HIGHLY ENANTIOSELECTIVE PALLADIUM-CATALYZED ALLYLIC ALKYLATION REACTIONS OF CARBOCYCLIC ENAMINONES AND ACYCLIC SUBSTRATES

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2017

(Defended December 19, 2016)

To my grandfather, John Goode,

And in loving memory of Alice Goode,

Charles Duquette and Rita Duquette

ACKNOWLEDGEMENTS

The work contained in this document reflects work that I have performed, at times on my own and at other times with close collaborators. However, reflecting on my experience at Caltech as a whole, I feel overwhelmed to consider the number of people who have supported me when I stumbled, pushed me when I stagnated, and celebrated and encouraged me when I succeeded. Without many of my acquaintances, old and new, I would not have been able to perform at the high caliber that a PhD dictates; late nights in lab can be long and lonely, but the shared experiences I have with my coworkers and friends from the last six years have improved me as a scientist and a person.

I would be remiss to not thank my advisor Professor Brian Stoltz first and foremost. It is difficult to enumerate or convey the number of small and enormous gestures Brian has made through the years that have made this thesis possible. As an advisor, he possesses the rare quality of allowing me to explore according to my intellectual interests and desires, to push projects in a direction that I truly believe in, so that I have had ownership over my research, and my discoveries felt like they came from my own mental capacities (tempered, as always, through discussions with Brian and my labmates). Perhaps even more valuable, this has allowed me to make mistakes – occasionally ones that I bitterly regretted, but always learned from and will never forget. I developed more as a scientist due to the freedom granted by Brian than I could ever have in a different environment. That said, Brian seems to have a preternatural ability to see when the leash has run too long and I've lost my way, and has reeled me back in

without being punitive (and often without me even realizing that he was saving me from myself).

Even more exceptionally, Brian has demonstrated a deep understanding and caring for me and other members of the lab during the true crises that unfortunately seem to happen to everyone at least once during their graduate career. I truly believe that this is a rare and extremely valuable quality in an advisor, and one that I will always carry with me and attempt to model myself after as a coworker and supervisor in future employment. As one example of the quality I am trying to describe, Brian was not only the first, but one of only a few people to visit me in the hospital after I had lung surgery. This sounds like a small thing, but I understood that it was a way of showing that my condition was personally important to him, and that my health and wellness were of a personal and not professional concern to him.

Following in the wake of this surgery, a torrent of personal crises that required too much mental and emotional energy to be compatible with the extreme demands of graduate school forced me to reconsider my ability to finish the program. I had all but determined to leave to program in order to take care of my personal business, but Brian suggested that I take a medical leave of absence and return after a year if I was able. Thankfully, this time was exactly what I needed in order to fulfill my other obligations, and I was able to return to Caltech to write this thesis. I would quite literally not have been able to complete this without Brian – I am deeply grateful to his generosity and sympathy throughout these trials.

Professor Sarah Reisman has been like a second advisor in many ways throughout the years. In addition to being the chairperson of my thesis committee, she has always

had an open door to discuss chemistry (and has provided a tremendous amount of encouragement and advice throughout the years), and also to discuss the other happenings of life as a graduate student. Seeing her career blossom into an imposing presence in the organic chemistry community has been a sight to behold, as is deserving of such an acutely intelligent and helpful person. She has been a role model for all of us, and has provided a many a laugh or sympathetic ear as the situation required.

Professor Theodor Agapie has also been extremely supportive as a member of my thesis committee. During our meetings, he has always had a keen eye for seeing the value in my ideas, and for gently pointing out their flaws. His input has been extremely enlightening and useful during these discussions and his attention to detail has revealed that he truly cares for his duties as a committee member.

Although Professor Harry Gray was a late addition to my committee, his affability and availability as a resource made me feel as if he had known me personally for years. I have found his input and advice to be very useful, and whenever we meet he has an intriguing and sometimes unexpected point to discuss, which has always been a joy. I always look forward to going to his office, even if it's just to try to schedule a defense date, because I know something interesting will come of it.

Dr. Scott Virgil is a pillar of the Caltech chemistry community, and is somebody to whom I am deeply indebted, as he has supported me in countless ways throughout my career. Whether it has been pulling up a reaction protocol from his own graduate career, helping to get a crystal structure, or fixing one of the countless machines that he seems to effortlessly orchestrate despite their daily abuse by every student who has ever touched a chemical at Caltech, he always provides help graciously and completely. Scott and his

incredibly kind wife Silva have always shown a genuine personal interest in my development as a scientist, and provided much encouragement and support throughout the years.

I would like to thank Felicia Hunt, who was the Associate Dean of Graduate Studies at the time when I began my medical leave of absence. She and Brian worked tirelessly together, and she showed genuine personal interest and sympathy for me, encouraging me to take the leave of absence and aiding in my return at the end of the year. Her kindness to myself and the other students at Caltech is exemplary, and I am deeply indebted to her for her help.

I must also thank Agnes Tong for her tremendous help in all things administrative over the course of my graduate studies, as well as for her help in carrying out my medical leave. Dr. David VanderVelde runs an immaculately tight ship, and helped me to carry out a number of NMR experiments throughout my studies, as well as with the occasional spectral interpretation. Tony worked hard to keep our floor and building clean all the time, and he was often the first person I would see in the early morning hours in lab. His good attitude and smile were always a way to start the day off with a little extra motivation.

There are too many lab mates that I have overlapped with during my tenure at Caltech to thank them all personally for what they have done for me, but everyone I have worked with here has done something that helped me, be it sharing experience with a procedure or reagent, lending some perspective when brainstorming or troubleshooting, or having the kind of casual conversation in lab that can sometimes be the difference

between hope and despair when running a one hundred-fraction column late into the night. Thank you to everyone who I have worked with – it has been an honor.

Dr. Corey Reeves was my hoodmate for most of my career at Caltech, which was probably one of the greatest windfalls of fortune I didn't know I had until about six months after we were assigned our hoods. Corey was a tireless worker, with a voracious motivation for and intellectual engagement with his work, and this attitude was contagious, pushing me into a good work ethic and mental state to begin graduate school. Perhaps more importantly, Corey was a true friend – in times of need, he was there to commiserate, and otherwise we shared a love for music that I'm not sure anyone else would have listened to with me. He taught me how to surf (I am perhaps being overgenerous to myself saying this) and together designed the greatest Frisbee golf course in Caltech, if not human, history. Corey's companionship was a boon throughout my studies, as it continues to be.

Dr. Doug Behenna was a massive influence and font of knowledge during my first year in the Stoltz lab. His genuine interest in and understanding of chemistry, as well as his incredible motivation, set an extremely high bar that I always strived for as a budding chemist. Throughout the beginning of my career he taught me so much that I hesitate to think how dumb I must have been before his positive influence. He was always incredibly generous – with his time and advice, as well as with help outside of the chemistry world – as long as you didn't touch his 250 mL sep funnel.

Dr. Allen Hong was another person whose work ethic and unfathomably deep passion for chemistry inspired me early in my graduate career, and he frequently shared

with me his knowledge, be it on paper or in the hood. I am certainly indebted to him for his help during those formative years.

I worked in the same bay as Dr. Alex Goldberg for approximately four years, and he was both a helpful mentor and good friend throughout. While his taste in music may have been somewhat lacking, he was quick to help out with a tricky procedure or problem, and always interested in what was going on in my life outside of school. His help and friendship throughout the years made working in the "Bogey Bay" ("we're above par… in the golf sense") a fun and productive experience.

My collaborators on publications – Kelly Kim, Magnus Bergner, Linda Chio and Drs. Jared Moore, Pavel Starkov, Alex Goldberg, Hendrik Klare, Nathan Bennett, Jimin Kim, Boger Liu, Alex Marziale, Rob Craig, Marc Liniger and Yoshitaka Numajiri – were all incredibly thorough in their work. They pushed hard to make that looming deadlines, located that tricky missing spectra, made that inexplicably difficult substrate, and pointed out that potentially disastrous spelling error, making working with each and every one of them a true pleasure. I was also Linda's SURF mentor, and her acuity and hard work made teaching, guiding and working with her a very positive experience.

I should also thank Kelly Kim, Nick O'Connor, Sam Shockley and Dr. Christopher Haley and all the other members of the strange but wonderful social group of the small office. Whether coming up with new ideas for potentially revolutionary products, having entire discussions only in Arrested Development quotes, or actually talking about relevant (and sometimes irrelevant) chemistry, they provided both companionship and intellectual stimulation that made the time between labwork much more enjoyable. I would also like to thank Dr. John "Sleeves" Steeves for his

companionship throughout graduate school. He was an excellent friend, and a real life example of stereotypical Canadian kindness.

I thank the NSF for their generous support in the form of a GRFP fellowship. The financial support they provided me through this fellowship made my research possible, and as long as the government continues to support basic science, I believe the future may continue to brighten, even if times ahead seem dark.

I have been best friends with Mike Pace since middle school, despite the fact that we have never lived in the same town, and usually lived in different states (or countries). He is the only person who has visited me wherever I lived, be it Boston, Los Angeles, or Germany. He has been everything to me that I could ask for in a lifelong friend, and we have had so many wonderful shared experiences, I know my life would not be half as enjoyable without him in it. I am lucky in life to have not only a brother by birth, but a brother by choice. His wife Olivia has also been a source of joy and support for me throughout the years, and I am glad that two such wonderful people as they have each other.

I cannot express how blessed I have been by the family that I have. They have been the greatest advantage and joy I could have asked for since birth. First, my mother Elizabeth Goode and father Jeffrey Duquette have always been supportive and understanding through all of my experiences in life. They have pushed me to great success, and bolstered my through disappointment. I know that I have their unconditional love and support, and there is no greater source of strength when all else feels lost. Thank you, mom and dad, for all that you have done for me, and all that you continue to do.

My brother Professor Nicolas Duquette recently began his independent career at USC, and he has always been an inspiration and a great friend to me. In our youth, his success was always the high water mark I measured myself by. In our adolescence, he was a role model, and introduced me to Radiohead and The Flaming Lips (as well as classics like The Who, The Rolling Stones, The Doors, The Beatles, etc.), thus beginning my obsession with real, good music. Now, as adults, I have the fortune of living in the same city as him for the first time in almost a decade, and his companionship and support is such a joy, and so crucial, it's hard for me to believe we lived apart for so long. Thank you, Nic, for all that you have taught me throughout the years. My sister-in-law Dr. Joanna Duquette is a perfect companion to Nic, and is a wonderful sister to me and member of the family. She is intelligent and fun to chat with, is interested in others, and is just generally a great person to be around. I love the time I get to spend with them as a family. Thank you to my nephew, Clive, for being the sweetest, most joyful nephew an uncle could ask for. I cannot wait to see what greatness lies ahead of you, and I hope that I can impart some wisdom (or at least do fun things with you that your parents won't let you do) along the way.

I was blessed to have all four of my grandparents, Charles and Rita Duquette and John and Alice Goode, through most of my young adulthood, and my memories with them will always be cherished. They were the rock that two fantastic families were built on, and the ultimate models of selflessness and love. My childhood was peerless for their influence, and as an adult now, I often reflect on what incredible people they were, and hope to live up to their legacy.

Finally, thank you to my partner (and my other best friend) Dr. Stephanie Phan. When we met, Stephanie was in her medical residency, I was in graduate school, and there weren't more than a couple of hours in any given week when one or both of us weren't working. But a couple of hours a week were all it took for me to know that I had found somebody who I want to spend my life with (and as many hours a week as we can manage). We have shared so many joyful experiences and weathered so many trials together that it is hard to imagine that we've been together for five years and not fifty. I feel like the best version of myself when I am with her, and she makes me want to push myself to always improve, though she cherishes me for exactly who I am. It is no exaggeration to say that she is the strongest person I know. She has endured incredible hardship throughout her life, and always triumphed; I have the utmost respect and admiration for her. She is intelligent, thoughtful, sympathetic and generous, and I love that we laugh at the same inexplicable things and are both fascinated by the unidentified bird that calls outside our window in the morning. Thank you for everything, Steph – I look forward to the years ahead.

ABSTRACT

The synthesis of quaternary stereocenters has been a longstanding challenge to organic chemists. These motifs are of paramount importance in the synthesis of natural products and other biologically active molecules. The Stoltz group has pursued the asymmetric decarboxylative allylic alkylation reaction using the Pd(PHOX) catalytic system as a methodology to this end for over two decades. More recently, the lactam substrate class has been found to proceed with exceptional enantiomeric excess as compared to their carbocyclic counterparts. Herein, we describe a body of work furthering the study of this reaction. We first sought to elucidate the origin of the increased selectivity seen in lactams by investigation of novel carbocyclic substrates. These studies culminated in the discovery of a novel substrate class, enaminones, which match the enantioselectivity of the lactam substrates and have the highest enantioselectivity seen in general carbocyclic substrates found with our catalytic system to date.

Applying synthetic methods for the synthesis of quaternary stereocenters of linear compounds further adds to the complexity and challenge, due to the lack of rigidity in most acyclic systems. We disclose a development for the formation of *de novo* quaternary stereocenters in acyclic systems applying C_2-symmetric biphosphine ligands in the palladium-catalyzed decarboxylative allylic alkylation reaction of amide enolates with well-defined olefin stereochemistry. This methodology allowed us to access a variety of acyclic compounds bearing quaternary stereocenters with good selectivity.

PUBLISHED CONTENT AND CONTRIBUTIONS

Bennet, N. B. et al. (2013). "Expanding Insight into Asymmetric Palladium-Catalyzed Allylic Alkylation of *N*-Heterocyclic Molecules and Cyclic Ketones". In: *Chemistry — A European Journal,* 19.14, 4414–4418. doi: 10.1002/chem.201300030.

DCD contributed to conception of the project, synthesis and characterization of substrates and products described in the publication, and participated in preparation of the data and the manuscript.

Bergner, M.; Duquette, D. C.; Chio, L.; Stoltz, B. M. (2015). "Exceedingly Efficient Synthesis of (±)-Grandifloracin and Acylated Analogues". In: *Organic Letters*, 17.12, pp. 3008–3010. doi: 10.1021/acs.orglett.5b01292.

DCD contributed to conception of the project, performed and aided in steps of the synthesis, and participated in preparation of the data and the manuscript.

Marziale, A. N. et al. (2015). "An Efficient Protocol for the Palladium-Catalyzed Asymmetric Decarboxylative Allylic Alkylation Using Low Palladium Concentrations and a Palladium(II) Precatalyst". In: *Advanced Synthesis & Catalysis* 357.10, pp. 2238–2245. doi: 10.1002/adsc.201500253.

DCD contributed to the synthesis and characterization of substrates and products described in the publication, and participated in preparation of the data and the manuscript.

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CHAPTER 1

Expanding Insight into the Asymmetric Palladium-Catalyzed Allylic Alkylation of N-Heterocyclic Molecules and Cyclic Ketones[†]

1.1 INTRODUCTION AND BACKGROUND

The asymmetric construction of quaternary stereocenters is a topic of great interest in the organic chemistry community. Among the available methods that afford this motif,[1] palladium-catalyzed decarboxylative allylic alkylation[2,3] has proven particularly effective and, over the last decade, our group has pursued this strategy employing chiral phosphinooxazoline (PHOX) ligands.[4,5] Our initial efforts in this area led to the preparation of enantioenriched α-quaternary ketones (e.g., **2a**) in good yields and enantioselectivities using (*S*)-*t*-BuPHOX (**3**)[5a–b] as a chiral ligand (Scheme 1.1A).[6] Since these early results, we have considerably expanded the scope,[7] demonstrated multiple applications,[8] and performed mechanistic investigations[9] of this powerful

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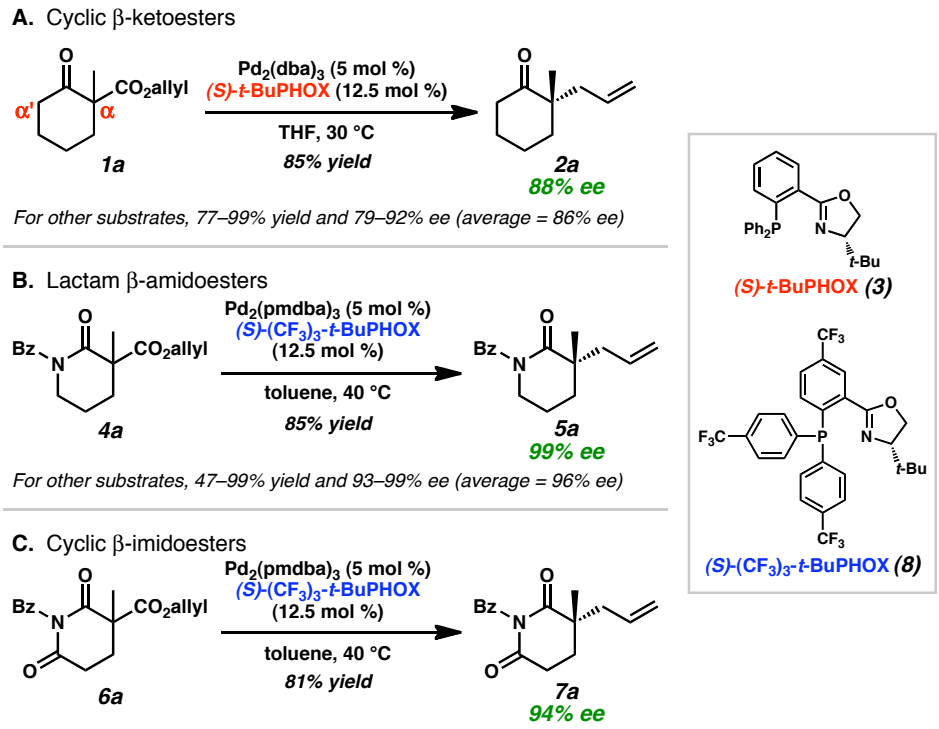
[†] This research was performed in collaboration with Drs. Nathan Bennett, Jimin Kim, Wen-Bo Liu Alexander N. Marziale, Douglas C. Behenna and Scott C. Virgil and has been published. See: Bennett, N. B.[‡]; Duquette, D. C.[‡]; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2013**, *19*, 4414–4418. [‡]N.B.B. and D.C.D contributed equally to this article.

transformation. Recently, we discovered that the allylic alkylation of lactams (**4a** to **5a**) and imides (**6a** to **7a**) with (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**)[5c] consistently proceeds with enantioselectivities substantially higher than any other substrate class previously examined in this system (Scheme 1.1B and C).[10] This observation prompted us to investigate which characteristics distinguish these molecules as superior alkylation substrates. The basic distinctions between these ketone and *N*-heterocyclic molecules are the deviation in electronic nature of the enolate and the identity of the α'-functionality (i.e., the group flanking the carbonyl at the site opposite of alkylation). Thus, we have designed several new alkylation substrates to examine the relative contribution of each effect. We have found that the exceptional enantioselectivities observed in the lactam/imide series are likely not a result of a purely electronic effect, but a combination of stereoelectronic and steric factors associated with the α'-substituent. To provide a more complete perspective on allylic alkylation selectivity, this chapter also discusses related research efforts performed by other groups.

Scheme 1.1. Comparison of allylic alkylation of ketones, lactams, and imides.

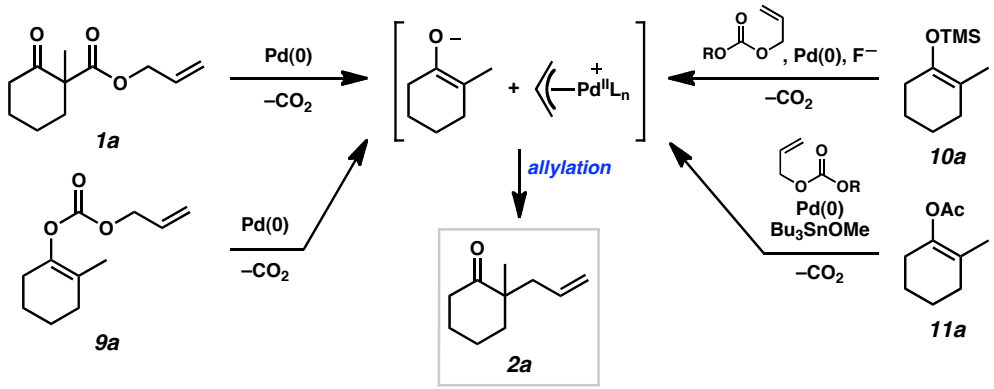


1.1.1 Pd-Catalyzed Asymmetric Allylic Alkylation Background

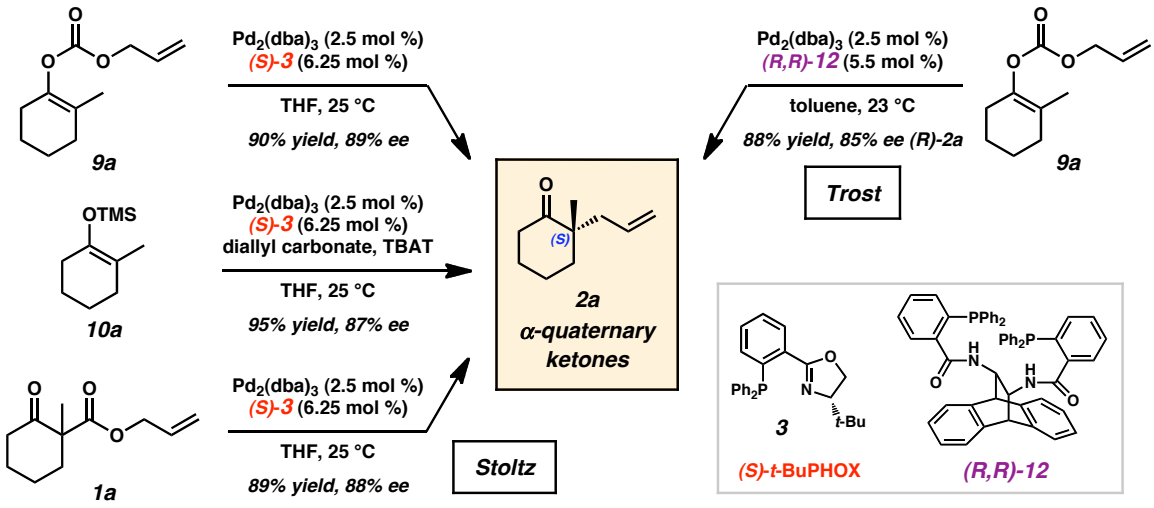
Our entry into asymmetric allylic alkylation methodology began in 2004, when we reported the preparation of α-quaternary cyclic ketones from allyl enol carbonates (**9**) and silyl enol ethers (**10**).[6a] Twenty years prior, Tsuji performed the regioselective allylation of these and other unstabilized enolate precursors under essentially neutral conditions with Pd(0) catalysts (Scheme 1.2).[11] Inspired by Tsuji's approach, we screened a series of chiral *P*,*P*-, *P*,*O*-, and *P*,*N*-ligands in the allylic alkylation of allyl enol carbonate **9a** with $Pd_2(dba)_3$ as a Pd(0) source. Gratifyingly, *P*,*N*-ligands generate the desired enantioenriched ketone product in good yield and ee, with (*S*)-*t*-BuPHOX (**3**) providing the greatest enhancement in selectivity (Scheme 1.3). Silyl enol ethers (**10**)

necessitate the addition of a fluoride source and allyl carbonate, but provide similar results.[6a] We later found that racemic β-ketoesters (**1**) are also excellent substrates under the standard enol carbonate conditions. Notably, β-ketoesters are easy to prepare, are often more stable than the corresponding allyl enol carbonates, and avoid regioselectivity issues in enolate formation with α,β-unsaturated substrates. Following our initial publication, Trost disclosed allylic alkylation conditions for allyl enol carbonates with their C_2-symmetric *P*,*P*-ligands (e.g., (*R*,*R*)-**12**, Scheme 1.3).[2a,12] These initial publications by Stoltz and Trost represent the first examples of the regioselective and enantioselective alkylation of ketones with multiple acidic sites. Although not discussed in this chapter, Hayashi,[13] Ito,[14] Trost,[2a,15] and Hou and Dai[16] have also performed asymmetric alkylation of ketones, however, their approaches require the substrate to possess an occluded α'-position (i.e., one deprotonation site) or a stabilizing α-group (i.e., favored deprotonation site).

Scheme 1.2. Various enolate precursors investigated in the Tsuji reaction.

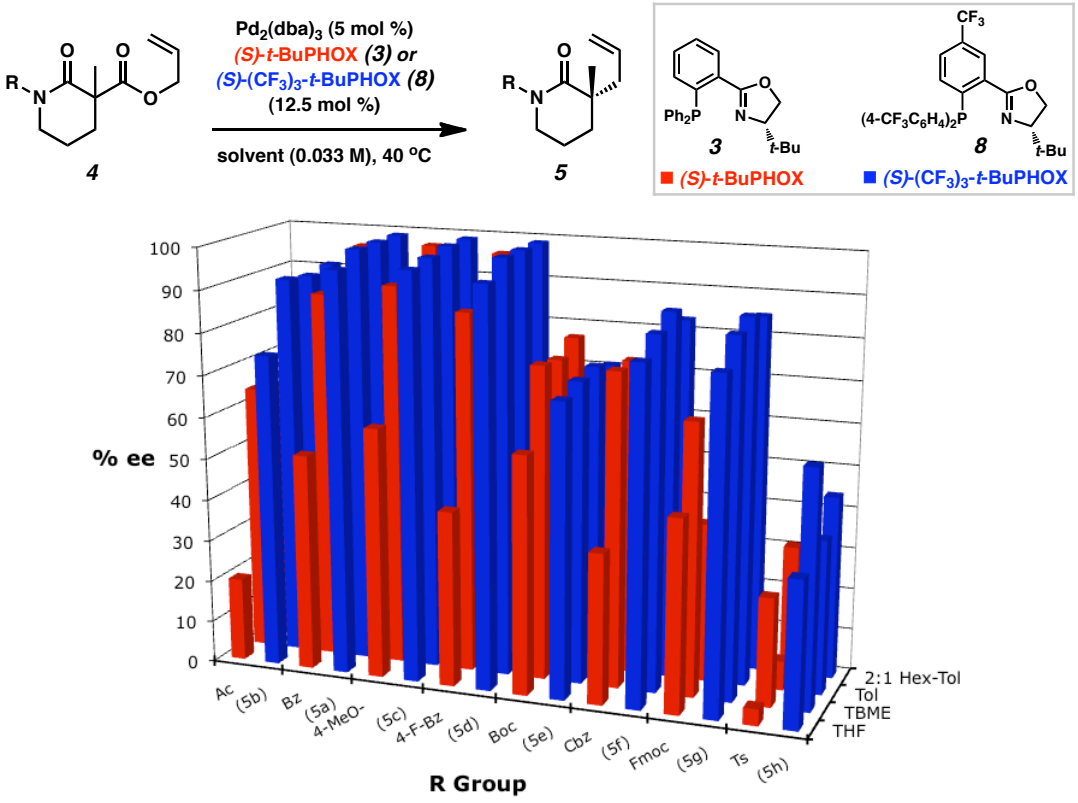


Scheme 1.3. Pd-catalyzed asymmetric allylic alkylations performed by Stoltz and Trost.



As part of our efforts to expand the reaction scope, we explored nitrogen-containing substrates including lactams.[10] Early efforts indicated the *N*-substituent plays a significant role in conversion and enantioselectivity. Notably, electron-rich lactams (*N*-group = Me or Bn) exhibit little to no conversion to the desired products and, as such, are poor alkylation substrates. We consequently prepared a variety of lactams with electron-withdrawing functionality (**4a**–**h**) and screened these molecules against two electronically differentiated chiral ligands, (*S*)-**3** and (*S*)-**8**, and four solvents of varying polarity: tetrahydrofuran (THF), *tert*-butyl methyl ether (TBME), toluene, and 2:1 hexane–toluene (Table 1.1). In general, higher enantioselectivities are observed in less polar solvents with (*S*)-**8** as a ligand. Among the *N*-substituent, benzoyl is optimal and provides nearly perfect selectivity. The transformation is also tolerant of various α-groups and ring sizes and additionally provides high ee for cyclic imides. By comparison, α-quaternary ketones are formed with approximately 10% lower ee, prompting us to question what characteristics distinguish lactams and imides as better substrates.

Table 1.1. Lactam allylic alkylation screen.[a]



					Enantiomeric Excess (% ee)[b]			
entry	substrate *4*	R	product *5*	ligand	THF	TBME	Toluene	2:1 Hex–Tol
1 2	*4b*	Ac	*5b*	*3* *8*	20 75	64 91[d]	62 90[d]	83 91[d]
3 4	*4a*	Bz	*5a*	*3* *8*	52 96	88 99	86 99	96 99
5 6	*4c*	4-MeO-Bz	*5c*	*3* *8*	60 97	91 98	87 99	97 99
7 8	*4d*	4-F-Bz	*5d*	*3* *8*	42 95	86 99	83 99	96 99
9 10	*4e*	Boc[c]	*5e*	*3* *8*	57 70	75 72	74 73	77 71
11 12	*4f*	Cbz	*5f*	*3* *8*	36 80	75 84	75 87	72 83
13 14	*4g*	Fmoc	*5g*	*3* *8*	46 79	65 85	38 87	45 85
15 16	*4h*	Ts[c]	*5h*	*3* *8*	4 35	26 57	7 37	31 44

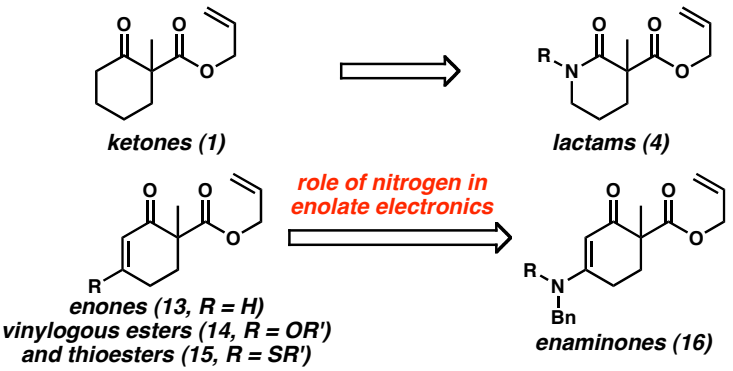
[a] *Conditions*: lactam **4** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C. [b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand. [c] Reaction performed with $Pd_2(pmdba)_3$ at 50 °C. [d] Reaction performed at 60 °C.

1.2 RESULTS AND DISCUSSION

1.2.1 Electronically Variable Substrates

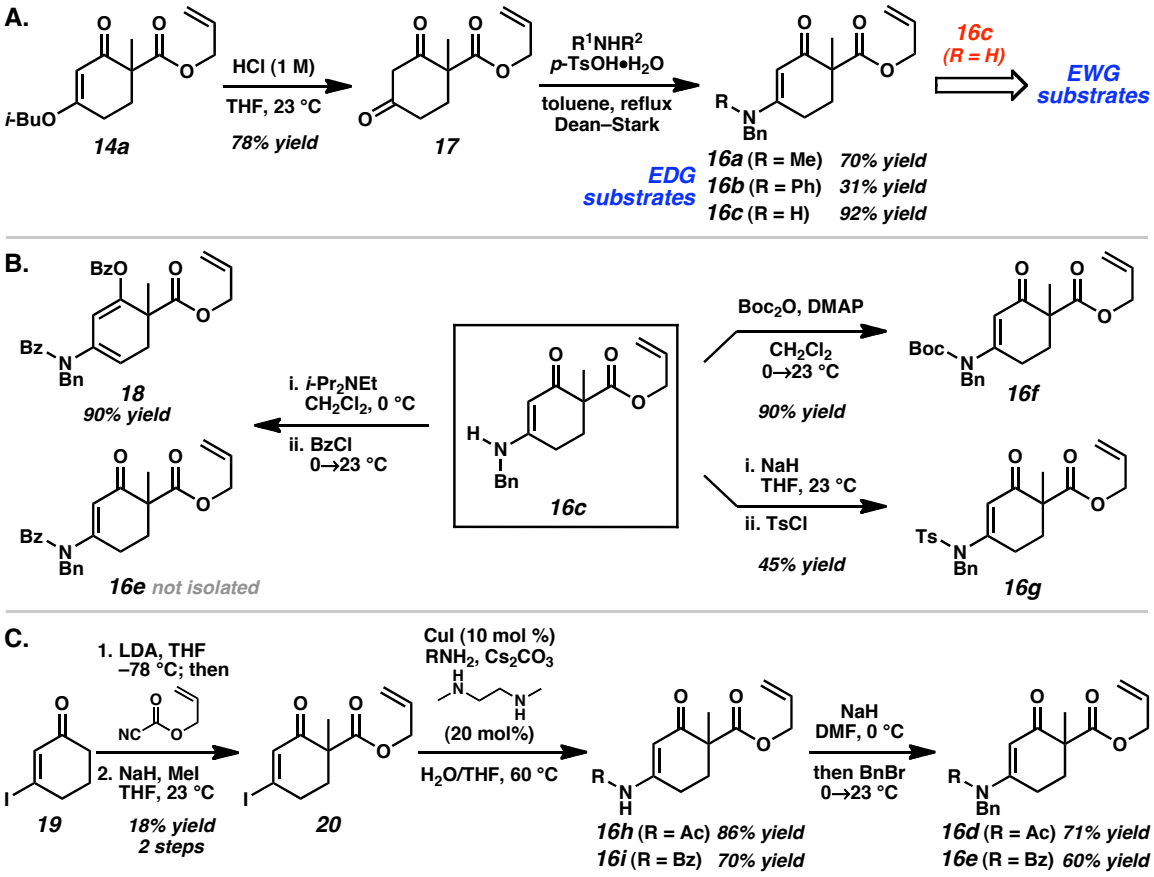
Initially, we hypothesized that the divergence in enolate electronics between the substrate classes depicted in Scheme 1.1 could be the major determining factor of the observed enantioselectivities. Insight from our previous work[9,10] suggested that selectivity in the alkylation of electron-poor and -rich molecules could be considerably different. To investigate the electronic effect of the nitrogen atom on alkylation selectivity without the influence of α'-functionality, we examined variably functionalized enaminones (**16**, i.e., vinylogous amides)[17] as electronic analogues of lactams (**4**, Figure 1.1). We were particularly drawn to this new class of compounds as our past experience with vinylogous esters (**14**)[18] and thioesters (**15**)[18b,19] would provide a foundation and comparison point.[20]

Figure 1.1. Ketone and lactam enantioselectivity divergence as inspiration for investigation of enolate electronics using vinylogous systems.



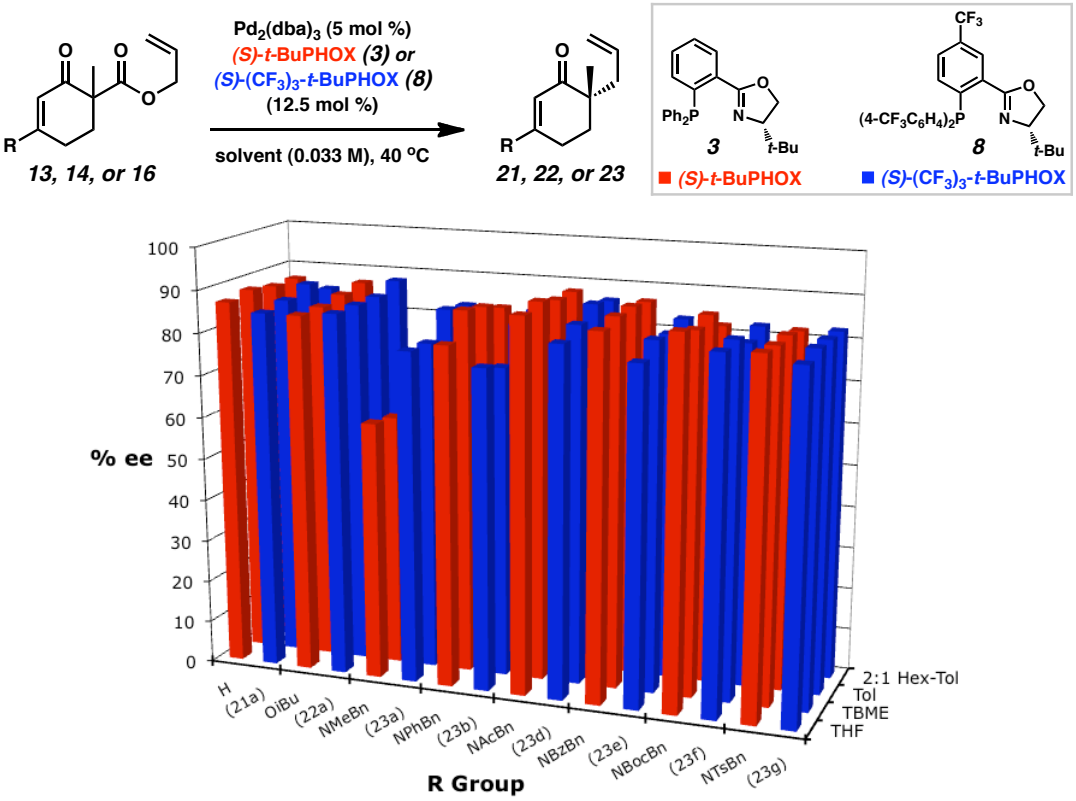
To this end, we prepared a number of racemic enaminone alkylation precursors from vinylogous ester **14a** (Scheme 1.4A). Treatment of vinylogous ester **14a** with hydrochloric acid in THF selectively removes the vinylogous group without hydrolyzing the carboxylic ester, as reported by Desmaële.[21] The resulting dione (**17**) can be condensed with an amine under dehydrative conditions to generate enaminones **16a**–**c**, which bear electron-donating groups.[22,23,24] To prepare substrates with electron-withdrawing functionality, we explored derivatization of enaminone **16c** to acetyl (**16d**), benzoyl (**16e**), tosyl (**16g**), and Boc (**16f**) accessorized products (Scheme 1.4B). The acylation of secondary enaminones using an amine base has previously been reported;[23a,25] however, exposure of intermediate **16c** to diisopropylethylamine (*i*-Pr_2NEt) and benzoyl chloride surprisingly produces diene **18** in 90% yield. We also examined other amine bases (e.g., pyridine and Et_3N), reagent stoichiometry, and the order of reagent addition, but in each case isolated a mixture of over acylated product and desired enaminone **16e**.[26] Similar results were obtained with acetyl chloride. The use of sodium hydride[27] eliminates over acylation, but provides enaminone **16e** with insufficient purity. Nevertheless, these conditions are amenable to the synthesis of tosyl enaminone **16g**, albeit in low yield.[28] The acylated and benzoylated enaminones (**16d** and **e**) can ultimately be obtained from iodoenone **19**[29] through a Buchwald coupling[30] and alkylation sequence (Scheme 1.4C). Boc functionalized enaminone **16f** is prepared without complication following the precedent of Hiemstra (Scheme 1.4B).[31]

Scheme 1.4. Preparation of enaminone alkylation precursors.



With a number of enaminones in hand, we screened a series of palladium-catalyzed decarboxylative allylic alkylation conditions (Table 1.2). Enaminone substrates that possess a hydrogen on the nitrogen (e.g., **16c** and **i**) generate a number of alkylation products with a Pd(PHOX) system and were consequently excluded from this study. The enaminone screen was performed in a manner similar to the previous investigation of lactams,[10,32] employing the ligands (*S*)-**3** and (*S*)-**8** and the same four solvents: tetrahydrofuran (THF), *tert*-butyl methyl ether (TBME), toluene, and 2:1 hexane–toluene.

Table 1.2. Enaminone allylic alkylation screen.[a]



					Enantiomeric Excess (% ee)[b]			
entry	substrate	R	product	ligand	THF	TBME	Toluene	2:1 Hex–Tol
1 2	*13a*	H	*21a*	*3* *8*	87 85	88 86	87 88	87 85
3 4	*14a*	O*i*-Bu	*22a*	*3* *8*	85 86	85 86	86 86	87 88
5 6	*16a*	NMe(Bn)	*23a*	*3* *8*	61 79	60 78	55 84	52 83
7 8	*16b*	NPh(Bn)	*23b*	*3* *8*	81 76	87 74	85 82	83 83
9 10	*16d*	NAc(Bn)	*23d*	*3* *8*	89 83	90 85	88 88	88 86
11 12	*16e*	NBz(Bn)	*23e*	*3* *8*	86 80	87 83	88 82	87 83
13 14	*16f*	NBoc(Bn)	*23f*	*3* *8*	87 84	86 84	87 81	82 83
15 16	*16g*	NTs(Bn)	*23g*	*3* *8*	84 82	83 83	83 83	82 83

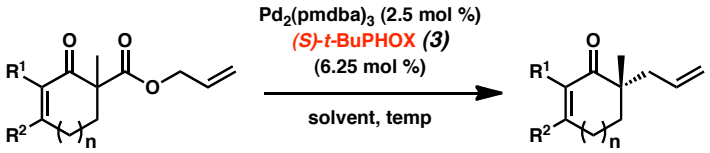
[a] *Conditions*: enone **13a**, vinylogous ester **14a**, or enaminone **16a, b, d–g** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C. [b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand.

We made several observations upon analysis of the ligand, solvent, and substrate trends that distinguished this substrate class considerably from the previously examined lactams. First, enaminones are obtained in modestly better selectivity with (*S*)-**3** as a ligand in most solvents (entries 7–16), with the exception of methyl enaminone **23a**, which significantly favors (*S*)-**8** (entries 5–6). Second, no significant solvent trend is observed for enaminones overall. Third, electron-rich enaminones (i.e., **16a** and **b**) display decreased enantioselectivities and also require extended reaction times for completion,[33] while enaminones bearing electron-withdrawing substituents (**23d**–**g**) are all generated in 80–90% ee. By comparison, lactam substrates perform with much higher enantioselectivity with ligand (*S*)-**8** in non-polar solvents.[10,34] Furthermore, the modest distinction in enantioselectivity for the electron-withdrawing enaminones sharply contrasts with the corresponding lactam series, where the *N*-substituent plays a considerable role, producing significant variation in selectivity.[10,35] These differences suggest that the *N*-functional group does not contribute to enantioselectivity solely through a perturbation of enolate electronics.

Beyond these considerations, the most striking feature of the screen is that enantioselectivities observed for enaminones **23d**–**g** are approximately equivalent to results obtained for enone **21a**,[36] vinylogous ester **22a**, previously investigated vinylogous molecules (Table 1.3),[18b,19] and even more general ketone substrates. Of all the enaminones screened, acetyl variant **23d** provides the highest selectivity at 90% ee in TBME, which is only marginally better than the optimal values for the related vinylogous systems. The modest differences between these vinylogous molecules (i.e., **21**–**23**)

further suggest that the electronic nature of the enolate is not likely the predominant factor in providing high enantioselectivity for lactams and imides.

Table 1.3. Alkylation of other vinylogous esters and thioesters.[a]



14/24 and 15/25 ***22/27 and 26/28***

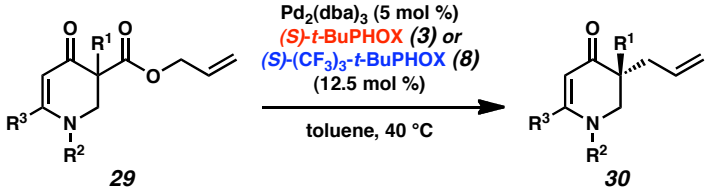
entry	substrate	n	R^1	R^2	product	solvent	temp (°C)	yield (%)	ee (%)[b]	ref.
1	***14b***	1	Me	O*i*-Bu	***22b***	toluene	80	86	75	19a
2	***15a***	1	Me	SPh	***26a***	toluene	50	85	92	19a
3	***15a***	1	Me	SPh	***26a***	benzene	50	61[c]	92	19a
4	***15a***	1	Me	SPh	***26a***	THF	50	88	92	19a
5	***15a***	1	Me	SPh	***26a***	1,4-dioxane	50	88	92	19a
6	***24a***	2	H	O*i*-Bu	***27a***	Et_2O	30	93	86	18b
7	***25a***	2	H	SPh	***28a***	Et_2O	30	86	89	18b

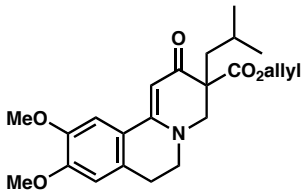
[a] *Conditions*: vinylogous ester **14**/**24** or vinylogous thioester **15**/**25**, $Pd_2(pmdba)_3$ (2.5 mol %), and *(S)-t*-BuPHOX (**3**) (6.25 mol %) in solvent at temp. [b] Determined by HPLC or SFC analysis. [c] β-Ketoester **15a** recovered in 26% yield.

While pursuing enaminones, we also briefly examined the related 2,3-dihydropyridin-4-ones, which possess the nitrogen within the ring (Table 1.4). Acylation and alkylation (or vice versa) of known dihydropyridinones[37,38,39] allows preparation of the reaction precursors **29a**–**d**. Under our standard palladium-catalyzed conditions, *N*-carboxybenzyl substituted product **30a** is formed with enantioselectivities similar to electronically related enaminones. Electron-rich 2,3-dihydropyridin-4-ones **30b** and **c** are curiously also generated in the same range. Even 2,3-dihydropyridin-4-one **30d** is produced in excellent enantioselectivity, despite the highly electron-rich nature of the

enolate. These results again allude to other factors beyond enolate electronics that direct alkylation selectivity.

Table 1.4. Allylic alkylation of 2,3-dihydropyridin-4-ones.[a]



entry	substrate *29*	R^1	R^2	R^3	product *30*	ligand	yield (%)	ee (%)[b]
1	*29a*	Me	Cbz	H	*30a*	*3*	80	86
2						*8*	98	84
3	*29b*	Me	Bn	H	*30b*	*3*	82	88
4						*8*	94	86
5	*29c*	*i*-Bu	Bn	H	*30c*	*3*	85	84
6						*8*	81	88
7	*29d*				*30d*	*8*	81	91

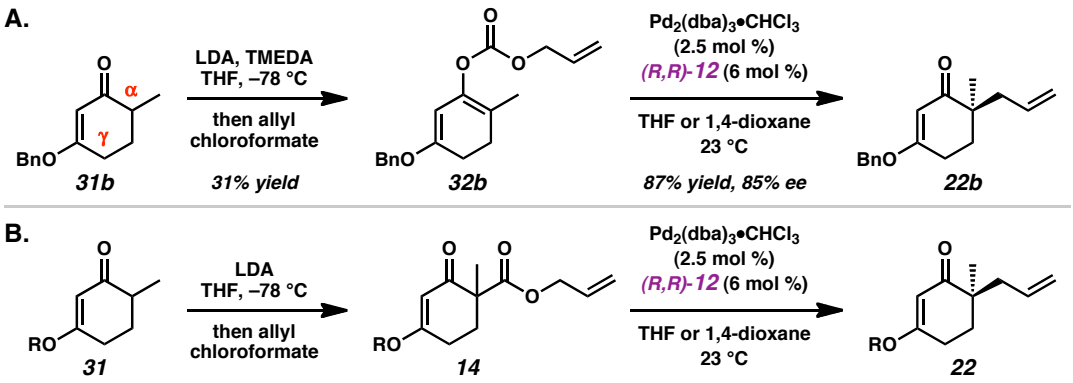
[a] *Conditions*: 2,3-dihydropyridin-4-ones **29**, $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in toluene (0.033 M) at 40 °C. [b] Determined by HPLC or SFC analysis. Red = with *(S)*-**3** as ligand and blue = with *(S)*-**8** as ligand.

1.2.1.1 Other Reports of Allylic Alkylation on Vinylogous Molecules

Trost has also reported the palladium-catalyzed allylic alkylation of vinylogous esters and thioesters employing their C_2-symmetric *P*,*P*-ligands. In particular, their 2006 study prepares a range of related α-quaternary vinylogous products using (*R*,*R*)-**12**.[20a] This effort first focused on the transformation of vinylogous esters into allyl enol carbonate alkylation precursors. However, enolate regioselectivity (α vs. γ deprotonation) is poor for a number of vinylogous alkoxy groups, except benzyl (**32b**),

although this carbonate product is formed in low yield (Scheme 1.5A). Several β-ketoesters were alternatively examined, but lower conversions were observed with these substrates than with enol carbonate **32b** (Scheme 1.5B). The best results were obtained with phenyl and Boc substituted β-ketoesters (**14e** and **f**), which have decreased electron-donating contribution from the vinylogous oxygen. Trost consequently investigated the analogous thioesters, reasoning that sulfur would have less orbital overlap. Vinylogous thioester **14b** performs with good yield and perfect enantioselectivity (Scheme 1.6), and a variety of other thioesters are also produced with good to excellent ee. Trost has also examined exocyclic vinylogous esters and carried the enantioenriched products onto the natural products hamigeran B[20b,c] and allocyathin B_2.[20d]

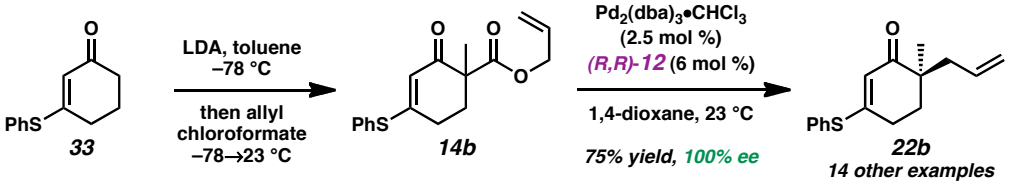
Scheme 1.5. Asymmetric allylic alkylation of vinylogous esters performed by Trost.



entry	substrate *31*	R^1	product *14*	yield (%)[b]	product *22*	yield (%)[b]	ee (%)[c]
1	*31b*	Bn	*14b*	87	*22b* [e]	51	91
2	*31c*	Et	*14c*	85	*22c* [d]	26	94
3	*31d*	*t*-Bu	*14d*	85	*22d* [d]	29	97
4	*31e*	Ph	*14e*	91	*22e* [d]	70	96
5	*31f*	Boc	*14f*	32	*22f* [e]	66	94

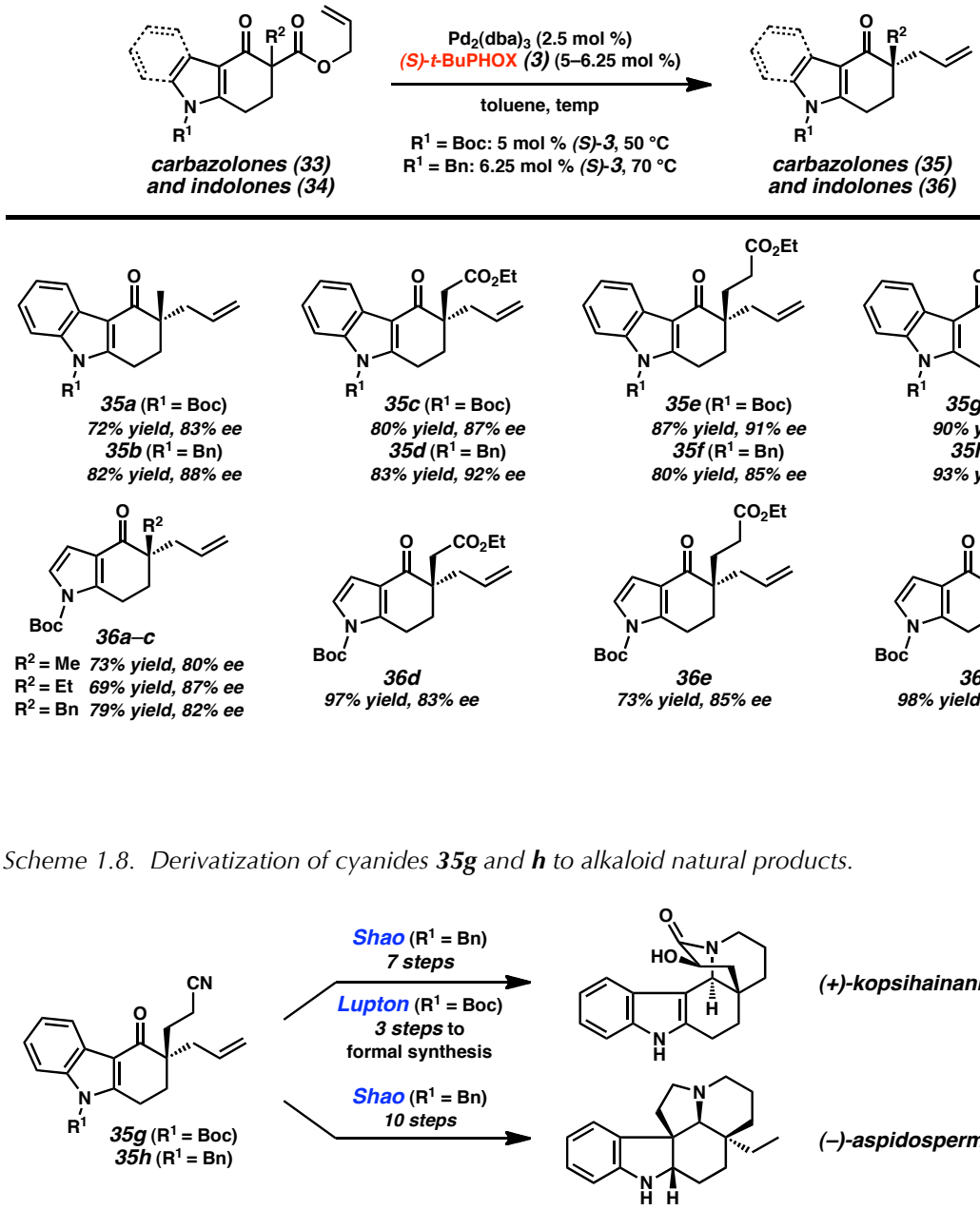
[a] *Conditions*: vinylogous ester **16**, $Pd_2(dba)_3$ (5 mol %), and *(R,R)*-**12** (6 mol %) in solvent (0.1 M) at 23 °C. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 1,4-dioxane as solvent. [e] THF as solvent.

Scheme 1.6. Asymmetric allylic alkylation of vinylogous thioesters performed by Trost.



Concurrent with our efforts on enaminones, Lupton[40] and Shao[41] independently published sequential reports on the Pd-catalyzed allylic alkylation of two other vinylogous amide classes, carbazolones (**33**) and indolones (**34**) (Scheme 1.7). The reaction parameters between the two papers are almost identical (Lupton: 5 mol% ligand, 50 °C; Shao: 6.25 mol % ligand, 70 °C)[42] and many of the substrates are also related. In these efforts, Lupton selects a Boc *N*-protecting group, while Shao employs a benzyl substituent. The enantioselectivities of the methyl/allyl α-quaternary carbazolones (**35a** and **b**) and indolones (**36a**) are comparable to our results with enaminones that possess electron-withdrawing functionality. Even the *N*-benzyl carbazolones are produced in good to excellent ee, unlike the enaminones that bear electron-rich groups (**23a** and **b**). In addition to screening several alkylation precursors, both laboratories advance their enriched cyanide alkylation products (**35g** and **h**) onto (+)-kopsihainanine A (**37**) through total and formal synthetic routes, and Shao also completes the alkaloid (–)-aspidospermidine (**38**, Scheme 1.8).

Scheme 1.7. Alkylation of carbazolone (Lupton, R^1 = Boc; Shao, R^1 = Bn) and indolone (Lupton) substrates reported in 2013.

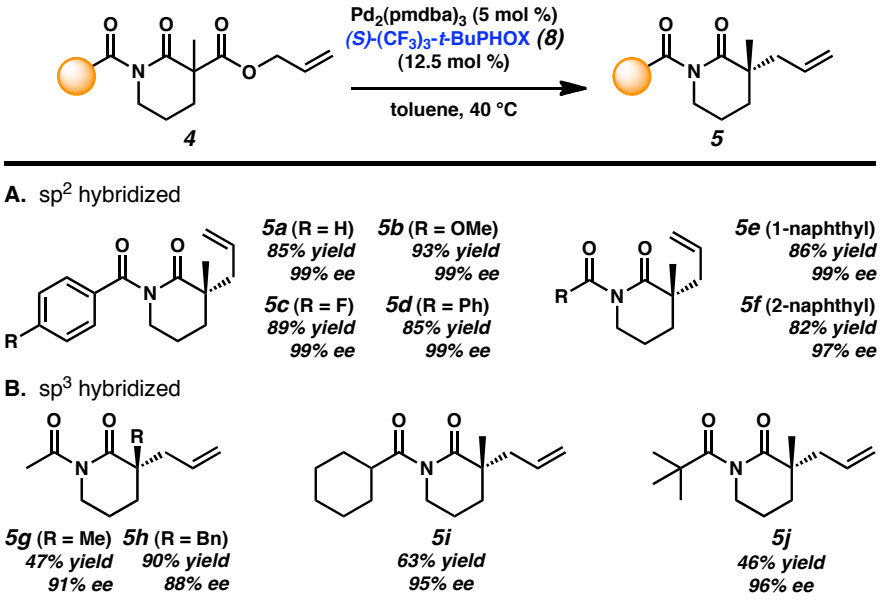


*Scheme 1.8. Derivatization of cyanides **35g** and **h** to alkaloid natural products.*

1.2.2 α'-Functionalized Substrates

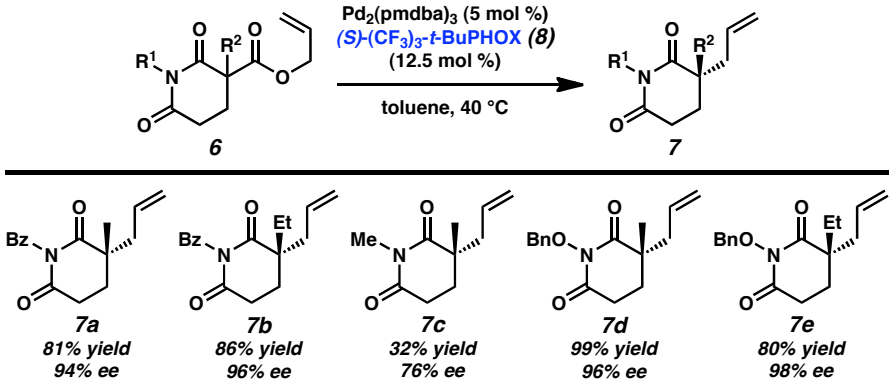
Having investigated the impact of enolate electronics, we diverted our efforts to study the influence of α'-functionality on alkylation selectivity (Scheme 1.9). Our previous lactam screen identified the benzoyl moiety as the optimal protecting group,[10] providing high to nearly perfect enantioselectivities for a variety of lactams (e.g., **5a**). Interestingly, both electron-rich and electron-poor benzoyl lactams (**5b**–**d**) as well as naphthoyl lactams (**5e** and **f**) display excellent ee, whereas acetyl lactams (e.g., **5g** and **h**) provide lower selectivity. This prompted us to question whether these results are due to a hybridization or steric effect. Consequently, we synthesized the bulky sp^3 hybridized cyclohexoyl lactam **4i** and pivaloyl lactam **4j**, which proceed in improved enantioselectivities compared to analogous acetyl lactam **4g**, supporting a steric effect.[43]

Scheme 1.9. Impact of various sp^3 and sp^2 acyl groups on allylic alkylation enantioselectivity for lactams.



In conjunction with our investigation of the asymmetric allylic alkylation of lactams, we found that *N*-benzoyl cyclic imides **7a** and **b** are furnished in excellent ee (Scheme 1.10). However, we observed that formation of *N*-methyl imide **7c** proceeds with moderate enantioselectivity and is hampered by low reactivity.[43] As this substrate also generates an intermediate imido enolate (as do lactams **5a**–**j**, Scheme 1.9), this result further supports our conclusion that enolate electronics do not play a major role in the enhanced enantioselectivities observed for *N*-benzoyl lactams. As such, we examined the influence of alternate *N*-substituents in the context of the allylic alkylation with imides.

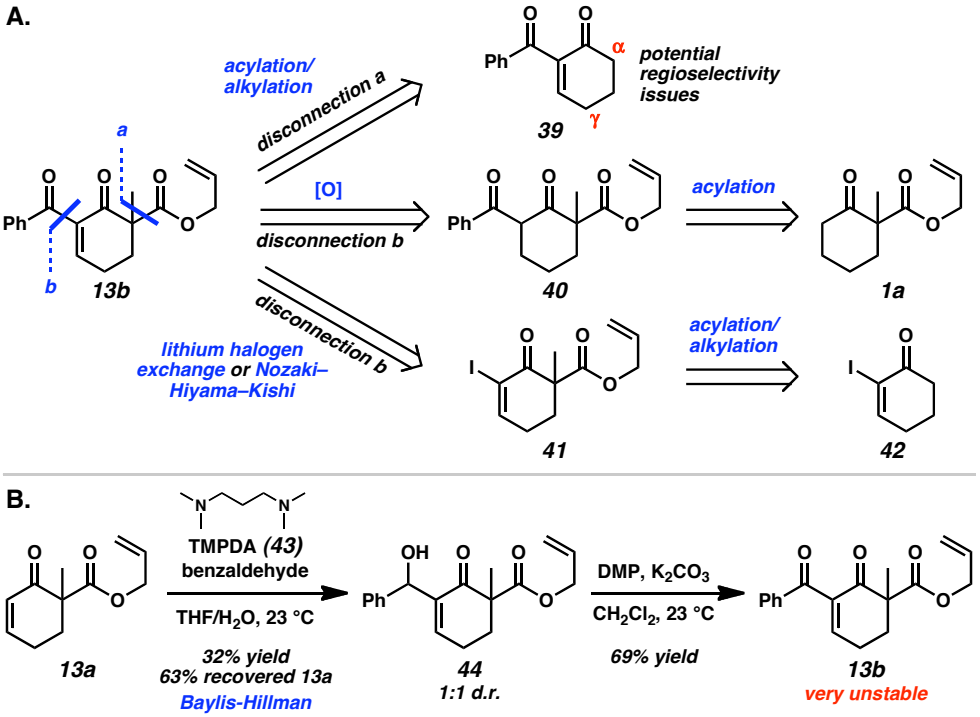
Scheme 1.10. Allylic alkylation of cyclic imides.



Gratifyingly, we identified *N*-benzyloxy imides as excellent substrates for this methodology, generating imides **7d** and **e** in yields and enantioselectivities comparable to their *N*-benzoyl counterparts. In conjunction with the results obtained for substituted *N*-acyl lactams **5g**–**j**, we reason that the nature of the α'-substituent leads to the observed enhancements in enantioselectivity, though enolate electronics have been shown to dramatically affect the reaction rate.

We sought to further probe the α'-group contribution without the influence of nitrogen and consequently focused on a series of α'-functionalized enones, including benzoyl enone **13b** (Scheme 1.11). Previous research suggested enolization regioselectivity issues may arise in acylating/alkylating enone **39** (α vs. γ, path A),[6b] prompting us to pursue approaches to enone **13b** through retrosynthetic disconnection of the benzoyl substituent (path B). Unfortunately, attempts to acylate and oxidize β-ketoester **1a** proved unsuccessful. Both lithium halogen exchange and Nozaki–Hiyama–Kishi coupling on iodoenone **41** also failed to install the benzoyl group. The synthesis of enone **13b** is ultimately possible via a Baylis–Hillman[44] reaction and oxidation sequence (Scheme 1.11B). A number of oxidants were examined in the latter transformation, but only Dess–Martin periodinane (DMP) proved successful. Benzoyl enone **13b** is very sensitive to alkene isomerization, and thus the addition of potassium carbonate as a buffer and the use of triethylamine deactivated silica gel for purification are necessary. Although we were able to prepare enone **13b**, stability issues make this molecule a poor alkylation substrate and prohibit the isolation of the desired methyl/allyl α-quaternary enone under our standard palladium-catalyzed conditions.

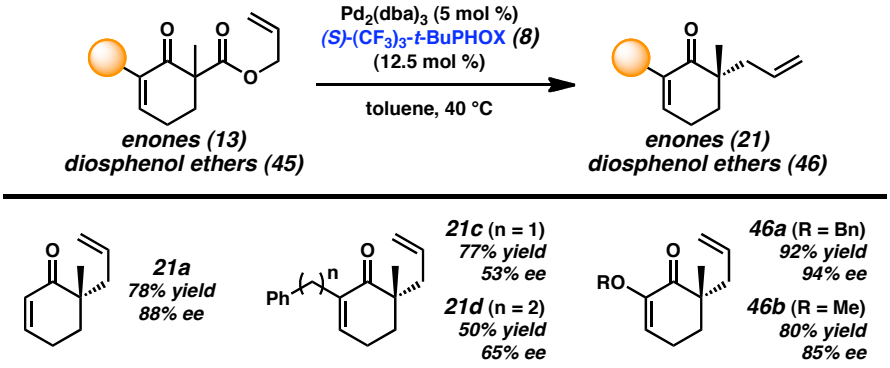
Scheme 1.11. Retrosynthetic approaches and successful route to benzoyl enone ***13b****.*



Despite the complications with benzoyl enone **13b**, we were able to synthesize enones **13c** and **d** and diosphenol ethers **45a** and **b** under standard acylation/alkylation conditions. To examine the relative merit of the steric and stereoelectronic effects associated with the α'-substituent, we subjected these substrates to the palladium-catalyzed alkylation parameters employed with lactams and imides (Scheme 1.12). In this transformation, enones **21c** and **d** are formed in low enantioselectivity. By contrast, benzyl diosphenol ether **46a**, which differs from **21d** only in the substitution of oxygen for a methylene group, is generated in 92% yield and 94% ee. This suggests that purely steric or π-stacking interactions are not the sole contributing factors to enantioselectivity. Rather, electronic effects of the α'-substituent exert an important influence on the stereoselectivity of the reaction. However, a certain amount of steric bulk appears critical

in obtaining high enantioselectivity as methyl diosphenol ether **46b** is produced in 85% ee. In comparison, analogous enone **21a**, which bears no α'-functionality, proceeds under the same conditions to afford enone **21a** in 88% ee,[36] with vinylogous amides and esters also in the ~80–90% ee range (*vide supra*). Overall, our studies on the role of the α'-substituent have culminated in the discovery of substrate **45a**, which proceeds with the greatest enantioselectivity observed in a Pd(PHOX) catalyst system for a carbocyclic substrate bearing an α-methyl and unsubstituted allyl moiety.

Scheme1.12. Allylic alkylation of α'-functionalized enones and diosphenol ethers.



1.3 CONCLUDING REMARKS

In summary, we have designed and evaluated a number of novel substrates to probe the influence of enolate electronics and the role of α'-functionality on selectivity in the palladium-catalyzed decarboxylative allylic alkylation. Based on these results, we reason that the high enantioselectivities observed with lactams and imides are a consequence of both electronic and steric effects associated with α'-substituents, and that enolate electronics alone contribute relatively little to the stereochemical outcome of the

reaction. These results led to further investigations in our group to determine the nature and origin of the effect of α'-substitution on this transformation and to use this insight to improve and expand our methods as described in the following chapter.

1.4 EXPERIMENTAL SECTION

1.1.1 MATERIALS AND METHODS

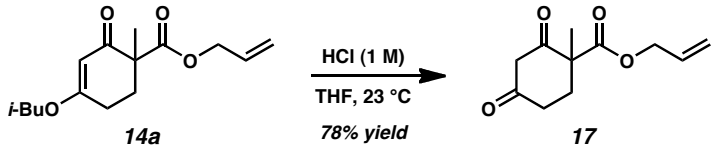
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[45] Acetone was used directly from a Sigma-Aldrich ACS reagent grade bottle. Brine solutions are saturated aqueous solutions of sodium chloride. Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. (*S*)-*t*-BuPHOX (**3**),[5ab] (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**),[5c] and allyl cyanoformate[46] were prepared by known methods. Reaction temperatures were controlled by an IKAmag temperature modulator. Reaction progress was monitored by thin-layer chromatography (TLC). 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. ICN silica gel (particle size 0.032-0.0653 mm) was used for flash column chromatography. Preparative HPLC purification was performed on an Agilent 1200 Series HPLC using an Agilent Prep-SIL column (5 μm, 30 x 250 mm) at ambient temperature with a flow rate of 50 mL/min. Separation was monitored by UV (λ = 254 nm) and fractions were collected at the valleys between peaks. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or benzene-d_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer (75 or 125 MHz respectively) and are reported relative to $CDCl_3$ (δ 77.16 ppm) or benzene-d_6 (δ 128.06

ppm). Variable temperature NMR experiments were performed on a Varian Inova 500 MHz spectrometer and are reported relative to residual DMSO (δ 2.50 ppm). Data for ^{1}H 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, dm = doublet of multiplets, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δppm). 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, *ee*). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD, AD-H, or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral SFC was performed with a JASCO 2000 series instrument or a Thar SFC utilizing Chiralpak (AD-H or AS-H) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm), or a Chiralpak IC column (4.6 mm x 10 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (GC-EI+, EI+, or FAB+) 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+).

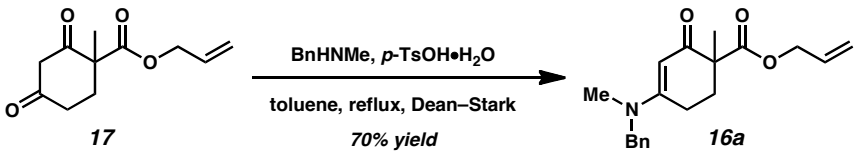
1.4.2 PREPARTIVE PROCEDURES

1.4.2.2 Preparation of Compounds Related to Enaminone Screen

1.4.2.2.1 *Enaminone Allylic Alkylation Precursors*

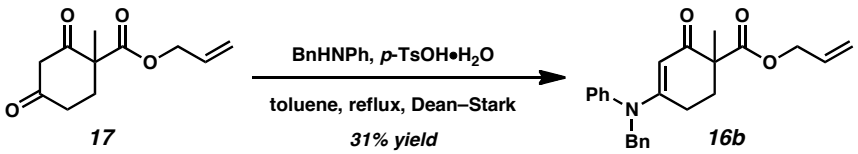


Dione 17. Procedure adapted from report by Desmaële.[21] A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with vinylogous ester **14a**[18c] (3.08 g, 11.58 mmol, 1.00 equiv), THF (30 mL, 0.39 M), and aq HCl (1 M in H_2O, 14.00 mL, 14.00 mmol, 1.21 equiv). The reaction mixture was initially a suspension that developed into a solution over time. After 7 h of vigorous stirring at ambient temperature, the reaction was diluted with EtOAc (30 mL) and transferred to a separatory funnel where the aqueous layer was extracted seven times with EtOAc. The combined organics (400 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 31 x 5 cm, 100% hexanes→20%→50% EtOAc in hexanes) to afford dione **17** (1.89 g, 11.58 mmol, 78% yield) as a pale yellow oil; R_f = 0.17 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) mixture of keto-enol tautomers, see spectra section; IR (Neat Film NaCl) 3500–2500 (broad stretch), 3088, 2983, 2939, 2657, 2591, 1734, 1595, 1457, 1413, 1383, 1358, 1343, 1309, 1272, 1249, 1190, 1114, 986, 932, 853 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{15}O_4$ $[M+H]^+$: 211.0965, found 211.0966.



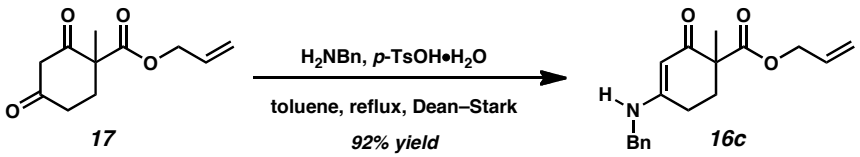
Enaminone 16a. A 50 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (465.4 mg, 2.21 mmol, 1.00 equiv), toluene (24 mL, 0.09 M), benzylmethylamine (320 µL, 2.48 mmol, 1.12 equiv), and *p*-toluenesulfonic acid monohydrate (42.3 mg, 0.22 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 2 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (200 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 3 cm, 100% hexanes→20%→50%→60%→70% EtOAc in hexanes) to afford enaminone **16a** (484.8 mg, 1.55 mmol, 70% yield) as a yellow/orange oil; R_f = 0.24 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.32–7.27 (m, 1H), 7.09 (d, J = 7.4 Hz, 2H), 5.93–5.83 (m, 1H), 5.29 (dq, J = 17.3, 1.5 Hz, 1H), 5.26 (s, 1H), 5.18 (dq, J = 10.5, 1.4 Hz, 1H), 4.66–4.56 (m, 2H), 4.51 (s, 2H), 2.96 (s, 3H), 2.74–2.63 (m, 1H), 2.56–2.45 (m, 2H), 1.95–1.84 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ193.9, 173.7, 164.3, 132.2, 129.1, 127.8, 126.7, 118.0, 98.1, 65.6, 55.2, 51.1, 38.5, 32.6, 24.4, 21.0; IR (Neat Film NaCl) 3063, 3028, 2933, 2873, 1733, 1615, 1585, 1563, 1557, 1495, 1455, 1415, 1377, 1352, 1332, 1295, 1258, 1222,

1203, 1174, 1113, 1028, 989, 929, 821, 735 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found 314.1754.



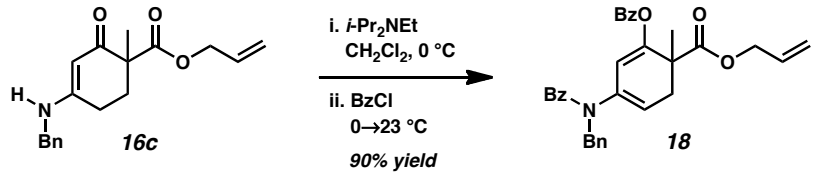
Enaminone 16b. A 50 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (500.3 mg, 2.38 mmol, 1.00 equiv), toluene (24 mL, 0.10 M), benzylphenylamine (480.0 mg, 2.62 mmol, 1.10 equiv), and *p*-toluenesulfonic acid monohydrate (45.6 mg, 0.24 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 8 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (200 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 26 x 3 cm, 100% hexanes→10%→15%→20%→30%→40% EtOAc in hexanes ***then*** SiO_2, 26.5 x 3 cm, 100% hexanes→ 5%→10%→15% →20%→30%→ 50% EtOAc in hexanes) to afford enaminone **16b** (276.6 mg, 0.74 mmol, 31% yield) as a yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.33–7.24 (m, 4H), 7.21–7.18 (m, 2H), 7.13–7.10 (m, 2H), 5.90 (dddd, J = 17.2, 10.7, 5.4, 5.4 Hz, 1H), 5.39 (s, 1H), 5.31 (dq, J = 17.2, 1.6 Hz, 1H), 5.21 (dq, J = 10.5, 1.4 Hz, 1H), 4.83 (s, 2H), 4.68–4.63 (m, 1H), 4.62–4.57 (m, 1H),

2.55–2.47 (m, 1H), 2.42 (ddd, J = 13.3, 6.1, 4.9 Hz, 1H), 2.33–2.27 (m, 1H), 1.84 (ddd, J = 13.5, 8.7, 4.9 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 173.3, 163.9, 144.3, 136.4, 132.2, 129.9, 128.9, 128.0, 127.9, 127.7, 127.1, 118.0, 100.4, 65.6, 56.8, 51.6, 32.9, 25.9, 21.0; IR (Neat Film NaCl) 3061, 3031, 2975, 2933, 2872, 1734, 1623, 1560, 1494, 1453, 1426, 1408, 1377, 1346, 1327, 1293, 1255, 1210, 1174, 1112, 1080, 1061, 1022, 989, 929, 885, 825, 779, 733, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}NO_3$ $[M+H]^+$: 376.1907, found 376.1903.



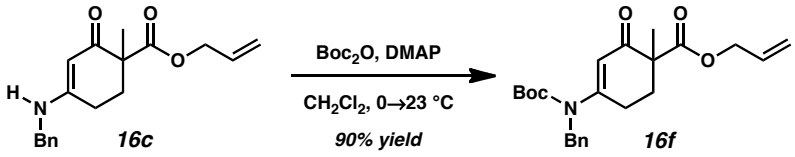
Enaminone 16c. A 250 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (1.89 g, 8.98 mmol, 1.00 equiv), toluene (90 mL, 0.10 M), benzylamine (1.1 mL, 10.04 mmol, 1.12 equiv), and *p*-toluenesulfonic acid monohydrate (169.0 mg, 0.89 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 5.5 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (50 mL) and transferred to a separatory funnel where the aqueous layer was extracted once with Et_2O and three times with dichloromethane. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 31 x 5 cm, 100% hexanes→20%→50% EtOAc in hexanes) to afford enaminone **16c** (2.48 g, 8.28 mmol, 92% yield) as a yellow solid; R_f =

0.27 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 3H), 7.29 (s, 2H), 5.95–5.82 (m, 1H), 5.30 (dq, J = 17.2, 1.6 Hz, 1H), 5.22 (s, 1H), 5.20 (dq, J = 10.5, 1.4 Hz, 1H), 4.62 (tt, J = 5.6, 1.5 Hz, 2H), 4.56 (br s, 1H), 4.24 (d, J = 5.0 Hz, 2H), 2.59 (ddd, J = 16.5, 8.8, 4.9 Hz, 1H), 2.50 (ddd, J = 13.3, 6.2, 4.9 Hz, 1H), 2.33 (dt, J = 16.6, 5.3 Hz, 1H), 1.91 (ddd, J = 13.6, 8.8, 5.0 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 173.4, 162.6, 136.7, 132.2, 129.1, 128.2, 128.0, 118.0, 96.7, 65.6, 52.1, 47.5, 32.4, 26.7, 21.1; IR (Neat Film NaCl) 3260, 3064, 2978, 2933, 2868, 1730, 1576, 1545, 1452, 1427, 1375, 1359, 1297, 1253, 1218, 1199, 1172, 1107, 1028, 987, 929, 822, 735 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{18}H_{21}NO_3$ $[M+\bullet]^+$: 299.1521, found 299.1522.



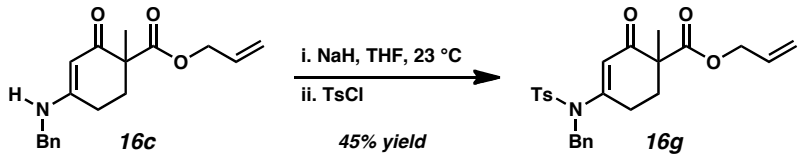
Diene 18. A 1 dram (4 mL) vial equipped with a stir bar and Teflon septa was charged with enaminone **16c** (49.9 mg, 0.167 mmol, 1.00 equiv) and lowered into a 0 °C bath (ice/water). Dichloromethane (1.7 mL, 0.10 M), *i*-Pr_2NEt (150 µL, 0.861 mmol, 5.17 equiv), and benzoyl chloride (40 µL, 0.345 mmol, 2.07 equiv) were added and the reaction was allowed to warm to room temperature over time. After 13 h, TLC analysis indicated consumption of starting material. The reaction was subsequently quenched with water (5 mL) and the aqueous layer was extracted four times with dichloromethane. The combined organics (50 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 26 x 1 cm, 5%→10%→15% EtOAc in hexanes) to afford diene **18** (75.8 mg, 0.149 mmol,

90% yield) as a yellow oil; R_f = 0.77 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07–8.02 (m, 2H), 7.65–7.59 (m, 1H), 7.56–7.51 (m, 2H), 7.50–7.45 (m, 2H), 7.39 (s, 2H), 7.37–7.32 (m, 3H), 7.32–7.30 (m, 2H), 7.28–7.24 (m, 1H), 6.20 (s, 1H), 5.81–5.72 (m, 1H), 5.22 (dt, J = 17.2, 1.4 Hz, 1H), 5.13 (dt, J = 10.3, 1.3 Hz, 1H), 4.97–4.79 (m, 3H), 4.56–4.43 (m, 2H), 2.75 (dd, J = 17.4, 4.6 Hz, 1H), 2.03 (dd, J = 17.4, 4.7 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 170.7, 164.0, 150.5, 137.2, 136.2, 136.1, 133.9, 131.7, 130.2, 130.0, 129.4, 129.0, 128.8, 128.5, 128.3, 128.1, 127.5, 120.2, 118.6, 113.4, 66.1, 50.6, 46.4, 35.1, 20.4; IR (Neat Film NaCl) 3062, 3030, 2981, 2934, 1740, 1646, 1600, 1577, 1495, 1451, 1400, 1349, 1326, 1244, 1176, 1145, 1112, 1077, 1050, 1023, 1001, 980, 935, 824, 797, 755 cm^{-1}; HRMS (MM: ESI-APCI+) calc'd for $C_{32}H_{30}O_5N$ $[M+H]^+$: 508.2118, found 508.2122.



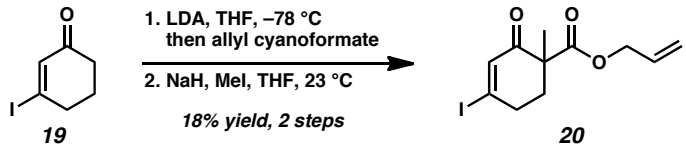
Enaminone 16f. A flame-dried 25 mL round-bottom flask containing a magnetic stir bar was loaded with enaminone **16c** (300.1 mg, 1.00 mmol, 1.00 equiv) and 4-dimethylaminopyridine (9.5 mg, 0.078 mmol, 7.8 mol %). The flask was charged with dichloromethane (10 mL, 0.10 M) and lowered into a 0 °C bath (ice/water). Di-*tert*-butyl dicarbonate (252.7 mg, 1.16 mmol, 1.15 equiv) was added, and the solution transitioned from yellow to clear. The ice bath was allowed to expire as the reaction was stirred overnight. After 22 h, the stir bar was removed from the flask, the reaction contents were concentrated under reduced pressure, and the resulting crude oil was purified by flash

column chromatography (SiO_2, 26.5 x 3 cm, 100% hexanes→5%→10%→15%→20% EtOAc in hexanes) to afford enaminone **16f** (360.0 mg, 0.90 mmol, 90% yield) as a pale yellow oil; R_f = 0.79 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 2H), 7.26–7.21 (m, 1H), 7.16–7.12 (m, 2H), 5.85 (dddd, J = 17.2, 10.5, 5.5, 5.5 Hz, 1H), 5.73 (t, J = 0.9 Hz, 1H), 5.27 (dq, J = 17.2, 1.6 Hz, 1H), 5.20 (dq, J = 10.5, 1.3 Hz, 1H), 4.80 (s, 2H), 4.58 (dddd, J = 5.6, 2.8, 1.5, 1.5 Hz, 2H), 2.92–2.77 (m, 2H), 2.45 (dt, J = 13.5, 5.3 Hz, 1H), 1.86 (ddd, J = 13.5, 7.7, 5.7 Hz, 1H), 1.42 (s, 9H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 172.6, 162.2, 152.9, 137.2, 131.9, 128.8, 127.5, 126.3, 118.3, 114.8, 83.0, 65.8, 53.0, 52.5, 33.6, 28.1, 27.5, 20.4; IR (Neat Film NaCl) 3090, 3064, 3034, 2978, 2935, 2873, 1718, 1662, 1654, 1595, 1497, 1453, 1425, 1369, 1344, 1317, 1300, 1248, 1210, 1150, 1113, 1029, 989, 937, 856, 815, 769, 737 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2118, found 400.2127.



Enaminone 16g. A flame-dried 25 mL round-bottom flask containing a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (95% by weight, 32.6 mg, 1.29 mmol, 1.29 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with THF (6 mL). Enaminone **16c** (300.3 mg, 1.00 mmol, 1.00 equiv) was added in one portion and the grey suspension bubbled and became a yellow solution over time. The flask was rinsed with additional THF (4 mL, 10 mL total, 0.10 M). The reaction was stirred vigorously for 70 min before *p*-toluenesulfonyl

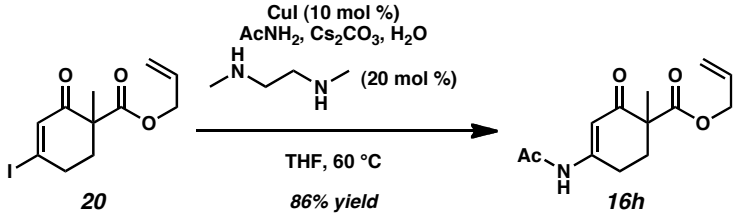
chloride (287.6 mg, 1.51 mmol, 1.50 equiv) was added in one portion. After 6 h, the flask was lowered into a 0 °C bath (ice/water) and quenched with water (reaction mixture bubbled). The mixture was transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 3 cm, 100% hexanes→5%→10%→15%→ 50% EtOAc in hexanes) to afford enaminone **16g** (203.8 mg, 0.45 mmol, 45% yield) as a yellow oil; R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.33–7.25 (m, 3H), 7.23 (d, J = 6.6 Hz, 2H), 5.75 (dddd, J = 17.3, 10.8, 5.6, 5.6 Hz, 1H), 5.68 (t, J = 1.1 Hz, 1H), 5.24–5.15 (m, 2H), 4.81–4.69 (m, 2H), 4.48 (dddd, J = 13.5, 5.6, 1.4, 1.4 Hz, 1H), 4.40 (dddd, J = 13.2, 5.6, 1.4, 1.4 Hz, 1H), 2.67–2.55 (m, 2H), 2.46 (s, 3H), 2.32 (dt, J = 13.9, 5.2 Hz, 1H), 1.69 (ddd, J = 13.8, 8.0, 5.9 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 171.9, 158.4, 144.8, 135.6, 135.3, 131.7, 130.2, 128.9, 128.1, 127.6, 127.5, 119.5, 118.5, 65.9, 53.0, 52.2, 32.4, 27.9, 21.8, 20.0; IR (Neat Film NaCl) 3064, 3032, 2981, 2935, 2873, 1735, 1669, 1596, 1496, 1454, 1424, 1359, 1321, 1292, 1255, 1164, 1115, 1089, 1058, 1028, 984, 910, 883, 816, 773, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{28}NSO_5$ $[M+H]^+$: 454.1683, found 454.1691.



β-Iodoenone 20. A 200 mL round-bottom flask equipped with a magnetic stir bar was charged with diisopropyl amine (1.52 mL, 10.85 mmol, 1.19 equiv) and THF (36 mL). The flask was lowered into a 0 °C bath (ice/water) and *n*-BuLi (4.5 mL, 2.3 M in hexanes, 10.35 mmol, 1.14 equiv) was added dropwise over several minutes. The reaction was stirred for 15 min before the ice bath was removed and replaced with a –78 °C bath (dry ice/acetone). β-Iodoenone **19**[29] (2.00 g, 9.09 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x 14 mL and 2 x 5 mL rinses, total added = 60 mL, 0.15 M), producing a yellow solution that transitioned to red over time. The reaction was stirred for 1 h before allyl cyanoformate (1.12 mL, 10.38 mmol, 1.14 equiv) was added dropwise. After 2.25 h, the reaction was quenched with sat. NH_4Cl solution and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was filtered through a short silica gel plug to afford an orange oil.

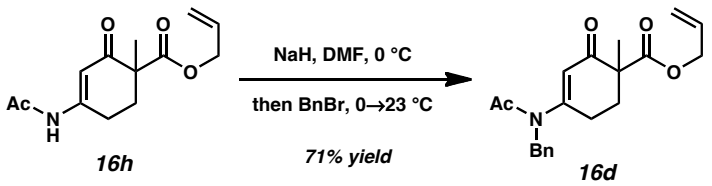
A 50 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (161.0 mg, 95% by weight, 6.37 mmol, 1.21 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with THF (6 mL). The crude orange oil from the previous step (1.61 g, 5.27 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x

5 mL + 3 x 2 mL, total added = 21.0 mL, 0.25 M). The grey suspension bubbled and became a yellow solution that transitioned to red over time. The reaction was stirred for 30 min before methyl iodide (400 μL, 6.43 mmol, 1.22 equiv) was added dropwise. After 3.5 h, the reaction was quenched with water and extracted four times with dichloromethane. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28.5 x 4 cm, 100% hexanes→5% EtOAc in hexanes) to afford β-Iodoenone **20** (536.3 mg, 1.68 mmol, 18% yield over two steps) as a yellow oil; R_f = 0.72 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dd, J = 2.2, 1.2 Hz, 1H), 5.94–5.79 (m, 1H), 5.32–5.26 (m, 1H), 5.24 (dt, J = 10.5, 1.1 Hz, 1H), 4.67–4.56 (m, 2H), 3.05–2.96 (m, 1H), 2.93–2.85 (m, 1H), 2.43 (dt, J = 13.8, 4.9 Hz, 1H), 1.95 (ddd, J = 14.0, 9.0, 5.3 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 171.7, 139.6, 131.6, 125.5, 118.8, 66.1, 52.7, 38.6, 35.0, 20.3; IR (Neat Film NaCl) 3084, 2982, 2936, 2868, 1732, 1682, 1597, 1455, 1424, 1378, 1333, 1295, 1246, 1169, 1098, 1033, 986, 926, 852, 770, 737 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{14}O_3I$ $[M+H]^+$: 320.9982, found 320.9981.



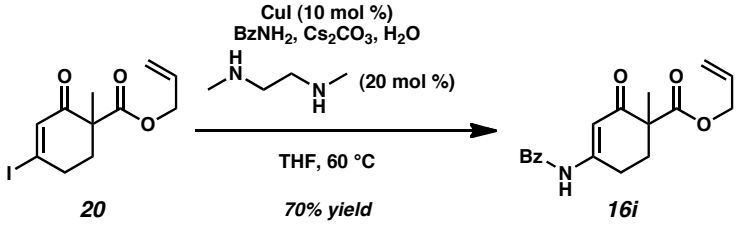
Enaminone 16h. Adapted from procedure by Buchwald.[30] CuI (24 mg, 0.13 mmol, 0.10 equiv), Cs_2CO_3 (624 mg, 1.92 mmol, 1.50 equiv) and acetamide (91 mg, 1.5 mmol, 1.2

equiv) were added to a 25 mL Schlenck bomb equipped with a stir bar under argon atmosphere. The Schlenck bomb was evacuated and backfilled with argon three times. A solution of vinyl iodide **20** (409 mg, 1.28 mmol, 1.00 equiv), *N*,*N*'-dimethylethylenediamine (23 mg, 0.26 mmol, 0.20 equiv) and nanopure water (23 mg, 1.3 mmol, 1.0 equiv) in THF (2.6 mL, 0.5 M) was added via syringe. The reaction flask was lowered into a 60 °C oil bath. After 12 h of stirring, TLC analysis indicated complete conversion of starting material. The reaction was subsequently diluted with 15 mL CH_2Cl_2, transferred to a separatory funnel and washed twice with 5% aqueous NH_4OH (10 mL). The combined aqueous layers were extracted twice with CH_2Cl_2 (15 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 12 x 3 cm, 20→33→50→67% EtOAc in hexanes) to afford enaminone **16h** (276 mg, 1.10 mmol, 86% yield) as a pale yellow oil; R_f = 0.10 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 6.60 (s, 1H), 5.90–5.77 (m, 1H), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.58 (dq, *J* = 5.6, 1.3 Hz, 2H), 2.78 – 2.64 (m, 1H), 2.62–2.43 (m, 1H), 2.54–2.45 (m, 1H), 2.11 (s, 3H), 2.02–1.83 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 172.5, 169.9, 155.9, 131.7, 118.5, 110.1, 65.9, 52.3, 31.9, 25.7, 25.0, 20.6; IR (Neat Film NaCl) 3299, 3135, 2937, 1728, 1626, 1520, 1456, 1426, 1370, 1259, 1220, 1184, 1114, 999, 939, 877 cm^{-1}; HRMS (MM: ESI-APCI+) *m*/*z* calc'd for $C_{13}H_{18}NO_4$ $[M+H]^+$: 252.1230, found 252.1219.

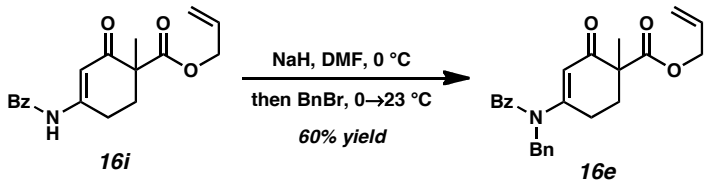


Enaminone 16d. In a 5 mL round bottom flask equipped with a stir bar under nitrogen atmosphere, enaminone **16h** (63 mg, 0.25 mmol, 1.0 equiv) was taken up in dry DMF (2.8 mL, 0.089 M) and cooled to 0 °C with an ice/water bath. Sodium hydride (60% suspension in mineral oil, 12 mg, 0.30 mmol, 1.2 equiv) was added to the mixture, accompanied by the formation of bubbles. The reaction was stirred for 1 h before the dropwise addition of benzyl bromide (36 μL, 0.30 mmol, 1.2 equiv) by syringe. The reaction temperature was maintained at 0 °C for 5 h before allowing the ice bath to gradually expire. After an additional 6 h at 23 °C, TLC analysis indicated complete conversion of starting material. The reaction was subsequently diluted with EtOAc (10 mL) and sat. NH_4Cl sol. (10 mL) and transferred to a separatory funnel. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted twice with EtOAc (2 x 10 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 15 x 3 cm, 20% acetone in hexanes) to afford enaminone **16d** (61 mg, 0.18 mmol, 71% yield) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.29–7.24 (m, 1H), 7.19–7.16 (m, 2H), 5.87–5.79 (m, 1H), 5.78 (s, 1H), 5.27 (dt, J = 17.2, 1.4 Hz, 1H), 5.21 (dt, J = 10.5, 1.3 Hz, 1H), 4.89–4.84 (m, 1H), 4.78–4.72 (m, 1H), 4.56 (dt, J = 5.7, 1.3 Hz, 2H), 2.58 (ddd, J = 9.3, 4.9, 1.6 Hz, 1H), 2.56–2.48 (m, 1H), 2.44 (dtd, J = 13.8, 4.8, 1.2 Hz, 1H), 2.16 (s, 3H), 1.87–1.78 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 172.0, 170.0,

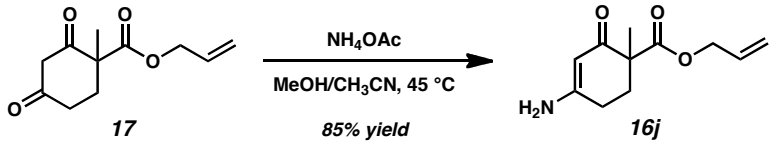
160.8, 136.5, 131.6, 129.0, 127.9, 127.5, 123.8, 1190, 66.1, 52.6, 50.8, 32.8, 27.3, 23.2, 20.2; IR (Neat Film NaCl) 3063, 3030, 2981, 2937, 2873, 1731, 1667, 1624, 1496, 1454, 1424, 1387, 1375, 1344, 1312, 1250, 1190, 1113, 1029, 986, 948, 882, 738 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{24}O_4N$ $[M+H]^+$: 342.1700, found 342.1705.



Enaminone 16i. Adapted from procedure by Buchwald.[30] Prepared from **20** in an analogous manner to **16h**. Purified by flash chromatography (SiO_2, 12 x 3 cm, 20→33→50% EtOAc in hexanes) to afford enaminone **16i** (220 mg, 0.702 mmol, 70% yield) as a pale yellow oil that solidified to a pale yellow amorphous solid upon standing at –20 °C; R_f = 0.10 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.83 – 7.74 (m, 2H), 7.56–7.47 (m, 1H), 7.47–7.40 (m, 2H), 6.70 (s, 1H), 5.88–5.75 (m, 1H), 5.25 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.55 (dq, *J* = 5.5, 1.5 Hz, 2H), 2.92–2.82 (m, 1H), 2.79–2.69 (m, 1H), 2.53 (dt, *J* = 13.7, 5.4 Hz, 1H), 1.99–1.87 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 172.5, 166.5, 155.6, 133.8, 132.7, 131.7, 128.9, 127.5, 118.4, 111.1, 65.8, 52.3, 32.0, 25.9, 20.5; IR (Neat Film NaCl) 3334, 2936, 1732, 1694, 1621, 1514, 1492, 1376, 1258, 1185, 1115, 1071, 1023, 931, 710 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1387, found 314.1381.



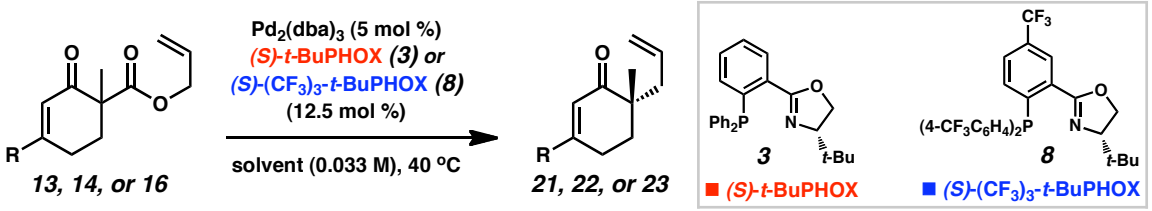
Enaminone 16e. Prepared from **16i** in an analogous manner to **16d**. Purified by flash chromatography (SiO_2, 15 x 3 cm, 20% acetone in hexanes) to afford enaminone **16e** (134 mg, 0.332 mmol, 60% yield) as a yellow oil; R_f = 0.63 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65–7.55 (m, 2H), 7.52–7.43 (m, 1H), 7.43–7.37 (m, 2H), 7.36–7.26 (m, 5H), 5.84 (s, 1H), 5.83–5.71 (m, 1H), 5.28–5.15 (m, 2H), 5.10–4.98 (m, 2H), 4.58–4.38 (m, 2H), 2.38–2.26 (m, 1H), 2.26–2.13 (m, 2H), 1.56 (s, 6H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 171.8, 161.8, 136.8, 136.0, 131.8, 131.6, 128.9, 128.8, 128.2, 127.9, 127.7, 127.7, 121.4, 118.5, 65.9, 52.8, 52.4, 32.6, 28.8, 20.2; IR (Neat Film NaCl) 2936, 1733, 1661, 1601, 1496, 1447, 1377, 1344, 1300, 1253, 1174, 1111, 974, 794, 724 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1856, found 404.1850.



Enaminone 16j. A flame-dried 50 mL round-bottom flask containing a stir bar was cycled into a glove box and loaded with ammonium acetate (185.3 mg, 2.40 mmol, 1.16 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with MeOH (1.5 mL). Dione **17** (437.5 mg, 2.08 mmol, 1.00 equiv) was transferred to the flask via cannula using MeOH (5 mL, total added = 6.5 mL, 0.32 M) and CH_3CN (6.5 mL, 0.32 M) rinses. The flask was lowered into a preheated oil bath (45

°C) and the reaction was heated for five days before TLC analysis indicated consumption of starting material. The reaction was cooled to room temperature and the contents were concentrated under reduced pressure. The resulting crude material was recrystallized twice with toluene to produce enaminone **16j** (369.0 mg, 1.76 mmol, 85% yield) as a white crystal; R_f = 0.18 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, J = 17.2, 10.4, 5.5, 5.5 Hz, 1H), 5.29 (dq, J = 17.2, 1.6 Hz, 1H), 5.25 (d, J = 0.8 Hz, 1H), 5.20 (dq, J = 10.5, 1.4 Hz, 1H), 4.61 (dddd, J = 5.4, 3.9, 1.5, 1.5 Hz, 2H), 4.53 (broad s, 2H), 2.60–2.52 (m, 1H), 2.49 (ddd, J = 13.3, 5.8, 5.0 Hz, 1H), 2.35–2.28 (m, 1H), 1.93–1.86 (m, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 173.3, 163.7, 132.1, 118.1, 99.9, 65.7, 51.6, 32.3, 26.0, 21.0; IR (Neat Film NaCl) 3338, 3189, 3064, 2983, 2934, 2873, 1735, 1654, 1551, 1437, 1383, 1358, 1291, 1253, 1216, 1194, 1175, 1103, 989, 930, 841, 824 cm^{-1}; HRMS (MM: ESI-APCI+) calc'd for $C_{11}H_{16}O_3N$ $[M+H]^+$: 210.1125, found 210.1119.

1.4.2.2.2 *General Procedure for Screening Reactions*



					Enantiomeric Excess (% ee)[b]			
entry	substrate	R	product	ligand	THF	TBME	Toluene	2:1 Hex–Tol
1 2	*13a*	H	*21a*	*3* *8*	87 85	88 86	87 88	87 85
3 4	*14a*	O*i*-Bu	*22a*	*3* *8*	85 86	85 86	86 86	87 88
5 6	*16a*	NMe(Bn)	*23a*	*3* *8*	61 79	60 78	55 84	52 83
7 8	*16b*	NPh(Bn)	*23b*	*3* *8*	81 76	87 74	85 82	83 83
9 10	*16d*	NAc(Bn)	*23d*	*3* *8*	89 83	90 85	88 88	88 86
11 12	*16e*	NBz(Bn)	*23e*	*3* *8*	86 80	87 83	88 82	87 83
13 14	*16f*	NBoc(Bn)	*23f*	*3* *8*	87 84	86 84	87 81	82 83
15 16	*16g*	NTs(Bn)	*23g*	*3* *8*	84 82	83 83	83 83	82 83

[a] *Conditions*: enone **13a**, vinylogous ester **14a**, or enaminone **16a, b, d–g** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C. [b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand.

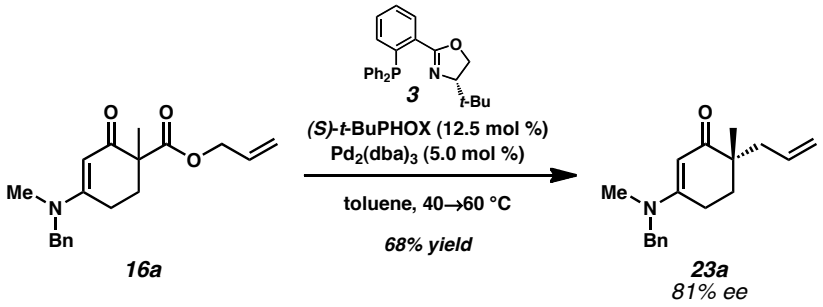
Enone 13a Screen Procedure. $Pd_2(dba)_3$ (2.4 mg, 0.00262 mmol, 0.05 equiv) and the appropriate PHOX ligand ((*S*)-*t*-BuPHOX (**3**): 2.5 mg, 0.00645 mmol, 0.125 equiv ***or*** (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**): 3.8 mg, 0.00643 mmol, 0.125 equiv) were added to an oven-dried 1 dram vial equipped with a magnetic stir bar. A separate oven-dried 1 dram vial was charged with enone **13a**[6] (10.0 mg, 0.0515 mmol, 1.00 equiv) and both vials were cycled into a nitrogen-filled glove box. The palladium/ligand vial was charged with

solvent (THF, TBME, toluene: 360 μL or 2:1 hexanes/toluene: 120 μL toluene and 340 μL hexanes) and stirred at ambient glove box temperature. After 30 min, enone **9a** was transferred to the reaction vial with several solvent rinses (THF, TBME, toluene: 3 x 400 μL, 1.56 mL total, 0.033 M or 2:1 hexanes/toluene: 400 μL toluene and 400 μL + 300 μL hexanes, 1.56 mL solvent total, 0.033 M). The vials were tightly sealed with a teflon lined cap and electrical tape, removed from the glove box, and lowered into a heating block set to 40 °C. After 2 days, the reaction were either loaded directly onto a column (toluene and 2:1 hexanes/toluene) or filtered through a celite plug and concentrated prior to chromatography (THF and TBME). All reactions were purified by flash column chromatography (SiO_2, ~22 x 1 cm, 2%→3% Et_2O in pentane), resuspended in Et_2O for analysis, and analyzed for enantiomeric excess with chiral GC. Characterization data for enone **21a** matches that previously reported.[6] As part of the screen, the yield was determined for enone **21a** with (*S*)-**8** in toluene (6.0 mg, 0.040 mmol, 78% yield).

Vinylogous Ester 14a and Enaminone Symyx Core Module Screen Procedure. All reagents were dispensed as solutions using a Symyx Core Module within a nitrogen-filled glovebox. Oven-dried half-dram vials were charged with a solution of the palladium source ($Pd_2(dba)_3$, 1.65 μmol, 0.05 equiv) in THF (400 μL). The palladium solutions were evaporated to dryness under reduced pressure using a Genevac centrifugal evaporator within the glovebox, and stirbars were added to the vials. The reaction vials were then charged with a solution of the PHOX ligand (4.13 μmol, 0.125 equiv) in the reaction solvent (300 μL) and stirred at 20 °C. After 30 min, a solution of vinylogous

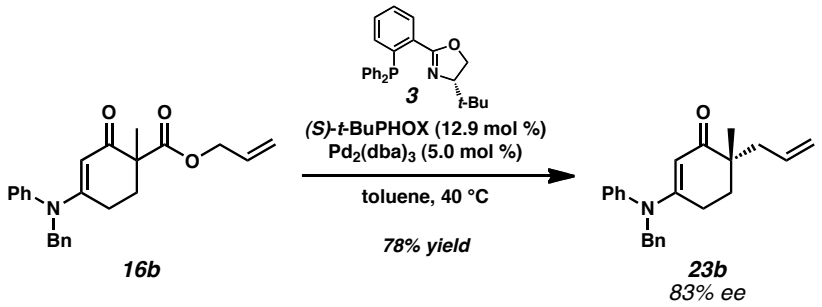
ester **14a** or the enaminone substrate (**16**, 33.0 μmol, 1.0 equiv) in the reaction solvent (700 μL) were added. The reaction vials were tightly capped and heated to the desired temperature (40 °C). The consumption of the starting material was observed by colorimetric change (from light yellow/green to red/orange) and after 5 days, the reactions were removed from the glovebox, filtered through a short silica gel plug (rinsing with EtOAc), concentrated under reduced pressure, resuspended in an appropriate solvent for analysis (HPLC: hexanes ***or*** SFC: MeOH), and analyzed for enantiomeric excess (see Methods for the Determination of Enantiomeric Excess). Characterization data for vinylogous ester **22a** matches that previously reported.[18c] Experimental procedures and characterization data for enaminones **23a**, **b**, **d**–**g** follow.

1.4.2.2.3 *Enaminone Allylic Alkylation Products*



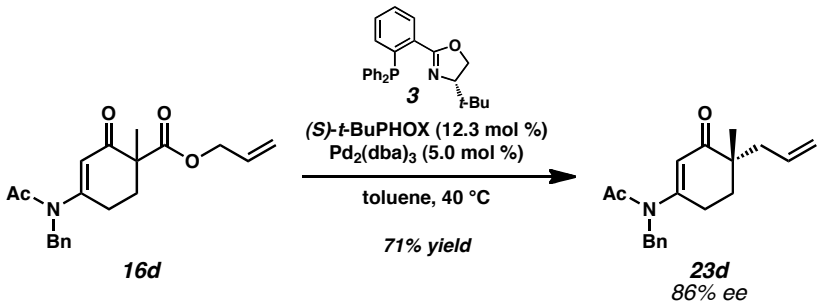
Enaminone 23a. $Pd_2(dba)_3$ (14.6 mg, 0.0159 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 15.5 mg, 0.0400 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16a** (1 M in toluene, 320 μL, 0.320 mmol, 1.00 equiv) and additional toluene (7.35 mL, total added = 9.67 mL, 0.033 M) were added, producing a

green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 5 days, the temperature was raised to 60 °C and heated for an additional day before the reaction mixture transitioned back to a red/orange solution. The reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→20%→30%→50% EtOAc in hexanes→ 100% EtOAc ***then*** SiO_2, 26.5 x 1.5 cm, 100% hexanes→20%→30%→40% EtOAc in hexanes) to afford enaminone **23a** (58.9 mg, 0.219 mmol, 68% yield) as a pale yellow oil; R_f = 0.12 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.31–7.26 (m, 1H), 7.10 (d, J = 7.2 Hz, 2H), 5.84–5.74 (m, 1H), 5.17 (s, 1H), 5.07–5.00 (m, 2H), 4.51 (s, 2H), 2.95 (s, 3H), 2.58–2.44 (m, 2H), 2.38 (dddd, J = 13.7, 7.1, 1.2, 1.2 Hz, 1H), 2.23–2.18 (m, 1H), 1.93 (ddd, J = 13.2, 7.5, 5.5 Hz, 1H), 1.71 (ddd, J = 13.7, 6.9, 5.4 Hz, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 163.7, 136.9, 135.2, 129.1, 127.7, 126.3, 117.5, 98.1, 55.0, 42.1, 41.8, 38.5, 32.8, 24.0, 22.6; IR (Neat Film NaCl) 3066, 3029, 2958, 2926, 2867, 1728, 1615, 1557, 1495, 1451, 1412, 1373, 1354, 1333, 1315, 1297, 1276, 1253, 1204, 1156, 1103, 1077, 1029, 1001, 924, 823, 792, 733 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{23}ON$ $[M+\bullet]^+$: 269.1780, found 269.1782; $[\alpha]_D^{25.0}$ –24.18 (c 1.04, $CHCl_3$, 81% ee); JASCO SFC conditions: 5% MeOH in CO_2, 5 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 10.45, minor = 9.60.



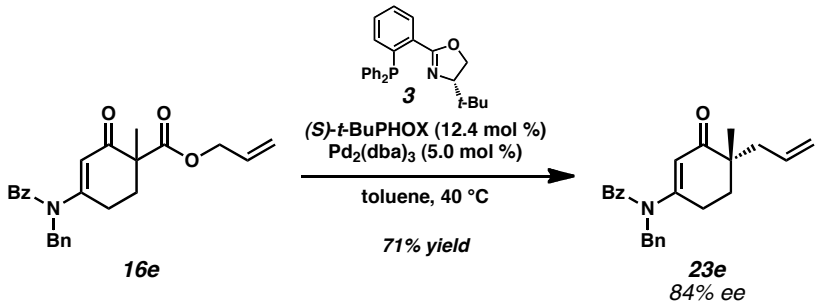
Enaminone 23b. $Pd_2(dba)_3$ (3.5 mg, 0.00382 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 3.8 mg, 0.00981 mmol, 12.9 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.5 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16b** (28.6 mg, 0.0762 mmol, 1.00 equiv) was transferred to the flask with several toluene rinses (1 x 0.81 mL + 2 x 0.5 mL, total added = 2.31 mL, 0.033 M), producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 4 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 100% hexanes→50% EtOAc in hexanes→100% EtOAc ***then*** SiO_2, 23.5 x 1 cm, 100% hexanes→10%→20%→30%→40% EtOAc in hexanes) to afford enaminone **23b** (19.7 mg, 0.0594 mmol, 78% yield) as a frosty colorless oil; R_f = 0.63 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.33–7.29 (m, 2H), 7.29–7.22 (m, 2H), 7.22–7.18 (m, 2H), 7.15–7.11 (m, 2H), 5.76 (dddd, J = 15.8, 11.3, 7.8, 7.0 Hz, 1H), 5.29 (s, 1H), 5.05–5.00 (m, 2H), 4.83 (s, 2H), 2.38 (dddd, J = 13.8, 7.1, 1.3, 1.3 Hz, 1H), 2.35–2.31 (m, 2H), 2.19 (dddd, J = 13.7, 7.8, 1.1, 1.1 Hz, 1H),

1.90–1.83 (m, 1H), 1.65 (ddd, J = 13.5, 6.5, 5.6 Hz, 1H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 163.3, 144.6, 136.7, 135.0, 129.8, 128.8, 128.0, 127.6, 127.5, 127.0, 117.6, 100.5, 56.7, 42.2, 42.0, 33.0, 25.5, 22.6; IR (Neat Film NaCl) 3063, 3031, 2959, 2926, 2863, 1622, 1563, 1494, 1453, 1426, 1404, 1374, 1351, 1329, 1275, 1204, 1156, 1078, 1060, 1028, 1002, 911, 830, 730 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{26}ON$ $[M+H]^+$: 332.2009, found 332.1999; $[\alpha]_D^{25.0}$ –29.79 (c 1.91, $CHCl_3$, 83% ee); JASCO SFC conditions: 5% MeOH in CO_2, 5 mL/min, Chiralpak AS-H column, λ = 254 nm, t_R (min): major = 8.60, minor = 6.48.



Enaminone 23d. $Pd_2(dba)_3$ (2.6 mg, 0.00284 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 2.7 mg, 0.00697 mmol, 12.3 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.51 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16d** (19.3 mg, 0.0565 mmol, 1.00 equiv) was transferred to the flask with several toluene rinses (4 x 0.3 mL, total added = 1.71 mL, 0.033 M), producing a yellow solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a

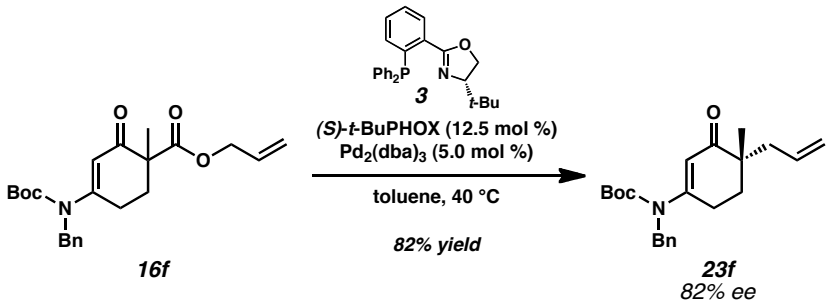
silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 5%→10%→20%→30% EtOAc in hexanes) to afford enaminone **23d** (12.0 mg, 0.0404 mmol, 71% yield) as a yellow oil; R_f = 0.46 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (ddt, J = 8.1, 6.7, 1.2 Hz, 2H), 7.30–7.23 (m, 1H), 7.19 (ddt, J = 7.3, 1.4, 0.7 Hz, 2H), 5.68 (t, J = 1.3 Hz, 1H), 5.66 (ddt, J = 16.9, 10.1, 7.3 Hz, 1H), 5.05 (ddt, J = 10.1, 1.9, 0.9 Hz, 1H), 4.99 (ddt, J = 17.0, 2.1, 1.4 Hz, 1H), 4.81 (s, 2H), 2.50–2.39 (m, 2H), 2.21 (ddt, J = 13.8, 7.3, 1.2 Hz, 1H), 2.17 (s, 3H), 2.10 (ddt, J = 13.8, 7.5, 1.1 Hz, 1H), 1.87 (dt, J = 13.8, 5.9 Hz, 1H), 1.69 (ddd, J = 13.8, 6.6, 5.7 Hz, 1H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 169.7, 160.1, 136.6, 133.6, 128.9, 127.9, 127.7, 123.8, 118.6, 50.9, 43.6, 40.8, 32.6, 27.1, 23.2, 21.5; IR (Neat Film NaCl) 3066, 2926, 2854, 1663, 1624, 1496, 1453, 1387, 1371, 1189, 991, 916 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1807, found 298.1794; $[\alpha]_D^{25.0}$ –14.12 (c 1.20, $CHCl_3$, 86% ee); Thar SFC conditions: 5% MeOH in CO_2, 3 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 8.45, minor = 10.35.



Enaminone 23e. $Pd_2(dba)_3$ (4.6 mg, 0.00502 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 4.8 mg, 0.0124 mmol, 12.4 mol %) were added to an oven-dried scintillation vial

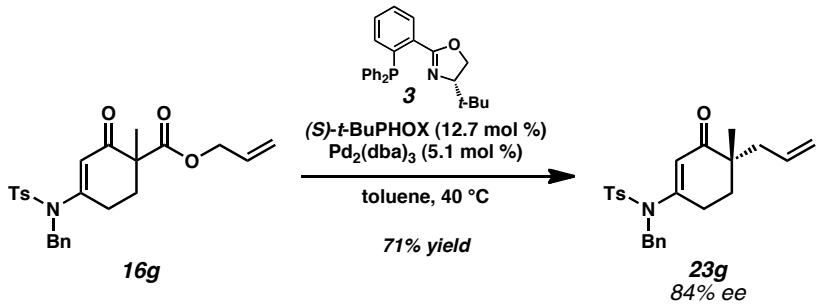
equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.93 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16e** (1 M in toluene, 100 μL, 0.100 mmol, 1.00 equiv) was transferred to the flask with more toluene (1 mL, total added including enaminone solution = 3.03 mL, 0.033 M), producing a yellow/orange solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 5%→10%→15% EtOAc in hexanes) to afford enaminone **23e** (26.3 mg, 0.0713 mmol, 71% yield, 95% purity) as a yellow oil; R_f = 0.57 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.59 (m, 2H), 7.50–7.43 (m, 1H), 7.39 (ddt, J = 8.2, 6.6, 1.1 Hz, 2H), 7.35–7.29 (m, 4H), 7.29–7.25 (m, 1H), 5.74 (t, J = 1.1 Hz, 1H), 5.54 (ddt, J = 17.3, 10.1, 7.4 Hz, 1H), 5.09 (d, J = 15.3 Hz, 1H), 5.00 (d, J = 15.3 Hz, 1H), 4.98 (dm, J = 9.9 Hz, 1H), 4.86 (dm, J = 17.0 Hz, 1H), 2.11–2.08 (m, 2H), 2.03 (dd, J = 14.2, 7.9 Hz, 1H), 1.95 (ddt, J = 13.8, 7.3, 1.2 Hz, 1H), 1.59 (ddd, J = 13.7, 6.5, 5.4 Hz, 1H), 1.41 (ddd, J = 13.4, 6.8, 5.3 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 170.8, 160.9, 136.8, 136.2, 133.6, 131.6, 128.9, 128.7, 128.1, 128.0, 127.9, 122.3, 118.4, 52.5, 43.3, 40.6, 32.4, 28.4, 21.3; IR (Neat Film NaCl) 3063, 3030, 2961, 2928, 2855, 1655, 1610, 1496, 1447, 1384, 1374, 1347, 1324, 1273, 1189, 1140, 1076, 1028, 1001, 974, 919, 792 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{24}H_{26}NO_2$ $[M+H]^+$: 360.1964, found 360.1956; $[\alpha]_D^{25.0}$ –26.61 (c 1.87, $CHCl_3$, 84% ee); Thar SFC

conditions: 7% MeOH in CO_2, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 18.14, minor = 20.28.



Enaminone 16f. $Pd_2(dba)_3$ (11.5 mg, 0.0126 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 12.1 mg, 0.0312 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16f** (1 M in toluene, 250 μL, 0.250 mmol, 1.00 equiv) and additional toluene (6.34 mL, total added = 7.59 mL, 0.033 M) were added, producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 28 x 3 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford enaminone **23f** (72.6 mg, 0.204 mmol, 82% yield) as a pale yellow oil; R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.26–7.22 (m, 1H), 7.17–7.14 (m, 2H), 5.69 (dddd, J = 16.8, 10.2, 7.4, 7.4 Hz, 1H), 5.63 (t, J = 0.9 Hz, 1H), 5.07–4.99 (m, 2H), 4.78 (s, 2H), 2.75 (tm,

J = 6.1 Hz, 2H), 2.29 (dddd, J = 13.7, 7.3, 1.2, 1.2 Hz, 1H), 2.13 (dddd, J = 13.7, 7.5, 1.2, 1.2 Hz, 1H), 1.90–1.84 (m, 1H), 1.71–1.65 (m, 1H), 1.43 (s, 9H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 161.6, 153.0, 137.4, 134.1, 128.8, 127.4, 126.4, 118.2, 115.4, 82.6, 52.9, 43.2, 41.2, 33.5, 28.2, 27.2, 21.9; IR (Neat Film NaCl) 3066, 3031, 3004, 2976, 2931, 2868, 1716, 1656, 1598, 1497, 1455, 1428, 1382, 1368, 1350, 1326, 1302, 1243, 1209, 1192, 1153, 1076, 1030, 998, 946, 916, 858, 779, 767, 734 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{30}O_3N$ $[M+H]^+$: 356.2229, found 356.2220; $[\alpha]_D^{25.0}$ –23.61 (c 0.92, $CHCl_3$, 82% ee); JASCO SFC conditions: 7% MeOH in CO_2, 5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.04, minor = 2.20.

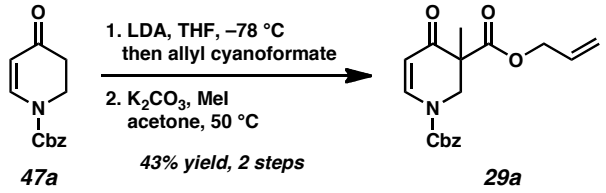


Enaminone 23g. $Pd_2(dba)_3$ (10.2 mg, 0.0111 mmol, 5.1 mol %) and (*S*)-*t*-BuPHOX (**3**, 10.8 mg, 0.0279 mmol, 12.7 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16g** (1 M in toluene, 220 μL, 0.220 mmol, 1.00 equiv) and additional toluene (5.46 mL, total added = 6.68 mL, 0.033 M) were added, producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture

transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 2 cm, 100% hexanes→5%→10%→15% EtOAc in hexanes) to afford enaminone **23g** (64.1 mg, 0.157 mmol, 71% yield) as a pale yellow oil; R_f = 0.55 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dm, J = 8.3 Hz, 2H), 7.35 (dm, J = 8.6 Hz, 2H), 7.33–7.26 (m, 3H), 7.25–7.22 (m, 2H), 5.60–5.50 (m, 2H), 4.98 (dm, J = 10.2 Hz, 1H), 4.86 (dm, J = 17.0 Hz, 1H), 4.74 (d, J = 15.0 Hz, 1H), 4.66 (d, J = 15.0 Hz, 1H), 2.56–2.44 (m, 2H), 2.46 (s, 3H), 1.99–1.86 (m, 2H), 1.70 (ddd, J = 13.9, 6.6, 5.3 Hz, 1H), 1.55 (ddd, J = 13.9, 7.2, 5.5 Hz, 1H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 157.74, 144.7, 135.4, 135.3, 133.7, 130.1, 128.9, 128.1, 127.9, 127.5, 120.7, 118.3, 53.1, 43.2, 40.6, 32.2, 27.9, 21.8, 21.3; IR (Neat Film NaCl) 3066, 3027, 2963, 2928, 2868, 1663, 1654, 1597, 1496, 1453, 1424, 1355, 1306, 1164, 1089, 1055, 1028, 1001, 912, 859, 814, 745 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{28}O_3NS$ $[M+H]^+$: 410.1784, found 410.1792; $[\alpha]_D^{25.0}$ –33.05 (c 0.37, $CHCl_3$, 84% ee); JASCO SFC conditions: 10% MeOH, 5 mL/min, AD-H column, λ = 210 nm, t_R (min): major = 5.60, minor = 4.73.

1.4.2.3 Preparation of 2,3-Dihydropyridin-4-ones

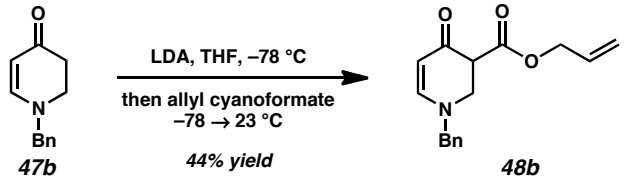
1.1.1.1.4 *2,3-Dihydropyridin-4-one Allylic Alkylation Precursors*



2,3-Dihydropyridin-4-one 29a. A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with diisopropyl amine (442 µL, 3.01 mmol, 1.20 equiv) and THF (28 mL). The flask was cooled to –78 °C bath (dry ice/IPA) and *n*-BuLi (1.30 mL, 3.01 mmol, 2.32 M in hexanes, 1.20 equiv) was added. The reaction was allowed to warm to 0 °C over 1 h. The solution was cooled back to –78 °C and added dropwise to a solution of 2,3-dihydropyridin-4-one **47a**[37] (580 mg, 2.51 mmol, 1.0 equiv) in THF (40 mL) at –78 °C using positive pressure cannulation. The reaction was stirred for 1 h at this temperature before allyl cyanoformate (300 µL, 2.88 mmol, 1.15 equiv) was added dropwise. The flask was removed from the bath, allowed to warm to room temperature slowly, and stirred overnight. The reaction was quenched with water and sat. NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduce pressure. The resulting yellow oil was purified by flash-chromatography (2:1 Et_2O/hexanes).

The yellow oil was transferred to an argon filled 25 mL Schlenk tube equipped with a magnetic stir bar using several acetone rinses (3 x 2 mL). K_2CO_3 (252 mg, 1.83 mmol, 2.0 equiv) and methyl iodide (115 µL, 1.84 mmol, 2.02 equiv) were added to the

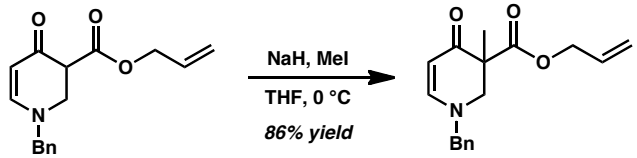
reaction. The resulting suspension was heated to 50 °C and vigorously stirred for 14 h. Upon completion, the reaction was allowed to cool to room temperature and filtered through a plug of celite. The resulting yellow solution was concentrated under reduced pressure and purified by flash-chromatography (1:1 Et_2O/hexanes) to afford 2,3-Dihydropyridin-4-one **29a** (210 mg, 0.64 mmol, 43% yield over two steps) as a yellow oil; R_f = 0.38 (1:1 Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (br s, J = 22.5 Hz, 1H), 7.45–7.31 (m, 5H), 5.82 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.37 (br s, 1H), 5.27 (s, 2H), 5.26 (dq, J = 17.1, 1.5 Hz, 1H), 5.20 (dq, J = 10.5, 1.3 Hz, 1H), 4.64 (dd, J = 13.5, 0.9 Hz, 1H), 4.59 (dt, J = 5.6, 1.5 Hz, 2H), 3.63 (d, J = 13.5 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ190.9, 170.1, 152.5, 142.7, 134.8, 131.3, 128.8, 128.7, 128.4, 118.6, 106.2, 69.2, 66.1, 51.6, 50.5, 17.9; IR (Neat Film, NaCl) 3076, 3034, 2965, 2929, 2360, 2922, 1729, 1668, 1605, 1498, 1456, 1418, 1393, 1344, 1302, 1205, 1157, 1101, 1029, 966, 917, 814, 763 cm^{-1}; HRMS (MM: ESI/APCI+) *m/z* calc'd for $C_{18}H_{20}NO_5$ $[M+H]^+$: 330.1335, found 330.1335.



47b *48b*

2,3-Dihydropyridin-4-one 48b. To a flame-dried 50 mL Schlenk round-bottom flask equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **47b**[38] (162.0 mg, 0.87 mmol) and THF (10 mL). The solution was cooled to –78 °C and LDA (0.1 M in THF, 9.10 mL, 0.91 mmol, 1.05 equiv) was added dropwise by syringe. After 1 h at –78 °C, allyl cyanoformate (105.2 mg, 0.96 mmol, 1.10 equiv) was added, and the reaction

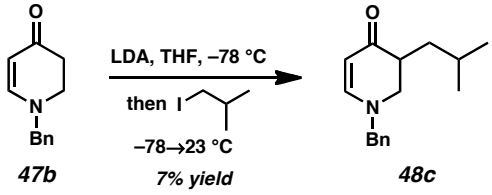
was stirred for another 3 h and then quenched with a sat. NH_4Cl sol. The reaction was transferred to a separatory funnel where the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The combined organics were washed with brine, dried over $MgSO_4$, fitered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography (SiO_2, 10 x 2.5 cm, 30% EtOAc → 50% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **48b** (104.8 mg, 0.38 mmol, 44% yield) as a yellow oil; R_f = 0.30 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.31 (m, 3H), 7.28–7.23 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 1H), 5.87 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.3 Hz, 1H), 5.06 (d, *J* = 7.5 Hz, 1H), 4.69–4.55 (m, 2H), 4.40 (d, *J* = 2.5 Hz, 2H), 3.76 (dd, *J* = 13.3, 8.7 Hz, 1H), 3.51 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.40 (dd, *J* = 8.7, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 168.8, 153.6, 135.1, 131.6, 129.1, 128.5, 127.8, 118.6, 97.7, 66.0, 60.0, 50.5, 48.4; IR (Neat Film NaCl) 3029, 2935, 2853, 1732, 1641, 1588, 1494, 1455, 1393, 1361, 1321, 1204, 1154, 1078, 1028, 991, 967, 935, 78, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{18}NO_3$ $[M+H]^+$: 272.1287, found 272.1314.



48b *29b*

2,3-Dihydropyridin-4-one 29b. To a flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (9.3 mg, 0.39 mmol, 1.00 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, charged with THF (3 mL), and cooled to 0 °C. A solution of 2,3-

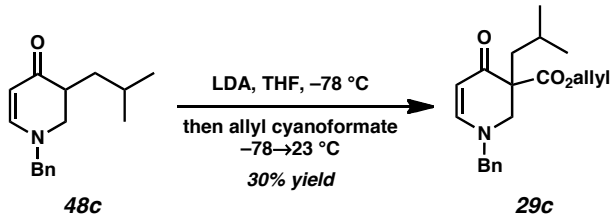
dihydropyridin-4-one **48b** (104.2 mg, 0.39 mmol, 1.00 equiv) was added by syringe and the mixture was stirred at 0 °C for 30 min. The reaction was quenched with water, transferred to a separatory funnel, and extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 10 x 2.5 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **29b** (95.9 mg, 0.34 mmol, 86% yield) as a colorless oil; R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.30 (m, 3H), 7.25–7.20 (m, 2H), 7.13 (d, *J* = 7.4 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.8, 5.5 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.3 Hz, 1H), 5.01 (d, *J* = 7.4 Hz, 1H), 4.56 (qdt, *J* = 13.4, 5.5, 1.5 Hz, 2H), 4.46–4.30 (m, 2H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.15 (d, *J* = 13.3 Hz, 1H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 171.7, 152.8, 135.2, 131.8, 129.1, 128.5, 128.1, 118.2, 97.1, 65.9, 60.1, 55.1, 51.4, 18.6; IR (Neat Film NaCl) 3029, 2979, 2934, 2871, 1732, 1642, 1592, 1494, 1455, 1393, 1372, 1359, 1343, 1295, 1223, 1166, 1115, 1028, 975, 937, 792, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1443, found 286.1480.



47b *7% yield* *48c*

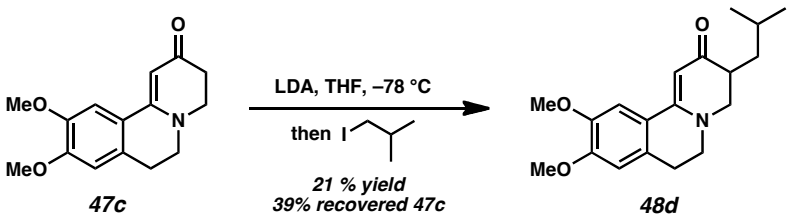
2,3-Dihydropyridin-4-one 48c. To a flame-dried 100 mL Schlenk round-bottom flask equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **47b**[38] (0.68 g, 3.63 mmol) and THF (30 mL). The solution was cooled to –78 °C and LDA (19.0 mL, 3.80

mmol, 1.05 equiv, 0.2 M in THF) was added dropwise by syringe. After 1 h at –78 °C, 1-iodo-2-methylpropane (0.87 g, 4.73 mmol, 1.30 equiv) was added, and the reaction was stirred for another 1 h at –78 °C, brought to room temperature, and stirred overnight. The reaction was quenched with a sat. NH_4Cl sol., transferred to a separatory funnel, and extracted with CH_2Cl_2 (50 mL x 3). The combined organics were washed with brine, dried over $MgSO_4$, fitered, and concentrated. The crude mixture was purified by flash chromatography (SiO_2, 10 x 3 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **48c** (58.2 mg, 0.24 mmol, 7% yield) as a yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.32 (m, 3H), 7.29–7.25 (m, 2H), 7.12 (d, J = 7.4 Hz, 1H), 4.96 (d, J = 7.4 Hz, 1H), 4.43–4.28 (m, 2H), 3.38 (dd, J = 13.0, 5.4 Hz, 1H), 3.08 (dd, J = 13.0, 7.7 Hz, 1H), 2.29 (ddt, J = 10.1, 7.6, 5.2 Hz, 1H), 1.56 (ddd, J = 14.0, 9.3, 5.0 Hz, 1H), 1.37 (dpd, J = 9.3, 6.6, 5.2, 1H), 1.18 (ddd, J = 13.7, 9.6, 5.3 Hz, 1H), 0.82 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 152.8, 135.8, 128.9, 128.3, 127.8, 97.7, 60.0, 50.4, 42.0, 37.5, 25.0, 23.3, 21.4; IR (Neat Film NaCl) 3029, 2954, 2868, 1633, 1593, 1494, 1463, 1455, 1385, 1361, 1302, 1210, 1161, 1077, 778, 730 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1701, found 244.1707.

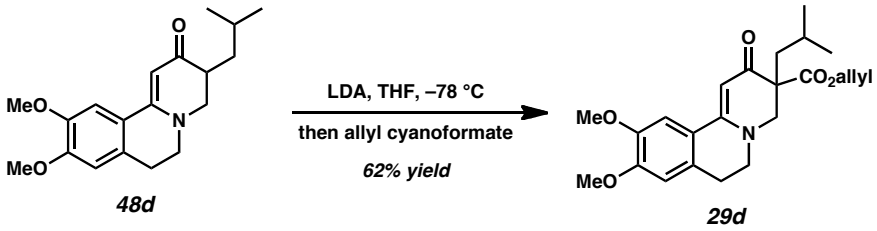


48c ***29c***

2,3-Dihydropyridin-4-one 29c. To a flame-dried 25 mL Schlenk tube equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **48c** (50.5 mg, 0.21 mmol) and THF (5 mL). After the solution was cooled to -78 °C, LDA (2.2 mL, 0.22 mmol, 1.06 equiv, 0.1 M in THF) was added dropwise by syringe. The mixture was stirred for 1 h at -78 °C and allyl cyanoformate (26.4 mg, 0.24 mmol, 1.20 equiv) was added. The reaction was stirred for another 3 h and quenched with saturated NH_4Cl aqueous. The aqueous layer was extracted with CH_2Cl_2 (30 mL x 4) and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash chromatography (SiO_2, 10 x 1 cm, 30% EtOAc in hexanes) to afford **29c** (19.8 mg, 0.06 mmol, 30% yield) as a yellow oil; R_f = 0.30 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.31 (m, 3H), 7.29–7.19 (m, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 5.86 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.96 (d, *J* = 7.3 Hz, 1H), 4.67–4.51 (m, 2H), 4.43 (s, 2H), 3.82 (d, *J* = 13.4 Hz, 1H), 3.27 (d, *J* = 13.4 Hz, 1H), 2.03 (dd, *J* = 14.2, 7.1 Hz, 1H), 1.64–1.45 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ187.7, 170.9, 152.2, 135.1, 131.7, 129.0, 128.1, 118.4, 96.7, 65.8, 60.1, 54.4, 52.6, 40.4, 24.6, 24.3, 23.2; IR (Neat Film NaCl) 3029, 2957, 2870, 1729, 1644, 1593, 1455, 1360, 1267, 1215, 1159, 1132, 1077, 1029, 971, 778, 735 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1913, found 328.1947.



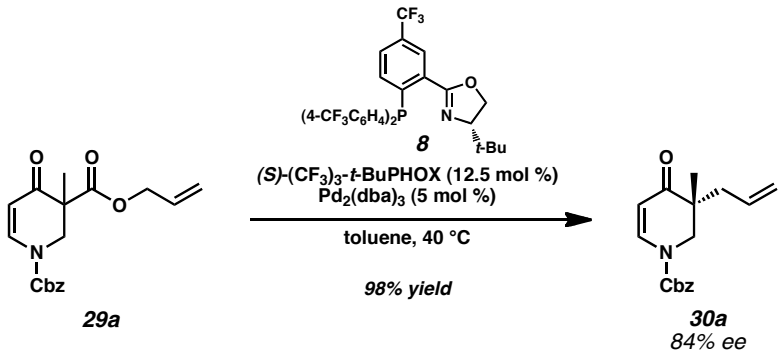
2,3-Dihydropyridin-4-one 48d. To a cooled (–78 °C) solution of **47c**[39] (0.67 g, 2.6 mmol, 1 equiv) in THF (25 mL) was added LDA (30 mL, 0.1 M, in THF, 30 mmol, 1.15 equiv) dropwise over 10 min. The reaction was stirred for 1 h before 1-iodo-2-methylpropane (0.57 g, 3.1 mmol, 1.20 equiv) was added dropwise. After 2 h, the reaction was brought to room temperature and stirred overnight. The reaction was quenched with sat. NH_4Cl sol. and transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture purified by flash column chromatography (SiO_2, 15 x 3 cm, 50% EtOAc in hexanes→100% EtOAc) to afford recovered **47c** (0.26 g, 1.01 mmol, 39% recovered) and also **48d** (0.17 g, 0.54 mmol, 21% yield) as a yellow solid; R_f = 0.20 (50% EtOAc in hexanes). Spectral data matches that reported previously.[47] NMR data is included to assist the reader. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.65 (s, 1H), 5.62 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.64 (dd, J = 12.5, 5.3 Hz, 1H), 3.45–3.24 (m, 3H), 2.94 (td, J = 6.3, 3.5 Hz, 2H), 2.51–2.35 (m, 1H), 1.80–1.59 (m, 2H), 1.36–1.19 (m, 1H), 0.96 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 156.6, 151.5, 148.1, 129.0, 120.9, 110.5, 108.4, 94.4, 56.1, 55.9, 49.2, 42.1, 37.6, 28.6, 25.6, 23.6, 21.9.



2,3-Dihydropyridin-4-one 29d. A solution of **48d** (149.1 mg, 0.47 mmol in 15 mol of THF) was cooled to –78 °C and LDA (5.2 mL, 0.1 M in THF, 0.52 mmol, 1.10 equiv) was added dropwise. The reaction was stirred for 1 h before allyl cyanoformate (60.2 mg, 0.54 mmol, 1.15 equiv) was added dropwise. After 12 h, the reaction was quenched with sat. NH_4Cl sol. and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography (SiO_2, 15 x 3 cm, 50% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **29d** (116.0 mg, 0.29 mmol, 62% yield) as a yellow solid; R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.66 (s, 1H), 5.87 (ddt, J = 17.2, 10.3, 5.6 Hz, 1H), 5.59 (s, 1H), 5.30 (dq, J = 17.2, 1.6 Hz, 1H), 5.17 (dq, J = 10.4, 1.3 Hz, 1H), 4.61 (ddt, J = 5.6, 2.7, 1.4 Hz, 2H), 4.05 (d, J = 13.0 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.62 (d, J = 13.1 Hz, 1H), 3.55 (ddd, J = 12.1, 8.1, 5.7 Hz, 1H), 3.43 (ddd, J = 12.2, 6.9, 5.4 Hz, 1H), 3.00–2.77 (m, 2H), 2.23–2.06 (m, 1H), 1.79–1.60 (m, 2H), 0.96 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 171.0, 155.7, 151.6, 148.0, 131.8, 129.0, 120.5, 118.3, 110.3, 108.4, 92.8, 65.7, 56.5, 56.0, 56.0, 54.5, 48.6, 40.4, 28.3, 25.0, 24.4, 23.5; IR (Neat Film NaCl) 2955, 1720, 1625, 1583, 1544, 1495, 1343, 1237, 1211, 1167, 11523, 1120, 1016

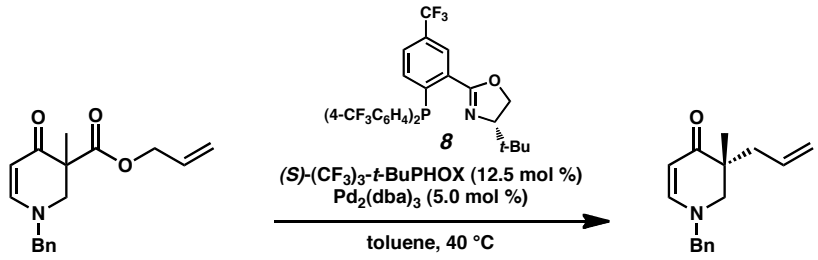
cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2124, found 400.2110.

1.4.2.3.5 *2,3-Dihydropyridin-4-one Allylic Alkylation Products*



2,3-Dihydropyridin-4-one 30a. 2,3-Dihydropyridin-4-one **29a** (27.6 mg, 0.084 mmol, 1.0 equiv) was preloaded in a 1 dram vial and cycled into a glove box. A separate 1 dram vial was loaded with (S)-$(CF_3)_3$-*t*-Bu-PHOX (**8**, 4.1 mg, 10.5 µmol, 0.125 equiv), $Pd_2(dba)_3$ (3.9 mg, 4.20 µmol, 0.05 equiv), and a magnetic stir-bar. Toluene (1.6 mL) was added and the black suspension was stirred at 30 °C in a heating block for 30 min. 2,3-Dihydropyridin-4-one **29a** was dissolved in 1 mL of toluene and added to the orange catalyst solution, causing an immediate color change to olive green. The vial was capped with a Teflon screw cap and the reaction was stirred for 14 h at 40 °C in the glove box. Upon completion of the reaction, the vial was allowed to cool to room temperature and removed from the glove box. The reaction was concentrated under reduced pressure and the resulting brown oil was purified by flash-chromatography (1:1 Et_2O/hexanes) to afford 2,3-dihydropyridin-4-one **30a** (23.7 mg, 0.083 mmol, 98%) as a colorless oil; R_f = 0.73 (1:1 Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.42–7.36 (m, 5H), 5.69 (td, J = 17.3, 7.5 Hz, 1H), 5.27 (d, J = 2.7 Hz, 3H), 5.05 (dd, J = 29.7, 13.4 Hz, 2H),

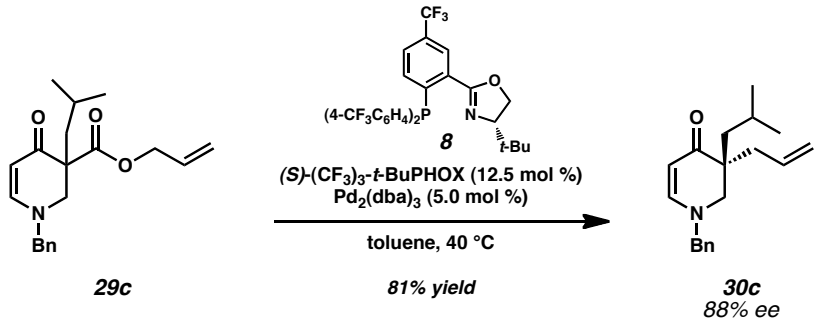
3.91 (d, J = 13.4 Hz, 1H), 3.58 (d, J = 11.8 Hz, 1H), 2.22 (ddd, J = 46.4, 13.8, 7.5 Hz, 2H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ198.3, 152.7, 141.7, 135.0, 132.6, 128.8, 128.7, 128.4, 119.2, 106.4, 69.1, 51.4, 43.4, 39.4, 19.5; IR (Neat Film, NaCl) 2922, 1728, 1673, 1602, 1498, 1453, 1416, 1381, 1342, 1305, 1232, 1200, 1144, 1119, 1088, 956, 913, 813, 761 cm^{-1}; HRMS (MM: ESI/APCI+) *m/z* calc'd for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1443, found 286.1438; $[\alpha]_D^{25.0}$ +9.88 (*c* 1.15, $CHCl_3$, 84% ee); Thar SFC conditions: 10% MeOH in CO_2, 3 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 2.80, minor = 3.13.



29b ***94% yield*** ***30b*** *86% ee*

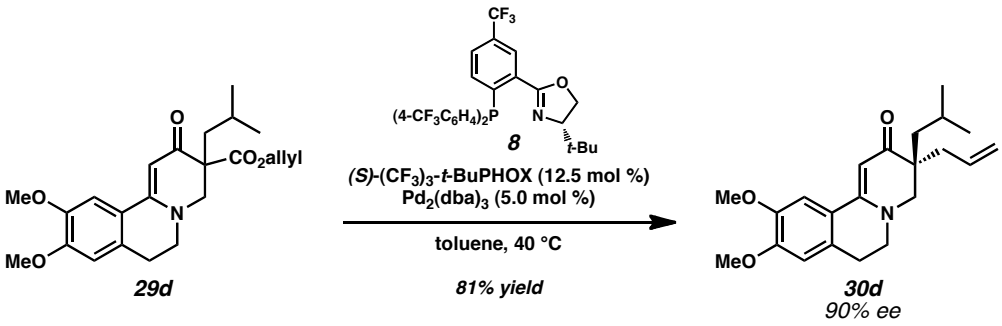
2,3-Dihydropyridin-4-one 30b. In a glove box, $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 3.7 mg, 0.00625 mmol, 12.5 mol %) were added to a scintillation vial equipped with a stir bar. The vial was charged with toluene (0.5 mL) and heated at 40 °C for 30 min. 2,3-Dihydropyridin-4-one **29b** (14.3 mg, 0.050 mmol, 1.00 equiv) and additional toluene (1.0 mL, total added = 1.5 mL, 0.033 M) were added, producing a green solution. The vial was sealed and stirred at 40 °C until the starting material was fully converted, determined by LCMS. The reaction was filtered through a celite pad, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 5 x 1 cm, 30% EtOAc in hexanes) to afford

2,3-dihydropyridin-4-one **30b** (11.3 mg, 0.047 mmol, 94% yield) as a yellow oil; R_f = 0.30 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 3H), 7.24–7.14 (m, 2H), 7.03 (d, *J* = 7.4 Hz, 1H), 5.54 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H), 4.94 (ddt, *J* = 9.9, 1.9, 0.9 Hz, 1H), 4.91–4.81 (m, 2H), 4.27 (d, *J* = 3.1 Hz, 2H), 3.07 (d, *J* = 13.0 Hz, 1H), 2.90 (d, *J* = 13.0 Hz, 1H), 2.22–1.97 (m, 2H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ196.5, 152.3, 135.6, 133.6, 129.0, 129.0, 129.0, 128.3, 128.0, 118.3, 96.9, 60.1, 55.9, 42.7, 39.7, 20.1, 20.0; IR (Neat Film NaCl) 3067, 3029, 2962, 2926, 1634, 1593, 1455, 1359, 1321, 1204, 1172, 1076, 1001, 916, 795 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO$ $[M+H]^+$: 242.1545, found 242.1553; $[\alpha]_D^{25.0}$ +86.46 (c 1.16, $CHCl_3$, 86% ee); HPLC conditions: 10% IPA in hexanes, 1 mL/min, Chiralcel OJ column, λ = 210 nm, t_R (min): major = 18.77, minor = 21.21.



2,3-Dihydropyridin-4-one 30c. In a glove box, $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 2.2 mg, 0.00375 mmol, 12.5 mol %) were added to a scintillation vial equipped with a stir bar. The vial was charged with toluene (0.5 mL) and heated at 40 °C for 30 min. 2,3-Dihydropyridin-4-one **29c** (9.8 mg, 0.030 mmol, 1.00 equiv) and additional toluene (0.5 mL, total added = 1.0 mL, 0.030 M) were added, producing a green solution. The vial was sealed and stirred at 40 °C until the starting

material was fully converted, determined by TLC. The reaction was filtered through a celite pad, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 5 x 1 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **30c** (6.9 mg, 0.024 mmol, 81% yield) as a yellow oil; R_f = 0.40 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.32 (m, 3H), 7.29–7.22 (m, 2H), 7.05 (d, *J* = 7.4 Hz, 1H), 5.62 (dddd, *J* = 17.1, 10.1, 7.8, 7.0 Hz, 1H), 5.00 (ddt, *J* = 10.1, 2.1, 1.0 Hz, 1H), 4.97–4.91 (m, 2H), 4.33 (s, 2H), 3.13 (d, *J* = 3.2 Hz, 2H), 2.34–2.24 (m, 1H), 2.16 (ddt, *J* = 14.1, 7.8, 1.1 Hz, 1H), 1.61 (qd, *J* = 6.7, 5.6 Hz, 1H), 1.47 (dd, *J* = 14.2, 6.3 Hz, 1H), 1.33 (dd, *J* = 14.2, 5.5 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 152.4, 135.7, 133.7, 129.1, 128.5, 128.1, 118.4, 97.1, 60.2, 56.0, 42.8, 39.8, 20.2.; IR (Neat Film NaCl) 3072, 3029, 2954, 2867, 1633, 1593, 1494, 1455, 1385, 1361, 1296, 1205, 1173, 1105, 1076, 1028, 998, 793, 736 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{26}NO$ $[M+H]^+$: 284.2014, found 284.2023; $[\alpha]_D^{25.0}$ +50.23 (c 0.65, $CHCl_3$, 88% ee); HPLC conditions: 7% IPA in hexanes, 1 mL/min, Chiralcel OJ column, λ = 210 nm, t_R (min): major = 11.44, minor = 14.80.

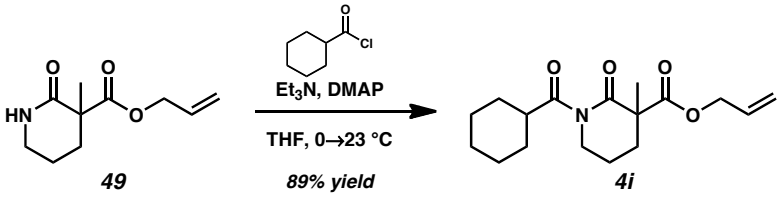


2,3-Dihydropyridin-4-one 30d. $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 2.2 mg, 0.00375 mmol, 12.5 mol %) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar, and the tube was backfilled with argon 3 times. The tube was charged with toluene (1 mL) and heated at 40 °C for 30 min, generating a red/orange solution. 2,3-Dihydropyridin-4-one **29d** (11.9 mg, 0.03 mmol, 1.00 equiv) were added and the tube was lowered into a heating block (40 °C). After 3 h, TLC analysis indicated the reaction was complete. Consequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, 10 x 2 cm, 50% EtOAc in hexanes) to afford dihydropyridine-4-one **30d** (8.6 mg, 0.0242 mmol, 81% yield) as yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.66 (s, 1H), 5.82 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.62 (s, 1H), 5.10–5.03 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.39 (s, 2H), 3.37 (td, J = 6.5, 1.5 Hz, 2H), 2.99–2.89 (m, 2H), 2.43 (ddt, J = 13.9, 7.2, 1.3 Hz, 1H), 2.25 (ddt, J = 14.0, 7.7, 1.1 Hz, 1H), 1.74 (hd, J = 6.6, 5.0 Hz, 1H), 1.66 (dd, J = 14.1, 6.5 Hz, 1H), 1.44 (dd, J = 14.1, 5.1 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 155.6, 151.4, 148.0, 134.7, 128.7, 120.8, 117.9, 110.4, 108.3, 94.3, 58.9, 56.0, 48.9, 46.1, 41.7, 39.2, 28.4, 25.1, 24.5, 24.1; IR (Neat Film NaCl) 2953, 1622, 1586,

1549, 1495, 1464, 1342, 1212, 1173, 1110, 1016, 913, 794 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{30}NO_3$ $[M+H]^+$: 356.2147, found 356.2221; $[\alpha]_D^{25.0}$ +32.49 (c 0.71, $CHCl_3$, 90% ee); HPLC conditions: 30% IPA in hexanes, 1 mL/min, Chiralpak AD column, λ = 254 nm, t_R (min): major = 21.87, minor = 18.59.

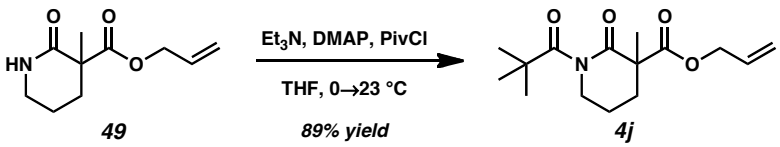
1.4.2.4 Preparation of Lactams

1.4.2.4.6 *Lactam Allylic Alkylation Precursors*



Lactam 4i. Lactam **49**[10] (117.8 mg, 0.597 mmol, 1.00 equiv) was transferred to a flame-dried 15 mL round-bottom flask using THF (4 x 0.5 mL + 1 x 0.4 mL rinses, total = 2.4 mL, 0.25 M). Et_3N (250 µL, 1.79 mmol, 3.00 equiv) and DMAP (9.3 mg, 0.0761 mmol, 13 mol%) were added and the flask was lowered into a 0 °C bath (ice/water). Cyclohexanecarbonyl chloride (160 µL, 1.20 mmol, 2.00 equiv) was added dropwise, and the reaction mixture transitioned from a solution to a white slurry. The ice bath expired gradually as the reaction was stirred overnight. After 15 h of stirring, no starting material remained by TLC analysis. The reaction was subsequently quenched with brine (15 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with EtOAc. The combined organics (100 mL) were rinsed twice with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100%

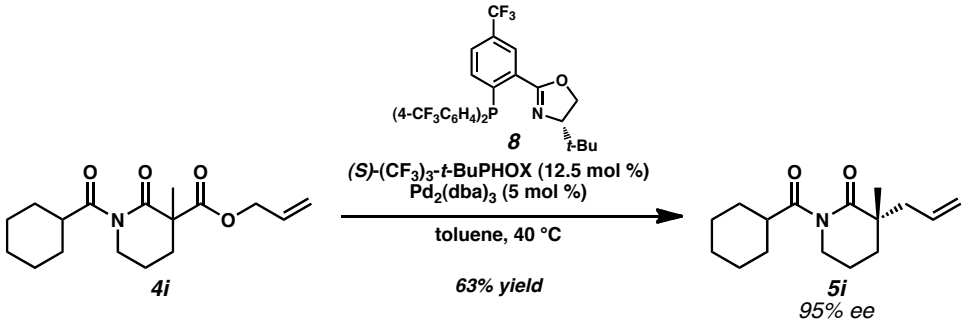
hexanes→10% EtOAc in hexanes) to afford lactam **4i** (163.5 mg, 0.532 mmol, 89% yield) as a yellow oil; R_f = 0.60 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, J = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.32 (dq, J = 17.2, 1.5 Hz, 1H), 5.25 (dq, J = 10.4, 1.2 Hz, 1H), 4.64 (ddt, J = 5.8, 2.5, 1.3 Hz, 2H), 3.77 (ddd, J = 13.1, 7.7, 5.1 Hz, 1H), 3.58 (dddd, J = 13.4, 7.0, 5.0, 1.1 Hz, 1H), 3.27 (tt, J = 11.4, 3.2 Hz, 1H), 2.42 (dddd, J = 13.4, 6.0, 4.9, 0.9 Hz, 1H), 1.95 (dtd, J = 10.5, 3.5, 1.8 Hz, 1H), 1.92–1.80 (m, 3H), 1.79–1.70 (m, 3H), 1.67 (dtt, J = 10.8, 3.2, 1.5 Hz, 1H), 1.52 (s, 3H), 1.47–1.34 (m, 2H), 1.34–1.16 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 173.5, 172.7, 131.4, 119.2, 66.4, 53.5, 45.7, 44.6, 33.1, 30.1, 29.6, 26.1, 25.9, 25.8, 23.0, 20.3; IR (Neat Film NaCl) 3086, 2931, 2855, 1738, 1694, 1652, 1479, 1451, 1378, 1330, 1301, 1249, 1218, 1196, 1159, 1134, 1073, 1053, 1032, 981, 957, 939, 896, 887, 842, 796, 773 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{26}O_4N$ $[M+H]^+$: 308.1856, found 308.1871.



Lactam 4j. Lactam **49**[9] (480 mg, 2.4 mmol, 1.0 equiv) in a 25 mL round-bottom flask equipped with a magnetic stir bar was taken up in THF (9.6 mL, 0.25 M). Et_3N (1.0 mL, 7.2 mmol, 3.0 equiv) and DMAP (29 mg, 0.24 mmol, 0.10 equiv) were added and the flask was lowered into a 0 °C bath (ice/water). Pivaloyl chloride (0.59 mL, 4.8 mmol, 2.0 equiv) was added dropwise and the reaction mixture transitioned from a solution to a white slurry. The ice bath expired gradually as the reaction was stirred overnight. After 24 h of stirring, TLC analysis indicated that conversion had ceased at approximately

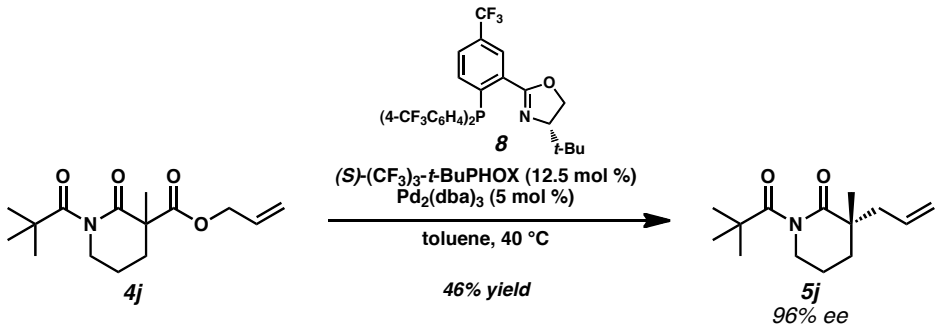
90%. The reaction was subsequently diluted with 20 mL EtOAc, quenched with brine (20 mL), and transferred to a separatory funnel where the aqueous layer was extracted three times with EtOAc (20 mL). The combined organics were washed twice with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 11 x 3 cm, 20% EtOAc in hexanes) to afford lactam **4j** (612 mg, 2.18 mmol, 89% yield) as a pale yellow oil; R_f = 0.37 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.70–4.59 (m, 2H), 3.62 (ddd, *J* = 12.8, 8.2, 4.9 Hz, 1H), 3.45 (dddd, *J* = 12.4, 6.2, 4.9, 1.0 Hz, 1H), 2.40 (dddd, *J* = 13.6, 7.1, 4.0, 1.0 Hz, 1H), 2.01–1.83 (m, 2H), 1.74 (ddd, *J* = 13.7, 9.5, 4.1 Hz, 1H), 1.52 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 172.5, 131.7, 119.2, 66.4, 52.5, 47.9, 44.5, 33.6, 28.0, 22.8, 20.3; IR (Neat Film NaCl) 3434, 2090, 1650, 1257, 1125 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{24}NO_4$ $[M+H]^+$: 282.1700, found 282.1705.

1.4.2.4.7 *Lactam Allylic Alkylation Products*



Lactam 5i. $Pd_2(dba)_3$ (16.4 mg, 0.0150 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 22.1 mg, 0.0374 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was

charged with toluene (2.06 mL) and stirred at ambient temperature for 30 min, generating a red/orange solution. Lactam **4i** (91.9 mg, 0.299 mmol, 1.00 equiv) was transferred to the scintillation vial with toluene (3 x 2 mL + 1 x 1 mL rinses, total = 9.06 mL, 0.033 M,) producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 7 days, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford recovered lactam **4i** (17.2 mg, 0.0560 mmol, 19% recovered) and lactam **5i** (49.8 mg, 0.189 mmol, 63% yield, 78% yield based on recovered lactam **4i**) as a yellow oil; R_f = 0.73 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 16.6, 10.4, 7.8, 6.9 Hz, 1H), 5.13–5.06 (m, 2H), 3.76–3.67 (m, 1H), 3.57–3.49 (m, 1H), 3.18 (tt, J = 11.4, 3.3 Hz, 1H), 2.51 (ddt, J = 13.6, 6.9, 1.2 Hz, 1H), 2.27 (ddt, J = 13.6, 7.8, 1.1 Hz, 1H), 1.90 (dddd, J = 12.7, 5.5, 2.9, 1.4 Hz, 1H), 1.87–1.72 (m, 7H), 1.67 (dtt, J = 10.8, 3.5, 1.5 Hz, 1H), 1.62–1.56 (m, 1H), 1.42 (dtdd, J = 12.9, 12.0, 11.2, 3.2 Hz, 2H), 1.35–1.19 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 179.5, 133.5, 118.9, 46.1, 45.8, 45.0, 44.5, 33.3, 30.0, 30.0, 26.1, 25.9, 25.9, 25.8, 19.8; IR (Neat Film NaCl) 3076, 2930, 2854, 1690, 1478, 1451, 1375, 1329, 1313, 1286, 1246, 1198, 1158, 1136, 1089, 1072, 1031, 996, 975, 919, 759 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{26}O_2N$ $[M+H]^+$: 264.1958, found 264.1945; $[\alpha]_D^{25.0}$ –96.13 (c 1.06, $CHCl_3$, 95% ee); JASCO SFC conditions: 1% IPA in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 222 nm, t_R (min): major = 2.53, minor = 2.13.

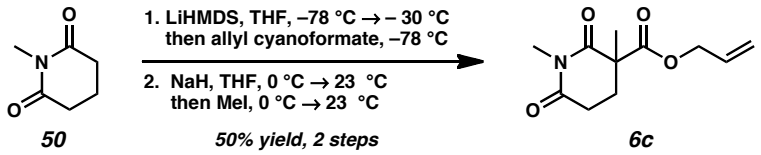


Lactam 5j. $Pd_2(pmdba)_3$ (27 mg, 25 μmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 37 mg, 63 μmol, 12.5 mol %) were added to an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar in a glove box. The vial was charged with toluene (12 mL) and stirred at ambient temperature (28 °C) for 30 min, resulting in a deep orange solution. Lactam **4j** (140 mg, 0.50 mmol, 1.0 equiv) was transferred to the scintillation vial with toluene (2 mL, total = 15 mL, 0.033 M), producing a light green solution. The vial was sealed with a Teflon-lined cap and lowered into a heating block (40 °C). After 16 days, TLC analysis indicated that conversion had ceased at approximately 50% and the vial was removed from the glove box and the reaction was filtered through a silica gel plug, rinsed with Et_2O, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 15 x 2.5 cm, 5% EtOAc in hexanes) to afford lactam **5j** (54 mg, 0.23 mmol, 46% yield) as a colorless oil; R_f = 0.58 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (dddd, *J* = 17.1, 10.2, 7.8, 7.0 Hz, 1H), 5.16–5.05 (m, 2H), 3.53–3.38 (m, 2H), 2.51 (ddt, *J* = 13.7, 7.0, 1.3 Hz, 1H), 2.28 (ddt, *J* = 13.7, 7.7, 1.1 Hz, 1H), 1.92–1.80 (m, 3H), 1.61–1.58 (m, 1H), 1.27 (s, 9H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 179.0, 133.7, 118.9, 48.5, 44.2, 43.4, 43.3, 33.4, 28.1, 25.0, 19.8; IR (Neat Film NaCl) 2963, 1684, 1482, 1457, 1391, 1282, 1259, 1156, 917 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{24}NO_2$ $[M+H]^+$: 238.1802,

found 238.1809; $[\alpha]_D^{25.0}$ –7.13 (c 2.45, $CHCl_3$, 96% ee); HPLC conditions: 5% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 7.95, minor = 6.52.

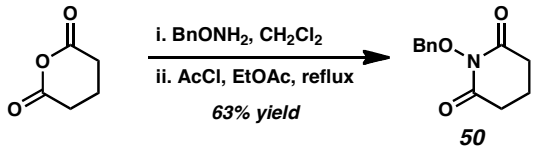
1.4.2.5 Preparation of Imides

1.4.2.5.8 *Imide Allylic Alkylation Precursors*



***N*-Methyl imide 6c.** A flame-dried 200 mL round-bottom flask containing a magnetic stir bar was cycled into a glove box and loaded with LiHMDS (5.69 g, 34.0 mmol, 1.7 equiv). The flask was removed from the glove box, reconnected to a manifold, and charged with THF (100 mL, 0.2 M) and lowered into a –78 °C bath. Imide **50**[48] (2.54 g, 20.0 mmol, 1.0 equiv) was added neat. After 1 h at –78 °C, the solution was warmed to 30 °C and stirred for 30 min before cooling back to –78 °C. Allyl cyanoformate (2.67 g, 24.0 mmol, 1.2 equiv) was added neat and the reaction was stirred for 1.5 h before TLC analysis indicated consumption of starting material. The reaction was subsequently quenched with brine and transferred to a separatory funnel where the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organics were rinsed twice with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 5 cm x 7 inches, 25%→30%→40% EtOAc in hexanes) to afford an intermediate oil (2.63 g, 0.45 mmol, 62% yield) that was moved on to the next step.

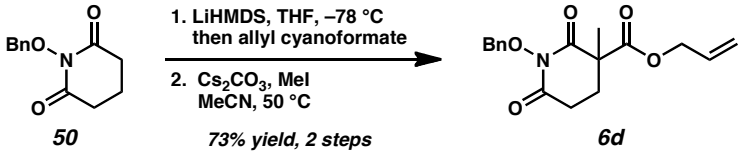
A flame-dried 200 mL flask equipped with a magnetic stir bar was charged with sodium hydride (60% in mineral oil, 312.5 mg, 7.81 mmol, 1.1 equiv) and THF (71 mL, 0.1 M) and cooled to 0 °C. A portion of the oil from the previous step (1.5 g, 7.10 mmol, 1.0 equiv) was added neat. After 1.5 h at 0 °C, the reaction was warmed to room temperature and stirred for 1 h before cooling back to 0 °C. Methyl iodide (886 μL, 14.20 mmol, 2.0 equiv) was added and the reaction was stirred for 2 h before warming to room temperature. After 15 h, the reaction was poured over a mixture of water and brine and transferred to a separatory funnel where the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organics were rinsed twice with aq. $Na_2S_2O_3$ (sat. solution half diluted) and twice with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 5 cm x 8 inches, 10% →20% EtOAc in hexanes) to afford imide **6c** (1.28 g, 5.69 mmol, 80% yield, 50% yield over two steps); R_f = 0.32 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.29 (dq, J = 17.2, 1.5 Hz, 1H), 5.25 (dq, J = 10.5, 1.2 Hz, 1H), 4.63 (ddt, J = 5.6, 4.1, 1.4 Hz, 2H), 3.18 (s, 3H), 2.72 (ddd, J = 18.1, 5.4, 4.4 Hz, 1H), 2.64 (ddd, J = 17.9, 11.6, 5.4 Hz, 1H), 2.35 (ddd, J = 13.9, 5.4, 4.4 Hz, 1H), 1.89 (ddd, J = 13.9, 11.6, 5.4 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 171.8, 171.3, 131.2, 119.3, 66.5, 50.9, 30.0, 28.7, 27.3, 21.9; IR (Neat Film NaCl) 2987, 2943, 1726, 1678, 1458, 1416, 1381, 1356, 1305, 1261, 1247, 1182, 1106, 1036, 993, 938 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{18}NO_4$ $[M+H]^+$: 226.1074, found 226.1078.



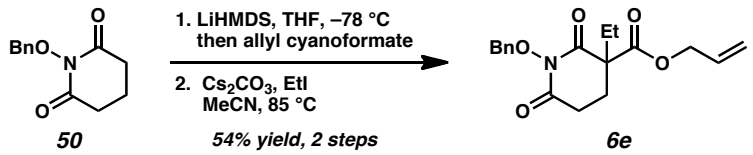
50

***N*-benzyloxyimide 50.** Benzyloxyamine hydrochloride (3.15 g, 19.7 mmol) in a 100 mL round-bottom flask was taken up in dichloromethane (30 mL) and saturated aqueous K_2CO_3 (30 mL) and stirred for 30 min. The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was extracted twice with dichloromethane (30 mL), the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. A portion of the resulting crude colorless oil (1.23 g, 10.0 mmol, 1.00 equiv) was diluted with dichloromethane (10 mL, 1.0 M) in a 50 mL round-bottom flask and glutaric anhydride (1.14 g, 10.0 mmol, 1.00 equiv) was added. An exotherm was observed, and the mixture was immediately concentrated under reduced pressure. The resulting residue was taken up in EtOAc (13 mL, 0.75 M) and acetyl chloride (2.00 mL, 2.81 mmol, 2.81 equiv) was added. A water condenser was affixed and the reaction was heated to a gentle reflux (oil bath, 85 °C) for 18 h. The reaction was diluted with EtOAc (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude solid was purified by flash column chromatography (SiO_2, 6 x 5 cm, 20% EtOAc in hexanes→50% Et_2O in dichloromethane) to afford *N*-benzyloxyimide **50** (1.37 g, 6.25 mmol, 63% yield) as a white solid; R_f = 0.64 (20% Et_2O in methylene chloride); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.45 (m, 2H), 7.41–7.29 (m, 3H), 5.01 (s, 2H), 2.74–2.60 (m, 4H), 1.94–1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.48 , 133.95 , 130.09 , 129.23 , 128.51 , 78.17 , 33.47 , 17.05; IR (Neat Film NaCl) 3033, 2957, 2902, 1689, 1457, 1381, 1350, 1331, 1251, 1175, 1134, 1087, 1056, 999,

968, 919, 893, 838, 759 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0968, found 220.0971.

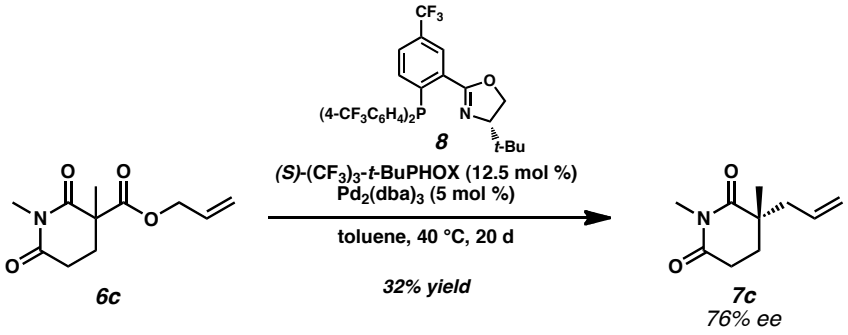


***N*-Benzyloxy imide 6d.** Acylation performed in manner analogous to *N*-methyl imide **6c** at –78 °C using *N*-benzyloxy imide **50** as starting material. Alkylation performed in manner analogous to β-ketoester **45a** at 50 °C. *N*-Benzyloxy imide **6d** was isolated after flash column chromatography (SiO_2, 17 to 25% EtOAc in hexanes) as a colorless oil (73% yield over two steps); R_f = 0.20 (20% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.37 (m, 3H), 5.87 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.01 (s, 2H), 4.66 (ddt, *J* = 13.0, 5.9, 1.3 Hz, 1H), 4.65 (ddt, *J* = 13.0, 5.9, 1.3 Hz, 1H), 2.72 (m, 2H), 2.30 (ddd, *J* = 14.1, 5.2, 4.0 Hz, 1H), 1.86 (ddd, *J* = 14.1, 11.8, 5.5 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.7, 167.9, 167.4, 133.9, 130.9, 130.1, 129.2, 128.5, 119.9, 77.9, 66.9, 52.1, 30.5, 28.5, 21.6; IR (Neat Film NaCl) 2943, 1738, 1733, 1708, 1451, 1255, 1200, 1168, 976 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{20}NO_5$ $[M+H]^+$: 318.1336, found 318.1339.

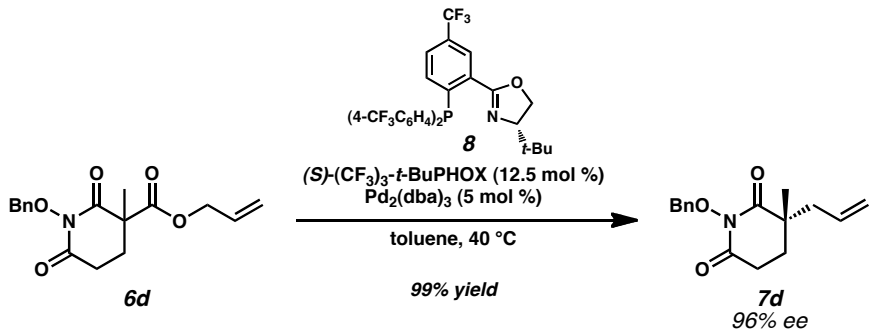


***N*-Benzyloxy imide 6e.** Acylation performed in manner analogous to *N*-methyl imide **6c** at –78 °C using *N*-benzyloxy imide **50** as starting material. Alkylation performed in manner analogous to β-ketoester **45a** at 85 °C using ethyl iodide. *N*-Benzyloxy imide **6e** was isolated after flash column chromatography (SiO_2, 14 to 20% EtOAc in hexanes) as a colorless oil (54% yield over two steps); R_f = 0.24 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.37 (m, 3H), 5.87 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.0 (s, 2H), 4.66 (dt, *J* = 5.9, 1.3 Hz, 2H), 2.74 (m, 2H), 2.22 (ddd, *J* = 14.0, 5.2, 3.5 Hz, 1H), 2.05(m, 2H), 1.96 (ddd, *J* = 14.0, 12.3, 5.4 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.2, 167.5, 167.1, 134.0, 131.0, 130.1, 129.3, 128.6, 120.0, 77.9, 66.8, 56.2, 30.4, 28.3, 24.8, 9.0; IR (Neat Film NaCl) 2943, 1733, 1713, 1648, 1454, 1237, 1190, 1168, 976, 752 cm^{-1}; HRMS (MM: ESI-APCI) *m*/*z* calc'd for $C_{18}H_{22}NO_5$ $[M+H]^+$: 332.1492, found 332.1493.

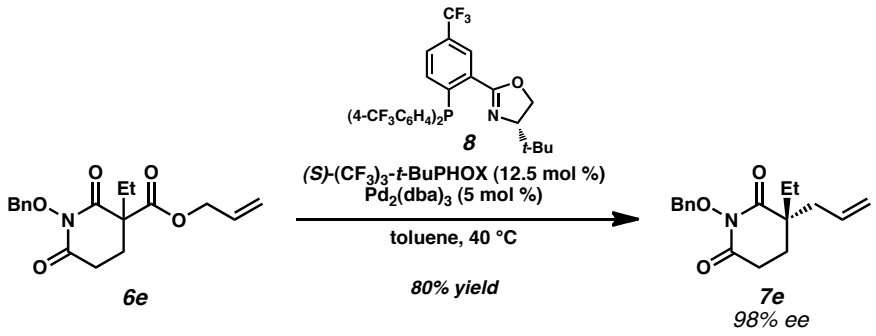
1.4.2.5.9 *Imide Allylic Alkylation Products*



***N*-Methyl imide 7c.** Prepared in a manner analogous to lactam **5h** using *N*-methyl imide **6c** as starting material. After 20 d, the reaction was filtered, concentrated, and *N*-Methyl imide **7c** was isolated following flash column chromatography (SiO_2, 3 cm x 10 inches, 5%→7%→9%→10% →12% EtOAc in hexanes) as an oil (32% yield); R_f = 0.36 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (dddd, J = 17.1, 10.2, 7.6, 7.1 Hz, 1H), 5.15–5.08 (m, 2H), 3.12 (s, 3H), 2.75–2.62 (m, 2H), 2.47 (ddt, J = 13.8, 7.1, 1.2 Hz, 1H), 2.29 (ddt, J = 13.8, 7.7, 1.1 Hz, 1H), 1.92 (ddd, J = 14.3, 8.6, 5.9 Hz, 1H), 1.66 (ddd, J = 14.0, 7.1, 5.8 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 172.5, 132.8, 119.5, 42.6, 41.7, 29.3, 27.8, 27.0, 23.4; IR (Neat Film NaCl) 2971, 2937, 2876, 1723, 1674, 1464, 1415, 1378, 1356, 1291, 1240, 1110, 1036, 998, 919 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{16}NO_2$ $[M+H]^+$: 182.1176, found 182.1178; $[\alpha]_D^{25.0}$ –54.19 (c 1.64, $CHCl_3$, 76% ee); HPLC conditions: 3% IPA in hexanes, 1 mL/min, Chiralpak AD column, λ = 210 nm, t_R (min): major = 11.94, minor = 17.86.



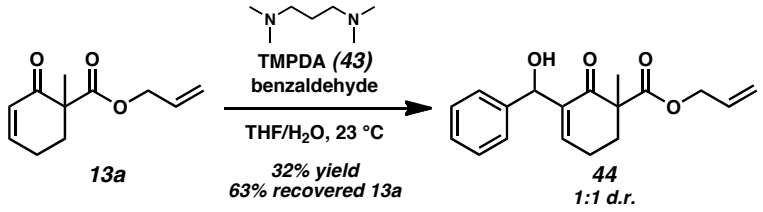
***N*-Benzyloxy imide 7d.** Prepared in a manner analogous to lactam **5h** using *N*-benzyloxy imide **6d** as starting material. *N*-Benzyloxy imide **7d** was isolated after flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a colorless oil (99% yield); R_f = 0.29 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 5.64 (dddd, *J* = 17.2, 10.2, 7.7, 7.1 Hz, 1H), 5.09–5.15 (m, 2H), 5.0 (s, 2H), 2.66–2.77 (m, 2H), 2.43 (ddt, *J* = 13.9, 7.1, 1.2 Hz, 1H), 2.26 (ddt, *J* = 13.9, 7.7, 1.2 Hz, 1H), 1.87 (ddd, *J* = 14.3, 8.5, 5.9 Hz, 1H), 1.60 (ddd, *J* = 14.3, 7.0, 5.7 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 168.1, 133.9, 132.3, 130.3, 129.2, 128.5, 119.9, 78.0, 43.1, 42.3, 29.7, 27.6, 23.1; IR (Neat Film NaCl) 3067, 2974, 2935, 1740, 1703, 1700, 1456, 1172, 978, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m*/*z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1437; $[\alpha]_D^{25.0}$ –58.59 (c 1.26, $CHCl_3$, 96% ee); Thar SFC conditions: 5% MeOH in CO_2, 3 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 4.03, minor = 3.64.



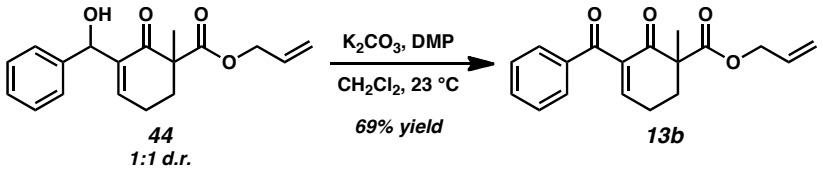
***N*-Benzyloxy imide 7e.** Prepared in a manner analogous to lactam **5h** using *N*-benzyloxy imide **6e** as starting material. *N*-Benzyloxy imide **7e** was isolated after flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a colorless oil (80% yield); R_f = 0.20 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 5.63 (dddd, *J* = 17.3, 10.3, 7.7, 6.9 Hz, 1H), 5.08–5.10 (m, 2H), 4.99 (s, 2H), 2.67–2.76 (m, 2H), 2.46 (ddt, *J* = 14.0, 6.9, 1.3 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.7, 1.1 Hz, 1H), 1.80 (ddd, *J* = 14.2, 7.9, 6.4 Hz, 1H), 1.76–1.71 (m, 1H), 1.70 (dq, *J* = 14.2, 7.5 Hz, 1H), 1.62 (dq, *J* = 14.2, 7.5 Hz, 1H), 0.86 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 168.0, 134.0, 132.6, 130.2, 129.2, 128.5, 119.6, 78.0, 46.5, 40.0, 29.5, 28.6, 24.7, 8.2; IR (Neat Film NaCl) 3033, 2972, 1739, 1702, 1699, 1455, 1169, 977, 751 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1591; $[\alpha]_D^{25.0}$ –35.98 (c 1.98, $CHCl_3$, 98% ee); Thar SFC conditions: 1% MeOH in CO_2, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): major = 14.34, minor = 13.39.

1.4.2.6 Preparation of Enones and Diosphenol Ethers

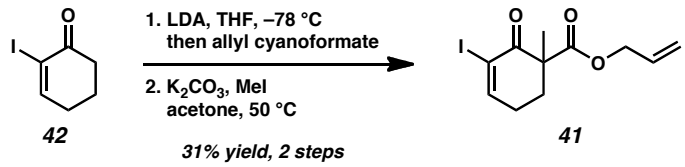
1.4.2.6.10 *Enone and Diosphenol Ether Allylic Alkylation Precursors*



Alcohol 44. Procedure adapted from the literature precedent of Kim.[44] A 15 mL round-bottom flask equipped with a stir bar was charged with enone **13a** (852.1 mg, 4.39 mmol, 1.94 equiv), THF (1.4 mL, 1.6 M), benzaldehyde (230 µL, 2.26 mmol, 1.00 equiv), H_2O (1.4 mL, 1.6 M), and TMPDA (**43**, 380 µL, 2.27 mmol, 1.00 equiv). The reaction mixture was a yellow suspension that transitioned to orange over time. After 6 days, the reaction was diluted with H_2O (10 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 25.5 x 3 cm, 100% hexanes→5%→10%→15%→20% EtOAc in hexanes) to afford recovered enone **13a** (536.0 mg, 2.76 mmol, 63% recovered) pale yellow oil and alcohol **44** (217.7 mg, 0.725 mmol, 32% yield, 45% yield based on recovered enone **13a**) as a yellow oil; R_f = 0.28 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) ~1:1 mixture of diastereomers, see Figure 1.42.1; IR (Neat Film NaCl) 3503 (broad), 3061, 3030, 2980 2934, 1735, 1672, 1492, 1452, 1424, 1379, 1291, 1246, 1187, 1165, 1111, 1018, 982, 936, 760 cm^{-1}; HRMS (EI+) calc'd for $C_{18}H_{20}O_4$ $[M+\bullet]^+$: 300.1362, found 300.1376.



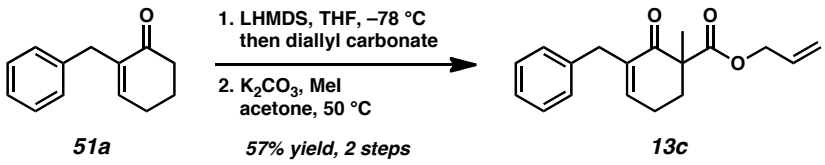
Enone 13b. A scintillation vial containing alcohol **44** (44.5 mg, 0.148 mmol, 1.00 equiv) was equipped with a stir bar, connected to a manifold, backfilled with Ar, and charged with CH_2Cl_2 (1 mL, 0.15 M). K_2CO_3 (62.5 mg, 0.452 mmol, 3.05 equiv) and DMP (96.3 mg, 0.227 mmol, 1.53 equiv) were added simultaneously to the vial. After 2 h of stirring, no starting material was detected by TLC analysis. Consequently, the reaction was diluted with CH_2Cl_2 (1 mL), filtered through a short celite plug rinsing with CH_2Cl_2, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 27 x 1 cm, 0.1% Et_3N in hexanes→0.1% Et_3N and 10% EtOAc in hexanes) to afford enone **13b** (30.4 mg, 0.102 mmol, 69% yield) as a yellow oil; Rf = 0.43 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 8.11–8.07 (m, 2H), 7.15–7.08 (m, 3H), 6.62 (ddd, J = 5.0, 2.9, 1.2 Hz, 1H), 5.61 (ddt, J = 17.1, 10.3, 5.7 Hz, 1H), 5.05 (dq, J = 17.2, 1.5 Hz, 1H), 4.92 (dq, J = 10.4, 1.3 Hz, 1H), 4.37 (dt, J = 5.7, 1.4 Hz, 2H), 2.11 (dddd, J = 13.5, 4.8, 3.4, 1.2 Hz, 1H), 2.04 (dddd, J = 20.1, 9.6, 5.1, 2.9 Hz, 1H), 1.59 (dtdd, J = 20.1, 5.1, 3.4, 1.4 Hz, 1H), 1.36–1.27 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 194.0, 193.6, 172.1, 150.9, 141.4, 137.6, 133.1, 132.0, 129.9, 128.5, 118.5, 65.9, 53.8, 33.5, 23.6, 20.6; IR (Neat Film NaCl) 3063, 3027, 2981, 2935, 2873, 2855, 2280, 1732, 1668, 1621, 1598, 1581, 1449, 1423, 1378, 1358, 1293, 1265, 1244, 1178, 1157, 1111, 988, 940, 814, 769, 712; HRMS (FAB+) cal'd for $C_{18}H_{18}O_4$ $[M+\bullet]^+$: 298.1205, found 298.1219.



α-Iodoenone 41. A 50 mL round-bottom flask equipped with a stir bar was charged with diisopropyl amine (450 μL, 3.21 mmol, 1.10 equiv) and THF (7 mL). The flask was lowered into a 0 °C bath (water/ice) and *n*-BuLi (1.26 mL, 2.43 M in hexanes, 3.06 mmol, 1.05 equiv) was added dropwise over several minutes. The reaction was stirred for 15 min before the ice bath was removed and replaced with a –78 °C bath (acetone/dry ice). α-Iodoenone **42** (641.3 mg, 2.91 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x 6 mL and 2 x 1 mL rinses, total added = 15 mL, 0.19 M), producing a yellow solution. The reaction was stirred for 1 h before allyl cyanoformate (330 μL, 3.06 mmol, 1.05 equiv) was added dropwise. After 2.5 h, no starting material was observed by ^{1}H NMR analysis and the reaction was subsequently quenched after an additional hour with sat. NH_4Cl solution (10 mL) and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 27.5 x 3 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford a yellow oil (R_f = 0.52, 30% EtOAc in hexanes) that was moved on to the next step.

The resulting yellow oil was transferred to an argon filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (ACS reagent grade, 5 x 2 mL). Additional acetone (3.2 mL, total added =

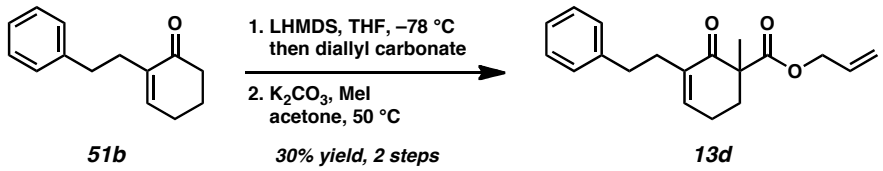
13.2 mL, 0.10 M), K_2CO_3 (367.6 mg, 2.66 mmol, 2.01 equiv), and MeI (170 μL, 2.73 mmol, 2.06 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 18 h, ^{1}H NMR analysis indicated residual starting material, and consequently more MeI (90 μL, total added = 260 μL, 4.18 mmol, 3.15 equiv) was added. After an additional 21 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with EtOAc and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 28 x 2 cm, 100% hexanes→5% EtOAc in hexanes) to afford α-iodoenone **41** (277.8 mg, 0.868 mmol, 31% yield over two steps) as a pale yellow oil; R_f = 0.63 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (ddd, J = 4.7, 3.3, 1.0 Hz, 1H), 5.85 (dddd, J = 17.2, 10.8, 5.5, 5.5 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.22 (dm, J = 10.5 Hz, 1H), 4.64 (dddd, J = 11.5, 6.3, 4.8, 1.5 Hz, 1H), 4.57 (dddd, J = 11.4, 6.2, 4.7, 1.5 Hz, 1H), 2.60–2.51 (m, 2H), 2.42–2.33 (m, 1H), 2.02–1.95 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 171.6, 158.1, 131.4, 118.7, 102.0, 66.1, 53.5, 33.3, 27.9, 21.3; IR (Neat Film NaCl) 3085, 2982, 2936, 2874, 2826, 1735, 1696, 1648, 1595, 1457, 1422, 1378, 1323, 1293, 1244, 1178, 1142, 1110, 1089, 1051, 966, 956, 930, 890, 864, 833, 782, 730 cm^{-1}; HRMS (FAB+) calc'd for $C_{11}H_{14}O_3I$ $[M+H]^+$: 320.9988, found 320.9993.



Enone 13c. A 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box, loaded with LHMDS (527.6 mg, 3.15 mmol, 2.10 equiv), removed from the glove box, and connected to an Ar-filled manifold. The flask was charged with THF (1 mL) and lowered into a 0 °C bath (ice/water). Enone **51a**[49] (279.0 mg, 1.50 mmol, 1.00 equiv) was cannula transferred slowly from a scintillation vial to the flask using several THF rinses (1 x 4 mL + 2 x 0.5 mL, total added = 6 mL, 0.25 M), generating a bright red/pink solution. After the addition was complete, the 0 °C bath was removed and the reaction was allowed to warm to room temperature. After 30 min, the flask was lowered back into the 0 °C bath and diallyl carbonate (230 µL, 1.60 mmol, 1.07 equiv) was added dropwise, generating an orange solution. The bath was allowed to expire overnight. After 18 h, the reaction was quenched with sat. NH_4Cl sol. (10 mL) and transferred to a separatory funnel where the aqueous layer was extracted five times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 21 x 2 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford a yellow oil.

The resulting yellow oil (285.8 mg, 1.06 mmol, 1.00 equiv) was transferred to an Ar-filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (1 x 1.5 mL + 3 x 0.5 mL, total added = 3 mL, 0.35 M). K_2CO_3 (292.7 mg, 2.12 mmol, 2.00 equiv) and methyl iodide (180 µL,

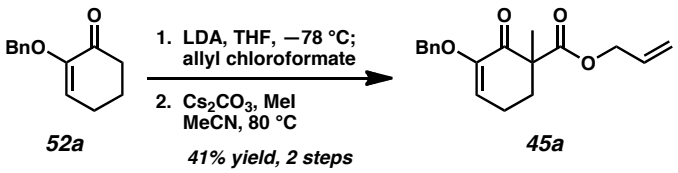
2.89 mmol, 2.73 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 11 h, ^{1}H NMR analysis indicated residual starting material, and consequently more methyl iodide (130 μL, total added = 310 μL, 4.98 mmol, 4.71 equiv) was added. After an additional 8.5 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with CH_2Cl_2 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 26.5 x 1.5 cm, 100% hexanes→5% EtOAc in hexanes) to afford enone **13c** (271.2 mg, 0.954 mmol, 64% yield over two steps, 90% purity) as a yellow oil. This yellow oil was diluted in EtOAc (50 mg/mL) and purified further by preparative HPLC (10% EtOAc in hexanes) to afford analytically pure enone **13c** (242.8 mg, 0.851 mmol, 57% yield over two steps) as a pale yellow oil; R_f = 0.59 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.21–7.14 (m, 3H), 6.50–6.45 (m, 1H), 5.78 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.24 (dq, J = 17.2, 1.5 Hz, 1H), 5.19 (dq, J = 10.5, 1.1 Hz, 1H), 4.53 (dm, J = 5.6 Hz, 2H), 3.58 (dq, J = 15.7, 1.7 Hz, 1H), 3.51 (dq, J = 15.6, 1.7 Hz, 1H), 2.52–2.40 (m, 2H), 2.34–2.24 (m, 1H), 1.94–1.86 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 172.6, 145.1, 139.5, 138.8, 131.8, 129.3, 128.5, 126.2, 118.4, 65.8, 53.6, 36.0, 33.7, 23.6, 20.6; IR (Neat Film NaCl) 3084, 3061, 3027, 2980, 2934, 1734, 1685, 1603, 1496, 1453, 1430, 1375, 1292, 1246, 1166, 1111, 1077, 1029, 984, 747 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1485, found 285.1482.



Enone 13d. A 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box, loaded with LHMDS (215.6 mg, 1.29 mmol, 2.12 equiv), removed from the glove box, and connected to an Ar-filled manifold. The flask was charged with THF (0.5 mL) and lowered into a 0 °C bath (ice/water). Enone **51b**[49] (122.0 mg, 0.609 mmol, 1.00 equiv) was cannula transferred slowly from a scintillation vial to the flask using several THF rinses (1 x 1 mL + 2 x 0.5 mL, total added = 2.5 mL, 0.24 M), generating a bright pink solution. After the addition was complete, the 0 °C bath was removed and the reaction was allowed to warm to room temperature. After 30 min, the flask was lowered back into the 0 °C bath and diallyl carbonate (100 μL, 0.697 mmol, 1.14 equiv) was added dropwise. The bath was allowed to expire overnight. After 18 h, the reaction was quenched with sat. NH_4Cl sol. (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted five times with Et_2O. The combined organics (70 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 1.5 cm, 100% hexanes→5% EtOAc in hexanes) to afford a yellow oil.

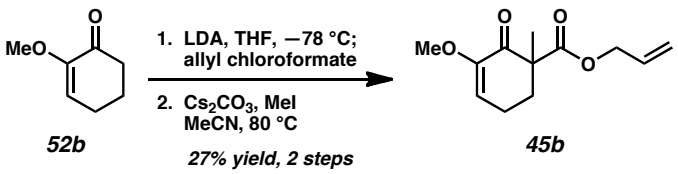
The resulting yellow oil (84.6 mg, 0.298 mmol, 1.00 equiv) was transferred to an Ar-filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (4 x 0.5 mL, total added = 2 mL, 0.15 M). K_2CO_3 (87.0 mg, 0.630 mmol, 2.12 equiv) and methyl iodide (100 μL, 1.61 mmol, 5.40 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered

into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 16 h, ^{1}H NMR analysis indicated residual starting material, and consequently more methyl iodide (130 μL, total added = 310 μL, 4.98 mmol, 4.71 equiv) was added. After an additional 8.5 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with CH_2Cl_2 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2% EtOAc in hexanes) to afford enone **13d** (75.6 mg, 0.253 mmol, 42% yield over two steps, 80% purity) as a yellow oil. This yellow oil was diluted with EtOAc (50 mg/mL) and purified further by preparative HPLC (10% EtOAc in hexanes, 50 mL/min) to afford analytically pure enone **13d** (54.1 mg, 0.181 mmol, 30% yield over two steps) as a pale yellow oil; R_f = 0.67 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.24 (m, 2H), 7.20–7.15 (m, 3H), 6.53 (ddq, J = 4.6, 3.3, 1.0 Hz, 1H), 5.87 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.29 (dq, J = 17.2, 1.5 Hz, 1H), 5.22 (dq, J = 10.5, 1.3 Hz, 1H), 4.65–4.57 (m, 2H), 2.74 (ddd, J = 13.4, 9.7, 6.1 Hz, 1H), 2.67 (ddd, J = 13.4, 9.3, 6.1 Hz, 1H), 2.57 (dddq, J = 13.8, 9.2, 6.4, 1.5 Hz, 1H), 2.52–2.37 (m, 2H), 2.29 (qt, J = 4.9, 1.3 Hz, 1H), 2.25 (ddt, J = 9.9, 4.8, 1.3 Hz, 1H), 1.88 (ddd, J = 13.4, 8.4, 5.3 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 172.7, 144.5, 142.0, 138.2, 131.8, 128.7, 128.4, 126.0, 118.5, 65.8, 53.6, 34.9, 33.6, 32.5, 23.5, 20.6; IR (Neat Film NaCl) 3026, 2930, 1733, 1683, 1603, 1495, 1456, 1377, 1244, 1167, 1109, 985, 931, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{23}O_3$ $[M+H]^+$: 299.1642, found 299.1638.



β-ketoester 45a. Diisopropylamine (390 μL, 2.78 mmol, 4.46 equiv) in a 10 mL round-bottom flask equipped with a magnetic stir bar was taken up in 2.0 mL THF and lowered into a 0 °C bath (ice/water). To the stirring solution was added *n*-butyl lithium (4.7 M solution in hexanes, 0.583 mL, 2.74 mmol, 4.40 equiv). This solution was stirred for 30 min before transferring the flask to a –78 °C bath (dry ice/acetone) and stirring the mixture for another 15 min. Benzyl diosphenol ether **52a**[50] (126 mg, 0.623 mmol, 1.00 equiv) in 1.1 mL THF (total = 3.1 mL, 0.2 M) was added dropwise by syringe, and the solution was stirred for 2 h. Allyl cyanoformate (270 μL, 2.49 mmol, 4.00 equiv) was added dropwise by syringe, and the reaction was stirred for 8 h until analysis by TLC showed complete consumption of starting material. The reaction was diluted with 2 mL EtOAc and quenched with 1.5 mL each saturated aqueous NH_4Cl and water. The –78 °C bath was removed and the biphasic mixture was warmed to room temperature. The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was extracted twice with EtOAc (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude yellow oil was taken up in acetonitrile (2.0 mL, 0.3 M) in a flame-dried 2-dram vial equipped with a magnetic stir bar. Cs_2CO_3 (264 mg, 0.810 mmol, 1.30 equiv) and methyl iodide (116 μL, 1,86 mmol, 3.00 equiv) were added, and the reaction was blanketed under argon and sealed with a Teflon-lined cap. The vial was placed in a heating block (80 °C) and stirred for 8 h until analysis by TLC showed complete consumption of

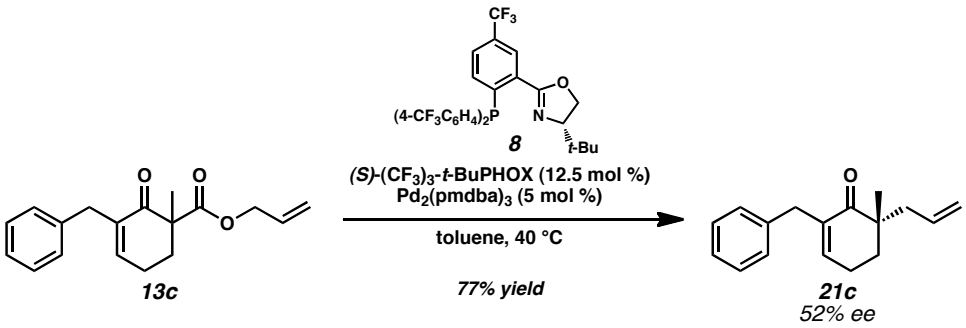
starting material. The reaction was diluted with 5 mL EtOAc, filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 12 x 1.5 cm, 20% Et_2O in hexanes) to afford β-ketoester **45a** (77 mg, 0.26 mmol, 41% yield over two steps) as a colorless oil; R_f = 0.34 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 5.93–5.79 (m, 2H), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.95–4.83 (m, 2H), 4.67–4.52 (m, 2H), 2.50–2.41 (m, 2H), 2.39–2.27 (m, 1H), 1.96–1.83 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 172.3, 149.7, 136.7, 131.7, 128.6, 128.0, 127.3, 118.8, 118.5, 70.1, 65.9, 54.3, 33.7, 21.7, 20.6; IR (Neat Film NaCl) 3394, 2916, 2167, 1996, 1692, 1627, 1455, 1251, 1153, 1110, 1056 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{21}O_4$ $[M+H]^+$: 301.1434, found 301.1422.



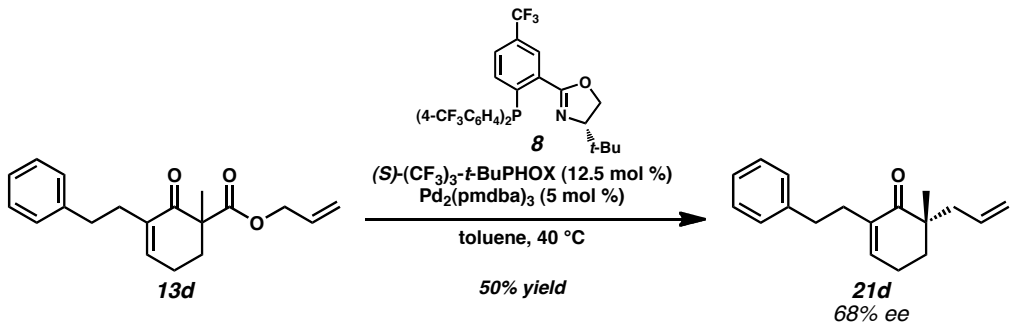
Diosphenol ether 45b. Prepared from **52b**[51] in an analogous manner to **45a**. Purified by flash chromatography (SiO_2, 15 x 3 cm, 20→40% Et_2O in hexanes) to afford diosphenol ether **45b** (57 mg, 0.25 mmol, 27% yield over two steps) as a colorless oil; R_f = 0.54 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96–5.80 (m, 1H), 5.78 (d, *J* = 4.5 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.67–4.55 (m, 2H), 3.60 (s, 3H), 2.56–2.43 (m, 2H), 2.42–2.32 (m, 1H), 1.95–1.85 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 172.2, 150.7, 131.7, 118.4, 115.2, 65.9, 55.2, 54.3, 33.9, 21.5, 20.6; IR (Neat Film NaCl) 2936, 2839, 1734, 1696, 1631, 1455, 1378,

1365, 1252, 1231, 1174, 1110, 1081, 1064, 979, 935, 824 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}O_4$ $[M+H]^+$: 225.1121, found 225.1122.

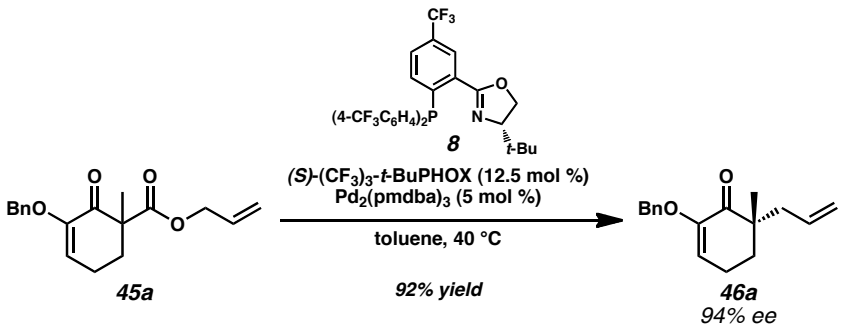
1.4.2.6.11 *Diosphenol Ether and Enone Allylic Alkylation Products*



Enone 21c. Prepared from **13c** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 12 x 2 cm, 10→20% Et_2O in hexanes) to afford enone **21c** (68 mg, 0.28 mmol, 77% yield) as a colorless oil and recovered enone **13c** (19 mg, 18% recovered); R_f = 0.70 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.20 (m, 2H), 7.23 – 7.10 (m, 3H), 6.46 (d, *J* = 4.0 Hz, 1H), 5.75 – 5.60 (m, 1H), 5.08 – 4.93 (m, 2H), 3.50 (dq, *J* = 3.3, 1.6 Hz, 2H), 2.41 – 2.23 (m, 3H), 2.16 (ddt, *J* = 13.7, 7.6, 1.2 Hz, 1H), 1.89 (ddd, *J* = 13.7, 6.4, 5.5 Hz, 1H), 1.74 (ddd, *J* = 13.6, 6.9, 5.5 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.06 , 144.55 , 140.04 , 137.98 , 134.25 , 129.19 , 128.45 , 126.11 , 118.09 , 44.49 , 41.21 , 36.03 , 33.41 , 23.03 , 21.90; IR (Neat Film NaCl) 3063, 3027, 2964, 2924, 1668, 1640, 1495, 1453, 1430, 1376, 1174, 1077, 996, 915, 749 cm^{-1}; $[\alpha]_D^{25.0}$ –200.23 (c 3.86, $CHCl_3$, 52% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1587, found 241.1575; JASCO SFC conditions: 3% MeOH in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.40, minor = 2.11.

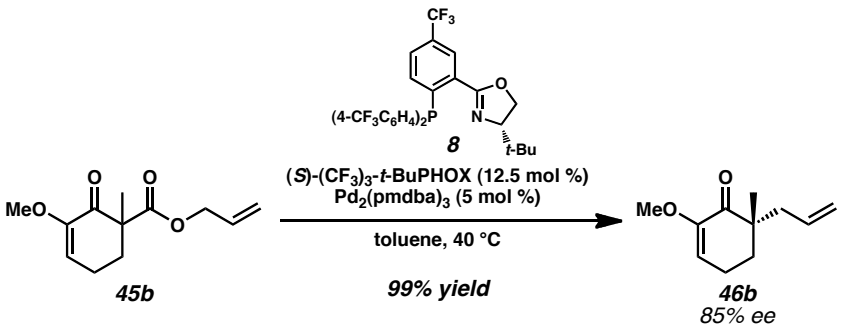


Enone 21d. Prepared from **13d** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 12 x 2 cm, 10→20% Et_2O in hexanes) to afford enone **13c** (17 mg, 67 μmol, 50% yield) as a colorless oil and recovered enone **13d** (8 mg, 20% recovered); R_f = 0.73 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.21 (m, 2H), 7.22–7.13 (m, 3H), 6.50 (t, *J* = 4.1 Hz, 1H), 5.74 (ddt, *J* = 16.8, 10.3, 7.4 Hz, 1H), 5.12–5.00 (m, 2H), 2.76–2.62 (m, 2H), 2.59–2.41 (m, 2H), 2.40–2.12 (m, 4H), 1.89 (ddd, *J* = 13.6, 6.7, 5.5 Hz, 1H), 1.72 (ddd, *J* = 13.6, 6.7, 5.5 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 144.2, 142.1, 137.4, 134.4, 128.7, 128.3, 125.9, 118.1, 44.4, 41.3, 35.2, 33.4, 32.4, 23.0, 22.0; IR (Neat Film NaCl) 3062, 3026, 2962, 2924, 2855, 1669, 1639, 1496, 1453, 1430, 1377, 1175, 1078, 995, 914, 747 cm^{-1}; $[\alpha]_D^{25.0}$ –32.55 (c 1.24, $CHCl_3$, 68% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{23}O$ $[M+H]^+$: 255.1743, found 255.1730; JASCO SFC conditions: 3% MeOH in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.41, minor = 2.17.



Diosphenol ether 46a. $Pd_2(pmdba)_3$ (4.2 mg, 3.8 μmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 5.7 mg, 9.6 μmol, 12.5 mol %) were added to an oven-dried 2-dram vial equipped with a magnetic stir bar in a glove box. The vial was charged with toluene (1.8 mL) and stirred at ambient temperature (28 °C) for 30 min, resulting in a deep orange solution. β-ketoester **45a** (23 mg, 77 μmol, 1.0 equiv) was transferred to the scintillation vial with toluene (0.5 mL, total = 2.3 mL, 0.033 M), producing a light green solution. The vial was sealed with a Teflon-lined cap and lowered into a heating block (40 °C). After 6 days, the reaction was complete by TLC and colorimetric analysis (the reaction mixture had reverted to an orange color) and was removed from the glove box. The reaction was filtered through a silica gel plug, rinsed with Et_2O, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 15 x 1.5 cm, 5%→10% Et_2O in hexanes) to afford diosphenol ether **46a** (18 mg, 70 μmol, 92% yield) as a colorless oil; R_f = 0.56 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.83 (t, *J* = 4.5 Hz, 1H), 5.74 (ddt, *J* = 16.7, 10.3, 7.4 Hz, 1H), 5.12–5.03 (m, 2H), 4.85 (s, 2H), 2.42–2.33 (m, 3H), 2.21 (ddt, *J* = 13.8, 7.6, 1.2 Hz, 1H), 1.89 (ddd, *J* = 13.7, 6.7, 5.6 Hz, 1H), 1.71 (ddd, *J* = 13.7, 6.6, 5.4 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 149.0, 136.8, 134.1, 128.6, 127.9, 127.4, 118.4, 118.0, 70.0, 45.4, 41.2, 33.1, 21.9, 20.9; IR (Neat Film NaCl) 2918, 2360, 1684,

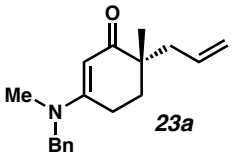
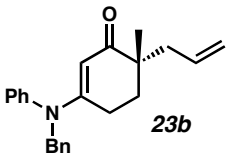
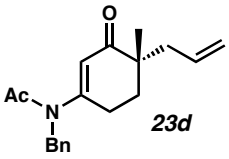
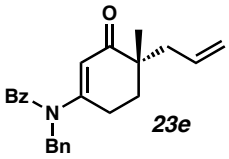
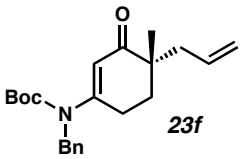
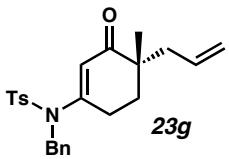
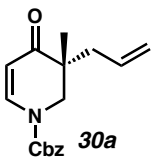
1628, 1457, 1220, 1204, 1094, 1050, 914, 736 cm^{-1}; $[\alpha]_D^{25.0}$ –12.01 (c 0.50, $CHCl_3$, 94% ee); HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{21}O_2$ $[M+H]^+$: 257.1536, found 257.1529; HPLC conditions: 7% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 7.24, minor = 8.27.

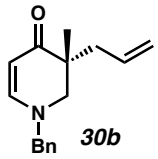
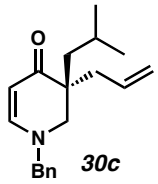
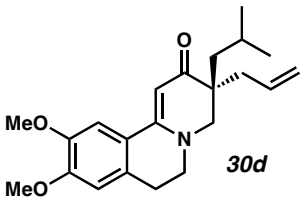
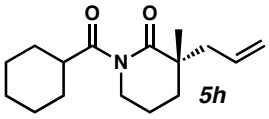
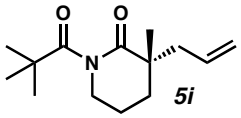
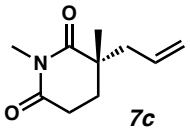
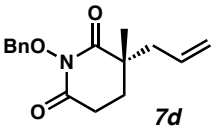
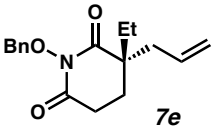


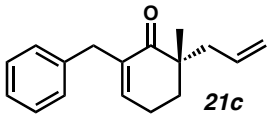
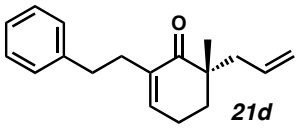
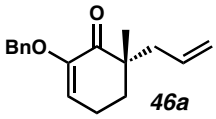
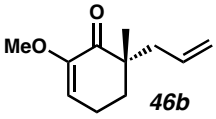
Diosphenol ether 46b. Prepared from **45b** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 10 x 3 cm, 5→10% Et_2O in hexanes) to afford diosphenol ether **45b** (111 mg, 0.616 mmol, 99% yield) as a colorless oil; R_f = 0.23 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.79–5.65 (m, 2H), 5.12–5.01 (m, 2H), 3.58 (s, 3H), 2.47–2.34 (m, 3H), 2.20 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 1.91 (ddd, *J* = 13.7, 6.8, 5.5 Hz, 1H), 1.72 (ddd, *J* = 13.7, 6.5, 5.4 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 150.0, 134.0, 118.4, 114.5, 55.1, 45.4, 41.2, 33.2, 21.9, 20.8; IR (Neat Film NaCl) 2929, 1687, 1631, 1455, 1375, 1225, 1095, 1056, 913 cm^{-1}; $[\alpha]_D^{25.0}$ –27.47 (c 6.00, $CHCl_3$, 85% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1223, found 181.1222; HPLC conditions: 2% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 13.41, minor = 12.23.

1.4.2.7 Determination of Enantiomeric Excess

Table 1.5. Methods for the determination of enantiomeric excess (chiral HPLC and SFC).

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 *23a*	SFC Chiralcel OD-H 5% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	10.45	9.60	81
2	 *23b*	SFC Chiralpak AS-H 5% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	8.60	6.48	83
3	 *23d*	SFC Chiralpak AD-H 5% MeOH in CO_2 isocratic, 3.0 mL/min 254 nm	8.45	10.35	86
4	 *23e*	SFC Chiralpak AD-H 7% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	8.04	8.97	87
5	 *23f*	SFC Chiralpak AD-H 7% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	4.04	2.20	82
6	 *23g*	SFC Chiralpak AD-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	5.60	4.73	84
7	 *30a*	SFC Chiralpak AD-H 10% MeOH in CO_2 isocratic, 3.0 mL/min 254 nm	2.80	3.13	84

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
8	 *30b*	HPLC Chiralcel OJ 10% IPA in hexanes isocratic, 1.0 mL/min 210 nm	18.77	21.21	86
9	 *30c*	HPLC Chiralcel OJ 7% IPA in hexanes isocratic, 1.0 mL/min 210 nm	11.44	14.80	88
10	 *30d*	HPLC Chiralpak AD 30% IPA in hexanes isocratic, 1.0 mL/min 254 nm	21.87	18.59	90
11	 *5h*	SFC Chiralcel OJ-H 1% IPA in CO_2 isocratic, 5.0 mL/min 222 nm	2.53	2.13	95
12	 *5i*	HPLC Chiralcel OD-H 5% IPA in hexanes isocratic, 1.0 mL/min 210 nm	7.95	6.52	96
13	 *7c*	HPLC Chiralpak AD 3% IPA in hexanes isocratic, 1.0 mL/min 210 nm	11.94	17.86	76
14	 *7d*	SFC Chiralcel OJ-H 1% MeOH in CO_2 isocratic, 3.0 mL/min 210 nm	4.03	3.64	96
15	 *7e*	SFC Chiralcel OB-H 1% MeOH in CO_2 isocratic, 2.5 mL/min 210 nm	14.34	13.39	98

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
16	 ***21c***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	2.40	2.11	52
17	 ***21d***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	2.41	2.17	68
18	 ***46a***	HPLC Chiralcel OD-H 7% IPA in hexanes isocratic, 1.0 mL/min 254 nm	7.24	8.27	94
19	 ***46b***	HPLC Chiralcel OD-H 2% IPA in hexanes isocratic, 1.0 mL/min 254 nm	13.41	12.23	85

1.5 NOTES AND REFERENCE

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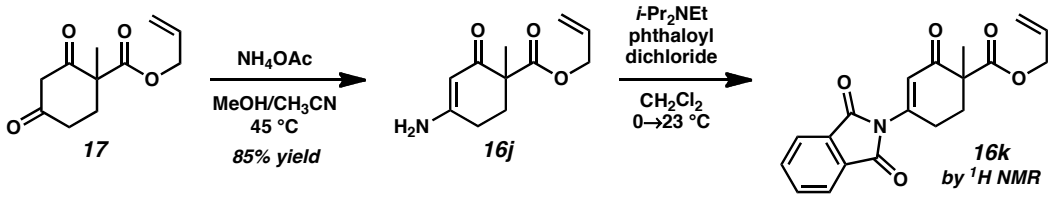
23a). ^{1}H NMR analysis suggests that the product was formed, but enaminone **16k** was not pursued further due to the results of the initial enaminone screen. See: Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, III , J. D. *J. Am. Chem. Soc.* **2009**, *131*, 8798–8804.



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(33) As mentioned previously, the corresponding electron-rich lactams (*N*-substituent = Me or Bn) exhibit little to no conversion to the desired products.

(34) For example, selectivities for lactam **5a** vary from 99% ee with (*S*)-**8** to 86% ee with (*S*)-**3** in toluene and to 96% ee with (*S*)-**8** in THF (Table 1.1).

(35) The distinction between *N*-substituents is most apparent when comparing benzoyl and tosyl lactams, which vary by ~40–80% ee depending on the conditions (see Table 1.1).

(36) Employing optimized conditions with (*S*)-**3** in Et_2O, enone **21a** has been isolated in 90% ee. See ref. 6b.

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(42) Interestingly, both groups found that Trost ligands failed to provide the desired α-quaternary products.

(43) The increase in steric bulk for substrates **4i** and **j** slows the reaction dramatically. Imide **7c** is also hampered by low reactivity. As such, these reactions with these substrates are often not run to completion and consequently have lower yields. See experimental section.

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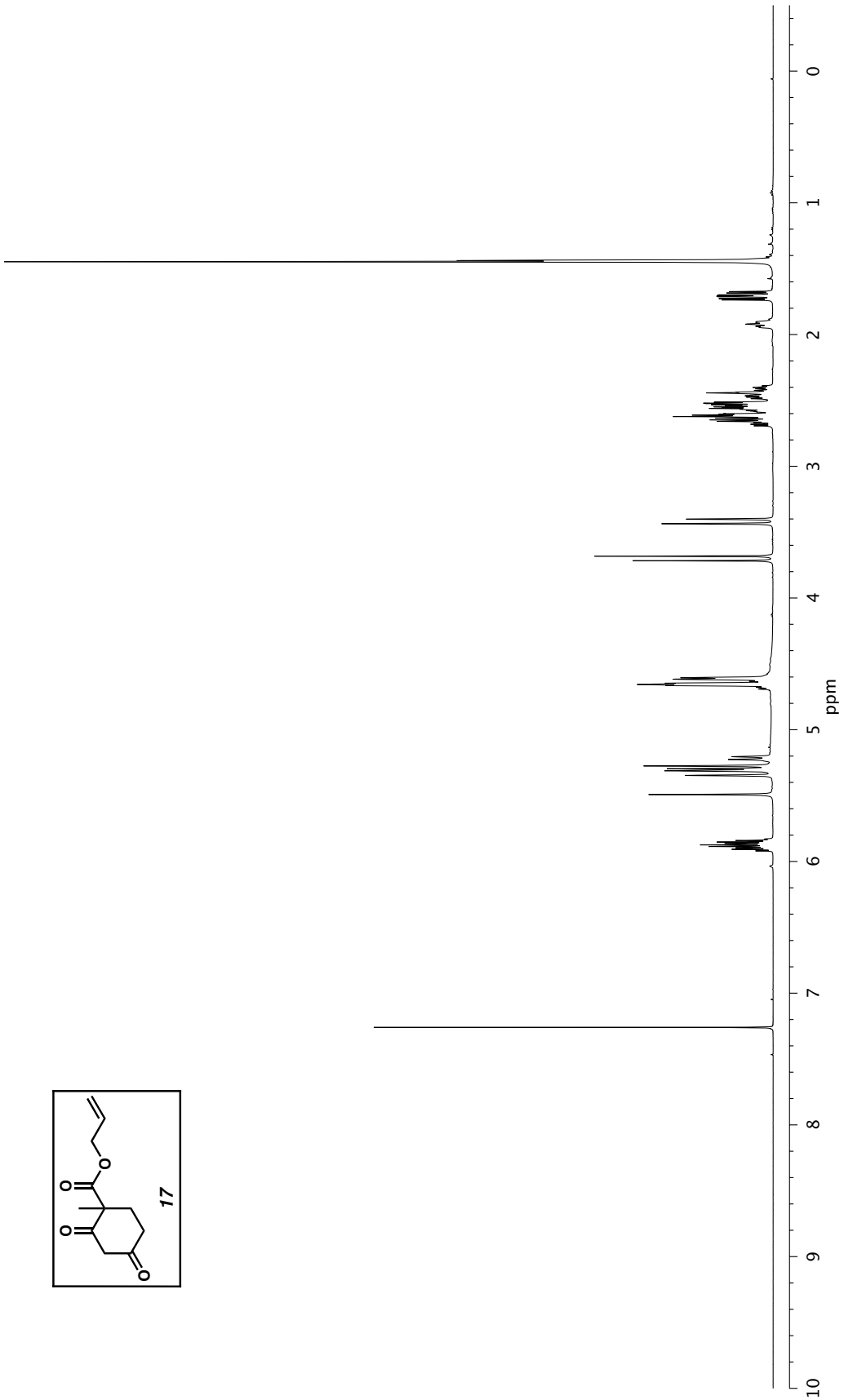
APPENDIX 1

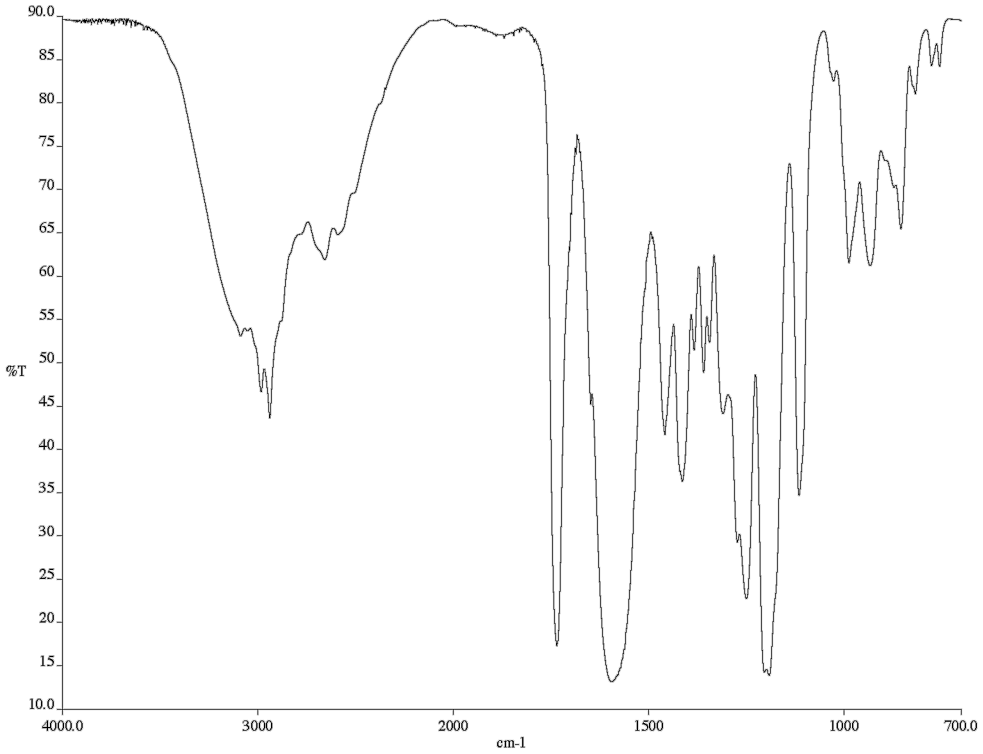
Spectra Relevant to Chapter 1:

Expanding Insight into the Asymmetric Palladium-Catalyzed

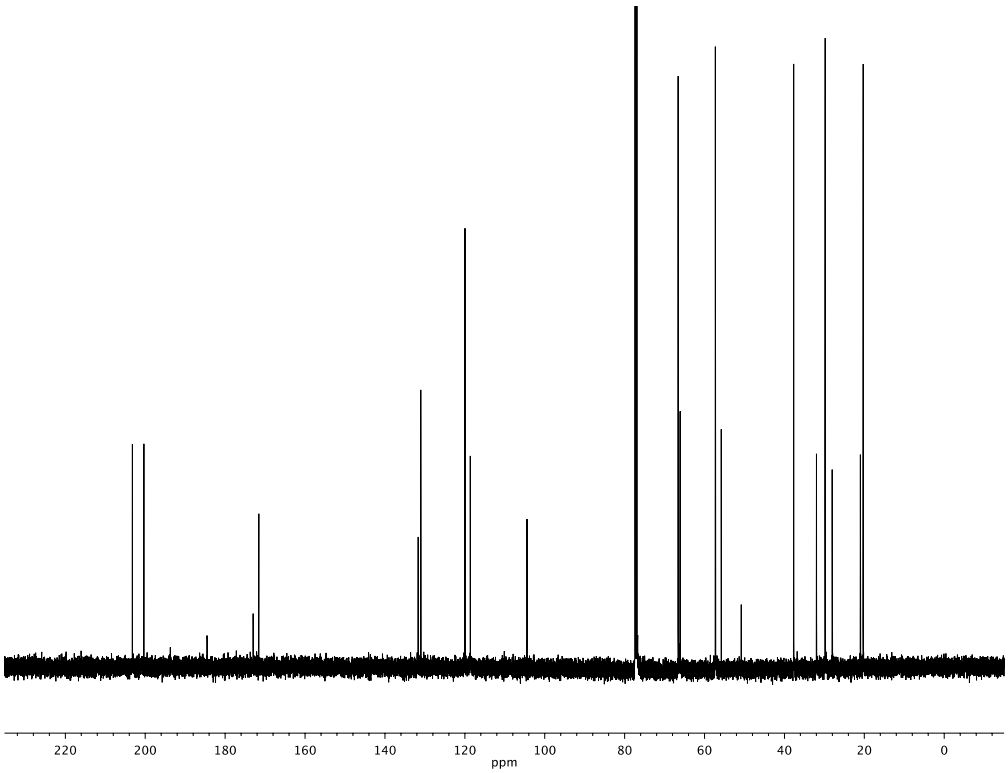
Allylic Alkylation of N-Heterocyclic Molecules and Cyclic Ketones



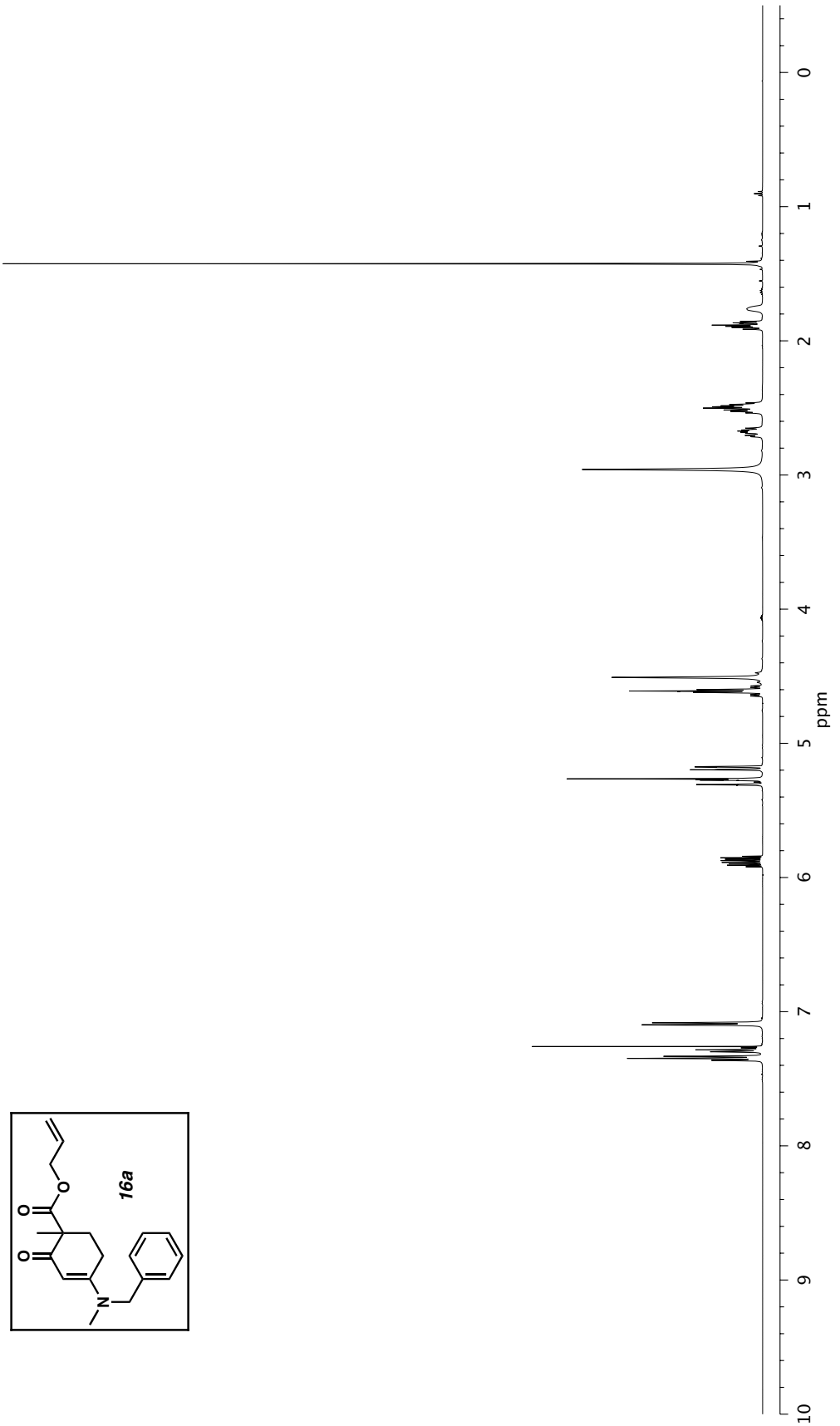
^{1}H NMR (500 MHz, $CDCl_3$) of compound **17**.



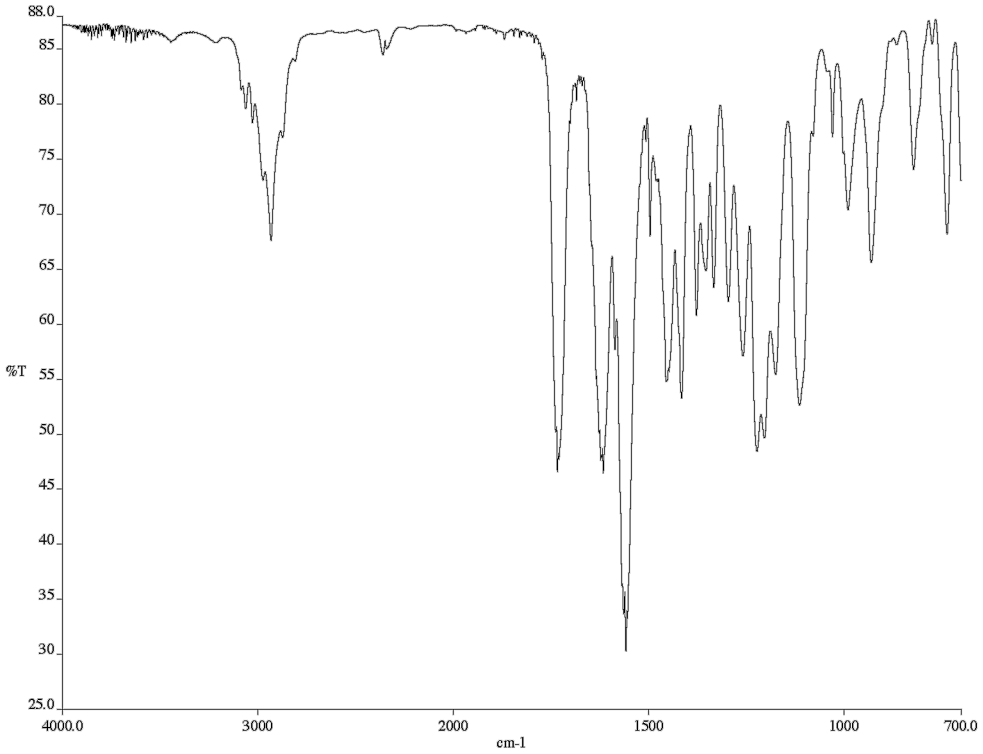
Infrared spectrum (thin film/NaCl) of compound **17**.



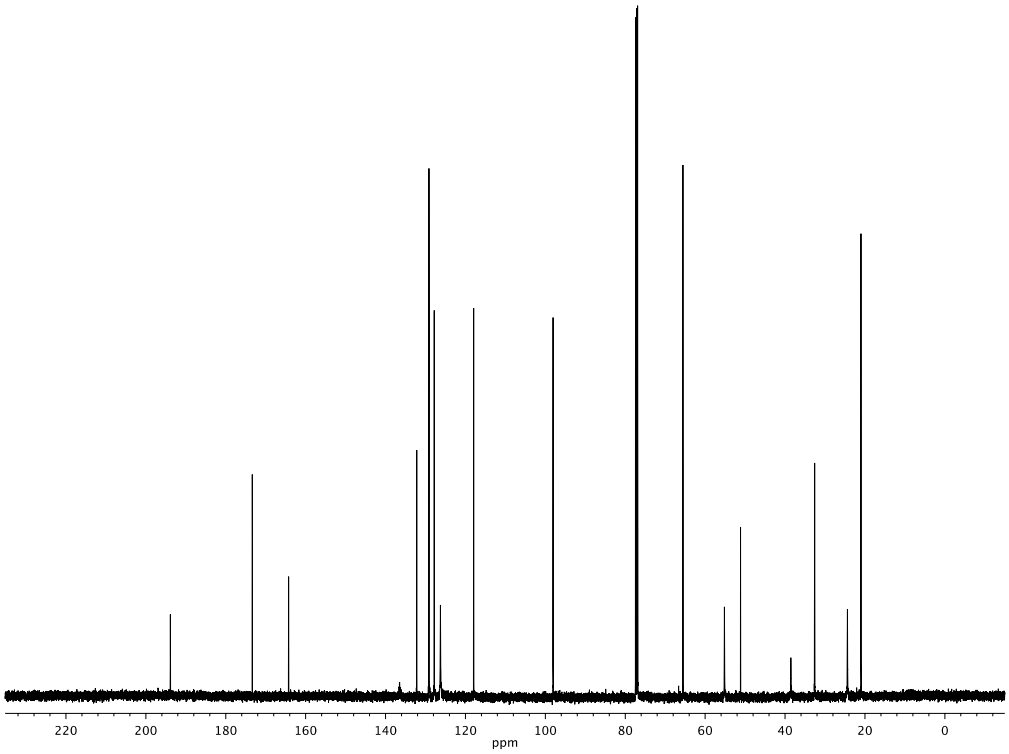
^{13}C NMR (125 MHz, $CDCl_3$) of compound **17**.



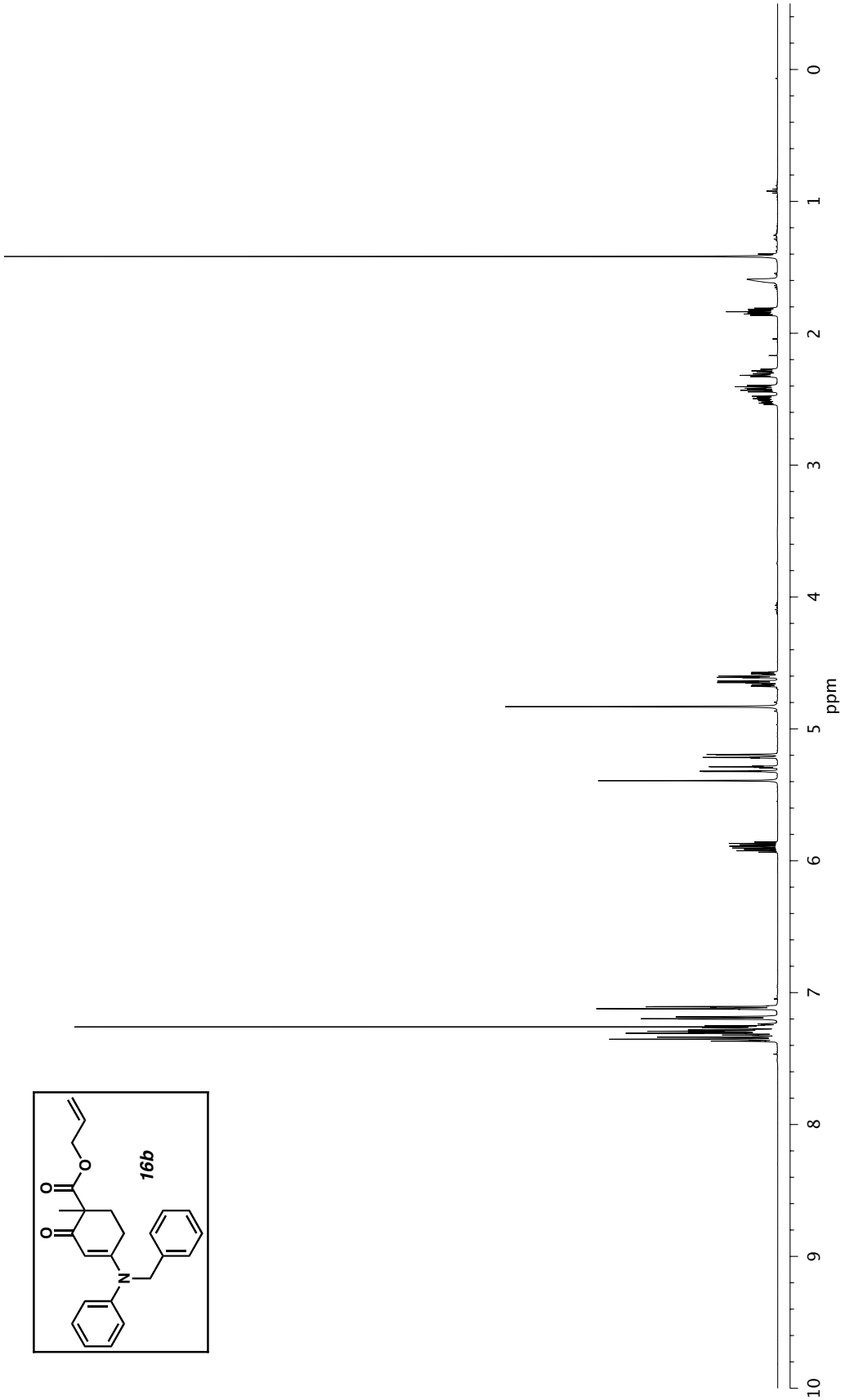
H NMR (500 MHz, $CDCl_3$) of compound **16a**.



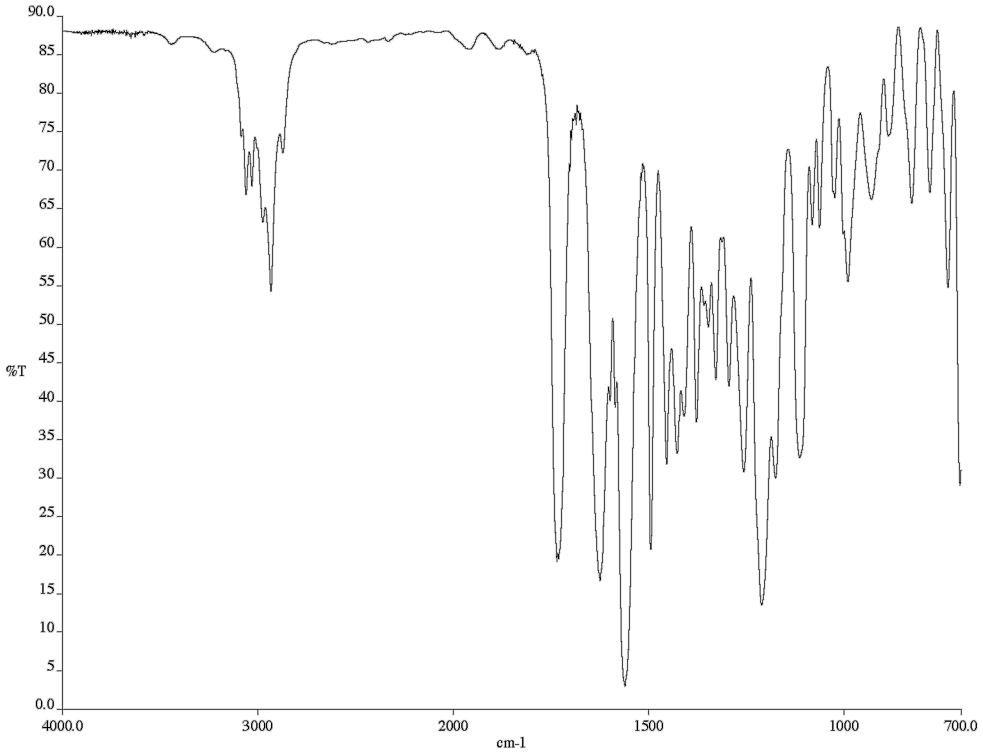
Infrared spectrum (thin film/NaCl) of compound **16a**.



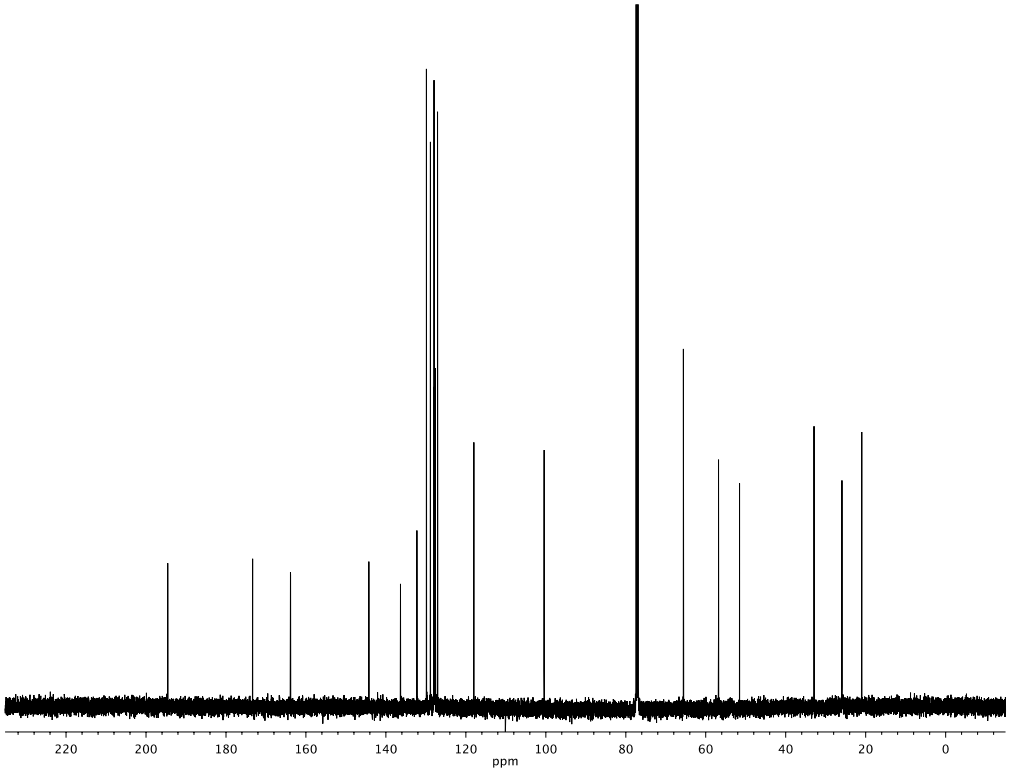
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16a**.



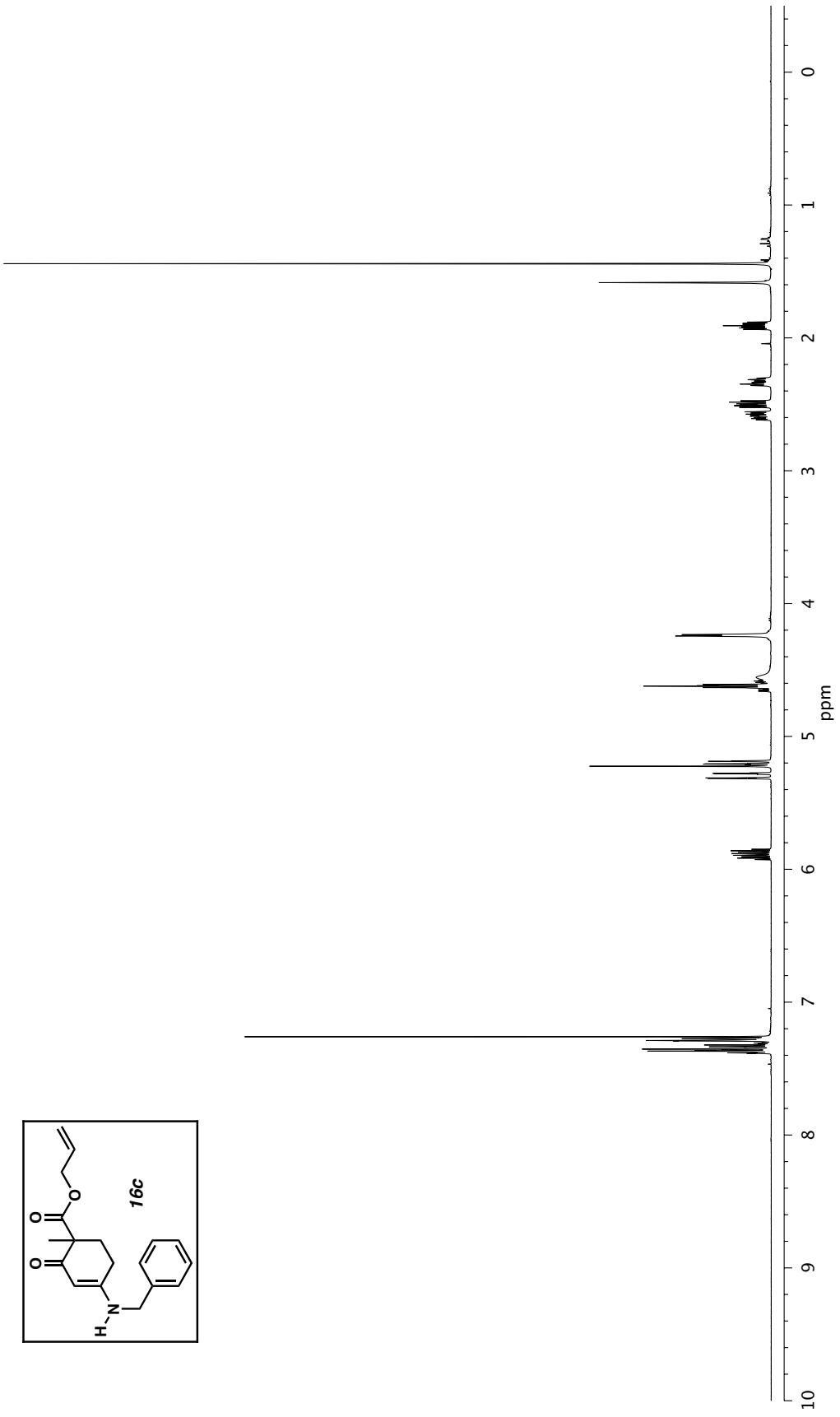
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16b**.



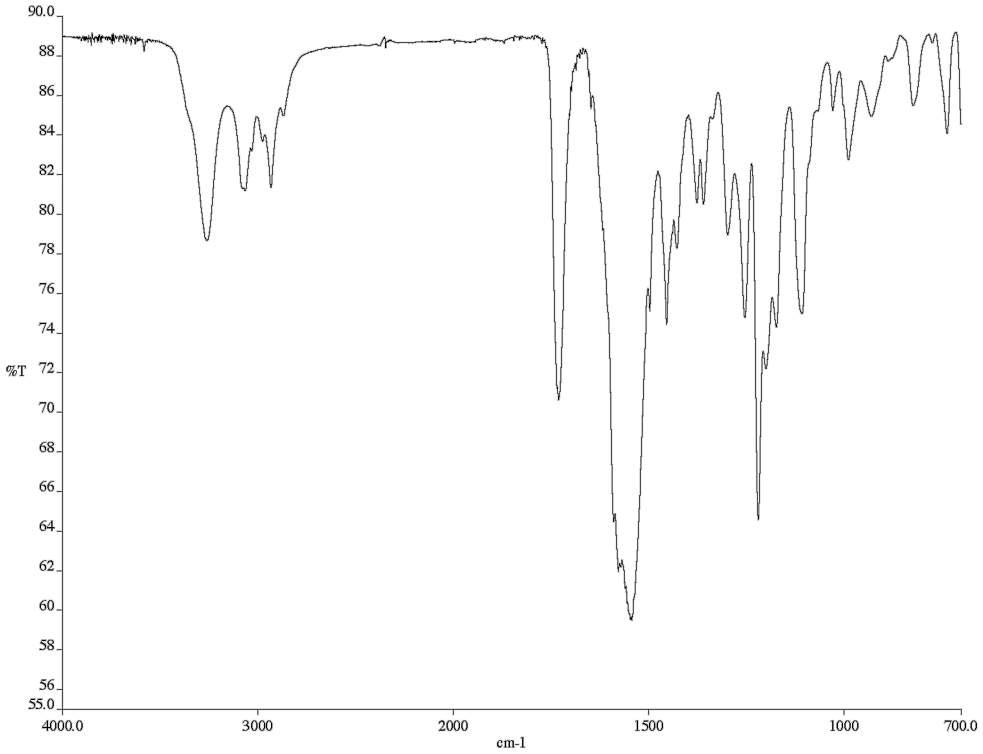
Infrared spectrum (thin film/NaCl) of compound **16b**.



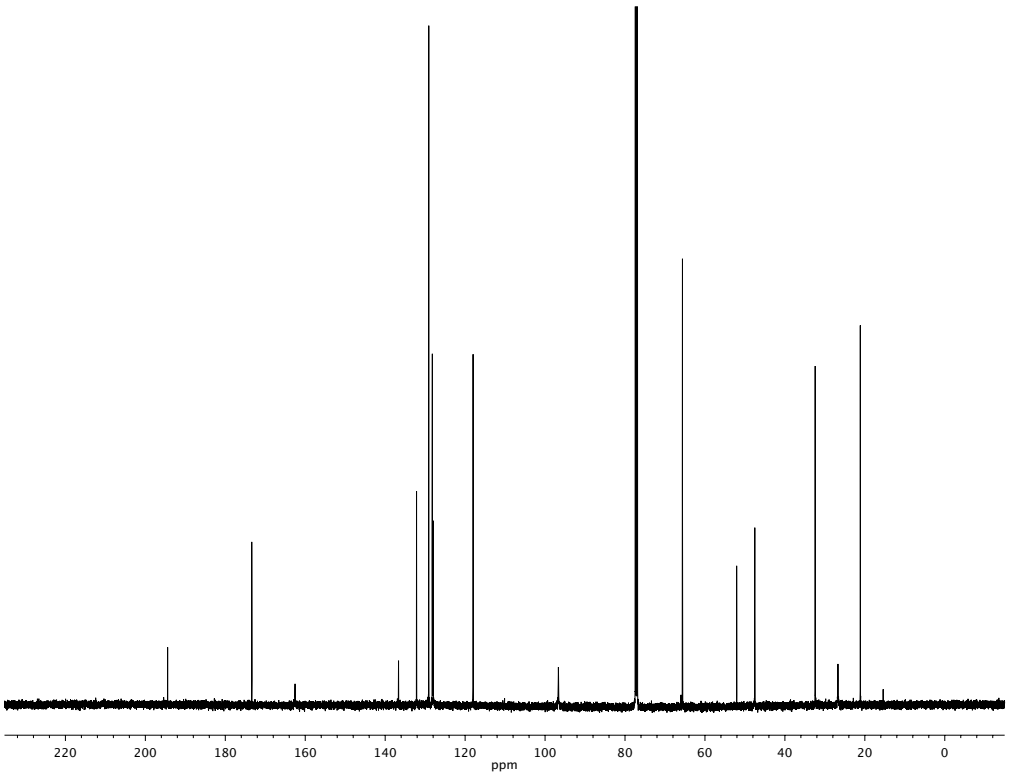
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16b**.



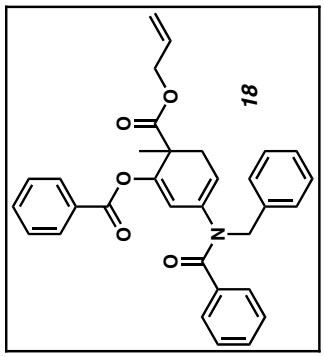
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16c**.



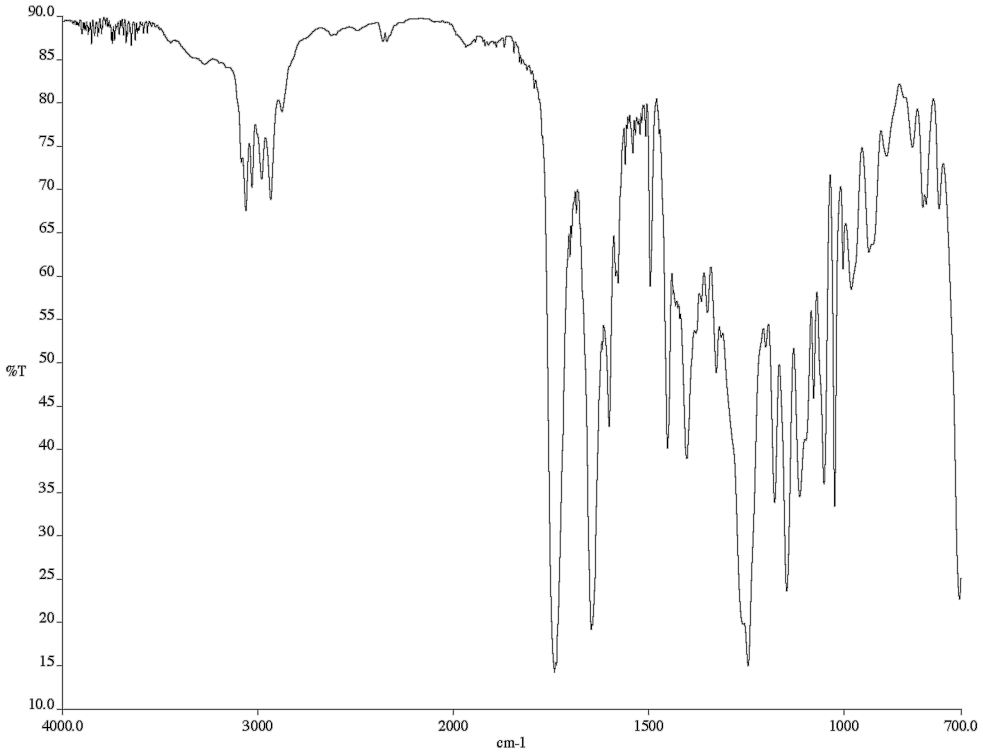
Infrared spectrum (thin film/NaCl) of compound **16c**.



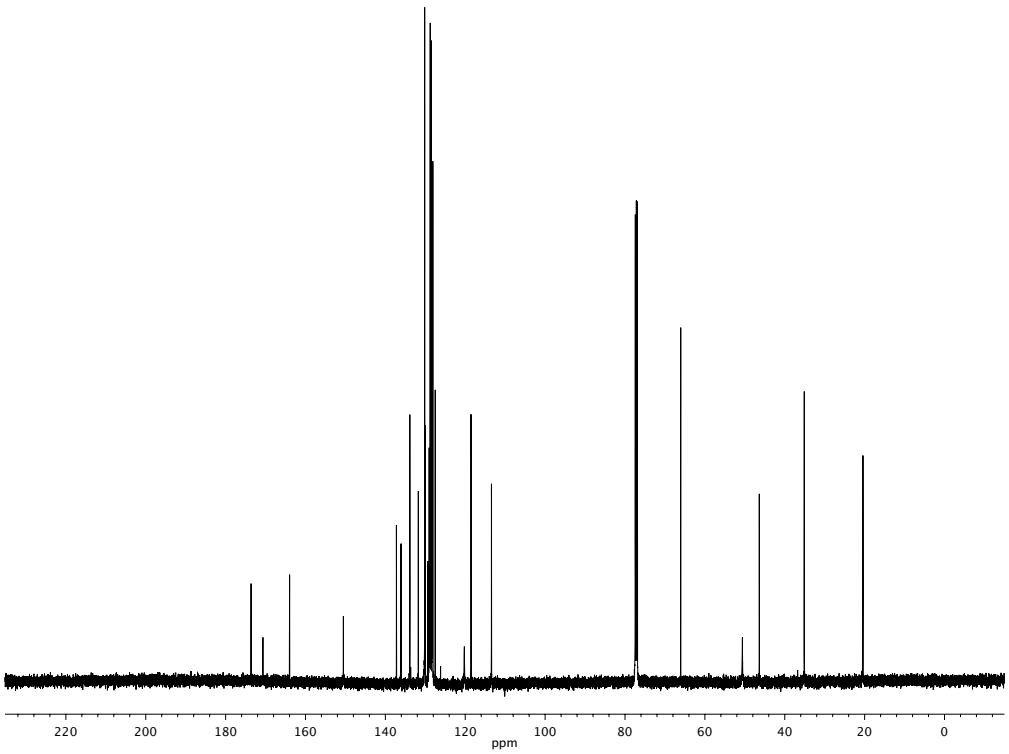
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16c**.



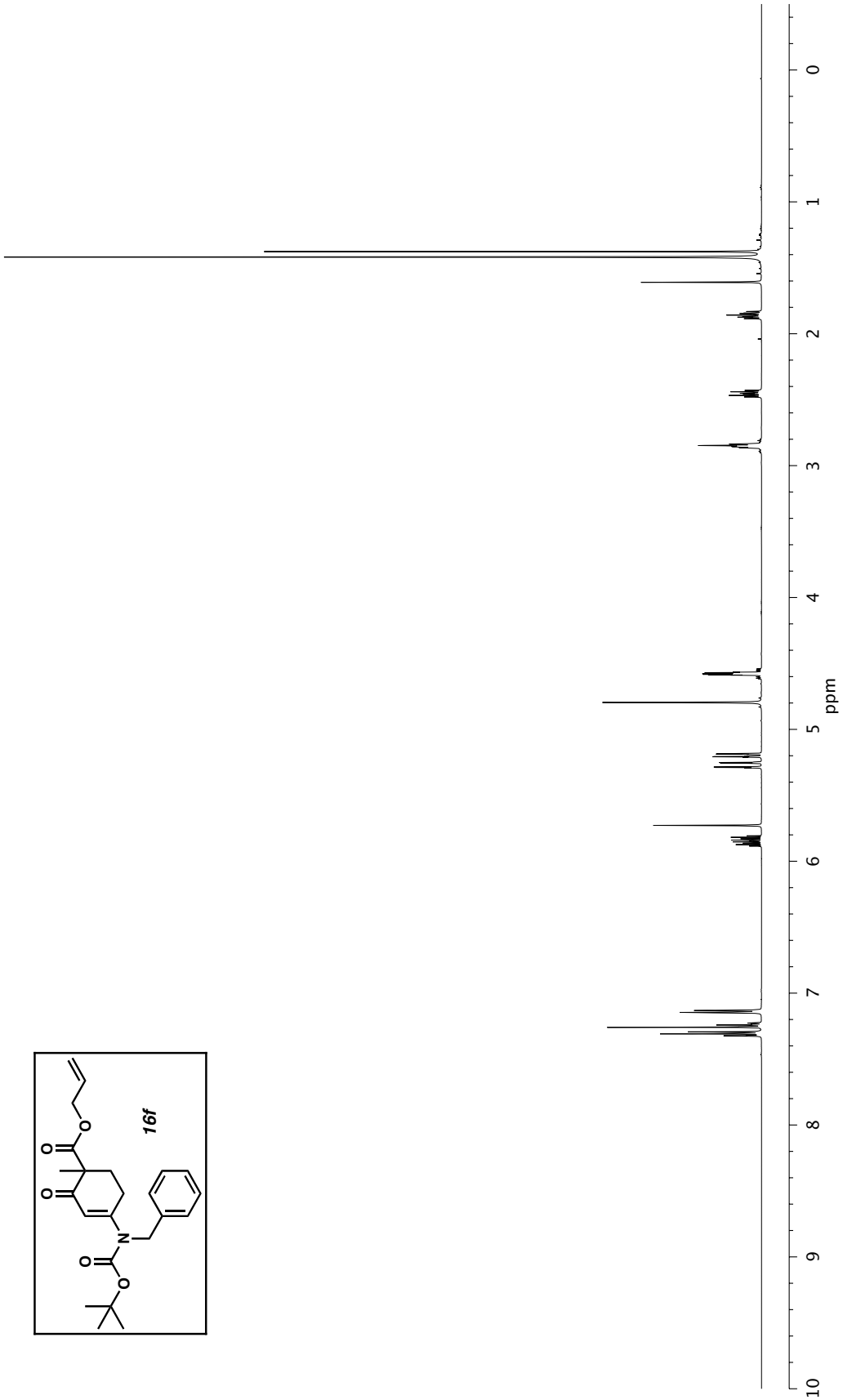
^{1}H NMR (500 MHz, $CDCl_3$) of compound **18**.



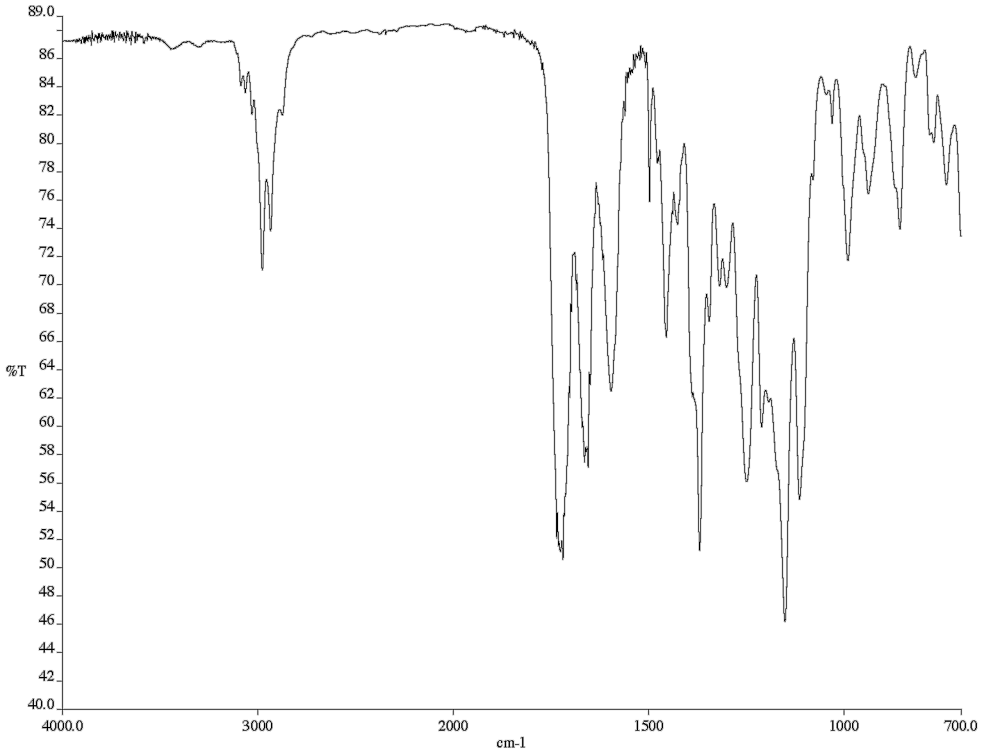
Infrared spectrum (thin film/NaCl) of compound **18**.



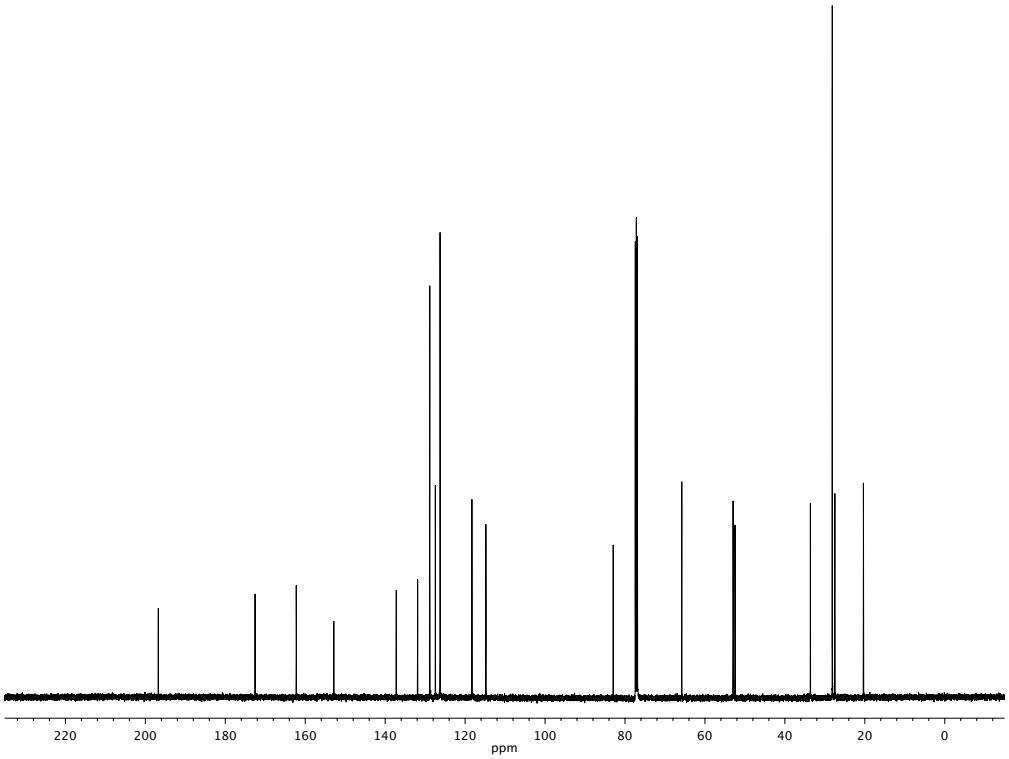
^{13}C NMR (125 MHz, $CDCl_3$) of compound **18**.



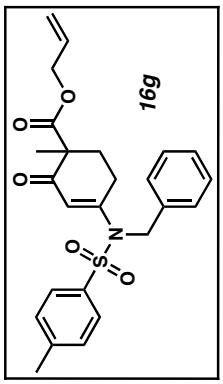
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16f**.

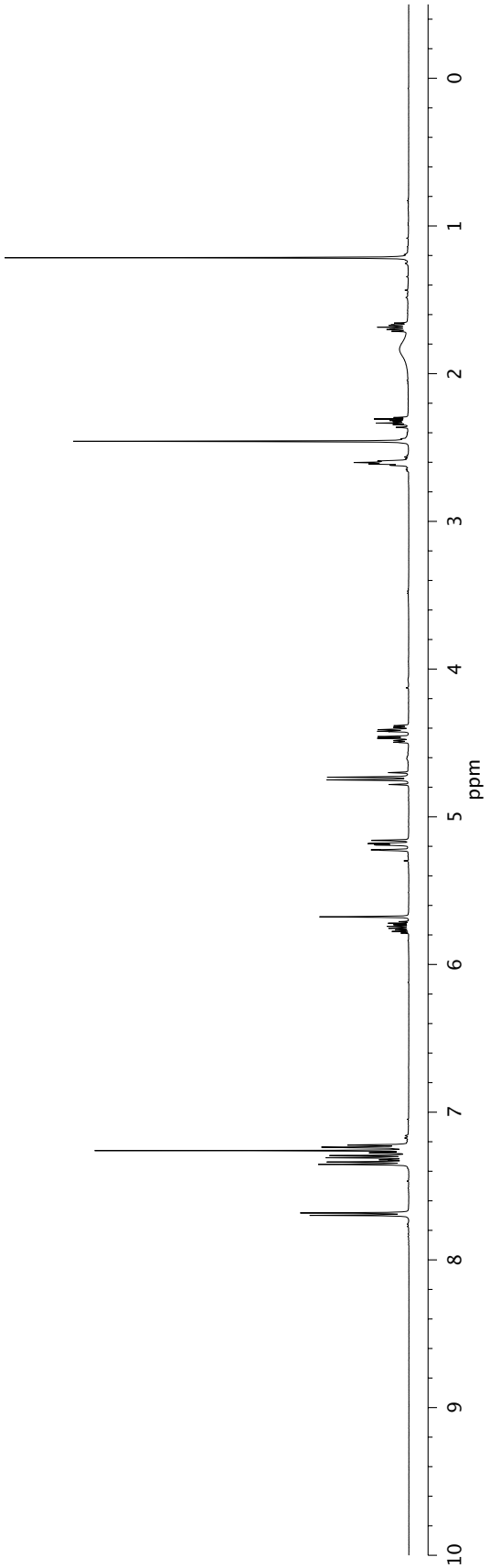


Infrared spectrum (thin film/NaCl) of compound **16f**.

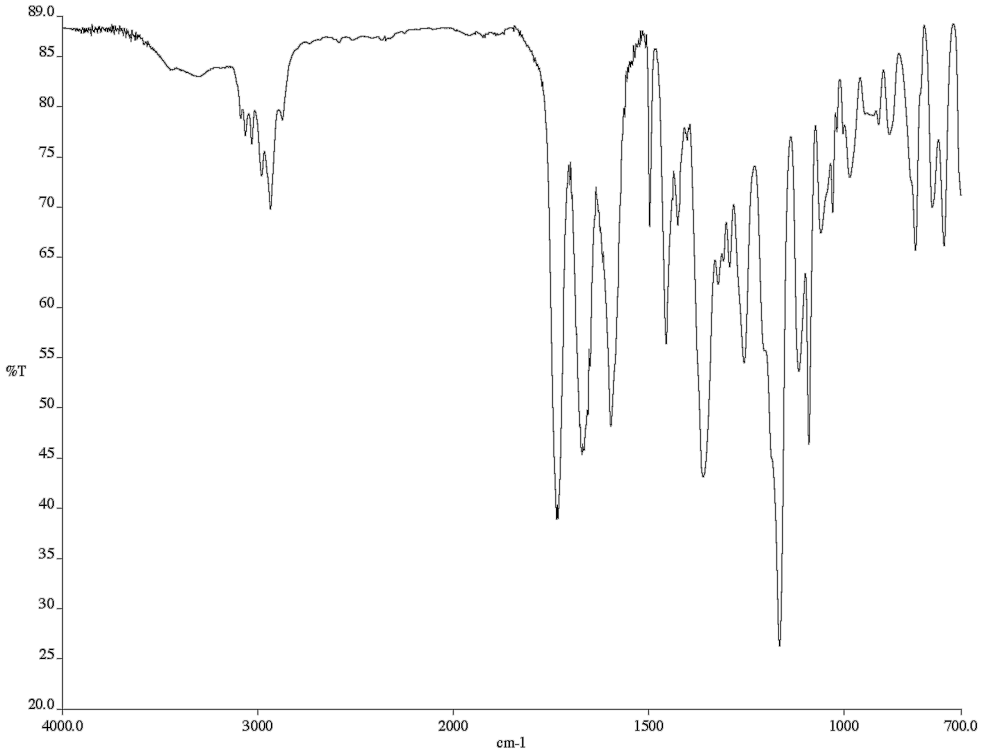


^{13}C NMR (125 MHz, $CDCl_3$) of compound **16f**.

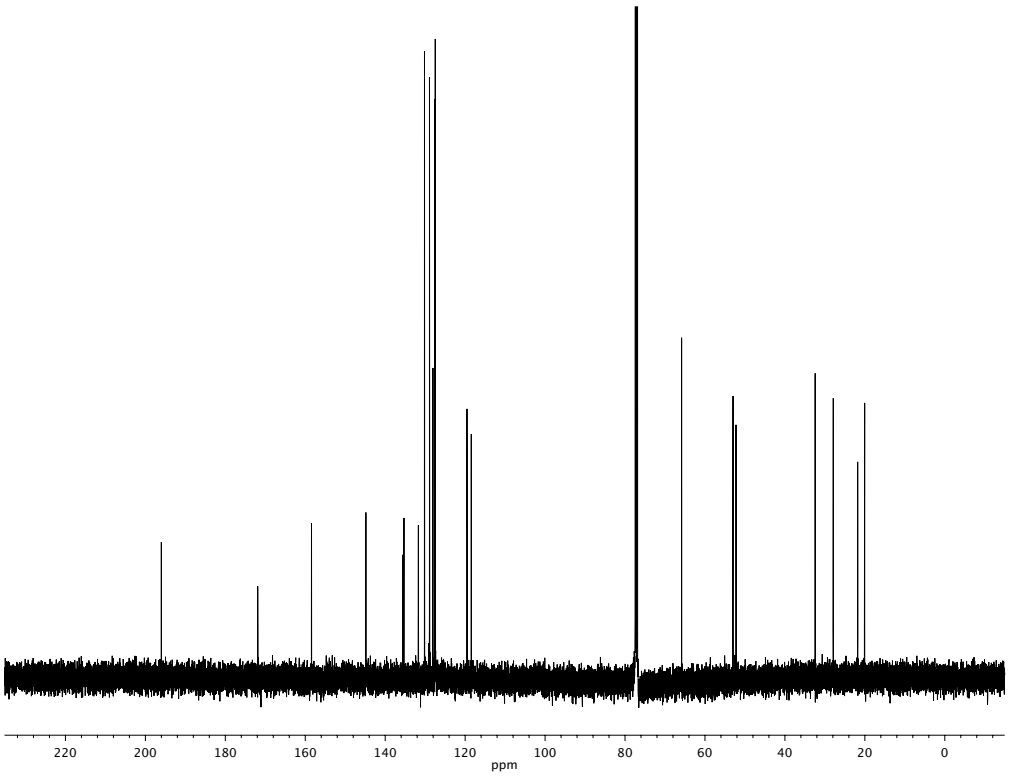




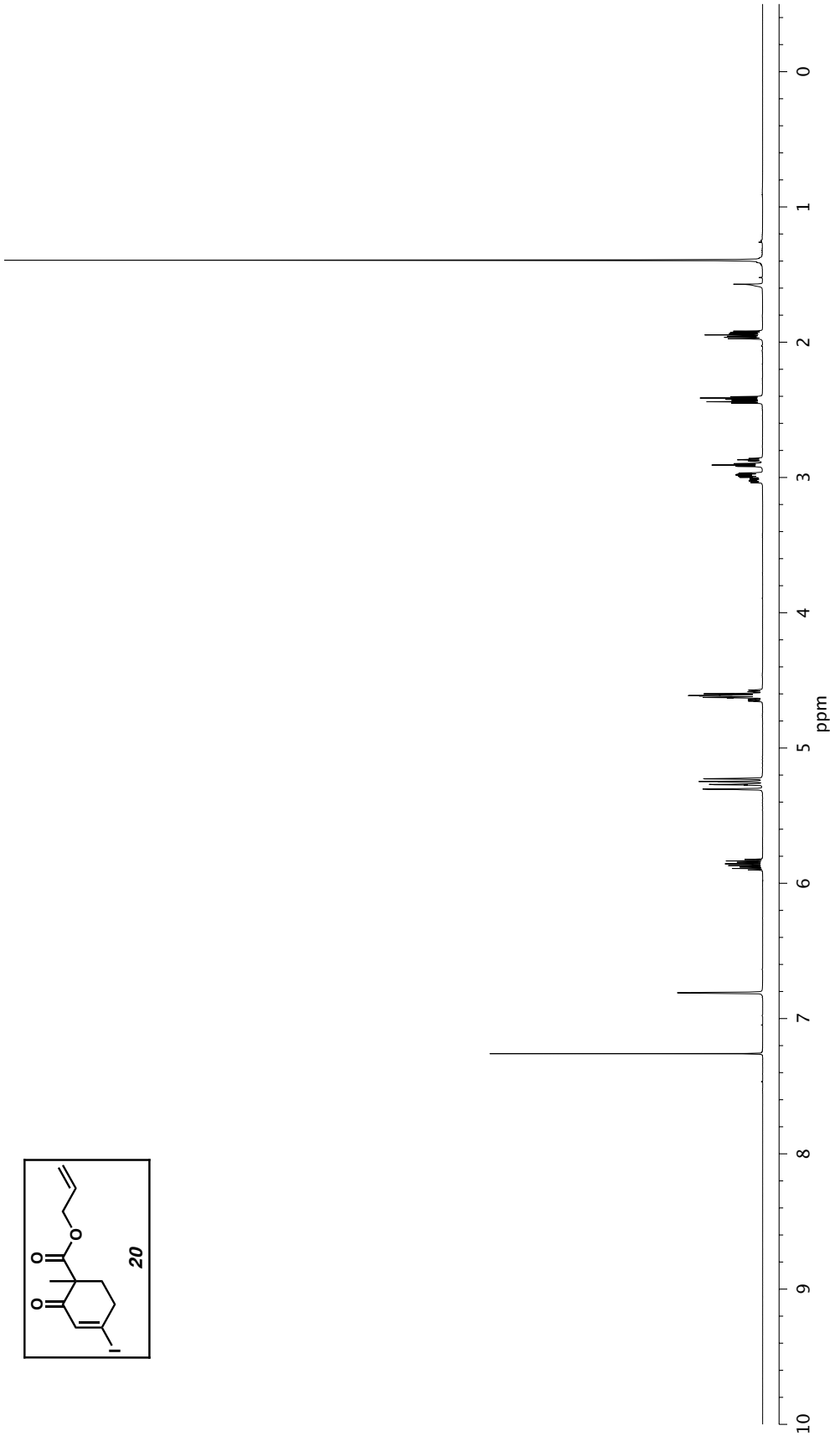
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16g**.



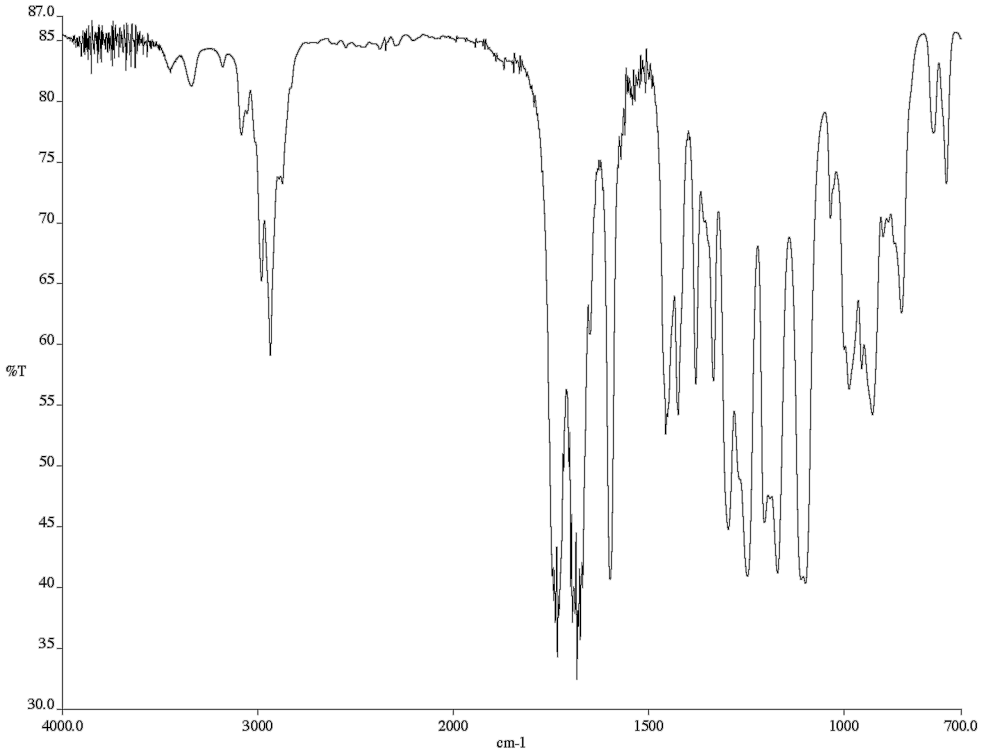
Infrared spectrum (thin film/NaCl) of compound **16g**.



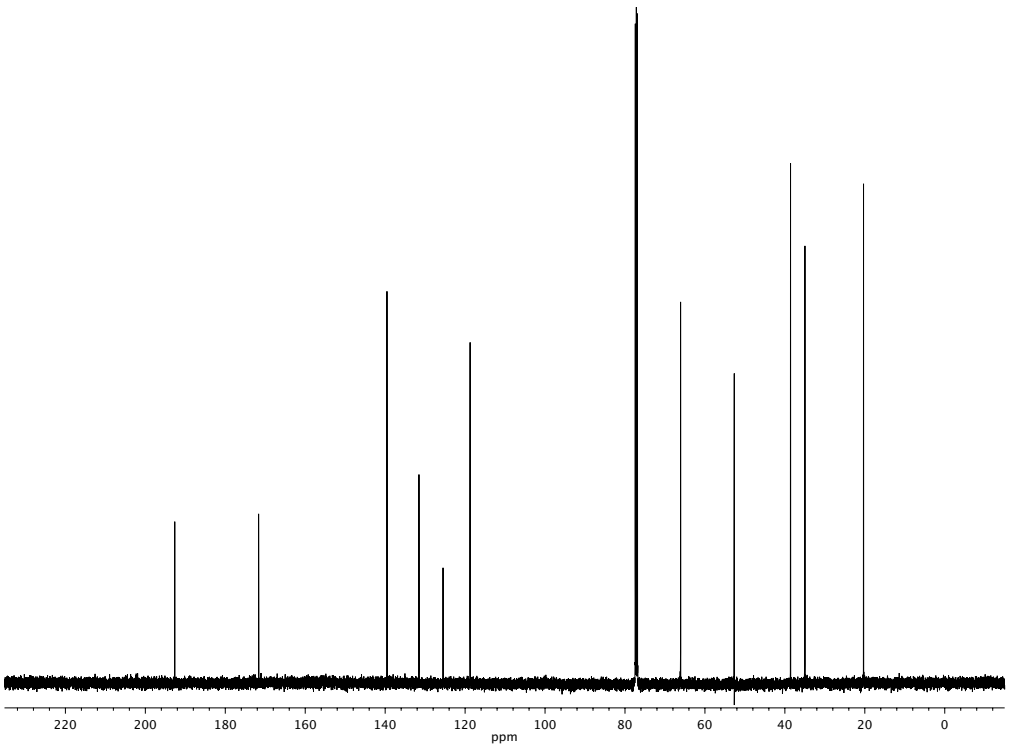
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16g**.



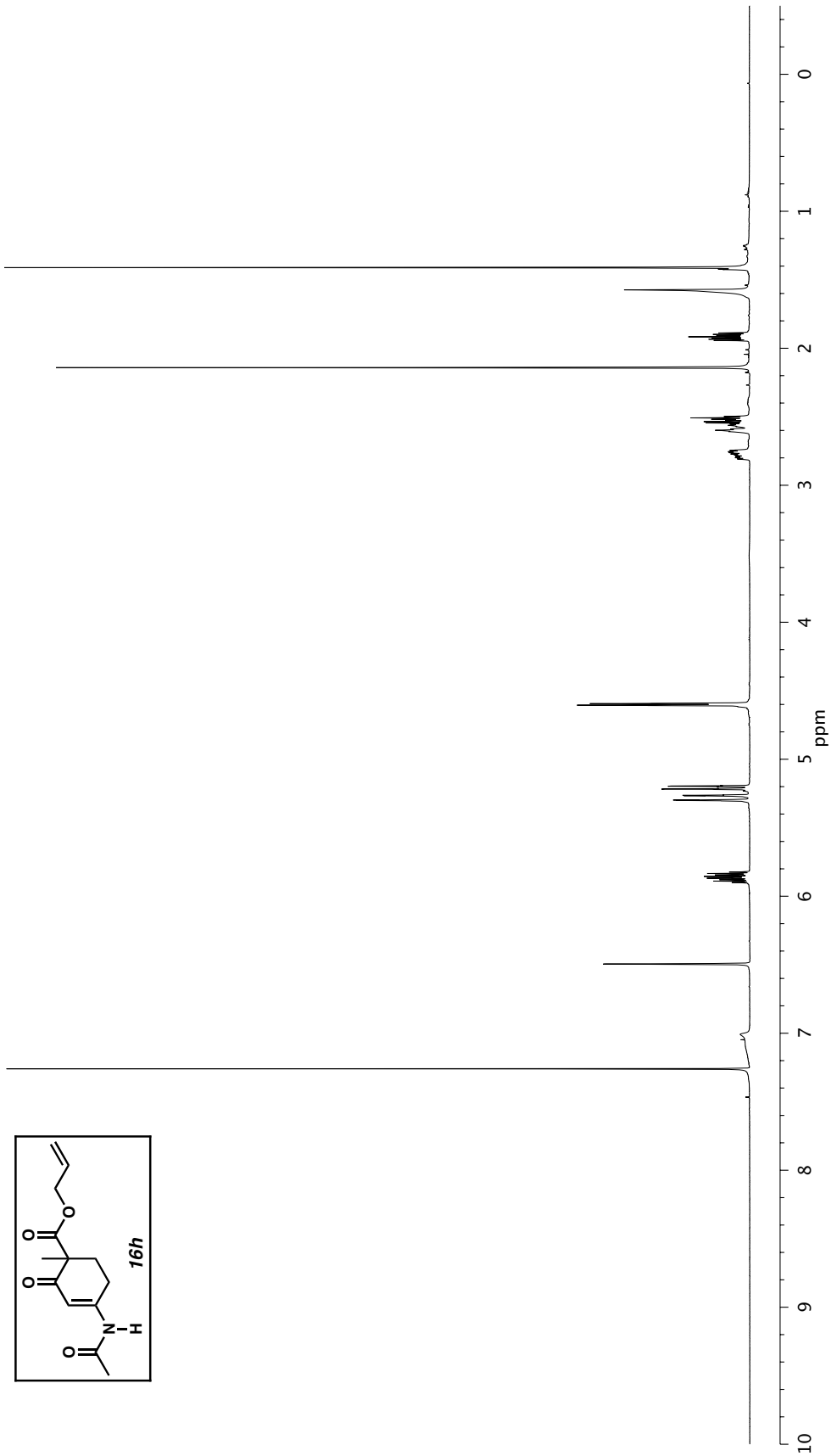
^{1}H NMR (500 MHz, $CDCl_3$) of compound **20**.



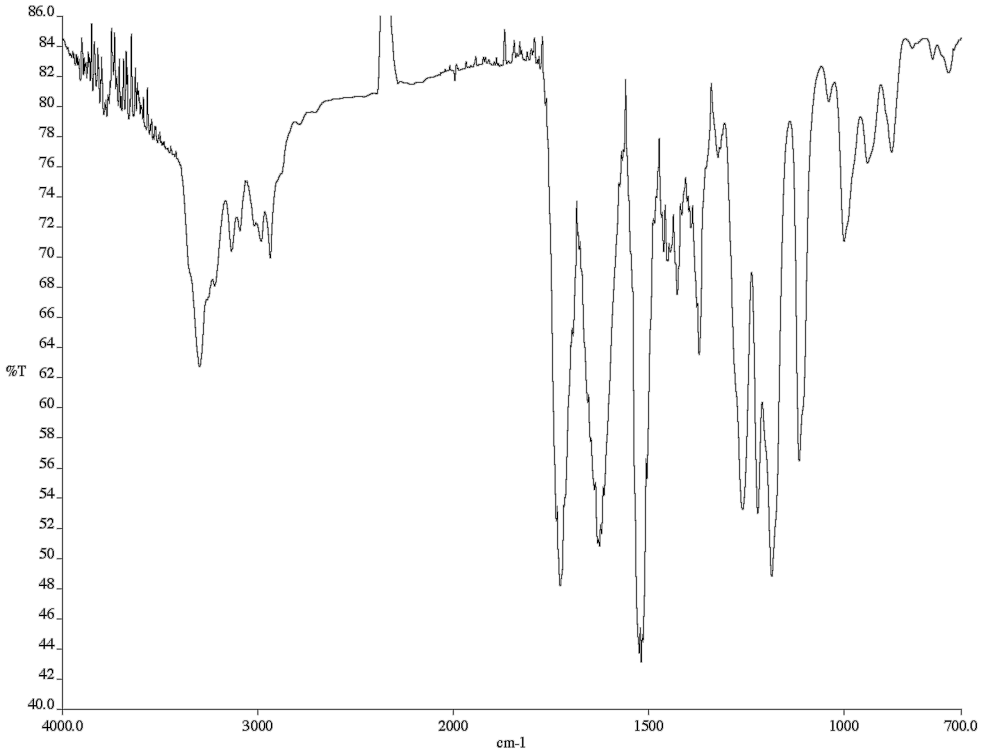
Infrared spectrum (thin film/NaCl) of compound **20**.



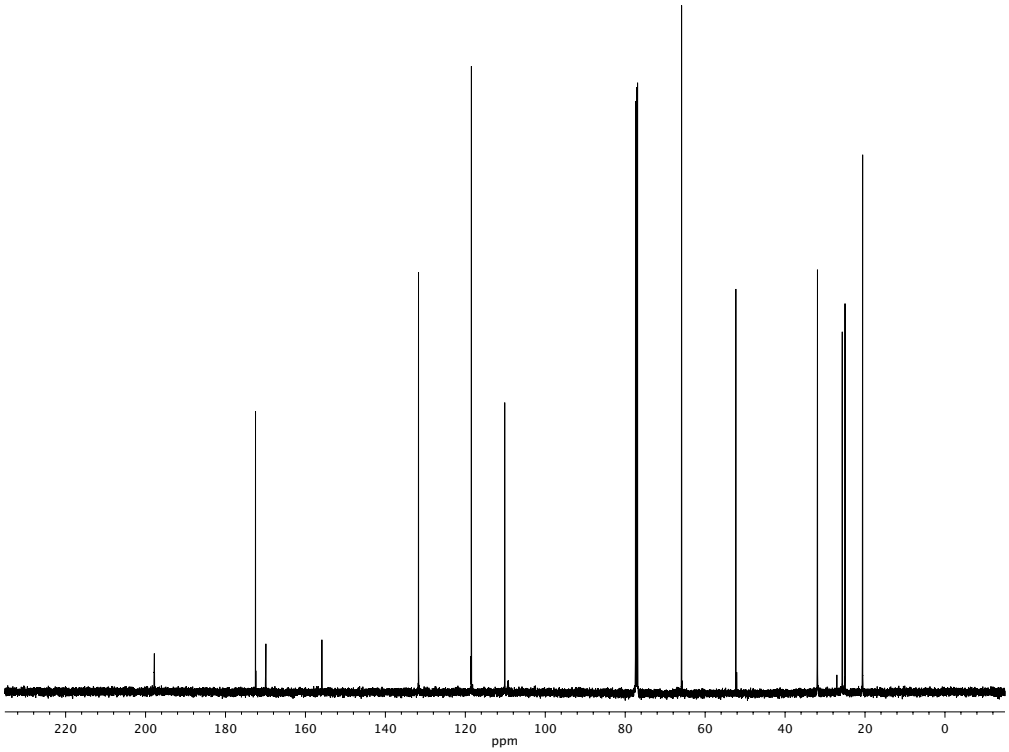
^{13}C NMR (125 MHz, $CDCl_3$) of compound **20**.



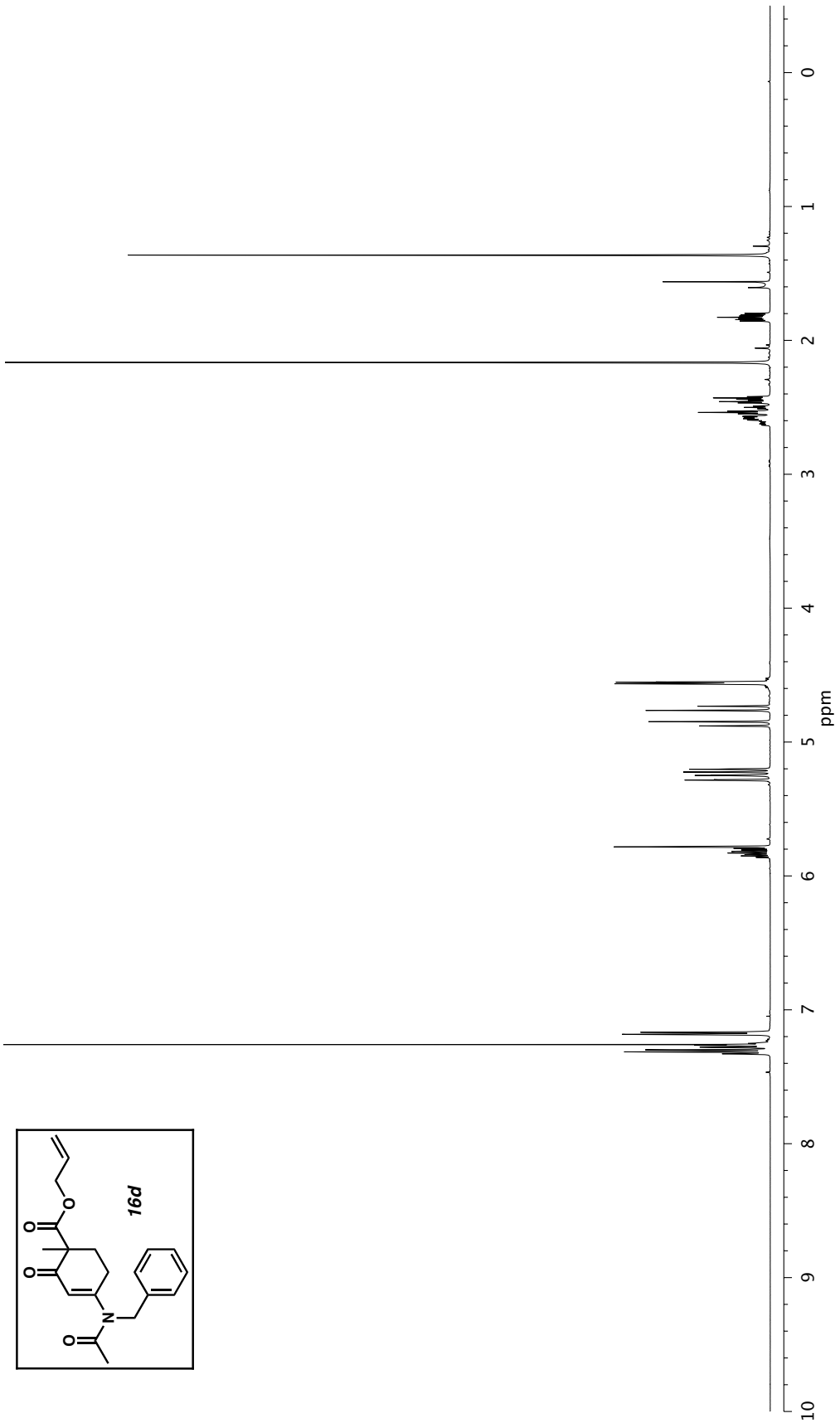
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16h**.



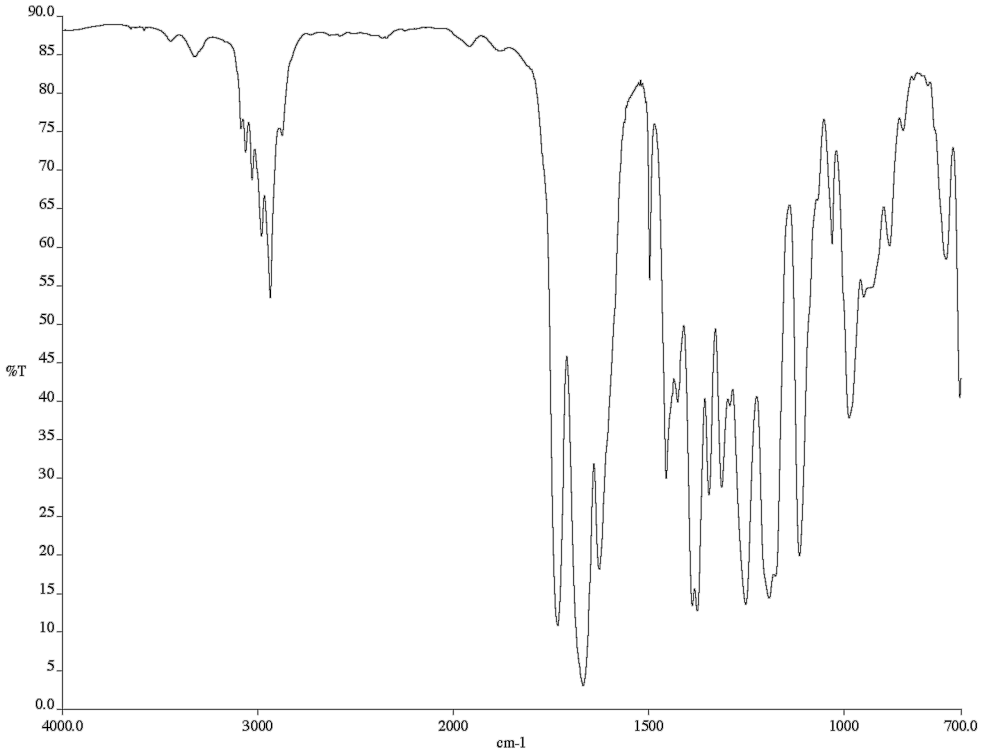
Infrared spectrum (thin film/NaCl) of compound **16h**.



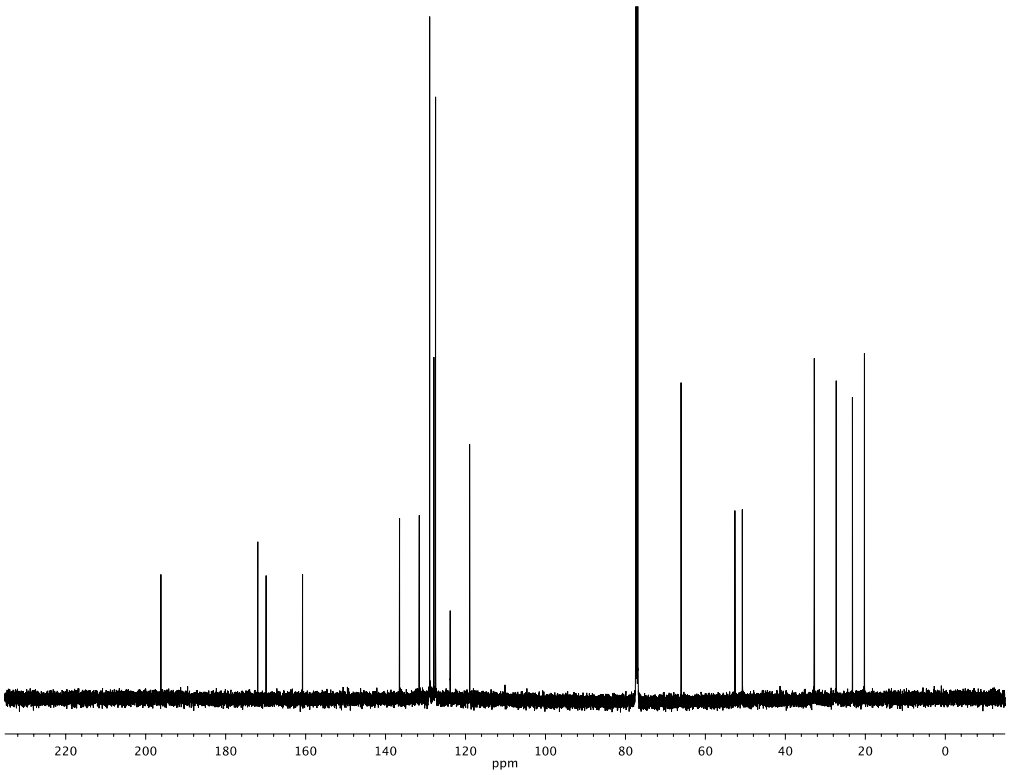
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16h**.



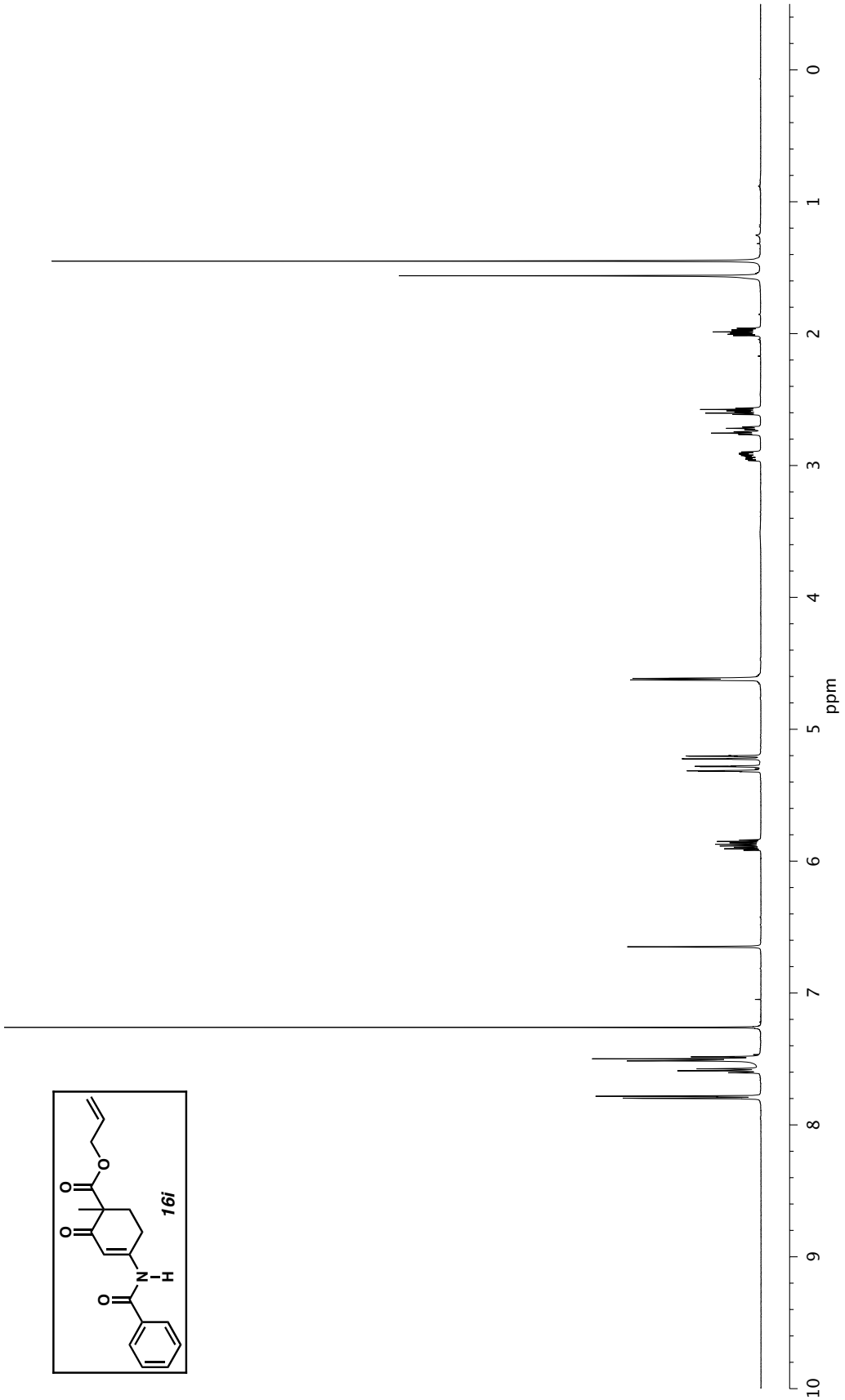
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16d**.



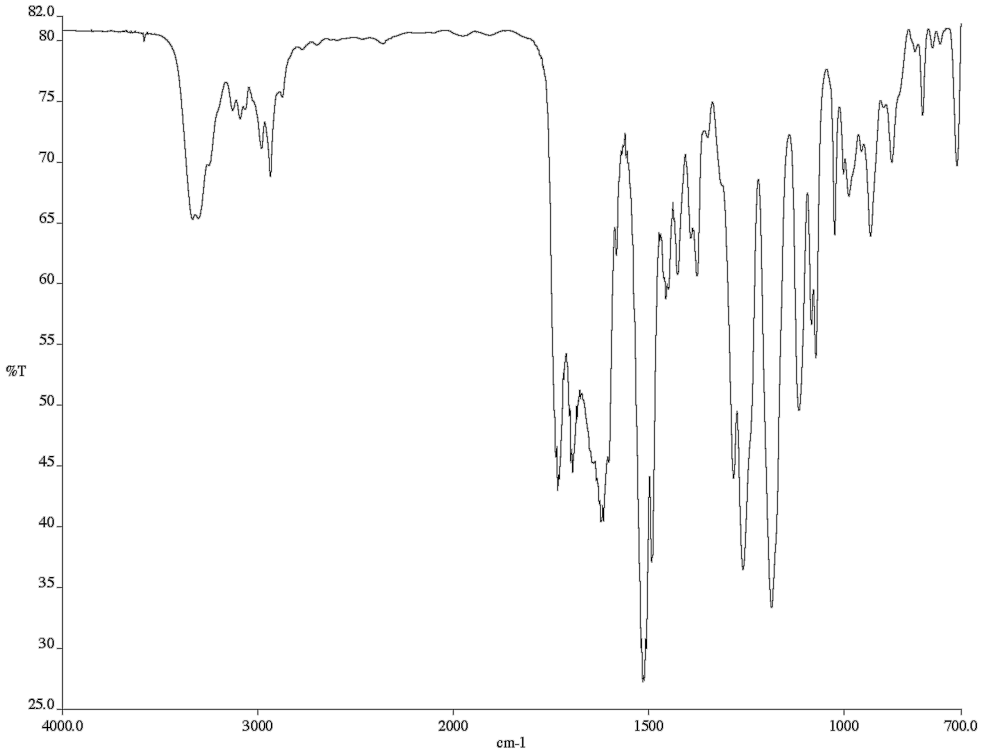
Infrared spectrum (thin film/NaCl) of compound **16d**.



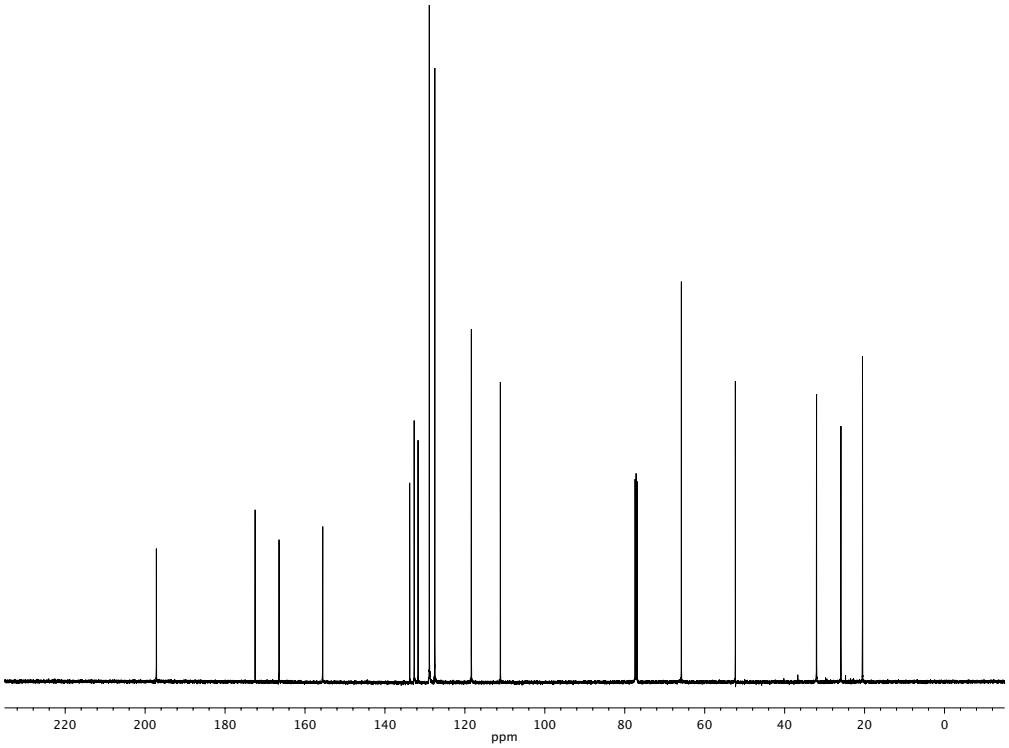
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16d**.



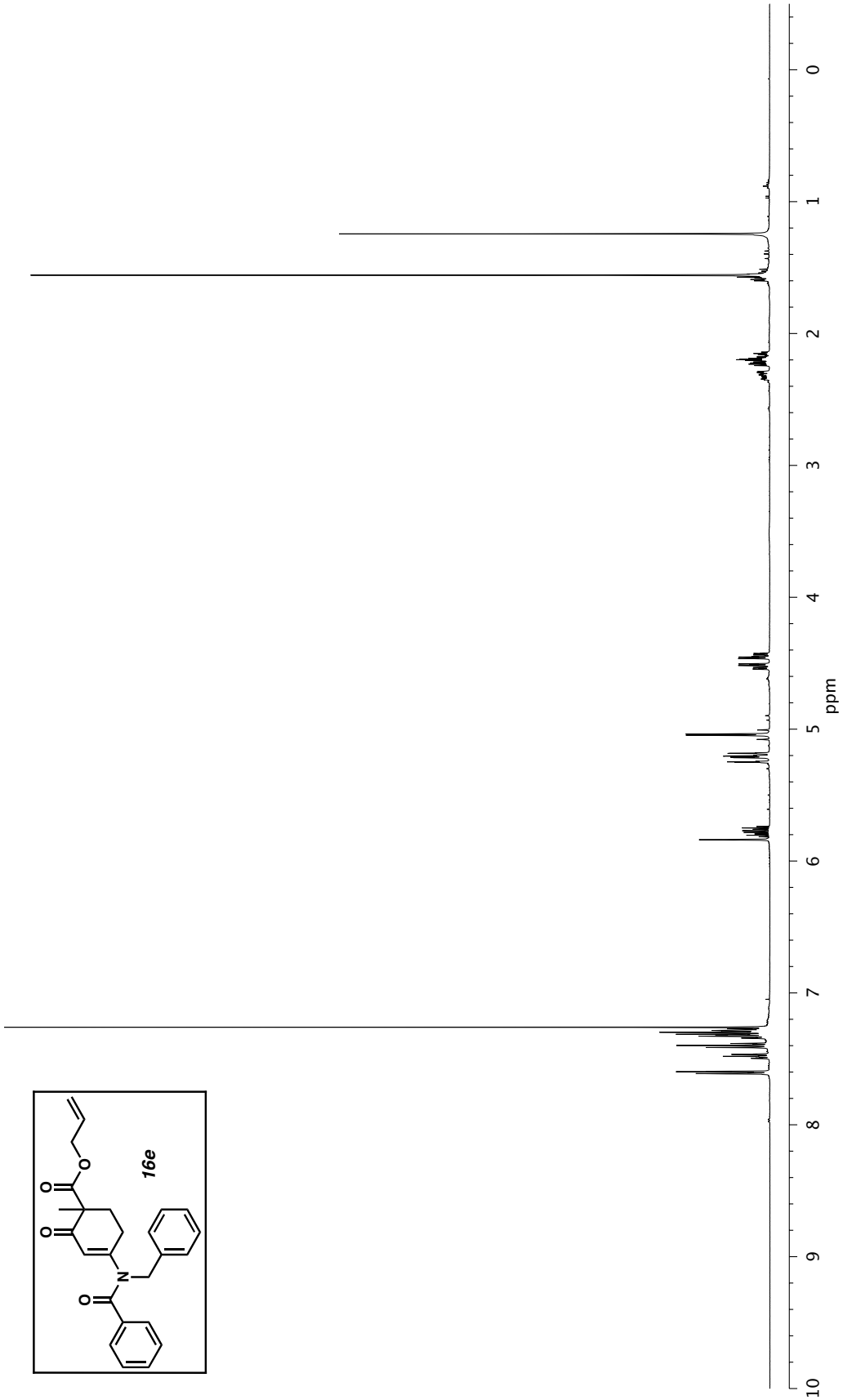
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16i**.



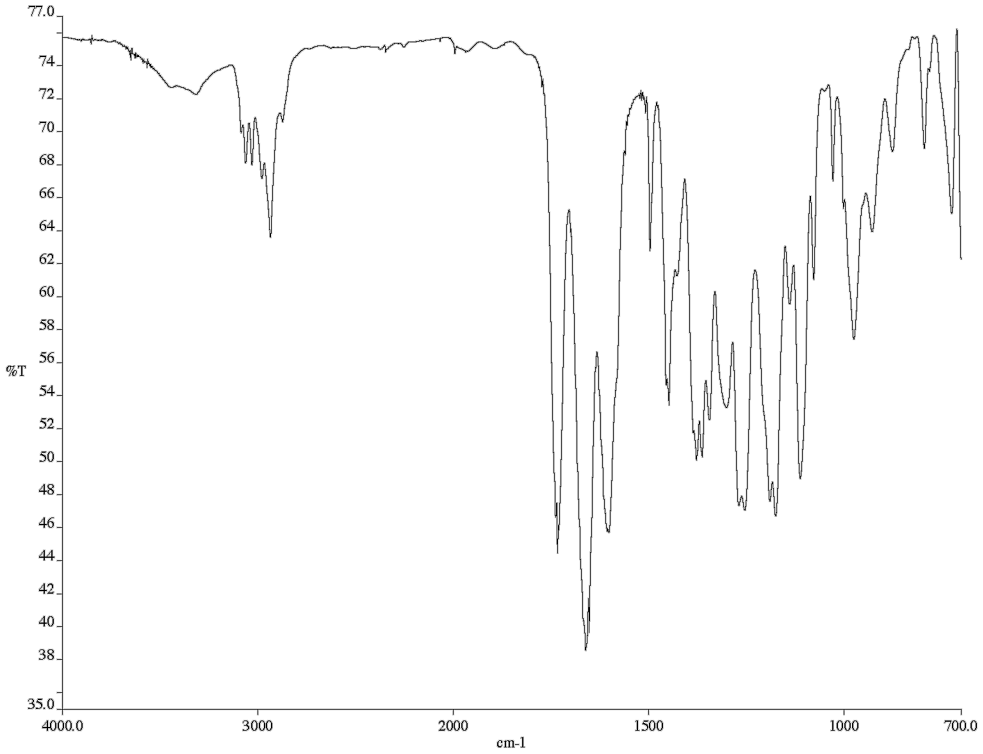
Infrared spectrum (thin film/NaCl) of compound **16i**.



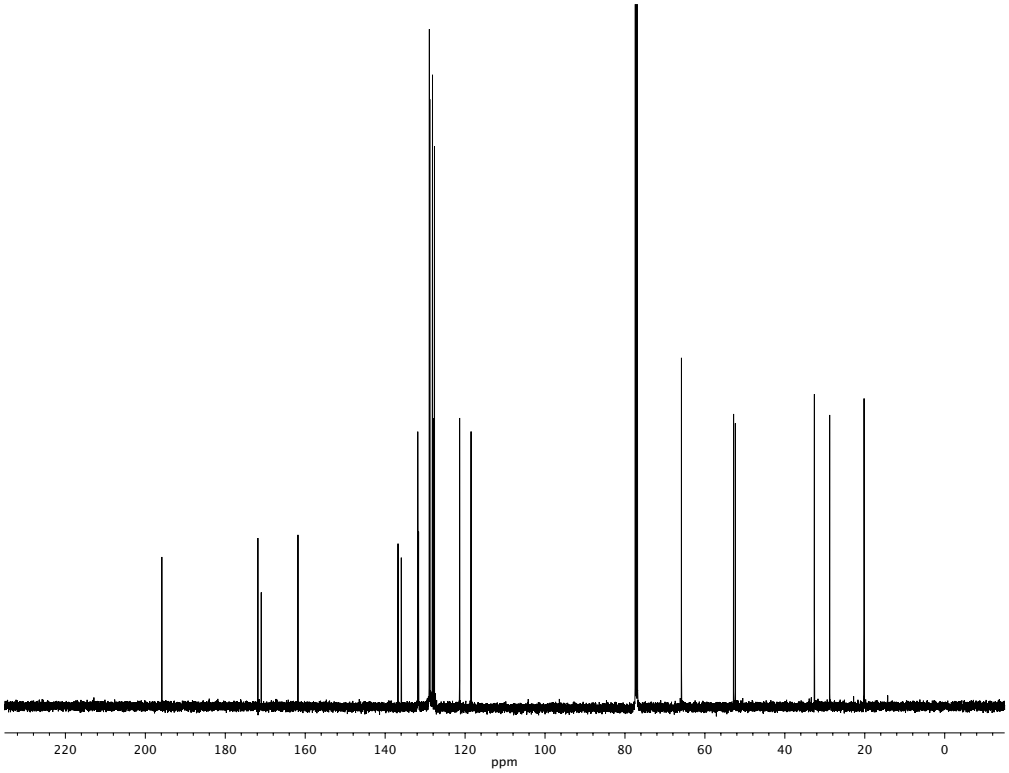
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16i**.



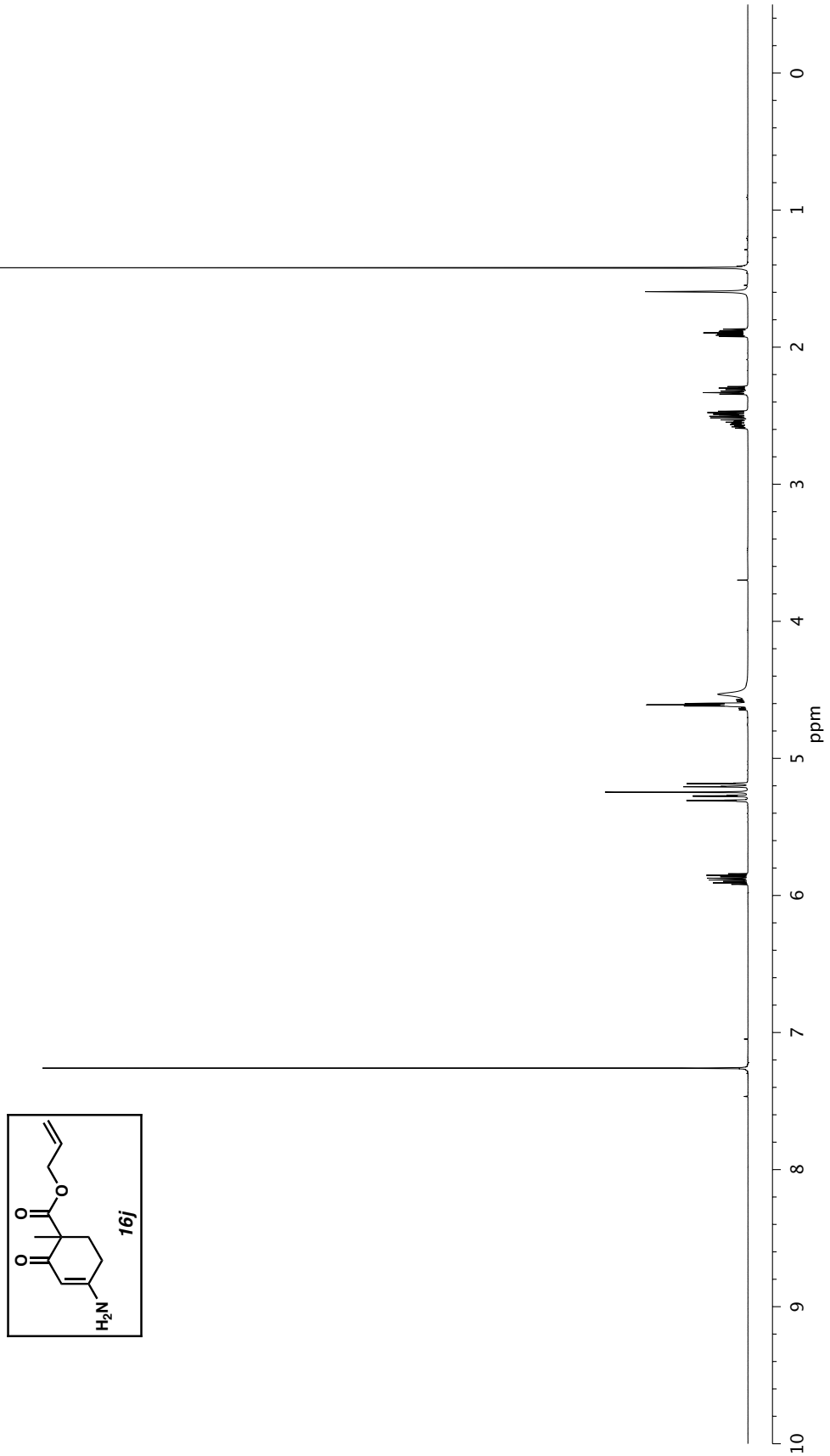
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16e**.



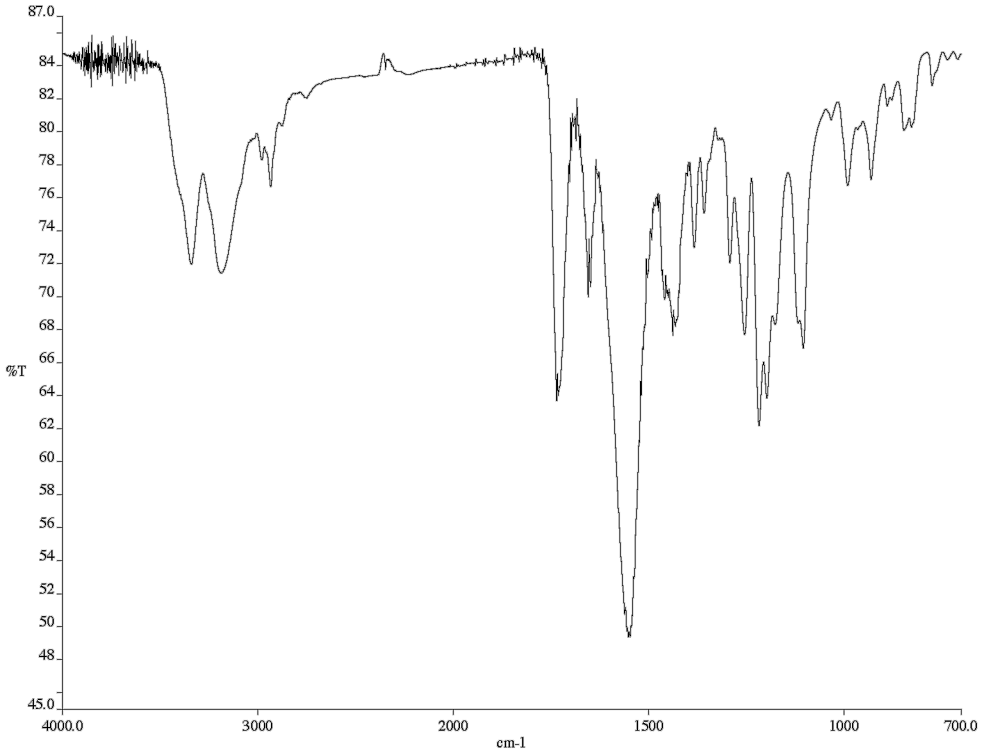
Infrared spectrum (thin film/NaCl) of compound **16e**.



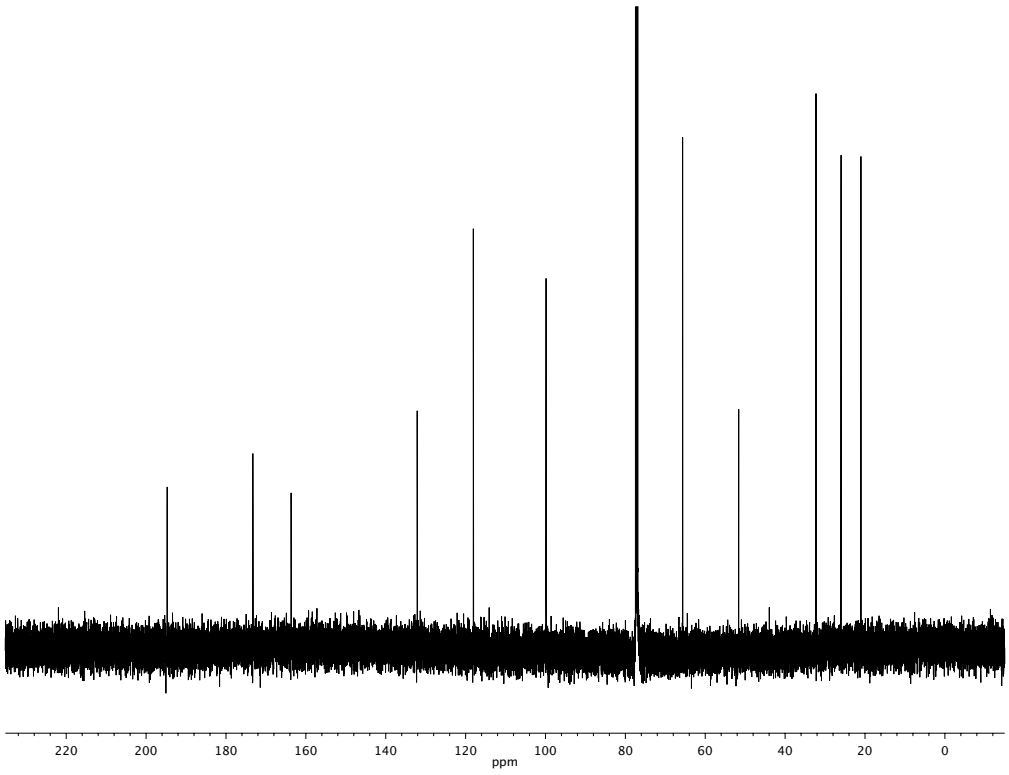
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16e**.



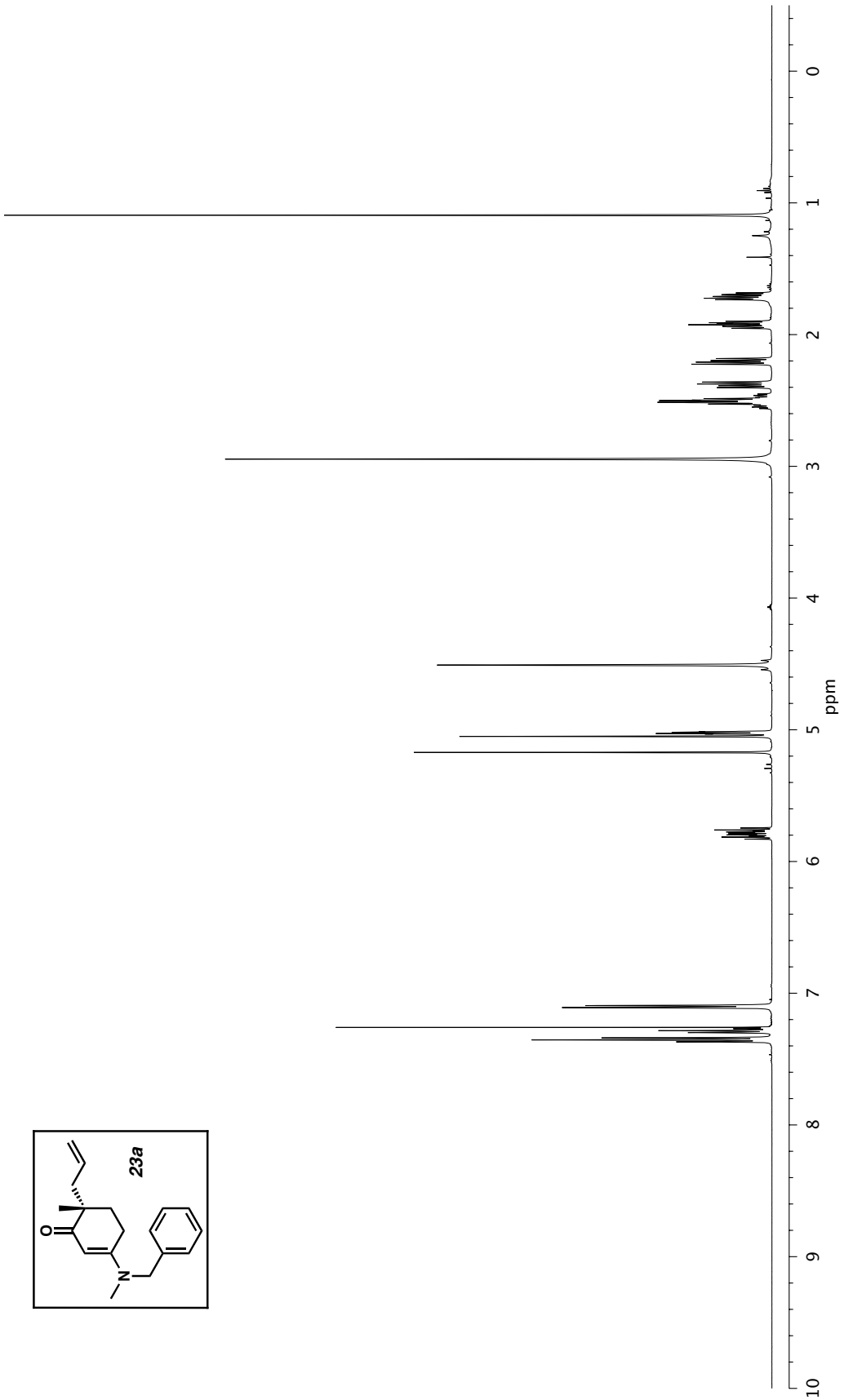
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16j**.



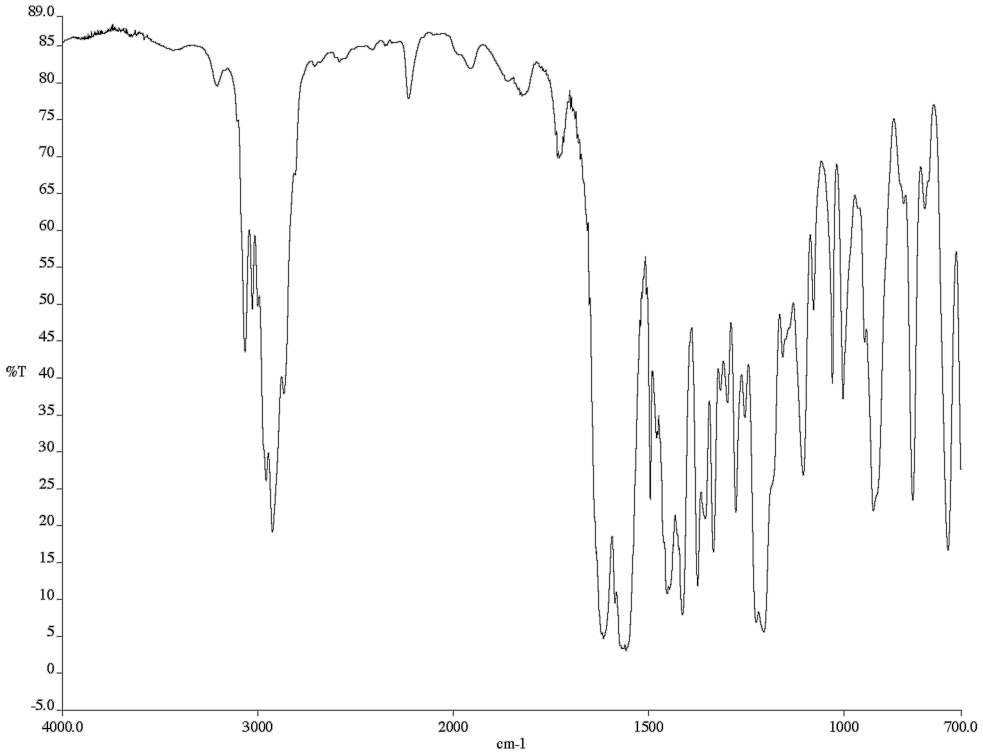
Infrared spectrum (thin film/NaCl) of compound **16j**.



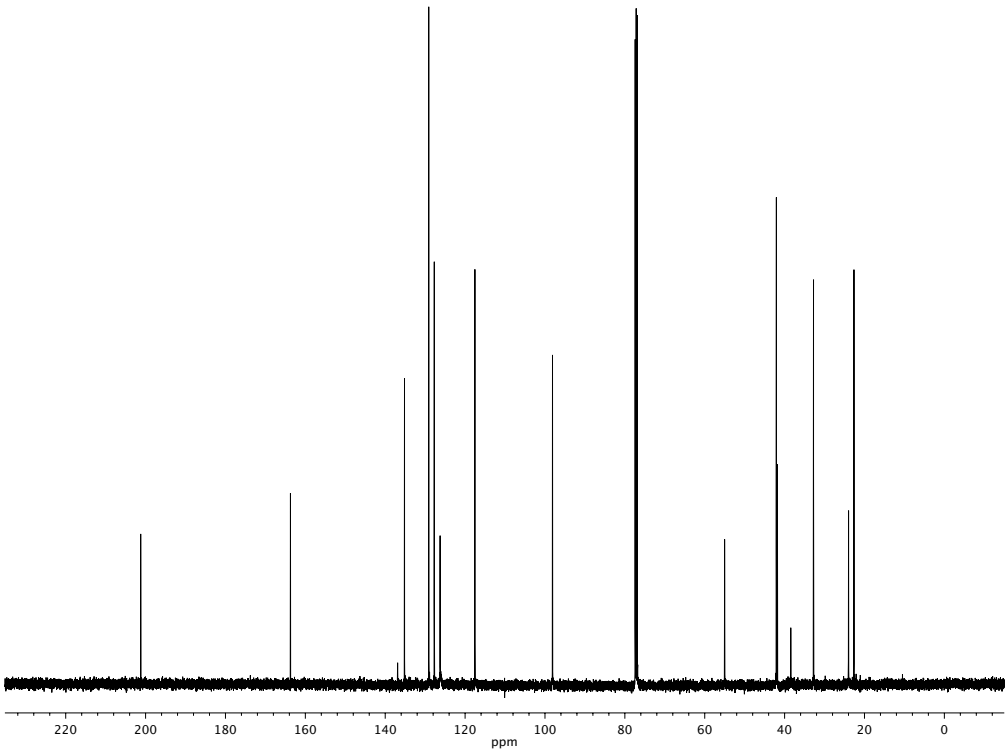
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16j**.



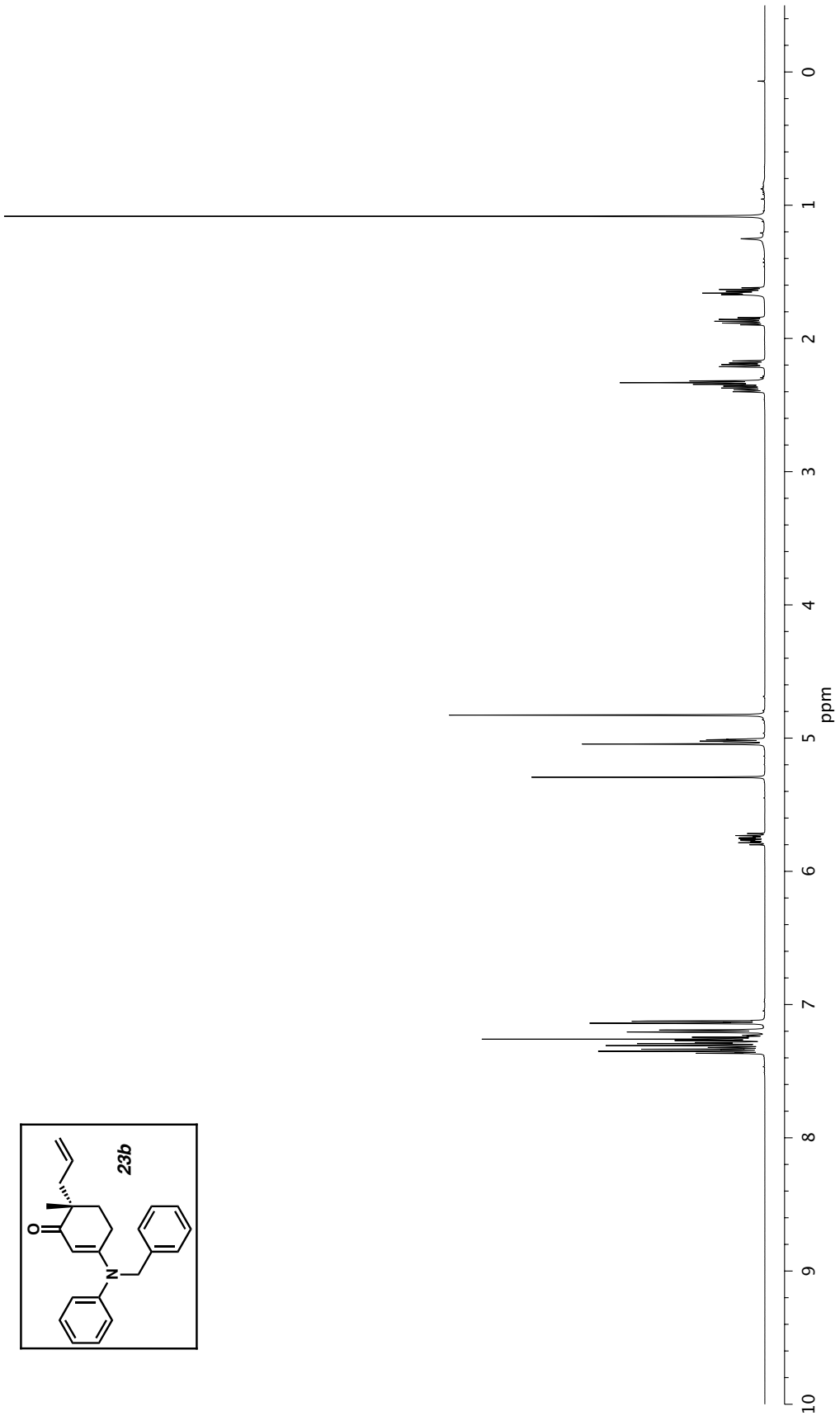
^{1}H NMR (500 MHz, $CDCl_3$) of compound **23a**.



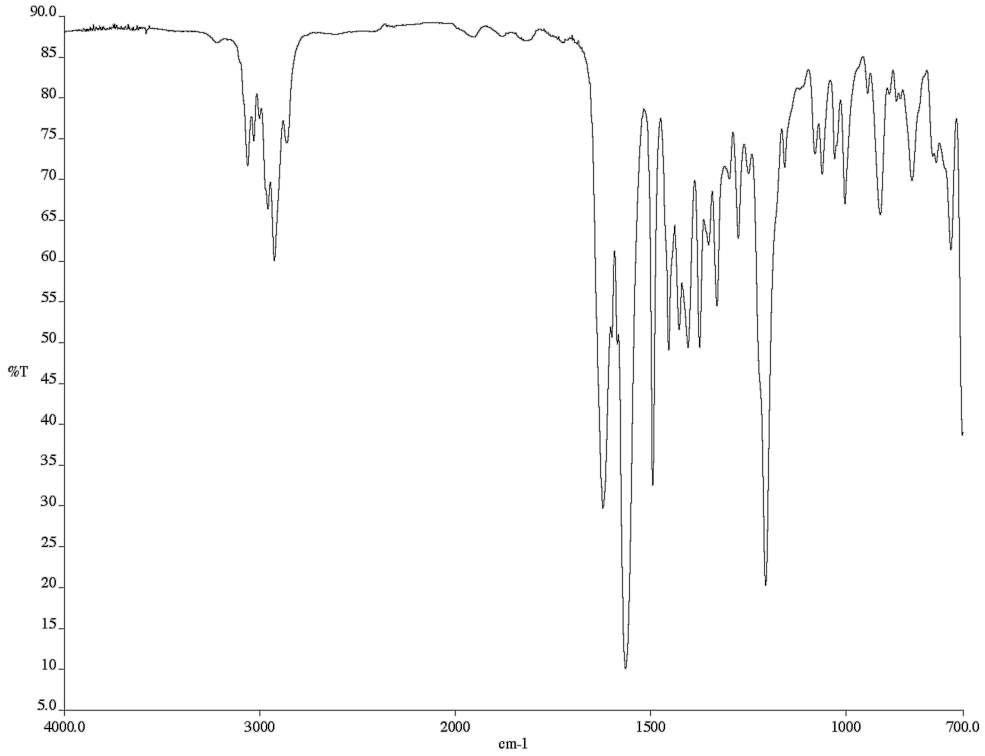
Infrared spectrum (thin film/NaCl) of compound **23a**.



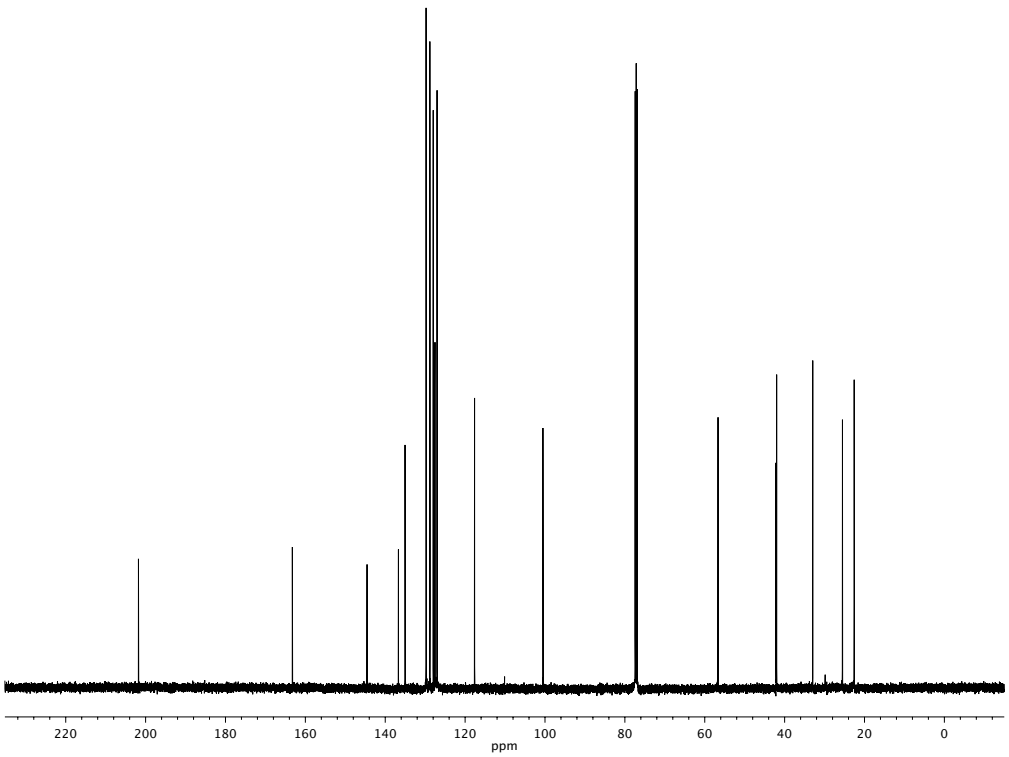
^{13}C NMR (125 MHz, $CDCl_3$) of compound **23a**.



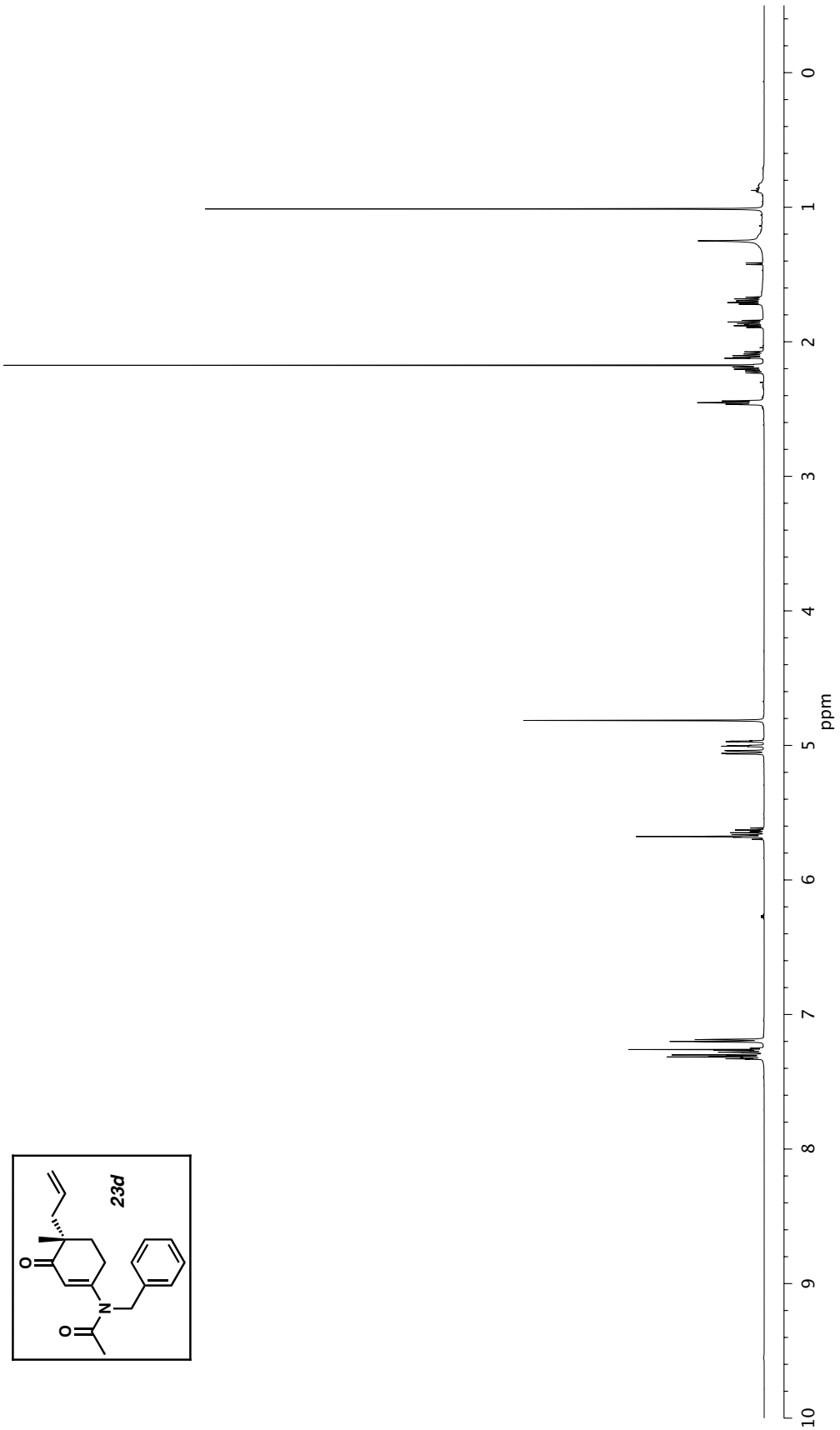
^{1}H NMR (500 MHz, $CDCl_3$) of compound **23b**.



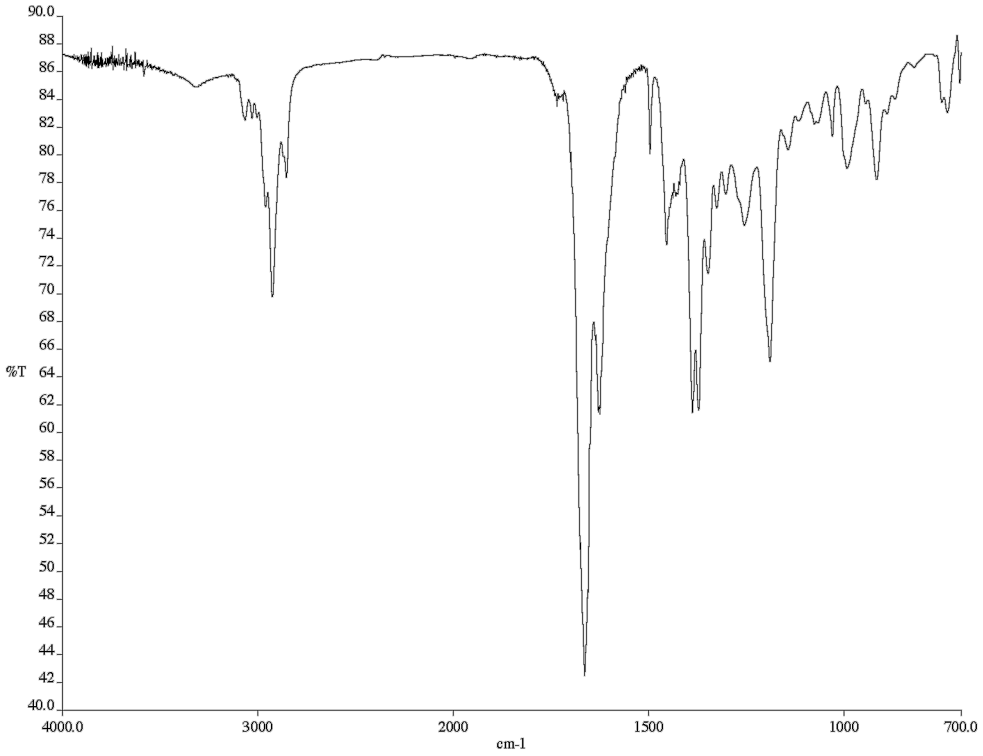
Infrared spectrum (thin film/NaCl) of compound **23b**.



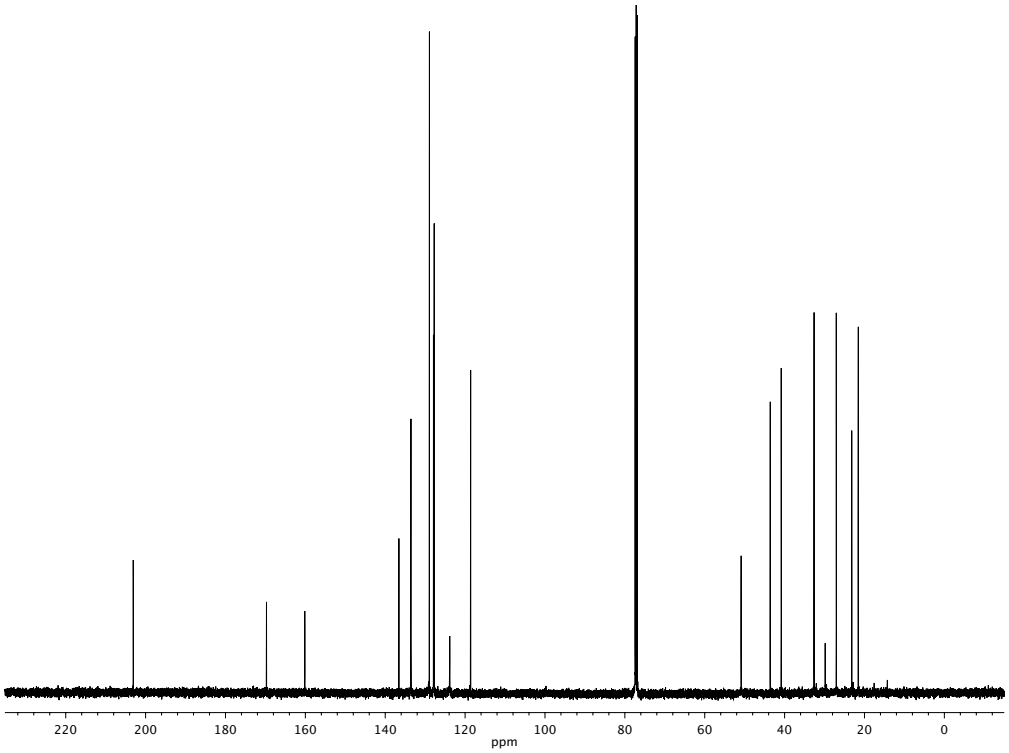
^{13}C NMR (125 MHz, $CDCl_3$) of compound **23b**.



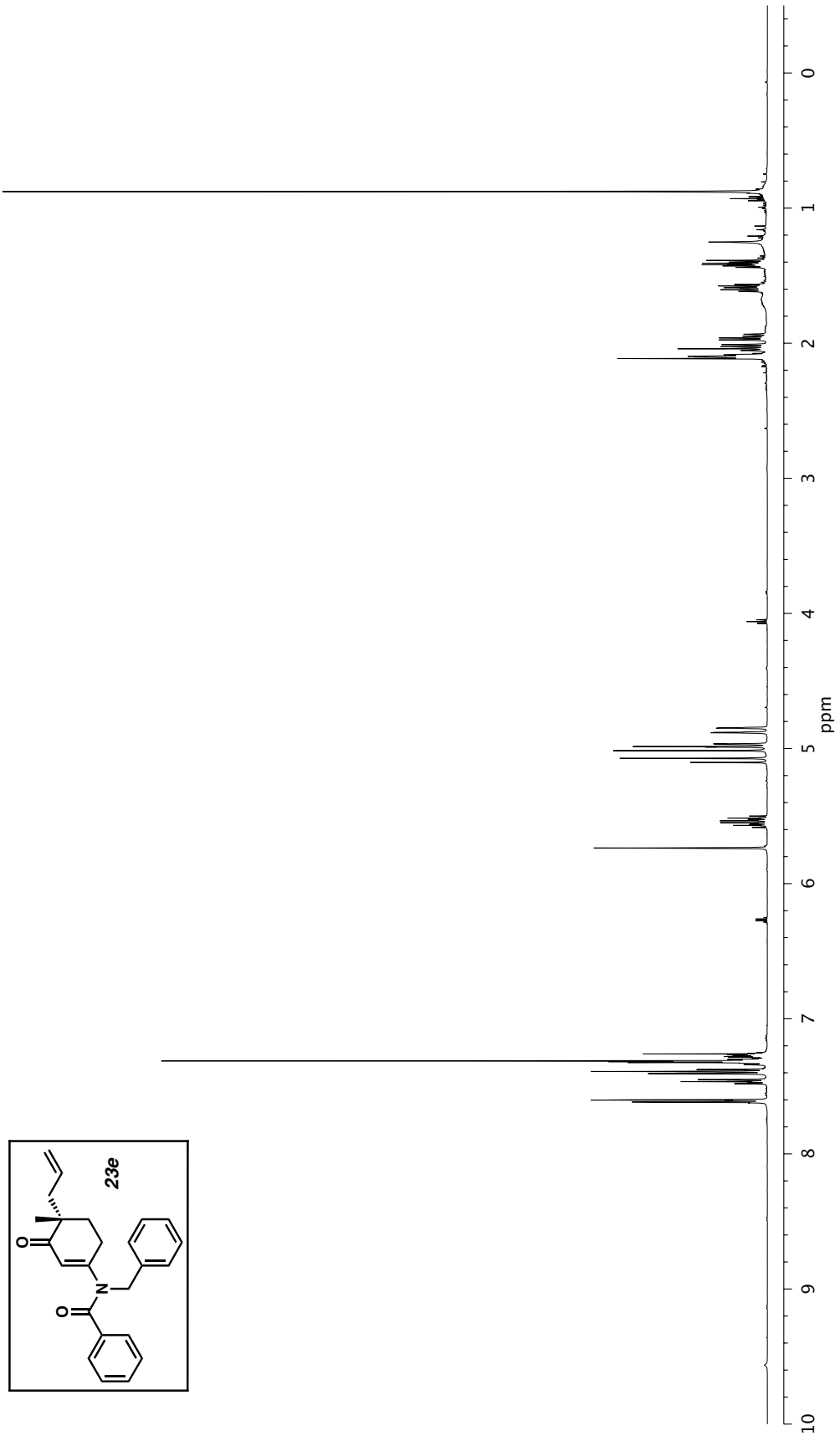
^{1}H NMR (500 MHz, $CDCl_3$) of compound **23d**.



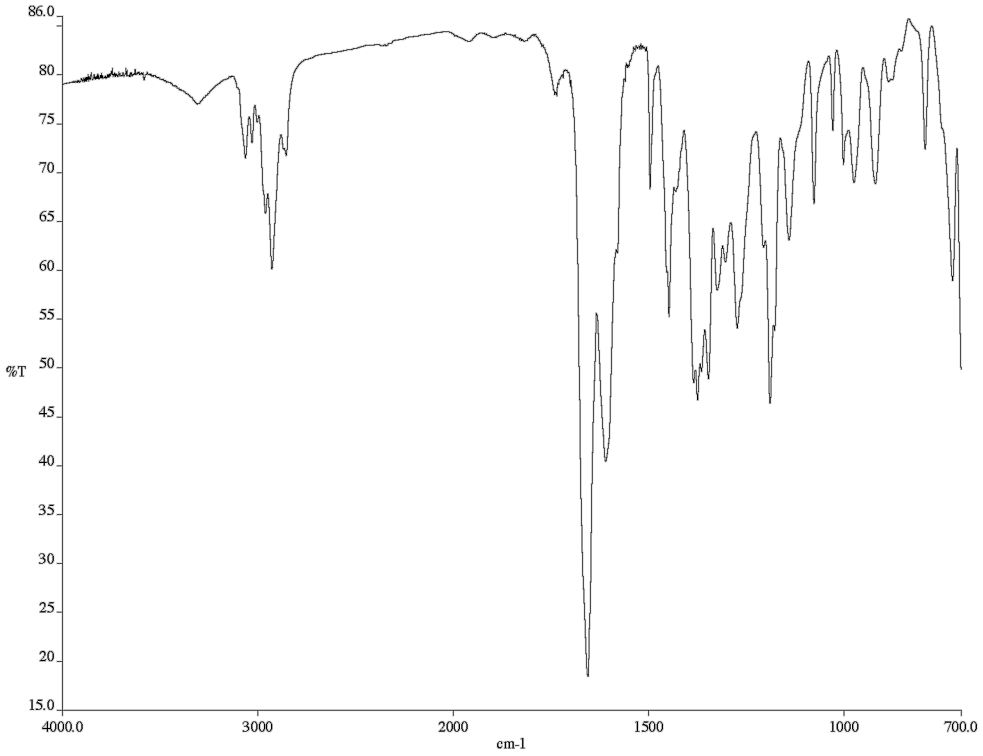
Infrared spectrum (thin film/NaCl) of compound **23d**.



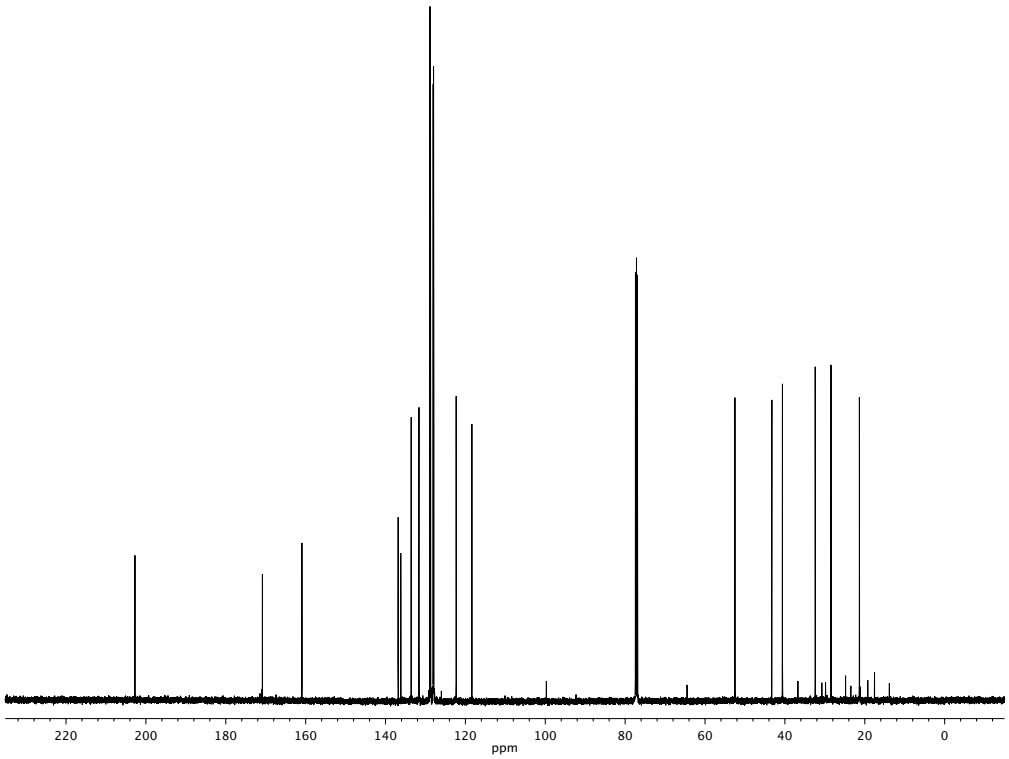
^{13}C NMR (125 MHz, $CDCl_3$) of compound **23d**.



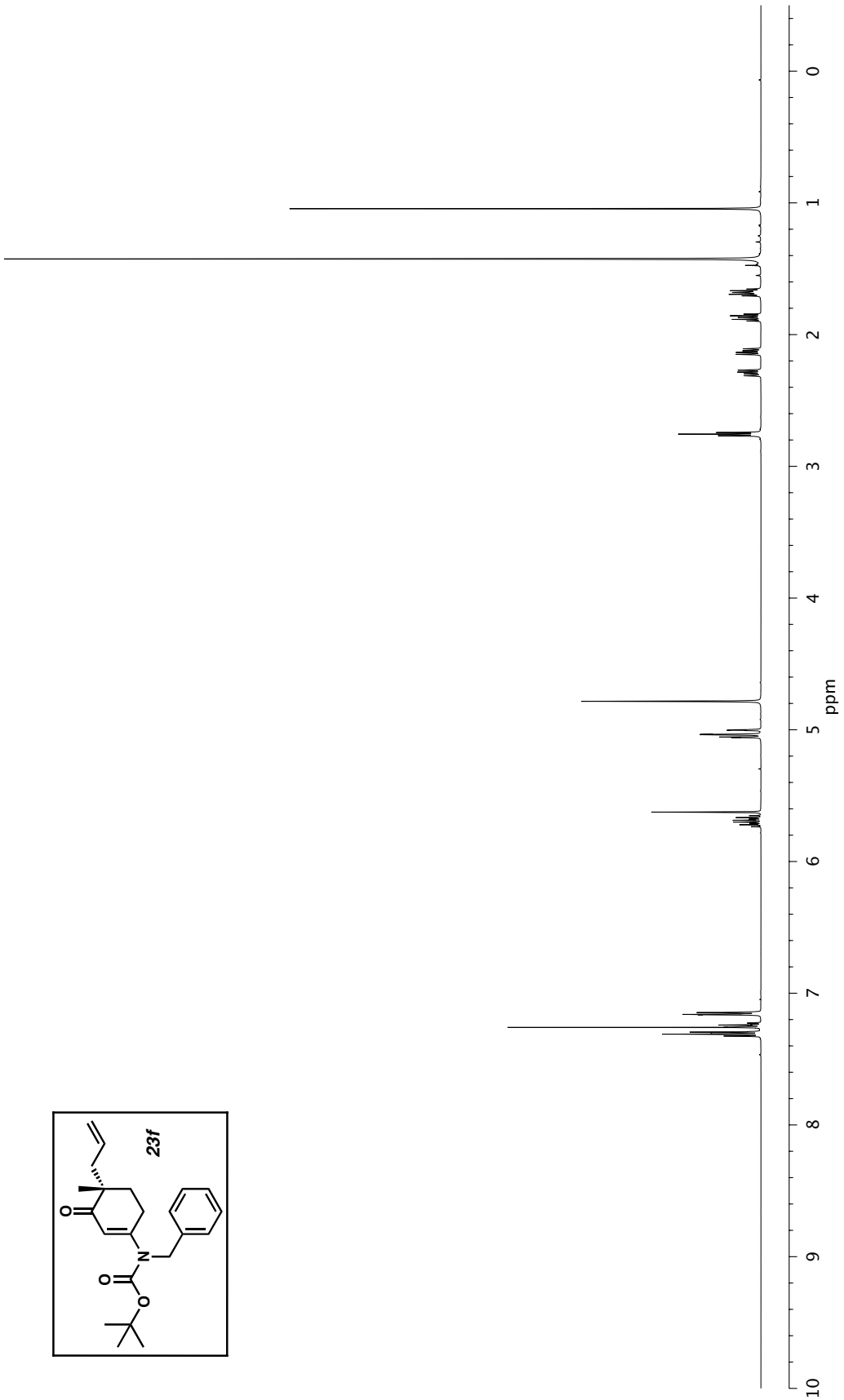
^{1}H NMR (500 MHz, $CDCl_3$) of compound **23e**.



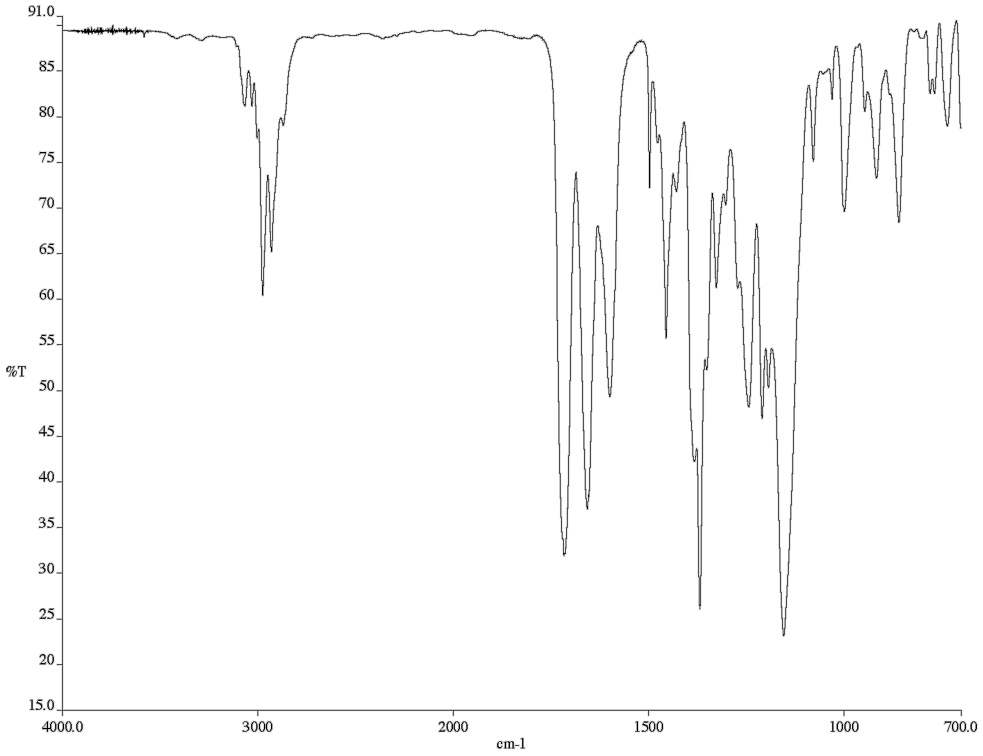
Infrared spectrum (thin film/NaCl) of compound **23e**.



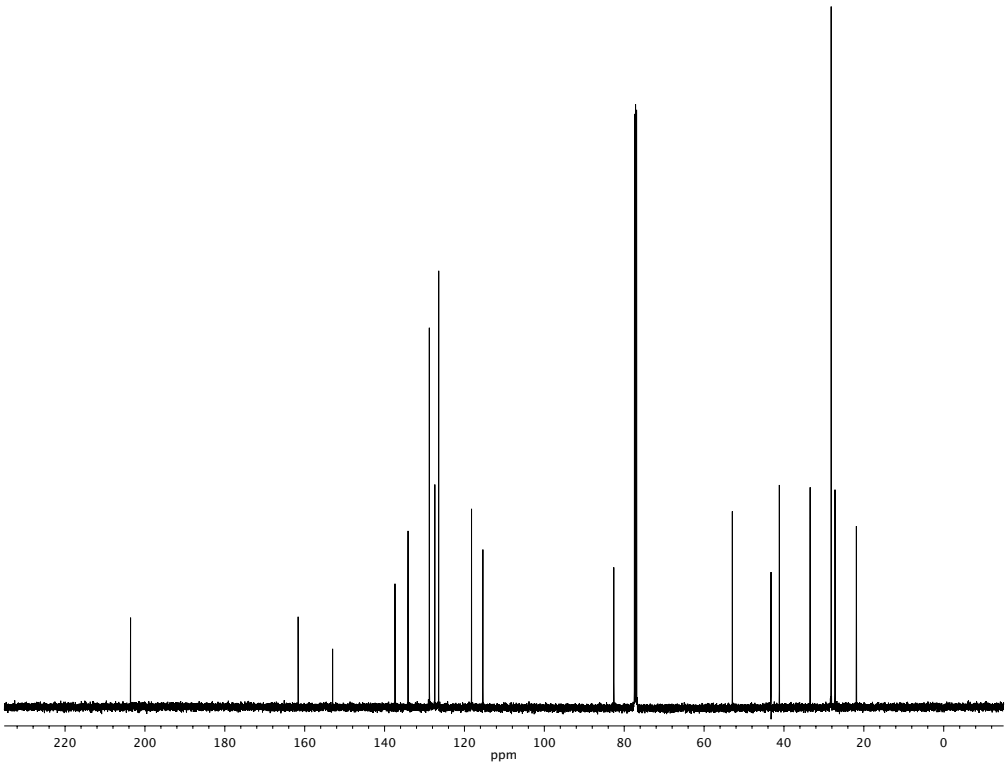
^{13}C NMR (125 MHz, $CDCl_3$) of compound **23e**.



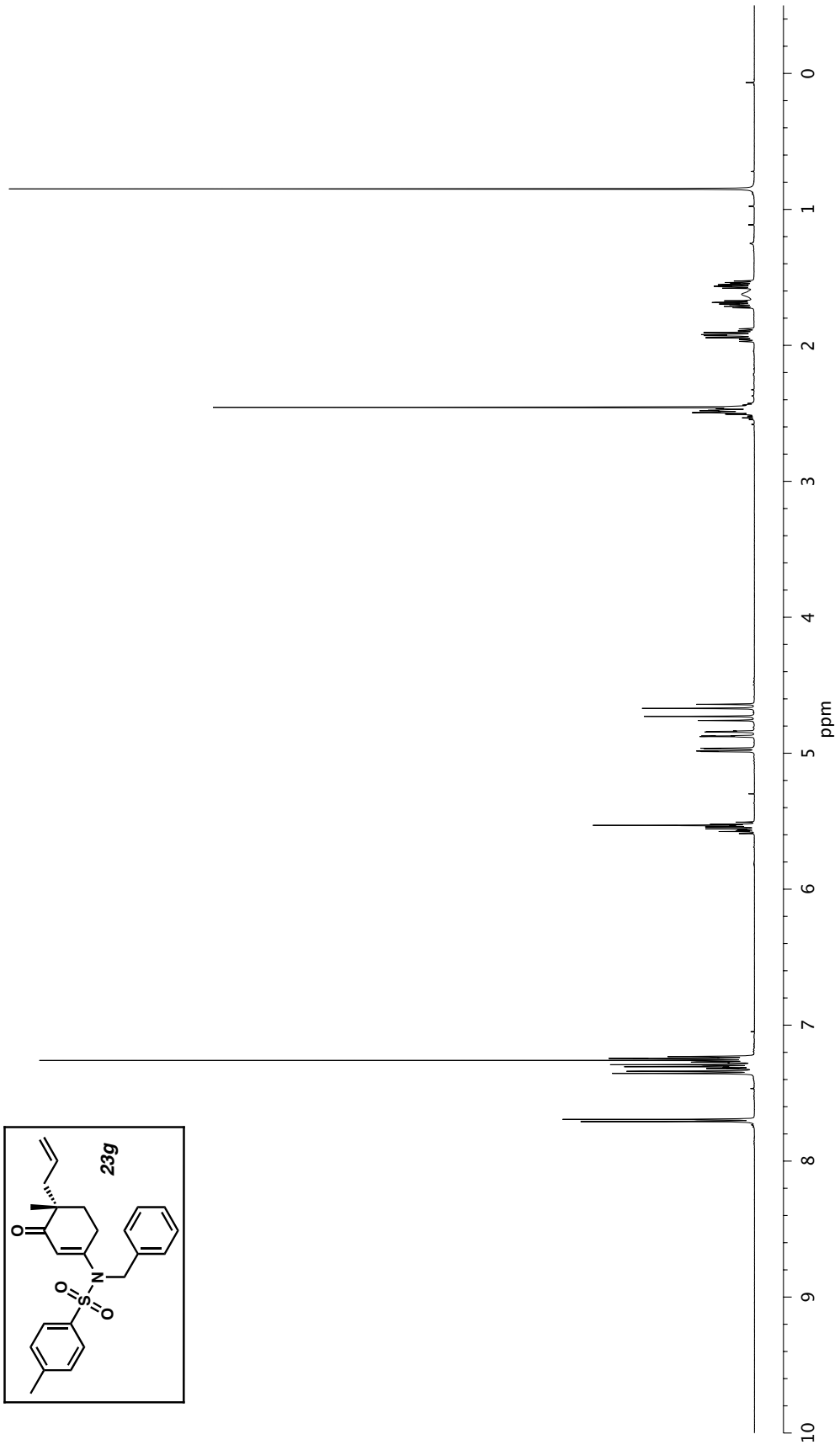
^{1}H NMR (500 MHz, $CDCl_3$) of compound **23f**.



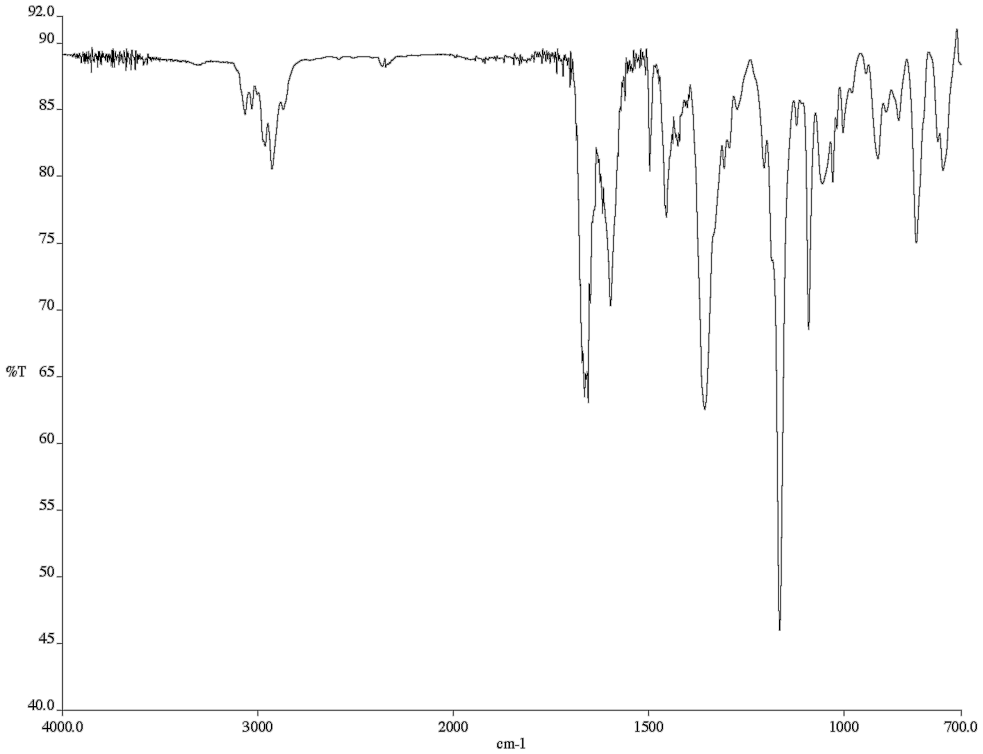
Infrared spectrum (thin film/NaCl) of compound **23f**.



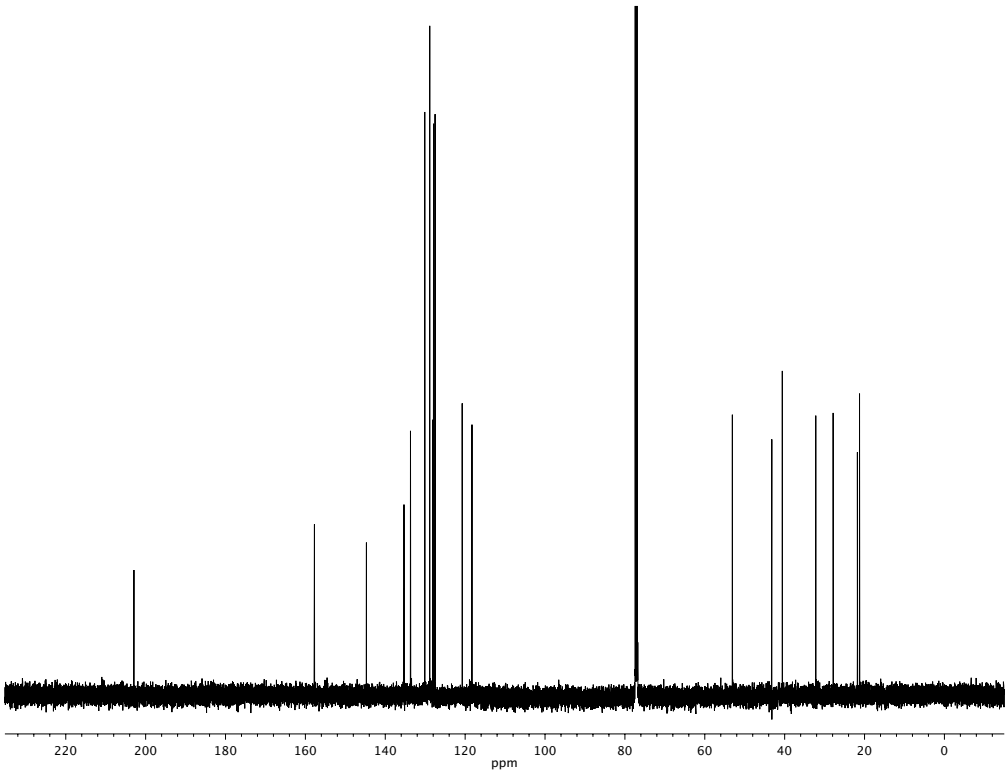
^{13}C NMR (125 MHz, $CDCl_3$) of compound **23f**.



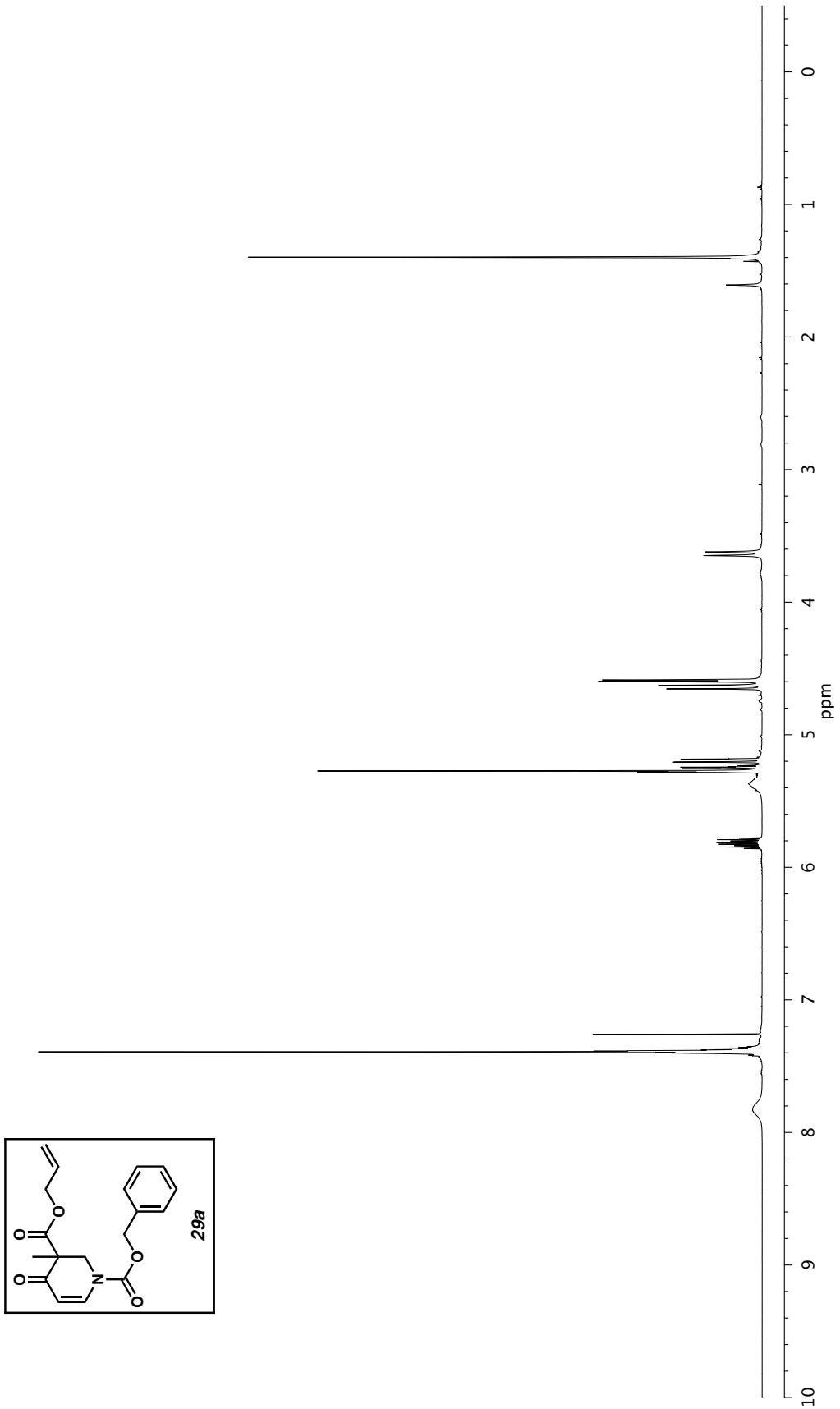
^{1}H NMR (500 MHz, $CDCl_3$) of compound **23g**.



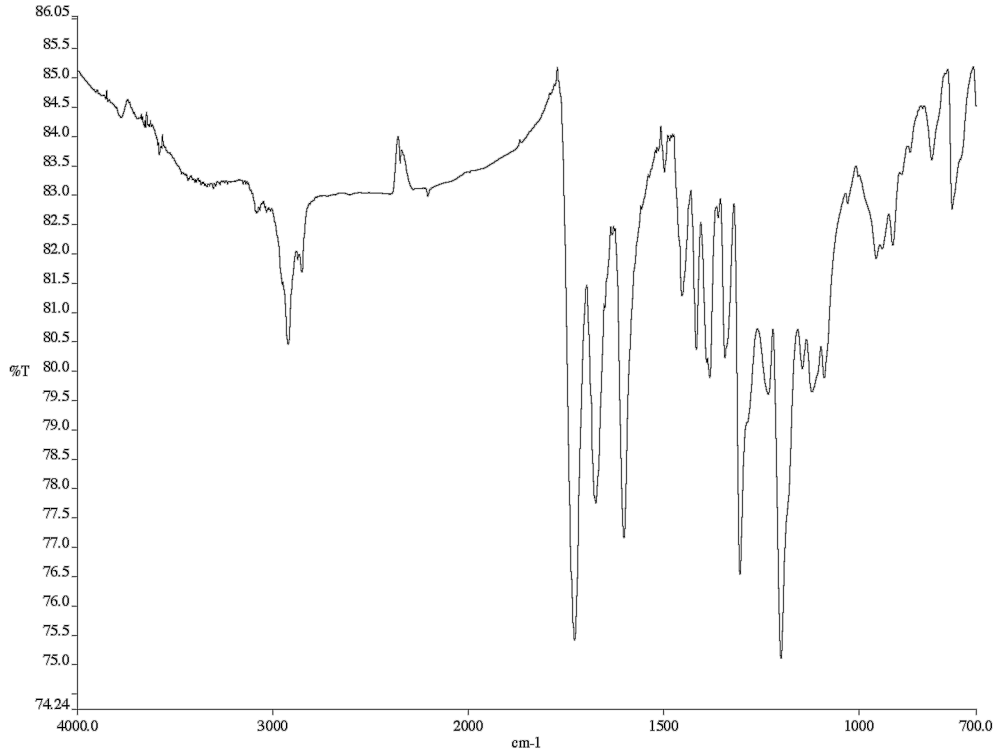
Infrared spectrum (thin film/NaCl) of compound **23g**.



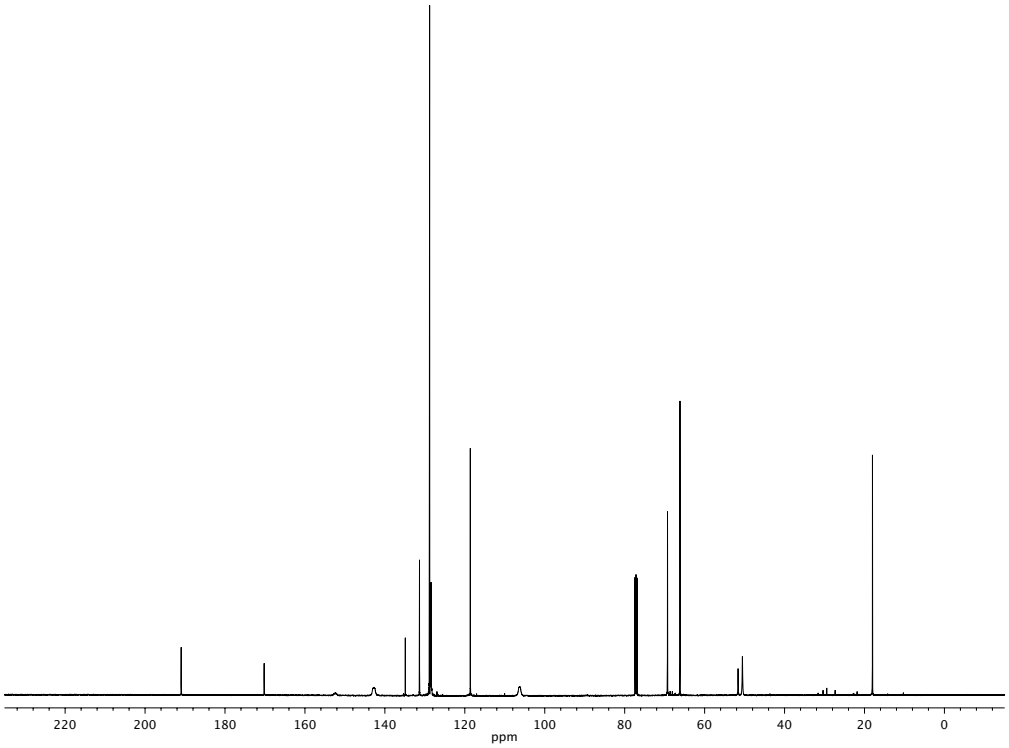
^{13}C NMR (125 MHz, $CDCl_3$) of compound **23g**.



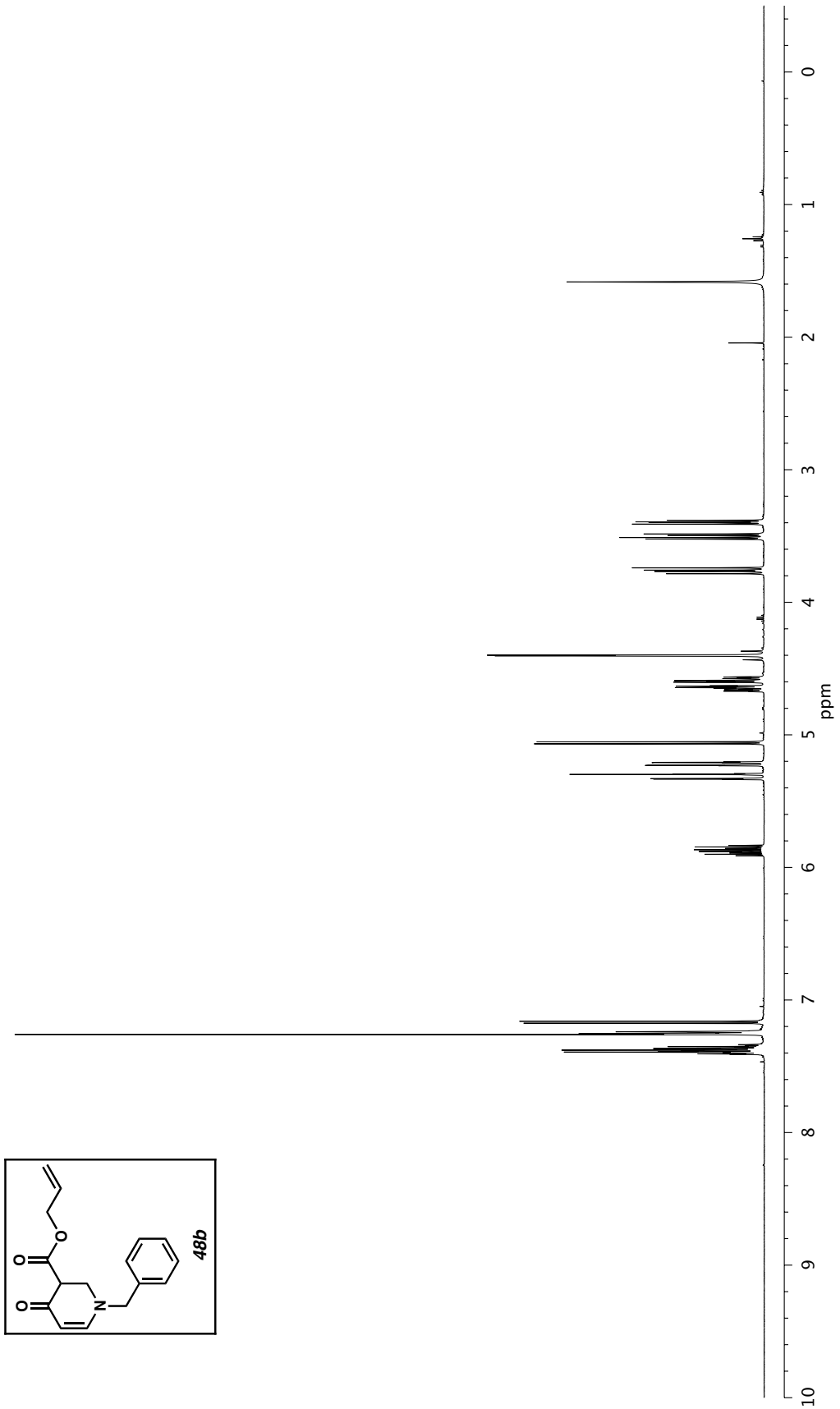
^{1}H NMR (500 MHz, $CDCl_3$) of compound **29a**.



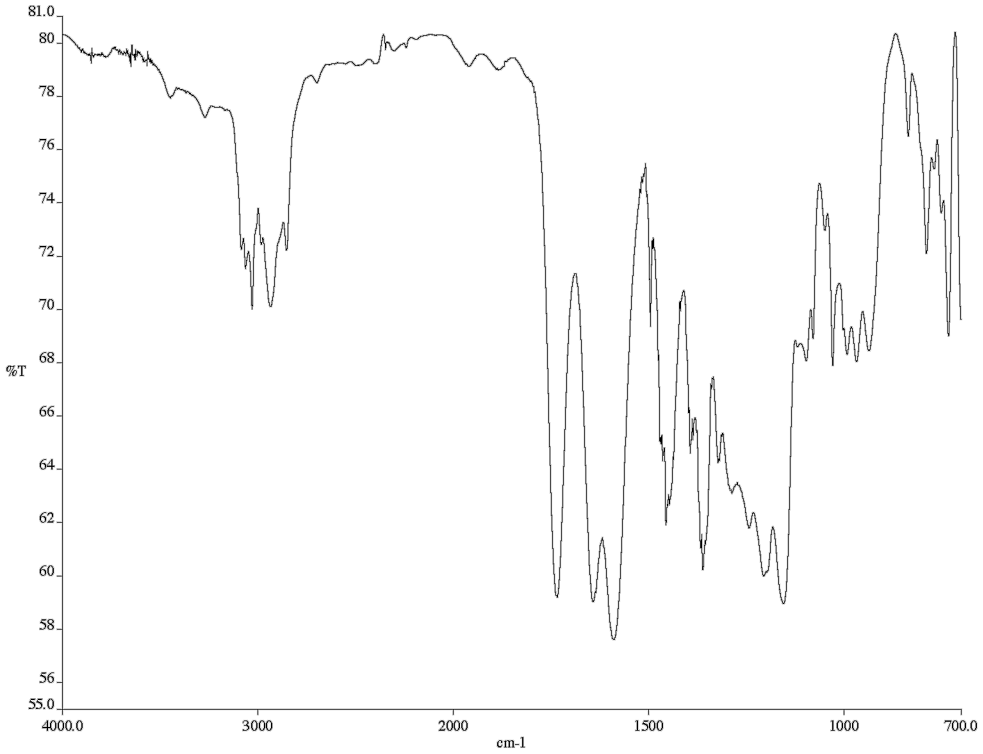
Infrared spectrum (thin film/NaCl) of compound **29a**.



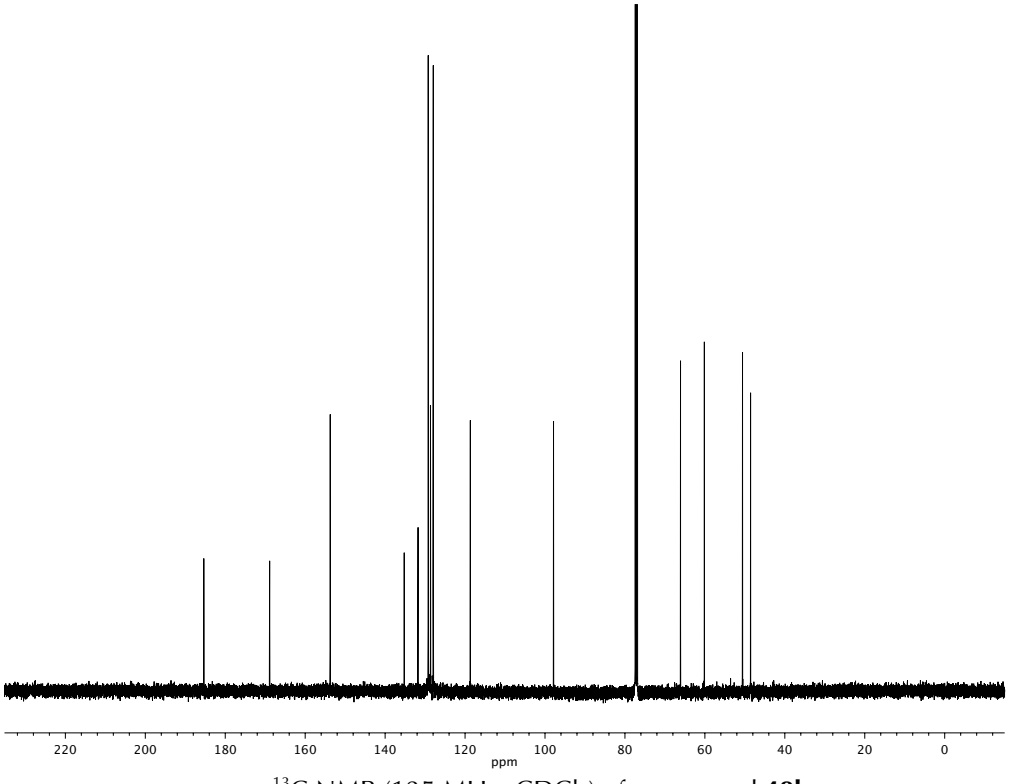
^{13}C NMR (125 MHz, $CDCl_3$) of compound **29a**.



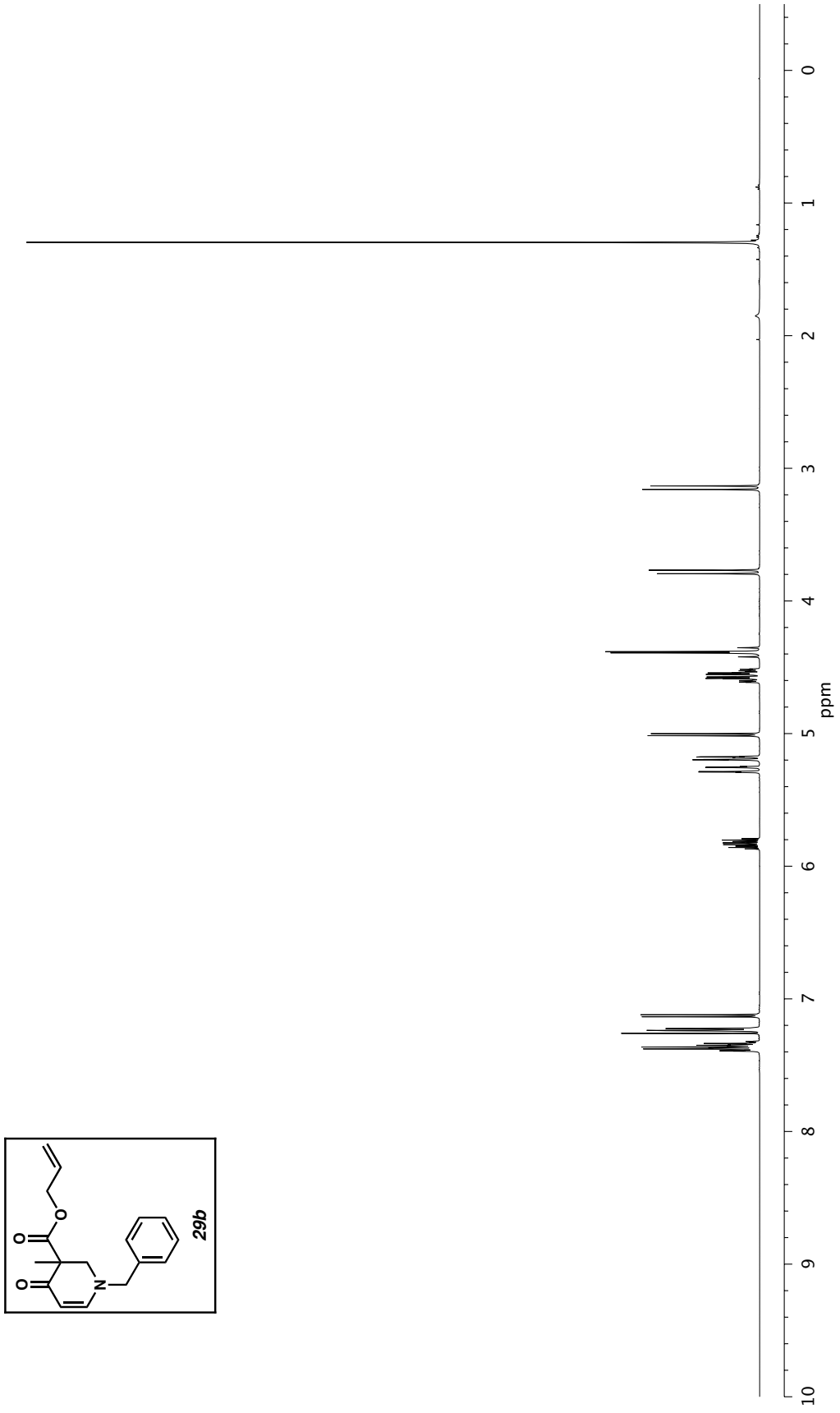
^{1}H NMR (500 MHz, $CDCl_3$) of compound **48b**.



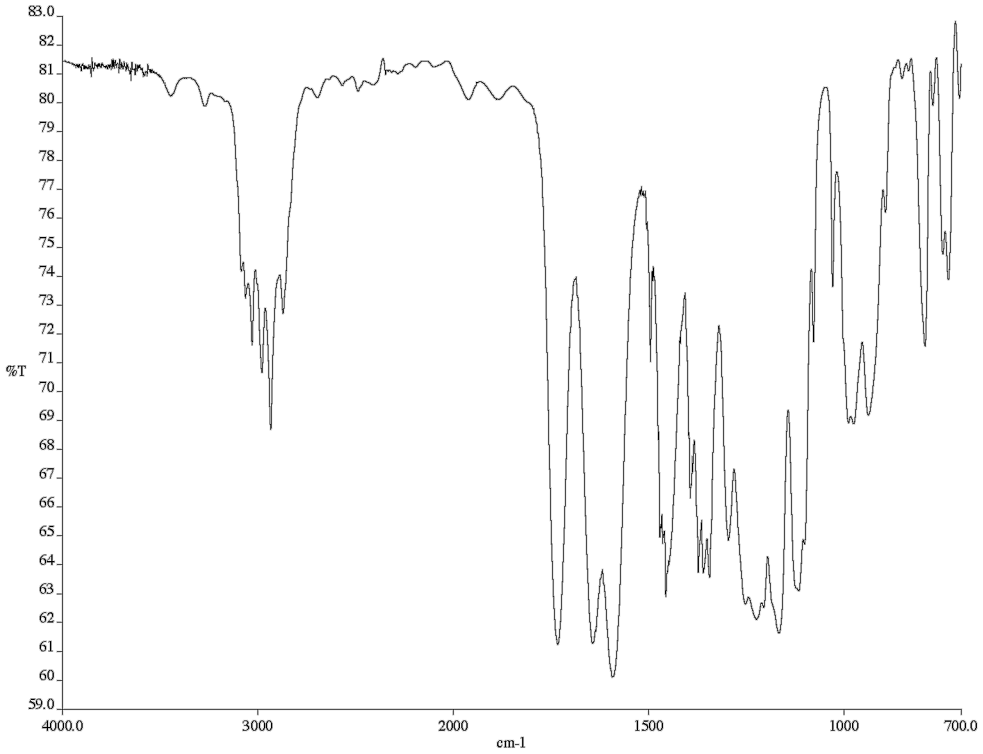
Infrared spectrum (thin film/NaCl) of compound **48b**.



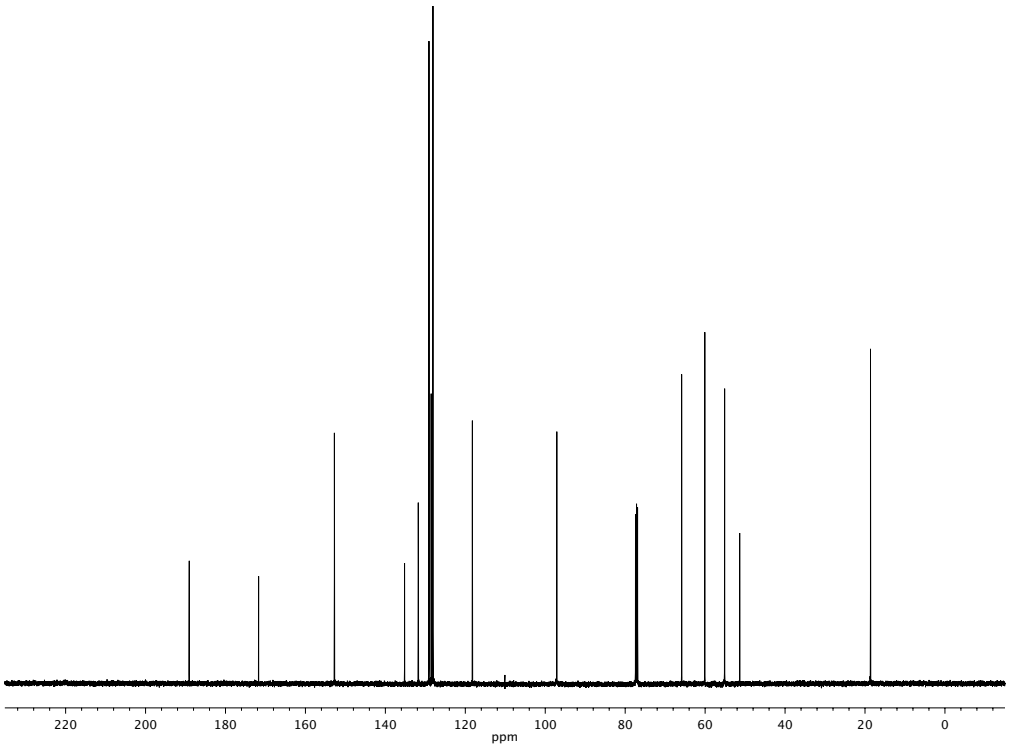
^{13}C NMR (125 MHz, $CDCl_3$) of compound **48b**.



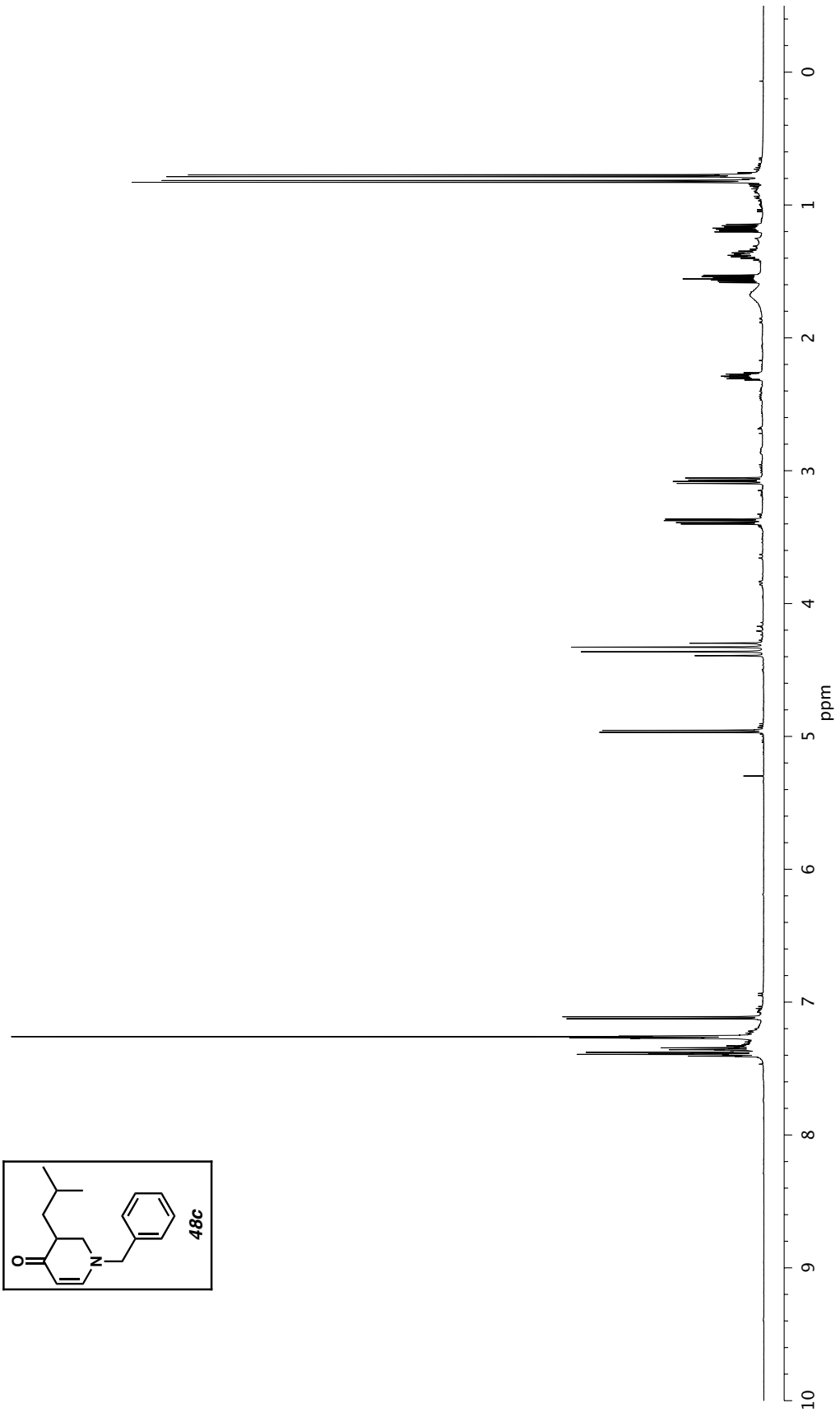
^{1}H NMR (500 MHz, $CDCl_3$) of compound **29b**.



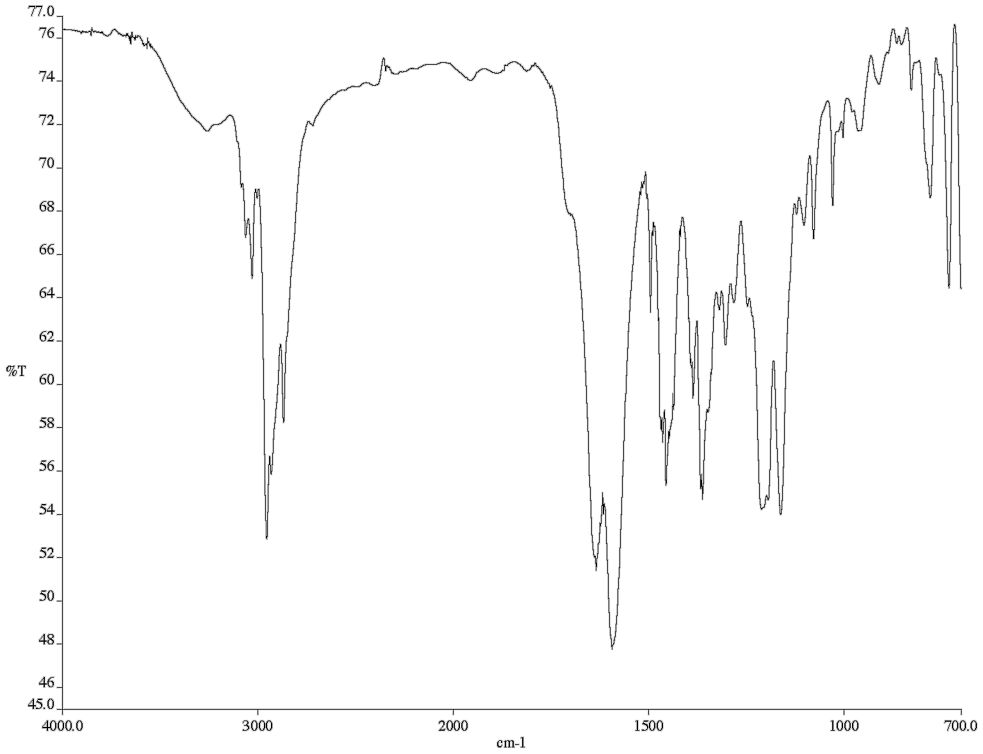
Infrared spectrum (thin film/NaCl) of compound **29b**.



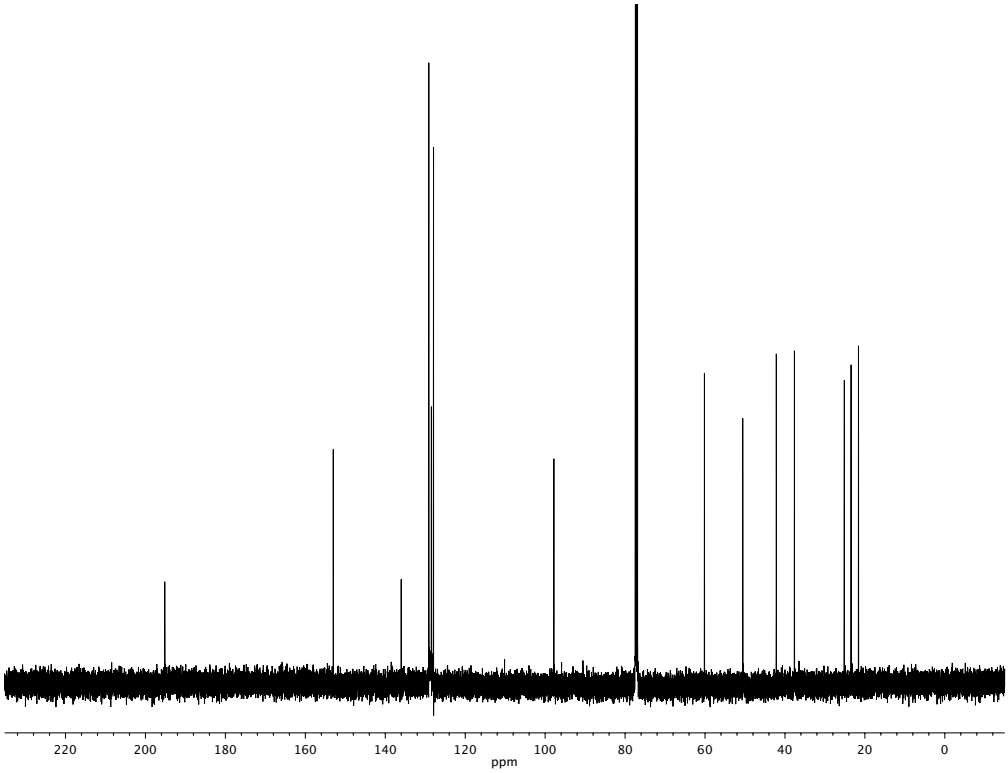
^{13}C NMR (125 MHz, $CDCl_3$) of compound **29b**.



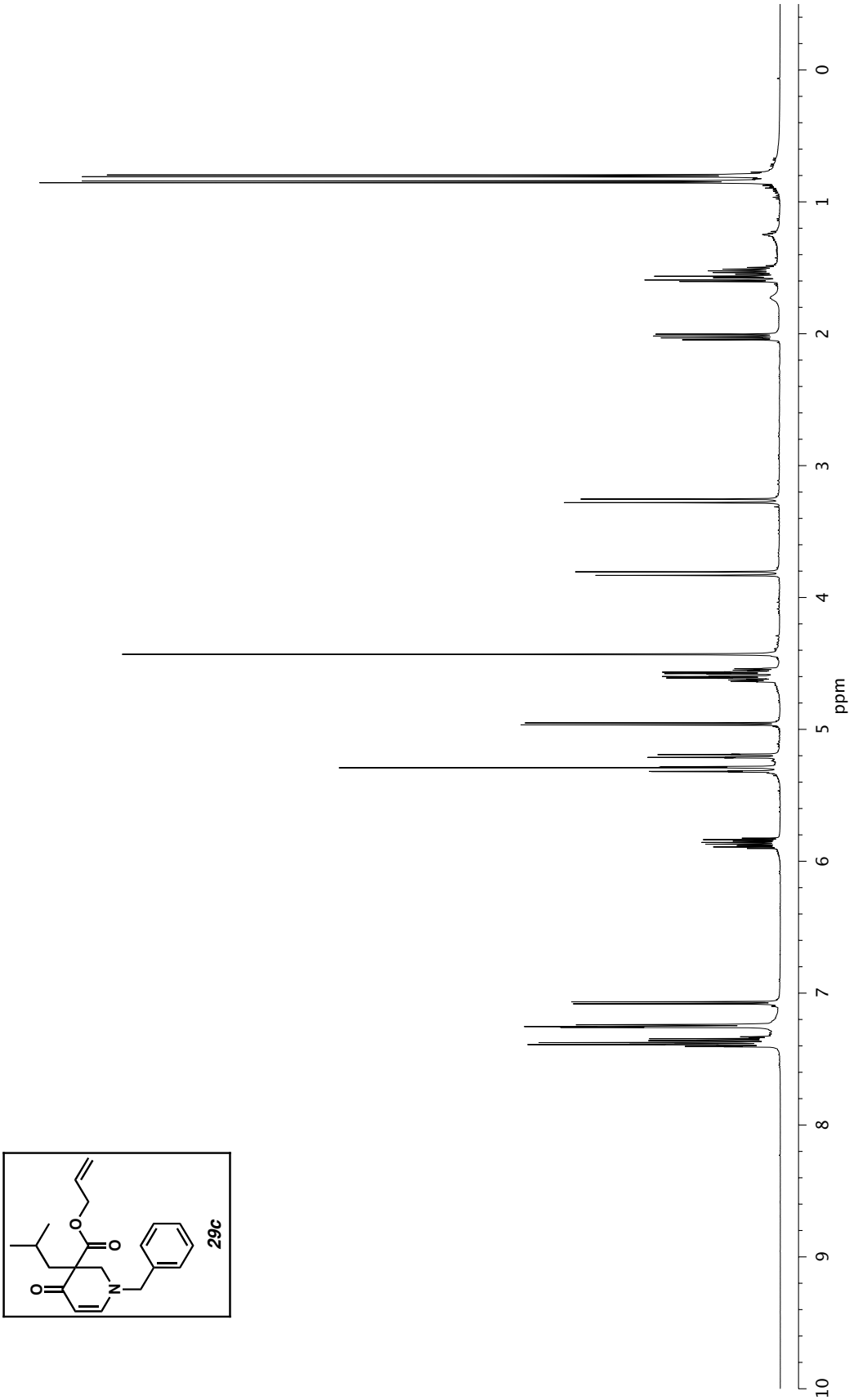
^{1}H NMR (500 MHz, $CDCl_3$) of compound **48c**.



Infrared spectrum (thin film/NaCl) of compound **48c**.

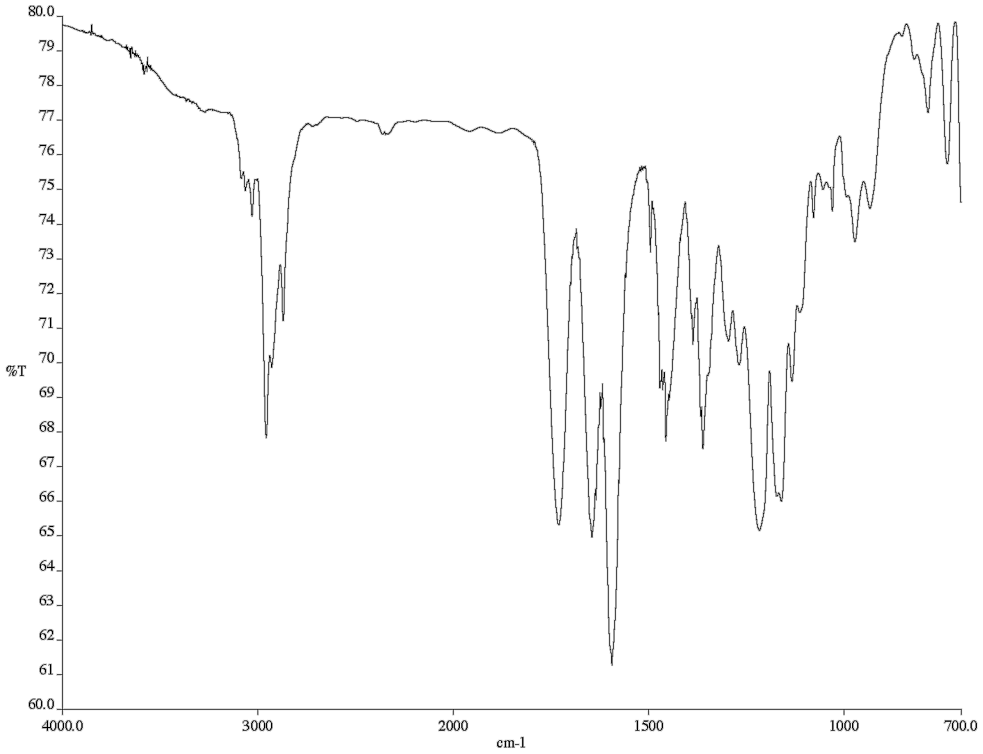


^{13}C NMR (125 MHz, $CDCl_3$) of compound **48c**.

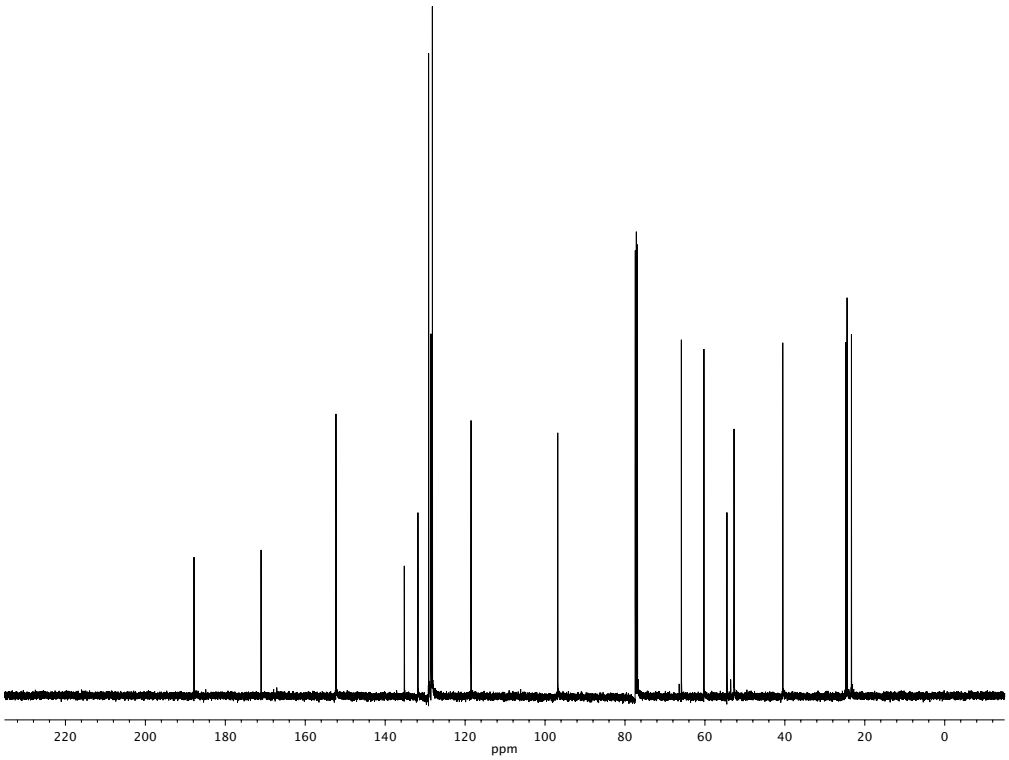


29c

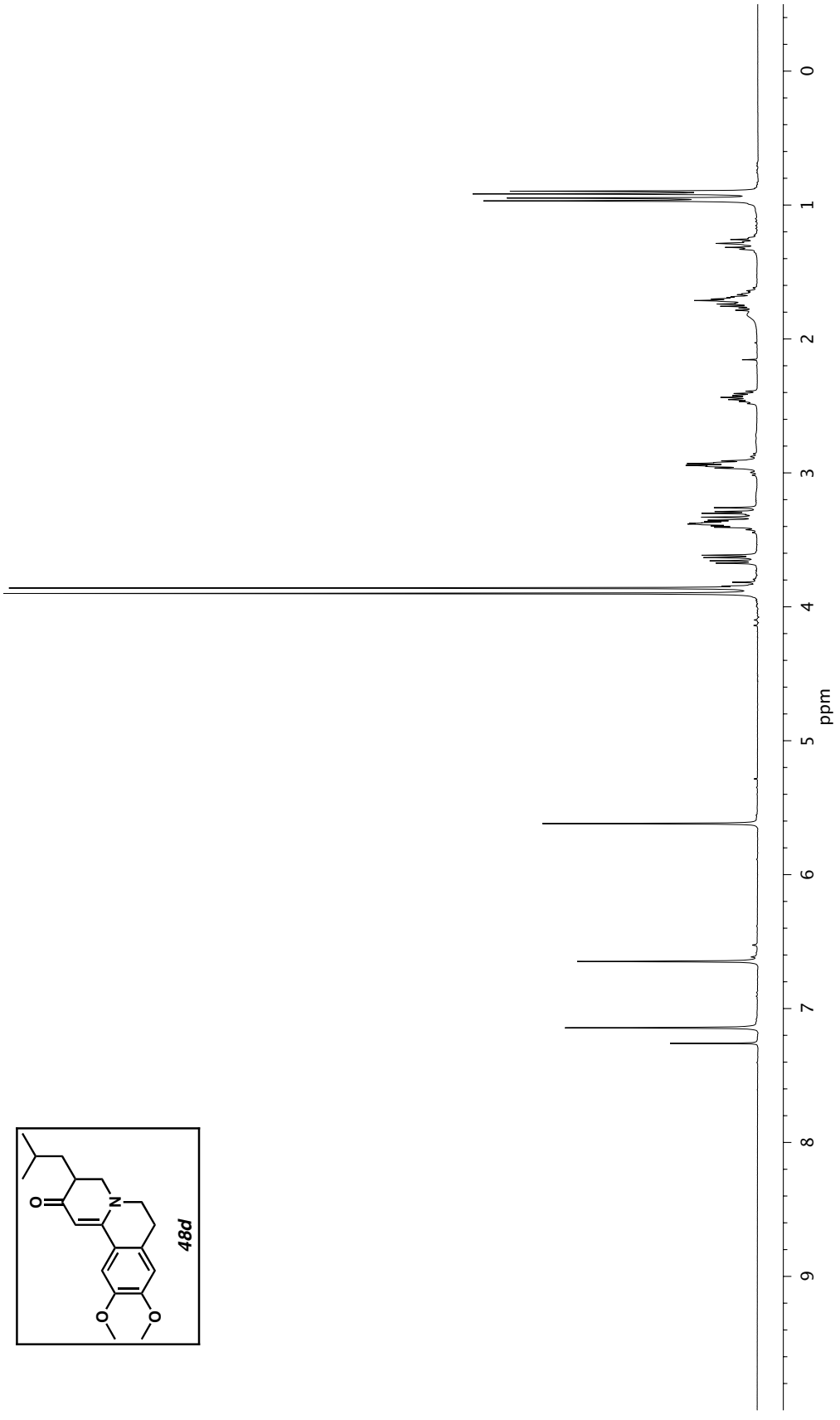
^{1}H NMR (500 MHz, $CDCl_3$) of compound **29c**.



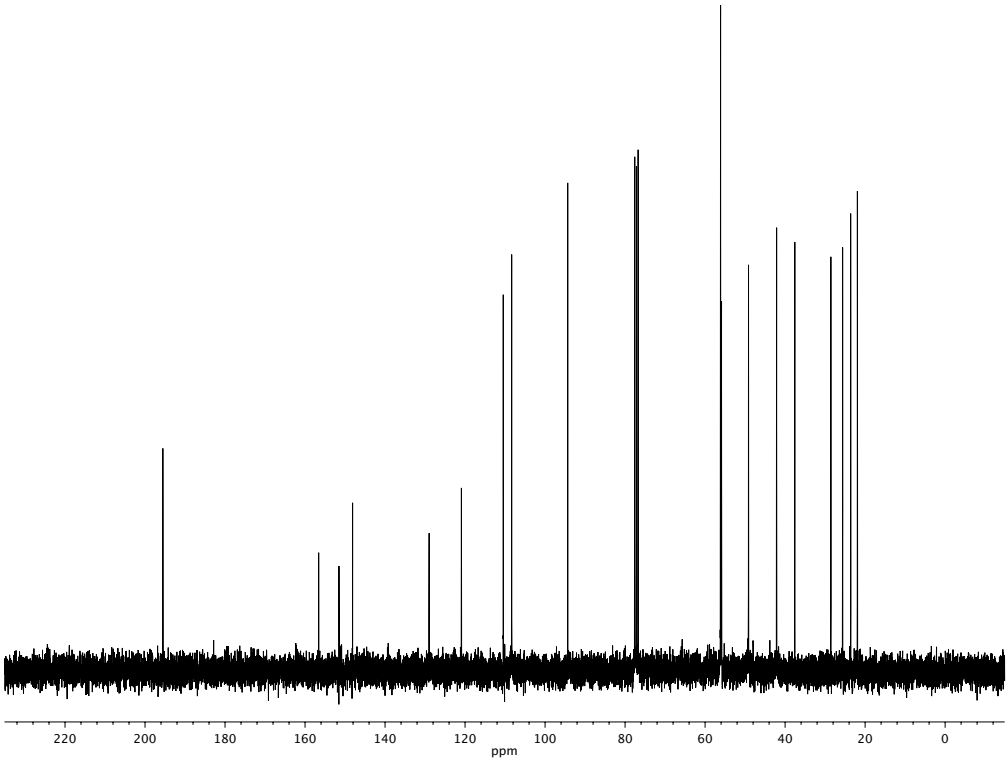
Infrared spectrum (thin film/NaCl) of compound **29c**.



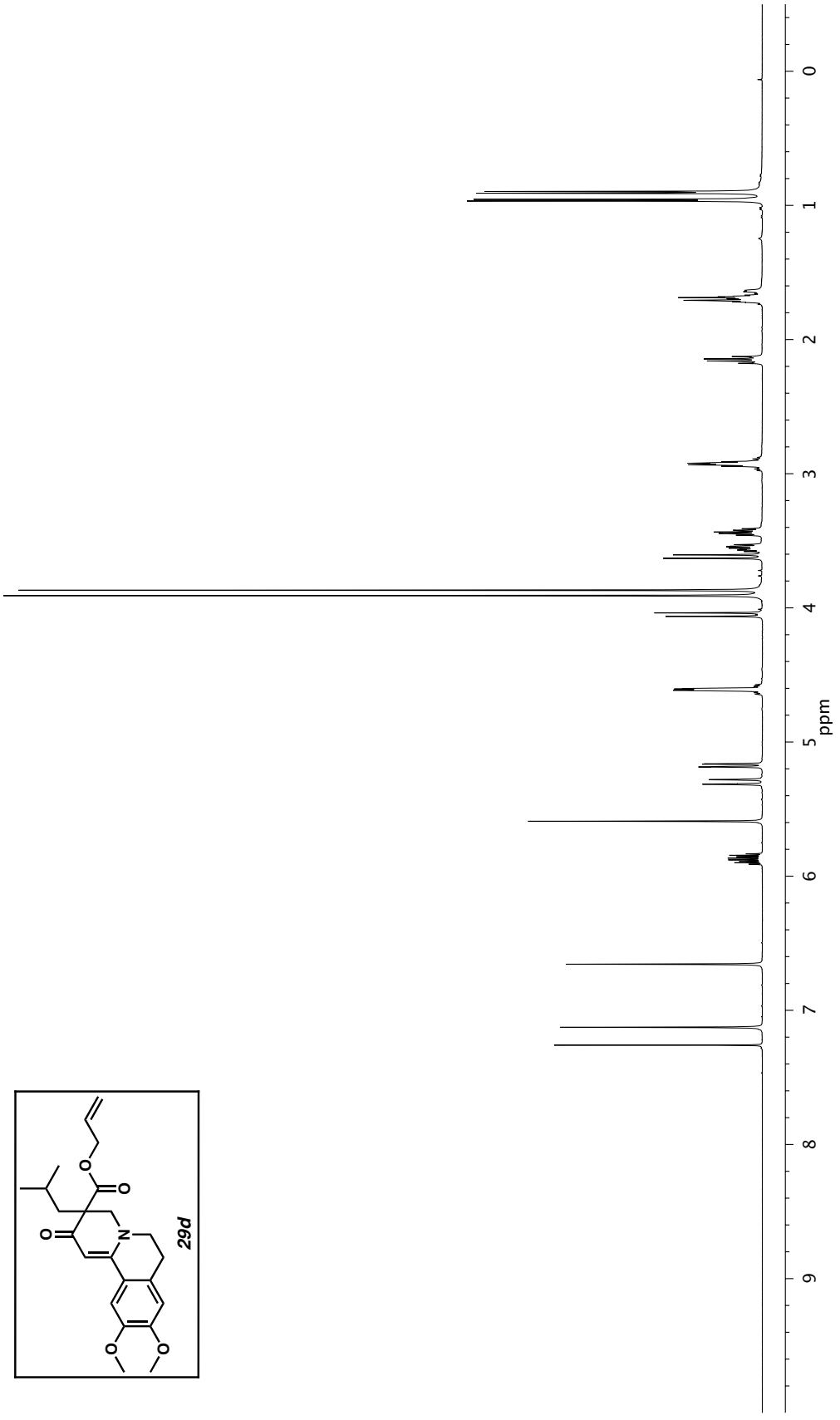
^{13}C NMR (125 MHz, $CDCl_3$) of compound **29c**.



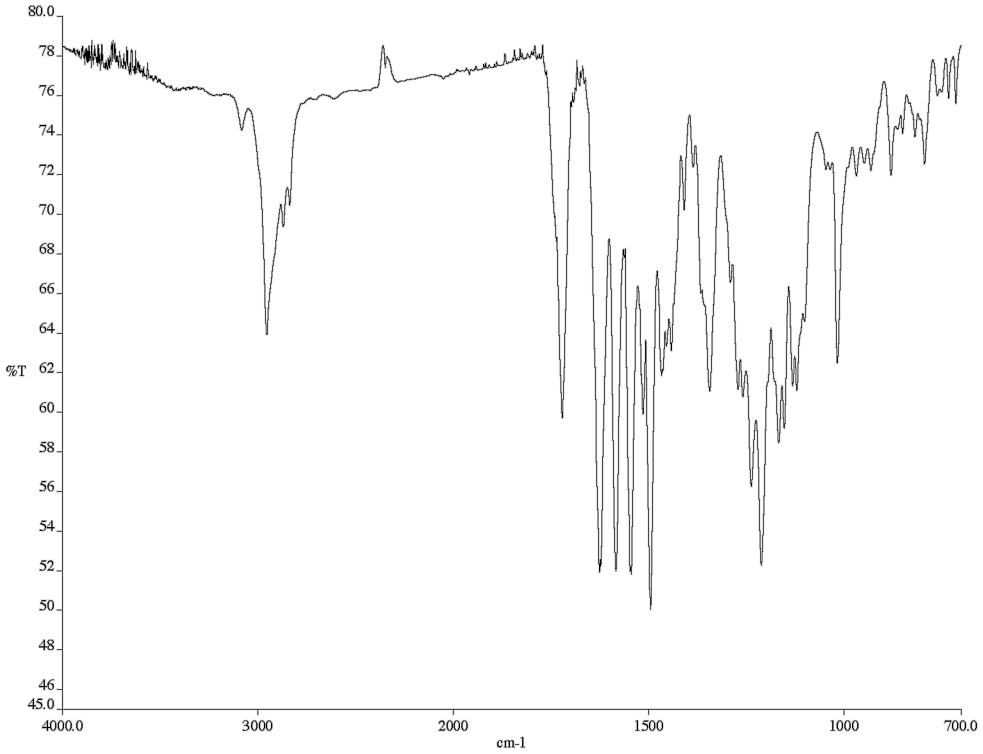
^{1}H NMR (500 MHz, $CDCl_3$) of compound **48d**.



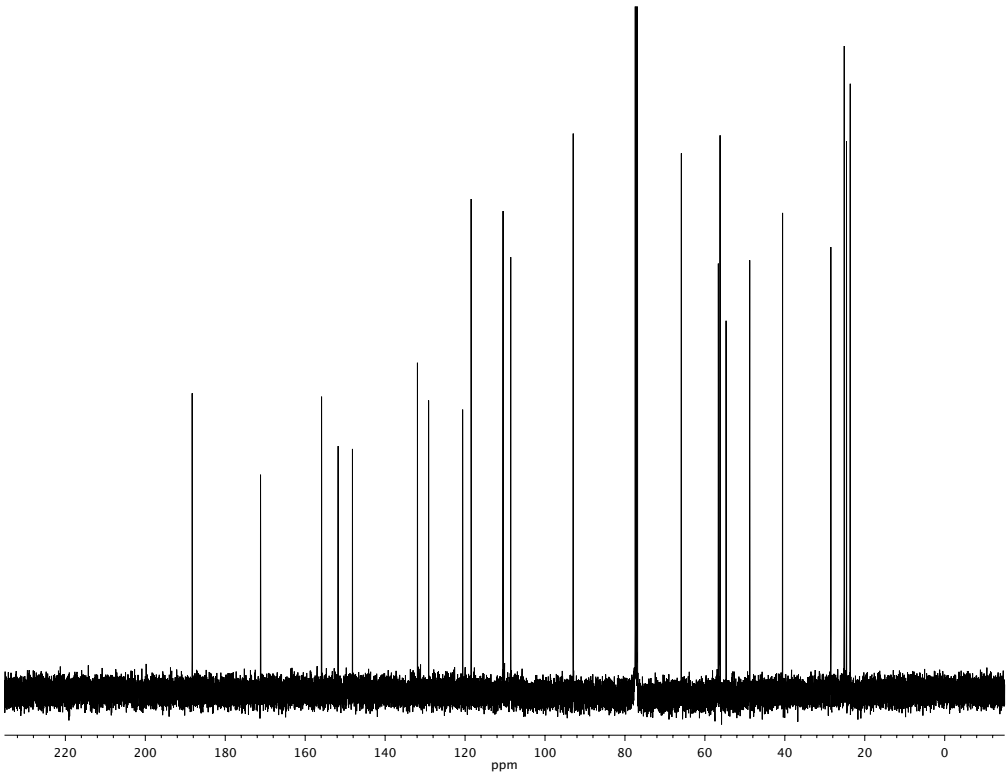
^{13}C NMR (125 MHz, $CDCl_3$) of compound **48d**.



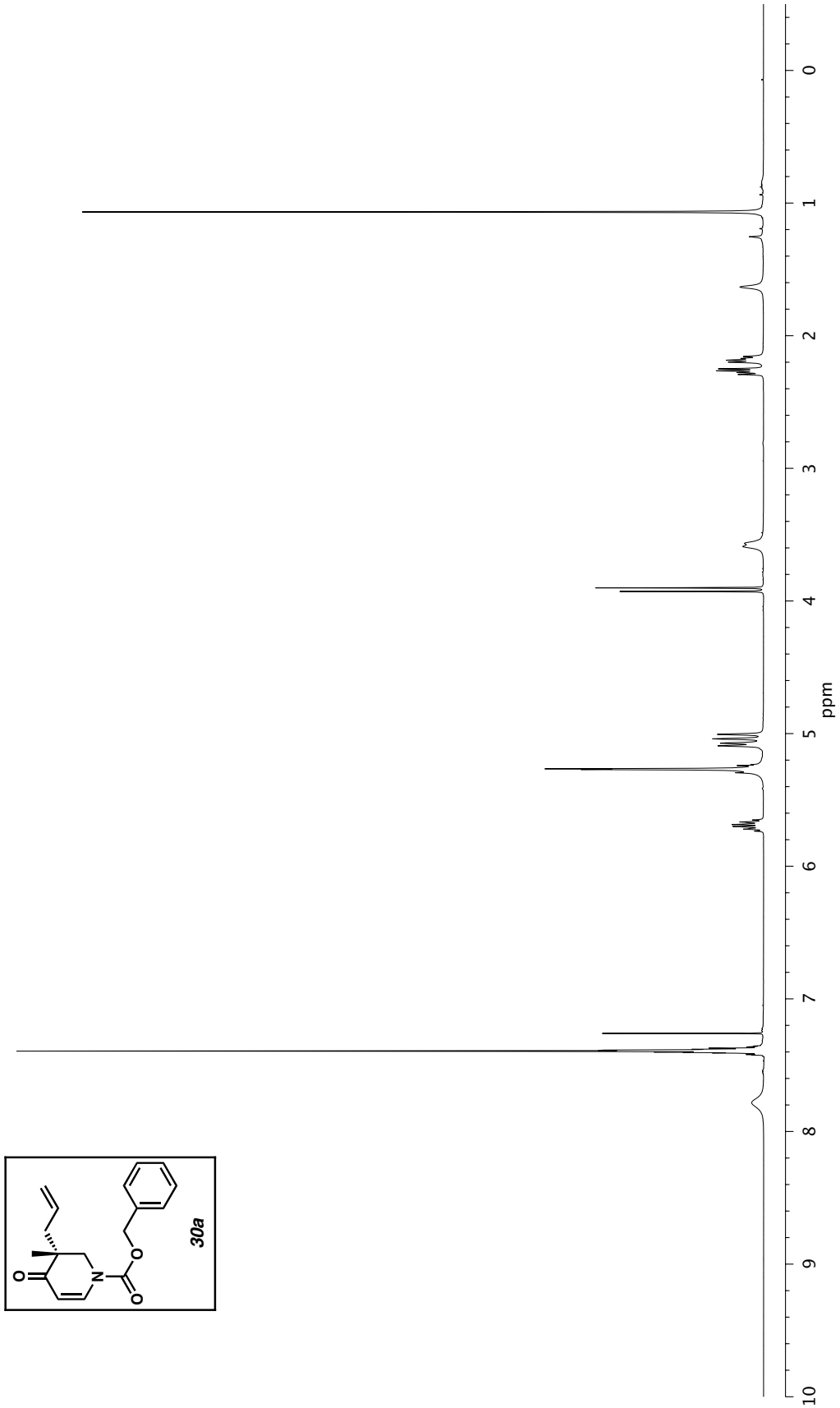
^{1}H NMR (500 MHz, $CDCl^{3}$) of compound **29d**.



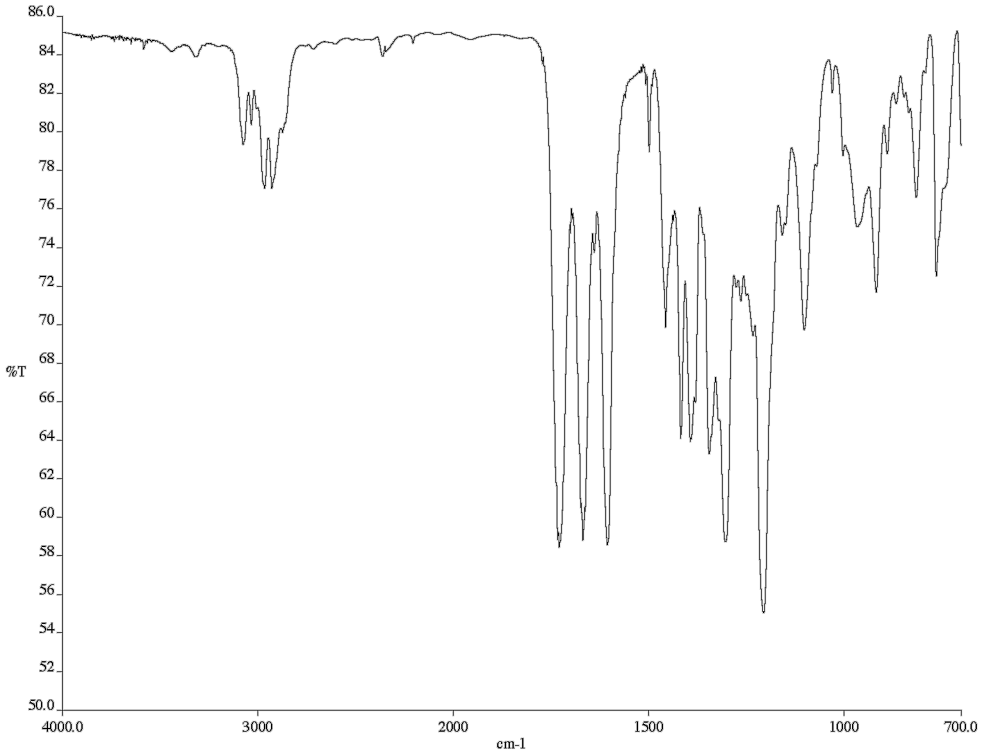
Infrared spectrum (thin film/NaCl) of compound **29d**.



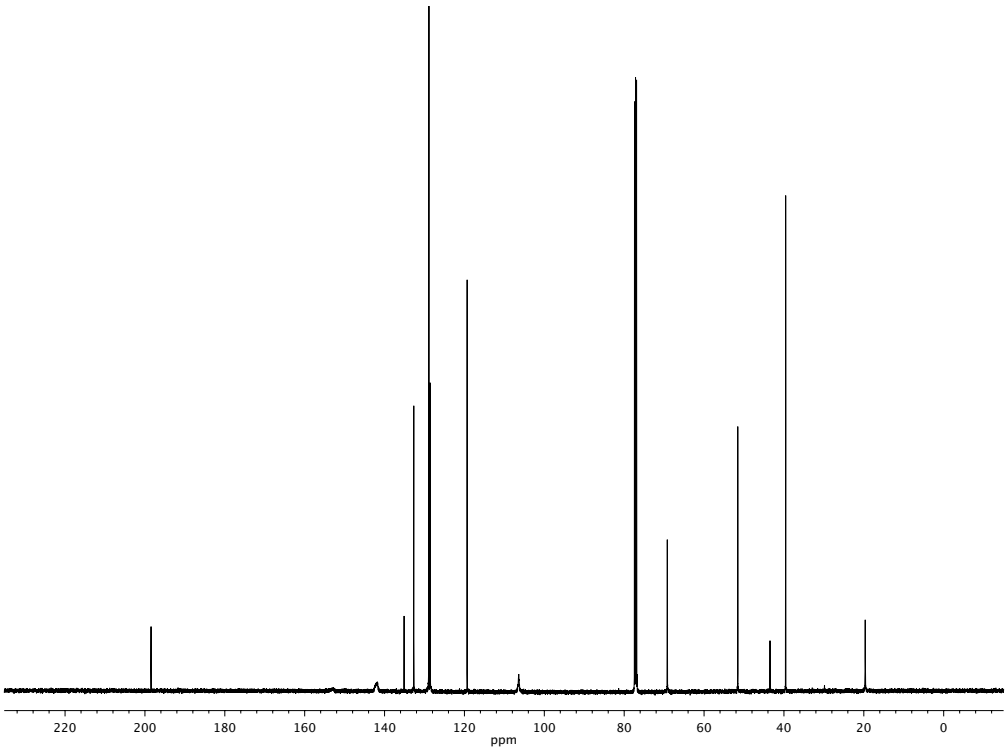
^{13}C NMR (125 MHz, $CDCl_3$) of compound **29d**.



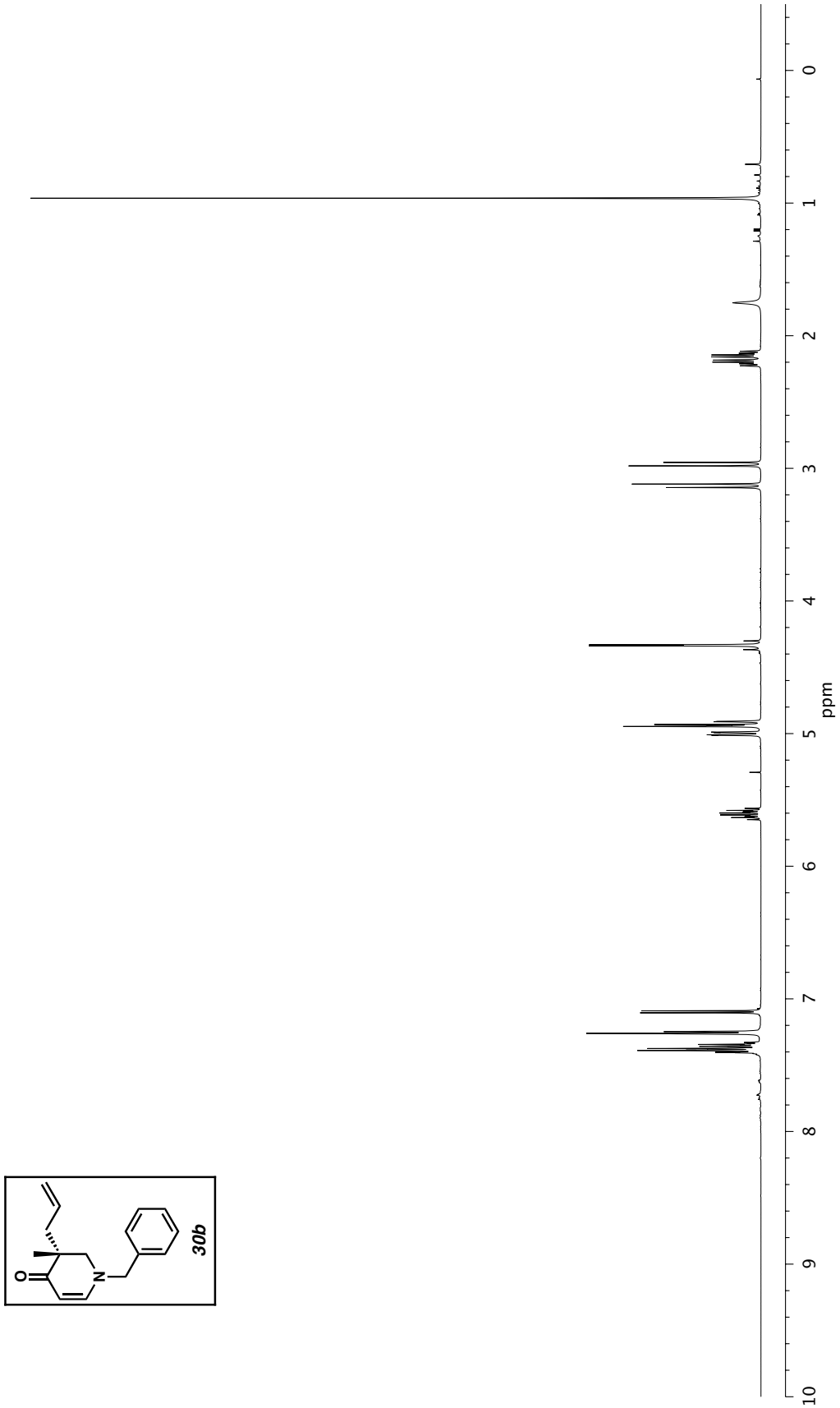
^{1}H NMR (500 MHz, $CDCl_3$) of compound **30a**.



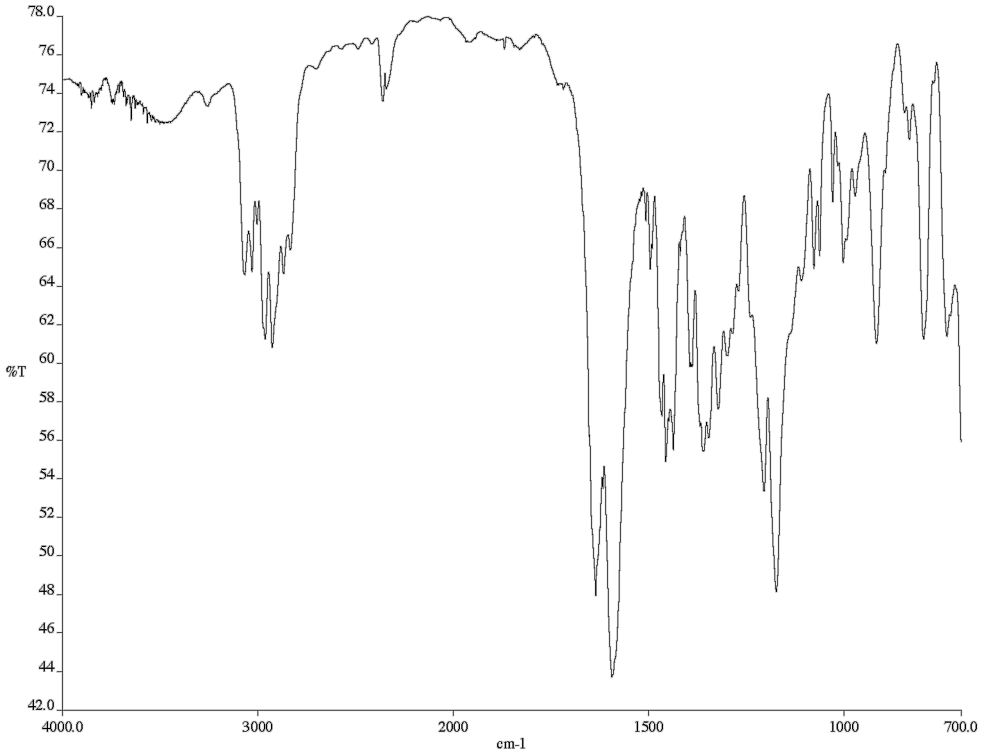
Infrared spectrum (thin film/NaCl) of compound **30a**.



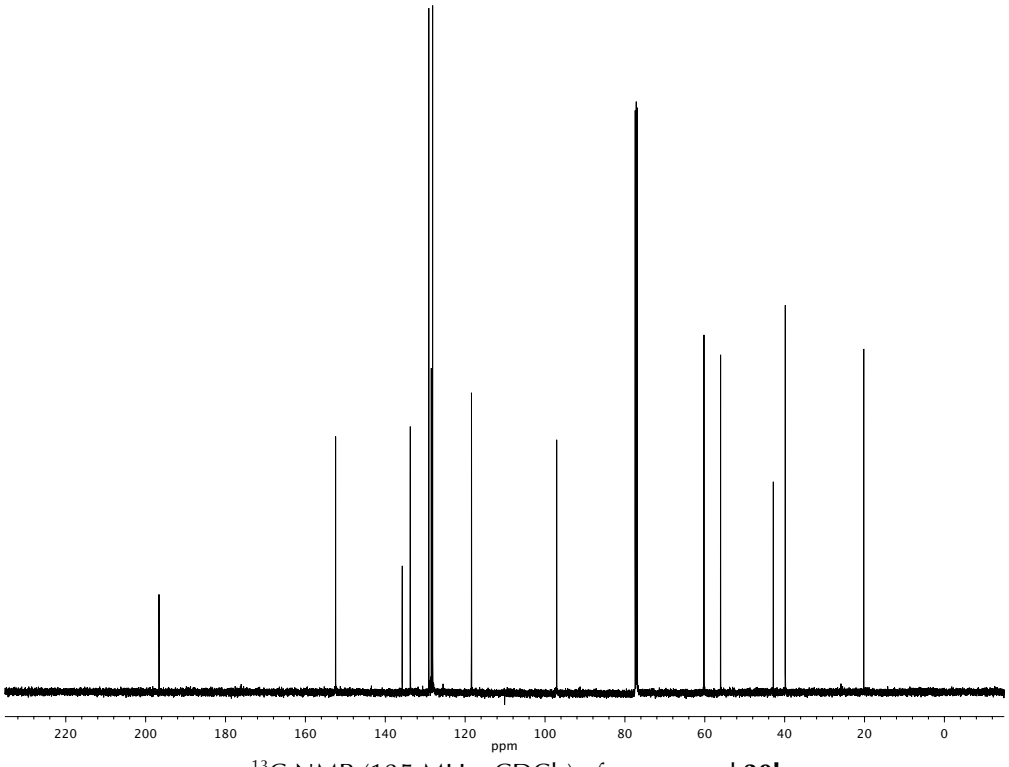
^{13}C NMR (125 MHz, $CDCl_3$) of compound **30a**.



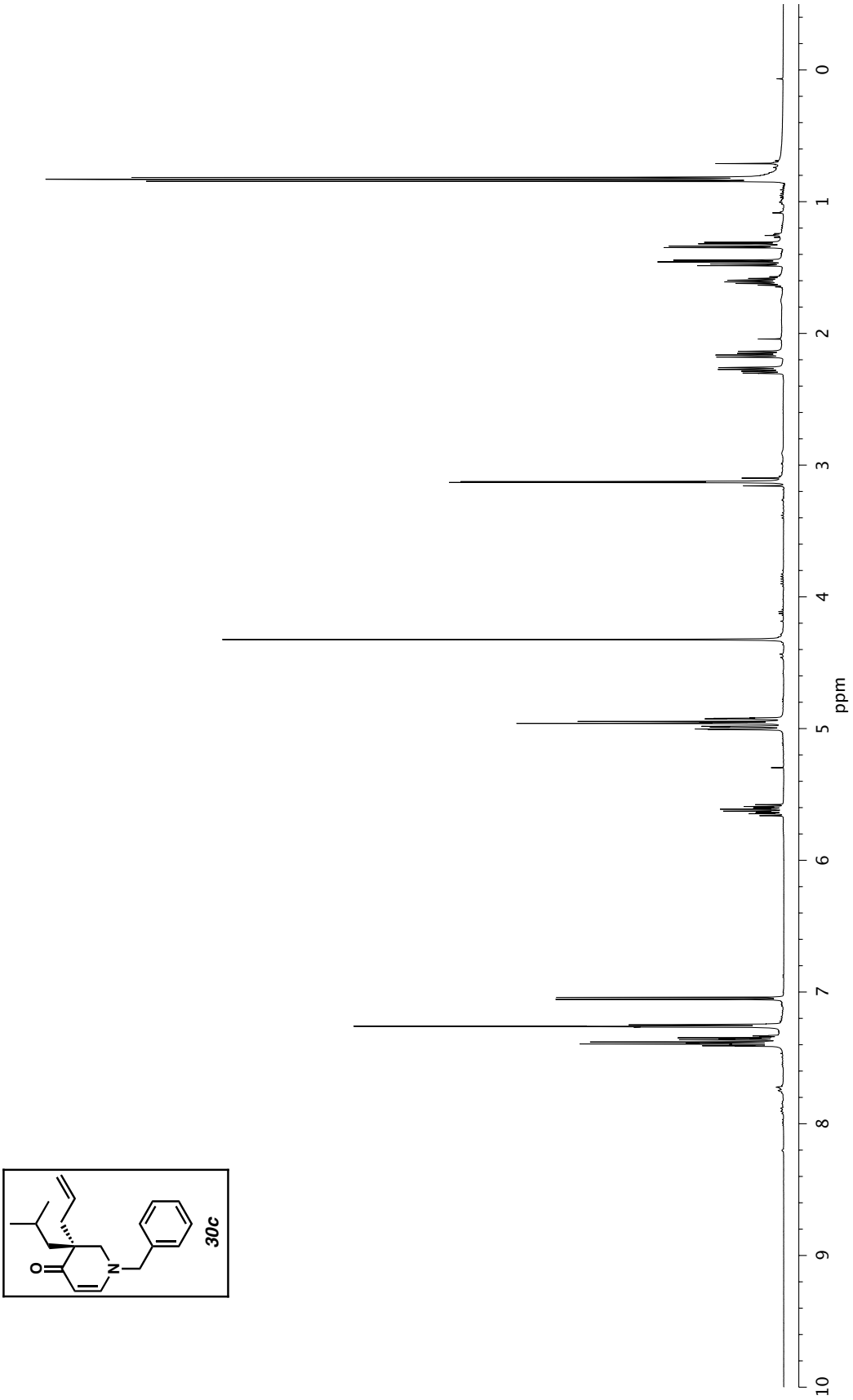
^{1}H NMR (500 MHz, $CDCl_3$) of compound **30b**.



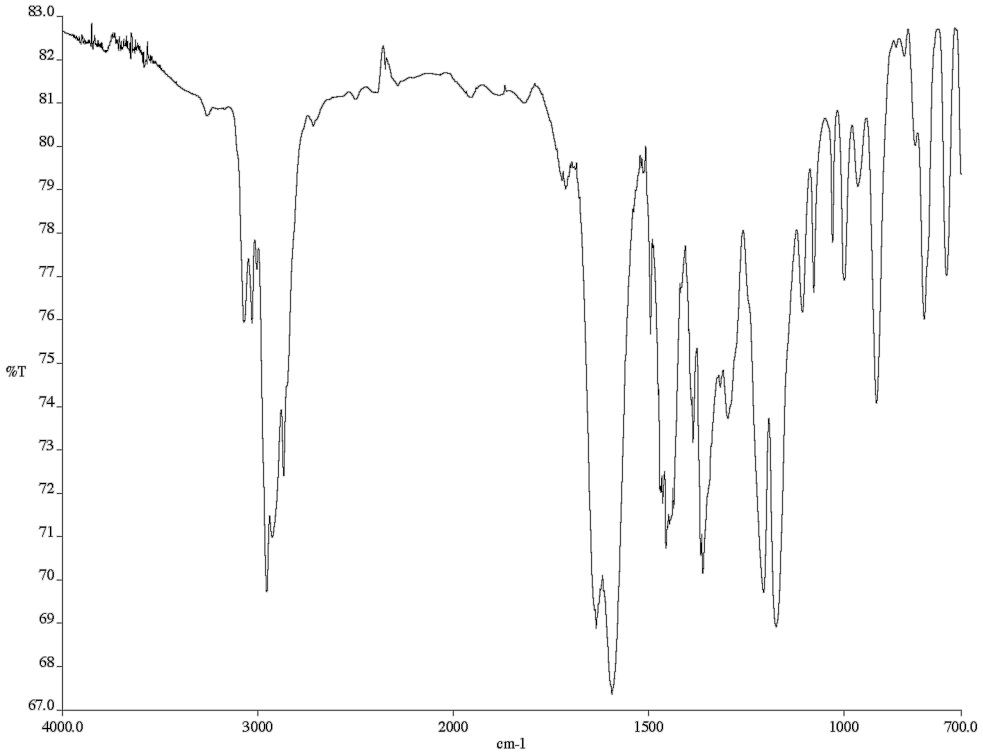
Infrared spectrum (thin film/NaCl) of compound **30b**.



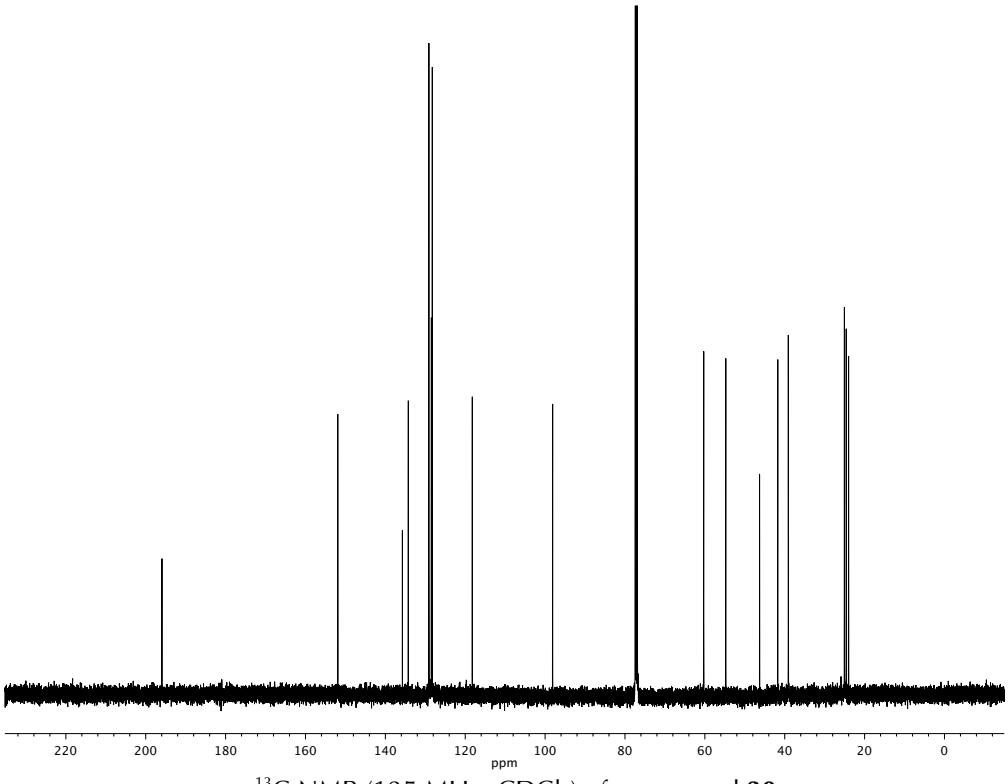
^{13}C NMR (125 MHz, $CDCl_3$) of compound **30b**.



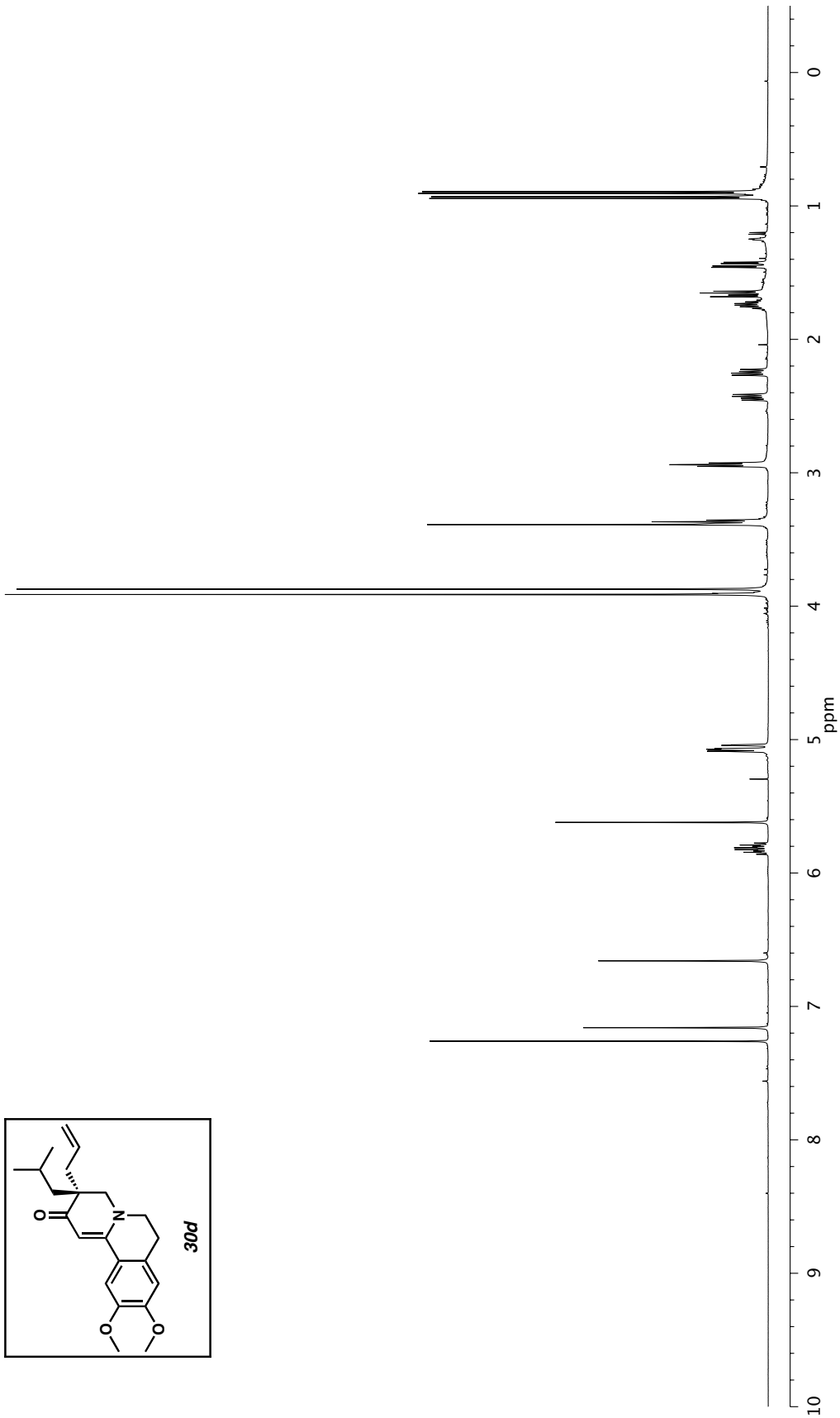
^{1}H NMR (500 MHz, $CDCl_3$) of compound **30c**.



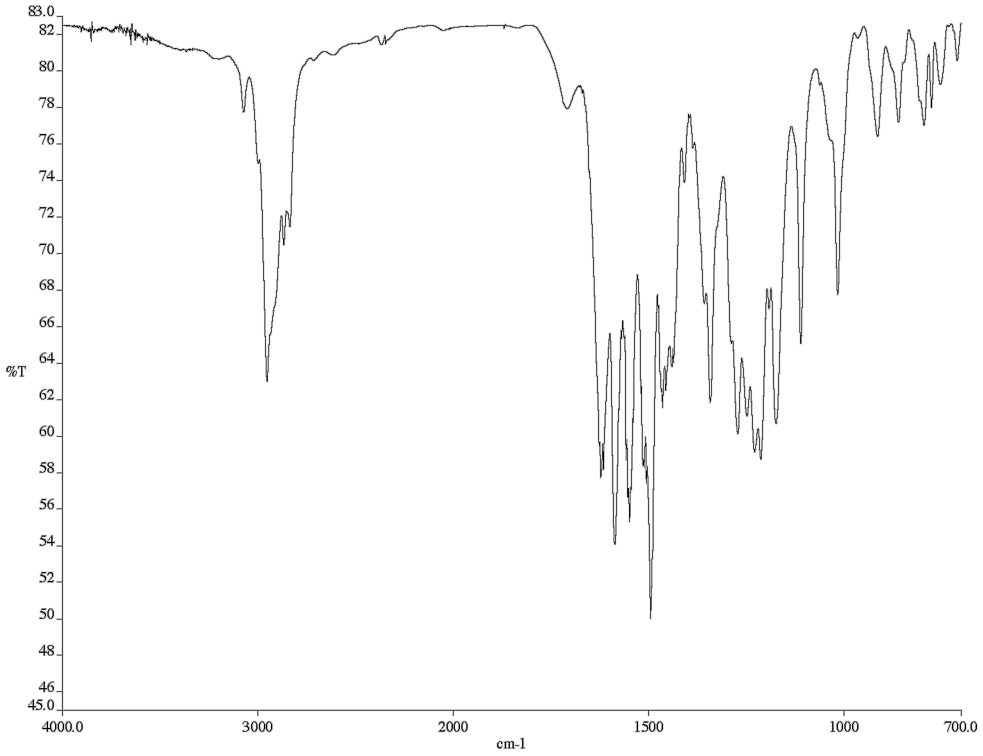
Infrared spectrum (thin film/NaCl) of compound **30c**.



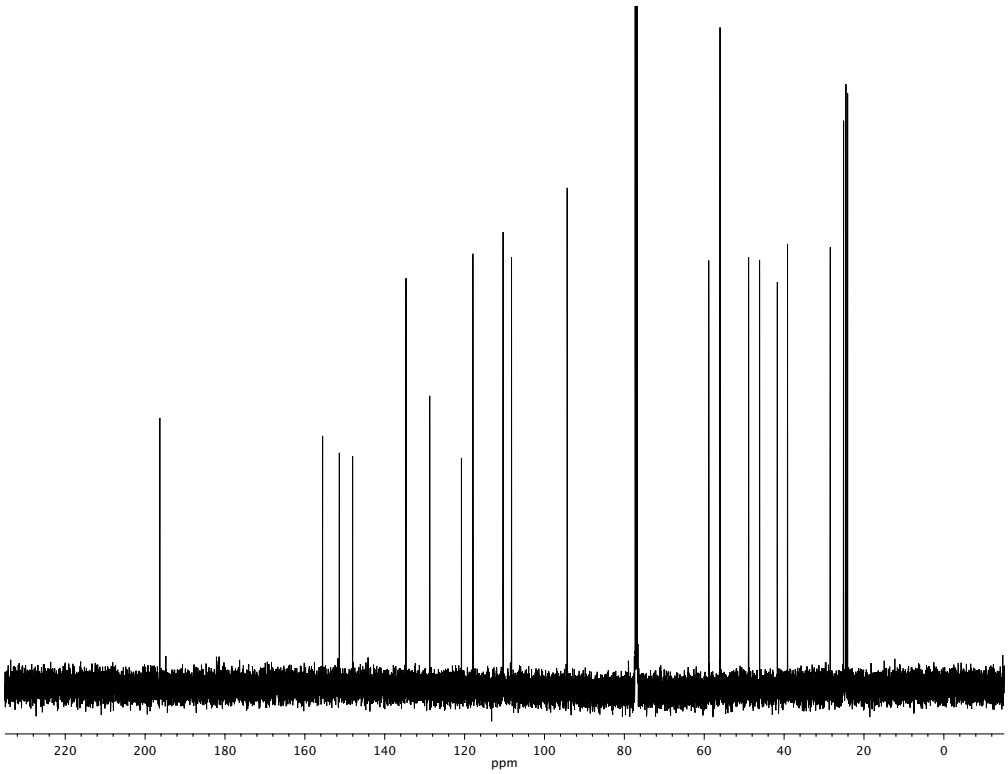
^{13}C NMR (125 MHz, $CDCl_3$) of compound **30c**.



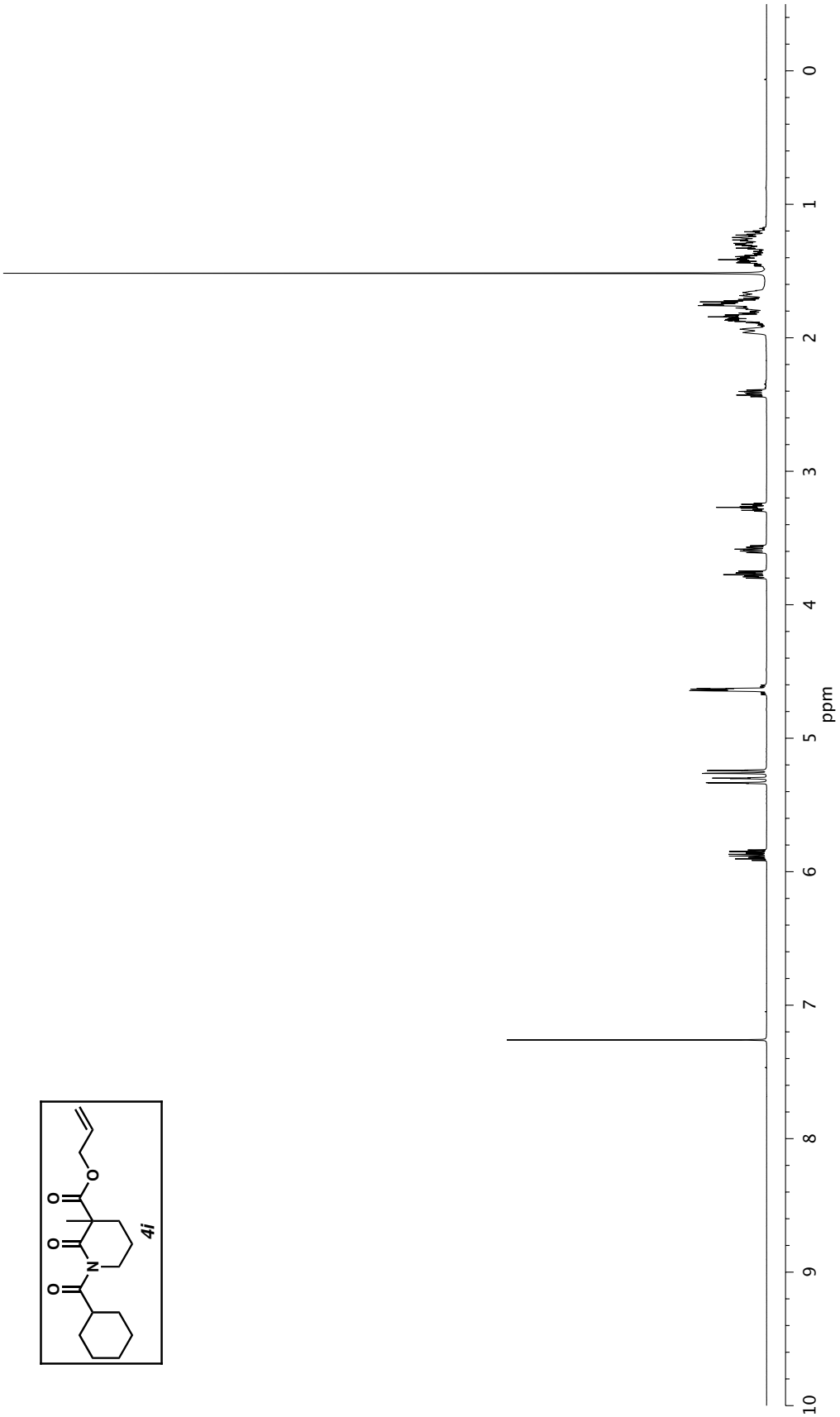
^{1}H NMR (500 MHz, $CDCl^{3}$) of compound **30d**.



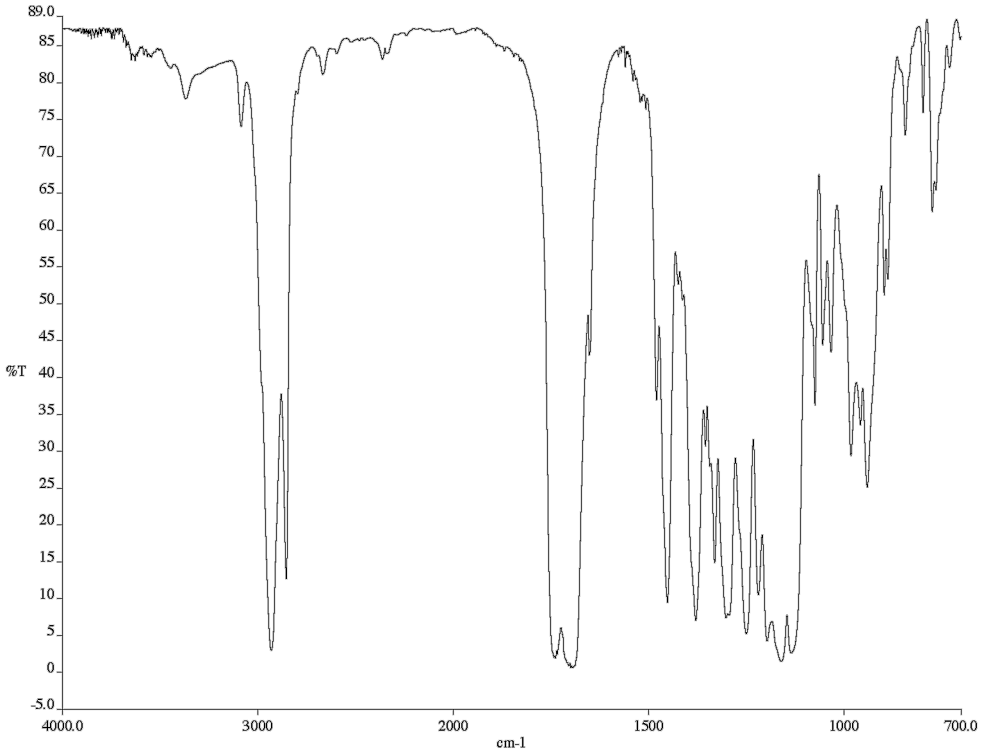
Infrared spectrum (thin film/NaCl) of compound **30d**.



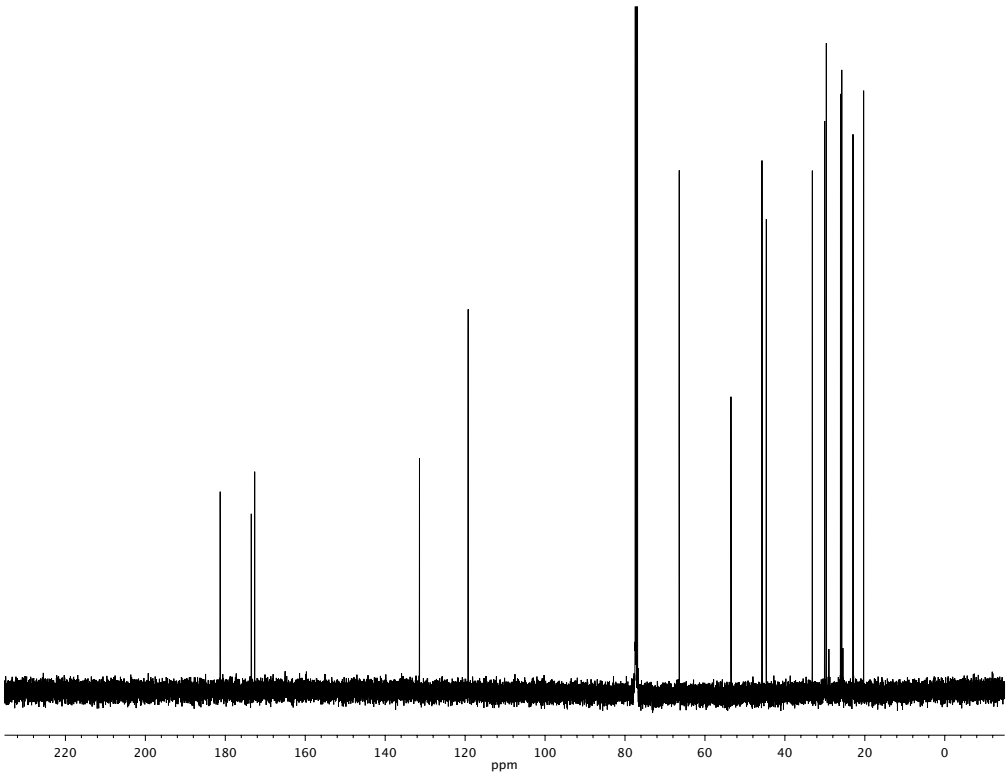
^{13}C NMR (125 MHz, $CDCl_3$) of compound **30d**.



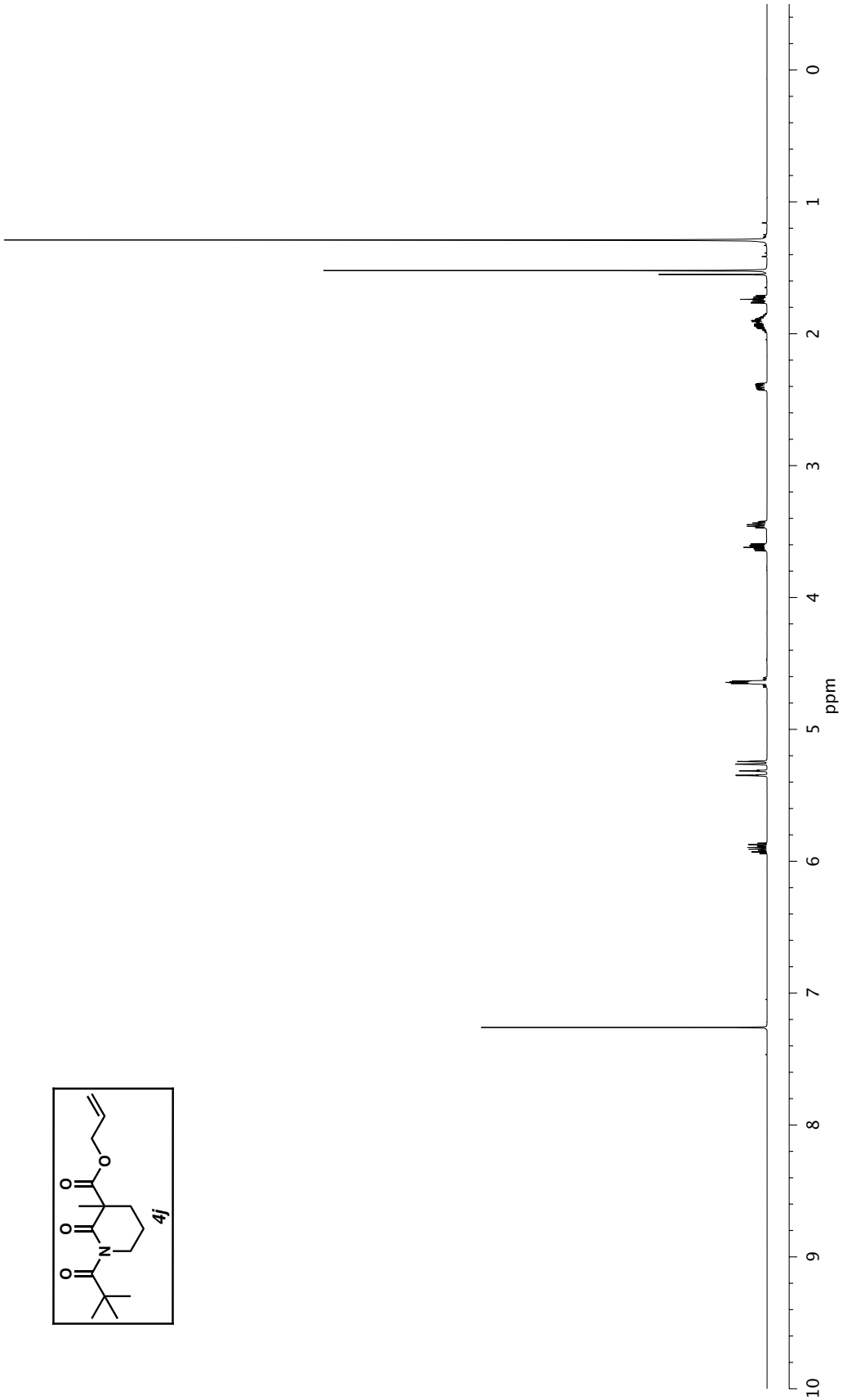
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4i**.



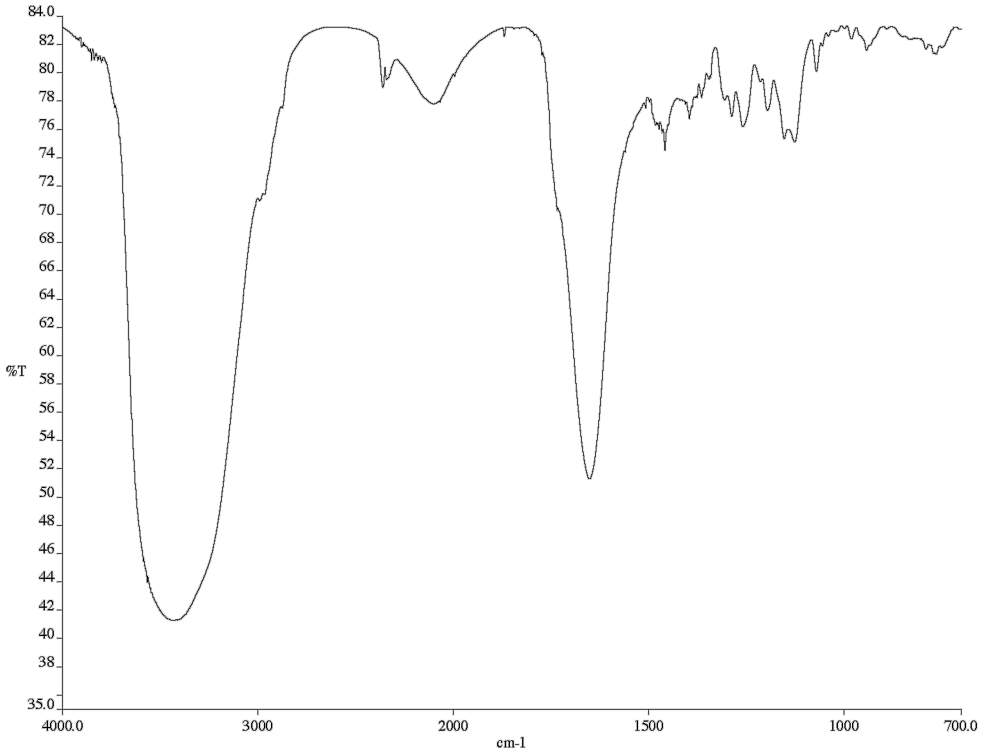
Infrared spectrum (thin film/NaCl) of compound **4i**.



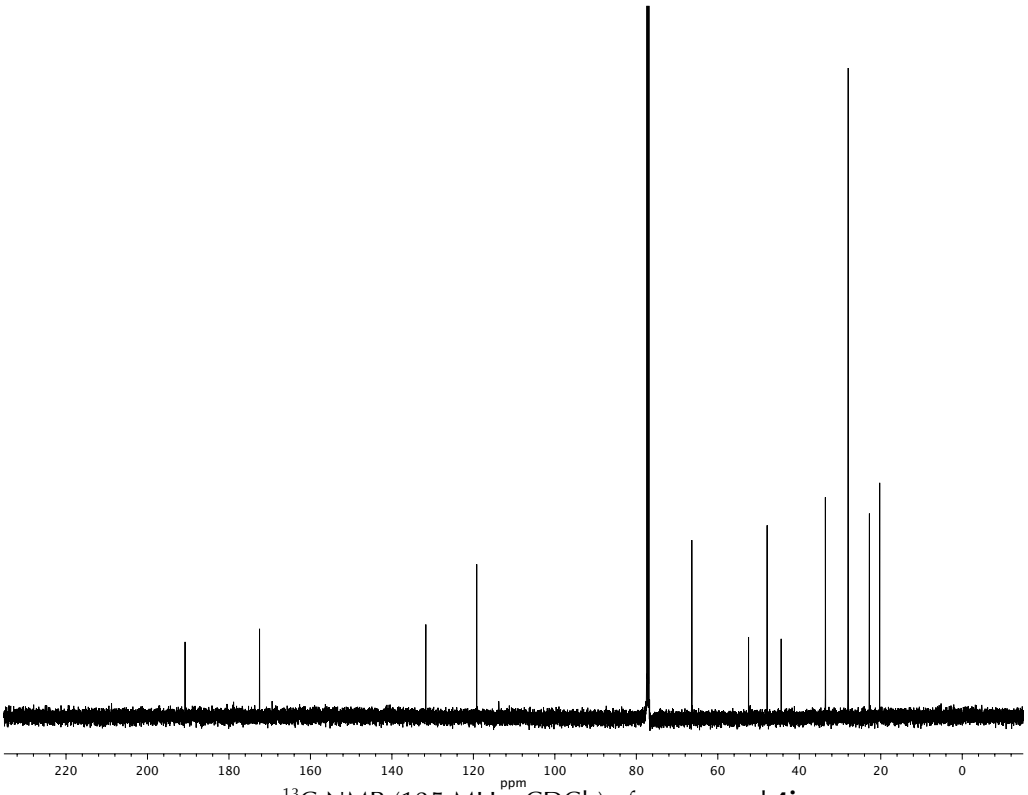
^{13}C NMR (125 MHz, $CDCl_3$) of compound **4i**.



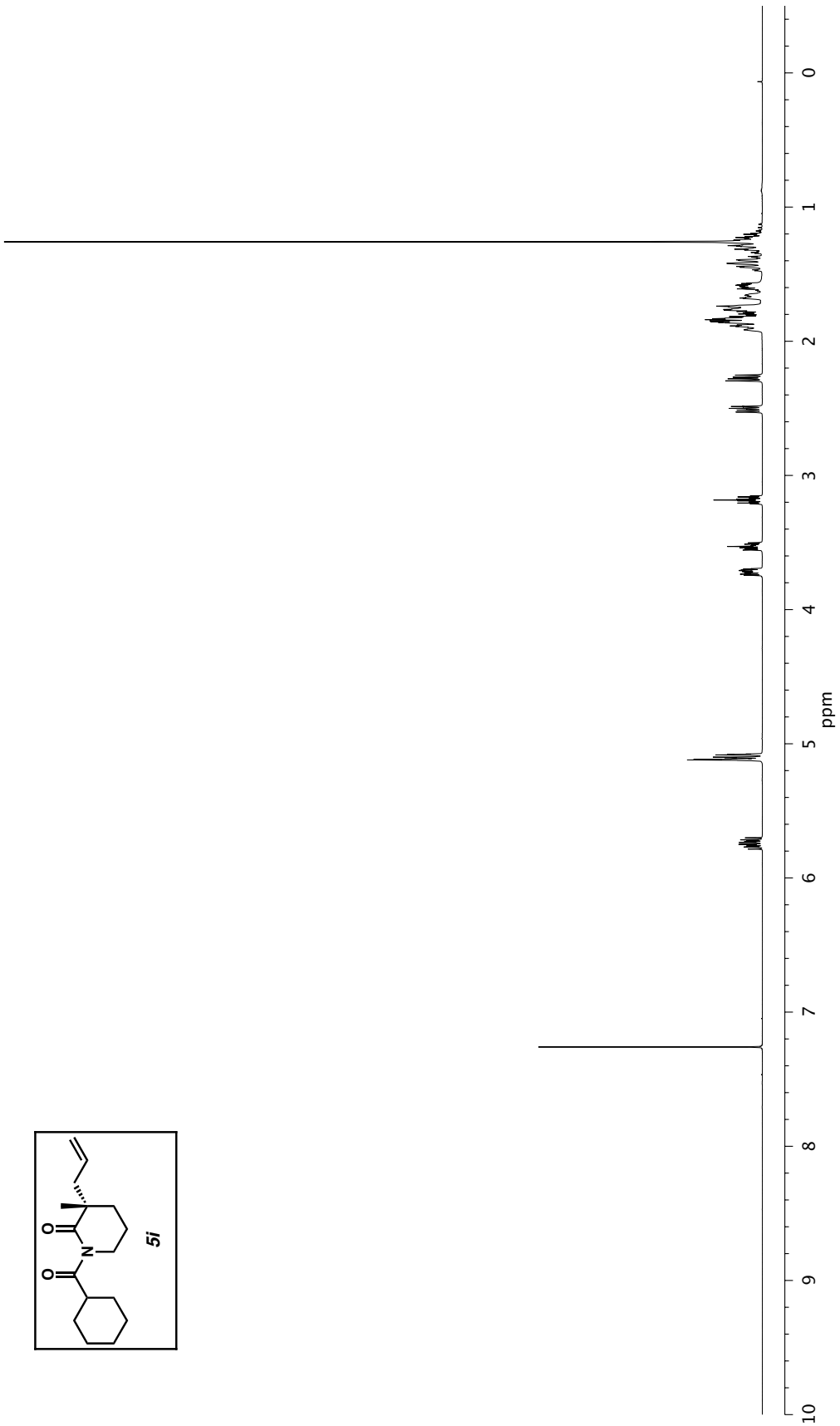
^{1}H NMR (500 MHz, $CDCl_3$) of compound **4j**.



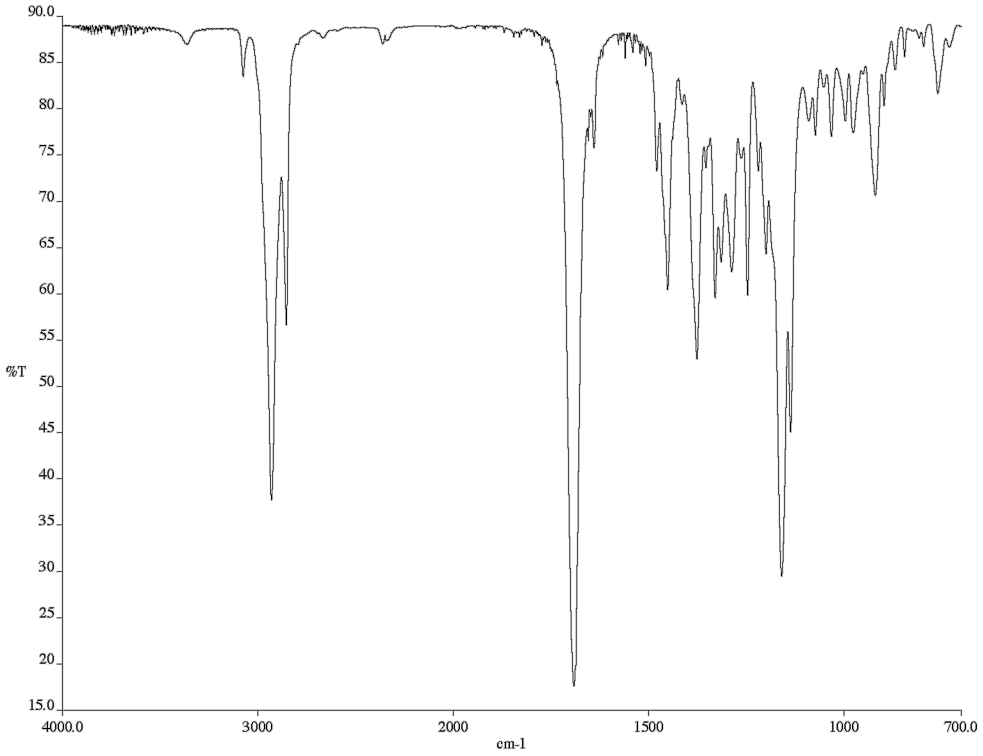
Infrared spectrum (thin film/NaCl) of compound **4j**.



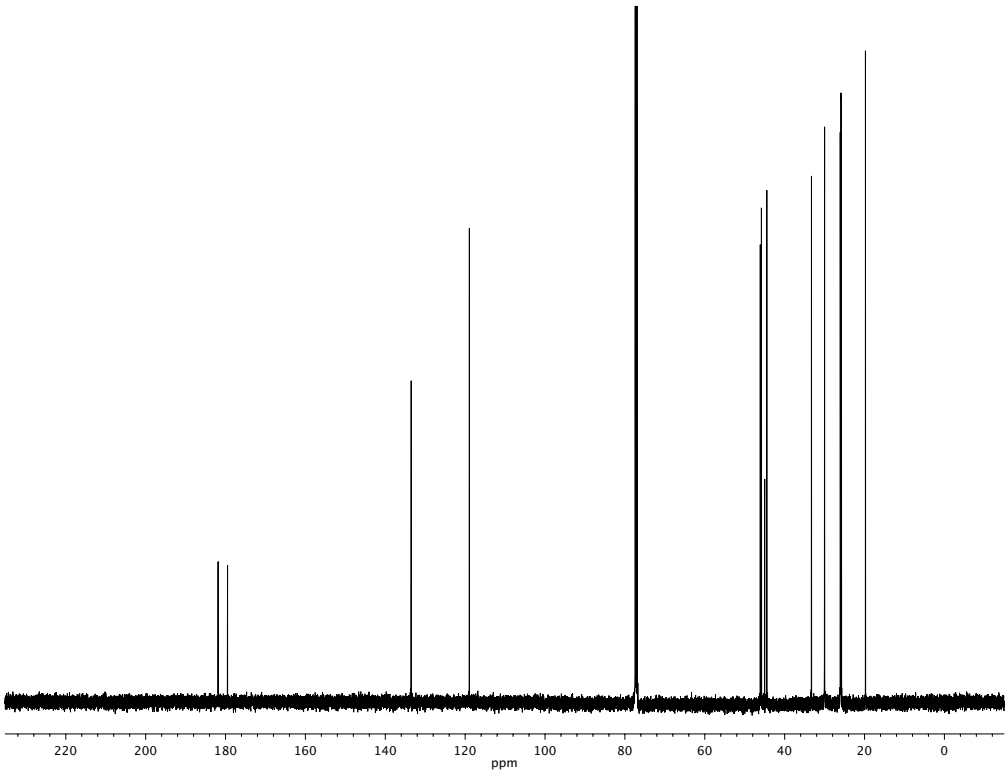
^{13}C NMR (125 MHz, $CDCl_3$) of compound **4j**.



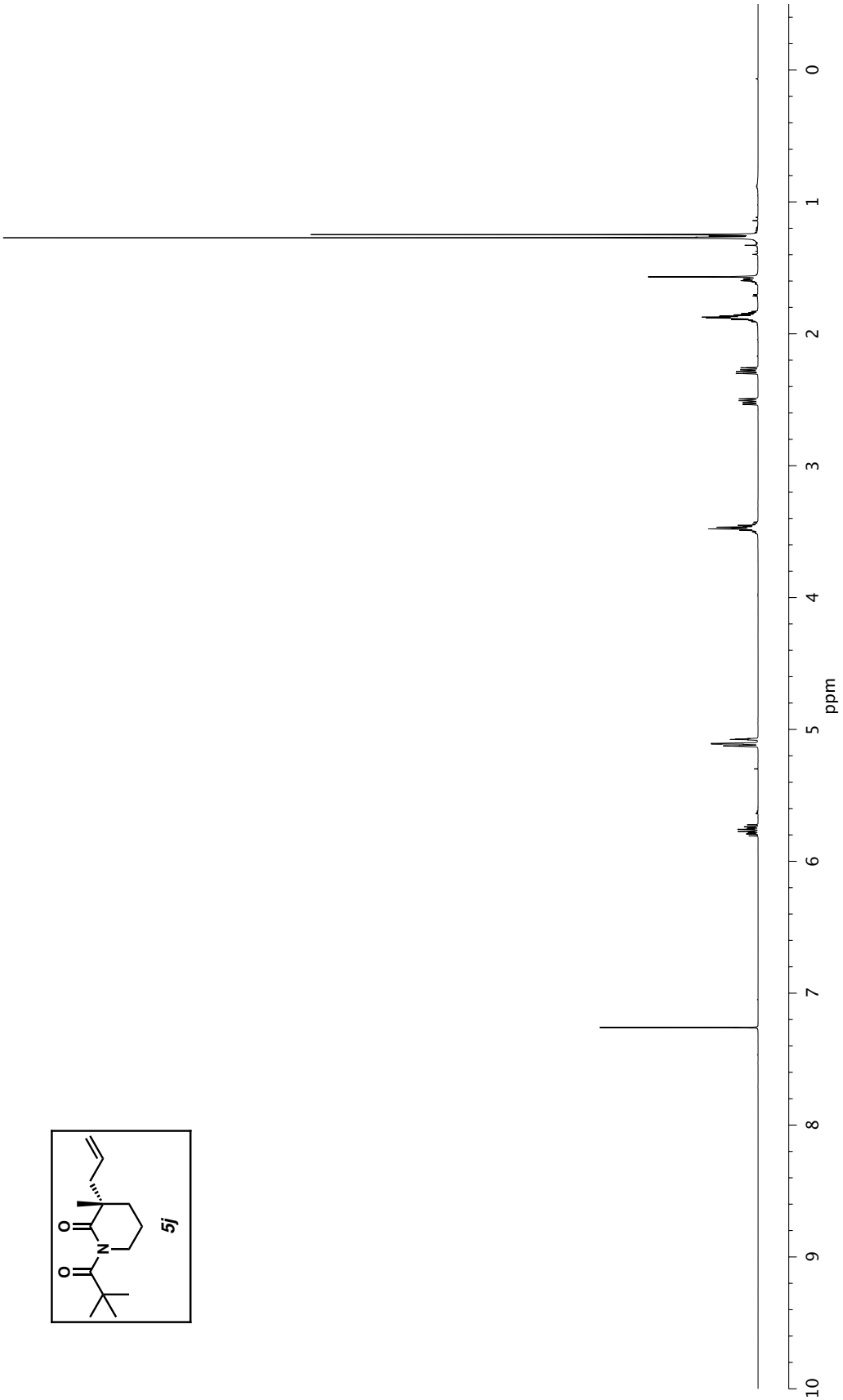
^{1}H NMR (500 MHz, $CDCl_3$) of compound **5i**.



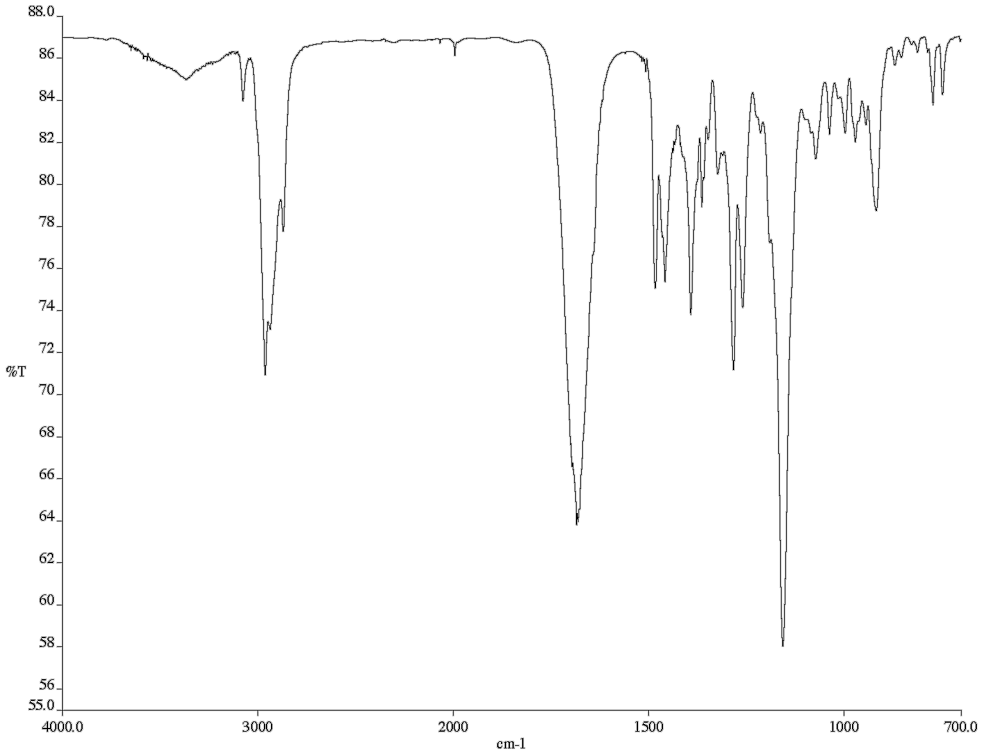
Infrared spectrum (thin film/NaCl) of compound **5i**.



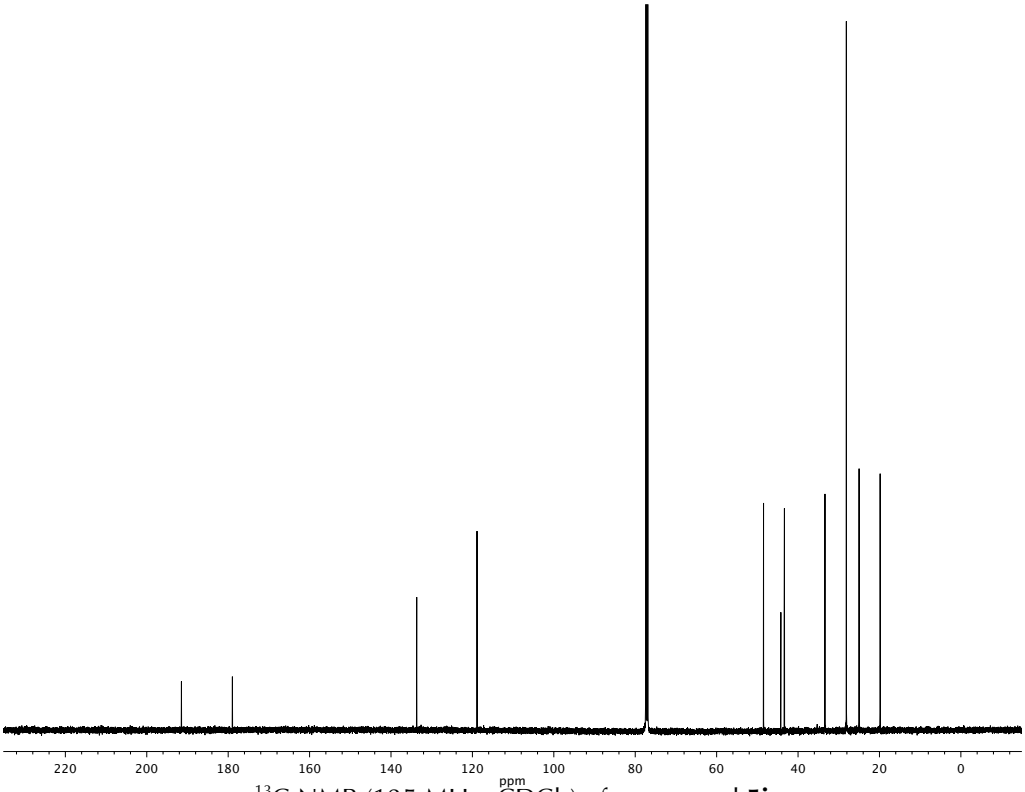
^{13}C NMR (125 MHz, $CDCl_3$) of compound **5i**.



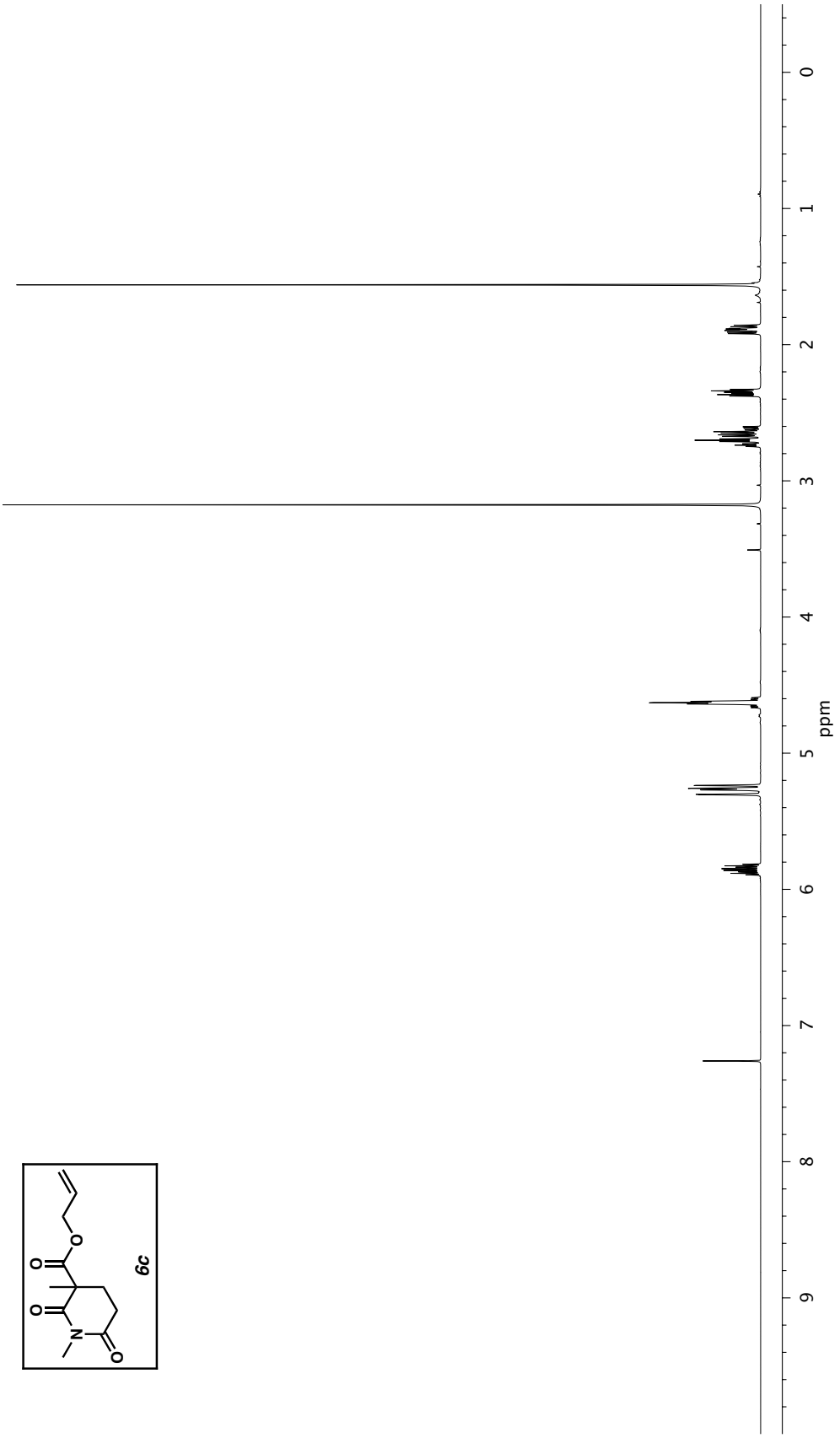
^{1}H NMR (500 MHz, $CDCl_3$) of compound **5j**.



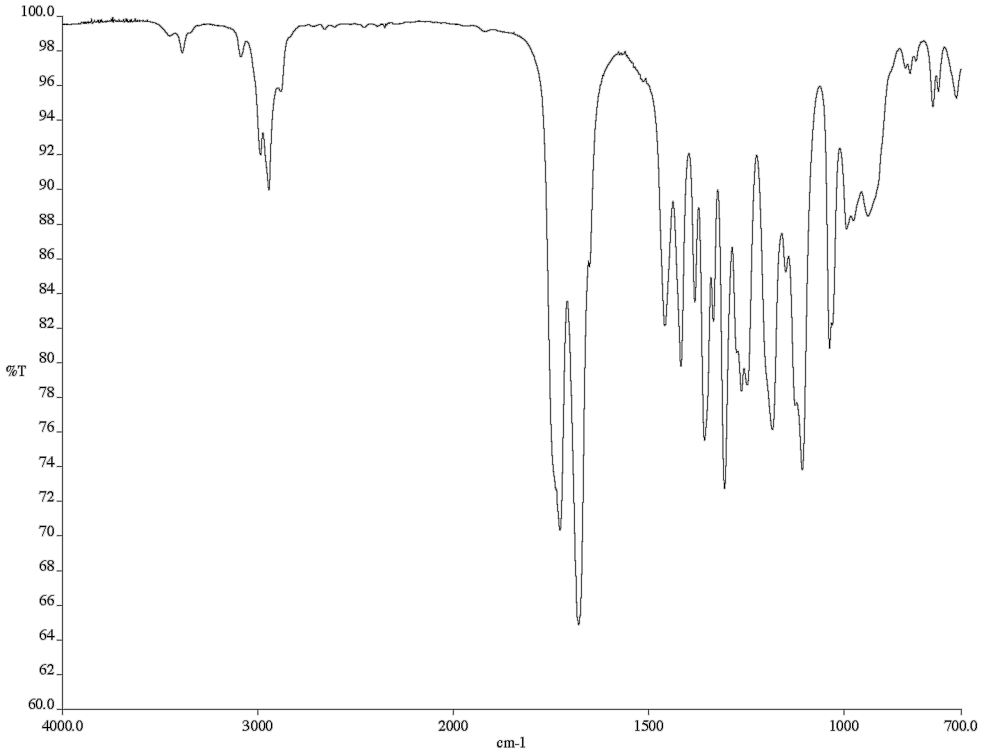
Infrared spectrum (thin film/NaCl) of compound **5j**.



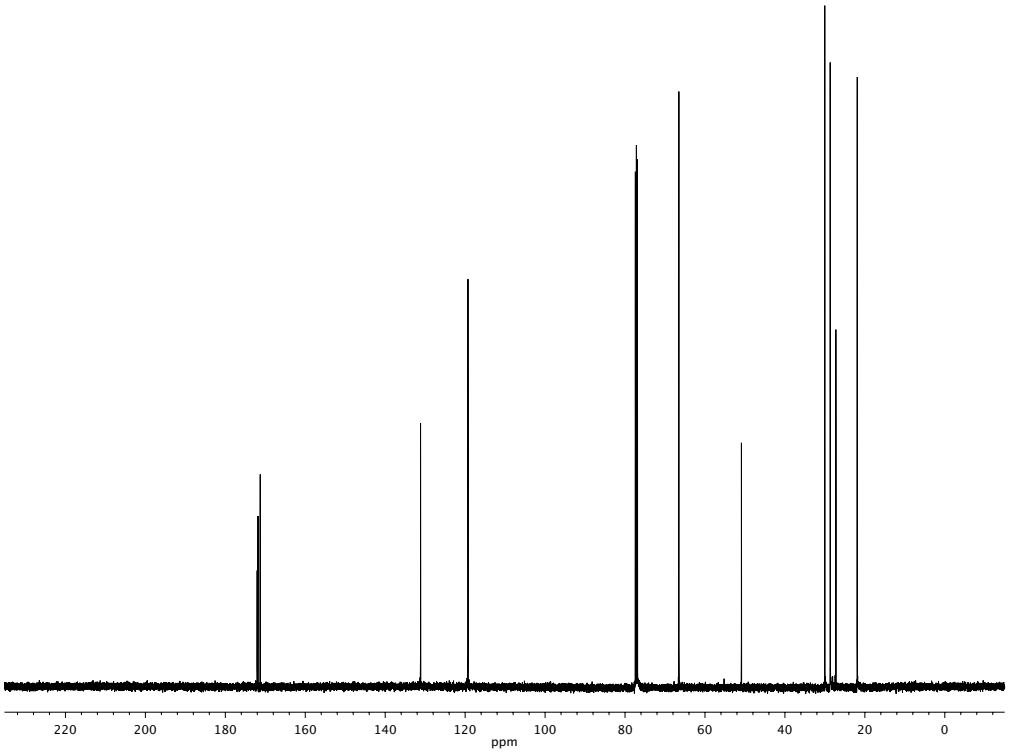
^{13}C NMR (125 MHz, $CDCl_3$) of compound **5j**.



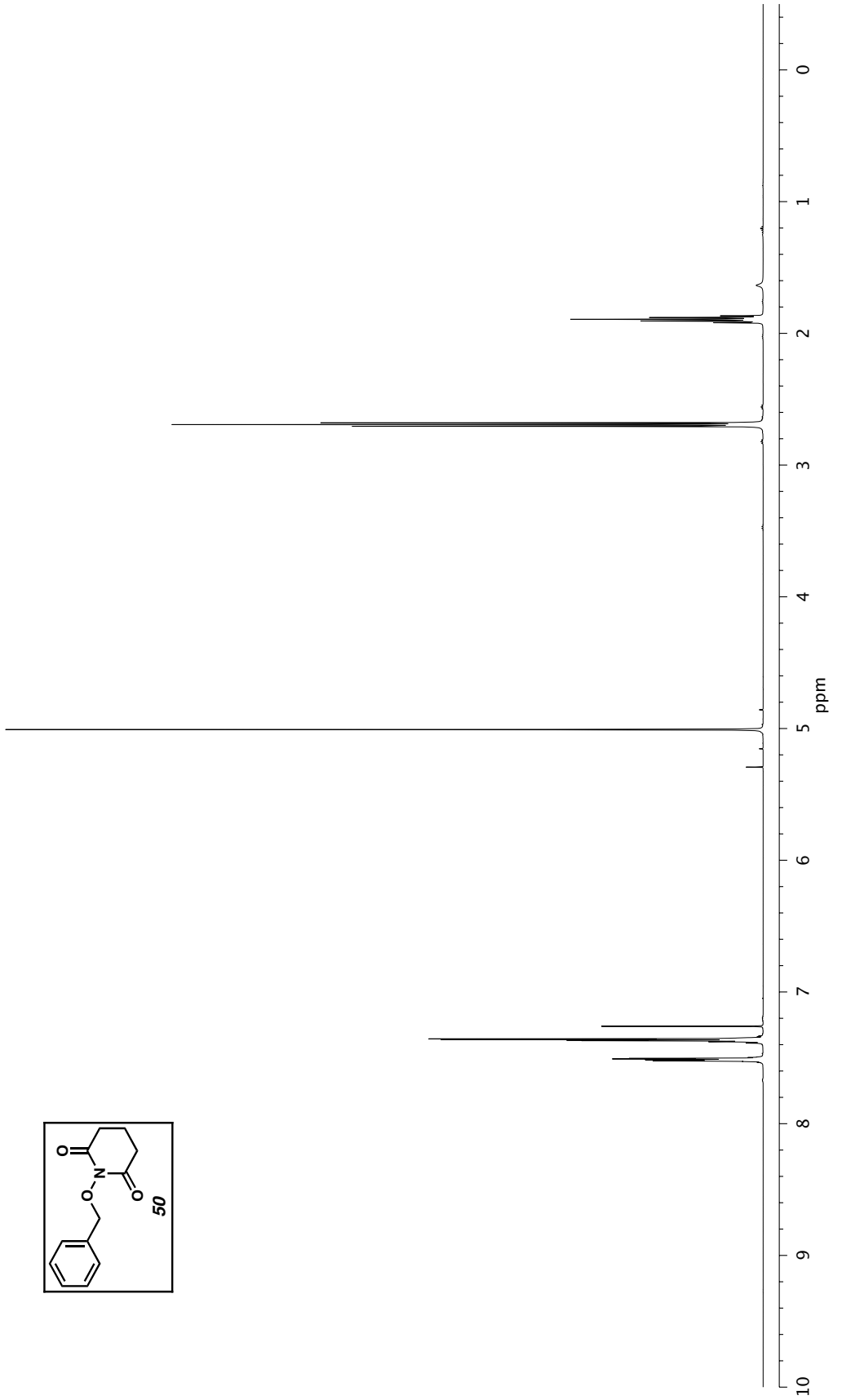
^{1}H NMR (500 MHz, $CDCl_3$) of compound **6c**.



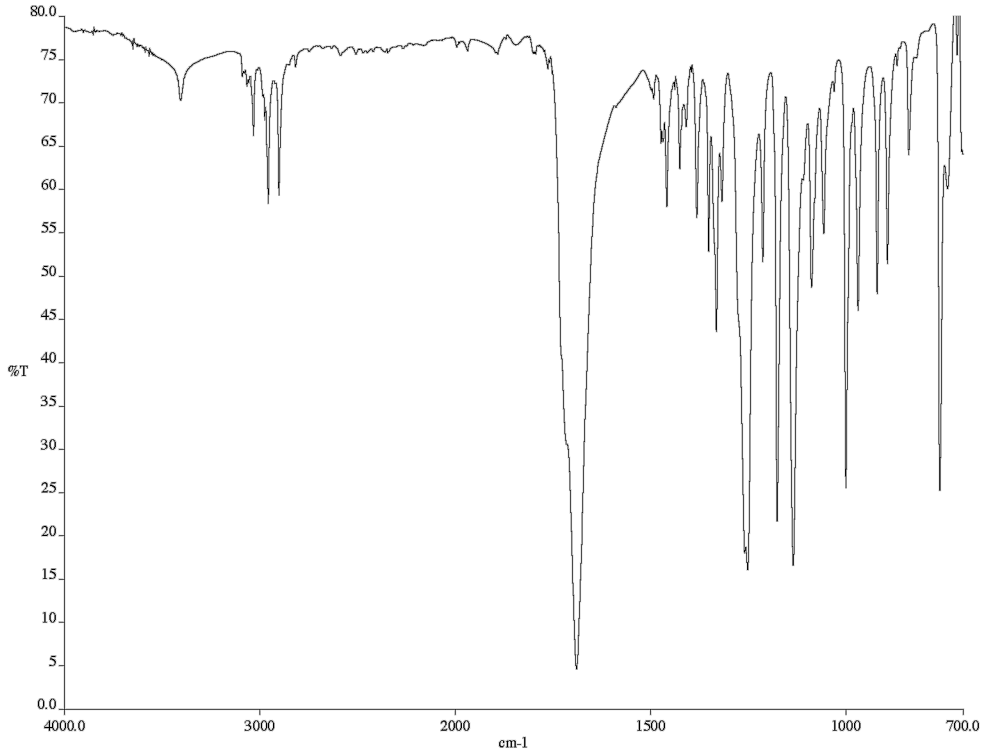
Infrared spectrum (thin film/NaCl) of compound **6c**.



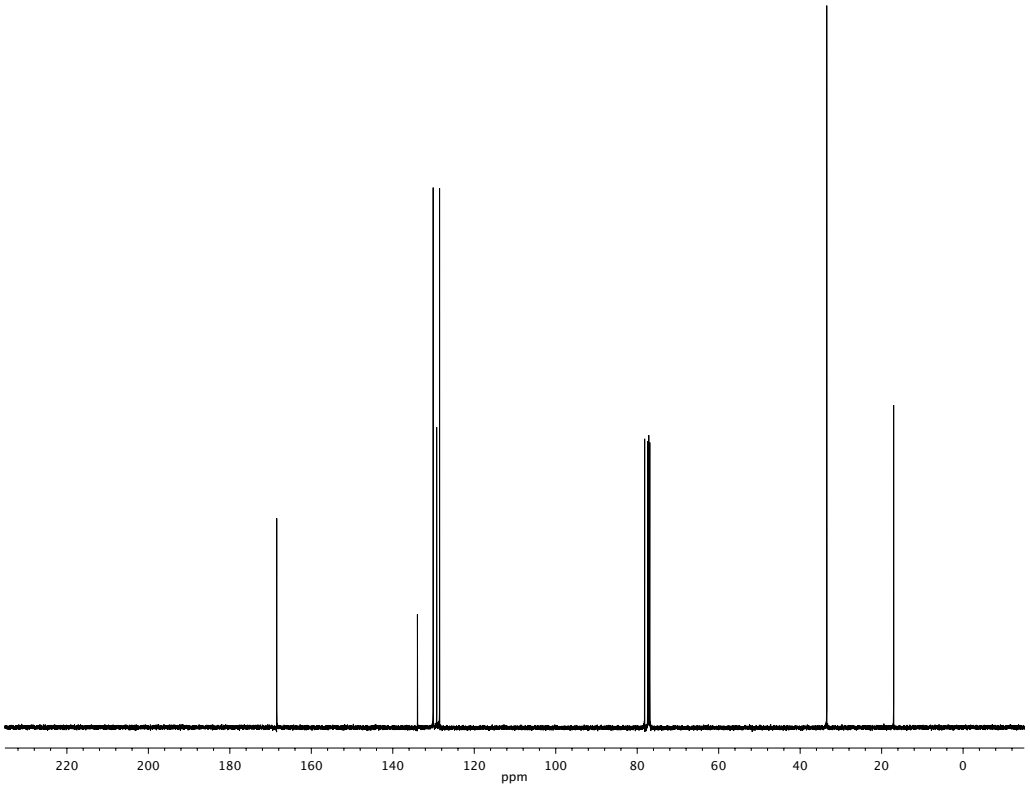
^{13}C NMR (125 MHz, $CDCl_3$) of compound **6c**.



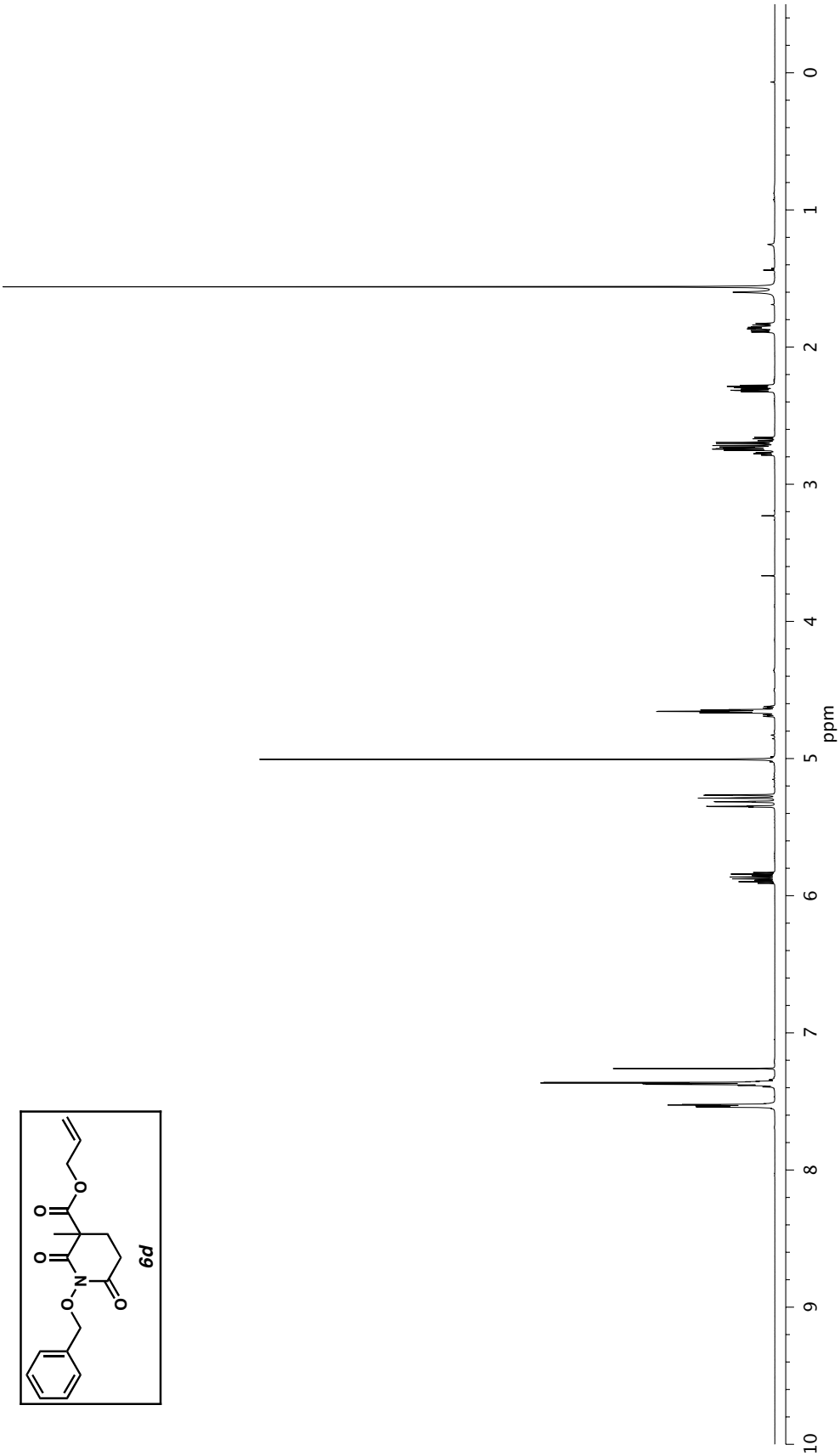
^{1}H NMR (500 MHz, $CDCl_3$) of compound **50**.



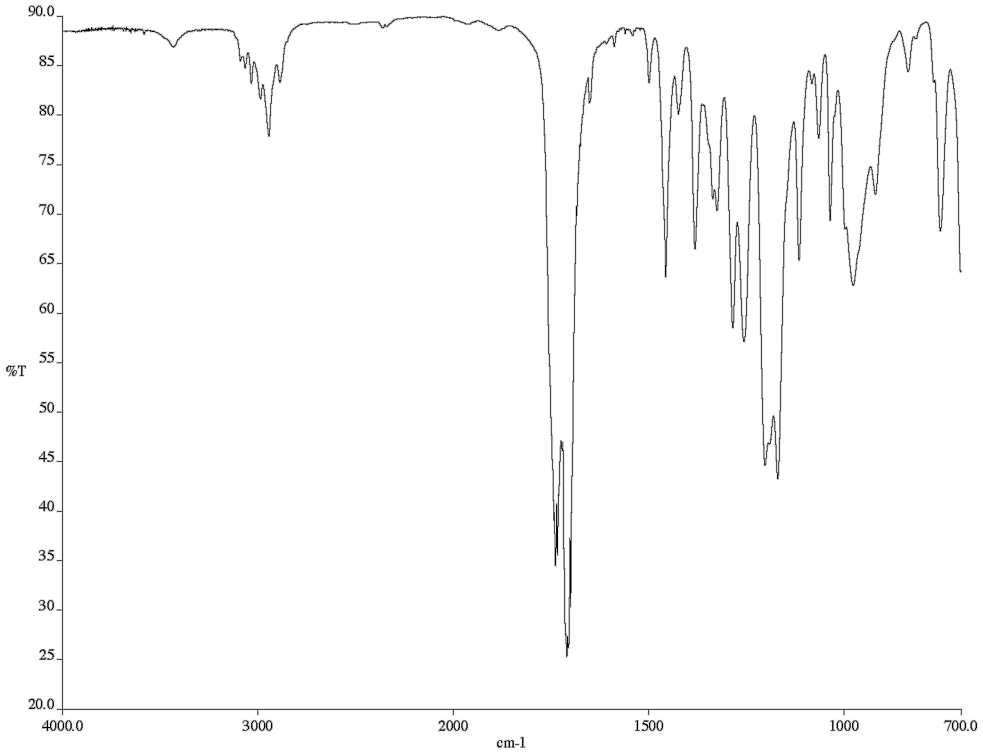
Infrared spectrum (thin film/NaCl) of compound **50**.



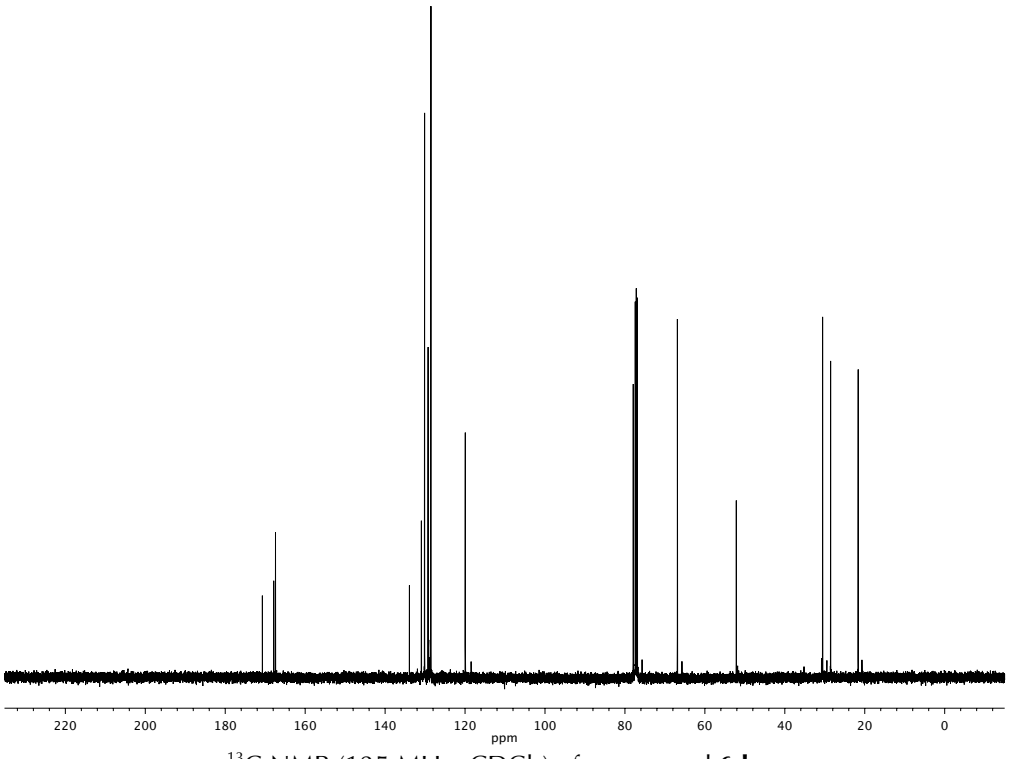
^{13}C NMR (125 MHz, $CDCl_3$) of compound **50**.



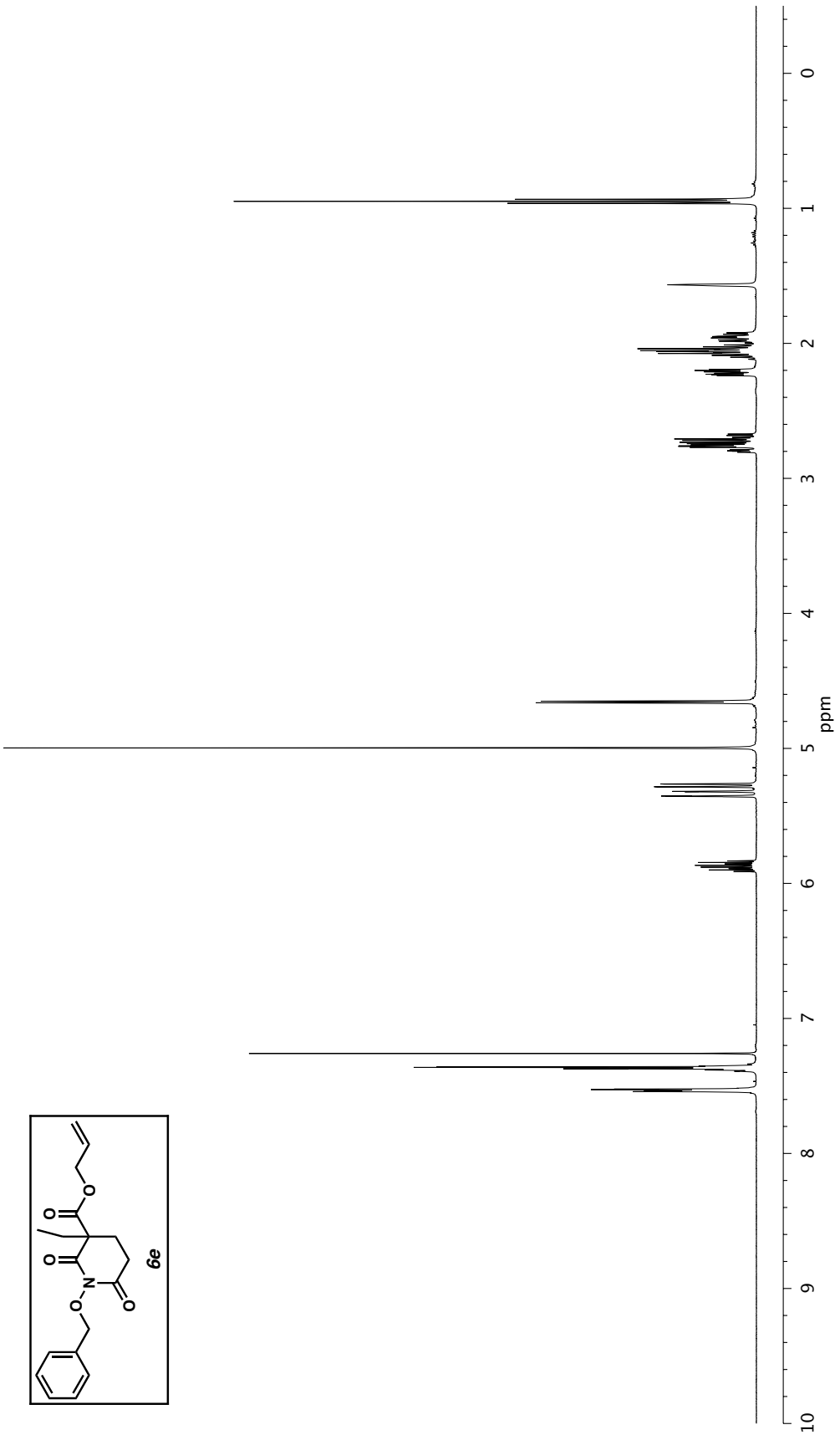
^{1}H NMR (500 MHz, $CDCl_3$) of compound **6d**.



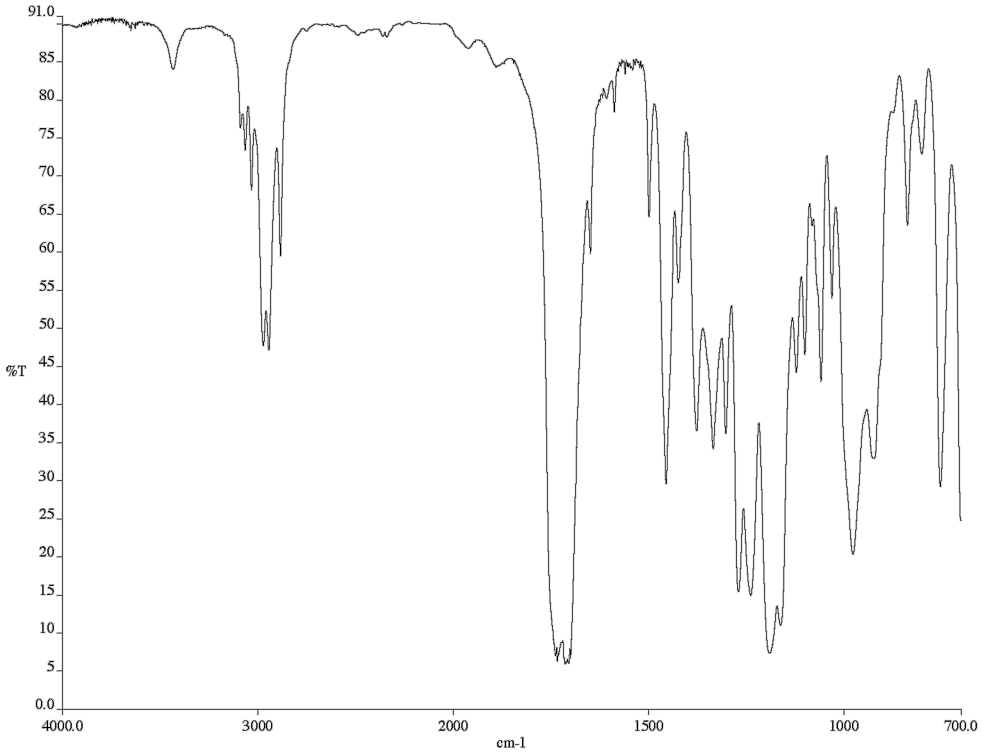
Infrared spectrum (thin film/NaCl) of compound **6d**.



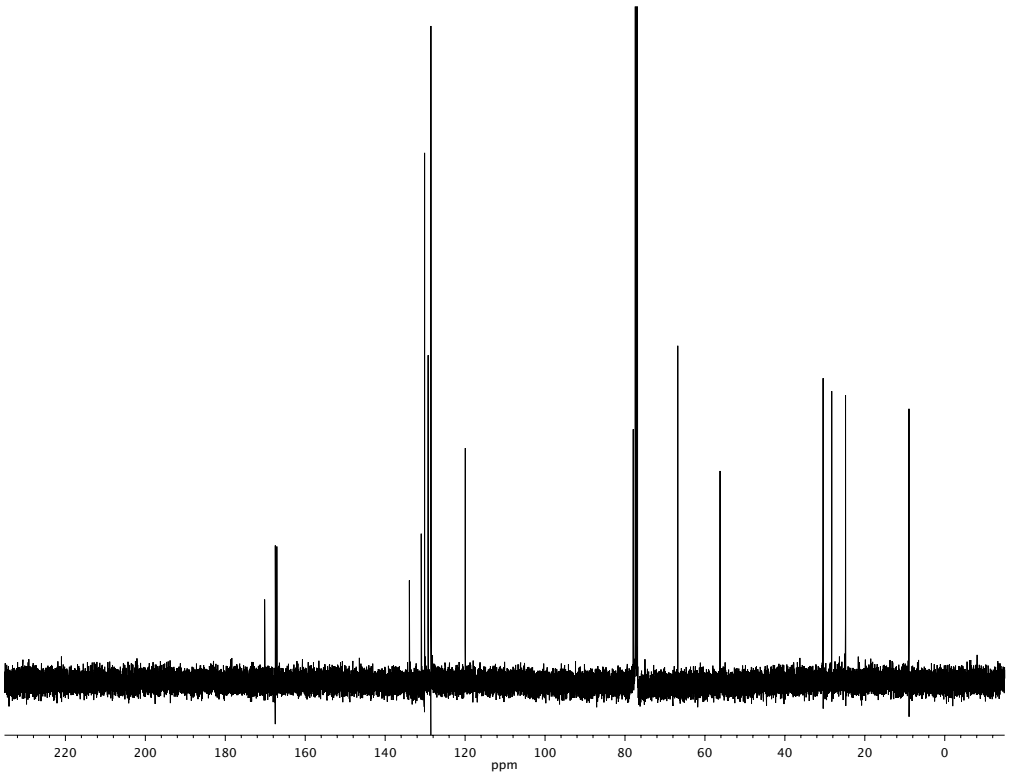
^{13}C NMR (125 MHz, $CDCl_3$) of compound **6d**.



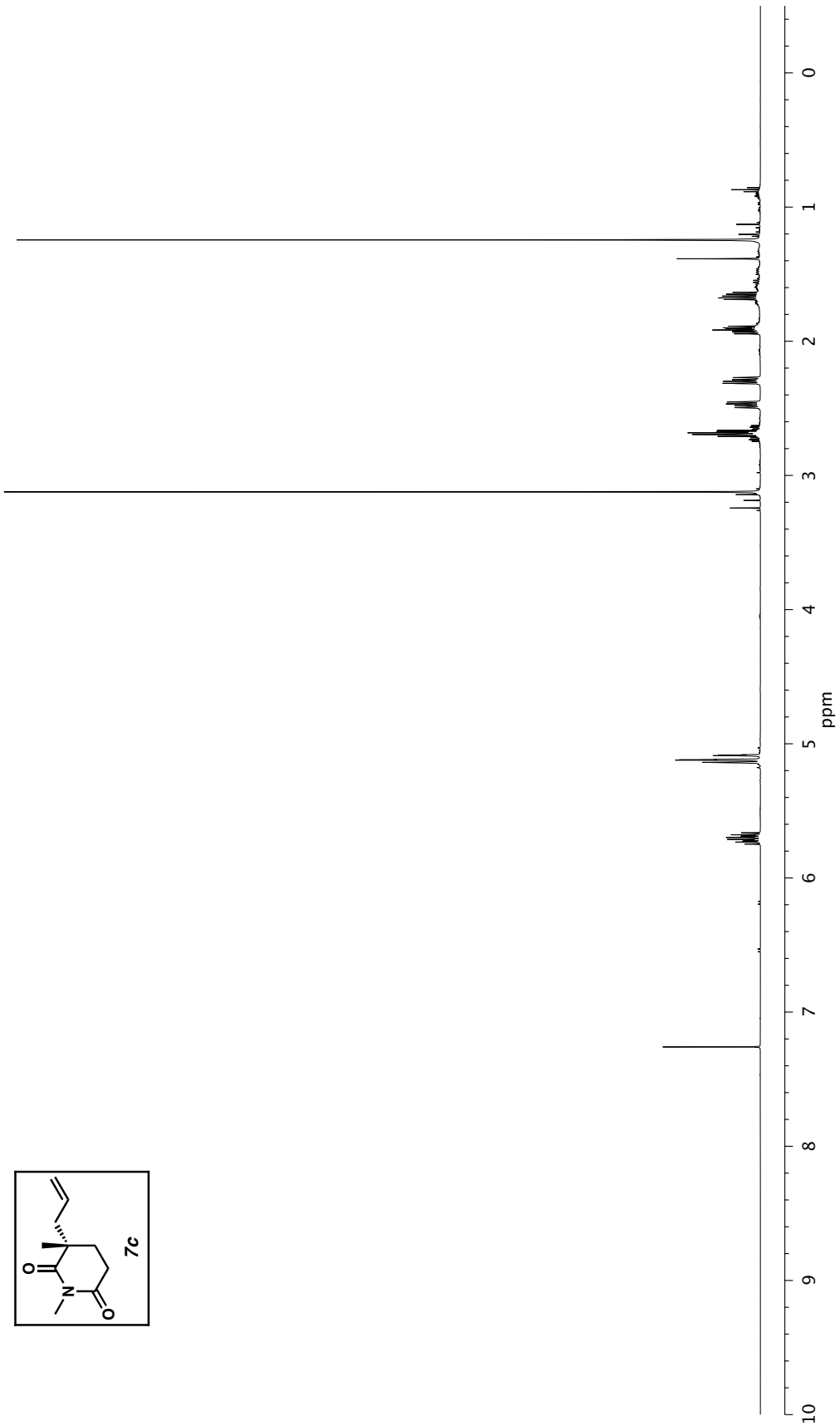
^{1}H NMR (500 MHz, $CDCl_3$) of compound **6e**.



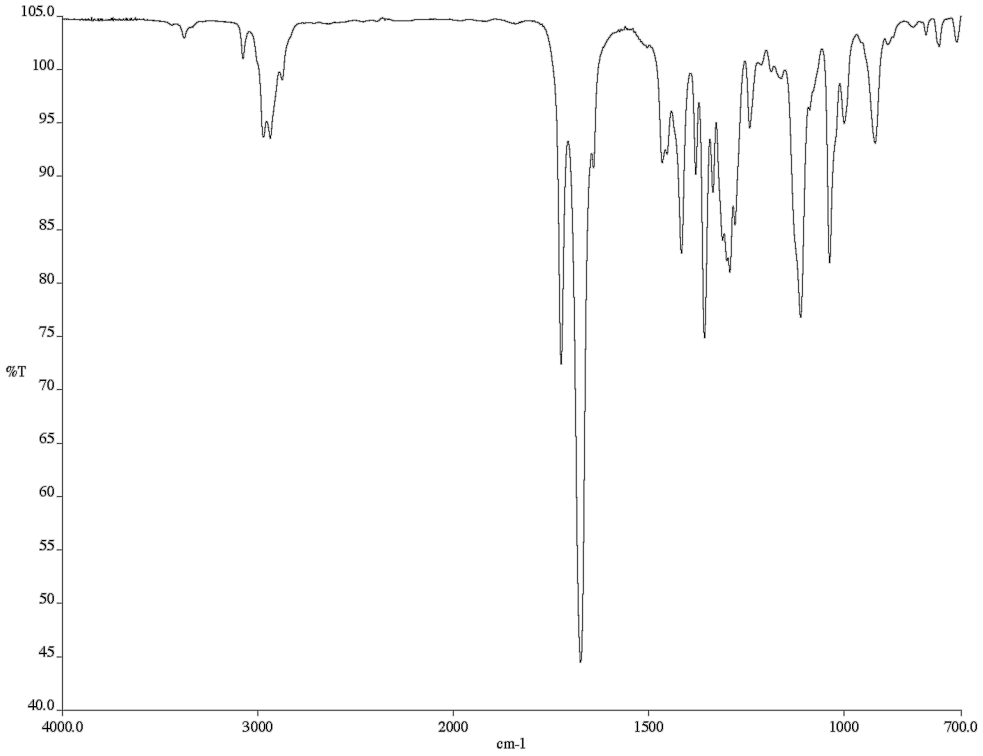
Infrared spectrum (thin film/NaCl) of compound **6e**.



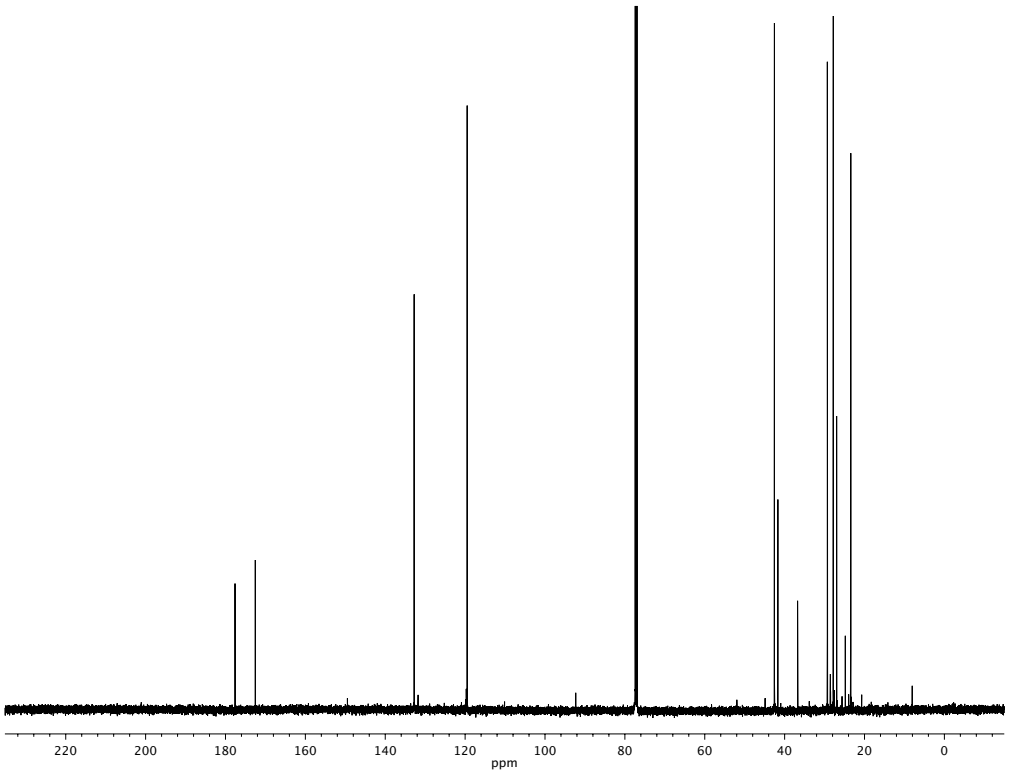
^{13}C NMR (125 MHz, $CDCl_3$) of compound **6e**.



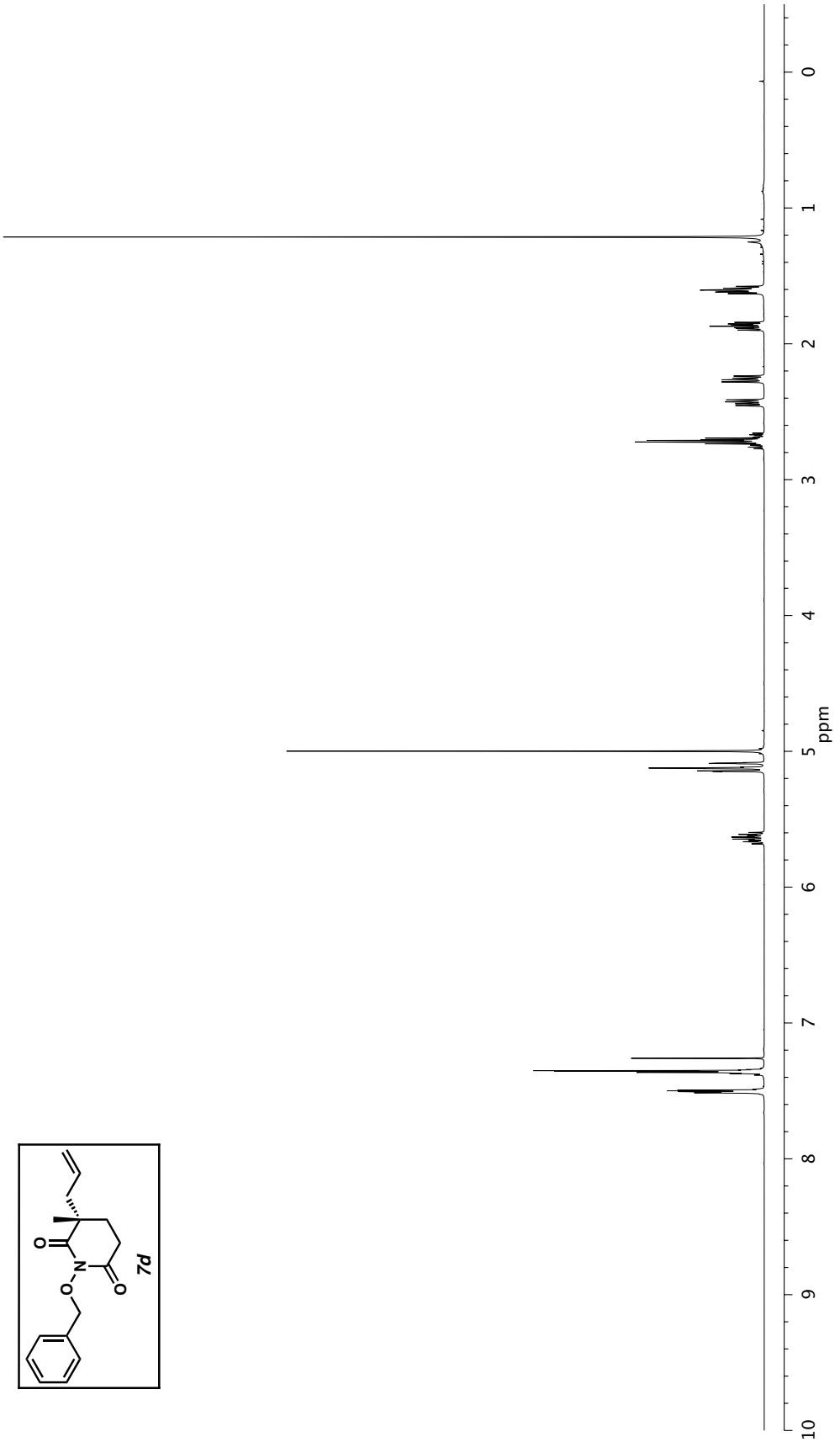
^{1}H NMR (500 MHz, $CDCl_3$) of compound **7c**.



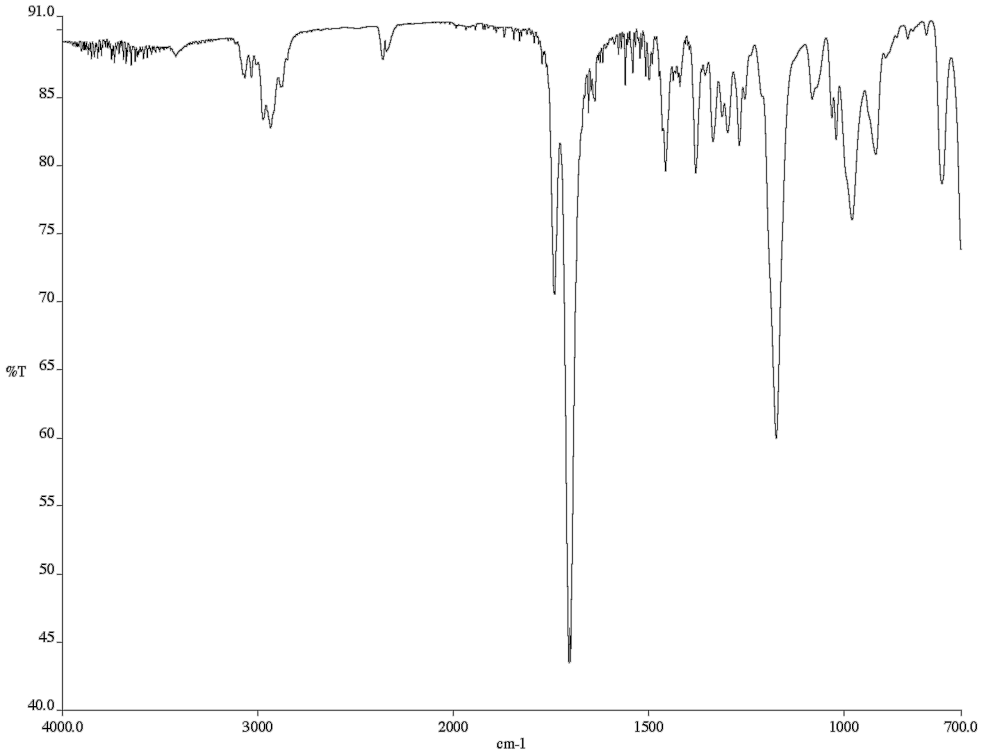
Infrared spectrum (thin film/NaCl) of compound **7c**.



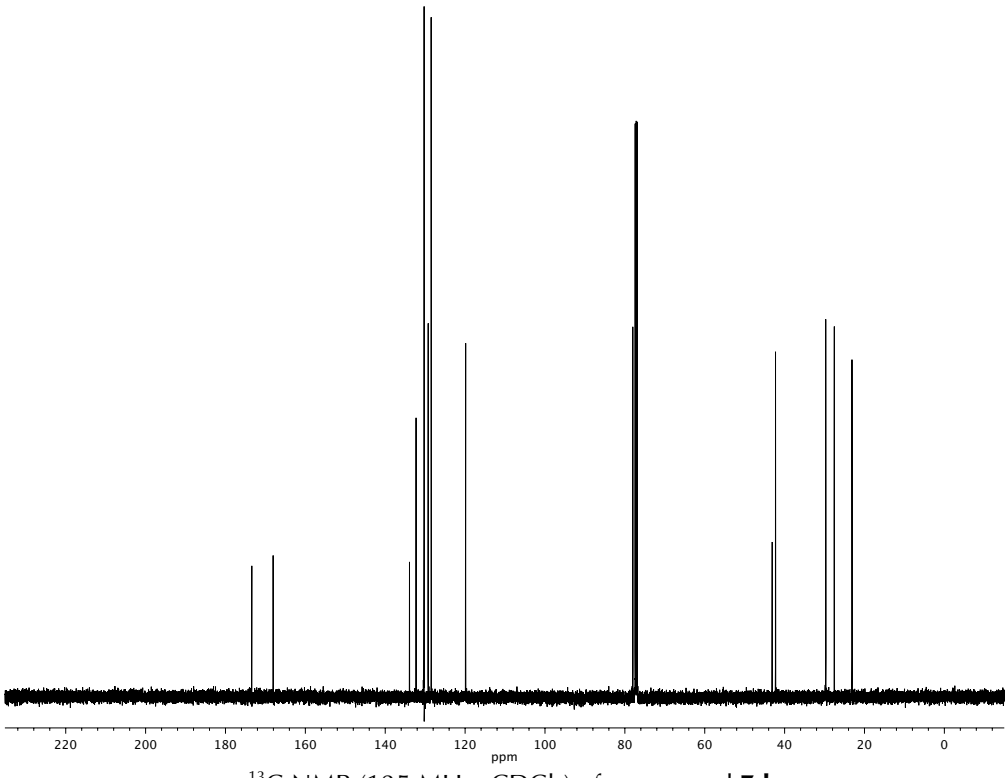
^{13}C NMR (125 MHz, $CDCl_3$) of compound **7c**.



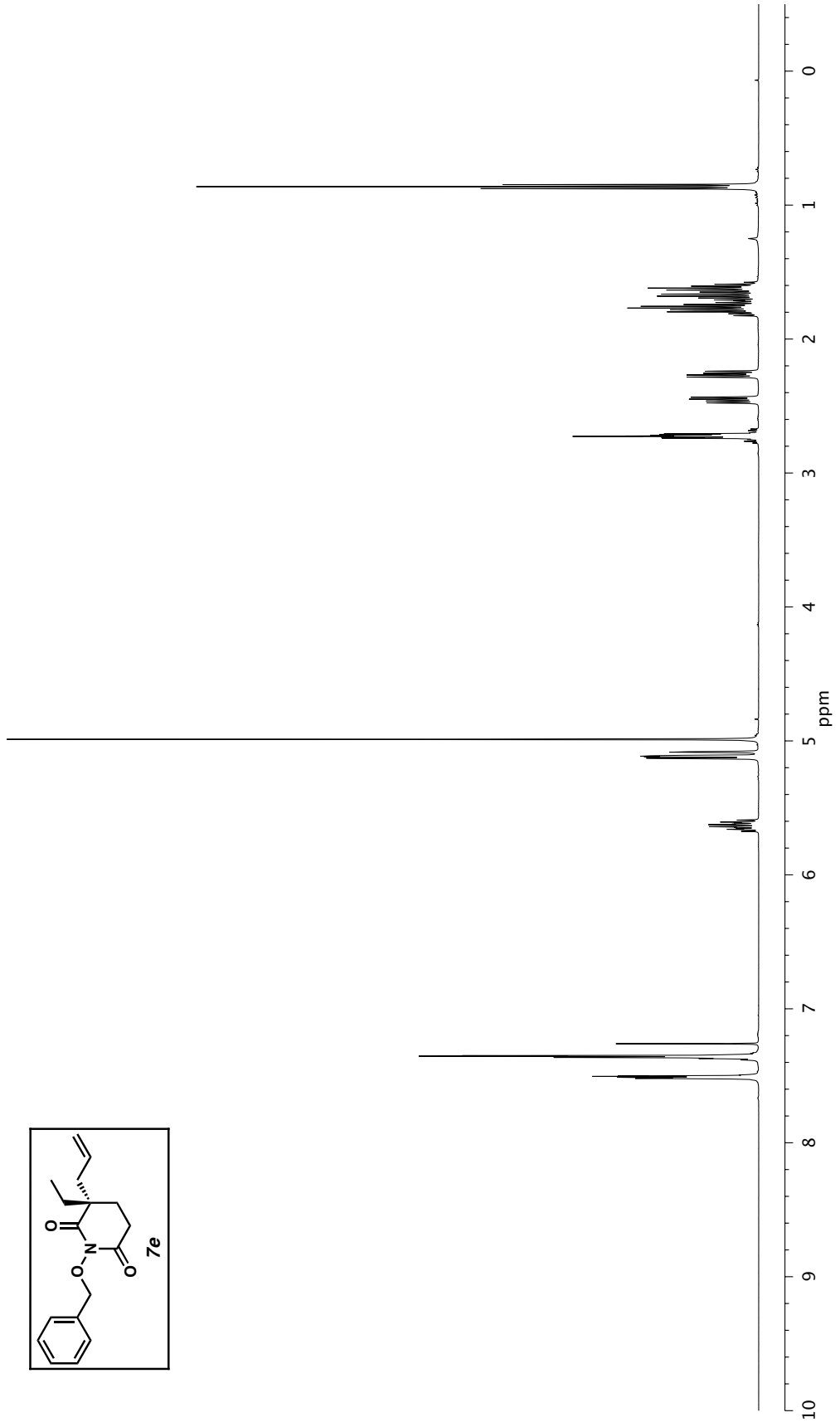
^{1}H NMR (500 MHz, CDCl^{3}) of compound **7d**.



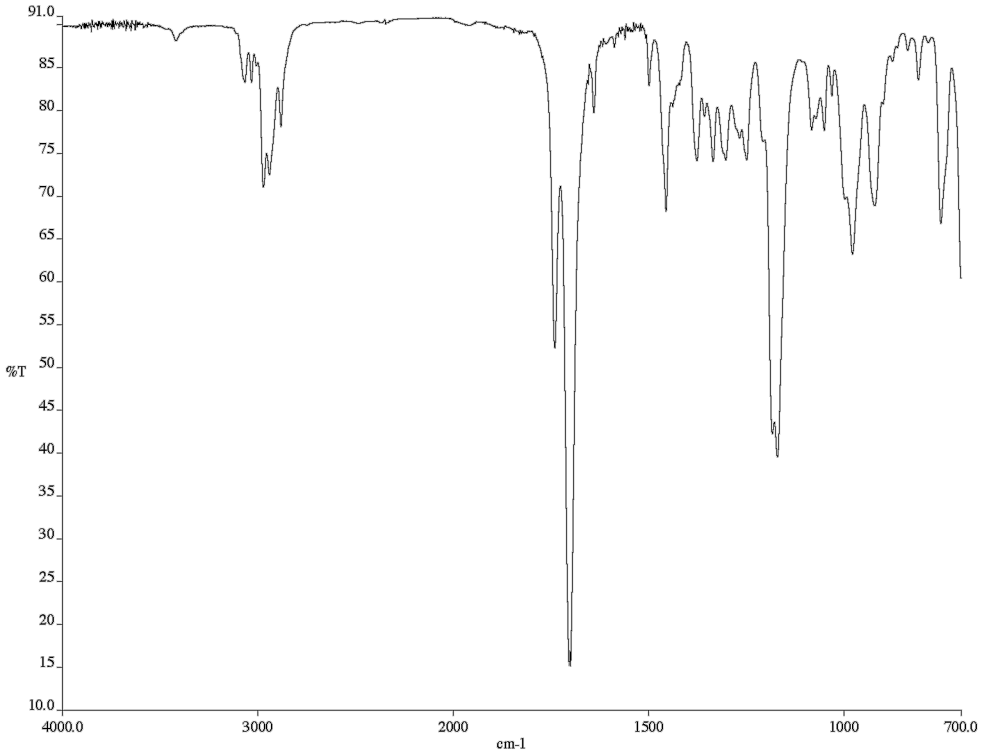
Infrared spectrum (thin film/NaCl) of compound **7d**.



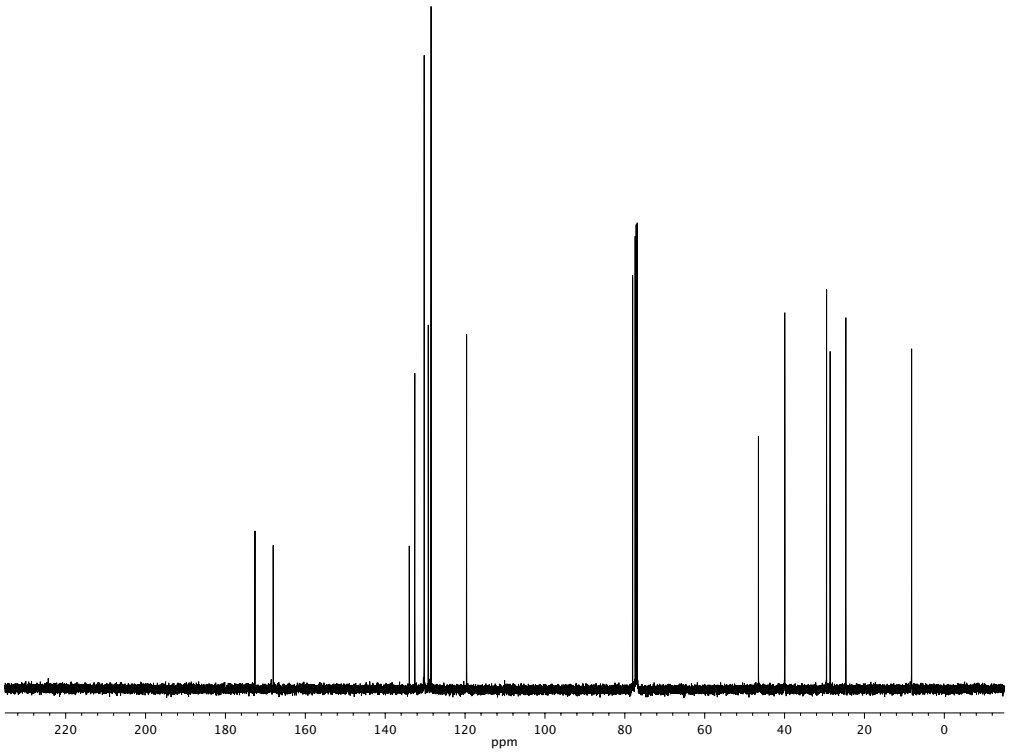
^{13}C NMR (125 MHz, $CDCl_3$) of compound **7d**.



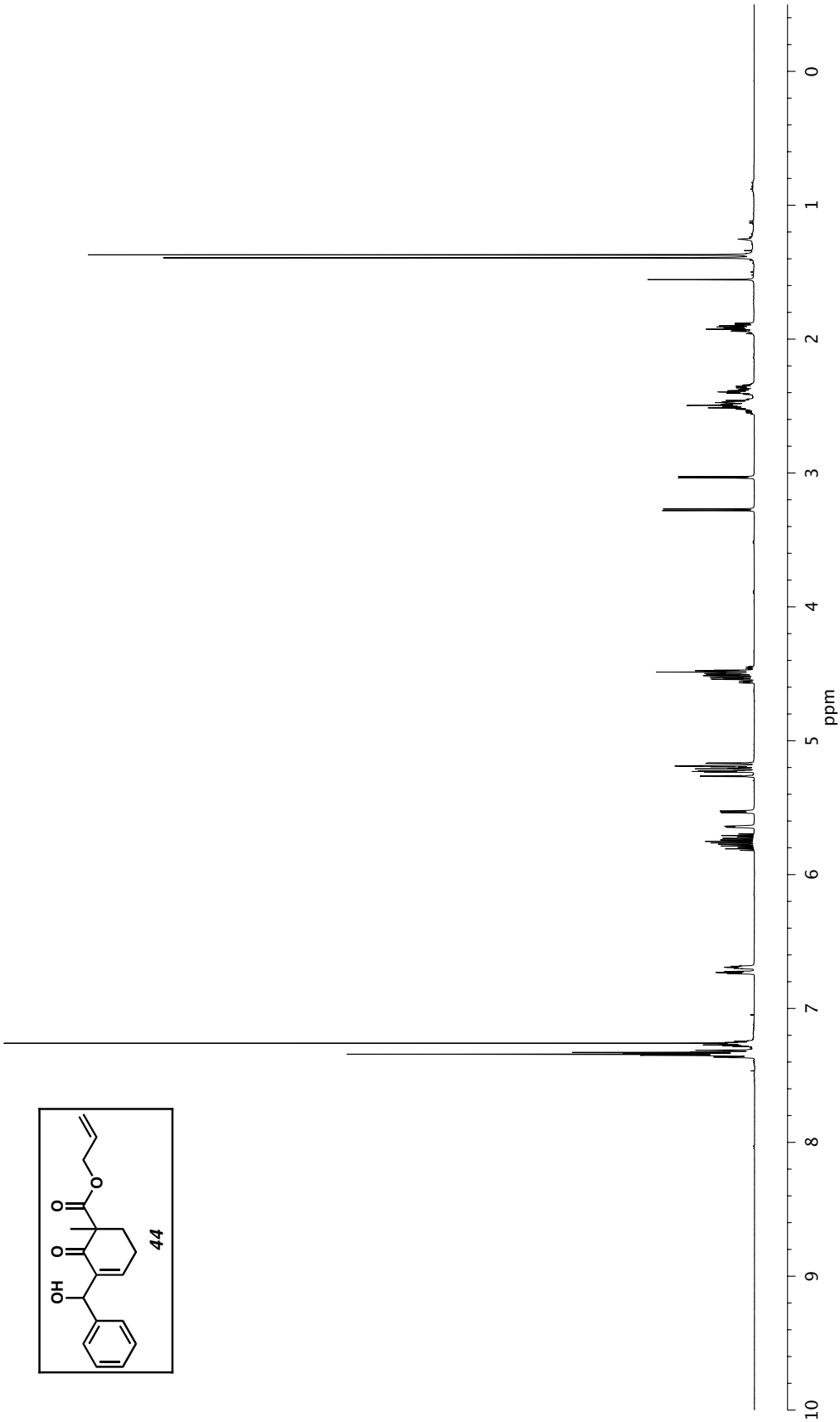
^{1}H NMR (500 MHz, $CDCl_3$) of compound **7e**.



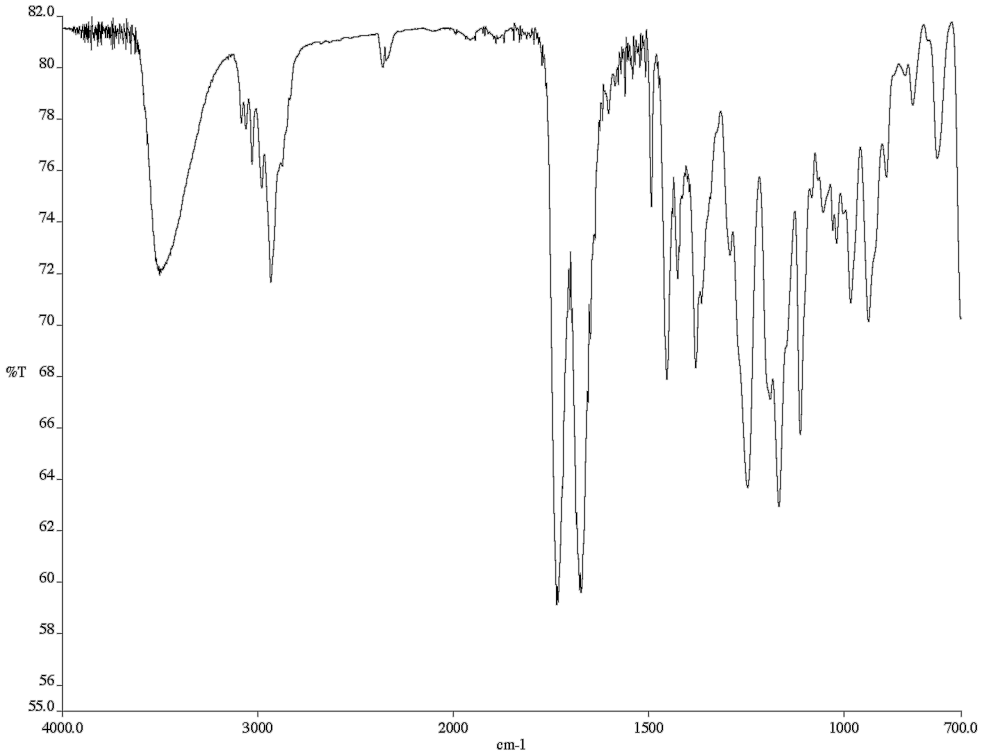
Infrared spectrum (thin film/NaCl) of compound **7e**.



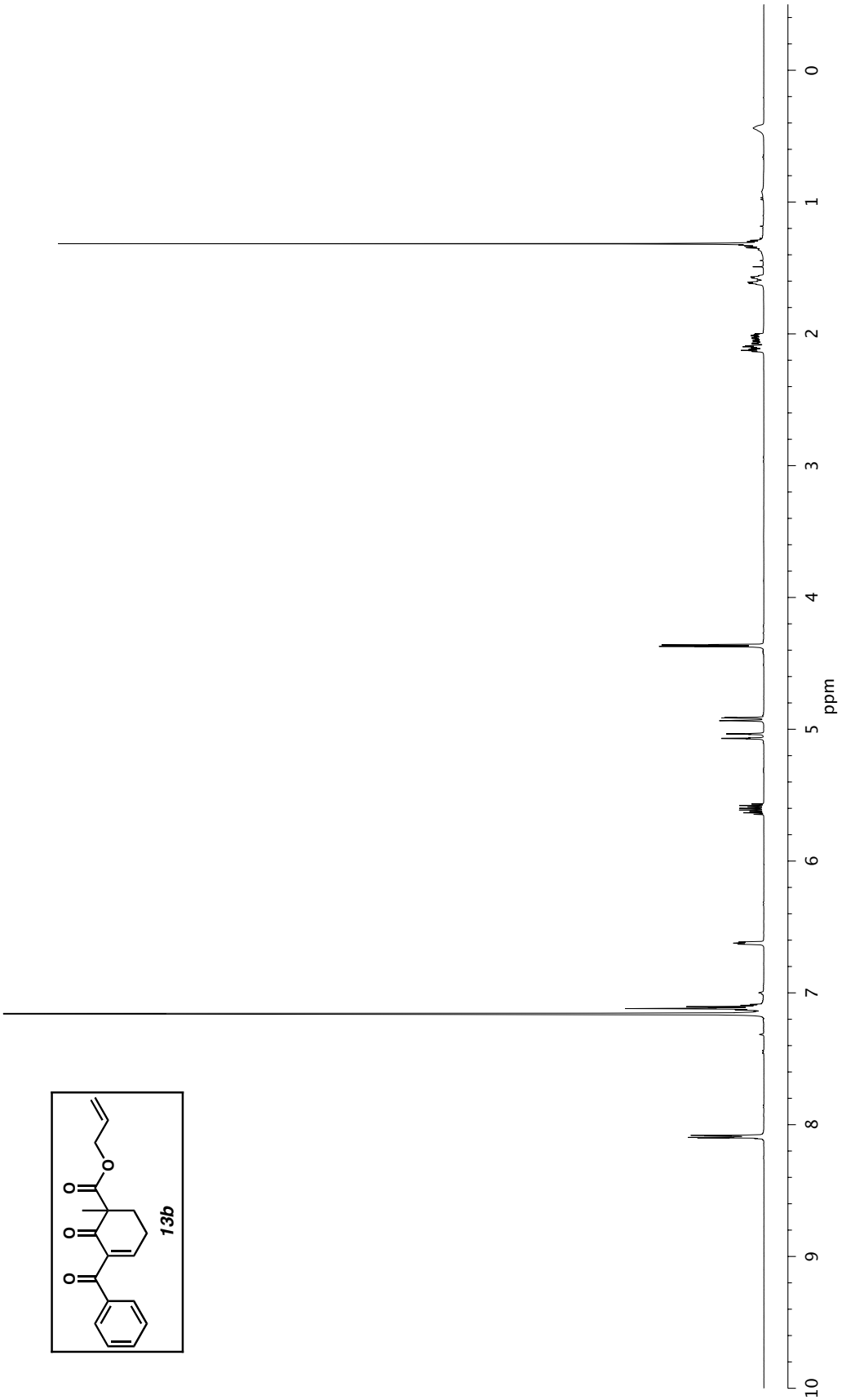
^{13}C NMR (125 MHz, $CDCl_3$) of compound **7e**.



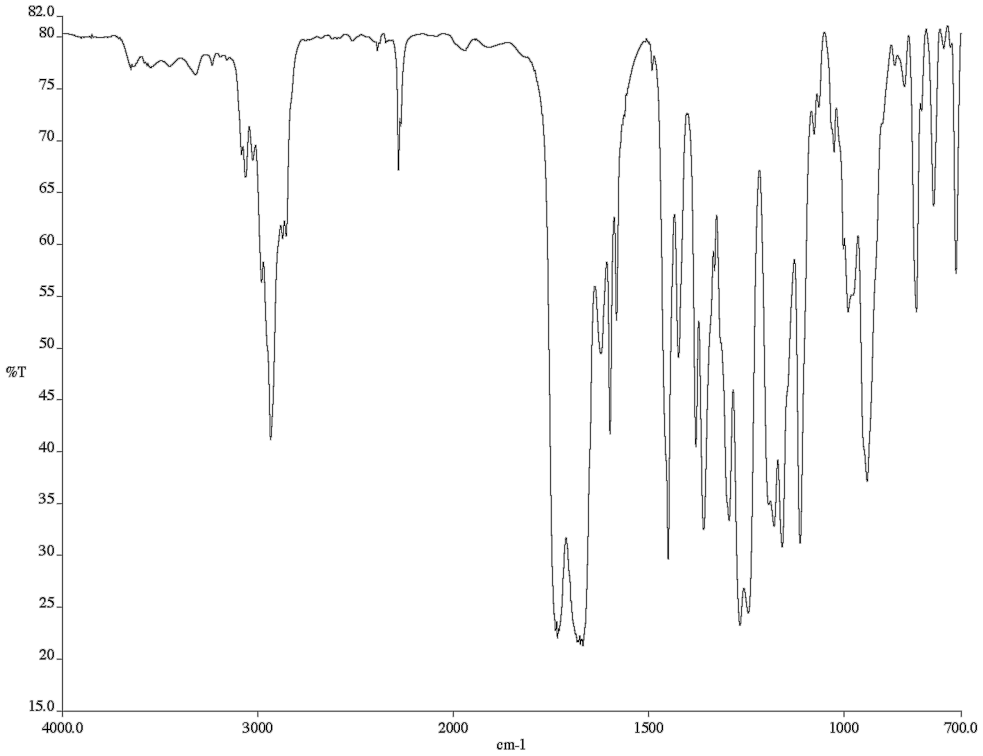
^{1}H NMR (500 MHz, $CDCl_3$) of compound **44**.



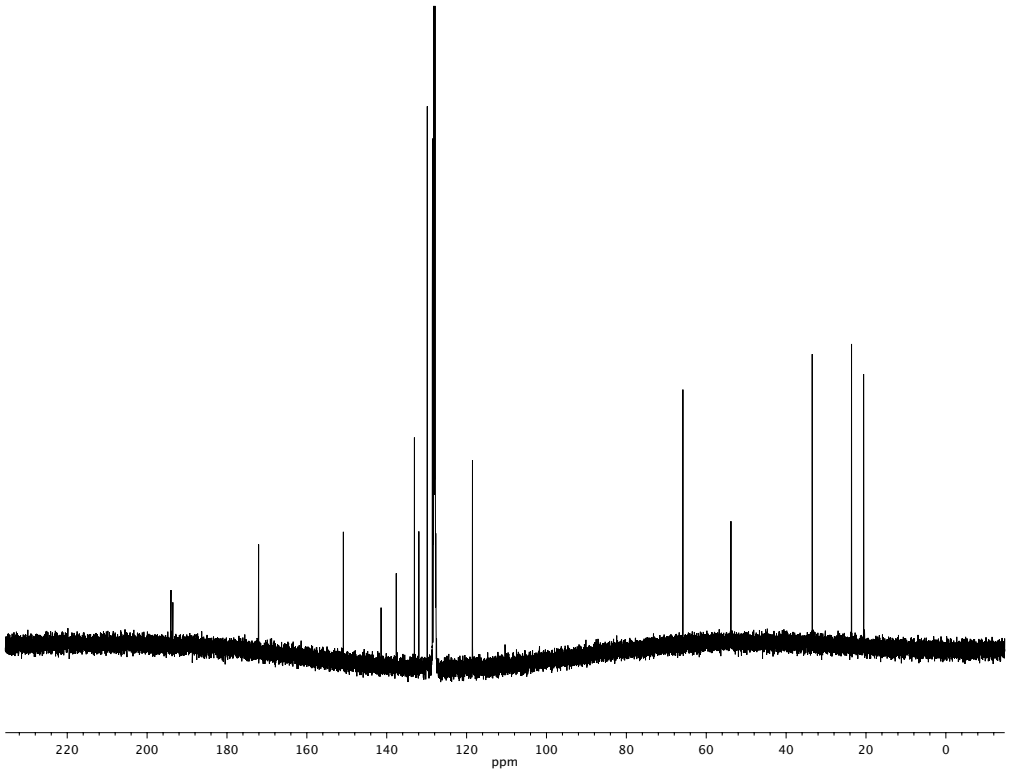
Infrared spectrum (thin film/NaCl) of compound **44**.



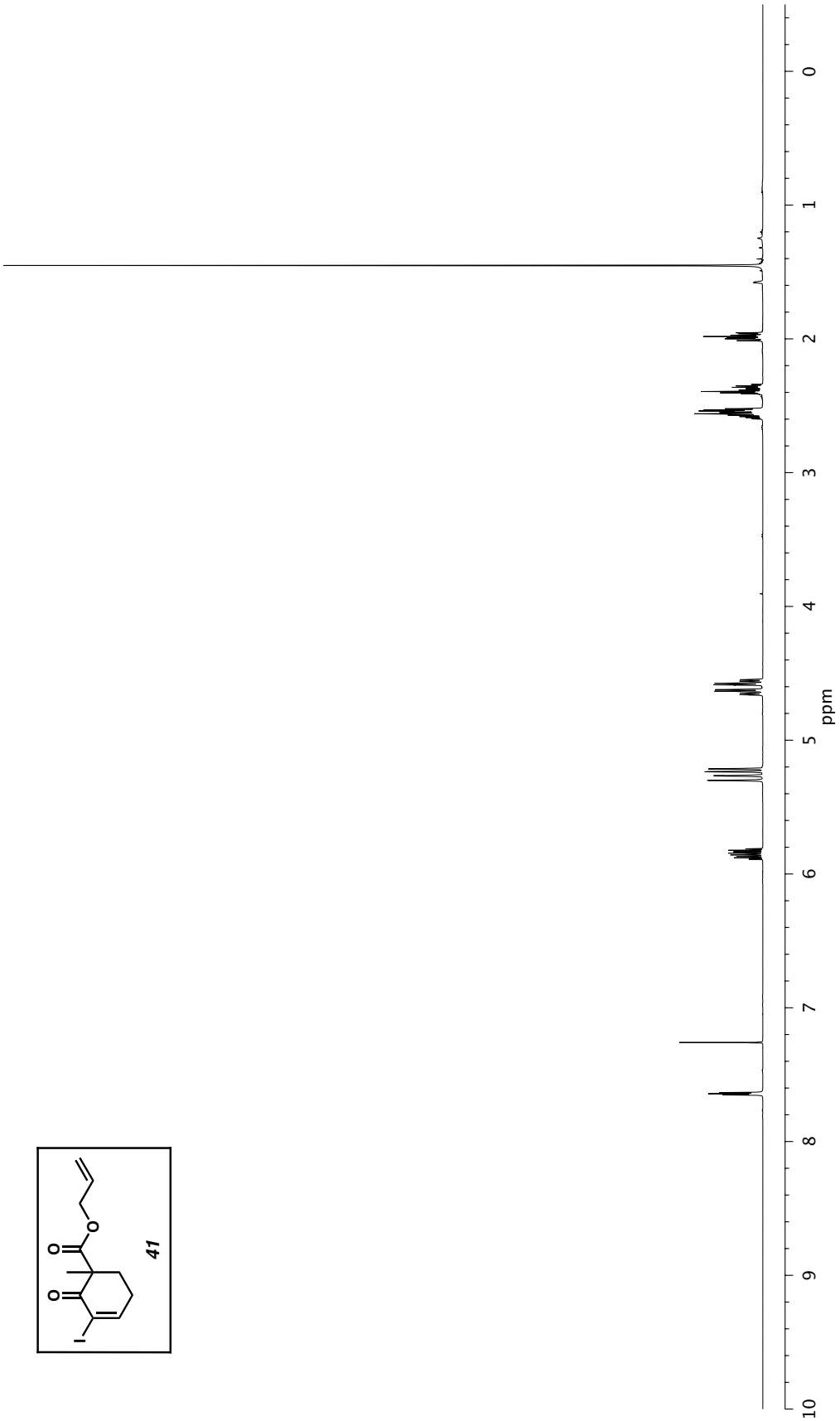
^{1}H NMR (500 MHz, C_6D_6) of compound **13b**.



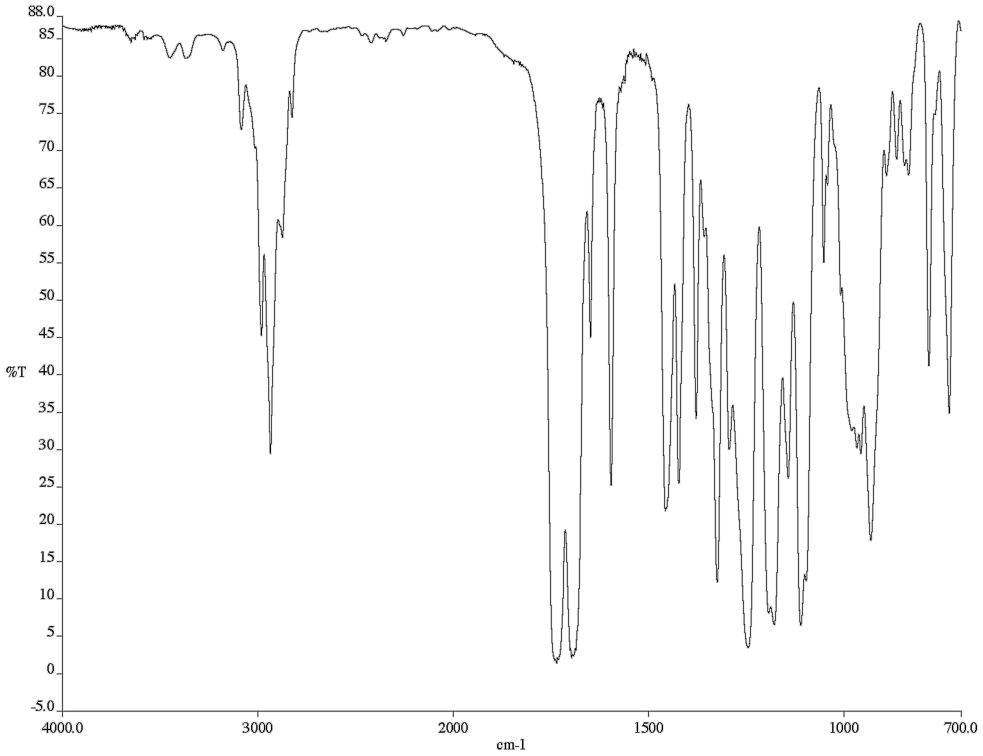
Infrared spectrum (thin film/NaCl) of compound **13b**.



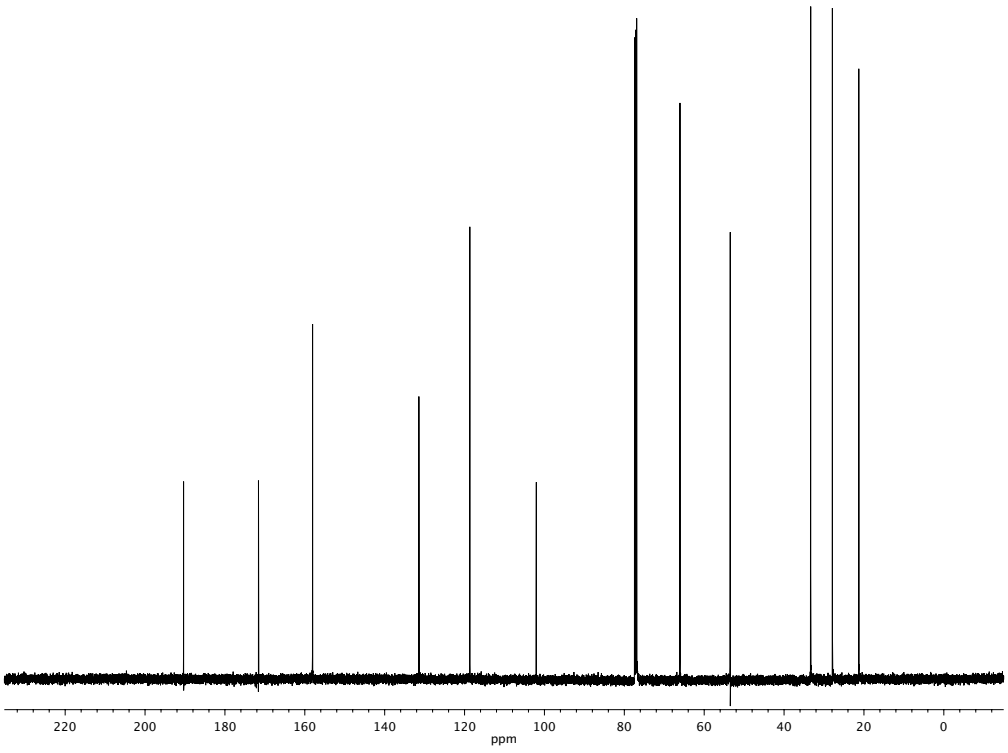
^{13}C NMR (125 MHz, C_6D_6) of compound **13b**.



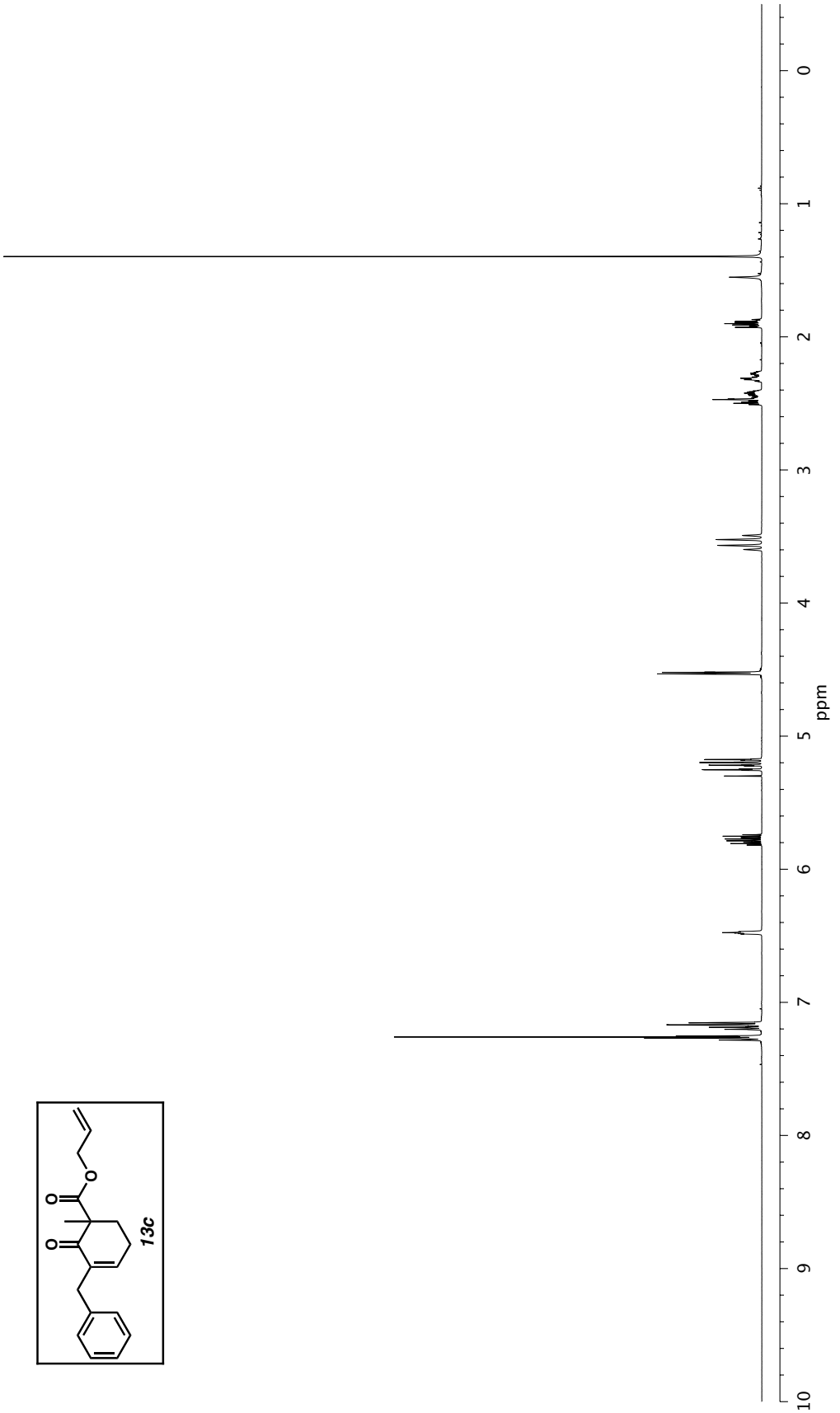
^{1}H NMR (500 MHz, $CDCl_3$) of compound **41**.



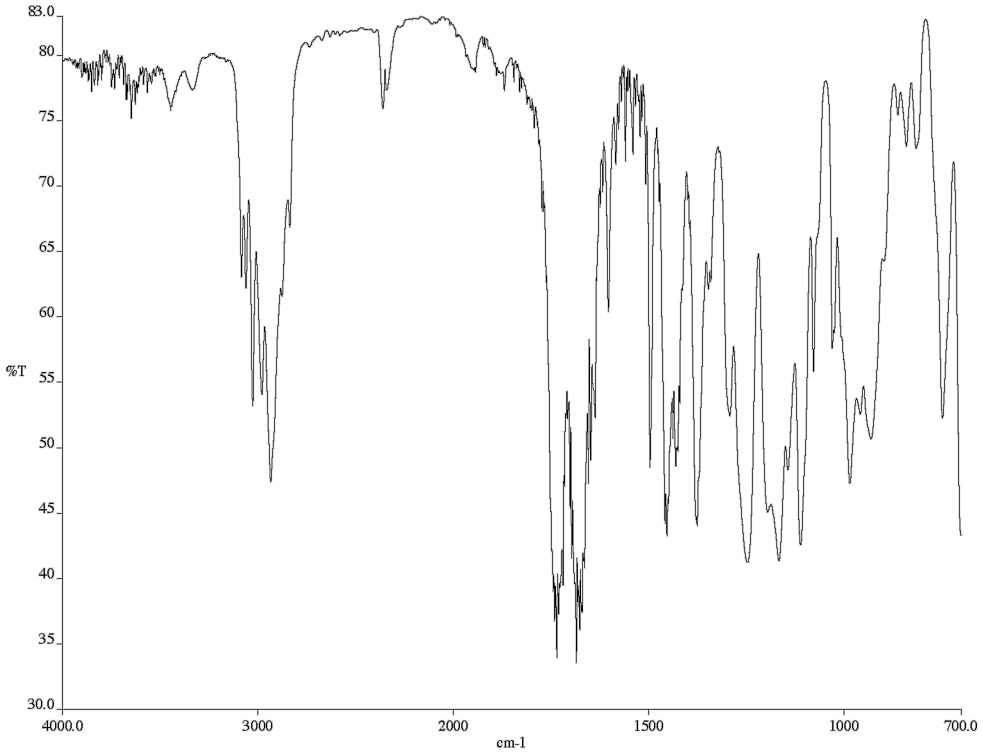
Infrared spectrum (thin film/NaCl) of compound **41**.



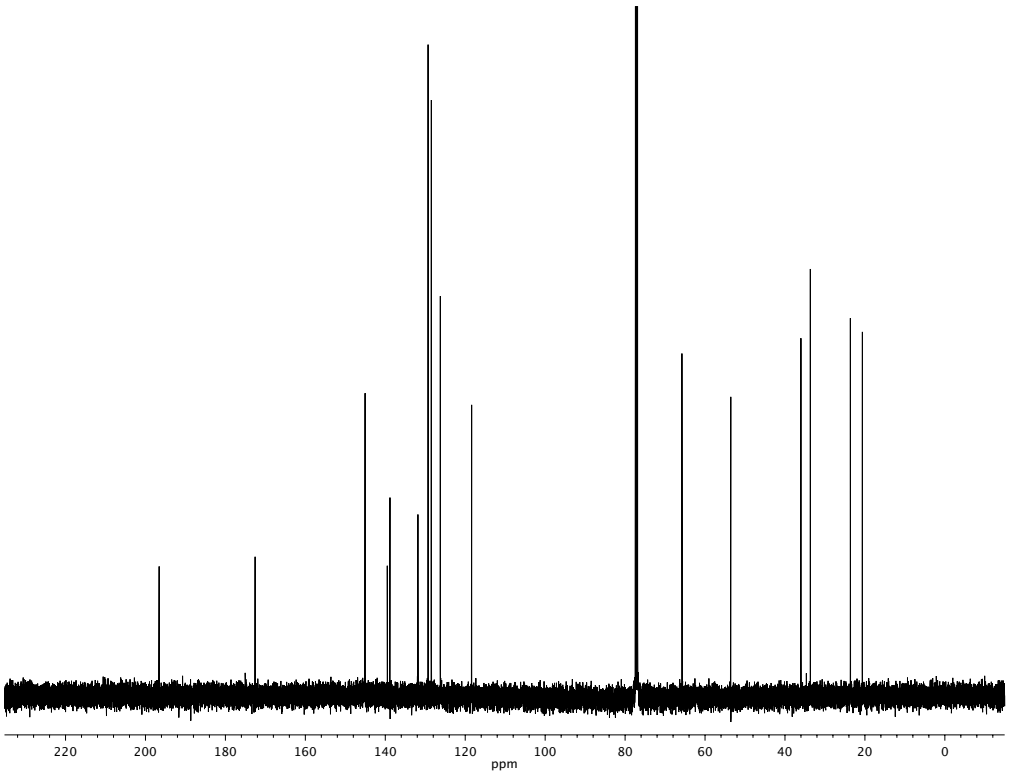
^{13}C NMR (125 MHz, $CDCl_3$) of compound **41**.



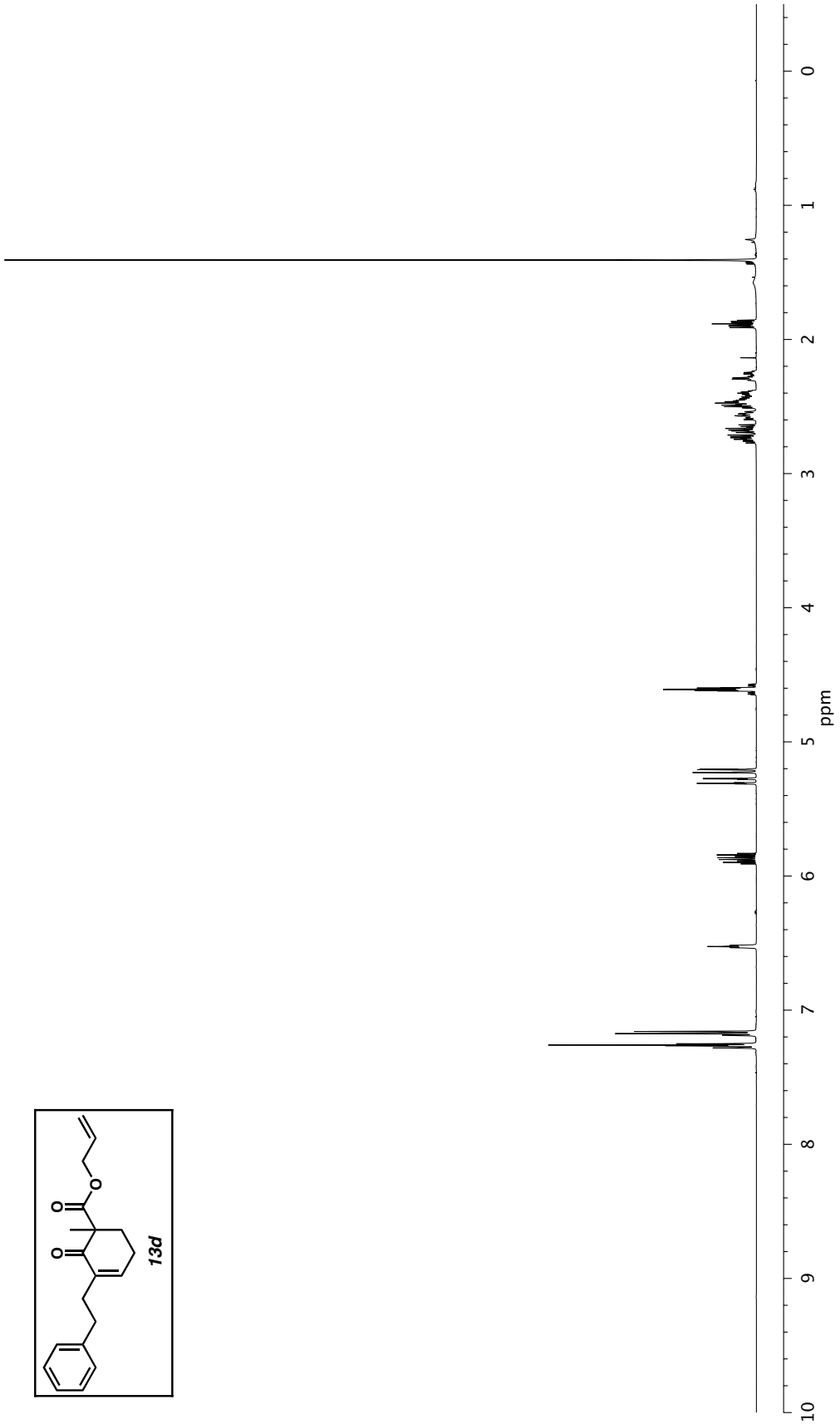
^{1}H NMR (500 MHz, $CDCl_3$) of compound **13c**.



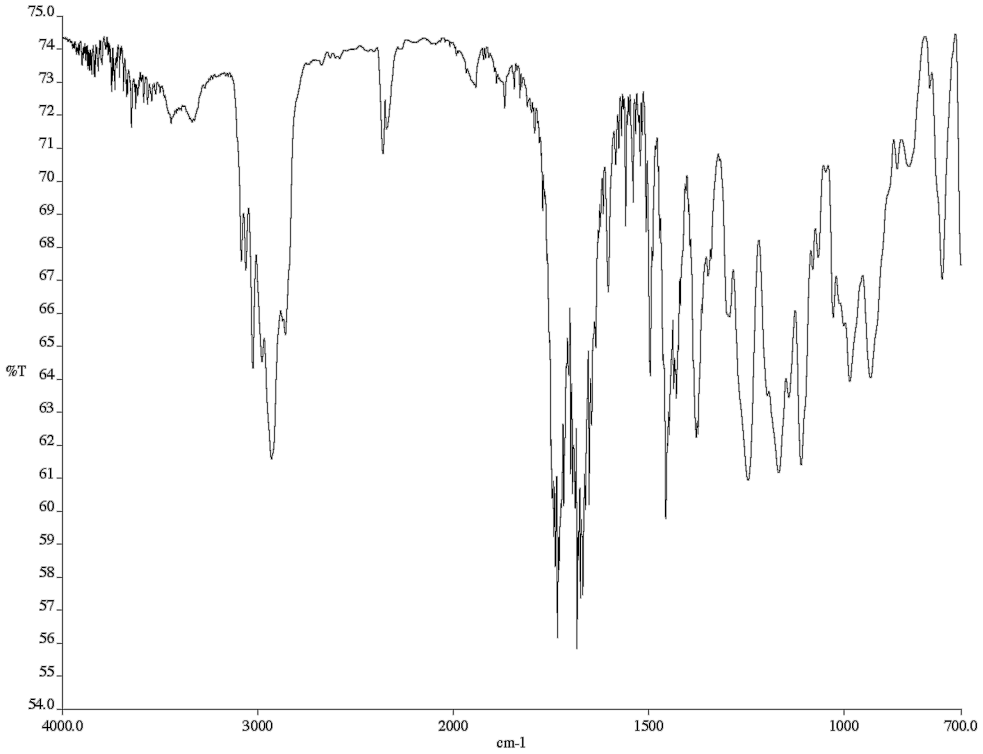
Infrared spectrum (thin film/NaCl) of compound **13c**.



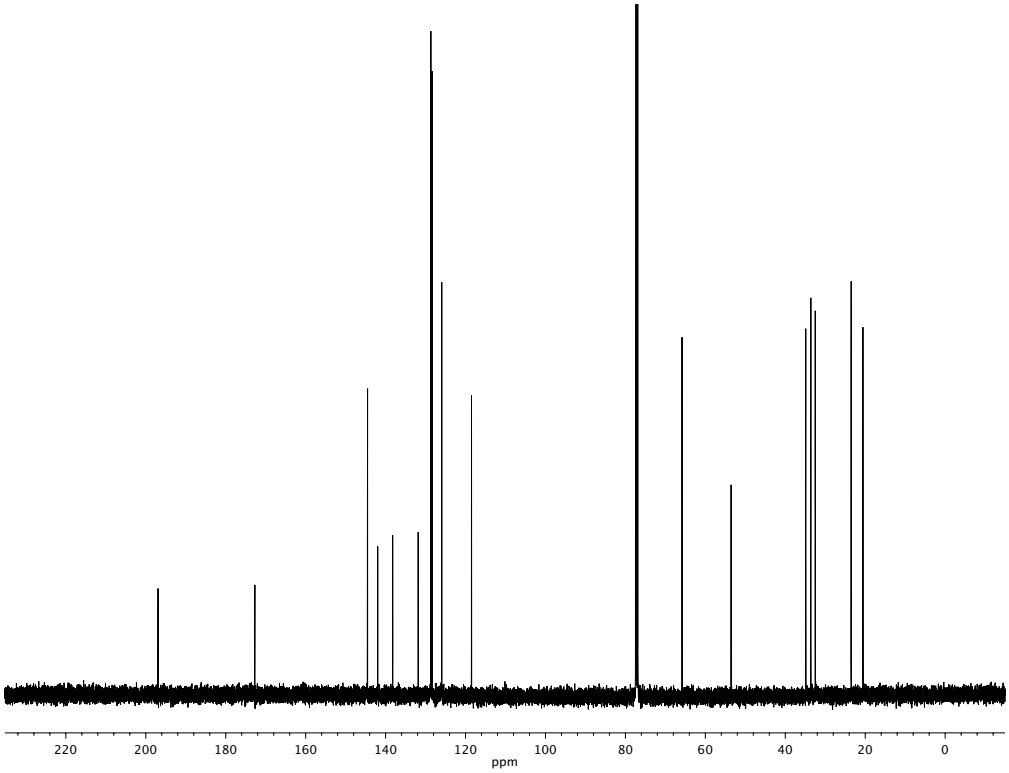
^{13}C NMR (125 MHz, $CDCl_3$) of compound **13c**.



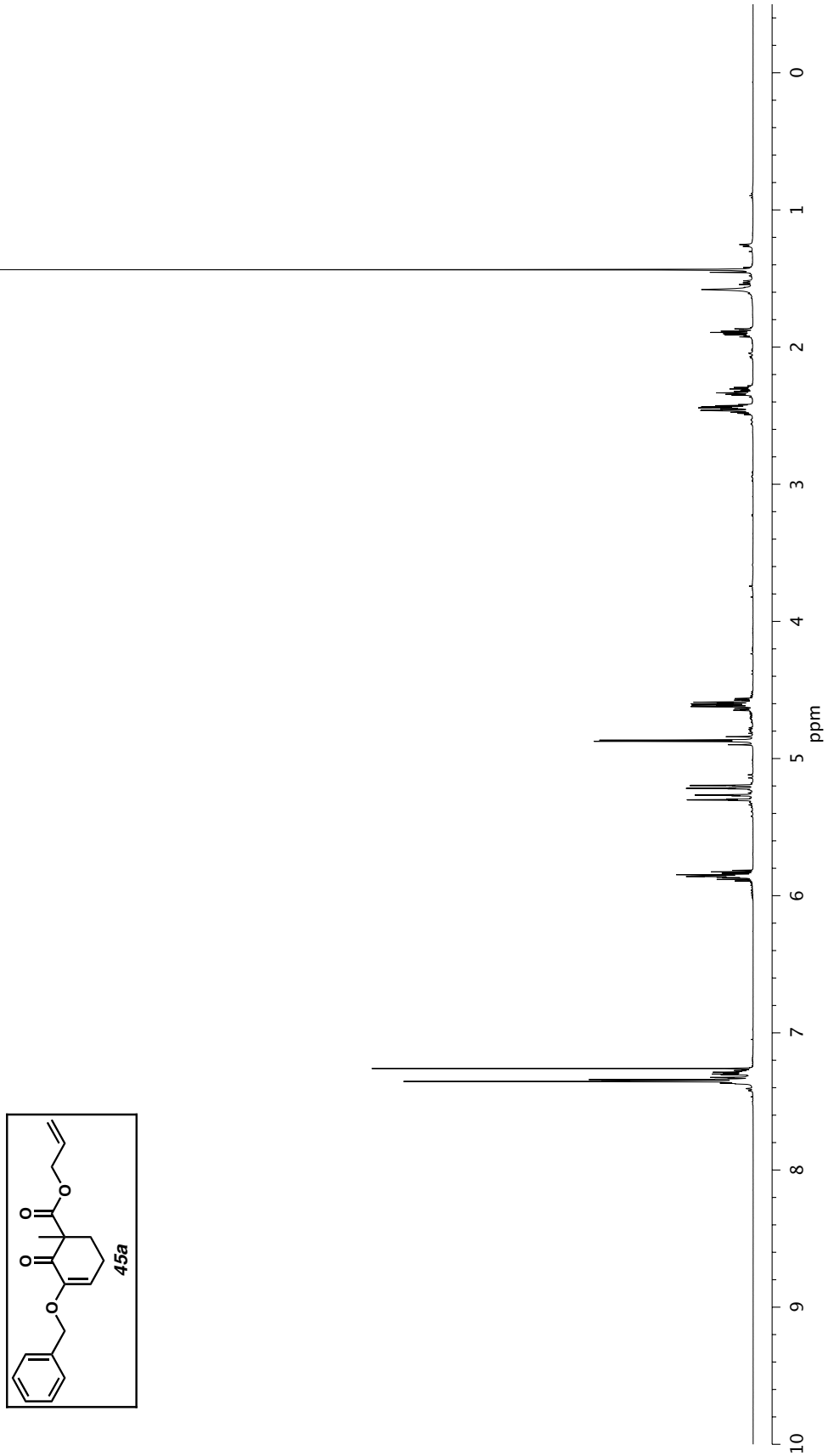
^{1}H NMR (500 MHz, $CDCl_3$) of compound **13d**.



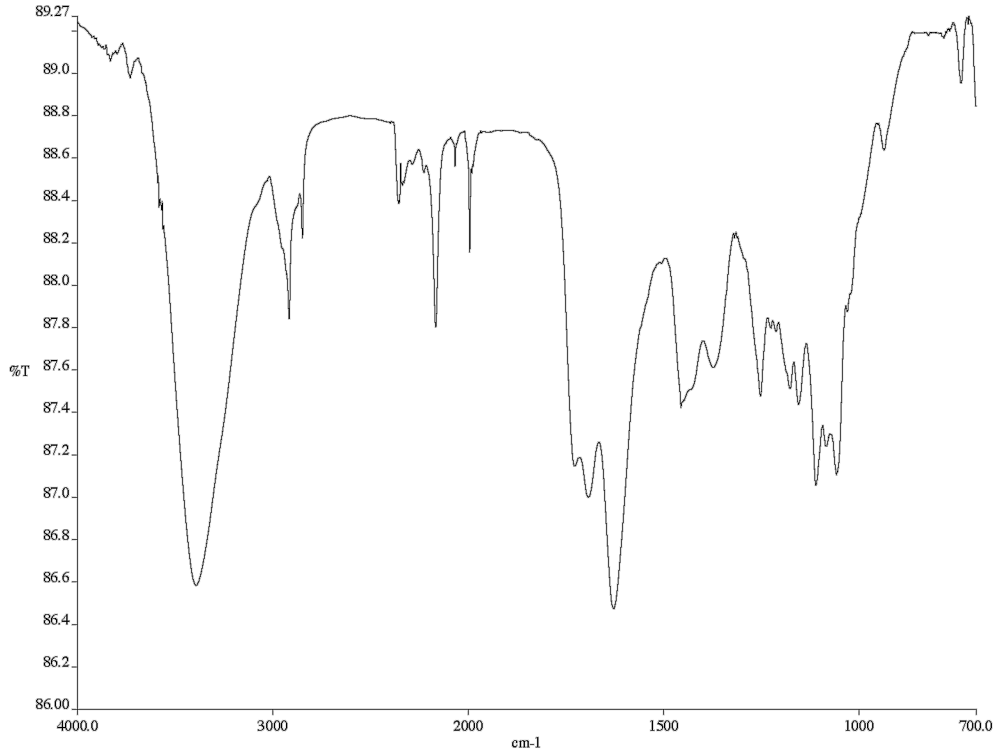
Infrared spectrum (thin film/NaCl) of compound **13d**.



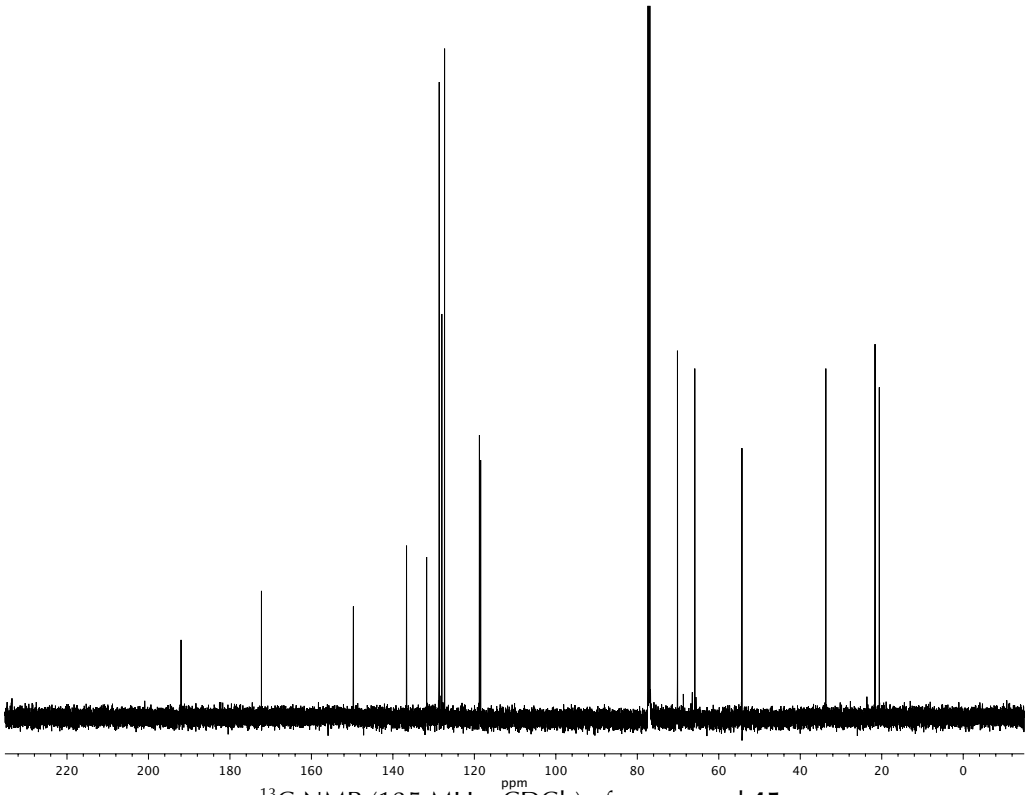
^{13}C NMR (125 MHz, $CDCl_3$) of compound **13d**.



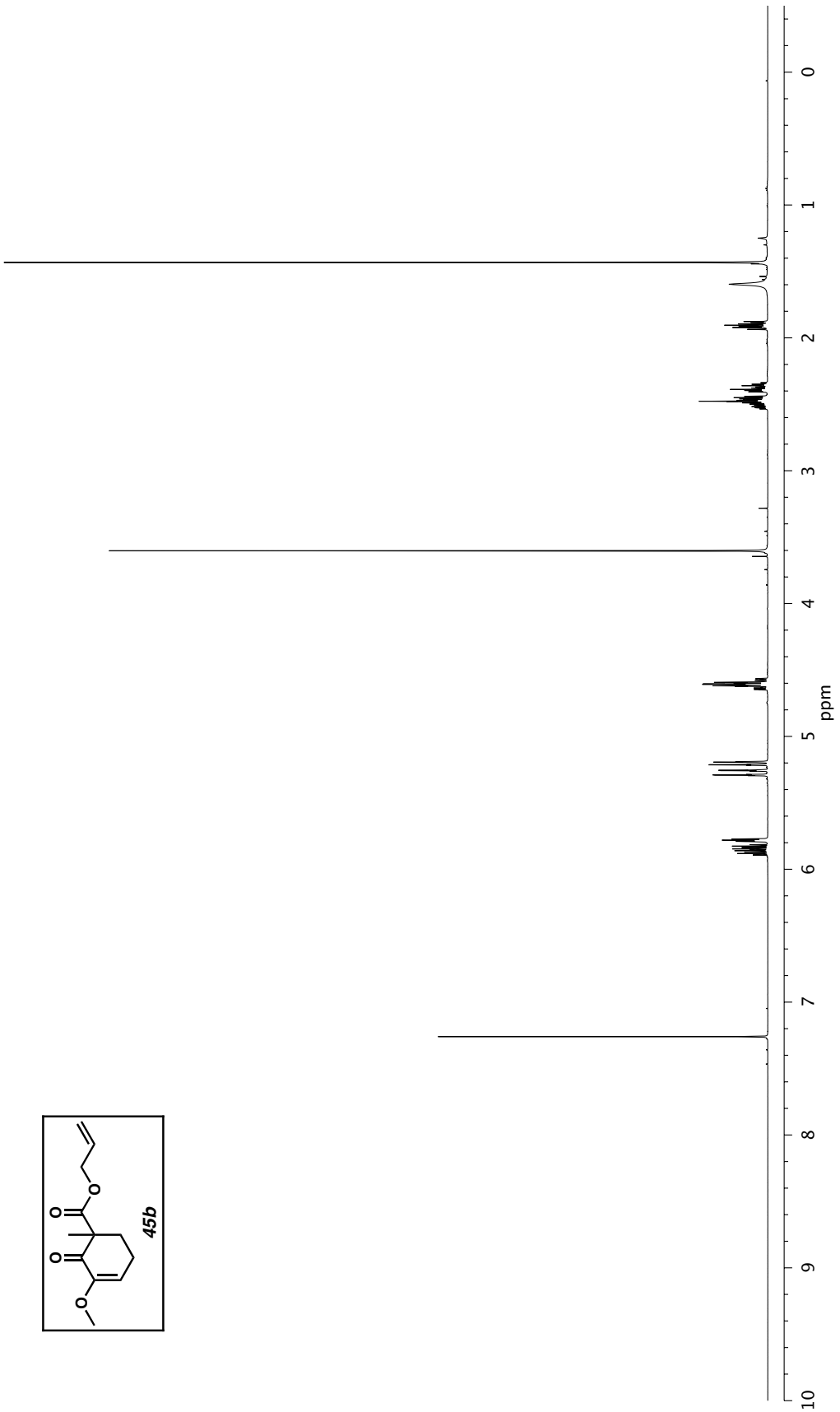
^{1}H NMR (500 MHz, $CDCl_3$) of compound **45a**.



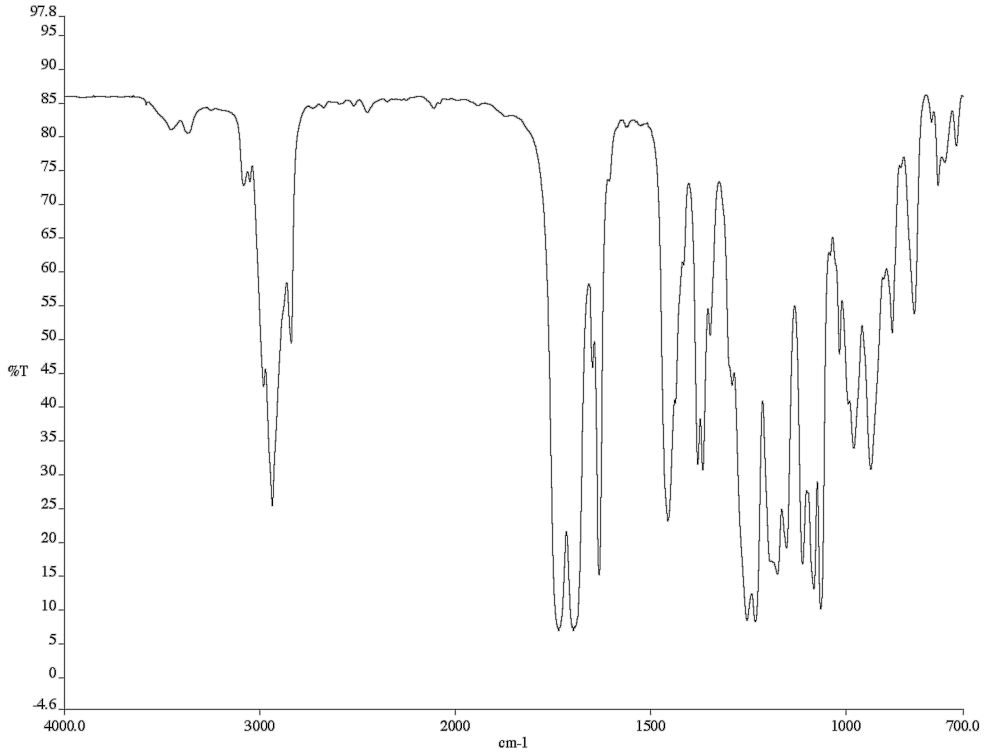
Infrared spectrum (thin film/NaCl) of compound **45a**.



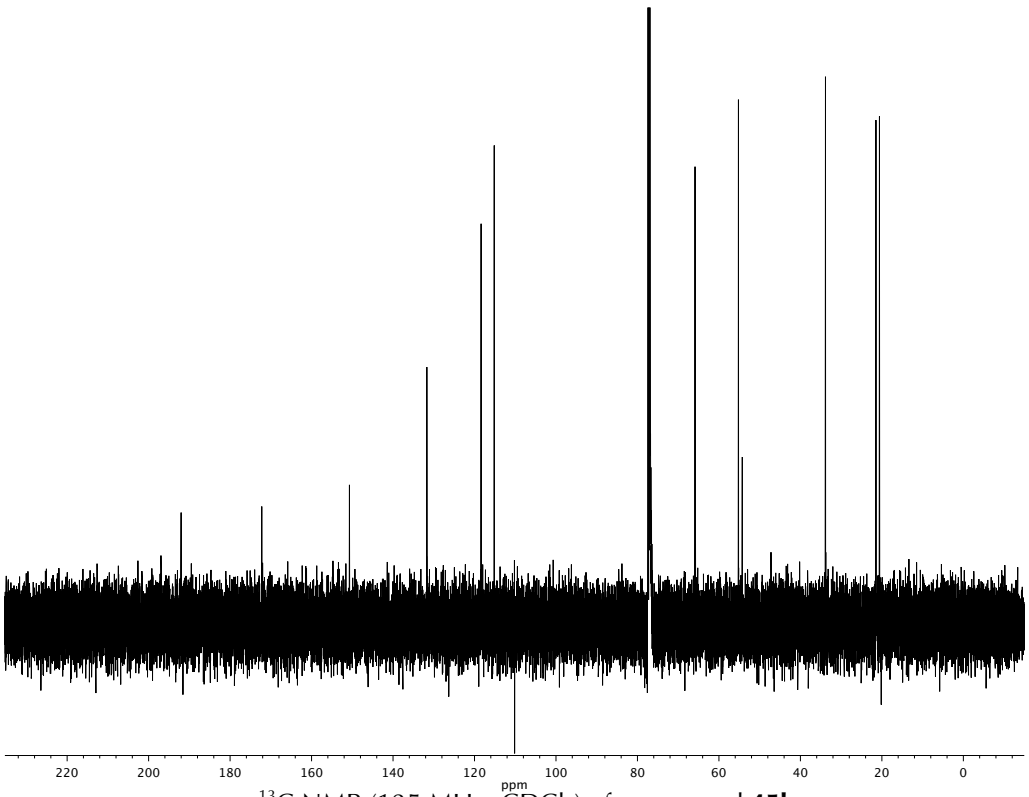
^{13}C NMR (125 MHz, $CDCl_3$) of compound **45a**.



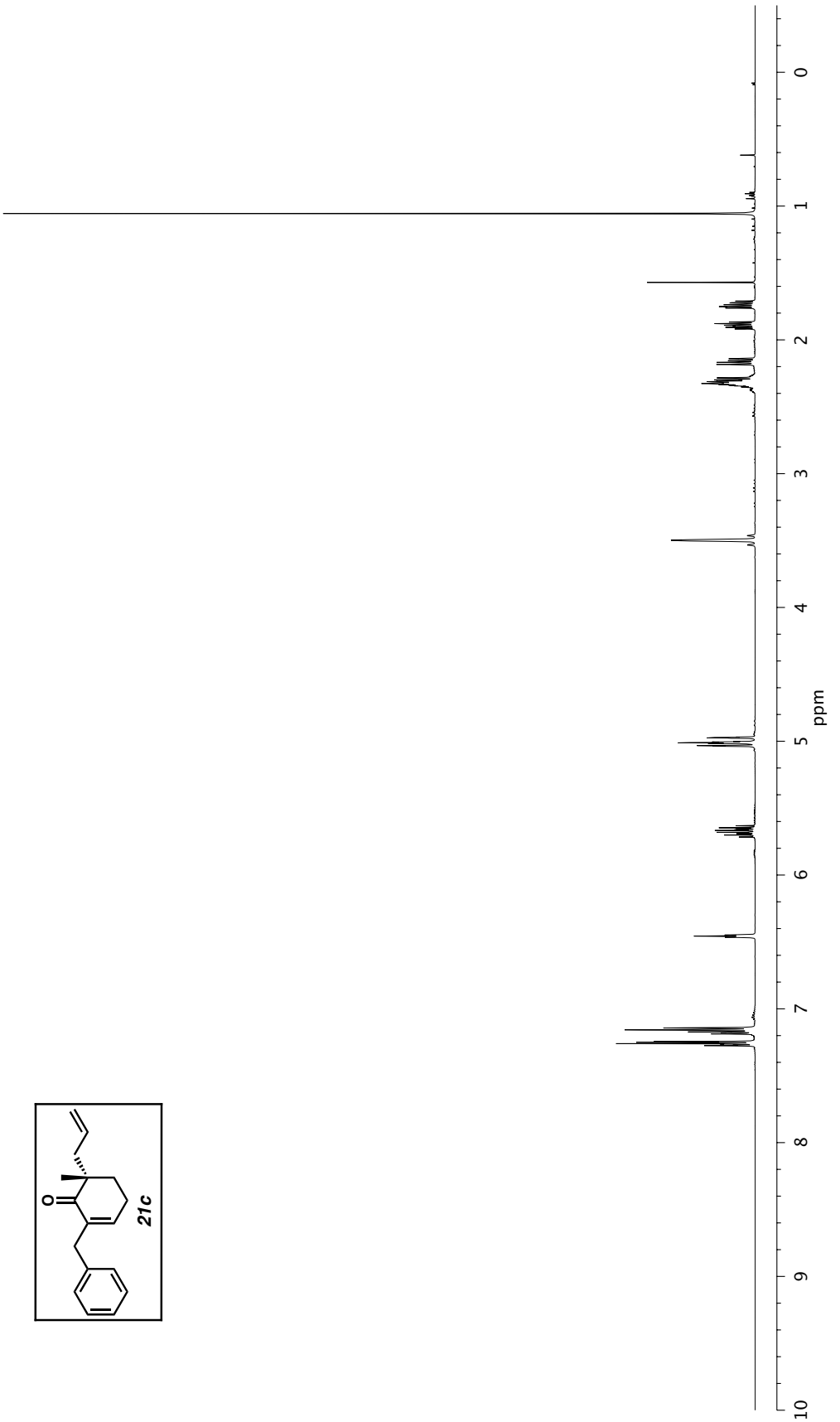
^{1}H NMR (500 MHz, $CDCl_3$) of compound **45b**.



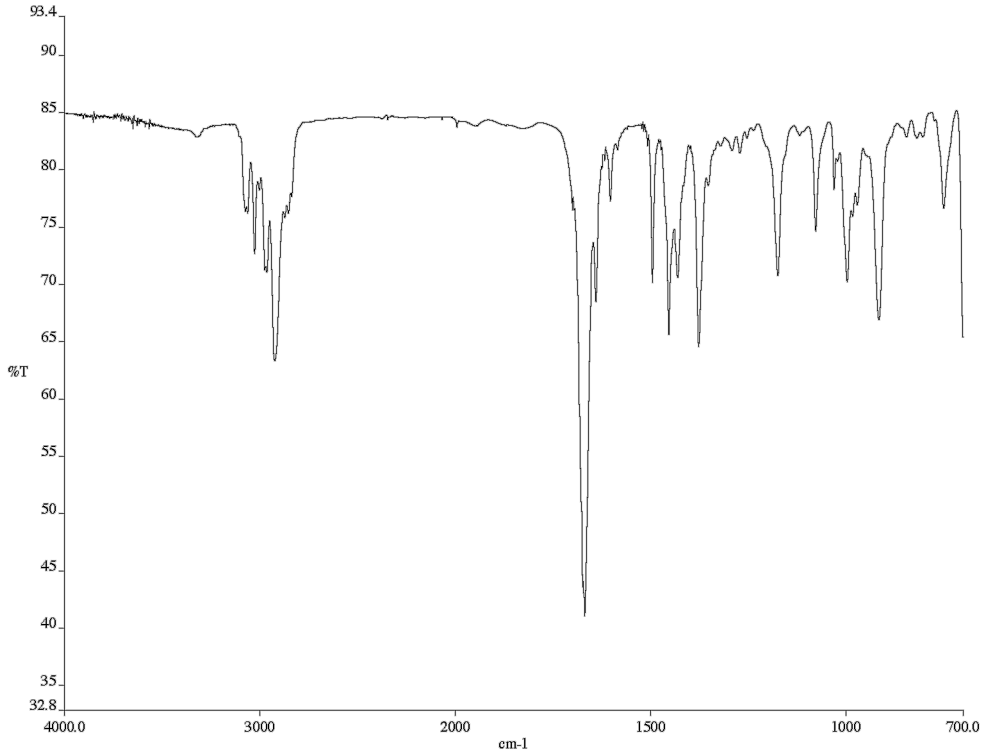
Infrared spectrum (thin film/NaCl) of compound **45b**.



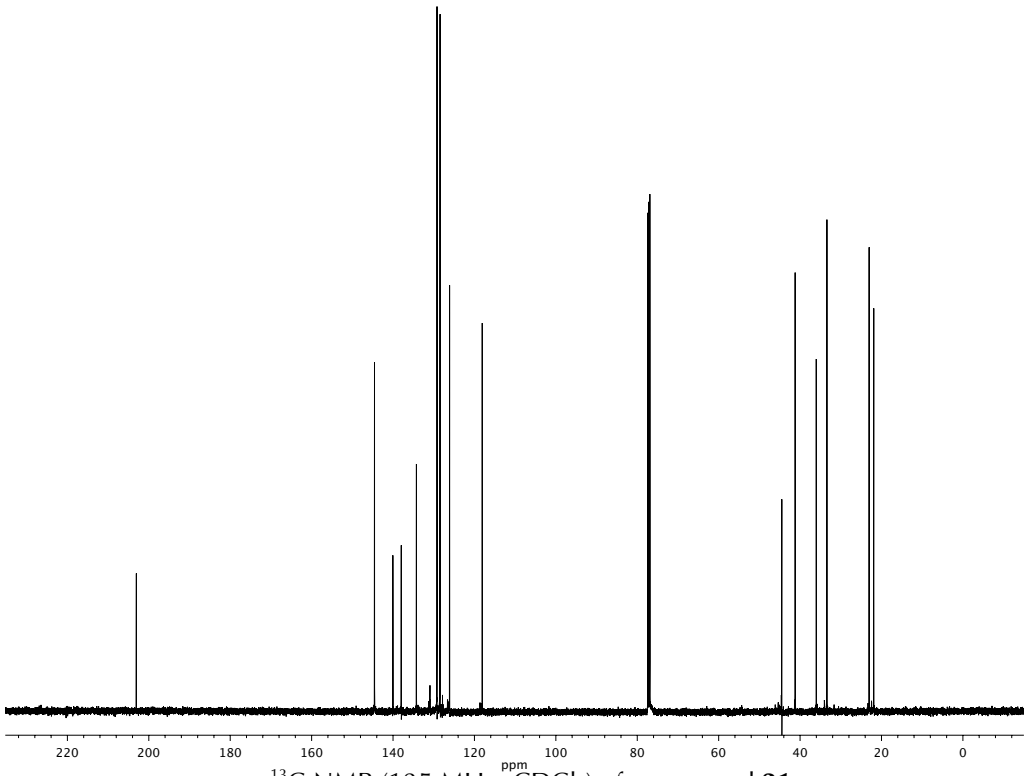
^{13}C NMR (125 MHz, $CDCl_3$) of compound **45b**.



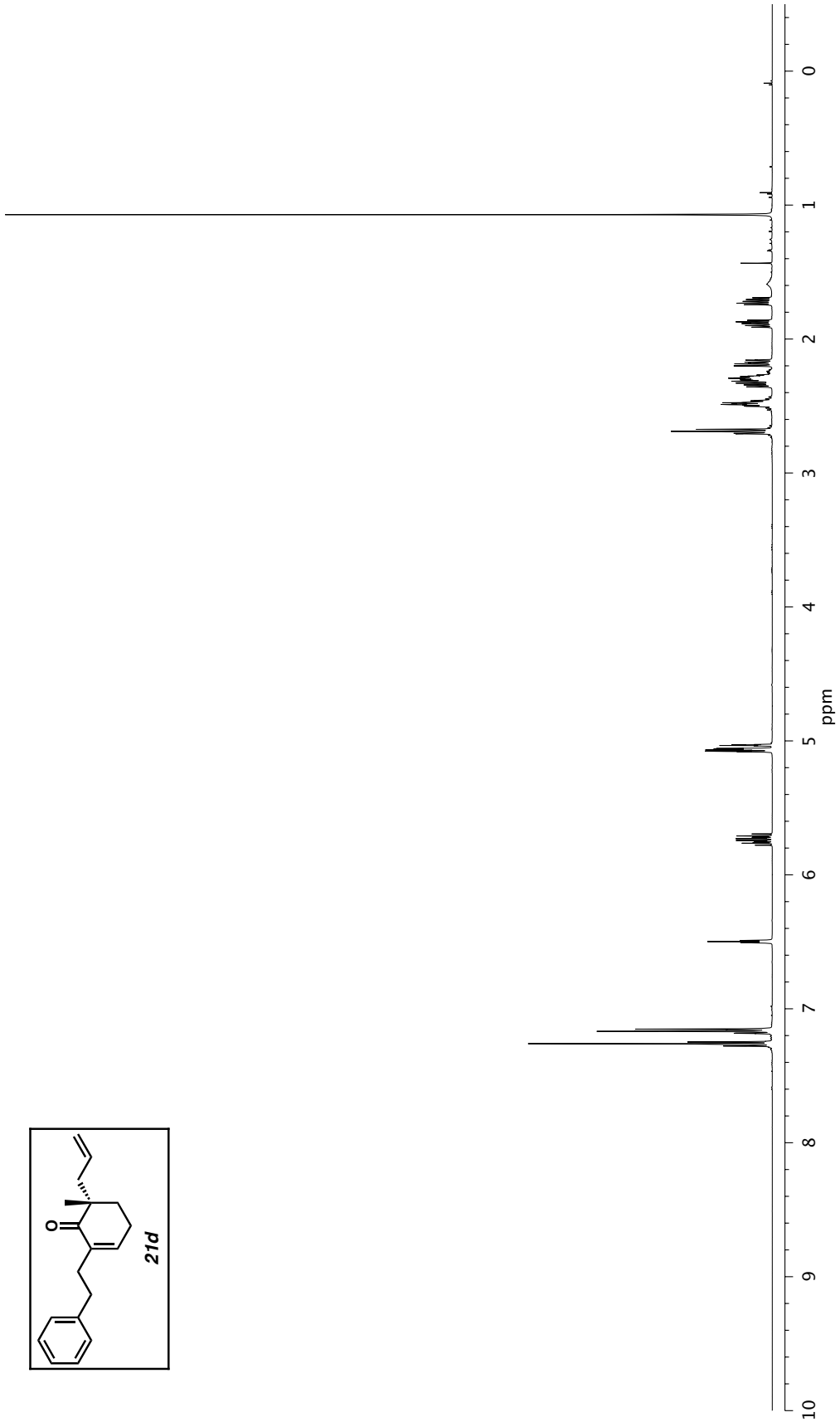
^{1}H NMR (500 MHz, $CDCl_3$) of compound **21c**.



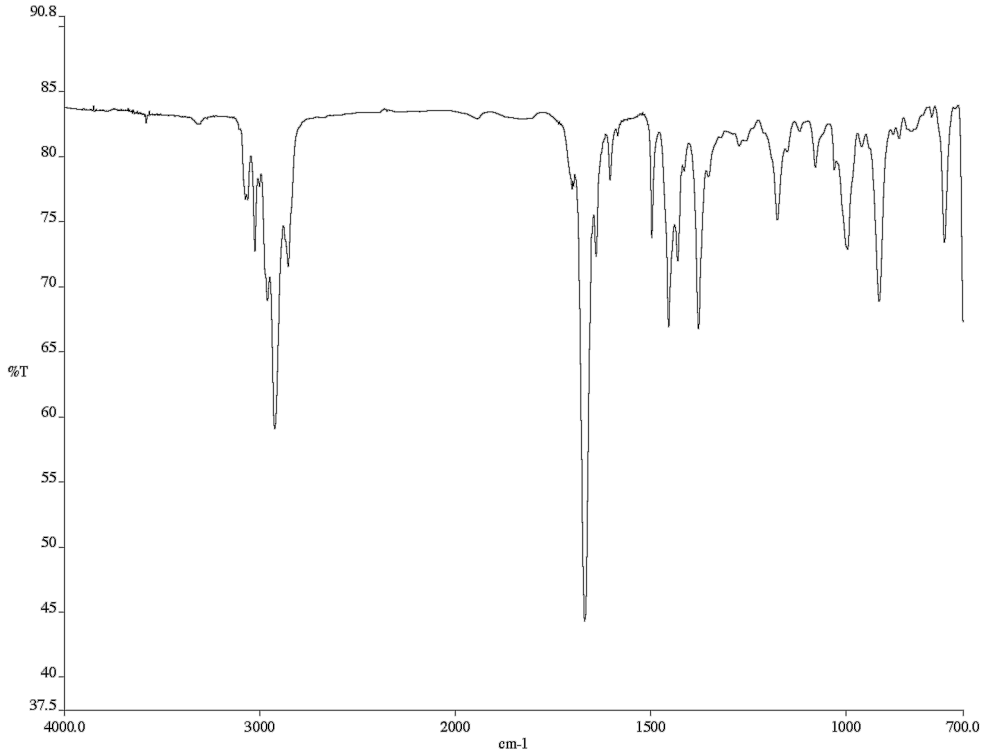
Infrared spectrum (thin film/NaCl) of compound **21c**.



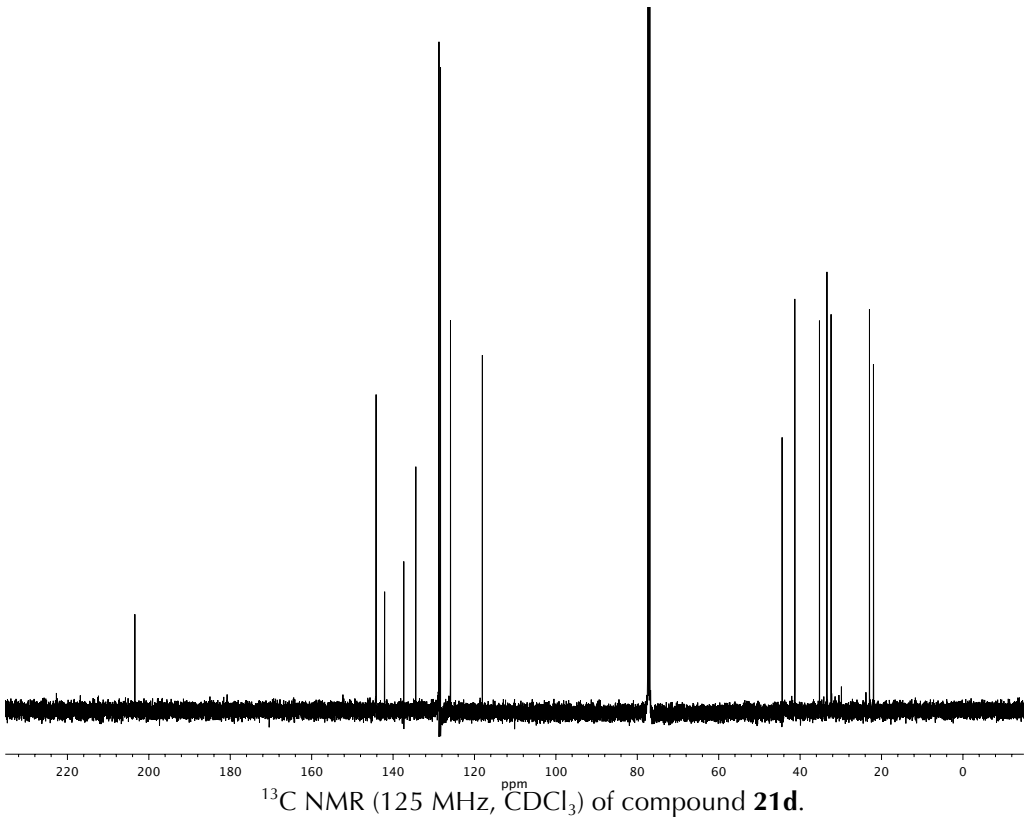
^{13}C NMR (125 MHz, $CDCl_3$) of compound **21c**.



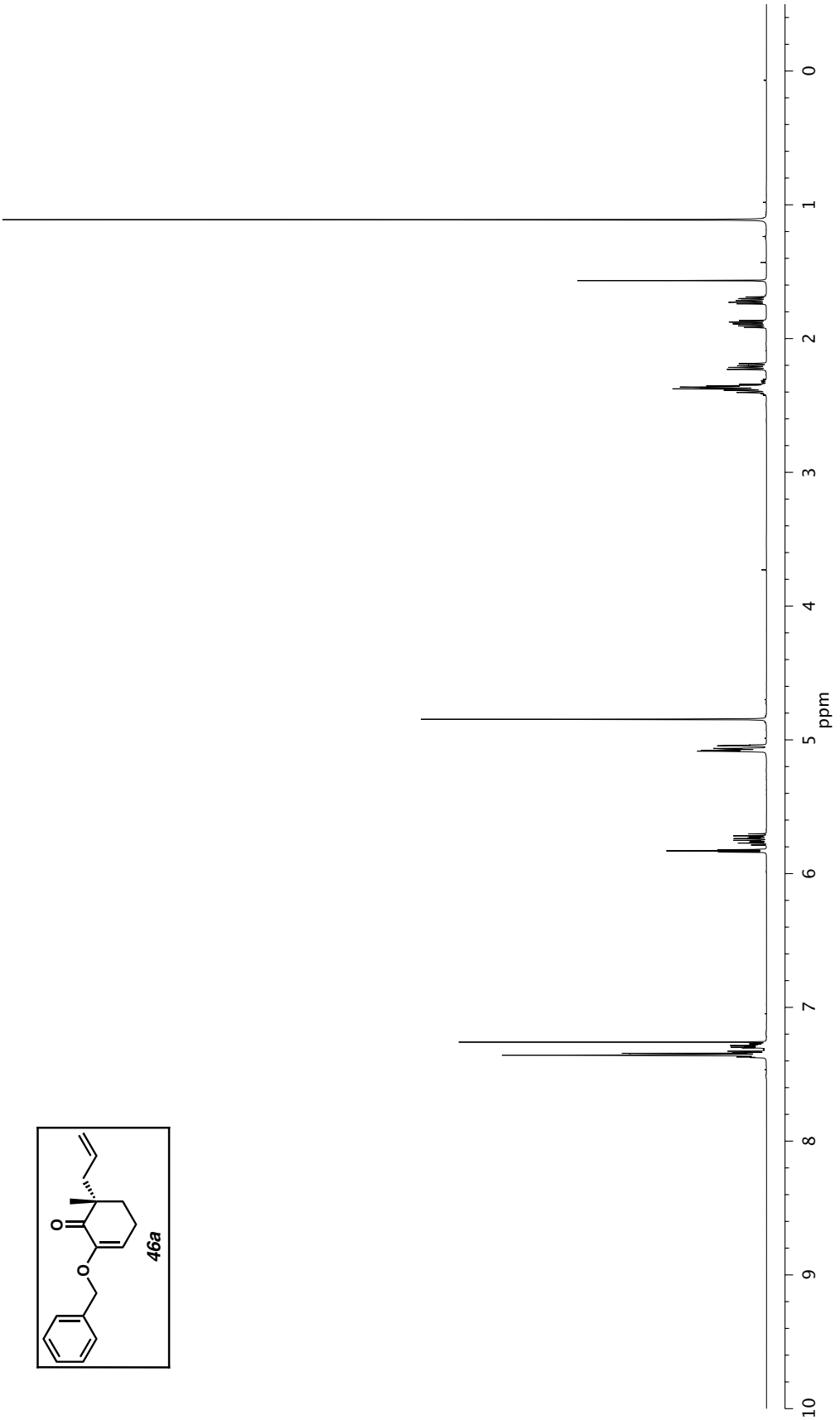
^{1}H NMR (500 MHz, $CDCl_3$) of compound **21d**.



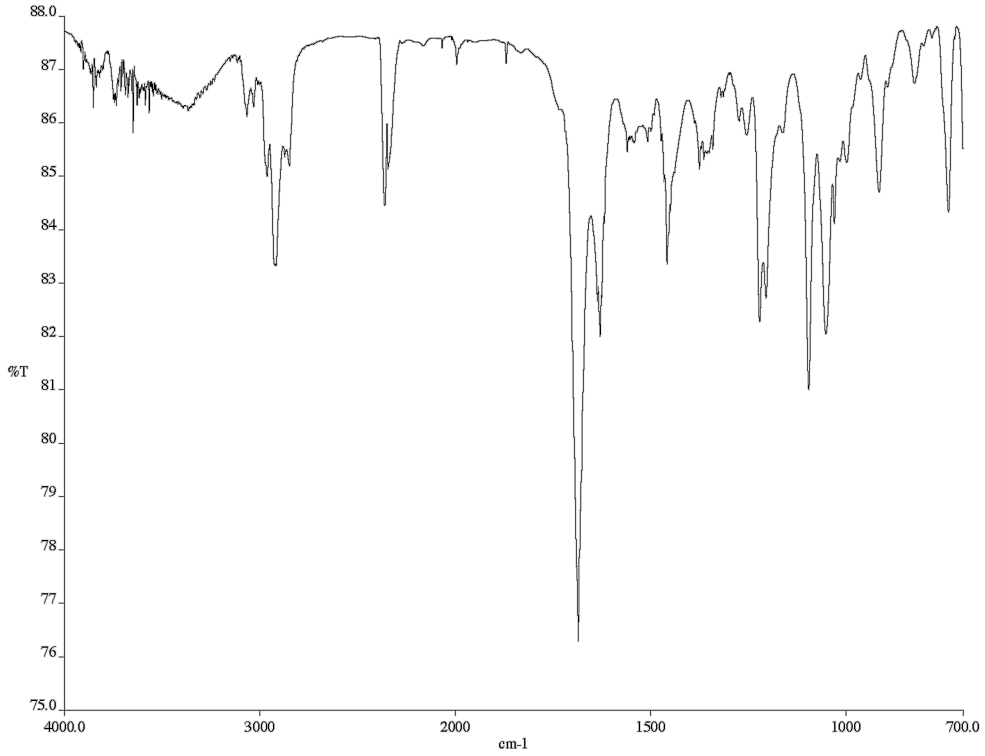
Infrared spectrum (thin film/NaCl) of compound **21d**.



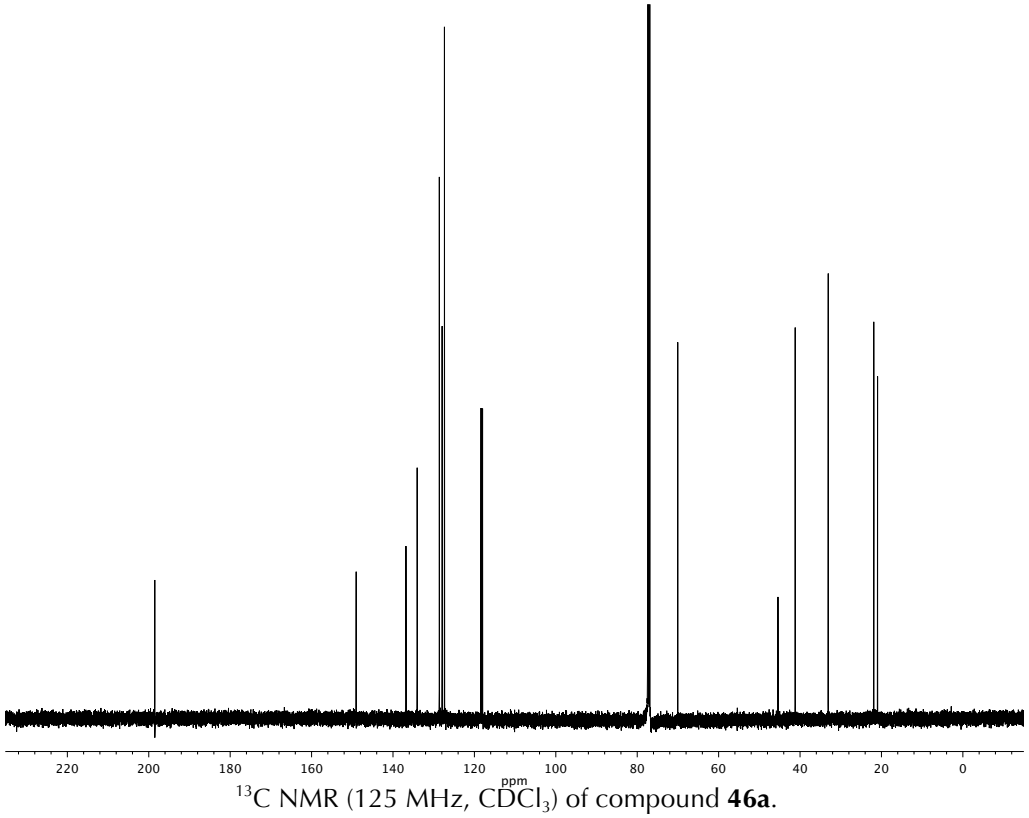
^{13}C NMR (125 MHz, $CDCl_3$) of compound **21d**.



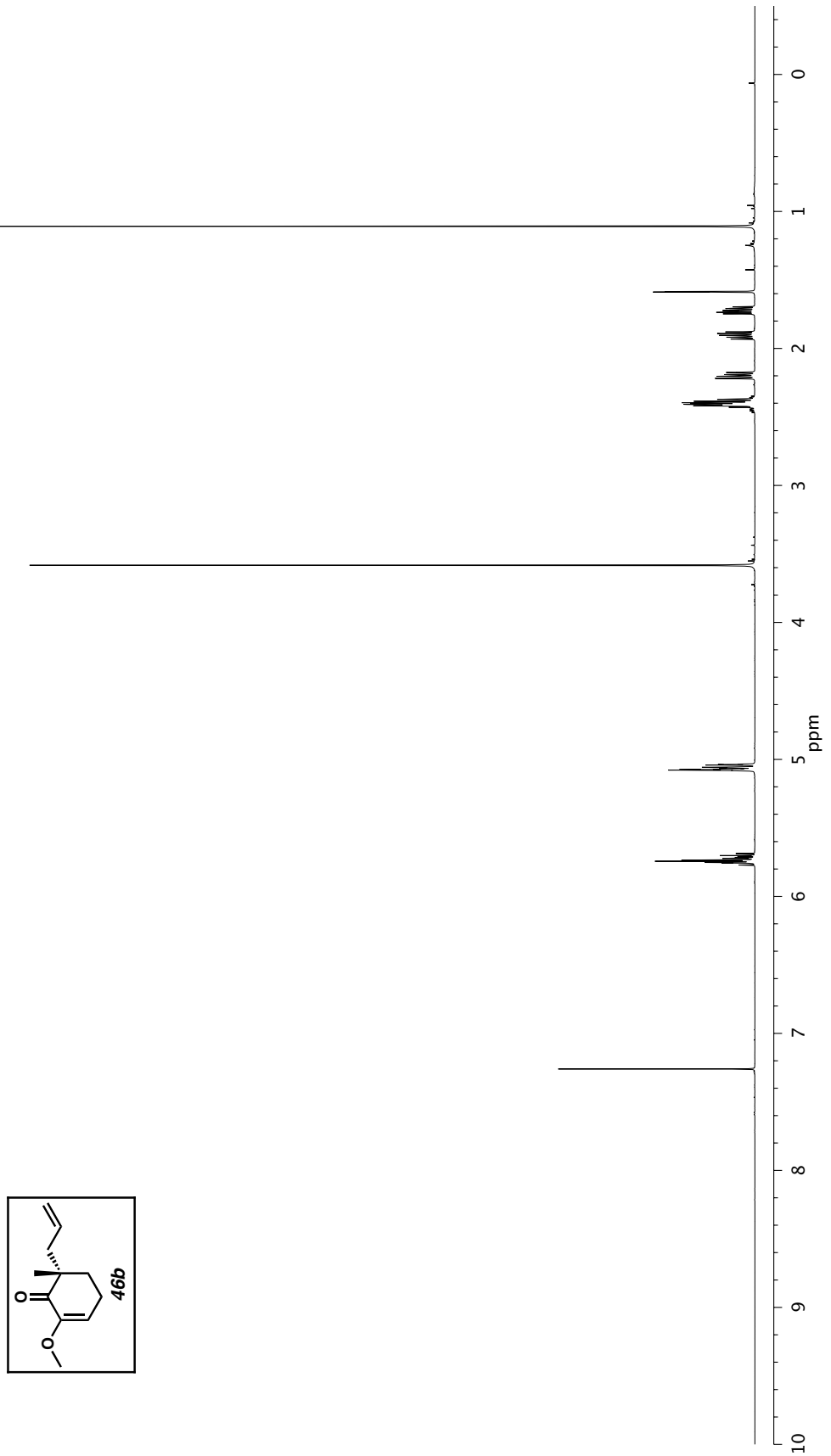
^{1}H NMR (500 MHz, $CDCl^3$) of compound **46a**.



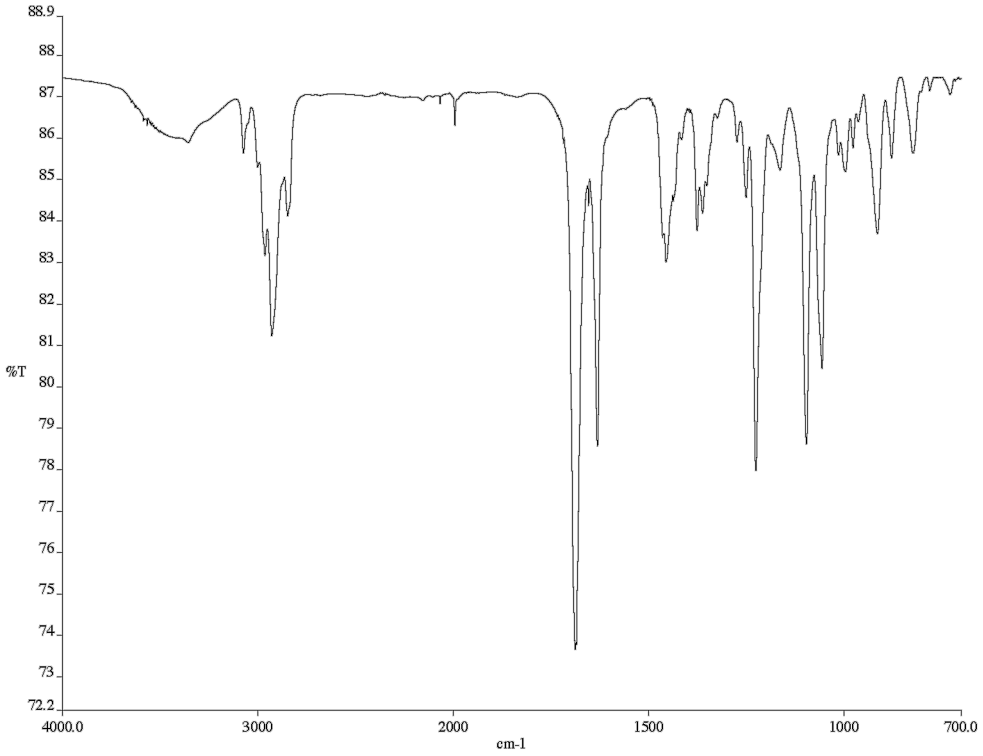
Infrared spectrum (thin film/NaCl) of compound **46a**.



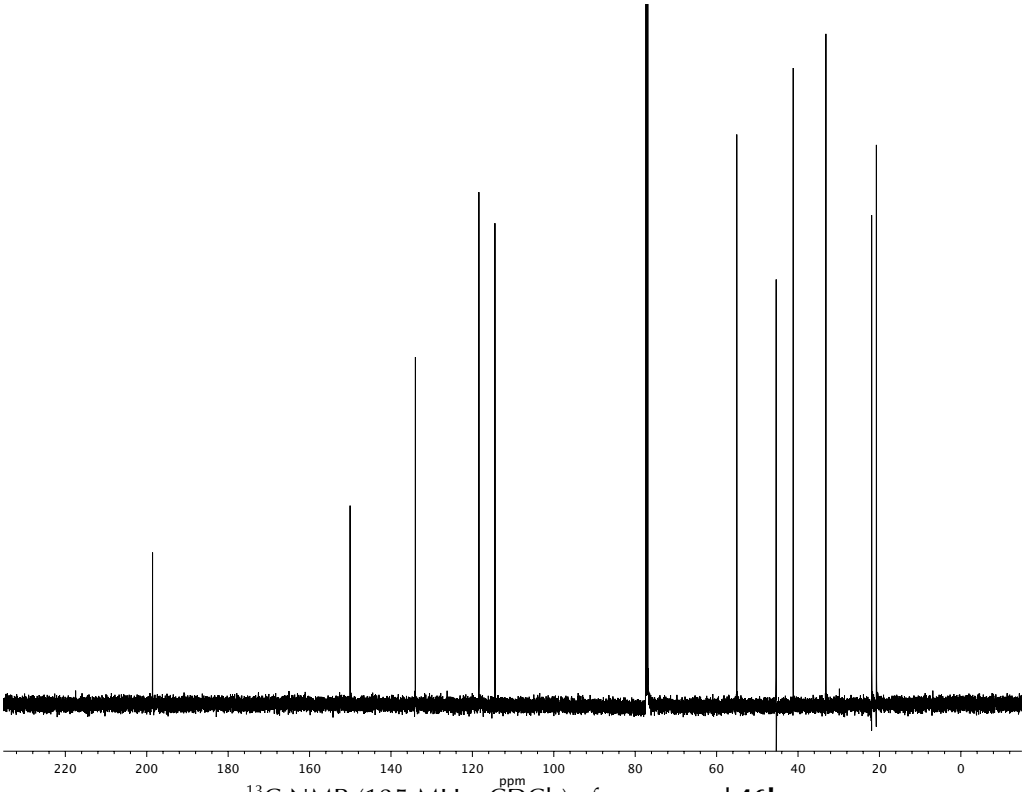
^{13}C NMR (125 MHz, $CDCl_3$) of compound **46a**.



^{1}H NMR (500 MHz, $CDCl^{3}$) of compound **46b**.



Infrared spectrum (thin film/NaCl) of compound **46b**.



^{13}C NMR (125 MHz, $CDCl_3$) of compound **46b**.

CHAPTER 2

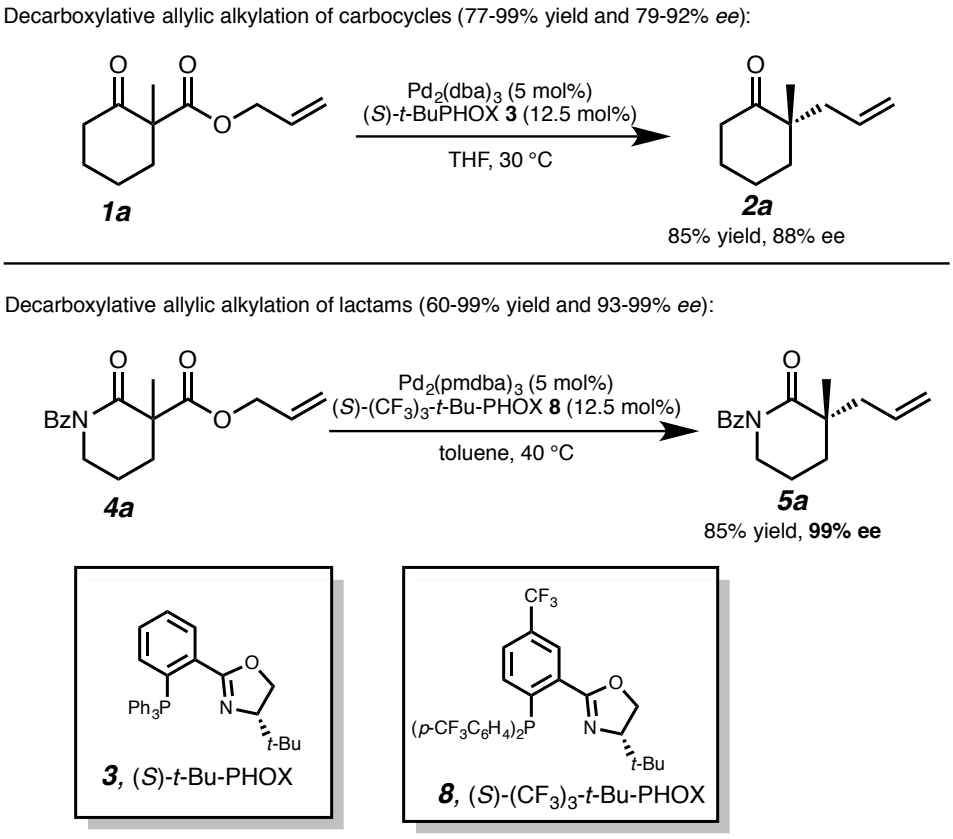
Highly Enantioselective Palladium-Catalyzed Decarboxylative Allylic Alkylation of Enaminones[†]

2.1 INTRODUCTION AND BACKGROUND

The asymmetric palladium-catalyzed decarboxylative allylic alkylation (DAA) reaction has long been an area of interest in our group (see Chapter 1.1).[1] Although carbocycles **1** were the first successful substrates to be utilized in this reaction with the ligand (*S*)-*t*-BuPHOX (**3**), enantioselectivity of this transformation was limited to the high 70% to low 90% *ee* range until the discovery that reaction of lactam substrates **5** utilizing trifluoromethylated ligand (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**) furnish products in enantioselectivities ranging from 93% to 99% (Scheme 2.1).[2]

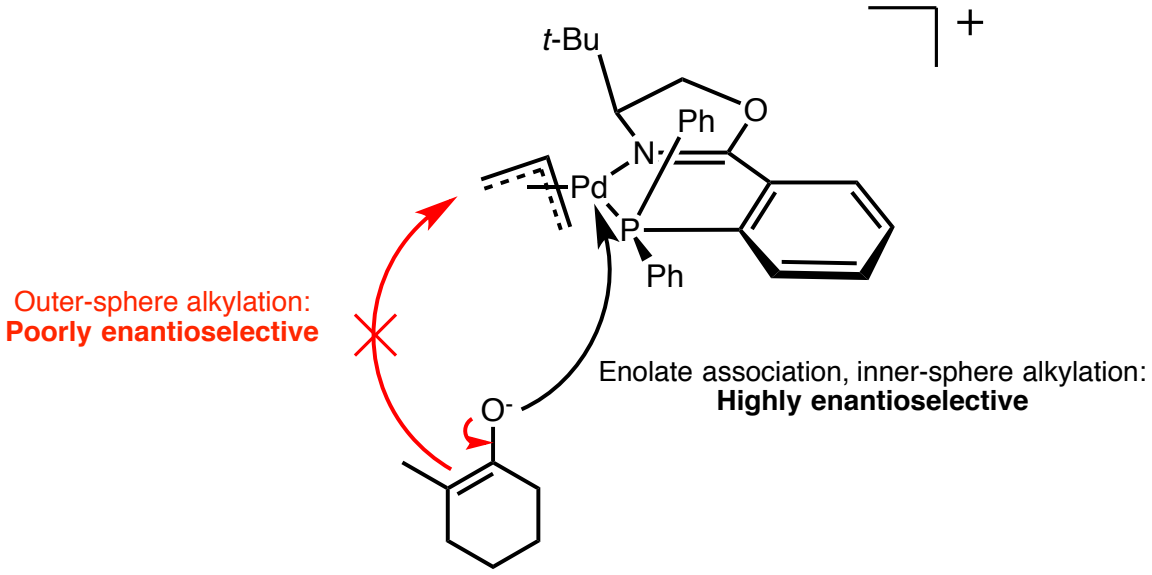
[†] This research was performed in collaboration with Louise Lefoulon and Dr. Jared A. Moore.

Scheme 2.1. Assymetric allylic alkylation carbocyclic and lactam substrates.



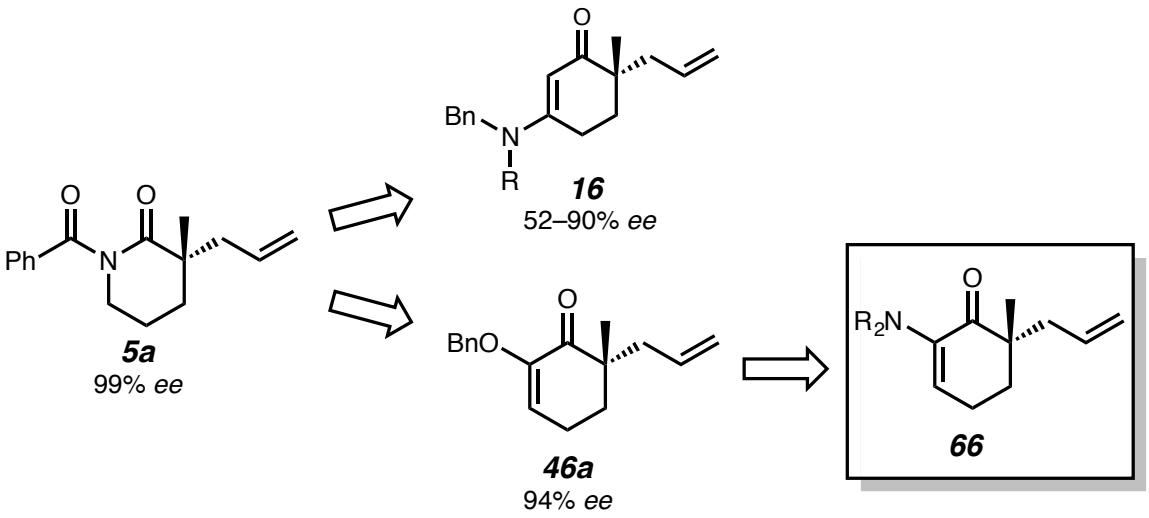
This prompted us to consider what distinguished the lactam substrate class, and if we could apply those properties to carbocyclic substrates to increase the reaction selectivity. Our initial efforts focused on enolate electronics, postulating that it was the electron-rich nature of the substrate favoring an inner-sphere alkylation mechanism thereby leading to increased selectivity.[3] Prior theoretical studies have supported the Pd(PHOX) catalytic system favoring an inner-sphere reaction mechanism, specifically noting that this reaction mechanism is favored due to the basic nature of the enolate electrophile leading to apical attack on the intermediate palladium π-allyl complex (Figure 2.1).[4]

Figure 2.1. Comparison of inner- and outer-sphere alkylation mechanisms in the DAA reaction.



Investigation of vinylogous amides (Figure 2.2, **16**) as carbocyclic lactam mimics, however, yielded enantioselectivities in the ordinary range for carbocyclic substrates. Despite this, we discovered that diosphenol ether substrate **46a** gave moderately higher enantioselectivities than previously investigated carbocycles. This result, combined with no trend correlating the steric bulk of the α′-substituent to the stereoselectivity of the transformation led us to postulate that there might be a stereoelectronic effect governing the differences in observed enantioselectivity (see Chapter 1.2). As such, we turned to the substrate class of en-2-aminones (Figure 2.2, **65**) to investigate if a stronger coordinating group at the α′-position would have the desired effect on the reaction selectivity.

Figure 2.2. Rationale for choice of enaminones as substrates.

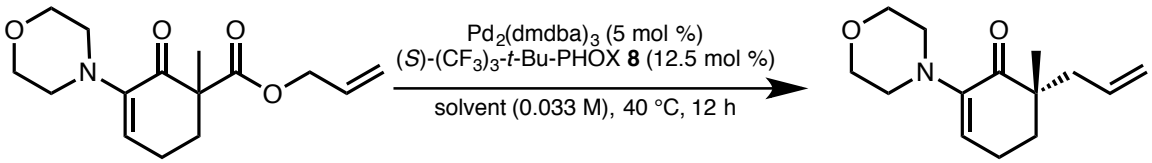


2.2 RESULTS AND DISCUSSION

2.2.1 Reaction Optimization

The enaminone class of substrates was readily accessible by standard acylation/alkylation protocols (see supporting information for details). The first substrate we investigated was morpholine-derived enaminone **65a**. To our delight, the corresponding product **66a** was furnished in 93% yield and 97% *ee* using (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**) (Table 2.1, entry 1). This result prompted us to perform an optimization for reaction medium, as previous reactions had proven to be somewhat variable according to the solvent used.[1,2] We were pleased to discover that the reaction retained its high enantioselectivity in a wide variety of solvents. Though we briefly investigated the effect of temperature on outcome of the reaction, we found that lowering the reaction temperature to 30 °C had no effect on the resulting *ee* (result not shown).

Table 2.1. Initial solvent screen for enaminone substrates.

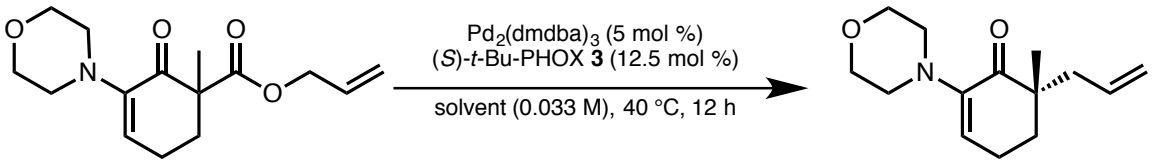


65a ***66a***

entry	solvent	% ee (chiral HPLC)
1	2:1 hex:tol	94
2	benzene	95
3	THF	95
4	DME	95
5	dioxane	94
6	Et_2O	97
7	MeCN	88
8	toluene	97
9	TBME	95
10	CPME	97
11	2-MeTHF	96
12	*i*-BuOAc	92
13	*i*-PrOAc	96
14	EtOAc	98

To our surprise, when we utilized the standard (*S*)-*t*-BuPHOX ligand (**3**) instead of its trifluoromethylated counterpart, the reaction retained its high enantioselectivity (Table 2.2). We determined ethyl acetate to be the optimal reaction medium, as a cheap, easy to work with, and relatively environmentally benign solvent.

*Table 2.2 Solvent screen using ligand **3**.*



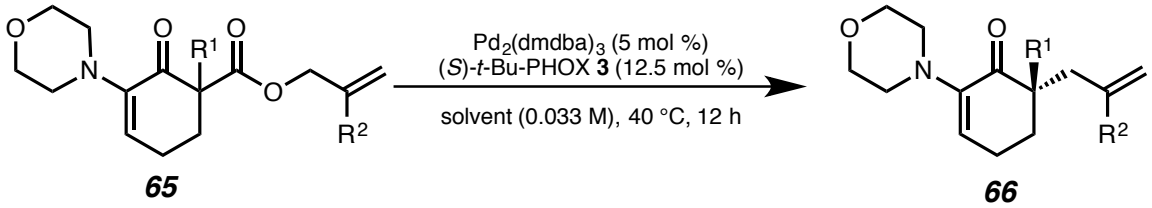
65a ***66a***

entry	solvent	% ee (chiral HPLC)
1	EtOAc	98
2	toluene	94
3	CPME	98

2.2.2 Substrate Scope

With optimized reaction conditions at hand, we desired to determine the generality of this substrate class as exceptional among carbocycles (Table 2.3). Substitution of the methyl group for a slightly larger ethyl group was unsurprisingly well tolerated, furnishing the product in 99% yield and 98% *ee* (**66b**, Table 2.3, entry 2). Substrates bearing larger alkyl chain substituents such as TBS ethers (**66c** and **66d**, Table 2.3, entries 3 and 4) also resulted in high yields and excellent enantioselectivity.

Table 2.3. Substrate scope of enaminones in the asymmetric DAA.



65 ***66***

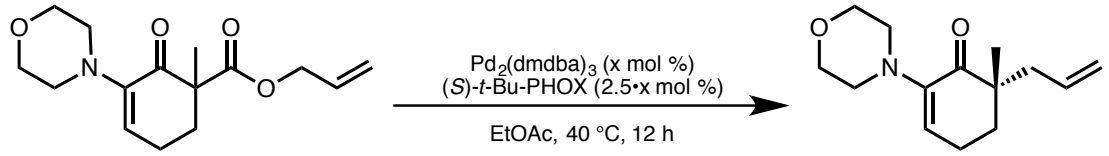
entry	product	R^1	R^2	% yield (isolated)	% *ee*
1	**66a**	Me	H	95	99
2	**66b**	Et	H	99	98
3	**66c**	CH_2OTBS	H	96	99
4	**66d**	CH_2CH_2OTBS	H	93	99
5	**66e**	$CH_2CH_2CO_2Me$	H	98	97
6	**66f**	$CH_2CH_2C(O)Me$	H	90	94
7	**66g**	CH_2CH_2CN	H	99	94
8	**66h**	Bn	H	95	96
9	**66i**	*p*-(OMe)-Bn	H	99	95
10	**66j**	*p*-(CF_3)-Bn	H	87	92
11	**66k**	Me	Cl	58	99
12	**66l**	Me	Me	92	99

Substrates with alkyl chains bearing electron-withdrawing ester, ketone and nitrile groups also performed admirably in the reaction (**66e-g**, Table 2.3, entries 8–10), with

enantioselectivities in the range of 94–97%. Benzyl substitution was somewhat well-tolerated, with benzyl, *para*-methoxybenzyl and *para*-trifluoromethylbenzyl substrates furnishing products in 96%, 95% and 92% *ee* respectively (**66h–j**, Table 2.3, entries 5–7).

Satisfied that the reaction was quite general with respect to the alkyl substitution, we found that substitution at the 2-position of the allyl group also furnished product with excellent selectivity, as in 2-chloro and 2-methylallyl products **66k** and **66l** (Table 2.3, entries 11 and 12), although product **66k** was obtained in significantly lower yield. Moreover, we found that this reaction was imminently scalable. Increasing the reaction scale from 0.465 mmol to 12.3 mmol, with a corresponding increase in concentration from 0.033 M to 0.33 M and decrease in catalyst loading from 5 mol % to 0.5 mol %, we maintained an excellent yield of 93% and no loss of enantioselectivity (Table 2.4).

Table 2.4. Increasing scale and reducing catalyst loading of the reaction.



65a ***66a***

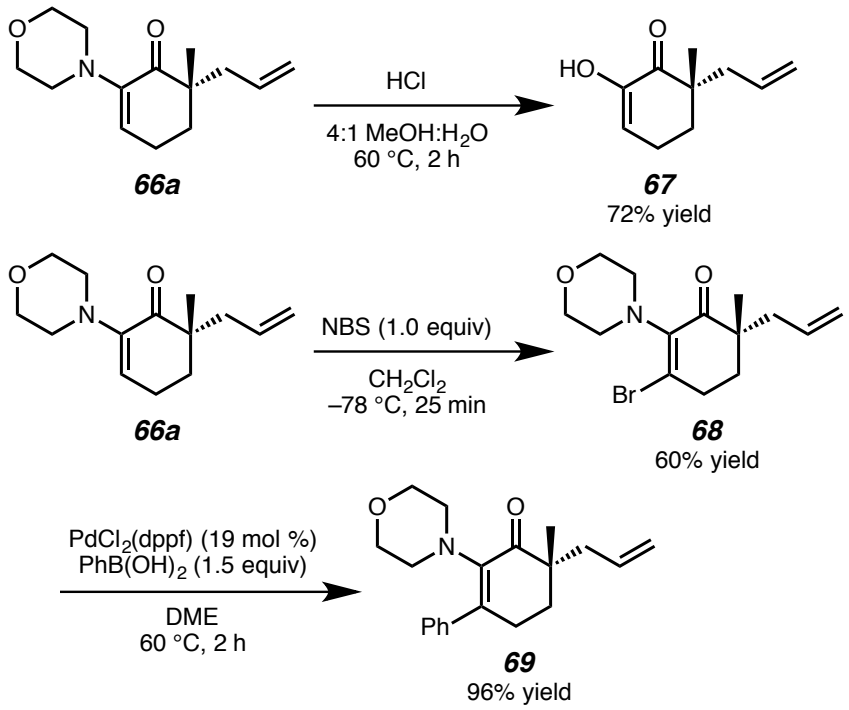
entry	scale (amount isolated product)	concentration (M)	catalyst loading (mol % $Pd_2(dmdba)_3$)	% yield (isolated)	% ee (chiral HPLC or SFC)
1	0.465 mmol (104 mg)	0.033	5	95	98
2	5.41 mmol (1.19 g)	0.1	1.67	94	99
3	12.3 mmol (2.69 g)	0.33	0.5	93	98

2.2.3 Derivitization of Enaminone Products

Given the excellent results with this class of substrates, we desired to determine the utility of the products for access to alternative building blocks in organic synthesis. Treatment of enaminone **66a** with hydrochloric acid in a methanol-water mixture

revealed the latent 1,2-diketone functionality (Scheme 2.2), yielding diketone **67** in 79% yield. Treatment with NBS resulted in bromination at the nucleophilic 3-position, yielding vinyl bromide **68** in 60% yield. This vinyl bromide proved to be an excellent substrate for the Suzuki–Miyaura cross-coupling, as reaction with phenyl boronic acid and $PdCl_2$dppf provided arylated enamine **69** in 96% yield.

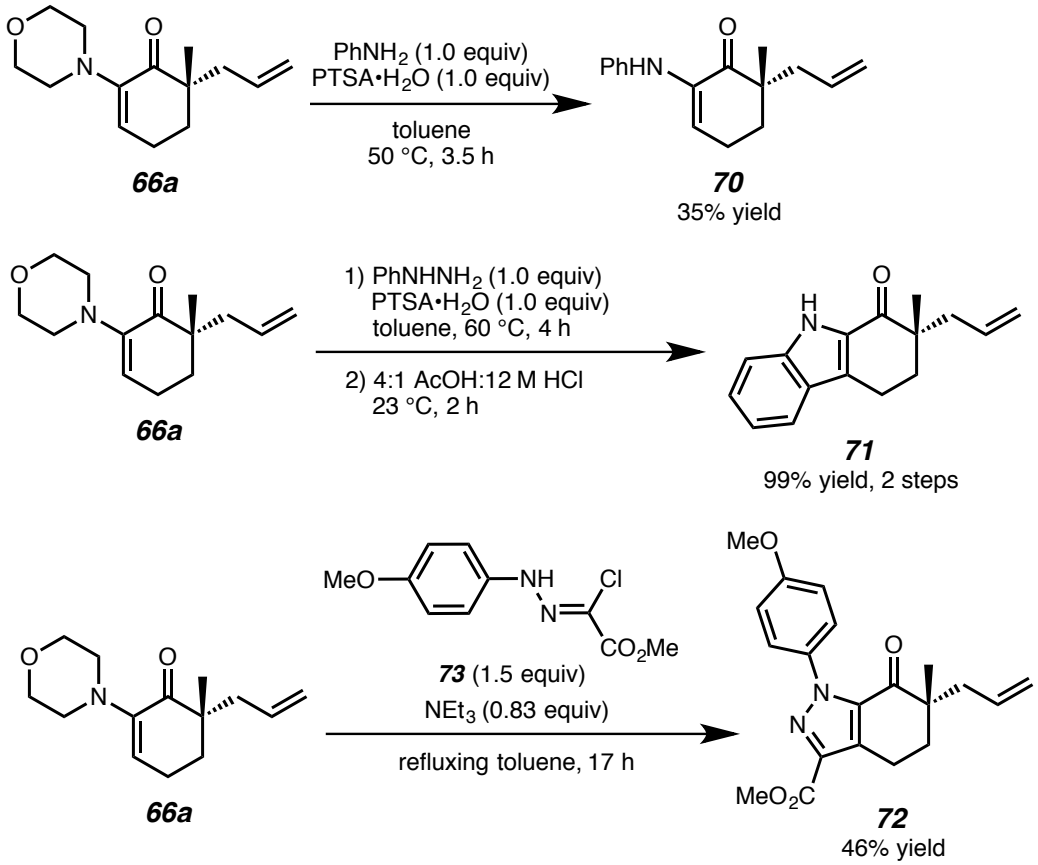
Scheme 2.2. Derivitization of enaminone products by hydrolysis and by bromination and Suzuki–Miyaura cross-coupling.



2-Morpholine substituted enaminones have been shown to undergo transamination, and have been used to in the synthesis of *N*,*N*-imino-enaminido ligands for hafnium and zirconium polymerization catalysts.[5] Reaction of **66a** with aniline yielded the transaminated product **70** in a modest 35% yield (Scheme 2.3). Reaction with more nucleophilic phenyl hydrazine, however, followed by treatment under Fischer indole conditions resulted in indole **71** in 99% yield over two steps. This result is

interesting, as it furnished the carbazolone with opposite connectivity between the cyclohexanone and indole systems as compared to the vinylogous amides previously investigated by our group (Chapter 1, Scheme 1.7), and used in the total syntheses of (+)-kosihainanine A and (–)-aspidospermidine by Lupton and Shao.[6]

Scheme 2.3. Derivitization of enaminone products by transamination and heterocycle formation



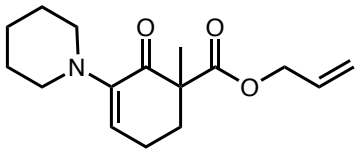
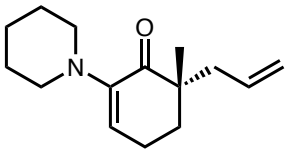
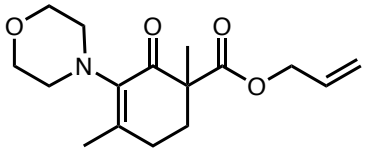
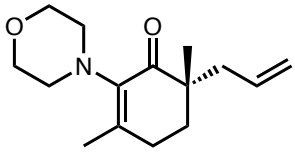
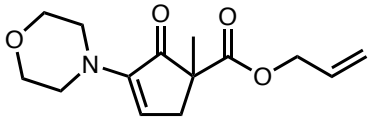
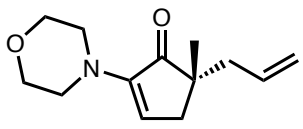
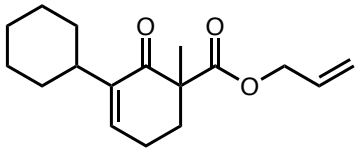
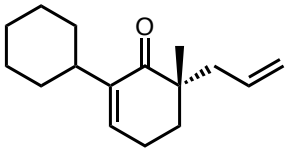
2-Morpholine substituted enaminones have also been used en route to pyrazole-based inhibitors of blood coagulation factor Xa by reaction with *para*-methoxyphenylchlorohydrazones.[7] Accordingly, we treated enaminone **66a** with reagent **73**, yielding corresponding pyrazole **72** in 46% yield (Scheme 2.3). Thus, the

functionality of our enaminone products can be used to access a variety of nucleophilic and electrophilic reactivities, and converted in various useful heterocyclic structures.

2.2.4 Insight from Related Structures

Although we had found an exceptional substrate class for our reaction, we desired to determine if this reflected a stereoelectronic effect as postulated. We began by testing piperidyl substrate **74** to determine if the distil oxygen of the morpholine substituent had any influence over the selectivity of the reaction (Table 2.5, entry 1). Piperidyl product **75** was obtained in 99% yield and 99% *ee*, indicating that the oxygen of the morpholine ring is not required for our observed selectivities.

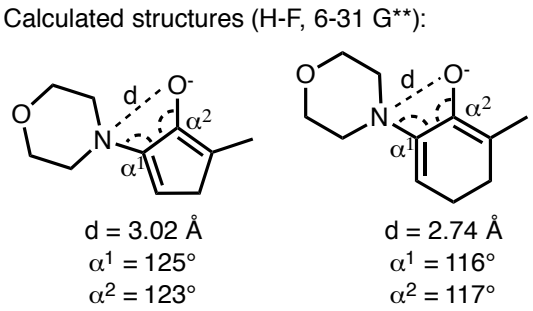
*Table 2.5. Asymmetric DAA of substrates related to enaminones **65**.*

entry	substrate	product	% yield (isolated)	% ee (chiral HPLC or SFC)
1	 ***74***	 ***75***	99	99
2	 ***76***	 ***77***	52	90
3	 ***78***	 ***79***	94	83
4	 ***80***	 ***81***	93	72

As we hypothesized the existence of a stereoelectronic interaction between the α′-substituent and the catalyst, we sought to perturb this effect by making changes to the steric environment of the amine functionality of the enaminone. Adding a methyl group to the 3-position of the enone prolonged the reaction time greatly, resulting in a 52% yield after reaction for seven days, and a marked decrease in enantioselectivity to 90% (**77**, Table 2.5, entry 2).[8] While this result is ambiguous, it could be due to a steric clash with the morpholine group in the transition state of the favored enantiomer, indicating that the geometrical arrangement of this group in the transition state of the enantiodetermining step is potentially crucial.

Five-membered enaminone **79** was obtained in good yield, but with a notably lower 83% ee (Table 2.5, entry 3). We note that the bond angles and distances between the enolate oxygen (bound to palladium in the inner-sphere reaction mechanism) and the morpholine group are considerably different, with the cyclopentenone-derived substrate having a morpholine group calculated to be approximately 0.3 Å further away (Figure 2.3). Should an interaction between the morpholine nitrogen and the palladium catalyst be the cause of increased enantioselectivity, this increase in distance and angle between enamine nitrogen and enolate oxygen could potentially account for the underperformance of enaminone **78**.

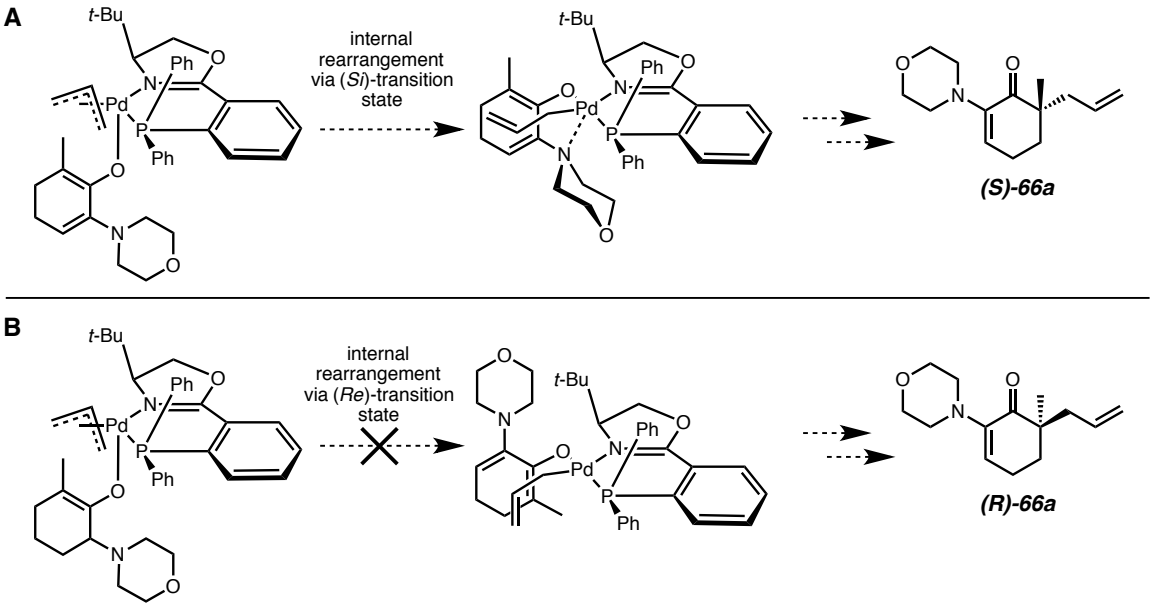
Figure 2.3. Calculated structures for 5- and 6-membered enaminone enolates.[9]



Lastly, to ensure that the observed effects were not simply steric, 2-cyclohexyl-cyclohexenone substrate **80** was subjected to reaction conditions, resulting in a 93% yield but a poor 72% *ee* (Table 2.5, entry 4). This indicates to us that the observed increase in enantioselectivity observed for enaminone substrate **65** is indeed electronic or stereoelectronic nature, and not the result of a simple steric clash.

Based on these results, we hypothesize that the α′-substituent has a reinforcing effect on the stereochemical outcome of the reaction by either an electronic attraction between the nitrogen lone pair and the palladium center of the catalyst, as in a Lewis acid-Lewis base interaction, or by an orbital overlap between the nitrogen lone pair and the vacant palladium $5p_z$ orbital, as in an associative ligand substitution reaction (Figure 2.4).

Figure 2.4. Mechanistic rationale for observed high enantioselectivities of enaminones.



Theoretical and experimental studies[4] of the Pd(PHOX) catalytic system in the asymmetric DAA reaction have shown that coordination of the enolate to the palladium π-allyl complex is followed by an enantiodetermining internal rearrangement to form a square-planar, η-1-bound palladium allyl complex. In the intermediate following the (*Si*) transition state (Figure 2.4, **A**), this rearrangement would place the morpholine moiety in the space formerly occupied by the enolate oxygen, i.e. with a good arrangement for interaction with the Pd metal center. In the intermediate following the (*Re*) transition state, the morpholine moiety would be distant from the metal center and therefore unable to interact with it (Figure 2.4, **B**). This model would also account for the observed increase in selectivity of lactam substrates[2] (through interaction of the exocyclic amide nitrogen with Pd) and the high performance of ligand (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**) in that context, by generating a more electron-poor Pd metal center. We hope that future mechanistic and theoretical studies may be performed on this and related substrate classes in order to refine this mechanistic hypothesis and determine the nature and origin of the observed high enantioselectivity in this reaction.

2.3 CONCLUDING REMARKS

In conclusion, we designed a novel substrate class for the palladium-catalyzed decarboxylative allylic alkylation based on observations made on previous lactam and vinylogous amide substrates. These enaminone substrates proved to be superlative in the reaction, resulting in generally high yields and enantioselectivities of 92–99%, with most products being above 95% *ee*. The products were shown to be versatile building blocks, demonstrating both nucleophilic and electrophilic reactivity as well as being amenable to conversion to various heterocyclic structures. Finally, by comparison to results from

substrates with different skeletal composition, we determined that the observed enantioselectivities are not due to a steric effect, and proposed a model invoking a potential interaction between the amine nitrogen of the enaminone and the Pd center of the catalyst during the enantiodetermining step of the transformation. It is our hope that further investigation of this and related substrate classes may provide further insight into the origin of the observed enantioselectivities, allowing for the design of further exceptional substrate classes or refinement of the catalytic system to improve the enantioselectivity for general substrates.

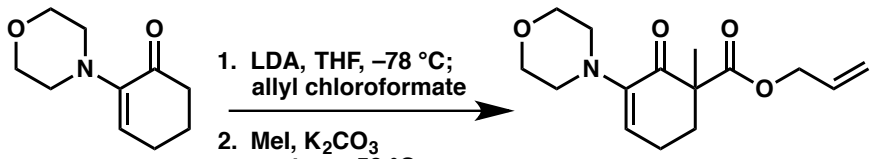
2.4 EXPERIMENTAL SECTION

2.4.1 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.[10] Acetone was used directly from a Sigma-Aldrich ACS reagent grade bottle. Brine solutions are saturated aqueous solutions of sodium chloride. Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. (*S*)-*t*-BuPHOX (**3**),[1a,b] and allyl cyanoformate[11] were prepared by known methods. Reaction temperatures were controlled by an IKAmag temperature modulator. Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, I_2, or $KMnO_4$ staining. ICN silica gel (particle size 0.032-0.0653 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer (75 or 125 MHz respectively) and are reported relative to $CDCl_3$ (δ 77.16 ppm). Data for ^{1}H 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, dm = doublet of multiplets, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C 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: $[\alpha]_D^{25}$ (concentration in g/100 mL, solvent, *ee*). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD, AD- H, or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralpak AD-H column, OD-H column, and OJ-H column obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (GC-EI+, EI+, or FAB+) 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+).

2.4.2 Substrate Synthesis

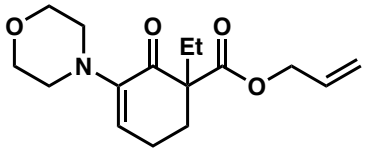


65a

Allyl 1-methyl-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65a)

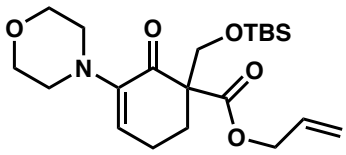
General procedure A: Diisopropylamine (1.77 mL, 12.7 mmol, 1.29 equiv) was taken up in 50 mL THF, cooled to 0 °C and 5.51 mL of a 2.19 M solution of n-butyllithium in hexanes (12.1 mmol, 1.22 equiv) was added dropwise. The mixture was stirred for 30 minutes and cooled to 78 °C. 2-morpholinocyclohex-2-en-1-one[12] (1.79 g, 9.88 mmol,

1.00 equiv) in 8 mL THF (0.17 M total) was added dropwise. The mixture was stirred for 90 minutes, quenched with 50 mL each of saturated aqueous NH_4Cl and water, diluted with 100 mL EtOAc and the phases were separated. The aqueous portion was again extracted with 100 mL EtOAc, and the combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo yielding 2.00 g of a pale yellow oil confirmed to be the desired acylated compound by crude ^1H NMR analysis. A 531 mg portion (2.00 mmol, 1.00 equiv) of this intermediate was taken up in 10 mL acetone (0.2 M) and K_2CO_3 (553 mg, 4.00 mmol, 2.0 equiv) and MeI (149 μL, 2.40 mmol, 1.20 equiv) were added. The reaction mixture was heated to 50 °C for 10 hours, cooled to room temperature, filtered using a fritted funnel and rinsed with 10 mL Et_2O. The reaction mixture was concentrated in vacuo and purified by column chromatography (SiO_2, 2.5 x 12 cm, 4→6→8% acetone in hexanes) to yield enaminone **65a** (347 mg, 1.24 mmol, 62% yield over 2 steps) as a pale yellow oil; Rf = 0.45 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 2H), 5.29 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.23 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.65 – 4.53 (m, 2H), 3.80 (qdd, *J* = 11.3, 6.3, 3.0 Hz, 4H), 3.04 – 2.96 (m, 2H), 2.63 – 2.56 (m, 2H), 2.56 – 2.49 (m, 1H), 2.46 (dddd, *J* = 13.6, 5.1, 3.1, 1.1 Hz, 1H), 2.38 (dtd, *J* = 19.1, 5.4, 3.1 Hz, 1H), 1.86 (ddd, *J* = 13.6, 9.7, 5.6 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 172.4, 131.6, 118.9, 66.9, 66.0, 54.2, 50.0, 33.3, 22.7, 20.6; IR (Neat Film, NaCl): 3447 (broad), 2955, 2855, 2067, 1733, 1695, 1617, 1450, 1378, 1264, 1248, 1222, 1175, 1145, 1119, 1020, 992, 948 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{22}NO_4$ $[M+H]^+$ 280.1543, found 280.1554.



Allyl 1-ethyl-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65b)

Synthesized according to general procedure A using ethyl iodide. The product was purified by column chromatography (SiO_2, 3.5 x 15 cm, 4→6→8→10→20% EtOAc in hexanes) to yield enaminone **65b** (468 mg, 1.60 mmol, 74% yield over 2 steps) as a pale yellow oil. R_f = 0.53 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.73 (ddd, *J* = 4.5, 3.5, 1.2 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.57 (dq, *J* = 5.8, 1.5 Hz, 2H), 3.78 (qdd, *J* = 11.3, 6.3, 3.0 Hz, 4H), 2.95 (ddd, *J* = 11.9, 6.3, 3.1 Hz, 2H), 2.55 (tddd, *J* = 8.9, 6.8, 5.2, 2.4 Hz, 3H), 2.46 – 2.32 (m, 2H), 1.95 (dq, *J* = 13.9, 7.5 Hz, 1H), 1.90 – 1.73 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 171.3, 146.8, 131.7, 128.2, 123.5, 119.0, 67.0, 65.8, 57.9, 50.0, 29.8, 27.0, 22.6, 9.1; IR (Neat Film, NaCl): 2961, 2855, 1732, 1694, 1617, 1448, 1378, 1300, 1264, 1220, 1167, 1120, 957, 934 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{24}NO_4$ $[M+H]^+$ 294.1700, found 294.1690.

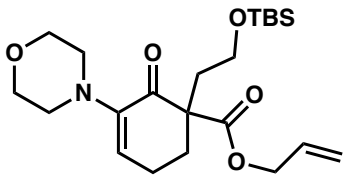


Allyl 1-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65c)

Diisopropylamine (1.77 mL, 12.7 mmol, 1.29 equiv) was taken up in 50 mL THF, cooled to 0 °C and 5.51 mL of a 2.19 M solution of n-butyllithium in hexanes (12.1 mmol, 1.22

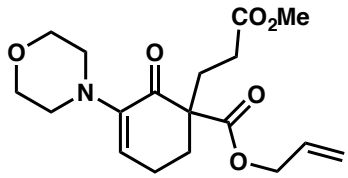
equiv) was added dropwise. The mixture was stirred for 30 minutes and cooled to 78 °C. 2-morpholinocyclohex-2-en-1-one (1.79 g, 9.88 mmol, 1.00 equiv) in 8 mL THF (0.17 M total) was added dropwise. The mixture was stirred for 90 minutes, quenched with 50 mL each of saturated aqueous NH_4Cl and water, diluted with 100 mL EtOAc and the phases were separated. The aqueous portion was again extracted with 100 mL EtOAc, and the combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo yielding 2.00 g of a pale yellow oil confirmed to be the desired acylated compound by crude ^{1}H NMR analysis. A 218 mg portion (0.822 mmol, 1.00 equiv) of this intermediate was taken up in 1.6 mL THF (0.5 M), cooled to 0 °C and and K_2CO_3 (247 mg, 2.47 mmol, 3.00 equiv) and 37% aqueous formaldehyde (156 μL, 5.67 mmol, 6.9 equiv) were added. The reaction was warmed to 23 °C and stirred for 4 hours, extracted with 2 x 5 mL EtOAc, dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography (SiO_2, 3 x 12 cm, 20→35% acetone in hexanes) to yield 133 mg of a pale yellow oil. This intermediate alcohol was taken up in CH_2Cl_2 (4.5 mL, 0.1 M) and TBSCl (75 mg, 0.49 mmol, 1.1 equiv) and imidazole (61 mg, 0.90 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 8 hours, concentrated in vacuo and purified by column chromatography (SiO_2, 2.5 x 14 cm, 20→35% EtOAc in hexanes) to yield enaminone **65c** (106 mg, 0.257 mmol, 29% yield over 3 steps) as a pale yellow oil; R*f* = 0.25 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.82 (m, 2H), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.57 (qdt, *J* = 13.2, 5.7, 1.4 Hz, 2H), 4.08 (d, *J* = 9.8 Hz, 1H), 3.88 (d, *J* = 9.8 Hz, 1H), 3.78 (qdd, *J* = 11.3, 6.1, 3.1 Hz, 4H), 2.92 – 2.84 (m, 2H), 2.70 – 2.61 (m, 2H), 2.60 (dd, *J* = 6.2, 3.3 Hz, 1H), 2.52 (dddd, *J* = 13.8, 5.4, 3.0, 1.1 Hz, 1H), 2.40 (dtd, *J* = 19.2, 5.6, 2.9 Hz, 1H), 2.02 (ddd, *J* =

13.8, 10.0, 5.8 Hz, 1H), 0.85 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 169.6, 146.7, 131.7, 125.0, 118.8, 66.9, 66.6, 66.0, 65.4, 59.9, 50.0, 29.8, 28.0, 25.9, 25.8, 22.5, 18.3, -5.5; IR (Neat Film, NaCl): 2955, 2929, 2894, 2856, 1734, 1690, 1616, 1462, 1448, 1379, 1262, 1217, 1120, 964 cm^{-1}; HRMS (APCI) *m/z* calc'd for $C_{21}H_{36}NO_5Si$ $[M+H]^+$ 410.2357, found 410.2342.



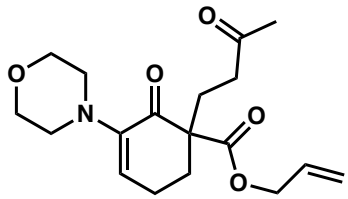
Allyl 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65d)

Synthesized according to general procedure A using (2-bromoethoxy)(*tert*-butyl)dimethylsilane and cesium carbonate. The product was purified by column chromatography (SiO_2, 3.5 x 15 cm, 5→10→20% EtOAc in hexanes) to yield enaminone **65d** (184 mg, 0.434 mmol, 49% yield over 2 steps) as a pale tan oil; R_f = 0.23 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.75 (s, 1H), 5.27 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.63 – 4.50 (m, 2H), 3.85 – 3.62 (m, 6H), 2.99 – 2.90 (m, 2H), 2.61 – 2.45 (m, 4H), 2.38 (dtd, *J* = 19.0, 5.5, 2.9 Hz, 1H), 2.14 (ddd, *J* = 13.9, 7.6, 6.1 Hz, 1H), 2.00 – 1.86 (m, 2H), 0.86 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 171.0, 131.7, 119.1, 66.9, 66.0, 59.7, 56.5, 50.0, 36.8, 30.8, 26.0, 22.7, 18.4, -5.2; IR (Neat Film, NaCl): 2955, 2928, 2855, 1733, 1695, 1616, 1447, 1378, 1263, 1209, 1120, 1100, 981, 935 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{38}NO_5Si$ $[M+H]^+$ 424.2514, found 424.2521.



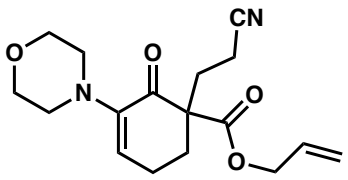
Allyl 1-(3-methoxy-3-oxopropyl)-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65e)

Synthesized according to general procedure A using methyl acrylate. The product was purified by column chromatography (SiO_2, 3 x 12 cm, 10→20% acetone in hexanes) to yield enaminone **65e** (223 mg, 0.635 mmol, 58% yield over 2 steps) as a yellow oil; R_f = 0.42 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 1H), 5.73 – 5.67 (m, 1H), 5.25 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (dq, *J* = 10.3, 1.2 Hz, 1H), 4.60 – 4.48 (m, 2H), 3.80 – 3.67 (m, 4H), 3.62 (s, 3H), 2.92 (ddd, *J* = 11.6, 6.3, 3.0 Hz, 2H), 2.56 – 2.26 (m, 7H), 2.18 (ddd, *J* = 14.0, 10.6, 5.6 Hz, 1H), 2.04 (ddd, *J* = 14.1, 10.8, 5.4 Hz, 1H), 1.84 (ddd, *J* = 14.5, 9.9, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 173.4, 170.9, 146.6, 131.4, 123.3, 119.2, 66.8, 66.1, 56.7, 51.7, 49.8, 30.7, 29.5, 28.9, 22.5; IR (Neat Film, NaCl): 2953, 2854, 2820, 1733, 1694, 1616, 1447, 1377, 1264, 1209, 1177, 1120, 983, 957 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{26}NO_6$ $[M+H]^+$ 352.1755, found 352.1771.



Allyl 3-morpholino-2-oxo-1-(3-oxobutyl)cyclohex-3-ene-1-carboxylate (65f)

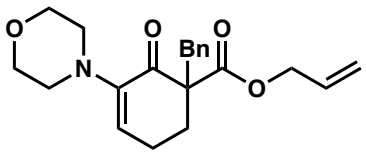
Synthesized according to general procedure A using methyl vinyl ketone. The product was purified by column chromatography (SiO_2, 3 x 12 cm, 20→35→50→65% EtOAc in hexanes) to yield enaminone **65f** (537 mg, 1.60 mmol, 74% yield over 2 steps) as a pale yellow oil that solidified on storage at –20 °C; R_f = 0.28 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.75 – 5.69 (m, 1H), 5.26 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.61 – 4.48 (m, 2H), 3.81 – 3.68 (m, 4H), 2.93 (ddd, *J* = 11.8, 6.3, 3.1 Hz, 2H), 2.66 – 2.31 (m, 7H), 2.15 – 2.04 (m, 4H), 1.98 (ddd, *J* = 14.2, 10.3, 5.3 Hz, 1H), 1.84 (ddd, *J* = 13.1, 10.0, 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 193.4, 171.2, 146.7, 131.4, 123.5, 119.3, 66.9, 66.0, 56.7, 49.9, 38.9, 31.1, 30.0, 30.0, 27.7, 22.6; IR (Neat Film, NaCl): 2956, 2854, 1721, 1615, 1447, 1372, 1299, 1264, 1209, 1179, 1120, 1095, 982, 939 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{26}NO_5$ $[M+H]^+$ 336.1805, found 336.1803.



Allyl 1-(2-cyanoethyl)-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65g)

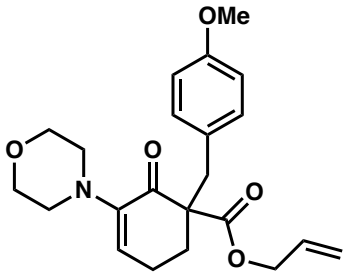
Synthesized according to general procedure A using acrylonitrile. The product was purified by column chromatography (SiO_2, 3 x 12 cm, 10→20% acetone in hexanes) to yield enaminone **65g** (247 mg, 0.776 mmol, 71% yield over 2 steps) as a colorless oil; R_f = 0.29 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.5, 10.4, 6.0 Hz, 1H), 5.77 – 5.73 (m, 1H), 5.33 – 5.21 (m, 2H), 4.66 – 4.54 (m, 2H), 3.83 – 3.69 (m, 4H), 2.95 (ddd, *J* = 11.8, 6.4, 3.0 Hz, 2H), 2.55 (dtt, *J* = 13.3, 9.9, 6.6 Hz, 4H), 2.41

(dqd, J = 14.7, 5.9, 5.4, 3.4 Hz, 3H), 2.21 (ddd, J = 14.0, 9.5, 5.9 Hz, 1H), 2.07 (ddd, J = 14.0, 9.6, 6.3 Hz, 1H), 1.94 – 1.84 (m, 1H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 192.6, 170.1, 170.1, 146.5, 131.0, 123.7, 119.8, 119.3, 66.8, 66.4, 56.4, 56.4, 49.8, 31.0, 30.1, 22.4, 13.2; IR (Neat Film, NaCl): 2956, 2854, 2247, 1734, 1690, 1617, 1448, 1375, 1264, 1208, 1119, 982, 947 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{23}N_2O_4$ $[M+H]^+$ 319.1652, found 319.1668.



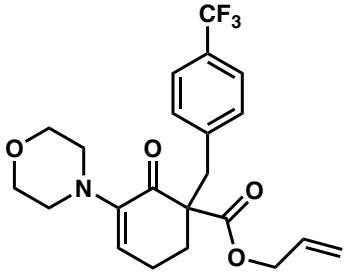
Allyl 1-benzyl-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65h)

Synthesized according to general procedure A using benzyl bromide. The product was purified by column chromatography (SiO_2, 2.5 x 15 cm, 4→6→8→10% acetone in hexanes) to yield enaminone **65h** (498 mg, 1.40 mmol, 65% yield over 2 steps) as a colorless oil; R_f = 0.23 (20% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.13 (m, 5H), 5.79 (ddt, J = 17.3, 10.4, 5.9 Hz, 1H), 5.71 (ddd, J = 4.5, 3.2, 1.2 Hz, 1H), 5.31 – 5.22 (m, 2H), 4.52 (dq, J = 5.9, 1.5 Hz, 2H), 3.87 – 3.72 (m, 4H), 3.26 (d, J = 13.7 Hz, 1H), 3.14 (d, J = 13.7 Hz, 1H), 2.96 (ddd, J = 11.9, 6.4, 3.0 Hz, 2H), 2.60 – 2.49 (m, 3H), 2.41 – 2.33 (m, 2H), 1.82 – 1.72 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 192.6, 170.5, 146.8, 136.4, 131.5, 130.7, 128.2, 128.2, 126.9, 123.9, 119.2, 66.9, 66.1, 58.7, 49.9, 39.8, 30.0, 22.7; IR (Neat Film, NaCl): 2956, 2854, 1734, 1691, 1615, 1447, 1377, 1263, 1207, 1176, 1118, 1085, 980, 937 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{26}NO_4$ $[M+H]^+$ 356.1856, found 356.1857.



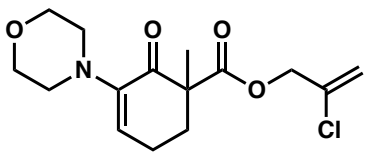
Allyl 1-(4-methoxybenzyl)-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65i)

Synthesized according to general procedure A using *p*-methoxybenzyl chloride. The product was purified by column chromatography (SiO_2, 3 x 15 cm, 5→10% acetone in hexanes) to yield enaminone **65i** (86 mg, 0.22 mmol, 21% yield over 2 steps) as a pale yellow oil; R_f = 0.72 (20% Et_2O in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 – 7.03 (m, 2H), 6.82 – 6.74 (m, 2H), 5.80 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.72 (t, *J* = 4.2 Hz, 1H), 5.28 (q, *J* = 1.5 Hz, 1H), 5.26 – 5.18 (m, 1H), 4.53 (dq, *J* = 5.9, 1.5 Hz, 2H), 3.87 – 3.70 (m, 6H), 3.21 – 3.08 (m, 2H), 2.96 (ddt, *J* = 11.6, 6.3, 2.5 Hz, 2H), 2.60 – 2.48 (m, 3H), 2.39 – 2.33 (m, 1H), 2.31 (td, *J* = 5.7, 2.2 Hz, 1H), 1.76 (ddd, *J* = 14.2, 10.4, 6.2 Hz, 1H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 192.7, 170.6, 158.6, 146.8, 131.7, 131.6, 128.3, 123.9, 119.2, 113.6, 66.9, 66.1, 58.8, 55.3, 50.0, 38.9, 30.0, 22.7; IR (Neat Film, NaCl): 2954, 2853, 1734, 1691, 1612, 1512, 1445, 1262, 1248, 1208, 1178, 1119, 1034, 981, 938 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{28}NO_5$ $[M+H]^+$ 386.1962, found 386.1948.



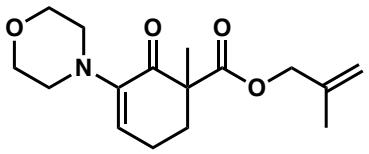
Allyl 3-morpholino-2-oxo-1-(4-(trifluoromethyl)benzyl)cyclohex-3-ene-1-carboxylate (65j)

Synthesized according to general procedure A using *p*-trifluoromethylbenzyl bromide. The product was purified by column chromatography (SiO_2, 3 x 25 cm, 2:1:1→2:2:1 hexanes:DCM:acetone) to yield enaminone **65j** (276 mg, 0.652 mmol, 60% yield over 2 steps) as a pale yellow oil; R_f = 0.78 (20% Et_2O in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 2H), 7.35 – 7.26 (m, 2H), 5.81 – 5.69 (m, 2H), 5.28 – 5.18 (m, 2H), 4.51 (dq, *J* = 5.9, 1.5 Hz, 2H), 3.80 (dddd, *J* = 30.5, 11.4, 6.4, 2.9 Hz, 4H), 3.32 – 3.16 (m, 2H), 2.97 (ddd, *J* = 11.8, 6.4, 3.0 Hz, 2H), 2.61 – 2.48 (m, 3H), 2.40 – 2.29 (m, 2H), 1.78 (ddd, *J* = 14.2, 10.4, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 170.3, 146.8, 140.7, 131.3, 131.2, 129.2 (q, *J* = 32.4 Hz), 125.3, 125.1 (q, *J* = 3.8 Hz), 123.8, 123.3, 119.5, 66.9, 66.3, 58.7, 49.9, 39.6, 30.4, 22.7; IR (Neat Film, NaCl): 2957, 2855, 1732, 1694, 1618, 1447, 1418, 1323, 1263, 1209, 1162, 1116, 1066, 1019, 981, 938 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{25}NO_4F$ $[M+H]^+$ 424.1730, found 424.1737.



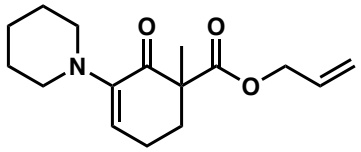
2-Chloroallyl 1-methyl-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65k)

Synthesized according to general procedure A using 2-chloroallyl cyanoformate (**83a**, see section 2.4.6). Product purified by flash chromatography (20→22% EtOAc/hexanes) to yield enaminone **65k** as a slightly yellow oil (470 mg, 1.50 mmol, 37% yield over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 – 5.79 (m, 1H), 5.46 – 5.43 (m, 1H), 5.41 – 5.39 (m, 1H), 4.75 – 4.68 (m, 1H), 4.67 – 4.59 (m, 1H), 3.87 – 3.73 (m, 4H), 3.04 – 2.95 (m, 2H), 2.65 – 2.58 (m, 2H), 2.58 – 2.35 (m, 3H), 1.94 – 1.84 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 171.9, 146.3, 135.4, 124.3, 115.8, 66.9, 66.7, 54.2, 49.9, 33.3, 22.6, 20.6; IR (Neat Film, NaCl) 2954, 2855, 1741, 1693, 1450, 1377 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{21}NClO_4$ $[M+H]^+$: 314.1154, found 314.1156.



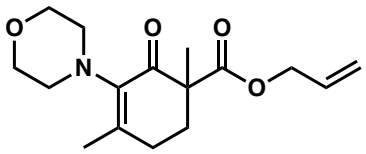
2-Methylallyl 1-methyl-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (65l)

Synthesized according to general procedure A using 2-methylallyl cyanoformate (**83b**, see section 2.4.6). Product purified by flash chromatography (20→24% EtOAc/hexanes) to yield enaminone **65l** as a slightly yellow oil (808 mg, 2.76 mmol, 56% yield over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 5.0, 3.5, 1.0 Hz, 1H), 4.94 – 4.92 (m, 1H), 4.92 – 4.90 (m, 1H), 4.55 – 4.47 (m, 2H), 3.86 – 3.74 (m, 4H), 3.04 – 2.96 (m, 2H), 2.62 – 2.50 (m, 3H), 2.50 – 2.44 (m, 1H), 2.43 – 2.35 (m, 1H), 1.87 (ddd, *J* = 13.5, 9.7, 5.6 Hz, 1H), 1.71 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 172.3, 146.3, 139.4, 123.9, 113.5, 68.4, 66.8, 54.1, 49.8, 33.3, 22.6, 20.6, 19.5; IR (Neat Film, NaCl) 2936, 2854, 1737, 1694, 1615, 1450, 1175, 1119, cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}NO_4$ $[M+H]^+$: 294.1700, found 294.1705.



Allyl 1-methyl-2-oxo-3-(piperidin-1-yl)cyclohex-3-ene-1-carboxylate (74)

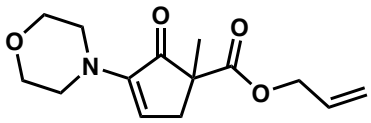
Synthesized according to general procedure A using 2-(piperidin-1-yl)cyclohex-2-en-1-one. The product was purified by column chromatography (SiO_2, 3 x 15 cm, 8→12→16% Et_2O in hexanes) to yield enaminone **74** (427 mg, 1.54 mmol, 59% yield over 2 steps) as a pale tan oil; R_f = 0.32 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 – 5.74 (m, 1H), 5.74 – 5.66 (m, 1H), 5.21 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.19 – 5.10 (m, 1H), 4.59 – 4.45 (m, 2H), 2.81 (ddd, *J* = 11.2, 7.2, 3.6 Hz, 2H), 2.45 (tdd, *J* = 9.3, 7.5, 4.3 Hz, 3H), 2.37 (dddd, *J* = 13.5, 5.0, 3.2, 1.1 Hz, 1H), 2.29 (dtd, *J* = 19.0, 5.4, 3.2 Hz, 1H), 1.77 (ddd, *J* = 13.4, 9.6, 5.6 Hz, 1H), 1.67 – 1.50 (m, 4H), 1.44 (p, *J* = 6.0 Hz, 2H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 172.3, 147.5, 131.6, 123.3, 118.5, 65.7, 54.0, 50.8, 33.2, 25.9, 24.3, 22.6, 20.5; IR (Neat Film, NaCl): 2934, 2851, 2802, 1735, 1696, 1613, 1452, 1387, 1248, 1222, 1175, 1110, 987, 943 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{24}NO_3$ $[M+H]^+$ 278.1751, found 278.1747.



Allyl 1,4-dimethyl-3-morpholino-2-oxocyclohex-3-ene-1-carboxylate (76)

Synthesized according to general procedure A using 3-methyl-2-morpholinocyclohex-2-en-1-one. The product was purified by column chromatography (SiO_2, 3 x 13 cm, 5→10→20% EtOAc in hexanes) to yield enaminone **76** (772 mg, 2.63 mmol, 74% yield

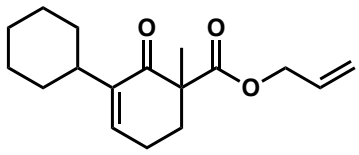
over 2 steps) as a pale yellow oil; R_f = 0.34 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.55 (qdt, *J* = 13.3, 5.6, 1.5 Hz, 2H), 3.72 – 3.61 (m, 4H), 2.94 (dt, *J* = 9.8, 4.4 Hz, 2H), 2.85 (dt, *J* = 11.4, 4.3 Hz, 2H), 2.49 (dddd, *J* = 19.2, 9.8, 5.3, 1.1 Hz, 1H), 2.38 (ddd, *J* = 13.6, 5.3, 3.6 Hz, 1H), 2.33 – 2.23 (m, 1H), 1.95 (d, *J* = 0.9 Hz, 3H), 1.79 (ddd, *J* = 13.6, 9.7, 5.5 Hz, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 172.5, 153.2, 142.1, 131.8, 118.4, 67.9, 65.7, 53.9, 50.3, 32.3, 29.2, 20.5, 19.6; IR (Neat Film, NaCl): 2935, 2848, 1734, 1680, 1452, 1375, 1259, 1190, 1168, 1114, 1070, 989 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{24}NO_4$ $[M+H]^+$ 294.1700, found 294.1701.



Allyl 1-methyl-3-morpholino-2-oxocyclopent-3-ene-1-carboxylate (78)

Synthesized according to general procedure A using 2-morpholinocyclopent-2-en-1-one. The product was purified by column chromatography (SiO_2, 3.5 x 12 cm, 2→4→6→8→10% EtOAc in DCM) to yield enaminone **78** (151 mg, 0.570 mmol, 21% yield over 2 steps) as a pale orange oil; R_f = 0.33 (10% EtOAc in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (t, *J* = 3.2 Hz, 1H), 5.92 – 5.78 (m, 1H), 5.32 – 5.22 (m, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.64 – 4.54 (m, 2H), 3.84 – 3.68 (m, 4H), 3.24 – 3.11 (m, 2H), 3.07 – 2.96 (m, 3H), 2.38 (dd, *J* = 18.2, 3.2 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 171.6, 148.6, 131.9, 131.8, 118.3, 66.6, 65.9, 54.1, 48.5, 37.8, 21.1; IR (Neat Film, NaCl): 2962, 2933, 2855, 1740, 1707, 1612, 1452, 1379, 1263, 1178, 1120,

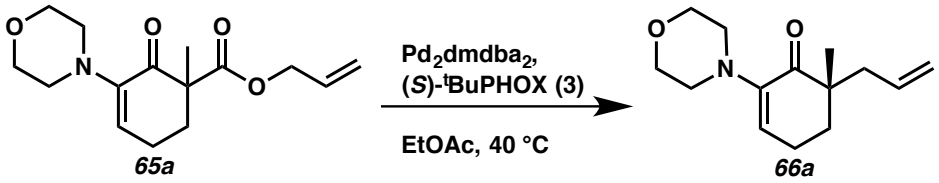
1068, 1022, 994 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{20}NO_4$ $[M+H]^+$ 266.1387, found 266.1391.



Allyl 3-methyl-2-oxo-[1,1'-bi(cyclohexan)]-6-ene-3-carboxylate (80)

Synthesized according to general procedure A using [1,1'-bi(cyclohexan)]-6-en-2-one.[13] The product was purified by column chromatography (SiO_2, 1.5 x 12 cm, 10% Et_2O in DCM) to yield enone **80** (51 mg, 0.185 mmol, 30% yield over 2 steps) as a pale yellow oil; R_f = 0.33 (10% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.54 – 6.48 (m, 1H), 5.85 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.64 – 4.52 (m, 2H), 2.59 – 2.50 (m, 1H), 2.50 – 2.40 (m, 2H), 2.38 – 2.26 (m, 1H), 1.92 – 1.81 (m, 1H), 1.80 – 1.60 (m, 5H), 1.55 (s, 1H), 1.40 – 1.22 (m, 5H), 1.21 – 1.04 (m, 2H), 1.04 – 0.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 172.8, 144.2, 140.9, 131.9, 118.5, 65.8, 53.6, 36.8, 33.4, 32.8, 32.3, 26.9, 26.8, 26.5, 23.6, 20.6; IR (Neat Film, NaCl): 2925, 2851, 1734, 1684, 1379, 1351, 1299, 1247, 1167, 1110, 981, 935 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$ 277.1798, found 277.1791.

2.4.3 Asymmetric Decarboxylative Allylic Alkylation of Enaminone Substrates

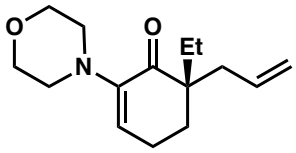


65a *66a*

(*S*)-6-allyl-6-methyl-2-morpholinocyclohex-2-en-1-one (66a)

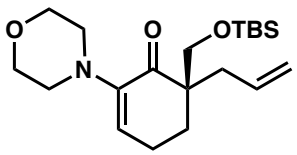
General procedure B: In a glove box under an atmostphere of N_2, Pd_2dmdba_3 (29.7 mg, 23.3 μmol, 5 mol %) and (*S*)-*t*-Bu PHOX (**3**, 22.5 mg, 58.2 μmol, 12.5 mol %) were taken up in 12 mL EtOAc. The catalystic was allowed to preform at 40 °C for 30 minutes, as indicated by the reaction mixture turning orange. At this point, enaminone substrate **65a** (130 mg, 0.465 mmol, 1.00 equiv) in 2 mL EtOAc (total concentration = 0.033 M) was added, causing the reaction mixture to turn green. The reaction mixture was sealed, removed from the glove box and stirred at 40 °C for 9 hours, until the reaction was complete as indicated by the mixture returning to an orange color (and confirmed by TLC analysis). The reaction mixture was filtered through a short plug of silica and rinsed with 25 mL EtOAC, concentrated in vacuo, and purified by column chromatography (SiO_2, 3 x 12 cm, 5→10% acetone in hexanes) to yield enaminone **66a** (104 mg, 0.442 mmol, 95% yield) as a colorless oil; R_f = 0.22 (20% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 5.88 (t, *J* = 4.5 Hz, 1H), 5.80 – 5.67 (m, 1H), 5.09 – 5.00 (m, 2H), 3.80 (ddd, *J* = 5.8, 3.5, 2.2 Hz, 4H), 2.82 (dt, *J* = 9.8, 4.5 Hz, 2H), 2.74 – 2.66 (m, 2H), 2.51 – 2.37 (m, 2H), 2.37 – 2.30 (m, 1H), 2.22 (ddq, *J* = 13.7, 7.6, 1.0 Hz, 1H), 1.88 (dt, *J* = 13.7, 6.0 Hz, 1H), 1.73 (ddd, *J* = 13.9, 6.9, 5.7 Hz, 1H), 1.09 (d,

J = 0.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 145.7, 134.2, 125.1, 118.2, 67.0, 50.6, 45.6, 41.4, 33.3, 22.0, 22.0; IR (Neat Film, NaCl): 2960, 2918, 2853, 2813, 1679, 1615, 1447, 1376, 1262, 1208, 1120, 1099, 1001, 990, 915 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1645, found 236.1641; $[\alpha]^{25}$ –315.66 (*c* 13.57, $CHCl_3$, 99% *ee*).



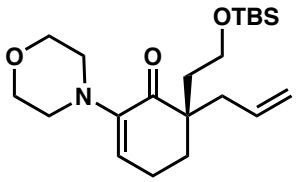
(*S*)-6-allyl-6-ethyl-2-morpholinocyclohex-2-en-1-one (66b)

Synthesized according to general procedure B using substrate **65b**. The product was purified by column chromatography (SiO_2, 3 x 12 cm, 5→10% acetone in hexanes) to yield enaminone **66b** (116 mg, 0.465 mmol, quantitative yield) as a colorless oil; R_f = 0.25 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (t, *J* = 4.4 Hz, 1H), 5.76 – 5.64 (m, 1H), 5.06 – 4.97 (m, 2H), 3.78 (ddd, *J* = 5.2, 3.8, 1.0 Hz, 4H), 2.81 – 2.75 (m, 2H), 2.75 – 2.66 (m, 2H), 2.40 (tdd, *J* = 5.9, 4.5, 1.4 Hz, 2H), 2.34 (ddt, *J* = 14.0, 6.9, 1.3 Hz, 1H), 2.23 (ddt, *J* = 14.0, 7.9, 1.1 Hz, 1H), 1.81 (t, *J* = 6.2 Hz, 2H), 1.59 (qd, *J* = 7.5, 1.3 Hz, 2H), 0.80 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 145.9, 134.4, 124.7, 117.9, 67.0, 50.6, 48.6, 38.8, 30.4, 27.0, 21.8, 8.4; IR (Neat Film, NaCl): 2962, 2933, 2854, 2814, 1678, 1616, 1447, 1377, 1263, 1208, 1120, 1070, 1099, 998 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{24}NO_2$ $[M+H]^+$ 250.1802, found 250.1813; $[\alpha]^{25}$ 5.52 (*c* 7.45, $CHCl_3$, 98% *ee*).



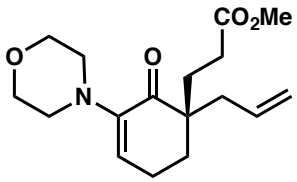
(*S*)-6-allyl-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-morpholinocyclohex-2-en-1-one (66c)

Synthesized according to general procedure B using substrate **65c**. The product was purified by column chromatography (SiO_2, 3 x 12 cm, 20% acetone in hexanes) to yield enaminone **66c** (164 mg, 0.445 mmol, 96% yield) as a pale tan oil; R_f = 0.33 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (t, *J* = 4.5 Hz, 1H), 5.76 – 5.64 (m, 1H), 5.06 – 4.98 (m, 2H), 3.79 (t, *J* = 4.6 Hz, 4H), 3.68 (d, *J* = 9.7 Hz, 1H), 3.62 (d, *J* = 9.7 Hz, 1H), 2.74 (t, *J* = 4.6 Hz, 4H), 2.47 – 2.35 (m, 3H), 2.26 (ddt, *J* = 13.7, 7.8, 1.1 Hz, 1H), 1.96 (ddd, *J* = 13.3, 7.1, 6.0 Hz, 1H), 1.89 (dt, *J* = 13.7, 5.9 Hz, 1H), 0.85 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 146.4, 134.1, 125.1, 118.0, 67.0, 66.1, 51.0, 50.5, 37.2, 28.5, 26.0, 21.7, 18.3, -5.4, -5.5; IR (Neat Film, NaCl): 2953, 2855, 1677, 1639, 1615, 1472, 1463, 1447, 1378, 1299, 1262, 1208, 1121, 973, 917 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{36}NO_3Si$ $[M+H]^+$ 366.2459, found 366.2466; $[\alpha]^{25}$ –111.67 (*c* 10.25, $CHCl_3$, 99% *ee*).



(*S*)-6-allyl-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-morpholinocyclohex-2-en-1-one (66d)

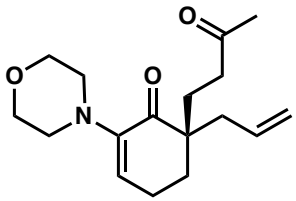
Synthesized according to general procedure B using substrate **65d**. The product was purified by column chromatography (SiO_2, 3 x 12 cm, 20% acetone in hexanes) to yield enaminone **66d** (165 mg, 0.432 mmol, 93% yield) as a colorless oil; R_f = 0.31 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, CDCl3) δ 5.87 (d, *J* = 4.5 Hz, 1H), 5.74 (dddd, *J* = 16.5, 10.5, 7.8, 6.9 Hz, 1H), 5.09 – 5.00 (m, 2H), 3.80 (t, *J* = 4.7 Hz, 4H), 3.70 (ddd, *J* = 10.2, 8.4, 6.1 Hz, 1H), 3.57 (ddd, *J* = 10.3, 8.6, 5.9 Hz, 1H), 2.76 (q, *J* = 3.5 Hz, 4H), 2.52 – 2.41 (m, 2H), 2.38 (ddt, *J* = 14.0, 6.8, 1.3 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.8, 1.1 Hz, 1H), 1.94 – 1.81 (m, 3H), 1.75 (ddd, *J* = 14.0, 8.4, 5.9 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 145.8, 134.2, 125.0, 118.3, 67.0, 59.5, 50.6, 47.8, 39.5, 37.0, 31.3, 26.1, 21.9, 18.4, -5.1, -5.2; IR (Neat Film, NaCl): 2953, 2928, 2855, 2817, 1679, 1616, 1448, 1262, 1207, 1121, 1098, 1030, 977, 914 cm^{-1}; HRMS (APCI) *m/z* calc'd for $C_{21}H_{38}NO_3Si$ $[M+H]^+$ 380.2615, found 380.2618; $[\alpha]^{25}$ – 9.38 (*c* 3.48, $CHCl_3$, 99% *ee*).



Methyl (*R*)-3-(1-allyl-3-morpholino-2-oxocyclohex-3-en-1-yl)propanoate (66e)

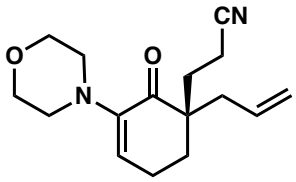
Synthesized according to general procedure B using substrate **65e**. The product was purified by column chromatography (SiO_2, 3 x 15 cm, 5→10→15→20→30→50% EtOAc in hexanes) to yield enaminone **66e** (140 mg, 0.456 mmol, 98% yield) as a colorless oil; R_f = 0.31 (20% EtOAc in hexanes); R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.70 (dddd, *J* = 16.6, 10.4, 7.7, 7.0 Hz, 1H), 5.11

– 5.02 (m, 2H), 3.83 – 3.77 (m, 3H), 3.65 (s, 3H), 2.81 – 2.73 (m, 3H), 2.45 (td, *J* = 6.1, 4.4 Hz, 2H), 2.39 – 2.29 (m, 2H), 2.29 – 2.23 (m, 1H), 2.23 – 2.15 (m, 1H), 1.95 (ddd, *J* = 14.1, 11.2, 5.4 Hz, 1H), 1.90 – 1.77 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 174.1, 145.8, 133.5, 125.1, 118.7, 77.4, 77.2, 76.9, 66.9, 51.8, 50.5, 50.4, 47.9, 39.1, 30.7, 29.4, 29.0, 21.7; IR (Neat Film, NaCl): 2950, 2853, 1735, 1676, 1617, 1437, 1375, 1263, 1207, 1174, 1119 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{26}NO_4$ $[M+H]^+$ 308.1856, found 308.1859; $[\alpha]^{25}$ 34.36 (*c* 16.49, $CHCl_3$, 97% *ee*).



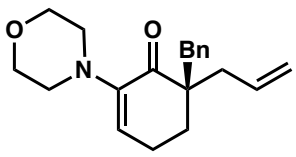
(*R*)-6-allyl-2-morpholino-6-(3-oxobutyl)cyclohex-2-en-1-one (66f)

Synthesized according to general procedure B using substrate **65f**. The product was purified by column chromatography (SiO_2, 3 x 12 cm, 20→35→50%) to yield enaminone **66f** (122 mg, 0.419 mmol, 90% yield) as a colorless oil; R_f = 0.35 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (t, *J* = 4.5 Hz, 1H), 5.69 (ddt, *J* = 16.7, 10.4, 7.3 Hz, 1H), 5.10 – 5.01 (m, 2H), 3.79 (t, *J* = 4.7 Hz, 4H), 2.78 (dt, *J* = 11.7, 4.7 Hz, 2H), 2.70 (dt, *J* = 11.5, 4.7 Hz, 2H), 2.54 – 2.44 (m, 2H), 2.44 – 2.39 (m, 1H), 2.38 – 2.27 (m, 2H), 2.25 (ddt, *J* = 14.0, 7.6, 1.2 Hz, 1H), 2.12 (s, 3H), 1.92 – 1.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 199.6, 145.9, 133.6, 118.7, 67.0, 50.7, 47.9, 39.3, 38.4, 31.0, 30.2, 30.2, 28.0, 21.8; IR (Neat Film, NaCl): 2921, 2853, 2814, 1716, 1674, 1615, 1446, 1369, 1262, 1206, 1167, 1119, 978, 922 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{26}NO_3$ $[M+H]^+$ 292.1907, found 292.1914; $[\alpha]^{25}$ 15.98 (*c* 10.28, $CHCl_3$, 94% *ee*).



(*R*)-3-(1-allyl-3-morpholino-2-oxocyclohex-3-en-1-yl)propanenitrile (66g)

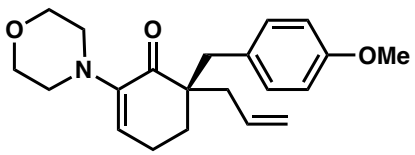
Synthesized according to general procedure B using substrate **65g**. The product was purified by column chromatography (SiO_2, 3 x 15 cm, 5→10→15→20→30→50% EtOAc in hexanes) to yield enaminone **66g** (217 mg, 0.465 mmol, quantitative yield) as a colorless oil; R_f = 0.30 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.66 (ddt, *J* = 16.9, 10.1, 7.4 Hz, 1H), 5.19 – 5.06 (m, 2H), 3.86 – 3.75 (m, 4H), 2.85 (dt, *J* = 9.7, 4.4 Hz, 2H), 2.68 (d, *J* = 12.3 Hz, 2H), 2.58 – 2.47 (m, 2H), 2.47 – 2.34 (m, 2H), 2.34 – 2.24 (m, 3H), 2.10 (ddd, *J* = 14.0, 10.1, 5.9 Hz, 1H), 1.96 – 1.83 (m, 2H), 1.80 (ddd, *J* = 14.1, 10.2, 5.8 Hz, 1H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 198.5, 145.7, 132.4, 125.4, 120.1, 119.5, 77.4, 77.2, 76.9, 66.9, 50.5, 48.0, 48.0, 38.8, 30.5, 30.3, 21.6, 12.3; IR (Neat Film, NaCl): 2929, 2854, 1675, 1448, 1263, 1205, 1118, 1000, 924 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{23}N_2O_2$ $[M+H]^+$ 275.1754, found 275.1753; $[\alpha]^{25}$ 29.26 (*c* 11.02, $CHCl_3$, 94% *ee*).



(*S*)-6-allyl-6-benzyl-2-morpholinocyclohex-2-en-1-one (66h)

Synthesized according to general procedure B using substrate **65h**. The product was purified by column chromatography (SiO_2, 3 x 15 cm, 5→10→20% acetone in hexanes)

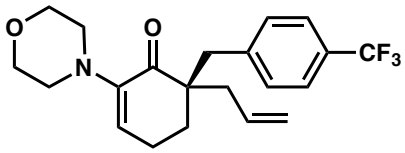
to yield enaminone **66h** (217 mg, 0.442 mmol, 95% yield) as a colorless oil; R_f = 0.20 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 2H), 7.22 – 7.17 (m, 1H), 7.17 – 7.08 (m, 2H), 5.88 (t, *J* = 4.5 Hz, 1H), 5.77 (dddd, *J* = 16.9, 10.2, 8.0, 6.6 Hz, 1H), 5.12 – 5.00 (m, 2H), 3.80 (dd, *J* = 5.2, 4.2 Hz, 4H), 3.07 (d, *J* = 13.5 Hz, 1H), 2.81 – 2.69 (m, 5H), 2.50 – 2.37 (m, 3H), 2.15 (ddt, *J* = 14.0, 8.1, 1.2 Hz, 1H), 1.80 (dt, *J* = 13.9, 5.8 Hz, 1H), 1.76 – 1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 146.3, 137.6, 134.1, 130.9, 128.1, 126.5, 125.2, 118.6, 67.0, 50.6, 49.9, 40.7, 39.8, 29.8, 21.9; IR (Neat Film, NaCl): 2919, 2854, 2814, 1675, 1614, 1447, 1263, 1205, 1119, 981, 923 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{26}NO_2$ $[M+H]^+$ 312.1958, found 312.1967; $[\alpha]^{25}$ –95.78 (*c* 4.69, $CHCl_3$, 96% *ee*).



(*S*)-6-allyl-6-(4-methoxybenzyl)-2-morpholinocyclohex-2-en-1-one (66i)

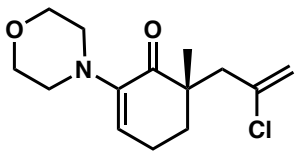
Synthesized according to general procedure B using substrate **65i**. The product was purified by column chromatography (SiO_2, 3 x 15 cm, 5→10→20% acetone in hexanes) to yield enaminone **66i** (159 mg, 0.465 mmol, quantitative yield) as a colorless oil; R_f = 0.17 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 – 6.98 (m, 2H), 6.83 – 6.73 (m, 2H), 5.87 (t, *J* = 4.5 Hz, 1H), 5.76 (dddd, *J* = 16.8, 10.2, 8.0, 6.6 Hz, 1H), 5.10 – 4.99 (m, 2H), 3.80 (t, *J* = 4.7 Hz, 3H), 3.68 (s, 3H), 3.01 (d, *J* = 13.8 Hz, 1H), 2.81 – 2.70 (m, 4H), 2.66 (d, *J* = 13.7 Hz, 1H), 2.47 – 2.38 (m, 3H), 2.13 (ddt, *J* = 13.9, 7.9, 1.1 Hz, 1H), 1.80 (dt, *J* = 13.9, 5.9 Hz, 1H), 1.71 (dt, *J* = 13.9, 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 158.3, 146.3, 134.1, 131.8, 129.5, 125.3, 118.5, 113.5, 67.0, 55.3, 55.2,

50.6, 50.0, 39.9, 39.8, 29.7, 21.9; IR (Neat Film, NaCl): 2930, 2853, 1675, 1611, 1512, 1447, 1263, 1248, 1205, 1178, 1119, 1035, 981, 923 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{28}NO_3$ $[M+H]^+$ 342.2064, found 342.2064; $[\alpha]^{25}$ –316.96 (*c* 12.93, $CHCl_3$, 95% *ee*).



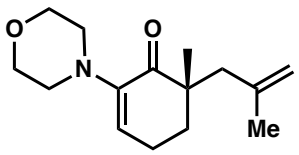
(*S*)-6-allyl-2-morpholino-6-(4-(trifluoromethyl)benzyl)cyclohex-2-en-1-one (66j)

Synthesized according to general procedure B using substrate **65j**. The product was purified by column chromatography (SiO_2, 3 x 15 cm, 5→10→20% acetone in hexanes) to yield enaminone **66j** (154 mg, 0.406 mmol, 87% yield) as a pale yellow oil; R_f = 0.20 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 5.88 (t, *J* = 4.5 Hz, 1H), 5.77 (dddd, *J* = 17.0, 10.2, 7.8, 6.8 Hz, 1H), 5.16 – 5.04 (m, 2H), 3.86 – 3.75 (m, 4H), 3.20 (d, *J* = 13.5 Hz, 1H), 2.83 – 2.75 (m, 2H), 2.75 – 2.66 (m, 3H), 2.54 – 2.43 (m, 1H), 2.43 – 2.33 (m, 2H), 2.22 (ddt, *J* = 14.0, 7.8, 1.2 Hz, 1H), 1.79 (dt, *J* = 13.8, 5.3 Hz, 1H), 1.70 (ddd, *J* = 13.9, 8.5, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 146.2, 142.1, 133.5, 131.2, 128.7 (q, *J* = 32.3 Hz), 127.7, 125.5, 125.3, 124.9 (q, *J* = 3.8 Hz), 123.3, 119.1, 66.9, 50.6, 50.0, 40.4, 39.8, 29.9, 21.8; IR (Neat Film, NaCl): 2928, 2855, 2817, 1678, 1616, 1448, 1325, 1263, 1163, 1119, 1067, 1019, 982, 923 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{25}NO_2F$ $[M+H]^+$ 380.1832, found 380.1835; $[\alpha]^{25}$ –22.43 (*c* 8.54, $CHCl_3$, 92% *ee*).



(*S*)-6-(2-chloroallyl)-6-methyl-2-morpholinocyclohex-2-en-1-one (66k)

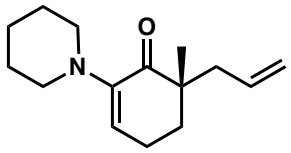
Synthesized according to general procedure B using substrate **65k**. The product was purified by column chromatography (20% EtOAc in hexanes) to afford enaminone **66k** as a colorless oil (25 mg, 93 μmol, 58% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (t, *J* = 4.5 Hz, 1H), 5.28 (dd, *J* = 1.1, 0.4 Hz, 1H), 5.16 – 5.15 (m, 1H), 3.86 – 3.76 (m, 4H), 2.94 – 2.88 (m, 2H), 2.85 (dd, *J* = 14.3, 0.9 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.53 (d, *J* = 14.3 Hz, 1H), 2.49 – 2.44 (m, 2H), 2.04 (ddd, *J* = 13.6, 7.4, 6.2 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 145.6, 138.9, 125.1, 116.7, 67.0, 50.5, 46.1, 45.6, 32.8, 22.5, 21.8; IR (Neat Film, NaCl) 2931, 2855, 1679, 1263, 1120cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_{21}NClO_2$ $[M+H]^+$: 270.1261, found 270.1259; $[\alpha]^{25}$ – 7.5 (*c* 0.8, $CHCl_3$, 99% *ee*).



(*S*)-6-methyl-6-(2-methylallyl)-2-morpholinocyclohex-2-en-1-one (66l)

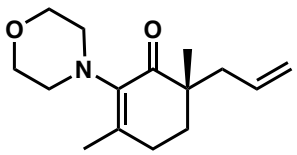
Synthesized according to general procedure B using substrate **65l**. The product was purified by column chromatography (20% EtOAc in hexanes) to afford enaminone **66l** as a colorless oil (25 mg, 100 μmol 92% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (t, *J* = 4.5 Hz, 1H), 5.28 (dd, *J* = 1.1, 0.4 Hz, 1H), 5.16 – 5.15 (m, 1H), 3.86 – 3.76 (m, 4H), 2.94 – 2.88 (m, 2H), 2.85 (dd, *J* = 14.3, 0.9 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.53 (d, *J* =

14.3 Hz, 1H), 2.49 – 2.44 (m, 2H), 2.04 (ddd, *J* = 13.6, 7.4, 6.2 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 145.6, 138.9, 125.1, 116.7, 67.0, 50.5, 46.1, 45.6, 32.8, 22.5, 21.8; IR (Neat Film, NaCl) 2931, 2855, 1679, 1263, 1120cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_{21}NClO_2$ $[M+H]^+$: 270.1261, found 270.1259; $[\alpha]^{25}$ – 7.5 (*c* 0.8, $CHCl_3$, 99% *ee*).



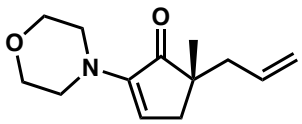
(*S*)-6-allyl-6-methyl-2-(piperidin-1-yl)cyclohex-2-en-1-one (75)

Synthesized according to general procedure B using substrate **74**. The product was purified by column chromatography (SiO_2, 3 x 15 cm, 10→20% acetone in hexanes) to yield enaminone **75** (107 mg, 0.459 mmol, 99% yield) as a colorless oil; R_f = 0.37 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (t, *J* = 4.5 Hz, 1H), 5.73 (ddt, *J* = 15.1, 10.1, 7.5 Hz, 1H), 5.06 – 4.98 (m, 2H), 2.70 (dt, *J* = 10.9, 5.2 Hz, 2H), 2.60 (dt, *J* = 11.2, 5.1 Hz, 2H), 2.47 – 2.29 (m, 3H), 2.21 (dd, *J* = 13.8, 7.7 Hz, 1H), 1.84 (dt, *J* = 12.7, 6.0 Hz, 1H), 1.67 (qq, *J* = 14.2, 8.2, 7.3 Hz, 5H), 1.49 (p, *J* = 6.0 Hz, 2H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 147.0, 134.4, 124.6, 118.0, 51.6, 45.5, 41.4, 33.4, 26.1, 24.5, 22.1, 22.0; IR (Neat Film, NaCl): 2931, 2852, 2798, 1680, 1613, 1451, 1384, 1217, 1093, 996, 913 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{24}NO$ $[M+H]^+$ 234.1852, found 234.1847; $[\alpha]^{25}$ –172.28 (*c* 6.64, $CHCl_3$, 99% *ee*).



(*S*)-6-allyl-3,6-dimethyl-2-morpholinocyclohex-2-en-1-one (77)

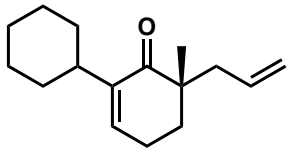
Synthesized according to general procedure B using substrate **76**. The product was purified by column chromatography (SiO_2, 3 x 12 cm, 10→20% Et_2O in hexanes) to yield enaminone **77** (60.2 mg, 0.241 mmol, 52% yield) as a pale yellow oil; R_f = 0.35 (29% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 16.8, 10.2, 7.4 Hz, 1H), 5.08 – 4.99 (m, 2H), 3.71 – 3.63 (m, 4H), 2.97 – 2.85 (m, 4H), 2.45 – 2.30 (m, 2H), 2.27 (ddt, *J* = 13.6, 7.2, 1.2 Hz, 1H), 2.18 (ddt, *J* = 13.6, 7.5, 1.2 Hz, 1H), 1.99 (d, *J* = 0.9 Hz, 3H), 1.82 (ddd, *J* = 13.7, 6.4, 5.6 Hz, 1H), 1.67 (ddd, *J* = 13.7, 7.2, 5.6 Hz, 1H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 153.4, 141.6, 134.3, 118.0, 77.4, 77.2, 76.9, 68.1, 50.6, 44.9, 41.3, 32.5, 28.7, 21.8, 19.8; IR (Neat Film, NaCl): 2912, 2847, 1664, 1452, 1374, 1294, 1259, 1190, 1114, 988, 911 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{24}NO_2$ $[M+H]^+$ 250.1802, found 250.1803; $[\alpha]^{25}$ 30.71 (*c* 3.52, $CHCl_3$, 90% *ee*).



(*R*)-5-allyl-5-methyl-2-morpholinocyclopent-2-en-1-one (79)

Synthesized according to general procedure B using substrate **78**. The product was purified by column chromatography (SiO_2, 3 x 10 cm, 10% acetone in hexanes) to yield enaminone **79** (97 mg, 0.438 mmol, 94% yield) as a pale tan oil; R_f = 0.23 (20% acetone in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (t, *J* = 3.1 Hz, 1H), 5.68 – 5.55 (m, 1H),

5.07 – 4.97 (m, 2H), 3.80 – 3.74 (m, 4H), 3.12 – 2.96 (m, 4H), 2.49 (dt, *J* = 18.2, 2.1 Hz, 1H), 2.27 – 2.16 (m, 2H), 2.12 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.09 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 149.3, 133.9, 131.6, 118.2, 66.7, 48.6, 46.8, 42.7, 37.2, 24.0; IR (Neat Film, NaCl): 2960, 2913, 2853, 1703, 1611, 1451, 1380, 1261, 1120, 1020, 993 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1489, found 222.1490; $[\alpha]^{25}$ –263.53 (*c* 6.76, $CHCl_3$, 83% *ee*).

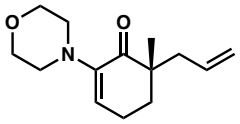
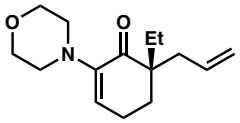
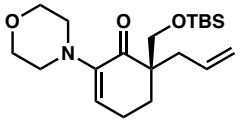
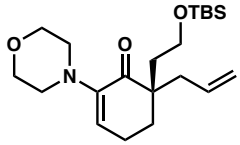
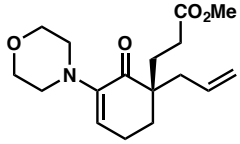
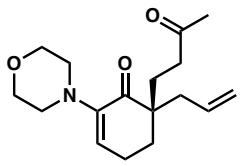


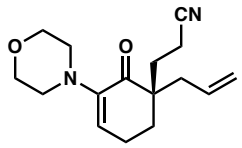
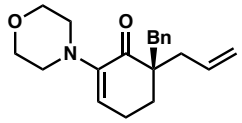
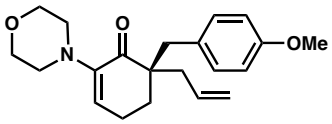
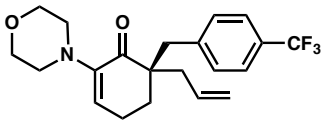
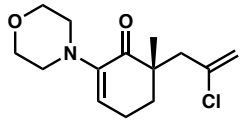
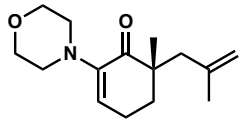
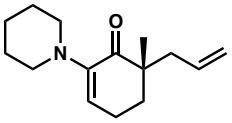
(*S*)-3-allyl-3-methyl-[1,1'-bi(cyclohexan)]-6-en-2-one (81)

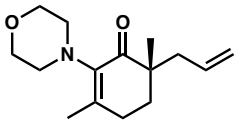
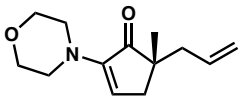
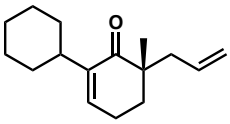
Synthesized according to general procedure B using substrate **80**. The product was purified by column chromatography (SiO_2, 1 x 12 cm, 5% Et_2O in hexanes) to yield enaminone **81** (11 mg, 47 μmol, 93% yield) as a pale yellow oil; R_f = 0.43 (5% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (td, *J* = 4.1, 1.0 Hz, 1H), 5.73 (ddt, *J* = 16.9, 10.4, 7.4 Hz, 1H), 5.08 – 4.99 (m, 2H), 2.52 (ttd, *J* = 12.0, 3.2, 1.4 Hz, 1H), 2.43 – 2.33 (m, 2H), 2.33 – 2.25 (m, 1H), 2.17 (ddt, *J* = 13.7, 7.5, 1.2 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.78 – 1.60 (m, 6H), 1.34 (qt, *J* = 12.2, 3.1 Hz, 2H), 1.21 – 0.95 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 143.4, 140.5, 134.5, 117.9, 44.4, 41.4, 36.4, 33.3, 33.1, 32.7, 26.9, 26.9, 26.6, 23.0, 22.0; IR (Neat Film, NaCl): 2922, 2849, 1669, 1448, 1175, 911 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{25}O$ $[M+H]^+$ 233.1900, found 233.1892; $[\alpha]^{25}$ –1.176 (*c* 0.43, $CHCl_3$, 72% *ee*).

2.4.4 Determination of Enantiomeric Excess

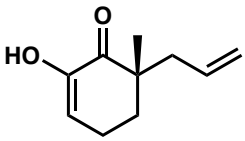
Table 2.6. Methods for the determination of enantiomeric excess.

entry	compound	assay method and conditions	retention time of minor isomer (min)	retention time of major isomer (min)	%ee
1	 ***66a***	SFC, 5% *i*PrOH in CO_2 2.5 mL/min, AD-H col.	5.91	5.62	*99*
2	 ***66b***	HPLC, 5% *i*PrOH in hexanes 1 mL/min, OD-H col.	8.77	9.14	*98*
3	 ***66c***	SFC, 3% *i*PrOH in CO_2 2.5 mL/min, AD-H col.	4.45	3.95	*99*
4	 ***66d***	SFC, 2% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	3.59	4.10	*99*
5	 ***66e***	SFC, 10% MeOH in CO_2 5 mL/min, AD-H col.	3.43	1.75	*97*
6	 ***66f***	SFC, 10% *i*PrOH in CO_2 5 mL/min, AD-H col.	2.27	1.81	*94*

entry	compound	assay method and conditions	retention time of minor isomer (min)	retention time of major isomer (min)	%ee
7	 ***66g***	SFC, 10% *i*PrOH in CO_2 5 mL/min, AD-H col.	2.19	2.40	***94***
8	 ***66h***	SFC, 8% MeOH in CO_2 5 mL/min, OJ-H col.	2.41	2.63	***96***
9	 ***66i***	SFC, 5% MeOH in CO_2 5 mL/min, OD-H col.	6.29	6.99	***95***
10	 ***66j***	SFC, 5% *i*PrOH in CO_2 5 mL/min, OJ-H col.	3.88	4.52	***92***
11	 ***66k***	SFC, 5% *i*PrOH in hexanes 2.5 mL/min, OD-H col.	8.6	7.8	***99***
12	 ***66l***	SFC, 5% *i*PrOH in hexanes 2.5 mL/min, AD-H col.	10.2	9.4	***99***
13	 ***75***	HPLC, 3% EtOH in hexanes 1 mL/min, AD col.	9.01	9.84	***99***

entry	compound	assay method and conditions	retention time of minor isomer (min)	retention time of major isomer (min)	%ee
14	 ***77***	HPLC, 1.5% *i*PrOH in hexanes 1 mL/min, OD-H col.	8.99	8.40	*90*
15	 ***77***	HPLC, 3% *i*PrOH in hexanes 1 mL/min, OD-H col.	14.22	17.7	*83*
16	 ***81***	SFC, 10% *i*PrOH in CO_2 2.5 mL/min, AD col.	3.08	3.52	*72*

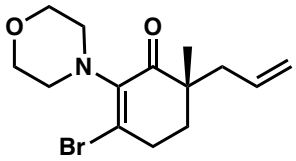
2.4.5 Derivatization of Enaminone Products



(*S*)-6-allyl-2-hydroxy-6-methylcyclohex-2-en-1-one (67)

Enaminone **66a** (297 mg, 1.26 mmol) was diluted in MeOH:water (4:1). HCl (0.1 mL, 37%) was added by syringe. The reaction mixture was stirred at 60°C under nitrogen for 2h. The mixture was cooled to room temperature and partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 two additional times. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (1→2% EtOAc/hexanes) to give diketone **21** (166 mg, 1.00 mmol, 79% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 – 5.97 (m, 1H), 5.80 – 5.58 (m, 1H), 5.15 – 4.94 (m, 2H), 2.45 – 2.29 (m, 2H), 2.18 (ddt, *J* = 13.8, 7.6, 1.1 Hz, 1H), 1.91 – 1.83 (m, 1H), 1.72 (ddd, *J* = 13.7, 6.5,

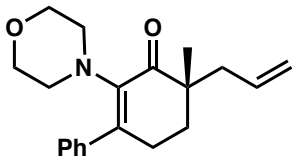
5.5 Hz, 1H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 145.4, 133.4, 118.6, 116.8, 43.9, 40.9, 33.5, 21.7, 20.2; IR (Neat Film, NaCl): 3428, 3076, 2975, 2935, 1721, 1640, 1455, 1217 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{13}O_2$ $[M+H-H_2]^+$ 165.0916, found 165.0916; $[\alpha]^{25}$ –5.95 (*c* 4.45, $CHCl_3$).



(6*S*) 3-bromo-6-methyl-2-(morpholin-4-yl)-6-(prop-2-en-1-yl)cyclohex-2-en-1-one (68)

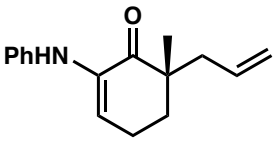
Enaminone **66a** (120 mg, 0.51 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4.5 mL, 0.1 M). The reaction mixture was cooled to –78 °C. NBS (91 mg, 0.51 mmol, 1.0 equiv), dissolved in CH_2Cl_2 (4.5 mL), was added drop-wise to the solution by syringe. The reaction mixture was stirred at –78 °C for 25 min. The solution was quenched with a solution of 10% K_2CO_3 (3 mL). The mixture was warmed to room temperature and extracted with 3 x CH_2Cl_2. The organic layers were combined, dried, filtered, and concentrated. The residue was purified by flash column chromatography (3% EtOAc/hexanes) to give the desired compound as a yellow oil (96 mg, 0.31 mmol, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddt, *J* = 16.7, 10.2, 7.4 Hz, 1H), 5.10 – 5.01 (m, 2H), 3.71 (ddd, *J* = 5.3, 3.8, 1.3 Hz, 4H), 3.06 – 2.99 (m, 2H), 2.97 – 2.92 (m, 2H), 2.93 – 2.83 (m, 2H), 2.28 (ddt, *J* = 13.8, 7.3, 1.2 Hz, 1H), 2.21 (ddt, *J* = 13.8, 7.5, 1.2 Hz, 1H), 1.88 (ddd, *J* = 13.8, 6.3, 5.7 Hz, 1H), 1.74 (ddd, *J* = 13.9, 7.2, 5.8 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 143.8, 141.9, 133.5, 118.7, 67.7, 50.2, 45.8,

40.9, 33.7, 33.3, 21.5; IR (Neat Film, NaCl) 2958, 2851, 1678, 1606, 1451, 1261, 1212, 1113, 1049, 920 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{21}BrNO_2$ $[M+H]^+$ 314.0750, found 314.0742; $[\alpha]^{25}$ –1.56 (*c* 1.68, $CHCl_3$).



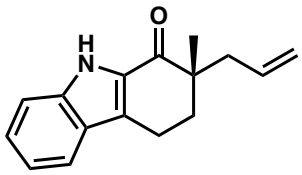
(*S*)-4-allyl-4-methyl-2-morpholino-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (69)

Compound **68** (54 mg, 0.17 mmol, 1.0 equiv) was dissolved in 7 mL of DME and 0.72 mL (4.5 equiv) of 1 M K_3PO_4. Phenylboronic acid (29 mg, 0.24 mmol, 1.5 equiv) and of $PdCl_2$(dppf) (26 mg, 32 μmol, 0.19 equiv) were added to the reaction mixture. The mixture was heated to 60 °C under nitrogen for 2h. The reaction mixture was cooled to room temperature and then extracted with 3x ethyl ether. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated. The reaction mixture was purified by flash column chromatography (3→6% EtOAc/hexanes) to give the product as bright yellow-orange oil (51 mg, 0.16 mmol, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.34 – 7.28 (m, 1H), 7.26 – 7.21 (m, 2H), 5.79 (ddt, *J* = 16.6, 10.4, 7.4 Hz, 1H), 5.12 – 5.04 (m, 2H), 3.53 (t, *J* = 4.6 Hz, 4H), 2.83 – 2.57 (m, 6H), 2.42 – 2.26 (m, 2H), 1.96 (dt, *J* = 13.7, 5.7 Hz, 1H), 1.85 (ddd, *J* = 13.5, 6.9, 6.2 Hz, 1H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 145.5, 141.0, 140.4, 134.1, 129.6, 128.1, 127.9, 127.8, 118.1, 115.3, 67.4, 51.1, 44.6, 41.2, 32.1, 28.9, 21.8; IR (Neat Film, NaCl): 2916, 2850, 2358, 1669, 1457, 1374, 1261, 1210, 1112, 1029, 978, 757, 698 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{26}NO_2$ $[M+H]^+$ 312.1958, found 312.1968; $[\alpha]^{25}$ 0.00 (*c* 0.76, $CHCl_3$).



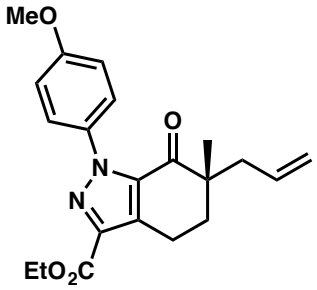
(*S*)-6-allyl-6-methyl-2-(phenylamino)cyclohex-2-en-1-one (70)

Compound **66a** (52 mg, 0.21 mmol, 1.0 equiv) was dissolved in 1.3 mL of toluene (0.16 M). PTSA monohydrate (39 mg, 0.21 mmol, 1.0 equiv) and aniline (20 μL, 0.22 mmol, 1.0 equiv) were added. The mixture was heated to 50°C for 3.5 h. Then the solution was diluted with ethyl acetate and washed 3 times with saturated aqueous $NaHCO_3$. The organic layer was combined, dried with Na_2SO_4, filtered, and concentrated. The reaction mixture was purified by flash column chromatography (2% EtOAc in hexanes) to yield compound **70** (18 mg, 75 μmol, 35% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.06 – 7.00 (m, 2H), 6.91 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.33 (t, *J* = 4.7 Hz, 1H), 5.75 (ddq, *J* = 16.8, 10.3, 7.5 Hz, 1H), 5.14 – 5.03 (m, 2H), 2.54 – 2.39 (m, 3H), 2.26 (ddt, *J* = 13.7, 7.6, 1.2 Hz, 1H), 1.98 (ddd, *J* = 13.6, 6.8, 5.4 Hz, 1H), 1.80 (ddd, *J* = 13.5, 6.8, 5.3 Hz, 1H), 1.17 (s, 3H) (N-H not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 142.3, 134.8, 134.0, 133.9, 121.1, 118.8, 118.5, 115.0, 44.4, 41.5, 33.1, 22.2, 21.0; IR (Neat Film, NaCl): 3364, 2926, 1668, 1634, 1600, 1515, 1442, 1306, 1203, 1014, 997, 916, 750, 691 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{20}NO$ $[M+H]^+$ 242.1539, found 242.1535; $[\alpha]^{25}$ –4.72 (*c* 2.18, $CHCl_3$).



(*S*)-2-allyl-2-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (71)

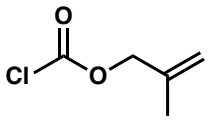
Enaminone **66a** (118 mg, 0.500 mmol, 1.00 equiv) was taken up in toluene (2 mL, 0.25 M) and PTSA monohydrate (95 mg, 0.50 mmol, 1.0 equiv) and phenyl hydrazine (54 mg, 0.50 mmol, 1.0 equiv) were added. The reaction was heated to 60 °C and stirred for 4 hours, cooled to room temperature, diluted with 1 mL saturated aqueous NH_4Cl and extracted with 3 x 5 mL EtOAc. The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo. The crude intermediate was taken up in 5 mL 4:1 AcOH:12 M HCl (0.1 M), stirred for 2 hours and ice (approx. 10 g) was added. The ice/reaction mixture was quenched with 5.0 M NaOH until a pH of 9–10 was achieved. The mixture was extracted with 3x20 mL EtOAc. The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography (SiO_2, 3 x 10 cm, 5→10→15% EtOAc in hexanes) to yield indole **71** (120 mg, 0.500 mmol, quantitative yield over 2 steps) as a yellow oil; R_f = 0.54 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.66 (dq, *J* = 8.1, 0.9 Hz, 1H), 7.49 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.15 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 5.87 (ddt, *J* = 16.6, 10.4, 7.4 Hz, 1H), 5.17 – 5.08 (m, 2H), 3.12 – 2.96 (m, 2H), 2.57 (ddt, *J* = 13.8, 7.2, 1.2 Hz, 1H), 2.38 (ddt, *J* = 13.8, 7.5, 1.2 Hz, 1H), 2.24 (ddd, *J* = 13.6, 7.1, 5.2 Hz, 1H), 2.05 (ddd, *J* = 13.6, 7.0, 5.2 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 196.3, 138.7, 134.4, 130.3, 128.0, 126.9, 125.9, 121.4, 120.4, 118.3, 112.9, 45.5, 41.5, 35.7, 22.1, 18.4; IR (Neat Film, NaCl): 3279, 3076, 2963, 2926, 1638, 1573, 1545, 1473, 1331, 1224, 1014, 992, 977, 916 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1383, found 240.1383; $[\alpha]^{25}$ –131.65 (*c* 7.84, $CHCl_3$).



Ethyl (*S*)-6-allyl-1-(4-methoxyphenyl)-6-methyl-7-oxo-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylate (72)

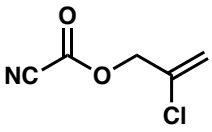
Enaminone **66a** (31 mg, 0.13 mmol, 1.0 equiv) and ethyl (*Z*)-2-chloro-2-(2-(4-methoxyphenyl)hydrazono)acetate[7] (**73**, 50 mg, 0.19 mmol, 1.5 equiv) were diluted in 0.4 mL of toluene (0.033M). Then, TEA (0.15 mL, 0.11 mmol, 0.83 equiv) was added. The reaction mixture was heated at the reflux for 17 h. The reaction mixture was cooled, quenched with water, extracted with ethyl acetate, washed with brine, and dried with Na_2SO_4. The product was purified by flash column chromatography (5→15% EtOAc/hexanes) to give the compound **72** as a yellow-orange oil (22 mg, , 6.0 μmol, 46% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 6.98 – 6.89 (m, 2H), 5.76 (ddt, *J* = 17.2, 10.1, 7.4 Hz, 1H), 5.15 – 5.02 (m, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.20 – 3.04 (m, 2H), 2.42 (ddt, *J* = 13.8, 7.1, 1.2 Hz, 1H), 2.27 (ddt, *J* = 13.8, 7.6, 1.1 Hz, 1H), 2.13 (ddd, *J* = 14.0, 6.7, 5.5 Hz, 1H), 1.98 (ddd, *J* = 13.9, 7.3, 5.5 Hz, 1H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 162.3, 160.1, 140.0, 135.2, 133.6, 132.9, 132.8, 127.1, 118.8, 113.8, 61.3, 55.7, 46.7, 40.8, 34.9, 21.6, 19.0, 14.6; IR (Neat Film, NaCl): 2917, 2357, 2340, 1691, 1515, 1301, 1251, 1195, 1127, 1026, 935 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$ 369.1809, found 369.1791; $[\alpha]^{25}$ –7.56 (*c* 0.45, $CHCl_3$).

2.4.6 Synthesis of Substituted Allyl Cyanoformates



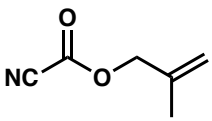
2-methylallyl carbonochloridate (82)

Prepared as reported for the 2-chloroallyl substrate from the report by Stoltz and coworkers.[14] The product was vacuum distilled (45–47 °C, 20 torr) to provide the product as a clear oil (7.48 g, 60% yield). Spectral data matches that reported in the literature.[15] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 – 5.07 (m, 1H), 5.07 – 5.04 (m, 1H), 4.71 (s, 2H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 137.9, 115.8, 75.0, 19.2.



2-chloroallyl carbonocyanidate (83a)

Prepared according to literature precedent.[14] Product vacuum distilled (62–65°C, 20 torr) to afford the product as a clear oil (6.13 g, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 – 5.59 (m, 1H), 5.57 (d, J = 2.1 Hz, 1H), 4.88 (d, J = 0.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 132.9, 118.5, 108.9, 69.7; IR (Neat Film, NaCl) 2249, 1759, 1640, 1230, 1180, 918 cm^{-1}; Anal. Calc'd for $C_5H_4NO_2Cl$: C, 41.26%; H, 2.77%; N, 9.62%; Cl, 24.36% ;Found: C, 41.22%; H, 2.79%, N, 9.49%; Cl, 24.18%.



2-methylallyl carbonocyanidate (83b)

Prepared according to procedure for cyanoformate **83a** from chloroformate **82**. Product vacuum distilled (60°C, 35 torr) to afford the product as a clear oil (3.61 g, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 – 5.06 (m, 2H), 4.73 (s, 2H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 137.2, 116.4, 109.3, 72.0, 19.3; IR (Neat Film, NaCl) 2246, 1762, 1227, 1242, 918 cm^{-1}; Anal. Calc'd for $C_6H_7NO_2$: C, 57.59%; H, 5.64%; N, 11.19%; Found: C, 57.59%; H, 5.49%; N, 11.11%.

2.5 NOTES AND REFERENCES

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(8) Interestingly, we noted that the recovered starting material of this reaction was isolated in 18% yield and 99% *ee*. Repeating this experiment and halting it at 12 hours, the recovered starting material was obtained in 75% yield and 16% *ee*. This corresponds to a modest s value of 3.3. This indicates a small but notable relative preference for one enantiomer of the starting material as a substrate for the stereoablative decarboxylation beginning the catalytic cycle of the reaction, which to our knowledge is only observed in this specific substrate.

(9) Computational details: Calculations were performed with the program package Spartan 10 using the Hartree-Fock density functional with the 6-31 G** basis set.

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(13) Prepared from 2-iodocyclohexenone and cyclohexylmagnesium bromide following the procedure from the following publication: Barriault, L.; Thomas, J. D. O.; Clément, R. *J. Org. Chem.* **2003**, *68*, 2317–2323.

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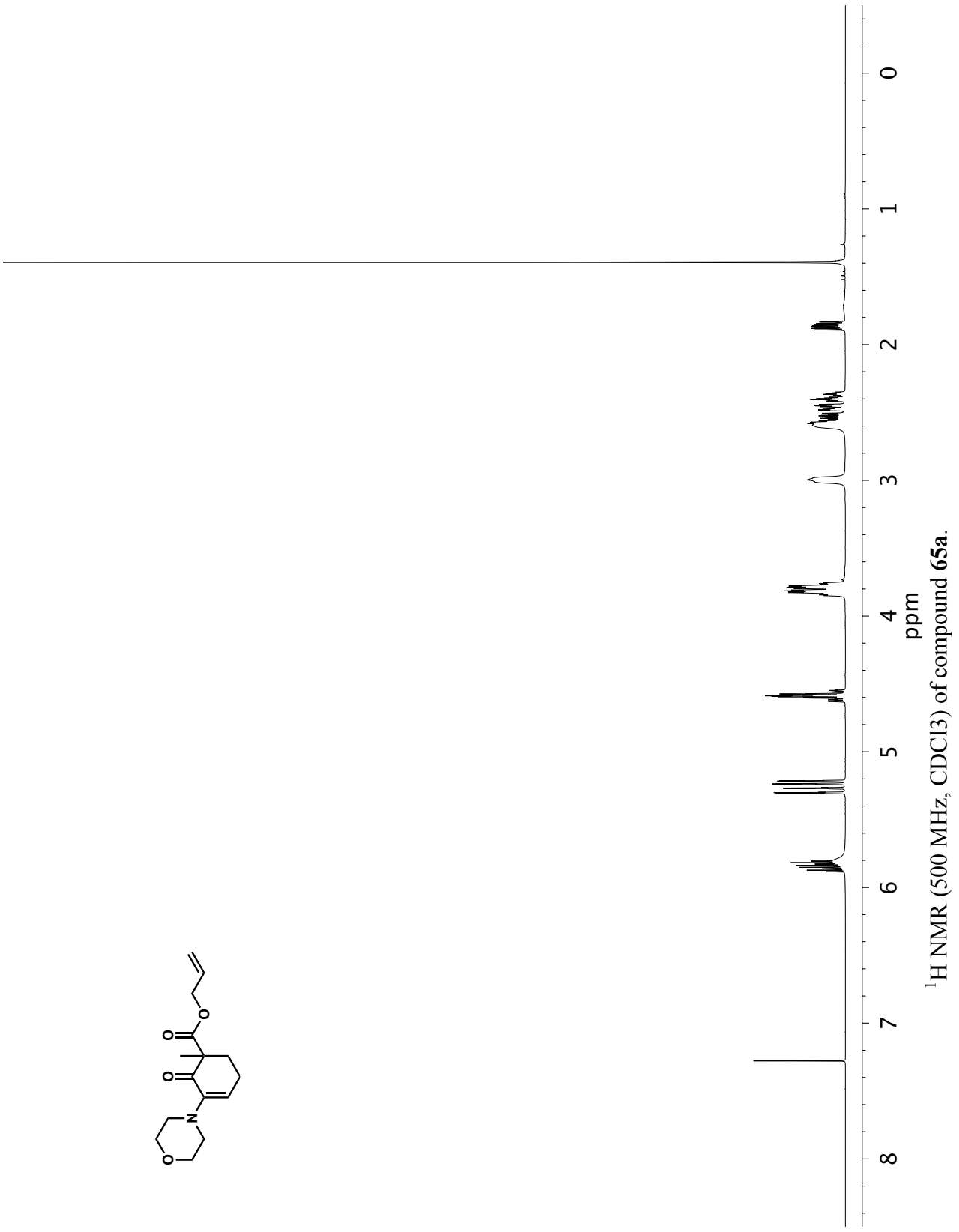
APPENDIX 2

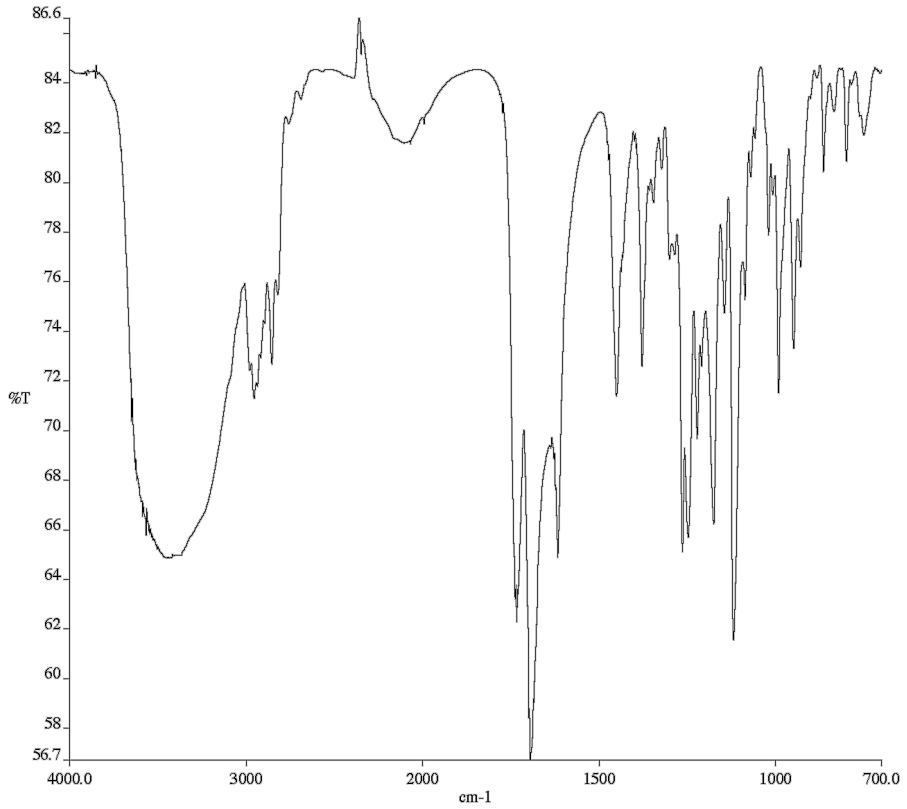
Spectra Relevant to Chapter 2:

Highly Enantioselective Palladium-Catalyzed

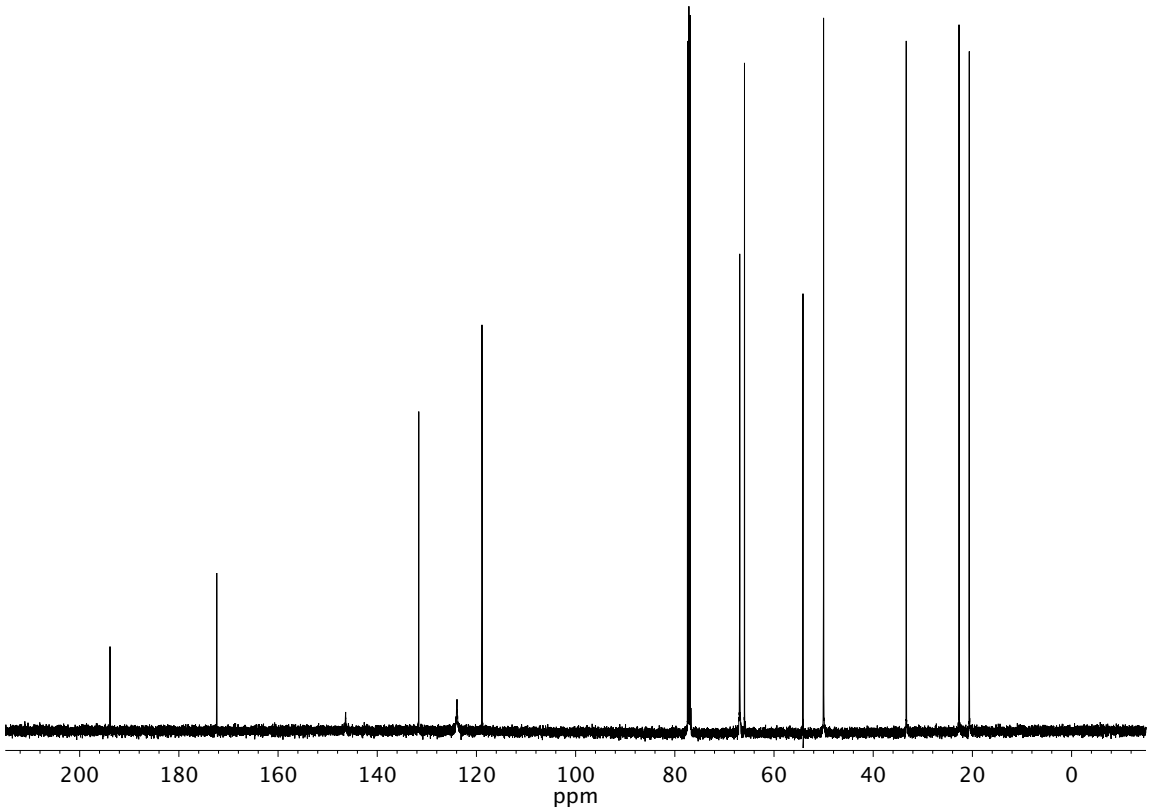
Asymmetric Decarboxylative Allylic Alkylation of Enaminones



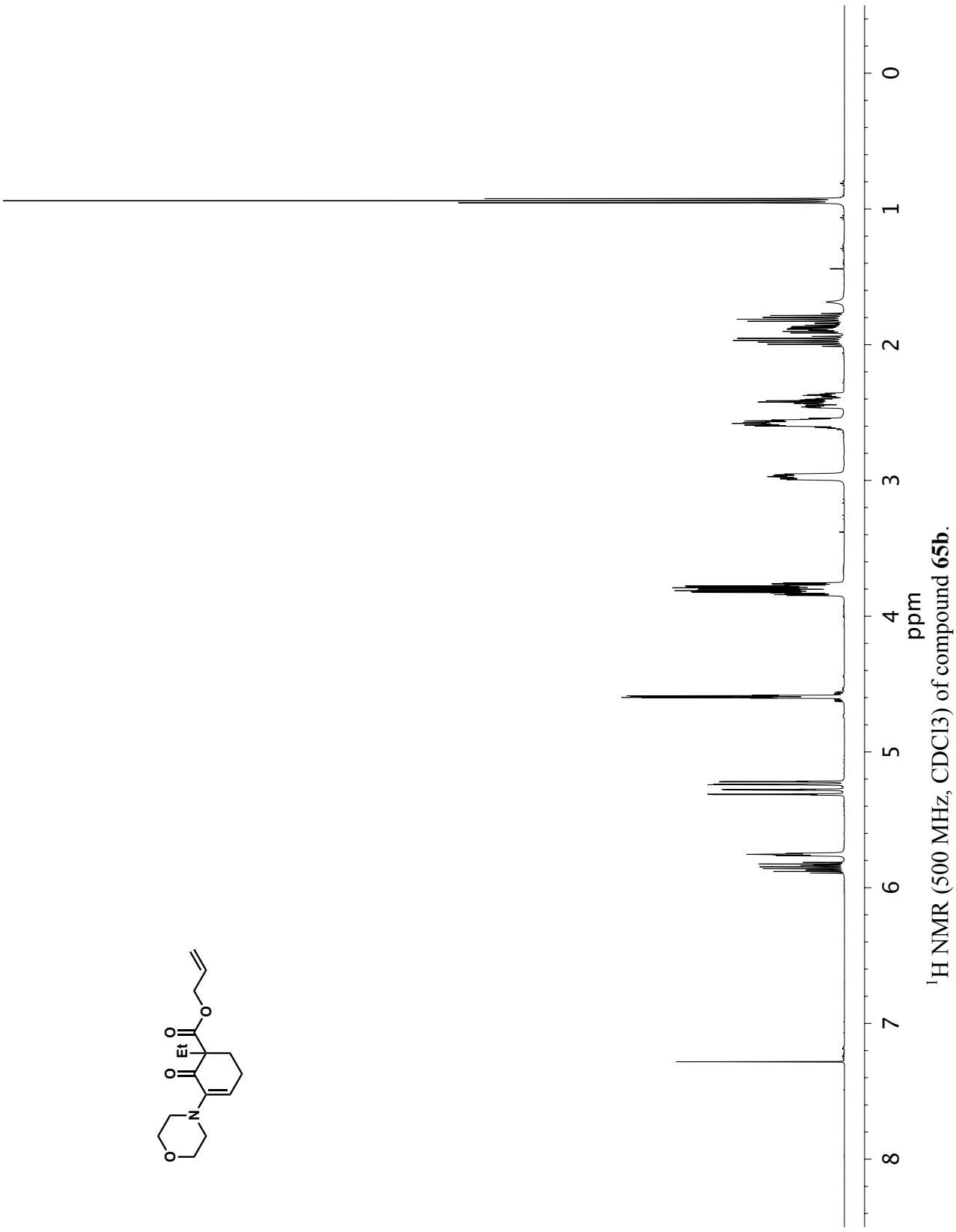
^{1}H NMR (500 MHz, CDCl3) of compound **65a**.



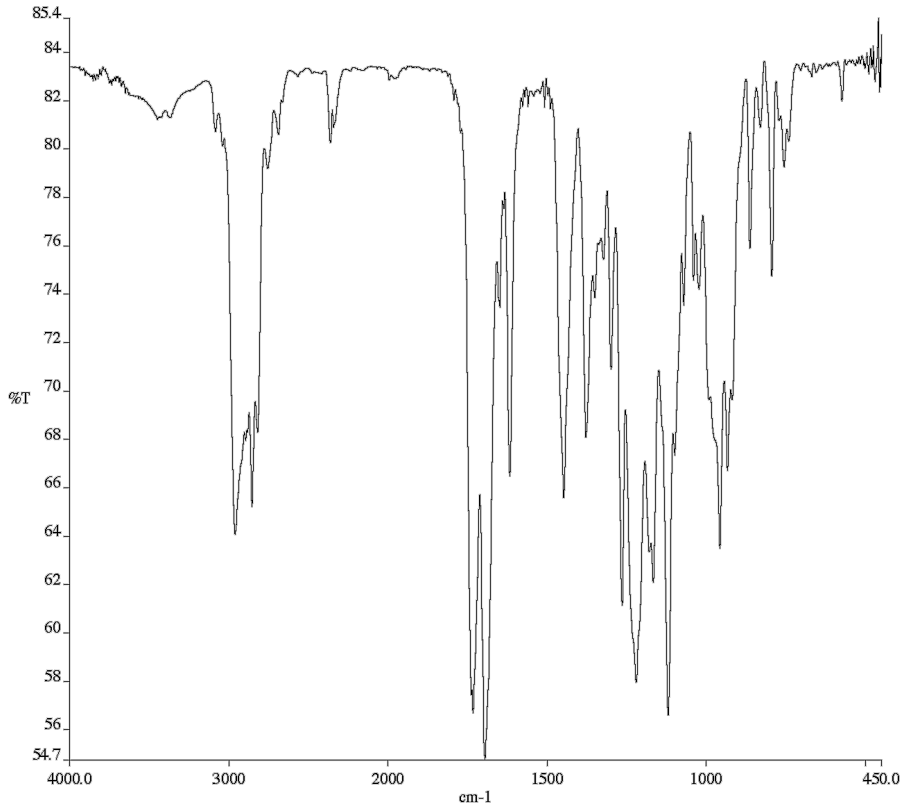
Infrared spectrum (Thin Film, NaCl) of compound **65a**.



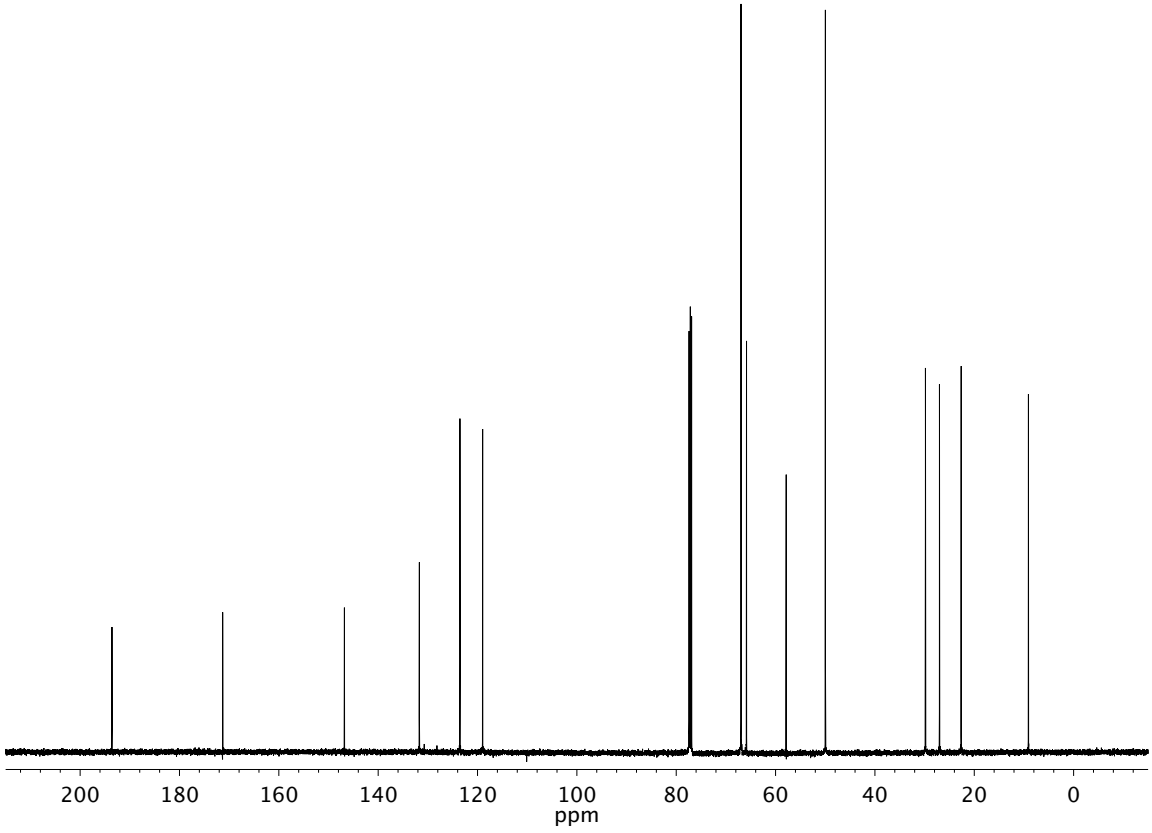
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65a**.



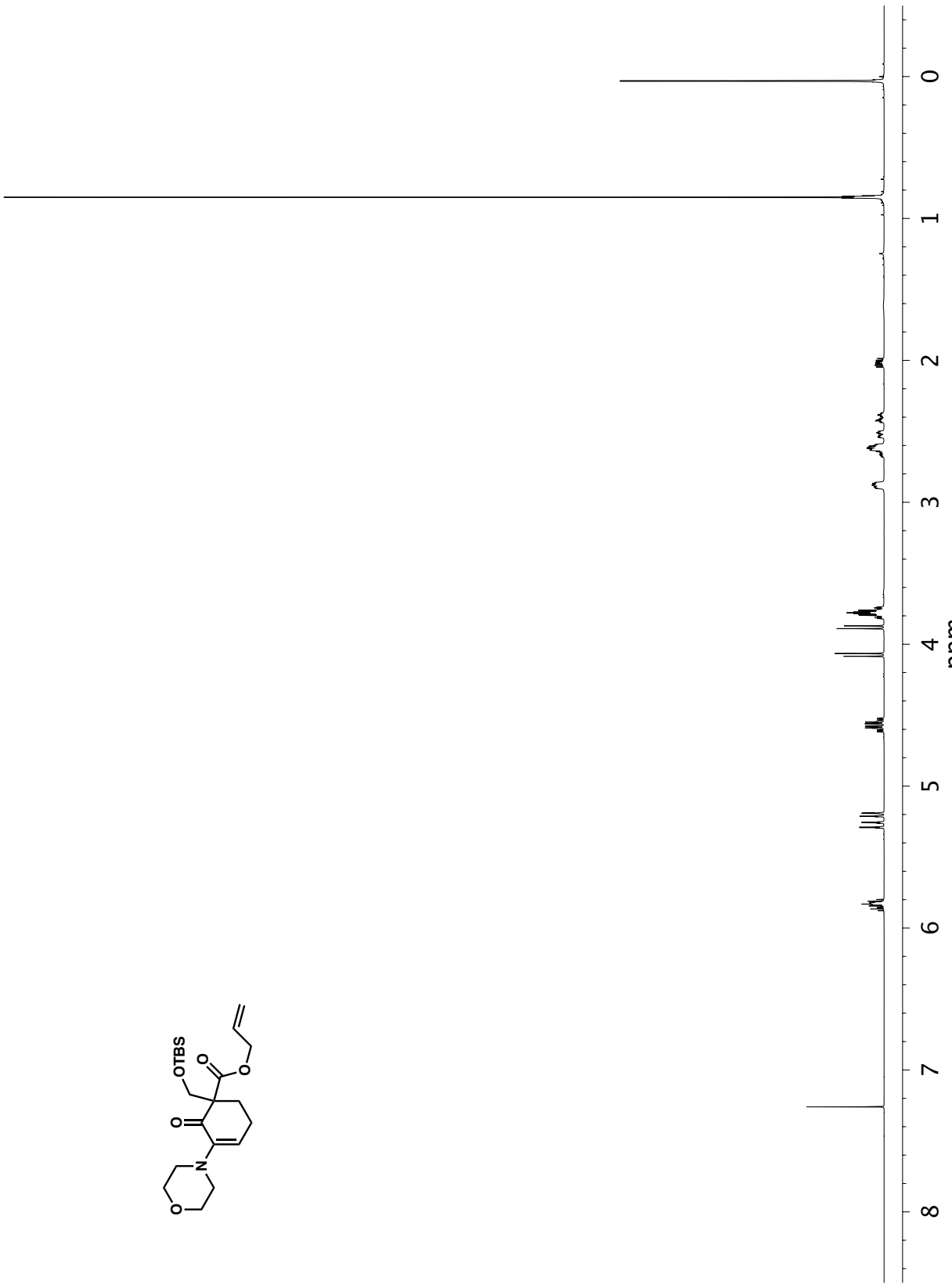
^{1}H NMR (500 MHz, CDCl3) of compound **65b**.



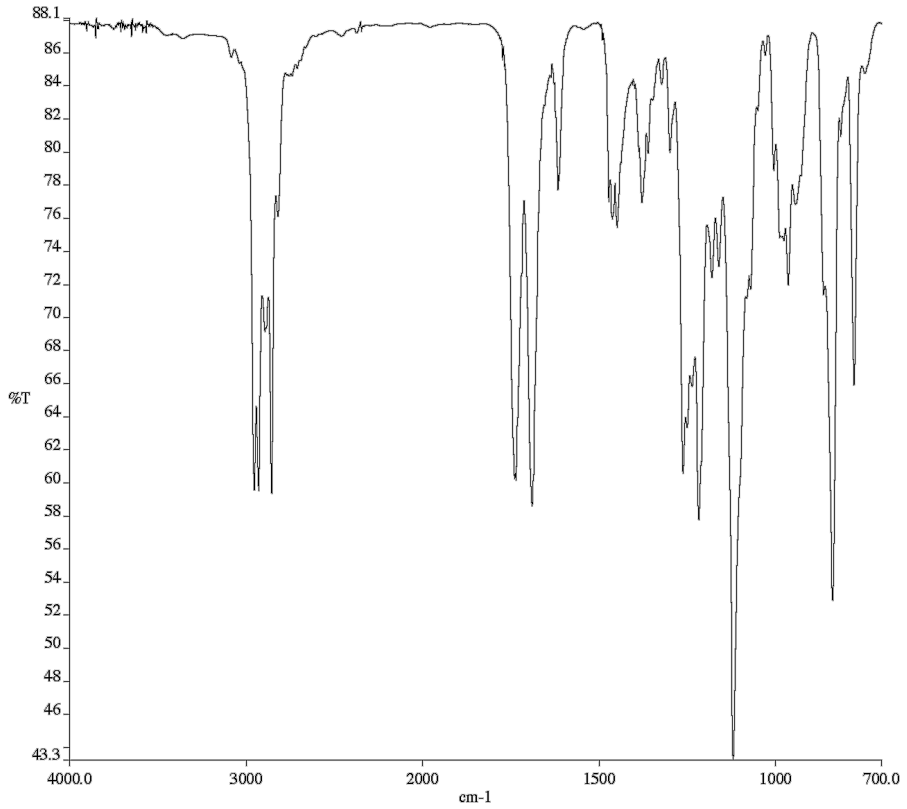
Infrared spectrum (Thin Film, NaCl) of compound **65b**.



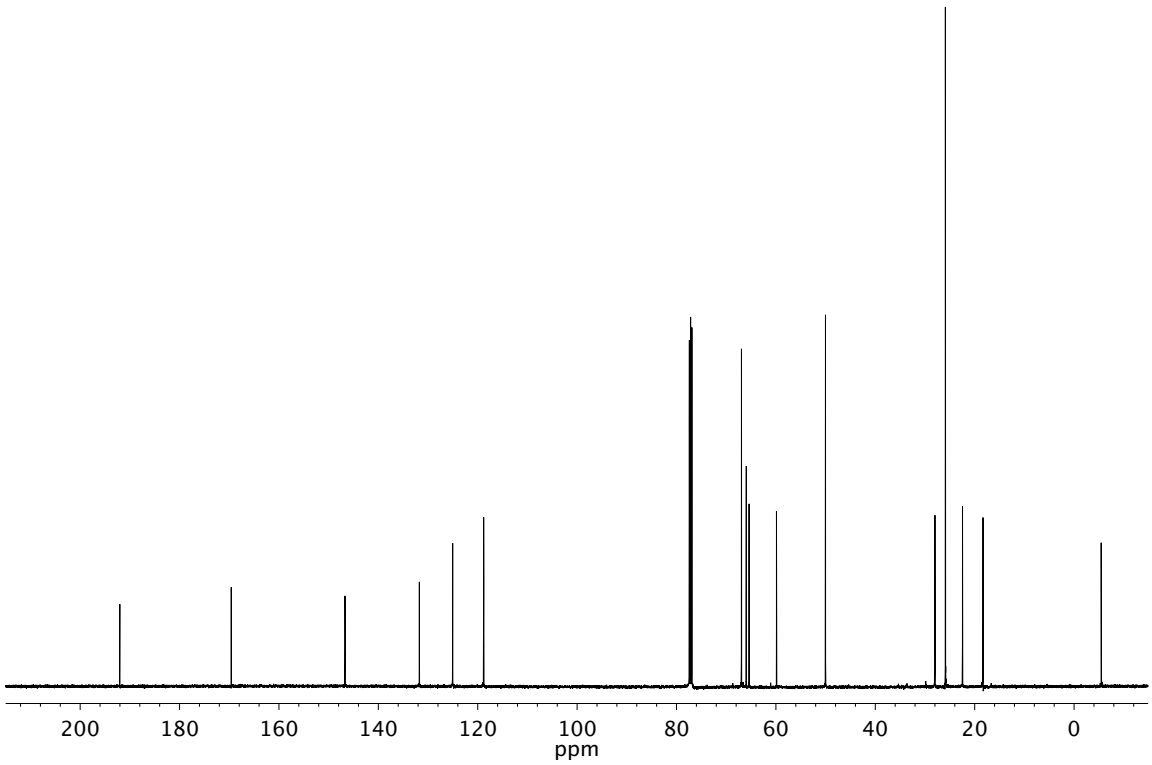
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65b**.



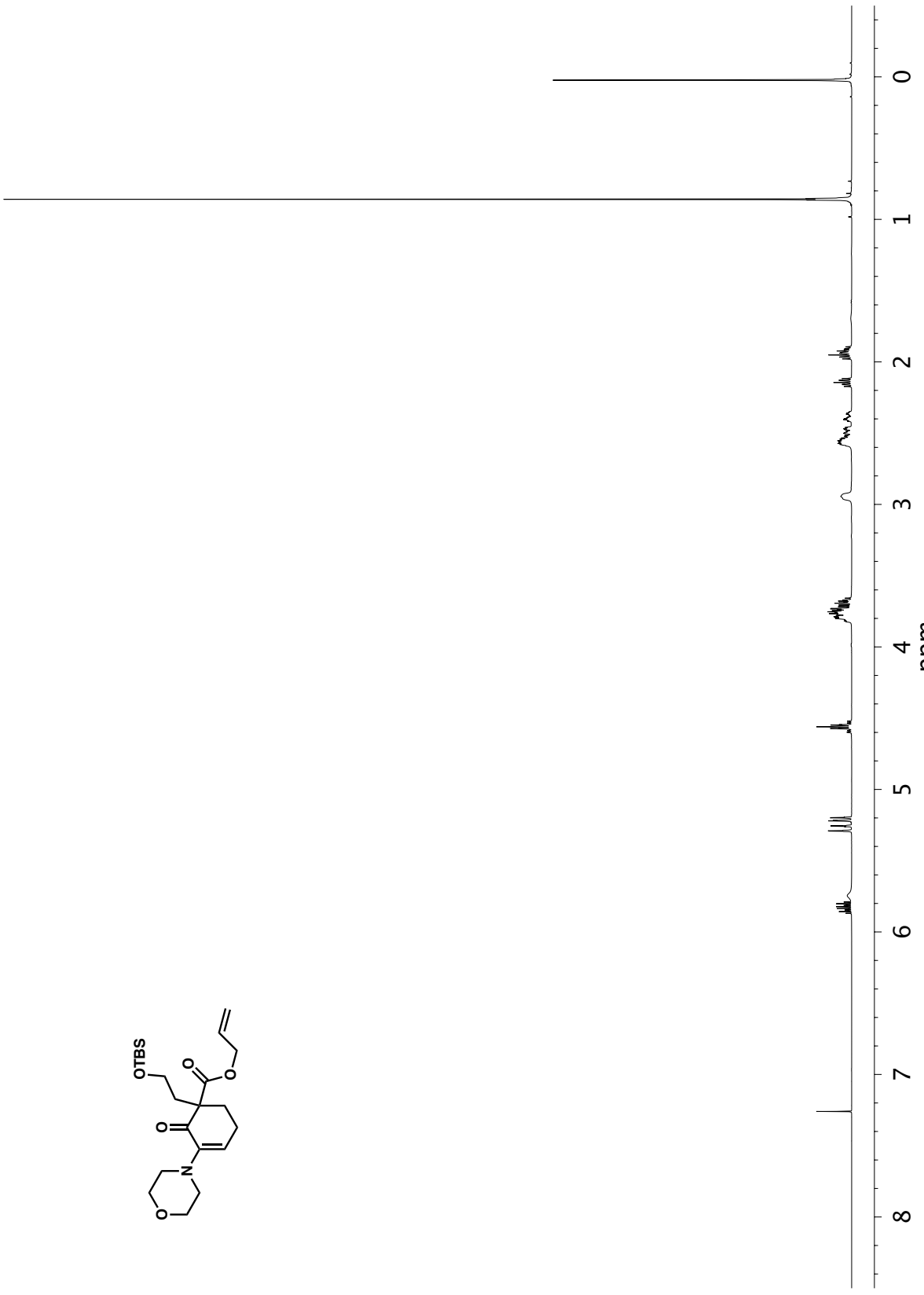
^{1}H NMR (500 MHz, CDCl3) of compound **65c**.



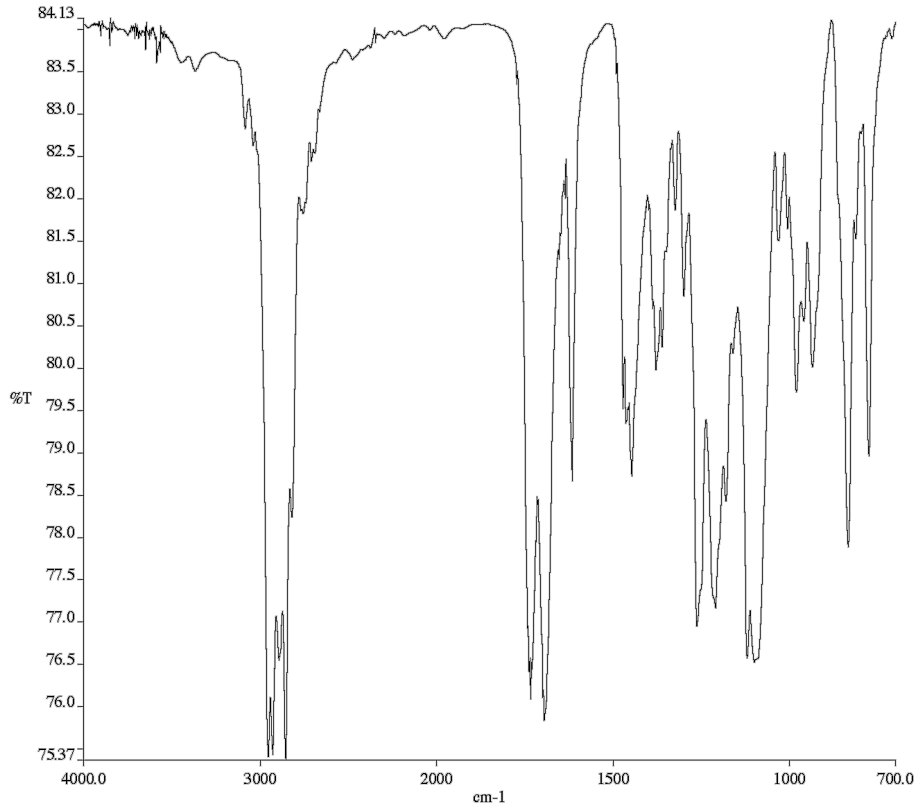
Infrared spectrum (Thin Film, NaCl) of compound **65c**.



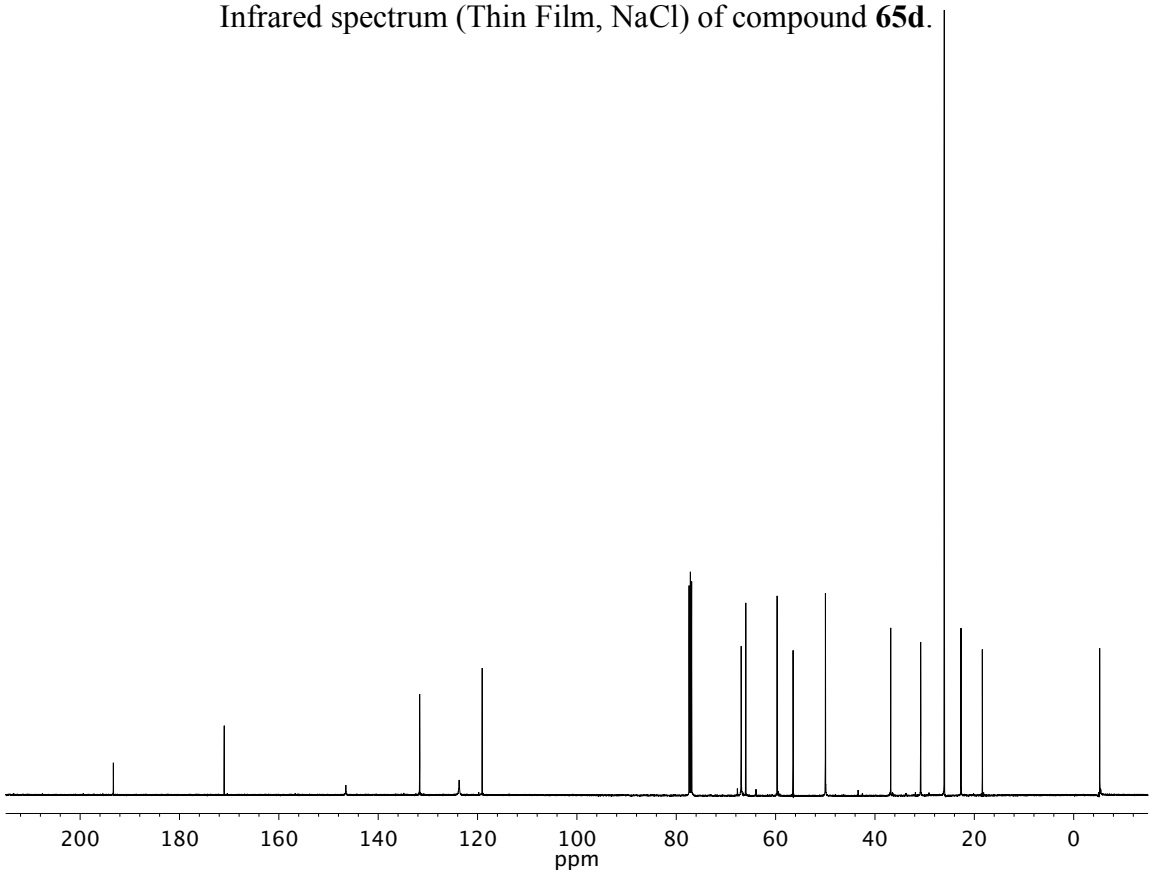
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65c**.



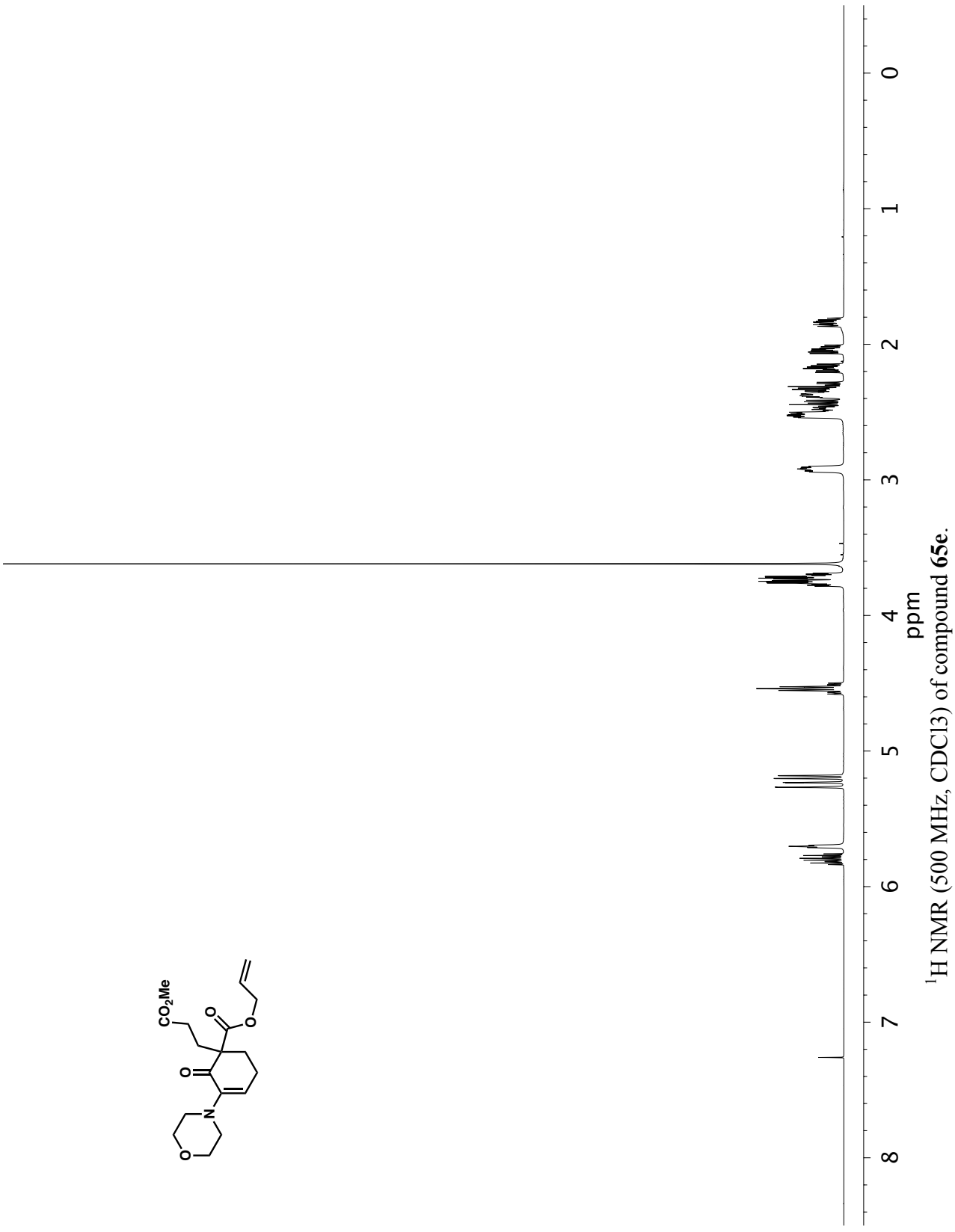
^{1}H NMR (500 MHz, CDCl3) of compound **65d**.



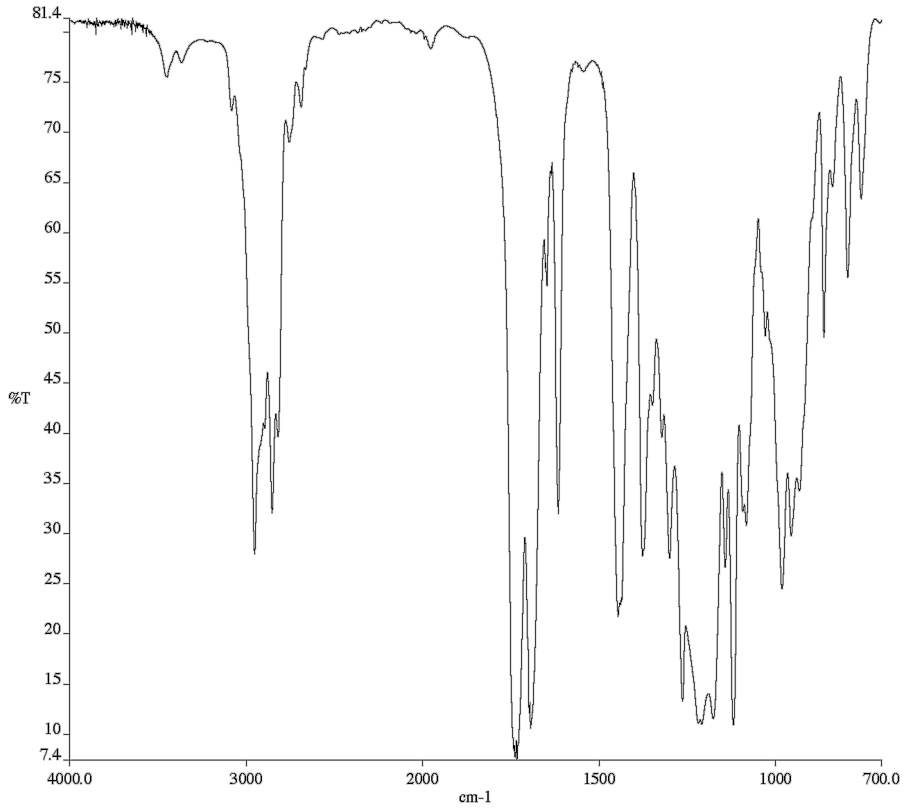
Infrared spectrum (Thin Film, NaCl) of compound **65d**.



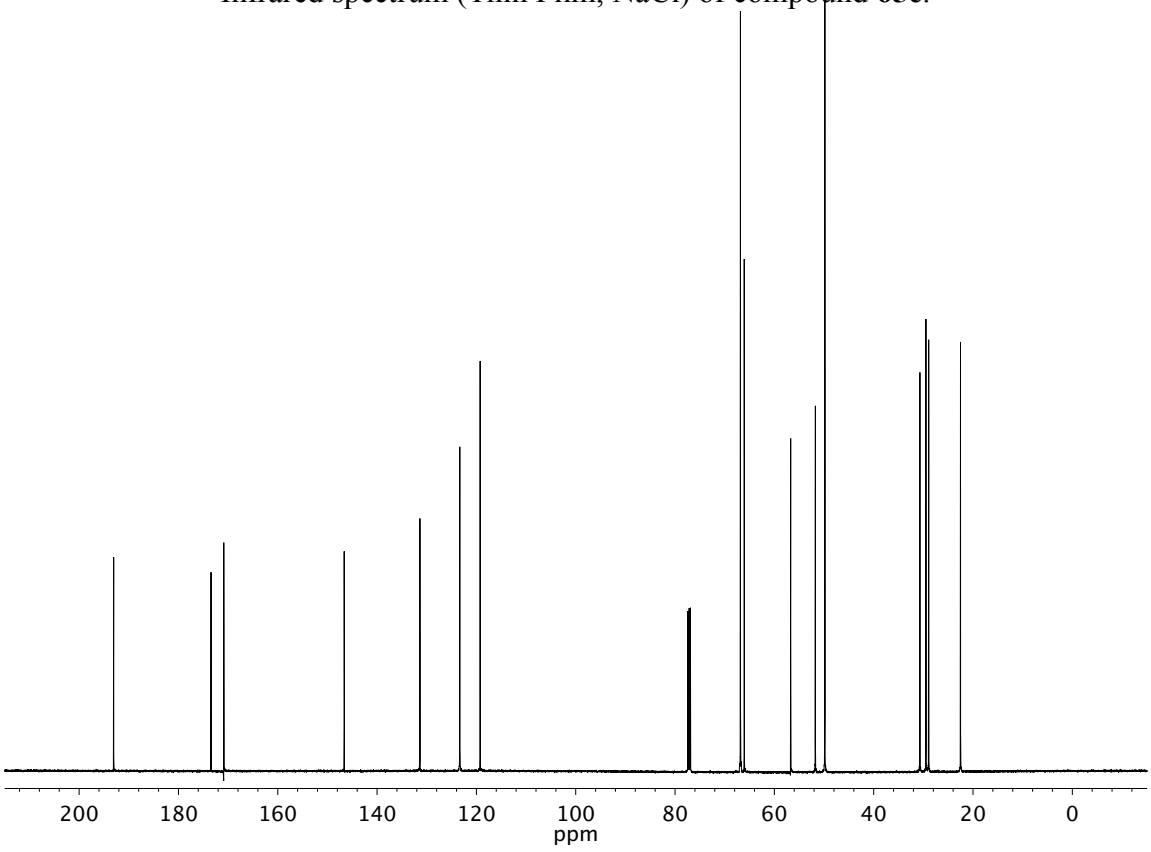
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65d**.



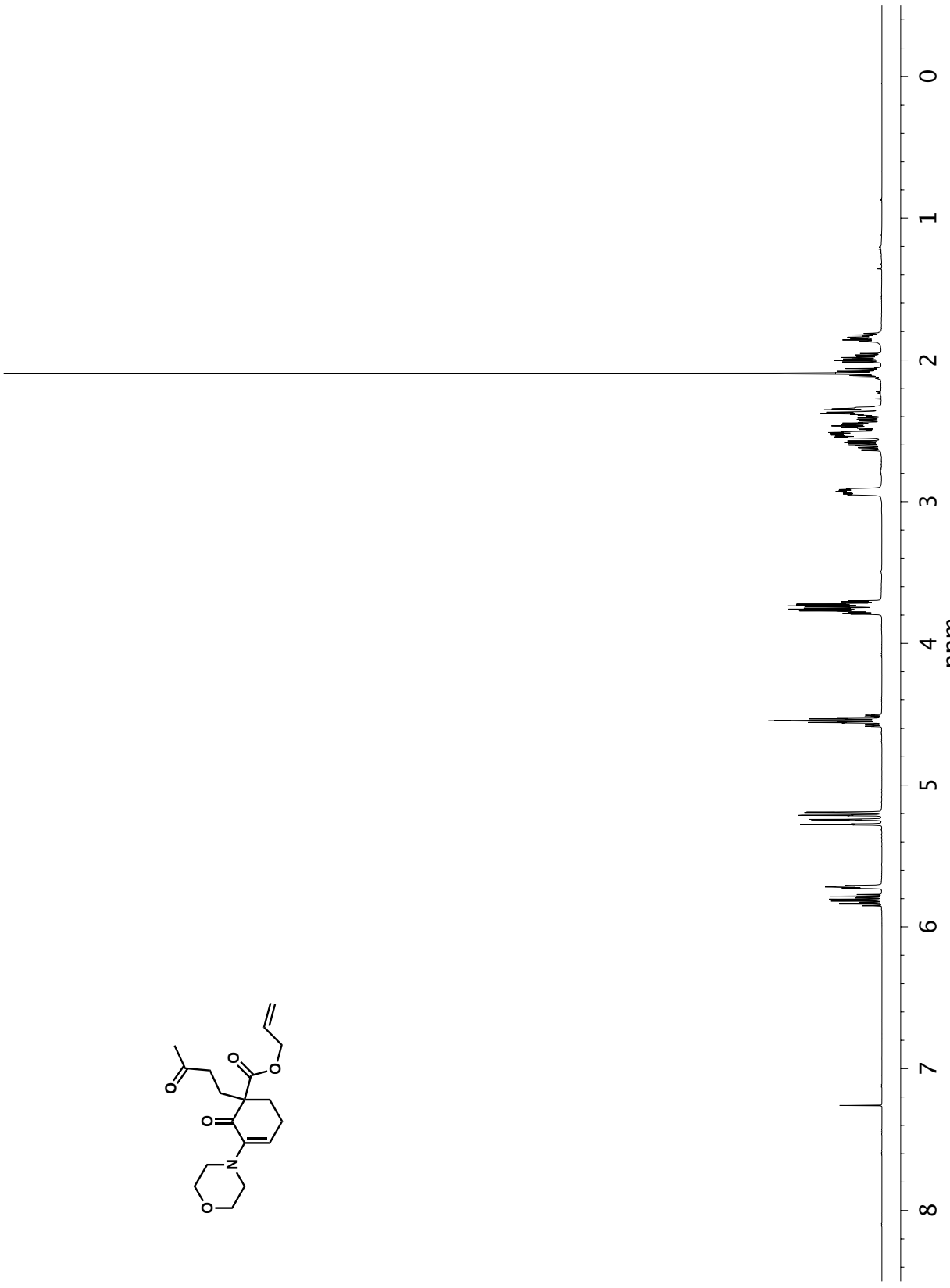
^{1}H NMR (500 MHz, CDCl3) of compound **65e**.



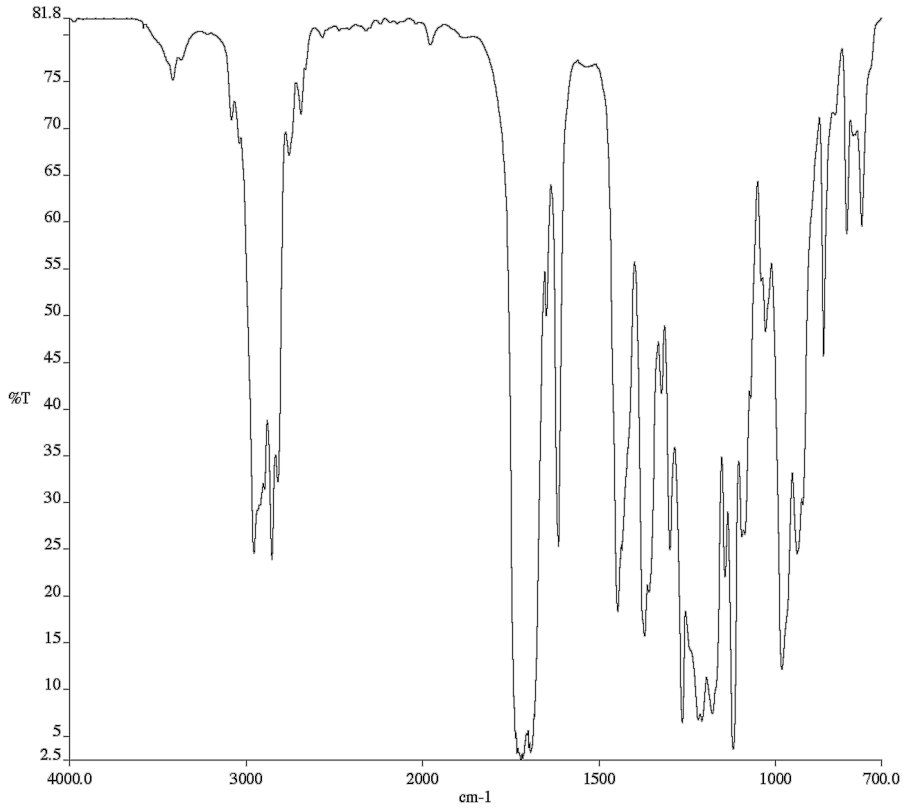
Infrared spectrum (Thin Film, NaCl) of compound **65e**.



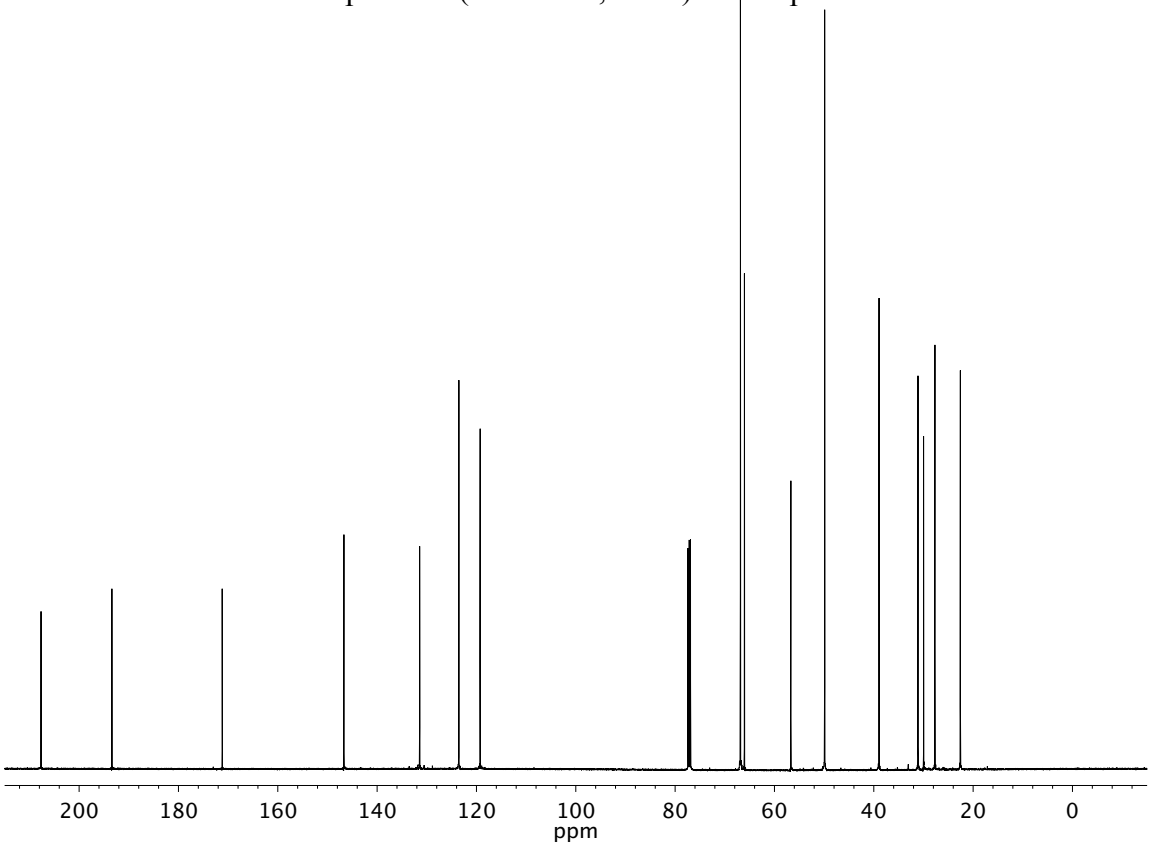
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65e**.



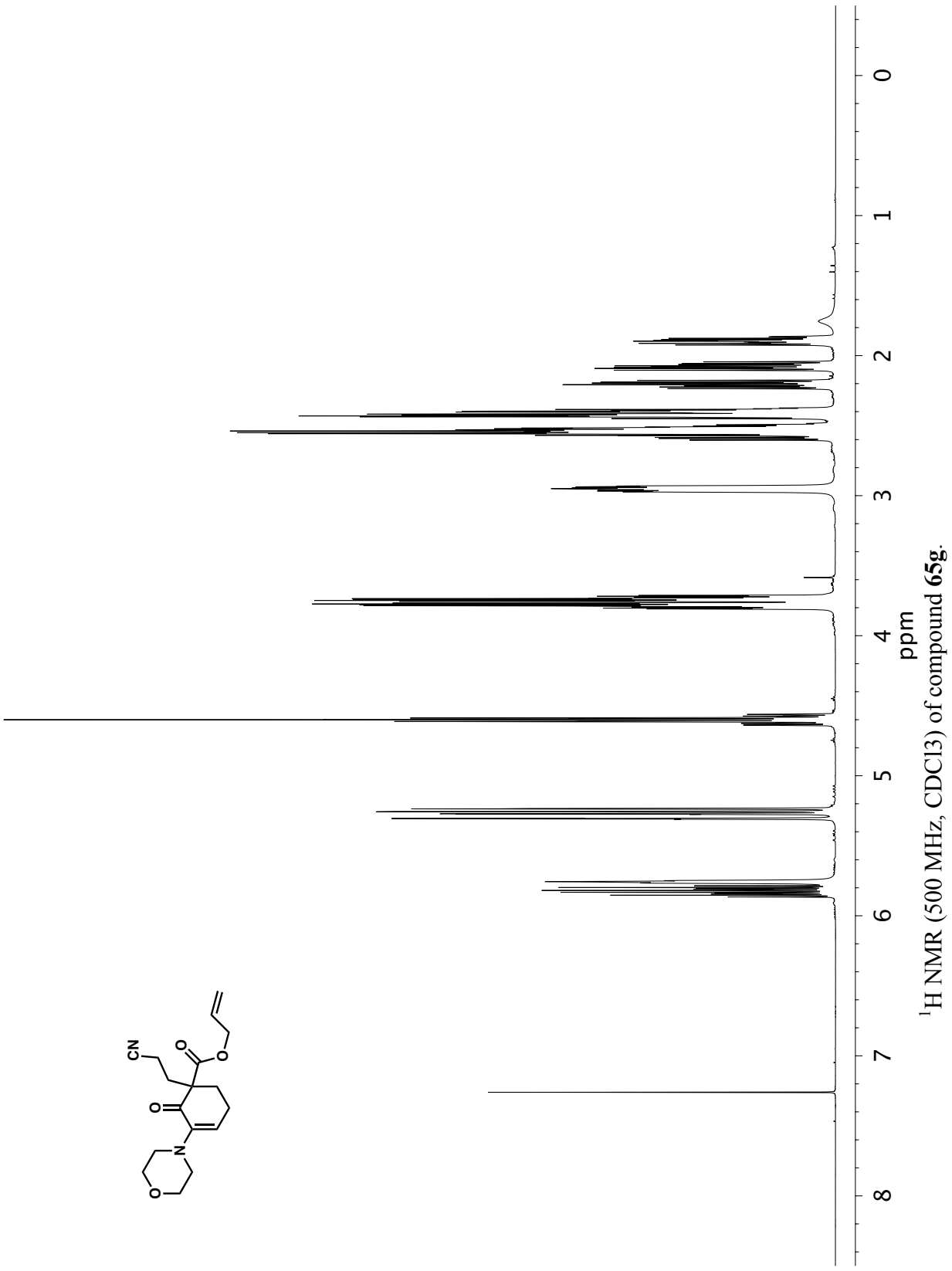
^{1}H NMR (500 MHz, CDCl3) of compound **65f**.



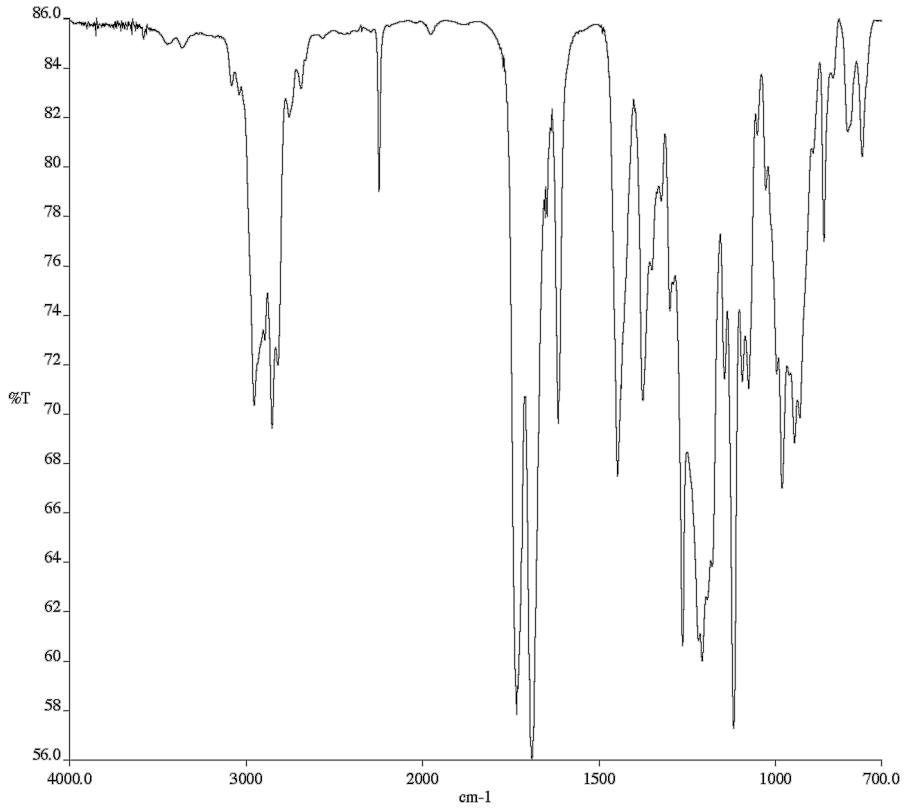
Infrared spectrum (Thin Film, NaCl) of compound **65f**.



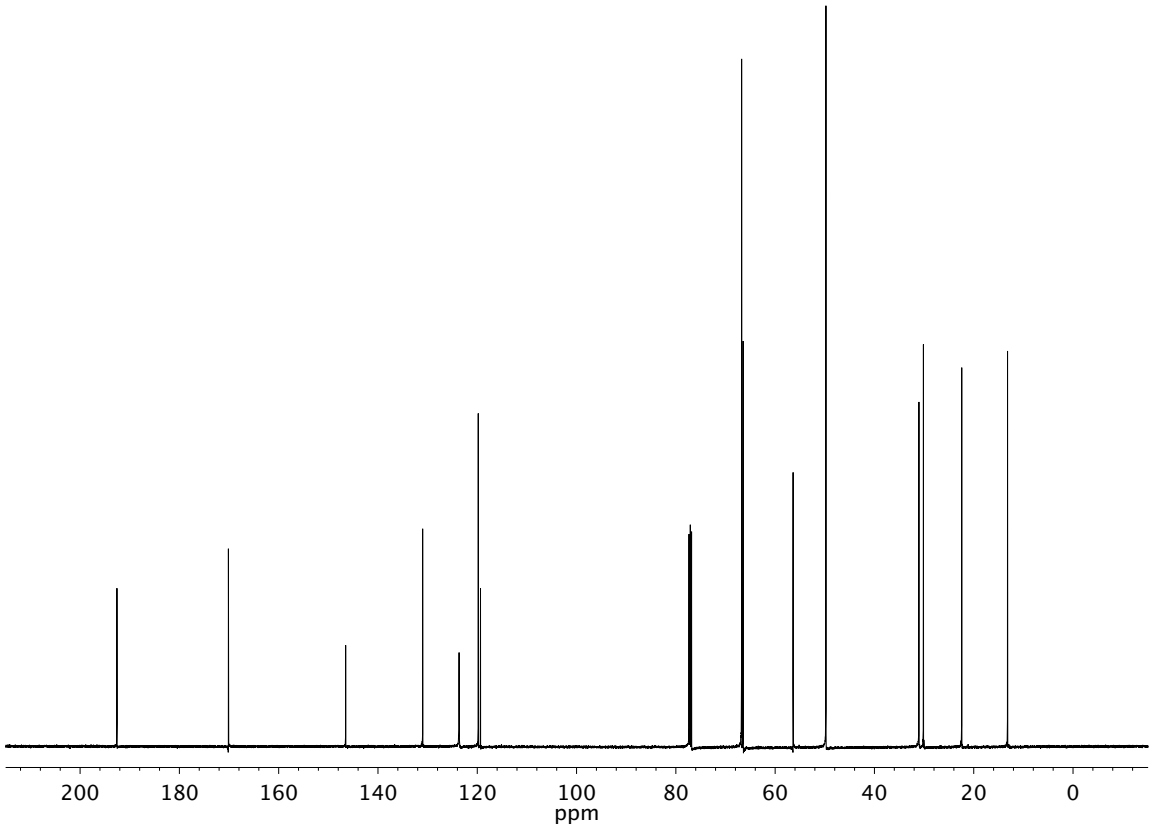
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65f**.



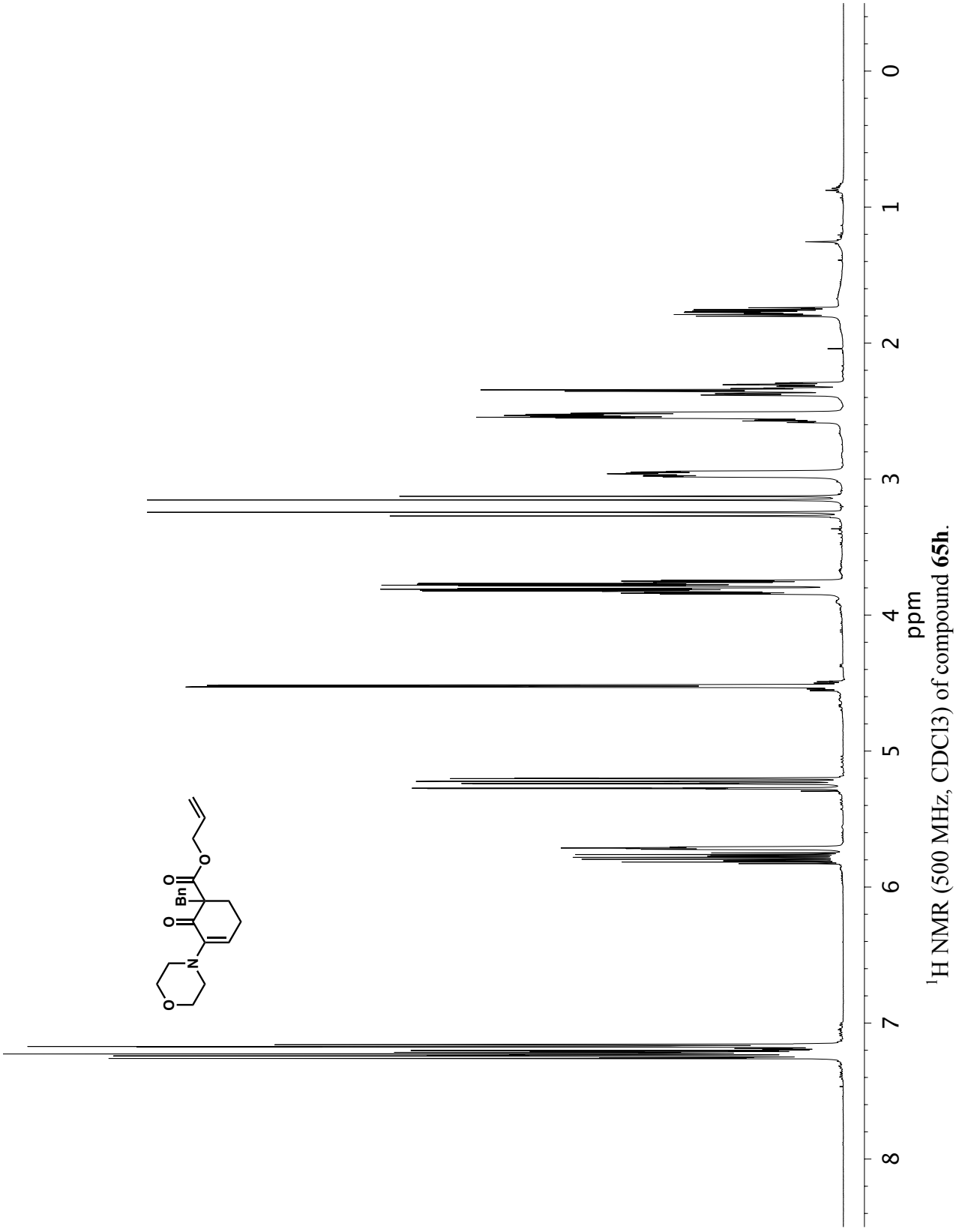
^{1}H NMR (500 MHz, CDCl3) of compound **65g**.



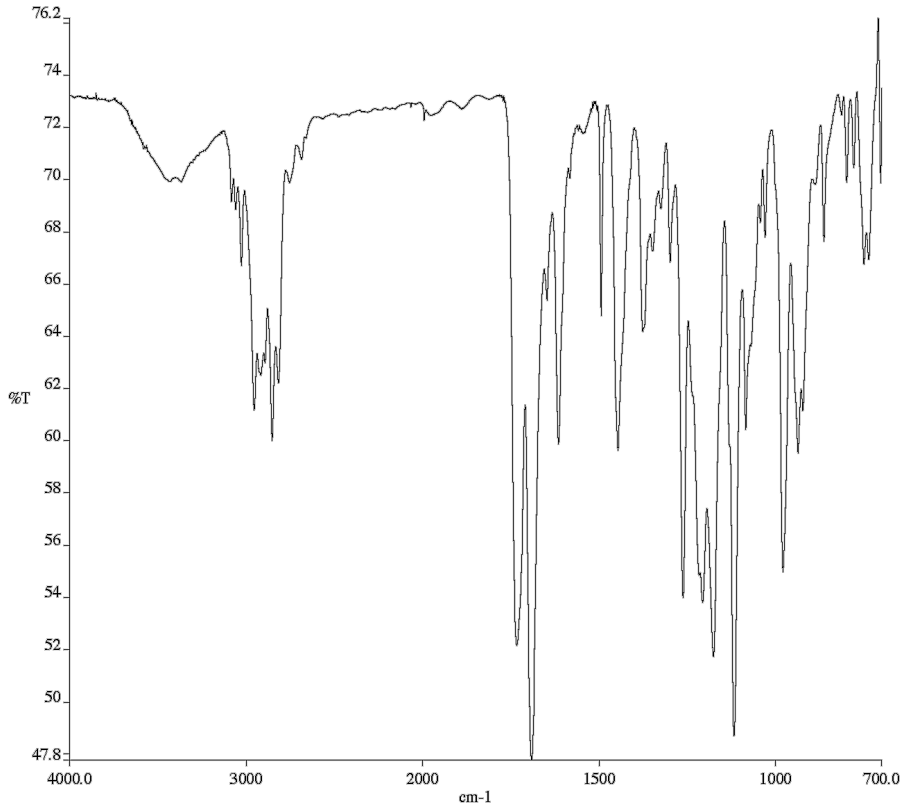
Infrared spectrum (Thin Film, NaCl) of compound **65g**.



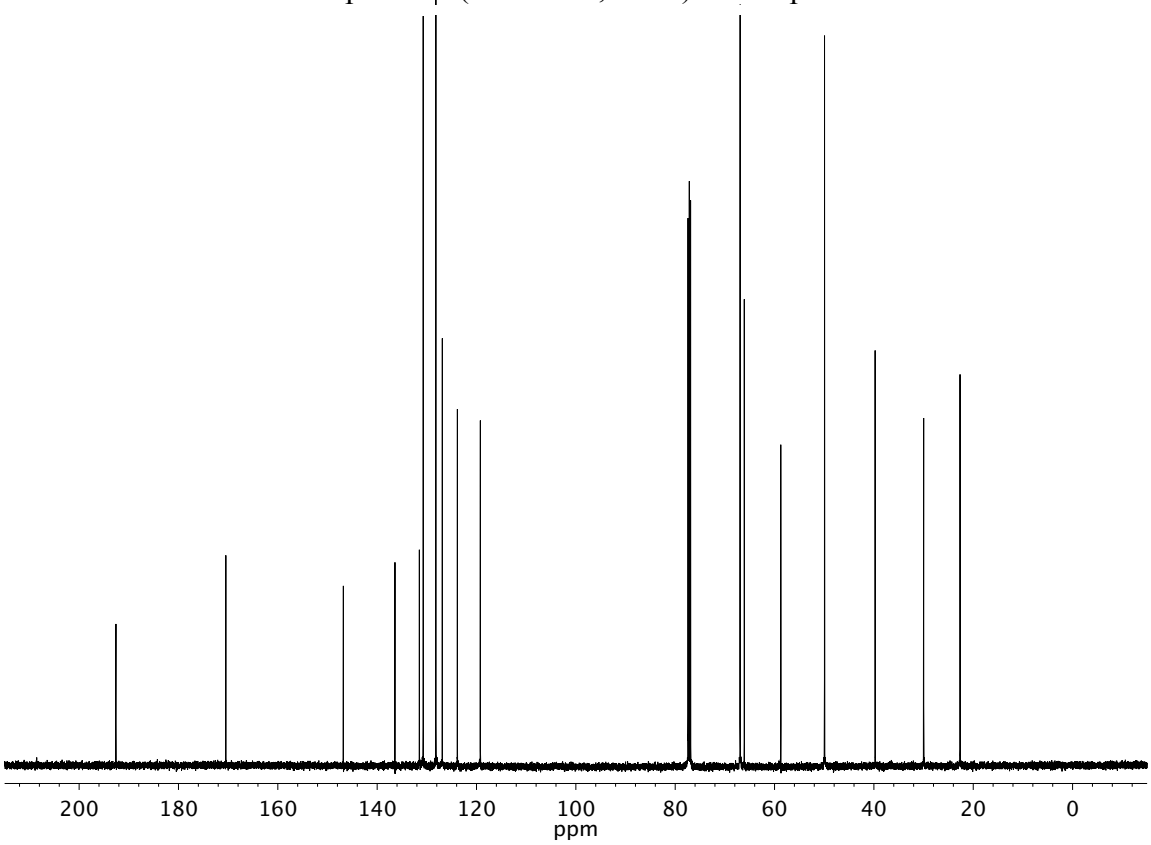
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65g**.



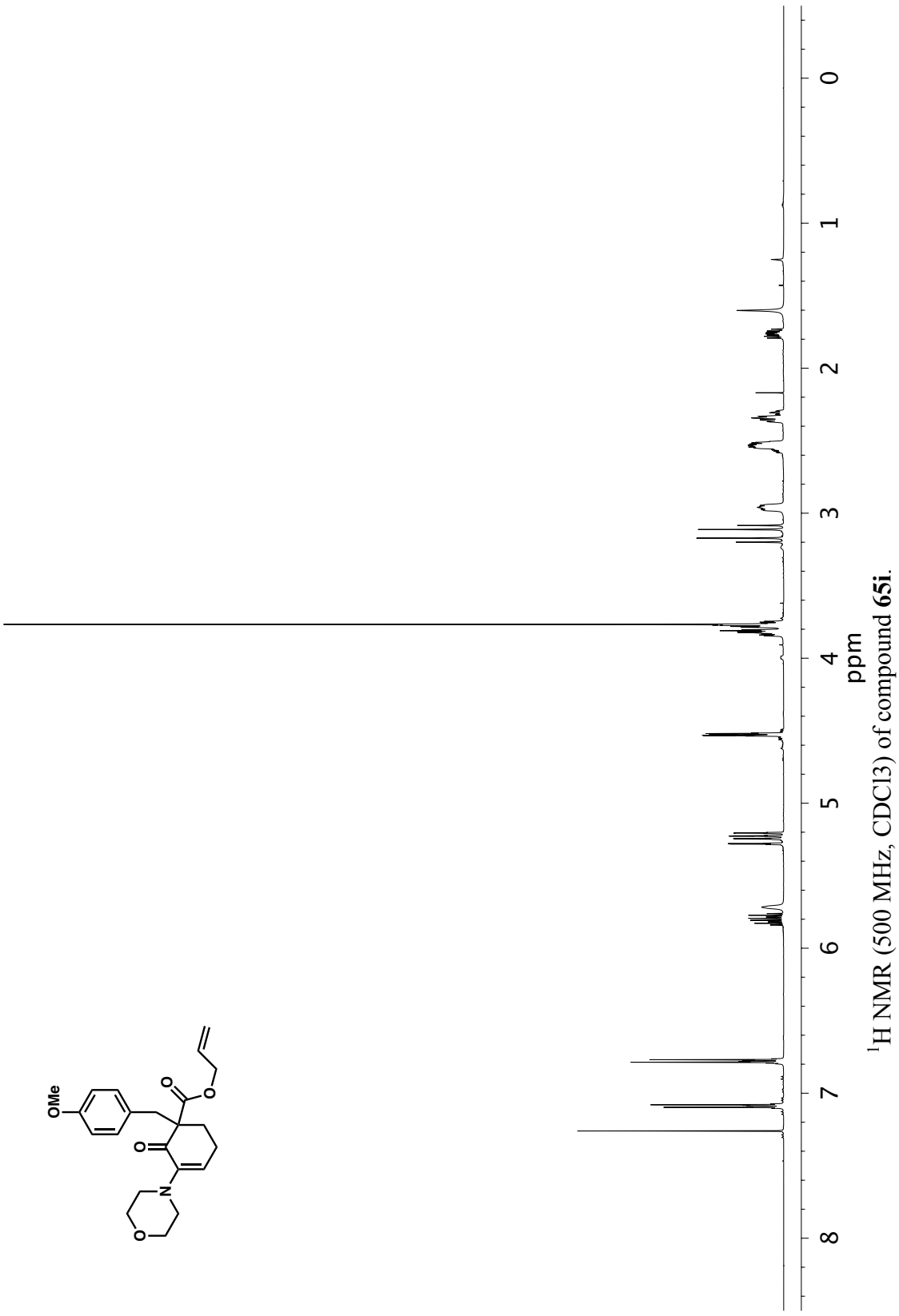
^{1}H NMR (500 MHz, CDCl3) of compound **65h**.



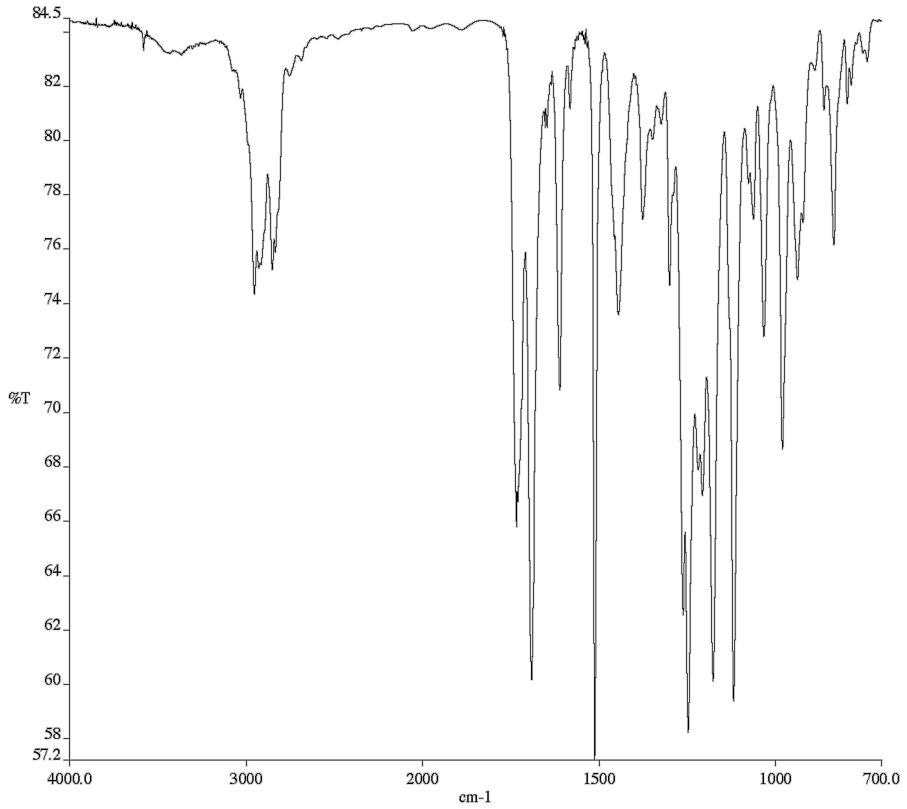
Infrared spectrum (Thin Film, NaCl) of compound **65h**



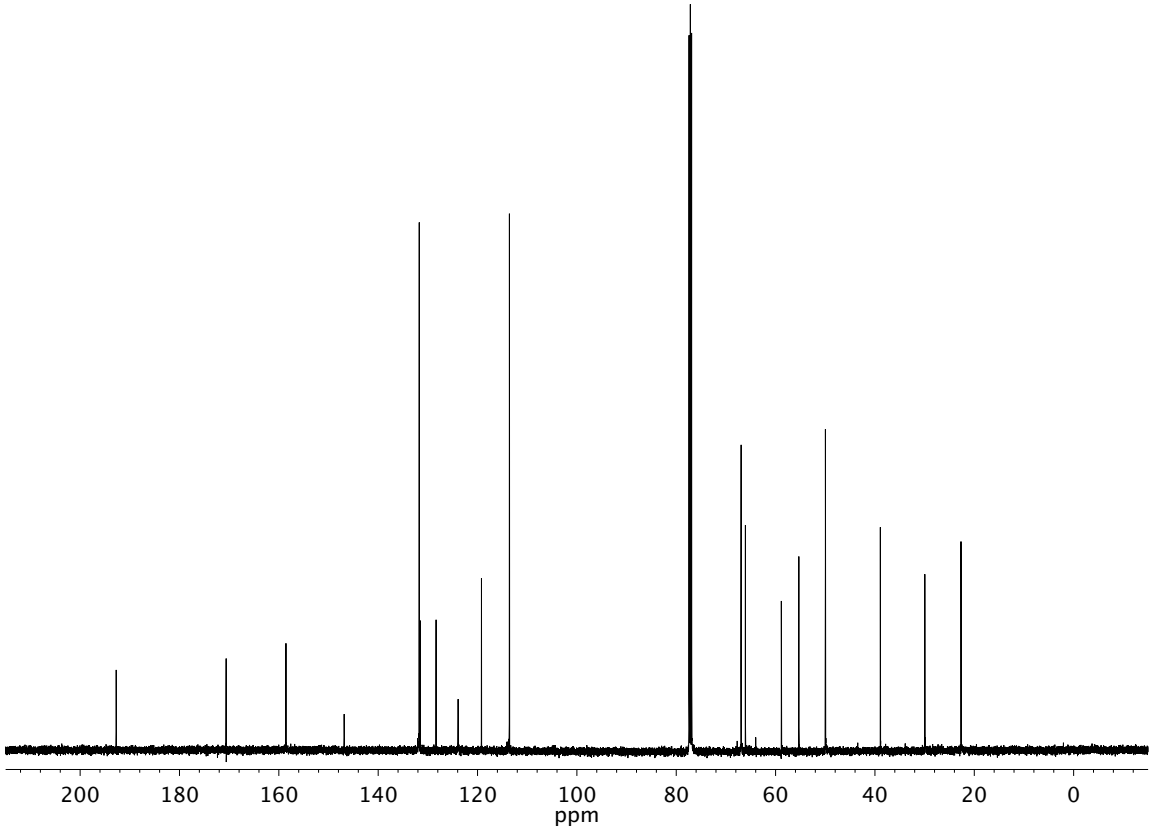
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65h**.



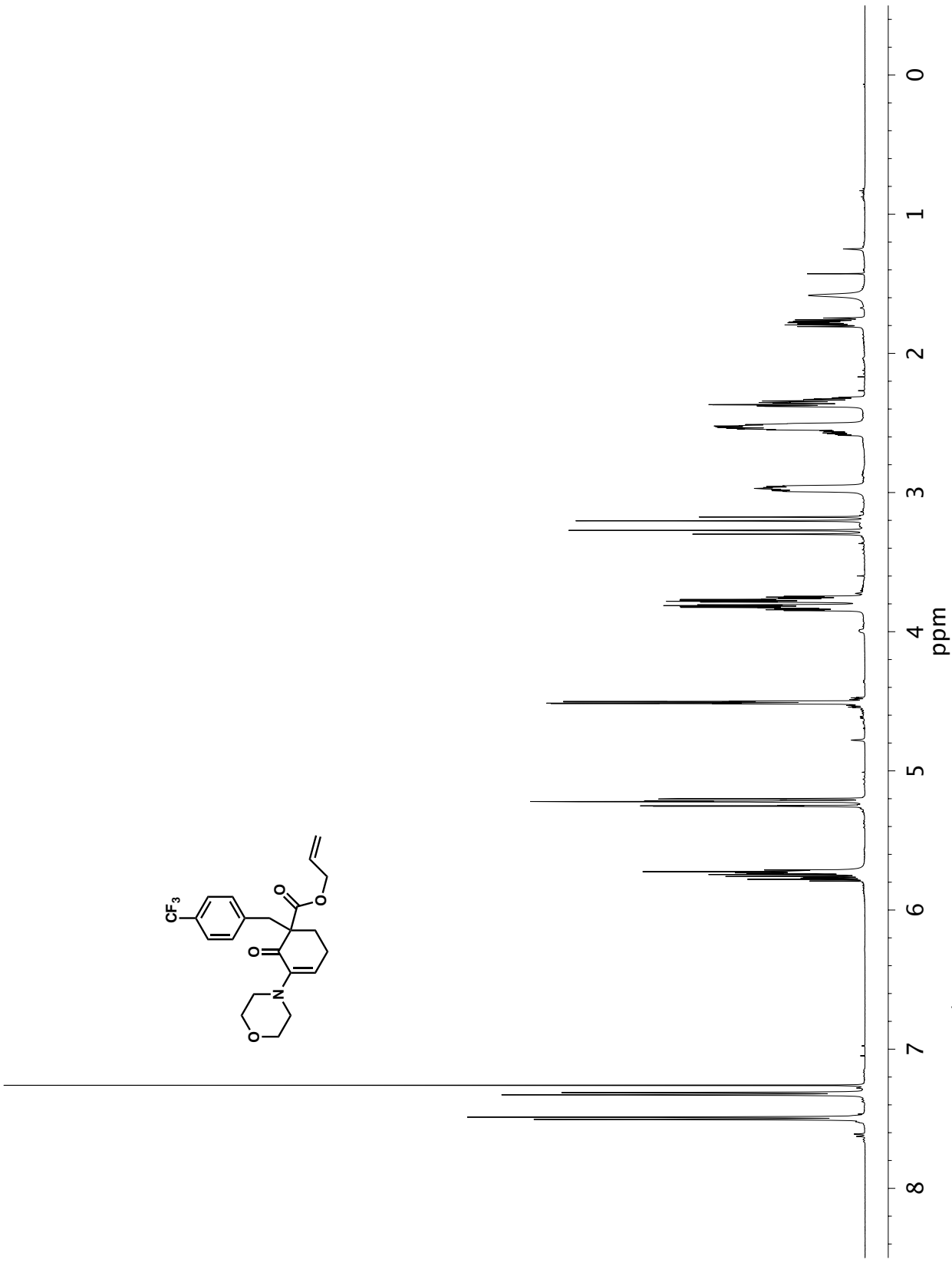
^{1}H NMR (500 MHz, CDCl3) of compound **65i**.



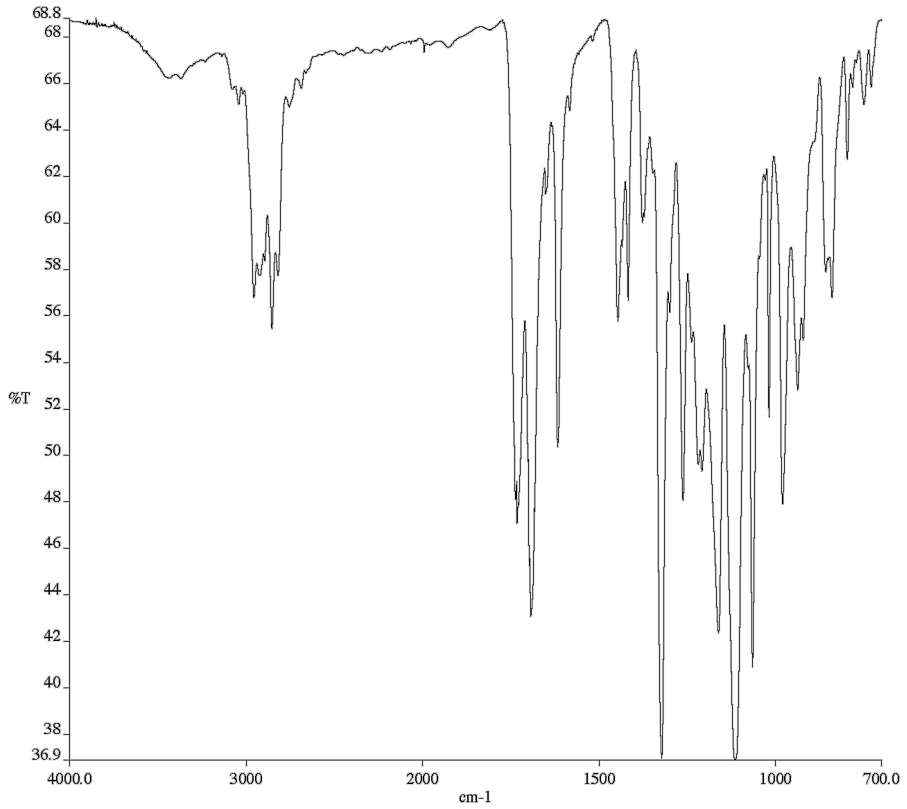
Infrared spectrum (Thin Film, NaCl) of compound **65i**.



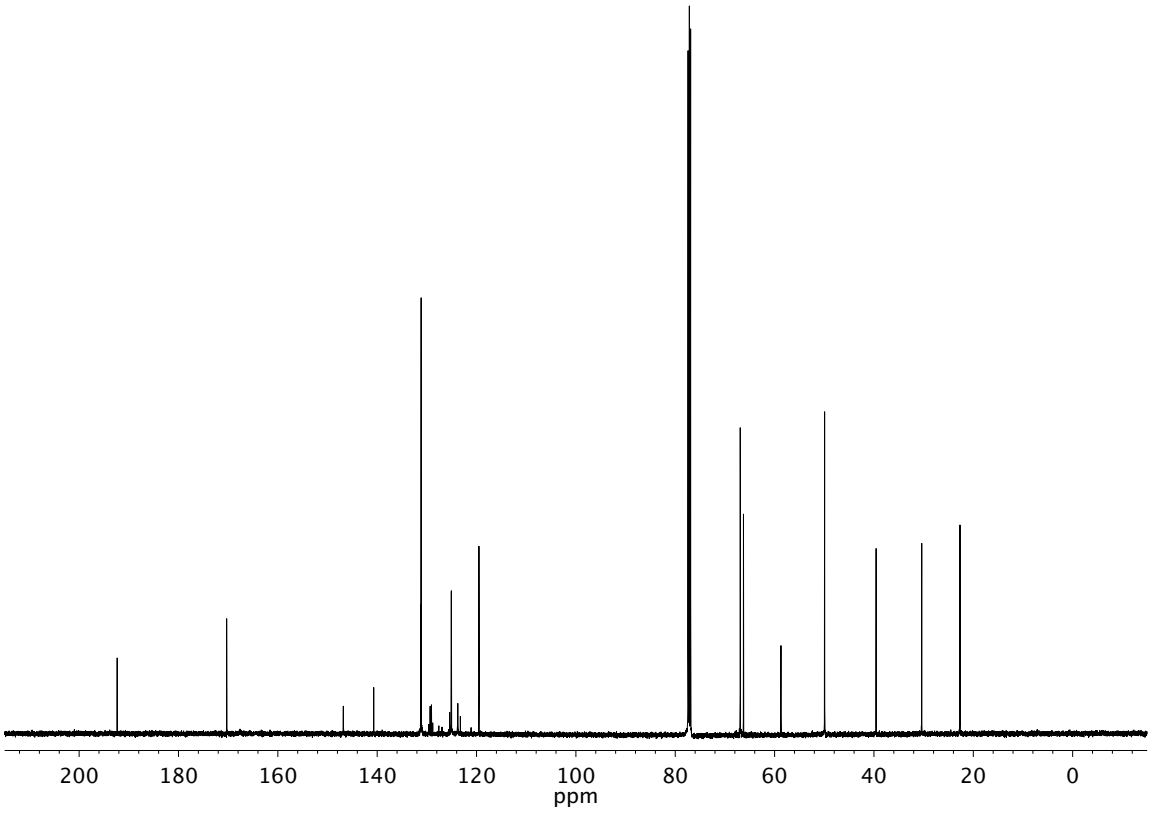
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65i**.



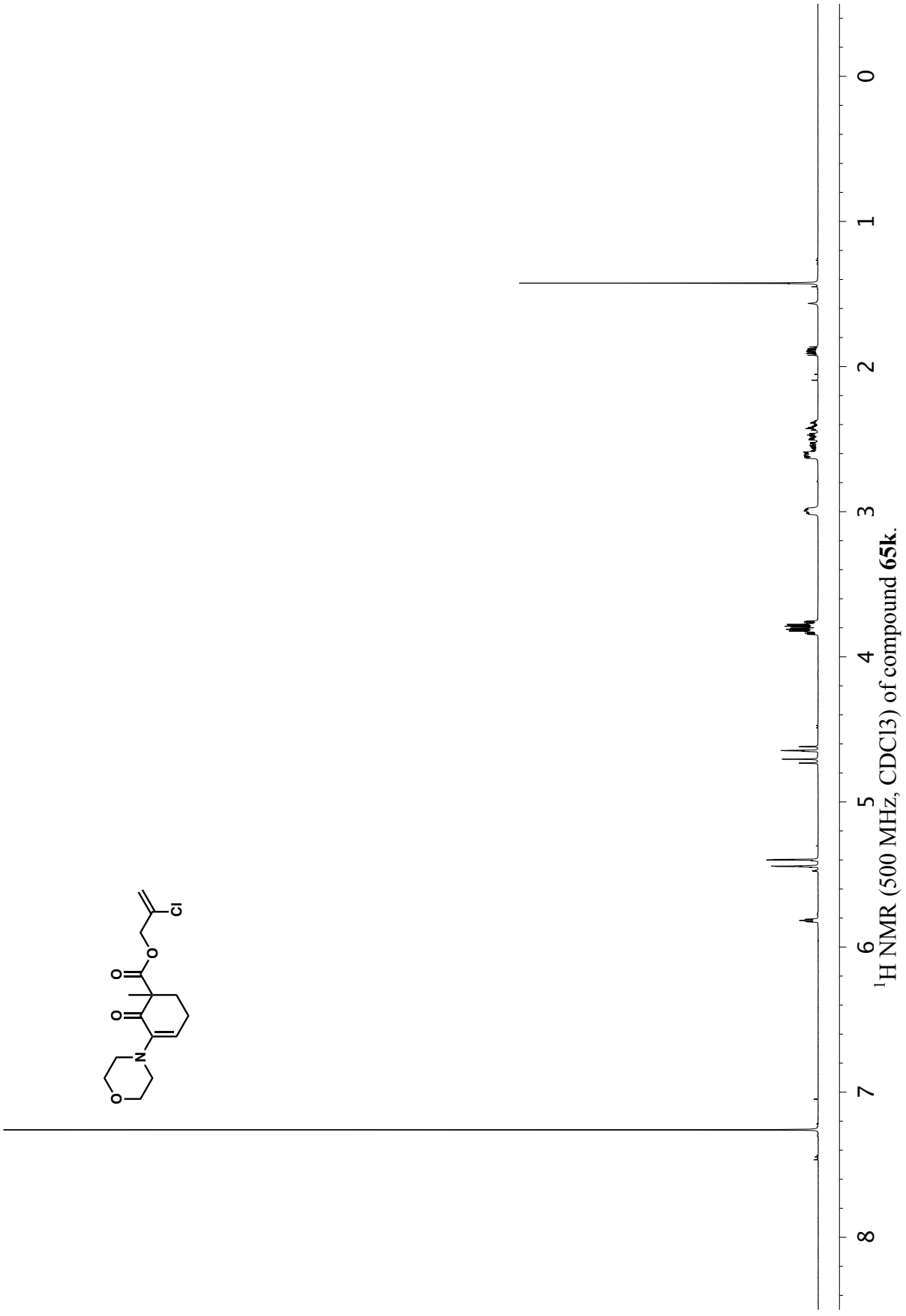
^{1}H NMR (500 MHz, CDCl3) of compound **65j**.



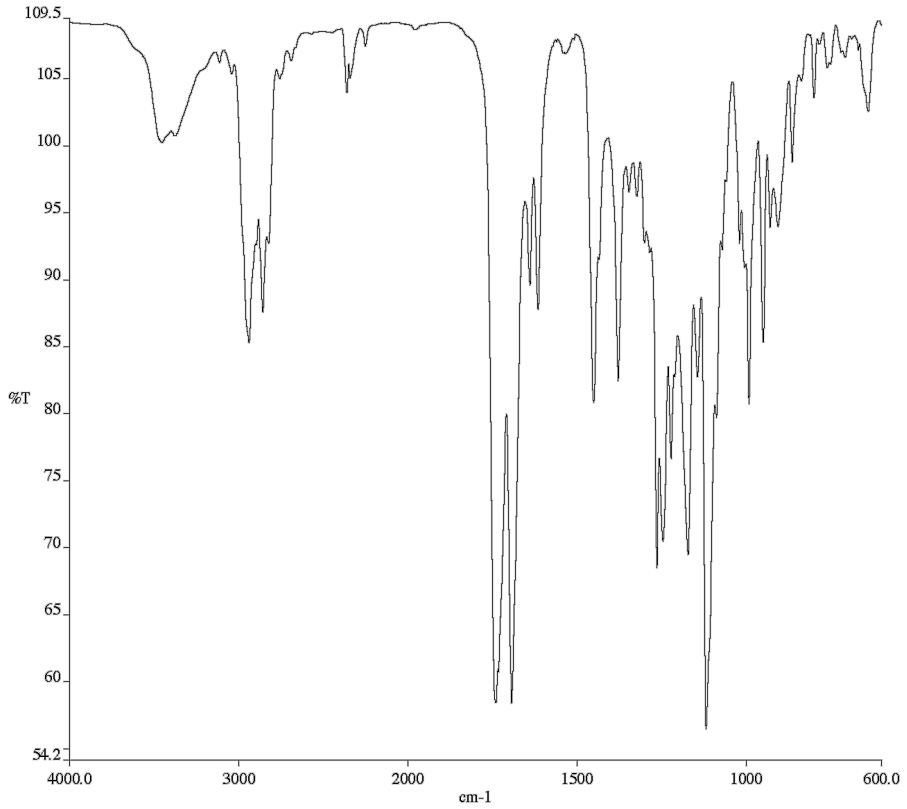
Infrared spectrum (Thin Film, NaCl) of compound **65j**.



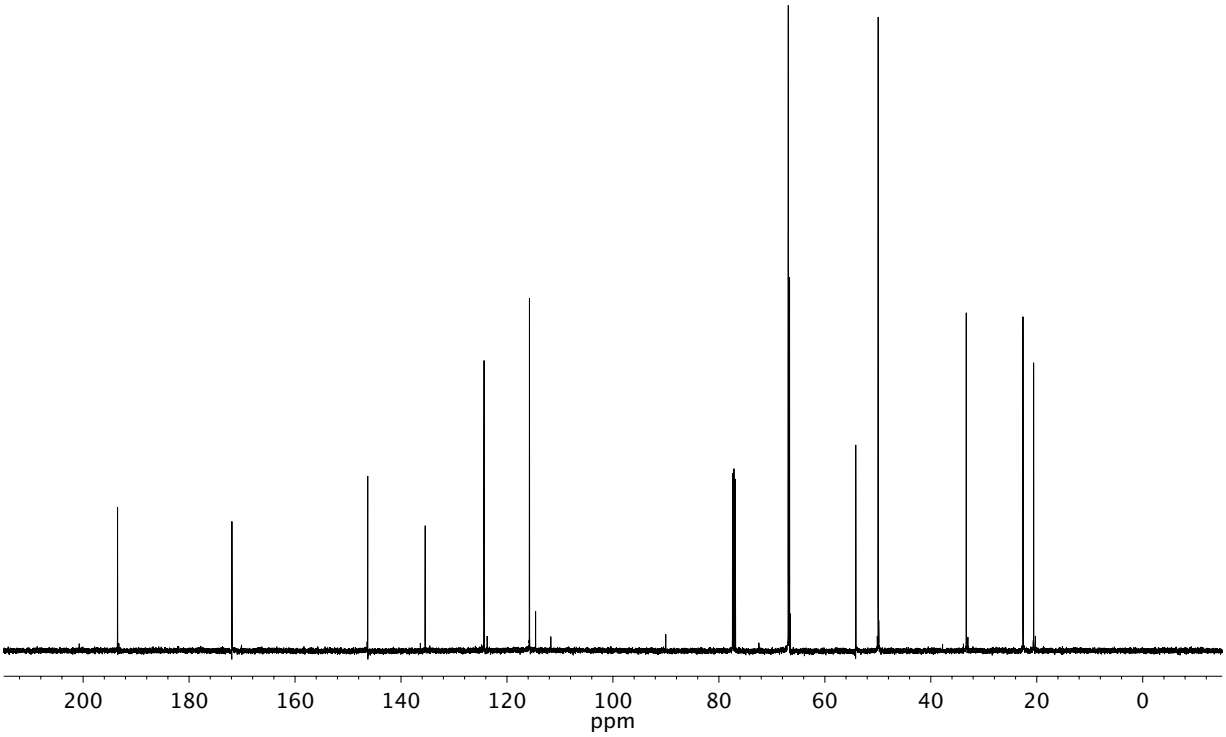
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65j**.



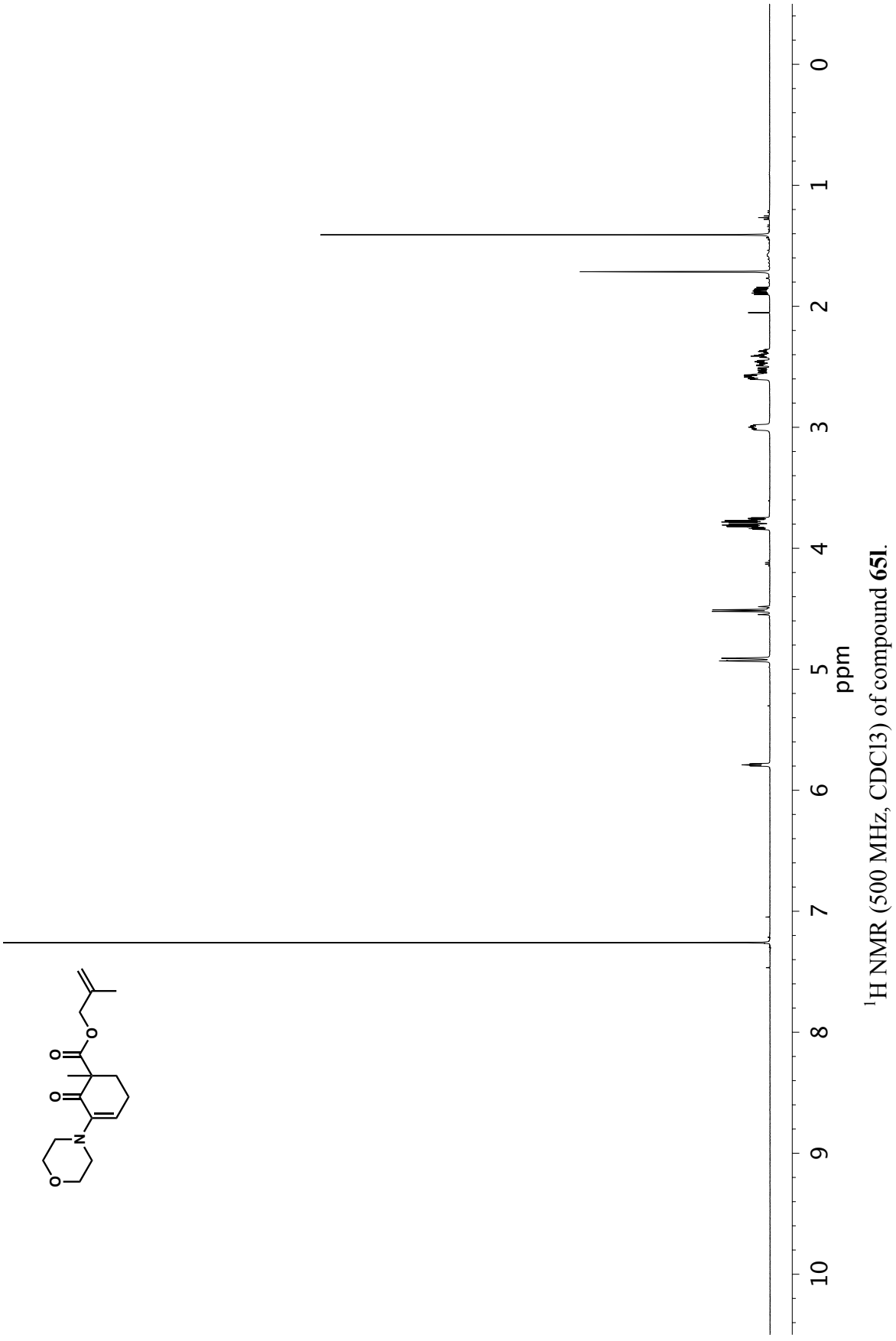
^{1}H NMR (500 MHz, CDCl3) of compound **65k**.



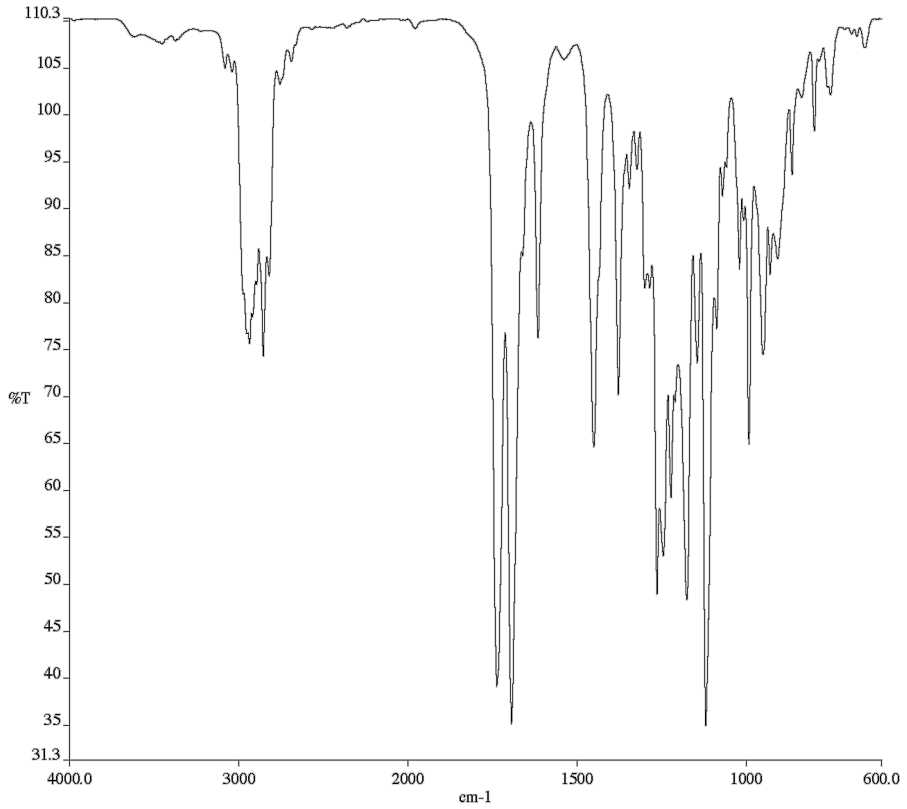
Infrared spectrum (Thin Film, NaCl) of compound **65k**.



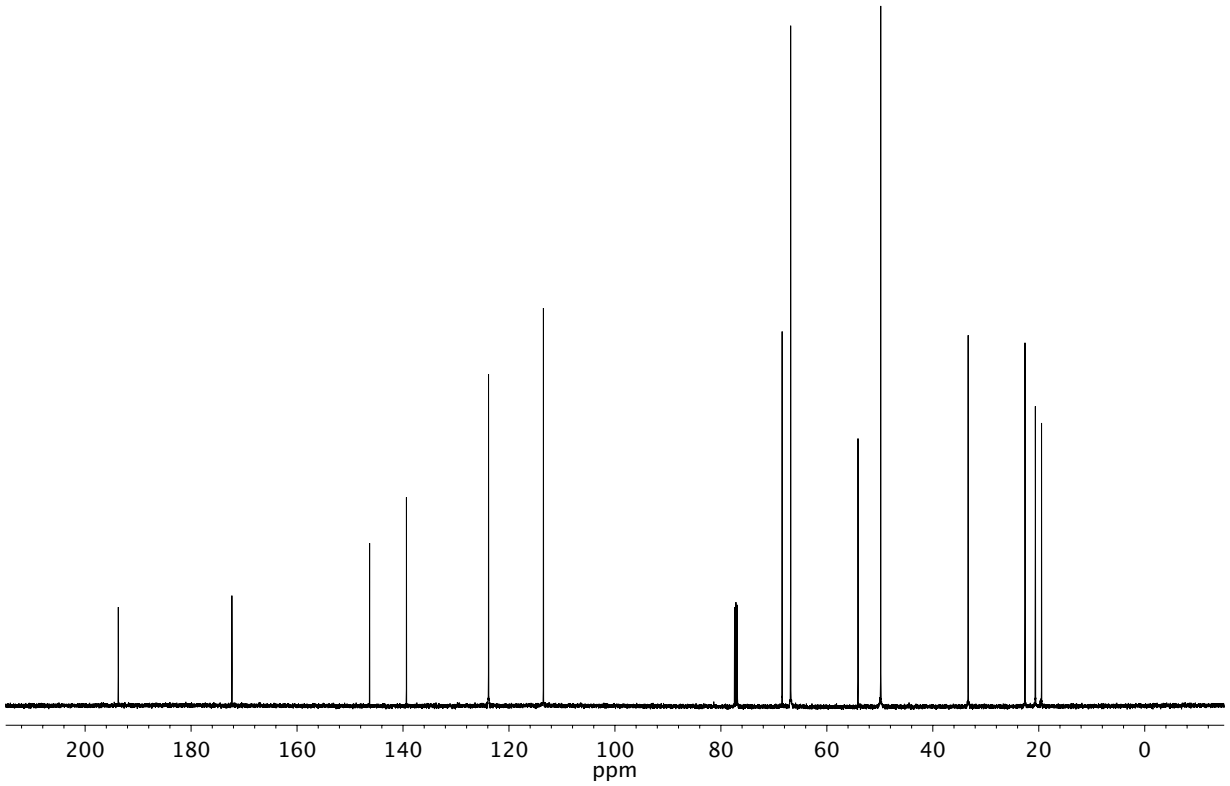
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65k**.



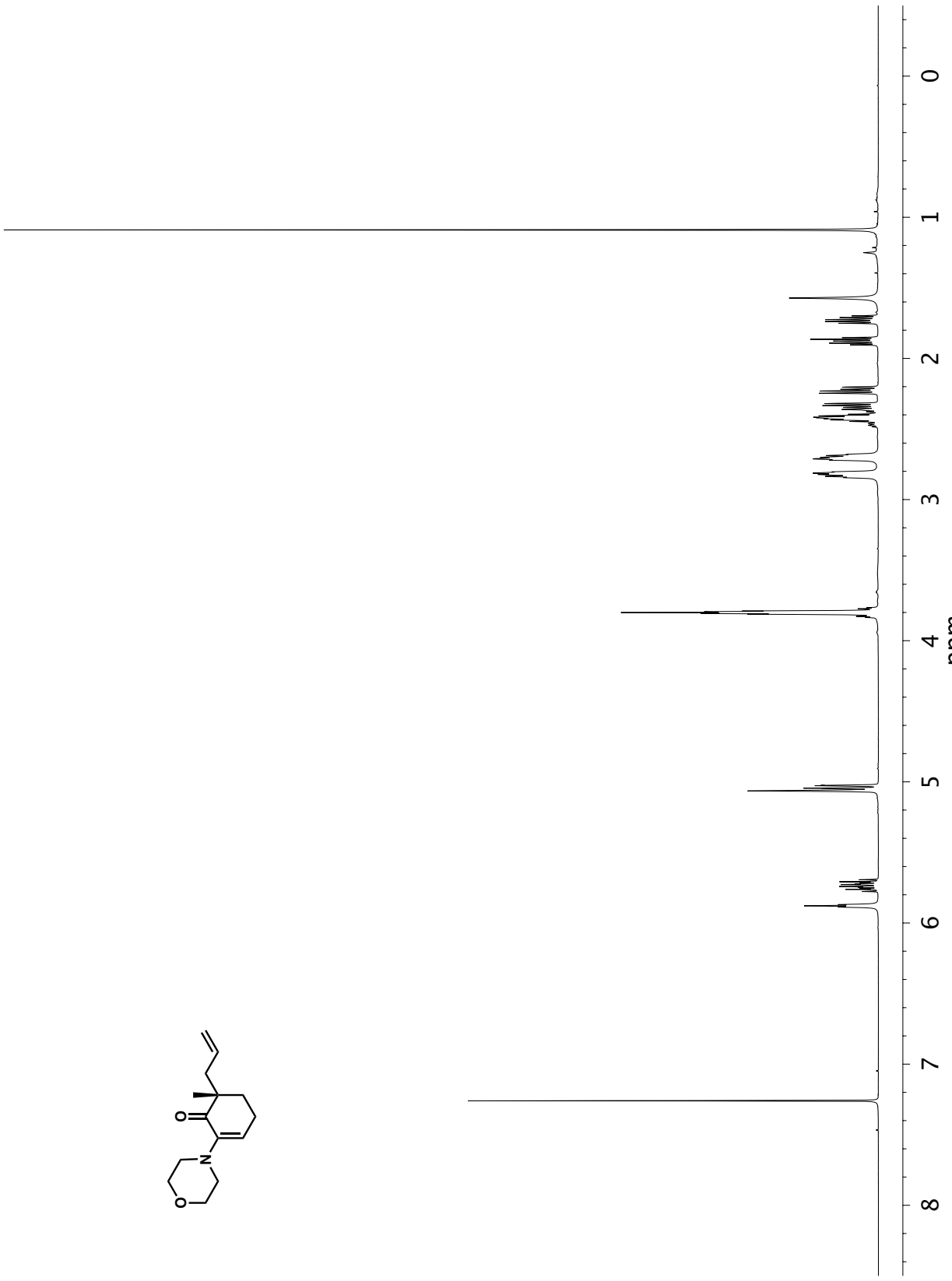
^{1}H NMR (500 MHz, CDCl3) of compound **65l**.



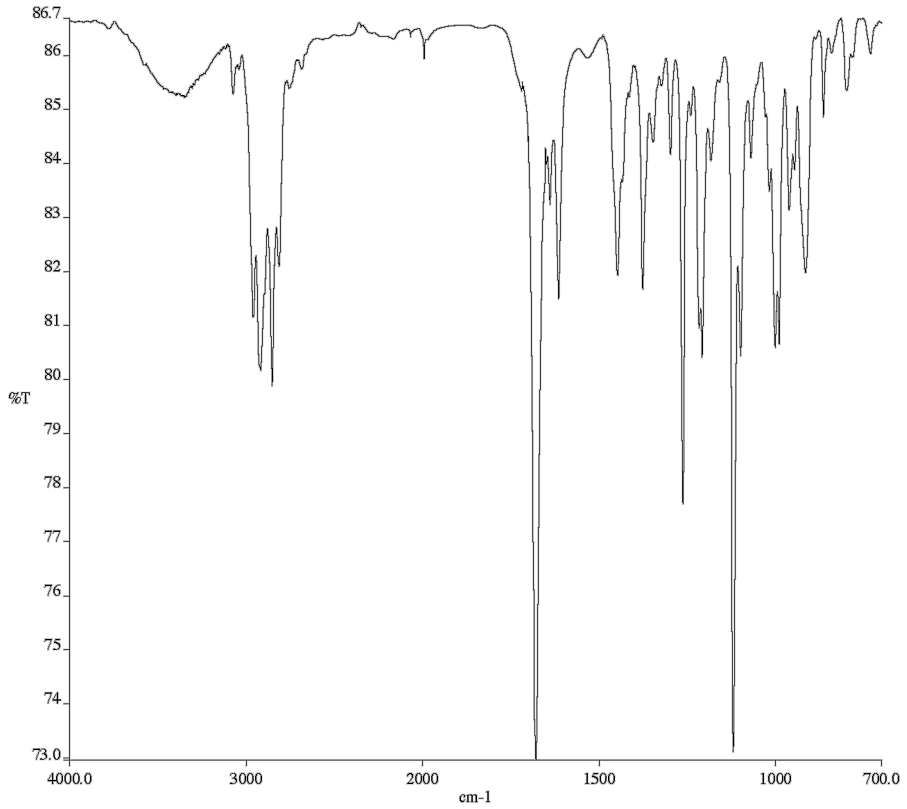
Infrared spectrum (Thin Film, NaCl) of compound **65l**



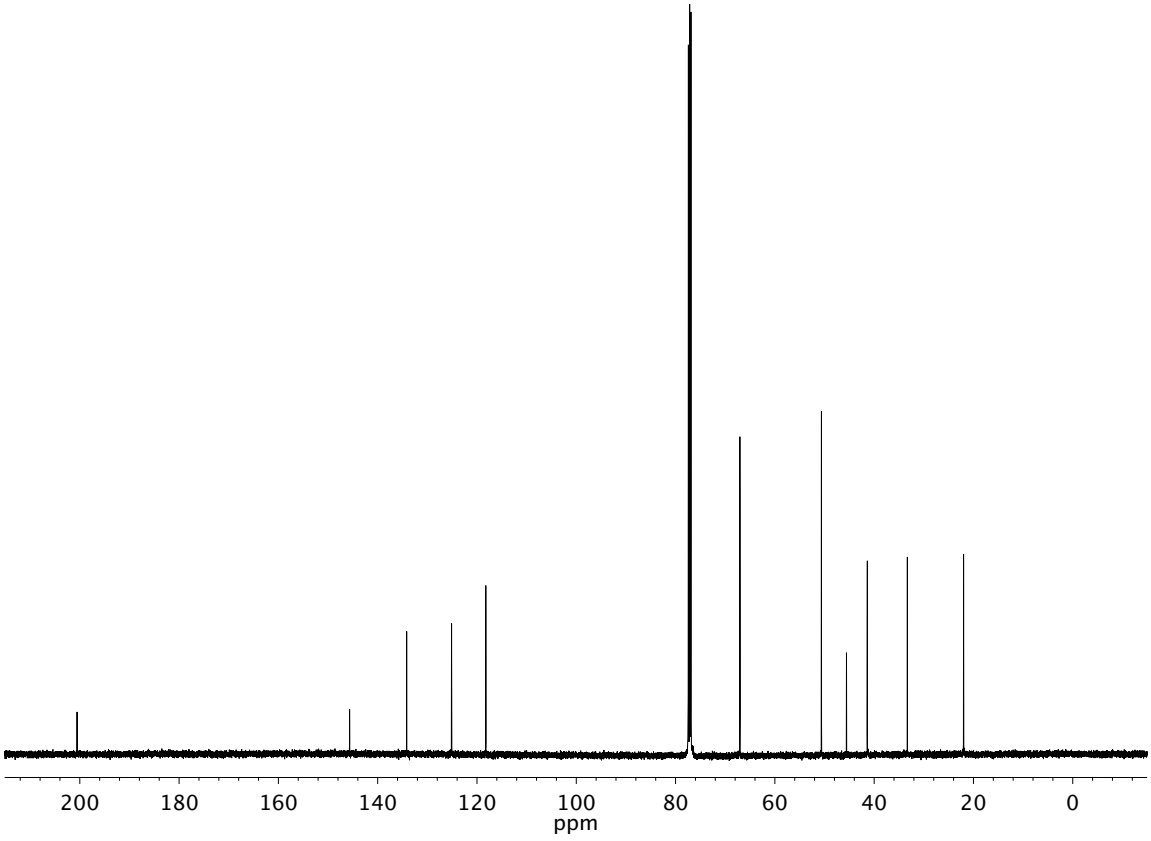
^{13}C NMR (125 MHz, $CDCl_3$) of compound **65l**.



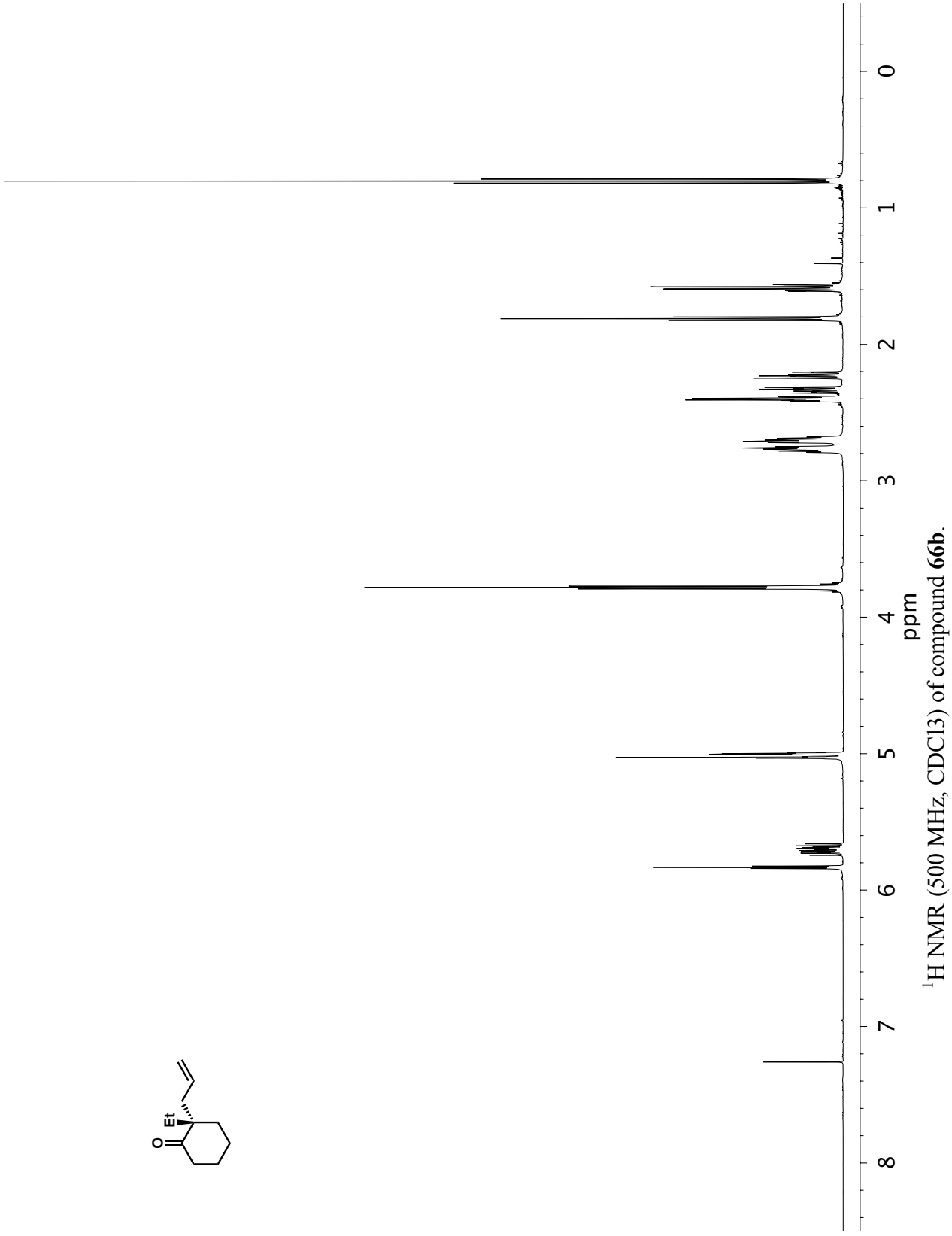
^{1}H NMR (500 MHz, CDCl3) of compound **66a**.



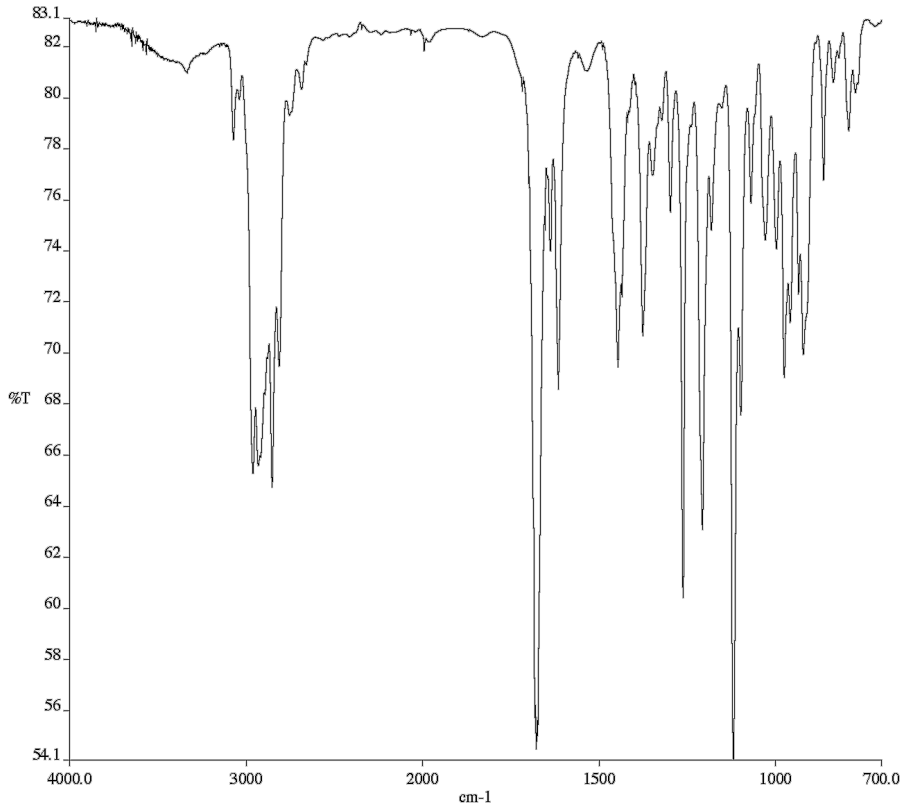
Infrared spectrum (Thin Film, NaCl) of compound **66a**.



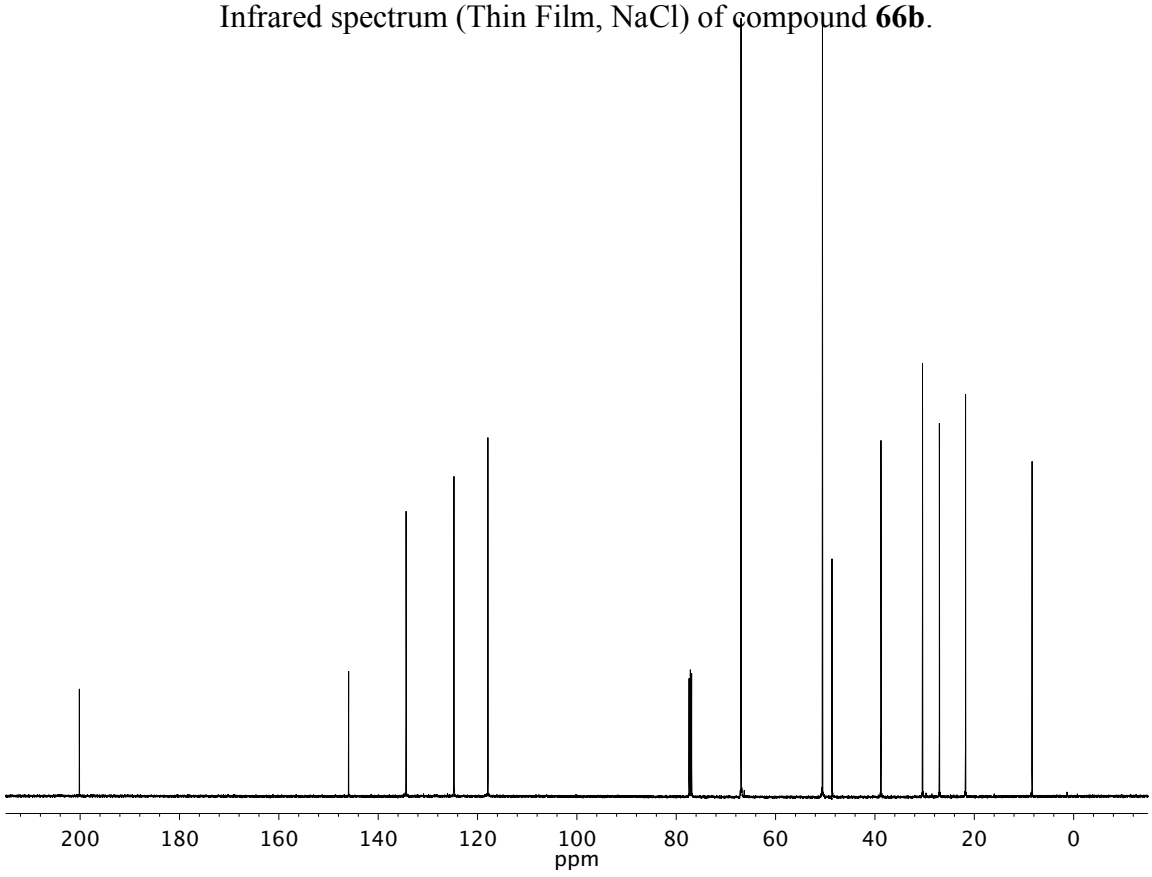
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66a**.



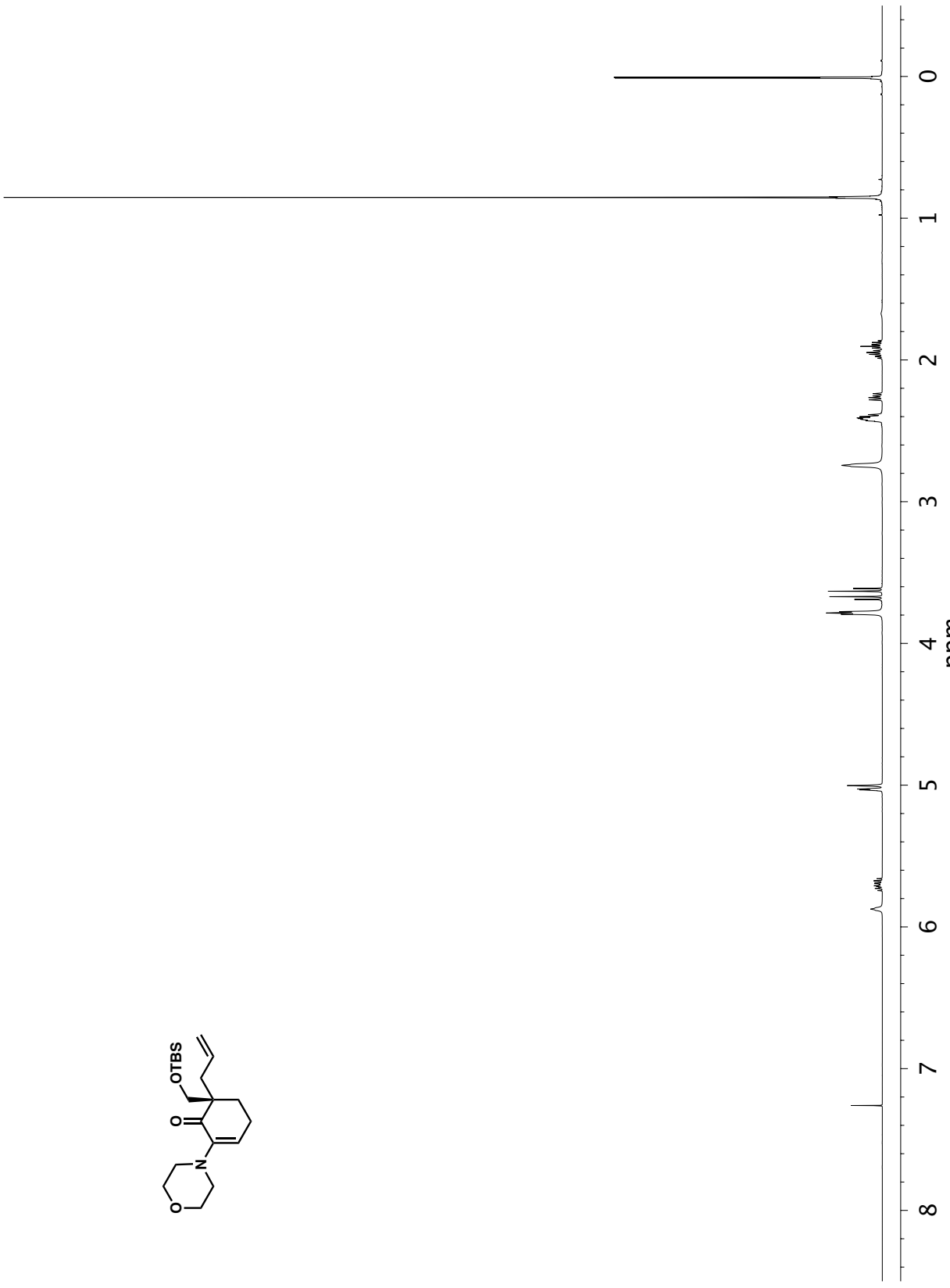
^{1}H NMR (500 MHz, CDCl3) of compound **66b**.



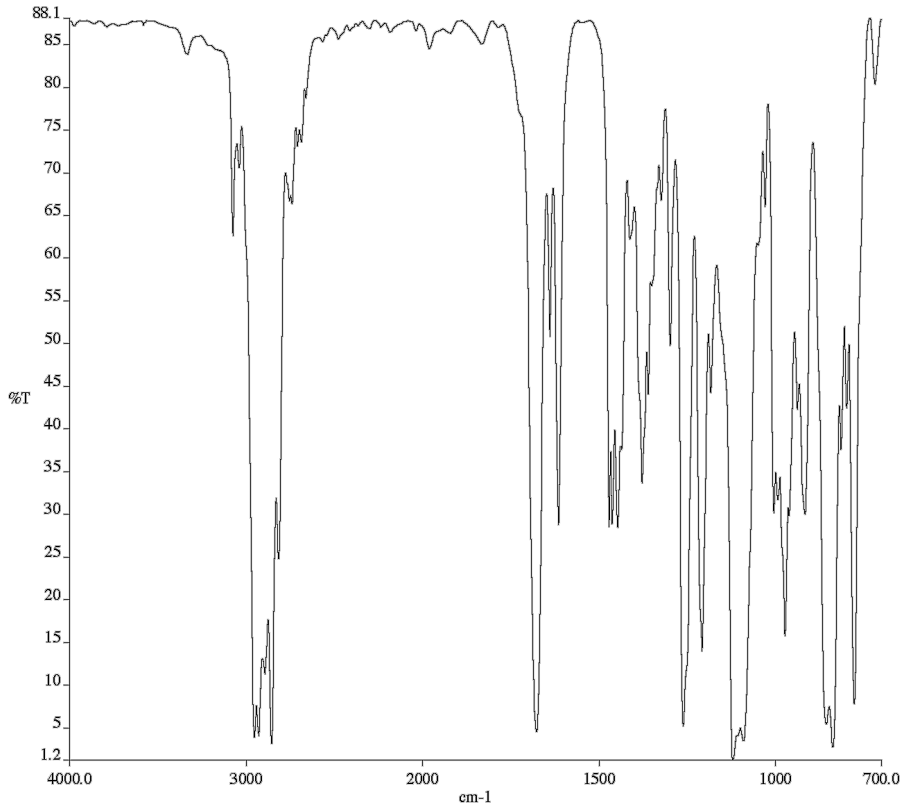
Infrared spectrum (Thin Film, NaCl) of compound **66b**.



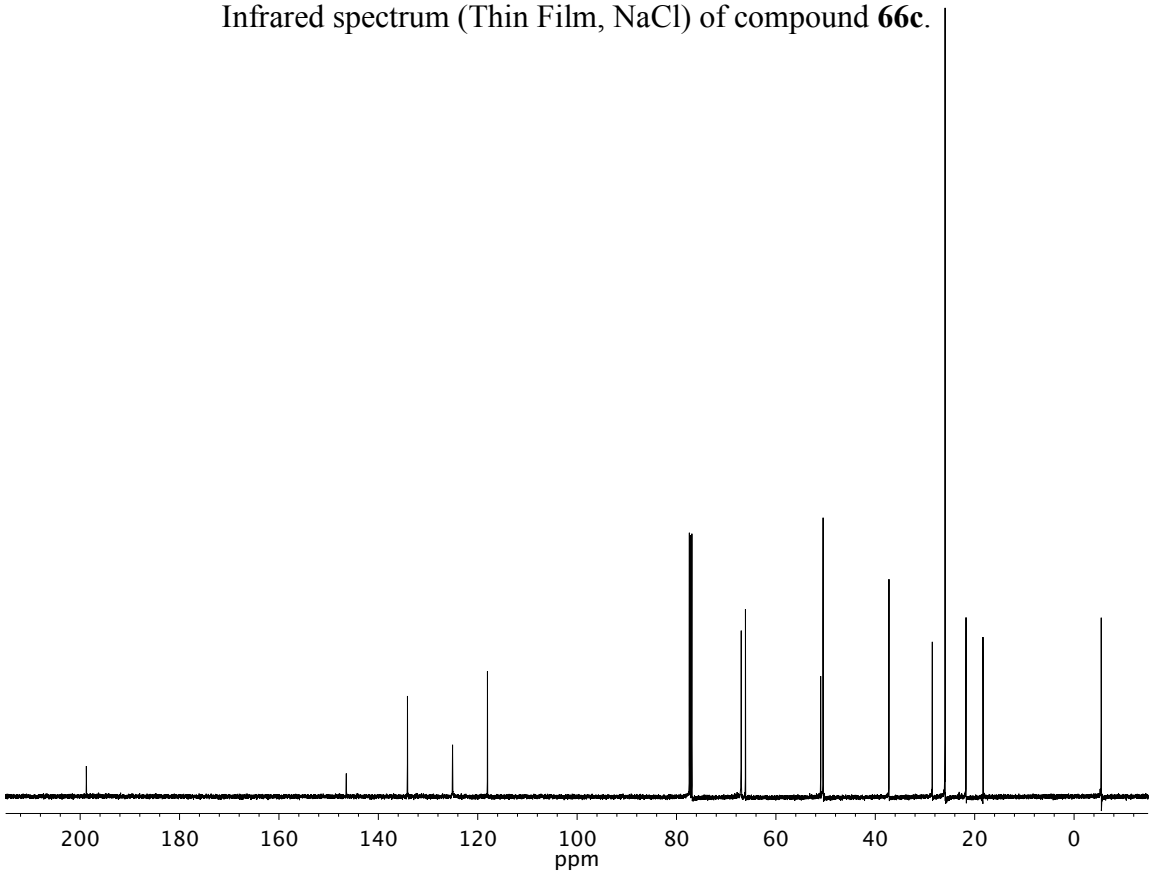
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66b**.



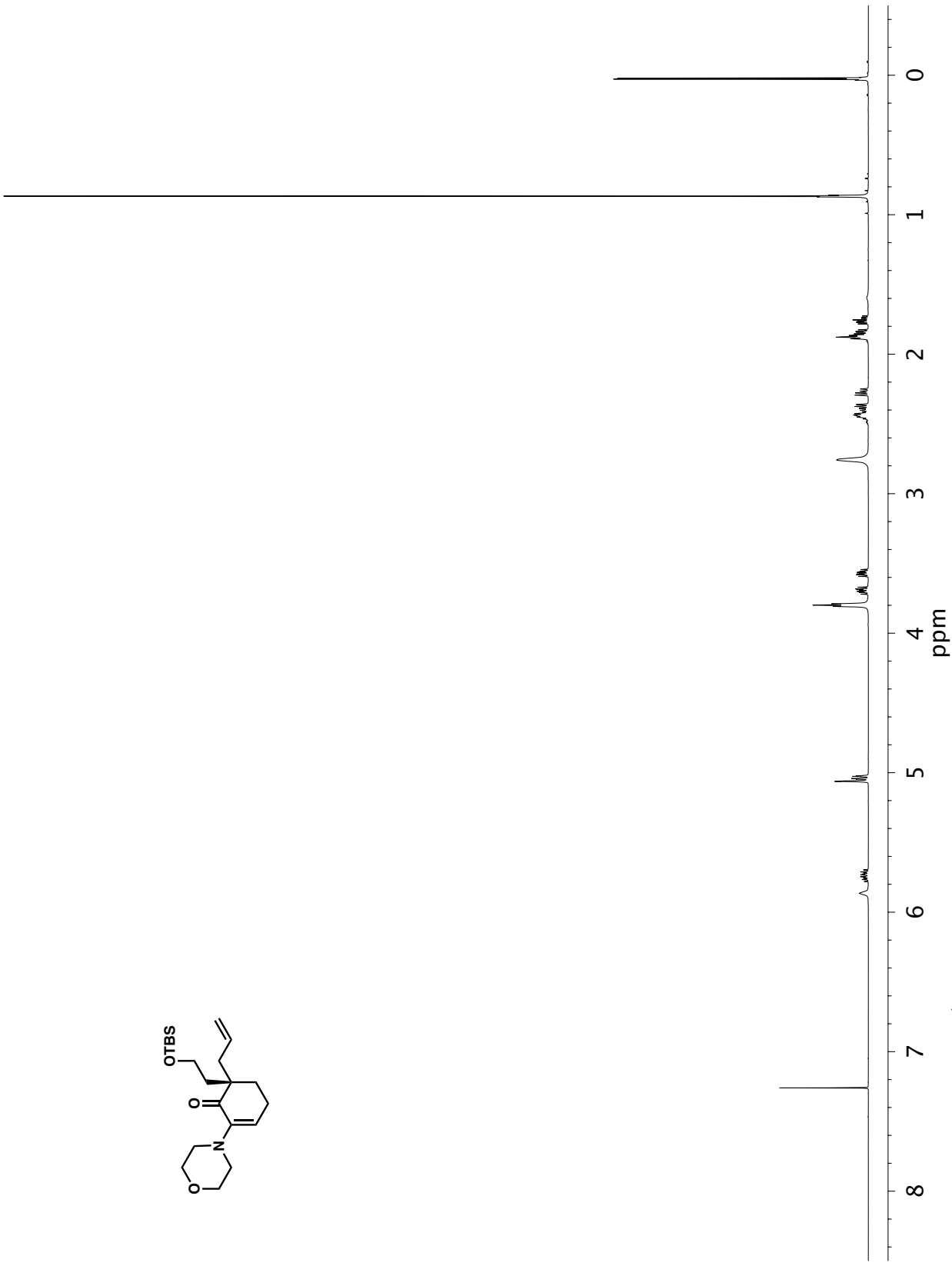
^{1}H NMR (500 MHz, CDCl3) of compound **66c**.



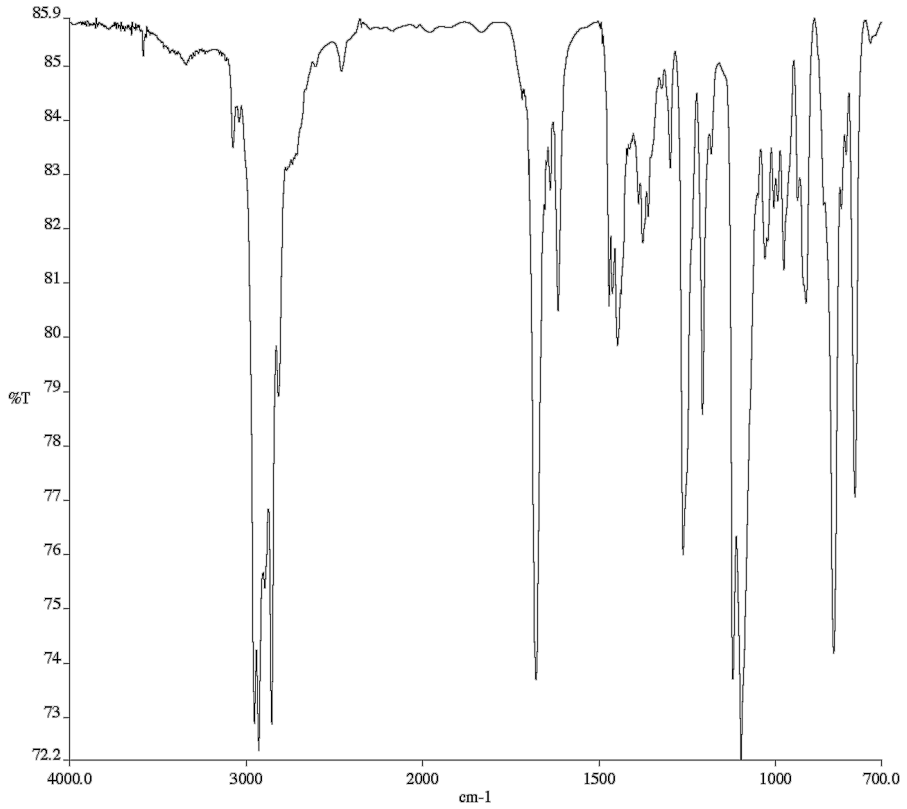
Infrared spectrum (Thin Film, NaCl) of compound **66c**.



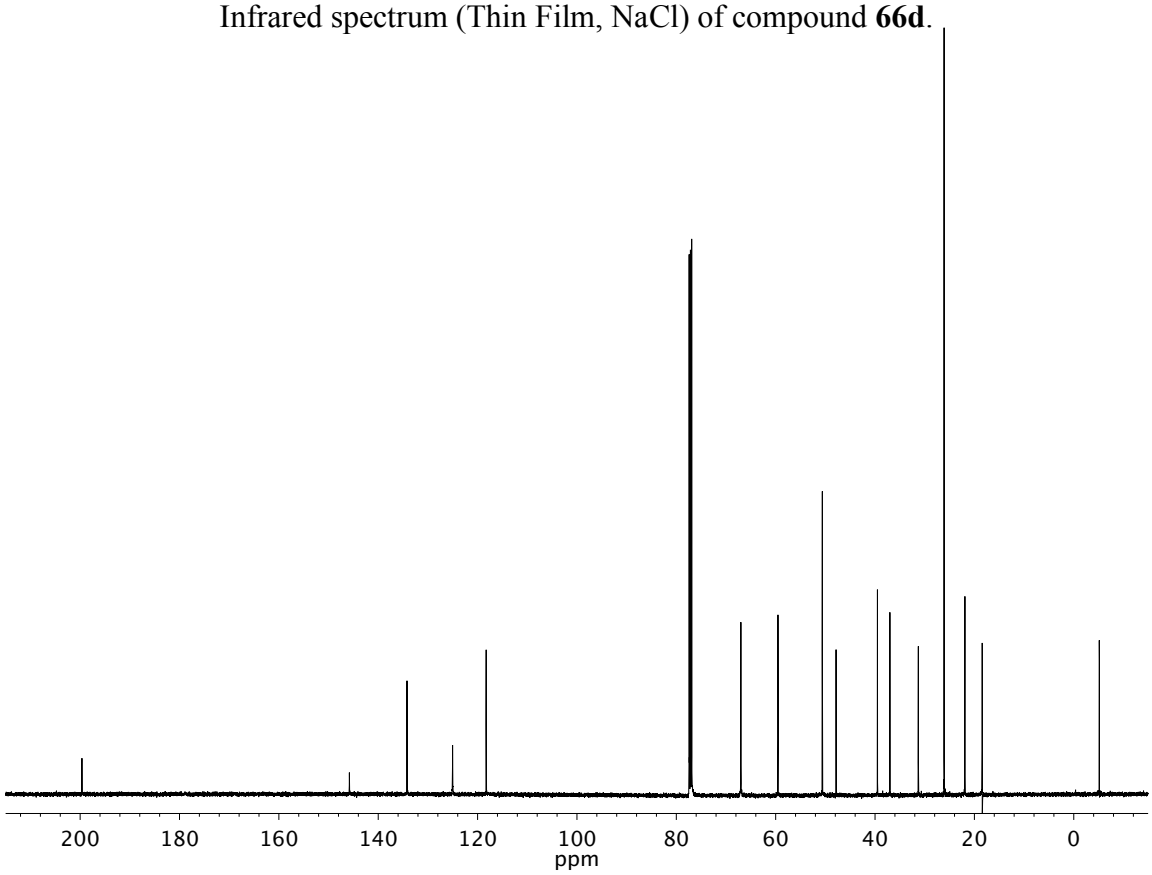
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66c**.



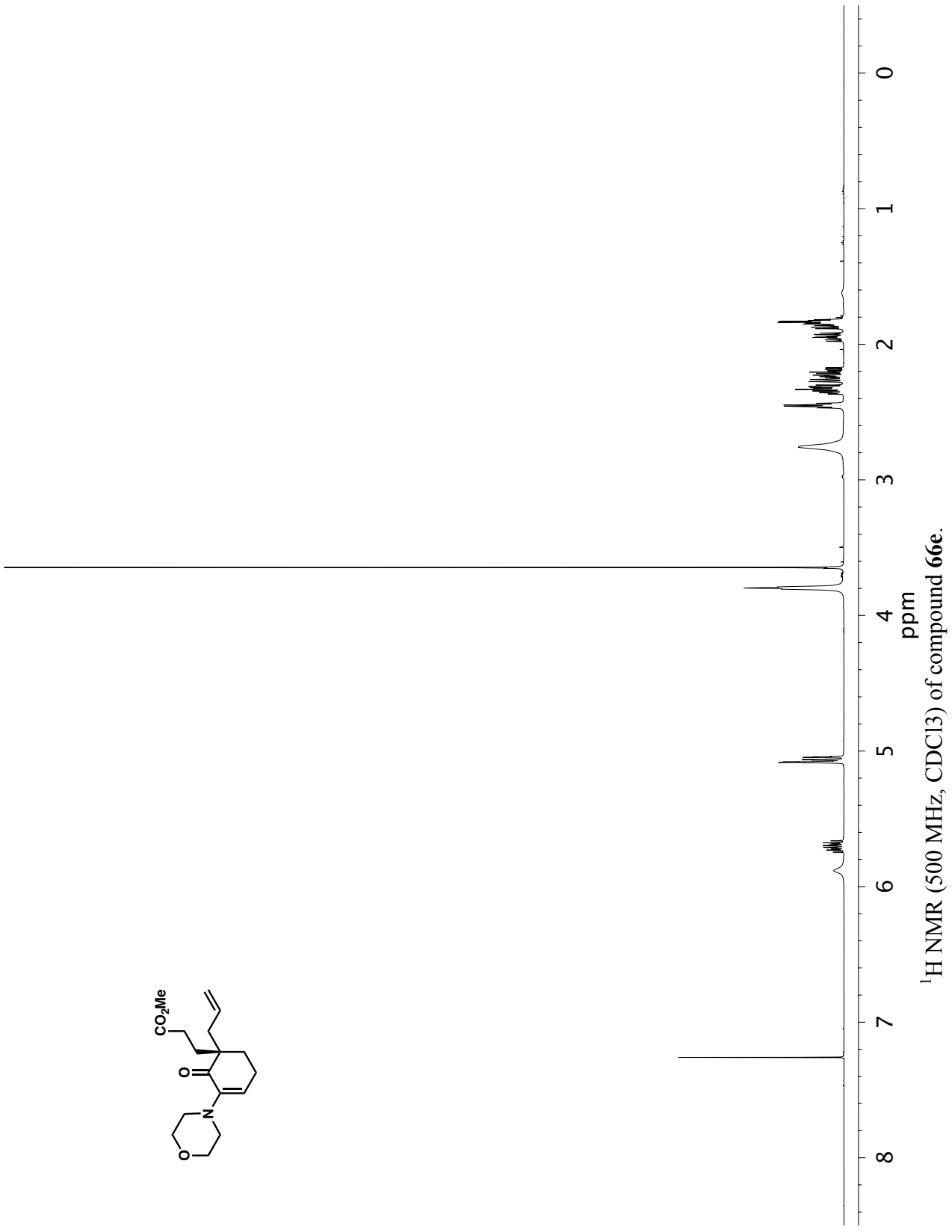
^{1}H NMR (500 MHz, CDCl3) of compound **66d**.



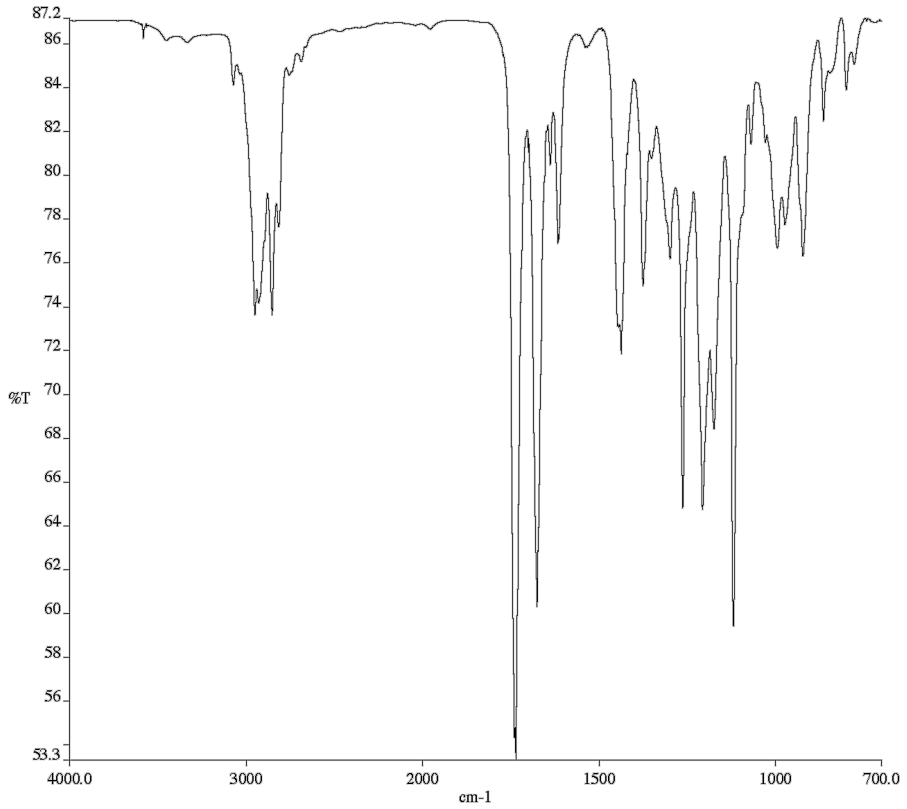
Infrared spectrum (Thin Film, NaCl) of compound **66d**.



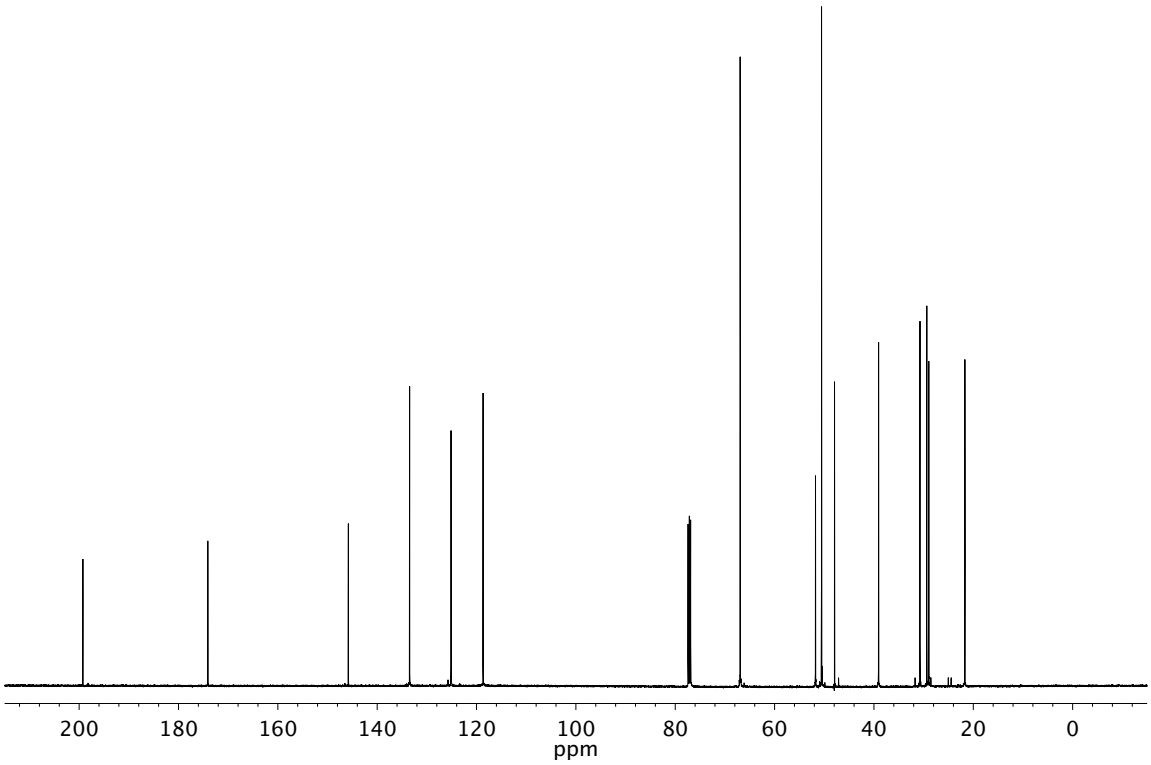
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66d**.



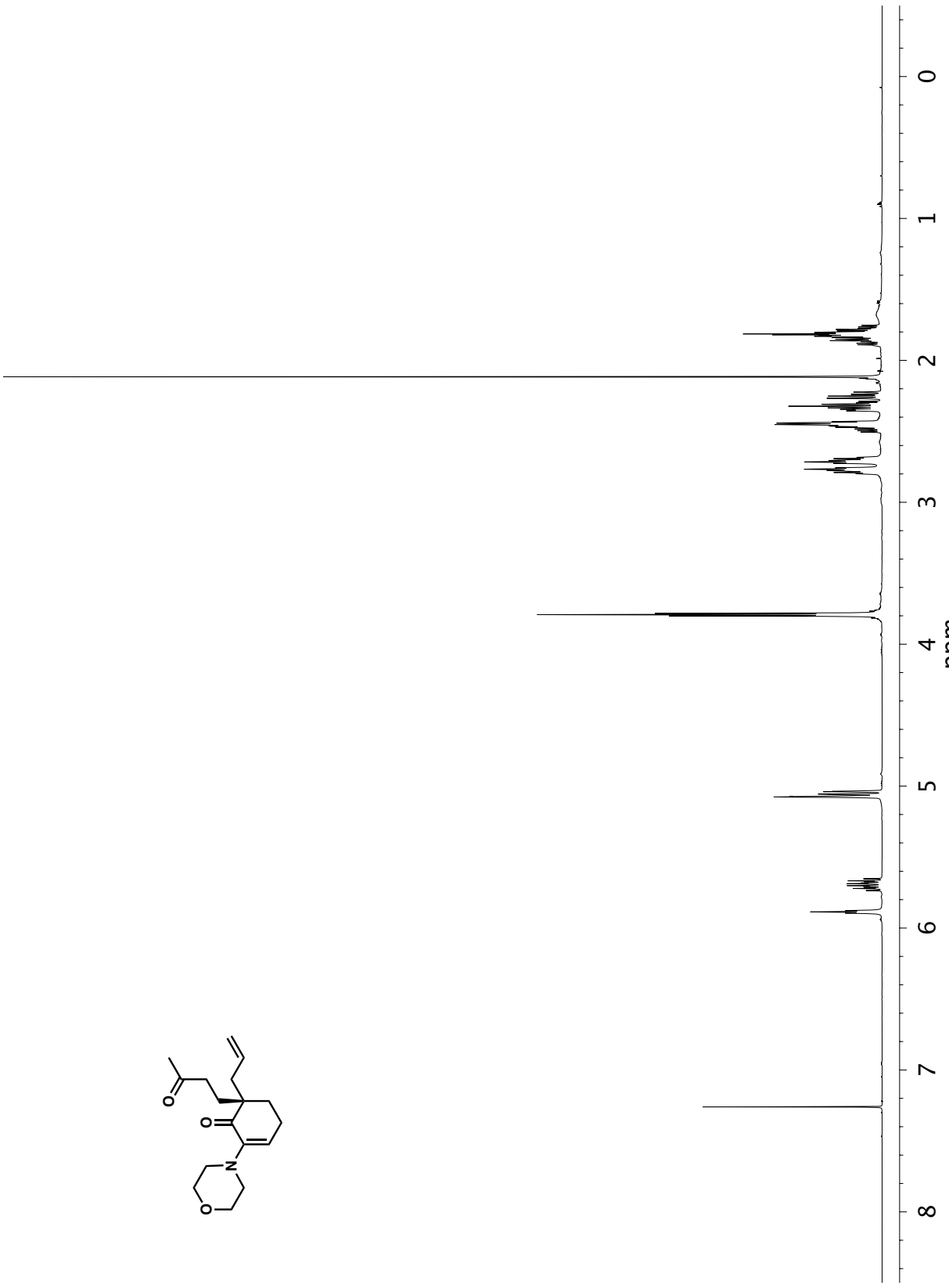
^{1}H NMR (500 MHz, CDCl3) of compound **66e**.



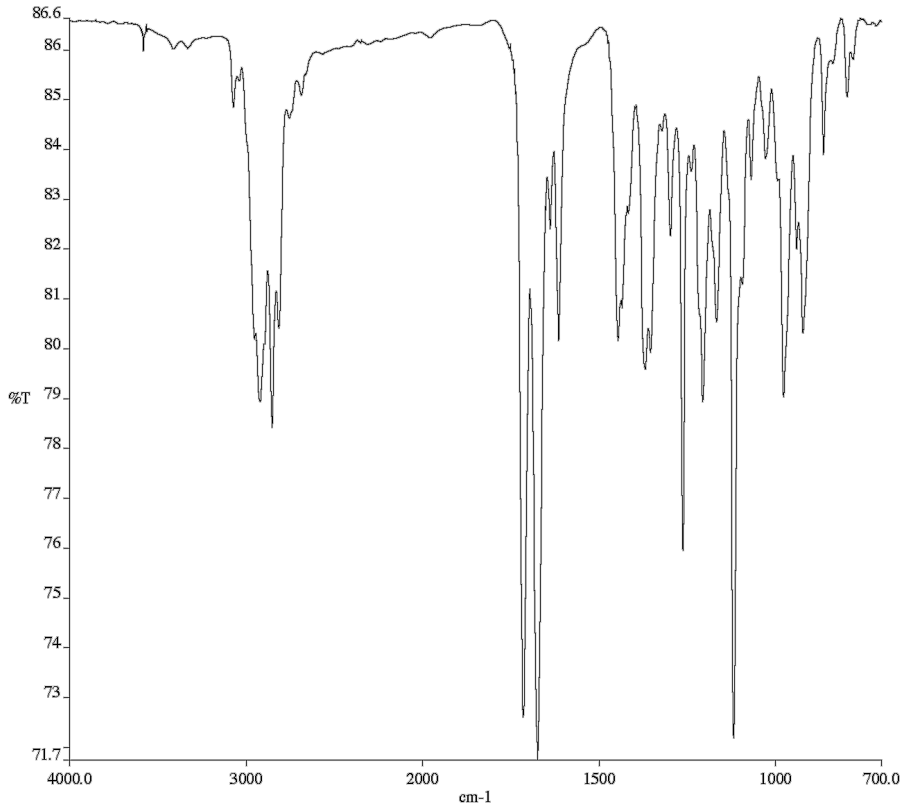
Infrared spectrum (Thin Film, NaCl) of compound **66e**.



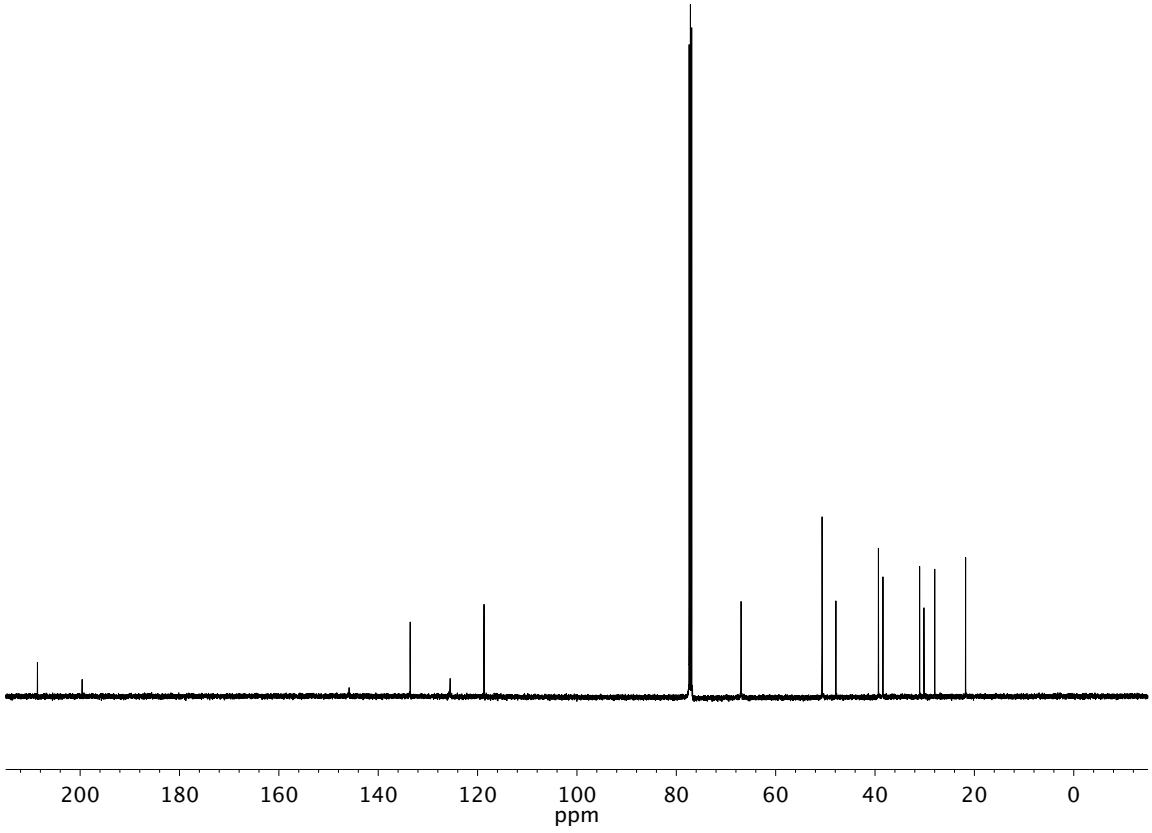
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66e**.



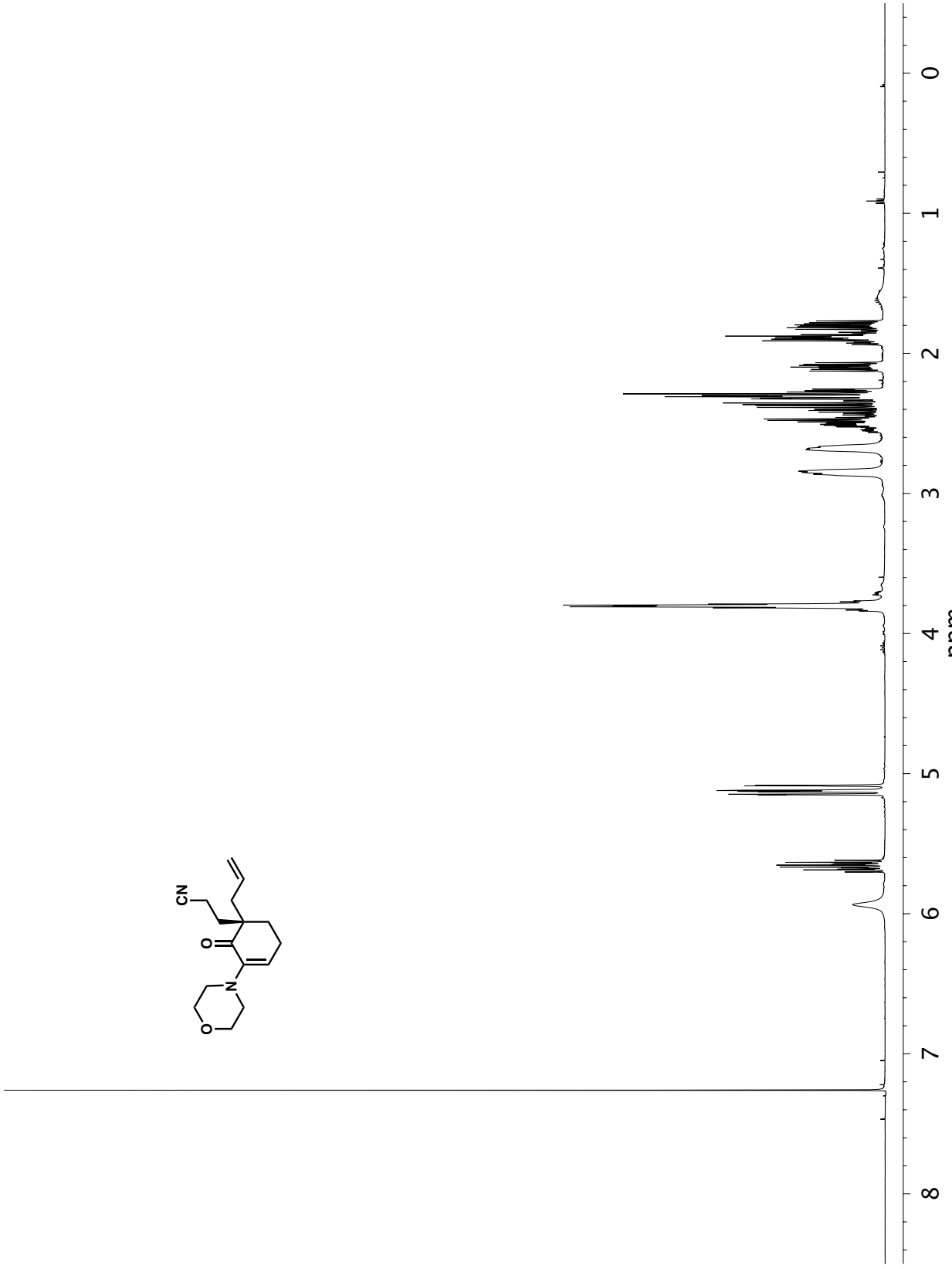
^{1}H NMR (500 MHz, CDCl3) of compound **66f**.



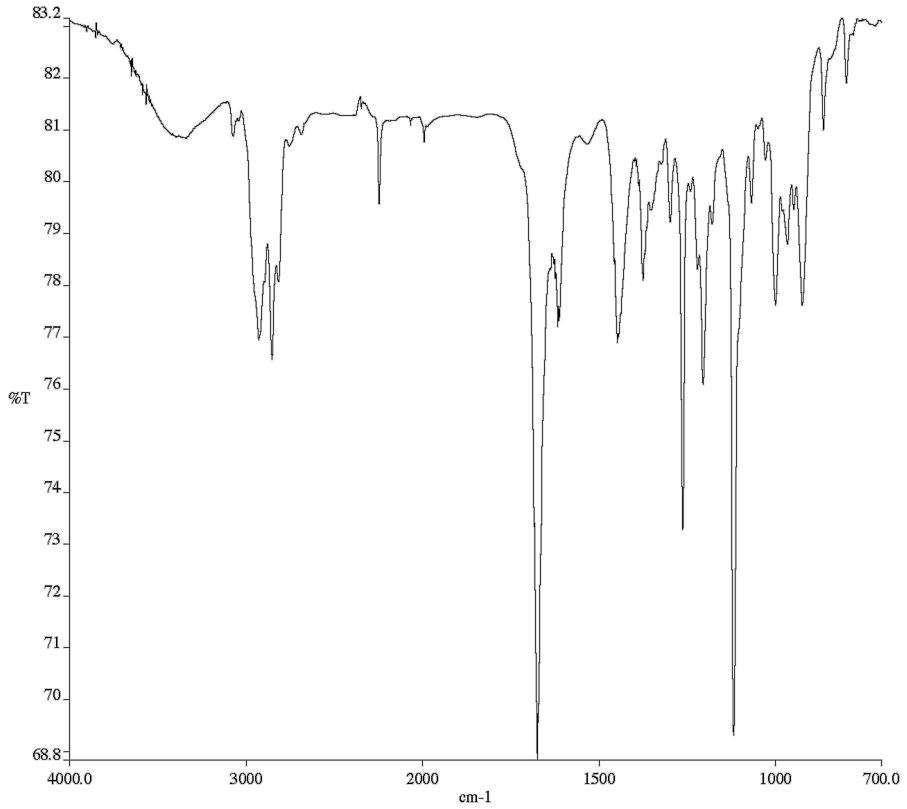
Infrared spectrum (Thin Film, NaCl) of compound **66f**.



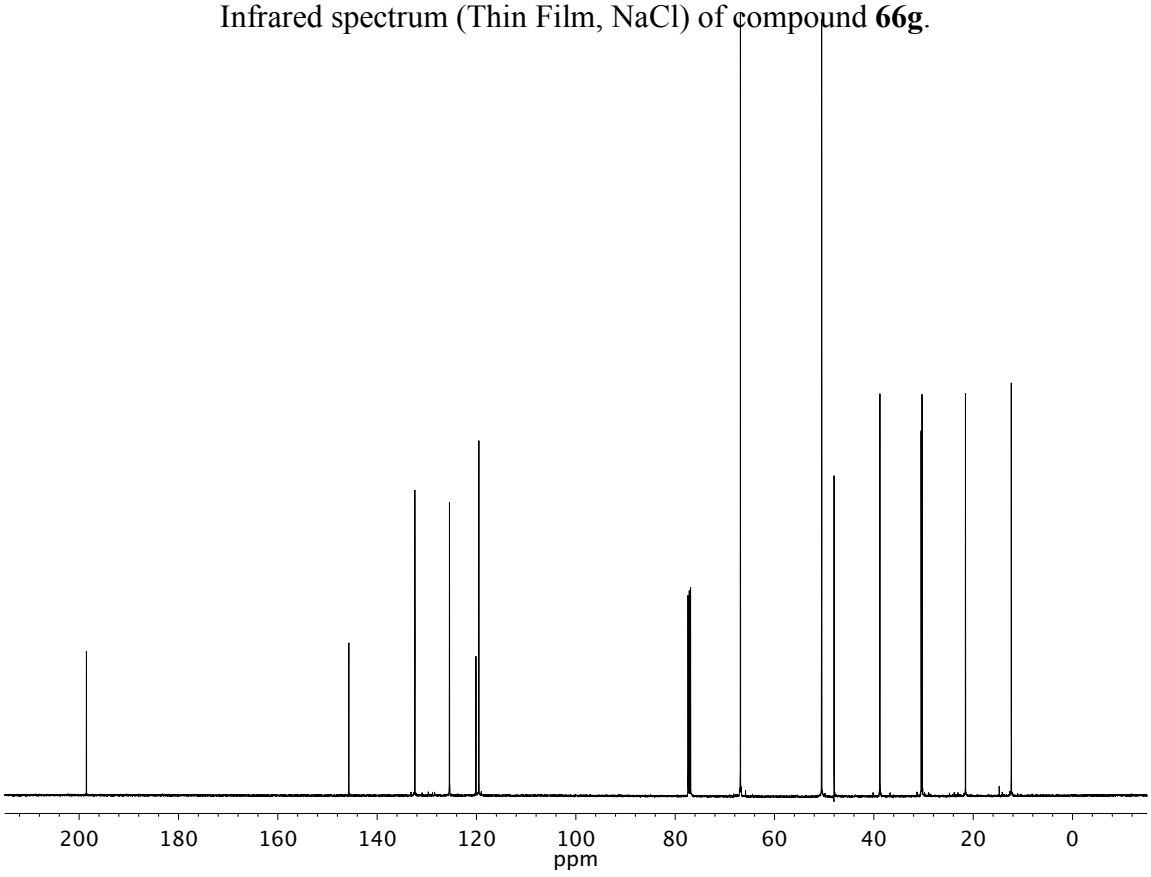
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66f**.



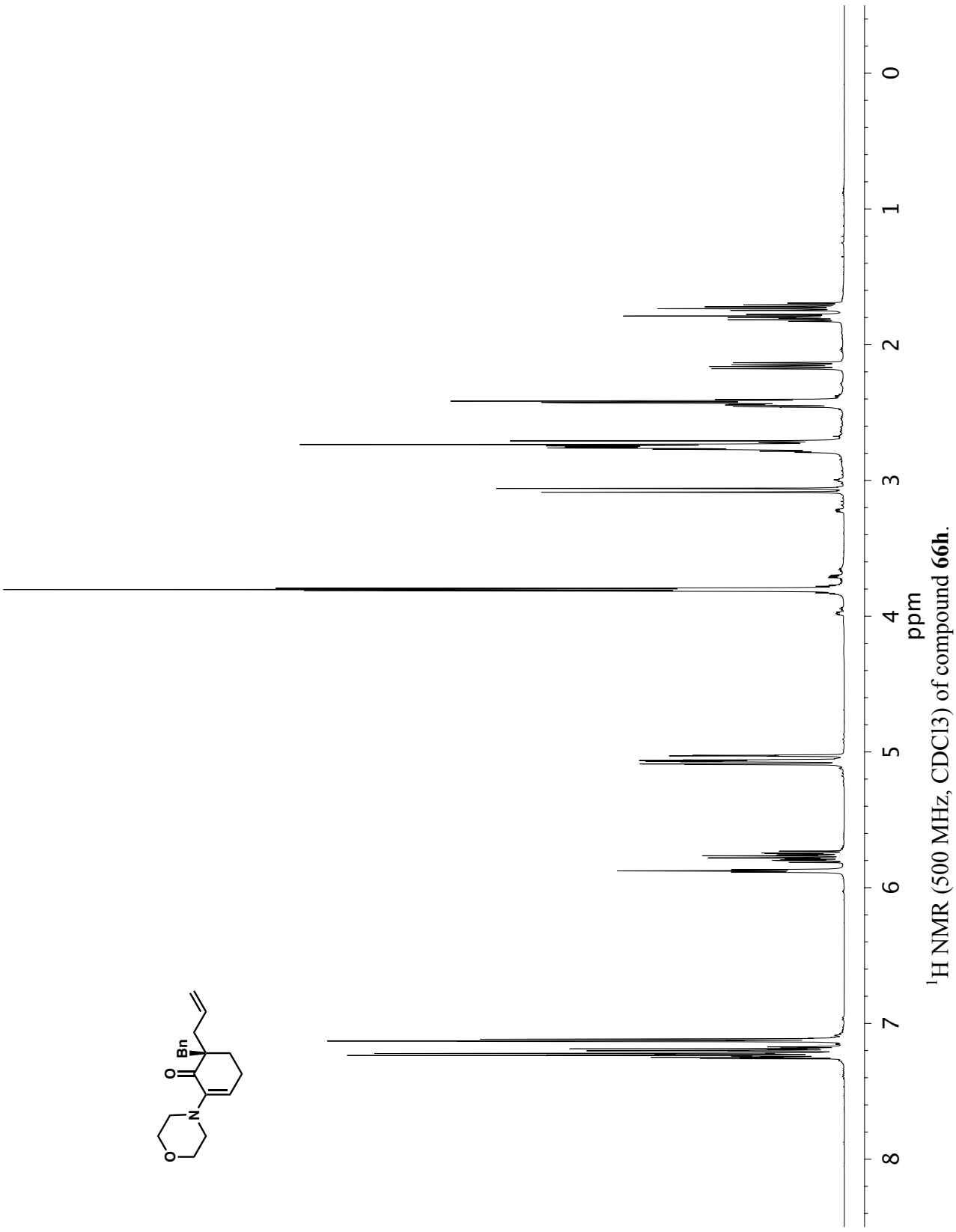
^{1}H NMR (500 MHz, CDCl3) of compound **66g**.



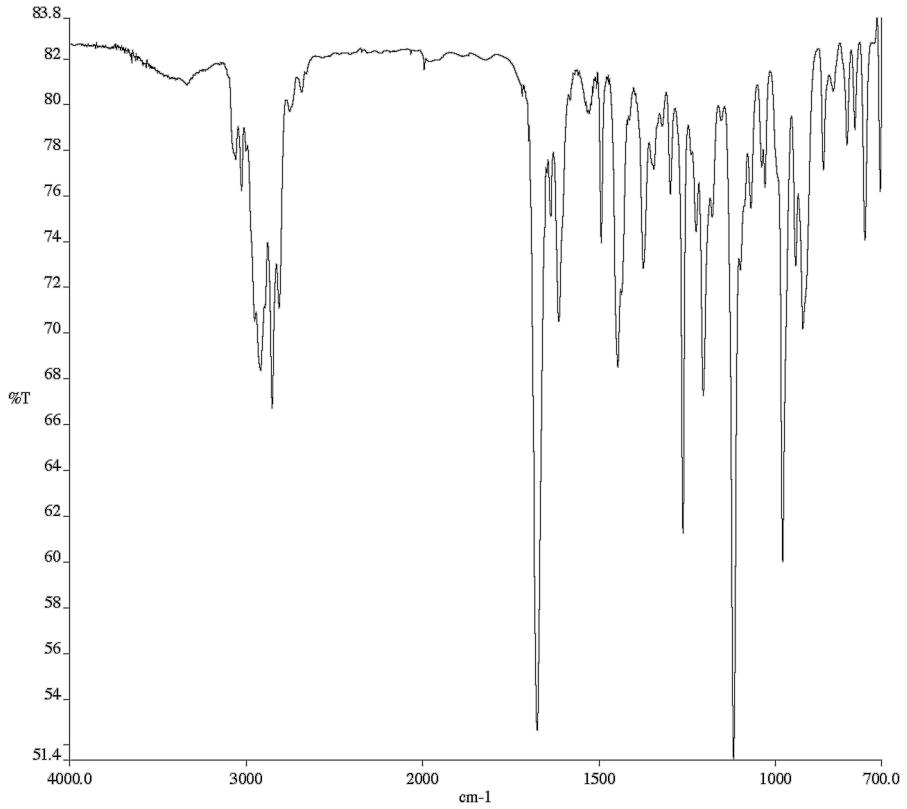
Infrared spectrum (Thin Film, NaCl) of compound **66g**.



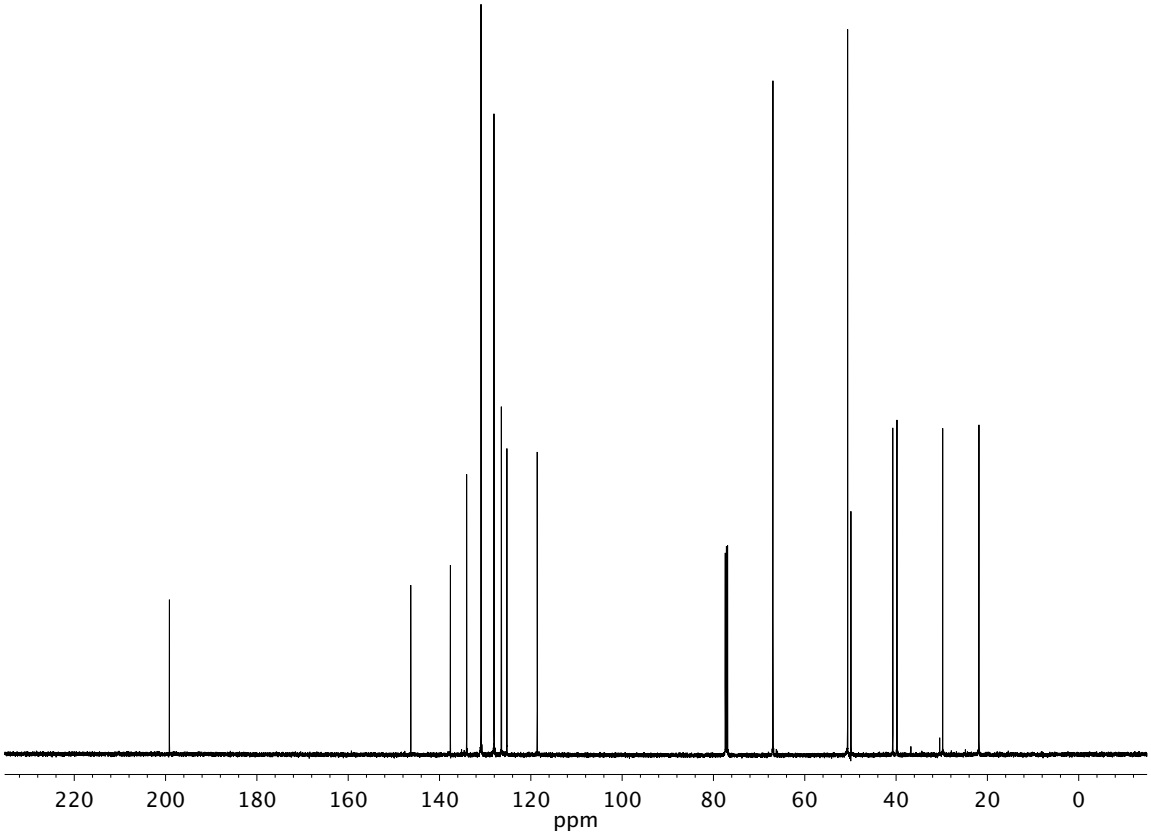
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66g**.



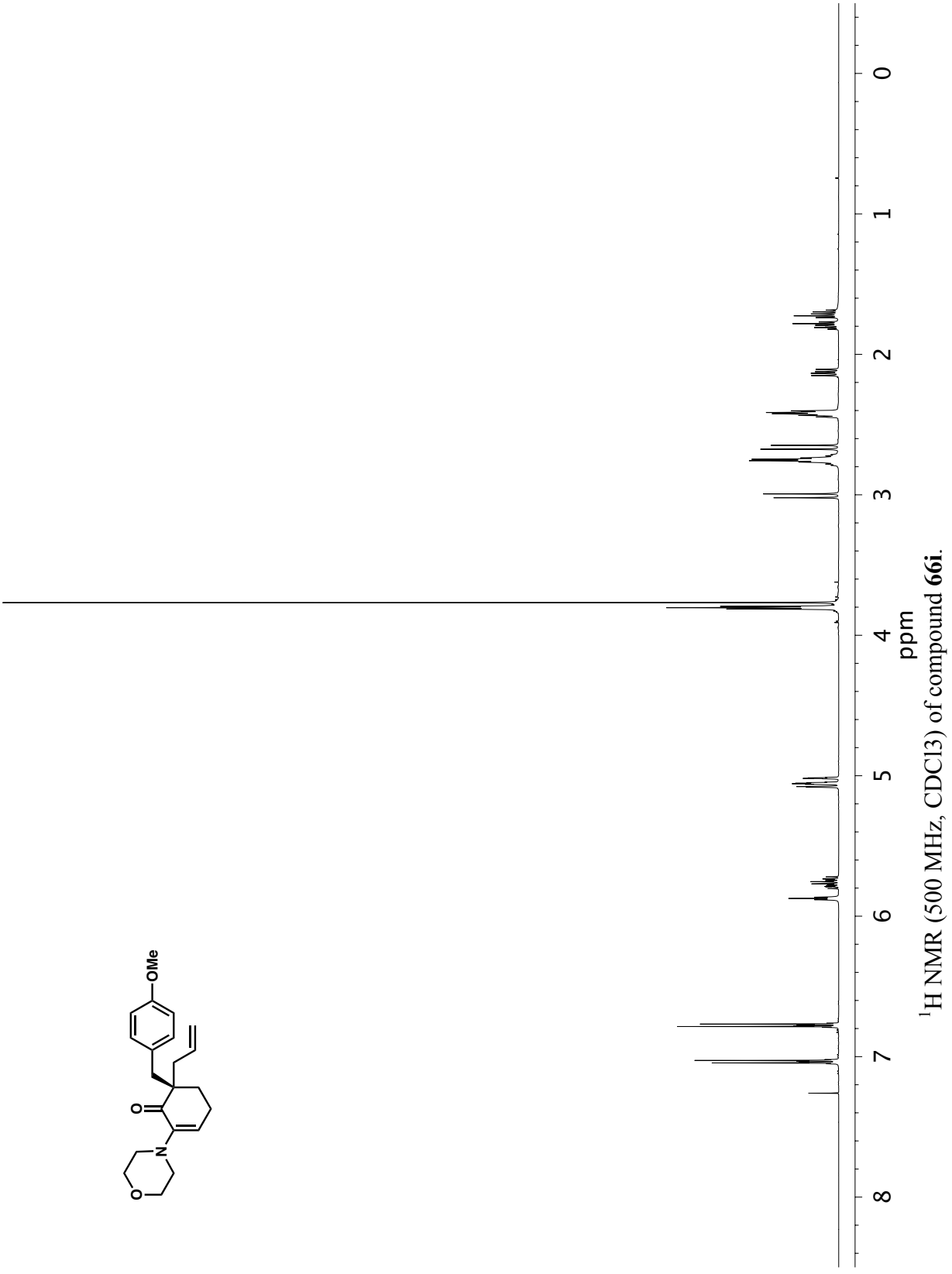
^{1}H NMR (500 MHz, CDCl3) of compound **66h**.



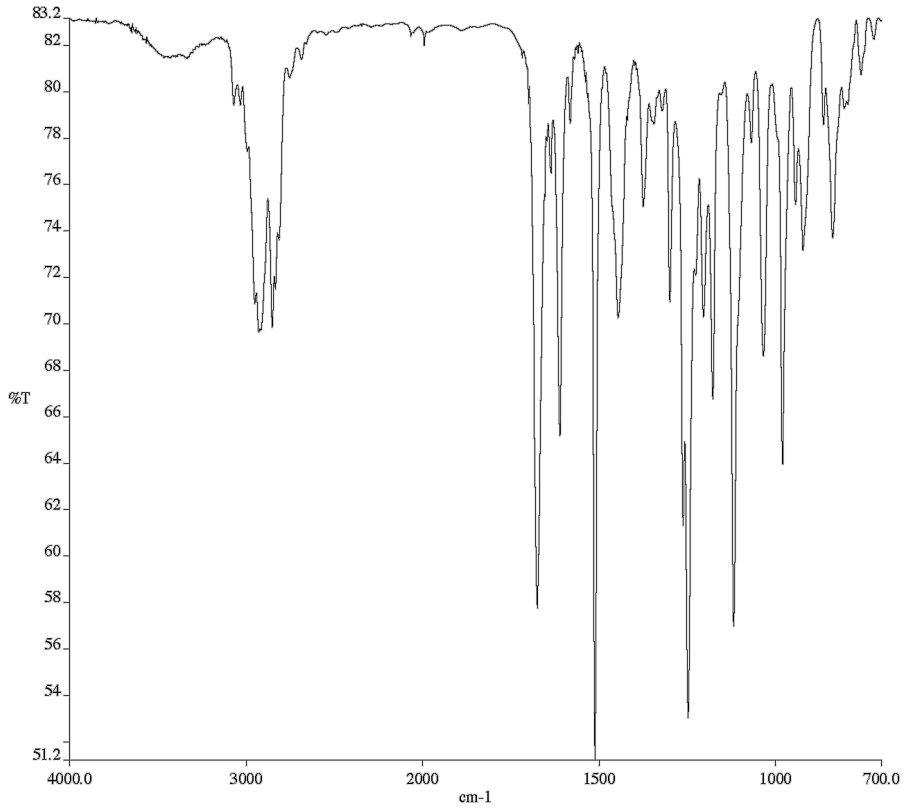
Infrared spectrum (Thin Film, NaCl) of compound **66h**.



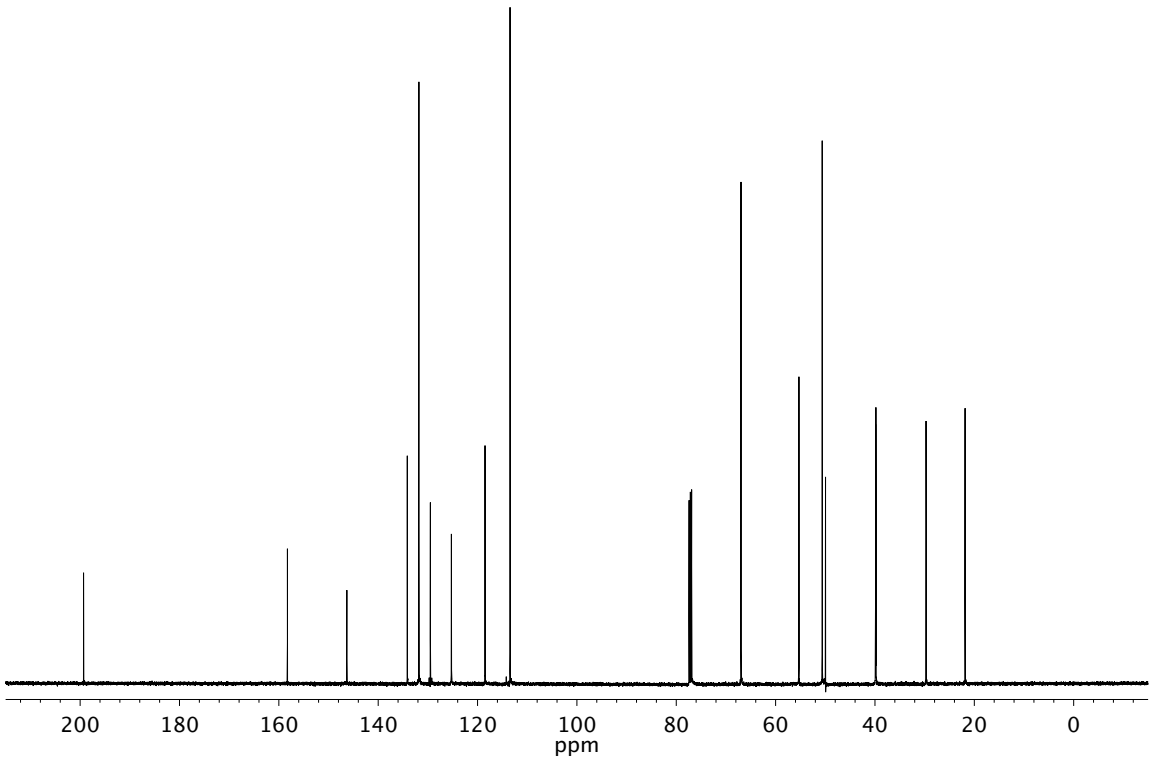
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66h**.



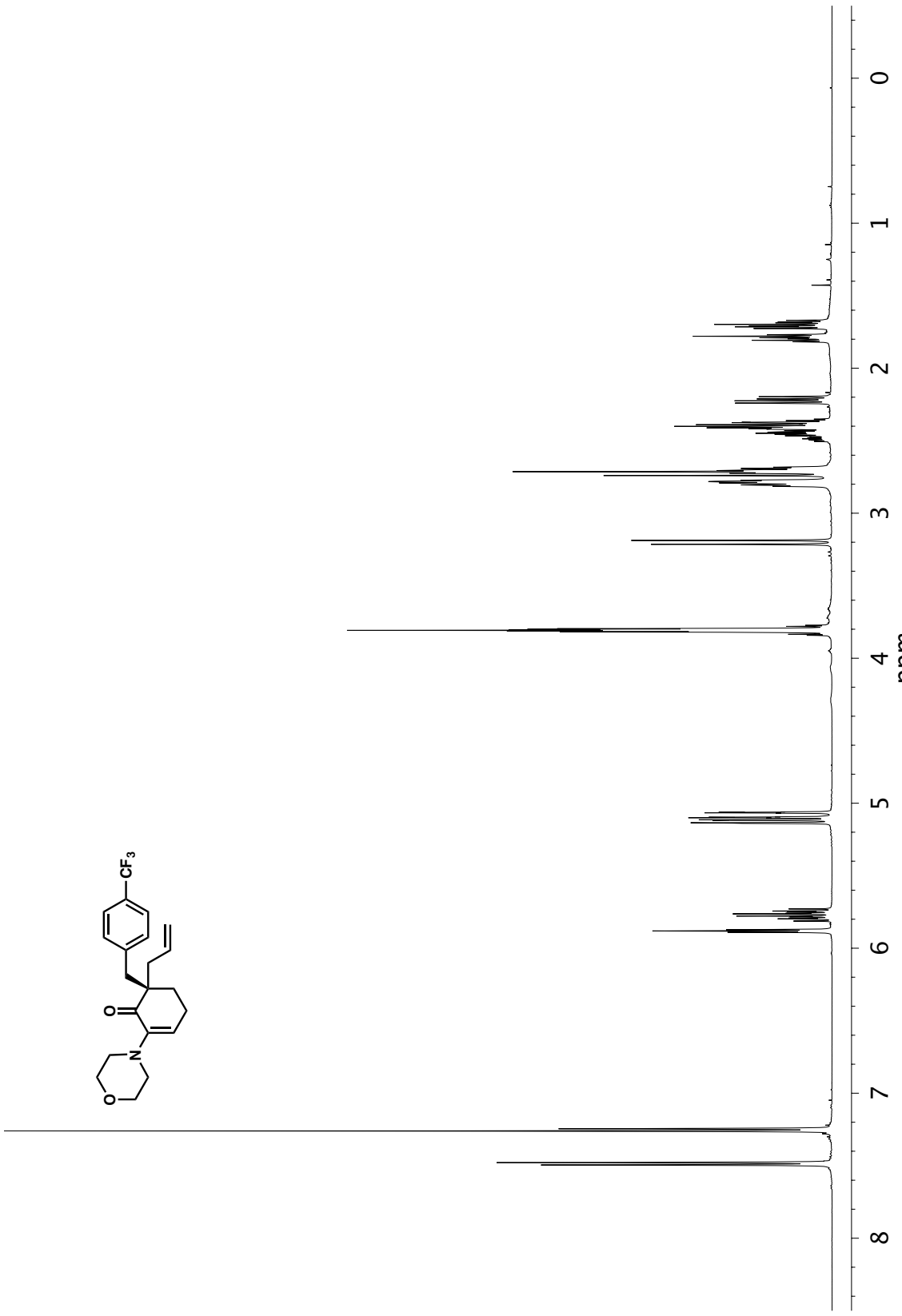
^{1}H NMR (500 MHz, CDCl3) of compound **66i**.



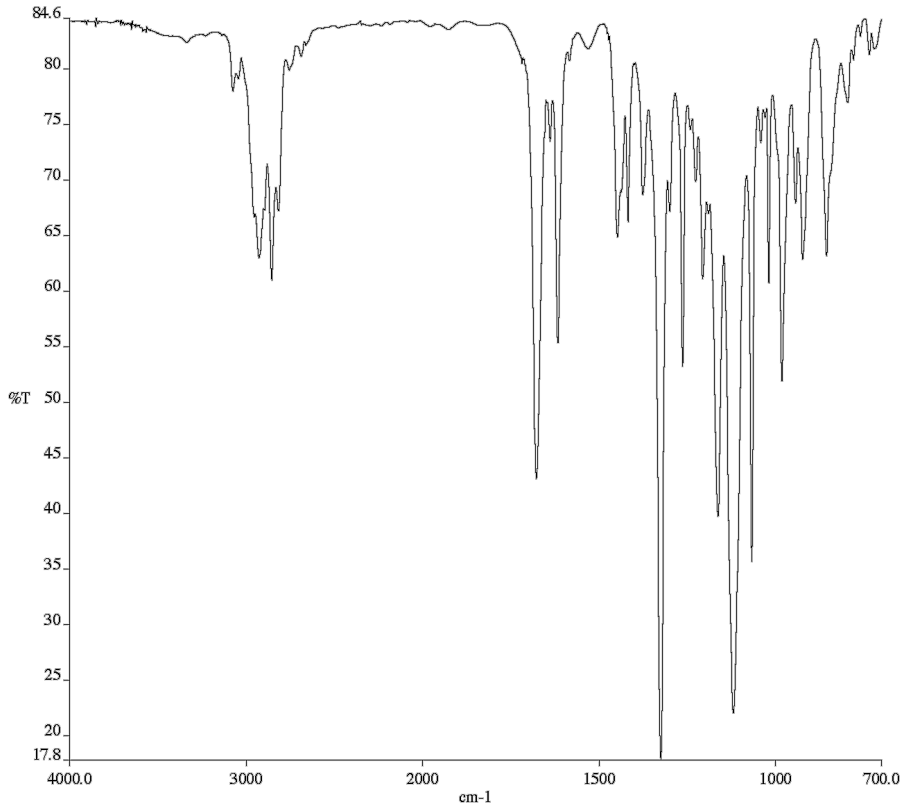
Infrared spectrum (Thin Film, NaCl) of compound **66i**.



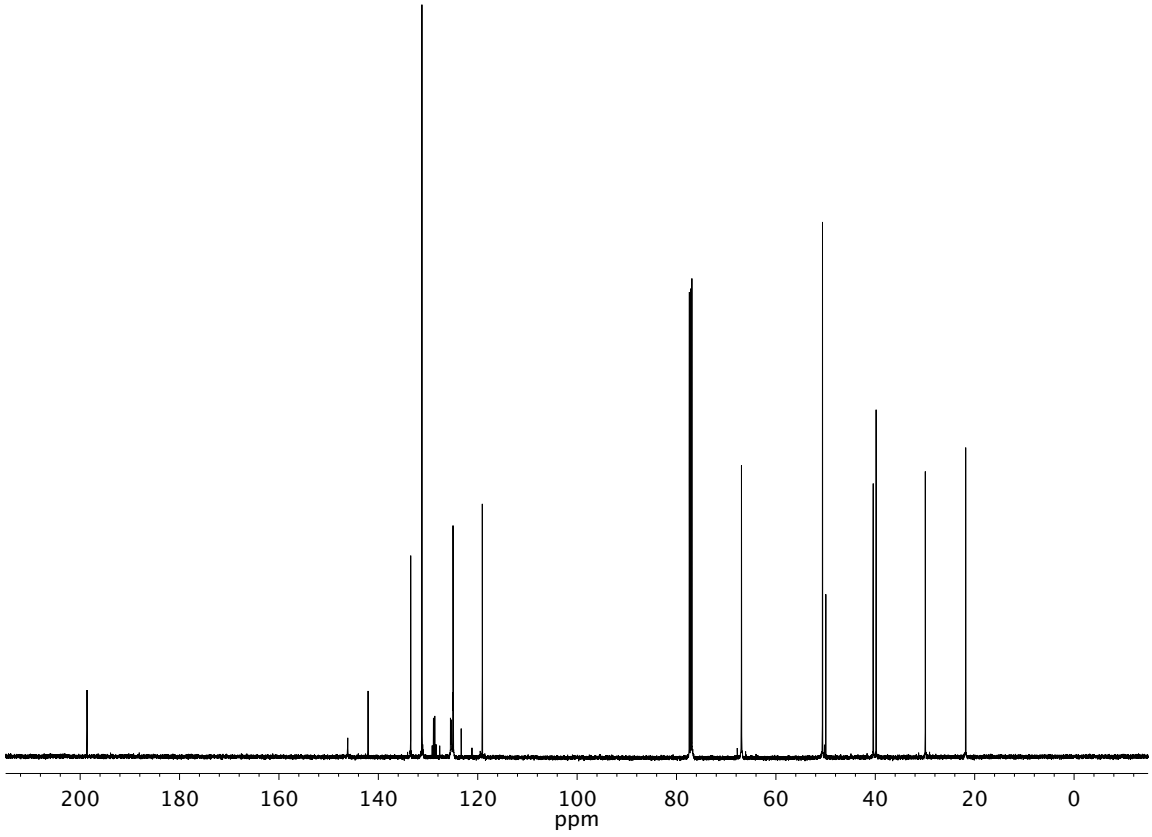
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66i**.



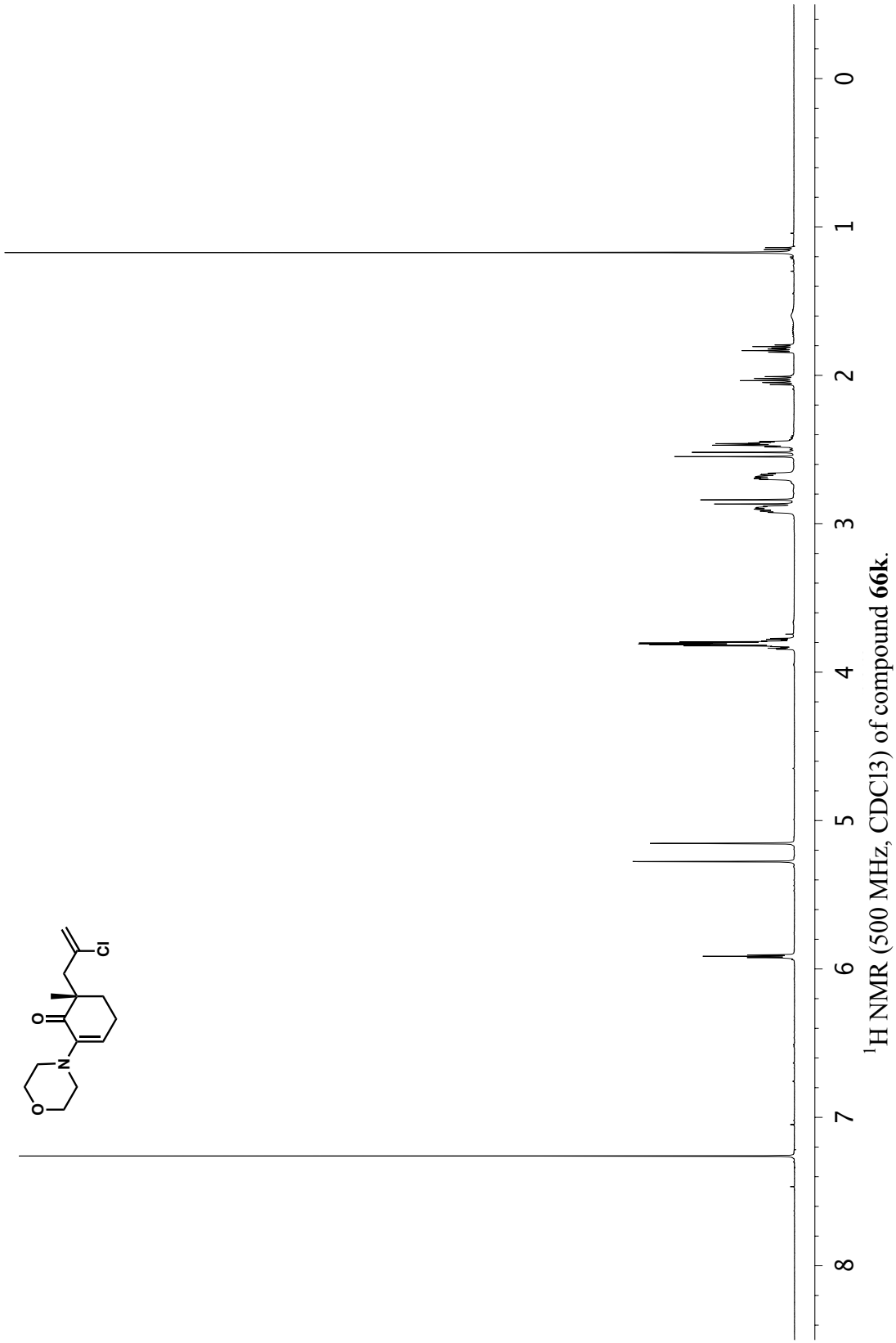
^{1}H NMR (500 MHz, CDCl3) of compound **66j**.



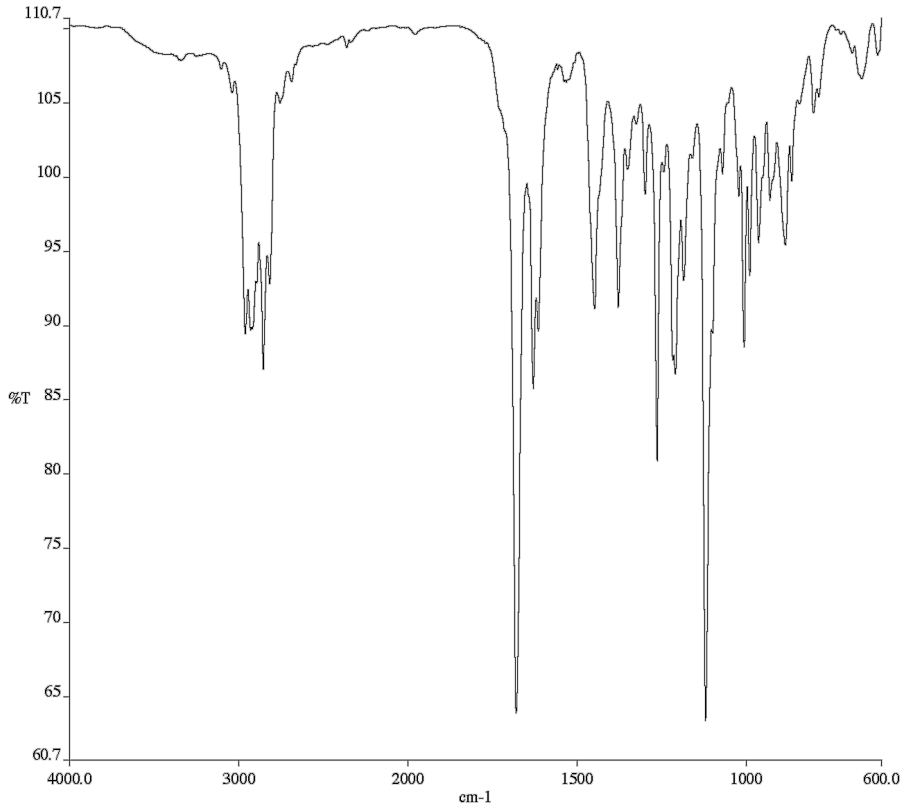
Infrared spectrum (Thin Film, NaCl) of compound **66j**.



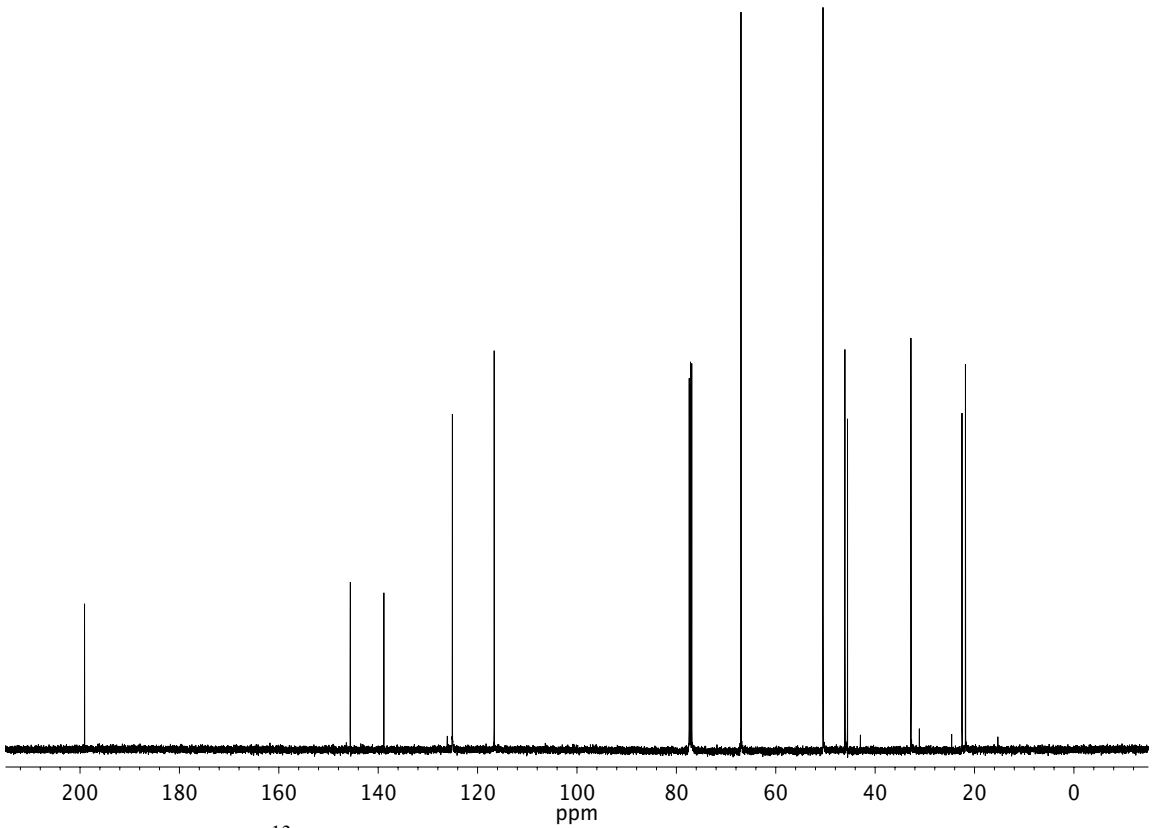
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66j**.



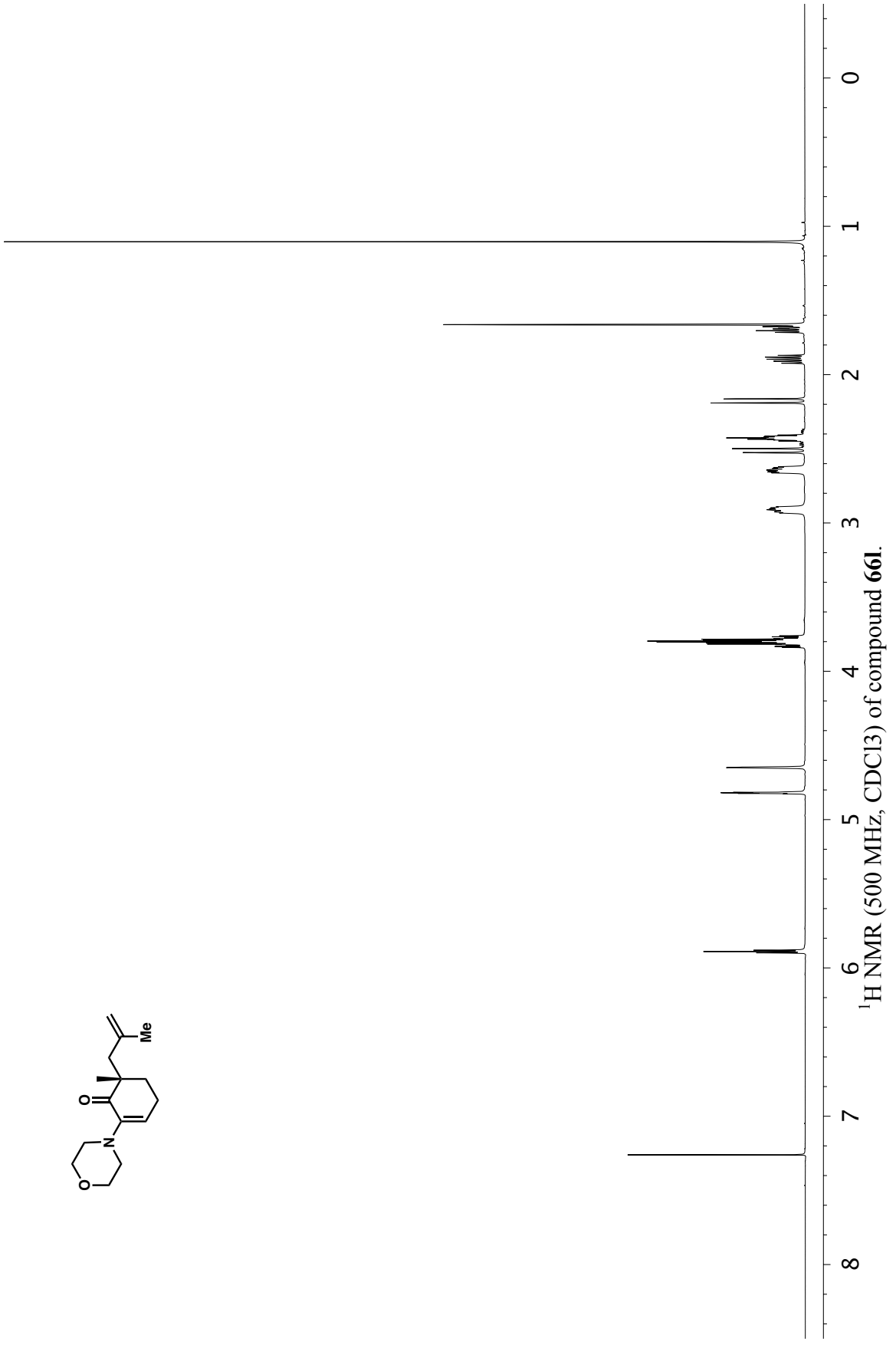
^{1}H NMR (500 MHz, CDCl3) of compound **66k**.



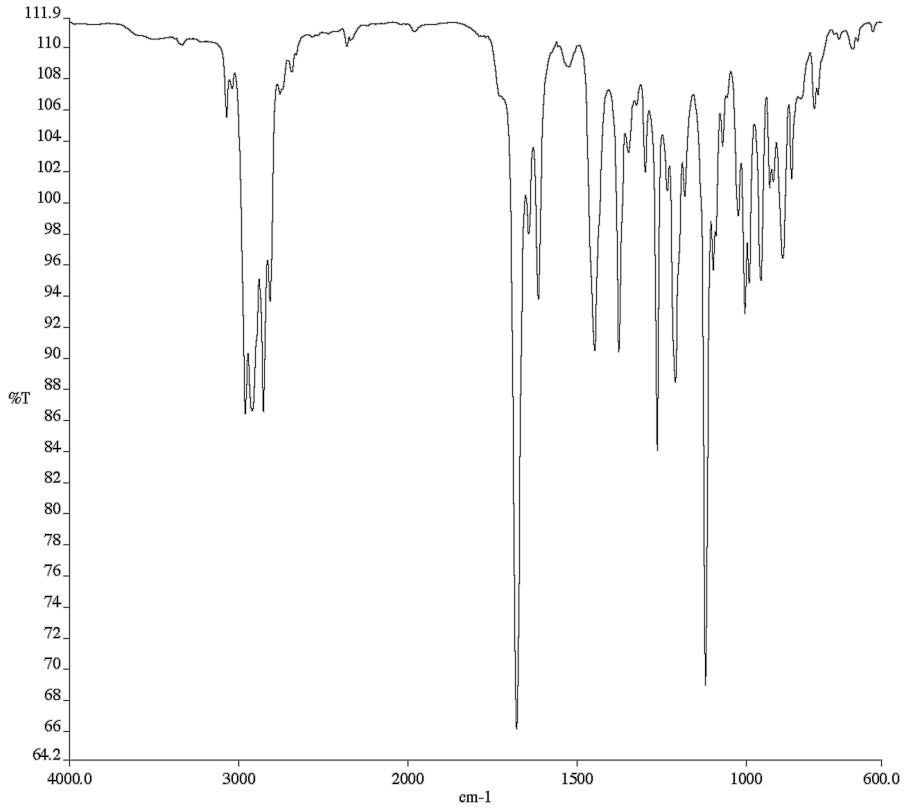
Infrared spectrum (Thin Film, NaCl) of compound **66k**.



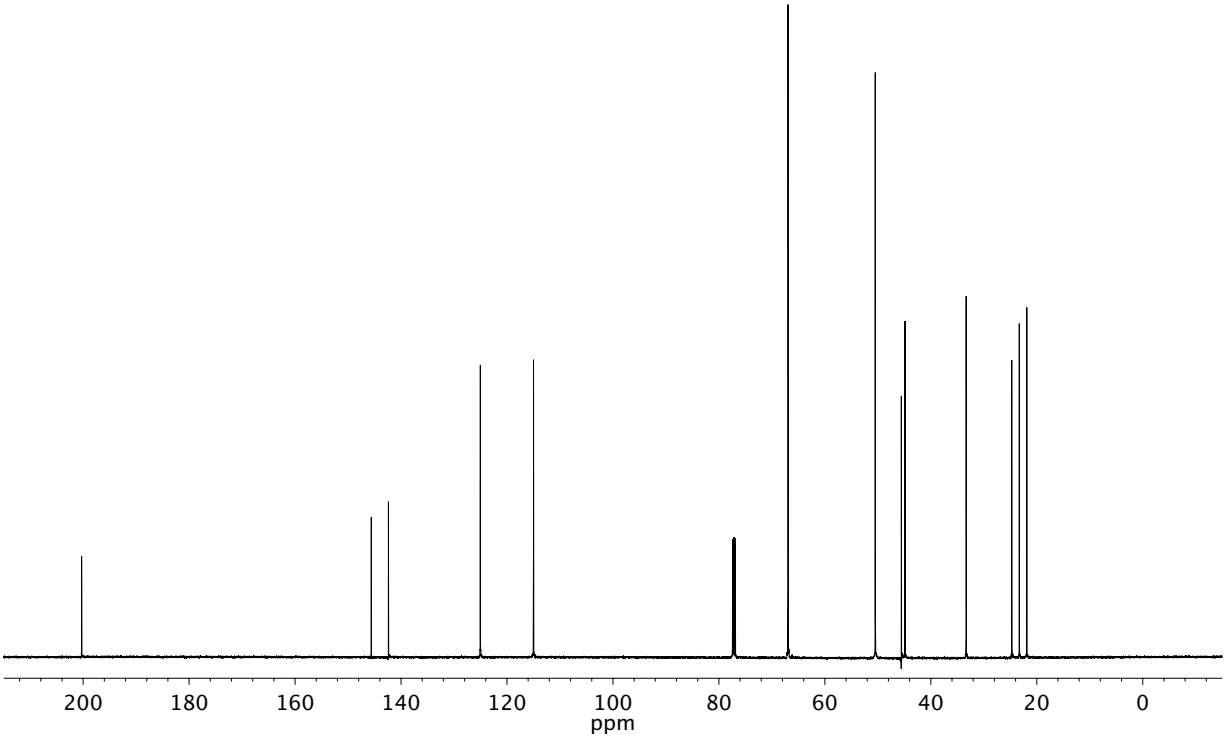
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66k**.



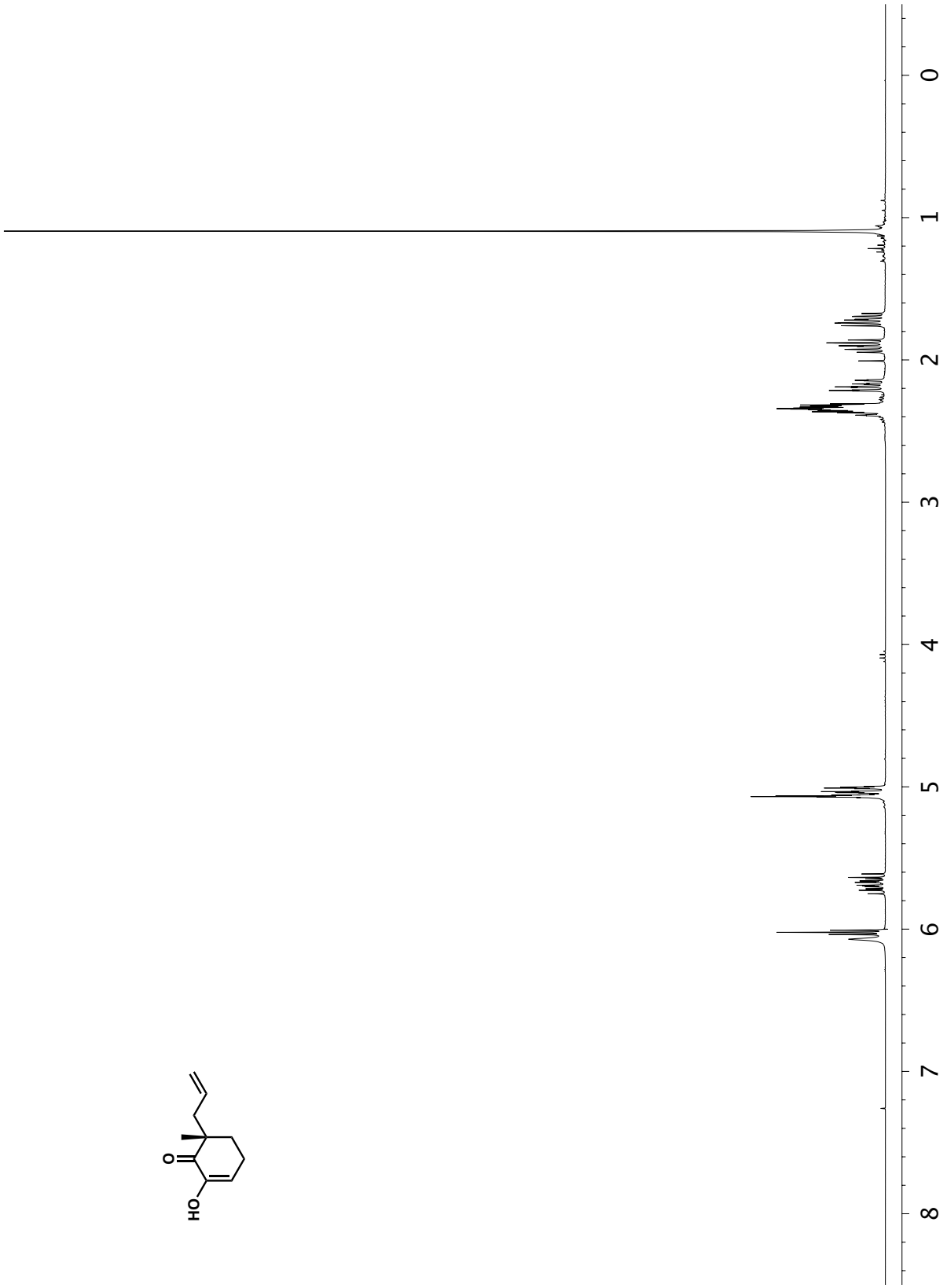
^{1}H NMR (500 MHz, CDCl3) of compound **66l**.



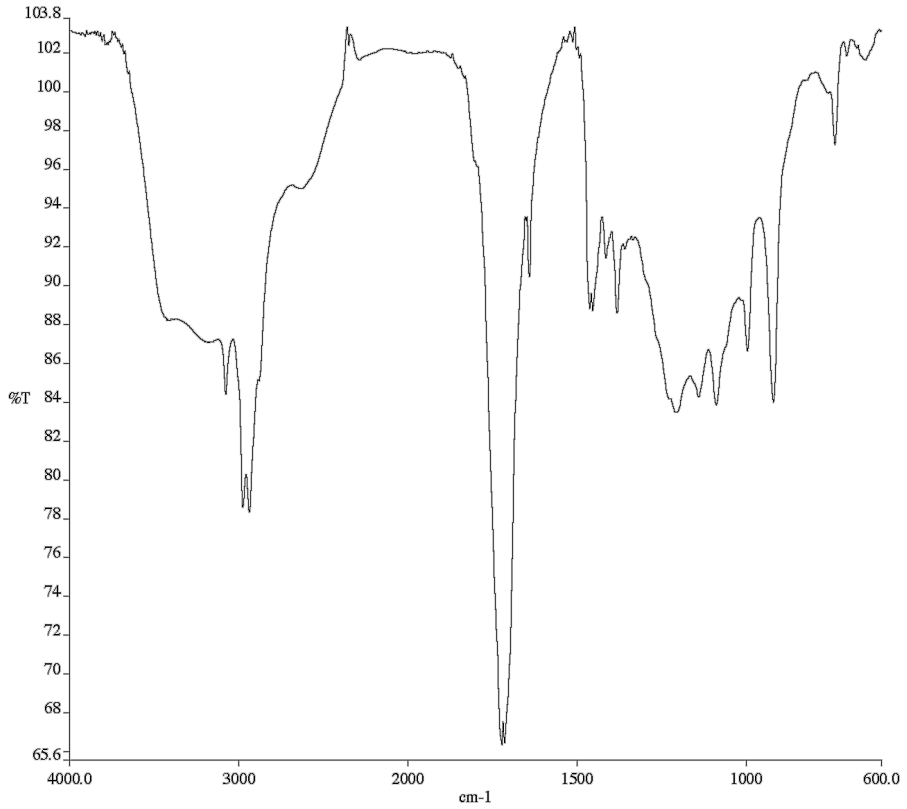
Infrared spectrum (Thin Film, NaCl) of compound **66l**.



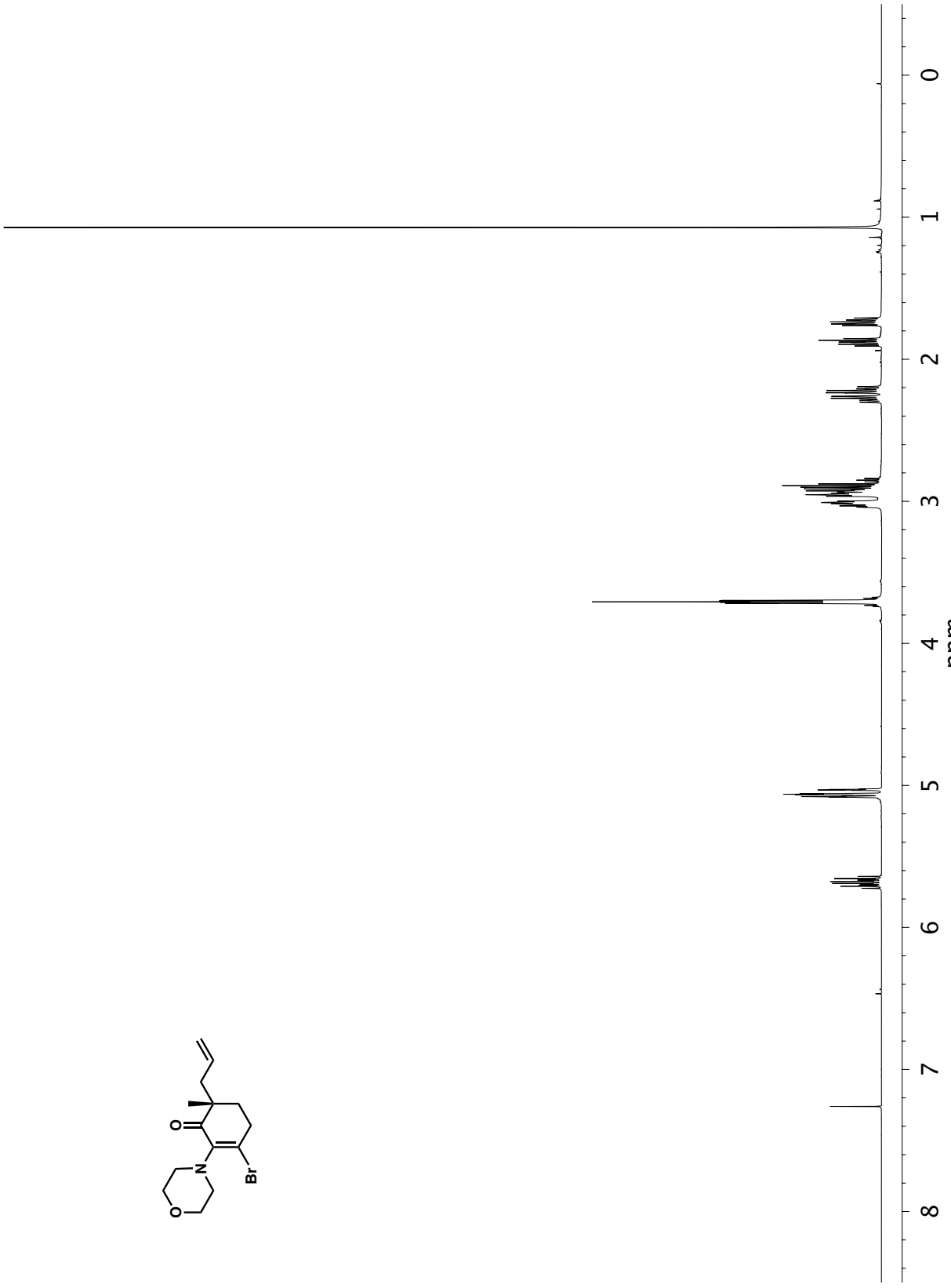
^{13}C NMR (125 MHz, $CDCl_3$) of compound **66l**.



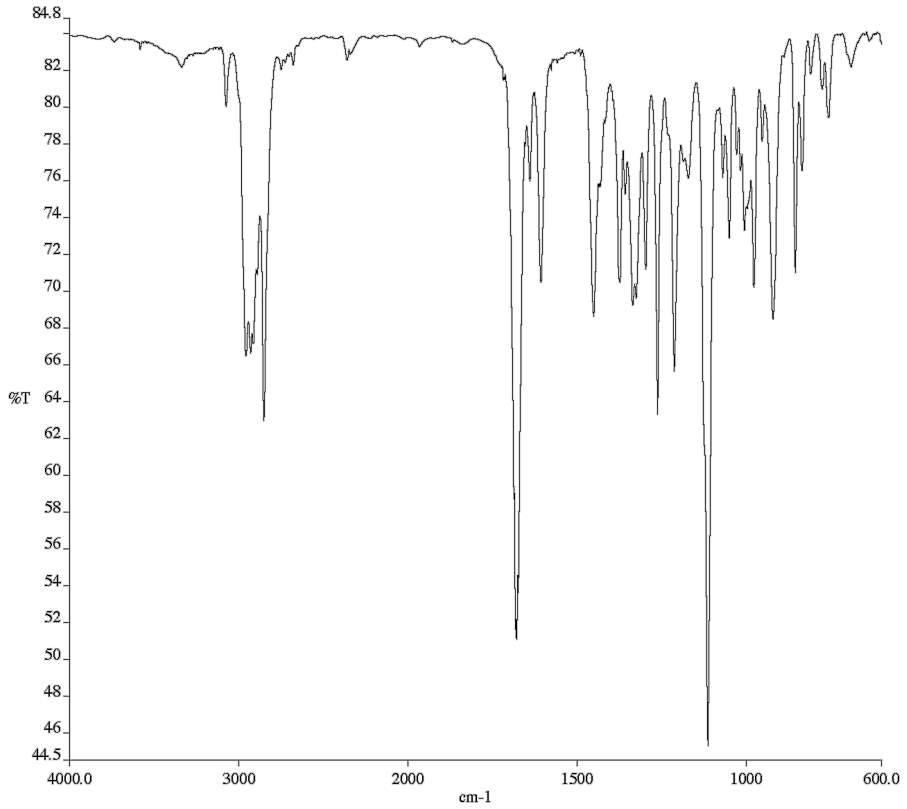
^{1}H NMR (500 MHz, CDCl3) of compound **67**.



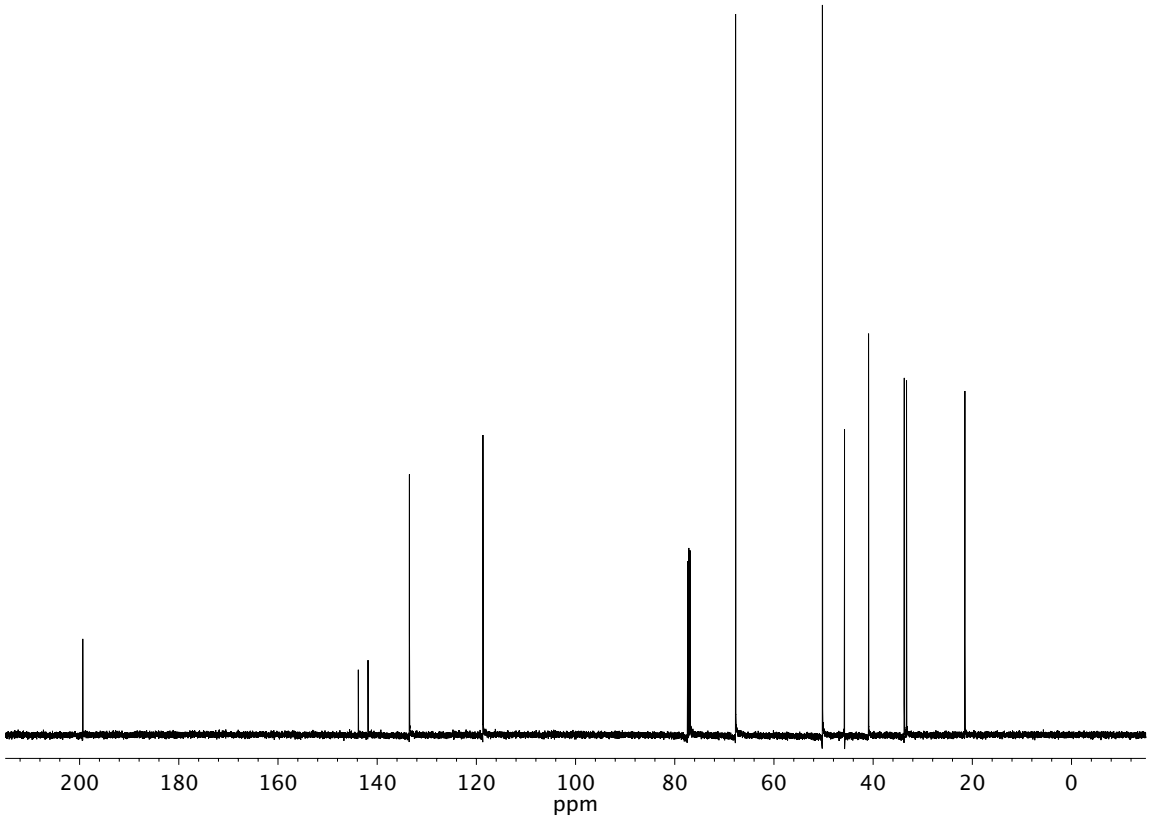
Infrared spectrum (Thin Film, NaCl) of compound **67**.



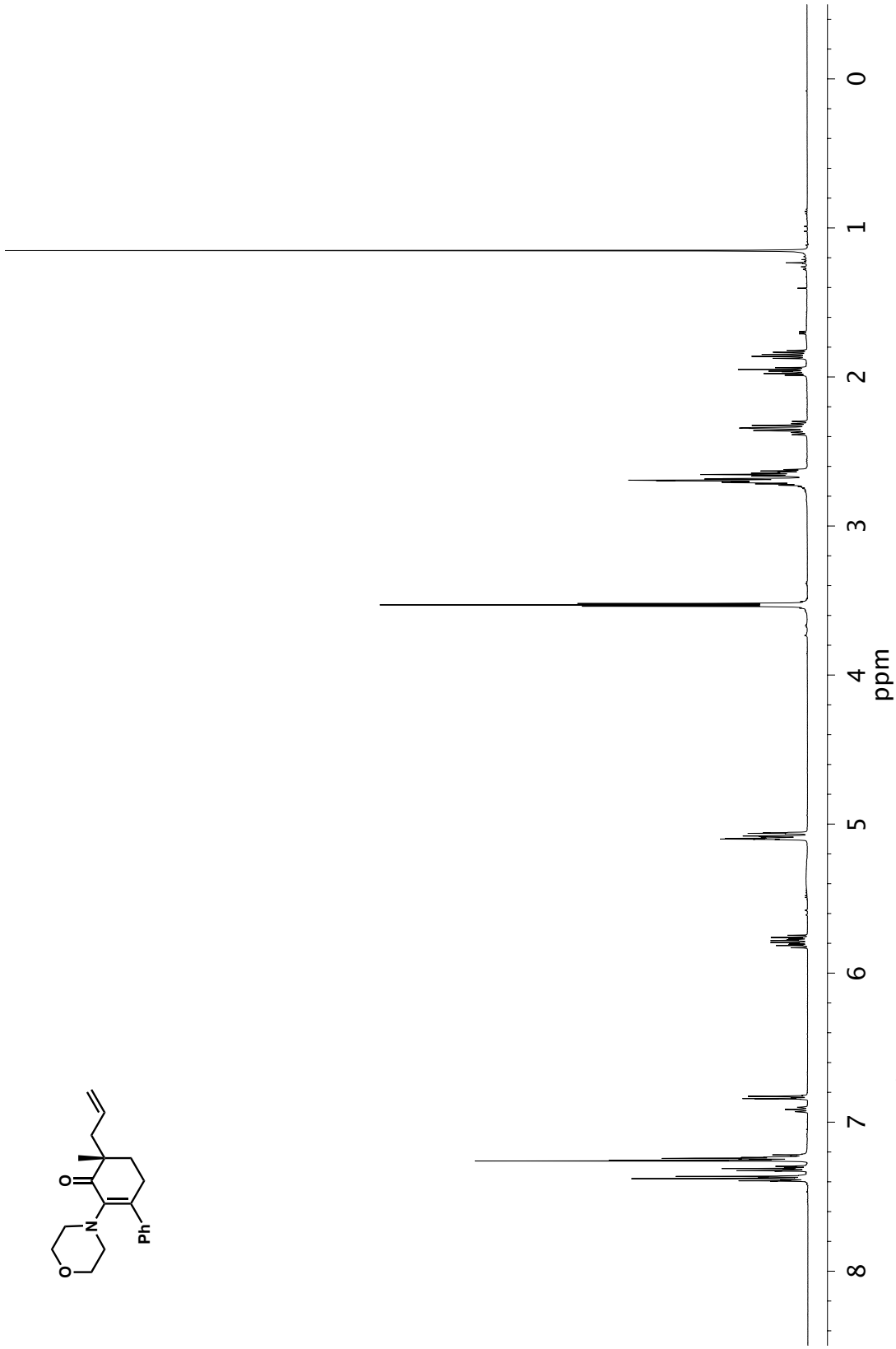
^{1}H NMR (500 MHz, CDCl3) of compound **68**.



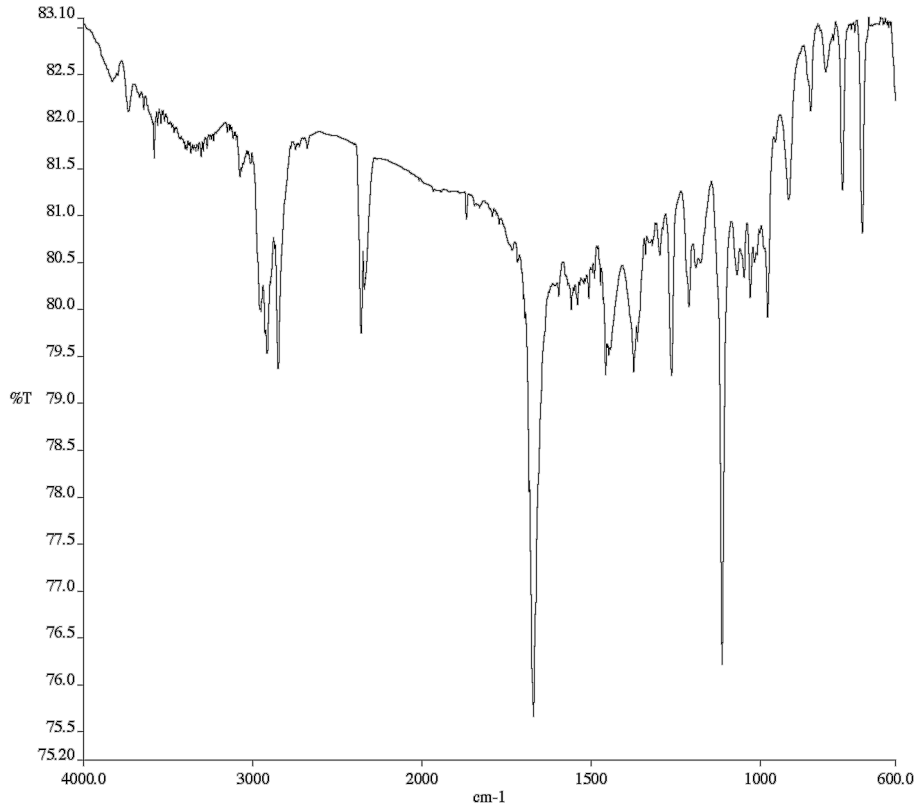
Infrared spectrum (Thin Film, NaCl) of compound **68**.



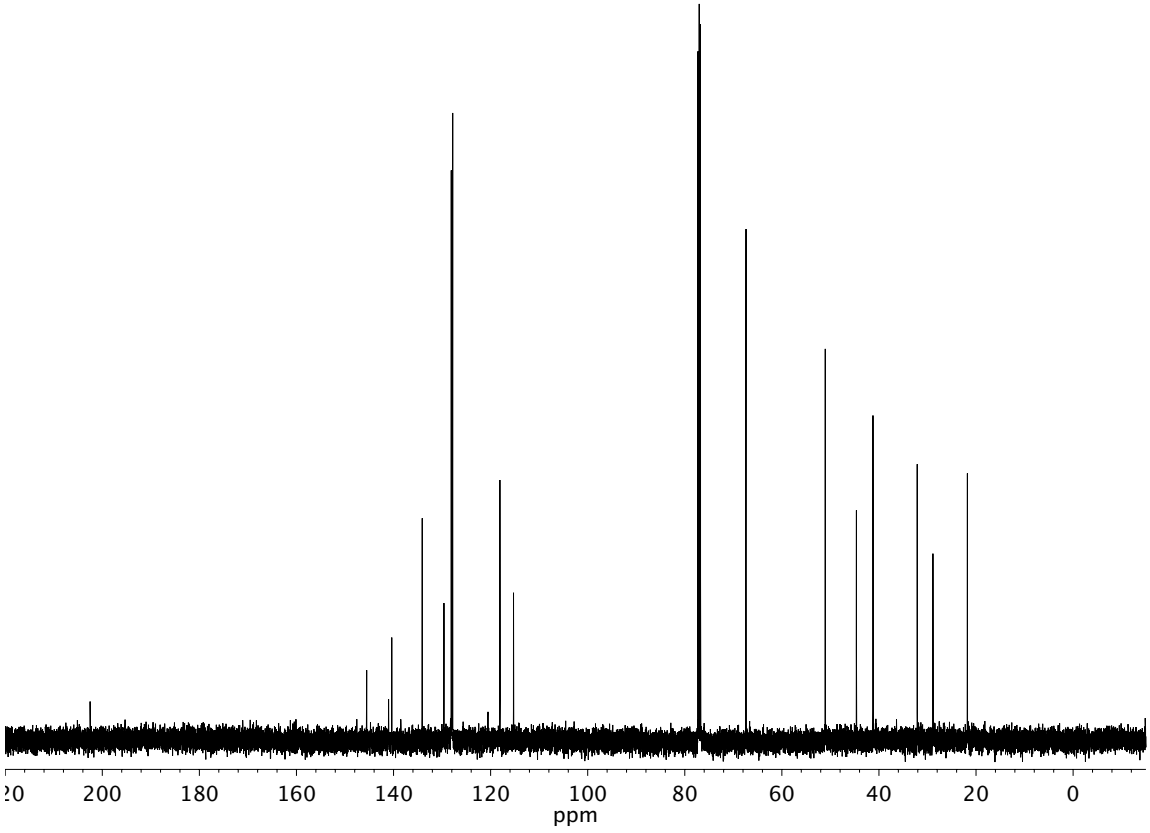
^{13}C NMR (125 MHz, $CDCl_3$) of compound **68**.



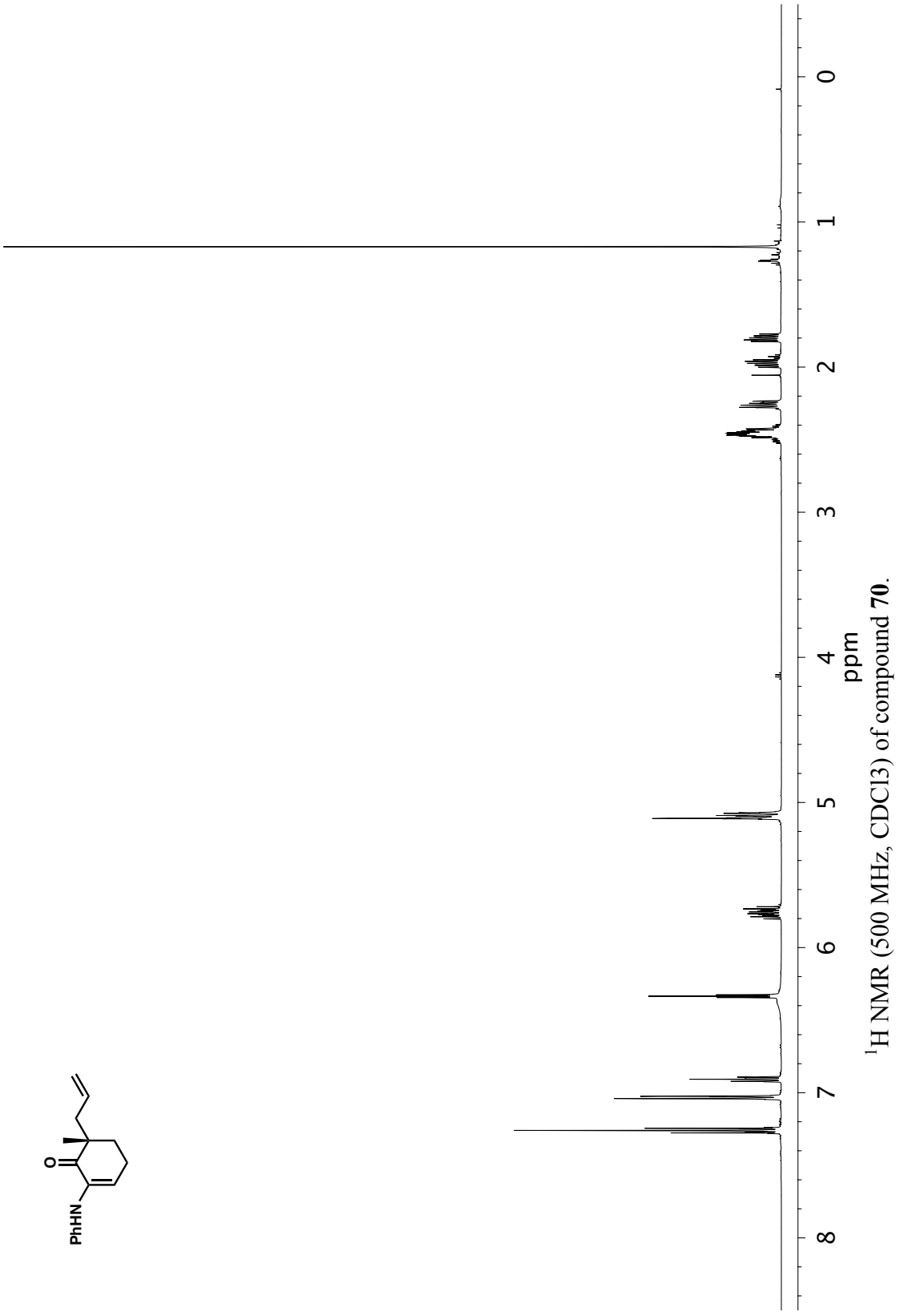
^{1}H NMR (500 MHz, CDCl3) of compound **69**.



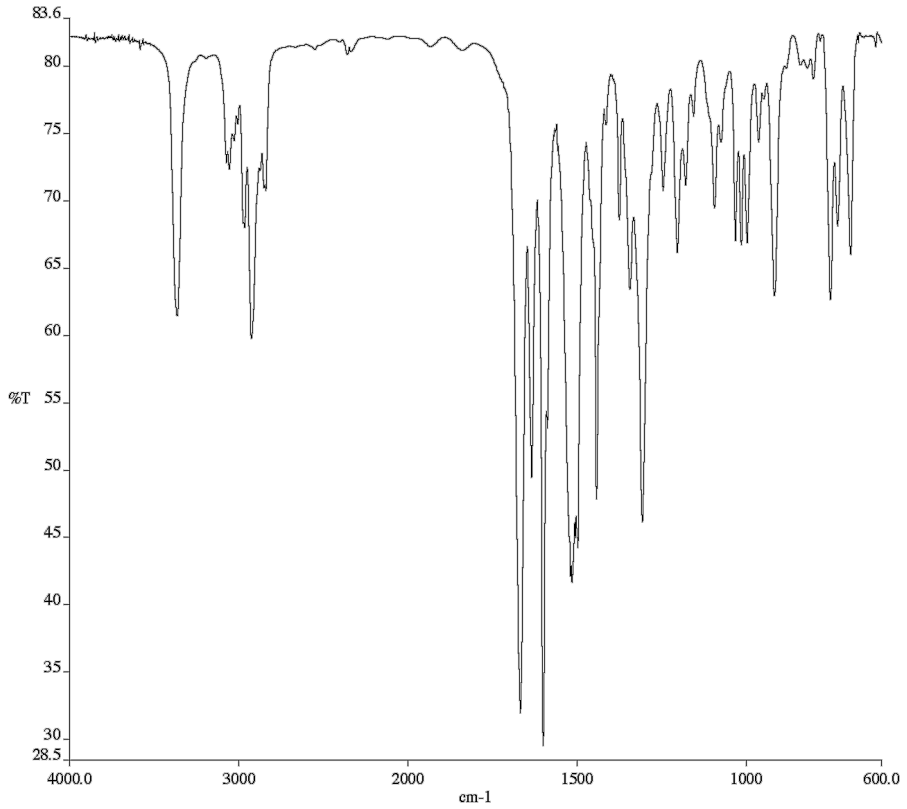
Infrared spectrum (Thin Film, NaCl) of compound **69**.



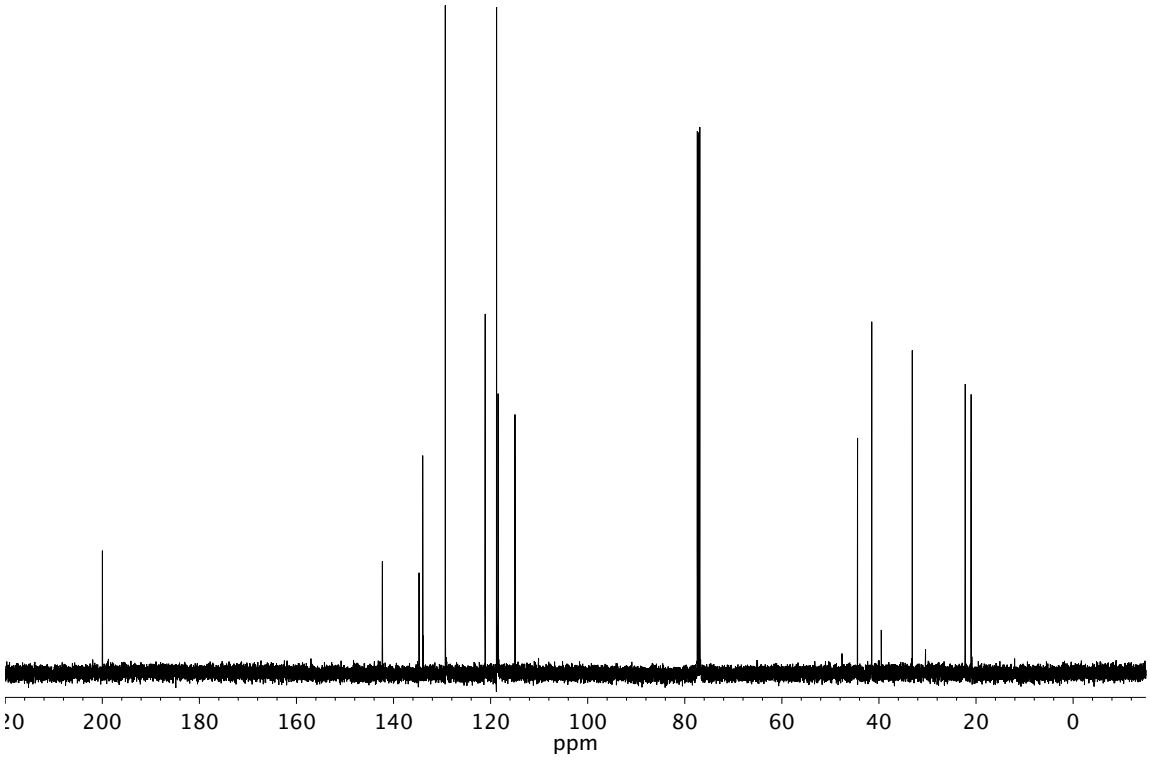
^{13}C NMR (125 MHz, $CDCl_3$) of compound **69**.



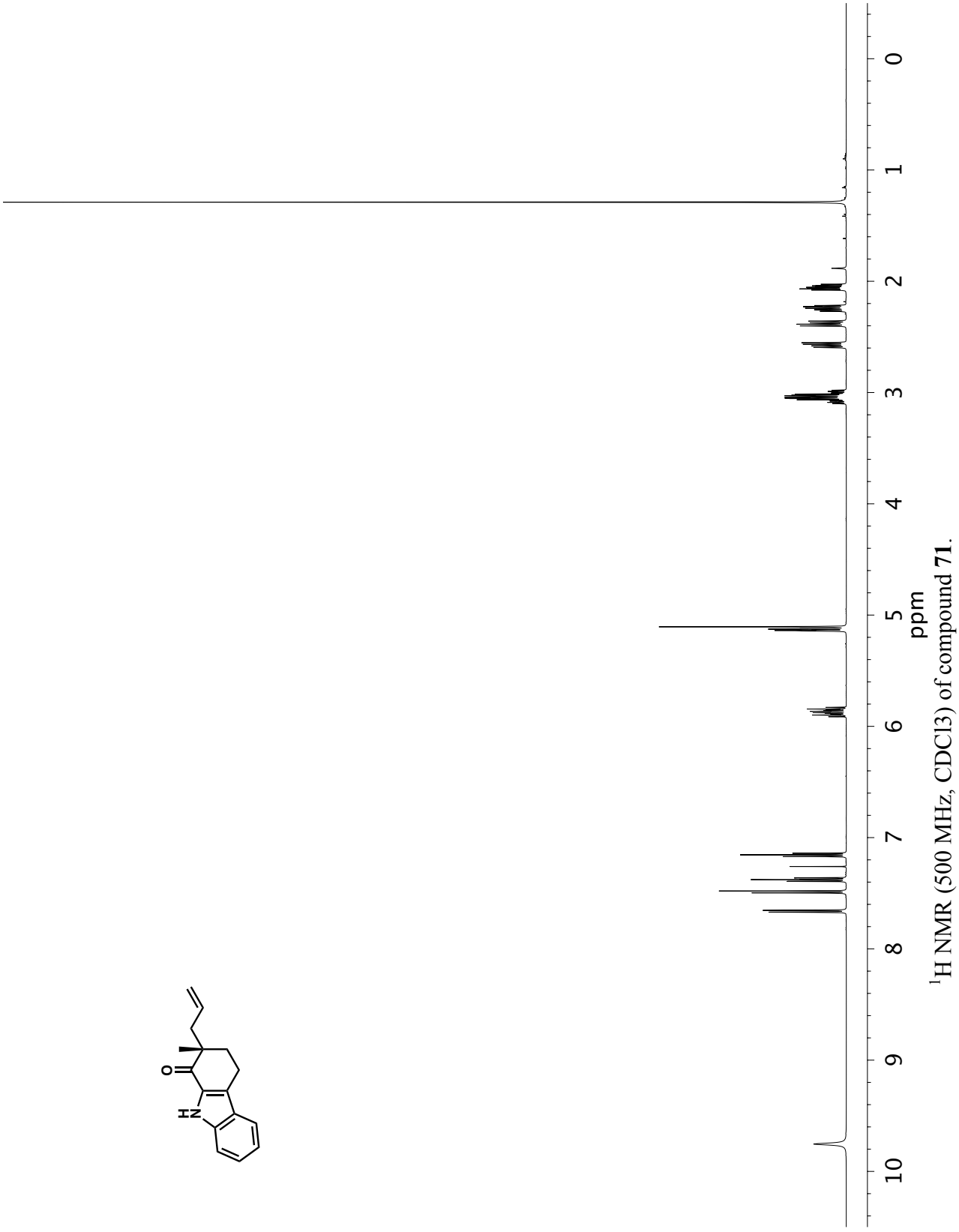
^{1}H NMR (500 MHz, CDCl3) of compound **70**.



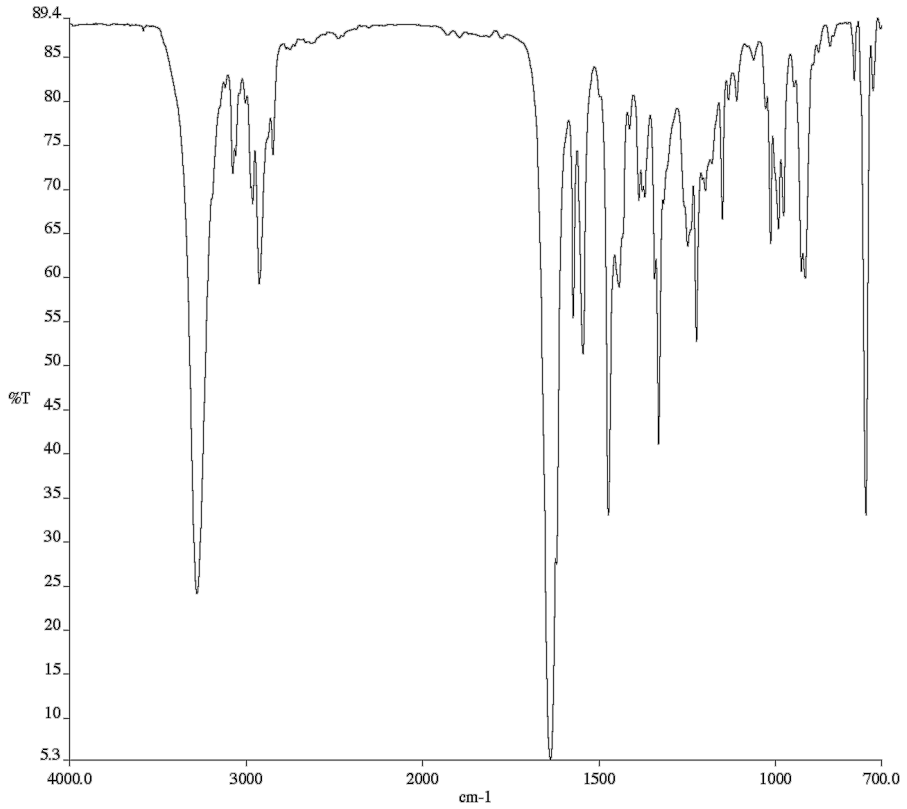
Infrared spectrum (Thin Film, NaCl) of compound **70**.



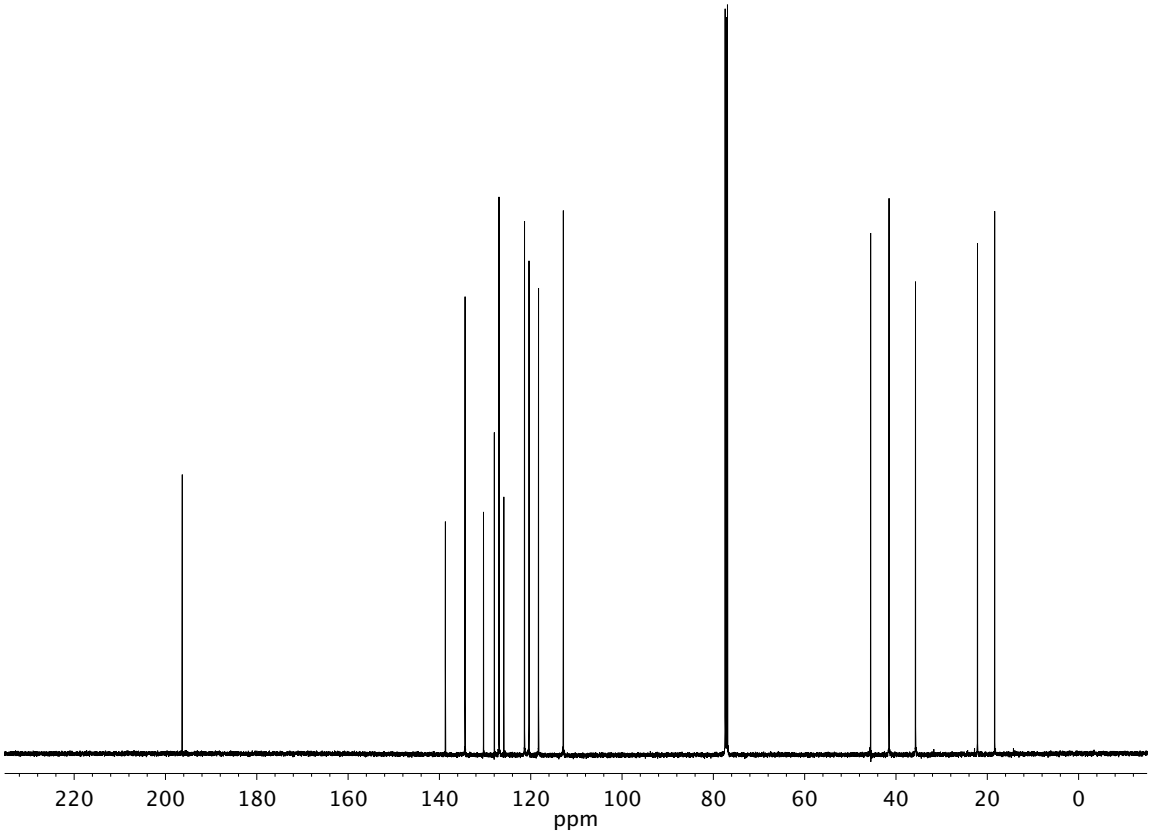
^{13}C NMR (125 MHz, $CDCl_3$) of compound **70**.



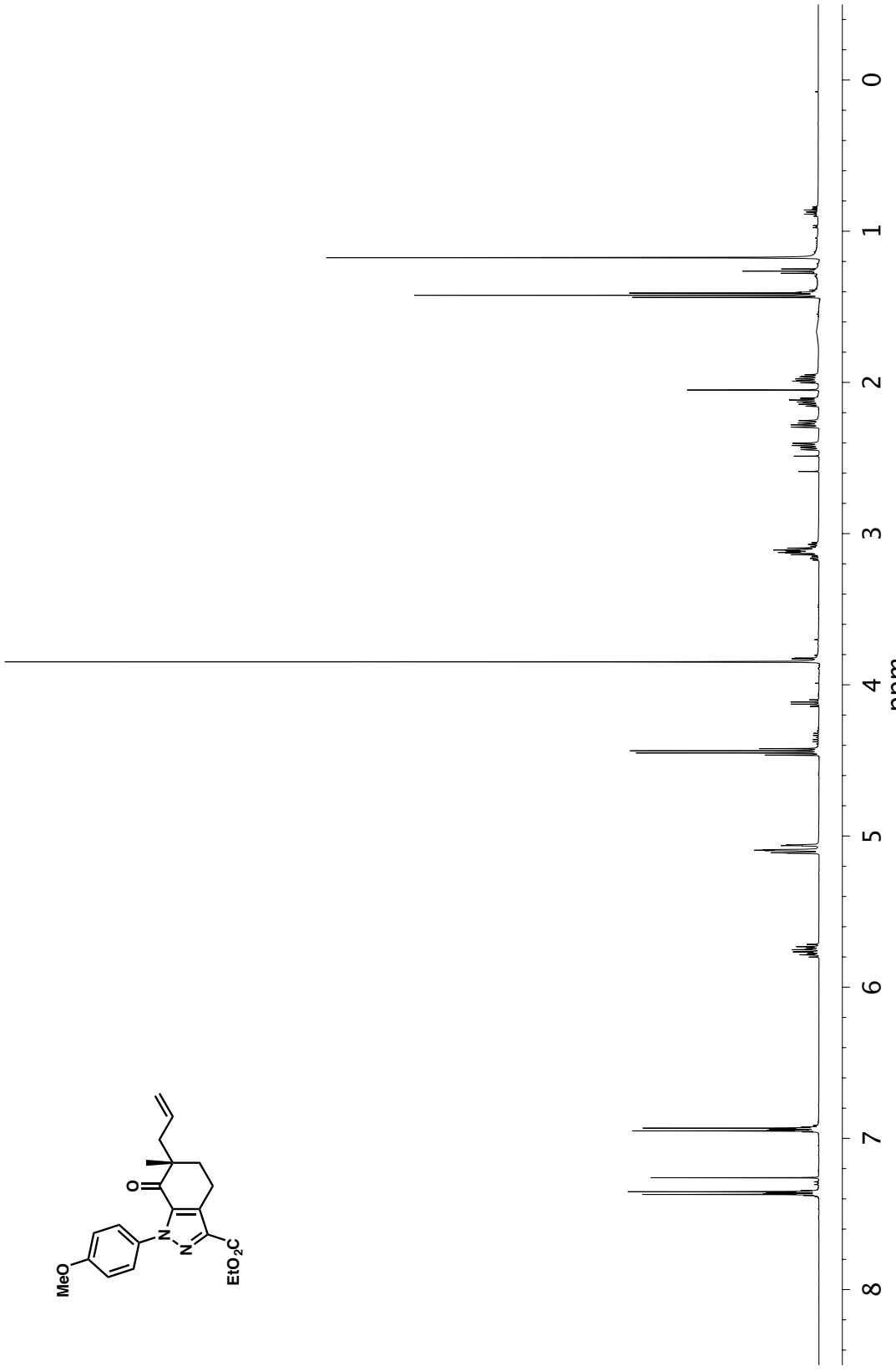
^{1}H NMR (500 MHz, CDCl3) of compound **71**.



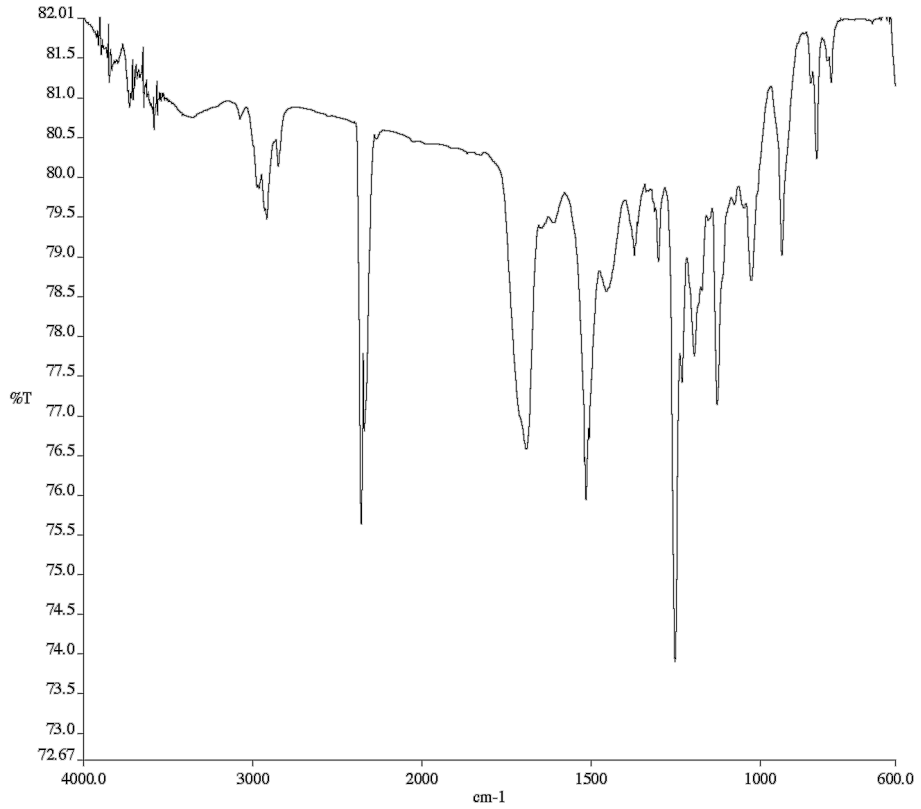
Infrared spectrum (Thin Film, NaCl) of compound **71**.



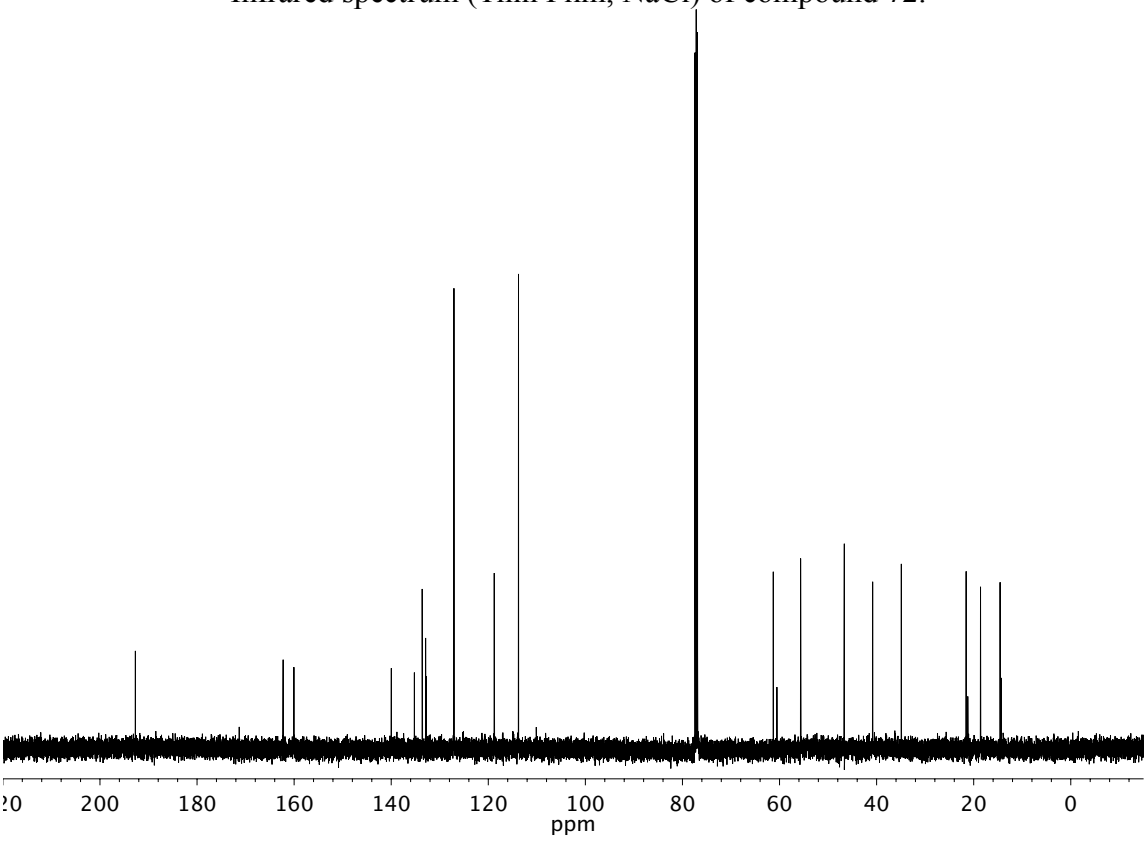
^{13}C NMR (125 MHz, $CDCl_3$) of compound **71**.



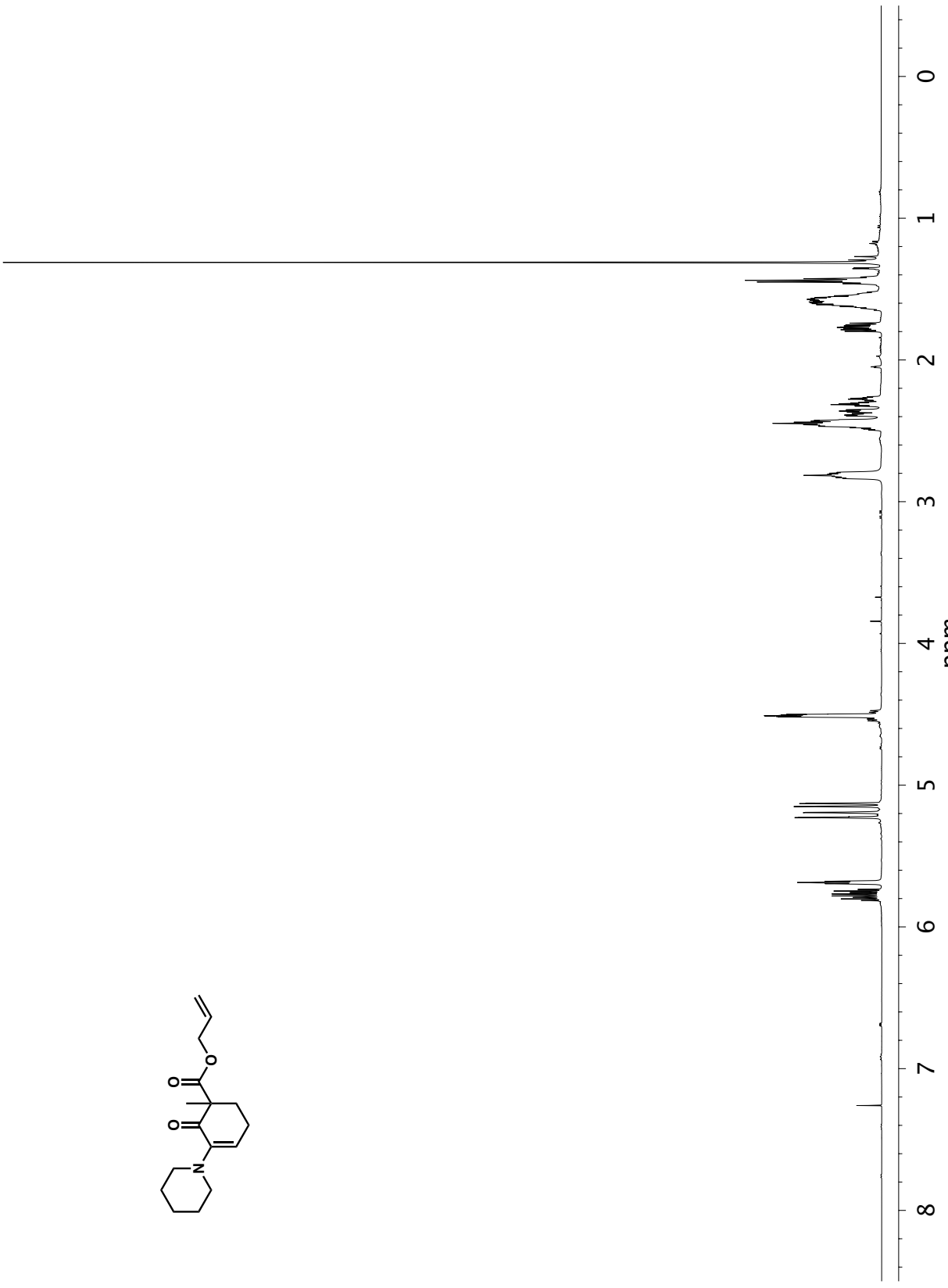
^{1}H NMR (500 MHz, CDCl3) of compound **72**.



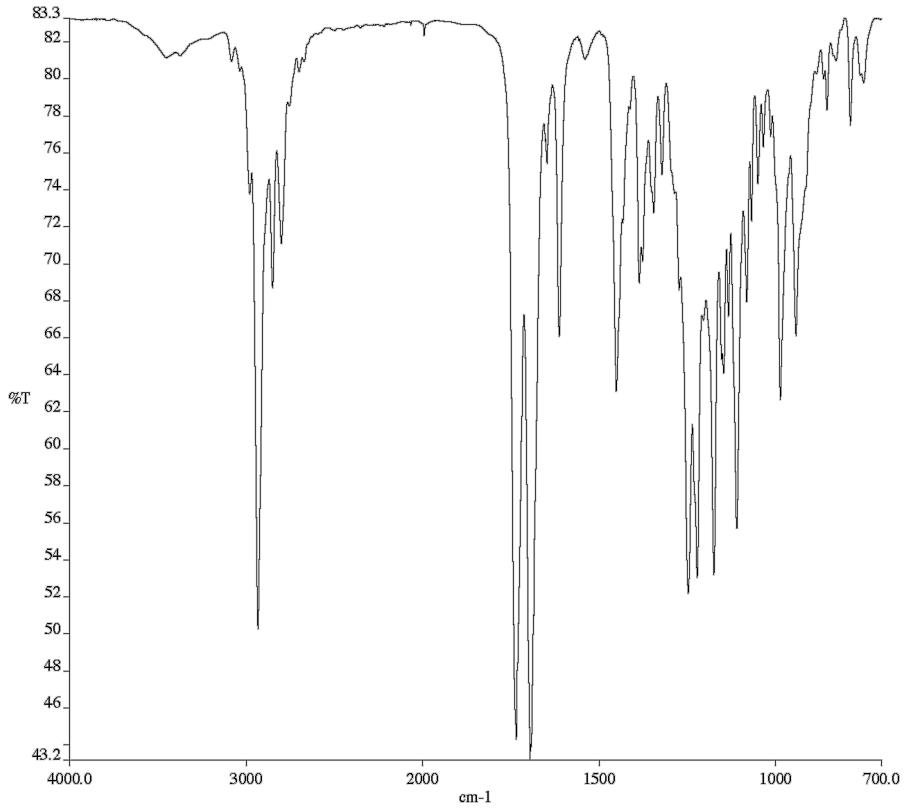
Infrared spectrum (Thin Film, NaCl) of compound **72**.



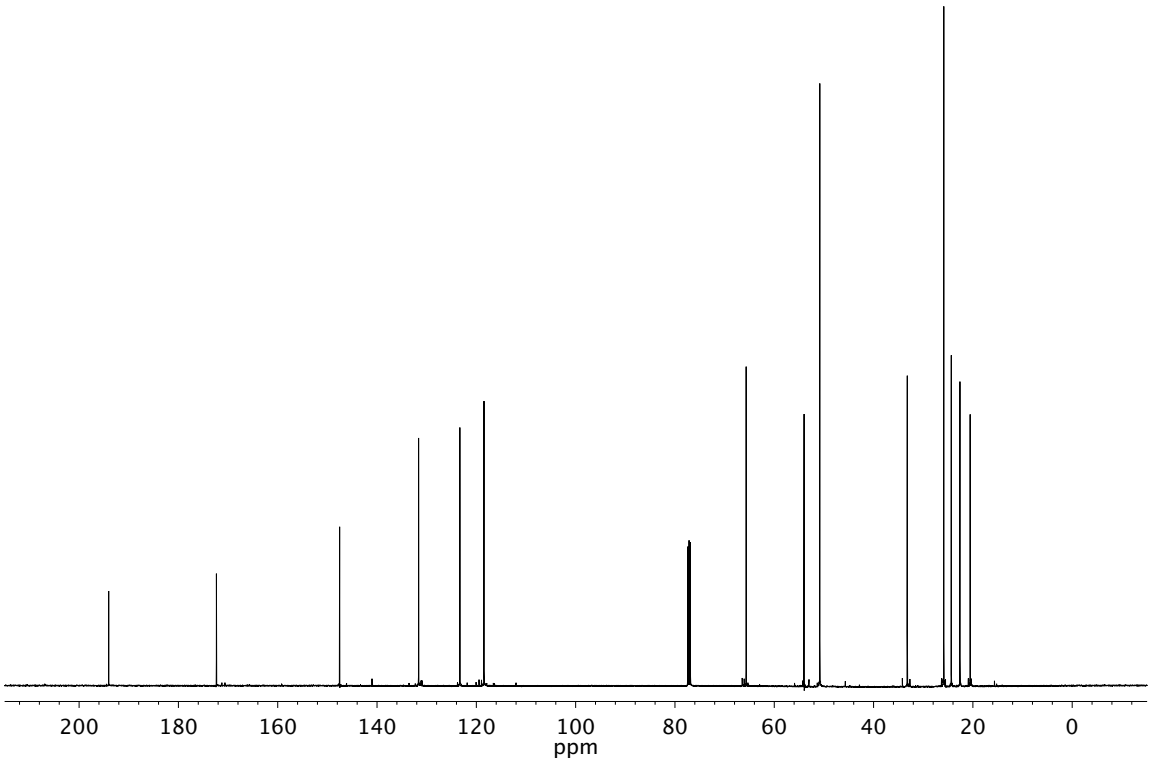
^{13}C NMR (125 MHz, $CDCl_3$) of compound **72**.



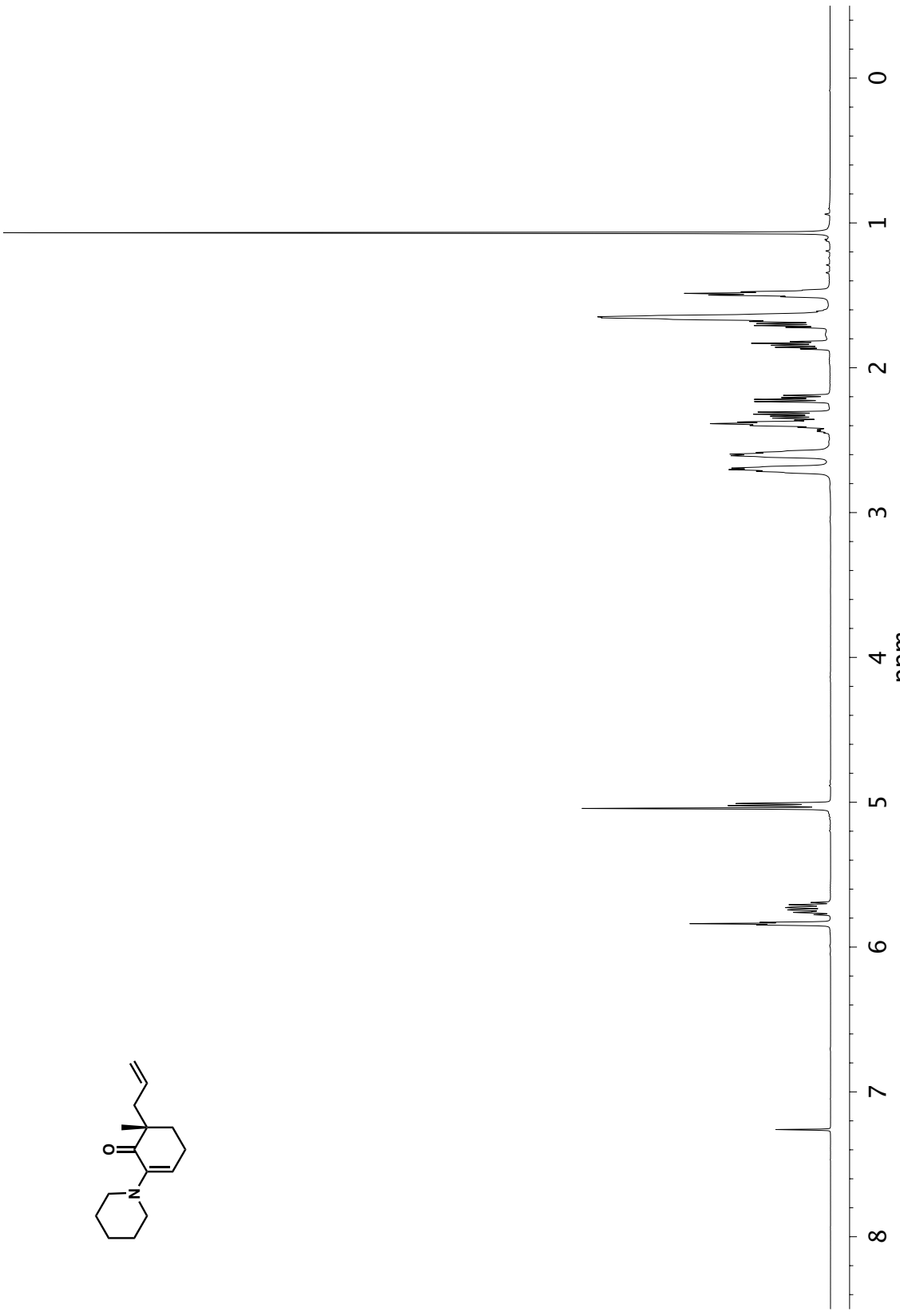
^{1}H NMR (500 MHz, CDCl3) of compound **74**.



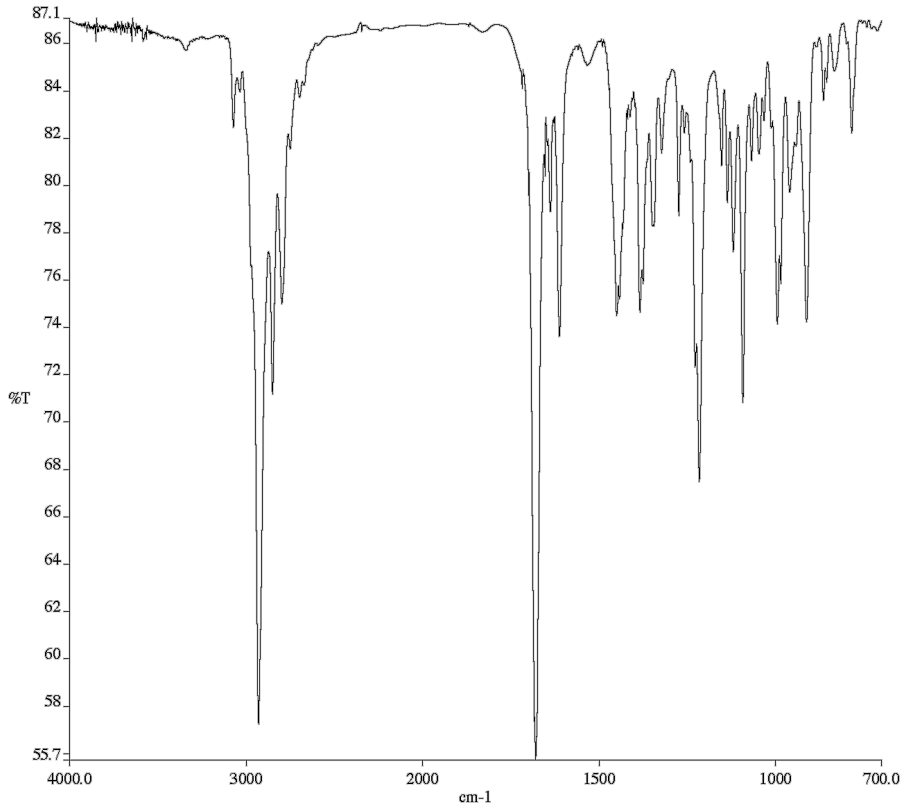
Infrared spectrum (Thin Film, NaCl) of compound **74**.



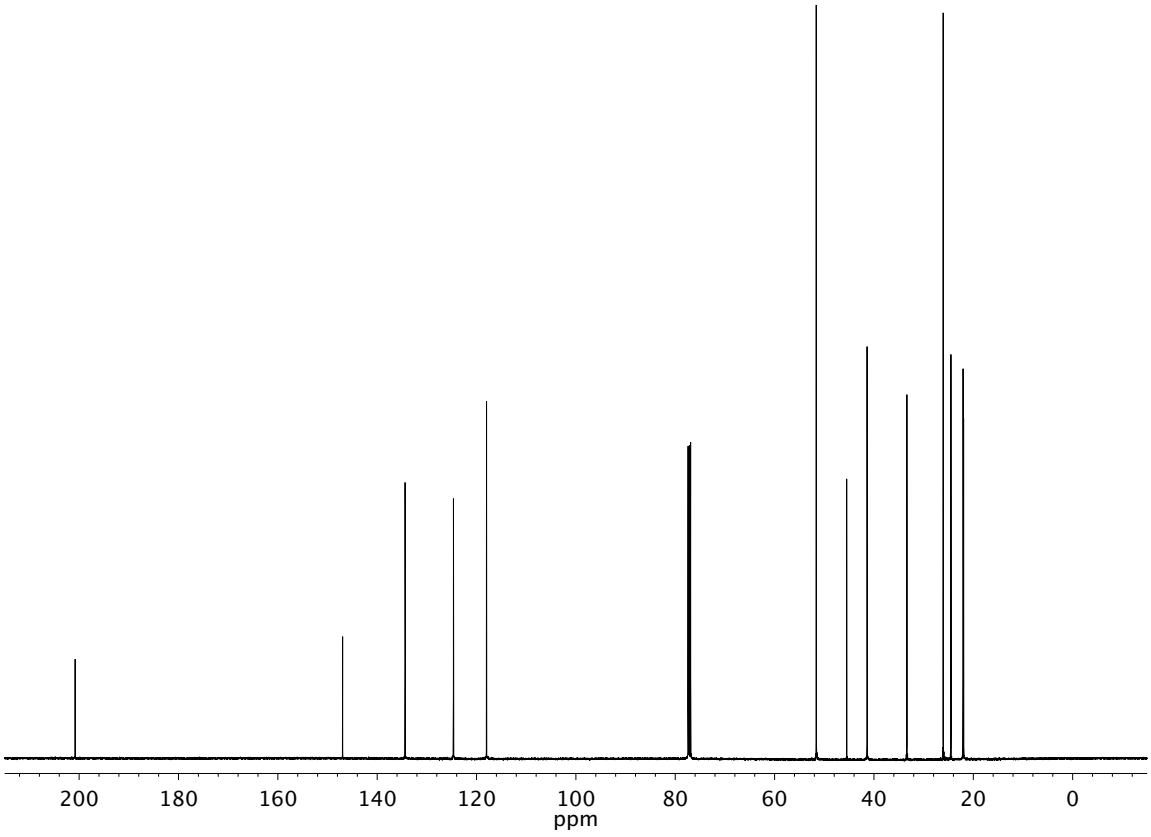
^{13}C NMR (125 MHz, $CDCl_3$) of compound **74**.



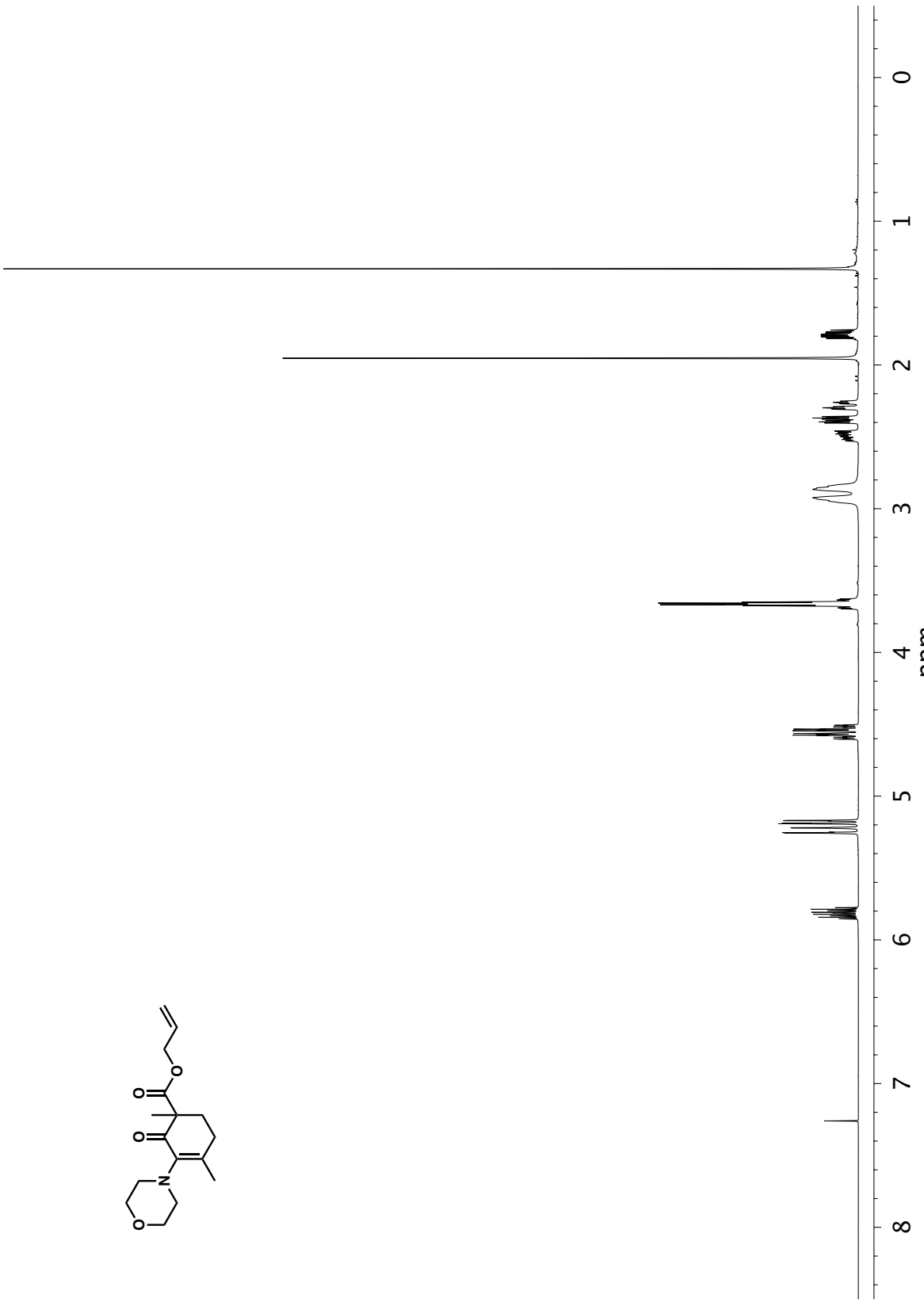
^{1}H NMR (500 MHz, CDCl3) of compound **75**.



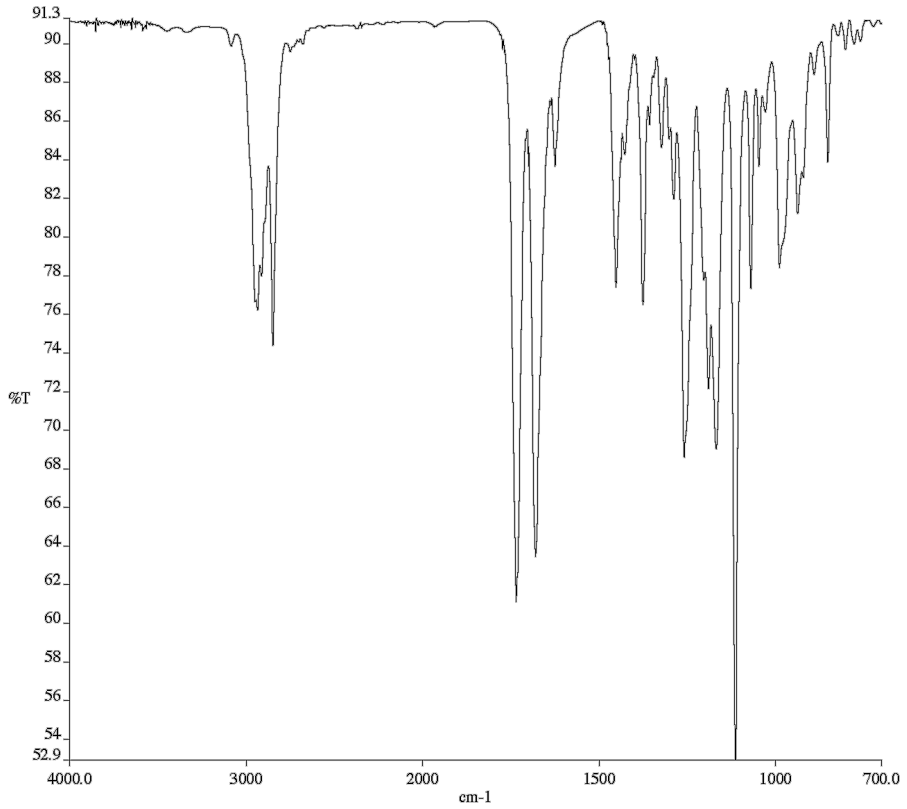
Infrared spectrum (Thin Film, NaCl) of compound **75**.



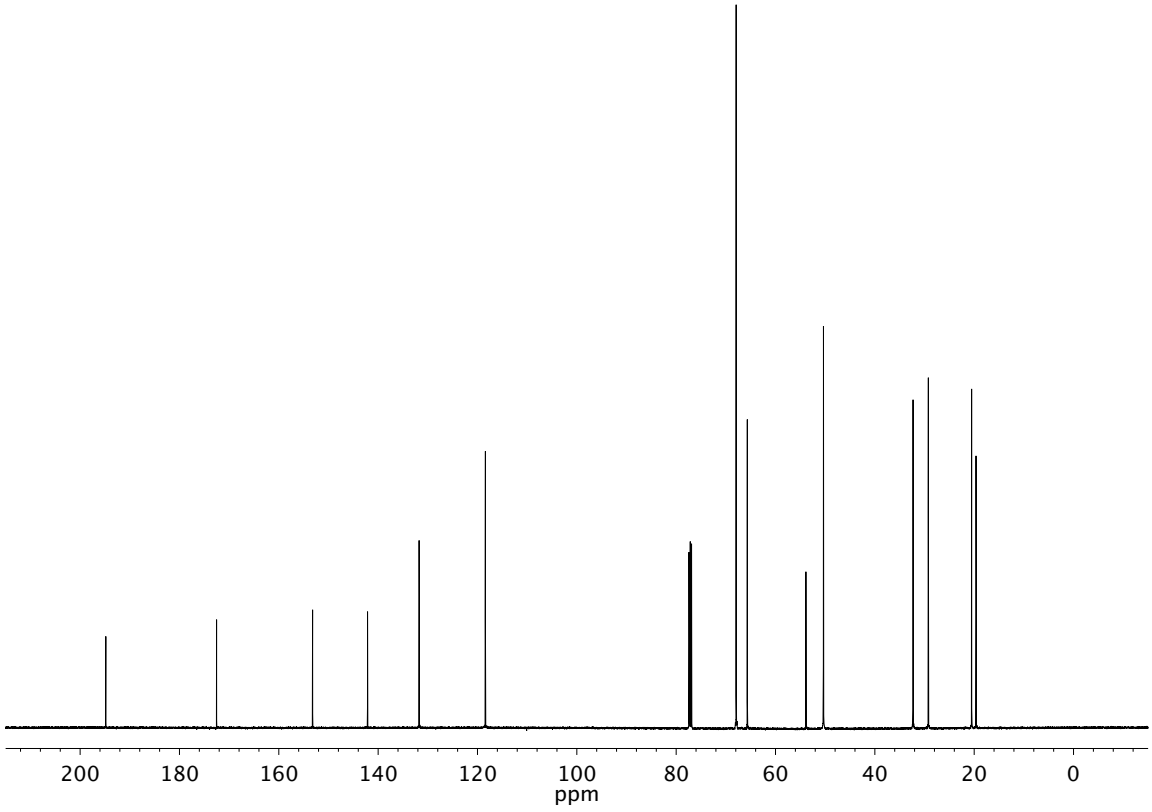
^{13}C NMR (125 MHz, $CDCl_3$) of compound **75**.



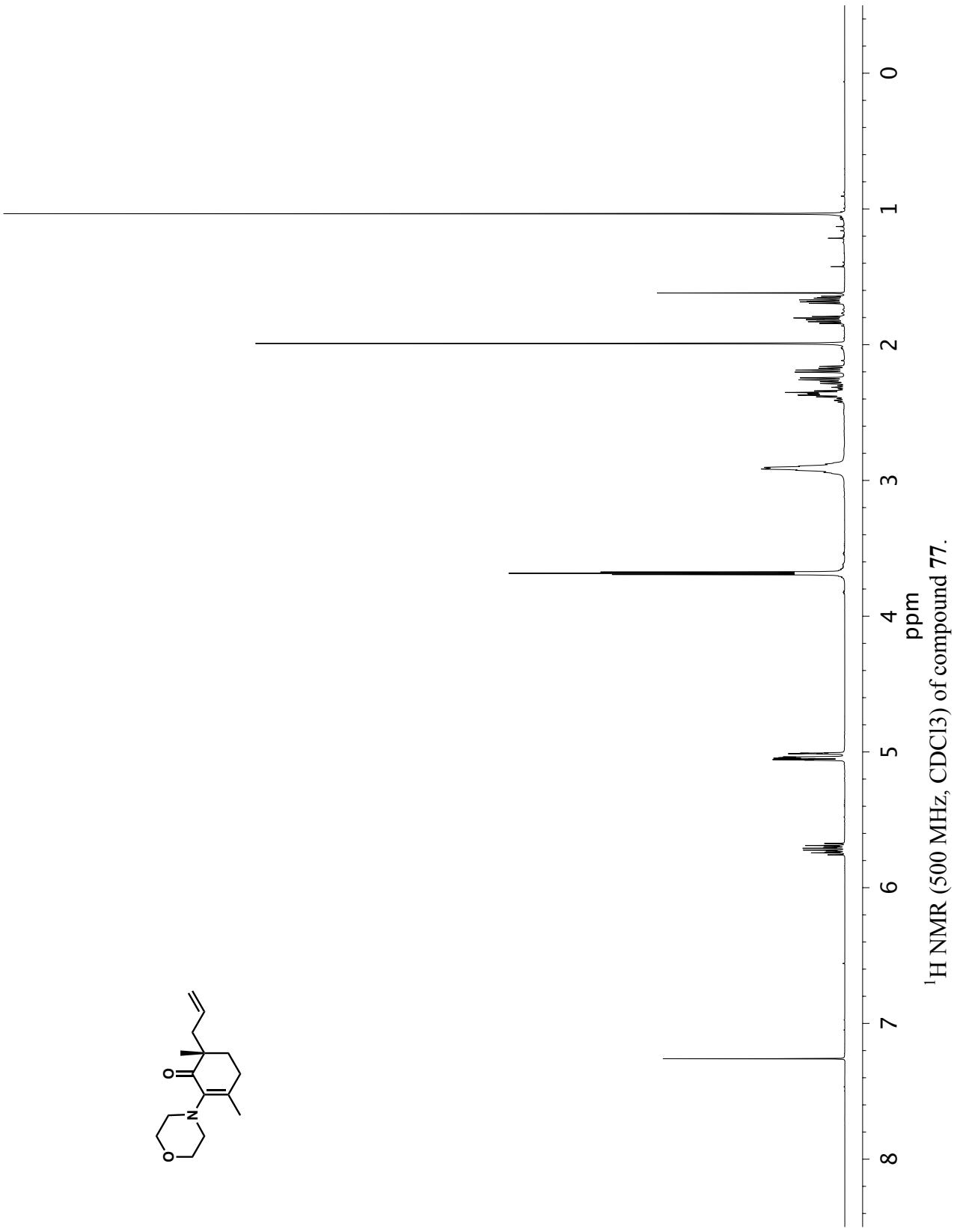
^{1}H NMR (500 MHz, CDCl3) of compound **76**.



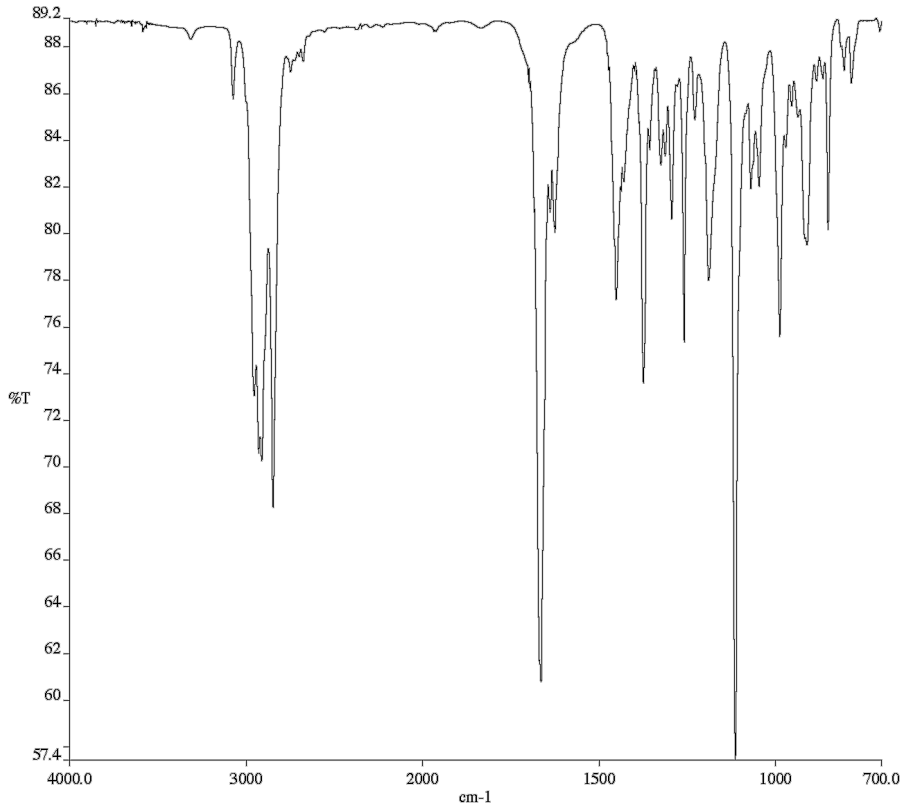
Infrared spectrum (Thin Film, NaCl) of compound **76**.



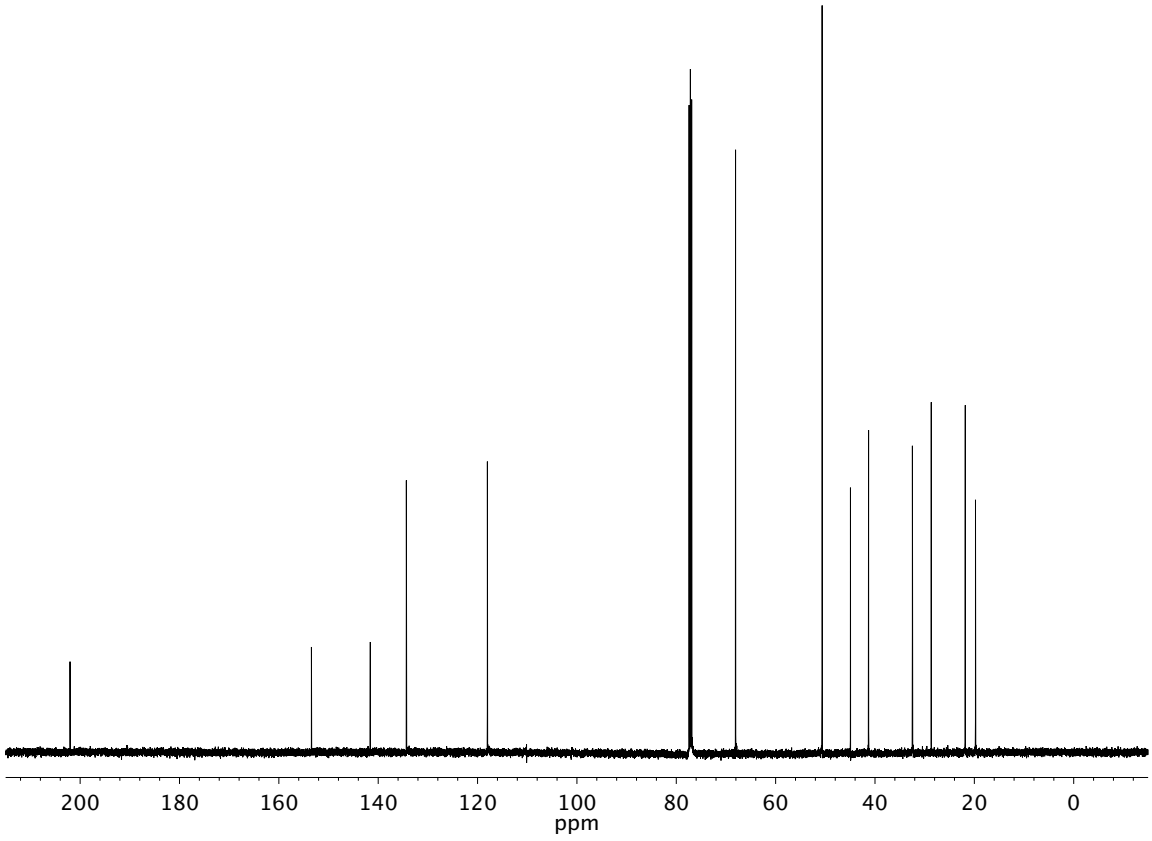
^{13}C NMR (125 MHz, $CDCl_3$) of compound **76**.



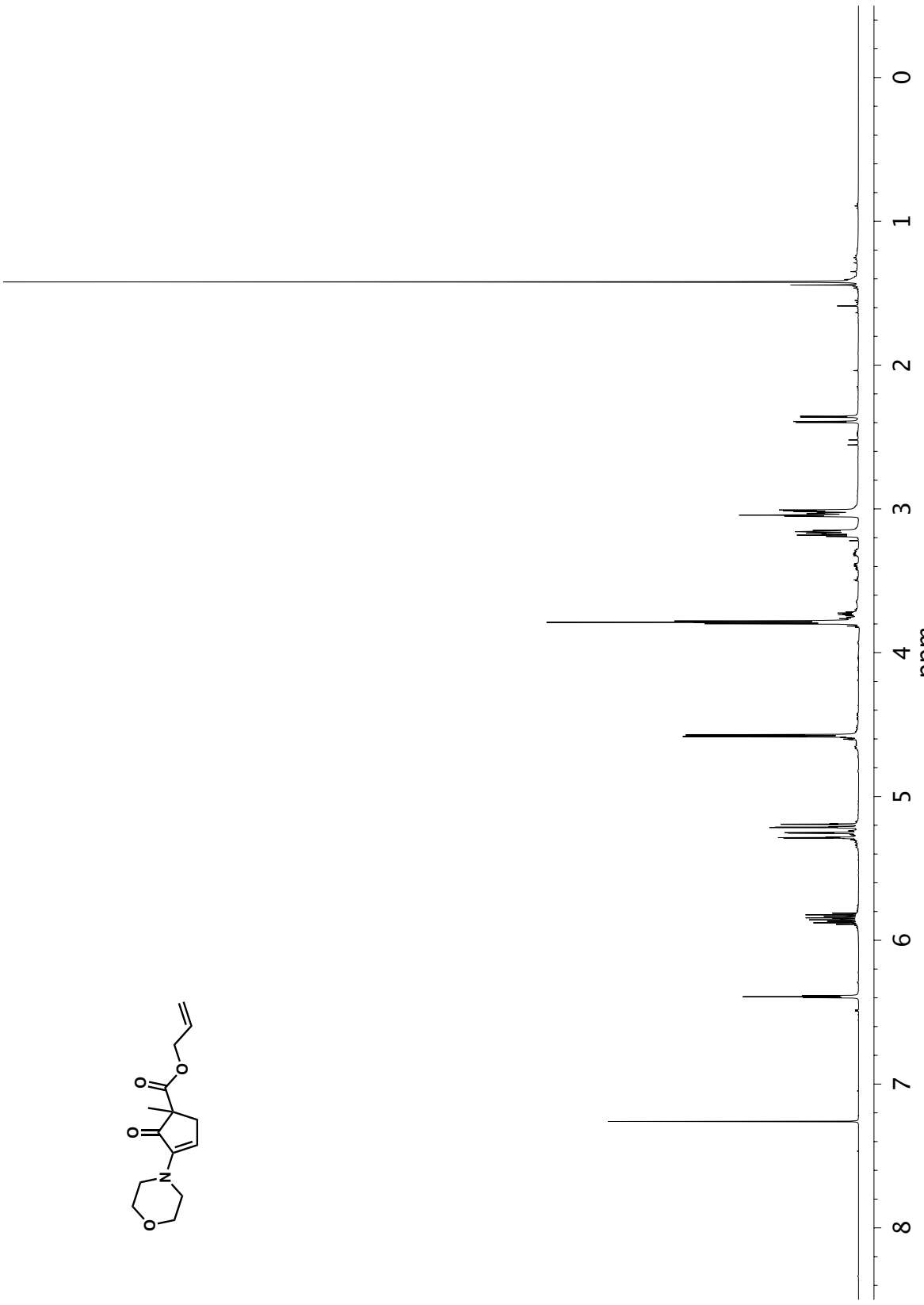
^{1}H NMR (500 MHz, CDCl3) of compound **77**.



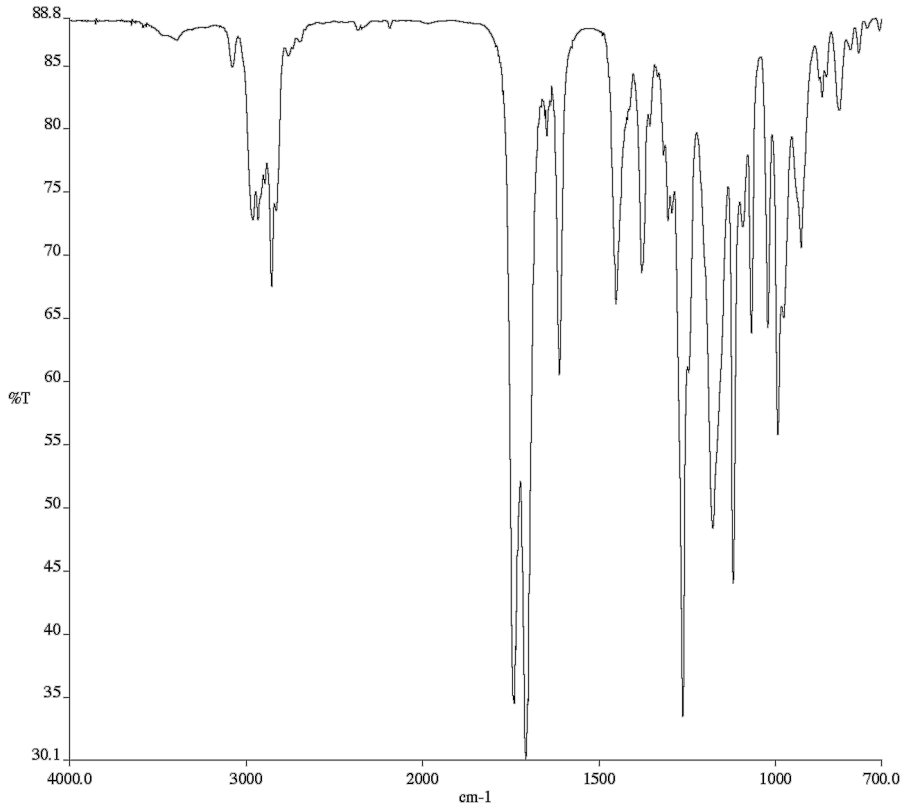
Infrared spectrum (Thin Film, NaCl) of compound **77**.



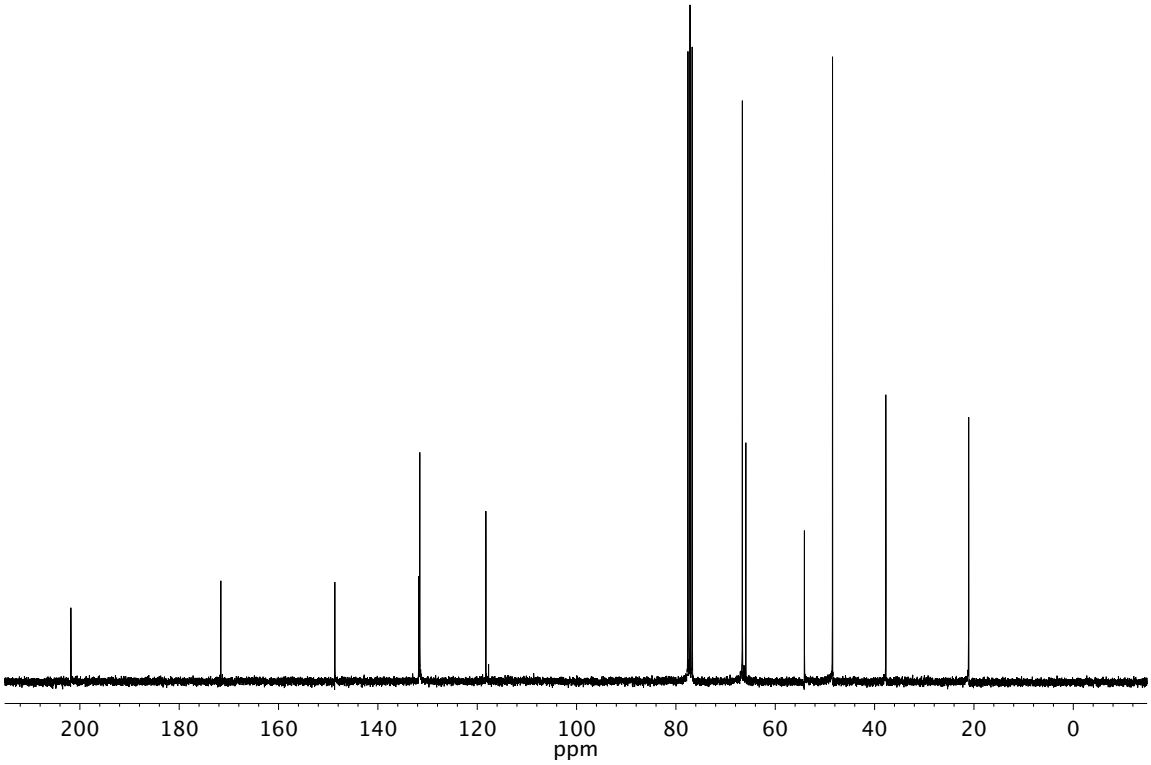
^{13}C NMR (125 MHz, $CDCl_3$) of compound **77**.



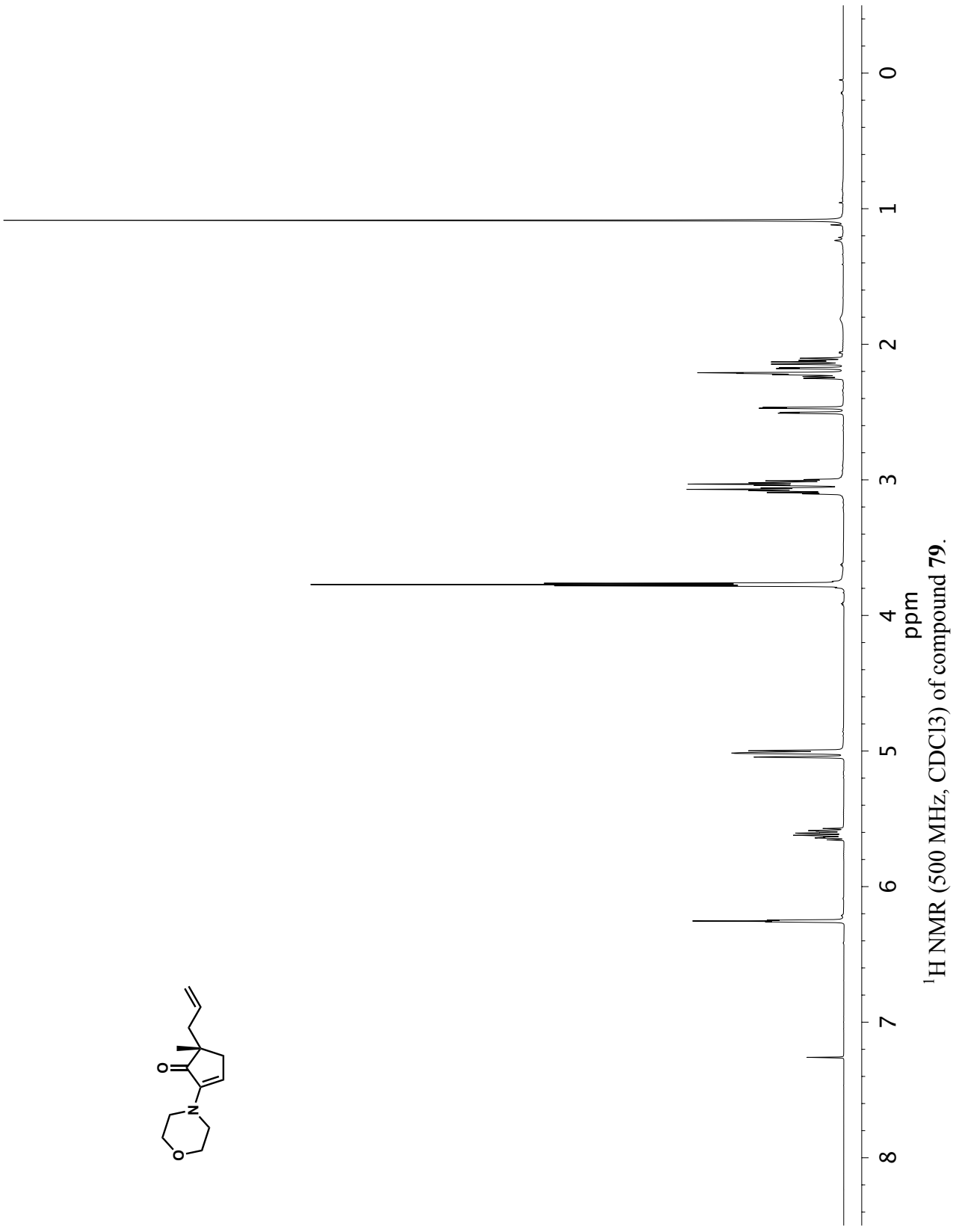
^{1}H NMR (500 MHz, CDCl3) of compound **78**.



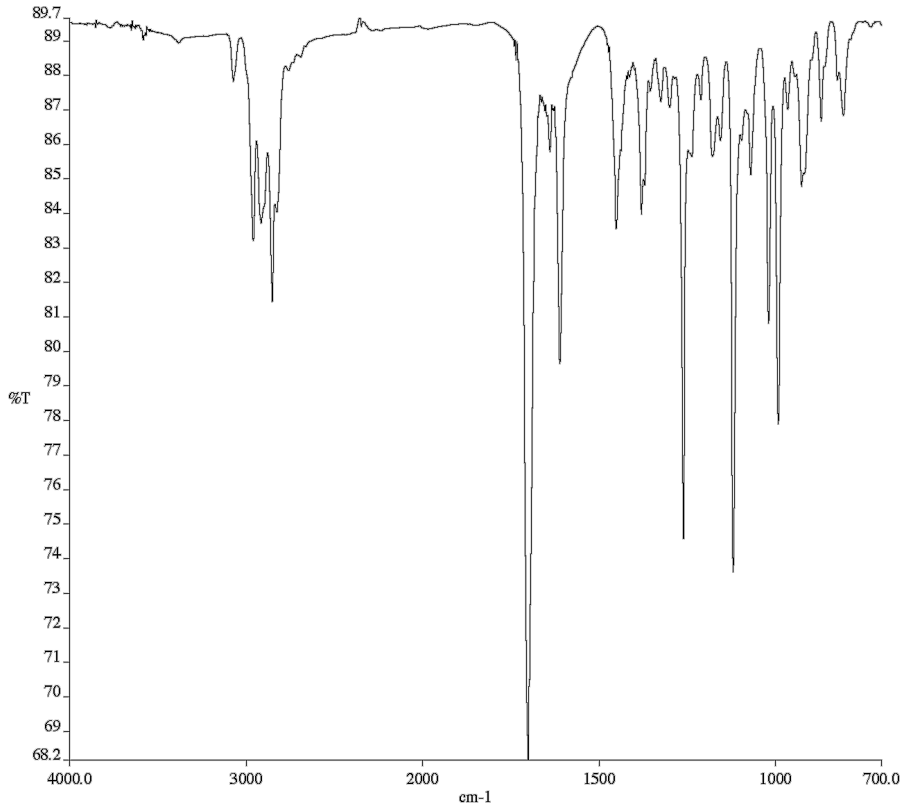
Infrared spectrum (Thin Film, NaCl) of compound **78**.



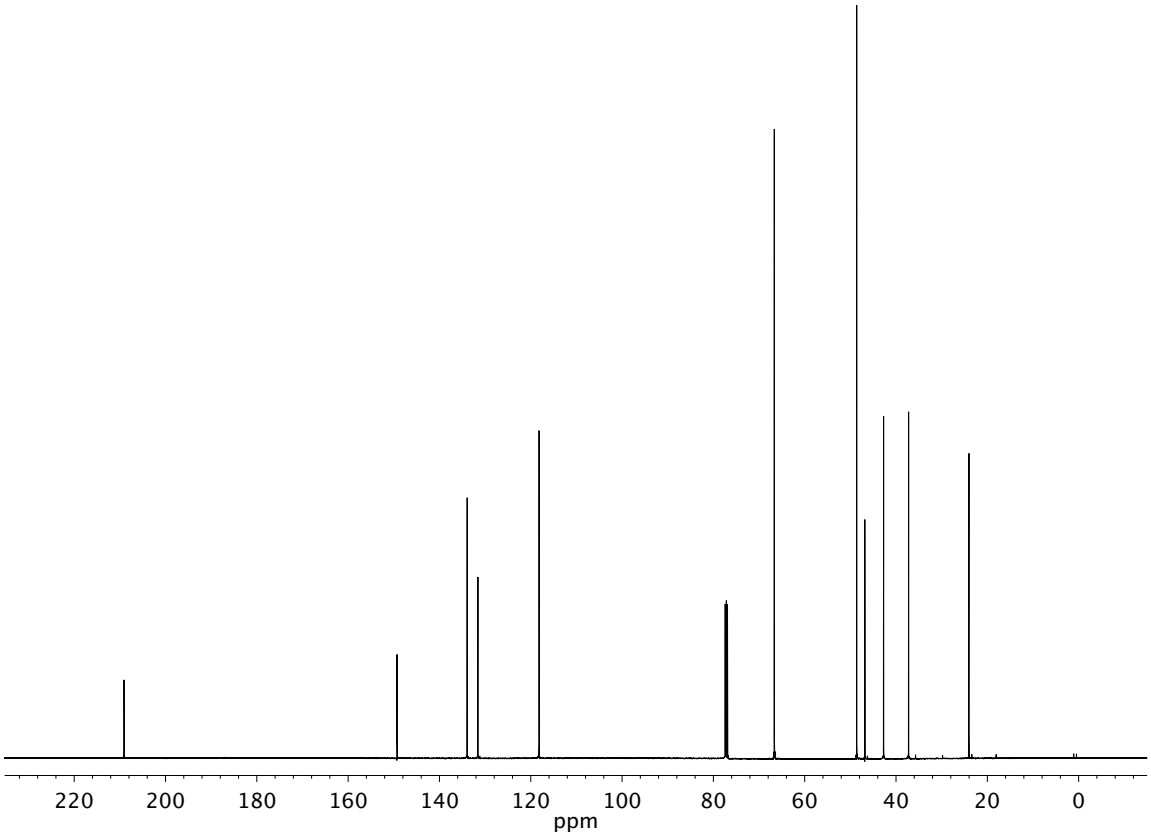
^{13}C NMR (125 MHz, $CDCl_3$) of compound **78**.



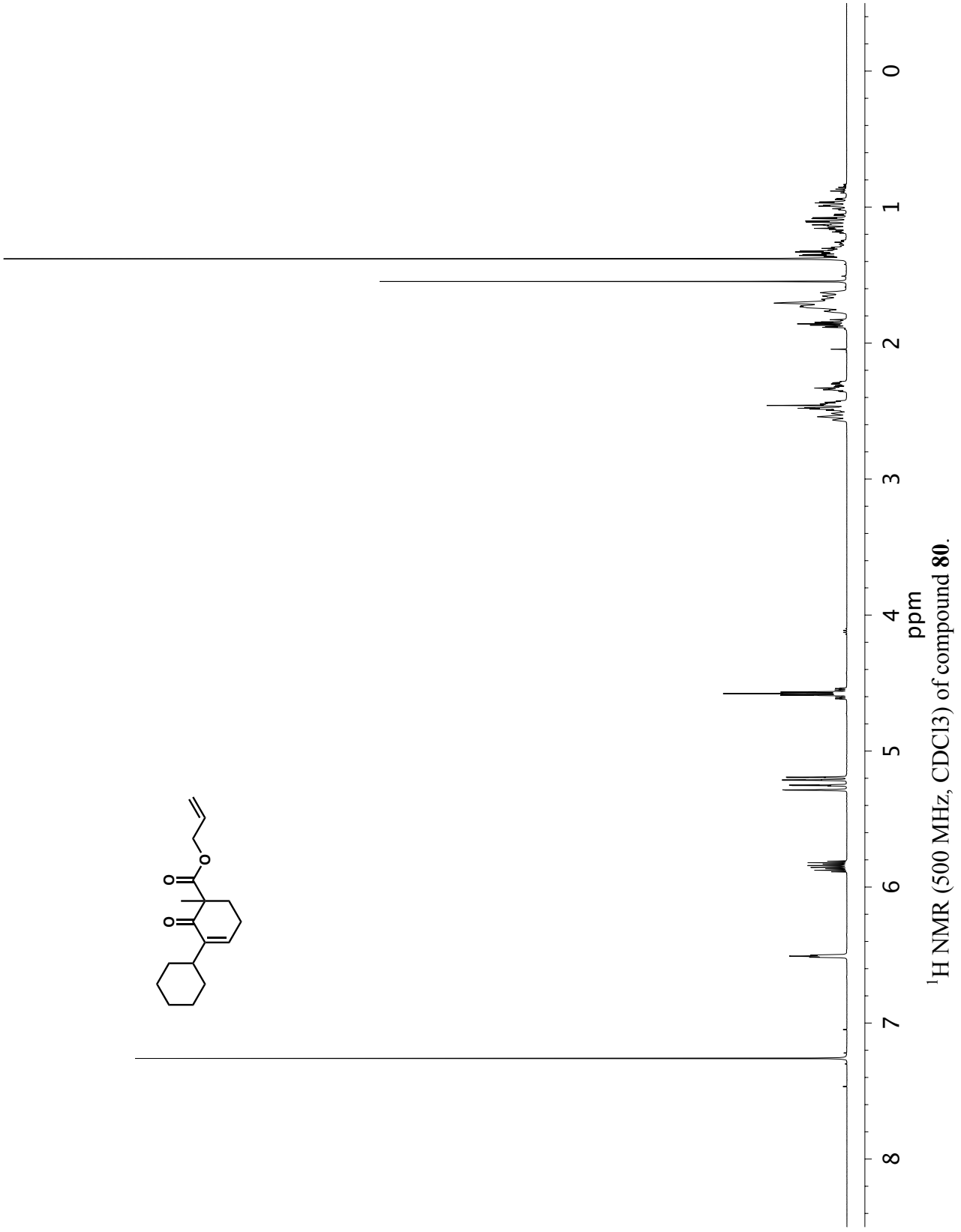
^{1}H NMR (500 MHz, CDCl3) of compound **79**.



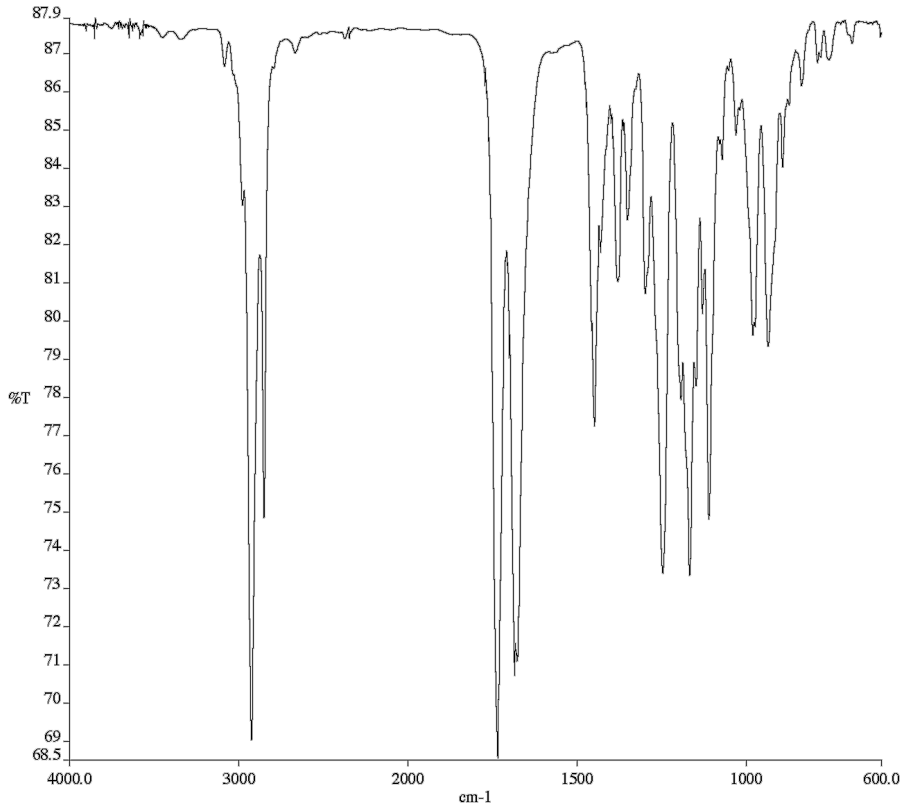
Infrared spectrum (Thin Film, NaCl) of compound **79**.



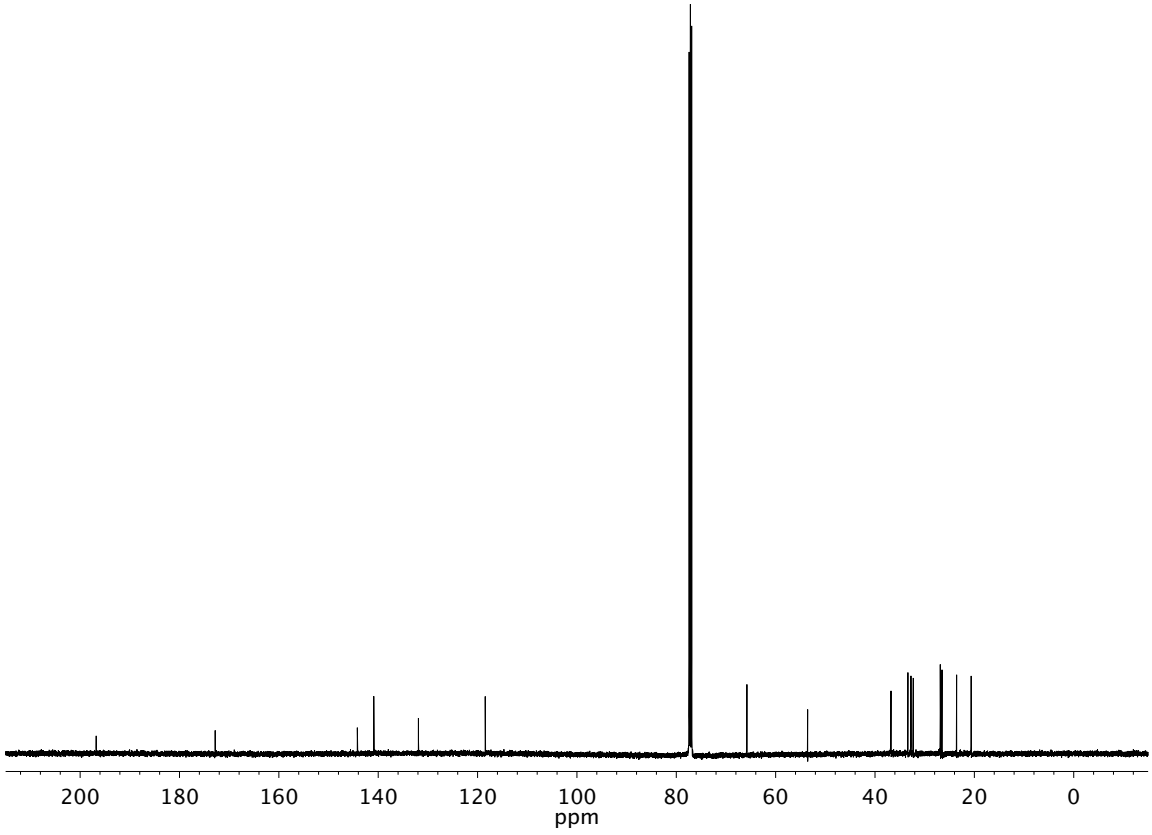
^{13}C NMR (125 MHz, $CDCl_3$) of compound **79**.



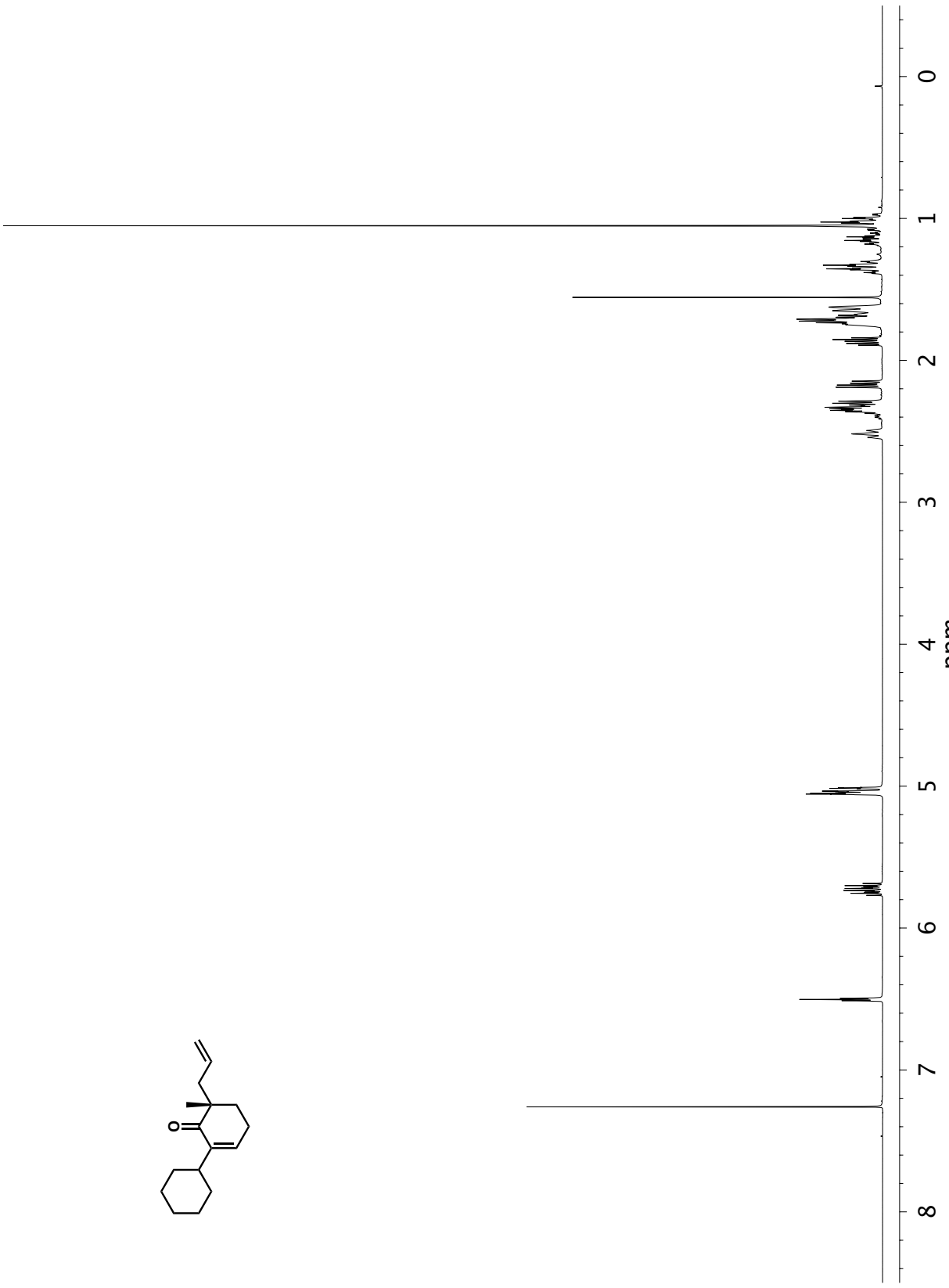
^{1}H NMR (500 MHz, CDCl3) of compound **80**.



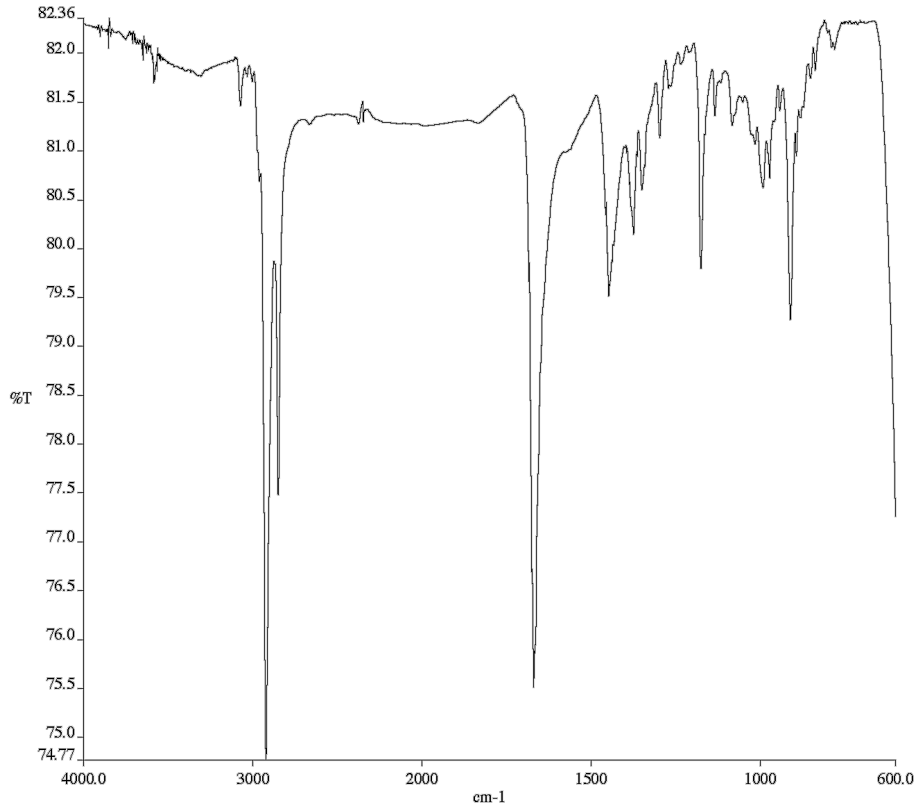
Infrared spectrum (Thin Film, NaCl) of compound **80**.



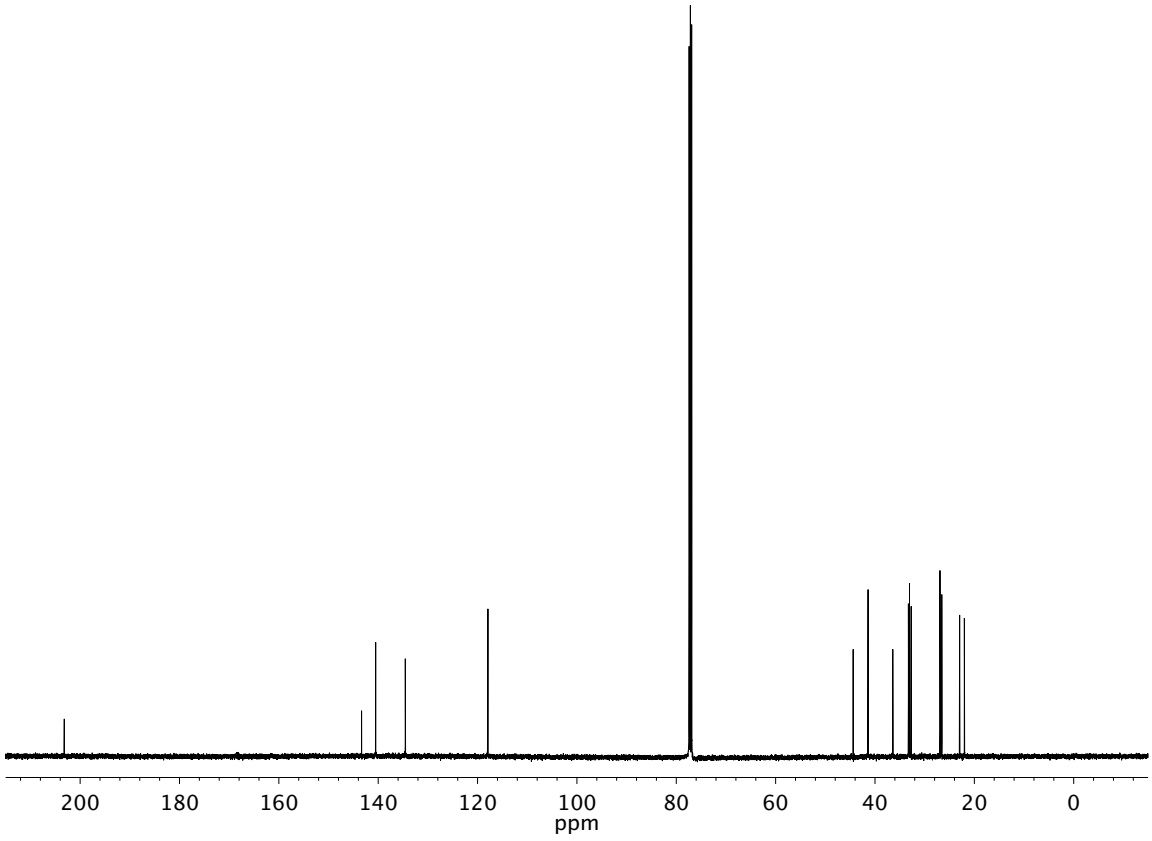
^{13}C NMR (125 MHz, $CDCl_3$) of compound **80**.



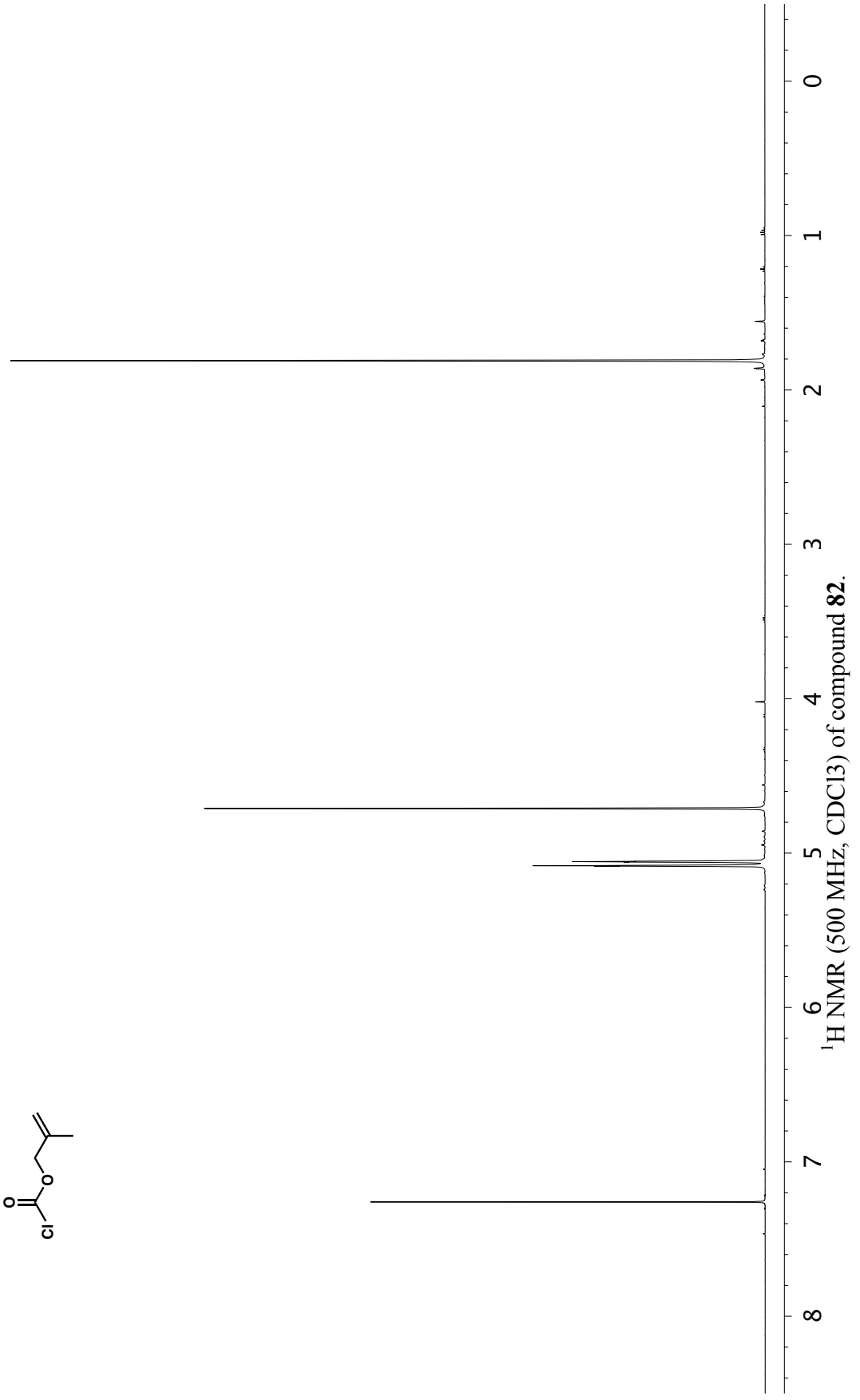
^{1}H NMR (500 MHz, CDCl3) of compound **81**.



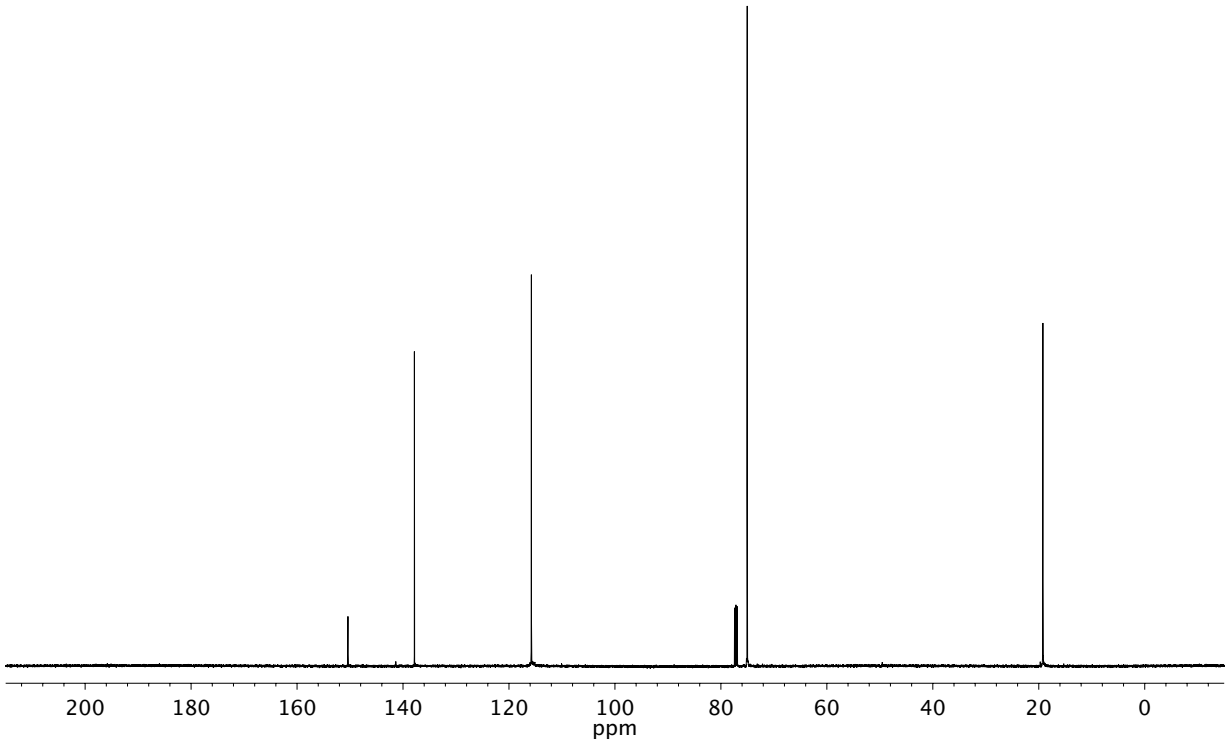
Infrared spectrum (Thin Film, NaCl) of compound **81**.



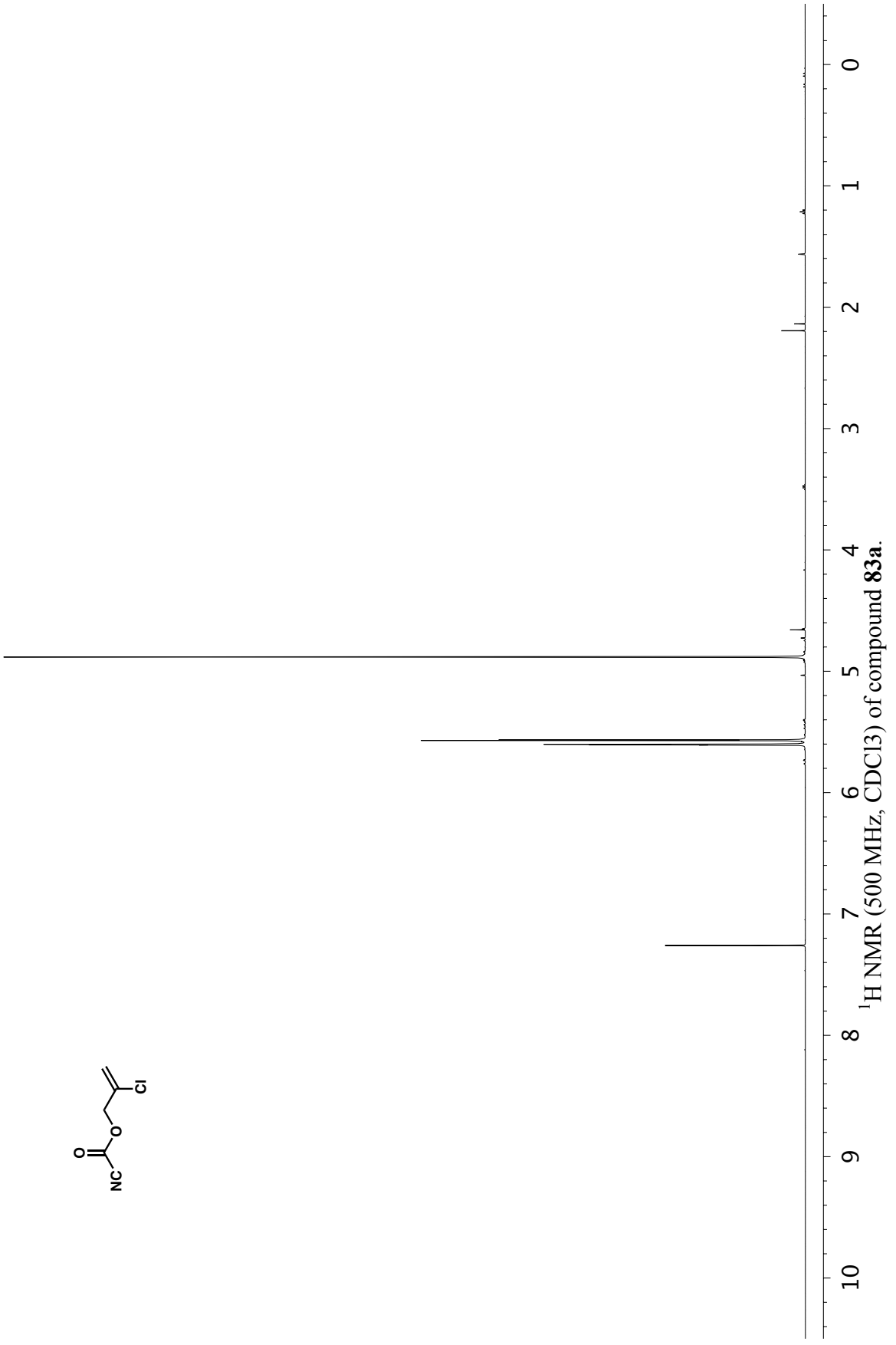
^{13}C NMR (125 MHz, $CDCl_3$) of compound **81**.



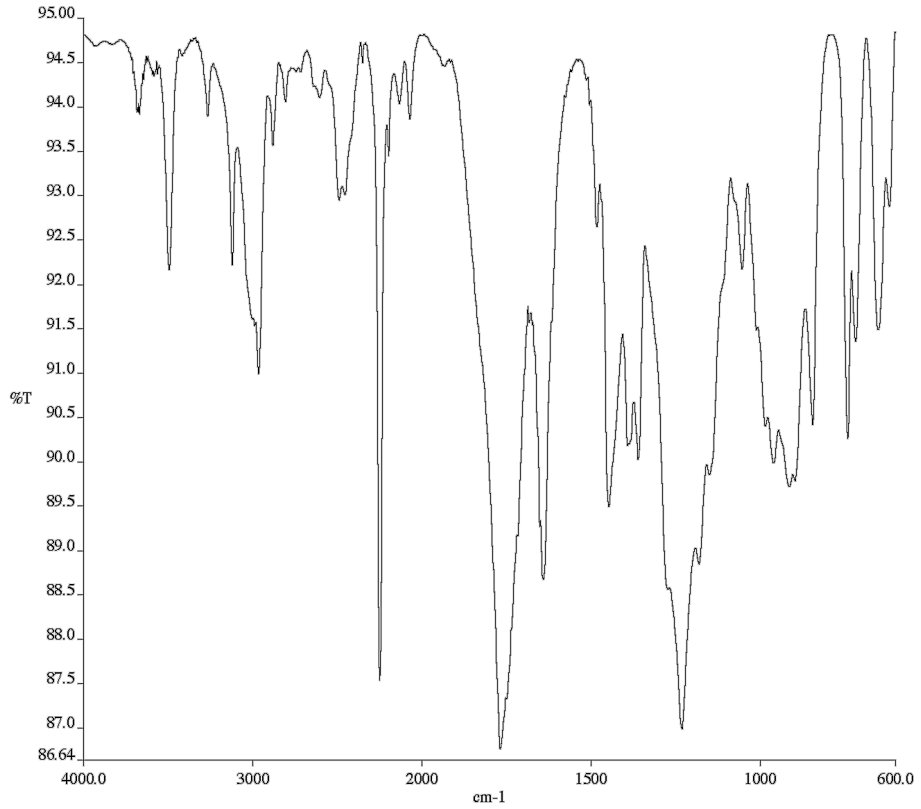
^{1}H NMR (500 MHz, CDCl3) of compound **82**.



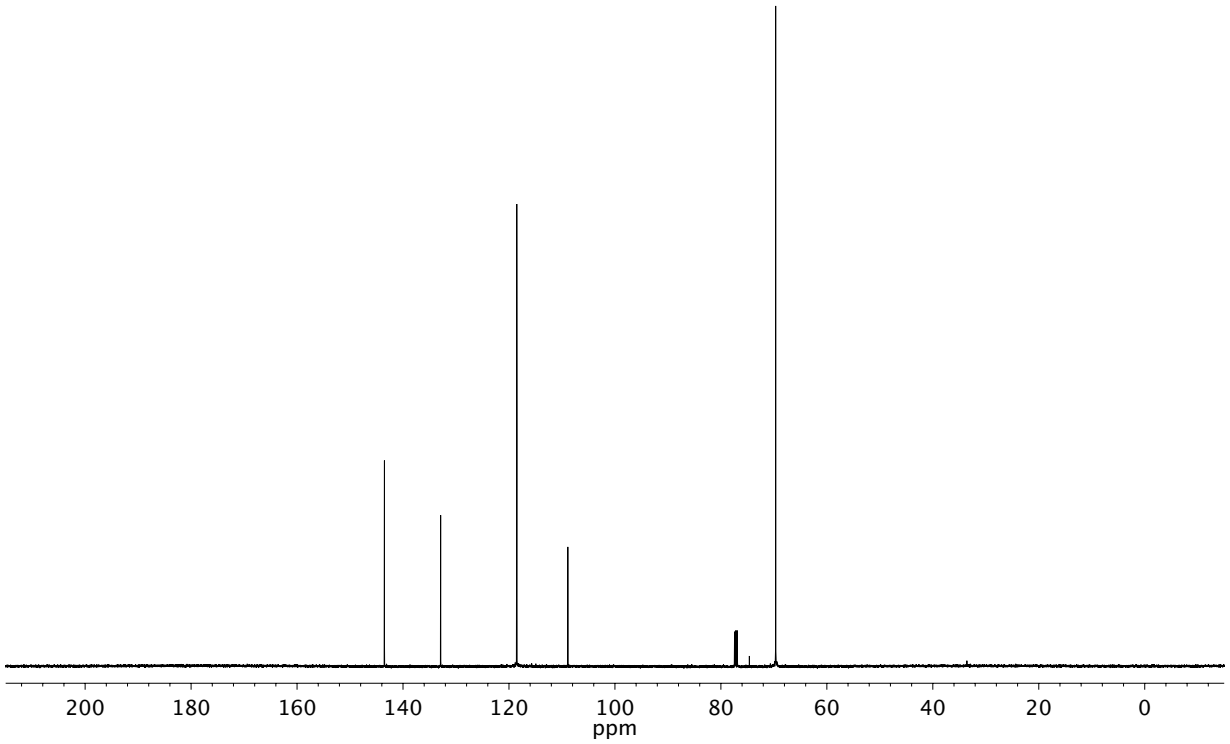
^{13}C NMR (125 MHz, $CDCl_3$) of compound **82**.



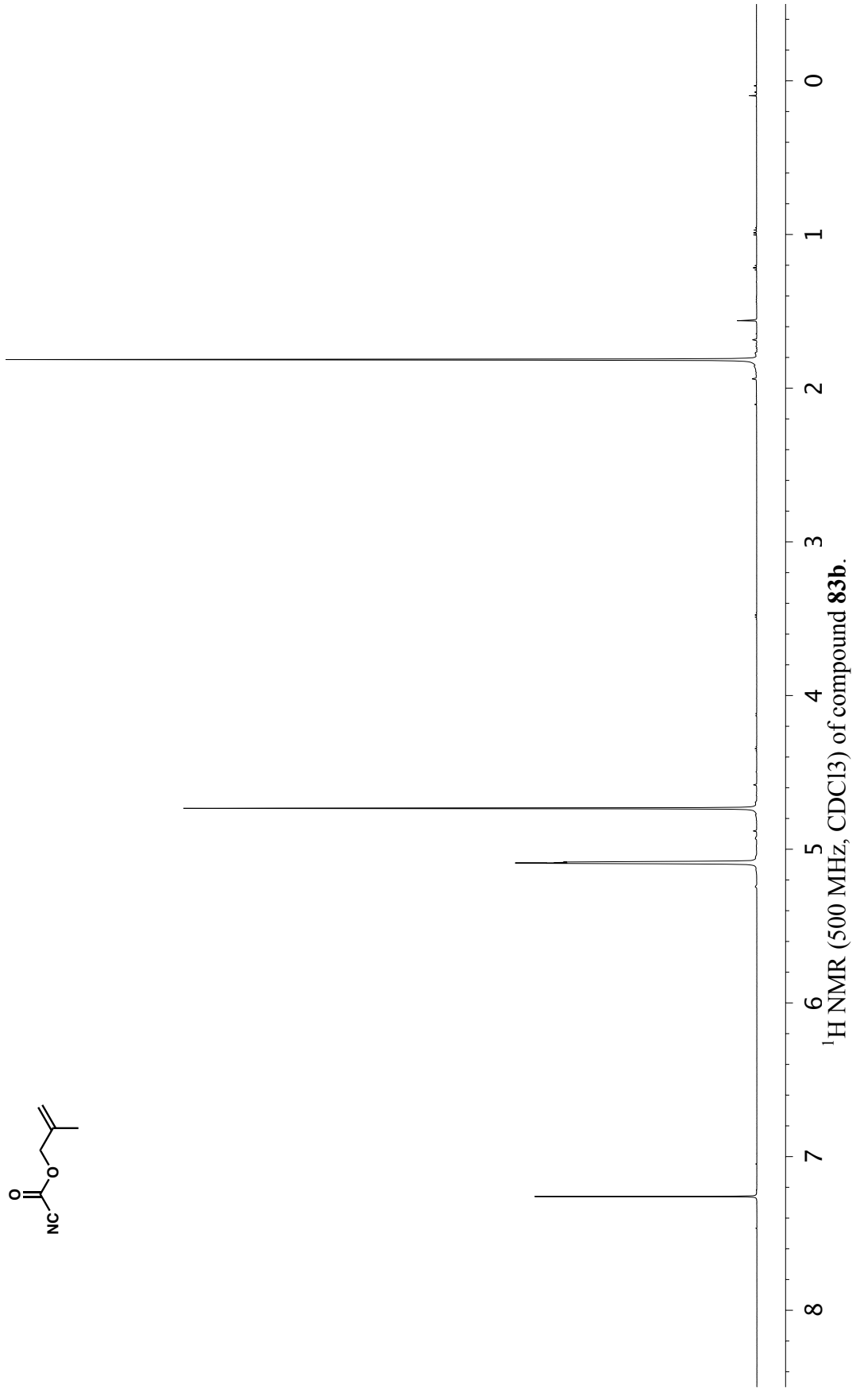
^{1}H NMR (500 MHz, CDCl3) of compound **83a**.



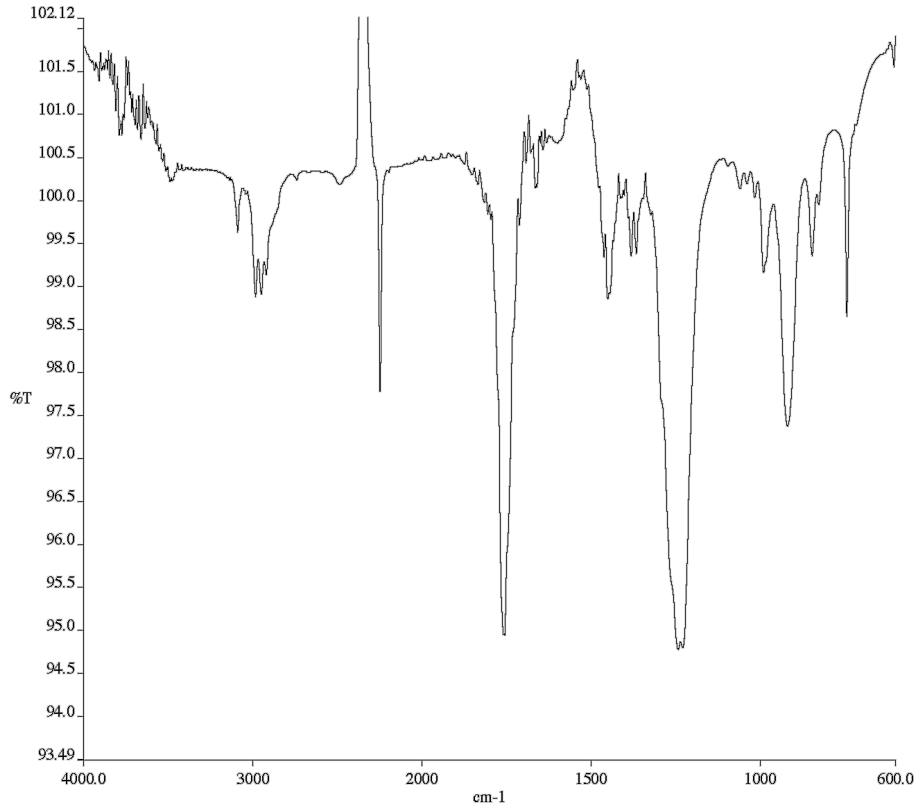
Infrared spectrum (Thin Film, NaCl) of compound **83a**.



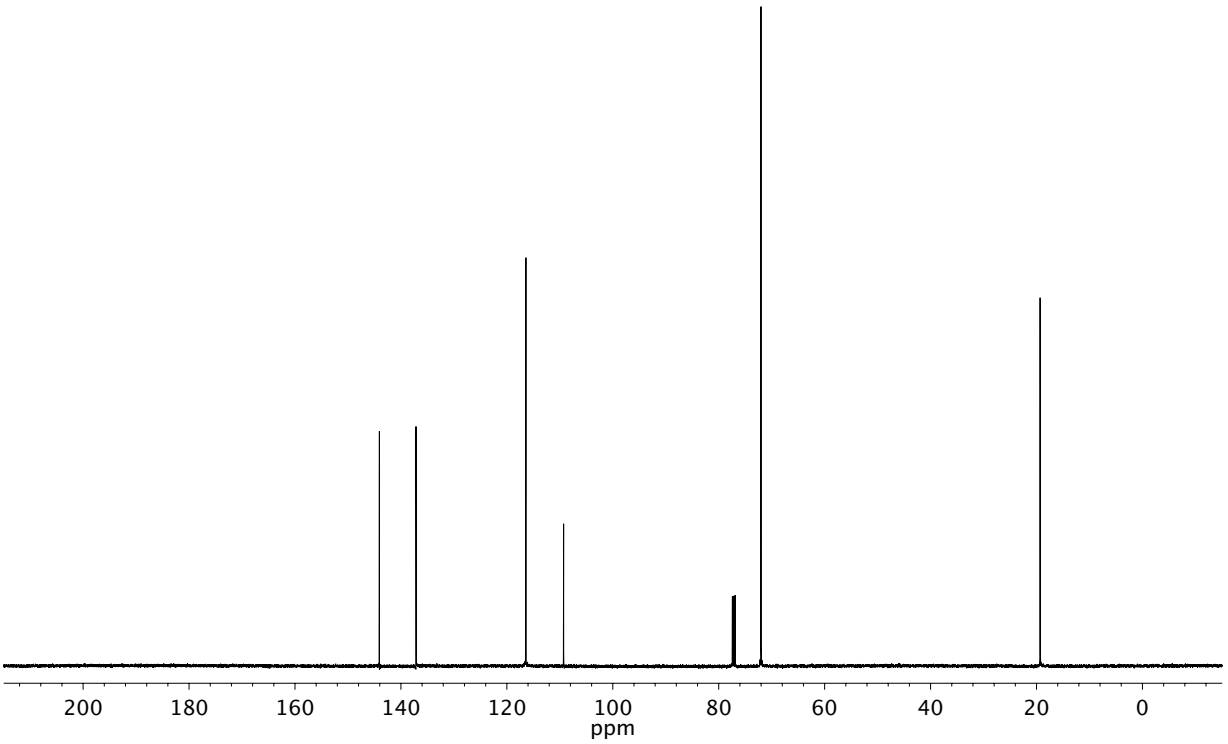
^{13}C NMR (125 MHz, $CDCl_3$) of compound **83a**.



^{1}H NMR (500 MHz, CDCl3) of compound **83b**.



Infrared spectrum (Thin Film, NaCl) of compound **83b**.



^{13}C NMR (125 MHz, $CDCl_3$) of compound **83b**.

CHAPTER 3

The Palladium-Catalyzed Asymmetric Decarboxylative Allylic Alkylation for Formation of De Novo Acyclic Quaternary Stereocenters[†]

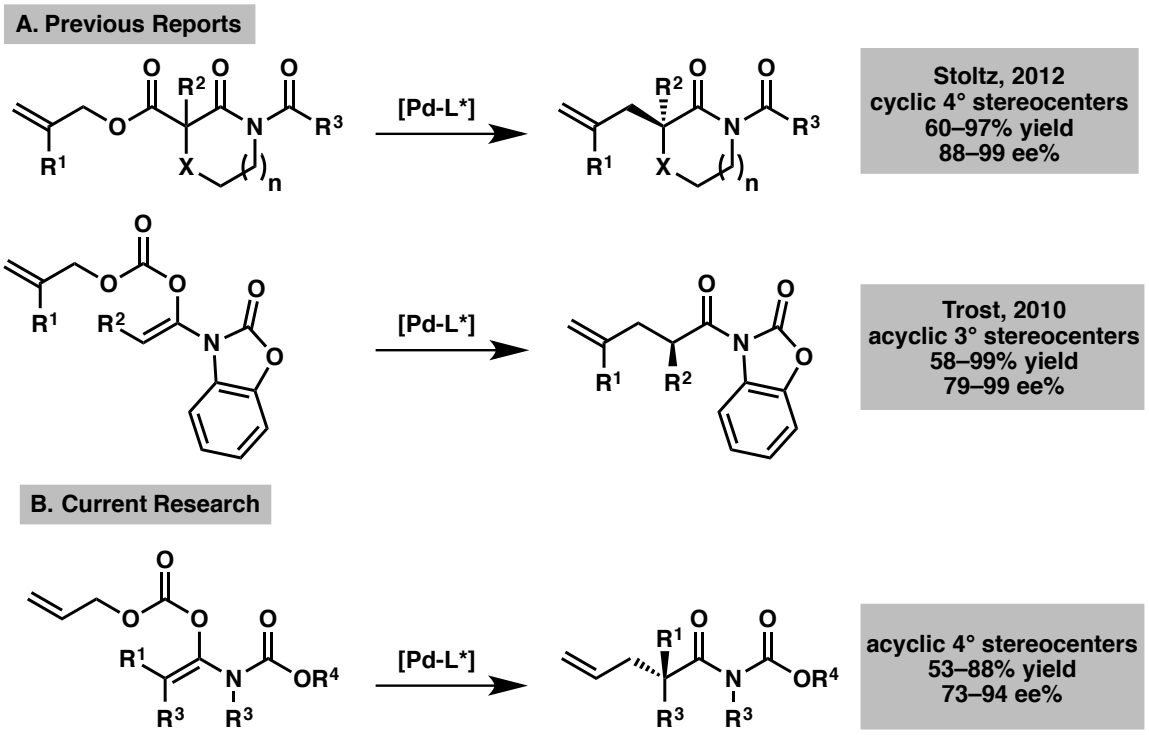
3.1 INTRODUCTION AND BACKGROUND

As discussed in previous chapters, synthesis of all-carbon quaternary stereocenters represents an important challenge to organic chemists. While methods for access to all-carbon to quaternary centers in cyclic systems are limited, synthesis of such moieties in acyclic systems is particularly challenging due to the lack of rigidity that can be utilized to establish a favored stereochemical outcome. Only a handful of methods exist to access all-carbon quaternary stereocenters from simple starting materials in an enantioselective manner.[1,2] Despite the recent surge in development of alternative surrogates[2e,2f] the prevailing majority of these approaches rely on either the use of stereodefined trisubstituted alkenes as substrates[2a–d] or the regioselective *in situ* formation of fully-substituted intermediates bearing heteroaromatic substitution[3] such as

[†] This research was performed in collaboration with Drs. Pavel Starkov and Jared A. Moore and Prof. Ilan Marek.

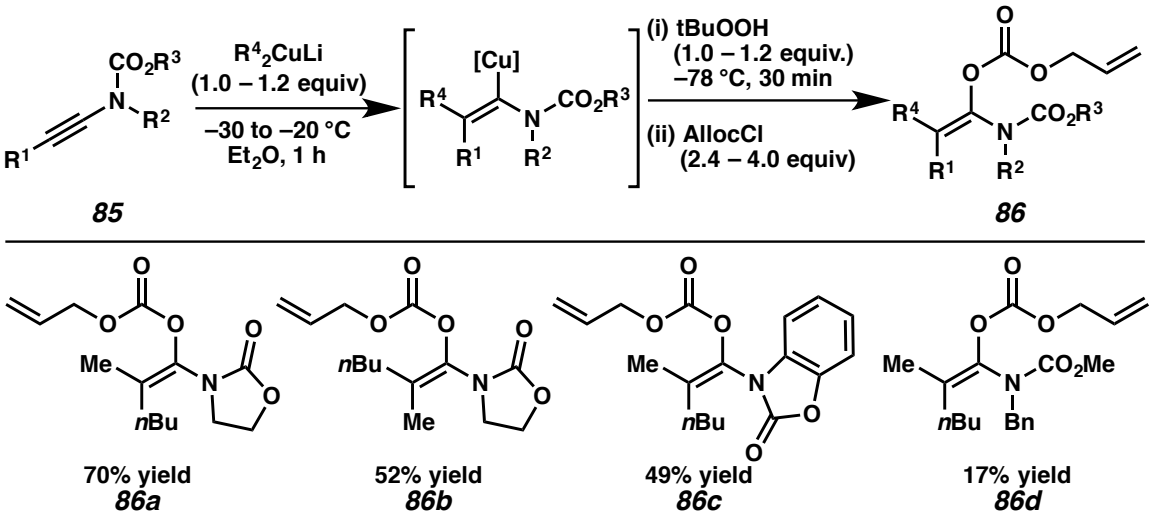
enamines[2g–l] and enolates[2j,3k] as well as ester,[2l,2m] thioester,[3n] and amide[2o,2p,4,6] enolates (Scheme 3.1).

Scheme 3.1. Asymetric allylic alkylation of amide enolates.



In acyclic systems, typical synthetic strategies (e.g. the use of sterically-hindered bases, directing groups or cyclic starting materials to favor *E* or *Z*-enolate formation by deprotonation or decarboxylation) may set distinct limits to the range of substrates relevant to the method. Therefore, developing more general routes to access differentially substituted enolates is an important challenge for the synthesis of all-carbon quaternary stereocenters in acyclic systems.

Scheme 3.2. One-pot method for the synthesis of stereodefined amide enolates.



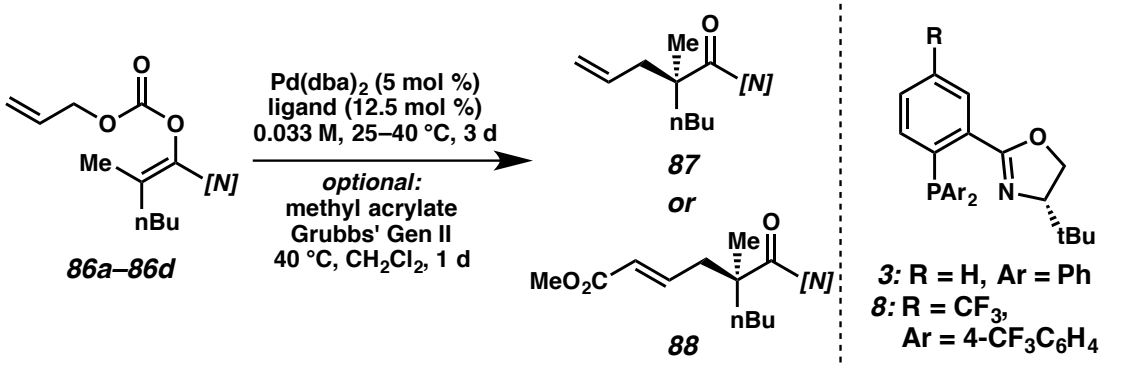
To this end, the Marek group has developed methods for the addition of organocuprates to ynecarbamates **85** to form vinyl cuprate intermediates in a stereodefined fashion (Scheme 3.2).[4] These intermediates may be trapped under oxidative conditions, maintaining stereochemical control, resulting in fully-substituted amide enolates **86** with well-defined stereochemistry. In particular, trapping with *tert*-butyl peroxide and allyl chloroformate yields a product which is particularly attractive as a substrate for the palladium-catalyzed decarboxylative allylic alkylation (DAA) reaction.[5,6] Given our group's experience and success with this reaction, we decided to pursue these substrates as a general entry into all-carbon quaternary centers in acyclic systems.

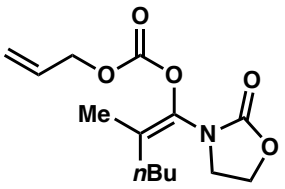
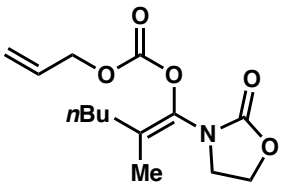
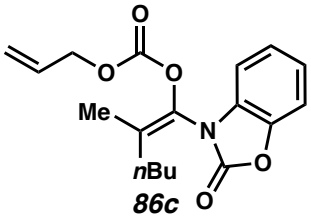
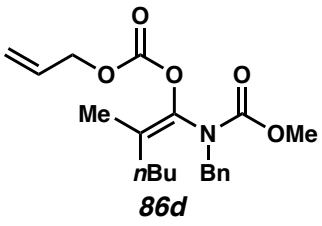
3.2 RESULTS AND DISCUSSION

3.2.1 Initial Screening Efforts

Our investigations began with a screen of a number of model substrates (Scheme 3.2) provided by the Marek group using the phosphinooxazoline (PHOX) ligand system previously found to be successful in our group (Table 3.1, next page). Due to the lack of a strong chromophore and difficulty in separation of some products (**87**), we found it to be necessary to perform an olefin cross-metathesis with methyl acrylate on the products of the DAA before analysis by chiral HPLC or SFC (**88**). While the tris(trifluoromethyl)-*tert*-butyl PHOX ligand **8** proved superior to the standard *tert*-butyl PHOX ligand **3** in all cases, neither ligand provided satisfactory enantioselectivity despite the wide range of solvents screened. The largest *ee* value obtained was with oxazolidinone substrate **86b** and CF_3-PHOX ligand **8**, with a value of 50% and 52% *ee* in THF and toluene respectively (Table 3.1, entries 10 and 11). Benzoxazolidinone substrate **86c** failed to produce material of higher than 10% *ee* under any conditions, while acyclic carbamate **86d** fared slightly better, delivering an *ee* of 38% in toluene with ligand **8** (Table 3.1, entry 24). Notably, reversing the enolate geometry resulted in an inversion of the stereochemical outcome of the reaction (i.e. between substrates **86a** and **86b**), indicating that the stereochemical information of the enolate was retained throughout the transformation.

Table 3.1. Initial screening efforts with PHOX ligands.



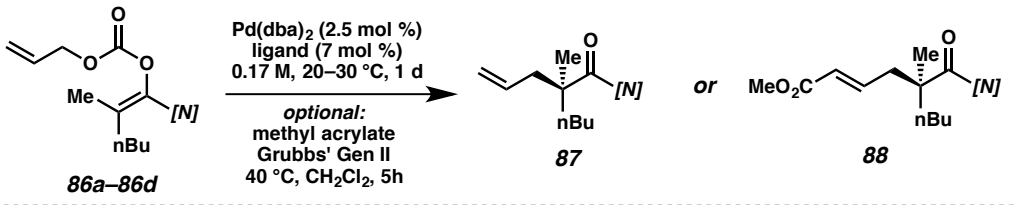
entry	substrate	ligand	solvent	ee%
1		3	THF	0
2			MTBE	1
3			PhMe	0
4		8	THF	15
5			MTBE	28
6	86a		PhMe	15
7		3	THF	–10
8			PhMe	–10
9			EtOAc	–4
10		8	THF	–50
11			PhMe	–52
12	86b		EtOAc	–34
13		3	THF	1
14			MTBE	4
15			PhMe	5
16		8	THF	9
17			MTBE	2
18	86c		PhMe	6
19		3	THF	4
20			MTBE	8
21			PhMe	12
22		8	THF	24
23			MTBE	24
24	86d		PhMe	38

Given the lack of success with the *P*,*N*-PHOX ligands, we turned to the C_2-symmetric, biphosphine ligands developed and employed by Trost and coworkers. In particular, these ligands were deemed promising due to the substantial difference in mechanism of enantioinduction established between the two systems.[7] While the PHOX ligands have been determined to react via a metal-bound, inner sphere Pd-enolate intermediate, the biphosphine class of ligands has been found to react via an outer sphere mechanism in which the enolate is not bound to the palladium allyl complex.

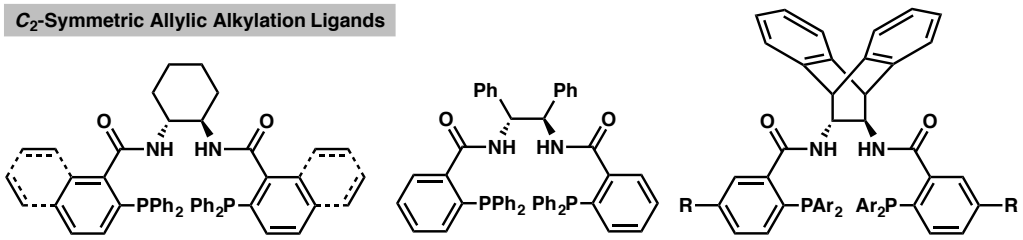
Gratifyingly, the diamine-linked *P*,*P*-ligands provided enhanced enantioselectivities compared to those observed with the PHOX ligands (Table 3.2, next page). Additionally, ethyl acetate, tetrahydrofuran, and dioxane were determined to be promising solvents for the reaction, while MTBE and acetonitrile provided far lower enantioselectivity, and dichloromethane resulted in poor conversion (not shown in table 3.2).

Out of the diamine scaffolds examined in our initial screens, anthracene-based ligand **92** gave consistently better results. Accordingly, we prepared and evaluated two additional derivatives to test the effect of additional steric bulk (**93**) and modulating the ligand electronics (**94**), akin to the differences observed between standard PHOX **3** and tris(trifluoromethyl)-PHOX ligand **8**. Multifunctional, bulky ligand **94** unfortunately hindered reactivity (Table 3.2, entries 10 and 25). Electron-deficient ligand **93**, however, gratifyingly furnished products with good selectivity, and in particular acyclic carbamate **86d** was found to proceed with 94% ee in ethyl acetate using this ligand (Table 3.2, entry 24). Also notable, with this ligand system acyclic carbamate **86d** outperformed the oxazolidinone substrate **86a**.

Table 3.2. Screening Results with P,P-Trost ligands.



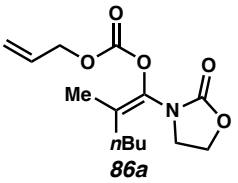
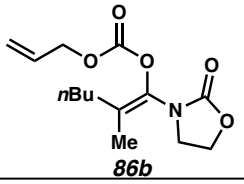
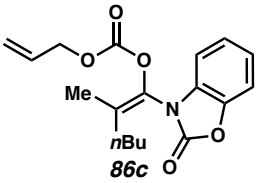
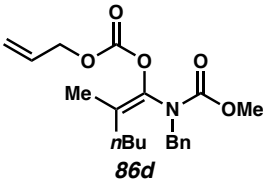
C_2-Symmetric Allylic Alkylation Ligands



89, aryl
90, napthyl

91

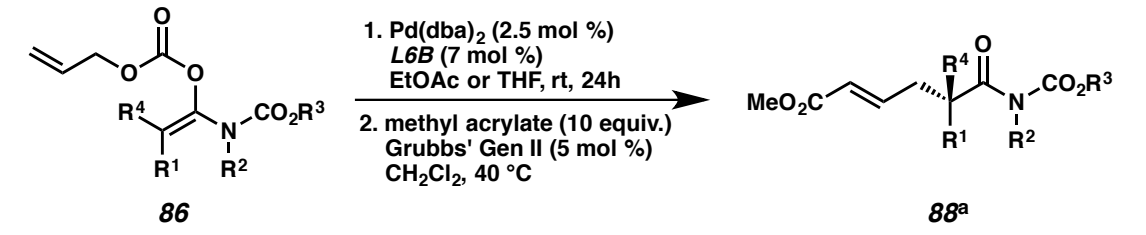
92, R = H, Ar = Ph
93, R = CF_3, Ar = 4-$CF_3C_6H_4$
94, R = H, Ar = 2-$CH_3C_6H_4$

entry	substrate	ligand	solvent	ee%
1		89	DO	54
2			THF	64
3		90	DO	70
4			THF	75
5		91	THF	–70
6		92	THF	70
7			EtOAc	72
8		93	THF	70
9			EtOAc	62
10		94	THF	NR
11		91	THF	47
12			EtOAc	46
13		92	THF	–30
14			EtOAc	–36
15		90	THF	32
16		92	THF	57
17		89	THF	–72
18		90	THF	–74
19		91	THF	60
20			EtOAc	68
21		92	THF	–85
22			EtOAc	–84
23		93	THF	–85
24			EtOAc	–94
25		94	THF	NR

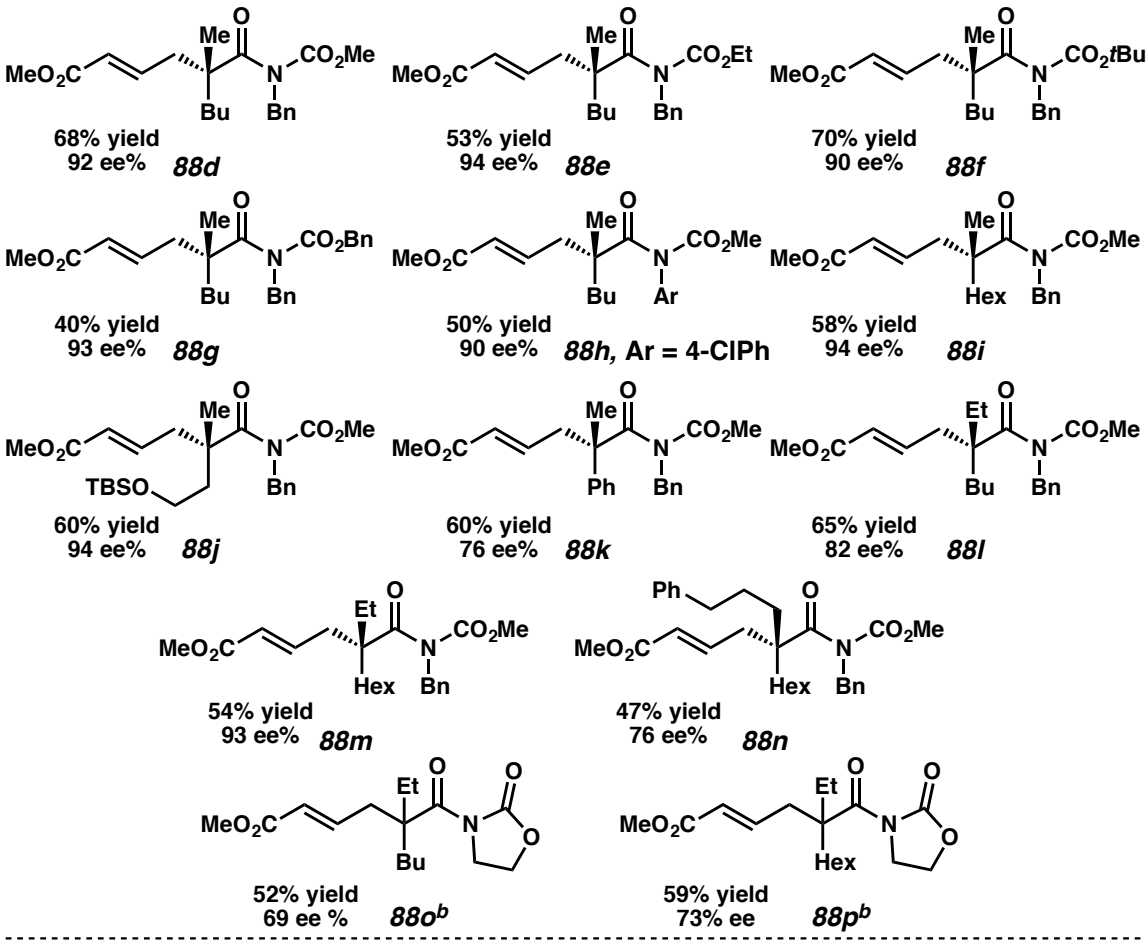
3.2.2 Substrate Scope

Given the success of substrate **86d**, the Marek group was able to furnish a number of additional amide enolate substrates for investigation (Table 3.3, next page).[8] Generally, these substrates yielded products with high enantioselectivities (≥90 ee%) and in moderate yield over the two-step DAA-metathesis sequence. Alteration of the substituent on the carbamate oxygen (**88d-g**) and nitrogen (**88h**) as well as simple changes to the larger substituent on the alkene (**88i, 88j**) was well tolerated and did not result in a substantial change in the observed ee. Phenyl substitution on the alkene, however, resulted in a dramatic decrease in *ee* to 76% (**88k**). Changing the (*E*)-methyl substituent to an ethyl group (**88l**) resulted in a slight loss of *ee* to 82%, but enantioselectivity was recovered upon enlarging the (*Z*)-butyl group to a hexyl group (**88m**). Adding further bulk to the (*E*)-substituent again resulted in a significant loss of enantioselectivity (**88n**). As noted in our previous screen, the enantioselectivity observed for cyclic carbamates **86o** and **86p** was also substantially diminished.

Table 3.3. Substrate scope for synthesis of linear quaternary stereocenters by DAA.



86 ***88***[a]

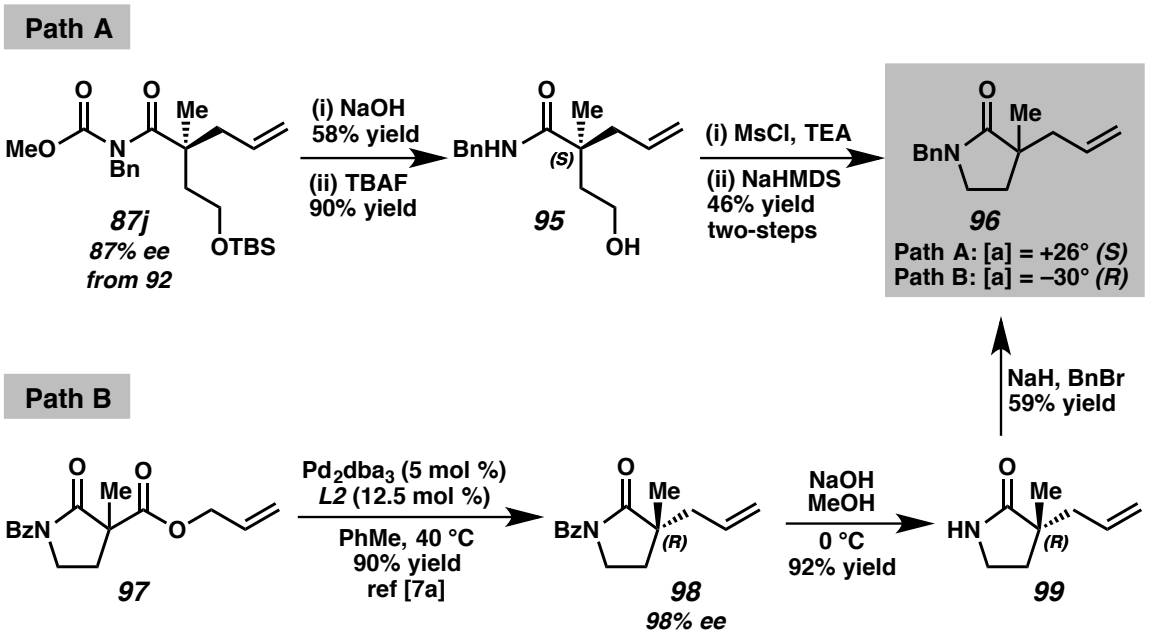


[a]Two-step yield. [b]Absolute stereochemistry not determined

3.2.3 Determination of Absolute Stereochemistry

In order to determine the absolute stereochemistry of the products, we converted acyclic product **87** to **96**, which allowed comparison by derivatization of known[6a] allylic alkylation product **97** (Scheme 3.3). Comparison of optical rotations allowed us to estabilish absolute stereochemistry as shown in Scheme 3.3, i.e. that reaction with the (*R,R*)-Trost ligands gave the (*S*)-quaternary linear carbamate.

Scheme 3.3. Determination of absolute stereochemistry.



3.3 CONCLUDING REMARKS

In conclusion, we developed a new method for the preparation of versatile building blocks containing a *de novo* created all-carbon quaternary stereocenter in unbiased acyclic systems. This was achieved through the use of the carbometalation-oxidation strategy developed by the Marek group to access fully-substituted, stereodefined amide enolates from ynecarbamates, testing various catalytic systems in the

asymmetric DAA reaction, and improvement upon existing ANDEN Trost ligands by modulation of ligand electronics. It is our hope that this method will prompt further investigation of these substrates for the synthesis of stereocenters in acyclic systems, use of the products of this reaction in total synthesis efforts, and further use of the newly developed electron-deficient ligand in other catalytic reactions.

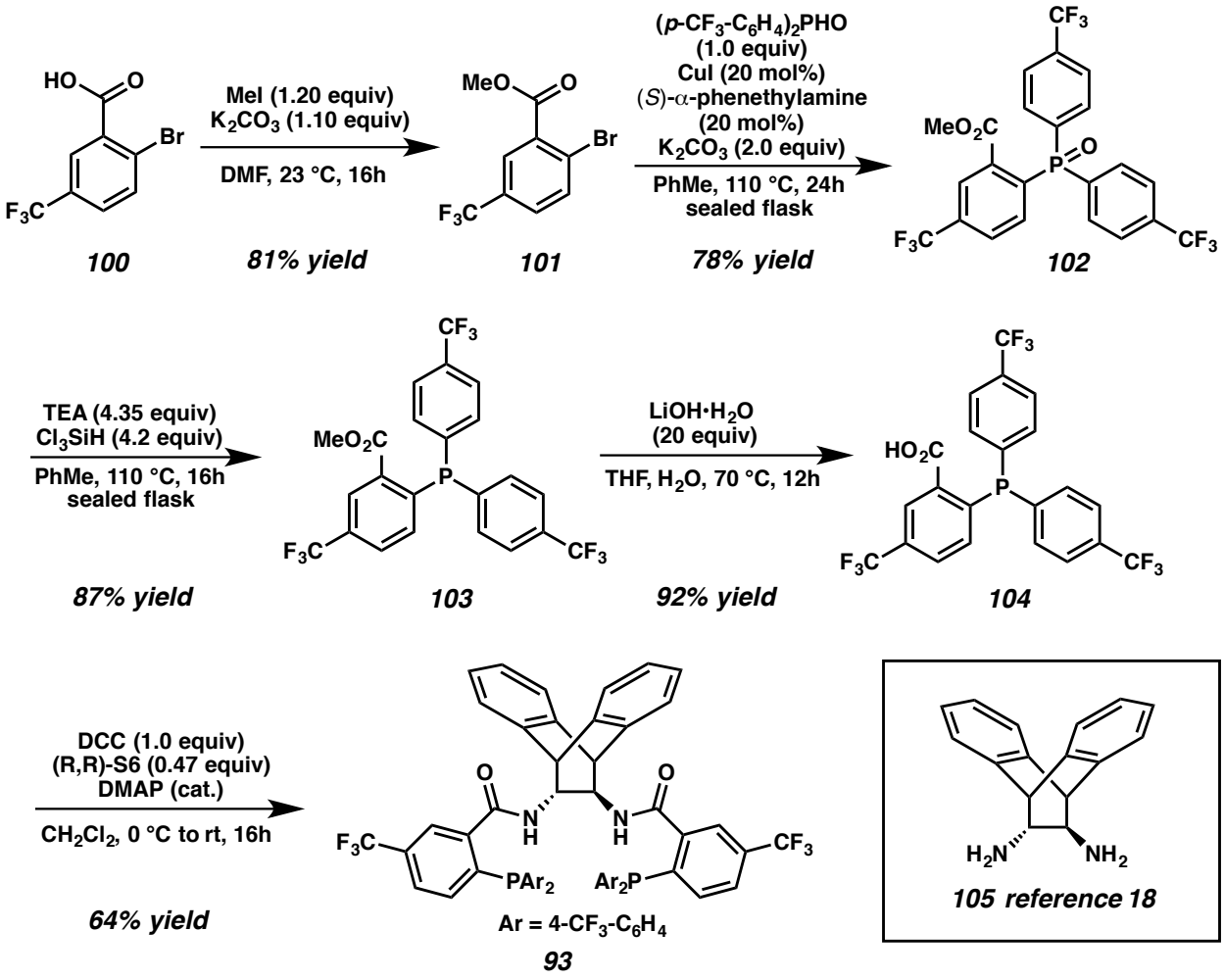
3.4 EXPERIMENTAL SECTION

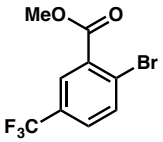
3.4.1 Materials and Methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried glassware under an nitrogen atmosphere using dry, deoxygentated solvents (distilled or passed over a column of activated alumina).[9] Commercially available reagents were used as received. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40- 63 nm) was used for flash chromatography. (*S*)-*t*-BuPHOX,[10] (*S*)-(CF_3)-*t*-BuPHOX,[11] and Bis(dibenzylideneacetone) palladium(0) ($Pd(dba)_2$) were prepared by known methods. Commercially available C-2 symmetric ligands ((*R*,*R*)-DACH-naphthyl Trost ligand, (*R*,*R*)-DACH-phenyl Trost ligand, (*R,R*)-ANDEN-Phenyl Trost Ligand) were purchased from Sigma Aldrich, used as received, and stored in a glovebox. Grubbs's Generation II catalyst was purchased from Materia inc. and used as received. ^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 77.16, respectively). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralpak AD-H column, OD-H column,

and OJ-H column 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 from the Caltech Center for Catalysis and Chemical Synthesis using an Agilent 6200 series TOF with an Agilent G1978A Multimode source in mixed (Multimode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

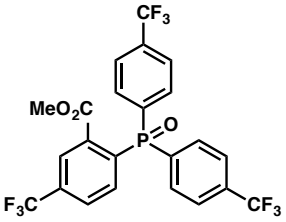
3.4.2 Ligand Synthesis





Methyl 2-bromo-5-(trifluoromethyl)benzoate (101)

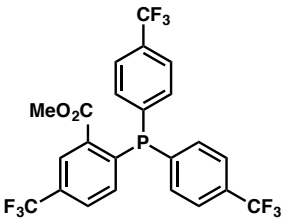
To an oven-dried round-bottom flask and magnetic stir bar was added 2-bromo-5-(trifluoromethyl)benzoic acid **(101)**[12] (1.91 g, 7.10 mmol) followed by anhydrous DMF (20.0 mL). The solution was stirred under nitrogen at room temperature. Solid potassium carbonate (1.08 g, 7.81 mmol) was added all at once followed by methyl iodide (0.53 mL, 8.52 mmol) dropwise by syringe. The reaction was stirred at room temperature for 16h. Afterward, the reaction mixture was poured into water (300 mL) and extracted with ethyl acetate (3 x 80 mL). The combined organic layers were washed with brine (50 mL), dried with sodium sulfate, filtered, and concentrated in vacuo to afford the product (1.83 g, 91% yield), which was not purified further. Characterization data matched literature values:[13] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.59 –7.56 (m, 1H), 3.97 (s, 3H).



Methyl 2-(bis(4-(trifluoromethyl)phenyl)phosphoryl)-5-(trifluoromethyl)benzoate (102)

Procedure adapted from Stankevič and Włodarcyk.[14] To an oven dried Schlenk tube equipped with a magnetic stir bar was added CuI (0.145 g, 0.761 mmol). The tube was

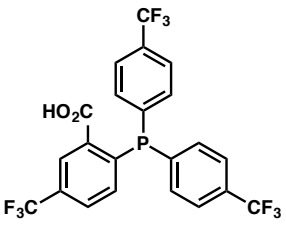
purged with nitrogen and (*S*)-α-phenylethylamine (0.100 mL, 0.760 mmol) was added with a micro-syringe followed by **101** (1.09 g, 3.8 mmol) dissolved in toluene (19.0 mL) with a syringe. The reaction mixture was stirred under nitrogen for 5 minutes at room temperature. Bis(4-(trifluoromethyl)phenyl)phosphine oxide (1.30 g, 3.84 mmol) was added to the reaction mixture all at once and stirring continued for five minutes. Potassium carbonate (1.05 g, 7.60 mmol) was added to the reaction mixture and the tube was sealed with a Teflon cap and electrical tape and heated to 110 °C behind a blast shield for 24 hours. The mixture was cooled to room temperature and the mixture was filtered through a pad of celite, eluting with dichloromethane. This mixture was concentrated in vacuo and purified by flash chromatography (30:70 to 35/65, EtOAc/hexanes) to provide the product as an amorphous white solid (1.61 g, 78% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 – 8.22 (m, 1H), 7.95 – 7.87 (m, 2H), 7.84 – 7.73 (m, 8H), 3.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7 (d, *J* = 2.5 Hz), 136.7 – 136.6 (m), 136.2 (d, *J* = 6.3 Hz), 135.8 (d, *J* = 10.4 Hz), 135.8 (m), 134.9 (qd, *J* = 34.2, 2.4 Hz), 134.2 (qd, *J* = 32.9, 3.0 Hz), 132.3 (d, *J* = 10.4 Hz), 128.5 (dq, *J* = 11.9, 3.6 Hz), 127.9 (dq, *J* = 7.2, 3.5 Hz), 125.7 (dq, *J* = 12.8, 3.7 Hz), 123.5 (q, *J* = 272.6 Hz), 123.0 (q, *J* = 273.1 Hz), 53.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.2, -63.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.7; IR (Neat Film, NaCl) 1737, 1440, 1324, 1269, 1131, 715 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{15}F_9O_3P$ $[M+H]^+$: 541.0610, found 541.0616.



Methyl 2-(bis(4-(trifluoromethyl)phenyl)phosphanyl)-5-(trifluoromethyl)benzoate (103)

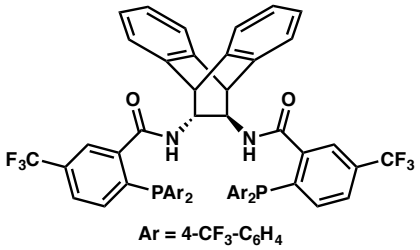
To an oven-dried Schlenk flask equipped with a magnetic stir bar was added **102** (0.650 g, 1.20 mmol) in toluene (17.5 mL). The mixture was stirred under flow of nitrogen at room temperature. Triethylamine (0.730 mL, 5.22 mmol) was added to the reaction mixture followed by trichlorosilane (0.510 mL, 5.04 mmol) with a syringe. At this stage, the reaction mixture was heated to 110 °C behind a blast shield for 16 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (40 mL), and quenched with a solution of saturated sodium bicarbonate (0.5 mL). The mixture was filtered through celite and eluted with ethyl acetate followed by drying with sodium sulfate. The mixture was filtered, concentrated in vacuo, and purified by flash chromatography (2:98 to 4:96, EtOAc/hexanes) to provide the product as a slightly yellow oil that solidified at –20 °C and remained solid at room temperature (0.55 g, 87% yield). The purified product slowly oxidizes in the time it takes to characterize; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (ddt, *J* = 3.6, 2.1, 0.7 Hz, 1H), 7.68 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.64 – 7.59 (m, 4H), 7.36 (dddd, *J* = 7.3, 6.5, 1.7, 0.8 Hz, 4H), 7.02 (ddt, *J* = 8.1, 3.3, 0.7 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9 (d, *J* = 2.4 Hz), 143.9 (d, *J* = 29.8 Hz), 141.4 (d, *J* = 13.7 Hz), 135.8 (d, *J* = 10.5 Hz), 134.9, 134.2 (d, *J* = 21.3 Hz), 131.5 (q, *J* = 32.6 Hz), 131.5 (q, *J* = 33.2 Hz), 128.9 (q, *J* = 3.5 Hz), 128.1 – 127.8 (m), 125.7 (dq, *J* = 7.5, 3.7 Hz), 124.0 (q, *J* = 272.4 Hz), 123.5 (q, *J* = 272.7 Hz), 53.0; ^{19}F

NMR (282 MHz, $CDCl_3$) δ –62.9, –63.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ –5.0; IR (Neat Film, NaCl) 1723, 1324, 1257, 1128, 832 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{23}H_{15}F_9O_2P$ $[M+H]^+$: 525.0660, found 525.0646.



2-(Bis(4-(trifluoromethyl)phenyl)phosphanyl)-5-(trifluoromethyl)benzoic acid (104): Compound **103** (0.550 g, 1.05 mmol) was charged into a round bottom flask equipped with a magnetic stir bar and was dissolved in THF (4.2 mL) at room temperature. Water (4.2 mL) was added to this solution followed by lithium hydroxide monohydrate (0.882 g, 21.0 mmol). The reaction mixture was sealed with a Teflon cap, stirred, and heated to 70 °C for 12 hours. The mixture was cooled to room temperature and diluted with ethyl acetate (50 mL). This mixture was added to a 10% aqueous citric acid solution (50 mL) and this phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (3:97 to 5:95, MeOH:CH_2Cl_2) to provide the product as a white amorphous solid (0.492 g, 92% yield); ^1H NMR (300 MHz, CD_3OD) δ 8.39 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 4H), 7.43 (t, *J* = 7.6 Hz, 4H), 7.07 (dd, *J* = 8.1, 3.4 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 168.5 (d, *J* = 5.1 Hz), 145.4 (d, *J* = 30.2 Hz), 143.9 (d, *J* = 14.6 Hz), 137.2 (d, *J* = 20.7 Hz), 136.0, 135.5 (d, *J* = 21.6 Hz), 132.1 (q, *J* = 32.3 Hz), 132.1 (q, *J* = 33.0

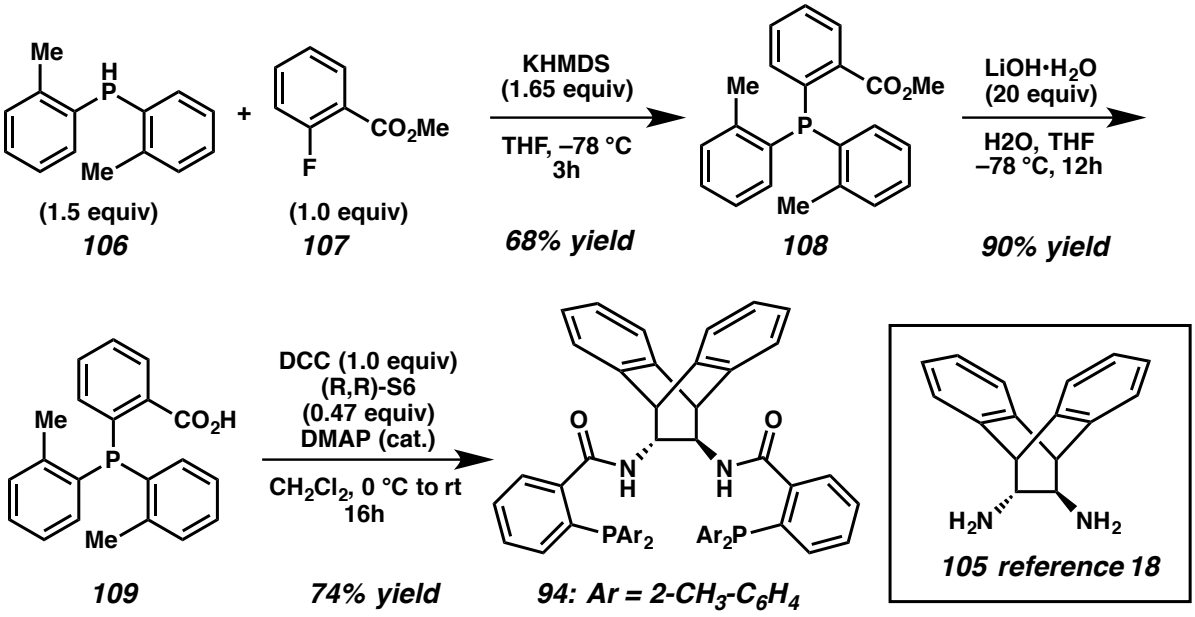
Hz), 129.5 (q, *J* = 3.4 Hz), 128.7 – 128.5 (m), 126.5 (dq, *J* = 7.4, 3.7 Hz), 125.5 (q, *J* = 271.5 Hz), 125.1 (q, *J* = 271.6 Hz); ^{19}F NMR (282 MHz, cd_3od) δ -64.3, -64.5; ^{31}P NMR (121 MHz, MeOD) δ -4.9; IR (Neat Film, NaCl) 1698, 1324, 1127, 832 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{11}F_9O_2P$ $[M-H]^-$: 509.0358, found 509.0369.

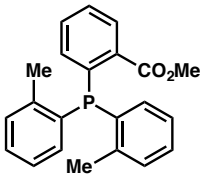


Electron deficient C-2 symmetric ligand (93):

To an oven-dried flask equipped with a magnetic stir bar was added chiral diamine **105**[15] (0.035 g, 0.149 mmol) and dichloromethane (2.6 mL) at room temperature under nitrogen. Benzoic acid **104** (0.160 g, 0.313 mmol) was added to the reaction and an insoluble mixture was formed. The reaction mixture was cooled to 0 °C and a single crystal of DMAP was added. DCC (0.065 g, 0.313 mmol) was added all at once and the mixture was slowly allowed to warm to room temperature overnight (12 hours). At this time, the cloudy mixture was filtered through celite, eluting with dichloromethane, and concentrated. The crude material was suspended in a small amount of diethylether and filtered once again through a pad of celite. This mixture was concentrated and purified by flash chromatography (8:92 to 10:90, EtOAc:hexanes) to provide the product as a white amorphous solid (0.116 g, 64% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 8H), 7.56 (d, *J* = 8.0 Hz, 4H), 7.40 (dd, *J* = 7.3, 1.3 Hz, 2H), 7.34 – 7.28 (m, 10H), 7.25 – 7.15 (m, 4H), 7.08 (dd, *J* = 8.1, 3.1 Hz, 2H), 5.82 (d, *J* = 7.7 Hz, 2H), 4.49 (d, *J* =

2.4 Hz, 2H), 4.15 – 4.08 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 141.7 (d, *J* = 28.3 Hz), 141.1 (dd, *J* = 25.5, 14.6 Hz), 140.6 , 140.3 (d, *J* = 25.0 Hz), 138.5, 135.5, 133.9 (dd, *J* = 20.8, 7.0 Hz), 131.9 (q, *J* = 33.3 Hz), 131.5 (qd, *J* = 32.6, 1.3 Hz), 127.5 (q, *J* = 3.4 Hz), 127.4, 127.1, 125.9, 125.7 (dt, *J* = 6.9, 3.6 Hz), 125.3, 124.3 – 123.9 (m), 123.97 (qd, *J* = 272.3, 5.8 Hz), 123.3 (q, *J* = 272.8 Hz), 57.8, 48.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.9, –62.9, –63.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ –10.70; IR (Neat Film, NaCl) 1659, 1509, 1397, 1325, 1172, 1130, 1061, 832 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{60}H_{37}F_{18}N_2O_2P_2$ $[M+H]^+$: 1221.2037, found 1221.2039; $[\alpha]^{25}$ –55.0 (*c* 3.17 $CHCl_3$).

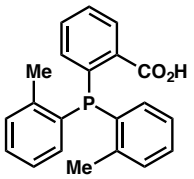




Methyl 2-(di-*o*-tolylphosphanyl)benzoate (108):

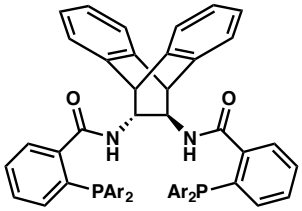
In a nitrogen filled glove box, an oven-dried round-bottom flask equipped with a magnetic stir bar was charged with di-(*o*-tolyl)phosphine (**106**) (0.321 g, 1.50 mmol). The flask was sealed with a cap equipped with a septa and electrical tape and removed from the glove box. The flask was then charged with THF (8.0 mL) under positive nitrogen pressure. This mixture was cooled to –78 °C in a dry ice/acetone bath. A freshly prepared solution of KHMDS (2.00 mL, 1.65 mmol, 0.825 M) was added to the mixture dropwise by syringe. The reaction mixture was stirred at this temperature for 30 min and then warmed to room temperature. Methyl-2-fluorobenzoate (**107**) (0.13 mL, 1.0 mmol) was added dropwise and the mixture was stirred for 2.5 hours. A precipitate formed and the reaction turned black in color. The mixture was quenched and diluted with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were dried with sodium sulfate, filtered, and evaporated in vacuo. The crude material was purified by flash chromatography (5:95, EtOAc:hexanes) to provide the product as a white amorphous solid (0.238 g, 68% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (ddd, *J* = 7.2, 3.9, 1.8 Hz, 1H), 7.42 (pd, *J* = 7.4, 1.7 Hz, 2H), 7.33 – 7.21 (m, 4H), 7.08 (td, *J* = 7.0, 6.5, 2.3 Hz, 2H), 6.97 (ddt, *J* = 7.7, 3.6, 1.6 Hz, 1H), 6.75 (ddd, *J* = 7.5, 4.3, 1.2 Hz, 2H), 3.77 (s, 3H), 2.44 (d, *J* = 1.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3 (d, *J* = 1.9 Hz), 142.6 (d, *J* = 27.7 Hz), 139.5 (d, *J* = 25.4 Hz), 136.1 (d, *J* = 11.4 Hz), 134.9 (d, *J* = 20.3 Hz), 134.5, 133.2, 132.2, 131.0 (d, *J* = 3.0 Hz), 130.2 (d, *J*

= 4.8 Hz), 128.8, 128.4, 126.2, 52.2, 21.4 (d, J = 22.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ –20.4; IR (Neat Film, NaCl) 3055, 1721, 1452, 1269, 1107, 749 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{22}O_2P$ $[M+H]^+$: 349.1352, found 349.1362.



2-(Di-*o*-tolylphosphanyl)benzoic acid (109):

Compound **108** (0.238 g, 0.683 mmol) was charged into a round bottom flask equipped with a magnetic stir bar and was dissolved in THF (2.8 mL) at room temperature. Water (2.8 mL) was added to this solution followed by lithium hydroxide monohydrate (0.574 g, 13.7 mmol). The reaction mixture was sealed with a Teflon cap, stirred and heated to 70 °C for 12 hours. The mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). This mixture was added to a 10% aqueous citric acid solution (50 mL) and this phase was extracted with ethyl acetate (2 x 30 mL). The combined organic phases were washed with brine, dried with sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (40:60, EtOAc:hexanes) to provide the product as a white amorphous solid (0.205 g, 90% yield). Characterization data matched literature values.[16] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.14–8.20 (m, 1H), 7.38–7.45 (m, 2H), 7.18–7.27 (m, 4H), 7.05 (t, J = 7.5 Hz, 2H), 6.96–7.01 (m, 1H), 6.68–6.72 (m, 2H), 2.40 (s, 6H); HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{18}O_2P$ $[M-H]^-$: 333.1044, found 333.1050.



Ar = 2-CH$_3$-C$_6$H$_4$

Sterically hindered C2-symmetric ligand (94):

To an oven-dried flask equipped with a magnetic stir bar was added **105**[15] (0.050 g, 0.212 mmol) and dichloromethane (3.0 mL) at room temperature under nitrogen. Benzoic acid **109** (0.150 g, 0.450 mmol) was added to the reaction and an insoluble mixture was formed. The reaction mixture was cooled to 0 °C and a single crystal of DMAP was added. DCC (0.093 g, 0.45 mmol) was added all at once and the mixture was slowly allowed to warm to room temperature overnight (12 hours). At this time, the cloudy mixture was filtered through celite, eluting with dichloromethane, and concentrated. The crude material was suspended in a small amount of diethylether and filtered once again through a pad of celite. This mixture was concentrated and purified by flash chromatography (20:80 to 40:60, Et_2O:pentane) to provide the product as a white amorphous solid (0.136 g, 74% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.39 – 7.20 (m, 14H), 7.15 – 7.06 (m, 4H), 7.04 – 6.93 (m, 6H), 6.88 (ddd, *J* = 7.5, 4.2, 1.3 Hz, 2H), 6.75 – 6.68 (m, 2H), 6.65 (dd, *J* = 7.6, 4.3 Hz, 2H), 5.74 (d, *J* = 7.1 Hz, 2H), 4.36 (s, 2H), 3.83 (d, *J* = 7.0 Hz, 2H), 2.35 (d, *J* = 4.6 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1 (d, *J* = 1.8 Hz), 142.6 – 142.2 (m), 141.0, 138.7, 135.3 (d, *J* = 10.8 Hz), 134.9, 134.2 (d, *J* = 18.4 Hz), 132.9 (d, *J* = 62.2 Hz), 130.5 (dd, *J* = 14.7, 4.6 Hz), 130.4, 129.2, 128.9 (d, *J* = 10.1 Hz), 128.0 (d, *J* = 6.1 Hz), 126.7 (d, *J* = 11.0 Hz), 126.4 (d, *J* = 30.4 Hz), 125.9, 124.8, 57.9, 48.6, 21.5 (dd, *J* = 21.6, 9.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ –26.5; IR (Neat Film, NaCl) 3054, 1658, 1501, 908, 748 cm^{-1}; HRMS

(MM: ESI-APCI) *m/z* calc'd for $C_{58}H_{51}N_2O_2P_2$ $[M+H]^+$: 869.3420, found 869.3433; $[\alpha]^{25}$ – 84.1 (*c* 1.83, $CHCl_3$).

3.4.3 Exploratory Allylic Alkylation Screen

Initially, we ran a series of screens to determine the best combination of ligand and solvent that provided the highest %ee for the allylic alkylation. The following procedure was followed to conduct these screens. This procedure is similar to that previously used by the Stoltz group.[6a] To separate enantiomers, the allylic alkylation products were derivitized using a cross metathesis with Grubbs-second generation catalyst and methyl acrylate. This procedure is similar to that previously used by the Stoltz group.[17]

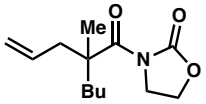
General Screening Procedure (from Table 1 and Table 2):

In a nitrogen-filled glove box, 38.0 mg $Pd(dba_2)$ was taken up in 10 mL THF. To each of 16 half-dram vials, 0.5 mL of this solution (1.90 mg $Pd(dba)_2$, 1.65 μmol, 0.100 equiv) was added. The THF was then removed by evacuation using a Genevac centrifugal evaporator within the glove box. To each of the vials was then added 500 μL of the reaction solvent followed by a small stirbar. Stock solutions of ligand (0.0165 M) were made in each reaction solvent. From these ligand stock solutions, 250 μL (4.13 μmol, 0.125 equiv) were added to the corresponding reaction vials. The resulting catalyst solutions were stirred in the glove box for 30 minutes at the indicated reaction temperature. Stock solutions of reaction substrate (0.132 M) were made in each reaction solvent. To the stirring catalyst solutions were added 250 μL (33.0 μmol, 1.00 equiv) of the corresponding substrate solution, resulting in a final reaction volume of 1.00 mL

(0.033 M with respect to substrate). The reactions were sealed with a Teflon-lined cap and stirred for the indicated reaction duration. The reactions were then removed from the glove box, diluted with 1 mL hexanes and filtered through a silica plug, concentrated in vacuo, taken up in $CDCl_3$, and analyzed by crude ^1H NMR to determine conversion.

The crude reaction mixtures in $CDCl_3$ were concentrated in vacuo in half-dram vials and returned to the glove box. To each half-dram vial was added 500 μL of methyl acrylate solution in CH_2Cl_2 (0.66M, 0.33 mmol, 10 equiv), followed by a small stir bar. The reactions were stirred for approximately 15 minutes. To the resulting solutions was added 500 μL each of a Grubbs second-generation Ru catalyst solution in CH_2Cl_2 (0.004 M, 2 μmol, 0.06 equiv). The reactions were then stirred at 40 °C for 3 hours, removed from the glove box, filtered through a silica plug, concentrated in vacuo, and analyzed by crude ^1H NMR to determine conversion and chiral SFC to determine enantiomeric excess. SFC conditions for each substrate can be found in a table at the end of the text portion of the SI.

3.4.3.1 Characterization data for compounds relevant to exploratory screen

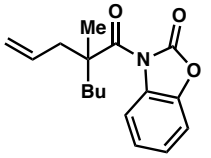


(*R*)-3-(2-Allyl-2-methylhexanoyl)oxazolidin-2-one (87a)

Prepared from **86a** or **86b**:

^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H), 5.10 – 5.01 (m, 2H), 4.42 – 4.34 (m, 2H), 4.09 – 3.98 (m, 2H), 2.92 – 2.84 (m, 1H), 2.36 (ddt, *J* = 14.1, 7.2,

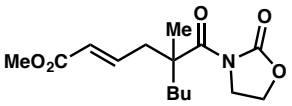
1.2 Hz, 1H), 2.10 (ddd, *J* = 13.7, 11.9, 4.6 Hz, 1H), 1.67 (ddd, *J* = 13.6, 12.4, 4.3 Hz, 1H), 1.31 (s, 3H), 1.30 – 1.19 (m, 3H), 1.15 – 1.03 (m, 1H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3, 152.4, 134.5, 117.8, 62.3, 49.0, 45.4, 41.0, 35.8, 27.0, 23.2, 22.5, 14.1; IR (Neat Film, NaCl) 2958, 2928, 1777, 1685, 1382, 1200 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{22}NO_3$ $[M+H]^+$: 240.1600, found 240.1601.



(*R*)-1-(2-Allyl-2-methylhexanoyl)indolin-2-one (87c)

Prepared from **86c**:

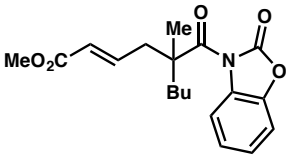
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 1H), 7.24 – 7.17 (m, 3H), 5.80 – 5.68 (m, 1H), 5.12 – 5.03 (m, 1H), 5.05 – 5.00 (m, 1H), 2.97 (dd, *J* = 14.1, 7.4 Hz, 1H), 2.48 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.18 (td, *J* = 12.6, 11.4, 4.3 Hz, 1H), 1.78 (td, *J* = 14.1, 3.8 Hz, 1H), 1.43 (s, 3H), 1.35 – 1.23 (m, 3H), 1.23 – 1.11 (m, 1H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3, 150.5, 143.0, 133.9, 129.4, 125.0, 124.6, 118.7, 116.1, 109.9, 50.5, 41.2, 36.1, 27.0, 23.3, 22.4, 14.1; IR (Neat Film, NaCl) 2958, 2932, 1795, 1479, 1299, 1027, 757 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1600, found 288.1603.



Methyl (*R*,*E*)-5-methyl-5-(2-oxooxazolidine-3-carbonyl)non-2-enoate (88a)

Prepared from **86a**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.86 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.40 (t, *J* = 8.0 Hz, 2H), 4.04 (t, *J* = 8.0 Hz, 2H), 3.71 (s, 3H), 3.01 (ddd, *J* = 14.5, 7.6, 1.5 Hz, 1H), 2.51 (ddd, *J* = 14.5, 7.9, 1.4 Hz, 1H), 2.01 (ddd, *J* = 13.8, 11.9, 4.8 Hz, 1H), 1.76 (ddd, *J* = 13.8, 12.1, 4.7 Hz, 1H), 1.34 (s, 3H), 1.31 – 1.24 (m, 2H), 1.24 – 1.07 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7, 166.8, 152.5, 145.4, 123.9, 62.4, 51.6, 49.0, 45.4, 39.8, 35.8, 27.0, 23.2, 22.4, 14.1; IR (Neat Film, NaCl) 2931, 2957, 1778, 1723, 1688, 1274, 1197 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{24}NO_5$ $[M+H]^+$: 298.1654, found 298.1650.



Methyl (*R*,*E*)-5-methyl-5-(2-oxo-2,3-dihydrobenzo[*d*]oxazole-3-carbonyl)non-2-enoate (88c)

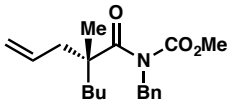
Prepared from **86c**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 1H), 7.26 – 7.19 (m, 3H), 6.90 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.90 (dt, *J* = 15.5, 1.4 Hz, 1H), 3.70 (s, 3H), 3.08 (ddd, *J* = 14.3, 7.5, 1.4 Hz, 1H), 2.66 (ddd, *J* = 14.3, 7.9, 1.4 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.94 – 1.84 (m, 1H), 1.46 (s, 3H), 1.36 – 1.14 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 166.6, 150.5, 144.5, 143.0, 129.2, 125.2, 124.8, 124.4, 116.2, 110.0, 51.7, 50.3, 39.9, 36.0, 27.0, 23.1, 22.0, 14.0; IR (Neat Film, NaCl) 2256, 1796, 1722, 1479, 1272, cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{24}NO_5$ $[M+H]^+$: 346.1654, found 346.1650.

3.4.4 Allylic Alkylation Substrate Library

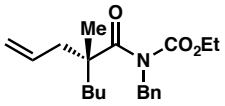
Representative Procedure:

Unless otherwise noted, the allylic alkylation reactions proceeded as follows: Outside of a glove box, an oven-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd(dba)_2$ (2.3 mg, 4.0 μmol, 4 mol%). A second oven-dried two-dram vial was charged with allylenolcarbonate **86d**–**86q** (0.1 mmol). Finally, a third oven-dried 2-dram vial was charged with C-2 symmetric ligand **89** or **90** (7.0 μmol). These three uncapped vials were brought into a nitrogen-filled glove box through a small antechamber with 4 x 5 minute vacuum cycles with nitrogen back-filling. To the vial containing compounds **86d**–**86q** was added or THF (0.3 mL) unless otherwise noted. To the vial containing C-2 symmetric ligand (**89** or **90**) was added THF (0.3 ml) unless otherwise noted. To the vial containing $Pd(dba)_2$ and a magnetic stir bar was added the entirety of the ligand solution and the reaction was capped, cooled to 20 °C and stirred for 30 min to form the catalyst. At this time, the entirety of the solution containing the substrate (**86d**–**86q**) was added to the catalyst mixture dropwise and the reactions were allowed to stir at 20 °C for 24h. The reaction mixtures were removed from the glove box through the small antechamber and diluted with hexanes (1mL). The mixture was filtered through a short plug of silica gel and eluted with ethyl acetate. The crude material was concentrated and purified by preparative TLC (EtOAc:hexanes mixtures) to provide the products as clear to slightly yellow oils (53–88% yield). Purified products were converted to the corresponding methyl acrylate species via cross metathesis for SFC analysis.



Methyl (*R*)-(2-allyl-2-methylhexanoyl)(benzyl)carbamate (87d)

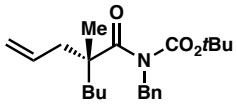
Representative Procedure H. Compound **87d** was prepared from allylenolcarbonate **86d** using General Procedure G (27.0 mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H), 5.63 – 5.53 (m, 1H), 5.03 – 4.93 (m, 2H), 4.76 (s, 2H), 3.76 (s, 3H), 2.58 (ddt, *J* = 13.7, 7.2, 1.3 Hz, 1H), 2.27 (ddt, *J* = 13.7, 7.6, 1.2 Hz, 1H), 1.78 (ddd, *J* = 13.4, 12.3, 4.5 Hz, 1H), 1.52 (ddd, *J* = 13.3, 12.4, 4.5 Hz, 1H), 1.27 – 1.14 (m, 2H), 1.19 (s, 3H), 1.16 – 1.04 (m, 1H), 1.06 – 0.91 (m, 1H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.9, 155.6, 137.8, 134.6, 128.5, 128.3, 127.5, 117.8, 53.5, 50.6, 50.54, 44.1, 39.6, 26.8, 23.4, 22.5, 14.1; IR (Neat Film, NaCl) 2932, 2872, 1738, 1681, 1444, 1156, 998, 916 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2064, found 318.2064; $[\alpha]^{25}$ –2.36 (*c* 2.40, $CHCl_3$, 92% ee).



Ethyl (*R*)-(2-allyl-2-methylhexanoyl)(benzyl)carbamate (87e)

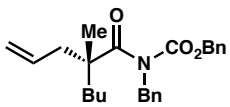
Representative Procedure H. Compound **87e** was prepared from allylenolcarbonate **86e** using General Procedure G (20.5 mg, 62% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.12 (m, 5H), 5.56 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.02 – 4.87 (m, 2H), 4.72 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.57 (ddd, *J* = 13.7, 7.1, 1.3 Hz, 1H), 2.25 (ddd, *J* = 13.7, 7.1, 1.3 Hz, 1H), 1.76 (td, *J* = 12.9, 4.5 Hz, 1H), 1.50 (td, *J* = 12.9, 4.5 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.20 – 1.13 (m, 2H), 1,17 (s, 3H), 1.12 – 1.02 (m, 1H), 1.02 – 0.92 (m, 1H),

0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 155.2, 138.0, 134.7, 128.4, 128.3, 127.4, 117.8, 63.0, 50.6, 50.5, 44.1, 39.5, 26.8, 23.4, 22.5, 14.3, 14.1; IR (Neat Film, NaCl) 2958, 2872, 1738, 1693, 1455, 1376, 1345, 1206, 1018 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{30}NO_3$ $[M+H]^+$: 332.2220, found 332.2219; $[\alpha]^{25}$ – 3.19 (*c* 1.70, $CHCl_3$, 94% ee).



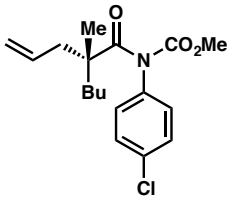
***tert*-Butyl (*R*)-(2-allyl-2-methylhexanoyl)(benzyl)carbamate (87f)**

Representative Procedure H. Compound **87f** was prepared from allylenolcarbonate **86f** using General Procedure G (10.8 mg, 88% yield, 0.034mmol scale): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 5H), 5.73 – 5.60 (m, 1H), 5.07 – 4.95 (m, 2H), 4.71 (s, 2H), 2.66 (ddt, *J* = 13.6, 7.2, 1.3 Hz, 1H), 2.32 (ddt, *J* = 13.5, 7.6, 1.2 Hz, 1H), 1.84 (ddd, *J* = 13.3, 12.0, 4.4 Hz, 1H), 1.56 (ddd, *J* = 13.2, 12.4, 4.5 Hz, 1H), 1.36 (s, 9H), 1.28 – 1.20 (m, 2H), 1.26 (s, 3H), 1.20 – 1.12 (m, 1H), 1.07 (dddd, *J* = 15.0, 12.6, 7.3, 4.3 Hz, 1H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.3, 153.9, 138.5, 134.9, 128.4, 128.1, 127.3, 117.7, 82.7, 50.8, 50.3, 44.1, 39.5, 27.9, 26.9, 23.4, 22.5, 14.2; IR (Neat Film, NaCl) 2958, 2931, 2872, 1736, 1682, 1368, 1212, 987, 699 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{34}NO_3$ $[M+H]^+$: 360.2539, found 360.2527; $[\alpha]^{25}$ -2.89 (*c* 0.8, $CHCl_3$, 90% ee).



Benzyl (*R*)-(2-allyl-2-methylhexanoyl)(benzyl)carbamate (87g)

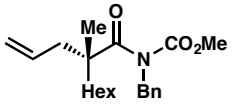
Representative Procedure H. Compound **87g** was prepared from allylenolcarbonate **86g** using General Procedure G (21.0 mg, 53% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 3H), 7.28 – 7.20 (m, 7H), 5.61 – 5.51 (m, 1H), 5.15 (s, 2H), 4.97 – 4.93 (m, 1H), 4.93 – 4.91 (m, 1H), 4.78 (s, 2H), 2.58 (ddt, *J* = 13.6, 7.1, 1.2 Hz, 1H), 2.25 (ddt, *J* = 13.6, 7.7, 1.2 Hz, 1H), 1.75 (ddd, *J* = 13.3, 12.1, 4.4 Hz, 1H), 1.50 (ddd, *J* = 13.3, 12.4, 4.4 Hz, 1H), 1.18 (s, 3H), 1.16 – 1.12 (m, 2H), 1.10 – 1.02 (m, 1H), 1.02 – 0.91 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 155.0, 137.9, 135.0, 134.6, 128.7, 128.7, 128.7, 128.5, 128.3, 127.5, 117.8, 68.7, 50.7, 50.6, 44.0, 39.4, 26.8, 23.3, 22.5, 14.1; IR (Neat Film, NaCl) 3067, 2957, 2932, 2872, 1732, 1696, 1456, 1386, 1347, 1192 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{25}H_{32}NO_3$ $[M+H]^+$: 394.2377, found 394.2376; $[\alpha]^{25}$ –3.88 (*c* 1.91, $CHCl_3$, 93% ee).



Methyl (*R*)-(2-allyl-2-methylhexanoyl)(4-chlorophenyl)carbamate (87h)

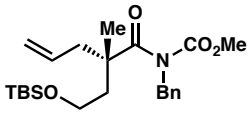
Representative Procedure H. Compound **87h** was prepared from allylenolcarbonate **86h** using General Procedure G (20.7 mg, 62% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 2H), 7.14 – 7.10 (m, 2H), 5.77 – 5.66 (m, 1H), 5.09 – 5.00 (m, 2H), 3.75 (s, 3H), 2.54 (ddt, *J* = 13.8, 7.2, 1.3 Hz, 1H), 2.28 (ddt, *J* = 13.8, 7.5, 1.2 Hz, 1H), 1.76 – 1.65 (m, 1H), 1.55 – 1.47 (m, 1H), 1.29 – 1.20 (m, 4H), 1.19 (s, 3H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.3, 154.8, 137.1, 134.0, 133.9, 129.5, 129.3, 118.5, 53.8, 51.0, 43.4, 39.1, 26.6, 23.3, 22.9, 14.1; IR (Neat Film, NaCl) 2957, 2933, 1742, 1731,

1491, 1439, 1245, 1091 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{25}NO_3Cl$ $[M+H]^+$: 338.1523, found 338.1531; $[\alpha]^{25}$ 2.64 (*c* 1.9, $CHCl_3$, 90% ee).



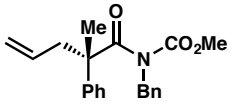
Methyl (*R*)-(2-allyl-2-methyloctanoyl)(benzyl)carbamate (87i)

Representative Procedure H. Compound **87i** was prepared from allylenolcarbonate **86i** using General Procedure G (24.0 mg, 69% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 3H), 7.26 – 7.22 (m, 2H), 5.58 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.02 – 4.94 (m, 2H), 4.76 (s, 2H), 3.76 (s, 3H), 2.58 (ddt, *J* = 13.7, 7.0, 1.2 Hz, 1H), 2.27 (ddt, *J* = 13.6, 7.6, 1.2 Hz, 1H), 1.77 (ddd, *J* = 13.3, 12.0, 4.4 Hz, 1H), 1.51 (ddd, *J* = 13.3, 12.0, 4.4 Hz, 1H), 1.19 (s, 3H), 1.28 – 1.14 (m, 6H), 1.16 – 1.06 (m, 1H), 1.05 – 0.95 (m, 1H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.88, 155.63, 137.81, 134.58, 128.45, 128.30, 127.49, 117.79, 53.54, 50.60, 50.57, 44.12, 39.90, 31.79, 29.97, 24.52, 22.73, 22.45, 14.22; IR (Neat Film, NaCl) 3067, 2950, 2930, 2858, 1738, 1694, 1455, 1445, 1351, 1208, 1000 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{32}NO_3$ $[M+H]^+$: 346.2377, found 346.2375; $[\alpha]^{25}$ –2.14 (*c* 2.18, $CHCl_3$, 94% ee).



Methyl (*S*)-benzyl(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methylpent-4-enoyl)carbamate (87j)

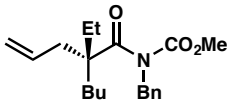
Representative Procedure H. Compound **87j** was prepared from allylenolcarbonate **86j** using General Procedure G (32.1 mg, 76% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 5H), 5.52 (ddt, *J* = 17.2, 10.1, 7.3 Hz, 1H), 4.99 – 4.90 (m, 2H), 4.74 (s, 2H), 3.73 (s, 3H), 3.54 – 3.44 (m, 2H), 2.58 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.27 (dd, *J* = 13.6, 7.5 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.84 – 1.76 (m, 1H), 1.20 (s, 3H), 0.83 (d, *J* = 0.7 Hz, 9H), -0.03 (d, *J* = 1.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.1, 155.5, 137.8, 134.3, 128.5, 128.2, 127.5, 118.1, 59.9, 53.6, 50.6, 49.2, 44.5, 41.9, 26.1, 22.7, 18.4, –5.2, –5.2; IR (Neat Film, NaCl) 2955, 2929, 2857, 1741, 1686, 1444, 1351, 1207, 1095, 837 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{38}NO_3$ $[M+H]^+$: 420.2570, found 420.2541; $[\alpha]^{25}$ – 6.23 (*c* 2.91, $CHCl_3$, 94% ee).



Methyl (*S*)-benzyl(2-methyl-2-phenylpent-4-enoyl)carbamate (87k)

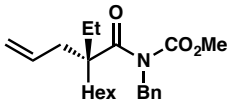
Representative Procedure H. Compound **87k** was prepared from allylenolcarbonate **86k** using General Procedure G (26.0 mg, 77% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 4H), 7.30 – 7.23 (m, 3H), 7.20 – 7.15 (m, 1H), 7.06 – 7.01 (m, 2H), 5.34 (dddd, *J* = 16.8, 10.3, 8.1, 6.5 Hz, 1H), 4.95 (ddt, *J* = 8.7, 2.2, 1.2 Hz, 1H), 4.93 (h, *J* = 1.2 Hz, 1H), 4.88 (s, 2H), 3.22 (s, 3H), 2.90 (ddt, *J* = 13.7, 8.2, 1.0 Hz, 1H), 2.55 (ddt, *J* = 13.6,

6.6, 1.4 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.7, 154.5, 143.7, 137.5, 134.3, 128.6, 128.5, 128.1, 127.6, 126.2, 125.9, 118.5, 54.0, 53.3, 50.1, 47.0, 23.8; IR (Neat Film, NaCl) 3064, 3007, 2954, 1755, 1674 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{23}NO_3$ $[M+H]^+$: 338.1751, found 338.1754; $[\alpha]^{25}$ + 71.01 (*c* 2.36, $CHCl_3$, 76% ee).



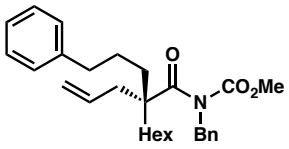
Methyl (*R*)-(2-allyl-2-ethylhexanoyl)(benzyl)carbamate (87l)

Representative Procedure H. Compound **87l** was prepared from allylenolcarbonate **86l** using General Procedure G (8.6 mg, 76% yield, 0.034 mmol scale). Note: this reaction was run in EtOAc and not THF; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H), 5.62 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.07 – 4.97 (m, 2H), 4.78 (s, 2H), 3.75 (s, 3H), 2.53 – 2.39 (m, 2H), 1.82 – 1.55 (m, 4H), 1.28 – 1.18 (m, 2H), 1.15 – 1.00 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.7, 155.6, 137.9, 134.7, 128.5, 128.3, 127.5, 117.7, 54.0, 53.6, 50.8, 39.1, 35.0, 28.1, 26.7, 23.4, 14.1, 9.0; IR (Neat Film, NaCl) 2958, 2933, 2873, 1741, 1732, 1682, 1443, 1350, 1206, 699 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{29}NO_3$ $[M+H]^+$: 332.2220, found 332.2216; $[\alpha]^{25}$ +0.64 (*c* 0.7, $CHCl_3$, 82% ee).



Methyl (*R*)-(2-allyl-2-ethyloctanoyl)(benzyl)carbamate (87m)

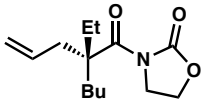
Representative Procedure H. Compound **87m** was prepared from allylenolcarbonate **86m** using General Procedure G (24.0 mg, 64% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.17 (m, 5H), 5.62 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.09 – 4.95 (m, 2H), 4.78 (s, 2H), 3.75 (s, 3H), 2.51 – 2.40 (m, 2H), 1.83 – 1.73 (m, 1H), 1.73 – 1.64 (m, 2H), 1.64 – 1.56 (m, 1H), 1.31 – 1.17 (m, 6H), 1.17 – 1.02 (m, 2H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.7, 155.6, 137.9, 134.7, 128.5, 128.3, 127.5, 117.7, 54.0, 53.6, 50.8, 39.1, 35.3, 31.8, 30.0, 28.1, 24.4, 22.8, 14.2, 9.0; IR (Neat Film, NaCl)2956, 2872, 1739, 1685, 1443, 1350, 1206, 1183, 998 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{34}NO_3$ $[M+H]^+$: 360.2533, found 360.2530; $[\alpha]^{25}$ +1.25 (*c* 1.90, $CHCl_3$, 93% ee).



Methyl (*S*)-(2-allyl-2-(3-phenylpropyl)octanoyl)(benzyl)carbamate (87n)

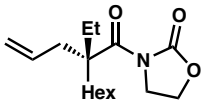
Representative Procedure H. Compound **87n** was prepared from allylenolcarbonate **86n** using General Procedure G (22.4 mg, 56% yield, 0.089 mmol scale); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.09 (m, 10H), 5.61 – 5.52 (m, 1H), 5.01 – 4.98 (m, 1H), 4.97 –4.96 (m, 1H), 4.76 (s, 2H), 3.67 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.43 (dq, *J* = 7.4, 1.3 Hz, 2H), 1.79 – 1.37 (m, 6H), 1.29 – 1.13 (m, 6H), 1.13 – 0.96 (m, 2H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.5, 155.5, 142.4, 137.8, 134.6, 128.6, 128.4, 128.4,

128.3, 127.5, 125.8, 117.8, 53.6, 53.5, 50.8, 39.6, 36.5, 35.7, 35.1, 31.8, 30.0, 26.3, 24.3, 22.7, 14.2; IR (Neat Film, NaCl) 2954, 2930, 1738, 1682, 1444, 1350, 1205, 1176, 699 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{29}H_{40}NO_3$ $[M+H]^+$: 450.3003, found 450.2995; $[\alpha]^{25}$ –0.11 (*c* 2.0, $CHCl_3$, 76% ee).



(*R*)-3-(2-Allyl-2-ethylhexanoyl)oxazolidin-2-one (87o)

Representative Procedure H. Compound **87o** was prepared from allylenolcarbonate **86o** using General Procedure G (16.3 mg, 67% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 5.69 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H), 5.11 – 5.01 (m, 2H), 4.38 (dd, *J* = 8.4, 7.6 Hz, 2H), 4.04 (dd, *J* = 8.5, 7.6 Hz, 2H), 2.68 – 2.54 (m, 2H), 2.05 – 1.76 (m, 4H), 1.33 – 1.23 (m, 2H), 1.21 – 1.04 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 152.4, 134.5, 117.9, 62.3, 52.7, 45.6, 36.6, 31.8, 26.6, 25.1, 23.3, 14.2, 8.8; IR (Neat Film, NaCl) 3076, 2960, 2931, 2874, 1778, 1682, 1468, 1384, 1202 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{24}NO_3$ $[M+H]^+$: 254.1756, found 254.1756; $[\alpha]^{25}$ 0.02 (*c* 1.45, $CHCl_3$, 69% ee).



(*R*)-3-(2-Allyl-2-ethyloctanoyl)oxazolidin-2-one (87p)

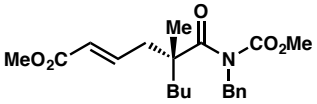
Representative Procedure H. Compound **387p** was prepared from allylenolcarbonate **86p** using General Procedure G (20.1 mg, 72% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 –

5.58 (m, 1H), 5.14 – 4.96 (m, 2H), 4.38 (t, J = 8.0 Hz, 2H), 4.04 (t, J = 8.0 Hz, 2H), 2.70 – 2.48 (m, 2H), 2.05 – 1.73 (m, 4H), 1.33 – 1.05 (m, 8H), 0.87 (t, J = 6.7 Hz, 3H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 152.4, 134.5, 117.9, 62.3, 52.8, 45.6, 36.6, 32.1, 31.8, 29.9, 25.1, 24.4, 22.8, 14.2, 8.8; IR (Neat Film, NaCl) 2958, 2926, 1779, 1682, 1467, 1383, 1228, 1194, 1107, 914 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{16}H_{28}NO_3$ $[M+H]^+$: 282.2069, found 282.2078; $[\alpha]^{25}$ 0.21 (*c* 1.67, $CHCl_3$, 73% ee).

3.4.5 Cross Metathesis Procedure

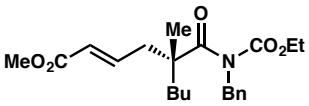
Representative Procedure I.

Unless otherwise noted, the cross metathesis procedure was executed as follows: The allylic alkylation substrates were loaded into a 2-dram vial equipped with a magnetic stirring bar and brought into a glove box. A solution of methacrylate (0.06M, 10 equiv.) in dichloromethane was added and the vial was capped with a Teflon lined screw-cap. The reaction mixture was stirred for 30 minutes. A solution of Grubbs generation II catalyst (6.6 mM, 5 mol%) in dichloromethane was added to the reaction. The mixture was sealed the cap and heated to 45 °C with stirring. After 5 hours, the reaction mixture was cooled to room temperature and removed from the glovebox. The reaction mixture was filtered through a silica plug, eluting with diethyl ether, and concentrated. The crude material was purified by preparative TLC (EtOAc/hexanes mobile phase) to afford the product, which was analyzed by SFC to determine the %ee of the allylic alkylation.



Methyl (*R*,*E*)-5-(benzyl(methoxycarbonyl)carbamoyl)-5-methylnon-2-enoate (88d)

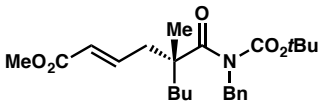
Representative Procedure I. Compound **88d** was prepared using General Procedure H with **87d** (26.9 mg, 85 μmol) to afford a clear oil (25.5 mg, 80% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 5H), 6.83 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.81 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.77 (s, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 2.76 (ddd, *J* = 14.0, 7.6, 1.5 Hz, 1H), 2.44 (ddd, *J* = 14.0, 7.9, 1.4 Hz, 1H), 1.77 (ddd, *J* = 13.4, 12.2, 4.4 Hz, 1H), 1.55 (ddd, *J* = 13.4, 12.4, 4.6 Hz, 1H), 1.23 (s, 3H), 1.22 – 1.15 (m, 2H), 1.12 – 1.01 (m, 1H), 0.96 (ttd, *J* = 11.9, 7.4, 4.4 Hz, 1H), 0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.0, 166.7, 155.5, 145.5, 137.6, 128.5, 128.2, 127.6, 123.8, 53.7, 51.6, 50.6, 50.6, 42.3, 39.7, 26.8, 23.3, 22.4, 14.1; IR (Neat Film, NaCl) 2957, 2872, 1726, 1686, 1439, 1350, 1272, 1195, 998 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{21}H_{33}N_2O_5$ $[M+NH_4]^+$: 393.2384, found 393.2376; $[\alpha]^{25}$ +12.17 (*c* 2.3, $CHCl_3$, 92% ee).



Methyl (*R*,*E*)-5-(benzyl(ethoxycarbonyl)carbamoyl)-5-methylnon-2-enoate (88e)

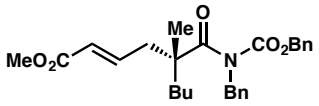
Representative Procedure I. Compound **88e** was prepared using General Procedure H with **87e** (17.4 mg, 53 μmol) to afford a clear oil (17.4 mg, 85% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 5H), 6.84 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.82 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.77 (s, 2H), 4.25 – 4.12 (m, 2H), 3.71 (s, 3H), 2.78 (ddd, *J* = 13.9, 7.5, 1.5 Hz, 1H), 2.46 (ddd, *J* = 13.9, 7.9, 1.4 Hz, 1H), 1.80 (ddd, *J* = 13.4, 12.3, 4.4 Hz, 1H),

1.63 – 1.52 (m, 1H), 1.25 (s, 3H), 1.24 (t, *J* = 9.1, 3H), 1.23 – 1.16 (m, 2H), 1.14 – 1.03 (m, 1H), 0.98 (ttd, *J* = 12.4, 7.5, 4.4 Hz, 1H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.1, 166.8, 155.1, 145.6, 137.8, 128.5, 128.2, 127.5, 123.8, 63.1, 51.6, 50.6, 50.5, 42.2, 39.6, 26.8, 23.3, 22.5, 14.3, 14.1; IR (Neat Film, NaCl) 1956, 2873, 1727, 1688, 1436, 1376, 1345, 1272, 1193, 1019, 986 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{35}N_2O_5$ $[M+NH_4]^+$: 407.2540, found 407.2538; $[\alpha]^{25}$ +9.70 (*c* 1.5, $CHCl_3$, 94% ee).



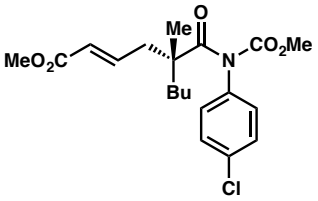
Methyl (*R*,*E*)-5-(benzyl(*tert*-butoxycarbonyl)carbamoyl)-5-methylnon-2-enoate (88f)

Representative Procedure I. Compound **88f** was prepared using General Procedure H with **87f** (9.3 mg, 26 μmol) to afford a clear oil (8.5 mg, 79% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H), 6.88 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.84 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.71 (s, 2H), 3.72 (s, 3H), 2.83 (ddd, *J* = 13.9, 7.5, 1.5 Hz, 1H), 2.50 (ddd, *J* = 13.9, 7.9, 1.4 Hz, 1H), 1.84 (ddd, *J* = 13.4, 12.1, 4.4 Hz, 1H), 1.59 (ddd, *J* = 13.4, 12.3, 4.5 Hz, 1H), 1.35 (s, 9H), 1.29 (s, 3H), 1.27 – 1.19 (m, 2H), 1.13 (dddd, *J* = 17.0, 7.8, 6.6, 4.6 Hz, 1H), 1.04 (tdd, *J* = 12.4, 8.3, 4.5 Hz, 1H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.3, 166.9, 153.9, 145.9, 138.3, 128.4, 128.0, 127.3, 123.7, 83.0, 51.6, 50.8, 50.3, 42.4, 39.6, 27.9, 26.9, 23.4, 22.5, 14.2; IR (Neat Film, NaCl) 2957, 2933, 1728, 1682, 1370, 1272, 1150, 987, 699 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{24}H_{36}NO_5$ $[M+H]^+$: 418.2593, found 418.2593; $[\alpha]^{25}$ +10.60 (*c* 0.85, $CHCl_3$, 90% ee).



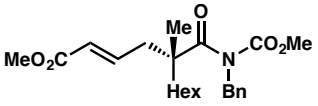
Methyl (*R*,*E*)-5-(benzyl((benzyloxy)carbonyl)carbamoyl)-5-methylnon-2-enoate (88g)

Representative Procedure I. Compound **88g** was prepared using General Procedure H with **87g** (20.9 mg, 53 μmol) to afford a clear oil (18.2 mg, 76% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 3H), 7.29 – 7.20 (m, 7H), 6.81 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.75 (dd, *J* = 15.5, 1.4 Hz, 1H), 5.15 (s, 2H), 4.79 (s, 2H), 3.71 (s, 3H), 2.73 (ddd, *J* = 14.0, 7.6, 1.4 Hz, 1H), 2.43 (ddd, *J* = 13.9, 7.9, 1.5 Hz, 1H), 1.76 (ddd, *J* = 13.5, 12.2, 4.5 Hz, 1H), 1.61 – 1.48 (m, 1H), 1.22 (s, 3H), 1.14 (p, *J* = 7.2 Hz, 2H), 1.10 – 0.99 (m, 1H), 0.94 (ttd, *J* = 12.3, 7.4, 4.3 Hz, 1H), 0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.2, 166.8, 154.9, 145.5, 137.7, 134.9, 128.8, 128.8, 128.7, 128.5, 128.2, 127.5, 123.8, 68.9, 51.6, 50.6, 50.5, 42.1, 39.5, 26.8, 23.2, 22.5, 14.1; IR (Neat Film, NaCl) 2955, 1725, 1688, 1386, 1346, 1272, 1192, 990, 698 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{27}H_{37}N_2O_5$ $[M+NH_4]^+$: 469.2697, found 469.2693; $[\alpha]^{25}$ +5.94 (*c* 1.7, $CHCl_3$, 93% ee).



Methyl (*R*,*E*)-5-((4-chlorophenyl)(methoxycarbonyl)carbamoyl)-5-methylnon-2-enoate (88h)

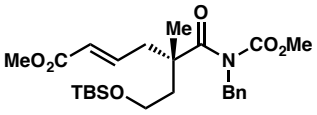
Representative Procedure I. Compound **88h** was prepared using General Procedure H with **87h** (19.8 mg, 59 μmol) to afford a clear oil (19.7 mg, 80% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.13 – 7.05 (m, 2H), 6.88 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.83 (dt, *J* = 15.3, 1.3 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 2.73 (ddd, *J* = 14.3, 7.6, 1.5 Hz, 1H), 2.44 (ddd, *J* = 14.1, 7.8, 1.4 Hz, 1H), 1.79 – 1.67 (m, 1H), 1.61 – 1.52 (m, 1H), 1.30 – 1.14 (m, 4H), 1.24 (s, 3H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.7, 166.7, 154.7, 144.8, 136.9, 134.1, 129.5, 129.3, 124.2, 54.0, 51.7, 51.2, 41.8, 39.4, 26.6, 23.2, 22.9, 14.1; IR (Neat Film, NaCl) 2956, 2873, 1728, 1658, 1492, 1439, 1272, 1247, 1198, 1092 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{26}NClO_5$ $[M+H-H_2]^+$: 395.1499, found 395.1476; $[\alpha]^{25}$ +7.94 (*c* 1.8, $CHCl_3$, 90% ee).



Methyl (*R*,*E*)-5-(benzyl(methoxycarbonyl)carbamoyl)-5-methylundec-2-enoate (88i)

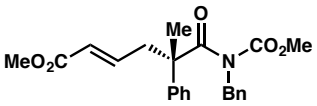
Representative Procedure I. Compound **88i** was prepared using General Procedure H with **87i** (17.3 mg, 51 μmol) to afford a clear oil (17.2 mg, 84% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H), 6.83 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.81 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.77 (s, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 2.75 (ddd, *J* = 14.0, 7.5, 1.4 Hz, 1H),

2.45 (ddd, *J* = 13.9, 8.0, 1.4 Hz, 1H), 1.77 (ddd, *J* = 13.4, 12.1, 4.4 Hz, 1H), 1.61 – 1.46 (m, 1H), 1.30 – 1.13 (m, 6H), 1.23 (s, 3H), 1.13 – 1.03 (m, 1H), 1.02 – 0.91 (m, 1H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.0, 166.8, 155.5, 145.5, 137.6, 128.5, 128.2, 127.6, 123.8, 53.7, 51.6, 50.6, 50.6, 42.3, 40.0, 31.7, 29.9, 24.5, 22.7, 22.4, 14.2; IR (Neat Film, NaCl) 2954, 2930, 2858, 1728, 1688, 1441, 1350, 1272, 1779, 998 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{23}H_{37}N_2O_5$ $[M+NH_4]^+$: 421.2697, found 421.2688; $[\alpha]^{25}$ +10.91 (*c* 1.6, $CHCl_3$, 94% ee).



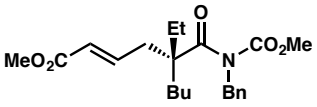
Methyl (*S*,*E*)-5-(benzyl(methoxycarbonyl)carbamoyl)-7-((*tert*-butyldimethylsilyl)oxy)-5-methylhept-2-enoate (88j)

Representative Procedure I. Compound **88j** was prepared using General Procedure H with **87j** (31.7 mg, 76 μmol) to afford a clear oil (28.5 mg, 79% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.17 (m, 5H), 6.79 (dq, *J* = 15.4, 7.8 Hz, 1H), 5.77 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.75 (s, 2H), 3.72 (s, 3H), 3.67 (s, 3H), 3.54 – 3.44 (m, 2H), 2.78 (ddd, *J* = 14.0, 7.6, 1.5 Hz, 1H), 2.47 (ddd, *J* = 14.0, 7.9, 1.5 Hz, 1H), 2.06 (ddd, *J* = 13.9, 7.8, 6.2 Hz, 1H), 1.86 (ddd, *J* = 13.9, 7.9, 6.3 Hz, 1H), 1.24 (s, 3H), 0.82 (s, 9H), -0.03 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.2, 166.7, 155.4, 145.3, 137.6, 128.6, 128.1, 127.6, 124.0, 59.8, 53.7, 51.6, 50.6, 49.3, 42.6, 41.8, 26.1, 22.7, 18.4, -5.2, -5.3; IR (Neat Film, NaCl) 2955, 2857, 1728, 1688, 1440, 1351, 1256, 1195, 1094, 994 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{40}NO_6Si$ $[M+H]^+$: 478.2625, found 478.2646; $[\alpha]^{25}$ +2.20 (*c* 2.6, $CHCl_3$, 94% ee).



Methyl (*S*,*E*)-6-(benzyl(methoxycarbonyl)amino)-5-methyl-6-oxo-5-phenylhex-2-enoate (88k)

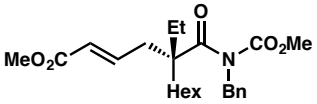
Representative Procedure I. Compound **88k** was prepared using General Procedure H with **87k** (26.0 mg, 77 μmol) to afford a clear oil (23.9 mg, 78% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.30 – 7.23 (m, 3H), 7.22 – 7.13 (m, 1H), 7.05 – 6.97 (m, 2H), 6.57 (ddd, *J* = 15.4, 8.3, 6.9 Hz, 1H), 5.71 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.89 (s, 2H), 3.67 (s, 3H), 3.22 (s, 3H), 3.01 (ddd, *J* = 13.9, 8.4, 1.2 Hz, 1H), 2.67 (ddd, *J* = 13.9, 6.9, 1.6 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.0, 166.6, 154.3, 145.1, 142.7, 137.4, 128.5, 128.5, 128.3, 127.7, 126.6, 125.8, 124.3, 54.1, 53.4, 51.5, 50.1, 45.9, 23.4; IR (Neat Film, NaCl) 2953, 1725, 1674, 1496, 1441, 1351, 1315, 1274, 1203, 1004, 700 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{23}H_{29}N_2O_5$ $[M+NH_4]^+$: 413.2071, found 413.2065; $[\alpha]^{25}$ +67.74 (*c* 2.2, $CHCl_3$, 76% ee).



Methyl (*R*,*E*)-5-(benzyl(methoxycarbonyl)carbamoyl)-5-ethylnon-2-enoate (88l)

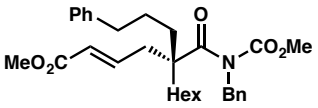
Representative Procedure I. Compound **88l** was prepared using General Procedure H with **87l** (7.3 mg, 22 μmol) to afford a clear oil (7.3 mg, 85% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.16 (m, 5H), 6.83 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.84 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.80 (s, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 2.62 (qdd, *J* = 14.4, 7.7, 1.5 Hz, 2H), 1.84

(dq, *J* = 14.8, 7.4 Hz, 1H), 1.75 (ddd, *J* = 13.8, 12.2, 4.7 Hz, 1H), 1.66 (dt, *J* = 14.3, 7.4 Hz, 1H), 1.59 (ddd, *J* = 13.8, 12.2, 4.7 Hz, 1H), 1.22 (p, *J* = 7.2 Hz, 2H), 1.15 – 0.97 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.8, 166.8, 155.5, 145.8, 137.7, 128.5, 128.2, 127.6, 123.6, 54.2, 53.7, 51.6, 50.8, 37.6, 35.2, 28.3, 26.7, 23.3, 14.1, 9.0; IR (Neat Film, NaCl) 2957, 2874, 1727, 1682, 1442, 1351, 1190, 700 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{35}N_2O_5$ $[M+NH_4]^+$: 407.2540, found 407.2537; $[\alpha]^{25}$ +1.32 (*c* 0.66, $CHCl_3$, 82% ee).



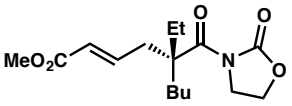
Methyl (*R*,*E*)-5-(benzyl(methoxycarbonyl)carbamoyl)-5-ethylundec-2-enoate (88m)

Representative Procedure I. Compound **88m** was prepared using General Procedure H with **87m** (19.0 mg, 53 μmol) to afford a clear oil (18.7 mg, 85% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.14 (m, 5H), 6.83 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.83 (dd, *J* = 15.5, 1.6 Hz, 1H), 4.79 (s, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.62 (qdd, *J* = 14.6, 7.7, 1.5 Hz, 2H), 1.84 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.78 – 1.70 (m, 1H), 1.69 – 1.54 (m, 2H), 1.30 – 1.15 (m, 6H), 1.15 – 0.97 (m, 2H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.8, 166.8, 155.5, 145.8, 137.7, 128.5, 128.2, 127.5, 123.6, 54.2, 53.7, 51.6, 50.7, 37.6, 35.5, 31.7, 29.9, 28.3, 24.5, 22.7, 14.2, 9.0; IR (Neat Film, NaCl) 2955, 1727, 1683, 1441, 1351, 1176 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{25}H_{39}N_2O_5$ $[M+NH_4]^+$: 435.2853, found 435.2853; $[\alpha]^{25}$ +2.25 (*c* 1.7, $CHCl_3$, 93% ee).



Methyl (*S*,*E*)-5-(benzyl(methoxycarbonyl)carbamoyl)-5-(3-phenylpropyl)undec-2-enoate (88n)

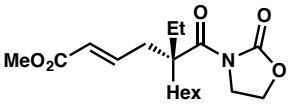
Representative Procedure I. Compound **88n** was prepared using General Procedure H with **87n** (21.6 mg, 48 mmol) to afford a clear oil (19.8 mg, 84% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.14 (m, 8H), 7.13 – 7.07 (m, 2H), 6.79 (dt, *J* = 15.4, 7.6 Hz, 1H), 5.79 (dt, *J* = 15.4, 1.3 Hz, 1H), 4.78 (s, 2H), 3.72 (s, 3H), 3.67 (s, 3H), 2.60 (dt, *J* = 7.7, 1.3 Hz, 2H), 2.53 (t, *J* = 7.4 Hz, 2H), 1.84 – 1.68 (m, 2H), 1.65 – 1.51 (m, 2H), 1.51 – 1.35 (m, 2H), 1.29 – 1.13 (m, 6H), 1.12 – 0.93 (m, 2H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.6, 166.7, 155.4, 145.6, 142.1, 137.6, 128.5, 128.5, 128.4, 128.2, 127.6, 125.9, 123.7, 53.8, 53.7, 51.6, 50.7, 38.2, 36.3, 35.8, 35.2, 31.7, 29.9, 26.3, 24.4, 22.7, 14.2; IR (Neat Film, NaCl) 3028, 2930, 2858, 1727, 1683, 1442, 1350, 1273, 1170, 699 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{31}H_{45}N_2O_5$ $[M+NH_4]^+$: 525.3323, found 525.3329; $[\alpha]^{25}$ +0.25 (*c* 1.8, $CHCl_3$, 76% ee).



Methyl (*R*,*E*)-5-ethyl-5-(2-oxooxazolidine-3-carbonyl)non-2-enoate (88o)

Representative Procedure I. Compound **88o** was prepared using General Procedure H with **87o** (15.2 mg, 60 μmol) to afford a clear oil (14.6 mg, 78% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.88 (dt, *J* = 15.5, 1.5 Hz, 1H), 4.48 – 4.31 (m, 2H), 4.05 (dd, *J* = 8.5, 7.6 Hz, 2H), 3.72 (s, 3H), 2.83 – 2.63 (m, 2H), 2.14 – 1.95 (m, 2H), 1.82 – 1.67 (m, 2H), 1.28 (h, *J* = 7.1 Hz, 2H), 1.22 – 1.12 (m, 1H), 1.06

(ttd, J = 12.3, 7.3, 4.5 Hz, 1H), 0.87 (t, J = 7.3 Hz, 3H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 166.8, 152.4, 145.5, 123.8, 62.4, 52.9, 51.6, 45.6, 35.6, 32.2, 26.7, 25.5, 23.2 14.1, 8.8; IR (Neat Film, NaCl) 2959, 2875, 1778, 1722, 1682, 1470, 1436, 1385, 1257, 1195, 1175, 1109, 1045 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{26}NO_5$ $[M+H]^+$: 312.1811, found 312.1791; $[\alpha]^{25}$ +0.50 (*c* 1.3, $CHCl_3$, 69% ee).

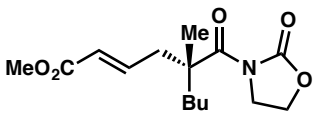
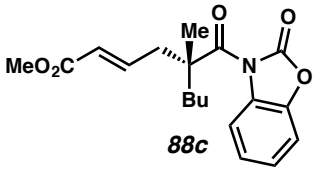
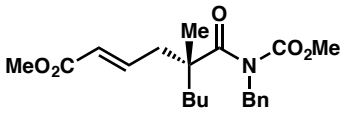
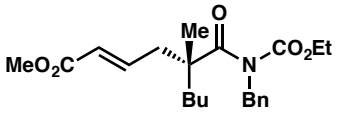
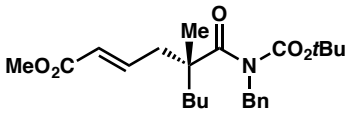
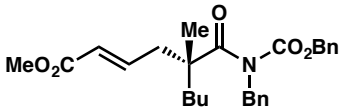
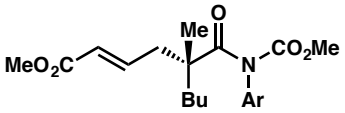


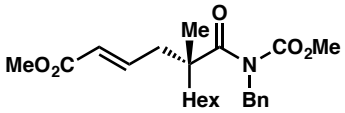
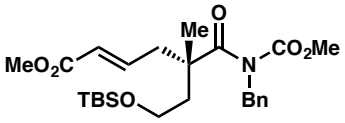
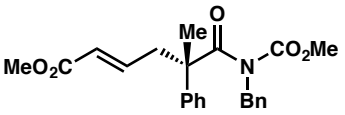
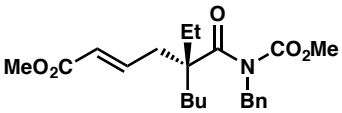
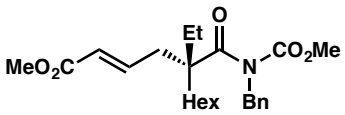
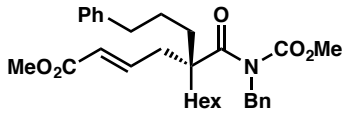
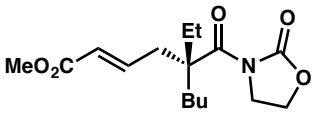
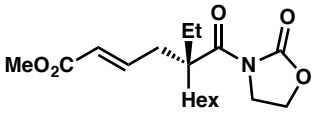
Methyl (*R*,*E*)-5-ethyl-5-(2-oxooxazolidine-3-carbonyl)undec-2-enoate (88p)

Representative Procedure I. Compound **88p** was prepared using General Procedure H with **87p** (16.5 mg, 59 μmol) to afford a clear oil (16.3 mg, 82% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 – 6.74 (m, 1H), 5.87 (dt, J = 15.5, 1.5 Hz, 1H), 4.39 (t, J = 8.0 Hz, 2H), 4.05 (t, J = 8.0 Hz, 2H), 3.71 (s, 3H), 2.86 – 2.62 (m, 2H), 2.14 – 1.91 (m, 2H), 1.84 – 1.66 (m, 2H), 1.31 – 1.12 (m, 7H), 1.12 – 1.00 (m, 1H), 0.86 (t, J = 6.8 Hz, 3H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 166.8, 152.4, 145.6, 123.7, 62.4, 52.9, 51.6, 45.6, 35.6, 32.4, 31.7, 29.7, 25.6, 24.4, 22.7, 14.2, 8.8; IR (Neat Film, NaCl) 2956, 2929, 2858, 1779, 1723, 1682, 1469, 1385, 1254, 1194, 1110, 1046 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{30}NO_5$ $[M+H]^+$: 340.2124, found 340.2116; $[\alpha]^{25}$ +2.41 (*c* 1.5, $CHCl_3$, 73% ee).

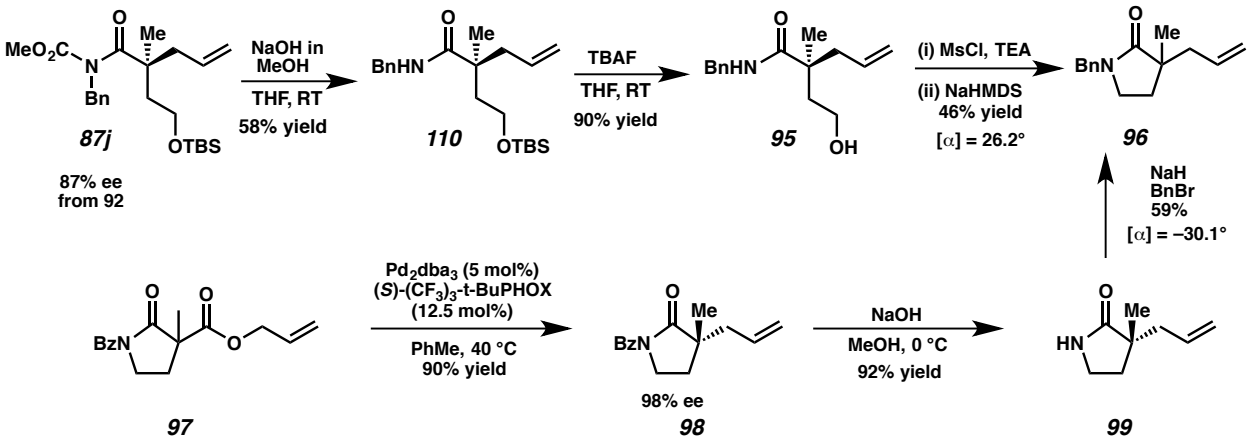
3.4.6 Determination of Enantiomeric Excess

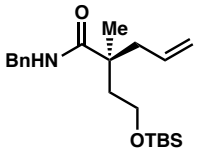
Table 3.4. Methods for the determination of enantiomeric excess.

entry	compound	assay method and conditions	retention time of minor isomer (min)	retention time of major isomer (min)	%ee
1	 ***88a***	SFC, 5% *i*PrOH in CO_2 2.5 mL/min, AD-H col.	5.31	5.87	*70*
2	 ***88c***	SFC, 5% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	5.55	6.82	*57**
					*used Ph-ANDEN ligand
3	 ***88d***	SFC, 5% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	7.00	9.65	*92*
4	 ***88e***	SFC, 5% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	6.80	9.33	*94*
5	 ***88f***	SFC, 2% *i*PrOH in CO_2 2.5 mL/min, OJ-H col.	3.05	3.64	*90*
6	 ***88g***	SFC, 15% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	4.45	5.69	*93*
7	 Ar = 4-ClC_6H_4 ***88h***	SFC, 5% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	6.28	8.73	*90*

entry	compound	assay method and conditions	retention time of minor isomer (min)	retention time of major isomer (min)	%ee
8	 ***88i***	SFC, 7% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	6.09	8.25	*94*
9	 ***88j***	SFC, 10% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	4.00	4.83	*94*
10	 ***88k***	SFC, 7% *i*PrOH in CO_2 2.5 mL/min, AD-H col.	8.77	9.66	*76*
11	 ***88l***	SFC, 10% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	3.58	4.39	*82*
12	 ***88m***	SFC, 7% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	5.67	7.40	*93*
13	 ***88n***	SFC, 10% *i*PrOH in CO_2 2.5 mL/min, AD-H col.	6.55	5.71	*76*
14	 ***88o***	SFC, 5% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	8.13	10.61	*69*
15	 ***88p***	SFC, 6% *i*PrOH in CO_2 2.5 mL/min, OD-H col.	7.73	10.18	*73*

3.4.7 Determination of Absolute Stereochemistry

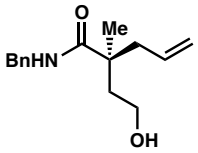




(*S*)-*N*-Benzyl-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-methylpent-4-enamide (110)

To an oven-dried round-bottom flask and magnetic stir bar was added **87j** (60 mg, 0.143 mmol) followed by anhydrous THF (1.4 mL). The solution was stirred under nitrogen at room temperature. A solution of NaOH in anhydrous methanol (0.17 mL, 1.0 M) was added dropwise by syringe. The reaction was stirred at room temperature for 45 min. Afterward, the reaction mixture was diluted with ethyl acetate and quenched with water. The mixture was partitioned between water and ethyl acetate and the aqueous layer was extracted two additional times with ethyl acetate. The combined organic layers were washed with brine (50 mL), dried with sodium sulfate, and filtered. This mixture was concentrated in vacuo and purified by flash chromatography (10/90 to 12/88 EtOAc/hexanes) to provide the product as an amorphous white solid (30.2 mg, 58% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 5H), 6.37 (s, 1H), 5.80 – 5.69 (m,

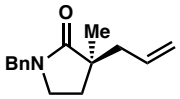
1H), 5.08 – 5.06 (m, 1H), 5.06 – 5.03 (m, 1H), 4.49 – 4.38 (m, 2H), 3.68 (td, *J* = 6.7, 1.5 Hz, 2H), 2.40 (ddt, *J* = 13.7, 7.1, 1.2 Hz, 1H), 2.27 (ddt, *J* = 13.7, 7.7, 1.1 Hz, 1H), 1.93 (dt, *J* = 13.7, 6.7 Hz, 1H), 1.69 (dt, *J* = 14.1, 6.7 Hz, 1H), 1.20 (s, 3H), 0.86 (s, 9H), 0.02 – -0.00 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 138.8, 134.3, 128.8, 127.9, 127.5, 118.3, 60.1, 44.7, 44.7, 43.7, 41.4, 26.1, 22.3, 18.4, -5.3, -5.3; IR (Neat Film, NaCl) 3343, 2955, 2929, 2856, 1640, 1531, 1254, 1095, 836 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{36}NO_2Si$ $[M+H]^+$: 362.2514, found 362.2515; $[\alpha]^{25}$ –2.93 (*c* 2.5, $CHCl_3$, 94% ee).



(*S*)-*N*-Benzyl-2-(2-hydroxyethyl)-2-methylpent-4-enamide (95)

To an oven-dried 2-dram vial and magnetic stir bar was added **S11** (30 mg, 0.083 mmol) followed by anhydrous THF (0.5 mL). The solution was stirred under nitrogen at room temperature. A solution of TBAF in anhydrous THF (0.17 mL, 1.0 M) was added dropwise by syringe. The reaction was stirred at room temperature for 2 h. Afterward, the reaction mixture was quenched with saturated ammonium chloride. The mixture was partitioned between water and dichloromethane and the aqueous layer was extracted two additional times with dichloromethane. The combined organic layers were washed with brine (50 mL), dried with sodium sulfate, and filtered. This mixture was concentrated in vacuo and purified by flash chromatography (60/40 EtOAc/hexanes) to provide the product as an oil (19.5 mg, 58% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H), 6.10 (s, 1H), 5.78 – 5.69 (m, 1H), 5.11 – 5.09 (m, 1H), 5.09 – 5.05 (m, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 3.78 (dt, *J* = 11.8, 6.1 Hz, 1H), 3.74 – 3.65 (m, 1H), 2.56 (s, 1H), 2.48

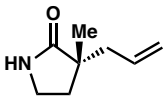
(ddt, *J* = 13.7, 7.0, 1.3 Hz, 1H), 2.22 (ddt, *J* = 13.7, 7.7, 1.2 Hz, 1H), 2.00 (ddd, *J* = 14.4, 7.3, 5.5 Hz, 1H), 1.70 (ddd, *J* = 14.4, 6.6, 5.4 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 138.3, 133.7, 128.9, 127.9, 127.7, 118.9, 59.3, 44.5, 44.4, 44.0, 41.5, 22.2; IR (Neat Film, NaCl) 3335, 2927, 1634, 1538, 1249 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{21}NO_2$ $[M+H]^+$: 248.1645, found 248.1651; $[\alpha]^{25}$ –61.06 (*c* 1.63, $CHCl_3$, 94% ee).



(*S*)-3-Allyl-1-benzyl-3-methylpyrrolidin-2-one ((*S*)-96):

To an oven-dried 2-dram vial and magnetic stir bar was added **95** (19.5 mg, 0.079 mmol) followed by anhydrous THF (0.20 mL). The solution was stirred under nitrogen at 0 °C. Triethylamine (12 μL, 0.087 mmol) was added dropwise by syringe followed by a solution of methanesulfonyl chloride in THF (0.10 mL, 0.79 M). The reaction was stirred at 0 °C for 0.5 h. A separate oven-dried 2-dram vial and magnetic stir bar was charged with NaHMDS (46 mg, 0.253 mmol) and THF (0.25 mL). The reaction mixture was canulated into the NaHMDS solution at 0 °C over 5 minutes. This solution was warmed to room temperature and stirred overnight. Afterward, the reaction mixture was quenched with saturated ammonium chloride. The mixture was partitioned between water and ethyl acetate and the aqueous layer was extracted two additional times with ethyl acetate. The combined organic layers were washed with brine (50 mL), dried with sodium sulfate and filtered. This mixture was concentrated in vacuo and purified by preparative TLC (40/60 EtOAc/hexanes) to provide the product as an oil (8.4 mg, 46%

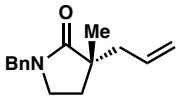
yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H), 5.82 –5.74 (m, 1H), 5.18 – 5.06 (m, 2H), 4.53 – 4.42 (m, 2H), 3.20 – 3.10 (m, 2H), 2.37 (ddt, *J* = 13.7, 6.7, 1.3 Hz, 1H), 2.25 (ddt, *J* = 13.8, 8.2, 1.1 Hz, 1H), 2.03 (ddd, *J* = 12.8, 8.2, 6.4 Hz, 1H), 1.73 (ddd, *J* = 12.9, 8.0, 5.5 Hz, 1H), 1.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 136.7, 134.1, 128.7, 128.1, 127.6, 118.4, 46.8, 44.1, 43.4, 42.3, 30.4, 23.2; IR (Neat Film, NaCl) 3002, 2962, 1686, 1454, 1431, 1291, 917, 701 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1539, found 230.1549; $[\alpha]^{25}$ 26.10 (*c* 0.70, $CHCl_3$, 94% ee).



(*R*)-3-Allyl-3-methylpyrrolidin-2-one (99):

To a round-bottom flask and magnetic stir bar was added **98**[6a] (98% ee) (80 mg, 0.33 mmol) followed by MeOH (4.0 mL). The solution was stirred under nitrogen at 0 °C. A solution of NaOH (0.61 mL, 2.0 M, 1.2 mmol) was added dropwise by syringe. The reaction was stirred at 0 °C for 1.5 h. The mixture was partitioned between brine and diethyl ether. The organic layer was washed with saturated sodium bicarbonate solution followed by brine, dried with sodium sulfate, and filtered. This mixture was concentrated in vacuo and purified by flash chromatography (80/20 to 100/0 EtOAc/hexanes) to provide the product as an amorphous white solid (28.3 mg, 62% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (s, 1H), 5.84 – 5.70 (m, 1H), 5.13 – 5.09 (m, 1H), 5.08 (p, *J* = 1.2 Hz, 1H), 3.34 – 3.19 (m, 2H), 2.33 – 2.25 (m, 1H), 2.19 (ddt, *J* = 13.6, 8.2, 1.1 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.86 – 1.76 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

182.9, 134.1, 118.4, 43.1, 42.0, 39.0, 33.0, 22.8; IR (Neat Film, NaCl) 3233, 3077, 2928, 1697, 1295, 915 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_8H_{14}NO$ $[M+H]^+$: 140.1070, found 140.1071; $[\alpha]^{25}$ –33.10 (*c* 2.27, $CHCl_3$, 98% ee).



(*R*)-3-Allyl-1-benzyl-3-methylpyrrolidin-2-one ((*R*)-96):

To an oven-dried 2-dram vial and magnetic stir bar was added **99** (28.3 mg, 0.203 mmol) followed by anhydrous DMF (1.0 mL). The solution was stirred under nitrogen at 0 °C. Sodium hydride (8.1 mg, 0.203 mmol) was added portion-wise over two minutes. The reaction was stirred at 0 °C for 40 min. To this solution was added benzyl bromide (30 μL, 0.256 mmol) dropwise through by syringe. This solution was warmed to room temperature and stirred for 2 h. Afterward, the reaction mixture was quenched with saturated ammonium chloride. The mixture was partitioned between water and ethyl acetate and the aqueous layer was extracted two additional times with ethyl acetate. The combined organic layers were washed with brine (50 mL), dried with sodium sulfate, and filtered. This mixture was concentrated in vacuo and purified by preparative TLC (40/60 EtOAc/hexanes) to provide the product as an oil (27 mg, 59% yield). Characterization data matched previously synthesized material; $[\alpha]^{25}$ –33.10 (*c* 2.27, $CHCl_3$, 98% ee).

3.5 NOTES AND REFERENCES

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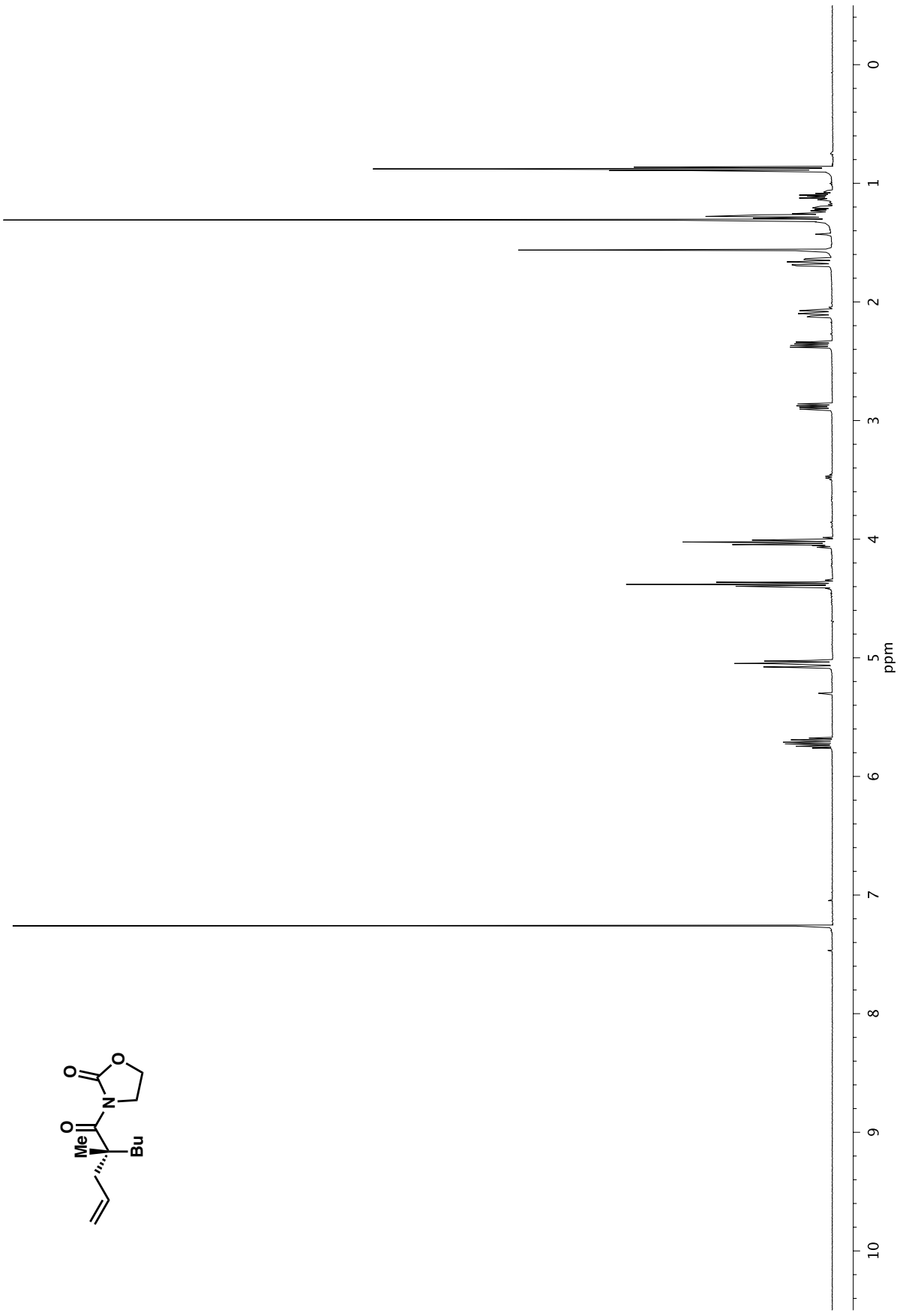
APPENDIX 3

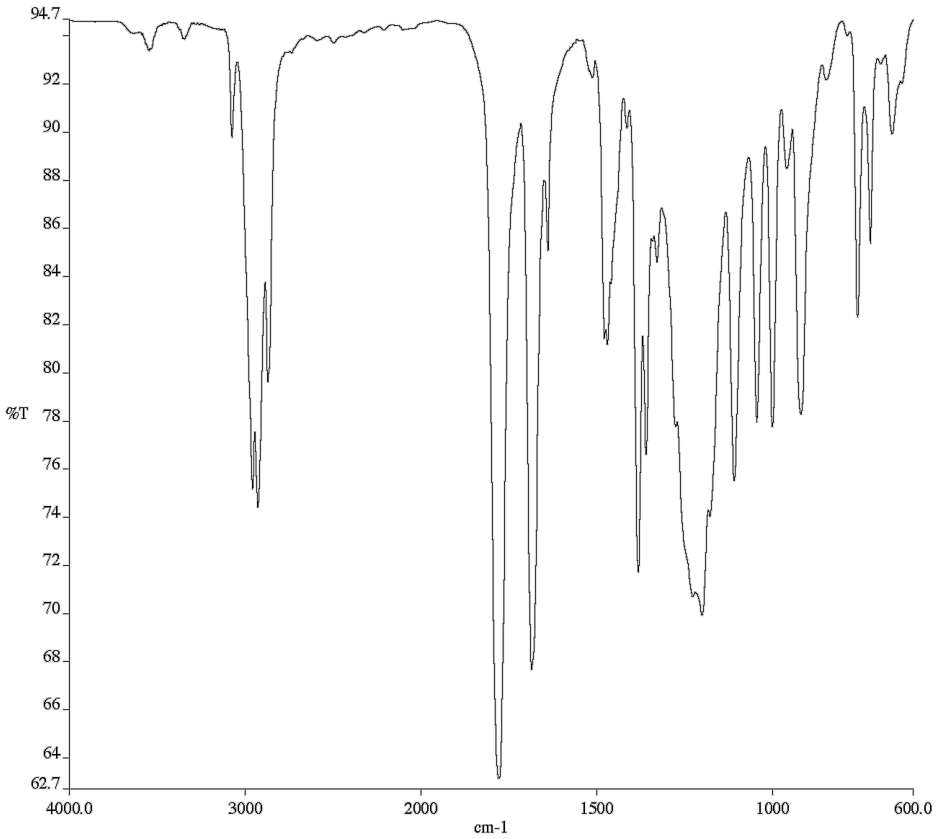
Spectra Relevant to Chapter 3:

The Palladium-Catalyzed Asymmetric Decarboxylative Allylic

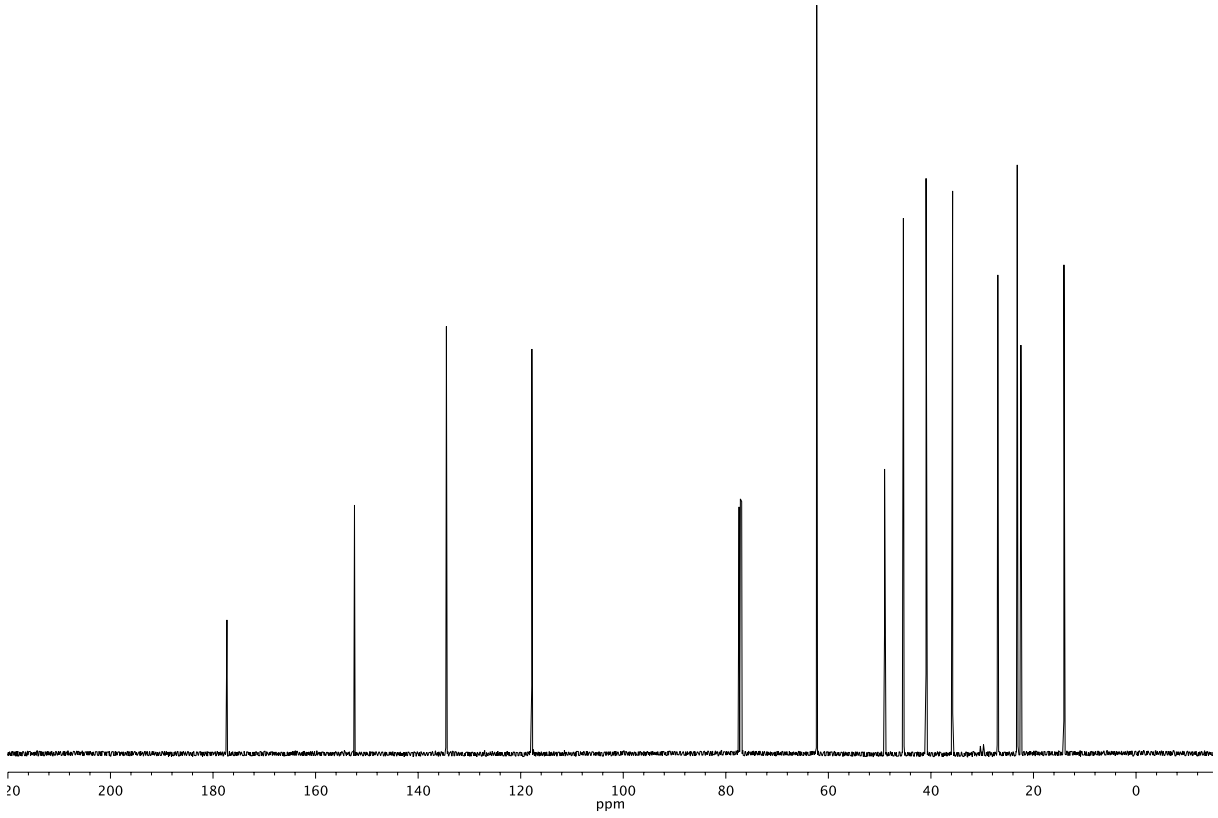
Alkylation for Formation of De Novo Acyclic Quaternary Stereocenters



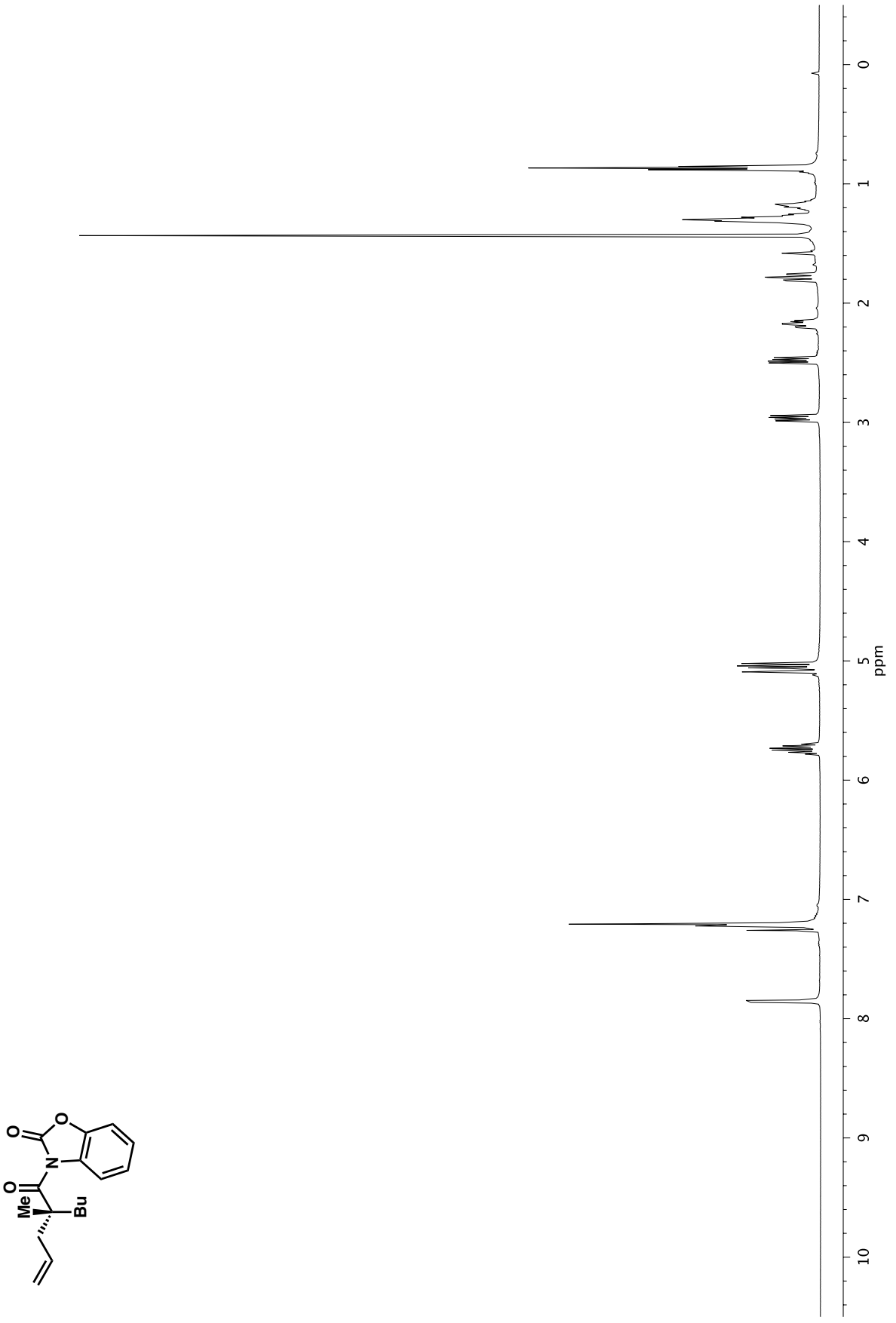
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87a**.



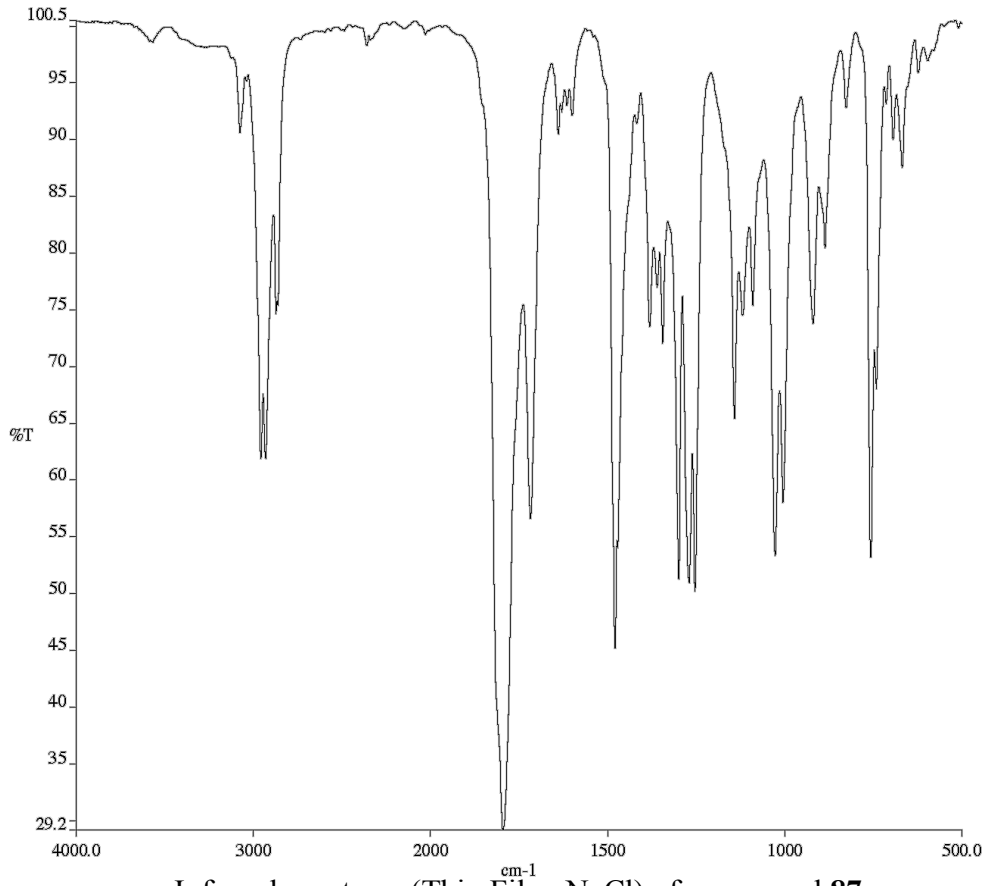
Infrared spectrum (Thin Film, NaCl) of compound **87a**.



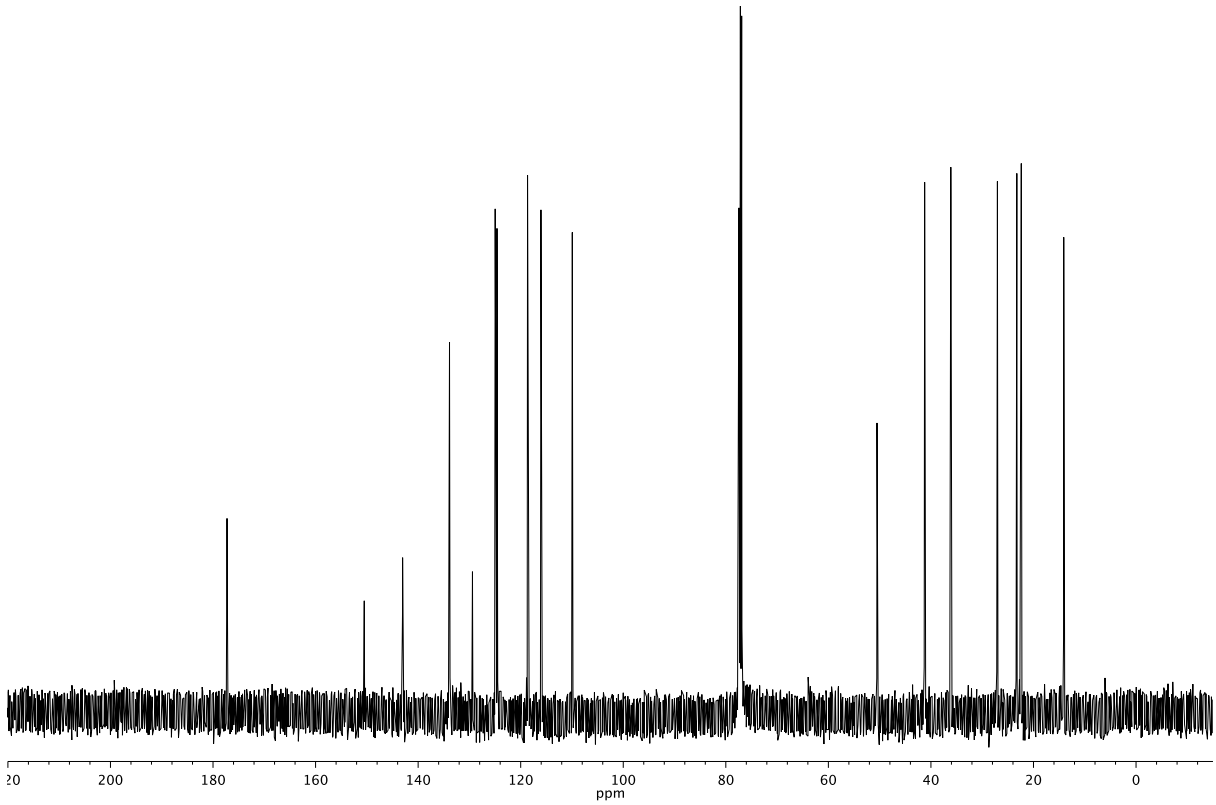
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87a**.



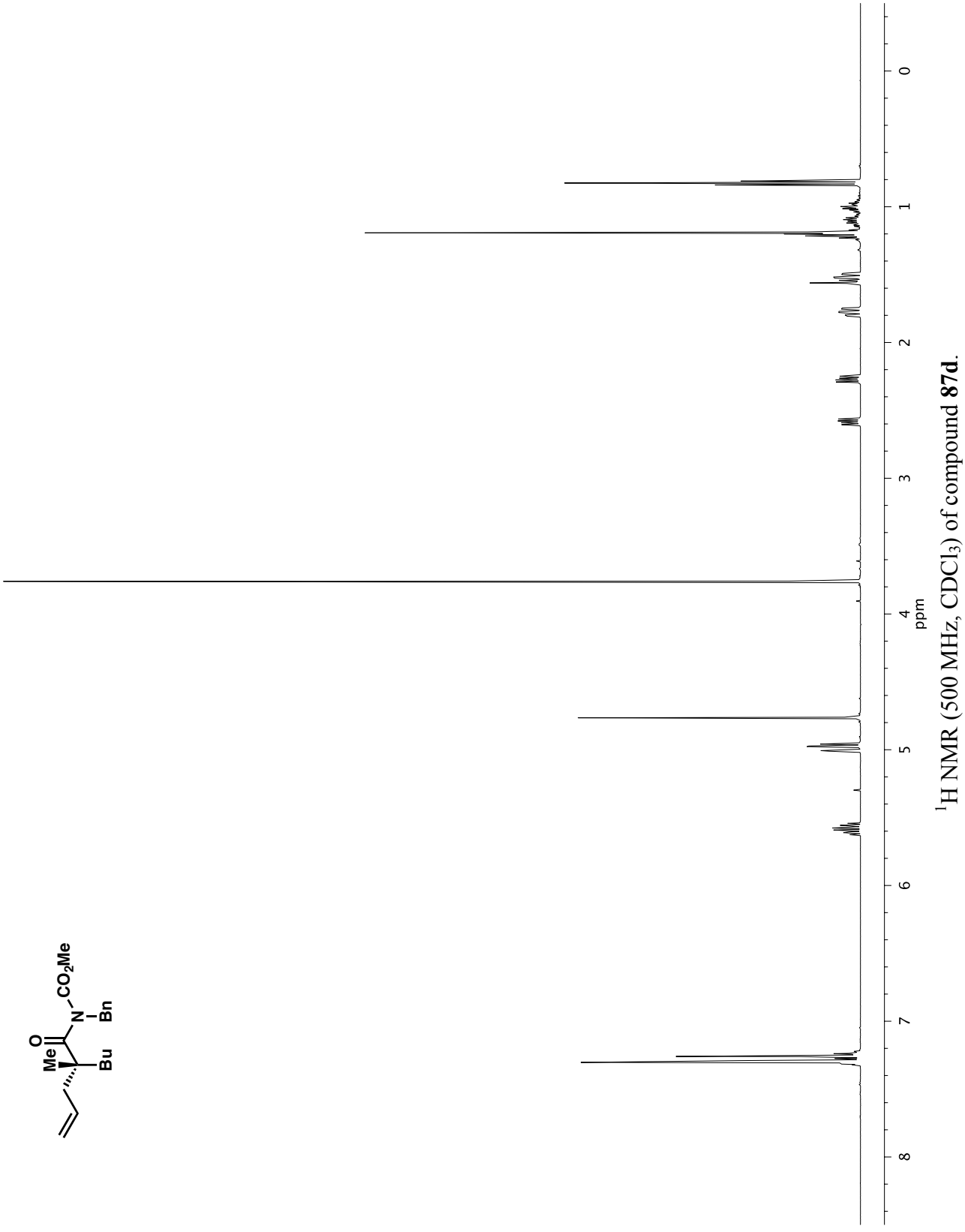
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87c**.



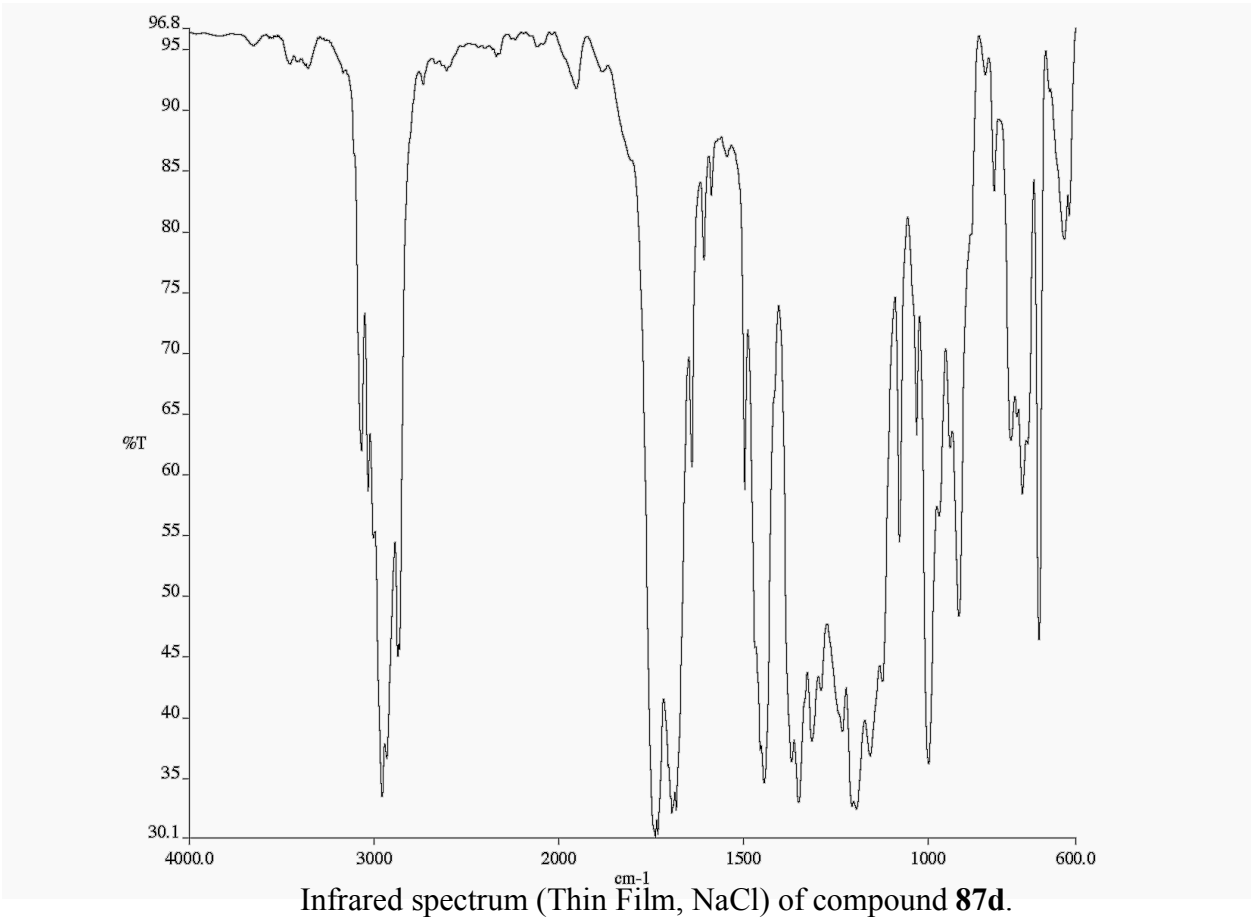
Infrared spectrum (Thin Film, NaCl) of compound **87c**.



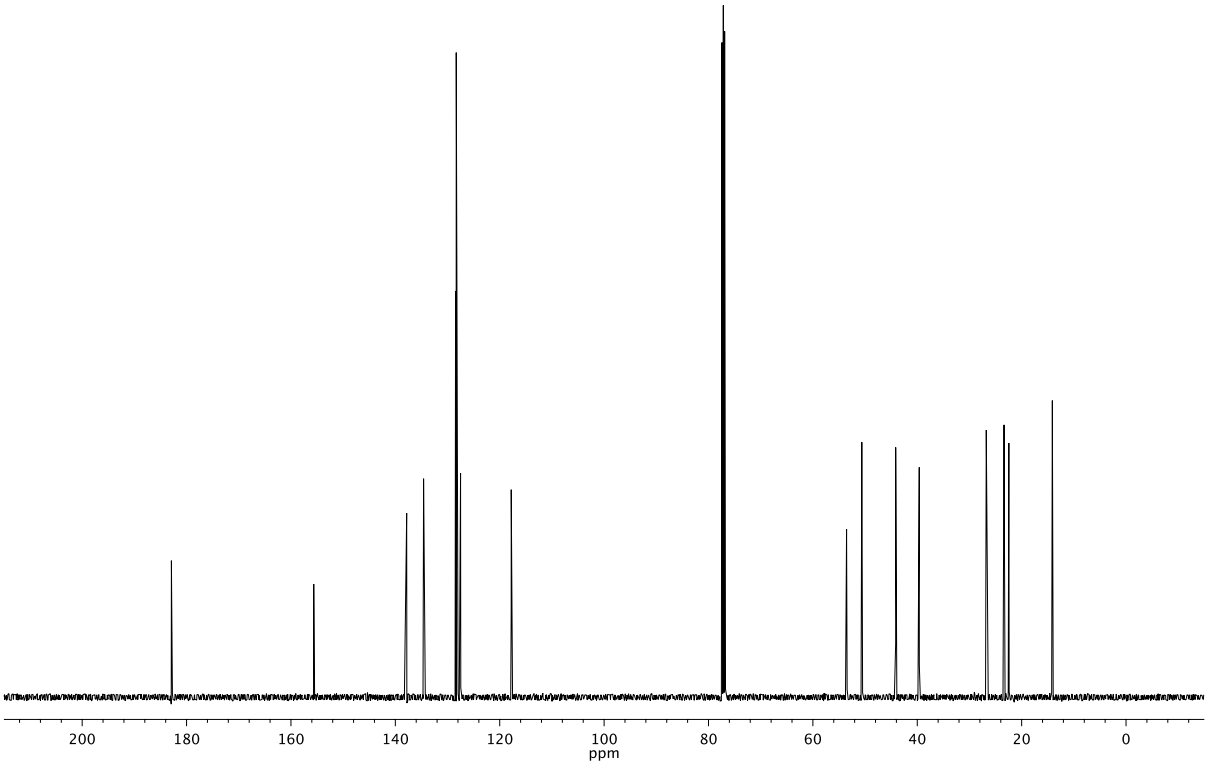
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87c**.



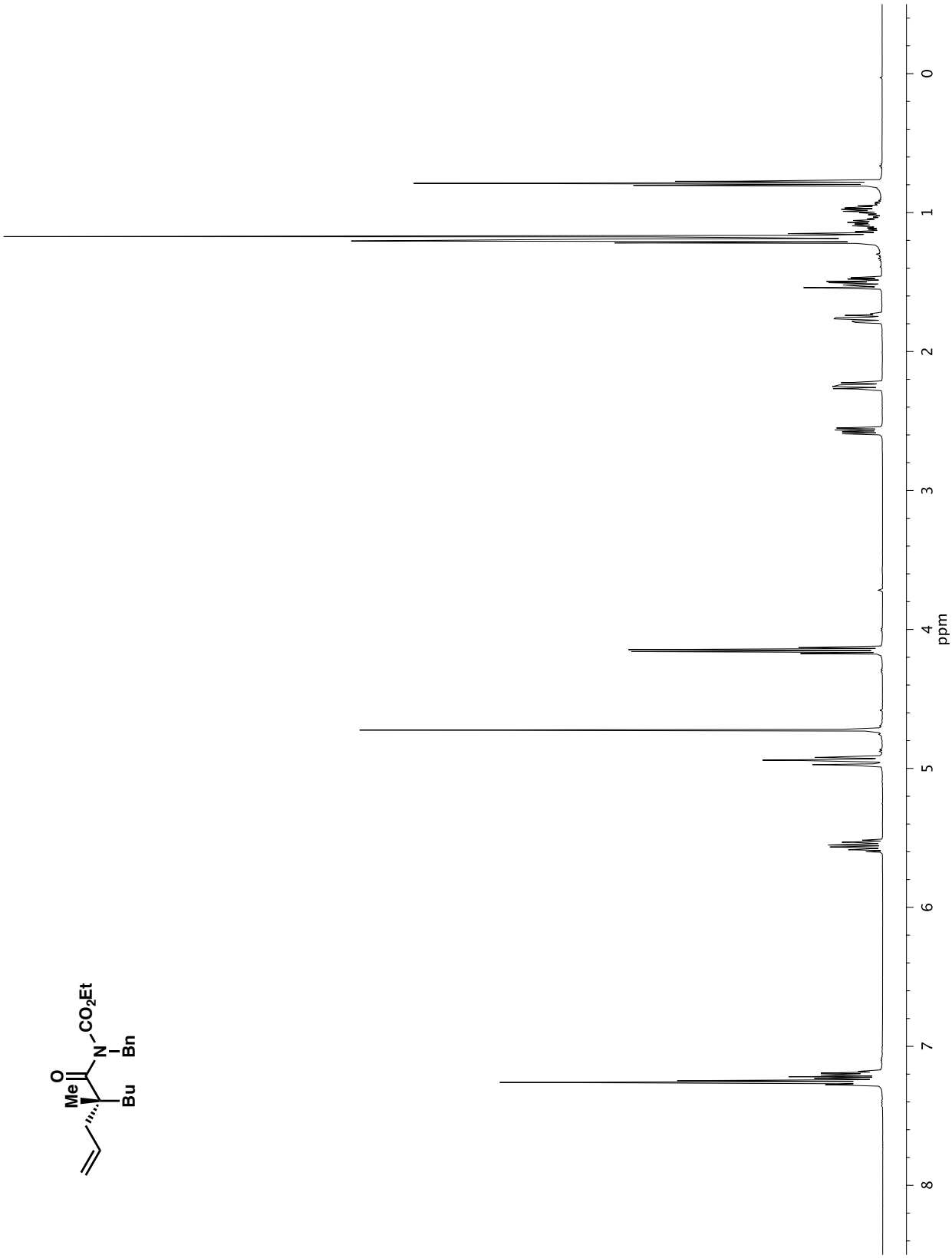
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87d**.



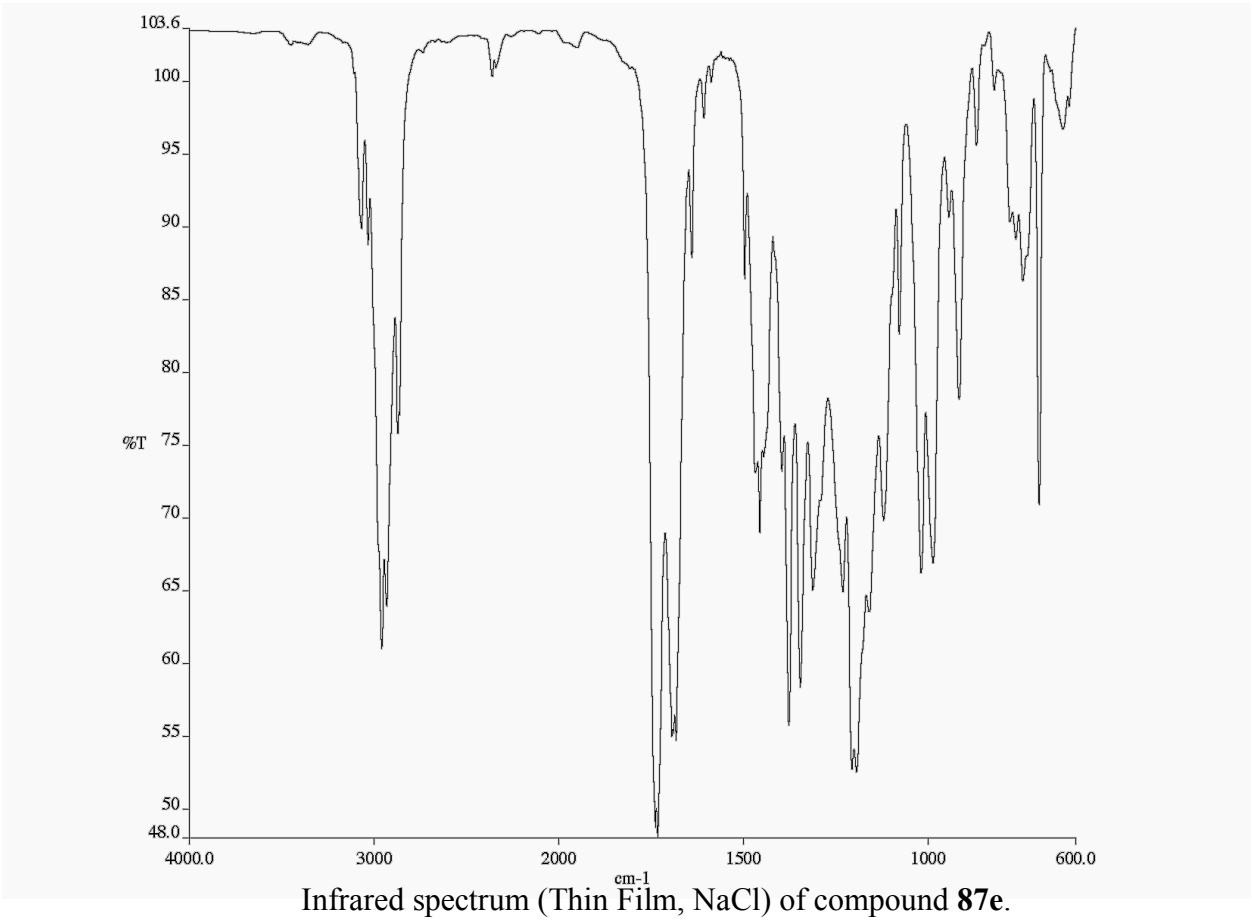
Infrared spectrum (Thin Film, NaCl) of compound **87d**.



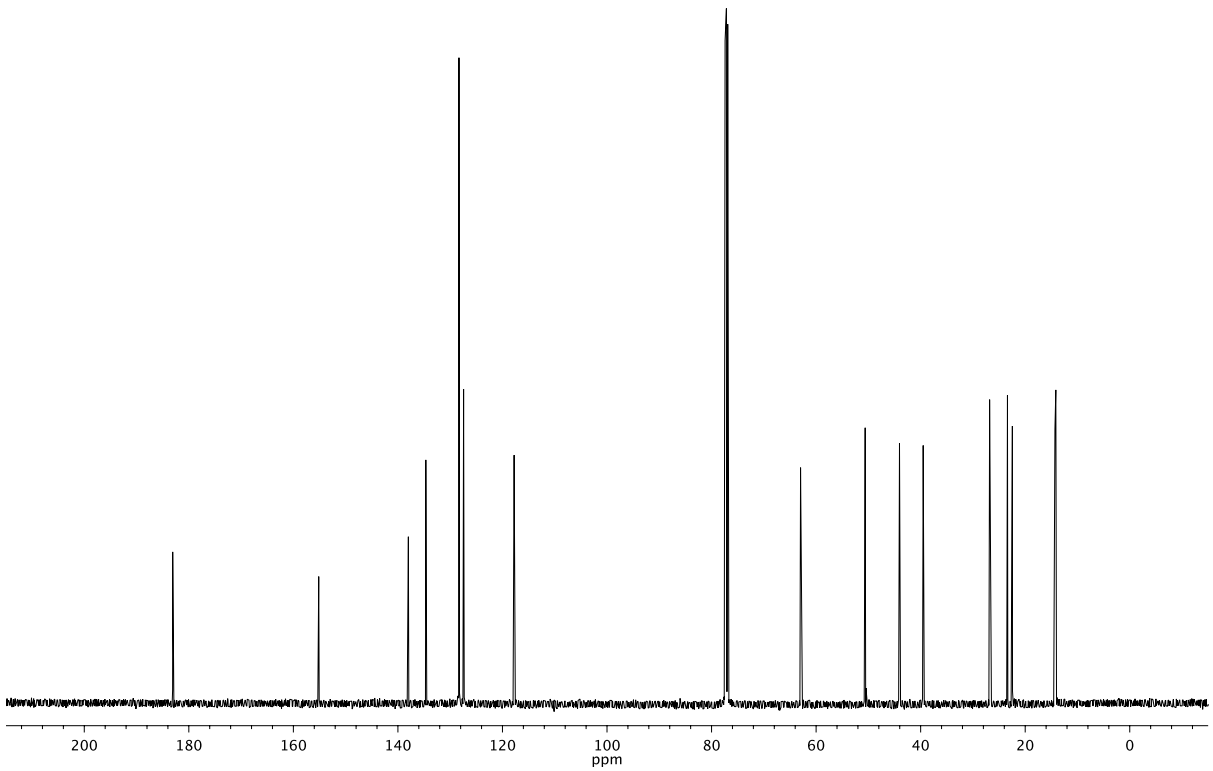
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87d**.



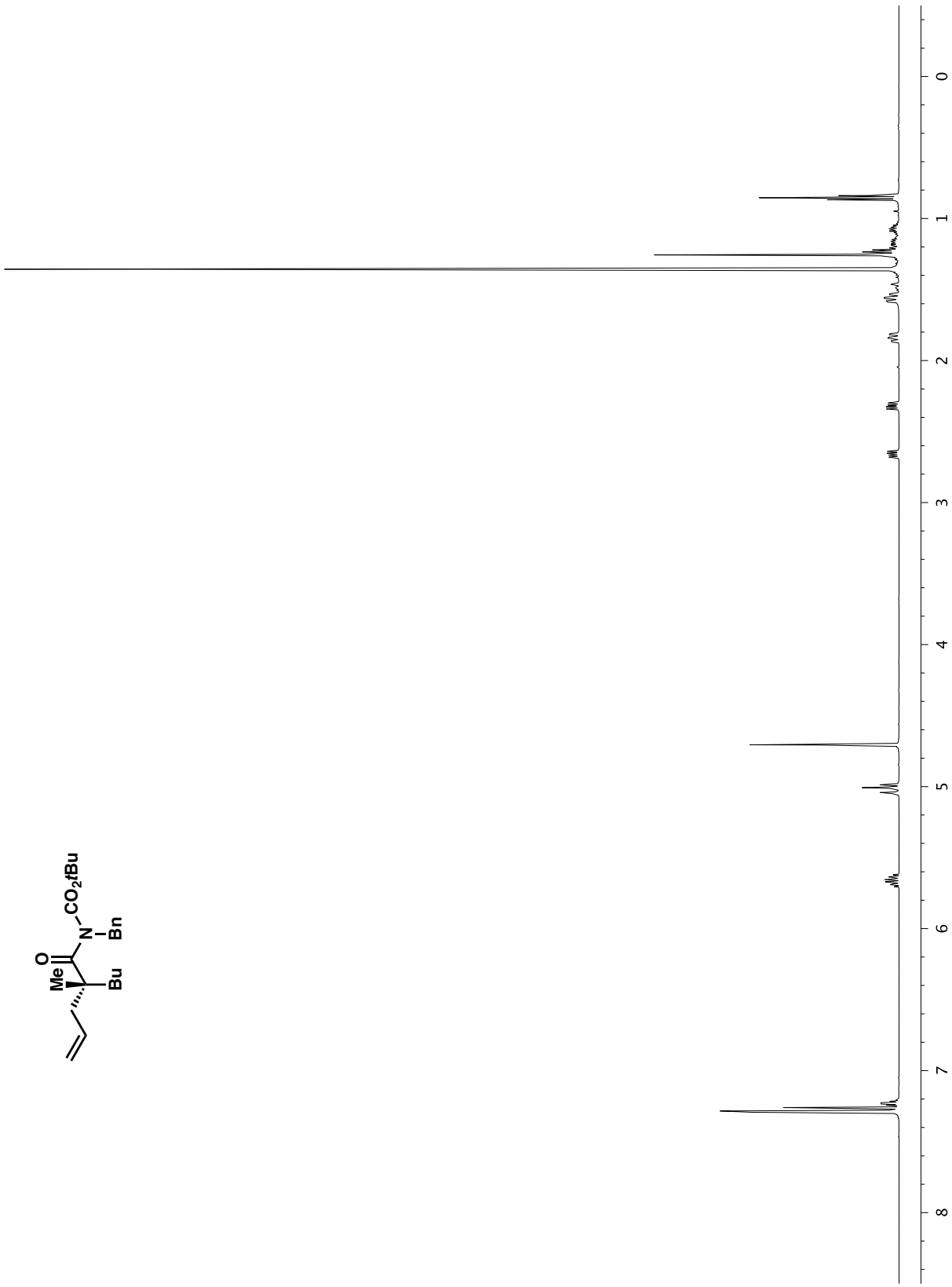
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87e**.



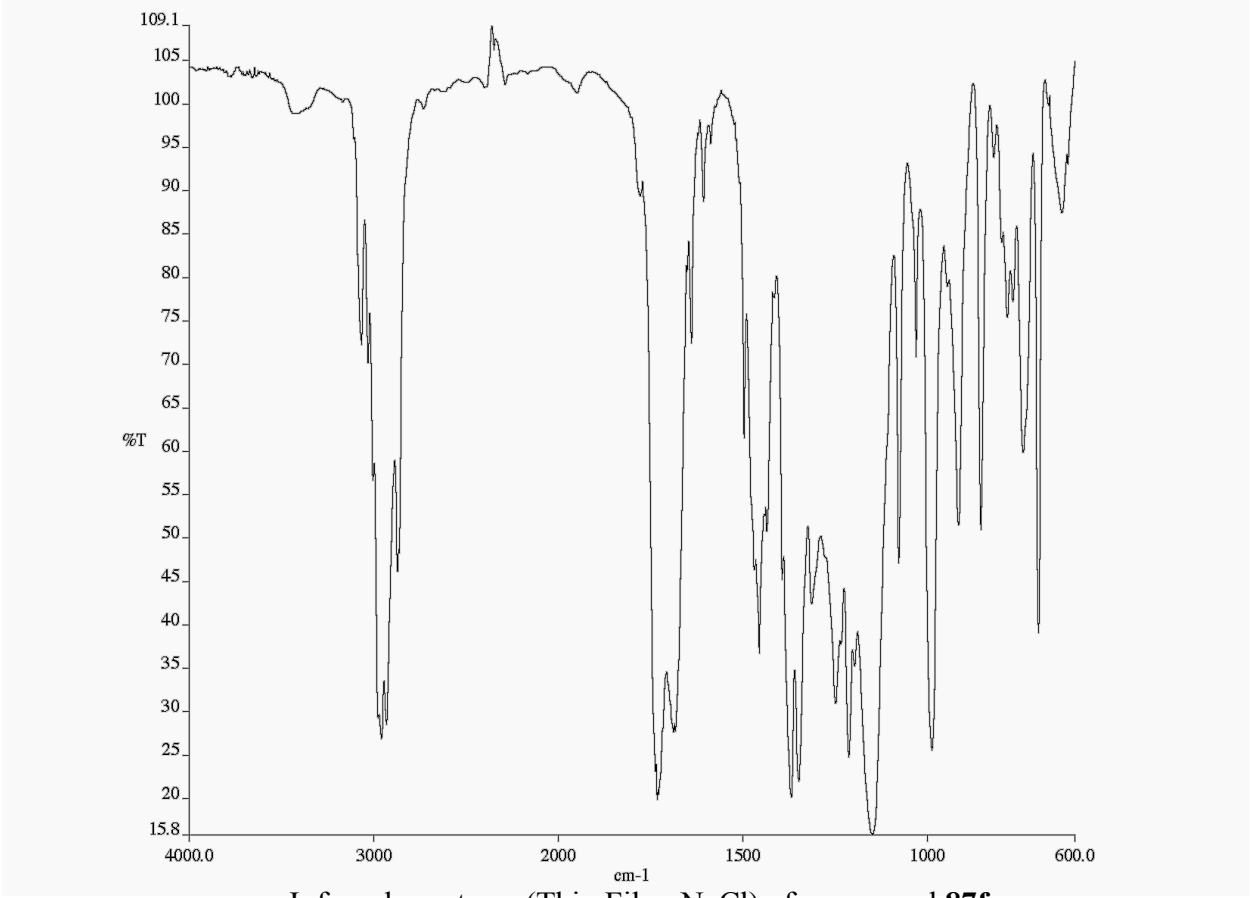
Infrared spectrum (Thin Film, NaCl) of compound **87e**.



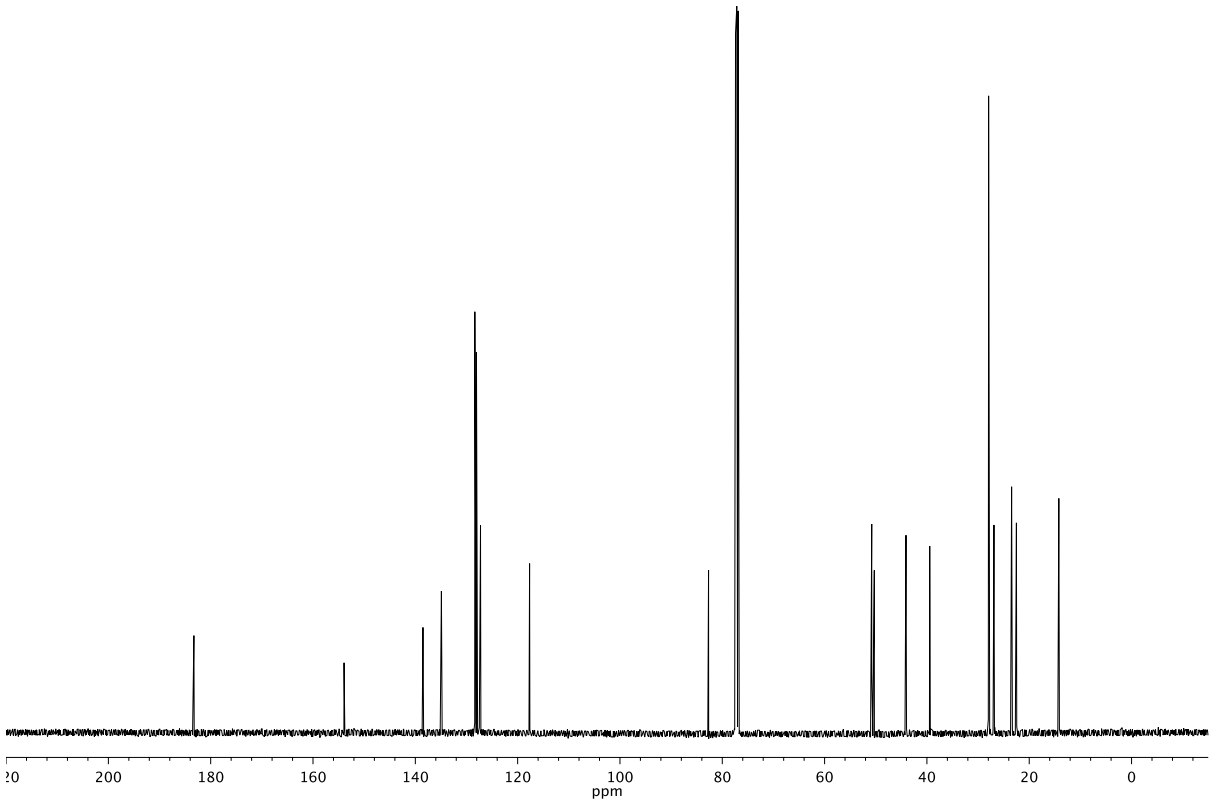
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87e**.



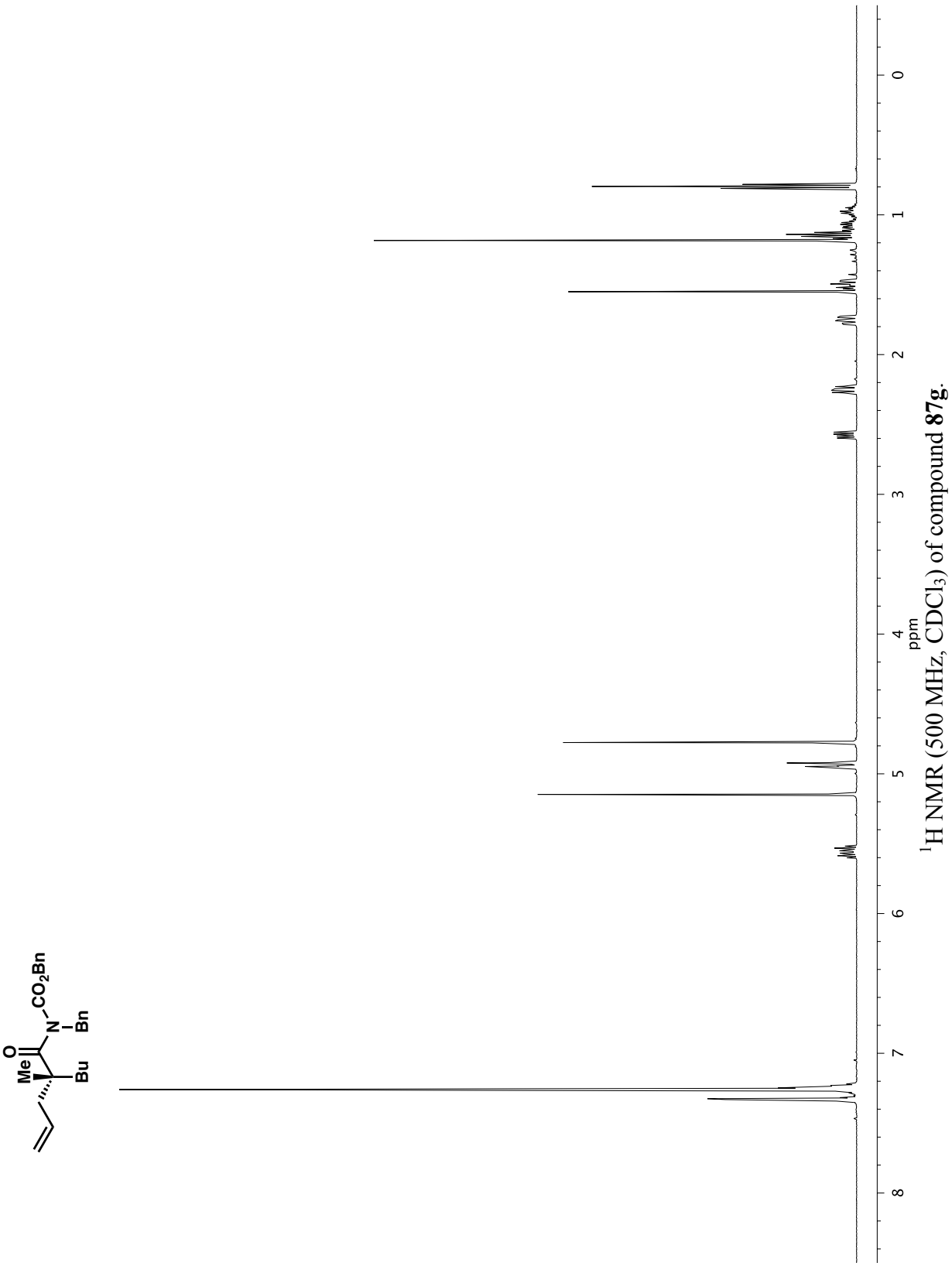
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87f**.



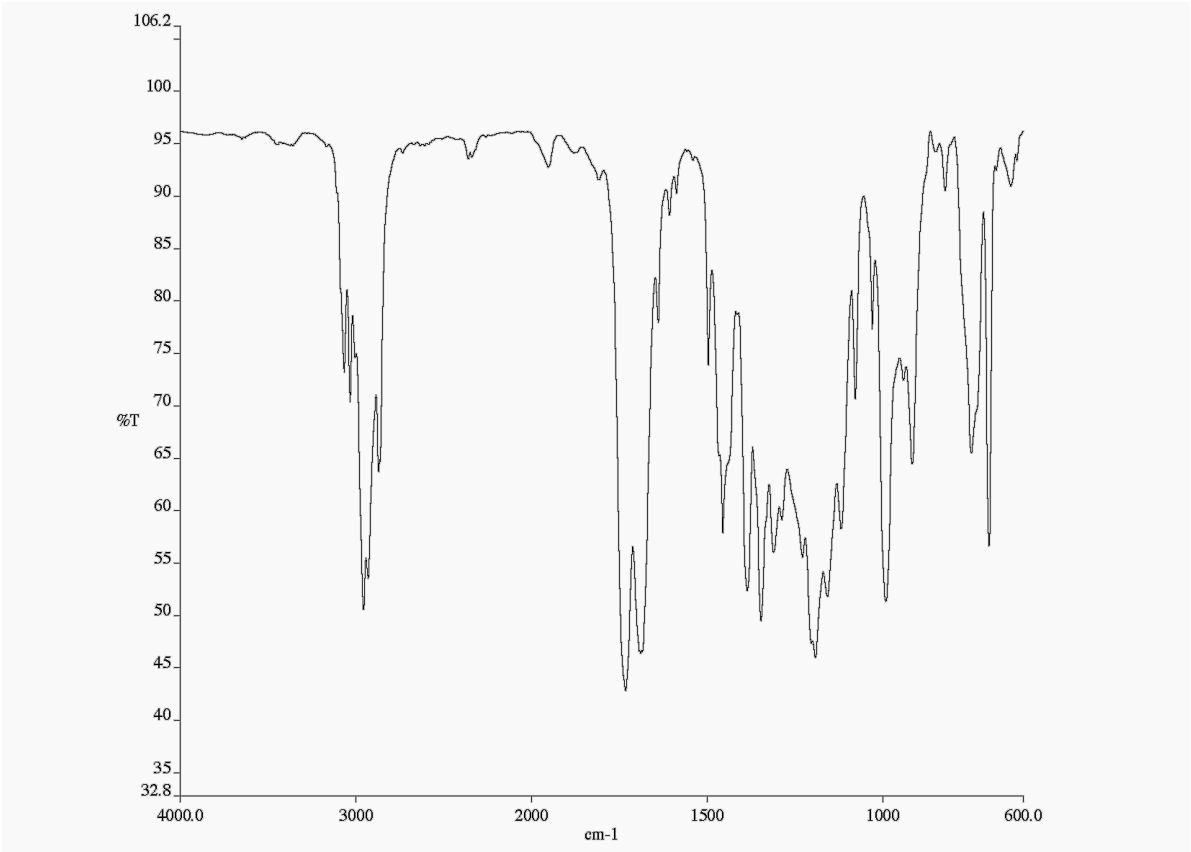
Infrared spectrum (Thin Film, NaCl) of compound **87f**.



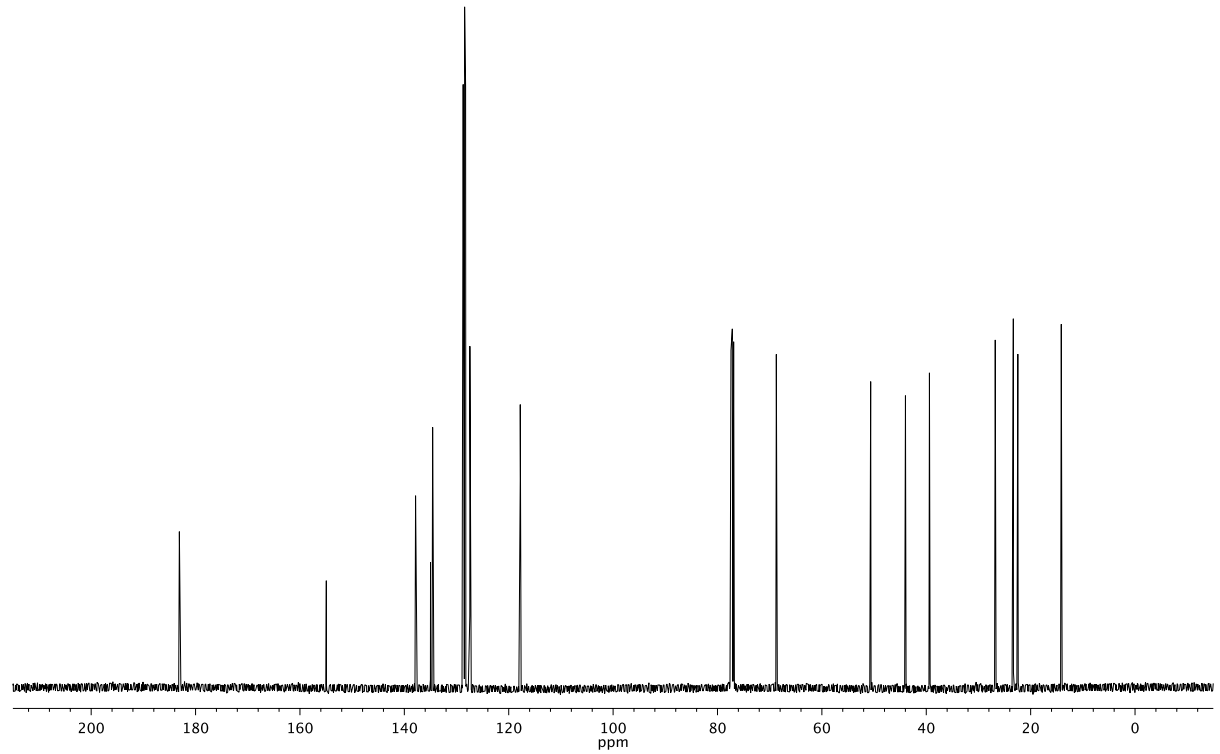
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87f**.



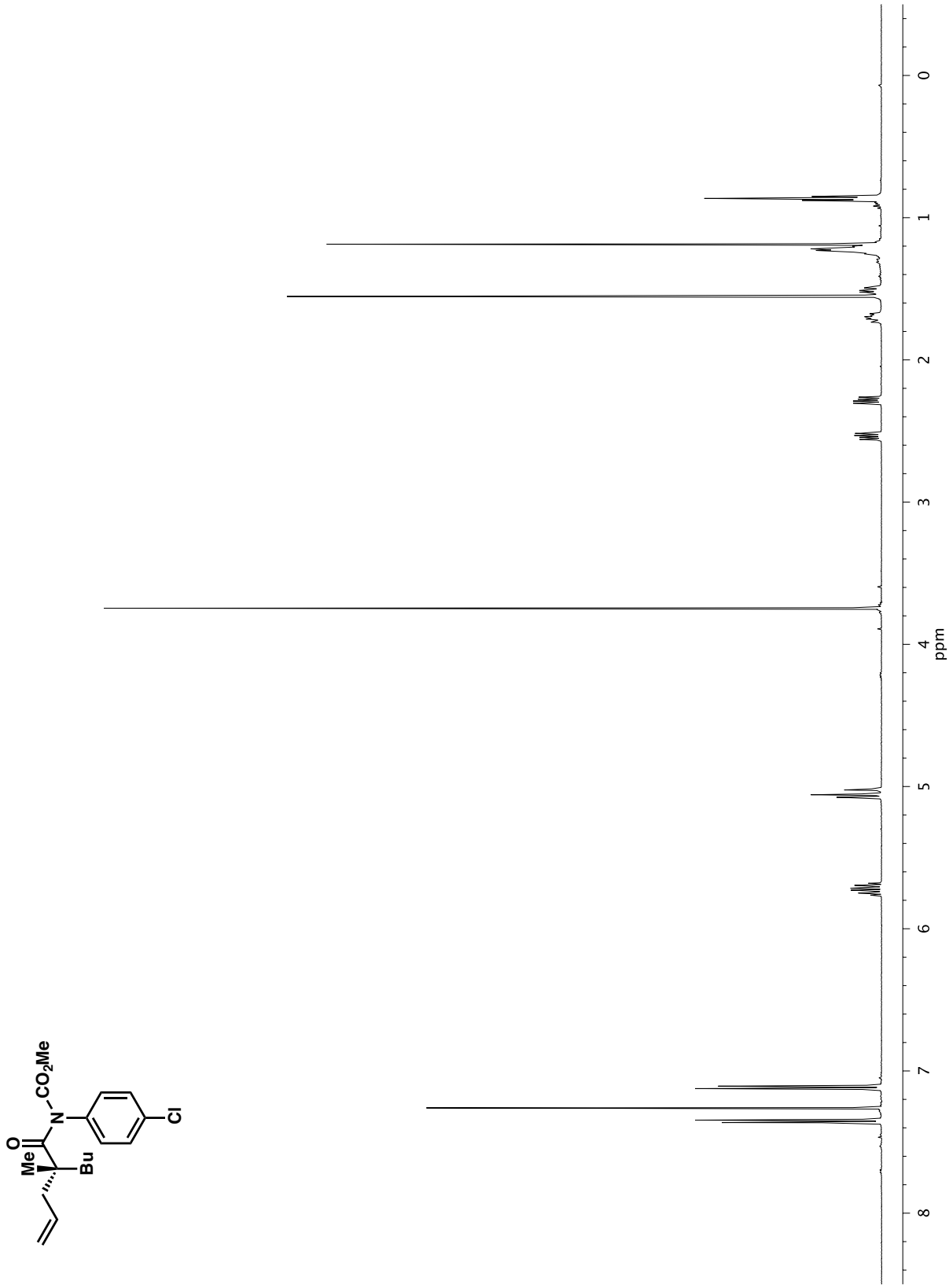
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87g**.



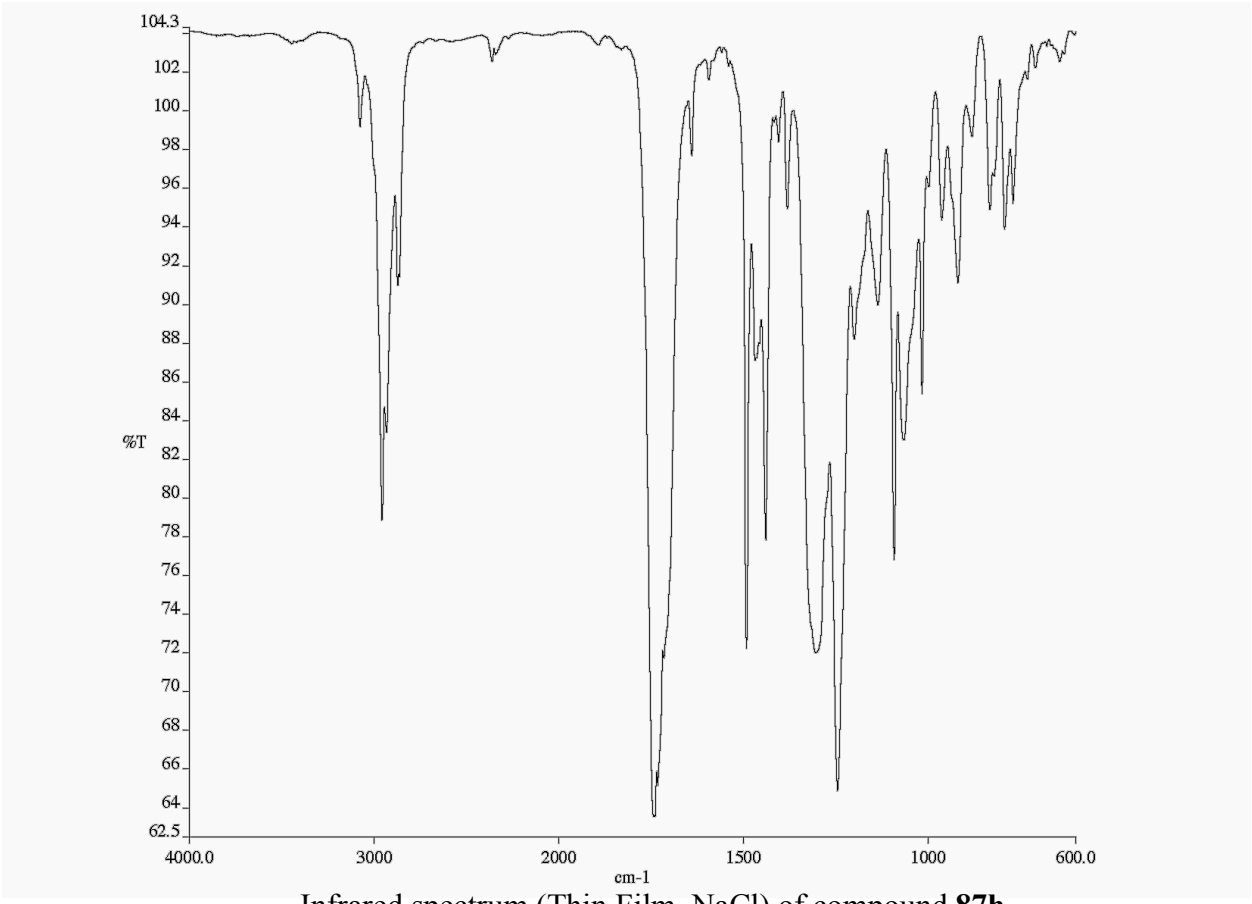
Infrared spectrum (Thin Film, NaCl) of compound **87g**.



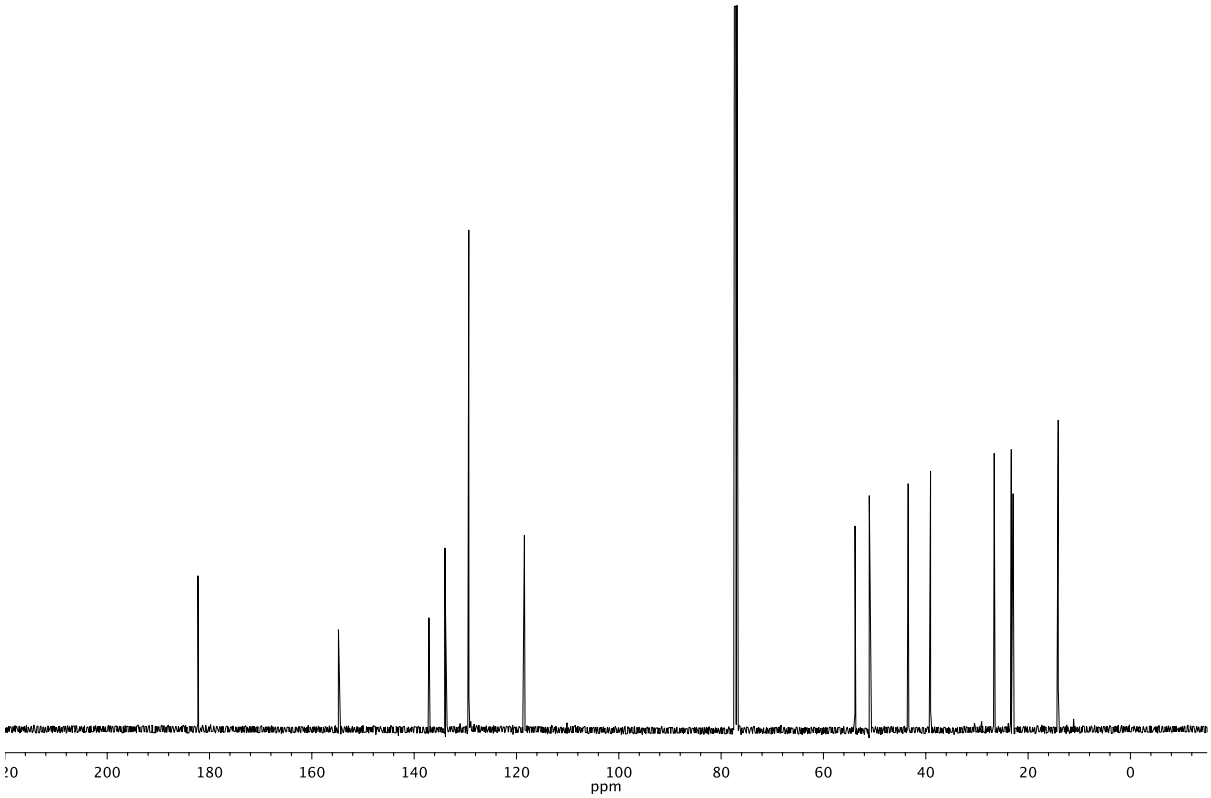
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87g**.



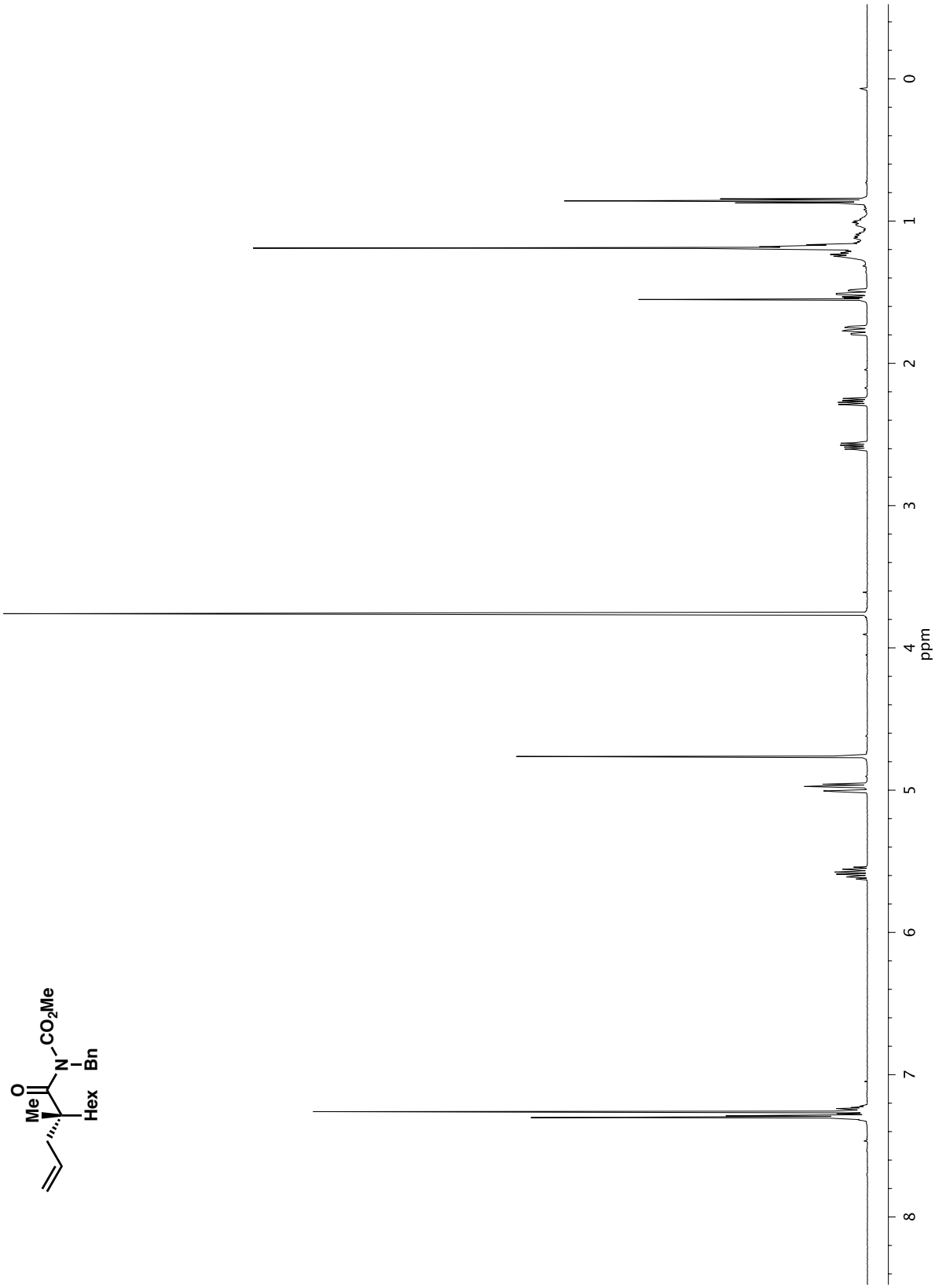
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87h**.



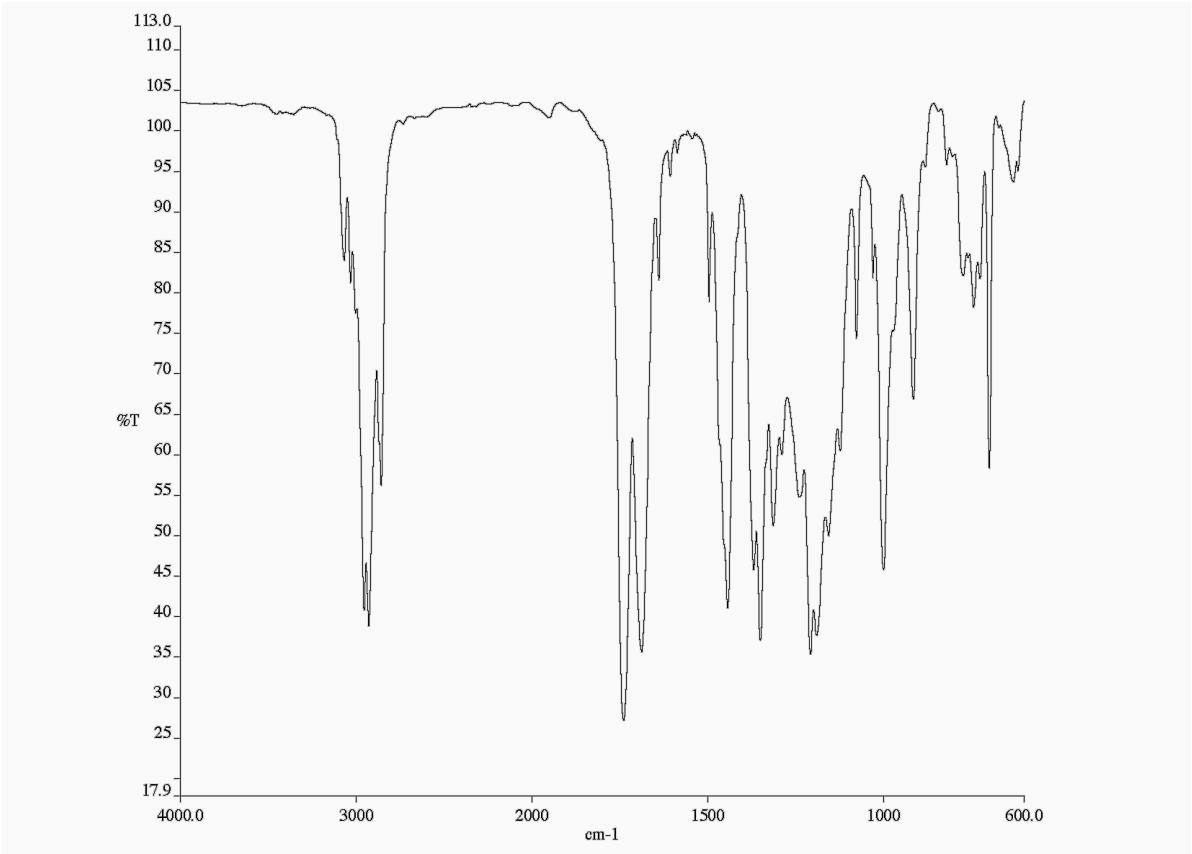
Infrared spectrum (Thin Film, NaCl) of compound **87h**.



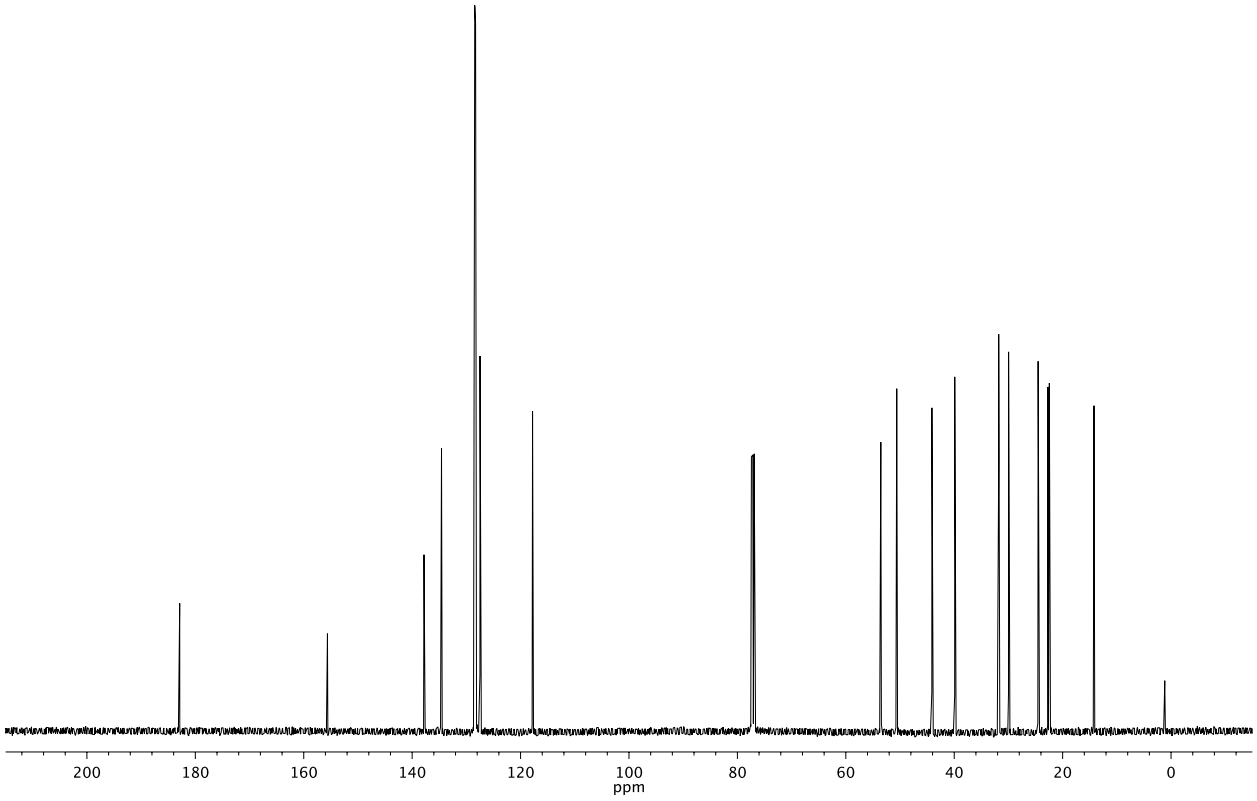
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87h**.



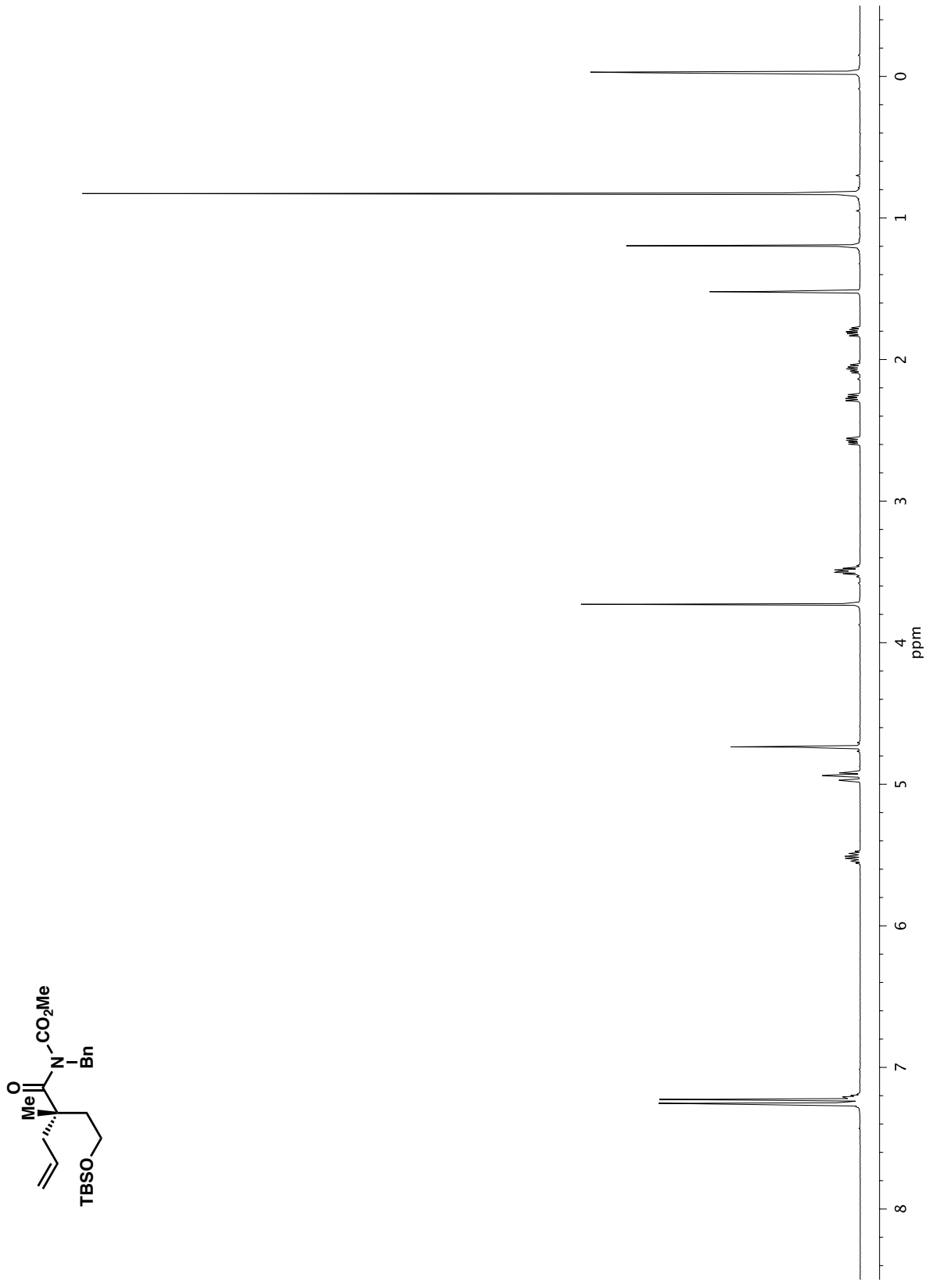
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87i**.



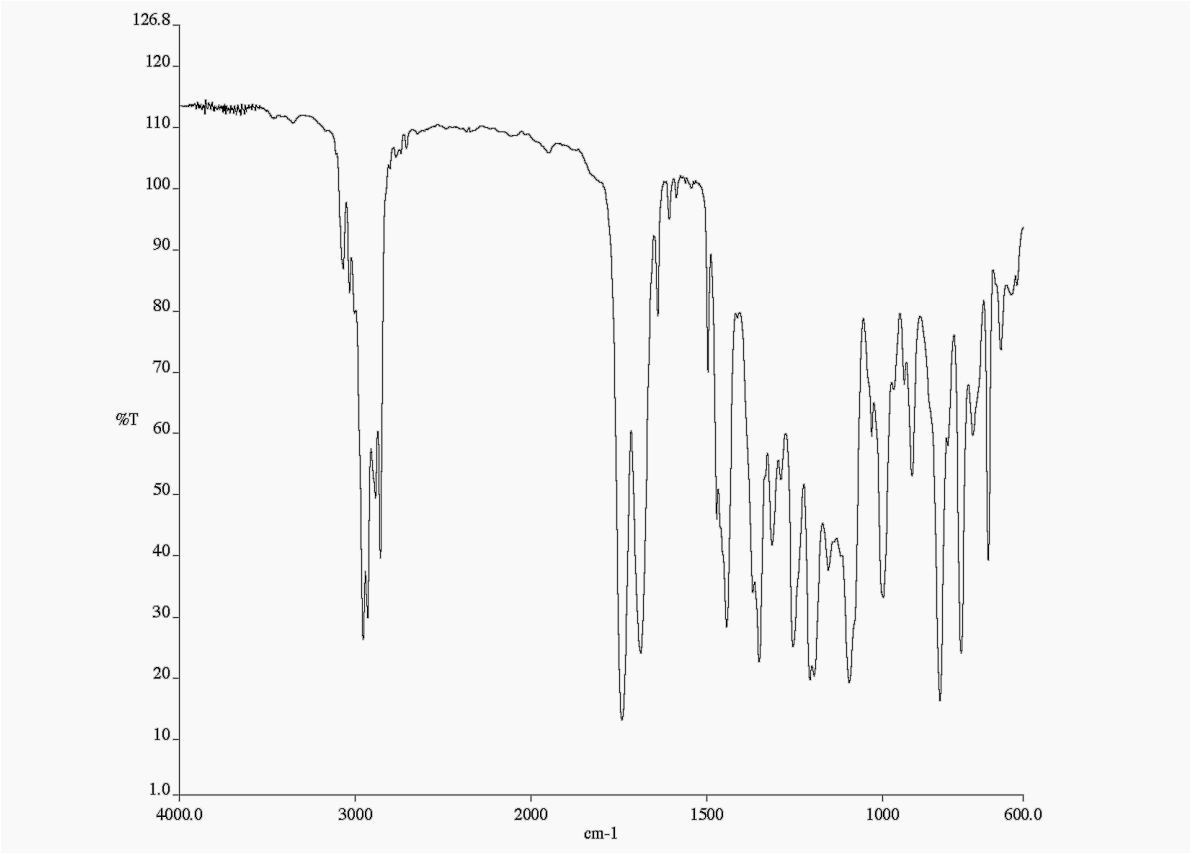
Infrared spectrum (Thin Film, NaCl) of compound **87i**.



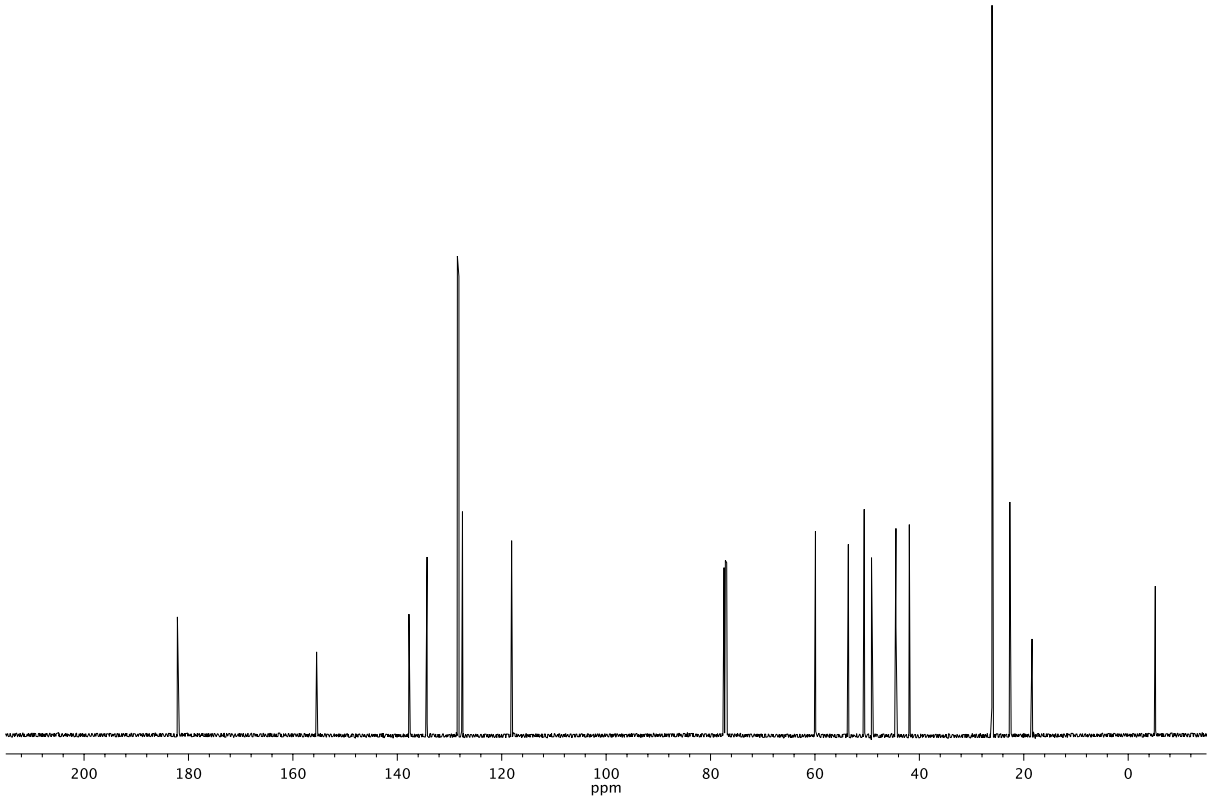
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87i**.



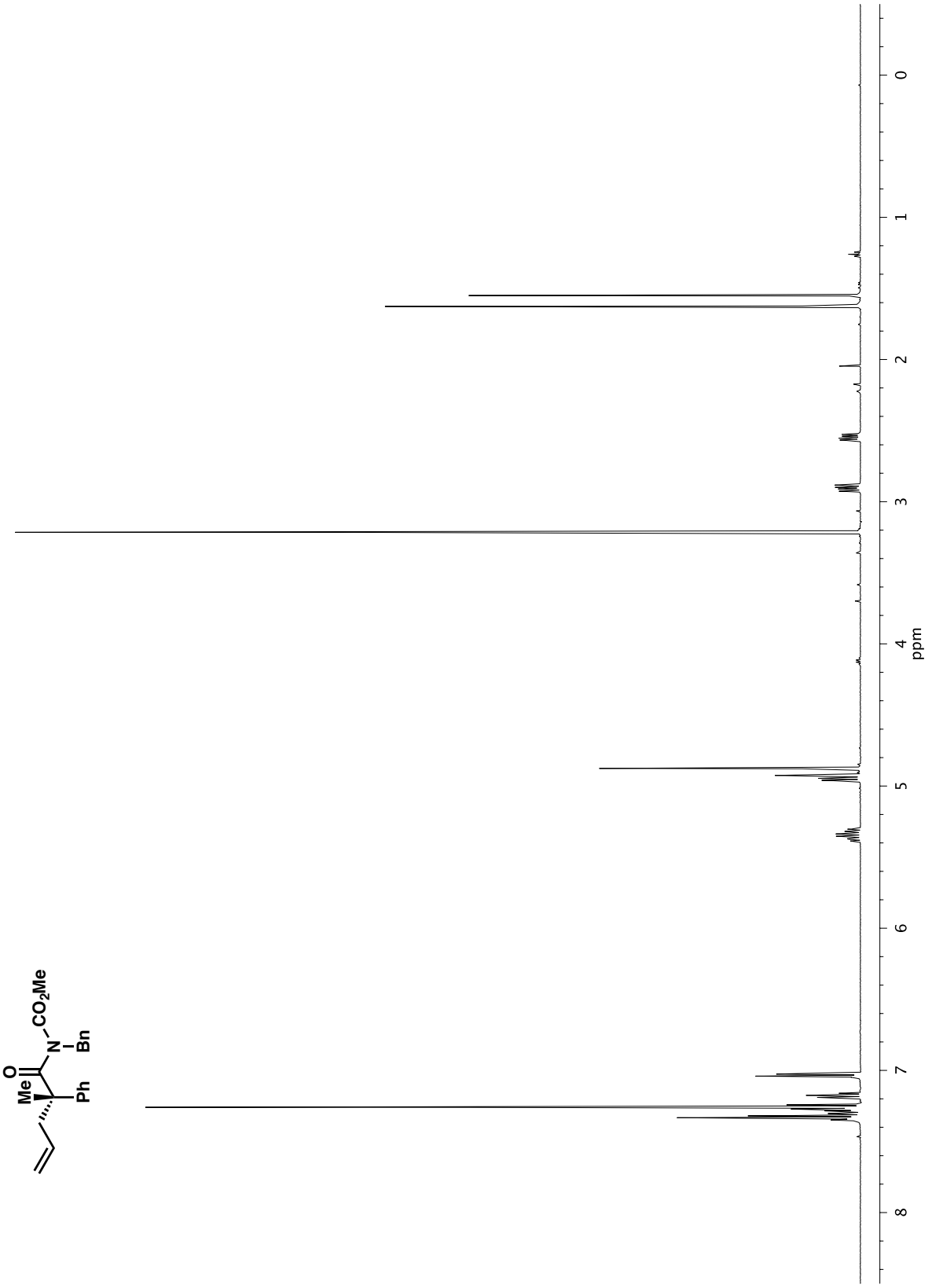
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87j**.



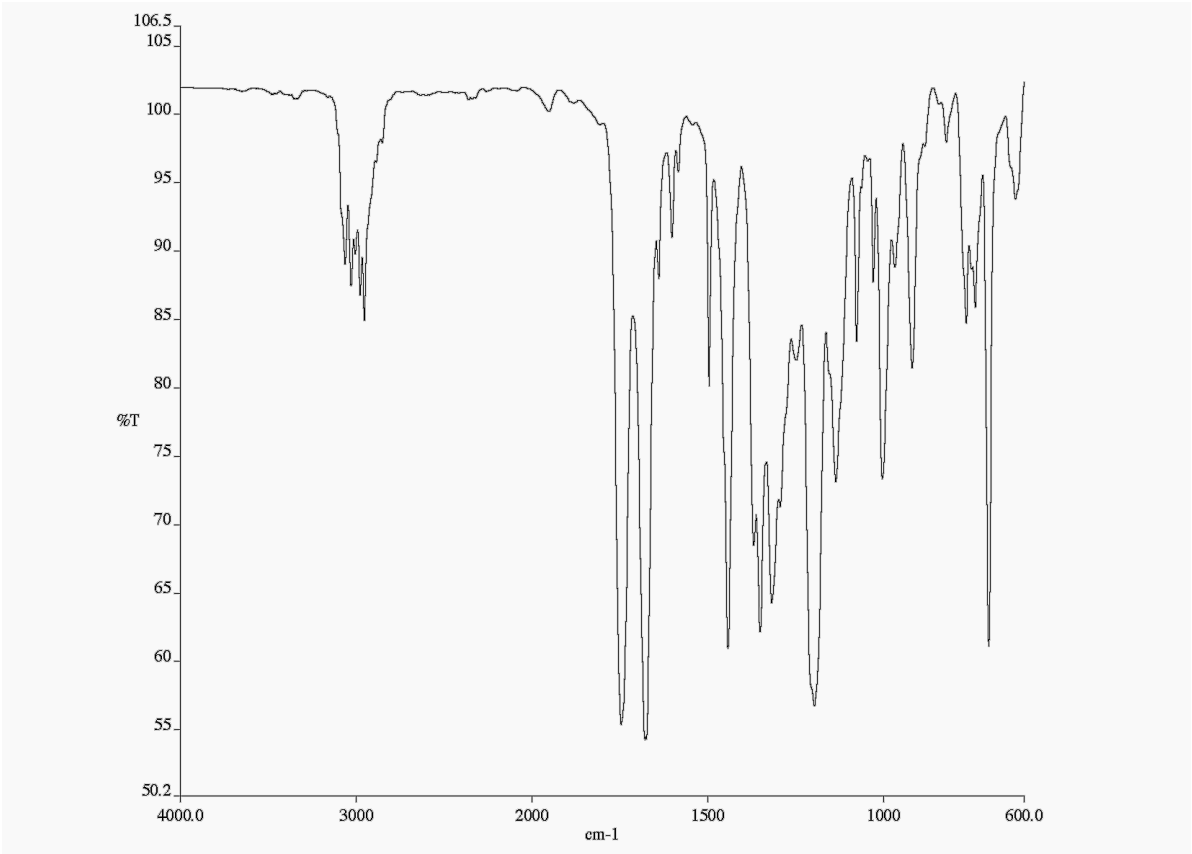
Infrared spectrum (Thin Film, NaCl) of compound **87j**.



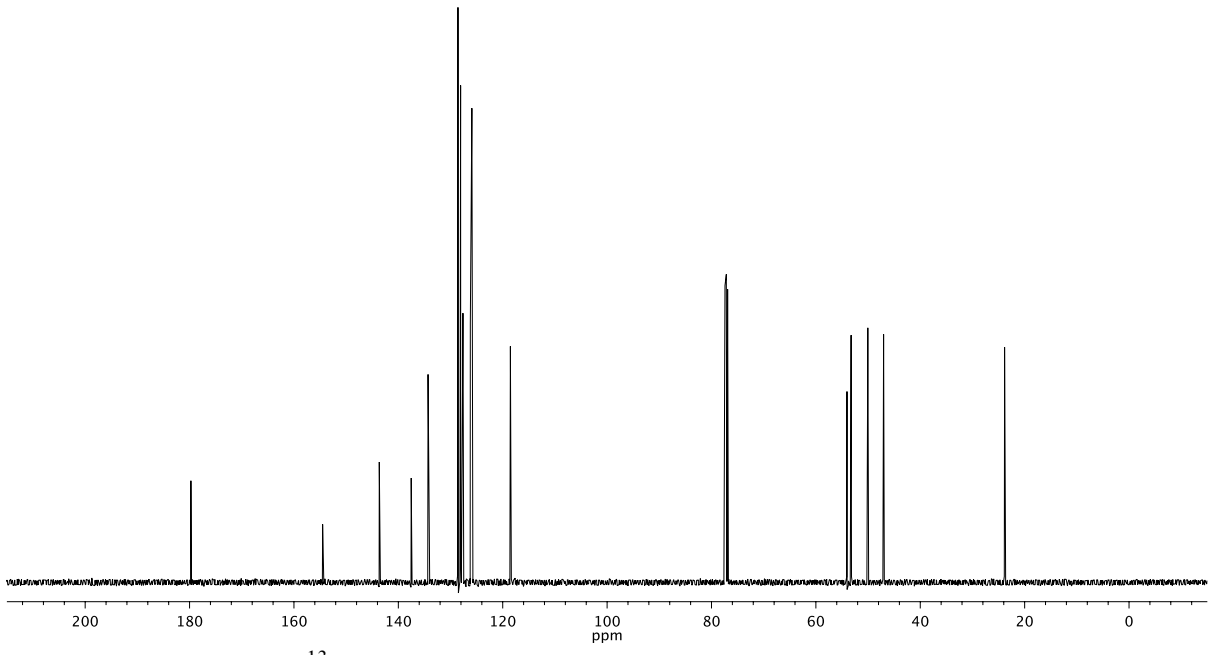
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87j**.



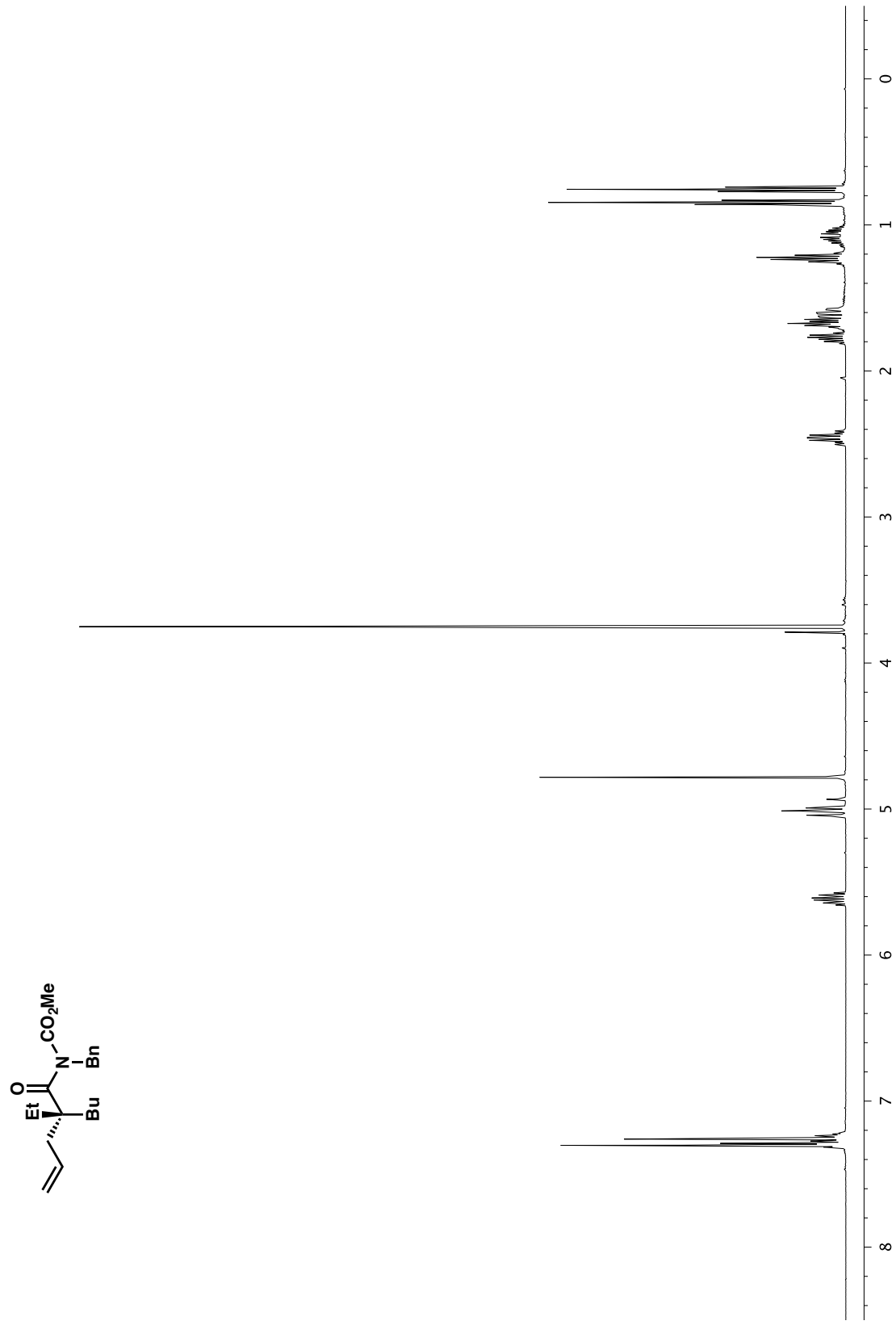
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87k**.



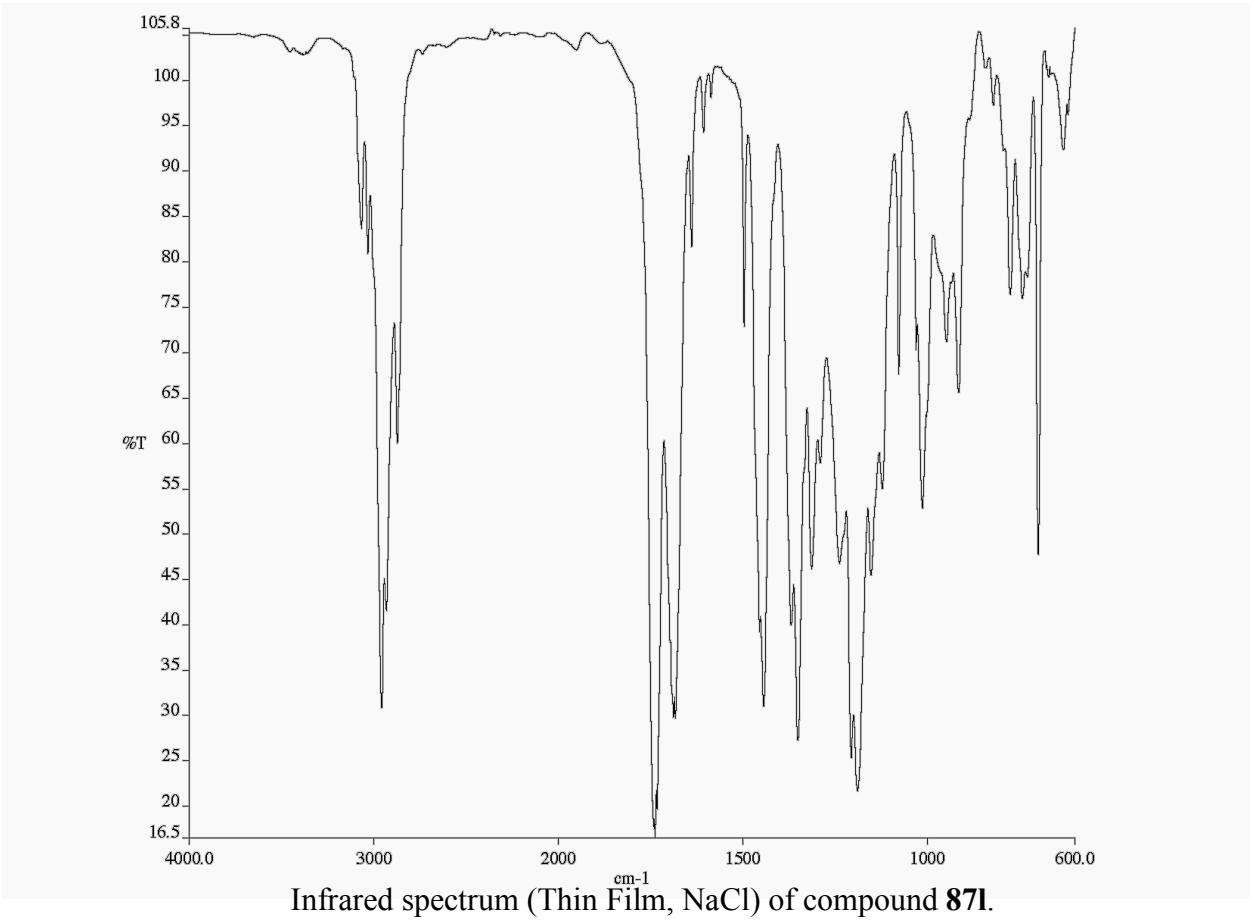
Infrared spectrum (Thin Film, NaCl) of compound **87k**.



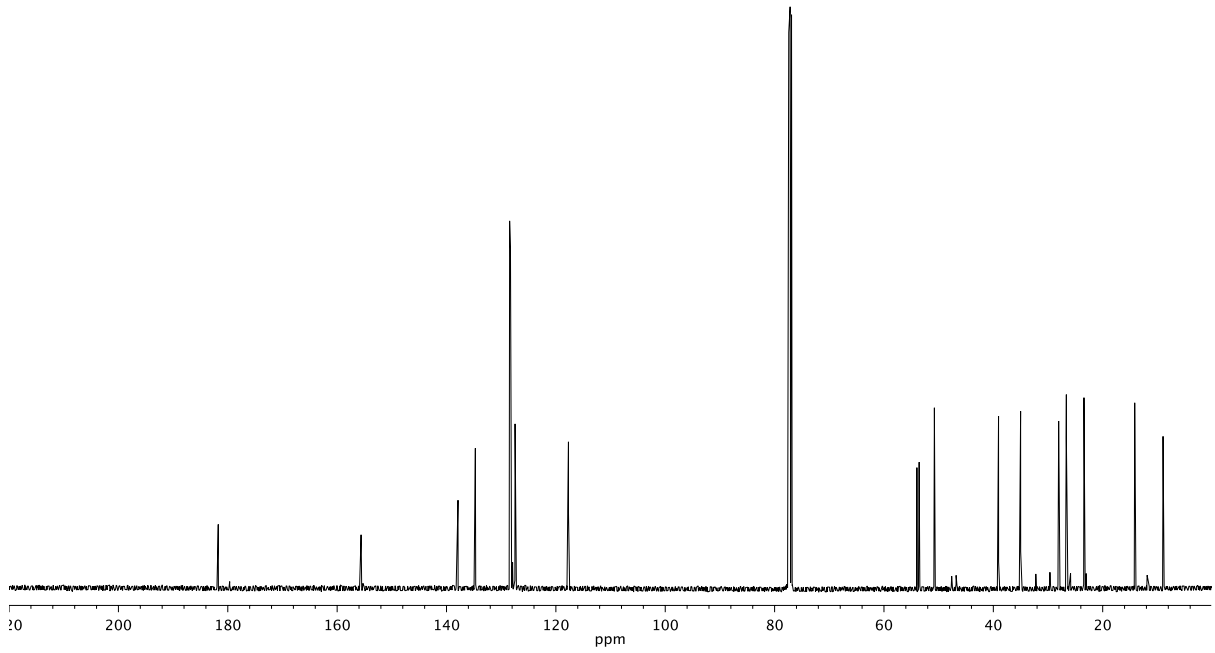
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87k**.



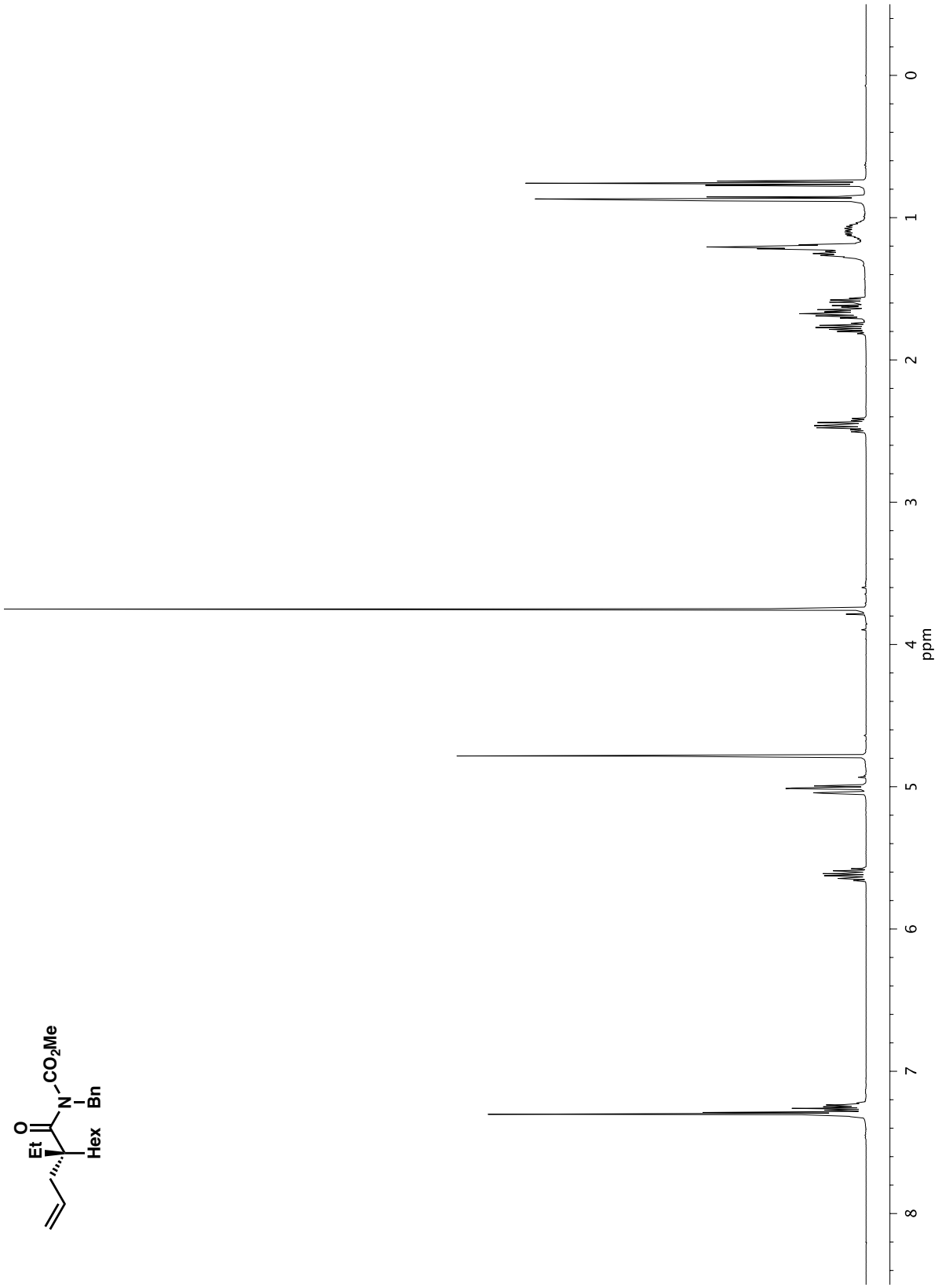
^{1}H NMR (500 MHz, $CDCl_3$) of compound **871**.



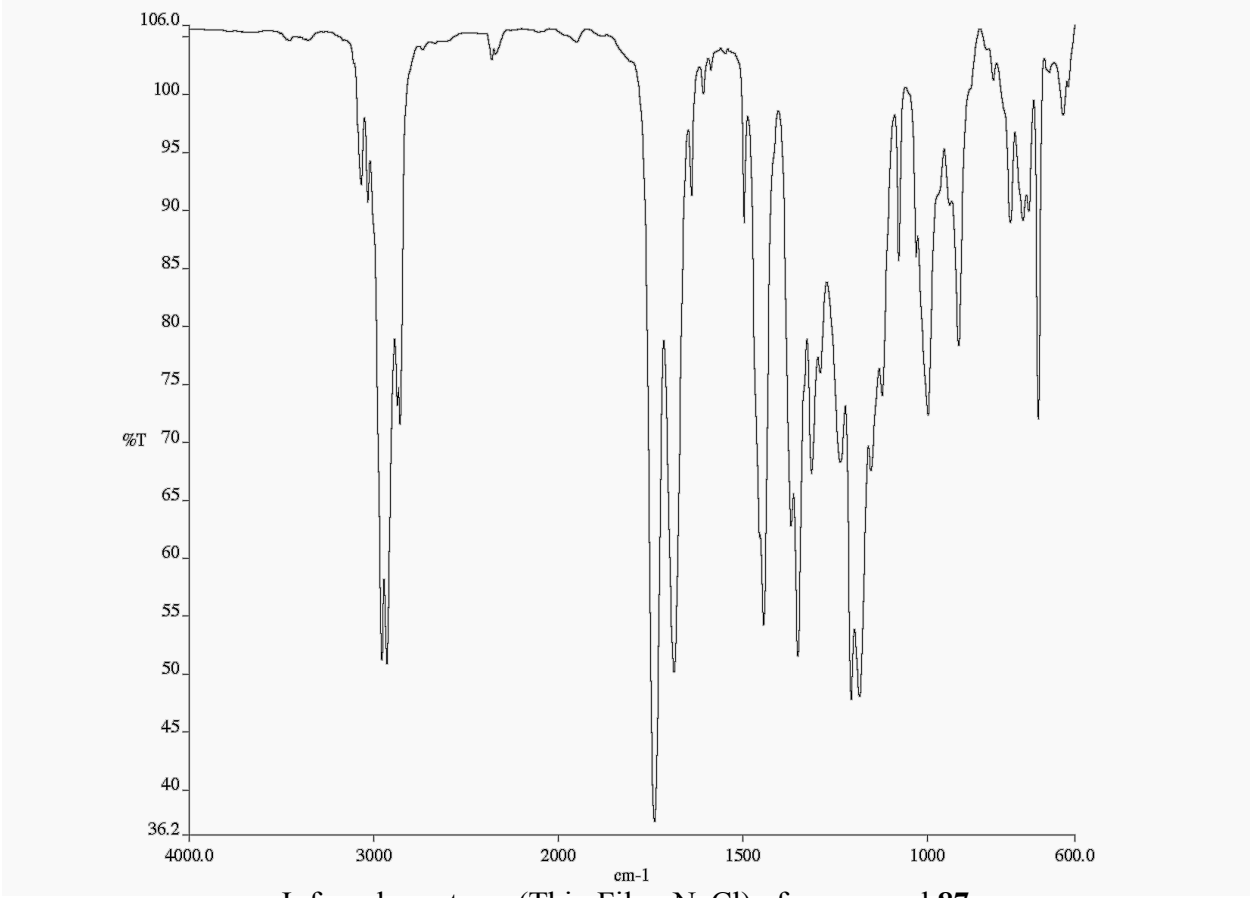
Infrared spectrum (Thin Film, NaCl) of compound **87l**.



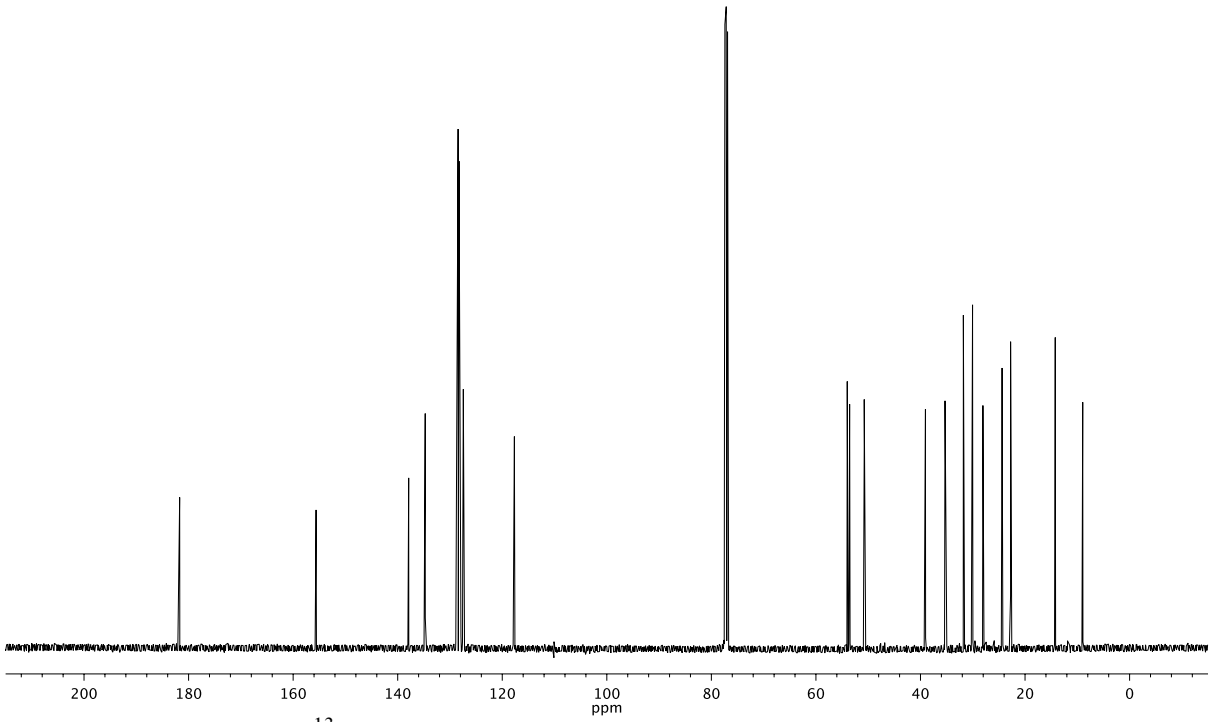
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87l**.



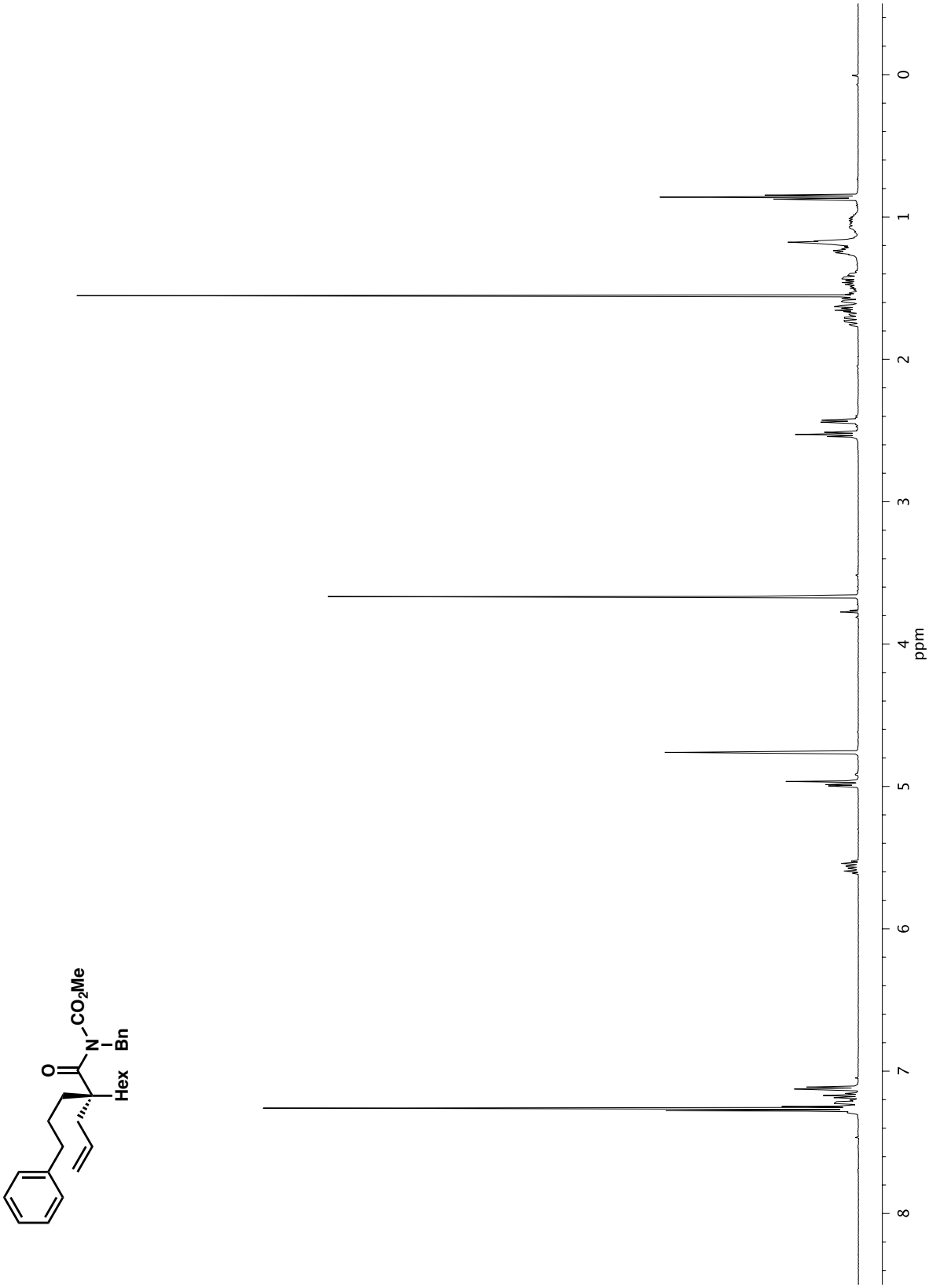
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87m**.



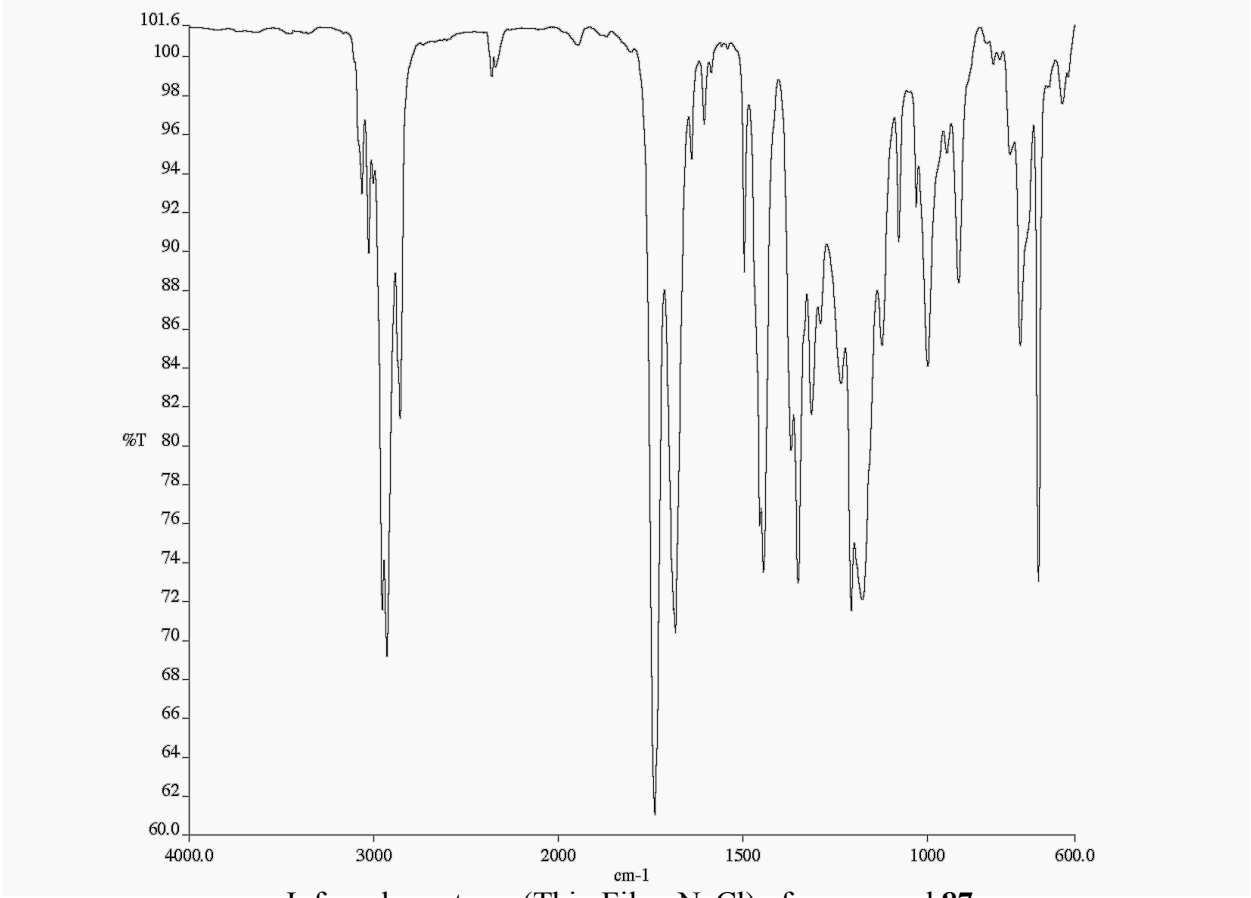
Infrared spectrum (Thin Film, NaCl) of compound **87m**.



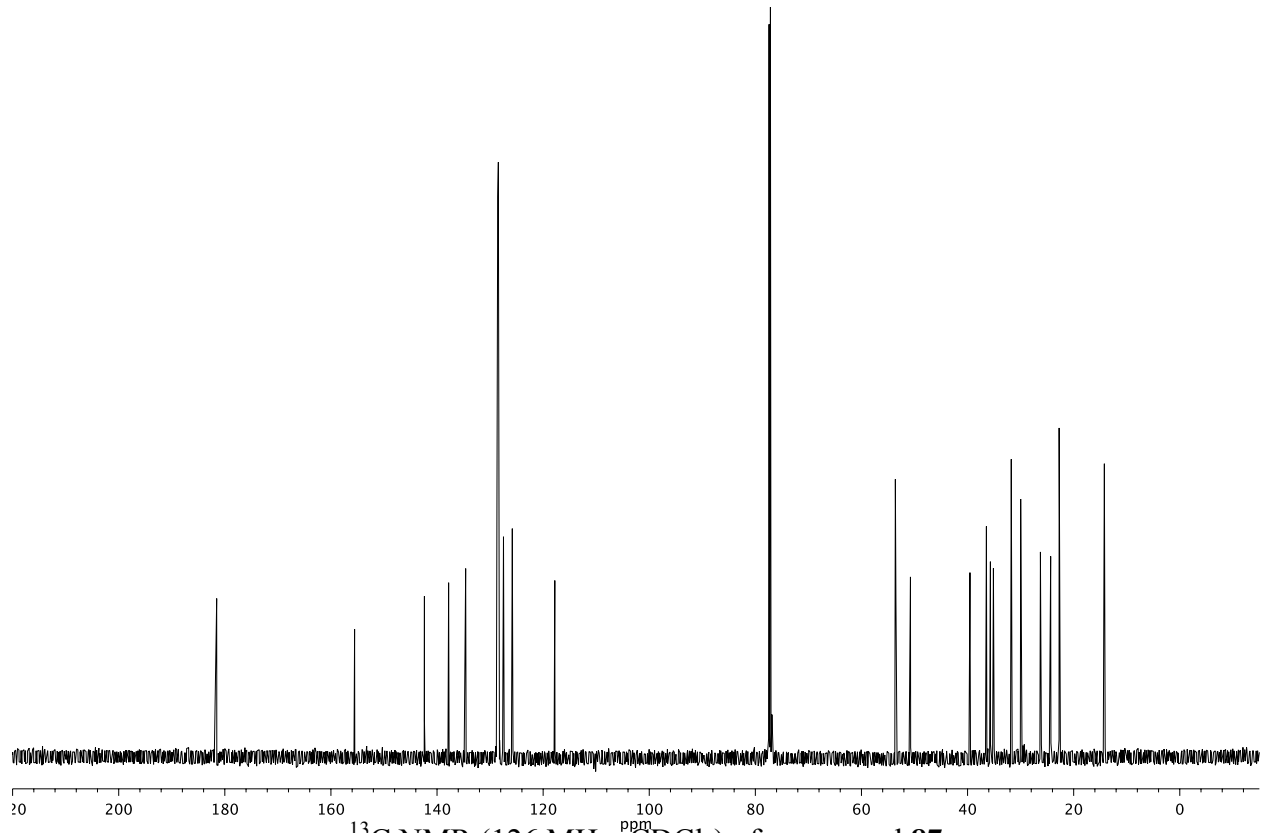
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87m**.



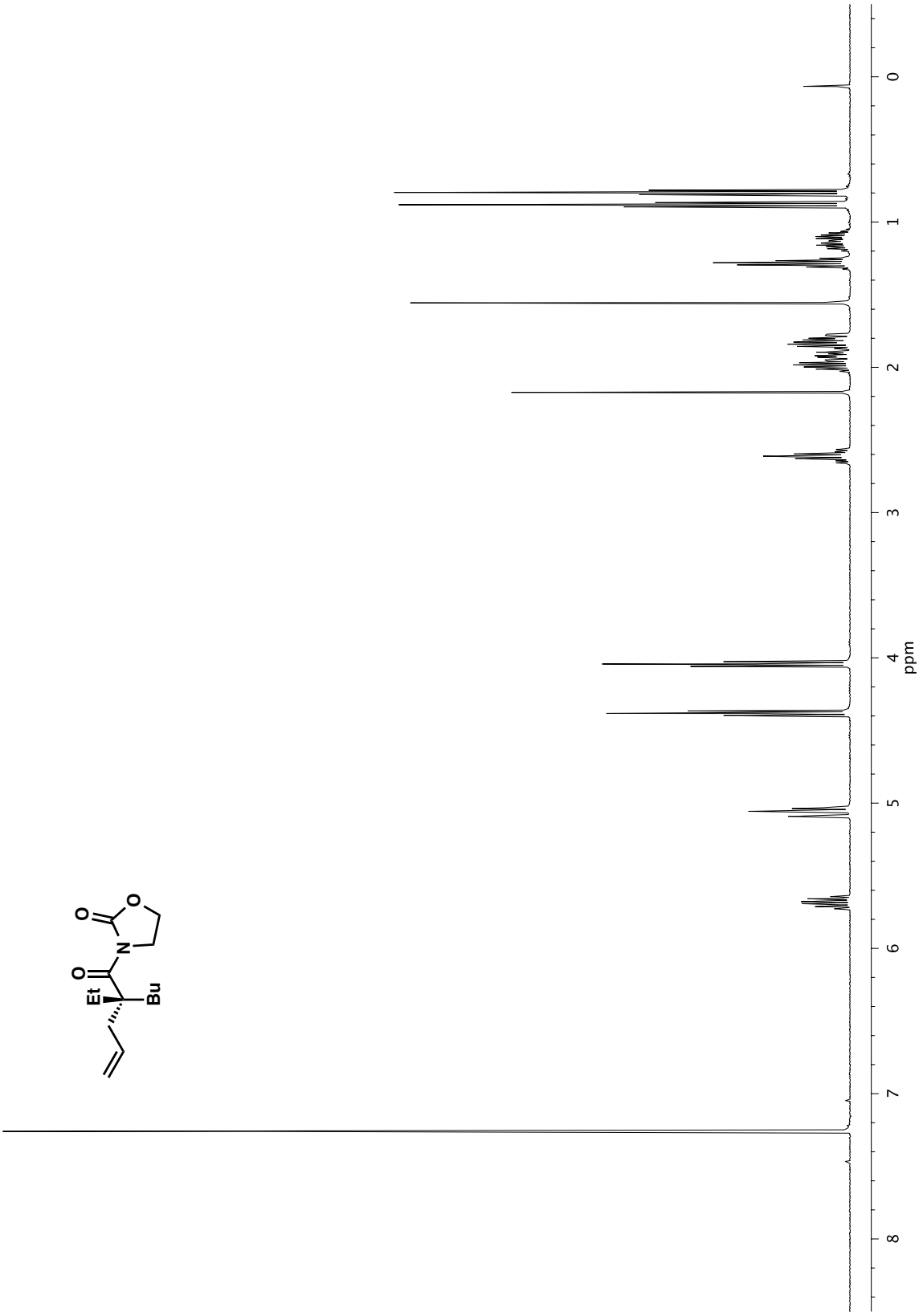
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87n**.



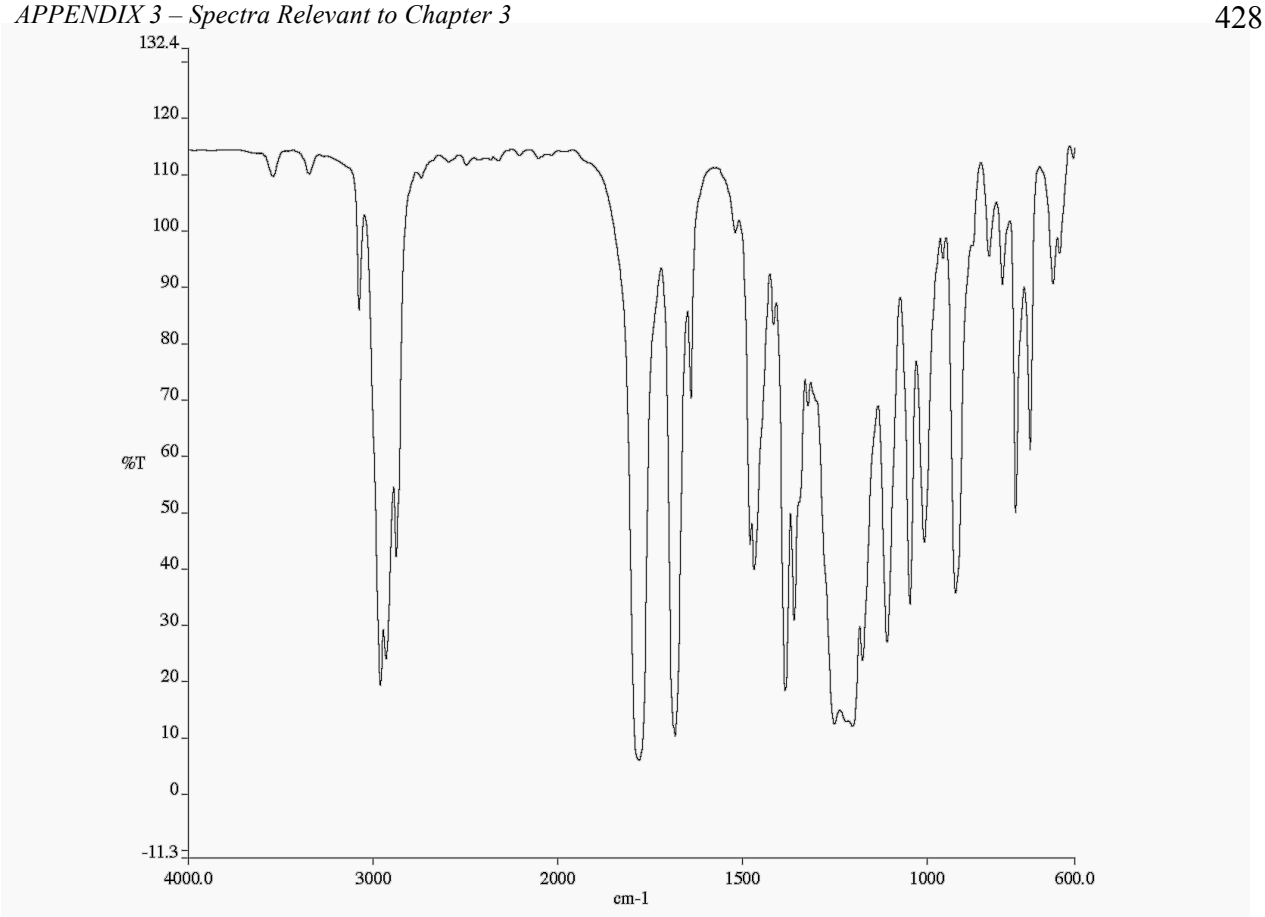
Infrared spectrum (Thin Film, NaCl) of compound **87n**.



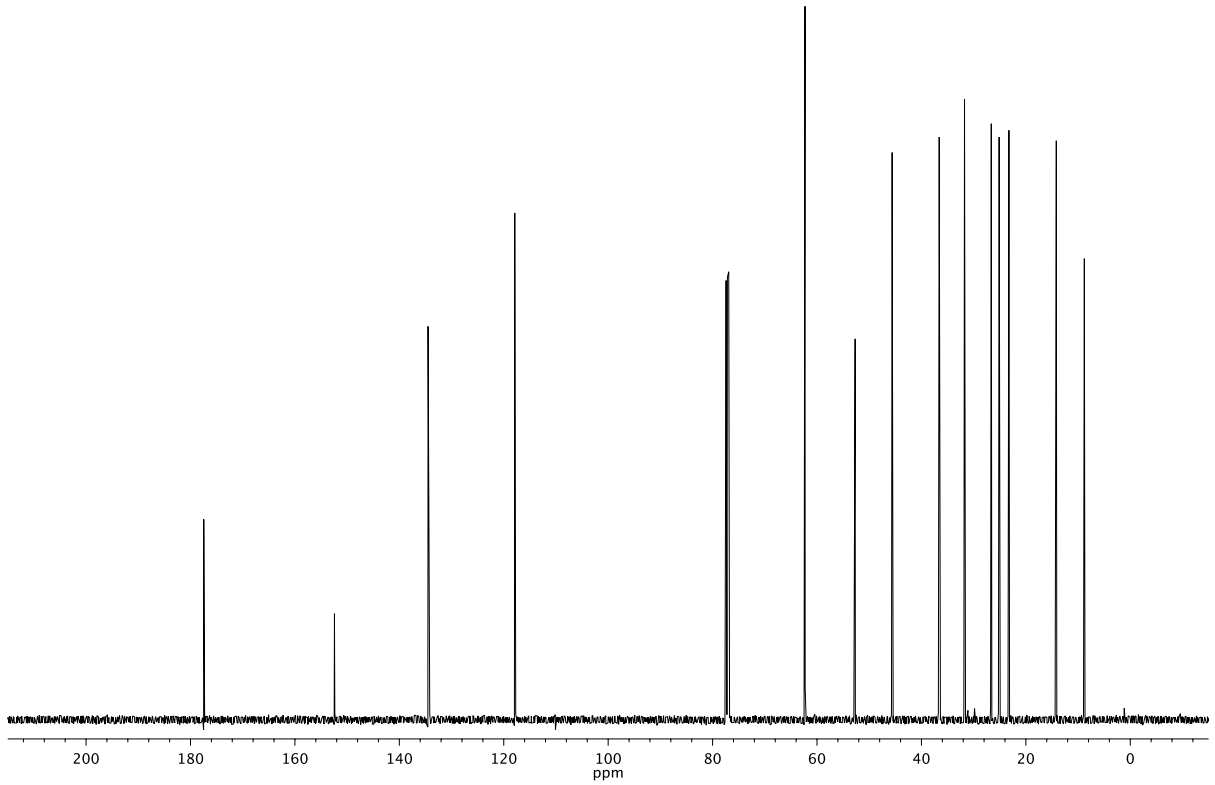
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87n**.



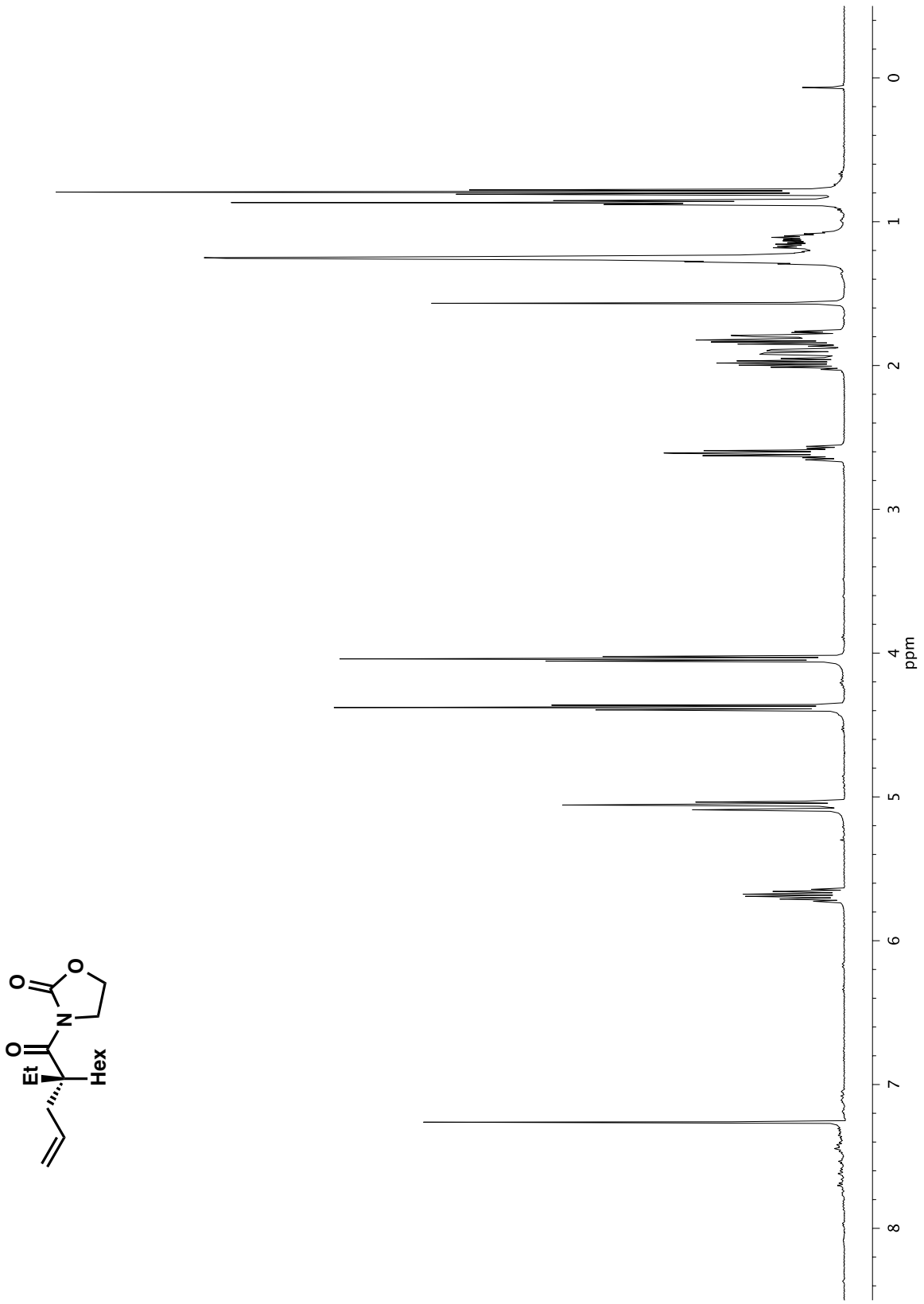
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87o**.



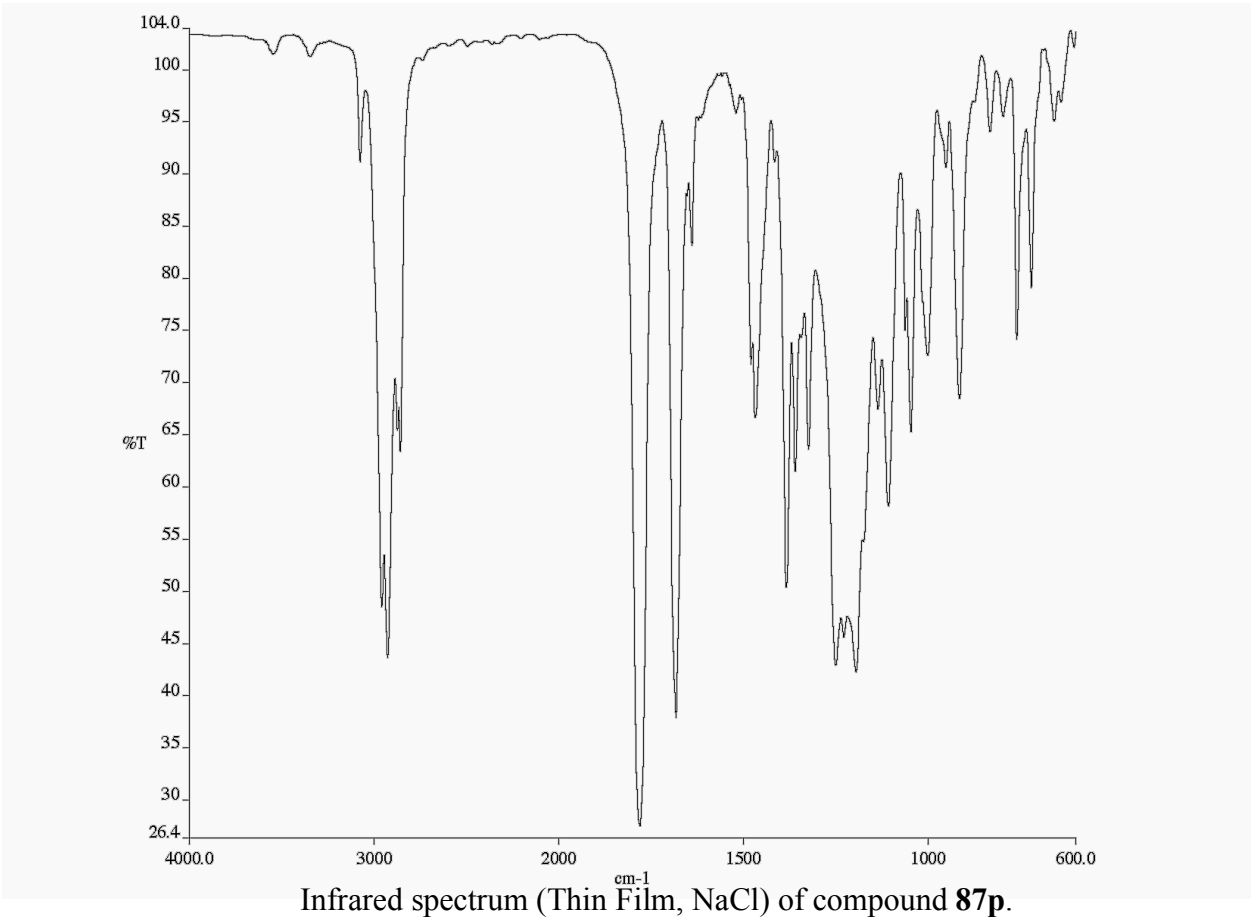
Infrared spectrum (Thin Film, NaCl) of compound **87o**.



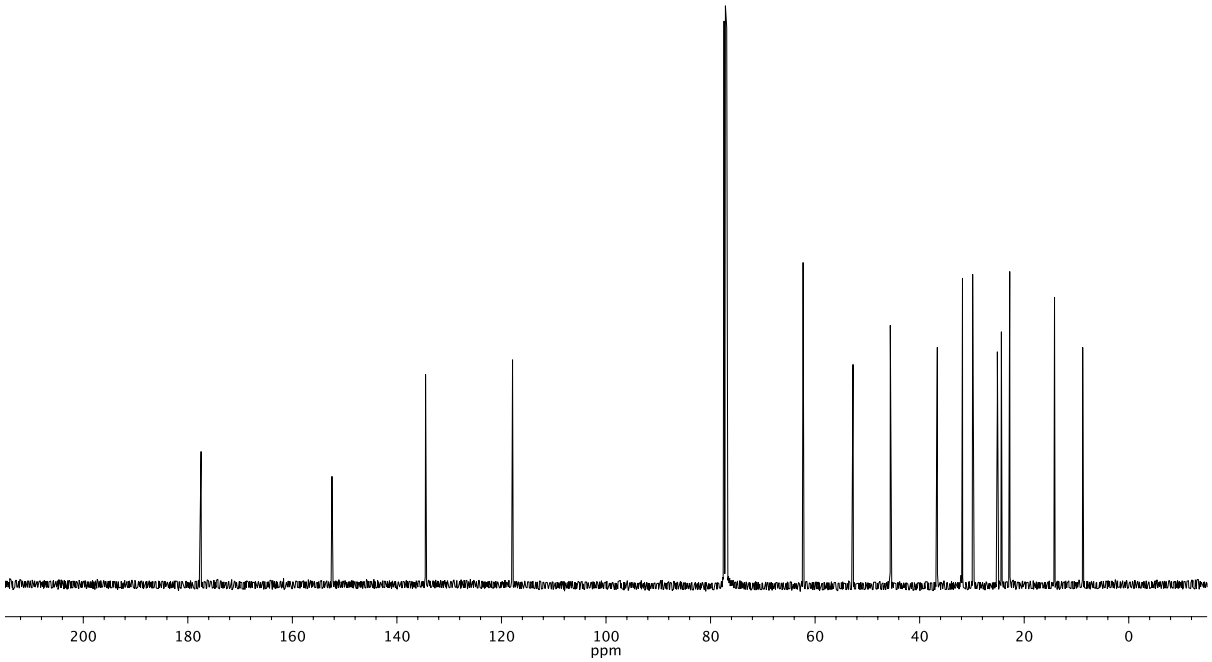
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87o**.



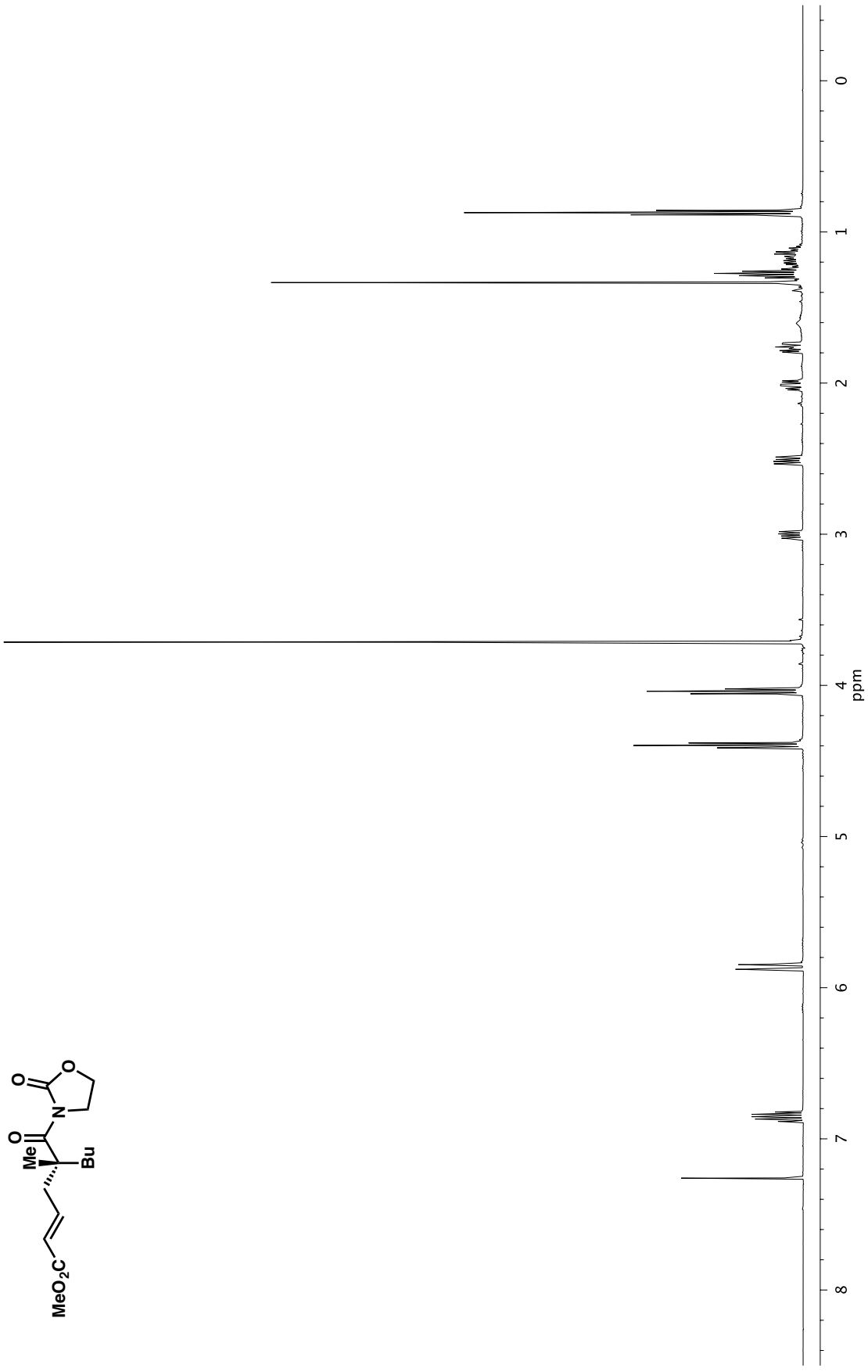
^{1}H NMR (500 MHz, $CDCl_3$) of compound **87p**.



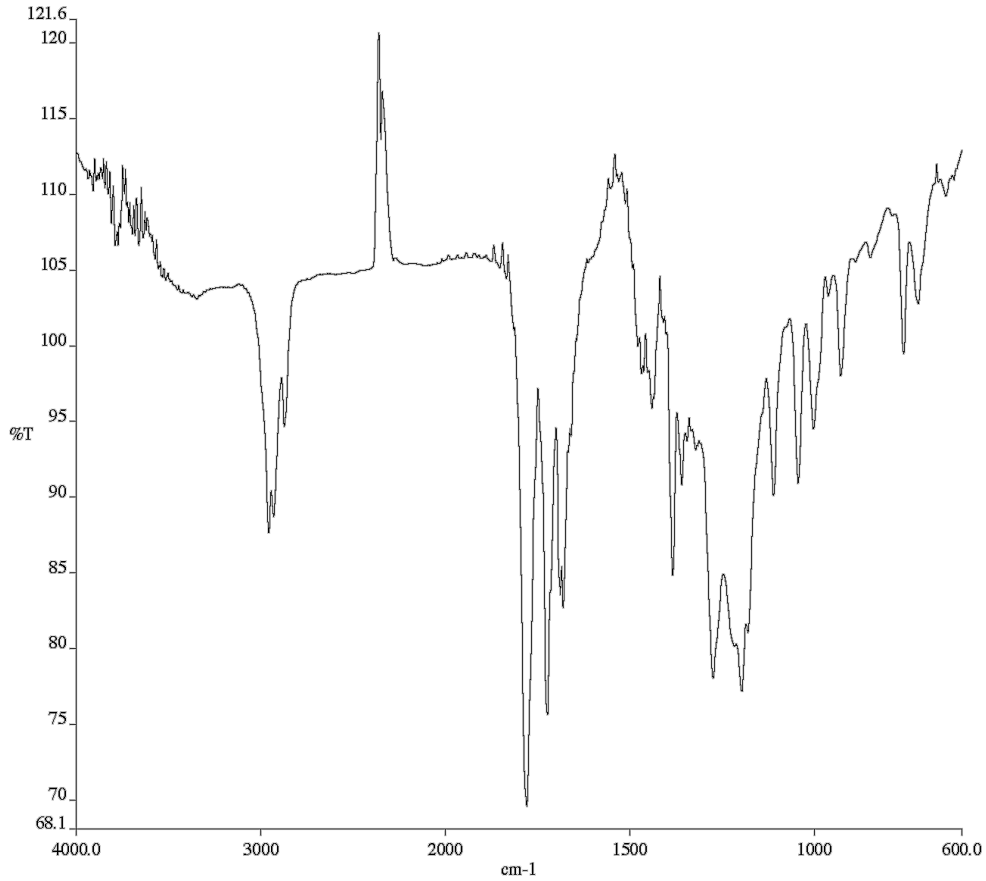
Infrared spectrum (Thin Film, NaCl) of compound **87p**.



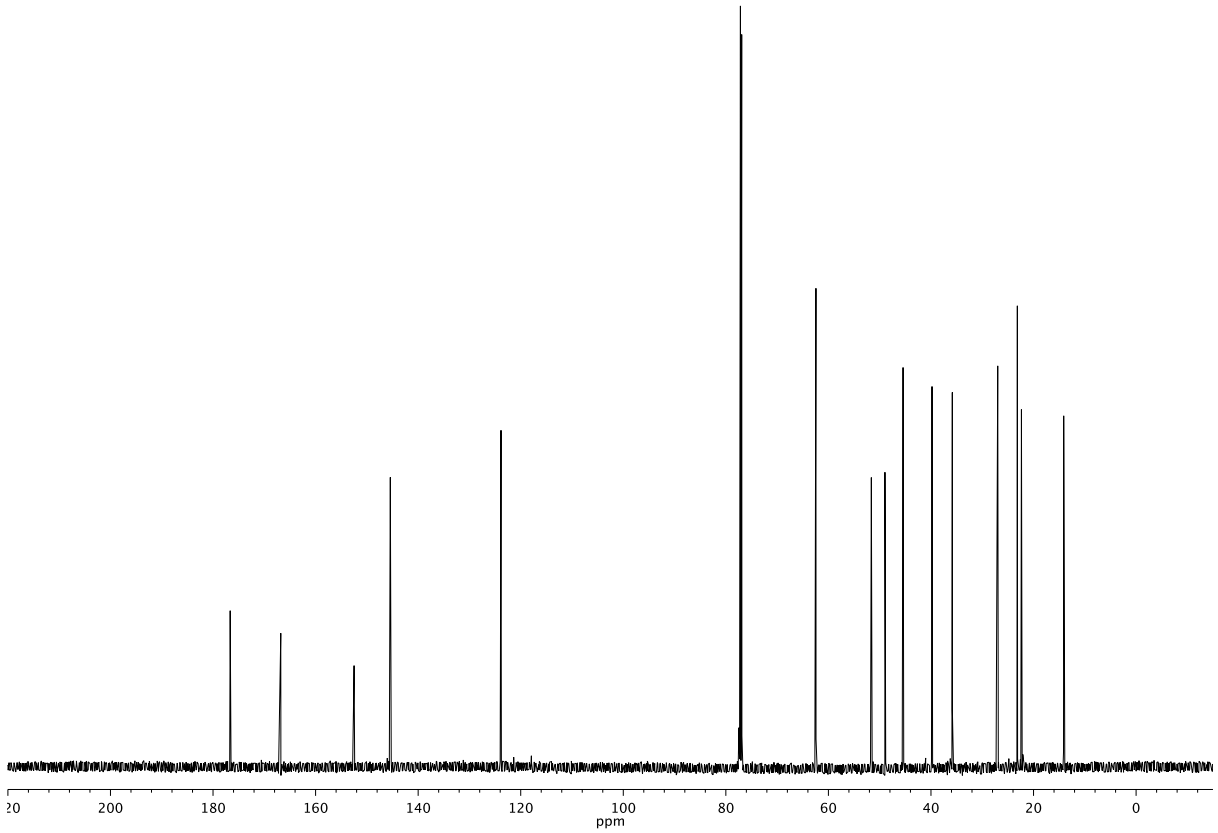
^{13}C NMR (126 MHz, $CDCl_3$) of compound **87p**.



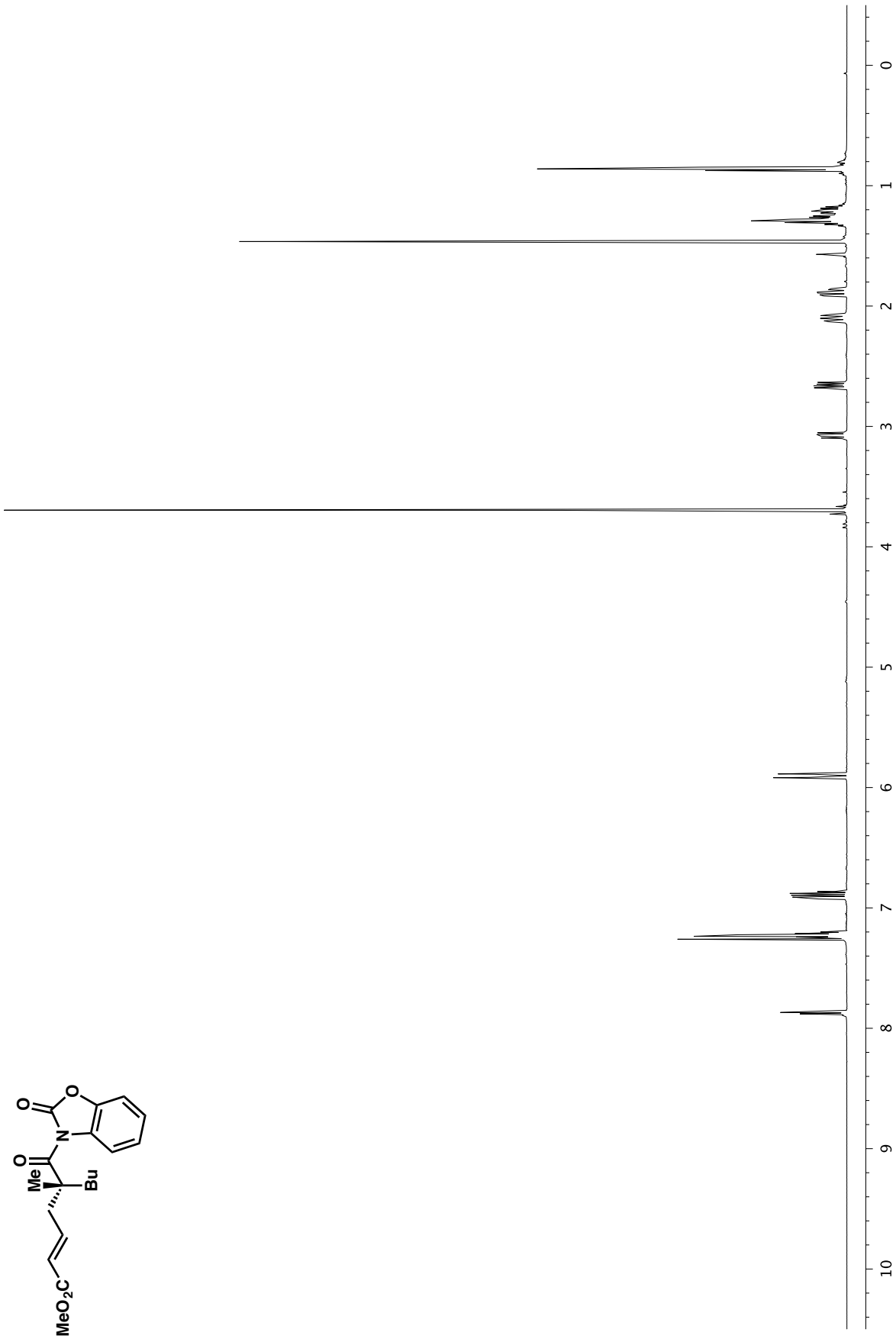
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88a**.



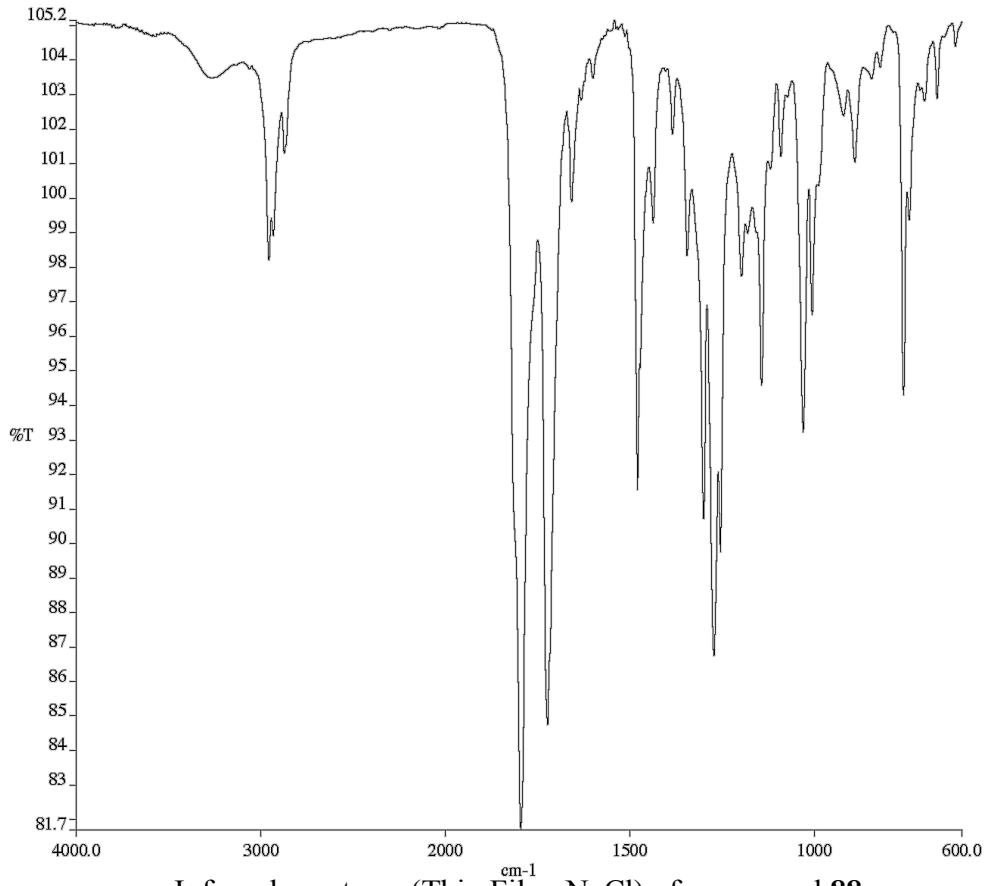
Infrared spectrum (Thin Film, NaCl) of compound **88a**.



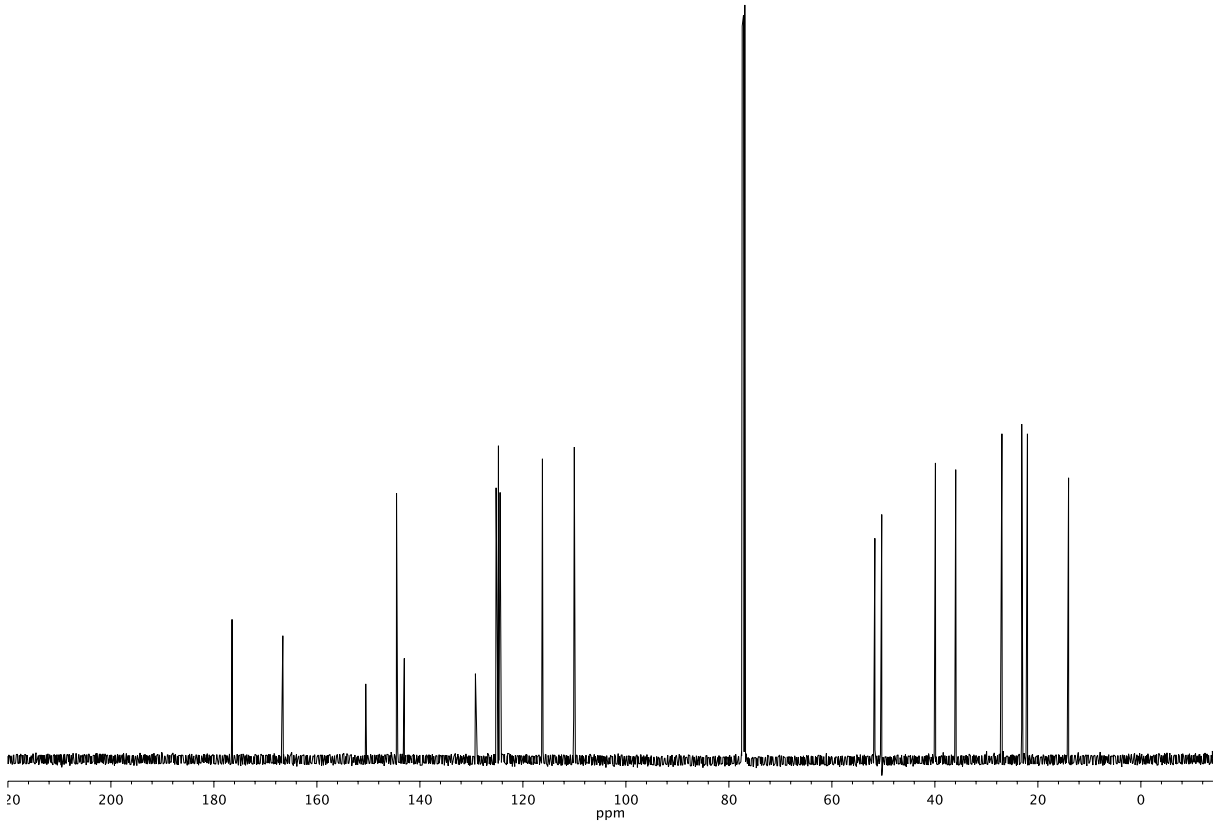
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88a**.



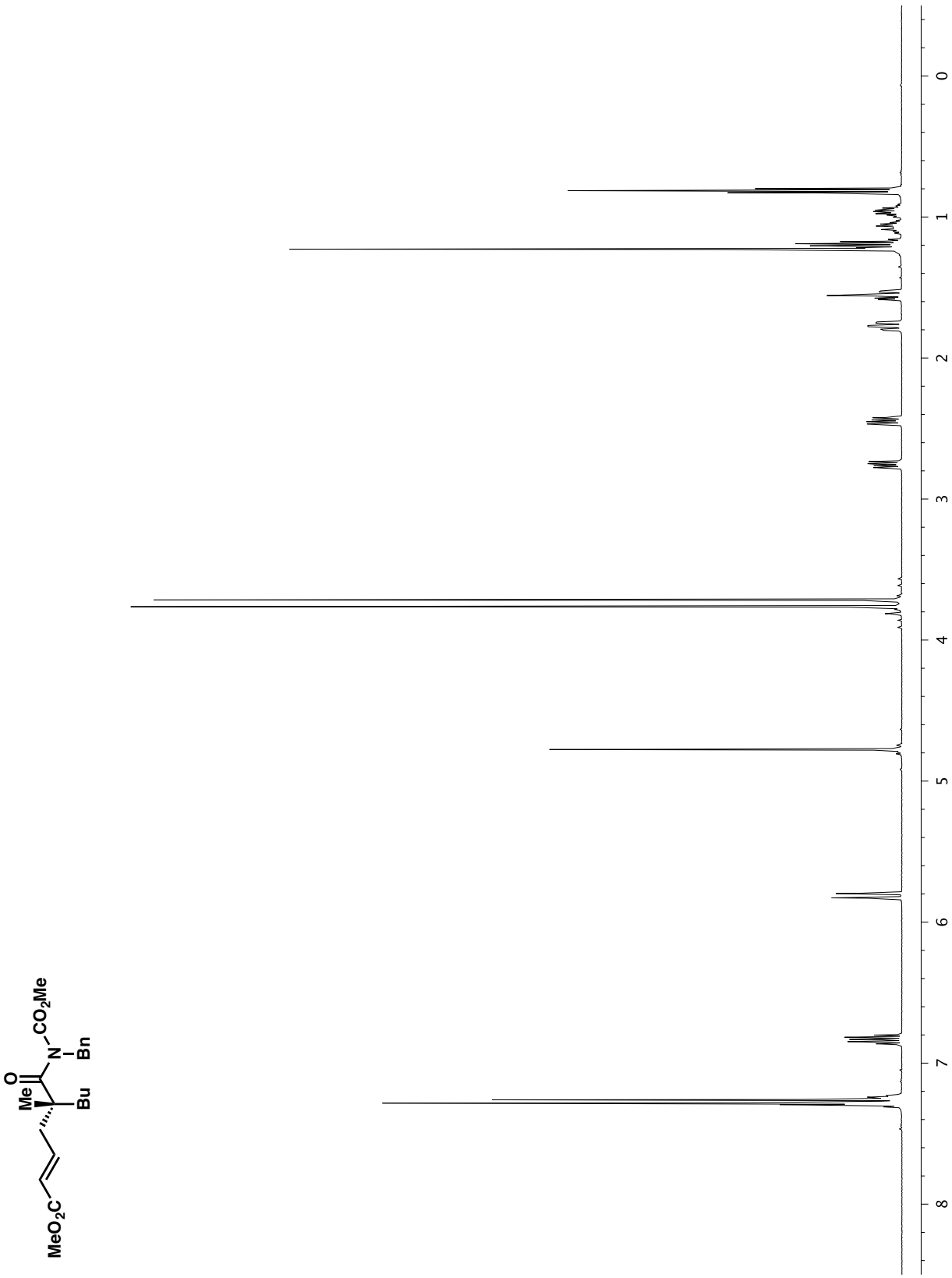
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88c**.



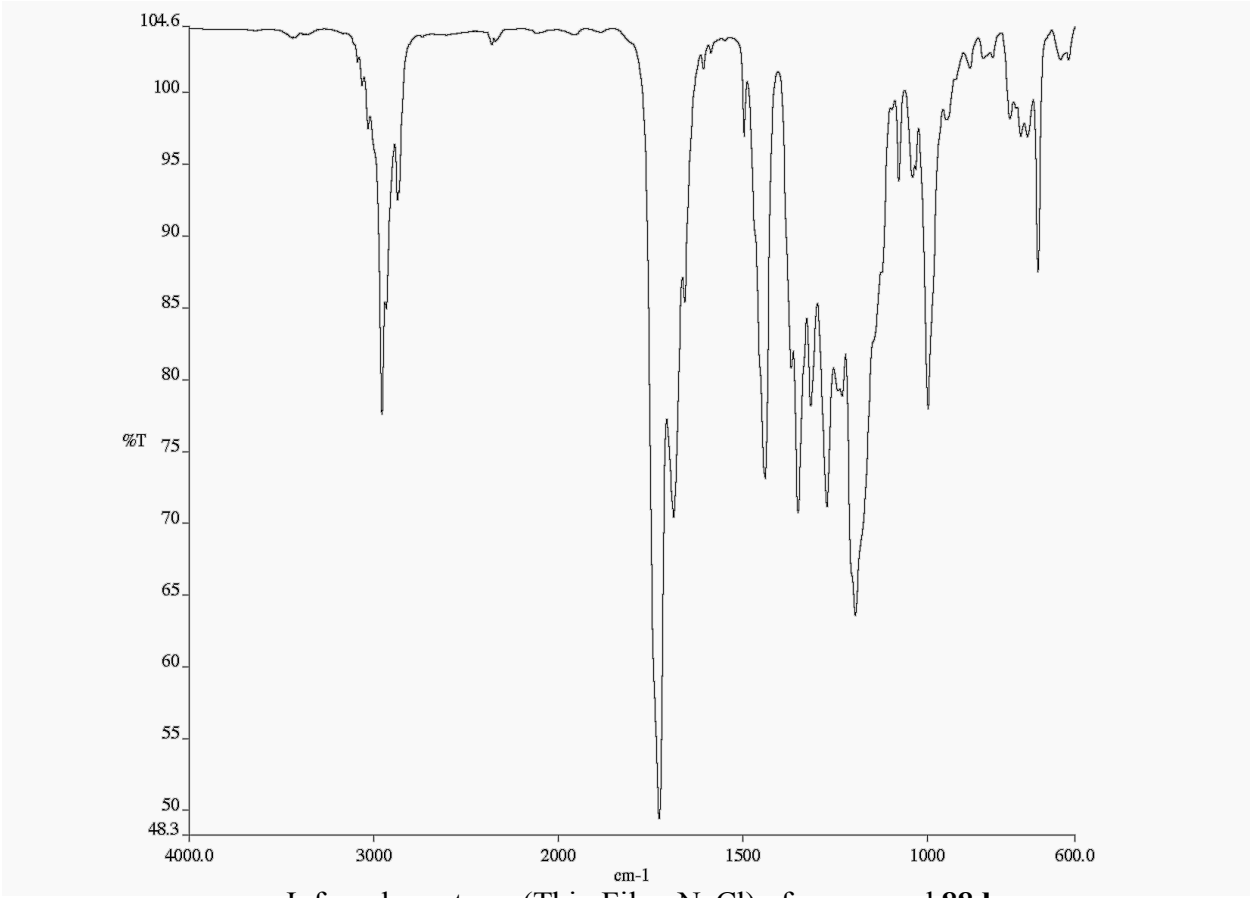
Infrared spectrum (Thin Film, NaCl) of compound **88c**.



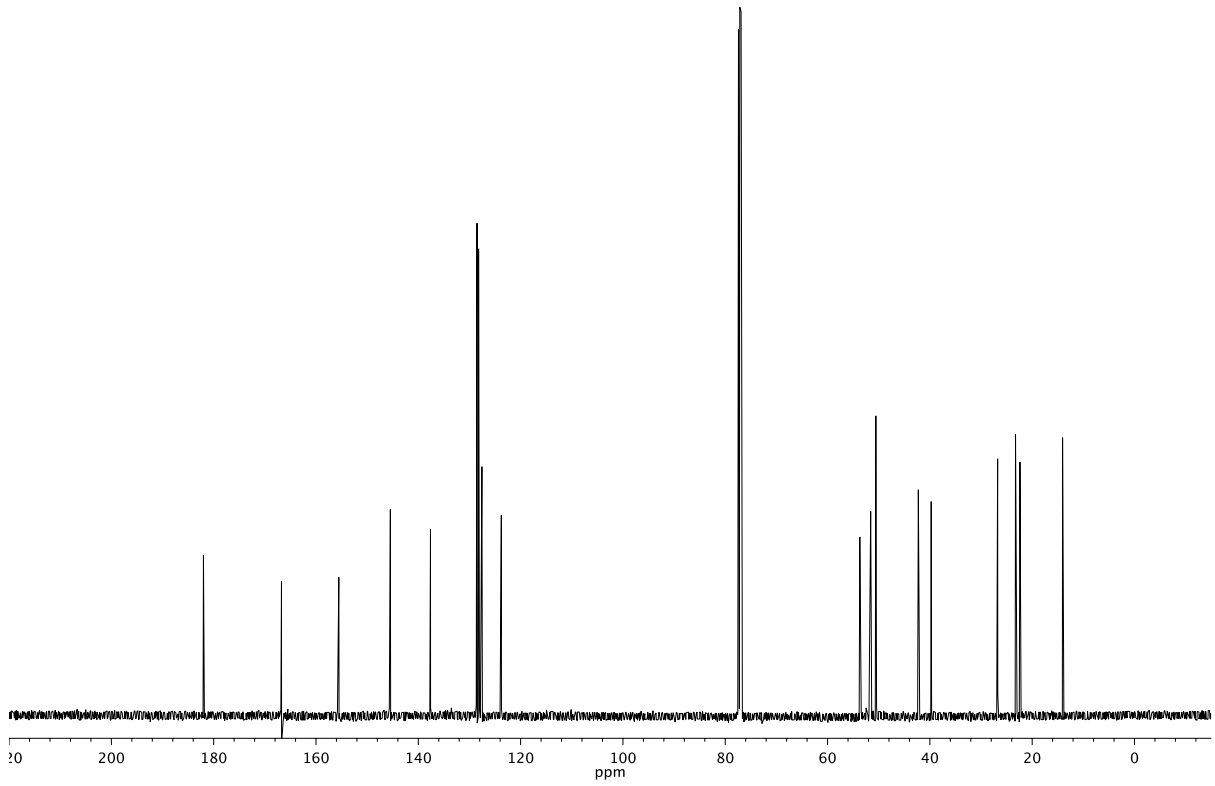
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88c**.



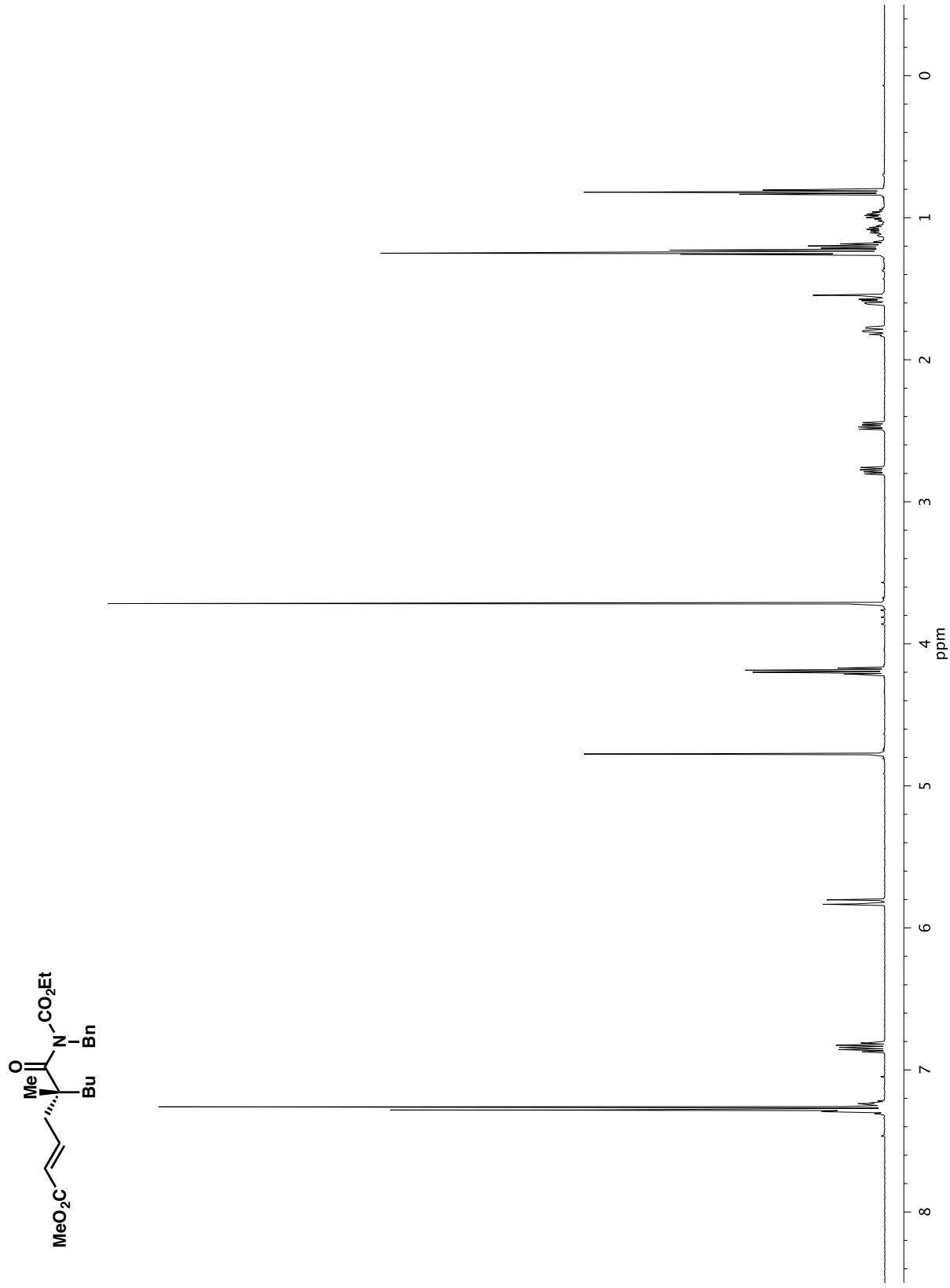
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88d**.



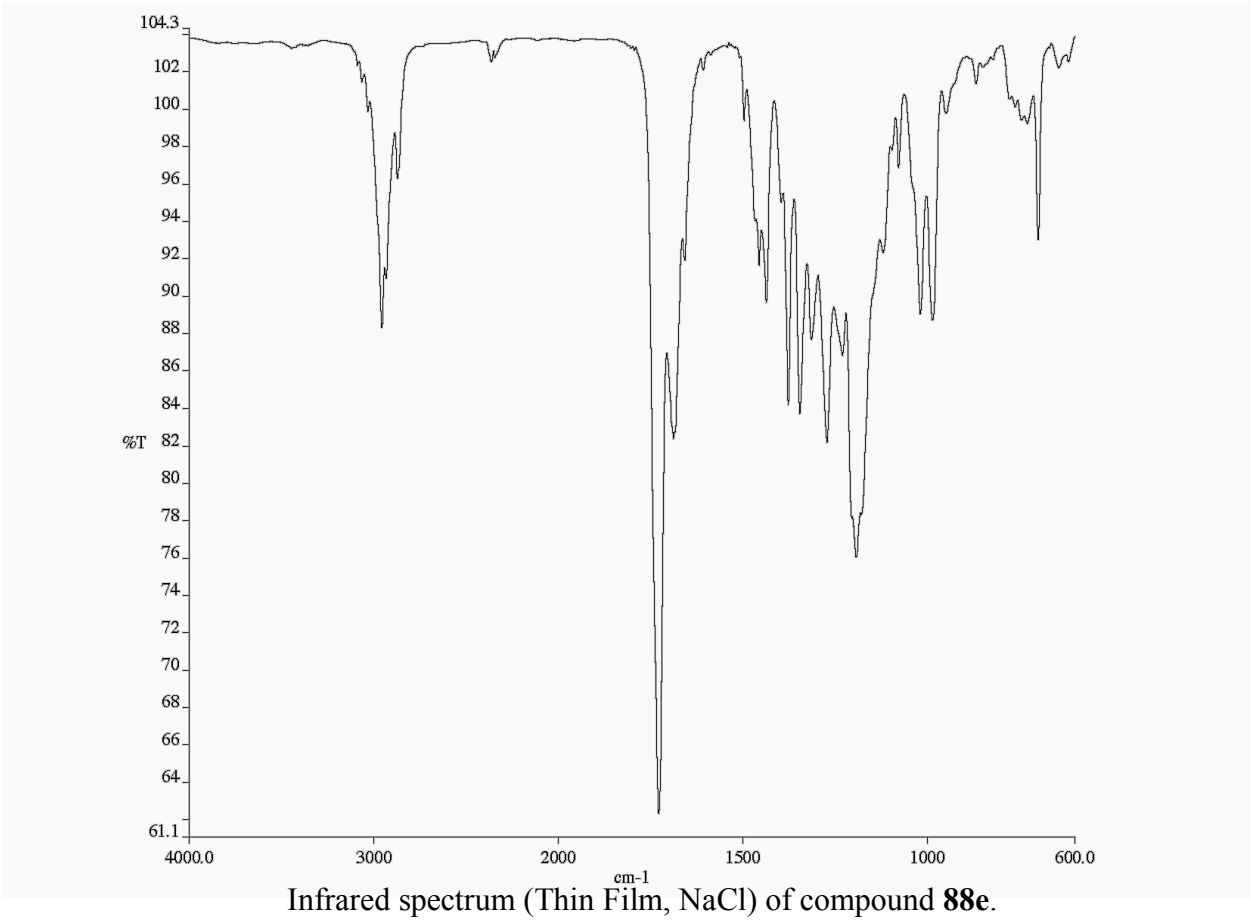
Infrared spectrum (Thin Film, NaCl) of compound **88d**.



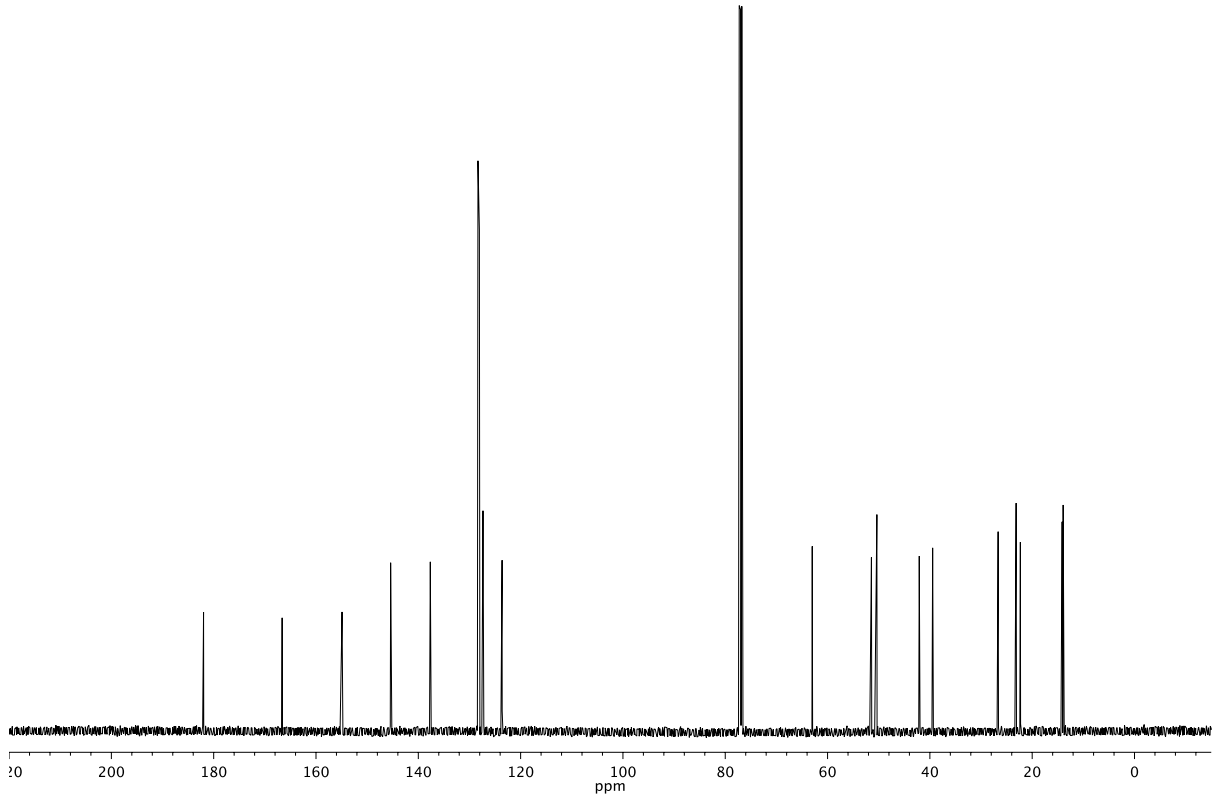
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88d**.



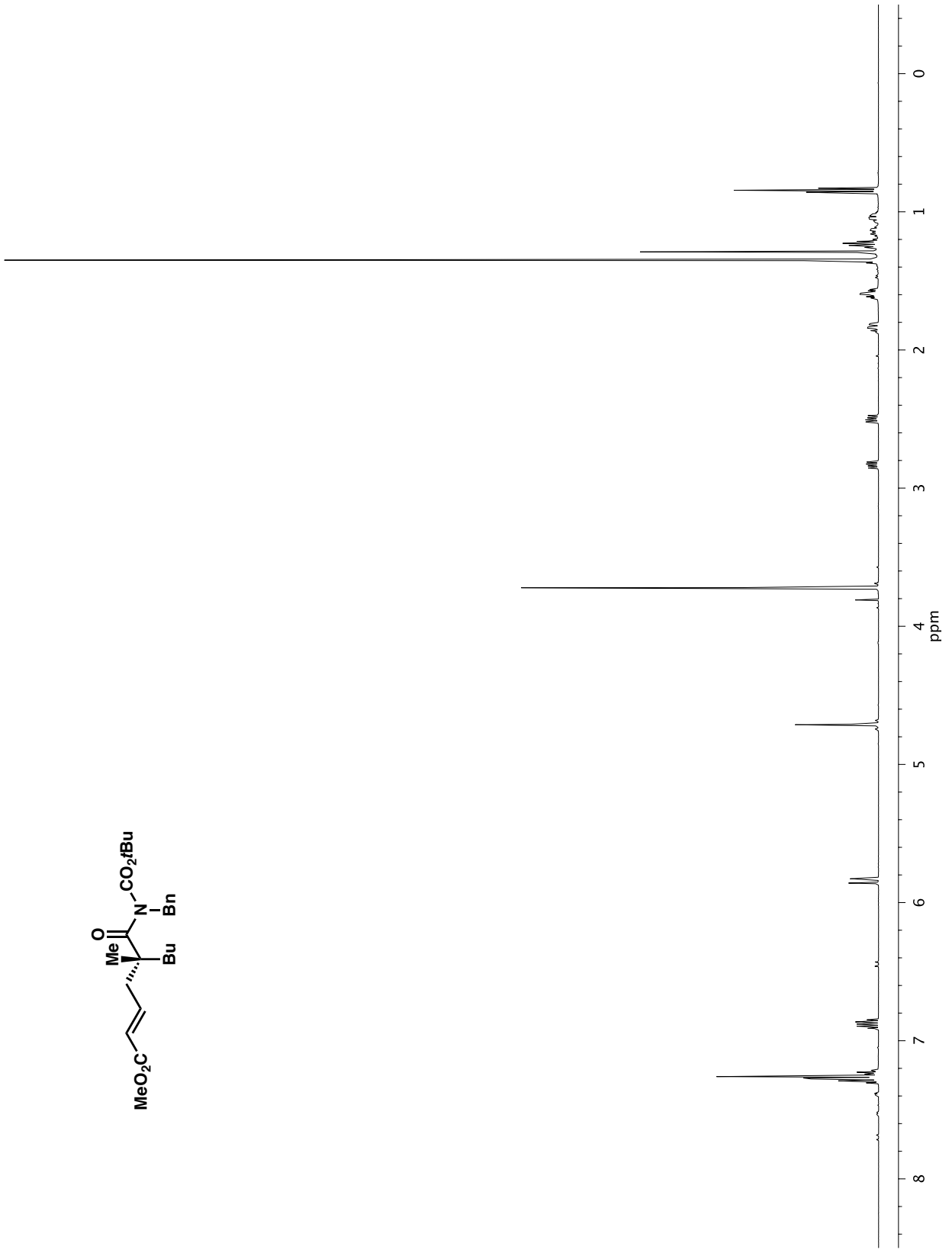
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88e**.



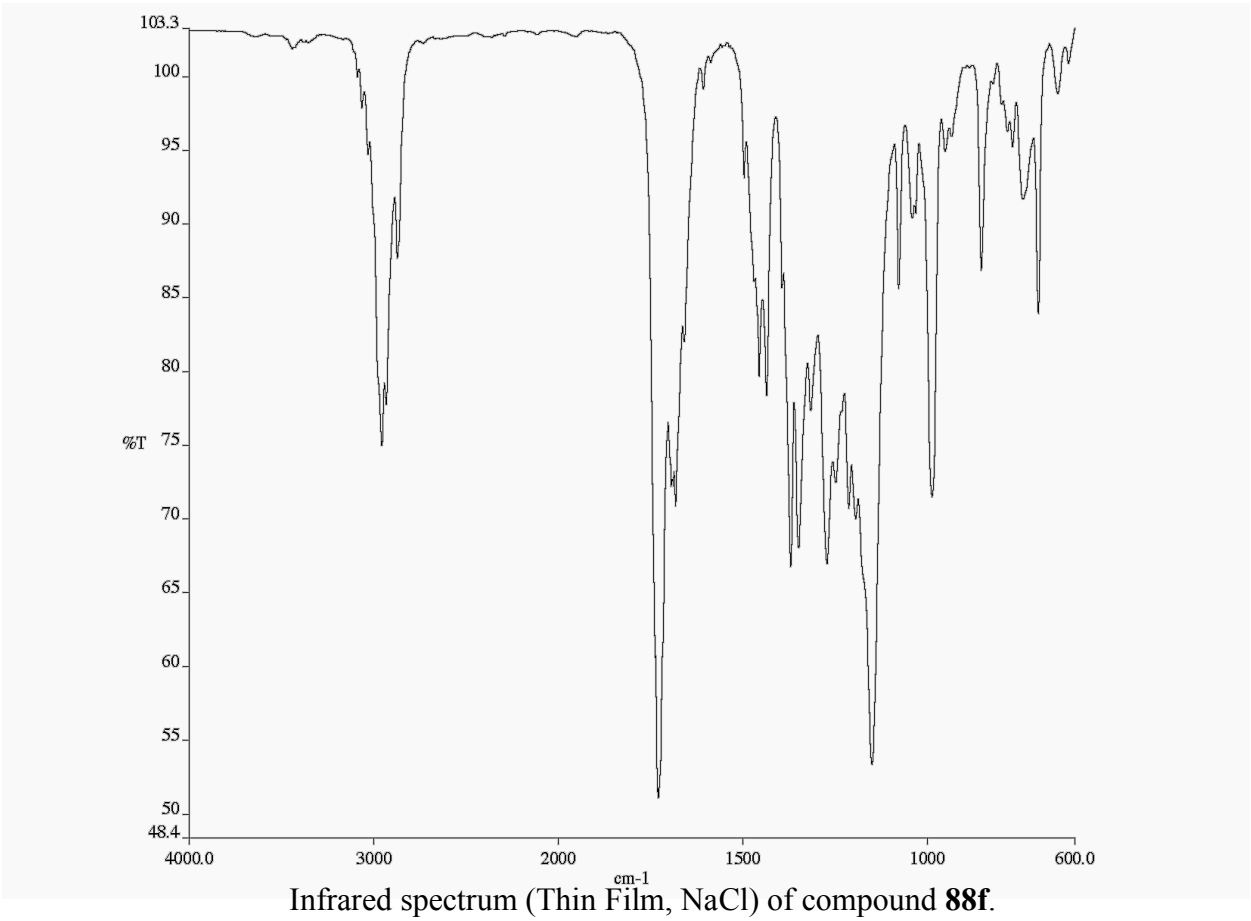
Infrared spectrum (Thin Film, NaCl) of compound **88e**.



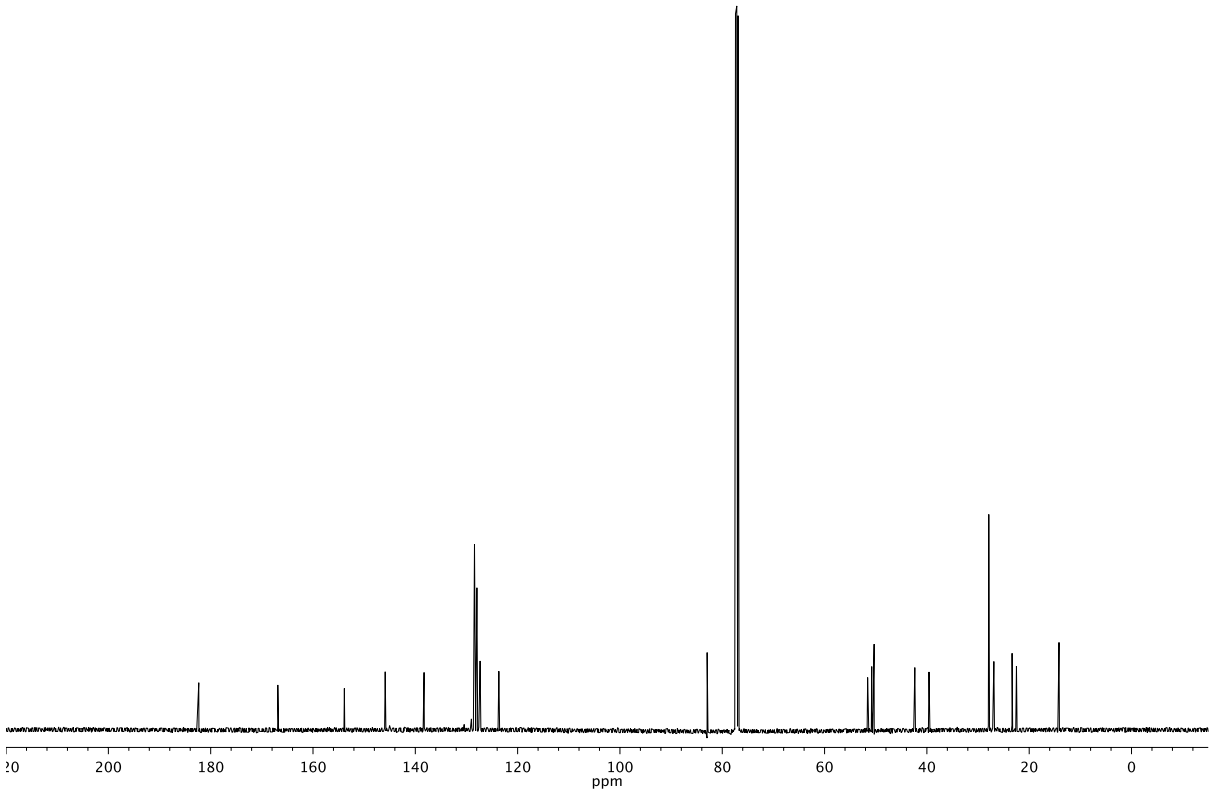
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88e**.



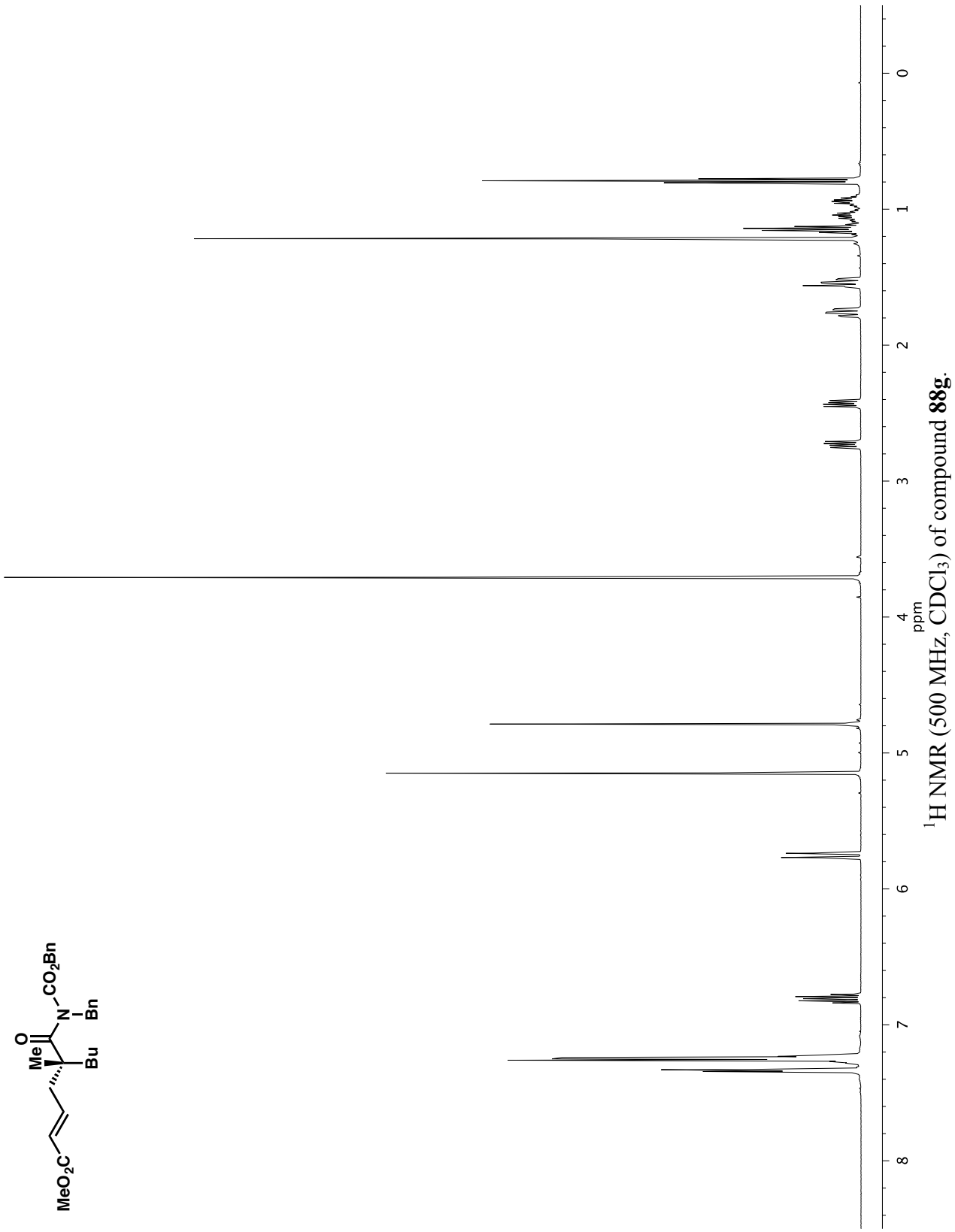
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88f**.



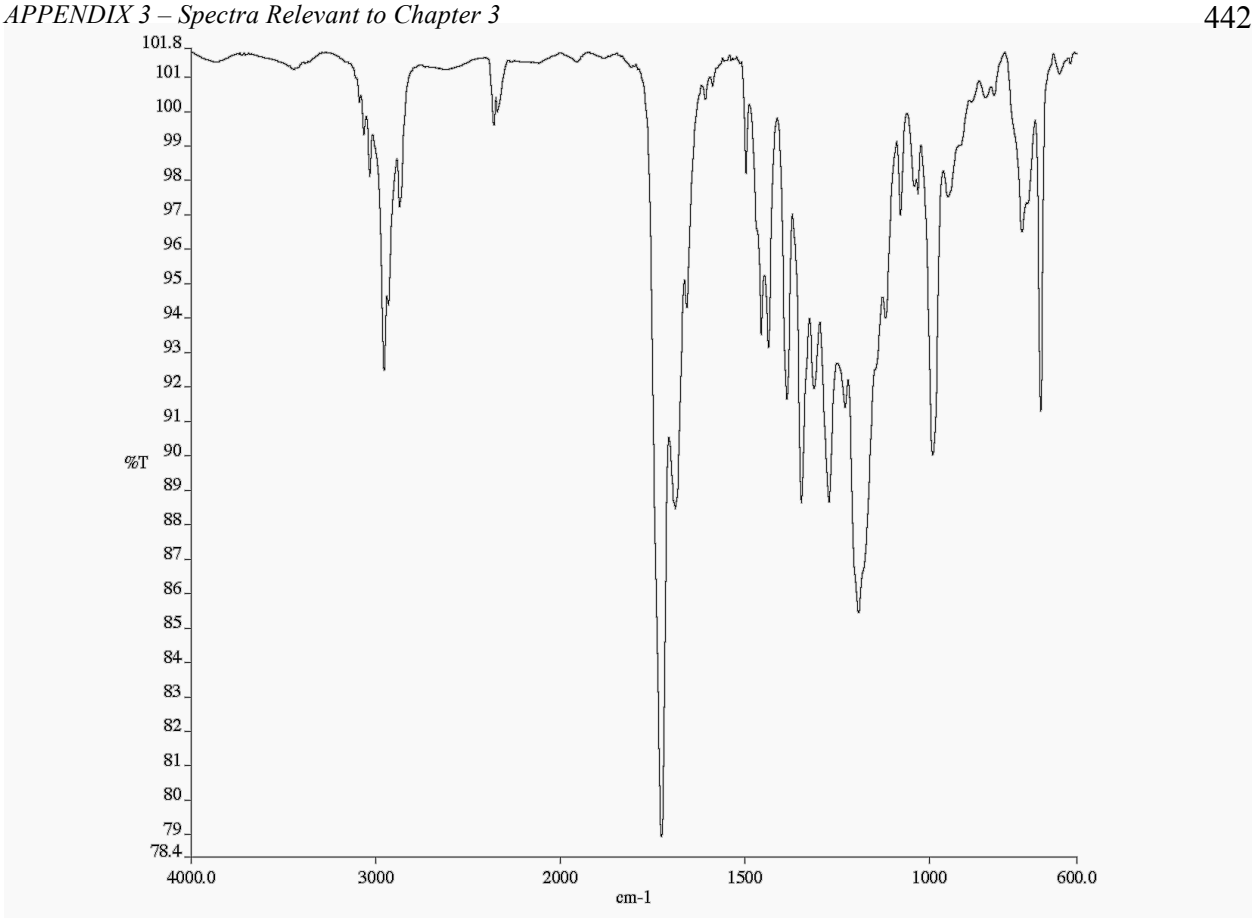
Infrared spectrum (Thin Film, NaCl) of compound **88f**.



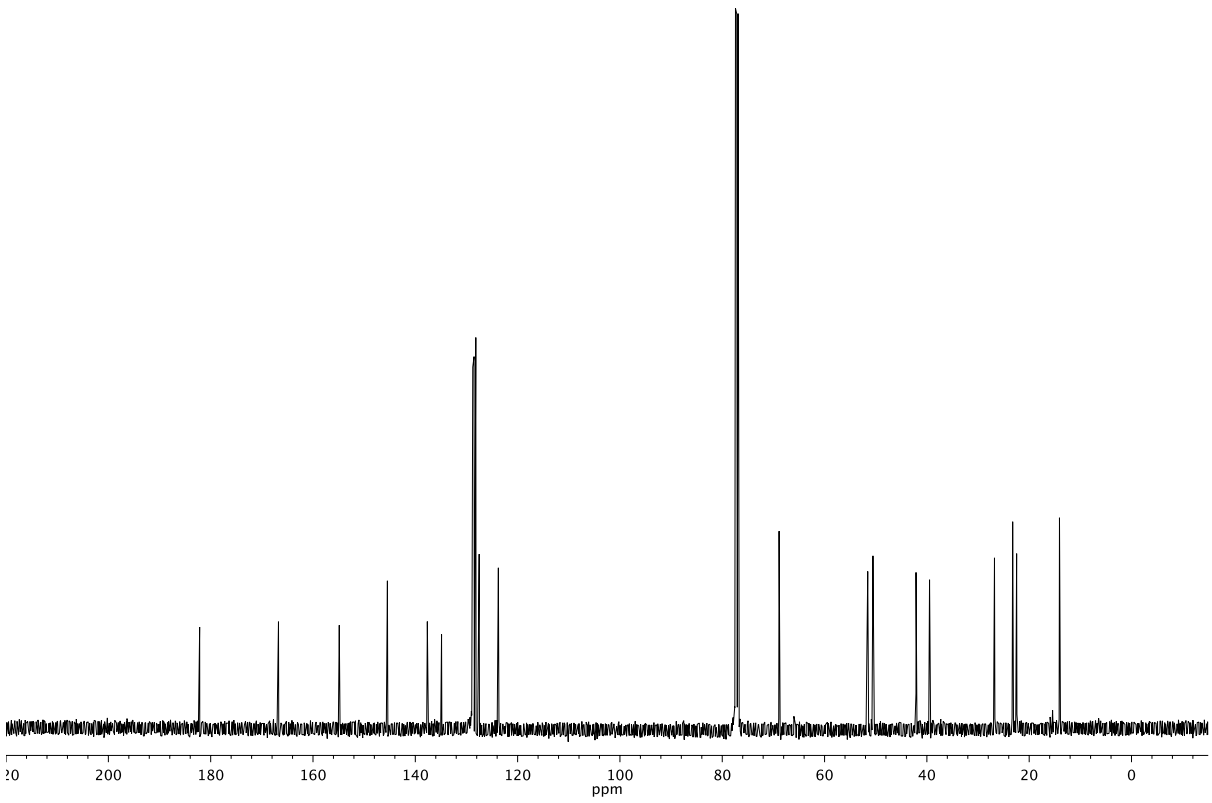
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88f**.



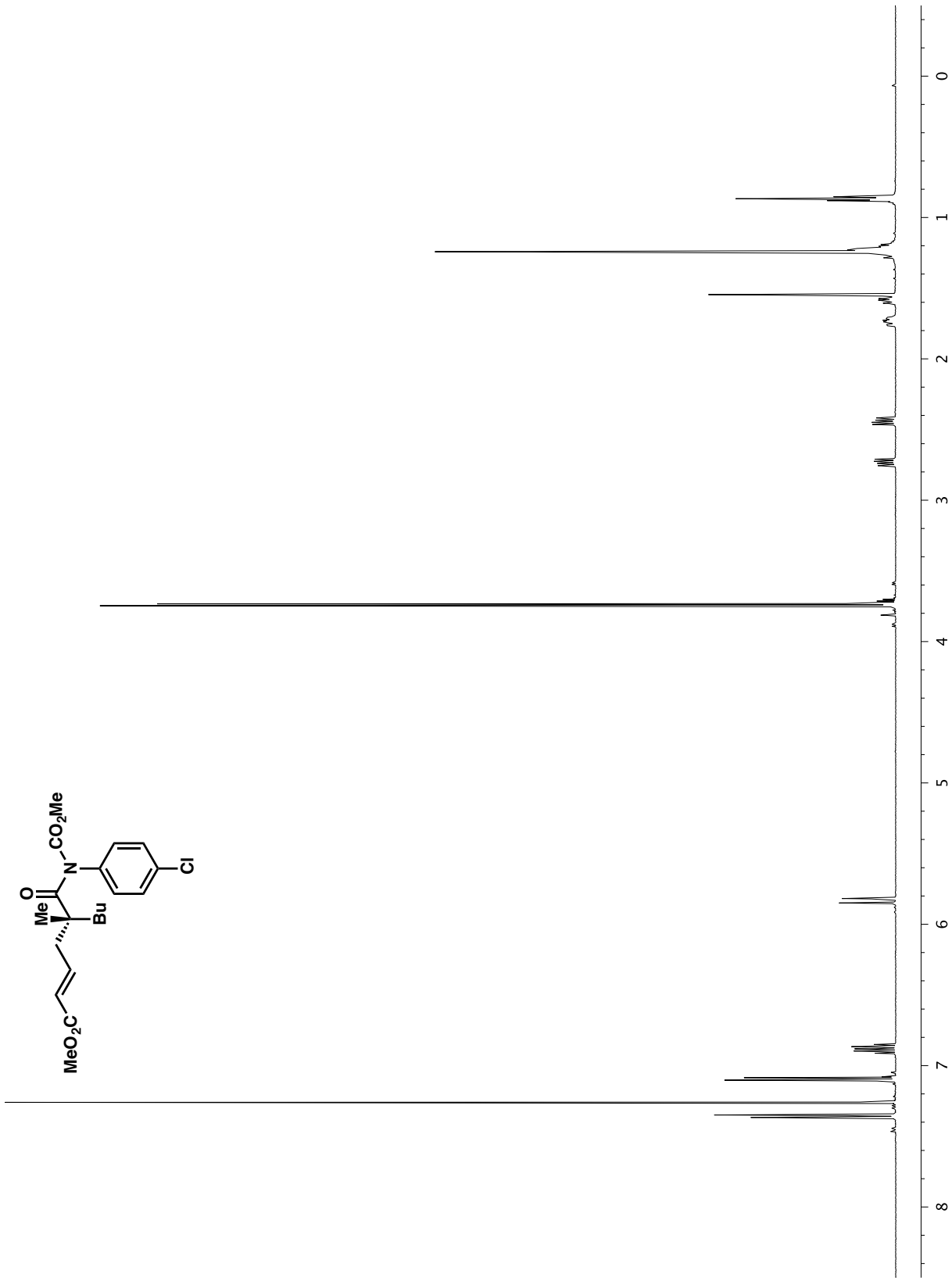
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88g**.



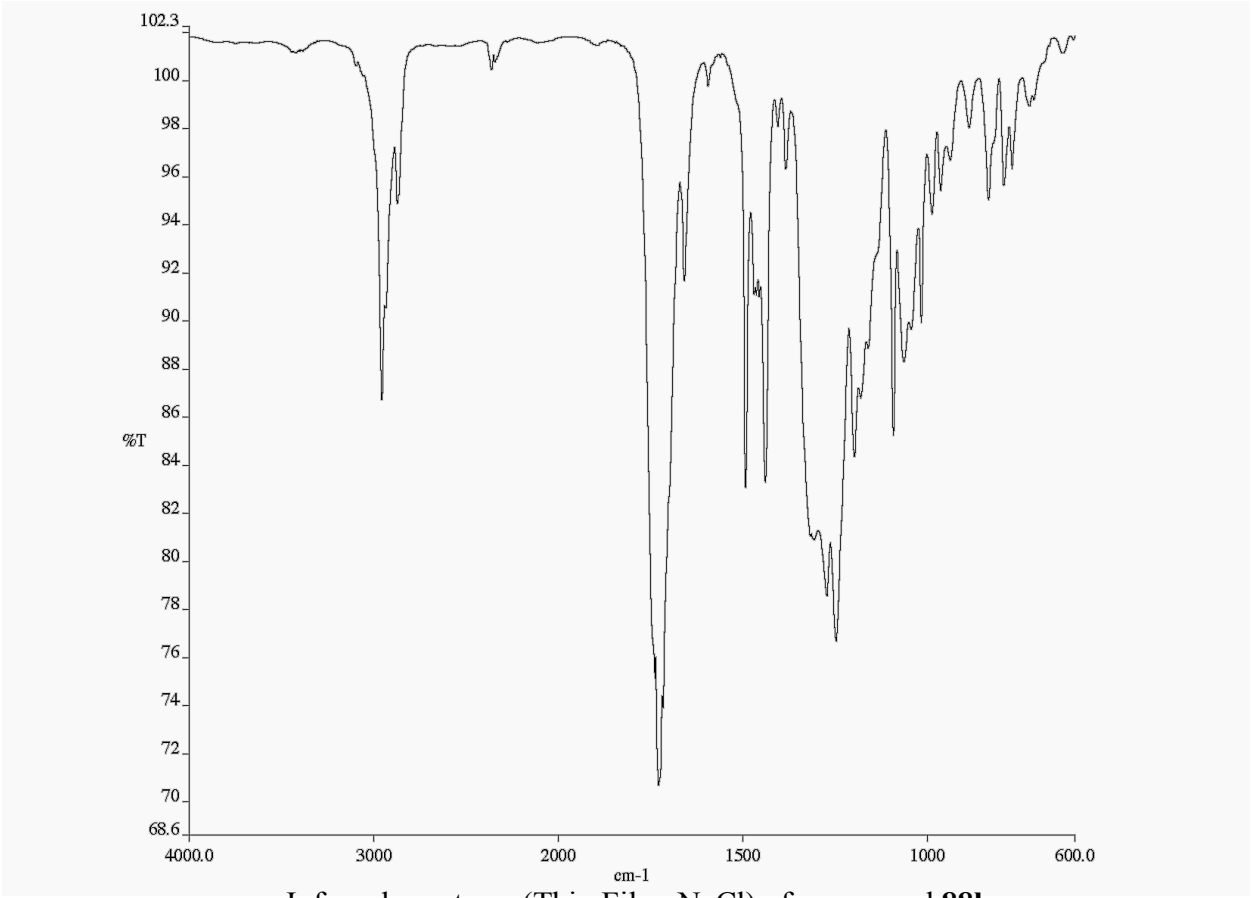
Infrared spectrum (Thin Film, NaCl) of compound **88g**.



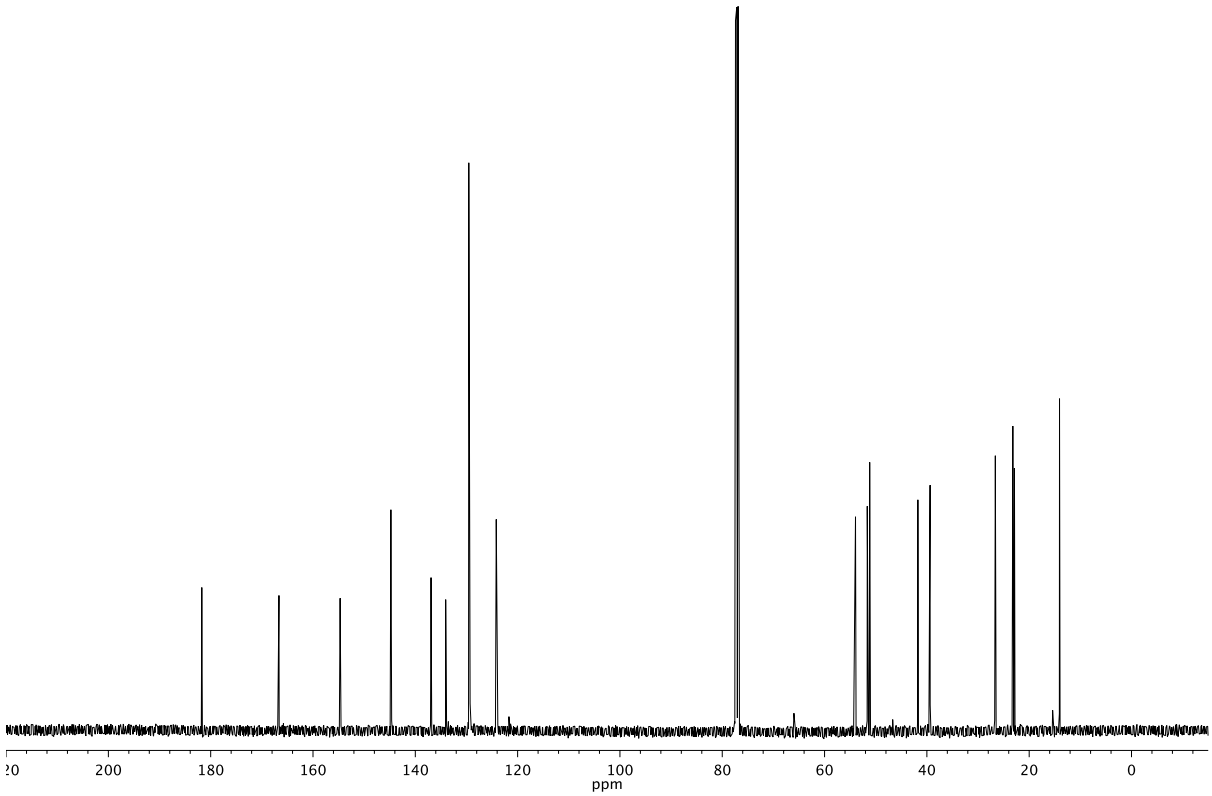
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88g**.



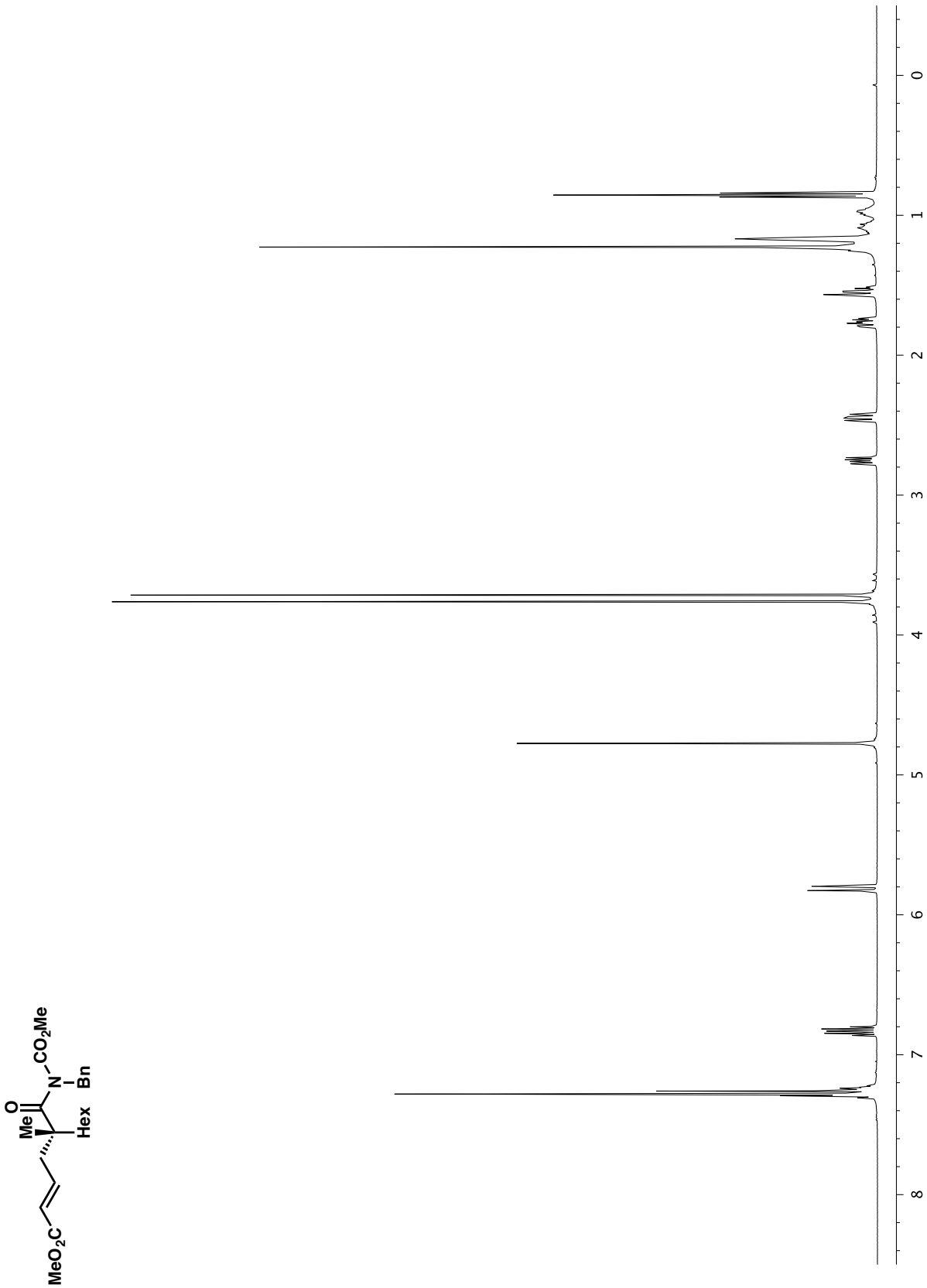
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88h**.



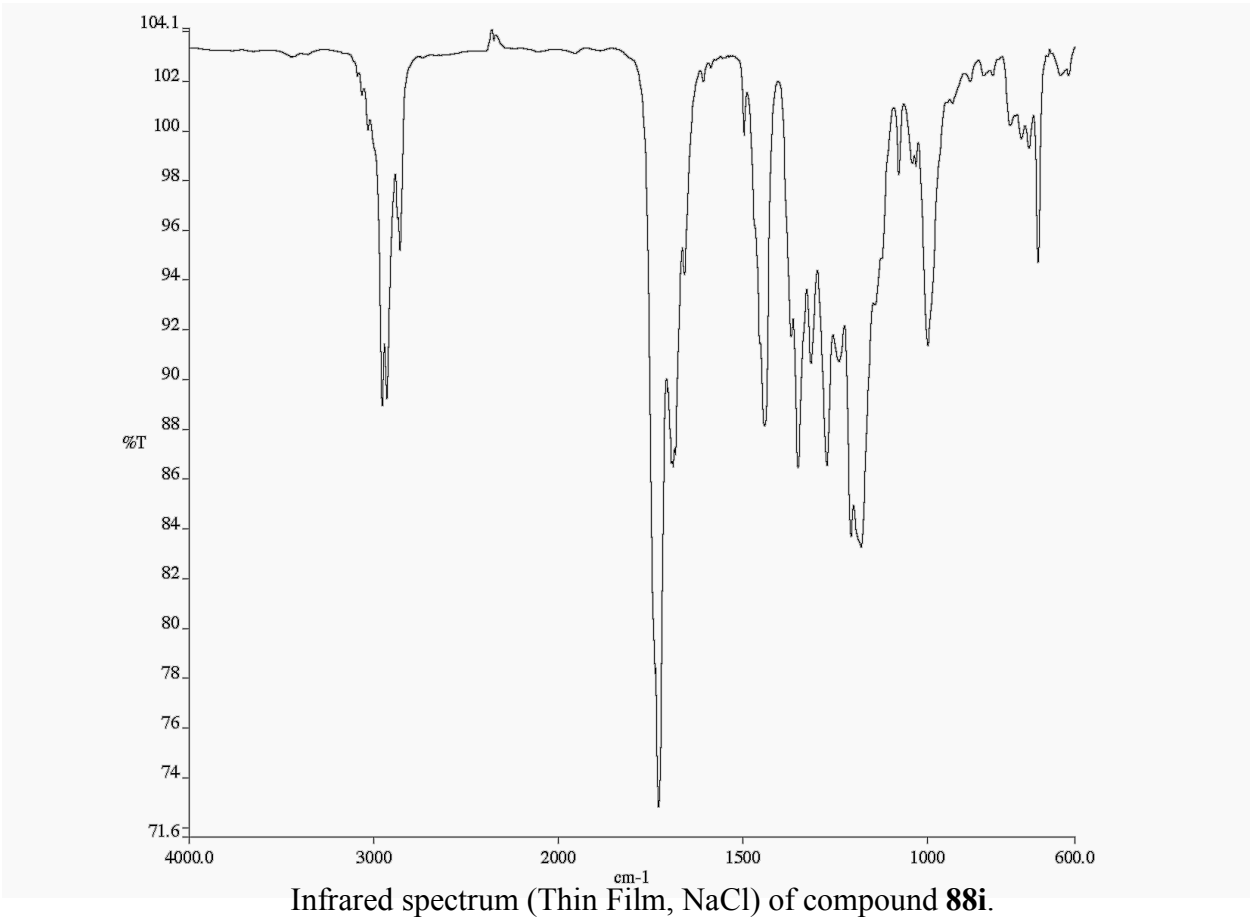
Infrared spectrum (Thin Film, NaCl) of compound **88h**.



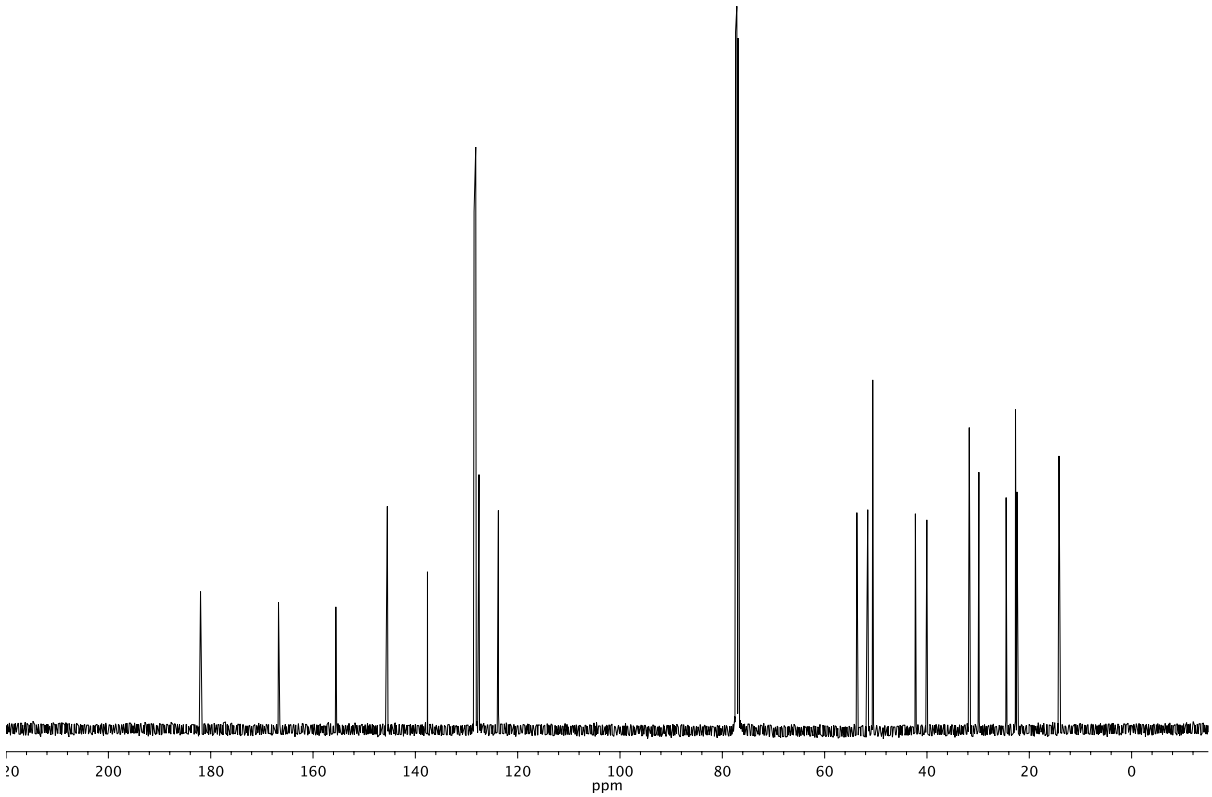
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88h**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **88i**.

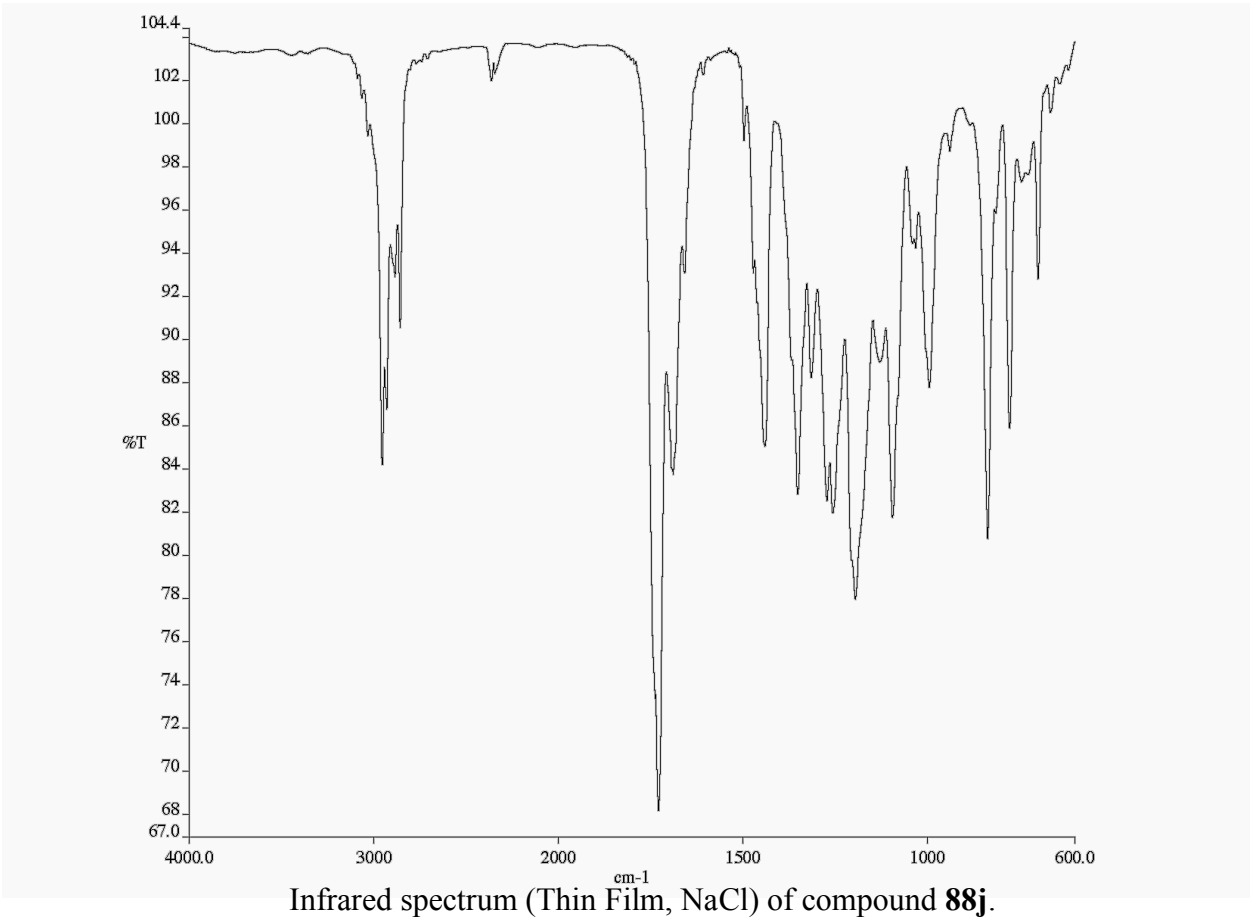


Infrared spectrum (Thin Film, NaCl) of compound **88i**.

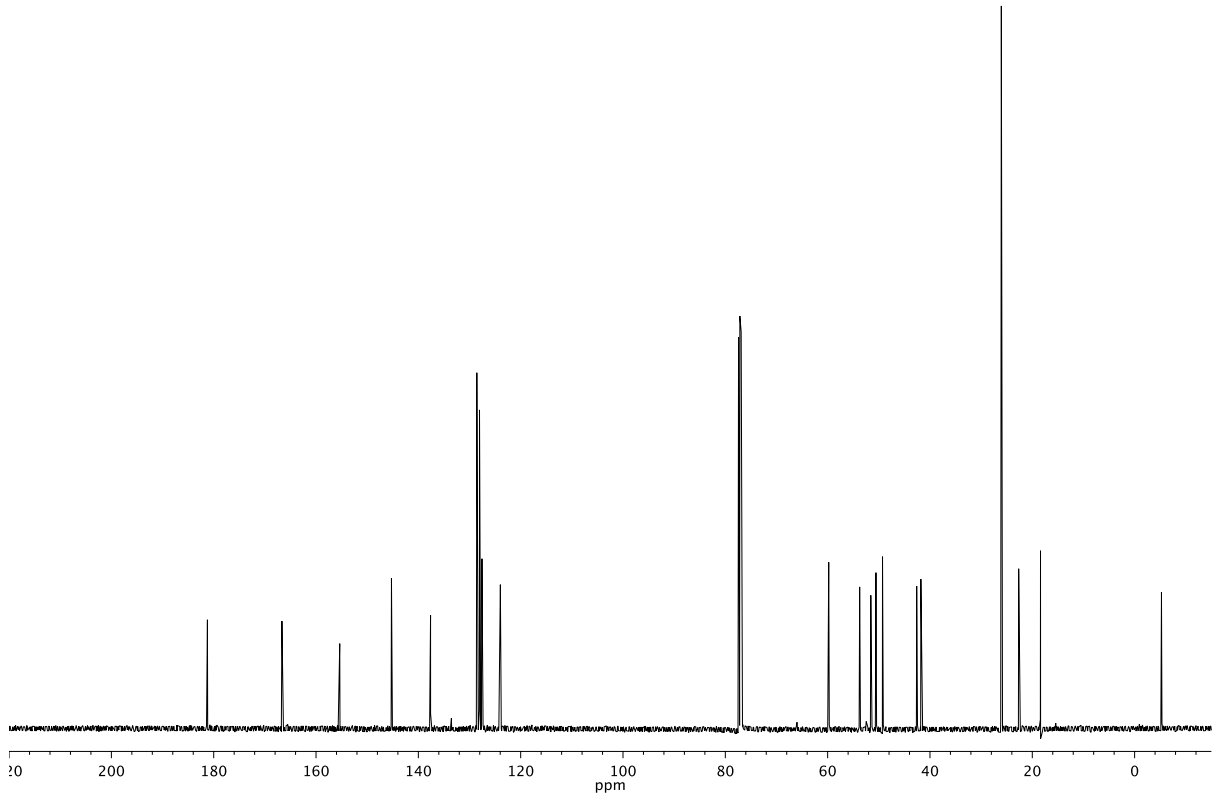


^{13}C NMR (126 MHz, $CDCl_3$) of compound **88i**.

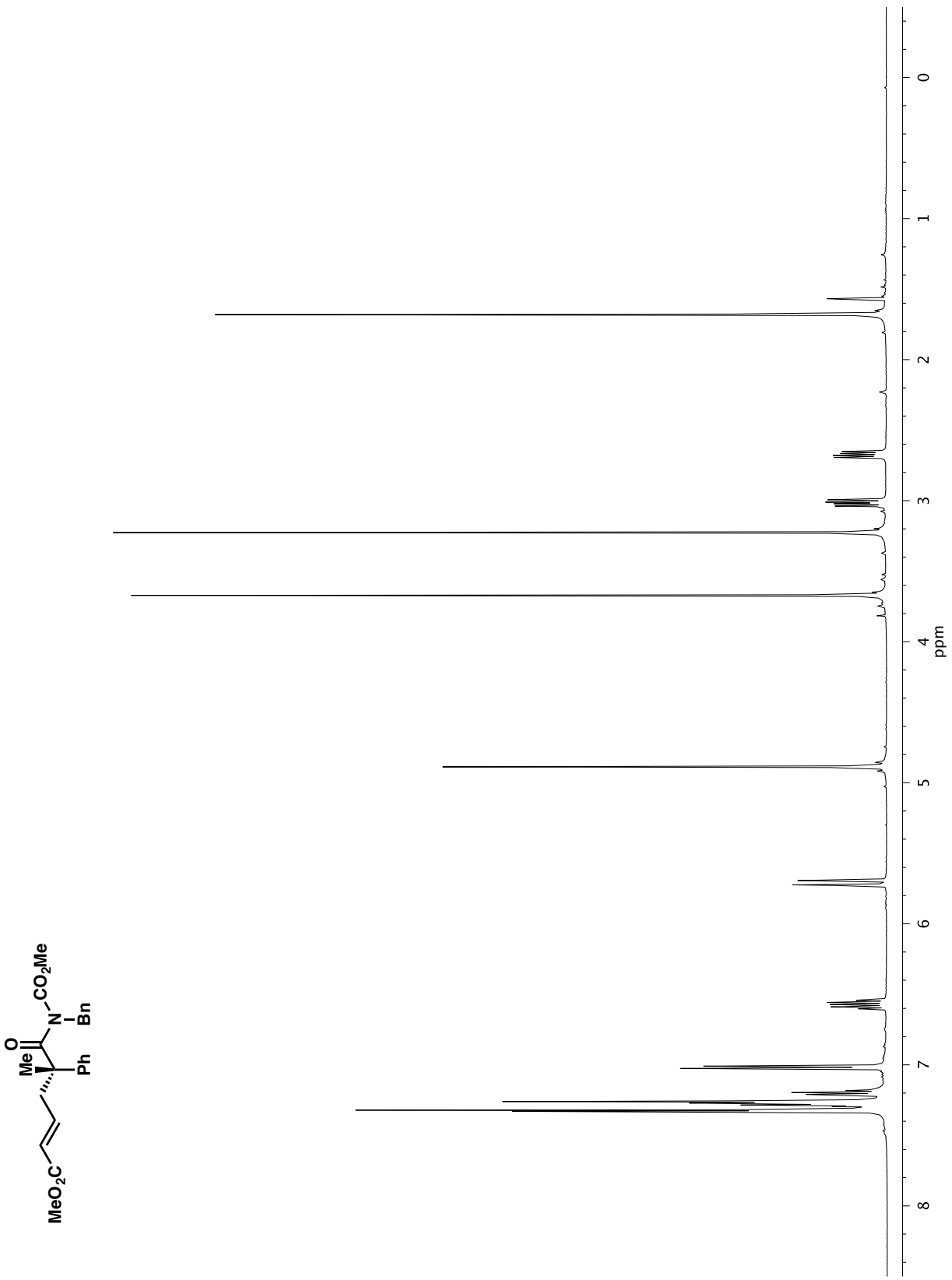
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88j**.



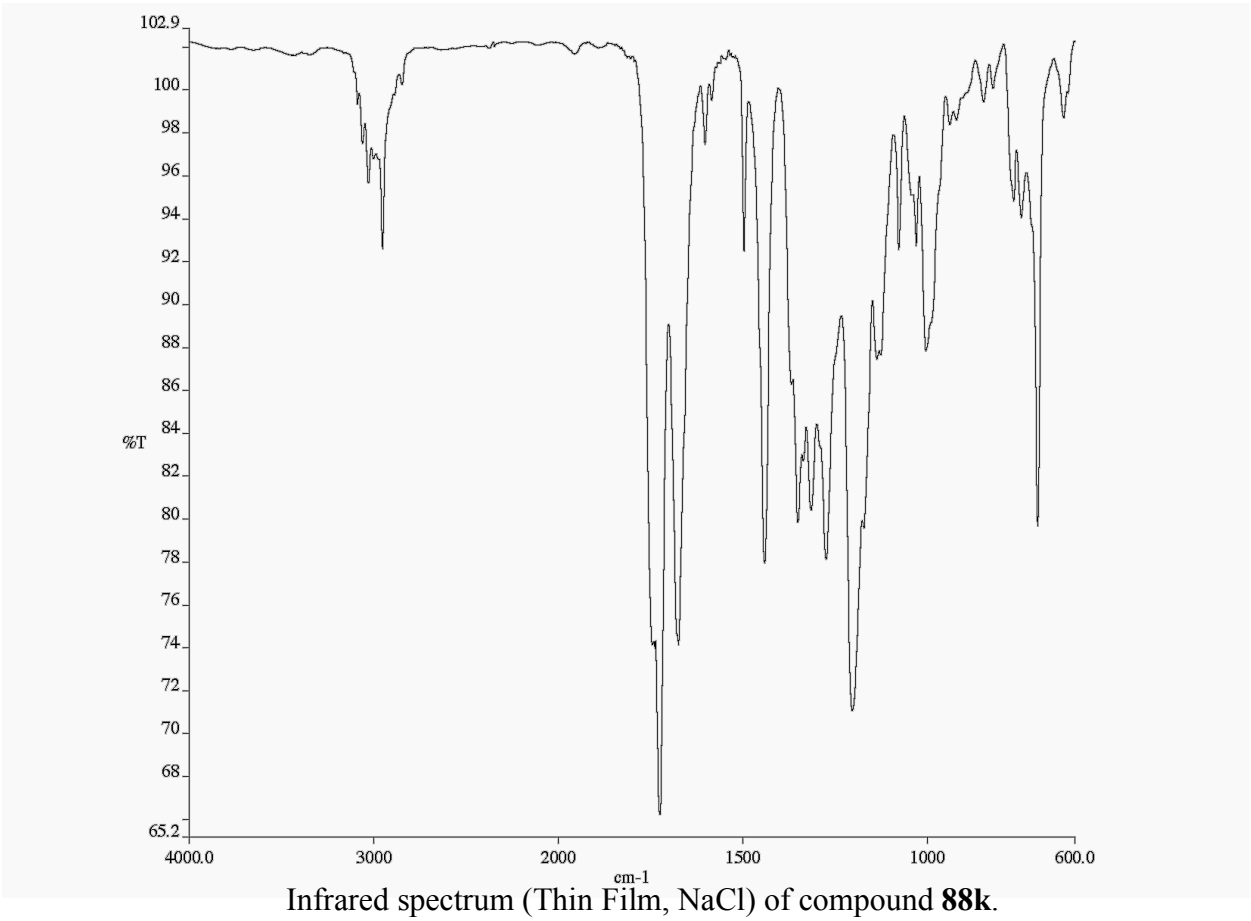
Infrared spectrum (Thin Film, NaCl) of compound **88j**.



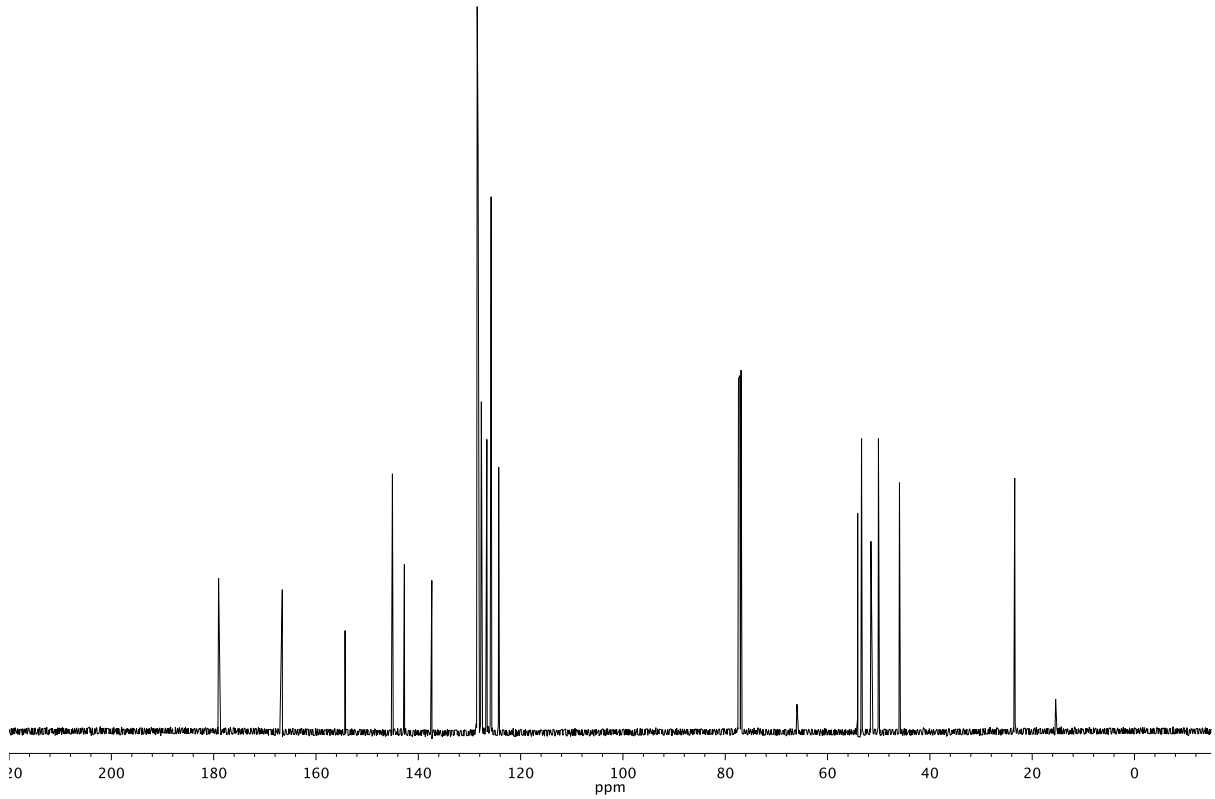
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88j**.



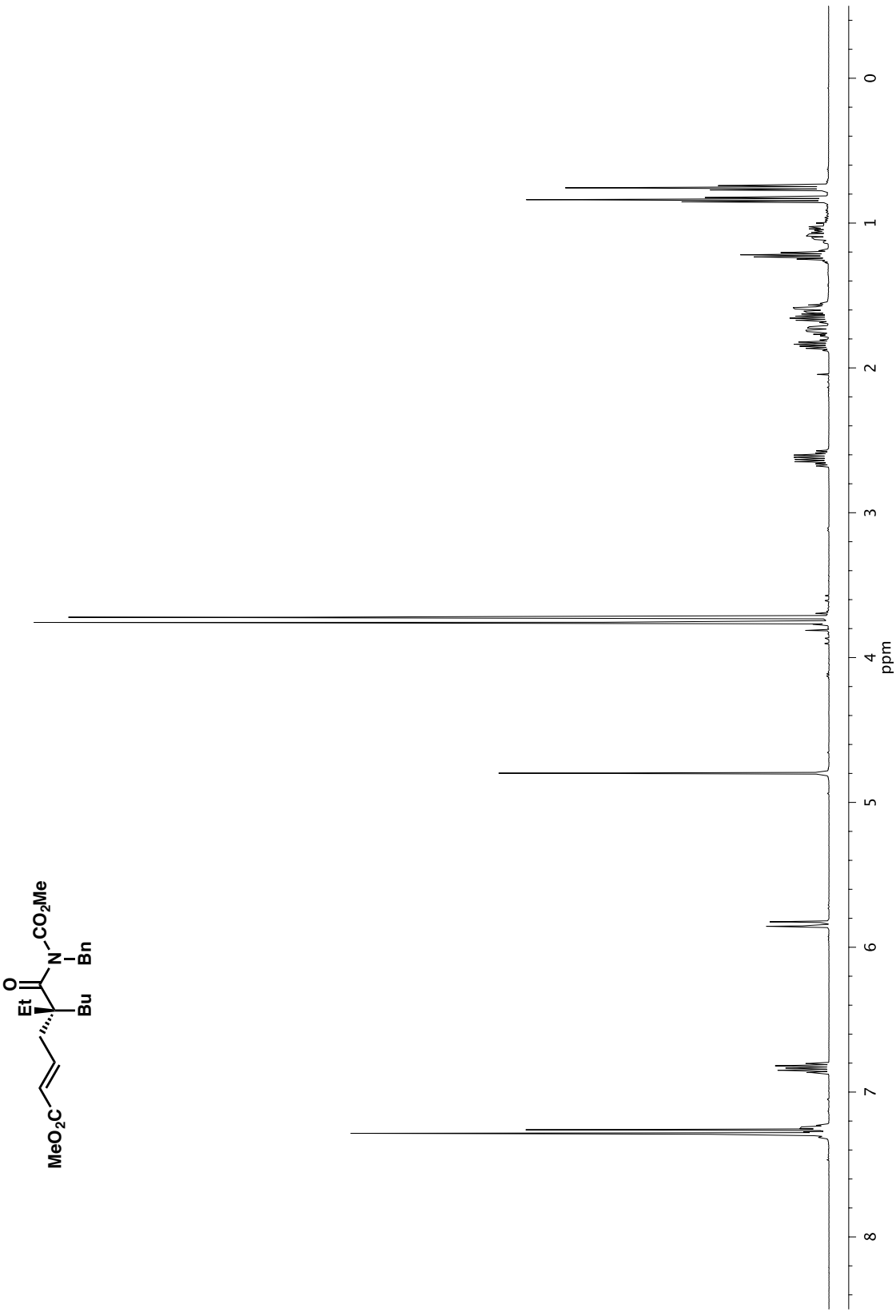
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88k**.



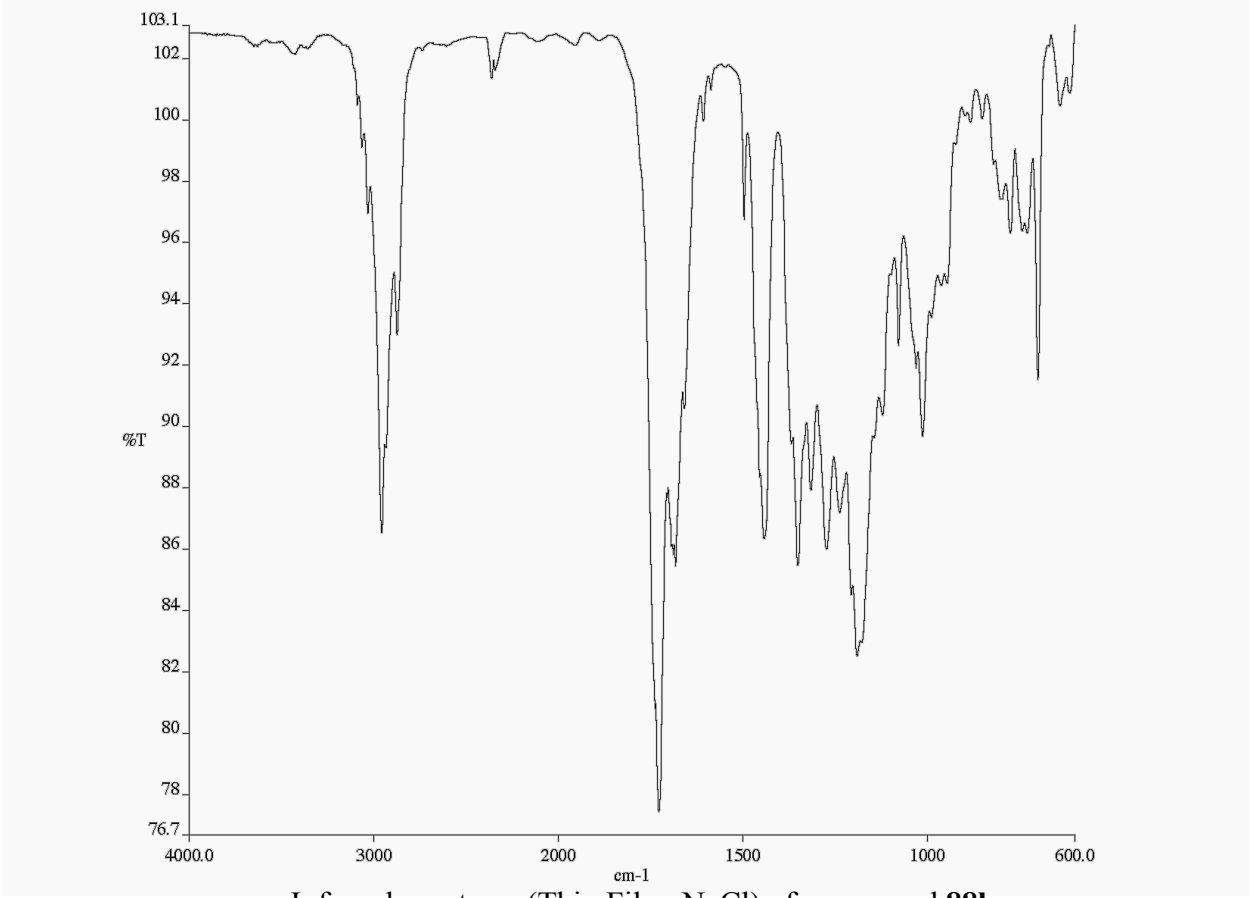
Infrared spectrum (Thin Film, NaCl) of compound **88k**.



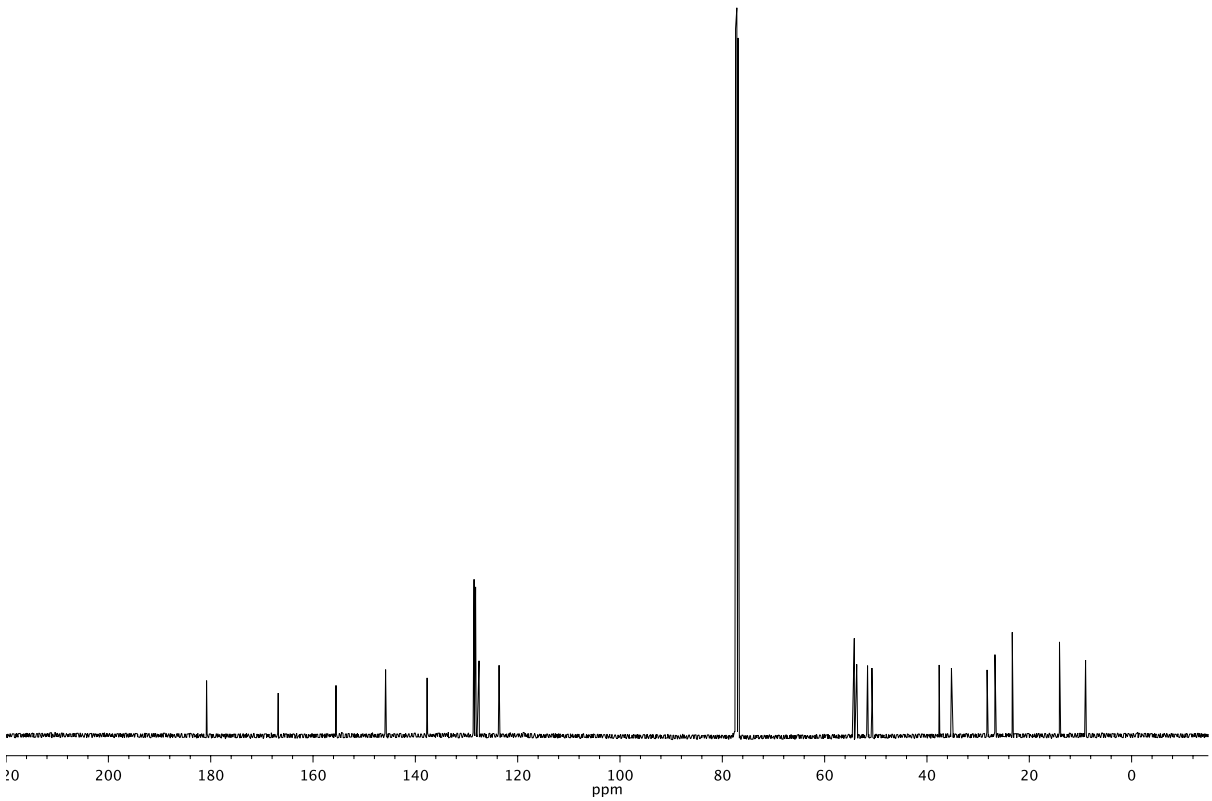
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88k**.



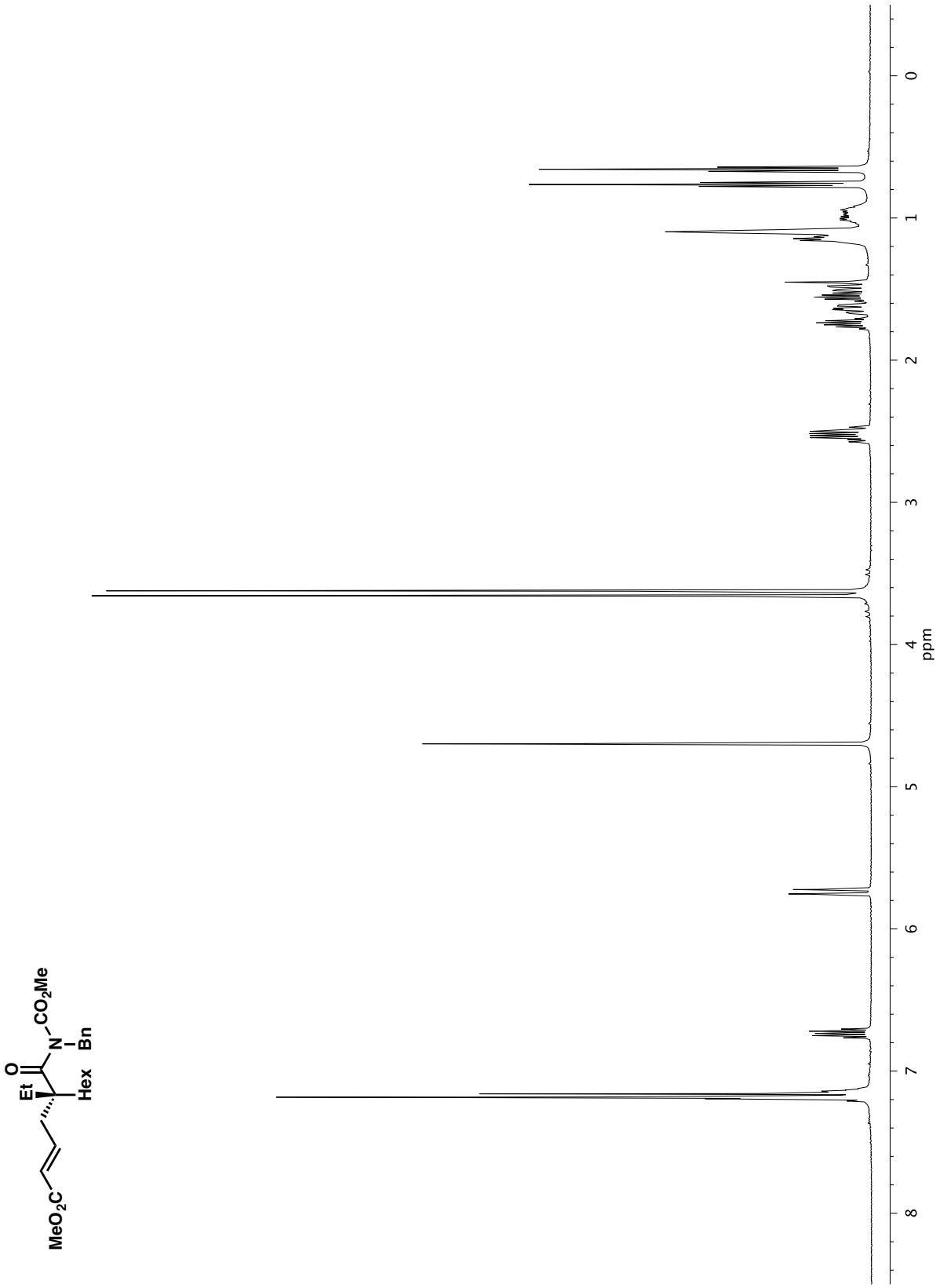
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88l**.



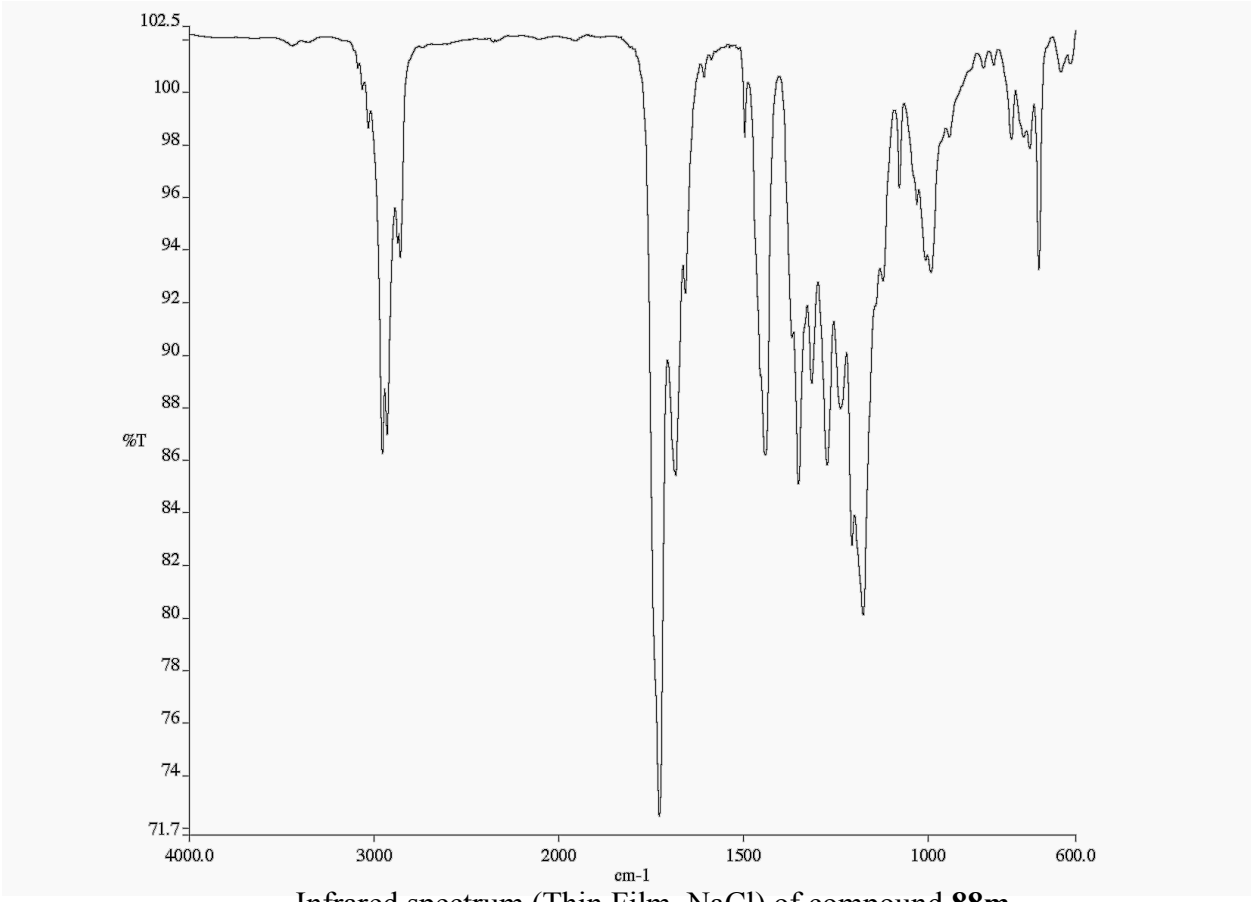
Infrared spectrum (Thin Film, NaCl) of compound **88l**.



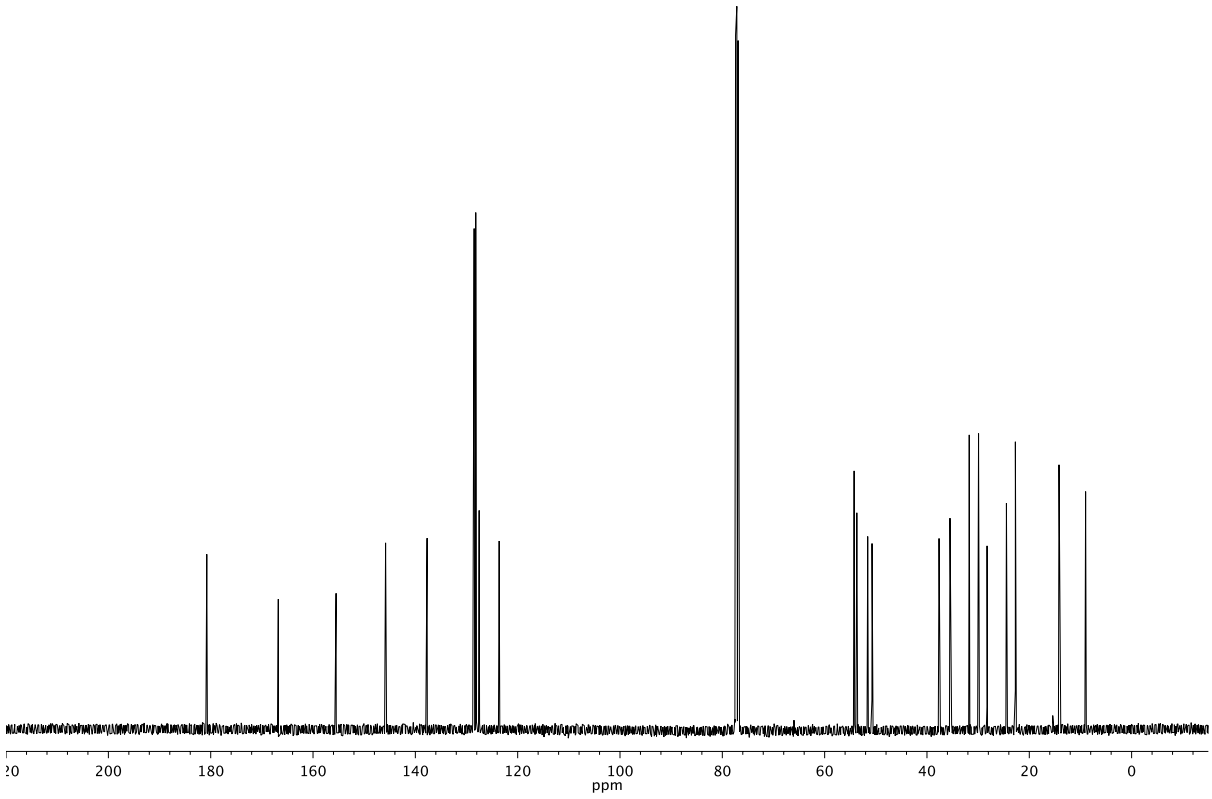
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88l**.



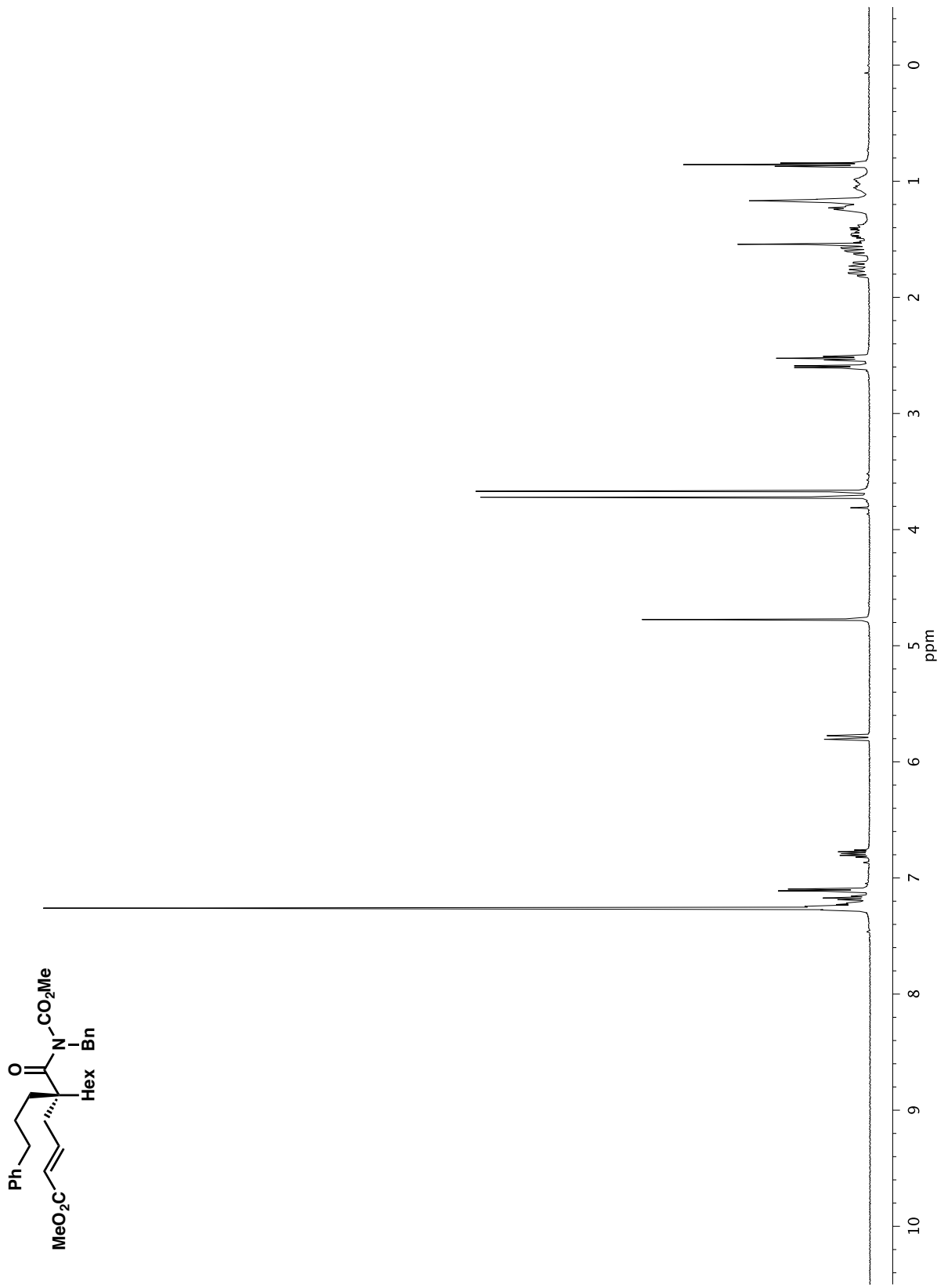
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88m**.



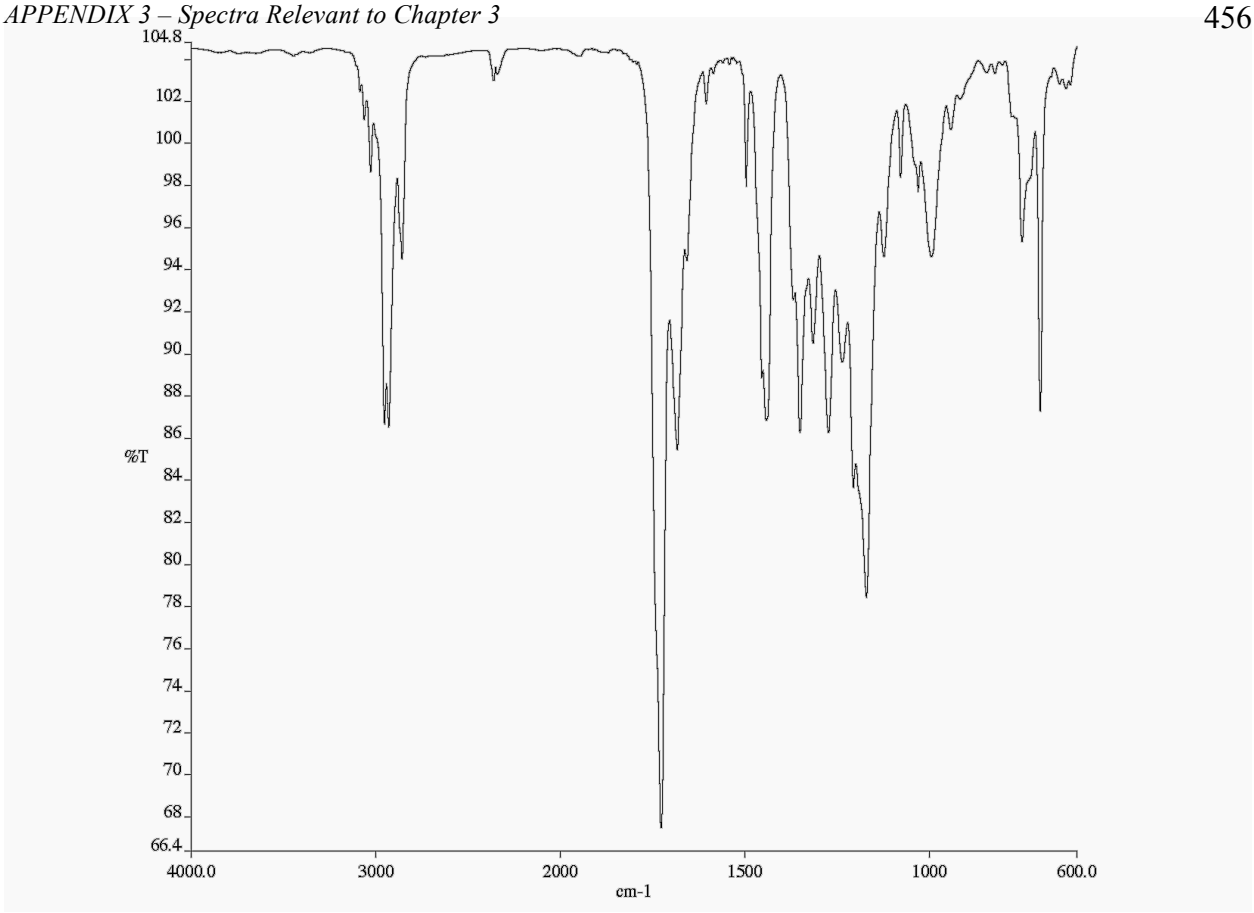
Infrared spectrum (Thin Film, NaCl) of compound **88m**.



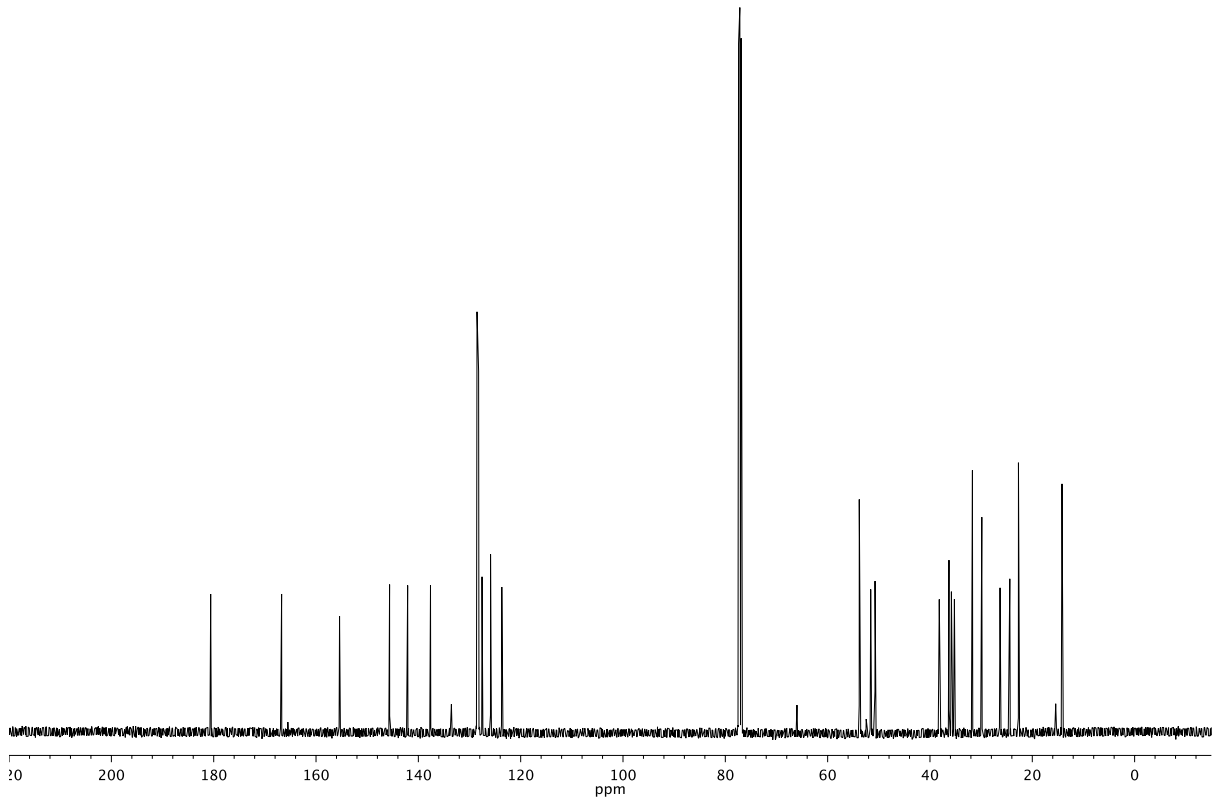
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88m**.



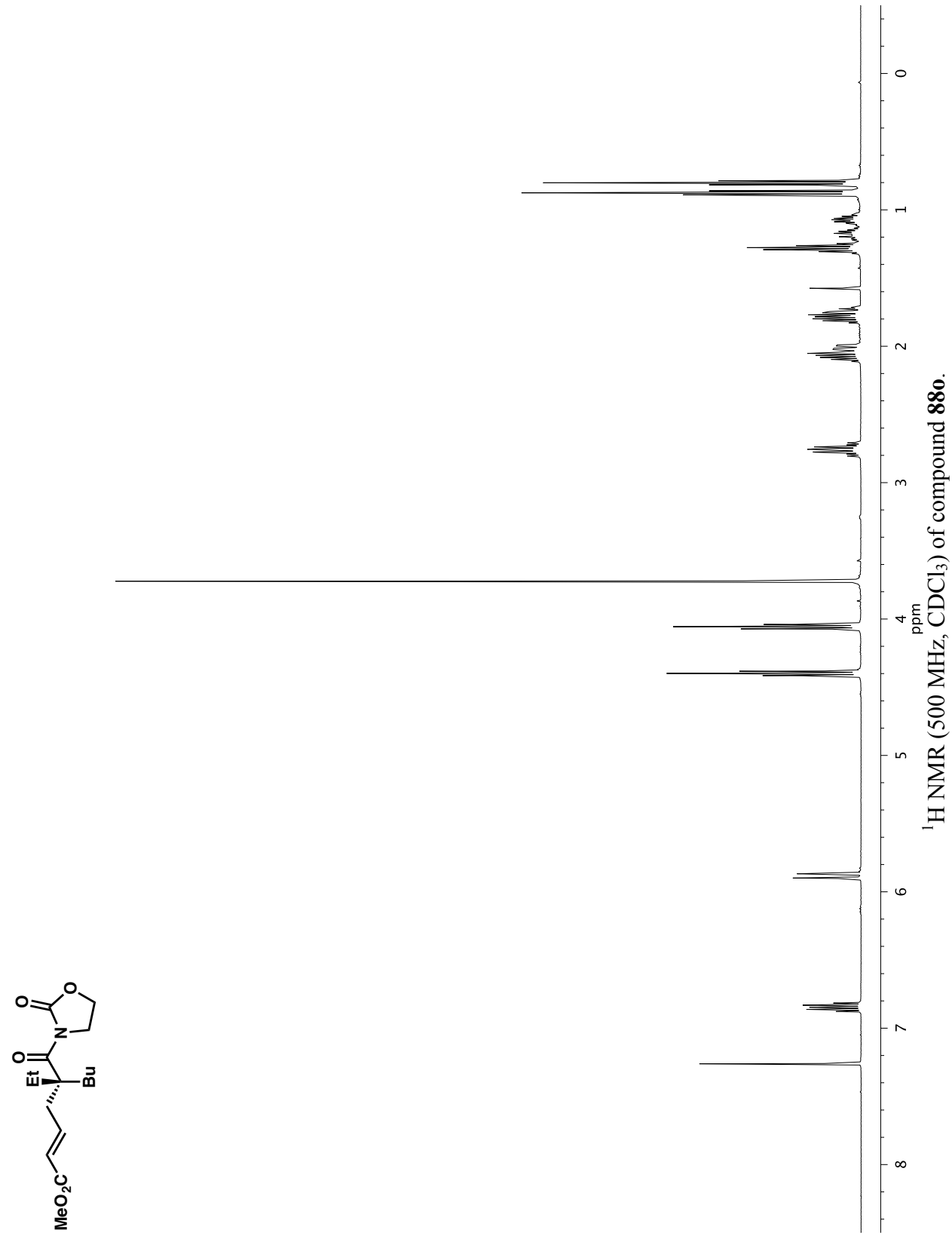
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88n**.



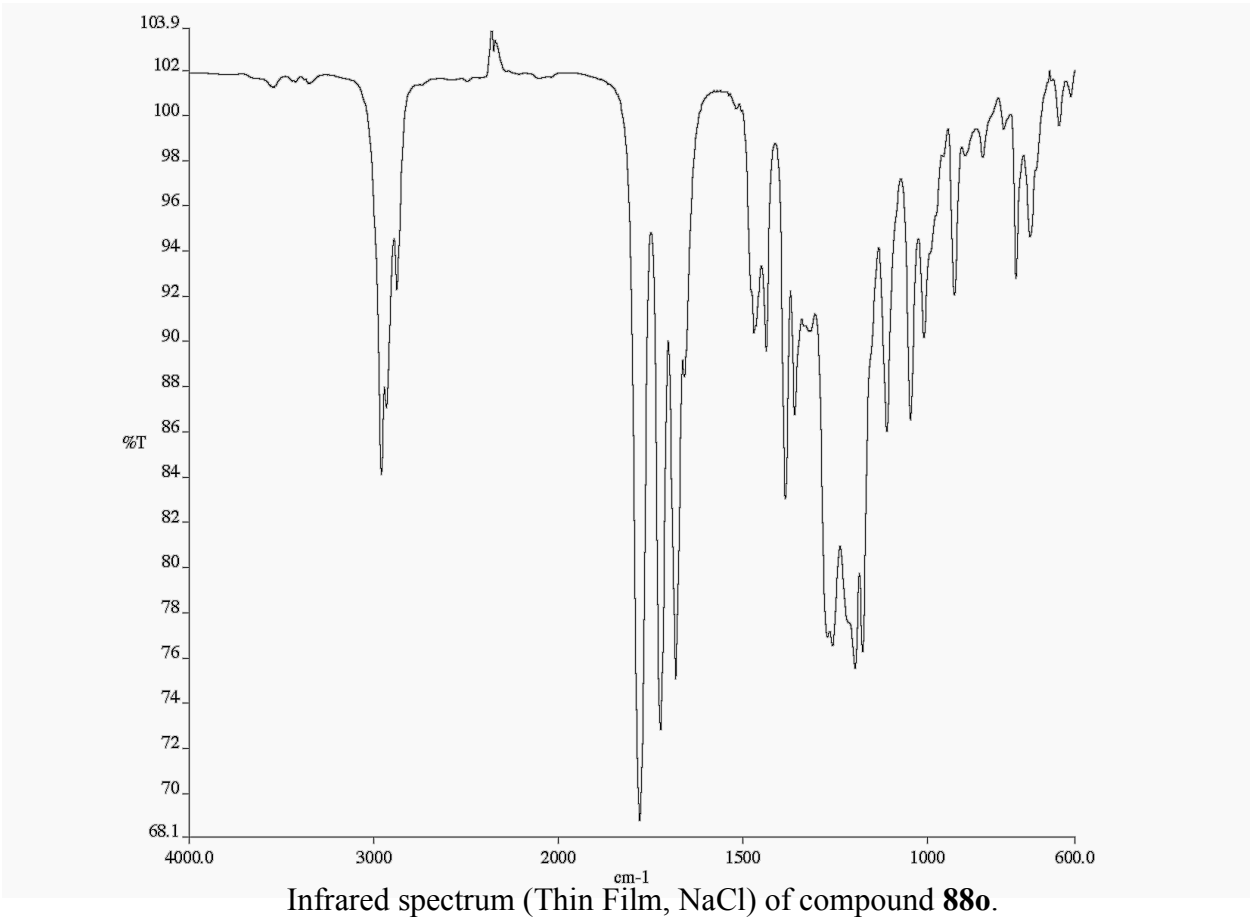
Infrared spectrum (Thin Film, NaCl) of compound **88n**.



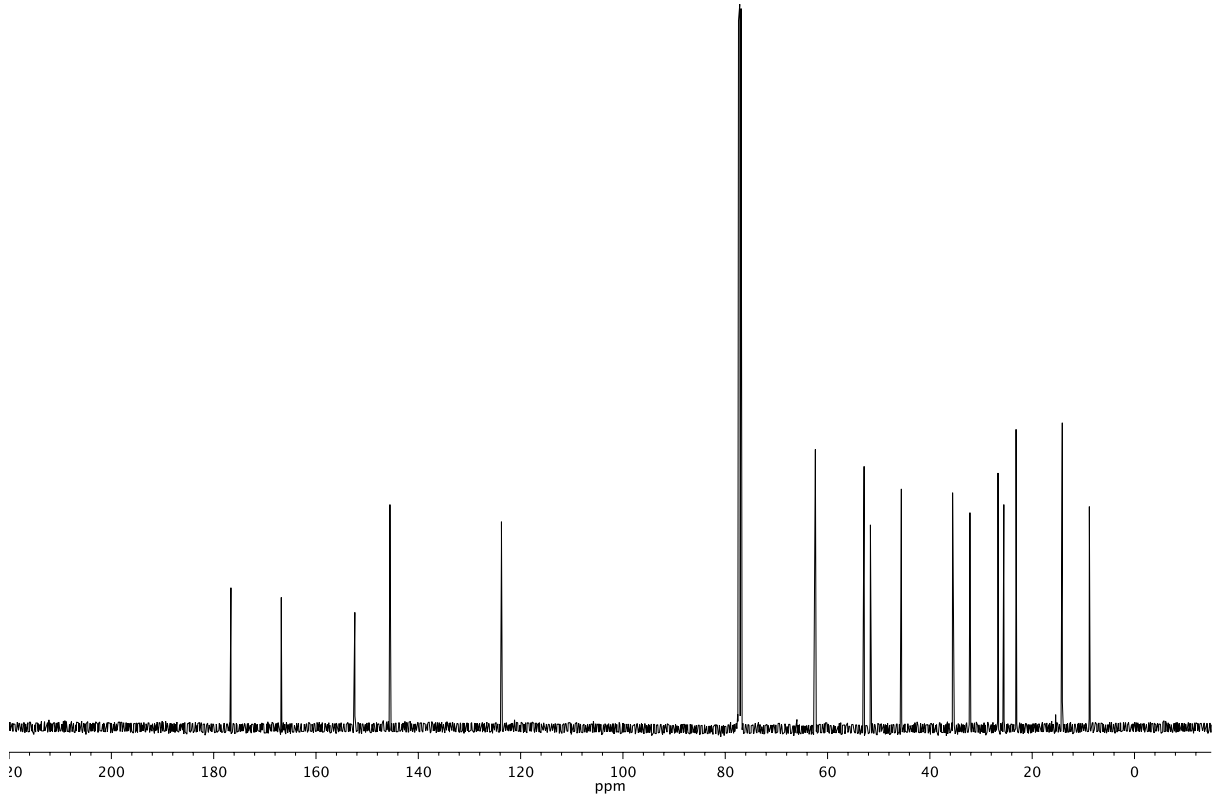
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88n**.



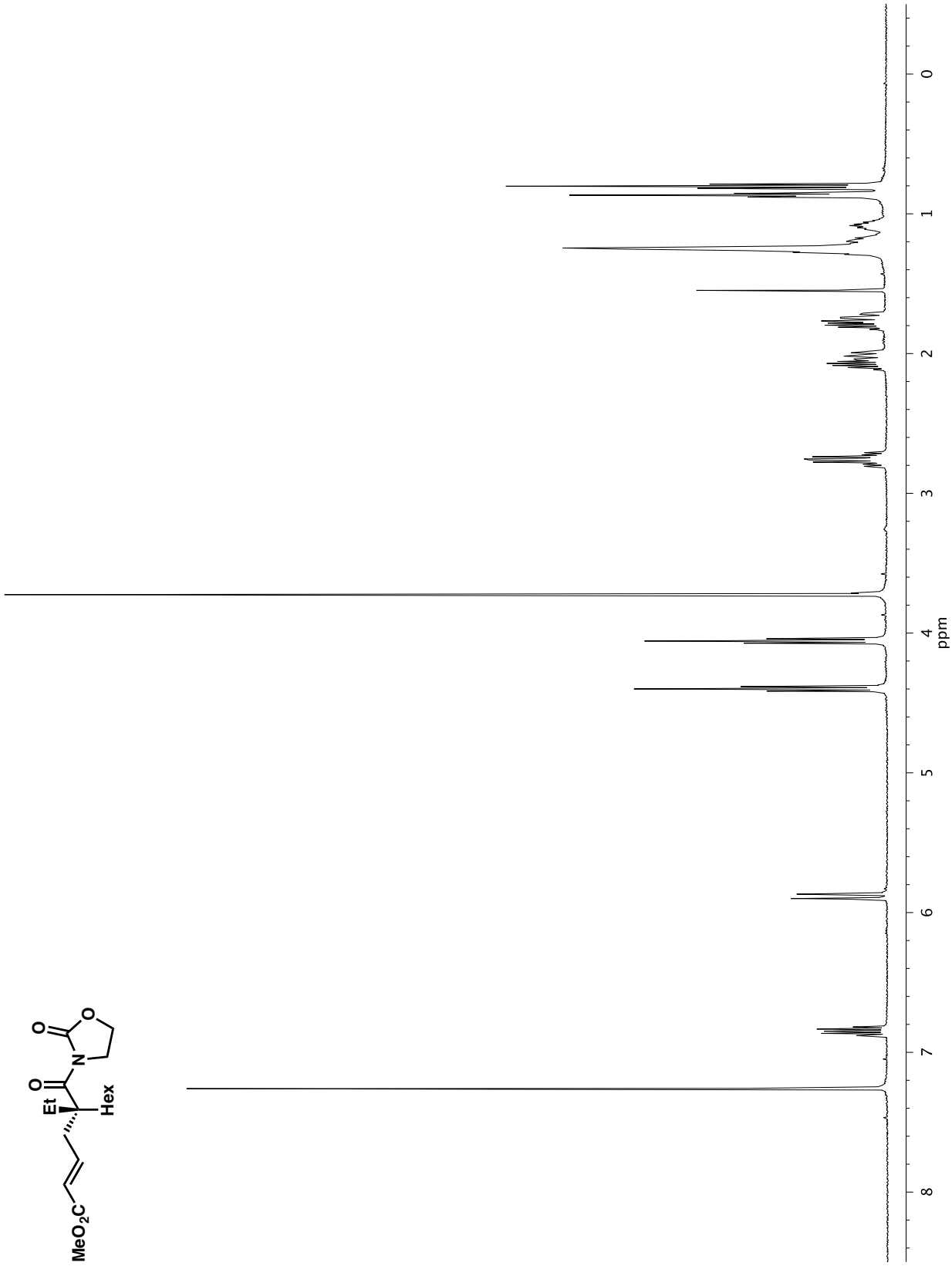
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88o**.



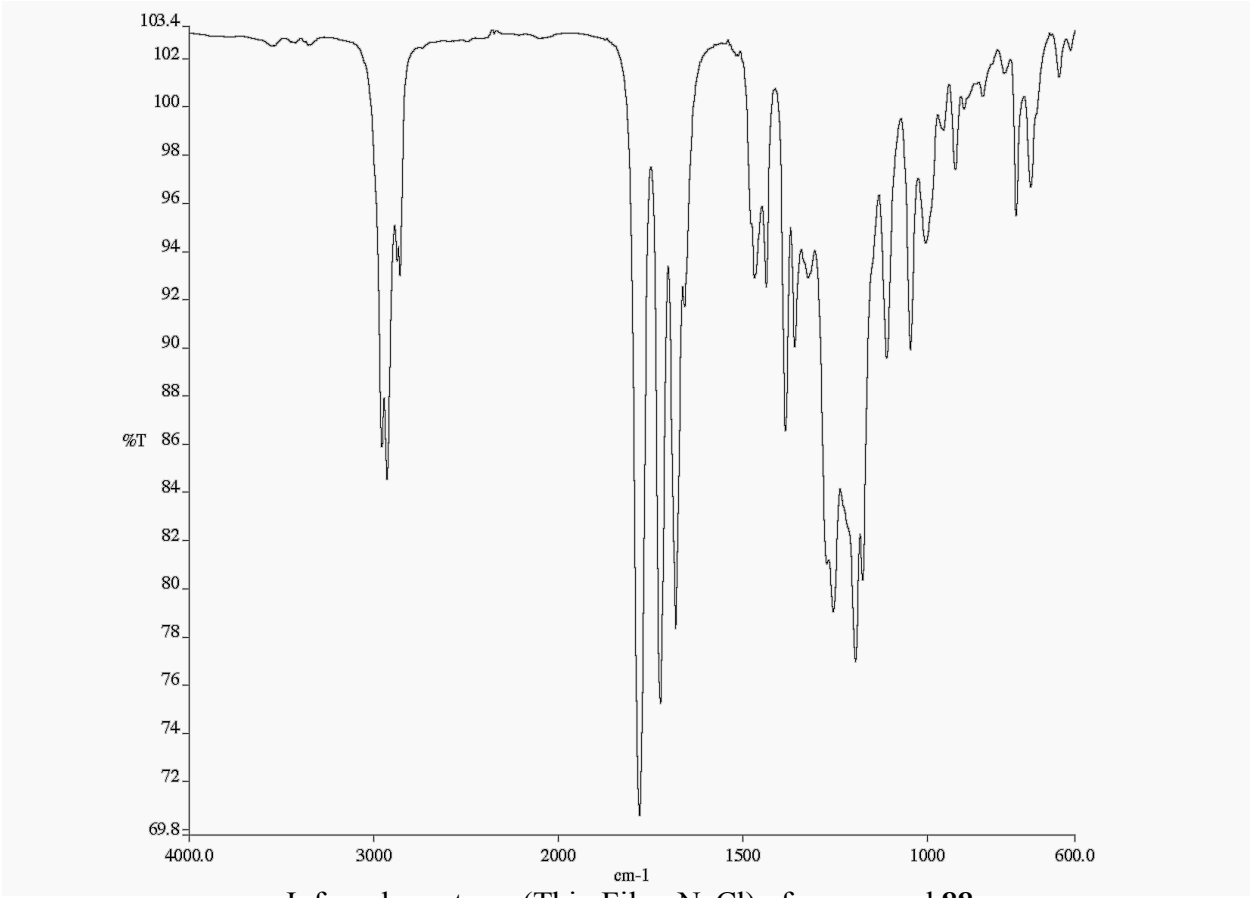
Infrared spectrum (Thin Film, NaCl) of compound **88o**.



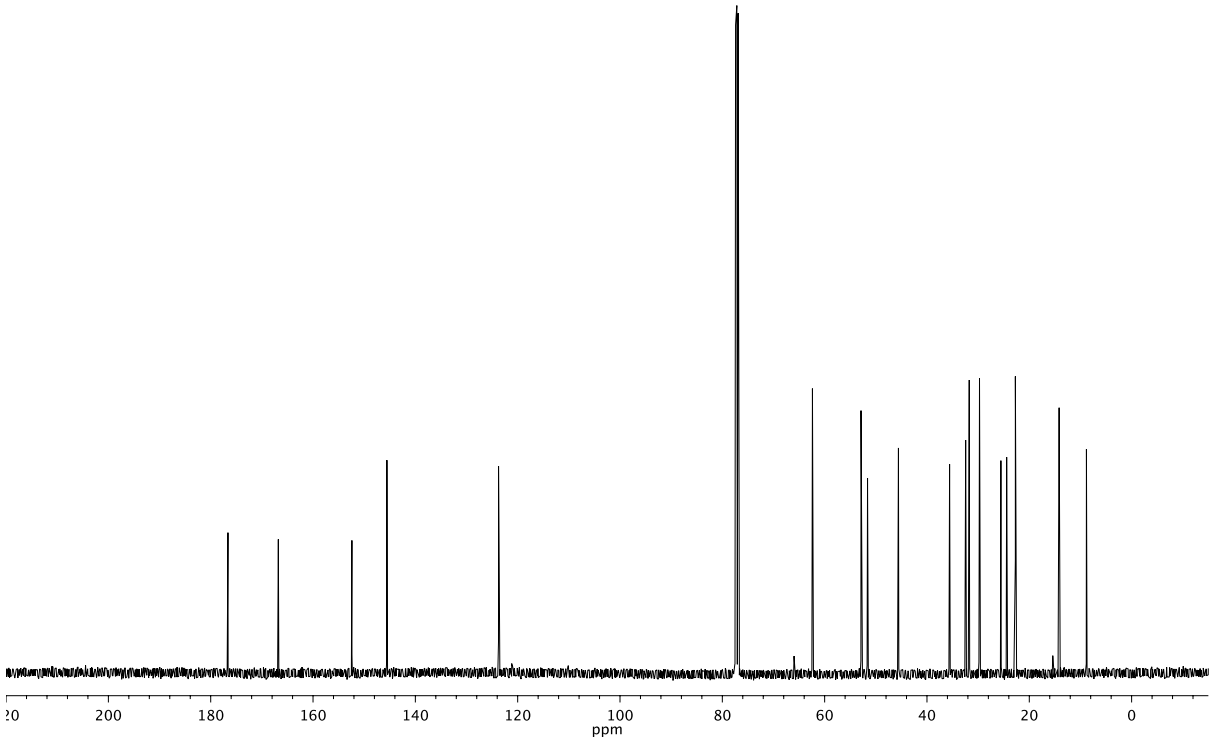
^{13}C NMR (126 MHz, $CDCl_3$) of compound **88o**.



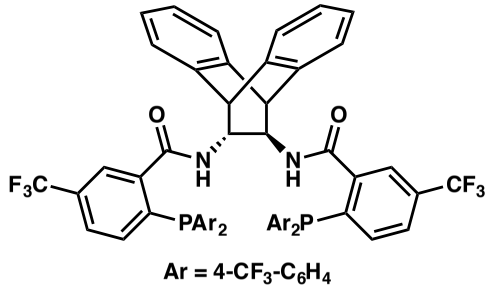
^{1}H NMR (500 MHz, $CDCl_3$) of compound **88p**.

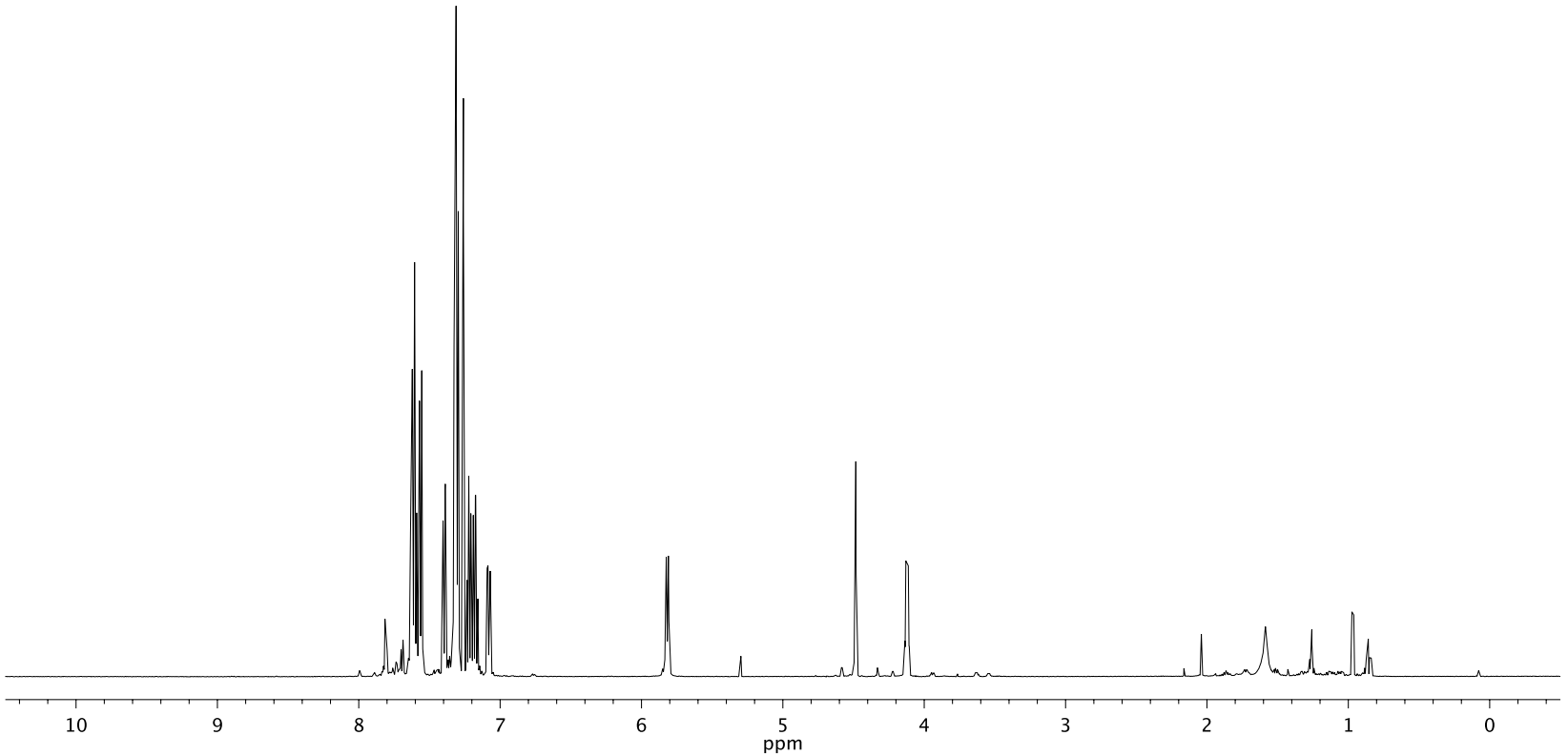


Infrared spectrum (Thin Film, NaCl) of compound **88p**.

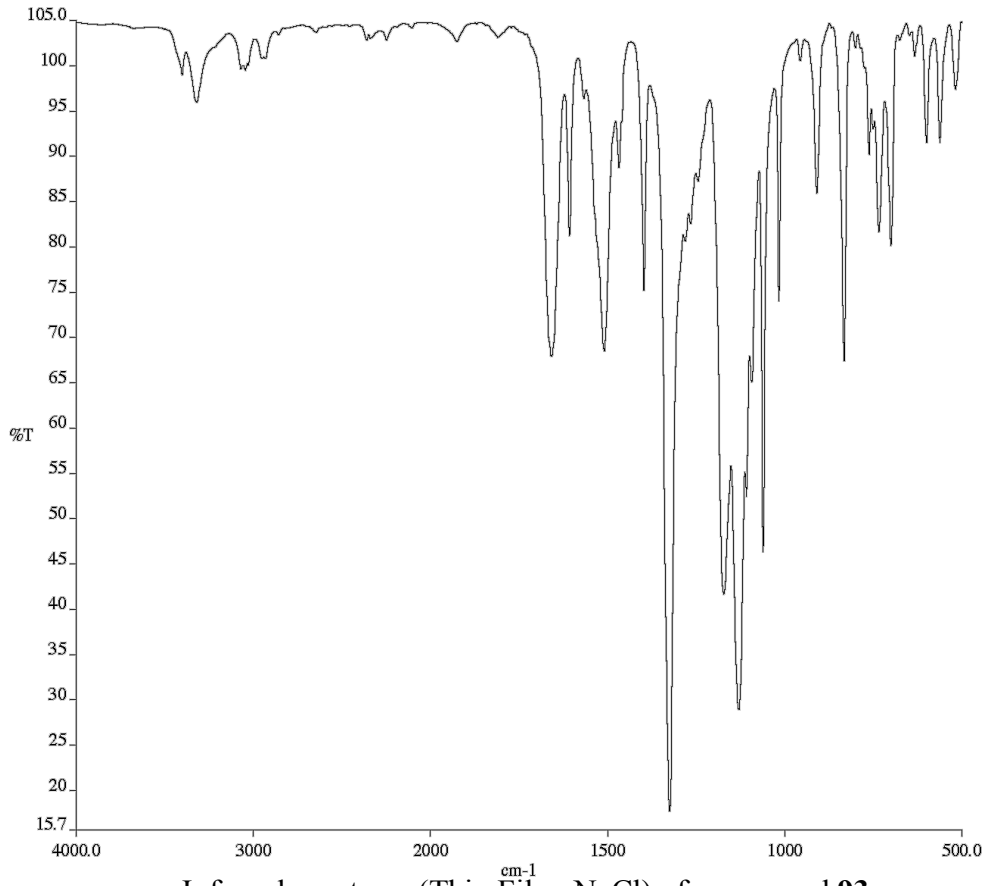


^{13}C NMR (126 MHz, $CDCl_3$) of compound **88p**.

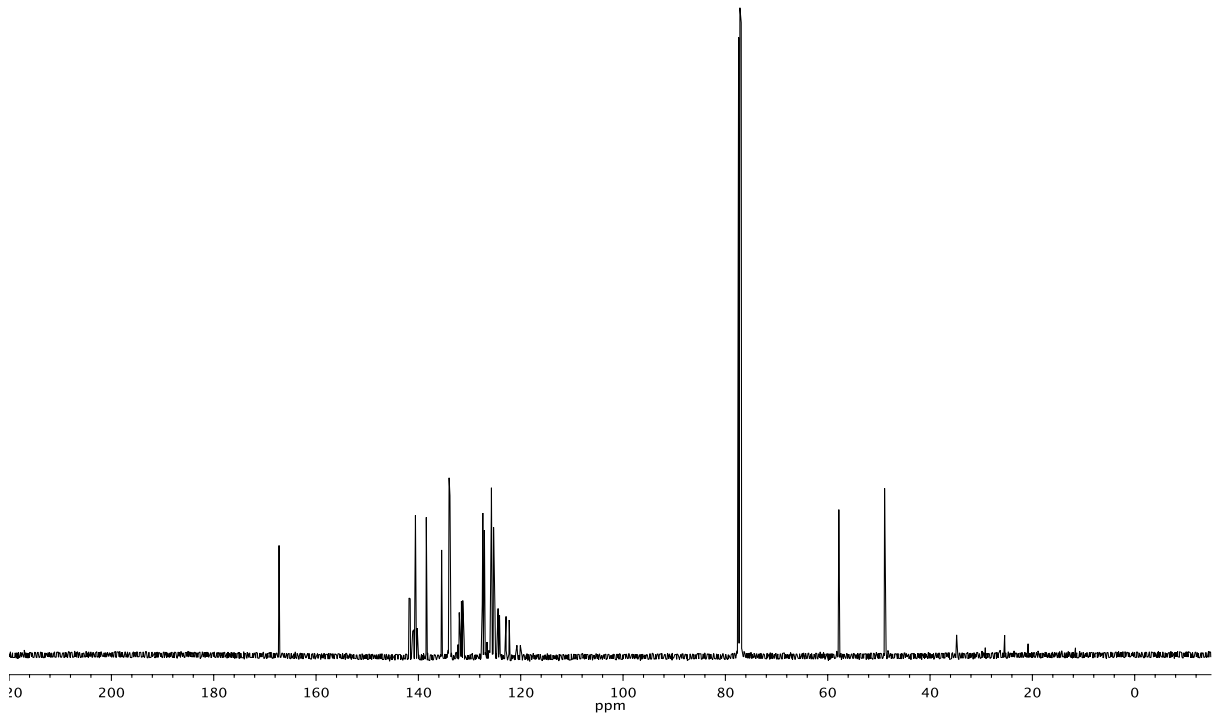




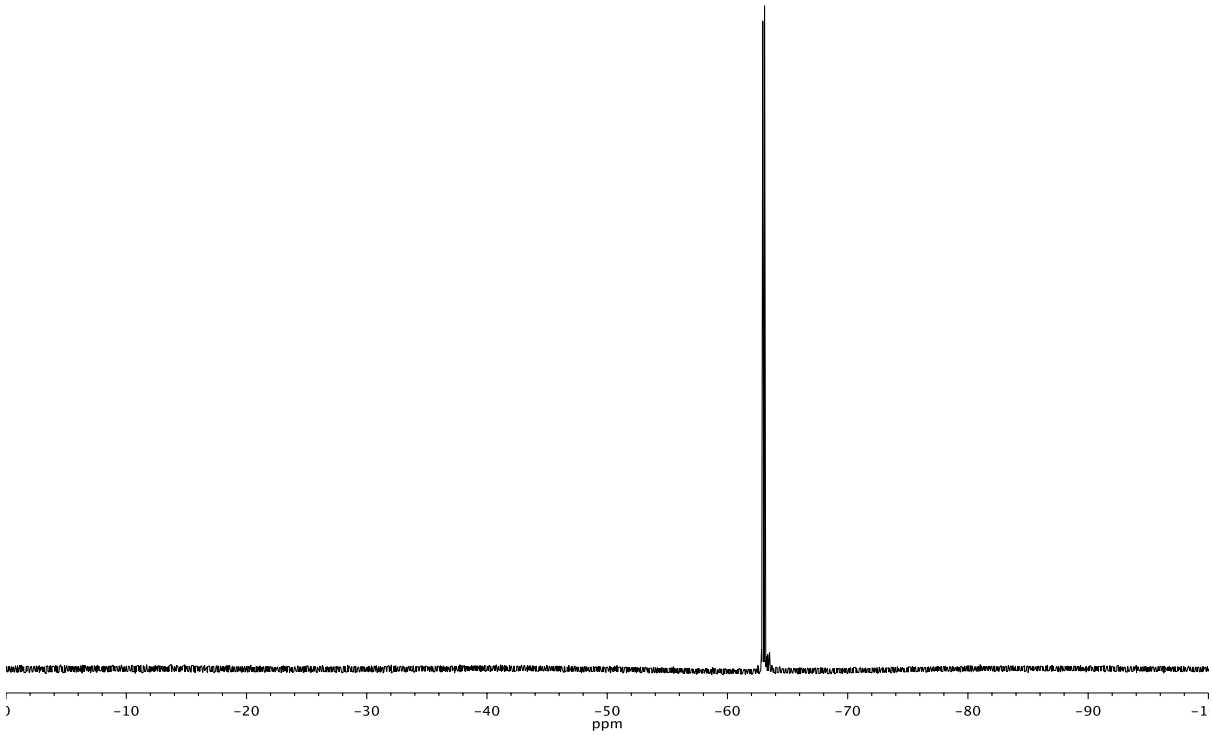
^{1}H NMR (500 MHz, $CDCl_3$) of compound **93**.



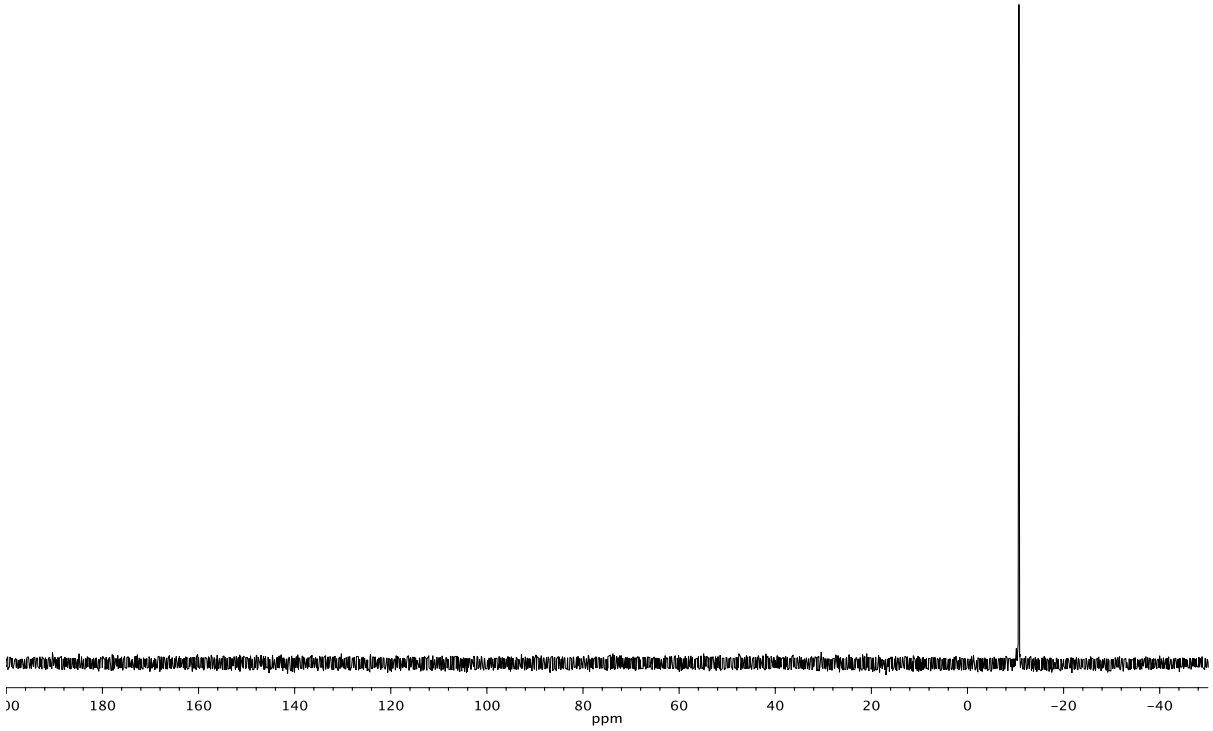
Infrared spectrum (Thin Film, NaCl) of compound **93**.



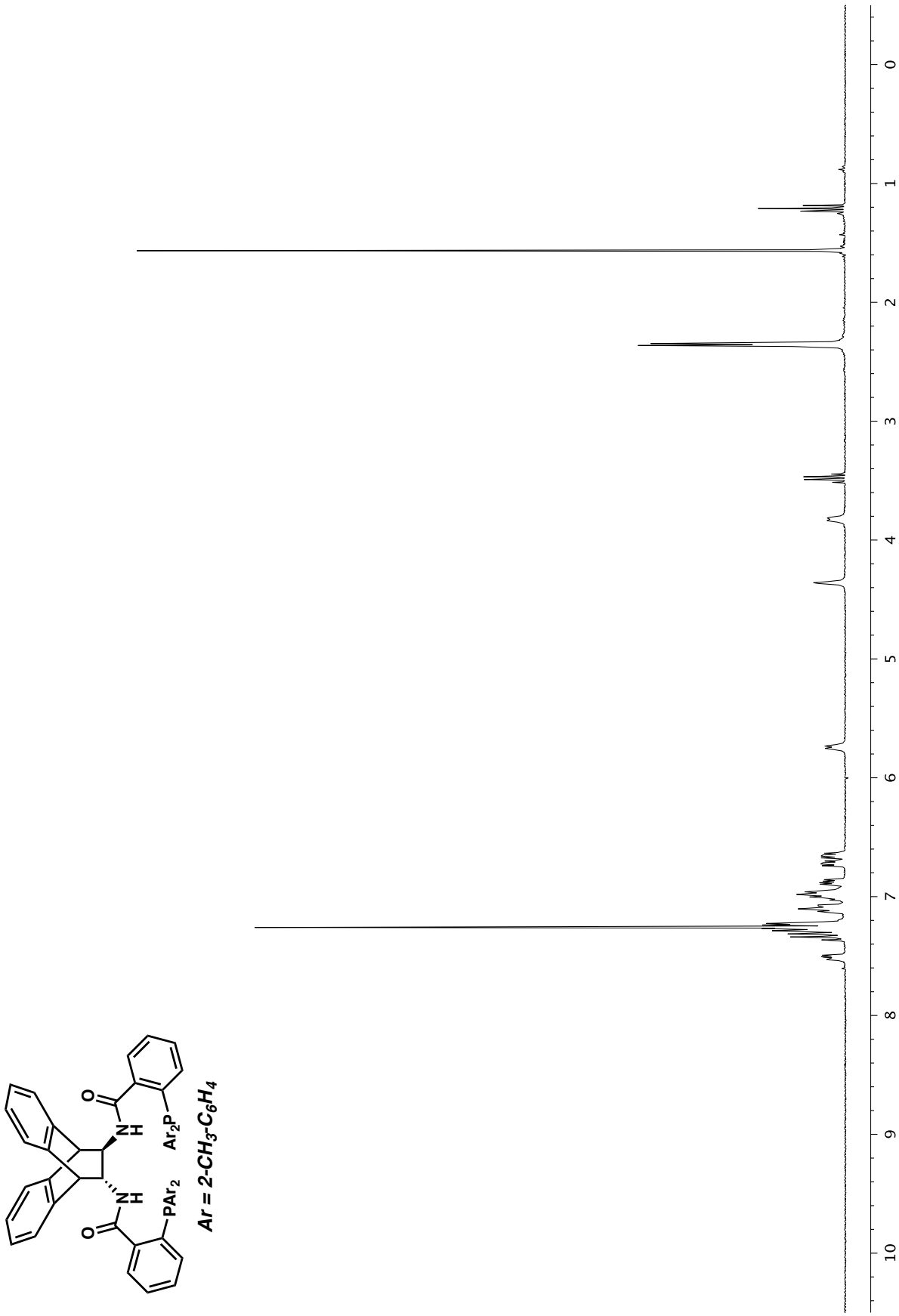
^{13}C NMR (126 MHz, $CDCl_3$) of compound **93**.



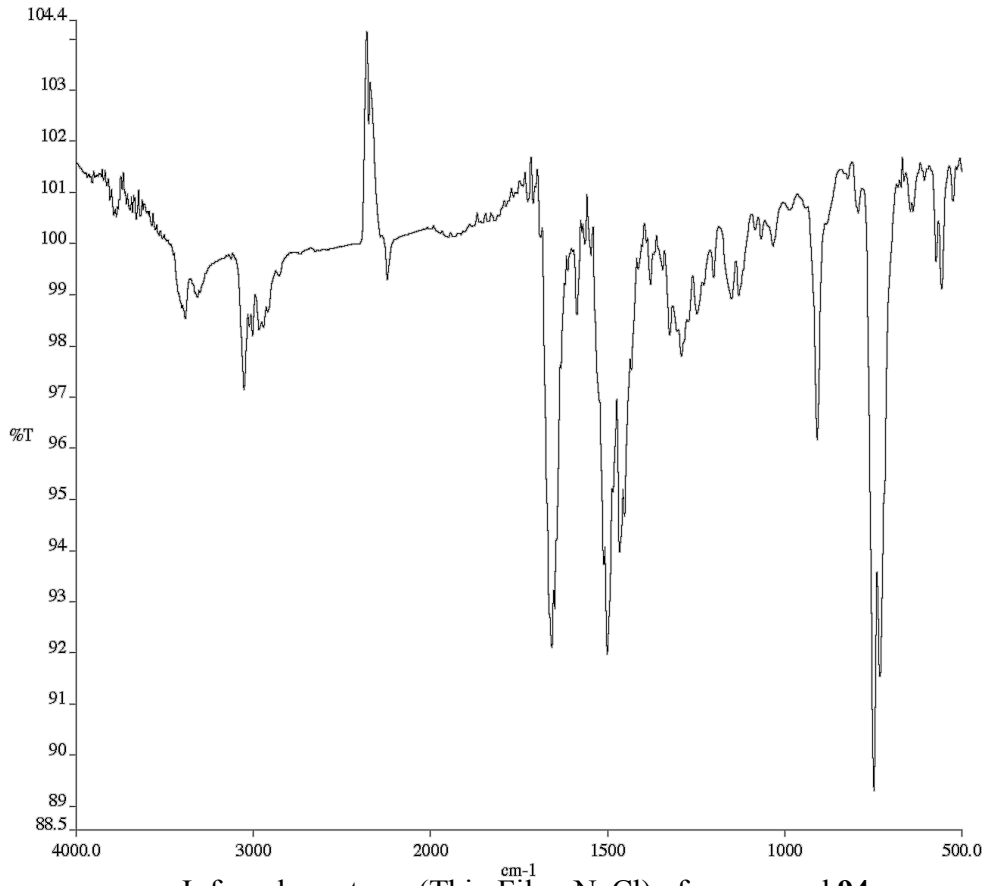
^{19}F NMR (282 MHz, $CDCl_3$) of compound **93**.



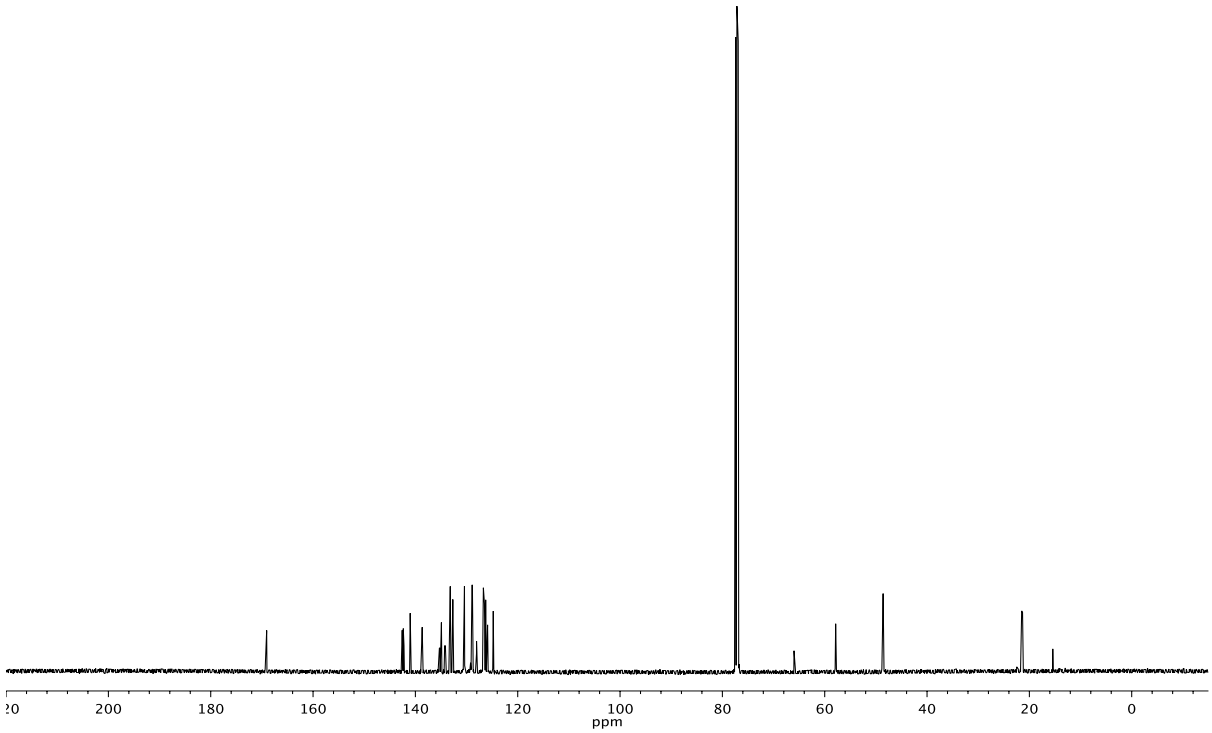
^{31}P NMR (121 MHz, $CDCl_3$) of compound **93**.



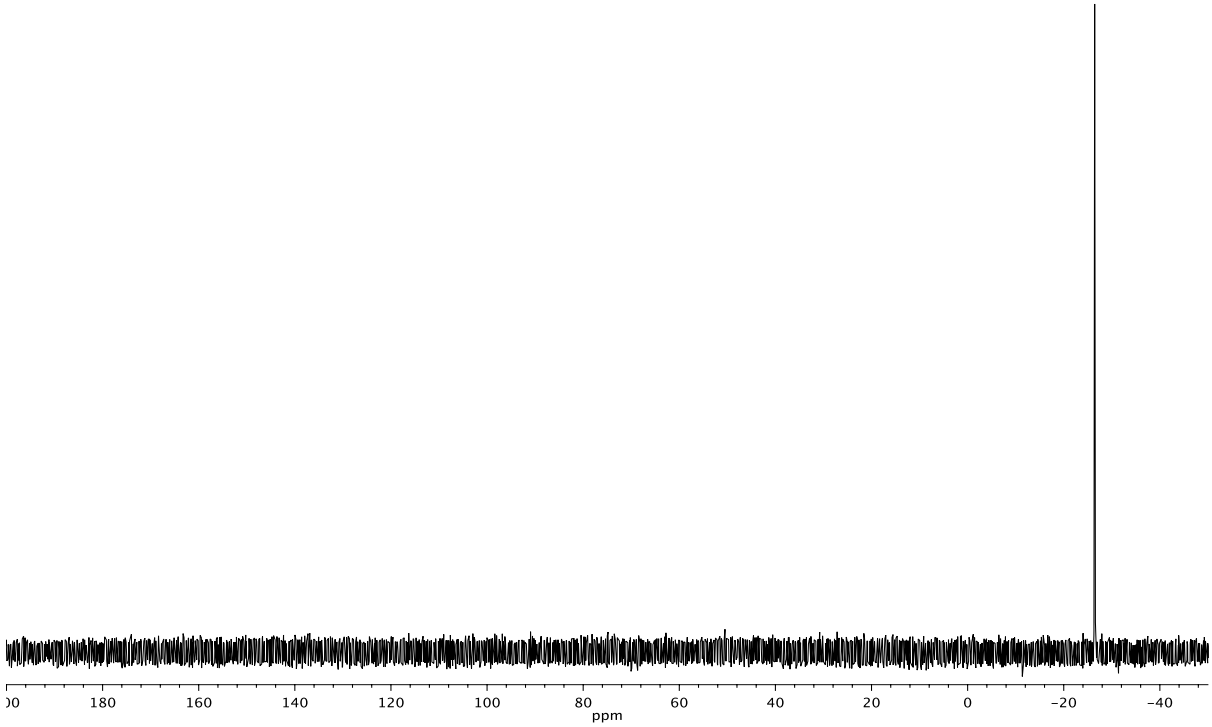
^{1}H NMR (500 MHz, $CDCl_3$) of compound **94**.



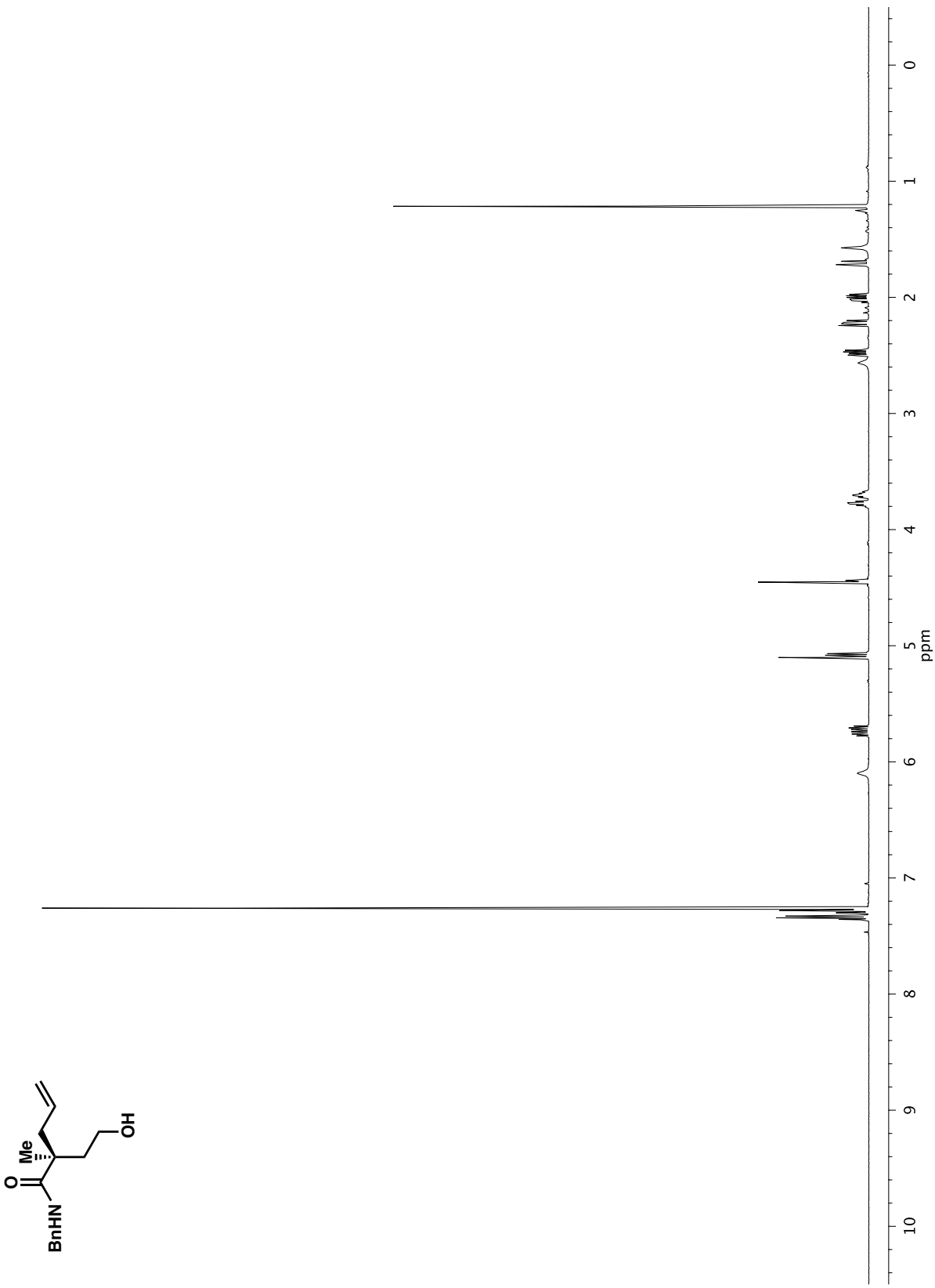
Infrared spectrum (Thin Film, NaCl) of compound **94**.



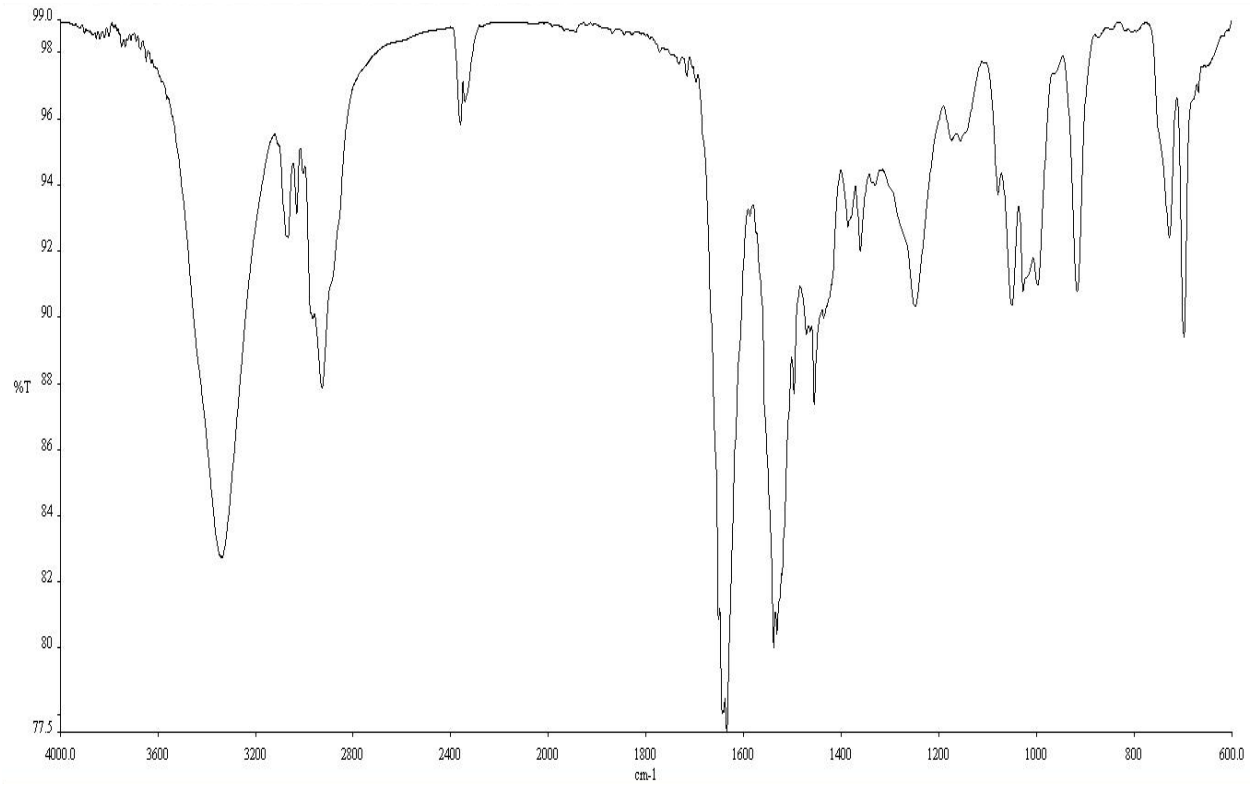
^{13}C NMR (126 MHz, $CDCl_3$) of compound **94**.



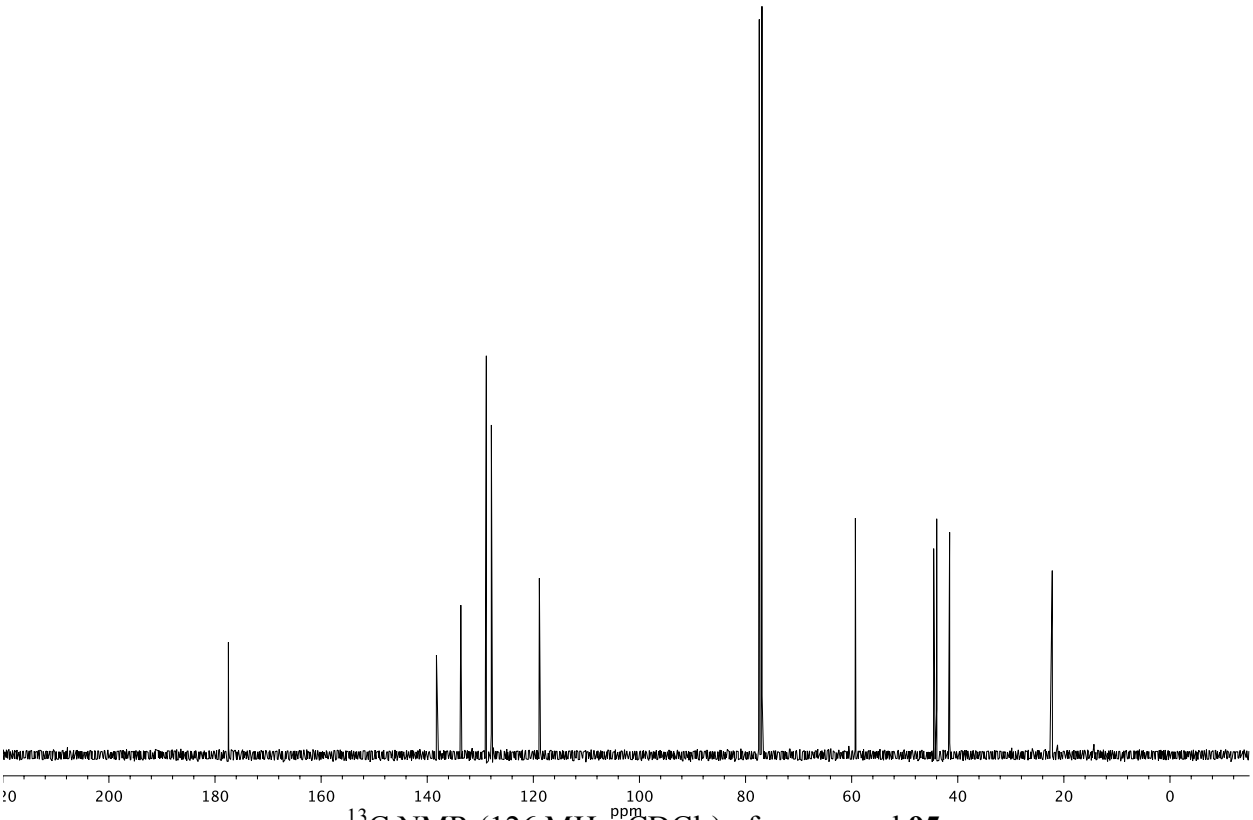
^{31}P NMR (121 MHz, $CDCl_3$) of compound **94**.



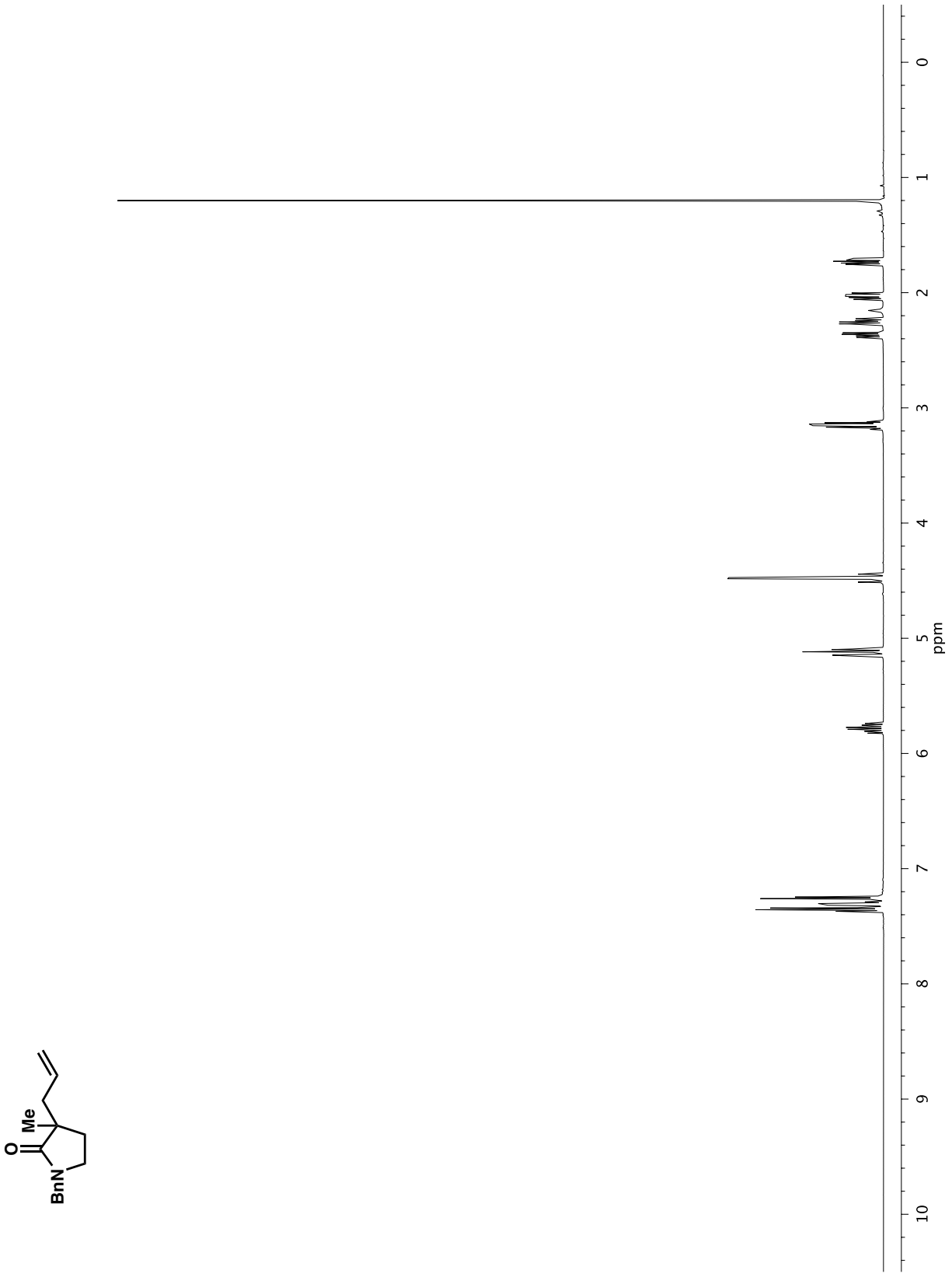
^{1}H NMR (500 MHz, $CDCl_3$) of compound **95**.



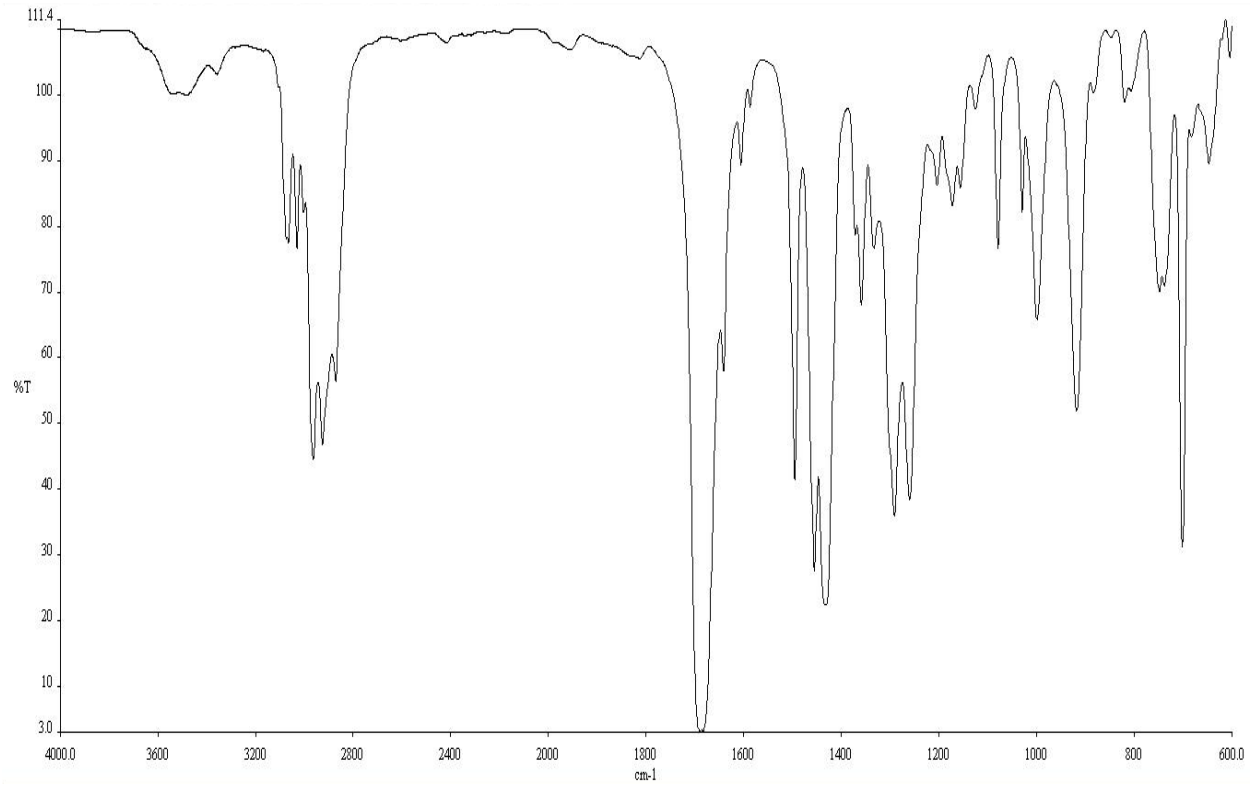
Infrared spectrum (Thin Film, NaCl) of compound **95**.



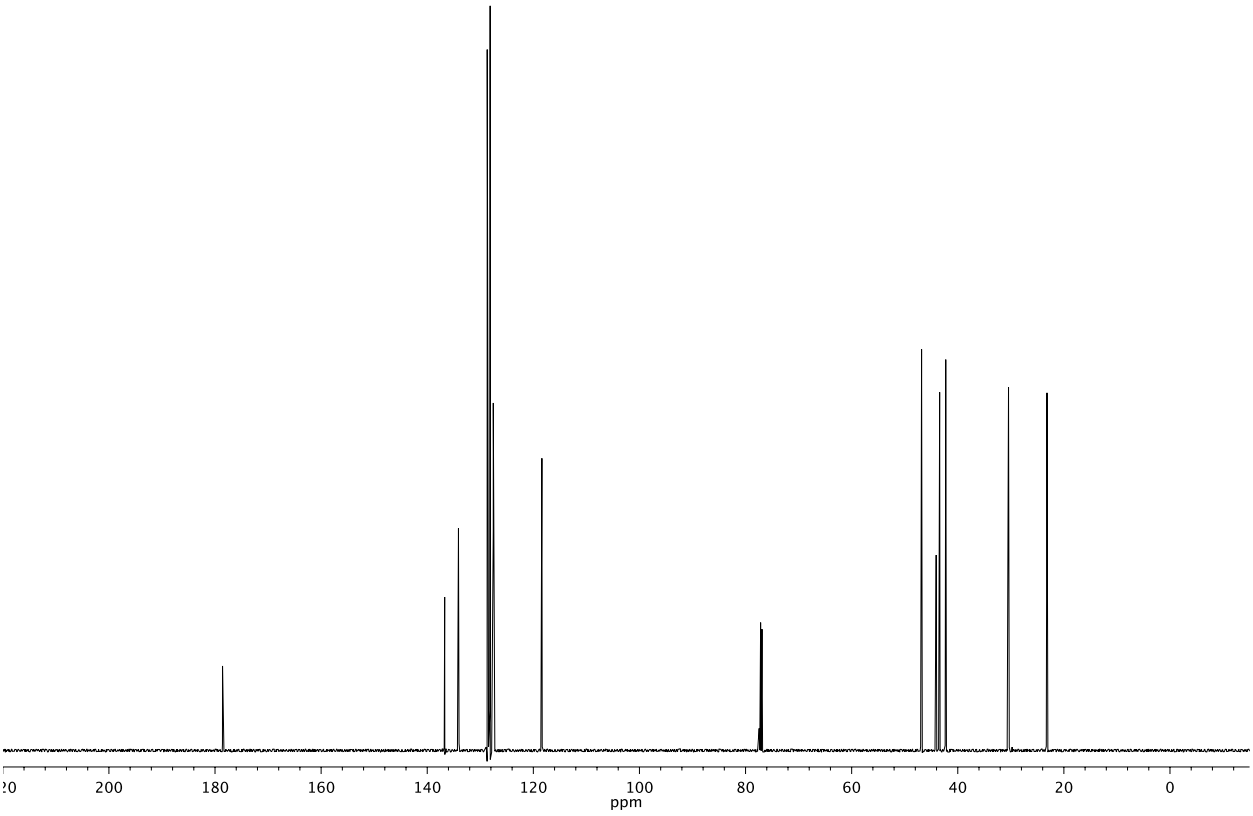
^{13}C NMR (126 MHz, $CDCl_3$) of compound **95**.



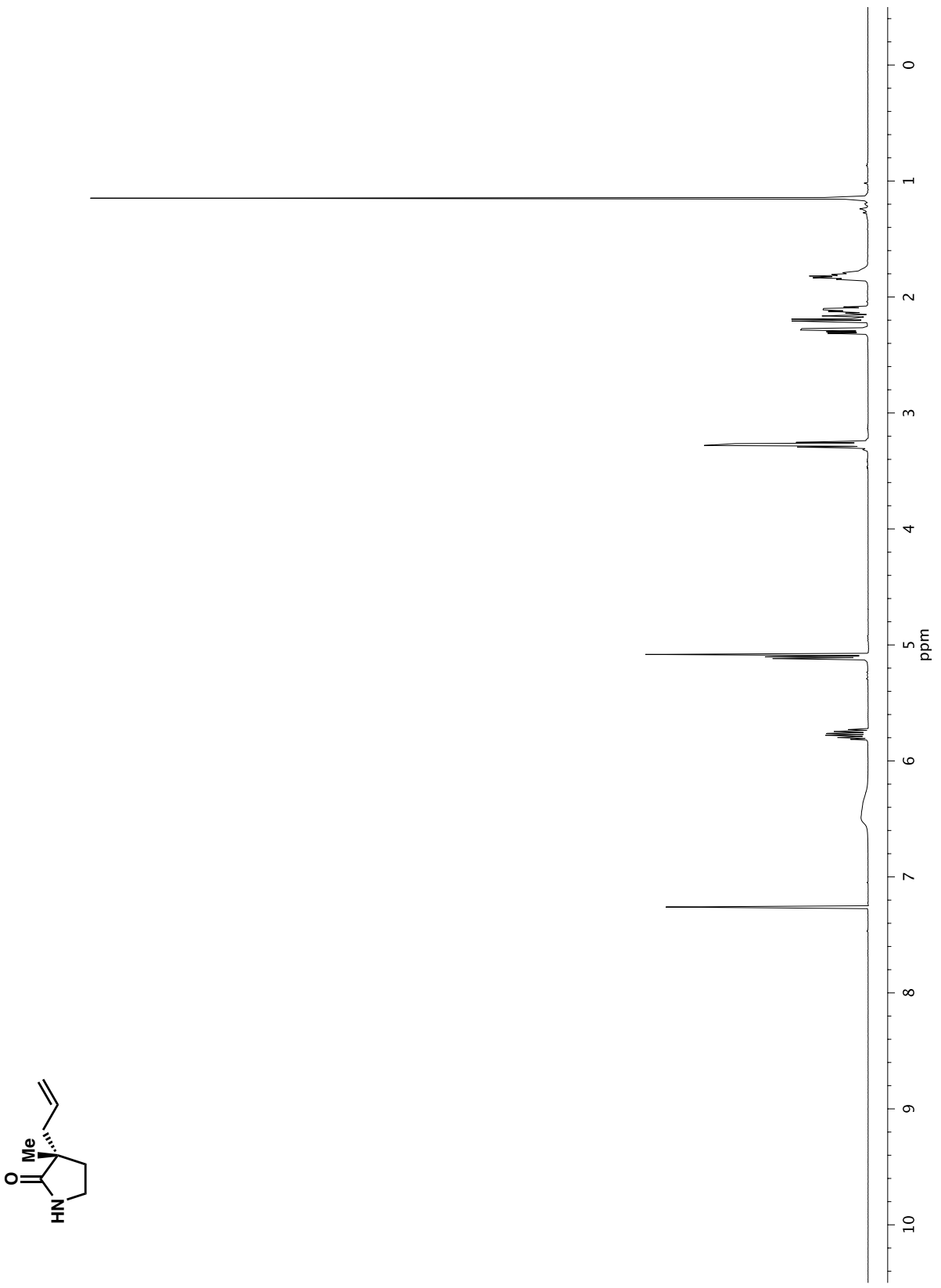
^{1}H NMR (500 MHz, $CDCl_3$) of compound **96**.



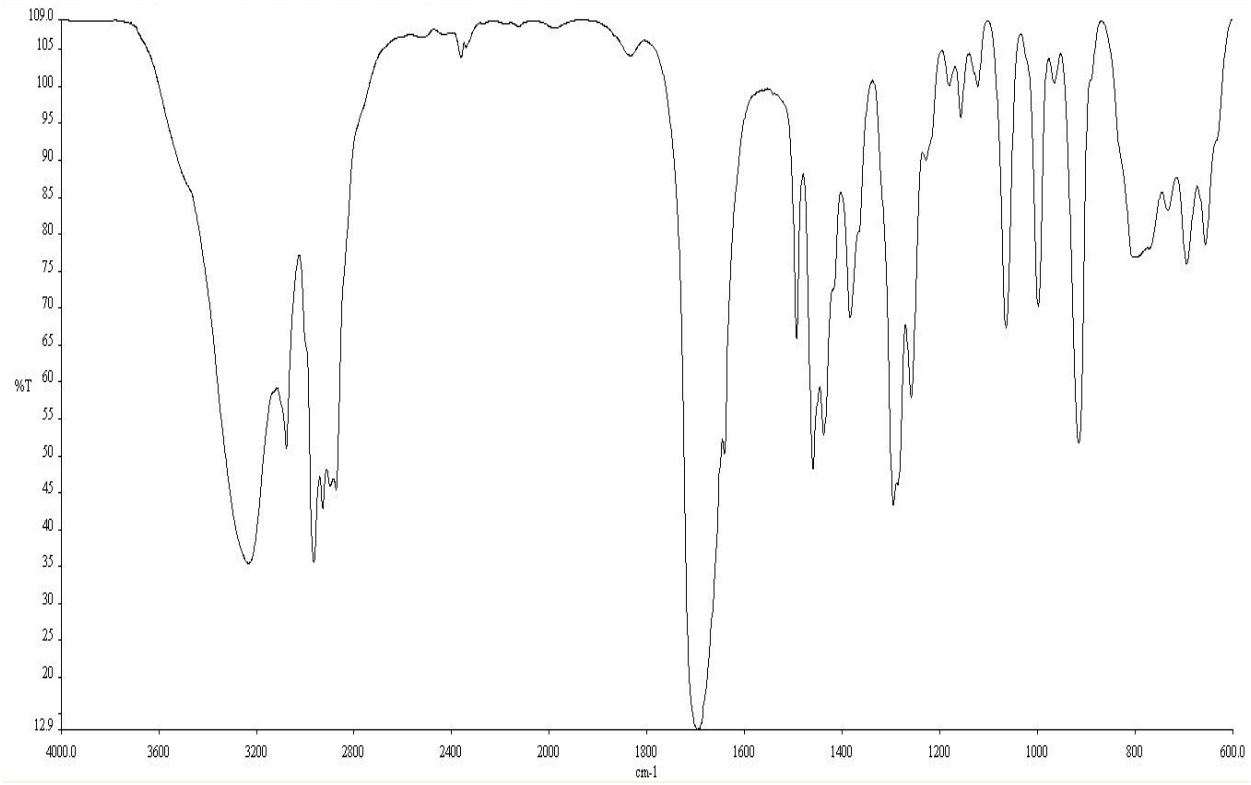
Infrared spectrum (Thin Film, NaCl) of compound **96**.



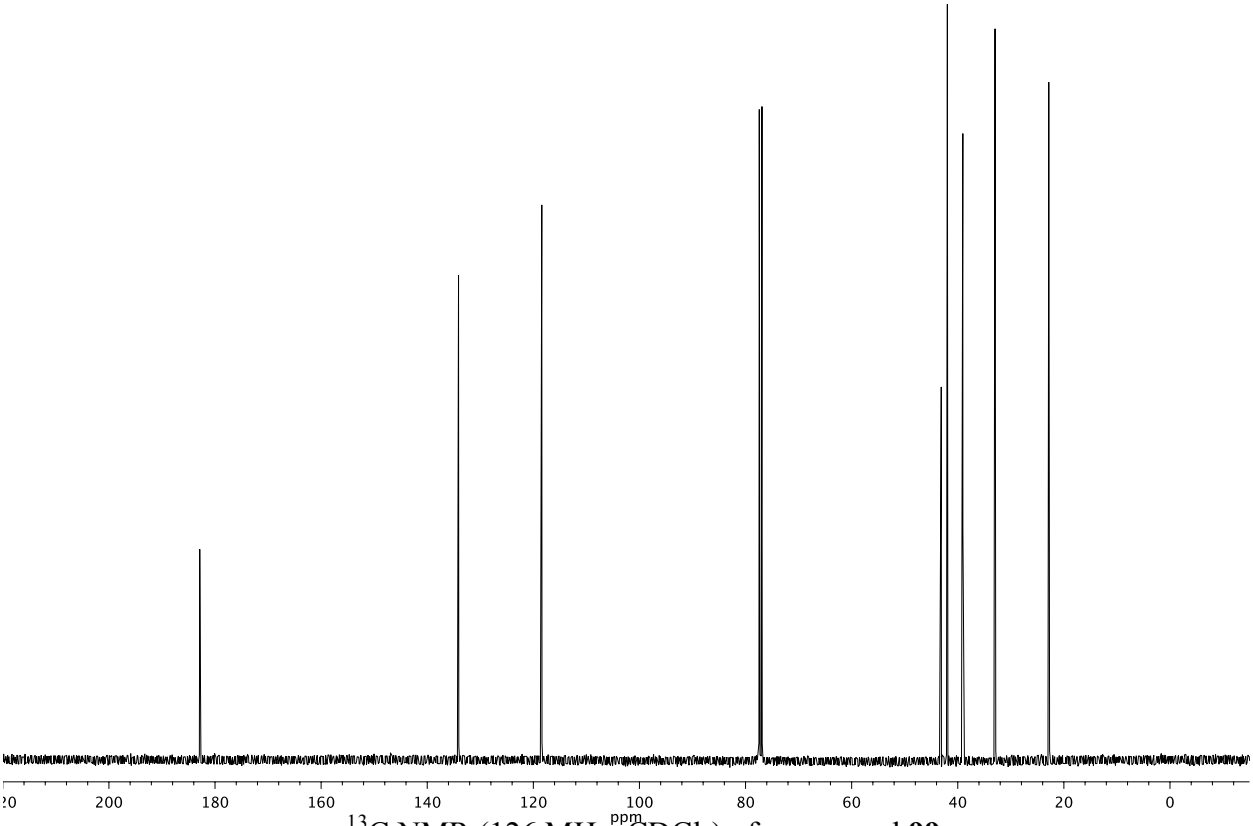
^{13}C NMR (126 MHz, $CDCl_3$) of compound **96**.



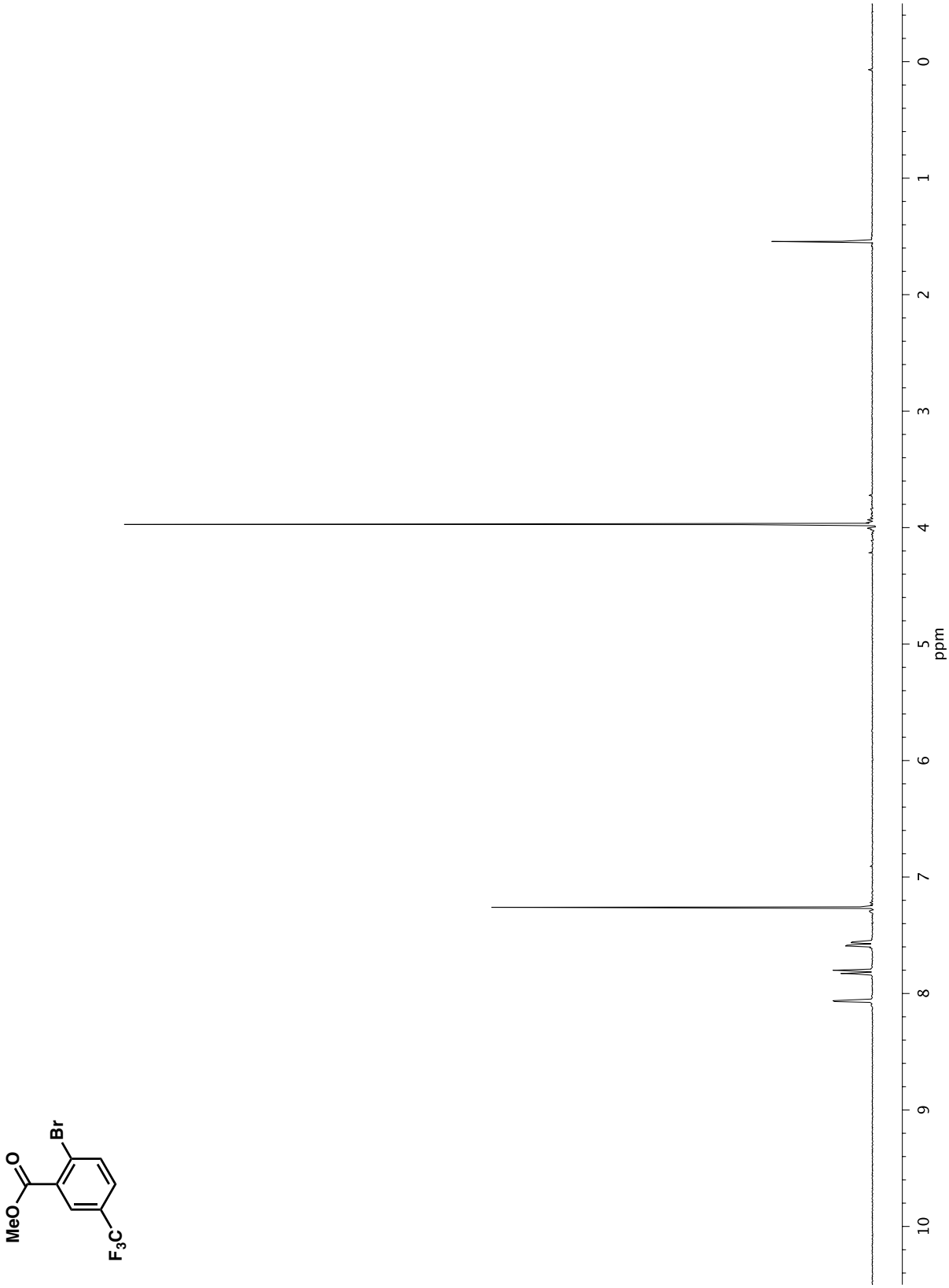
^{1}H NMR (500 MHz, $CDCl_3$) of compound **99**.



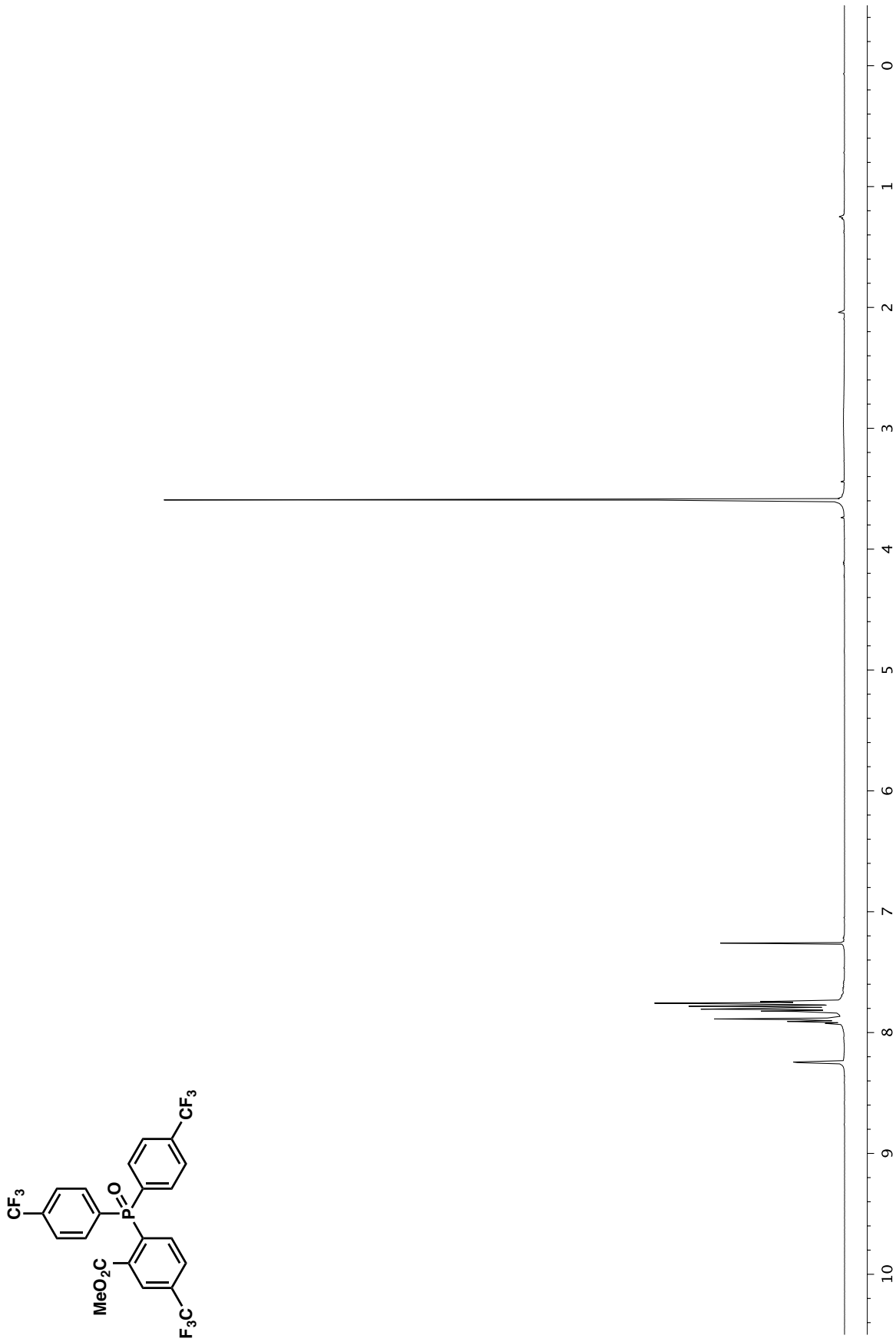
Infrared spectrum (Thin Film, NaCl) of compound **99**.



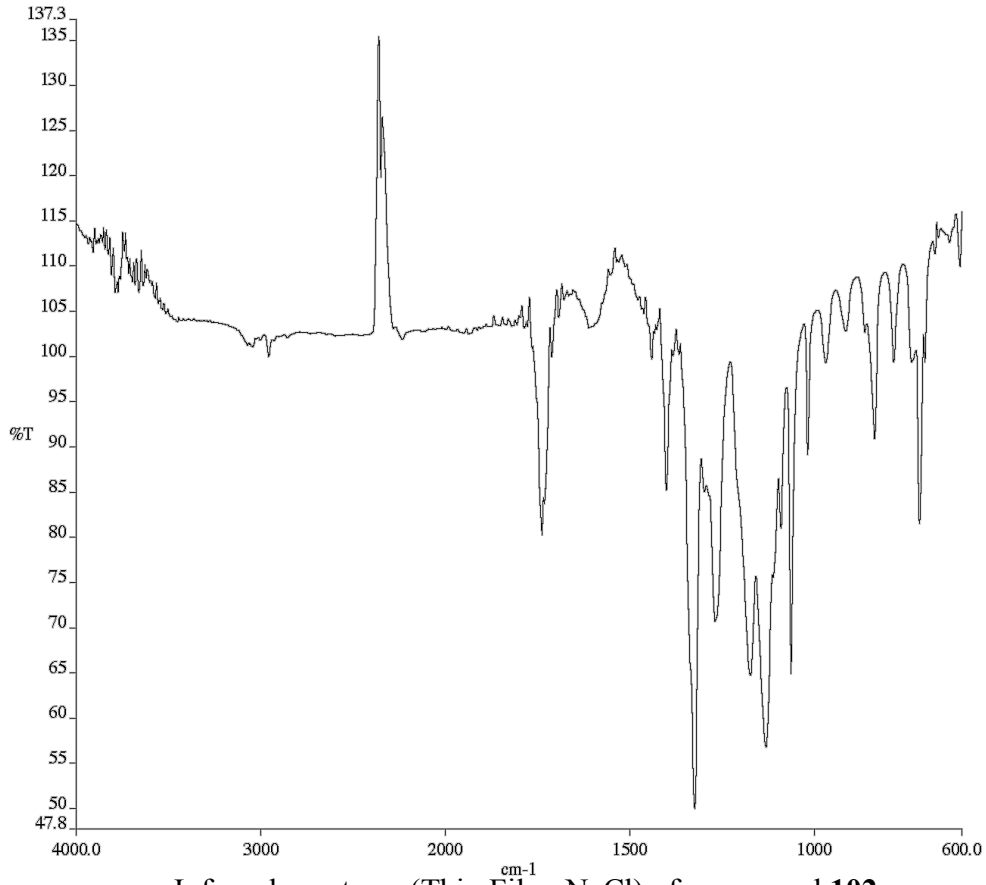
^{13}C NMR (126 MHz, $CDCl_3$) of compound **99**.



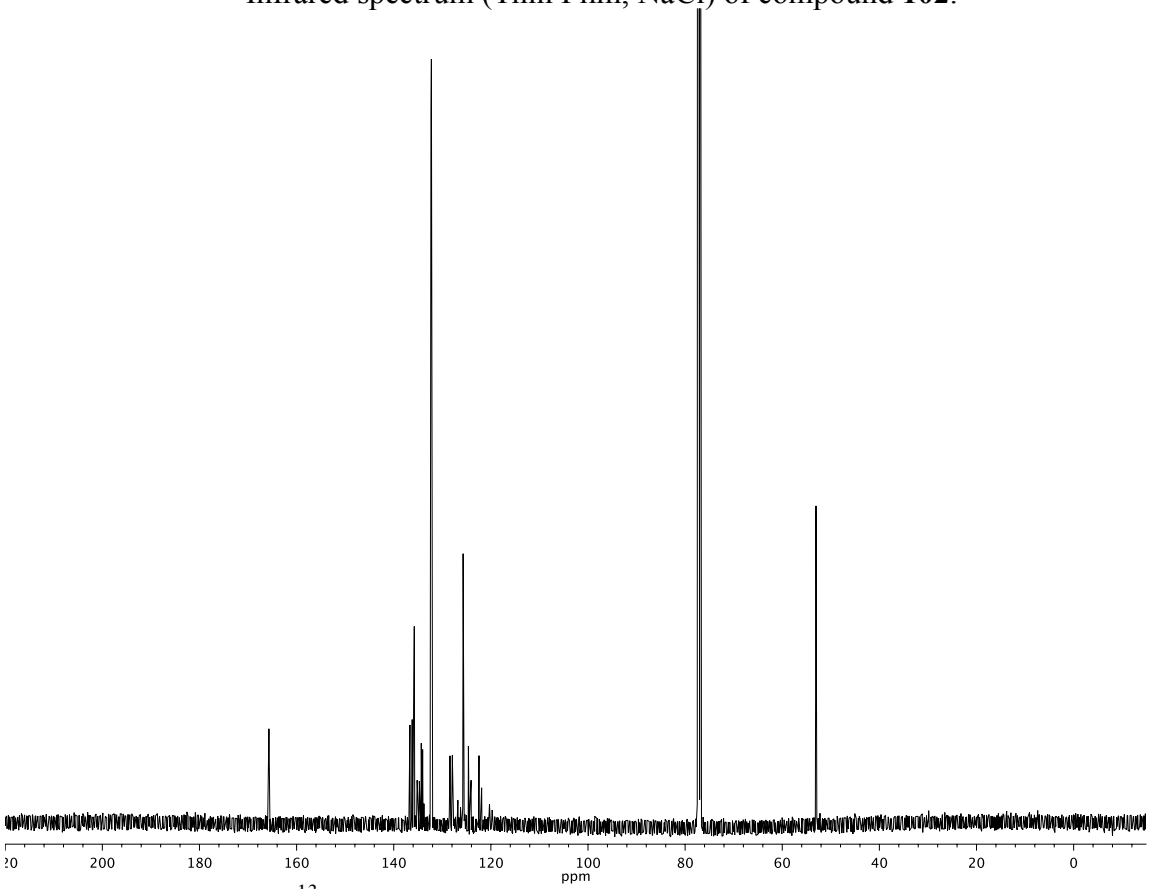
^{1}H NMR (300 MHz, $CDCl_3$) of compound **101**.



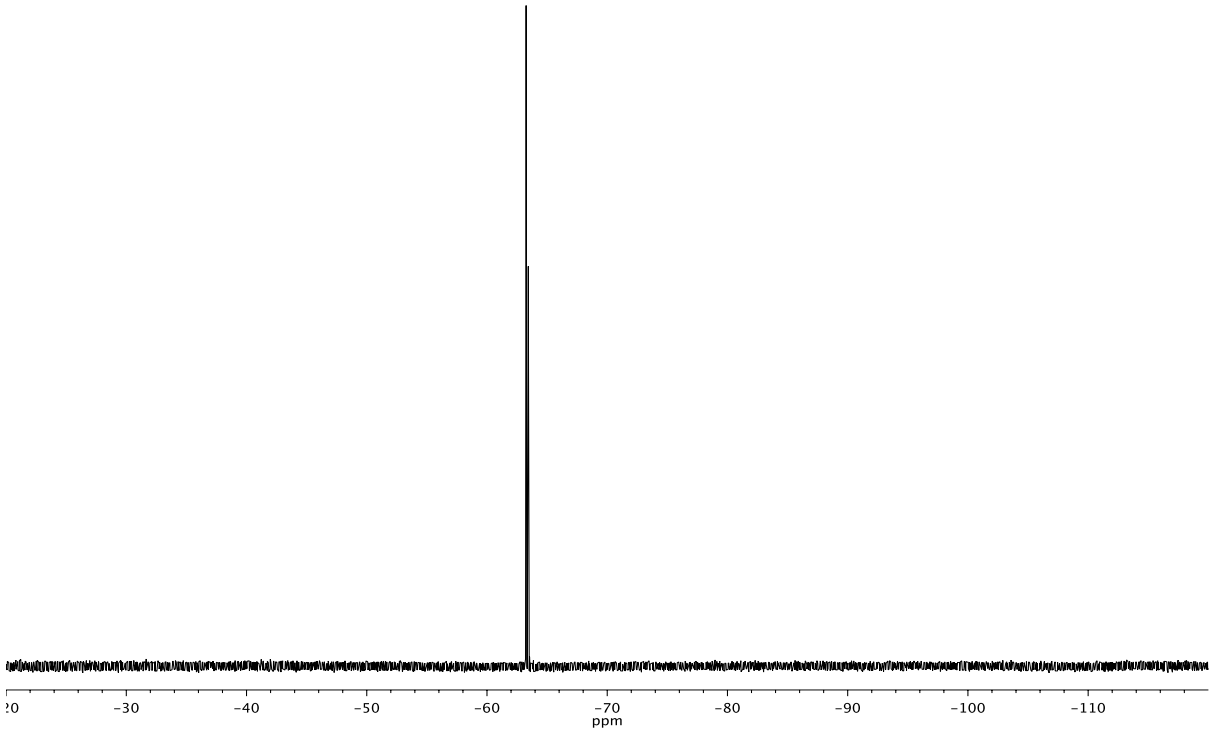
^{1}H NMR (500 MHz, $CDCl_3$) of compound **102**.



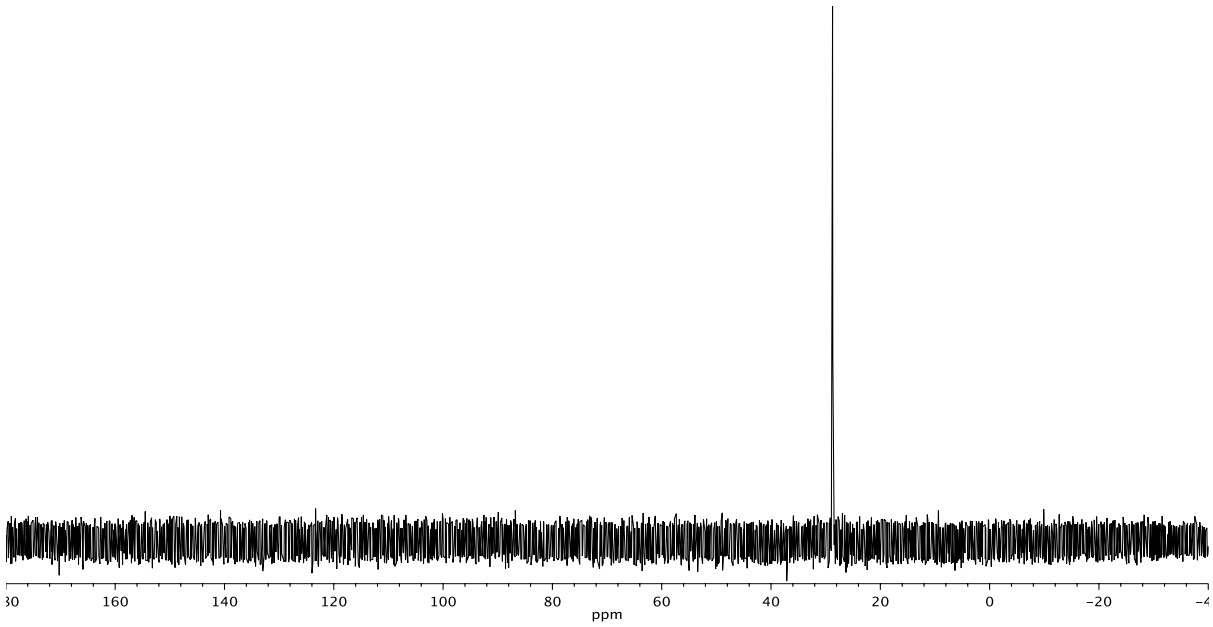
Infrared spectrum (Thin Film, NaCl) of compound **102**.



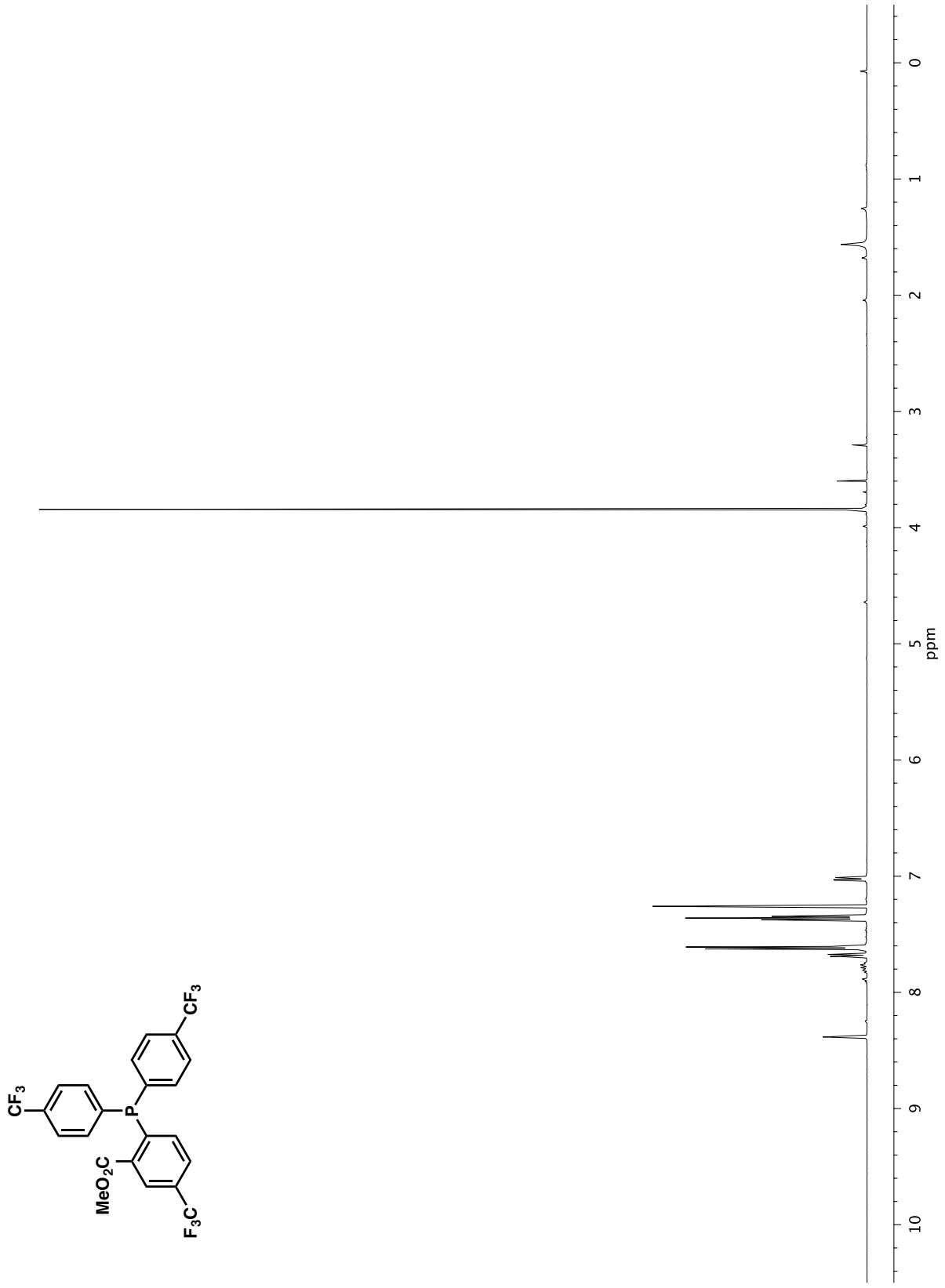
^{13}C NMR (126 MHz, $CDCl_3$) of compound **102**.



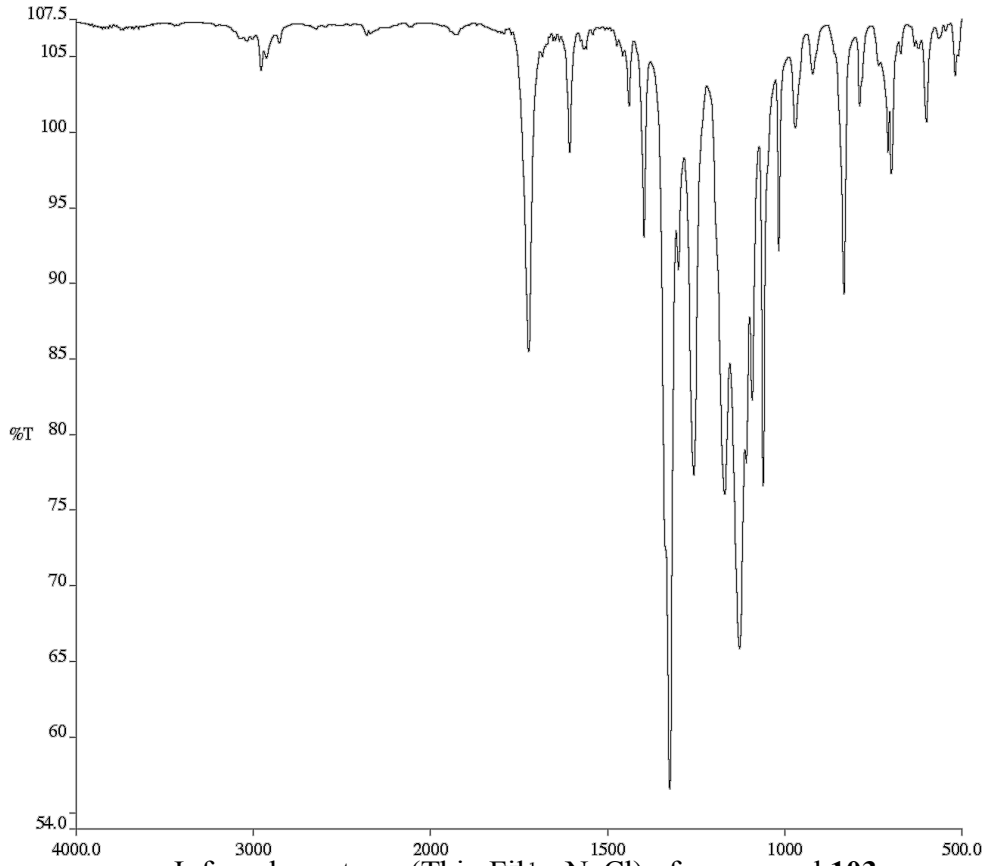
^{19}F NMR (282 MHz, $CDCl_3$) of compound **102**.



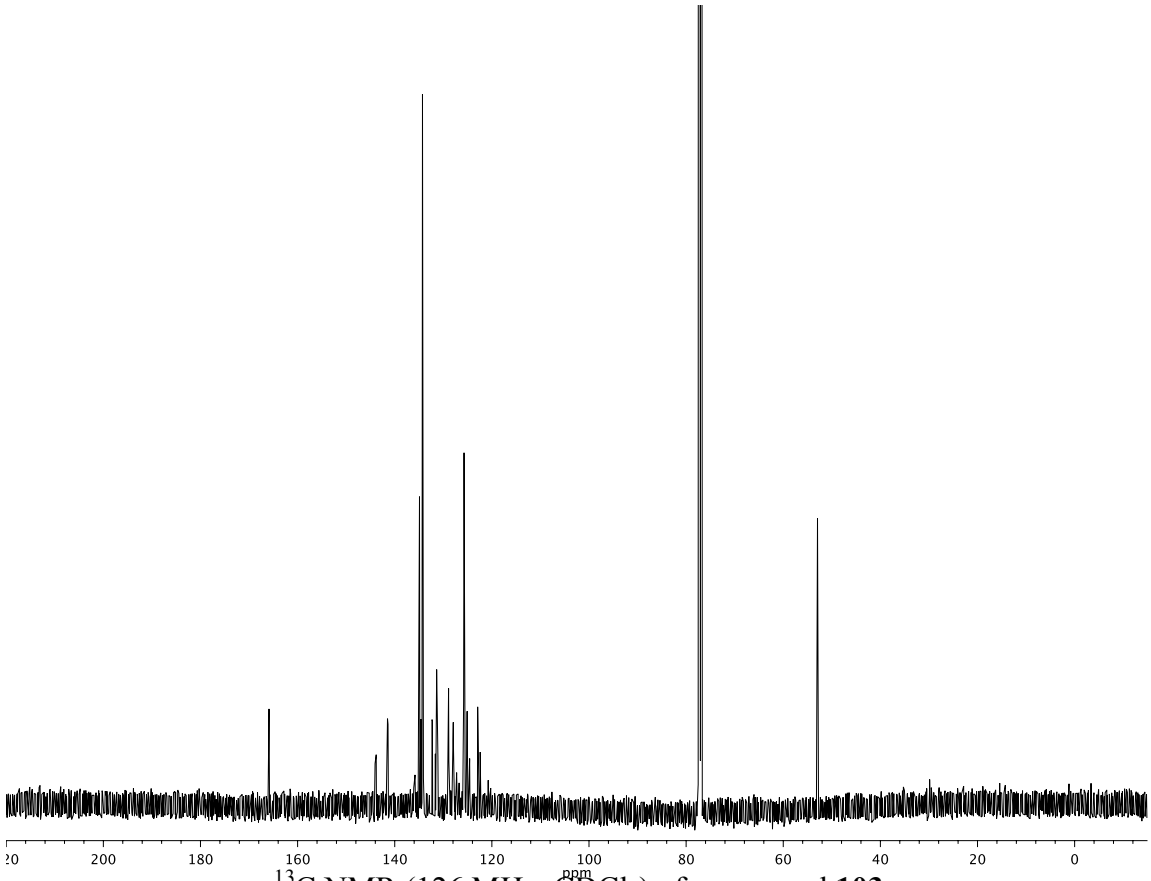
^{31}P NMR (121 MHz, $CDCl_3$) of compound **102**.



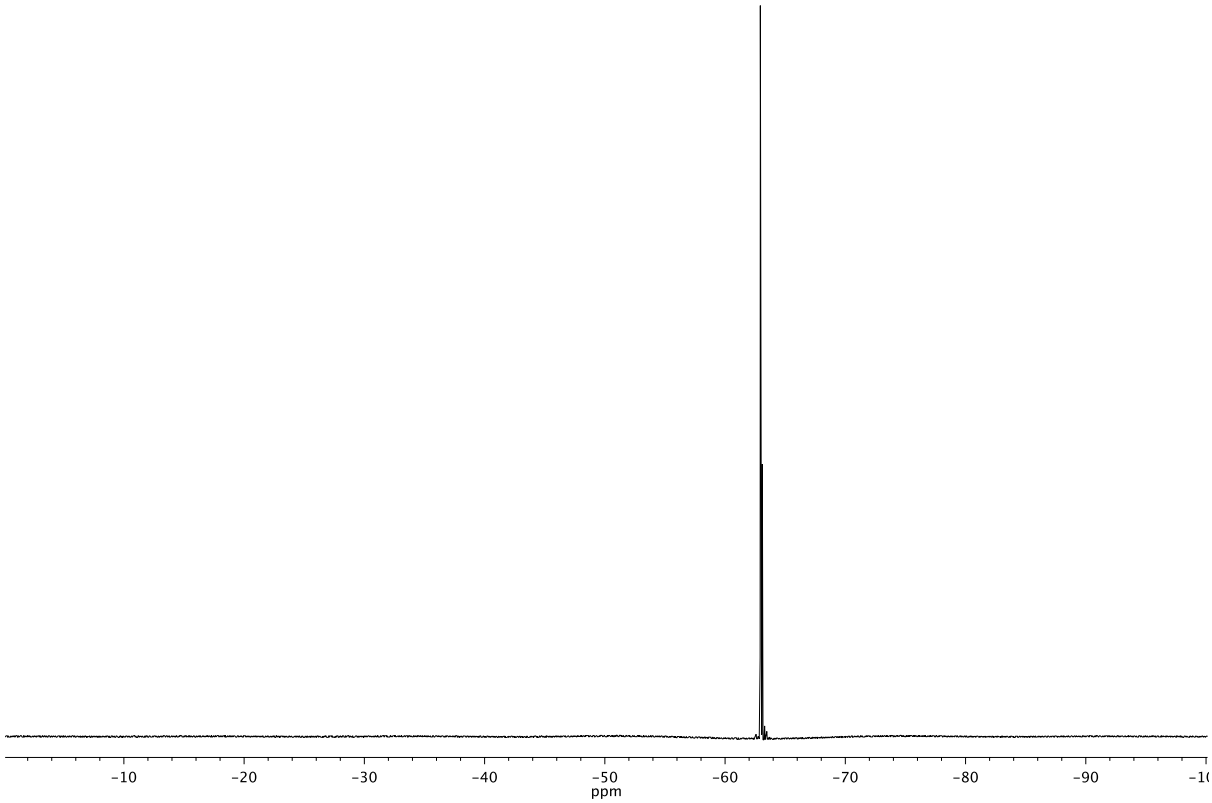
^{1}H NMR (500 MHz, $CDCl_3$) of compound **103**.



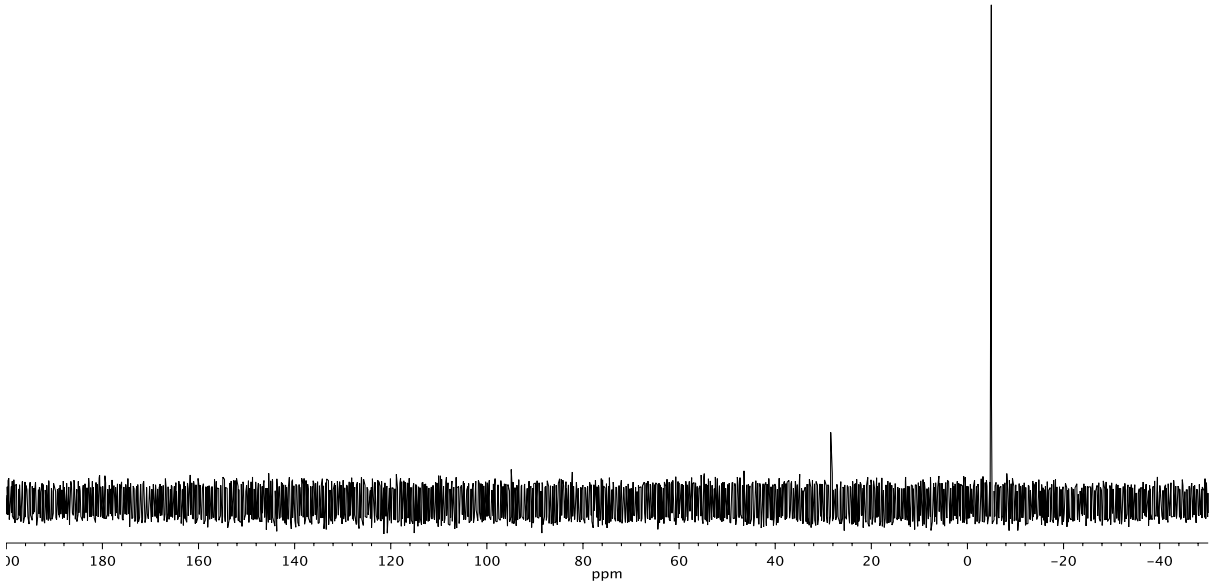
Infrared spectrum (Thin Film, NaCl) of compound **103**.



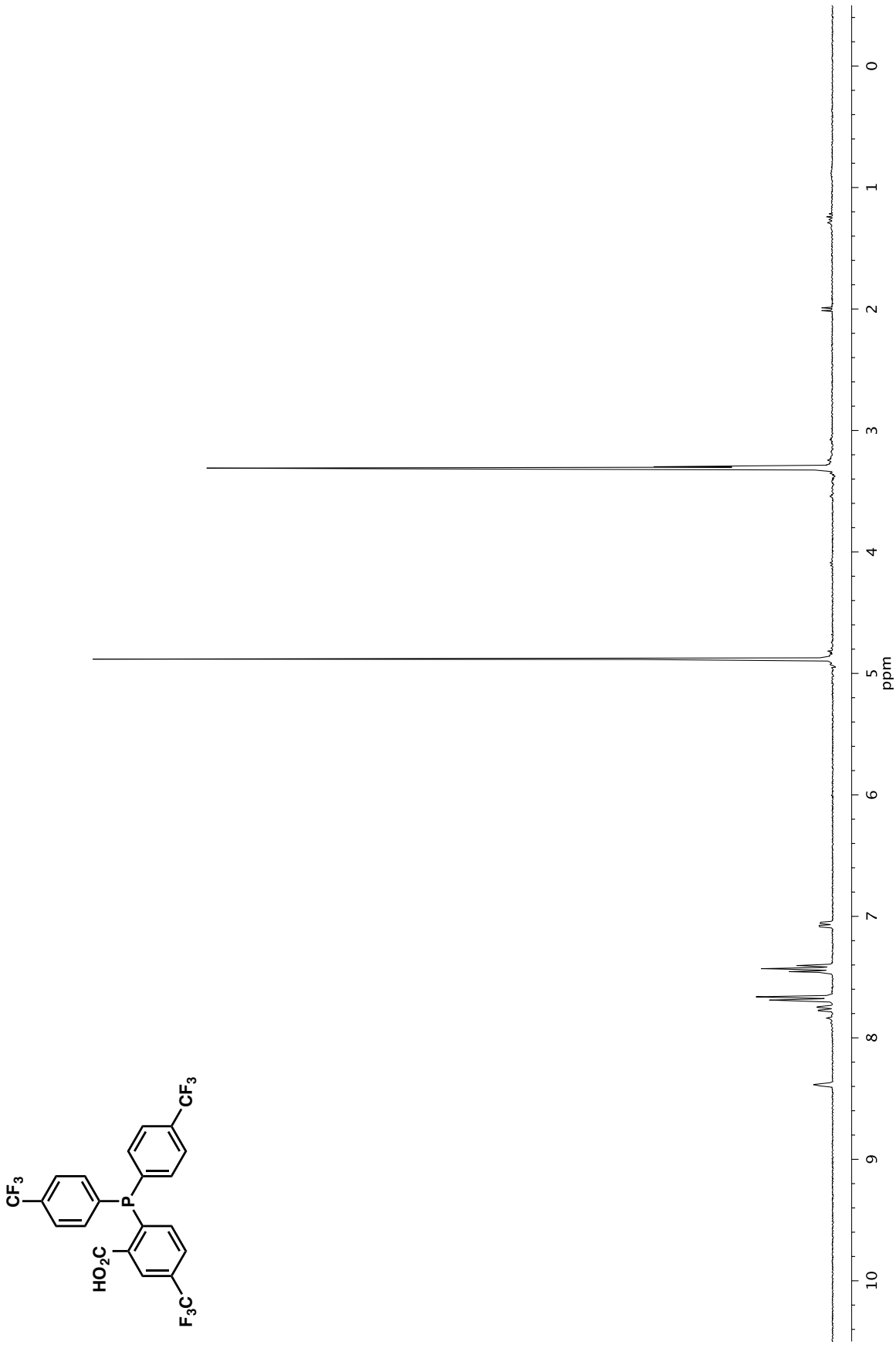
^{13}C NMR (126 MHz, $CDCl_3$) of compound **103**.



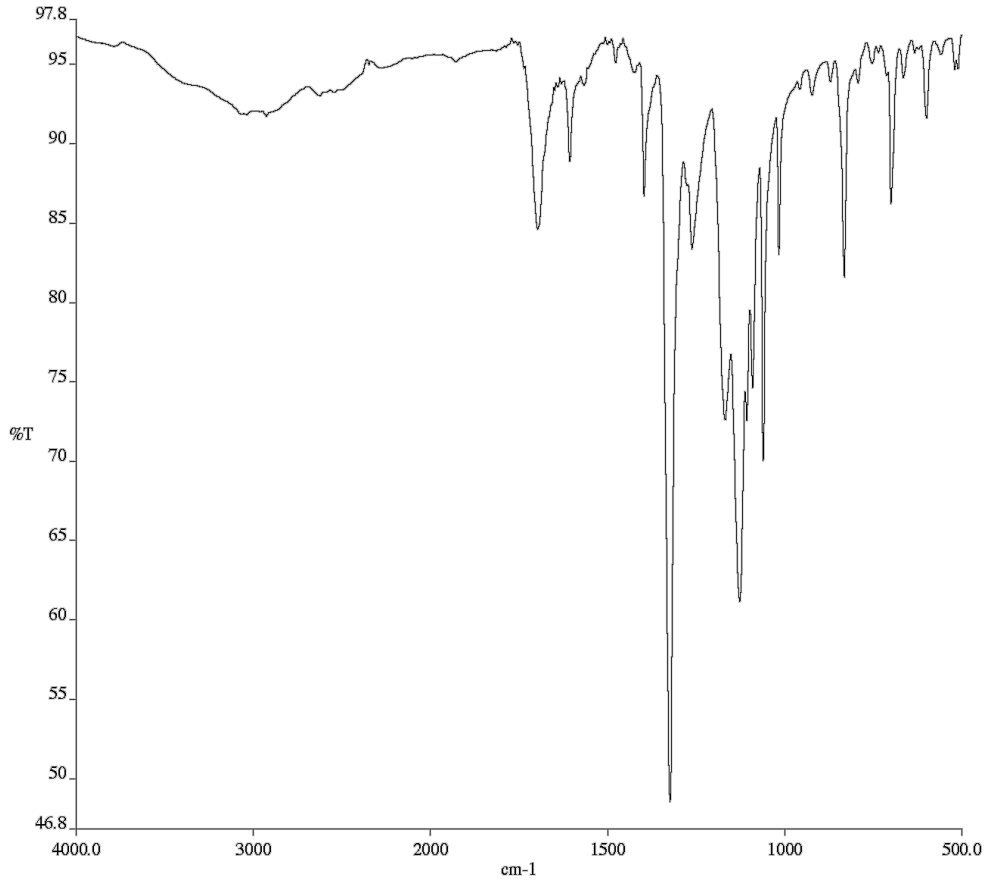
^{19}F NMR (282 MHz, $CDCl_3$) of compound **103**.



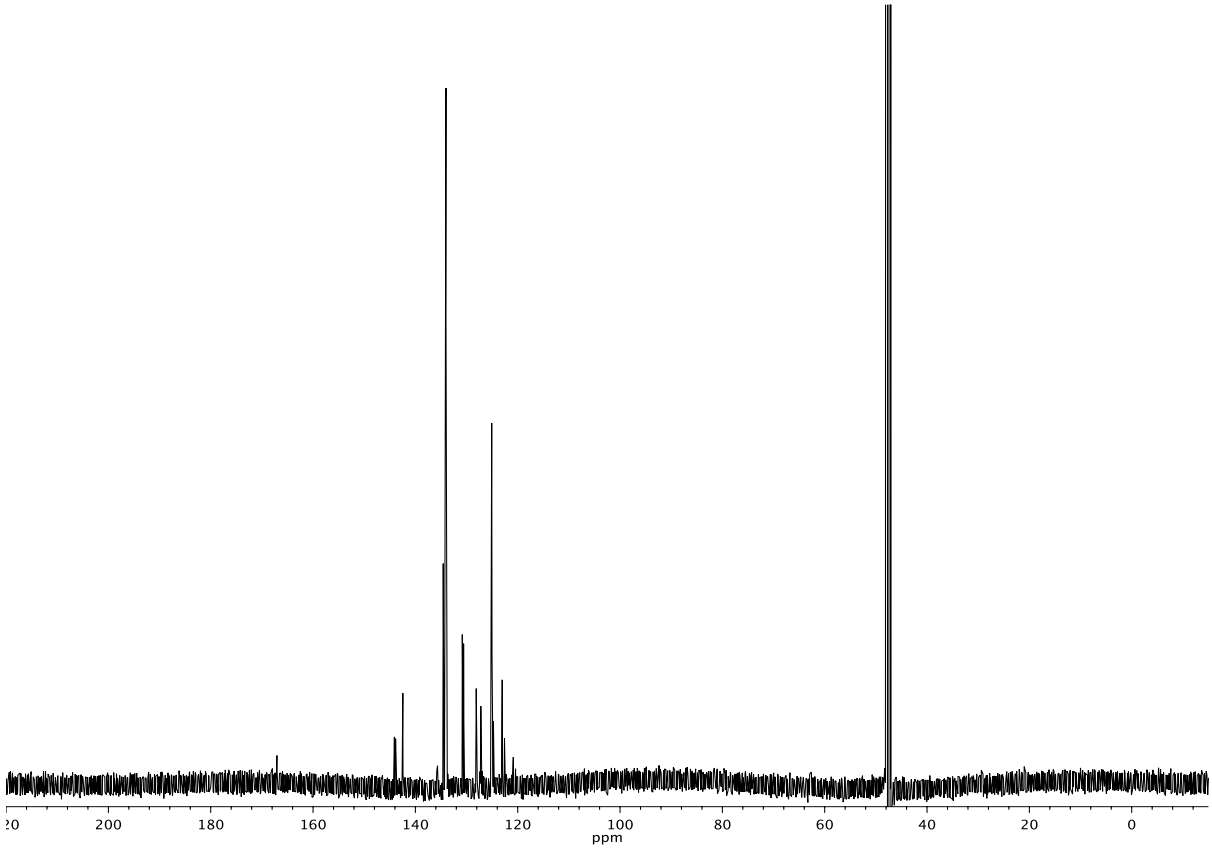
^{31}P NMR (121 MHz, $CDCl_3$) of compound **103**.



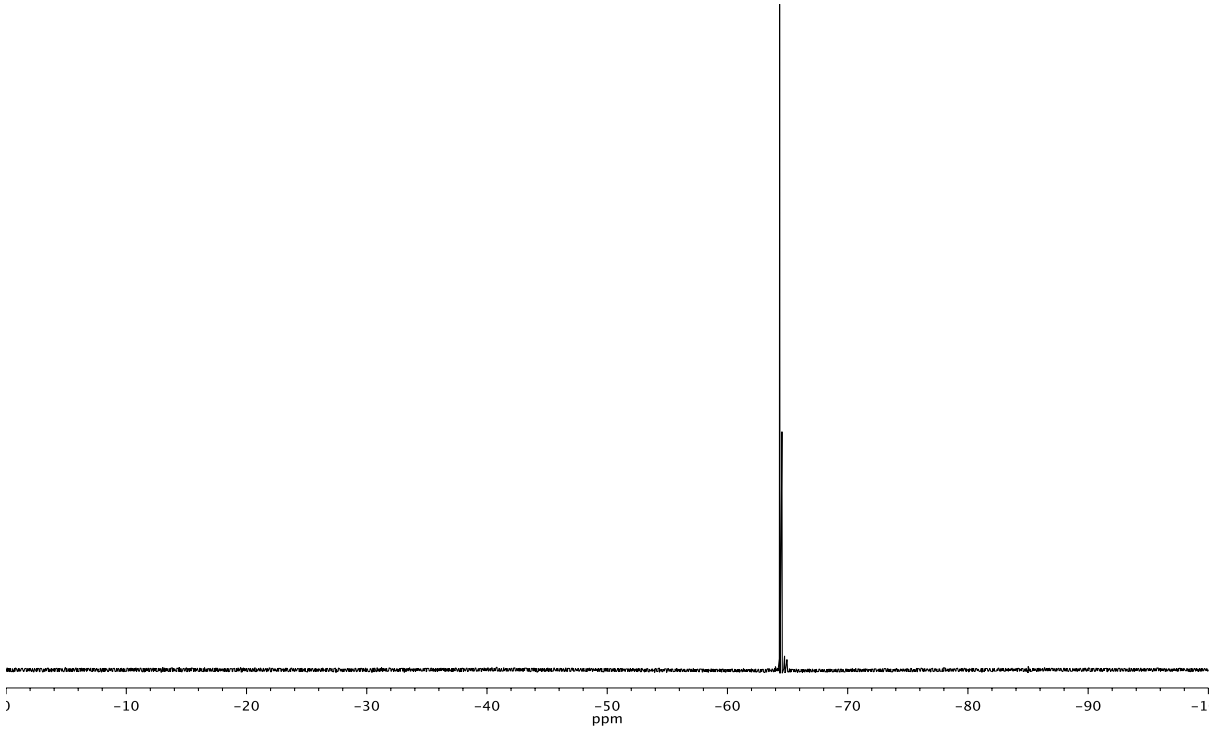
^{1}H NMR (500 MHz, $CDCl_3$) of compound **104**.



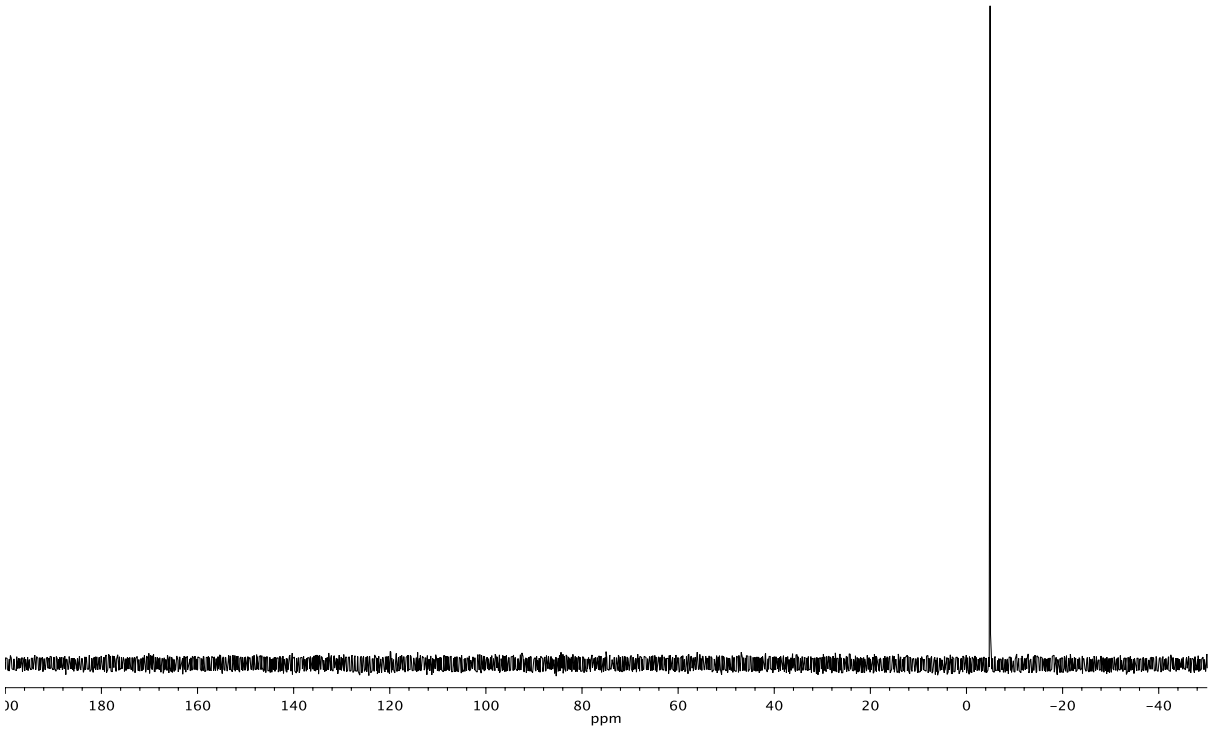
Infrared spectrum (Thin Film, NaCl) of compound **104**.



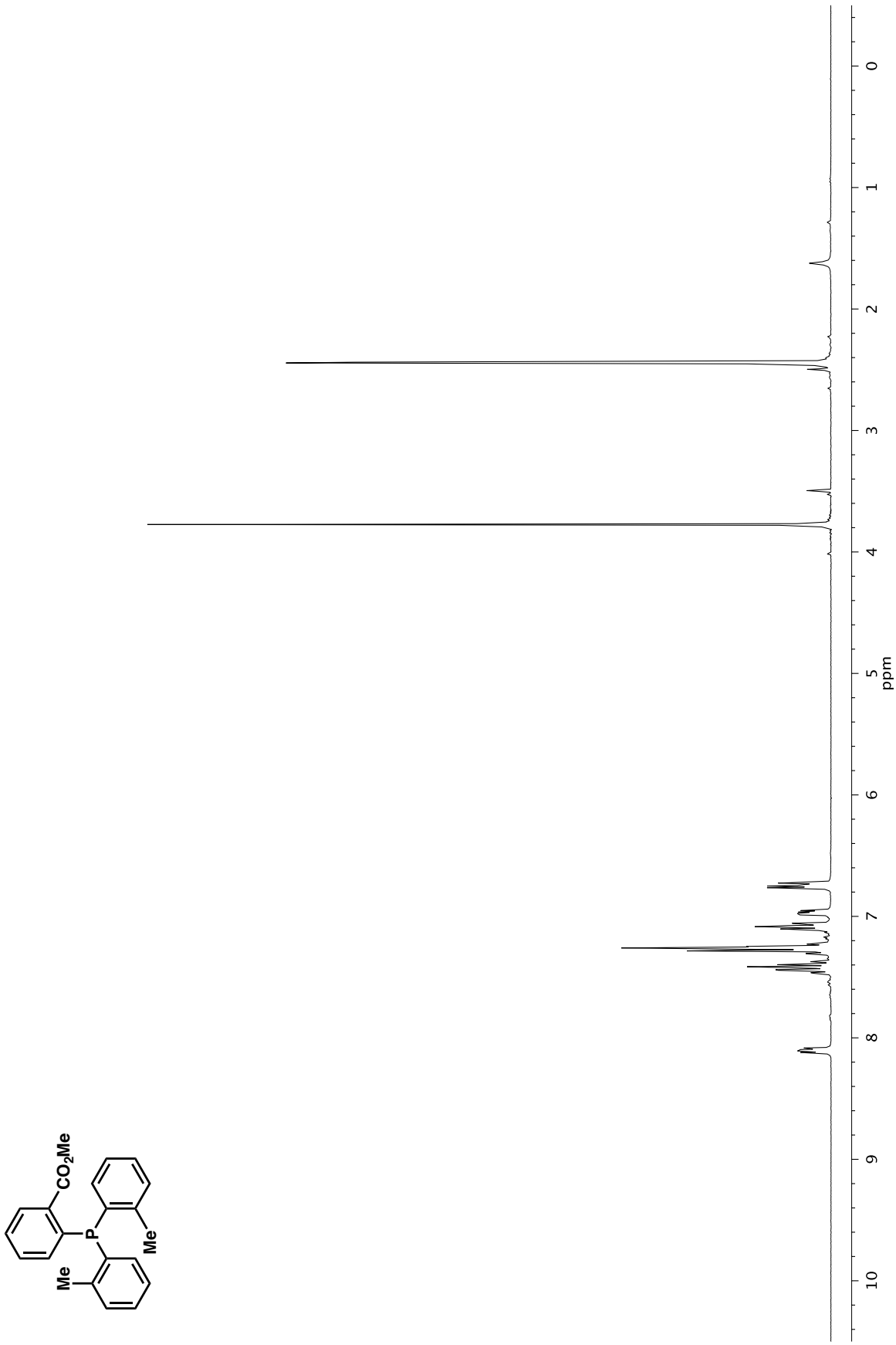
^{13}C NMR (126 MHz, $CDCl_3$) of compound **104**.



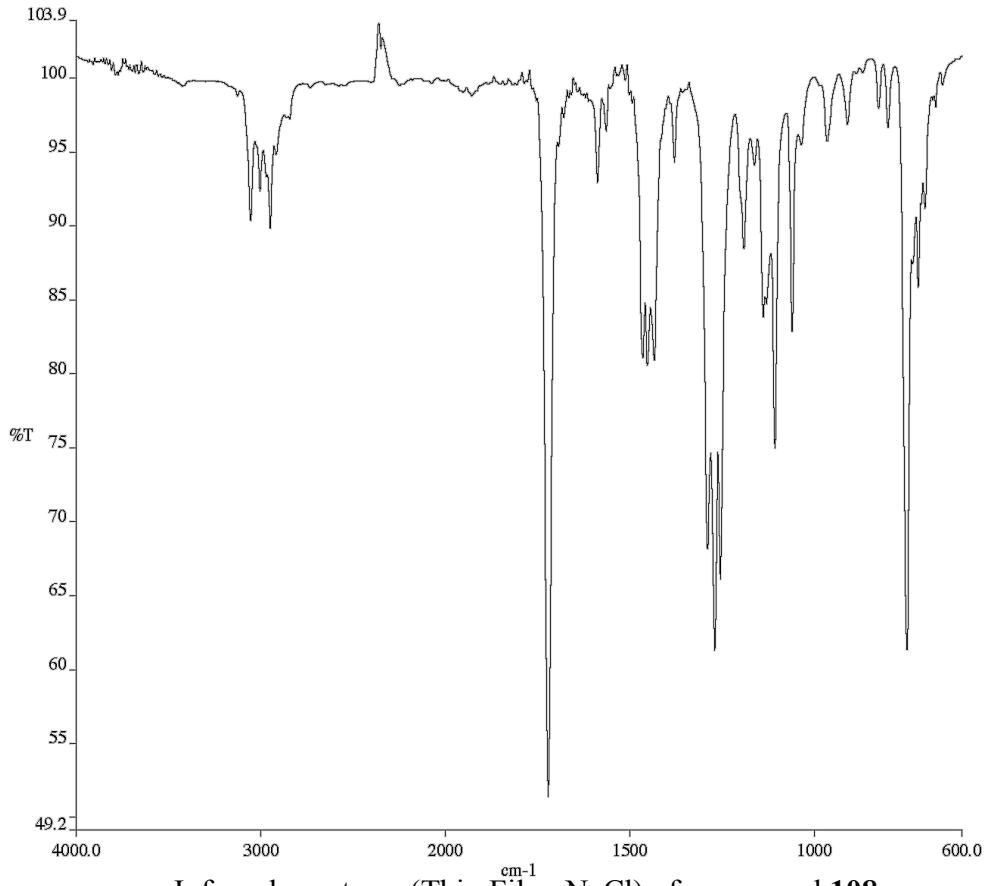
^{19}F NMR (282 MHz, $CDCl_3$) of compound **104**.



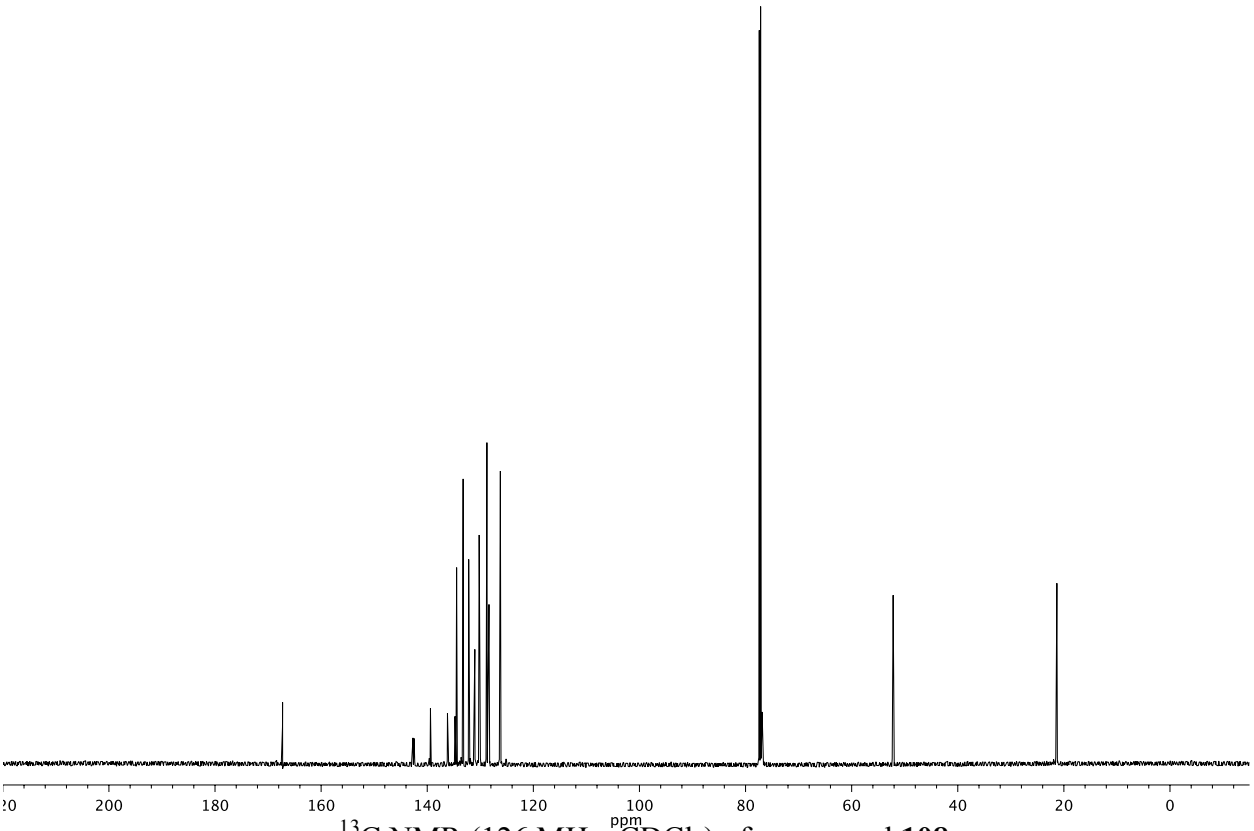
^{31}P NMR (121 MHz, $CDCl_3$) of compound **104**.



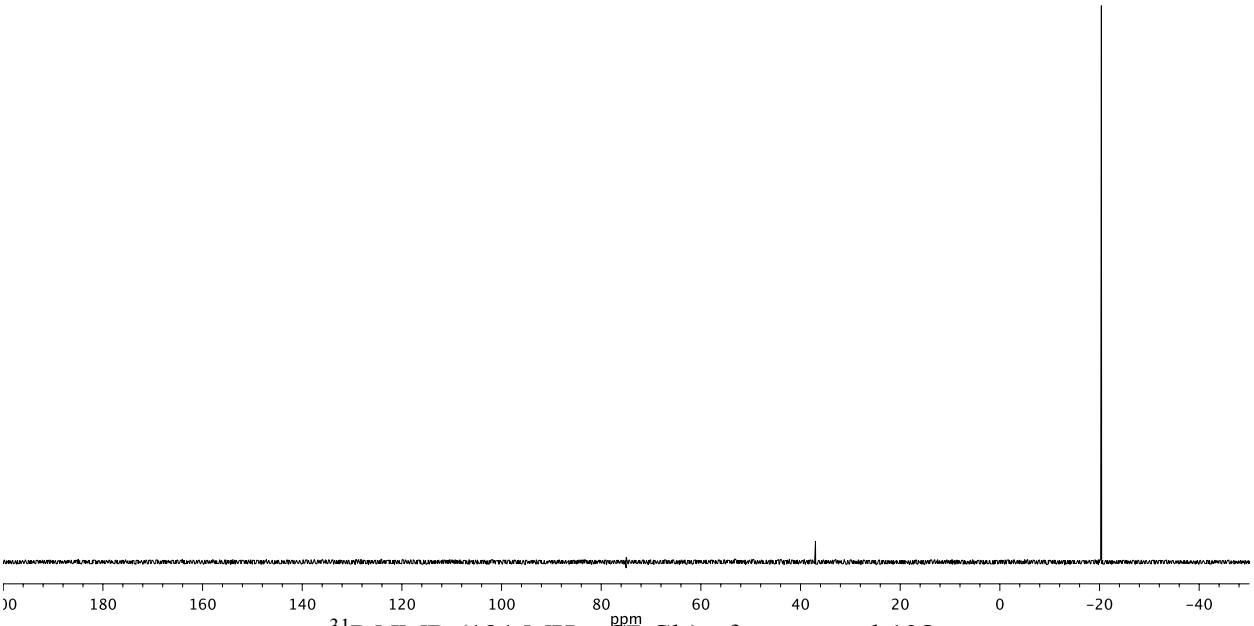
^{1}H NMR (500 MHz, $CDCl_3$) of compound **108**.



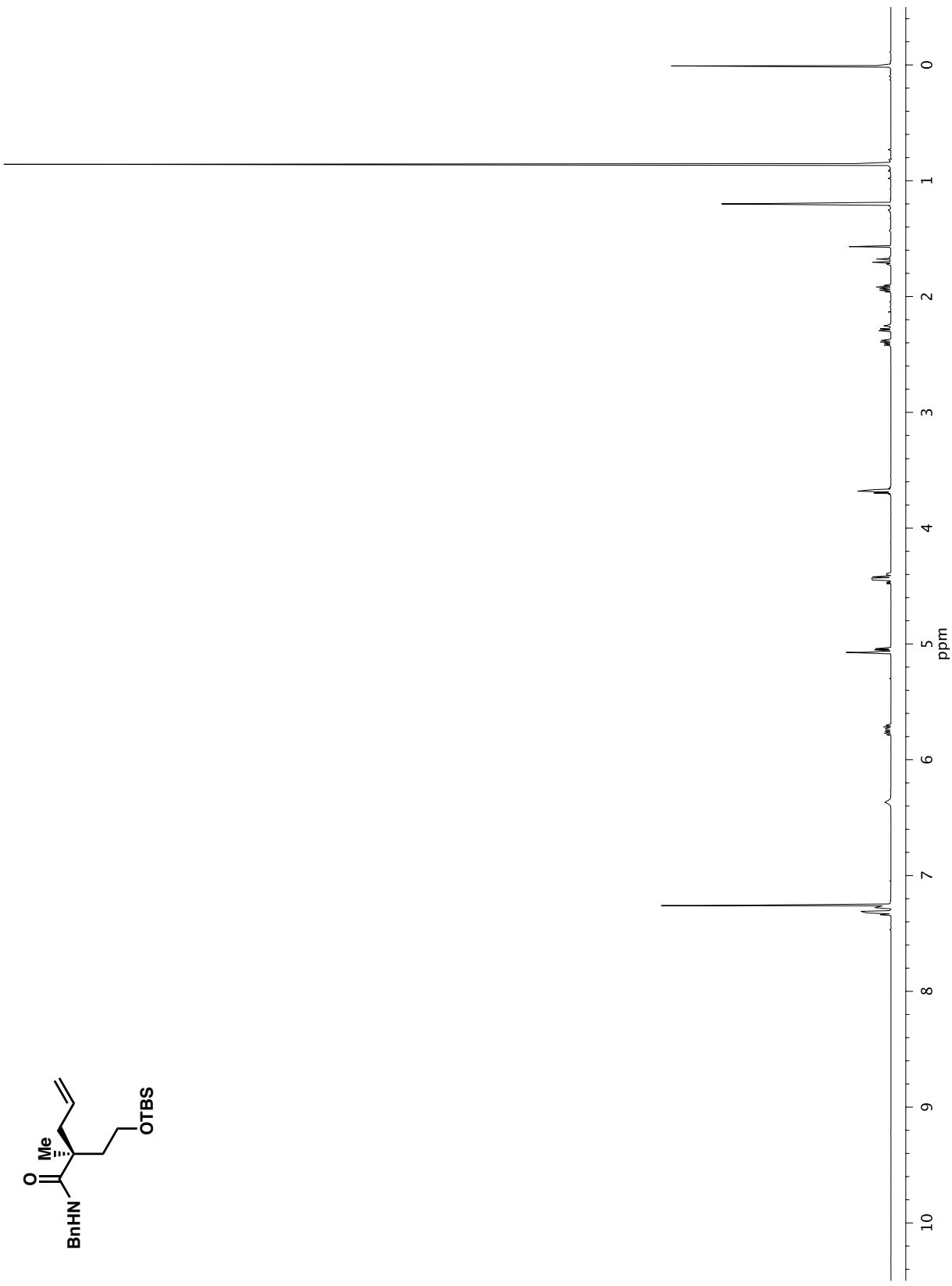
Infrared spectrum (Thin Film, NaCl) of compound **108**.



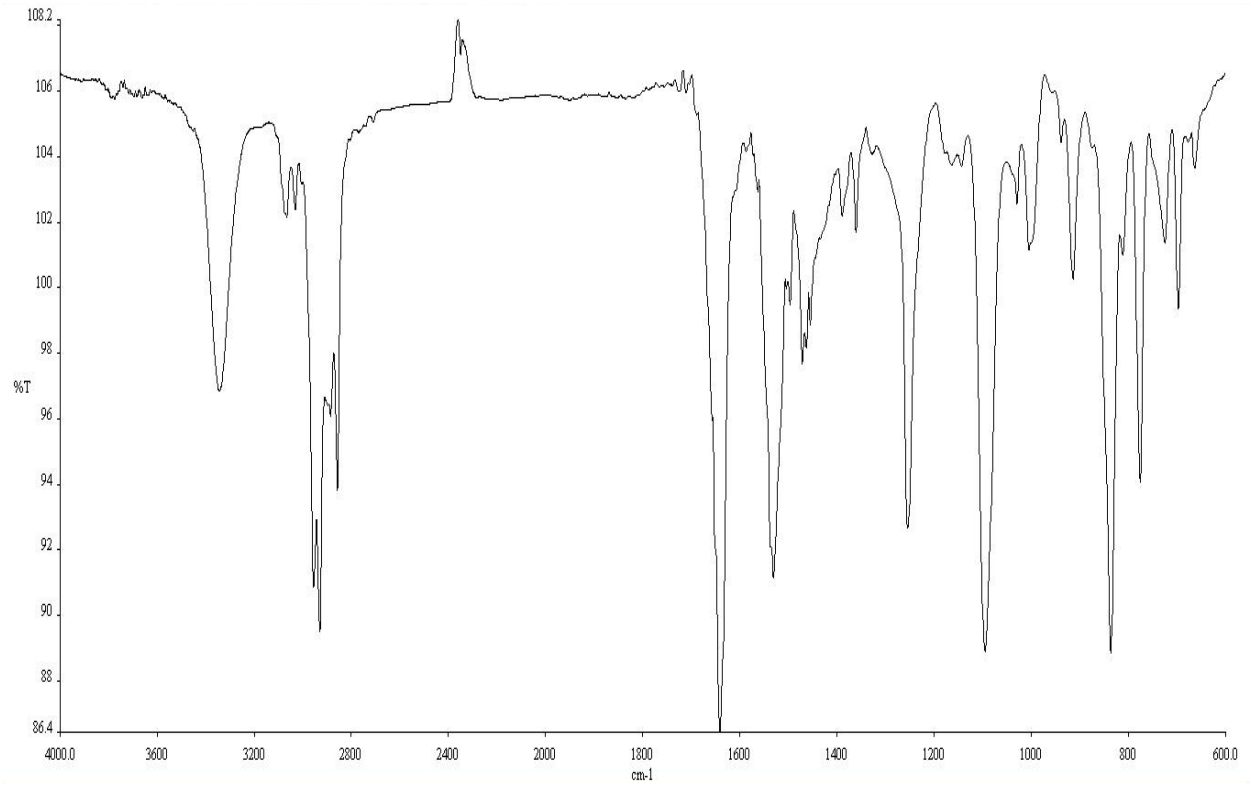
^{13}C NMR (126 MHz, $CDCl_3$) of compound **108**.



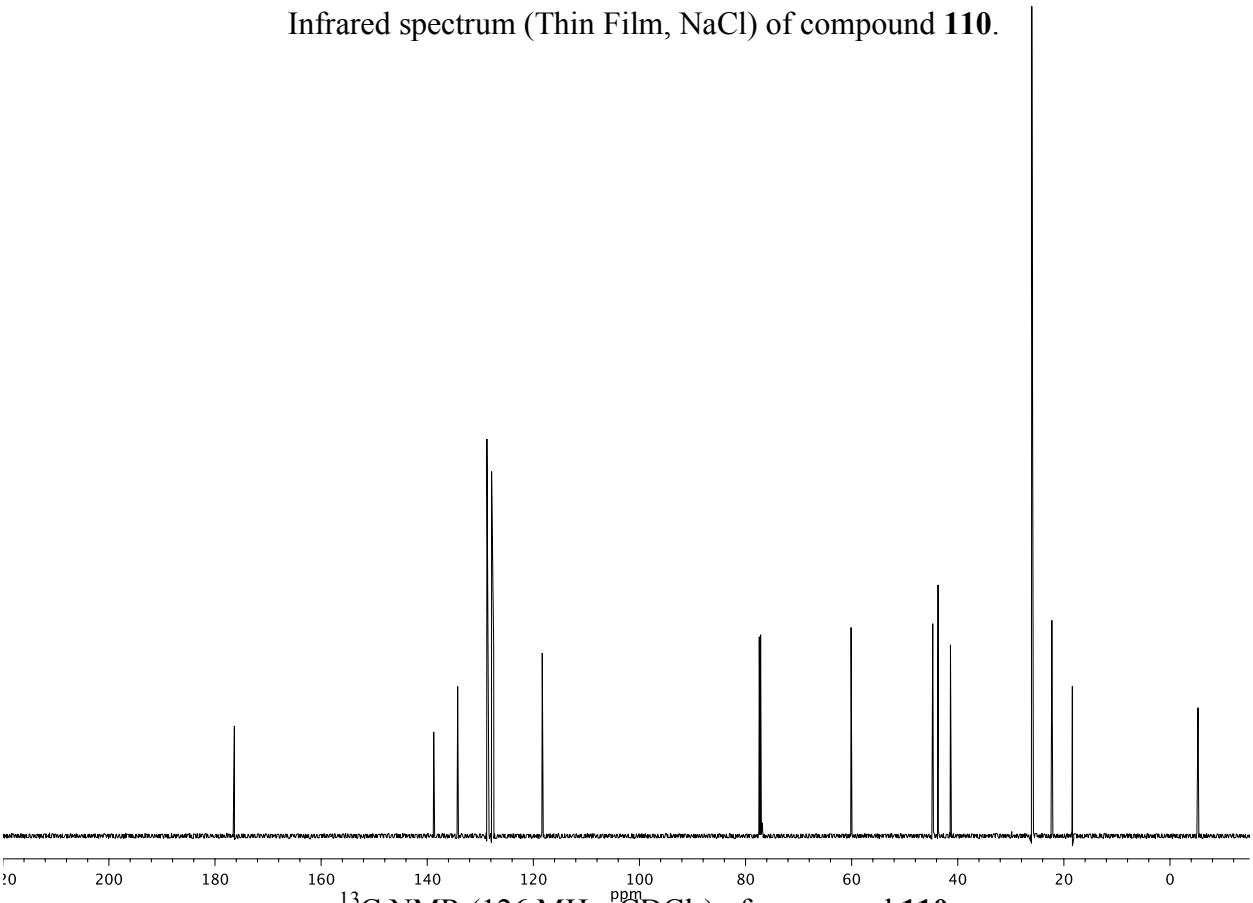
^{31}P NMR (121 MHz, $CDCl_3$) of compound **108**.



^{1}H NMR (500 MHz, $CDCl_3$) of compound **110**.



Infrared spectrum (Thin Film, NaCl) of compound **110**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **110**.

APPENDIX 4

A Highly Efficient Protocol for the Palladium-Catalyzed Asymmetric Decarboxylative Allylic Alkylation Using Low Catalyst Loading[†]

4.1 INTRODUCTION AND BACKGROUND

Despite the importance of palladium-catalyzed decarboxylative asymmetric alkylation in total synthesis, its application on an industrial scale is hampered by the need for high catalyst loadings (2.5–5.0 mol %). The high cost of palladium significantly increases the cost of each reaction. Furthermore, high catalyst loadings also increase the risk of poisoning downstream chemistry or contaminating active pharmaceutical ingredients.[1]

These drawbacks have prevented application of the enantioselective allylic alkylation on a larger scale. The application of transition metal catalysis to industry-scale

[†] This research was performed in collaboration with Dr. Alex Marziale, Dr. Robert A. Craig, II, Kelly Kim and Dr. Marc Liniger and has been published. See: Marziale, A. N.; Duquette, D. C.; Craig, R. A., II; Kim, K. E.; Liniger, M.; Stoltz, B. M. *Adv. Synth. Catal.* **2015**, *357*, 2238–2245.

synthesis requires transformations that are safe, robust, cost-effective, and scalable.[2] Consequently, there remains a significant need to develop new reaction protocols that employ lower catalyst concentrations and hence facilitate the scale-up of such transformations.

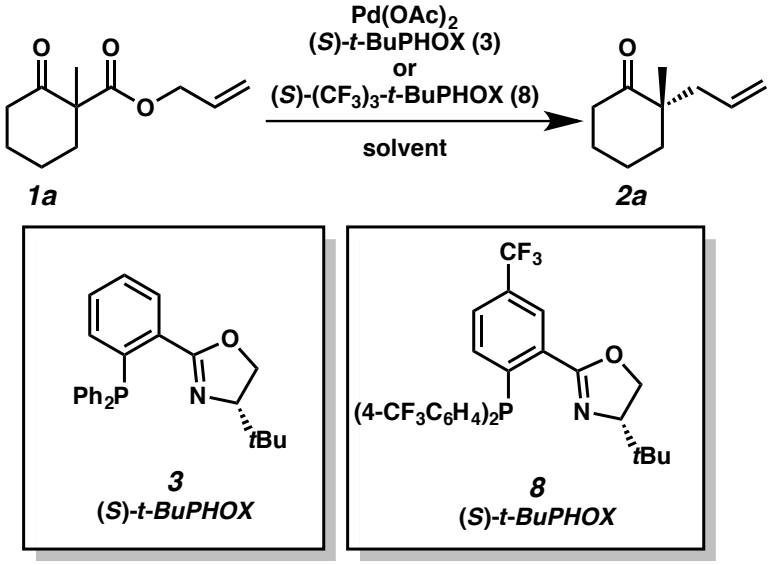
Consequently, we began to question the existing protocols and reinvestigated critical reaction parameters such as the palladium source, catalyst loading, solvent and temperature, with respect to the scalability of our reaction and its compatibility with industry requirements. This chapter describes a new protocol we developed towards these ends.

4.2 RESULTS AND DISCUSSION

4.2.1 Exploring New Palladium Sources and Optimization

We first turned our attention to the palladium source in an effort to replace the oxygen-sensitive $Pd_2(dba)_3$ used in our original conditions. Therefore, the original catalytic enantioconvergent decarboxylative allylic alkylation of allyl 1-methyl-2-oxocyclohexanecarboxylate was chosen as a model reaction (Scheme 4.1).[3]

Scheme 4.1. The catalytic enantioconvergent decarboxylative allylic alkylation.



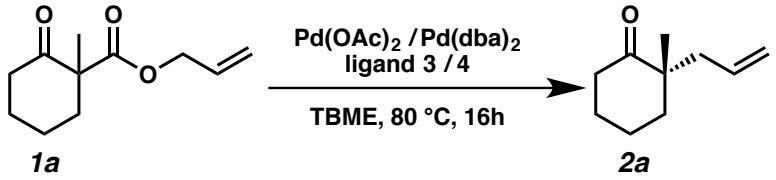
The catalytic cycle of the allylic alkylation operates starting from a zerovalent palladium source and is believed to involve a palladium (0/II) redox cycle.[4] While utilization of $Pd_2(dba)_3$ renders *in situ* reduction of the catalyst obsolete, its application is not only hampered by increased sensitivity to oxygen, but the dibenzylideneacetone ligand is also challenging to separate from non-polar reaction products.

In their original reports Tsuji and co-workers performed the allylic alkylation reactions in the presence of $Pd(OAc)_2$ and PPh_3.[5] We adopted this strategy and started screening a variety of Pd(II) sources in combination with the chiral phosphinooxazoline ligands (*S*)-*t*-BuPHOX **3**[6] and (*S*)-$(CF_3)_3$-*t*-BuPHOX **8**.[7]

When comparing $Pd(OAc)_2$ and $Pd(dba)_2$ at 1.0 mol % palladium in combination with a tenfold excess of PHOX ligands **3** or **8** respectively, in TBME at 80 °C we were pleased to find that both palladium sources exhibited comparable catalytic performance (Table 4.1). At lower palladium concentrations, however, $Pd(OAc)_2$ was clearly superior, delivering quantitative yields and good enantioselectivity at only 0.1 mol % Pd (entries 5

and 6). When 0.1 mol % $Pd(dba)_2$ was used to form the catalyst, a dramatic decrease in yields was observed (entires 7 and 8).

Table 4.1. Initial screening efforts with a $Pd(OAc)_2$ precatalyst.



1a ***2a***

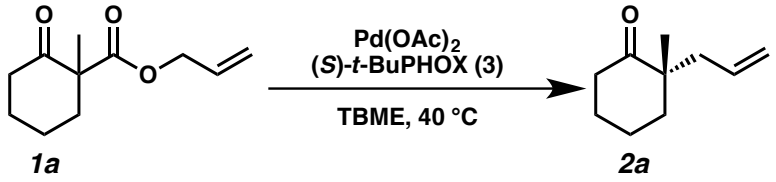
Entry	Ligand [mmol]	Pd source [mmol]	Yield [%]	ee [%]
1	3 [10.0]	$Pd(OAc)_2$ [1.0]	99	86
2	8 [10.0]	$Pd(OAc)_2$ [1.0]	99	82
3	3 [10.0]	$Pd(dba)_2$ [1.0]	99	84
4	8 [10.0]	$Pd(dba)_2$ [1.0]	90	82
5	3 [10.0]	$Pd(OAc)_2$ [0.1]	99	79
6	8 [10.0]	$Pd(OAc)_2$ [0.1]	99	83
7	3 [10.0]	$Pd(dba)_2$ [0.1]	12	n.d.
8	8 [10.0]	$Pd(dba)_2$ [0.1]	14	n.d.

We then became interested to see if other palladium(II) sources were equally suited to catalyze the decarboxylative allylic alkylation. Consequently, a total of eight different commercially available Pd(II) precursors were examined in our model reaction in the presence of ligand **3**.[8] While with $Pd(OAc)_2$ a quantitative yield for the desired allylic alkylation product was obtained, none of the other palladium sources promoted any conversion of the substrate. We reason that the limited solubility of these palladium salts in TBME likely prevented catalysis.

Limited to $Pd(OAc)_2$ as the only viable palladium precursor, we turned our attention to minimizing the catalyst loading. A screening of six different catalyst loadings, ranging from 0.05 mol % to 1.0 mol %, was performed (Table 4.2). All

reactions were conducted in the presence of a tenfold excess of ligand with respect to palladium, in TBME at 40 °C.[9]

Table 4.2. Optimization of catalyst loading.

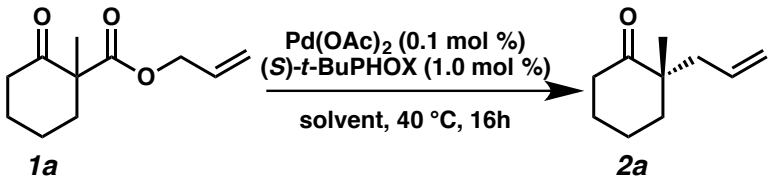


1a ***2a***

Entry	Pd [mol %]	(*S*)-*t*-BuPHOX [mol %]	Yield [%]	ee [%]
1	1.0	10.0	99	90
2	0.50	5.0	99	90
3	0.25	2.50	99	90
4	0.15	1.50	99	89
5	0.10	1.0	90	89
6	0.05	0.50	10	89

Under these reaction conditions, palladium loadings as low as 0.10 mol % were sufficient to deliver the desired allylic alkylation product in 90% yield and high enantioselectivity (Table 4.2, entry 5). To obtain a quantitative yield of ketone **2a**, the catalyst loading was increased to 0.15 mol % of $Pd(OAc)_2$ (Table 4.2, entry 4). Enantioselective allylic alkylation reactions are typically performed in solvents such as THF, DCM, dioxane or diethylether.[3, 9b, 9c, 10] While these solvents are common for academic laboratory scale, their use prohibits conducting the reaction in an industry setting.[11] We sought to overcome this limitation and performed a solvent screening with a total of ten different solvents that are considered to be safe, sustainable, and cost-efficient (Table 4.3).[10, 12]

Table 4.3. Optimization of the reaction medium.



1a ***2a***

Entry	solvent	Yield [%]	ee [%]
1	TBME	88	89
2	EtOAc	12*	74
3	MeCN	trace	-
4	Isopropyl acetate	28	64
5	Isobutyl acetate	17	-
6	Dimethylacetamide	trace	-
7	Toluene	52	80
8	2-Me-THF	21	89
9	*t*-AmylOH	-*	-
10	Acetone	-*	57

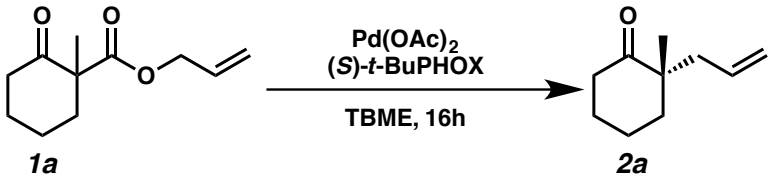
***Reaction run at 60 °C**

Conversion of allyl 1-methyl-2-oxocyclohexane-carboxylate in TBME resulted in high yields and good enantioselectivity (Table 4.3, entry 1). When the reaction was performed in various alkyl acetates the yields dropped dramatically, to 12%, 28%, and 17% respectively (Table 4.3, entires 2, 4 and 5). Similarly low yields were observed for reactions performed in acetonitrile, dimethylacetamide, 2-Me-THF, and acetone (Table 4.3, entries 3, 6, 8 and 10). Moderate conversion was found when the reaction was performed in toluene (Table 4.3, entry 7). Consequently, all further experiments were carried out in TBME.

At this point, we considered that the palladium concentration could be lowered further by performing the reaction at higher temperatures, and we were interested in the influence of increased reaction temperature on stereoselectivity. All experiments were

performed in TBME with a tenfold excess of ligand **3** (Table 4.4). A palladium loading as low as 0.075 mol % afforded ketone **2a** in 99% yield when the reaction was performed at 80 °C, which corresponds to a turnover number of 1320 for the *in situ* formed catalyst. Nevertheless, a slightly lower enantioselectivity of 84% was observed in this case (Table 4.4, entry 1). At 60 °C and 40 °C, palladium loadings of 0.10 and 0.125 mol % respectively were sufficient to deliver the desired product in quantitative yield and high enantioselectivity (Table 4.4, entries 2 and 3).

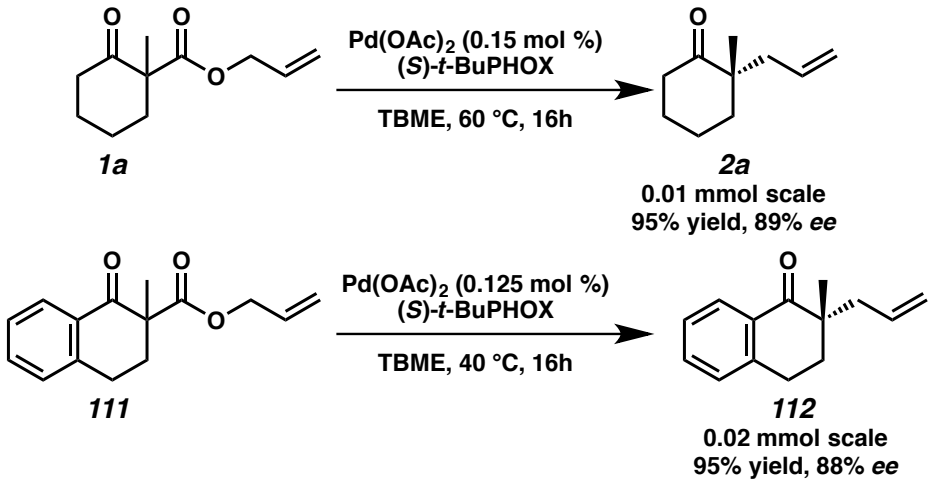
Table 4.4. Optimization of the palladium loading at varying temperatures.



Entry	Pd [mol %]	T [° C]	Yield [%]	ee [%]
1	0.075	80	99	84
2	0.1	60	99	88
3	0.125	40	99	89

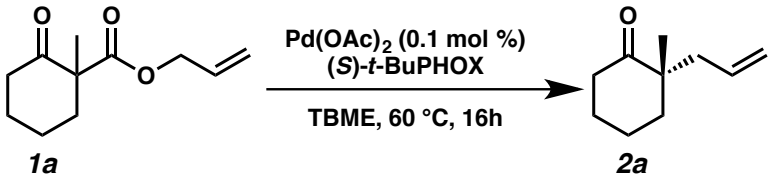
We then applied the protocol to the 10 and 20 mmol scale synthesis of alpha-quaternary ketones **2a** and **112** (Scheme 4.2). Both reactions were performed in TBME with a tenfold excess of ligand **3**. In experiment 1, 1.96 g (10.0 mmol) of cyclohexanone **1a** was converted in the presence of 0.15 mol % (3.37 mg) of $Pd(OAc)_2$ at 60 °C. The corresponding product **2a** was isolated by distillation in 95% yield and 89% *ee*. Similarly, tetralone substrate **111** was applied on a 20 mmol scale (4.89 g) in the enantioselective allylic alkylation at 40°C. The desired product **112** was purified by flash chromatography and isolated in 95% yield and 88% ee.

Scheme 4.2. Application of the developed protocol on scale.



Satisfied with the scalability of our new allylic alkylation conditions, we turned our attention to reducing the ligand loading. A series of six experiments employing different quantities of ligand, from 0.20 mol % to 1.00 mol %, in the presence of 0.10 mol % $Pd(OAc)_2$ were performed (Table 4.5). A ligand loading of 0.4 mol %, which corresponds to a 4-fold excess of ligand with respect to palladium, was sufficient to provide the desired product in quantitative yield and high enantioselectivity (Table 4.5, entry 4). Only at a loading of 0.20 mol % of ligand **3** was a slight decrease in enantioselectivity observed (Table 4.5, entry 5).

Table 4.5. Optimization of ligand loading.

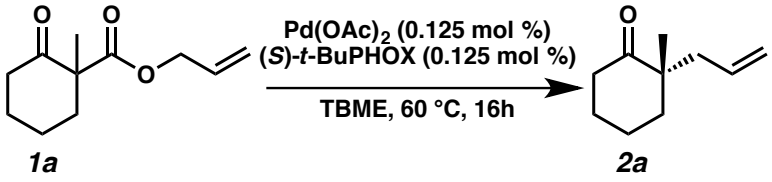


1a ***2a***

Entry	(*S*)-*t*-BuPHOX [mol %]	Yield [%]	ee [%]
1	1.00	99	88
2	0.80	99	89
3	0.60	99	88
4	0.40	99	88
5	0.20	99	86

Finally, we investigated the influence of concentration on reactivity. A brief study across five different substrate concentrations was executed (Table 4.6). We were pleased to find that the decarboxylative alkylation reaction could be performed in high concentrations of up to 0.4 M without any negative impact on yield or enantiomeric excess (Table 4.6, entry 1). When the reaction was performed at higher dilution (0.033 mol/l) a slight decrease in yield and optical purity was observed (Table 4.5, entry 5).

Table 4.6. Optimization of reaction concentration.



1a ***2a***

Entry	concentration [M]	Yield [%]	ee [%]
1	0.4	99	88
2	0.2	99	88
3	0.1	99	89
4	0.05	99	89
5	0.033	91	87

4.2.2 Substrate Scope

After optimizing all critical reaction parameters for the conversion of cyclohexanone substrate **1a**, we sought to investigate the substrate scope of this novel protocol. To demonstrate its broad applicability, a total of ten compounds were subjected to the improved reaction parameters (Table 4.6).

Table 4.7. Substrate scope of the new protocol.

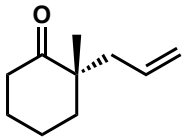
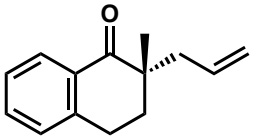
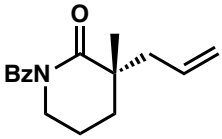
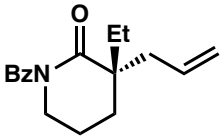
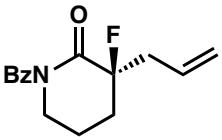
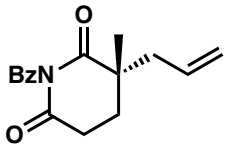
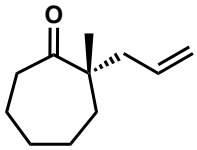
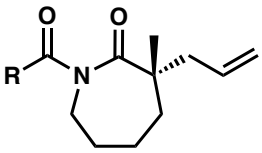
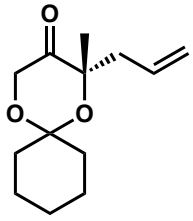
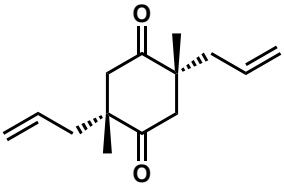
Entry	Product	Protocol	Pd [mol %]	Yield [%]	ee [%]
1	 *2a*	old	5.00	89	88
		new	0.125	99	89
2	 *112*	old	8.00	97	92
		new	0.125	85	89
3	 *5a*	old	10.0	85	99
		new	0.50	81	95
4	 *5k*	old	10.0	97	99
		new	0.30	85	97
5	 *5l*	old	10.0	89	99
		new	0.125	80	99

Table 4.7. Substrate scope of the new protocol (cont'd).

Entry	Product	Protocol	Pd [mol %]	Yield [%]	ee [%]
6	 ***7a***	old	10.0	91	94
		new	0.125	99	88
7	 ***113***	old	5.00	83	87
		new	0.10	97	70
8	 ***114*** R = *p*-MeO-C_6H_4	old	5.00	83	93
		new	0.125	95	90
9	 ***115***	old	-	-	-
		new	0.10	79	90
10	 ***116***	old	5.0	78	99
		new	0.25	97	99

For experimental details, see: Marziale, A. N.; Duquette, D. C.; Craig, R. A., II; Kim, K. E.; Liniger, M.; Stoltz, B. M. *Adv. Synth. Catal.* **2015**, *357*, 2238–2245.

Asymmetric allylic alkylation to generate products **2a** and **112** was discussed previously in detail (Table 4.7, entries 1–2). Lactam (**5a**, **5k** and **5l**) and piperidone products (**7a**) were obtained in good yields and enantioselectivities (Table 4.7, entries 3–6). The protocol could also be applied to seven-membered rings; however, despite a near

quantitative yield, a reduced enantiomeric excess of 70% was observed for ketone **113** (Table 4.7, entry 7). In contrast, seven-membered caprolactam **114** was isolated in 95% yield and 90% *ee* (Table 4.7, entry 8). Notably, cyclohexyl ketal **115** was generated in 79% yield and good enantioselectivity through intermolecular allylic alkylation of the corresponding silyl enol ether and allyl methanesulfonate (Table 4.7, entry 9).

Finally, cyclohexanedione **116**, which is a critical intermediate in the synthesis of (–)-cyanthiwigin F,[13] could be accessed through double enantioselective allylic alkylation of the corresponding bis(β-ketoester) in excellent yield and near perfect enantioselectivity using only 0.25 mol % palladium (Table 4.7, entry 10). This corresponds to 5% of the palladium loading used in the original protocol. Despite the considerable reduction in catalyst concentration, the yield for this reaction was improved to 97% (Table 4.7, entry 10).

4.3 CONCLUDING REMARKS

In conclusion, we have reported a novel and highly efficient protocol for the decarboxylative enantioselective allylic alkylation using palladium acetate and loadings below 0.50 mol %. For simple quaternary ketone products metal loadings as low as 0.075 mol % effectively catalyzed the reaction and generated the desired products in high yields and enantioselectivities. Thereby, turnover numbers of up to 1320 could be reached. Furthermore, a variety of critical reaction parameters such as temperature, concentration, ligand stoichiometry, and choice of solvent were optimized to increase the scalability and lower the cost basis for palladium catalyzed allylic alkylation reactions. The method is broadly applicable among a variety of substrate classes and is tolerant of

most functional groups because of the neutral reaction conditions and modest reaction temperatures. We anticipate these advances will promote the continued use of palladium-catalyzed allylic alkylation reactions as means of installing quaternary sterocenters in multi-step syntheses in academic laboratories, and hope to see these reactions used to synthesize valuable molecules in the chemical and pharmaceutical industry.

4.4 NOTES AND REFERENCES

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(8) Palladium(II) sources applied in screening: $Pd(OAc)_2$, $PdCl_2$, $Pd(PhCN)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$, $PdBr_2$, $Pd(acac)_2$, $[Pd(allyl)Cl]_2$, $Pd(TFA)_2$.

(9) The high excess of ligand was chosen to facilitate formation of the active catalyst through *in situ* reduction of $Pd(OAc)_2$. We reasoned that the PHOX ligand hereby acts as the reductive agent.

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APPENDIX 5

Synthesis of (±)-Grandifloracin and Acylated Analogues[†]

5.1 INTRODUCTION AND BACKGROUND

Pancreatic cancer is one of the most severe forms of cancer, with a 5-year survival rate of only 3–5%. This high mortality rate has not improved during the last four decades of chemotherapeutic research.[1] To date, there has not been any report of an effective treatment against the disease, and the agents used against other types of cancer have been shown to have little to no effect on pancreatic cancer.[2] It has been hypothesized that this might be the result of pancreatic cancer cells being hypovascular and thereby able to proliferate in a nutrient-deficient and hypoxic environment.[3] The lack of viable treatments for, and the severity of pancreatic cancer create a pressing need to develop new drugs to combat the disease.[4]

One means to overcome these challenges is to develop anti-austerity agents. These drugs target the biochemical pathways that allow cancer cells to thrive under low

[†] This research was performed in collaboration with Magnus Bergner and Linda Chio and has been published. See: Bergner, M.; Duquette, D. C.; Chio, L.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 3008.

nutrition, thereby reducing or halting the cancerous cells' ability to survive in hypovascular conditions without affecting the surrounding cells.[4] A recent breakthrough came in 2012 when the Awale group extracted (+)-grandifloracin from the stem of *Uvaria dac*.[5] (+)-Grandifloracin was shown to be a potent anti-austerity agent against pancreatic cancer cell lines, PANC-1 (PC_{50} 14.5 μM), PSN-1 (PC_{50} 32.6 μM), MIA PaCa-2 (PC_{50} 17.5 μM) and KLM-1 (PC_{50} 32.7 μM).[6] Interestingly, the first isolation of grandifloracin from *Uvaria grandiflora* in 1997[7] was later shown to be the (–)-enantiomer of grandifloracin.[8]

In a comprehensive study of (+)-grandifloracin, its mode of action was determined to be the induction of autophagic programmed cell death in PANC-1 cells rather than through typical apoptotic modes.[9] This evidence strongly supports the potential efficacy of anti-austerity agents in the treatment of pancreatic cancer.

The first synthesis of grandifloracin in racemic form was reported in 2007 by Quideau and coworkers.[10] This synthesis hinged on a hydroxylative dearomatization of 2-hydroxybenzyl benzoate, which subsequently underwent a spontaneous Diels-Alder cyclodimerization to directly yield (±)-grandifloracin, albeit in a modest 30% yield. A subsequent asymmetric syntheses of (+)-grandifloracin by Lewis and coworkers similarly made use of a spontaneous Diels-Alder reaction of a chiral cyclohexa-2,4-dienone obtained after a five step sequence following the microbial oxidative dearomatization of benzoic acid.[7] Notably, Toste and coworkers have also reported the synthesis of a fluorinated (–)-grandifloracin derivative[11] utilizing an asymmetric dearomative fluorination and cyclodimerization of silyloxymethylphenol, followed by deprotection

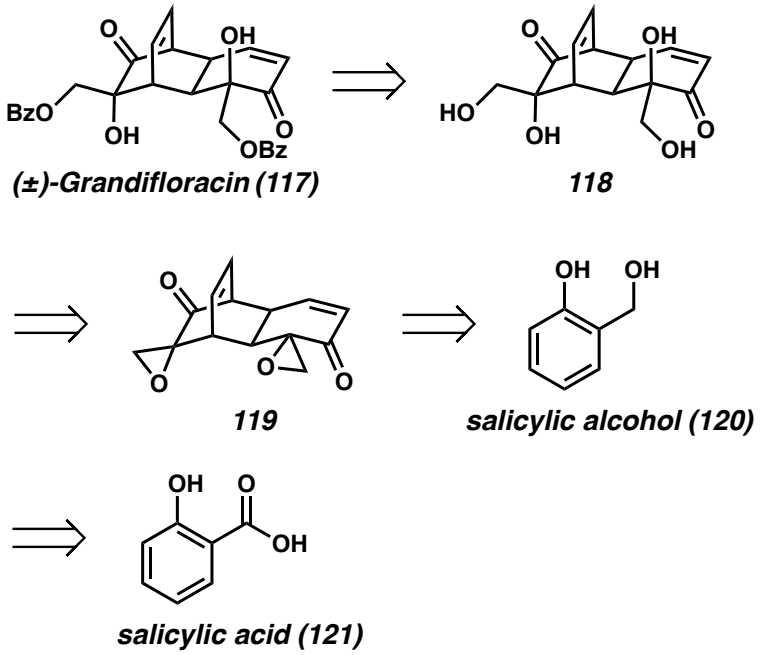
and acylation in a single step. However, they note that the corresponding benzoate ester only gave trace conversion in the fluorination step.

While the linchpin Diels-Alder cyclodimerization is highly efficient in constructing the backbone of grandifloracin, its use can also be limiting for potential diversification for the study of structure-activity relationships. In each of the syntheses of the natural product, the hydroxymethyl group is protected as a benzoate ester prior to the cyclodimerization step. As such, any derivative must either be obtained by a deprotection-acylation sequence, adding extra steps to such a library synthesis, or by carrying each individual acyl group through the Diels-Alder step. This is potentially troublesome, as electronically differentiated substrates can perform with substantially varying yields.[12] As such, when planning our synthesis, we sought to carry a free hydroxymethyl group through the cyclodimerization in order to facilitate subsequent derivatization for biological study of analogues of the natural product.

5.2 RESULTS AND DISCUSSION

5.2.1 Retrosynthetic Analysis

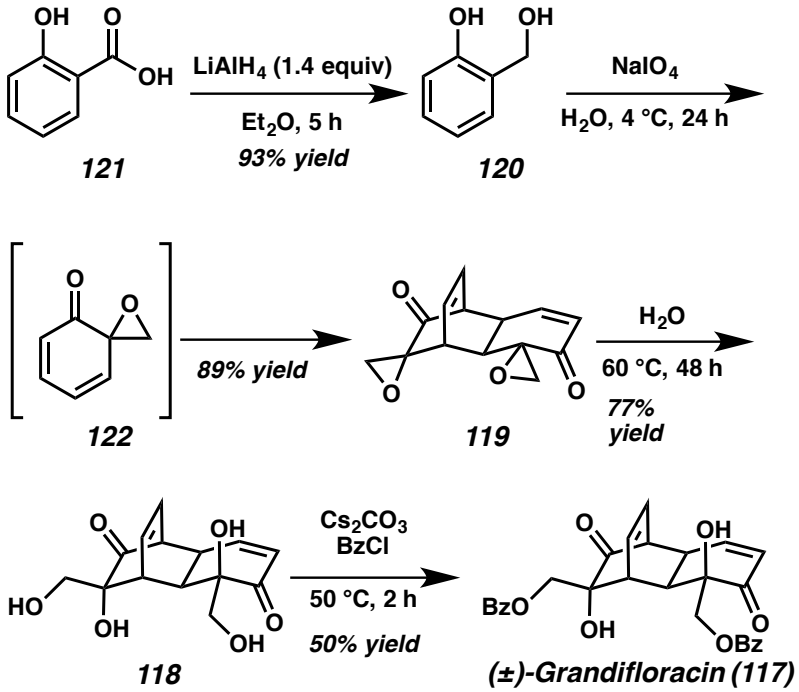
Scheme 5.1. Retrosynthetic analysis of (±)-grandifloracin.



The aim of this project was to develop an even more efficient synthetic route to (±)-grandifloracin than previously employed that would permit late-stage diversification of a key intermediate. To achieve this, we devised a strategy (Scheme 5.1) in which removal of the benzoyl groups of grandifloracin (**117**) yields the core-structure as a diol (**118**), which would be amenable to derivatization by selective acylation of the free hydroxymethyl groups. This key tetraol was anticipated to arise from a double epoxide-opening of the known bis-spiroepoxy-dienedione **119**.[13] This key intermediate can be readily prepared through an oxidative dearomatization of salicylic alcohol (**120**) and subsequent Diels–Alder homodimerization.

5.2.2 Synthesis of (±)-Grandifloracin

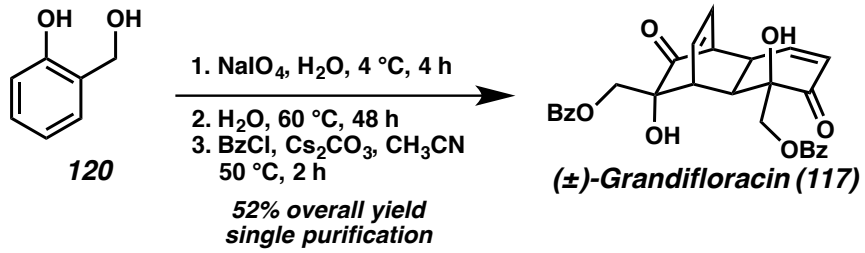
Scheme 5.2. Synthesis of (±)-grandifloracin.



Salicylic acid (**121**) was reduced by $LiAlH_4$ to give the corresponding salicylic alcohol (**120**, 93% yield). The alcohol was then subjected to known oxidative dearomatization with sodium periodate ($NaIO_4$) in water to afford spiroepoxycyclohexadienone (**122**).[12] Diene **122** spontaneously undergoes a Diels–Alder dimerization to yield the dispirooxirane **119** in a remarkably stereoselective and efficient overall process (89% yield of a >10:1 mixture of diastereomers). The two epoxides were smoothly opened by gentle heating in water over two days to yield the core tetraol **118** (77% yield).[14] The tetraol was treated with benzoyl chloride to furnish (±)-grandifloracin (50% yield), completing the total synthesis in only four steps from salicylic acid in an overall yield of 32% (Scheme 5.2). Gratifyingly, we were able to identify suitable chromatographic conditions to allow separation of (+)- and (–)-grandifloracin by

preparative chiral HPLC. Even after separation of the two enantiomers, the yield for each antipode is still significantly higher than the previously reported enantioselective total synthesis of (+)-grandifloracin.[7]

Scheme 5.3. Telescoped synthesis of (±)-grandifloracin.



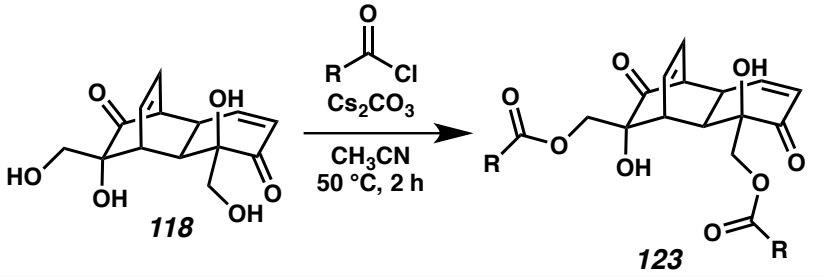
This rapid and efficient four-step synthesis of (±)-grandifloracin (**1**) was further improved by eliminating intermediate recrystallization steps (Scheme 5.3). Salicylic alcohol was telescoped through the synthetic route without any purification until the final compound. This resulted in a yield of 52% over the last three steps, and an excellent overall 48% yield. This procedure allowed us facile access to over 200 mg of the racemic natural product, and was amenable to even larger scale for the synthesis of analogs (*vide infra*).

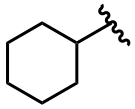
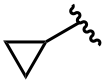
5.2.3 Synthesis of Acylated Analogues of (±)-Grandifloracin

To investigate the effect of the acyl substituents present on the natural product, a small library of analogues was synthesized (Table 5.1). Introduction of a methyl group in the *para*, *meta* or *ortho* position (**123a-c**) of the phenyl group was well tolerated in the acylation reaction, proceeding in roughly the same yields as with benzoyl chloride. Replacement of the phenyl ring with a cyclic alkyl group (**123f-g**) slightly increased the yield of acylation. While the introduction of an electron-donating *para*-methoxy group (**123d**) substantially increased the yield of the acylation reaction, the introduction of an electron-withdrawing *para*-cyano group (**123e**) significantly lowered the yield. This trend

was also observed when we attempted to synthesize the *para*-nitro analogue, which failed due to lack of reactivity. The moderate yield in the acylation step is believed to arise from competing elimination of the α-hydroxy group of the B-ring.[15]

Table 5.1. Synthesis of acylated analogues of (±)-grandifloracin.



entry	product	R	yield [%]
1	***123a***	2-Me-C_6H_4	48
2	***123b***	3-Me-C_6H_4	51
3	***123c***	4-Me-C_6H_4	55
4	***123d***	4-OMe-C_6H_4	69
5	***123e***	4-CN-C_6H_4	25
6	***123f***		58
7	***123g***		55

5.3 CONCLUDING REMARKS

In summary, we have completed a highly efficient synthesis of (±)-grandifloracin, which is amenable to late-stage diversification for the synthesis of analogues. In a recent study, analogue **123d** has been shown to have an increased anti-proliferative effect compared with grandifloracin on PANC-1 and HT-29 (human colon cancer) cells, both in nutrient rich (10% fetal bovine serum) and in nutrient deprived conditions (0.5% fetal bovine serum).[16] This indicates that there is an incentive to develop further grandifloracin analogues for the study and treatment of pancreatic cancer.

5.4 NOTES AND REFERENCES

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(6) Although the PC_{50} values for (+)-Grandifloracin are double digit mM, the most potent antiausterity agent known, arctigenin, is only an order of magnitude more potent in identical assays (PANC-1 assay PC50 ~0.51-1.7 mM). By contrast, clinical agents such as gemcitabine and paclitaxel shown no activity (PC_{50} >100 mM).[3b, 5]

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(13) (a) Adler, E.; Brasen, S.; Miyake, H. *Acta Chem. Scand.* **1971**, *25*, 2055. (b) Bender, D. R.; Brennan, J.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 3354. (c) Buist, G. J.; Bunton, C. A.; Hipperson, W. C. P. *J. Chem. Soc. B* **1971**, 2128. (d) For a recent example, see: Singh, V.; Das, B.; Jarhad, D. B.; Mobin, S. M. *Tetrahedron* **2015**, *71*, 560.

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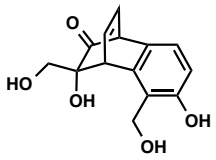
(15) This hypothesis is supported by the isolation of a side product from the reaction which has tentatively been assigned as the following phenol tautomer of the result of a base-mediated elimination of tetraol **118**:



(16) Ali Khan, M.; Wood, P. J.; Lamb-Guhren, N. M.; Caggiano, L.; Kociok-Köhn, G.; Tosh, D.; Lewis, S. E. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2815.

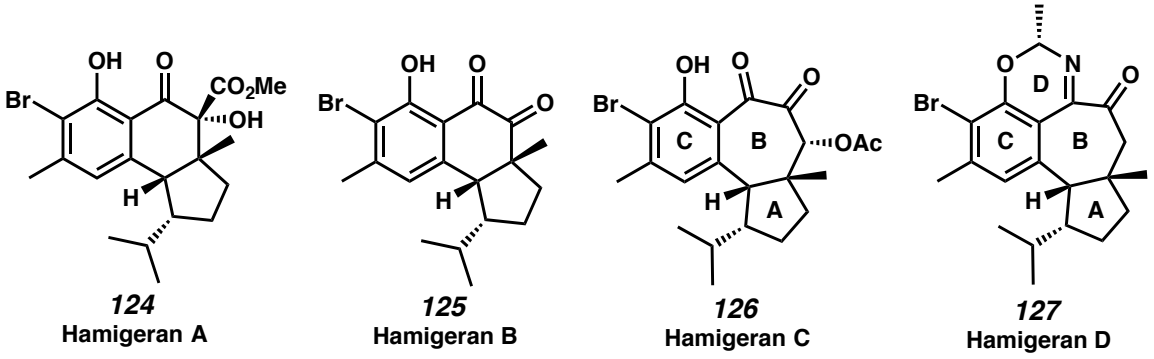
APPENDIX 6

Progress Towards the Total Synthesis of Hamigerans C and D

6.1 INTRODUCTION AND BACKGROUND

The hamigeran family of natural products was isolated in 1999 from marine sponge *Hamigera tarangaensis* by Cambie and coworkers (Figure 6.1).[1] While all four members of the family possess moderate cytotoxicity in P-388 leukemia cells (IC_{50} = 31.6, 13.5, 16.0 and 8.0 μM for hamigerans A, B, C and D, respectively), hamigeran B (**125**) displays 100% *in vitro* inhibition against both Herpes and Polio viruses.

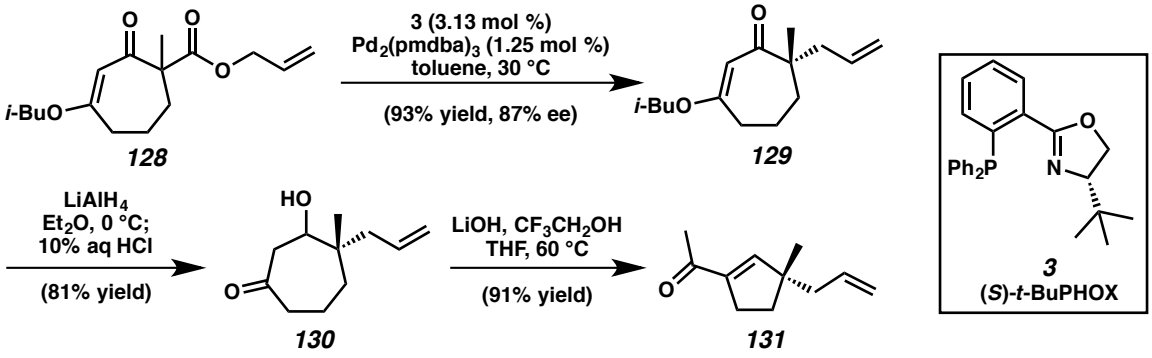
Figure 6.1. The hamigeran family of natural products.



Due to this attractive biological activity and the synthetically challenging 6-6-5 tricyclic structure bearing three consecutive stereocenters on the congested A-ring, hamigeran B has been the target of continual efforts of many synthetic organic chemists. Hamigeran B (along with hamigeran A and several analogs) was first synthesized in 2003 by Nicolau and coworkers[2a,b] and since has succumbed to a number of syntheses,[2] including epimeric and formal syntheses. In contrast, no syntheses of hamigerans C or D (**126** and **127**), which share a unique 6-7-5 tricyclic core, have been reported in the literature, presumably in part to the relative scarcity of methods for the synthesis of 7-membered rings as compared to their 6-membered counterparts.

The Stoltz group has developed a methodology for the asymmetric synthesis of γ-quaternary acylcyclopentenes (Scheme 6.1, **131**) by a retro-aldol/aldol condensation sequence resulting in a two-carbon contraction of vinylogous esters of cycloheptenone (**129**).[3] The versatility of this intermediate and the excellent scalability of this sequence inspired us to pursue the synthesis natural products with cores containing densely-functionalized cyclopentanes with quaternary carbon stereocenters, making hamigerans C and D ideal targets.

Scheme 6.1. Synthesis of acylcyclopentenes by ring contraction.

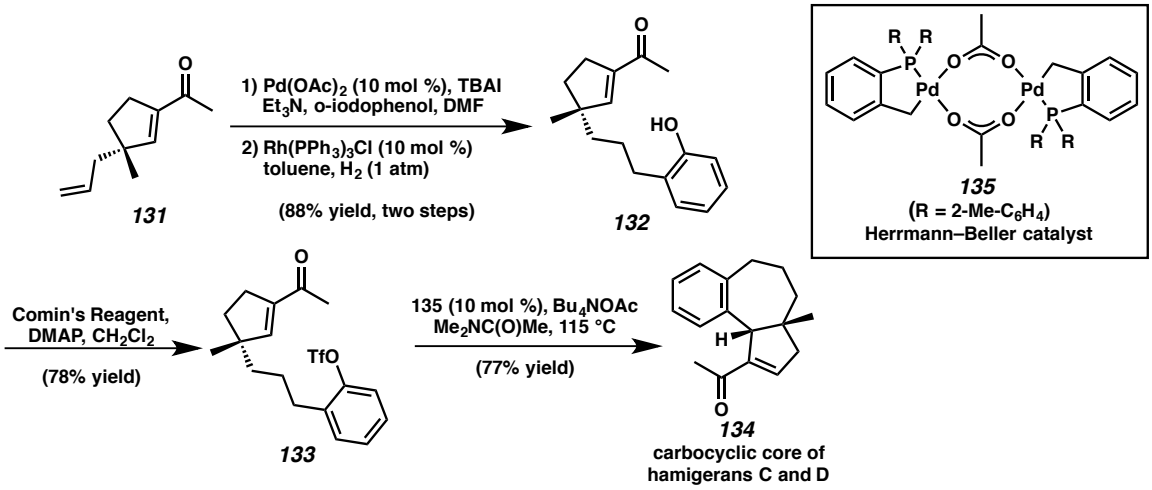


6.2 RESULTS AND DISCUSSION

6.2.1 Synthesis of a Model System and Retrosynthetic Analysis

Studies toward the syntheses of hamigerans C and D were initiated during our investigations of the asymmetric synthesis of γ-quaternary acylcyclopentenes.[3] From acylcyclopentene **131**, we were able to assemble the 6-7-5 carbocyclic core of hamigerans C and D (**134**) in good overall yield over four synthetic steps, featuring two sequential Heck cross-coupling reactions (Scheme 6.2).

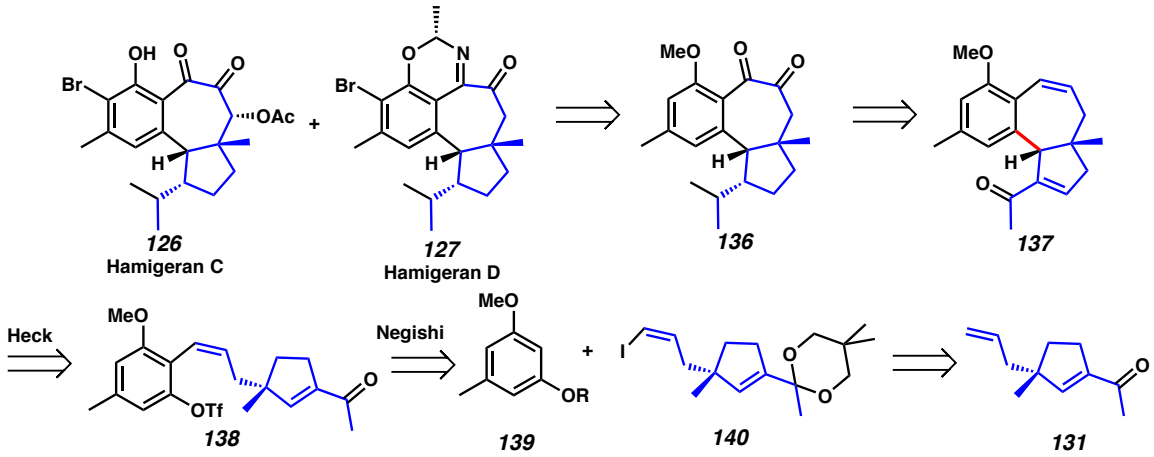
Scheme 6.2. Synthesis of the 6-7-5 carbocyclic core of hamigerans C and D.[3]



Notably lacking on tricycle **134**, however, is substitution on the aromatic C-ring and any functional handle on the benzannulated cycloheptyl B-ring of the natural products. The latter is due to the (*E*)-selectivity in the coupling of **9** with *o*-iodophenol. The resulting olefin must be hydrogenated in order to perform the second Heck coupling, resulting in loss of the otherwise useful olefin moiety. As such, we envisioned a retrosynthetic strategy that would allow us to perform the first cross-coupling reaction to yield a (*Z*)-olefin with an appropriately substituted aromatic ring (Scheme 6.3). Such a strategy would allow us to obtain a tricyclic intermediate (**137**) with all of the necessary

functional handles in place to complete the first total syntheses of both of these natural products.

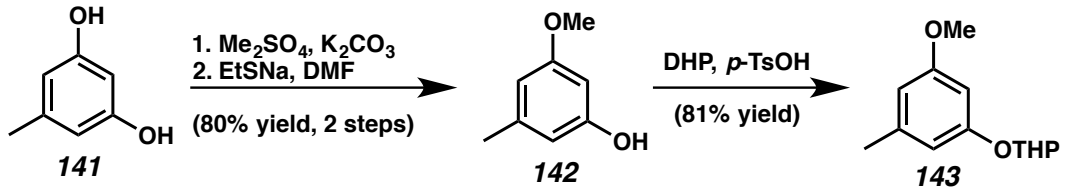
Scheme 6.3. Retrosynthetic analysis of hamigerans C and D.



6.2.2 *Synthesis of Negishi Coupling Partners*

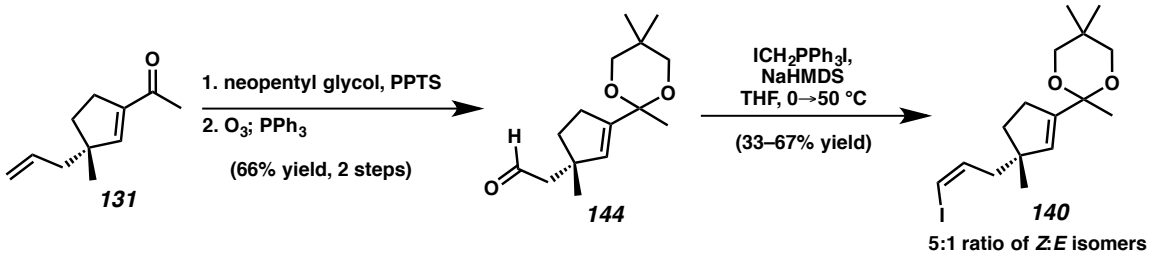
Our first synthetic efforts were directed toward synthesis of Negishi coupling partners **139** and **140**. We desired a differentially protected orcinol derivative, as one phenol group would need to be deprotected and converted to an aryl triflate for the planned Heck cross-coupling, while the other phenol would be need to be robustly protected as a methyl ether to be revealed late in the synthesis as the phenol present in hamigeran C or the phenol precursor to the oxazine moiety of Hamigeran D. Synthesis of the *O*-methyl-*O'*-tetrahydro-2-pyranylorcinol **139** was accomplished by dimethylation and mono-demethylation of orcinol (**141**),[4a] followed protection as a THP ether[5b] in 64% yield over three steps (Scheme 6.4).

*Scheme 6.4. Synthesis of Negishi cross-coupling partner **139**.*



Synthesis of (*Z*)-vinyl iodide **140** represented synthesis of a novel target from acylcyclopentene **131**. Following the established procedure for ketal protection of the enone,[3] the resulting diene could be selectively ozonolyzed to yield aldehyde **144** in 66% yield over 2 steps. However, yields obtained using the (*Z*)-iodomethylenation procedure reported by Stork[5] proved unreliable upon several repeated experiments (Scheme 6.5).

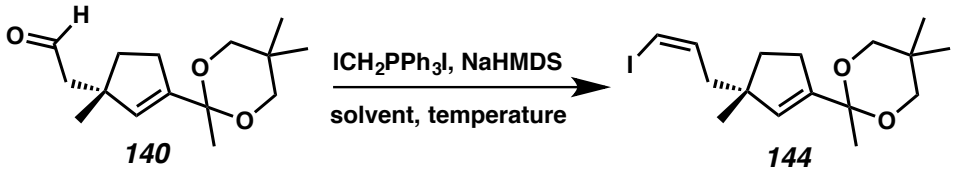
*Scheme 6.5. Initial efforts towards Negishi cross-coupling partner **140**.*



While mass-balance for this transformation was consistent, varying amounts of starting material contaminated by deprotection side-products were reisolated, with yields of the desired vinyl iodide **140** ranging from 33–67%. Moreover, the 5:1 ratio of *Z*:*E* isomers (as determined by integration of the terminal vinyl proton in the ^{1}H NMR spectrum) could not be separated by chromatography through gel of silica, alumina, or silver nitrate-impregnated silica with a wide variety of eluent combinations. We saw this as an early opportunity to address optimization of our synthetic route, as formation of (*Z*)-olefin **138** was considered paramount to our ability to access an intermediate with functionality on the B-ring such as **136**.

As unreacted starting material appeared to be the cause of loss of yield in this transformation, we considered that, given the quaternary center proximal to the aldehyde of **144**, nucleophilic approach by the Wittig reagent was extremely hindered. We reasoned that the Wittig reagent was instead acting as a base, deprotonating the α-position of **144** to yield an unreactive enolate. We began optimization studies by increasing the temperature at which aldehyde was added to the solution of Wittig reagent (Table 6.1).

*Table 6.1. Optimization of synthesis of **144**: solvent and temperature effects.*



140 ***144***

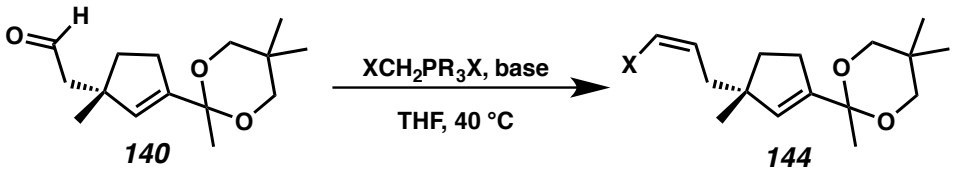
Solvent	Temperature	Z:E Ratio	Yield
THF	0→50 °C	5:1	33–67%
THF	40 °C	5:1	66–87%
THF	30 °C	5:1	63%
Benzene	50 °C	1.3:1	85%

Raising the temperature of addition to 40 °C and maintaining that temperature throughout the reaction yielded a consistent boost in yield (66–87%) without any detriment to the (*Z*)-selectivity. Reaction at 30 °C also appeared to be an improvement, though longer reaction times resulted in increased appearance of side products resulting from deprotection of the ketal. By increasing the temperature to 50 °C and performing the reaction in benzene, we were able to achieve a good yield, but noted a dramatic decrease in selectivity from 5:1 to 1.3:1 in favor of the (*Z*)-olefin.

Satisfied with the improved yields obtained by performing the reaction with an addition temperature of 40 °C, we sought to improve the (*Z*)-selectivity by modifying the

nature of the Wittig reagent. We imagined that modification of the aggregation state of the deprotonated Wittig salt by modifying the counterion or base used or by chelation of the counterion by hexamethylphosphoramide (HMPA), could benefit the selectivity of the reaction (Table 6.2).

*Table 6.2. Optimization of synthesis of **144**: alternate Wittig reagents.*



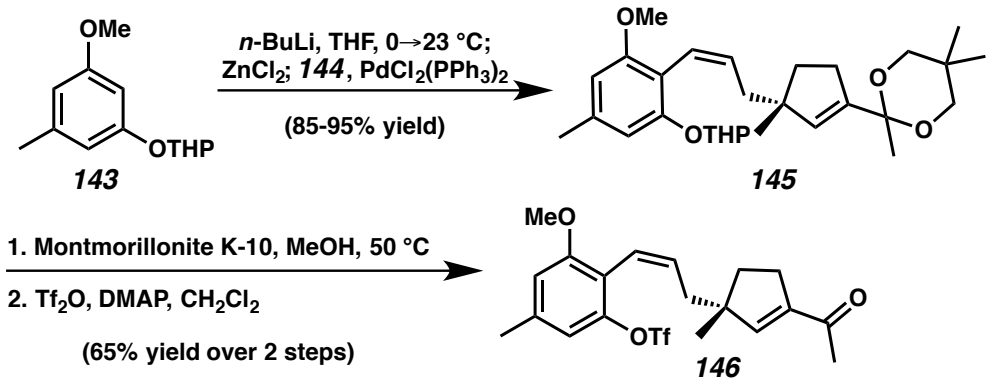
R	Base	X	*Z*:*E* Ratio
Ph	NaHMDS	I	5:1
Ph	LiHMDS	I	2.5:1
Ph	LiHMDS (5:1 THF:HMPA)	I	1.5:1
Ph	KHMDS	I	3.3:1
Ph	NaOt-Bu	I	2.3:1
Ph	NaHMDS	Br	1.4:1
n-Bu	NaHMDS	I	2.0:1
o-Tol	NaHMDS	I	0.9:1

Unfortunately, substitution of sodium hexamethyldisilylamide (HMDS) for lithium or sodium HMDS both resulted in a decrease in selectivity for the desired (*Z*)-olefin, as did addition of HMPA or the use of sodium *t*-butoxide. Moreover, tuning of the sterics of the Wittig reagent itself by substituting (iodomethyl)triphenylphosphonium iodide for the less bulky (bromomethyl)triphenylphosphonium bromide or (iodomethyl)tri-*n*-butylphosphonium iodide also resulted in a decrease in selectivity. To our surprise, the more sterically-hindered (iodomethyl)tri-*o*-tolylphosphonium iodide gave a modest selectivity of 0.9:1 in favor of the undesired (*E*)-olefin. As such, we returned to the use of our original Wittig reagent and base and proceeded with our synthetic studies.

6.2.3 Synthesis of an Elaborated Core of Hamigerans C and D

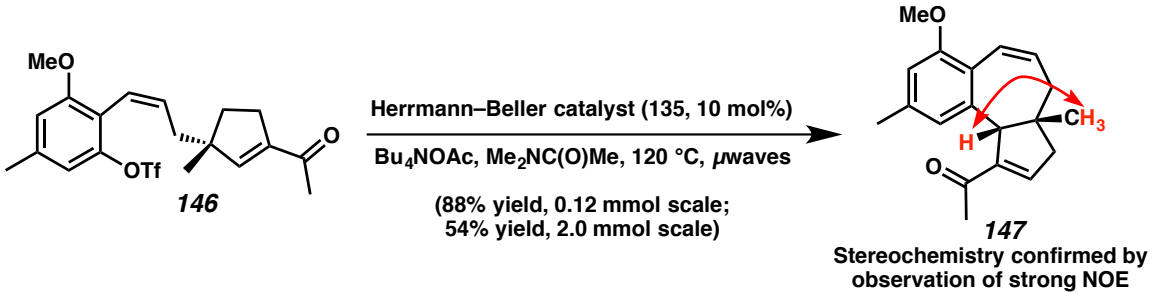
With the proposed Negishi cross-coupling partners in hand, we began investigations of this reaction. We anticipated being able to affect a selective deprotonation of **143** *ortho*- to the two ether substituents with *n*-butyllithium, followed by transmetallation with zinc(II) chloride to afford the Negishi coupling partner for vinyliodide **144** (Scheme 6.6.).

*Scheme 6.6. Negishi cross coupling of **143** and **144**.*



Gratifyingly, this reaction proceeded in good yield to afford **145** as a single product with respect to the deprotonation of **143**. Removal of both acetal and THP protecting groups proceeded smoothly using Montmorillonite K-10 clay in methanol at 50 °C, the crude product of which was >95% pure by ^{1}H NMR and could be used directly in the following step. We also found that triflation of the intermediate phenol could be affected using trifluoromethanesulfonyl anhydride and DMAP over a slightly longer reaction time but without loss of yield when compared to the more costly Comin's reagent (*N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide)), furnishing the desired aryl triflate **146** in 55–62% yield from Negishi coupling partners **143** and **145** over three steps.

Scheme 6.7. Intramolecular Heck reaction of ***146****.*

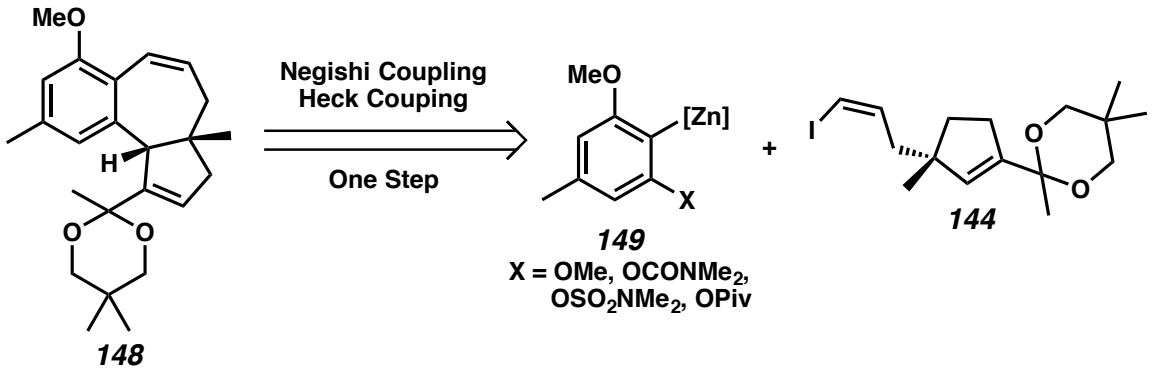


Aryl triflate **146** was subjected to conditions developed for the model Heck reaction (Scheme 6.2), modified to be run in a microwave reactor, yielding excellent results on small scale (Scheme 6.7). However, upon scale up, cleavage of the triflate caused a significant decrease in yield, and a large amount of an undesired acylated side-product was obtained.

6.2.4 Attempts Toward a Negishi-Heck Cascade Reaction

Considering that we performed two palladium(0)-catalyzed cross-coupling reactions in the span of four synthetic steps, resulting in a longer synthesis and lower overall yield, we began to consider the possibility of performing both metal-catalyzed *C*–*C* bond-forming reactions in a single step. In considering the use of a Negishi cross-coupling as the first of the two bond-forming events, we realized that deprotonation *ortho*- to a triflate, iodide or bromide would result in formation of benzyne,[6] which would lead to undesired side-reactivity. As such, our approach would demand use of a worse nucleofuge, X, than a halide that could still undergo C–X oxidative insertion by a transition metal (Scheme 6.8).

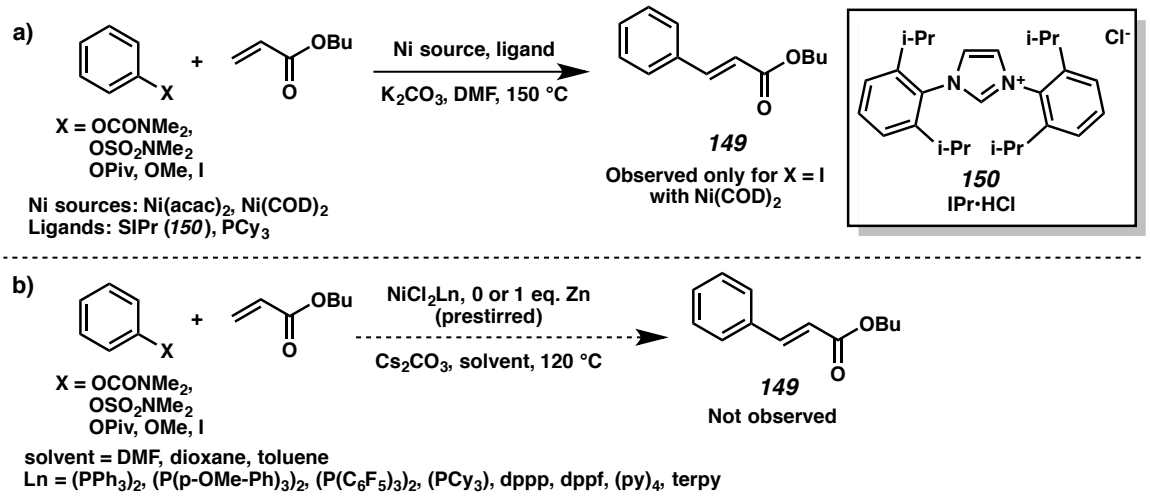
Scheme 6.8. Proposed Negishi-Heck cascade reaction.



Nickel-catalyzed cross-couplings of various phenol derivatives have become an area of intense research, with Kumada, Negishi and Suzuki-type couplings of aryl methyl ethers, carbamates, sulfamates and pivalates prevailing.[7] Inamoto and coworkers have reported the coupling of aryl bromides and iodides with *n*-butylacrylate using nickel(II) diacetylacetonate and *N*-heterocyclic carbene ligands to yield Heck-type products.[8a] Watson and coworkers have also reported the coupling of pivalates with styrene derivatives furnishing 1,2-diarylalkenes in good yield with nickel(0) dicyclooctadiene (cod) and 1,1'-bis(diphenylphosphino)ferrocene (dppf).[8b] Given this precedent, we imagined being able to first affect an Negishi cross-coupling between aryl zinc species **149** and our (*Z*)-vinyl iodide **144**, followed by an intramolecular Heck reaction by oxidative insertion into an unactivated aryl-oxygen bond to directly yield the desired tricyclic core of hamigerans C and D **148** in a single step. However, attempts to affect the nickel-catalyzed Heck cross coupling of *n*-butylacrylate and phenyl methyl ether, pivalate, dimethyl sulfamate or dimethyl carbamate resulted in no detection of product **149** by HPLC-MS (compared to a standard of genuine product) using either $Ni(cod)_2$ or $Ni(acac)_2$ as a nickel source and using the *N*-heterocyclic carbene derived from **150** or tricyclohexylphosphine as a ligand (Scheme 6.9a). Attempts to use nickel(0) complexes

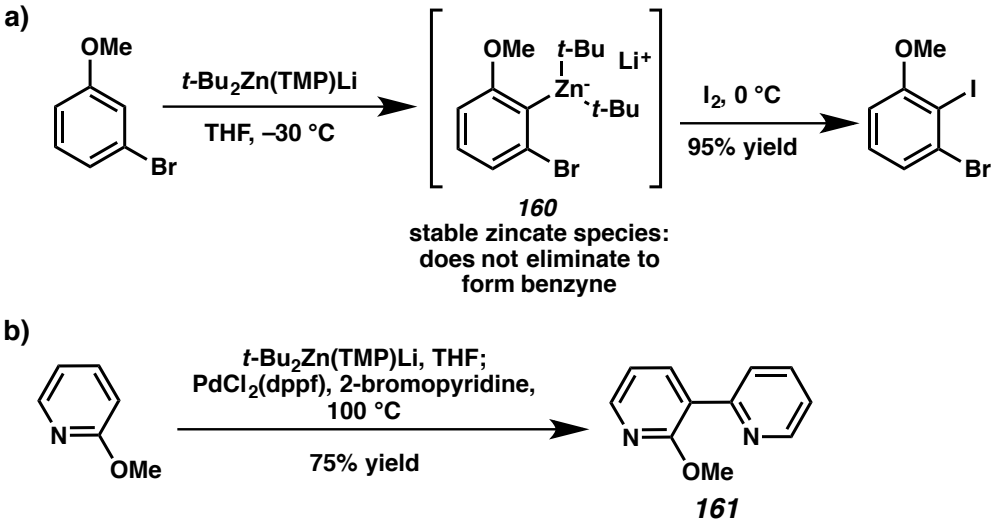
from nickel(II) complexes *in situ* with or without zinc as a reductant[9] in a variety of solvents similarly did not affect the desired transformation (Scheme 6.9b). We observed that only using iodobenzene and $Ni(cod)_2$ were we able to detect any coupling product.

Scheme 6.9. Unsuccessful attempts at a Ni-catalyzed Heck reaction.



Given these discouraging results, we considered another possibility. If we were to require a halide as a Heck coupling partner for the second cross-coupling, perhaps we could find an aryl zinc species that would not eliminate an *ortho*-halide to form benzyne. Uchiyama and coworkers have reported that *ortho*-deprotonation of aryl bromides with lithium di-*t*-butyl(2,2,6,6-tetramethylpiperidino) zincate (t-Bu_2Zn•Li(TMP)) does not result in elimination to form benzyne, even when warmed to room temperature (Scheme 6.10).

Scheme 6.10. Literature precedence for use of zincates in the Negishi cross-coupling.

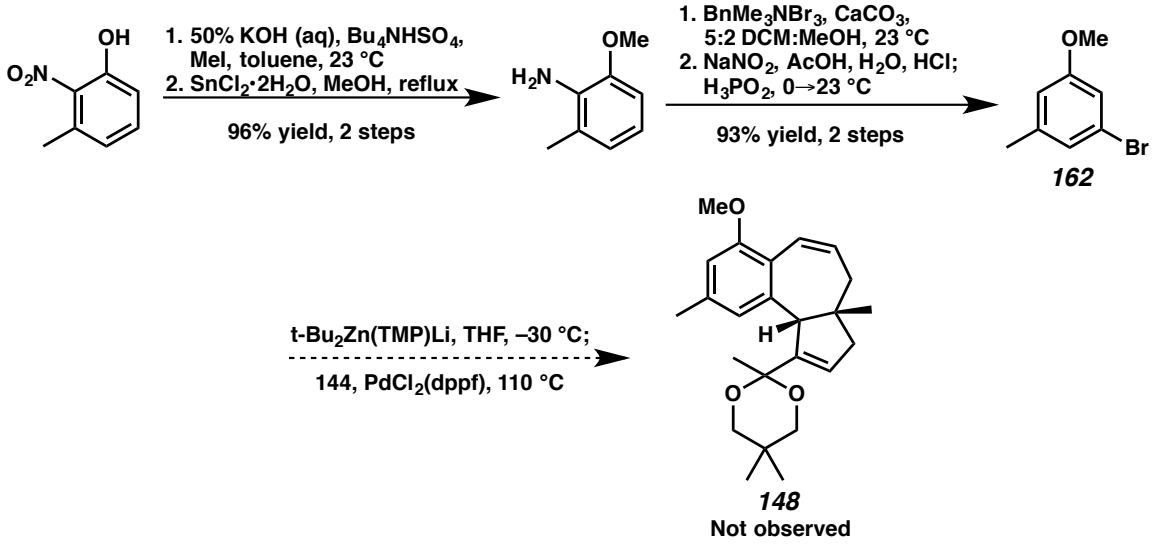


The resulting zincate species **160** can react with electrophiles such as molecular iodine or aldehydes to form the expected products in good to excellent yields (Scheme 10a).[10a] Encouragingly, Hevia has reported the use of these zincate intermediates in Negishi-type cross-coupling reactions to form bi-heteroarylspecies (e.g. **161**) in moderate to good yields (Scheme 10b).[10b] As such, we envisioned an *o*-bromo zincate species such as **160** to be an excellent candidate for our proposed Negishi–Heck cascade.

Following literature precedent, 3-methyl-2-nitrophenol was methylated,[11a] and the resulting nitro anisole was reduced with tin(II) chloride in methanol.[11b] *Para*-bromination of the resultant aniline with benzyltrimethylammonium tribromide an subsequent reduction of the aniline with hypophosphorous acid under Sandmeyer conditions[11c] yielded the desired 3-bromo-5-methylanisole **162** in 89% yield over four steps. Upon subjection of **162** to Uchiyama's deprotonation protocol and Hevia's cross-coupling conditions,[10] complete consumption of both starting materials and formation of

several products were observed. However, neither the exact mass for ketal **148** nor deprotected ketone **147** could not be found by HPLC-MS of the crude reaction mixture, and no product was isolated, though further investigations were precluded by material limitations.

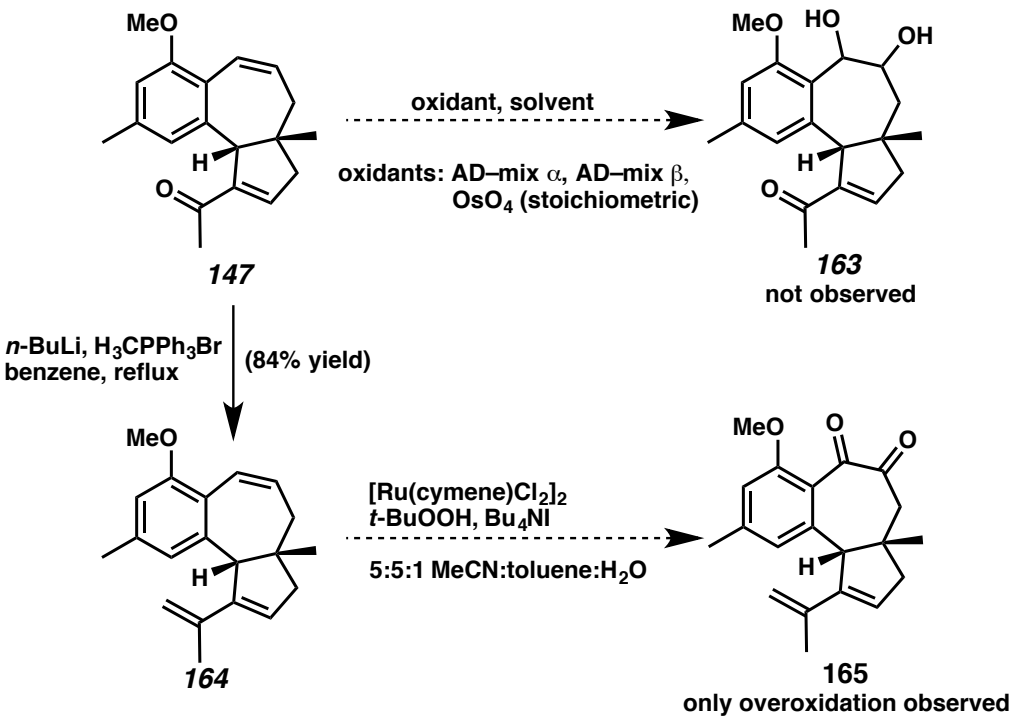
Scheme 6.11. Attempts at a zincates Negishi cross-coupling.



6.2.5 Elaboration of the Hamigeran C and D Core

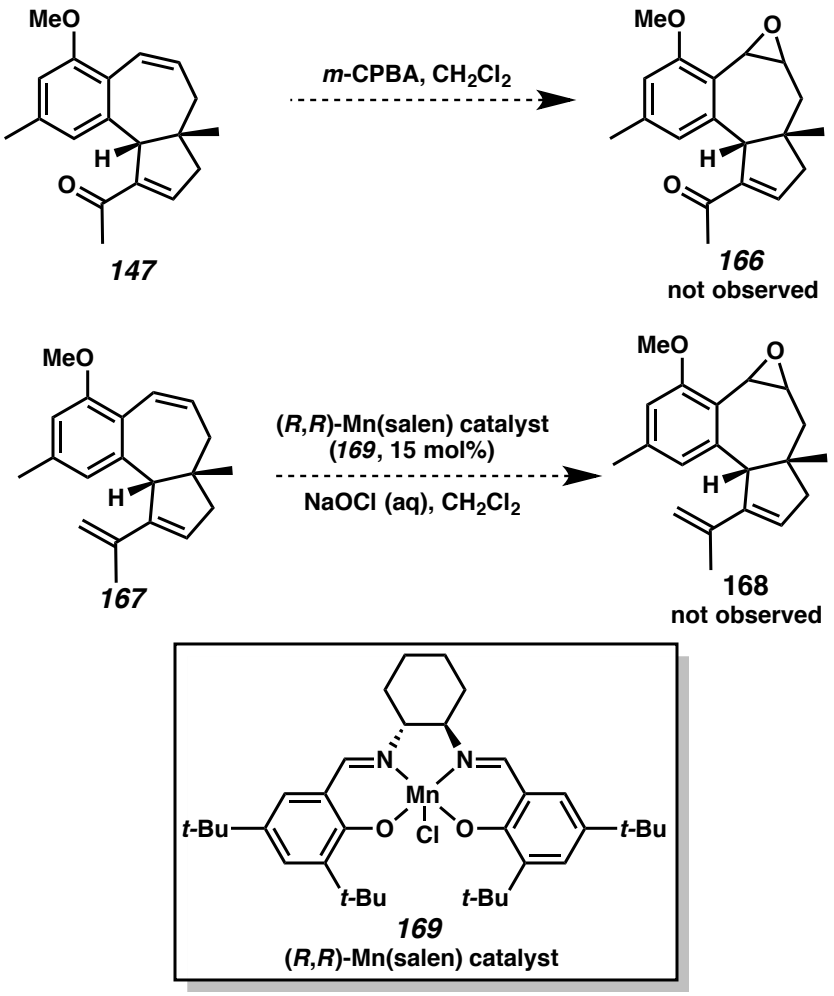
With functionalized tricyclic core of hamigerans C and D (**147)** in hand, we turned our attention to oxidation of the B-ring to install the two necessary oxygen atoms present in both natural products. While we initially anticipated a facile dihydroxylation of the electron-rich styrene, this transformation proved non-trivial. In fact, treatment of **147** with AD–mix α or β or stoichiometric osmium tetroxide in either *t*-butanol/water or a quaternary solvent mixture of water, *t*-butanol, carbon tetrachloride and acetone used by Clive in the dihydroxylation of a similar intermediate in his hamigeran B synthesis[2d] all failed to furnish any product of oxidation (Scheme 6.12).

Scheme 6.12. Initial round of oxidation attempts.



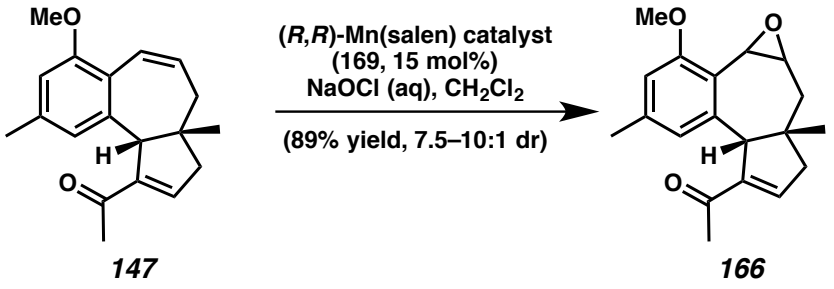
Wittig olefination with bromomethyltriphenylphosphonium bromide and *n*-butyllithium in refluxing benzene yielded triene **164** in 84% yield, but attempts to selectively oxidize the styrenyl olefin of **164** with *t*-butyl hydroperoxide and dichloro ruthenium(II) cymene dimer[12] (Scheme 12, **165**) resulted in rapid overoxidation of starting material, as evidenced by the disappearance of all signals in the olefin region of the crude ^{1}H NMR spectrum. Attempts to selectively oxidize the styrenyl olefin of **164** with electrophilic epoxidizing reagents such as *m*-CPBA resulted in only oxidation of the enone moiety, while use of the Jacobsen (*R*,*R*)-Mn(salen) epoxidation catalyst **169** in hopes of selectively oxidizing the cis-olefin of triene **167** also failed (Scheme 6.13).

Scheme 6.13. Second round of oxidation attempts.



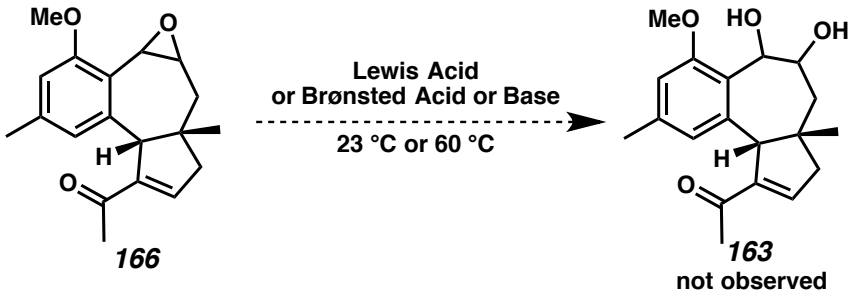
At last, epoxidation of enone **147** was affected in a mixture of aqueous bleach and dichloromethane with (*R*,*R*)-(Mn)salen epoxidation catalyst **169** to afford epoxide **166** in 89% yield and 7.5–10:1 d.r. (Scheme 16.4)

Scheme 6.14. Successful oxidation of the hamigeran C and D core.



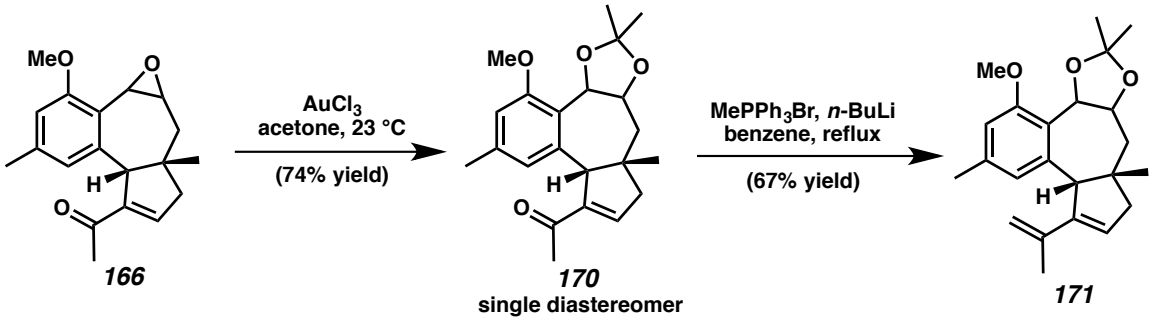
We next turned our attention to the opening of epoxide **166** in order to protect this presumably sensistive functional group to allow the necessary manipulations of the A-ring. To our surprise, a number of Lewis and Brønsted acids as well as Brønsted bases in a number of solvents failed to afford expected diol **163** even at elevated temperatures (Scheme 6.15).

Scheme 6.15. Unsuccessful attempts at epoxide opening.



After the failure of extensive screening to yield reliable hydrolysis conditions, we discovered that treatment of **166** with catalytic gold(III) chloride in dry acetone[13] directly yielded protected diol **170** by in 74% yield as a single diastereomer (Scheme 6.16). The final carbon of hamigerans C and D could be installed by submitting acetal **170** to previously established Wittig conditions (Scheme 6.12) to yield diene **171**.

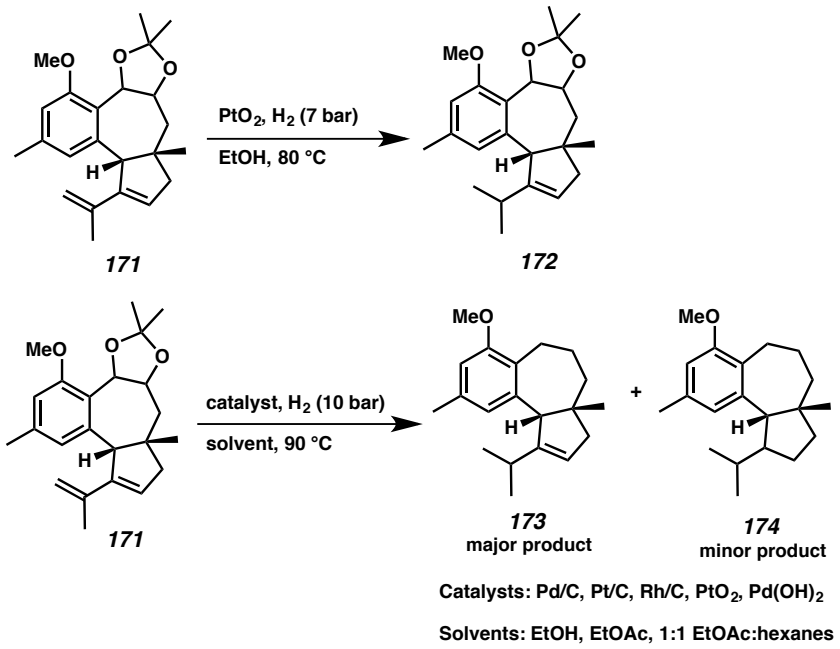
Scheme 6.16. Epoxide opening and installation of the final carbon of Hamigerans C and D.



With advanced intermediate **171** in hand, we set our sights on setting the final isopropyl stereocenter of the A-ring. We anticipated that hydrogenation of diene **171**

would furnish the desired stereocenter based on the concavity of the tricyclic core assembled. Initial attempts to hydrogenate diene **171**, however, resulted only in isolation of the product of hydrogenation of the more accessible olefin, **172** (Scheme 6.17).

*Scheme 6.17. Failed hydrogenation attempts of diene **171**.*

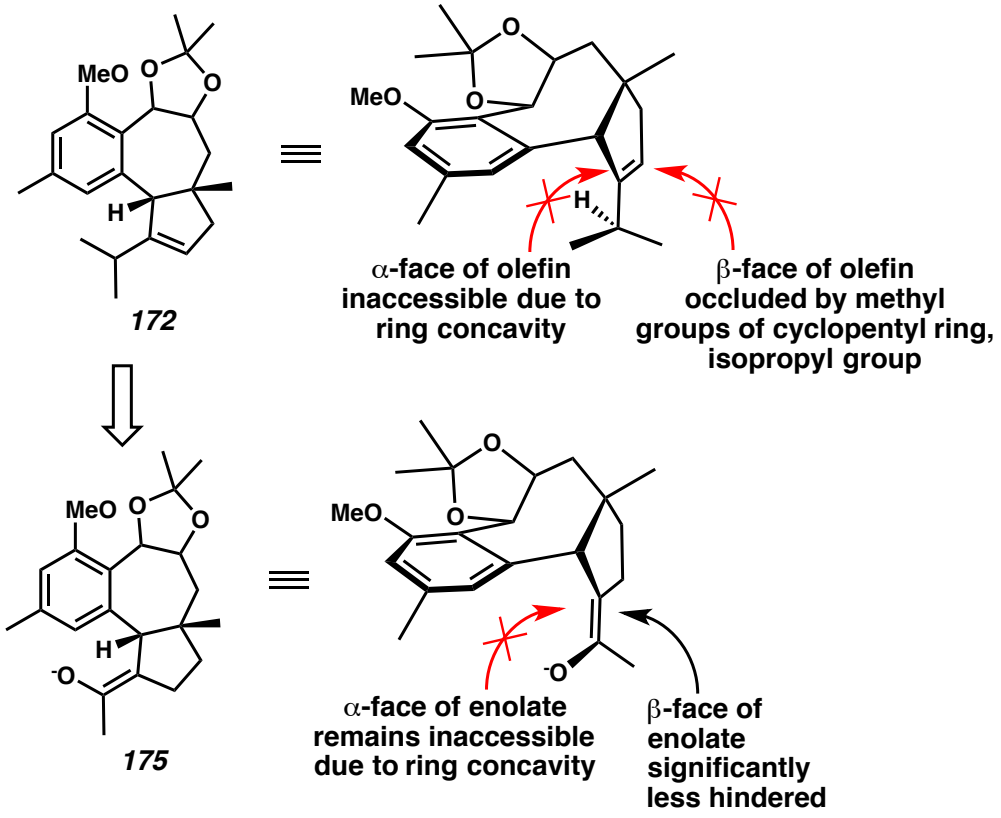


Under more forcing conditions with a number of catalysts and solvents, products resulting from hydrogenolysis of the acetal moiety were observed, typically as a mixture consisting mostly of trisubstituted olefin **173** with a small amount of fully hydrogenated **174** (diastereomeric ratio of **174** was not determined due to the small amount observed and the difficulty of separating the two extremely non-polar products).

Further inspection of mono-olefin intermediate of the hydrogenation **172** reveals that, upon hydrogenation, the isopropyl moiety must rotate such that the hydrogen is facing into the convex face of the molecule to prevent a severe steric interaction. This results in the occlusion of the olefin β-face by both the isopropyl group as well as the

nearby quaternary carbon, while the α-face is inaccessible due to the concavity of the molecule's core (Figure 6.2).

Figure 6.2. Analysis of challenges in the attempted hydrogenation reactions.



We imagine that this hurdle could be overcome by instead setting this stereocenter by protonation of enolate **175**. Due to the absence of the isopropyl substituent, the β-face of the olefin is significantly more accessible than in that of **172**. Thus, by setting this stereocenter before imposing the steric demands of the isopropyl group, we hope to be able to circumvent the problem that it appears we created for ourselves in our attempts to hydrogenate **172**.

6.3 CONCLUDING REMARKS

In conclusion, we have synthesized advanced intermediate **171**, bearing all of the carbon atoms present in Hamigerans C and D and all of the necessary functional handles required to complete their synthesis. We have proposed a method to circumvent the problems encountered in hydrogenation to set the final stereocenter, at which point elaboration of the aromatic C ring and oxidation state manipulations are all that would be required to complete these syntheses. We have also proposed a tandem Negish-Heck reaction that, while of yet unsuccessful, could represent a useful method for the synthesis of benzannulated molecules. We hope that completion of the synthesis of these molecules could allow for further biological testing, and set precedence for the synthesis of similar 6-7-5 tricyclic systems.

5.4 NOTES AND REFERENCES

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ABOUT THE AUTHOR

Doug Duquette was born in Springfield, MA to Jeffrey Duquette and Elizabeth Goode and spent his early years in western Massachusetts. From an early age, he was drawn to science, and in high school was inspired by his chemistry teacher to pursue chemistry in college.

At Harvard, he performed research in the lab group of Professor David A. Evans during the school year, and during the summers interned for Merck and Pfizer. He found a special interest in organic chemistry, and graduated in 2009 with his BA and MA in chemistry. After graduation, he spent a year in Germany on the Congress-Bundestag Youth Exchange Fellowship. There, he studied at the University of Mainz and had an internship with Boehringer-Ingelheim.

Upon returning from Germany, he moved to Pasadena, CA to begin his graduate studies under Professor Brian M. Stoltz. His research focused on expansion of the scope and deepening of the understanding of the palladium-catalyzed asymmetry decarboxylative allylic alkylation reaction, especially in the context of enaminones and acyclic substrates. While at Caltech, he met his partner, Dr. Stephanie Phan, with whom he has happily lived with for four years.

Outside of the lab, Doug enjoys playing ultimate Frisbee, reading the novels Dostoevsky, hiking and dabbling at the guitar. Following his graduation from Caltech, Doug will remain near his family in Los Angeles and teach a lab course at Occidental College before embarking on his independent career.