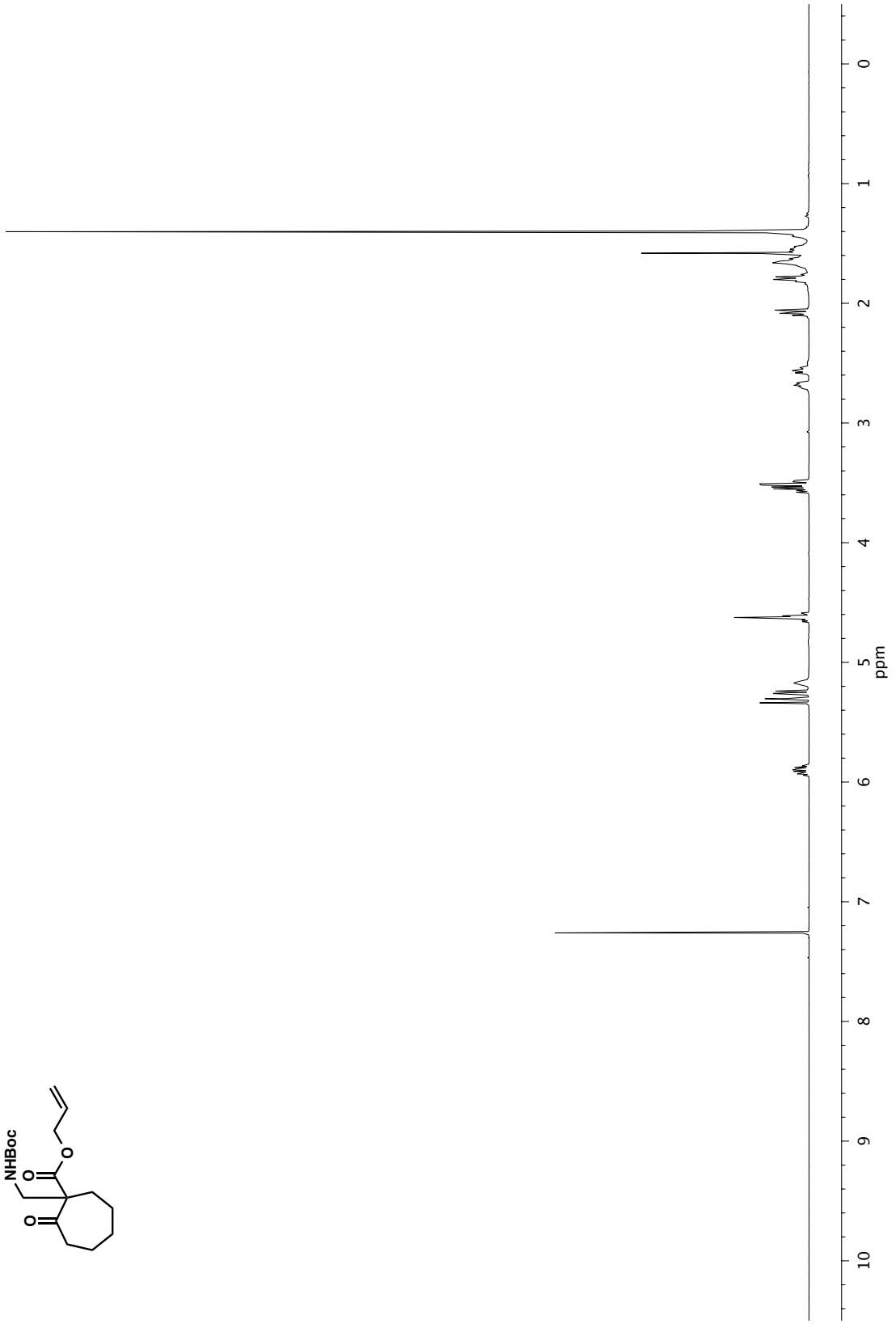


Figure A9.46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245b**.

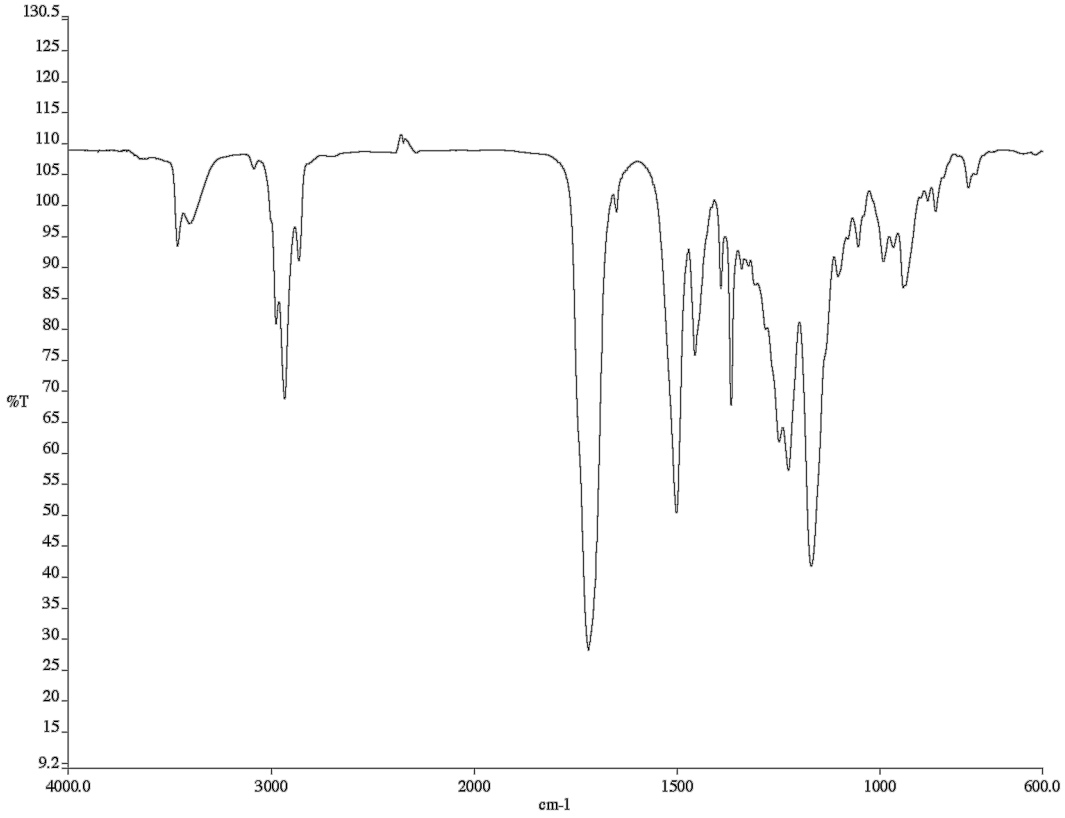


Figure A9.47. Infrared spectrum (Thin Film, NaCl) of compound **245b**.

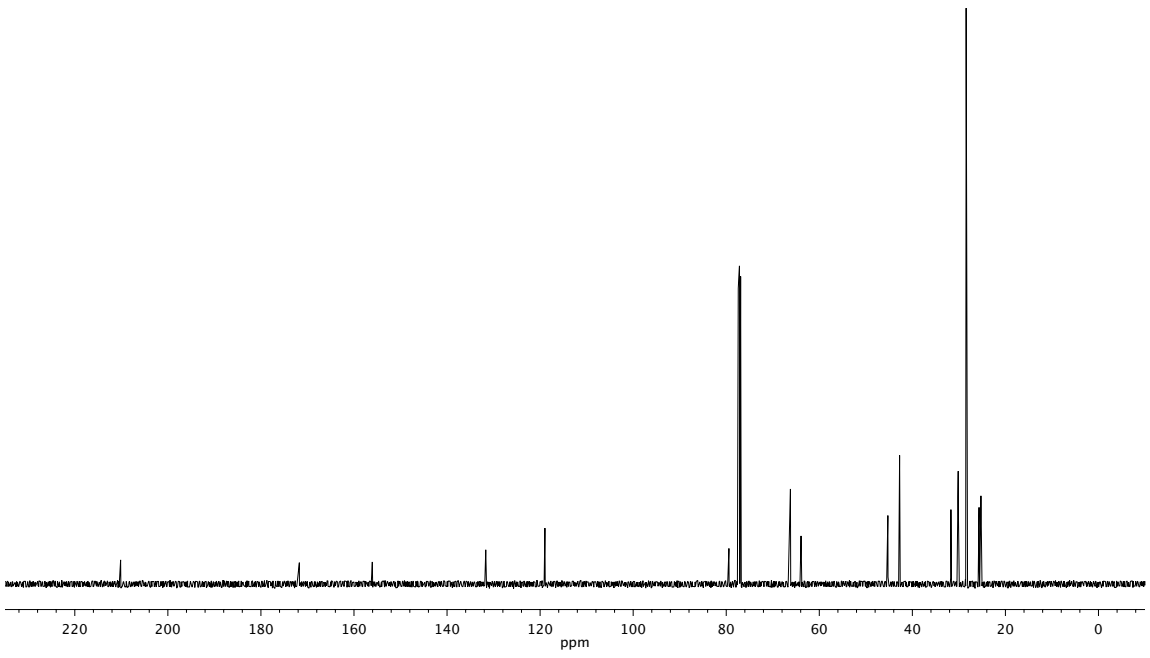


Figure A9.48. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245b**.

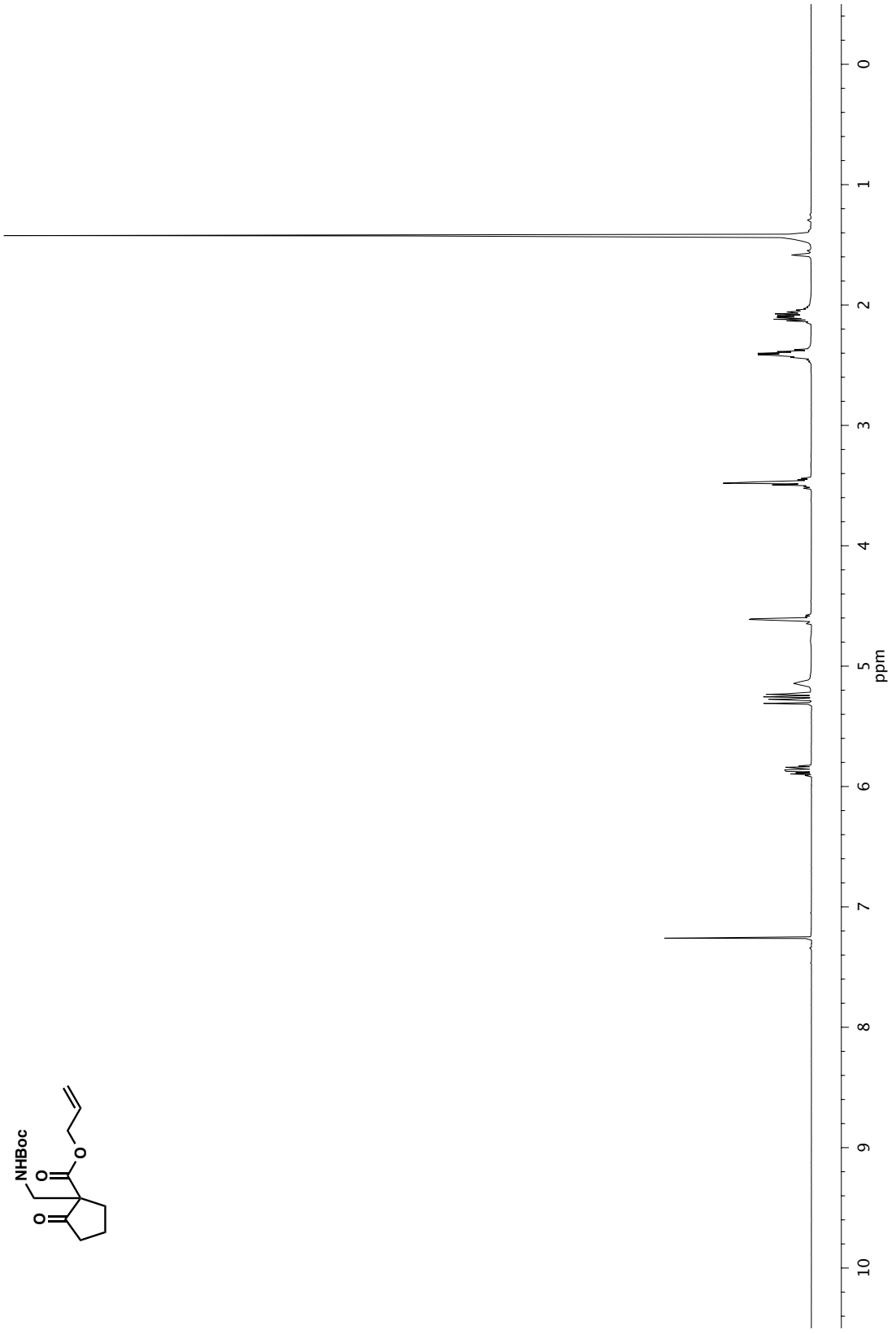


Figure A9.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245c**.

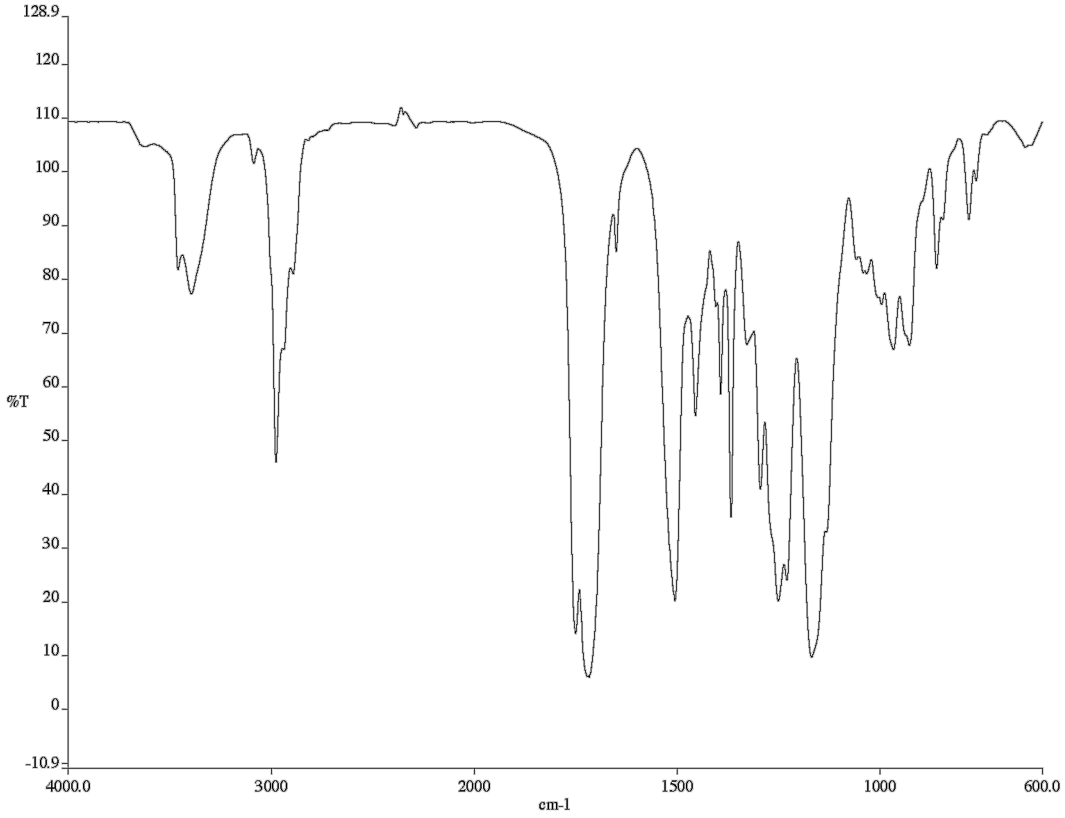


Figure A9.50. Infrared spectrum (Thin Film, NaCl) of compound **245c**.

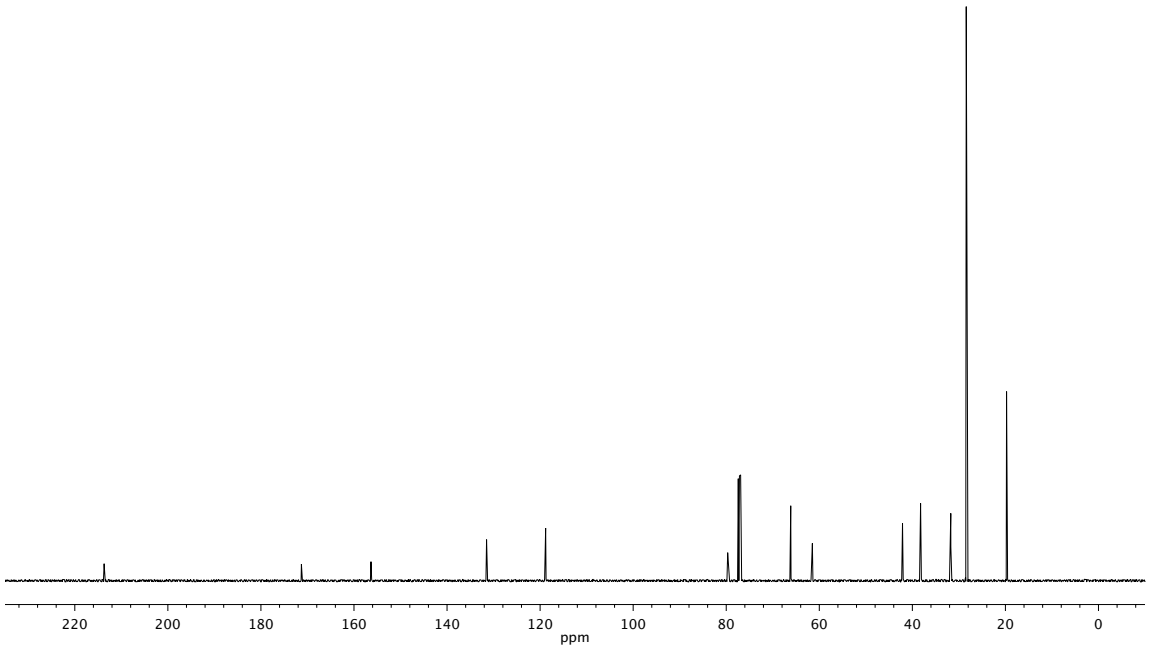


Figure A9.51. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245c**.

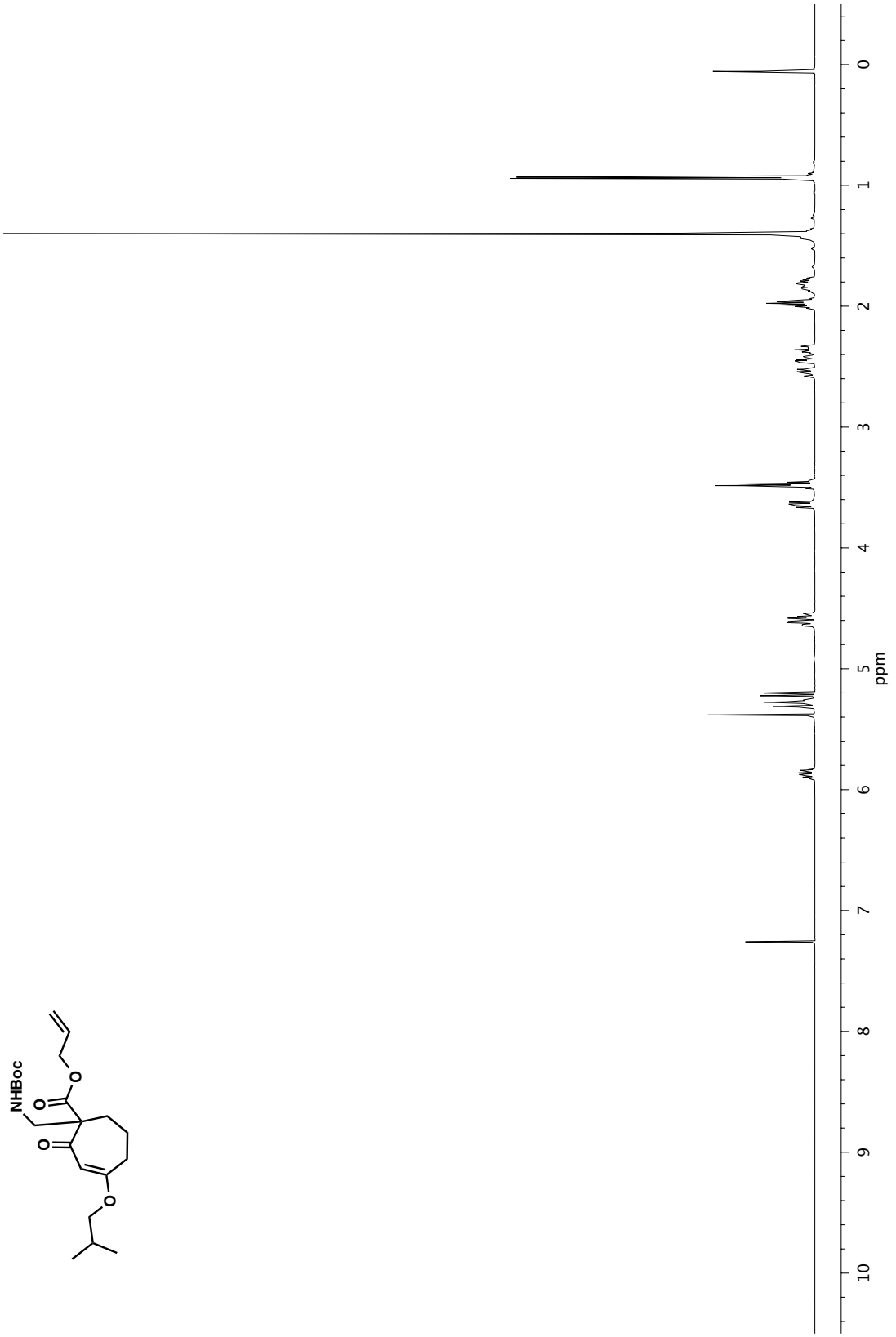


Figure A9.52. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245d**.

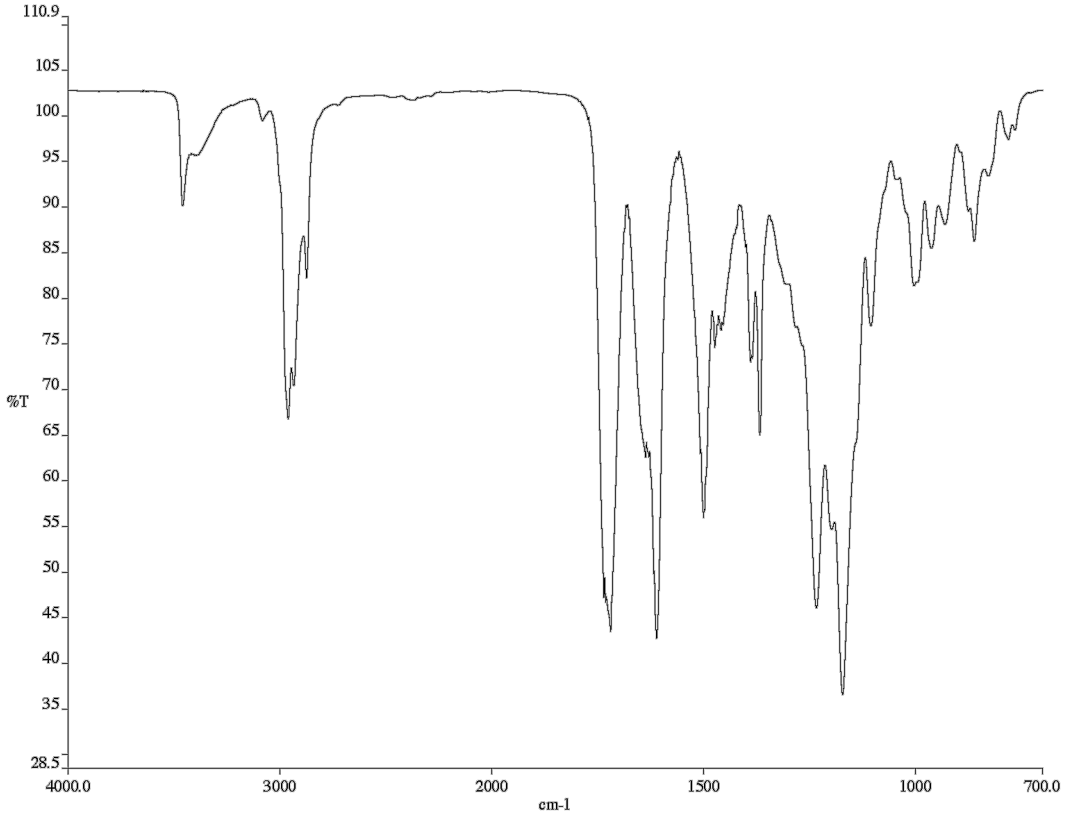


Figure A9.53. Infrared spectrum (Thin Film, NaCl) of compound **245d**.

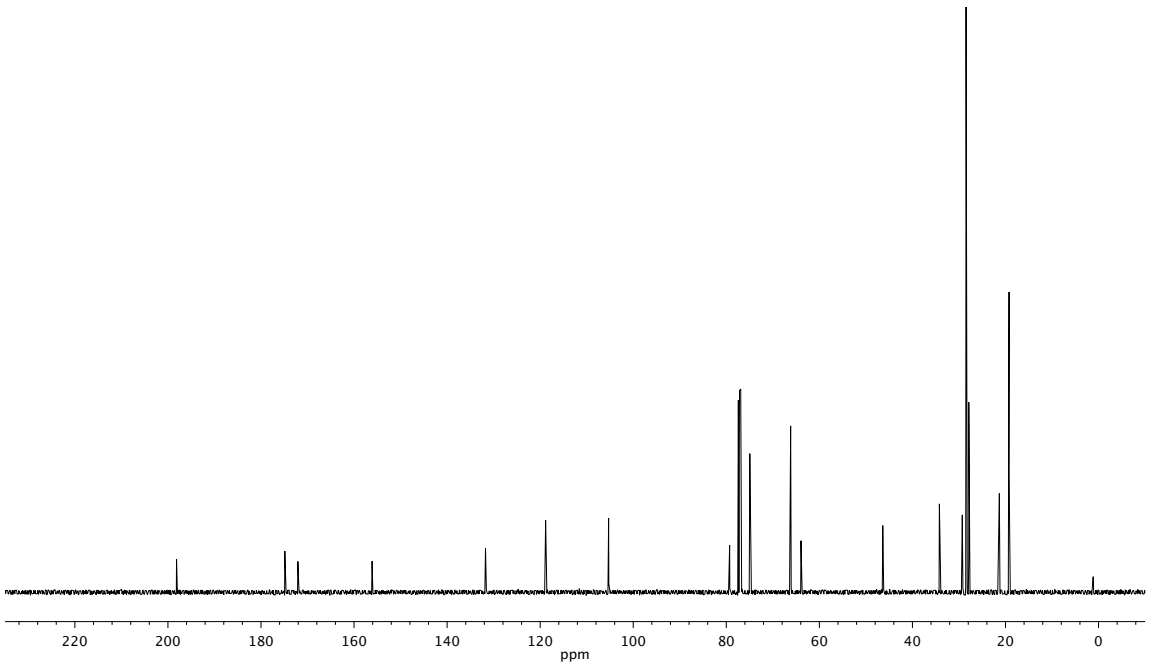


Figure A9.54. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245d**.

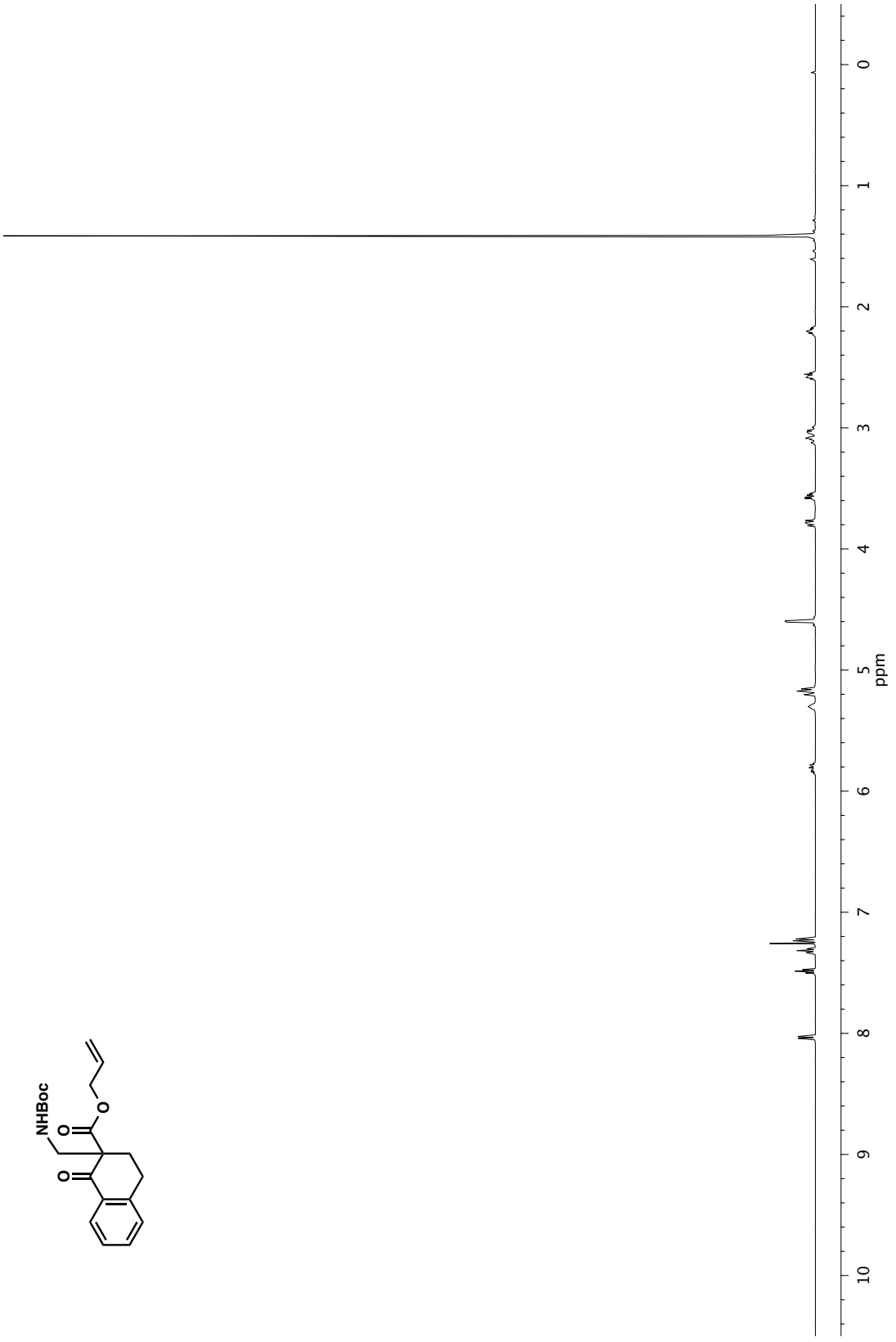


Figure A9.55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245e**.

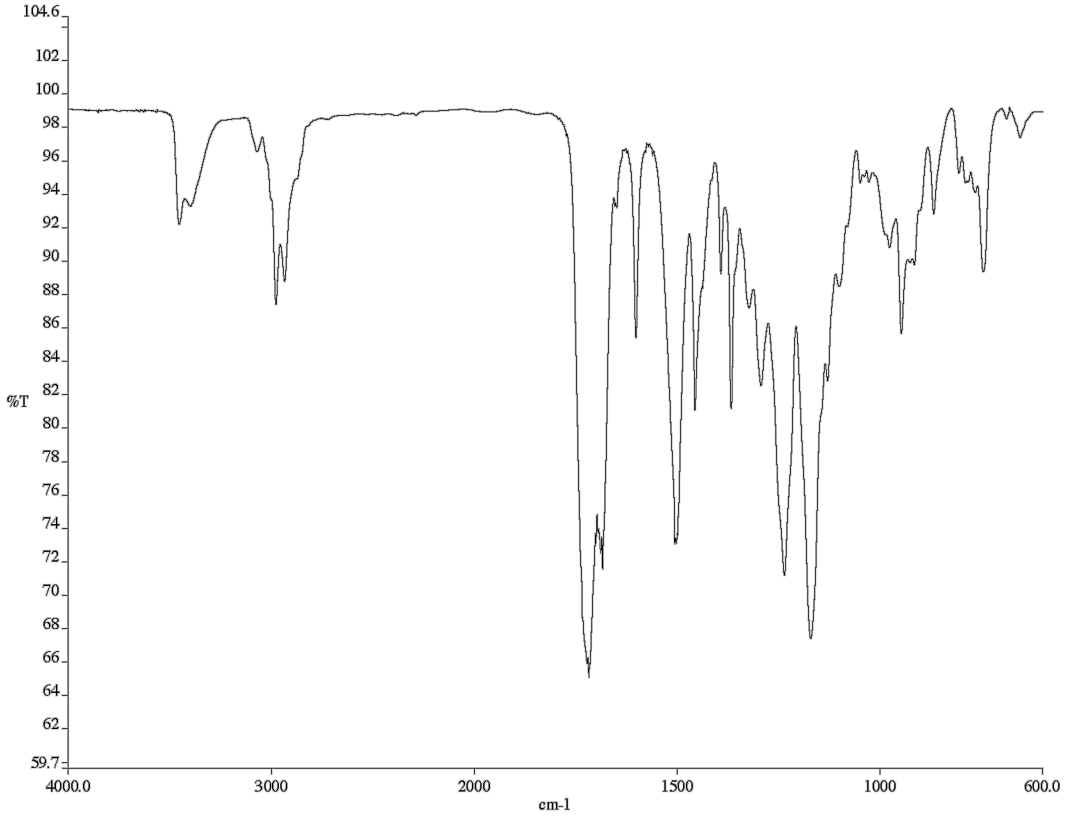


Figure A9.56. Infrared spectrum (Thin Film, NaCl) of compound **245e**.

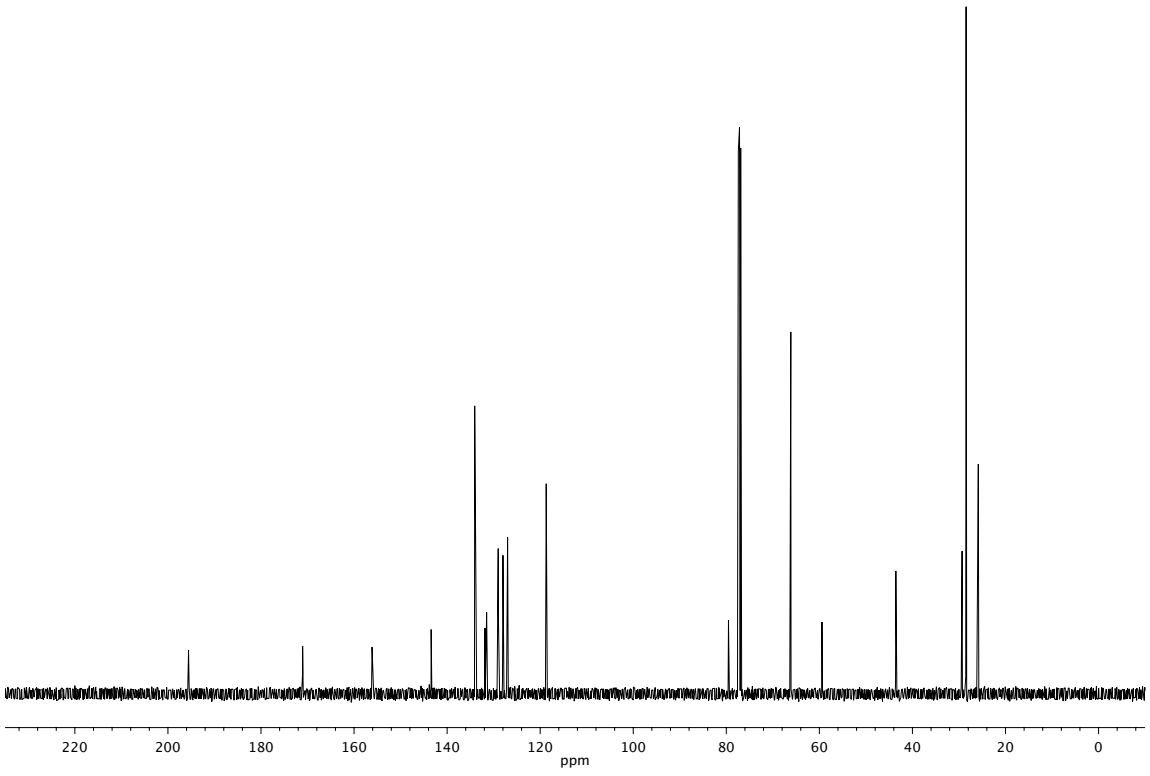


Figure A9.57. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245e**.

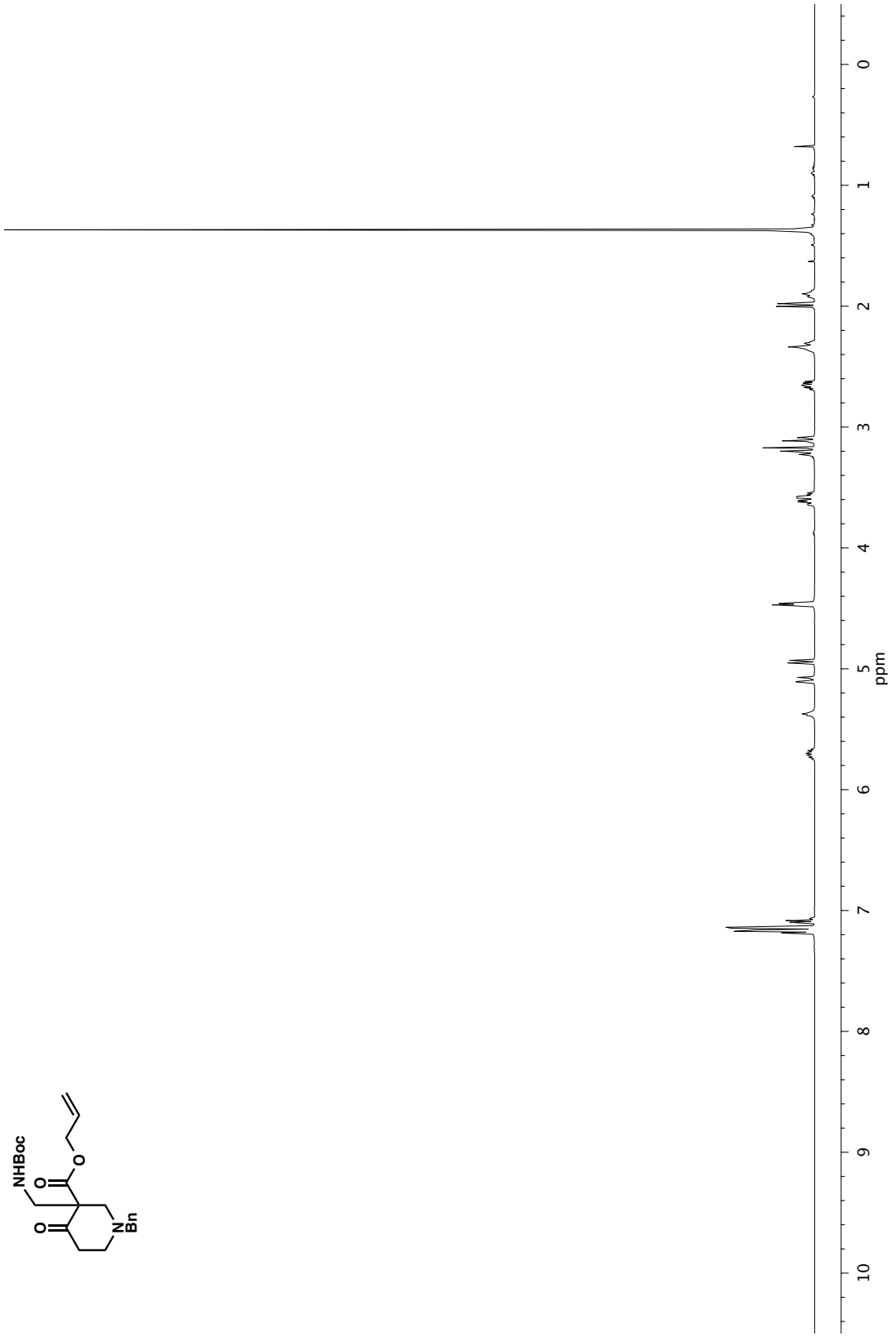


Figure A9.58. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245f**.

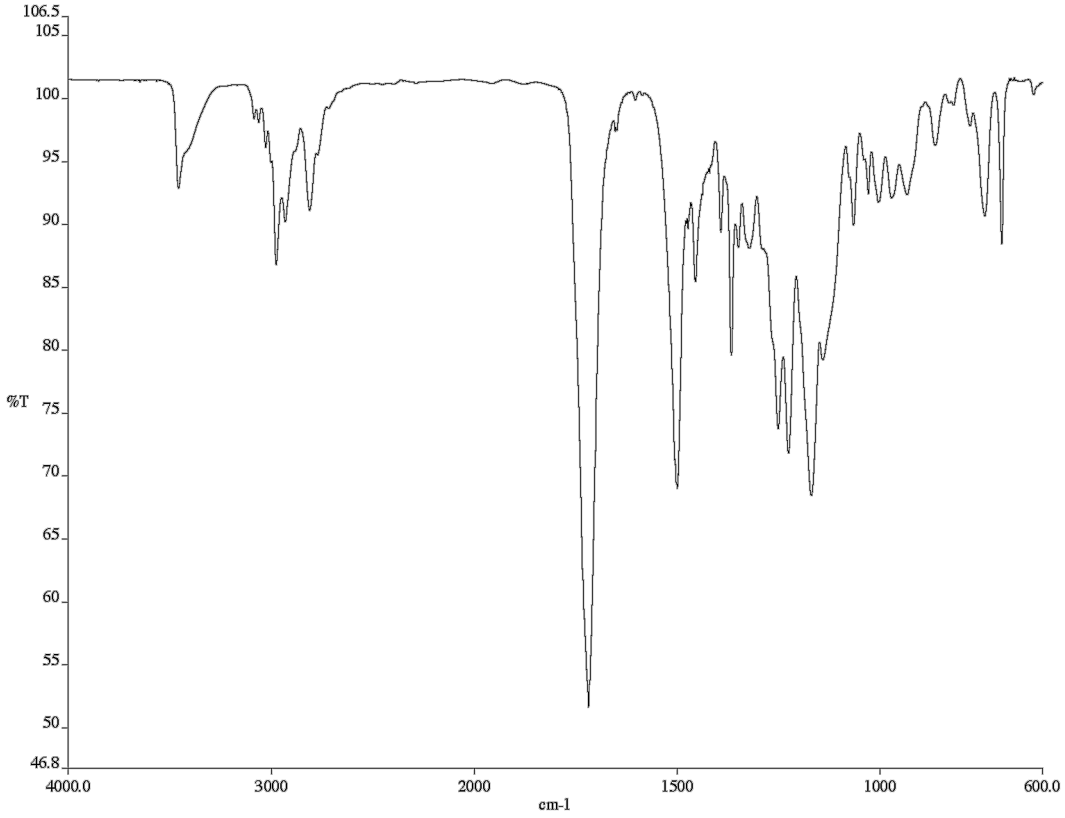


Figure A9.59. Infrared spectrum (Thin Film, NaCl) of compound **245f**.

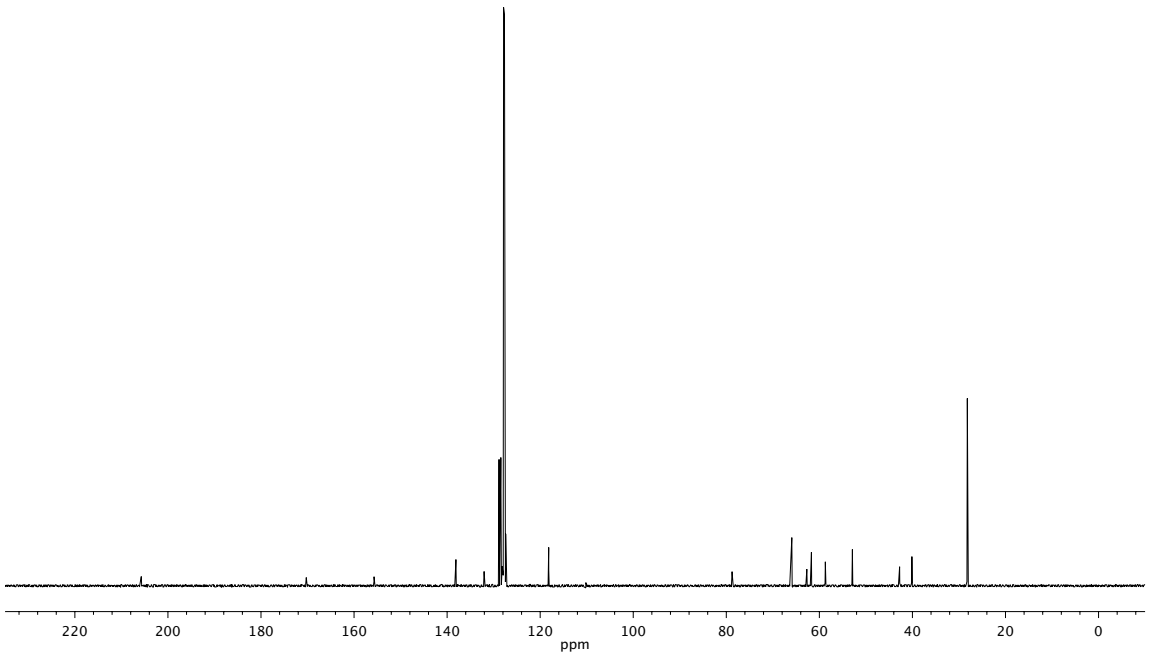


Figure A9.60. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245f**.

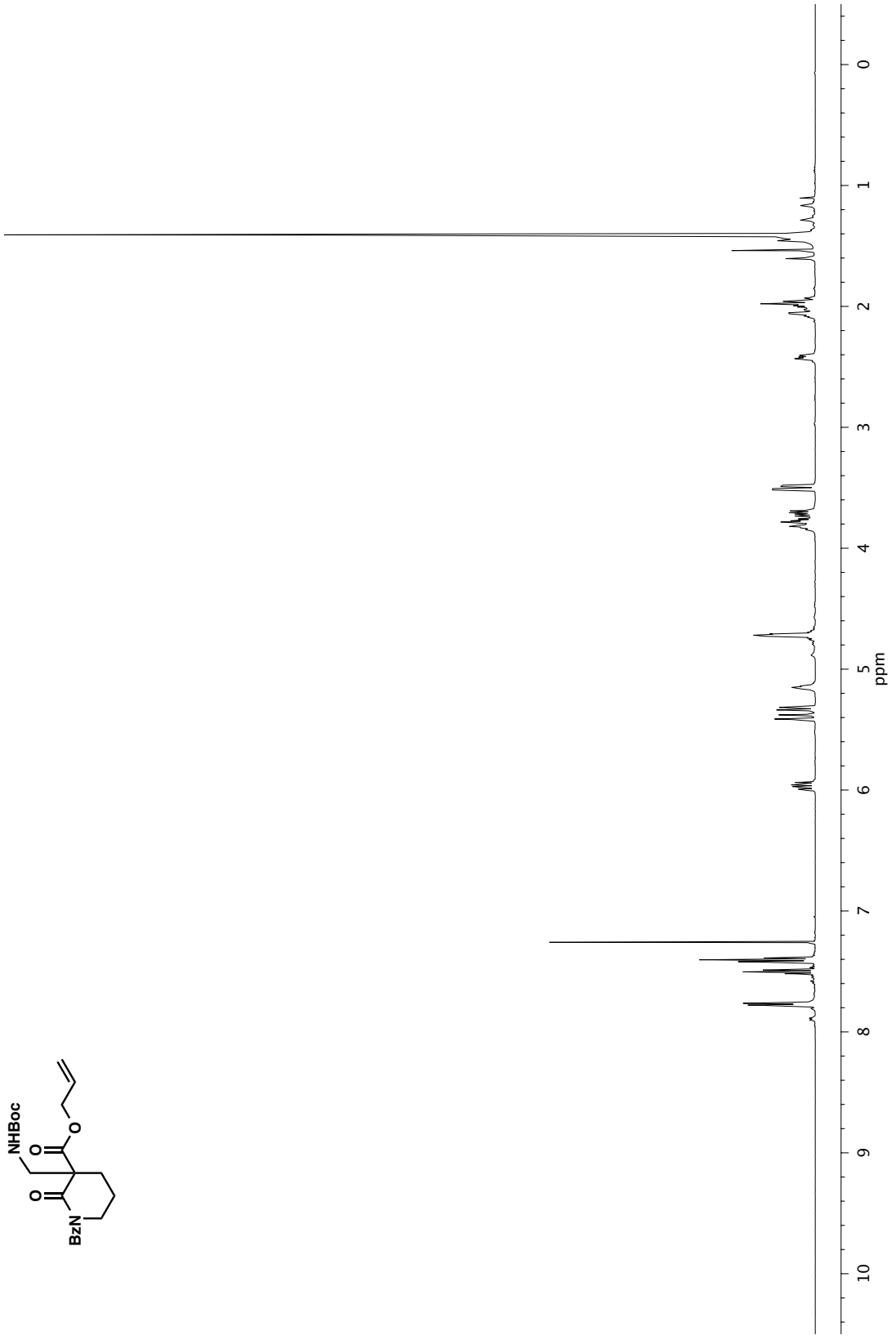


Figure A9.61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245g**.

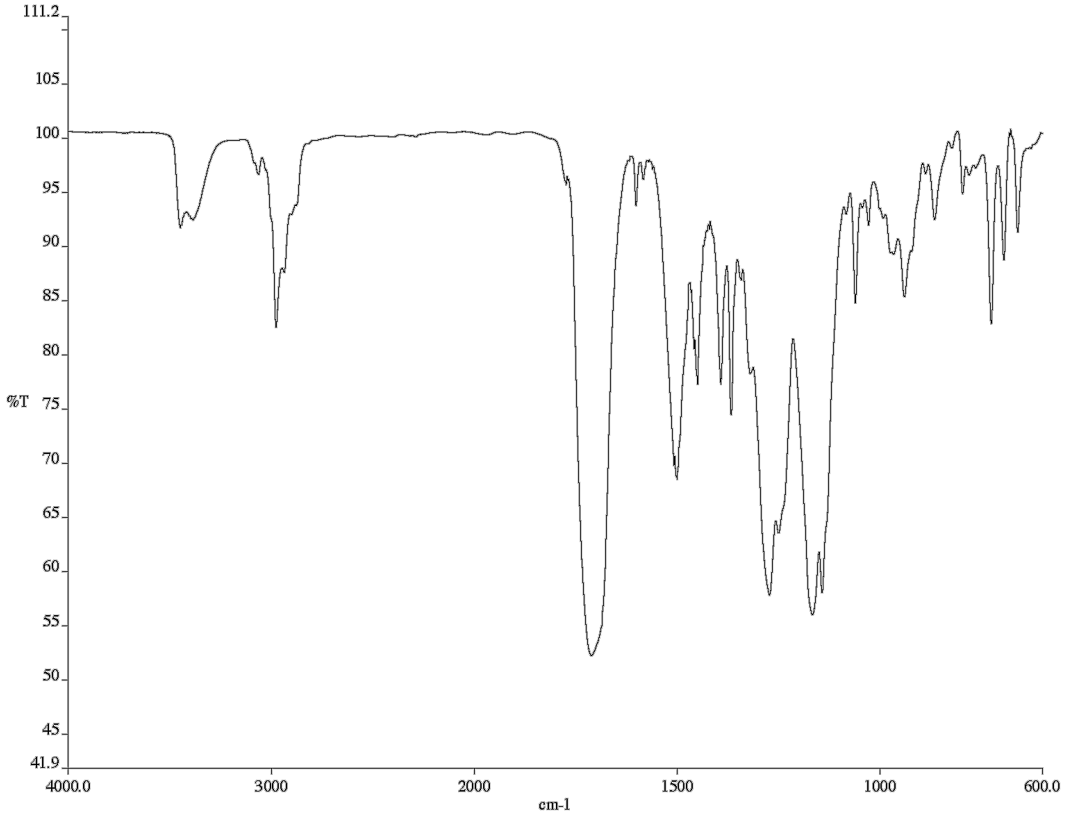


Figure A9.62. Infrared spectrum (Thin Film, NaCl) of compound **245g**.

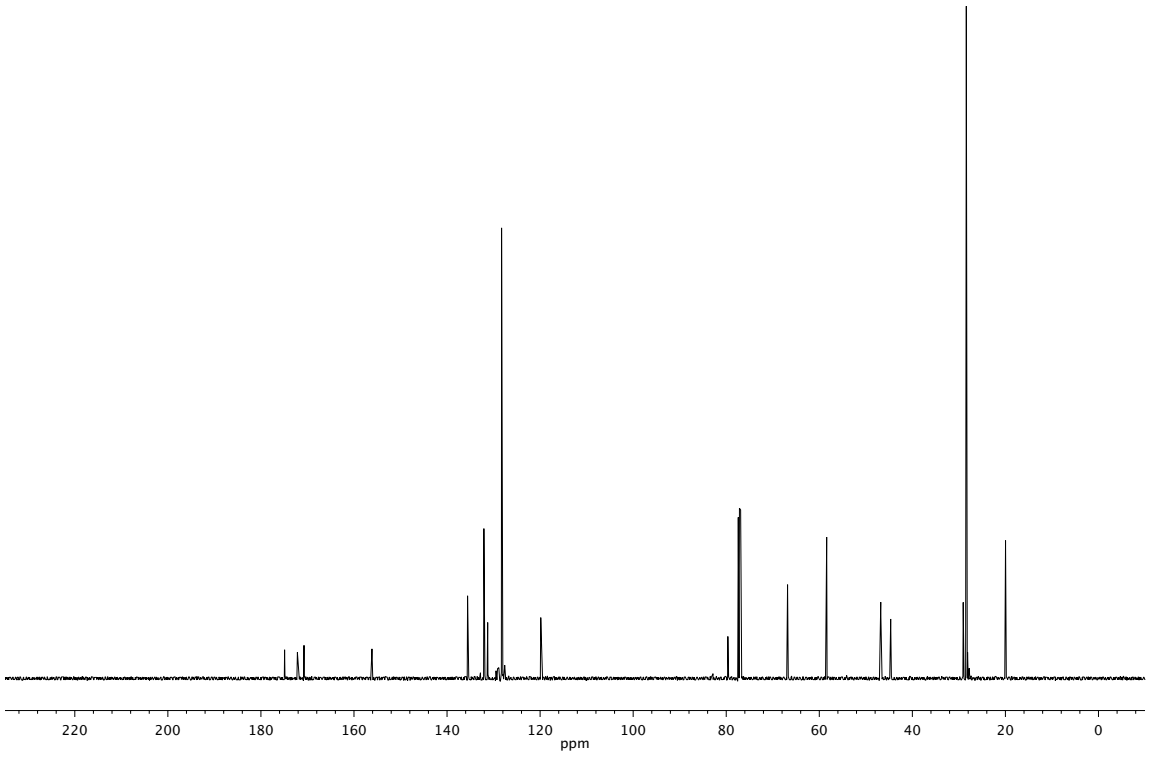


Figure A9.63. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245g**.

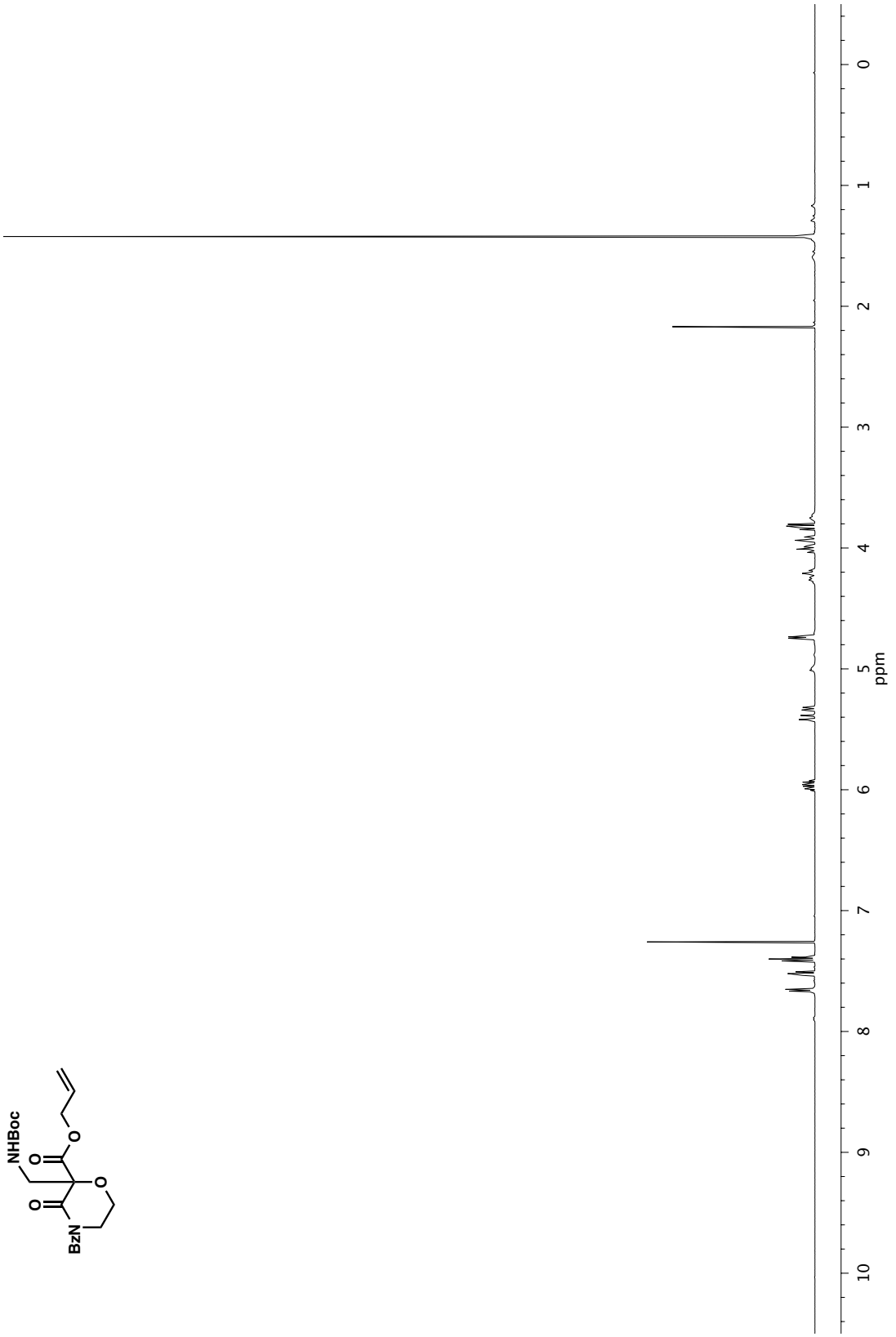


Figure A9.64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245h**.

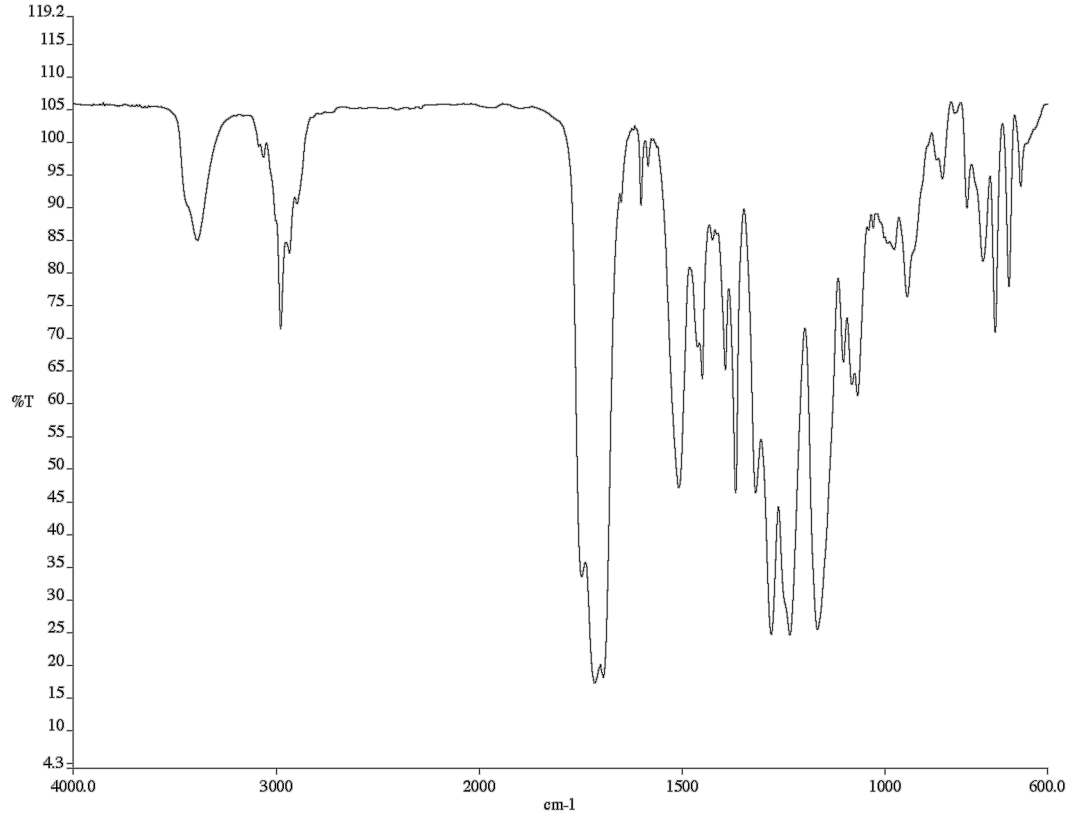


Figure A9.65. Infrared spectrum (Thin Film, NaCl) of compound **245h**.

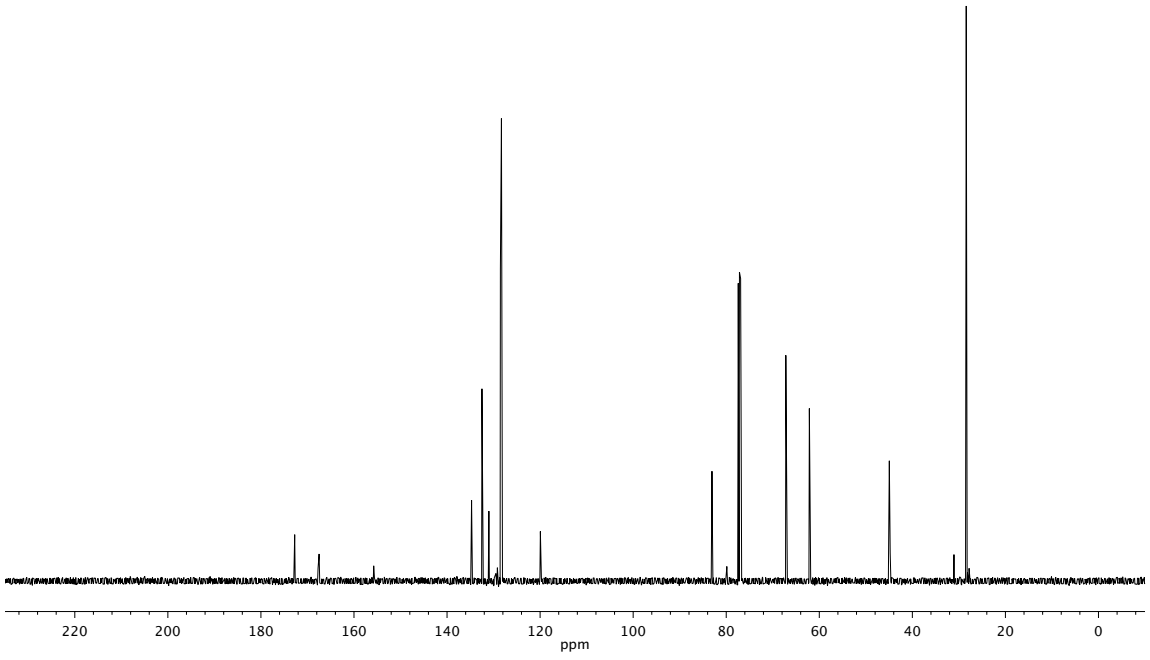


Figure A9.66. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245h**.

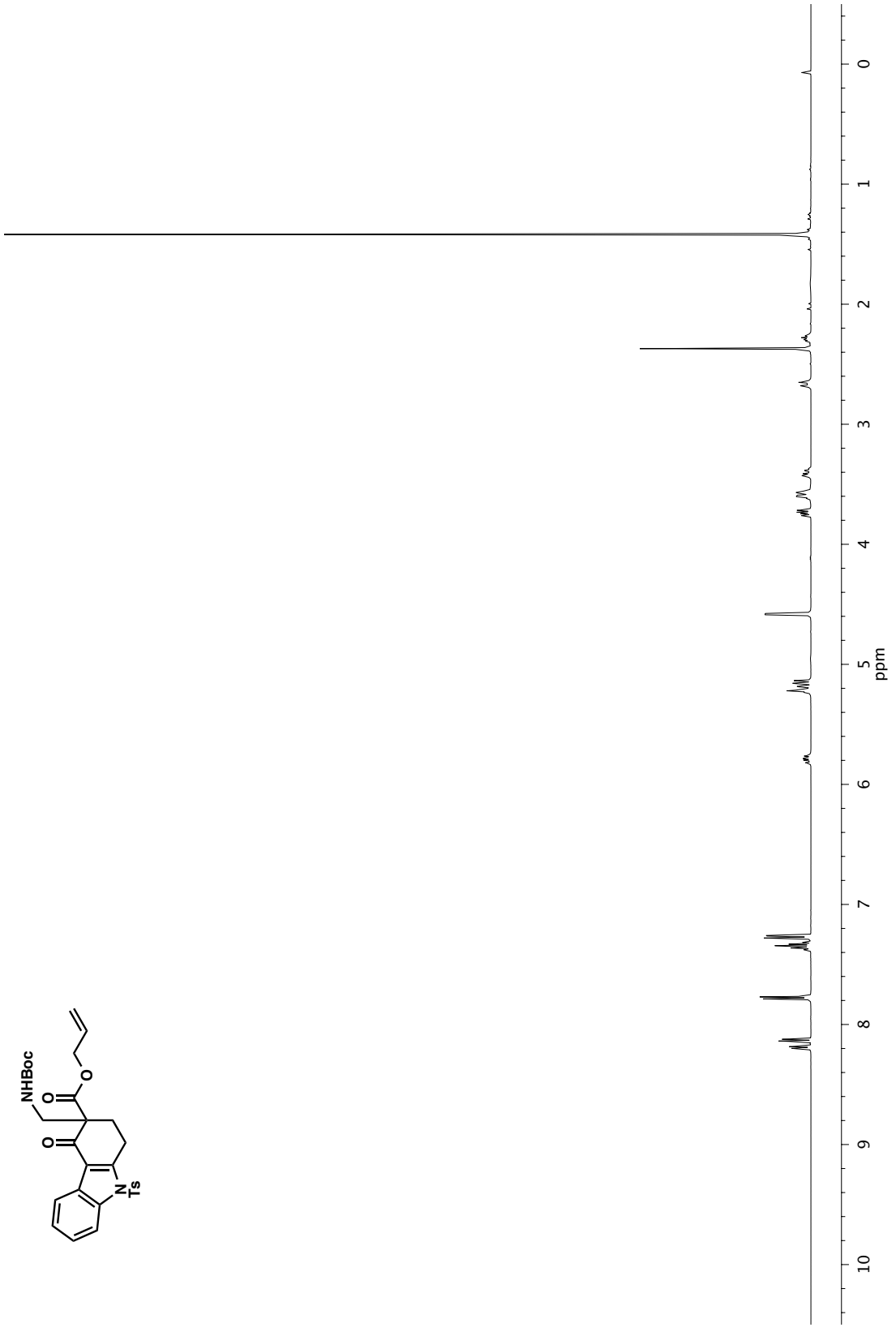


Figure A9.67. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245i**.

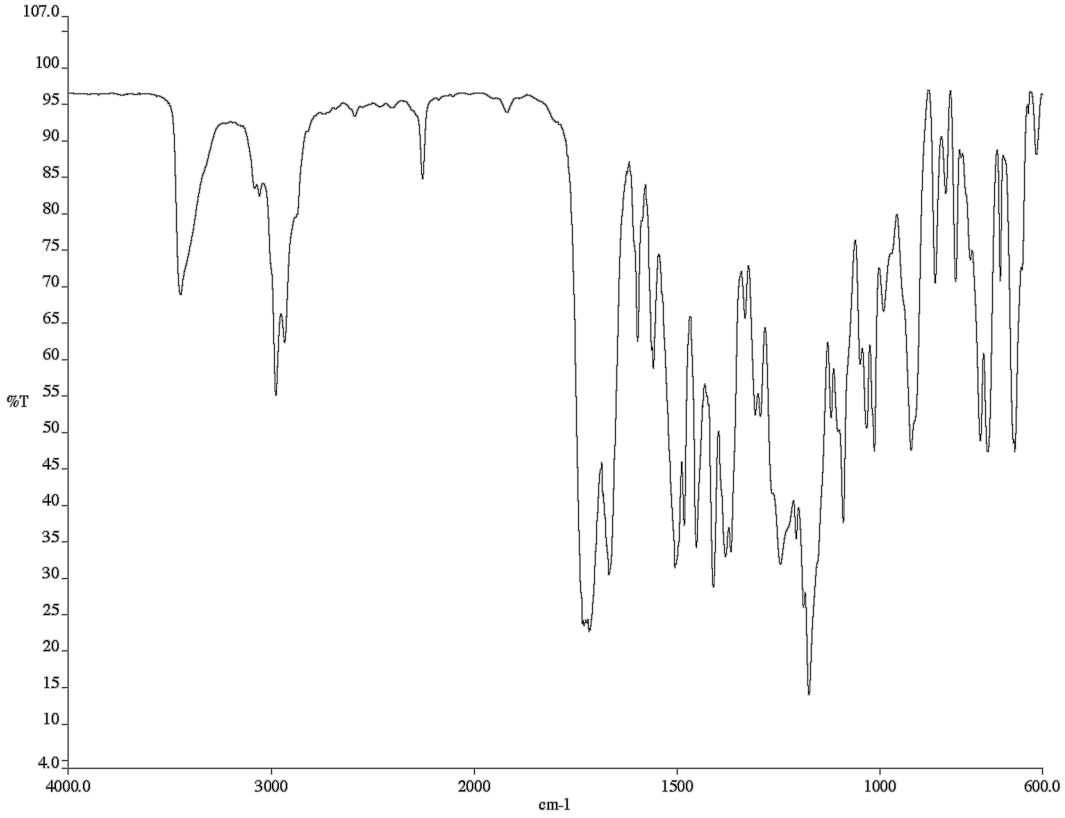


Figure A9.68. Infrared spectrum (Thin Film, NaCl) of compound **245i**.

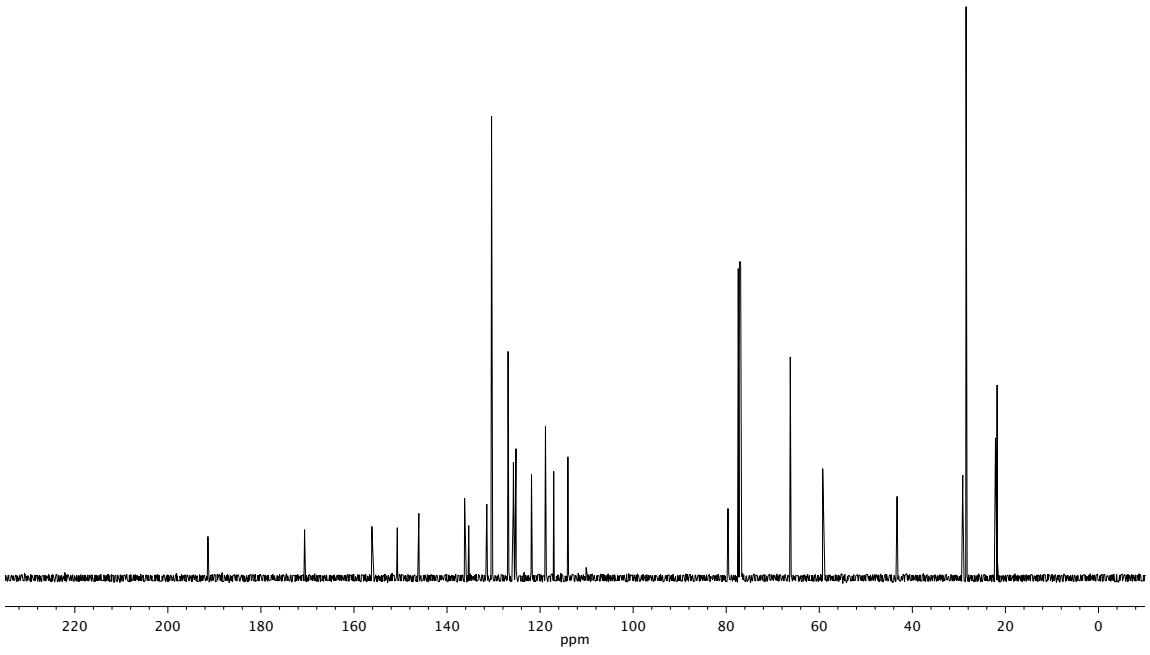


Figure A9.69. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245i**.

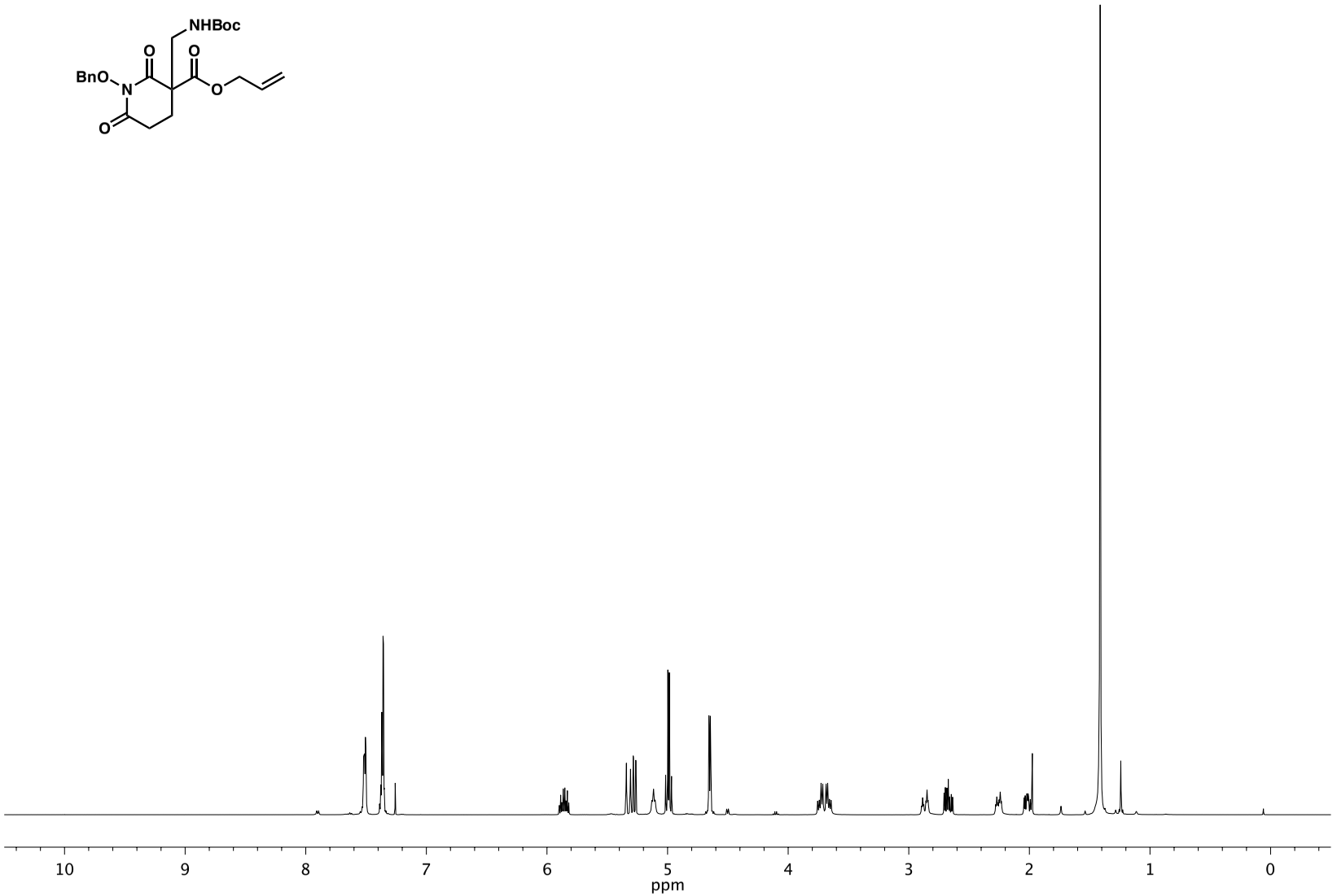


Figure A9.70. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245j**.

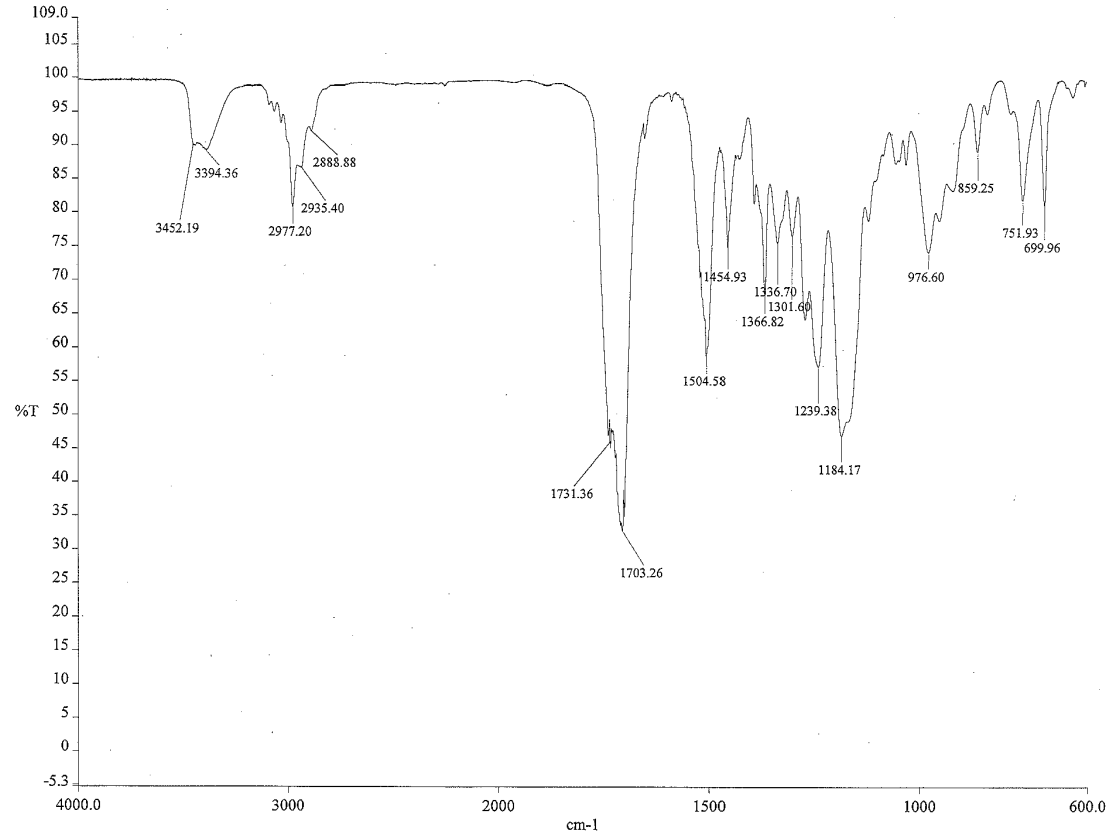


Figure A9.71. Infrared spectrum (Thin Film, NaCl) of compound **245j**.

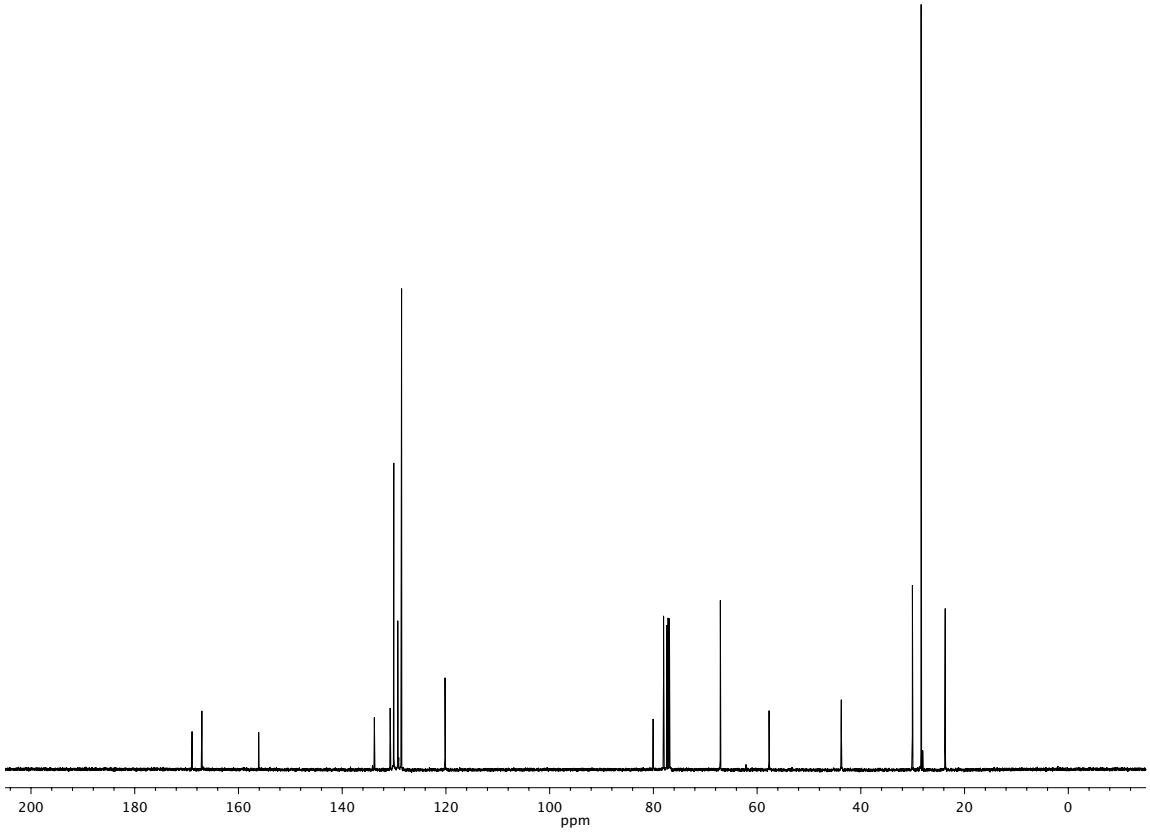


Figure A9.72. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **245j**.

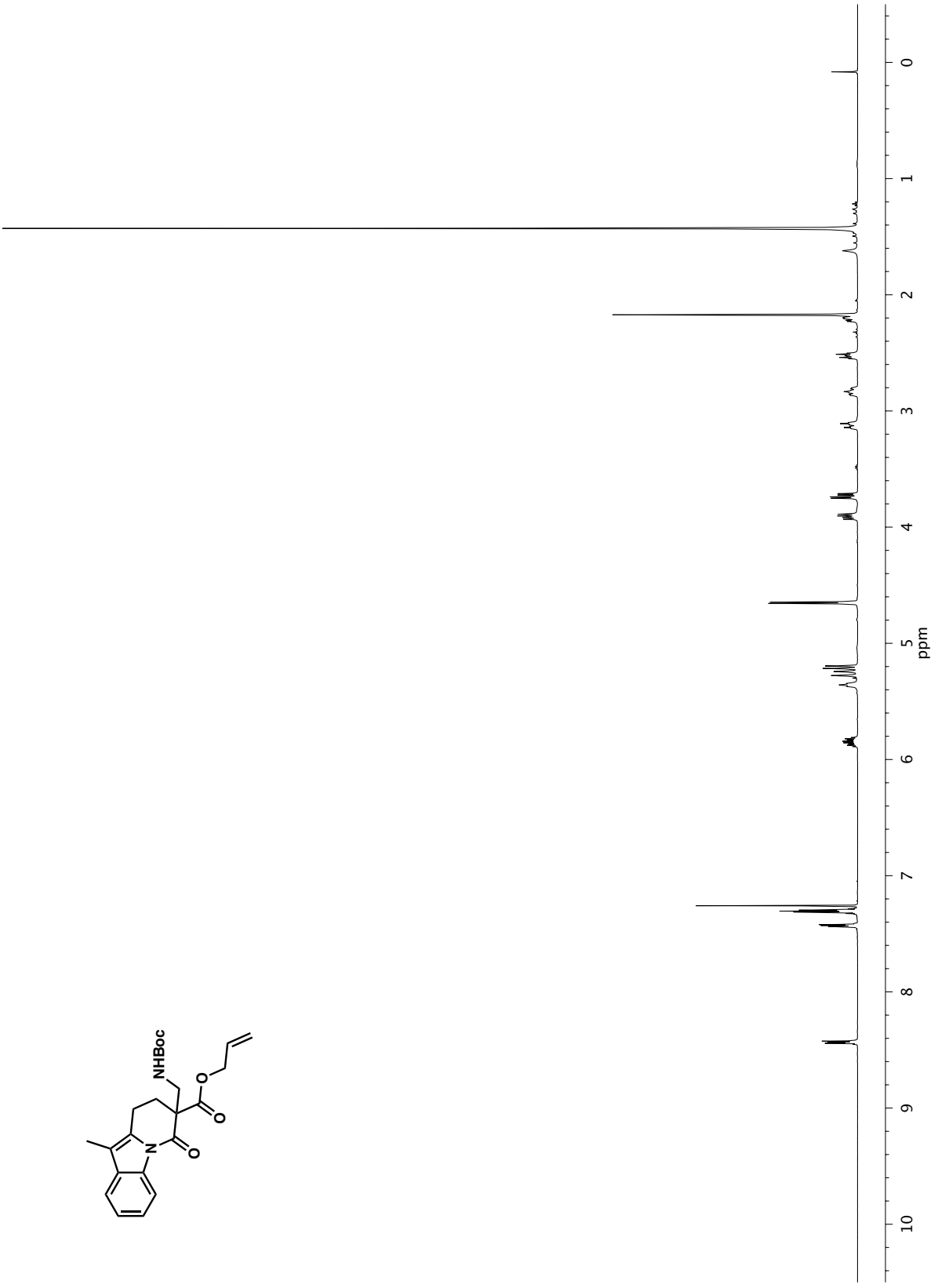


Figure A9.73. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **172g**.

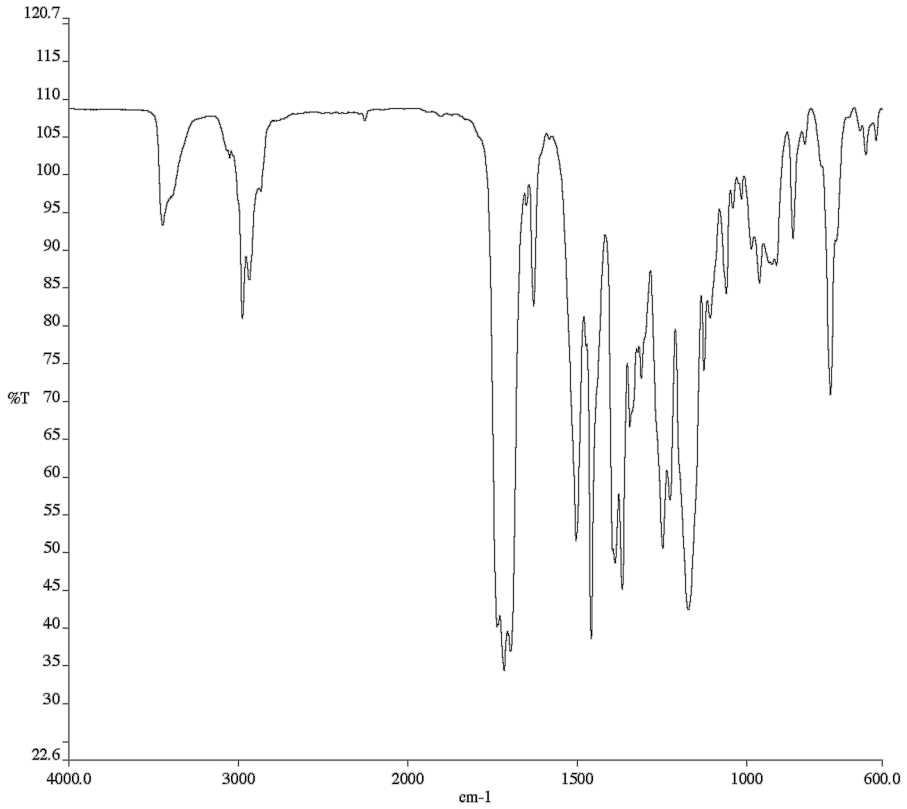


Figure A9.74. Infrared spectrum (Thin Film, NaCl) of compound **172g**.

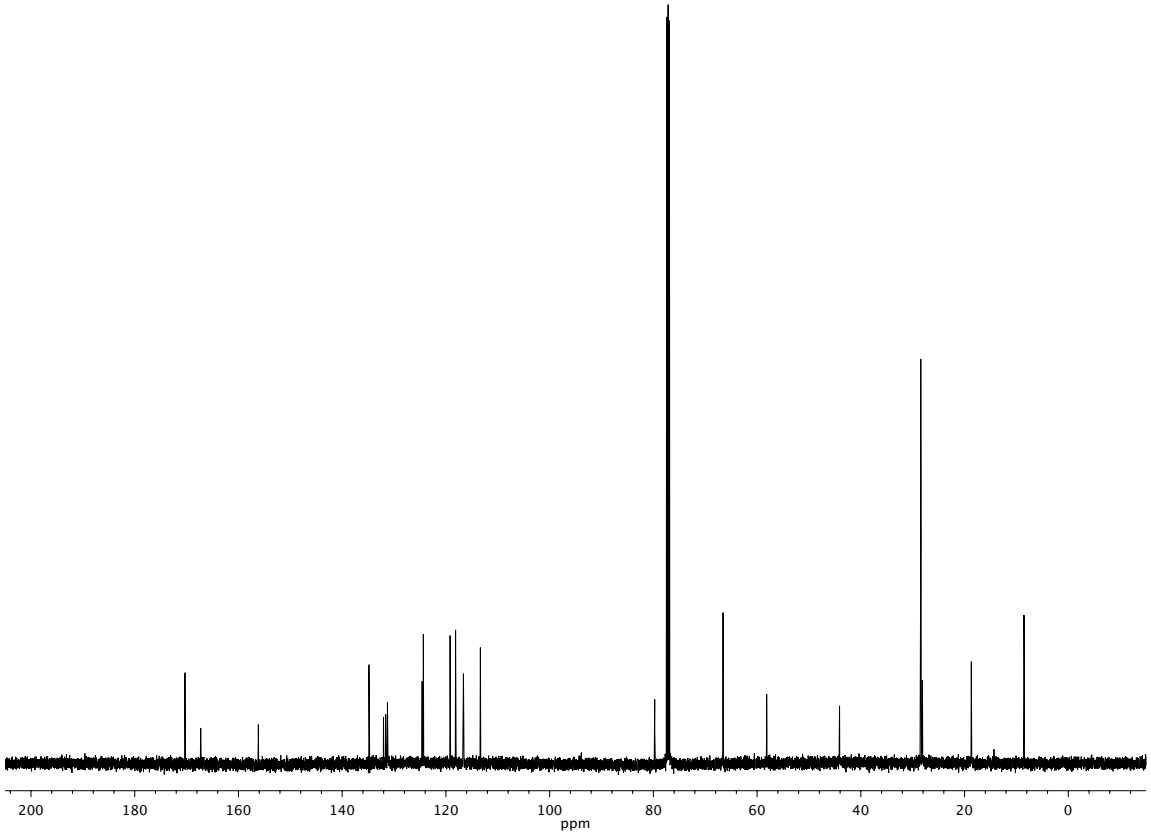


Figure A9.75. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **172g**.

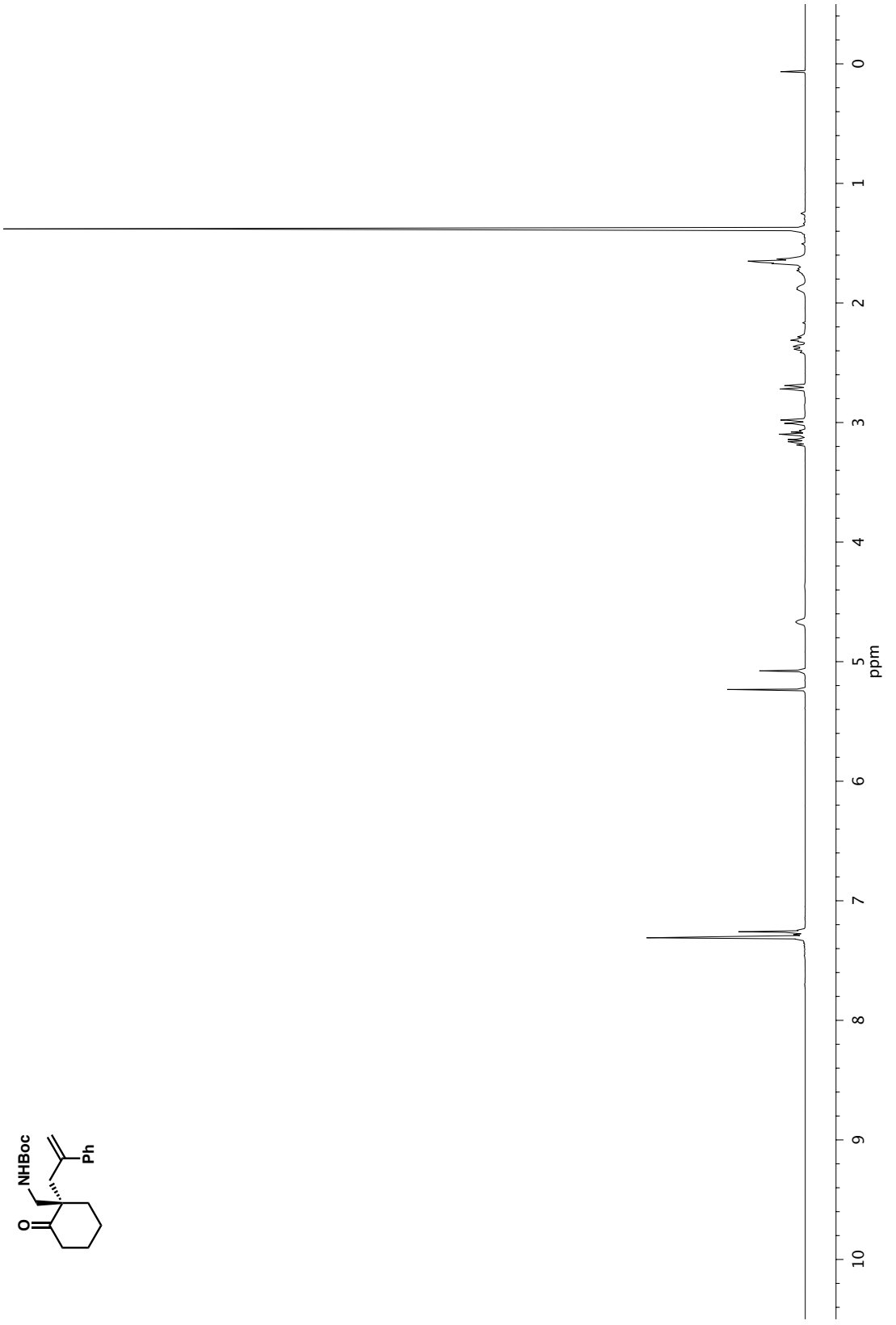


Figure A9.76. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246a**.

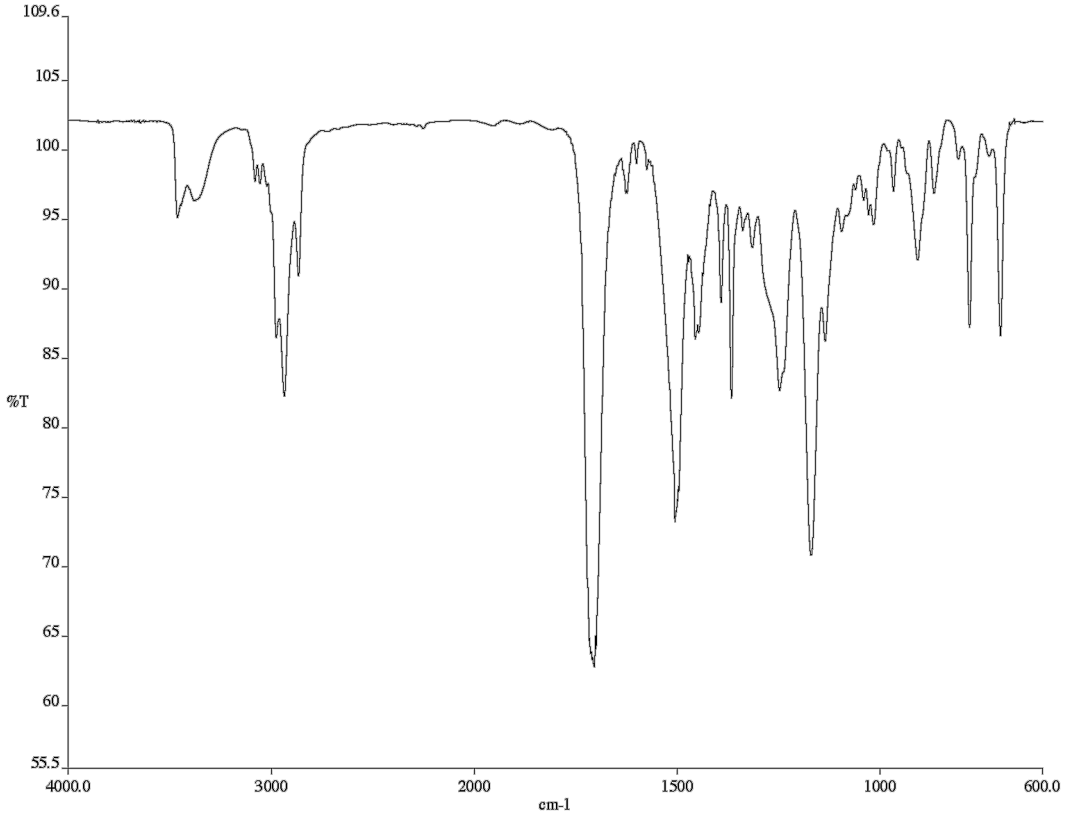


Figure A9.77. Infrared spectrum (Thin Film, NaCl) of compound **246a**.

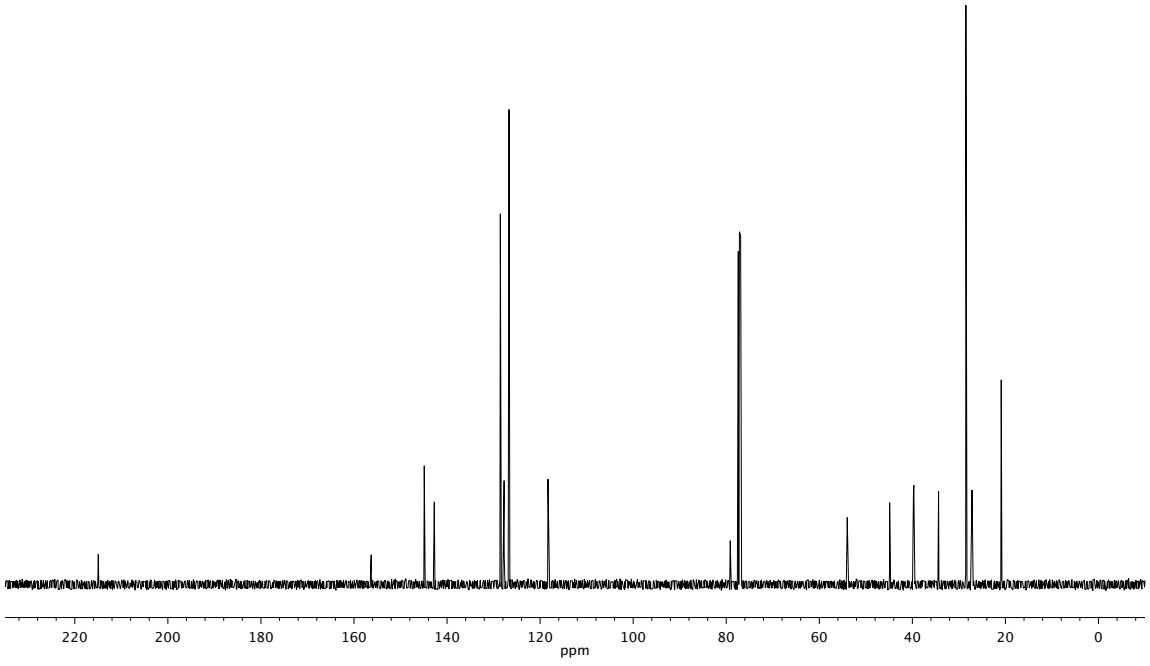


Figure A9.78. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246a**.

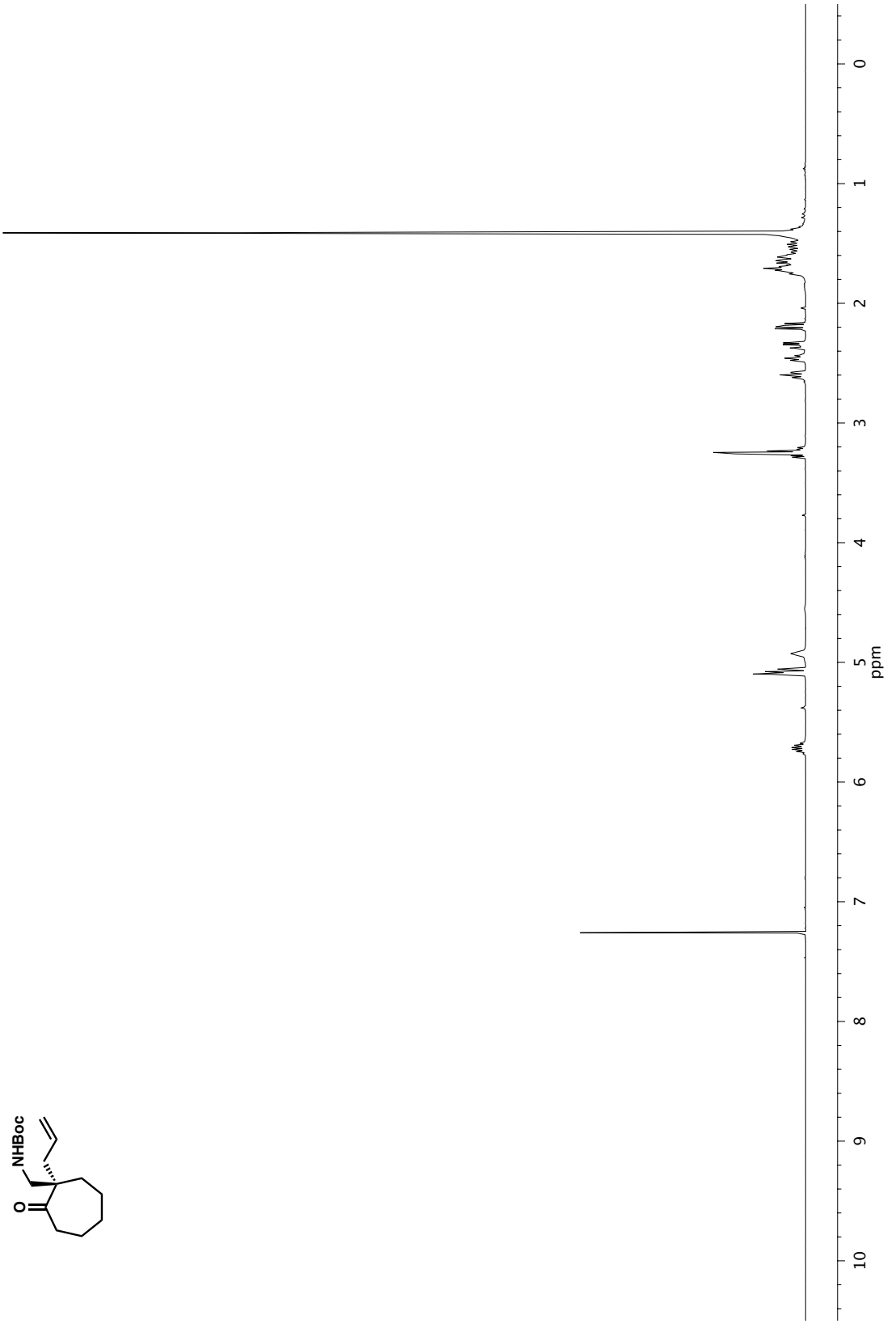


Figure A9.79. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246b**.

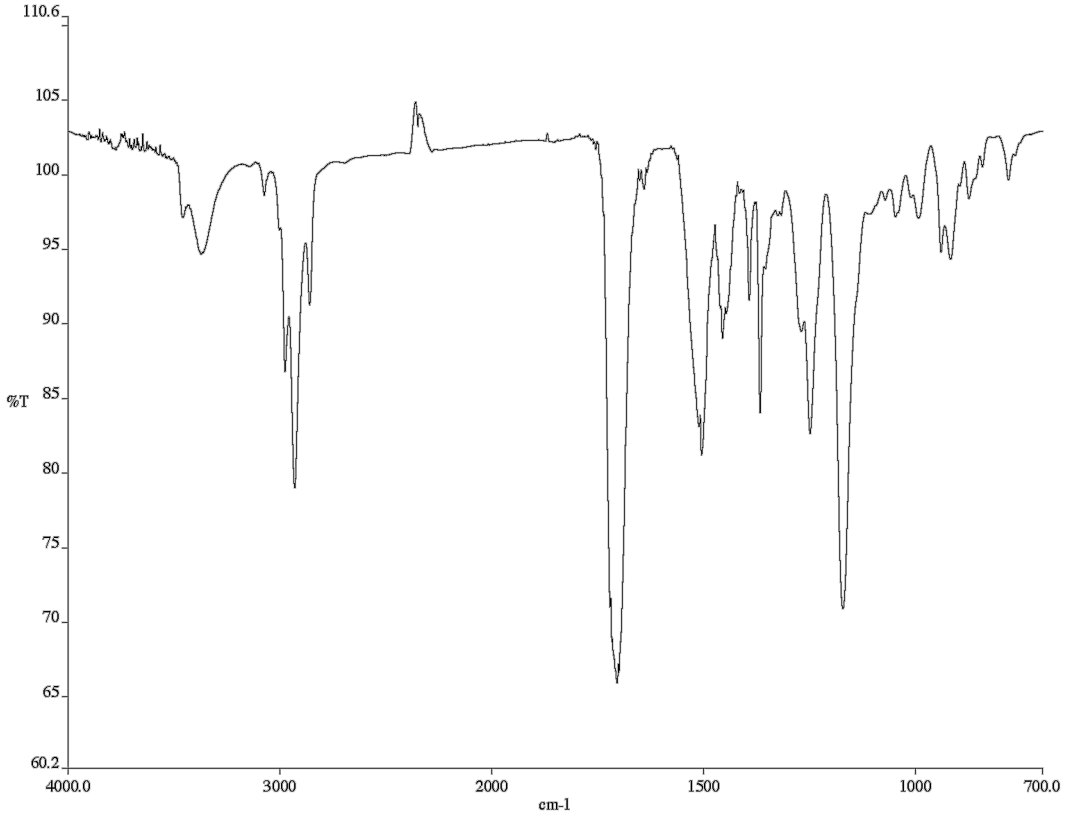


Figure A9.80. Infrared spectrum (Thin Film, NaCl) of compound **246b**.

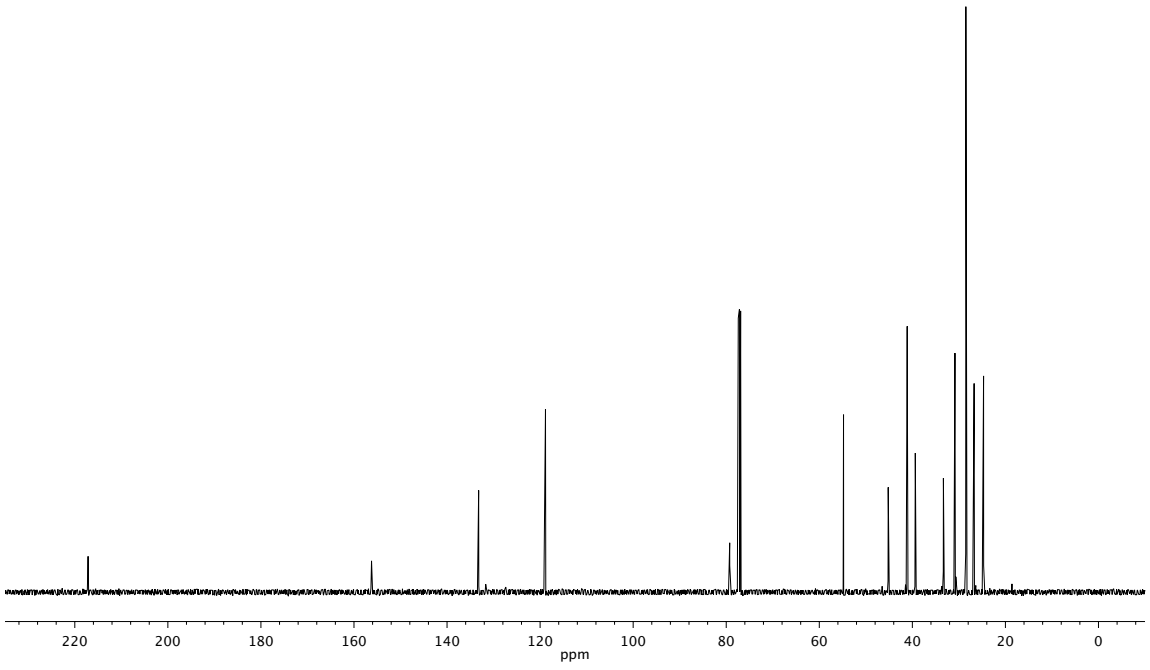


Figure A9.81. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246b**.

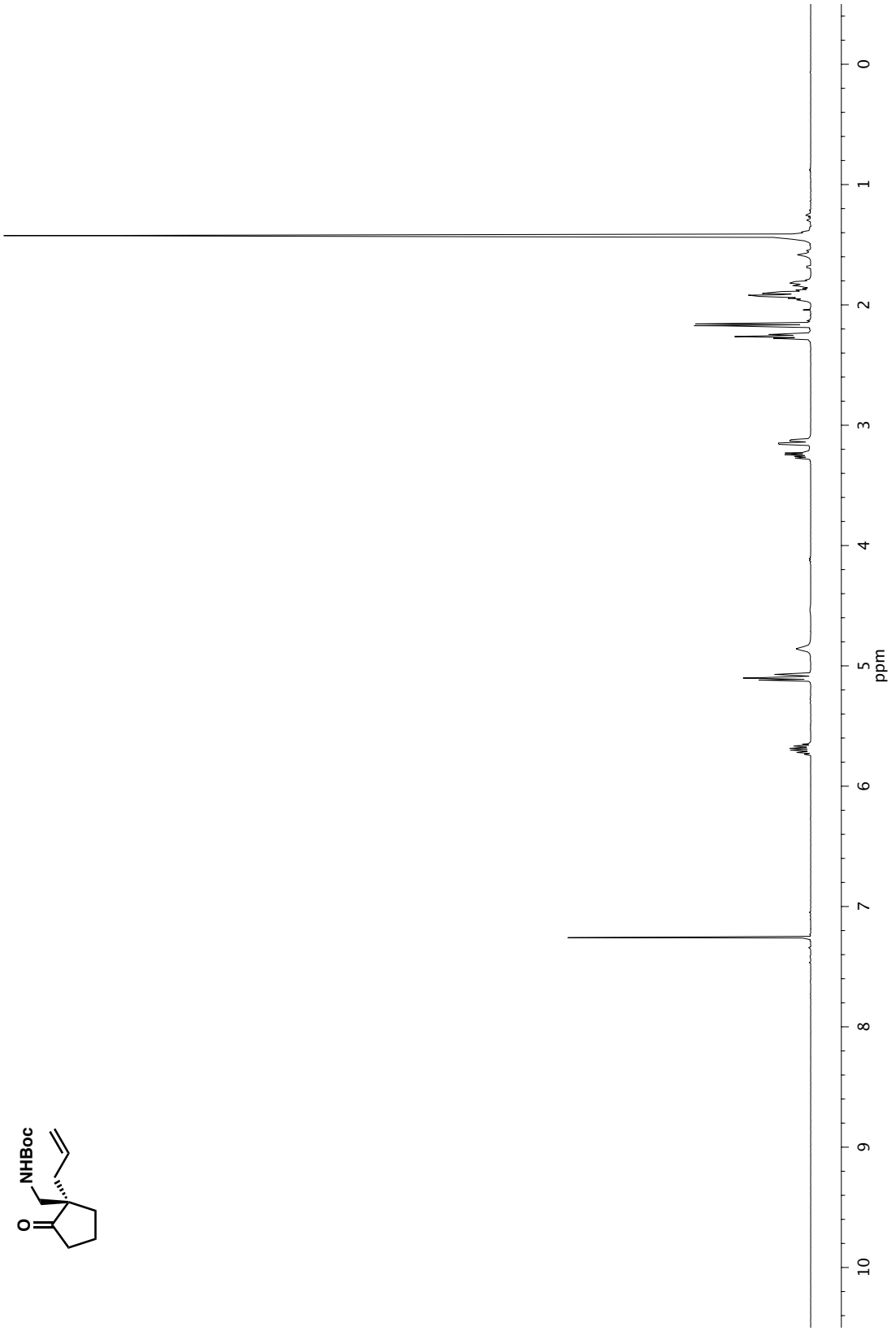


Figure A9.82. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246c**.

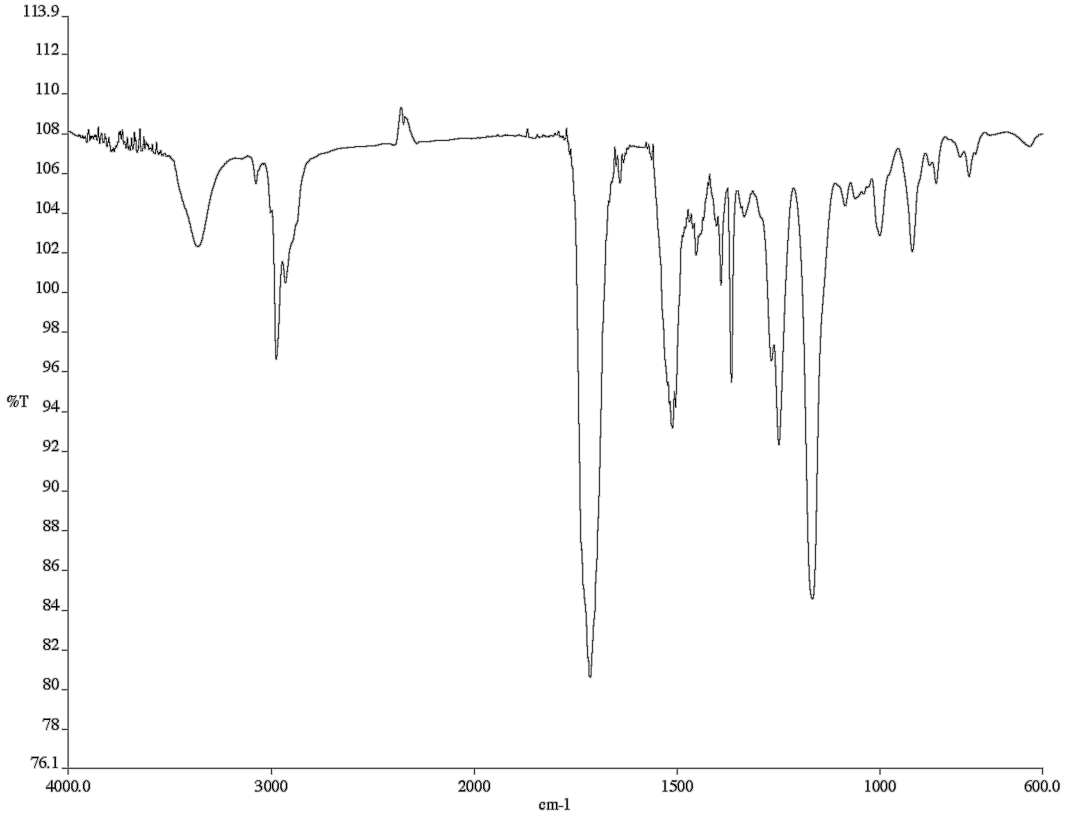


Figure A9.83. Infrared spectrum (Thin Film, NaCl) of compound **246c**.

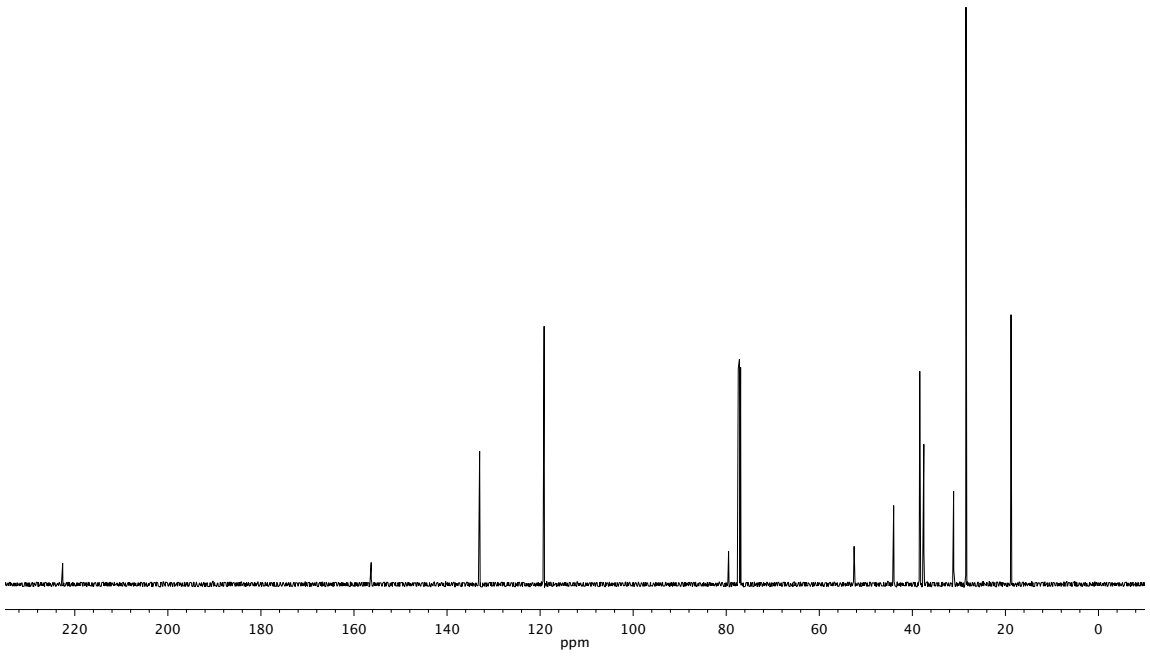


Figure A9.84. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246c**.

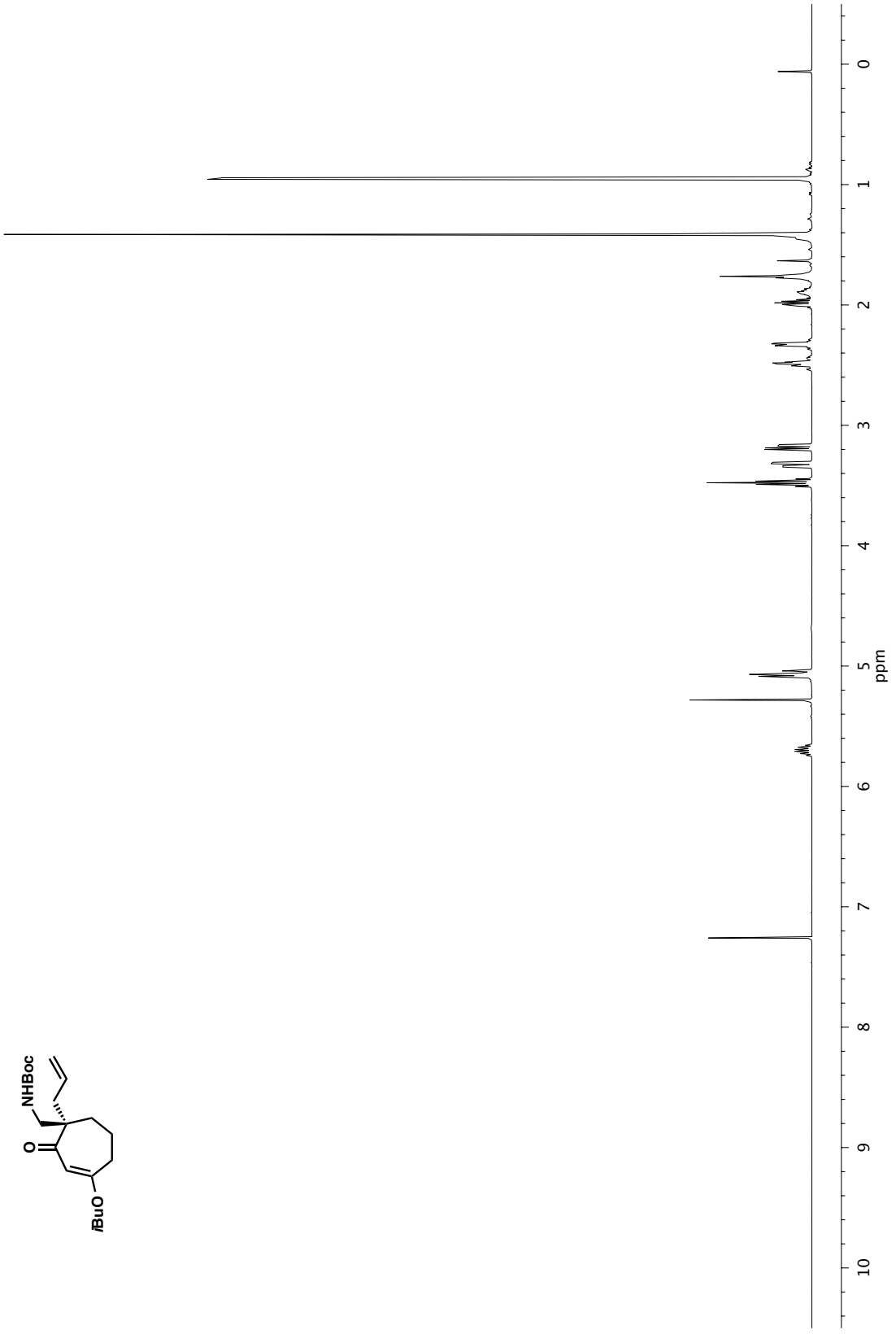


Figure A9.85. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246d**.

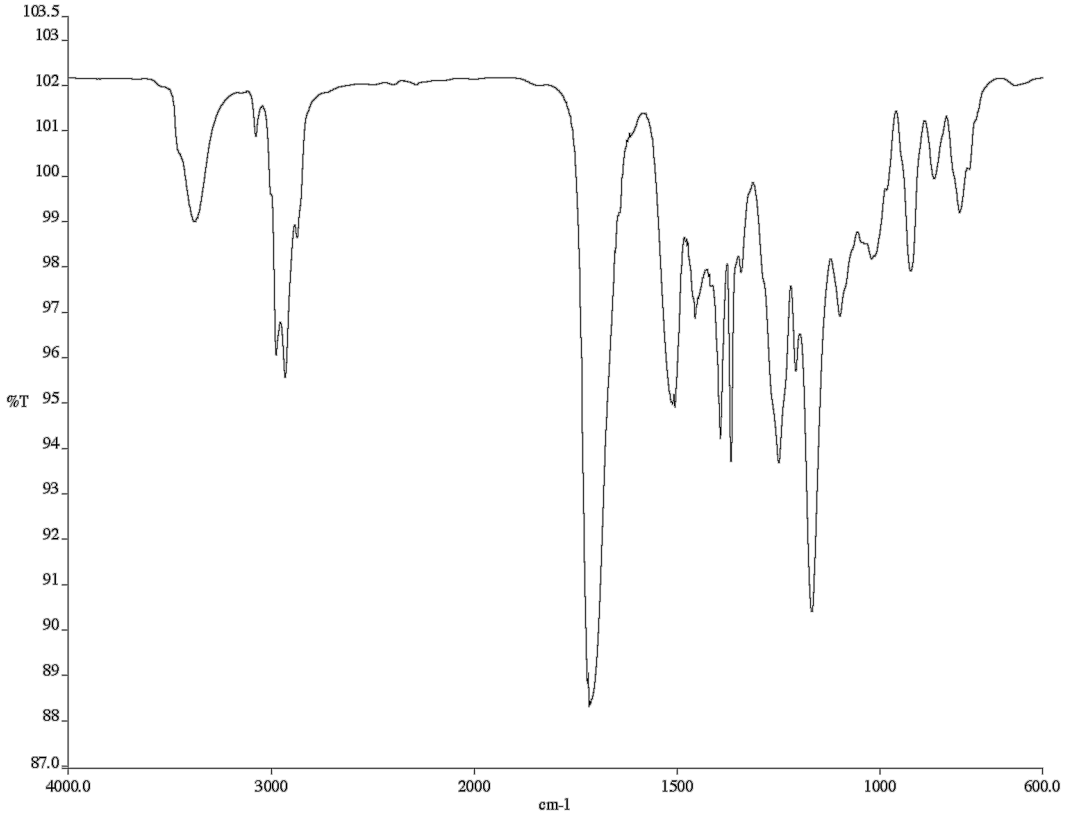


Figure A9.86. Infrared spectrum (Thin Film, NaCl) of compound **246d**.

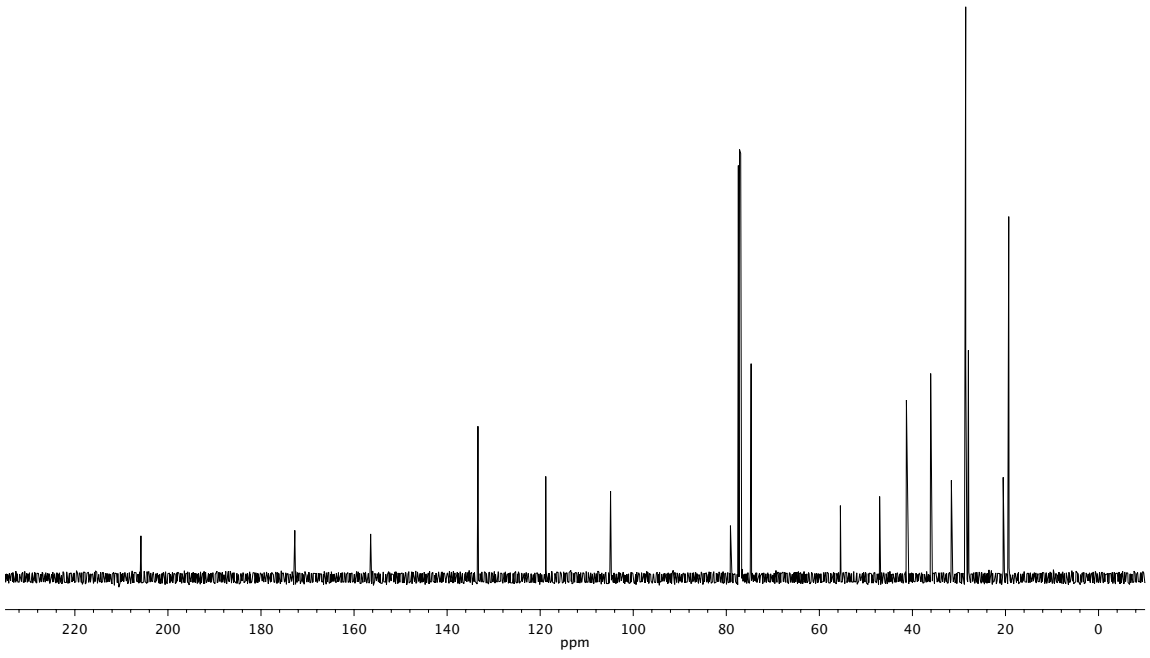


Figure A9.87. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246d**.

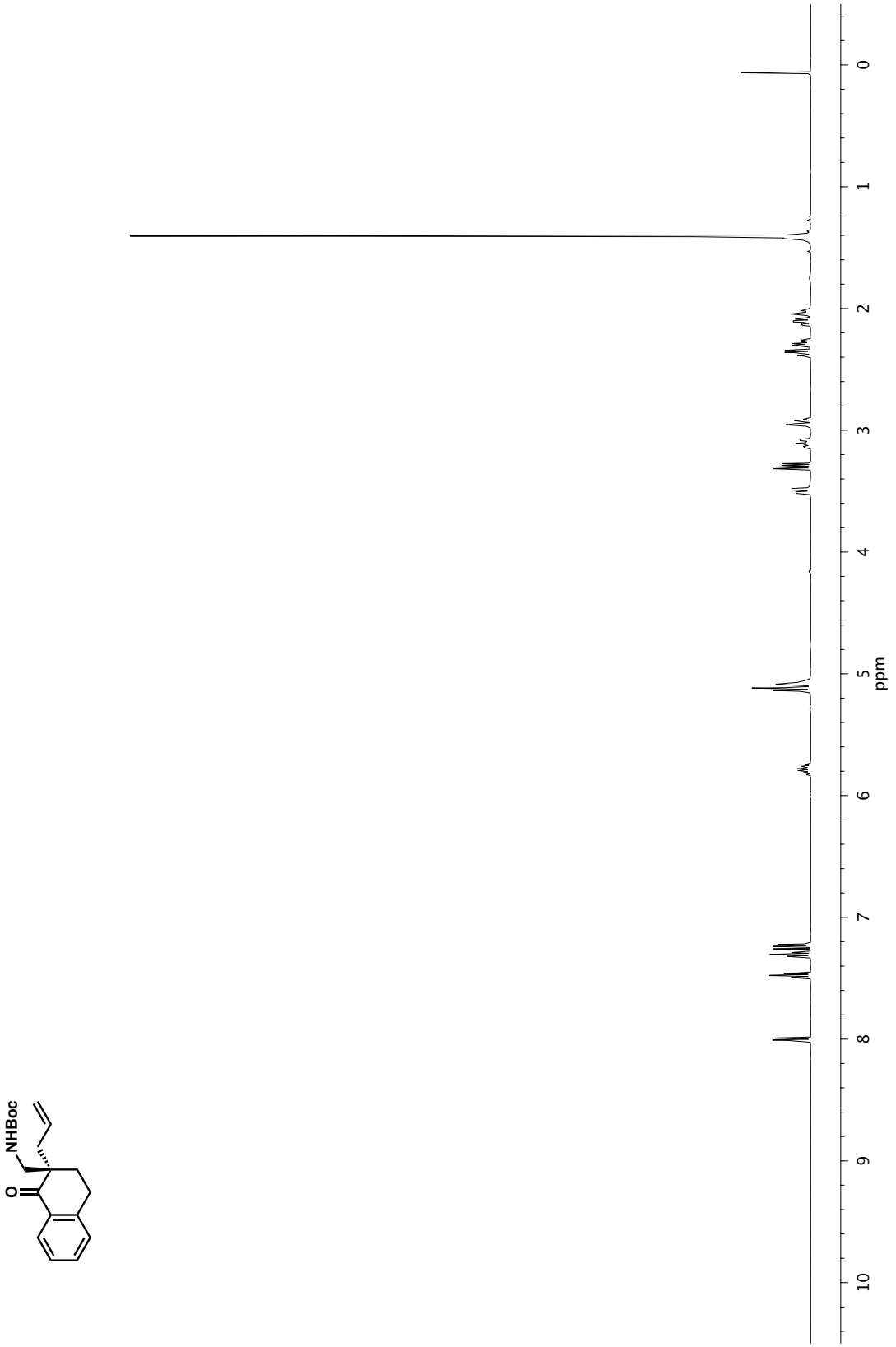


Figure A9.88. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246e**.

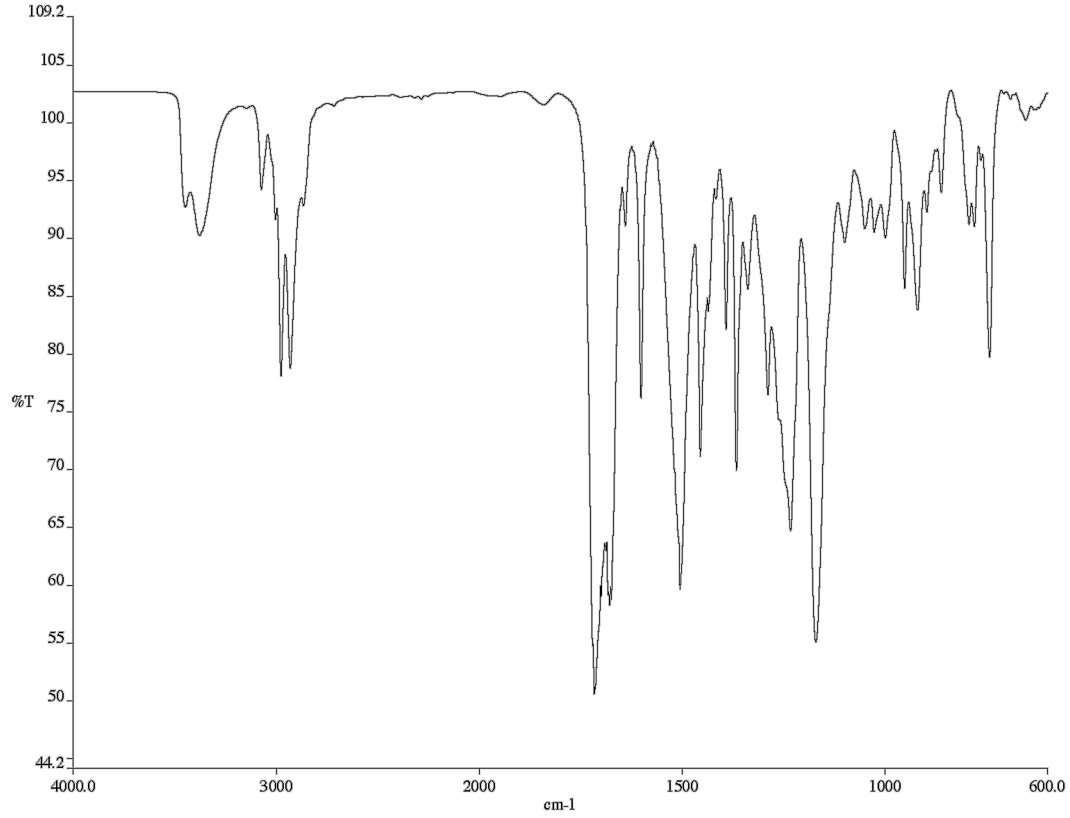


Figure A9.89. Infrared spectrum (Thin Film, NaCl) of compound **246e**.

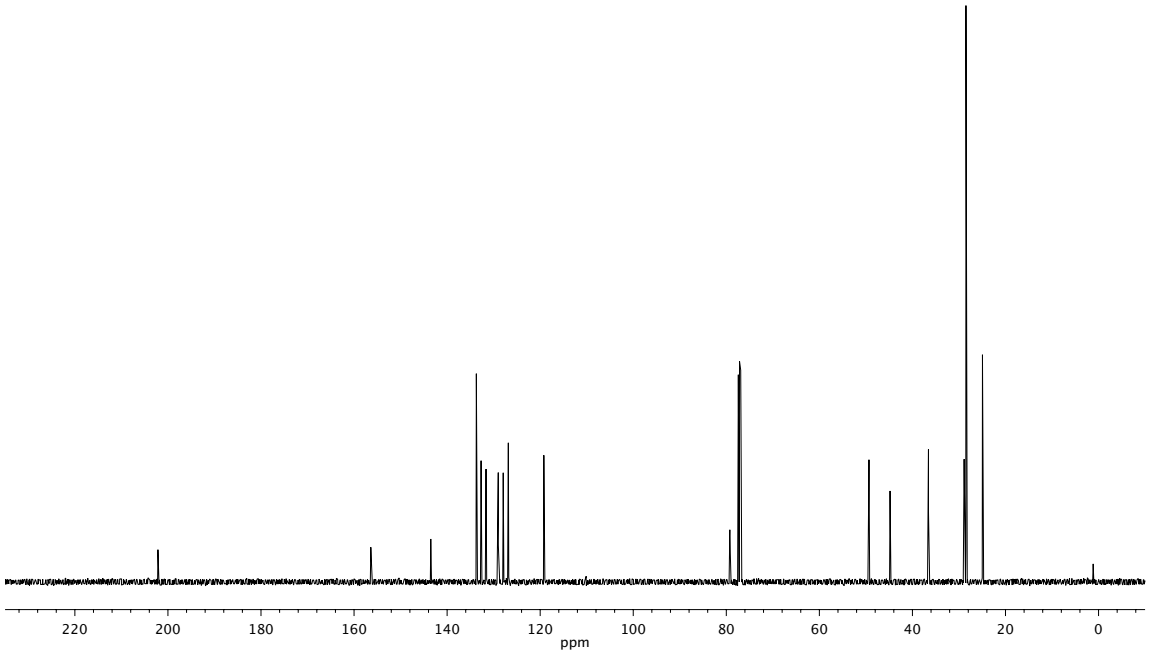


Figure A9.90. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246e**.

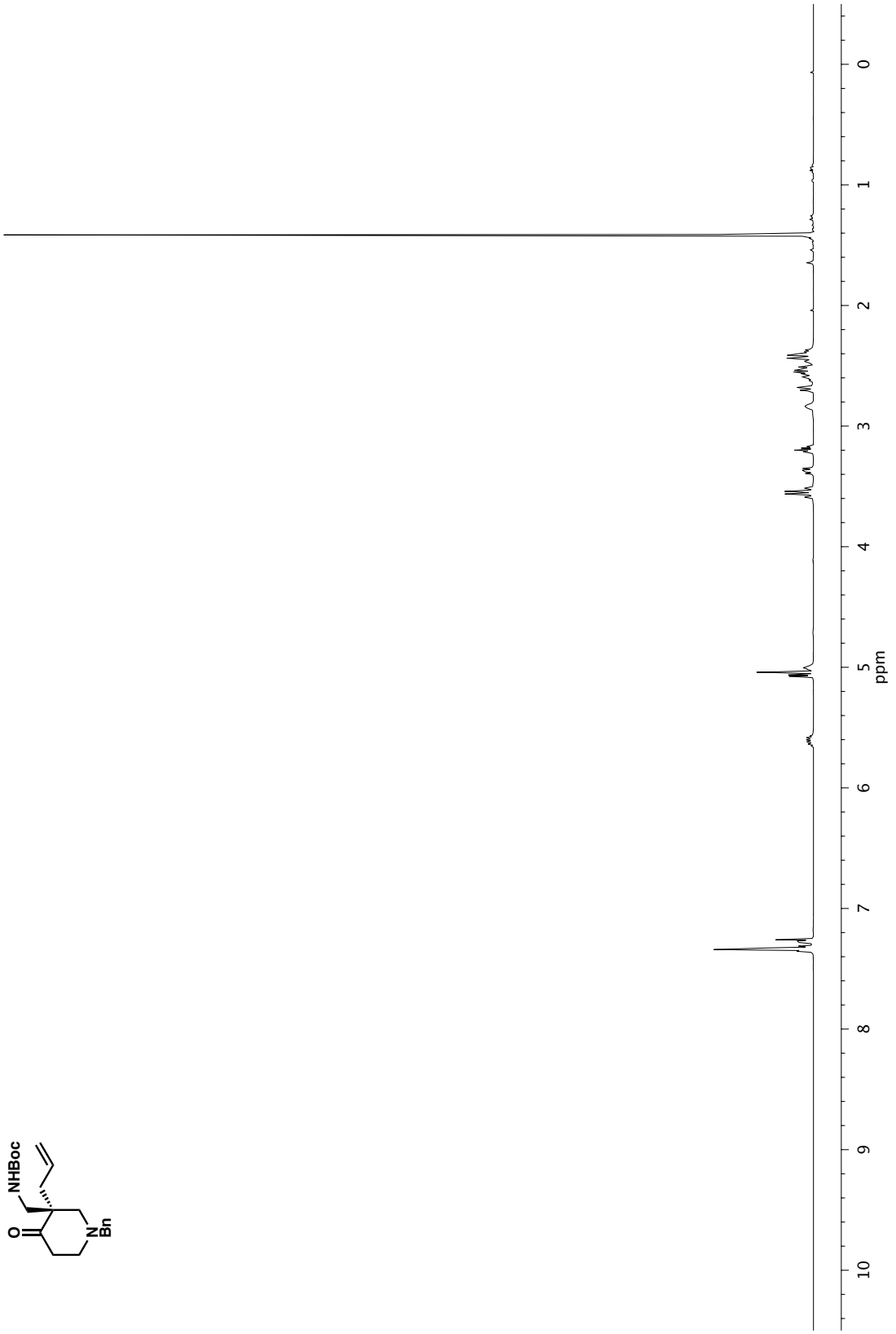


Figure A9.91. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246f**.

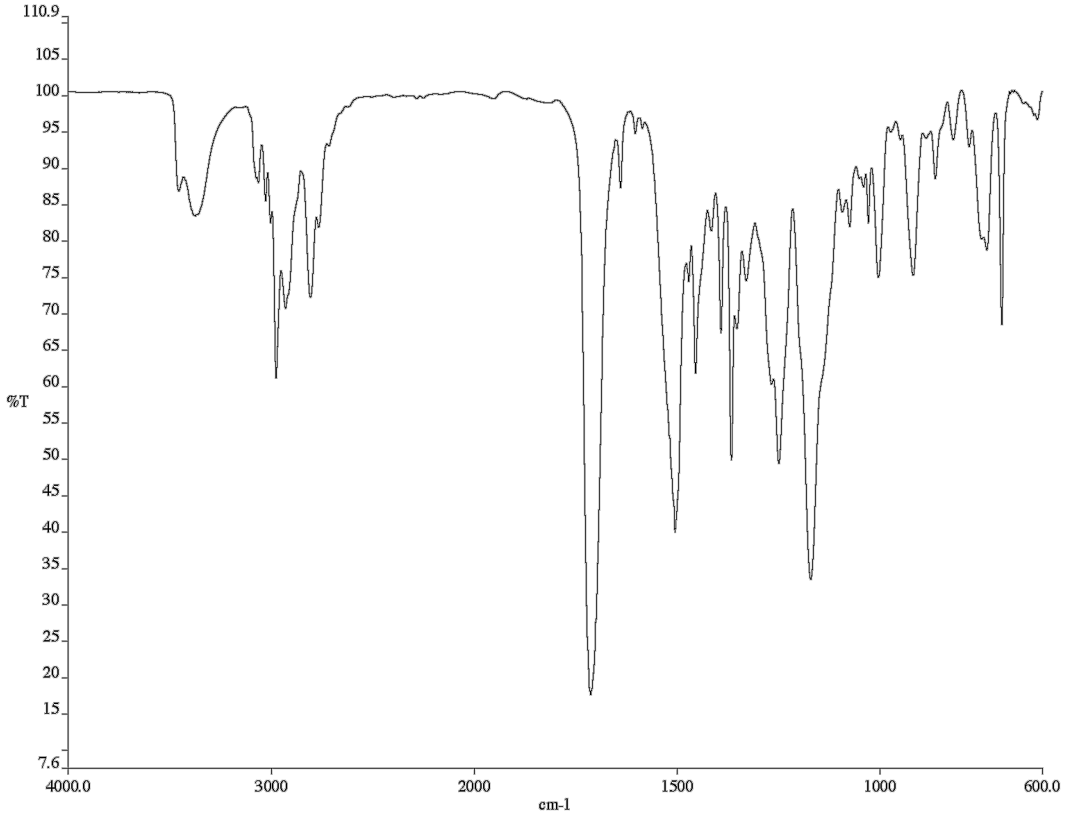


Figure A9.92. Infrared spectrum (Thin Film, NaCl) of compound **246f**.

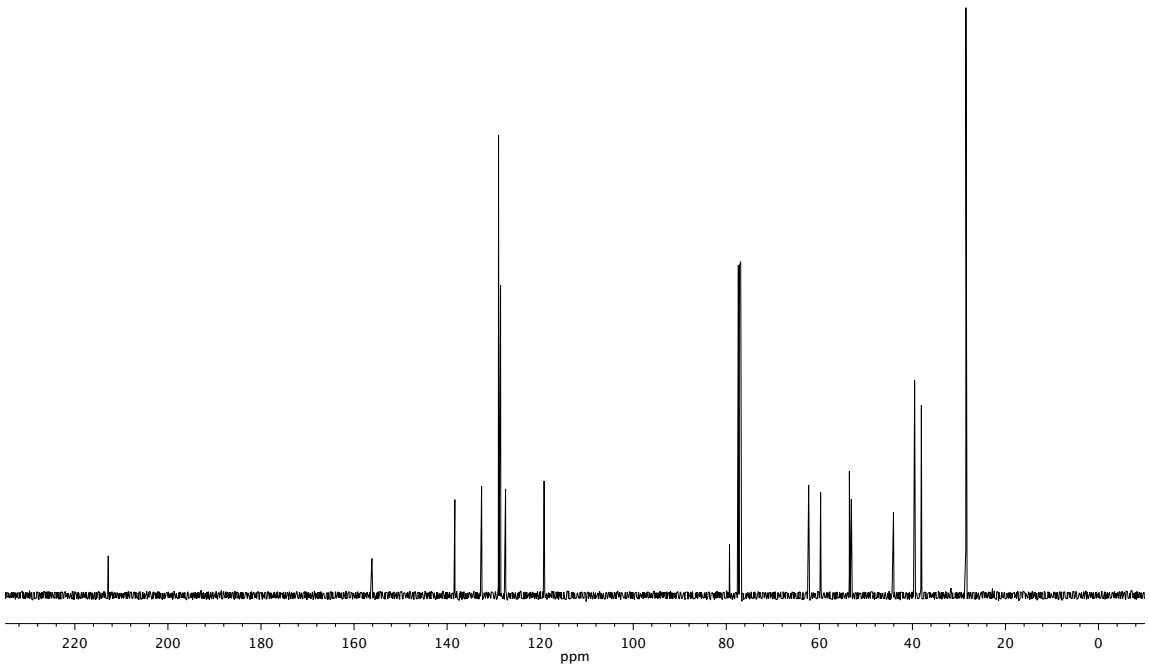


Figure A9.93. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246f**.

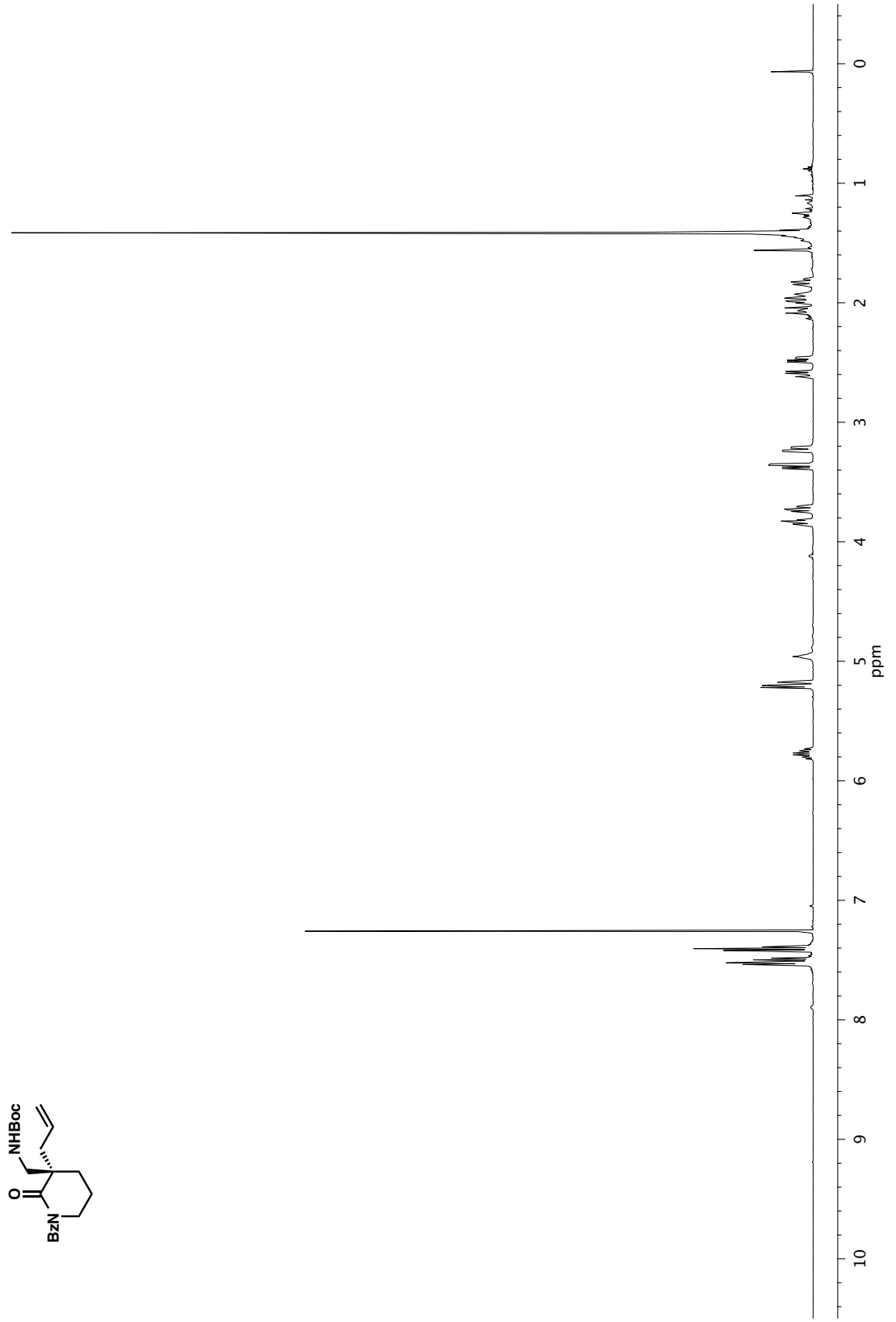


Figure A9.94. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246g**.

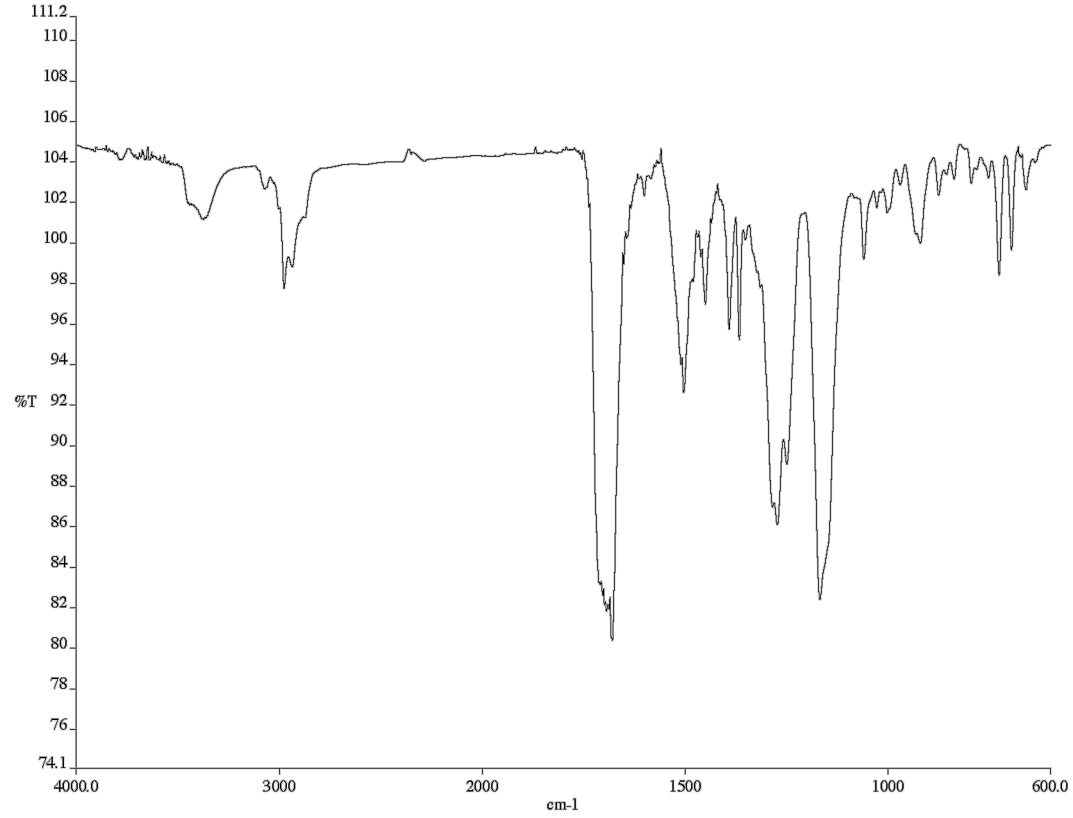


Figure A9.95. Infrared spectrum (Thin Film, NaCl) of compound **246g**.

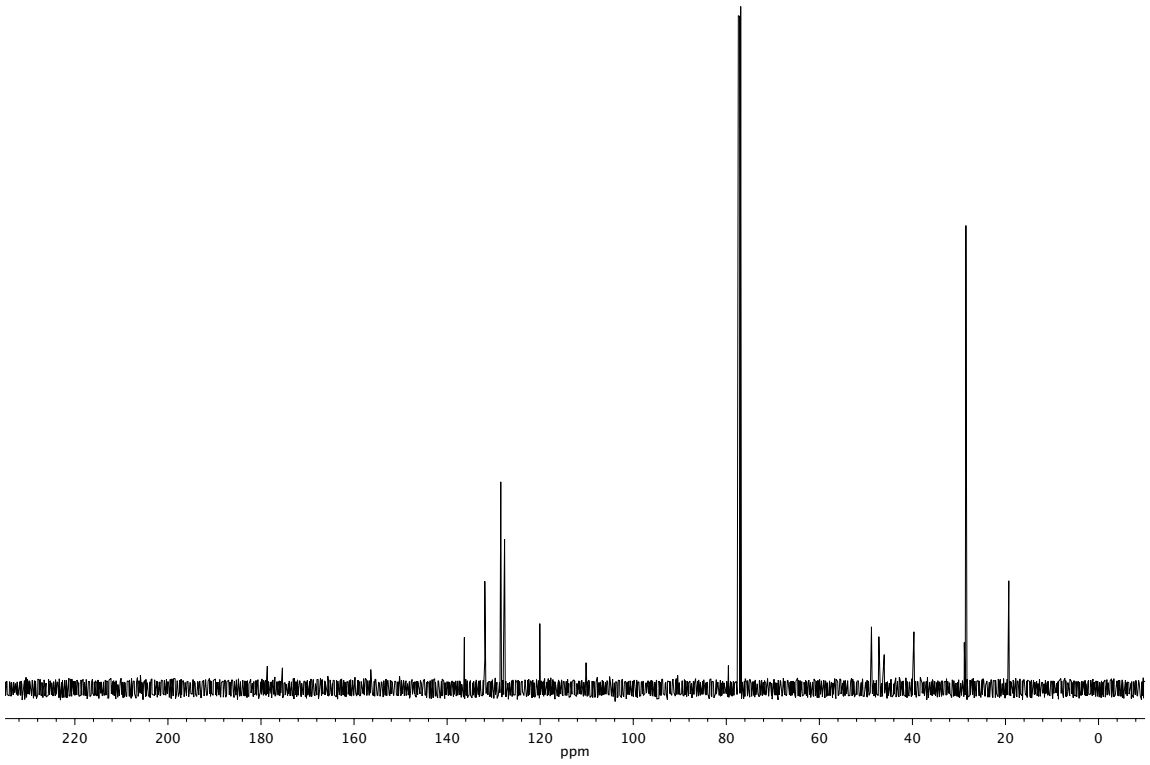


Figure A9.96. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246g**.

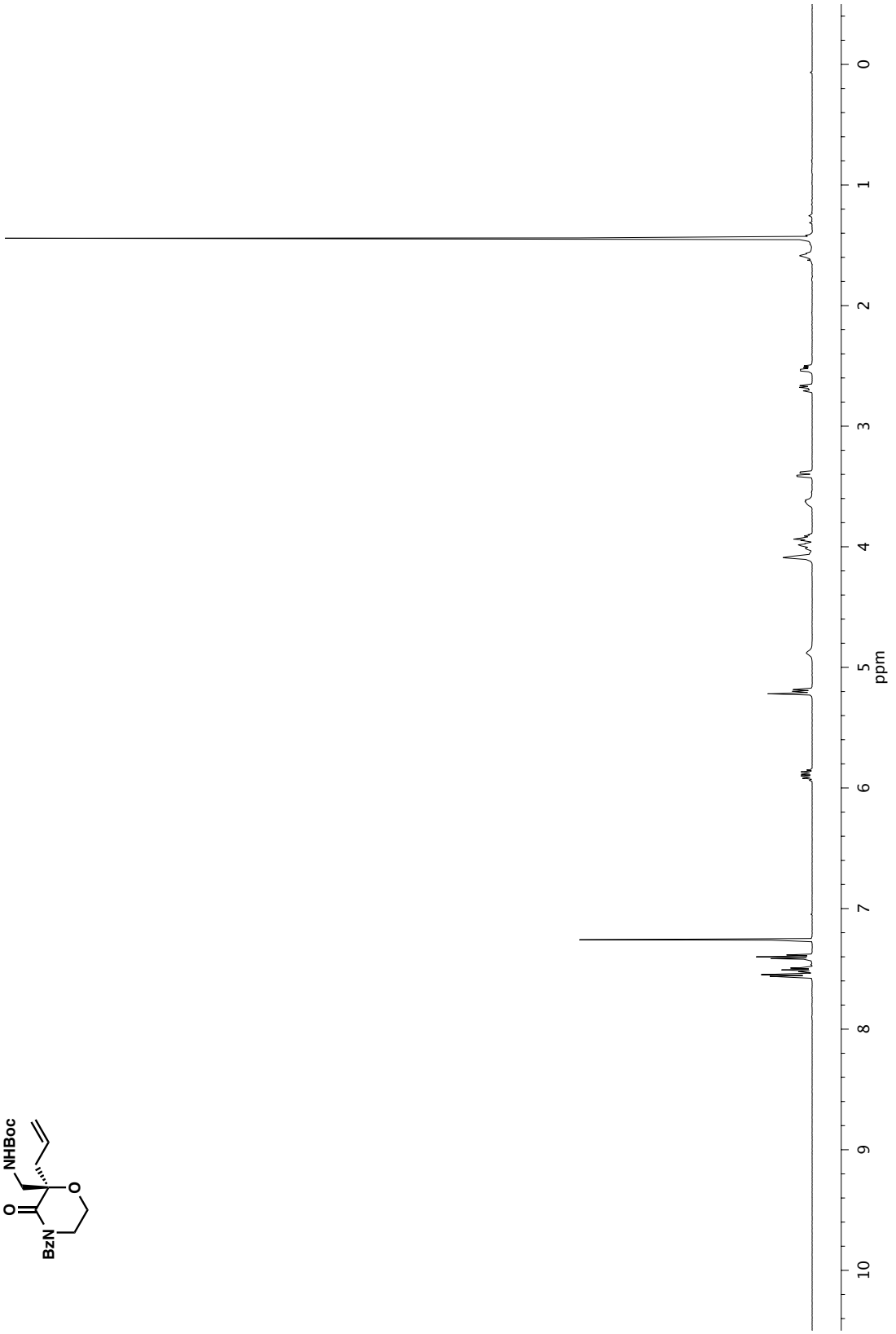


Figure A9.97. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246h**.

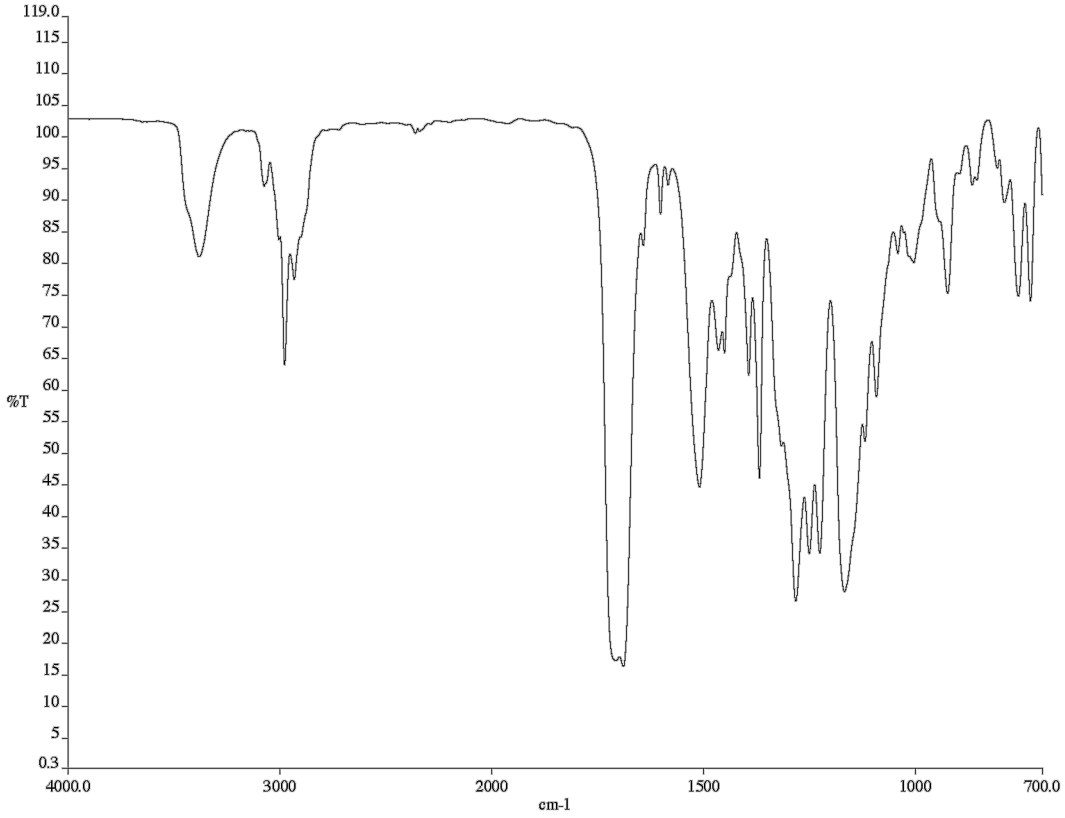


Figure A9.98. Infrared spectrum (Thin Film, NaCl) of compound **246h**.

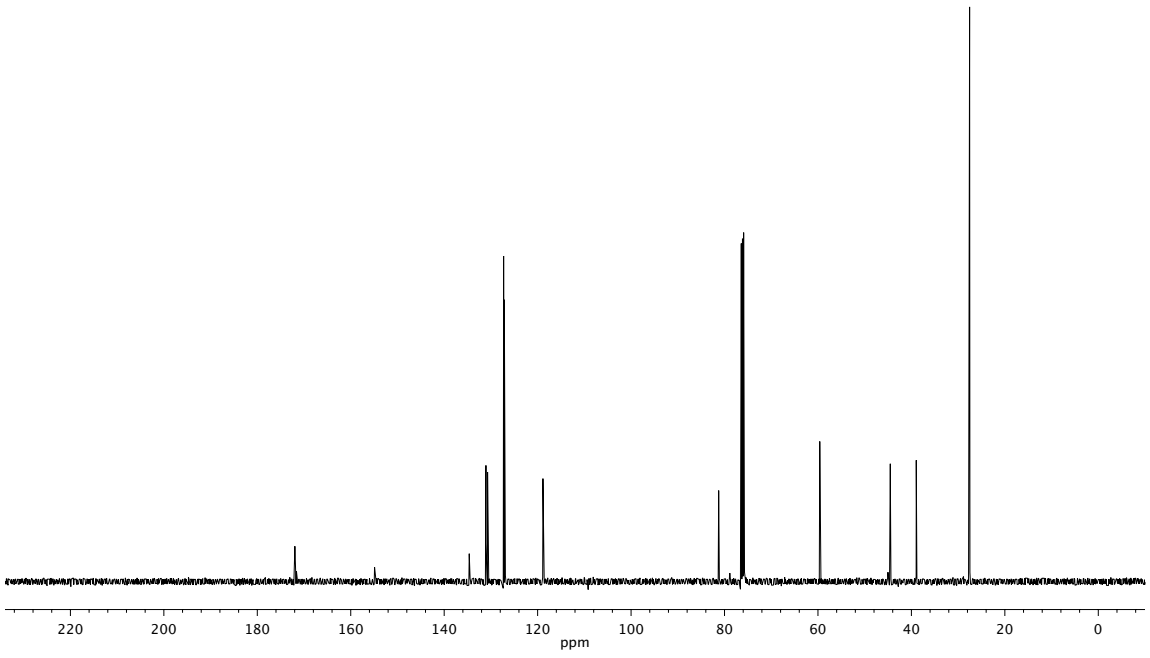


Figure A9.99. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246h**.

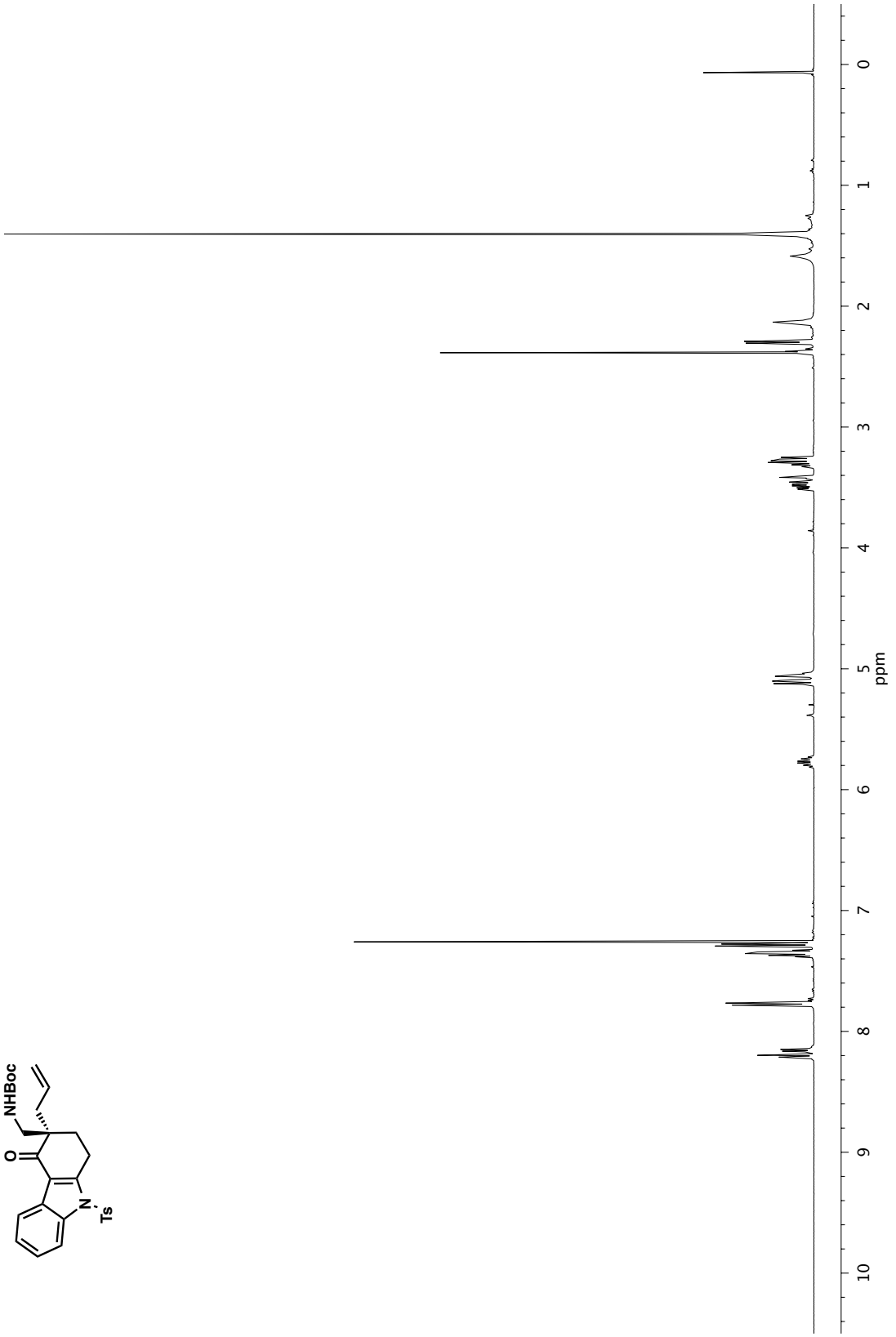


Figure A9.100. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246i**.

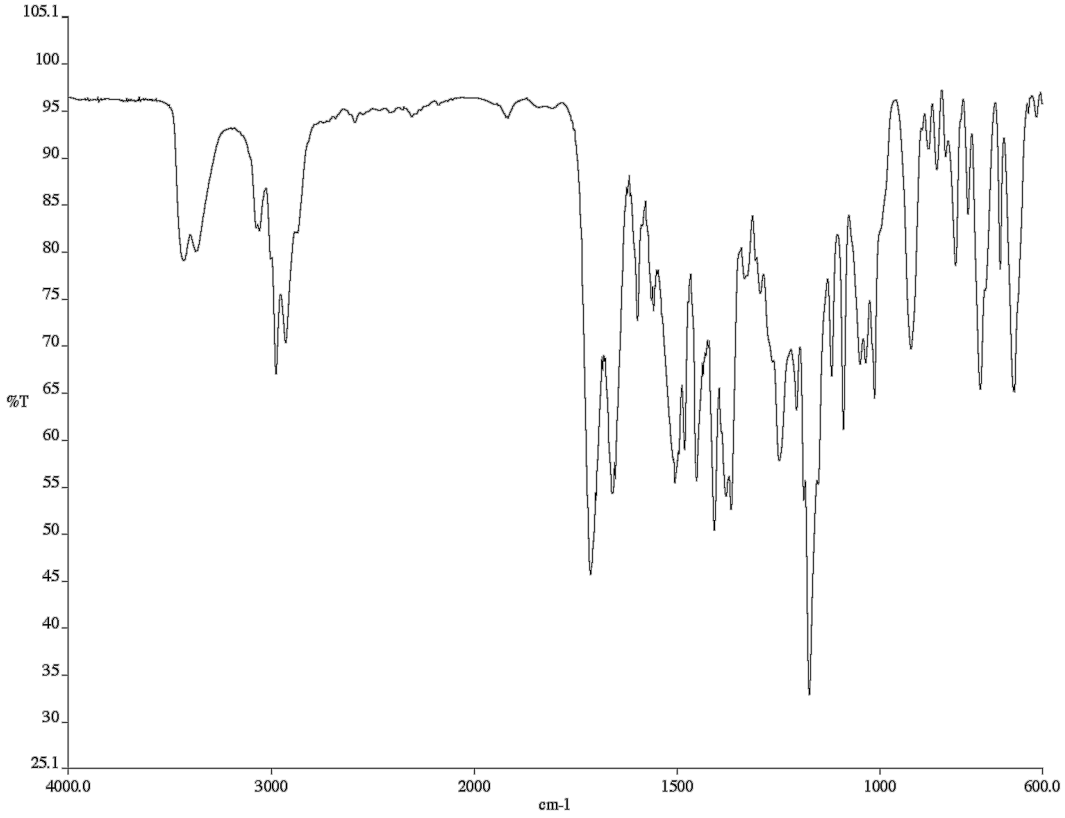


Figure A9.101. Infrared spectrum (Thin Film, NaCl) of compound **246i**.

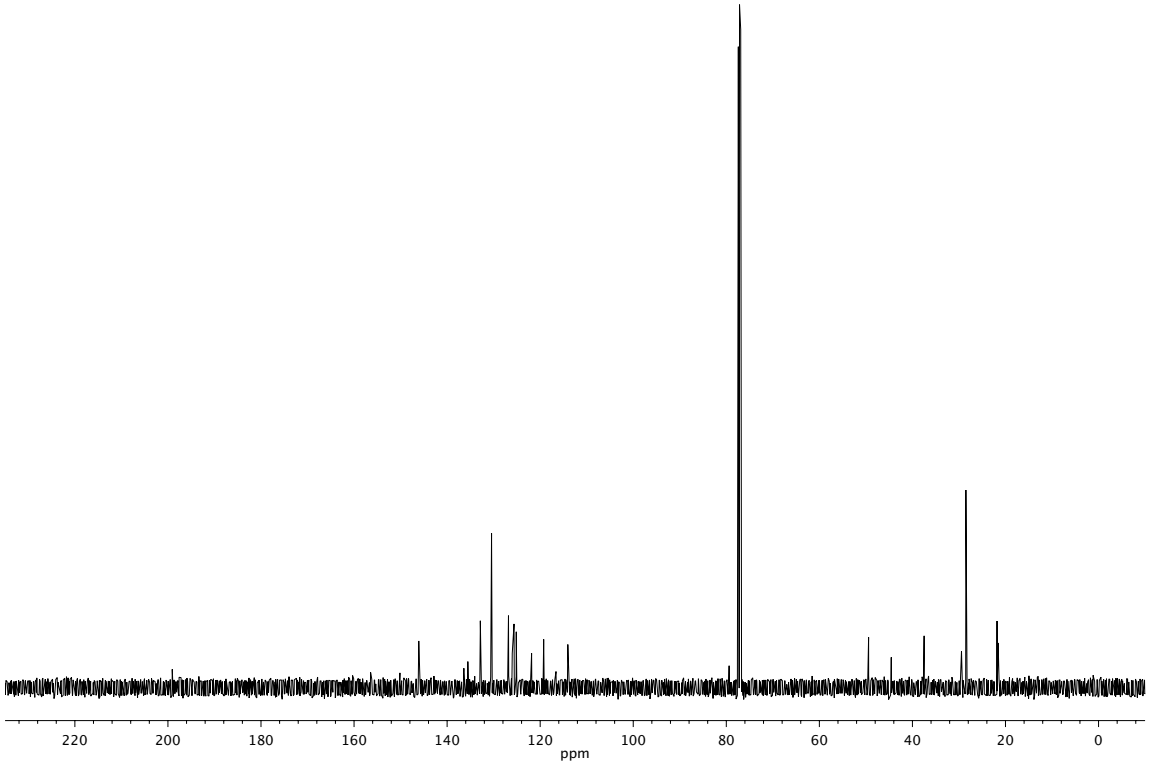


Figure A9.102. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246i**.

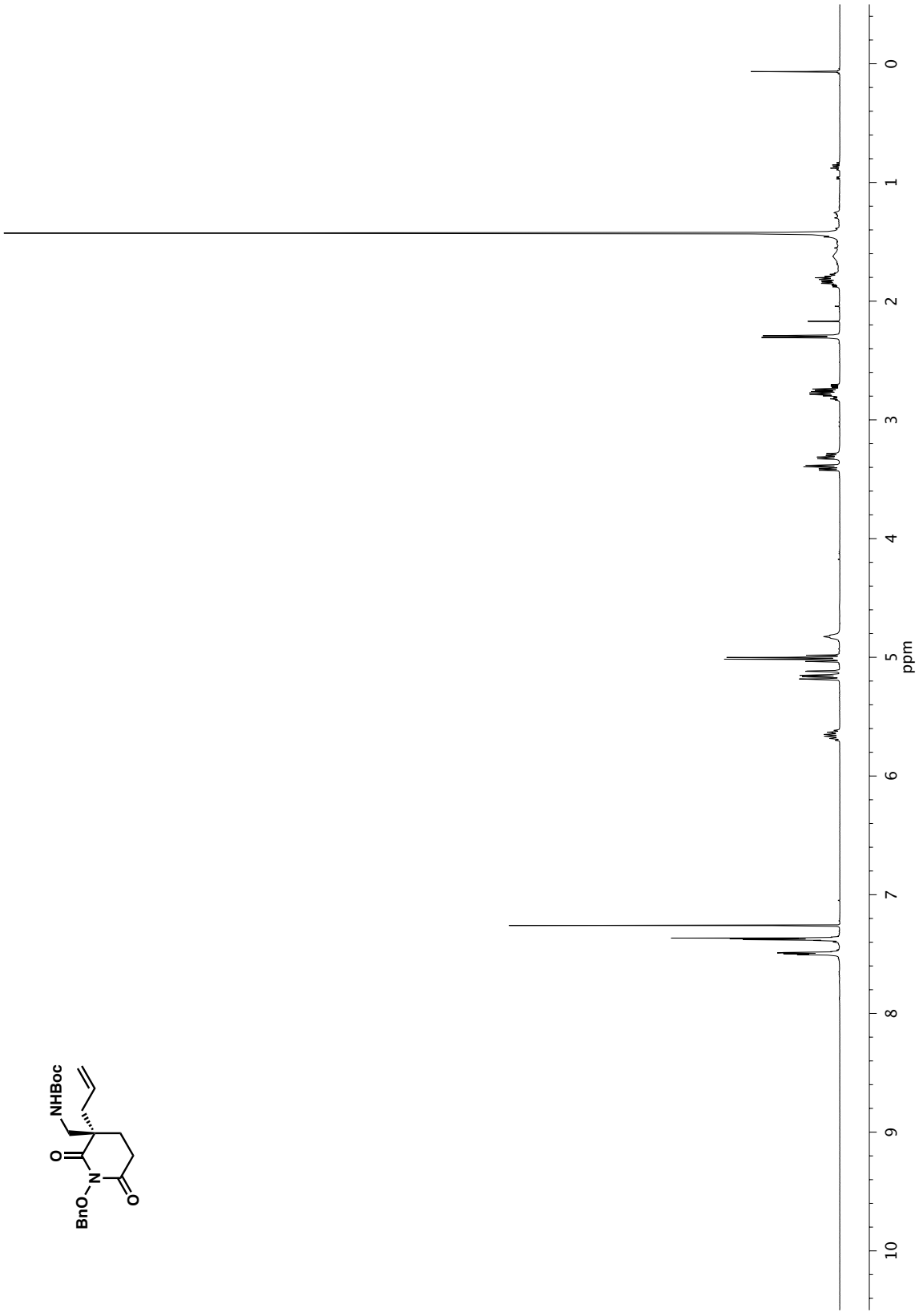


Figure A9.103. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246j**.

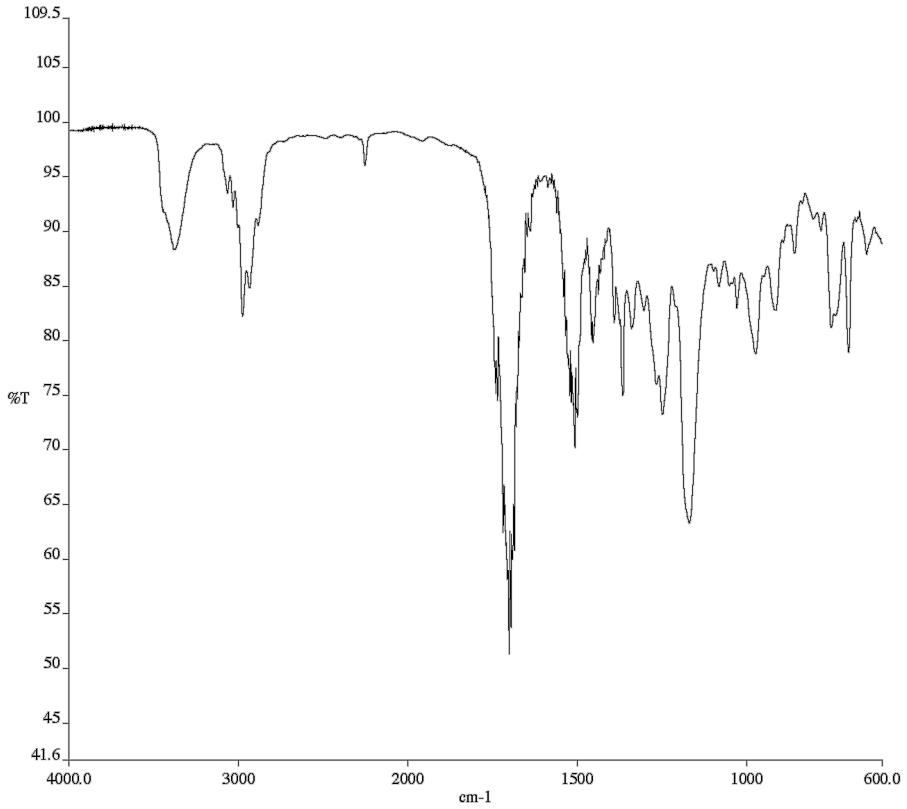


Figure A9.104. Infrared spectrum (Thin Film, NaCl) of compound **246j**.

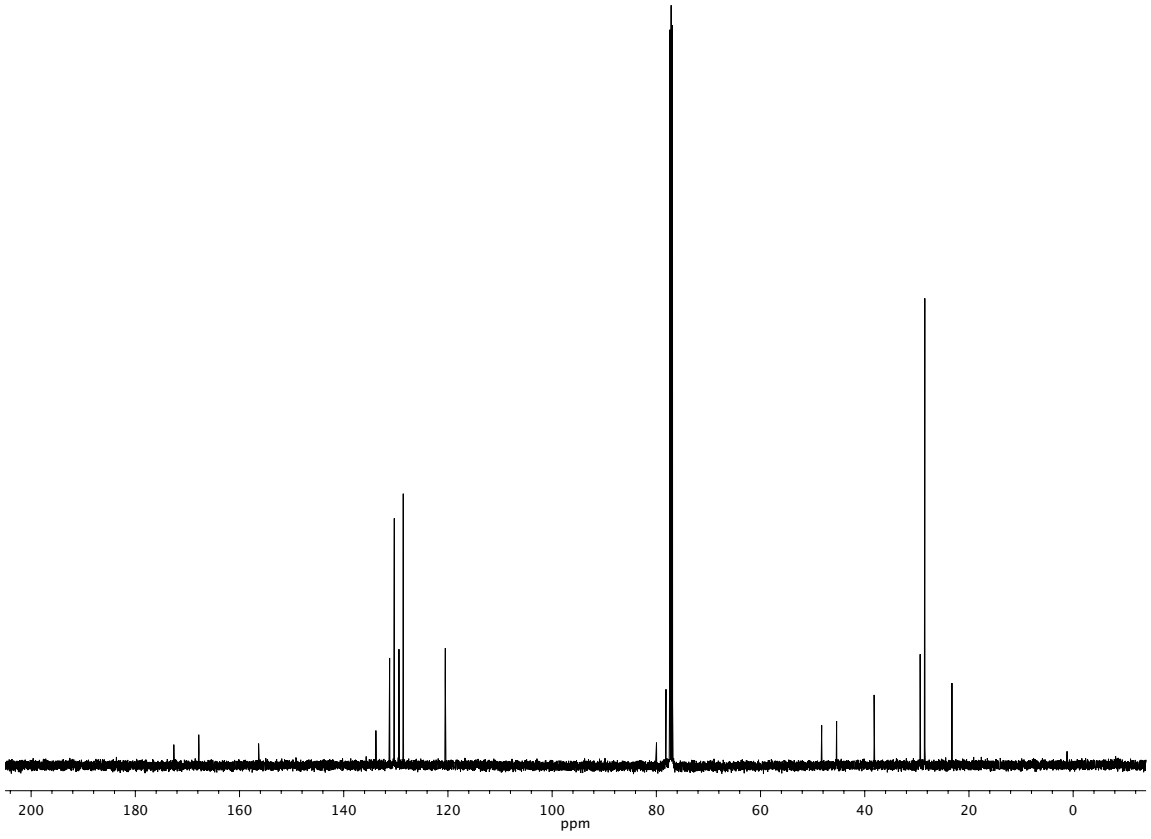


Figure A9.105. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **246j**.

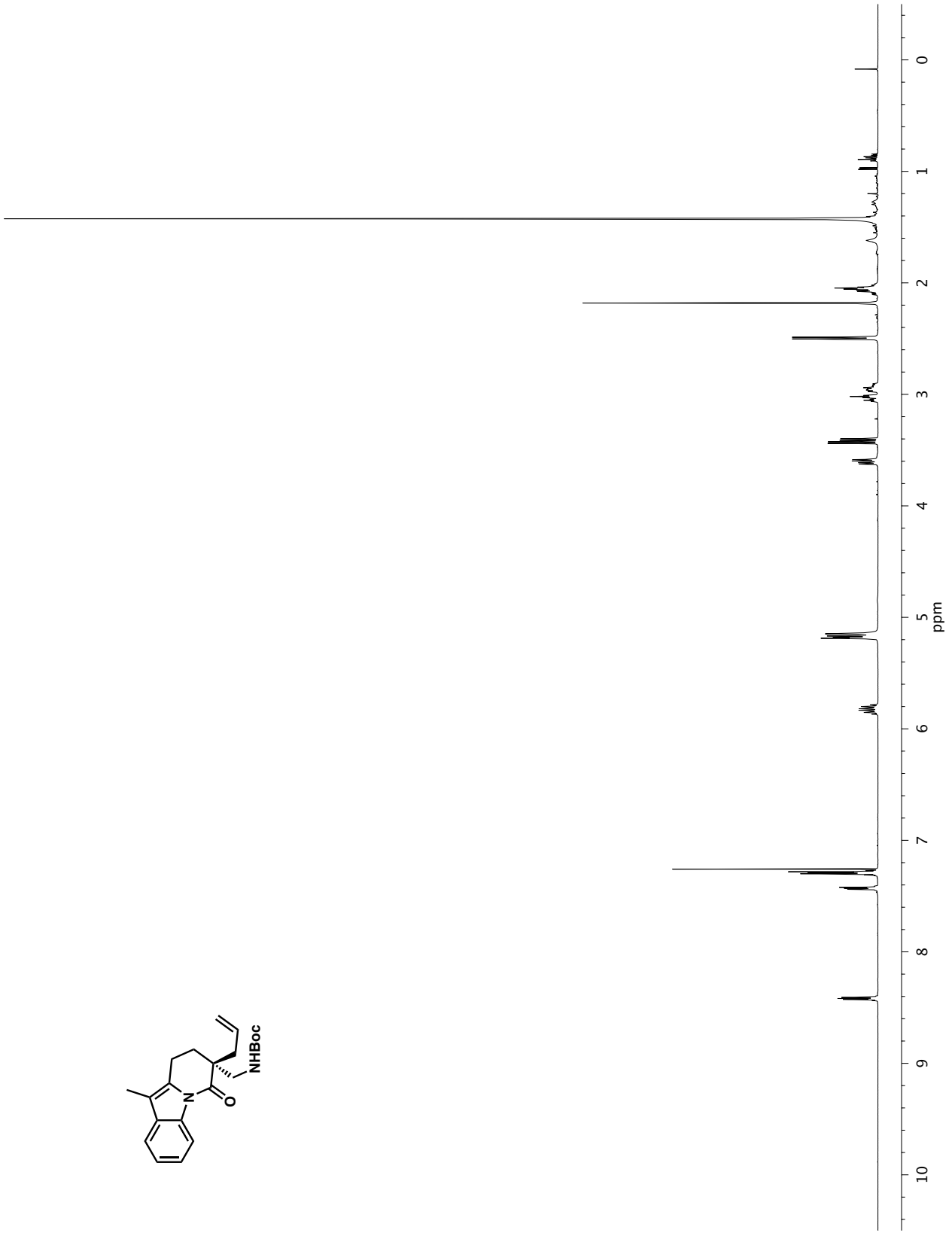


Figure A9.106. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165g**.

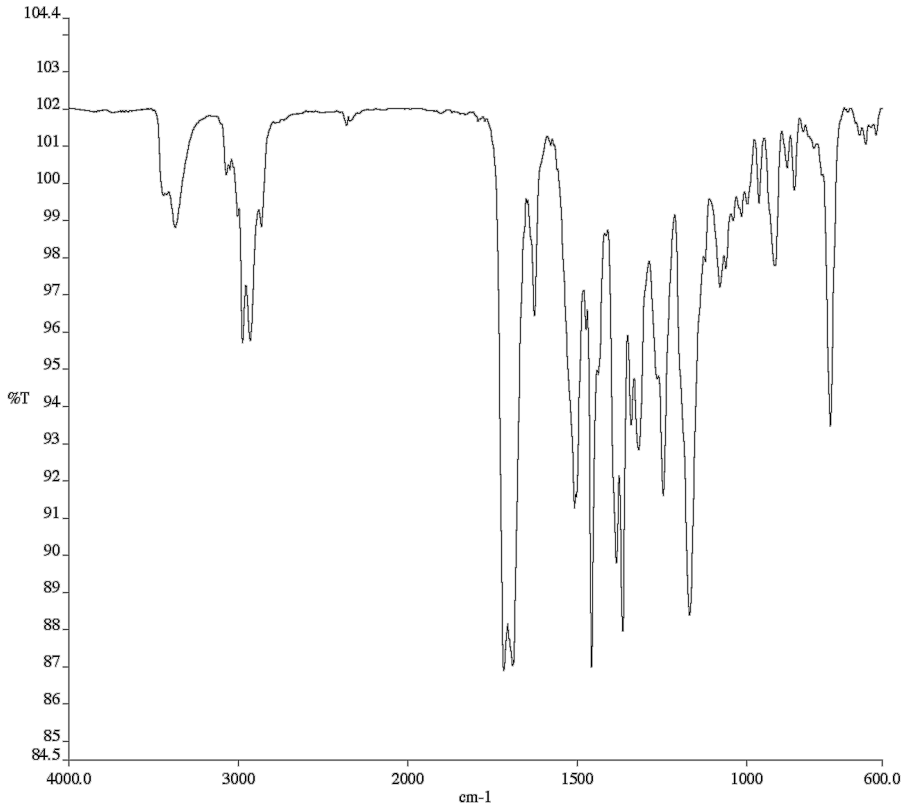


Figure A9.107. Infrared spectrum (Thin Film, NaCl) of compound **165g**.

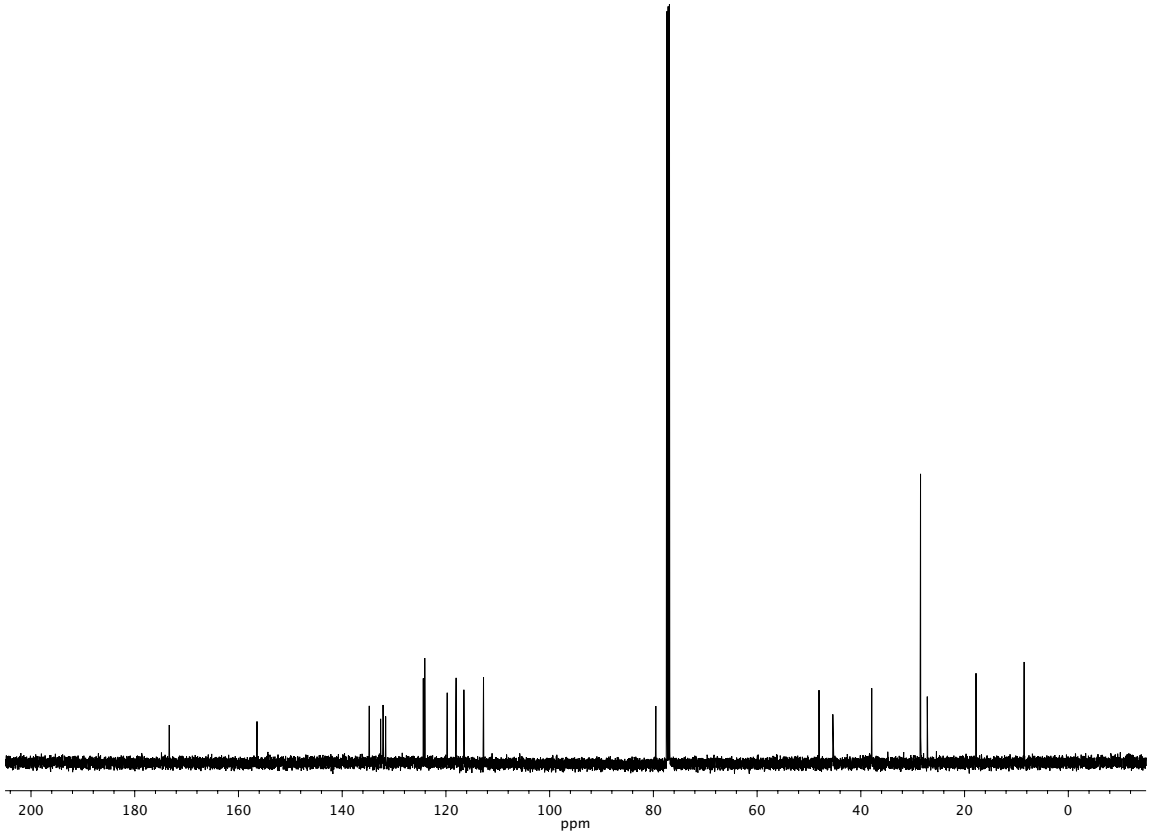


Figure A9.108. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **165g**.

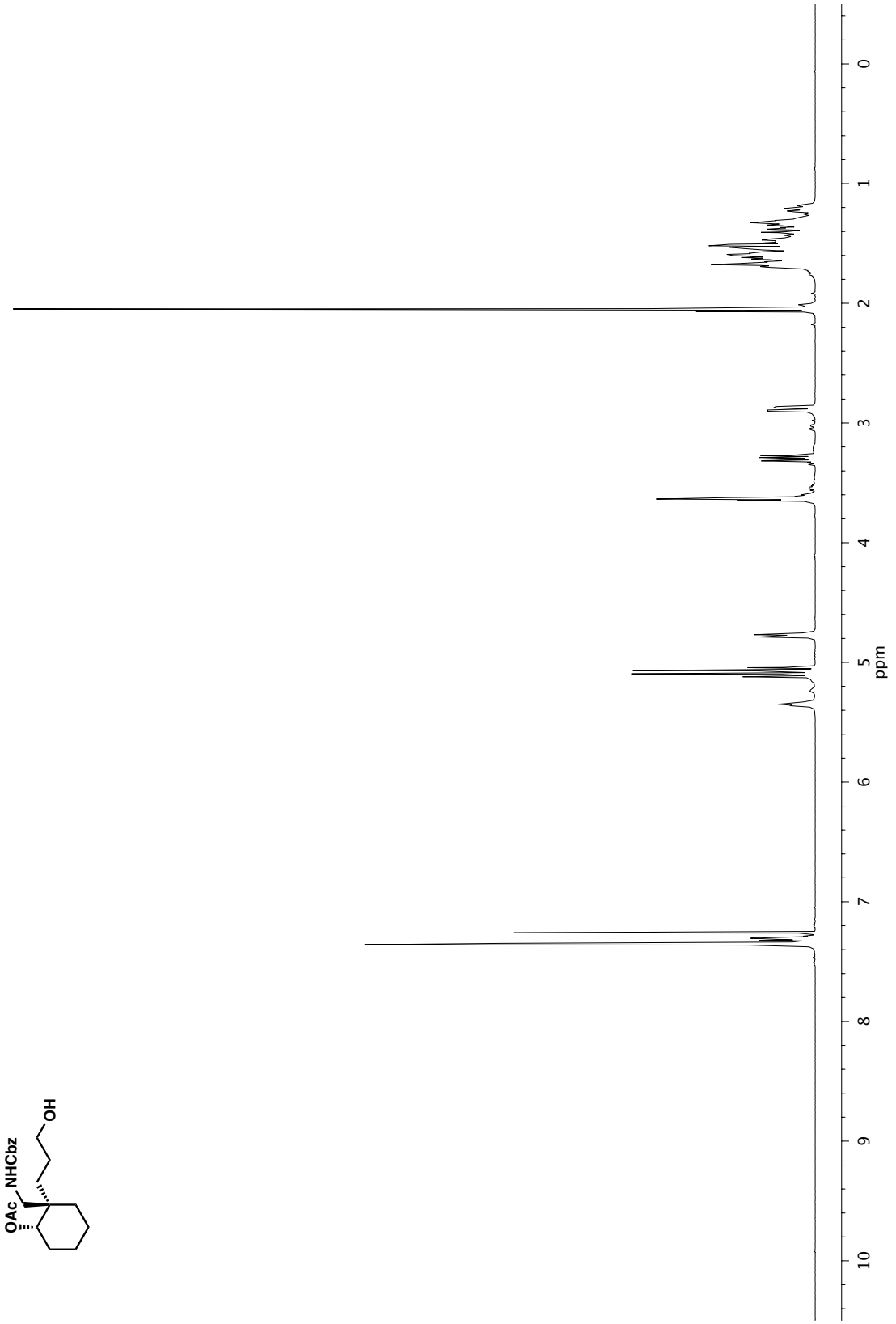


Figure A9.109. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **248**.

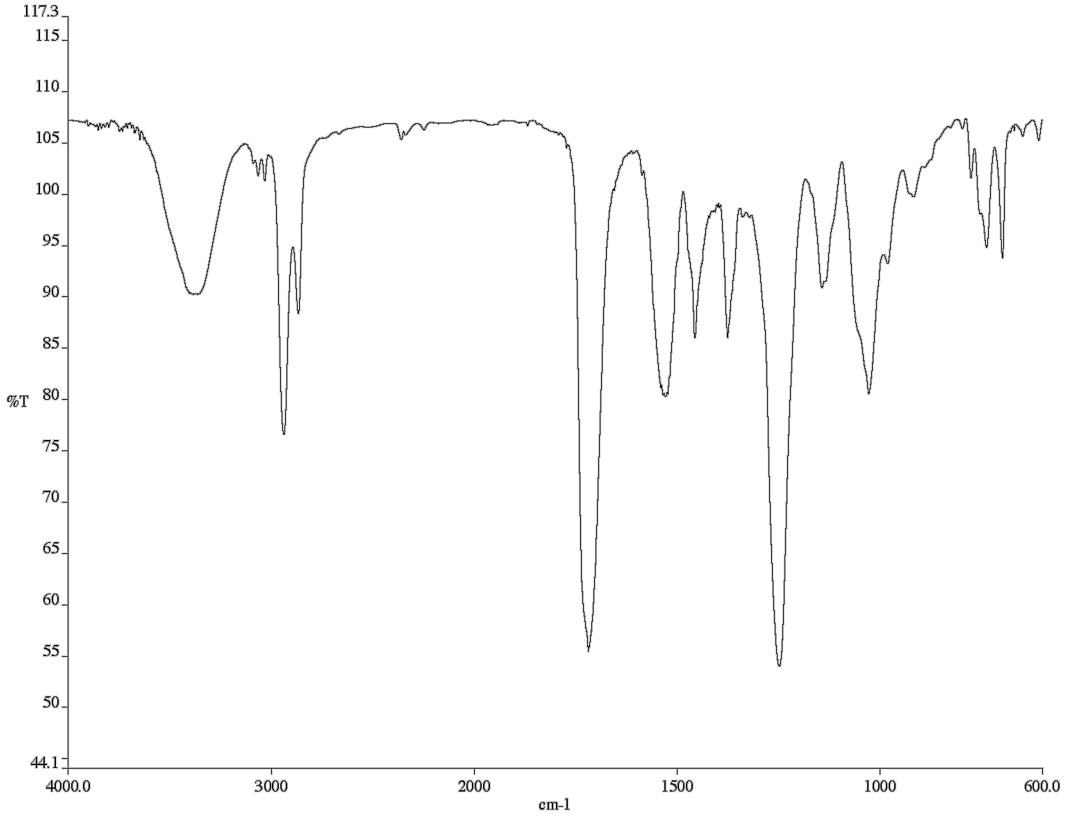


Figure A9.110. Infrared spectrum (Thin Film, NaCl) of compound **248**.

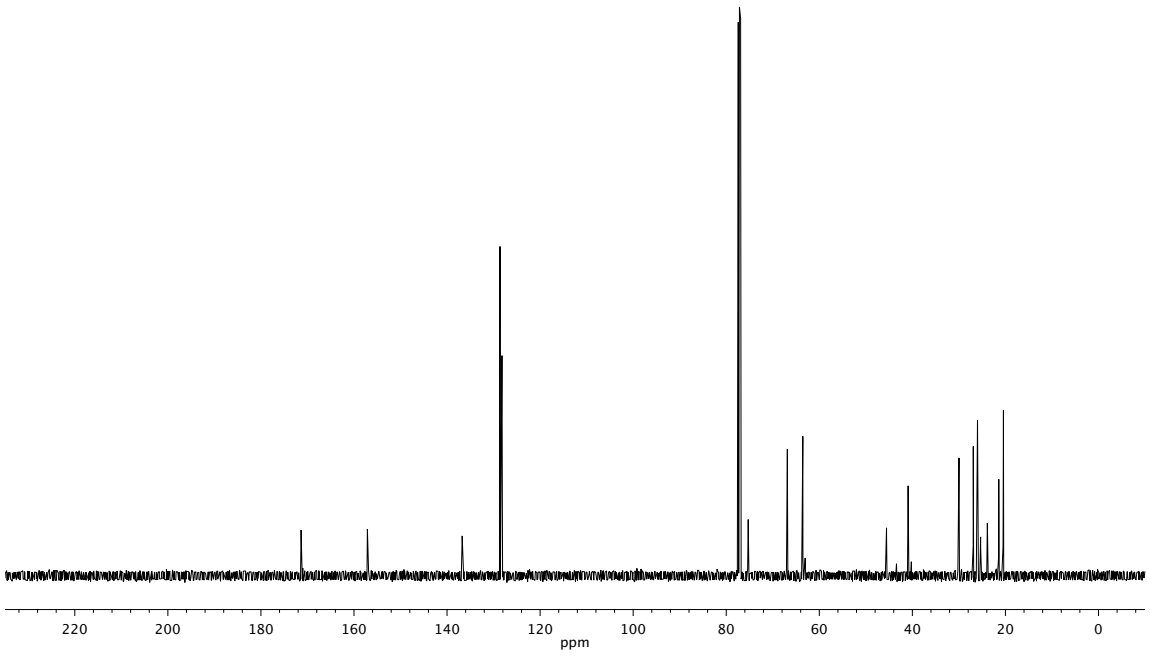


Figure A9.111. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **248**.

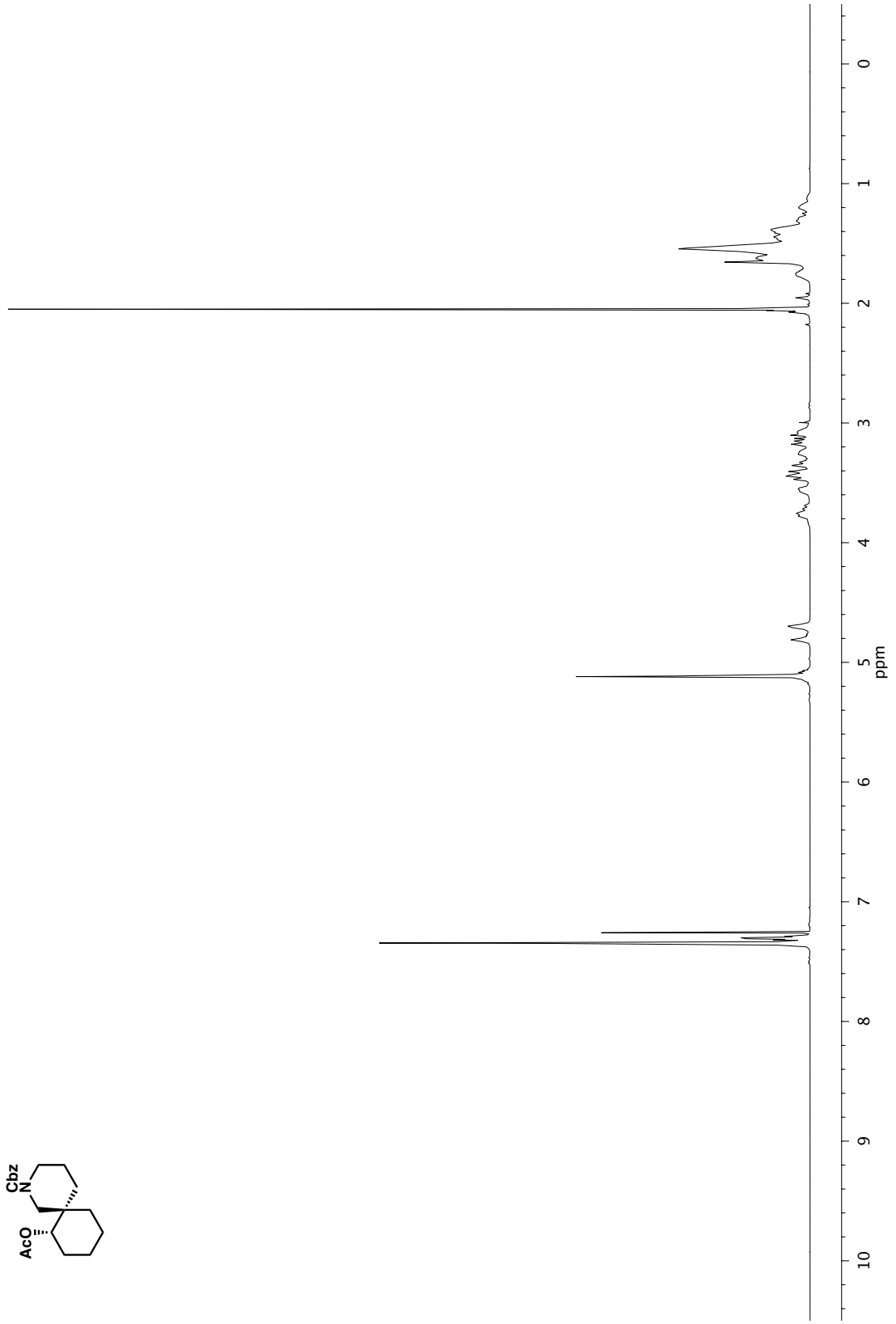


Figure A9.112. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **249**.

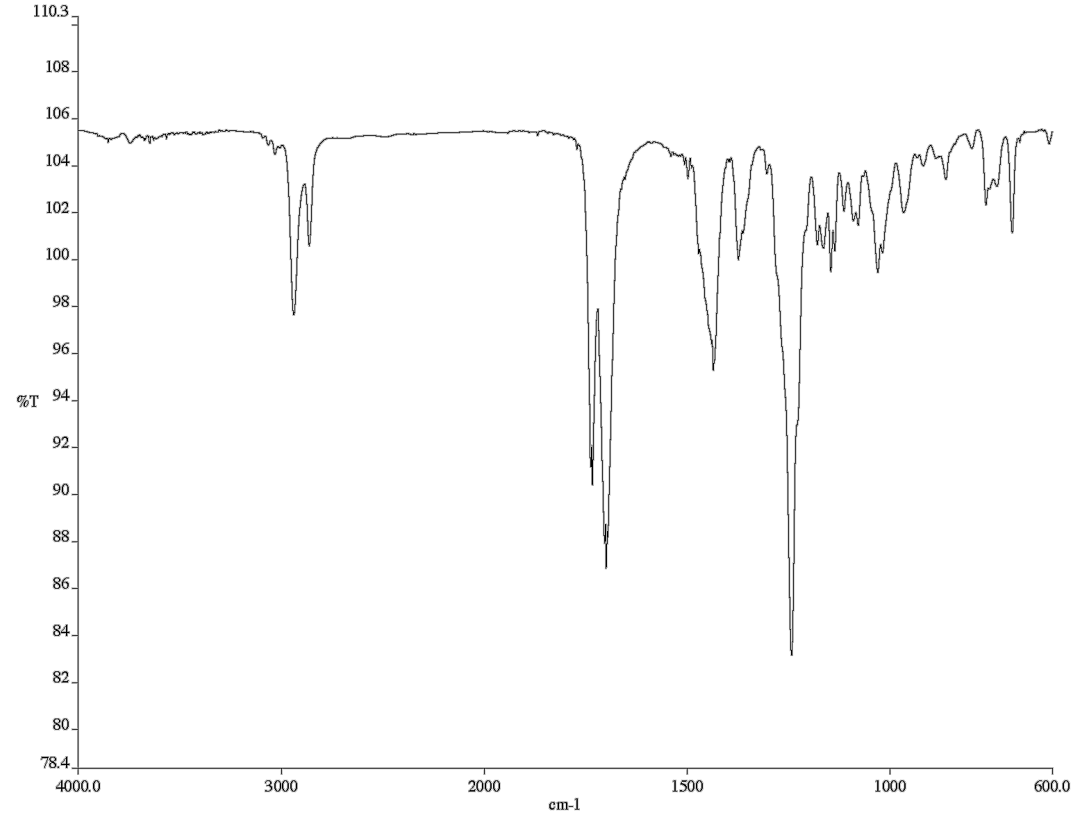


Figure A9.113. Infrared spectrum (Thin Film, NaCl) of compound **249**.

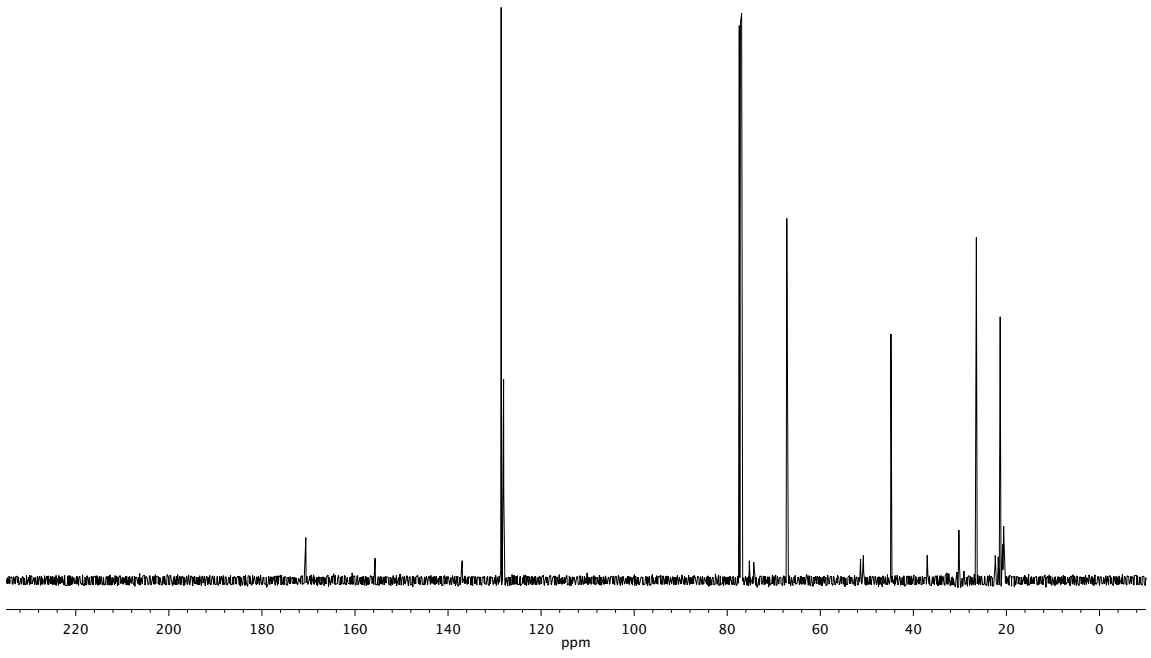


Figure A9.114. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **249**.

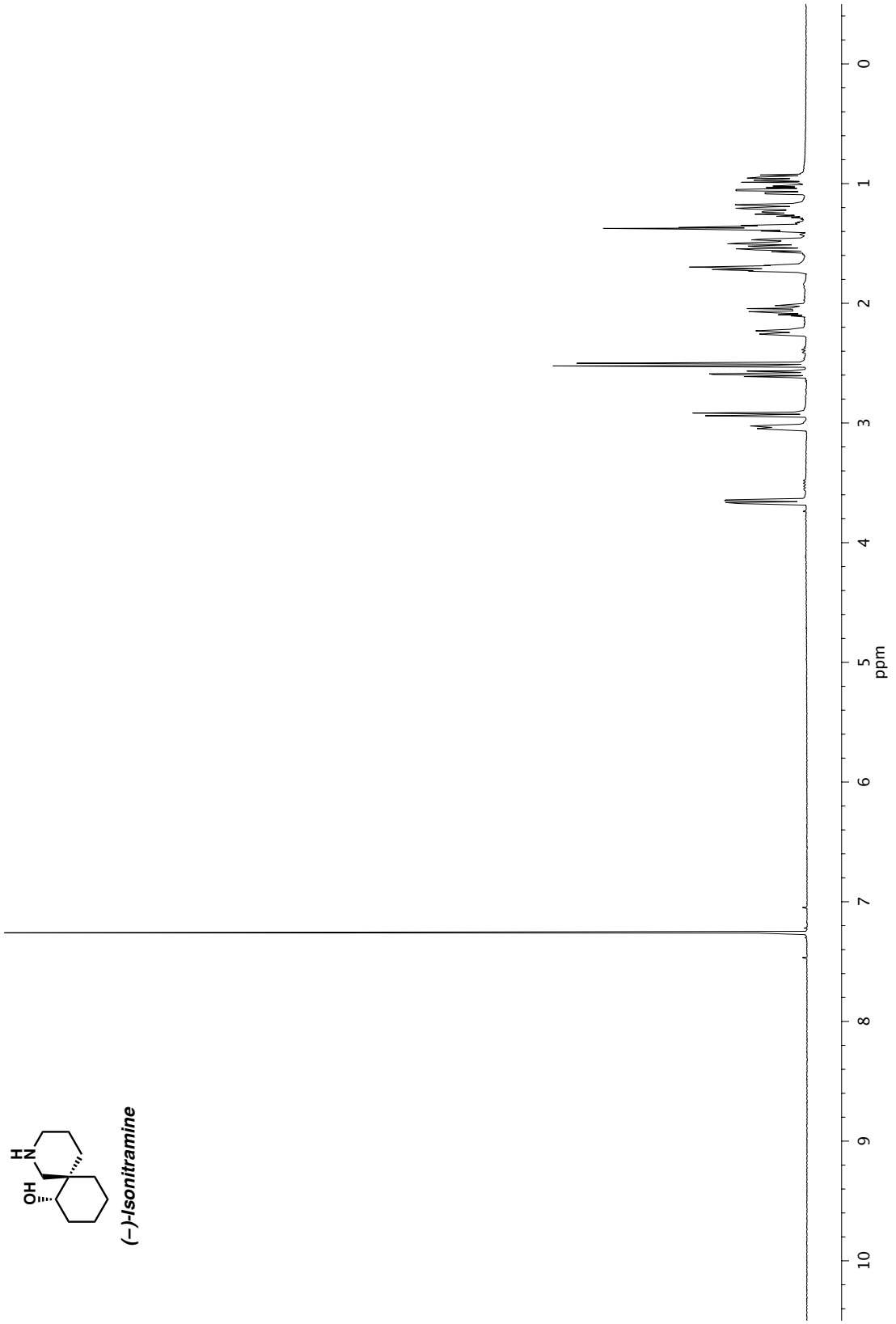


Figure A9.115. ^{1}H NMR (500 MHz, $CDCl_3$) of (–)-Isonitramine (**241**).

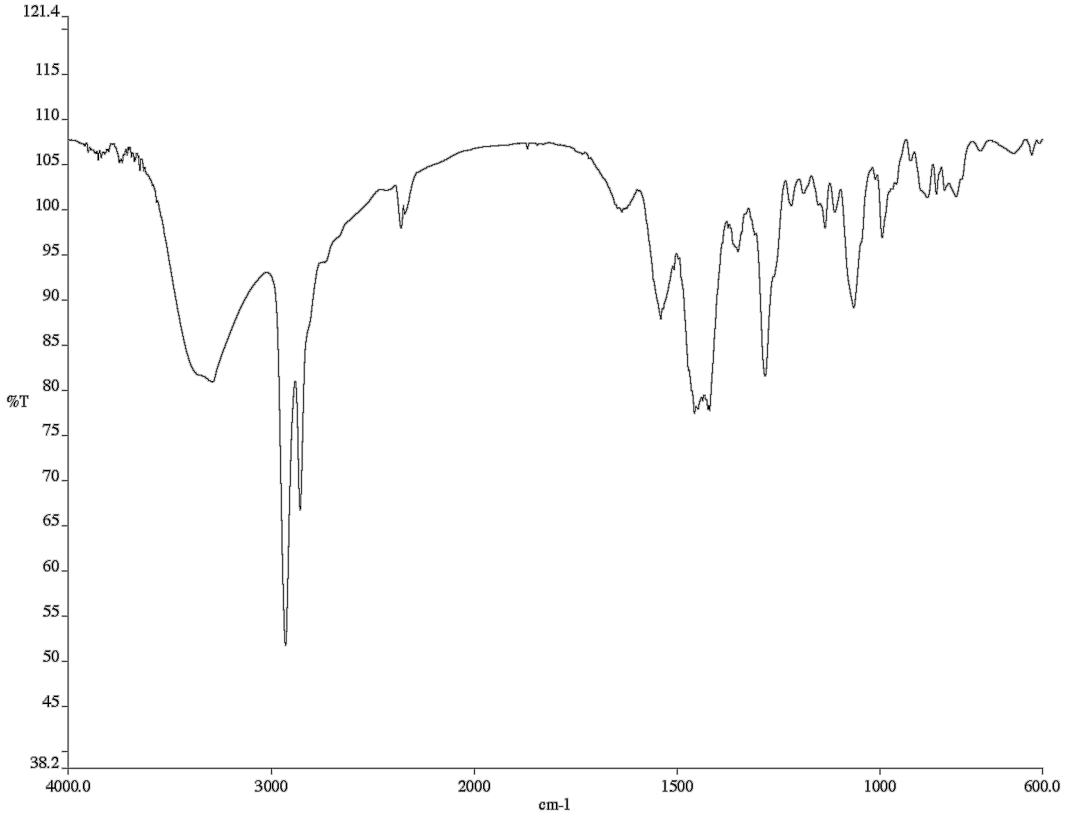


Figure A9.116. Infrared spectrum (Thin Film, NaCl) of (–)-Isonitramine (**241**).

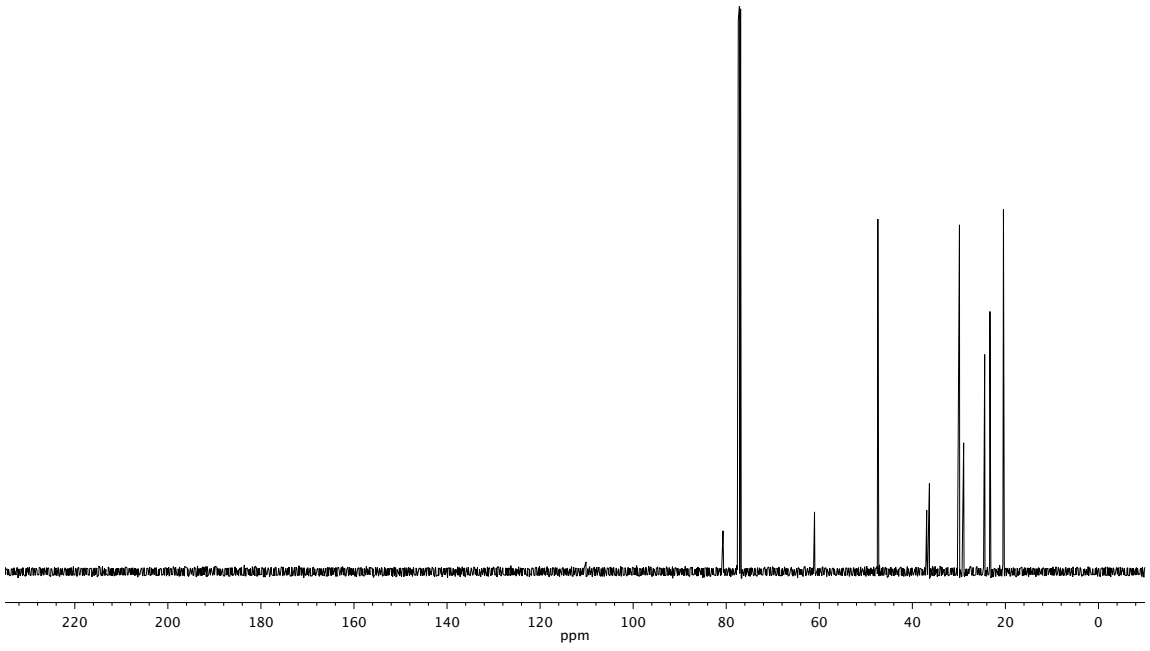


Figure A9.117. ^{13}C NMR (126 MHz, $CDCl_3$) of (–)-Isonitramine (**241**).

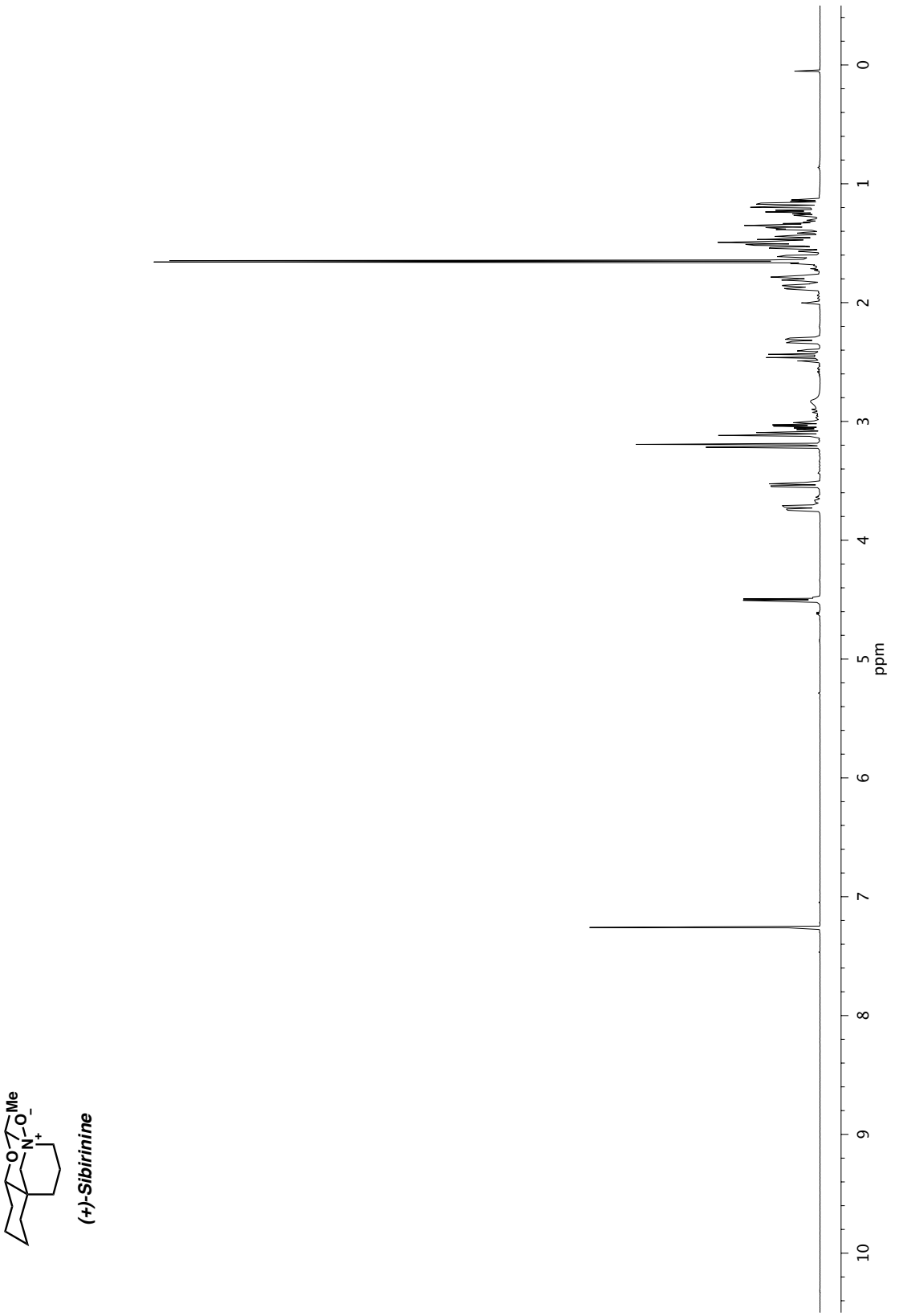


Figure A9.118. ^{1}H NMR (500 MHz, $CDCl_3$) of (+)-Sibirinine (**242**).

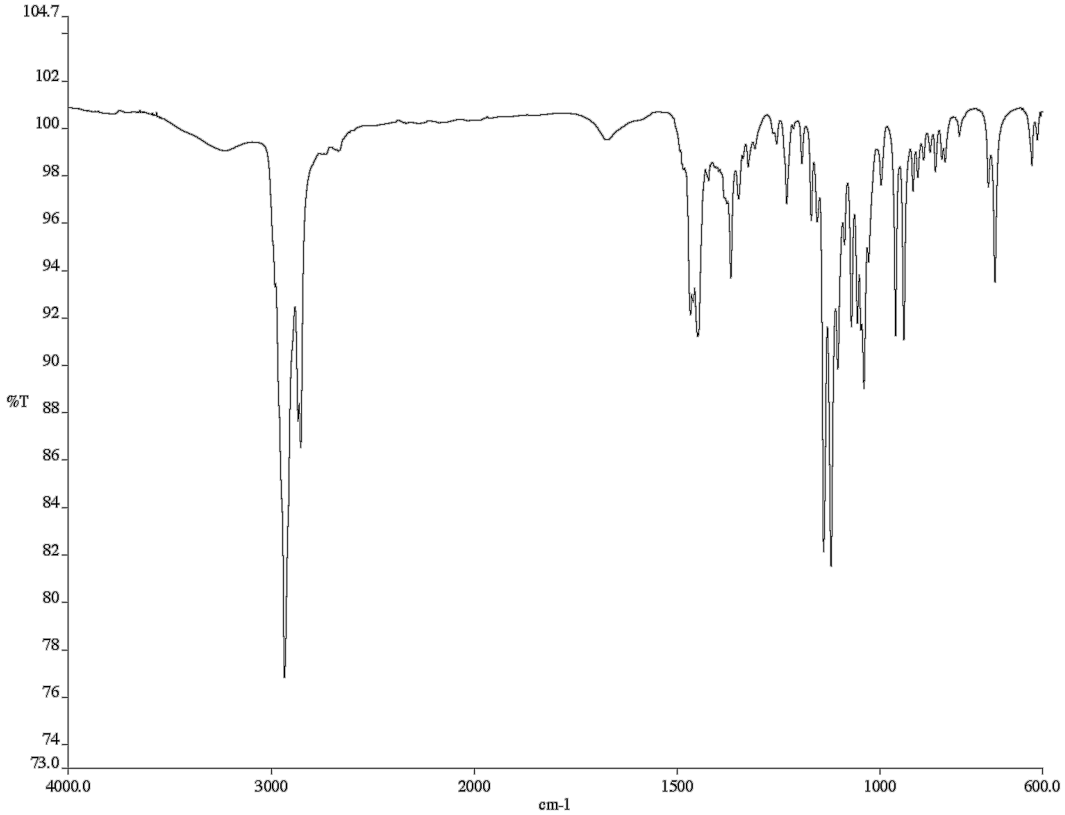


Figure A9.119. Infrared spectrum (Thin Film, NaCl) of (+)-Sibirinine (**242**).

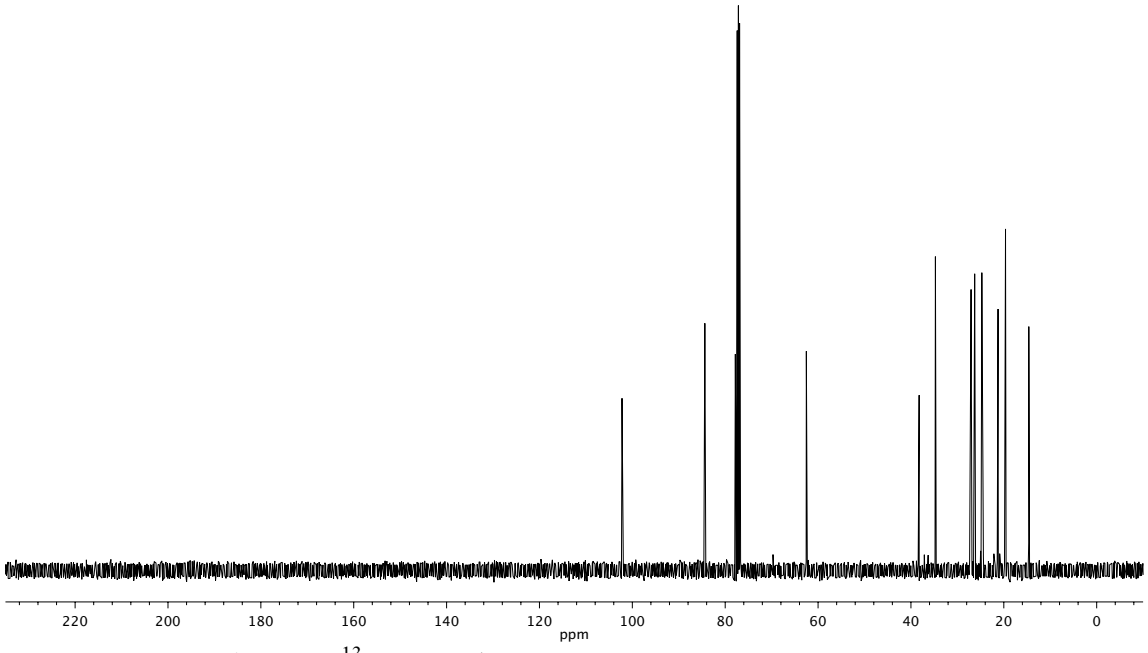


Figure A9.120. ^{13}C NMR (126 MHz, $CDCl_3$) of (+)-Sibirinine (**242**).

Comprehensive Bibliography

Abe, F.; Yamauchi, T. *Phytochemistry* **1994**, *35*, 169–171.

Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, *13*, 909–912.

Achenbach, H. *Tetrahedron Lett.* **1967**, *8*, 1793–1797.

Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431–4439.

Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.

Bajtos, B.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, *7*, 1072–1077.

Battersby, A. R.; Gregory, H. *J. Chem. Soc.* **1963**, 22–32.

Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133.

Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223.

Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem.–Eur. J.* **2013**, *19*, 4414–4418.

Bian, Z.; Marvin, C. C.; Pettersson, M.; Martin, S. F. *J. Am. Chem. Soc.* **2014**, *136*, 14184–14192.

Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. *Tetrahedron Lett.* **1961**, *2*, 485–492.

Burnell, R. H.; Medina, J. D.; Ayer, W. A. *Can. J. Chem.* **1966**, *44*, 28–31.

Cava, M. P.; Talapatra, S. K.; Nomura, K.; Weisbach, J. A.; Douglas, B.; Shoop, E. C. *Chem. Ind.* **1963**, 1242–1243.

Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem.* **2011**, *9*, 5334–5336.

Chen, J.; Li, X.; Li, N.; Lu, J.; Xu, X.; Duan, H.; Qin, L. *Chem. Nat. Compd.* **2012**, *48*, 834–835.

Chen, W.-S.; Li, S.-H.; Kirfel, A.; Will, G.; Breitmaier, E. *Liebigs Ann. Chem.* **1981**, 1886–1892.

Chen, Z.; Zhou, S.; Jia, Y. *J. Org. Chem.* **2015**, *80*, 12545–12551.

Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486–3487.

Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507–2510.

Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112.

Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.

Craig, R. A., II; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160–5163.

Crow, W. D.; Michael, M. *Aust. J. Chem.* **1955**, *8*, 129–135.

Danishefsky, S.; Prisbylla, M.; Lipisko, B. *Tetrahedron Lett.* **1980**, *21*, 805–808.

David, B.; Sévenet, T.; Morgat, M.; Guénard, D.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Motil. Cytoskeleton* **1994**, *28*, 317–326.

David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Païs, M.; Wright, M.; Guénard, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155–2158.

De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 5767–5770.

Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226–7232.

Deyine, A.; Poirier, J.-M.; Duhamel, L.; Duhamel, P. *Tetrahedron Lett.* **2005**, *46*, 2491–2493.

Djerassi, C.; Archer, A. A. P. G.; George, T.; Gilbert, B.; Shoolery, J. N.; Johnson, L. F. *Experientia* **1960**, *16*, 532–534.

Djerassi, C.; Budzikiewicz, H.; Wilson, J. M.; Gosset, J.; Le Men, J.; Janot, M.-M. *Tetrahedron Lett*. **1962**, *3*, 235–239.

Dufour, M.; Gramain, J.-C.; Husson, H.-P.; Sinibaldi, M.-E.; Troin, Y. *J. Org. Chem*. **1990**, *55*, 5483–5490.

Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 981–984.

Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1988**, *110*, 6917–6918.

Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett*. **2004**, *6*, 4435–4438.

Feng, T.; Cai, X.-H.; Liu, Y.-P.; Li, Y.; Wang, Y.-Y.; Luo, X.-D. *J. Nat. Prod*. **2010**, *73*, 22–26.

Feng, T.; Cai, X.-H.; Zhao, P.-J.; Du, Z.-Z.; Li, W.-Q.; Luo, X.-D.; *Planta Med*. **2009**, *75*, 1537–1541.

Feng, T.; Li, Y.; Liu, Y.-P.; Cai, X.-H.; Wang, Y.-Y.; Luo, X.-D. *Org. Lett*. **2010**, *12*, 968–971.

Ferreira Filho, J. M.; Gilbert, B.; Kitagawa, M.; Paes Leme, L. A.; Durham, L. J. *J. Chem. Soc. C,* **1966**, 1260–1266.

Fischer, E.; Hess, O. *Ber*. **1884**, *17*, 559–568.

Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 2241–2245.

Fleury-Brégeot, N.; Presset, M.; Beaumard, F.; Colombel, V.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem*. **2012**, *77*, 10399–10408.

Francois, D.; Lallemand, M.-C.; Selkti, M.; Tomas, A.; Kunesch, N.; Husson, H.-P. *Angew. Chem., Int. Ed*. **1998**, *37*, 104–105.

Fraude, G. *Ber. Dtsch. Chem. Ges*. **1878**, *11*, 2189–2191.

Gartshore, C. J.; Lupton, D. W. *Angew. Chem. Int. Ed*. **2013**, *52*, 4113–4116.

Gartshore, C. J.; Lupton, D. W. *Aust. J. Chem.* **2013**, *66*, 882–890.

Goh, S. H.; Ali, A. R. M. *Tetrahedron Lett.* **1986**, *27*, 2501–2504.

Goh, S. H.; Wei, C.; Ali, A. R. M. *Tetrahedron Lett.* **1984**, *25*, 3484–3484.

Govindachari, T. R.; Nagarajan, K.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 433–444.

Greshoff, M. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3537–3550.

Guggisberg, A.; Hesse, M.; Von Philipsborn, W.; Nagarajan, K.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 2321–2337.

Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787–1789.

Hájíček, J. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1681–1767.

Hájíček, J. *Collect. Czech. Chem. Commun.* **2007**, *72*, 821–898.

Hájíček, J. *Collect. Czech. Chem. Commun.* **2011**, *76*, 2023–2083.

Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525–1529.

Hamashima, Y.; Sasamoto, N.; Umebayashi, N.; Sodeoka, M. *Chem.-Asian J.* **2008**, *3*, 1443–1455.

Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 56–57.

He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.

Hesse, O. *Ber. Dtsch. Chem. Ges.* **1980**, *13*, 2308–2309.

Hong, A. Y.; Bennett, N. B.; Krout, M. R.; Jensen, T.; Harned, A. M.; Stoltz, B. M. *Tetrahedron* **2011**, *67*, 10234–10248.

Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.

Ibragimov, A. A.; Abdullaev, N. D.; Osmanov, Z.; Yunusov, S. Y. *Khimiya Prir. Soedin.* **1987**, 685–689.

Ibragimov, A. A.; Osmanov, Z.; Tashchodzhaev, B.; Abdullaev, N. D.; Yagudaev, M. R.; Yunusov, S. Y. *Khimiya Prir. Soedin.* **1981**, 623–629.

Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528–6531.

Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett.* **2000**, *2*, 1625–1627.

Janot, M.-M.; Pourrat, H.; Le Men, J. *Bull. Soc. Chim. Fr.* **1954**, 707–708.

Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990–12993.

Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563–14572.

Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chem.–Eur. J.* **2012**, *18*, 6729–6732.

Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188.

Kam, T.-S.; Lim, K.-H. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: Amsterdam, **2008**; *Vol. 66*, 1–111.

Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995–5998.

King, B. W. Lactam Derivatives as Inhibitors of Matrix Metalloproteinases and/or TNF-Alpha Converting Enzyme. US Patent 2004266751, December 30, 2004.

Kleinman, E. F. *in Comprehensive Organic Synthesis*, Vol. 2 (Eds.: Trost, B. M.; Flemming, I.; Heathcock, C. H.), Pergamon, Oxford, **1991**, chapter. 4.1.

Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2002**, *43*, 1079–1080.

Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362–1364.

Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.

Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015***, 54*, 179–183.

Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641.

Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

Kump, C.; Dugan, J. J.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 1237–1243.

Kump, C.; Schmid, H. *Helv. Chim. Acta* **1962**, *45*, 1090–1050.

Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–510.

Leng, L.; Zhou, X.; Liao, Q.; Wang, F.; Song, H.; Zhang, D.; Liu, X.-Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 3703–3707.

Lewin, G.; Bernadat, G.; Aubert, G.; Cresteil, T. *Tetrahedron* **2013**, *69*, 1622–1627.

Li, H.; Cheng, P.; Jiang, L.; Yang, J.-L.; Zu, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 2754–2757.

Li, Z.; Geng, Q.; Lv, Z.; Pritchett, B. P.; Baba, K.; Numajiri, Y.; Stoltz, B. M.; Liang, G. *Org. Chem. Front.* **2015**, *2*, 236–240.

Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117–4121.

Lim, K.-H.; Hiraku, O.; Komiyama, K.; Koyano, T.; Hayashi, M.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1302–1307.

Lim, S.-H.; Sim, K.-M.; Abdullah, Z.; Hiraku, O.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1380–1383.

Liu, Y.; Liniger, M.; McFadden, R. M.; Roizen, J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T.; Virgil, S. C.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2014**, *10*, 2501–2512.

Lopchuk, J. M. in *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A., Eds.; Elsevier: Oxford, UK, **2011**; *Vol. 23*, 1–25.

Low, Y.-Y.; Hong, F.-J.; Lim, K.-H.; Thomas, N. F.; Kam, T.-S. *J. Nat. Prod.* **2014**, *77*, 327–338.

Ma, D.; Tang, G.; Kozikowski, A. P. *Org. Lett.* **2002**, *4*, 2377–2380.

Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647–8651.

Männig, D.; Nöth, H. *Angew. Chem. Int. Ed.* **1985**, *24*, 878–879.

Matsumoto, K.; Hashimoto, S.; Otani, S.; Atnita, F.; Osugi, J. *Synthetic Commun.* **1984**, *14*, 585–590.

McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

Medina, J. D.; Di Genova, L. *Planta Med.* **1979**, *37*, 165–167.

Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4572–4576.

Medley, J. W.; Movassaghi, M. *Org. Lett.* **2013**, *15*, 3614–3617.

Mewald, M.; Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 11634–11639.

Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673–4676.

Milborrow, B. V.; Djerassi, C. *J. Chem. Soc. C* **1969**, 417–424.

Mingoia, F.; Vitale, M.; Madec, D.; Prestat, G.; Poli, G. *Tetrahedron Lett.* **2008**, *49*, 760–763.

Mizutani, M.; Inagaki, F.; Nakanishi, T.; Yanagihara, C.; Tamai, I.; Mukai, C. *Org. Lett.* **2011**, *13*, 1796–1799.

Mizutani, M.; Yasuda, S.; Mukai, C. *Chem. Commun.,* **2014**, *50*, 5782–5785.

Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.

Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 194–211.

Mokrý, J.; Kompiš, I. *Chem. Zvesti* **1963**, *17*, 852–860.

Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157–159.

Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 4568–4571.

Motegi, M.; Nugroho, A. E.; Hirasawa, Y.; Arai, T.; Hadi, A. H. A.; Morita, H. *Tetrahedron Lett.* **2012**, *53*, 1227–1230.

Müller, S.; Webber, M. J.; List, B. *J. Am. Chem. Soc.* **2011**, *133*, 18534–18537.

Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248–7251.

Nicolaou, K. C.; Dalby, S. M.; Majumder, U. *J. Am. Chem. Soc.* **2008**, *130*, 14942–14943.

Numajiri, Y.; Jiménez-Osés, G.; Wang, B.; Houk, K. N.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 1082–1085.

Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2015**, *137*, 1040–1043.

O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547.

Pandey, G.; Kumara, C. P. *Org. Lett.* **2011**, *13*, 4672–4675.

Pandey, G.; Kumara, C. P.; Burugu, S. K.; Puranik, V. G. *Eur. J. Org. Chem.* **2011**, 7372–7377.

Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

Park, Y.; Lee, Y. J.; Hong, S.; Lee, M.; Park, H.-G. *Org. Lett.* **2012**, *14*, 852–854.

Pritchett, B. P.; Kikuchi, J.; Numajiri, Y.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 13529–13532.

Pyuskyulev, B.; Kompis, I.; Ognyanov, I.; Spiteller, G. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1289–1294.

Quirion, J.-C.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 3311–3314.

Randriambola, L.; Quirion, J.-C.; Kan-Fan, C.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 2123–2126.

Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6718–6721.

Rodríguez, J. G.; Urrutia, A. *Tetrahedron* **1998**, *54*, 15613–15618.

Saxton, J. E. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, **1998**; *Vol. 51*, 1–197.

Saxton, J. E. in *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, **1998**; *Vol. 50*, 343–376.

Shen, X.-L.; Zhao, R.-R.; Mo, M.-J.; Peng, F.-Z.; Zhang, H.-B.; Shao, X.-H. *J. Org. Chem.* **2014**, *79*, 2473–2480.

Sikriwal, D.; Kant, R.; Maulik, P. R.; Dikshit, D. K. *Tetrahedron* **2010**, *66*, 6167–6173.

Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873.

Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909–8914.

Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1991**, 462–464.

Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621–5623.

Teuber, H.-J.; Worbs, E.; Cornelius, D. *Arch. Pharm.* **1982**, *315*, 388–396.

Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003–2006.

Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642–2645.

Tramontini, M. Syntesis 1973, 703–775.

Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791–1837.

Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109–3112.

Trost, B. M.; Saget, T.; Hung, C.-I. *J. Am. Chem. Soc.* **2016**, *138*, 3659–3662.

Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847.

Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357.

Tsuji, J. Palladium Reagents and Catalysts–New Perspectives for the 21st Century; John Wiley & Sons, Ltd.: 2004.

Tsuji, J.; Nisar, M.; Shimizu, I.; Minami, I. *Synthesis* **1984**, 1009.

Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–256.

Vellucci, J. K.; Beaudry, C. M. *Org. Lett.* **2015**, *17*, 4558–4560.

Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102–15108.

Walser, A.; Djerassi, C. *Helv. Chim. Acta.* **1965**, *48*, 391–404.

Wei, Y.; Zhao, D.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12988–12991.

White, K. L.; Mewald, M.; Movassaghi, M. *J. Org. Chem.* **2015**, *80*, 7403–7411.

White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389.

Wu, Y.; Suehiro, M.; Kitajima, M.; Matsuzaki, T.; Hashimoto, S.; Nagoaka, M.; Zhang, R.; Takayama, H. *J. Nat. Prod.* **2009**, *72*, 204–209.

Xu, J. Palladium Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Unstabilized Enolates: Scope, Mechanism and Synthetic Applications. Ph.D. Dissertation, Stanford University, Palo Alto, CA, 2008.

Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3272–3276.

Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127–19130.

Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712–6724.

Xue, S.; Yu, S.; Deng, Y. H.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271–2274.

Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857–8867.

Yang, R.; Qiu, F. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 6015–6018.

Yi, W.; Zhao, D.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12988–12991.

Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444–11449.

Zhong, X.; Li, Y.; Han, F.-S. *Chem. Eur. J.* **2012**, *18*, 9784–9788.

Zhou, B.; Du, J.; Yang, Y.; Li, Y. *Chem.–Eur. J.* **2014**, *20*, 12768–12772.

Zhou, S.; Jia, Y. *Org. Lett.* **2014**, *16*, 3416–3418.

Zhuo, C.-X.; You, S.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 10056–10059.

Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228.

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About the Author

Beau Patrick Pritchett was born in Fairfax, Virginia on January 7th, 1990 to parents Jean Marie Pritchett and Patrick Robert Pritchett. He has an older sister, Shelly Pritchett Melton, and a younger sister Allison Jean Pritchett. Beau lived overseas (the Philippines and Panamá) for all five years of elementary school while his parents were stationed in the American Embassies in Manila and Panamá City. After moving back stateside, to Sterling, Virginia, Beau attended the Thomas Jefferson High School for Science and Technology, which at the time was the top-ranked high school in the country. The outstanding faculty and gifted student body at TJ helped fuel his passion for mathematics and engineering, though he still carved out time for varsity football, baseball and the school jazz band…not to mention the 50-mile round-trip commute each day!

Beau next attended Tulane University in New Orleans, Louisiana, where he graduated Summa Cum Laude in both Chemistry and Chemical Engineering. Like many who pursue advanced studies in organic synthesis, Beau was first inspired by his sophomore organic chemistry courses. Professor Harry Ensley, who was one of E.J. Corey's Ph.D. students from the 1970's, presented the material with equal parts charm and austerity. After taking Professor Ensley's graduate synthesis course the following year, it was clear that Beau would be leaving engineering at the altar to pursue doctoral studies in Chemistry.

In 2012, Beau moved to Pasadena, California to begin doctoral studies under the guidance of Professor Brian Stoltz at the California Institute of Technology. His graduate work has largely focused on the total synthesis of complex natural products, spanning from terpenoids to alkaloids. He hopes to combine the synthetic skills and intuition developed throughout his tenure in the Stoltz lab with the process engineering perspective that he honed as an undergraduate to make meaningful contributions to human medicine. Beau is excited to begin this journey when he heads North this summer to start his professional career at Gilead Sciences in Foster City, California.