CONVERGENT METHODS FOR SYNTHESIZING RINGS IN THE CONTEXT OF NATURAL PRODUCT SYNTHESIS:

I. Development of a Tandem Stille-Oxa-Electrocyclization Reaction, and Progress Toward the Total Synthesis of Saudin

II. Development of the Direct Acyl-Alkylation of Arynes, and its Application Toward the Total Synthesis of Amurensinine

Thesis by

Uttam Krishan Tambar

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

2006

(Defended December 6, 2005)

To my big brother

ACKNOWLEDGEMENTS

This is by far the most important part of my thesis. Synthetic chemists often define their achievements in terms of the number of natural products they have made or the number of novel reactions they have developed. Yet, I realize that my greatest achievements have been the professional and personal relationships I have developed that have gotten me to this stage in life. So it is with tremendous gratitude that I write these acknowledgements to show my appreciation to some of the people who have helped me throughout the years.

Caltech is an amazing place to conduct research, and its commitment to excellence is showcased by the individuals who kindly agreed to serve on my thesis committee: Professors David MacMillan, Robert Grubbs, and Jonas Peters. Dave MacMillan is a motivated and fearless scientist who is never afraid of thinking big. I cannot begin to describe how much I have learned from Dave through all of our discussions. He has had a tremendous influence on how I think of chemistry, and I hope to continue to learn from him in the future. Bob Grubbs may be the most down-to-earth genius on the planet. The Nobel Prize committee could not have given the award to a better human being. I am grateful for all the scientific and career advice Bob has provided me over the years. Jonas Peters has a tremendous energy and excitement for chemistry, and it is always inspiring to be around him. Jonas was the first person at Caltech to playfully chastise me for ignoring the details of metals in my proposed catalytic cycles, and I am thankful for this. I consider myself very fortunate to have had this opportunity to interact with the members of my committee and other distinguished faculty members at Caltech, and I look forward to staying in touch with them.

At Caltech I have learned some of my most valuable lessons from my peers. I would like to express my gratitude to the entire chemistry class that arrived at Caltech in the fall of 2000. This is an amazing group of people, and I have benefited so much from all of our time together. We have been through a lot over the last few years, and I feel so fortunate that they have always been there to support me. I would like to thank the members of my class in the Stoltz group. Our advisor has high standards for his graduate students because he was fortunate enough to have a rookie class like them. We all had a part in turning this young lab into a chemical powerhouse. A special thanks to Sarah Spessard, Neil Garg, Jeremy May, Raissa Trend (she came in 2001, but she's wise beyond her years), and Jeff Bagdanoff for making my experience at Caltech so pleasant. We had some incredible times over the years. Thank god for Amigos (Adios…) and the Christmas parties (electrical cart).

When I first came to graduate school, the older students at Caltech helped to shape me as a scientist. Jake Wiener, Arnab Chatterjee, Vy Dong, and Steve Goldberg provided a great deal of guidance during the early years. I must also thank the amazing Richmond Sarpong. His persistent enthusiasm is a great source of inspiration. I would not have the strength to stay in synthetic chemistry without his support. And of course I must thank the humble Taichi Kano, my partner in crime for the saudin project. Once, during group meeting, someone asked Taichi why he didn't sign up for more group jobs. He replied that he had the most difficult group job: taking care of Uttam! This statement was absolutely true. He taught me how to perform chemistry in lab and how to emotionally survive chemistry outside of lab. I am sure he will continue to be an important influence in my life for many years to come.

A special thanks to my other co-workers as well. I don't know what I did in my previous life to deserve the honor of working with Sekar Govindasamy, John F. Zepernick, and David C. Ebner. They are very talented chemists and even better people. Having a supportive bay mate can make a significant difference in graduate school. Thank you Yeeman Ramtohul, J. T. Mohr, and John Enquist for making it a pleasure to come to lab.

The friendships I have developed with the entire Stoltz group (past and present) will last a lifetime. It is such a supportive environment for conducting research. Ryan Zeidan, the original Playmaker, is like a little brother to me, and he has always been there to help me in my times of need. I have every intention to send my children to Ryan's home for their summer vacations so that he can teach them how to play football. Blake Green always knew how to make me laugh, and I will always appreciate that. Dan Caspi is known for being the computer guru of the group, but to me he is so much more. He has made Caltech tremendously fun, and I could not have made it through without his advice and sense of humor. There's no doubt in my mind that we will continue to make our yearly trips even once I leave Caltech. Viva Las Vegas, yah tu sabes! I would also like to thank Ernie Cruz. If everyone in the world had a friend like Ernie, the world would be a much happier place. Lunch will never be the same without him. I hope some day I can convince Gina and Ernie to move to the east coast. Until then, I guess I will have to make many trips out here to Pasadena.

I want to thank Dan Caspi, Raissa Trend, David Edner, and the magnanimous Jenny Roizen, who kindly and patiently took the time to proofread my thesis. They deserve credit for any coherence in the following pages. I am grateful for the support and friendship of the wonderful staff at Caltech: Dian Buchness, Lynne Martinez, Linda Syme, Mona Shahgholi, Scott Ross, Larry Henling, Mike Day, Tom Dunn, Rich Gerhart,

Joe Drew, Moises Renteria, and Terry James. They do the behind the scenes work that makes it possible for us to conduct our research.

Thanks also to my friends beyond the Stoltz group. The eating club has made my last couple of years at Caltech my happiest years. Thank you for always making me laugh. I would especially like to thank Melanie Pribisko for always being there to support me. I hope Mel never changes who she is.

At this point, I would like to thank Erna Knolmar for all of her support and words of encouragement. In many ways she has become like family. I think Harry Stoltz should probably thank the older graduate students in our group, because his mother had great practice in parenting while she took care of many of us. There were days during graduate school when I was convinced that I was the worst chemist in the world. But I knew that even on those days Erna would believe in my abilities as a chemist. Somehow Erna would always know when I needed to hear words of encouragement. She probably does not realize how much her support has meant to me over the years.

As much as my time at Caltech has shaped me over the past five-plus years, individuals in my pre-Caltech life have helped define me.

My desire to seek answers for unanswered questions, which eventually drove me to pursue graduate studies in chemistry, was developed when I was very young. I would like to take this opportunity to thank all my childhood teachers. I had the pleasure of attending the United Nations International School from kindergarten through twelfth grade. During this time, I was guided by the most inspiring people. Specifically, I would like to thank the wonderful teachers of UNIS Queens, who helped a skinny, little, quiet Indian boy come out of his shell. I would also like to thank my high school teachers, Mrs. Sylvia Gordon, Mr. Anthony Doyle, and Mr. Jean Pierre Jouas. Mr. Jouas was the first person to encourage me to pursue a career in science, and I always feel what I do today is simply an extension of what he taught me.

Before I came to Caltech, I was fortunate enough to develop some amazing friendships that have withstood the test of time. I would like to thank my childhood friends, the crew. Over the years, they have always been there to support me, and they have taught me the true meaning of friendship. College was the first period in my life where I was living away from my family. Fortunately, I met an amazing group of people that made me feel at home. I would like to thank my Mather House brothers, especially my roommates who became my new family, and the rest of my new extended family throughout the hallways of our dorm. I would also like to thank the South Asian Association and all its members, who helped me stay connected to my roots and always reminded me of who I was.

My time at Harvard was great and helped me grow intellectually. I will always be grateful to Professor Cynthia Friend for giving me my first research opportunity. Her support throughout the years (even once I came to Caltech) has been priceless. I would also like thank Professor Stuart Schreiber, who helped me fall in love with organic chemistry. He has an amazing ability to think beyond the traditional boundaries of our field, and I feel fortunate to have had the opportunity to learn from him. In the Schreiber group I had the pleasure of working with some amazing scientists, including Derek Tan, Michael Foley, and Finny Kuruvilla. I would like to thank them for giving me a chance.

I must thank the most important people in my life, my family. I am nothing without them. My brother, Udai K. Tambar, is my best friend, my mentor, and my biggest pillar of support. I have known him for as long as I have known myself, and on most days I feel that he knows me better than I know myself. I could not imagine living a single day of my life without his support and guidance. My mother, Neelam Tambar, is the backbone of our family. She has sacrificed everything to ensure that my brother and I would always be able to strive for our goals. She deserves this Ph.D. as much as I do. My father, Balvir K. Tambar, is my role model in life. I need to thank him for developing my insatiable passion for pursuing knowledge. He has also taught me the value of hard work and humility. If I end up being one tenth the man that my father is, I will be a great man. I would also like to thank the two newest members of our family. My sister-in-law, Aparna Tambar, is an amazing person. She has always been willing to support me, especially during the toughest days of graduate school. Our family would not be complete without her. And of course I must thank my nephew, Karthik K. Tambar. His very existence is a source of inspiration. There is no doubt in my mind that he will achieve all of his goals in life. I would like to thank my extended family, especially my grandmother (Nani). She has always believed in me. I only hope that she realizes how much I love her.

Now that I have thanked my teachers, my co-workers, my friends, and my family, I must thank the only person in this world who seems to fit in all of these categories. How do I even begin to thank Brian Stoltz. I've known Brian for a long time now, and I have never had a difficult time saying anything to him. So it is ironic that I am having difficulty expressing my gratitude. How can I thank a person who has done everything in his power to make sure that I succeed in life. I'm getting emotional just thinking about it.

Intellectually, Brian has been an ideal advisor. I met him in the fall of 1998, when I was a skinny undergraduate student and he was a slim postdoc. At the time he was a Teaching Fellow for my advanced organic chemistry course. Seven years and fifty pounds later, Brian and I have both changed a great deal, but I am still learning so much from him. There is no doubt in my mind that I will be a student of Brian Stoltz for the

remainder of my life. As an advisor, he has always encouraged me to explore my ideas, and he has always guided me in the right direction. Brian's work ethic is inspiring, and his uncontrollable excitement for chemistry is contagious. Whenever I was losing motivation for a project, I knew that a five minute conversation with him would be enough to inspire me. Perhaps the only mistake Brian has made in his life has been to cheer for the Red Sox. Ah well, I guess no one is perfect.

The world knows Brian as a prolific, brilliant chemist. His intellect is only surpassed by his humility. And he is by far the hardest working person I know. But most of the world probably does not know that Brian is also an amazing friend. He has always been there to congratulate me on the happiest days of my life, and he has always been the first one to pick me up on the most difficult days of my life. I am able to sit here today and write my acknowledgements because of Brian's support. Although the occasion of my thesis defense marks the end of my time as a member of Brian's group, it also marks the beginning of a lifelong friendship.

ABSTRACT

Cyclic molecular structures are ubiquitous in chemistry. Efficient and convergent methods to synthesize these rings are of great importance, specifically in the context of natural product synthesis. The development of two methods for the synthesis of the core structures of the natural products saudin and amurensinine are described.

First, the development of the tandem Stille-oxa-electrocyclization will be discussed in the context of synthetic efforts with saudin. The labdane diterpenoid saudin was isolated in 1985 by Mossa and Cassady from the leaves of the *Clutia richardiana (L.)* family *Euphorbiaceae*. The natural product was found to induce hypoglycemia in mice and therefore could be an appealing lead structure for the development of new agents to treat diabetes. A diastereoselective tandem Stille-oxa-electrocyclization reaction has been developed, which provides access to the core structure of saudin in a rapid and convergent manner. Additionally, this new reaction has been extended to the convergent preparation of related polycyclic pyran systems. Progress has been made on the advancement of these complex pyran systems toward the synthesis of saudin.

Secondly, the development of the direct acyl-alkylation of arynes will be described in the context of the total synthesis of the isopavine natural product amurensinine. The isopavine alkaloids are promising lead structures for the treatment of neuronal disorders such as as Parkinson's disease, Down's syndrome, Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's chorea. All members of this family of natural products contain a seven-membered benzannulated carbocycle. To address the challenge of synthesizing the isopavines, an efficient and mild acyl-alkylation of arynes has been developed. The method forms *ortho*-disubstituted aromatic products that would otherwise be difficult to synthesize. Additionally, the method is used to synthesize medium-sized benzannulated carbocycles, such as the seven-membered ring structure in the isopavine alkaloids, by the ring-expansion of cyclic β-ketoesters. Overall, the transformation results in the formation of two new C–C bonds by the net insertion of an aryne into the α,β C-C σ-bond of a β-ketoester. This reaction has been applied in the total synthesis of amurensinine.

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER ONE

CHAPTER TWO

APPENDIX TWO

APPENDIX THREE

CHAPTER THREE

APPENDIX FIVE

CHAPTER FOUR

APPENDIX SEVEN

LIST OF SCHEMES

CHAPTER ONE

CHAPTER TWO

APPENDIX ONE

APPENDIX FOUR

CHAPTER THREE

CHAPTER FOUR

APPENDIX SIX

LIST OF TABLES

APPENDIX THREE

APPENDIX FOUR

CHAPTER THREE

APPENDIX EIGHT

LIST OF ABBREVIATIONS

p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl, acetate
AIBN	2,2'-azobisisobutyronitrile
app.	apparent
aq.	aqueous
atm	atmosphere
Bn	benzyl
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
°C	degrees Celsius
calc'd	calculated
CCDC	Cambridge Crystallographic Data Centre
m-CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
ee	enantiomeric excess
equiv	equivalent
EI	electrospray ionization
Et	ethyl

FAB	fast atom bombardment
g	gram(s)
h	hour(s)
η^3	trihapto
[H]	reduction
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
hν	light
Hz	hertz
IR	infrared (spectroscopy)
J	coupling constant
λ	wavelength
L	liter
m	multiplet or milli
m	meta
m/*z*	mass to charge ratio
μ	micro
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
nbd	norbornadiene
NMP	N-methylpyrrolidinone
NMR	nuclear magnetic resonance
nOe	Nuclear Overhauser Effect
[O]	oxidation
*t*OcNC	*tert*-octyl isocyanide

p	para
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
PhMe	toluene
ppm	parts per million
Pr	propyl
i-Pr	*iso*-propyl
pyr	pyridine
q	quartet
rt	room temperature
R_F	retention factor
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet

CHAPTER ONE

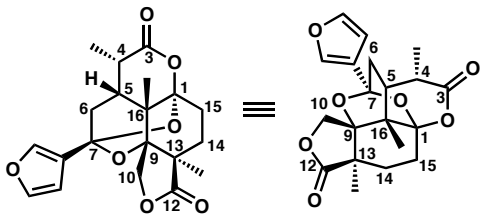
A Brief History of Saudin

1.1 Background and Introduction

1.1.1 Isolation and Proposed Biosynthesis

The caged diterpenoid saudin (**1**) was isolated in 1985 by Mossa and Cassady from the leaves of the *Clutia richardiana (L.)* family *Euphorbiaceae*, a toxic plant indigenous to the western and southern mountains of Saudi Arabia.[1] The complex polycyclic architecture was delineated by single crystal X-ray analysis and shown to be that depicted in Figure 1.1.1.

Figure 1.1.1



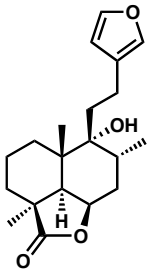
Saudin (1)

This unusual polycyclic natural product is presumably related to the labdane diterpenes (Figure 1.1.2). Within this family of natural products, saudin is a member of

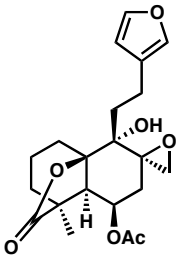
the furanoid labdanes (**2-4**), which may arise biosynthetically from the related pre-furanoid labdanes (**5-8**).

Figure 1.1.2

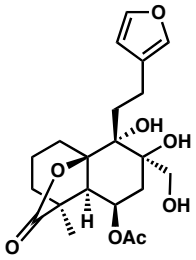
Furanoid Labdanes



Marrubiin (2)

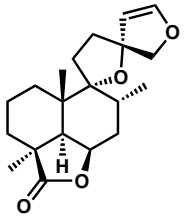


Nepetaefuran (3)

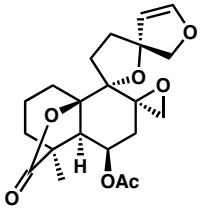


Nepetaefuranol (4)

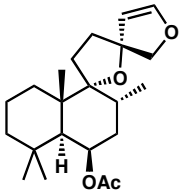
Pre-Furanoid Labdanes



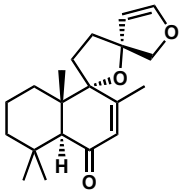
Premarrubiin (5)



Nepetaefolin (6)



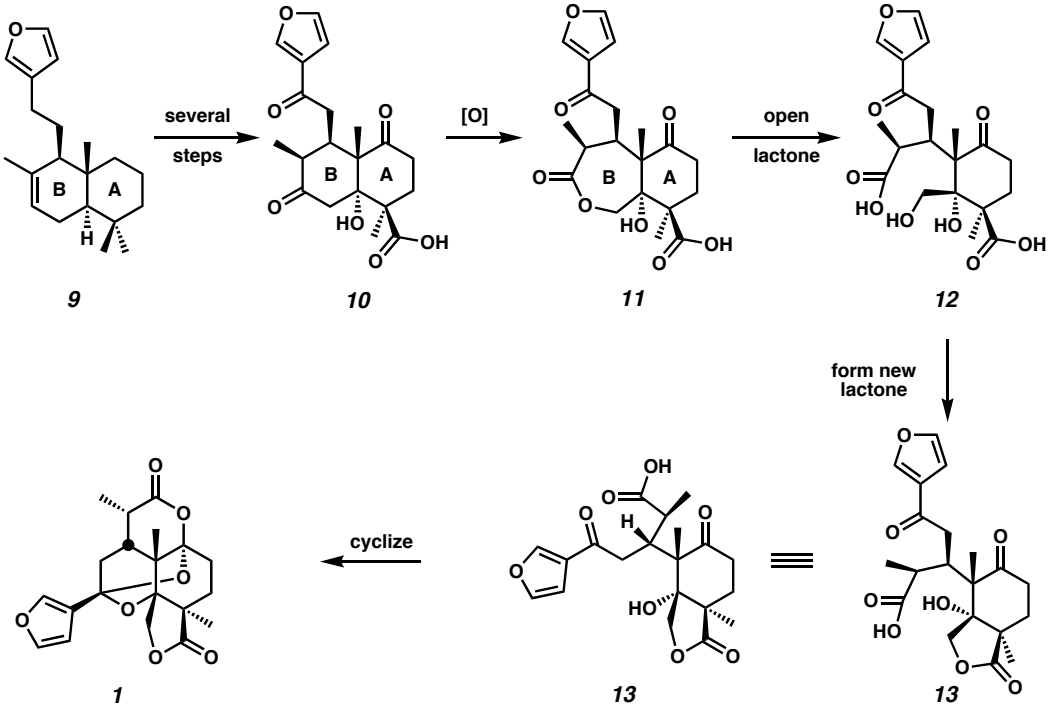
Prerotundifuran (7)



Presolidagenone (8)

In their original report on the isolation of saudin, Mossa and Cassady proposed a biosynthesis of the natural product based on its structural relationship to other labdane diterpenes (Scheme 1.1.1). Converstion of labdane precursor **9**[2] to triketone **10**, followed by oxidative expansion of the B ring, could lead to ε-lactone **11**. This intermediate could then undergo a series of hydrolysis and rearrangement steps to give the caged structure of saudin (**11→12→13→1**).

Scheme 1.1.1



1.1.2 Biological Activity

Three years after isolating and disclosing the structure of saudin (**1**), Mossa and co-workers reported the biological activity of this the novel caged diterpenoid.[3] Importantly, saudin was found to induce hypoglycemia in mice, both in vitro and in vivo. Given its potent hypoglycemic activity and oral bioavailability, saudin is an appealing lead structure for the development of new agents to treat diabetes mellitus. Unlike many other hypoglycemic agents, saudin's ability to reduce the glucose levels in mice and rats seems to be unrelated to the cellular pathways for insulin secretion. This unique mode of

action may provide a complementary form of treatment for diabetes mellitus, specifically in cases where other hypoglycemic agents have failed.

Diabetes mellitus, a group of diseases characterized by hyperglycemia, affects nearly 18.2 million people (6.3% of the population) and is the sixth leading cause of death in the United States (over 200,000 deaths per year).[4] In most cases it is the result of defective metabolism of insulin by the body. The disease is controllable in most patients using a regimen of diet, insulin injections, and oral hypoglycemic agents.[5]

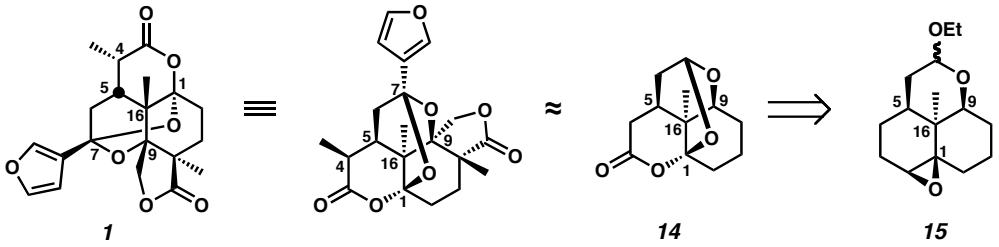
1.2 Synthetic Studies

In the twenty years since the isolation of saudin, a number of approaches to the synthesis of this natural product have been reported. Recently this effort resulted in the elegant syntheses of (±)-saudin by Winkler and (–)-saudin by Boeckman. These approaches, along with other incomplete synthetic efforts, are presented in this section.

1.2.1 González-Sierra's Approach[6]

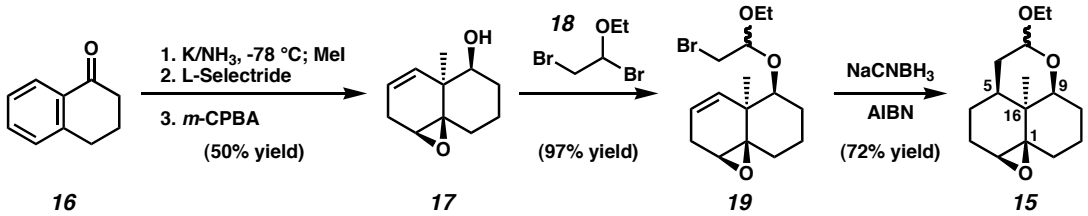
González-Sierra has developed an efficient strategy for generating the stereocenters at C(1), C(5), C(9), and C(16) of saudin (Scheme 1.2.1). His approach has focused on the construction of the polycyclic lactone **14**, which is a simplified model system for saudin. This intermediate may be accessed from epoxy-acetal **15**.

Scheme 1.2.1



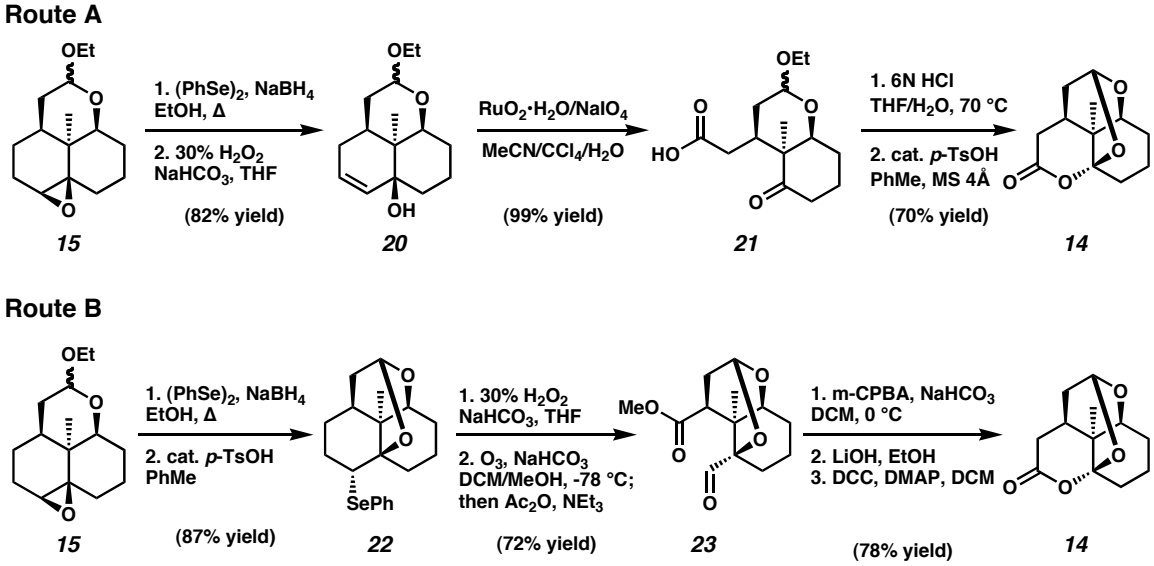
Epoxy-acetal **15** was synthesized rapidly from α-tetralone (**16**) via an intramolecular radical cyclization of bromoacetal **19** (Scheme 1.2.2). Importantly, this reaction sequence sets the correct relative stereochemistry at C(5), C(9), and C(16).

Scheme 1.2.2



With Epoxy-acetal **15** in hand, González-Sierra has developed two routes for the synthesis of lactone **14** (Scheme 1.2.3). In both cases, the decalin system was oxidatively degraded and recyclized to form the desired lactone functionality. The application of these strategies for the total synthesis of saudin is currently under investigation.

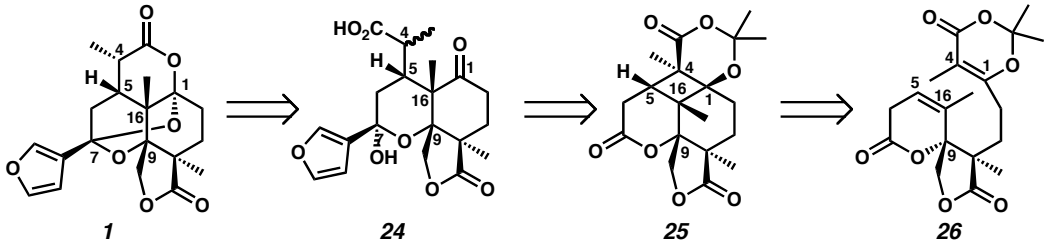
Scheme 1.2.3



1.2.2 Winkler's Approach[7]

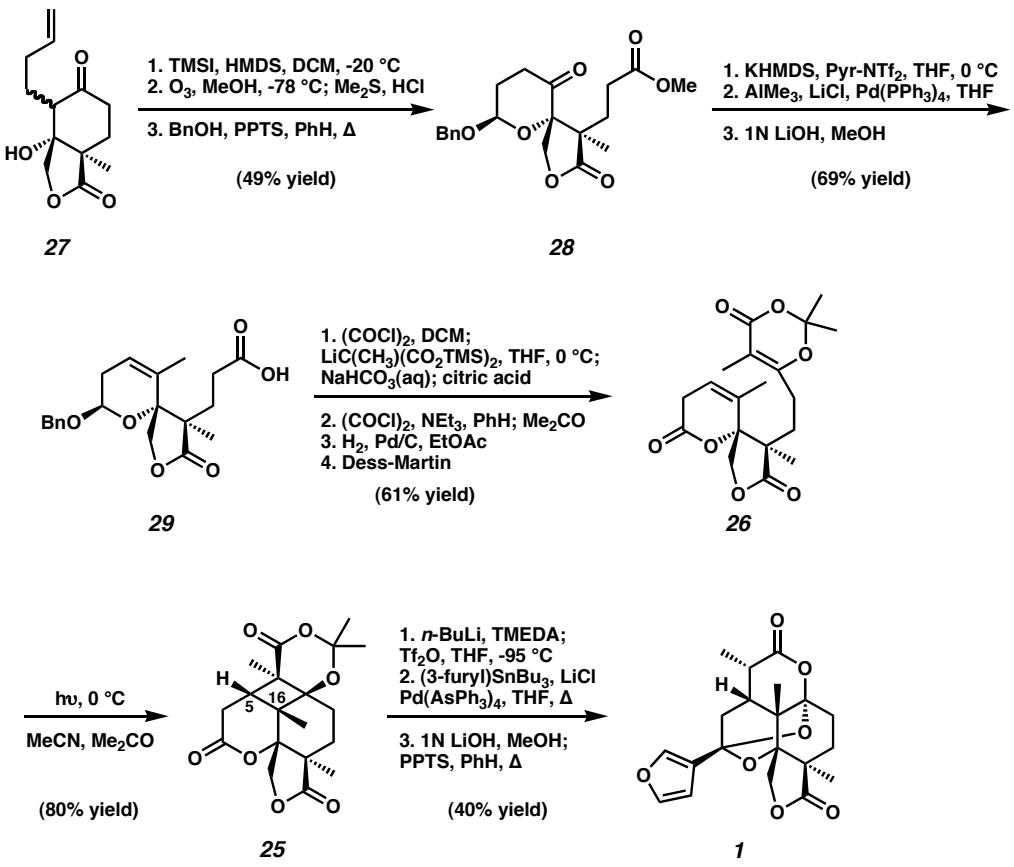
In 1999, Winkler reported the first total synthesis of (±)-saudin. The key step in this elegant strategy was an intramolecular [2+2] dioxenone photocycloaddition to generate the quaternary carbon center at C(16) (Scheme 1.2.4).

Scheme 1.2.4



Bicyclic ketone **27** was efficiently transformed into dioxenone **26** through a sequence that involved an oxidative cleavage of the six-membered ring structure in the starting material. Tricyclic dioxenone **26** underwent a highly diastereoselective [2+2] photocycloaddition to set the correct relative stereochemistry at C(5) and C(16) (Scheme 1.2.5). The cycloaddition product **25** was then easily converted to saudin following cyclobutane fragmentation and acetal constitution.

Scheme 1.2.5



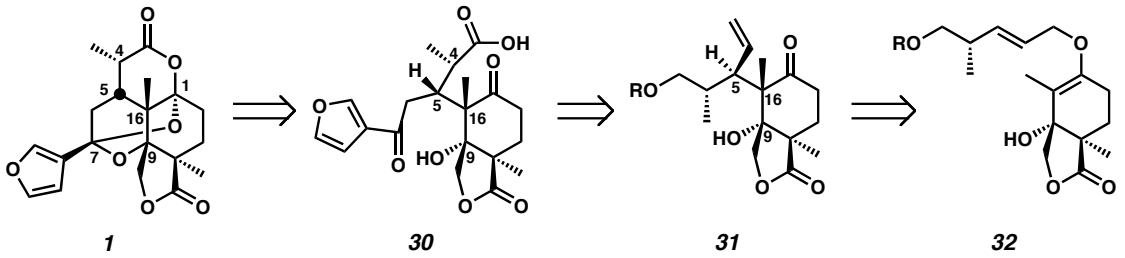
1.2.3 Boeckman's Approach[8,9]

Although Winkler was able to synthesize (±)-saudin, the absolute stereochemistry of the natural product was only established by Boeckman's total synthesis of (–)-saudin in 2002.

In his original strategy, Boeckman wanted to generate the correct relative stereochemistry at C(5) and C(16) via a Claisen rearrangement of enol ether **32** (Scheme

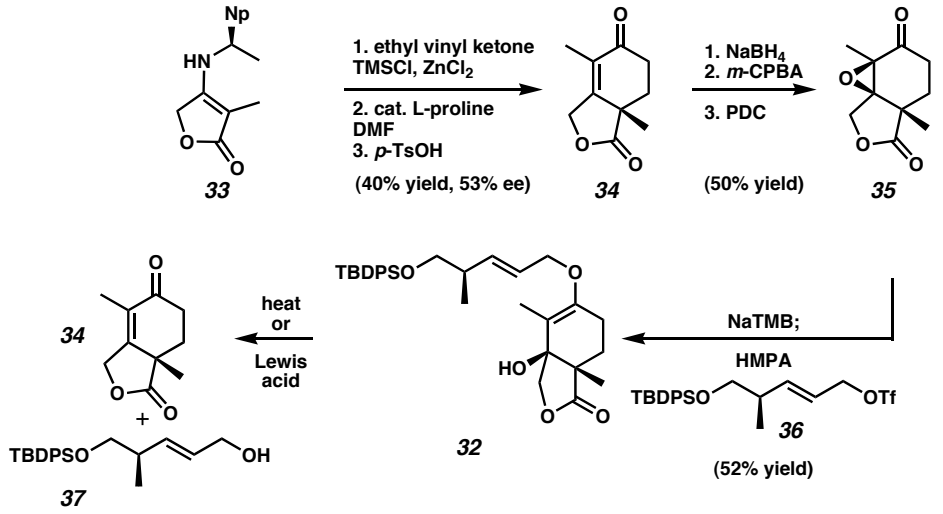
1.2.6). The diastereoselective formation of these two stereocenters proved to be a difficult task.

Scheme 1.2.6



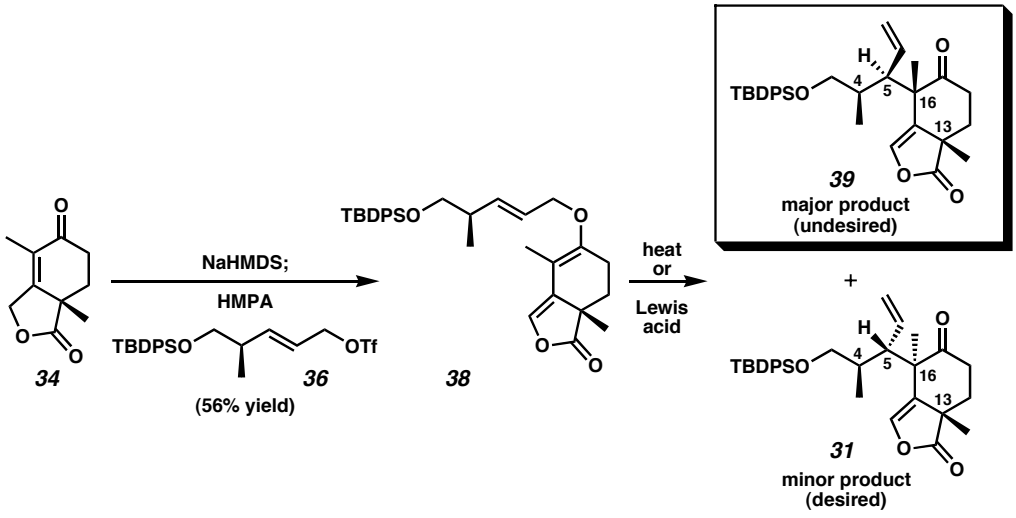
Although enol ether **32** was synthesized in 89% enantiomeric excess from chiral enamine **33**, the desired Claisen rearrangement was never realized under thermal or lewis acidic conditions (Scheme 1.2.7). In most cases the substrate for the Claisen rearrangement underwent hydrolytic decomposition to enone **34** and allylic alcohol **37**. This is presumably due to the susceptibility of enol ether **32** to β-hydroxy elimination.

Scheme 1.2.7



To address the instability of enol ether **32** to Claisen rearrangement conditions, an alternate Claisen strategy was explored. Enone **34** was converted to the extended enol ether **38**, which lacked the labile β-hydroxy functionality present in enol ether **32** (Scheme 1.2.8). Gratifyingly, this intermediate underwent a Claisen rearrangement. Unfortunately, the major product under both thermal and lewis acidic conditions was the undesired diastereomer **39**. Although the stereocenters at C(4) and C(5) could eventually be epimerized, the incorrect relative stereochemistry between the two quaternary carbon centers at C(13) and C(16) proved to be a fatal flaw in this synthetic strategy. It appeared that the bicyclic framework of enol ether **38** needed to be modified.

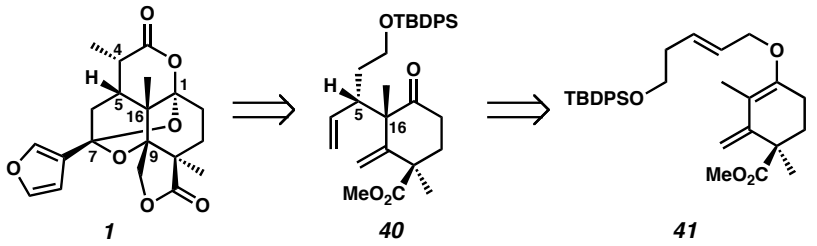
Scheme 1.2.8



Since the Claisen rearrangement approach did not provide the desired relative stereochemistry for the bicyclic enol ether class of substrates, Boeckman and co-workers

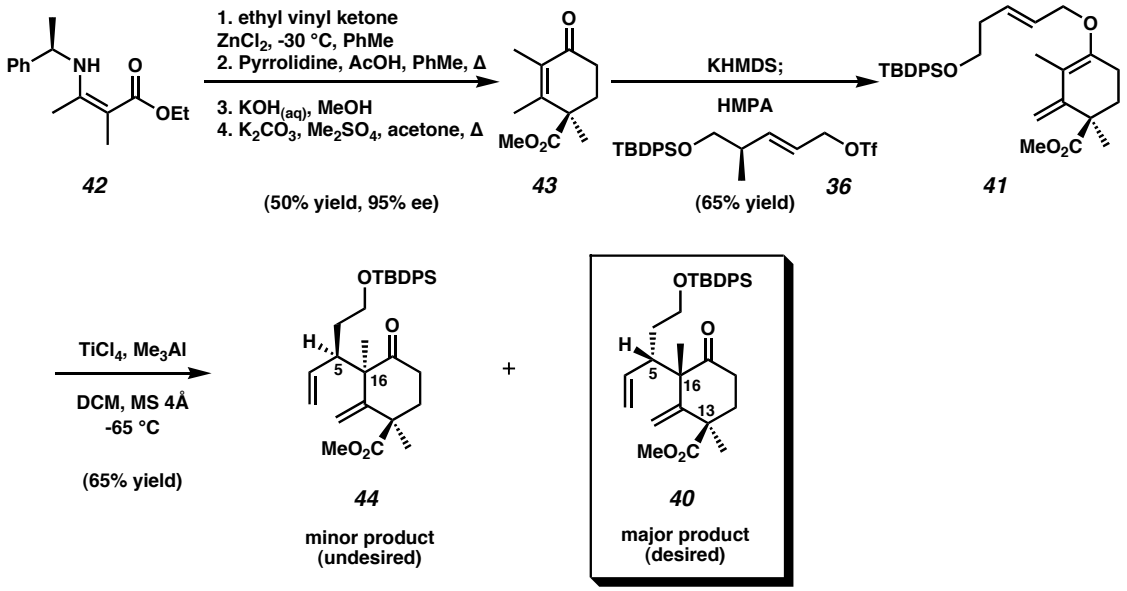
eventually made drastic modifications to the Claisen substrate (i.e., **41**, Scheme 1.2.9). In this new strategy, the lactone functionality would be installed later in the synthesis.

Scheme 1.2.9



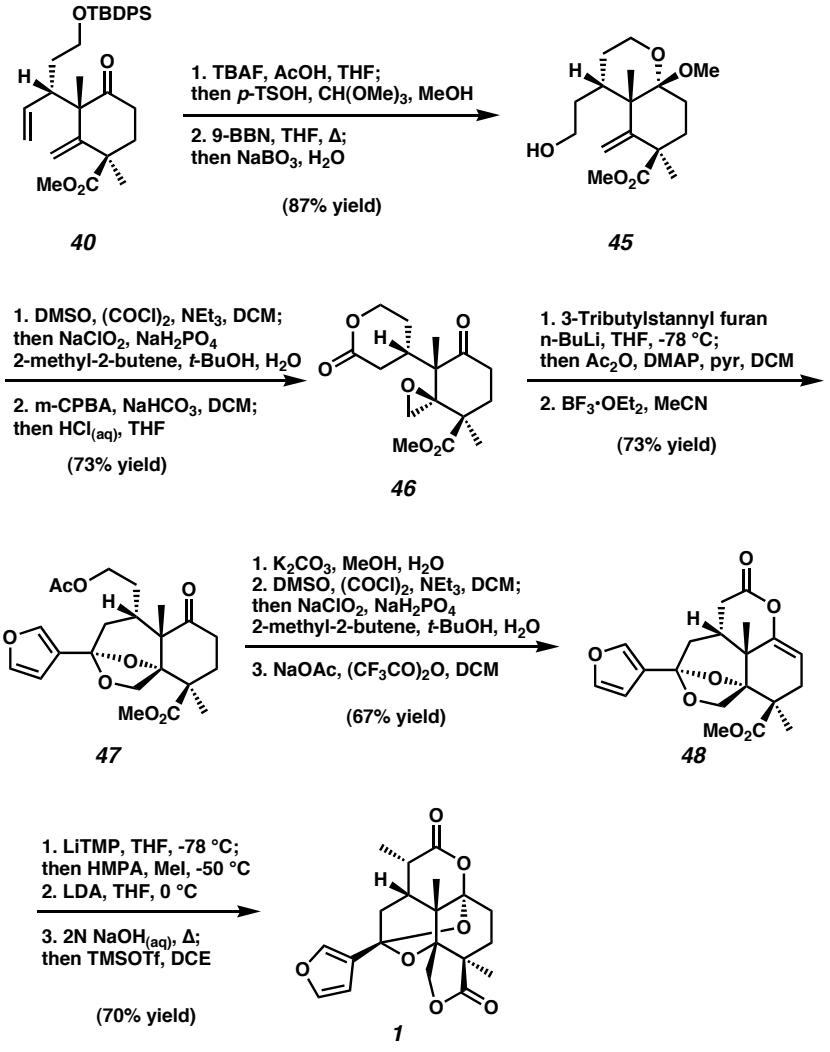
In analogy to the synthesis of bicyclic enol ether **38**, enol ether **41** was efficiently generated in high enantiomeric excess from chiral enamine **42** (Scheme 1.2.10). Gratifyingly, the lewis acid promoted Claisen rearrangement of this new enol ether yielded ketone **40** with the desired stereochemistry at C(5), C(13), and C(16).

Scheme 1.2.10



Claisen product **40** was then converted to (–)-saudin by a series of steps, which ultimately established the absolute stereochemistry of the natural product (Scheme 1.2.11).

Scheme 1.2.11



1.3 Conclusion

The caged diterpenoid saudin is a member of the furanoid labdane family of natural products. It has been shown to exhibit hypoglycemogenic bioactivity in mice and rats and is therefore a potential therapeutic agent for the treatment of diabetes mellitus. Considerable attention has been given to the synthesis of this natural product, which has culminated in two completed total synthesis by Winkler and Boeckman. In all of these aforementioned synthetic studies, saudin's unique structural complexity has served as the inspiration for the development of innovative chemistry. Although the strategies developed to construct saudin have been elegant, we were interested in developing a method that would build the core structure of the natural product in a more direct and convergent manner.

1.4 Notes and References

(1) Mossa, J. S.; Cassady, J. M.; Antoun, M. D.; Byrn, S. R.; McKenzie, A. T.; Kozlowski, J. F.; Main, P. *J. Org. Chem.* **1985**, *50*, 916-918.

(2) Although it may appear that labdane precursor **9** would lead to the non-natural enantiomers of the labdane diterpenes shown in Figure 1.1.2, in some cases both enantiomers of labdane diterpenes have been isolated. This suggests that both enantiomers of labdane precursor **9** may exist in nature. For recent examples of natural *ent*-labdane diterpenoids, see: (a) Matsud, T. Kuroyanagi, M.; Sugiyama, S.; Umehara, K.; Ueno, A.; Nishi, K. *Chem. Pharm. Bull.* **1994**, *42*, 1216-1225. (b) Fujita, T.; Fujitani, R.; Takeda, Y.; Takanishi, Y.; Yamada, T.; Kido, M. Miura, I. *Chem. Pharm. Bull.* **1984**, *32*, 2117-2125. (c) Jantan, I. Waterman, P. G. *Phytochemistry*, **1994**, *37*, 1477-1479. (d) Reddy, M. K.; Reddy, M. V. B.; Gunasekar, D.; Murthy, M. M.; Caux, C.; Bodo, B. *Phytochemistry*, **2003**, *62*, 1271-1275.

(3) Mossa, J. S.; El-Denshary, E. S. M.; Hindawi, R.; Ageel, A. M. *Int. J. Crude Drug Res.* **1988**, *26*, 81-87.

(4) Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2003. Rev

ed. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2004.

(5) Davis, S. N.; Granner, D. K. Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Panceas. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*; Hardman, J. G., Limbard, L. E., Eds.; McGraw-Hill: New York, 1996; pp 1487-1517.

(6) (a) Labadie, G. R.; Cravero, R. M.; Gonzalez-Sierra, M. *Synth. Comm.* **1996**, *26*, 4671-4684. (b) Labadie, G. R.; Luna, L. E.; Gonzalez-Sierra, M.; Cravero, R. M. *Eur. J. Org. Chem.* **2003**, *17*, 3429-3434.

(7) Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425-7426.

(8) (a) Fang, Y. Studies Directed Toward the Total Synthesis of (–)-Saudin. Ph.D. Thesis, University of Rochester, Rochester, CA, 1991. (b) Neeb, M. J. Studies on the Total Synthesis of (–)-Saudin. Ph.D. Thesis, University of Rochester, Rochester, CA, 1995.

(9) Boeckman, R. K., Jr.; Ferreira, M. R. R.; Mitchell, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190-191.

CHAPTER TWO

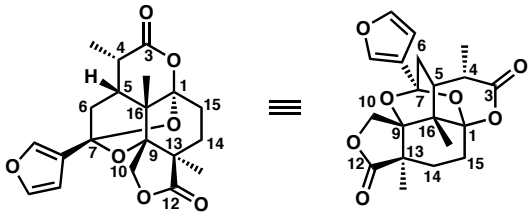
Progress Toward the Total Synthesis of Saudin: The Development of a Tandem Stille-Oxa-Electrocyclization Reaction[†]

2.1 Background

2.1.1 Introduction

We initiated research directed toward the total synthesis of the caged diterpenoid saudin (**1**) in late 2000. As described in Chapter 1, Mossa and Cassady disclosed the structure and biological activity of saudin 20 years ago.[1] The chemical structure of **1** was proved unambiguously by single crystal X-ray analysis to be that depicted in Figure 2.1.1. Importantly, saudin (**1**) was found to induce hypoglycemia in mice and therefore could be an appealing lead structure for the development of new agents to treat diabetes.

Figure 2.1.1



Saudin (1)

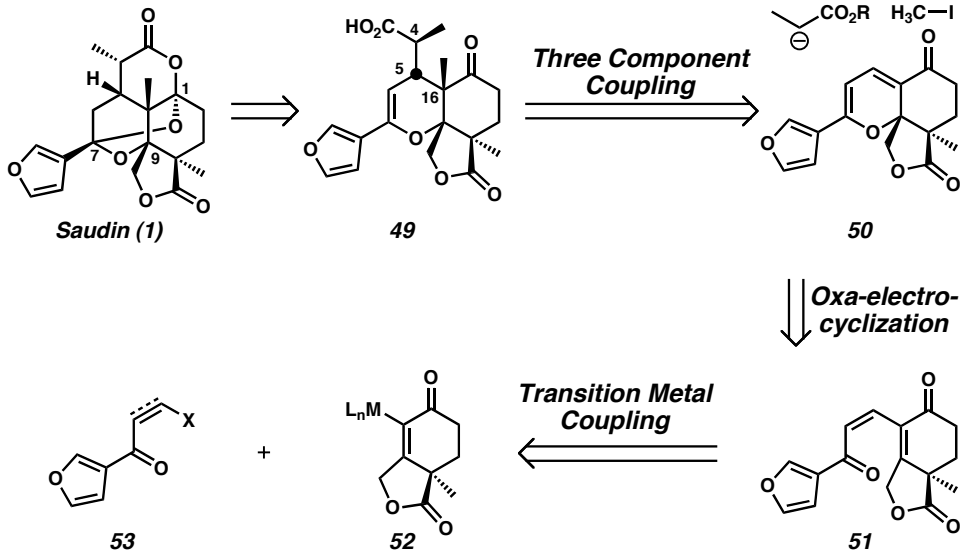
[†] This work was performed in collaboration with Dr. Taichi Kano, a postdoctoral scholar in the Stoltz group at the California Institute of Technology.

Our choice of saudin as a target molecule was based on its potent hypoglycemogenic bioactivity and unique structure. Additionally, we viewed this highly oxygenated, caged natural product as an ideal template for the discovery and development of new chemical reactions.

2.1.2 Retrosynthetic Analysis of Saudin

Our retrosynthetic analysis of saudin is outlined in Scheme 2.1.1. The polycyclic structure of saudin (**1**) exhibits an impressive array of functionality and stereochemistry that includes eight oxygenated carbons, seven stereocenters (two of which are quaternary centers and a total of five which are tetrasubstituted), two lactone rings, and a 3-substituted furan. Initial retrosynthetic disconnection of the C(1) and C(7) acetals exposes carboxylic acid **49** (Scheme 2.1.1), which, upon cleavage of the C(4)-C(5) linkage and removal of the C(16)-methyl in a retro three component coupling, arises from lactone **50**. Opening the pyran ring of **50** in a retro-oxa-electrocyclization provides dienone **51**, a substrate that is suited for disconnection across the C(16)-C(5) linkage via a number of possible transition metal-mediated coupling reactions (e.g., Stille, Suzuki, Sonogashira, and Heck) between enone **52** and furan **53**.

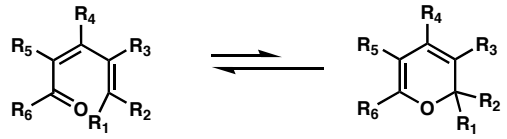
Scheme 2.1.1



2.1.3 Oxa-Electrocyclization Reactions in Natural Product Synthesis

The oxa-electrocyclization reaction is a relatively under-utilized transformation in organic synthesis.[2] This is primarily due to the existence of an unfavorable equilibrium in between the open *cis*-dienone (**54**) and the closed α-pyran (**54**) (Scheme 2.1.2). While the dienone structure is usually favored thermodynamically, in some cases the proper selection of functional groups and structural features in the molecule can control the equilibrium ratio to favor the α-pyran.[3]

Scheme 2.1.2



***cis*-dienone (54)** **α-pyran (55)**

Recently, thermodynamically favorable oxa-electrocyclization reactions have been exploited in the context of natural product synthesis, which has led to the total syntheses of torreyanic acid by Porco,[4] the epoxyquinols by Hayashi,[5] and the antimalarial naphthoquinones by Trauner.[6] Interestingly, an oxa-electrocyclization reaction was proposed to exist in the biosynthetic pathways for all these natural products. As described in Chapter 1, the putative biosynthetic pathway of saudin (**1**) does not involve an oxa-electrocyclization. In an attempt to expand the synthetic utility of this pericyclic transformation, we were interested in employing the oxa-electrocyclization in a more inconspicuous, non-biomimetic manner to rapidly synthesize the α-pyran core of saudin.

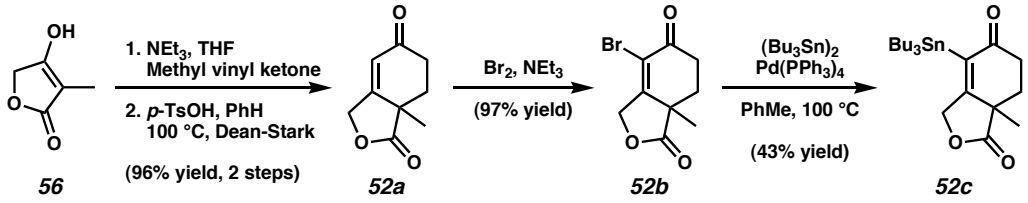
2.2 First Generation Strategy Based on a Michael Addition

2.2.1 Efficient Synthesis of the Core of Saudin

We initiated our study of the synthesis of saudin by preparing variants of enone **52** and furan **53**, with the hope that we would unite the two compounds through a

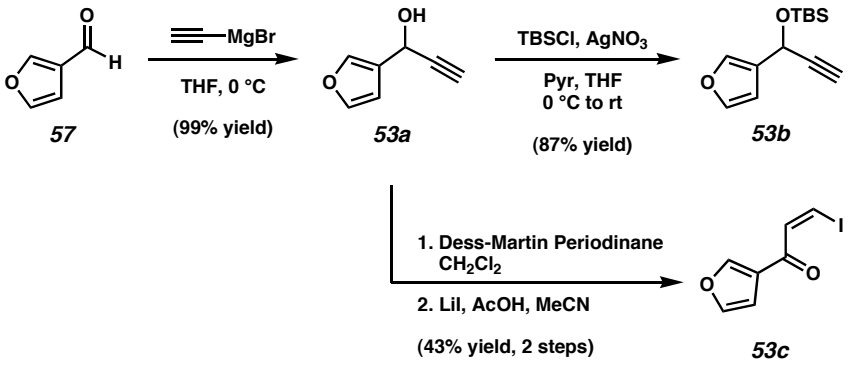
transition metal-catalyzed reaction. The preparation of enone **52a** proceeded via the Robinson annulation of tetronic acid **56** and methyl vinyl ketone (Scheme 2.2.1).[7] This enone was then cleanly converted to bromoenone **52b** by exposure to Br_2 and Et_3N.[8] The resulting product was easily transformed under Stille conditions to vinyl stannane **52c**,[9] albeit in modest yield, which was a viable intermediate for several transition metal-mediated couplings.

Scheme 2.2.1



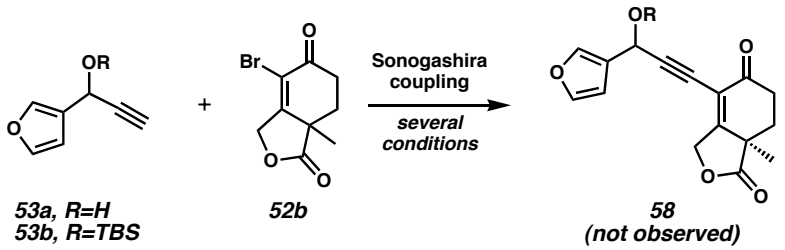
The other coupling partners for these metal-mediated coupling strategies were synthesized from furaldehyde **57** in a straightforward manner (Scheme 2.2.2). Treatment of this aldehyde with ethynyl Grignard produced propargyl alcohol **53a**, which was smoothly protected as the TBS-ether **53b**. Alternatively, the vinyl iodide derivate (**53c**) was synthesized in a two-step procedure from alcohol **53a**. Although oxidation of this alcohol failed under several conditions (Swern oxidation, Ley oxidation, and chromium-based oxidations), Dess-Martin periodinane[10] cleanly provided the desired ynone, which was then converted to vinyl iodide **53c** by treatment with LiI and AcOH in MeCN.[11]

Scheme 2.2.2



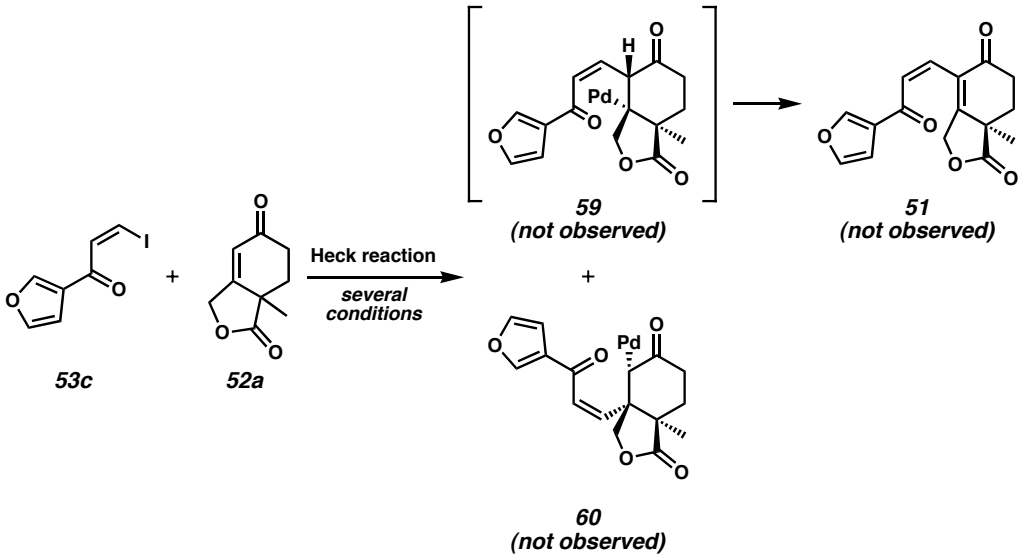
With these coupling partners in hand, a series of Sonogashira reactions were explored between bromoenone **52b** and alkynes **53a-b** (Scheme 2.2.3). Unfortunately, the coupling was not realized, though several conditions were tried. We discovered that analogs of bicyclic enone **52** are moderately unstable under a variety of basic conditions.

Scheme 2.2.3



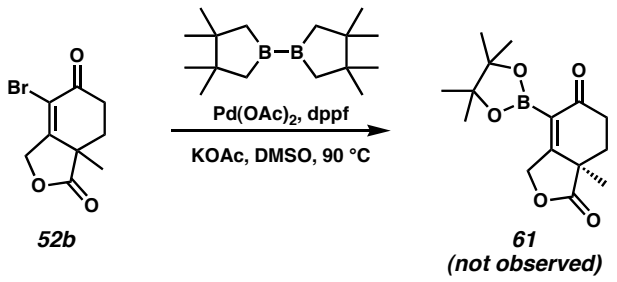
Alternatively, coupling via a Heck reaction of **53c** and **52a** was explored (Scheme 2.2.4).[12] Unfortunately, this strategy was not realized under either the standard Heck conditions or the modified Jeffery conditions.[13] The difficulty of this transformation may be attributed to the hindered Pd complex that would be generated by olefin insertion and the resulting anti relationship of the Pd and hydride in the cyclic structure[14] (i.e., **59**), along with the potential for regioisomeric insertion across the olefin (i.e., **60**).

Scheme 2.2.4



In an attempt to investigate Suzuki coupling reactions,[15] the conversion of vinyl bromide **52b** to the corresponding vinyl boronic ester **61** was attempted (Scheme 2.2.5). But, once again, the basic conditions of the reaction merely degraded the starting material.

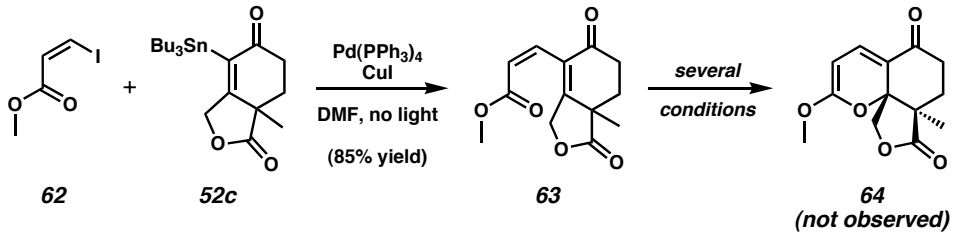
Scheme 2.2.5



Finally, we attempted to couple the two segments under Stille conditions.[16] Using a model system we were able to couple vinyl stannane **52c** with *cis*-vinyl iodide **62** under modified Stille conditions,[17] which yielded dienone **63** (Scheme 2.2.6). This result established that the bicyclic enone core structure was stable, at least under Stille

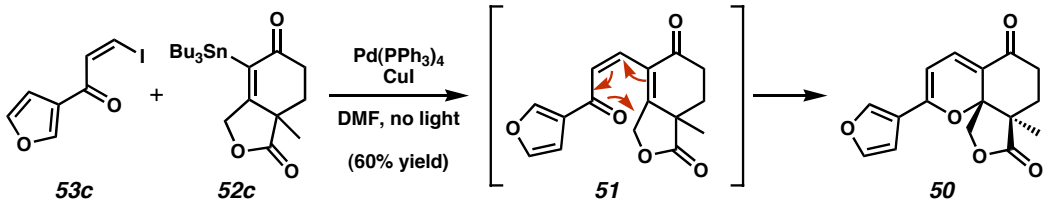
conditions. The oxa-electrocyclization of enone **63** was attempted under several conditions without success (heat, UV light, and Lewis acids).

Scheme 2.2.6



Although the electrocyclization of model substrate **63** was unsuccessful, we decided to apply the Stille coupling strategy to fully elaborated substrates en route to saudin (**1**). A series of conditions were examined for the Stille coupling of vinyl stannane **52c** and vinyl iodide **53c**, and no product was observed with several common Pd sources, additives, and solvents. We then employed the conditions used in the model system to generate dienone **63** with the anticipation that the desired Stille product **51** would be produced. To our pleasant surprise, however, the combination of catalytic $Pd(PPh_3)_4$, CuI, and DMF with the exclusion of light facilitated the coupling of **52c** and **53a** to yield furan appended tricycle **50** – the result of a tandem Stille-oxa-electrocylization reaction – as a single diastereomer (Scheme 2.2.7). Interestingly, the presence of CuI and the absence of light were both essential for the success of this transformation.[18]

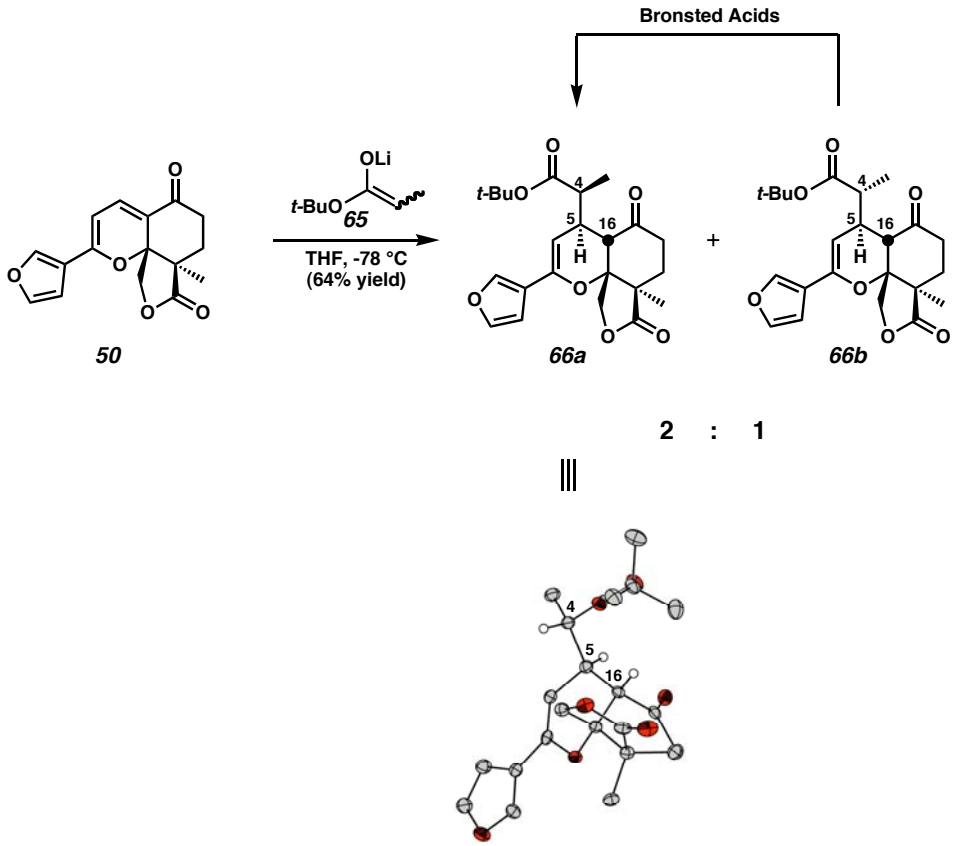
Scheme 2.2.7



2.2.2 Advancing Furan Appended Tricycle 50

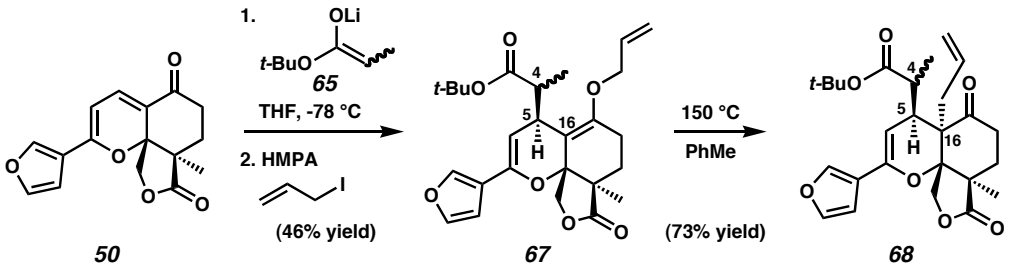
The synthesis of polycycle **50** represented an efficient diastereoselective route to the core structure of saudin. At this stage a series of 1,4-additions to this furan appended tricycle were explored. Under Mukaiyama-Michael conditions, the compound (**50**) decomposed.[19] Under anionic conditions, however, enolate **65** selectively reacted in a 1,4 fashion to yield a thermodynamic mixture of **66a** and **66b** (Scheme 2.2.8). Unfortunately, several attempts to react the carbon enolates of **66a-b** with methyl iodide and other electrophiles were unsuccessful.[20] X-ray structure analysis eventually revealed that the Michael addition product (**66a**) was actually the undesired diastereomer at C(5) than that which was needed for elaboration to saudin (Scheme 2.2.8).

Scheme 2.2.8



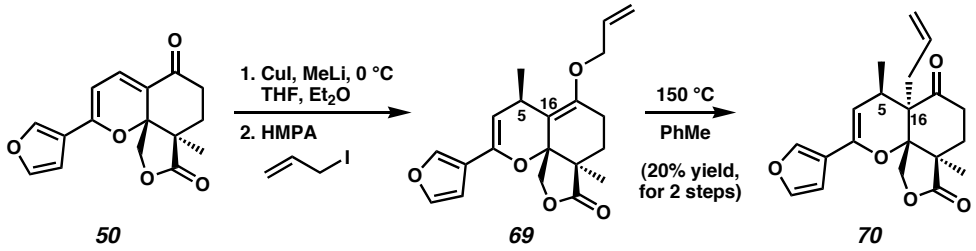
We envisioned that perhaps the stereochemistry at C(5) of ketoesters **66a** and **66b** sterically prohibited methylation at C(16), and an indirect C-alkylation could be achieved by O-allylation followed by a Claisen rearrangement. Treatment of polycycle **50** with enolate **65** followed by allyl iodide afforded the enol ether **67**, which rearranged thermally to ketone **68** (Scheme 2.2.9). The stereochemistry at the newly established quaternary carbon C(16) was most likely determined by the stereochemistry at C(5), as it was again inverted relative to the stereochemistry found in the natural product.

Scheme 2.2.9



While enolate equivalents like **65** attacked enone **50** from the β-face, we were hopeful that other nucleophiles would react from the α-face, which would map correctly onto the natural product. To test this hypothesis we reacted enone **50** with a simple methyl cuprate and then exposed the resulting enolate to allyl iodide and HMPA (Scheme 2.2.10). The vinyl allyl ether then underwent a thermal Claisen rearrangment. Unfortunately, the stereochemistry at both C(5) and C(16) were epimeric to that present in the natural product (i.e., **70**).

Scheme 2.2.10



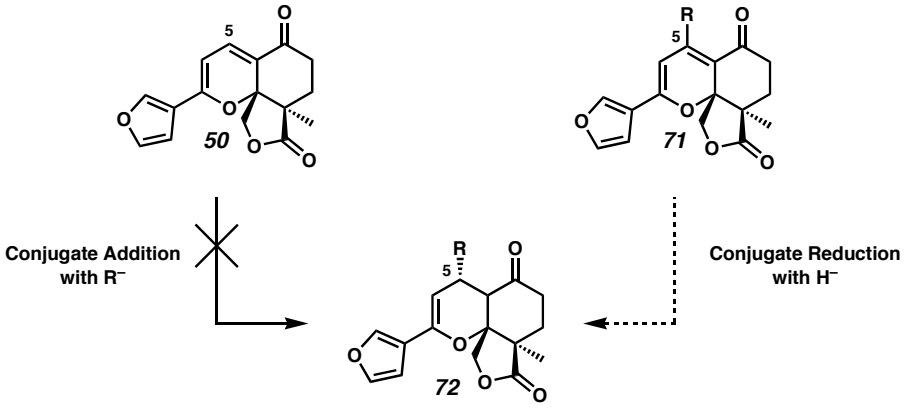
2.3 Second Generation Strategy Based on a 1,4-Reduction

2.3.1 Modified Strategy for the Synthesis of Saudin

Although we were disappointed by our inability to access the desired diastereomer of ketone **68** or **70**, there was enough flexibility in the synthetic strategy to investigate other potential solutions without abandoning the tandem Stille-oxa-electrocyclization approach.

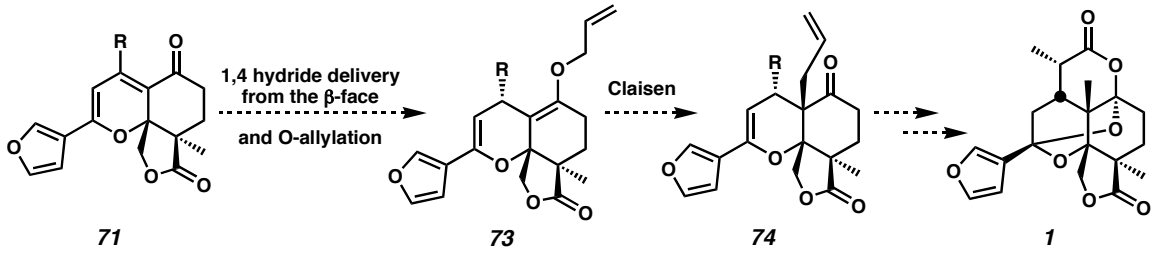
Initially our strategy for the synthesis of saudin called for a diastereoselective conjugate addition of a carbon nucleophile into enone **50** to access a C(5) substituted product (i.e., **72**, Scheme 2.3.1). The stereochemistry of the 1,4 additions to polycycle **50** suggested that the β-face may be preferred for nucleophiles adding in a conjugate fashion. This hypothesis could be tested by synthesizing a more functionalized polycycle (**71**), which would then be subjected to a 1,4 hydride reduction (Scheme 2.3.1). In addition to providing a more convergent route to saudin, this new strategy would also probe the generality of our tandem Stille-oxa-electrocyclization methodology.

Scheme 2.3.1



If the hydride also attacked from the β-face, the resulting product would have the correct stereochemistry at the β-position, which would hopefully lead to the correct stereochemistry at the α-position via a Claisen rearrangement (i.e., **74**, Scheme 2.3.2).

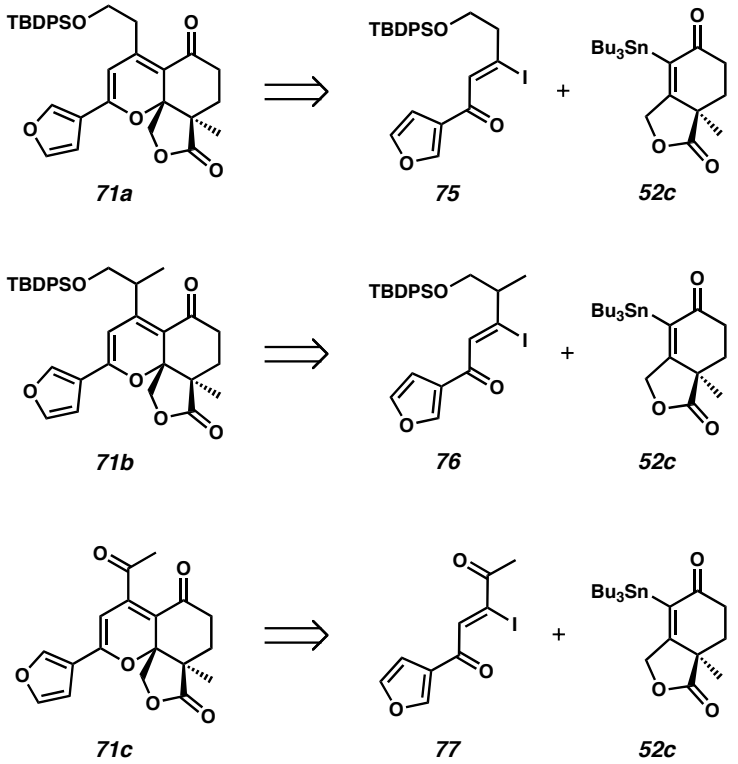
Scheme 2.3.2



2.3.2 Synthesis of Modified Furan Appended Tricycles

Initial exploration of the new strategy began with polycycles **71a-c**, which required the preparation of three new vinyl iodides (i.e., **75**, **76**, **77**, Scheme 2.3.3).

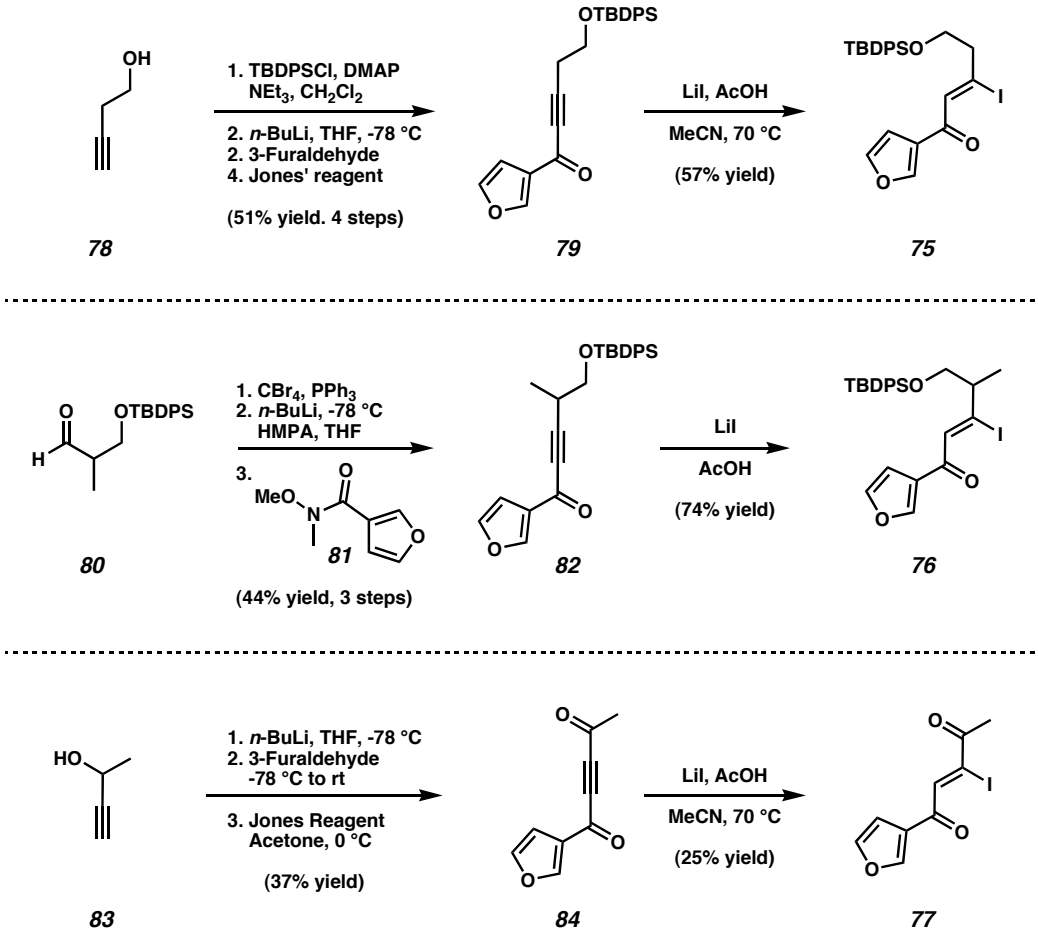
Scheme 2.3.3



The synthesis of vinyl iodide **75** commenced with the silyl protection of alcohol **78** (Scheme 2.3.4). Subsequent treatment with *n*-butyllithium followed by 3-furaldehyde yielded the coupled alcohol, which was oxidized with Jones' reagent to produce ynone **79**. Conversion of **79** to vinyl iodide **75** was effected by treatment of the ynone (**79**) with LiI and AcOH in MeCN to generate the desired *cis*-vinyl iodide (**75**) in good yield and as a single olefin isomer. The synthesis of vinyl iodide **76** is also depicted in Scheme 2.3.4. Aldehyde **80** was converted to an alkynyl anion by the Corey-Fuchs procedure.[21] Subsequent quenching of the anion with Weinreb amide **81** yielded ynone **82**, which was readily converted to vinyl iodide **76** as a single olefin isomer with LiI and AcOH. Vinyl iodide **77** was rapidly synthesized from 1-butyn-3-ol (**83**), which was first coupled to 3-

furaldehyde (Scheme 2.3.4). Double oxidation of the resulting propargylic diol furnished ynone **84**, which was treated with LiI and AcOH in MeCN to yield the desired vinyl iodide **77**.

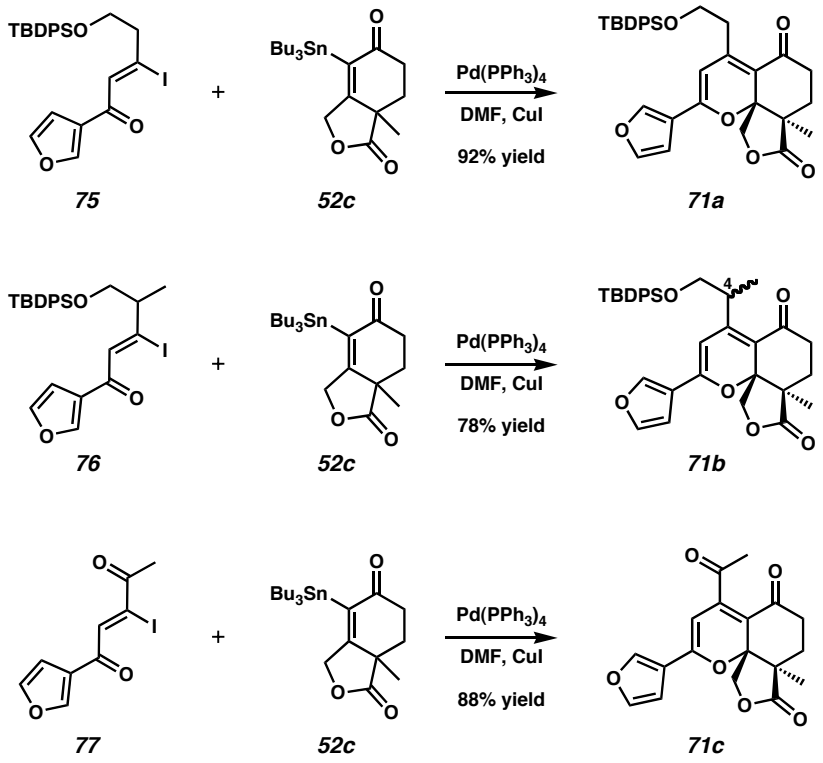
Scheme 2.3.4



With these three new vinyl iodides in hand (**75-77**), the key Stille-oxa-electrocyclization reactions were attempted. Under previously optimized conditions, smooth coupling occurred between stannane **52c** and vinyl iodides **75**, **76**, and **77** to form the desired polycycles **71a**, **71b**, and **71c** in 92%, 78%, and 88% yield, respectively

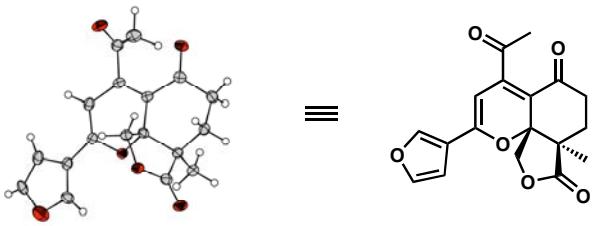
(Scheme 2.3.5). Products **71a** and **71c** were formed as single diastereomers, whereas **71b** was produced as a 1:1 mixture of diastereomers at C(4).

Scheme 2.3.5



The bond connectivity and relative stereochemistry of **71c** were unambiguously confirmed by single crystal X-ray diffraction of the diketone (Figure 2.3.1).

Figure 2.3.1

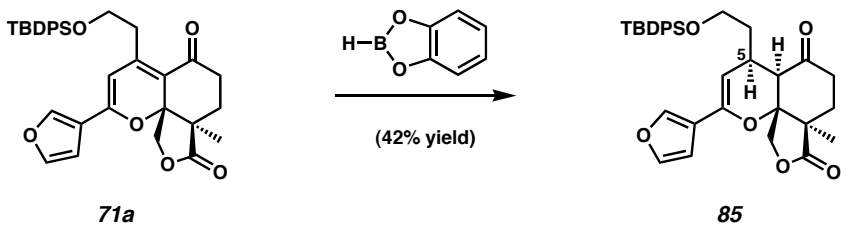


71c

2.3.3 1,4-Reduction of Substituted Enone 71a

At this point, although the 1,4 addition of carbon nucleophiles to enone **50** seemed to give the C(5)-α-H-diastereomer, we were ready to test our hypothesis on the diastereoselective 1,4-reduction of enone **71a**. To realize the 1,4 hydride reduction product, polycycle **71a** was subjected to a variety of conditions. In most cases the sterically hindered starting material was unreactive.[22] Treatment with catecholborane resulted in a 1,4-reduction, but surprisingly the hydride was delivered from the α-face of the enone (i.e., **85**, Scheme 2.3.6).[23] When polycycle **71a** was reacted with a multitude of in situ generated "Cu–H" species, the resulting ketone did exhibit the desired C(5) stereochemistry needed for elaboration to the natural product. Unfortunately, the yields of these reactions were prohibitively low.

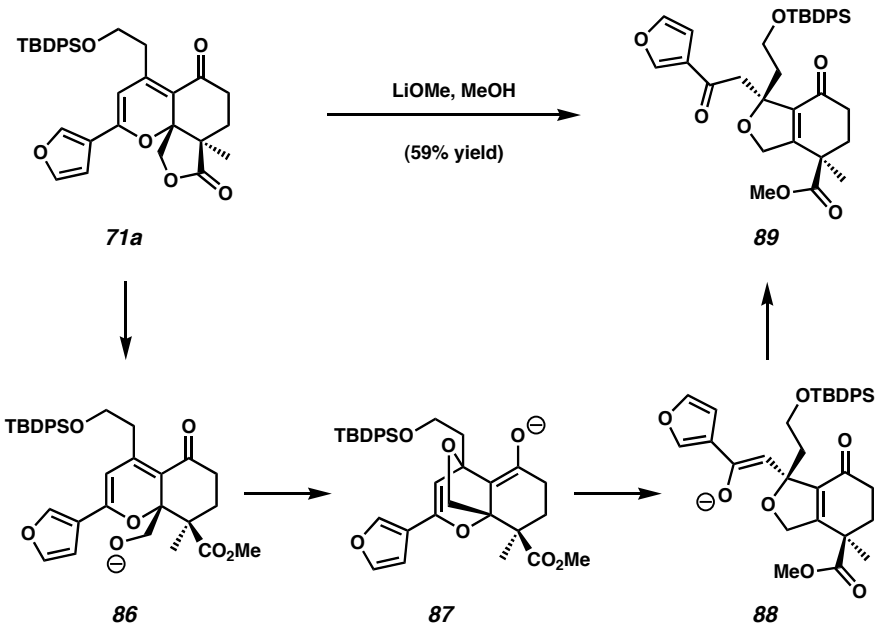
Scheme 2.3.6



71a ***85***

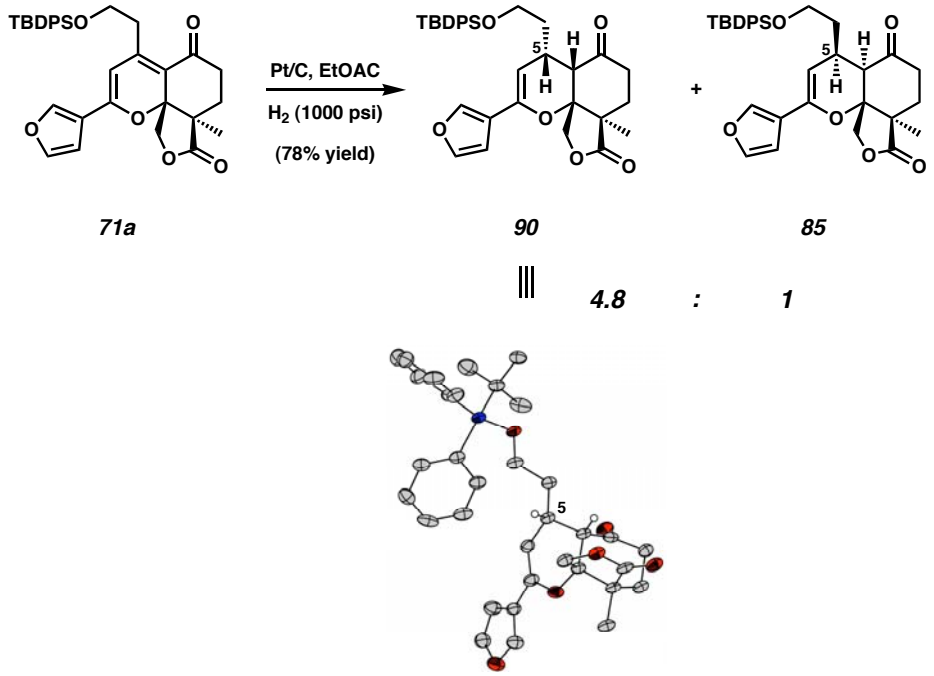
Presumably, the 1,4-reduction of enone **71a** from the β-face was hindered by the caged nature of the lactone functionality. We reasoned that this steric obstacle could be reduced by modifying the topology of our polycyclic structures. Specifically, we wanted to open the lactone in enone **71a**, with the hope of drastically changing the steric environment around the tetrasubstituted olefin. Although treating enone **71a** with LiOMe led to the opening of the lactone, the liberated alkoxide then underwent an undesired intramolecular 1,4-addition, followed by a β-elimination, to generate diketone **89** (Scheme 2.3.7). We concluded from this result that the selective opening of the lactone was not a trivial transformation given the dense array of functionality in the products of our tandem Stille-oxa-electrocyclization reaction.

Scheme 2.3.7



Finally, after much investigation, we obtained the desired ketone (**90**) in good yield by treating enone **71a** with Pt/C under a high pressure atmosphere of hydrogen gas (Scheme 2.3.8). This constituted a diastereoselective reduction of a tetrasubstituted olefin. The stereochemistry of the major product (**90**) was established by single crystal X-ray diffraction.

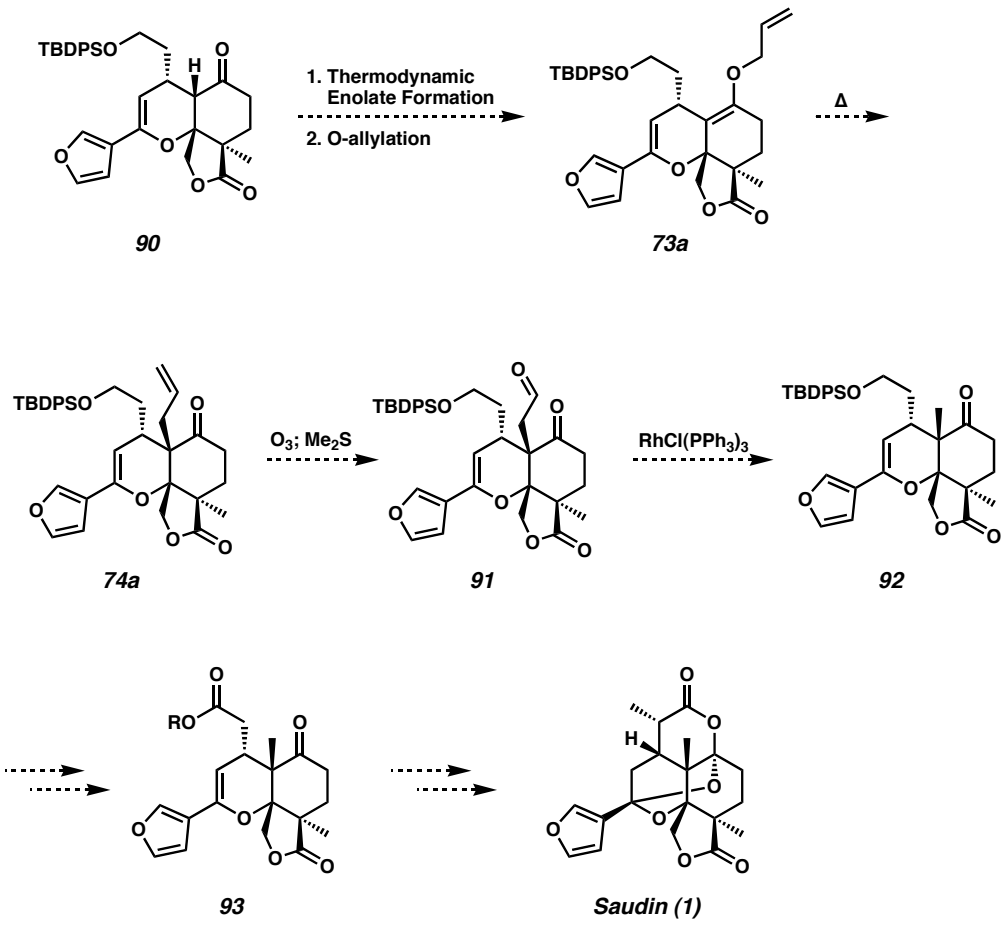
Scheme 2.3.8



2.3.4 Proposal For the Completion of Saudin

With access to ketone **90**, future work will target the installation of the α-quaternary carbon at C(16) via the Claisen rearrangement strategy and other more direct C-alkylation methods. One potential strategy for the completion of saudin (**1**) is shown in Scheme 2.3.9. If the thermodynamic enolate of ketone **90** can be formed, this intermediate will be treated with allyl iodide to generate enol ether **73a**, which could undergo a thermal Claisen rearrangement to generate ketone **74a**. Oxidation of the terminal olefin in ketone **74a** to an aldehyde, followed by Rh(I) catalyzed decarbonylation, could yield α-methyl ketone **92**. Facile functional group interconversions would then lead to ketoester **93**, which could be transformed easily to the natural product saudin (**1**).

Schem 2.3.9



2.4 Conclusion

Our studies toward the total synthesis of (±)-saudin (**1**) have produced an efficient, rapid, and diastereoselective construction of the natural product's core. While conjugate additions to polycycle **50** yielded products of undesired stereochemistry, intermediate **71a** was advanced to a structure with the desired stereochemistry for

elaboration to saudin (i.e., **90**). In the process of our work, we have also developed a novel tandem Stille-oxa-electrocyclization sequence that delivers a wide range of pyran structures in a convergent and rapid fashion. Current efforts are focused on expanding the substrate scope of this tandem reaction sequence as well as advancing ketone **90** to saudin.

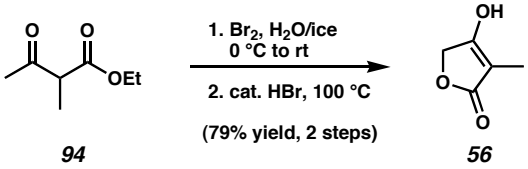
2.5 Experimental Section

2.5.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using anhydrous, deoxygenated solvents. Commercially obtained reagents were used as received. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032 - 0.063 mm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and

integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer or a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. X-ray crystallographic structures were obtained by Mr. Larry M. Henling and Dr. Mike W. Day at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory.

2.5.2 Preparative Procedures

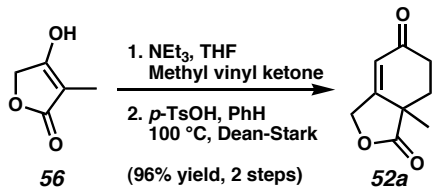


94 *56*

Methyl tetronic acid 56. This is a modification of a known literature procedure.[24] To a solution of ethylmethyl acetoacetate **94** (50 mL, 353 mmol) in deionized water (100 mL) cooled to 0 °C was slowly added bromine (18 mL, 353 mmol) in a dropwise fashion over 2 h. Following addition, the ice bath was allowed to warm to 23 °C, and the reaction mixture was stirred for 12 h. The organic layer was separated and dried over Na_2SO_4 and evaporated in vacuo to provide the desired bromoketone (81.08 g, 353 mmol) as a clear oil, which was used in the next step without further purification: ^1H

NMR (300 MHz, $CDCl_3$) δ 4.28 (dq, J = 7.2, 0.9 Hz, 1H), 2.43 (s, 3H), 1.97 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H).

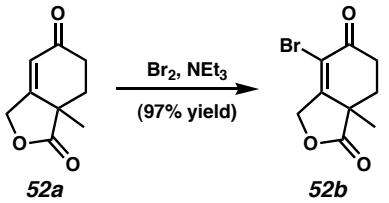
To the bromoketone from the previous step (81.08 g, 353 mmol) was added 12 drops of HBr (48% *w*/*v* in H_2O) in a dropwise fashion. Following addition, the reaction mixture was refluxed at 100 °C and allowed to stir for 12 h. The reaction was cooled to 23 °C. The precipitate was vacuum filtered and rinsed with ethyl acetate. The concentrated filtrate was resubmitted to the reaction conditions twice. The filtrates from the three reaction cycles were combined to yield methyl tetronic acid **56** (31.86 g, 79% yield) as a white solid: mp 185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.74 (s, 1H), 4.55 (s, 2H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.3, 173.0, 94.5, 66.6, 6.0; IR (KBr pellet) 2984, 2695, 1598, 1448 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_5H_6O_3]^+$: m/z 114.0317, found 114.0313.



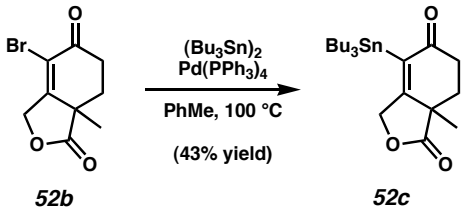
Enone 52a. To a cooled (0 °C) solution of methyl tetronic acid **56** (150 g, 1.31 mol) in THF (1.3 L) was added Et_3N (366 mL, 2.63 mol). Methyl vinyl ketone (131 mL, 1.58 mol) was then slowly added over 15 min. After stirring for 30 min, the reaction mixture was washed with 1 N HCl (1 L). The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo to provide the conjugate addition product (242.2 g, 1.31

mol) as a yellow oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, *J* = 16.8 Hz, 1H), 4.63 (d, *J* = 16.8 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 2.09-1.95 (m, 2H), 1.31 (s, 3H).

To a solution of this conjugate addition product (242.2 g, 1.31 mol) in benzene (650 mL) was added *p*-TsOH (24.9 g, 131 mol). The mixture was refluxed with azeotropic removal of H_2O (Dean-Stark trap). After stirring for 40 h, the reaction mixture was allowed to cool to 23 °C and concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (300 mL) and washed with water (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (2:1 hexanes/EtOAc eluent) provided enone **52a** (211 g, 96% yield over 2 steps) as a clear oil: R_F 0.40 (1:3 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.01 (dd, *J* = 14.6, 2.1 Hz, 1H), 4.83 (d, *J* = 14.6 Hz, 1H), 2.60-2.36 (m, 2H), 2.22-1.92 (m, 2H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 177.5, 161.6, 122.2, 68.2, 41.3, 32.6, 29.5, 20.7; IR (thin film/NaCl) 2940, 1780, 1676 cm^{-1}; HRMS (EI^+) calc'd for $[C_9H_{10}O_3]^+$: *m/z* 166.0630, found 166.0629.

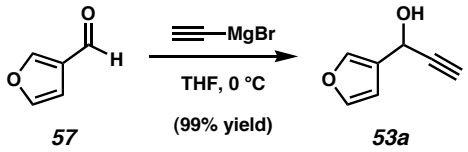


Bromoenone 52b. To a solution of enone **52a** (5.0 g, 30 mmol) in CH_2Cl_2 (60 mL) cooled to 0 °C was added a solution of Br_2 (1.7 mL, 33 mmol) in CH_2Cl_2 (30 mL) in a dropwise fashion over 15 min. When the addition was complete, Et_3N (4.6 mL, 33 mmol) was quickly added. After stirring for 5 min, the reaction mixture was washed with water (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) provided bromoenone **52b** (7.16 g, 97% yield) as a clear oil: R_F 0.30 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 2H), 2.83-2.77 (m, 2H), 2.33-2.14 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 176.7, 160.2, 117.8, 69.4, 45.2, 33.3, 29.5, 21.7; IR (thin film/NaCl) 2935, 1782, 1689, 1655 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_9H_9O_3Br]^+$: 243.9735, found 243.9732.



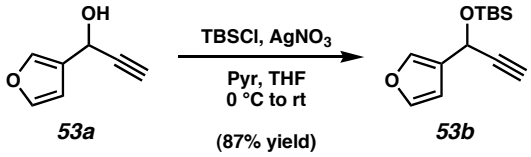
Vinyl stannane 52c. A solution of bromoenone **52b** (5.0 g, 20.4 mmol), $(Bu_3Sn)_2$ (20.6 mL, 40.8 mmol), $Pd(PPh_3)_4$ (306 mg, 0.265 mmol), and $NaHCO_3$ (8.57 g,

102 mol) in toluene (200 mL) was stirred at -78 °C under reduced pressure for 30 min. The mixture was then stirred at reflux. After 24 h, the reaction mixture was allowed to cool to 23 °C and filtered through a short pad of Celite (pentane eluent). The filtrate was concentrated in vacuo to an oil, which was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to give vinyl stannane **52c** as a clear oil (4.0 g, 43% yield): R_F 0.45 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, *J* = 14.7 Hz, 1H), 4.79 (d, *J* = 14.7 Hz, 1H), 2.67-2.47 (m, 2H), 2.23 (ddd, *J* = 13.3, 5.3, 2.1 Hz, 1H), 2.04 (td, *J* = 13.3, 6.6 Hz, 1H), 1.48 (s, 3H), 1.47-1.24 (m, 13H), 1.03-0.86 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 178.4, 169.6, 139.5, 69.9, 42.2, 32.1, 29.2, 28.3, 27.2, 21.6, 13.7, 11.0; IR (thin film/NaCl) 2956, 2926, 1785, 1655, 1625 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{21}H_{35}O_3Sn]^+$: 455.1608, found 455.1603.



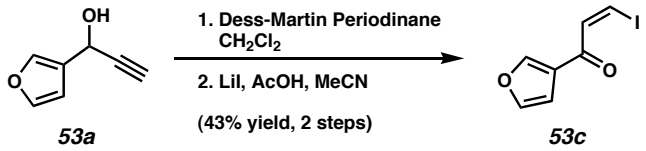
Alcohol 53a. To a solution of 3-furaldehyde **57** (17.3 mL, 200 mmol) in THF (170 mL) cooled to 0 °C was added ethynyl magnesium bromide (0.5 M in Et_2O, 500 mL, 250 mmol) slowly via an addition funnel over 2 h. Following addition, the ice bath was allowed to warm to 23 °C, and the mixture was stirred for 5 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (500 mL) and extracted with Et_2O (2 x 400 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (2:1

hexanes/EtOAc eluent) provided alcohol **53a** (25.41 g, 99% yield) as a clear oil: R_F 0.25 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, *J* = 0.8 Hz, 1H), 7.37 (t, *J* = 1.7 Hz, 1H), 6.48 (d, *J* = 0.8 Hz, 1H), 5.35 (d, *J* = 1.3 Hz, 1H), 3.14 (s, 1H), 2.58 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 140.4, 126.0, 109.2, 83.2, 73.5, 57.0; IR (thin film/NaCl) 3293, 1505, 1158, 1021 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_7H_6O_2]^+$: 122.0368, found 122.0367.



TBS-ether 53b. To a cooled (0 °C) solution of alcohol **53a** (235.2 mg, 2.00 mmol) in THF (9.6 mL) were added $AgNO_3$ (491 mg, 2.89 mmol), Pyridine (623 μl, 7.70 mmol), and TBSCl (435 mg, 2.89 mmol). After 5 min, the reaction mixture was warmed to 23 °C. The reaction was stirred for 10 h and then passed through a short pad of Celite (Et_2O eluent). The solution was washed with water (15 mL). The aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided TBS-ether **53b** (411.6 mg, 87% yield) as a clear oil: R_F 0.68 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 0.8 Hz, 1H), 7.20 (t, *J* = 1.7 Hz, 1H), 6.28 (d, *J* = 1.1 Hz, 1H), 5.28 (d, *J* = 1.1 Hz, 1H), 2.35 (d, *J* = 2.1 Hz, 1H), 0.77 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 139.8, 127.2, 109.3, 84.0, 72.9, 58.2, 25.9, 18.5, -4.4, -4.8; IR (thin film/NaCl)

3309, 2957, 2931, 2858, 1254, 1087, 1062 cm^{-1}; HRMS (EI^+) *m*/*z* calc'd for $[C_{13}H_{20}O_2Si]^+$: 236.1233, found 236.1232.

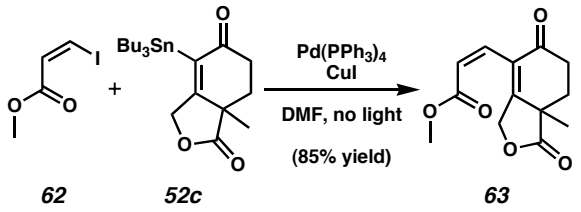


53a *53c*

Vinyl Iodide 53c. To a solution of Dess-Martin Periodinane (1.91 g, 4.50 mmol) in CH_2Cl_2 (18 mL) cooled to 0 °C was added alcohol **53a** (500 mg, 4.09 mmol) in CH_2Cl_2 (3 mL). After 1 h the reaction was quenched by addition of a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under a slight reduction of pressure (produced by a water aspirator) while submerged in a cold bath (0 °C). The resulting oil was purified by flash chromatography on silica gel (3:1 petroleum ether/ether eluent) to provide the volatile ynone product (442 mg, 3.68 mmol) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.20-8.19 (m, 1H), 7.46-7.45 (m, 1H), 6.83-6.82 (m, 1H), 3.26 (d, *J* = 1.2 Hz, 1H).

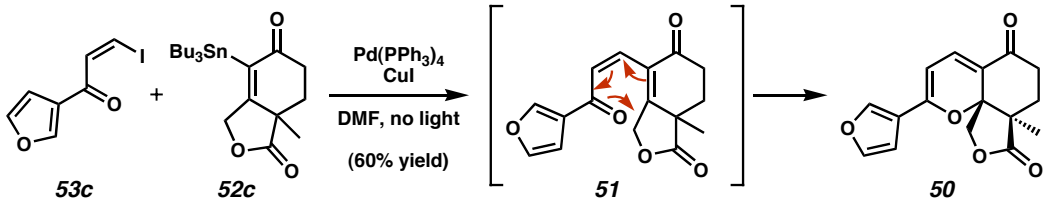
To a solution of the volatile ynone (5 g, 41.6 mmol) and LiI (6.13 g, 45.8 mmol) in MeCN (42 mL) was added glacial AcOH (2.63 mL, 45.8 mmol). Following addition, the mixture was stirred for 2 h and then poured into ice water (75 mL). Solid K_2CO_3 was added until bubbling ceased, and the mixture was extracted with Et_2O (2 x 75 mL). The combined organic layers were dried over $MgSO_4$. After filtration, the residue was

concentrated under reduced pressure. Purification by flash chromatography (10:1 pentane/ether eluent) provided vinyl iodide **53c** (5.46 g, 43% yield over 2 steps) as a yellow solid: R_F 0.29 (5:1 pentane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 1.4, 0.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 1.9, 1.4 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 1.9, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 183.0, 147.7, 144.8, 133.9, 129.0, 109.3, 91.6; IR (thin film/NaCl) 3130, 1655, 1295 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_7H_5O_2I]^+$: 247.9335, found 247.9346.



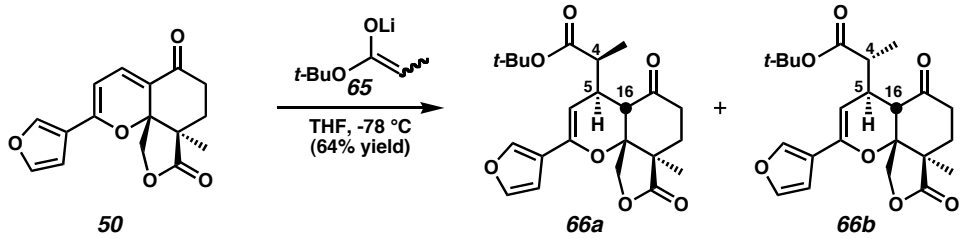
Enone 63. To a mixture of $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), vinyl stannane **52c** (50 mg, 0.12 mmol), and vinyl iodide **62**[25] (30 mg, 0.12 mmol) was added DMF (2.5 mL). CuI (17.5 mg, 0.09 mmol) was added, and the flask was protected from ambient light. After stirring for 9 h, the mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided enone **63** (25.5 mg, 85% yield): R_F 0.25 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (ddd, *J* = 12.2, 1.9, 0.8 Hz, 1H), 6.15 (d, *J* = 12.2 Hz, 1H), 5.02 (dd, *J* = 15.0, 2.0 Hz, 1H), 4.72 (dd, *J* = 15.0, 0.7 Hz, 1H), 3.69 (s, 3H), 2.77-2.53 (m, 2H), 2.32-2.11 (m, 2H), 1.61 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 195.4, 177.9, 165.5, 158.7, 136.0, 128.7, 125.6, 77.7, 68.6, 51.9, 42.0, 33.0, 29.9, 21.0; IR (thin film/NaCl) 2952, 1781, 1722, 1675, 1197, 1179 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{14}O_5]^+$: 250.0841, found 250.0844.



Polycycle 50. To a mixture of $Pd(PPh_3)_4$ (1.16 g, 1.0 mmol), vinyl stannane **52c** (9.0 g, 20.0 mmol), and vinyl iodide **53a** (6.13 g, 24.7 mmol) was added DMF (100 mL). Freshly recrystallized CuI[26] (3.81 g, 20.0 mmol) was added, and the flask was cooled to -78 °C under vacuum. The reaction mixture was protected from ambient light. After 30 min of degassing, the mixture was allowed to warm to 23 °C under N_2. After stirring for 12 h, the mixture was diluted with water (200 mL) and extracted with Et_2O (2 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) provided polycycle **50** (3.37g, 60% yield) as an orange solid: R_F 0.31 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.44 (t, *J* = 1.7 Hz, 1H), 7.33 (d, *J* = 6.8 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 5.88 (d, *J* = 6.3 Hz, 1H), 4.78 (d, *J* = 10.7 Hz, 1H), 4.07 (d, *J* = 10.7 Hz, 1H), 2.59-2.45 (m, 2H), 2.09-2.02 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 179.1, 153.8, 144.6, 143.3, 134.7, 121.1, 118.3, 107.5, 99.5, 85.8, 71.9, 44.8, 33.2, 28.0, 14.5; IR (thin film/NaCl) 3131, 2947,

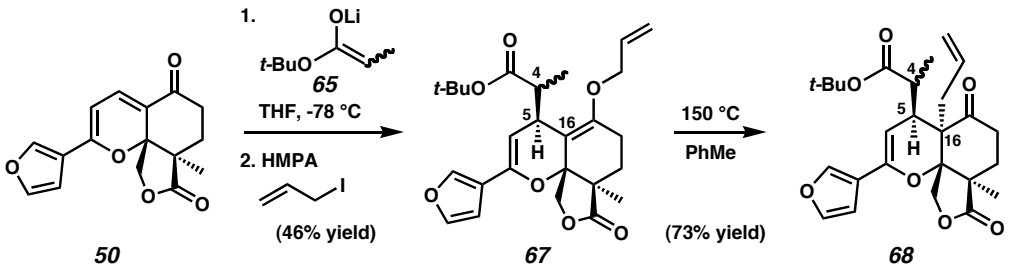
1782, 1673, 1561, 1526, 1160, 1015 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{14}O_5]^+$: 286.0841, found 286.0838.



Michael Products 66a-b. To a solution of $HN(i\text{-}Pr)_2$ (610 μL, 4.38 mmol) in THF (4.4 mL) cooled to 0 °C was added *n*-butyllithium (2.2 M in hexanes, 2.08 mL, 4.38 mmol). After 5 min the mixture was cooled to -78 °C, and a solution of *t*-butyl propionate (657 μL, 4.38 mmol) in THF (4.4 mL) was slowly added along the sides of the flask in a dropwise fashion. Following addition, the mixture was stirred for 30 min, and then a solution of polycycle **50** (250 mg, 0.875 mmol) in THF (4.4 mL) was slowly added over 2 min. After 15 min the reaction was quenched with 1 N HCl (10 mL) and the cold bath was removed. After 1 h of stirring, the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) provided a 2 : 1 mixture of ketone **66a** as a white solid and its C(4) epimer **66b** as an oil (232.1 mg combined, 64% yield). For **66a**, suitable crystals for X-ray diffraction were grown from Et_2O by slow evaporation.

*Ketone **66a**:* R_F 0.45 (1:1 hexanes/EtOAc); mp 148 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 7.03-7.02 (m, 1H), 6.23-6.21 (m, 2H), 4.91 (d, *J* = 2.4 Hz, 1H), 3.84 (d, *J* = 10.3 Hz, 1H), 3.77 (d, *J* = 10.7 Hz, 1H), 3.34-3.30 (m, 1H), 2.80 (d, *J* = 7.8 Hz, 1H), 2.49-2.43 (m, 1H), 2.42-2.35 (m, 1H), 1.95-1.88 (m, 1H), 1.65-1.61 (m, 2H), 1.45 (s, 9H), 1.25 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.6, 178.8, 173.5, 145.9, 144.0, 140.3, 122.4, 107.6, 98.9, 83.5, 81.1, 74.4, 50.3, 46.7, 43.8, 34.7, 34.2, 30.2, 28.3, 17.3, 13.7; IR (thin film/NaCl) 2977, 1783, 1722, 1160 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{23}H_{29}O_7]^+$: 417.1913, found 417.1904.

*Ketone **66b**:* R_F 0.54 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (s, 1H), 6.91 (t, *J* = 1.7 Hz, 1H), 6.10-6.08 (m, 1H), 5.05 (d, *J* = 2.9 Hz, 1H), 3.82 (d, *J* = 10.3 Hz, 1H), 3.72 (d, *J* = 10.7 Hz, 1H), 3.35-3.31 (m, 1H), 2.60 (d, *J* = 6.8 Hz, 1H), 2.47-2.40 (m, 1H), 2.19-2.11 (m, 1H), 1.86-1.79 (m, 1H), 1.59-1.51 (m, 1H), 1.48-1.41 (m, 1H), 1.33 (s, 9H), 1.14 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.1, 178.5, 174.4, 145.9, 144.0, 140.3, 122.5, 107.6, 96.8, 83.5, 81.1, 74.1, 51.1, 46.7, 43.5, 34.7, 33.8, 30.3, 28.3, 17.3, 13.6; IR (thin film/NaCl) 2977.02, 1783, 1721, 1157 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{23}H_{29}O_7]^+$: 417.1913, found 417.1926.



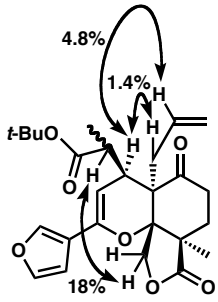
Claisen Product 68. To a solution of HN(*i*-Pr)$_2$ (130 μL, 0.933 mmol) in THF (1.8 mL) cooled to 0 °C was added *n*-butyllithium (2.5 M in hexanes, 375 μL, 0.933 mmol). After 5 min the mixture was cooled to -78 °C, and a solution of *t*-butyl propionate (140 μL, 0.933 mL) in THF (1.8 mL) was slowly added along the sides of the flask in a dropwise fashion. Following addition, the mixture was stirred for 25 min, and then a solution of polycycle **50** (50 mg, 0.175 mmol) in THF (1.8 mL) was slowly added over 2 min. After 15 min the reaction was transferred via cannula into a 23 °C solution of allyl iodide (900 μL) and HMPA (900 μL). Following addition, the mixture was stirred for 80 min and then quenched with H_2O (15 mL). The mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided enol ether **67** (37.1 mg, 46% yield) as a clear oil, which was used immediately in the next step.

Enol ether **67** (32.6 mg, 0.0714 mmol) in toluene (4 mL) was transferred to a sealable flask. The flask was sealed, and the reaction vessel was heated to 175 °C behind a blast shield. After 2.5 h the mixture was cooled to 23 °C and concentrated in vacuo. Purification by preparatory thin layer chromatography on silica gel (0.5 mm, 3:1

hexanes/EtOAc eluent) provided a 2.7:1 diastereomeric mixture (Diastereomer 1 : Diastereomer 2) of Claisen products **68** (23.8 mg combined, 73% yield) as clear oils.

Diastereomer 1: R_F 0.31 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.26 (s, 1H), 6.93 (t, *J* = 1.7 Hz, 1H), 6.10 (dd, *J* = 1.9, 0.8 Hz, 1H), 5.77-5.60 (m, 1H), 4.98-4.86 (m, 2H), 4.82 (d, *J* = 5.8 Hz, 1H), 3.93 (d, *J* = 10.5 Hz, 1H), 3.52 (t, *J* = 6.5 Hz, 1H), 3.30 (d, *J* = 10.5 Hz, 1H), 2.33 (t, *J* = 6.5 Hz, 1H), 2.17 (t, *J* = 7.4 Hz, 1H), 2.12-1.98 (m, 1H), 1.78-1.69 (m, 1H), 1.63 (s, 9H), 1.37 (s, 3H), 1.30-1.27 (m, 1H), 1.01 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.1, 178.6, 175.8, 143.9, 143.0, 140.1, 132.4, 122.4, 119.1, 107.8, 99.0, 86.0, 80.2, 69.9, 56.7, 46.0, 41.5, 38.9, 36.5, 35.3, 30.2, 28.6, 17.5, 17.0; IR (thin film/NaCl) 2977, 1784, 1722, 1156 cm^{-1}; HRMS (FAB$^+$) *m*/*z* calc'd for $[C_{26}H_{31}O_7]^+$: 455.2070, found 455.2089.

Claisen product **68** *(Diastereomer 1)* was assigned the indicated relative stereochemistry based on the shown nOe interactions.

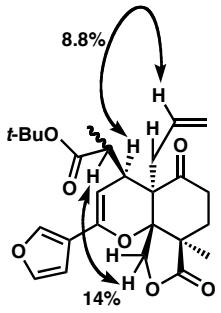


68 (Diastereomer 1)

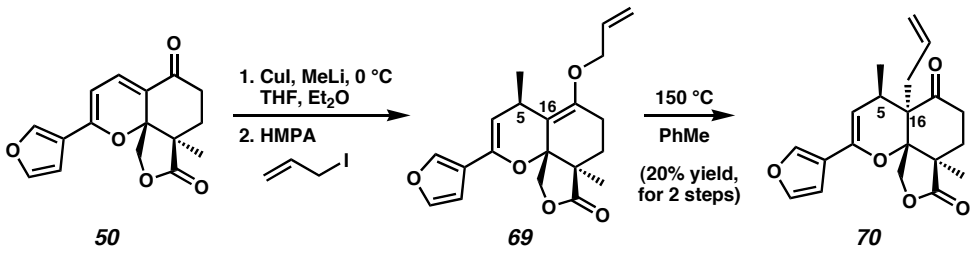
Diastereomer 2: R_F 0.38 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.27 (s, 1H), 6.91 (t, *J* = 1.8 Hz, 1H), 6.17 (dd, *J* = 1.7, 0.8 Hz, 1H), 5.50-5.36 (m, 1H), 5.32 (d, *J* = 5.5 Hz, 1H), 4.94-4.74 (m, 3H), 3.88 (d, *J* = 11.6 Hz, 1H), 2.54-2.41 (m, 2H), 2.36-2.15 (m, 2H), 2.07-1.95 (m, 1H), 1.69 (d, *J* = 6.6 Hz, 3H), 1.55-1.41 (m, 1H), 1.37

(s, 3H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.3, 179.4, 174.3, 144.0, 142.7, 140.4, 132.1, 122.4, 119.8, 107.7, 99.4, 85.0, 80.9, 72.7, 57.2, 46.2, 43.2, 41.7, 38.5, 36.1, 30.5, 28.3, 21.8, 18.4; IR (thin film/NaCl) 2977, 1782, 1719, 1150 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{26}H_{33}O_7]^+$: 457.2226, found 457.2213.

Claisen product **68** *(Diastereomer 2)* was assigned the indicated relative stereochemistry based on the shown nOe interactions.



68 (Diastereomer 2)



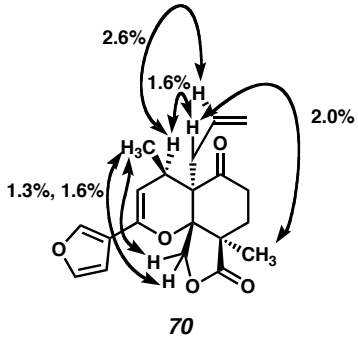
50 ***69*** ***70***

Methyl Claisen Product 70. A solution of MeLi in Et_2O (1.29 mL, 2.07 mmol) was slowly added to a mixture of CuI (197 mg, 1.03 mmol) in Et_2O (2.5 mL) at 0 °C in a dropwise fashion. Following addition, the mixture was stirred for 10 min at 0 °C, and then a solution of polycycle **50** (60 mg, 0.210 mmol) in THF (2 mL) was added. After 30 min the reaction was transferred via cannula into a flask at 23 °C containing allyl iodide

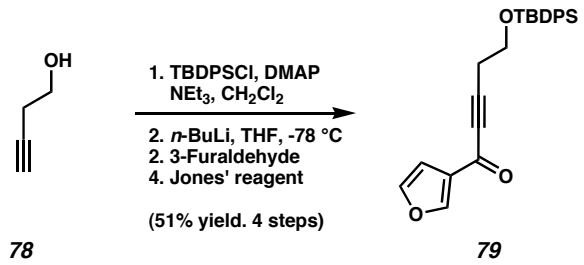
(500 μL) and HMPA (500 μL). Following addition the mixture was stirred for 2 h and then quenched with brine (10 mL). The mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (8:1 hexanes/EtOAc eluent) provided enol ether **69** (14.1 mg, 20% yield) as a clear oil, which was used immediately in the next step.

Enol ether **69** (14.1 mg, 0.412 mmol) in toluene (1 mL) was transferred to a sealable flask. The flask was sealed, and the reaction vessel was heated at 150 °C behind a blast shield. After 4.5 h, the mixture was cooled to 23 °C and concentrated under reduced pressure to provide Claisen product **70** (14.1 mg, 100% yield) as a clear oil: R_F 0.67 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.29 (s, 1H), 6.98 (t, *J* = 2.0 Hz, 1H), 6.16-6.14 (m, 1H), 5.55-5.46 (m, 1H), 4.96-4.92 (m, 1H), 4.84-4.78 (m, 1H), 4.73 (d, *J* = 5.4 Hz, 1H), 4.10 (d, *J* = 10.7 Hz, 1H), 3.42 (d, *J* = 10.7 Hz, 1H), 2.53-2.46 (m, 1H), 2.28 (d, *J* = 7.3 Hz, 2H), 2.05-1.97 (m, 1H), 1.73-1.65 (m, 1H), 1.60-1.52 (m, 1H), 1.41-1.37 (m, 1H), 1.36 (s, 3H), 0.91 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.0, 179.5, 143.9, 142.3, 140.2, 132.7, 122.6, 119.2, 107.8, 103.5, 85.1, 72.6, 55.4, 46.0, 38.0, 36.0, 31.7, 30.5, 18.9, 17.3; IR (thin film/NaCl) 2944, 1779, 1712, 1113 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{22}O_5]^+$: 342.1467, found 342.1462.

Methyl Claisen product **70** was assigned the indicated relative stereochemistry based on the shown nOe interactions.



70



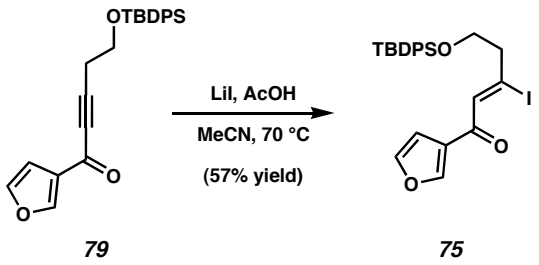
78 *79*

Ynone 79. To a solution of alcohol **78** (1.73 mL, 22.9 mmol), *t*-butyldiphenylsilyl chloride (5.72 g, 22 mmol), and DMAP (98 mg, 0.8 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (3.1 mL, 22 mmol). After stirring for 1 h, the reaction was washed with H_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was dissolved in benzene (10 mL) and concentrated in vacuo to azeotropically remove water, and the resulting protected alcohol was taken on to the next step without further purification.

The product from the previous step was dissolved in THF (40 mL) and cooled to –78 °C. To this solution was slowly added *n*-butyllithium (2.5 M in hexanes, 8.8 mL, 22

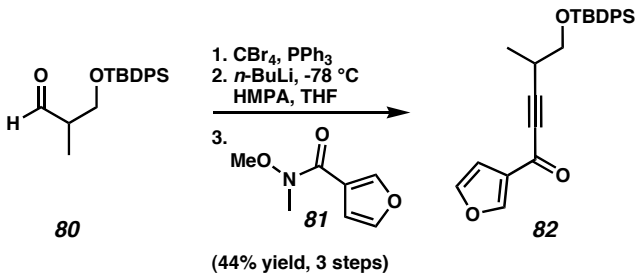
mmol). After 20 min 3-furaldehyde (1.9 mL, 22 mmol) was slowly added. Following addition, the mixture was warmed to 23 °C and stirred for 10 min. The reaction was quenched with 1 N HCl (40 mL). The mixture was concentrated in vacuo to remove THF, and the resulting solution was extracted with ether (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and the resulting coupled alcohol was taken onto the next step without further purification.

The crude product from the previous step was dissolved in acetone (40 mL) and cooled to 0 °C. To this solution was added Jones' reagent[27] (2.67 M, 15 mL, 40 mmol). After stirring for 10 min, *i*-PrOH (5 mL) was added to quench the remaining oxidant. The reaction was diluted with ether (100 mL) and extracted with a 1:1 mixture of brine and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (30:1 hexanes/EtOAc eluent) provided ynone **79** (4.47 g, 51% yield): R_F 0.56 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 1.3, 0.8 Hz, 1H), 7.75-7.66 (m, 5H), 7.48-7.35 (m, 6H), 6.81 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.88 (t, *J* = 6.6 Hz, 2H), 2.68 (t, *J* = 6.5 Hz, 2H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 150.6, 144.6, 135.7, 135.0, 133.4, 130.1, 129.8, 129.4, 128.0, 127.9, 108.6, 90.6, 80.8, 61.7, 27.0, 26.8, 23.4, 19.4; IR (thin film/NaCl) 2931, 2858, 2217, 1642, 1428, 1308, 1164, 1112 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{25}H_{26}O_3Si]^+$: 402.1651, found 402.1664.



79 *75*

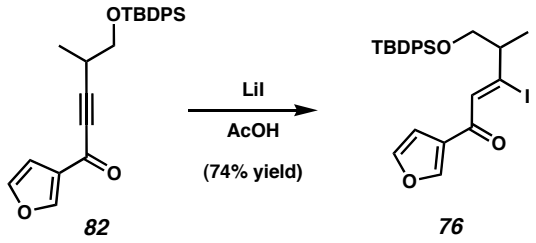
Vinyl Iodide 75. To a solution of ynone **79** (402 mg, 1.0 mmol) and LiI (147 g, 1.1 mmol) in MeCN (1.0 mL) was added glacial AcOH (63 μL, 1.1 mmol). Following addition, the mixture was refluxed for 20 h. The mixture was concentrated in vacuo and purified by flash chromatography (50:1 to 4:1 hexanes/EtOAc eluent) to provide vinyl iodide **75** (302 mg, 57% yield): R_F 0.45 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.75-7.68 (m, 4H), 7.45 (dd, *J* = 1.3, 0.8 Hz, 1H), 7.25-7.19 (m, 6H), 6.77 (t, *J* = 1.7 Hz, 1H), 6.72 (t, *J* = 1.1 Hz, 1H), 6.68 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 2.61 (dt, *J* = 5.9, 0.9 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 182.5, 147.4, 144.7, 136.4, 136.3, 135.6, 134.1, 132.0, 130.5, 130.2, 129.2, 128.5, 128.2, 113.6, 109.6, 62.7, 51.2, 27.4, 27.3, 27.1, 19.8, 19.6; IR (thin film/NaCl) 2930, 2857, 1662, 1591, 1428, 1157, 1112 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{25}H_{28}O_3SiI]^+$: 531.0853, found 531.0856.



Ynone 82. To a solution of PPh_3 (8.53 g, 32.5 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added a solution of CBr_4 (5.4 g, 16.3 mmol) in CH_2Cl_2 (4 mL). After 10 min, aldehyde **80**[28] (2.66 g, 8.13 mmol) in CH_2Cl_2 (6 mL) was slowly added. Following addition, the reaction was stirred for 4 h at 0 °C. A small scoop of Celite was added to the reaction mixture, which was then slowly poured onto a stirring solution of Celite in petroleum ether (500 mL). The mixture was filtered, and the filtrate was concentrated in vacuo and purified by flash chromatography on silica gel (20:1 petroleum ether/EtOAc eluent) to provide the vinyl dibromide (3.46 g, 91% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.41 (m, 6H), 6.27 (d, J = 8.7 Hz, 1H), 3.55 (m, 2H), 2.69 (m, 1H), 1.06 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H).

To a solution of the resulting vinyl dibromide (2.29 mg, 4.91 mmol) in THF (25 mL) cooled to -78 °C was slowly added *n*-butyllithium (2.5 M in hexanes, 4.3 mL, 10.8 mmol). After 15 min, the mixture was warmed to 0 °C. The reaction was stirred for 30 min at this temperature and then cooled back to -78 °C. HMPA (2.5 mL) was added, and the mixture was stirred for 20 min. The reaction was then warmed to -40 °C, and a solution of Weinreb amide **81**[29] (1.73 g, 11.1 mmol) in THF (12.5 mL) was slowly added. The cold bath was allowed to warm to 23 °C, and after 2.5 h the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with ether (3 x 50

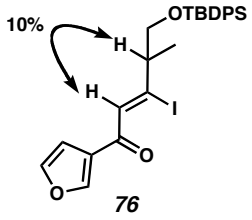
mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided ynone **82** (989.2 mg, 48% yield, 44% yield over 2 steps) as a clear oil: R_F 0.54 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 1.3, 0.8 Hz, 1H), 7.70-7.65 (m, 4H), 7.47-7.34 (m, 7H), 6.80 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.78 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.67 (dd, *J* = 9.7, 6.5 Hz, 1H), 2.95-2.82 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 150.6, 144.6, 135.8, 133.4, 133.4, 130.1, 129.4, 128.0, 108.6, 95.1, 80.6, 77.4, 67.0, 29.7, 27.0, 19.5, 16.7; IR (thin film/NaCl) 2932, 2858, 2215, 1643, 1113 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{26}H_{27}O_3Si]^+$: 415.1730, found 415.1727.



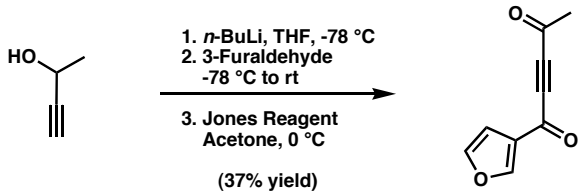
Vinyl Iodide 76. To a solution of ynone **82** (387 mg, 0.929 mmol) in glacial AcOH (10 mL) was added LiI (250 mg, 1.86 mmol). Following addition, the mixture was stirred for 10 h and then poured onto ice water (50 mL). Solid K_2CO_3 was added until bubbling ceased, and the mixture was extracted with Et_2O (4 x 50 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (20:1

hexanes/EtOAc eluent) provided vinyl iodide **76** (373.5 mg, 74% yield) as a yellow oil: R_F 0.50 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.78-7.71 (m, 4H), 7.54 (dd, *J* = 1.3, 0.8 Hz, 1H), 7.27-7.20 (m, 6H), 6.83 (d, *J* = 0.8 Hz, 1H), 6.79 (t, *J* = 1.7 Hz, 1H), 6.70 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.68 (dd, *J* = 10.2, 7.6 Hz, 1H), 3.51 (dd, *J* = 10.1, 5.1 Hz, 1H), 2.31-2.19 (m, 1H), 1.12 (s, 9H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 183.4, 147.7, 144.7, 136.5, 136.3, 136.3, 134.3, 134.1, 131.1, 130.5, 130.5, 130.5, 129.0, 128.5, 123.4, 109.6, 67.9, 51.2, 27.4, 27.4, 19.9, 17.9; IR (thin film/NaCl) 2931, 2858, 1664, 1590, 1156, 1112 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{26}H_{30}O_3SiI]^+$: 545.1009, found 545.0997.

Vinyl iodide **76** was assigned the (Z) stereochemistry based on a 10% nOe interaction between the vinyl hydrogen and the allylic hydrogen.



76

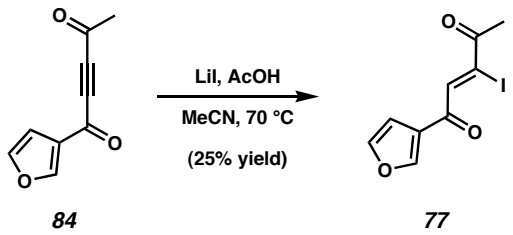


83 ***84***

Ynone 84. Alcohol **83** (3.14 mL, 40 mmol) was dissolved in THF (80 mL) and cooled to -78 °C. To this solution was slowly added *n*-butyllithium (2.5 M in hexanes, 32

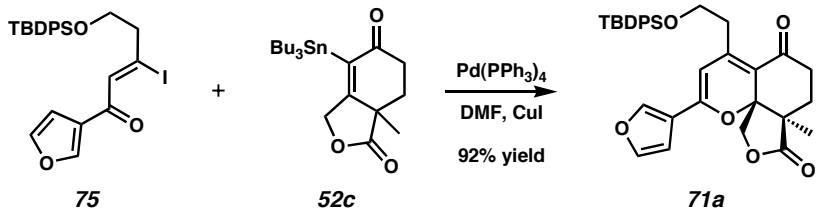
mL, 80 mmol) over 5 min. After 20 min, 3-furaldehyde (3.63 mL, 42 mmol) was slowly added. Following addition, the mixture was warmed to 23 °C and stirred for 10 min. The reaction was quenched with 1 N HCl (100). The mixture was concentrated in vacuo to remove THF, and the resulting solution was extracted with ether (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting coupled alcohol was taken onto the next step without further purification.

The product from the previous step was dissolved in acetone (100 mL) and cooled to 0 °C. To this solution was added Jones' reagent (2.67 M, 35 mL, 93 mmol). After stirring for 10 min, *i*-PrOH (5 mL) was added to quench the remaining oxidant. The reaction was diluted with ether (150 mL) and extracted with a 1:1 mixture of brine and saturated aqueous $NaHCO_3$ (150 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) provided ynone **84** (2.37 g, 37% yield): R_F 0.37 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.49 (t, *J* = 1.7 Hz, 1H), 6.83 (dd, *J* = 1.9, 0.8 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 169.4, 151.4, 145.4, 128.6, 108.3, 83.6, 83.0, 32.8; IR (thin film/NaCl) 3133, 1681, 1641, 1556, 1510, 1305, 1200, 1156 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_9H_6O_3]^+$: 162.0317, found 162.0321.



84 *77*

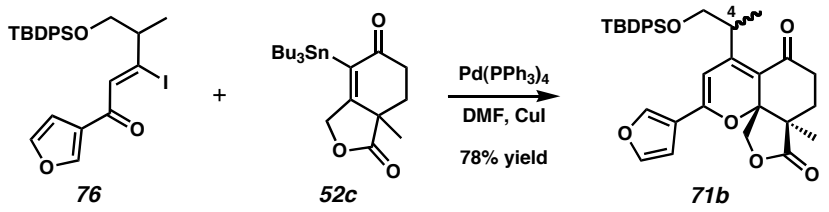
Vinyl Iodide 77. To a solution of ynone **84** (2.37 g, 14.6 mmol) and LiI (2.15 g, 16.1 mmol) in MeCN (160 mL) was added glacial AcOH (922 μL, 1.1 mmol). Following addition, the mixture was refluxed for 20 h. The mixture was concentrated in vacuo and purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide vinyl iodide **77** (1.0 g, 25% yield): R_F 0.27 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 6.86 (dd, *J* = 1.3, 0.8 Hz, 1H), 6.65 (dd, *J* = 2.0, 1.5 Hz, 1H), 6.50 (s, 1H), 6.41 (dd, *J* = 2.1, 0.8 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.8, 180.7, 148.5, 144.8, 135.4, 127.4, 118.1, 109.2, 25.6; IR (thin film/NaCl) 3134, 1706, 1654, 1576, 1512, 1156 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_9H_7O_3I]^+$: 289.9440, found 289.9432.



75 *52c* *71a*

Polycycle 71a. Vinyl stannane **52c** (1.78 g, 3.90 mmol) and vinyl iodide **75** (2.07 g, 3.90 mmol) were subjected to the tandem Stille-oxa-electrocyclization conditions, as described above for the synthesis of polycycle **50**. Purification by flash chromatography

(3:1 hexanes/EtOAc eluent) provided polycycle **71a** (2.05 g, 3.59 mmol) as an orange solid: R_F 0.26 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.66-7.61 (m, 4H), 7.45-7.32 (m, 7H), 6.46 (d, *J* = 2.1 Hz, 1H), 5.82 (s, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 3.97-3.88 (m, 3H), 3.10 (dt, *J* = 2.4, 6 Hz, 2H), 2.68-2.37 (m, 2H), 2.04-2.00 (m, 2H), 1.54 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 179.2, 151.5, 144.3, 143.1, 135.6, 133.7, 133.6, 129.7, 127.7, 120.7, 113.9, 107.3, 105.5, 86.5, 71.5, 63.3, 44.9, 36.6, 35.0, 27.8, 26.9, 19.3, 14.9; IR (thin film/NaCl) 2932, 2858, 1785, 1659, 1112 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{34}H_{37}O_6Si]^+$: 569.2359, found 569.2346.

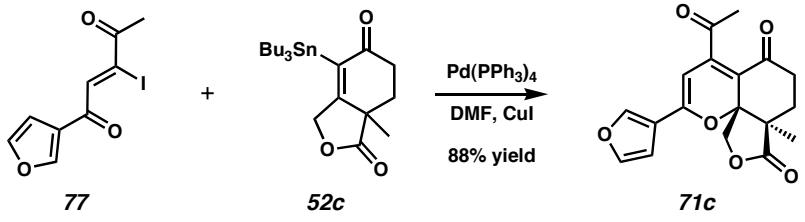


Polycycle 71b. Vinyl stannane **52c** (611 mg, 1.34 mmol) and vinyl iodide **76** (665 mg, 1.22 mmol) were subjected to the tandem Stille-oxa-electrocyclization conditions, as described above for the synthesis of polycycle **50**. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) provided a 1:1 diastereomeric mixture of polycycle **71b** (554 mg, 78% yield) as an orange oil.

Diastereomer 1: R_F 0.27 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.71-7.63 (m, 4H), 7.28 (d, *J* = 0.8 Hz, 1H); 7.21-7.18 (m, 6H), 6.85 (t, *J* = 1.7 Hz, 1H), 6.15 (s, 1H), 6.06 (dd, *J* = 1.9, 0.8 Hz, 1H), 5.74 (s, 1H), 4.80-4.66 (m, 1H), 4.28 (d, *J* = 11.0 Hz, 1H), 3.69-3.55 (m, 2H), 3.30 (d, *J* = 11.0 Hz, 1H), 2.31-2.04 (m, 2H), 1.54-1.43

(m, 2H), 1.40 (s, 3H), 1.18-1.10 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 195.2, 178.8, 153.7, 152.3, 144.5, 143.4, 136.3, 136.2, 134.3, 134.2, 130.4, 130.3, 128.7, 128.5, 128.4, 128.3, 121.7, 116.5, 107.9, 99.8, 87.3, 71.0, 67.6, 45.5, 36.2, 36.0, 28.4, 27.3, 19.8, 15.6, 15.4; IR (thin film/NaCl) 2930, 1784, 1654, 1522, 1110 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{35}H_{39}O_6Si]^+$: 583.2516, found 583.2534.

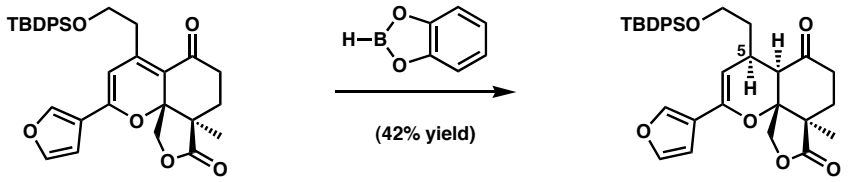
Diastereomer 2: R_F 0.23 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.84-7.75 (m, 4H), 7.28-7.20 (m, 6H), 6.83 (t, *J* = 1.8 Hz, 1H), 6.14 (s, 1H), 6.07 (t, *J* = 1.1 Hz, 1H), 5.93 (s, 1H), 4.72-4.62 (m, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 3.91 (d, *J* = 5.8 Hz, 2H), 3.48 (d, *J* = 11.0 Hz, 1H), 2.15-1.99 (m, 2H), 1.44-1.36 (m, 2H), 1.30 (s, 3H), 1.16 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 194.7, 178.7, 155.2, 152.3, 144.6, 143.5, 136.5, 136.4, 134.3, 134.3, 130.5, 121.7, 115.2, 107.7, 101.0, 87.5, 74.9, 71.1, 68.6, 45.3, 36.2, 35.8, 33.4, 28.0, 27.6, 27.5, 20.0, 15.9, 15.2; IR (thin film/NaCl) 2931, 1784, 1657, 1515, 1112 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{35}H_{39}O_6Si]^+$: 583.2516, found 583.2533.



77 ***52c*** ***71c***

Polycycle 71c. Vinyl stannane **52c** (1.57 g, 3.45 mmol) and vinyl iodide **77** (1.0 g, 3.45 mmol) were subjected to the tandem Stille-oxa-electrocyclization conditions, as described above for the synthesis of polycycle **50**. Purification by flash chromatography

(2:1 hexanes/EtOAc eluent) provided polycycle **71c** (1.0 g, 88% yield) as an orange solid. Suitable crystals for X-ray diffraction were grown from 1:1 hexanes/EtOAc by slow evaporation: R_F 0.24 (1:1 hexanes/EtOAc); mp 142 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 6.78 (t, *J* = 1.7 Hz, 1H), 6.18 (s, 1H), 5.90 (dd, *J* = 1.9, 0.8 Hz, 1H), 5.36 (s, 1H), 4.19 (d, *J* = 11.4 Hz, 1H), 3.20 (d, *J* = 11.2 Hz, 1H), 2.17 (s, 3H), 1.95-1.88 (m, 2H), 1.40-1.22 (m, 2H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 201.9, 192.8, 178.1, 154.9, 149.9, 145.1, 144.8, 144.2, 107.7, 98.3, 86.3, 70.5, 44.8, 33.4, 29.1, 27.7, 26.6, 14.4; IR (thin film/NaCl) 3135, 2918, 1782, 1705, 1668, 1560, 1519, 1499, 1161 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{18}H_{16}O_6]^+$: 328.0947, found 328.0946.

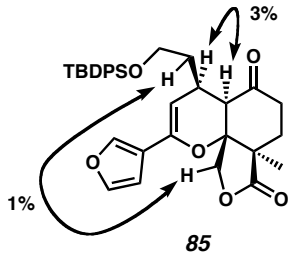


71a *85*

Ketone 85. To a solution of enone **71a** (36.7 mg, 0.0645 mmol) in THF (500 μL) was added catecholborane (20 μL, 0.194 mmol). The mixture was stirred for 90 min and then quenched with MeOH (500 μL). The mixture was diluted with Et_2O (20 mL) and extracted with a 2:1 mixture of 1 N NaOH and saturated aqueous NH_4Cl (4 x 7 mL). The combined aqueous layers were extrated with Et_2O (10 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by preparatory thin layer chromatography on silica gel (0.5 mm, 3:1 hexanes/EtOAc eluent) provided ketone **85**

(15.5 mg, 42% yield) as a clear oil: R_F 0.27 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.67 (m, 5H), 7.48-7.34 (m, 7H), 6.32 (s, 1H), 5.31 (d, *J* = 5.5 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.09 (d, *J* = 10.4 Hz, 1H), 3.86 (t, *J* = 6.0 Hz, 2H), 3.00 (d, *J* = 4.9 Hz, 1H), 2.91-2.82 (m, 1H), 2.69-2.54 (m, 1H), 2.50-2.28 (m, 2H), 2.10-1.97 (m, 3H), 1.51 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 203.4, 178.3, 143.8, 143.2, 140.2, 136.5, 136.4, 134.6, 134.5, 130.5, 130.5, 122.9, 107.8, 101.6, 84.8, 78.0, 71.3, 63.5, 49.7, 45.9, 36.2, 35.0, 30.2, 27.9, 27.5, 19.9, 13.8; IR (thin film/NaCl) 2931, 1784, 1719, 1105 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{34}H_{39}O_6Si]^+$: 571.2516, found 571.2492.

Ketone **85** was assigned the indicated relative stereochemistry based on the shown nOe interactions.

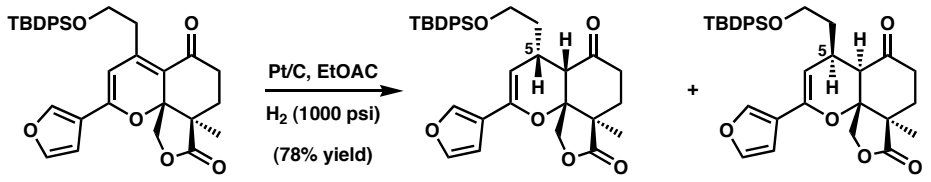


85

71a ***89***

Diketone 89. To a solution of lactone **71a** (75.7 mg, 0.133 mmol) in MeOH (1.75 mL) was added LiOH (32 mg, 1.33 mmol). The mixture was stirred for 30 min and then quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc

(3 x 5 mL). The combined organic layers were dried over Na_2SO_4. After filtration the residue was concentrated under reduced pressure. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) provided diketone **89** (47.0 mg, 59% yield) as a clear oil: R_F 0.52 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.69-7.60 (m, 5H), 7.42-7.35 (m, 6H), 6.69 (dd, *J* = 1.9, 0.8 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 15.7 Hz, 1H), 3.86-3.73 (m, 1H), 3.52-3.44 (m, 1H), 3.37 (s, 3H), 3.24-3.20 (m, 3H), 2.38-2.20 (m, 4H), 1.92-1.81 (m, 1H), 1.29 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 192.9, 173.6, 159.4, 148.4, 144.2, 135.7, 133.9, 129.7, 129.0, 127.9, 108.7, 90.2, 74.2, 60.0, 52.6, 48.7, 43.9, 42.4, 35.7, 35.0, 27.0, 26.9, 23.0, 19.3; IR (thin film/NaCl) 2930, 1735, 1675, 1111 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{35}H_{41}O_7Si]^+$: 601.2622, found 601.2631.



71a ***90*** ***85***

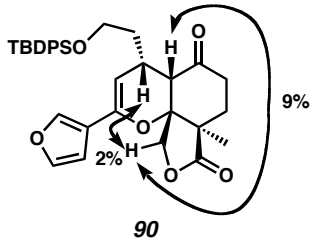
4.8 : 1

Ketone 90. Two batches of enone **71a** (2.3348 g, 4.105 mmol each) were separately dissolved in EtOAc (11 mL each). To these mixtures were added 10% Pt/C (560 mg in each mixture). The mixtures were then transferred to a H_2 bomb and stirred for 9 h under an atmosphere of pressurized H_2 (1000 psi). The two mixtures were then combined and passed through a short pad of silica gel to remove the Pt/C (EtOAc eluent).

Purification by flash chromatography (5:1 hexanes/EtOAc eluent) provided ketone **90** (1.287 g, 27.5% yield) as a white solid, the C(16) epimer of ketone **90** (1.745 g, 37.2% yield) as a clear oil,[30] and ketone **85** (0.627 g, 13.4% yield) as a clear oil. For **90**, suitable crystals for X-ray diffraction were grown from Et_2O by slow evaporation.

*Ketone **90**:* R_F 0.45 (2:1 hexanes/EtOAc); mp 131 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.79-7.71 (m, 5H), 7.32-7.21 (m, 6H), 6.97 (t, *J* = 1.7 Hz, 1H), 6.15-6.12 (m, 1H), 4.94 (s, 1H), 3.93 (d, *J* = 9.6 Hz, 1H), 3.82-3.72 (m, 1H), 3.67-3.57 (m, 2H), 3.26 (q, *J* = 7.0 Hz, 2H), 2.75-2.65 (m, 1H), 2.47 (d, *J* = 4.3 Hz, 1H), 2.26-2.16 (m, 2H), 1.92-1.83 (m, 2H), 1.18 (s, 9H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 205.6, 177.9, 143.8, 143.6, 139.5, 136.4, 136.3, 134.2, 134.1, 130.6, 130.5, 122.9, 107.9, 101.2, 84.5, 73.3, 62.7, 47.1, 46.3, 37.3, 34.2, 30.9, 28.2, 27.5, 27.3, 19.8, 18.8; IR (thin film/NaCl) 2931, 2858, 1784, 1727, 1111 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{34}H_{39}O_6Si]^+$: 571.2516, found 571.2502.

Ketone **90** was assigned the indicated relative stereochemistry based on the shown nOe interactions.



90

2.6 Notes and References

(1) Mossa, J. S.; Cassady, J. M.; Antoun, M. D.; Byrn, S. R.; McKenzie, A. T.; Kozlowski, J. F.; Main, P. *J. Org. Chem.* **1985**, *50*, 916-918.

(2) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; pp 260-375.

(3) For an early example of the isomerization of dienones to α-pyrans, see: Büchi, G.; Yang, N. C. *J. Am. Chem. Soc.* **1957**, *79*, 2318-2323.

(4) (a) Li, C.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 10484-10485. (b) Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095-5106.

(5) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192-3194.

(6) (a) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554-9555. (b) Malerich, J. P.; Maimone, T. J.; Elliott, G. I.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276-6283.

(7) Prisbylla, M. P.; Takabe, K.; White, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 762-763.

(8) Johnson, C. R.; Kozak, J. *J. Org. Chem.* **1994**, *59*, 2910-2912.

(9) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49-58.

(10) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

(11) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709-713.

(12) For a general review on Heck reactions, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066.

(13) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113-10130.

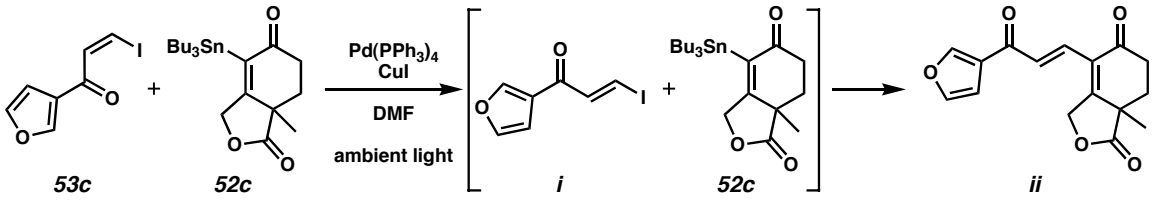
(14) In our analysis of the failed Heck strategy, we are ignoring the possibility of anti-β-hydride elimination. Although there are isolated examples of this phenomenon, these cases are usually limited to exceptionally activated olefin systems. For recent examples of anti-β-hydride elimination, see: (a) Lautens, M.; Fang, Y. Q. *Org. Lett.* **2003**, *5*, 3679-3682. (b) Maeda, K.; Farrington, E. J.; Galardon, E.; John, B. D.; Brown, J. M. *Adv. Synth. Catal.* **2002**, *344*, 104-109. (c) Shea, K. M.; Lee, K. L.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 2353-2356.

(15) (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457-2483. (b) Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147-168.

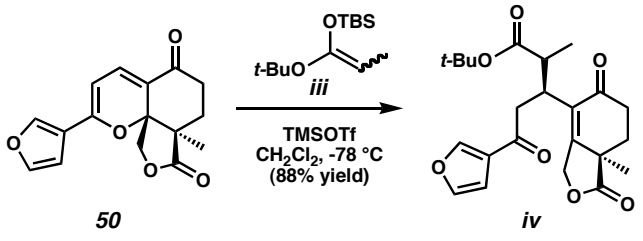
(16) For a general review on the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React*. **1997**, *50*, 1-652.

(17) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029-12046.

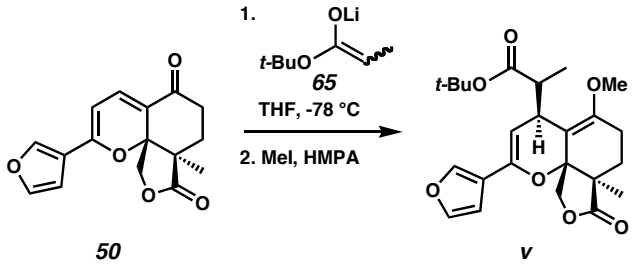
(18) In the presence of light, *trans*-dienone ***ii*** was formed, presumably as a result of cis-trans isomerization of vinyl iodide **53a** to ***i***, followed by Stille coupling:



(19) Specifically, polycycle **50** underwent 1,4-addition, but unfortunately proceeded with undesired β-hydroxy elimination to cleave the pyran substructure:



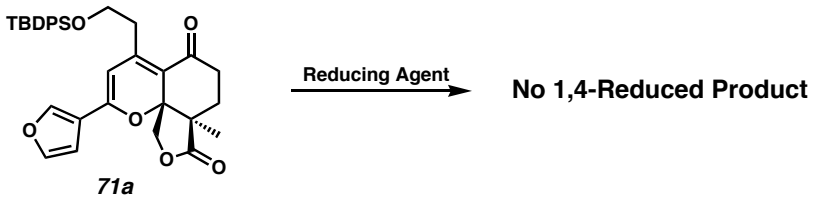
(20) Interestingly, when methyl iodide was added in the presence of HMPA, the enolate product was methylated on oxygen, not carbon, thus producing the methyl enol ether ***v***:



50 ***v***

(21) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912-4913.

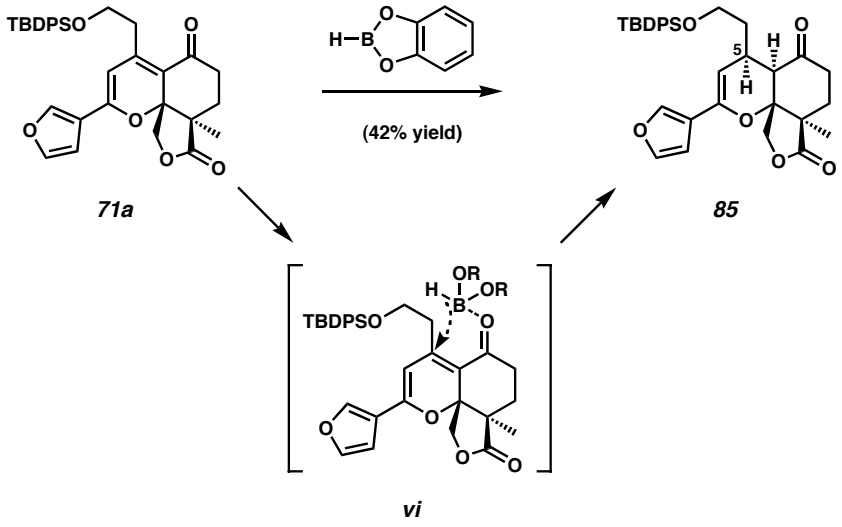
(22) Several conjugate reduction conditions were explored. Unfortunately, in most cases the tetrasubstituted olefin was resitant to reduction. Some of the unsuccessful condition reduction conditions are listed below:



71a

Reducing Agent	
Li/NH_3	$[CuH(PPh_3)]_6/R_3SiH$
HN=NH	$RhCl(PPh_3)_3$/Catecholborane
CuI-$LiAlH_4$	Pd/C, H_2 (with varying H_2 pressures)
$NaBH_4$	Pd black, H_2 (with varying H_2 pressures)
L--selectride	PtO_2, H_2 (with varying H_2 pressures)
K-selectride	$RhCl(PPh_3)_3$, H_2 (with varying H_2 pressures)
$Pd(PPh_3)_4/Bu_3SnH$	Rh/Alumina, H_2 (with varying H_2 pressures)

(23) Although we do not have a detailed explanation for why catecholborane delivers a hydride from the α-face, we believe it may due to an intramolecular delivery of the hydride nucleophile (i.e., ***vi***). This mode of nucleophillic attack differs from the putative intermolecular delivery of carbon nucleophiles from the β-face, which was discussed earlier in the chapter.



(24) For the synthesis of **56**, see: Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 635-640.

(25) For the synthesis of **62**, see: Piers, E.; Wong, T.; Coish, P.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816-1819.

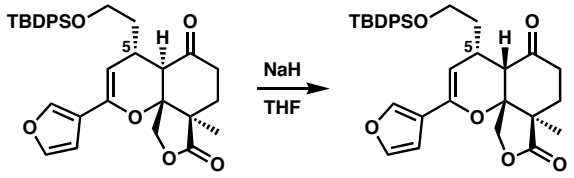
(26) Dieter, R. K; Silks, L. A.; Fishpaugh, J. A.; Kastner, M. E. *J. Am. Chem. Soc*. **1985**, *107*, 4679-4692.

(27) For a synthesis of of Jones' reagent, see: Kashima, C.; Shimizu, M.; Omote, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2694-2697.

(28) For the synthesis of **80**, see: Kiyooka, S; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967-7978.

(29) For the synthesis of **81**, see: Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocycl. Chem.* **1996**, *33*, 1313-1317.

(30) The C(16) epimer of ketone **90** (i.e., ***vii***) was easily converted to ketone **90** by simple bases such as NaH:

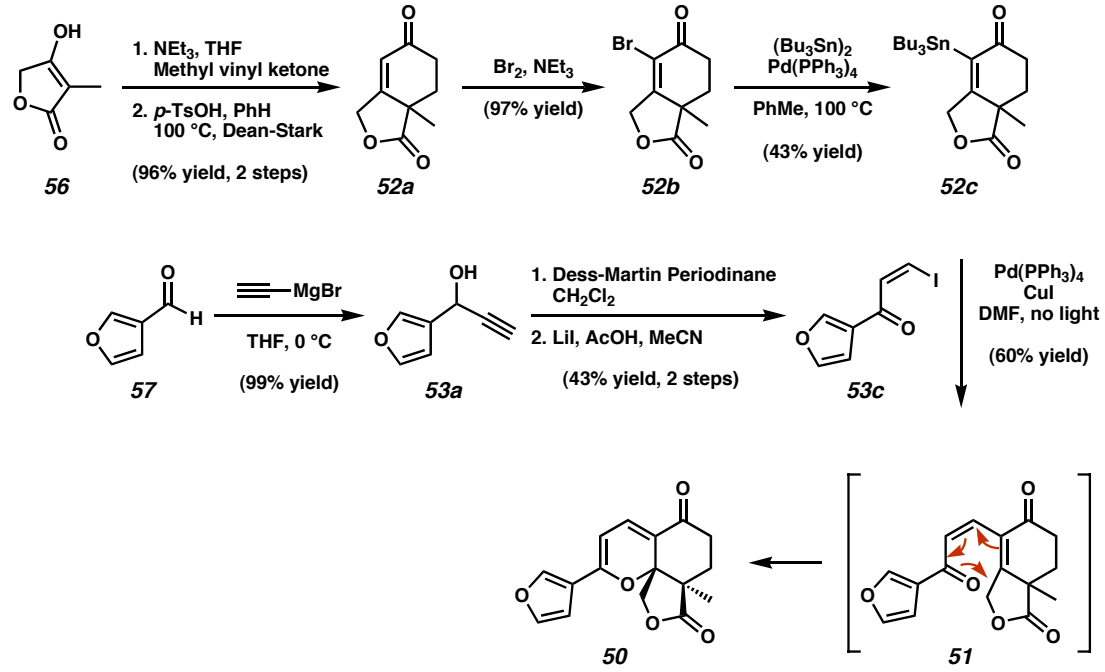


vii ***90***

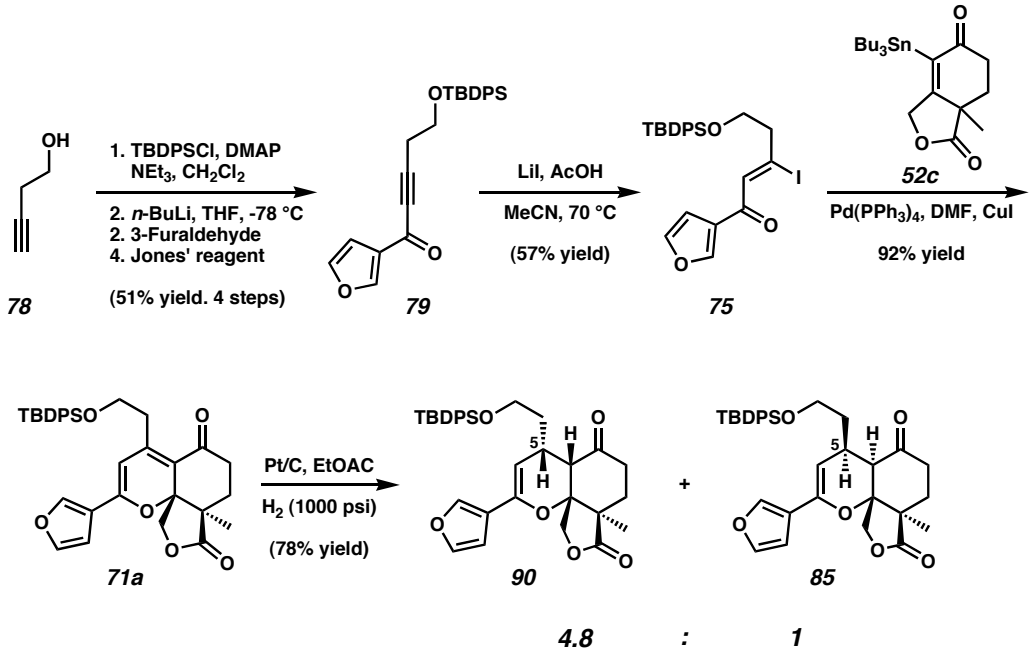
APPENDIX ONE

Summary of Synthetic Progress Toward Saudin (1)

Scheme A1.1 The synthesis of polycycle **50**.



Scheme A1.2 The synthesis of ketone **90**.



APPENDIX TWO

Spectra Relevant to Chapter Two:

Studies Directed Toward the Total Synthesis of Saudin and the Development of a Tandem Stille-Oxa-Electrocyclization Reaction

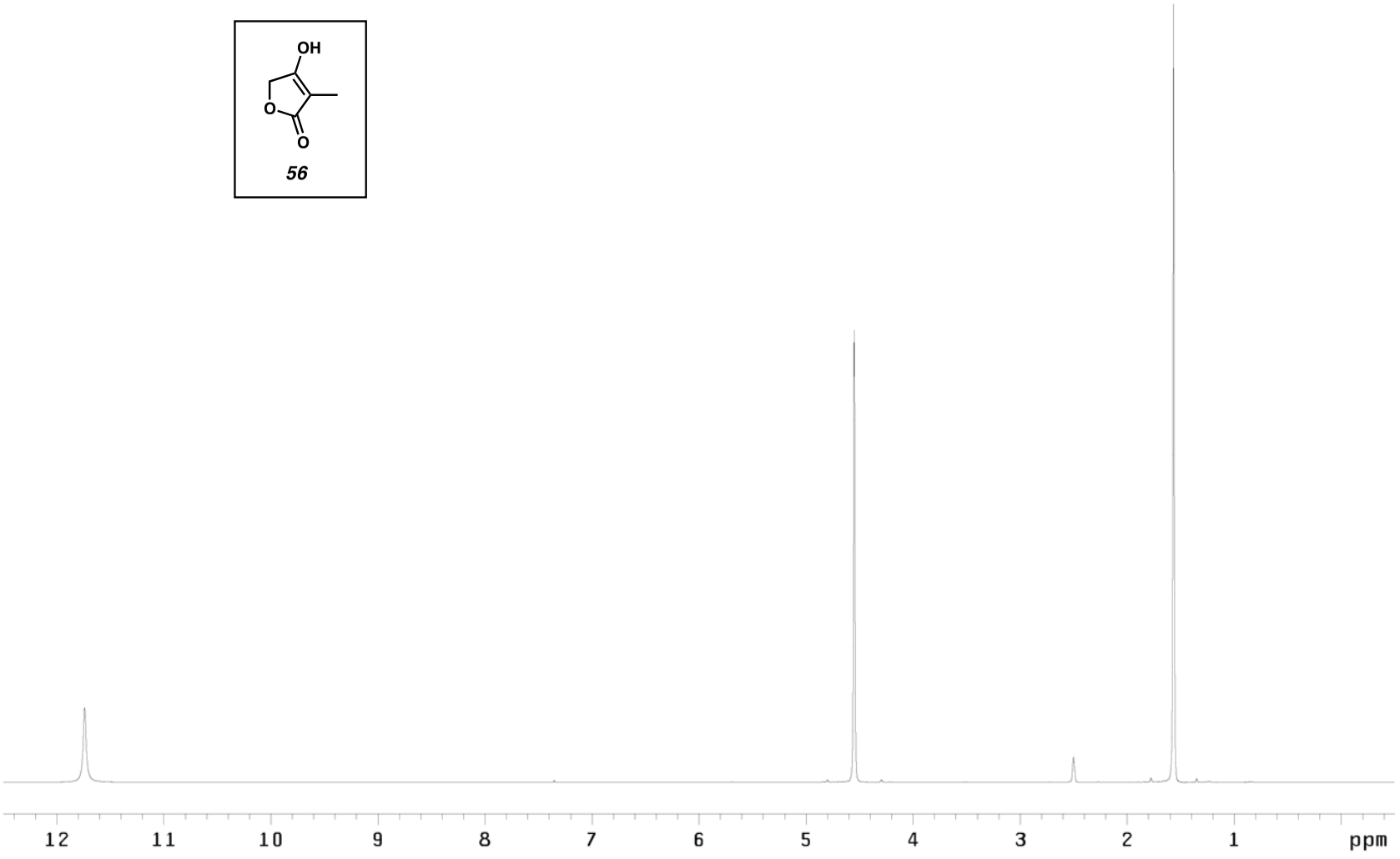


Figure A2.1 ^{1}H NMR (300 MHz, DMSO-d_6) of compound **56**.

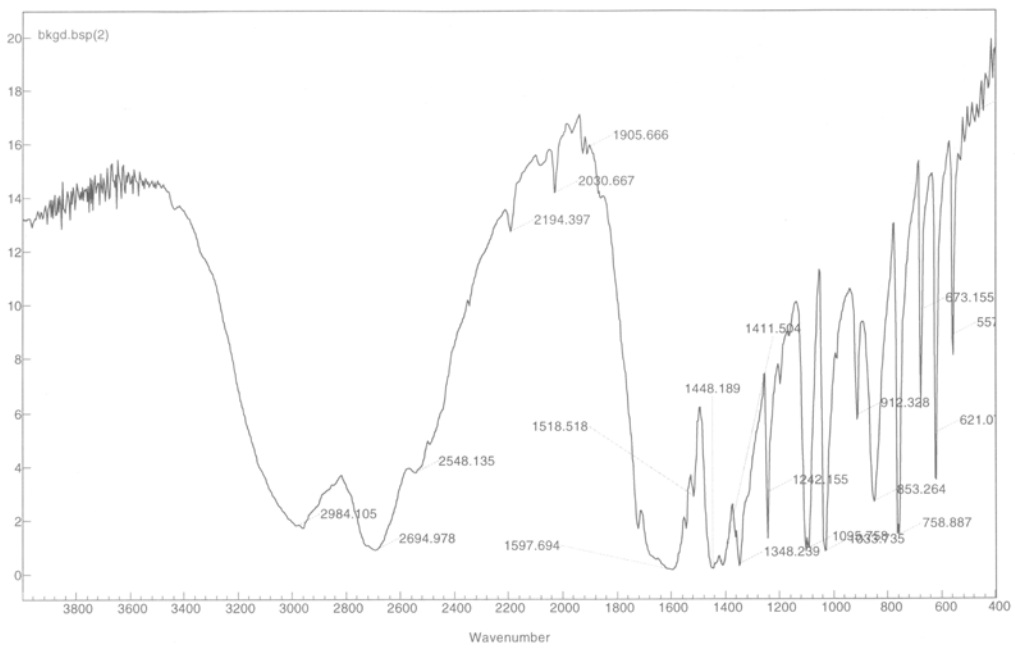


Figure A2.2 Infrared spectrum (KBr pellet) of compound **56**.

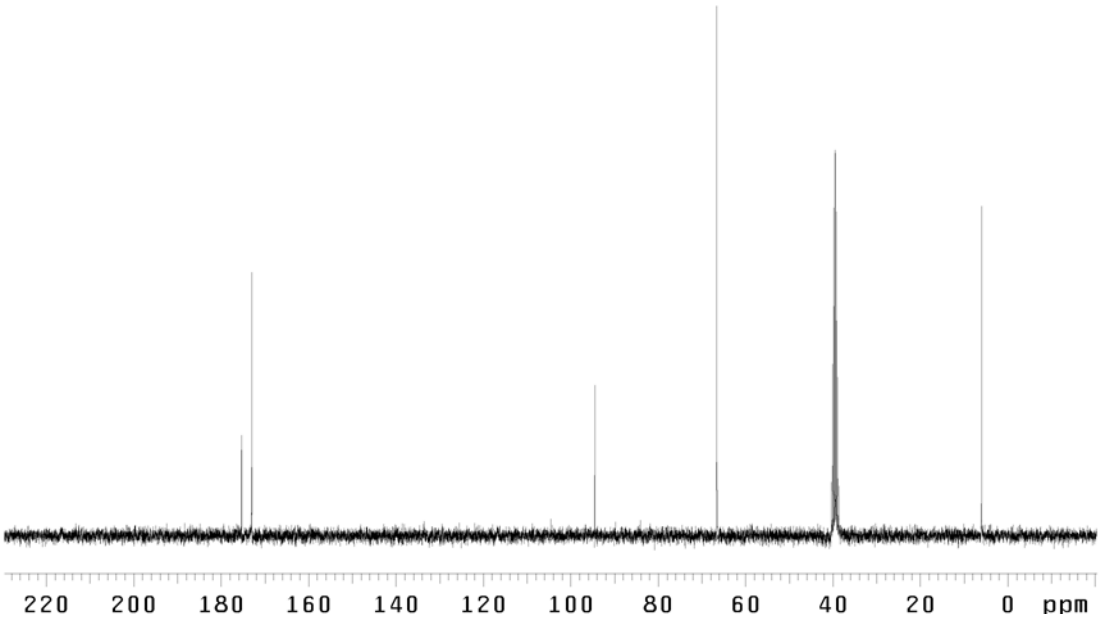
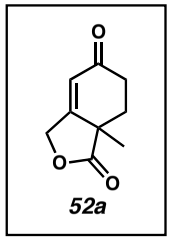


Figure A2.3 ^{13}C NMR (75 MHz, DMSO-d_6) of compound **56**.



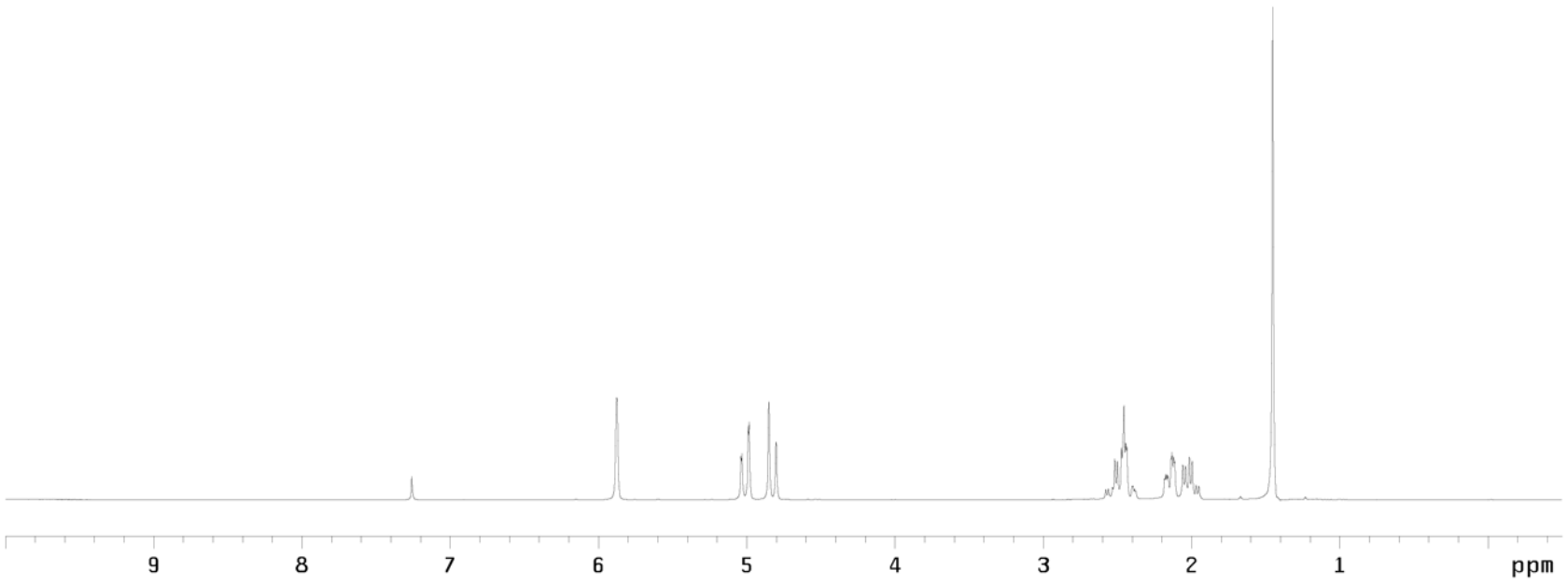


Figure A2.4 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **52a**.

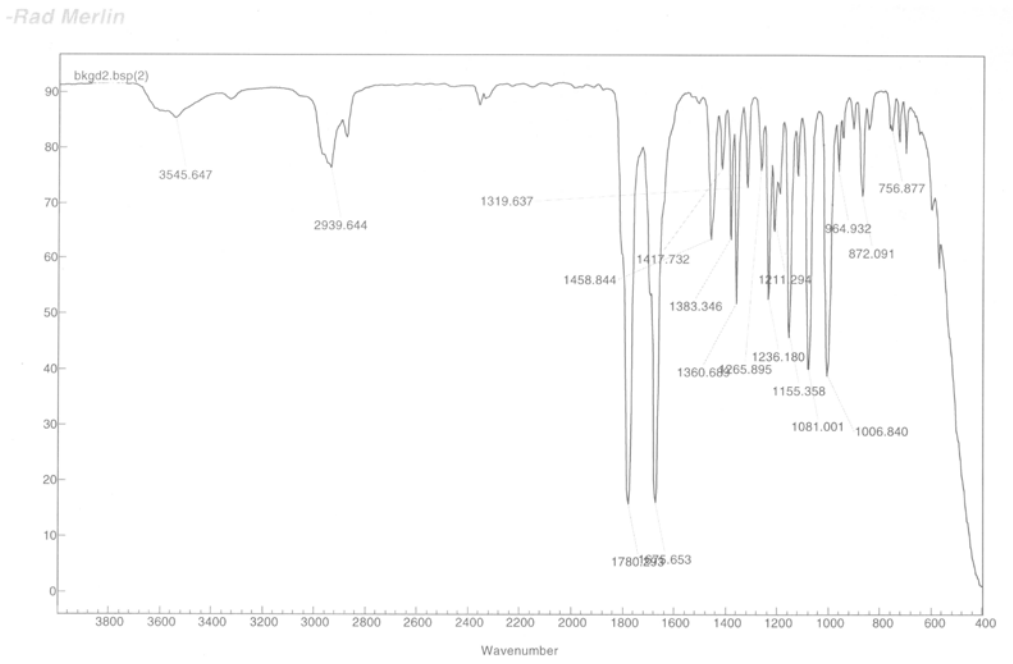


Figure A2.5 Infrared spectrum (thin film/NaCl) of compound **52a**.

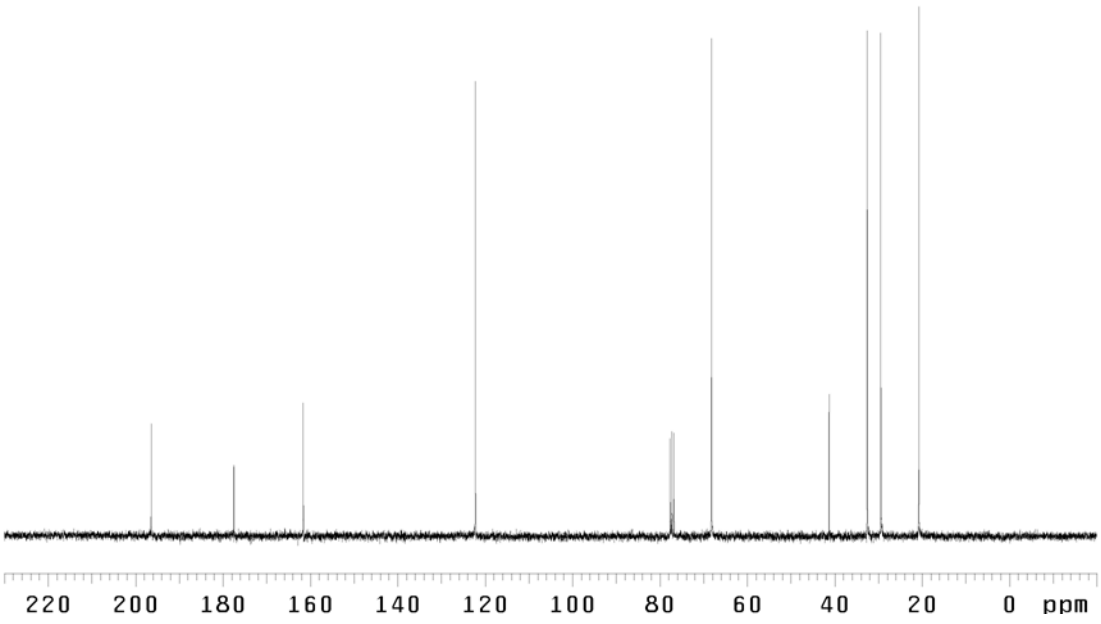


Figure A2.6 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **52a**.

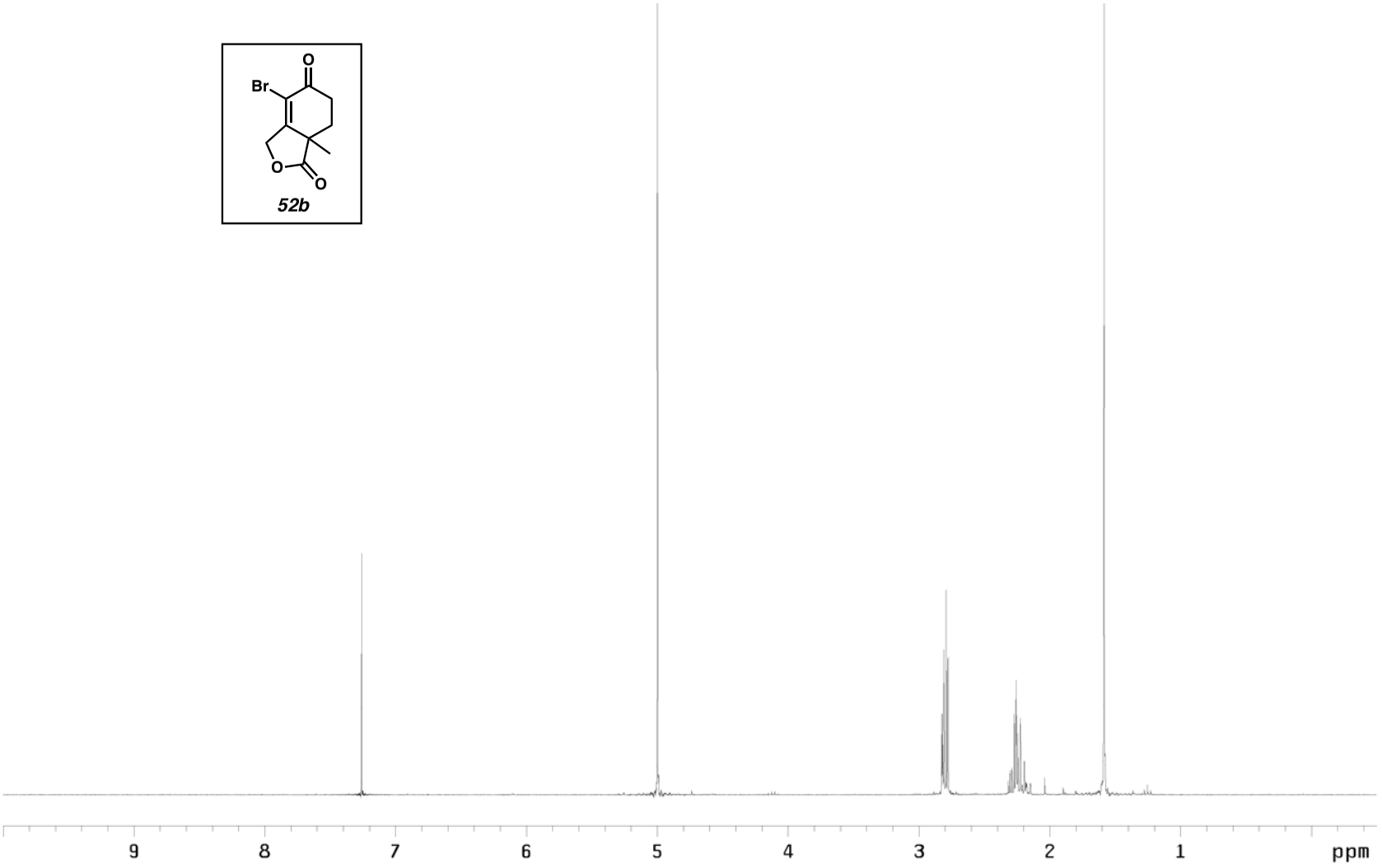


Figure A2.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **52b**.

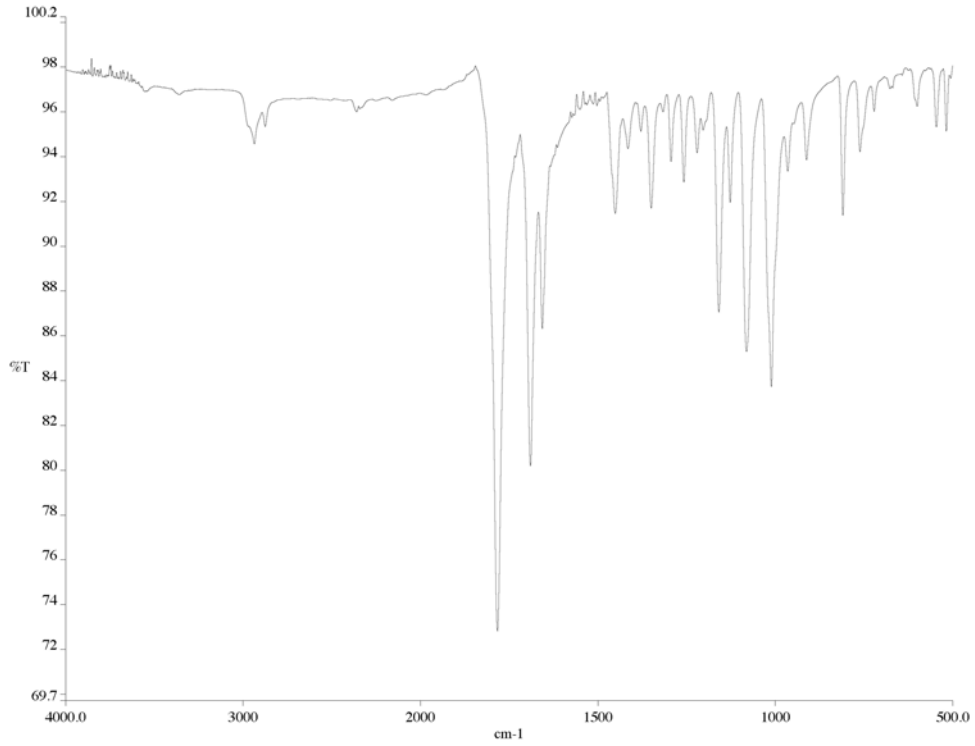


Figure A2.8 Infrared spectrum (thin film/NaCl) of compound **52b**.

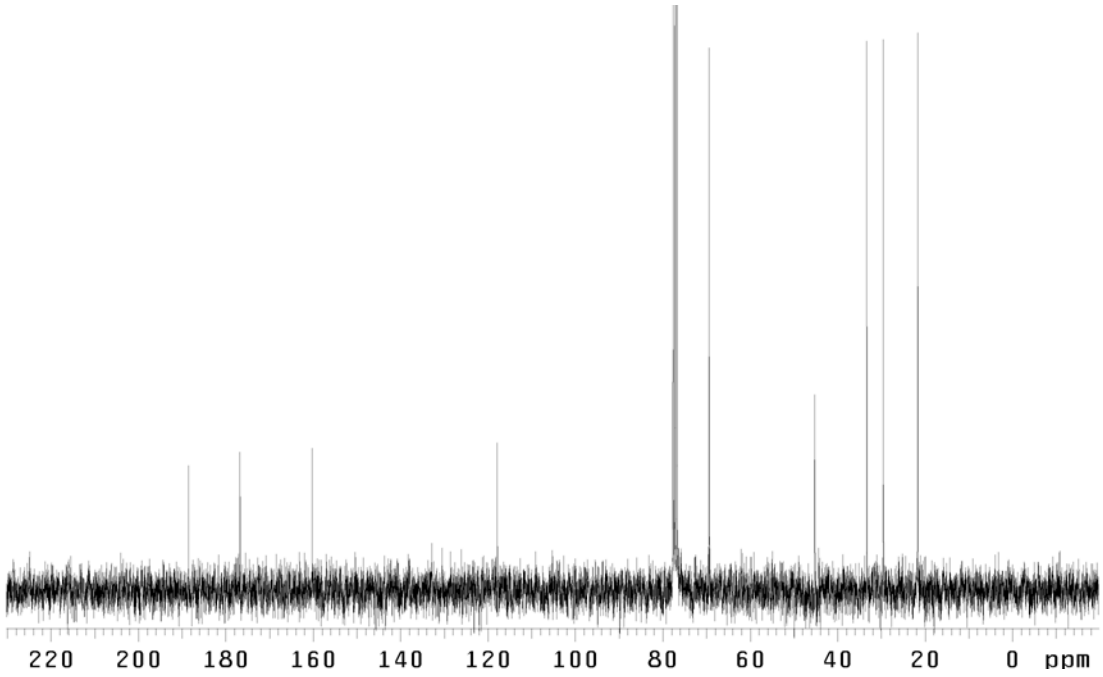


Figure A2.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **52b**.

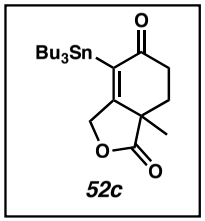


Figure A2.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **52c**.

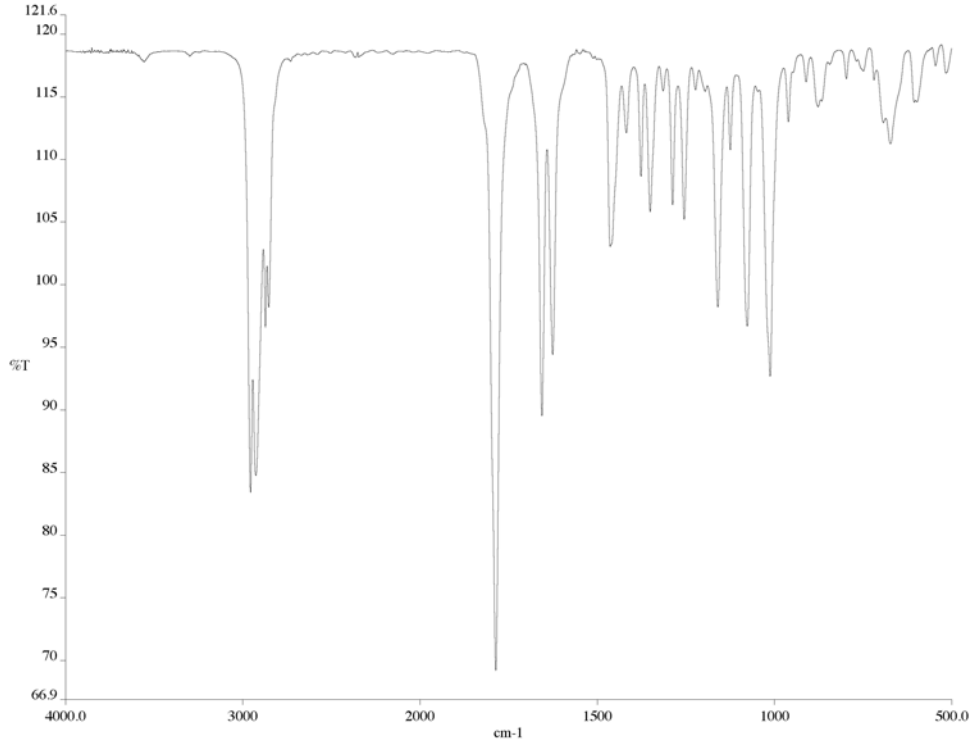


Figure A2.11 Infrared spectrum (thin film/NaCl) of compound **52c**.

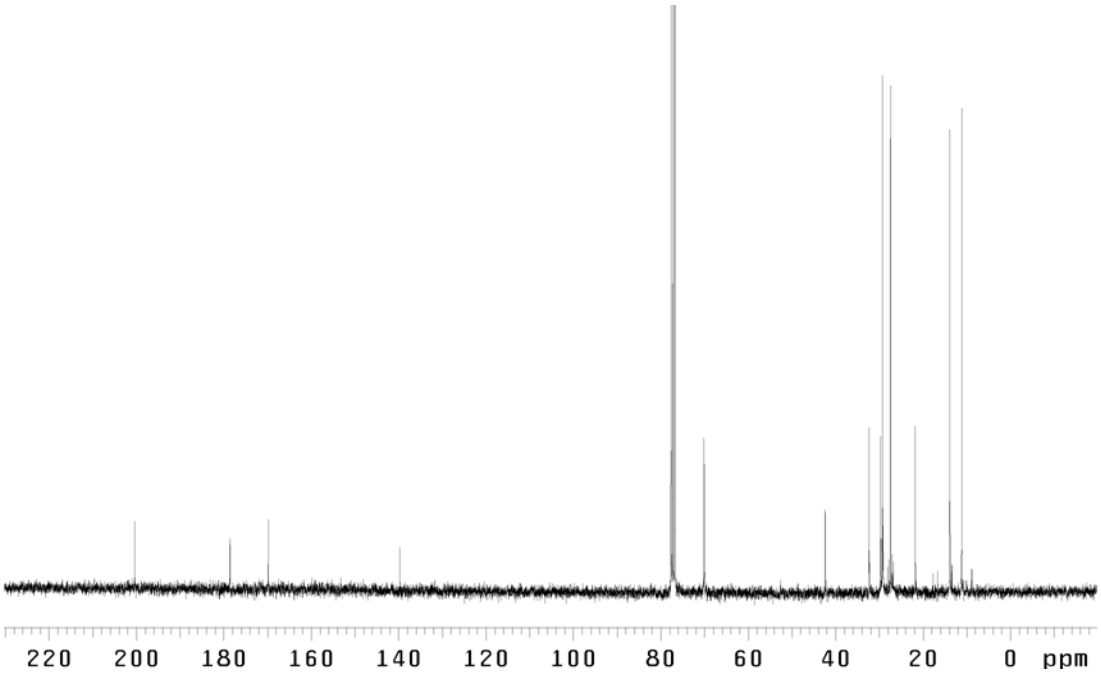


Figure A2.12 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **52c**.

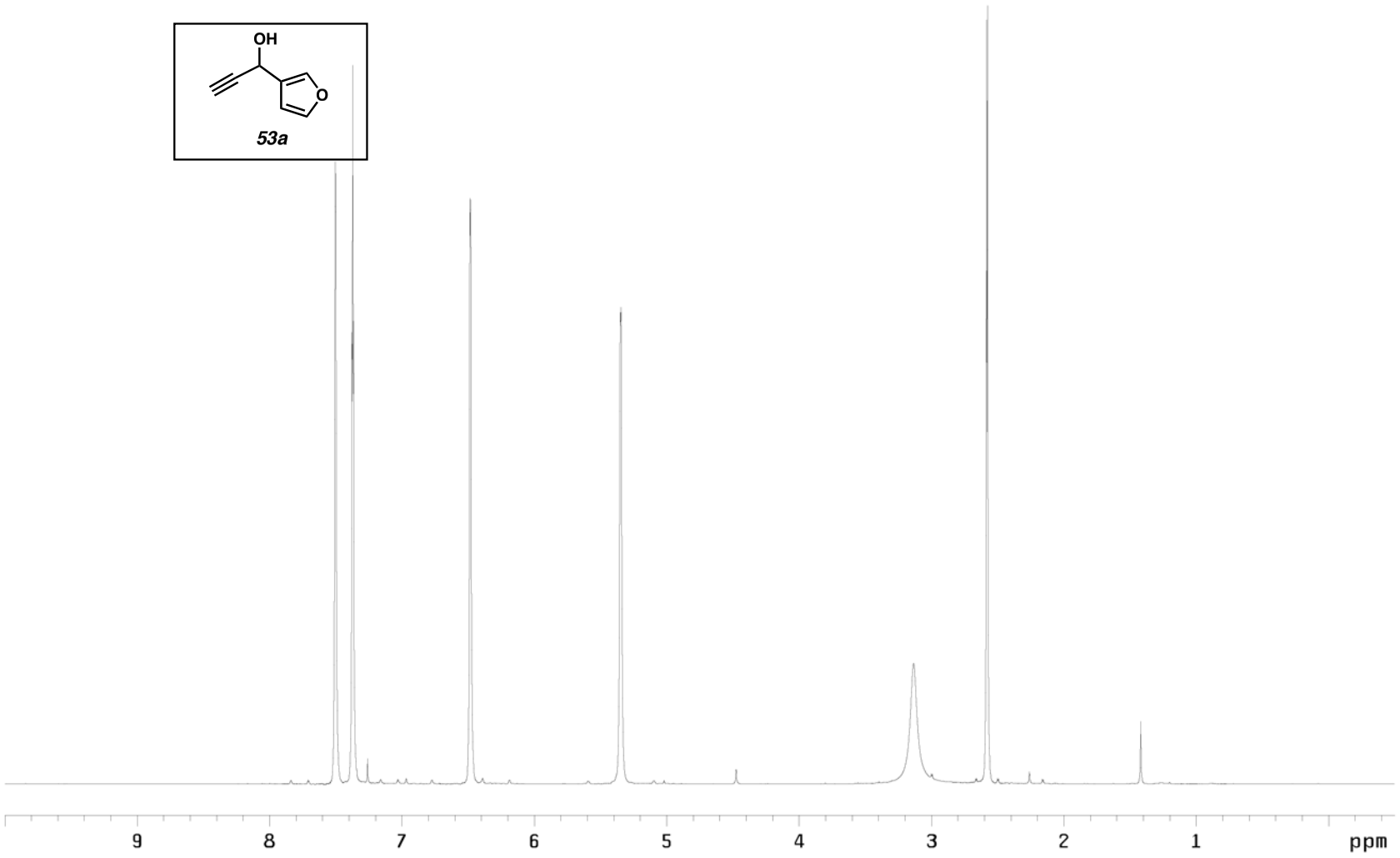


Figure A2.13 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53a**.

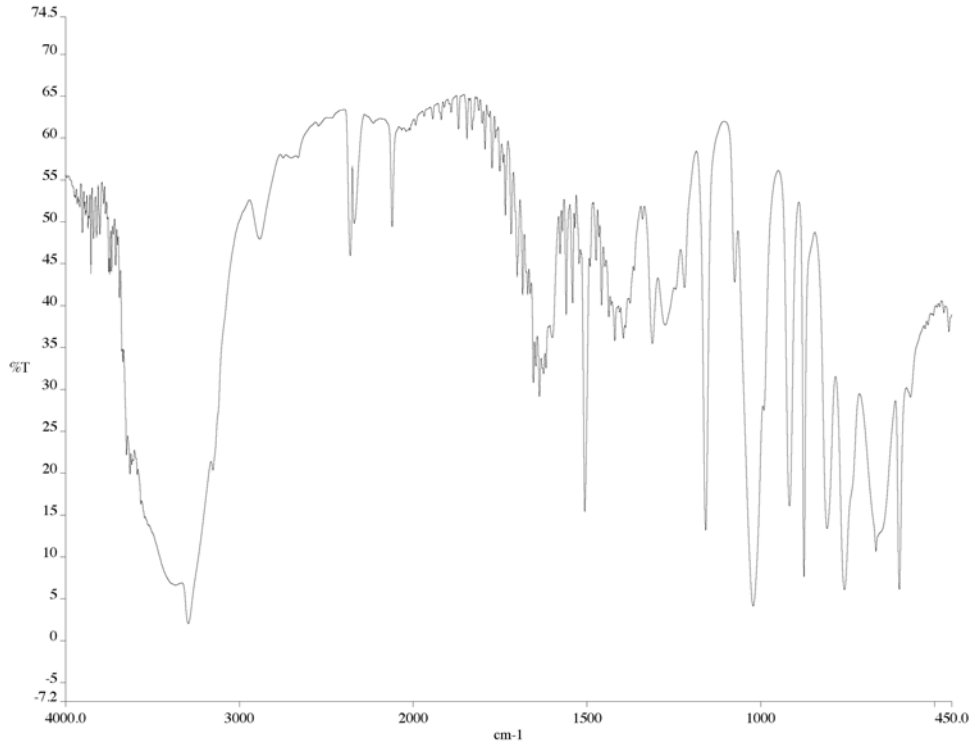


Figure A2.14 Infrared spectrum (thin film/NaCl) of compound **53a**.

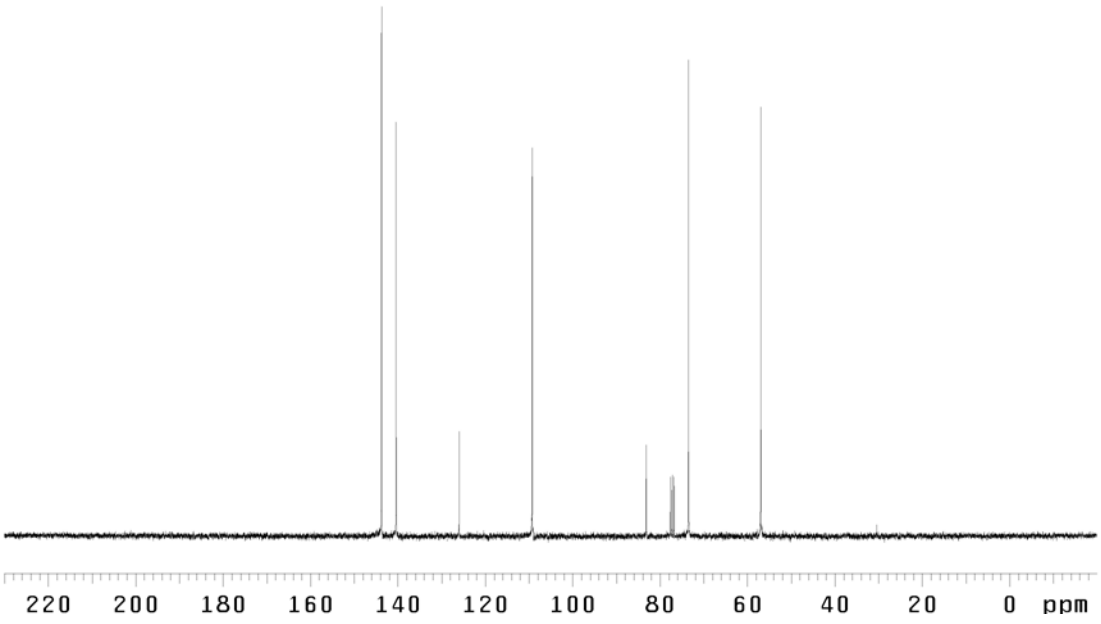


Figure A2.15 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53a**.

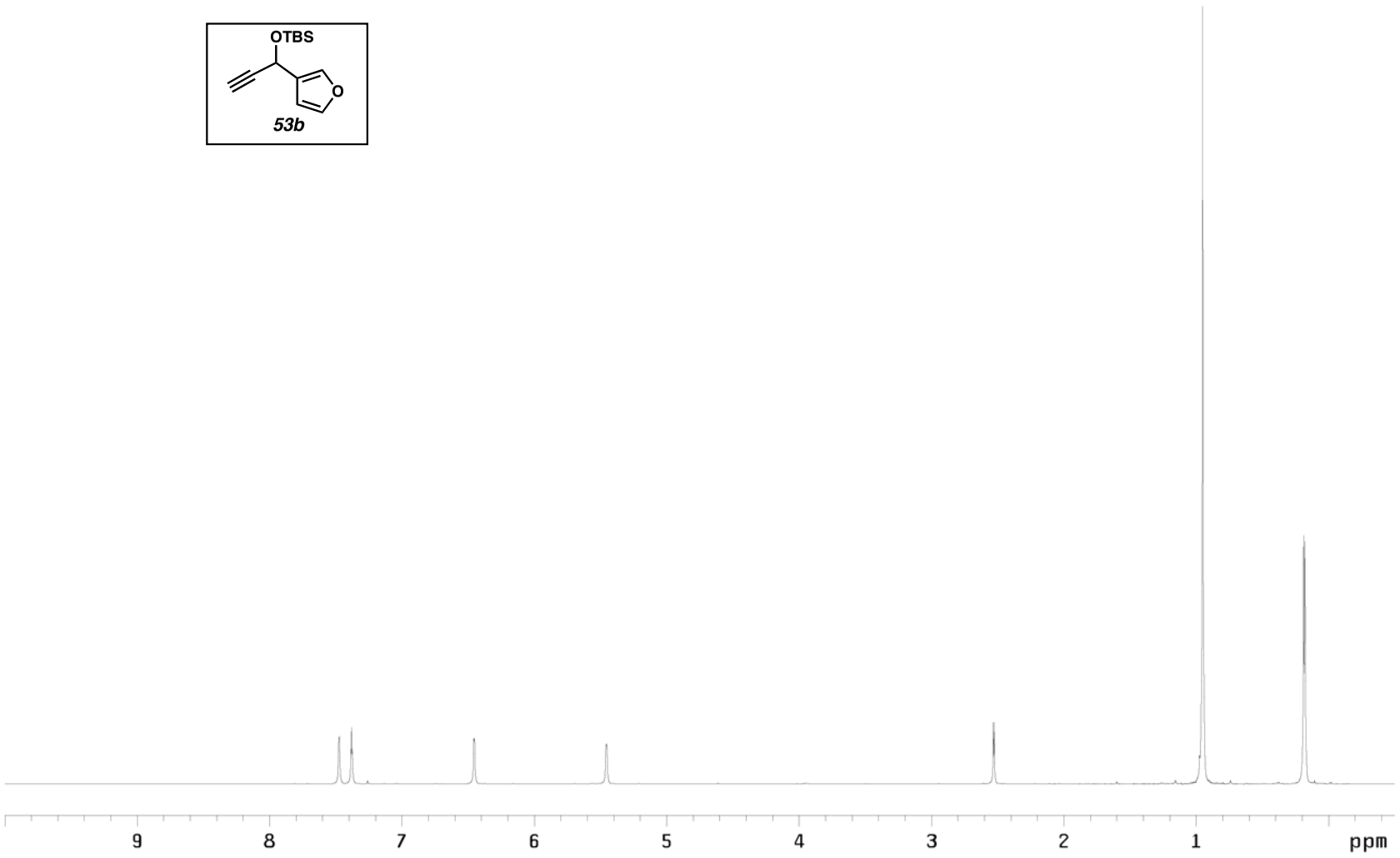


Figure A2.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53b**.

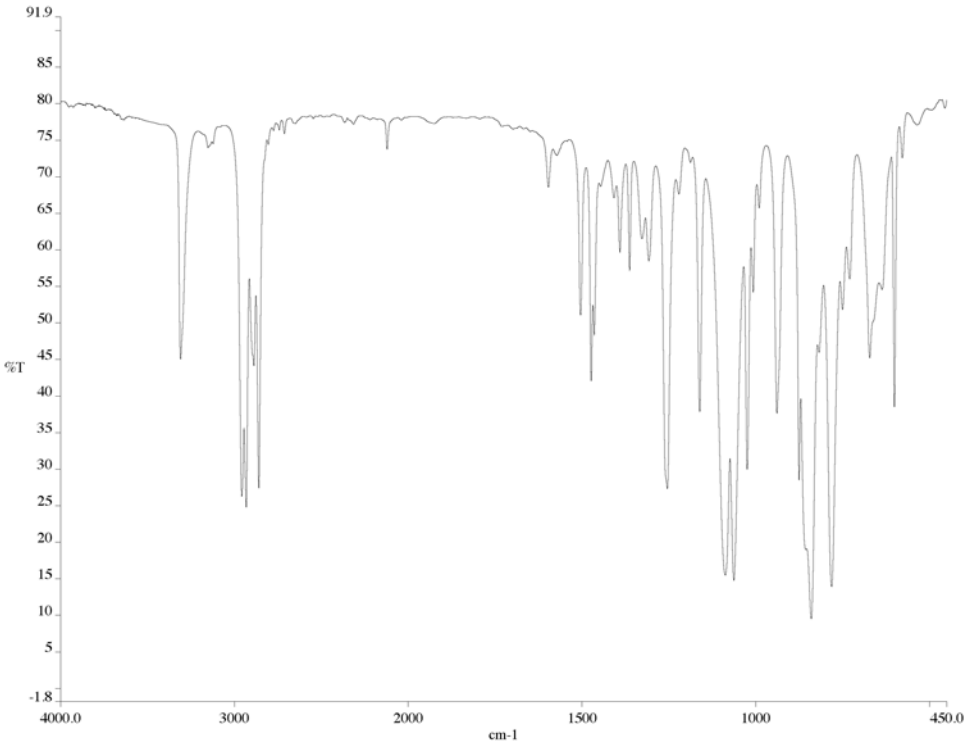


Figure A2.17 Infrared spectrum (thin film/NaCl) of compound **53b**.

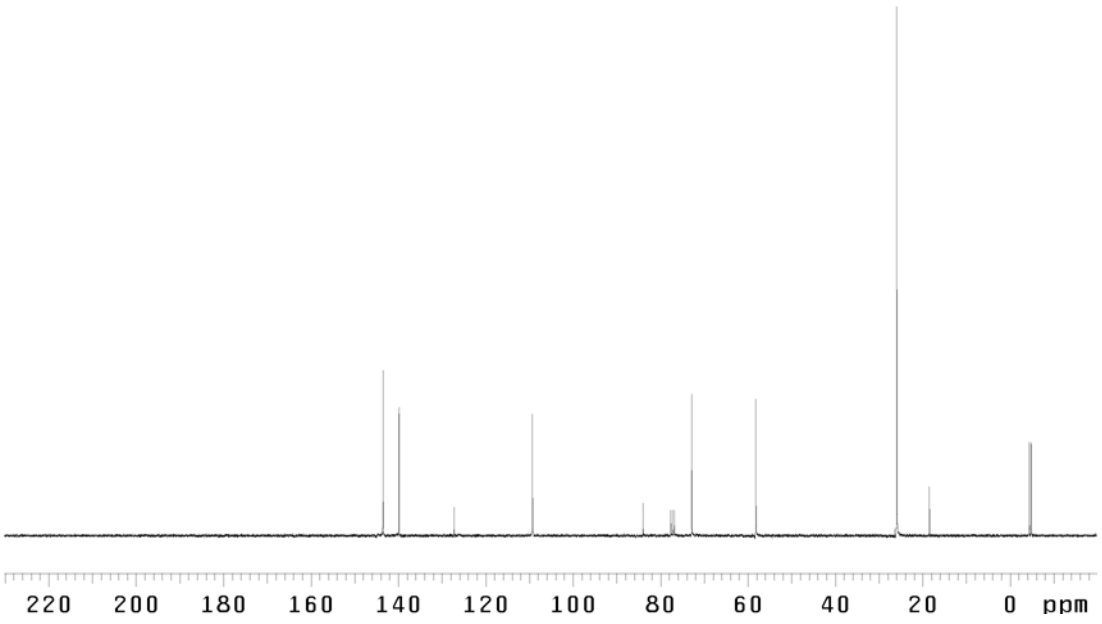


Figure A2.18 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53b**.

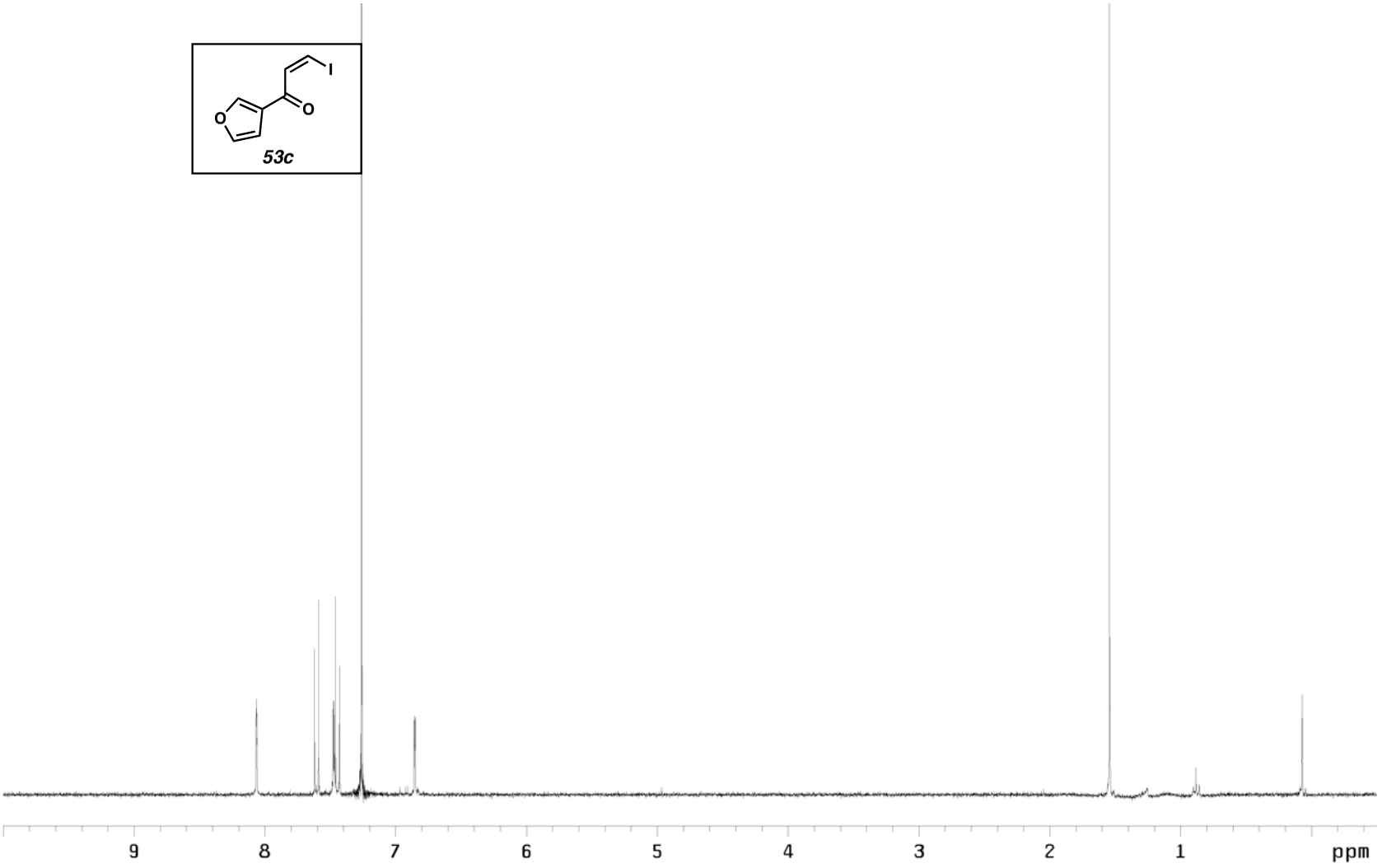


Figure A2.19 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53c**.

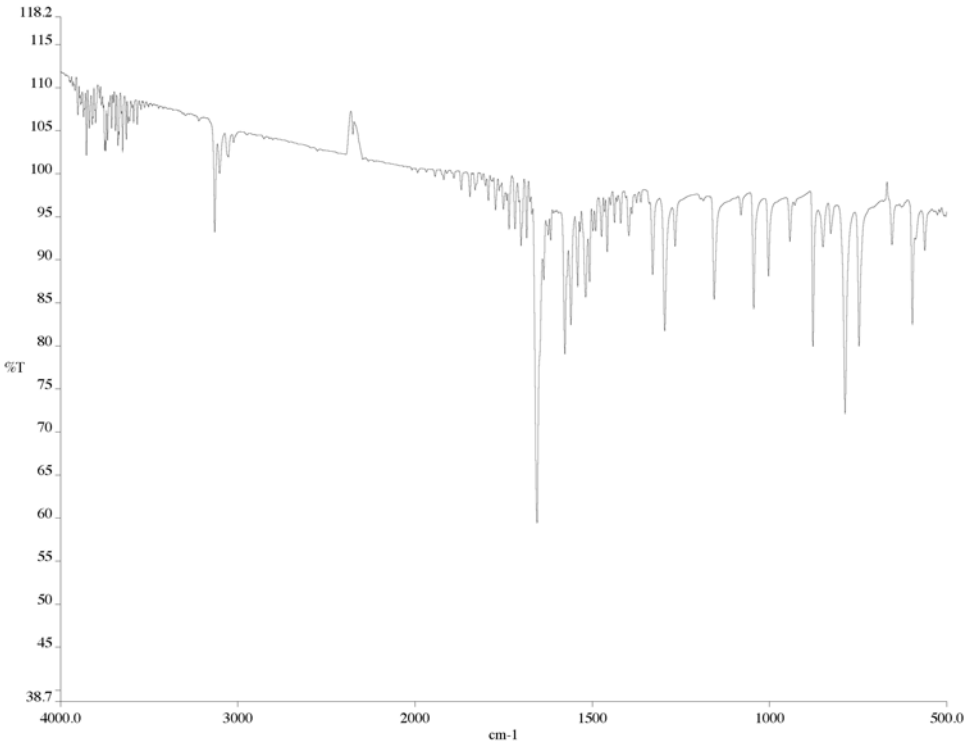


Figure A2.20 Infrared spectrum (thin film/NaCl) of compound **53c**.

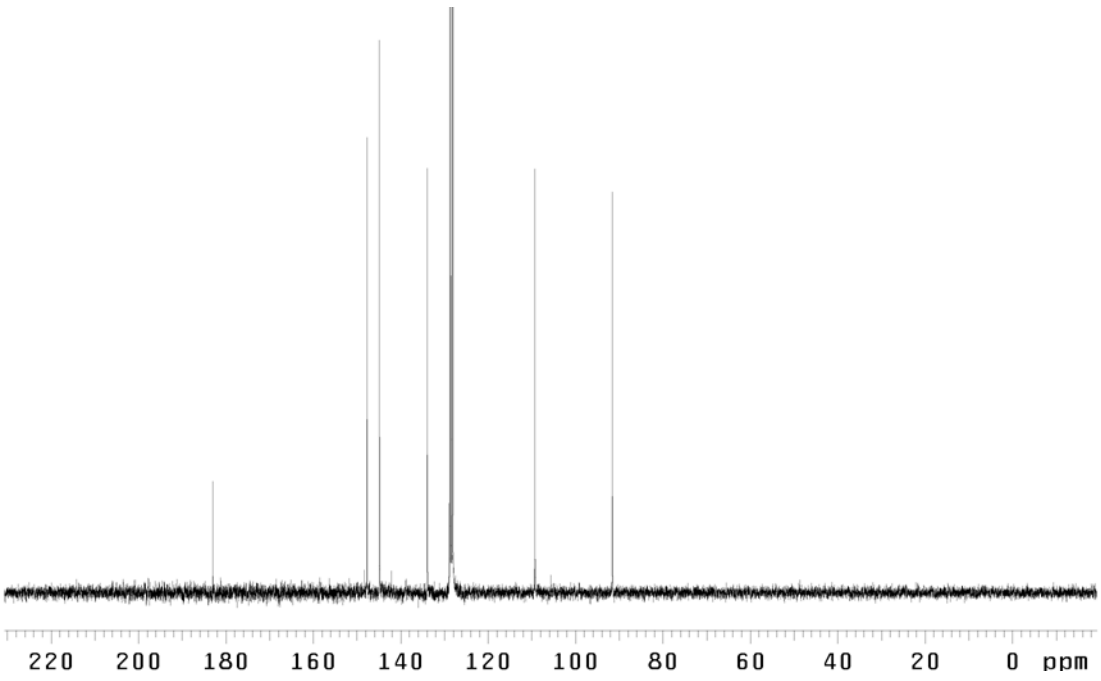


Figure A2.21 ^{13}C NMR (75 MHz, C_6D_6) of compound **53c**.

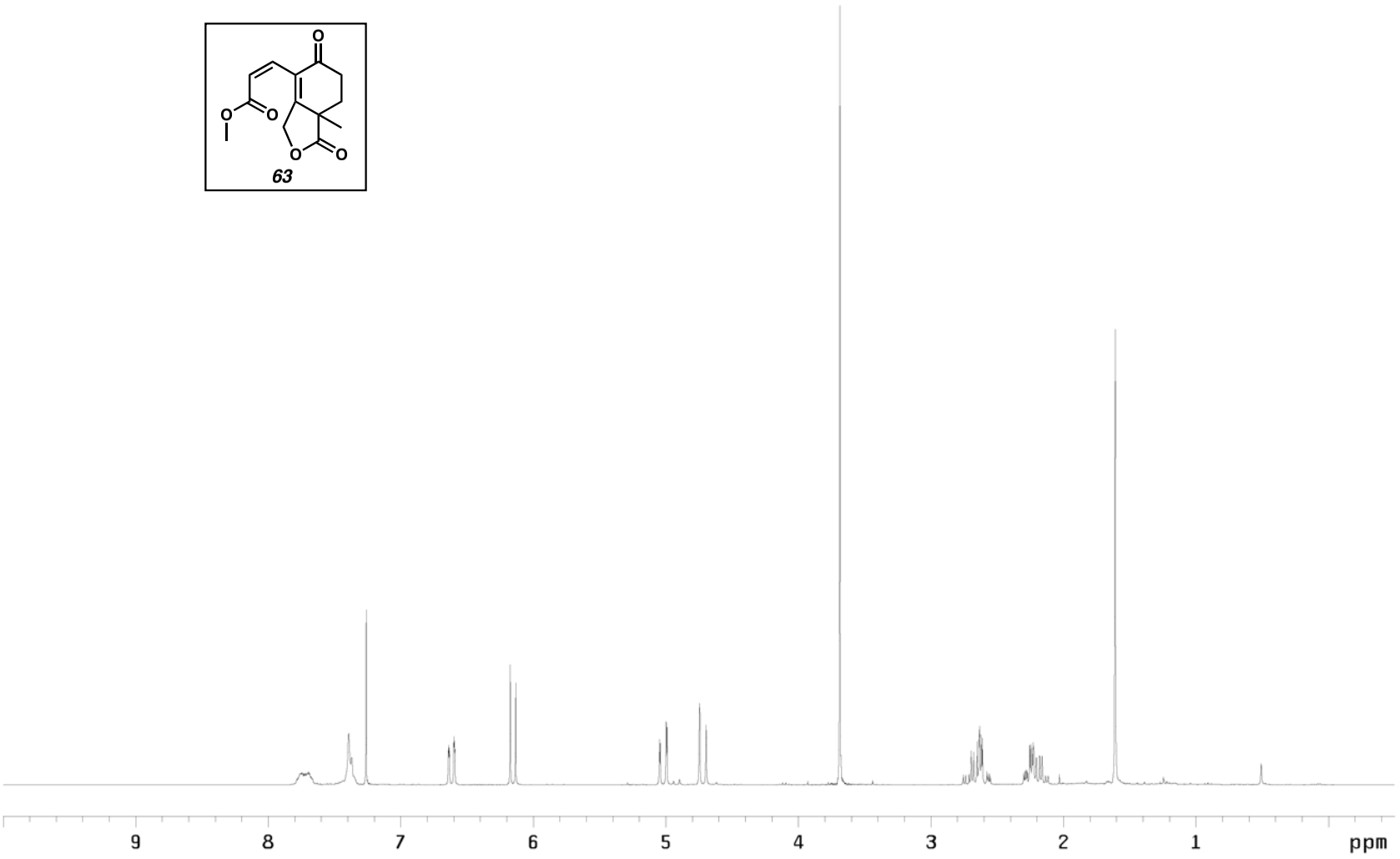


Figure A2.22 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **63**.

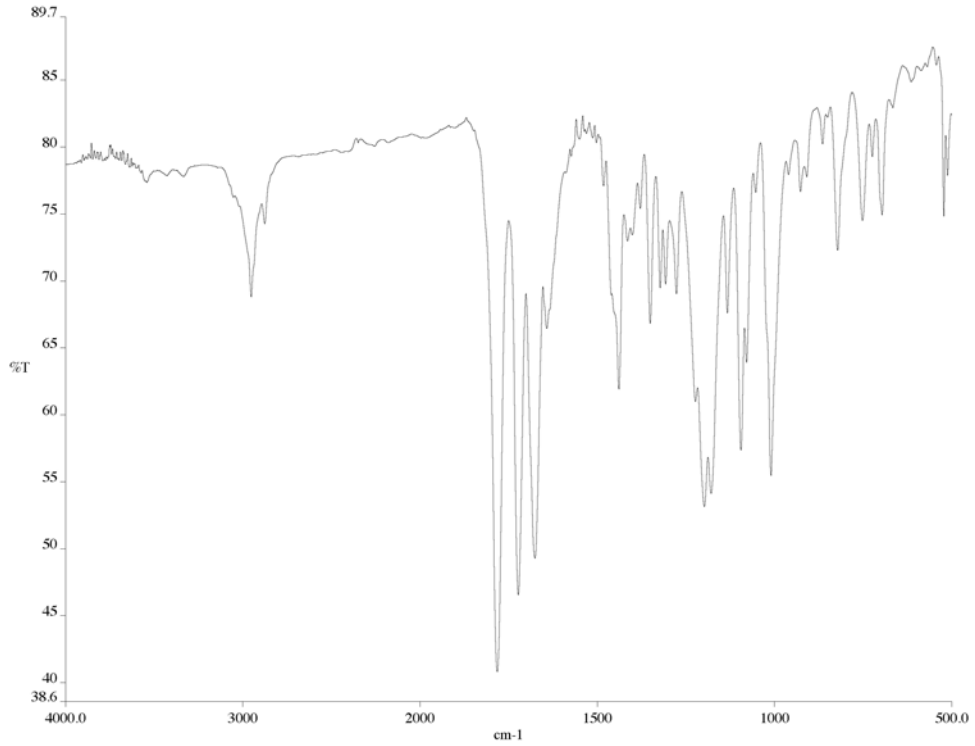


Figure A2.23 Infrared spectrum (thin film/NaCl) of compound **63**.

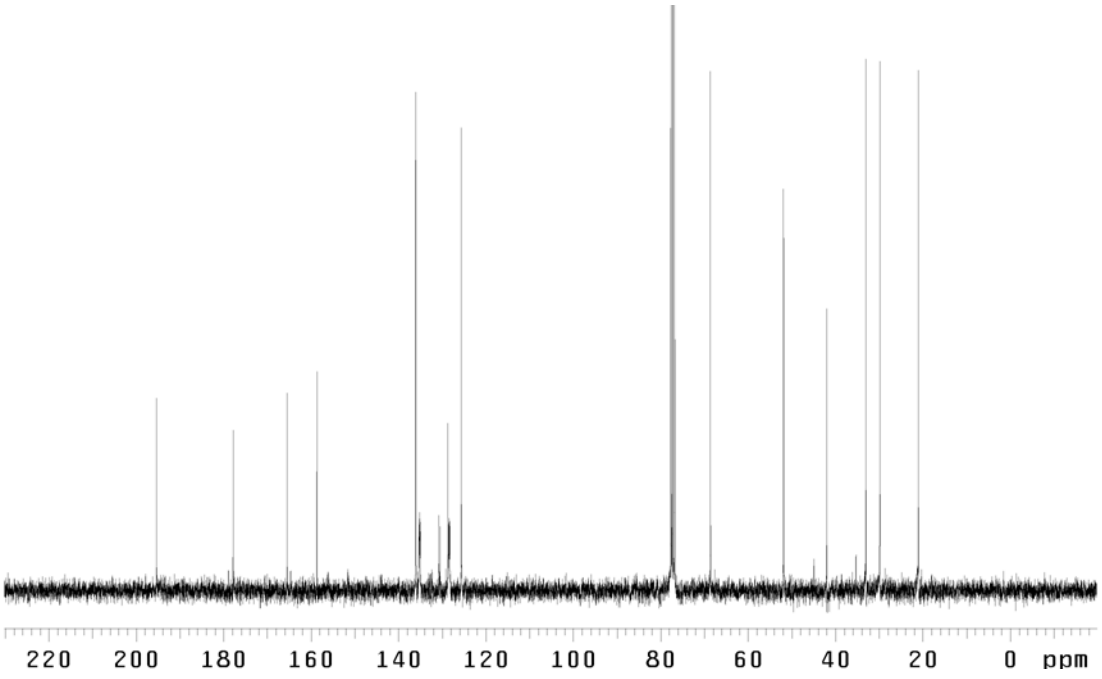


Figure A2.24 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **63**.

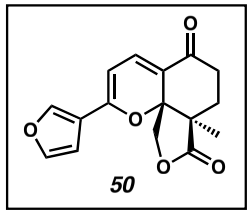


Figure A2.25 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **50**.

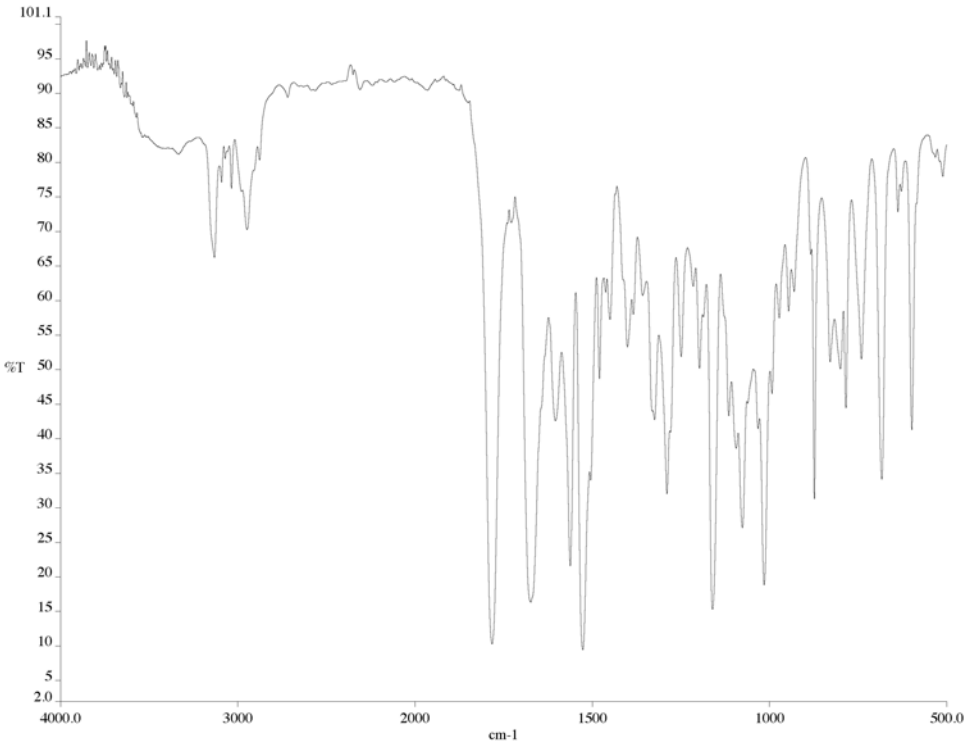


Figure A2.26 Infrared spectrum (thin film/NaCl) of compound **50**.

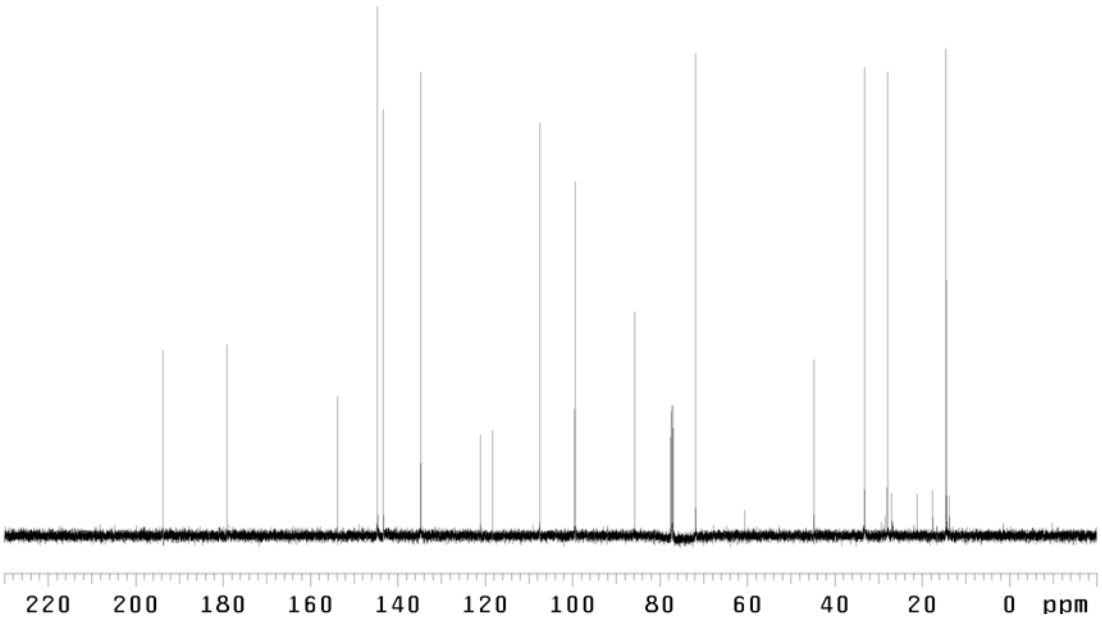


Figure A2.27 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **50**.

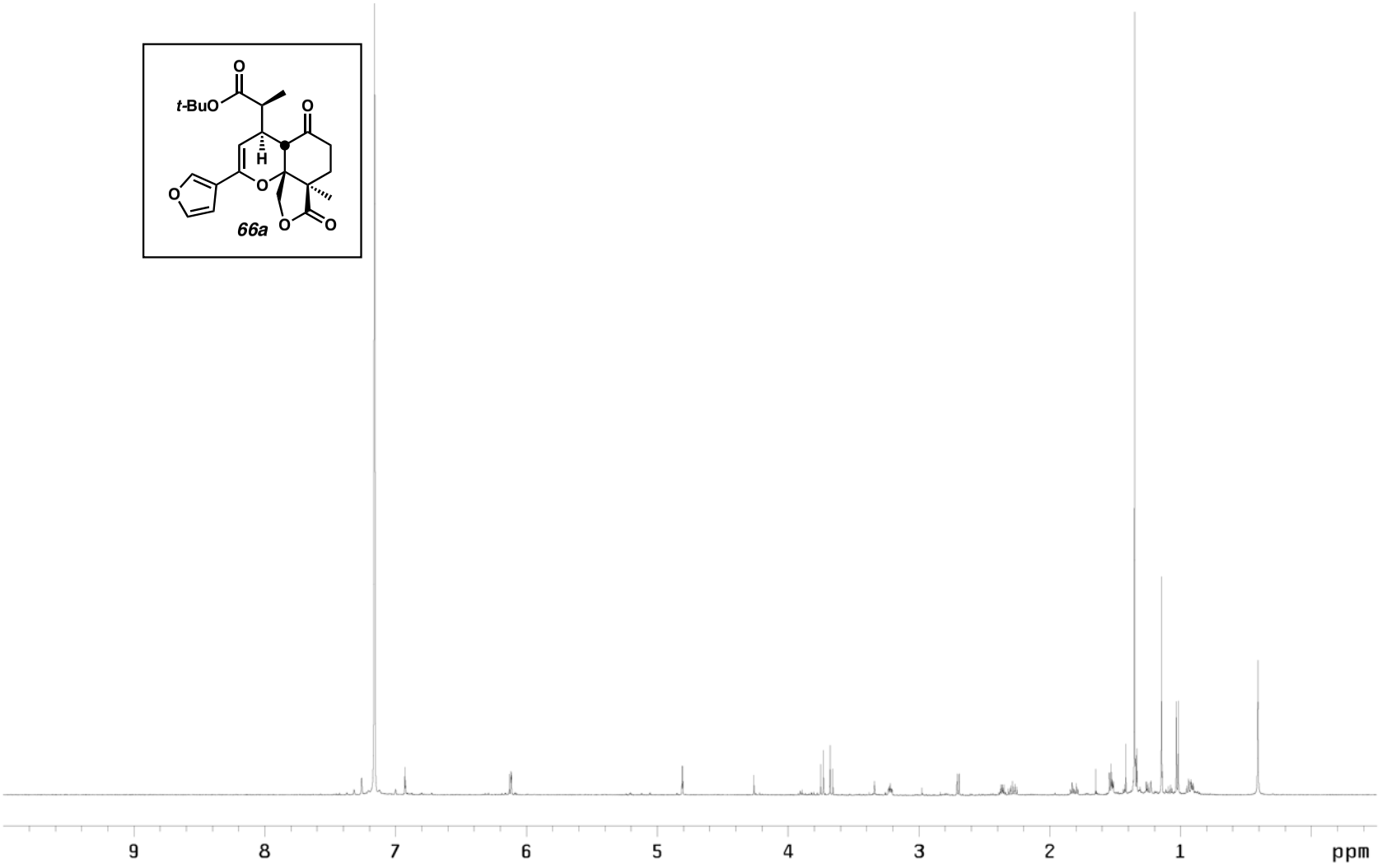


Figure A2.28 ^{1}H NMR (500 MHz, C_6D_6) of compound **66a**.

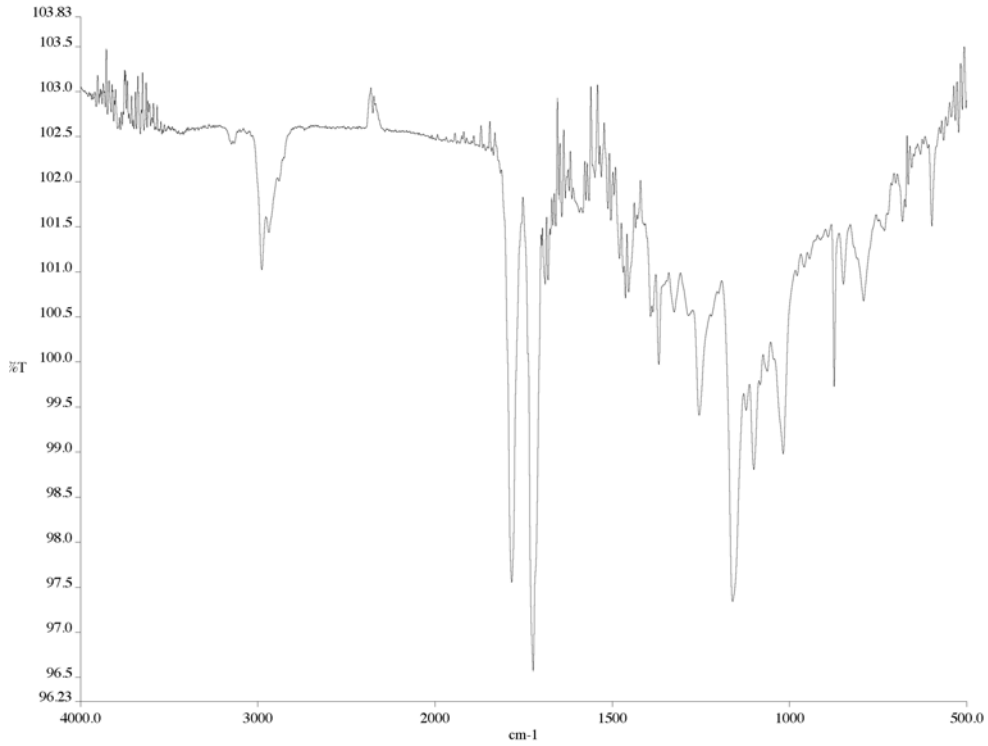


Figure A2.29 Infrared spectrum (thin film/NaCl) of compound **66a**.

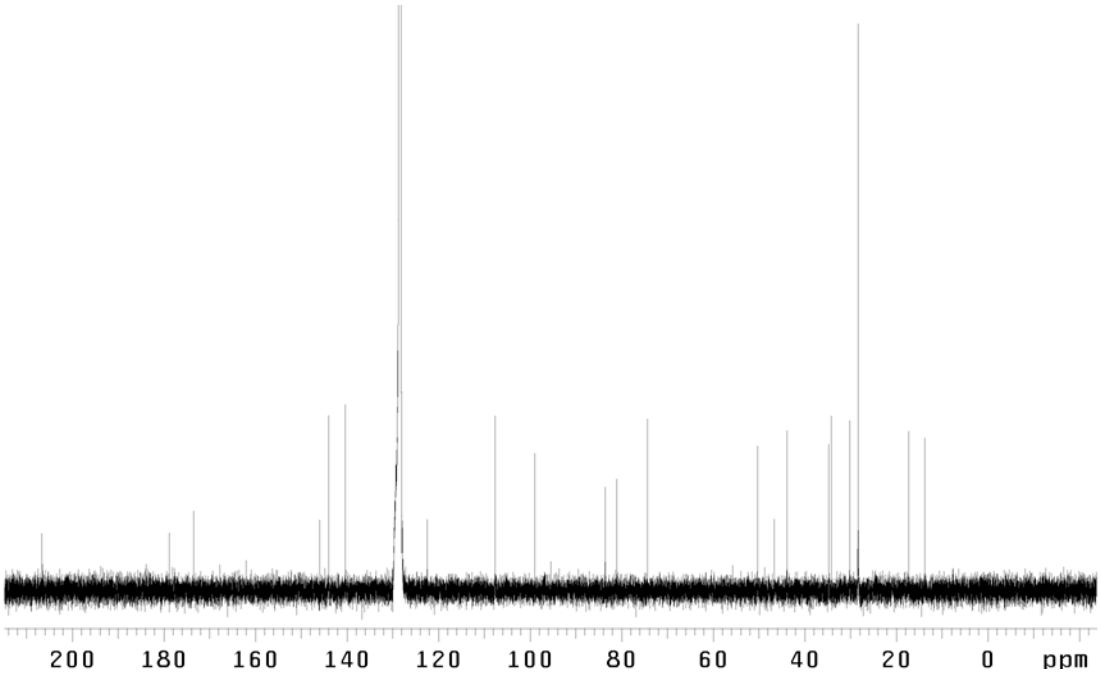


Figure A2.30 ^{13}C NMR (125 MHz, C_6D_6) of compound **66a**.

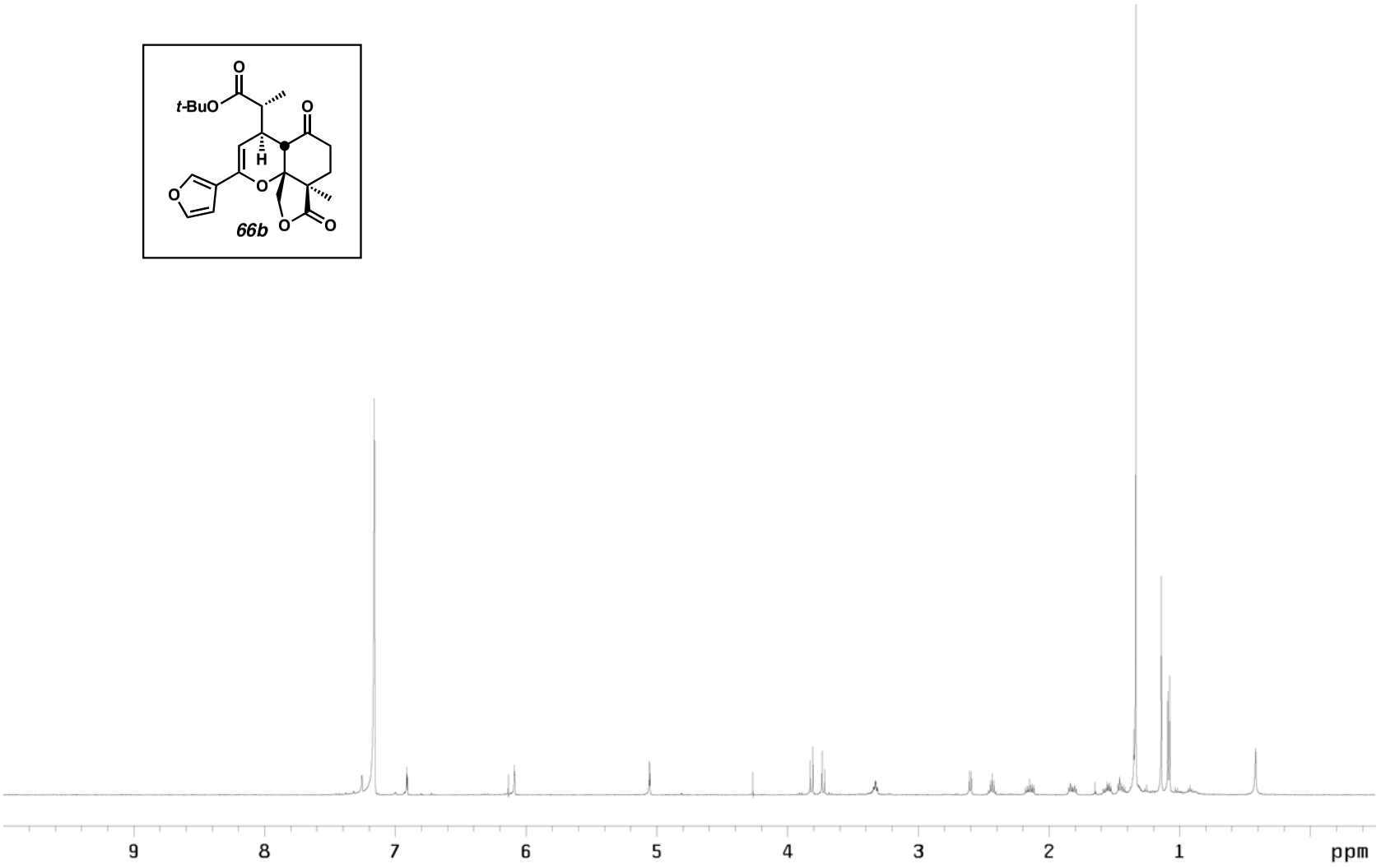


Figure A2.31 ^{1}H NMR (500 MHz, C_6D_6) of compound **66b**.

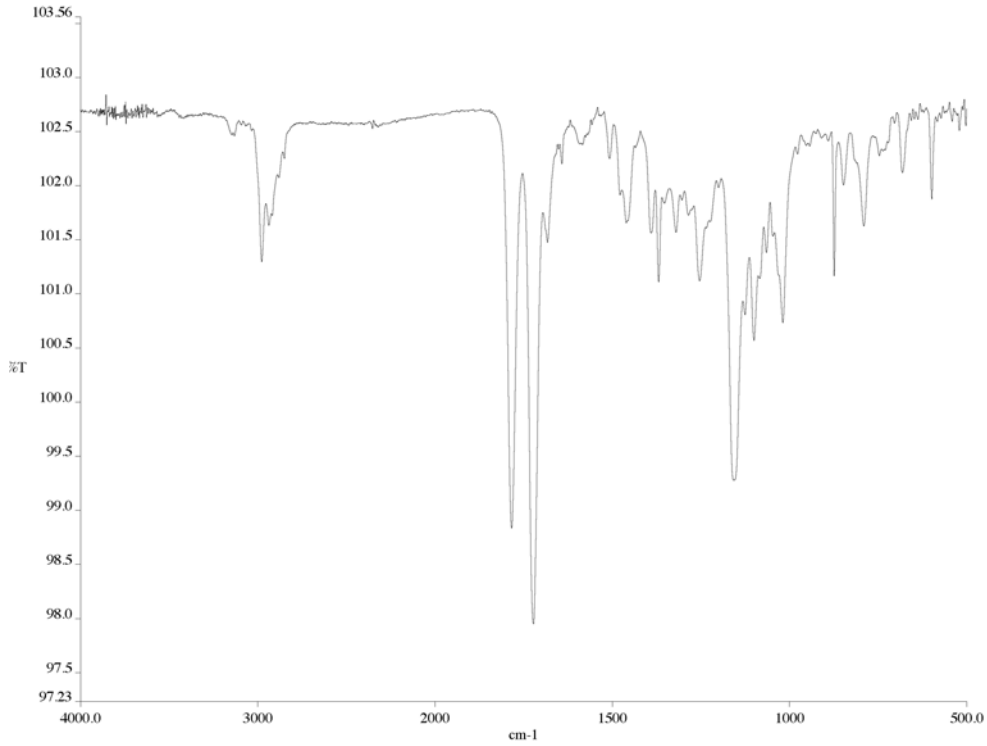


Figure A2.32 Infrared spectrum (thin film/NaCl) of compound **66b**.

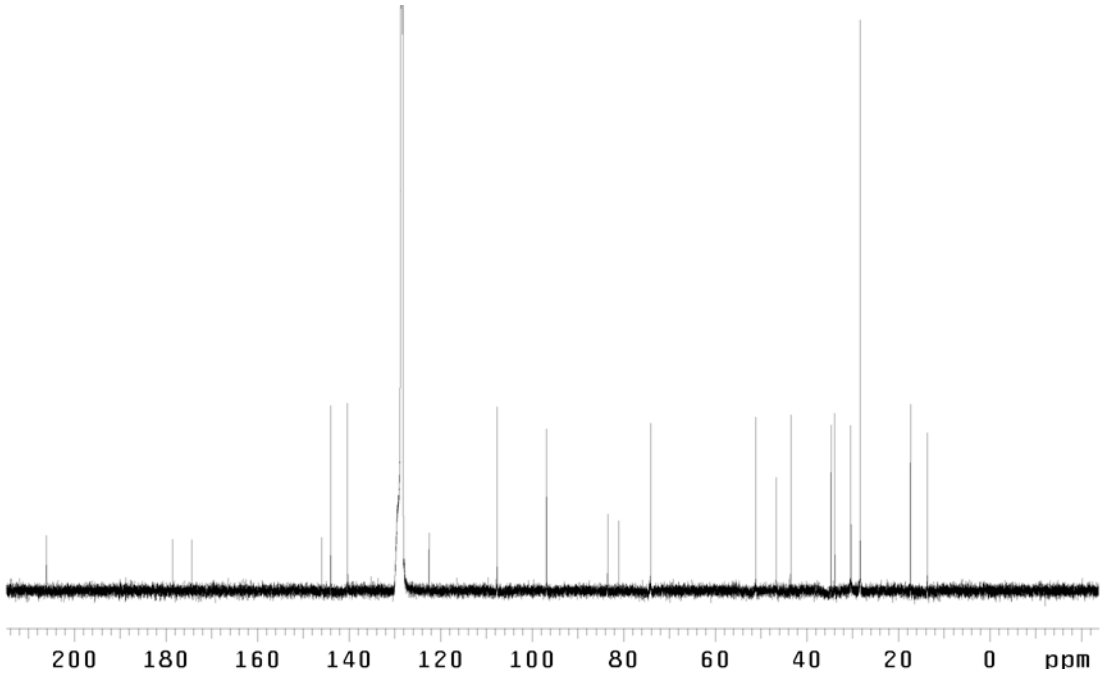


Figure A2.33 ^{13}C NMR (125 MHz, C_6D_6) of compound **66b**.

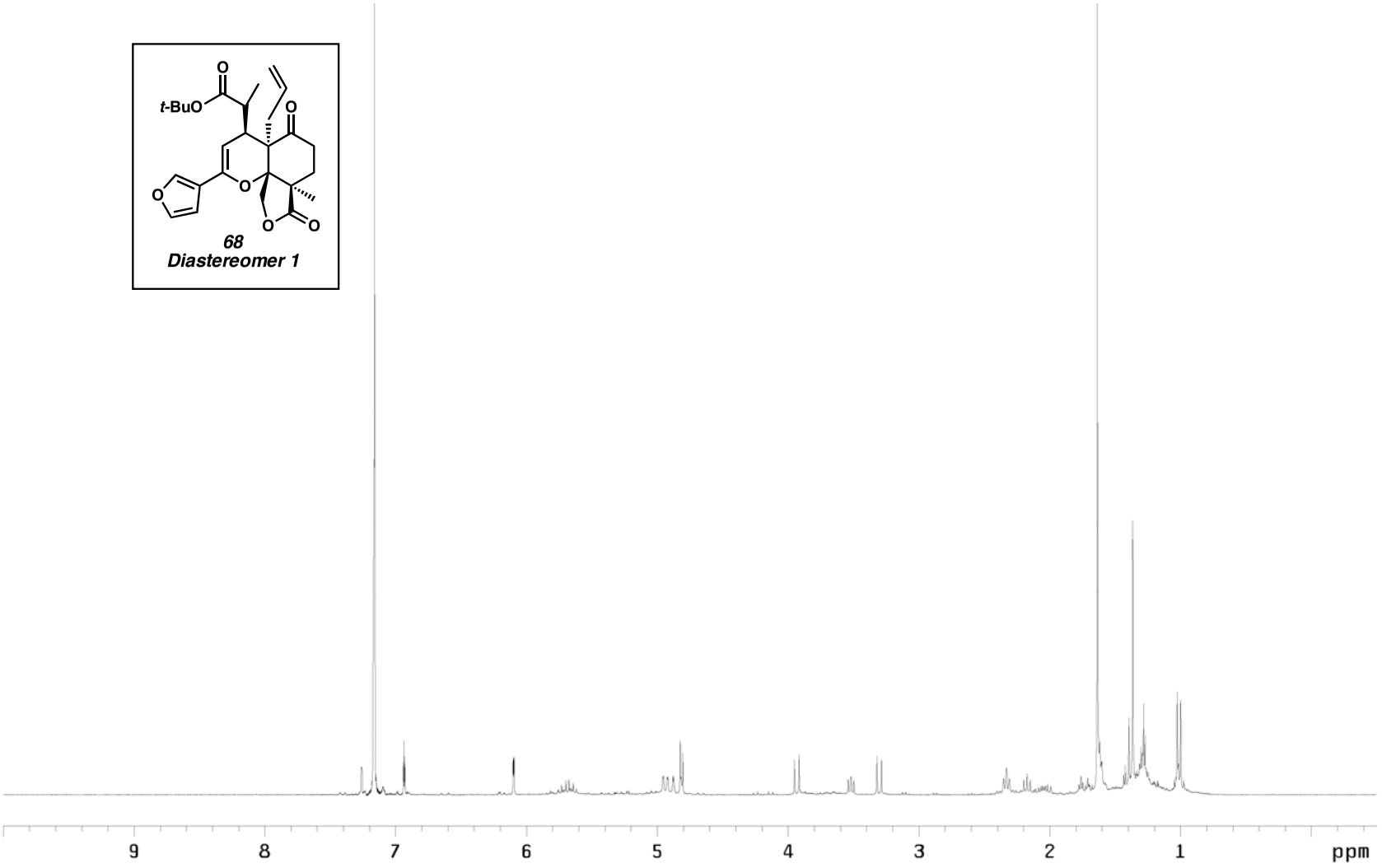


Figure A2.34 ^{1}H NMR (300 MHz, C_6D_6) of compound **68(1)**.

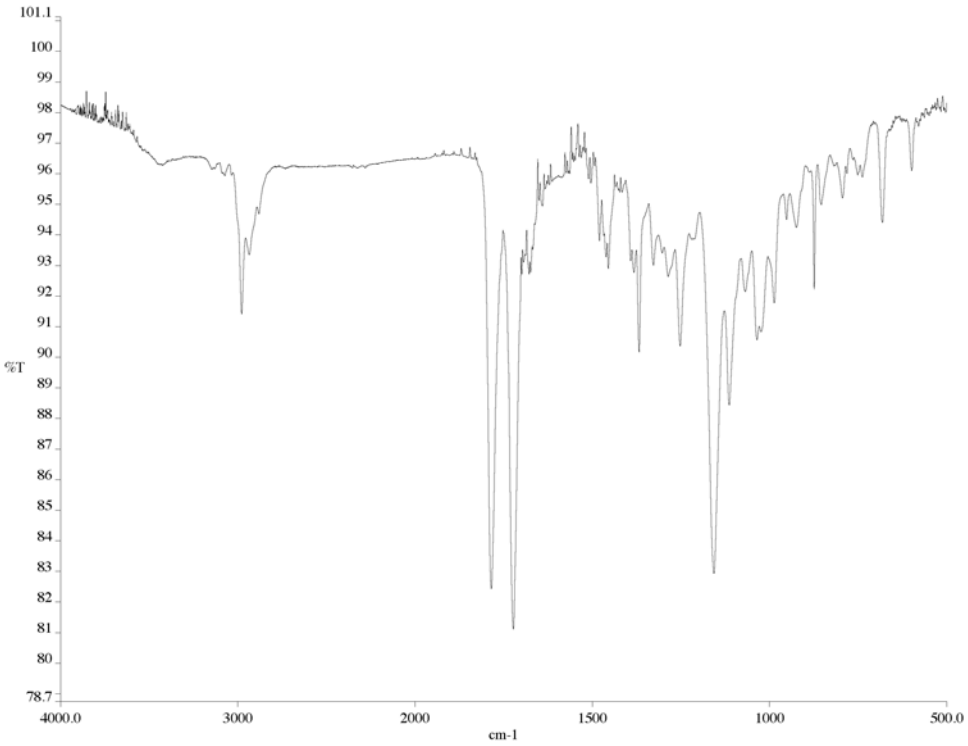


Figure A2.35 Infrared spectrum (thin film/NaCl) of compound **68(1)**.

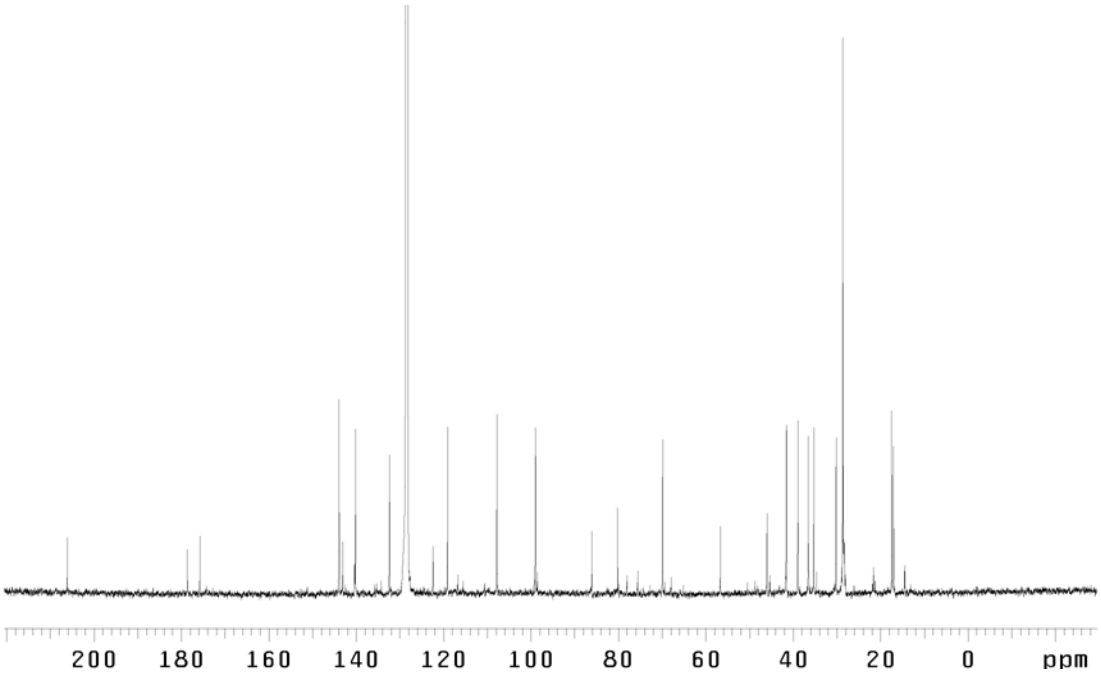


Figure A2.36 ^{13}C NMR (125 MHz, C_6D_6) of compound **68(1)**.

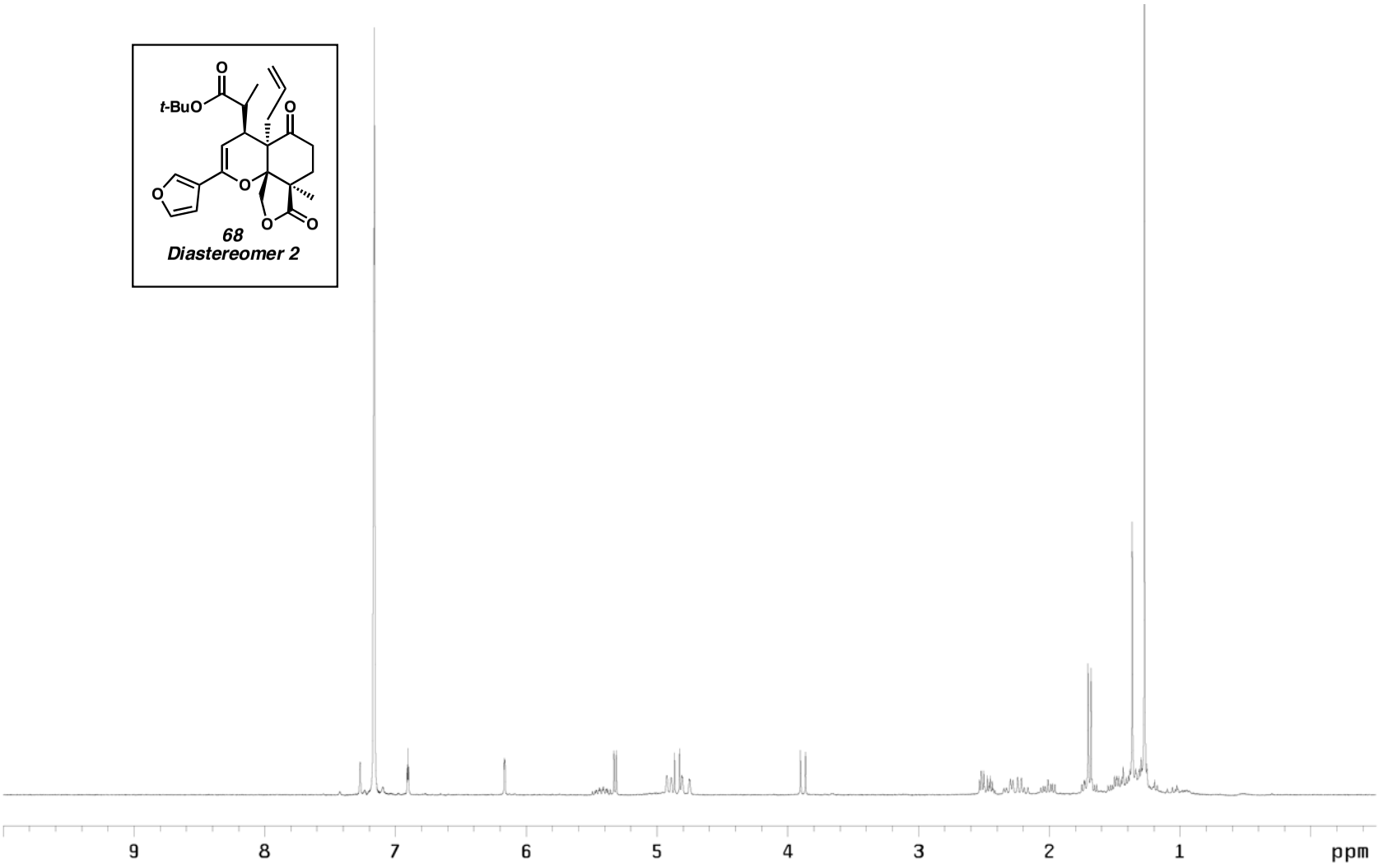


Figure A2.37 ^{1}H NMR (300 MHz, C_6D_6) of compound **68(2)**.

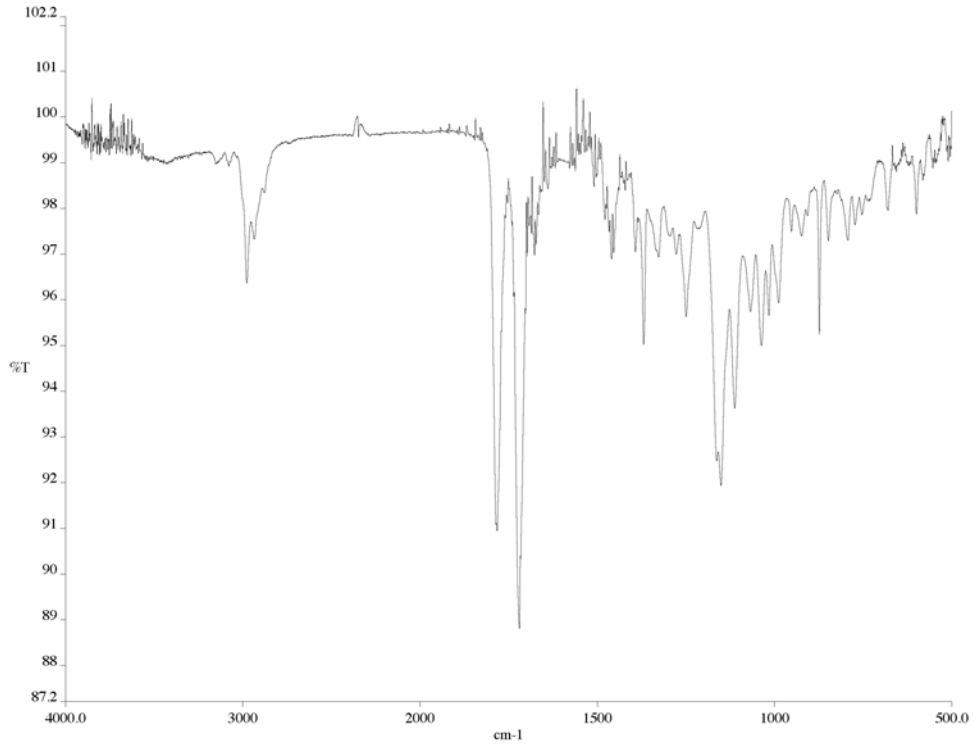


Figure A2.38 Infrared spectrum (thin film/NaCl) of compound **68(2)**.

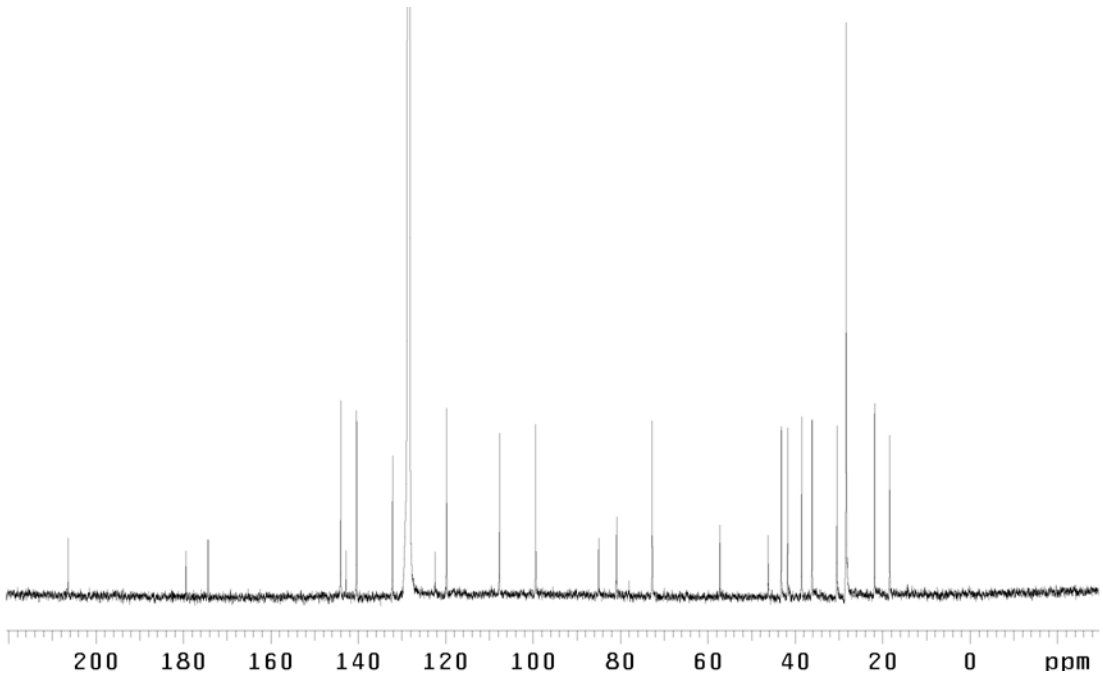


Figure A2.39 ^{13}C NMR (125 MHz, C_6D_6) of compound **68(2)**.

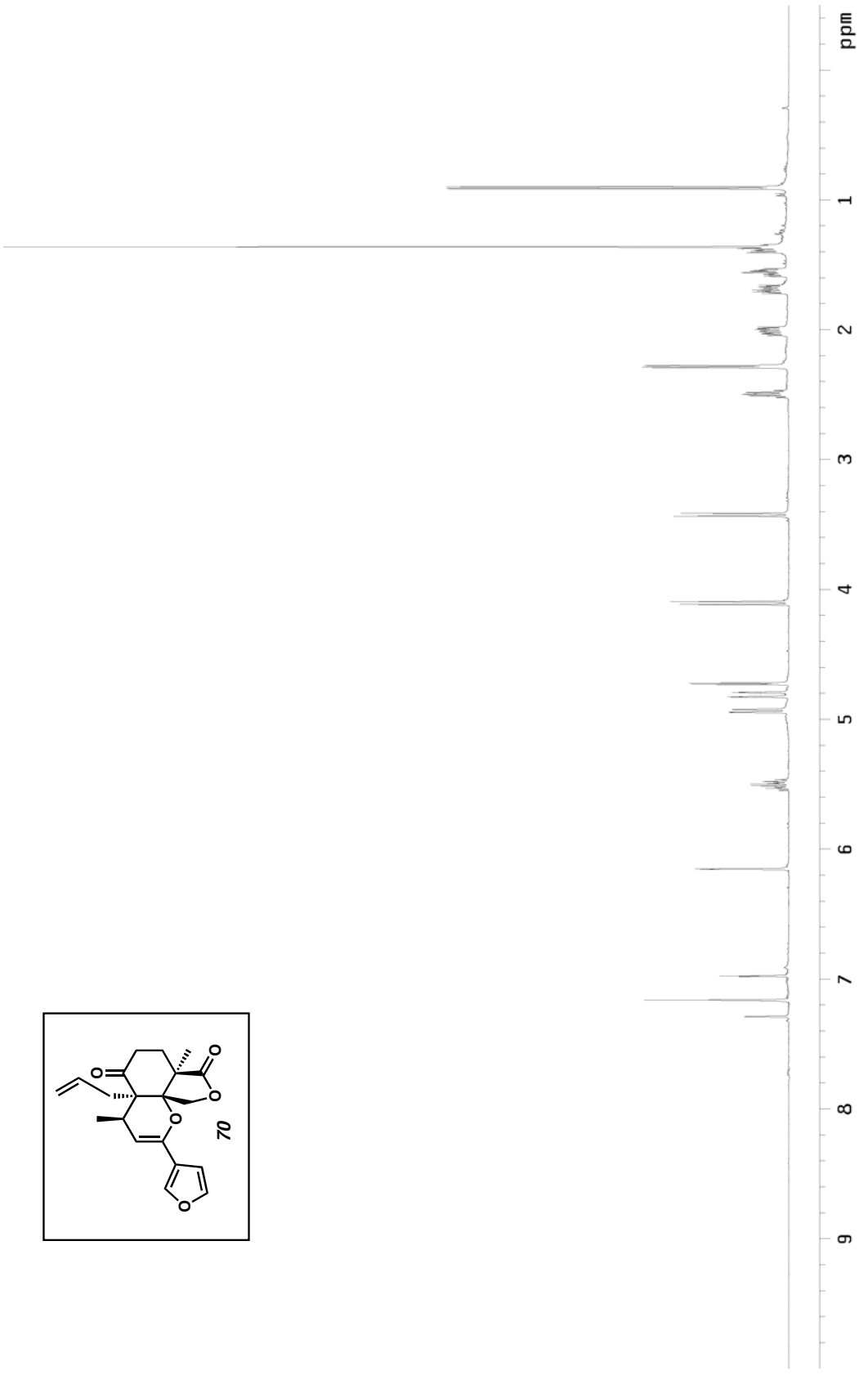


Figure A2.40 ^{1}H NMR (500 MHz, C_6D_6) of compound **70**.

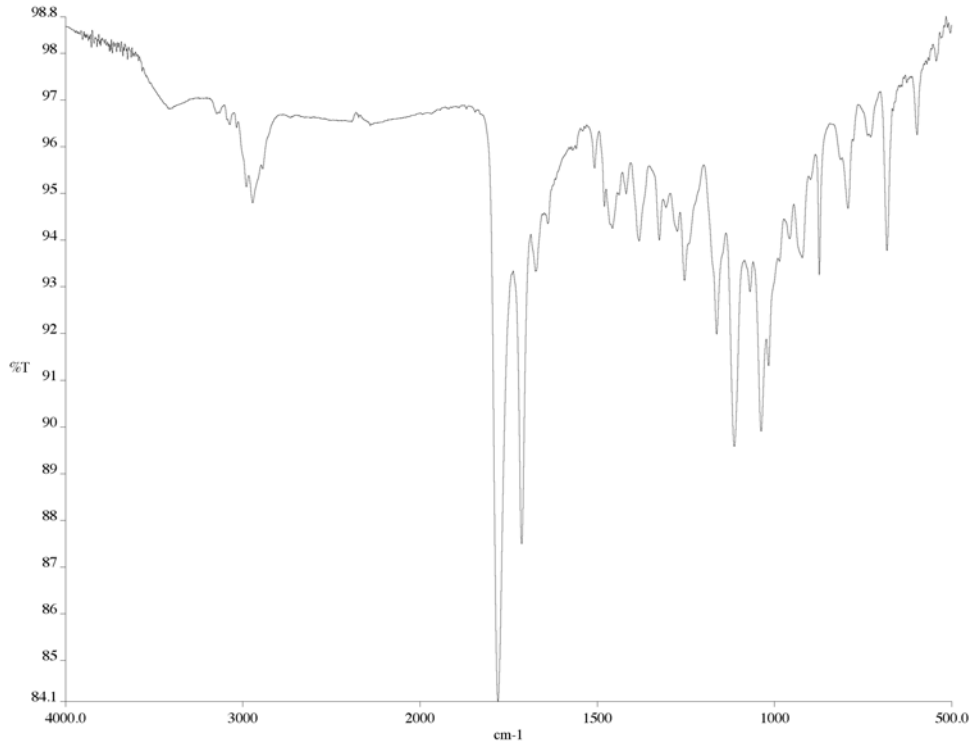


Figure A2.41 Infrared spectrum (thin film/NaCl) of compound **70**.

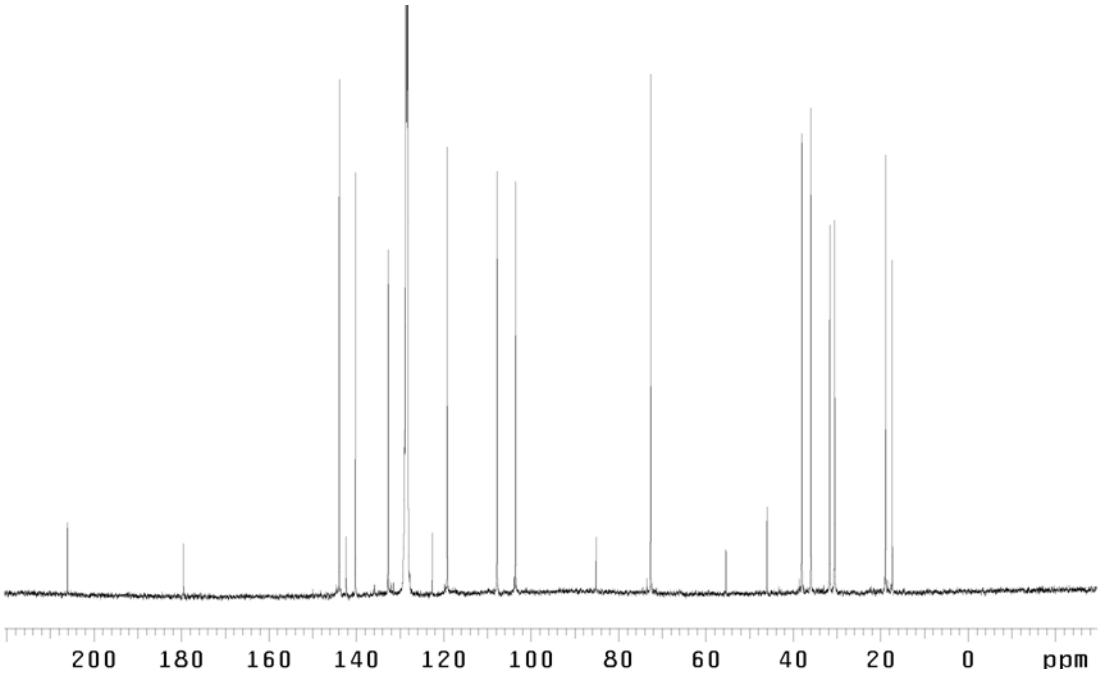


Figure A2.42 ^{13}C NMR (125 MHz, C_6D_6) of compound **70**.

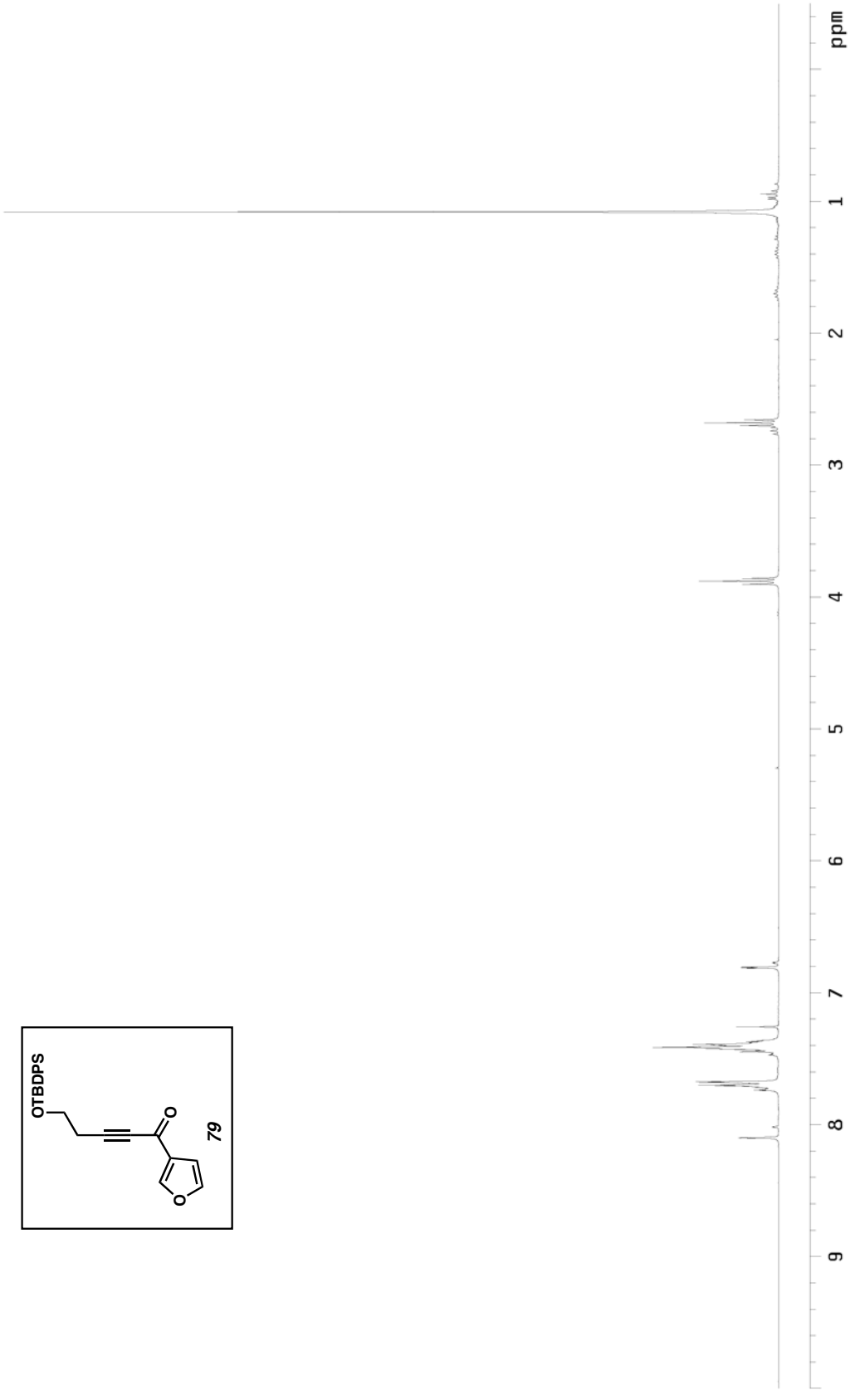


Figure A2.43 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **79**.

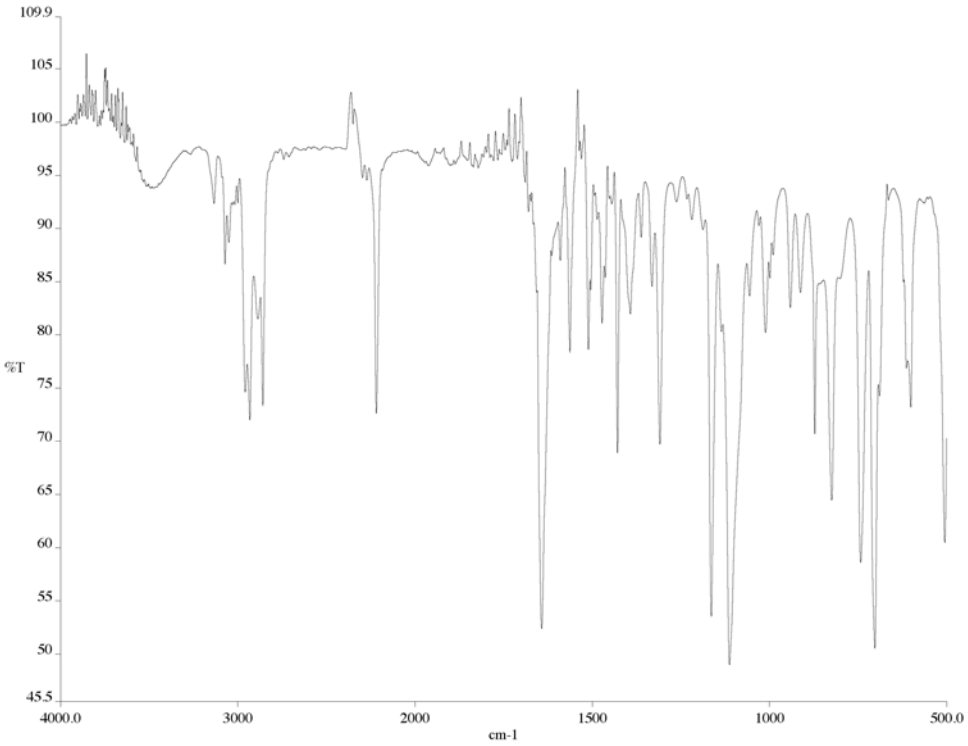


Figure A2.44 Infrared spectrum (thin film/NaCl) of compound **79**.

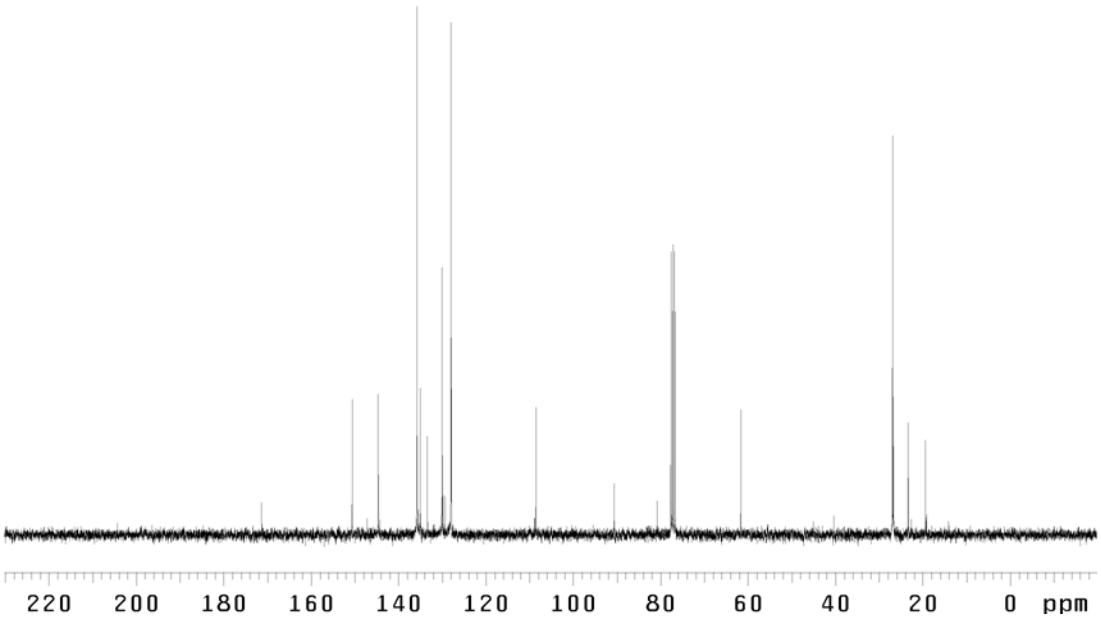


Figure A2.45 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **79**.

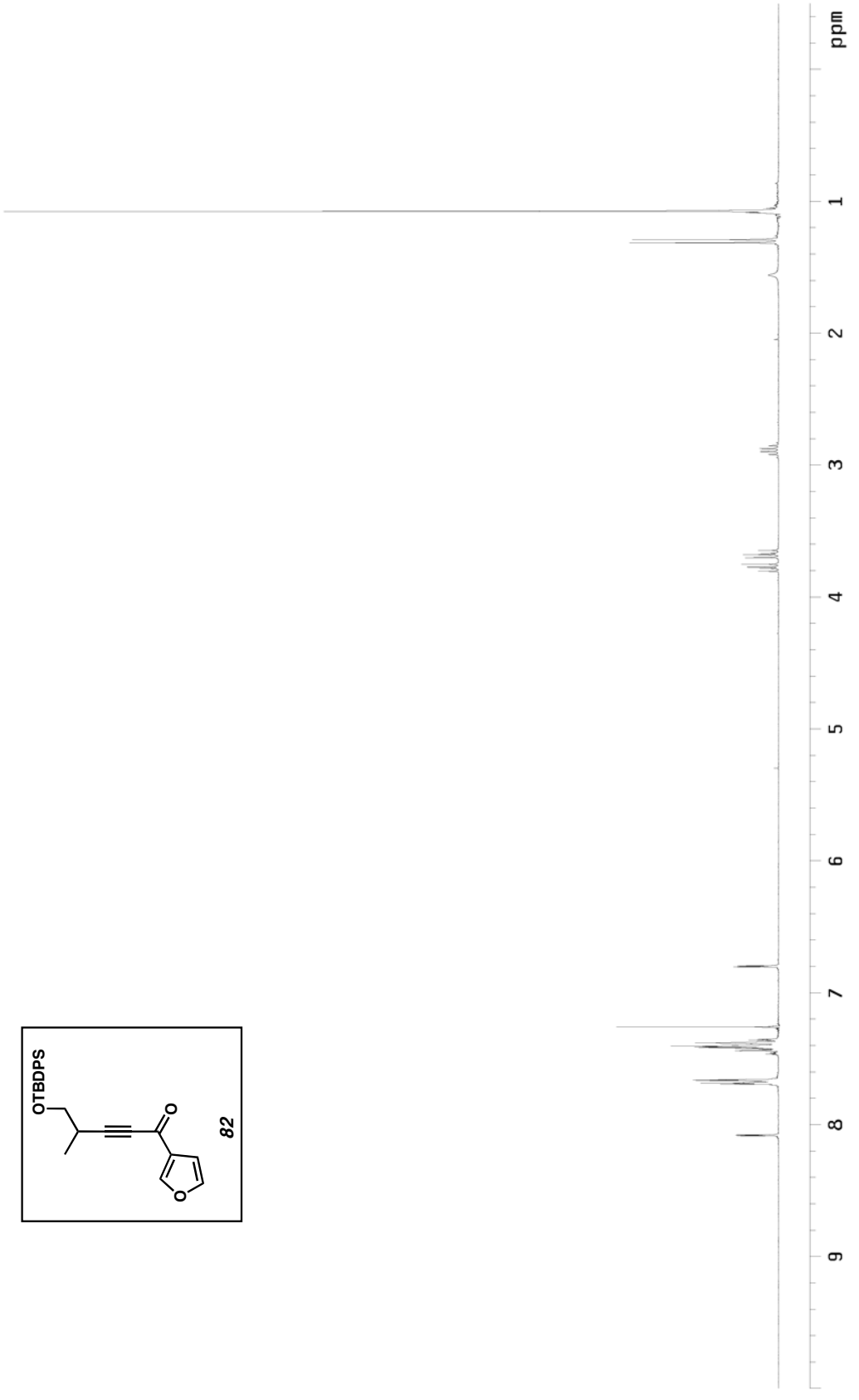


Figure A2.46 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **82**.

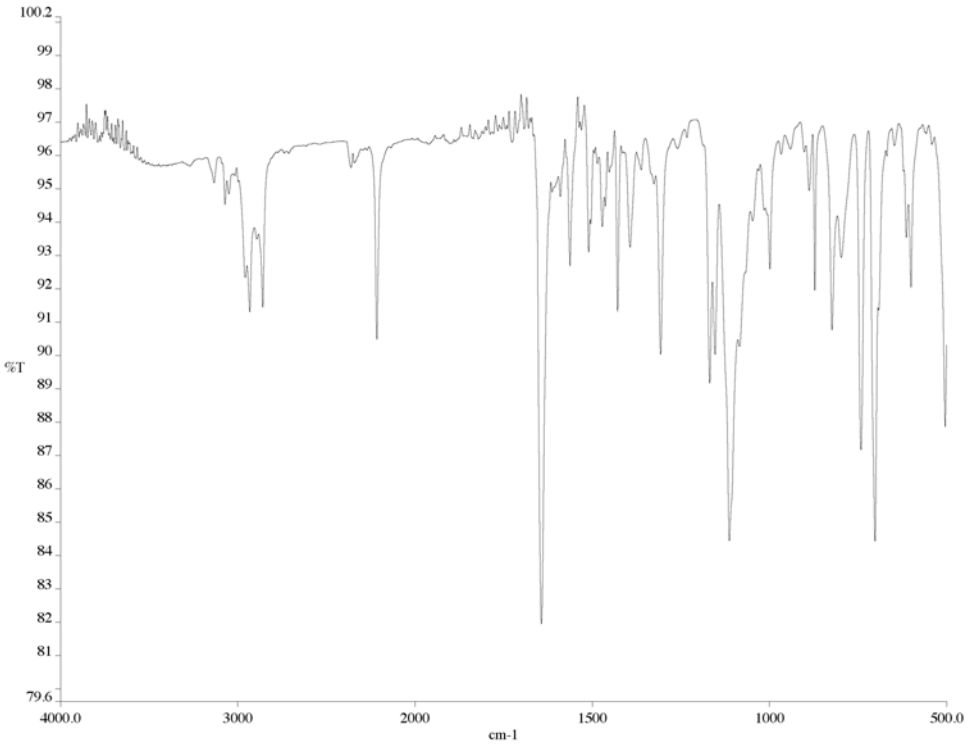


Figure A2.47 Infrared spectrum (thin film/NaCl) of compound **82**.

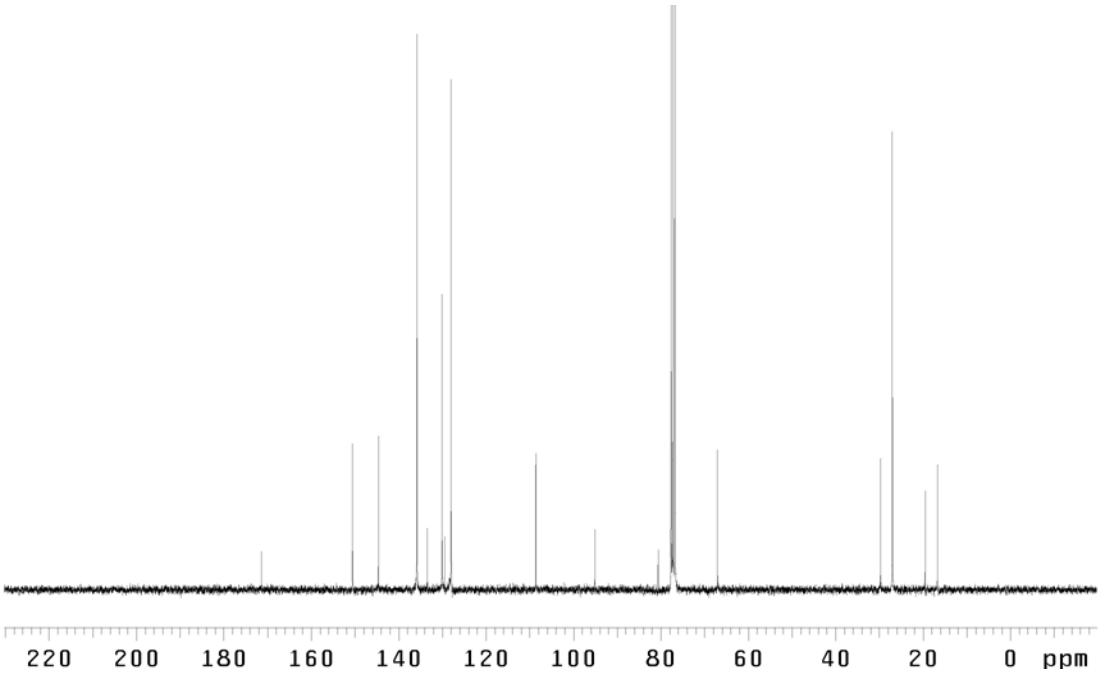


Figure A2.48 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **82**.

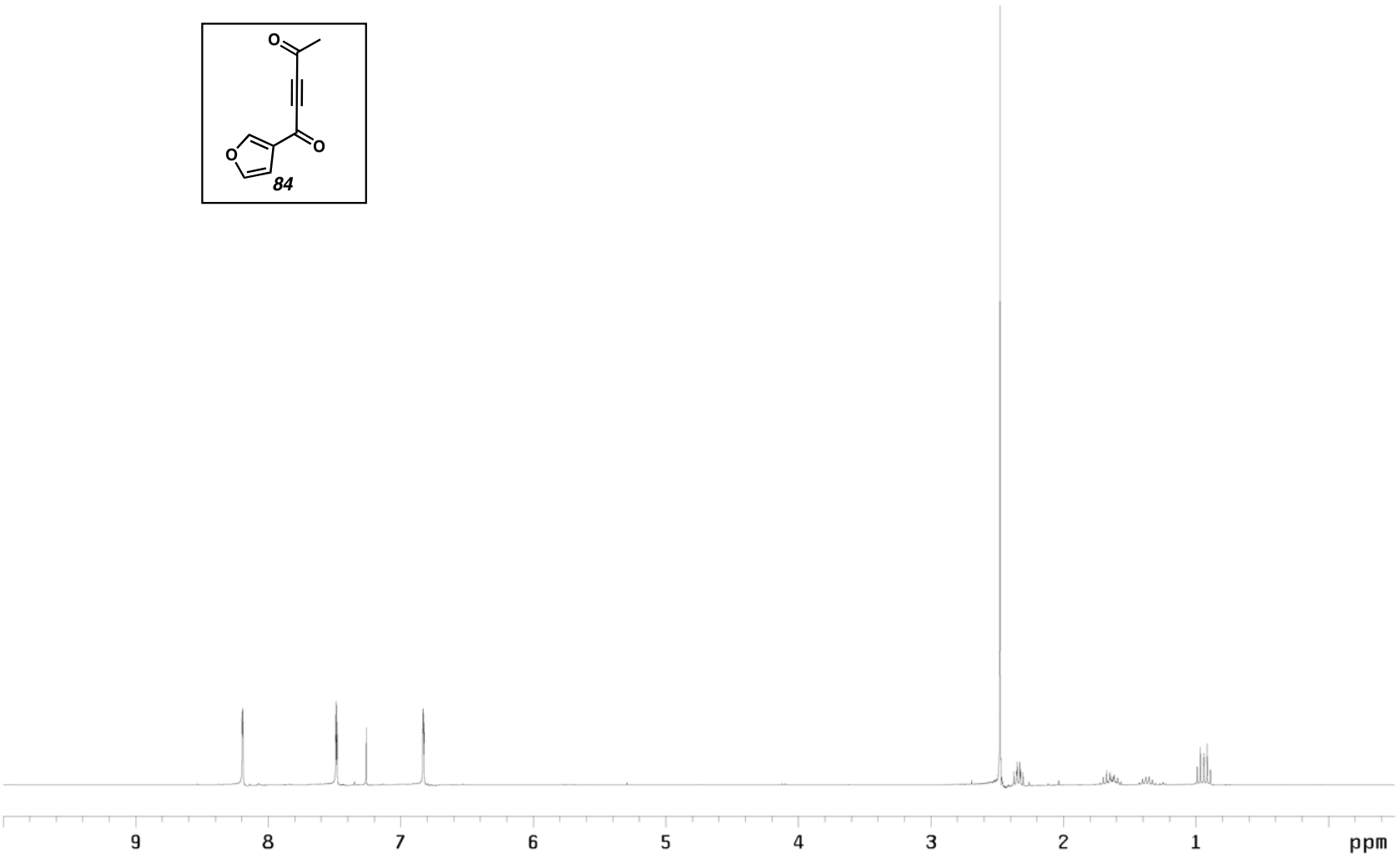


Figure A2.49 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **84**.

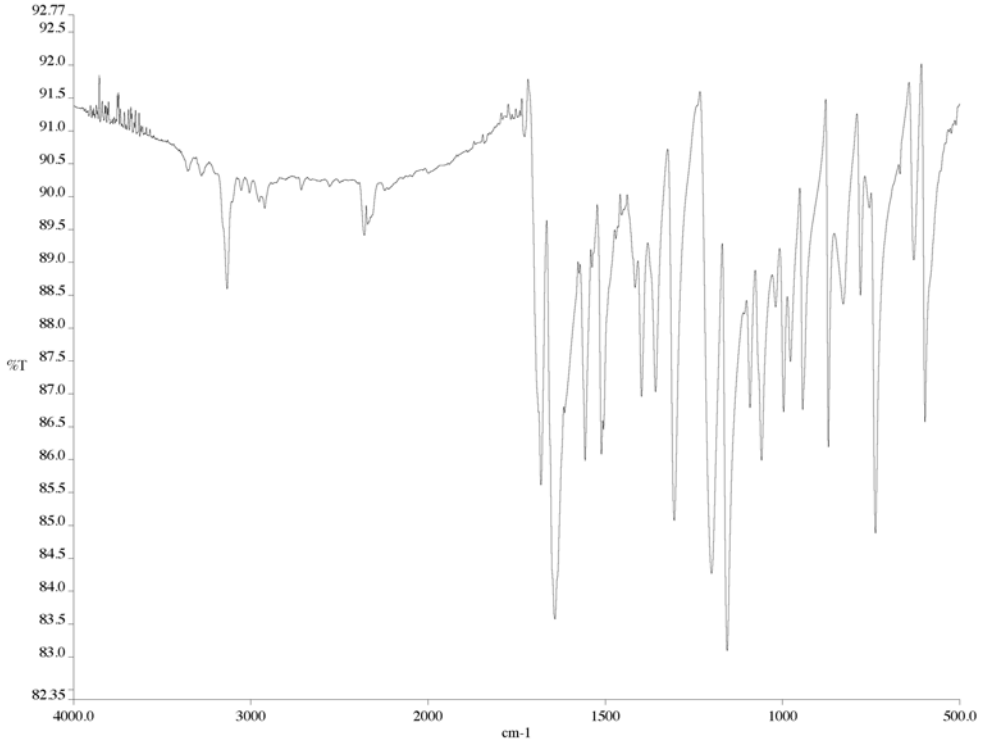


Figure A2.50 Infrared spectrum (thin film/NaCl) of compound **84**.

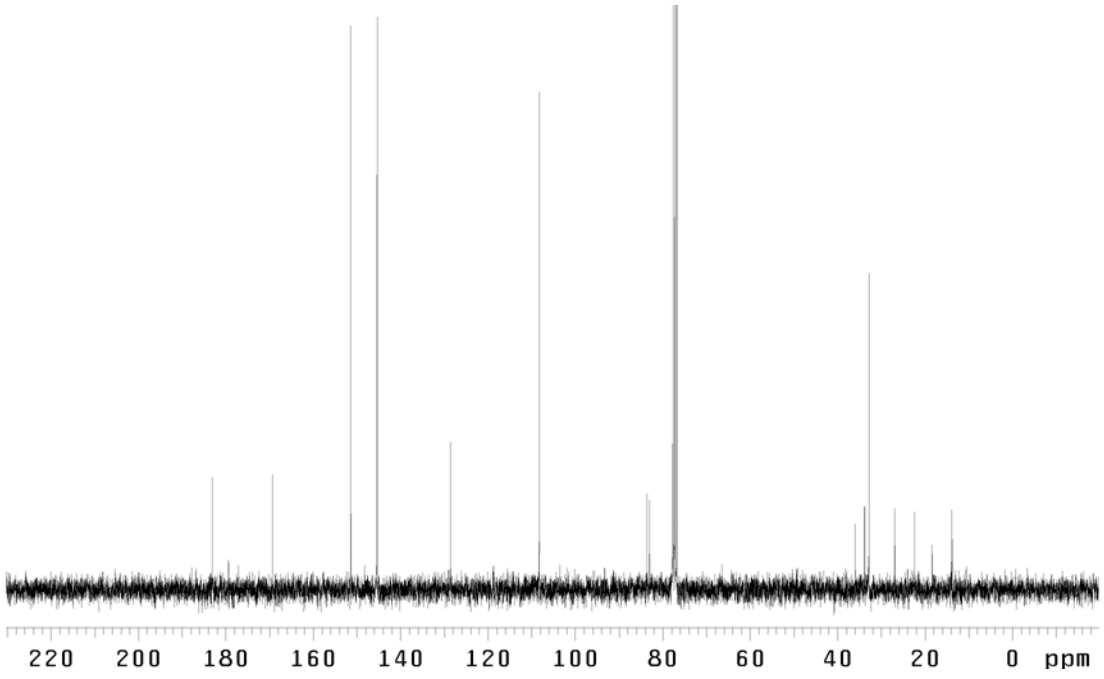


Figure A2.51 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **84**.

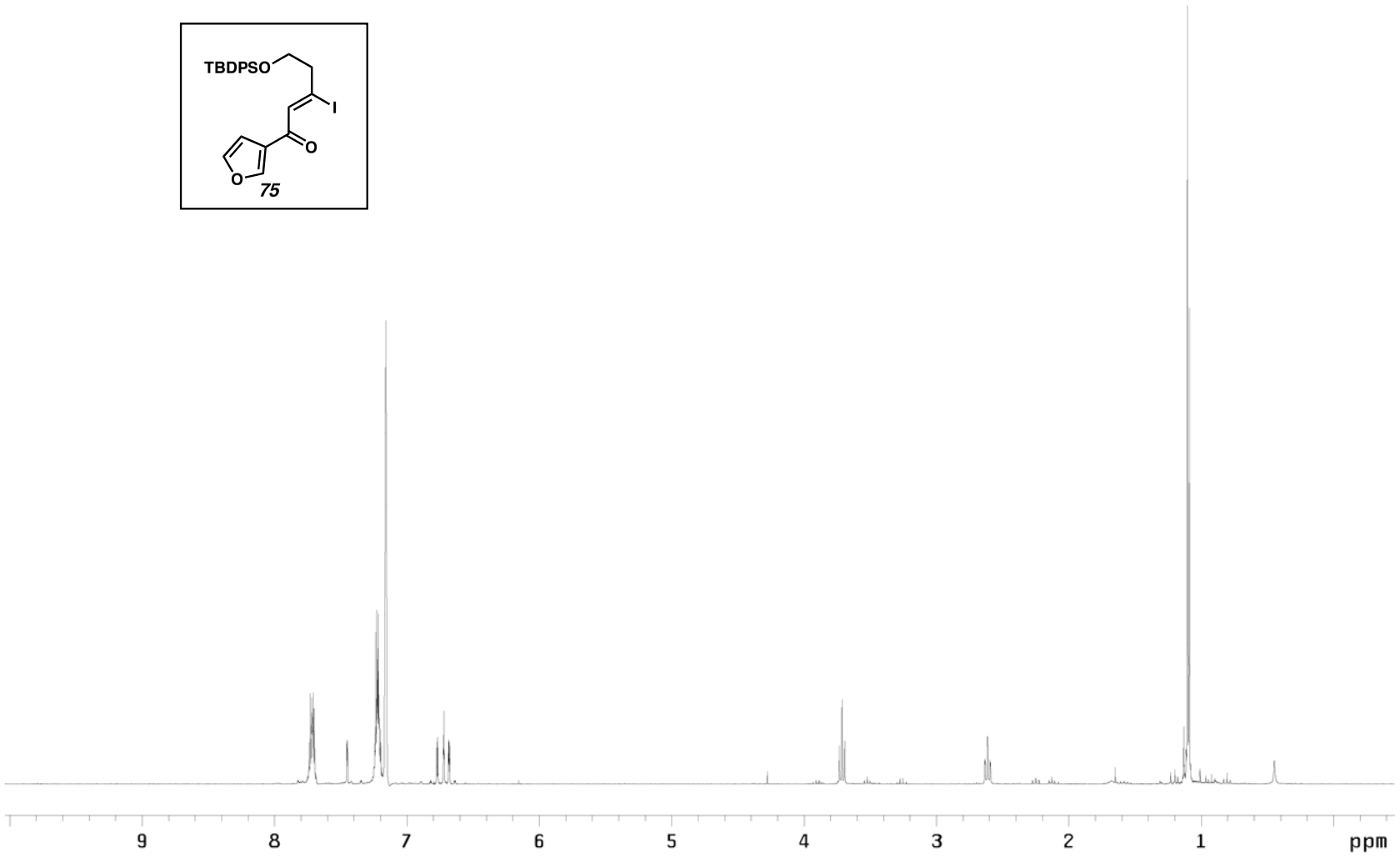


Figure A2.52 ^{1}H NMR (300 MHz, C_6D_6) of compound **75**.

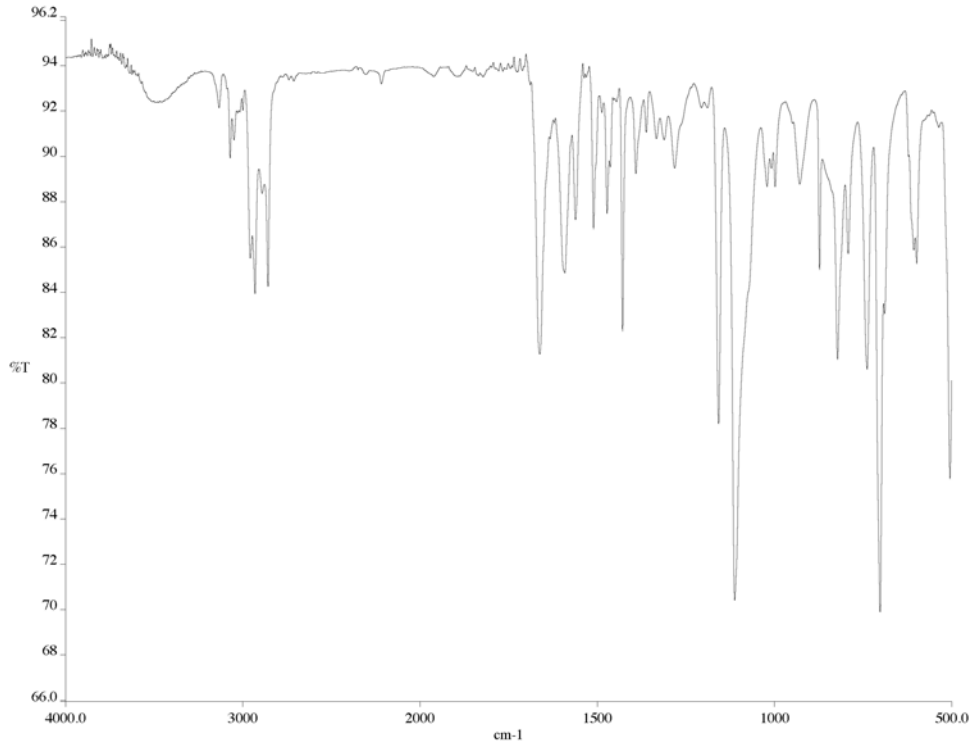


Figure A2.53 Infrared spectrum (thin film/NaCl) of compound **75**.

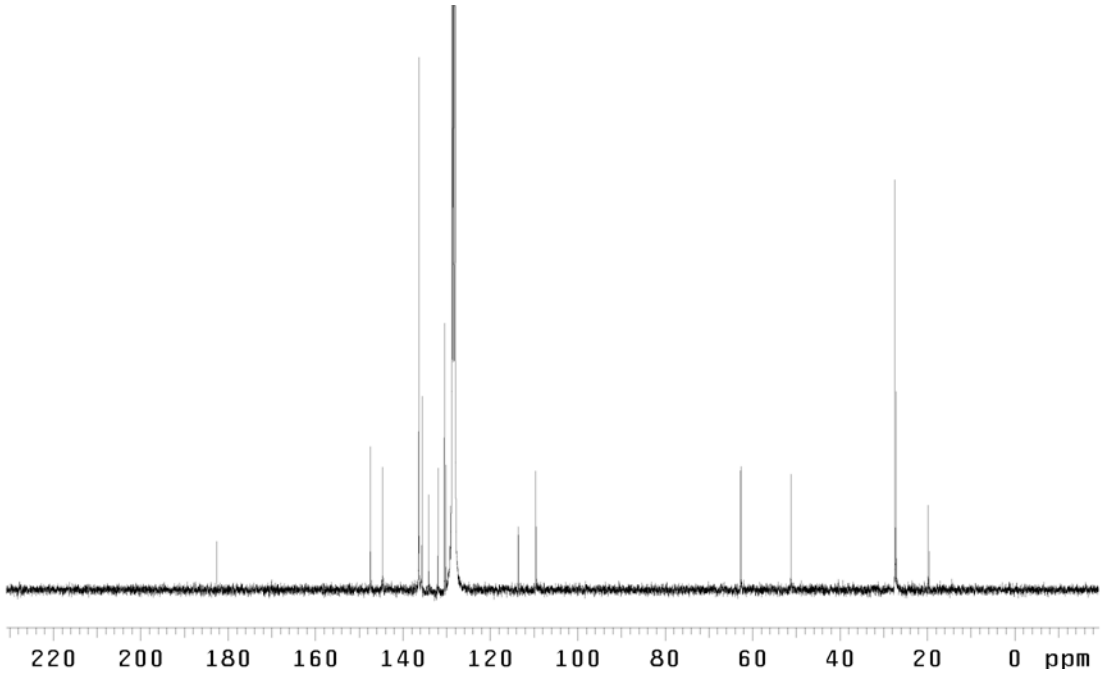


Figure A2.54 ^{13}C NMR (75 MHz, C_6D_6) of compound **75**.

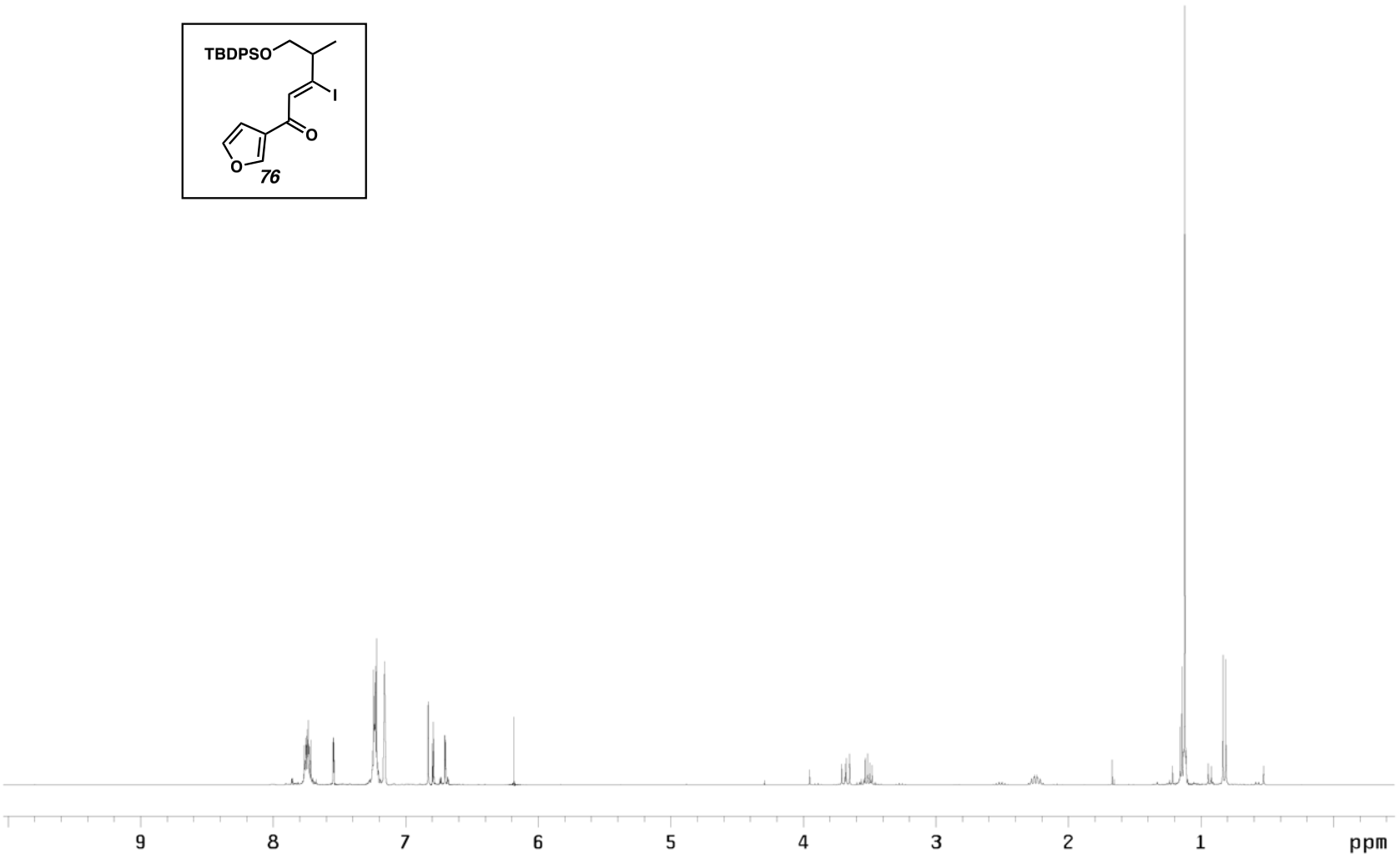


Figure A2.55 ^{1}H NMR (300 MHz, C_6D_6) of compound **76**.

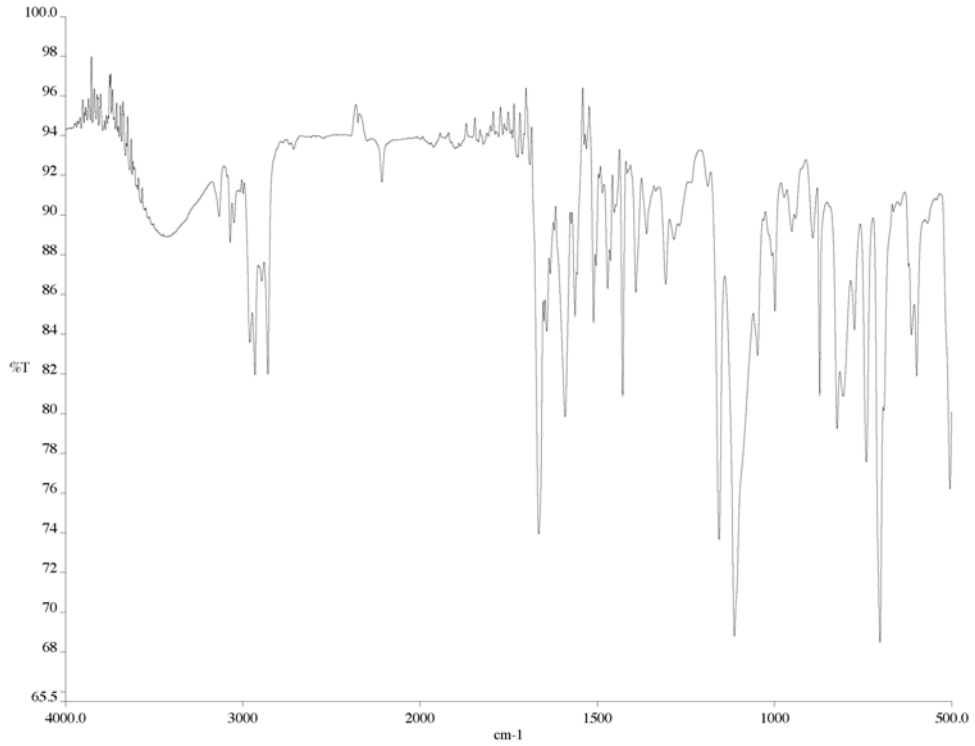


Figure A2.56 Infrared spectrum (thin film/NaCl) of compound **76**.

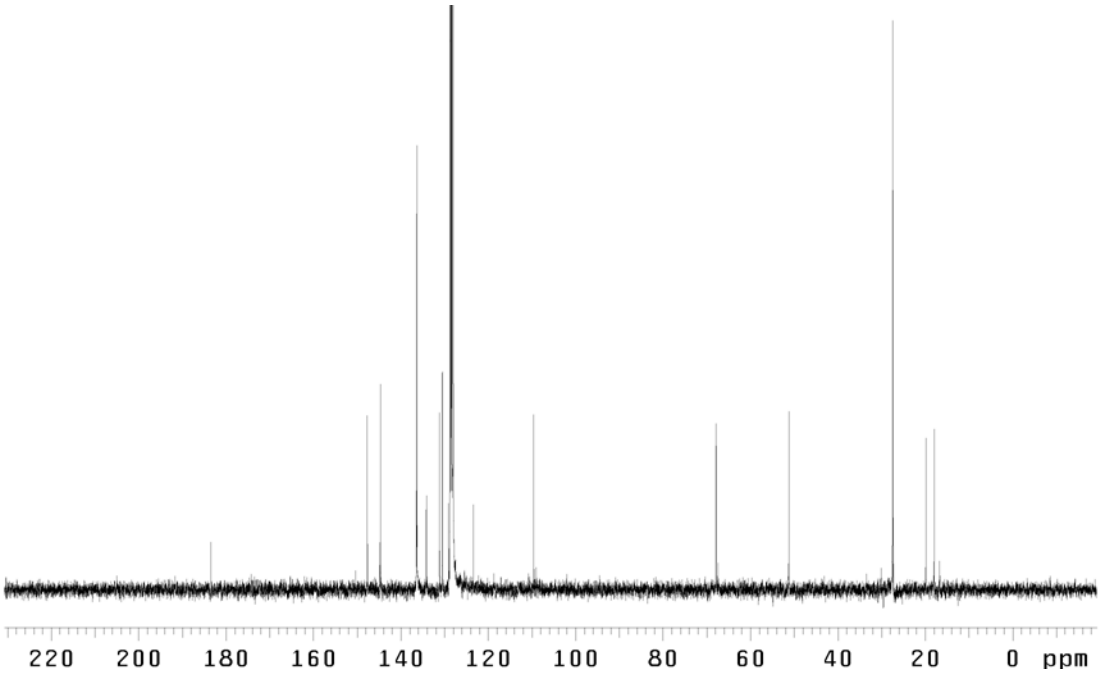


Figure A2.57 ^{13}C NMR (75 MHz, C_6D_6) of compound **76**.

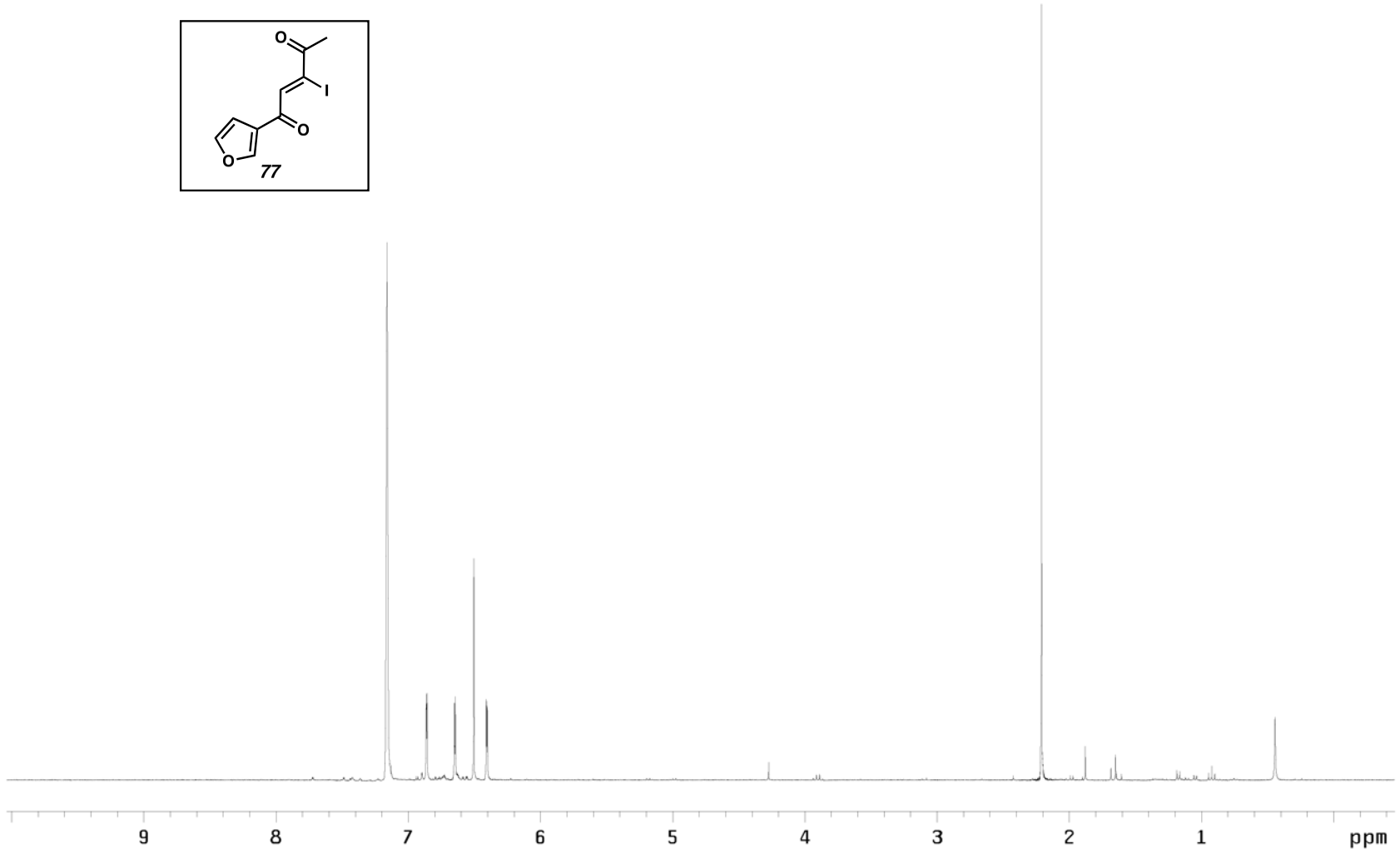


Figure A2.58 ^{1}H NMR (300 MHz, C_6D_6) of compound **77**.

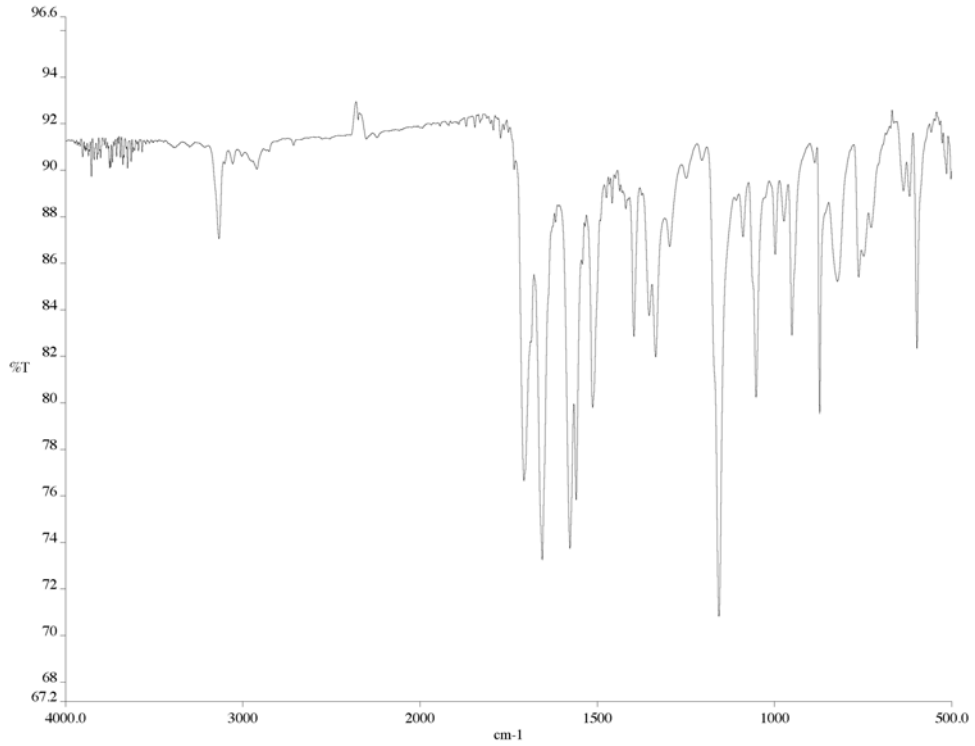


Figure A2.59 Infrared spectrum (thin film/NaCl) of compound **77**.

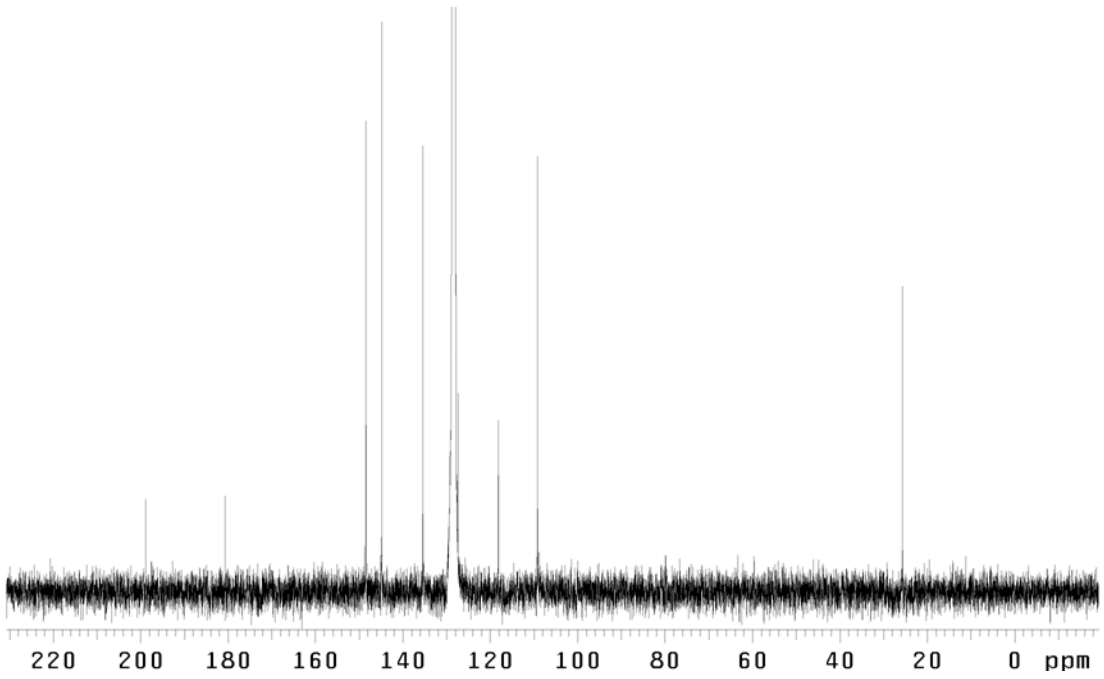


Figure A2.60 ^{13}C NMR (75 MHz, C_6D_6) of compound **77**.

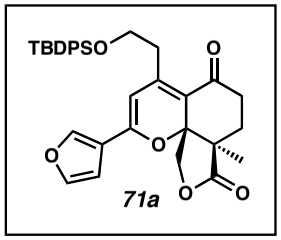


Figure A2.61 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **71a**.

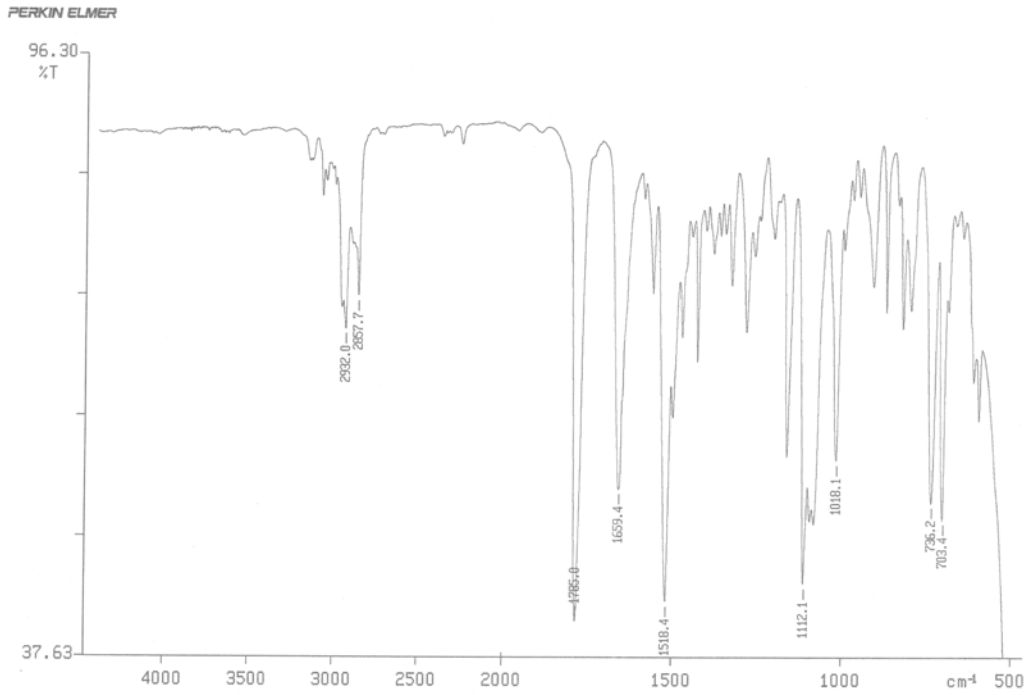


Figure A2.62 Infrared spectrum (thin film/NaCl) of compound **71a**.

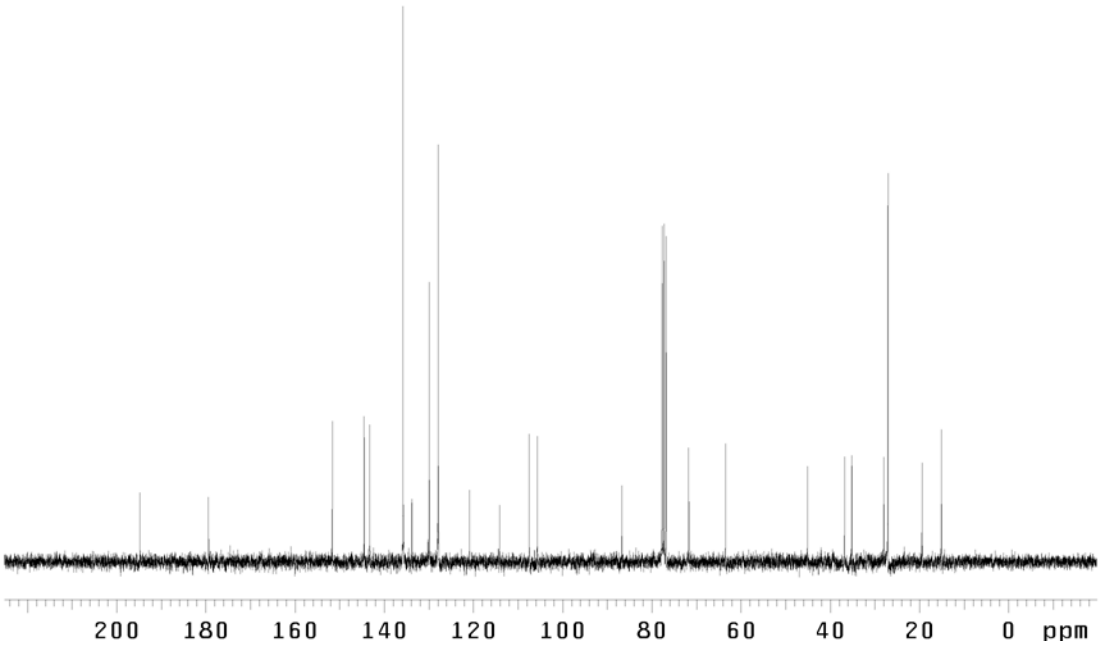


Figure A2.63 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **71a**.

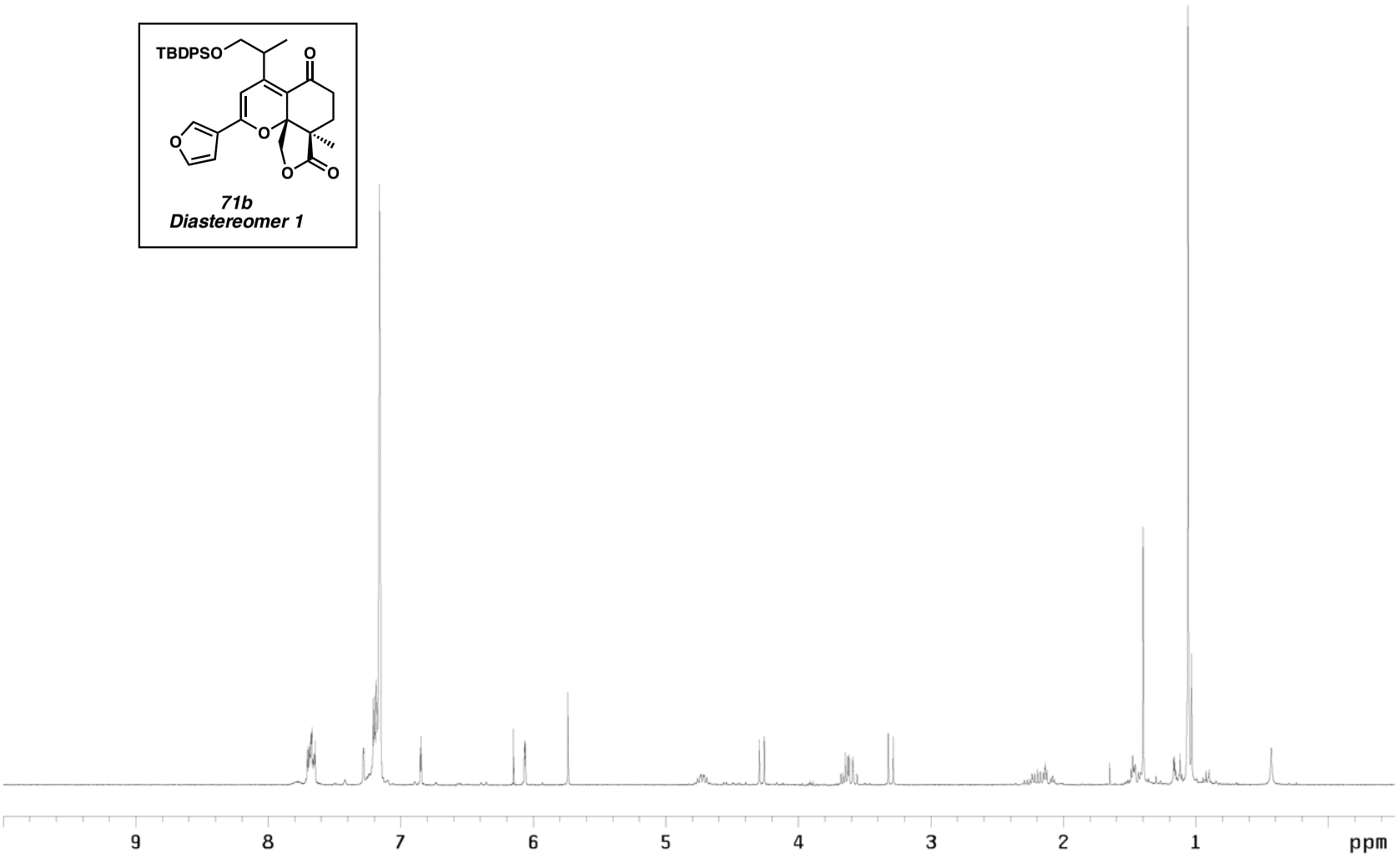


Figure A2.64 ^{1}H NMR (300 MHz, C_6D_6) of compound **71b(1)**.

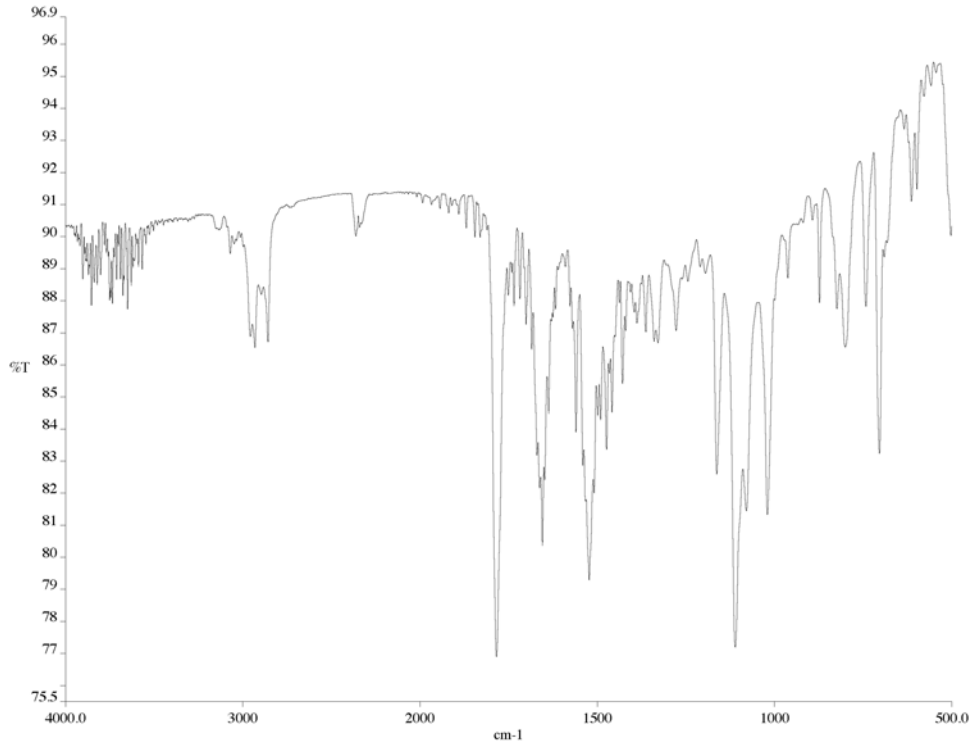


Figure A2.65 Infrared spectrum (thinfilm/NaCl) of compound **71b(1)**.

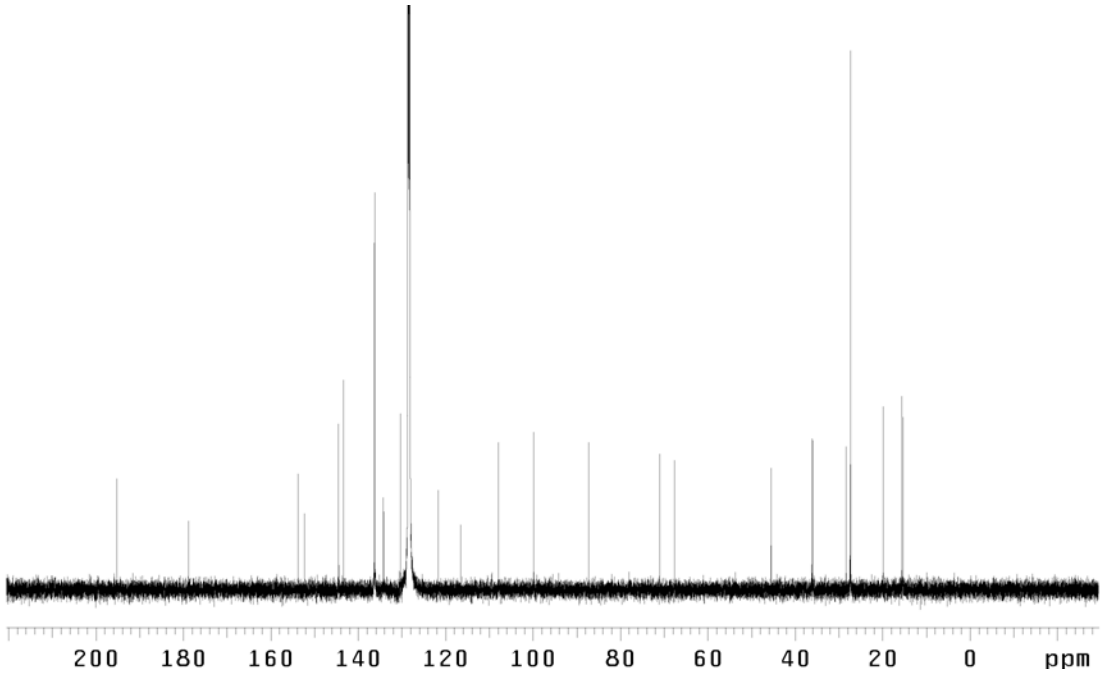


Figure A2.66 ^{13}C NMR (125 MHz, C_6D_6) of compound **71b(1)**.

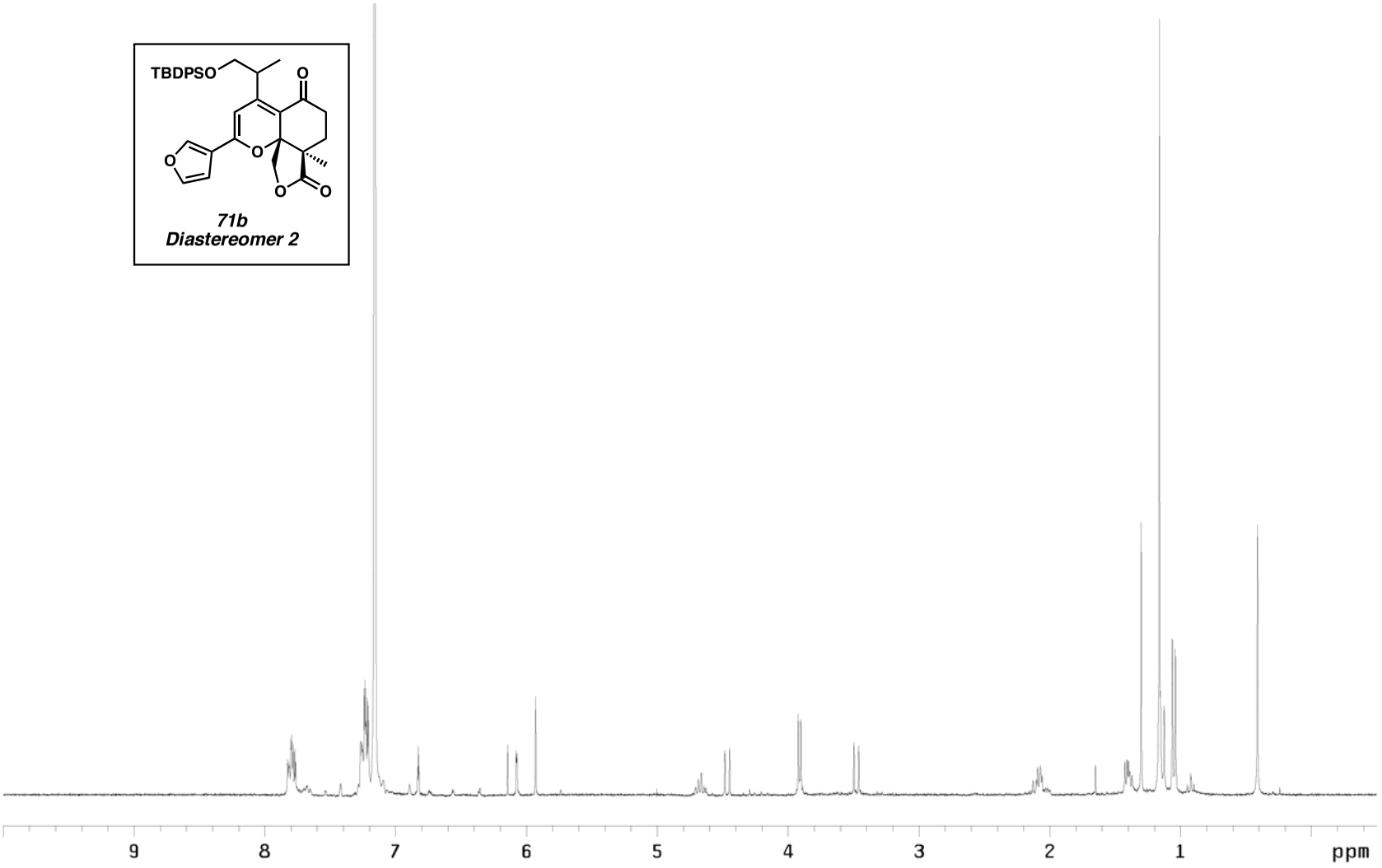


Figure A2.67 ^{1}H NMR (300 MHz, C_6D_6) of compound **71b(2)**.

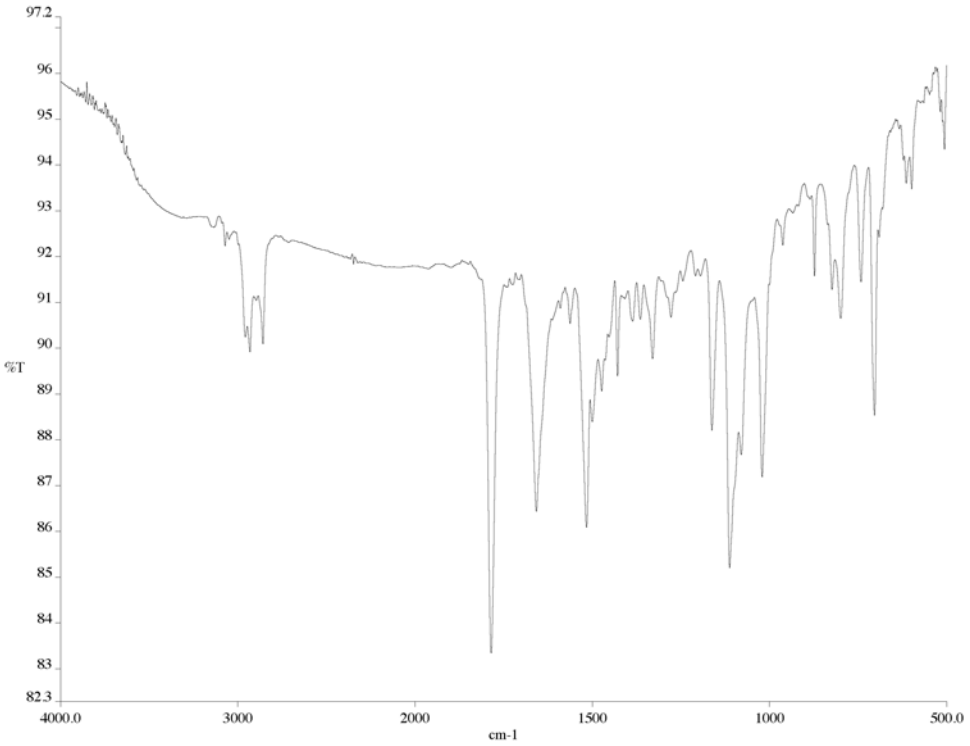


Figure A2.68 Infrared spectrum (thinfilm/NaCl) of compound **71b(2)**.

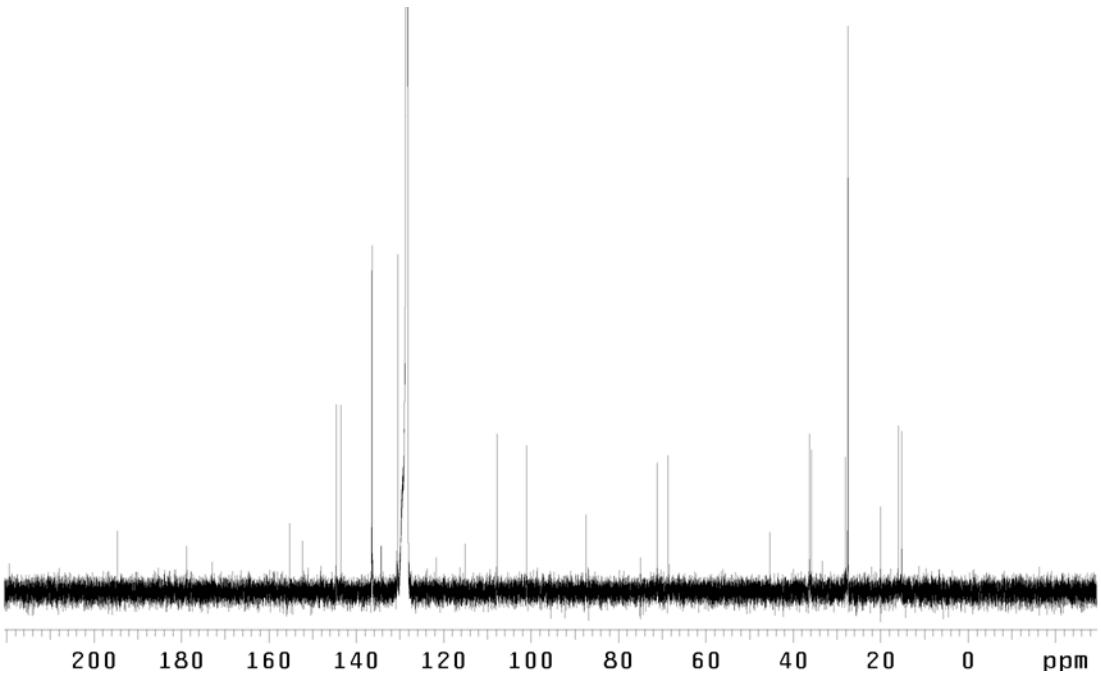


Figure A2.69 ^{13}C NMR (125 MHz, C_6D_6) of compound **71b(2)**.

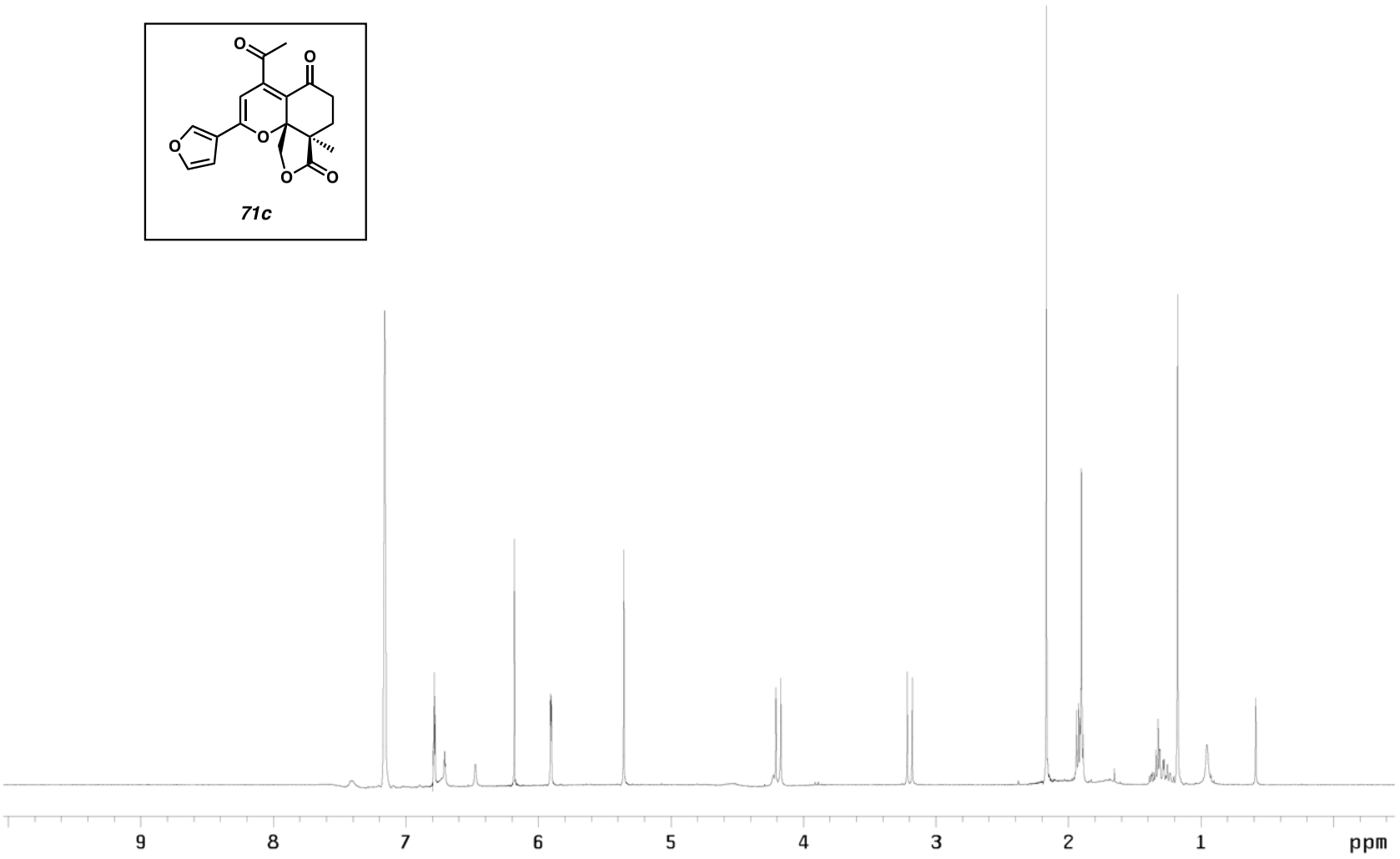


Figure A2.70 ^{1}H NMR (300 MHz, C_6D_6) of compound **71c**.

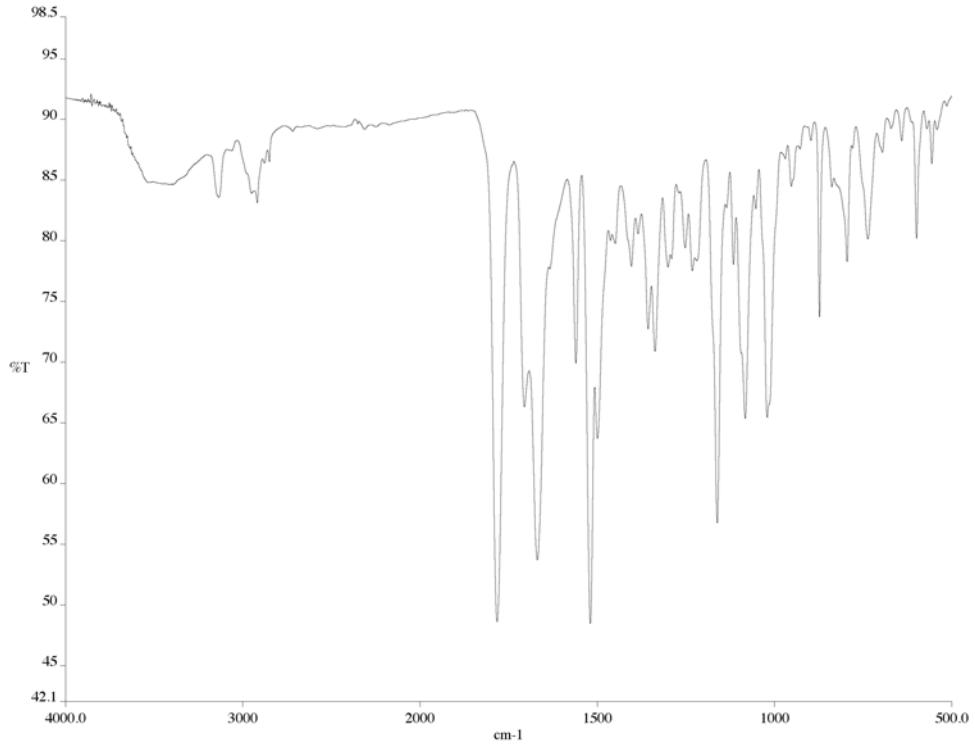


Figure A2.71 Infrared spectrum (thin film/NaCl) of compound **71c**.

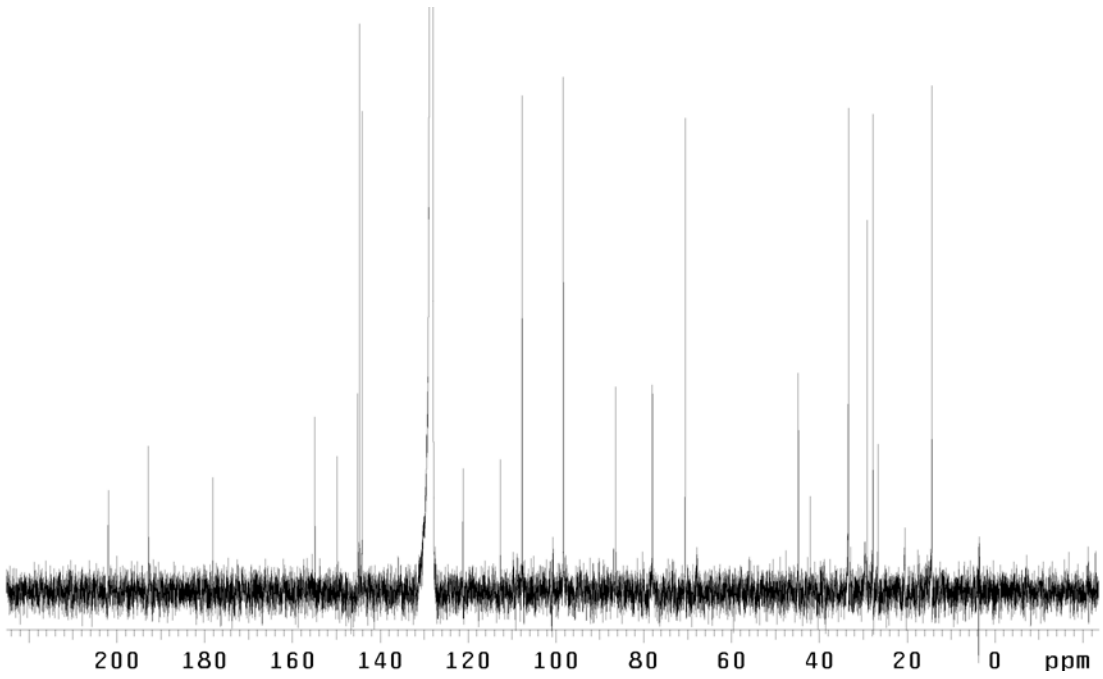


Figure A2.72 ^{13}C NMR (75 MHz, C_6D_6) of compound **71c**.

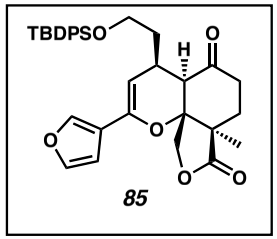


Figure A2.73 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **85**.

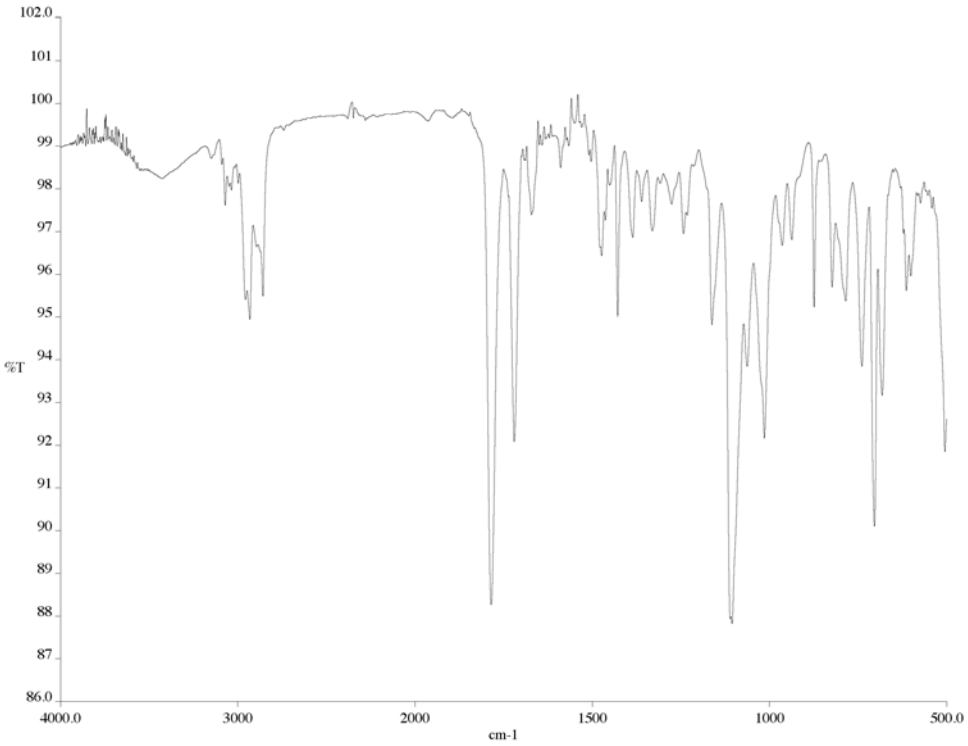


Figure A2.74 Infrared spectrum (thin film/NaCl) of compound **85**.

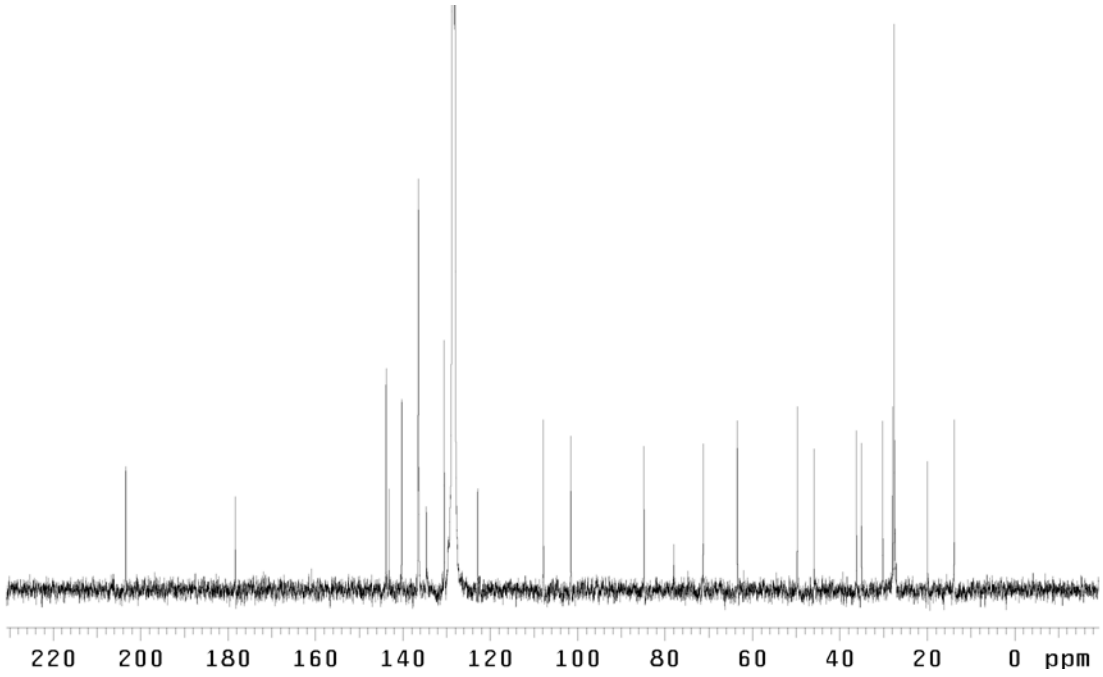


Figure A2.75 ^{13}C NMR (75 MHz, C_6D_6) of compound **85**.

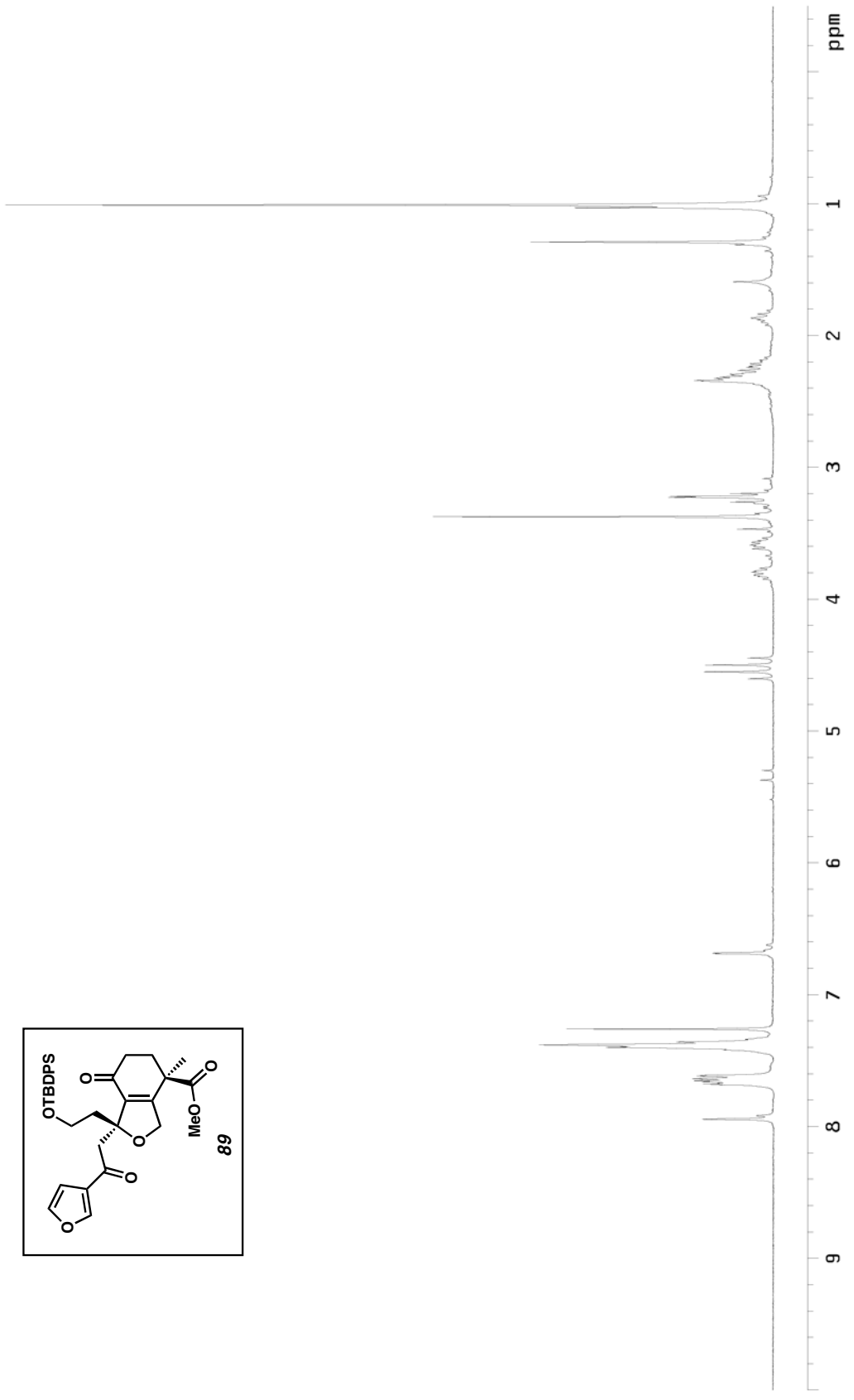


Figure A2.76 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **89**.

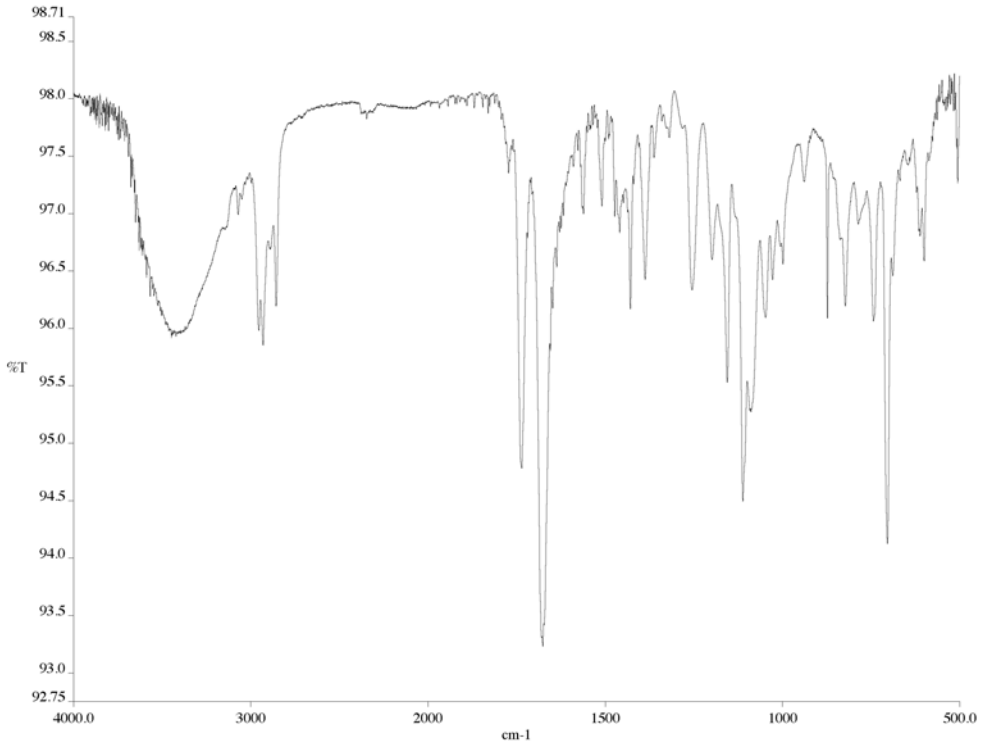


Figure A2.77 Infrared spectrum (thin film/NaCl) of compound **89**.

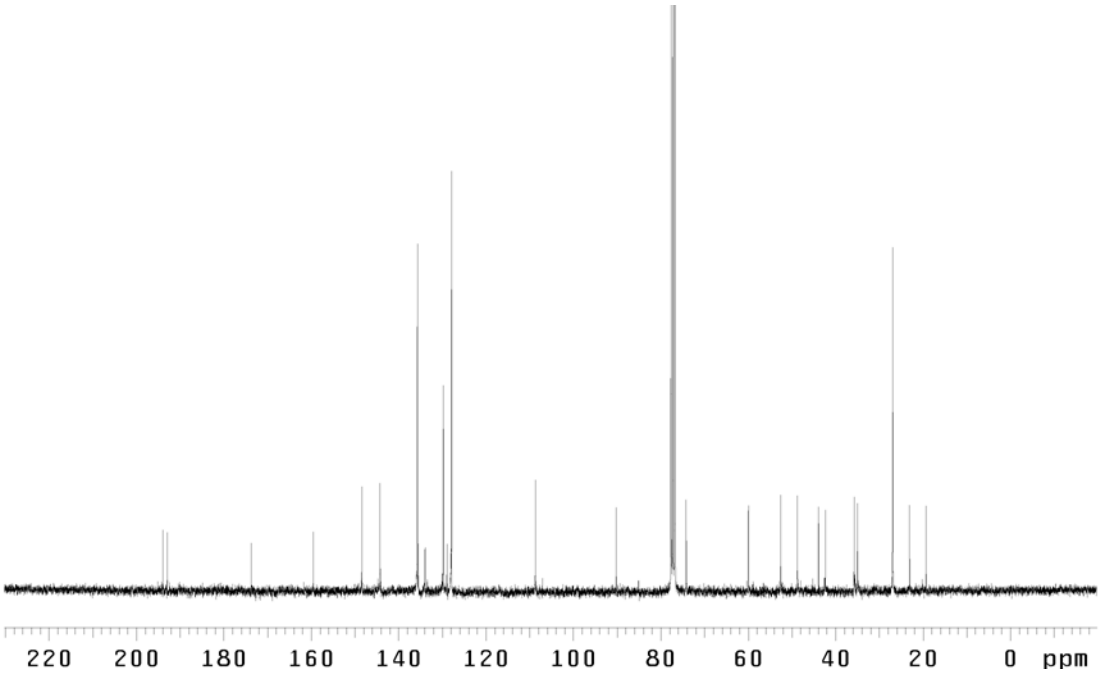


Figure A2.78 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **89**.

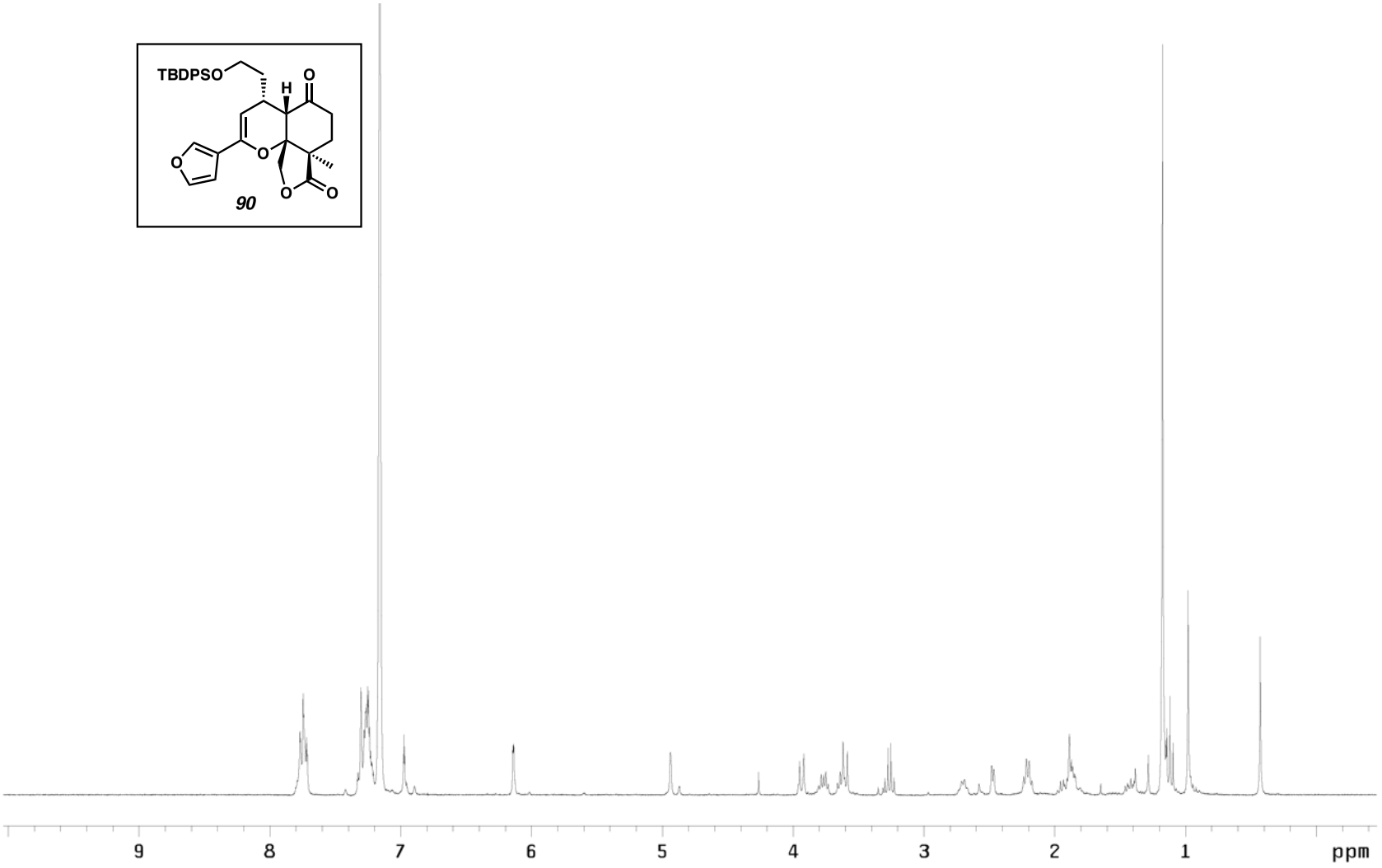


Figure A2.79 ^{1}H NMR (300 MHz, C_6D_6) of compound **90**.

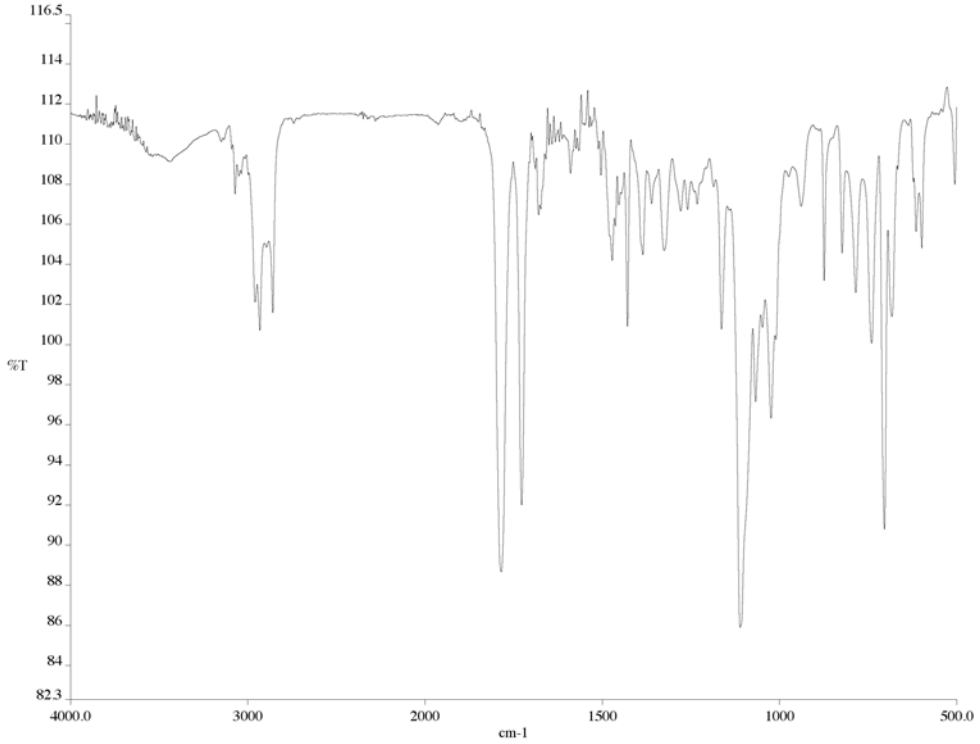


Figure A2.80 Infrared spectrum (film) of compound **90**.

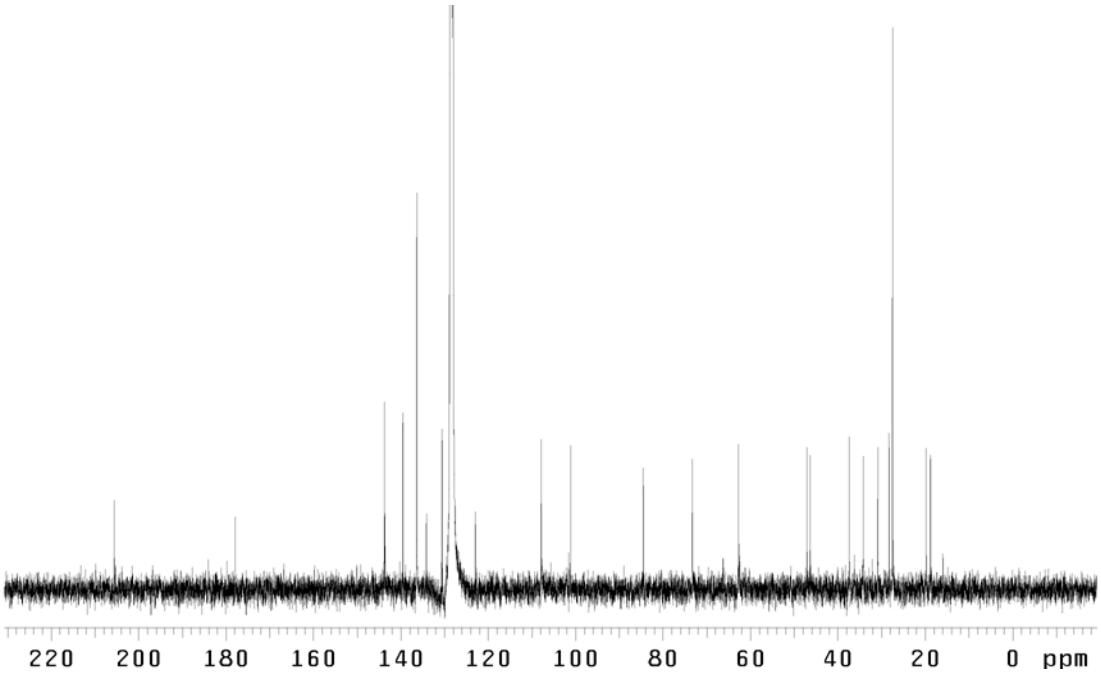


Figure A2.81 ^{13}C NMR (75 MHz, C_6D_6) of compound **90**.

APPENDIX THREE

X-ray Crystallography Reports Relevant to Chapter Two: Studies Directed Toward the Total Synthesis of Saudin and the Development of a Tandem Stille-Oxa-Electrocyclization Reaction

A3.1 Crystal Structure Analysis of 66a

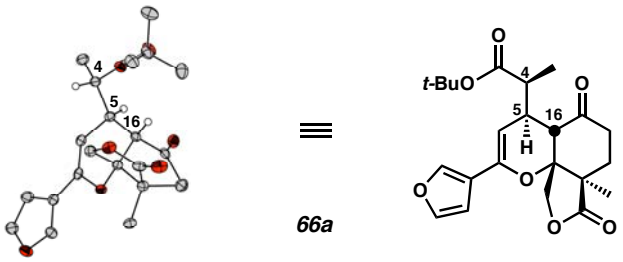


Figure A3.1.1 Ketone **66a** is shown with 50% probability ellipsoids. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 175515.

Table A3.1.1 Crystal data and structure refinement for **66a** (CCDC 175515).

Empirical formula	$C_{23}H_{28}O_7$
Formula weight	416.45
Crystallization Solvent	Ether
Crystal Habit	Irregular fragment
Crystal size	Not measured
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 12296 reflections used in lattice determination	2.22 to 28.17°
Unit cell dimensions	a = 8.2333(6) Å b = 25.9013(19) Å β= 95.7760(10)° c = 9.8295(7) Å
Volume	2085.5(3) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/c$
Density (calculated)	1.326 Mg/m^3
F(000)	888
Data collection program	Bruker SMART v5.054
θ range for data collection	1.57 to 28.23°
Completeness to θ = 28.23°	95.1 %
Index ranges	$-10 \le h \le 10$, $-32 \le k \le 34$, $-12 \le l \le 12$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.22
Reflections collected	30345
Independent reflections	4886 [R_{int}= 0.0543]
Absorption coefficient	0.098 mm^{-1}
Absorption correction	None

Table A3.1.1 **(cont.)**

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	4886 / 0 / 383
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.845
Final R indices [$I>2\sigma(I)$, 3765 reflections]	R1 = 0.0418, *w*R2 = 0.0643
R indices (all data)	R1 = 0.0574, *w*R2 = 0.0657
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Largest diff. peak and hole	0.404 and -0.295 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table A3.1.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **66a** (CCDC 175515). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	8639(1)	3834(1)	4601(1)	29(1)
O(2)	8194(1)	4245(1)	2608(1)	22(1)
O(3)	11695(1)	2720(1)	142(1)	21(1)
O(4)	7428(1)	3279(1)	66(1)	16(1)
O(5)	3617(1)	3010(1)	-2777(1)	24(1)
O(6)	13803(1)	4143(1)	617(1)	26(1)
O(7)	11834(1)	4617(1)	1480(1)	19(1)
C(1)	8369(2)	3813(1)	3377(1)	20(1)
C(2)	8169(2)	3333(1)	2491(1)	17(1)
C(3)	6399(2)	3144(1)	2504(1)	20(1)
C(4)	9385(2)	2914(1)	3023(1)	21(1)
C(5)	9899(2)	2586(1)	1863(1)	20(1)
C(6)	10710(2)	2902(1)	842(1)	16(1)
C(7)	10239(2)	3476(1)	740(1)	15(1)
C(8)	8477(1)	3547(1)	1078(1)	15(1)
C(9)	7933(2)	4112(1)	1170(1)	18(1)
C(10)	7624(2)	3422(1)	-1270(1)	15(1)
C(11)	6141(2)	3297(1)	-2143(1)	16(1)
C(12)	5839(2)	3328(1)	-3601(1)	22(1)
C(13)	4324(2)	3153(1)	-3926(1)	25(1)
C(14)	4762(2)	3105(1)	-1705(1)	19(1)
C(15)	9002(2)	3622(1)	-1634(1)	16(1)
C(16)	10525(2)	3693(1)	-674(1)	15(1)
C(17)	11219(2)	4255(1)	-723(1)	17(1)
C(18)	12034(2)	4328(1)	-2041(1)	22(1)
C(19)	12456(2)	4333(1)	509(1)	18(1)
C(20)	12799(2)	4717(1)	2823(1)	22(1)
C(21)	14328(2)	5015(1)	2589(2)	33(1)
C(22)	11655(2)	5045(1)	3566(2)	27(1)
C(23)	13149(2)	4212(1)	3576(2)	30(1)

Table A3.1.3 Bond lengths [Å] and angles [°] for **66a** (CCDC 175515).

O(1)-C(1)	1.2027(14)
O(2)-C(1)	1.3503(15)
O(2)-C(9)	1.4497(14)
O(3)-C(6)	1.2103(14)
O(4)-C(10)	1.3887(13)
O(4)-C(8)	1.4295(14)
O(5)-C(14)	1.3640(14)
O(5)-C(13)	1.3722(15)
O(6)-C(19)	1.2084(14)
O(7)-C(19)	1.3457(14)
O(7)-C(20)	1.4939(14)
C(1)-C(2)	1.5174(17)
C(2)-C(4)	1.5313(18)
C(2)-C(3)	1.5387(17)
C(2)-C(8)	1.5399(16)
C(3)-H(3A)	0.985(12)
C(3)-H(3B)	0.995(13)
C(3)-H(3C)	1.001(13)
C(4)-C(5)	1.5171(18)
C(4)-H(4A)	0.996(13)
C(4)-H(4B)	0.981(12)
C(5)-C(6)	1.5033(17)
C(5)-H(5A)	0.959(13)
C(5)-H(5B)	0.979(13)
C(6)-C(7)	1.5372(17)
C(7)-C(8)	1.5312(16)
C(7)-C(16)	1.5394(16)
C(7)-H(7)	0.954(12)
C(8)-C(9)	1.5374(17)
C(9)-H(9A)	0.992(12)
C(9)-H(9B)	0.978(12)
C(10)-C(15)	1.3289(16)
C(10)-C(11)	1.4572(16)
C(11)-C(14)	1.3491(17)
C(11)-C(12)	1.4314(17)
C(12)-C(13)	1.3354(18)
C(12)-H(12)	0.956(13)
C(13)-H(13)	0.971(13)
C(14)-H(14)	0.958(12)
C(15)-C(16)	1.5030(17)
C(15)-H(15)	0.926(11)
C(16)-C(17)	1.5649(16)
C(16)-H(16)	1.004(11)
C(17)-C(19)	1.5158(17)
C(17)-C(18)	1.5292(17)
C(17)-H(17)	1.001(12)
C(18)-H(18A)	0.999(13)
C(18)-H(18B)	0.956(13)
C(18)-H(18C)	1.004(13)
C(20)-C(22)	1.5102(19)
C(20)-C(21)	1.5142(19)

C(20)-C(23)	1.5169(19)
C(21)-H(21A)	1.015(15)
C(21)-H(21B)	0.987(15)
C(21)-H(21C)	0.973(16)
C(22)-H(22A)	0.996(15)
C(22)-H(22B)	0.953(14)
C(22)-H(22C)	0.990(15)
C(23)-H(23A)	0.988(14)
C(23)-H(23B)	1.033(15)
C(23)-H(23C)	0.977(15)

C(1)-O(2)-C(9)	110.26(9)
C(10)-O(4)-C(8)	114.18(9)
C(14)-O(5)-C(13)	105.68(10)
C(19)-O(7)-C(20)	121.01(9)
O(1)-C(1)-O(2)	121.41(11)
O(1)-C(1)-C(2)	127.58(12)
O(2)-C(1)-C(2)	111.01(10)
C(1)-C(2)-C(4)	110.80(11)
C(1)-C(2)-C(3)	107.69(10)
C(4)-C(2)-C(3)	111.03(11)
C(1)-C(2)-C(8)	101.83(10)
C(4)-C(2)-C(8)	113.66(10)
C(3)-C(2)-C(8)	111.35(10)
C(2)-C(3)-H(3A)	110.4(7)
C(2)-C(3)-H(3B)	111.8(7)
H(3A)-C(3)-H(3B)	109.0(10)
C(2)-C(3)-H(3C)	111.1(7)
H(3A)-C(3)-H(3C)	106.1(10)
H(3B)-C(3)-H(3C)	108.2(10)
C(5)-C(4)-C(2)	111.27(11)
C(5)-C(4)-H(4A)	108.8(7)
C(2)-C(4)-H(4A)	109.3(7)
C(5)-C(4)-H(4B)	109.8(7)
C(2)-C(4)-H(4B)	108.9(7)
H(4A)-C(4)-H(4B)	108.7(10)
C(6)-C(5)-C(4)	111.88(11)
C(6)-C(5)-H(5A)	109.2(8)
C(4)-C(5)-H(5A)	110.9(8)
C(6)-C(5)-H(5B)	106.3(7)
C(4)-C(5)-H(5B)	109.4(7)
H(5A)-C(5)-H(5B)	109.1(11)
O(3)-C(6)-C(5)	122.32(12)
O(3)-C(6)-C(7)	121.28(11)
C(5)-C(6)-C(7)	116.39(10)
C(8)-C(7)-C(6)	109.85(10)
C(8)-C(7)-C(16)	112.76(10)
C(6)-C(7)-C(16)	110.59(10)
C(8)-C(7)-H(7)	108.3(7)
C(6)-C(7)-H(7)	103.6(7)
C(16)-C(7)-H(7)	111.3(7)
O(4)-C(8)-C(7)	108.07(9)
O(4)-C(8)-C(9)	110.07(10)
C(7)-C(8)-C(9)	114.49(10)

O(4)-C(8)-C(2)	108.12(9)
C(7)-C(8)-C(2)	113.49(10)
C(9)-C(8)-C(2)	102.37(9)
O(2)-C(9)-C(8)	105.54(10)
O(2)-C(9)-H(9A)	105.0(7)
C(8)-C(9)-H(9A)	115.9(7)
O(2)-C(9)-H(9B)	108.0(6)
C(8)-C(9)-H(9B)	110.3(7)
H(9A)-C(9)-H(9B)	111.4(9)
C(15)-C(10)-O(4)	122.84(11)
C(15)-C(10)-C(11)	128.00(11)
O(4)-C(10)-C(11)	109.11(10)
C(14)-C(11)-C(12)	105.87(11)
C(14)-C(11)-C(10)	125.18(11)
C(12)-C(11)-C(10)	128.91(11)
C(13)-C(12)-C(11)	106.55(12)
C(13)-C(12)-H(12)	128.2(8)
C(11)-C(12)-H(12)	125.3(8)
C(12)-C(13)-O(5)	110.94(12)
C(12)-C(13)-H(13)	134.9(8)
O(5)-C(13)-H(13)	114.1(8)
C(11)-C(14)-O(5)	110.96(11)
C(11)-C(14)-H(14)	134.4(8)
O(5)-C(14)-H(14)	114.6(7)
C(10)-C(15)-C(16)	124.02(11)
C(10)-C(15)-H(15)	116.5(7)
C(16)-C(15)-H(15)	119.3(7)
C(15)-C(16)-C(7)	109.17(10)
C(15)-C(16)-C(17)	112.24(10)
C(7)-C(16)-C(17)	117.18(10)
C(15)-C(16)-H(16)	108.1(6)
C(7)-C(16)-H(16)	106.5(6)
C(17)-C(16)-H(16)	103.0(6)
C(19)-C(17)-C(18)	110.08(11)
C(19)-C(17)-C(16)	108.54(10)
C(18)-C(17)-C(16)	109.53(10)
C(19)-C(17)-H(17)	107.9(6)
C(18)-C(17)-H(17)	110.9(6)
C(16)-C(17)-H(17)	109.9(7)
C(17)-C(18)-H(18A)	110.3(7)
C(17)-C(18)-H(18B)	111.1(7)
H(18A)-C(18)-H(18B)	108.5(10)
C(17)-C(18)-H(18C)	111.2(7)
H(18A)-C(18)-H(18C)	106.8(10)
H(18B)-C(18)-H(18C)	108.7(10)
O(6)-C(19)-O(7)	124.86(12)
O(6)-C(19)-C(17)	123.54(11)
O(7)-C(19)-C(17)	111.53(10)
O(7)-C(20)-C(22)	102.87(10)
O(7)-C(20)-C(21)	109.31(11)
C(22)-C(20)-C(21)	110.83(12)
O(7)-C(20)-C(23)	109.84(10)
C(22)-C(20)-C(23)	110.28(12)
C(21)-C(20)-C(23)	113.22(13)

C(20)-C(21)-H(21A)	108.3(8)
C(20)-C(21)-H(21B)	108.3(8)
H(21A)-C(21)-H(21B)	105.0(12)
C(20)-C(21)-H(21C)	112.3(9)
H(21A)-C(21)-H(21C)	113.3(12)
H(21B)-C(21)-H(21C)	109.4(12)
C(20)-C(22)-H(22A)	108.9(8)
C(20)-C(22)-H(22B)	110.6(8)
H(22A)-C(22)-H(22B)	107.8(11)
C(20)-C(22)-H(22C)	110.4(8)
H(22A)-C(22)-H(22C)	108.7(11)
H(22B)-C(22)-H(22C)	110.4(11)
C(20)-C(23)-H(23A)	107.6(8)
C(20)-C(23)-H(23B)	109.3(8)
H(23A)-C(23)-H(23B)	109.6(11)
C(20)-C(23)-H(23C)	111.1(9)
H(23A)-C(23)-H(23C)	109.6(11)
H(23B)-C(23)-H(23C)	109.6(12)

Table A3.1.4 Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **66a** (CCDC 175515). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	359(6)	331(6)	178(5)	-64(4)	65(4)	-105(5)
O(2)	270(5)	198(5)	213(5)	-44(4)	69(4)	-27(4)
O(3)	213(5)	210(5)	222(5)	7(4)	44(4)	44(4)
O(4)	162(5)	186(5)	133(4)	-1(4)	13(4)	-35(4)
O(5)	191(5)	320(6)	211(5)	-10(4)	-1(4)	-60(4)
O(6)	162(5)	292(6)	312(5)	-56(4)	5(4)	25(4)
O(7)	165(5)	185(5)	225(5)	-37(4)	2(4)	0(4)
C(1)	167(7)	234(7)	217(7)	-31(6)	71(6)	-49(6)
C(2)	178(7)	182(7)	148(6)	-10(5)	29(5)	-20(5)
C(3)	214(8)	207(8)	191(7)	3(6)	62(6)	-33(6)
C(4)	219(8)	246(8)	165(7)	41(6)	25(6)	-11(6)
C(5)	198(7)	178(7)	235(7)	46(6)	15(6)	35(6)
C(6)	131(7)	183(7)	167(6)	-12(5)	-33(5)	-6(5)
C(7)	136(7)	160(7)	139(6)	-14(5)	-4(5)	-19(5)
C(8)	146(7)	152(7)	151(6)	-13(5)	9(5)	-12(5)
C(9)	169(7)	182(7)	193(7)	-10(6)	40(6)	4(6)
C(10)	196(7)	116(6)	135(6)	3(5)	20(5)	32(5)
C(11)	175(7)	132(6)	165(6)	-12(5)	20(5)	8(5)
C(12)	225(8)	242(8)	188(7)	5(6)	28(6)	-33(6)
C(13)	269(8)	295(8)	175(7)	11(6)	-19(6)	-46(6)
C(14)	179(7)	217(7)	174(7)	-26(6)	3(6)	-9(5)
C(15)	186(7)	153(7)	129(6)	4(5)	28(5)	11(5)
C(16)	149(7)	142(7)	166(6)	-2(5)	36(5)	0(5)
C(17)	148(7)	141(7)	229(7)	12(5)	38(6)	0(5)
C(18)	202(8)	199(8)	254(8)	30(6)	61(6)	-14(6)
C(19)	164(7)	133(7)	258(7)	10(5)	50(6)	-34(5)
C(20)	187(7)	212(7)	234(7)	-53(6)	-43(6)	-7(6)
C(21)	260(9)	359(10)	372(10)	-110(8)	20(7)	-86(8)
C(22)	255(9)	265(9)	282(9)	-66(7)	-2(7)	5(7)
C(23)	361(10)	263(9)	261(8)	-40(7)	-58(7)	58(7)

Table A3.1.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **66a** (CCDC 175515).

	x	y	z	U_{iso}
H(3A)	6160(14)	3071(5)	3447(13)	19(3)
H(3B)	5599(15)	3402(5)	2092(12)	23(4)
H(3C)	6220(15)	2812(5)	1989(13)	26(4)
H(4A)	10372(16)	3080(5)	3503(12)	26(4)
H(4B)	8875(14)	2696(5)	3677(12)	17(3)
H(5A)	10626(16)	2316(5)	2205(13)	26(4)
H(5B)	8931(16)	2431(5)	1363(12)	21(3)
H(7)	10949(15)	3634(5)	1448(12)	18(3)
H(9A)	8579(15)	4368(5)	702(12)	19(3)
H(9B)	6765(15)	4144(4)	879(11)	11(3)
H(12)	6599(16)	3449(5)	-4201(13)	26(4)
H(13)	3621(16)	3110(5)	-4773(13)	29(4)
H(14)	4421(15)	3026(5)	-825(12)	22(4)
H(15)	9019(14)	3702(4)	-2550(12)	12(3)
H(16)	11412(14)	3478(4)	-1018(11)	12(3)
H(17)	10319(14)	4511(4)	-665(11)	14(3)
H(18A)	12311(15)	4700(5)	-2164(12)	26(4)
H(18B)	13014(16)	4130(5)	-2023(12)	25(4)
H(18C)	11283(16)	4225(5)	-2864(13)	27(4)
H(21A)	13993(17)	5336(6)	2039(14)	37(4)
H(21B)	14823(17)	5145(5)	3480(15)	39(4)
H(21C)	15119(19)	4804(6)	2172(15)	47(5)
H(22A)	12173(17)	5117(5)	4507(15)	39(4)
H(22B)	10658(17)	4866(5)	3648(13)	28(4)
H(22C)	11439(17)	5378(6)	3083(13)	37(4)
H(23A)	13729(16)	4295(5)	4480(14)	32(4)
H(23B)	12061(19)	4029(6)	3706(14)	43(4)
H(23C)	13828(18)	3986(6)	3074(15)	44(5)

A3.2 Crystal Structure Analysis of 71c

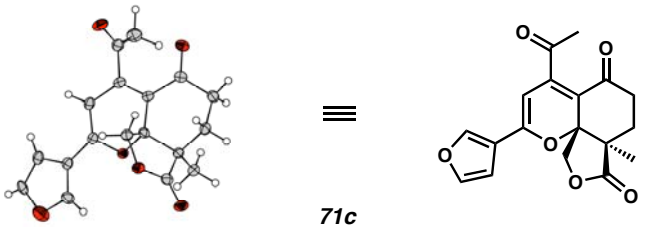


Figure A3.2.1 Polycycle **71c** is shown with 50% probability ellipsoids. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 201414.

Table A3.2.1 Crystal data and structure refinement for **71c** (CCDC 201414).

Empirical formula	$C_{18}H_{16}O_6$
Formula weight	328.31
Crystallization Solvent	Hexanes/ethylacetate
Crystal Habit	Fragment
Crystal size	0.28 x 0.22 x 0.15 mm^3
Crystal color	Yellow

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 7975 reflections used in lattice determination	2.26 to 28.15°
Unit cell dimensions	a = 12.3799(11) Å b = 7.2521(7) Å β= 101.892(2)° c = 17.2138(15) Å
Volume	1512.3(2) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/n$
Density (calculated)	1.442 Mg/m^3
F(000)	688
Data collection program	Bruker SMART v5.054
θ range for data collection	1.86 to 28.22°
Completeness to θ = 28.22°	94.4 %
Index ranges	$-15 \le h \le 16$, $-9 \le k \le 9$, $-22 \le l \le 21$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	21320
Independent reflections	3525 [R_{int}= 0.0530]
Absorption coefficient	0.109 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9838 and 0.9701

Table A3.2.1 **(cont.)**

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	3525 / 0 / 281
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.948
Final R indices [$I>2\sigma(I)$, 2658 reflections]	R1 = 0.0425, *w*R2 = 0.0689
R indices (all data)	R1 = 0.0606, *w*R2 = 0.0710
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Largest diff. peak and hole	0.376 and -0.393 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table A3.2.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **71c** (CCDC 201414). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	7557(1)	-202(1)	-1544(1)	32(1)
O(2)	9763(1)	1794(1)	-583(1)	23(1)
O(3)	9007(1)	2746(1)	3057(1)	27(1)
O(4)	8289(1)	483(1)	2230(1)	22(1)
O(5)	7079(1)	2940(1)	971(1)	18(1)
O(6)	3873(1)	3651(2)	1211(1)	39(1)
C(1)	6423(1)	1692(2)	-309(1)	20(1)
C(2)	7531(1)	1661(2)	-435(1)	18(1)
C(3)	8392(1)	1951(2)	179(1)	17(1)
C(4)	9524(1)	2132(2)	62(1)	18(1)
C(5)	10385(1)	2853(2)	743(1)	22(1)
C(6)	10145(1)	2438(2)	1559(1)	21(1)
C(7)	8975(1)	3043(2)	1635(1)	17(1)
C(8)	8765(1)	2161(2)	2391(1)	21(1)
C(9)	8083(1)	134(2)	1380(1)	20(1)
C(10)	8135(1)	2030(2)	997(1)	17(1)
C(11)	6232(1)	2420(2)	372(1)	18(1)
C(12)	5164(1)	2845(2)	541(1)	18(1)
C(13)	4133(1)	2958(2)	1(1)	22(1)
C(14)	3386(1)	3403(2)	410(1)	23(1)
C(15)	4958(1)	3270(2)	1271(1)	25(1)
C(16)	7661(1)	1354(2)	-1282(1)	22(1)
C(17)	7785(2)	2990(2)	-1776(1)	29(1)
C(18)	8853(1)	5134(2)	1645(1)	22(1)

Table A3.2.3 Bond lengths [Å] and angles [°] for **71c** (CCDC 201414).

O(1)-C(16)	1.2118(16)
O(2)-C(4)	1.2302(15)
O(3)-C(8)	1.2008(15)
O(4)-C(8)	1.3562(17)
O(4)-C(9)	1.4550(16)
O(5)-C(11)	1.3639(15)
O(5)-C(10)	1.4564(16)
O(6)-C(15)	1.3551(18)
O(6)-C(14)	1.3979(19)
C(1)-C(11)	1.3495(19)
C(1)-C(2)	1.433(2)
C(1)-H(1)	0.947(14)
C(2)-C(3)	1.3548(18)
C(2)-C(16)	1.5151(19)
C(3)-C(4)	1.4630(19)
C(3)-C(10)	1.5061(18)
C(4)-C(5)	1.507(2)
C(5)-C(6)	1.5238(19)
C(5)-H(5A)	1.013(14)
C(5)-H(5B)	0.982(15)
C(6)-C(7)	1.5453(19)
C(6)-H(6A)	0.963(14)
C(6)-H(6B)	1.007(14)
C(7)-C(8)	1.5191(19)
C(7)-C(10)	1.5352(18)
C(7)-C(18)	1.524(2)
C(9)-C(10)	1.5325(19)
C(9)-H(9A)	0.956(15)
C(9)-H(9B)	1.028(14)
C(11)-C(12)	1.4439(19)
C(12)-C(15)	1.367(2)
C(12)-C(13)	1.4186(19)
C(13)-C(14)	1.313(2)
C(13)-H(13)	0.963(14)
C(14)-H(14)	0.706(15)
C(15)-H(15)	0.951(15)
C(16)-C(17)	1.487(2)
C(17)-H(17A)	0.951(18)
C(17)-H(17B)	1.000(17)
C(17)-H(17C)	0.990(17)
C(18)-H(18A)	1.024(15)
C(18)-H(18B)	0.972(15)
C(18)-H(18C)	0.986(15)
C(8)-O(4)-C(9)	109.86(10)
C(11)-O(5)-C(10)	116.28(10)
C(15)-O(6)-C(14)	105.53(12)
C(11)-C(1)-C(2)	118.85(14)
C(11)-C(1)-H(1)	118.0(8)
C(2)-C(1)-H(1)	122.5(8)

C(3)-C(2)-C(1)	120.16(13)
C(3)-C(2)-C(16)	123.44(13)
C(1)-C(2)-C(16)	116.37(12)
C(2)-C(3)-C(4)	121.86(12)
C(2)-C(3)-C(10)	116.87(12)
C(4)-C(3)-C(10)	121.25(12)
O(2)-C(4)-C(3)	121.49(13)
O(2)-C(4)-C(5)	120.57(13)
C(3)-C(4)-C(5)	117.86(12)
C(4)-C(5)-C(6)	114.14(12)
C(4)-C(5)-H(5A)	105.8(8)
C(6)-C(5)-H(5A)	110.0(8)
C(4)-C(5)-H(5B)	108.1(8)
C(6)-C(5)-H(5B)	109.9(8)
H(5A)-C(5)-H(5B)	108.6(11)
C(5)-C(6)-C(7)	112.68(12)
C(5)-C(6)-H(6A)	109.4(8)
C(7)-C(6)-H(6A)	108.0(8)
C(5)-C(6)-H(6B)	107.4(8)
C(7)-C(6)-H(6B)	110.9(8)
H(6A)-C(6)-H(6B)	108.5(11)
C(8)-C(7)-C(10)	101.65(11)
C(8)-C(7)-C(18)	111.96(12)
C(10)-C(7)-C(18)	115.50(12)
C(8)-C(7)-C(6)	106.35(11)
C(10)-C(7)-C(6)	108.23(11)
C(18)-C(7)-C(6)	112.29(12)
O(3)-C(8)-O(4)	121.56(13)
O(3)-C(8)-C(7)	128.07(13)
O(4)-C(8)-C(7)	110.30(11)
O(4)-C(9)-C(10)	105.25(11)
O(4)-C(9)-H(9A)	107.7(9)
C(10)-C(9)-H(9A)	111.4(9)
O(4)-C(9)-H(9B)	111.4(8)
C(10)-C(9)-H(9B)	110.5(8)
H(9A)-C(9)-H(9B)	110.5(11)
O(5)-C(10)-C(3)	110.50(10)
O(5)-C(10)-C(7)	106.03(10)
C(3)-C(10)-C(7)	116.40(11)
O(5)-C(10)-C(9)	107.60(11)
C(3)-C(10)-C(9)	113.81(11)
C(7)-C(10)-C(9)	101.72(11)
C(1)-C(11)-O(5)	121.35(13)
C(1)-C(11)-C(12)	126.13(13)
O(5)-C(11)-C(12)	112.43(11)
C(15)-C(12)-C(13)	106.02(13)
C(15)-C(12)-C(11)	125.81(13)
C(13)-C(12)-C(11)	128.15(13)
C(14)-C(13)-C(12)	107.52(14)
C(14)-C(13)-H(13)	124.6(9)
C(12)-C(13)-H(13)	127.9(9)
C(13)-C(14)-O(6)	110.62(15)
C(13)-C(14)-H(14)	136.8(13)
O(6)-C(14)-H(14)	112.3(13)

O(6)-C(15)-C(12)	110.27(14)
O(6)-C(15)-H(15)	117.5(9)
C(12)-C(15)-H(15)	132.2(9)
O(1)-C(16)-C(2)	118.03(13)
O(1)-C(16)-C(17)	123.07(14)
C(2)-C(16)-C(17)	118.53(13)
C(16)-C(17)-H(17A)	108.8(10)
C(16)-C(17)-H(17B)	111.6(9)
H(17A)-C(17)-H(17B)	108.0(14)
C(16)-C(17)-H(17C)	112.2(9)
H(17A)-C(17)-H(17C)	107.1(13)
H(17B)-C(17)-H(17C)	108.9(13)
C(7)-C(18)-H(18A)	109.3(8)
C(7)-C(18)-H(18B)	111.6(8)
H(18A)-C(18)-H(18B)	110.3(12)
C(7)-C(18)-H(18C)	108.4(8)
H(18A)-C(18)-H(18C)	109.7(12)
H(18B)-C(18)-H(18C)	107.5(12)

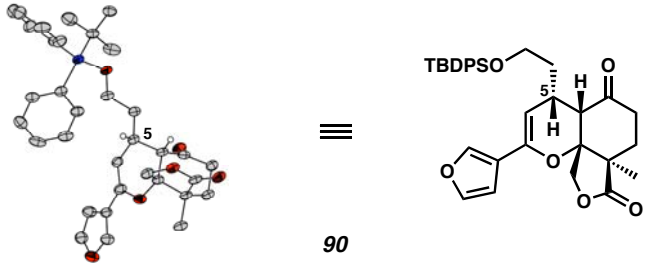
Table A3.2.4 Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **71c** (CCDC 201414). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	418(7)	297(6)	249(6)	-92(5)	72(5)	-20(5)
O(2)	260(6)	276(6)	180(6)	23(4)	93(5)	30(5)
O(3)	301(6)	360(6)	136(6)	-24(5)	30(5)	22(5)
O(4)	269(6)	256(6)	146(5)	28(4)	46(4)	-23(5)
O(5)	162(5)	229(5)	155(5)	-18(4)	26(4)	11(4)
O(6)	329(7)	498(8)	371(7)	25(6)	133(6)	42(6)
C(1)	194(8)	211(8)	173(8)	14(6)	1(7)	-24(6)
C(2)	248(8)	126(7)	164(8)	9(6)	48(6)	5(6)
C(3)	213(8)	148(7)	151(7)	7(6)	39(6)	16(6)
C(4)	236(8)	154(7)	168(8)	44(6)	59(6)	28(6)
C(5)	194(9)	256(9)	220(8)	8(7)	61(7)	-4(7)
C(6)	186(8)	250(9)	167(8)	1(6)	13(7)	-14(7)
C(7)	167(8)	212(8)	135(7)	-3(6)	22(6)	0(6)
C(8)	167(8)	257(8)	195(8)	10(6)	34(6)	40(6)
C(9)	216(9)	234(8)	152(8)	7(6)	42(7)	-15(7)
C(10)	154(7)	188(7)	165(7)	7(6)	45(6)	26(6)
C(11)	197(8)	162(7)	161(7)	31(6)	19(6)	-21(6)
C(12)	206(8)	160(7)	184(8)	13(6)	40(6)	-20(6)
C(13)	241(9)	205(8)	216(9)	33(6)	25(7)	-47(7)
C(14)	113(9)	313(9)	256(9)	79(7)	35(7)	21(7)
C(15)	195(9)	326(9)	236(9)	5(7)	47(7)	30(7)
C(16)	189(8)	270(9)	177(8)	-14(6)	15(6)	19(7)
C(17)	360(11)	336(10)	175(9)	44(7)	42(8)	8(9)
C(18)	228(9)	234(8)	207(9)	-31(7)	36(7)	-18(7)

Table A3.2.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **71c** (CCDC 201414).

	x	y	z	U_{iso}
H(1)	5805(11)	1389(18)	-713(8)	19(4)
H(5A)	10412(11)	4230(20)	661(8)	28(4)
H(5B)	11101(12)	2324(19)	701(8)	25(4)
H(6A)	10670(12)	3082(19)	1959(8)	23(4)
H(6B)	10250(11)	1070(20)	1653(8)	19(4)
H(9A)	7364(13)	-399(19)	1229(8)	28(4)
H(9B)	8668(12)	-733(19)	1235(8)	22(4)
H(13)	3987(12)	2801(19)	-567(9)	28(4)
H(14)	2817(13)	3610(20)	328(9)	27(5)
H(15)	5430(12)	3399(19)	1778(9)	27(4)
H(17A)	7096(15)	3620(20)	-1906(10)	47(5)
H(17B)	8001(13)	2630(20)	-2283(10)	44(5)
H(17C)	8333(13)	3880(20)	-1492(9)	38(5)
H(18A)	8984(11)	5666(19)	1121(9)	26(4)
H(18B)	8131(13)	5499(19)	1731(8)	25(4)
H(18C)	9410(12)	5627(19)	2091(9)	27(4)

A3.3 Crystal Structure Analysis of 90



90

Figure A3.3.1 Ketone **90** is shown with 50% probability ellipsoids. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 197200.

Table A3.3.1 Crystal data and structure refinement for **90** (CCDC 197200).

Empirical formula	$C_{34}H_{38}O_6Si$
Formula weight	570.73
Crystallization Solvent	Benzene
Crystal Habit	Fragment
Crystal size	0.30 x 0.26 x 0.24 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 12272 reflections used in lattice determination	2.41 to 27.51°
Unit cell dimensions	a = 10.3188(7) Å b = 10.5705(8) Å β= 92.9410(10)° c = 27.269(2) Å
Volume	2970.5(4) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/c$
Density (calculated)	1.276 Mg/m^3
F(000)	1216
Data collection program	Bruker SMART v5.054
θ range for data collection	1.50 to 28.26°
Completeness to θ = 28.26°	93.9 %
Index ranges	$-13 \le h \le 13$, $-14 \le k \le 13$, $-35 \le l \le 35$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	49441
Independent reflections	6912 [R_{int}= 0.0683]
Absorption coefficient	0.124 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9709 and 0.9638

Table A3.3.1 **(cont.)**

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	6912 / 0 / 522
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.686
Final R indices [$I>2\sigma(I)$, 4526 reflections]	R1 = 0.0491, *w*R2 = 0.0689
R indices (all data)	R1 = 0.0835, *w*R2 = 0.0712
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Largest diff. peak and hole	0.534 and -0.364 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table A3.3.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **90** (CCDC 197200). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Si(1)	2828(1)	9991(1)	2058(1)	24(1)
O(1)	4132(1)	6866(1)	133(1)	33(1)
O(2)	51(1)	4263(1)	-799(1)	36(1)
O(3)	-763(1)	6000(1)	-466(1)	30(1)
O(4)	1492(1)	8495(1)	-683(1)	31(1)
O(5)	2833(1)	11714(1)	-1323(1)	39(1)
O(6)	2483(1)	8760(1)	1706(1)	26(1)
C(1)	1069(2)	7330(2)	-477(1)	24(1)
C(2)	1800(2)	7014(2)	17(1)	23(1)
C(3)	3127(2)	6442(2)	-55(1)	26(1)
C(4)	3089(2)	5294(2)	-380(1)	29(1)
C(5)	2507(2)	5661(2)	-886(1)	28(1)
C(6)	1184(2)	6286(2)	-870(1)	25(1)
C(7)	146(2)	5373(2)	-720(1)	29(1)
C(8)	-396(2)	7321(2)	-413(1)	30(1)
C(9)	756(2)	6771(2)	-1385(1)	31(1)
C(10)	1766(2)	8152(2)	364(1)	25(1)
C(11)	2258(2)	9287(2)	100(1)	30(1)
C(12)	2051(2)	9419(2)	-384(1)	30(1)
C(13)	2508(2)	10459(2)	-680(1)	27(1)
C(14)	3375(2)	11462(2)	-530(1)	37(1)
C(15)	3529(2)	12177(2)	-922(1)	36(1)
C(16)	2225(2)	10654(2)	-1160(1)	33(1)
C(17)	2423(2)	7959(2)	873(1)	26(1)
C(18)	1803(2)	8820(2)	1236(1)	27(1)
C(19)	1354(2)	10465(2)	2386(1)	25(1)
C(20)	187(2)	9866(2)	2284(1)	36(1)
C(21)	-939(2)	10165(2)	2533(1)	42(1)
C(22)	-853(2)	11039(2)	2901(1)	44(1)
C(23)	306(2)	11618(2)	3031(1)	47(1)
C(24)	1383(2)	11359(2)	2769(1)	41(1)
C(25)	3332(2)	11291(2)	1640(1)	25(1)
C(26)	4203(2)	11045(2)	1272(1)	30(1)
C(27)	4499(2)	11948(2)	929(1)	35(1)
C(28)	3931(2)	13125(2)	942(1)	39(1)
C(29)	3075(2)	13413(2)	1300(1)	35(1)
C(30)	2782(2)	12501(2)	1645(1)	29(1)
C(31)	4151(2)	9415(2)	2501(1)	28(1)
C(32)	3668(2)	8237(2)	2761(1)	32(1)
C(33)	5347(2)	9070(3)	2216(1)	43(1)
C(34)	4556(3)	10399(2)	2891(1)	46(1)

Table A3.3.3 Bond lengths [Å] and angles [°] for **90** (CCDC 197200).

Si(1)-O(6)	1.6437(12)
Si(1)-C(19)	1.8717(18)
Si(1)-C(25)	1.8745(18)
Si(1)-C(31)	1.8779(18)
O(1)-C(3)	1.2182(19)
O(2)-C(7)	1.197(2)
O(3)-C(7)	1.365(2)
O(3)-C(8)	1.452(2)
O(4)-C(12)	1.3799(19)
O(4)-C(1)	1.4312(19)
O(5)-C(15)	1.368(2)
O(5)-C(16)	1.371(2)
O(6)-C(18)	1.432(2)
C(1)-C(8)	1.531(2)
C(1)-C(2)	1.544(2)
C(1)-C(6)	1.547(2)
C(2)-C(3)	1.519(2)
C(2)-C(10)	1.533(2)
C(2)-H(2)	0.977(14)
C(3)-C(4)	1.502(2)
C(4)-C(5)	1.526(2)
C(4)-H(4A)	0.969(16)
C(4)-H(4B)	0.967(16)
C(5)-C(6)	1.519(2)
C(5)-H(5A)	0.937(16)
C(5)-H(5B)	0.971(16)
C(6)-C(7)	1.513(2)
C(6)-C(9)	1.540(2)
C(8)-H(8A)	0.987(16)
C(8)-H(8B)	1.003(17)
C(9)-H(9A)	1.004(17)
C(9)-H(9B)	0.988(18)
C(9)-H(9C)	0.999(18)
C(10)-C(11)	1.501(2)
C(10)-C(17)	1.526(2)
C(10)-H(10)	0.995(15)
C(11)-C(12)	1.333(2)
C(11)-H(11)	0.946(15)
C(12)-C(13)	1.456(2)
C(13)-C(16)	1.341(2)
C(13)-C(14)	1.433(2)
C(14)-C(15)	1.326(3)
C(14)-H(14)	0.949(17)
C(15)-H(15)	0.923(18)
C(16)-H(16)	0.969(17)
C(17)-C(18)	1.511(2)
C(17)-H(17A)	0.962(16)
C(17)-H(17B)	0.931(16)
C(18)-H(18A)	1.025(14)
C(18)-H(18B)	0.965(15)
C(19)-C(20)	1.376(2)

C(19)-C(24)	1.407(2)
C(20)-C(21)	1.412(3)
C(20)-H(20)	0.955(17)
C(21)-C(22)	1.363(3)
C(21)-H(21)	0.900(18)
C(22)-C(23)	1.374(3)
C(22)-H(22)	0.92(2)
C(23)-C(24)	1.380(3)
C(23)-H(23)	1.08(2)
C(24)-H(24)	1.02(2)
C(25)-C(30)	1.399(2)
C(25)-C(26)	1.407(2)
C(26)-C(27)	1.381(3)
C(26)-H(26)	0.992(16)
C(27)-C(28)	1.376(3)
C(27)-H(27)	0.975(17)
C(28)-C(29)	1.385(3)
C(28)-H(28)	0.915(16)
C(29)-C(30)	1.389(3)
C(29)-H(29)	0.923(14)
C(30)-H(30)	0.949(15)
C(31)-C(32)	1.529(3)
C(31)-C(34)	1.530(3)
C(31)-C(33)	1.535(3)
C(32)-H(32A)	0.965(19)
C(32)-H(32B)	0.962(17)
C(32)-H(32C)	0.989(17)
C(33)-H(33A)	0.99(2)
C(33)-H(33B)	0.98(2)
C(33)-H(33C)	1.05(2)
C(34)-H(34A)	0.962(19)
C(34)-H(34B)	0.981(19)
C(34)-H(34C)	1.06(2)

O(6)-Si(1)-C(19)	109.50(7)
O(6)-Si(1)-C(25)	106.52(7)
C(19)-Si(1)-C(25)	110.59(8)
O(6)-Si(1)-C(31)	104.27(7)
C(19)-Si(1)-C(31)	111.17(8)
C(25)-Si(1)-C(31)	114.41(8)
C(7)-O(3)-C(8)	109.54(14)
C(12)-O(4)-C(1)	120.28(13)
C(15)-O(5)-C(16)	105.20(15)
C(18)-O(6)-Si(1)	124.65(11)
O(4)-C(1)-C(8)	111.89(15)
O(4)-C(1)-C(2)	112.50(14)
C(8)-C(1)-C(2)	109.92(14)
O(4)-C(1)-C(6)	107.80(13)
C(8)-C(1)-C(6)	100.70(14)
C(2)-C(1)-C(6)	113.46(14)
C(3)-C(2)-C(10)	116.14(15)
C(3)-C(2)-C(1)	112.18(14)
C(10)-C(2)-C(1)	110.10(14)
C(3)-C(2)-H(2)	106.4(8)

C(10)-C(2)-H(2)	108.5(8)
C(1)-C(2)-H(2)	102.5(9)
O(1)-C(3)-C(4)	122.83(17)
O(1)-C(3)-C(2)	123.55(16)
C(4)-C(3)-C(2)	113.61(16)
C(3)-C(4)-C(5)	109.00(16)
C(3)-C(4)-H(4A)	109.7(9)
C(5)-C(4)-H(4A)	108.5(10)
C(3)-C(4)-H(4B)	109.3(9)
C(5)-C(4)-H(4B)	113.0(9)
H(4A)-C(4)-H(4B)	107.3(13)
C(6)-C(5)-C(4)	113.43(15)
C(6)-C(5)-H(5A)	110.5(10)
C(4)-C(5)-H(5A)	106.7(10)
C(6)-C(5)-H(5B)	108.6(10)
C(4)-C(5)-H(5B)	110.0(10)
H(5A)-C(5)-H(5B)	107.5(13)
C(7)-C(6)-C(5)	112.31(16)
C(7)-C(6)-C(9)	106.55(15)
C(5)-C(6)-C(9)	109.58(15)
C(7)-C(6)-C(1)	100.75(13)
C(5)-C(6)-C(1)	115.55(15)
C(9)-C(6)-C(1)	111.52(15)
O(2)-C(7)-O(3)	121.04(17)
O(2)-C(7)-C(6)	128.96(17)
O(3)-C(7)-C(6)	110.00(15)
O(3)-C(8)-C(1)	104.39(15)
O(3)-C(8)-H(8A)	105.9(9)
C(1)-C(8)-H(8A)	111.7(9)
O(3)-C(8)-H(8B)	111.9(9)
C(1)-C(8)-H(8B)	110.7(9)
H(8A)-C(8)-H(8B)	111.9(13)
C(6)-C(9)-H(9A)	108.0(9)
C(6)-C(9)-H(9B)	110.6(10)
H(9A)-C(9)-H(9B)	110.3(13)
C(6)-C(9)-H(9C)	114.1(10)
H(9A)-C(9)-H(9C)	106.2(14)
H(9B)-C(9)-H(9C)	107.5(14)
C(11)-C(10)-C(17)	113.45(16)
C(11)-C(10)-C(2)	108.15(15)
C(17)-C(10)-C(2)	115.73(15)
C(11)-C(10)-H(10)	106.1(9)
C(17)-C(10)-H(10)	107.1(9)
C(2)-C(10)-H(10)	105.6(9)
C(12)-C(11)-C(10)	121.20(18)
C(12)-C(11)-H(11)	118.3(9)
C(10)-C(11)-H(11)	120.3(9)
C(11)-C(12)-O(4)	123.46(17)
C(11)-C(12)-C(13)	126.02(17)
O(4)-C(12)-C(13)	110.13(14)
C(16)-C(13)-C(14)	105.43(17)
C(16)-C(13)-C(12)	126.59(17)
C(14)-C(13)-C(12)	127.95(17)
C(15)-C(14)-C(13)	106.89(19)

C(15)-C(14)-H(14)	125.6(10)
C(13)-C(14)-H(14)	127.5(10)
C(14)-C(15)-O(5)	111.17(19)
C(14)-C(15)-H(15)	132.6(12)
O(5)-C(15)-H(15)	116.1(12)
C(13)-C(16)-O(5)	111.29(18)
C(13)-C(16)-H(16)	130.8(10)
O(5)-C(16)-H(16)	117.9(10)
C(18)-C(17)-C(10)	109.36(16)
C(18)-C(17)-H(17A)	106.5(9)
C(10)-C(17)-H(17A)	111.1(9)
C(18)-C(17)-H(17B)	111.4(10)
C(10)-C(17)-H(17B)	109.2(10)
H(17A)-C(17)-H(17B)	109.3(13)
O(6)-C(18)-C(17)	110.81(15)
O(6)-C(18)-H(18A)	109.6(8)
C(17)-C(18)-H(18A)	110.0(8)
O(6)-C(18)-H(18B)	108.3(9)
C(17)-C(18)-H(18B)	109.0(9)
H(18A)-C(18)-H(18B)	109.1(12)
C(20)-C(19)-C(24)	116.33(18)
C(20)-C(19)-Si(1)	120.30(14)
C(24)-C(19)-Si(1)	123.19(15)
C(19)-C(20)-C(21)	122.3(2)
C(19)-C(20)-H(20)	119.8(11)
C(21)-C(20)-H(20)	117.7(11)
C(22)-C(21)-C(20)	118.8(2)
C(22)-C(21)-H(21)	123.7(12)
C(20)-C(21)-H(21)	117.5(12)
C(21)-C(22)-C(23)	121.0(2)
C(21)-C(22)-H(22)	118.6(13)
C(23)-C(22)-H(22)	120.1(13)
C(22)-C(23)-C(24)	119.4(2)
C(22)-C(23)-H(23)	123.7(12)
C(24)-C(23)-H(23)	116.9(12)
C(23)-C(24)-C(19)	122.1(2)
C(23)-C(24)-H(24)	118.0(12)
C(19)-C(24)-H(24)	119.9(12)
C(30)-C(25)-C(26)	116.67(17)
C(30)-C(25)-Si(1)	122.66(14)
C(26)-C(25)-Si(1)	120.39(14)
C(27)-C(26)-C(25)	121.8(2)
C(27)-C(26)-H(26)	117.0(10)
C(25)-C(26)-H(26)	121.2(10)
C(28)-C(27)-C(26)	119.9(2)
C(28)-C(27)-H(27)	120.8(10)
C(26)-C(27)-H(27)	119.3(10)
C(27)-C(28)-C(29)	120.3(2)
C(27)-C(28)-H(28)	121.7(11)
C(29)-C(28)-H(28)	118.1(11)
C(28)-C(29)-C(30)	119.6(2)
C(28)-C(29)-H(29)	122.0(10)
C(30)-C(29)-H(29)	118.3(10)
C(29)-C(30)-C(25)	121.74(19)

C(29)-C(30)-H(30)	118.1(9)
C(25)-C(30)-H(30)	120.1(9)
C(32)-C(31)-C(34)	108.36(17)
C(32)-C(31)-C(33)	109.37(17)
C(34)-C(31)-C(33)	108.35(19)
C(32)-C(31)-Si(1)	108.58(13)
C(34)-C(31)-Si(1)	112.96(14)
C(33)-C(31)-Si(1)	109.17(13)
C(31)-C(32)-H(32A)	111.1(10)
C(31)-C(32)-H(32B)	109.1(10)
H(32A)-C(32)-H(32B)	110.5(14)
C(31)-C(32)-H(32C)	110.1(10)
H(32A)-C(32)-H(32C)	107.6(14)
H(32B)-C(32)-H(32C)	108.3(14)
C(31)-C(33)-H(33A)	110.3(11)
C(31)-C(33)-H(33B)	111.8(12)
H(33A)-C(33)-H(33B)	106.9(16)
C(31)-C(33)-H(33C)	108.3(11)
H(33A)-C(33)-H(33C)	110.2(15)
H(33B)-C(33)-H(33C)	109.4(16)
C(31)-C(34)-H(34A)	114.2(12)
C(31)-C(34)-H(34B)	110.1(11)
H(34A)-C(34)-H(34B)	101.4(16)
C(31)-C(34)-H(34C)	109.4(11)
H(34A)-C(34)-H(34C)	112.9(16)
H(34B)-C(34)-H(34C)	108.4(16)

Table A3.3.4 Anisotropic displacement parameters ($Å^2 x\ 10^4$) for **90** (CCDC 197200). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	236(3)	306(3)	166(3)	-13(2)	11(2)	-33(2)
O(1)	279(8)	449(8)	263(8)	-59(6)	-6(6)	-61(7)
O(2)	462(9)	375(8)	249(8)	-81(6)	78(6)	-163(7)
O(3)	278(8)	389(8)	241(7)	-41(6)	36(6)	-103(6)
O(4)	406(8)	307(7)	199(7)	8(6)	-43(6)	-130(6)
O(5)	466(9)	398(8)	313(8)	87(7)	15(7)	-48(7)
O(6)	314(7)	328(7)	136(7)	-24(6)	-3(5)	-36(6)
C(1)	249(11)	294(11)	171(10)	0(8)	-3(8)	-59(8)
C(2)	263(11)	290(11)	143(10)	-8(8)	21(8)	-93(9)
C(3)	327(12)	296(11)	168(10)	43(8)	-2(9)	-74(9)
C(4)	290(12)	317(13)	254(11)	-35(9)	22(9)	-43(10)
C(5)	297(12)	362(13)	196(11)	-53(10)	37(9)	-76(10)
C(6)	267(11)	324(11)	155(10)	-23(8)	17(8)	-84(9)
C(7)	299(11)	427(13)	130(10)	-40(9)	5(8)	-86(10)
C(8)	320(12)	370(13)	221(12)	-45(10)	8(10)	-59(10)
C(9)	296(13)	437(14)	184(11)	-29(10)	6(9)	-89(11)
C(10)	267(11)	301(11)	179(10)	-21(8)	12(9)	-37(9)
C(11)	403(13)	262(11)	231(11)	-42(9)	22(9)	-61(10)
C(12)	386(12)	306(11)	206(11)	-40(9)	-5(9)	-104(9)
C(13)	329(11)	294(11)	193(10)	-2(9)	8(8)	-33(9)
C(14)	455(14)	371(13)	265(13)	13(10)	-52(10)	-114(11)
C(15)	435(14)	307(13)	327(13)	-1(10)	13(11)	-94(11)
C(16)	354(12)	367(12)	259(12)	31(10)	-21(9)	-80(10)
C(17)	295(13)	296(12)	192(11)	-2(9)	25(9)	-73(10)
C(18)	251(12)	390(13)	180(11)	-5(9)	7(9)	-67(10)
C(19)	284(11)	270(11)	203(10)	32(8)	1(8)	-4(9)
C(20)	316(12)	501(14)	260(11)	-37(11)	3(9)	34(11)
C(21)	295(13)	665(17)	305(12)	67(12)	-30(10)	-48(12)
C(22)	441(15)	509(15)	394(14)	53(12)	146(12)	154(12)
C(23)	598(17)	377(14)	435(15)	-2(11)	166(13)	43(12)
C(24)	500(15)	386(13)	349(13)	-22(10)	151(11)	-36(11)
C(25)	217(10)	338(11)	198(10)	-23(9)	-39(8)	-71(9)
C(26)	292(12)	377(13)	223(11)	4(10)	-15(9)	-86(10)
C(27)	326(13)	487(15)	228(12)	12(10)	-4(10)	-134(11)
C(28)	364(13)	502(15)	277(13)	158(11)	-101(10)	-176(12)
C(29)	326(13)	340(14)	357(13)	47(11)	-133(10)	-30(11)
C(30)	221(11)	419(13)	227(11)	25(10)	-58(9)	-44(10)
C(31)	258(11)	364(11)	204(10)	16(9)	-11(8)	-53(9)
C(32)	265(13)	426(14)	253(12)	65(11)	-11(10)	3(10)
C(33)	232(12)	674(18)	388(15)	199(14)	10(11)	5(12)
C(34)	533(17)	465(16)	369(15)	26(12)	-159(13)	-115(13)

Table A3.3.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **90** (CCDC 197200).

	x	y	z	U_{iso}
H(2)	1269(14)	6339(13)	147(5)	15(4)
H(4A)	2545(15)	4651(15)	-243(6)	27(5)
H(4B)	3953(16)	4944(15)	-391(6)	29(5)
H(5A)	3101(15)	6208(14)	-1025(6)	24(5)
H(5B)	2426(15)	4918(15)	-1094(6)	32(5)
H(8A)	-608(15)	7565(14)	-77(6)	24(5)
H(8B)	-856(16)	7867(15)	-668(6)	31(5)
H(9A)	748(15)	6032(15)	-1617(6)	34(5)
H(9B)	1355(17)	7431(16)	-1493(6)	38(5)
H(9C)	-140(18)	7133(15)	-1409(6)	39(6)
H(10)	831(16)	8316(14)	412(6)	25(5)
H(11)	2661(14)	9960(14)	278(5)	24(5)
H(14)	3790(16)	11587(15)	-215(7)	35(5)
H(15)	4040(18)	12875(17)	-976(7)	45(6)
H(16)	1708(16)	10161(15)	-1397(6)	37(5)
H(17A)	2301(14)	7109(15)	987(6)	23(5)
H(17B)	3307(16)	8122(14)	859(6)	22(5)
H(18A)	1800(13)	9734(14)	1110(5)	15(4)
H(18B)	919(16)	8551(14)	1273(5)	23(5)
H(20)	141(16)	9170(16)	2061(6)	37(6)
H(21)	-1667(18)	9728(17)	2450(7)	47(6)
H(22)	-1570(19)	11186(17)	3078(7)	56(7)
H(23)	440(20)	12270(20)	3335(8)	84(8)
H(24)	2220(20)	11840(20)	2859(8)	79(8)
H(26)	4631(15)	10209(16)	1246(6)	35(5)
H(27)	5122(16)	11746(15)	684(6)	36(5)
H(28)	4105(16)	13738(15)	718(6)	29(5)
H(29)	2716(14)	14207(14)	1328(5)	16(5)
H(30)	2168(15)	12708(13)	1879(6)	15(4)
H(32A)	4317(18)	7919(15)	2996(7)	40(6)
H(32B)	3437(16)	7601(16)	2520(7)	35(6)
H(32C)	2888(17)	8444(15)	2941(6)	33(5)
H(33A)	6017(19)	8670(17)	2438(7)	51(6)
H(33B)	5747(19)	9821(19)	2075(7)	61(7)
H(33C)	5054(19)	8444(18)	1932(8)	63(7)
H(34A)	3867(19)	10662(18)	3092(7)	48(7)
H(34B)	4779(18)	11198(18)	2733(7)	51(6)
H(34C)	5390(20)	10069(18)	3099(8)	75(7)

APPENDIX FOUR

The Development and Scope of an Alternate Tandem Stille-Oxa-Electrocyclization Reaction[†]

A4.1 Background and Introduction

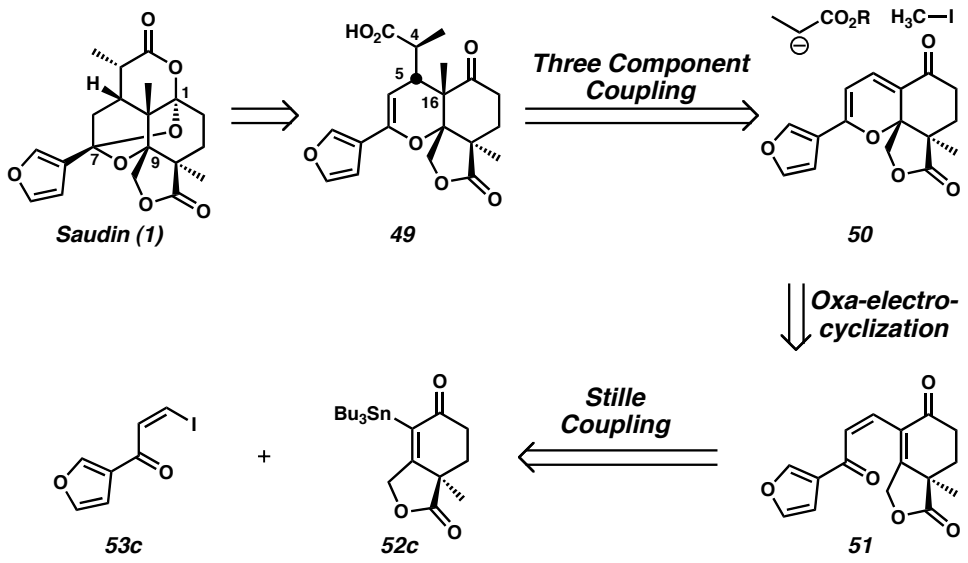
A4.1.1 Application of the Tandem Stille-Oxa-Electrocyclization Toward the Partial Synthesis of Saudin

Metal-mediated coupling reactions are essential tools for the synthetic chemist and are among the most important methods for forming carbon-carbon bonds. Tandem reactions are also useful since they can rapidly and efficiently build up complex molecular architectures. With these key features in mind, a palladium-catalyzed tandem Stille-oxa-electrocyclization has been developed in our group based upon work toward the total synthesis of saudin (**1**).[1]

The key disconnection in our synthetic strategy for saudin (**1**) is the opening of the 2H-pyran **50** via a retro-oxa-electrocyclization to reveal oxatriene **51**, followed by disconnection across the C(5)-C(16) bond via a Stille coupling (Scheme A4.1.1). This reveals the relatively simple coupling partners **52c** and **53c**.

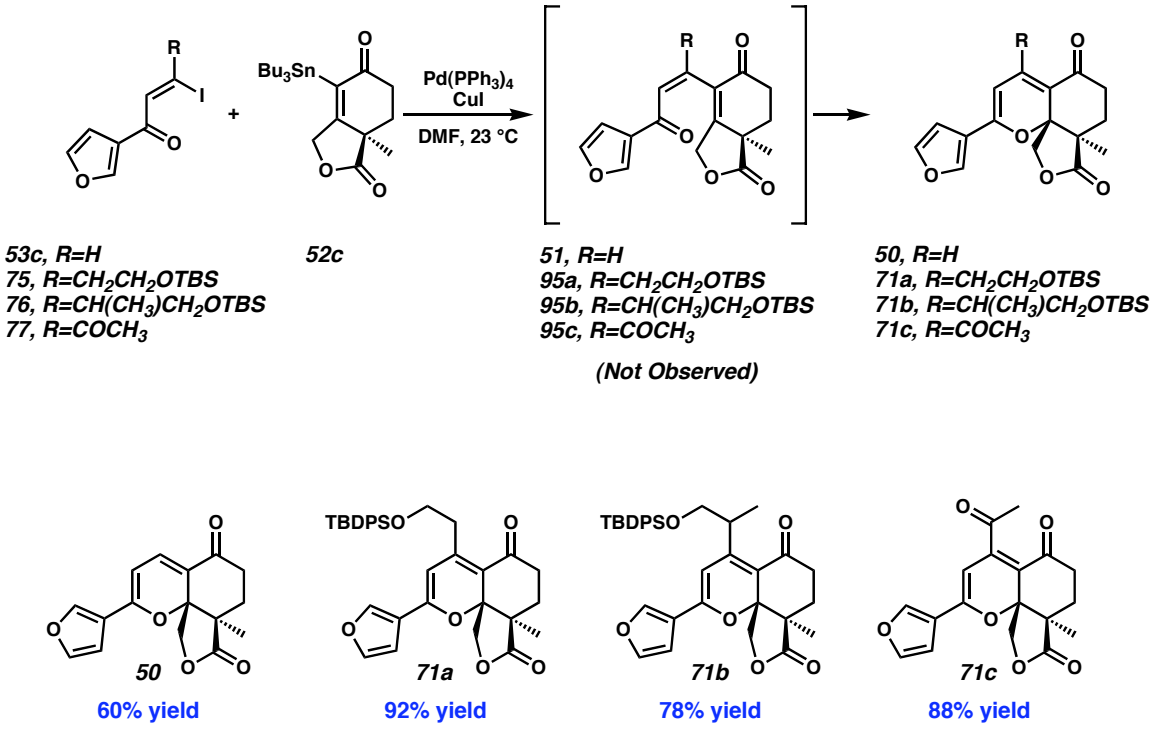
[†] This work was performed in collaboration with Taichi Kano, a postdoctoral scholar in the Stoltz group, and John F. Zepernick, a graduate student in the Stoltz group at the California Institute of Technology.

Scheme A4.1.1



When iodoenones **53c**, **75**, **76**, and **77** were treated with stannane **52c** under Cu(I)-accelerated Stille conditions, the desired coupling reactions occurred (Scheme A4.1.2). However, products **51** and **95a-c** were not observed. Instead, the substrates reacted further, undergoing an oxa-electrocyclization to yield substituted pyrans **50** and **71a-c**. This tandem reaction, which rapidly builds up the core structure of saudin, was selected for further investigation to evaluate its utility as a more general synthetic methodology.

Scheme A4.1.2

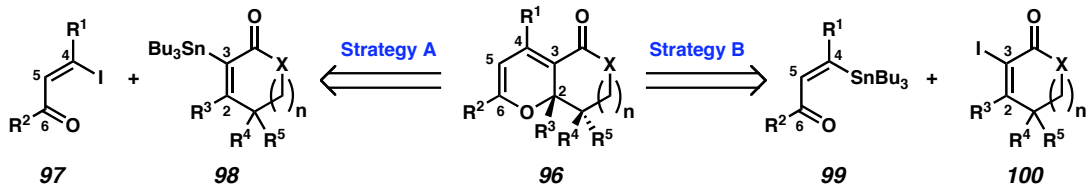


A4.1.2 An Alternate Tandem Stille-Oxa-Electrocyclization Strategy

The tandem Stille-oxa-electrocyclization has several interesting features: it is highly diastereoselective, convergent, and requires mild reaction conditions with low catalyst loading. These mild conditions are particularly noteworthy given the rather sterically hindered nature of the coupling partners. The reaction is also of interest since oxa-electrocyclizations are relatively under-utilized in organic synthesis. Recently there have been notable, though isolated, examples used in the syntheses of torreyanic acid by Porco[2], the epoxyquinols by Hayashi,[3] and the antimalarial naphthoquinones by Trauner.[4]

In pursuing this reaction as part of a general synthetic strategy for the formation of 2H-pyrans (**96**), we realized that there are two variants of this methodology: strategy A couples a 4-*cis*-iodoenone (**97**) with a 2-stannylenone (**98**), and strategy B couples a 4-*cis*-stannylenone (**99**) with a 2-iodoenone (**100**) (Scheme A4.1.3). Our earlier work had shown the viability of strategy A in the context of our synthetic efforts with saudin. Since different strategies may be better suited for different classes of pyrans, we were interested in expanding our tandem methodology by exploring the viability of strategy B. We were also interested in expanding the scope of this tandem reaction to include pyrans with varying substitution at positions 2, 3, and 6 of the ring system. We would like to now present our results on the development of a more general version of the tandem Stille-oxa-electrocyclization as a method for synthesizing highly substituted pyrans.

Scheme A4.1.3

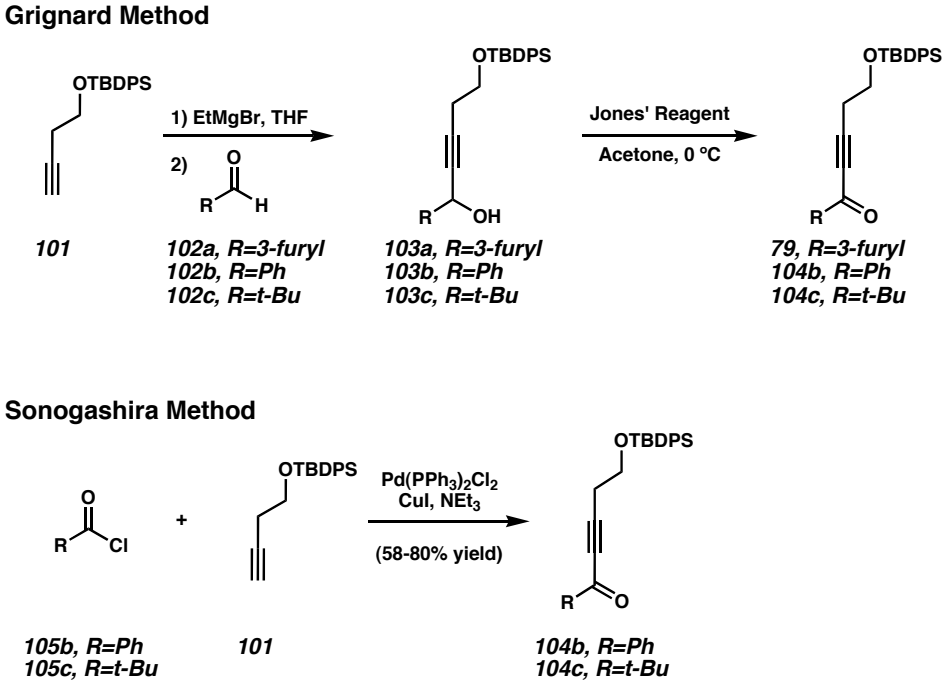


A4.2 Development of an Alternate Tandem Stille-Oxa-Electrocyclization Reaction

A4.2.1 Synthesis of the 4-*cis*-Stannylenone Substrates for the Tandem Stille-Oxa-Electrocyclization

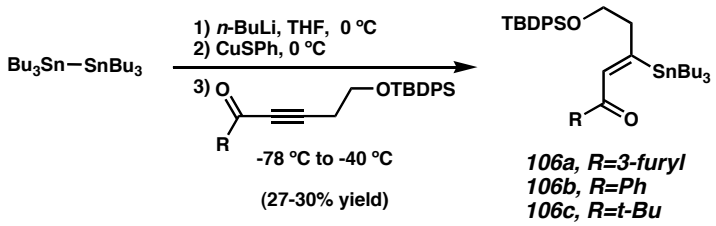
Two different routes were utilized to synthesize the 4-*cis*-stannylenone coupling partners for strategy B of our tandem methodology. The first route involved addition of a Grignard reagent into an aldehyde followed by a Jones' oxidation to form alkynones **79**, **104b**, and **104c** (Scheme A4.2.1). Alternatively, the same alkynones were made directly via a Sonogashira coupling between a terminal acetylene and an acid chloride (Scheme A4.2.1).[5]

Scheme A4.2.1



Alkynones **79**, **104b**, and **104c** were then converted to (Z)-vinyl stannanes (Scheme A4.2.2). Hexabutylditin was treated with *n*-butyl lithium, followed by the addition of copper thiophenol. This generated $(Bu_3Sn)CuSPhLi$ in situ, which was then reacted with alkynones **79**, **104b**, and **104c** to give vinyl stannanes **106a-c** with exclusively the desired olefin geometry.[6]

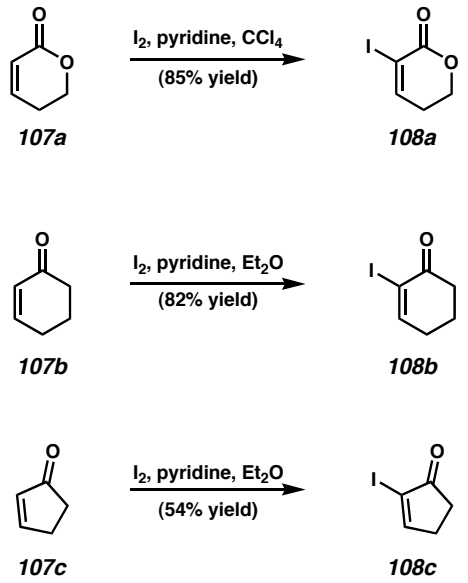
Scheme A4.2.2



A4.2.2 Synthesis of the 2-Iodoenone Substrates for the Tandem Stille-Oxa-Electrocyclization

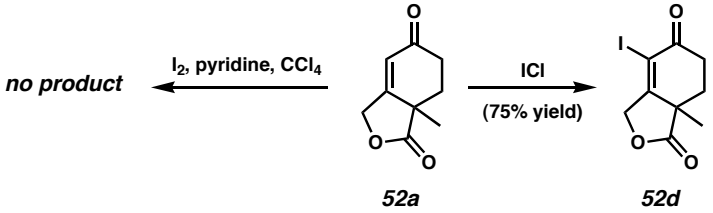
In order to examine the scope of the reaction, vinyl iodides **108a-c** were synthesized from the readily available enones **107a-c** (Scheme A4.2.3). These iodoenones feature varying ring sizes and differing amounts of steric bulk around the ring. In addition, vinyl iodide **108a** contains a lactone.

Scheme A4.2.3



Subjection of enone **52a** to the standard iodination conditions did not yield the desired product (Scheme A4.2.4). However, treatment with ICl provided iodoenone **52d** in good yield.

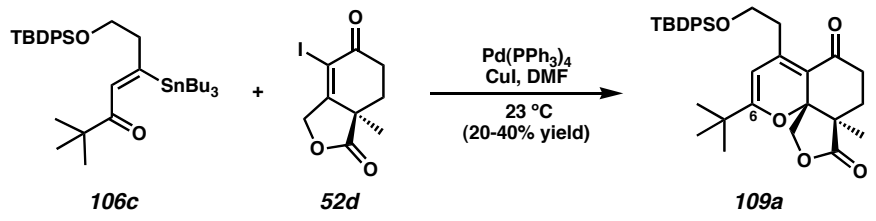
Scheme A4.2.4



A4.2.3 Optimization of the Alternate Tandem Stille-Oxa-Electrocyclization

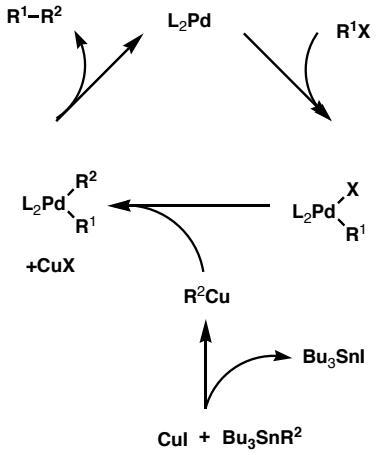
With a variety of stannanes and iodoenones in hand, the efficiency of the reaction was investigated. The bicyclic iodoenone **52d** served as a good test substrate to examine various substituents in the 6-position of the resulting 2H-pyran. Stannane **106c** successfully underwent both the Stille coupling and the oxa-electrocyclization in tandem when coupled to iodoenone **52d**. However, the reaction conditions that worked so well for strategy A of our tandem reaction were less successful for strategy B (Scheme A4.2.5). Pyran **109a** was produced in low and variable yields, presumably because of decomposition of 4-stannyl enone **106c**.

Scheme A4.2.5



Previous studies in our group demonstrated that copper(I) iodide was necessary for this Stille coupling to proceed. This copper effect in Stille couplings has been well studied,[7,8] and different mechanisms have been proposed depending upon the reaction medium.[9,10] In the case of very polar solvents such as DMF or NMP, copper(I) salts are believed to undergo Cu/Sn transmetallation, resulting in the formation of an organocopper species (Scheme A4.2.6).

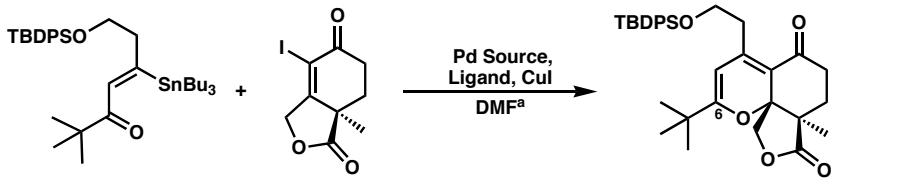
Scheme A4.2.6



In an attempt to further optimize our reaction, the amount of copper(I) iodide was varied. When substoichiometric amounts of copper(I) iodide were used, the stannane was not consumed, which suggested that somehow the presence of stoichiometric copper was leading to an undesired side reaction of the vinyl stannane (Table A4.2.1, entries 2 and 3). In two control experiments, iodoenone **52d** was excluded from the reaction (Table A4.2.1, entries 4 and 5). Decomposition of vinyl stannane **106c** was observed in the presence of copper(I) iodide (Table A4.2.1, entry 4), while no decomposition was seen in the absence of copper(I) iodide (Table A4.2.1, entry 5). From these results, it was

hypothesized that copper(I) was undergoing oxidation to a copper(II) species, which is known to facilitate the homocoupling of vinyl stannanes.[11] In order to test this hypothesis, the reaction was run in an inert atmosphere glovebox, thus rigorously excluding oxygen. To our delight, the desired product was obtained in high yield (Table A4.2.1, entry 6).

Table A4.2.1



106c *52d* *109a*

Entry	Pd Source	Ligand	CuI (mol%)	Other	Stannane consumed?	Yield
1	$Pd_2(dba)_3$	PPh_3	100%		yes	45%[b]
2	$Pd_2(dba)_3$	PPh_3	5%		no	trace
3	$Pd(PPh_3)_4$		0%		no	no reaction
4	$Pd(PPh_3)_4$		100%	no iodoenone 5a	yes	decomposition
5	$Pd(PPh_3)_4$		0%	no iodoenone 5a	no	no reaction
6	$Pd(PPh_3)_4$		100%	in glovebox	no	94%[b]

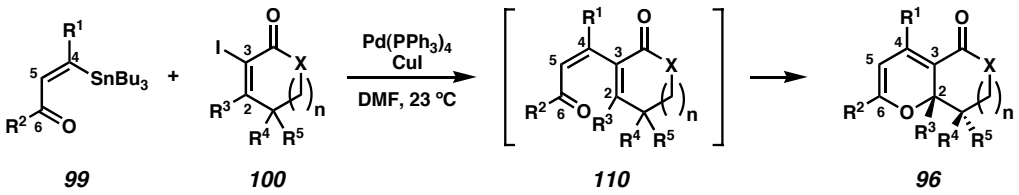
[a] 5 mol% Pd, 20 mol% ligand, 0.1 M in **5a**, 1 equiv **5a**, 1.2 equiv **14c**. [b] Isolated yield.

A4.2.4 Substrate Scope of the Alternate Tandem Stille-Oxa-Electrocyclization

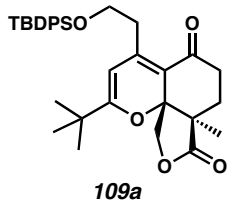
Having found that rigorously anaerobic conditions were optimal for this reaction, we examined other substrates. Vinyl stannes **106a**, **106b**, and **106c** (Scheme A4.2.2)

were successfully coupled with vinyl iodides **108a** (Scheme A4.2.3) and **52d** (Scheme A4.2.4) to produce pyrans **109a-e** and **71a** in good to excellent yields (Scheme A4.2.7).

Scheme A4.2.7

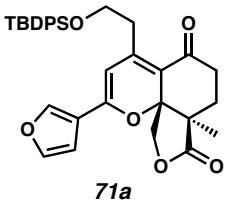


99 ***100*** ***110*** ***96***



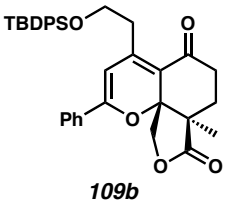
109a

94% yield



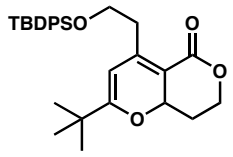
71a

92% yield



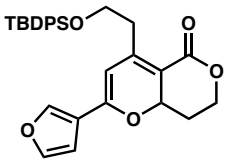
109b

94% yield



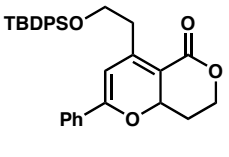
109c

67% yield



109d

65% yield



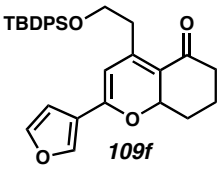
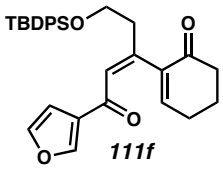
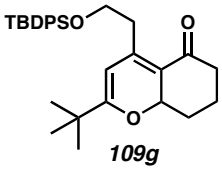
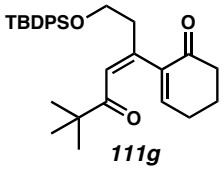
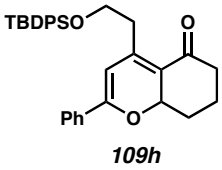
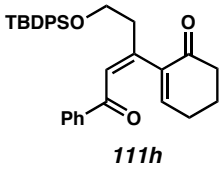
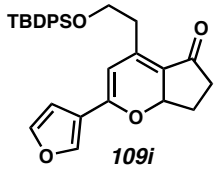
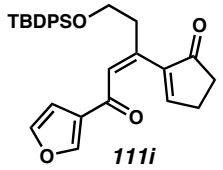
109e

92% yield

When we subjected vinyl iodides **108b** and **108c** (Scheme A4.2.3) to our tandem reaction conditions with various vinyl stannanes, the Stille couplings were successful, but the oxa-electrocyclizations yielded an equilibrium mixture of products (Table A4.2.2). These equilibrium mixtures were difficult to characterize because the species in solution were rapidly interconverting on the NMR timescale, causing the peaks in the NMR spectrum to be very broad. To alleviate this problem, the ^{1}H NMR spectra were taken at

–30 ºC. These products were obtained in useful yields and often in a good ratio of cyclized to uncyclized product.

Table A4.2.2

Cyclized Product	Uncyclized Product	Ratio (Cyclized:Uncyclized)[a]	Yieldb
 *109f*	 *111f*	7 : 1	90%
 *109g*	 *111g*	10 : 1	66%
 *109h*	 *111h*	10 : 1	73%
 *109i*	 *111i*	1 : 3	62%

[a] Ratio determined by 1H NMR spectroscopy. b Isolated yield.

A4.3 Theoretical Studies on the Tandem Stille-Oxa-Electrocyclization

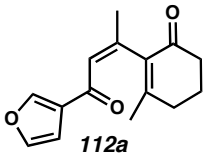
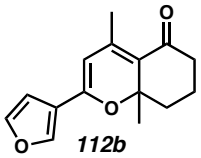
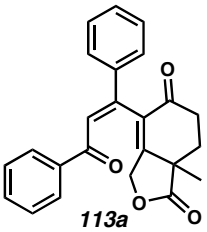
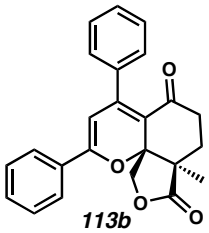
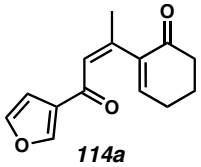
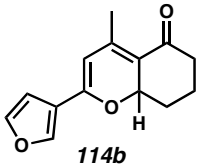
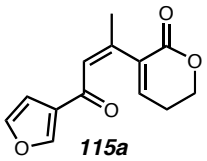
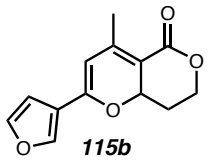
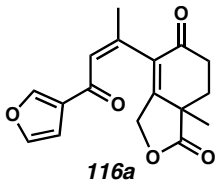
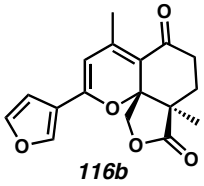
One of the key difficulties in developing the oxa-electrocyclization as a useful synthetic tool is a typically small – or even unfavorable – thermodynamic driving force

for the reaction. This often leads to the formation uncyclized products or equilibrium mixtures of products. Rather than relying solely on trial and error, we turned to theoretical calculations to examine substrates for the tandem Stille-oxa-electrocyclization reaction.

Using Spartan '02 for Macintosh, AM1 calculations were performed to evaluate the enthalpy of reaction for the conversion of 1,3,5-oxatriene to 2H-pyran (Table A4.3.1). In order to simplify the calculations, methyl groups were used to approximate longer alkyl groups in the 4-position of the pyran ring. The theoretical results agreed well with the experimental observations. In the cases where the calculated enthalpy was endothermic, the analogous 2H-pyran products were not observed experimentally (Table A4.3.1, entries 1 and 2). In the cases where the calculated enthalpy was exothermic, the 2H-pyrans were obtained as the major products from the tandem Stille-oxa-electrocyclization process (Table A4.3.1, entries 3, 4, and 5). While these methods are not as precise as higher level calculations,[12] they offer some degree of predictive power for evaluating potential oxa-electrocyclization substrates.

Table A4.3.1

Enthalpy of Reaction for Oxaelectrocyclizations

Entry	1,3,5-oxatriene	2H-pyran	ΔH (kcal/mol)[a]
1	 ***112a***	 ***112b***	2.046
2	 ***113a***	 ***113b***	0.083
3	 ***114a***	 ***114b***	-3.71
4	 ***115a***	 ***115b***	-3.84
5	 ***116a***	 ***116b***	-1.62

[a] AM1 result based on lowest energy conformation of 1,3,5-hexatriene and 2H-pyran.

A4.4 Conclusion

The tandem Stille-oxa-electrocyclization reaction is a general method for the synthesis of highly substituted 2H-pyrans. Versatility in this methodology has been

shown by developing both variants of this reaction (strategy A and strategy B). This work demonstrates the utility of tandem reactions for the construction of complex molecular architectures and also shows the potential of using oxa-electrocyclizations in synthesis.

A4.5 Experimental Section

A4.5.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using anhydrous, deoxygenated solvents. Commercially obtained reagents were used as received. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032 - 0.063 mm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a

Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer or a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

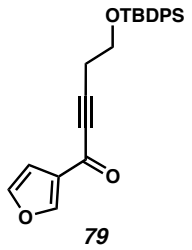
A4.5.2 Preparative Procedures

General Procedure for the Preparation of Propargyl Alcohols. A terminal alkyne (18 mmol, 1 equiv) was added to a stirred solution of ethyl magnesium bromide (18 mmol, 1 equiv) in Et_2O (10 mL) at 23 ºC. This reaction mixture was stirred for 30 min. Aldehyde (21 mmol, 1.2 equiv) was then added dropwise, and the reaction mixture was stirred until the reaction reached completion as determined by TLC. After quenching with 1 N HCl, the organic layer was washed three times with water and once with brine. The organic layer was separated and dried over $MgSO_4$. Following concentration in vacuo, the resulting crude mixture was carried on to the oxidation step without further purification.

General Procedure for the Preparation of Ynones by Jones' Oxidation. The crude propargyl alcohol (7.2 mmol, 1 equiv) was dissolved in acetone (15 mL). This solution was cooled to 0 ºC, and Jones' reagent (15 mmol, 2.1 equiv) was added slowly. After stirring for 30 min, the excess Jones' reagent was quenched with isopropanol. The

reaction mixture was extracted three times with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. After drying over $MgSO_4$ and concentrating in vacuo, the crude ynone was purified by flash chromatography.

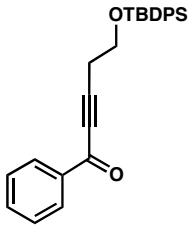
General Procedure for the Preparation of Ynones via the Sonogashira Reaction. A Schlenk tube was charged with CuI (0.2mmol, 2 mol%), $Pd(PPh_3)_2Cl_2$ (0.06 mmol, 0.5 mol%), and the terminal alkyne (10.8 mmol, 1 equiv). Next, NEt_3 (22 mL) was added to the Schlenk tube, and the mixture was degassed by the freeze-pump-thaw method. An acid chloride (14.2 mmol, 1.3 equiv) was then added dropwise to the reaction mixture at 23 ºC. After stirring for 12 h, water was added to the mixture, which was then extracted three times with pentane. The combined organic layers were washed thrice with water and once with brine and dried over $MgSO_4$. After concentrating in vacuo, the crude ynone was purified by flash chromatography.



79

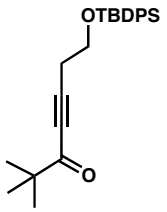
Ynone 79. Purification by flash chromatography (30:1 hexanes/EtOAc eluent) provided ynone **79** (51% yield) as a clear oil: ^{1}H NMR (300 MHz, CDCl3) δ 8.10 (dd, J = 1.3, 0.8 Hz, 1H), 7.75-7.66 (m, 5H), 7.48-7.35 (m, 6H), 6.81 (dd, J = 1.9, 0.8 Hz, 1H), 3.88 (t, J = 6.6 Hz, 2H), 2.68 (t, J = 6.5 Hz, 2H), 1.08 (s, 9H); ^{13}C NMR (75 MHz,

CDCl3) δ 171.3, 150.6, 144.6, 135.7, 135.0, 133.4, 130.1, 129.8, 129.4, 128.0, 127.9, 108.6, 90.6, 80.8, 61.7, 27.0, 26.8, 23.4, 19.4; IR (thin film/NaCl) 2931, 2858, 2217, 1642, 1428, 1308, 1164, 1112 cm^{-1}; HRMS (EI+) m/z calc'd for $[C_{25}H_{26}O_3Si]$+: 402.1651, found 402.1664.



104b

Ynone 104b. Purification by flash chromatography (8:1 hexanes:EtOAc eluent). Provided ynone **104b** (27% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17-8.14 (m, 2H), 7.73-7.69 (m, 4H), 7.583 (tt, *J* = 9.6, 1.5 Hz, 1H), 7.47-7.35 (m, 8H), 3.92 (t, *J* = 6.6 Hz, 2H), 2.748 (t, *J* = 6.6 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 136.8, 135.6, 134.0, 133.2, 129.9, 129.7, 128.5, 127.8, 93.8, 80.4, 61.5, 26.8, 23.5, 19.2; IR (thin film/NaCl) 2931, 2858, 2238, 2207, 1645, 1645, 1264, 1113 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{27}H_{27}O_2Si]^+$: 411.1780, found 411.1792.

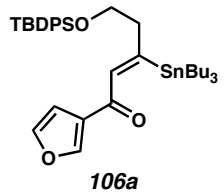


104c

Ynone 104c. Purification by flash chromatography (1:1 hexanes:DCM eluent) provided ynone **104c** (58% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (m, 4H), 7.4-7.36 (m, 6H), 3.83 (t, *J* = 6.6 Hz, 2H), 2.63 (t, *J* = 6.6 Hz, 2H), 1.20 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 135.6, 133.3, 129.8, 127.8, 92.6, 79.5, 61.5, 44.6, 26.8, 26.1, 23.3, 19.2; IR (thin film/NaCl) 2932, 2859, 2211, 1810, 1670 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{25}H_{31}O_2Si]^+$: 391.2093, found 391.2098.

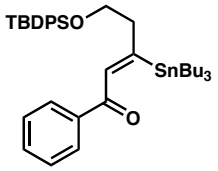
General Procedure for the Preparation of (Z)-Vinyl Stannanes. To a stirred solution of bis(tributyltin) (4.5 mmol, 1.2 equiv) in THF (40 mL) at 0 ºC was added *n*-butyllithium (4.5 mmol, 1.2 equiv). After stirring for 30 min, CuSPh (4.5 mmol, 1.2 equiv) was added. After an additional 30 min of stirring, the reaction mixture was cooled to –78 ºC. Alkynone (3.8 mmol, 1 equiv) was added slowly to the reaction mixture, which was stirred for 30 min at –78 ºC. The reaction was then warmed to –40 ºC, stirred for 1 h, and allowed to warm to room temperature. Saturated aqueous NH_4Cl was added to quench the reaction, and the mixture was extracted with Et_2O. To the separated organic layer was added methanol, forming a yellow slurry that was filtered through

celite. The filtrate was concentrated in vacuo to provide the crude (Z)-vinyl stannane, which was then purified by flash column chromatography.



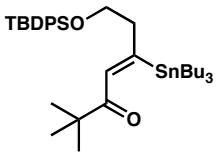
106a

Stannane 106a. Purification by flash chromatography (100:1 hexanes:EtOAc → 25:1 hexanes:EtOAc eluent) provided stannane **106a** (49% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.70-7.64 (m, 5H), 7.46-7.34 (m, 6H), 7.22 (s, 1H), 6.83 (d, *J* = 1.1 Hz, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 2.76 (t, *J* = 6.2 Hz, 2H), 1.58-1.35 (m, 6H), 1.35-1.19 (m, 6H), 1.05 (s, 9H), 0.96-0.77 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 173.7, 147.7, 144.2, 135.8, 135.4, 134.0, 129.9, 128.6, 127.9, 109.3, 62.9, 43.4, 29.5, 27.7, 27.1, 14.0, 11.3, 9.0; IR (thin film/NaCl) 2955.89, 2925.30, 1651.69, 1559.99, 1157.70, 1111.94 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{37}H_{53}O_3SiSn]^+$: 693.2786, found 693.2779.



106b

Stannane 106b. Purification by flash chromatography (10:1 hexanes:EtOAc → 6:1 hexanes:EtOAc eluent) provided stannane **106b** (31% yield) as a clear clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.70-7.67 (m, 4H), 7.63 (s, 1H), 7.55 (m, 1H), 7.48-7.35 (m, 8H), 3.79 (t, *J* = 6.6 Hz, 2H), 2.83 (t, *J* = 6.6 Hz, 2H), 1.48-1.42 (m, 6H), 1.29-1.25 (m, 6H), 1.06 (s, 9H), 0.99-0.93 (m, 6H), 0.85 (t, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 175.4, 138.3, 135.6, 134.1, 133.8, 132.6, 129.7, 128.5, 128.5, 127.7, 62.9, 43.5, 29.3, 27.5, 26.9, 19.3, 13.8, 11.2; IR (thin film/NaCl) 1651 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{39}H_{55}O_2SiSn]^+$: 703.2993, found 703.3007.

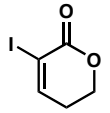


106c

Stannane 106c. Purification by flash chromatography (50:1 hexanes:EtOAc eluent) provided stannane **106c** (28% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (m, 4H), 7.46-7.35 (m, 6H), 7.11 (s, 1H), 3.70 (t, *J* = 6.65 Hz, 2H), 2.69 (t, *J* = 6.65 Hz, 2H), 1.44-1.34 (m, 6H), 1.26-1.22 (m, 7H), 1.13 (s, 9H), 1.04 (s, 9H), 0.89-0.81 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 171.4, 135.6, 133.8, 133.6, 129.6, 127.7,

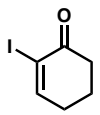
62.9, 43.2, 42.5, 29.3, 27.5, 26.9, 26.4, 19.2, 13.7, 11.0; IR (thin film/NaCl) 2956, 2857, 1671, 1113 cm^{-1}; HRMS (EI+) *m/z* calc'd for $[C_{33}H_{51}O_2SiSn]^+$: 627.2680, found 627.2666.

General Procedure for the Preparation of Iodoenones from I_2/Pyridine. The enone (1.16 mmol) was dissolved in CCl_4 or Et_2O (1 ml) and pyridine (1 ml). A solution of iodine (0.9 g, 3.4 mmol) in 1:1 pyridine : CCl_4 or Et_2O (6 mL) was then slowly added at 0 ºC. The reaction was quenched with aqueous sodium thiosulfate and the mixture was extracted with CH_2Cl_2. The organic layer was then washed once with brine and dried over $MgSO_4$. Following concentration in vacuo, the crude product was purified by flash chromatography.



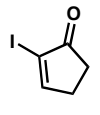
108a

Iodopyranone 108a. Purification by flash chromatography (10:1 hexanes:EtOAc eluent) provided iodopyranone **108a** (85% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (t, *J* = 4.65 Hz, 1H), 4.48 (t, *J* = 6 Hz, 2H), 2.52 (dt, *J* = 4.65, 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 154.4, 89.5, 67.0, 28.2; IR (thin film/NaCl) 1724 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_5H_6O_2I]^+$: 224.9413, found 224.9405.



108b

Iodocyclohexenone 108b. Purification by flash chromatography (4:1 hexanes:EtOAc eluent) provided iodocyclohexenone **108b** (82% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (t, *J* = 4.5 Hz, 1H), 2.70-2.66 (m, 2H), 2.47 (dt, *J* = 4.5, 6 Hz, 2H), 2.15-2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 159.5, 103.9, 37.3, 30.0, 22.9; HRMS (FAB+) *m/z* calc'd for $[C_6H_8OI]^+$: 222.9620, found 222.9622.

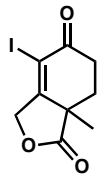


108c

Iodocyclopentenone 108c. Purification by flash chromatography (4:1 hexanes:EtOAc eluent) provided iodocyclopentenone **108c** (54% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dt, *J* = 0.9, 3 Hz, 1H), 2.78-2.74 (m, 2H), 2.50-2.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 169.7, 102. 9, 31.3, 31.0.

General Procedure for the Preparation of Iodoenones from ICl. The enone (6 mmol) was dissolved in CH_2Cl_2 (12 ml). A solution of ICl (1.0 M in CH_2Cl_2, 9.9 mL, 9.9 mmol) was then slowly added at 0 ºC. After 4 h, NEt_3 (1.4 mL, 9.9 mmol) was added at

0 °C. The mixture was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$. Following concentration in vacuo, the crude product was purified by flash chromatography.

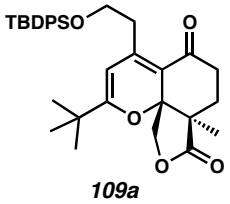


52d

Bicyclic Iodoenone 52d. Purification by flash chromatography (4:1 hexanes:EtOAc eluent) provided iodoenone **52d** (75% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (d, *J* = 15 Hz, 1H), 4.83 (d, *J* = 15 Hz, 1H), 2.86-2.81 (m, 2H), 2.31-2.13 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 176.8, 166.5, 99.1, 73.2, 46.0, 32.0, 29.5, 21.6; HRMS (FAB+) *m/z* calc'd for $[C_9H_{10}O_3I]^+$: 292.9675, found 292.9685.

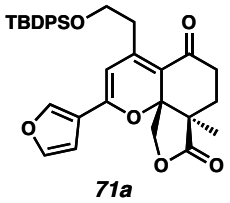
General Procedure for Tandem Stille-oxa-electrocyclization Reactions. $Pd(PPh_3)_4$ (0.0033 mmol, 5 mol%), CuI (0.057 mmol, 1 equiv), and the iodoenone (0.057 mmol, 1 equiv) were weighed into an oven-dried vial. The stannane (0.068 mmol, 1.2 equiv) was concentrated in vacuo from benzene in a separate flask. These materials were taken into the glovebox. The stannane was dissolved in DMF (0.7 mL), and the resulting solution was transferred into the vial containing the other reagents. The reaction was

stirred for 24 h. Water was then added, and the reaction mixture was extracted with Et_2O. The organic layer was dried by passing it through a short pad of silica gel. The material was concentrated in vacuo to yield the crude product, which could then be purified by flash column chromatography. Sometimes after flashing a compound, some alkyl tin contaminants remained. These were removed by dissolving the material in acetonitrile and washing three times with hexanes. Concentrating the acetonitrile layer in vacuo produced the desired product free of alkyl tin byproducts.



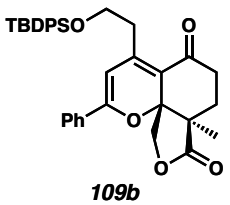
109a

***tert*-Butyl Appended Tricycle 109a.** Purification by flash chromatography (hexanes → 5:1 hexanes/EtOAc eluent) provided polycycle **109a** (94% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H), 7.46-7.33 (m, 6H), 5.45 (s, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 3.97-3.83 (m, 3H), 3.11 (dt, *J* = 12.0, 5.0 Hz, 1H), 2.84-2.75 (m, 1H), 2.62-2.46 (m, 1H), 2.38 (dt, 1H), 1.95 (q, *J* = 5 Hz, 2H), 1.47 (s, 3H), 1.11 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 179.4, 168.7, 151.8, 135.6, 133.7, 129.7, 127.7, 112.9, 103.4, 86.0, 71.4, 63.5, 44.9, 36.7, 35.7, 35.0, 27.8, 27.2, 26.9, 19.3, 14.7; IR (thin film/NaCl) 2932, 2858, 1787, 1663 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{34}H_{43}O_5Si]^+$: 559.2880, found 559.2878.



71a

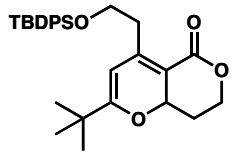
Furan Appended Tricycle 71a. Purification by flash chromatography (10:1 hexanes:EtOAc → 7:1 hexanes:EtOAc eluent) provided polycycle **71a** (92% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.66-7.61 (m, 4H), 7.45-7.32 (m, 7H), 6.46 (d, *J* = 2.1 Hz, 1H), 5.82 (s, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 3.97-3.88 (m, 3H), 3.10 (dt, *J* = 2.4, 6.0 Hz, 2H), 2.68-2.23 (m, 2H), 2.04-2.00 (m, 2H), 1.54 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 179.2, 151.5, 144.3, 143.1, 135.6, 133.7, 133.6, 129.7, 172.7, 120.7, 113.9, 107.3, 105.5, 86.5, 71.5, 63.3, 44.9, 36.6, 35.0, 27.8, 26.9, 19.3, 14.9; IR (thin film/NaCl) 2932, 2858, 1785, 1659, 1112 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{34}H_{37}O_6Si]^+$: 569.2359, found 569.2346.



109b

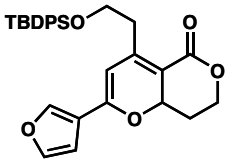
Phenyl Appended Tricycle 109b. Purification by flash chromatography (hexanes → 5:1 hexanes/EtOAc eluent) provided polycycle **109b** (94% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 5H), 7.39 (m, 10H), 6.15 (s, 1H), 4.76 (d, *J* =

11 Hz, 1H), 3.95 (m, 3H), 3.10 (t, *J* = 6 Hz, 2H), 2.58 (m, 1H), 2.44 (dt, *J* = 7.4, 13.5 Hz, 1H), 2.05 (m, 2H), 1.57 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 179.3, 156.4, 151.5, 135.6, 133.7, 132.1, 131.0, 129.7, 128.8, 127.7, 126.1, 114.2, 105.5, 86.7, 71.5, 63.3, 45.0, 36.7, 35.0, 27.8, 26.9, 19.3, 14.9; IR (thin film/NaCl) 2931, 2857, 1786, 1662 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{36}H_{39}O_5Si]^+$: 579.2567, found 579.2565.



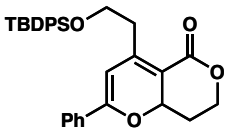
109c

***tert*-Butyl Appended Bicycle 109c.** Purification by flash chromatography (hexanes → 5:1 hexanes:EtOAc eluent) provided bicycle **109c** (67% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.44-7.33 (m, 6H), 5.54 (s, 1H), 4.44 (t, *J* = 5.3 Hz, 1H), 4.32 (m, *J* = 6 Hz, 1H), 4.18 (m, 1H), 3.07 (m, 1H), 2.88 (m 1H), 2.26 (q, *J* = 5.3 Hz, 2H), 1.12 (s, 9H), 1.0 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 164.9, 153.2, 135.7, 133.8, 129.6, 127.6, 105.0, 104.0, 72.8, 63.7, 63.5, 35.7, 35.6, 29.0, 27.9, 26.9, 19.2; IR (thin film/NaCl) 2960, 2858, 1706, 1543, 1113 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{30}H_{37}O_4Si]^+$: 489.2461, found 489.2473.



109d

Furan Appended Bicycle 109d. Purification by flash chromatography (hexanes → 10:1 hexanes:EtOAc eluent) provided polycycle **109d** (65% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.65 (d, *J* = 6.5 Hz, 4H), 7.41-7.26 (m, 7H), 6.49 (s, 1H), 5.91 (s, 1H), 4.67 (t, *J* = 5.0 Hz, 1H), 4.37-4.22 (m, 2H), 3.93 (t, *J* = 6.0 Hz, 2H), 3.11-3.01 (m, 2H), 2.33 (q, *J* = 5.0 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 153.9, 153.1, 144.2, 143.0, 135.9, 134.0, 131.1, 129.8, 127.9, 120.8, 108.0, 106.4, 73.1, 63.9, 63.3764, 35.9, 29.3, 27.1, 19.4; IR (thin film/NaCl) 2931, 2857, 1703, 1530, 1113 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{30}H_{33}O_5Si]^+$: 501.2097, found 501.2105.



109e

Phenyl Appended Bicycle 109e. Purification by flash chromatography (hexanes → 5:1 hexanes/EtOAc eluent) provided polycycle **109e** (92% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.67 (m, 5H), 7.31-7.42 (m, 10H), 6.25 (s, 1H), 4.70 (t, *J* = 5.5 Hz, 1H), 4.39 (m, 1H), 4.26 (m, 1H), 3.95 (t, *J* = 6.0 Hz, 2H), 3.15 (m, 1H), 3.05 (m, 1H), 2.39 (t, *J* = 6.0 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0,

159.1, 153.1, 135.9, 134.0, 132.4, 130.7, 129.8, 128.8, 127.9, 126.4, 106.5, 106.4, 73.3, 63.9, 63.6, 35.9, 29.3, 27.1, 19.4; IR (thin film/NaCl) 2931, 2857, 1703, 1532, 1104 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{32}H_{35}O_4Si]^+$: 511.2305, found 511.2315.

A4.6 Notes and References

(1) Tambar, U. K.; Kano, T.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2413-2416.

(2) (a) Li, C.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 10484-10485. (b) Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095-5106.

(3) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192-3194.

(4) (a) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554-9555. (b) Malerich, J. P.; Maimone, T. J.; Elliott, G. I.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276-6283.

(5) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777-778.

(6) For similar reaction conditions, see: Nielsen, T. E.; Cubillo de Dios, M. A.; Tanner, D. *J. Org. Chem.* **2002**, *67*, 7309-7313.

(7) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359-5364.

(8) Han, X.; Stoltz, B.M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

(9) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905-5911.

(10) A. L. Casado, Espinet, P. *Organometallics* **2003**, *22*, 1305-1309.

(11) Han, X.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1871-1872.

(12) For more rigorous calculations of simpler 1,3,5-oxatriene systems, see: Rodriguez-Otero, J. *J. Org. Chem.* **1999**, *64*, 6842-6848.

CHAPTER THREE

Development of the Direct Acyl-Alkylation of Arynes

3.1 Background and Introduction

3.1.1 A Brief History of Benzyne

In 1953, Professor John D. Roberts published a communication on the existence of benzyne (**117**), an electronically neutral and unstable benzene ring with a triple bond (Figure 3.1.1).[1] During the last 50 years, this discovery has had a profound impact on the field of organic chemistry.

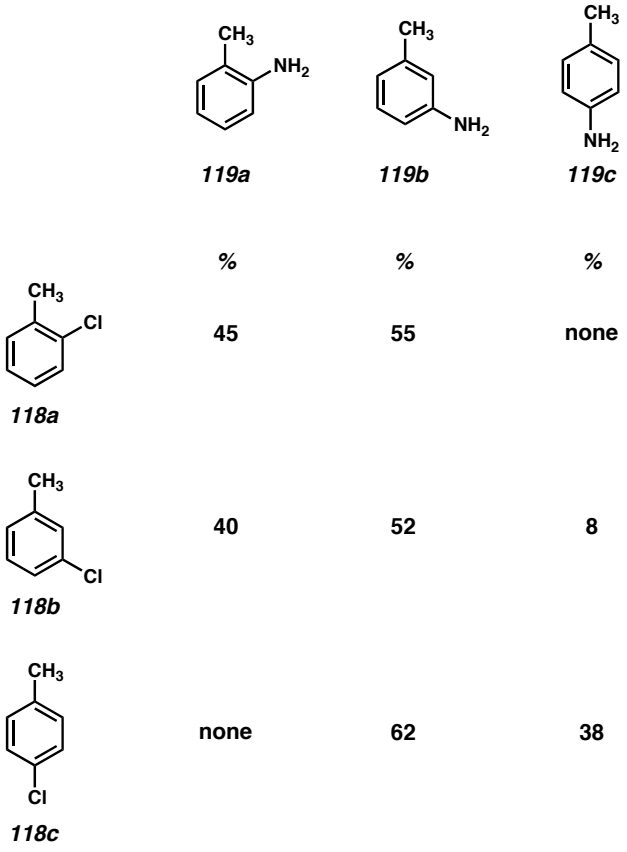
Figure 3.1.1

117

The discovery of benzyne (**117**) was made in the context of Professor Roberts' work to elucidate the mechanism for forming anilines from substituted chloroarenes and metal amides. Before 1953, many chemists believed that metal amides attacked the aromatic ring in an S_NAr fashion, but this mechanism could not account for all of the experimental data on the amination of unsymmetrical haloarenes. For example, while studying the distribution of amination products when sodium amide reacted with

chloromethylbenzenes **118a-c** (Scheme 3.1.1), Professor Roberts observed that both the 2- and 3-chloromethylbenzenes (**118a** and **118b**) formed a mixture of the 2- and 3-methylanilines (**119a** and **119b**).

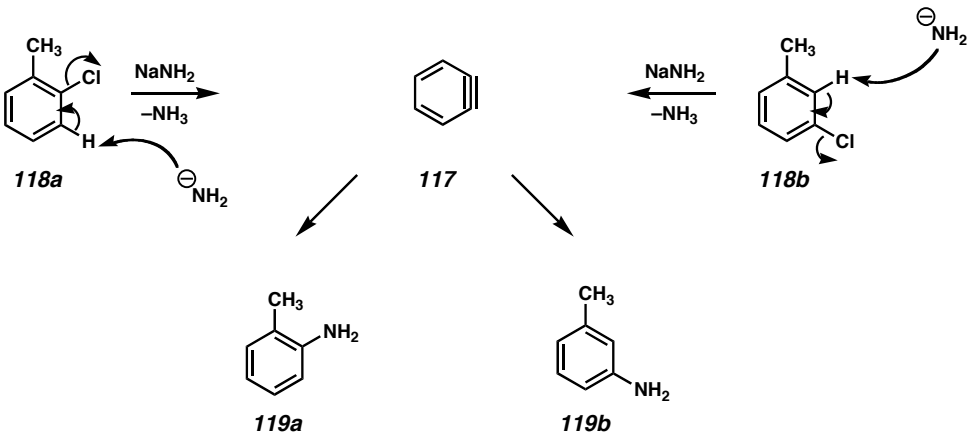
Scheme 3.1.1



Based on this observation and other related studies, Professor Roberts suggested the transient existence of benzyne (**117**) during the amination of halobenzenes (Scheme 3.1.2).[2] Detailed ^{14}C and ^{2}H labeling experiments on the mechanism of aminations of halobenzenes supported this idea.[3] In the last few decades, the existence of benzyne has been proposed to explain the observed reactivity of haloarenes in the presence of other

strong bases.[4] Although there has been some indirect evidence for benzyne based on spectroscopic data and isotope labeling experiments, benzyne was only trapped as a stable guest in hemicarcerand in 2001, 50 years after Professor Roberts' original discovery.[5]

Scheme 3.1.2



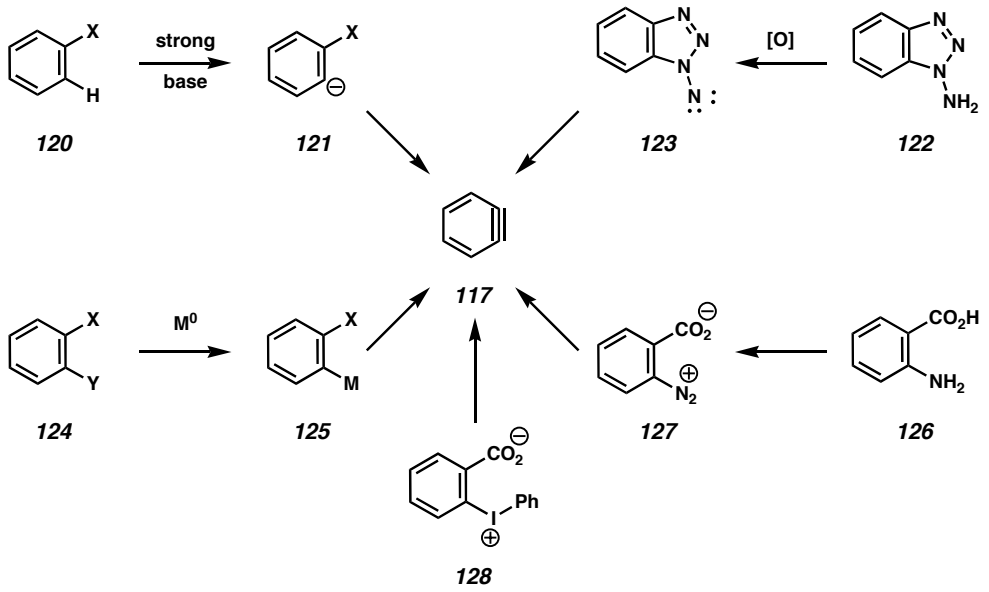
3.1.2 Generation of Arynes

While arynes have historically received much attention from physical organic chemists, their use as reagents in synthetic organic chemistry has been somewhat limited.[6] This is partially attributable to the strongly basic conditions needed to generate arynes and the often uncontrolled reactivity exhibited by these species, even at very low temperatures. Because of their extreme reactivity, arynes must be generated in situ and used immediately. This has limited their use in the development of selective organic

reactions because the harsh conditions that are used to generate arynes may have an adverse effect on other reactants.

Recent advances in the generation of arynes have increased the synthetic utility of these reactive intermediates. The most common methods for generating arynes are summarized in Scheme 3.1.3. Although these are useful methods, in many cases they are still incompatible with certain functionality. Specifically, they may lead to the deprotonation, oxidation, or reduction of other reactants.

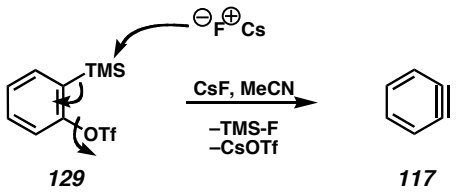
Scheme 3.1.3



In 1983 Kobayashi described a mild method for the in situ preparation of benzyne (**117**) at moderate temperatures that exploits the fluoride-induced elimination of *ortho*-silyl aryltriflates (e.g., **129**, Scheme 3.1.4).[7] Recently this method has been used to develop mild reactions involving aryne intermediates. This chapter details the use of

Kobayashi's aryne generation for the direct insertion of arynes into traditionally inert σ-bonds.[8]

Scheme 3.1.4

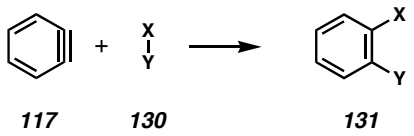


3.1.3 Aryne Insertion into Inert σ-bonds

The direct insertion into traditionally inert σ-bonds is a growing area of chemical research.[9] Specifically, insertions into C-H and C-C bonds are of great interest to synthetic chemists. One strategy for the activation of C-H and C-C bonds relies on the use of reactive reagents that are both kinetically and thermodynamically unstable and therefore more likely to react with these inert σ-bonds. Although Professor Roberts discovered benzyne 50 years ago, only recently have organic chemists realized the potential for this reactive intermediate to insert directly into σ-bonds (Scheme 3.1.5). In 2004, when we began our studies into the reactivity of benzyne, to the best of our knowledge there were still no reported methods on the direct insertion of arynes into C-H or C-C bonds. Nevertheless, there were several examples of aryne insertions into other inert σ-bonds, which produced *ortho*-disubstituted arene systems that would be difficult

to make otherwise (i.e., **131**, Scheme 3.1.5). These insertion reactions are presented in this section.

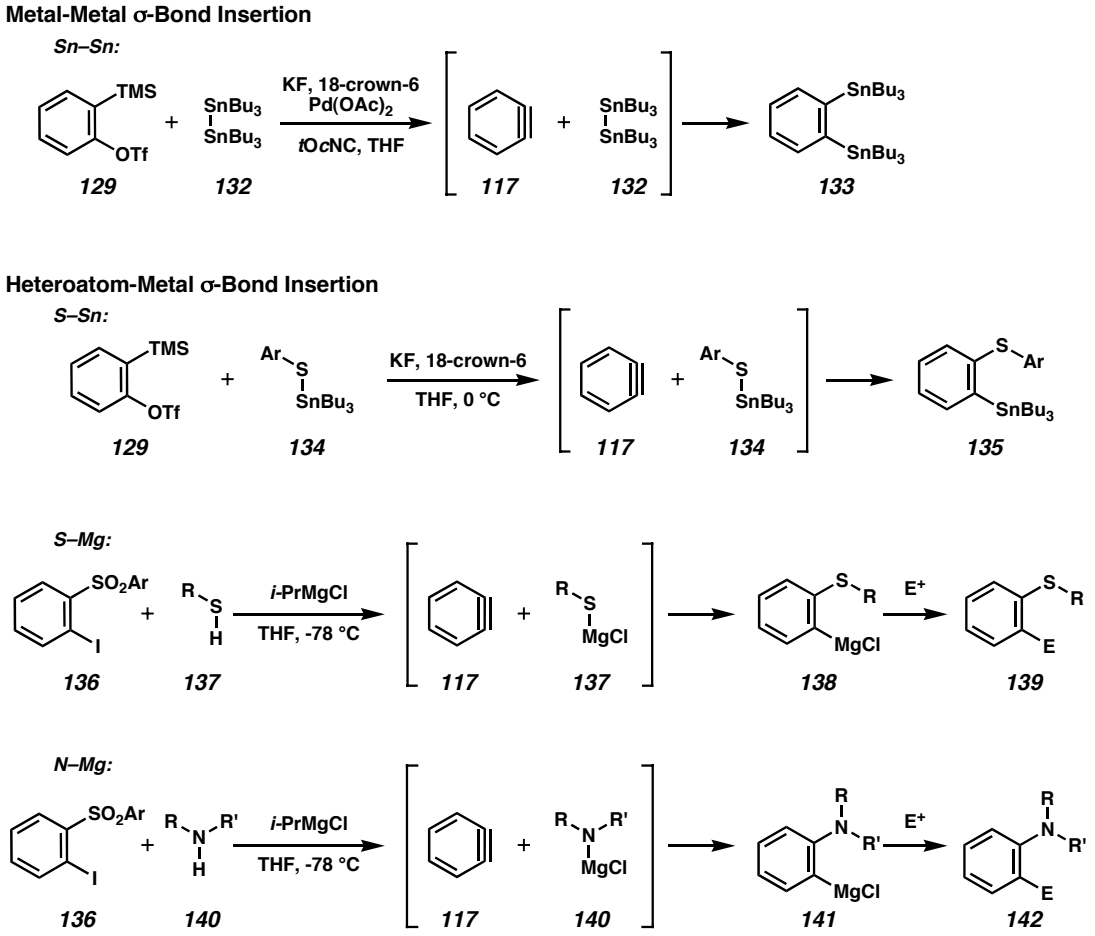
Scheme 3.1.5



117 ***130*** ***131***

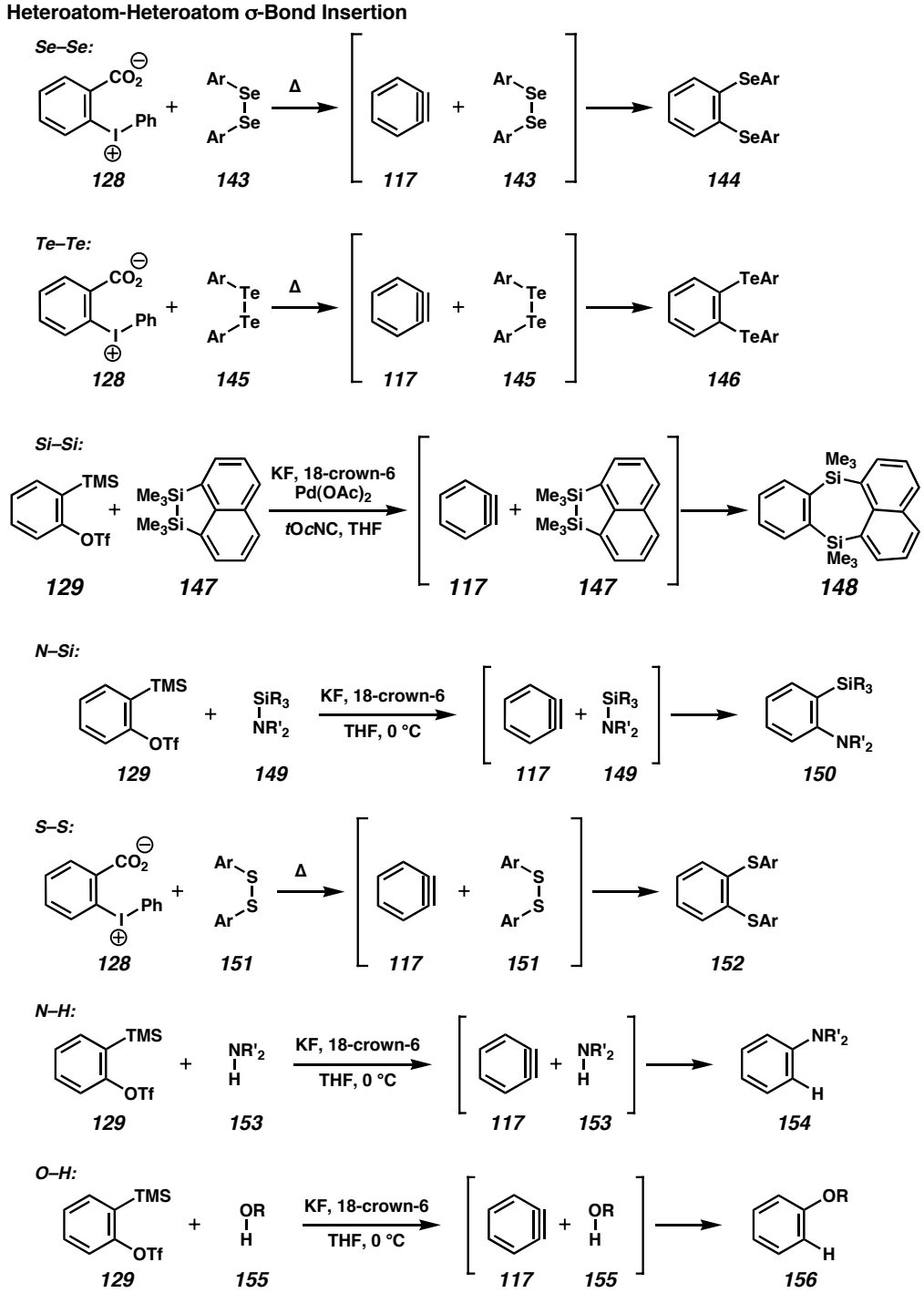
In many cases, σ-bonds containing metal atoms are more susceptible to insertion with arynes. As a result, arynes have been shown to insert into metal-metal σ-bonds, such as Sn-Sn,[10] and heteroatom-metal σ-bonds, such as S-Sn,[11] S-Mg, and N-Mg[12] (Scheme 3.1.6). The products of these reactions contain aryl-metal bonds, which may be further functionalized with electrophiles using known organic transformations (e.g., **139** and **142**).

Scheme 3.1.6



Arynes can also insert into heteroatom-heteroatom σ-bonds, including Se-Se, Te-Te,[13] Si-Si,[14] N-Si,[15] S-S,[16] N-H,[17] and O-H (Scheme 3.1.7).[18] Most notably, the N-H and O-H insertion reactions produce synthetically useful anilines (**154**) and phenols (**156**).

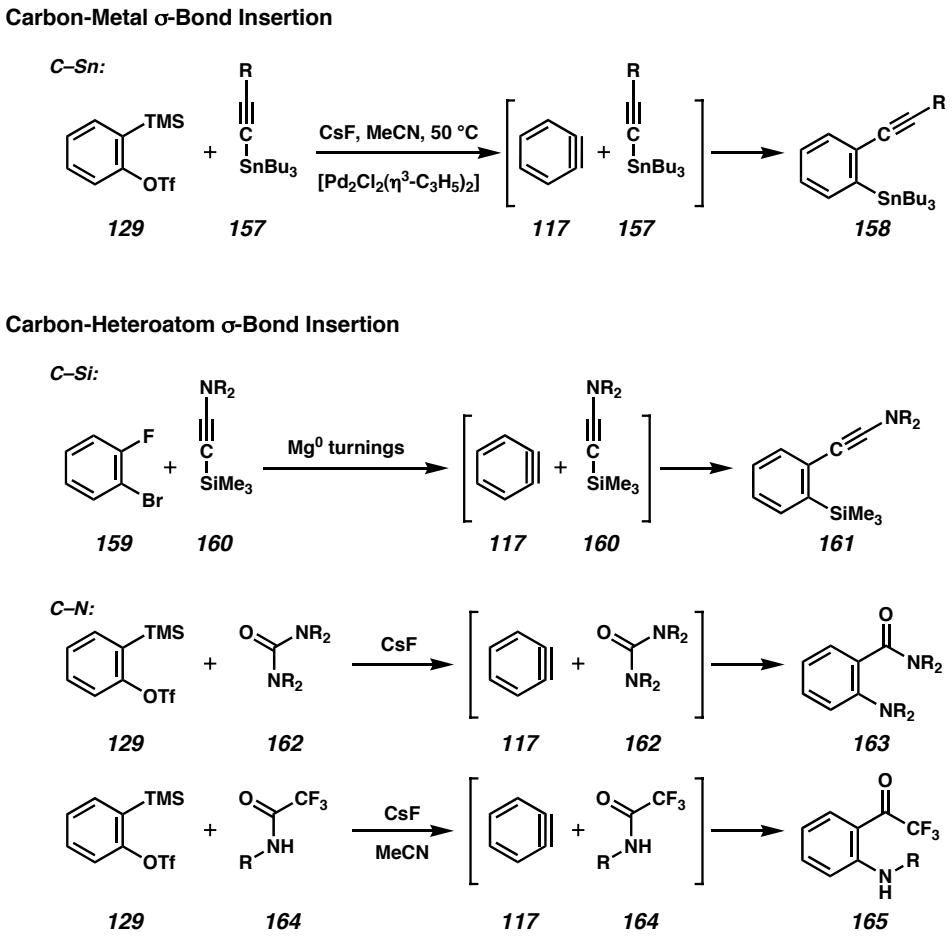
Scheme 3.1.7



The development of mild and direct aryne insertions into carbon containing σ-bonds would produce synthetically useful arenes in an efficient manner. Initial progress

in this area has focused on insertion into carbon-metal σ-bonds, including C-Sn (Scheme 3.1.8).[19] Recently, aryne insertions into carbon-heteroatom σ-bonds, such as C-Si[20] and C-N,[21] have also been reported.

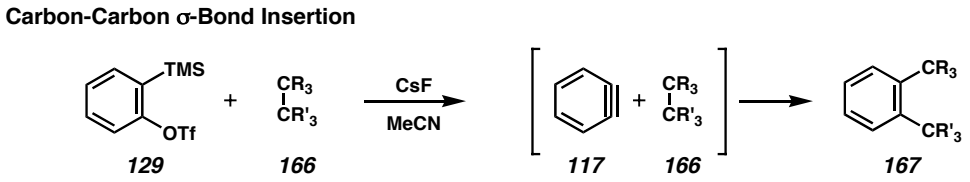
Scheme 3.1.8



Although there have been significant advances in the field of aryne insertion into σ-bonds, at the onset of our explorations into aryne chemistry there were no reports on the direct aryne insertion in C-C σ-bonds. These reactions would construct *ortho*-carbon-substituted arene frameworks (**167**) that are difficult to make by known methods (Scheme

3.1.9). In the next section, we describe our efforts to develop this mild and direct C-C insertion reaction.

Scheme 3.1.9



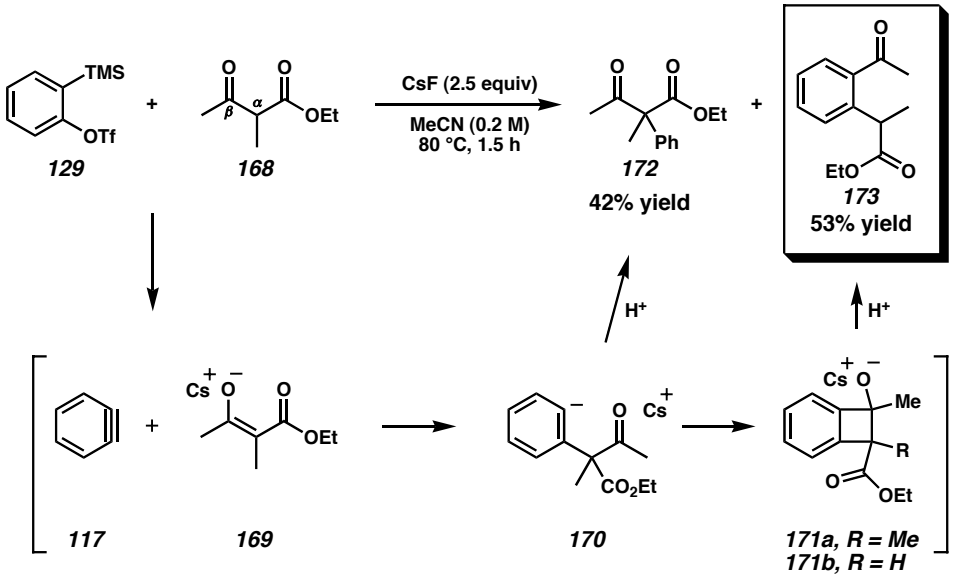
3.2 Development of the Acyl-Alkylation of Arynes

3.2.1 Serendipitous Discovery

As described in the previous section, in 1983 Kobayashi reported a mild method for the in situ preparation of benzyne (**117**) at moderate temperatures that exploits the fluoride-induced elimination of *ortho*-silyl aryltriflates (Scheme 3.1.4). We envisioned that arynes generated by this method could serve as a platform for the production of quaternary benzylic stereocenters. Specifically, we anticipated that the mild conversion of **129** to benzyne (**117**) in the presence of β-ketoester **168** would produce **172** (Scheme 3.2.1). To our surprise, in addition to obtaining the expected β-ketoester **172**, we observed the interesting *ortho*-substituted product **173** in comparable yield. The acyl-alkylation product **173** is the net result of benzyne insertion into the α,β C–C single bond of the β-ketoester, presumably by a formal [2+2] cycloaddition/fragmentation cascade

(i.e., **129→117→170→171a→173**). While aryne insertions into metal–metal, heteroatom-metal, heteroatom-heteroatom, carbon-metal, and carbon-heteroatom σ-bonds have been reported under mild conditions, we were intrigued by our result because it represents the first mild and direct aryne insertion into a carbon–carbon σ-bond.[22,23] The following sections will describe our explorations into the scope of this acyl-alkylation of arynes as an efficient method for the generation of interesting *ortho*-disubstituted arenes and benzannulated carbocycles.

Scheme 3.2.1

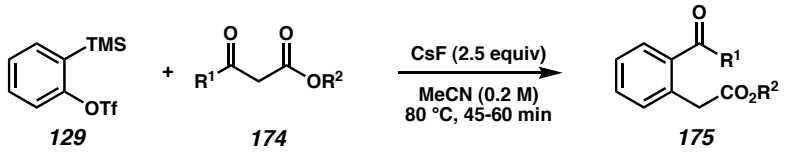


3.2.2 Acyl-Alkylation of Benzyne with Simple β-Ketoesters

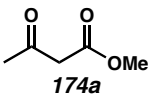
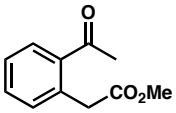
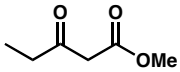
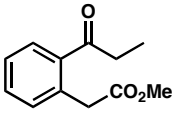
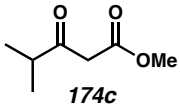
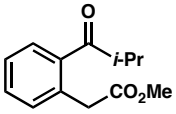
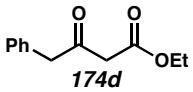
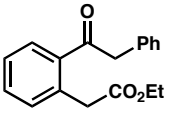
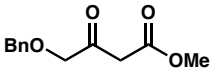
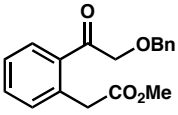
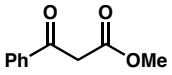
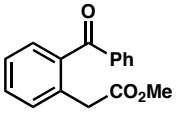
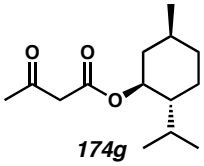
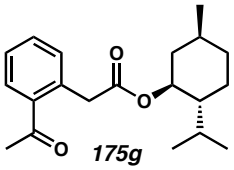
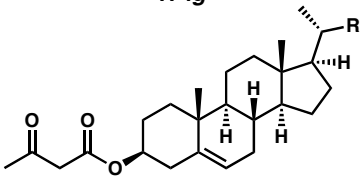
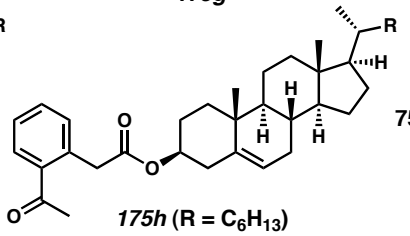
As we began our investigation into the formation of the acyl-alkylation product, we hypothesized that β-ketoesters lacking α-substitution might form the putative

benzocyclobutene intermediate (i.e., **171b**, Scheme 3.2.1) more readily, thus suppressing the α-arylation product. In support of this hypothesis, higher yields of the *ortho*-disubstituted product were obtained from the treatment of non α-substituted β-ketoesters (i.e., **174a-h**) with **129** in the presence of CsF (Table 3.2.1). The reaction tolerates substitution at the γ-position (entries 2-6), including aliphatic and aromatic groups. Heteroatoms may also be incorporated into the β-ketoester sidechain, albeit in slightly lower yields (entry 5). Additionally, the ester moiety can be varied while maintaining the efficiency of the reaction. For example, β-ketoesters of more complex alcohols such as menthol and cholesterol provide the desired acyl-alkylation products in good yield (entries 7 and 8). In general, the mild reaction conditions allow for a considerable degree of substitution on the β-ketoester subunit.

Table 3.2.1



129 *174* *175*

entry	*substrate* [a]	*product*	*yield* [b]
1	 *174a*	 *175a*	90%
2	 *174b*	 *175b*	78%
3	 *174c*	 *175c*	84%
4[c]	 *174d*	 *175d*	85%
5	 *174e*	 *175e*	53%
6	 *174f*	 *175f*	99%
7	 *174g*	 *175g*	72%
8	 *174h* (R = C_6H_{13})	 *175h* (R = C_6H_{13})	75%

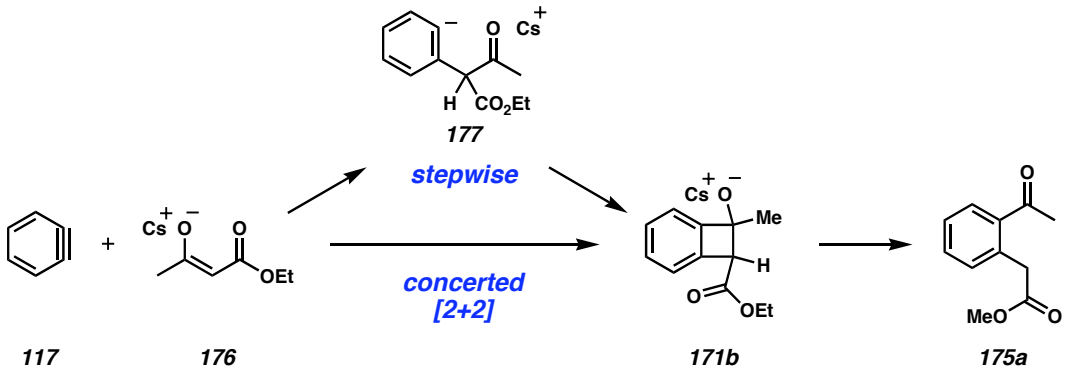
[a] 1.25 equiv of **129** relative to β-ketoester **174**. [b] Isolated yield.

[c] 2 equiv of **129** relative to **174d**.

3.2.3 Mechanistic Insight into the Acyl-Alkylation of Benzyne

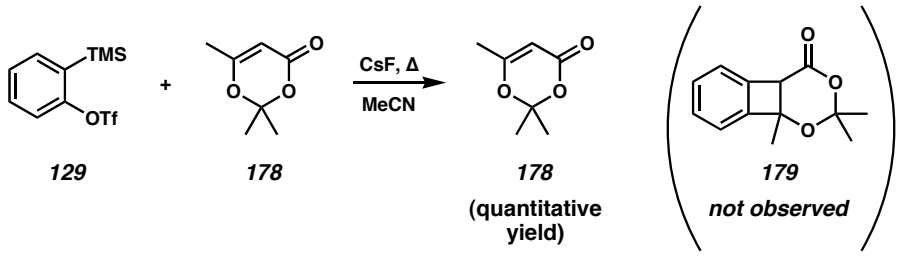
Although we were confident of the need to form the benzocyclobutene **171b** en route to the acyl-alkylated arene product **175a**, we were uncertain whether this four-membered ring structure was formed by a concerted [2+2] cycloaddition or in a more stepwise fashion (i.e., **117**→**177**→**171b**, Scheme 3.2.2).

Scheme 3.2.2



To probe this mechanistic subtlety, we subjected enol ether **178** to the reaction conditions (Scheme 3.2.3). This stable compound is a surrogate for enolate **176**. We reasoned that enol ether **178** would only be able to react with benzyne (**117**) in a concerted [2+2] fasion. Under the optimized reaction conditions, enol ether **178** was recovered in almost quantitative yield. Since the stepwise formation of benzocyclobutene **179** is inaccessible to enol ether **178**, we reasoned that the formation of the four-membered intermediate in the acyl-alkylation reaction must likely proceed in a stepwise fashion.

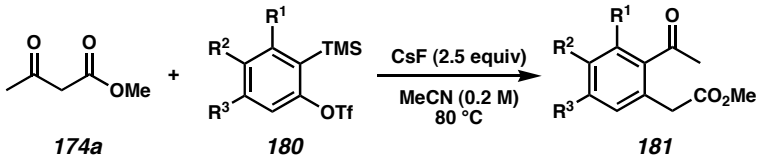
Scheme 3.2.3



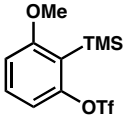
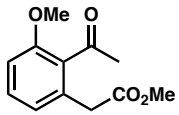
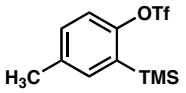
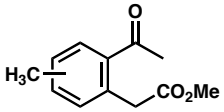
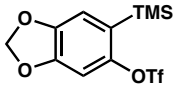
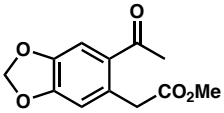
3.2.4 Acyl-Alkylation of Other Arynes

We next examined the coupling of substituted aryne precursors **180a-c** with methyl acetoacetate **174a** (Table 3.2.2). To our delight, this simple β-ketoester reacted with arynes possessing mono-substitution at the *ortho*- and *meta*-positions (entries 1-2) as well as disubstitution (entry 3) to produce high yields of the corresponding acyl-alkylation products (**181a-c**). Additionally, entries 1 and 3 demonstrate that heteroatom substituents are well tolerated. Of particular note is the complete regioselectivity and excellent isolated yield observed in the coupling of methoxy substituted aryne precursor **180a** with **174a**. This high selectivity points toward stepwise production of the key benzocyclobutene intermediate, analogous to the mechanism depicted in Scheme 3.2.3.

Table 3.2.2



174a *180* *181*

entry	*aryne precursor* [a]	*product*	*yield* [b]
1	 *180a*	 *181a*	95%
2[c]	 *180b*	 *181b*	82%[d]
3	 *180c*	 *181c*	75%

[a] 2 equiv of **180** relative to **174a**. [b] Isolated yield. [c] 1.25 equiv of **180b** relative to **174a**.

[d] Mixture of *meta*- and *para*- regioisomers (1.2 : 1).

3.2.5 Acyl-Alkylation of Benzyne with Cyclic β-Ketoesters: Ring Expansion

At this stage, we revisited β-ketoesters with α-substitution. We anticipated difficulty for such reactions based on our original observation that competitive formation of α-arylated products occurred, presumably due to steric congestion en route to the key benzocyclobutene. Nevertheless, we believed that these reactions could provide efficient access to an interesting class of structures that would otherwise be difficult to obtain. Specifically, we envisioned that cyclic β-ketoesters would undergo ring expansion to

furnish medium-sized carbocycles, which continue to be difficult structures to synthesize despite their prevalence in natural products and drug substances.[24] Gratifyingly, the expansion of a 5-membered ring (**182a**) furnished a 7-membered carbocycle (**185a**) in 50% yield (Scheme 3.2.4). We then applied our optimized conditions to a series of cyclic β-ketoesters of varying ring-size (Table 3.2.3). As a result, we were able to synthesize several 7-membered benzannulated structures in synthetically useful yields by employing 5-membered ring β-ketoesters (entries 1-3). While the insertion into a 6-membered ring was less efficient (entry 4), the expansion of a 7-membered ring furnished a 9-membered carbocycle in 69% yield (entry 5).

Scheme 3.2.4

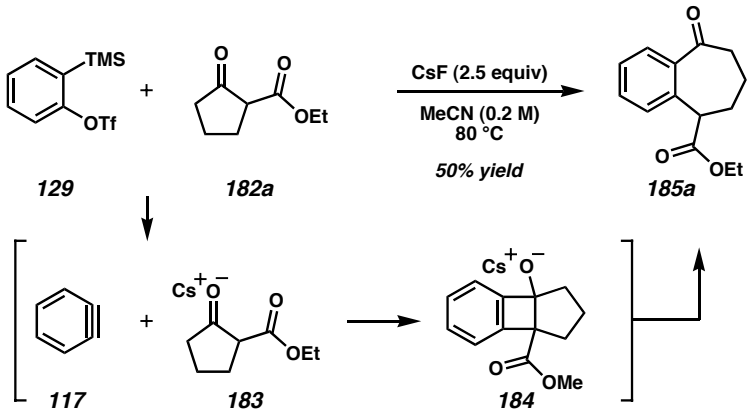
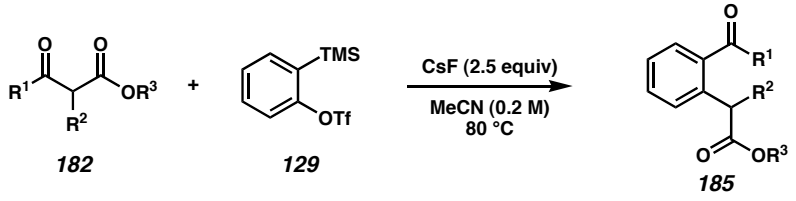
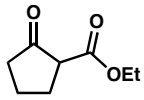
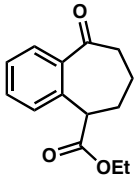
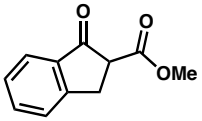
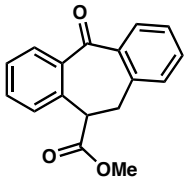
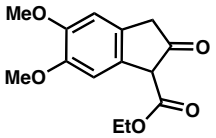
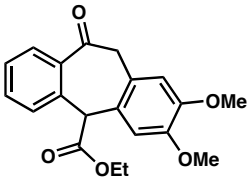
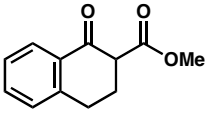
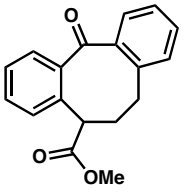
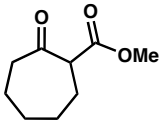
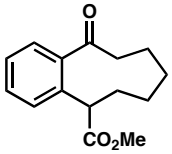


Table 3.2.3



entry	*substrate* [a]	*product*	*yield* [b,c]
1	 *182a*	 *185a*	50%
2	 *182b*	 *185b*	61%
3	 *182c*	 *185c*	65%
4	 *182d*	 *185d*	45%
5	 *182e*	 *185e*	69%

[a] 1.25 equiv of **129** relative to β-ketoester **182**. [b] Isolated yield. [c] In some cases the α-arylated β-ketoester was isolated as the major side product. See experimental section (3.4.3).

3.3 Conclusion

In summary, we have developed a mild, direct, and efficient process for the acyl-alkylation of arynes to produce interesting *ortho*-substituted arenes via an unusual reaction cascade. Overall, the transformation results in the formation of two new C–C bonds by the net insertion of an arene unit into the α,β C-C σ-bond of a β-ketoester. This facile methodology provides convergent, single-step, high-yielding access to a variety of substituted arenes and benzannulated structures that would otherwise be difficult to obtain. Notably, cyclic β-ketoesters can be expanded to generate medium-sized carbocycles.

3.4 Experimental Section

3.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry, deoxygenated solvents. Commercially obtained reagents were used as received. Cesium fluoride was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E.

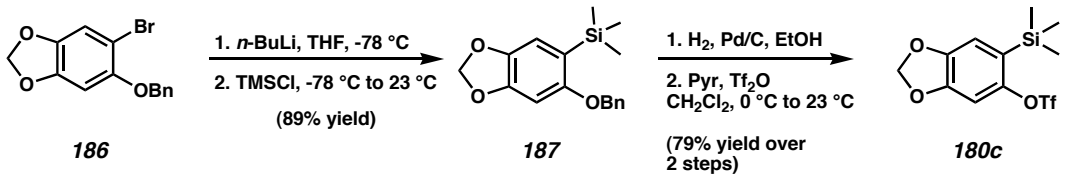
Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032 - 0.063 mm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{19}F NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to CF_3COOH (δ -76.54). Data for ^{19}F NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

3.4.2 Preparative Procedures

Synthesis of Aryne Precursors

Aryne precursor 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**129**) was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Aryne precursors 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**180a**)[25] and 4-

methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**180b**)[26] were prepared according to literature procedures.



186 *187* *180c*

Aryl intermediate 187. A flame-dried reaction flask equipped with a magnetic stir bar was charged with benzyl protected sesamol **186**[27] (325 mg, 1.06 mmol, 1.0 equiv) in THF (3.5 mL, 0.3 M), and the mixture was cooled to –78 °C in a dry ice/acetone bath. A 2.5 M solution of *n*-BuLi in hexanes (634 μL, 1.59 mmol, 1.5 equiv) was added slowly at -78 °C. After 15 min, TMSCl (200 μL, 1.59 mmol, 1.5 equiv) was added slowly at -78 °C. After 5 min the cold bath was removed and the reaction mixture was allowed to warm to 23 °C. After 15 min the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL). The organics were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided aryl intermediate **187** (282 mg, 89% yield) as a clear oil: R_F 0.57 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.29 (m, 5H), 6.85 (s, 1H), 6.53 (s, 1H), 5.91 (s, 2H), 5.01 (s, 2H), 0.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 149.6, 141.5, 137.3, 128.7, 128.0, 127.5, 119.3, 113.7, 101.3, 95.2, 71.0, -0.5; IR (thin film/NaCl) 2953, 2894,

1606, 1502, 1473, 1410, 1386, 1243, 1177, 1042 cm^{-1}; HRMS (EI^+) calc'd for $[C_{17}H_{20}O_3Si]^+$: *m/z* 300.1182, found 300.1187.

Aryne Precursor 180c. A reaction flask equipped with a magnetic stir bar was charged with aryl intermediate **187** (1.24 g, 4.13 mmol, 1 equiv) in absolute EtOH (17 mL, 0.25 M). To this mixture was added 10% Pd/C (440 mg, 0.413 mmol, 0.1 equiv), and the reaction vessel was stirred at 23 °C under a balloon of H_2 (1 atm). After 14 h the mixture was filtered through a short pad of celite (Et_2O eluent), and the solvent was evaporated under reduced pressure to afford a colorless oil, which was used immediately without further purification.

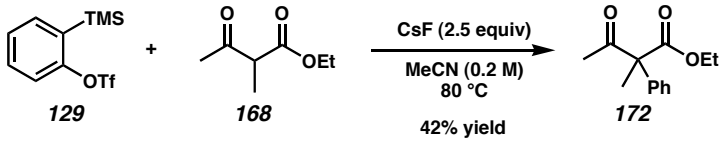
A flame-dried reaction flask equipped with a magnetic stir bar was charged with the *ortho*-silyl phenol in CH_2Cl_2 (20 mL, 0.2 equiv), and the mixture was cooled to 0 °C. Pyridine (1.05 mL, 13 mmol, 3 equiv) and Tf_2O (1.46 mL, 8.67 mmol, 2 equiv) were sequentially added, and the reaction mixture was allowed to warm to 23 °C. After 5.5 h the mixture was extracted with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organics were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (10:1 hexanes/CH_2Cl_2 eluent) provided aryne precursor **180c** (1.12 g, 79% yield) as a clear oil: R_F 0.54 (3:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.84 (s, 1H), 6.03 (s, 2H), 0.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 148.8, 147.1, 125.1, 113.4, 113.4, 102.6, 102.5, -0.5; ^{19}F NMR (300 MHz, $CDCl_3$) δ -74.63; IR (thin film/NaCl) 2960, 2903, 1479, 1422, 1247, 1216, 1141, 984, 843 cm^{-1}; HRMS (EI^+) calc'd for $[C_{11}H_{13}O_5F_3SiS]^+$: *m/z* 342.0205, found 342.0211.

Synthesis of β-Ketoester Substrates

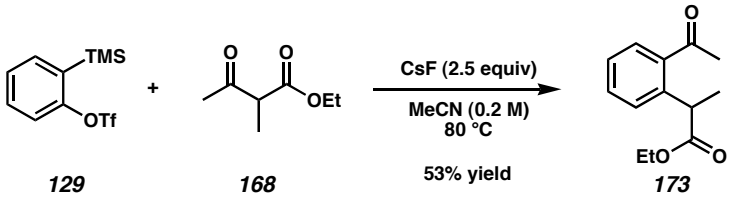
Methyl acetoacetate (**174a**), ethyl 2-methyl-3-oxobutanoate (**168**), ethyl 2-oxocyclopentanecarboxylate (**182a**), and methyl 2-oxocycloheptanecarboxylate (**182e**) were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Substrates **174b,**[28] **174c,**[29] **174d,**[30] **174e,**[31] **174f,**[32] **174g,**[33] **174h,**[34] **182b,**[35] **182c,**[36] and **182d**[37] were prepared according to literature procedures.

Representative procedure for the acyl-alkylation of arynes (Tables 3.2.1, 3.2.2, and 3.2.3): A flame-dried 11 cm long reaction tube equipped with a magnetic stir bar was charged with acetonitrile (2 mL). Methyl acetoacetate (**174a**) (43.2 μL, 0.4 mmol, 1.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**129**) (121.4 μL, 0.5 mmol, 1.25 equiv), and cesium fluoride (152 mg, 1.0 mmol, 2.5 equiv) were sequentially added to the flask. A septum was placed on the reaction vessel, and the mixture was then heated at 80 °C for 45-60 min. When benzyne precursor **129** was consumed by TLC analysis, the mixture was extracted with brine (4 mL). The aqueous layer was extracted with Et_2O (3 x 4 mL). The organics were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and purified by flash chromatography.

3.4.3 Spectral Data

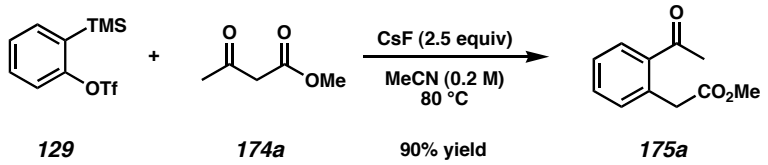


172. Purification by flash chromatography (20:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (37.1 mg, 42% yield) as a clear oil: R_F 0.36 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.10 (s, 3H), 1.77 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 172.1, 138.8, 128.8, 127.9, 127.5, 64.9, 61.8, 27.4, 21.6, 14.2; IR (thin film/NaCl) 2986, 1715, 1251 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{16}O_3]^+$: *m/z* 220.1100, found 220.1089.

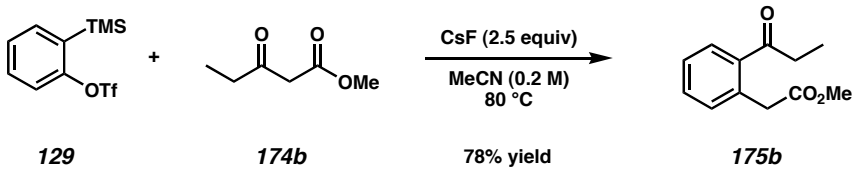


173. Purification by flash chromatography (20:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (46.4 mg, 53% yield) as a clear oil: R_F 0.42 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.49-7.29 (m, 3H), 4.41 (q, *J* = 7.0 Hz, 1H), 4.17-4.05 (m, 2H), 2.59 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 174.8, 140.4, 137.8,

132.0, 129.3, 128.8, 126.9, 60.8, 41.7, 29.9, 18.4, 14.3; IR (thin film/NaCl) 2982, 1731, 1687, 1201 cm^{-1}; HRMS (EI^+) calc'd for $[C_{13}H_{16}O_3]^+$: *m/z* 220.1100, found 220.1091.

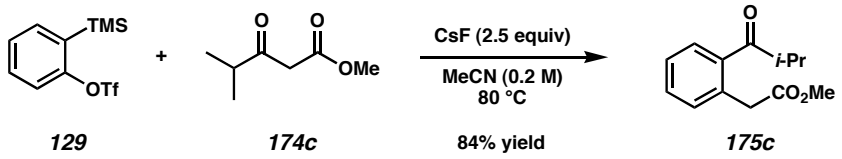


175a. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (69 mg, 90% yield) as a clear oil: R_F 0.46 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.47-7.33 (m, 2H), 7.24-7.20 (m, 1H), 3.91 (s, 2H), 3.66 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 172.0, 137.1, 134.4, 132.8, 132.1, 130.1, 127.5, 51.9, 40.2, 28.8; IR (thin film/NaCl) 3001, 2952, 1739, 1683 cm^{-1}; HRMS (EI^+) calc'd for $[C_{11}H_{12}O_3]^+$: *m/z* 192.0787, found 192.0787.

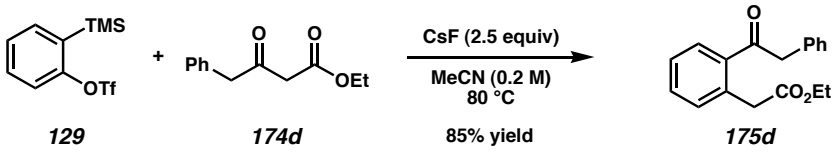


175b. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (64.7 mg, 78% yield) as a clear oil: R_F 0.32 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.48-

7.31 (m, 2H), 7.26-7.22 (m, 1H), 3.92 (s, 2H), 3.68 (s, 3H), 2.97 (q, *J* = 7.3 Hz, 2H), 1.18 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 172.2, 137.7, 134.2, 132.7, 131.8, 129.1, 127.5, 52.0, 40.1, 34.0, 8.4; IR (thin film/NaCl) 2979, 2951, 1739, 1685, 1225, 1165 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{12}H_{14}O_3]^+$: *m/z* 206.0943, found 206.0933.

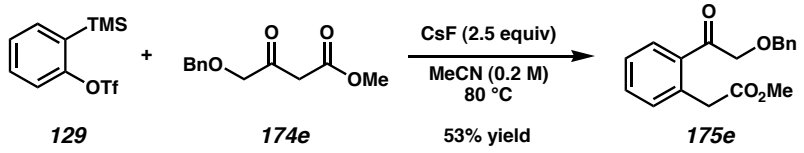


175c. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (71.9 mg, 84% yield) as a clear oil: R_F 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 1H), 7.53-7.25 (m, 3H), 3.91 (s, 2H), 3.72 (s, 3H), 3.56-3.44 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 172.2, 137.2, 134.7, 132.9, 131.7, 128.9, 127.5, 52.0, 40.0, 37.7, 19.0; IR (thin film/NaCl) 2973, 1741, 1683, 1229, 1165 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{16}O_3]^+$: *m/z* 220.1100, found 220.1094.



129 *174d* 85% yield *175d*

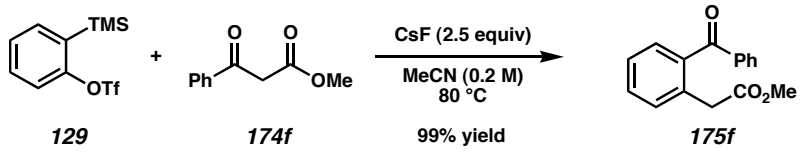
175d. Purification by flash chromatography (20:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (95.5 mg, 85% yield) as a clear oil: R_F 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.49-7.24 (m, 8H), 4.28 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 2H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 171.7, 137.6, 134.7, 132.8, 131.9, 129.8, 129.4, 128.8, 128.7, 127.5, 127.0, 60.9, 47.8, 40.1, 14.4; IR (thin film/NaCl) 3362, 2982, 1732, 1690, 1216, 1175 cm^{-1}; HRMS (EI^+) calc'd for $[C_{18}H_{18}O_3]^+$: *m/z* 282.1256, found 282.1266.



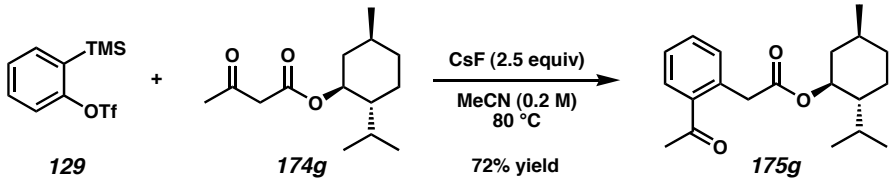
129 *174e* 53% yield *175e*

175e. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (66.2 mg, 53% yield) as a clear oil: R_F 0.28 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.48 (app. dt, *J* = 7.6, 1.4 Hz, 1H), 7.41-7.27 (m, 7H), 4.68 (s, 2H), 4.67 (s, 2H), 3.97 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 172.1, 137.5, 135.3, 134.7, 132.9,

132.4, 129.0, 128.7, 128.3, 128.2, 127.5, 73.6, 73.4, 52.2, 39.7; IR (thin film/NaCl) 3030, 2950, 1736, 1700, 1230, 1213, 1167, 1110 cm^{-1}; HRMS (EI^+) calc'd for (M-H) $[C_{18}H_{17}O_4]^+$: *m/z* 297.1127, found 297.1136.

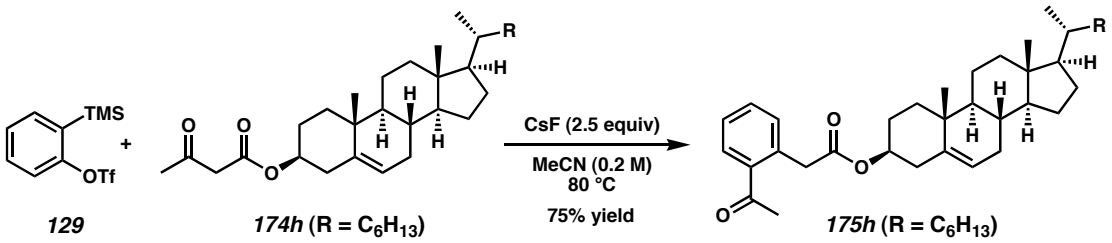


175f. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (101 mg, 99% yield) as a clear oil: R_F 0.38 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.79 (m, 1H), 7.61-7.54 (m, 1H), 7.50-7.30 (m, 7H), 3.90 (s, 2H), 3.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 171.8, 138.4, 137.9, 134.1, 133.1, 131.9, 131.0, 130.5, 130.2, 128.4, 126.7, 52.0, 38.8; IR (thin film/NaCl) 2951, 1739, 1662, 1270 cm^{-1}; HRMS (EI^+) calc'd for $[C_{16}H_{14}O_3]^+$: *m/z* 254.0943, found 254.0952.



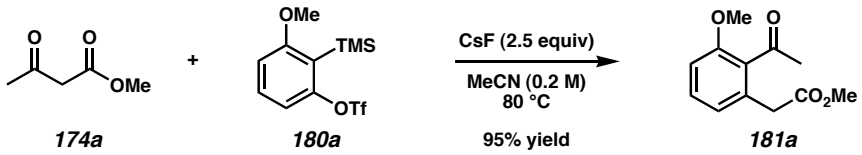
175g. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (90.7 mg, 72% yield) as a clear oil: R_F 0.50

(3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.51-7.34 (m, 2H), 7.28 (dd, *J* = 7.4, 1.1 Hz, 1H), 4.76-4.66 (m, 1H), 3.97 (s, 2H), 2.62 (s, 3H), 2.11-2.02 (m, 1H), 1.98-1.86 (m, 1H), 1.75-1.64 (m, 2H), 1.58-1.33 (m, 3H), 1.11-1.00 (m, 2H), 0.93 (d, *J* = 4.3 Hz, 3H), 0.91 (d, *J* = 5.1 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 171.3, 137.7, 134.6, 132.7, 131.9, 129.8, 127.4, 74.8, 47.2, 41.0, 40.6, 34.4, 31.6, 29.0, 26.3, 23.6, 22.2, 20.9, 16.5; IR (thin film/NaCl) 2955, 2929, 2870, 1732 1687, 1258, 1172 cm^{-1}; HRMS (EI^{+}) calc'd for $[C_{20}H_{28}O_3]^{+}$: *m/z* 316.2039, found 316.2034.

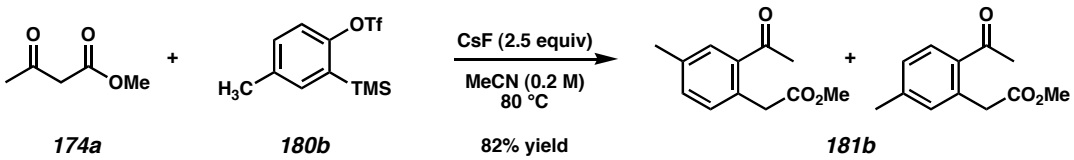


175h. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (163.5 mg, 75% yield) as a clear oil: R_F 0.50 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.48-7.33 (m, 2H), 7.24 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.36 (d, *J* = 5.1 Hz, 1H), 4.72-4.55 (m, 1H), 3.91 (d, *J* = 1.6 Hz, 2H), 2.59 (s, 3H), 2.35 (d, *J* = 7.7 Hz, 2H), 2.05-1.76 (m, 5H), 1.70-1.05 (m, 21H), 1.02 (s, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.86 (dd, *J* = 6.5, 1.2 Hz, 6H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 171.2, 139.9, 137.5, 134.7, 132.8, 132.1, 130.0, 127.5, 122.7, 74.6, 56.9, 56.3, 50.2, 42.5, 40.7, 39.9, 39.7, 38.2, 37.2, 36.8, 36.4, 36.0, 32.1, 32.0, 29.0, 28.4, 28.2, 27.9, 24.5, 24.0, 23.0, 22.8, 21.2, 19.5, 18.9, 12.0; IR

(thin film/NaCl) 3451, 2946, 2868, 1732, 1686, 1258, 1170 cm^{-1}; HRMS (EI^+) calc'd for $[C_{37}H_{54}O_3]^+$: *m/z* 546.4073, found 546.4080.

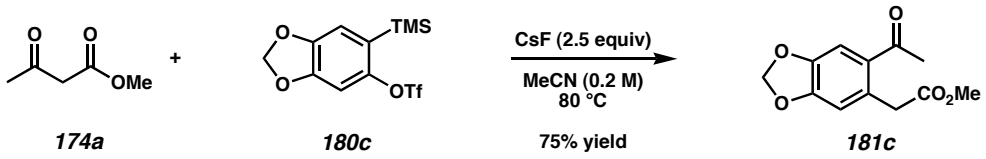


181a. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (84.6 mg, 95% yield) as a clear oil: R_F 0.29 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 1H), 6.90-6.81 (m, 2H), 3.84 (s, 3H), 3.68 (s, 2H), 3.66 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 171.9, 157.3, 132.7, 131.2, 130.8, 123.6, 110.4, 55.8, 52.2, 38.3, 32.3; IR (thin film/NaCl) 3005, 2952, 2842, 1738, 1691, 1598, 1583, 1471, 1438, 1351, 1267 cm^{-1}; HRMS (EI^+) calc'd for $[C_{12}H_{14}O_4]^+$: *m/z* 222.0892, found 222.0892.

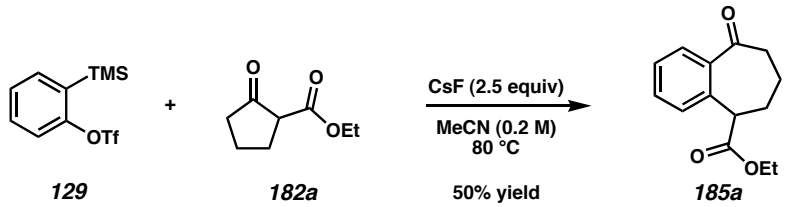


181b. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation products as a 1.2:1 mixture of inseparable isomers (67.9 mg, 82% yield) as a clear oil: R_F 0.26 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz,

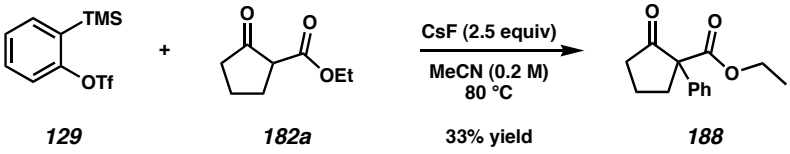
$CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.05 (s, 1H), 3.90 (s, 2H), 3.89 (s, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 2.58 (s, 3H), 2.56 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 200.7, 172.4, 172.3, 143.0, 137.3, 137.1, 134.9, 134.3, 133.9, 132.9, 132.7, 131.5, 130.9, 130.8, 129.6, 128.2, 52.0, 40.6, 39.9, 28.9, 28.8, 21.6, 21.2; IR (thin film/NaCl) 2952, 1740, 1680 cm^{-1}; HRMS (EI^+) calc'd for $[C_{12}H_{14}O_3]^+$: *m/z* 206.0943, found 206.0945.



181c. Purification by flash chromatography (7:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (70.7 mg, 75% yield) as a clear oil: R_F 0.18 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.70 (s, 1H), 6.03 (s, 2H), 3.84 (s, 2H), 3.69 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 172.2, 150.6, 146.9, 131.2, 130.7, 113.0, 110.5, 102.2, 52.0, 40.7, 28.9; IR (thin film/NaCl) 1738, 1678, 1613, 1507, 1491, 1375, 1274, 1245 cm^{-1}; HRMS (EI^+) calc'd for $[C_{12}H_{12}O_5]^+$: *m/z* 236.0685, found 236.0692.

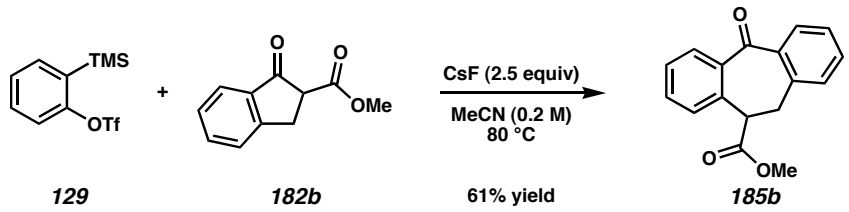


185a. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (46.9 mg, 51% yield) as a clear oil: R_F 0.32 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.51-7.40 (m, 1H), 7.42-7.35 (m, 1H), 7.22-7.18 (m, 1H), 4.25-4.16 (m, 2H), 4.02 (dd, *J* = 7.4, 5.6 Hz, 1H), 2.84-2.73 (m, 1H), 2.70-2.57 (m, 1H), 2.47-2.33 (m, 1H), 2.16-2.03 (m, 1H), 1.92-1.76 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 173.4, 139.7, 136.8, 132.1, 128.8, 128.7, 127.8, 61.4, 49.0, 41.0, 28.5, 20.4, 14.2; IR (thin film/NaCl) 2939, 1730, 1681, 1254, 1188 cm^{-1}; HRMS (EI^+) calc'd for $[C_{14}H_{16}O_3]^+$: *m/z* 232.1100, found 232.1095.

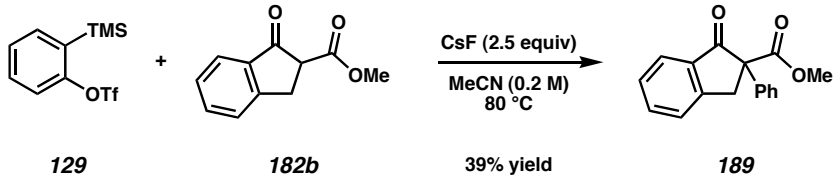


188. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) provided the α-arylated product (30.3 mg, 33% yield) as a clear oil: R_F 0.42 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.94-2.82 (m, 1H), 2.59-2.44 (m, 2H), 2.42-2.27 (m, 1H), 2.10-1.86 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 170.9, 136.4, 128.7, 127.8, 127.6, 65.2, 62.1, 38.0, 35.1, 19.5, 14.2; IR (thin film/NaCl) 2976, 1747, 1712, 1445, 1212 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{14}H_{16}O_3]^+$: *m/z* 232.1100, found 232.1099.

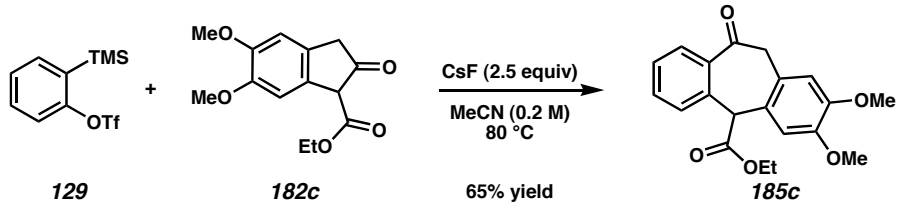


185b. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (63.9 mg, 61% yield) as a clear oil: R_F 0.31 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.53-7.30 (m, 4H), 7.24-7.18 (m, 2H), 4.26 (t, *J* = 4.8 Hz, 1H), 3.56 (d, *J* = 5.1 Hz, 2H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 172.5, 138.8, 138.6, 138.4, 137.5, 132.7, 131.5, 130.6, 130.3, 129.6, 128.9, 128.0, 127.4, 52.4, 50.6, 37.8; IR (thin film/NaCl) 2951, 1737, 1649, 1599, 1292, 1240, 1170 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{17}H_{14}O_3]^+$: *m/z* 266.0943, found 266.0941.



129 *182b* 39% yield *189*

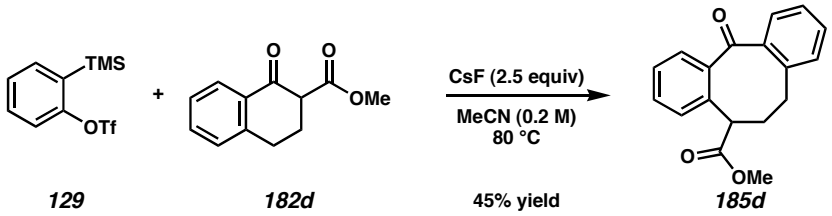
189. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) provided the α-arylated product (42 mg, 39% yield) as a clear oil: R_F 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.54 (app. dt, *J* = 7.4, 1.2 Hz, 1H), 7.42-7.14 (m, 7H), 4.13 (d, *J* = 17.3 Hz, 1H), 3.6 (s, 3H), 3.47 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 171.2, 138.9, 135.9, 135.2, 128.9, 128.5, 128.2, 127.8, 127.5, 126.4, 125.3, 65.6, 53.5, 41.0; IR (thin film/NaCl) 2952, 1745, 1716, 1606, 1211 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{17}H_{14}O_3]^+$: *m/z* 266.0943, found 266.0934.



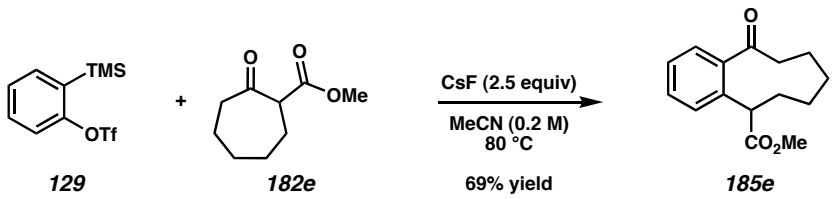
129 *182c* 65% yield *185c*

185c. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (75.7 mg, 65% yield) as a clear oil: R_F 0.12 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.52-7.30 (m, 3H), 6.87 (s, 1H), 6.76 (s, 1H), 4.88 (s, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 4.24-4.13 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.72 (d, *J* = 15.4 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 194.8, 171.4, 148.8, 148.0, 139.9, 134.8, 133.1, 131.3, 131.0, 129.8, 128.3, 124.7, 114.0, 113.8, 62.1, 59.4, 56.3, 56.2, 49.5, 14.4; IR (thin film/NaCl) 2978, 2937, 1728, 1673, 1598, 1518, 1262, 1230, 1201, 1112, 1025 cm^{-1}; HRMS (EI^+) calc'd for $[C_{20}H_{20}O_5]^+$: *m/z* 340.1311, found 340.1326.



185d. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (50 mg, 45% yield) as a clear oil: R_F 0.39 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.94 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.57-7.49 (m, 2H), 7.47-7.30 (m, 2H), 7.24-7.16 (m, 2H), 3.88 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.62 (s, 3H), 2.71-2.53 (m, 2H), 2.20-1.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 173.7, 141.3, 140.7, 139.2, 136.7, 133.9, 133.0, 131.3, 131.1, 130.8, 127.7, 127.2, 126.3, 52.3, 45.3, 35.6, 30.6; IR (thin film/NaCl) 2951, 1736, 1638, 1595, 1292, 1254, 1219 cm^{-1}; HRMS (EI^+) calc'd for $[C_{18}H_{16}O_3]^+$: *m/z* 280.1100, found 280.1108.



129 *182e* 69% yield *185e*

185e. Purification by flash chromatography (20:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (67.6 mg, 69% yield) as a clear oil: R_F 0.29 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.17 (m, 4H), 3.95 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.66 (s, 3H), 2.96-2.85 (m, 1H), 2.84-2.72 (m, 1H), 2.07-1.80 (m, 4H), 1.77-1.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 174.5, 143.3, 134.9, 130.1, 127.9, 127.2, 124.9, 52.3, 46.0, 43.5, 32.3, 26.0, 25.4, 23.8; IR (thin film/NaCl) 2936, 2860, 1732, 1693, 1435, 1249, 1201 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{15}H_{18}O_3]^+$: *m/z* 246.1256, found 246.1255.

3.4.4 Independent Chemical Correlation / Structural Proof

Acyl-alkylation product **175a** was independently prepared according to a literature procedure.[38] The product obtained through our methodology was identical by all spectroscopic data to the compound prepared by this alternative method. Spectroscopic data for acyl-alkylation product **175f** was identical to all the reported data in the literature.[39]

3.5 Notes and References

(1) Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290-3291.

(2) Roberts, J. D. *The Right Place at the Right Time: John D. Roberts*; In Profiles, Pathways, and Dreams: Autobiographies of Eminent Chemists; Seeman, J. I., Ed.; American Chemical Society: Washington, DC, 1990.

(3) For a full account on the mechanism of amination of halobenznes, see: Roberts, J. D.; Semenow, D. A.; Simmons, H. E.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601-611.

(4) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp. 483-515.

(5) Warmuth, R. *Eur. J. Org. Chem.* **2001**, 423-437.

(6) For a recent review on the use of arynes in organic synthesis, see: Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701-730.

(7) Himeshima, Y; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211-1214.

(8) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340-5341.

(9) *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999.

(10) For aryne insertions into Sn-Sn σ-bonds, see: Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5052-5055.

(11) For aryne insertions into S-Sn σ-bonds, see: Yoshida, H.; Terayama, T.; Ohshita, J.; Kunai, A. *Chem. Comm.* **2004**, 1980-1981.

(12) For aryne insertions into N-Mg and S-Mg σ-bonds, see: Lin, W.; Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4258-4261.

(13) For aryne insertions into Se-Se and Te-Te σ-bonds, see: Petragnani, N.; Toscano, V. G. *Chem. Ber.* **1970**, *103*, 1652-1653.

(14) For aryne insertions into Si-Si σ-bonds, see: (a) Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2004**, *125*, 6638-6639. (b) Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *Organometallics* **2005**, *24*, 156-162.

(15) For aryne insertions into N-Si σ-bonds, see: Yoshida, H.; Minabe, T.; Ohshita, J.; Kunai, A. *Chem. Comm.* **2005**, 3454-3456.

(16) For aryne insertions into S-S σ-bonds, see: Nakayama, J.; Tajiri, T.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2907-2908.

(17) For aryne insertions into N-H σ-bonds, see: Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673-4675.

(18) For aryne insertions into O-H σ-bonds, see: Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99-102.

(19) For aryne insertions into C-Sn σ-bonds, see: Yoshida, H.; Honda, Y.; Shirakawa, E.; Hiyama, T. *Chem. Comm.* **2001**, 1880-1881.

(20) For aryne insertions into C-Si σ-bonds, see: Sato, Y.; Kobayashi, Y.; Sugiura, M.; Shirai, H. *J. Org. Chem.* **1978**, *43*, 199-202.

(21) For aryne insertions into C-N σ-bonds, see: (a) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 3247-3249. (b) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112-13113.

(22) To the best of our knowledge, this type of transformation has not been previously described for β-ketoesters. Moreover, direct coupling of carbon nucleophiles of the type Nuc-H with aryne precursors has not been reported. For examples of

lithium and potassium enolate additions to benzyne to give cyclobutoxides followed by fragmentation, see: (a) Caubere, P.; Loubinoux, B. *Bull. Soc. Chim. Fr.* **1968**, 3008-3012. (b) Guyot, M.; Molho, D. *Tetrahedron Lett.* **1973**, *14*, 3433-3436. (c) Geoffroy, P.; Mouaddib, A.; Carre, M. C.; Caubere, P. *Tetrahedron Lett.* **1988**, *29*, 1385-1388. (d) Jamart-Gregoire, B.; Leger, C.; Caubere, P. *Tetrahedron Lett.* **1990**, *31*, 7599–7602. (e) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471-9479. (f) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525. (g) Wang, A.; Tandel, S.; Zhang, H.; Huang, Y.; Holdeman T. C.; Biehl, E. R. *Tetrahedron* **1998**, *54*, 3391–3400.

(23) Subsequent to the publication of our work, other examples of direct aryne insertions into C-C σ-bonds have emerged. See: (a) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Comm.* **2005**, 3292-3294. (b) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tet. Lett.* **2005**, *46*, 6729-6731.

(24) Yet, L. *Chem. Rev.* **2000**, *100*, 2963-3007.

(25) Pena, D.; Perez, D.; Guitian, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827-5828.

(26) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7280-7286.

(27) Witiak, D. T.; Kim, S. K.; Tehim, A. K.; Sternitzke, K. D.; McCreery, R. L. et al. *J. Med. Chem.* **1988**, *31*, 1437-1445.

(28) Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889-1902.

(29) Phukan, P.; Mohan, J. Madan; and Sudalai, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *24*, 3685-3690.

(30) Selwood, D. L.; Brummell, D. G.; Budworth, J. ; Burtin, G. E.; Campbel, R. O.; Chana, S. S.; Charles, I. G.; Fernandez, P. A.; Glen, R. C.; Goggin, M. C.; Hobbs, A.J.; et al. *J. Med. Chem.* **2001**, *44*, 78-93.

(31) Zheng, S.-L.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2002**, *4*, 889-892.

(32) Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488-7494.

(33) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958-964.

(34) Nudelman, A.; Kelner, R.; Broida, N.; Gottlieb, H. E. *Synthesis* **1989**, *5*, 387-388.

(35) Emelen, K. V.; Wit, T. D.; Hoornaert, G. J.; Compernolle, F. *Org. Lett.* **2000**, *2*, 3083-3086.

(36) Taylor, J. B. et al. *J. Med. Chem.* **1970**, *13*, 1226-1227.

(37) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587-3606.

(38) Cruces, J.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Tetrahedron Lett.* **2001**, *42*, 4825-4828.

(39) Rupard, J. H.; Paulis, T.; Janowsky, A.; Smith, H. E. *J Med. Chem.* **1989**, *32*, 2261-2268.

APPENDIX FIVE

Spectra Relevant to Chapter Three:

Development of the Direct Acyl-Alkylation of Arynes

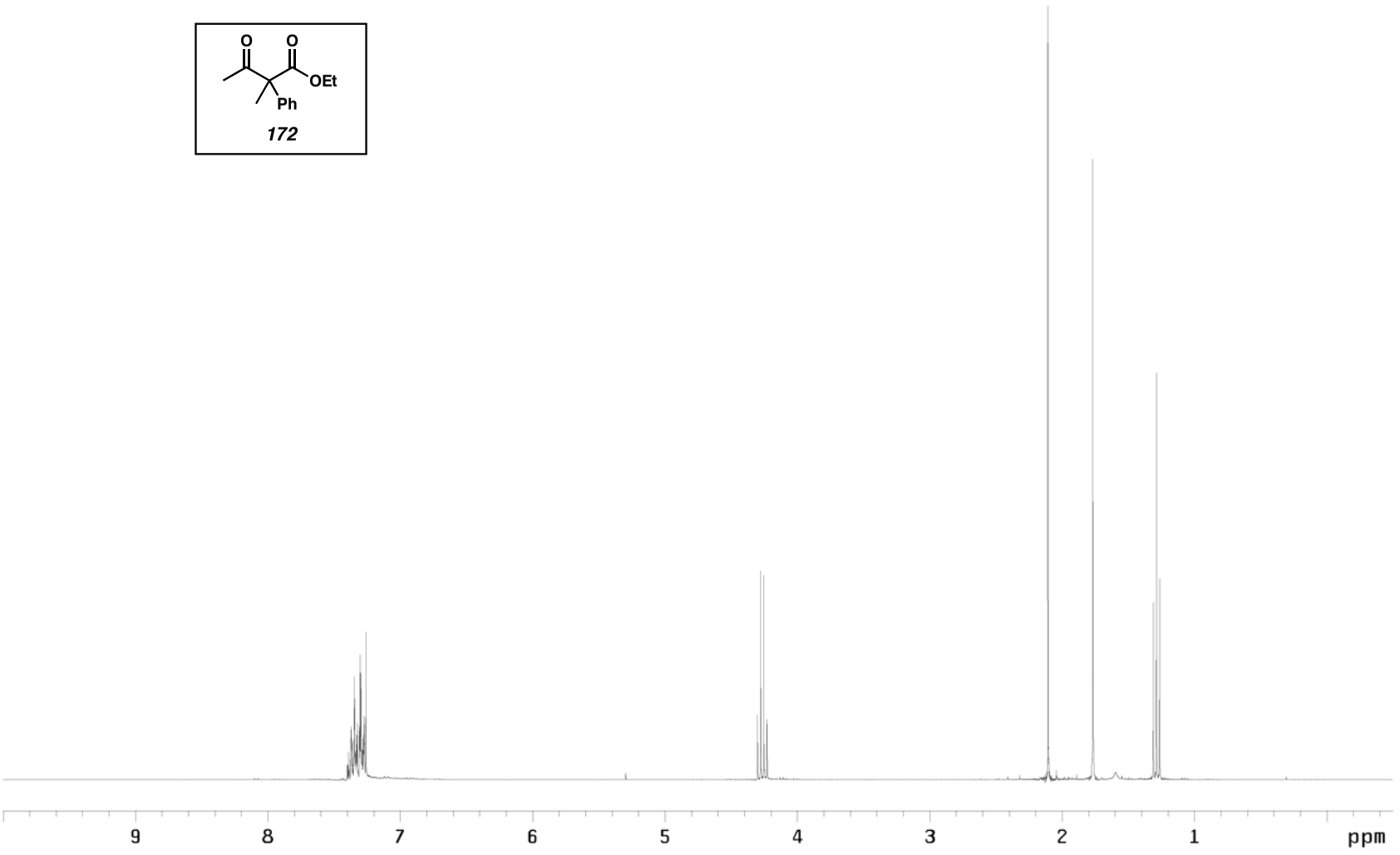


Figure A5.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **172**.

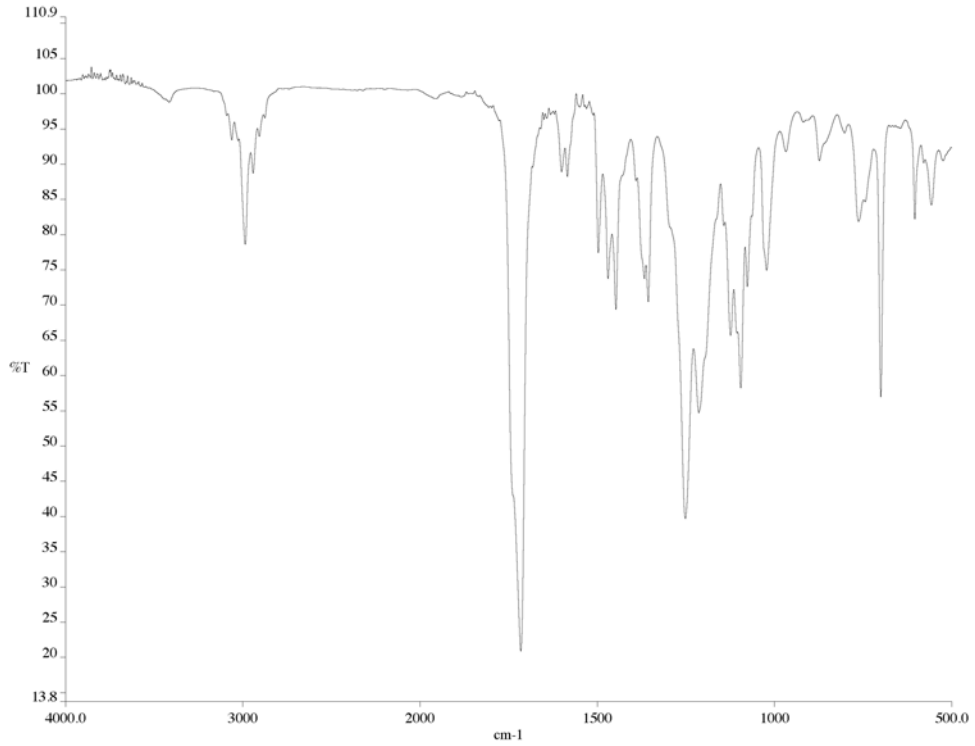


Figure A5.2 Infrared spectrum (thin film/NaCl) of compound **172**.

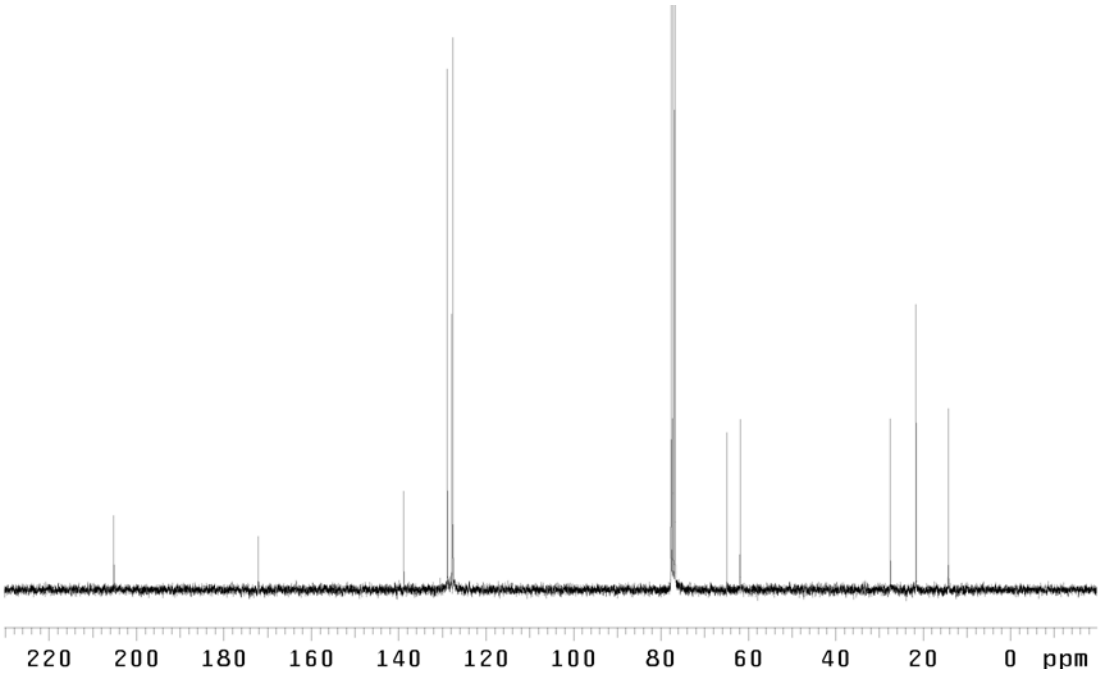


Figure A5.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **172**.

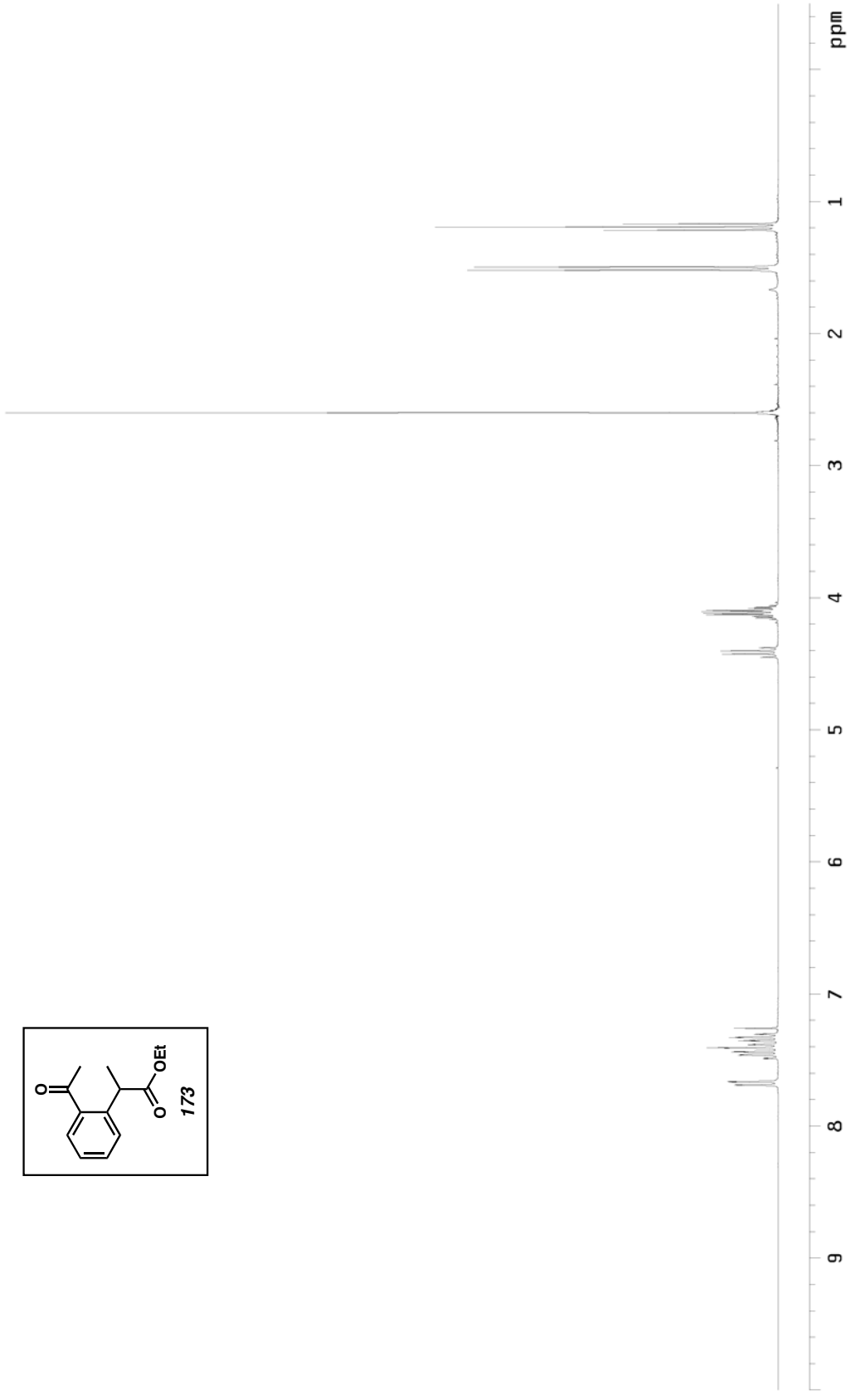


Figure A5.4 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **173**.

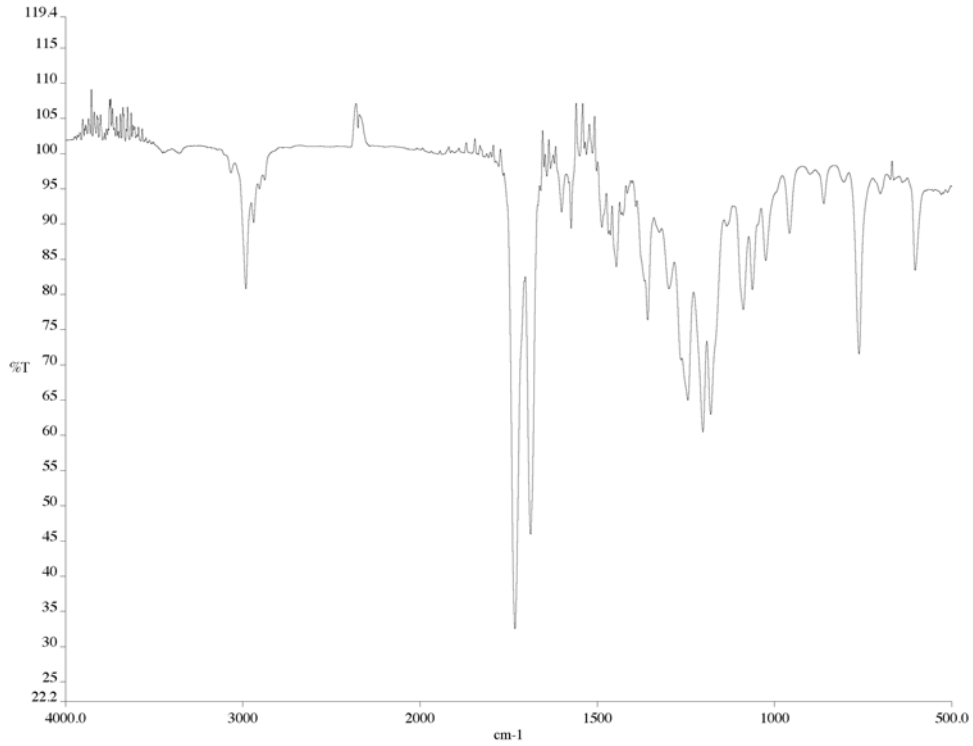


Figure A5.5 Infrared spectrum (thin film/NaCl) of compound **173**.

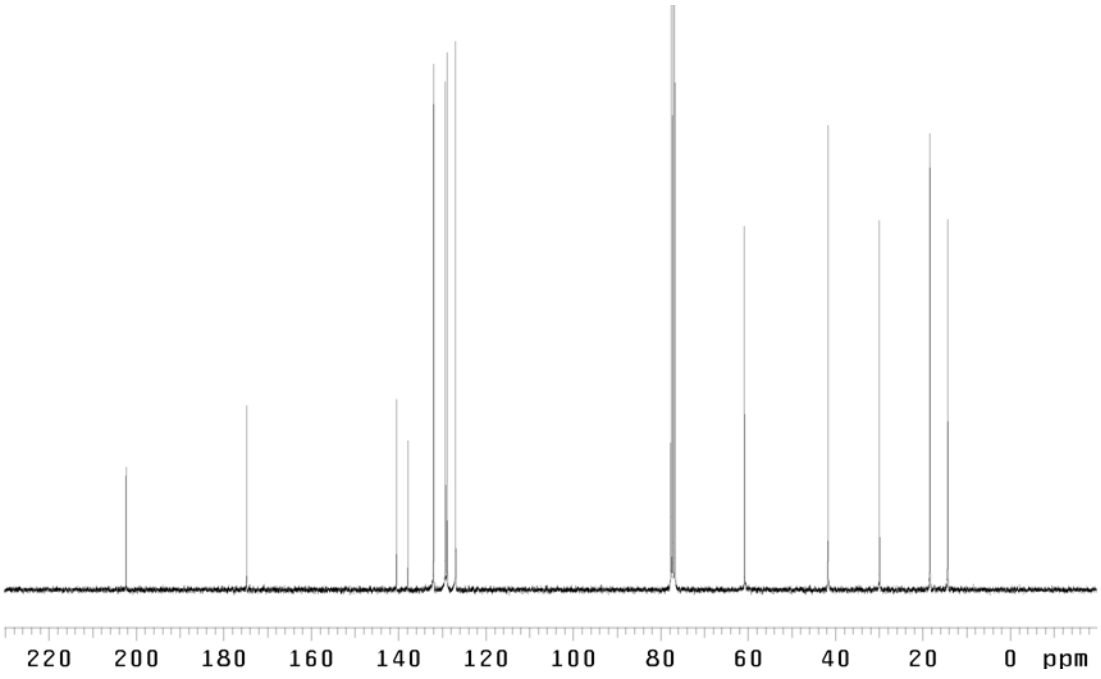


Figure A5.6 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **173**.

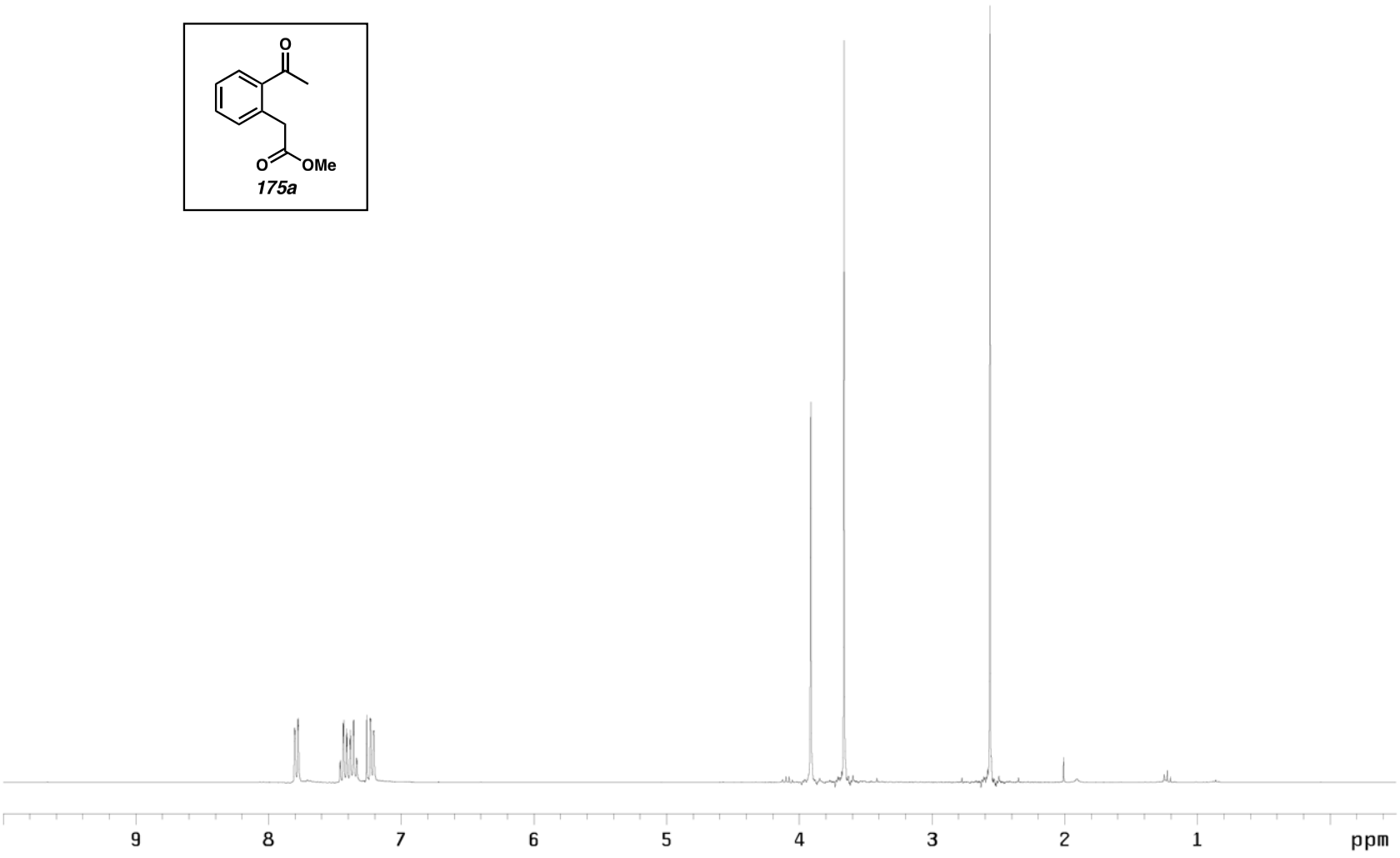


Figure A5.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **175a**.

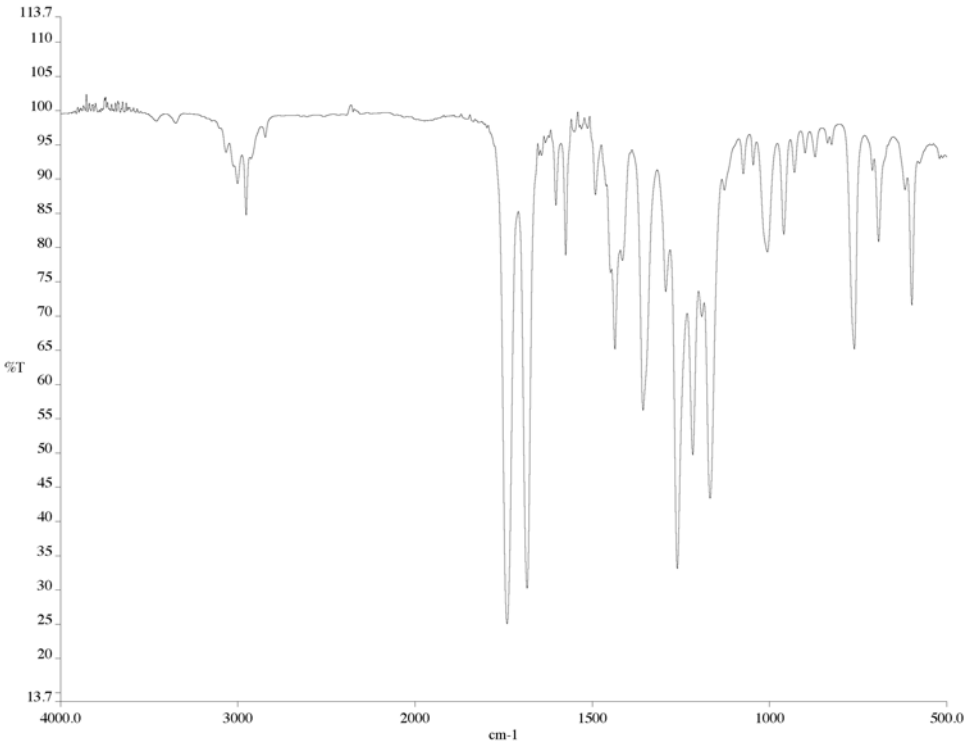


Figure A5.8 Infrared spectrum (thin film/NaCl) of compound **175a**.

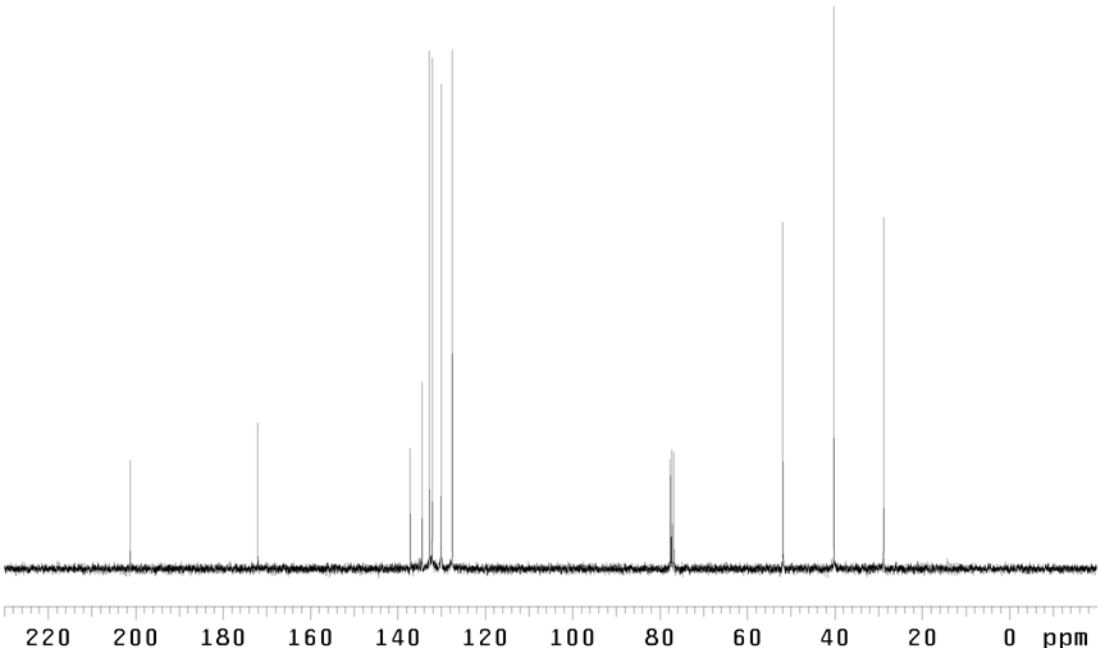


Figure A5.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **175a**.

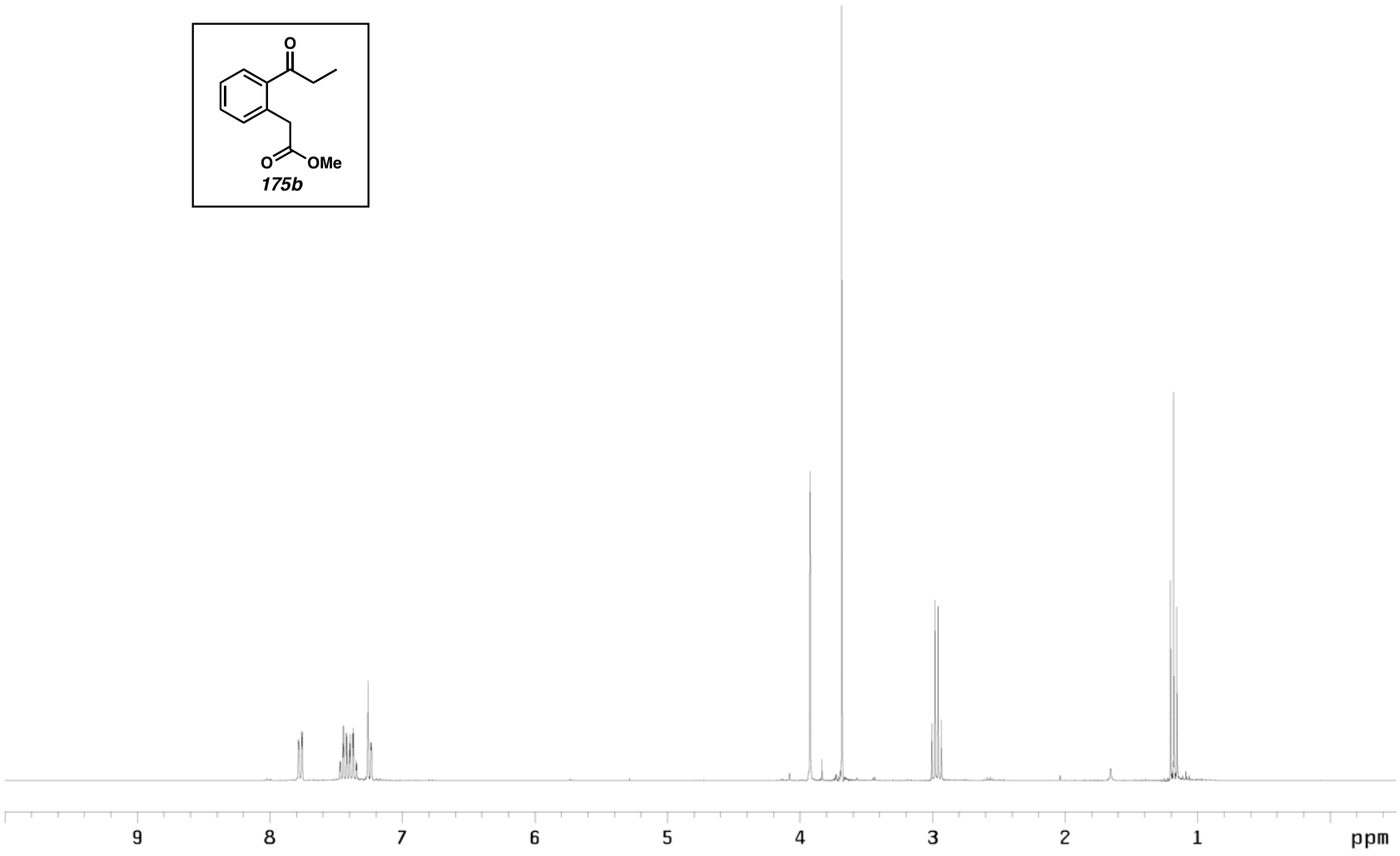


Figure A5.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **175b**.

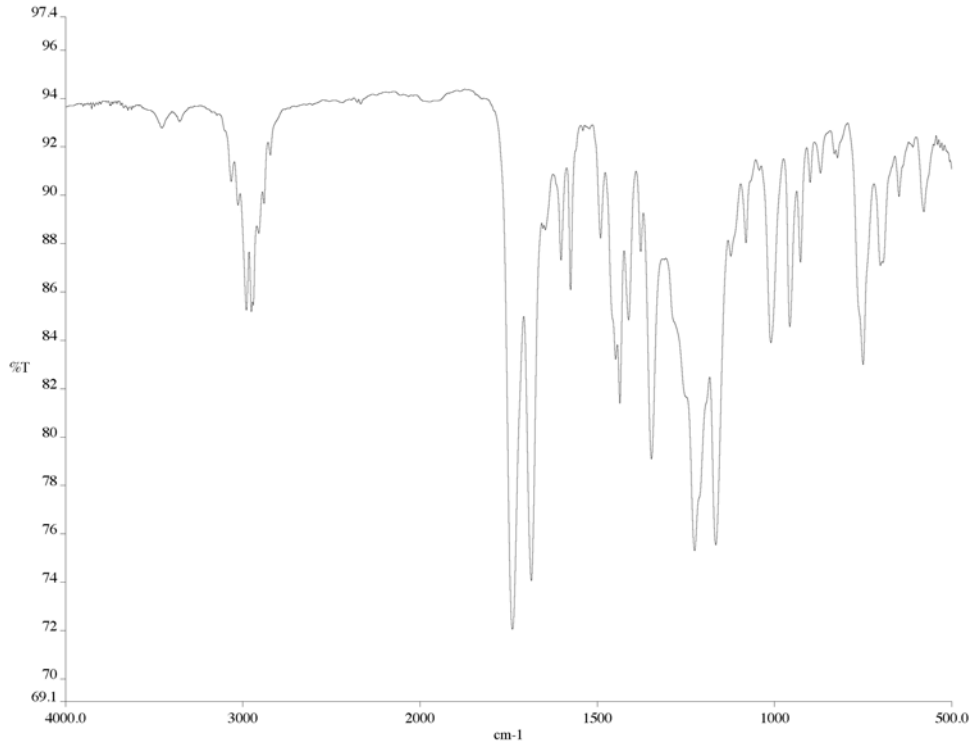


Figure A5.11 Infrared spectrum (thin film/NaCl) of compound **175b**.

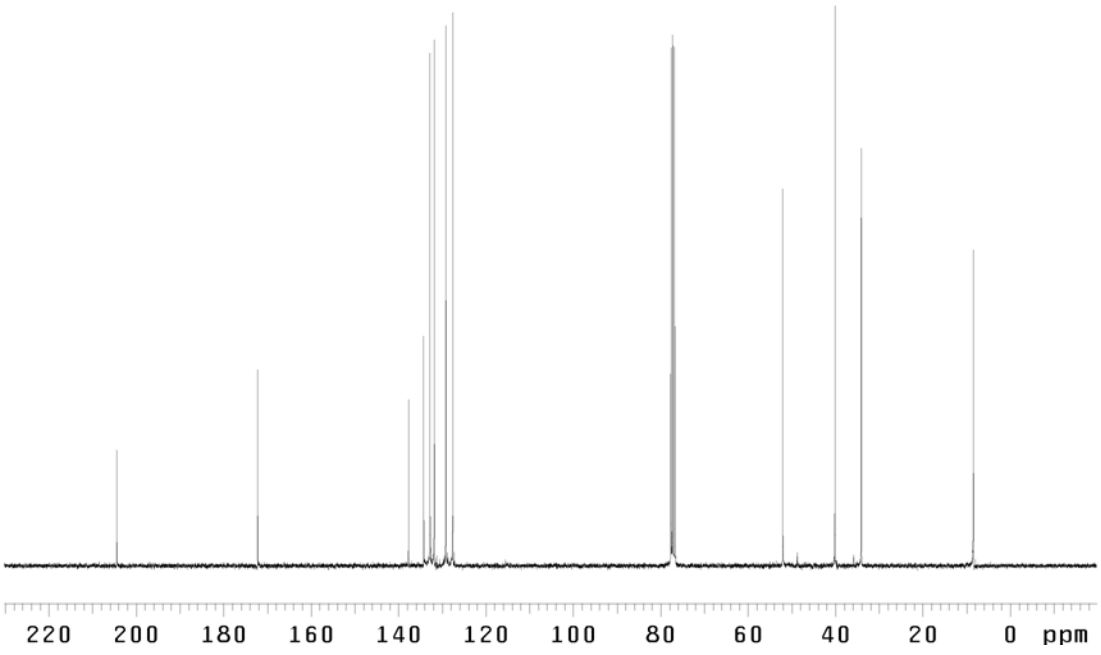


Figure A5.12 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **175b**.

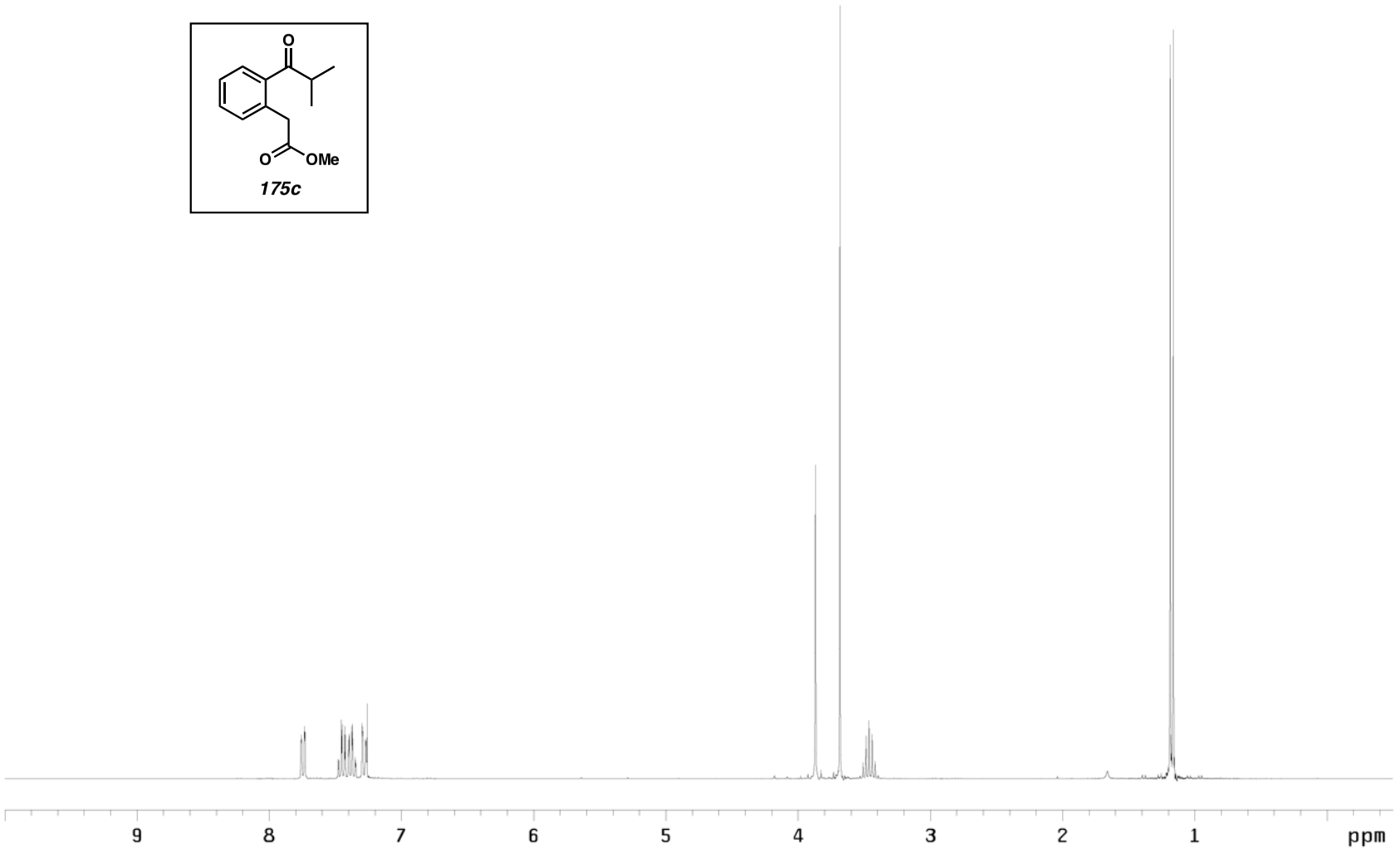


Figure A5.13 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **175c**.

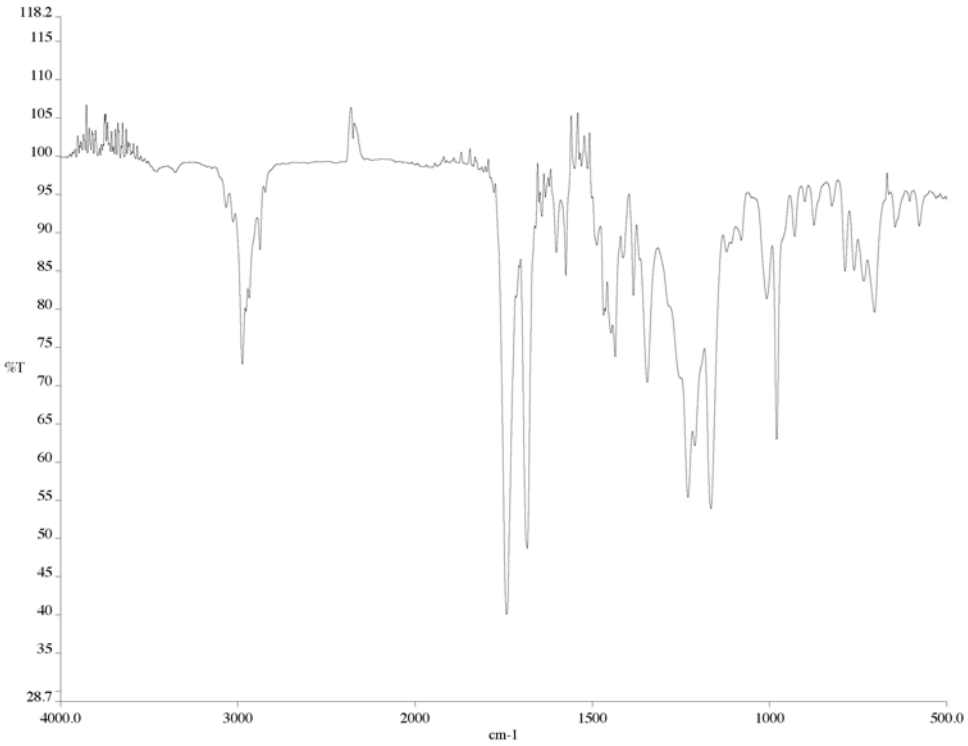


Figure A5.14 Infrared spectrum (thin film/NaCl) of compound **175c**.

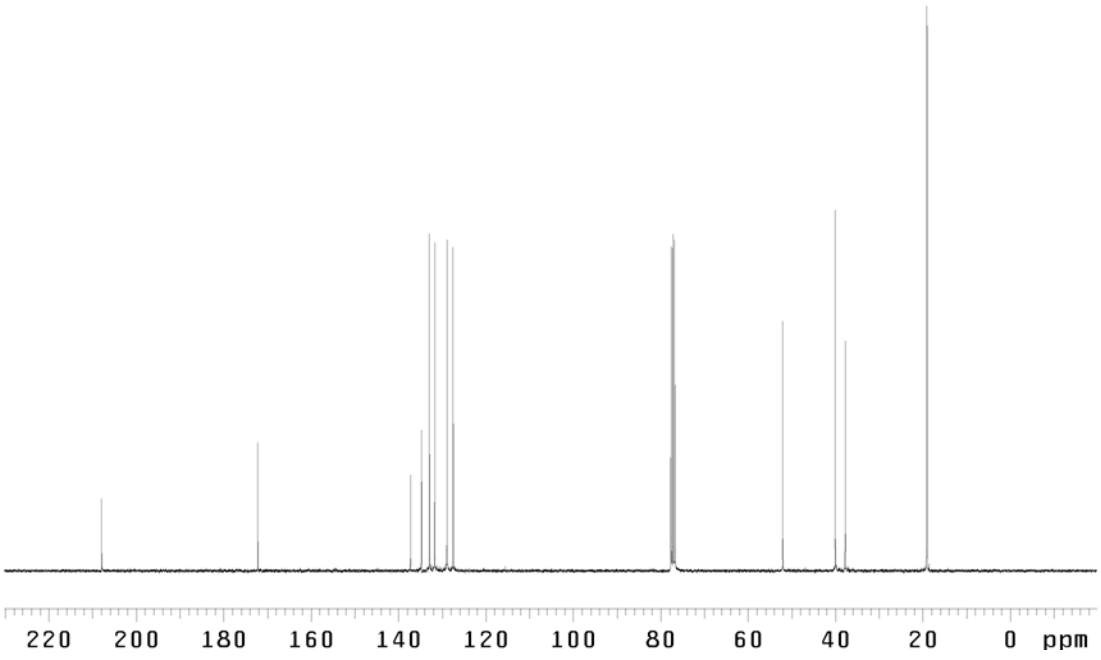


Figure A5.15 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **175c**.

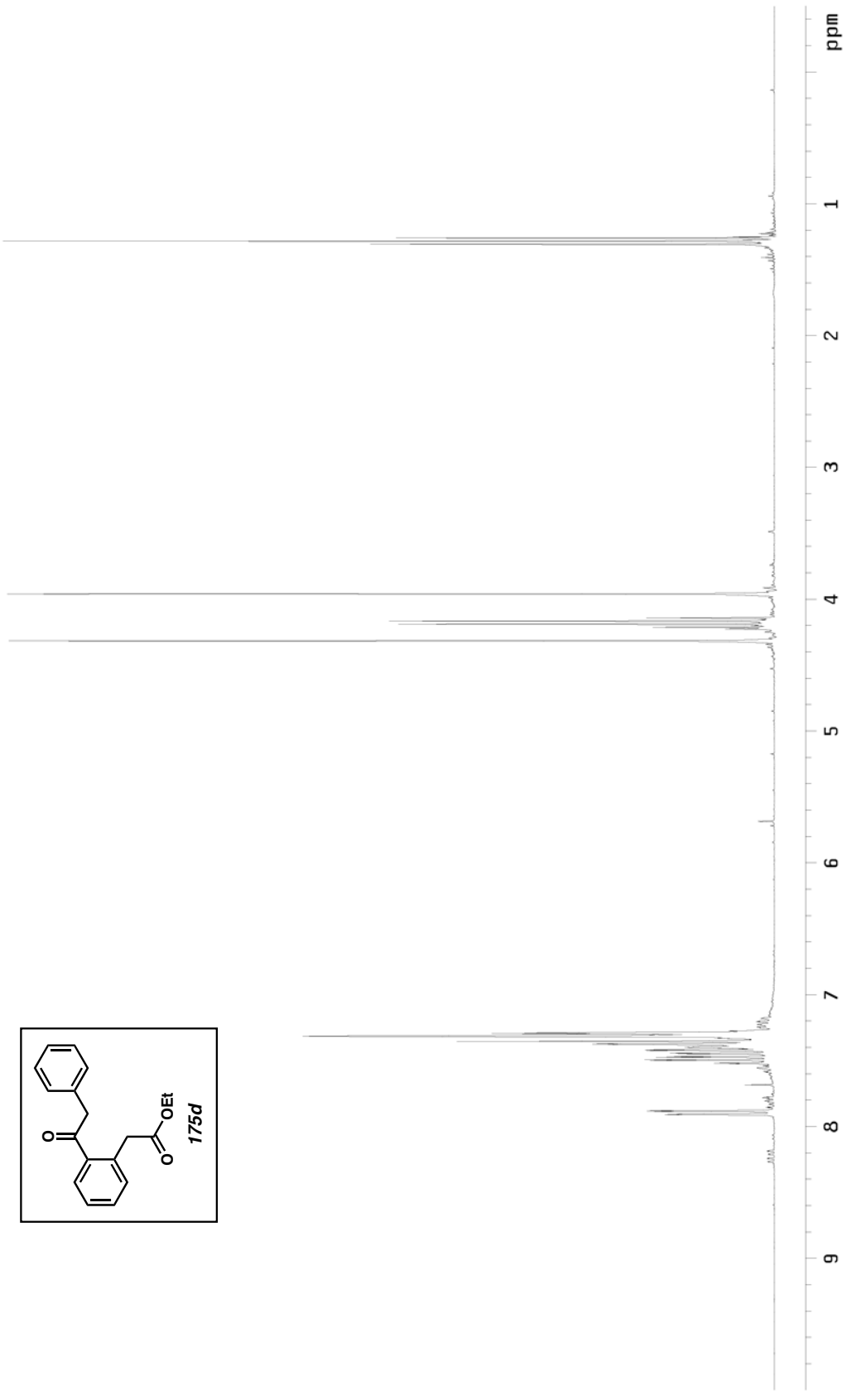


Figure A5.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **175d**.

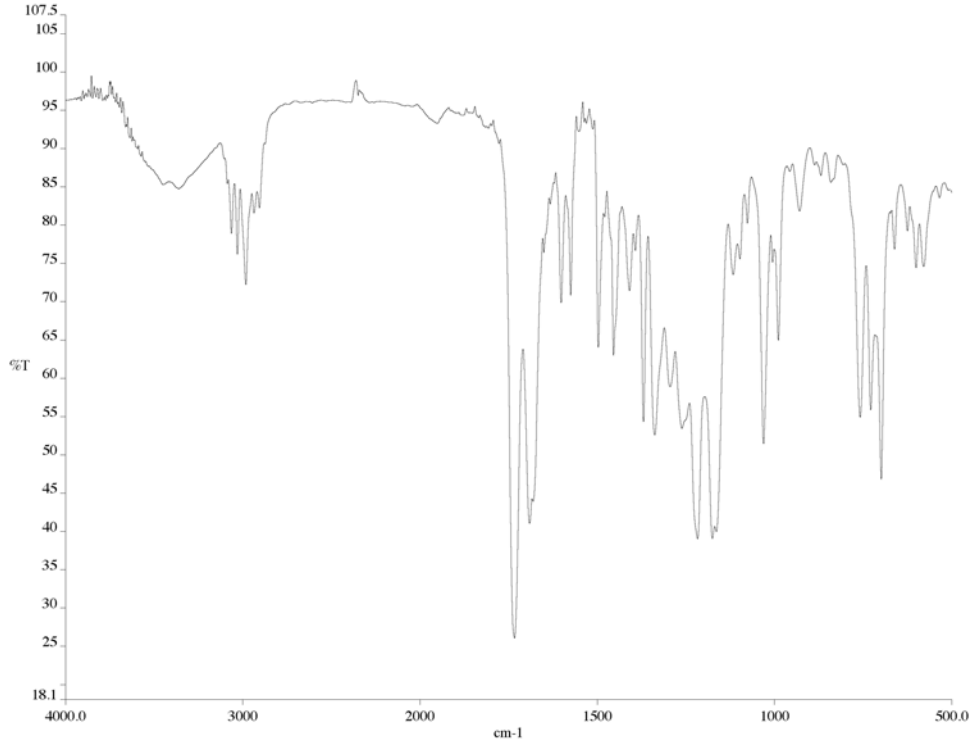


Figure A5.17 Infrared spectrum (thin film/NaCl) of compound **175d**.

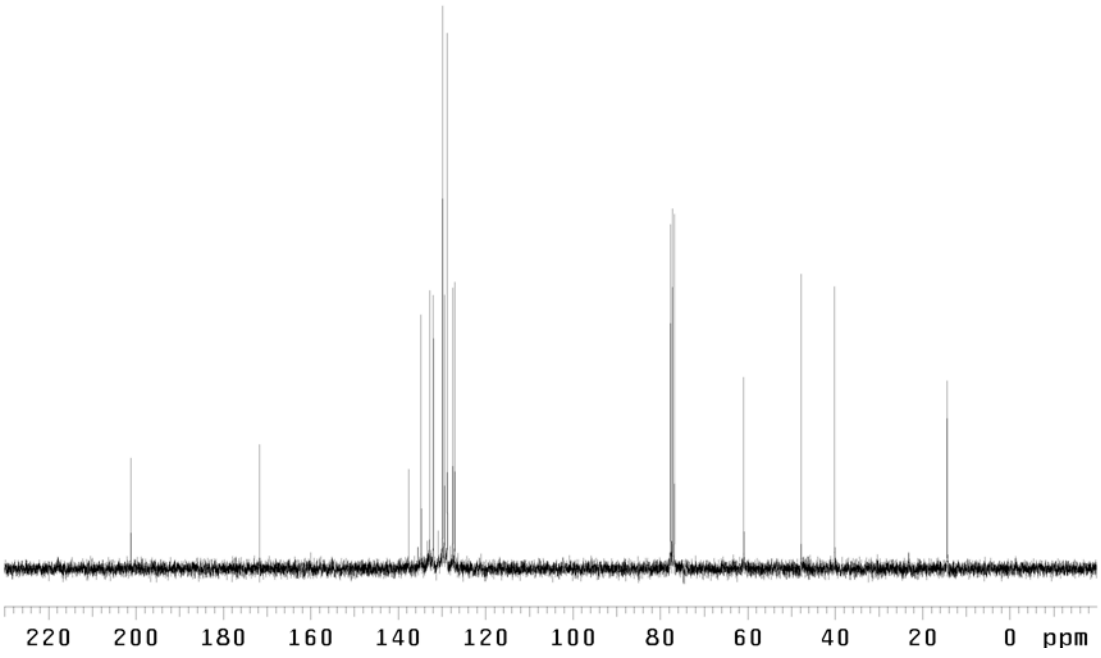


Figure A5.18 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **175d**.

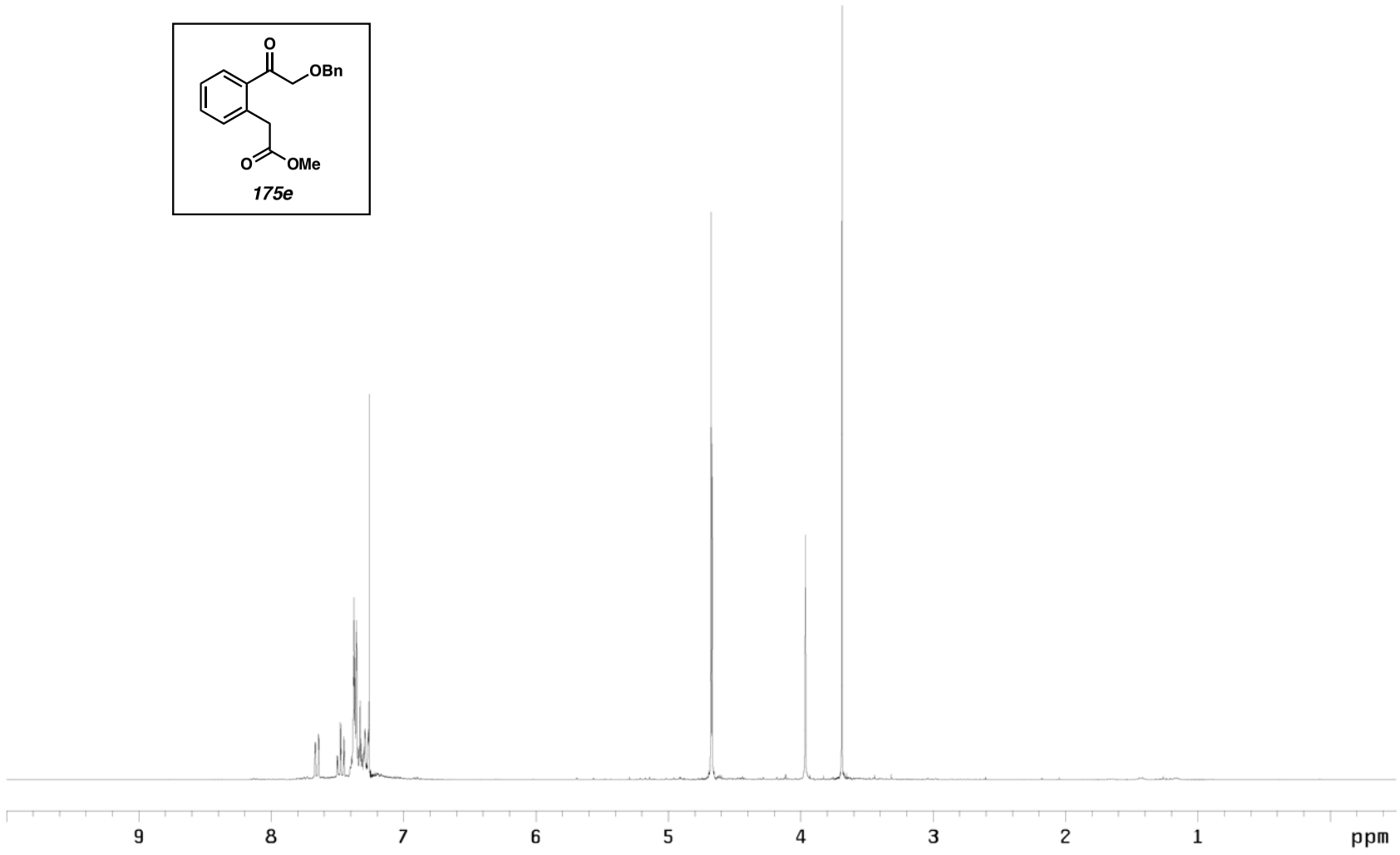


Figure A5.19 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **175e**.

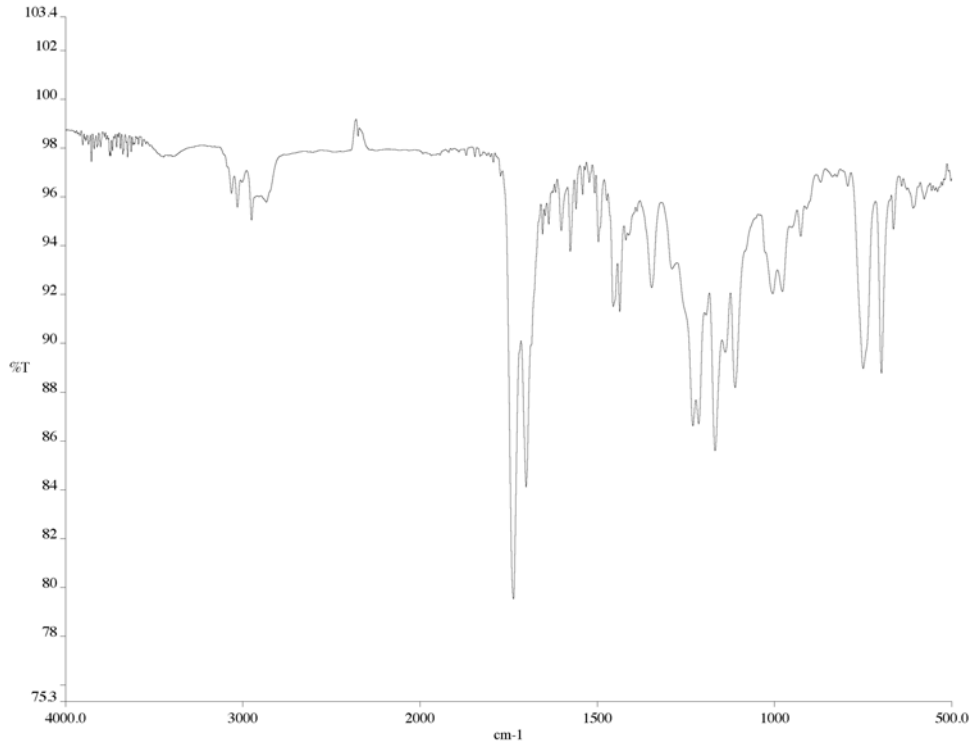


Figure A5.20 Infrared spectrum (thin film/NaCl) of compound **175e**.

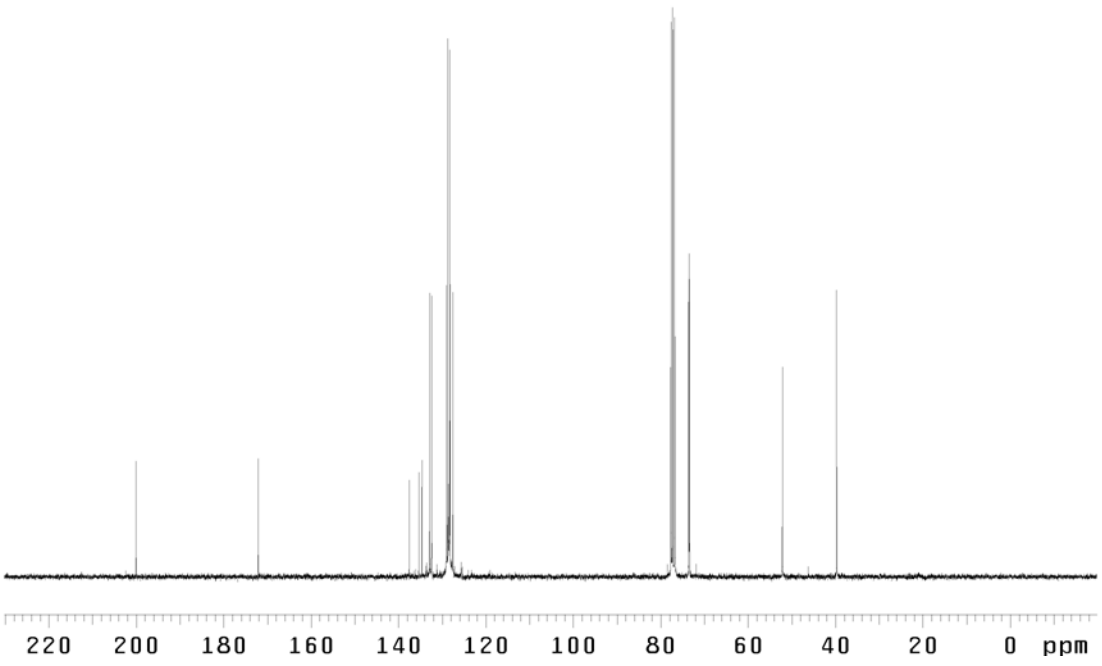


Figure A5.21 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **175e**.

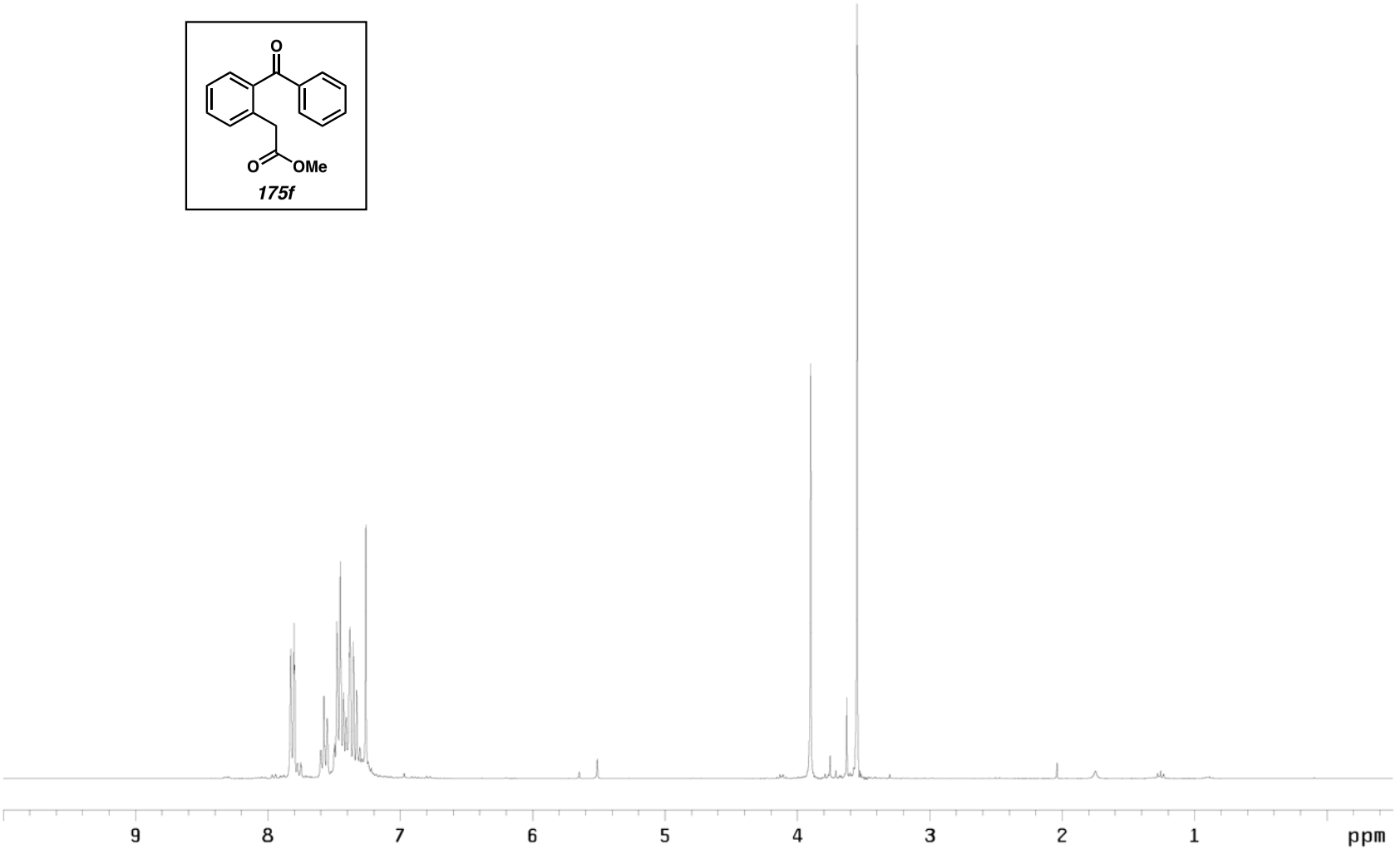


Figure A5.22 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **175f**.

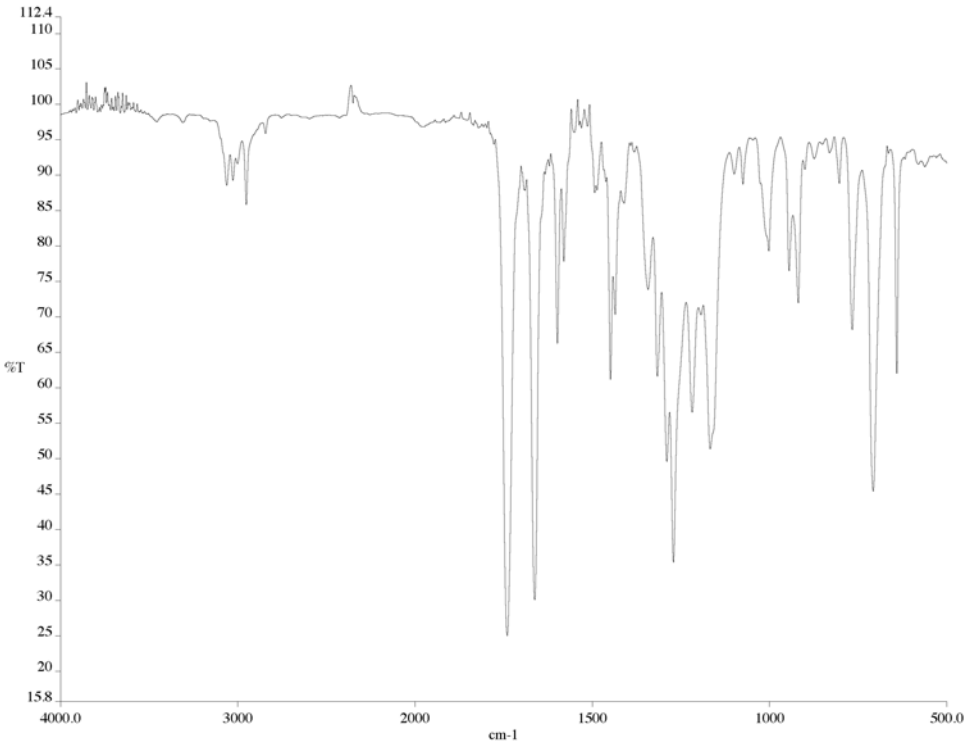


Figure A5.23 Infrared spectrum (thin film/NaCl) of compound **175f**.

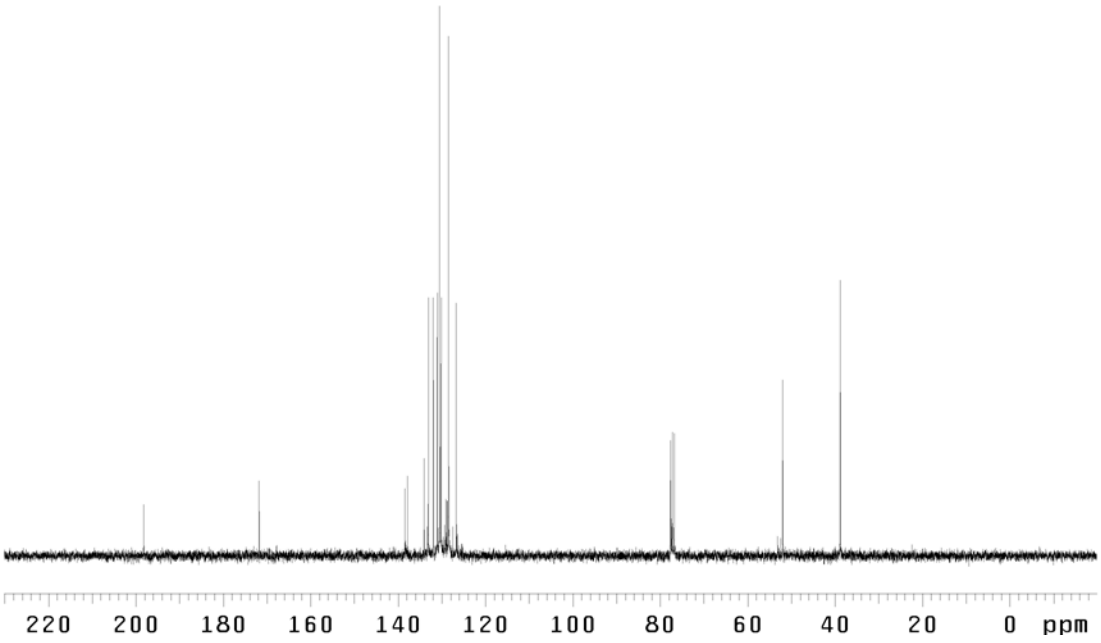


Figure A5.24 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **175f**.

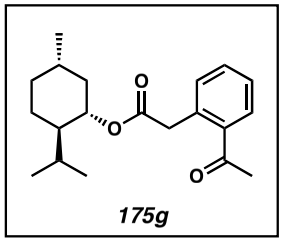


Figure A5.25 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **175g**.

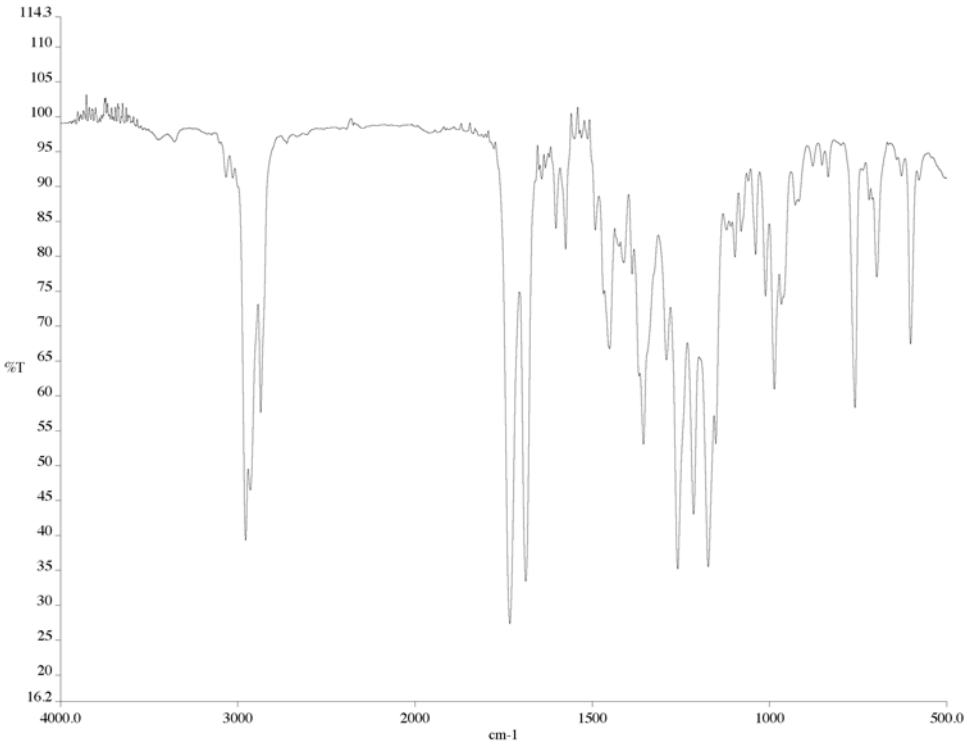


Figure A5.26 Infrared spectrum (thin film/NaCl) of compound **175g**.

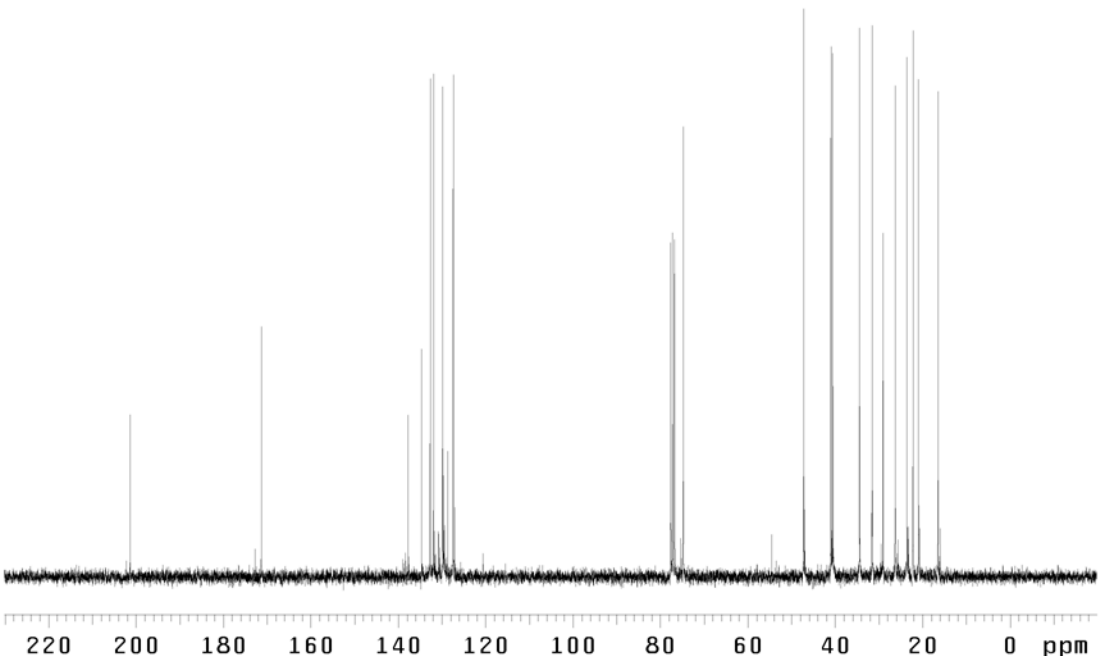


Figure A5.27 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **175g**.

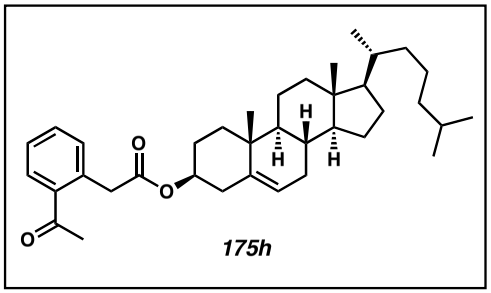


Figure A5.28 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **175h**.

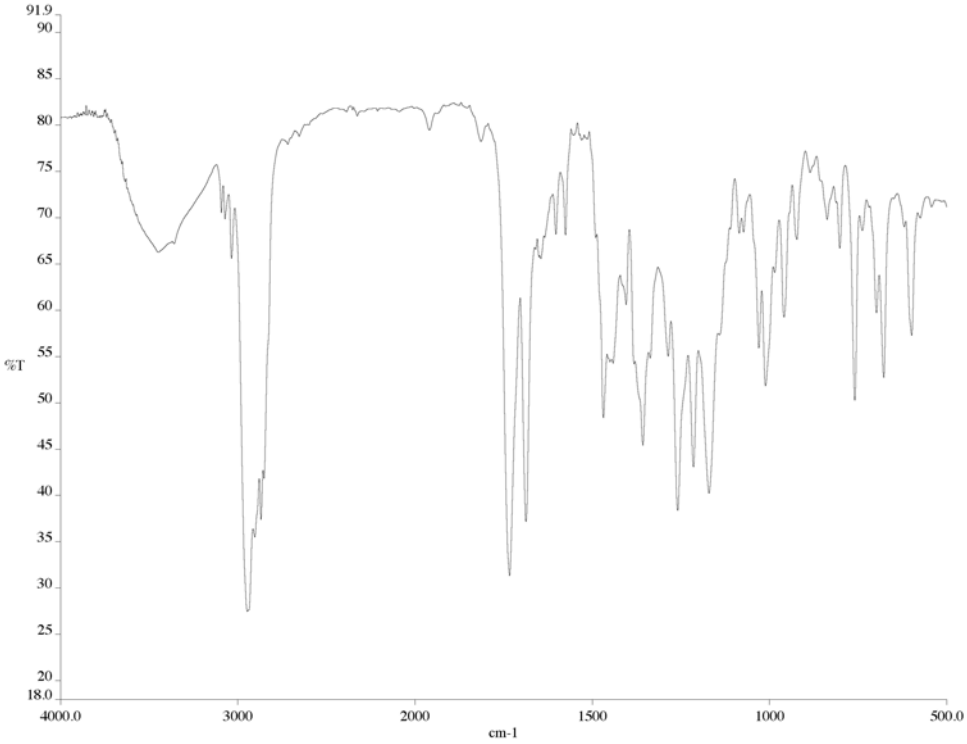


Figure A5.29 Infrared spectrum (thin film/NaCl) of compound **175h**.

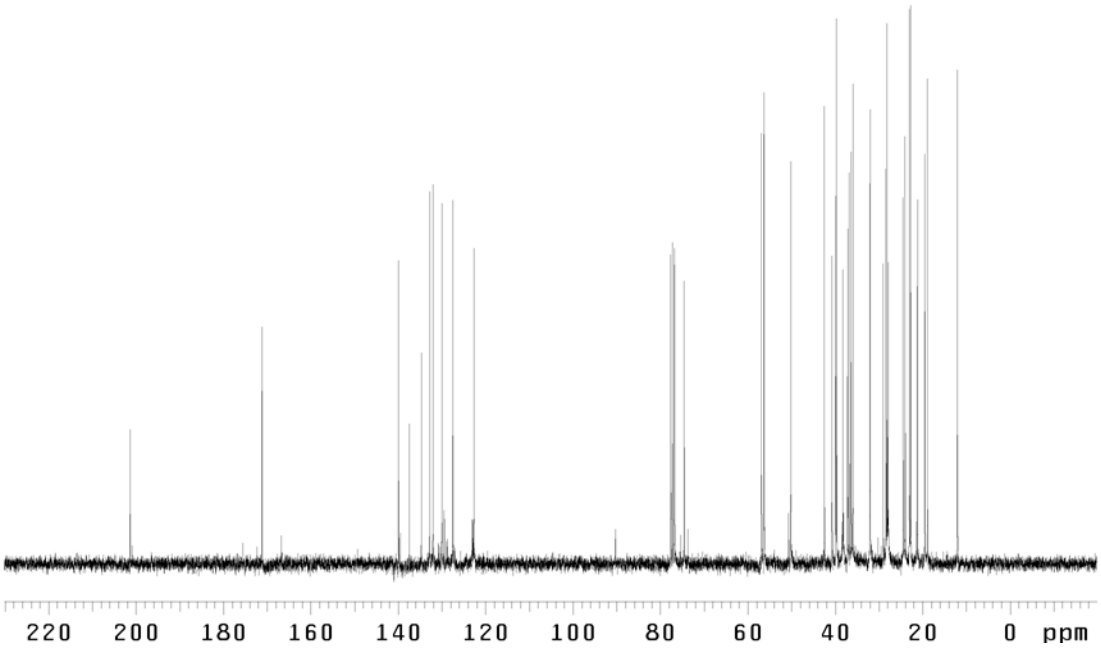


Figure A5.30 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **175h**.

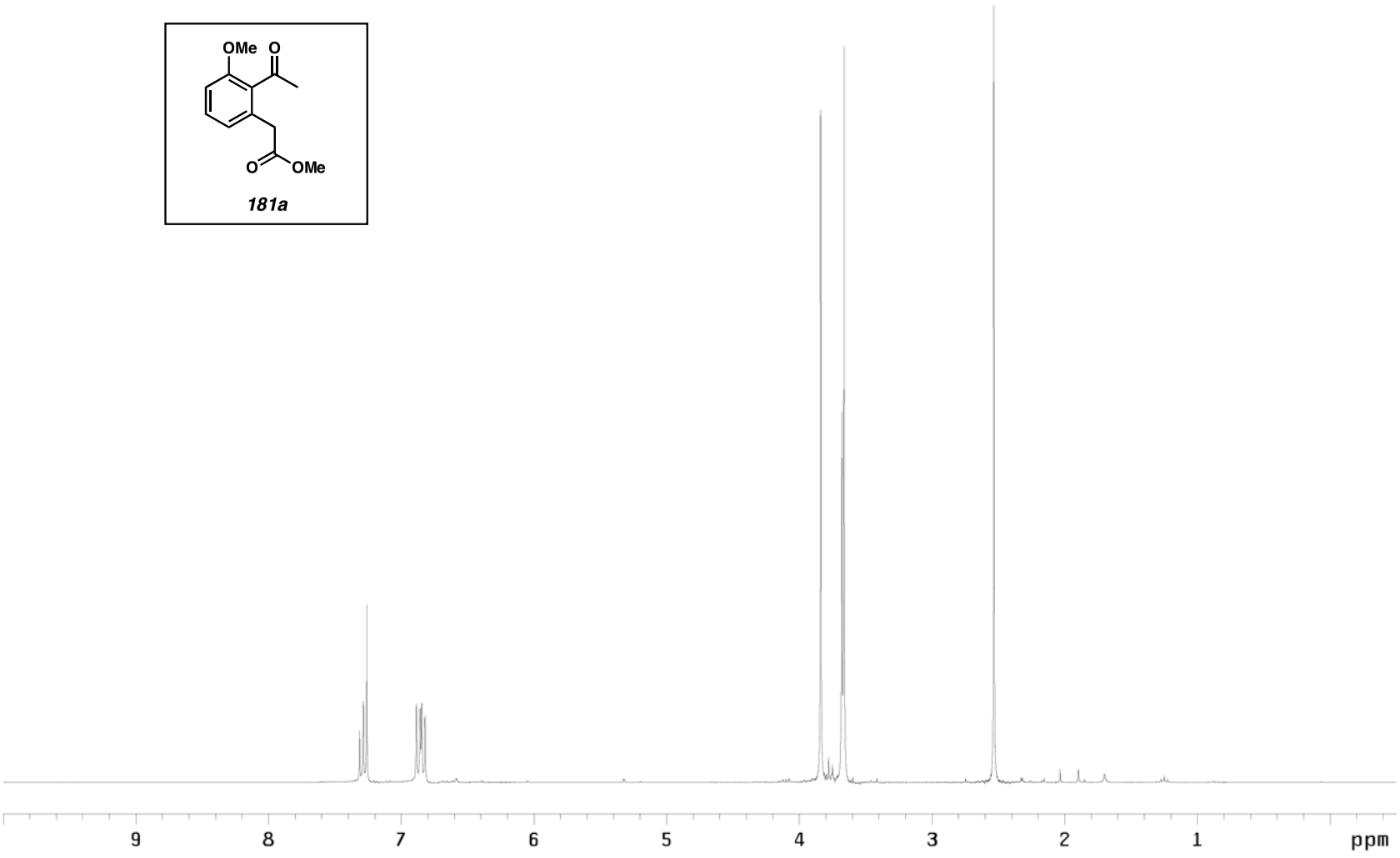


Figure A5.31 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **181a**.

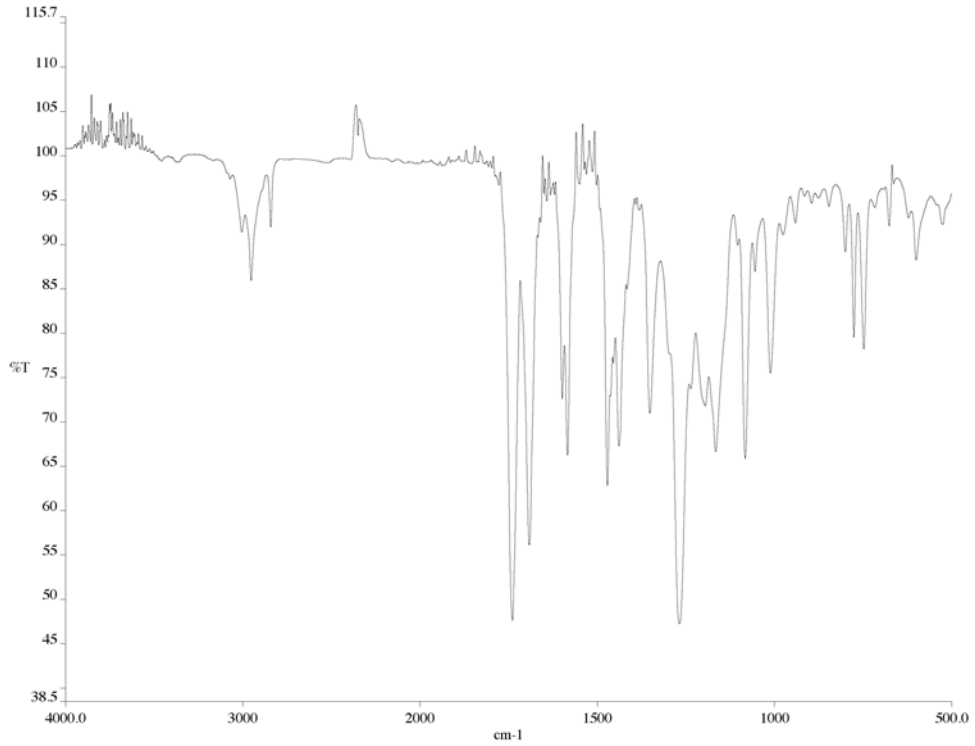


Figure A5.32 Infrared spectrum (thin film/NaCl) of compound **181a**.

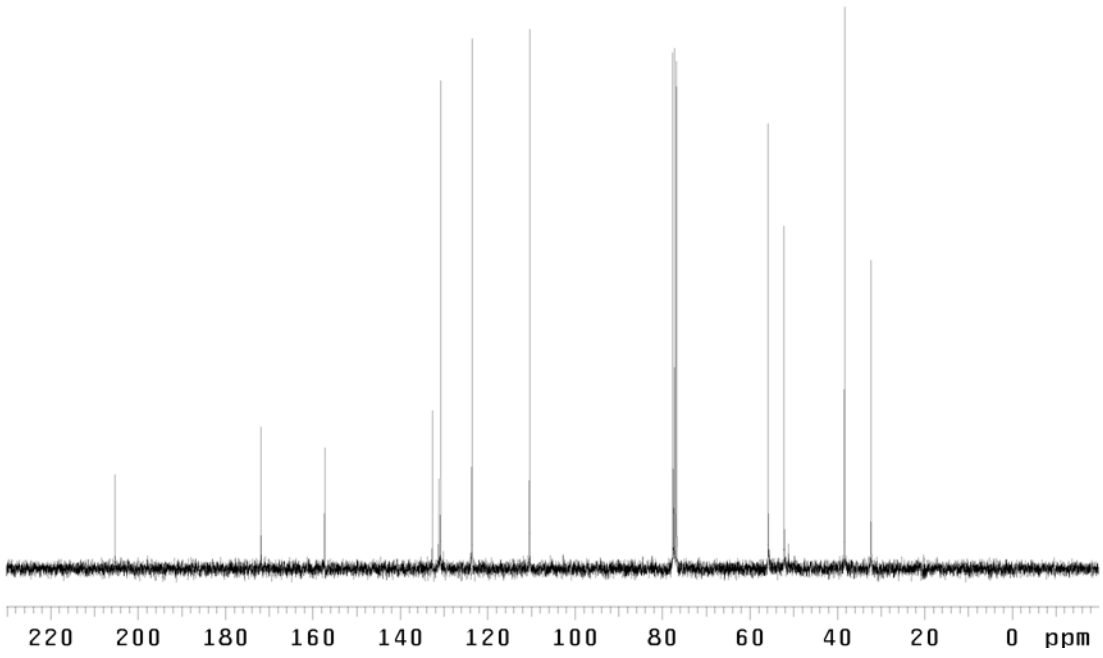


Figure A5.33 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **181a**.

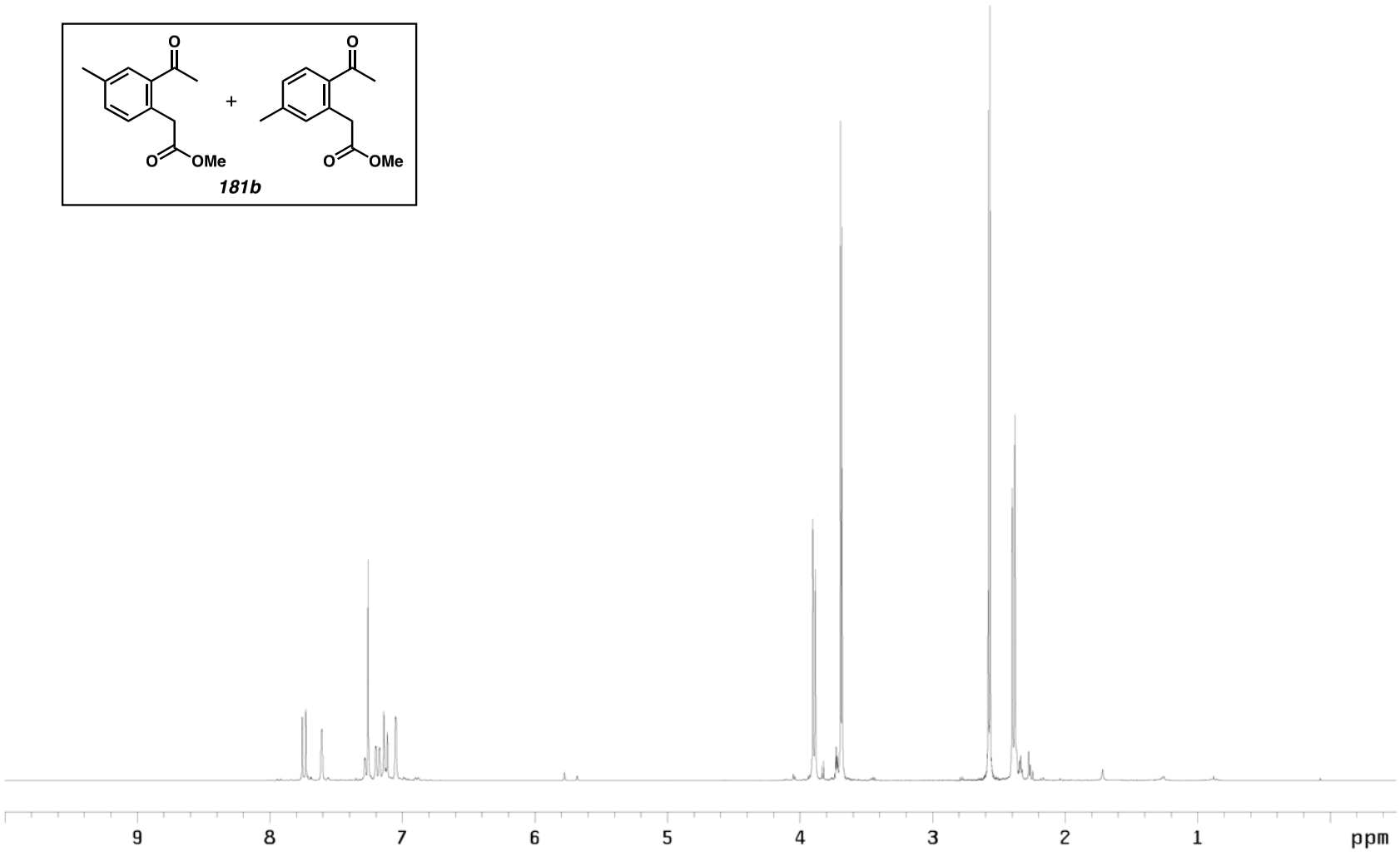


Figure A5.34 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **181b**.

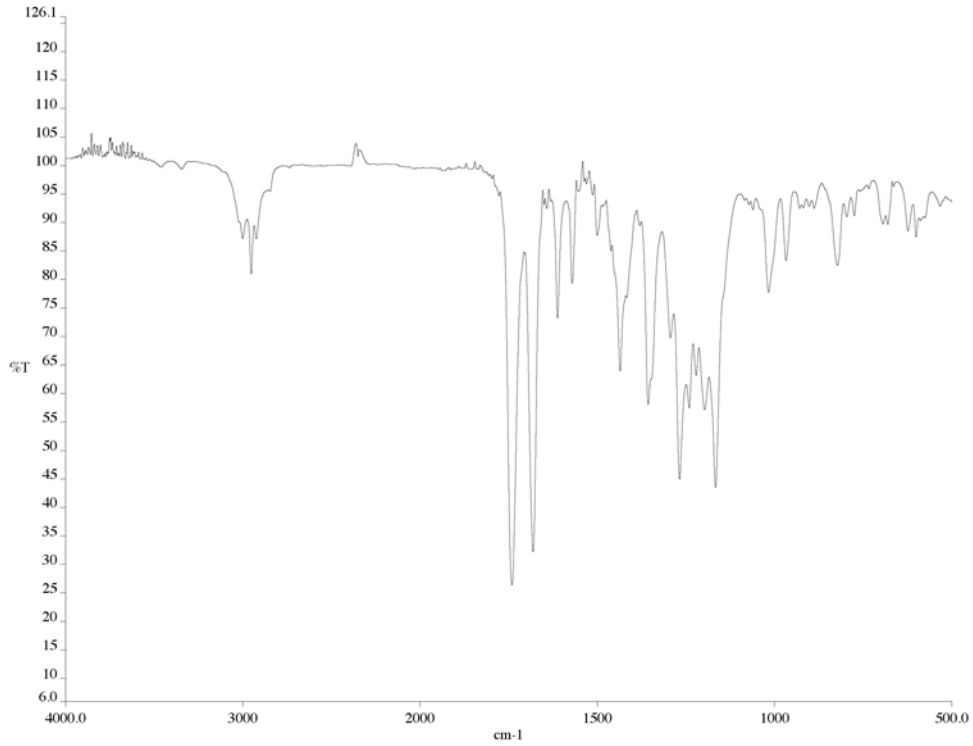


Figure A5.35 Infrared spectrum (thin film/NaCl) of compound **181b**.

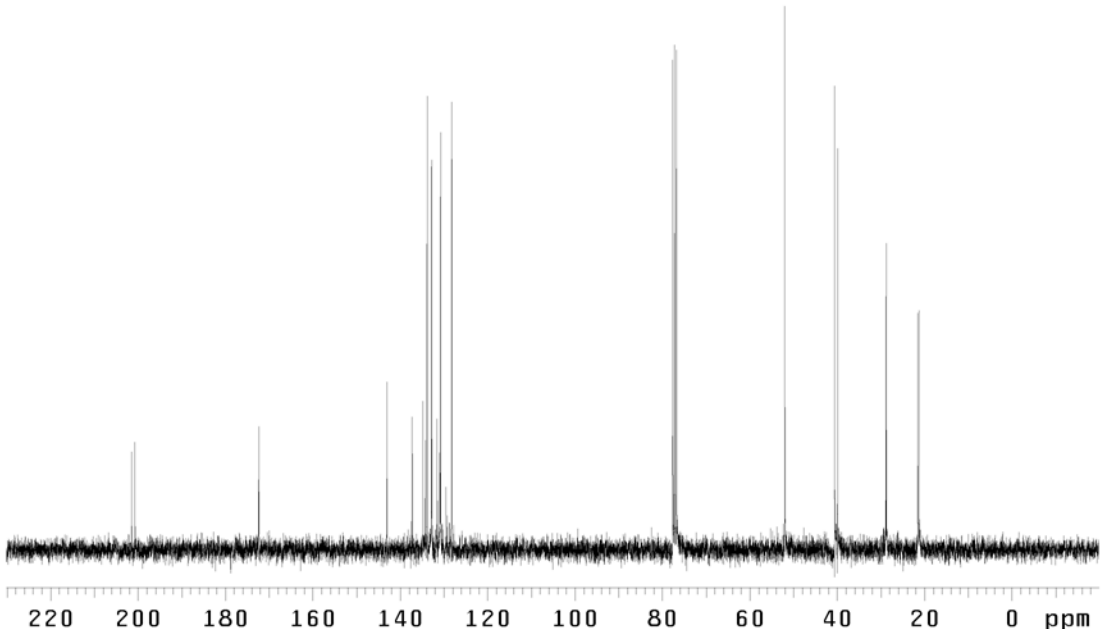


Figure A5.36 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **181b**.

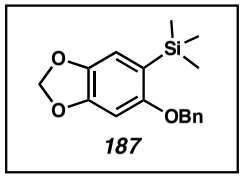


Figure A5.37 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **187**.

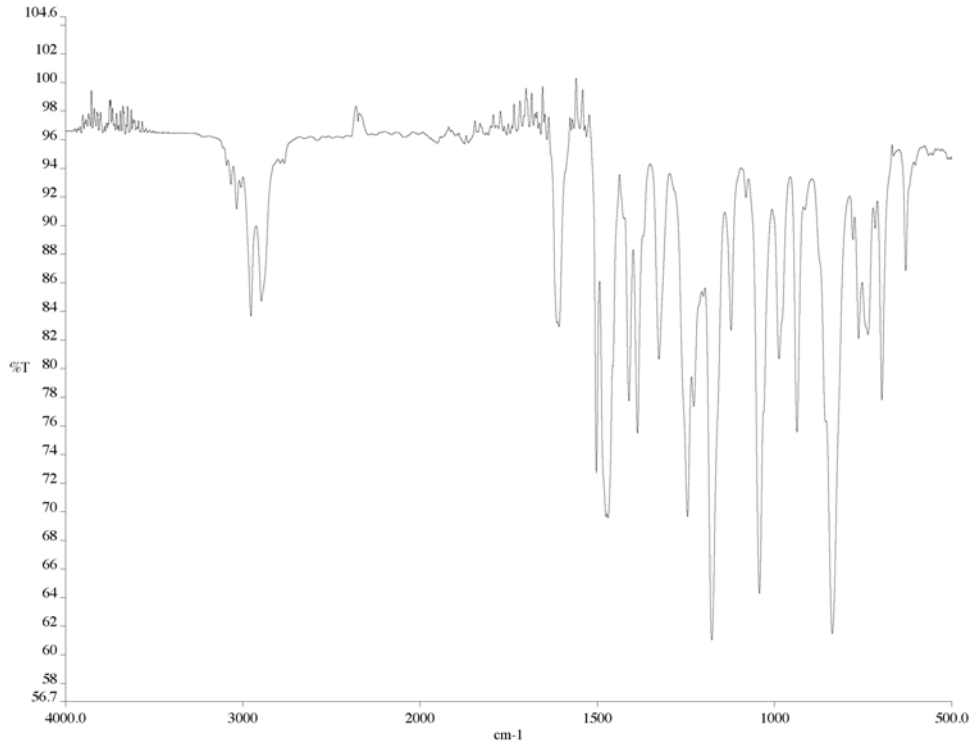


Figure A5.38 Infrared spectrum (thin film/NaCl) of compound **187**.

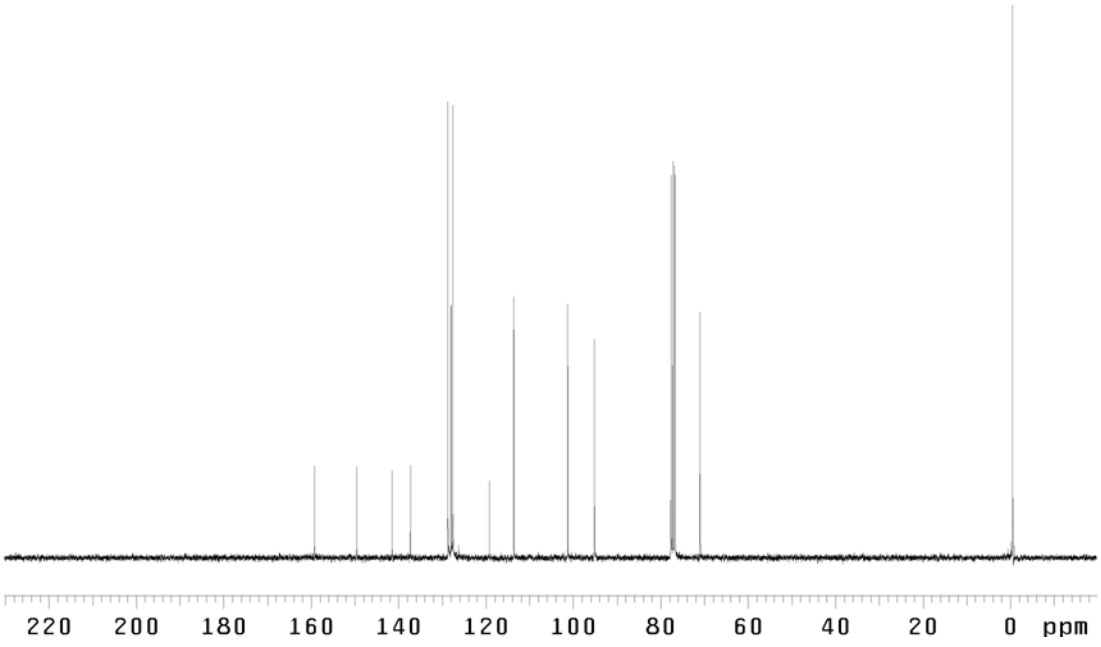


Figure A5.39 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **187**.

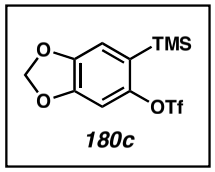


Figure A5.40 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **180c**.

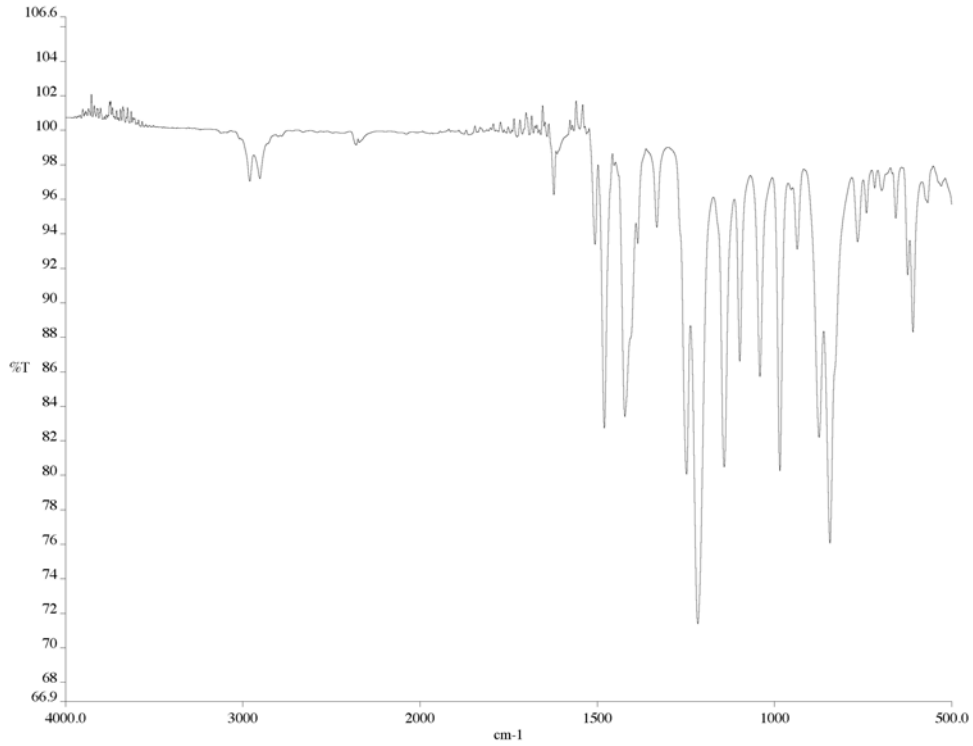


Figure A5.41 Infrared spectrum (thin film/NaCl) of compound **180c**.

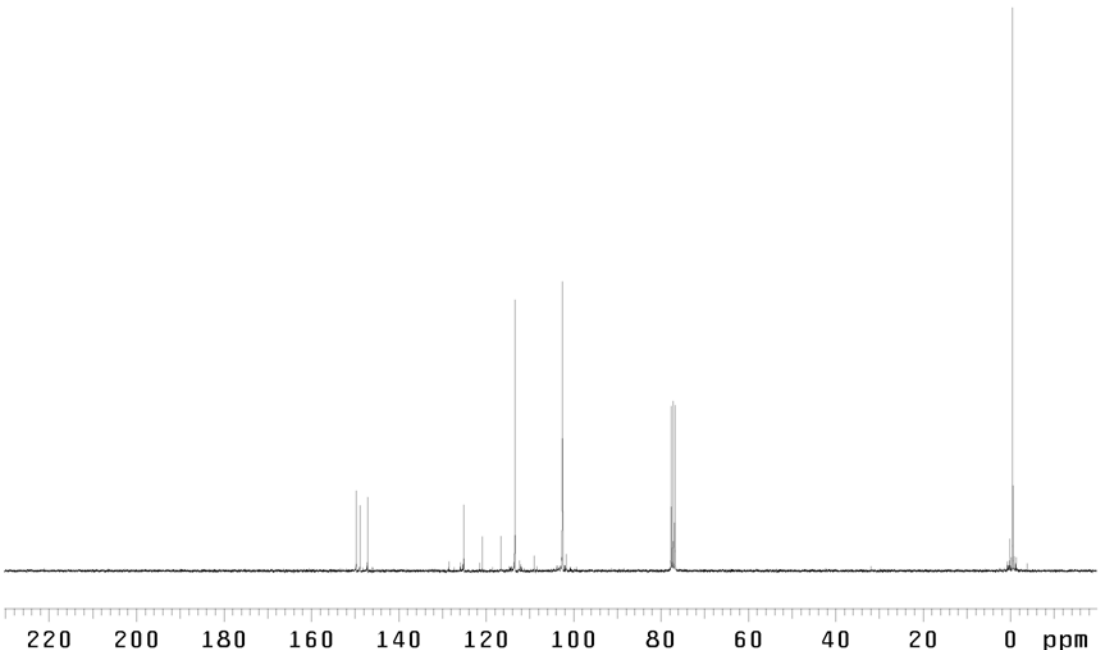


Figure A5.42 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **180c**.

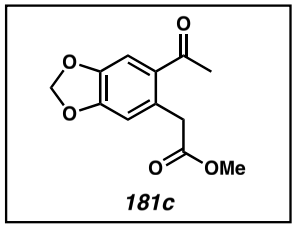


Figure A5.43 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **181c**.

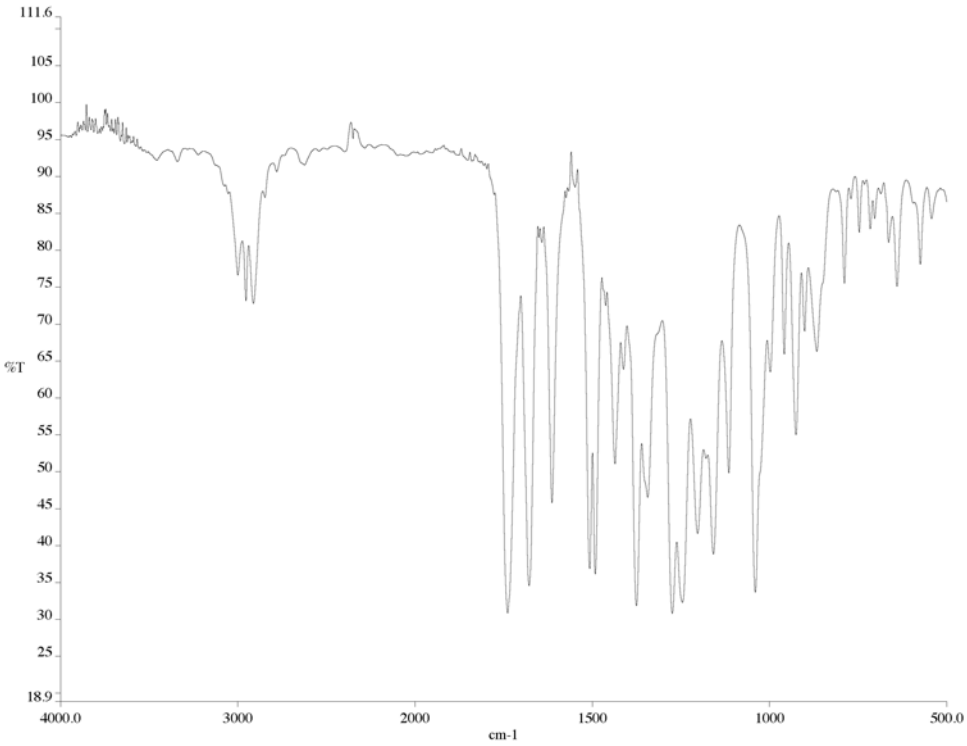


Figure A5.44 Infrared spectrum (thin film/NaCl) of compound **181c**.

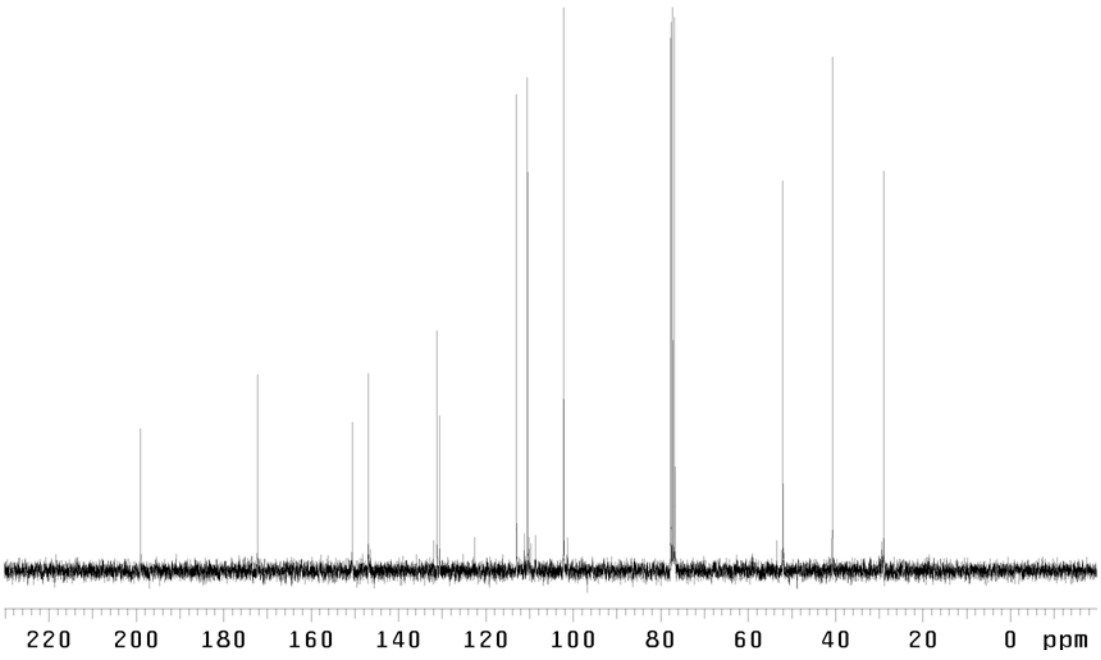


Figure A5.45 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **181c**.

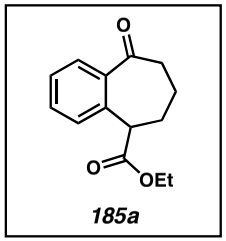


Figure A5.46 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **185a**.

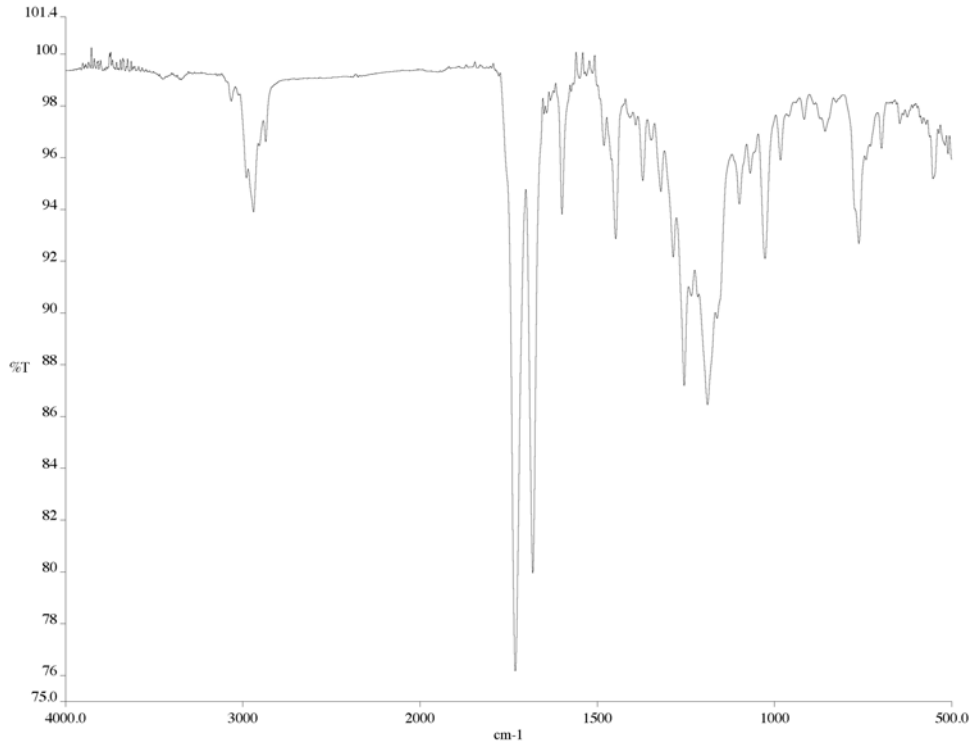


Figure A5.47 Infrared spectrum (thin film/NaCl) of compound **185a**.

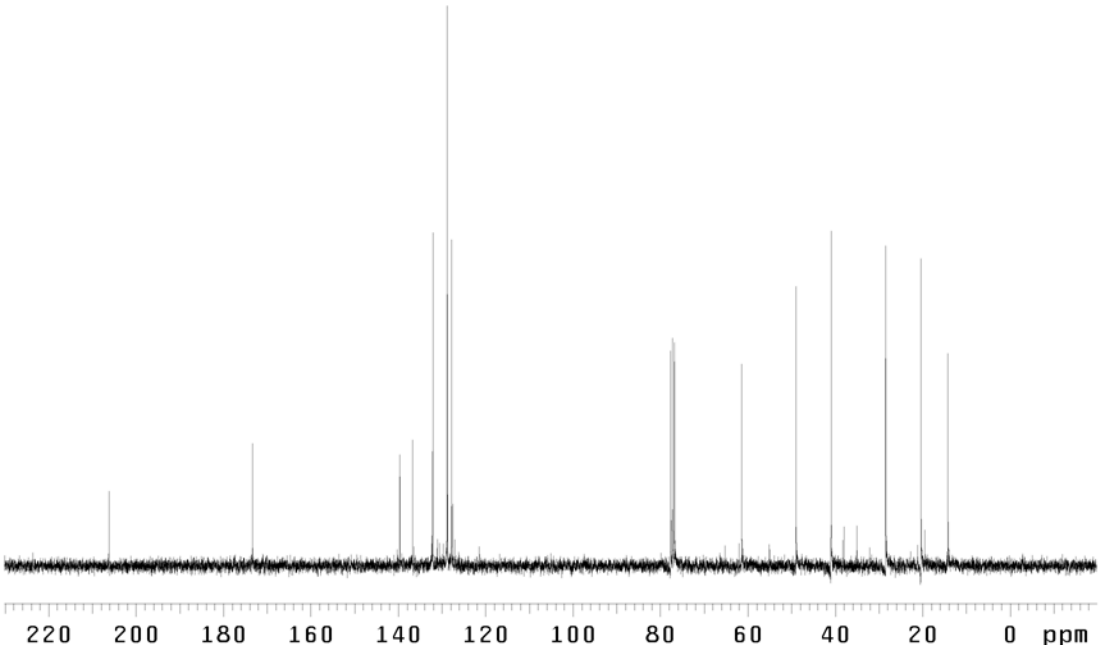


Figure A5.48 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **185a**.

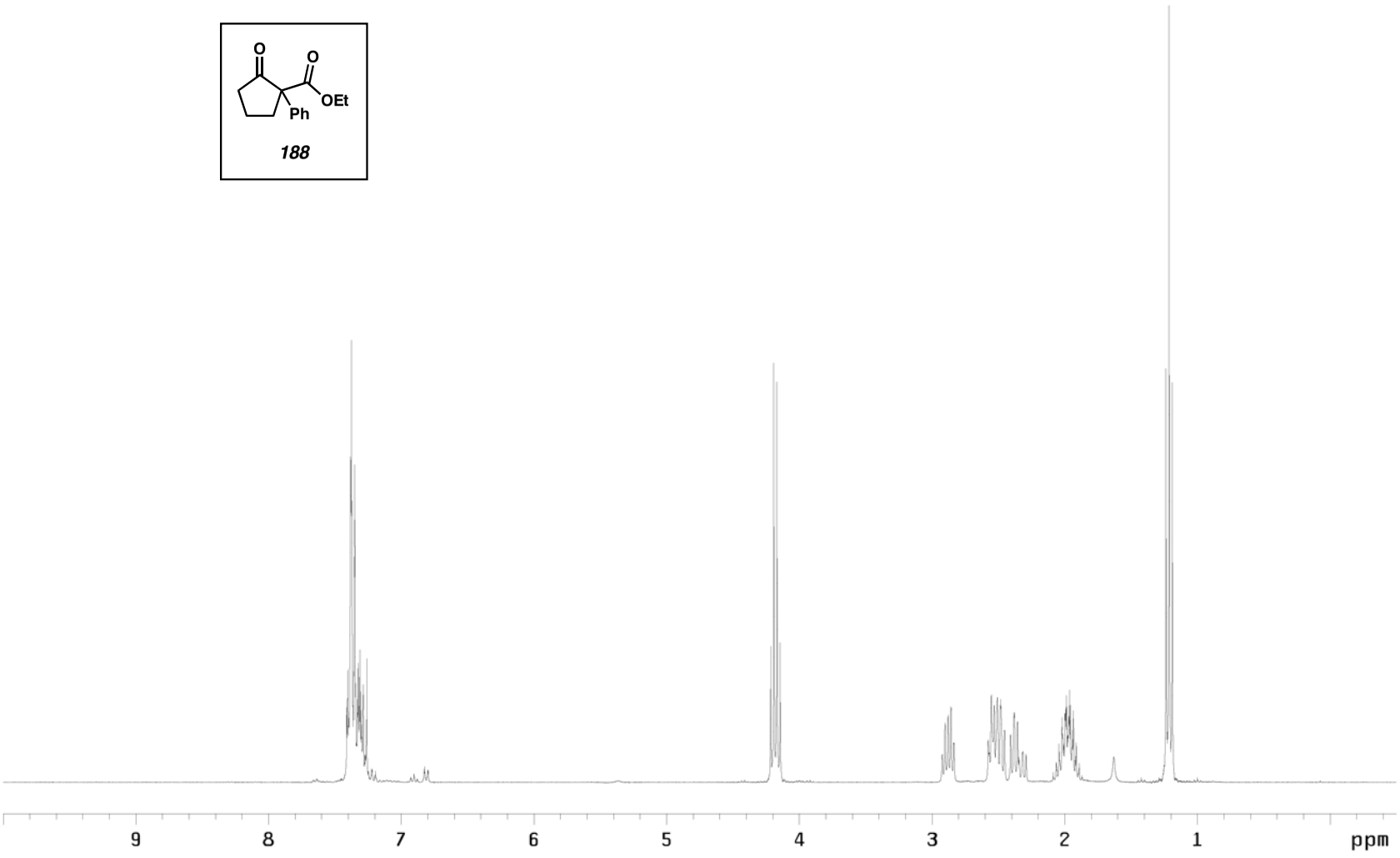


Figure A5.49 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **188**.

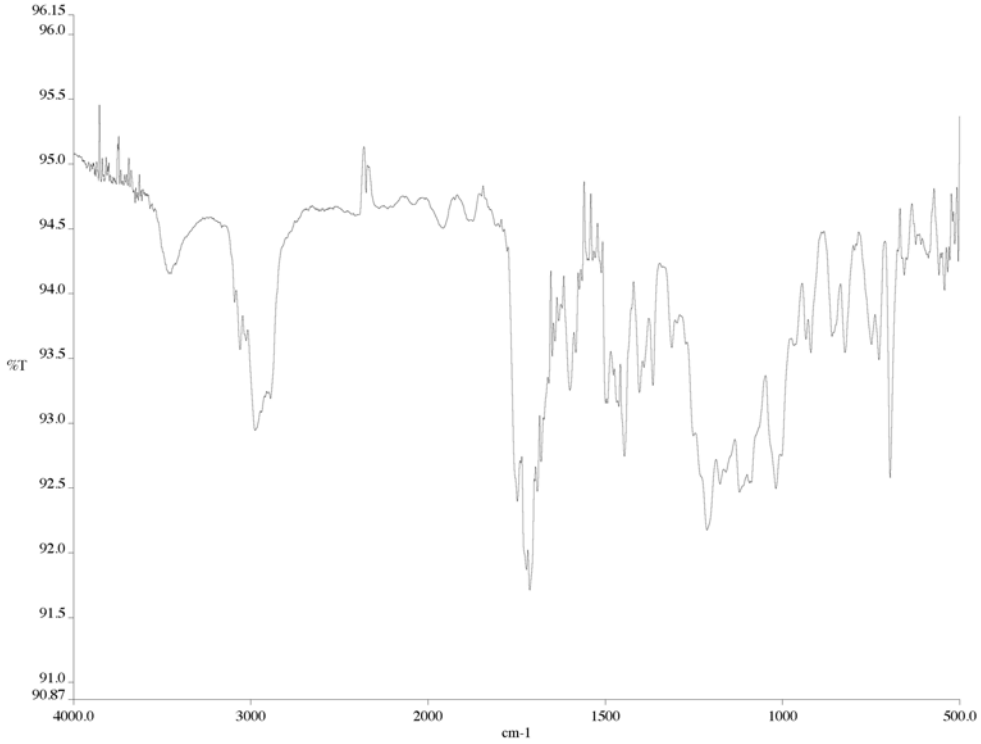


Figure A5.50 Infrared spectrum (thin film/NaCl) of compound **188**.

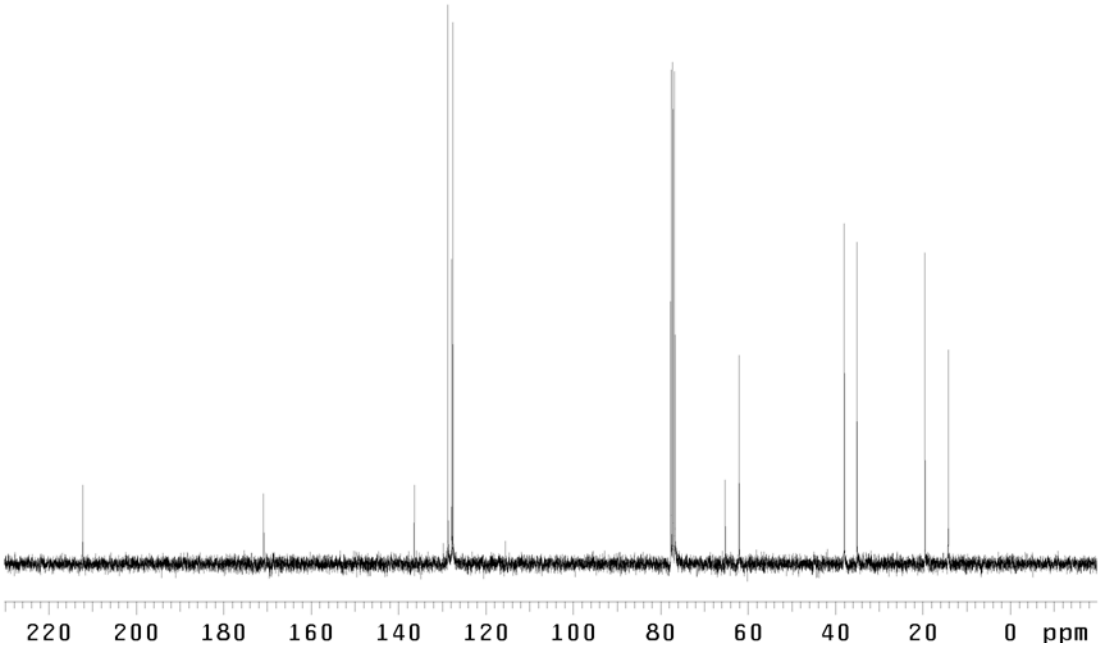


Figure A5.51 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **188**.

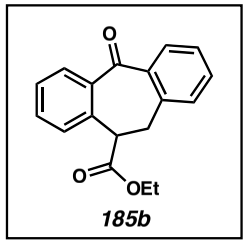


Figure A5.52 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **185b**.

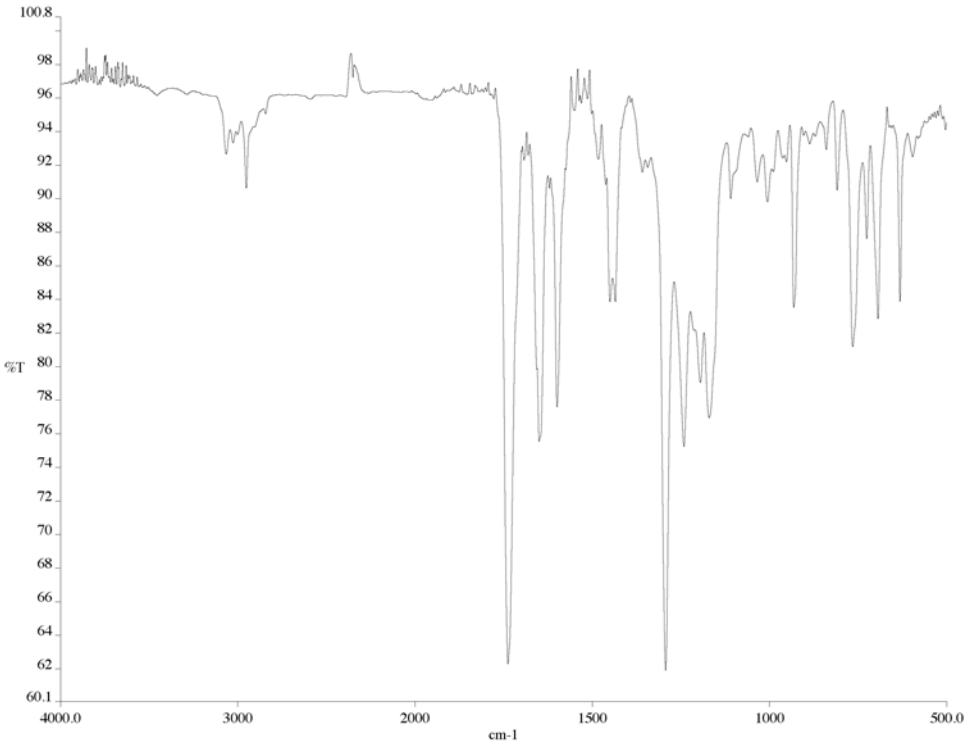


Figure A5.53 Infrared spectrum (thin film/NaCl) of compound **185b**.

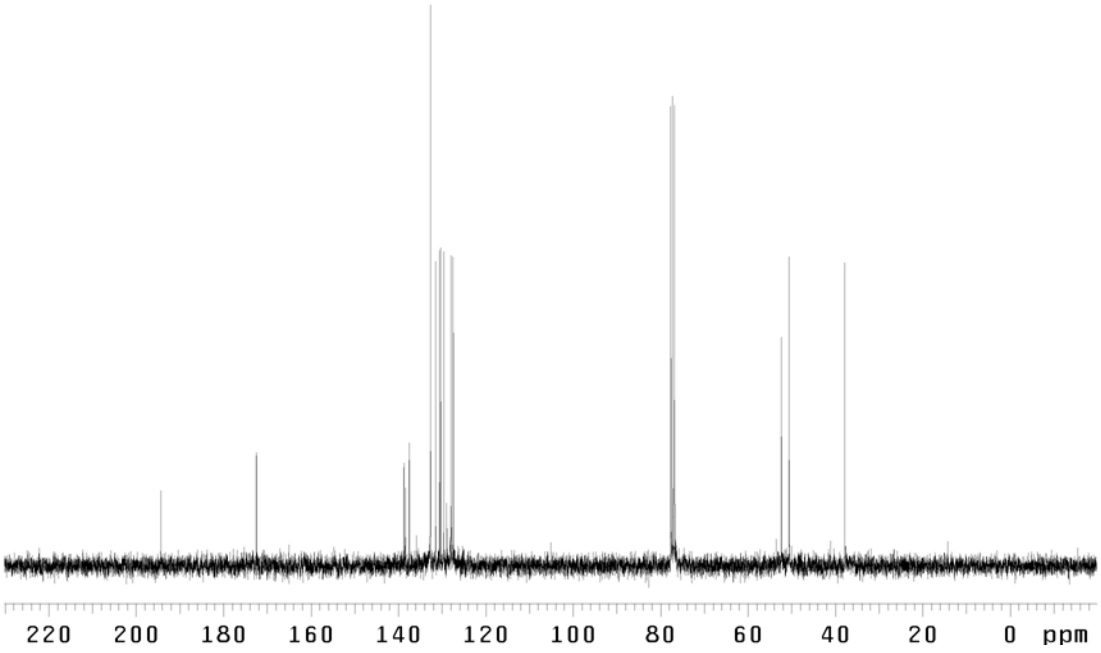


Figure A5.54 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **185b**.

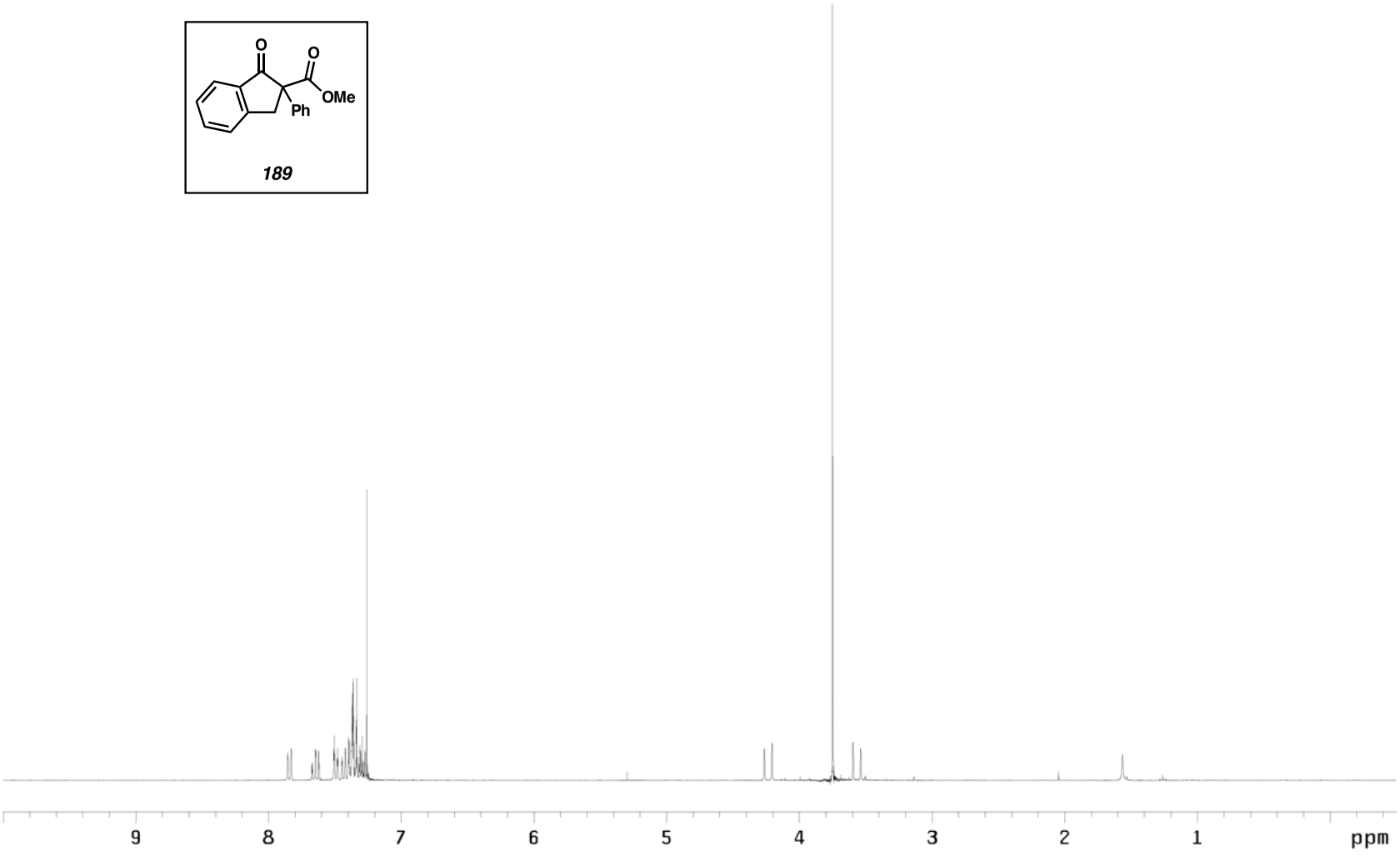


Figure A5.55 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **189**.

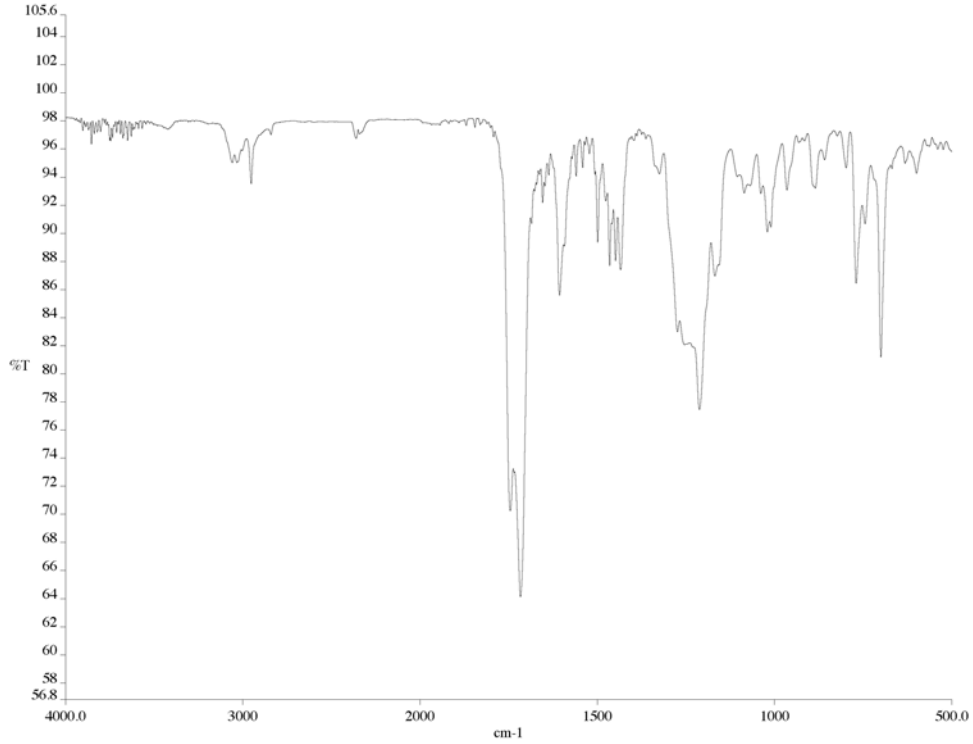


Figure A5.56 Infrared spectrum (thin film/NaCl) of compound **189**.

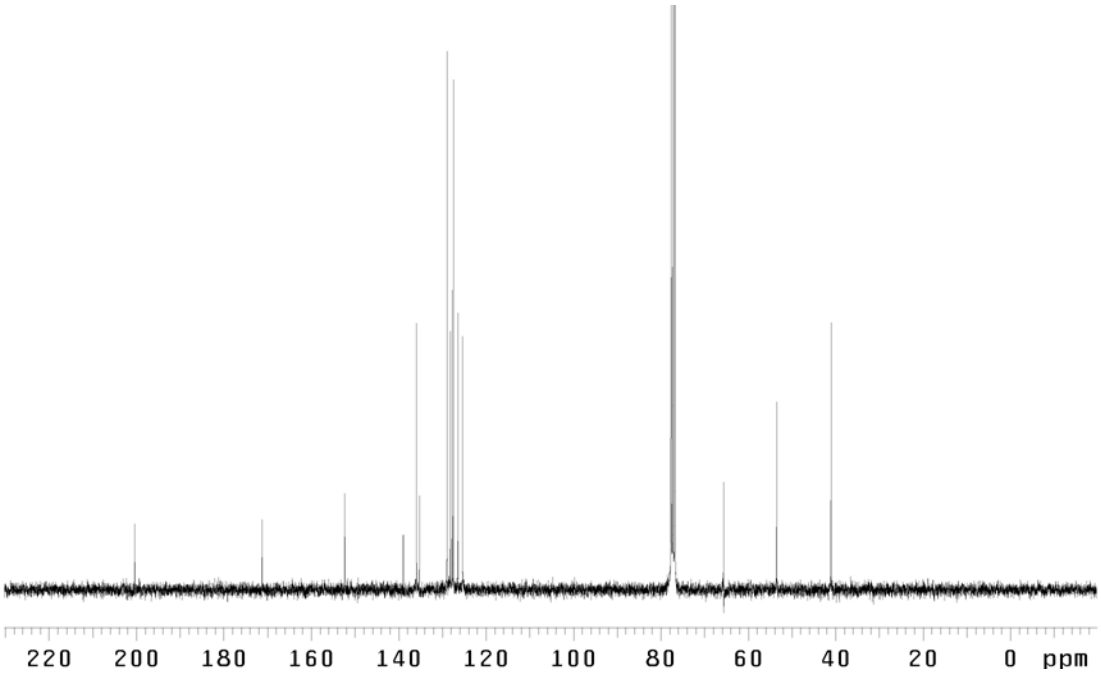


Figure A5.57 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **189**.

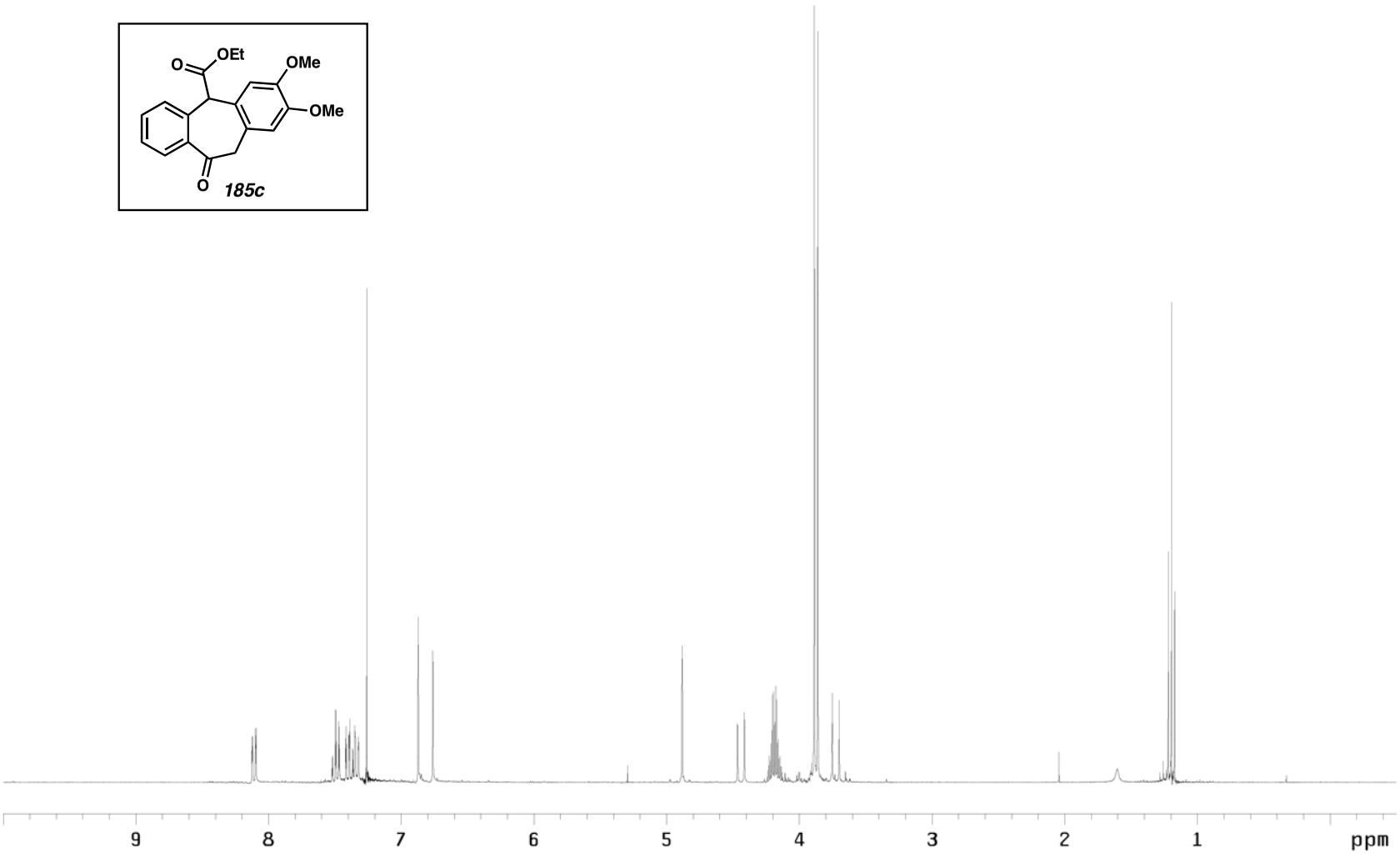


Figure A5.58 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **185c**.

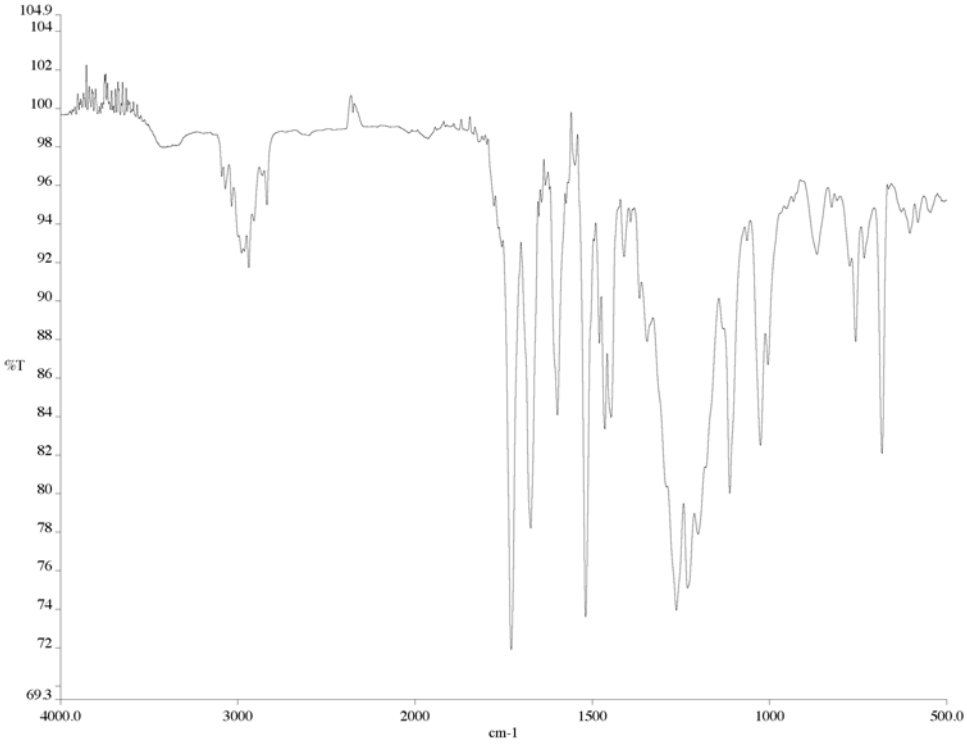


Figure A5.59 Infrared spectrum (thin film/NaCl) of compound **185c**.

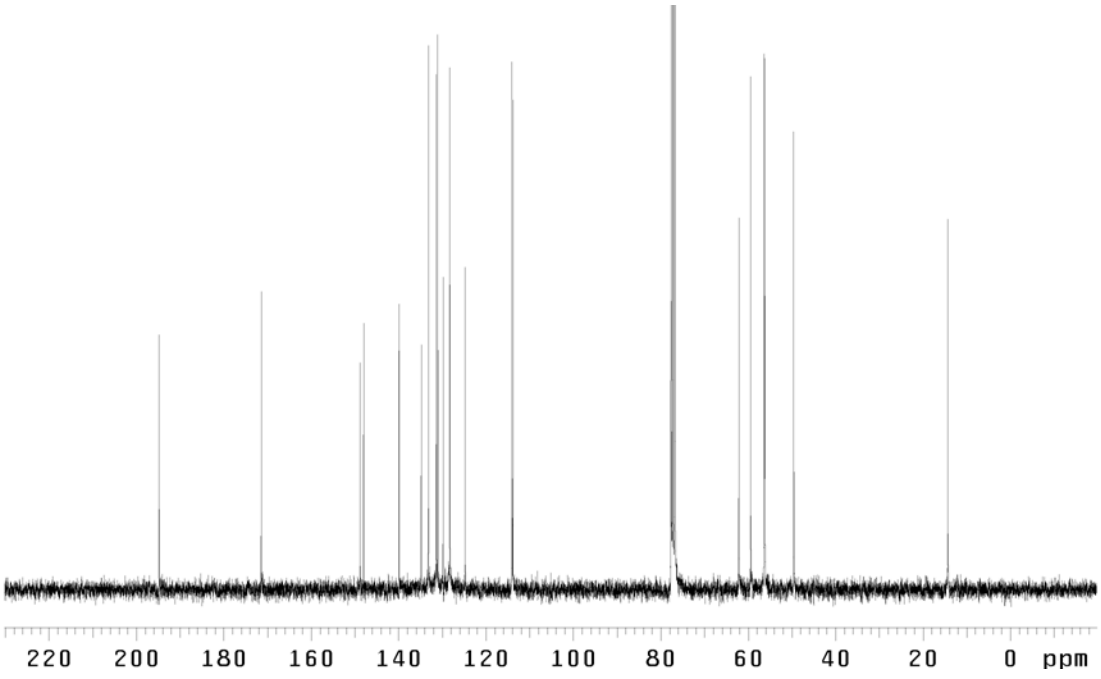


Figure A5.60 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **185c**.

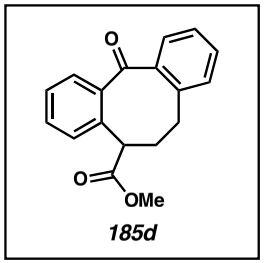


Figure A5.61 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **185d**.

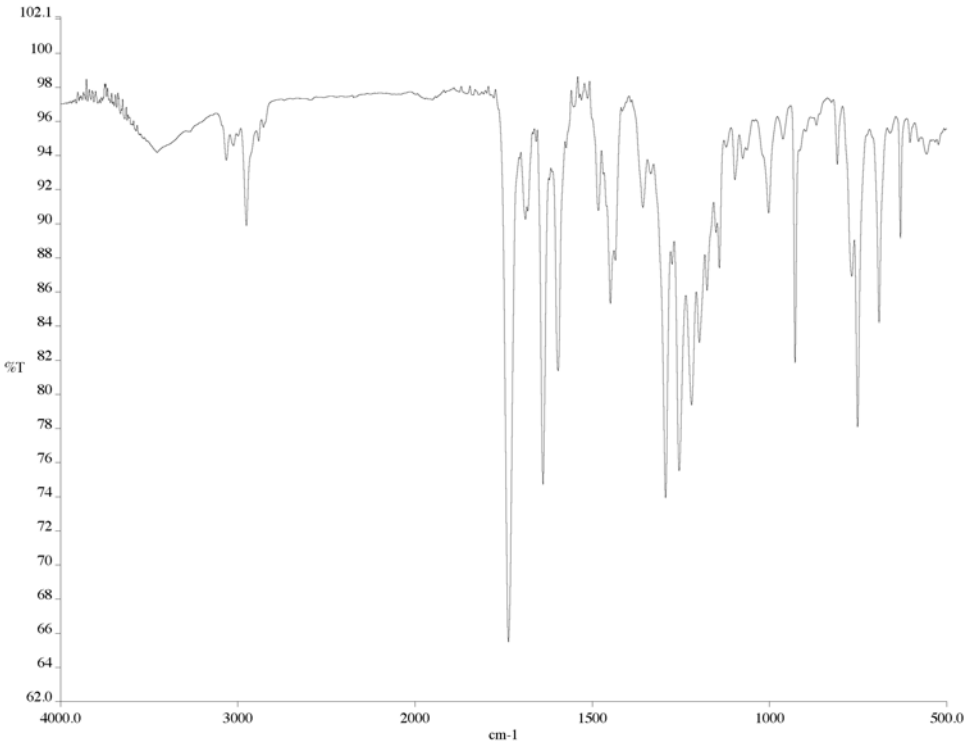


Figure A5.62 Infrared spectrum (thin film/NaCl) of compound **185d**.

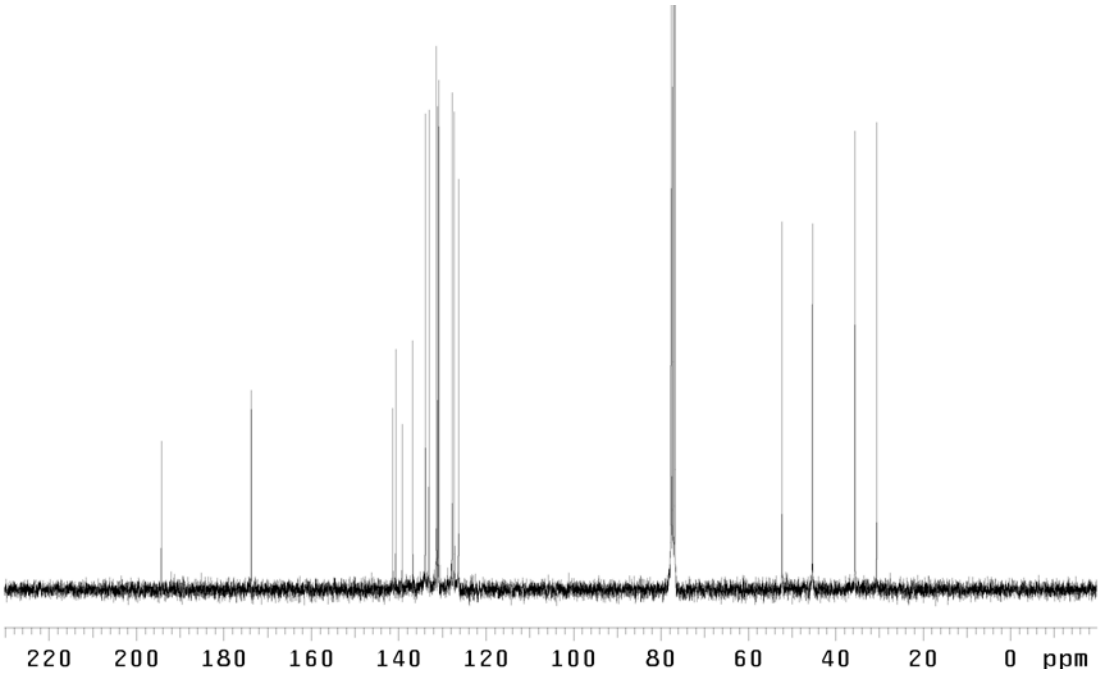


Figure A5.63 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **185d**.

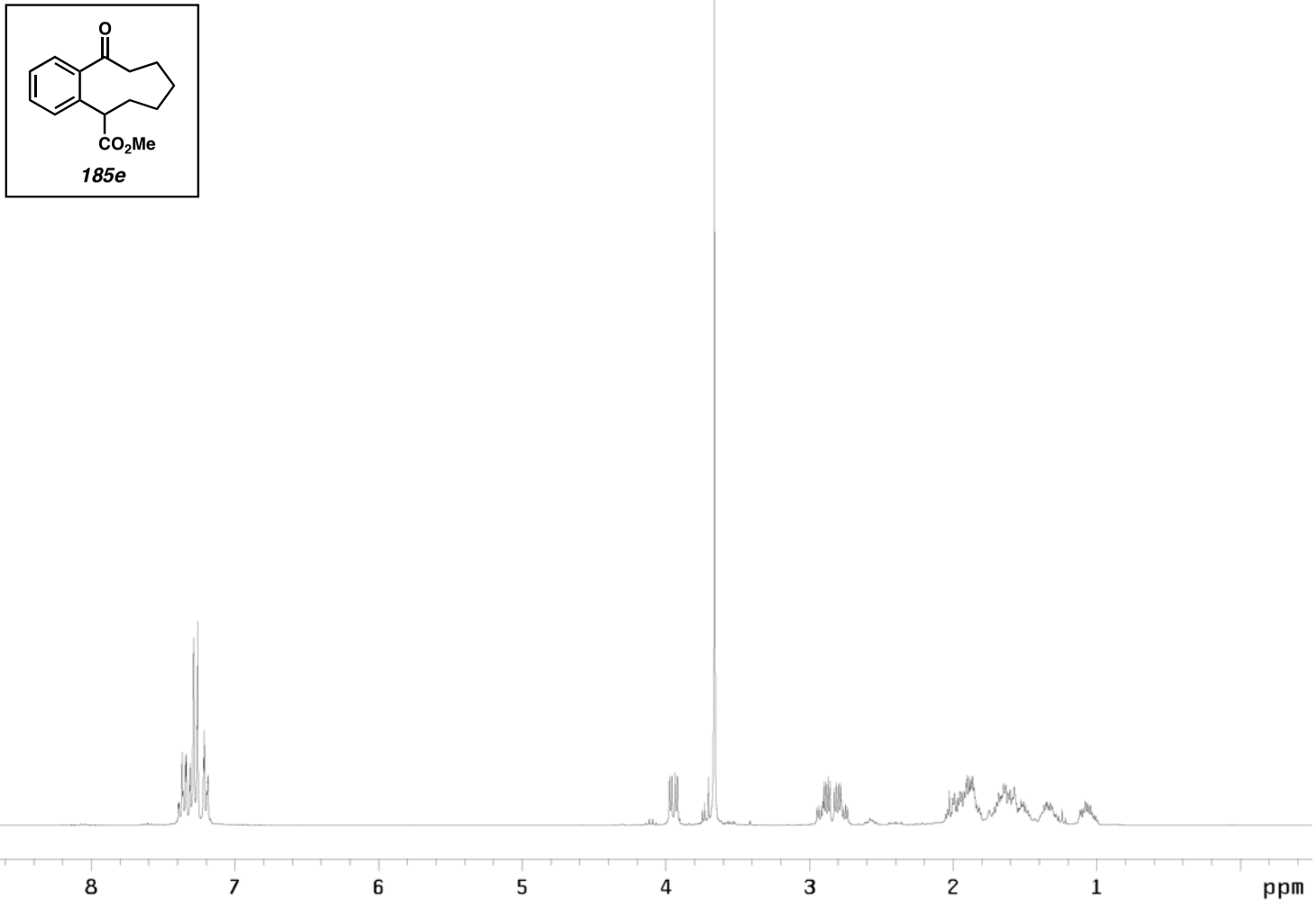


Figure A5.64 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **185e**.

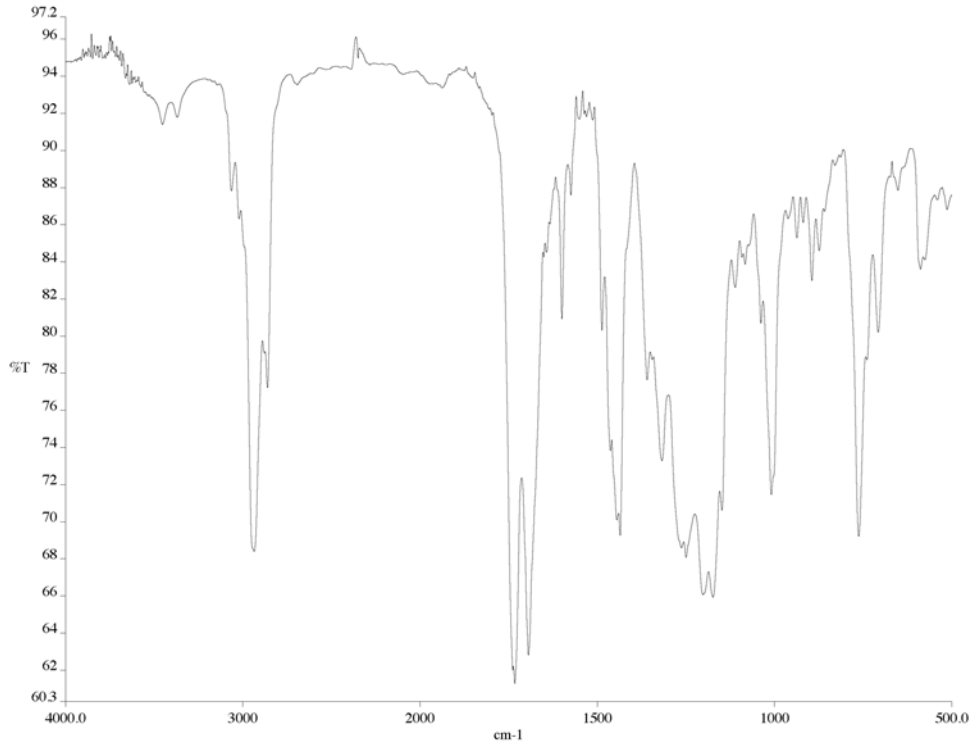


Figure A5.65 Infrared spectrum (thin film/NaCl) of compound **185e**.

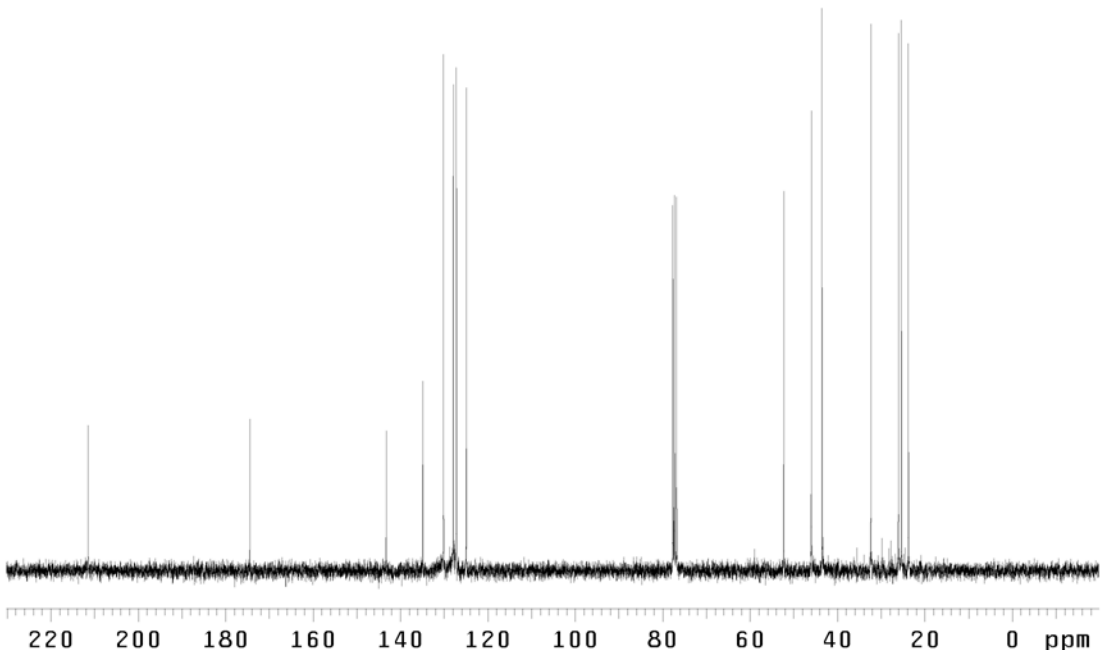


Figure A5.66 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **185e**.

CHAPTER FOUR

A Convergent Synthesis of Amurensinine Via Selective C-H and C-C Insertion Reactions[†]

4.1 Background and Introduction

4.1.1 C-H and C-C Insertion Reactions in Natural Product Synthesis

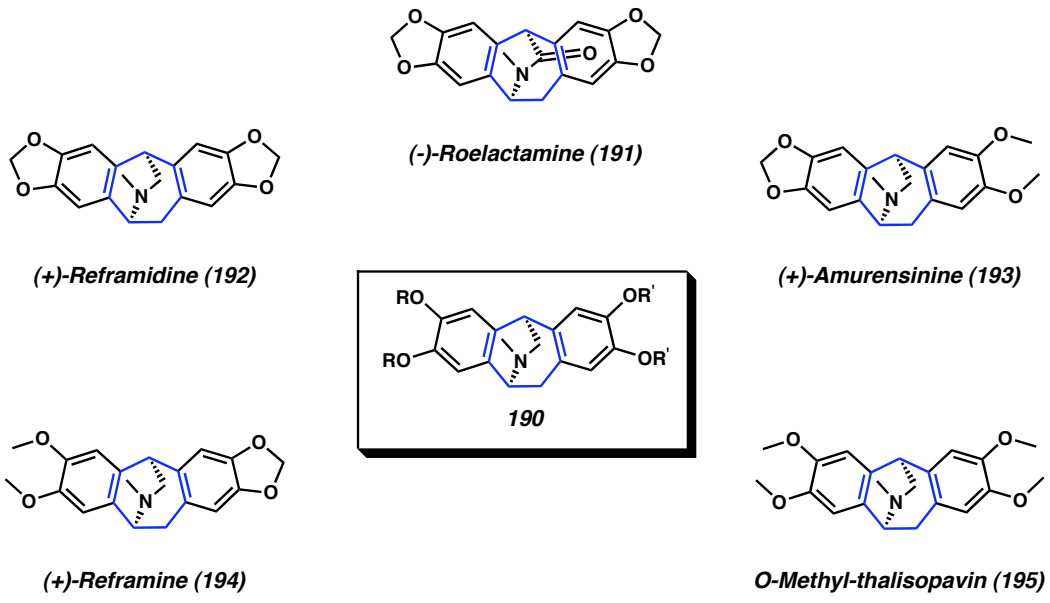
The activation of traditionally inert C-X bonds has become an important area of chemical research.[1] Unfortunately, the application of selective C-H and C-C activation reactions in the context of complex natural product synthesis has been limited because of the shear abundance of these two types of bonds in most organic molecules. The development of mild C-H[2] and C-C[3] insertion reactions may ultimately change the way synthetic chemists approach natural product synthesis by allowing efficient disconnections that would be forbidden under traditional retrosynthetic analysis. In this chapter we present a convergent and enantioselective synthesis of the natural product amurensinine that takes advantage of direct, mild, and selective C-H and C-C insertion reactions.

[†] This work was performed in collaboration with David C. Ebner, a graduate student in the Stoltz group at the California Institute of Technology.

4.1.2 Isopavine Natural Products

The synthesis of the isopavine natural products (Figure 4.1.1) and related non-natural structures has received considerable attention because of the important pharmacological properties of this family of alkaloids. Specifically, they have been shown to be promising lead structures for the treatment of neuronal disorders such as Parkinson's disease, Down's syndrome, Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's chorea.[4] All members of this group of natural products possess a tetracyclic structure containing a seven-membered benzannulated carbocycle (i.e., **190**, Figure 4.1.1). Despite the tremendous interest in the isopavines by the scientific community, few examples of the total syntheses of these natural products have been reported in the literature.[5]

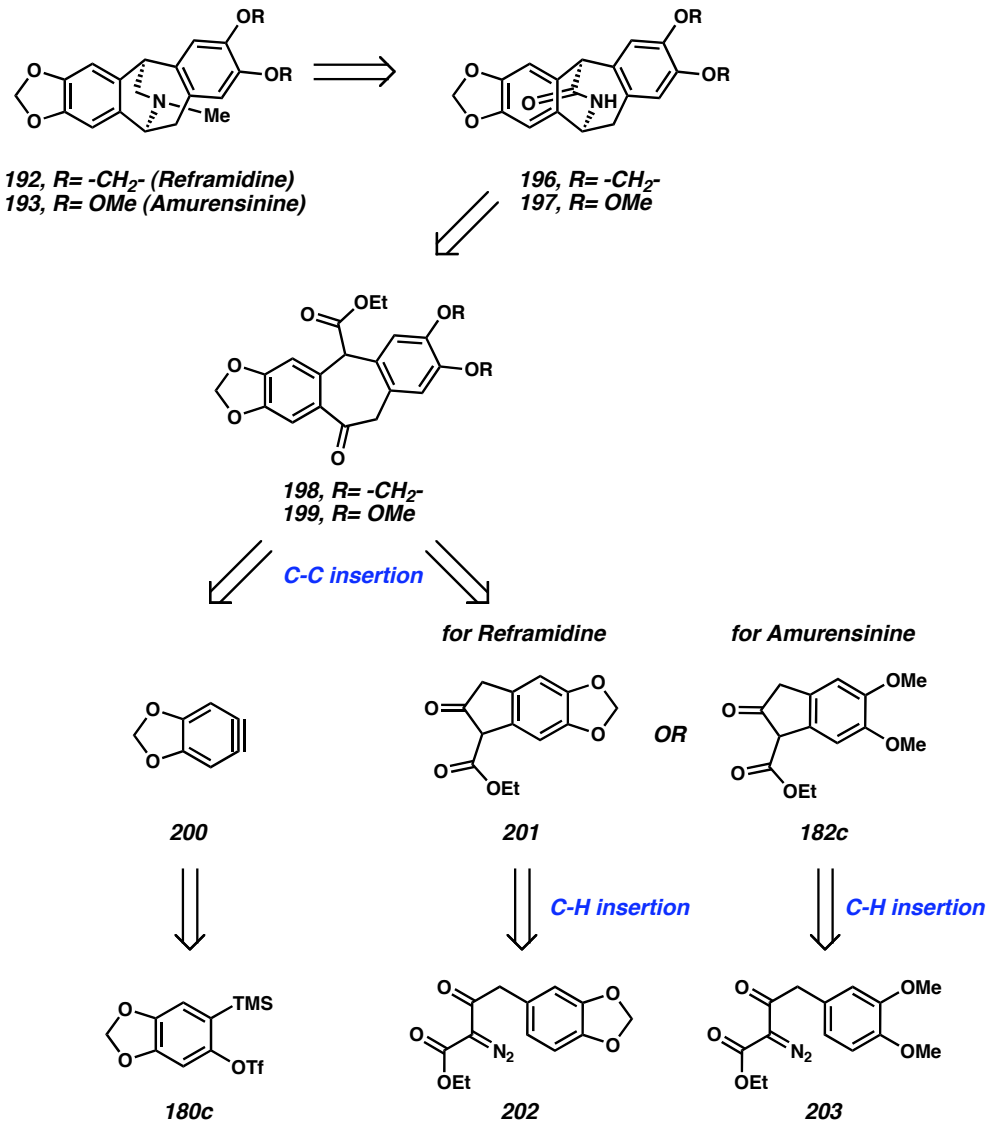
Figure 4.1.1



4.1.3 Retrosynthetic Analysis of Amurensinine and Reframidine

Reframidine (**192**) and amurensinine (**193**) are two members of the isopavine family. Our retrosynthetic strategy for the preparation of these alkaloids is shown in Scheme 4.1.1. Initial functional group interconversion of the tertiary amines in the natural products exposes lactams **196** and **197** as synthetic intermediates. We reasoned that these lactams could be accessed from ketoesters **198** and **199**, which contain seven-membered benzannulated carbocycles. These seven-membered ring structures are retrons for the direct and mild C-C insertion reaction discussed in chapter 3. Aryne **200** and β-ketoesters **201** and **182c** are then revealed as suitable substrates for the C-C insertion reaction. Aryne **200** may be generated in situ from trimethylsilyl triflate **180c**, while β-ketoesters **201** and **182c** may be synthesized by selective rhodium-catalyzed C-H insertion reactions of diazo compounds **202** and **203**, respectively.

Scheme 4.1.1

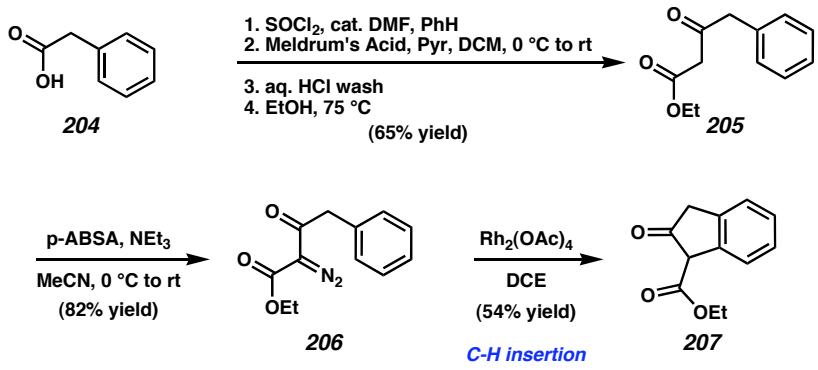

OR
OR
N
Me
O
O
192, R= -CH2- (Reframidine)
193, R= OMe (Amurensinine)
O
NH
196, R= -CH2-
197, R= OMe
OEt
198, R= -CH2-
199, R= OMe
C-C insertion
for Reframidine
for Amurensinine
OR
OMe
OEt
200
201
182c
C-H insertion
C-H insertion
TMS
OTf
N2
180c
202
203

4.2 Synthesis of Amurensinine

4.2.1 Model Studies on the C-H/C-C Insertion Strategy for the Isopavines

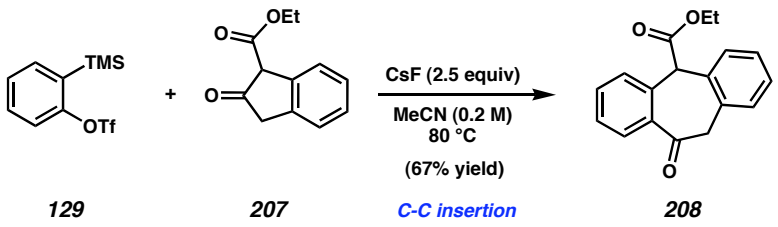
To test the viability of our strategy for synthesizing the isopavines, we commenced our efforts with the construction of a model system for ketoesters **198** and **199**. As reported in the literature for a similar substrate,[6] the unfunctionalized β-ketoester **207** was generated rapidly via a selective rhodium-catalyzed C-H insertion reaction (Scheme 4.2.1). Phenylacetic acid **204** was first converted to acyclic β-ketoester **205**, which was then diazotized to form intermediate **206**. This diazoketoester was treated with $Rh_2(OAc)_4$ in DCE, which resulted in a selective C-H insertion reaction to form cyclic β-ketoester **207**.

Scheme 4.2.1



This model β-ketoester **207** was then coupled with trimethylsilyl triflate **129** to yield the desired model ketoester **208** in 67% isolated yield (Scheme 4.2.2).

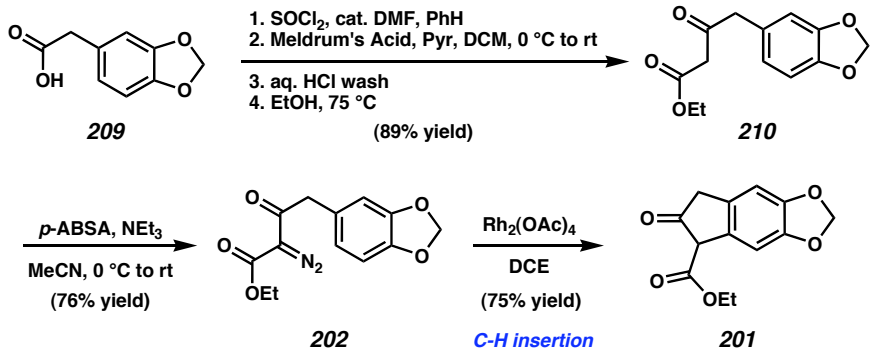
Scheme 4.2.2



4.2.2 Synthetic Efforts Toward the Synthesis of Reframidine

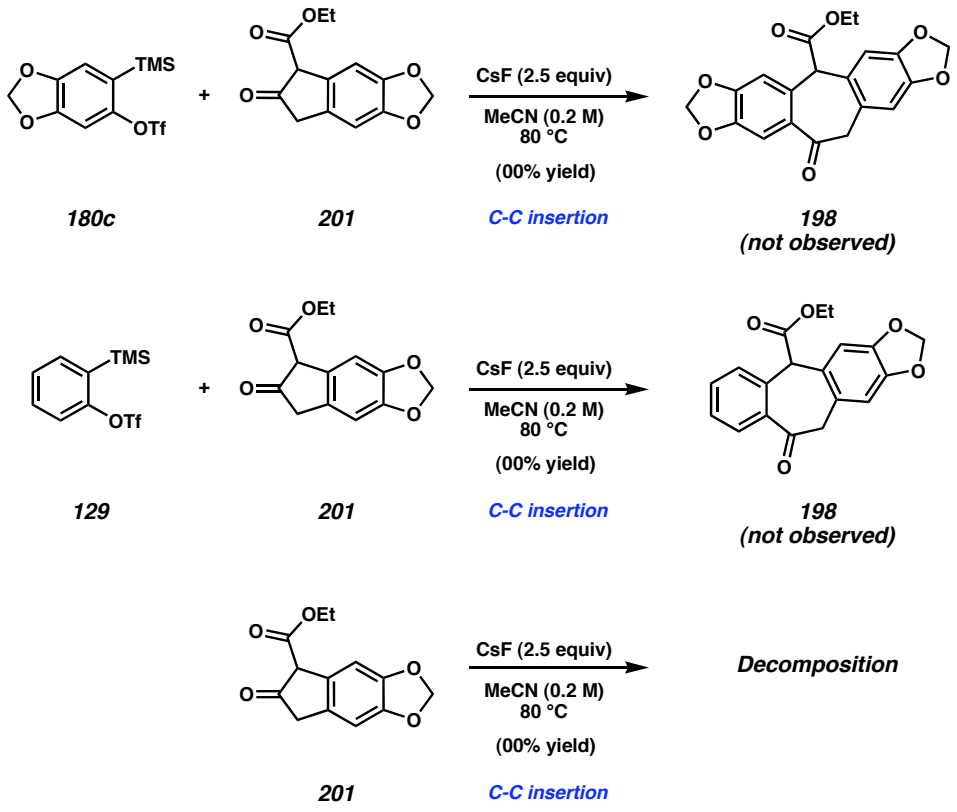
After establishing the viability of the C-H/C-C insertion strategy for synthesizing the core structure of the isopavines, we turned our attention to the synthesis of reframidiine (**192**, Figure 4.1.1). The fully functionalized β-ketoester **201** was synthesized rapidly from phenylacetic acid **209** (Scheme 4.2.3). Interestingly, diazo intermediate **202** underwent a highly position-selective C-H insertion reaction to produce the desired β-ketoester **201**.[7]

Scheme 4.2.3



Unfortunately, all attempts to couple β-ketoester **201** with trimethylsilyl triflates **180c** and **129** were unsuccessful (Scheme 4.2.4). In fact, simple exposure of β-ketoester **201** to the reaction conditions in the absence of any trimethylsilyl triflate led to decomposition. We reasoned that the methylenedioxy functionality in the β-ketoester was unstable to the conditions.

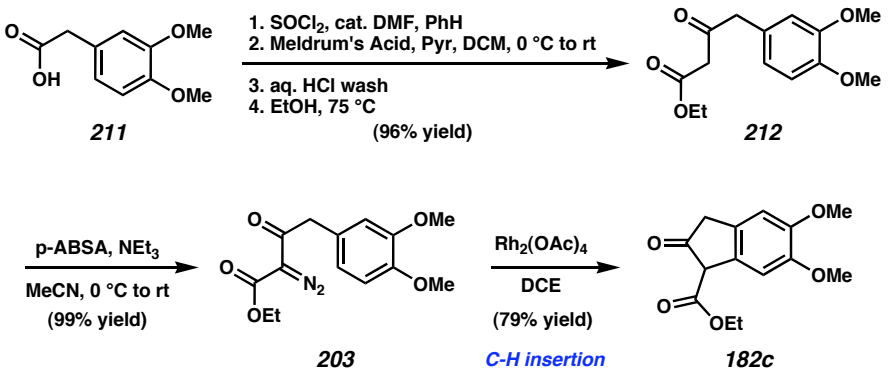
Scheme 4.2.4



4.2.3 Synthesis of the Core Structure of Amurensinine

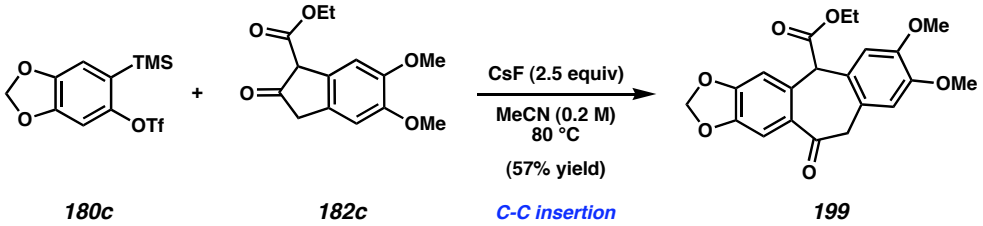
We then attempted to synthesize the core structure of amurensinine (**193**, Figure 4.1.1) by the same strategy, with the hope that the corresponding dimethoxy functionality in β-ketoester **182c** would be more stable to the reaction conditions. Phenylacetic acid **211** was easily converted to the desired β-ketoester **182c**, once again with highly position-selective C-H insertion of diazo intermediate **203** (Scheme 4.2.5).

Scheme 4.2.5



Gratifyingly, the coupling of β-ketoester **182c** and aryne precursor **180c** under our standard reaction conditions produced ketoester **199** in 57% isolated yield (Scheme 4.2.6). This transformation represents a direct and mild C-C insertion reaction to generate the polycyclic carbon framework of amurensinine (**193**).

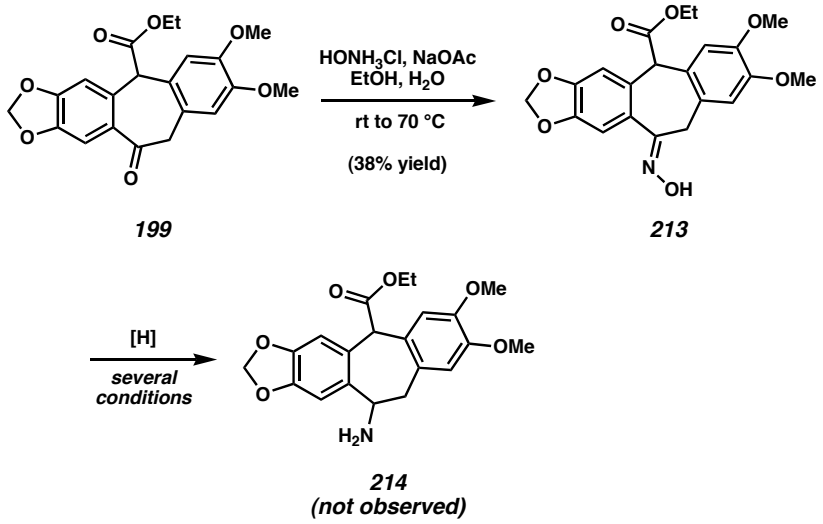
Scheme 4.2.6



4.2.4 Completion of the Total Synthesis of Amurensinine

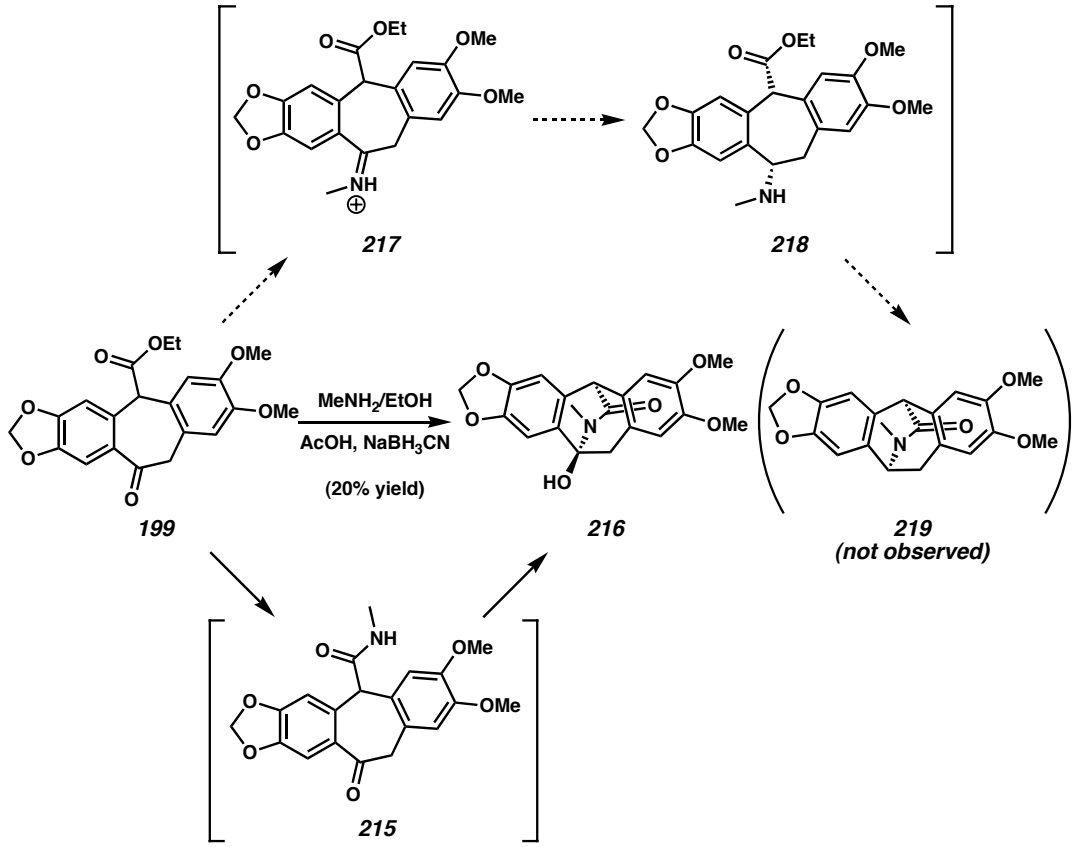
At this point, all that remained for completing the synthesis of amurensinine (**193**) was a series of functional group interconversions of ketoester **199**. Most notably, an atom of nitrogen needed to be added to the molecule. Initial efforts for nitrogen insertion focused on oximation followed by selective reduction to a primary amine (Scheme 4.2.7). Although oxime **213** was easily synthesized from ketoester **199**, the reduction of the oxime to aminoester **214** was not observed under several conditions.

Scheme 4.2.7



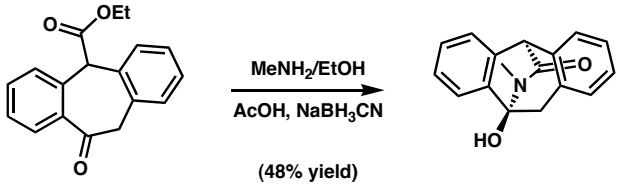
Next, we attempted to insert nitrogen into the molecule by reductive amination with methylamine (Scheme 4.2.8). Ketoester **199** was treated with excess methylamine in the presence of acetic acid and $NaCNBH_3$. Instead of observing the desired lactam **219**, we isolated aminal **216**. It seemed that amine addition into the ester was more facile than amine addition into the electronically deactivated and sterically hindered ketone of ketoester **199**.

Scheme 4.2.8



Surprisingly, a similar reaction occurred when model ketoester **208** was subjected to the reductive amination conditions (Scheme 4.2.9). Since the ketone functionality in this compound was not electronically deactivated towards nucleophillic attack, this suggested the importance of steric factors in the selective reactivity of the ester.

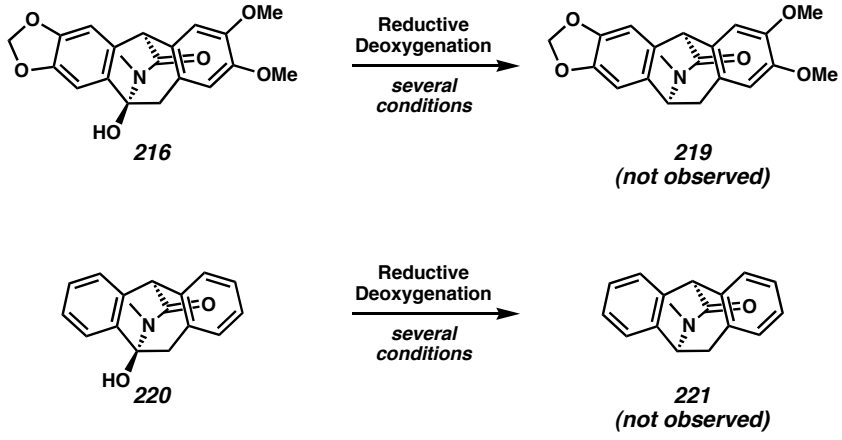
Scheme 4.2.9



208 ***220***

Unfortunately, all attempts to reductively deoxygenate aminal **216** or the model aminal **220** were unsuccessful (Scheme 4.2.10). All reported examples for the reductive deoxgenation of aminals presumably proceed through an iminium intermediate; but in our system this would lead to structures containing anti-Bredt olefins (i.e., **222** and **223**). Therefore, another strategy was needed.

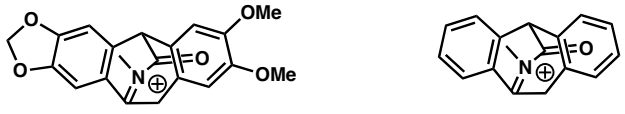
Scheme 4.2.10



216 ***219 (not observed)***

220 ***221 (not observed)***

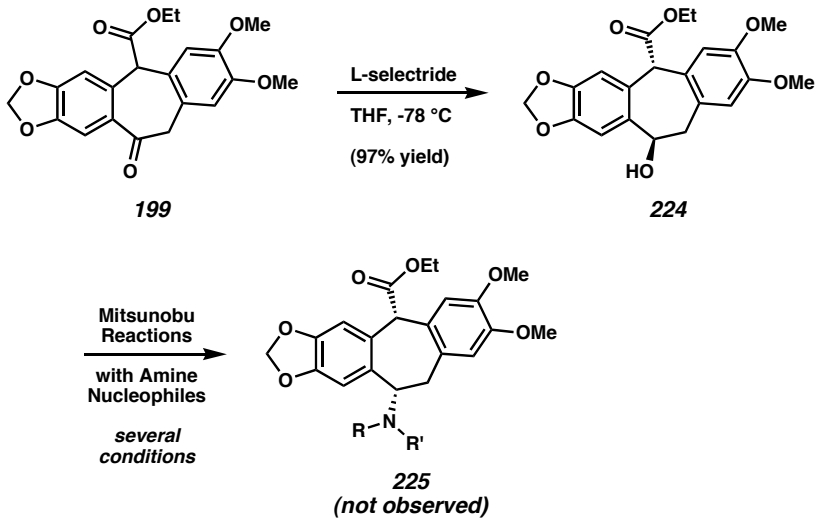
anti-Bredt Olefins (not observed):



222 ***223***

We then attempted to insert nitrogen into the molecule by a Mitsunobu reaction strategy.[8] The selective conversion of ketoester **199** to *trans*-hydroxy ester **224** was realized with L-selectride (Scheme 4.2.11).[9] Unfotunately, subjection of this alcohol to Mitsunobu conditions with amine nucleophiles led to decomposition in most cases.[10]

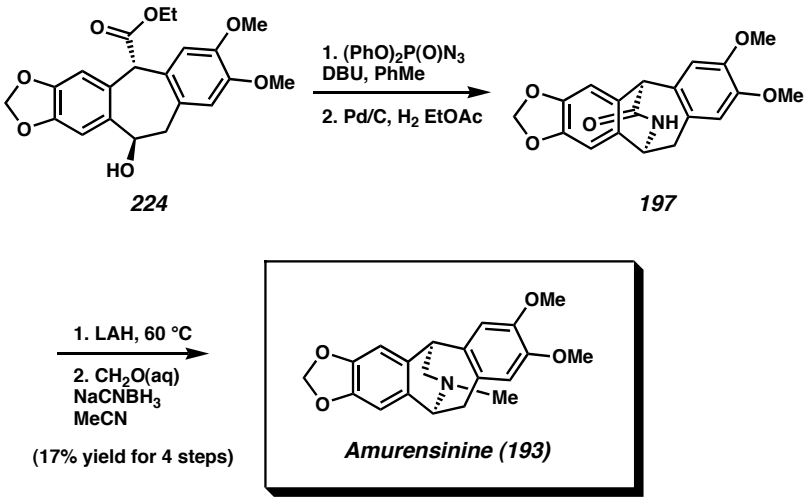
Scheme 4.2.11



Since the direct addition of an amine nucleophile into hydroxyester **224** was unsuccessful, we attempted a more indirect addition of an azide nucleophile, which would be reduced at a later stage to the corresponding amine. This two-step procedure for amine installation was realized by treating hydroxyester **224** with $(PhO)_2P(O)N_3$ in the presence of DBU,[11] followed by reduction with Pd/C under an atmosphere of H_2 (Scheme 4.2.12). To our pleasant surprise, the resulting aminoester spontaneously formed the desired lactam **197**. Simple reduction of the lactam with LAH and subsequent reductive amination of formaldehyde with the resulting secondary amine yielded the

natural product amurensinine (**193**). The spectroscopic data for synthetic amurensinine (**193**) matched the data reported in the literature.[5i]

Scheme 4.2.12



4.3 Conclusion

In summary, we have developed a convergent synthesis of amurensinine (**193**) that takes advantage of sequential C-H and C-C insertion reactions to build the core structure of the natural product in a rapid fashion. The synthesis is 14 total steps from known starting materials, with a longest linear count of only 11 steps from commercially available phenylacetic acid **211**. Our work highlights the utility of selective C-H and C-C insertion reactions in the context of natural product synthesis. Application of C-H, C-C, and other inert C-X insertion reactions toward the synthesis of related natural products is currently under investigation.

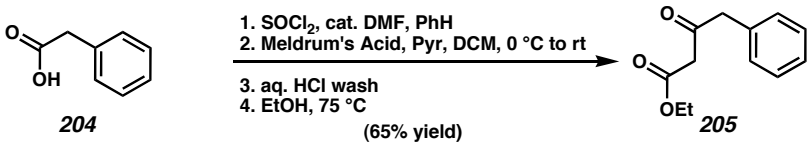
4.4 Experimental Section

4.4.1 Materials and Methods

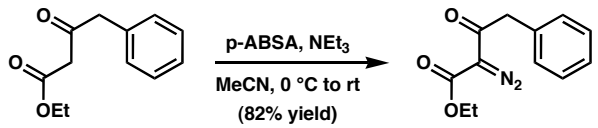
Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry, deoxygenated solvents. Commercially obtained reagents were used as received. Cesium fluoride was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032 - 0.063 mm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{19}F NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to CF_3COOH (δ -76.54). Data for ^{19}F NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in terms of

frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

4.4.2 Preparative Procedures

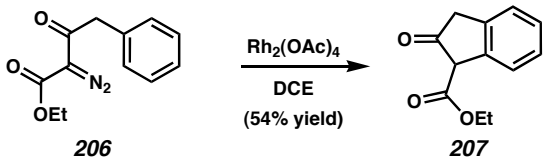


β-ketoester 205. To a solution of phenylacetic acid **204** (2.0 g, 14.7 mmol) in benzene (15 mL) was added thionyl chloride (2.14 ml, 29.4 mmol) and 10 drops of DMF. After stirring for 3 hours, the reaction mixture was concentrated under reduced pressure. The resulting crude acid chloride was then dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. To this solution was added pyridine (2.4 mL, 29.4 mmol) and Meldrum's acid (2.12 g, 14.7 mmol). After stirring at 0 °C for 2 minutes, the mixture was stirred at room temperature for 8 hours. The reaction was then extracted with 10% aqueous HCl (20 mL) and H_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was then dissolved in absolute EtOH (25 mL) and refluxed at 75 °C. After 11 hours, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided β-ketoester **205** (1.96 g, 65% yield) as a clear oil. The characterization data matched the data reported in the literature.[12]

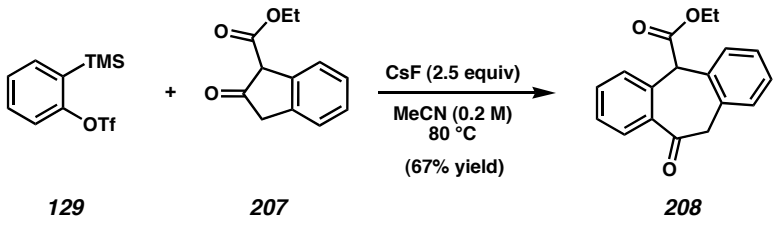


205 *206*

Diazoketoester 206. To a cooled solution (0 °C) of β-ketoester **205** (981 mg, 4.75 mmol) in acetonitrile (18 mL) was added p-ABSA (1.26 ml, 5.23 mmol) and NEt_3 (2 mL, 5.23 mmol). After stirring at 0 °C for 1 minute, the mixture was stirred at room temperature for 90 minutes. The reaction was extracted with 10% aqueous NaOH (20 mL). The aqueous layer was then washed with Et_2O (3 x 8 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided diazoketoester **206** (906 mg, 82% yield) as a clear oil. The characterization data matched the data reported in the literature.[13]

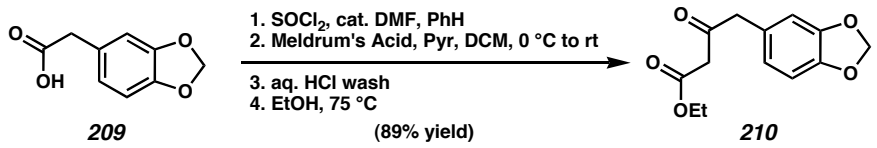


β-ketoester 207. A two-necked flask equipped with an addition funnel and an N_2 inlet was charged with a catalytic amount of $Rh_2(OAc)_4$ (80 mg, 0.18 mmol) and DCE (14 mL). A solution of diazoester **206** (837 mg, 3.60 mmol) in DCE (14 mL) was added dropwise over 1 hour via the addition funnel. After stirring for 3 hours at room temperature, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided β-ketoester **207** (398 mg, 54% yield) as a clear oil. The characterization data matched the data reported in the literature.[14]

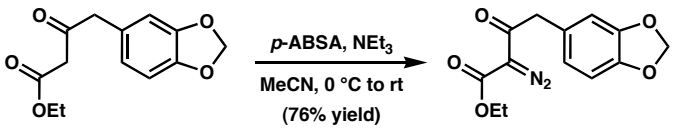


Model ketoester 208. To a flask containing acetonitrile (6.6 mL) was added β-ketoexter **207** (271 mg, 1.33 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**129**) (402 μL, 1.66 mmol) , and cesium fluoride (402 mg, 3.32 mmol). After refluxing at 80 °C for 45 minutes, the reaction mixture was cooled to room temperature and extracted with brine (10 mL). The aqueous layer was back-extracted with Et_2O (3 x 5

mL). The organics were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided model ketoester **208** (249 mg, 67% yield) as a clear oil: R_F 0.48 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.50 (td, *J* = 10.5, 3.7 Hz, 1H), (7.43-7.34 (m, 4H), 7.28-7.23 (m, 2H), 5.01 (s, 1H), 4.49 (d, *J* = 15.7 Hz, 1H), 4.28-4.10 (m, 2H), 3.87 (d, *J* = 15.7 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 171.3, 139.7, 137.5, 134.6, 133.3, 132.6, 131.4, 130.9, 130.6, 130.4, 128.5, 128.3, 127.8, 62.1, 59.9, 50.1, 14.2; IR (thin film/NaCl) 2981, 1729, 1674, 1197 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{18}H_{16}O_3]^+$: *m/z* 280.1100, found 280.1089.

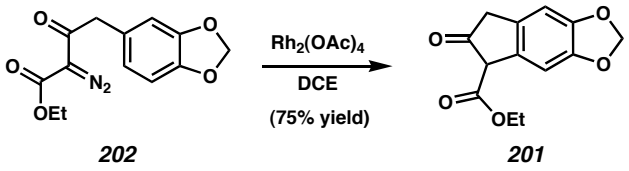


β-ketoester 210. Following the procedure for the synthesis of **205**, phenylacetic acid **209** (1 g, 5.55 mmol) was converted to acyclic β-ketoester **210**. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided β-ketoester **210** (1.24 g, 89% yield) as a clear oil: R_F 0.40 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 7.7 Hz, 1H), 6.70-6.62 (m, 2H), 5.95 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 2H), 3.44 (s, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 167.3, 148.2, 147.2, 127.0, 123.0, 110.1, 108.8, 101.3, 61.6, 49.8, 48.3, 14.3; IR (thin film/NaCl) 2901, 1712, 1630, 1488, 1443, 1244 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{13}H_{14}O_5]^+$: 250.0841, found 250.0832.

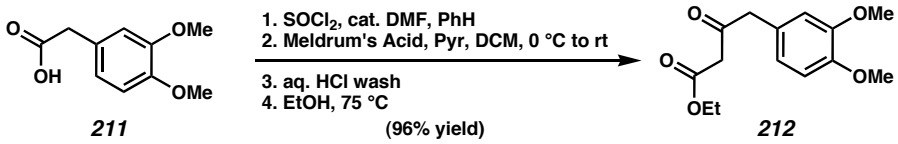


210 *202*

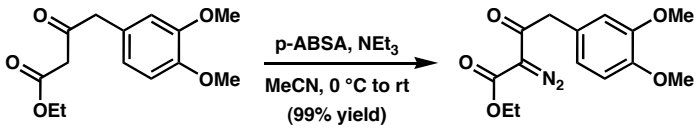
Diazoketoester 202. Following the procedure for the synthesis of **206**, β-ketoester **210** (461 mg, 1.84 mmol) was converted to diazoketoester **202**. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided diazoketoester **202** (386 mg, 76% yield) as a clear oil: R_F 0.41 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.74 (s, 2H), 5.92 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.09 (s, 2H), 1.33 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 161.4, 147.9, 146.9, 127.8, 123.0, 110. 3, 108.4, 101.1, 61.7, 45.5, 14.5; IR (thin film/NaCl) 2983, 2137, 1713, 1650, 1503, 1490, 1325, 1247 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{13}H_{13}N_2O_5]^+$: 277.0824, found 277.0820.



β-ketoester 201. Following the procedure for the synthesis of **207**, diazoketoester **202** (184 mg, 0.666 mmol) was converted to β-ketoester **201**. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided β-ketoester **201** (124 mg, 75% yield) as a white solid: R_F 0.44 (3:1 hexanes/EtOAc); mp 108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.93 (s, 1H), 7.16 (s, 1H), 6.82 (s, 1H), 5.93 (s, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.48 (s, 2H), 1.44 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 168.9, 146.9, 144.5, 133.5, 126.0, 105.6, 105.3, 102.4, 100.9, 60.8, 37.8, 14.6; IR (thin film/NaCl) 2984, 1657, 1590, 1500, 1470, 1314 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{12}O_5]^+$: *m/z* 248.0685, found 248.0682.

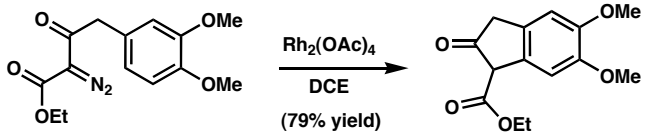


β-ketoester 212. Following the procedure for the synthesis of **205**, phenylacetic acid **211** (1 g, 5.1 mmol) was converted to β-ketoester **212**. Purification by flash chromatography (5:1→3:1→1:1 hexanes/EtOAc eluent gradient) provided β-ketoester **212** (1.31 g, 96% yield) as a clear oil. The characterization data matched the data reported in the literature.[15]



212 *203*

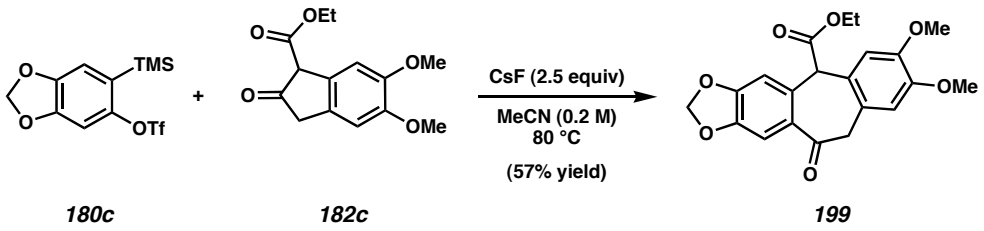
Diazoketoester 203. Following the procedure for the synthesis of **206**, β-ketoester **212** (445 mg, 1.67 mmol) was converted to diazoketoester **203**. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) provided diazoketoester **203** (487 mg, 99% yield) as a clear oil: R_F 0.50 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.00-6.94 (m, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.12 (s, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.51 (s, 3H), 3.43 (s, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 190.1, 161.4, 150.4, 149.7, 127.5, 122.7, 114.5, 112.7, 75.8, 61.6, 56.0, 55.9, 45.7, 14.5; IR (thin film/NaCl) 2938, 2836, 2136, 1714, 1650, 1515, 1263, 1029 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{14}H_{16}N_2O_5]^+$: *m/z* 292.1059, found 292.1070.



203 *182c*

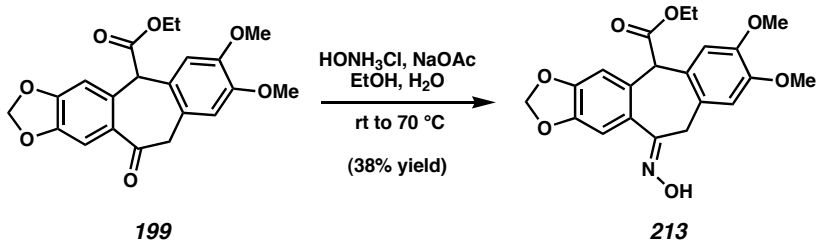
β-ketoester 182c. Following the procedure for the synthesis of **207**, diazoketoester **203** (3.64 g, 12.46 mmol) was converted to β-ketoester **182c**. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided β-ketoester **182c** (2.61 g,

79% yield) as a white solid: R_F 0.52 (1:1 hexanes/EtOAc); mp 117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.85 (s, 1H), 7.23 (s, 1H), 6.92 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.52 (d, *J* = 0.8 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 148.7, 146.3, 132.6, 125.1, 108.6, 105.2, 105.2, 105.0, 60.7, 56.6, 56.2, 37.8, 14.6; IR (thin film/NaCl) 2976, 2833, 1650, 1602, 1494, 1469, 1305 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{14}H_{16}O_5]^+$: 264.0998, found 264.1003. HRMS (FAB+) *m/z* calc'd for $[C_{14}H_{16}O_5]^+$: 264.0998, found 264.1003.



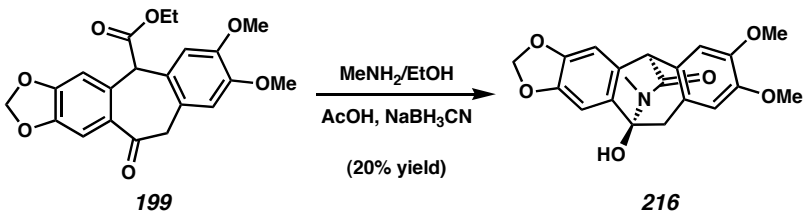
Ketoester 199. Following the procedure for the synthesis of **208**, β-ketoester **182c** (415 mg, 1.57 mmol) and aryne precursor **180c** (898 mg, 2.62 mmol) were coupled to form ketoester **199**. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided ketoester **199** (348 mg, 57% yield) as a clear oil: R_F 0.23 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 8.02 (s, 1H), 6.67 (s, 1H), 6.53 (s, 1H), 6.45 (s, 1H), 6.16 (s, 1H), 5.14 (d, *J* = 1.3 Hz, 1H), 5.10 (d, *J* = 1.3 Hz, 1H), 4.59 (d, *J* = 15.4 Hz, 1H), 4.54 (s, 1H), 3.95-3.86 (m, 2H), 3.82 (d, *J* = 15.4 Hz, 1H), 3.42 (s, 3H), 3.24 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 192.4, 171.4, 151.7, 150.2, 149.1, 148.5, 137.1, 130.6, 130.5, 125.9, 115.6, 114.9, 111.4, 110.8, 102.1, 61.9, 59.7, 56.31, 55.9, 50.0, 14.4;

IR (thin film/NaCl) 2908, 1727, 1663, 1616, 1518, 1506, 1485, 1254 cm^{-1}; HRMS (EI^+) calc'd for $[C_{21}H_{20}O_7]^+$: *m/z* 384.1209, found 384.1212.

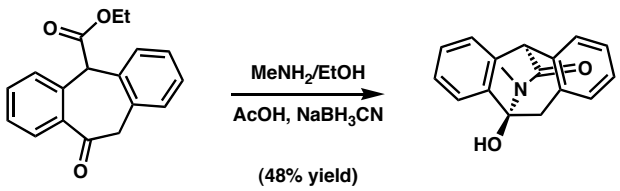


199 ***213***

Oxime 213. To a solution of ketoester **199** (81 mg, 0.21 mmol) in EtOH (2 mL) and H_2O (2 mL) was added $NaOAc•3H_2O$ (86 mg, 0.63 mmol) and $HONH_2•HCl$ (44 mg, 0.63 mmol). After stirring at 70 °C for 4.5 hours, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided oxime **213** (32 mg, 38% yield) as a clear oil: R_F 0.36 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, C_6D_6) δ 7.46 (s, 1H), 6.65 (s, 1H), 6.47 (s, 1H), 6.23 (s, 1H), 5.24 (d, *J* = 1.3 Hz, 1H), 5.18 (d, *J* = 1.3 Hz, 1H), 4.46-4.37 (m, 2H), 4.26 (d, *J* = 19.7 Hz, 1H), 4.11-3.83 (m, 2H), 3.44 (s, 3H), 3.31 (s, 3H), 1.65 (s, 1H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 171.4, 157.1, 149.8, 149.2, 148.9, 148.0, 134.5, 131.9, 127.2, 116.0, 114.9, 110.5, 109.6, 101.7, 78.1, 61.8, 58.0, 56.3, 56.0, 33.9, 14.5; IR (thin film/NaCl) 3446, 2905, 1733, 1520, 1506, 1487, 1230 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{21}H_{21}NO_7]^+$: 399.1318, found 399.1306.

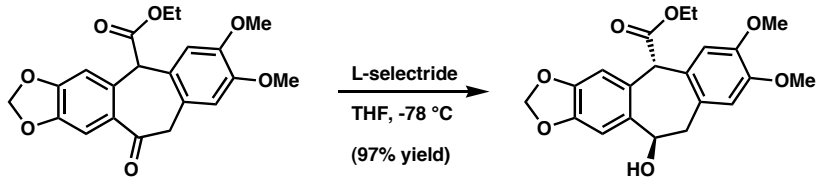


Aminal 216. To a solution of ketoester **199** (61.7 mg, 0.16 mmol) in ethanolic $MeNH_2$ (33% by wt., 2 mL) was added glacial AcOH (200 μL) and $NaBH_3CN$ (50 mg, 0.80 mmol). After stirring at room temperature for 30 minutes, the reaction mixture was extracted with saturated aqueous $NaHCO_3$ (4 mL) and Et_2O (3 x 3 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:3 hexanes/EtOAc eluent) provided aminal **216** (11.6 mg, 20% yield) as a clear oil: R_F 0.17 (1:3 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 6.45 (s, 1H), 5.95 (d, *J* = 1.3 Hz, 1H), 5.88 (d, *J* = 1.3 Hz, 1H), 4.28 (s, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.68 (s, 1H), 3.39 (d, *J* = 16.7 Hz, 1H), 3.02 (s, 3H), 3.00 (d, *J* = 16.7 Hz, 1H), 1.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 148.6, 148.0, 147.7, 147.2, 133.1, 131.4, 127.4, 124.7, 114.4, 112,0, 106.0, 103.3, 101.5, 85.5, 56.7, 56.2, 56.2, 39.9, 26.0; IR (thin film/NaCl) 2922, 1656, 1641, 1519, 1483 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{20}H_{20}NO_6]^+$: 370.1291, found 370.1295.



208 *220*

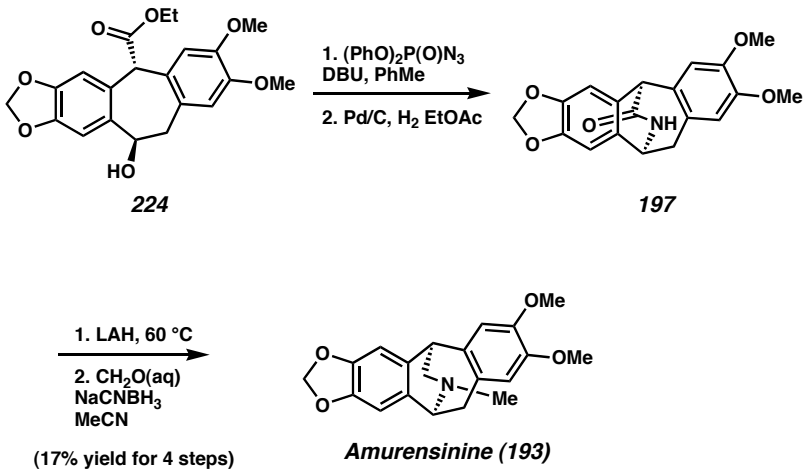
Model aminal 220. Following the procedure for the synthesis of **216**, ketoester **208** (33.4 mg, 0.12 mmol) was converted to model aminal **220**. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided model aminal **220** (31 mg, 48% yield) as a clear oil: R_F 0.38 (1:3 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.53 (m, 1H), 7.28-7.17 (m, 4H), 7.14-7.09 (m, 2H), 6.99-6.93 (m, 1H), 4.49 (s, 1H), 4.46 (s, 1H), 3.51 (d, *J* = 17.0 Hz, 1H), 3.11 (d, *J* = 17.0 Hz, 1H), 2.95 (s, 3H) 1.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 139.5, 137.1, 134.8, 133.0, 131.6, 129.2, 129.1, 127.8, 127.6, 127.2, 125.1, 121.9, 85.5, 57.6, 40.5, 25.9; IR (thin film/NaCl) 3258, 1642, 1390 cm^{-1}; HRMS (EI^+) calc'd for $[C_{17}H_{15}NO_2]^+$: *m/z* 265.1103, found 265.1113.



199 *224*

Hydroxyester 224. To a solution of ketoester **199** (52.9 mg, 0.138 mmol) in THF (1.5 mL) at –78 °C was added a 1.0 M solution of L-selectride in THF (200 μL, 0.206 mmol) in a dropwise fashion. The resulting solution was stirred for 25 minutes at –78 °C

and then quenched with saturated aqueous NH_4Cl (5 mL). After stirring at room temperature for 25 minutes, the mixture was extracted with Et_2O (4 x 5 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided aminal **224** (51.4 mg, 97% yield) as a yellow solid: R_F 0.33 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 6.69 (s, 1H), 5.94 (d, *J* = 1.5 Hz, 1H), 5.92 (d, *J* = 1.0 Hz, 1H), 5.02-4.96 (m, 1H), 4.59 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.50 (dd, *J* = 15.1, 2.4 Hz, 1H), 2.93 (dd, *J* = 15.1, 6.8 Hz, 1H), 1.73 (d, *J* = 8.3 Hz, 1H), 1.62 (s, 1H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 148.4, 147.6, 147.6, 146.9, 135.2, 129.6, 128.0, 127.3, 114.9, 114.5, 111.3, 110.7, 101.4, 69.4, 61.8, 58.5, 56.2, 56.1, 39.6, 14.3; IR (thin film/NaCl) 3500, 2937, 1725, 1610, 1520, 1486, 1244 cm^{-1}; HRMS (EI^+) calc'd for $[C_{21}H_{22}O_7]^+$: *m/z* 386.1366, found 386.1366.



Lactam 197. To a solution of hydroxyester **224** (9.7 mg, 0.025 mmol) in toluene (500 μL) at 0 °C was added $(PhO)_2P(O)N_3$ (27 μL, 0.126 mmol) and DBU (19 μL, 0.126 mmol). The resulting solution was stirred for 30 minutes at 0 °C and then stirred at room temperature for 12 hours. The reaction was then quenched with H_2O (3 mL) and extracted with Et_2O (3 x 3 mL). The organics were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude azide was passed through a short pad of SiO_2 with EtOAc eluent and concentrated under reduced pressure. To a solution of the azide in EtOAc (1.5 mL) was added Pd/C (10% by wt., 15 mg). The reaction flask was placed under a balloon of H_2 gas (1 atm) and stirred at room temperature for 9 hours. The reaction mixture was then passed through a short pad of Celite with Et_2O eluent and concentrated under reduced pressure. Lactam **197** was used in the next step without further purification: R_F 0.25 (10% MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 6.55-6.52 (m, 1H), 6.49 (s, 1H), 5.94 (d, *J* = 1.5 Hz, 1H), 5.88 (d, *J* = 1.5 Hz, 1H), 4.58-4.54 (m, 1H), 4.21 (d, *J* = 2.0 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.28 (dd, *J* = 16.8, 4.6 Hz, 1H), 3.07 (dd, *J* = 17.1, 2.4 Hz,

1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 148.8, 147.6, 147.2, 146.7, 134.1, 130.0, 128.1, 125.2, 114.7, 112.1, 106.7, 105.6, 101.4, 56.7, 56.2, 56.1, 53.6, 36.9; IR (thin film/NaCl) 3221, 2916, 1680, 1517, 1485, 1465, 1246 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{19}H_{18}NO_5]^+$: 340.1185, found 340.1181.

Amurensinine (193). To a solution of crude lactam **197** in THF (1 mL) was added LAH (30 mg, 0.0751 mmol). The resulting solution was stirred for 8 hours at 60 °C. The reaction mixture was then cooled to 0 °C and quenched with H_2O (30 μL), 15% aqueous NaOH (30 μL), and H_2O (90 μL). The slurry was stirred at room temperature for 25 minutes, passed through a short pad of Celite with Et_2O eluent, and concentrated under reduced pressure. To a solution of the crude secondary amine in acetonitrile (1 mL) was added $NaCNBH_3$ (10 mg, 0.159) and aqueous formaldehyde (37% by wt., 50 μL). After stirring at room temperature for 2 hours, the reaction mixture was extracted with H_2O (2 mL). The aqueous layer was back-extracted with CH_2Cl_2 (3 x 3 mL). The organics were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by preparatory thin layer chromatography on silica gel (0.25mm, 10% MeOH/$CHCl_3$ eluent) provided amurensinine **193** (1.5 mg, 17% yield for 4 steps) as a clear thin film/NaCl: R_F 0.18 (10% MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.72 (s, 1H), 6.61 (s, 1H), 6.52 (s, 1H), 5.93 (d, *J* = 1.5 Hz, 1H), 5.86 (d, *J* = 1.5 Hz, 1H), 4.00-3.91 (m, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.70-3.56 (m, 3H), 2.98-2.85 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 147.0, 146.5, 134.9, 134.2, 126.2, 114.4, 111.3, 107.7, 106.5, 101.4, 101.0, 63.1, 59.8, 56.2, 56.1, 45.8, 45.5, 37.8, 29.9; IR (thin film/NaCl) 2916, 2848, 1607, 1517, 1482, 1249 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{20}H_{21}NO_4]^+$: *m/z* 339.1471, found 339.1469.

4.5 Notes and References

(1) Gossage, R. A.; van Koten, G. A General Survey and Recent Advances in the Activation of Unreactive Chemical Bonds by Metal Complexes. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 1-8.

(2) (a) For stoichiometric reactions involving the activation of C-H bonds, see: Jones, W. D. Activation of C-H Bonds: Stoichiometric Reactions. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 9-46. (b) For catalytic reactions involving the activation of C-H bonds, see: Kakiuchi, F.; Murai, S. Activation of C-H Bonds: Catalytic Reactions. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 47-79.

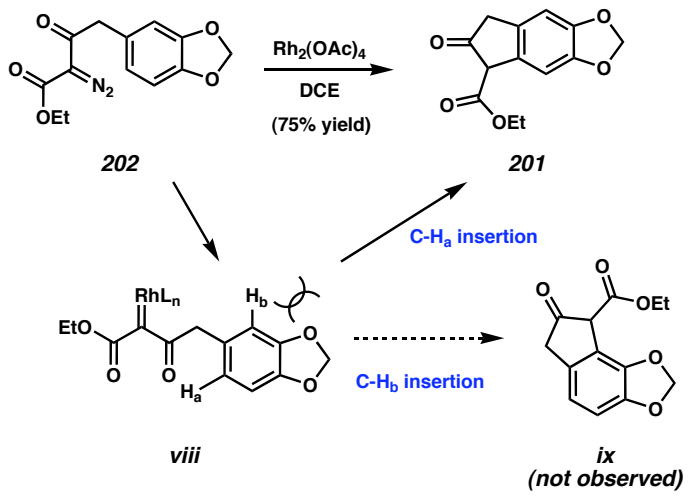
(3) Murakami, M.; Ito, Y. Cleavage of Carbon-Carbon Single Bonds by Transition Metals. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 97-129.

(4) For discussions on the biological activity of the isopavine alkaloids, see: (a) Weber, E.; Keana, J.; Barmettler, P. PCT Int. Appl. WO 12575, **1990**; *Chem. Abstr*. **1991**, *115*, 106019w. (b) Childers, W. E.; Abou-Gharbia, M. A. U.S. Patent 4940789, 1990; *Chem. Abstr*. **1990**, *113,* 191190w.

(5) For syntheses of natural and non-natural isopavines, see, for example: (a) Gozler, B. In *The Alkaloids*; Academic Press: New York, 1987; Vol. 31, pp 342-355. (b) Yasuda, M.; Hamasuna, S.; Yamano, K.; Kubo, J.; Shima, K. *Heterocycles* **1992**, *34*, 965-977. (c) Kametani, T.; Higashiyama, K.; Honda, T. *Chem. Pharm. Bull.* **1984**, *32*, 1614-1618. (d) Jung, M. E.; Miller, S. J. *J. Am. Chem. Soc*. **1981**, *103*, 1984-1992. (e) Dyke, S. F.; Kinsman, R. G.; Warren, P.; White, A. W .C. *Tetrahedron* **1978**, *34*, 241-245. (f) Dyke, S. F.;; Ellis, A. C.; Kinsman, R. G.; White, A. W .C. *Tetrahedron* **1974**, *30*, 1193-1199. (g) Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601-607. (h) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095-5108. (i) Carrillo, L.; Badia, D.; Dominguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716-6721.

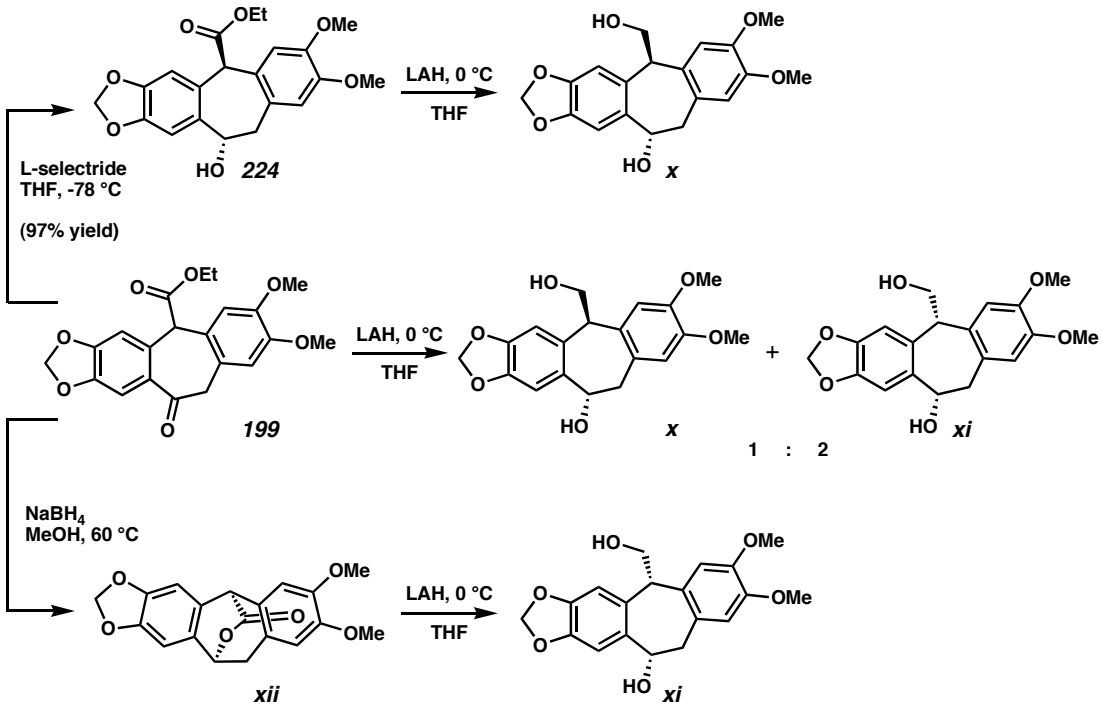
(6) Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc*. **1986,** *108*, 7686-7693. In this paper there are no examples of C-H insertion into unsymmetrical aromatic systems such as **202** and **203**.

(7) This high position-selectivity is most likely governed by the differing steric environments of H_a and H_b in rhodium-carbneoid ***viii***:

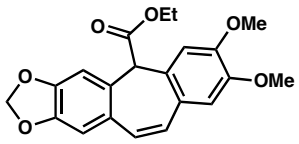


(8) For a recent review on the latest advances in amine synthesis by Mitsunobu strategies, see: Kan, T.; Fukuyama, T. *Chem. Comm.* **2004**, 353-359.

(9) Although we have no direct nOe or X-ray crystallographic evidence for the relative stereochemistry of hydroxyester **224**, we have indirect chemical evidence based on the observed products of related transformations:



(10) The decomposition products most likely involved elimination to the stilbenyl system ***xiii***:



xiii

(11) Thompson, A. S.; Humphrey,G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886-5888.

(12) Selwood, D. L.; Brummell, D. G.; Budworth, J. ; Burtin, G. E.; Campbel, R. O.; Chana, S. S.; Charles, I. G.; Fernandez, P. A.; Glen, R. C.; Goggin, M. C.; Hobbs, A.J.; et al. *J. Med. Chem.* **2001**, *44*, 78-93.

(13) Padwa, A.; Sa, M. M.; Weingarten, M. D. *Tetrahedron* **1997**, *53*, 2371-2386.

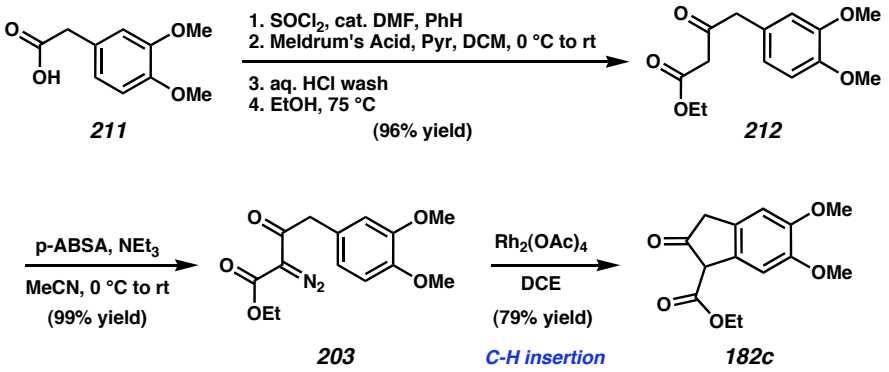
(14) Treibs, W.; Schroth, W. *Justis Liebigs Ann. Chem.* **1961**, 82-96.

(15) Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932-7936.

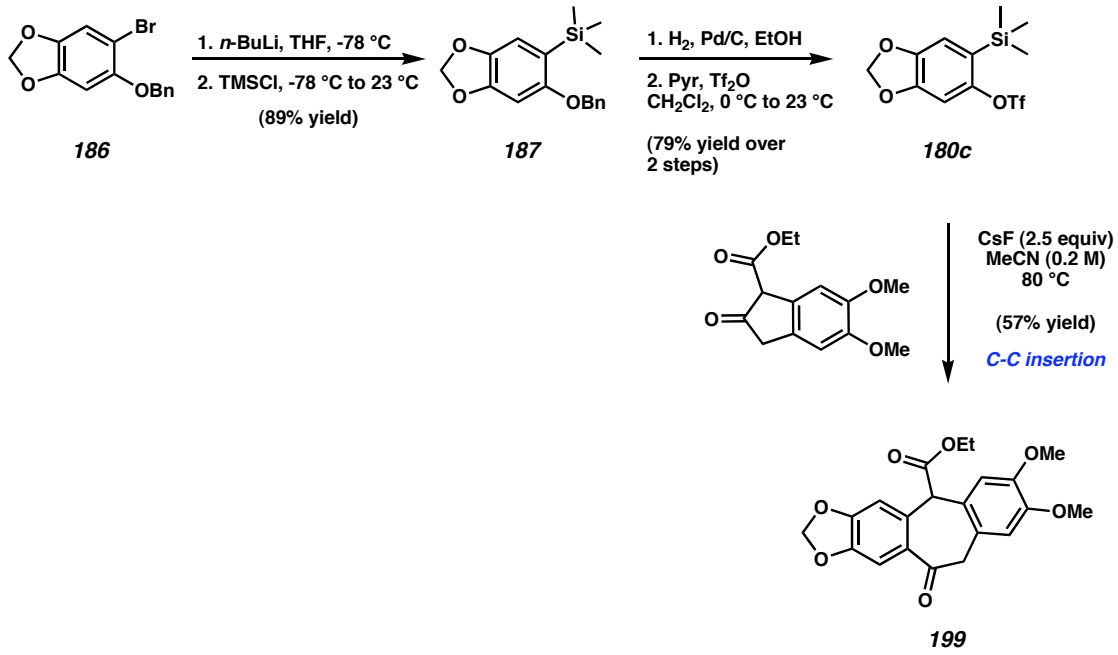
APPENDIX SIX

Synthetic Summary for Amurensinine (193)

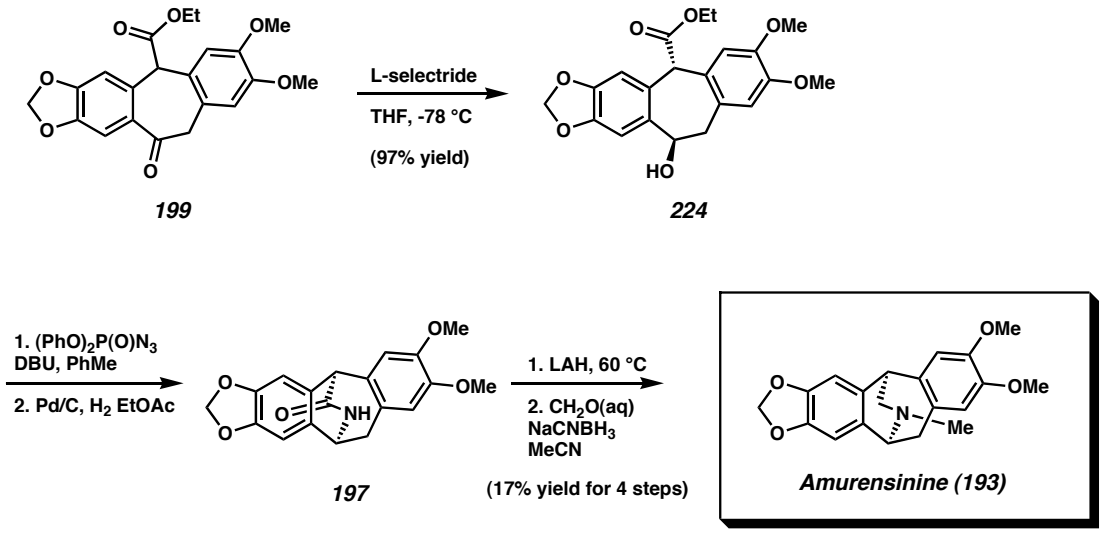
Scheme A6.1 The synthesis of β-ketoester **182c**.



Scheme A6.2 The synthesis of ketoester **199**.



Scheme A6.3 The synthesis of amurensinine (**193**).



APPENDIX SEVEN

Spectra Relevant to Chapter Four:

Total Synthesis of Amurensinine

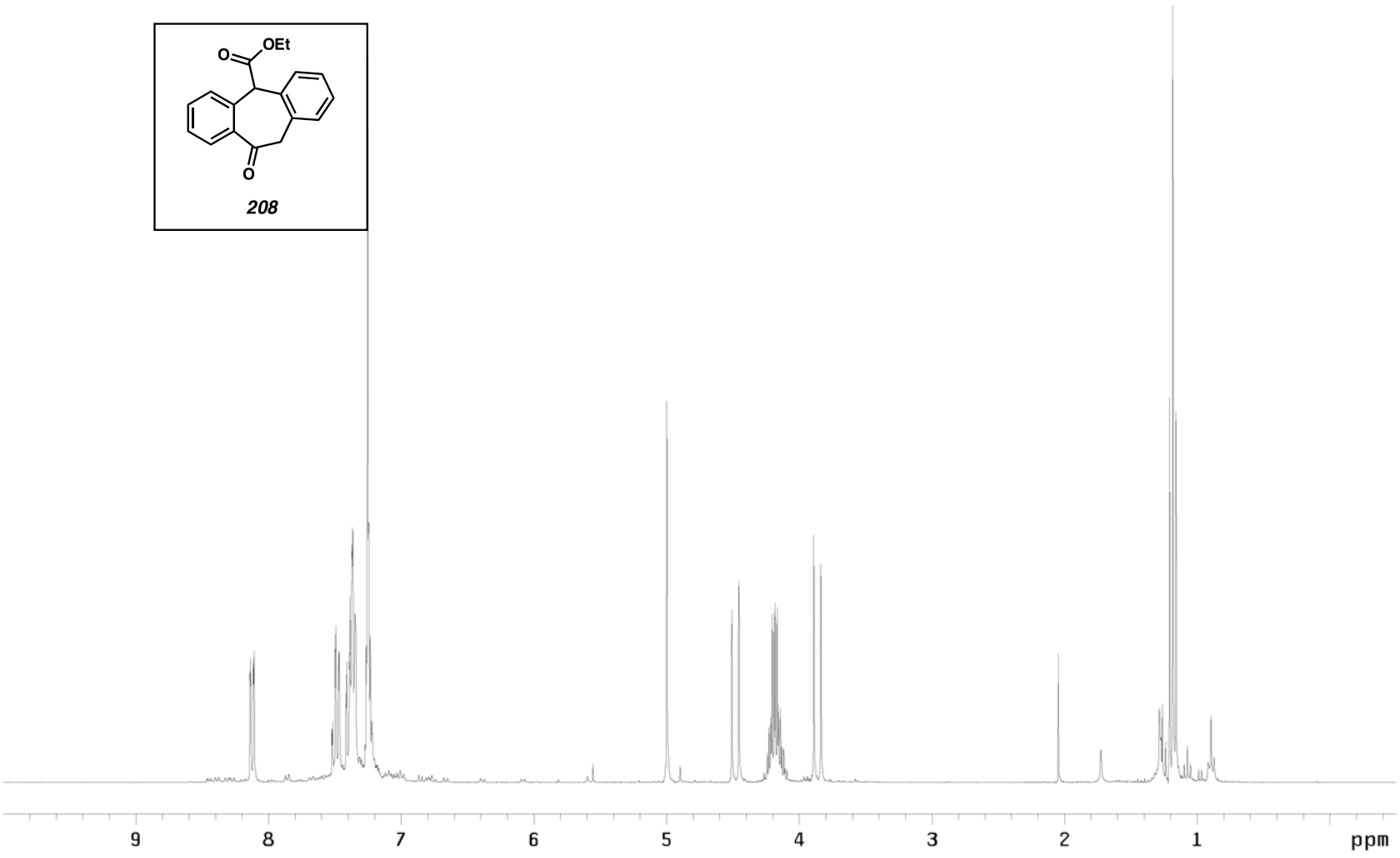


Figure A7.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **208**.

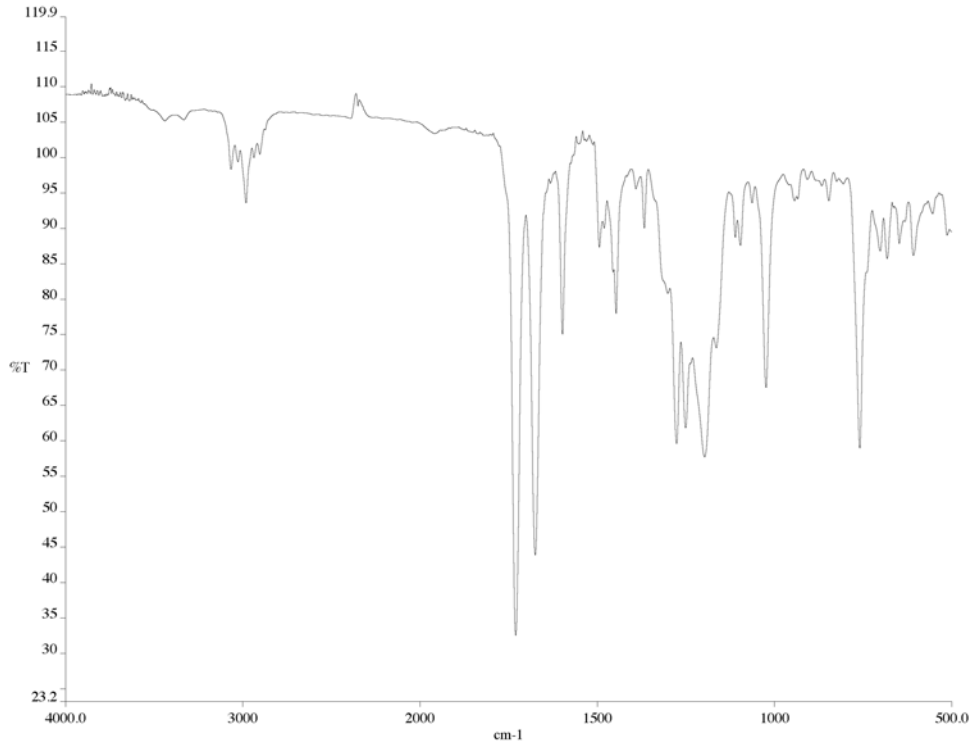


Figure A7.2 Infrared spectrum (thin film/NaCl) of compound **208**.

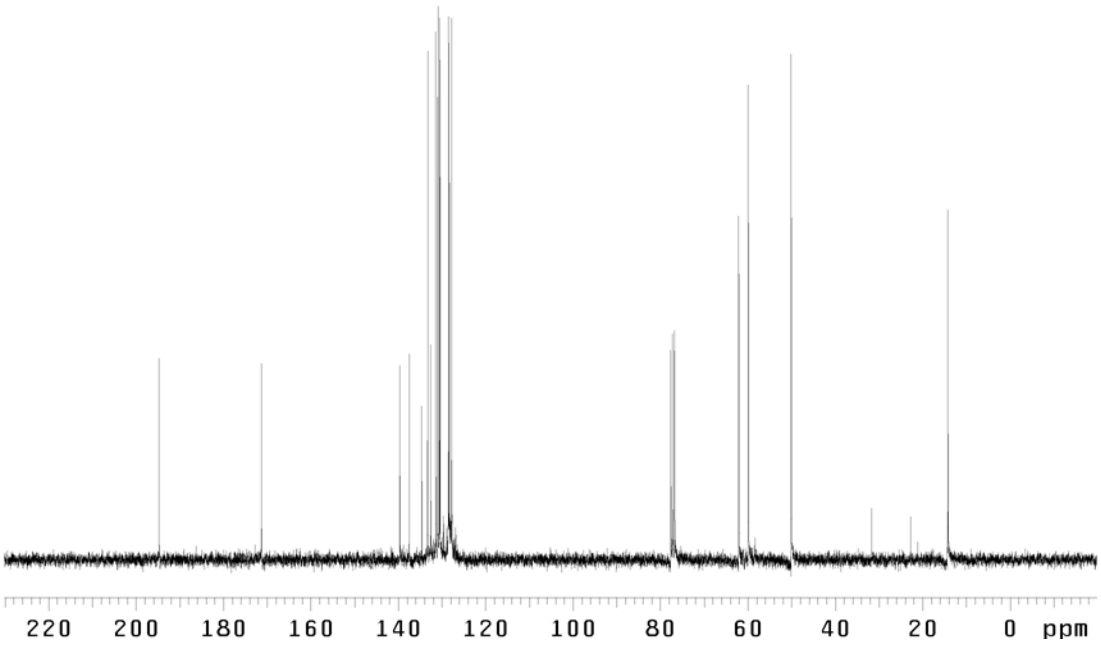


Figure A7.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **208**.

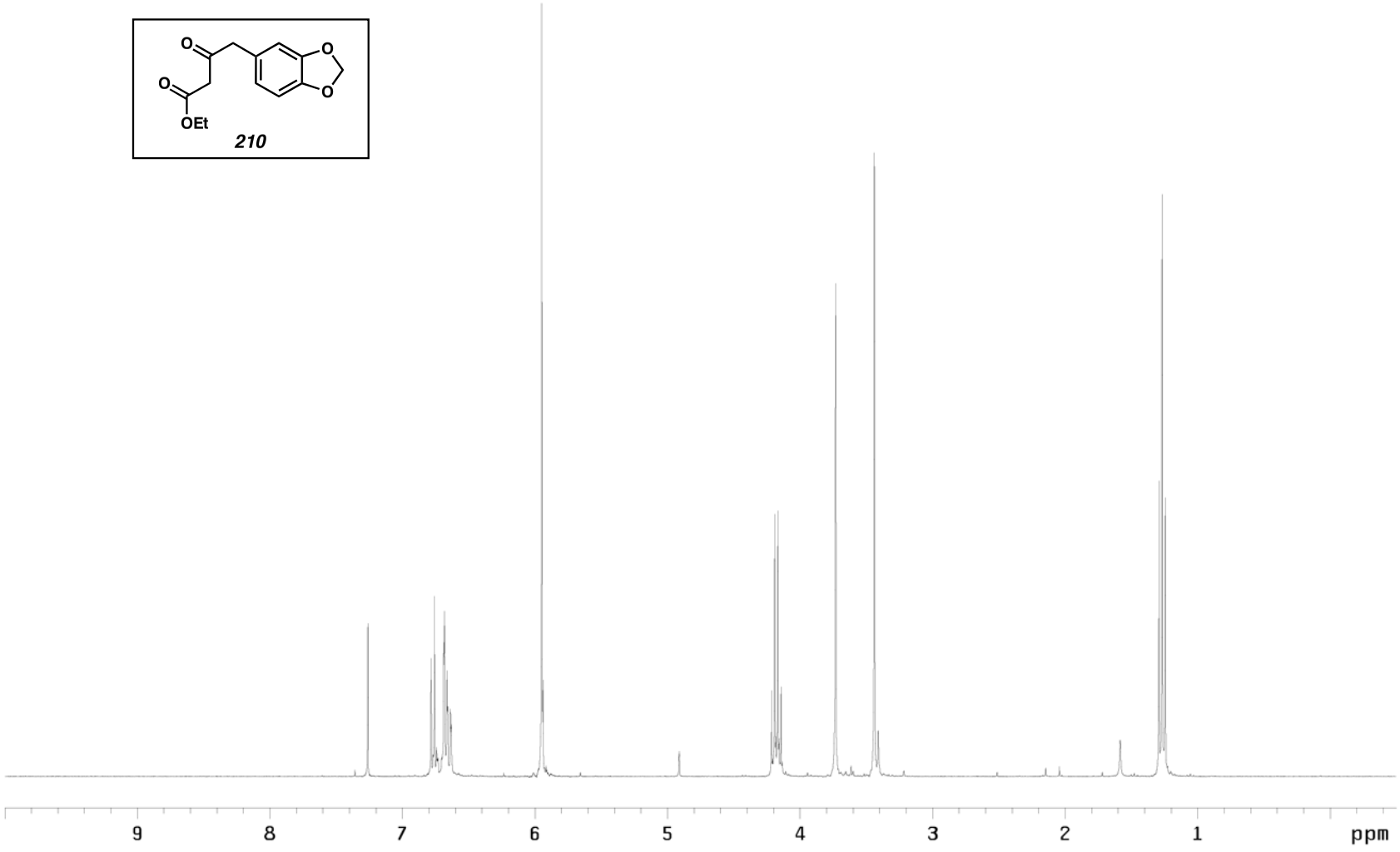


Figure A7.4 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **210**.

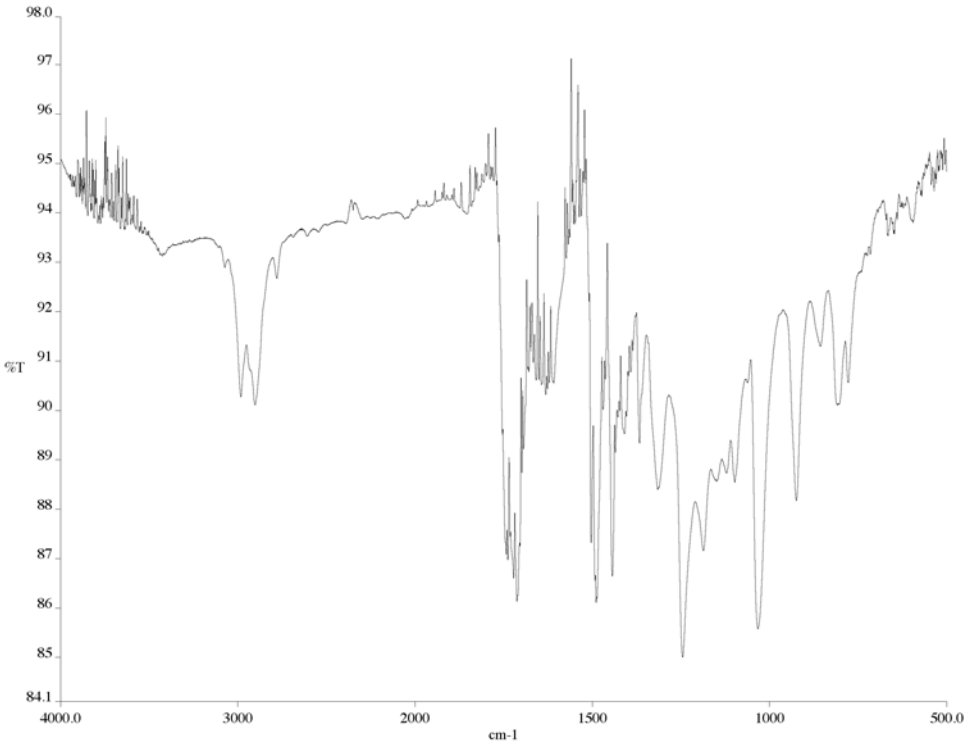


Figure A7.5 Infrared spectrum (thin film/NaCl) of compound **210**.

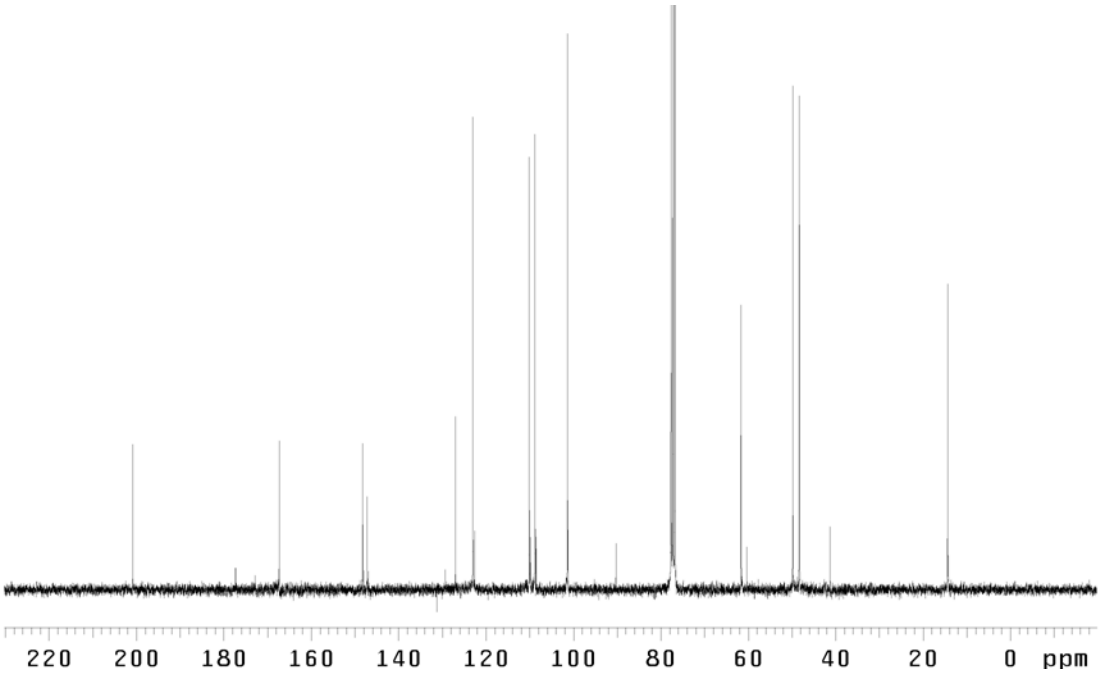


Figure A7.6 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **210**.

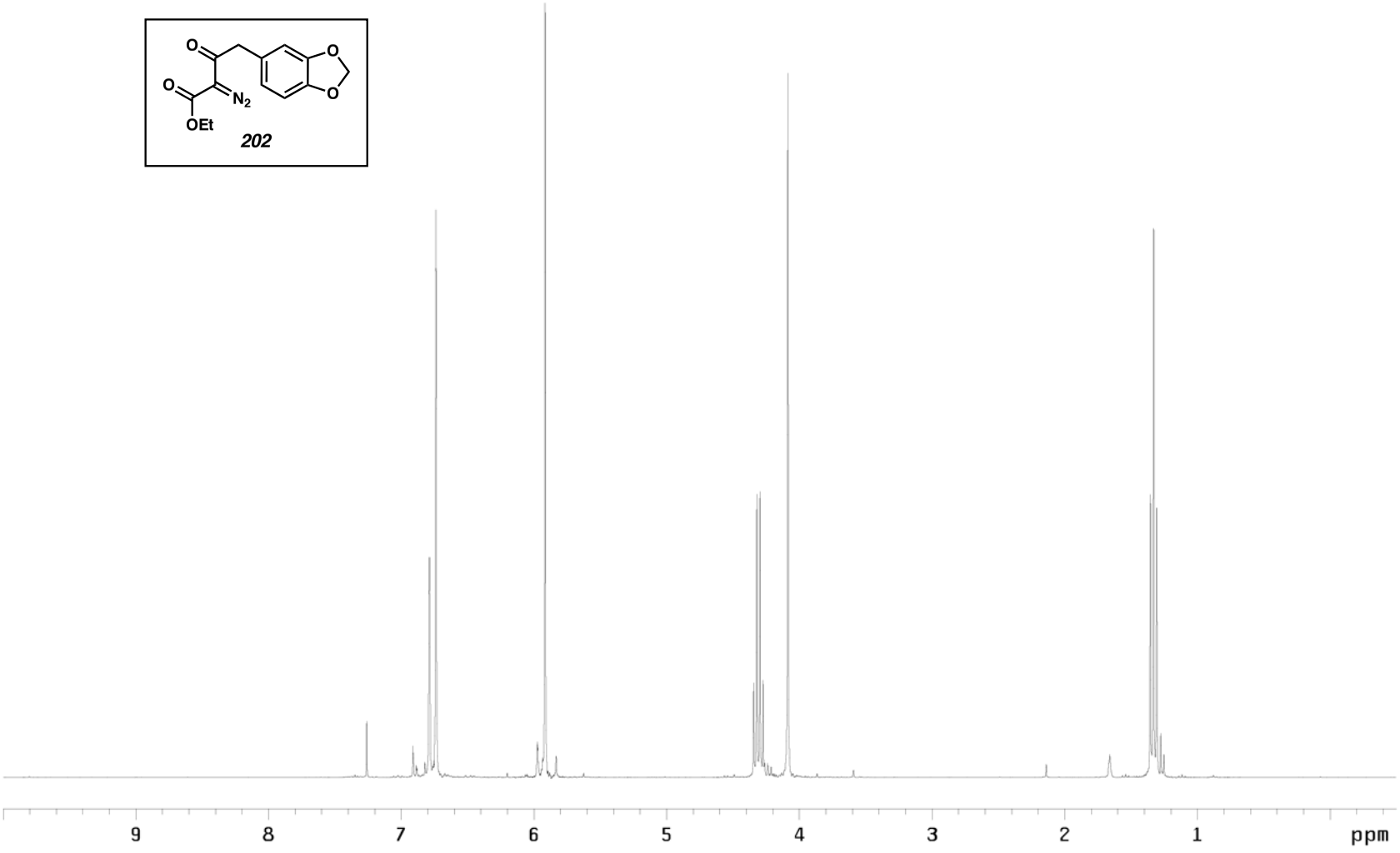


Figure A7.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **202**.

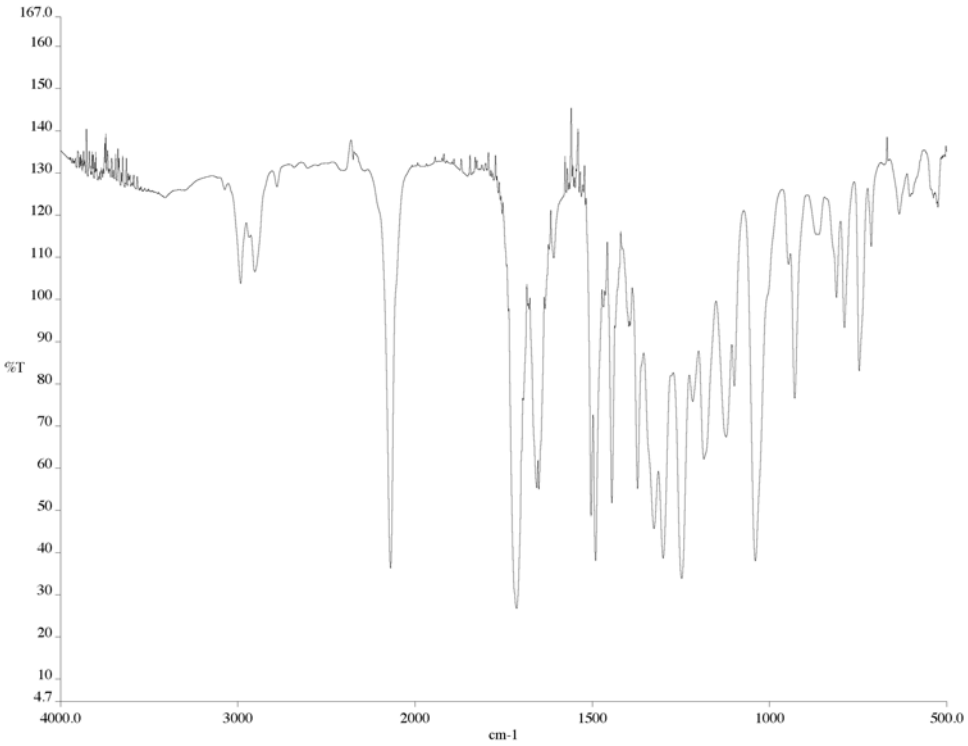


Figure A7.8 Infrared spectrum (thin film/NaCl) of compound **202**.

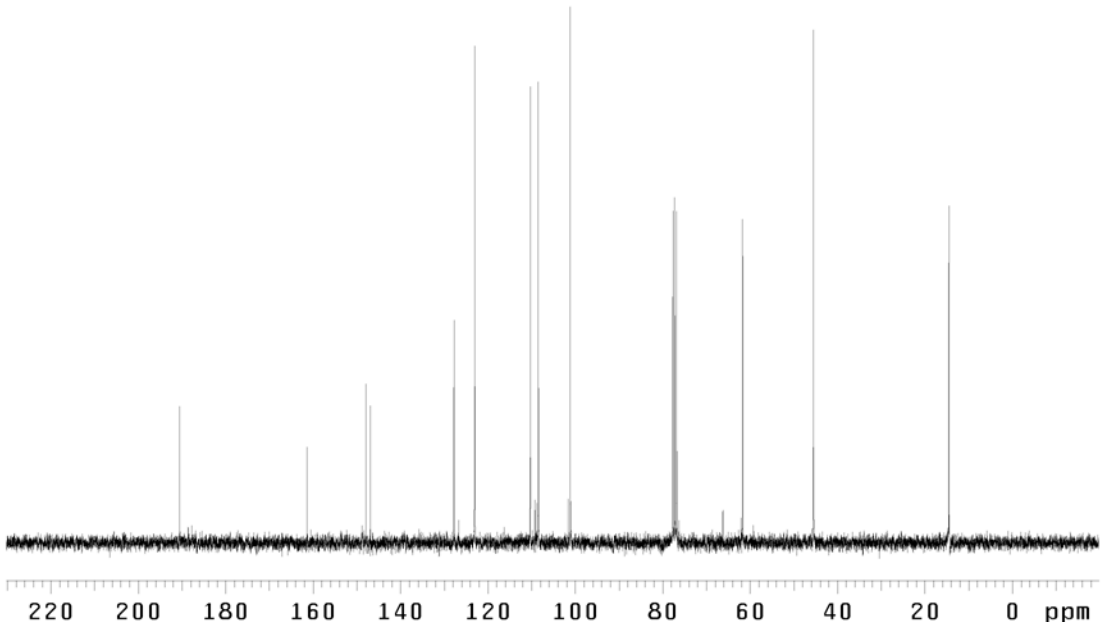


Figure A7.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **202**.

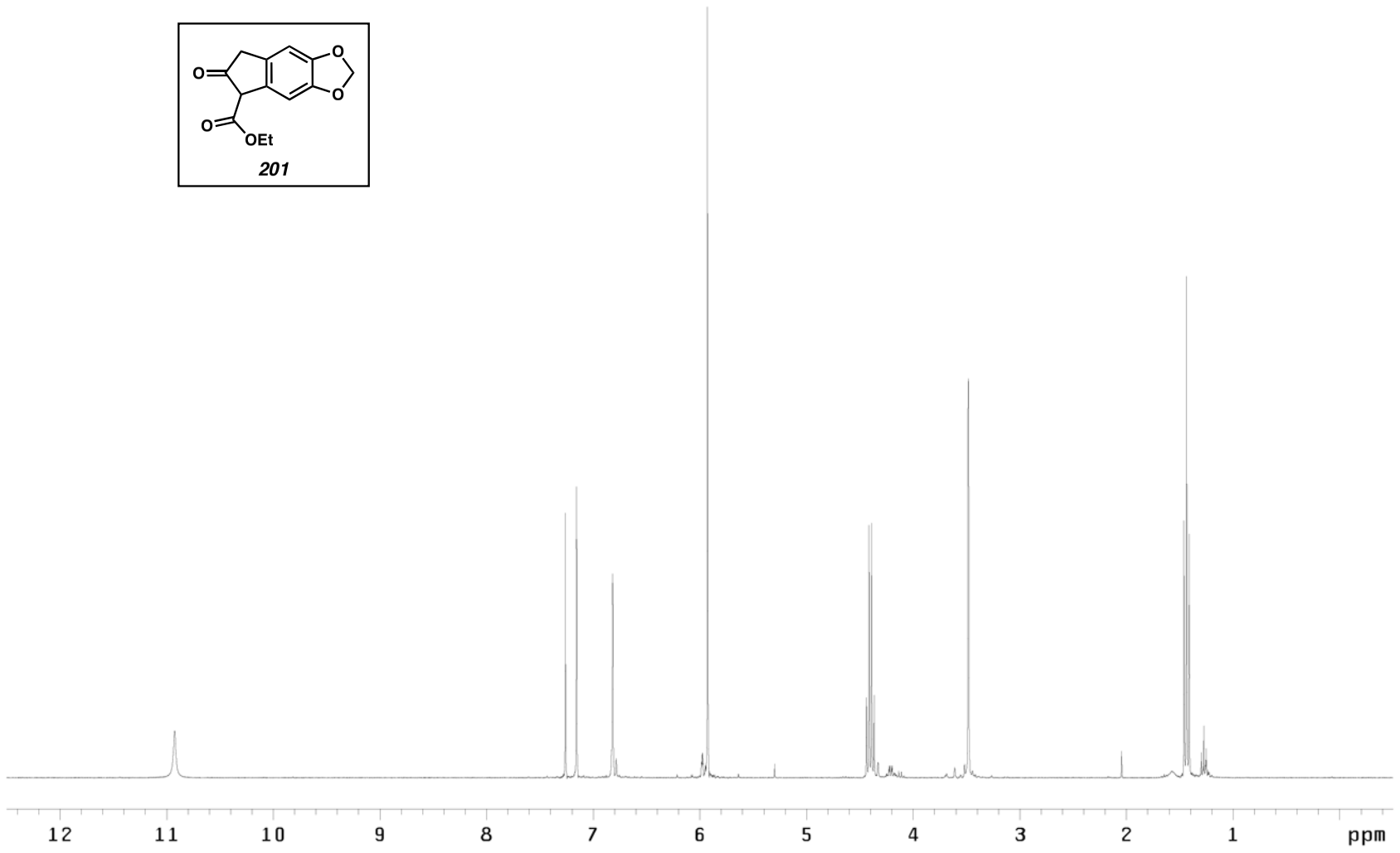


Figure A7.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **201**.

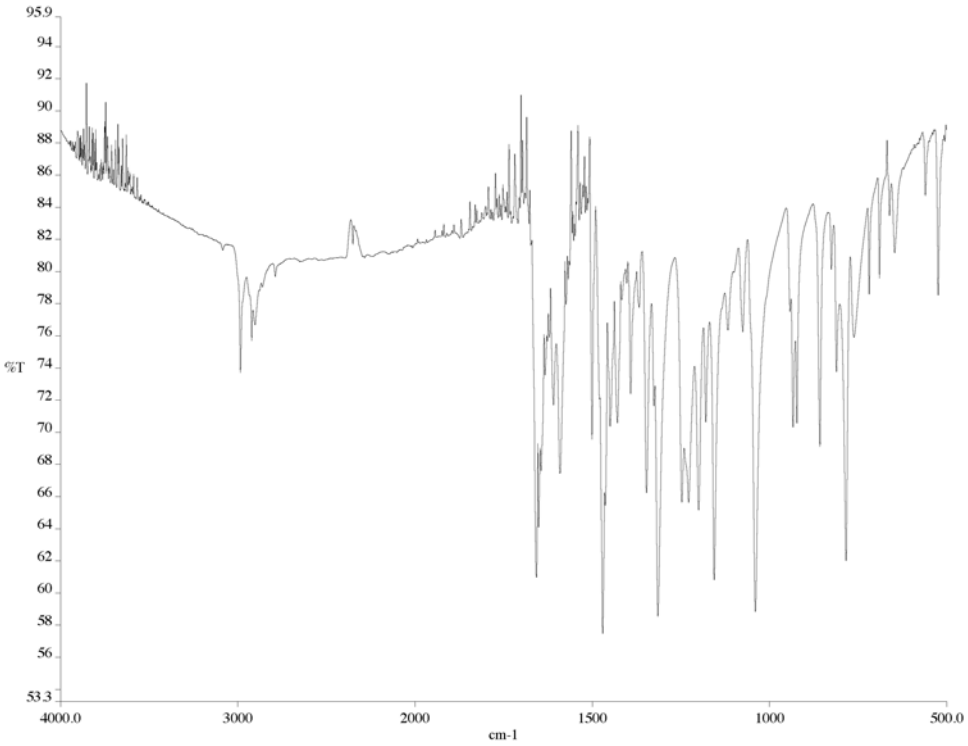


Figure A7.11 Infrared spectrum (thin film/NaCl) of compound **201**.

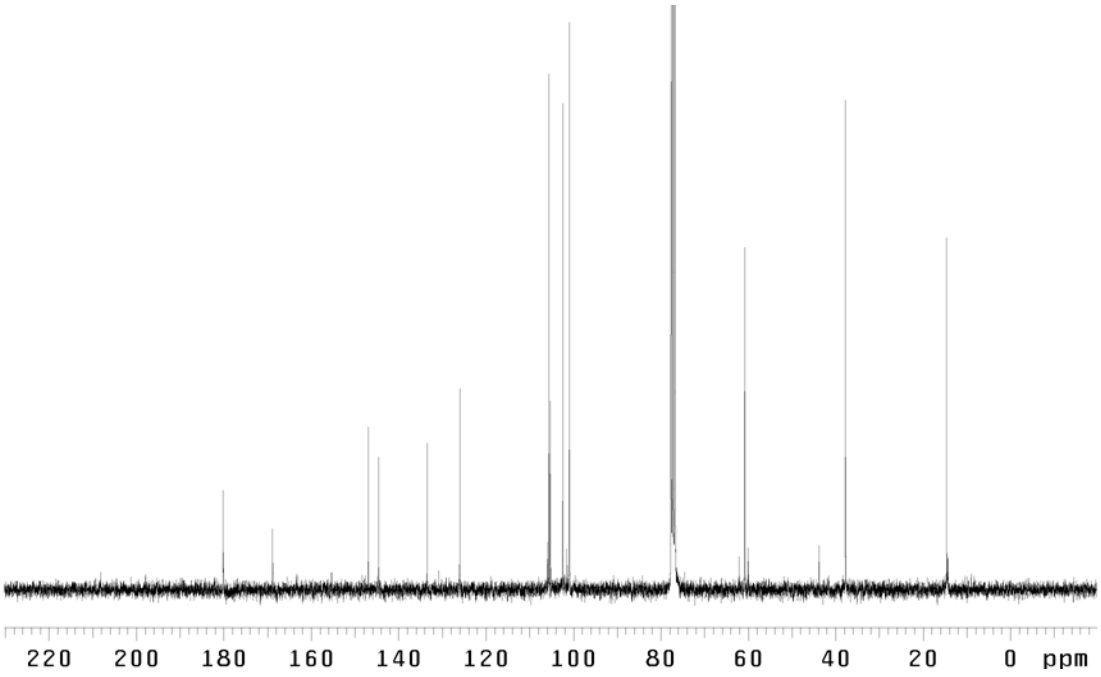


Figure A7.12 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **201**.

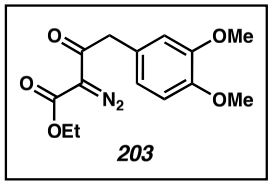


Figure A7.13 ^{1}H NMR (300 MHz, C_6D_6) of compound **203**.

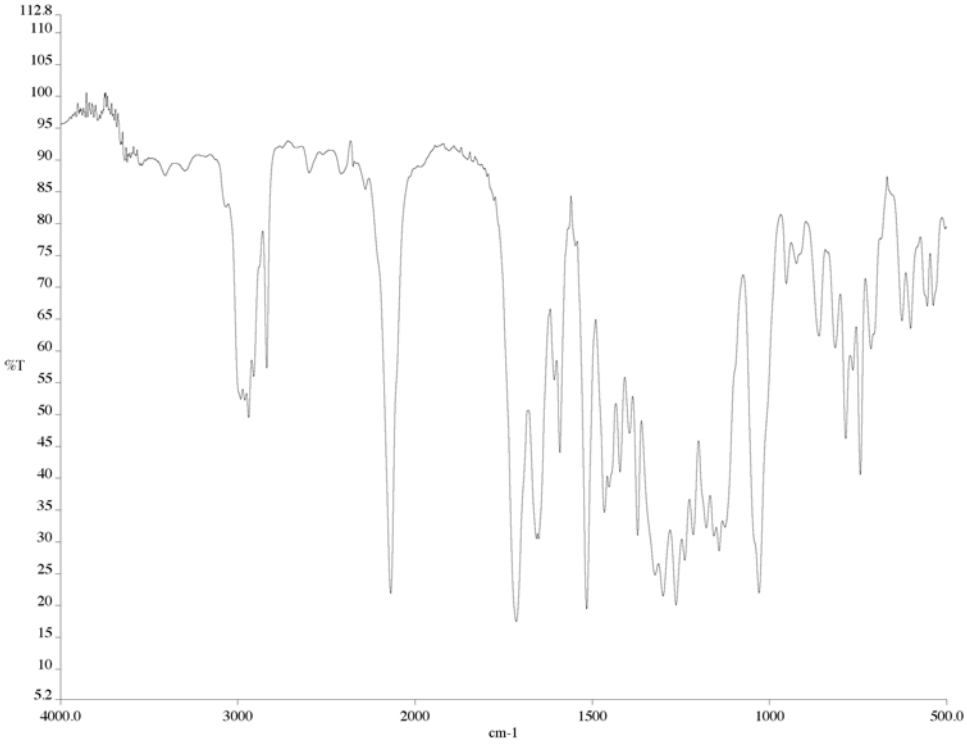


Figure A7.14 Infrared spectrum (thin film/NaCl) of compound **203**.

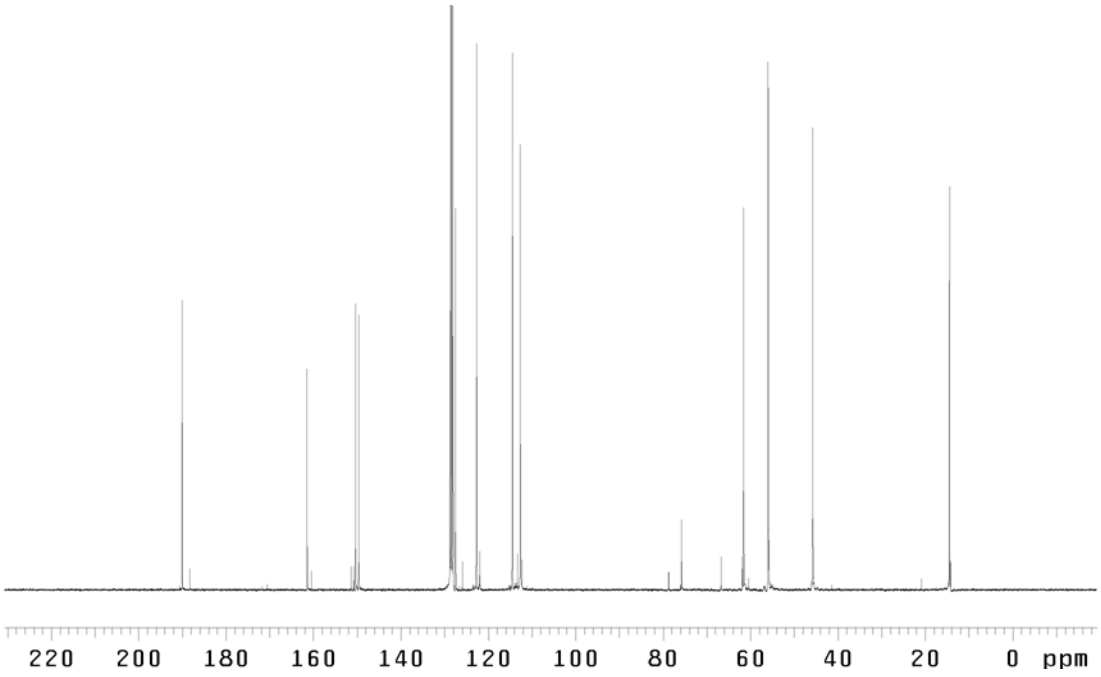


Figure A7.15 ^{13}C NMR (75 MHz, C_6D_6) of compound **203**.

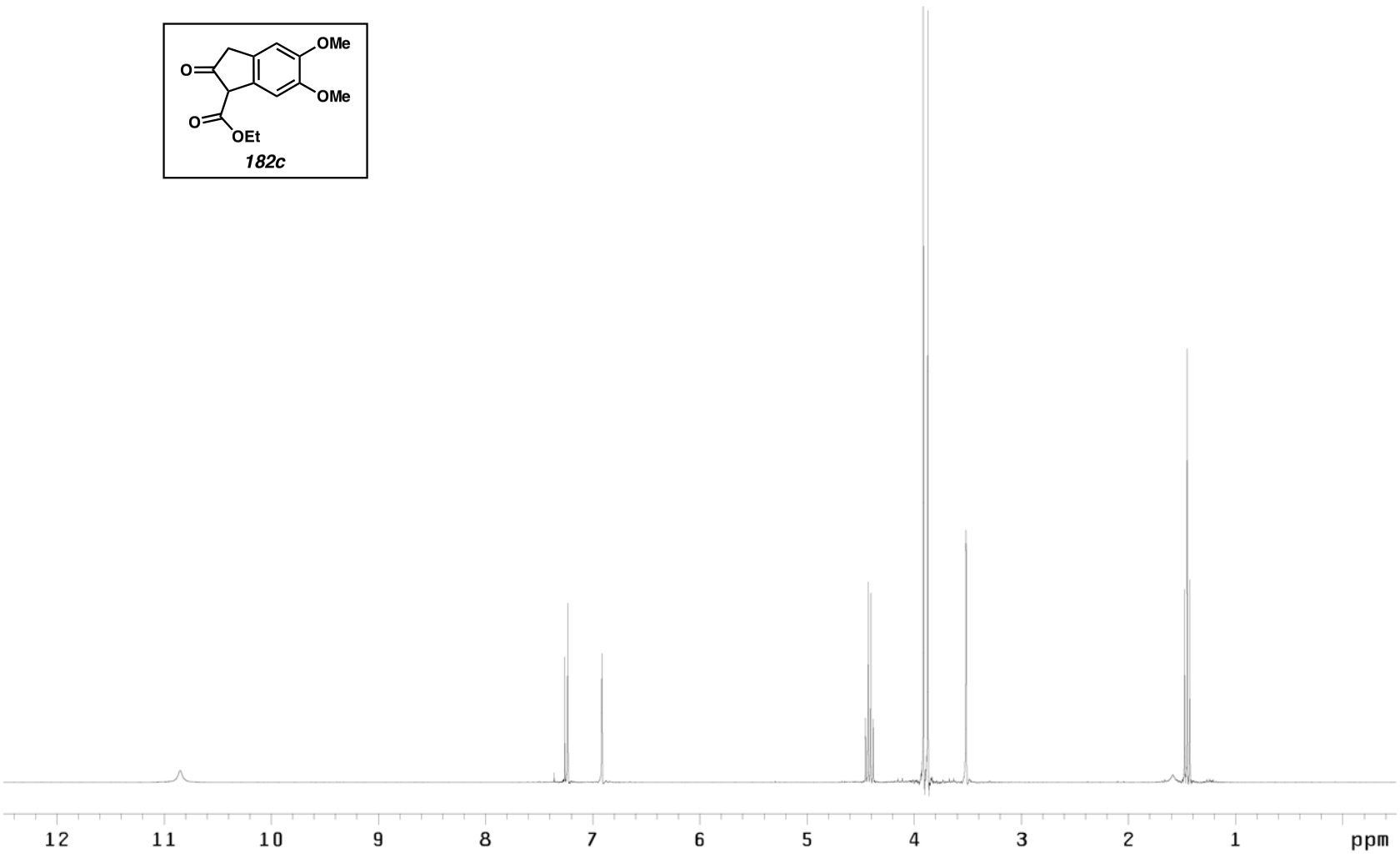


Figure A7.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **182c**.

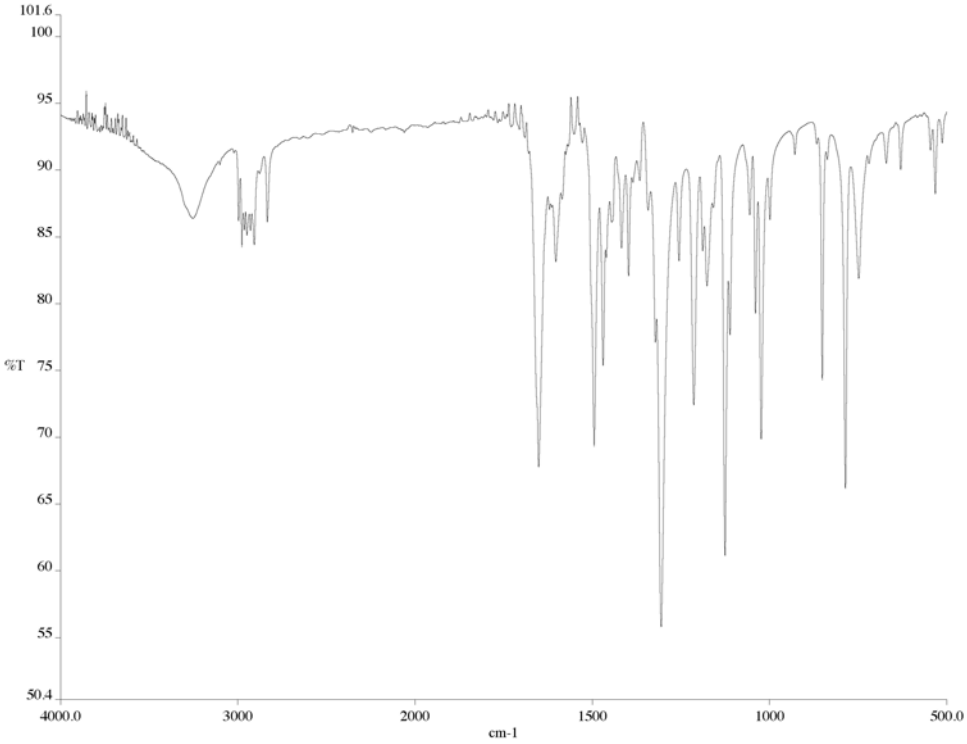


Figure A7.17 Infrared spectrum (thin film/NaCl) of compound **182c**.

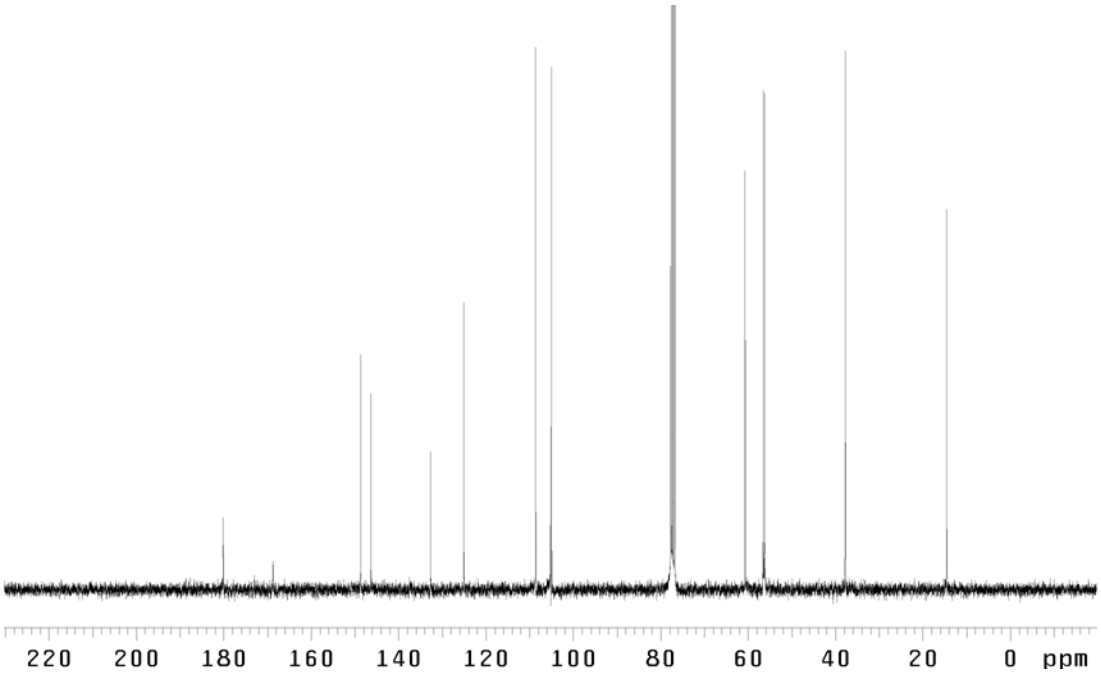


Figure A7.18 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **182c**.

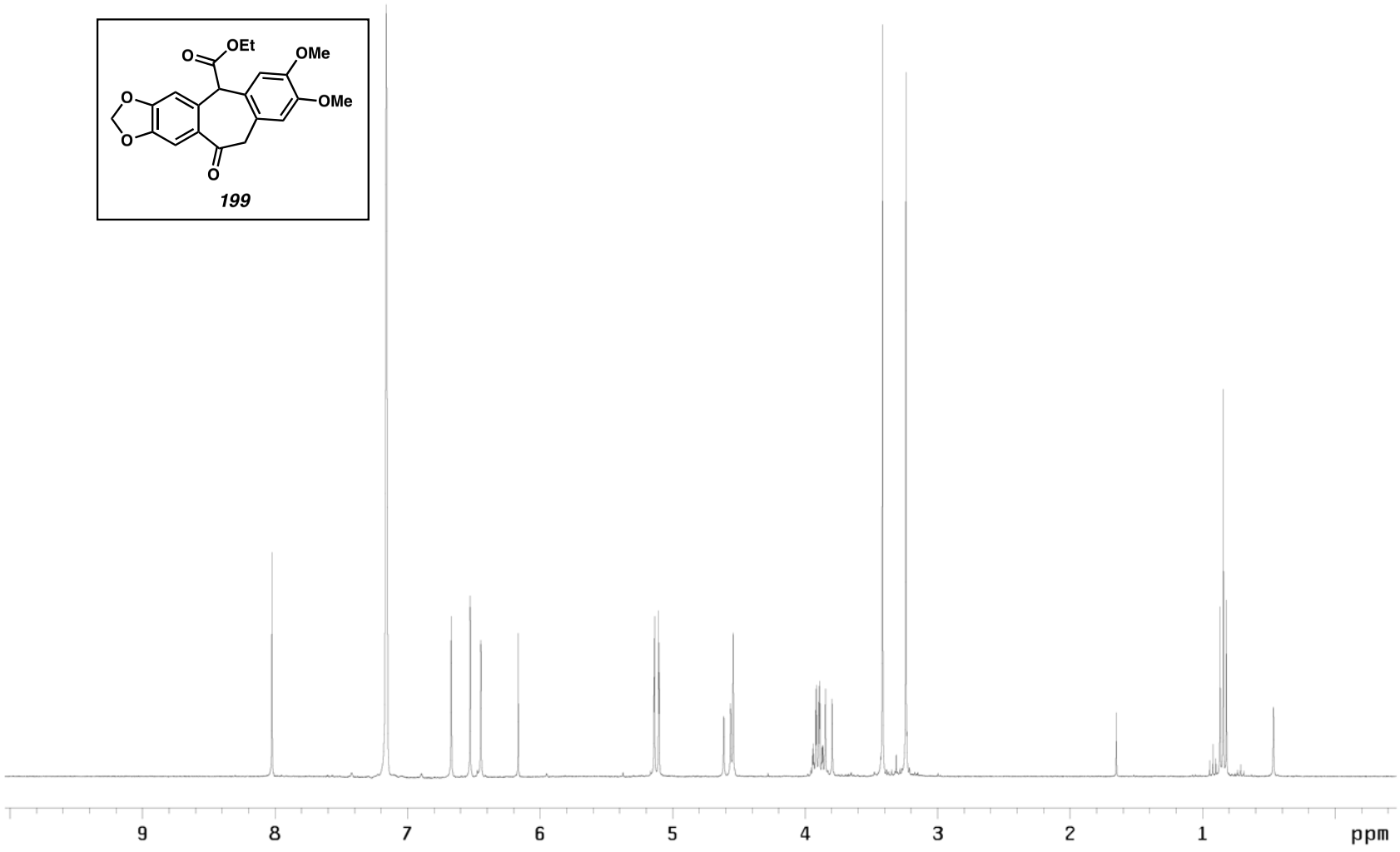


Figure A7.19 ^{1}H NMR (300 MHz, C_6D_6) of compound **199**.

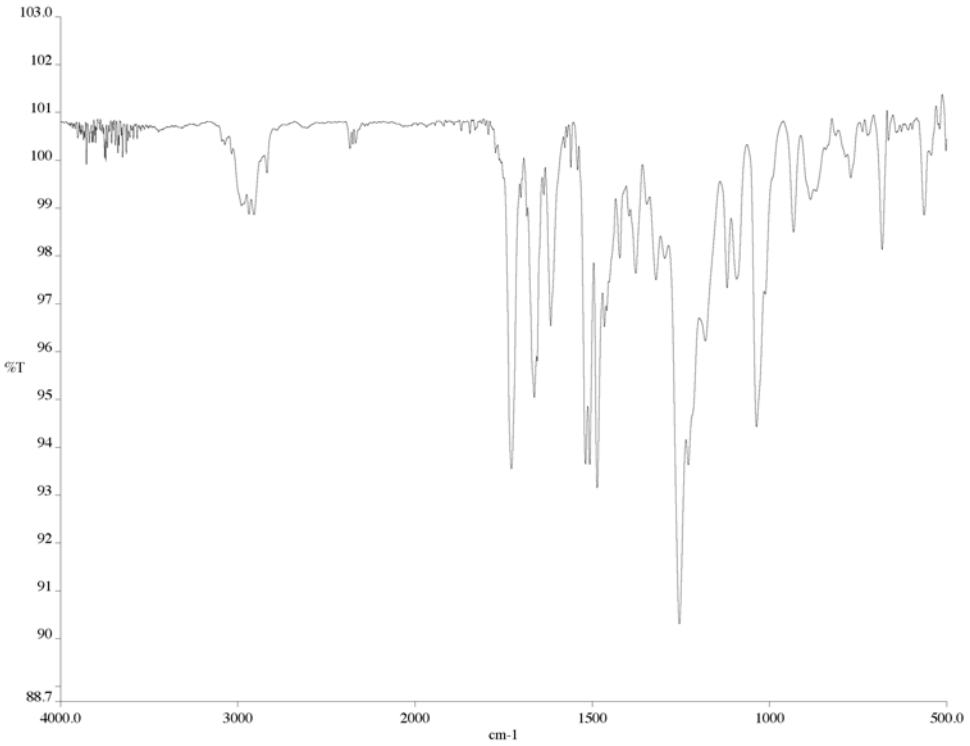


Figure A7.20 Infrared spectrum (thin film/NaCl) of compound **199**.

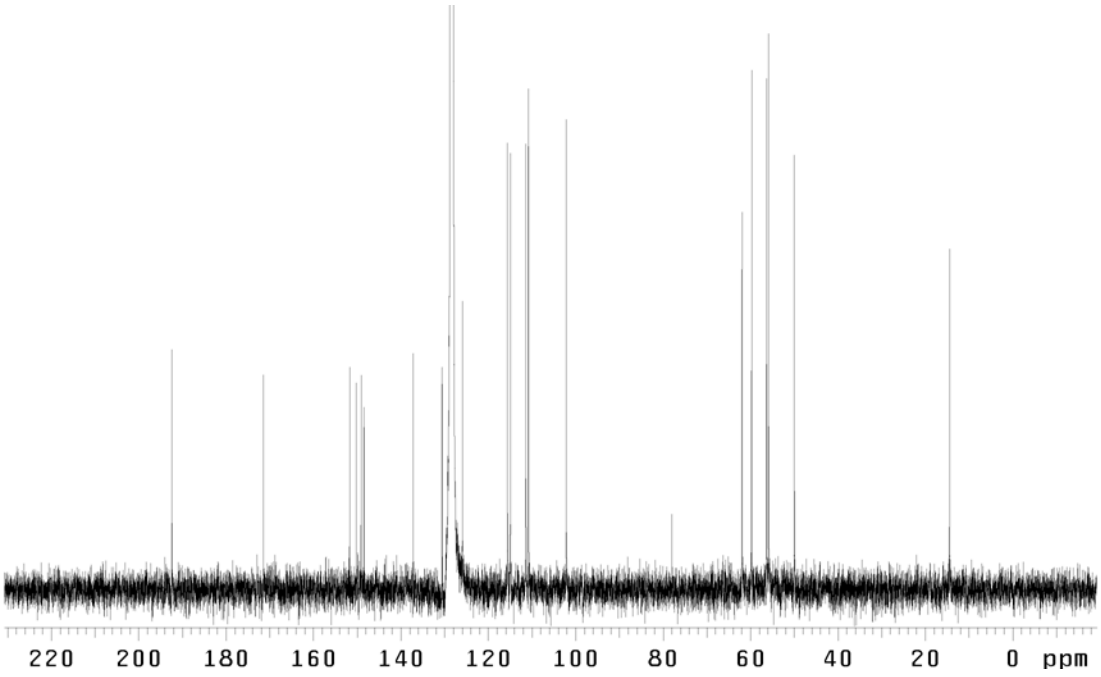


Figure A7.21 ^{13}C NMR (75 MHz, C_6D_6) of compound **199**.

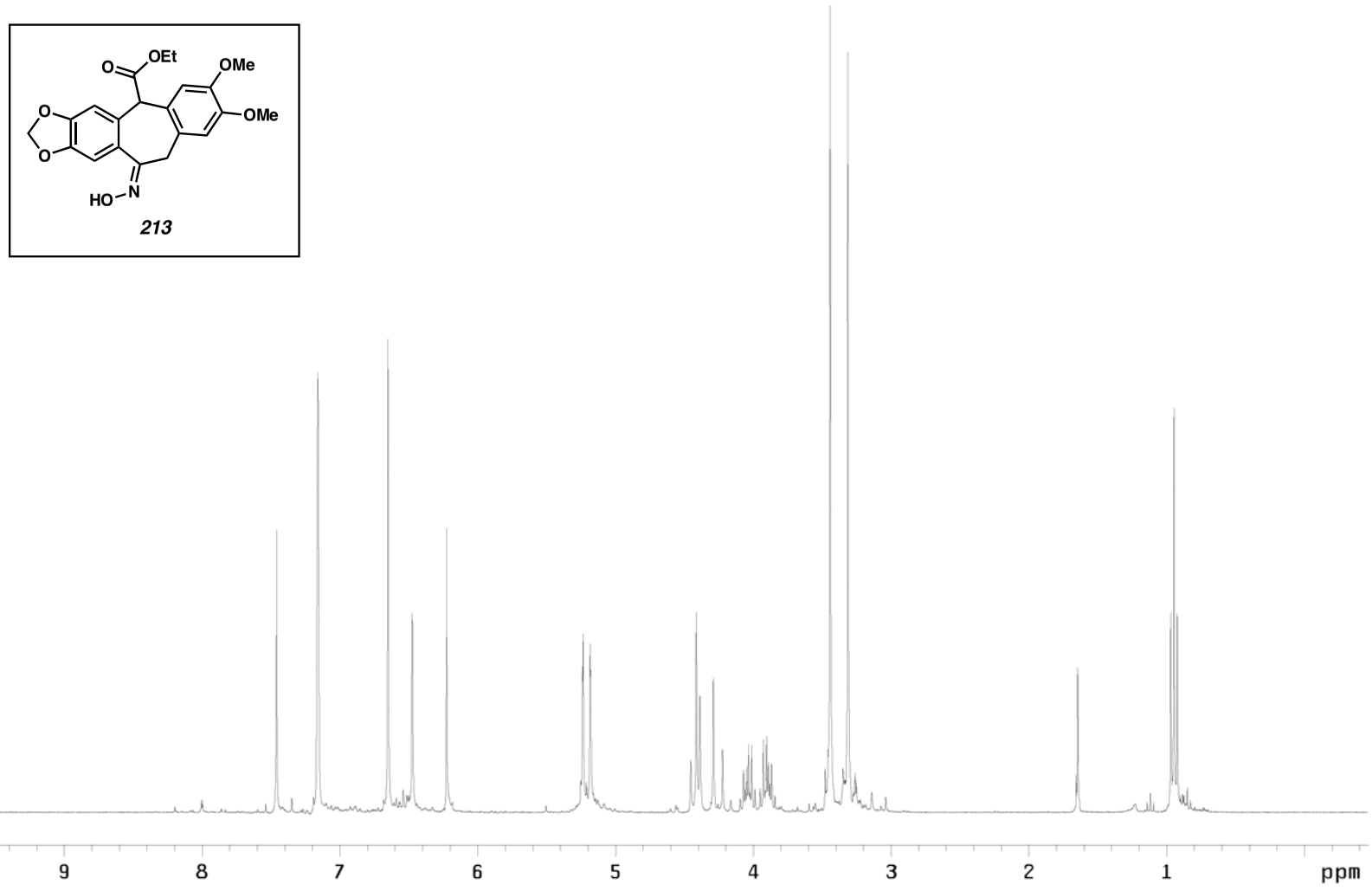


Figure A7.22 ^{1}H NMR (300 MHz, C_6D_6) of compound **213**.

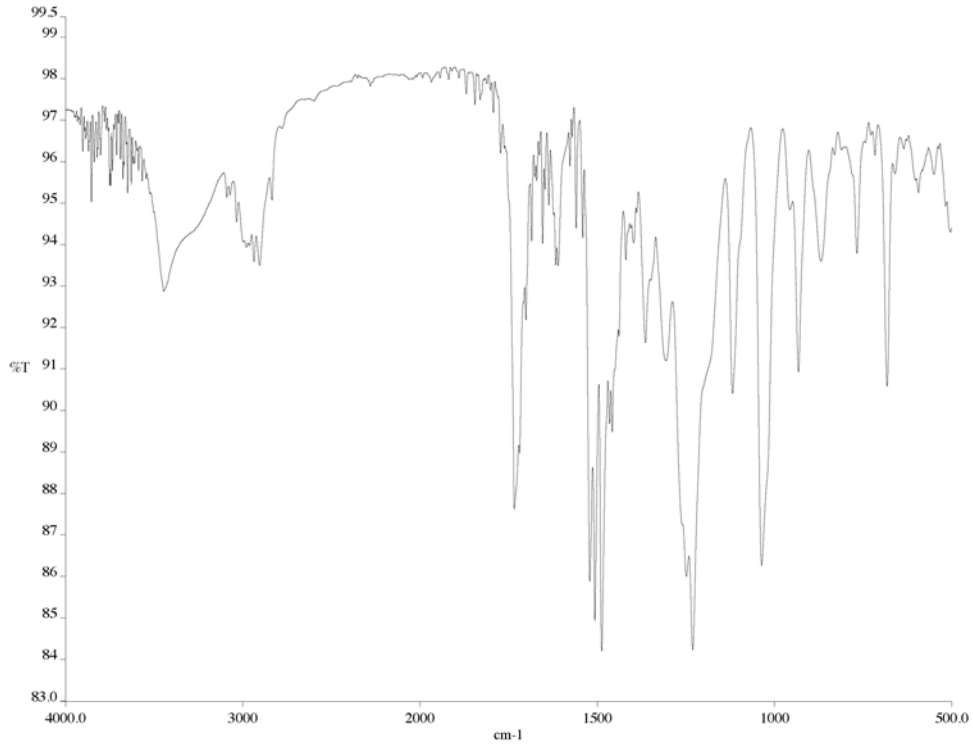


Figure A7.23 Infrared spectrum (thin film/NaCl) of compound **213**.

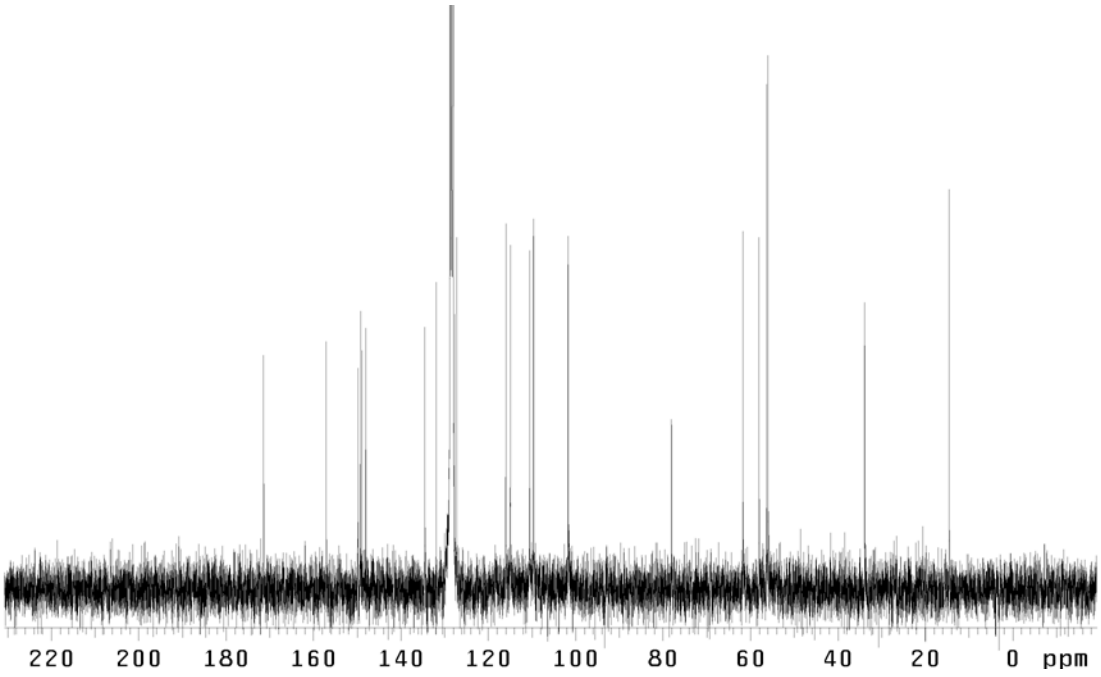


Figure A7.24 ^{13}C NMR (75 MHz, C_6D_6) of compound **213**.

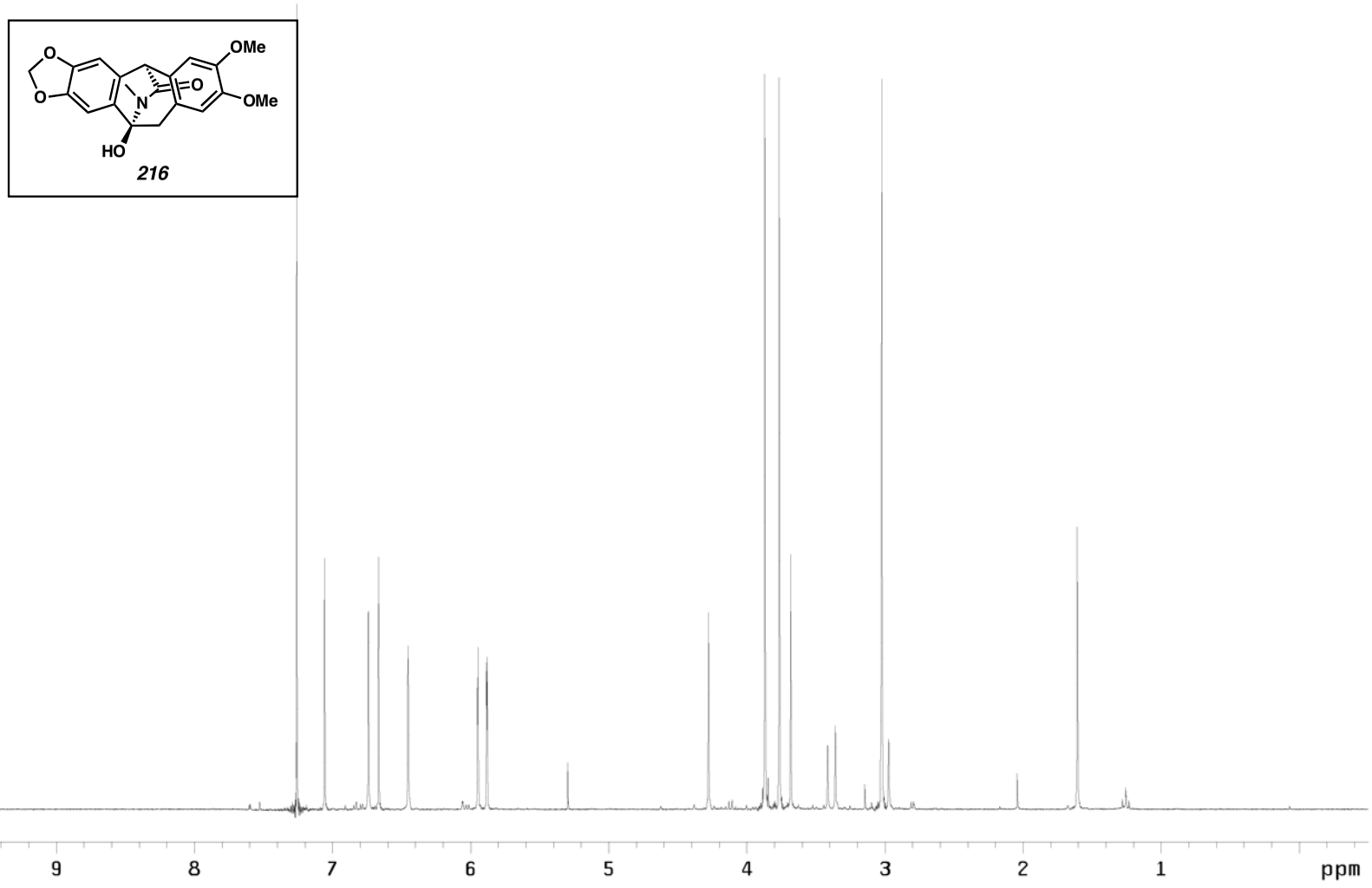


Figure A7.25 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **216**.

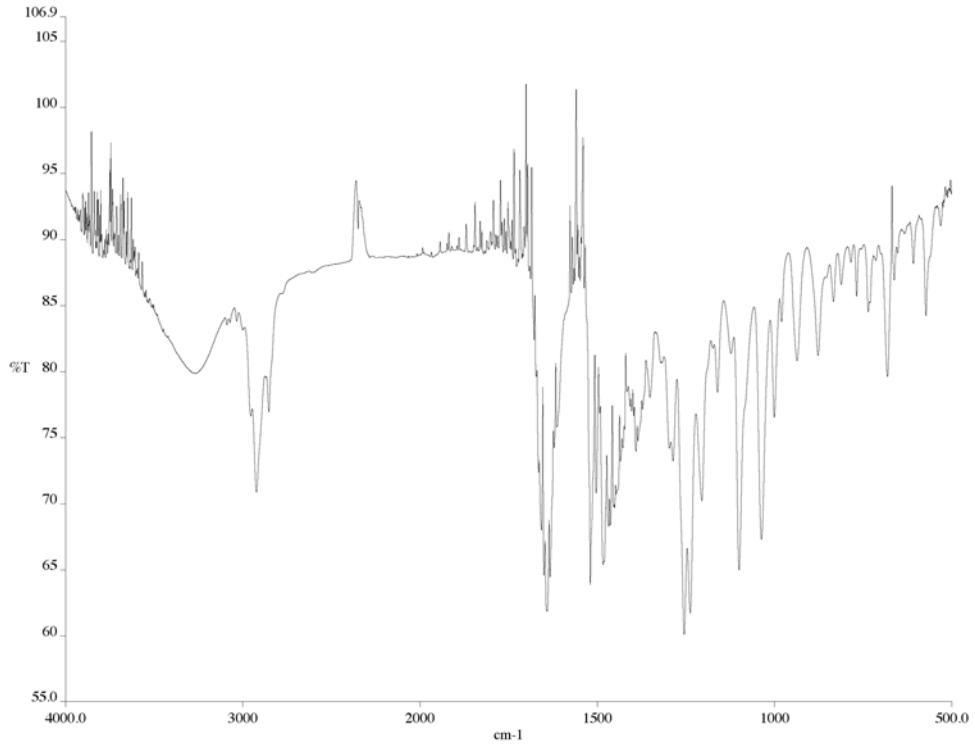


Figure A7.26 Infrared spectrum (thin film/NaCl) of compound **216**.

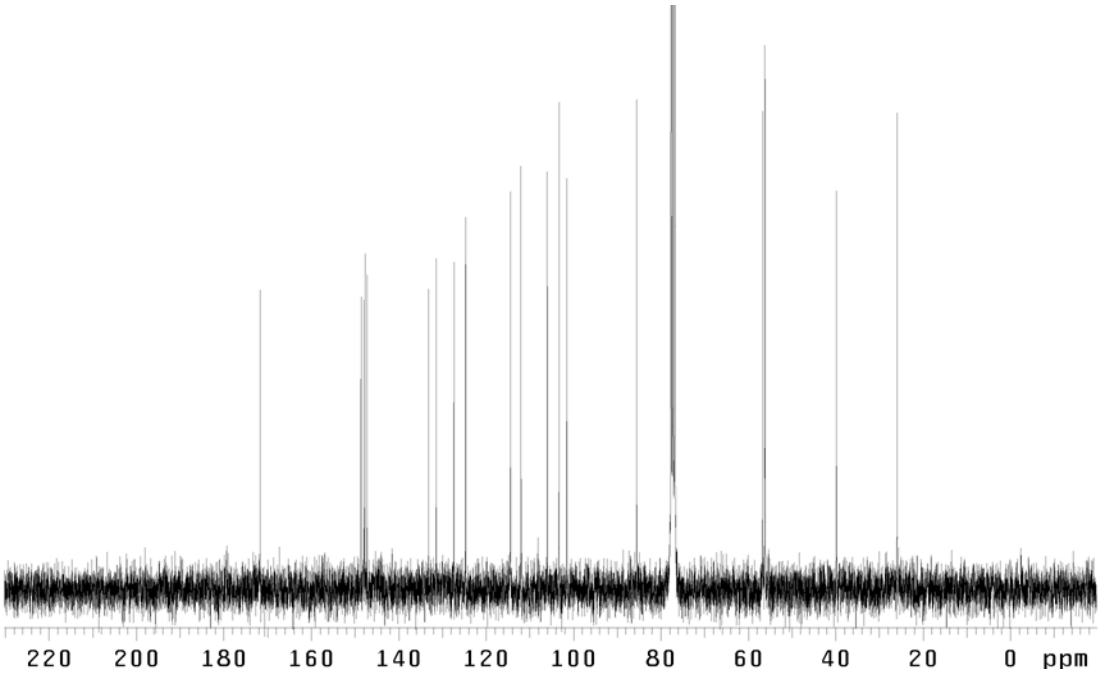


Figure A7.27 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **216**.

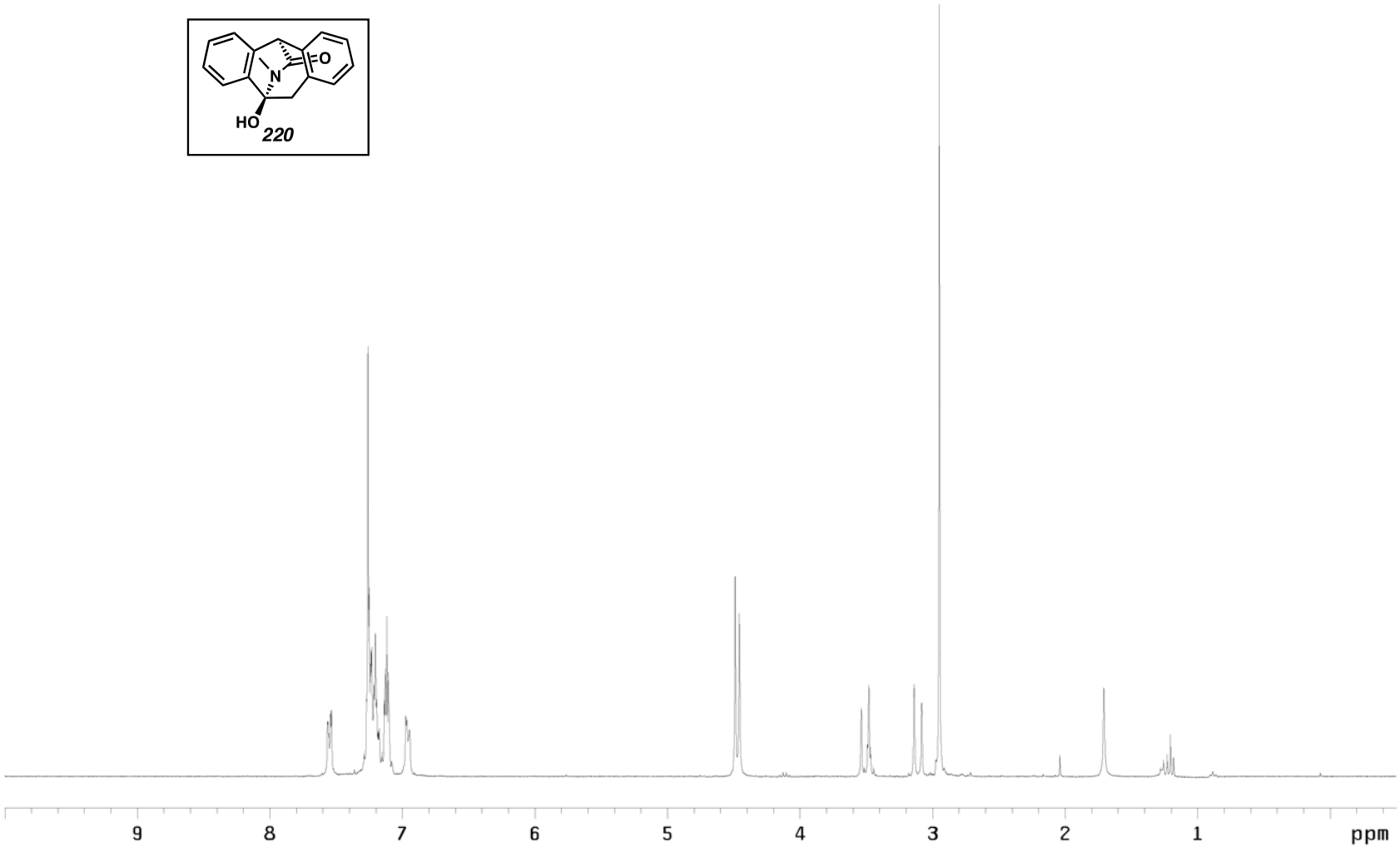


Figure A7.28 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **220**.

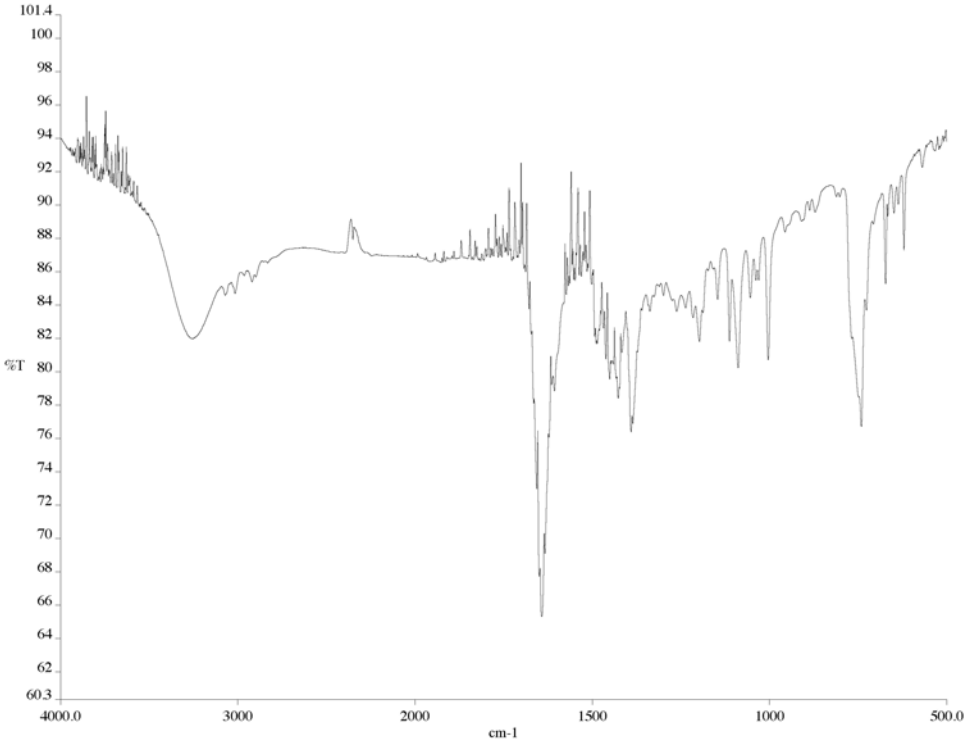


Figure A7.29 Infrared spectrum (thin film/NaCl) of compound **220**.

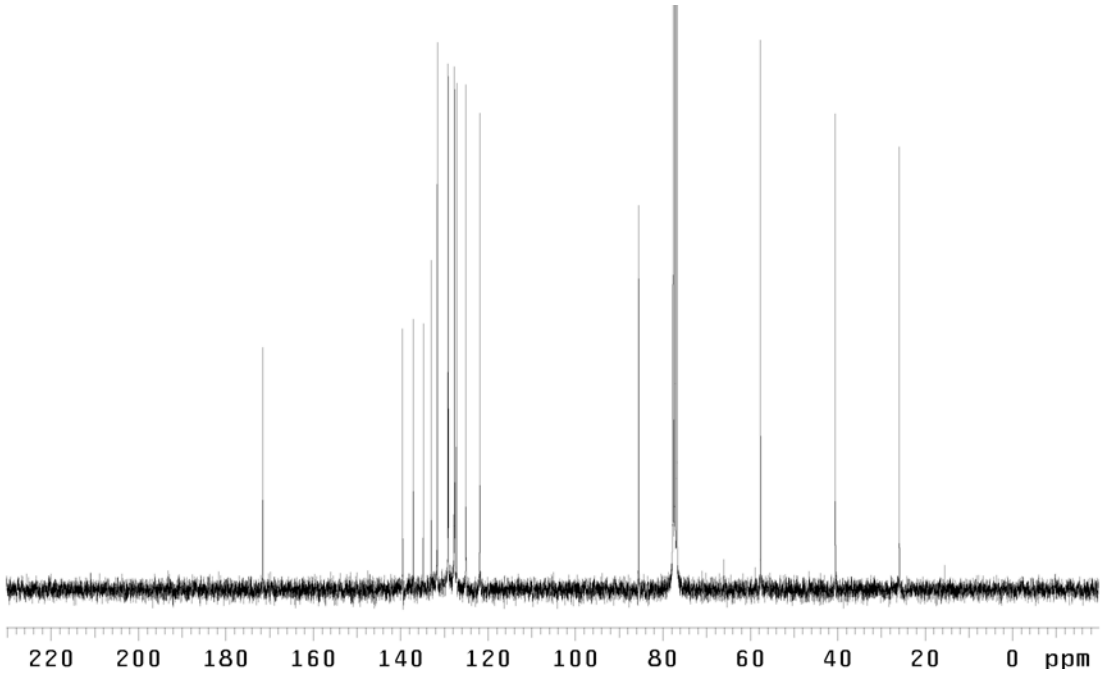


Figure A7.30 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **220**.

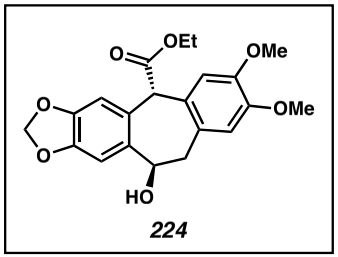


Figure A7.31 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **224**.

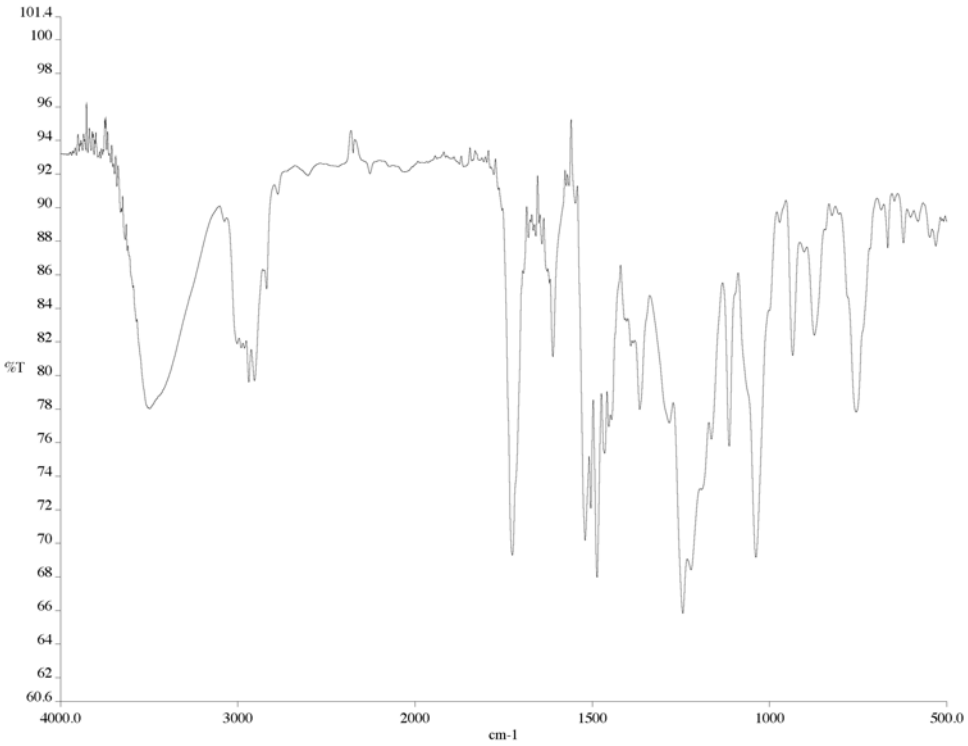


Figure A7.32 Infrared spectrum (thin film/NaCl) of compound **224**.

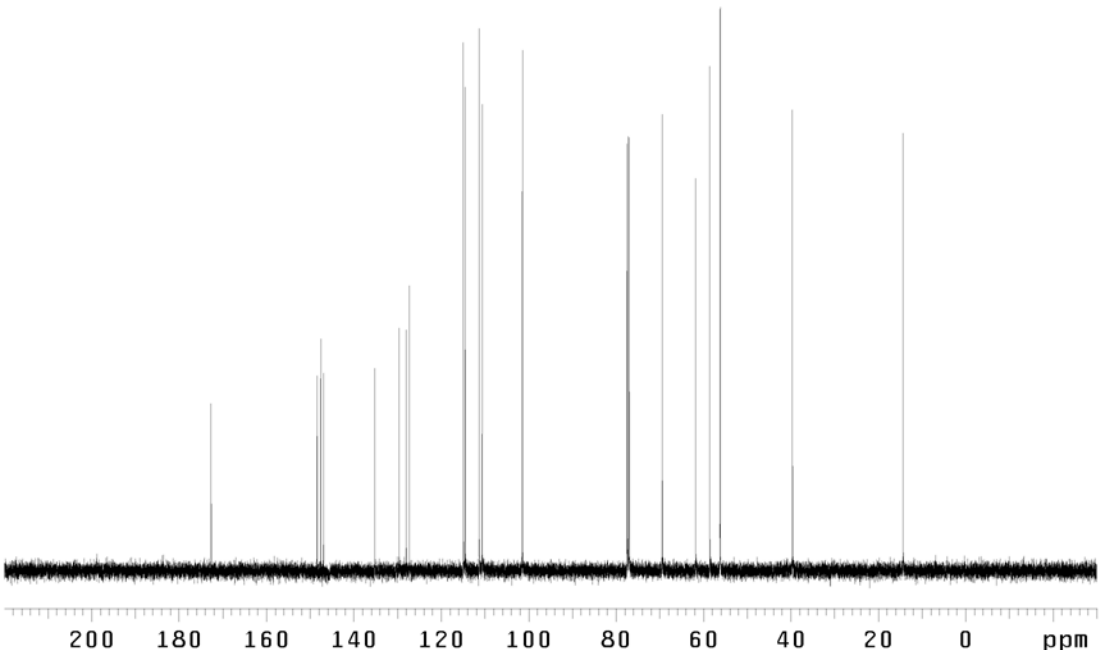
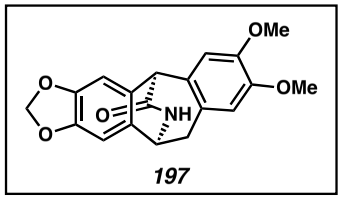


Figure A7.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **224**.



197

Figure A7.34 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **197**.

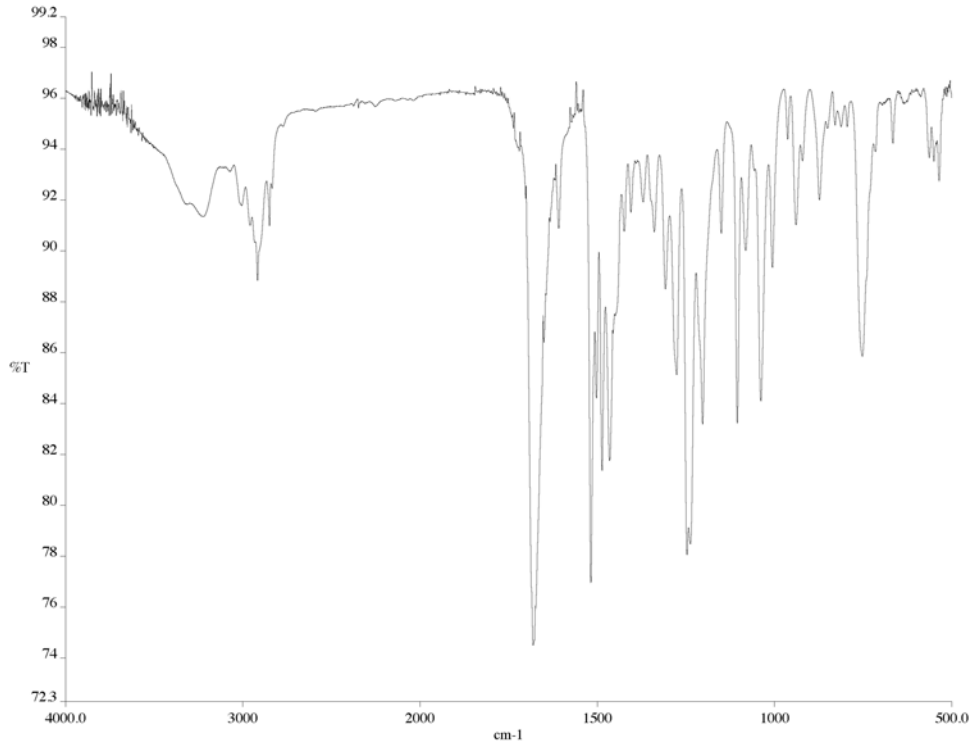


Figure A7.35 Infrared spectrum (thin film/NaCl) of compound **197**.

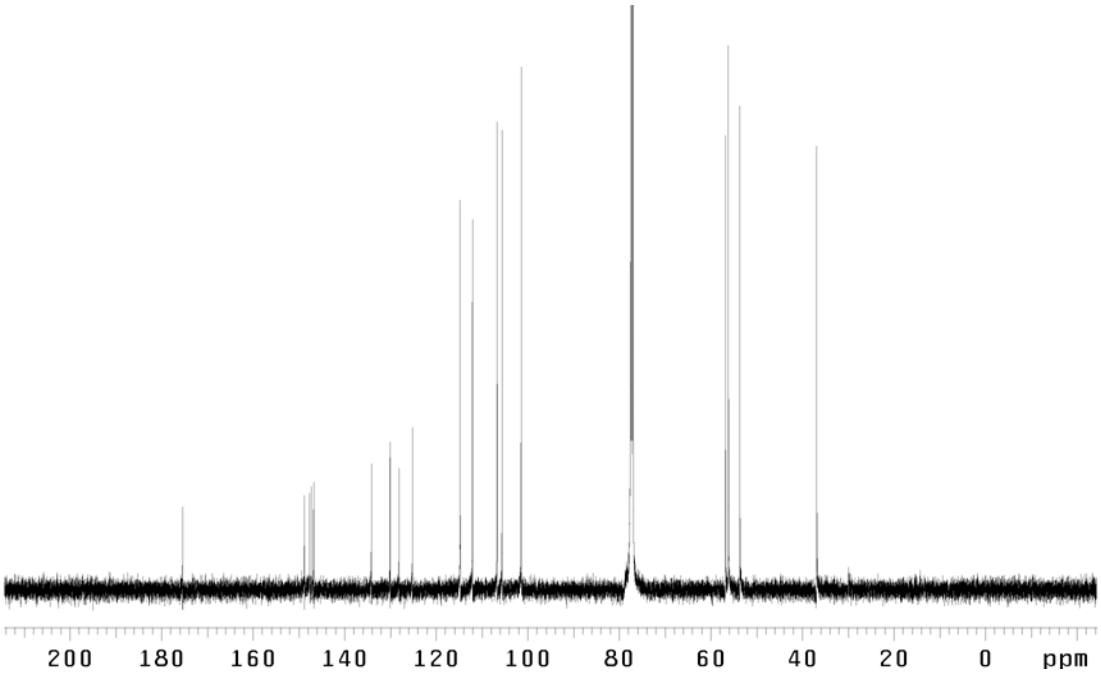


Figure A7.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **197**.

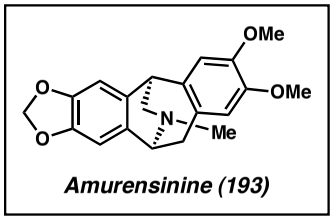


Figure A7.37 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **193**.

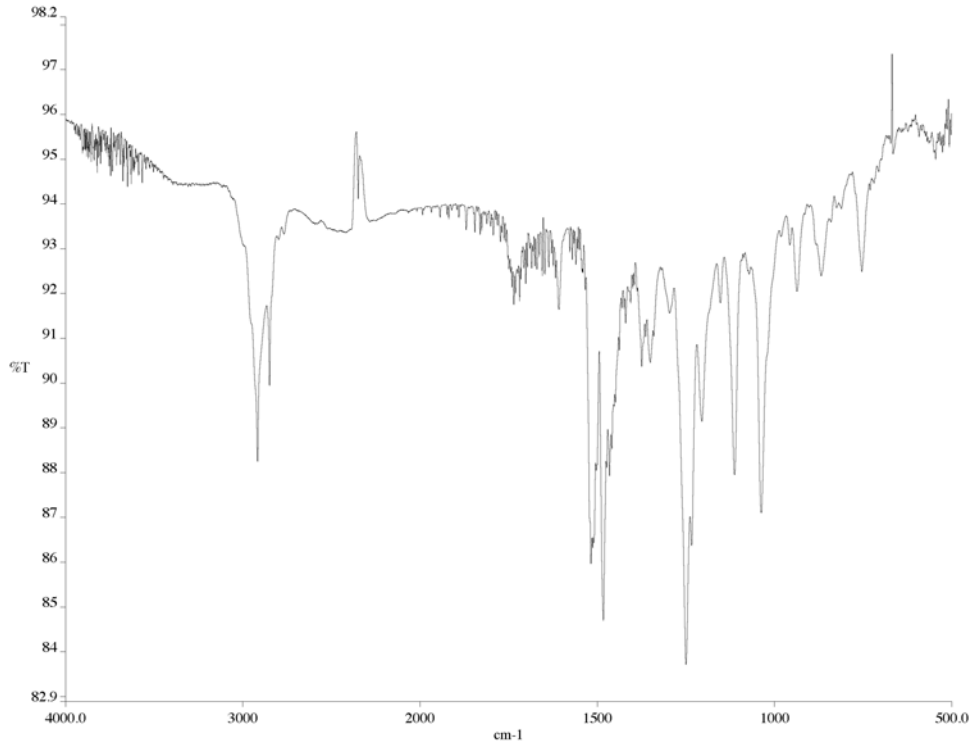


Figure A7.38 Infrared spectrum (thin film/NaCl) of compound **193**.

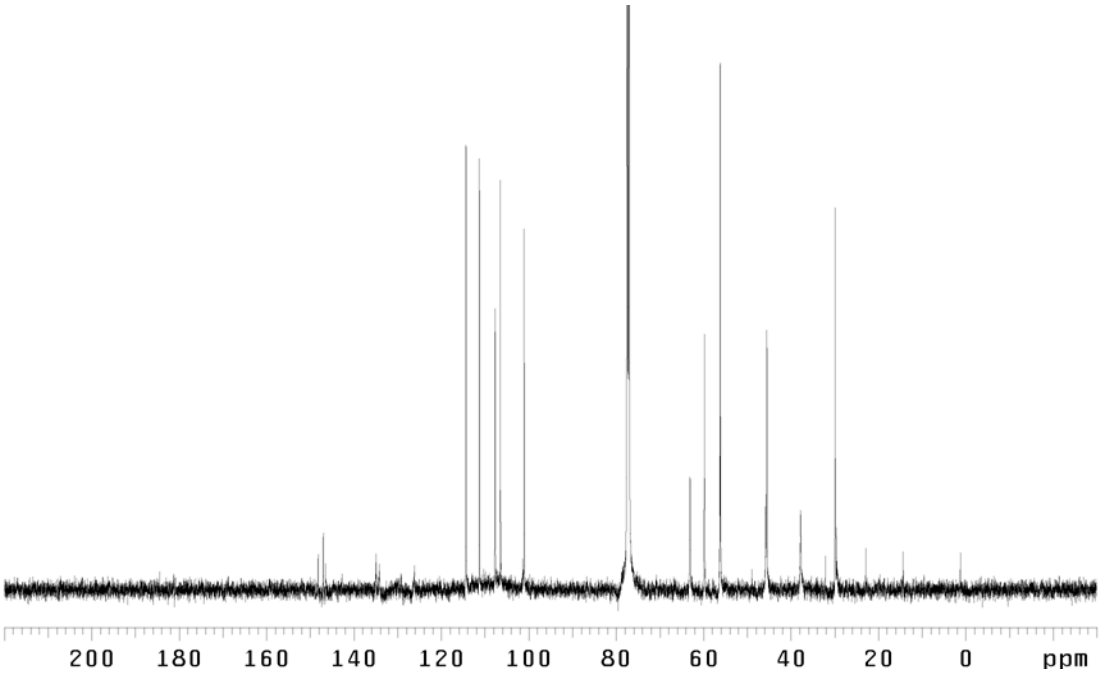


Figure A7.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **193**.

APPENDIX EIGHT

Notebook Cross-Reference

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound, both hardcopy and electronic characterization folders have been created that contain copies of the original ^{1}H NMR, ^{13}C NMR, and IR spectra. All notebooks and spectral data are stored in the Stoltz archives.

Table A8.1 **Compounds Appearing in Chapter 2: Progress Toward the Total Synthesis of Saudin: The Development of a Tandem Stille-Oxa-Electrocyclization Reaction**

Compound	^{1}H NMR	^{13}C NMR	IR
56	UKTVII-173	UKTVII-173	UKTVII-173
52a	UKTXV-127	UKTXV-127	UKTXV-127
52b	UKTVII-57	UKTVII-57	UKTVII-57
52c	UKTXXI-281	UKTXXI-281	UKTXXI-281
53a	UKTIII-287	UKTIII-287	UKTIII-287
53b	UKTXVII-181	UKTXVII-181	UKTXVII-181
53c	UKTI-263	UKTIV-75	UKTIV-75
63	UKTXX-59	UKTXX-59	UKTXX-59
50	UKTXV-141	UKTXV-141	UKTXV-141
66a	UKTIII-227	UKTIII-227	UKTIII-227
66b	UKTIII-227	UKTIII-227	UKTIII-227
68(1)	UKTXIV-243	UKTXIV-243	UKTXIV-243
68(2)	UKTXIV-243	UKTXIV-243	UKTXIV-243
70	UKTXV-139	UKTXV-139	UKTXV-139
79	UKTVII-205	UKTVII-205	UKTVII-205
82	UKTX-137	UKTX-137	UKTX-137
84	UKTXX-55	UKTXX-55	UKTXX-55
75	UKTXX-51	UKTXX-51	UKTXX-51

Compound	^{1}H NMR	^{13}C NMR	IR
76	UKTXX-47	UKTXX-47	UKTXX-47
77	UKTXX-57	UKTXX-57	UKTXX-57
71a	JFZII-245	JFZII-245	JFZII-245
71b(1)	UKTV-175	UKTV-175	UKTV-175
71b(2)	UKTV-177	UKTV-177	UKTV-177
71c	TKII-282	TKII-282	TKII-282
85	UKTVI-99	UKTIX-75	UKTIX-75
89	UKTXXI-283	UKTXXI-283	UKTVII-71
90	UKTIX-267	UKTIX-267	UKTIX-267

Table A8.2 **Compounds Appearing in Chapter 3:**

Development of the Direct Acyl-Alkylation of Arynes

Compound	^{1}H NMR	^{13}C NMR	IR
172	UKTXIX-279	UKTXIX-279	UKTXIX-279
173	UKTXIX-279	UKTXIX-279	UKTXVIII-243
175a	UKTXIX-51	UKTXIX-51	UKTXIX-51
175b	UKTXVIII-245	UKTXVIII-245	UKTXVIII-245
175c	UKTXVIII-247	UKTXVIII-247	UKTXVIII-247
175d	UKTXIX-97	UKTXIX-97	UKTXIX-97
175e	UKTXVIII-249	UKTXVIII-249	UKTXVIII-249
175f	UKTXVIII-241	UKTXVIII-241	UKTXVIII-241
175g	UKTXIX-35	UKTXIX-35	UKTXIX-35
175h	UKTXIX-37	UKTXIX-37	UKTXIX-37
181a	UKTXVIII-299	UKTXVIII-299	UKTXVIII-299
181b	UKTXIX-33	UKTXIX-33	UKTXIX-33
187	UKTXIX-213	UKTXIX-213	UKTXIX-213
180c	UKTXIX-219	UKTXIX-219	UKTXIX-189
181c	UKTXIX-199	UKTXIX-199	UKTXIX-199
185a	UKTXVIII-255	UKTXVIII-255	UKTXVIII-255
188	UKTXIX-281	UKTXIX-281	UKTXIX-281
185b	UKTXIX-41	UKTXIX-41	UKTXIX-41
189	UKTXIX-41	UKTXIX-41	UKTXIX-41
185c	UKTXIX-103	UKTXIX-103	UKTXIX-103
185d	UKTXIX-253	UKTXIX-253	UKTXIX-253
185e	UKTXIX-283	UKTXIX-283	UKTXIX-283

Table A8.3 **Compounds Appearing in Chapter 4:**

A Convergent Synthesis of Amurensinine Via Selective C-H and C-C Insertion Reactions

Compound	^{1}H NMR	^{13}C NMR	IR
208	UKTXX-149	UKTXX-149	UKTXX-149
210	UKTXX-169	UKTXX-169	UKTXX-169
202	UKTXX-193	UKTXX-193	UKTXX-193
201	UKTXX-195	UKTXX-195	UKTXX-195
203	UKTXXI-37	UKTXXI-37	UKTXXI-37
182c	UKTXXI-213	UKTXXI-213	UKTXXI-213
199	UKTXIX-227	UKTXIX-227	UKTXIX-227
213	UKTXX-137	UKTXX-137	UKTXX-137
216	UKTXX-173	UKTXX-173	UKTXX-159
220	UKTXX-171	UKTXX-171	UKTXX-171
224	UKTXXI-87	UKTXXI-87	UKTXXI-87
197	UKTXXI-185	UKTXXI-185	UKTXXI-185
193	UKTXXI-201	UKTXXI-201	UKTXXI-149

COMPREHENSIVE BIBLIOGRAPHY

A. L. Casado, Espinet, P. *Organometallics* **2003**, *22*, 1305-1309.

Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49-58.

Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066.

Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029-12046.

Boeckman, R. K., Jr.; Ferreira, M. R. R.; Mitchell, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190-191.

Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587-3606.

Büchi, G.; Yang, N. C. *J. Am. Chem. Soc.* **1957**, *79*, 2318-2323.

Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932-7936.

Carrillo, L.; Badia, D.; Dominguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716-6721.

Caubere, P.; Loubinoux, B. *Bull. Soc. Chim. Fr.* **1968**, 3008-3012.

Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2003. Rev ed. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2004.

Childers, W. E.; Abou-Gharbia, M. A. U.S. Patent 4940789, 1990; *Chem. Abstr.* **1990**, *113,* 191190w.

Cruces, J.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Tetrahedron Lett.* **2001**, *42*, 4825-4828.

Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471-9479.

Davis, S. N.; Granner, D. K. Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Panceas. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*; Hardman, J. G., Limbard, L. E., Eds.; McGraw-Hill: New York, 1996; pp 1487-1517.

Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

Dieter, R. K; Silks, L. A.; Fishpaugh, J. A.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679-4692.

Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958-964.

Dyke, S. F.; Kinsman, R. G.; Warren, P.; White, A. W .C. *Tetrahedron* **1978**, *34*, 241-245.

Dyke, S. F.;; Ellis, A. C.; Kinsman, R. G.; White, A. W .C. *Tetrahedron* **1974**, *30*, 1193-1199.

Emelen, K. V.; Wit, T. D.; Hoornaert, G. J.; Compernolle, F. *Org. Lett.* **2000**, *2*, 3083-3086.

Fang, Y. Studies Directed Toward the Total Synthesis of (–)-Saudin. Ph.D. Thesis, University of Rochester, Rochester, CA, 1991.

Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905-5911.

Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1-652.

Fujita, T.; Fujitani, R.; Takeda, Y.; Takanishi, Y.; Yamada, T.; Kido, M. Miura, I. *Chem. Pharm. Bull.* **1984**, *32*, 2117-2125.

Geoffroy, P.; Mouaddib, A.; Carre, M. C.; Caubere, P. *Tetrahedron Lett*. **1988**, *29*, 1385-1388.

Gossage, R. A.; van Koten, G. A General Survey and Recent Advances in the Activation of Unreactive Chemical Bonds by Metal Complexes. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 1-8.

Gozler, B. In *The Alkaloids*; Academic Press: New York, 1987; Vol. 31, pp 342-355.

Guyot, M.; Molho, D. *Tetrahedron Lett*. **1973**, *14*, 3433-3436.

Han, X.; Corey, E. J. *Org. Lett*. **1999**, *1*, 1871-1872.

Han, X.; Stoltz, B.M.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 7600-7605.

Himeshima, Y; Sonoda, T.; Kobayashi, H. *Chem. Lett*. **1983**, 1211-1214.

Jamart-Gregoire, B.; Leger, C.; Caubere, P. *Tetrahedron Lett*. **1990**, *31*, 7599–7602.

Jantan, I. Waterman, P. G. *Phytochemistry*, **1994**, *37*, 1477-1479.

Jeffery, T. *Tetrahedron* **1996**, *52*, 10113-10130.

Johnson, C. R.; Kozak, J. *J. Org. Chem.* **1994**, *59*, 2910-2912.

Jones, W. D. Activation of C-H Bonds: Stoichiometric Reactions. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 9-46.

Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889-1902.

Jung, M. E.; Miller, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 1984-1992.

Kakiuchi, F.; Murai, S. Activation of C-H Bonds: Catalytic Reactions. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 47-79.

Kametani, T.; Higashiyama, K.; Honda, T. *Chem. Pharm. Bull.* **1984**, *32*, 1614-1618.

Kan, T.; Fukuyama, T. *Chem. Comm.* **2004**, 353-359.

Kashima, C.; Shimizu, M.; Omote, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2694-2697.

Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp. 483-515.

Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocycl. Chem.* **1996**, *33*, 1313-1317.

Kiyooka, S; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967-7978.

Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 635-640.

Labadie, G. R.; Cravero, R. M.; Gonzalez-Sierra, M. *Synth. Comm.* **1996**, *26*, 4671-4684.

Labadie, G. R.; Luna, L. E.; Gonzalez-Sierra, M.; Cravero, R. M. *Eur. J. Org. Chem.* **2003**, *17*, 3429-3434.

Lautens, M.; Fang, Y. Q. *Org. Lett.* **2003**, *5*, 3679-3682.

Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095-5106.

Li, C.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 10484-10485.

Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359-5364.

Lin, W.; Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4258-4261.

Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112-13113.

Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673-4675.

Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99-102.

Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709-713.

Maeda, K.; Farrington, E. J.; Galardon, E.; John, B. D.; Brown, J. M. *Adv. Synth. Catal.* **2002**, *344*, 104-109.

Malerich, J. P.; Maimone, T. J.; Elliott, G. I.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276-6283.

Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554-9555.

Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; pp 260-375.

Matsud, T. Kuroyanagi, M.; Sugiyama, S.; Umehara, K.; Ueno, A.; Nishi, K. *Chem. Pharm. Bull.* **1994**, *42*, 1216-1225.

Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095-5108.

Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

Mossa, J. S.; Cassady, J. M.; Antoun, M. D.; Byrn, S. R.; McKenzie, A. T.; Kozlowski, J. F.; Main, P. *J. Org. Chem.* **1985**, *50*, 916-918.

Mossa, J. S.; El-Denshary, E. S. M.; Hindawi, R.; Ageel, A. M. *Int. J. Crude Drug Res.* **1988**, *26*, 81-87.

Murakami, M.; Ito, Y. Cleavage of Carbon-Carbon Single Bonds by Transition Metals. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Topics in Organometallic Chemistry Series, Vol. 3; Springer-Verlag: Berlin and New York, 1999; pp 97-129.

Nakayama, J.; Tajiri, T.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2907-2908.

Neeb, M. J. Studies on the Total Synthesis of (–)-Saudin. Ph.D. Thesis, University of Rochester, Rochester, CA, 1995.

Nielsen, T. E.; Cubillo de Dios, M. A.; Tanner, D. *J. Org. Chem.* **2002**, *67*, 7309-7313.

Nudelman, A.; Kelner, R.; Broida, N.; Gottlieb, H. E. *Synthesis* **1989**, *5*, 387-388.

Padwa, A.; Sa, M. M.; Weingarten, M. D. *Tetrahedron* **1997**, *53*, 2371-2386.

Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912-4913.

Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701-730.

Pena, D.; Perez, D.; Guitian, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827-5828.

Petragnani, N.; Toscano, V. G. *Chem. Ber.* **1970**, *103*, 1652-1653.

Phukan, P.; Mohan, J. Madan; and Sudalai, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *24*, 3685-3690.

Piers, E.; Wong, T.; Coish, P.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816-1819.

Prisbylla, M. P.; Takabe, K.; White, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 762-763.

Reddy, M. K.; Reddy, M. V. B.; Gunasekar, D.; Murthy, M. M.; Caux, C.; Bodo, B. *Phytochemistry*, **2003**, *62*, 1271-1275.

Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601-607.

Roberts, J. D. *The Right Place at the Right Time: John D. Roberts*; In Profiles, Pathways, and Dreams: Autobiographies of Eminent Chemists; Seeman, J. I., Ed.; American Chemical Society: Washington, DC, 1990.

Roberts, J. D.; Semenow, D. A.; Simmons, H. E.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601-611.

Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290-3291.

Rodriguez-Otero, J. *J. Org. Chem.* **1999**, *64*, 6842-6848.

Rupard, J. H.; Paulis, T.; Janowsky, A.; Smith, H. E. *J Med. Chem.* **1989**, *32*, 2261-2268.

Sato, Y.; Kobayashi, Y.; Sugiura, M.; Shirai, H. *J. Org. Chem.* **1978**, *43*, 199-202.

Selwood, D. L.; Brummell, D. G.; Budworth, J. ; Burtin, G. E.; Campbel, R. O.; Chana, S. S.; Charles, I. G.; Fernandez, P. A.; Glen, R. C.; Goggin, M. C.; Hobbs, A.J.; et al. *J. Med. Chem.* **2001**, *44*, 78-93.

Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525.

Shea, K. M.; Lee, K. L.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 2353-2356.

Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192-3194.

Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168.

Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488-7494.

Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc.* **1986,** *108*, 7686-7693.

Tambar, U. K.; Kano, T.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2413-2416.

Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340-5341.

Taylor, J. B. et al. *J. Med. Chem.* **1970**, *13*, 1226-1227.

Thompson, A. S.; Humphrey,G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886-5888.

Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777-778.

Treibs, W.; Schroth, W. *Justis Liebigs Ann. Chem.* **1961**, 82-96.

Wang, A.; Tandel, S.; Zhang, H.; Huang, Y.; Holdeman T. C.; Biehl, E. R. *Tetrahedron* **1998**, *54*, 3391–3400.

Warmuth, R. *Eur. J. Org. Chem.* **2001**, 423-437.

Weber, E.; Keana, J.; Barmettler, P. PCT Int. Appl. WO 12575, **1990**; *Chem. Abstr.* **1991**, *115*, 106019w.

Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425-7426.

Witiak, D. T.; Kim, S. K.; Tehim, A. K.; Sternitzke, K. D.; McCreery, R. L. et al. *J. Med. Chem.* **1988**, *31*, 1437-1445.

Yasuda, M.; Hamasuna, S.; Yamano, K.; Kubo, J.; Shima, K. *Heterocycles* **1992**, *34*, 965-977.

Yet, L. *Chem. Rev.* **2000**, *100*, 2963-3007.

Yoshida, H.; Honda, Y.; Shirakawa, E.; Hiyama, T. *Chem. Comm.* **2001**, 1880-1881.

Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2004**, *125*, 6638-6639.

Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *Organometallics* **2005**, *24*, 156-162.

Yoshida, H.; Minabe, T.; Ohshita, J.; Kunai, A. *Chem. Comm.* **2005**, 3454-3456.

Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 3247-3249.

Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5052-5055.

Yoshida, H.; Terayama, T.; Ohshita, J.; Kunai, A. *Chem. Comm.* **2004**, 1980-1981.

Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Comm.* **2005**, 3292-3294.

Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tet. Lett.* **2005**, *46*, 6729-6731.

Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7280-7286.

Zheng, S.-L.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2002**, *4*, 889-892.

INDEX

ABOUT THE AUTHOR

Uttam Krishan Tambar was born on November 22, 1978 in Barnsley, a small town in Yorkshire, England. He was the second son of Balvir K. Tambar and Neelam Tambar. From day one, Uttam was fortunate to have the guidance of his older brother, Udai K. Tambar.

At the tender age of six months, Uttam moved with his family to Delhi, India, where they would spend almost three years. In December 1982, the family arrived in Queens, NY, which would become their new home. As a young immigrant in the bustling Big Apple, Uttam fell in love with the New York Mets, the World Series champions of 1986. Although his parents did not understand their son's passion for the sport of baseball, they supported him in his little league career.

Uttam had the pleasure of attending the United Nations International School from kindergarten to the twelfth grade. In addition to being introduced to chemistry, he developed many amazing friendships with people from every corner of the world.

In 1996, Uttam moved to Cambridge, MA to attend Harvard University. While pursuing a major in chemistry and physics, he was exposed to the joys of chemical research. Under the guidance of Stuart Schreiber and Cynthia Friend, he began to appreciate molecular beauty at a new level. He soon decided to pursue a career in organic chemistry.

In 2000, Uttam moved to the California Institute of Technology in Pasadena, CA to join the laboratory of Brian M. Stoltz. By December 2005, twenty-three years after he first came to the USA, he earned his Ph.D. for the development of convergent methods to synthesize rings in the context of natural product synthesis. Uttam will join the laboratory of James L. Leighton at Columbia University in early 2006 for his postdoctoral studies.