EXPLOITING THE REACTIVITY OF ARYNES IN THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

Thesis by

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To my parents,
Tony and Karen,
and my sister, Vicky

ACKNOWLEDGMENTS

Every January, Brian Stoltz begins our year with the "State of the Lab" group meeting. Every January, Brian reiterates a simple phrase that says it all about his approach toward teaching and mentoring his students: "This should be the intellectual experience of a lifetime." I think that brief sentiment captures exactly how I feel at the completion of my graduate studies in his research group. Since joining the Stoltz lab in October 2005, Brian has been the single most supportive, encouraging, motivating, and understanding advisor for whom a graduate student could ask. It is impossible to capture here in words the indelible impact he has had on me over the past six years. The work that follows in this thesis would not have been possible without his unflinching support. Not only has Brian shared his seemingly endless knowledge of chemistry with us, but he has also shared his family with us on many occasions. I am very grateful to Brian's wife, Erna, and his two sons, Harry and Teddy, for opening their home to us on many occasions. Over the years, you have become like family to me and Chris and we look forward to having Harry and Teddy as ring bearers in our wedding next July in New York.

It is an understatement to say that Professor Peter Dervan, chairman of my thesis committee, has genuinely contagious enthusiasm. At key points during my graduate career, such as my candidacy and recent proposal defense, his ever-present smile always put me at ease. Furthermore, Peter's insights into my research and proposals have continuously guided and encouraged me.

One of the most exciting events during my time here at Caltech was the arrival of Professor Sarah Reisman and the start of her research group. It has been such a privilege

to watch her group grow since 2008 and I look forward to see all that they will achieve. I've also been fortunate to have Sarah join my thesis committee as its final member. As a young woman who plans to pursue an academic career, Sarah has been an invaluable role model and a source of constant guidance for me. Sometimes as a student it's difficult to envision life as a young professor (or really life after graduate school at all); Sarah has offered a window onto the process and helped me focus my own goals going forward.

I would like to add my thanks for the final member of my committee, Professor William Goddard. As the sole non-organic chemist on my committee, Bill always provided an alternative perspective on my research and proposals. I appreciated his thoughtful, yet often difficult, questions.

Another significant arrival for our division and for me personally was that of Dr. Scott Virgil in 2007. At times, when Brian was traveling, Scott has been a second mentor to me. His attention to details is legendary and he has saved me a lot of work on more than a few instances. Scott is one of the most approachable resources in the division and much of our research in the Stoltz lab bears his fingerprints. One of my favorite memories of Scott was when he hurried through the Church basement labs following his new Steinway baby grand piano that was bound for his office. I spent many evenings playing that piano and will miss the impromptu lessons from Scott. My Mozart is much improved because of them. I would be remiss if I didn't mention Scott's wonderful wife, Silva, at this time. Scott and Silva might be the two kindest and most generous people I have had the pleasure of knowing. It's impossible to have a conversation with Silva and not come away from it with a smile on your face. I am very grateful for Silva's warmth and friendship.

Prior to my arrival at Caltech, there were two teachers who steered me down the path toward chemistry. At NYU, I had the privilege of performing undergraduate research for over three years in the lab of Professor Marc Walters. Marc took me into his lab as a freshman when he had no graduate students to mentor me. It is definitely an understatement to say that he is a patient man. Of everything I learned from Marc at NYU, I value the independence as a researcher that he offered me at a young age.

The second teacher whose influence opened my young eyes to chemistry was my high school chemistry teacher, Ms. Denice Gamper. Ms. Gamper made chemistry approachable and interesting in both my sophomore chemistry class and the AP course senior year. I certainly wouldn't have shown early interest in research if not for her dedication to teaching her passion, and for that I am thankful.

I began my time in the Stoltz group in 204 Church sharing a bay with John Phillips, a postdoc in the group. I honestly had no experience as an organic chemist upon starting in the lab, but John was kind and patient enough to teach me the basics. John can still lay claim to owning the largest music collect of all my former baymates; he had a 500 GB external hard drive filled with all his music. After John left the group, Jonny Gordon moved into the bay as a first year graduate student. I'll just say that every day with Jonny was a bit of an adventure.

In March 2010, the group packed up and moved across the San Pasqual walk to our new labs in Schlinger. During my time here, I've been very lucky to have Jimin Kim as my hoodmate. She is one of the easiest people to work with and equally kind; whoever takes my place as Jimin's hoodmate is very lucky.

The open floor plan of our new Schlinger space has made for a more social and close-knit lab. Along with Jimin, I've had some really fantastic baymates since we relocated. Working next to Thomas Jensen was certainly a motivating experience. I don't know if I've known a more efficient, thorough, or outstanding chemist; there's a good reason for that rumor about Thomas being a robot. For the past year or so, I've worked along side Jeff Holder and Rob Craig, two younger graduate students in the lab. My time with Jeff and Rob has given me a glimpse of what it is like to have little brothers and I'm grateful to them for that. I can't say that I've ever had more fun at my hood than I have with Jeff and Rob when the Thursday night "crazies" arrive. Although, I'll be glad if "party boy" never makes another appearance.

Throughout this thesis, I describe in detail a number of the projects I've had the pleasure of pursuing during my time in the Stoltz lab. While I am proud of this work, it pales in comparison to my feelings about my time with Pradeep Bugga, an undergraduate researcher I mentored for almost three years. Of all I've accomplished over the past six years, I consider Pradeep my biggest success. We certainly had a bit of a rough start, but Pradeep eventually grew from my student into a legitimate project partner. It was difficult for me when he left to begin his graduate studies in September 2010 at Northwestern University, but I have no doubt that he will make his current advisor as proud as I am. I wish him all the best in his studies and thank him deeply for teaching me how to be an effective mentor.

While most of my labmates have influenced me in some way, some have had a considerable impact on my development as a chemist and as a person. Kevin Allan joined the Stoltz group a year before me and quickly became a mentor and close friend of

mine. It would take more space than I have here to detail the multitude of things that I've learned from Kevin. If I had one milligram of an important compound and had to trust one person to perform the next step, it would be Kevin. He's meticulous and incredibly talented. While we never worked on a project together, I can't remember a day while we were both in the Stoltz group that I didn't talk to him about chemistry. His influence on the work in this thesis is significant, and not just because he edited most of it. I've looked up to Kevin for a long time (not just because he's taller than I am) and value our friendship very much. On a less serious note, if it weren't for Kevin, I wouldn't be disappointed by columns that run more than 20 fractions.

John Enquist was Kevin's baymate for several years and a continual source of knowledge and assistance for me. I always aspired to have even half of John's work ethic. John has provided me a perfect outlet for my baking endeavors; we developed a great system of swapping baked goods for video game advice at some point that benefited us both greatly. I have John to thank for beating my first ever video game (and for a lot of other things too!).

In summer of 2007, Andy McClory joined the lab as a postdoc and quickly became everyone's favorite chemistry resource. When someone has an obscure chemistry question, there's a very good chance that Andy has the answer. He's the only person I've ever met who reads *Organic Syntheses* back issues before going to sleep at night. As great a labmate as he was, Andy has been an incredibly supportive and caring friend. Since he moved on to Genentech, I've missed having Andy at our dinner table on Saturday nights.

Although I will be departing from the group very shortly, I'm comforted by the fact that all these amazing colleagues of mine are just an email or phone call away at any moment. It's actually quite amazing how close many of us remain after leaving Caltech. Russell Smith and his wife, Lindsay, have become some of my closest friends and are always incredibly thoughtful. Chris and I will miss our double-dates and other fun outings with them both. Floh Vogt has been an excellent chemistry resource for me, while managing to somehow keep Chris in line. His "Ziva-isms" have been thoroughly entertaining and I'll miss his Queen night on Wednesdays (though not those Abba Mondays). Chris Henry always managed to maintain an uncanny level of calm despite often hectic circumstances. I envy him for this. We could never have made the move to Schlinger without his instrumentation expertise and persistent can-do attitude. Kathrin Höferl-Prantz was never afraid to take charge and lay down the law, remaining ever refined and graceful while doing so. I appreciated her attitude and spunk very much. Finally, Amanda Jones and her husband, Jon Eilbes, were fixtures at many of our game nights and weekend get-togethers.

Despite Brian's assertion that in graduate school you can only have one hobby, I've had a lot of fun over the past six years. I'm very grateful for the Stoltz lab softball team, the Stereoablators, for letting me live my lifelong dream of being a professional baseball player. It's easy to get those clutch hits when you have little Teddy Stoltz on the sidelines chanting "Go, Pan, go!" We may not have made the playoffs this past year, but at least we brought down our fights:wins ratio.

In my first weeks as a graduate student here I met two people who would grow to be some of my best friends. Paul Clark, a Grubbs lab alumnus and Chris's former

roommate, has always been one of our most reliable friends. Nothing ever seemed to ruffle his feathers. Zach Marshall, our token non-chemist friend, always made sure we took adequate ice cream breaks (the Coldstone owner knows him by name) before he left us for the LHC in Geneva. In the end of October 2005, Zach introduced us to his family, who immediately adopted us in a way. Kathe Marshall and her family have been exceptionally loving and generous to us since and I will especially miss them. Together with Zach, Paul, and Chris, I've spent many wonderful weekends with the Marshall and Bonnan families in Malibu; those times in Malibu are some of my best memories from my time here.

Not only does Caltech have exceptional faculty, the staff is first-rate as well. There are a great number of people who take on often thankless jobs helping students like me make it through. Since my first year, I've seen the instrumentation facilities grow into some of the best in the world. As a GLA in the NMR facility, I had the opportunity to work closely with Dave VanderVelde and Scott Ross for several years, learning the intricacies of NMR spectroscopy in the process. Mona Shahgholi and Naseem Torian in the Mass Spectroscopy facility have found masses for every compound I've ever submitted. Tom Dunn never ceases to amaze me: he can fix anything that has a plug or takes batteries. His expertise is only matched by his exceptional kindness and dedication to the division. On a side note, Tom has the coolest office in the division, in my opinion. Joe Drew in the chemistry stockroom has found every package that of mine has gone missing during my time here. Sometime in my second year, I learned that if you need something done in the division, Paul Carroad can make it happen. Paul has been especially helpful in assisting our lab's move from Crellin, Church, and Gates to the new

Schlinger labs. We are all very thankful to him for his time and patience with that huge undertaking. Diane Buchness, Laura Howe, and Agnes Tong in the graduate office have been instrumental in keeping me on track to graduate. They've always made me feel welcome and at home since I arrived here six years ago. Finally, Lynne Martinez always brightens my day and somehow manages to keep our group organized despite our best efforts to the contrary.

Lee Coleman and Helena Kopecky deserve immense thanks and appreciation for keeping me sane for the majority of my graduate career. They are simply the best at what they do. I would also like to add my thanks for Maria Lopez for her patience in dealing with my often unpredictable schedule.

My time at Caltech was made extra special by many of the unbelievable opportunities I've had that wouldn't have been available elsewhere. For over two years, I had the privilege of serving as a student advisor for the design and construction of our new labs in Schlinger. This was one of the most valuable and rewarding experiences I've had at Caltech and I must thank Tony Parker and the many architects and lab planners for realizing our visions for the new labs.

There is a small army of labmates who have made sure I don't say anything embarrassing in this thesis through their painstaking proofreading and editing. My deepest thanks to Chris Gilmore, Pradeep Bugga, Nathan Bennett, Rob Craig, Corey Reeves, and Jeff Holder. Additionally, Kevin Allan, Florian Vogt, and Phil Wu took the time to read this entire thesis; I honestly cannot thank them enough for doing so. Finally, Christopher Haley probably had the most painful proofreading task of everyone in checking the compound numbers throughout this document. As there are almost 1000

individual compounds in this thesis, his counting skills were thoroughly tested. Thank you for being so thorough.

Chris Gilmore has literally been everything to me during my time here at Caltech from the very first day of new graduate student orientation in September 2005. He started as my closest friend and labmate, eventually became my boyfriend, is currently my fiancé, and most recently became my project partner. I like to jokingly say, "he was such an excellent project partner, I decided to marry him!" In all seriousness though, at every turn, I continue to be awed by him. The one thing I admire most about him however is his seemingly endless pursuit of new knowledge, not just in chemistry, but in all sorts of disciplines. He never tires of learning something new and it speaks to his drive, determination, and love of life. Outside of my family, I have never met someone who has been so unwaveringly supportive of me; for that I cannot begin to express thanks. I consider myself unbelievably lucky to not only leave here with a Ph.D., but to also have found the man who I will marry. Chris, I love you and can't wait to say "I do" next summer in New York.

A little more than two years ago, Chris's family relocated from North Carolina to Pasadena. I've had such a great time getting to know Jane, Dennis, Brian, and Ellen, and am very thankful for the countless dinners I've shared with them. They have opened their home and hearts to me from the day I met them and I can't imagine joining a more wonderful family. They've made Pasadena feel like home in so many ways.

Finally, I owe all the thanks in the world to my family. My parents, Karen and Tony Tadross, have been incredibly supportive of me throughout this entire endeavor, even though I realize it was difficult for them to see their little girl move across the country. I

can say, without exaggeration, that I would be both broke and homeless without them. I like to think that each of my parents gave me a little piece of them that has made graduate school easier. My dad always taught me to be prepared when going into something new and unknown; that's why he told me to never go anywhere without a roll of duct tape in your trunk. Anticipating potential problems and roadblocks has been key to my development as a scientist. My mom is a true problem solver and instilled in me the belief that for every obstacle there's a creative solution. That attitude has helped me keep an optimistic outlook when not much was working in the lab. I don't think I could have done this otherwise.

My younger sister, Vicky, has become one of my best friends since I moved here. We are separated by four years and didn't really get along well until I moved 3000 miles away. Funny how that happens. We talk almost every day now (sometimes twice a day or more!) and I hope we stay as close as we are now when I return to the east coast. I honestly cannot believe Vicky is the same little sister as she was when I first left New York. Aside from the obvious income difference, she's grown into a beautiful, smart, and driven young woman who I know will go very far. I'm very proud of her.

Many people who know me know I have a love of all things musical theater. I would like to close with a quote from the musical *Wicked* that is so very appropriate for everyone who has been a part of this experience with me and supported me over the past six years.

"So let me say before we part,
so much of me
is made of what I learned from you.
You'll be with me
Like a handprint on my heart"
–Stephen Schwartz

ABSTRACT

Within 14 years of the seminal experiments of J. D. Roberts leading to the first proposal of the structure of benzyne, synthetic organic chemists recognized the potential to exploit this highly reactive intermediate (and its substituted variants) in the synthesis of natural products. More specifically, it was recognized that arynes offered the strategic advantage of rapidly functionalizing an aromatic ring by forming multiple carbon–carbon or carbon–heteroatom bonds in a single operation, often in a regioselective manner. Herein are reported three separate efforts aimed at constructing natural products by aryne-based methodologies. In each of the studies described in the following chapters, the implementation of new aryne technologies developed in our group to natural product synthesis has resulted in concise, convergent, and general strategies to our targets.

The first project discussed in this work is the enantioselective total synthesis of (–)-curvularin by an acyl-alkylation reaction of a protected resorcinylic silyl aryl triflate aryne precursor with a β-ketolactone. Application of this strategic disconnection resulted in a six-step convergent synthesis of the polyketide natural product, the shortest to date. These efforts also resulted in the syntheses of curvulin and diplodialide C.

In our efforts toward the total synthesis of two naturally occurring HIV integrase inhibitors, integrastatins A and B, we attempted to utilize a sequence involving an acyl-alkylation followed by an *ortho*-Fries-type rearrangement to access the tetracyclic core of the natural products. However, this proved to be a significant challenge and led to the development of an alternative route to the tetracyclic integrastatin core by a Wacker cyclization of a diol onto a pendant olefin.

Finally, ongoing progress toward the synthesis of the bis-tetrahydroisoquinoline natural product jorumycin is detailed. In a departure from the efforts toward curvularin and the integrastatins, jorumycin has been targeted through the application of a combination of aryne annulation and acyl-alkylation/condensation methodologies aimed at the synthesis of a functionalized bis-isoquinoline intermediate. Reduction of this key bis-isoquinoline to a bis-tetrahydroisoquinoline and subsequent lactamization provided the pentacyclic core of jorumycin and related natural products in only two steps from simple isoquinoline building blocks.

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LIST OF ABBREVIATIONS

A	adenine
$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
BINAP	(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl

Bz	benzoyl
C	cytosine
c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
^{14}C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane

dba	dibenzylideneacetone
DBDMH	*N*,*N*'-dibromo-5,5-dimethylhydantoin
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutyl aluminum hydride
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)

E^+	electrophile
E	trans (entgegen) olefin geometry
EC_{50}	median effective concentration (50%)
EDCI	*N*-(3-Dimethylaminopropyl)-*N*-2-ethylcarbodiimide hydrochloride
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G	guanine
h	hour(s)
^1H	proton
^2H	deuterium
^3H	tritium
[H]	reduction
HATU	2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
$h\nu$	light

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
iNOS	human-inducible nitric oxide synthase
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
KHMDS	potassium bis(trimethylsilyl)amide
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LICA	lithium isopropylcyclohexylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion

m	meta
μ	micro
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular seives
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile

o	ortho
[O]	oxidation
t-Oct	*tert*-octyl (1,1,3,3-tetramethylbutyl)
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
Piv	pivalate
pK_a	acid dissociation constant
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
RCM	ring-closing metathesis

REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
s	selectivity factor = $k_{rel(fast/slow)} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C = conversion
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase
Su	succinimide
t	triplet
T	thymine
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Tr	triphenylmethane (trityl)
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

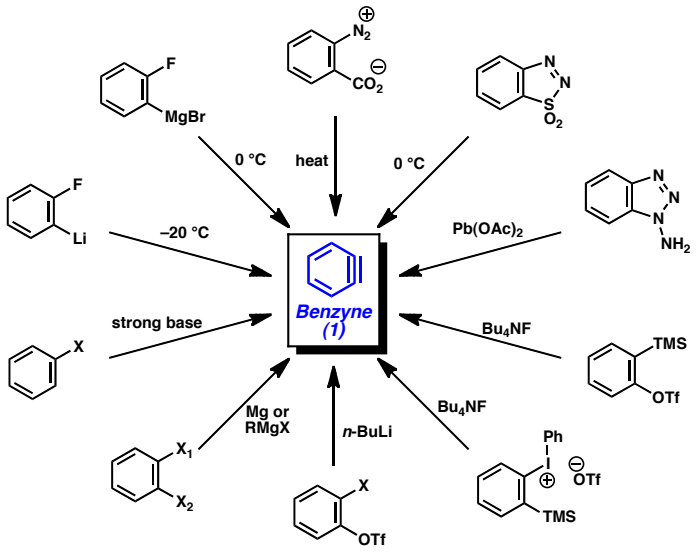
Chapter 1

A Comprehensive History of Arynes in Natural Product Total Synthesis

1.1 INTRODUCTION

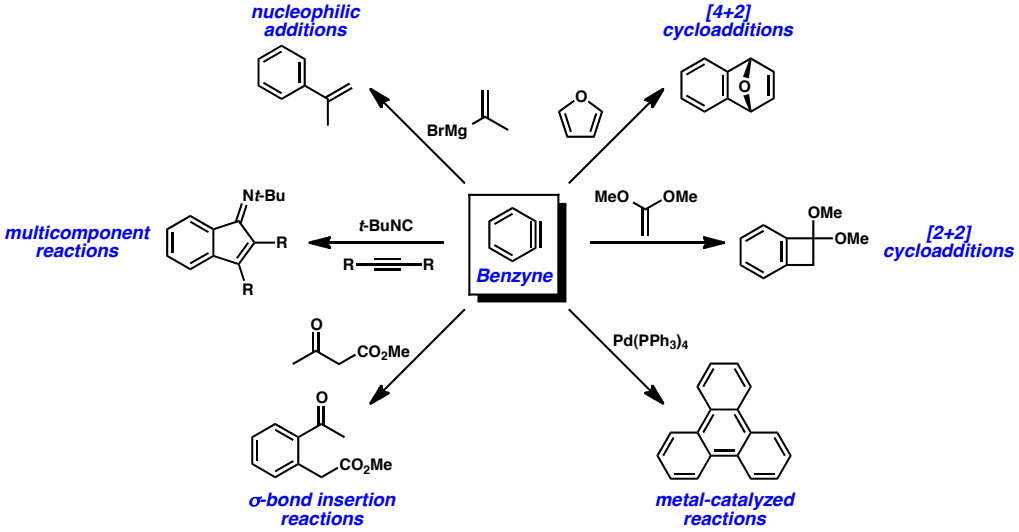
Within 14 years of the seminal experiments of J. D. Roberts leading to the first proposal of the structure of benzyne (**1**),[1] synthetic organic chemists recognized the potential to exploit this highly reactive intermediate (and its substituted variants) in the total synthesis of natural products. More specifically, it was recognized that arynes offered the strategic advantage of rapidly functionalizing an aromatic ring by forming multiple carbon–carbon or carbon–heteroatom bonds in a single operation, often in a regioselective manner. Initially, the scope of synthetic applications was somewhat limited by the harsh conditions required to produce the aryne species.[2] Many of these methods required strong bases, such as *n*-BuLi, or high temperatures (Scheme 1.1). However, with the development of milder methods for the generation of arynes came increased interest in employing them in the synthesis of more complex polycyclic systems. Most recently, the use of *o*-silyl aryl triflates as aryne precursors has allowed generation of the reactive intermediate under almost neutral conditions.[3]

*Scheme 1.1. Methods for the generation of benzyne (**1**).*



To date, over 75 individual natural products have been prepared using arynes to generate key synthetic intermediates. Herein are recounted the reports of total syntheses that utilize arynes in ways that build complexity or introduce motifs essential to the completion of their targets. The methods by which the authors featured in this review accomplish this task reflect the versatility of arynes as reactive intermediates for synthesis (Scheme 1.2).[4,2g] For the purposes of organization, the syntheses are divided into subgroups on the basis of the type of aryne transformation: 1) nucleophilic additions or multicomponent reactions, 2) σ-bond insertion reactions, 3) [4 + 2] and [2 + 2] cycloaddition strategies, and 4) metal-catalyzed aryne reactions. It should be noted that only completed natural product syntheses have been detailed in this review; formal total syntheses and efforts toward natural products have not been included.

*Scheme 1.2. Representative reactions of benzyne (**1**).*[5]



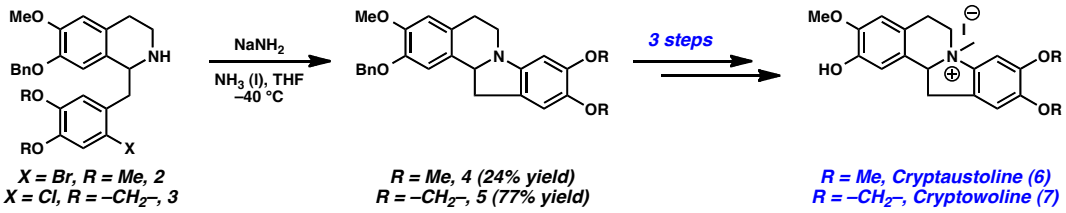
1.2 NUCLEOPHILIC ADDITION AND MULTICOMPONENT REACTION STRATEGIES

Strategies for the total synthesis of natural products that rely on nucleophilic additions to arynes (including multicomponent approaches) predominate in the literature over other approaches. The examples presented in this section have been divided into two groups: nucleophilic additions that form only a single new carbon–carbon or carbon–heteroatom bond to the intermediate aryne, and multicomponent reactions, in which three or more components are united in such a way that two new bonds to the aryne are formed in a single operation. Syntheses that employ nucleophilic addition strategies represent some of the oldest known applications of arynes to total synthesis, while multicomponent approaches to natural products have only emerged within the past decade.

1.2.1 Nucleophilic Additions to Arynes

The first instance in which arynes were applied to the total synthesis of natural products was reported by Kametani and co-workers at Tohoku University in 1967.[6] Kametani's synthesis of cryptaustoline (**6**) and cryptowoline (**7**) marked the beginning of a long-term research program to utilize aryne intermediates in alkaloid synthesis that would span more than 10 years. In the synthesis of cryptaustoline (**6**) and cryptowoline (**7**), substituted tetrahydroisoquinolines **2** and **3** were treated with sodamide in liquid ammonia to generate tetracycles **4** and **5**, respectively, by nucleophilic addition of the secondary amine to a pendant aryne (Scheme 1.3). From this point, tetracycle **4** was converted to cryptaustoline (**6**) over three steps, while tetracycle **5** afforded cryptowoline (**7**).

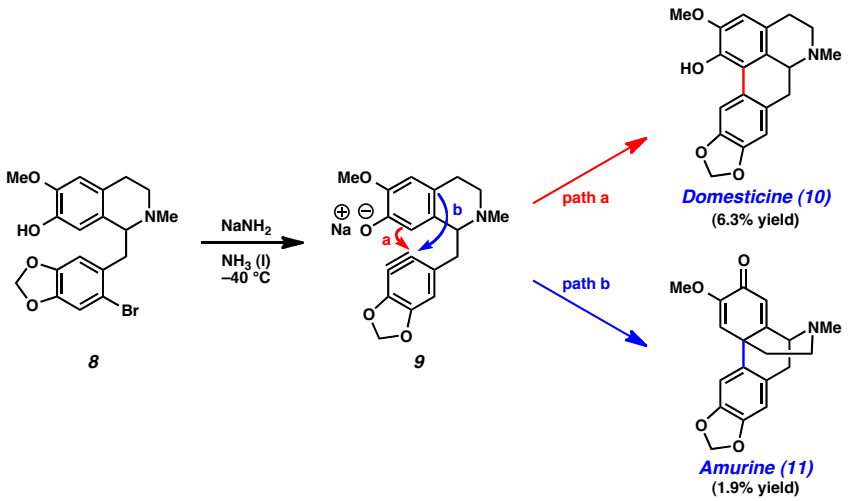
*Scheme 1.3. Kametani's 1967 synthesis of cryptaustoline (**6**) and cryptowoline (**7**).*



Building on this synthetic strategy, Kametani next reported the syntheses of domesticine (**10**) and amurine (**11**) (Scheme 1.4).[7,8] *N*-Methylation of tetrahydroisoquinoline intermediates such as **2** and **3** and removal of the benzyl protective group led to alternative reactivity in the key aryne cyclization, allowing access to a different class of alkaloids. Upon treatment of phenol **8** with sodamide in liquid ammonia, the authors isolated low yields of both domesticine (**10**) and amurine (**11**),

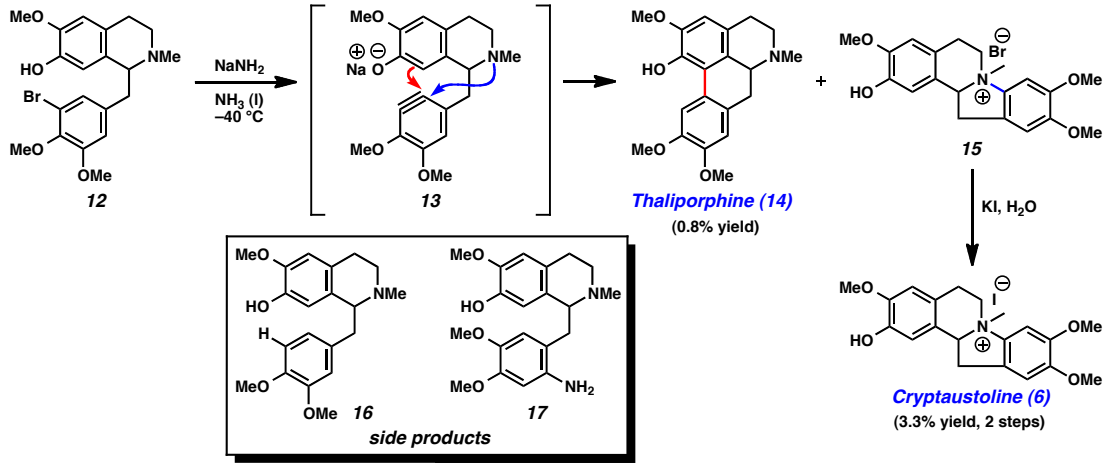
resulting from attack of the phenoxide *ortho* (path a, blue bond) and *para* (path b, red bond) positions, respectively, on the aryne (**9**). Notably, the formation of amurine results in a dearomatization upon aryne cyclization.

*Scheme 1.4. Kametani's 1971 synthesis of domesticine (**10**) and amurine (**11**).*



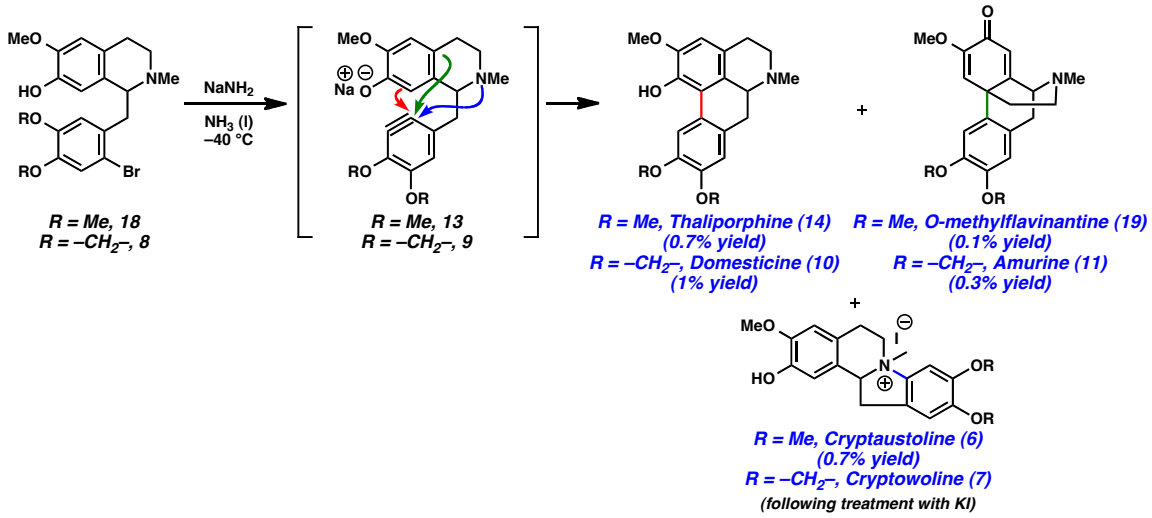
Similarly, aryne cyclization of phenol **12** under these same conditions resulted in the formation of a mixture of compounds, including thaliporphine (**14**) (Scheme 1.5).[9] Following extraction of thaliporphine (**14**) and two additional side products (**16** and **17**), concentration of the aqueous washes and treatment with potassium iodide also afforded cryptaustoline (**6**).

*Scheme 1.5. Kametami's 1972 synthesis of thaliporphine (**14**) and cryptaustoline (**6**).*



In their final report on this work, Kametani and co-workers extended their synthetic efforts one step further to prepare three different natural products from a single aryne precursor in one pot (Scheme 1.6).[10] Depending on the substitution, treatment of either tetrahydroisoquinoline **18** or **8** with sodamide in liquid ammonia yielded cryptaustoline (**6**) (following treatment with potassium iodide), thaliporphine (**14**), and *O*-methylflavinantine (**19**), or cryptowoline (**7**) (following treatment with potassium iodide), domesticine (**10**), and amurine (**11**), respectively.

*Scheme 1.6. Kametani's 1973 one-pot synthesis of cryptaustoline (**6**), thaliporphine (**14**), and O-methylflavinantine (**19**); and cryptowoline (**7**), domesticine (**10**), and amurine (**11**).*

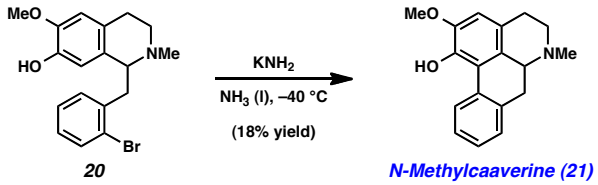


It should be noted that subsequent to Kametani's publication of the syntheses featured in Scheme 1.6, Kessar and Gandhi reported an identical approach to domesticine (**10**), cryptaustoline (**6**), cryptowoline (**7**), amurine (**11**), *N*-methylcaaverine (**21**), and thalicmidine with similarly low yields.[11] Generally speaking, the consistently low yields reported in early aryne-based total syntheses stem from competing reactivity pathways and reflect the infant state of such synthetic methods. Interestingly, the structure given by Kessar for thalicmidine is identical to Kametani's thaliporphine (**14**). Furthermore, the only natural product prepared by Kessar that was not targeted by Kametani was *N*-methylcaaverine (**21**), which was isolated upon aryne cyclization of tetrahydroisoquinoline **20** in 18% yield (Scheme 1.7).

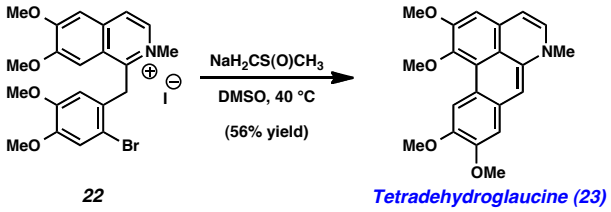
Furthermore, Castedo and co-workers extended this aryne cyclization method to include the synthesis of more oxidized relatives of natural products like thaliporphine (**14**) and domesticine (**10**). In the synthesis of tetradehydroglaucine (**23**), aryne

cyclization of *N*-methyl isoquinolinium iodide **22** directly afforded the natural product upon treatment with sodium dimsylate (Scheme 1.8).[12]

*Scheme 1.7. Kessar's 1975 synthesis of N-methylcaaverine (**21**).*

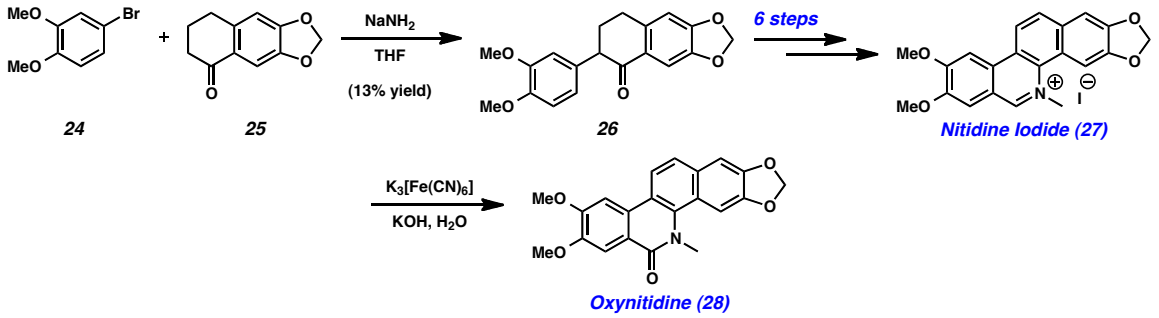


*Scheme 1.8. Castedo's 1987 synthesis of tetradehydroglaucine (**23**).*



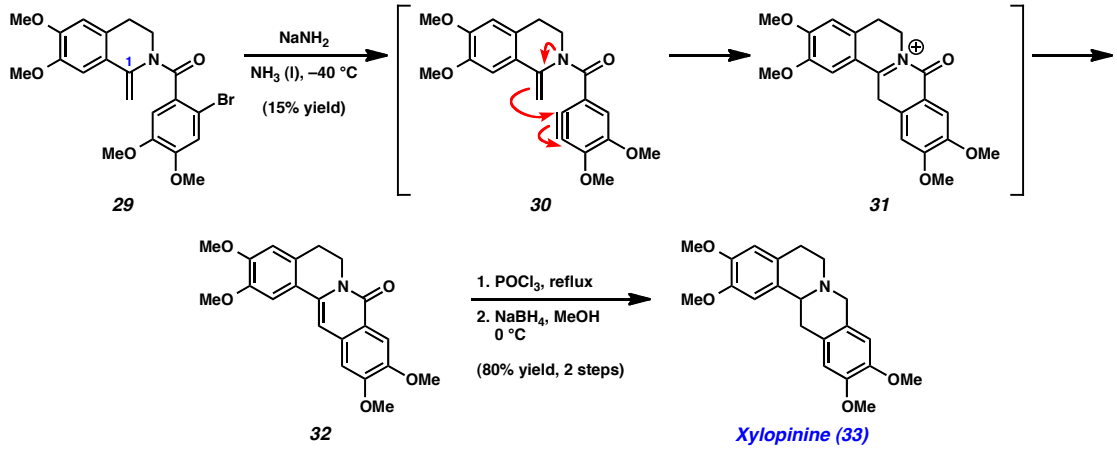
Kametani and co-workers next turned their attention to a slightly different isoquinoline-derived alkaloid framework in their synthesis of oxynitidine (**28**) and nitidine iodide (**27**) (Scheme 1.9).[13] In this case, advanced intermediate **26** was prepared by arylation of α-tetralone **25** with the aryne generated in situ from aryl bromide **24**. Arylated α-tetralone **26** was converted to nitidine iodide (**27**) over six additional steps. Subsequent oxidation of nitidine iodide (**27**) provided oxynitidine (**28**).

*Scheme 1.9. Kametani's 1973 synthesis of nitidine iodide (**27**) and oxynitidine (**28**).*



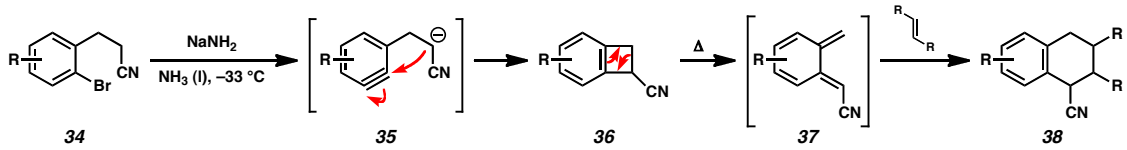
The final alkaloid synthesis in which Kametani and co-workers employed arynes deviates somewhat from the examples detailed above.[14] In the synthesis of xylopinine (**33**), a protoberberine alkaloid, treatment of C(1)-methylene isoquinoline derivative **29** with sodamide in liquid ammonia resulted in enamine cyclization onto the pendant aryne, furnishing tetracycle **32** upon deprotonation (Scheme 1.10). Finally, reduction of both the lactam and enamine by a two-step sequence afforded xylopinine (**33**).

*Scheme 1.10. Kametani's 1977 synthesis of xylopinine (**33**).*



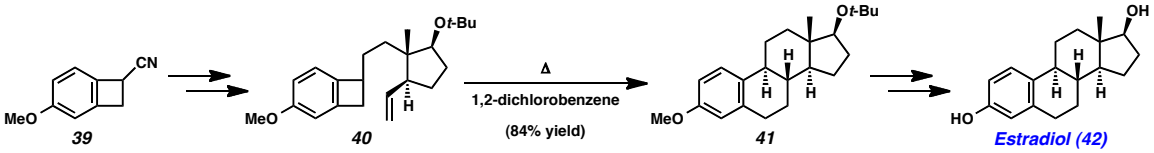
Outside the realm of alkaloid synthesis, Kametani also explored how arynes could expedite the synthesis of steroid structures. In one example, treatment of nitrile **34** with sodamide in liquid ammonia resulted in formation of benzocyclobutene **36** via intermediate aryne **35** (Scheme 1.11).[15] Benzocyclobutenes, such as **36**, have proven to be valuable intermediates for the in situ generation of *o*-quinone dimethides (**37**). Intramolecular Diels–Alder reactions of such *o*-quinone dimethides with tethered dienophiles have provided an efficient entry into tetralene synthesis. Kametani has used this method in several instances to accomplish the formal synthesis of naturally occurring steroids.

Scheme 1.11. Kametani's synthesis of benzocyclobutenes via intramolecular nitrile arylation.



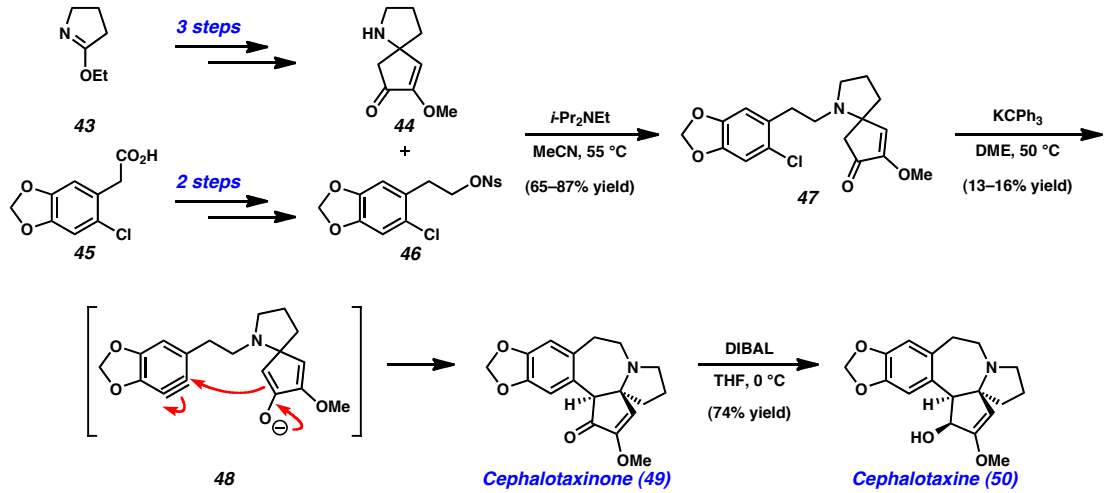
In the synthesis of estradiol (**42**), Kametani elaborated benzocyclobutene **39** to enantioenriched cyclopentane **40**, the precursor for the key Diels–Alder cycloaddition (Scheme 1.12).[16] Upon heating, benzocyclobutene **40** underwent a 4π electrocyclic ring opening and subsequent Diels–Alder reaction to afford tetracycle **41**, which was converted to estradiol (**42**) over two steps.

*Scheme 1.12. Kametani's 1978 synthesis of estradiol (**42**).*



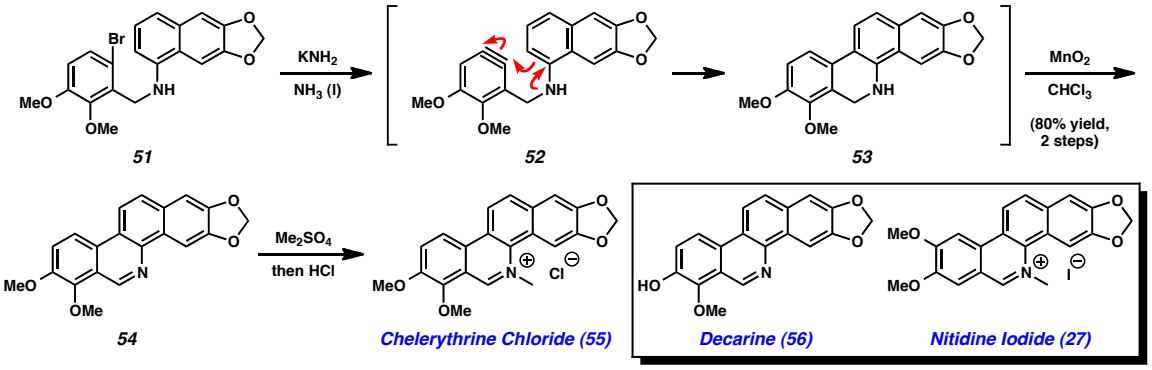
During this same time period, Semmelhack and co-workers reported a concise and convergent approach to the cephalotaxus alkaloids (**49** and **50**) based on a late-stage aryne cyclization strategy.[17] Beginning with 2-ethoxy-1-pyrroline (**43**), heterospirocycle **44** was generated in three steps, while nosylate **46** was prepared over a two-step sequence beginning with carboxylic acid **45** (Scheme 1.13). Following coupling of nosylate **46** with pyrrolidine **44**, treatment of tertiary amine **47** with excess potassium triphenylmethide produced cephalotaxinone (**49**) directly by enolate addition to the pendant aryne (e.g., intermediate **48**). Diastereoselective reduction of cephalotaxinone (**49**) with DIBAL then produced cephalotaxine (**50**). In total, Semmelhack and co-workers was able to achieve the synthesis of cephalotaxinone (**49**) and cephalotaxine (**50**) in only five and six steps, respectively, from 2-ethoxy-1-pyrroline (**43**).

*Scheme 1.13. Semmelhack's 1972 synthesis of cephalotaxinone (**49**) and cephalotaxine (**50**).*



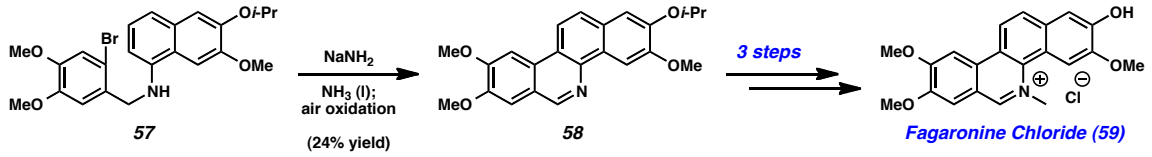
Concurrent with Kametani's efforts toward the synthesis of isoquinoline-containing alkaloids (vide supra), Kessar and co-workers targeted other members of this class of compounds through different aryne-centered strategies. In the synthesis of chelerythrine chloride (**55**), Kessar forged a key carbon–carbon bond by treatment of aryl bromide **51** with potassium amide in liquid ammonia (Scheme 1.14).[18] The tetracyclic product of this aryne cyclization (**54**) was then methylated to afford the natural product (**55**). This same strategy was employed again by Kessar in the subsequent syntheses of decarine (**56**)[19] and nitidine iodide (**27**).[20]

*Scheme 1.14. Kessar's synthesis of chelerythrine chloride (**55**) (1974), decarine (**56**) (1984), and nitidine iodide (**27**) (1988).*



Just months after Kessar's synthesis of chelerythrine chloride (**55**), Stermitz and co-workers employed an identical strategy in their synthesis of the alkaloid fagaronine chloride (**59**) (Scheme 1.15).[21] Aryne cyclization of aryl bromide **57** produced tetracycle **58**, which was converted to fagaronine chloride (**59**) over three steps.

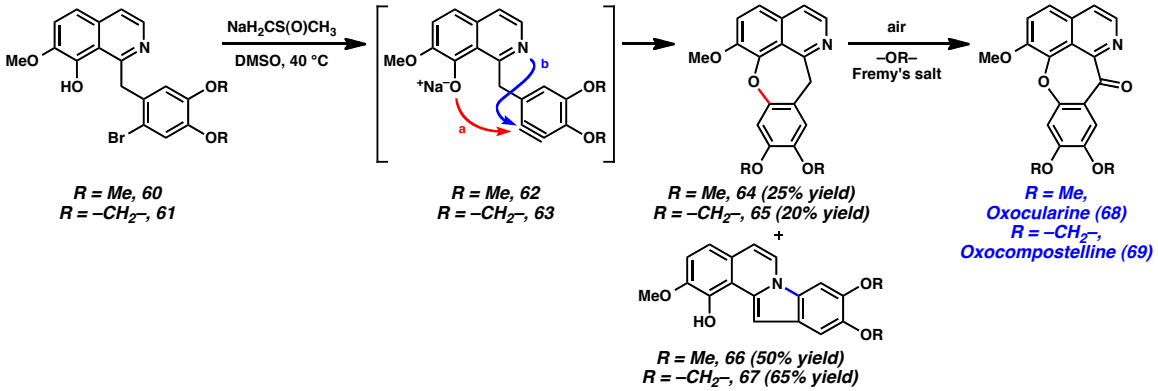
*Scheme 1.15. Stermitz's 1974 synthesis of fagaronine chloride (**59**).*



Whereas the previously described synthetic efforts all focused on the formation of new carbon–carbon and carbon–nitrogen bonds, Castedo's synthesis of oxocularine (**68**) and oxocompostelline (**69**) sought to forge carbon–oxygen bonds between an intermediate aryne and a pendant phenolate.[22] In the key aryne cyclization, treatment of isoquinoline **60** or **61** with sodium dimsylate led to the isolation of two new products

each (**64** and **66**, or **65** and **67**, respectively) resulting from competing addition of nitrogen or oxygen to the aryne (path a or b) (Scheme 1.16). Though isolated as the minor products of aryne cyclization, cyclic ethers **65** and **64** were readily oxidized either in air or through the use of Fremy's salt to afford oxocularine (**68**) and oxocompostelline (**69**).

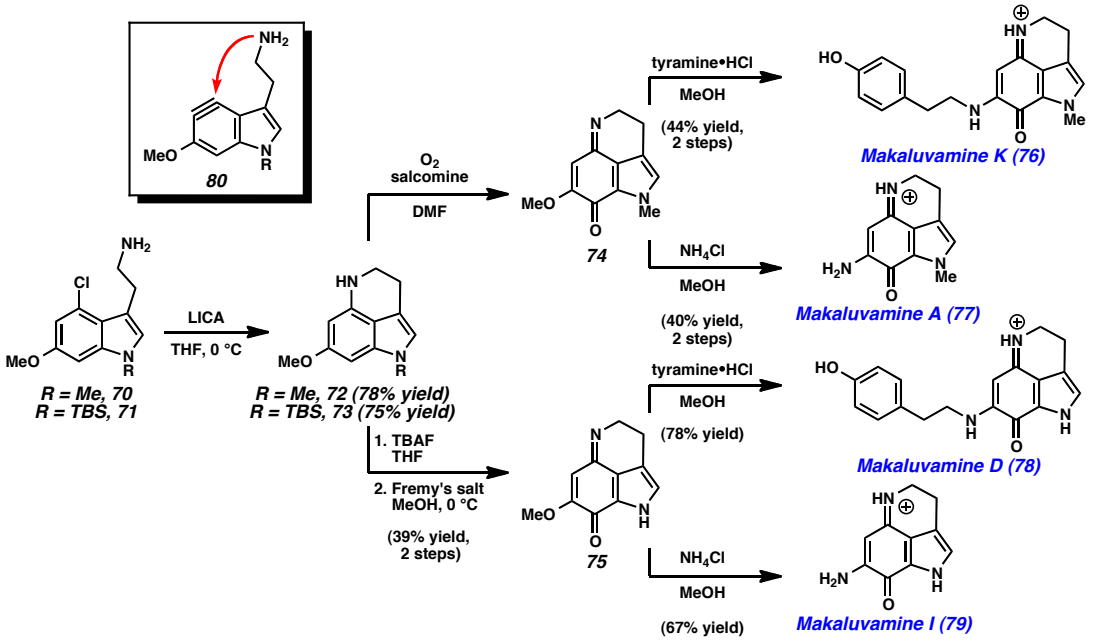
*Scheme 1.16. Castedo's 1983 synthesis of oxocularine (**68**) and oxocompostelline (**69**).*



To this point, all natural product syntheses employing a nucleophilic addition strategy relied on simple monocyclic arynes as the electrophilic reaction parter. In 1998, Iwao and co-workers turned to a 4,5-indolyne intermediate in their synthesis of makaluvamines A (**77**), D (**78**), I (**79**), and K (**76**) (Scheme 1.17).[23] Beginning with tryptamine intermediates **70** and **71**, and differing only in the indole nitrogen functionality, treatment with lithum isopropylcyclohexylamide (LICA) resulted in cyclization of the pendant amine onto the transient 4,5-indolyne (**80**), affording tricycles **72** and **73**, respectively, in very good yields. From here two paths diverge: for R = Me, oxidation of tricycle **72** with oxygen and salcomine yielded the iminoquinone (**74**).

Alternatively, for R = TBS (**73**), desilylation of the indole nitrogen was followed by oxidation to iminoquinone **75**. Makaluvamines A (**77**) and I (**79**) were completed by treatment of iminoquinones **74** and **75**, respectively, with ammonium chloride in methanol. Alternatively, iminoquinones **74** and **75** were converted to makaluvamines K (**76**) and D (**78**), respectively, upon addition of with tyramine hydrochloride.

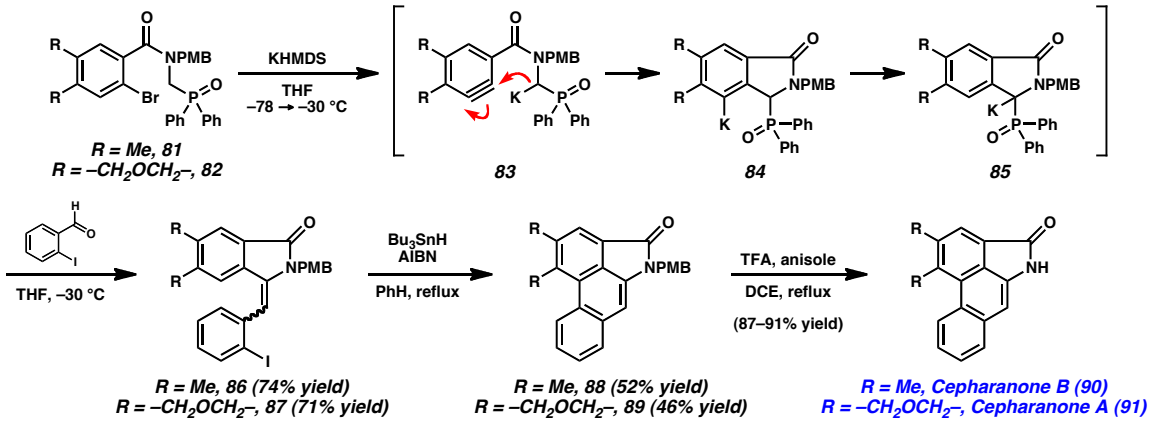
*Scheme 1.17. Iwao's 1998 synthesis of makaluvamines A (**77**), D (**78**), I (**79**), and K (**76**).*



Beginning in the late 1990s, Couture and co-workers embarked on a research program aimed at the synthesis of the aristolactam alkaloids by a general route involving a tandem aryne cyclization/olefination and radical cyclization. Their initial report focused on the synthesis of cepharanone A (**91**) and B (**90**)[24] and was soon followed by the synthesis of three more members of this alkaloid class, velutinam (**103**), taliscanine (**101**), and enterocarpam II (**102**).[25] In the synthesis of cepharanone A (**91**) and B (**90**),

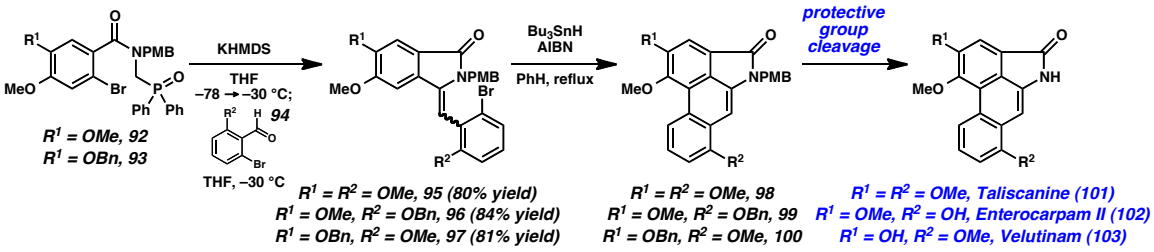
amides **81** and **82** were treated with excess KHMDS to effect simultaneous aryne generation and formation of phosphonate anion **83** (Scheme 1.18).[24] Following the initial cyclization of the pendant carbanion onto the aryne, isomerization of the resulting aryl anion (**84**) to the α-amino carbanion (**85**) preceded addition of *o*-iodobenzaldehyde and subsequent olefinination. The products of this tandem sequence, isoindolinones **86** and **87** (as a mixture of *E* and *Z* isomers), underwent smooth radical cyclization upon treatment with Bu_3SnH and AIBN to yield tetracycles **88** and **89**, respectively. Finally, cleavage of the *N*-protective groups furnished cepharanone A (**91**) and B (**90**).

*Scheme 1.18. Couture's 1997 synthesis of cepharanone A (**91**) and B (**90**).*



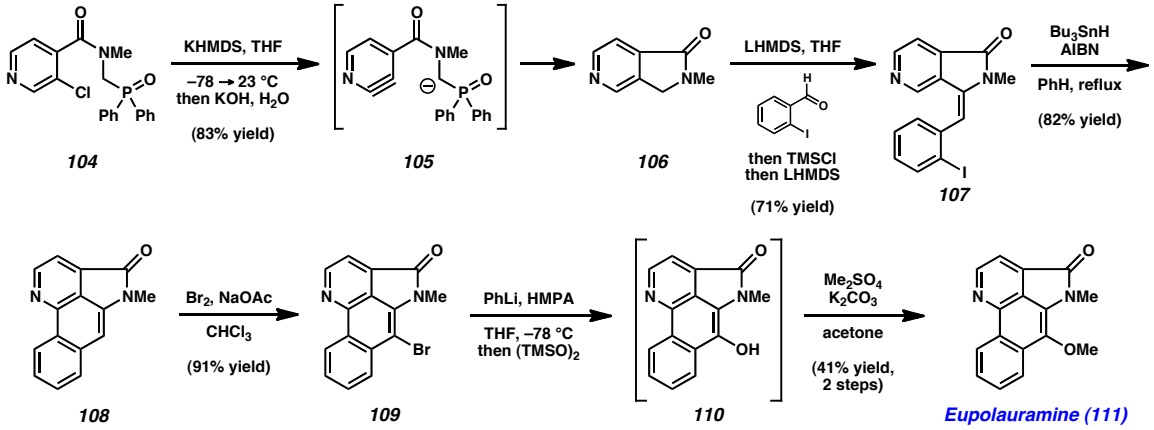
This strategy was subsequently applied by the same group to the syntheses of additional aristolactam natural products **101**–**103**.[25] Amides **92** and **93** were converted to the respective isoindolinones (**95**–**97**) by the tandem aryne cyclization/olefination and radical cyclization sequence (Scheme 1.19). Finally, cleavage of the protective groups yielded velutinam (**103**), taliscanine (**101**), and enterocarpam II (**102**).

*Scheme 1.19. Couture's 1998 synthesis of velutinam (**103**), taliscanine (**101**), and enterocarpam II (**102**).*



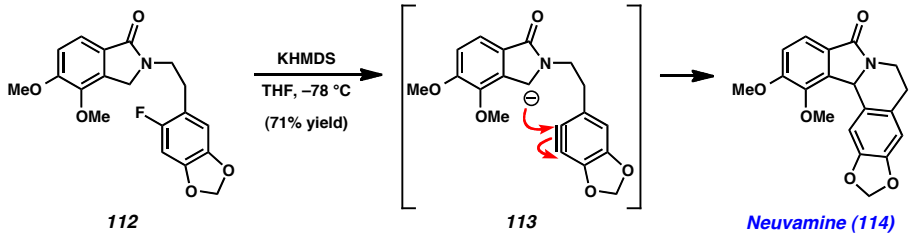
A final natural product synthesis reported by Couture utilizing the aryne cyclization/olefination/radical cyclization sequence was that of eupolauramine (**111**) (Scheme 1.20).[26] This work is distinguished by the intermediacy of a 2,3-pyridyne (**105**) in place of the standard aryne employed above; the synthesis of eupolauramine (**111**) is one of only three syntheses to date to feature a pyridyne intermediate. Pyridyne cyclization of amide **104** produced azaisoindolinone **106** in good yield upon cleavage of the phosphoryl group. By performing the olefination in a stepwise fashion on azaisoindolinone **106**, excellent selectivity for the desired *E* isomer was achieved. Radical cyclization of iodide **107** yielded tetracycle **108**, which was advanced to eupolauramine (**111**) over three steps.

*Scheme 1.20. Couture's 2001 synthesis of eupolauramine (**111**).*



In a departure from the examples shown in Schemes 1.18–1.20, Couture targeted the isooxindoloisoquinoline natural product neuvamine (**114**) by a simpler aryne nucleophilic addition.[27] Elimination of fluoroarene **112** with KHMDS and simultaneous deprotonation of the pendant isooxindole resulted in formation of the pentacyclic natural product neuvamine (**114**) (Scheme 1.21).

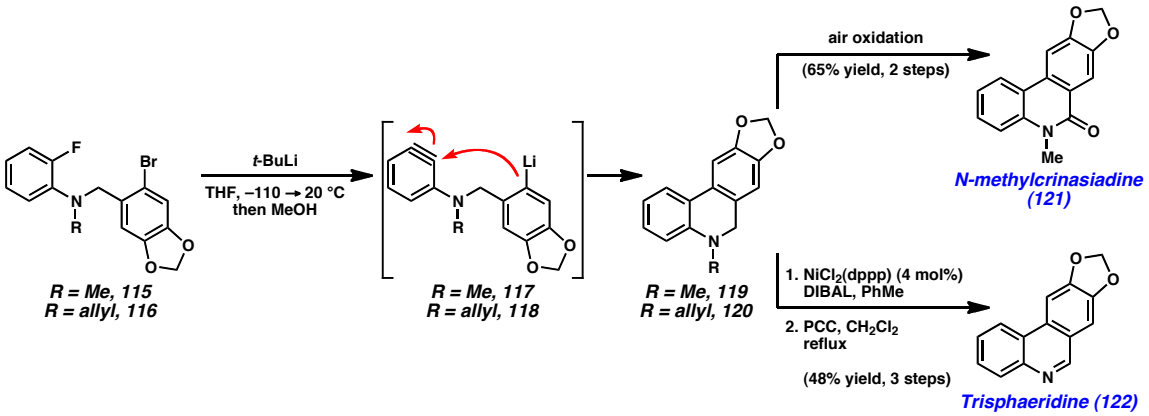
*Scheme 1.21. Couture's 2004 synthesis of neuvamine (**114**).*



A unique approach to a pair of *Amaryllidaceae* alkaloids, trisphaeridine (**122**) and *N*-methylcrinasiadine (**121**), was reported in 2007 by Sanz and co-workers.[28] Their strategy relies upon the generation of an aryne through dehydrofluorination with

concomitant lithium-halogen exchange of a pendant aryl bromide (Scheme 1.22). In the event, treatment of either *N*-methyl aniline **115** or *N*-allyl aniline **116** with *t*-BuLi generated the intermediate aryne tethered to the aryl lithium species (**117** and **118**), which underwent cyclization to yield tetracycles **119** and **120**, respectively. Notably, with strict temperature control, aryne formation occurs selectively on the fluoroarene, while lithium-halogen exchange is exclusive to the aryl bromide. Furthermore, Sanz and Barluenga have shown that this approach can be generalized to give access to a wide range of polycyclic aromatic structures.[29] *N*-allyl tetracycle **120** was advanced to trisphaeridine (**122**) by deallylation and oxidation, while the *N*-methyl variant (**119**) was converted to *N*-methylcrinasiadine (**121**) by air oxidation.

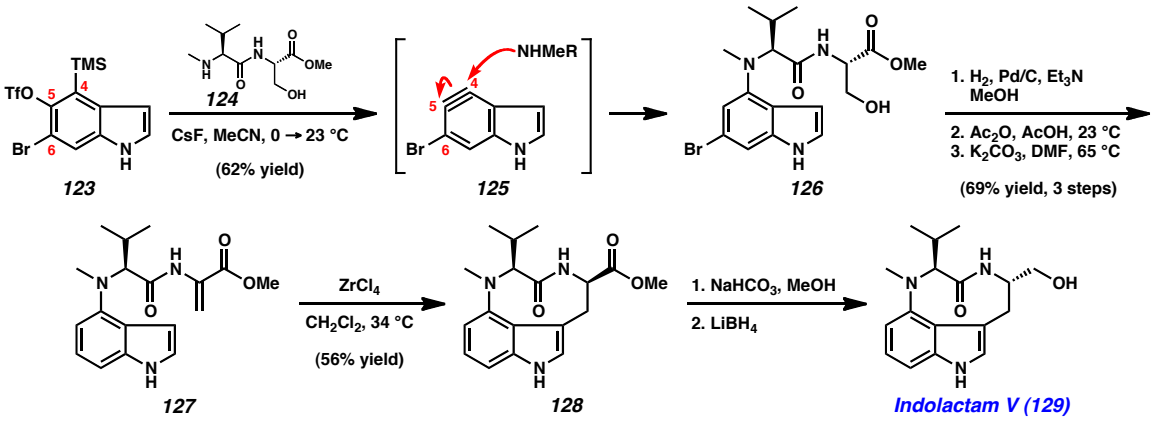
*Scheme 1.22. Sanz's 2007 synthesis of trisphaeridine (**122**) and N-methylcrinasiadine (**121**).*



In addition to Iwao's synthesis of the makaluvamines (vide supra), Garg and co-workers recently employed a 4,5-indolyne intermediate en route to the macrocyclic lactam natural product, indolactam V (**129**) (Scheme 1.23).[30,31] In this case, the intermolecular nucleophilic addition of peptide **124** to 6-bromo-4,5-indolyne (**125**),

generated in situ from silyl aryl triflate **123**, proceeds regioselectively to provide the 4-amino-6-bromo indole product (**126**) exclusively. Remarkably, the presence of the 6-bromo substituent reverses the native selectivity (i.e., addition to the 5-position) for nucleophilic additions to 4,5-indolyne.[31a,b] At this point, reduction of the bromide and elimination of the primary alcohol produced enamide **127**, which underwent conjugate addition with diastereoselective protonation upon treatment with $ZrCl_4$ to generate macrocycle **128**. Finally, epimerization of the newly formed C(9) stereocenter and reduction of the ester afforded indolactam V (**129**).

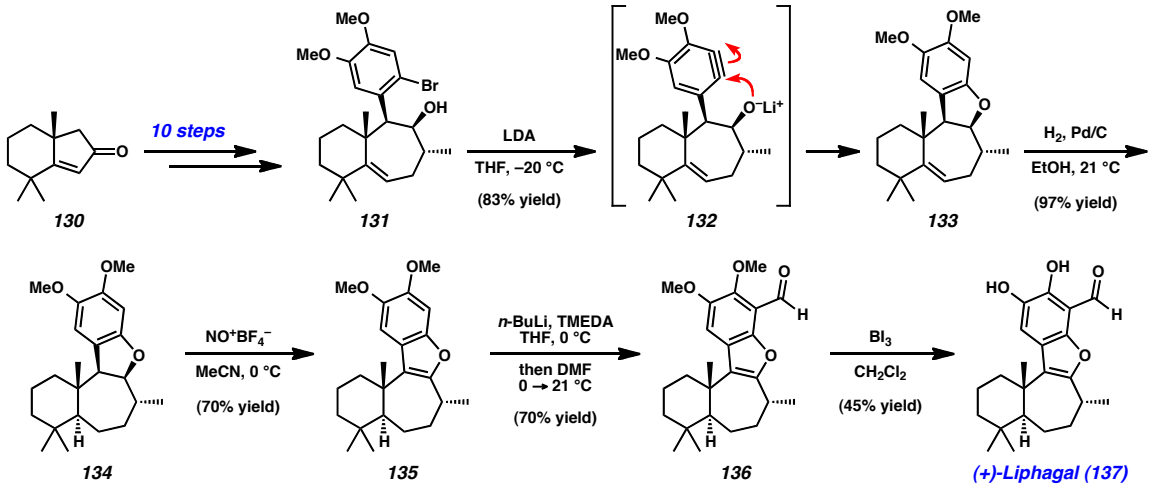
*Scheme 1.23. Garg's 2011 synthesis of indolactam V (**129**).*



The most recent example of nucleophilic addition to arynes in total synthesis was reported by Stoltz and co-workers in their synthesis of the tetracyclic meroterpenoid (+)-liphagal (**137**) (Scheme 1.24).[32] More specifically, an aryne cyclization was used to close the final ring of the natural product. Toward this end, secondary alcohol **131**, which was constructed over ten steps from enantioenriched enone **130**, was successfully converted to dihydrobenzofuran **133** through the intermediacy of aryne **132**. Notably, a number of

alternative methods to form this key carbon–oxygen bond, including palladium-catalyzed etherifications, failed to yield the desired product. Furthermore, reduction of the trisubstituted olefin of dihydrobenzofuran **133** to generate the trans-fused [6,7] ring system of tetracycle **134** could only be accomplished following the aryne cyclization. From this point, the synthesis of (+)-liphagal (**137**) was completed by oxidation of the dihydrobenzofuran (**134**), formylation, and demethylation.

*Scheme 1.24. Stoltz's 2011 synthesis of (+)-liphagal (**137**).*

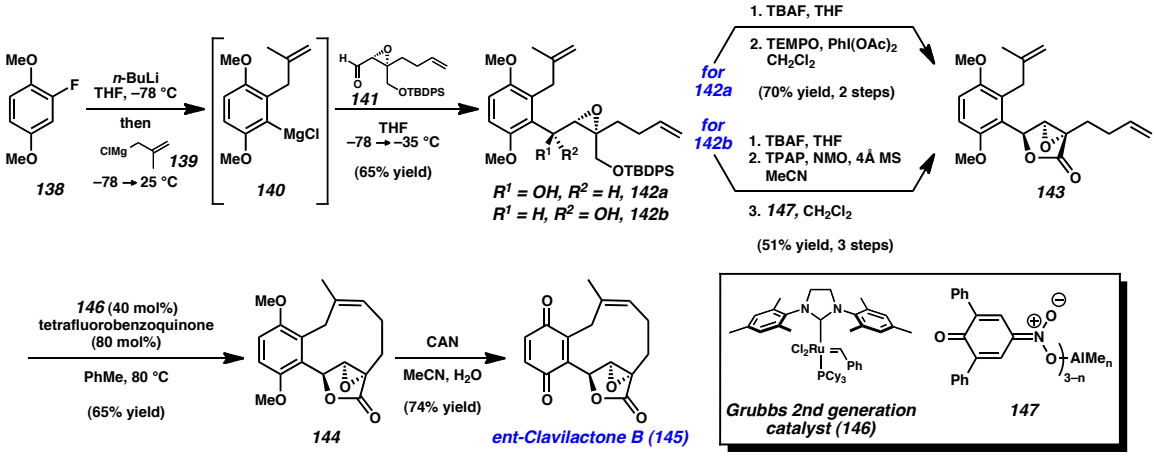


1.2.2 Multicomponent Reactions of Arynes

In general, arynes are well suited to function as a relay species for multicomponent reactions. For over 70 years,[33] research groups have sought to develop three- and four-component methods for the rapid preparation of 1,2-disubstituted arenes.[34,5b] Despite the efficiency of such methodologies, only three approaches to natural products in the literature to date have employed multicomponent aryne strategies.

The first was Barrett's synthesis of *ent*-clavilactone B (**145**) by a three-component coupling involving an aryne, an organomagnesium reagent, and an aldehyde (Scheme 1.25).[35] More specifically, treatment of fluoroarene **138** with *n*-BuLi resulted in the formation of an aryne to which methallylmagnesium chloride **139** was added. Next, the newly formed intermediate arylmagnesium species (**140**) underwent addition to the third component, aldehyde **141**, yielding benzylic alcohol **142** as a 2:1 mixture of diastereomers. The separable diastereomers **142a** and **142b** were individually converted to lactone **143** over two and three steps, respectively. Finally, ring-closing metathesis using a Grubbs second generation catalyst (**146**) and oxidation afforded *ent*-clavilactone B (**145**).

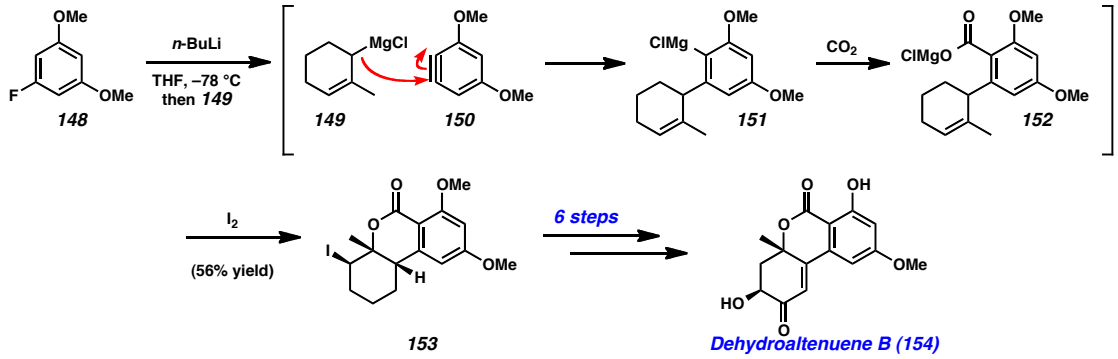
*Scheme 1.25. Barrett's 2006 synthesis of ent-clavilactone B (**145**).*



More recently, in their synthesis of dehydroaltenuene B (**154**), Barrett and co-workers made excellent use of a four-component aryne coupling reaction to build the tricyclic core of the natural product (Scheme 1.26).[36] Beginning with elimination of

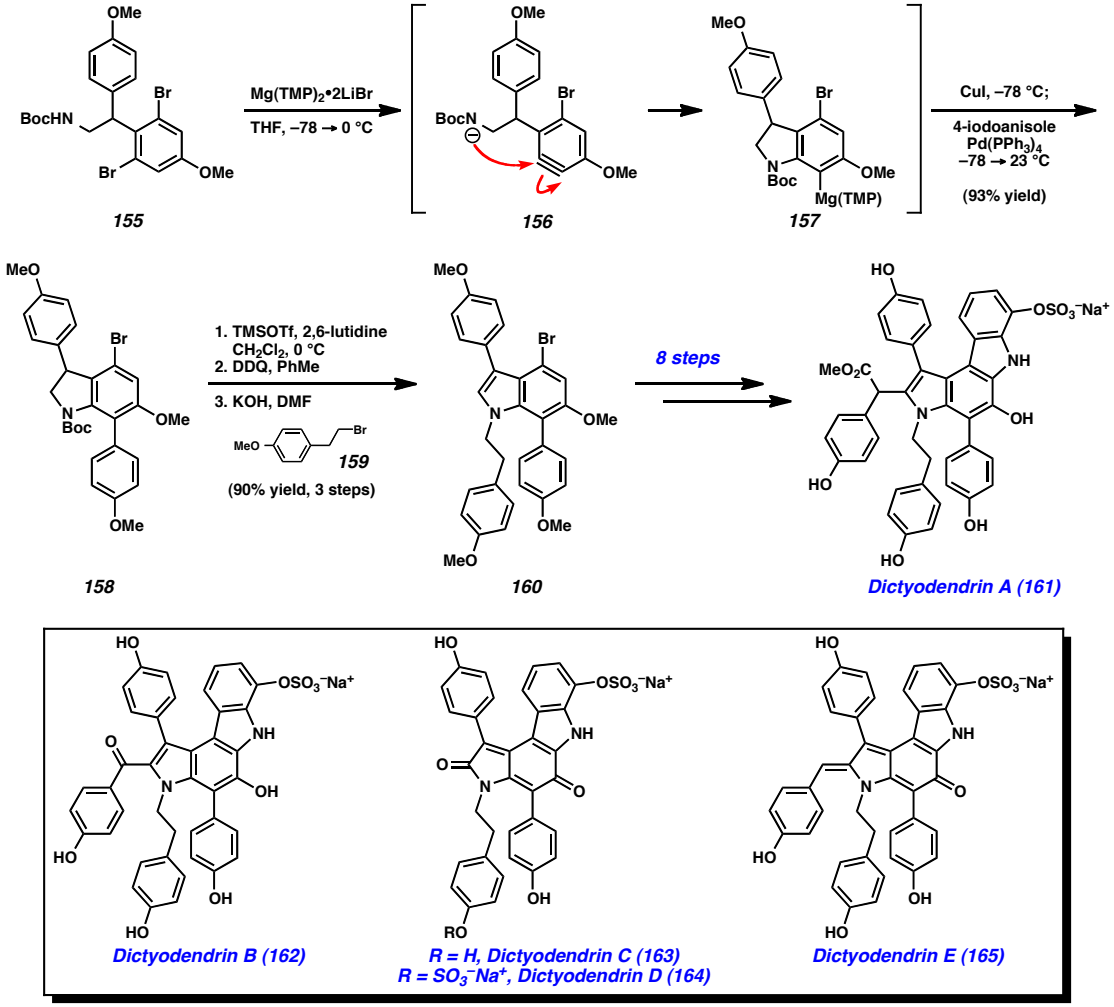
fluoroarene **148** to generate aryne **150**, sequential addition of cyclohexenylmagnesium chloride **149**, carbon dioxide, and iodine generated iodolactone **153**. The authors propose that the reaction proceeds through addition of organomagnesium reagent **149** to aryne **150**, followed by carboxylation of the resulting arylmagnesium species (**151**), and finally diastereoselective iodolactonization. The multicomponent adduct (**153**) was then converted to dehydroaltenuene B (**154**) over a series of six additional steps.

*Scheme 1.26. Barrett's 2008 synthesis of dehydroaltenuene B (**154**).*



The most recent use of an aryne multicomponent coupling strategy was reported by Tokuyama and co-workers in their synthesis of dictyodendrins A–E (**161**–**165**).[37] In this case, an initial intramolecular nucleophilic addition of a nitrogen anion into a pendant aryne (**155** → **156**) was linked to a palladium-catalyzed Kumada–Tamao coupling to append *p*-iodoanisole. The product of this three-component coupling (**158**) was then advanced over a three-step sequence to indole **160**, which was subsequently converted to dictyodendrin A (**161**) over eight steps. This same strategy was also applied to the synthesis of dictyodendrins B (**162**), C (**163**), D (**164**), and E (**165**).

*Scheme 1.27. Tokuyama's 2010 synthesis of dictyodendrins A–E (**161–165**).*



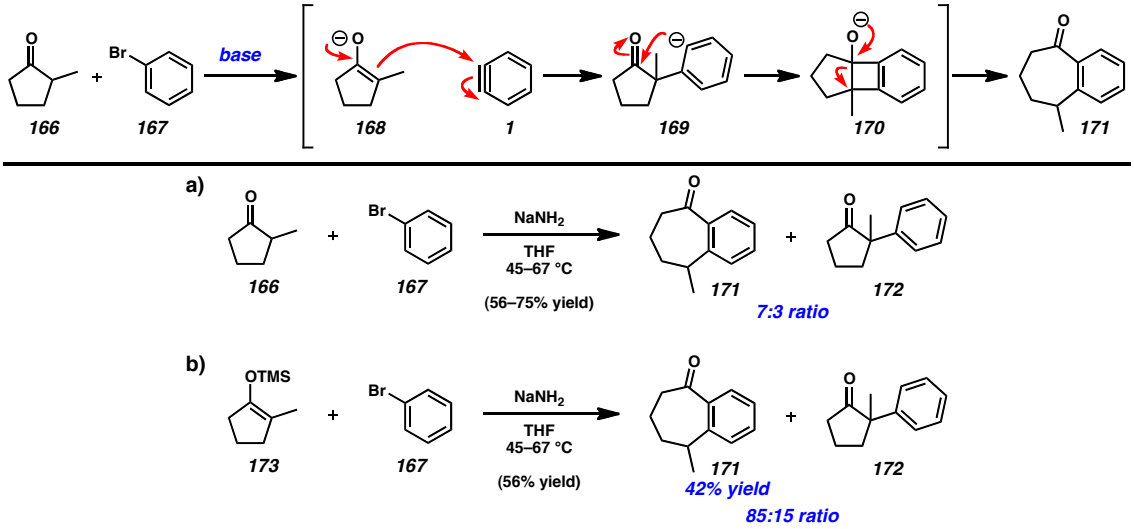
1.3 BOND INSERTION REACTION STRATEGIES

Carbon–carbon bond insertion reactions are some of the most recent methodologies to emerge from the aryne literature. Remarkably, their use was first reported in the context of total synthesis, while generalized methods were not disclosed until 2005.[5a,38,39] Since these initial reports, a number of additional carbon–carbon bond insertion methods have been disclosed.[40,34d] All of these general methods have been

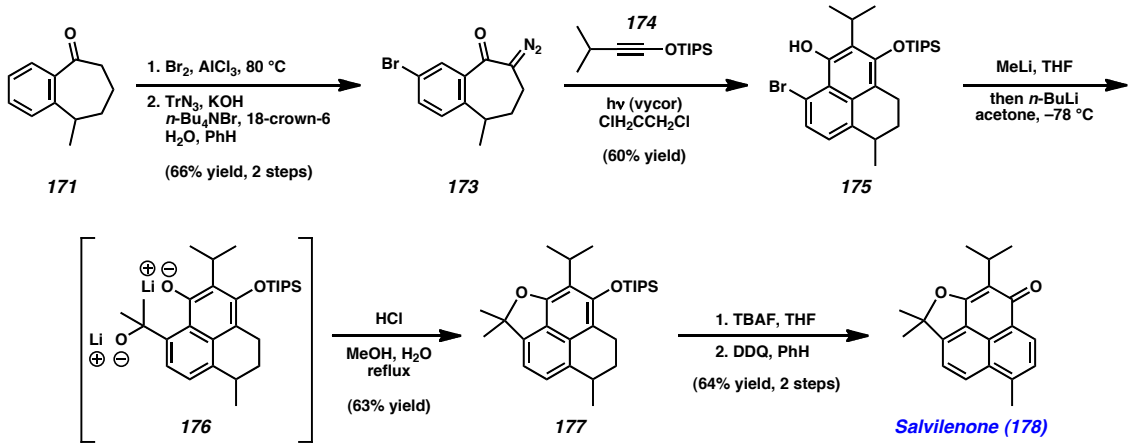
enabled by the development of silyl aryl triflate precursors,[3] which allow mild generation of arynes in the presence of a wide range of functional groups.

The earliest example of a total synthesis employing a σ-bond insertion reaction of an aryne in the synthesis of a natural product was completed by Danheiser and co-workers. Their total synthesis of salvilenone (**178**) employed a ring-expansive carbon–carbon bond insertion reaction between an aryne and a ketone enolate (Scheme 1.28).[41] More specifically, ring expansion of 2-methylcyclopentanone (**166**) with benzyne (**1**), generated in situ from bromobenzene (**167**) under basic conditions, produced benzannulated cycloheptanone **171** in addition to α-arylation product **172** in a 7:3 ratio (Scheme 1.28a). Importantly, this ratio could be improved to 85:15 by employing the silyl enol ether 2-methylcyclopentanone (**166**), ultimately providing benzannulated cycloheptanone **171** in 42% isolated yield (Scheme 1.28b). Regioselective bromination of the arene ring followed by α-diazotization provided α-diazoketone **173** (Scheme 1.29). In the key transformation, irradiation of α-diazoketone **173** in the presence of alkyne **174** resulted in a cascade reaction consisting of Wolff rearrangement, [2 + 2] ketene cycloaddition, 4π electrocyclic ring opening, and 6π electrocyclic ring closing to furnish tricycle **175**. From this point, completion of salvilenone (**178**) was readily accomplished by annulation of the final ring, desilylation, and oxidation. In full, salvilenone (**178**) was prepared in 7 steps and 9% overall yield from 2-methylcyclopentanone (**166**) and bromobenzene (**167**).

*Scheme 1.28. Danheiser's ring–expansive carbon–carbon bond insertion of benzyne (**1**) into 2-methylcyclopentanone (**166**).*



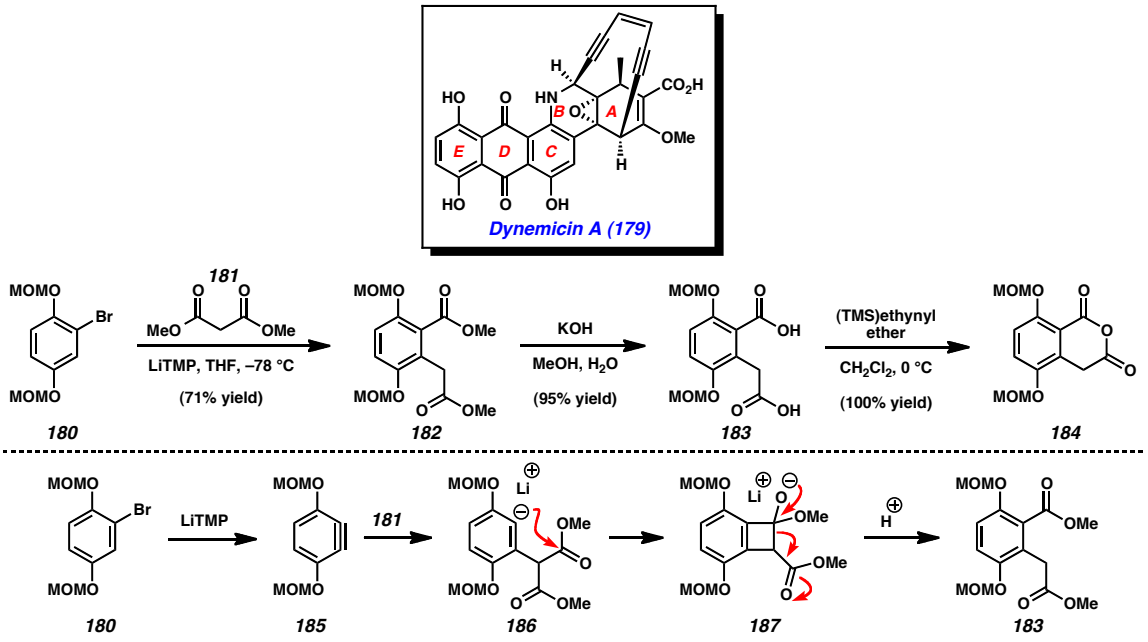
*Scheme 1.29. Danheiser's 1994 synthesis of salvilenone (**178**).*



Soon after Danheiser's ring-expansive C–C bond insertion studies, the Danishefsky group employed a σ-bond insertion of dimethyl malonate (**181**) with a functionalized aryne en route to the enediyne antibiotic dynemicin A (**179**).[42] Much like the enediynes calicheamicin[43] and esperamicin[44], dynemicin A (**179**) has demonstrated

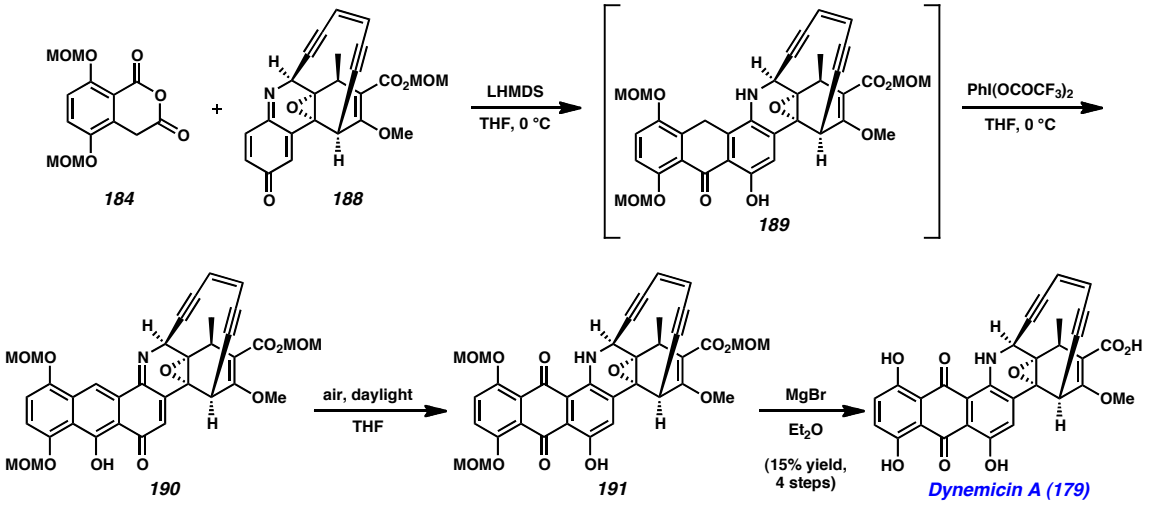
potent antitumor activity (Scheme 1.30).[45] Danishefsky and co-workers focused their approach to the natural product on a late-stage convergent assembly of the hexacyclic ring system, one half of which contained the sensitive enediyne functionality. The second fragment was readily accessed in three steps beginning with the carboxy-alkylation of the aryne derived from bromoarene **180** with the lithium salt of dimethyl malonate (**181**) to yield diester **182**. Although the reaction of a malonate with an aryne had been reported prior to this synthesis, the yields were significantly lower and the desired carboxy-alkylation products were accompanied by extensive side product formation.[46] Saponification of the diester was followed by treatment with (trimethylsilyl)ethynyl ether to furnish cyclic anhydride **184**, which comprises the D and E rings of the natural product.

*Scheme 1.30. Dynemicin A (**179**) and the synthesis of cyclic anhydride **184** by carboxy-alkylation of arynes (1995).*



With a suitable DE-ring fragment in hand, cyclic anhydride **184** was joined to enediyne-containing ABC-ring fragment **188** (Scheme 1.31). Deprotonation of cyclic anhydride **184** and addition to quinone imine **188** resulted in a formal [4 + 2] cycloaddition and loss of CO_2 to yield a putative anthrone (**189**), which was immediately oxidized to the anthracendiol (**190**). Further oxidation to the corresponding anthraquinone (**191**) followed by global deprotection yielded dynemicin A (**179**) in 15% yield over the final four steps.

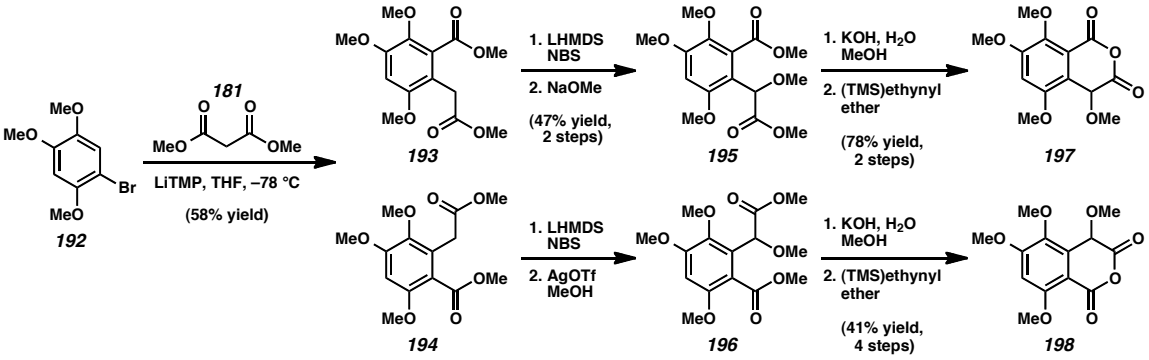
*Scheme 1.31. Completion of Danishefsky's synthesis of dynemicin A (**179**) (1995).*



As in the Danishefsky synthesis of dynemicin A, Kita and co-workers employed a carboxy-alkylation with dimethyl malonate (**181**) en route to fredericamycin A (**208**).[47] However, in this case, an unsymmetrical aryne derived from trimethoxy bromoarene **192** was employed (Scheme 1.32). As a result, the carboxy-alkylation proceeded with little regioselectively to give a mixture of two separable isomeric products (**193** and **194**) in a 2:3 ratio. Following separation, diesters **193** and **194** were each converted to their

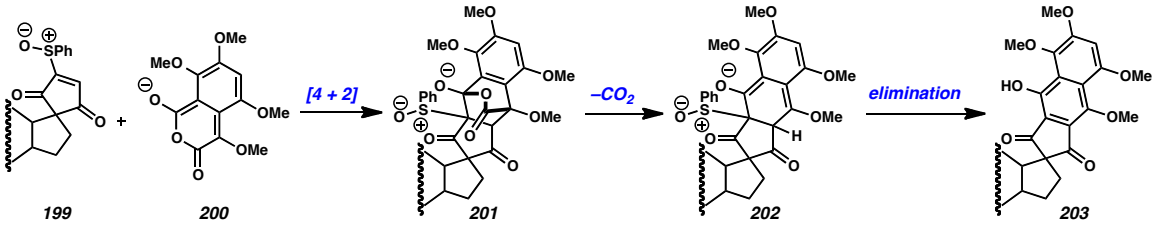
respective α-methoxy cyclic anhydrides, **197** and **198**, which represent the A and B rings of the natural product.

*Scheme 1.32. Synthesis of cyclic anhydrides **197** and **198** by a carboxy-alkylation route (1999).*

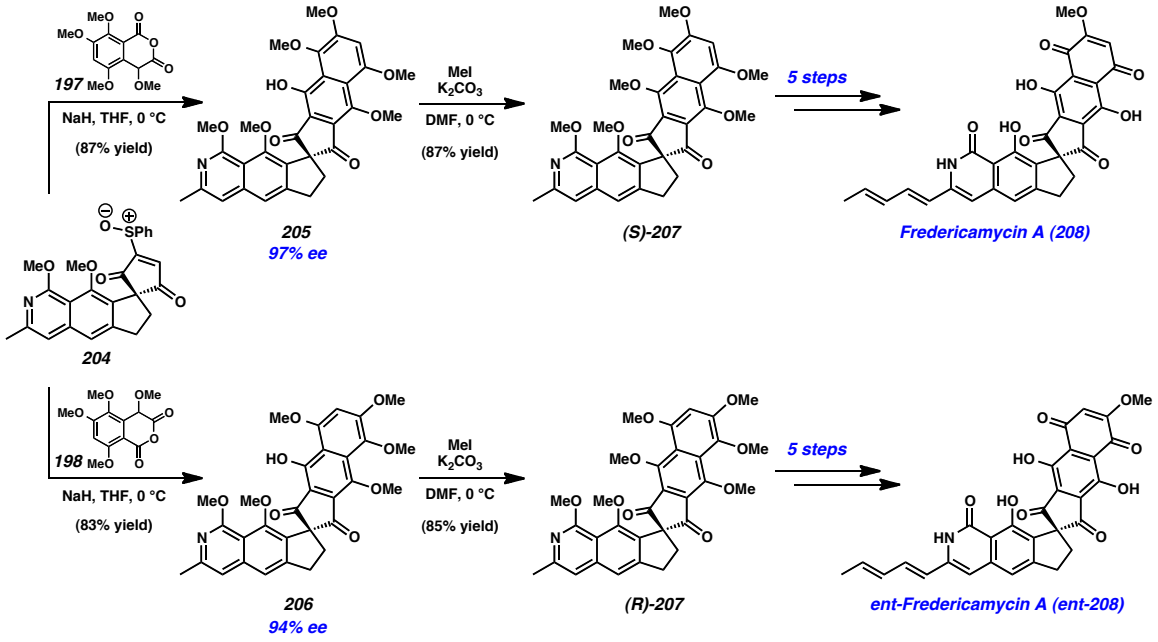


At the time of this work, the absolute configuration of fredericamycin A (**208**) was unknown. Strategically, the authors devised a way to convert each isomeric cyclic anhydride (**197** and **198**) into each enantiomer of the natural product by coupling them to an enantioenriched CDEF-ring fragment (**204**). Mechanistically, upon treatment of **197** or **198** with base, a reactive pyrone structure was generated (**200**) capable of reacting with dienophile **199** by a formal [4 + 2] cycloaddition (Scheme 1.33). Subsequent CO_2 extrusion and syn elimination then produced the fully aromatized products. In the event, cycloadducts **205** and **206** were isolated in 97% and 94% ee, respectively (Scheme 1.34). Methylation of the free phenols yielded the enantiomeric ethers (**(*R*)-207** and **(*S*)-207**). Finally, over a series of five steps, each of these intermediates (**(*R*)-207** and **(*S*)-207**) was converted to a each enantiomer of the natural product (**208** and ***ent*-208**). Ultimately, Kita and co-workers determined that the compound bearing the *S* absolute configuration at the single stereocenter was the naturally occurring fredericamycin.

Scheme 1.33. Mechanism for coupling of the AB-ring fragment and CDEF-ring fragment.



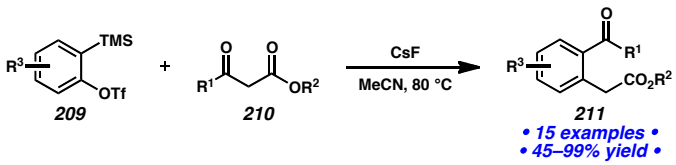
*Scheme 1.34. Kita's 1999 stereodivergent approach to fredericamycin (**208**).*



Despite the previous two examples of aryne acyl-alkylation with malonate-derived nucleophiles, a thorough examination of this specific reactivity was not undertaken until 2005 when Stoltz and co-workers reported the reaction of arynes derived from silyl aryl triflates[3] (e.g., **209**) with β-ketoesters (e.g., **210**) (Scheme 1.35).[38] Of particular interest is the ring-expansive variant of this transformation, employing cyclic β-ketoesters. To date, the Stoltz group has employed this method in the enantioselective syntheses of two natural products: the isopavine alkaloid amurensinine (**216**) and the

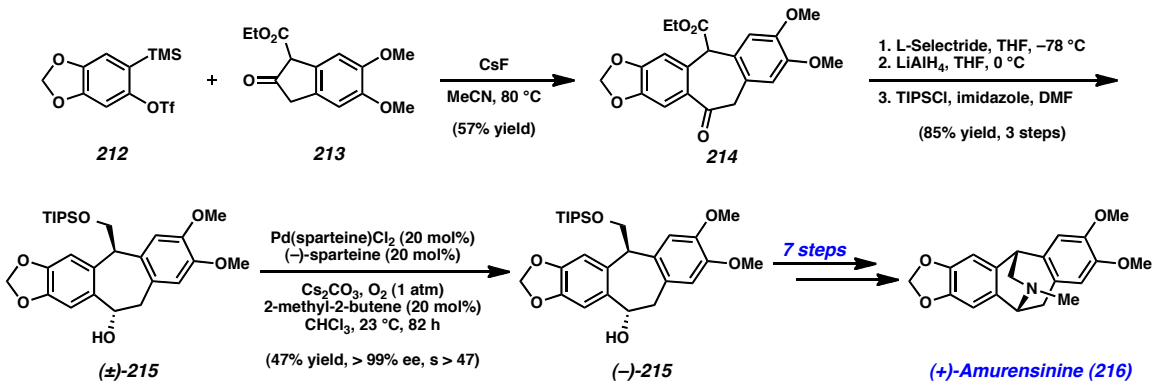
benzannulated macrolatone curvularin (**221**). In each of these examples, the acyl-alkylation reaction is used to construct key C–C bonds between a functionalized aryne and a β-ketoester to convergently assemble the natural products.

Scheme 1.35. Stoltz's acyl-alkylation of arynes with β-ketoesters.



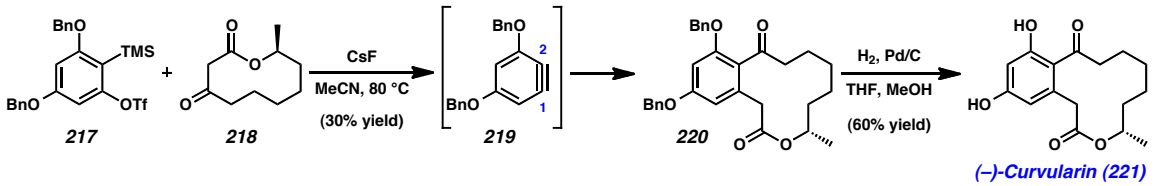
In the enantioselective total synthesis of (+)-amurensinine (**216**), the tetracyclic core of the alkaloid (**214**) was targeted by an acyl-alkylation of a sesamol-derived aryne (generated in situ from silyl aryl trflate **212**) with benzannulated β-ketoester **213** (Scheme 1.36).[48] In this case, the aryne formation and the subsequent acyl-alkylation are triggered by a mild fluoride source, instead of the strong bases used in prior examples. The resulting tetracycle (**214**) contained all but one of carbons present in the natural product. To render the synthesis enantioselective, Stoltz and co-workers employed a palladium-catalyzed oxidative kinetic resolution of activated alcohols.[49] Following diastereoselective reduction and selective protection of the primary alcohol, oxidative kinetic resolution of secondary benzylic alcohol **(±)-215** provided enantioenriched alcohol **(–)-215** in 47% yield and >99% ee, corresponding to a selectivity factor of >47. From this point, the final ring of amurensinine was installed, completing the natural product in seven additional steps. Overall, the enantioselective synthesis of (+)-amurensinine was completed in 12 steps from silyl aryl triflate **212** and β-ketoester **213**.

*Scheme 1.36. Stoltz's 2006 synthesis of (+)-amurensinine (**216**).*



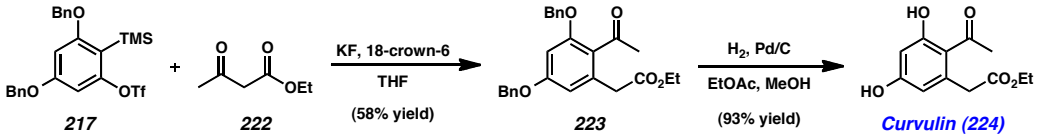
In a second application of a ring-expansive aryne acyl-alkylation, the Stoltz lab reported the enantioselective synthesis of (–)-curvularin (**221**), a benzannulated macrolactone natural product.[50] The 12-membered lactone of the natural product was targeted by the reaction of an unsymmetrical aryne (**219**) (generated in situ from silyl aryl triflate **217**) with 10-membered β-ketolactone **218** (Scheme 1.37). Prior to this work, β-ketolactones had not been employed as substrates in the acyl-alkylation reaction. Application of the acyl-alkylation transformation in this way results in regioselective formation of the benzannulated lactone, without any formation of the undesired isomeric product derived from initial nucleophilic addition to C(2). Finally, debenzylation revealed the resorcinol core, completing (–)-curvularin (**221**) in six steps from known compounds.

*Scheme 1.37. Stoltz's 2010 enantioselective synthesis of (–)-curvularin (**221**).*

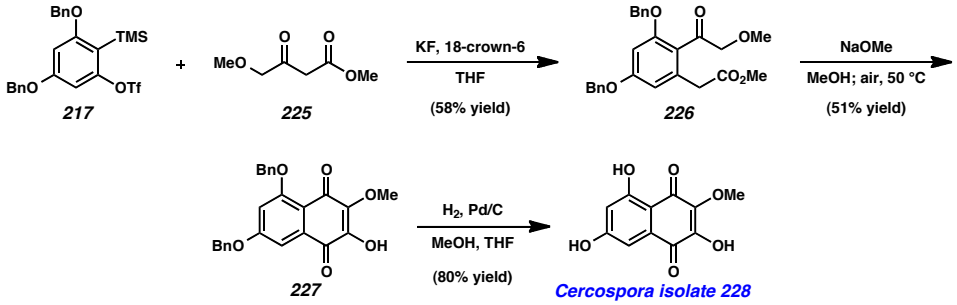


Concurrent with their report on (–)-curvularin, Stoltz and co-workers reported two additional syntheses of natural products utilizing the same protected resorcinylic silyl aryl triflate (**217**).[51] Acyl-alkylation of silyl aryl triflate **217** with ethyl acetoacetate (**222**) under modified conditions followed by debenzylation produced curvulin (**224**), an acyclic relative of curvularin often isolated from the same natural sources (Scheme 1.38). Alternatively, acyl-alkylation of precursor **217** with γ-methoxy-β-ketoester **225**, followed by base-mediated cyclization and aerobic oxidation yielded hydroxynaphthoquinone **227** (Scheme 1.39) Debenzylation of this intermediate (**227**) provided *Cercospora* isolate **228**.

*Scheme 1.38. Stoltz's 2010 synthesis of curvulin (**224**).*

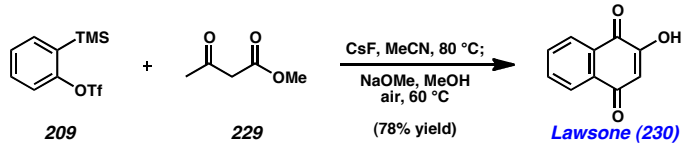


*Scheme 1.39. Stoltz's 2010 synthesis of Cercospora isolate **228**.*



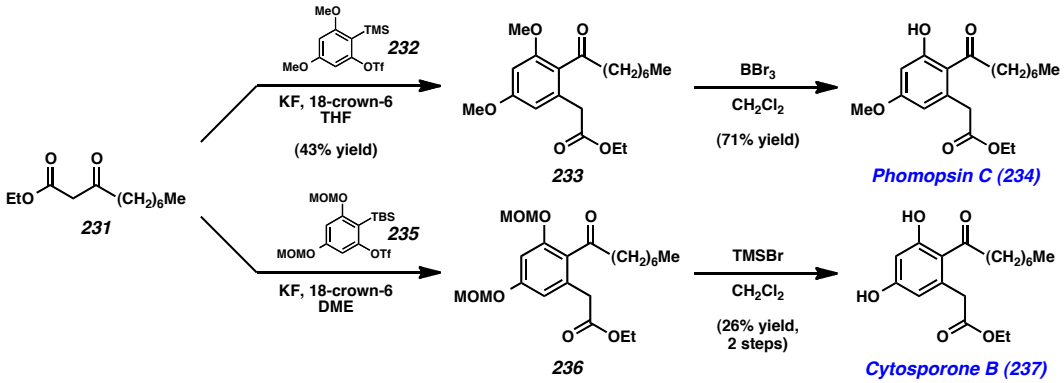
The acyl-alkylation/condensation/air oxidation method for the formation of hydroxynaphthoquinones was further developed into a one-pot procedure by Stoltz and co-workers.[52] This streamlined method was demonstrated by the one step synthesis of lawsone (**230**) from unsubstituted silyl aryl triflate **209** and methyl acetoacetate (**229**) by treatment of the acyl-alkylation product with sodium methoxide in situ (Scheme 1.40).

*Scheme 1.40. Stoltz's 2009 synthesis of lawsone (**230**).*



Shortly after publication of Stoltz's syntheses of (–)-curvularin and related natural products, Yoshida and co-workers employed a similar strategy toward cytosporone B (**237**) and phomopsin C (**234**) (Scheme 1.41).[53] Acyl-alkylation of ethyl 3-oxodecanoate (**231**) with unsymetrical dimethoxy aryne precursor **232** regioselectively yielded arene **233** as a single isomer in modest yield. Subsequent selective mono-demethylation then afforded phomopsin C (**234**). Alternatively, acyl-alkylation of silyl aryl triflate **235** with ethyl 3-oxodecanoate (**231**) provided arene **236**, which was converted into cytosporone B (**237**) upon cleavage of the methoxymethyl ether groups.

*Scheme 1.41. Yoshida's 2010 syntheses of phomopsin C (**234**) and cytosporone B (**237**).*



1.4 [4 + 2] AND [2 + 2] ARYNE CYCLOADDITION STRATEGIES

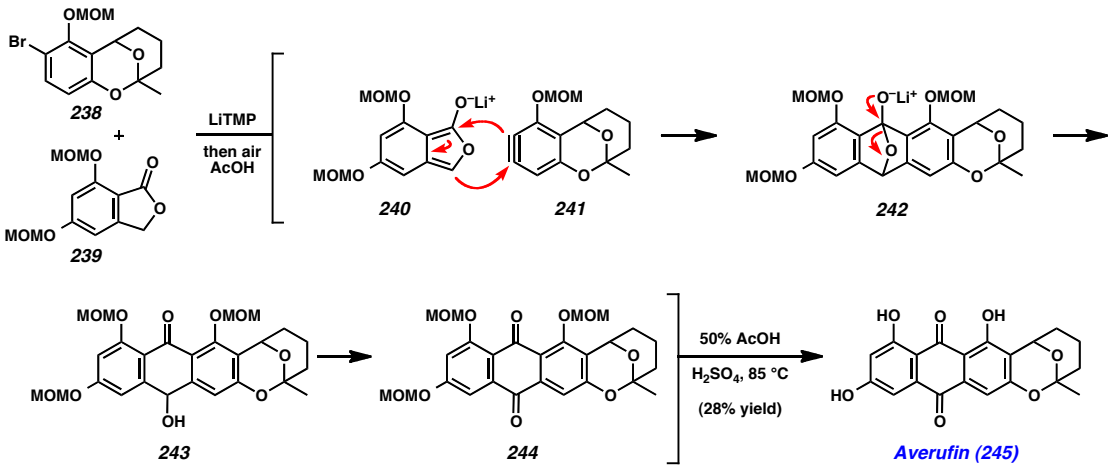
1.4.1 [4 + 2] Aryne Cycloaddition Strategies

The prevalence of [4 + 2] aryne cycloadditions as a strategy for natural product total synthesis is second in the literature only to the use of nucleophilic additions. However, despite the large volume of such approaches, there remain significant limitations to the application of aryne [4 + 2] cycloadditions. Notably, the majority of examples described herein, with a few exceptions, require constrained dienes, most commonly furans. The use of acyclic dienes in natural product synthesis is still a considerable challenge and represents an under-explored area of aryne methodology.

Mechanistically, although some of the [4 + 2] cycloadditions may proceed by a concerted mechanism, it is more likely that the majority of examples discussed herein occur by stepwise processes. Generally speaking, substitution on both the aryne and the diene components can heavily influence the reaction pathway to favor one mechanism over the other.

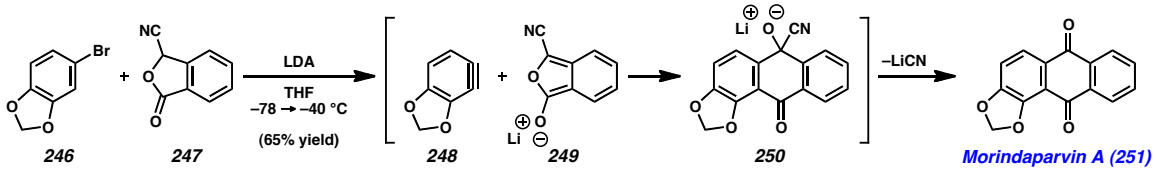
The first example of the application of an aryne [4 + 2] cycloaddition (formal, stepwise, or concerted) in the synthesis of a natural product comes from Townsend and co-workers' preparation of averufin (**245**) in 1981 (Scheme 1.42).[54] Averufin (**245**) was targeted by a formal aryne [4 + 2] cycloaddition reaction that would build the central quinone ring from a benzannulated lactone (**239**) and an aryl bromide (**238**). In the key transformation, treatment of aryl bromide **238** and lactone **239** with LiTMP resulted in enolization of the lactone (**239**) and concomitant formation of aryne **241**. Regioselective addition of enolate **240** to aryne **241** was followed by addition of the resulting aryl anion to the lactone to generate a hemiacetal (**242**). Elimination of the alkoxide from the tetrahedral intermediate furnished pentacycle **243**, which then underwent addition of acetic acid and exposure to air, resulting in oxidation to the quninone (**244**). Finally, removal of the methoxy methyl ether protecting groups yielded averufin (**245**).

*Scheme 1.42. Townsend's 1981 synthesis of averufin (**245**).*



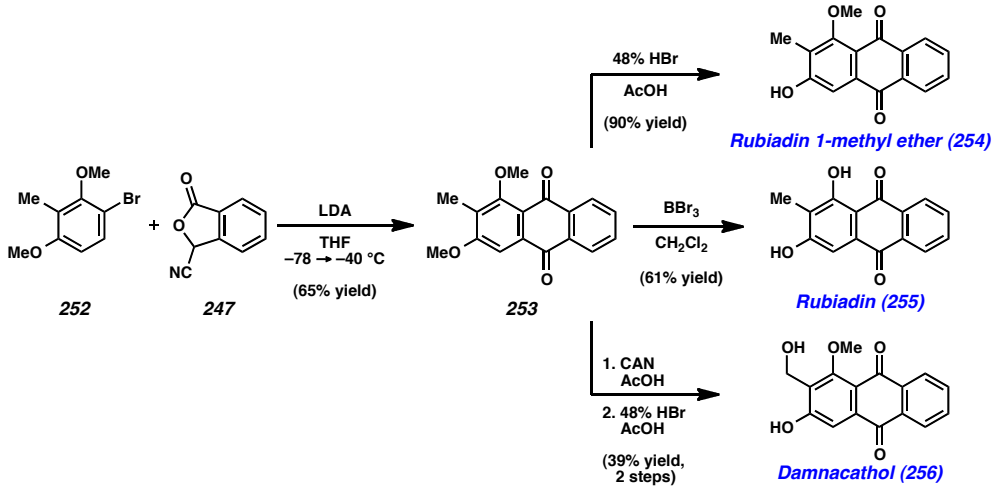
Following Townsend's work on averufin (**245**), Biehl and co-workers employed this same strategy to the synthesis of four different anthraquinone natural products, morindaparvin A (**251**), rubiadin 1-methyl ether (**254**), rubiadin (**255**), and damnacathol (**256**). In the first example, morindaparvin A (**251**) was accessed by reaction of 3-cyanophthalide **247** with aryl bromide **246** in the presence of LDA (Scheme 1.43).[55] Notably, the use of a 3-cyanophthalide (**247**) in place of a lactone removed the need for subsequent air oxidation as in the case of averufin. Instead, cycloaddition and fragmentation generated cyanohydrin **250**, which furnished the anthraquinone directly upon ejection of cyanide.

*Scheme 1.43. Biehl's 1989 synthesis of morindaparvin A (**251**).*



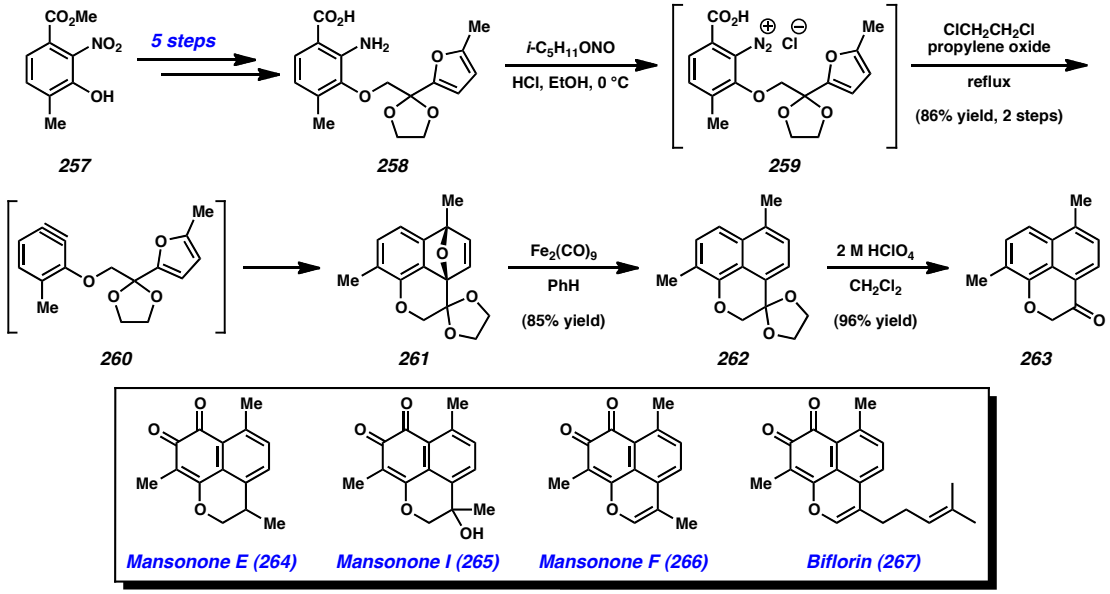
The second of Biehl's reports applied this same method to the synthesis of rubiadin (**266**), rubiadin 1-methyl ether (**254**), and damnacathol (**256**) (Scheme 1.44).[56] Replacing dioxolane **246** with trisubstituted bromoarene **252** led to anthraquinone **253**, the point of divergence from which the three products were targeted. Mono-demethylation with HBr in acetic acid produced rubiadin 1-methyl ether (**254**), while bis-demethylation with excess BBr_3 furnished rubiadin (**255**). Alternatively, benzylic oxidation of anthraquinone **253** followed by mono-demethylation yielded damnacathol (**256**).

*Scheme 1.44. Biehl's 1995 synthesis of rubiadin (**255**), rubiadin 1-methyl ether (**254**), and damnacathol (**256**).*



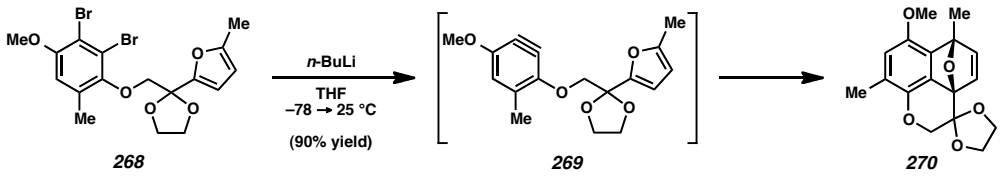
In the same year as Townsend's seminal report of an aryne [4 + 2] cycloaddition employed in total synthesis, Best and Wege published the total synthesis of mansonone E (**264**).[57] Additional syntheses of mansonones I (**265**) and F (**266**) and biflorin (**267**) were reported the following year from a common intermediate.[58] In this work, Best and Wege report the first intramolecular Diels–Alder reaction of an aryne by tethering an anthranilic acid-derived aryne precursor[2d,e] to a furan. Preparation of cycloaddition precursor **258** was accomplished in five steps beginning with phenol **257** (Scheme 1.45). Upon treatment of anthranilic acid **258** with *i*-$C_5H_{11}ONO$ in acidic ethanol, an intermediate diazonium hydrochloride (**259**) was generated that then underwent spontaneous thermal decomposition to the aryne (**260**). Cycloaddition between the aryne and the pendant furan then produced pentacyclic cycloadduct **261** in 86% yield. Subsequent deoxygenation and acetal cleavage yielded tricycle **263**, which was readily converted to mansonones E (**264**), I (**265**), and F (**266**) and biflorin (**267**).

*Scheme 1.45. Best and Wege's 1981 synthesis of mansonone precursor **263**.*



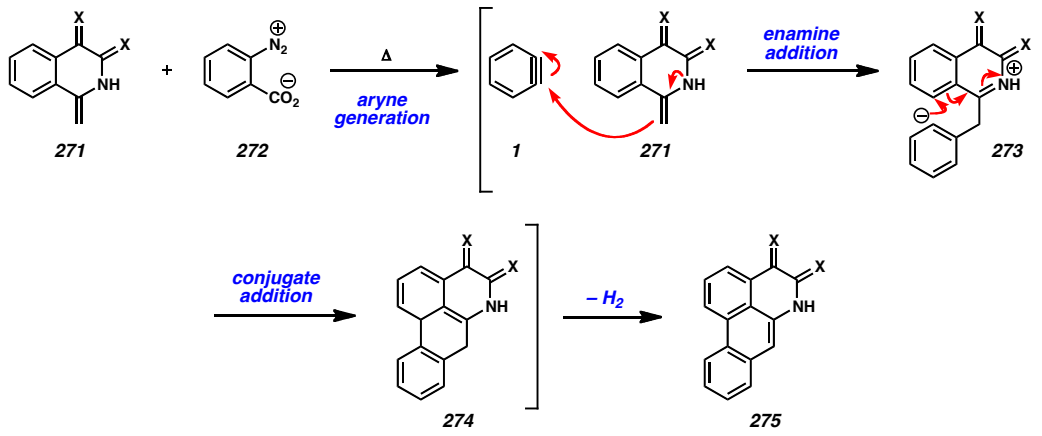
Given the potential risk of explosion associated with use of anthranilic acid-derived aryne precursors,[59] Best and Wege noted that the key intramolecular Diels–Alder cycloaddition can also be performed by elimination of the corresponding *o*-dibromide compound (**268**) with *n*-BuLi, producing cycloadduct **270** in 90% yield (Scheme 1.46).

*Scheme 1.46. Alternative aryne generation in the intramolecular aryne Diels–Alder toward mansonone E (**264**).*



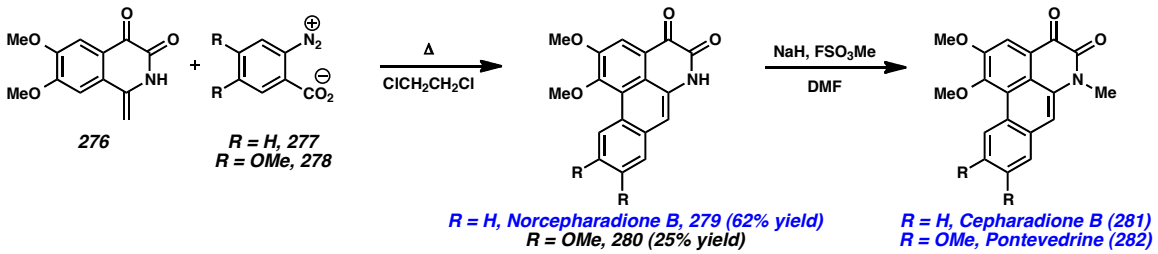
Beginning in the mid-1980s, Castedo and co-workers embarked on a program spanning more than 10 years in which they investigated the synthesis of various isoquinoline-derived alkaloids by intermolecular aryne Diels–Alder cycloadditions. One of the various general strategies they developed relied upon the [4 + 2] cycloaddition of substituted arynes (both symmetrical and unsymmetrical) with 1-methylene-substituted isoquinoline derivatives such as **271** to generate aporphinoid alkaloids (Scheme 1.47).[60] Mechanistically, this annulation can be envisioned to proceed in a stepwise fashion beginning with an enamine addition of isoquinoline derivative **271** to an aryne (**1**) to generate an intermediate aryl anion (**273**). The aryl anion (**273**) can then undergo a dearomatizing conjugate addition to the pendant iminium ion to produce tetracycle **274**, which then undergoes a formal loss of hydrogen to give rise to aromatized tetracycle **275**. By varying the substitution on both the 1-methylene isoquinoline derivative (**271**) and the aryne (**1**), a variety of alkaloids were prepared, including PO-3 (**299**), norcepharadione B (**279**), cepharadione B (**281**), duguenaine (**292**), pontevedrine (**282**), *O*-methylatheroline (**294**), and lysicamine (**293**).[61]

Scheme 1.47. Castedo general approach to the aporphinoid alkaloids.



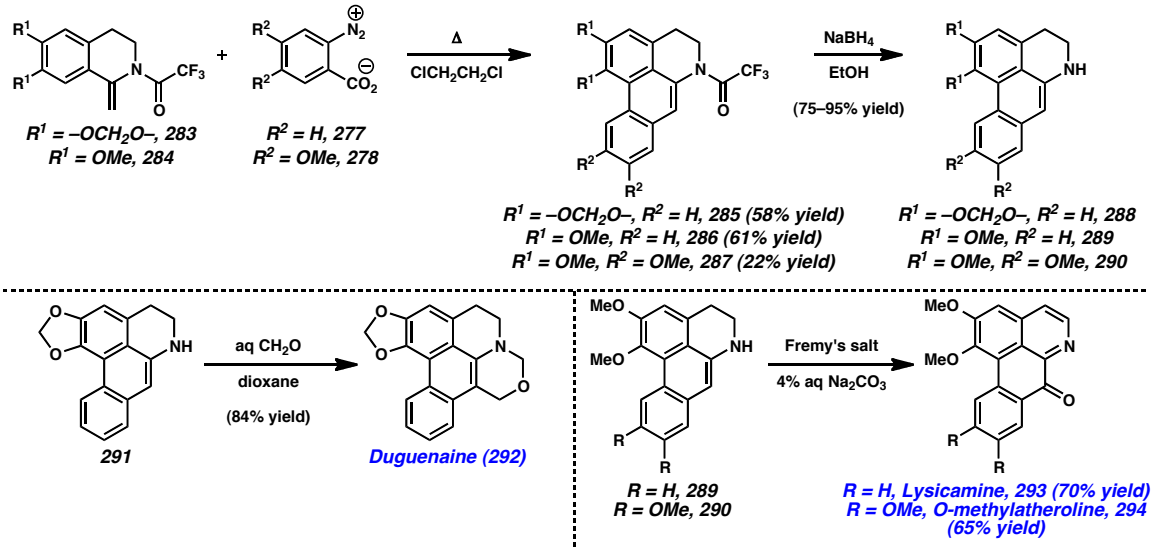
In the syntheses of norcepharadione B (**279**), cepharadione B (**281**), and pontevedrine (**282**), reaction of 6,7-dimethoxy-1-methylene isoquinoline-3,4-dione (**276**) with either benzenediazonium-2-carboxylate (**277**) or its dimethoxy relative (**278**) yielded norcepharadione B (**279**) and des-methyl pontevedrine (**280**), respectively (Scheme 1.48).[61a] *N*-methylation of each of these compounds (**279** and **280**) furnished the natural products cepharadione B (**281**) and pontevedrine (**282**).

*Scheme 1.48. Castedo's 1991 syntheses of norcepharadione B (**279**), cepharadione B (**281**), and pontevedrine (**282**).*



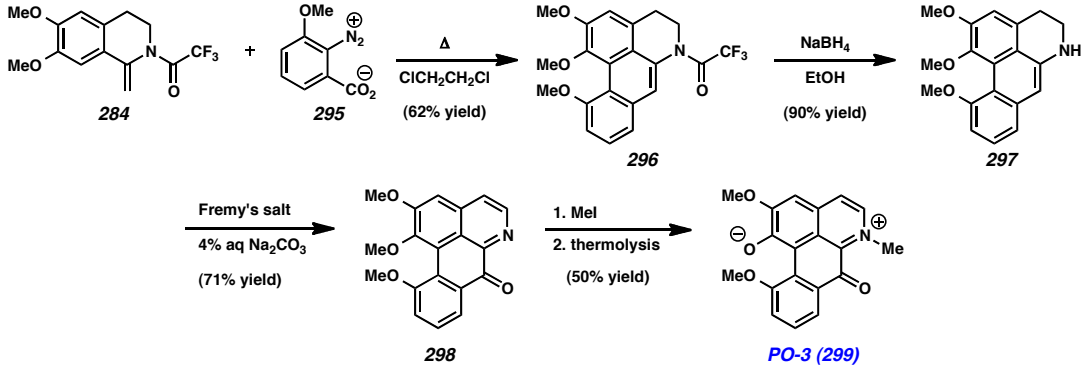
A variation on this theme produced duguenaine (**292**), lysicamine (**293**), and *O*-methylatheroline (**294**) by employing differentially substituted 1-methylene-3,4-dihydro isoquinoline cycloaddition partners (**283** and **284**) (Scheme 1.49).[61a] The cycloadducts of these aryne [4 + 2] reactions (**285**–**287**) were each treated with $NaBH_4$ to remove the labile trifluoroacetaamides. Condensation of pentacycle **291** with formaldehyde furnished duguenaine (**292**) in 84% yield. Alternatively, oxidation of tetracycles **289** and **290** with Fremy's salt provided the isoquinoline alkaloids lysicamine (**293**) and *O*-methylatheroline (**294**) in 70% and 65% yields, respectively.

*Scheme 1.49. Castedo's 1991 syntheses of duguenaine (**292**), lysicamine (**293**), and O-methylatheroline (**294**).*



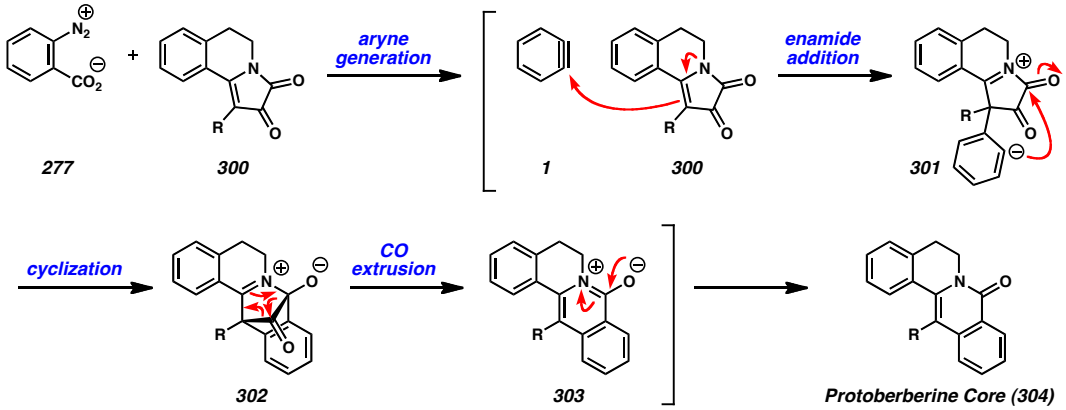
Finally, the synthesis of the alkaloid PO-3 (**299**) highlights the excellent selectivity displayed by this particular [4 + 2] cycloaddition when applied to unsymmetrical arynes, such as that derived from 3-methoxy benzenediazonium-2-carboxylate (**295**) (Scheme 1.50).[61] Following the cycloaddition, removal of the *N*-trifluoroacetyl protective group, oxidation with Fremy's salt, methylation, and thermolysis provided PO-3 (**299**).

*Scheme 1.50. Castedo's 1985 synthesis of PO-3 (**299**).*



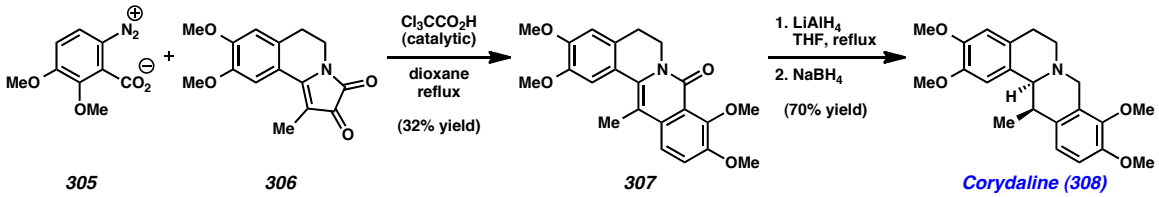
As part of their ongoing program aimed at the development of new aryne [4 + 2] cycloadditions for alkaloid total synthesis, Castedo and co-workers targeted another class of isoquinoline-derived natural products—the protoberberines—by the cycloaddition of isoquinolinepyrrolinediones (e.g., **300**) with arynes (e.g., **1**) (Scheme 1.51).[62] Mechanistically, this reaction sequence begins with enamide addition to the aryne, generating intermediate aryl anion **301**. Instead of the conjugate addition observed in the synthesis of the aporphinoids (vide supra), transannular addition of the aryl anion to the amide carbonyl produces bicyclic intermediate **302**, which undergoes subsequent CO extrusion and tautomerization to furnish tetracycle **304**.

Scheme 1.51. Castedo's tandem [4 + 2] cycloaddition/CO extrusion approach to the protoberberine alkaloids.



This transformation was applied to the total synthesis of the protoberberine alkaloid corydaline (**308**) beginning with cycloaddition of pyrrolinedione **306** and dimethoxy benzenediazonium carboxylate (**305**) to regioselectively provide tetracycle **307** in modest yield (Scheme 1.52).[62] Amide reduction followed by treatment of the resulting enamine with $NaBH_4$ furnished corydaline (**308**).

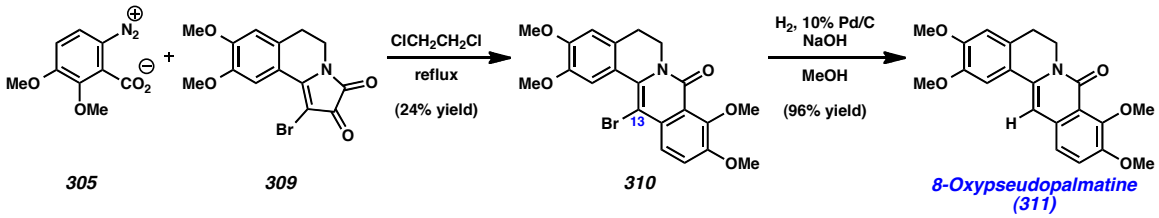
*Scheme 1.52. Castedo's 1986 synthesis of corydaline (**308**).*



Analogous to corydaline, 8-oxypseudopalmatine (**311**) and decarbomethoxydihydrogambirtannine (**314**) were prepared by the tandem [4 + 2] cycloaddition/CO extrusion sequence.[63] Combination of bromopyrrolinedione **309** with

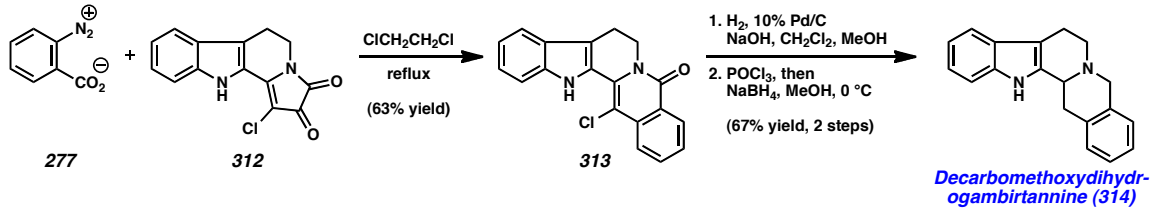
4,5-dimethoxy benzenediazonium-2-carboxylate **309** under standard thermolysis conditions produced tetracycle **310** in a modest 24% yield (Scheme 1.53). The presence of a bromine substituent on the pyrrolinedione prevents further arylation at C(13) following the initial cycloaddition and CO extrustion. Hydrogenolysis of the bromide provided 8-oxypseudopalmatine (**311**).

*Scheme 1.53. Castedo's 1988 synthesis of 8-oxypseudopalmatine (**311**).*



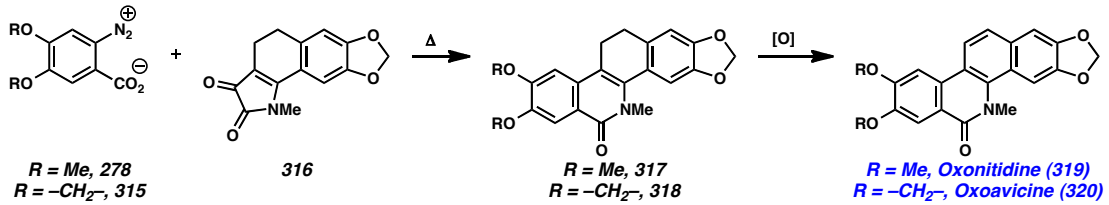
In the synthesis of decarbomethoxydihydrogambirtannine (**314**), the reaction of β-carboline-derived chloropyrrolinedione **312** and benzenediazonium-2-carboxylate (**277**) generated pentacyclic intermediate **313** in good yield (Scheme 1.54).[63b] Upon hydrogenolysis of the chloride and reduction of the amide, decarbomethoxydihydrogambirtannine (**314**) was obtained.

*Scheme 1.54. Castedo's 1992 synthesis of decarbomethoxydihydrogambirtannine (**314**).*



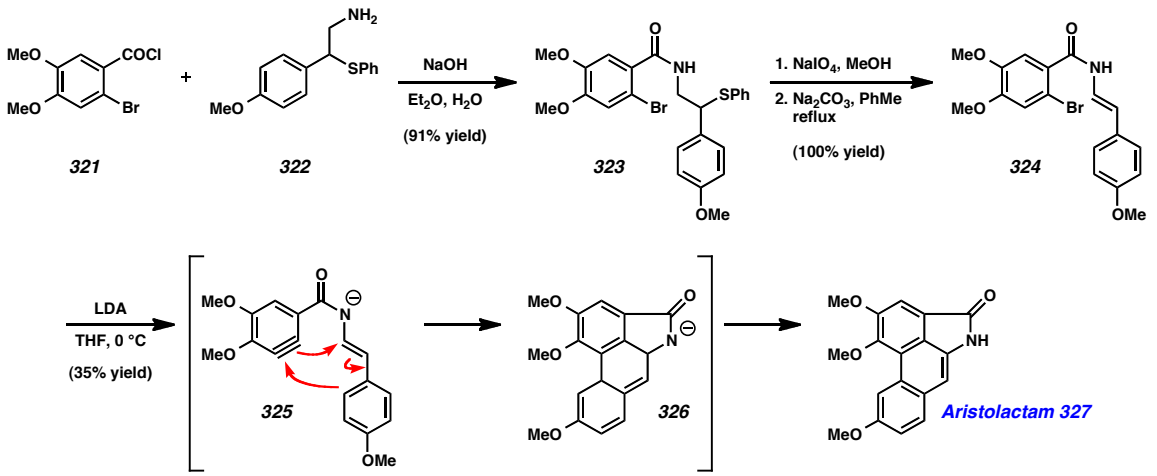
Similarly, oxoavicine (**320**) and oxonitidine (**319**) could be accessed by [4 + 2] cycloaddition and CO extrusion with pyrrolinedione **316** and aryne precursors **315** and **278**, respectively (Scheme 1.55).[64] The resulting cycloadducts (**317** and **318**) were converted to oxonitidine (**319**) and oxoavicine (**320**), respectively, upon oxidation.

*Scheme 1.55. Castedo's 1989 synthesis of oxoavicine (**320**) and oxonitidine (**319**).*



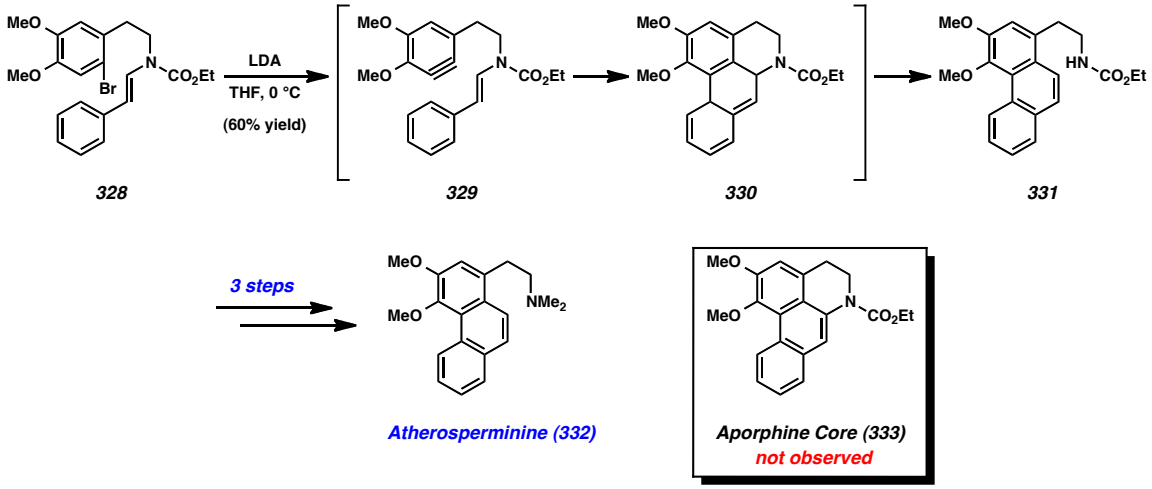
In 1989, Castedo and co-workers reported syntheses of the aristolactam and phenanthrene alkaloids featuring novel aryne [4 + 2] cycloaddition strategies.[65] In these examples, the cycloaddition occurs between a tethered aryne-diene pair in an intramolecular aryne Diels–Alder reaction. In the synthesis of naturally occurring aristolactam **327**, a suitable substrate (**324**) for cycloaddition was prepared by coupling of acid chloride **321** with amine **322**, followed by oxidation and elimination (Scheme 1.56).[65a] Upon treatment of amide **324** with LDA at decreased temperatures, elimination of the bromide produced the aryne (**325**), which underwent a [4 + 2] cycloaddition with the pendant styrene functionality. Aerobic aromatization of the newly formed 6-membered ring furnished the natural product, aristolactam **327**.

Scheme 1.56. Castedo's 1989 synthesis of aristolactam ***327****.*



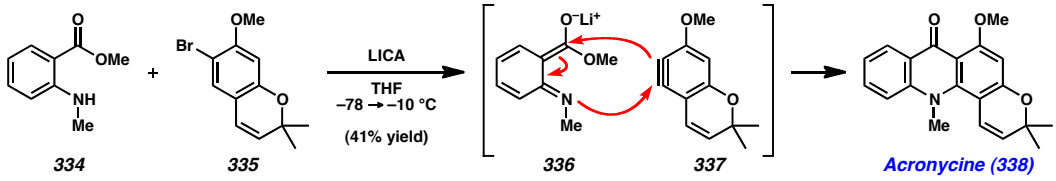
Following the synthesis of aristolactam **327**, Castedo attempted to extend this strategy to the analogous synthesis of the aporphine ring system.[65b] However, attempts to accomplish the intramolecular aryne Diels–Alder on urethane **328** with LDA at decreased temperature did not produce the expected tetracycle (**333**) (Scheme 1.57). Instead, phenanthrene **331** was isolated as the major product in 60% yield. Presumably this product arises from a pathway beginning with the desired intramolecular [4 + 2] cycloaddition following aryne generation; however, the initial adduct (**330**) then undergoes fragmentation during aromatization to form phenanthrene **331**. Despite this surprising result, phenanthrene **331** was converted to the natural product atherosperminine (**332**) in three steps.[66] Notably, the [4 + 2] cycloadditions employed in this example and in the synthesis of aristolactam **327** feature an acyclic diene, an uncommon occurrence in aryne Diels–Alder methodology.

*Scheme 1.57. Castedo's 1995 synthesis of atherosperminine (**332**).*



The group of Watanabe and co-workers investigated the synthesis of acronycine (**338**) by a formal [4 + 2] cycloaddition between anthranilate **334** and the unsymmetrical aryne (**337**) derived from aryl bromide **335** (Scheme 1.58).[67] Sequential bond formation consisting of vinylogous lithium amide (**336**) addition to the aryne (**337**) and aryl anion addition into the pendant ester resulted in direct formation of acronycine (**338**) in 41% yield.

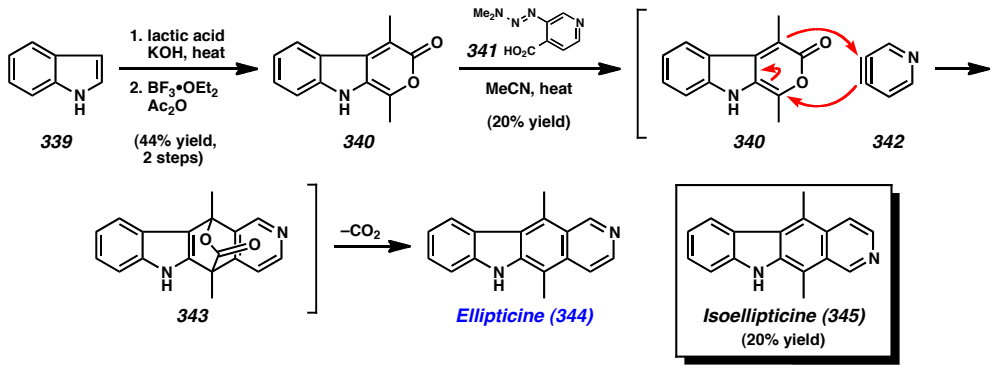
*Scheme 1.58. Watanabe's 1984 synthesis of acronycine (**338**).*



In the mid-1980s, the groups of both Moody[68] and Gribble[69] separately reported very similar approaches to the alkaloid ellipticine (**344**) using a 3,4-pyridyne intermediate. These reports, separated by only two months, represent the first use of pyridyne in total synthesis.

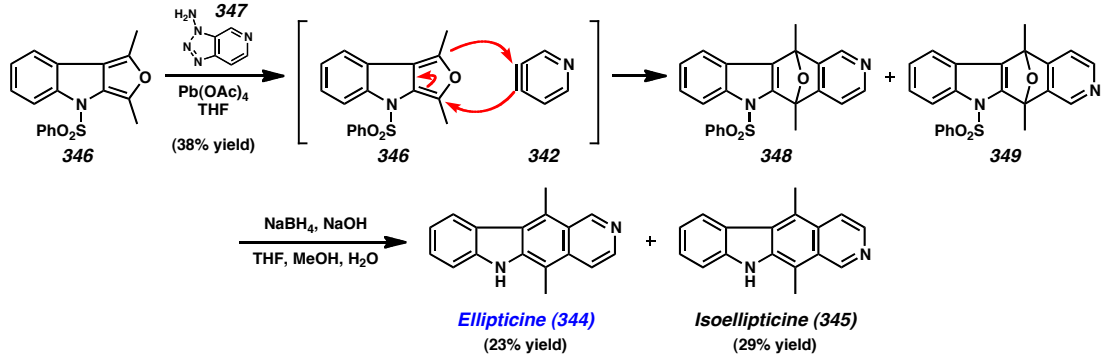
Moody's three-step synthesis of ellipticine (**344**) begins with conversion of indole (**339**) to pyrone **340** (Scheme 1.59).[68] Upon thermal decomposition of triazine **341**, nonselective [4 + 2] cycloaddition of pyrone **340** with 3,4-pyridyne (**342**) yielded a 1:1 separable mixture of ellipticine (**344**) and isoellipticine (**345**), following extrusion of CO_2.

*Scheme 1.59. Moody's 1984 synthesis of ellipticine (**344**).*



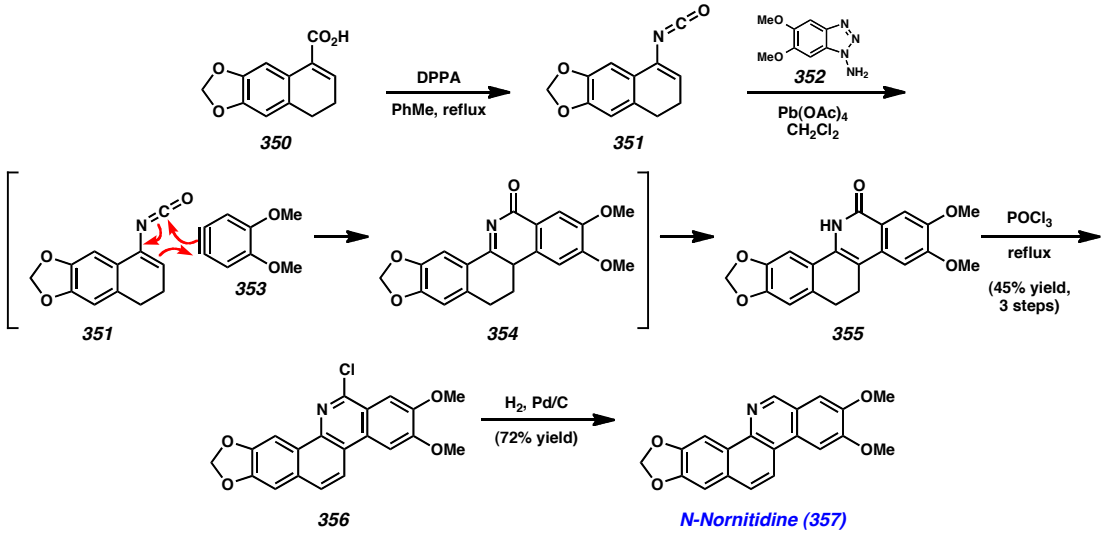
By comparison, Gribble and co-workers relied upon a [4 + 2] cycloaddition between furan **346** and 3,4-pyridyne (**342**) in their synthesis of ellipticine (**344**) (Scheme 1.60).[69] The oxabicyclic product (**348**/**349**) was formed as a mixture of inseparable isomers, which were readily converted to ellipticine (**344**) and isoellipticine (**345**) upon reaction with sodium borohydride.

*Scheme 1.60. Gribble's 1984 synthesis of ellipticine (**344**).*



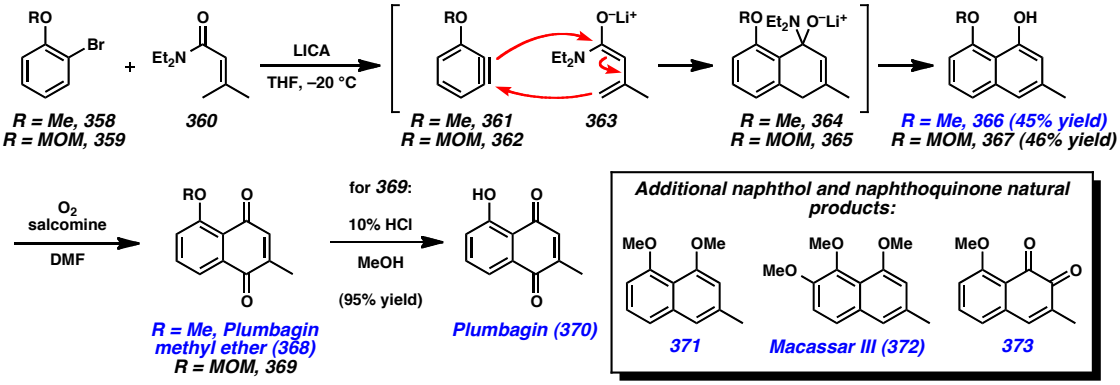
Soon after the extensive work of Castedo and co-workers involving the synthesis of isoquinoline-derived alkaloids, the Rigby group reported a convergent route to the naturally occurring isoquinoline *N*-nornitidine (**357**) employing a [4 + 2] cycloaddition between an aryne and a vinyl isocyanate (Scheme 1.61).[70] To this end, vinyl isocyanate **351** was prepared by a Curtius rearrangement of acid **350**. Upon decomposition of the *N*-aminobenzotriazole (**352**) to the corresponding aryne (**353**) with stoichiometric $Pb(OAc)_4$, a [4 + 2] cycloaddition between the aryne (**353**) and the vinyl isocyanate (**351**) produced pentacyclic isoquinolone **355** following tautomerization of the initial cycloadduct (**354**). Once again, this serves as a rare example of the use of an acyclic diene in an aryne [4 + 2] cycloaddition. Subsequent exposure of the isoquinolone (**355**) to refluxing $POCl_3$ directly generated the fully aromatized chloroisoquinoline (**356**) in 45% yield for the three-step sequence beginning with acid **350**. Finally, hydrogenolysis of the chloride under standard conditions afforded *N*-nornitidine (**357**).

*Scheme 1.61. Rigby's 1991 synthesis of N-nornitidine (**357**).*



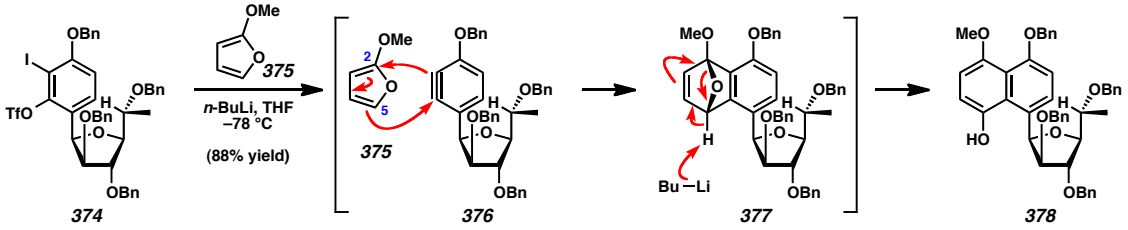
Departing from alkaloid synthesis, Watanabe and co-workers have targeted a variety of naphthol and naphthoquinone natural products by [4 + 2] cycloadditions of arynes with acylic dienolate-type dienes (Scheme 1.62).[71] In the synthesis of plumbagin (**370**) and plumbagin methyl ether (**368**), treatment of either aryl bromide **358** or **359** with *N,N*-diethylsenecioamide (**360**) in the presence of LICA resulted in the regioselective intermolecular [4 + 2] cycloaddition between aryne **361** or **362** and dienolate **363** to furnish naphthols **366** (itself an unnamed natural isolate of *Diospyros melanoxylon* ROXB) and **367**, respectively. These compounds were readily oxidized to their corresponding naphthoquinones with oxygen and salcomine, affording plumbagin methyl ether (**368**) and quinone **369**. The latter was converted to plumbagin (**370**) upon acidic hydrolysis of the methoxy methyl ether protective group. Additional naphthol and naphthoquinone natural products prepared by these methods are shown in Scheme 1.62.

*Scheme 1.62. Watanabe's 1986 synthesis of plumbagin methyl ether (**368**), plumbagin (**370**), and other naphthol and naphthoquinone natural products.*



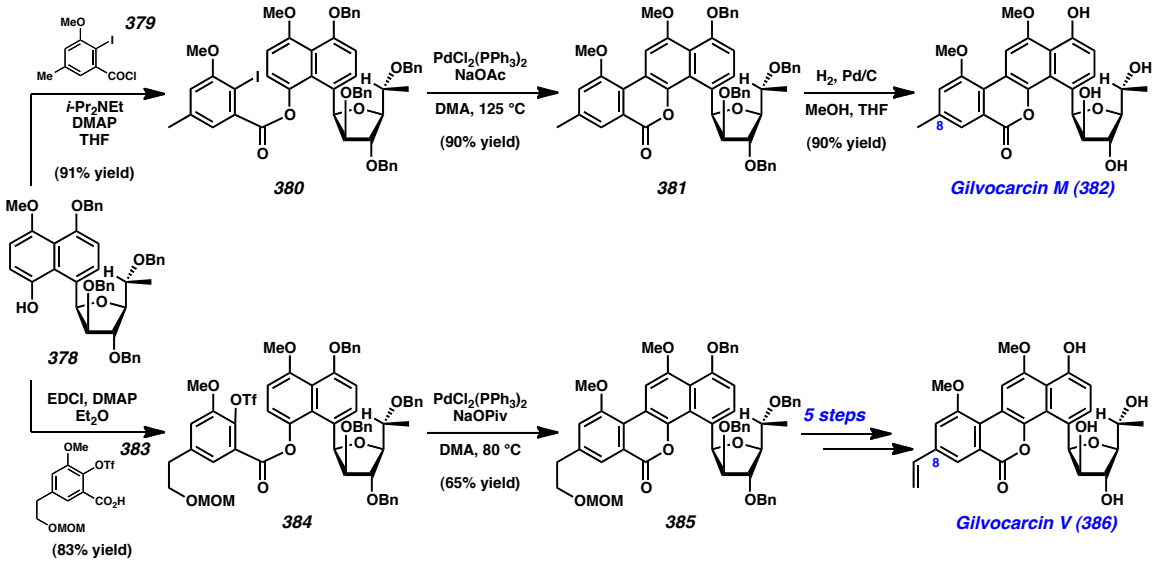
In 1992, Suzuki and co-workers reported the synthesis of gilvocarcin M (**382**), a member of the *C*-glycoside antibiotics that bear a common aromatic core with pendant rare sugars.[72] This work, including Suzuki's later synthesis of gilvocarcin V (**386**), includes the first example of an intermolecular furan-aryne Diels–Alder reaction applied in total synthesis. More specifically, the [4 + 2] cycloaddition between the aryne generated from *ortho*-iodotriflate **374** and 2-methoxyfuran (**375**) produced naphthol **378** as the principle product in 88% yield following aromatization (Scheme 1.63). Importantly, the selective formation of naphthol **378** in favor of the alternative isomeric cycloadduct (isolated in 7% yield) demonstrates the predominance of electronic factors over steric interactions in determining the regiochemical outcome of addition to unsymmetrical arynes. In this case, the more nucleophilic C(5) position of the furan undergoes addition to the position *meta* to the inductively withdrawing benzyloxy group on the intermediate aryne (**376**). Under the basic reaction conditions, deprotonation of the initial cycloadduct (**377**) led to ring-opening aromatization, yielding naphthol **378**.

Scheme 1.63. Suzuki's 1992 synthesis of naphthol ***378*** *en route to the gilvocarcin antibiotics.*



Naphthol **378** served as a key intermediate in the synthesis of both gilvocarcin M and V, which differ only in the identity of the C(8) substituent. Acylation of the hydroxyl group of naphthol **378** with either acid chloride **379** or carboxylic acid **383** produced aryl esters **380** and **384**, respectively (Scheme 1.64). Treatment of iodide **380** or triflate **384** with a palladium source resulted in ring-closing C–H functionalization to afford tetracycles **381** and **385**, respectively. Global deprotection of tetracycle **381** furnished gilvocarcin M (**382**), while tetracycle **385** required five additional steps for installation of the C(8) vinyl group and completion of gilvocarcin V (**386**). Furthermore, the synthesis of these two natural products determined the absolute configuration of the gilvocarcins to be the opposite of that originally proposed at the time of isolation.[73] The enantiomer prepared by Suzuki (shown in Schemes 1.63 and 1.64) was proven to be the non-natural enantiomer of the gilvocarcins.

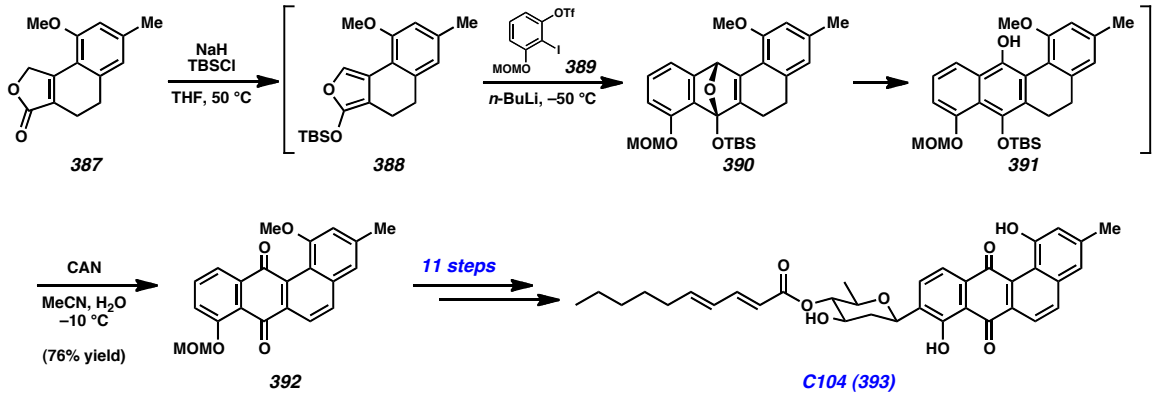
*Scheme 1.64. Completion of gilvocarcin M (**382**) and V (**386**) by Suzuki and co-workers (1992).*



Soon after their synthesis of the gilvocarcins, Suzuki and co-workers reported the total synthesis of antibiotic C104 (**393**), a member of the angucycline class of antibiotics.[74] The tetracyclic aromatic core of the natural product was prepared by a regioselective intermolecular aryne Diels–Alder cycloaddition with a functionalized furan serving as the diene. In fact, the authors were able to carry out a one-pot procedure consisting of in situ generation of silyloxyfuran **388** from butenolide **387**, followed by the [4 + 2] cycloaddition with the aryne derived from iodoaryl triflate **389** (Scheme 1.65). The cycloadduct initially formed by this sequence (**390**) undergoes ring-opening aromatization under the reaction conditions to yield tetracycle **391**. However, this intermediate was found to be unstable and was thus treated with CAN upon workup to give the quinone (**392**) as the final product of this sequence. Importantly, the aryne cycloaddition proceeded with a high degree of regioselectivity to provide quinone (**392**) in greater than a 14:1 ratio over the minor isomeric quinone. Over 11 subsequent

synthetic operations, quinone **392** was advanced to antibiotic C104 (**393**), thereby establishing the absolute configuration of the natural product.

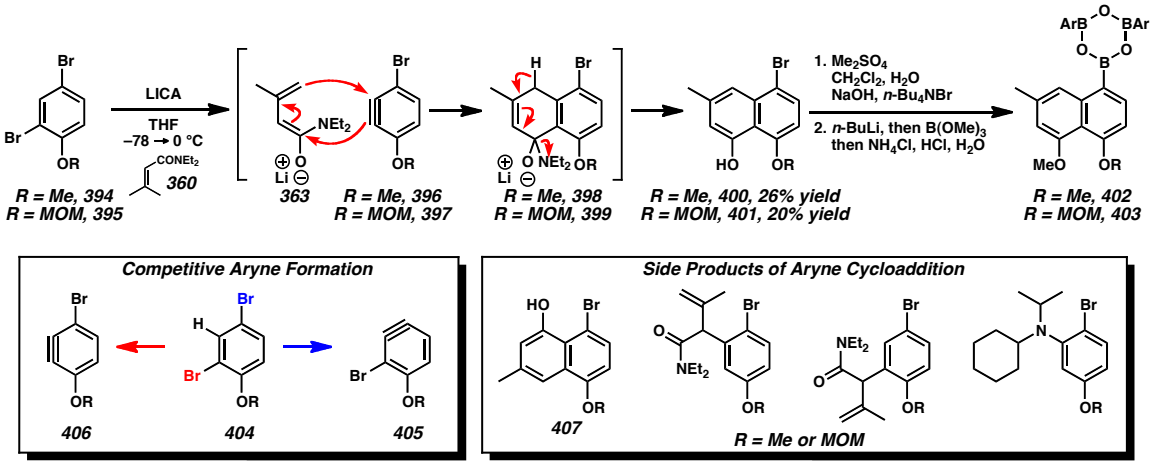
*Scheme 1.65. Suzuki's 1995 synthesis of antibiotic C104 (**393**).*



Among the examples in the literature of aryne [4 + 2] cycloadditions in natural product synthesis that have employed acyclic dienes are Hoye's syntheses of michellamines A–C (**413**–**415**),[75] korupensamine C (**409**), and ancistrobrevine B (**411**)[76]. In each of these syntheses, the Diels–Alder reaction between the dienolate of *N*,*N*-diethylsenecioamide (**360**) and the aryne generated in situ from 2,4-dibromo phenol derivatives **394** and **395** resulted in the selective formation of naphthols **400** and **401**, respectively (Scheme 1.66). Close examination of the aryne precursors (**394** and **395**) reveals that, upon removal of the proton between both bromides, two potential arynes could result from base-promoted dehydrohalogenation: **405** and **406**. Although a number of side products are observed in this reaction in addition to the desired product, they all arise from reaction with the *para*-bromo aryne (**406**). Furthermore, the cycloaddition itself proceeds with good selectivity for naphthols **400** and **401** over isomeric naphthol

407 (5:1 ratio of **400**:**407**). The desired naphthol products (**400** and **401**) were subsequently converted to their respective boroxines (**402** and **403**) through methylation of the free phenol and borylation.

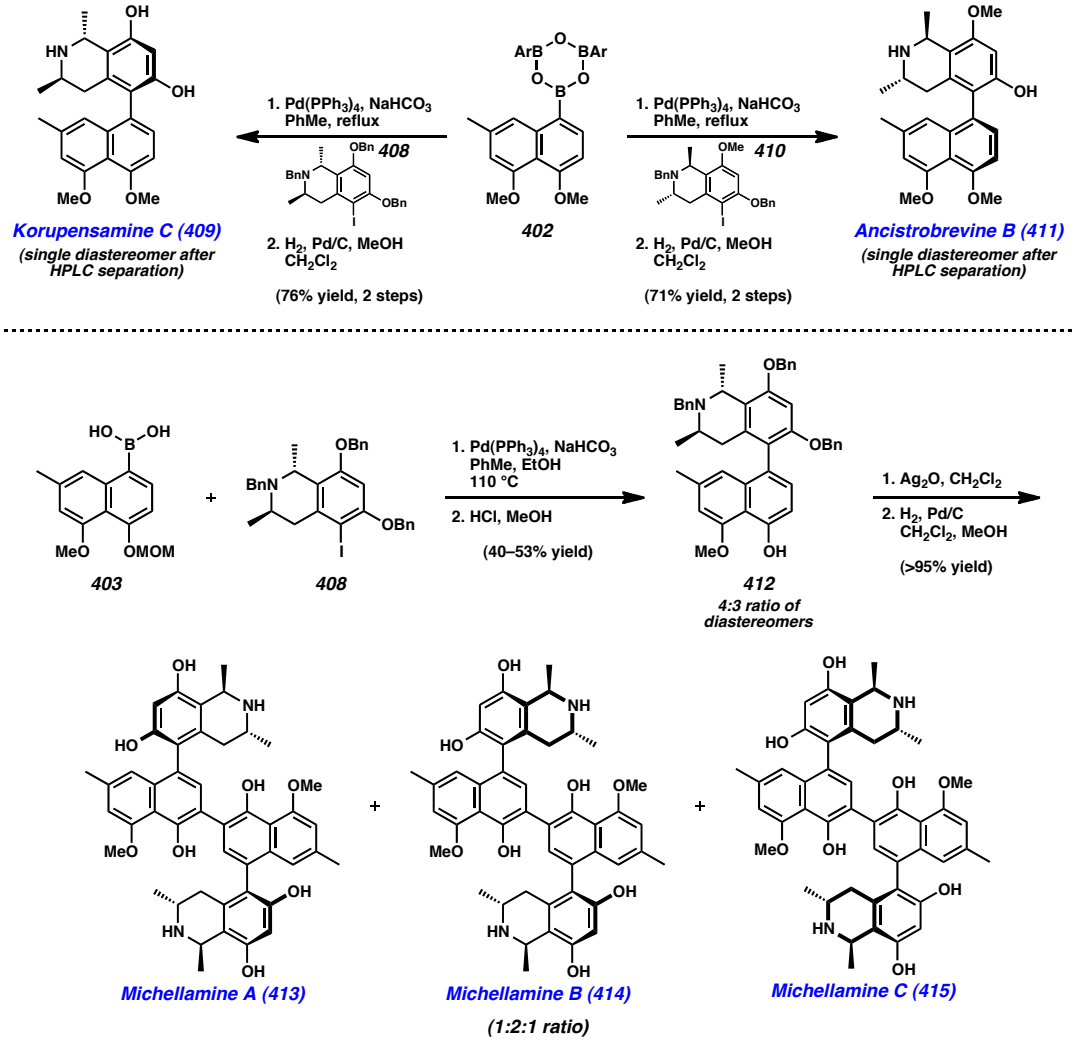
*Scheme 1.66. Synthesis of naphthyl boroxines (**402** and **403**) by aryne Diels–Alder cycloadditions (1994).*



Upon synthesis of the required boroxines (**402** and **403**), palladium-catalyzed biaryl coupling with either iodotetrahydroisoquinolines **408** or **410** yielded a pair of naphthyl tetrahydroisoquinolines, which were separately advanced to korupensamine C (**409**) and ancistrobrevine B (**411**), respectively, upon cleavage of the benzyl groups and separation by HPLC (Scheme 1.67). Completion of the michellamines (**413**–**415**) (as an inseparable mixture) was achieved in a similar manner through coupling of boronic acid **403** with iodotetrahydroisoquinolines **408** followed by removal of the methoxymethyl ether to yield naphthyl tetrahydroisoquinoline **412** as a 4:3 mixture of diastereomers.

Oxidative dimerization, reduction/global deprotection, and HPLC separation provided michellamines A, B, and C in a ratio of 1:2:1.

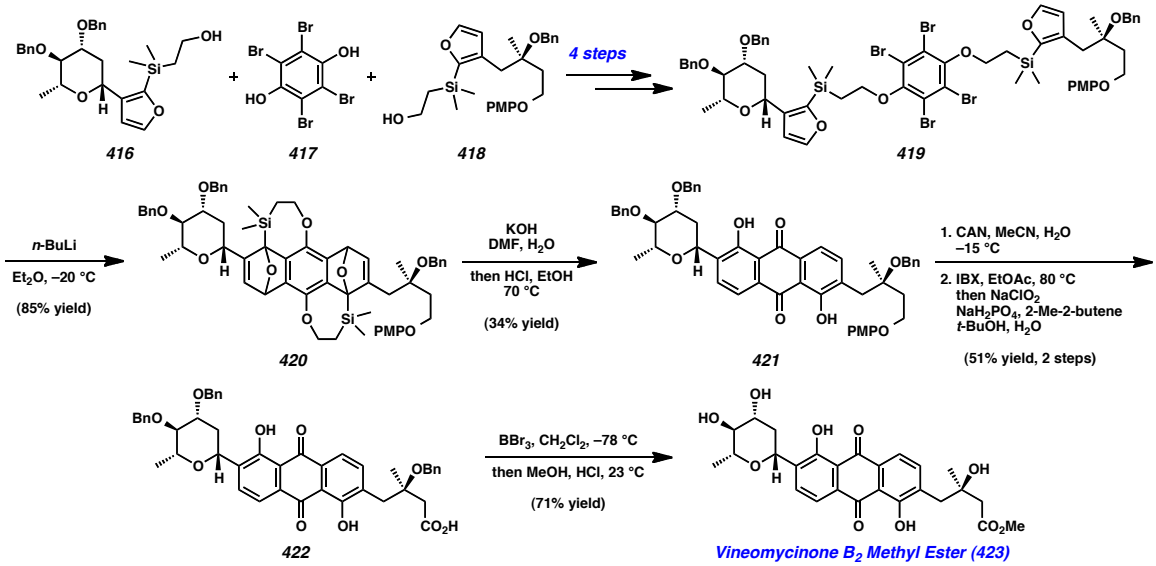
*Scheme 1.67. Hoye's syntheses of korupensamine C (**409**), ancistrobrevine B (**411**), and michellamines A–C (**413**–**415**) (1994 and 1996).*



More recently, Martin and co-workers have employed aryne-furan Diels–Alder reactions en route to the glycosidic antibiotic vineomycinone B_2 methyl ester (**423**).[77] In this unique approach, the authors rely upon a tandem tethered [4 + 2] cycloaddition

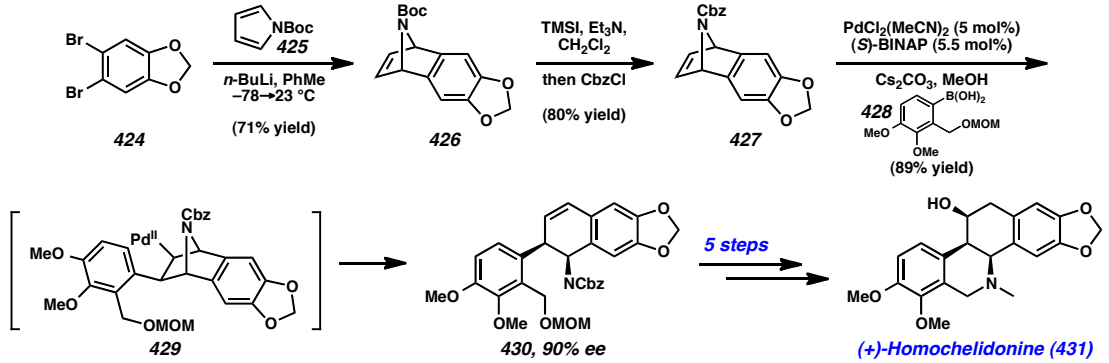
strategy to append both aromatic rings of the tricyclic core to a central diaryne. To this end, a tandem cycloaddition precursor (**419**) was constructed by sequential Mitsunobu reactions beginning with phenol **417** and furanyl fragments **416** and **418** (Scheme 1.68). Treatment of tetrabromoarene **417** with *n*-BuLi triggered a cascade sequence consisting of two separate intramolecular aryne-furan [4 + 2] cycloadditions to yield cycloadduct **419** as an inconsequential mixture of diastereomers in excellent yield. Cleavage of the silyl tethers and oxidation of the system was accomplished by treatment of biscycloadduct **420** with base followed by acid, affording anthrarufin **421** upon air oxidation. Critically, use of the silyl tethers dictated the regioselectivity of the cycloadditions to provide only the desired anthrarufin isomer (**421**). Finally, the synthesis of vineomycinone B_2 methyl ester (**423**) was completed by a three-step sequence involving protecting group removal and alteration of the side chain oxidation state.

*Scheme 1.68. Martin's 2006 synthesis of vineomycinone B_2 methyl ester (**423**) by tandem tethered aryne cycloadditions.*



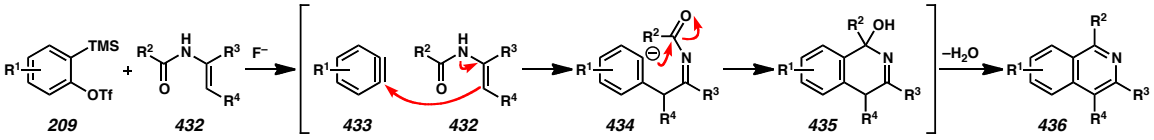
Departing from aryne Diels–Alder reactions with furans, Lautens and co-workers utilized a [4 + 2] cycloaddition between an aryne derived from dibromoarene **424** and *N*-Boc-pyrrole (**425**) to access azabicycle **426** en route to the alkaloid (+)-homochelidonine (**431**) (Scheme 1.69).[78] In this case, the tetracyclic product (**426**) does not undergo immediate ring opening. Instead, following exchange of the carbamate, treatment of azabicycle **427** with a chiral palladium catalyst and arylboronic acid **428** resulted in an asymmetric migratory insertion of the *meso* azabicycle (**427**) into an aryl palladium(II) species, forming intermediate **429**. Following this insertion event, β-elimination of the bridging heteroatom afforded homoallylic carbamate **430** in 90% ee.[79] Finally, homoallylic carbamate **430** was converted into (+)-homochelidonine (**431**) over five synthetic steps.

*Scheme 1.69. Lautens' 2007 synthesis of (+)-homochelidonine (**431**).*



In 2008, Stoltz and co-workers reported a unique annulation of *N*-acyl enamines and arynes to generate isoquinolines.[80] The reaction is believed to proceed through a formal [4 + 2] addition reaction between the *N*-acyl enamine (**432**) and the aryne (**433**, derived from silyl aryl triflate **209**) followed by dehydrative aromatization under the reaction conditions (Scheme 1.70). By this method, any position on the isoquinoline heterocyclic scaffold can be readily functionalized, rendering it ideal for use in natural product total synthesis. To date, the Stoltz group has reported two different syntheses employing this novel aryne annulation.

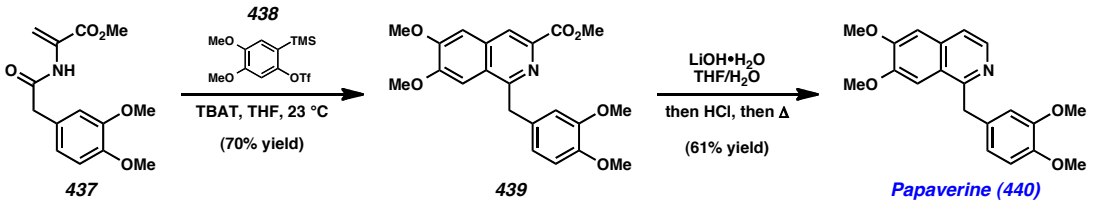
Scheme 1.70. Stoltz's aryne annulation with N-acyl enamines to produce isoquinolines.



In the synthesis of the papaverine, a clinically used non-narcotic antispasmotic agent, annulation of the aryne generated in situ from silyl aryl triflate **438** with *N*-acyl enamine **437** (available in one step from homoveratric acid and serine methyl ester)

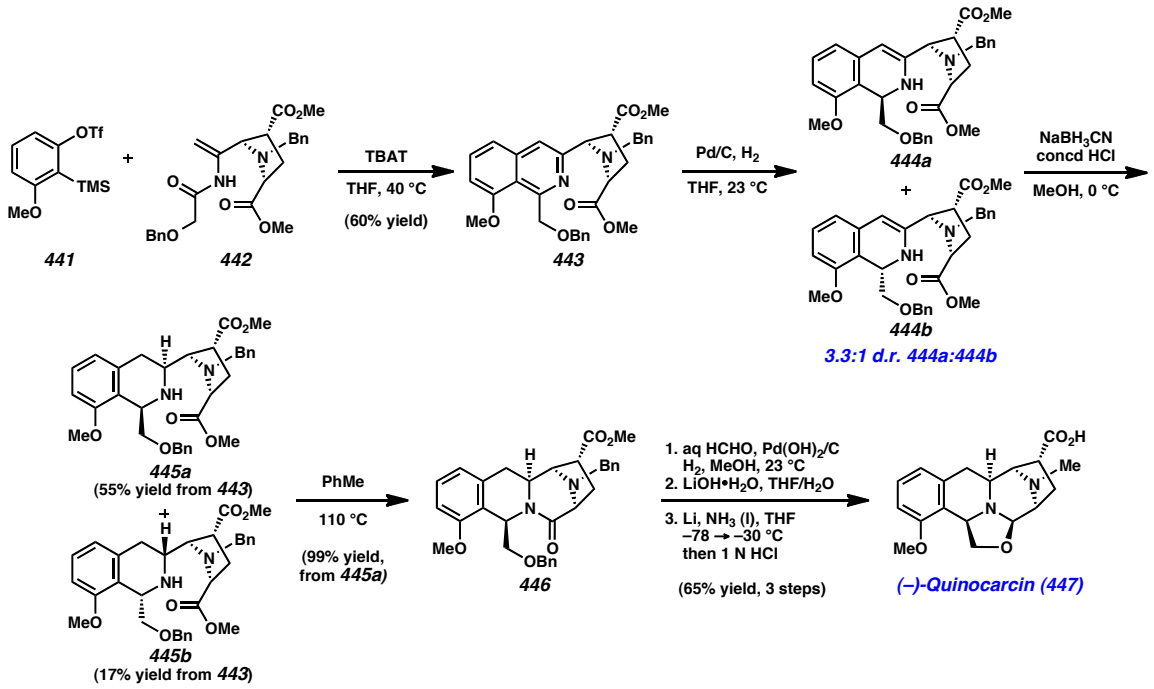
produced tetrasubstituted isoquinoline **439** in good yield (Scheme 1.71).[80] Saponification and thermal decarboxylation furnished the natural product (**440**) in three steps.

*Scheme 1.71. Stoltz's 2008 synthesis of papaverine (**440**).*



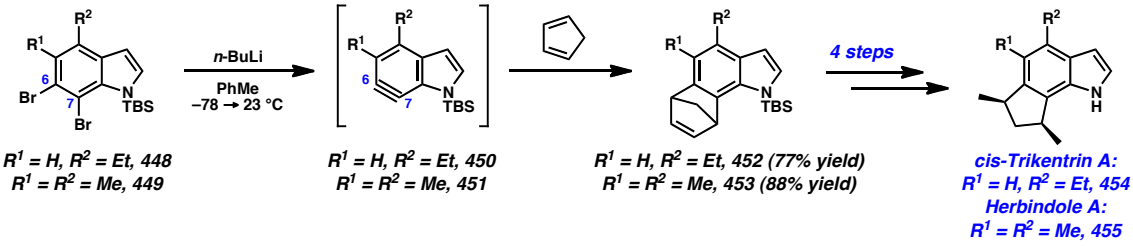
A greater extension of this work can be seen in Stoltz's synthesis of the tetrahydroisoquinoline antitumor antibiotic (–)-quinocarcin (**447**) (Scheme 1.72).[81] The success of the approach hinged on the sequential regioselective aryne annulation and diastereoselective reduction of the isoquinoline to generate the tetrahydroisoquinoline found in the natural product. Annulation of the aryne derived from 3-methoxy silyl aryl triflate **441** with enantioenriched *N*-acyl enamine **442** (available in 4 steps from known compounds) yielded isoquinoline **443** as a single isomer. Subsequent two-step reduction of the isoquinoline proceeded with 3:1 diastereoselectivity for the initial reduction and complete diastereoselectivity for the secondary reduction of the resulting enamine, affording tetrahydroisoquinoline **445a** as the major diastereomer in 55% yield. Following thermal lactamization to yield tetracycle **446**, (–)-quinocarcin (**447**) was completed by a three-step sequence involving debenzylation/reductive methylation, saponification, and reductive closure of the oxazolidine ring. Overall, this 11-step enantioselective synthesis of (–)-quinocarcin (**447**) is the shortest to date.

*Scheme 1.72. Stoltz's 2008 enantioselective synthesis of (–)-quinocarcin (**447**).*



The most recent example of the application of an aryne [4 + 2] cycloaddition to natural product synthesis is Buszek's syntheses of *cis*-trikentrin A (**454**) and herbindole A (**455**).[82] This work significantly differs from the various syntheses described above in that the aryne counterpart is a 6,7-indolyne. More specifically, elimination of 6,7-dibromoindoles **448** and **449** with *n*-BuLi generated the corresponding 6,7-indolynes (**450** and **451**), which, upon treatment with cyclopentadiene, underwent a [4 + 2] cycloaddition to afford tetracycles **452** and **453**, respectively (Scheme 1.73). These intermediates were then advanced to *cis*-trikentrin A (**454**) and herbindole A (**455**), respectively, over four steps.

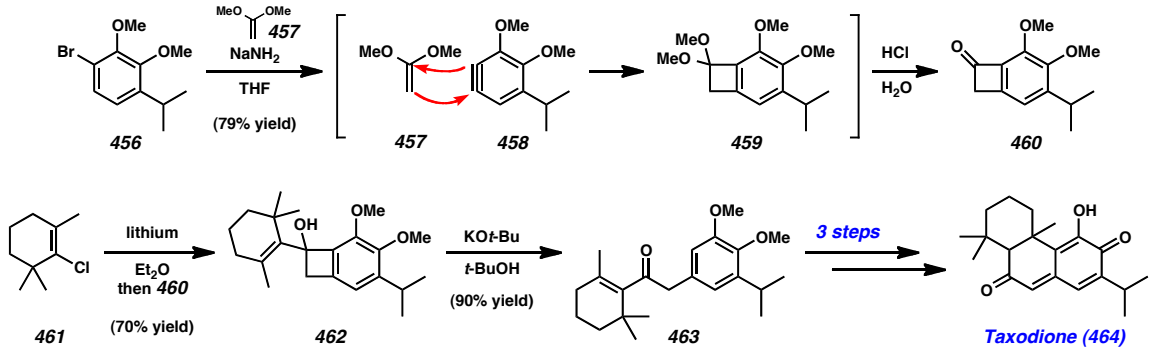
*Scheme 1.73. Buszek's 2009 syntheses of cis-trikentrin A (**454**) and herbindole A (**455**).*



1.4.2 [2 + 2] Aryne Cycloaddition Strategies

Aryne [2 + 2] cycloadditions are some of the most poorly developed and underutilized methods, largely due to significant side product formation. To date, there has been only one reported total synthesis employing an aryne [2 + 2] cycloaddition. In 1982, Stevens and co-workers disclosed the synthesis the quinone methide diterpene, taxodione (**464**), by a convergent route including a [2 + 2] cycloaddition between an aryne and a ketene acetal (Scheme 1.74).[83] In the event, treatment of aryl bromide **456** with sodamide in THF in the presence of 1,1-dimethoxyethylene (**457**) resulted in regioselective formation of benzocyclobutene **459**, which was immediately hydrolyzed to benzocyclobutenone **460**. Addition of the organolithium reagent derived from vinyl chloride **461** to the benzocyclobutenone (**460**) and regioselective, yet contrasteric, ring fragmentation of the resulting benzocyclobutenol (**462**) yielded enone **463**, which was readily advanced to taxodione (**464**).

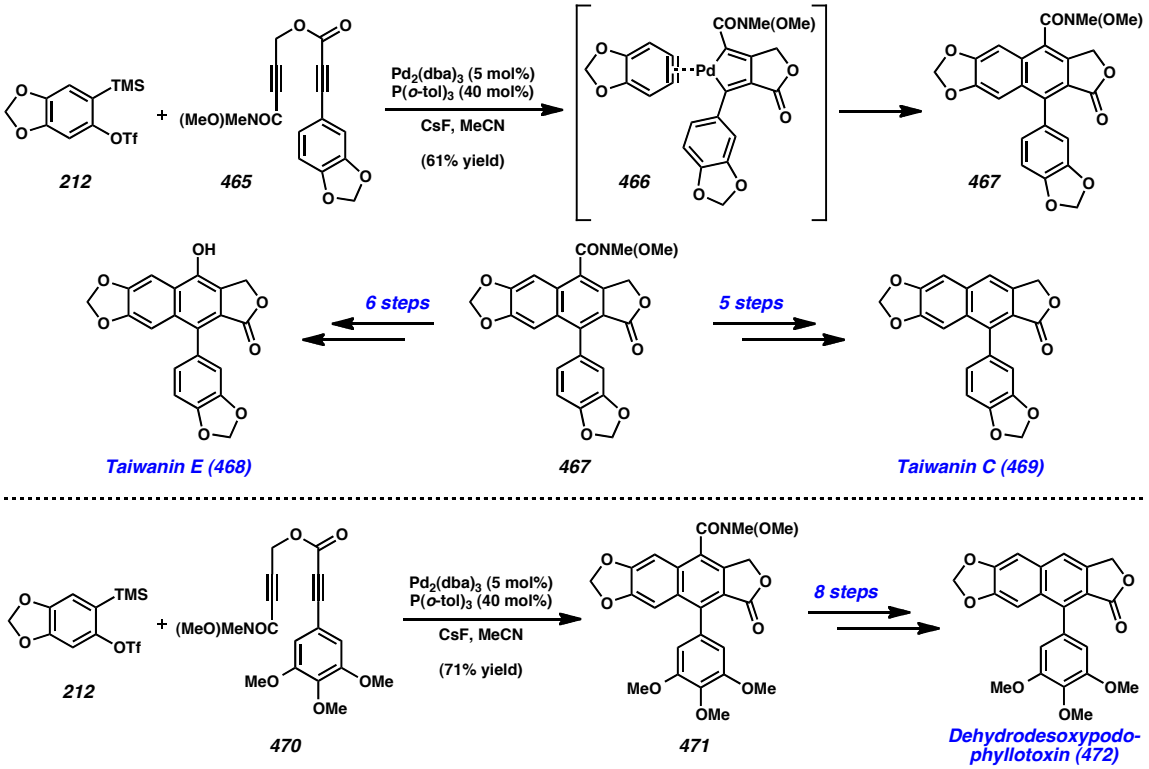
*Scheme 1.74. Stevens' 1982 synthesis of taxodione (**464**).*



1.5 METAL CATALYZED ARYNE REACTION STRATEGIES

Among all of the known reactions involving arynes, metal-catalyzed processes are still considered to be underdeveloped. In fact, metal-catalyzed reactions of arynes have only been employed in total synthesis on one occasion by Mori and co-workers en route to a series of aryl-naphthalene lignans.[84] In this elegant approach, the naphthyl portions of taiwanins C (**469**) and E (**468**) and dehydrodesoxypodophyllotoxin (**472**) were targeted by a palladium-catalyzed [2 + 2 + 2] cocyclization of an aryne and diyne. Cocyclization of sesamol-derived diyne **465** with the aryne generated in situ from silyl aryl triflate **212** resulted in formation of arylnaphthalene **467**, which was subsequently converted to taiwanin E (**468**) in six additional steps and taiwanin C (**469**) over five steps (Scheme 1.75). Alternatively, use of diyne **470** (derived from 3-(trimethoxyphenyl)propiolic acid) in the palladium-catalyzed [2 + 2 + 2] cocyclization afforded trimethoxyarylnaphthalene **471**, which was advanced to dehydrodesoxypodophyllotoxin (**472**) over eight synthetic transformations.

*Scheme 1.75. Mori's 2004 synthesis of taiwanin C (**469**), taiwanin E (**468**), and dehydrodesoxypodophyllotoxin (**472**).*



1.6 CONCLUDING REMARKS

When J. D. Roberts first assigned the structure of benzyne in 1953, few could have recognized the significant synthetic potential of this highly reactive intermediate. However, to the benefit of the synthetic organic chemistry community, the manifold types of reactivity possessed by arynes have been explored and exploited largely through efforts aimed at the synthesis of natural products. Since the first aryne-based total synthesis in 1967, there has been a progression from early strategies that monofunctionalize aryne intermediates to approaches that utilize the full potential of the uniquely reactive triple bond to generate 1,2-disubstituted arenes. While there has been

significant progress in expanding the utility of arynes in organic synthesis, there is still work that remains in increasing the yields of theses processes and minimizing background reactions. Fortunately, the recent resurgence in aryne research promises to improve what is already known while adding to the known compendium of aryne transformations.

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Chapter 2

The Total Synthesis of (–)-Curvularin

2.1 INTRODUCTION

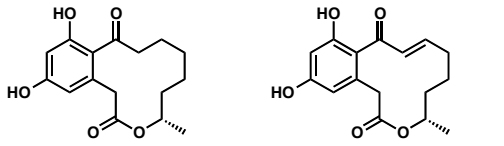
2.1.1 Benzannulated Natural Products

Benzannulated macrolactones are an ever-growing class of natural products with potential therapeutic and agrochemical applications. As part of our ongoing research directed toward the development of new reactions of arynes, we have targeted these natural products in a general sense by using an acyl-alkylation reaction between an aryne and a β-ketolactone. As a demonstration of this strategic disconnection, we chose as our initial target (–)-curvularin, a polyketide natural product isolated from several species of the mold *Curvularia* that has recently been shown to be an inhibitor of human-inducible nitric oxide synthase expression. The development of a general and convergent synthesis of curvularin would provide access to valuable benzannulated macrolactone natural products and various synthetic analogs for biological evaluation.

2.1.2 Isolation and Structural Determination of (–)-Curvularin and Related Natural Products

The benzannulated macrolactone natural product (–)-curvularin (**221**) was first isolated in 1956 by Musgrave and co-workers from a mold of the species *Curvularia* (Figure 2.1).[1] Over the next several years, the structure was determined by a combination of degradation and reactivity studies without the aid of NMR experiments.[2] Curvularin was isolated along with a related natural product, (–)-α,β-dehydrocurvularin (**473**); despite its similarity to curvularin, the structure of α,β-dehydrocurvularin was not elucidated until 1967.[3] Following the first isolation reports, curvularin (and related natural products) has since been isolated from a number of other fungal species, such as *Penicillium*,[4] *Cochiobolus*, and *Alternaria*.

*Figure 2.1. (S)-(–)-Curvularin (**221**) and (S)-α,β-dehydrocurvularin (**473**).*

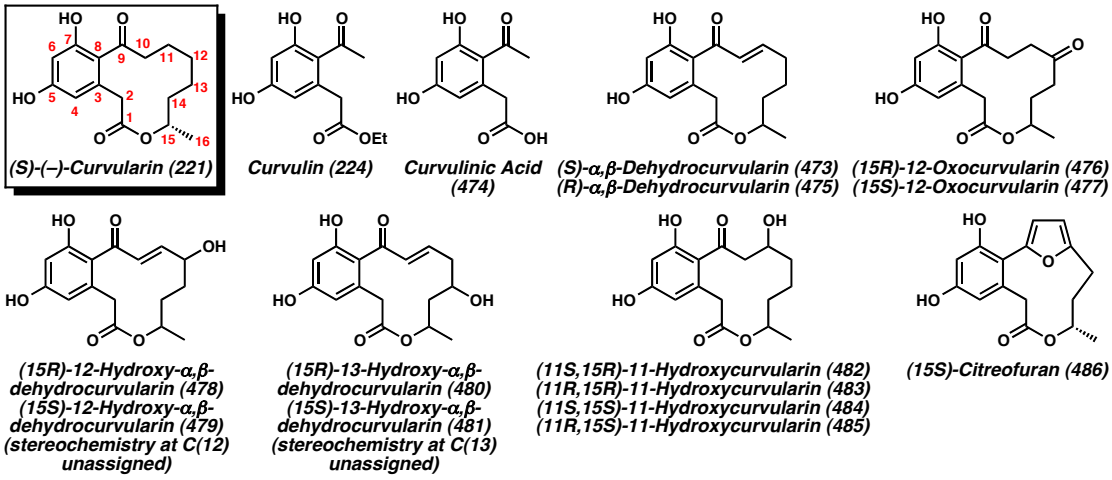


(S)-(–)-Curvularin (221) ***(S)-α,β-Dehydrocurvularin (473)***

Since the initial discovery of curvularin (**221**) and its α,β-dehydro relative (**473**), several other members of the curvularin family have been isolated from a range of natural sources (Figure 2.2). Among the earliest curvularin relatives isolated were curvulin (**224**) and curvulinic acid (**474**) from *Curvularia siddiqui* and *Curvularia ellisii*.[5] These compounds are unique in this family of natural products for lacking the characteristic benzannulated macrolactone. In addition to these isolates, several relatives of curvularin

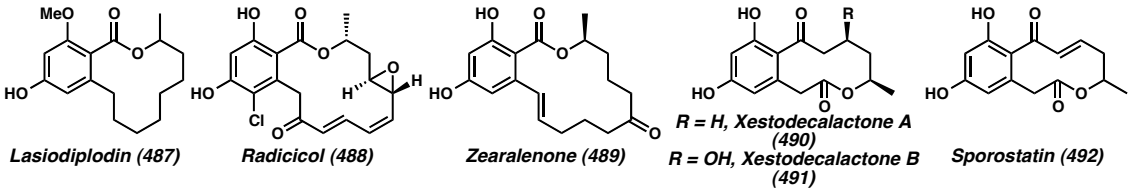
containing the signature 12-membered lactone have been found in nature, including various β-hydroxycurvularins (**482**–**485**), γ- and δ-hydroxy-α,β-unsaturated curvularins (**478**–**481**), and 12-oxocurvularin (**476** and **477**).[6] Notably, these structural relatives have been isolated in enantiopure forms with both *R* and *S* absolute configurations at the C(15) stereocenter. This difference in absolute configuration appears to be due to stereochemical variability in polyketide biosynthesis in different fungal sources. The final noteworthy member of the curvularin family, citreofuran (**486**), contains a bridging furan ring within the macrolactone moiety.[7]

*Figure 2.2. Curvularin (**221**) and related natural products.*



In addition to the curvularins, there are a large number of biogenetically-related septa-, octa-, and nonaketide natural products that possess benzannulated macrocycles resulting from alternative biosynthetic cyclizations of linear precursors. These polyketides include lasiodiplodin (**487**),[8] radicicol (**488**),[9] zearalenone (**489**),[10] the xestodecalactones (**490** and **491**),[11] and sporostatin (**492**),[12] to name a few (Figure 2.3).

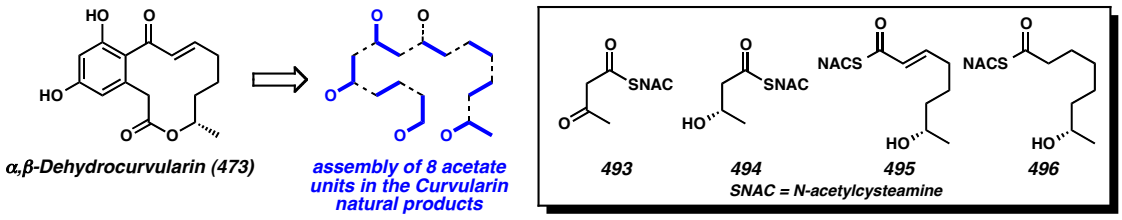
Figure 2.3. Polyketide benzannulated macrocyclic natural products.



2.1.3 Biosynthetic Studies of (–)-Curvularin

Curvularin and related natural products are biosynthesized by a polyketide pathway in nature. Vederas and co-workers have studied some aspects of the biosynthesis of α,β-dehydrocurvularin in *Alternaria cinerariae* with ^{13}C and ^{2}H labeling studies.[13] They first determined that α,β-dehydrocurvularin arises from the condensation of eight acetate units in the expected head-to-tail arrangement typical of polyketide biogenesis (Figure 2.4). From here, the oxidation states and identities of several intermediates bound to polyketide synthase (PKS) enzymes were identified; these intermediates include diketides **493** and **494** and tetraketide **495**. Importantly, tetraketide **496** was not incorporated by the PKS enzymes into the natural products, indicating that α,β-dehydrocurvularin (**473)** might be the initial product of the PKS biosynthetic pathway.

*Figure 2.4. Acetate assembly in α,β-dehydrocurvularin (**473**) and potential starting material for PKS enzymes.*

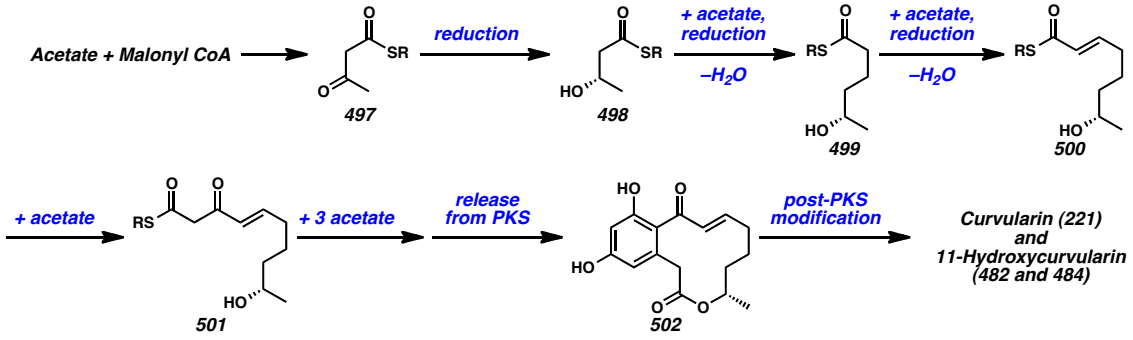


This result seems to suggest that curvularin (**221**) is produced via α,β-dehydrocurvularin (**473**) in nature by a post-PKS transformation. In attempts to verify this potential pathway, Vederas investigated the potential for oxidation of curvularin (**221**) to α,β-dehydrocurvularin (**473**) by cytochrome P_{450} enzymes. However, a series of experiments showed that P_{450} enzymes are not involved in the oxidation of curvularin (**221**) (or other reduced structures) to α,β-dehydrocurvularin (**473**).

During the course of these investigations, Vederas also isolated quantities of 11-hydroxycurvularin (**482** and **484**) as a 2.6:1 mixture of diastereomers at C(11) displaying identical labeling patterns to the α,β-dehydrocurvularin isolated with it. Further experiments, however, demonstrated that the co-occurrence of 11-hydroxycurvularin (**482** and **484**) with α,β-dehydrocurvularin (**473**) is not due to any fungal transformation but instead is a result of conjugate addition of water catalyzed by some component in the media.

These studies have led Vederas and co-workers to postulate the biosynthetic pathway leading to α,β-dehydrocurvularin (**473**), curvularin (**221**) and 11-hydroxycurvularin (**482** and **484**) shown in Scheme 2.1. Importantly, this pathway supports the hypothesis that tetraketide **501** possesses the final oxidation state installed by the PKS enzyme. Incorporation of the last four acetate units by the PKS enzyme does not require any reduction, suggesting that α,β-dehydrocurvularin (**473**) is the initial product of the polyketide pathway. Curvularin (**221**) and 11-hydroxycurvularin (**482** and **484**) are the products of subsequent post-PKS transformations.

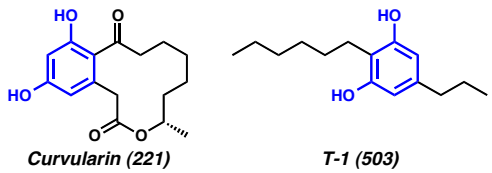
*Scheme 2.1. Proposed biosynthesis of curvularin (**221**).*



2.1.4 Biological Activity of (–)-Curvularin

Some of the earliest biological studies on curvularin and α,β-dehydrocurvularin demonstrated its cytotoxic activity toward sea urchin embryogenesis by acting as a spindle poison during cell division.[14] Curvularin was able to effectively inhibit cell division at concentrations of 2.5 μg/mL by disordering microtubule centers in centrosomes and inducing barrel-shaped spindles. α,β-Dehydrocurvularin was somewhat more active, inhibiting cell division at a concentration of 1.2 μg/mL. Itoh and co-workers noted that the efficacy of curvularin (**221**) is strikingly similar to a compound called T-1 (**503**) (Figure 2.5), which also possesses a 2,4-dihydroxybenzene core.[15] Although T-1 is about 100 times more active than curvularin, Itoh postulates that the 2,4-dihydroxybenzene moiety is required for induction of barrel-shaped spindles.

*Figure 2.5. Common structural motifs in curvularin (**221**) and T-1 (**503**).*



In addition to its effect on cell division, curvularin and related compounds are well known for their phytotoxicity. In fact, many of the known fungal sources of curvularin are plant pathogens. Studies by Robeson and co-workers determined LD_{50} values of 21 and 15 μg/mL for curvularin and α,β-dehydrocurvularin, respectively, in assays with cucumber protoplasts.[16]

The de Souza group has evaluated the antimycobacterial activity of curvularin and α,β-dehydrocurvularin against *Mycobacterium tuberculosis* H37Rv, a multiple drug-resistant bacteria responsible for tuberculosis.[17] The minimal inhibitory concentration (MIC) values for curvularin and α,β-dehydrocurvularin were 642 and 40 μmol/L, respectively. Furthermore, IC_{50} values were also determined to be 300 and 30 μmol/L for curvularin and α,β-dehydrocurvularin, respectively. In this study, which examined a range of natural isolates against *M. tuberculosis*, phenolic compounds displayed the greatest activity. Despite the significant antimycobacterial activity displayed by both these fungal isolates, the selectivity indices (SI) were only 0.47 and 0.75 for curvularin and α,β-dehydrocurvularin, respectively. It is generally accepted that SI values above 10 are good indications of the therapeutic safety and effectiveness of a potential drug candidate against tuberculosis.

In addition to *M. tuberculosis* H37Rv, curvularin and α,β-dehydrocurvularin have each been tested against a variety of fungal, bacterial, and tumor cell lines. Xie and coworkers found that curvularin and α,β-dehydrocurvularin were both weakly bioactive against the fungi *Saccharomyces cerevisiae* Hansen (MIC values of 750 and 375 μg/mL, respectively) and *Sclerotinia sclerotiorum* (MIC values of >3000 μg/mL, each).[18] Furthermore, α,β-dehydrocurvularin showed significant activity against the bacterial

strain *Staphylococcus aureus* (MIC value of 375 μg/mL), while curvularin was inactive against this strain.

This same study by Xie also examined the activity of curvularin and α,β-dehydrocurvularin against four cancer cell lines and determined IC_{50} values for each. The results are shown in Table 2.1, with Taxol activity shown for comparison.

Table 2.1. IC_{50} values of curvularin and α,β-dehydrocurvularin against cancer cell lines.

	A549	***HeLa***	***Ehrlich***	***MCF-7***
Curvularin	142.6	92.5	47.8	113.6
α,β-Dehydrocurvularin	15.3	10.3	20.4	19.8
Taxol	4.5	7.4	8.6	3.2

IC_{50} values in μg/mL

Most recently, curvularin was found to be an inhibitor of human-inducible nitric oxide synthase (iNOS) expression in the human epithelial alveolar cell line A549/8.[19] Aberrant iNOS expression, leading to excessive nitric oxide (NO) production, has been implicated in several human diseases, such as rheumatoid arthritis, multiple sclerosis, asthma, colitis, psoriasis, neurodegenerative diseases, as well as transplant rejection, tumor development, and septic shock. One approach to block iNOS-dependent NO production is the suppression of iNOS induction by targeting the interferon-γ Janus kinase and signal transducer and activator of transcription (IFN-γ-JAK-STAT) pathway with small molecules. Kleinert and co-workers have found that curvularin inhibits cytokine-induced activity of the human iNOS promoter, cytokine-induced iNOS mRNA expression, and cytokine-induced NO production in a concentration-dependent manner. From these studies, it appears that curvularin prevents tyrosine (Tyr701) phosphorylation of STAT1, thereby disrupting the IFN-γ-JAK-STAT pathway to iNOS induction.

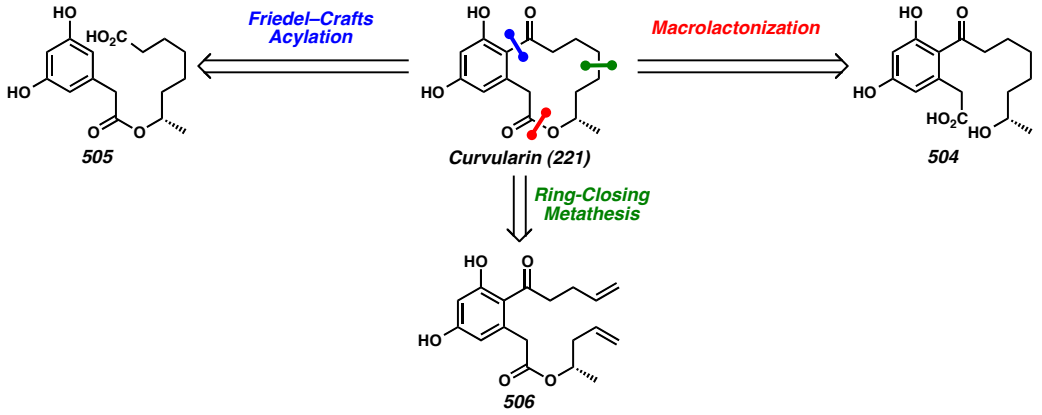
2.2 PREVIOUS SYNTHETIC EFFORTS TOWARD (–)-CURVULARIN

2.2.1 Introduction

There have been numerous synthetic efforts toward curvularin since its first isolation in 1956. Of these efforts, four have resulted in completed total syntheses of the natural product prior to our synthesis. Several other groups have completed syntheses of the benzannulated framework of curvularin as well as protected variants of the natural product.

While several approaches have been examined to forge the 12-membered benzannulated macrolactone, three strategies predominate. The most obvious disconnection for the 12-membered ring is along the C–O bond of the lactone to give a α,ω-hydroxyacid intermediate (**504**) (Scheme 2.2). However, despite the simplicity of this approach, all but one attempt in the literature to form this bond have failed (vide infra). Alternatively, the macrolactone of curvularin can be disconnected by an intramolecular Friedel–Crafts acylation of a symmetric resorcinol derivative (**505**). This is by far the most commonly reported method for generating the 12-membered ring. The final, and most recently applied, strategy for macrocyclization relies on a ring-closing metathesis (RCM) of an appropriately substituted α,ω-diene (**506**).

*Scheme 2.2. Common approaches toward curvularin (**221**).*



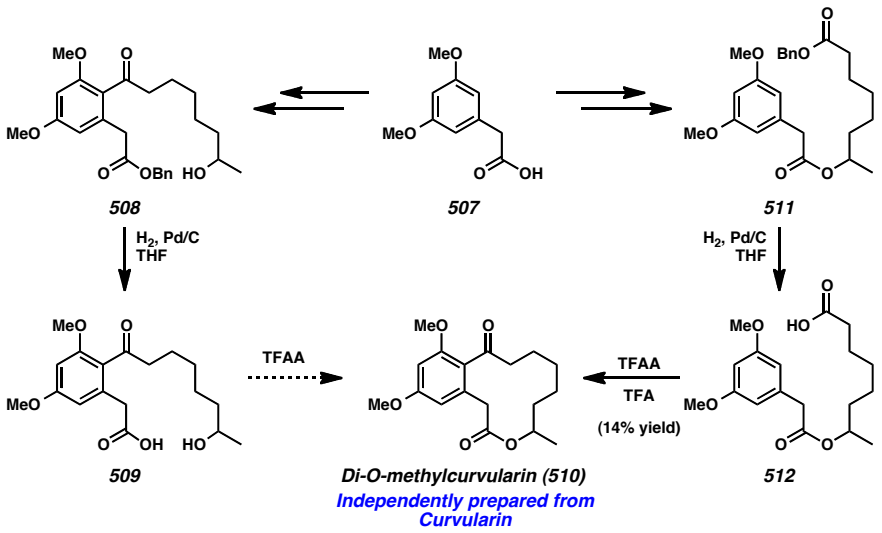
Although each of these disconnections provides access to the natural product, their common linear strategic approach imposes numerous limitations to synthetic efficiency. In general, to access the cyclization precursors (e.g., **504**–**506**), the required functionality must be built off a single aromatic ring. To prepare intermediates such as **504** and **506**, this means that each half of the 12-membered macrocycle is separately appended to the resorcinylic fragment.

2.2.2 Studies Toward the Total Synthesis of Curvularin

Some of the earliest synthetic studies toward curvularin were performed by Baker, Bycroft, and Roberts in an attempt to confirm the postulated structure of the natural product.[20] In their first report, several attempts were made to form the 12-membered ring by a macrolactonization event from hydroxyacid **509** (Scheme 2.3). Baker and co-workers note that all attempts to lactonize the hydroxyacid (**509**) using trifluoroacetic anhydride or DCC under a variety of conditions failed to yield any quantites of macrolactone **510**. Abandoning this approach, they turned their attention to an alternative disconnection involving an intramolecular Friedel–Crafts acylation of protected

resorcinol derivative **512** via benzyl ester **511**. In the event, treatment of carboxylic acid **512** with a mixture of trifluoroacetic acid and trifluoroacetic anhydride at room temperature provided di-*O*-methylcurvularin (**510**), albeit in only 14% isolated yield. With this compound in hand, a sample of curvularin (**221**) isolated from *Curvularia* was doubly methylated; the product of this reaction (**510**) matched the product of the Friedel–Crafts acylation (**510**), thus confirming the structure of curvularin (**221**). Importantly, Baker and co-workers never attempted to demethylate the two phenolic ethers of **510** to produce curvularin (**221**).

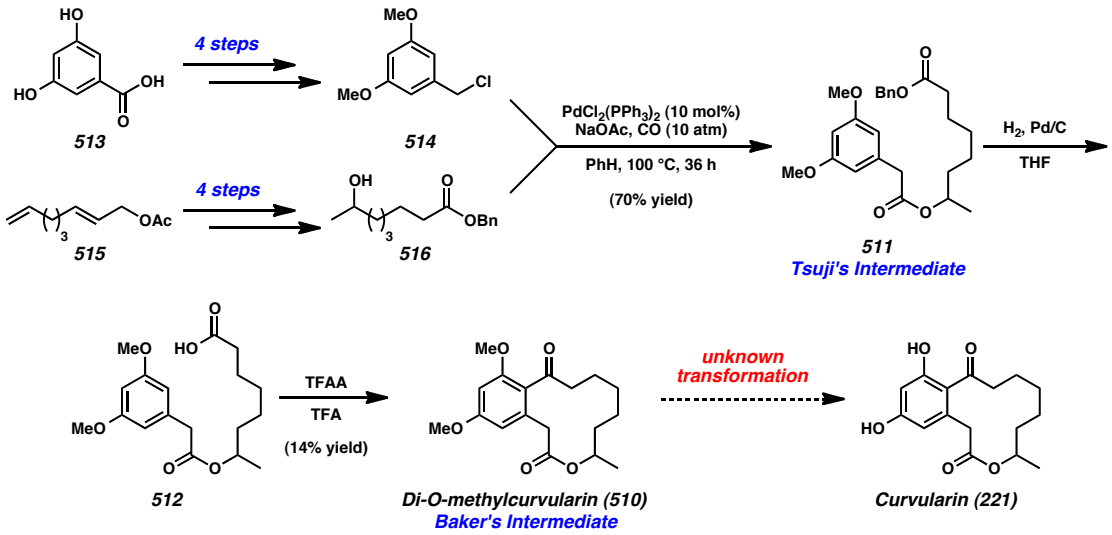
*Scheme 2.3. Baker's' approach to di-O-methylcurvularin (**510**).*



Following the structural proof of curvularin, Tsuji and co-workers sought to build the framework of curvularin in a more rapid fashion.[21] Their strategy focused on a carbonylative Pd-catalyzed coupling of a benzyl chloride (**514**) and a secondary alcohol (**516**) (Scheme 2.4). Secondary alcohol **516** was prepared in 4 steps from acetate **515**, while 3,5-dimethoxybenzyl chloride (**514**) was prepared in 4 steps from resorcinylic acid

513. Treatment of benzyl chloride **514** and secondary alcohol **516** with catalytic $PdCl_2(PPh_3)_2$ under an atmosphere of carbon monoxide generated ester **511** in 70% isolated yield. At this point, Tsuji and co-workers claim that the conversion of ester **511** to curvularin (**221**) is a known process, citing the early work of Baker and co-workers (vide supra). However, this appears to be an erroneous claim of a formal total synthesis of curvularin (**221**); ester **511** has only been converted to di-*O*-methylcurvularin (**510**) in previous literature reports. As previously stated, to date there are no reports of the conversion of di-*O*-methylcurvularin (**510**) to curvularin (**221**) by demethylation.

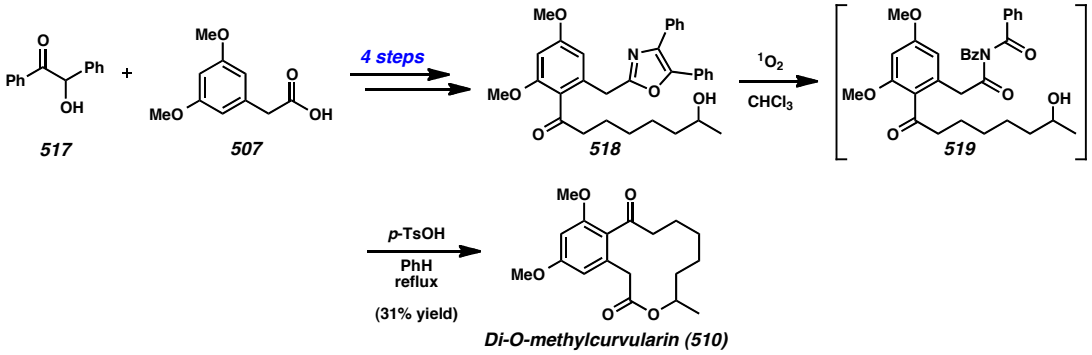
*Scheme 2.4. Tsuji's synthesis of di-O-methylcurvularin (**510**).*



Despite great effort to close the macrocycle of curvularin by macrolactonization reactions, only one report has demonstrated the viability of this approach. Wasserman and co-workers found that macrolactonization could be effected by masking the carboxylic acid functionality as a diphenyl oxazole.[22] Oxazole **518**, bearing a pendant secondary alcohol, was prepared in 4 steps from the known compounds α-hydroxy

ketone **517** and carboxylic acid **507** (Scheme 2.5). Upon reaction with singlet oxygen, the oxazole functionality (**518**) was converted to a reactive triimide (**519**), which was trapped by the pendant alcohol upon acidic activation to yield macrolactone **510**. This single example of macrolactonization directed toward curvularin resulted in the synthesis of di-*O*-methylcurvularin (**510**).

*Scheme 2.5. Wasserman's macrolactonization approach to di-O-methylcurvularin (**510**).*

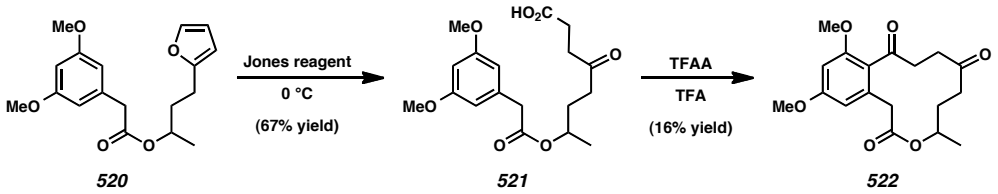


Subsequent to Wasserman's publication, Subba Rao and co-workers reported the same oxazole-based macrolactonization to produce di-*O*-methylcurvularin (**510**).[23] Like Tsuji, however, Subba Rao erroneously asserts that synthesis of di-*O*-methylcurvularin (**510**) constitutes a formal total synthesis of curvularin (**221**), citing the 1967 publication by Baker, Bycroft, and Roberts (vide supra).

Synthetic studies of compounds related to curvularin, both natural and non-natural, followed these early efforts toward the natural product's benzannulated ring system. The majority of these published reports use the ubiquitous intramolecular Friedel–Crafts acylation strategy to close the 12-membered lactone ring.

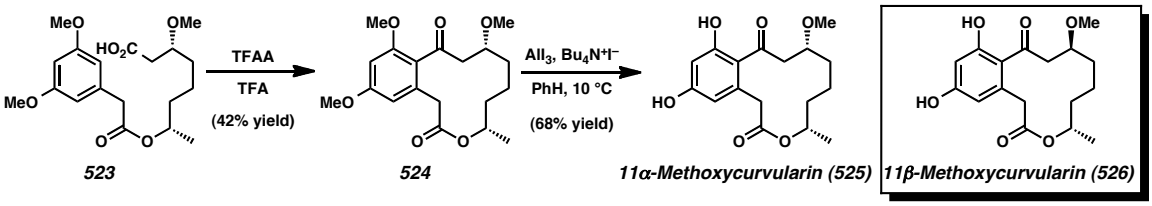
Ayyangar and co-workers targeted the framework of 12-oxocurvularin (**476**) and citreofuran (**486**) in their synthesis of di-*O*-methyl-12-oxocurvularin (**522**).[24] Following preparation of furan **520**, oxidative ring opening of the furan to ketoacid **521** and intramolecular Friedel–Crafts acylation provided di-*O*-methyl-12-oxocurvularin (**522**) in 16% yield (Scheme 2.6).

*Scheme 2.6. Ayyangar's synthesis of di-O-methyl-12-oxocurvularin (**522**).*



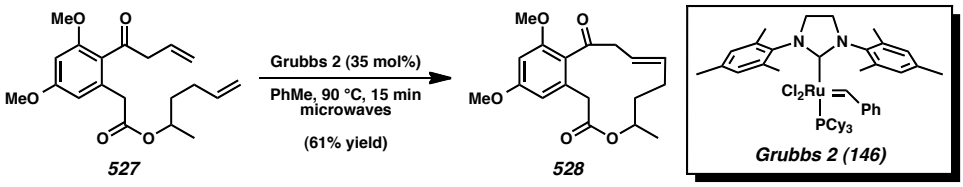
Similarly, Pan and co-workers completed the first total syntheses of the natural products 11α- (**525**) and 11β-methoxycurvularin (**526**).[25] Intramolecular Friedel–Crafts acylation of β-methoxyacid **523** resulted in a 42% isolated yield of macrocycle **524**, a significantly higher yield than that reported for substrates lacking the methoxy group (Scheme 2.7). Furthermore, this report is the only one in which the methyl ethers were successfully cleaved, revealing the resorcinol core and furnishing the natural product. Although the synthetic sequence shown only includes 11α-methoxycurvularin (**525**), the same sequence was executed for the 11β-diastereomer (**526**). Subsequent to Pan's report, Yadav and co-workers utilized the same final two transformations to generate these natural products in nearly identical yields.[26]

*Scheme 2.7. Pan's synthesis of 11α- (**525**) and 11β-methoxycurvularin (**526**).*



The final synthetic study of the curvularin framework was reported by Kuwahara and co-workers and employed a ring-closing metathesis (RCM) to close the 12-membered macrolactone.[27] Kuwahara notes that this highy optimized RCM, which required microwave irradiation with 35 mol% catalyst **146**, only generated the desired product (**528**) as the *E*-isomer and without any undesired olefin migration (Scheme 2.8). Furthermore, cleavage of the two methyl ethers proved to be unsuccessful with a variety of Lewis acids.

*Scheme 2.8. Kuwahara's RCM approach to curvularin (**221**).*

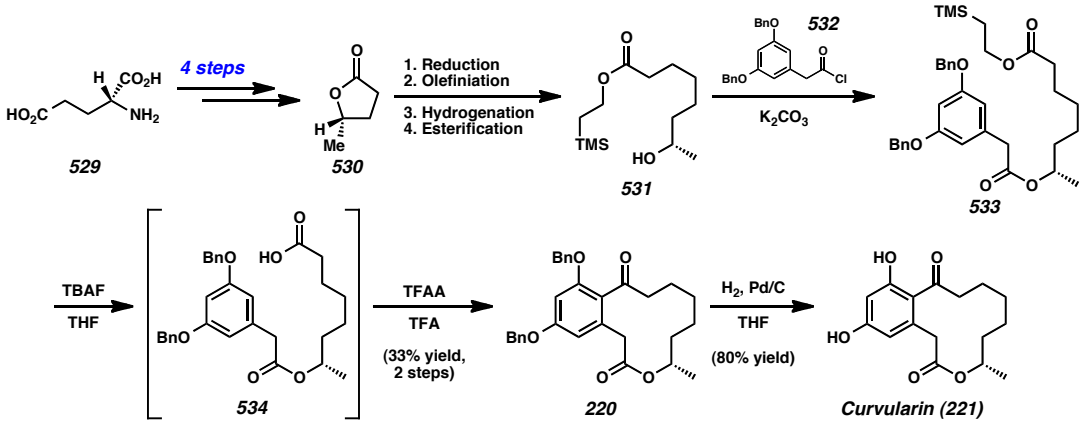


2.2.3 Previous Total Syntheses of Curvularin

The first total synthesis of curvularin was reported in 1977 by Gerlach.[28] Building upon difficulties reported by previous groups (vide supra), Gerlach protected the resorcinol of curvularin at an early stage with removable benzyl groups and relied on an intramolecular Friedel–Crafts acylation of 2-(trimethylsilyl)ethyl ester **533** to forge the

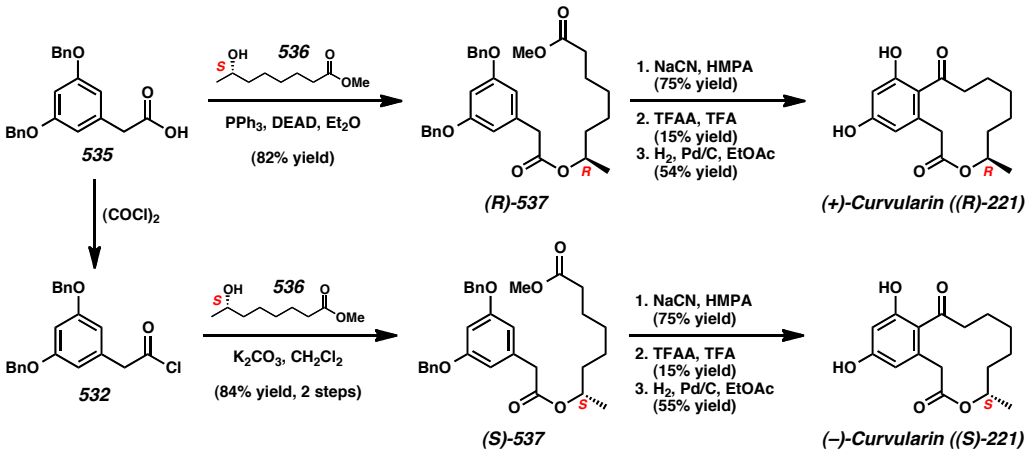
12-membered macrolactone (Scheme 2.9). Following the racemic synthesis of curvularin by this route, Gerlach rendered the route enantioselective by beginning his synthesis with (–)-(*S*)-γ-valerolactone (**530**). It is unclear exactly how the chiral (*S*)-γ-valerolactone was prepared and subsequently advanced to chiral ester **531**, since the synthetic sequence is not explicitly shown. However, it appears from the references in this report that chiral lactone **530** was prepared from (*R*)-glutamic acid (**529**) over a series of four steps. From this point, likely reduction of lactone **530** to the lactol, olefination, hydrogenation, and esterification with 2-trimethylsilylethanol could have produced the hydroxyester (**531**) used in the racemic synthesis of curvularin. Secondary alcohol **531** was next acylated with acyl chloride **532** to yield diester **533**, which, upon exposure to a fluoride source, provided acid **534**. In the final two steps of the synthesis, intramolecular Friedel–Crafts acylation and hydrogenolysis of the benzyl ethers furnished the natural product, (–)-curvularin (**221**), in eight linear steps from (*S*)-γ-valerolactone (**530**).

*Scheme 2.9. Gerlach's total synthesis of (–)-curvularin (**221**).*



The second synthesis of curvularin was published in 1997 by Bracher and Schulte and employs an enantiodivergent route to access both enantiomers of curvularin from a single enantiomer of secondary alcohol **(*S*)-536** (available in 2 synthetic steps from (*S*)-propylene oxide) (Scheme 2.10).[29] Beginning with carboxylic acid **535**, Mitsunobu reaction with secondary alcohol **(*S*)-536** provided ester **(*R*)-537** with complete inversion of stereochemistry. Alternatively, conversion of the acid (**535**) to the acid chloride (**532**) and esterification with secondary alcohol **(*S*)-536** yielded ester **(*S*)-537**. Intermediates **(*S*)-537** and **(*R*)-537** were then each advanced through a sequence involving saponification of the methyl ester, intramolecular Friedel–Crafts acylation, and debenzylation to furnish (*S*)- and (*R*)-curvularin, respectively, in six linear steps from (*S*)-propylene oxide.

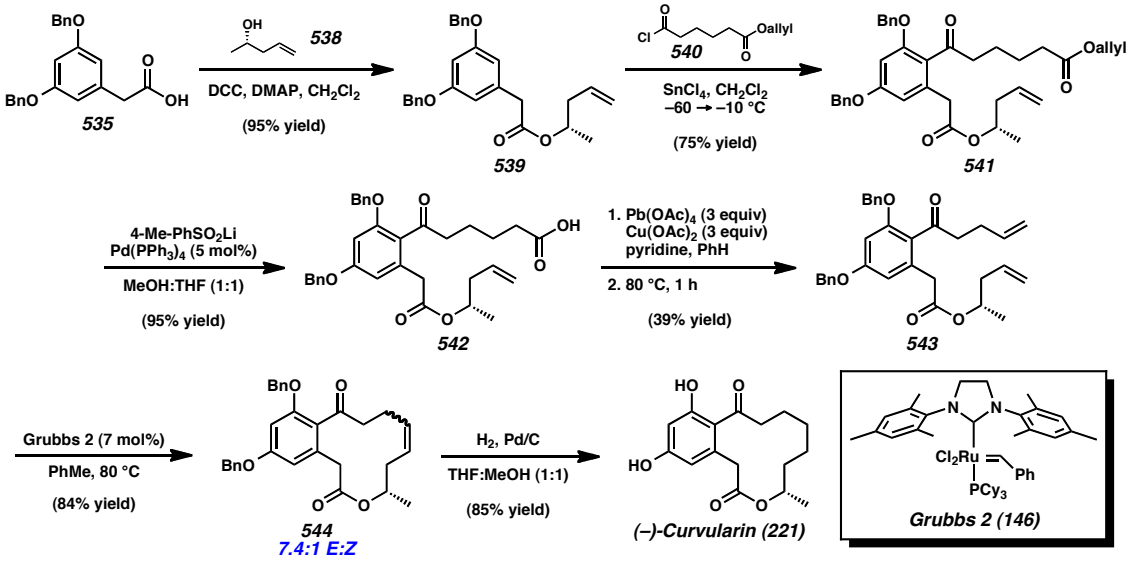
*Scheme 2.10. Bracher's total synthesis of (–)- and (+)-curvularin (**221**).*



More recently, alternative strategies to close the macrolactone of curvularin have been investigated. In particular, ring-closing metathesis has proven to be a viable method to construct the 12-membered ring in significantly higher yields than the ubiquitous

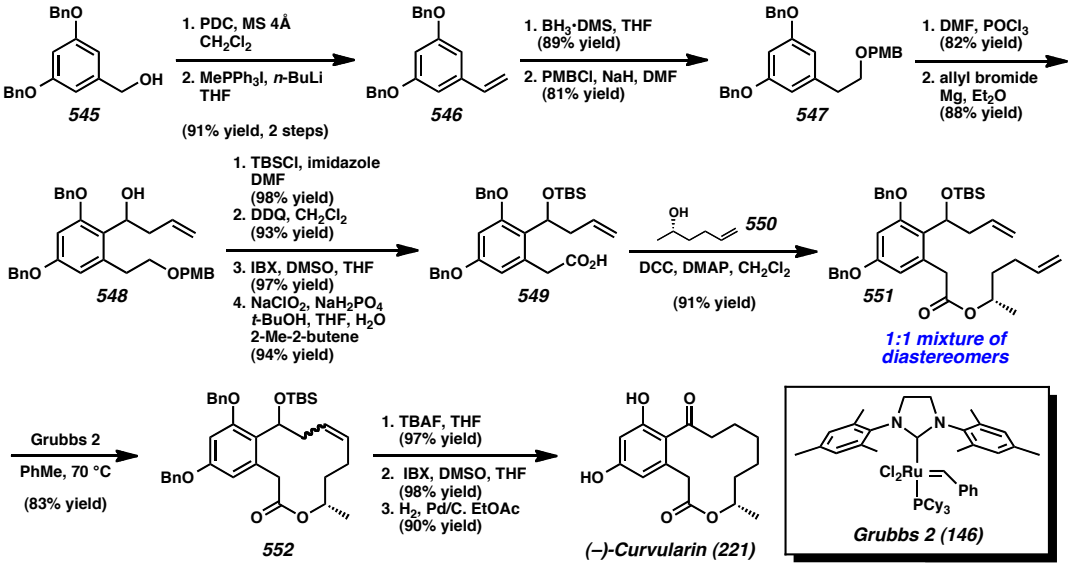
intramolecular Friedel–Crafts acylation reaction. In 2008, Kunz first published a RCM approach to curvularin and several analogs for biological studies.[30] Preparation of a RCM substrate began with coupling of acid **535** and chiral secondary alcohol **538** to generate ester **539** (Scheme 2.11). Intermolecular Friedel–Crafts acylation of ester **539** with adipic acid derivative **540** (available in two steps from adipic acid) led to allyl ester **541**, which was subsequently deallylated by palladium catalysis to yield the acid (**542**). Kochi decarboxylation of carboxylic acid **542** then provided diene **543** in a modest 39% yield for RCM studies. Upon treatment with the Grubbs 2nd generation catalyst in toluene at 80 °C, diene **543** underwent smooth ring closing to produce macrloactone **544** in 84% yield and as a 7.4:1 mixture of E:Z olefin isomers. Finally, reduction of the olefin and debenzylation were accomplished simultaneously under palladium reduction conditions to yield (–)-curvularin (**221**) in seven linear steps from adipic acid.

*Scheme 2.11. Kunz's total synthesis of (–)-curvularin (**221**).*



The final reported total synthesis of curvularin, by Mohapatra and co-workers, also utilizes a RCM to close the 12-membered ring.[31] However, RCM along the C(11)–C(12) bond was targeted instead of the C(12)–C(13) bond, as in the synthesis by Kunz. The result is a synthesis that is longer than Kunz's and includes significant protecting group manipulation. Beginning with benzyl alcohol **545**, oxidation and Wittig olefination provided styrene **546** (Scheme 2.12). This intermediate (**546**) was converted to the primary PMB-protected alcohol (**547**) by hydroboration, oxidation, and alkylation with PMBCl. Arene **547** was formylated with DMF and subsequently allylated to generate benzyl alcohol **548**. Protection of the secondary alcohol as a silyl ether followed by cleavage of the PMB ether and two-step oxidation furnished carboxylic acid **549**. Acid **549** was next coupled to chiral secondary alcohol **550**, yielding diene **551** as a 1:1 mixture of diastereomers. Ring-closing metathesis of diene **551** with Grubbs 2nd generation catalyst (**146**) resulted in macrolactone **552** as an unspecified mixture of E and Z isomers in a combined 83% yield. In the final steps of the synthesis, the secondary alcohol was desilylated and oxidized, and the olefin and benzyl ethers were reduced to provide (–)-curvularin (**221**) in 15 linear steps from benzyl alcohol **545**.

*Scheme 2.12. Mohapatra's total synthesis of (–)-curvularin (**221**).*

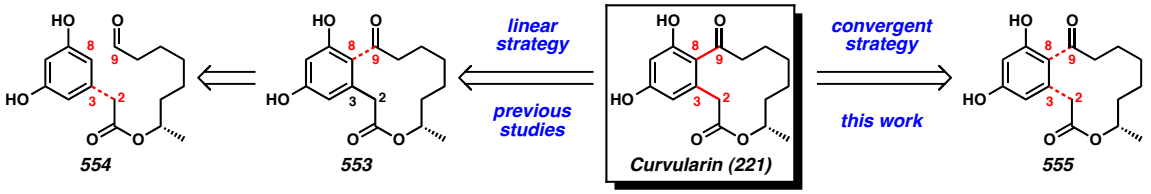


2.3 A CONVERGENT APPROACH TO (–)-CURVULARIN

2.3.1 Retrosynthetic Analysis

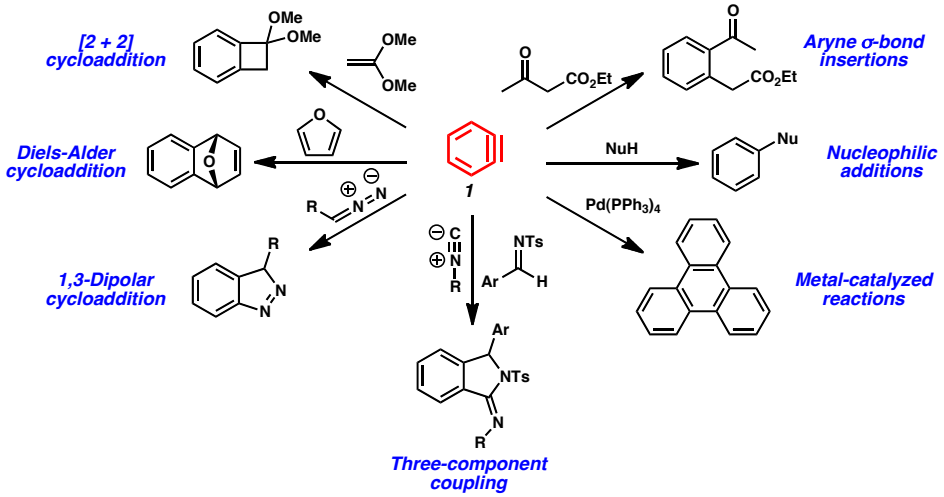
The common feature of the three approaches (i.e., macrolactonization, intramolecular Friedel–Crafts acylation, and ring-closing metathesis) employed toward the synthesis of the curvularin framework is that they all require a stepwise formation of the C(2)–C(3) and C(8)–C(9) bonds that connect the resorcinylic core to the macrolactone (Scheme 2.13). In designing our strategy toward the curvularin scaffold, we aimed to eliminate this linearity in the synthesis by convergently bringing together two separate fragments: an aromatic fragment and a macrolactone fragment (i.e., **555**). In doing so, we sought to form both the C(2)–C(3) and the C(8)–C(9) bonds in a single transformation.

*Scheme 2.13. Comparison of previous linear approaches to curvularin (**221**) to a convergent assembly strategy.*



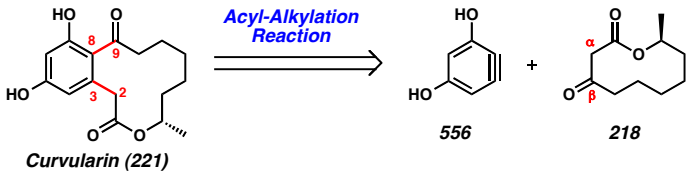
One powerful strategy for achieving a convergent assembly of curvularin is to employ aryne intermediates in order to form the C(8)–C(9) and C(2)–C(3) concomitantly. Throughout their history, arynes have demonstrated versatile reactivity, participating in cycloaddition, polar, multicomponent, and even transition metal-catalyzed reactions (Scheme 2.14).[32,33] Beyond their diverse modes of reactivity, arynes have the ability to form two new carbon–carbon or carbon–heteroatom bonds to the aromatic ring in a single step, allowing for a rapid and convergent synthesis of highly functionalized arenes. One facet of aryne reactivity that is critical to their application in synthesis is the regioselectivity with which unsymmetrically substituted arynes undergo addition.[34] When they bear polarizing substitution, exquisite levels of regioselectivity are often achievable, permitting the preparation of highly functionalized unsymmetrically substituted arene products.[35] Because of these properties as reactive intermediates, arynes provide an excellent alternative to well-known classical methods of aromatic functionalization that have significant limitations.

*Scheme 2.14. Representative reactions of benzyne (**1**).*



For these reasons, we targeted curvularin using an acyl-alkylation reaction of an appropriately substituted aryne (**556**) with a β-ketolactone (**218**) (Scheme 2.15). This powerful transformation, developed by our group in 2005, represents a formal insertion into the C(α)–C(β) bond of the β-ketolactone (**218**), forms two new C–C bonds in a single synthetic step (C(2)–C(3) and C(8)–C(9)), and expands the β-ketolactone (**218**) by two carbons. This strategic disconnection is the cornerstone of our rapid and convergent synthesis of (–)-curvularin. To this point, however, the acyl-alkylation reaction of an aryne with a lactone substrate had never been examined. As such, we sought to answer two key questions before embarking on our synthetic effort: 1) whether β-ketolactone **218** would be a competent acyl-alkylation substrate and 2) whether an unsymmetrical aryne such as **556** could react in a regioselective manner to give only the acyl-alkylation product that corresponds to the structure of curvularin.

*Scheme 2.15. Retrosynthetic analysis of (–)-curvularin (**221**).*



2.3.2 The Direct Acyl-Alkylation of Arynes: Discovery and Substrate Scope [†,36,37]

Traditionally, the Stoltz lab has sought to develop new and innovative methods to synthesize all-carbon quaternary stereocenters.[38] As part of these efforts, we envisioned that electrophilic arynes could serve as substrates for the formation of benzylic all-carbon quaternary centers. Specifically, we postulated that arynes, generated from *o*-silyl aryl triflate precursors[39] (**209**) by the action of fluoride ion, could undergo addition by a β-ketoester substrate (**557**) to produce α-quaternary-β-ketoesters, such as **558** (Scheme 2.16). To our surprise, though, α-arylation product **558** was the minor product of the process; the major product was acyl-alkylated arene **559**. The acyl-alkylation product (**559**) is the result of benzyne insertion into the α,β C–C bond of the β-ketoester and presumably occurs by a formal [2 + 2] cycloaddition/fragmentation cascade (i.e., **560** → **561** → **562** → **563**). This result represents the first mild and direct aryne insertion into a carbon–carbon bond.[40,41]

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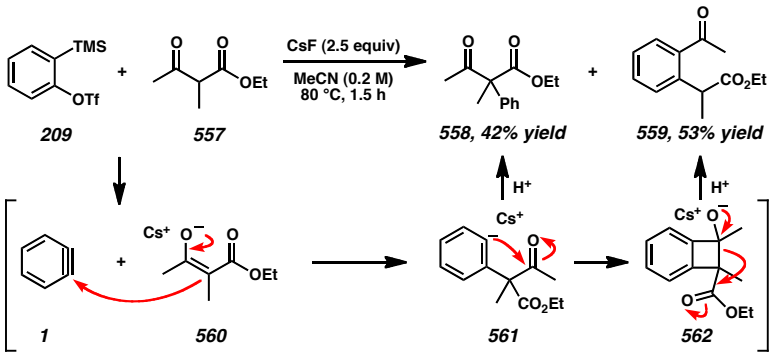
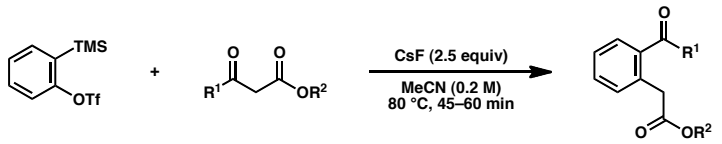
† The work described in this section was performed by former Stoltz group graduate students Prof. Uttam K. Tambar and Dr. David C. Ebner. The initial discovery of the acyl-alkylation of arynes, reaction optimization, and substrate scope investigations were carried out by Prof. Uttam K. Tambar.

Scheme 2.16. The direct acyl-alkylation of arynes.

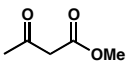
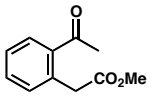
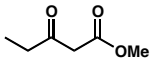
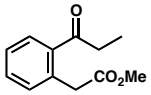
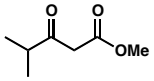
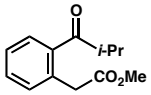
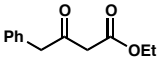
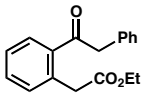
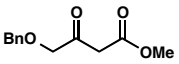
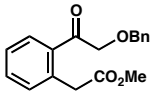
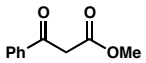
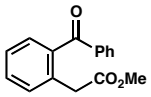
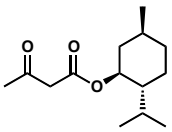
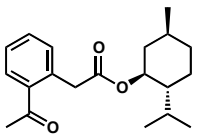
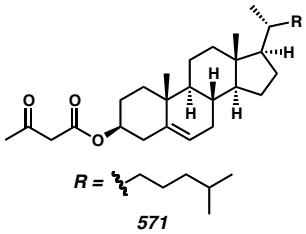
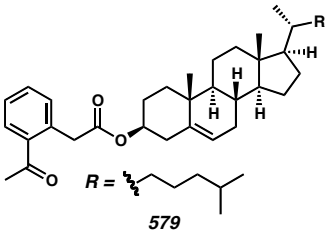


Following brief optimization studies to minimize the formation of α-arylation side products, the substrate scope of this process was investigated. In general, we found that β-ketoesters possessing α-substitution furnish higher levels of α-arylation side product than β-ketoesters lacking substitution at this position. Examination of a range of α-unsubstituted-β-ketoesters resulted in a wide range of acyl-alkylation products bearing aliphatic (**572**–**574**), aryl (**577**), benzyl (**575**), and heteroatomic substitution (**576**) (Table 2.2). Additionally, the ester moiety may be varied while maintaining good yields (**578** and **579**). Furthermore, the reaction of methyl acetoacetate (**229**) with *o*-silyl aryl triflate **209** can be performed on scales greater than five grams and has been the subject of an *Organic Syntheses* procedure.[36b]

Table 2.2. Acyl-alkylation of arynes substrate scope: substituted β-ketoesters.



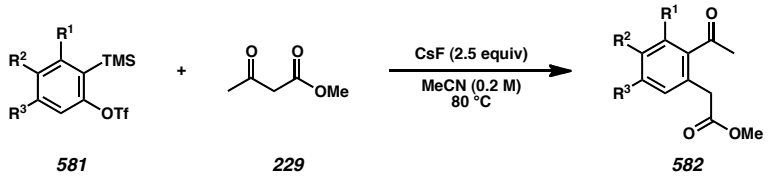
209 ***563*** ***564***

entry	β-ketoester[a]	product	yield
1	 ***229***	 ***572***	90%
2	 ***565***	 ***573***	78%
3	 ***566***	 ***574***	84%
4[b]	 ***567***	 ***575***	85%
5	 ***568***	 ***576***	53%
6	 ***569***	 ***577***	99%
7	 ***570***	 ***578***	72%
8	 ***571***	 ***579***	75%

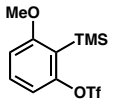
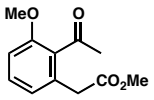
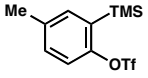
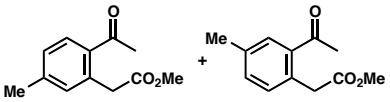
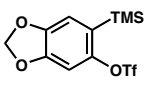
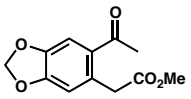
[a] Reaction performed with 1.25 equiv *ortho*-silyl aryl triflate ***209*** relative to β-ketoester ***563***.
[b] Reaction performed with 2 equiv *ortho*-silyl aryl triflate ***209*** relative to β-ketoester ***567***.

We next turned our attention to examination of substitution on the silyl aryl triflate reaction partners. These early studies showed that substituted silyl aryl triflates bearing monosubstitution at the *ortho* (**441**) and *meta* (**583**) positions as well as disubstitution (**212**) produced the corresponding acyl-alkylated arenes (**584**–**587**) in good yields (Table 2.3). Of particular note is the complete regioselectivity observed for the reaction of an *ortho*-methoxy aryne to furnish acyl-alkylation product **584** as a single isomer. This indicates a likely stepwise mechanism leading to the key alkoxybenzocyclobutene intermediate (**562**) featured in Scheme 2.16. In the case of less polarizing substituents on the aryne precursor, such as methyl silyl aryl triflate **583**, little to no selectivity for a given acyl-alkylation isomer was observed (**585** and **586**).

Table 2.3. Acyl-alkylation of arynes substrate scope: substituted silyl aryl triflates.



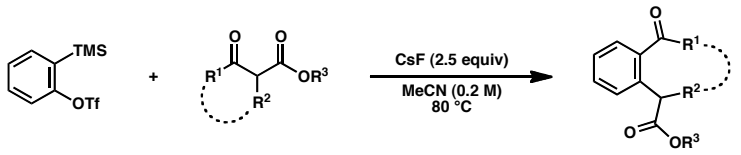
581 ***229*** ***582***

entry	*ortho*-silyl aryl triflate[a]	product	yield
1	 ***441***	 ***584***	95%
2[b]	 ***583***	 ***585*** ***586***	82% (1 : 1)
3	 ***212***	 ***587***	75%

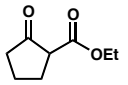
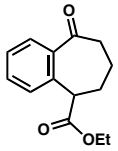
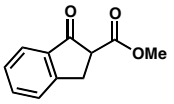
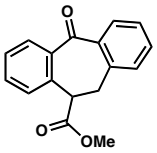
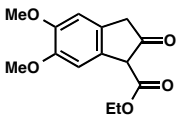
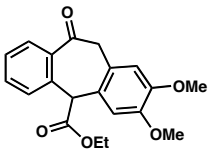
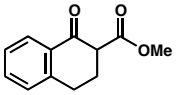
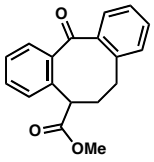
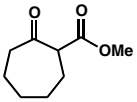
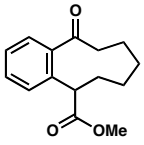
[a] Reaction performed with 2 equiv *ortho*-silyl aryl triflate ***581*** relative to β-ketoester ***229***.
[b] Reaction performed with 1.25 equiv *ortho*-silyl aryl triflate ***583*** relative to β-ketoester ***229***.

An interesting variation on the acyl-alkylation was uncovered when linear β-ketoesters were replaced with cyclic β-ketoesters. Although these β-ketoester substrates contain substitution at the α-position (**590–593**, **213**), they underwent facile acyl-alkylation to yield benzannulated acyl-alkylation products that were ring-expanded by two carbon atoms. The medium-sized rings furnished by this process continue to be difficult structures to synthesize despite their prevalence in natural products and drug substances.[42] However, application of our optimized acyl-alkylation conditions to a series of cyclic β-ketoesters (**590–593**, **213**) led to formation of a range of bi- and tricyclic benzannulated carbocycles (**594–598**) in good yields (Table 2.4). Importantly, the reaction conditions are not limited to those employing CsF in acetonitrile, and often yields can be increased by altering the fluoride source, solvent, and temperature of these transformation. For example, the product in entry 1 of Table 2.4 can be obtained in 93% yield upon use of KF/18-crown-6 in THF at room temperature (Scheme 2.17)

Table 2.4. Ring-expansive acyl-alkylation reactions.

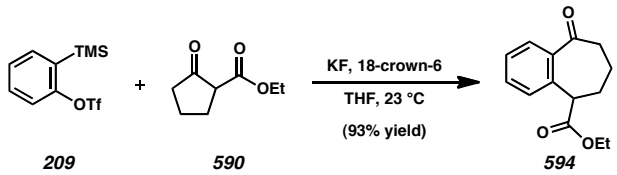


209 ***588*** ***589***

entry	β-ketoester[a]	product	yield[b]
1	 ***590***	 ***594***	50%
2	 ***591***	 ***595***	61%
3	 ***213***	 ***596***	65%
4	 ***592***	 ***597***	45%
5	 ***593***	 ***598***	69%

[a] Reaction performed with 1.25 equiv *ortho*-silyl aryl triflate ***209*** relative to β-ketoester ***588.***
[b] The α-arylated β-ketoester was isolated as the major side product in these reactions.

*Scheme 2.17. Optimized ring-expansive acyl-alkylation of silyl aryl triflate **209** and cylic β-ketoester **590**.*



209 *590* *594*

2.3.3 Regioselective Acyl-Alkylation of Highly Substituted Arynes[†,35]

It has been well established that substituted arynes undergo nucleophilic attack with levels of regioselectivity dependent on the identity of substituents and their locations relative to the reactive aryne triple bond.[34] In our own investigations, we have observed fully regioselective acyl-alkylation (i.e., **584**) with the aryne (**599**) generated in situ from a 3-methoxy-substituted silyl aryl triflate (**441**) (Scheme 2.18). Beyond this example, we have observed similar regioselectivity in aryne heteroannulation reactions of *N*-acyl dehydroamino esters with the same silyl aryl triflate precursor (**441**) to yield methoxy-substituted isoquinoline **600**.[43] Each of these products (**584** and **600**) stems presumably from initial attack at C(1) of the aryne (**599**), which suggests that the *ortho*-methoxy substituent electronically polarizes the triple bond and sterically shields the adjacent atom to favor this reactivity. More recently, we have been able to exploit this selectivity in aryne acyl-alkylation/condensation sequences to produce either substituted hydroxynaphthoquinones (**602**) or hydroxyisoquinolines (**601**).[44] These observations led us to investigate whether more highly functionalized silyl aryl triflates would also exhibit the predicted regioselectivity seen for silyl aryl triflate **441**.

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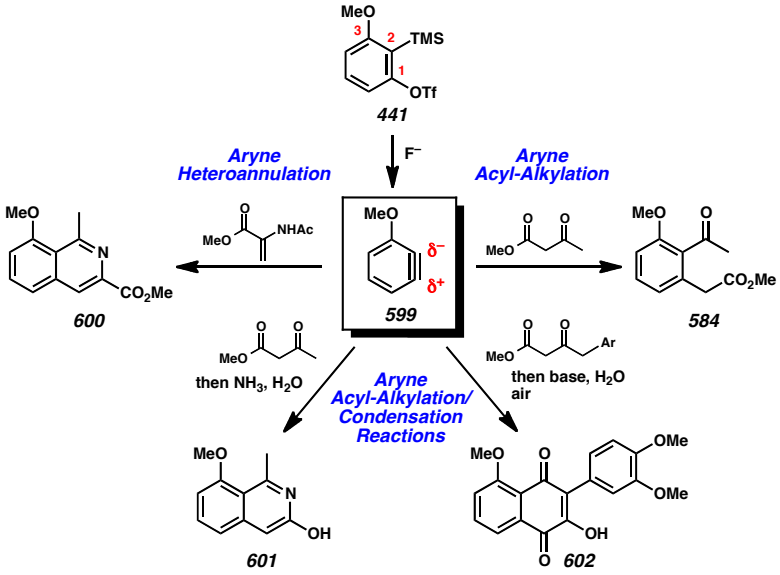
† The work described in this section was completed in collaboration with Christopher D. Gilmore, a current graduate student in the Stotltz research group, and Pradeep Bugga, a former undergraduate researcher in the Stoltz group.

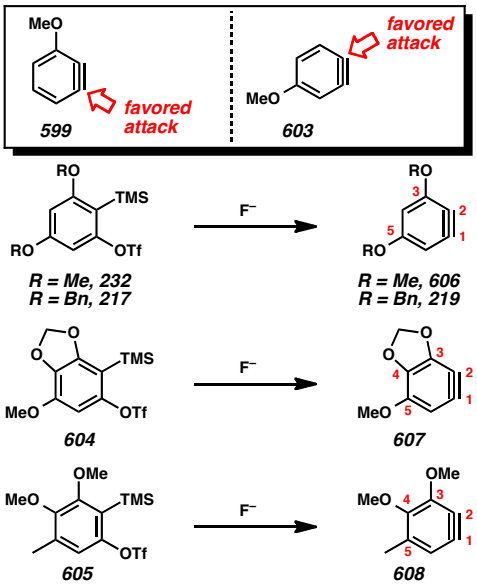
*Scheme 2.18. Regioselective reactions of 3-methoxybenzyne (**599**).*



Specifically, we chose to examine whether unsymmetrically substituted polyalkoxy silyl aryl triflates would react regioselectively. Similar to the 3-methoxy aryne (**599**), 4-methoxy aryne **603** also reacts in a regioselective manner,[45,41n] although more modestly than aryne **599** (Scheme 2.19). On the basis of these data, we chose to examine two silyl aryl triflates (**232** and **217**) bearing alkoxy groups at both C(3) and C(5), in which it is possible for the two alkoxy substituents to favor opposing sites of nucleophilic attack upon the aryne triple bond (**606** and **219**). Investigation of the reactivity of precursors **232** and **217** would establish whether the influence exerted by the C(3) substituent can override that of the C(5) alkoxy group. Two additional silyl aryl triflates (**604** and **605**) we have targeted feature methoxy groups at C(3) and C(4) of the arynes (**607** and **608**), offering the potential for enhanced selectivity due to cooperative electronic polarization of the triple bond. Furthermore, precursors **604** and **605** incorporate additional substitution at C(5); to the best of our knowledge, arynes **607** and

608 are the first examples of trisubstituted arynes derived from silyl aryl triflate precursors.[46]

Scheme 2.19. Targeted polyalkoxy arynes.

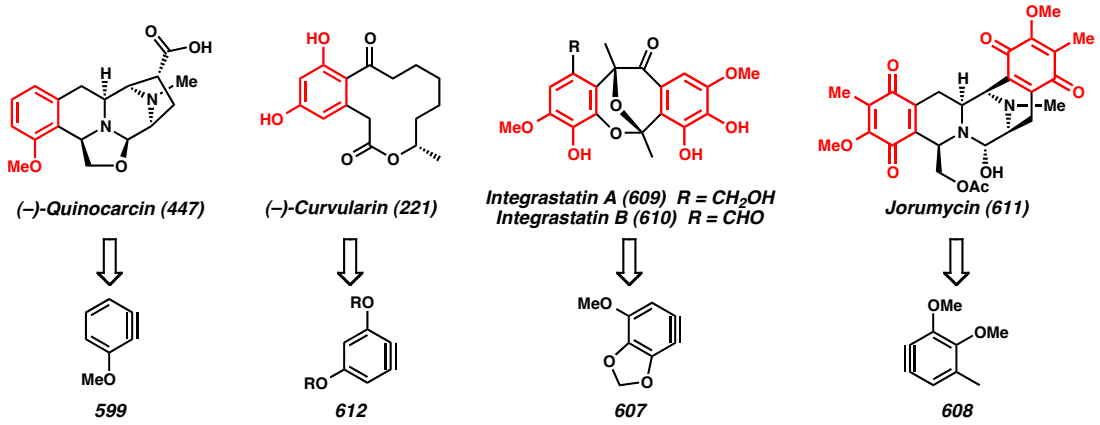


On the basis of the observation that aryne adducts derived from the 3-methoxy silyl aryl triflate (**599**) have been employed in the context of total synthesis (Figure 2.6, **447**),[47] we believe that these more highly substituted nonsymmetrical precursors (**607**, **608**, and **612**) will provide valuable entry points into more complex natural products (e.g., **221**, **609**, **610**, and **611**) were they also to react in a regioselective manner. In general, the use of aryne-based methods enables the convergent construction of functionalized arenes, thereby circumventing the difficulties associated with traditional late-stage elaboration of embedded aromatic rings.

As a demonstration of the advantages of this strategy, we report the synthesis and regioselective reactions of four novel silyl aryl triflates (**217**, **232**, **604**, and **605**) and the

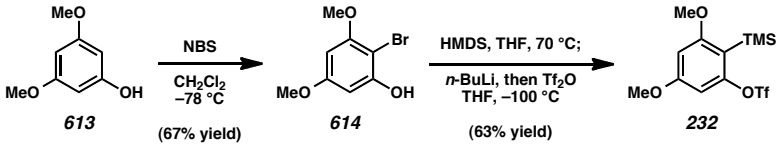
application of one of these precursors (**217**) to the synthesis of a simple hydroxynaphthoquinone natural product. In fact, these particular aromatic substitution motifs were targeted for their prevalence in classes of natural products that possess both diverse structures and significant biological activity (**447**, **221**, **609**, **610**, and **611**).

Figure 2.6. Representative natural products containing highly oxygenated arenes.



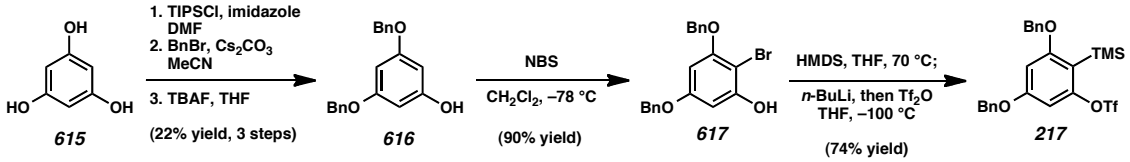
The first aryne precursor we targeted was a protected resorcinylic silyl aryl triflate (**232**) (Scheme 2.20). Preparation of dimethoxy silyl aryl triflate **232** began with bromination of commercially available 3,5-dimethoxyphenol (**613**) at low temperature to form *o*-bromophenol **614**. This compound was then converted to the silyl aryl triflate (**232**) by a known one-pot procedure involving silylation of the phenol, lithium-halogen exchange, silyl group migration, and triflation.[48]

*Scheme 2.20. Preparation of silyl aryl triflate **232**.*



Although dimethoxy silyl aryl triflate **232** contains functionality present in several natural products, removal of the methyl groups would be required to access a large number of these targets.[49] To avoid the potentially harsh Lewis acidic conditions commonly used to cleave the methyl groups (e.g., BCl_3),[50] we designed a dibenzyl variant of precursor **217** (Scheme 2.21). Beginning with phloroglucinol (**615**), a sequence including monosilylation, dibenzylation, and desilylation generated phenol **616**, which was subsequently brominated to produce bromophenol **617**. Bromophenol **617** was then converted to silyl aryl triflate **217** as before.

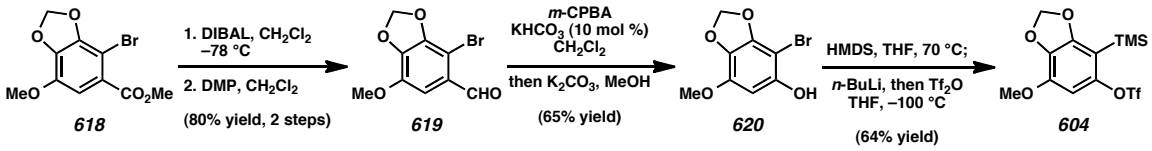
*Scheme 2.21. Preparation of silyl aryl triflate **217**.*



Following our preparation of silyl aryl triflates **232** and **217**, we progressed to more highly substituted variants. Specifically, we targeted a trioxygenated aryne derived from silyl aryl triflate **604** (Scheme 2.22). Beginning with brominated methyl gallate derivative **618**,[51] reduction with DIBAL followed by Dess–Martin oxidation provided aldehyde **619** in excellent yield. Baeyer–Villiger oxidation with *m*-CPBA and basic

methanolysis of the resulting formate ester produced bromophenol **620**, which was readily converted into silyl aryl triflate **604**.

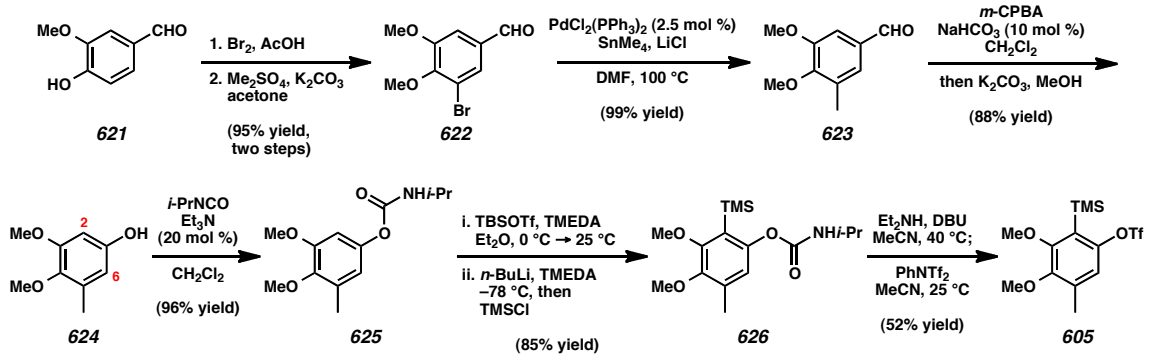
*Scheme 2.22. Preparation of silyl aryl triflate **604**.*



We next turned our attention to the preparation of silyl aryl triflate **605** because of the prevalence of its substitution motif in several bioactive natural products. We began with a regioselective bromination of vanillin (**621**) to provide exclusively the 5-bromo product, which was methylated to produce bromo dimethoxy benzaldehyde **622** (Scheme 2.23).[52] Next, Stille coupling of the bromoarene (**622**) with tetramethyltin enabled the introduction of the 5-methyl substituent to generate arene **623**.[53] Further elaboration of this intermediate via one-pot Baeyer–Villiger oxidation and cleavage of the resultant formate ester yielded intermediate phenol **624**. All attempts to install a bromide selectively at C(2) of phenol **624** failed, instead resulting in exclusive bromination at C(6). In order to selectively functionalize phenol **624**, we turned to a recently disclosed 3-step procedure for the general synthesis of *o*-silyl aryl triflates by Garg, et al.[54] Analysis of this approach indicated that conversion of the phenol to a carbamate might facilitate silylation at C(2) over C(6). Application of this sequence to our intermediate (**624**) allowed the direct *ortho*-silylation of carbamate **625** to produce the 2-silyl carbamate (**626**) exclusively. Subsequent cleavage of the carbamate and triflation of the

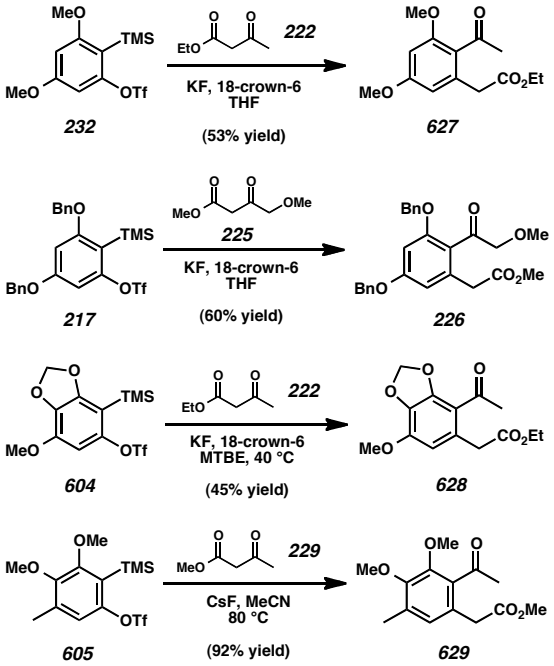
resulting phenoxide furnished the desired aryne precursor (**605**) in 5 steps from known aldehyde **623**.

*Scheme 2.23. Preparation of silyl aryl triflate **605** by directed ortho-lithiation of phenol derivative **625**.*



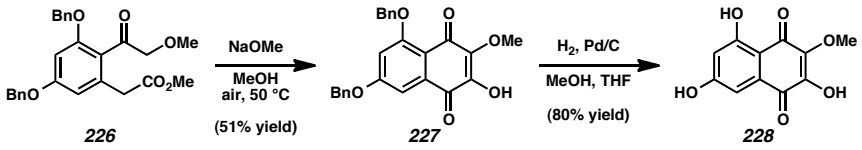
Following preparation of silyl aryl triflates **217**, **232**, **604**, and **605**, we examined their reactivities in acyl-alkylation reactions with various β-ketoesters (**222**, **225**, and **229**) (Scheme 2.24).[55] To our delight, in each of these reactions only a single insertion product was observed. For silyl aryl triflates **232** and **217**, the closer *o*-alkoxy substituent completely overrides any influence of the distal alkoxy group. In the case of acyl-alkylation of precursors **604** and **605**, slightly modified conditions varying solvent and fluoride sources were required to generate the desired products. The presence of methoxy groups at both the *ortho* and *meta* positions of the arynes derived from **604** and **605** potentially influences the regioselectivity of their reactions in a cooperative manner.

*Scheme 2.24. Acyl-alkylation reactions of polyalkoxy silyl aryl triflates **232**, **217**, **604**, and **605**.*



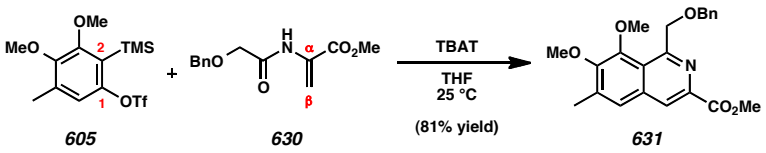
Furthermore, we were able to verify the regioselective formation of arene **226** in the acyl-alkylation of silyl aryl triflate **217** with β-ketoester **225** by its conversion to a naturally occurring hydroxynaphthoquinone (**228**),[56] previously isolated from a species of the fungus *Cercosporta* (Scheme 2.25). Cyclization and oxidation of ketoester **226** under basic conditions yielded quinone **227**. Subsequent debenzylation produced hydroxynaphthoquinone **228**, thus confirming the structure of arene **226**.[44,57]

*Scheme 2.25. Conversion of ketoester **226** to Cercospora isolate **228**.*



In addition to acyl-alkylaton, exposure of silyl aryl triflate **605** to tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) in the presence of *N*-acyl enamine **630** produced a single isomer of the product isoquinoline (**631**) in good yield (Scheme 2.26).[43] Indeed, **631** corresponds to the isoquinoline produced from initial C(β) nucleophilic addition of enamide **630** at C(1) of the aryne derived from precursor **605**.

*Scheme 2.26. Regioselective aryne heteroannulation of enamide **630** with silyl aryl triflate **605** to yield isoquinoline **631**.*

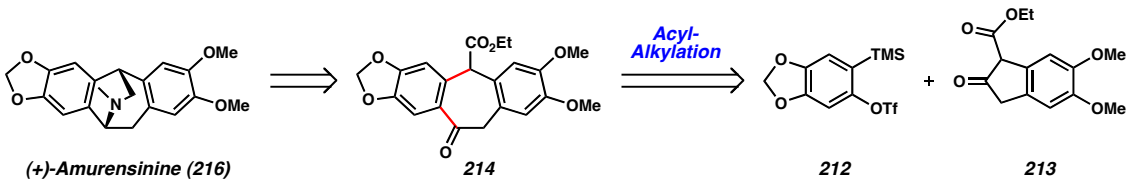


The regioselectivity displayed in these reactions underscores the importance of methods that facilitate the direct and predictable introduction of highly substituted arene components. Our ability to employ these arynes in the syntheses of complex polycyclic natural products hinges on the regioselectivity observed for silyl aryl triflates **232**, **217**, **604**, and **605** in a variety of aryne annulation reactions. In conjunction with their ability to form multiple C–C and C–N bonds in a single transformation, these arynes have enabled convergent approaches to several natural product classes, including the curvularins, the integrastatins, and bis-tetrahydroisoquinoline alkaloids such as jorumycin.

2.3.4 The Enantioselective Total Synthesis of (+)-Amurensinine[†,58,59,37]

The first natural product completed by employing our acyl-alkylation approach was (+)-amurensinine (**216**) (Scheme 2.27). Amurensinine is a member of the isopavine family of alkaloids, which are exemplified by a characteristic tetracyclic tetrahydroisoquinoline core structure consisting of a doubly benzannulated azabicyclo[3.2.2]nonane.[60] Upon close examination of the products in Table 2.4 (vide supra), we recognized that tricyclic acyl-alkylation product **596** bears a close resemblance to the carbocyclic framework (**214**) of the alkaloid (+)-amurensinine (**216**). In fact, β-ketoester **213** already contained all the required aromatic functionality for the eastern half of amurensinine; replacement of the parent silyl aryl triflate (**209**) with a substituted aryne precursor (**212**) would provide access to the natural product.

*Scheme 2.27. Retrosynthetic analysis of amurensinine (**216**).*

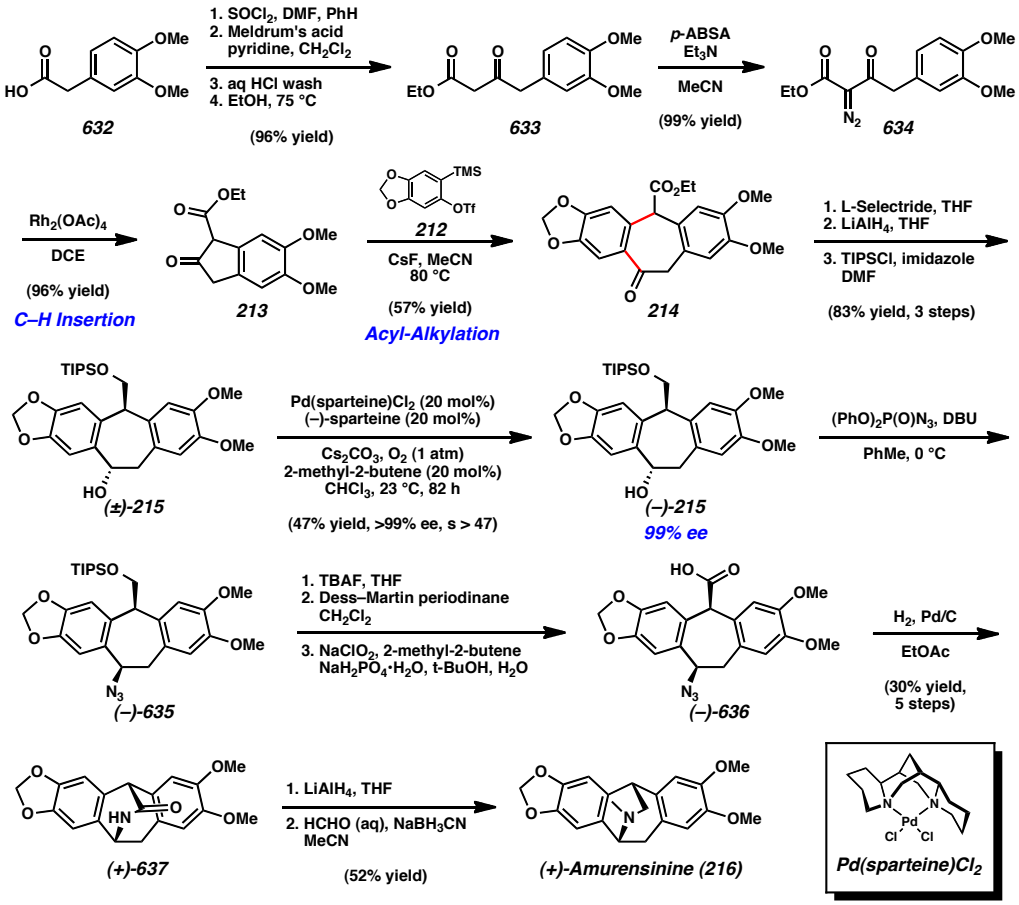


In the forward sense, β-ketoester was prepared beginning with homologation of homoveratric acid (**632**) to acyclic β-ketoester **633** (Scheme 2.28). Treatment of β-ketoester **633** with *p*-ABSA resulted in formation of α-diazo-β-ketoester, which underwent completely regioselective rhodium-catalyzed C–H bond insertion to produce the desired cyclic β-ketoester (**213**).

[†] The work described in this section was accomplished jointly by Prof. Uttam K. Tambar and Dr. David C. Ebner, two former graduate students in the Stoltz research group.

In the key bond-forming transformation, treatment of β-ketoester **213** with sesamol-derived aryne precursor **212** in the presence of CsF yielded ketoester **214**, a compound that contains the entire carbocyclic framework of amurensinine. Application of the acyl-alkylation reaction to this system resulted in the formation of two new C–C bonds to convergently unite the two halves of the natural product.

*Scheme 2.28. The total synthesis of (+)-amurensinine (**216**).*



With tetracycle **214** in hand, we turned our attention to rendering the synthesis enantioselective. Following ketone reduction, diastereoselective ester reduction, and selective silylation of the primary alcohol, benzyl alcohol **(±)-215** was subjected to

palladium-catalyzed oxidative kinetic resolution conditions to produce **(–)-215** in 47% yield and >99% ee, corresponding to an s-factor of >47.[61] From here, all that remained was closure of the tetrahydroisoquinoline ring. The nitrogen was installed by Mitsunobu inversion of the benzyl alcohol with DPPA to generate benzyl azide **(–)-635**, which was subsequently desilylated and oxidized to the corresponding acid (**636**). Reduction of the azide resulted in spontaneous lactamization, and exhaustive reduction of the lactam followed by reductive methylation yielded the natural product, (+)-amurensinine (**(+)-216**).

2.4 THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF (–)-CURVULARIN

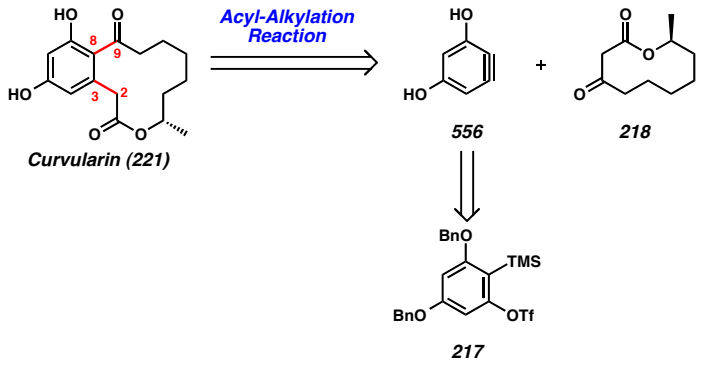
Importantly, the total synthesis of amurensinine demonstrated the viability of the ring-expansive acyl-alkylation in the synthesis of complex polycyclic natural product architectures. The ability to convergently assemble these carbocyclic frameworks from simple and easily accessible starting materials is a significant advantage of such an aryne-based strategy over more traditional approaches. As such, we sought to further test the limits of this transformation through its application to additional polycyclic natural products. More specifically, we targeted natural products containing unsymmetrically substituted arene moieties, beginning with (–)-curvularin.

2.4.1 Retrosynthetic Analysis Revisited

Returning to our retrosynthetic analysis of (–)curvularin (**221**), we initially disconnected the benzannulated macrolactone framework of the natural product along the C(2)–C(3) and C(8)–C(9) bonds by an acyl-alkylation reaction of resorcinylic aryne **556**

and chiral β-ketolactone **218** (Scheme 2.29). To reiterate, lactones had not been investigated as substrates for the acyl-alkylation reaction to this point and their viability in this transformation was not initially clear. Turning to the aryne precursor, since the free phenolic groups on aryne **556** would likely interfere with the desired reactivity, we opted to protect these groups as benzyl ethers, leading back to silyl aryl triflate **217**. Previous studies had already shown that silyl aryl triflate **217** undergoes regioselective acyl-alkylation and that the benzyl ethers could be readily cleaved under standard hydrogenolysis conditions (vide supra).[35]

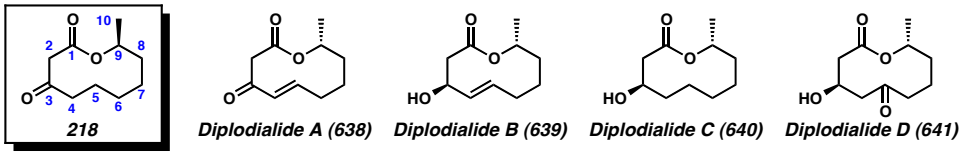
*Scheme 2.29. Retrosynthetic analysis of (–)-curvularin (**221**).*



With aryne precursor **217** already in hand, we initially focused our attention on chiral β-ketolactone **218**. Importantly, β-ketolactones such as **218** represent a substrate class that had not previously been investigated in aryne acyl-alkylation reactions and would be amenable to the preparation of other members of this class of natural products. Furthermore, by applying this retrosynthetic disconnection to curvularin, we recognized that the β-ketolactone fragment (**218**) mapped onto the carbon framework of the diplodialide natural products (**638**–**641**),[62] revealing an unusual synthetic (i.e.,

nonbiomimetic) link between the two natural product families (Figure 2.7). Thus, the development of a general synthesis of benzannulated macrolactone natural products, such as curvularin, via ring-expansive aryne insertion chemistry from the diminutive macrolactone would provide access to these valuable natural products and numerous synthetic analogs for biological evaluation.

*Figure 2.7. β-Ketolactone **218** and the diplodialide polyketide natural products (**638–641**).*



2.4.2 Previous Syntheses of β-Ketolactone 218 and the Diplodialide Natural Products

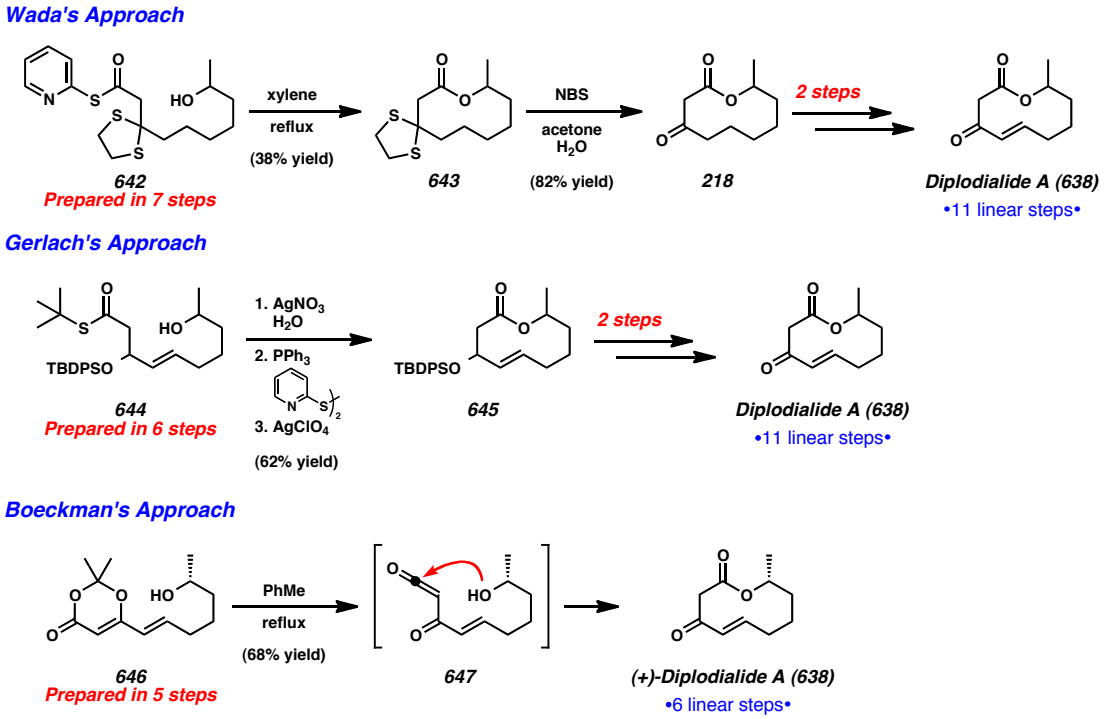
The synthesis of medium-sized rings is an under-appreciated challenge in organic synthesis. Two main factors account for this difficulty: enthalpic and entropic barriers.[63] Generally speaking, the development of transannular interactions in the transition states for medium-sized ring formations leads to significant enthalpic costs in both the transition state and the product. Furthermore, there is a substantial entropic cost in the transition state for cyclizations to form 8-, 9-, 10-, and 11-membered rings. For these reasons, effective methods for the synthesis of medium-sized rings are scarce and often require inconvenient experimental conditions, such as high dilution, to encourage cyclization. As it will become clear, simple modifications to cyclization substrates can often lead to dramatic and unpredictable differences in reactivity. This problem is well

exemplified by synthetic efforts toward β-ketolactone **218** and the diplodialide natural products (**638**–**641**).

β-Ketolactone **218** has been previously prepared in the literature by a number of different methods, including macrolactonization, ring-closing metathesis, ring expansion, ring contraction, and aldol reactions. In devising a route to β-ketolactone **218**, known total syntheses of the diplodalide natural products were also considered as potential strategies due to the similarity between these structures. In fact, β-ketolactone **218** has been previously utilized as an intermediate in the total syntheses of several diplodialides (vide infra).

The most prevalent strategy employed in the synthesis of the diplodialide natural products is macrolactonization from an appropriate hydroxyacid surrogate. In all these efforts, and indeed in all known efforts toward these structures, high dilution techniques must be used to minimize formation of dimeric and oligomeric esters. The groups of Wada[64] and Gerlach[65] each relied on macrolactonization of thioesters (**642** and **644**, respectively) according to the method of Mukaiyama to form the decanolide (Scheme 2.30). While Gerlach performs the macrolactonization with the *E*-olefin present (**644**), Wada opted instead to proceed through β-ketolactone **218** en route to diplodialide A (**638**). Alternatively, Boeckman[66] accessed diplodialide A (**638**) by macrolactonization of vinyl dioxolenone **646**; thermolysis of dioxolenone **646** produces an intermediate reactive ketene (**647**) that is subsequently trapped by the pendant alcohol to yield diplodialide A (**638**) directly in 68% yield.

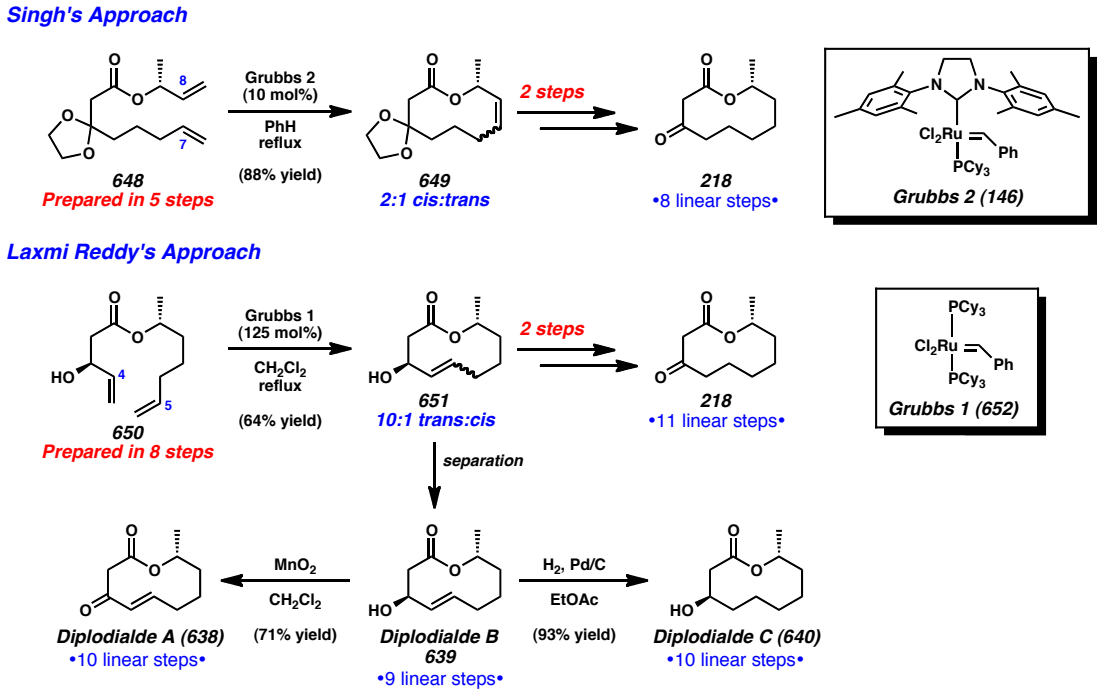
Scheme 2.30. Macrolactonization approaches to the diplodialide natural products.



The groups of Singh[67] and Laxmi Reddy[68] targeted the diplodialides through ring-closing metathesis reactions to form the 10-membered ring (Scheme 2.31). Singh prepared diene **648** as a RCM substrate with the aim of forming the C(7)–C(8) bond. Treatment of diene **648** with Grubbs 2nd generation catalyst (**146**) in refluxing benzene resulted in formation of decanolide **649** in 88% yield as a 2:1 mixture of cis and trans olefin isomers. Conversion of the isomeric mixture of **649** to β-ketolactone **218** completed the formal total synthesis of diplodialide A (**638**). Laxmi Reddy, on the other hand, chose to close the 10-membered ring along the C(4)–C(5) bond by RCM of allylic alcohol **650** with superstoichiometric Grubbs 1st generation catalyst (**652**), generating lactone **651** in 64% yield as a 10:1 mixture of trans and cis olefins. Separation of the major trans isomer, diplodialide B (**639**), constituted a formal synthesis of diplodialide A

(**638**); alternatively, the diplodialide B (**639**) was then successfully converted to diplodialide C (**640**) by olefin hydrogenation.

Scheme 2.31. RCM approaches to the diplodialides natural products.

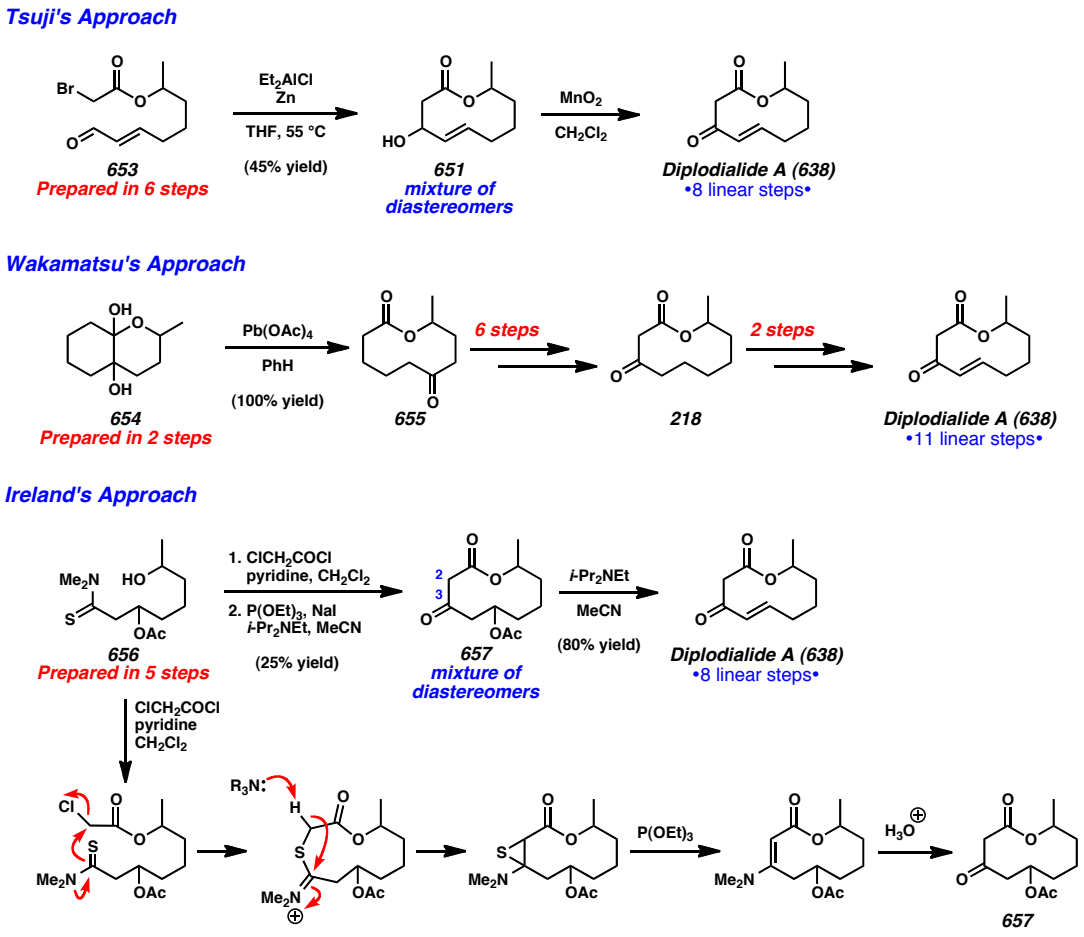


The final three approaches employed either Reformatsky cyclization, ring expansion, or ring contraction methods to construct the challenging 10-membered ring. Tsuji and co-workers[69] prepared α-bromo ester **653**, which, upon treatment with zinc, generated β-hydroxyester **651** (Scheme 2.32). Oxidation with MnO_2 then furnished diplodialide A (**638**).

Wakamatsu[70] investigated the preparation of the macrolactone from a decalin substrate by ring expansion. Treatment of diol **654** with lead tetraacetate resulted in ketoester **655**. This was further elaborated to β-ketolactone **218** over an additional 6 steps, completing the formal total synthesis of diplodialide A (**638**) as a result.

Finally, Ireland relied on a sulfide-based ring contraction strategy to form the C(2)–C(3) bond of diplodialide A (**638**).[71] Thioamide **656** was successfully converted to macrolatone **657** in 25% yield upon treatment with chloroacetyl chloride followed by triethylphosphite. Elimination of the acetate then provided diplodialide A (**638**) in eight synthetic steps.

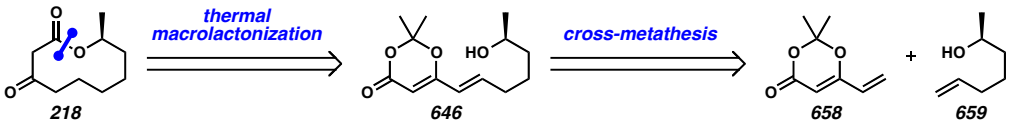
*Scheme 2.32. Tsuji's, Wakamatsu's, and Ireland's approaches to diplodialide A (**638**).*



2.4.3 β-Ketolactone Synthesis: Macrolactonization Studies

In evaluating each of these strategies, we sought to prepare targeted β-ketolactone **218** in a concise and enantioselective fashion. Among the shortest of the routes presented above is Boeckman's thermal macrolactonzation of dioxolenone substrates (e.g., **646**) in only six steps.[66] Our initial attempts to prepare β-ketoester **218** targeted this retrosynthetic disconnection (Scheme 2.33). While Boeckman prepared dioxolenone **646** by sequential olefination reactions, we proposed a more straightforward cross-metathesis-based route to this macrolactonization substrate, beginning with vinyl dioxolenone **658** and chiral secondary alcohol **659**.

*Scheme 2.33. Retrosynthetic analysis of β-ketolactone **218** by macrolactonization.*

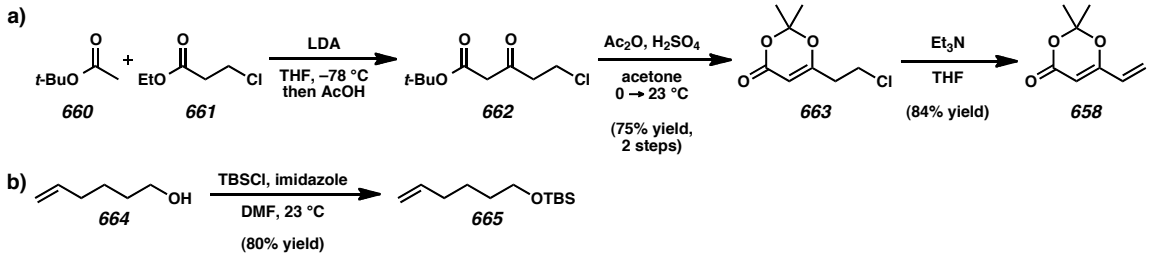


Vinyl dioxolenone (**658**) has been previously prepared in the literature and was readily accessed in 3 steps beginning with Claisen condensation of *t*-butyl acetate (**660**) and ethyl 3-chloropropionate (**661**) to yield β-ketoester **662** (Scheme 2.34).[72] Treatment of β-ketoester **662** with acetic anhydride, acetone, and sulfuric acid generated chloro dioxolenone **663,** which was converted to vinyl dioxolenone **658** by elimination with triethylamine.

Initial cross-metathesis investigations were carried out with a model system alcohol substrate (**665**) lacking the stereogenic methyl group. The model system cross-

metathesis partner, silylated alcohol **665**, was prepared from commercially available 5-hexen-1-ol (**664**) by simple protection with TBSCl.

*Scheme 2.34. a) Synthesis of vinyl dioxolenone **658**. b) Synthesis of protected alcohol **665**.*

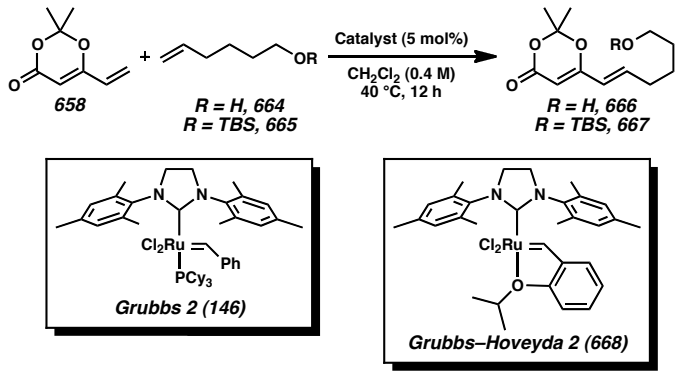


With vinyl dioxolenone **658** and protected alcohol **665** in hand, we turned our attention to the cross-metathesis reaction to generate disubstituted olefin **667** (Scheme 2.35).[73] Early efforts utilized the Grubbs 2nd generation ruthenium metathesis catalyst[74] (**146**) in 5 mol% in refluxing dichloromethane with equimolar amounts of the two metathesis partners (**658** and **665**). We were encouraged to isolate 28% yield of the desired product, but observed modest levels of dimerization of protected alcohol **665** as a side product (**669**). Furthermore, attempts to use dimer **669** in the metathesis process yielded no desired product (**667**), indicating that dimerization was not reversible under the reaction conditions. To circumvent these issues, the molar equivalents of dioxolenone **658** were increased optimally to three, keeping all other reaction parameters the same. To our delight, we were able to isolate cross-metathesis product **667** in 81% yield. Additionally, only trace quantities of dimer **669** were isolated and the majority of unreacted dioxolenone **658** could be recovered and resubmitted to the reaction conditions.

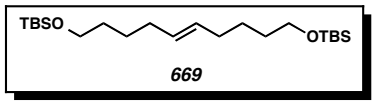
Seeking to improve upon this route, attempts were made to perform the cross-metathesis on unprotected 5-hexen-1-ol (**664**) in order to eliminate two steps from the

overall synthesis. A thorough screen of several Grubbs metathesis catalysts ultimately provided alcohol **666** in 26% yield using Grubbs–Hoveyda 2nd generation catalyst[75] (**668**) in 5 mol% in refluxing dichloromethane with equimolar amounts of vinyl dioxolenone **658** and 5-hexen-1-ol (**664**). The poor yield of this transformation led us to return to protected alcohol **665** as the cross-metathesis partner for vinyl dioxolenone **658**.

*Scheme 2.35. Optimization of cross-metathesis with vinyl dioxolenone **658**.*

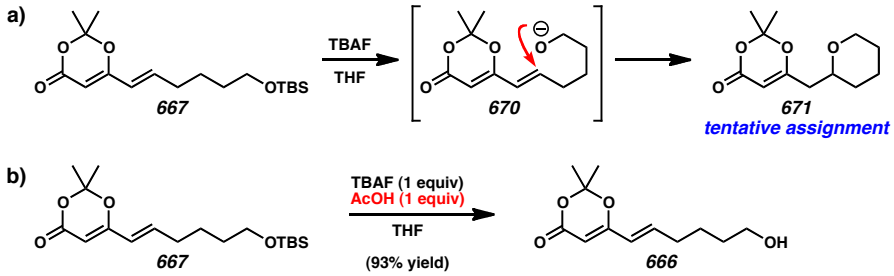


entry	catalyst	R	equiv *658*	yield
1	*146*	TBS	1.0	28%
2	*146*	TBS	3.0	81%
3	*668*	H	1.0	26%



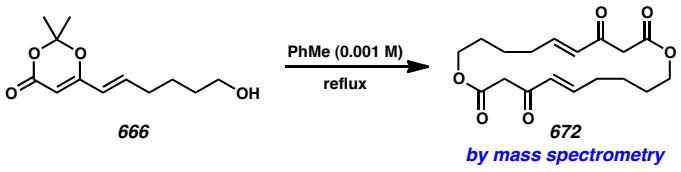
Following cross-metathesis of vinyl dioxolenone **658** and protected alcohol **665**, desilylation was attempted with tetra-*n*-butylammonium fluoride (TBAF) in THF (Scheme 2.36). To our surprise, however, we were unable to isolate primary alcohol **666**; the alkoxide formed under the desilylation conditions appears to have added in a conjugate fashion to the vinyl dioxolenone (**670**), presumably resulting in formation of a tetrahydropyran ring (**671**). This unwanted reactivity was avoided by buffering the TBAF with equimolar amounts of acetic acid, resulting in isolation of the primary alcohol (**666**) in 93% yield.

*Scheme 2.36. Desilylation of dioxolenone **667** with a) TBAF and b) acetic acid-buffered TBAF.*



With alcohol **666** in hand, we shifted our focus to effecting the thermal macrolactonization to produce des-methyl diplodialide A. However, under the conditions given by Boeckman for this transformation,[66] we were disappointed to find that none of the macrolactone was formed, despite the use of high dilution techniques (1.0 mM concentration) and slow addition of alcohol **666** over several hours (Scheme 2.37). In fact, the sole identifiable compound from these reactions was cyclic dimer **672** (observed only by mass spectrometry). Unable to optimize this process, we opted to pursue β-ketolactone **218** by other means.

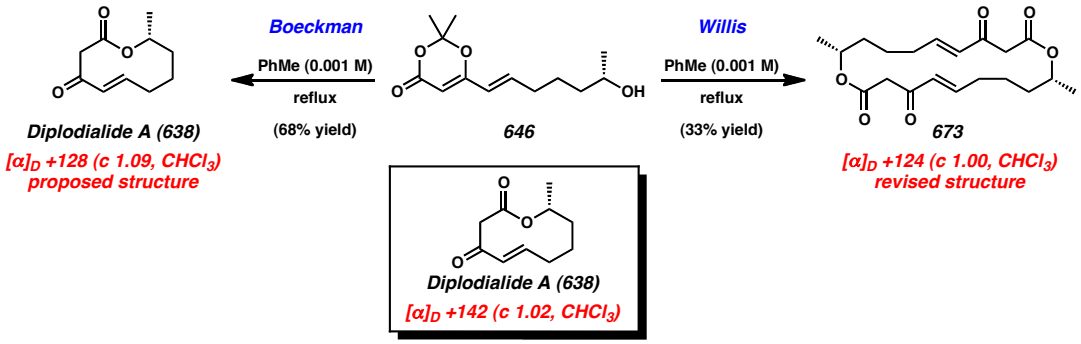
*Scheme 2.37. Attempted thermal macrolactonization of dioxolenone **666**.*



Interestingly, following our work toward β-ketolactone **218** by the thermal macrolactonization route, Willis and co-workers published a revision to the decanolide structure reported by Boeckman.[76] During attempts to reproduce the synthesis of diplodialide A (**638**), Willis noted that their isolated product possessed a similar optical

rotation, $[\alpha]_D$ +124 (*c* 1.0, $CHCl_3$), to that of Boeckman's product, $[\alpha]_D$ +128 (*c* 1.09, $CHCl_3$), while the optical rotation of the natural product (**638**) had been previously reported as $[\alpha]_D$ +142 (*c* 1.02, $CHCl_3$) (Scheme 2.38). Furthermore, the NMR spectra of Willis' material and the natural product displayed small but significant differences in the chemical shifts of several signals. Finally, observation of the mass of dimer **673** and correlation of ^{1}H NMR data with that of Ley and co-workers[77] for dimer **673** led Willis to conclude that Boeckman had incorrectly assigned dimer **673** as diplodialide A (**638**).

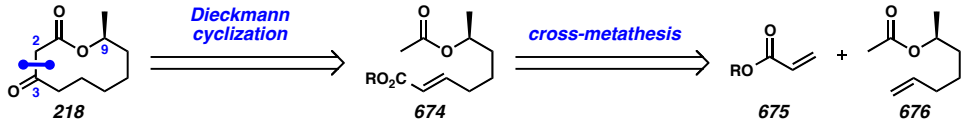
*Scheme 2.38. Structural misassignment in Boeckman's reported synthesis of diplodialide A (**638**).*



2.4.4 β-Ketolactone Synthesis: Dieckmann Cyclization Studies

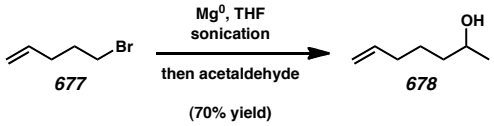
Following the macrolactonization studies toward β-ketolactone **218**, we chose to investigate an alternate disconnection of the 10-membered ring by various Dieckmann cyclizations (Scheme 2.39).[78] We initially targeted cyclization along the C(2)–C(3) bond from linear substrates such as **674**, which could be accessed in turn from acetate **676** by cross-metathesis with various acrylates (**675**).

*Scheme 2.39. Retrosynthetic analysis of β-ketolactone **218** by Dieckmann cyclization.*



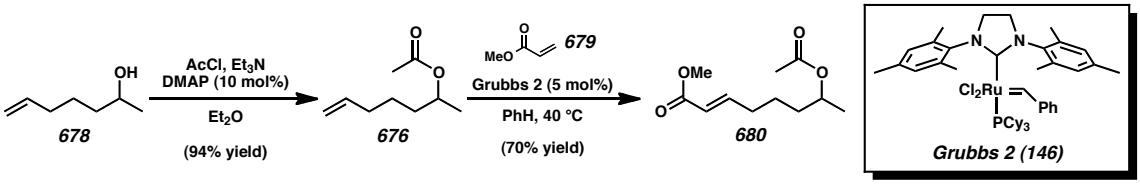
For some of these studies, we opted to work with starting materials bearing the C(9) methyl group instead of model alcohol 5-hexen-1-ol (**664**). Preparation of 6-hepten-2-ol (**678**) in a racemic sense was straightforward beginning with commercially available 5-bromo-1-pentene (**677**) (Scheme 2.40). Formation of the Grignard reagent, followed by quenching with freshly distilled acetaldehyde yielded the secondary alcohol (**678**) in 70% yield.[79]

*Scheme 2.40. Racemic synthesis of secondary alcohol **678**.*



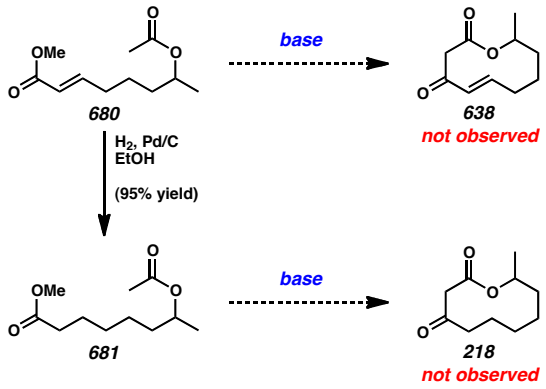
Secondary alcohol **678** was next advanced to diester **680** beginning with acetylation of the alcohol to yield acetate **676** (Scheme 2.41). Cross-metathesis with methyl acrylate (**679**) proceeded in excellent yield, producing diester **680** exclusively as the *Z*-isomer.

*Scheme 2.41. Synthesis of diester **680** for Dieckmann cyclization studies.*



Initial examination of Dieckmann condensation reactions focused on unsaturated diester **680** as a substrates. Several bases were screened for this transformation, though none but LDA provided anything other than starting material (Scheme 2.42). Use of LDA in THF at –78 °C provided small quantities of a compound lacking the olefinic protons observed by ^{1}H NMR in the starting material indicating that enoate **680** may act as a conjugate electrophile under the reaction conditions. In response to this unwanted reactivity at the β-position and in order to impart additional flexibility on the system, enoate **680** was hydrogenated to give diester **681**. Unfortunately, exposure of this fully saturated substrate (**681**) to a variety of bases never yielded any tractable products.

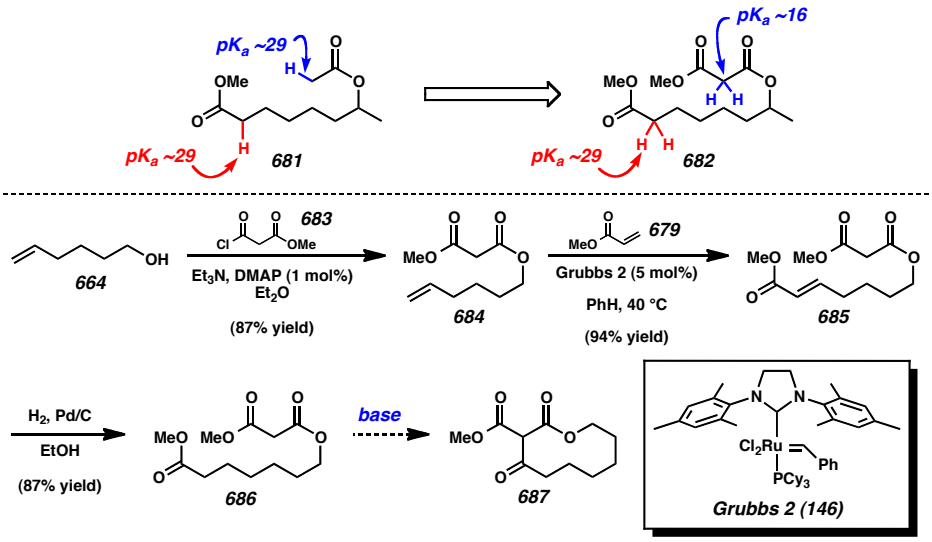
*Scheme 2.42. Unsuccessful attempts at Dieckmann cyclization of diesters **680** and **681**.*



A final modification to these diester substrates that was examined was the replacement of the acetate group with a mixed malonate. By lowering the pK_a value of the desired site of enolization (i.e., as in mixed malonate **682**), selectivity for 10-membered ring formation would be significantly higher than for diester **681**, which possesses multiple acidic sites with similar pK_a values (Scheme 2.43).[80] A model system of mixed malonate **682** was prepared beginning with acetylation of 5-hexen-1-ol (**664**)

with methyl malonyl chloride (**683**). Cross-metathesis of the resulting mixed malonate (**684**) with methyl acrylate (**679**), followed by hydrogenation of the olefin yielded Dieckmann cyclization substrate **685**. To our disappointment, though, upon treatment with a number of different bases, including NaH, LDA, and Et_3N, mixed malonate **685** failed to produce any 10-membered ring products. In many cases, decomposition of mixed malonate **686** quickly occurred under the reaction conditions.

*Scheme 2.43. Preparation of mixed malonate **682** and attempted Dieckmann cyclizations.*

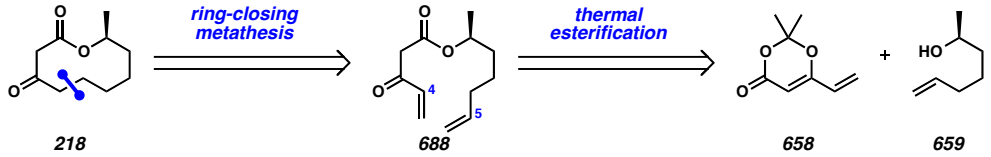


2.4.5 β-Ketolactone Synthesis: Ring-Closing Metathesis Studies and the Synthesis of (±)-Diplodialide C

With the failure of the Dieckmann cyclization strategy to generate any 10-membered ring products, we moved on to the final retrosynthetic disconnection of β-ketolactone **218**. Our initial plan involved formation of the C(4)–C(5) bond by a ring-closing metathesis from vinyl β-ketoester **688** (Scheme 2.44). Fortuitously, vinyl β-

ketoester **688** could be prepared from two previously prepared compounds: vinyl dioxolenone **658** and secondary alcohol **659**.

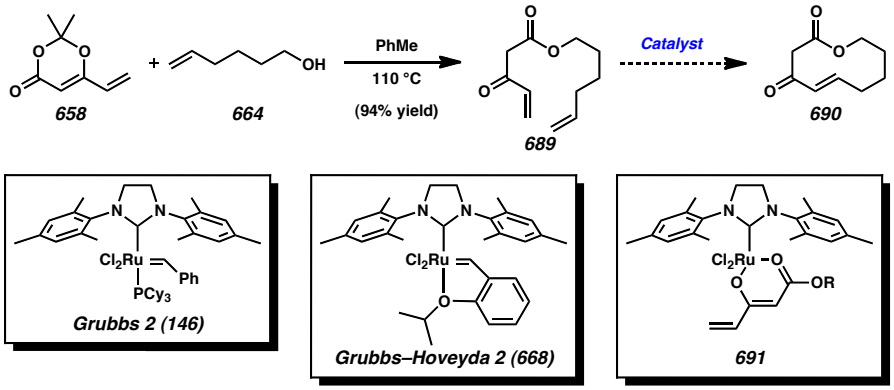
*Scheme 2.44. Retrosynthetic analysis of β-ketolatone **218** by ring-closing metathesis.*



In essence, this synthetic plan reverses the order of operations from that of the macrolactonization attempts (vide supra). Instead of joining dioxolenone **658** and secondary alcohol **659** by cross-metathesis followed by macrolactonization, this new strategy would join the two fragments by thermal esterification and close the macrocycle with a ring-closing metathesis reaction.

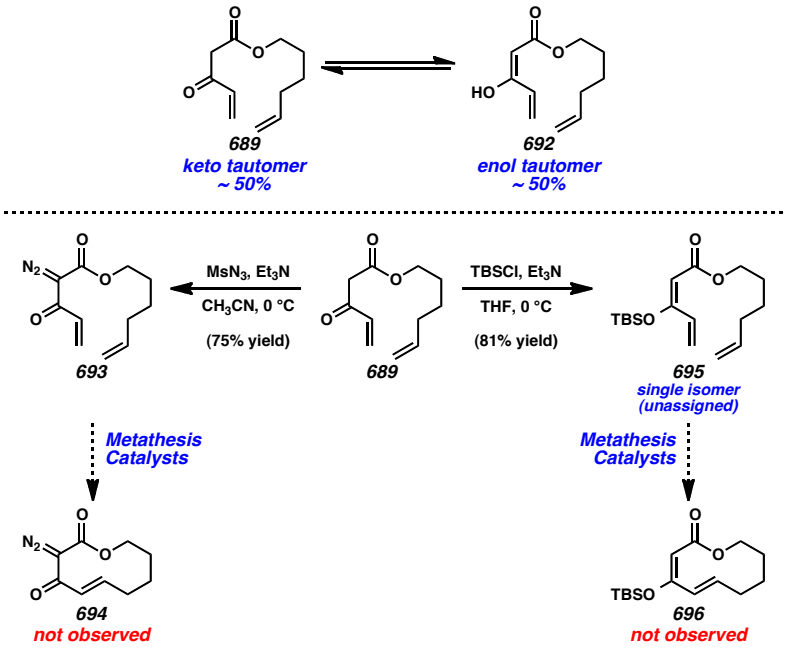
Initial studies into this approach were performed with the model system alcohol, 5-hexen-1-ol (**664**). Simple heating of vinyl dioxolenone **658** with 5-hexen-1-ol (**664**) resulted in formation of vinyl β-ketoester **689** in excellent yield (Scheme 2.45).[81] However, neither Grubbs 2nd generation catalyst (**146**) nor the more active Grubbs–Hoveyda 2nd generation catalyst (**668**) were able to effect the ring-closing of vinyl β-ketoester **689**. In the ring-closing metathesis reactions using Grubbs 2nd generation catalyst (**146**), catalyst deactivation appeared to be significant at early stages of the reaction. One potential reason for catalyst deactivation could be the formation of a stable six-membered chelate with the substrate (e.g., **691**). On the other hand, attempted ring-closing metathesis with the Grubbs–Hoveyda catalyst (**668**) led to significant starting material decomposition and oligomerization.

Scheme 2.45. Synthesis and attempted ring-closing metathesis of vinyl β-ketoester ***689****.*



Given the decomposition of catalyst **146** in the presence of vinyl β-ketoester **689**, we considered modifications that could be made to the ring-closing metathesis substrate (**689**) to circumvent these difficulties. The ^{1}H NMR of vinyl β-ketoester **689** shows a significant quantity (~50%) of enol tautomer present in the sample, which has the potential to negatively impact cyclization. Two strategies were explored to avoid problems associated with the enol tautomer: 1) installation of a temporary blocking group at the α-position, and 2) masking of the enol as the corresponding silyl enol ether. For a temporary blocking group to prevent enolization, a diazo functionality was selected; upon treatment of vinyl β-ketoester with MsN_3 and Et_3N, α-diazo-β-ketoester **693** was formed in 75% yield (Scheme 2.46). Alternatively, vinyl β-ketoester **689** was converted to a single (unassigned) isomer of TBS enol ether **695** by reaction with TBSCl and Et_3N in 81% yield. When α-diazo-β-ketoester **693** and silyl enol ether **695** were each subjected to ring-closing metathesis conditions, however, no cyclic products were formed. In fact, α-diazo-β-ketoester **693** returned only starting material, while silyl enol ether **695** yielded small quantities of vinyl β-ketoester **689** in addition to recovered starting material (**695**).

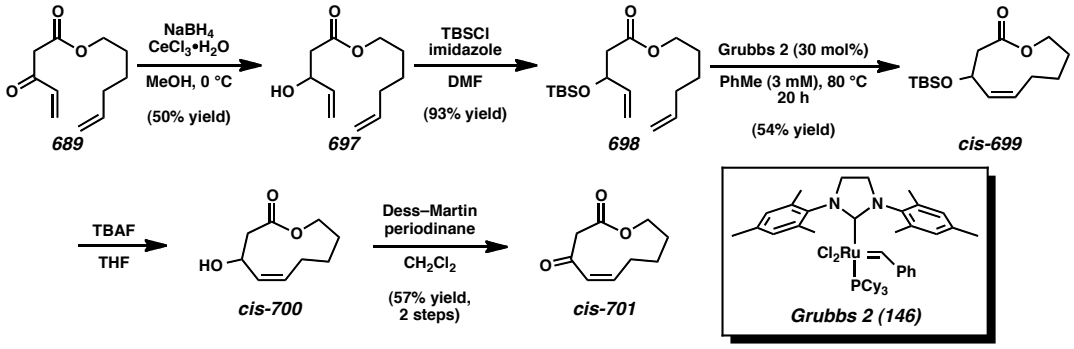
*Scheme 2.46. Synthesis of vinyl β-ketoester derivatives **693** and **695** and ring-closing metathesis attempts.*



Although use of α-diazo-β-ketoester **693** and silyl enol ether **695** as ring-closing metathesis substrates prevents reactivity issues arising from the presence of enol tautomer **692**, it also likely introduces significant conformational restrictions that could prohibit such substrates from cyclizing. It is well-known that the level of unsaturation can significantly impact the success of ring-closing for medium-sized rings. With this in mind, the enone of vinyl β-ketoester **689** was reduced in a 1,2-fashion under Luche's conditions to yield allylic alcohol **697**, which was immediately protected as a silyl ether (**698**) (Scheme 2.47). To our delight, upon treatment of silyl ether **698** with Grubbs 2nd generation catalyst (**146**) in toluene at 80 °C, lactone **699** was generated in 54% isolated yield as a single olefin isomer. Critical to the success of this ring-closing metathesis was the continuous slow addition of solutions of both silyl ether **698** and Grubbs 2nd

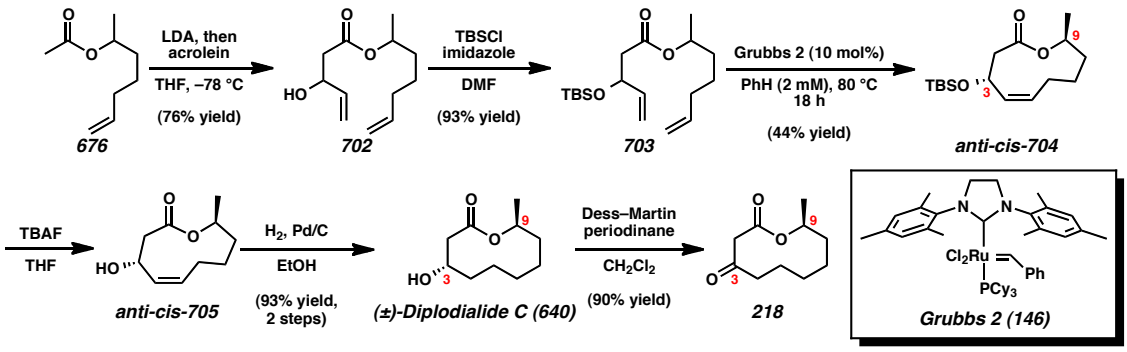
generation catalyst (**146**) throughout the course of the 20-hour reaction. At this point, we were unable to assign the olefin geometry in lactone **699**. In order to determine the olefin geometry of lactone **699**, it was converted to enone **701** by desilylation and Dess–Martin oxidation. By ^{1}H NMR, the olefin geometry of enone **701** was then assigned as cis (J = 12.2 Hz).

*Scheme 2.47. Synthesis of lactone **701** and assignment of the olefin geometry.*



With this key initial result in hand, we turned our attention toward ring-closing metathesis of substrates bearing the C(9) methyl group of β-ketolactone **218**. While β-ketolactone **218** could be constructed in a way analogous to that of lactone **701**, a significantly shorter route was devised to access ring-closing metathesis substrate **703**. Beginning with acetate **676**, which was previously employed in the Dieckmann cyclization studies, diene **703** was constructed in two steps by an aldol reaction with acrolein followed by protection as the silyl ether (Scheme 2.48). This sequence generated diene **703** as a 1:1 mixture of diastereomers; this mixture would eventually be inconsequential since the silyl ether will be converted to the C(3) ketone in β-ketolactone **218**.

*Scheme 2.48. Successful ring-closing metathesis of silyl ether **703** and synthesis of (±)-diplodialide C (**640**).*

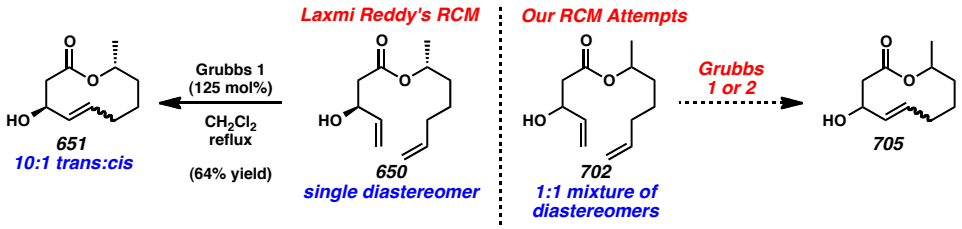


Upon treatment of the diastereomeric mixture of diene **703** with Grubbs 2nd generation catalyst (**146**), we were intrigued to find that lactone **704** was isolated in 44% yield as a single diastereomer having the cis olefin geometry exclusively. To the best of our knowledge, only two other examples of a resolution of diastereomers by ring-closing metathesis using an achiral catalyst are known.[82]

Due to the configurational flexibility of 10-membered lactone **704**, the relative stereochemistry of the C(3) silyl ether and C(9) methyl group were unable to be assigned. However, desilylation and hydrogenation of lactone **704** produced a compound whose data matched that of diplodialide C (**640**), which features the C(3) alcohol and C(9) methyl groups oriented in an anti relative configuration. Thus, lactone **704** was assigned the same anti relative configuration of the C(3) silyl ether and C(9) methyl group, in addition to the previously assigned cis olefin. Furthermore, we found that diplodialide C (**640**) was easily oxidized to the key β-ketolactone (**218**) required for the synthesis of curvularin.

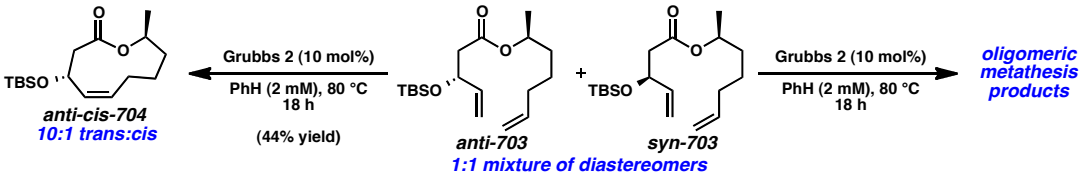
It should be noted that Laxmi Reddy and co-workers reported successful ring-closing metathesis of allylic alcohol **650** with Grubbs 1st generation catalyst (**652**) in 64% yield (Scheme 2.49).[68] However, this transformation required the use of a superstoichiometric amount of catalyst **652** (125 mol%). Attempts to directly form β-hydroxylactone **705** from allylic alcohol **702** with several metathesis catalysts failed to produce macrocycle **705** in more than 10% isolated yield.

*Scheme 2.49. Laxmi Reddy's RCM of allylic alcohol **650** compared with our efforts.*



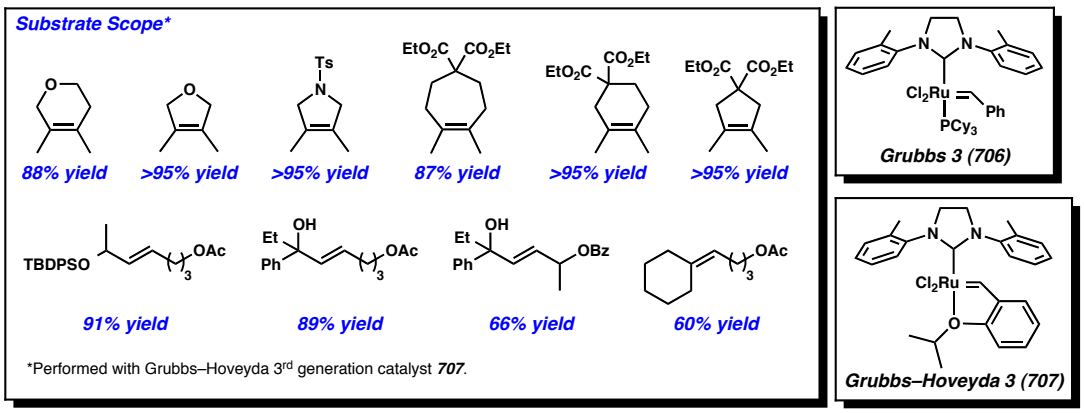
While the resolution of the 1:1 mixture of diastereomeric silyl ethers (**703**) by ring-closing metathesis is notable, more than half of the material was simultaneously lost through unproductive metathesis pathways (Scheme 2.50) All attempts to overcome this resolution by altering solvent, concentration, and temperature detrimentally affected the process. We believe that the bulky mesityl groups flanking the *N*-heterocyclic carbene ligand on the catalyst **146** hinders the ring-closing process due to unfavorable interactions with one or both of the stereocenters present in silyl ether ***cis*-703**.

Scheme 2.50. Resolution of silyl ethers ***cis*-703** and ***trans*-703** *by Grubbs 2nd generation metathesis catalyst* ***146***.



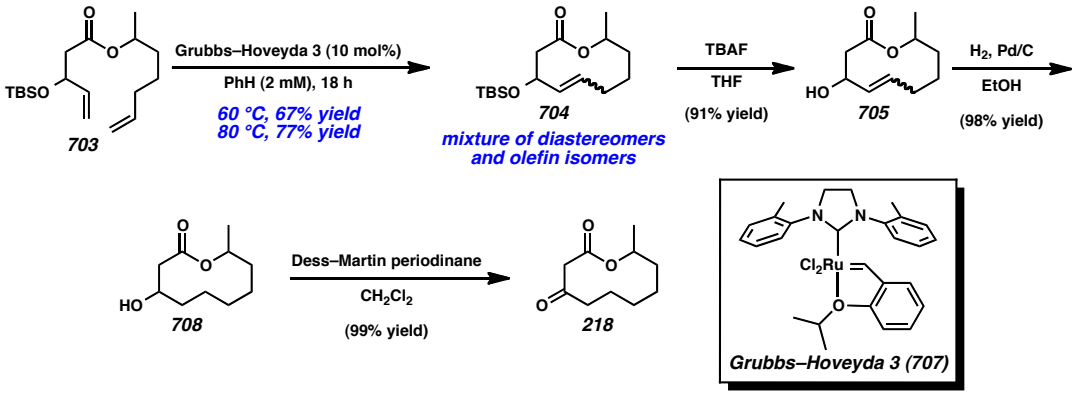
Fortuitously, concurrent with these studies, a new metathesis catalyst bearing less sterically encumbered *ortho*-tolyl groups on the *N*-heterocyclic carbene ligand was reported by Grubbs and co-workers.[83] This Grubbs 3rd generation catalyst (**706**) displayed remarkable activity for the formation of more sterically congested olefins that had remained inaccessible using previous generations of catalysts (Figure 2.8). In addition to the phosphine-ligated catalyst (**706**), a variant containing the isopropoxy benzylidene ligand, referred to as the Grubbs–Hoveyda 3rd generation catalyst (**707**), was also excellent for these transformations. Notably, the Grubbs–Hoveyda 3rd generation catalyst possesses significantly better thermal stability than the phosphine-ligated Grubbs 3rd generation catalyst.

Figure 2.8. The Grubbs 3rd generation catalysts.



Because of the higher temperatures required for ring-closing metathesis of silyl ether **703**, we examined the Grubbs–Hoveyda 3rd generation catalyst (**707**) for this transformation. To our delight, in the first reaction with this catalyst, ring closing of the 1:1 diastereomeric mixture of silyl ether **703** proceeded to form lactone **704** as a mixture of diastereomers and olefin isomers in 67% isolated yield (Scheme 2.51). Increasing the temperature of the reaction from 60 °C to 80 °C further increased the yield to 77%. Importantly, no material was lost in this ring-closing metathesis due to resolution of the diastereomeric mixture of silyl ether **703**. Furthermore, the diastereomeric mixture of lactone **704** was readily converted to β-ketolactone **218** by sequential desilylation, hydrogenation, and Dess–Martin oxidation.

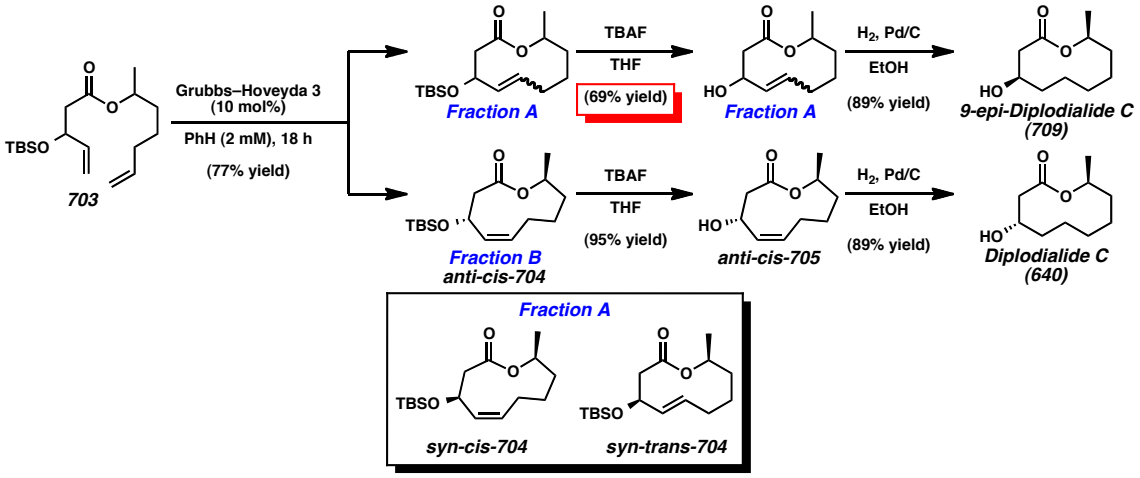
*Scheme 2.51. Ring-closing metathesis of silyl ether **703** with Grubbs–Hoveyda 3rd generation catalyst.*



We were interested in determining the composition of the diastereomeric mixture of lactone **703**, but were only able to partially separate the isomers into two fractions (Scheme 2.52). Fraction A contained up to 3 diastereomers in an undetermined ratio. This mixture was desilylated with TBAF and reduced to yield 9-epi-diplodialide C (**709**).

We therefore concluded that two of the diastereomers present in fraction A were ***syn-cis*-704** and ***syn-trans*-704**. However, these experiments do not confirm that only two diastereomers are present in fraction A; the yield for desilylation is significantly lower than expected and suggests that a third diastereomer, ***anti-trans*-704**, is present but unstable to the reaction conditions for desilylation. Further experiments were needed to test this theory. Fraction B, which was diastereomerically pure, contained only the compound previously assigned as ***anti-cis*-704**. This was again verified by desilylation and olefin hydrogenation, furnishing diplodialide C (**640**).

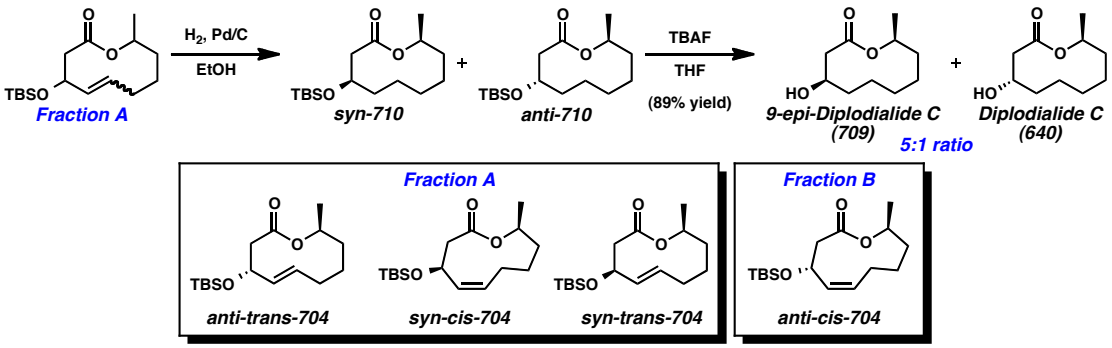
*Scheme 2.52. Partial determination of the diastereomeric mixture resulting from ring-closing metathesis of silyl ether **703**.*



In order to determine whether fraction A contained two or three diastereomers, we changed the order of operations for the desilylation and hydrogenation sequence shown in Scheme 2.52. If fraction A contained a third diastereomer, namely ***anti-trans*-704** diastereomer, hydrogenation might reveal its presence. Furthermore, subsequent desilylation would then lead to a mixture of 9-epi-diplodialide C (**709**) and diplodialide C

(**640**). To our delight, hydrogenation of fraction A led to isolation of a mixture of two compounds, indicating that this fraction indeed contains three diastereomers (Scheme 2.53) We were further pleased to find that desilylation produced a 5:1 mixture of 9-epi-diplodialide C (**709**) and diplodialide C (**640**). This confirms that all four potential diastereomers, ***anti-cis*-704**, ***anti-trans*-704**, ***syn-cis*-704**, and ***syn-trans*-704**, are formed during ring-closing metathesis of silyl ether **703** with Grubbs–Hoveyda 3rd generation catalyst (**707**). However, because of potential differences in reactivity under desilylation and hydrogenation conditions, we were unable to determine the ratio of diastereomers formed directly by the ring-closing metathesis. At best, we have concluded that following hydrogenation and desilylation, in that particular order, the ratio of ***anti-cis*-704** : ***syn-cis*-704** : ***syn-trans*-704** : ***anti-trans*-704** is 3.5 : 1.6 : 1.0 : trace.

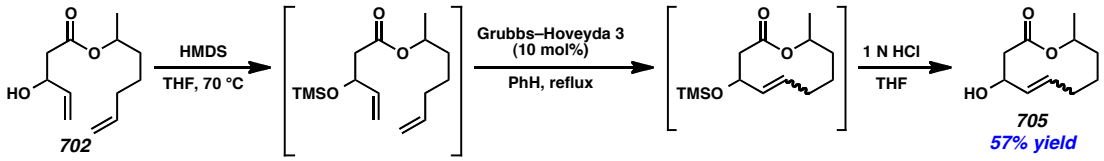
*Scheme 2.53. Determination of all diastereomeric mixture components resulting from ring-closing metathesis of silyl ether **703**.*



Although the sequence of ring-closing metathesis followed by desilylation, hydrogenation, and Dess–Martin oxidation was an efficient means of generating β-ketolactone **218**, we sought to streamline the overall process in two separate ways. The

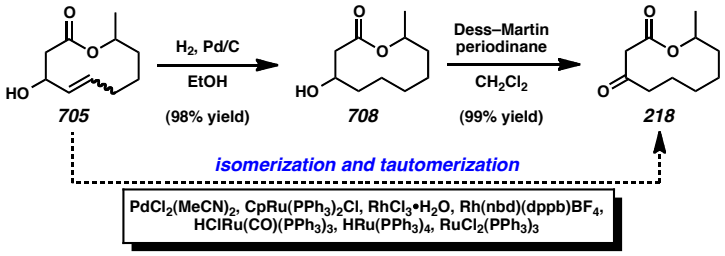
first was to develop a one-pot silylation–ring-closing metathesis–desilylation procedure beginning from allylic alcohol **702** (Scheme 2.54). This would have the net effect of cutting two synthetic steps from our overall route. Gratifyingly, silylation with hexamethyldisilazide (HMDS) followed by ring-closing metathesis with Grubbs–Hoveyda 3rd generation catalyst (**707**) and acidic hydrolysis of the trimethylsilyl group generated β-hydroxylactone **705** as the expected mixture of diastereomers and olefin isomers in 57% yield. This mixture was then readily converted to β-ketolactone **218** by hydrogenation and Dess–Martin oxidation (Scheme 2.51).

Scheme 2.54. Development of a one-pot silylation–ring-closing metathesis–desilylation procedure.



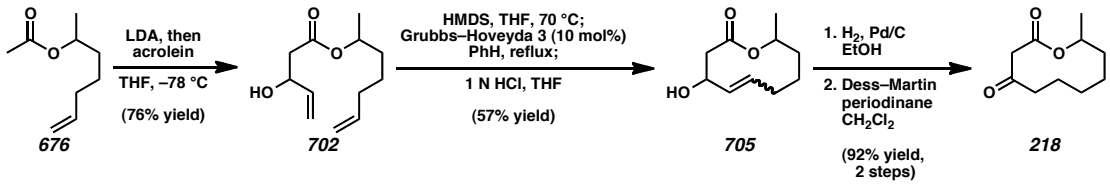
A second improvement we attempted to make to the synthesis of β-ketolacone **218** was to combine the hydrogenation and Dess–Martin oxidation operations into one step. As these two synthetic steps result in no net change in the overall oxidation state of the molecule, we sought to bypass these redox manipulations by carrying out an olefin isomerization reaction (Scheme 2.55). Unfortunately, examination of a significant number of catalysts known for their isomerization activity never led to any formation of β-ketolactone **218**.[84] In many cases, the high temperatures required for olefin isomerization led to decomposition of β-hydroxylactone **705**.

*Scheme 2.55. Attempted isomerization reactions of β-hydroxylactone **705**.*



In the culmination of these studies, we were able to access β-ketolactone **218** in just four synthetic steps from known acetate **676** (Scheme 2.56). The overall yield for this process is 40% and allowed us to generate multigram quantities of β-ketolactone **218** for upcoming acyl-alkylation studies. However, we had yet to devise a method for the asymmetric synthesis of β-ketolactone **218**.

*Scheme 2.56. Synthesis of β-ketolactone **219** from acetate **676**.*

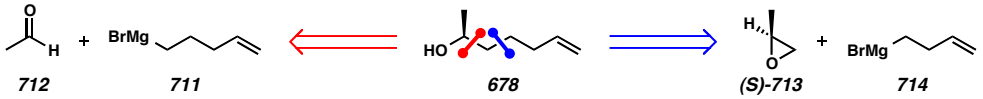


2.4.6 Enantioselective β-Ketolactone Synthesis

In devising an asymmetric route to β-ketolactone **218**, we recognized that chiral secondary alcohol **678** would be our main target for synthesis. All reactions that follow secondary alcohol **678** in the synthetic sequence leading to β-ketolactone **218** would not affect the absolute configuration of the single stereocenter; thus, this stereocenter could be set early in the synthesis. In the racemic sense, secondary alcohol **678** was prepared by a Grignard addition of butenylmagnesium bromide **711** to acetaldehyde (**712**)

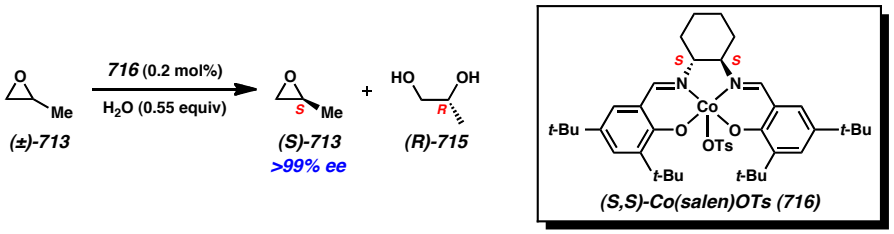
(Scheme 2.57). However, asymmetric versions of this transformation were not a viable route to secondary alcohol **678**. An alternative disconnection of secondary alcohol would involve nucleophilic ring-opening of a chiral epoxide. Since (*S*)-propylene oxide ((***S*)-713**) is a readily available chiral building block, enantioenriched secondary alcohol **(*S*)-678** was targeted by this method.

*Scheme 2.57. Retrosynthetic analysis of chiral secondary alcohol **(S)-713**.*



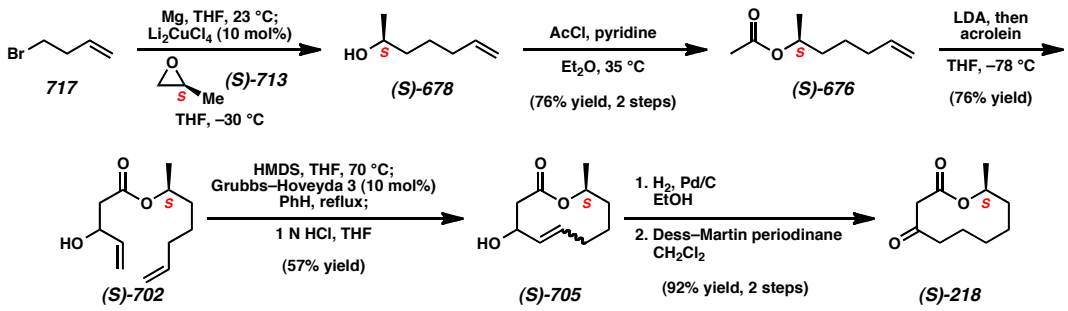
Although (*S*)-propylene oxide ((***S*)-713**) is commercially available,[85] it was prepared from racemic propylene oxide (**713**) on large scale by hydrolytic kinetic resolution according to the method described by Jacobsen and co-workers (Scheme 2.58).[86] Hydrolysis of racemic propylene oxide (**713**) in the presence of (*S*,*S*)-Co(salen)OTs (**716**) with water resulted in the isolation of unreacted (*S*)-propylene oxide ((***S*)-713**) in greater than 99% *ee*, which could be distilled from the enantioenriched diol product ((***R*)-715**). This procedure enabled the preparation of quantities of (*S*)-propylene oxide ((***S*)-713**) in excess of 20 grams at one time.

*Scheme 2.58. Jacobsen hydrolytic kinetic resolution to produce (S)-propylene oxide (**713**).*



With (*S*)-propylene oxide in hand, we turned our attention to the key epoxide opening reaction with the butenylmagnesium bromide reagent prepared in situ from commercially available 4-bromo-1-butene (**717**) (Scheme 2.59). At low temperature, using Li_2CuCl_4 as a catalyst, (*S*)-propylene oxide ((***S*)-713**) was selectively opened at the less substituted position to yield chiral secondary alcohol **678**.[87] Because alcohol **678** is volatile, it was immediately acetylated to furnish acetate **676** in 76% yield over the two-step sequence. Aldol reaction of chiral acetate **676** with acrolein then produced allylic alcohol **702** as a 1:1 mixture of enantioenriched syn and anti diastereomers. The diastereomeric mixture of allylic alcohols (**702**) was then advanced through the one-pot silylation-ring-closing metathesis-desilylation sequence to yield β-hydroxylactone **705** as a mixture of diastereomers and olefin isomers. Finally, hydrogenation and Dess–Martin oxidation of β-hydroxylactone **705** generated enantioenriched β-ketolactone **218** for acyl-alkylation studies in >99% ee.

*Scheme 2.59. Asymmetric synthesis of β-ketolactone **218**.*

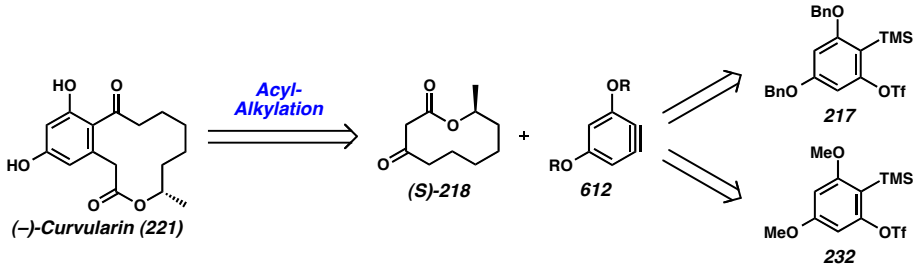


2.4.7 Acyl-Alkylation Studies and Completion of (–)-Curvularin

Having developed an efficient means to produce multigram quantities of β-ketolactone **218**, we sought to employ this intermediate in an acyl-alkylation reaction

with a suitably protected resorcinylic aryne to construct the benzannulated macrocyclic framework of curvularin (Scheme 2.60). To accomplish this, several different silyl aryl triflates (e.g., **217** and **232**) were investigated in acyl-alkylation reactions with β-ketolactone **218**.

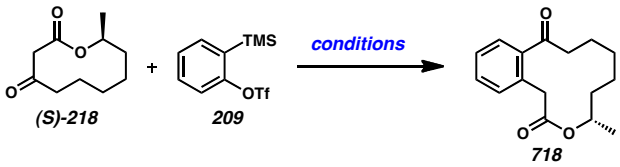
*Scheme 2.60. Acyl-alkylation reactions toward curvularin (**221**).*



We initially examined acyl-alkylation of β-ketolactone **218** with the unsubstituted silyl aryl triflate (**209**) to determine if these types of substrates were suitable for the transformation. Prior to these studies, only cyclic β-ketoesters bearing exocyclic ester groups had been investigated as substrates for acyl-alkylation. A range of conditions was examined for this reaction beginning with KF/18-crown-6 in THF at 60 °C (Table 2.5). To our delight, benzannulated macrolactone **718** was isolated in 52% yield along with 17% recovered β-ketolactone **218** (entry 1). Replacement of the KF/18-crown-6 fluoride source with TBAT led to a decreased yield of 37% (entry 2). Further optimization of reactions in THF with either TBAT or KF/18-crown-6 proved difficult. Alternatively, the use of CsF in acetonitrile at 80 °C provided low yields of benzannulated macrolactone **718** in addition to several side products (entry 3). Slow addition of the aryne precursor (**209**) over 1.5 hours led to a significant increase in the yield to 57%, while slightly

decreasing the number of side products (entry 4). Finally, lowering the temperature to 40 °C in combination with the slow addition of silyl aryl triflate **209** led to 61% isolated yield of benzannulated macrolactone **718** (entry 5).

*Table 2.5. Acyl-alkylation reactions of silyl aryl triflate **209** with β-ketolactone **218**.*



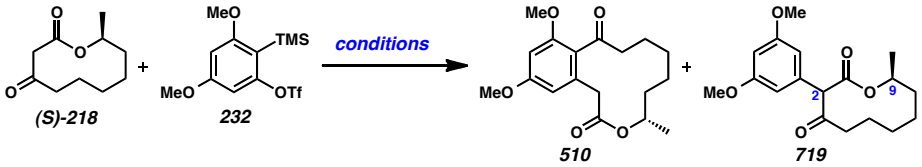
entry	F^- source	solvent	temperature	yield
1	KF/18-crown-6	THF	60 °C	52%
2	TBAT	THF	60 °C	37%
3	CsF	MeCN	80 °C	<10%
4[a]	CsF	MeCN	80 °C	57%
5[a]	CsF	MeCN	40 °C	61%

[a] Reaction performed with slow addition of silyl aryl triflate **209** over 1.5 hours.

Next, unsubstituted silyl aryl triflate **209** was replaced with dimethoxy aryne precursor **232** in acyl-alkylation reactions with β-ketolactone **218** (Table 2.6). In this case, both KF/18-crown-6 and TBAT in THF were ineffective fluoride sources for the insertion reaction (entries 1 and 2). Upon use of CsF in acetonitrile, dimethylcurvularin (**510**) was isolated along with significant quantities of the corresponding α-arylation product (**719**). In all cases, the α-arylation product was formed as a single isomer resulting from regioselective addition of β-ketolactone **218** to the putative dimethoxy aryne (**606**); furthermore, α-arylation product **719** was always isolated as a single (unassigned) diastereomer at the C(2) and C(9) positions. Under the standard acyl-alkylation conditions, insertion product **510** and α-arylation product **719** were formed in almost a 1:1 ratio, with insertion product **510** isolated in 32% yield (entry 3). Decreasing

the ratio of silyl aryl triflate **232** to β-ketolactone **218** from 1.2:1 to 1:1 somewhat improved the ratio of insertion to α-arylation, leading to an increased yield of macrolactone **510** (entry 4). Further decreasing the ratio of silyl aryl triflate **232** to β-ketolactone **218** to 1:1.2 slightly decreased the yield of insertion product **510** to 36% while increasing the yield of α-arylation product **719** (entry 5). We next investigated the impact of fluoride equivalents on the reaction. Decreasing the equivalents of CsF to 1.0 led to a high ratio of insertion (**510**) to α-arylation products (**719**), but resulted in incomplete conversion of **232** and recovery of β-ketolactone **218** (entry 6). On the other hand, increasing the amount of CsF to 15 equivalents resulted in a 10:1 ratio of insertion to α-arylation products and a 36% isolated yield of macrolactone **510** (entry 7). Finally, maintaining 15 equivalents of CsF while increasing the silyl aryl triflate (**232**) amount to 2 equivalents decreased the ratio of insertion to α-arylation to 1.23:1, leaving the yield of insertion product **510** unaffected (entry 8).

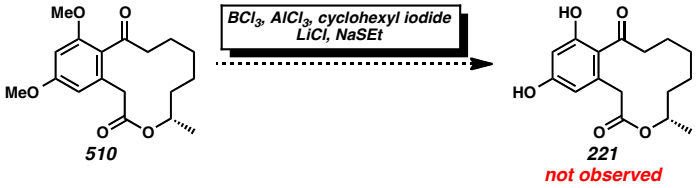
*Table 2.6. Acyl-alkylation reactions of dimethoxy silyl aryl triflate **232** with β-ketolactone **218**.*



entry	F^- source (equiv)	solvent	temperature	equiv ***218***	equiv ***232***	yield ***510***	ratio ***510:719***
1	KF/18-crown-6 (3.0)	THF	60 °C	1.0	1.2	–	–
2	TBAT (3.0)	THF	60 °C	1.0	1.2	–	–
3	CsF (3.0)	MeCN	80°C	1.0	1.2	32%	1.0:1.03
4	CsF (3.0)	MeCN	80°C	1.0	1.0	38%	1.4:1.0
5	CsF (3.0)	MeCN	80°C	1.2	1.0	36%	1.1:1.0
6	CsF (1.0)	MeCN	80°C	1.0	1.0	27%	4.6:1.0
7	CsF (15.0)	MeCN	80°C	1.0	1.0	36%	10.0:1.0
8	CsF (15.0)	MeCN	80°C	1.0	2.0	37%	1.23:1.0

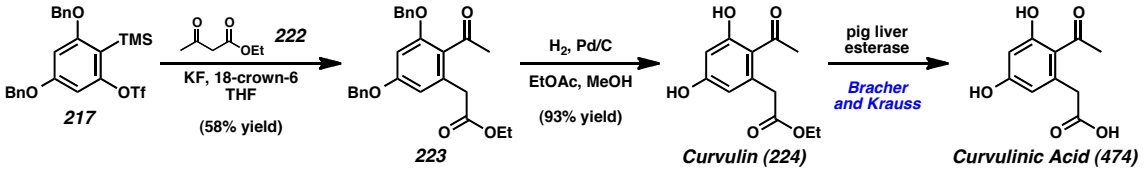
Although the yields of dimethylcurvularin (**510**) were modest, we were able to investigate demethylation reactions to convert **510** to curvularin (**221**). As anticipated from previous studies, attempts to accomplish this transformation in our laboratory with several reagents, including BCl_3,[88] $AlCl_3$,[89] cyclohexyl iodide,[90] LiCl,[91] and NaSEt,[92] all failed, resulting in either recovered starting material or decomposition (Scheme 2.61).

*Scheme 2.61. Attempted demethylation reactions of dimethylcurvularin (**510**).*



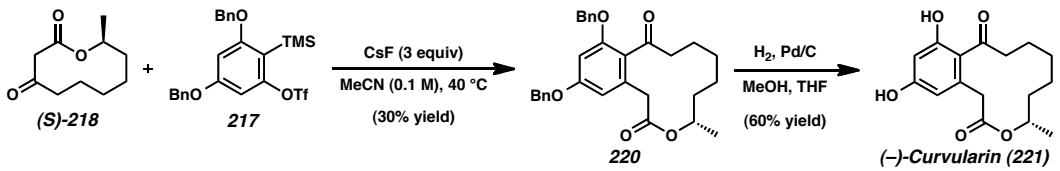
Given the difficulty observed for demethylation of dimethylcurvularin (**510**), focus was shifted to use of a dibenzyl silyl aryl triflate (**217**) alternative. Prior to acyl-alkylation reactions of silyl aryl triflate **217** with β-ketolatone **218**, we sought to verify that the benzyl groups could be easily cleaved under reported conditions. Acyl-alkylation of silyl aryl triflate **217** with ethyl acetoacetate (**222**) yielded ketoester **223** in 58% yield as a single isomer (Scheme 2.62). In order to verify the regioselectivity of insertion, the ketoester was advanced through hydrogenolysis over palladium on carbon to provide curvulin (**224**), an isolate of several species of *Curvularia*, in 93% yield.[5] The synthesis of curvulin (**224**) also constitutes a formal synthesis of curvulinic acid (**474**), which has been obtained from curvulin by saponification with pig liver esterase.[93]

*Scheme 2.62. Synthesis of curvulin (**224**) and formal synthesis of curvulinic acid (**474**).*



Encouraged by these preliminary findings, we turned our attention to the acyl-alkylation of silyl aryl triflate **217** with β-ketolactone **218** and completion of (–)-curvularin (**221**) (Scheme 2.63). As in the case of dimethoxy silyl aryl triflate **232**, both TBAT and KF/18-crown-6 fluoride sources failed to produce any acyl-alkylation products. In general, yields were moderate across a wide range of conditions similar to those listed in Table 6. Under optimized conditions, reaction of 1.5 equivalents of silyl aryl triflate **217** with 1.0 equivalent of β-ketolactone **218** and 3.0 equivalents CsF in acetonitrile at 40 °C provided dibenzylcurvularin (**220**) in 30% yield. Finally, hydrogenolysis of the benzyl ethers[28] produced (–)-curvularin (**221**) in 60% yield (8% overall yield in only 6 linear steps from acetate **676**). Spectral data of the synthetic curvularin matched that collected for the natural sample in all respects.

*2.63. Completion of (–)-curvularin (**221**) by acyl-alkylation of silyl aryl triflate **217** with β-ketolactone **218**.*



2.5 CONCLUDING REMARKS

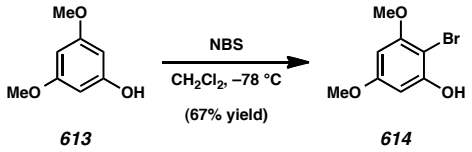
In conclusion, we have successfully completed the total syntheses of the natural products (–)-curvularin (**221**), (–)-diplodialide C (**640**), and curvulin (**224**). A unique resolution of diastereomers by ring-closing metathesis allowed for the preparation of diplodialide C from a mixture of diastereomeric dienes. Application of the aryne acyl-alkylation en route to curvularin resulted in a general synthesis that we anticipate will be applicable to a number of related natural and non-natural analogs. Importantly, we have devised an innovative and convergent route to these structures that generates two new carbon–carbon bonds in a single operation, avoiding the need to perform tedious macrolactonization reactions to build the 12-membered lactone of curvularin. Furthermore, the aryne insertion technology has provided a synthetic bridge between two biosynthetically distinct classes of compounds, the diplodialides and curvularin. The utilization of these methods in additional complex settings is currently underway in our laboratories.

2.6 EXPERIMENTAL SECTION

2.6.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received with the exception of acrolein, which was distilled over hydroquinone under an argon atmosphere prior to use. Syringe-pump additions were performed using a kdScientific single syringe pump. 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 by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 (at 500 MHz and 125 MHz, respectively) 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), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Optical rotations were measured on a Jasco P-1010 polarimeter using a 50 mm path-length cell.

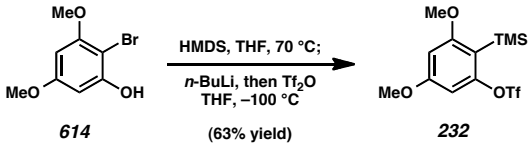
2.6.2 Preprative Procedures and Spectroscopic Data



613 *614*

Bromophenol 614

A solution of phenol **613** (100 mg, 0.649 mmol) in CH_2Cl_2 (6.4 mL) was prepared and cooled to –78 °C. *N*-Bromosuccinimide (NBS, 115 mg, 0.649 mmol) was added and the reaction was maintained at –78 °C until phenol **613** was consumed by TLC analysis. The reaction was quenched at –78 °C with 10% aqueous K_2CO_3 solution (2 mL) and warmed to room temperature. The reaction was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield bromophenol **614** (101.9 mg, 67% yield): R_f = 0.28 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (d, J = 2.7 Hz, 1H), 6.12 (d, J = 2.7 Hz, 1H), 5.67 (s, 1H), 3.86 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.69, 156.79, 153.84, 93.21, 92.50, 91.04, 56.27, 55.54; IR (NaCl/film) 3482, 2942, 1592, 1466, 1350, 1312, 1212, 1155, 1099, 1025, 813 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_8H_9O_3{}^{79}Br$ $[M]^+$: 231.9735, found 231.9744.

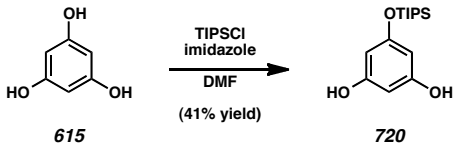


Silyl aryl triflate 232

Bromophenol **614** (515 mg, 2.21 mmol) and hexamethyldisilazide (922 μL, 4.42 mmol) were combined in THF (5 mL). The solution was heated to 70 °C and maintained for 5 h. The reaction was cooled to room temperature and concentrated under vacuum. The resulting oil was immediately taken on to the next step.

The crude residue was taken up in THF (15 mL) and cooled to –100 °C. *n*-Butyllithium (2.17 M in hexanes, 1.12 mL, 2.43 mmol) was added slowly and the reaction was allowed to warm to –82 °C. The reaction was cooled again to –100 °C and maintained between –100 °C and –82 °C for 30 minutes. After this period, triflic anhydride (446 μL, 2.65 mmol) was added at –100 °C. The reaction was warmed to –80 °C, quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL), and subsequently warmed to room temperature. The reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (25:1 petroleum ether:diethyl ether eluent) to yield silyl aryl triflate **232** (493 mg, 63% yield): R_f = 0.34 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (d, J = 2.0 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 0.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.36, 162.69, 155.52, 118.82 (q, J = 320.9 Hz), 112.29, 98.32, 98.31, 98.29, 98.28, 97.56, 55.77, 55.69, 1.08; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.07; IR (NaCl/film) 2960, 1609, 1565, 1460, 1407, 1311, 1245, 1213, 1141, 1094, 1053, 961, 846

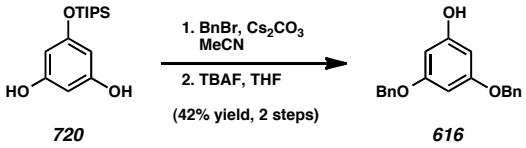
cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{17}O_5F_3SSi$ [M+H]$^+$: 358.0518, found 358.0511.



615 *720*

Silylphenol 720

Phloroglucinol (**615**, 500 mg, 3.96 mmol) and imidazole (90 mg, 1.32 mmol) were combined in DMF (16 mL). Chlorotriisopropylsilane (TIPSCl, 283 μL, 1.32 mmol) was added and the resulting solution was maintained at room temperature for 36 hours. After this period, the reaction was diluted with diethyl ether (25 mL). The organic layer was washed with water (25 mL) and brine (25 mL), dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield **720** (154.1 mg, 41% yield) as a clear oil: R_f = 0.20 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (d, *J* = 2.2 Hz, 2H), 5.97 (t, *J* = 2.1 Hz, 1H), 5.07 (s, 2H), 1.30–1.18 (m, 3H), 1.09 (d, *J* = 7.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.08, 157.02, 100.38, 96.18, 17.89, 12.60; IR (NaCl/film) 3391, 2945, 2868, 1624, 1602, 1493, 1145, 1018, 881, 837, 818, 783, 689, 662 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{15}H_{27}O_3Si$ [M+H]$^+$: 283.1724, found 283.1723.

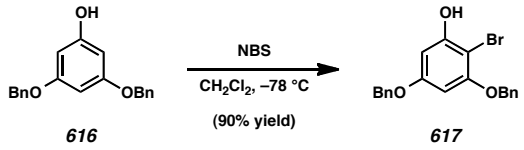


720 *616*

Phenol 616

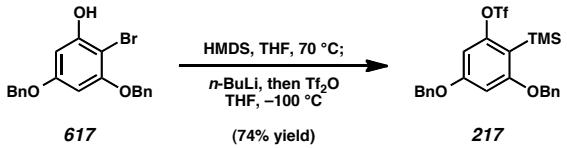
Silylphenol **720** (135 mg, 0.478 mmol) and Cs_2CO_3 (343 mg, 1.05 mmol) were combined in acetonitrile (5 mL). Benzyl bromide (119 μL, 1.00 mmol) was added and the resulting suspension was maintained at room temperature with stirring until silylphenol **720** was fully consumed by TLC analysis. Upon completion, the reaction was diluted with diethyl ether (25 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and immediately carried on to the next step.

The crude residue was taken up in THF (5 mL). Tetra-*n*-butylammonium fluoride solution (1 M in THF, 717 μL) was added and the solution was maintained at room temperature until the starting material had been fully consumed by TLC analysis. Upon completion, the reaction was diluted with diethyl ether (25 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield phenol **616** (62 mg, 42% yield over two steps): R_f = 0.26 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.32 (m, 10H), 6.29 (t, J = 2.1 Hz, 1H), 6.13 (d, J = 2.1 Hz, 2H), 5.17 (s, 1H), 5.00 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.79, 157.27, 136.74, 128.62, 128.06, 127.57, 95.48, 95.03, 70.14; IR (NaCl/film) 3391, 3032, 2931, 1600, 1498, 1453, 1377, 1214, 1152, 1053, 820, 735, 697 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{19}O_3$ $[M+H]^+$: 307.1329, found 307.1327.



Bromophenol 617

A solution of phenol **616** (20 mg, 0.065 mmol) in CH_2Cl_2 (1.3 mL) was prepared and cooled to –78 °C. *N*-Bromosuccinimide (NBS, 11.6 mg, 0.0653 mmol) was added and the reaction was maintained at –78 °C until phenol **616** was consumed by TLC analysis. The reaction was quenched at –78 °C by the addition of 10% aqueous K_2CO_3 solution (500 μL) and warmed to room temperature. The reaction was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield bromophenol **617** (22.6 mg, 90% yield): R_f 0.33 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.46 (m, 2H), 7.46–7.39 (m, 6H), 7.39–7.33 (m, 2H), 6.39 (d, J = 2.7 Hz, 1H), 6.28 (d, J = 2.7 Hz, 1H), 5.71 (s, 1H), 5.11 (s, 2H), 5.02 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.74, 155.94, 153.91, 136.44, 136.33, 128.67, 128.61, 128.17, 128.01, 127.57, 127.04, 94.75, 94.63, 92.06, 70.80, 70.35; IR (NaCl/film) 3491, 1594, 1453, 1189, 1160, 1093, 1023, 810, 736, 696 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{16}O_3{}^{79}Br$ $[M–H]^-$: 383.0288, found 383.0300; *m/z* calc'd for $C_{20}H_{16}O_3{}^{81}Br$ $[M–H]^-$: 385.0270, found 385.0281.

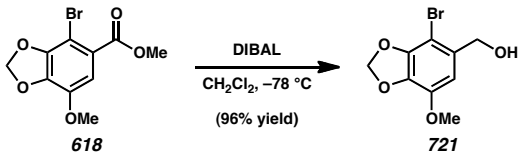


Silyl aryl triflate 217

Bromophenol **617** (310 mg, 0.805 mmol) and hexamethyldisilazide (361 μL, 1.77 mmol) were combined in THF (3.2 mL). The solution was heated to 70 °C and maintained for 5 h. The reaction was cooled to room temperature and concentrated under vacuum. The resulting oil was immediately taken on to the next step.

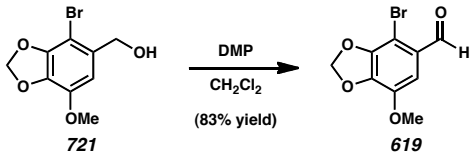
The crude residue was taken up in THF (11 mL) and cooled to –100 °C. *n*-Butyllithium (2.5 M in hexanes, 381 μL, 0.952 mmol) was added slowly and the reaction was allowed to warm to –82 °C. The reaction was cooled again to –100 °C and maintained between –100 °C and –82 °C for 30 minutes. After this period, triflic anhydride (175 μL, 1.04 mmol) was added at –100 °C. The reaction was warmed to –80 °C, quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL), and subsequently warmed to room temperature. The reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (50:1 petroleum ether:diethyl ether eluent) to yield silyl aryl triflate **217** (328 mg, 74% yield): $R_f = 0.55$ (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.33 (m, 10H), 6.59 (d, J = 2.0 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 5.03 (s, 2H), 5.02 (s, 2H), 0.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.40, 161.69, 155.47, 136.10, 136.07, 128.93, 128.85, 128.57, 128.46, 128.00, 127.80, 118.8 (q, J = 320.9 Hz), 112.76, 99.48, 99.30, 71.05, 70.67, 1.19; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.04; IR (NaCl/film) 2954, 1604,

1562, 1417, 1214, 1140, 1089, 1026, 952, 844, 736, 697 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{24}F_3O_5SSi$ $[M–H]^-$: 509.1071, found 509.1062.



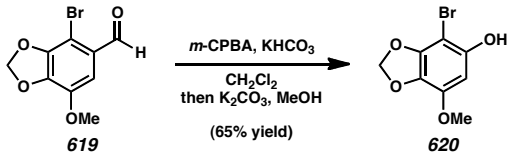
Benzyl alcohol 721

A solution of methyl ester **618** (3.0 g, 10.4 mmol) in CH_2Cl_2 (100 mL) was prepared and cooled to –78 °C. Diisobutylaluminum hydride (DIBAL, 4.1 mL, 22.8 mmol) was added dropwise and the reaction was maintained at –78 °C until methyl ester **618** was consumed by TLC analysis. The reaction was quenched at –78 °C by the addition of saturated aqueous sodium potassium tartrate solution (25 mL) and then warmed to room temperature. The reaction was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield benzylic alcohol **721** (2.6 g, 96% yield): R_f = 0.33 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.05 (s, 2H), 4.66 (d, *J* = 5.8 Hz, 2H), 3.90 (s, 3H), 1.99 (t, *J* = 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.00, 142.90, 135.00, 133.49, 108.42, 101.94, 93.34, 64.47, 56.75; IR (NaCl/film) 3187, 2904, 1628, 1486, 1465, 1446, 1343, 1165, 1106, 1038, 968, 931, 824, 701 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_8O_3{}^{79}Br$ $[M–OH]^+$: 242.9651, found 242.9648; *m/z* calc'd for $C_9H_8O_3{}^{81}Br$ $[M–OH]^+$: 244.9632, found 244.9629.



Aldehyde 619

A solution of Dess–Martin periodinane (2.94 g, 6.92 mmol) in CH_2Cl_2 (28 mL) was prepared under nitrogen. Alcohol **721** (1.63 g, 6.24 mmol) in CH_2Cl_2 (72 mL) was added and the reaction was maintained under nitrogen until alcohol **721** was fully consumed by TLC analysis. The reaction was quenched by the addition of a 1:1 v/v solution of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (60 mL total volume). The reaction was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL) and subsequently dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (hexanes → 7:3 hexanes:ethyl acetate eluent) to yield aldehyde **619** (1.34 g, 83% yield): R_f = 0.37 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.24 (s, 1H), 6.16 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 147.4, 143.5, 140.9, 127.6, 109.5, 103.0, 98.8, 56.8; IR (NaCl/film) 1683, 1619, 1485, 1446, 1351, 1315, 1169, 1112, 1048, 993, 928, 654 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_8O_4{}^{79}Br$ $[M+H]^+$: 258.96, found 258.9597; *m/z* calc'd for $C_9H_8O_4{}^{81}Br$ $[M+H]^+$: 260.9581, found 260.9578.

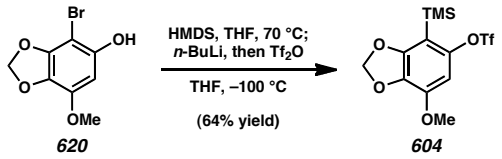


Bromophenol 620

A flask was charged with aldehyde **619** (100 mg, 0.386 mmol) and $KHCO_3$ (4 mg, 0.04 mmol) under a nitrogen atmosphere. To this was added *m*-CPBA (20 mg, 0.116 mmol) as a solution in CH_2Cl_2 (4 mL). Four additional portions of *m*-CPBA (20 mg, 0.116 mmol, each) were added as CH_2Cl_2 solutions (0.25 mL, each) at three-hour intervals. Nine hours following the final *m*-CPBA addition, the reaction was quenched by the addition of saturated $NaHCO_3$ aqueous solution (1 mL) and diluted with CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was further washed with CH_2Cl_2 (10 mL). The combined organic layers were sequentially washed with water (10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), and brine (10 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under vacuum to yield a crystalline solid.

The crude solid (103 mg) was taken up in a 10% solution of K_2CO_3 in methanol (7.5 mL). The resultant suspension was maintained with stirring at room temperature until the starting material had been completely consumed by TLC analysis. Following this period, the reaction was concentrated under vacuum, diluted with water (10 mL), and acidified to pH 1.5 with 6 N HCl. **Warning:** vigorous gas evolution. The aqueous solution was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield bromophenol **620** (62 mg, 65% yield) as a white solid: $R_f = 0.20$ (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.99 (s, 2H), 5.18 (s, 1H), 3.86 (s,

3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.42, 147.02, 143.93, 130.01, 102.37, 95.12, 83.45, 57.12, 57.10.; IR (NaCl/film) 3093, 2899, 1642, 1454, 1350, 1167, 1109, 1051, 971, 935, 874, 797, 700 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_8H_7O_4{}^{79}Br$ $[M]^+$: 245.9522, found 245.9525; *m/z* calc'd for $C_8H_7O_4{}^{81}Br$ $[M]^+$: 247.9502, found 247.9506.

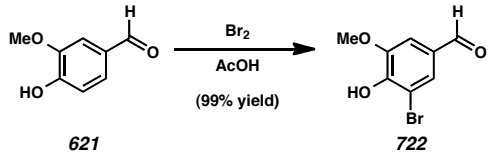


Silyl aryl triflate 604

Bromophenol **620** (149.6 mg, 0.606 mmol) and hexamethyldisilazide (253 μL, 1.21 mmol) were combined in THF (1.2 mL). The solution was heated to 70 °C and maintained for 8 h. The reaction was cooled to room temperature and concentrated under vacuum. The resulting oil was immediately taken on to the next step.

The crude residue was taken up in THF (8 mL) and cooled to –100 °C. *n*-Butyllithium (2.5 M in hexanes, 266 μL, 0.666 mmol) was added slowly and the reaction was allowed to warm to –82 °C. The reaction was cooled again to –100 °C and maintained between –100 °C and –82 °C for 30 minutes. After this period, triflic anhydride (122 μL, 0.727 mmol) was added at –100 °C. The reaction was warmed to –80 °C, quenched by the addition of saturated aqueous sodium bicarbonate solution (4 mL), and subsequently warmed to room temperature. The reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (50:1 petroleum ether:diethyl ether eluent) to yield silyl aryl triflate **604** (144.6 mg, 64% yield): R_f = 0.36 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 1H),

5.99 (s, 2H), 3.89 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.99, 148.40, 144.10, 133.88, 118.76 (q, J = 300.56 Hz), 107.02, 101.78, 101.32, 57.02, 0.23; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.07; IR (NaCl/film) 2058, 2901, 1645, 1487, 1419, 1388, 1294, 1244, 1211, 1140, 1111, 1046, 984, 893, 845, 802 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{15}O_6SiSF_3$ $[M+H]^+$: 372.0311, found 372.0321.

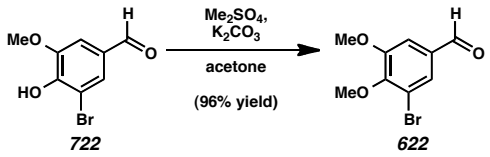


621 *722*

3-Bromovanillin (722)

The following procedure was adopted from a literature report by Rao and Stuber.[52] A single-neck, 2 L round-bottom flask was charged with vanillin (**621**, 50 g, 328.6 mmol). Glacial acetic acid was added (1.1 L, 3.0 M). Following this, a mechanical stirrer was affixed to the flask through the neck and, with vigorous but even stirring, the vanillin dissolved to form a pale yellow solution. At this point, neat bromine (16.84 mL, 361.5 mmol) was added in a rapid dropwise fashion to the stirring solution through the flask neck to produce a deep red-orange solution. Following addition, the reaction was maintained with vigorous stirring for 90 minutes, after which time TLC analysis indicated formation of the product (R_f = 0.32, 15% ethyl acetate in hexanes). The reaction also resulted in the formation of a bright orange-yellow precipitate when nearing completion. Upon completion of the reaction, the mechanical stirrer was disengaged and the contents of the reaction flask were poured onto chilled deionized water (0 °C, 600 mL), resulting in further precipitation of a pale yellow solid from the bright orange aqueous layer. The reaction flask was washed into this flask with more chilled water.

While still cooled, the contents of the 1 L Erlenmeyer flask were filtered over a glass frit to separate the desired solid product. The isolated solid product (**722**, 75.25 g, 99% yield) was transferred to a flask and dried under vacuum for a period of 8 hours.

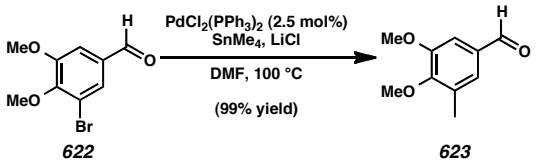


722 *622*

3-bromo-4,5-dimethoxy benzaldehyde (622)

To a 1 L round-bottom flask was added anhydrous K_2CO_3 (113.56 g, 821.6 mmol), followed by a solution of bromobenzaldehyde **722** (75.25 g, 325.66 mmol) in reagent grade acetone (700 mL). A mechanical stirrer was affixed to the reaction flask, and vigorous stirring was required to generate an evenly distributed, maroon suspension. To this stirring mixture was added Me_2SO_4 (77.74 mL, 821.69 mmol) over 1 minute via funnel. The reaction was left to stir vigorously at 25 °C for 8 hours, at which point TLC analysis confirmed the conversion of phenol **722** to a less polar product. The reaction contents were then vacuum filtered over a glass frit to separate residual solid K_2CO_3. The filtered solid was washed with acetone (2 x 100 mL) and methanol (100 mL). The organic filtrate was concentrated to an orange oil and purified by flash chromatography (5% → 50% ethyl acetate in hexanes eluent) to yield bromobenzaldehyde **622** (76.6 g, 96% yield), which was isolated as a white powder: R_f = 0.56 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.67 (d, J = 1.80 Hz, 1H), 7.40 (d, J = 1.85 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.83, 154.17, 151.81, 133.03, 128.77, 117.92, 110.09, 60.83, 56.25; IR (NaCl/film) 2945, 2860, 1692, 1588, 1566, 1486, 1469, 1452, 1420, 1393, 1380, 1312, 1281, 1240, 1212, 1144,

1133, 1048, 993, 855, 840 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_9BrO_3$ $[M]^+$: 243.9735, found 243.9731.

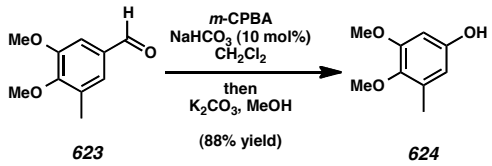


622 *623*

3,4-dimethoxy-5-methylbenzaldehyde (623)

A 250 mL round-bottom flask was charged with lithium chloride (4.32 g, 102.00 mmol) and then flame dried. To this flask was added a solution of benzaldehyde **622** (5.0 g, 20.40 mmol) in *N*,*N*-dimethylformamide (200 mL) that had been rigorously sparged with argon. Next, $PdCl_2(PPh_3)_2$ (0.358 g, 0.51 mmol) was added to the stirring mixture, producing a bright yellow-orange solution that was stirred vigorously. A reflux condenser was affixed to the top of the reaction flask before adding, dropwise, neat tetramethyltin (7.06 mL, 51.0 mmol). The reaction vessel was sealed under an argon atmosphere and heated to reflux in 100 °C oil bath. The reaction was maintained at reflux for 3 hours; during this period the color of the solution changed to dark red-orange.[94] TLC analysis of the reaction after this period showed full consumption of the starting material. The reaction was cooled to room temperature and then quenched by the addition of H_2O (200 mL). The aqueous layer was thoroughly extracted with ethyl acetate (5 x 200 mL), and the combined organic layers were washed with brine (150 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to furnish benzaldehyde **623** as a colorless oil (3.63 g, 99% yield): $R_f = 0.42$ (10% ethyl acetate in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.17 (d, J = 1.71 Hz, 1H), 7.16 (d, J = 0.60 Hz, 1H),

3.78 (s, 3H), 3.77 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.14, 153.02, 152.70, 126.95, 108.79, 60.05, 55.65, 15.75; IR (NaCl/film) 2939, 2833, 1693, 1586, 1491, 1465, 1422, 1387, 1329, 1299, 1233, 1140, 1096, 1003, 856 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{12}O_3$ $[M]^+$: 180.0786, found 180.0779.

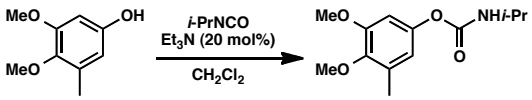


623 ***624***

3,4-dimethoxy-5-methylphenol (624)

A 250 mL round-bottom flask was charged with anhydrous $NaHCO_3$ (0.467 g, 0.56 mmol). To this, was added a solution of benzaldehyde **623** (1.00 g, 5.55 mmol) in CH_2Cl_2 (11 mL). This mixture was vigorously stirred until the $NaHCO_3$ fully dissolved. At this point, *m*-CPBA (1.92 g, 11.10 mmol) was added as a solid in a single portion to the pale yellow solution. Immediately, the solution turned bright yellow, and was maintained with stirring at 25 °C under an atmosphere of N_2. Notable accumulation of precipitate resulted in increasing turbidity of the solution, and after 6 hours, TLC analysis indicated formation of a new product (R_f = 0.22, hexanes) and consumption of benzaldehyde **623**. At this time, methanol (110 mL) and anhydrous K_2CO_3 (2.30 g, 16.65 mmol) were added, and the solution turned maroon in color. The reaction was maintained at 25 °C for 12 hours, resulting in formation of a new polar product. The reaction was stopped by concentration under vacuum to yield a dark maroon solid. This solid was dissolved in H_2O (100 mL), and then neutralized with concentrated aqueous HCl (6 mL). **Warning:** vigorous gas evolution. The resulting suspension was extracted with CH_2Cl_2 (5 x 100 mL), and the combined organic extracts were washed with

saturated aqueous $NaHCO_3$ (2 x 200 mL) to remove benzoate byproducts. The organic layers were dried with Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (30% ethyl acetate in hexanes eluent) to provide phenol **624** (0.822 g, 4.89 mmol, 88% yield) as a white solid: R_f = 0.30 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, J = 2.80 Hz, 1H), 6.20 (d, J = 2.80 Hz, 1H), 4.53 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.36, 151.78, 141.12, 132.41, 108.36, 98.17, 60.35, 55.69, 15.85; IR (NaCl/film) 3272, 2957, 1614, 1483, 1463, 1440, 1430, 1348, 1268, 1226, 1219, 1196, 1181, 1154, 1096, 1001, 854, 772, 737 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_9H_{12}O_3$ $[M]^+$: 168.0786, found 168.0753.

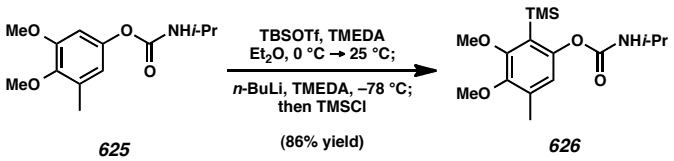


624 *625*

Isopropyl carbamate 625

This procedure was adopted from the literature procedure reported by Bronner, et al.[54] A 100 mL round-bottom flask was charged with a solution of phenol **624** (1.696 g, 10.08 mmol) in CH_2Cl_2 (35 mL). The solution was stirred at 25 °C under an atmosphere of N_2 before neat isopropyl isocyanate (1.483 mL, 15.12 mmol) was added via syringe. The solution turned orange, and after 5 minutes of stirring, freshly distilled Et_3N (0.281 mL, 2.02 mmol) was added via syringe to effect the formation of a dark purple solution. The reaction was maintained with stirring for 18 hours at 25 °C. Following this period, TLC analysis showed conversion of phenol **624** to a single product. The reaction was concentrated to an orange-brown residue and purified by flash chromatography (5% ethyl

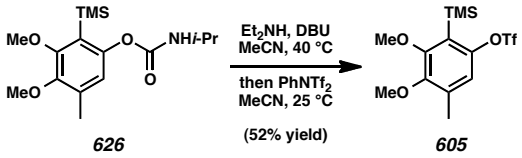
acetate in hexanes eluent) to provide isopropyl carbamate **625** as a clear, pale yellow oil (2.404 g, 94% yield): R_f = 0.48 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, J = 2.65 Hz, 1H), 6.54 (d, J = 2.65 Hz, 1H), 2.79 (s, 1H), 3.87 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.24 (s, 3H), 1.23 (d, J = 7.25 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.92, 152.87, 146.66, 144.62, 115.29, 104.21, 60.15, 55.78, 43.44, 22.93, 15.91; IR (NaCl/film) 3326, 2972, 2936, 1715, 1604, 1529, 1490, 1466, 1422, 1332, 1220, 1190, 1175, 1142, 1095, 1050, 1009, 936, 854, 773 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{13}H_{19}NO_4$ $[M]^+$: 253.1314, found 253.1319.



TMS carbamate 626

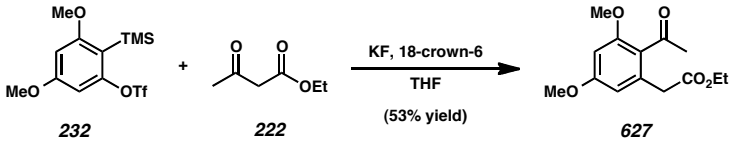
This procedure was adopted from the literature procedure reported by Bronner, et al.[54] To a 25 mL round-bottom flask was added a solution of isopropyl carbamate **625** (2.404 g, 9.49 mmol) in diethyl ether (94 mL), followed by freshly distilled TMEDA (1.56 mL, 10.44 mmol) via syringe. The solution was cooled to 0 °C in an ice water bath. Upon temperature equilibration (15 minutes), neat distilled TBSOTf (2.398 mL, 10.44 mmol) was added. The resulting solution was maintained for 10 minutes at 0 °C and then the flask was allowed to warm to 23 °C over 30 minutes. At this point, TLC analysis showed formation of a less polar product (R_f = 0.81, 15% ethyl acetate in hexanes) corresponding to the *N*-silylated intermediate. Additional TMEDA was added to the mixture via syringe (5.688 mL, 37.964 mmol). The reaction was then cooled to –78 °C in a dry ice and acetone bath with vigorous stirring to avoid aggregation of triflate salts.

Next, *n*-BuLi solution (2.32 M in hexanes, 16.36 mL, 37.96 mmol) was added dropwise down the side of the flask of the cold solution. The solution was maintained with stirring at –78 °C for 4 hours, after which time freshly distilled TMSCl (8.432 mL, 66.437 mmol) was added dropwise to the flask. The reaction vessel, in the cold bath, was allowed to warm to 23 °C over the course of two hours. At this point, TLC analysis indicated the presence of a single, new product. Saturated aqueous $NaHSO_4$ solution (50 mL) was added and stirred with the reaction mixture for 1 hour. The layers were separated and the organic layer was washed with an additional 50 mL of the $NaHSO_4$ solution. The combined aqueous layers were then extracted with diethyl ether (3 x 50mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and then concentrated under vacuum to a colorless crystalline solid. Purification via flash chromatography (5% → 20% ethyl acetate in hexanes eluent) provided pure TMS carbamate **626** (2.63 g, 86% yield): R_f = 0.63 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.69 (d, J = 7.08 Hz, 1H), 3.89 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.23 (s, 3H), 1.23 (d, J = 6.75, 6H), 0.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.69, 153.00, 149.33, 147.28, 133.33, 121.79, 118.88, 59.19, 58.54, 42.27, 21.88, 14.83, 0.13; IR (NaCl/film) 3326, 2971, 2937, 1710, 1601, 1530, 1464, 1384, 1370, 1324, 1247, 1220, 1193, 1179, 1080, 1026, 987, 844, 810, 759 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{27}NO_4Si$ $[M+H]^+$: 326.1734, found 326.1725.



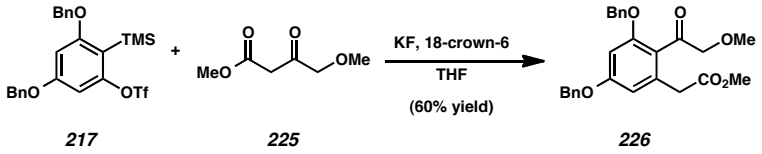
Silyl aryl triflate 605

This procedure was adopted from the literature procedure reported by Bronner, et al.[54] A 250 mL round-bottom flask was charged with a solution of TMS carbamate **626** (2.63 g, 8.10 mmol) in acetonitrile (80 mL). To this was added diethylamine (1.01 mL, 9.71 mmol), followed by DBU (1.82 mL, 12.14 mmol). The reaction was carefully monitored by TLC as it was heated to 40 °C in an oil bath. After 10 minutes, TLC anaylsis indicated complete consumption of the starting material and conversion to two spots (R_{f1} = 0.78 and R_{f2} = 0.60).[95] The reaction was immediately removed from the oil bath and a solution of $PhNTf_2$ (4.34 g, 12.14 mmol) in acetonitrile (24 mL) was added via syringe. The reaction was maintained with stirring for 12 hours at 23 °C, at which point the reaction solution was washed with saturated aqueous $NaHSO_4$ (2 x 50 mL) and brine (100 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum to an orange oil, and purified via flash chromatography (5% ethyl acetate in hexanes eluent) to yield silyl aryl triflate **605** (1.57 g, 52% yield) as a pale yellow oil: R_f = 0.68 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.27 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.72, 150.74, 149.21, 135.84, 117.49 (q, J = 320 Hz), 124.53, 117.96, 60.79, 60.03, 16.43, 1.41; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.10; IR (NaCl/film) 2956, 2858, 1600, 1464, 1420, 1383, 1368, 1292, 1248, 1213, 1179, 1142, 1068, 1023, 982, 930, 873, 846, 764 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{19}F_3O_5SSi$ $[M]^+$: 372.0675, found 372.0674.



Ketoester 627

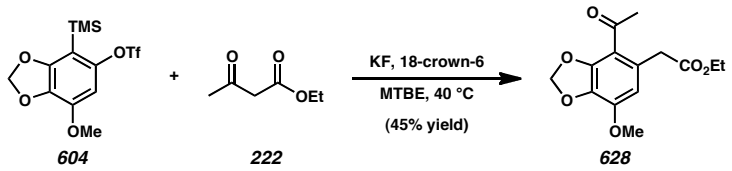
Silyl aryl trilfate **232** (52 mg, 0.144 mmol) and ethyl acetoacetate (**222**, 15 mg, 0.115 mmol) were combined in THF (1.2 mL). To this was sequentially added 18-crown-6 (91 mg, 0.346 mmol) and KF (20 mg, 0.346 mmol). The resulting suspension was maintained at room temperature with vigorous stirring until silyl aryl triflate **232** had been completely consumed by TLC analysis. Following this period the reaction was diluted with diethyl ether (10 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield ketoester **627** (16.2 mg, 53% yield): R_f = 0.23 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (d, J = 2.3 Hz, 1H), 6.37 (d, J = 2.2 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.70 (s, 2H), 2.52 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.83, 171.31, 161.51, 159.31, 134.98, 123.82, 108.12, 97.48, 60.84, 55.60, 55.39, 39.21, 32.26, 14.19; IR (NaCl/film) 2979, 2941, 1732, 1682, 1602, 1461, 1425, 1318, 1263, 1203, 1159, 1093, 1029, 947, 836 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{14}H_{19}O_5$ $[M+H]^+$: 267.1232, found 267.1231.



217 *225* *226*

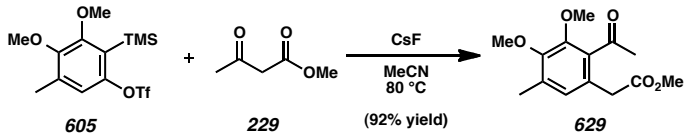
Ketoester 226

To a solution of silyl aryl triflate **217** (65.5 mg, 0.128 mmol) and β-ketoester **225** (15 mg, 0.103 mmol) in THF (1.0 mL) was sequentially added 18-crown-6 (81.3 mg, 0.308 mmol) and KF (17.9 mg, 0.308 mmol). The resulting suspension was maintained with vigorous stirring until β-ketoester **225** had been completely consumed by TLC analysis. Following this period, the reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL x 2) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield ketoester **226** (26.8 mg, 60% yield): R_f = 0.13 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.30 (m, 10H), 6.57 (d, J = 2.2 Hz, 1H), 6.51 (d, J = 2.2 Hz, 1H), 5.06 (s, 2H), 5.05 (s, 2H), 4.50 (s, 2H), 3.73 (s, 2H), 3.69 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.33, 171.56, 161.19, 158.90, 136.17, 136.12, 135.72, 128.71, 128.70, 128.40, 128.28, 127.72, 127.57, 120.95, 109.95, 99.36, 78.78, 70.99, 70.24, 59.08, 52.04, 39.07; IR (NaCl/film) 2947, 1734, 1700, 1601, 1436, 1375, 1319, 1160, 1124, 1073, 739 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{26}H_{26}O_6$ $[M+H]^+$: 434.1729, found 434.1720.



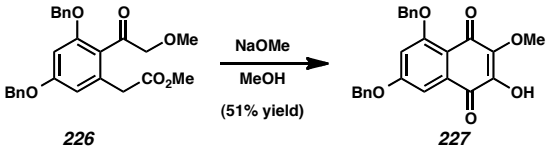
Ketoester 628

To a solution of silyl aryl triflate **604** (23.8 mg, 0.0639 mmol) and ethyl acetoacetate (**222**, 4.1 mL, 0.0320 mmol) in *tert*-butyl methyl ether (MTBE, 0.32 mL) was added 18-crown-6 (25.3 mg, 0.0959 mmol) and KF (5.6 mg, 0.0959 mmol). The resulting suspension was heated in an oil bath to 40 °C and maintained for a period of 1 hour. Following this time, the reaction was cooled to room temperature, diluted in diethyl ether (25 mL), and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield ketoester **628** (4 mg, 45% yield): R_f = 0.49 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.07 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.81 (s, 2H), 2.55 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 147.4, 143.5, 140.9, 127.6, 109.5, 103.0, 98.8, 56.8; IR (NaCl/film) 2985, 2904, 1731, 1674, 1632, 1427, 1312, 1281, 1162, 1100, 940, 854 cm^{-1}; HRMS (MM:ESI-APCI) *m/z* calc'd for $C_{14}H_{16}O_6$ $[M+H]^+$: 281.1020, found 281.1020.



Ketoester 629

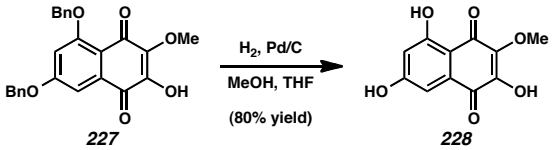
To a round-bottom flask was added oven-dried CsF (0.053 g, 0.348 mmol), followed by a solution of methyl acetoacetate (**229**, 0.025 mL, 0.232 mmol) in acetonitrile (1 mL). Next, aryne precursor **605** was added via syringe (0.108 g, 0.290 mmol), and the reaction was maintained with stirring in an oil bath at 80 °C for 2 hours. The reaction was cooled to 25 °C, concentrated under vacuum, and the crude reaction mixture was adsorbed onto Celite (1 g). Ketoester **629** was purified by flash chromatography (10% ethyl acetate in hexanes eluent) and isolated as a colorless oil (57 mg, 92 % yield): $R_f = 0.56$ (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 1H), 3.88 (s, 3H), 3.83, (s, 3H), 3.68 (s, 3H), 3.62 (s, 2H), 2.55 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.42, 171.97, 150.74, 150.32, 134.33, 134.06, 128.55, 126.63, 61.14, 60.05, 51.95, 37.73, 32.23, 15.85; IR (NaCl/film) 2951, 2849, 1740, 1692, 1604, 1568, 1484, 1451, 1437, 1400, 1351, 1306, 1269, 1200, 1167, 1147, 1078, 1040, 1012 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{18}O_5$ $[M]^+$: 266.1154, found 266.1152.



226 *227*

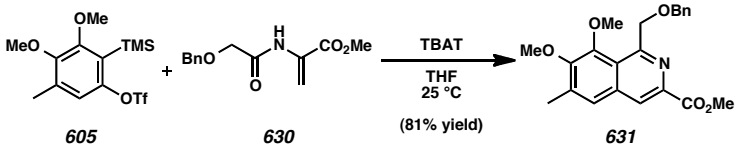
Hydroxynaphthoquinone 227

To NaH (60 wt. % dispersion in mineral oil, 12.3 mg, 0.308 mmol) in a vial was added MeOH (1.0 mL), and the resulting suspension was stirred for 10 minutes. **Warning:** vigorous gas evolution. A separate solution of ketoester **226** (26.8 mg, 0.0617 mmol) in MeOH (1.0 mL) was prepared. Slowly the solution of NaOMe was added to the solution of ketoester **226** and maintained with stirring at room temperature for 20 minutes. Following this period, the vial was opened to the atmosphere and heated at 60 °C until ketoester **226** has been fully consumed by TLC analysis. Upon completion, the reaction was cooled to room temperature and diluted with ethyl acetate (10 mL). The resulting solution was washed with 1 N K_2CO_3 solution (5 x 15 mL), the combined aqueous extracts were acidified with 6 N HCl to pH 1.5, and the acidic solution was extracted with ethyl acetate (15 mL x 3). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography to yield hydroxynaphthoquinone **227** (13 mg, 51% yield): R_f = 0.43 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.1 Hz, 2H), 7.48–7.29 (m, 9H), 6.86 (d, J = 2.5 Hz, 1H), 6.55 (s, 1H), 5.21 (s, 2H), 5.18 (s, 2H), 4.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.23, 179.01, 163.28, 160.84, 140.79, 140.13, 135.84, 135.40, 133.06, 128.80, 128.65, 128.55, 127.87, 127.65, 126.58, 113.08, 106.98, 104.88, 70.92, 70.71, 60.69; IR (NaCl/film) 3367, 2944, 1653, 1592, 1440, 1318, 1207, 1169, 1052, 1010, 736 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{25}H_{20}O_6$ $[M+H]^+$: 416.1260, found 416.1251.



3-Methoxy-2,5,7-trihydroxy-1,4-naphthaquinone (228)

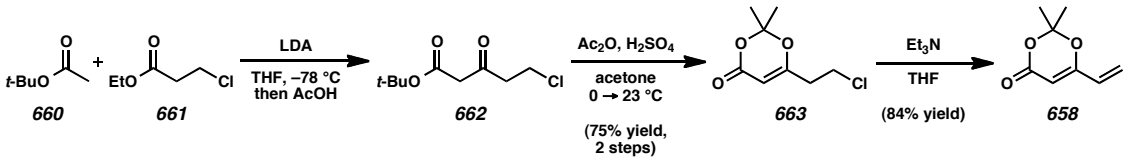
To a solution of hydroxynaphthoquinone **227** (9.7 mg, 0.0233 mmol) in MeOH/THF (1:1 (v/v) mixture, 2 mL total volume) was added 10 wt. % Pd/C (12.4 mg, 0.0116 mmol). A hydrogen balloon was attached to the system and the suspension was maintained under the H_2 atmosphere with vigorous stirring at room temperature until hydroxynaphthoquinone **227** had been fully consumed by TLC analysis. The suspension was filtered through Celite, concentrated under vacuum, and purified by flash chromatography (1:1 dichloromethane:ethyl acetate eluent) to yield 3-methoxy-2,5,7-trihydroxy-1,4-naphthaquinone (**228**, 4.4 mg, 80% yield): R_f = 0.17 (1:1 dichloromethane:ethyl acetate); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.92 (d, J = 1.8 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 185.46, 181.62, 163.54, 163.48, 147.64, 140.50, 132.08, 107.91, 107.76, 106.93, 59.89; IR (NaCl/film) 3305, 1611, 1467, 1284, 1170, 1096 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{11}H_8O_6$ [M]$^+$: 236.0321, found 236.0357.



Isoquinoline 631

A 100 mL round-bottom flask was charged with TBAT (0.225 g, 0.416 mmol). To this flask was added a solution of *N*-acyl enamide **630** (0.049 g, 0.208 mmol) in THF

(21 mL). Finally, aryne precursor **605** was added (0.116 g, 0.312 mmol) via syringe. The pale yellow solution turned bright yellow while stirring at 25 °C for 8 hours. The reaction was stopped by adsorbing the contents onto celite (1 g) and purifying the reaction mixture via flash chromatography (5% → 30% ethyl acetate in hexanes eluent), providing the desired isoquinoline **631** (64 mg, 81% yield) as a pale yellow solid: R_f = 0.22 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.53 (s, 1H) 7.43 (d, J = 6.9 Hz, 2H) 7.32 (t, J = 7.28 Hz, 3H) 5.32 (s, 2H) 4.73 (s, 2H) 4.05 (s, 2H) 3.96 (s, 6H) 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.54, 155.93, 152.57, 149.20, 139.38, 138.46, 138.37, 134.31, 128.24, 128.20, 128.16, 127.47, 125.06, 123.56, 74.74, 73.00, 61.00, 60.06, 52.71, 16.92; IR (NaCl/film) 2948, 2856, 1738, 1716, 1667, 1616, 1558, 1486, 1453, 1402, 1354, 1333, 1310, 1263, 1130, 1089, 1055, 1008, 950, 909, 784, 742 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{23}NO_5$ $[M]^+$: 381.1576, found 381.1571.



Vinyl dioxolenone 658

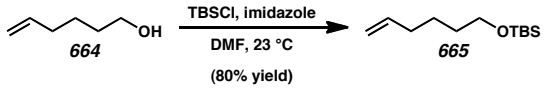
A solution of *i*-Pr_2NH (6.27 mL, 44.7 mmol) in THF (100 mL) was cooled to –78 °C. To this solution was slowly added *n*-BuLi (2.50 M solution in hexanes, 18.0 mL, 44.7 mmol). The resulting solution was maintained with stirring at –78 °C for 30 minutes, after which time *t*-butyl acetate (**660**, 6.0 mL, 44.7 mmol) was slowly added. The solution was maintained for 15 minutes with stirring at –78 °C. Meanwhile, a solution of ethyl 3-chloro propionate (**661**, 3.05 mL, 22.4 mmol) in THF (50 mL) was

cooled to –78 °C. This solution was transferred slowly by cannula to the stirring –78 °C solution of *t*-butyl acetate enolate. Following addition, the reaction was quenched by the slow addition of acetic acid (20 mL). The reaction was then warmed to room temperature and diluted with Et_2O (50 mL). The resulting solution was washed sequentially with water (50 mL), aqueous 20% K_2CO_3 solution (2 x 30 mL), and brine (50 mL). The organic layer was dried with Na_2SO_4 and concentrated under vacuum to yield β-ketoester **662**. The crude pale yellow oil (4.63 g) was immediately used without further purification.

Crude β-ketoester **662** (4.63 g, 22.4 mmol), acetic anhydride (6.34 mL, 67.2 mmol), and acetone (3.30 mL, 44.8 mmol) were combined in a round-bottom flask and cooled to 0 °C with an ice bath. Sulfuric acid (1.24 mL, 22.4 mmol) was added dropwise by syringe. The ice bath was removed, the reaction was warmed to room temperature, where it was maintained with stirring for 16 hours. Following this period, the reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (70 mL, 2 x 50 mL). The combined organic extraxts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 → 7:1 → 5:1 → 4:1 → 3:1 → 2:1 → 1:1 hexanes:ethyl acetate eluent) to yield dioxolenone **663** (3.21 g, 75% yield, 2 steps).

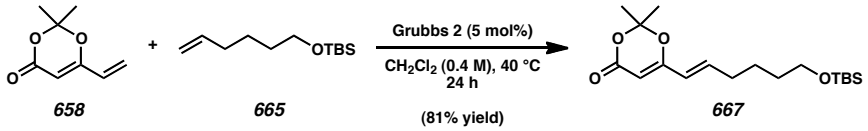
Dioxolenone **663** (3.21 g, 16.8 mmol) was taken up in THF (42 mL) at room temperature. Et_3N (4.70 mL, 33.7 mmol) was added and the reaction was maintained with stirring at room temperature for 20 hours or until complete by TLC analysis. Upon completion, the reaction was diluted with Et_2O (50 mL) and washed sequentially with water (40 mL) and brine (40 mL). The organics were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 pentane:ethyl ether eluent) to

yield vinyl dioxolenone **658** (2.17 g, 84% yield) as a clear oil. Data for vinyl dioxolenone **658** matched the reported literature values.[72]



Silyl ether 665

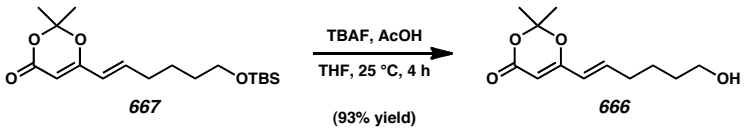
5-Hexen-1-ol (**664**, 1.2 mL, 9.98 mmol) and imidazole (1.02 g, 15.0 mmol) were combined in a round-bottom flask in DMF (20 mL). TBSCl (1.66 g, 10.98 mmol) was added and the reaction was maintained with stirring at room temperature until complete by TLC analysis. Upon completion, the reaction was diluted with Et_2O (50 mL) and washed with water (25 mL) and brine (25 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (95:5 hexanes:ethyl ether eluent) to yield silyl ether **665** (1.72 g, 80% yield) as a clear oil. Data for silyl ether **665** matched the reported literature values.[96]



Silyl ether 667

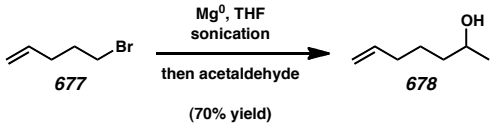
To a solution of Grubbs 2nd generation catalyst (**146**, 117 mg, 0.138 mmol) in dichloromethane (10 mL) was added a solution of vinyl dioxolenone **658** (1.28 g, 8.30 mmol) and silyl ether **665** (593 mg, 2.80 mmol) in dichloromethane (10 mL). The reaction was heated at 40 °C for 12 hours. Upon completion, the reaction mixture was cooled to ambient temperature, concentrated under vacuum, and purified by flash chromatography (20:1 hexanes:ethyl acetate eluent) to yield silyl ether **667** (772 mg, 81%

yield): R_f 0.34 (5:1 hexanes:ethyl acetate). Silyl ether **667** was immediately used in the next step.



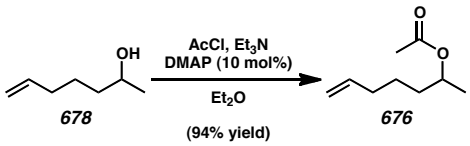
Primary alcohol 666

To a solution of silyl ether **667** (845 mg, 2.48 mmol) in THF (12.5 mL) was added TBAF (1 M in THF, 4.96 mL) and acetic acid (284 μL, 4.95 mmol). Upon completion by TLC, the reaction solution was diluted with Et_2O (50 mL) and washed with water (25 mL) and brine (25 mL). The combined organics were dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (1:1 hexanes:ethyl acetate eluent) to yield primary alcohol **666** (561 mg, 93% yield): R_f = 0.16 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.91 (dt, *J* = 15.5, 1.5 Hz, 1H), 5.24 (s, 1H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.25 (qd, *J* = 7.2, 1.4 Hz, 2H), 1.70 (s, 6H), 1.66–1.52 (m, 4H), 1.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 162.5, 142.5, 122.9, 106.5, 93.4, 62.5, 53.7, 32.5, 32.1, 25.1, 24.8; IR (NaCl/film) 3423, 2939, 2864, 1723, 1652, 1591, 1391, 1276, 1205, 1061, 1019 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{19}O_4$ $[M+H]^+$: 227.13, found 227.13.



Secondary alcohol 678

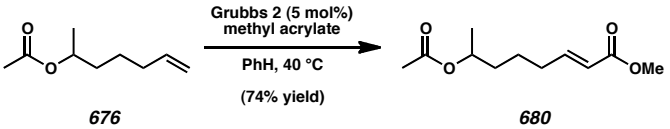
A round-bottom flask was charged with Mg turnings (500 mg, 20.2 mmol) and THF (5 mL). 1,2-Dibromoethane (80 μL) was added to activate the Mg turnings and the suspension was sonicated for 1 hour at room temperature. Following this period, 5-bromo-1-pentene (**677**, 1.0 mL, 8.4 mmol) was added to the Mg turning suspension over 10 minutes as a solution in THF (20 mL). The suspension was further sonicated for 3 hours, at which time acetaldehyde (2 mL, 35.6 mmol) was added slowly with sonication as a solution in THF (2 mL). Following addition of acetaldehyde, the reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL). The reaction was extracted with Et_2O (100 mL) and the organic layer was then washed with brine (20 mL). Finally, the organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield secondary alcohol **678** (632 mg, 70% yield) as a clear oil. All spectroscopic data for secondary alcohol **678** matched that in the literature.[79]



Acetate 676

To a solution of secondary alcohol **678** (632 mg, 5.5 mmol) in Et_2O (50 mL) was added DMAP (68 mg, 0.55 mmol), Et_3N (2.31 mL, 16.6 mmol), and acetyl chloride (472 μL, 6.64 mmol). The resulting suspension was maintained at room temperature with

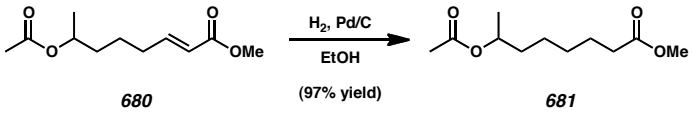
stirring until complete by TLC analysis. After this period, the reaction was quenched by the addition of 10% citric acid aqueous solution (25 mL). The biphasic solution was then extracted with additional ether (50 mL). The organic layer was washed with brine (25 mL), dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 pentane:ethyl ether eluent) to yield acetate **676** (1.30 g, 94% yield) as a clear oil. All spectroscopic data for acetate **676** matched that in the literature.[79]



676 *680*

Methyl ester 680

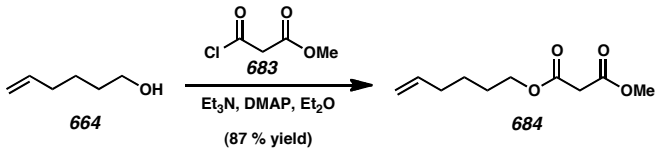
Acetate **676** (100 mg, 0.640 mmol) and methyl acrylate (288 μL, 3.20 mmol) were combined in benzene (7 mL). Grubbs 2nd generation catalyst (**146**, 27 mg, 0.0320 mmol) was added and the reaction was heated under a nitrogen atmosphere at 40 °C until complete by TLC. Upon completion, the reaction solution was cooled to ambient temperature, concentrated under vacuum, and purified by flash chromatography (5:1 pentane:ethyl ether eluent) to yield **680** (137 mg, 74% yield): R_f = 0.19 (5:1 pentane:ethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dt, J = 15.7, 7 Hz, 1H), 5.78 (dt, J = 15.7, 1.5 Hz, 1H), 4.85 (m, 1H), 3.68 (s, 3H), 2.17 (m, 2H), 1.99 (s, 3H), 1.50 (m, 4H), 1.43 (d, J = 11.3 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 167.3, 148.8, 121.7, 70.7, 51.8, 35.7, 32.1, 24.0, 21.5, 20.0; IR (NaCl/film) 2948, 1727, 1656, 1437, 1373, 1246, 1206, 1173, 1020 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{19}O_4$ $[M+H]^+$: 215.13, found 215.13.



680 *681*

Diester 681

To a solution of enoate **680** (81 mg, 0.378 mmol) in ethanol (4 mL) was added 10% palladium on carbon (10% w/w, 8.1 mg). The reaction vessel was purged, flushed with hydrogen, and maintained under 1 atm of hydrogen for 8 hours. Upon completion, the reaction mixture was filtered through a celite plug and concentrated under vacuum to yield **681** (81.7 mg, 97% yield): R_f = 0.39 (3:1 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (m, 1H), 3.62 (s, 3H), 2.57 (t, J = 7.41 Hz, 2H), 1.98 (s, 3H), 1.41 (m, 8H), 1.15 (d, J = 6.18 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 170.9, 71.0, 51.6, 35.8, 34.1, 29.1, 25.2, 24.9, 21.5, 20.1; IR (NaCl/film) 2939, 2862, 1736, 1437, 1372, 1246, 1170, 1022 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{21}O_4$ $[M+H]^+$: 217.14, found 217.14.

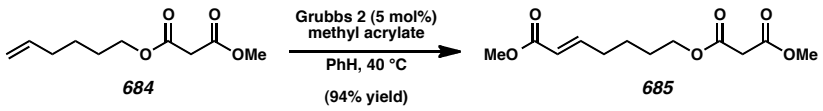


664 *684*

Mixed malonate 684

To a solution of alcohol **664** (500 mg, 5.00 mmol) in ether (10 mL) at 0 °C was sequentially added triethylamine (835 μL, 6.00 mmol), DMAP (6 mg, 0.005 mmol), and methyl malonyl chloride (**683**, 642 μL, 6.00 mmol). The reaction was allowed to warm to ambient temperature. Upon completion by TLC, the reaction was washed with 10% aqueous citric acid (3 x 15 mL) and brine (15 mL). The organics were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1

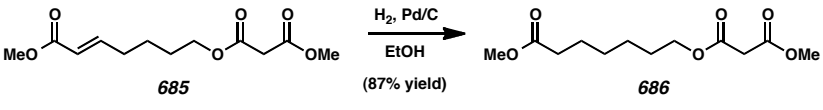
hexanes:ethyl acetate eluent) to yield mixed malonate **684** (1.00 g, 87% yield). Mixed malonate **684** was immediately carried on to the next step.



684 *685*

Enoate 685

Malonate **684** (866 mg, 4.32 mmol) and methyl acrylate (1.95 mL, 21.6 mmol) were combined in benzene (21 mL). Grubbs 2nd generation catalyst (**146**, 184 mg, 0.216 mmol) was added and the reaction was heated under a nitrogen atmosphere at 40 °C until complete by TLC. Upon completion, the reaction solution was cooled to ambient temperature, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield **685** (1.05 g, 94% yield): R_f = 0.23 (3:1 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (dt, *J* = 15.7, 7 Hz, 1H), 5.83 (dt, *J* = 15.7, 1.7 Hz, 1H), 4.15 (t, *J* = 6.3 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.38 (s, 2H), 2.23 (m, 2H), 1.68 (m, 2H), 1.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 166.7, 148.8, 121.7, 120.1, 65.4, 52.8, 51.7, 41.6, 31.8, 28.1, 24.5; IR (NaCl/film) 2954, 1755, 1737, 1438, 1336, 1275, 1200, 1151, 1024 cm^{-1}.

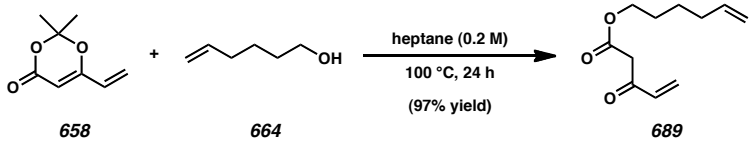


685 *686*

Mixed malonate 686

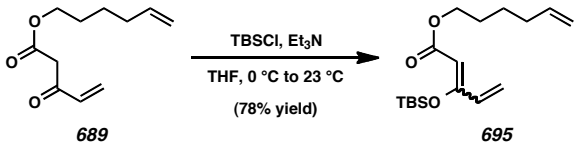
To a solution of enoate **685** (1.05 g, 4.07 mmol) in ethanol (8 mL) was added 10% palladium on carbon (5% w/w, 52.5 mg). The reaction vessel was purged, flushed with hydrogen, and maintained under 1 atm of hydrogen for 8 hours. Upon completion,

the reaction mixture was filtered through a celite plug and concentrated under vacuum to yield **686** (1.06 g, 87% yield): R_f = 0.30 (3:1 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (t, *J* = 6.59 Hz, 2H), 3.74 (s, 3H), 3.66 (s, 3H), 3.37 (s, 2H), 2.30 (t, *J* = 7.41 Hz, 2H), 1.63 (m, 4H), 1.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.09, 167.02, 166.55, 65.50, 52.49, 51.49, 41.37, 33.91, 28.65, 28.23, 25.44, 24.75; IR (NaCl/film) 2952, 2861, 1736, 1437, 1337, 1271, 1200, 1154, 1021 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{21}O_6$ $[M+H]^+$: 261.1333, found 261.1339.



Vinyl β-ketoester 689

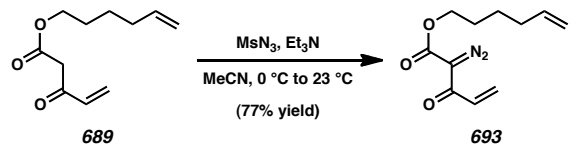
Dioxolenone **658** (200 mg, 1.30 mmol) and alcohol **664** (156 μL, 1.30 mmol) were combined in heptane (6 mL) and heated to reflux. After 10 hours, the reaction solution was concentrated under vacuum to yield **689** (237.5 mg, 97% yield) as a mixture of keto and enol tautomers: R_f = 0.61 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.80 (s, 1H), 6.42 (dd, *J* = 17.6, 10.6 Hz, 1H), 6.27 (d, *J* = 17.6 Hz, 1H), 6.10 (dd, *J* = 5.4, 2.8 Hz, 1H), 5.97 (d, *J* = 10.6 Hz, 1H), 5.86–5.73 (m, 1H), 5.55 (dd, *J* = 7.5, 4.5 Hz, 1H), 5.08 (s, 1H), 5.06–4.92 (m, 2H), 4.16 (dd, *J* = 13.8, 7.0 Hz, 2H), 3.63 (s, 1H), 2.13–2.04 (m, 2H), 1.67 (qd, *J* = 13.2, 6.7 Hz, 2H), 1.46 (tt, *J* = 17.6, 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 172.8, 168.7, 138.3, 135.8, 131.2, 130.2, 122.6, 114.9, 100.0, 91.8, 65.4, 64.2, 46.5, 46.1, 33.2, 33.1, 28.1, 27.1, 25.1, 25.0 ; IR (NaCl/film) 2938, 1741, 1703, 1688, 1659, 1641, 1422, 1236, 1149, cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{17}O_3$ $[M+H]^+$: 196.11, found 196.11.



689 *695*

Silyl enol ether 695

To a solution of **689** (100 mg, 0.510 mmol) and triethylamine (107 μL, 0.765 mmol) at 0 °C in THF (3 mL) was added TBSCl (115 mg, 0.765 mmol). After 4 hours, the reaction was warmed to ambient temperature, diluted with 25 mL ether, and filtered through a celite plug. The filtrate was concentrated under vacuum and purified by flash chromatography on silica gel (50:1 to 20:1 pentane:ether eluent) to yield **695** (123 mg, 78% yield): R_f = 0.57 (10:1 pentane:ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.92 (dd, *J* = 17.3, 2.2 Hz, 1H), 5.80 (m, 1H), 5.46 (m, 1H), 5.17 (d, *J* = 1.38 Hz, 1H), 4.98 (comp m, 2H), 4.09 (t, *J* = 6.88 Hz, 2H), 2.09 (m, 2H), 1.67 (m, 2H), 1.46 (m, 2H), 0.98 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 168.9, 143.0, 135.4, 126.1, 119.3, 105.6, 68.3, 37.9, 32.8, 30.2, 29.9, 22.9, –4.3; IR (NaCl/film) 2932, 2860, 1711, 1636, 1574, 1472, 1414, 1336, 1303, 1257, 1138, 1068, 1003 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{31}O_3Si$ $[M+H]^+$: 311.20, found 311.20.

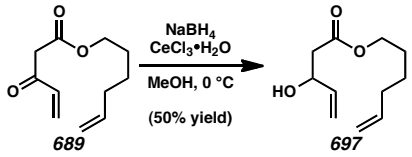


689 *693*

α-Diazo-β-ketoester 693

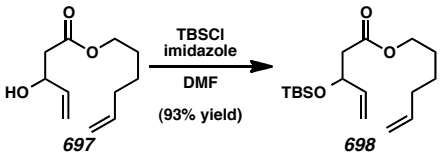
To a solution of **689** (200 mg, 1.02 mmol) in acetonitrile (8 mL) at 0 °C was added mesyl azide (617 mg, 5.10 mmol) as a solution in acetonitrile (2 mL). Triethylamine (852 μL, 6.11 mmol) was then added dropwise to the reaction at 0 °C.

After 10 minutes, the reaction was warmed to room temperature, concentrated under vacuum, and purified by flash chromatography on silica gel (20:1 pentane:ether eluent) to yield **693** (169.1 mg, 77% yield) as a yellow oil: R_f = 0.50 (5:1 pentane:ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 17.1, 10.2 Hz, 1H), 6.38 (dd, *J* = 17.1, 1.9 Hz, 1H), 5.68 (comp m, 2H), 4.95 (m, 2H), 4.21 (t, *J* = 6.87 Hz, 2H), 2.05 (m, 2H), 1.67 (m, 2H), 1.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.0, 161.3, 138.2, 131.7, 128.7, 115.3, 65.6, 33.4, 28.2, 25.2; IR (NaCl/film) 3078, 2938, 2133, 1720, 1650, 1606, 1404, 1317, 1289, 1222, 1138, 1022 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{15}O_3N_2$ $[M+H]^+$: 223.11, found 223.11.



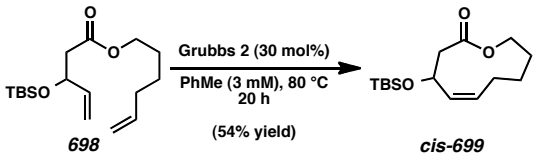
β-Hydroxyester 697

To a solution of vinyl β-ketoester **689** (100 mg, 0.510 mmol) in MeOH (1.3 mL) was added $CeCl_3$•$7H_2O$ (190 g, 0.510 mmol). The suspension was cooled to 0 °C and $NaBH_4$ (19.3 mg, 0.510 mmol) was added slowly. The reaction was then allowed to warm to room temperature, where it was maintained with stirring until vinyl β-ketoester **689** was consumed by TLC analysis. The reaction was quenched by the addition of water (5 mL) and subsequently extracted with ethyl acetate (3 x 20 mL). The combined organic layers were died with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield β-hydroxyester **697** (50.2 mg, 50% yield), which was immediately carried on to the next step.



Silyl ether 698

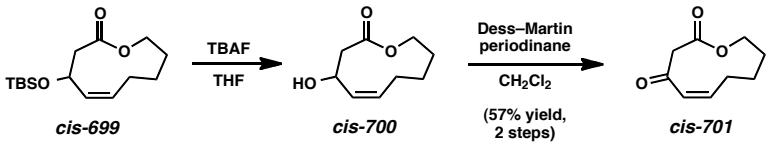
To a solution of β-hydroxyester **697** (50 mg, 0.255 mmol) in DMF (1 mL) was added sequentially imidazole (41.7 mg, 0.612 mmol) and TBSCl (76.9 mg, 0.510 mmol). The resulting solution was maintained at room temperature with stirring until β-hydroxyester **697** was consumed by TLC analysis. At this time, the reaction was diluted with diethyl ether (25 mL) and washed with water (2 x 25 mL) and brine (25 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield silyl ether **698** (58.2 mg, 93% yield), which was immediately carried on to the next step.



Lactone *cis*-699

Silyl ether **698** (50 mg, 0.160 mmol) and Grubbs 2nd generation catalyst (**146**, 40.8 mg, 0.048 mmol) were each taken up individually in toluene (20 mL each). A 3-neck reaction flask equipped with a condenser was charged with toluene (20 mL) and subsequently heated to 80 °C. The toluene solutions of silyl ether **698** and Grubbs 2nd generation catalyst (**146**) were each added simultaneously to the reaction flask containing the toluene solvent by syringe pump over 24 hours. Following this period, the solution was maintained with stirring at 80 °C for an additional 12 hours. The solution was then

cooled to room temperature, concentrated under vacuum, and purified by flash chromatography (20:1 pentane:ethyl ether eluent) to yield lactone ***cis*-699** (24.4 mg, 54% yield), which was immediately carried on to the next step.



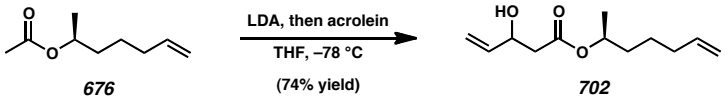
cis-699 *cis*-700 *cis*-701

β-Ketolactone 701

To a solution of lactone ***cis*-699** (24.4 mg, 0.086 mmol) in THF (1 mL) was added TBAF (1 M solution in THF, 94.4 μL, 0.094 mmol). The resulting solution was maintained with stirring at room temperature until lactone ***cis*-699** had been consumed by TLC analysis. The reaction was diluted with ethyl ether (30 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$ and concentrated under vacuum. The crude allylic alcohol (***cis*-700**) was used without further purification for the next step.

The crude allylic alcohol (***cis*-700**) (14.5 mg, 0.086 mmol) was taken up in CH_2Cl_2 (1 mL). Dess–Martin periodinane (72.8 mg, 0.172 mmol) was added as a solid and the resulting suspension was maintained with stirring at room temperature until allylic alcohol ***cis*-700** was fully consumed by TLC analysis. The reaction was then quenched by the addition of a 1:1 v/v mixture of saturated $Na_2S_2O_3$ and $NaHCO_3$ aqueous solutions (5 mL total volume). The biphasic solution was vigorously stirred for 30 minutes, after which time the reaction was diluted with ethyl ether (20 mL). The organic phase was washed with brine (10 mL), dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield β-

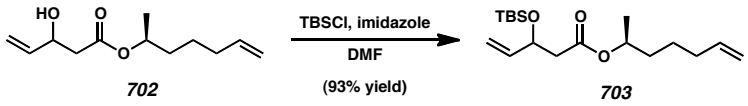
ketolactone ***cis*-701** (8.2 mg, 57% yield): R_f = 0.32 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (dt, *J* = 12.1, 1.4 Hz, 1H), 5.70 (dt, *J* = 12.1, 8.2 Hz, 1H), 4.35–4.19 (m, 2H), 3.42 (s, 2H), 2.40 (dtd, *J* = 8.0, 6.4, 1.4 Hz, 2H), 1.80–1.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.27, 166.15, 137.98, 130.01, 66.89, 50.58, 28.42, 26.71, 24.95; IR (NaCl/film) 2957, 2919, 2858, 1747, 1703, 1698, 1451, 1440, 1395, 1290, 1256, 1166, 1095, 1036, 943, 796 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{12}O_3$ $[M]^{+\bullet}$: 168.0786, found 168.0786.



β-Hydroxyester 702

To a solution of diisopropyl amine (987 μL, 7.04 mmol) in THF (28 mL) at –78 °C was added *n*-butyllithium (2.5 M solution in hexanes, 2.82 mL) dropwise. After 30 minutes, acetate **676** (1.00 g, 6.40 mmol) was added at –78 °C as a solution in THF (2 mL). After 20 minutes, acrolein (856 μL, 12.8 mmol) was added as a solution in THF (2.5 mL) and the reaction was maintained for 20 minutes at –78 °C. The reaction solution was quenched with 10 mL saturated amminium chloride solution and warmed to ambient temperature. The reaction was diluted with brine (20 mL) and subsequently extracted with diethyl ether (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield **702** (1.04 g, 74% yield) as a 1:1 mixture of diastereomers: R_f = 0.42 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.85–5.72 (m, 1H), 5.33 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.17

(dt, J = 10.5, 1.4 Hz, 1H), 5.06–4.92 (m, 3H), 4.54 (d, J = 4.0 Hz, 1H), 3.00 (dd, J = 10.3, 4.6 Hz, 1H), 2.58 (dd, J = 16.2, 4.0 Hz, 1H), 2.55–2.46 (m, 1H), 2.07 (q, J = 6.9 Hz, 2H), 1.68–1.57 (m, 1H), 1.57–1.32 (m, 4H), 1.24 (d, J = 1.4 Hz, 1.5H), 1.23 (d, J = 1.4 Hz, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.16, 172.14, 139.02, 138.54, 115.60, 115.59, 115.07, 71.79, 71.76, 69.23, 69.16, 41.57, 41.56, 35.50, 35.49, 33.65, 33.64, 24.86, 24.84, 20.20; IR (NaCl/film) 3448, 2978, 2936, 1730, 1422, 1378, 1272, 1178, 1125, 1039 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.1485, found 213.1478; $[\alpha]^{22}_D$ +7.51° (c 0.96, CH_2Cl_2).

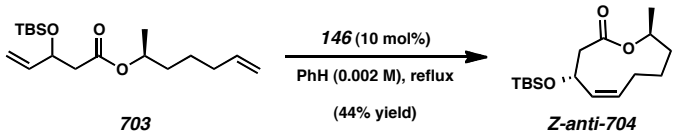


702 ***703***

Silyl ether 703

To a solution of β-hydroxyester **702** (1.01 g, 4.76 mmol) in DMF (10 mL) was added imidazole (485 mg, 7.14 mmol) and *tert*-butyl(chloro)dimethyl silane (TBSCl, 860 mg, 5.71 mmol). The reaction was maintained at room temperature until β-hydroxyester **702** was fully consumed by TLC analysis. Upon completion, the reaction was diluted with ethyl ether (50 mL) and washed with water (25 mL) and brine (25 mL). The organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (25:1 hexanes:ethyl acetate eluent) to yield silyl ether **703** (1.43 g, 93% yield) as a 1:1 mixture of diastereomers: R_f = 0.43 (10:1 petroleum ether:ethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90–5.71 (m, 2H), 5.22 (dt, J = 17.2, 1.4 Hz, 1H), 5.06 (d, J = 10.4 Hz, 1H), 5.03–4.97 (m, 1H), 4.95 (ddd, J = 10.2, 2.0, 1.0 Hz, 1H), 4.93–4.84 (m, 1H), 4.57 (dd, J = 13.3, 6.1 Hz, 1H), 2.52 (ddd, J = 14.7, 7.6, 1.9 Hz, 1H), 2.41 (ddd, J =

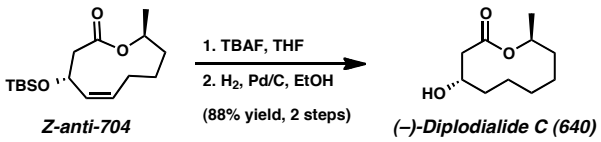
14.8, 5.6, 0.6 Hz, 1H), 2.05 (q, *J* = 6.7 Hz, 2H), 1.67–1.31 (m, 5H), 1.21 (d, *J* = 3.0 Hz, 1.5H), 1.20 (d, *J* = 3.0 Hz, 1.5H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.73, 175.69, 145.34, 145.31, 143.44, 143.43, 119.76, 119.74, 119.64, 119.61, 76.04, 75.96, 75.87, 75.81, 48.90, 40.34, 38.53, 38.49, 30.81, 30.80, 29.67, 29.64, 25.01, 24.94, 23.13, 0.63, 0.03, 0.00; IR (NaCl/film) 2931, 1734, 1463, 1374, 1253, 1180, 1126, 1086, 956, 924, 836, 778 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{35}O_3Si$ $[M+H]^+$: 327.2350, found 327.2345; $[\alpha]^{25}_D$ +2.77° (*c* 0.55, $CHCl_3$).



β-Silyloxy lactone *Z-anti*-704

A solution of silyl ether **703** (25 mg, 0.0766 mmol) in benzene (40 mL) in a 3-neck flask equipped with a condenser was heated to reflux under a nitrogen atmosphere. Meanwhile, a solution of Grubbs 2nd generation catalyst (**146**, 6.5 mg, 0.00766 mmol) in benzene (10 mL) was prepared in a conical flask. A syringe filled with argon gas was loaded into a syringe pump and connected to the flask containing catalyst **146**. A cannula was inserted into the catalyst solution and connected to the refluxing substrate flask. With the aid of the syringe pump, the catalyst solution was added by cannula to the refluxing substrate solution over a period of 10 hours. Following the addition, the reaction was further maintained at reflux for 10 hours. Upon completion, the reaction was cooled to room temperature, quenched with ethyl vinyl ether (500 μL), concentrated under vacuum, and purified by flash chromatography (50:1 petroleum ether:ethyl ether eluent) to yield ***Z-anti*-704** (10 mg, 44% yield): R_f = 0.32 (10:1 petroleum ether:ethyl

ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (ddd, *J* = 11.1, 9.0, 2.0 Hz, 1H), 5.35–5.25 (m, 1H), 5.15–5.03 (m, 1H), 5.00–4.88 (m, 1H), 2.79 (dd, *J* = 14.3, 5.8 Hz, 1H), 2.59 (m, 1H), 2.31 (dd, *J* = 14.2, 10.8 Hz, 1H), 2.13–1.96 (m, 2H), 1.90 (m, 2H), 1.50–1.30 (m, 3H), 1.26 (d, *J* = 6.7 Hz, 4H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.51, 137.66, 135.14, 75.67, 70.21, 48.94, 34.27, 31.59, 30.69, 27.08, 23.04, 22.04, 0.38, 0.00; IR (NaCl/film) 2944, 1736, 1444, 1248, 1067 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{30}O_3Si$ $[M+H]^+$: 299.2037, found 299.2037; $[\alpha]^{25}_D$ –12.1° (*c* 0.56, $CHCl_3$).



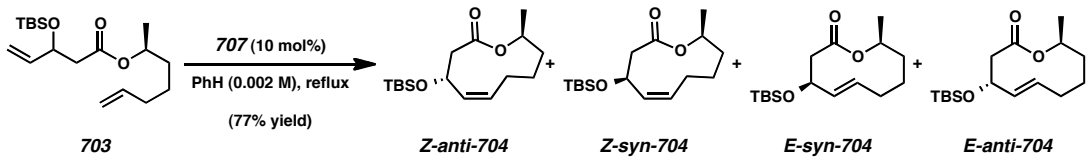
Z-anti-704 *(–)-Diplodialide C (640)*

(–)-Diplodialide C (640)

Tetra-*n*-butylammonium fluoride solution (1 M in THF, 131 μL, 0.131 mmol) was added to a solution of ***Z-anti*-704** (32.6 mg, 0.109 mmol) in THF (1.0 mL). The solution was maintained at room temperature until the starting material was consumed by TLC analysis. Upon completion, the reaction was diluted with ethyl ether (25 mL) and washed with water (3 x 10 mL) and brine (10 mL). The organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent).

The purified residue (19.1 mg, 0.104 mmol) was taken up in anhydrous ethanol (1.0 mL). To this solution was added 10 wt. % Pd/C (11 mg, 0.0104 mmol) and a hydrogen balloon. The reaction was maintained at room temperature with vigorous stirring until the starting material had been consumed by TLC analysis. Upon

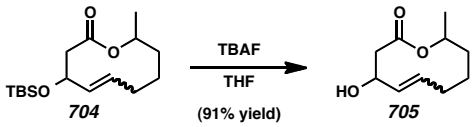
completion, the reaction was filtered through a silica plug, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield (–)-diplodialide C (**640**, 17.1 mg, 88% yield, 2 steps): R_f = 0.17 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11–4.92 (m, 1H), 4.45–4.30 (m, 1H), 2.84 (dd, *J* = 15.4, 3.8 Hz, 1H), 2.36 (dd, *J* = 15.5, 10.0 Hz, 1H), 2.05–1.87 (m, 1H), 1.83–1.34 (m, 8H), 1.25 (comp m, 4H), 1.17–0.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.64, 73.15, 66.42, 43.54, 36.95, 31.56, 25.46, 23.43, 22.86, 19.37; IR (NaCl/film) 3400, 2935, 1726, 1705, 1452, 1356, 1251, 1145, 1032, 963, 867 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{19}O_3$ $[M+H]^+$: 187.1329, found 187.1323; $[\alpha]^{26}_D$ +34.6° (*c* 0.50, $CHCl_3$).



β-Silyloxy lactone 704

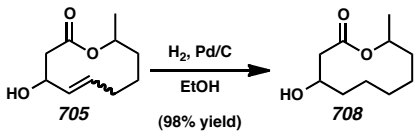
A solution of silyl ether **703** (300 mg, 0.918 mmol) in benzene (450 mL) in a 3-neck flask equipped with a condenser was heated to reflux under a nitrogen atmosphere. Meanwhile, a solution of Grubbs–Hoveyda third generation catalyst (**707**, 52.5 mg, 0.0918 mmol) in benzene (10 mL) was prepared in a conical flask. The catalyst solution was added to the refluxing substrate solution over a period of 10 hours by syringe pump using the method described for preparation of silyl ether ***Z-anti*-704**. Following the addition, the reaction was further maintained at reflux for 10 hours. Upon completion, the reaction was cooled to room temperature, quenched with ethyl vinyl ether (1 mL), concentrated under vacuum, and purified by flash chromatography (25:1 petroleum ether:ethyl ether eluent) to yield **704** (210.8 mg, 77% yield) as a complex mixture of

diastereomers and olefin isomers: $R_f = 0.32$ (10:1 petroleum ether:ethyl ether); For ^{1}H and ^{13}C NMR data, see Figures A2.37.1 and A2.37.3; IR (NaCl/film) 3429, 2953, 2929, 2857, 1739, 1655, 1472, 1360, 1278, 1245, 1077, 966, 861, 837, 777, 735 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{30}O_3Si$ $[M+H]^+$: 299.2037, found 299.2032; $[\alpha]^{23}_D$ –13.5° (*c* 0.69, $CHCl_3$).



Allylic alcohol 705

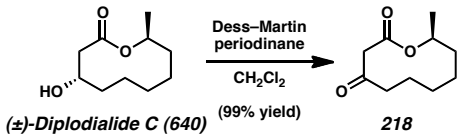
To a solution of lactone **704** (476 mg, 1.60 mmol) in THF (16 mL) was added TBAF (1 M solution in THF, 1.76 mL, 1.76 mmol). The resulting solution was maintained with stirring at room temperature until lactone **704** had been consumed by TLC analysis. Following this time, the reaction was diluted with diethyl ether (25 mL) and washed sequentially with water (2 x 15 mL) and brine (15 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (2:1 hexanes:ethyl acetate eluent) to yield allylic alcohol **705** (270 mg, 91% yield). Allylic alcohol **705** was used in the next step immediately.



β-Hydroxylactone 708

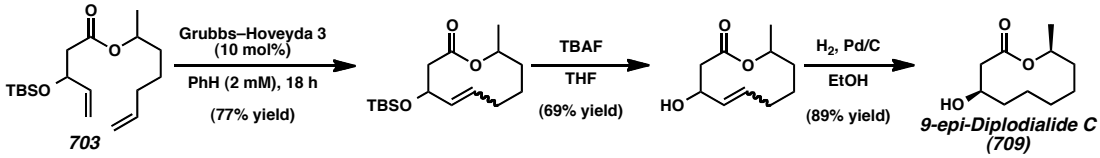
To a solution of allylic alcohol **705** (270 mg, 1.47 mmol) in ethanol (7.5 mL) was added 10 wt.% Pd/C (46.8 mg, 0.044 mmol). The reaction flask was then equipped with

an H_2 balloon. The resulting suspension was maintained under an atmosphere of hydrogen (1 atm) with vigorous stirring at room temperature until allylic alcohol **705** had been consumed by TLC analysis. Following this time, the reaction was filtered through Celite, rinsing with CH_2Cl_2. The filtrate was concentrated under vacuum to yield β-hydroxylactone **708** (268 mg, 98% yield). The crude product was used in the next step without further purification.



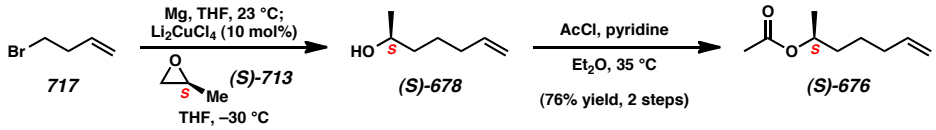
β-Ketolactone 218

To a solution of (±)-diplodialide C (**640**, 268 mg, 1.44 mmol) in CH_2Cl_2 (8 mL) was added Dess–Martin periodinane (916 mg, 2.16 mmol). The resulting solution was maintained with stirring at room temperature until diplodialide C (**640**) had been fully consumed by TLC analysis. Following this time, the reaction was quenched by the addition of a 1:1 v/v mixture of saturated $Na_2S_2O_3$ and $NaHCO_3$ aqueous solutions (10 mL total volume) and then stirred vigorously for 30 minutes. The biphasic solution was then diluted with CH_2Cl_2 (10 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield β-ketolactone **218** (262 mg, 99% yield). See experimental details for β-ketolactone **(*S*)-218** for complete spectroscopic information.



9-epi-Diplodialide C (709)

For detailed synthetic procedures, please refer to β-silyloxy lactone **704**, allylic alcohol **705**, and β-hydroxylactone **708** (vide supra). R_f = 0.17 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00–4.81 (m, 1H), 4.08–3.91 (m, 1H), 2.59 (ddd, *J* = 11.8, 4.2, 0.8 Hz, 1H), 2.41 (dd, *J* = 11.8, 9.7 Hz, 1H), 1.81–1.45 (m, 6H), 1.45–1.26 (m, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.03 (ddd, *J* = 11.7, 8.2, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.17, 72.43, 69.79, 44.09, 35.40, 31.21, 26.64, 21.61, 20.86, 20.32; IR (NaCl/film) 3434, 2938, 1727, 1470, 1288, 1184, 1137, 1045, 970 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{19}O_3$ $[M+H]^+$: 187.1334, found 187.1341.

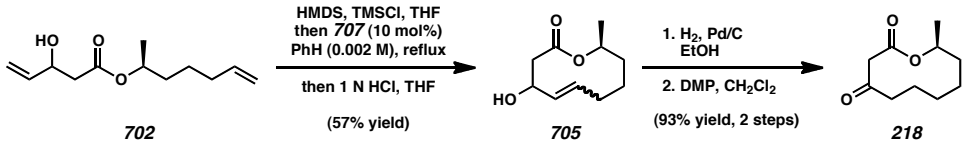


(*S*)-Acetate 676

A flame-dried reaction flask was charged with Mg turnings (837 mg, 34.4 mmol). To this was added THF (30 mL) and 1,2-dibromoethane (20 μL), and the resulting suspension was maintained for 5 minutes with stirring at room temperature. Following this time, 4-bromo-1-butene (**717**, 2.09 mL, 20.7 mmol) was added, and the reaction was maintained at room temperature with stirring for 1 hour. In the meantime, a solution of (*S*)-propylene oxide (**(*S*)-713**, 1.20 mL, 17.2 mmol) and Li_2CuCl_4 (0.5 M in THF, 3.44 mL, 1.72 mmol) in THF (30 mL) was cooled to –30 °C. The Grignard reagent solution

was added by cannula to the cold solution of (*S*)-propylene oxide and Li_2CuCl_4, being careful to maintain the temperature of the reaction flask at –30 °C. Following addition, the reaction was maintained at –30 °C for 30 minutes and then quenched by the addition of saturated NH_4Cl aqueous solution (6 mL) and water (6 mL). The biphasic solution was then warmed to room temperature for work-up. Diethyl ether (100 mL) and water (25 mL) were added and the layers were separated. The organic layer was washed with brine (25 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude secondary alcohol (**(*S*)-678**) was carried on to the next step without further purification.

To a solution of crude secondary alcohol (**(*S*)-678**) and acetyl chloride (2.44 mL, 34.3 mmol) in diethyl ether (25 mL) was slowly added pyridine (2.78 mL, 34.3 mmol). Following addition, additional diethyl ether (10 mL) was added to aid stirring. The reaction was then heated to reflux and maintained with stirring at reflux until secondary alcohol **(*S*)-678** had been consumed by TLC analysis. Upon completion, the reaction was diluted with diethyl ether (25 mL) and washed with 1 N HCl (3 x 20 mL) and brine (20 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 pentane:diethyl ether eluent) to yield acetate **(*S*)-676** (2.04 g, 76% yield, 2 steps). All spectroscopic data was consistent with that published in the literature.[97]



702 *705* *218*

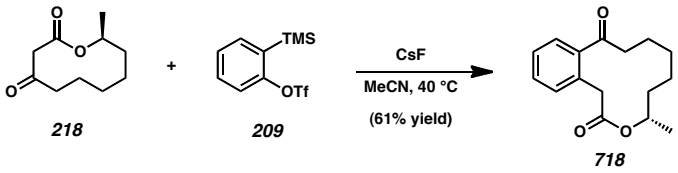
β-Ketolactone 218

β-Hydroxyketone **702** (50 mg, 0.236 mmol) was combined with hexamethyldisilazane (HMDS, 49.2 μL, 0.236 mmol) and chlorotrimethyl silane (TMSCl, 10 μL, 0.079 mmol) in THF (2.5 mL) and heated to 70 °C for a period of 5 h. After this period, the reaction was filtered and concentrated under vacuum. The residue was then taken up in benzene (110 mL) in a flame-dried 3-neck flask equipped with a condenser and heated to reflux under a nitrogen atmosphere. Meanwhile, a solution of Grubbs–Hoveyda 3rd generation catalyst (**707**, 13.4 mg, 0.0236 mmol) in benzene (10 mL) was prepared in a conical flask. The catalyst solution was added to the refluxing substrate solution over a period of 10 hours by syringe pump using the method described for the preparation of ***Z-anti*-704**. Following the addition, the reaction was further maintained at reflux for 10 hours. Upon completion, the reaction was cooled to room temperature, quenched with ethyl vinyl ether (500 μL), and concentrated under vacuum. The resulting residue was taken up in THF (2 mL) and 1 N hydrochloric acid solution (2 mL) and maintained at room temperature for 2 h. Following this period, the reaction was diluted with Et_2O (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield β-hydroxylactone **705** (25 mg, 57% yield) as a mixture of diastereomers and olefin isomers.

β-Hydroxylactone **705** (29.8 mg, 0.162 mmol) was taken up in anhydrous ethanol (2 mL). To this solution was added 10 wt.% Pd/C (17.2 mg, 0.0162 mmol). A hydrogen balloon was added and the reaction was maintained with vigorous stirring until β-hydroxylactone **705** was consumed by TLC analysis. Upon completion, the reaction was

filtered through silica and the filtrate was concentrated under vacuum. The crude residue was used without further purification.

The crude residue was taken up in CH_2Cl_2 (2 mL). To this solution was added Dess–Martin periodinane (DMP, 103 mg, 0.243 mmol) and the reaction was maintained with stirring until all starting material had been consumed by TLC analysis. Following this period, the reaction was quenched by addition of a 1:1 v/v mixture of saturated sodium bicarbonate and saturated sodium thiosulfate solutions (1 mL total volume) and stirred for a period of 30 minutes. The biphasic solution was then diluted with CH_2Cl_2 (25 mL) and washed with water (10 mL) and brine (10 mL). The organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield β-ketolactone **218** (27 mg, 93% yield, 2 steps): $R_f = 0.38$ (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22–4.95 (m, 1H), 3.41 (d, J = 15.1 Hz, 1H), 3.36 (d, J = 15.1 Hz, 1H), 2.74 (ddd, J = 14.3, 10.1, 4.4 Hz, 1H), 2.28 (ddd, J = 14.2, 6.8, 5.0 Hz, 1H), 2.02–1.90 (m, 1H), 1.83 (dddd, J = 14.4, 8.6, 3.4, 2.1 Hz, 1H), 1.74–1.63 (m, 1H), 1.62–1.52 (m, 1H), 1.50–1.38 (m, 2H), 1.35–1.28 (m, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.22–1.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.90, 167.39, 74.77, 51.96, 39.54, 33.76, 26.78, 23.62, 22.39, 20.52; IR (NaCl/film) 2935, 1742, 1711, 1265, 1175, 1126, 1071, 961 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{10}H_{17}O_3$ $[M+H]^+$: 185.1172, found 185.1173; $[\alpha]^{25}_D$ +130.6° (*c* 1.53, MeOH).

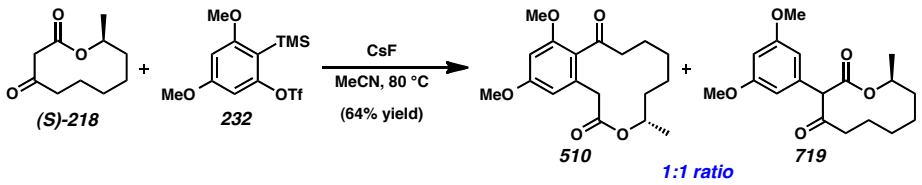


218 *209* *718*

Lactone 718

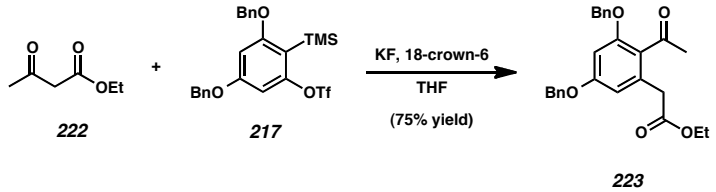
β-Ketolactone **218** (10 mg, 0.0543 mmol) and CsF (24.7 mg, 0.163 mmol) were combined in MeCN (0.5 mL) and heated in a sealed vial to 40 °C. Silyl aryl triflate **209** (19 μL, 0.0651 mmol) was added to the β-ketolactone suspension over a period of 1.5 hours. The suspension was maintained at 40 °C with stirring after the addition of aryne precursor **209** until β-ketolactone **218** has been consumed by TLC analysis. Upon completion, the reaction was cooled to room temperature, concentrated under vacuum, and purified by flash chromatography to yield lactone **718** (8.6 mg, 61% yield) as a mixture of ester and enol tautomers in a 1.0:0.06 ratio (as determined by ^{1}H NMR): R_f = 0.26 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 5.6, 3.6 Hz, 0.06H), 7.68 (dd, J = 7.7, 1.3 Hz, 1H), 7.44 (td, J = 7.5, 1.4 Hz, 1H), 7.41–7.34 (m, 1H), 7.34–7.31 (m, 0.21H), 7.31–7.28 (m, 1H), 6.94–6.90 (m, 0.07H), 6.05 (s, 0.06H), 5.13–5.02 (m, 0.06H), 5.02–4.88 (m, 1H), 4.25 (d, J = 16.0 Hz, 1H), 3.87 (d, J = 16.0 Hz, 1H), 3.42 (ddd, J = 14.3, 9.1, 2.5 Hz, 0.06H), 3.11 (ddd, J = 14.4, 8.1, 3.7 Hz, 1H), 2.73 (ddd, J = 14.4, 8.5, 3.8 Hz, 1H), 2.56 (ddd, J = 14.3, 9.7, 2.7 Hz, 0.07H), 1.90 (d, J = 6.7 Hz, 0.08H), 1.82–1.68 (m, 2H), 1.57–1.25 (m, 6H), 1.13 (d, J = 6.4 Hz, 0.30H), 1.11 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.71, 170.42, 138.15, 134.23, 132.61, 131.40, 130.40, 129.80, 128.75, 128.40, 127.27, 127.11, 126.55, 71.99, 54.06, 40.66, 40.57, 40.27, 31.39, 31.13, 26.13, 25.95, 23.02, 22.44, 22.22, 20.02, 19.77; IR (NaCl/

film) 2929, 1724, 1447, 1244, 756 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{21}O_5$ $[M+H]^+$: 261.1485, found 261.1489; $[\alpha]^{26}_D$ +10.2° (*c* 0.87, $CHCl_3$).



Di-*O,O'*-methyl curvularin (510) and α-arylation product 719

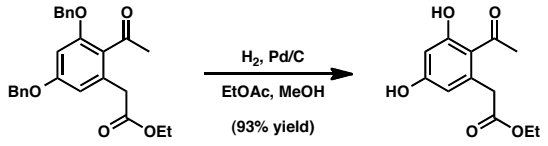
To a solution of β-ketolactone **218** (10 mg, 0.0543 mmol) and silyl aryl triflate **232** (23.3 mg, 0.0651 mmol) in MeCN (300 μL) was added CsF (24.7 mg). The resulting suspension was heated to 80 °C in a sealed vial and maintained at that temperature with stirring until β-ketolactone **218** was fully consumed by TLC analysis. Upon completion, the contents of the reaction were adsorbed directly onto SiO_2 and purified by flash chromatography (20:1 hexanes:ethyl acetate eluent) to yield Di-*O,O'*-methyl curvularin (**510**, 5.5 mg, 32% yield) and α-arylation product **719** (5.7 mg, 32% yield). Data for di-*O,O'*-methyl curvularin (**510**) matched the reported literature values.[20,21,22] α-Arylation product **719**: R_f = 0.33 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (t, J = 2.2 Hz, 1H), 6.15 (d, J = 2.2 Hz, 2H), 5.13 (m, 1H), 4.92 (s, 1H), 3.76 (s, 6H), 3.35 (m, 1H), 2.23 (m, 1H), 1.91–1.48 (m, 8H), 1.29 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.56, 167.46, 161.74, 155.26, 100.12, 98.87, 97.99, 70.53, 55.65, 33.19, 30.83, 27.16, 26.84, 20.53, 20.38; IR (NaCl/film) 2934, 1698, 1615, 1455, 1366, 1352, 1268, 1205, 1151, 1050, 840 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{25}O_5$ $[M+H]^+$: 321.1697, found 321.1697.



222 ***217*** ***223***

Di-*O,O'*-benzyl curvulin (223)

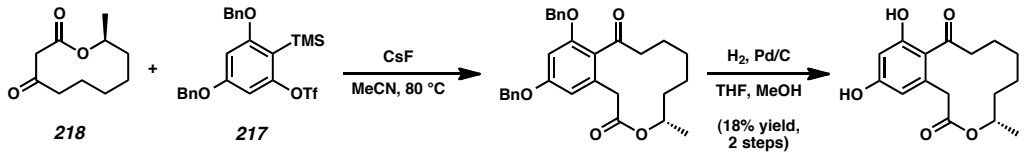
Silyl aryl triflate **217** (65 mg, 0.127 mmol) and ethyl acetoacetate (**222**, 10.8 μL, 0.0849 mmol) were combined in THF (1 mL). 18-Crown-6 (67.3 mg, 0.255 mmol) and KF (14.8 mg, 0.255 mmol) were added sequentially. The suspension was maintained with vigorous stirring at room temperature for a period of 18 hours. Following this time, the reaction was diluted with ethyl ether (10 mL) and washed with water (2 x 5 mL) and brine (10 mL). The organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield di-*O,O'*-benzyl curvulin (**223**, 26.7 mg, 75% yield): R_f = 0.30 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.31 (m, 10H), 6.56 (d, J = 2.2 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 5.07 (s, 2H), 5.06 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.71 (s, 2H), 2.52 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.87, 171.28, 160.58, 158.32, 136.29, 136.08, 135.01, 128.67, 128.66, 128.21, 128.18, 127.56, 127.43, 124.43, 109.39, 99.43, 70.72, 70.19, 60.88, 39.17, 32.45, 14.20; IR (NaCl/film) 2980, 1731, 1680, 1601, 1453, 1434, 1369, 1317, 1262, 1161, 1085, 1027, 834, 738, 697 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{27}O_5$ $[M+H]^+$: 419.1853, found 419.1838.



223 ***Curvulin (224)***

Curvulin (224)

Di-*O,O'*-benzyl curvulin (**223**, 12.6 mg, 0.030 mmol) was dissolved in a 1:1 v/v mixture of ethyl acetate (1 mL) and methanol (1 mL). To this solution was added 10 wt. % Pd/C (3.2 mg, 0.0030 mmol) and a hydrogen balloon. The reaction was maintained with vigorous stirring at room temperature until the starting material had been consumed by TLC analysis. Upon completion, the reaction was filtered, concentrated under vacuum, and purified by flash chromatography (2:1 hexanes:ethyl acetate eluent) to yield curvulin (**224**, 6.6 mg, 93% yield): R_f = 0.28 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.37 (d, J = 2.4 Hz, 1H), 6.34 (d, J = 2.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.80 (s, 2H), 2.53 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 202.57, 170.69, 160.97, 160.64, 137.09, 118.57, 111.46, 101.84, 60.19, 39.80, 31.28, 13.61; IR (NaCl/film) 3412, 1706, 1636, 1264, 1166, 1024 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{15}O_5$ $[M+H]^+$: 239.0914, found 239.0917.



218 ***217*** ***220*** ***(–)-Curvularin (221)***

(–)-Curvularin (221)

β-Ketolactone **218** (15 mg, 0.0814 mmol) and CsF (37.1 mg, 0.244 mmol) were combined in MeCN (800 μL) and heated in a sealed vial to 80 °C. Silyl aryl triflate **217**

(62.3 mg, 0.122 mmol) was added to the β-ketolactone suspension as a 500 μL MeCN solution over a period of 1.5 hours. The suspension was maintained at 40 °C with stirring following the addition of aryne precursor **217** until β-ketolactone **218** has been consumed by TLC analysis. The reaction was cooled to room temperature and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield lactone **220** (11.3 mg, 30% yield), which was immediately carried on to the next step.

Lactone **220** (11.3 mg, 0.0239 mmol) was taken up in a 1:1 v/v mixture of THF and MeOH (2 mL each). To this solution was added 10 wt. % Pd/C (14 mg, 0.0131 mmol) and a hydrogen balloon. The reaction was maintained at room temperature with vigorous stirring until lactone **220** had been consumed by TLC analysis. The suspension was filtered and the filtrate concentrated under vacuum. The resulting crude residue was purified by flash chromatography (7:3 hexanes:ethyl acetate eluent) to yield (–)-curvularin (**221**, 4.0 mg, 60% yield): R_f = 0.24 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.39 (d, J = 2.3 Hz, 1H), 6.34 (d, J = 2.3 Hz, 1H), 4.91 (m, 1H), 3.78 (d, J = 15.7 Hz, 1H), 3.70 (d, J = 15.7 Hz, 1H), 3.11 (ddd, J = 15.5, 8.5, 3.0 Hz, 1H), 2.77 (ddd, J = 15.5, 9.7, 3.0 Hz, 2H), 1.81–1.68 (m, 1H), 1.66–1.18 (m, 7H), 1.12 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 205.77, 170.10, 159.24, 157.34, 136.04, 120.46, 111.32, 101.64, 71.66, 43.07, 38.80, 32.00, 26.63, 23.68, 22.59, 19.68; IR (NaCl/film) 3428, 1644, 1461, 1266, 1162, 845 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{16}H_{21}O_5$ $[M+H]^+$: 293.1384, found 293.1385; $[\alpha]^{27}_D$ –31.2° (c 0.12, EtOH).

2.7 NOTES AND REFERENCES

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(94) Cessation of the reaction occurs when exposed to air, and large amounts of Pd(0) black deposits result in a grey solution and reduced yields.

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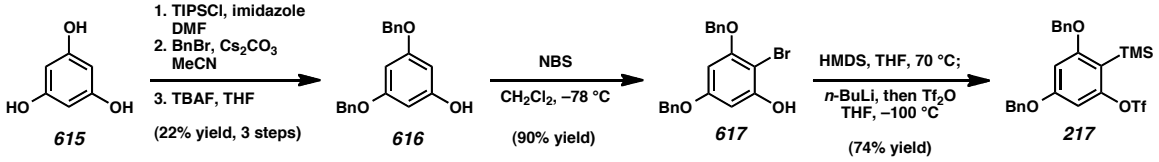
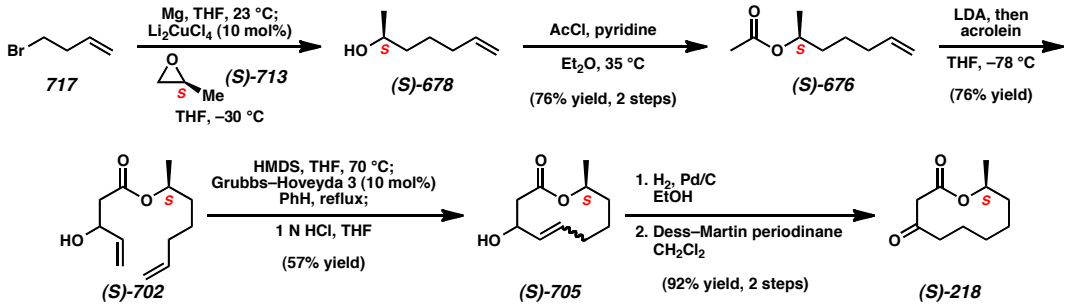
APPENDIX 1

Synthetic Summary for (–)-Curvularin

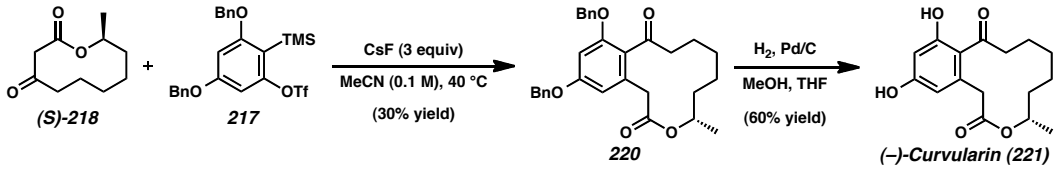
Scheme A1.1. Synthesis of silyl aryl triflate ***217****.*



Scheme A1.2. Synthesis of β-ketolactone ***218****.*



*Scheme A1.3. Synthesis of (–)-curvularin (****221****).*



APPENDIX 2

Spectra Relevant to Chapter 2:

The Total Synthesis of (–)-Curvularin

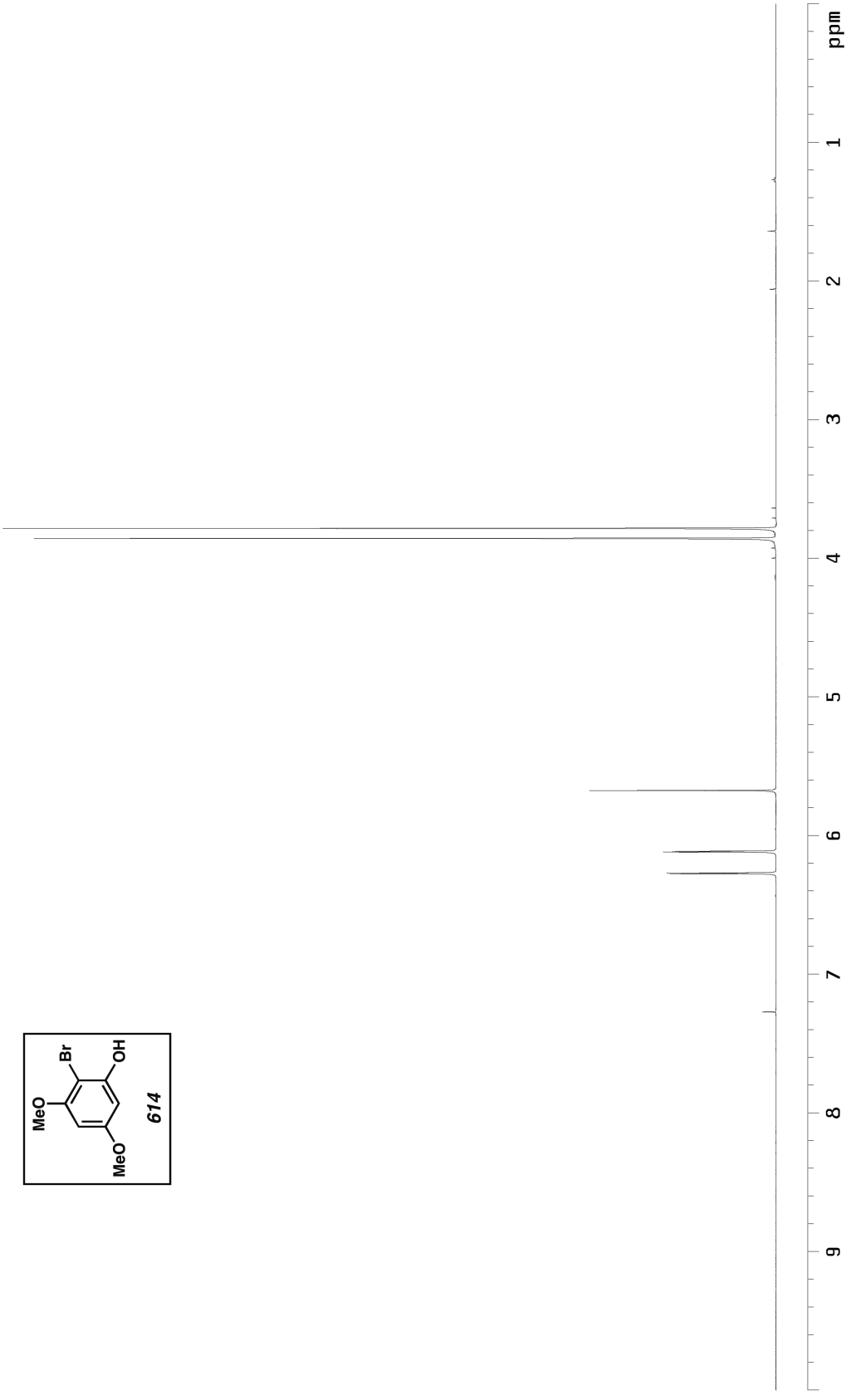


Figure A2.1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **614**.

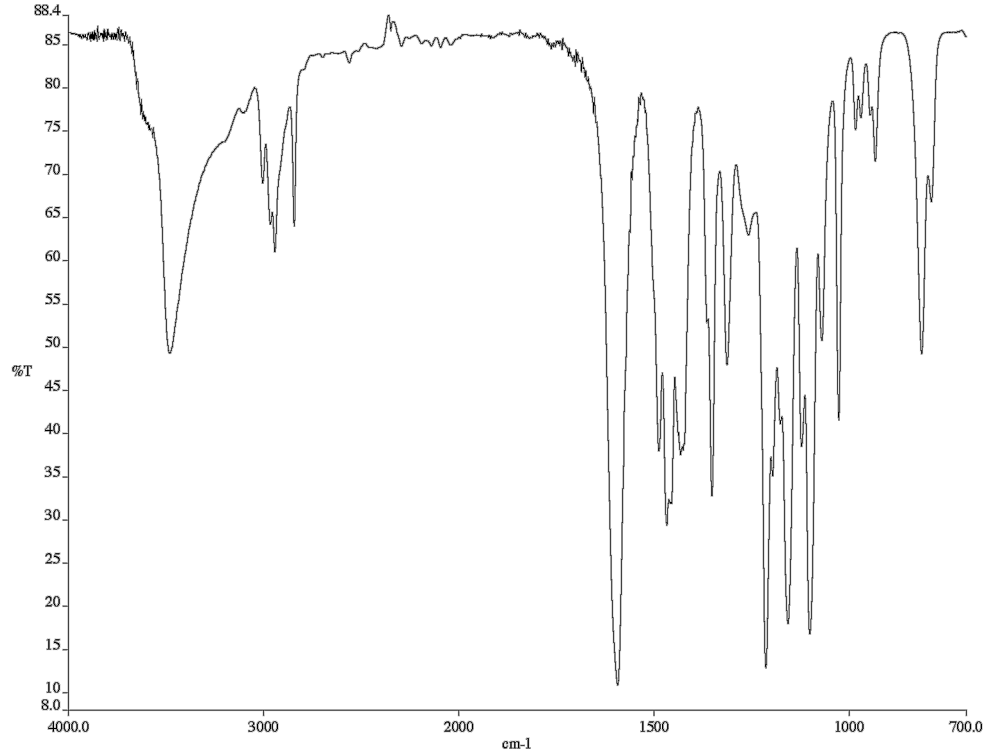


Figure A2.1.2 Infrared spectrum (thin film/NaCl) of compound **614**.

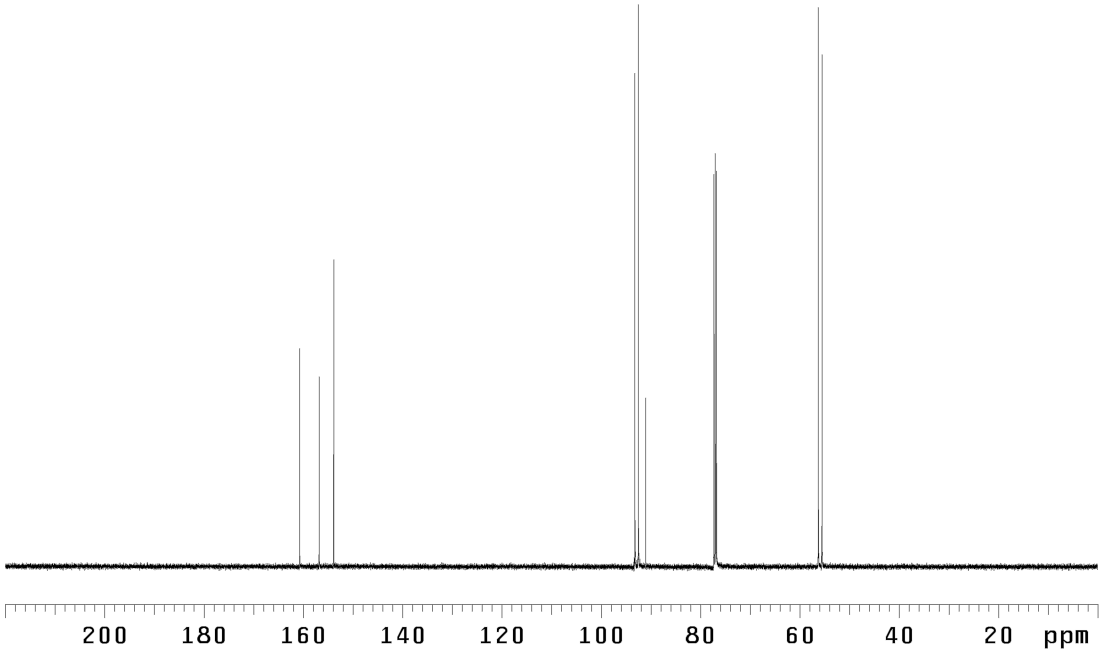


Figure A2.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **614**.

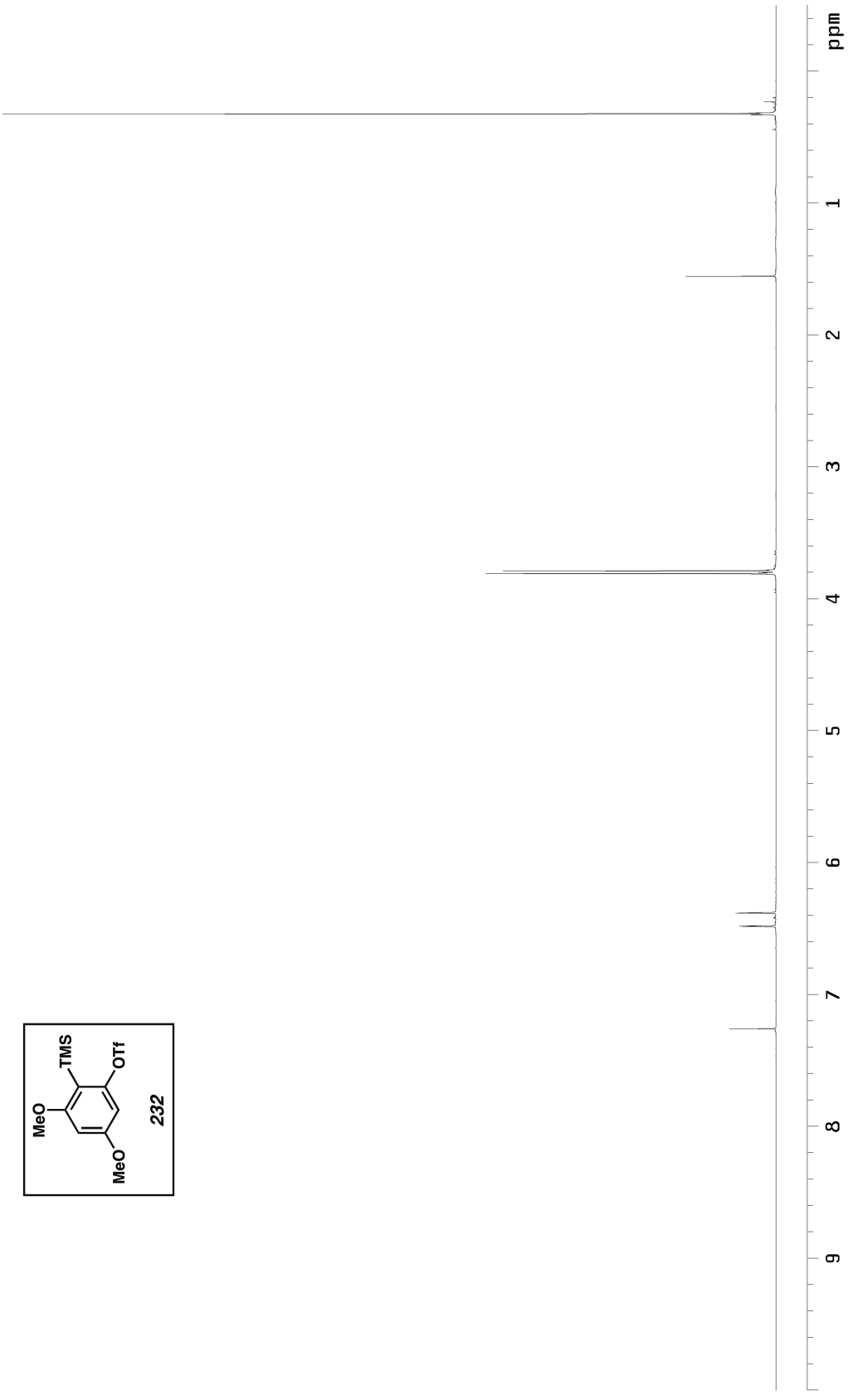


Figure A2.2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **232**.

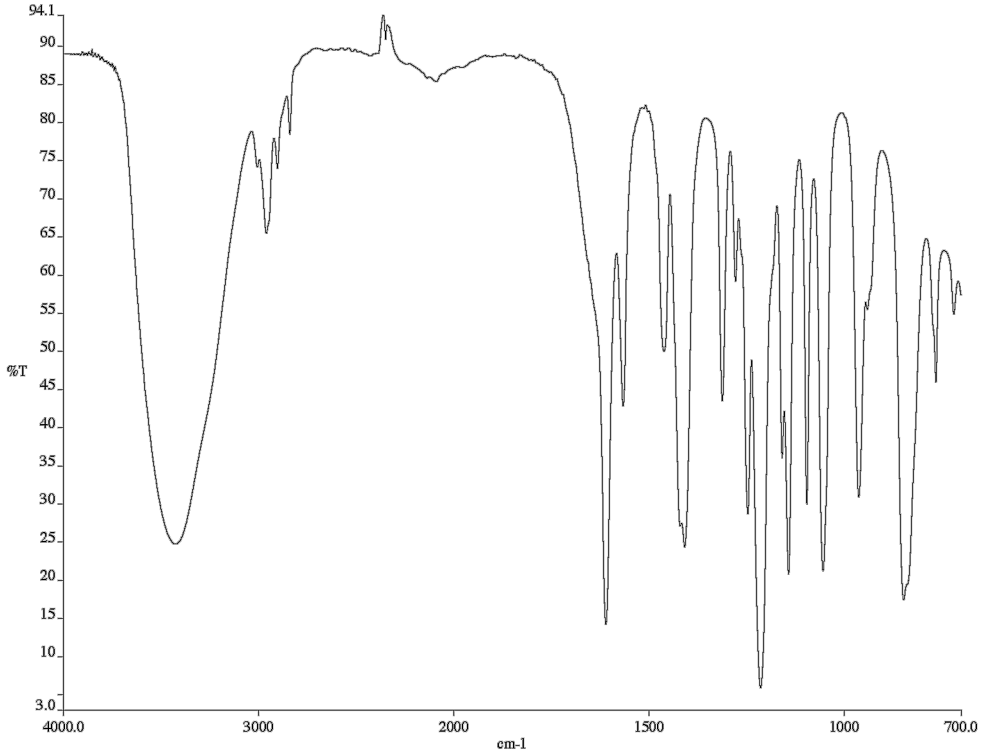


Figure A2.2.2 Infrared spectrum (thin film/NaCl) of compound **232**.

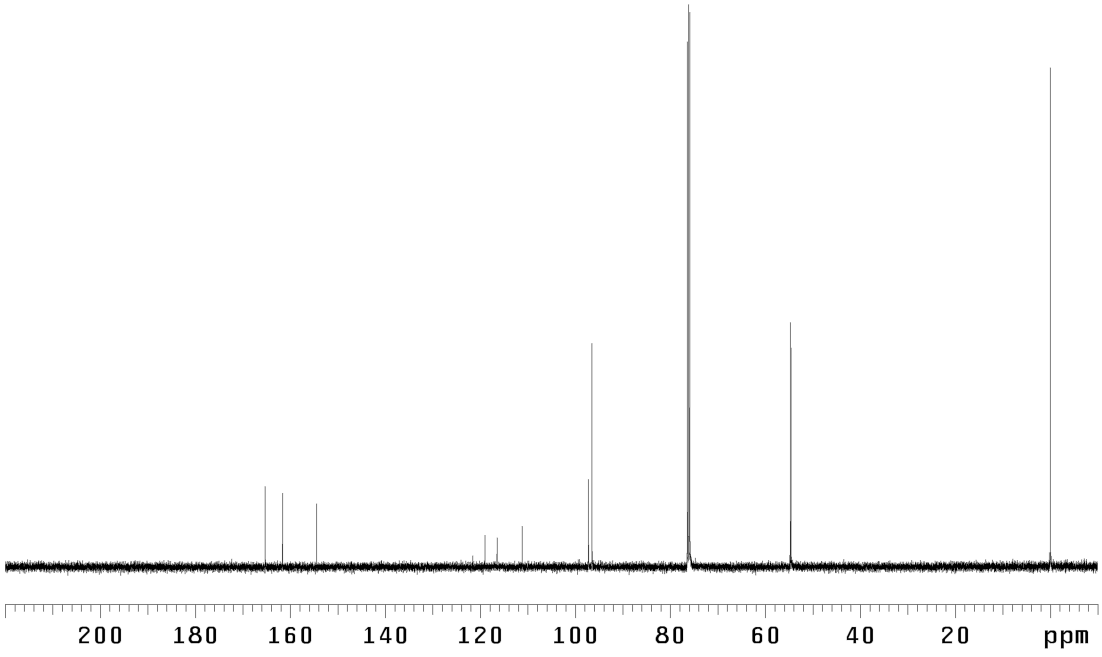


Figure A2.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **232**.

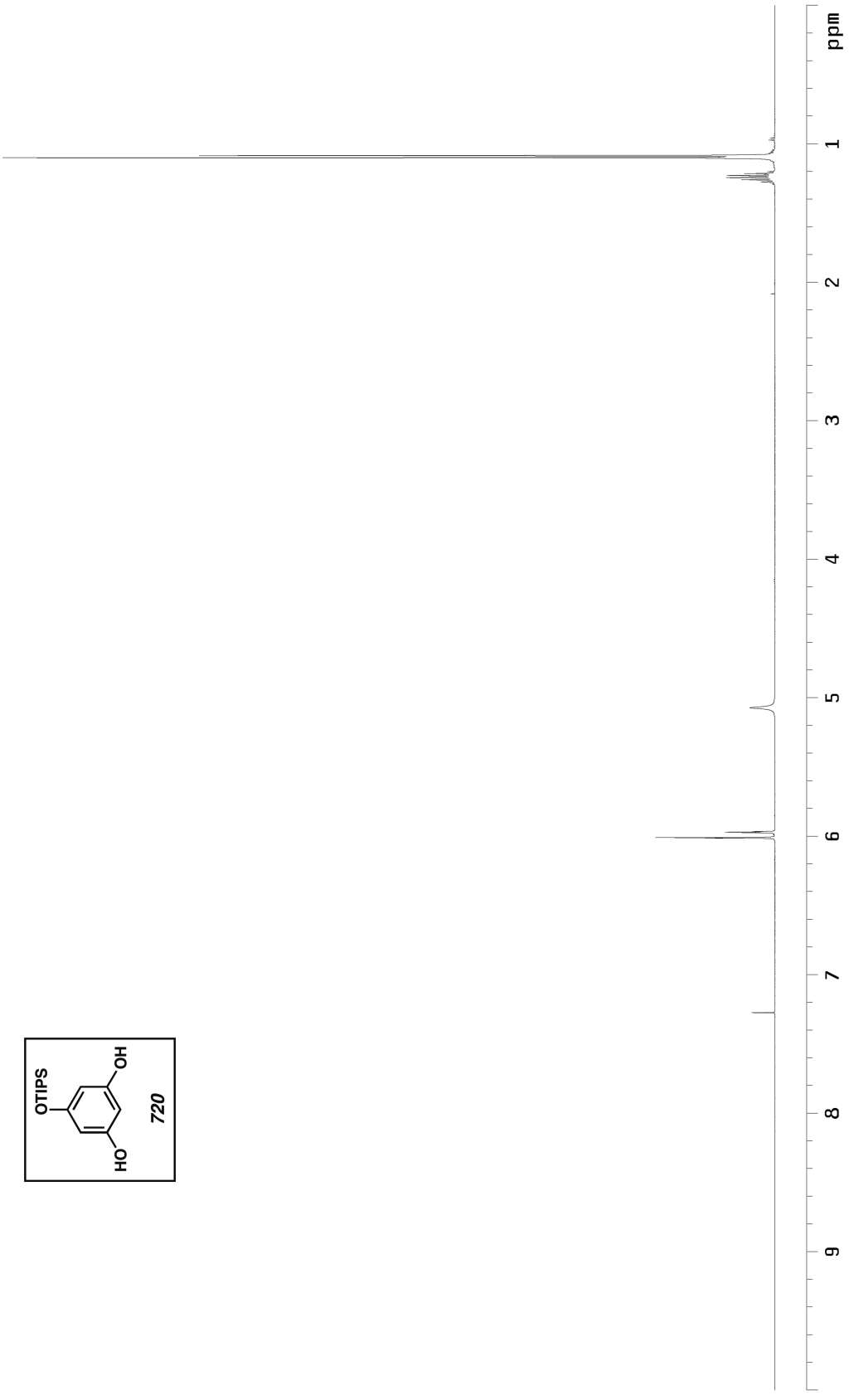


Figure A2.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **720**.

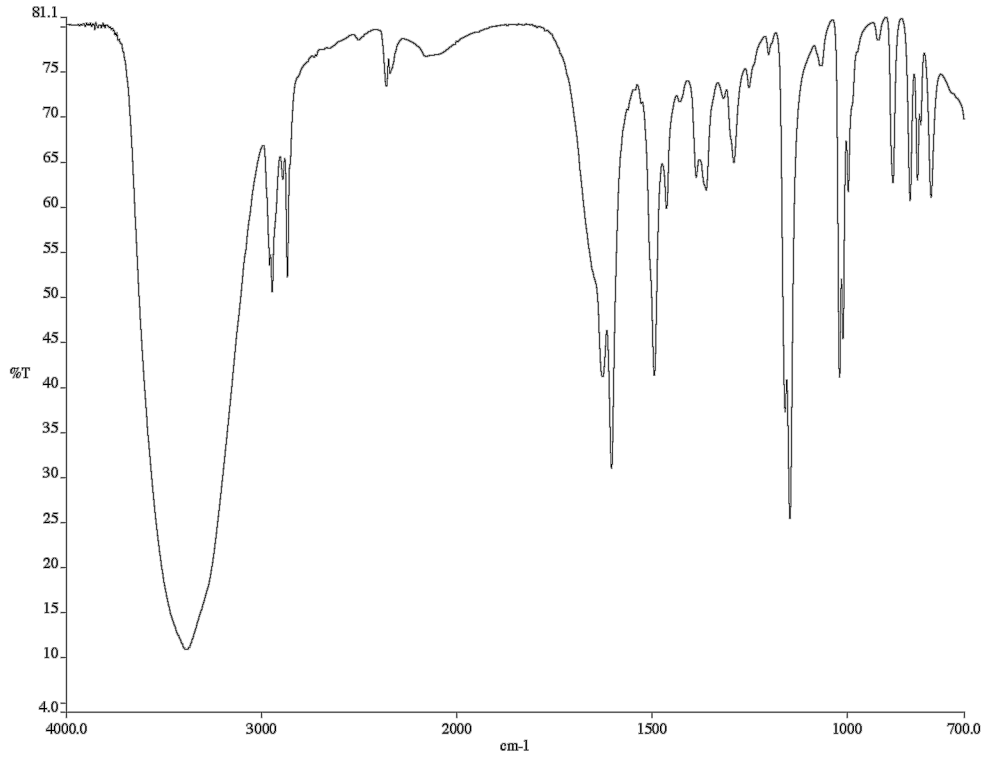


Figure A2.3.2 Infrared spectrum (thin film/NaCl) of compound **720**.

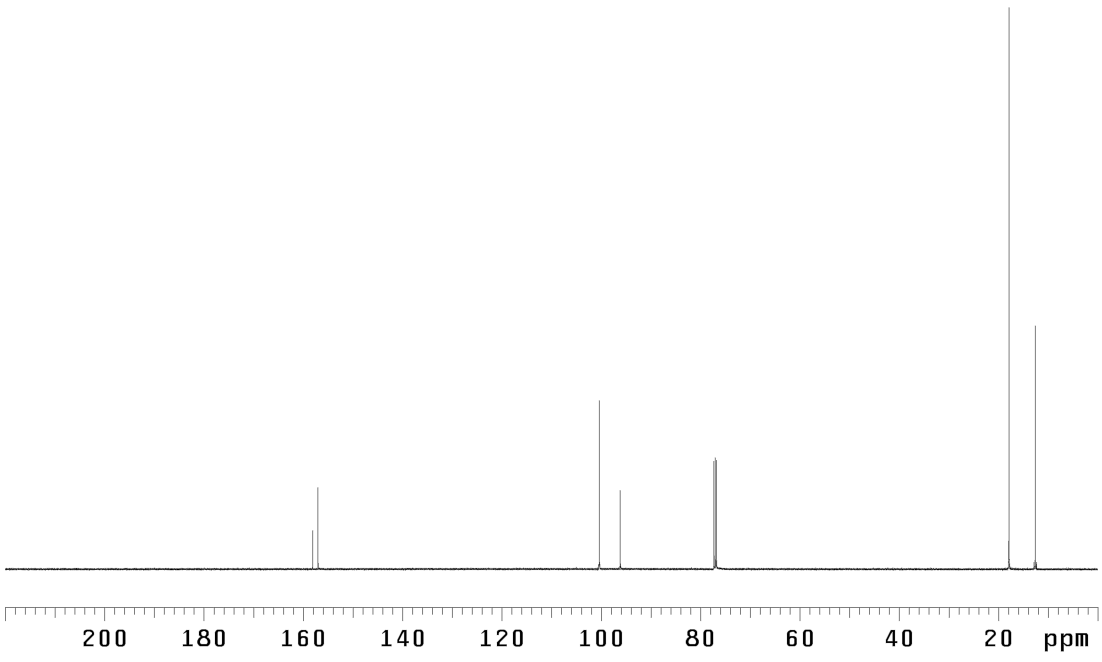


Figure A2.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **720**.

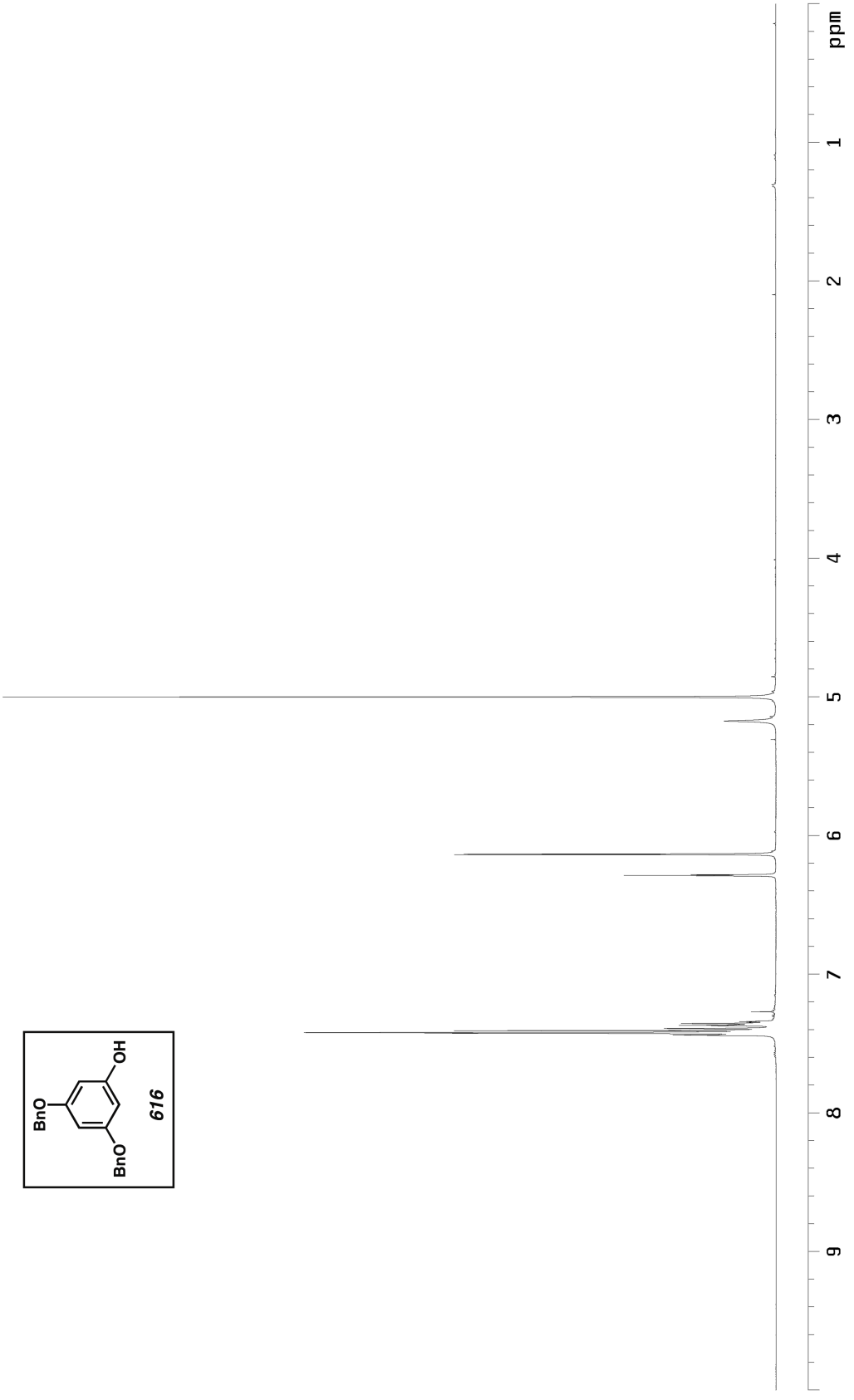


Figure A2.4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **616**.

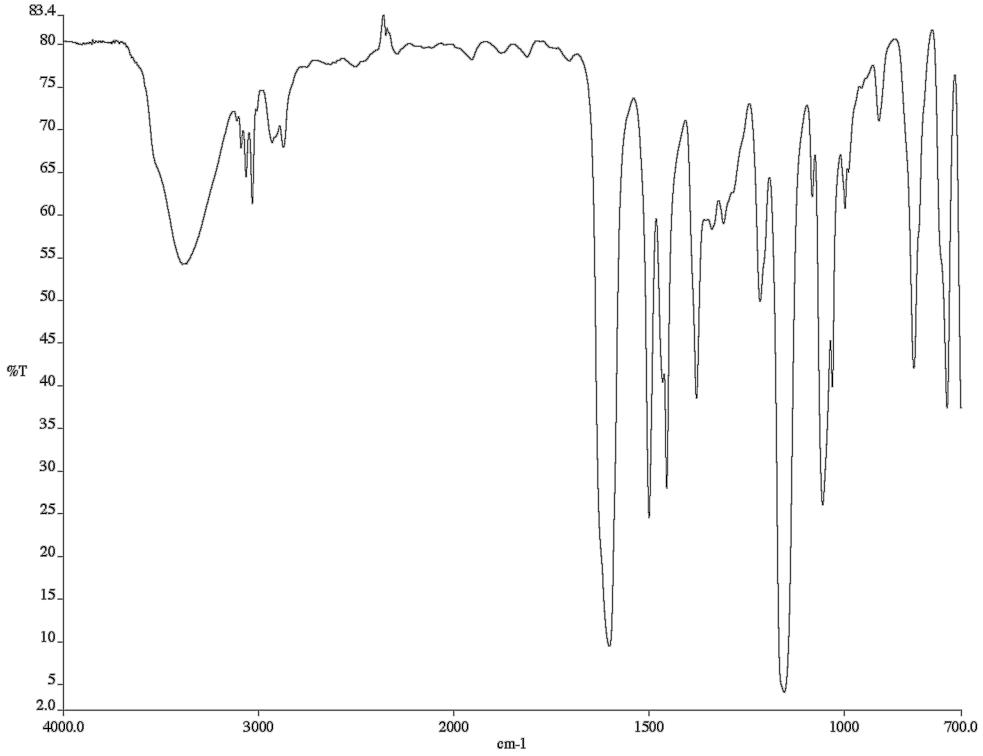


Figure A2.4.2 Infrared spectrum (thin film/NaCl) of compound **616**.

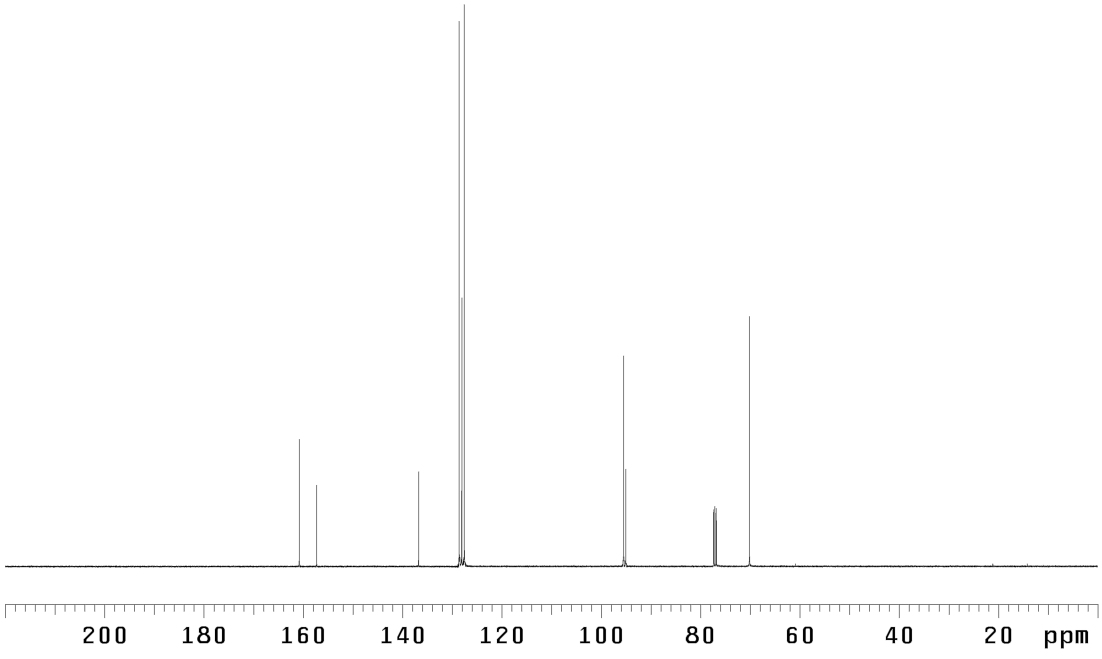


Figure A2.4.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **616**.

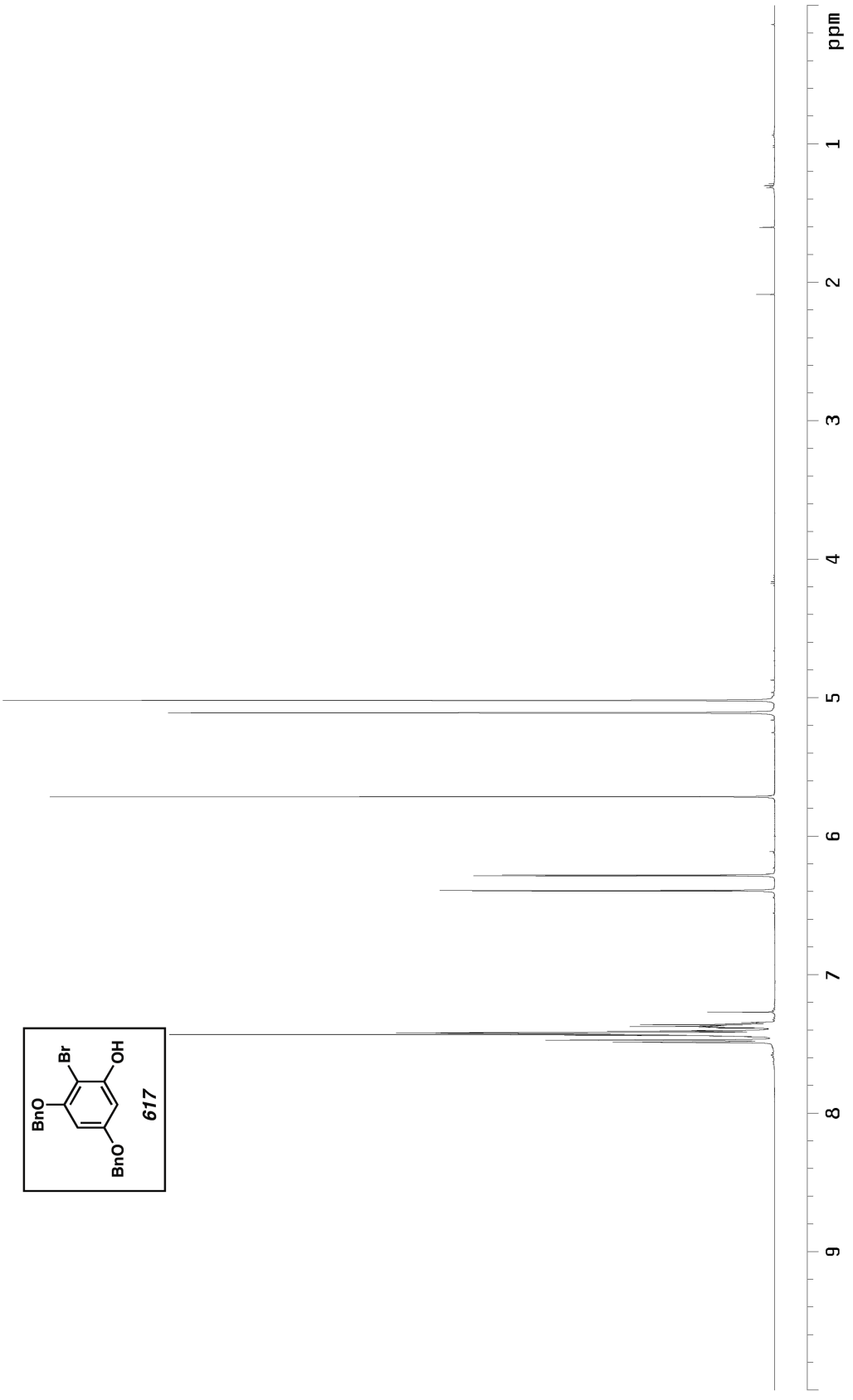


Figure A2.5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **617**.

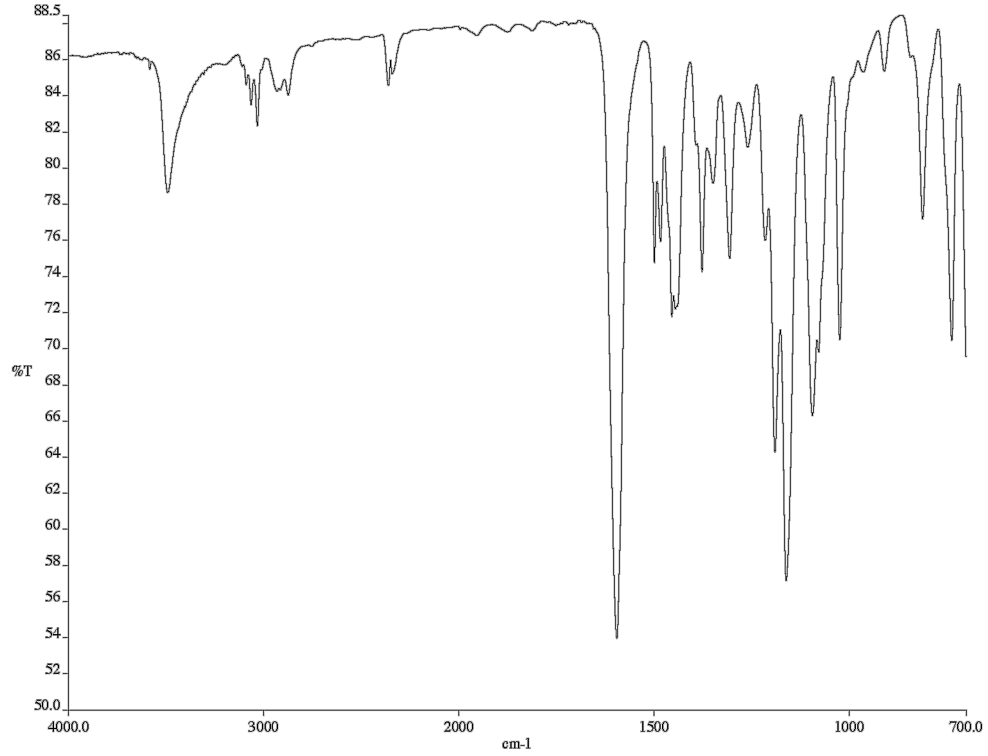


Figure A2.5.2 Infrared spectrum (thin film/NaCl) of compound **617**.

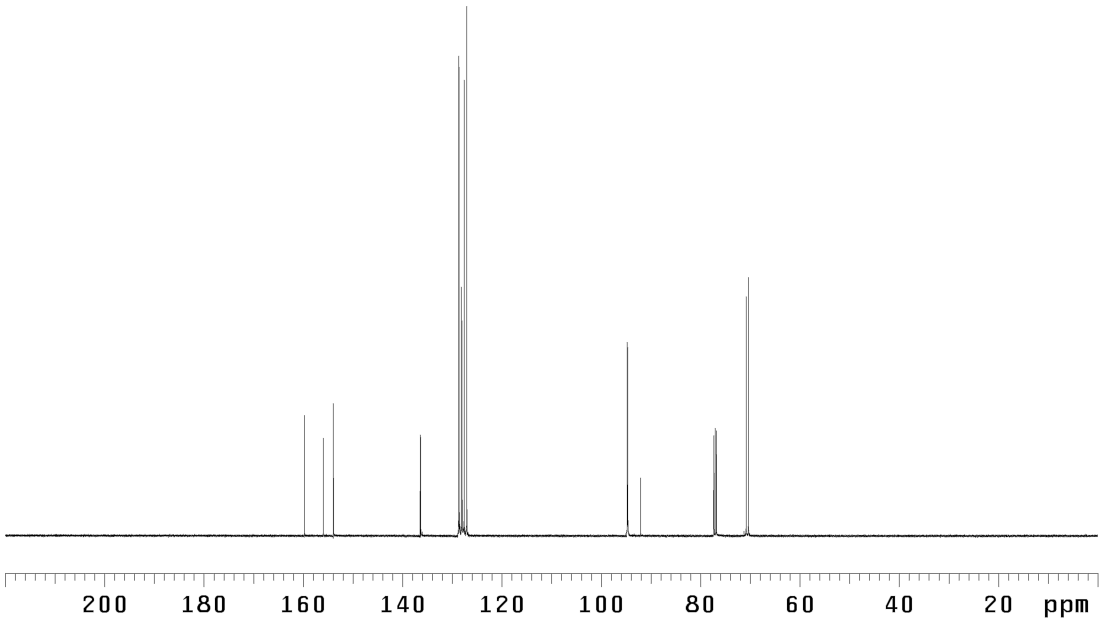


Figure A2.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **617**.

Figure A2.6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **217**.

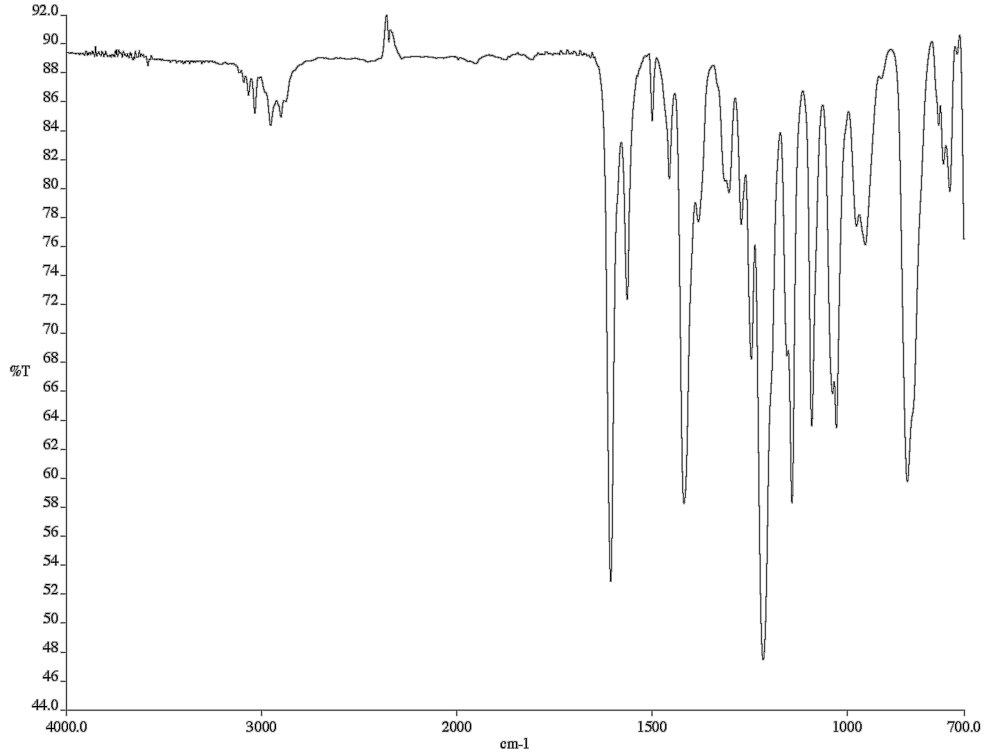


Figure A2.6.2 Infrared spectrum (thin film/NaCl) of compound **217**.

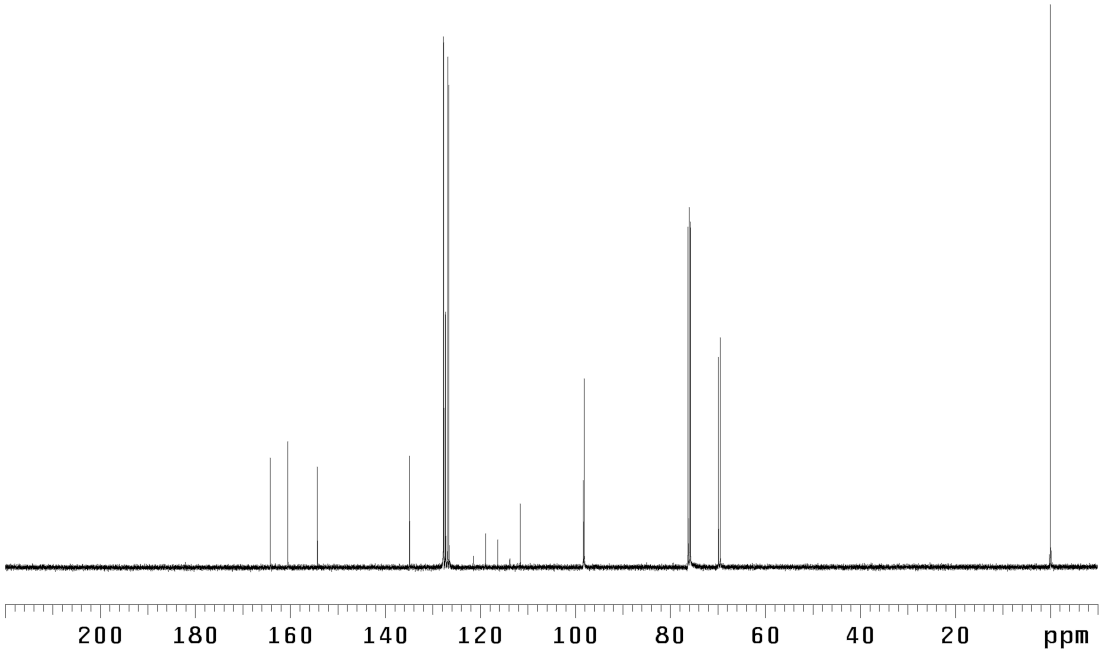


Figure A2.6.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **217**.

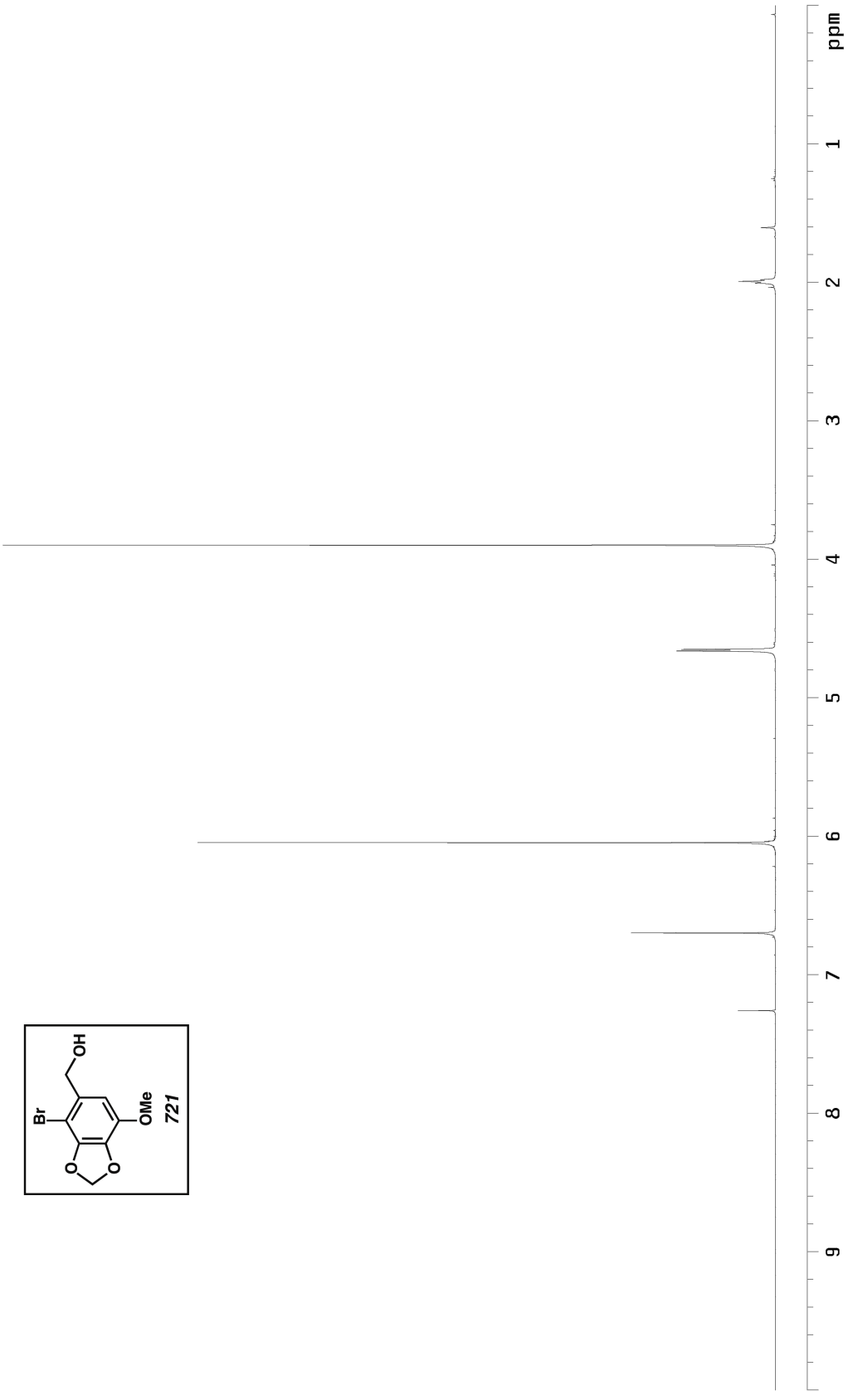


Figure A2.7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **721**.

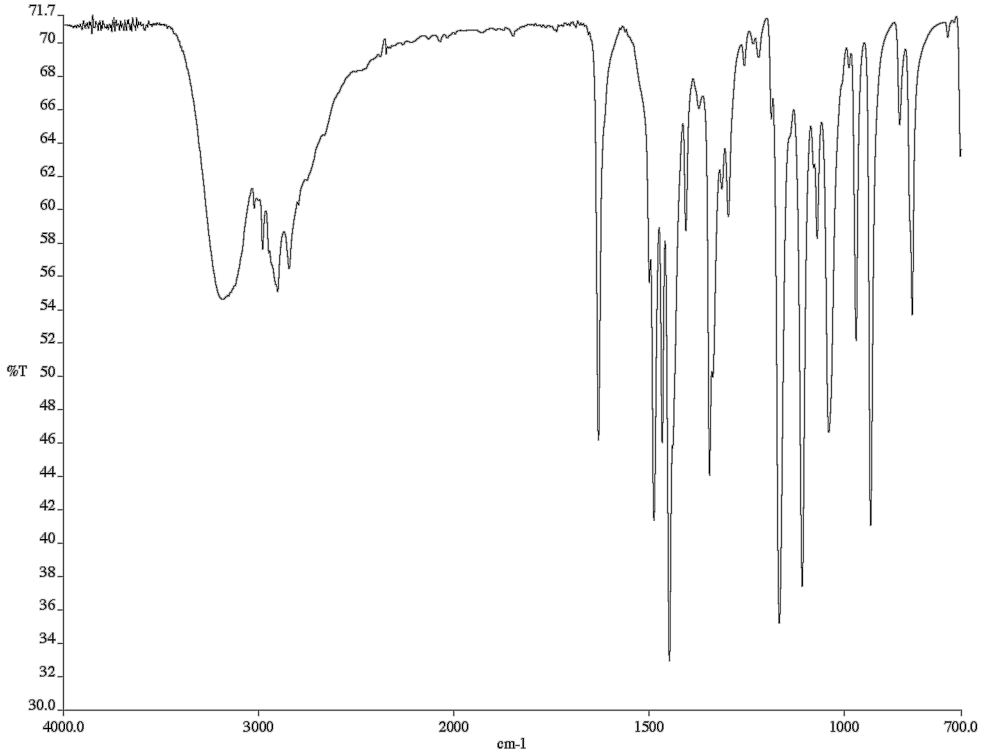


Figure A2.7.2 Infrared spectrum (thin film/NaCl) of compound **721**.

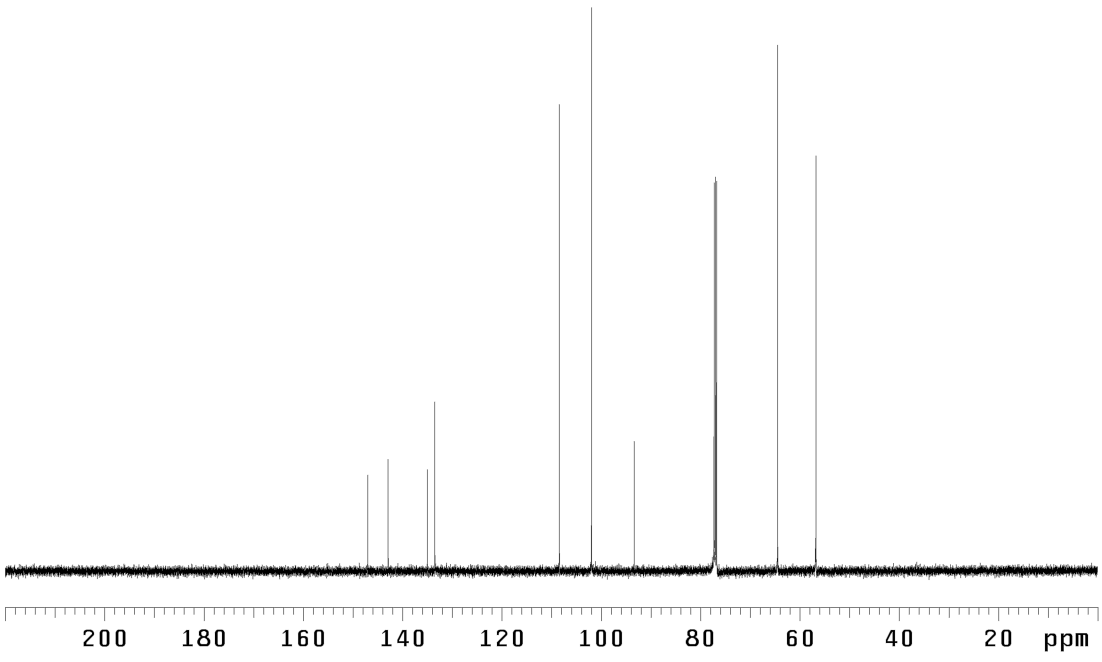


Figure A2.7.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **721**.

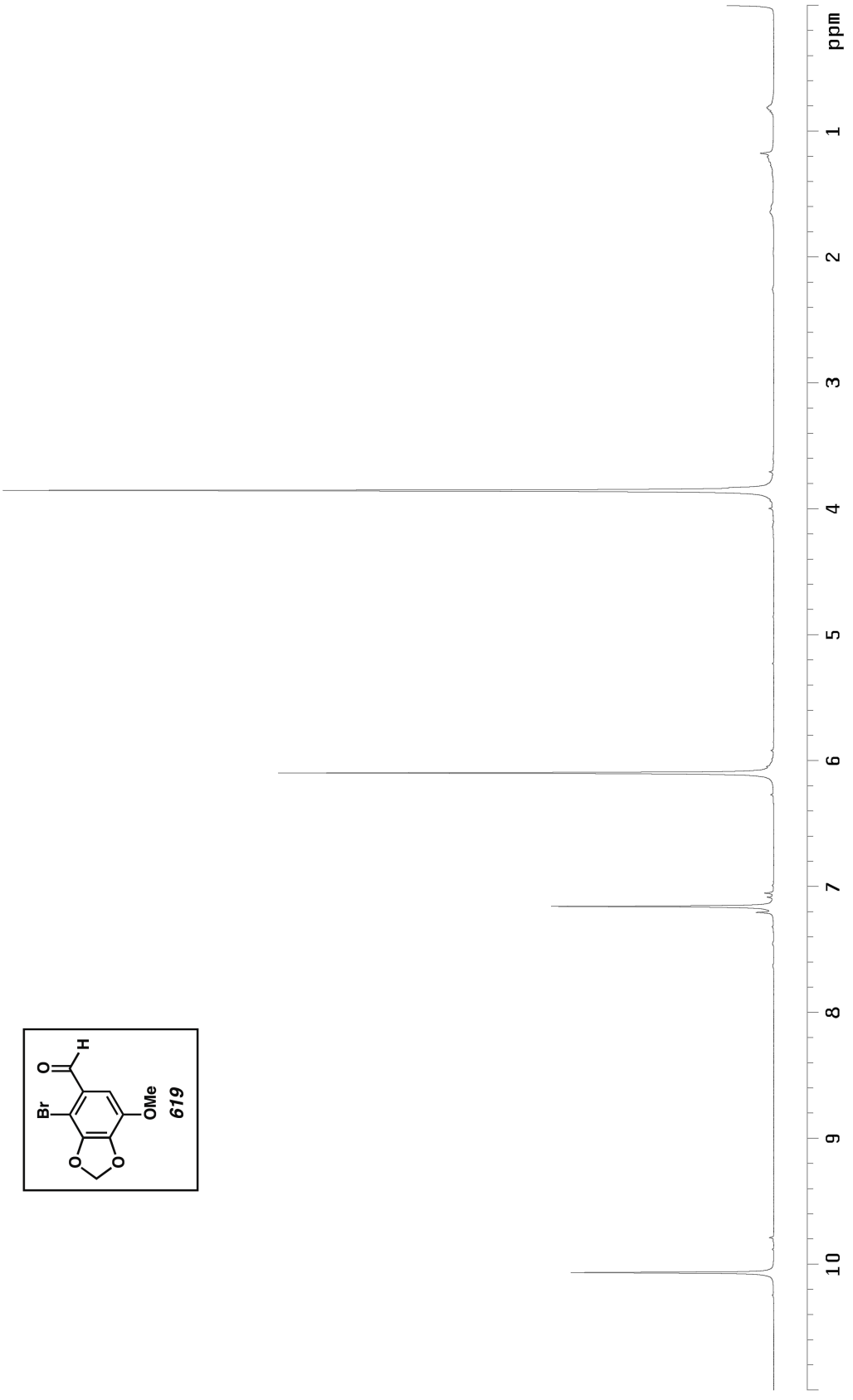


Figure A2.8.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **619**.

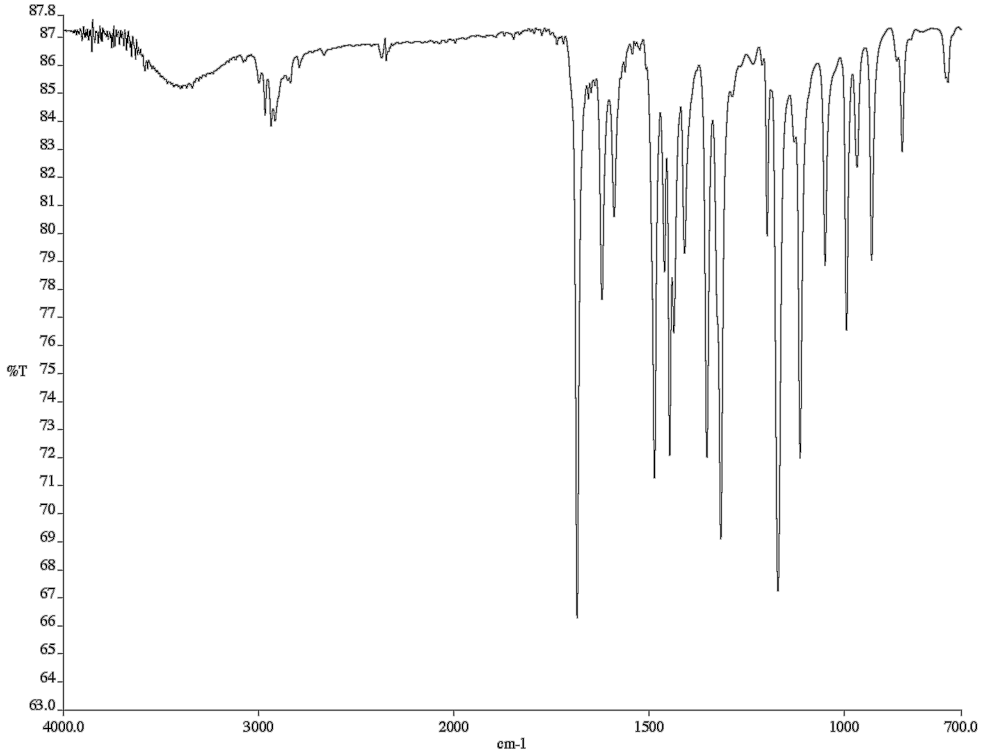


Figure A2.8.2 Infrared spectrum (thin film/NaCl) of compound **619**.

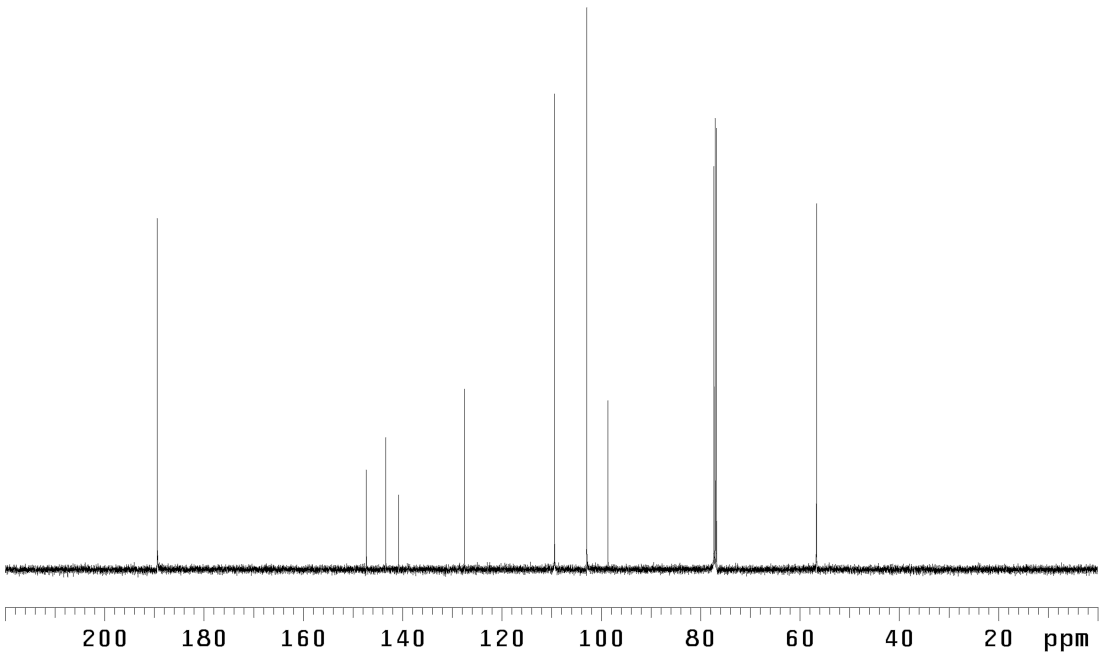


Figure A2.8.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **619**.

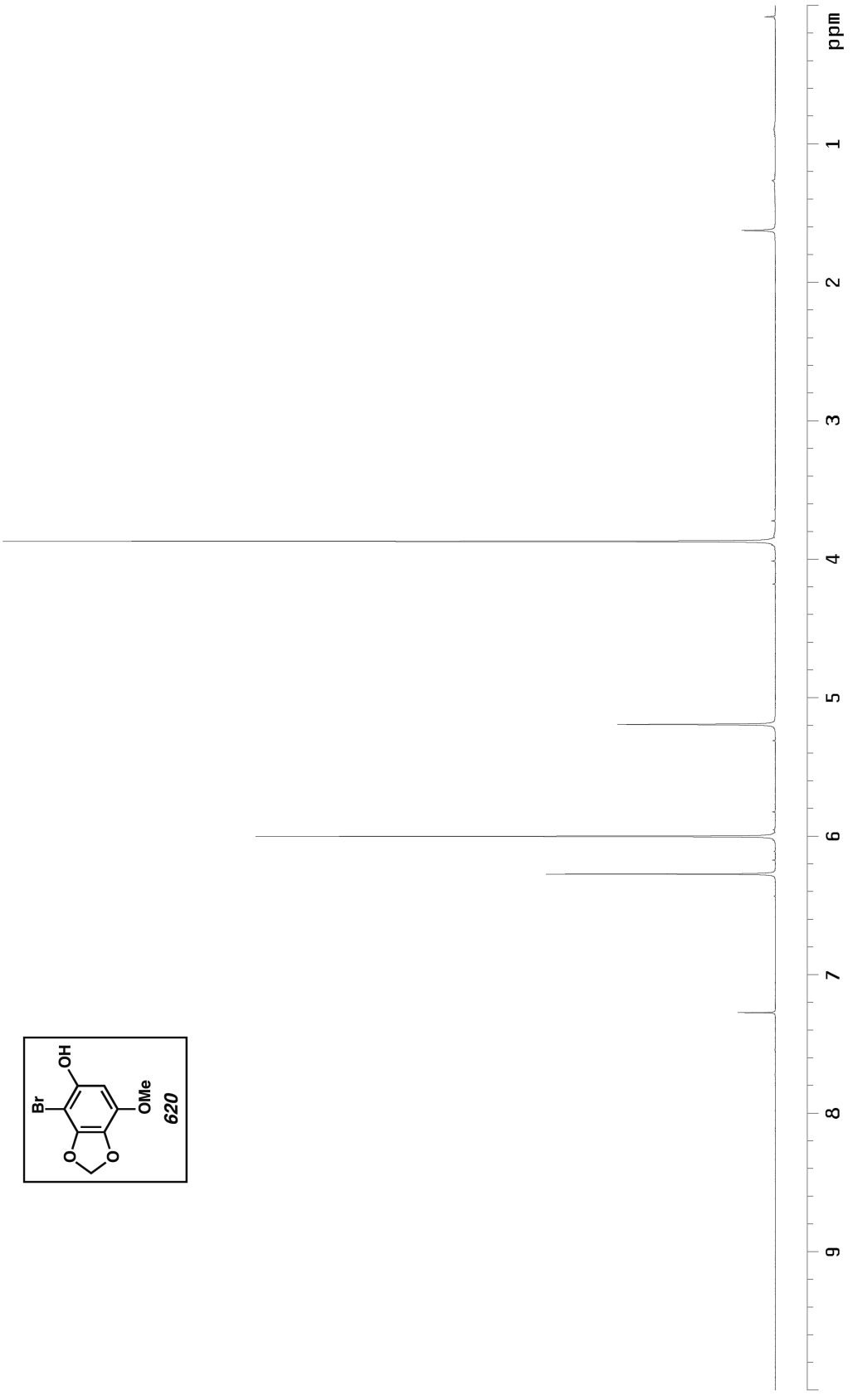


Figure A2.9.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **620**.

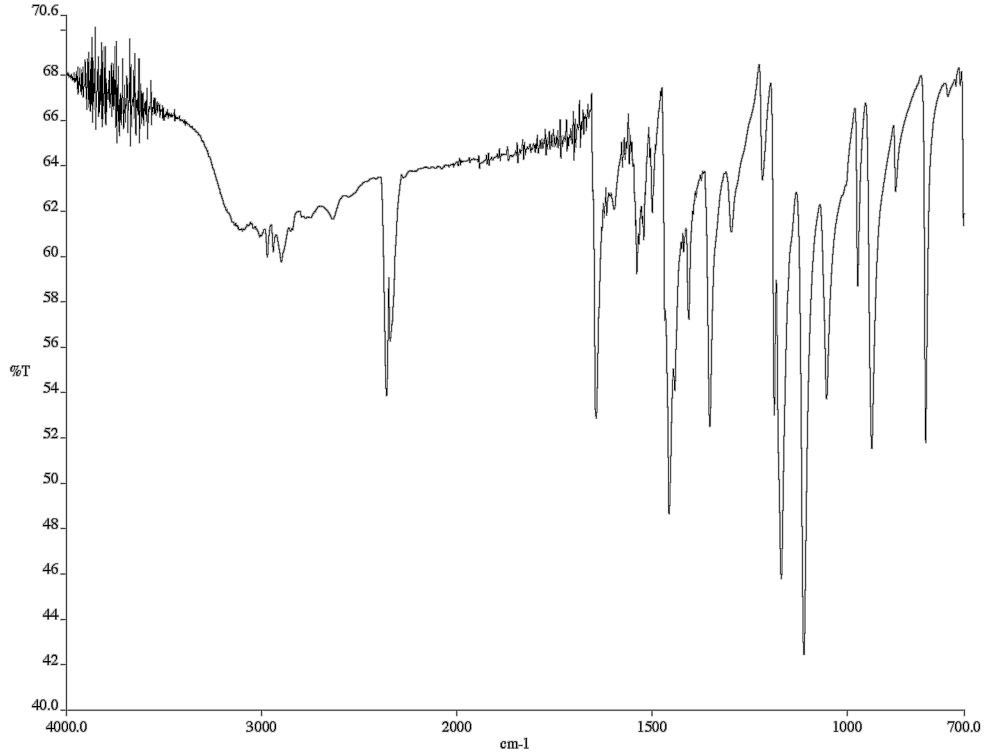


Figure A2.9.2 Infrared spectrum (thin film/NaCl) of compound **620**.

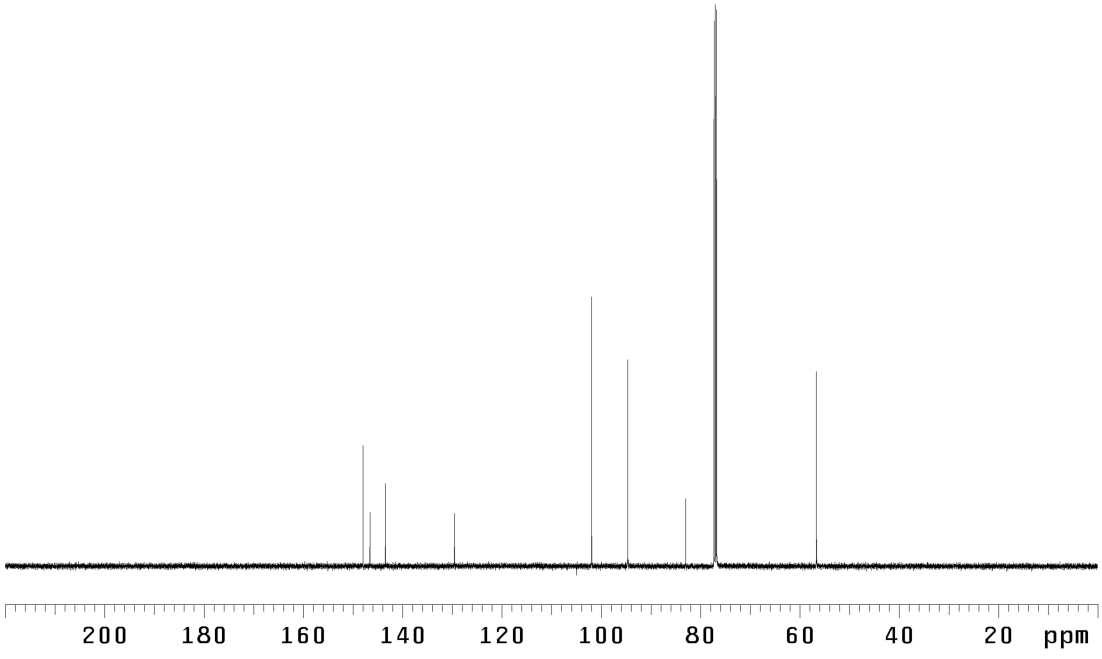


Figure A2.9.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **620**.

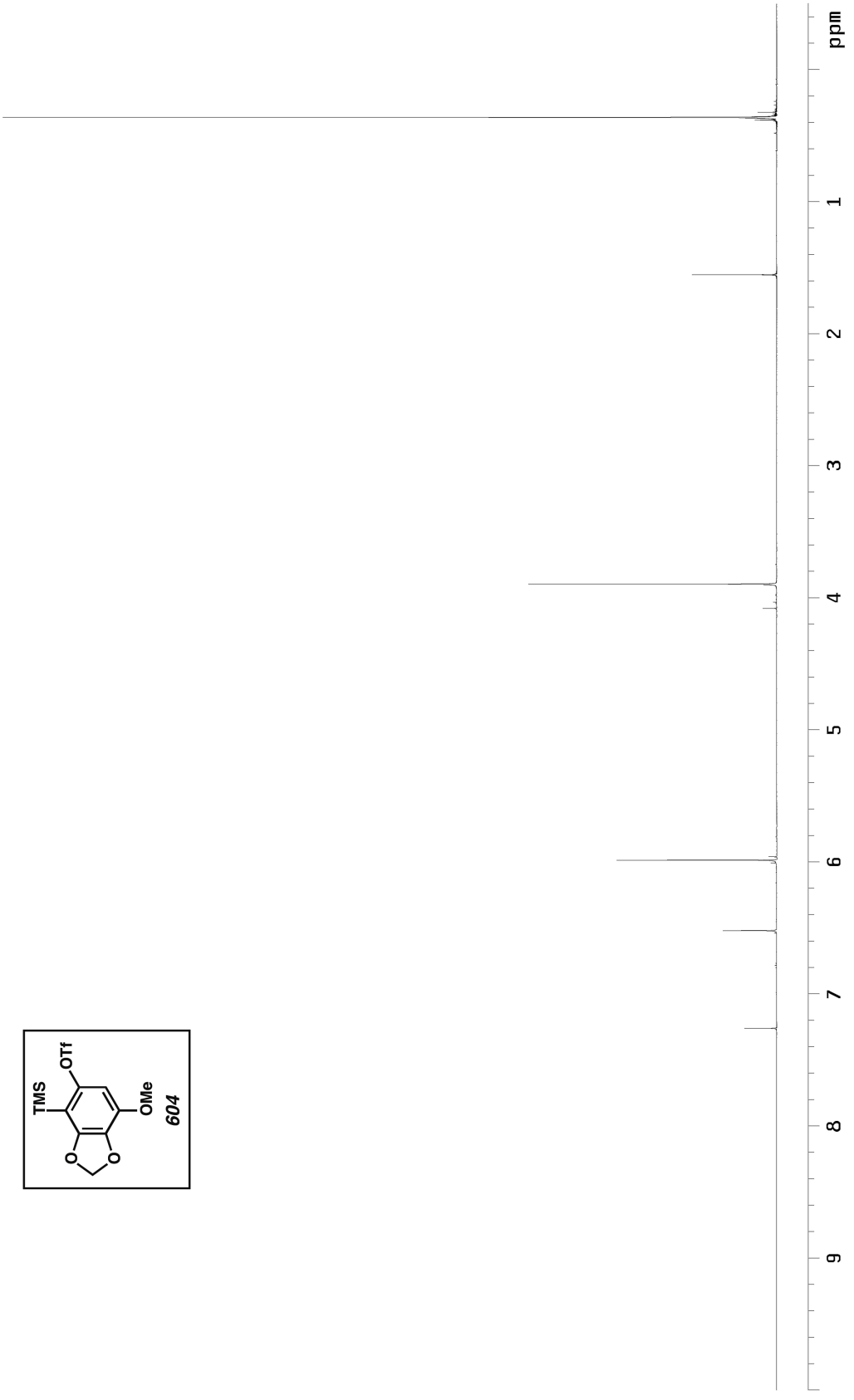


Figure A2.10.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **604**.

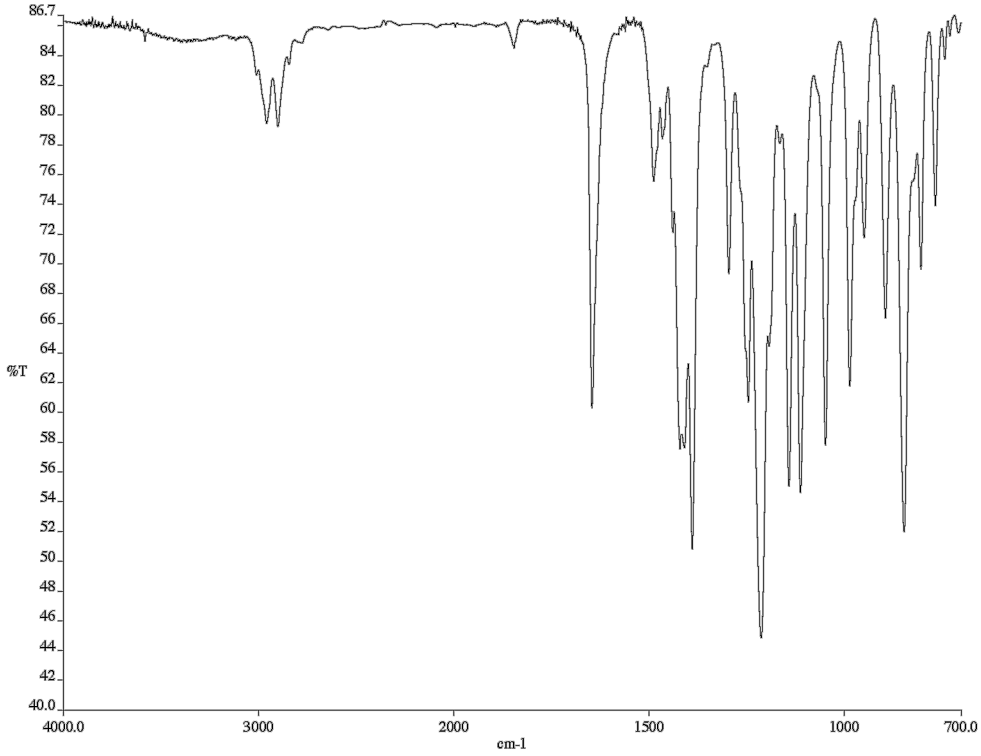


Figure A2.10.2 Infrared spectrum (thin film/NaCl) of compound **604**.

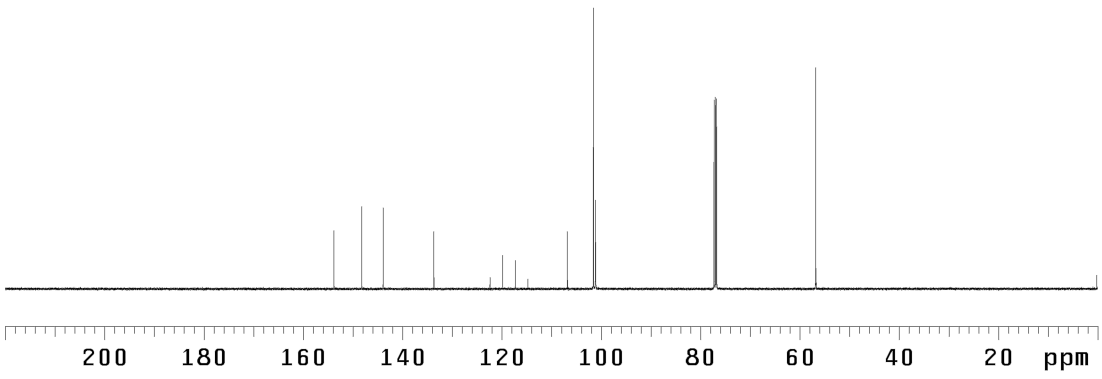


Figure A2.10.3 ^{13}C NMR (500 MHz, $CDCl_3$) of compound **604**.

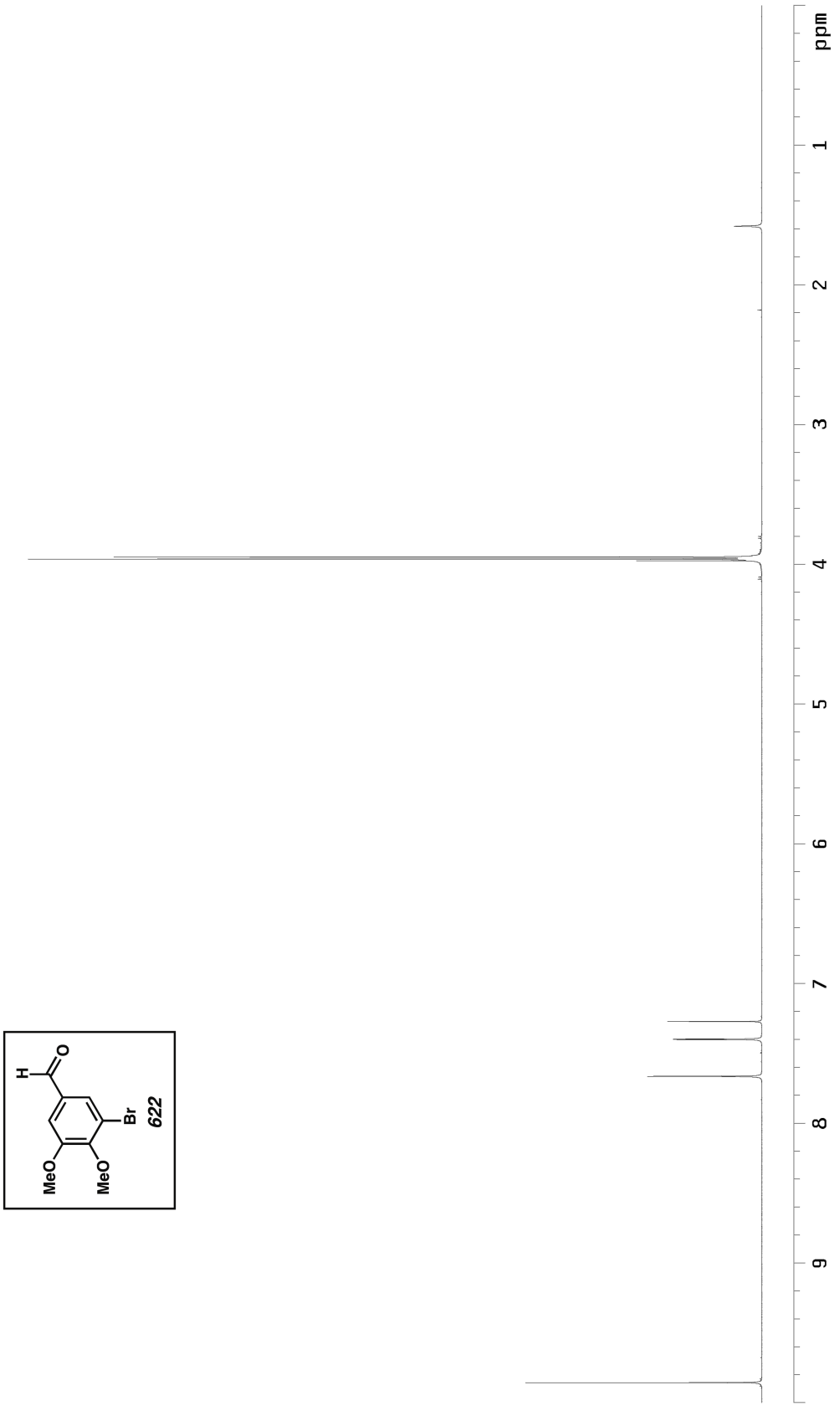


Figure A2.11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **622**.

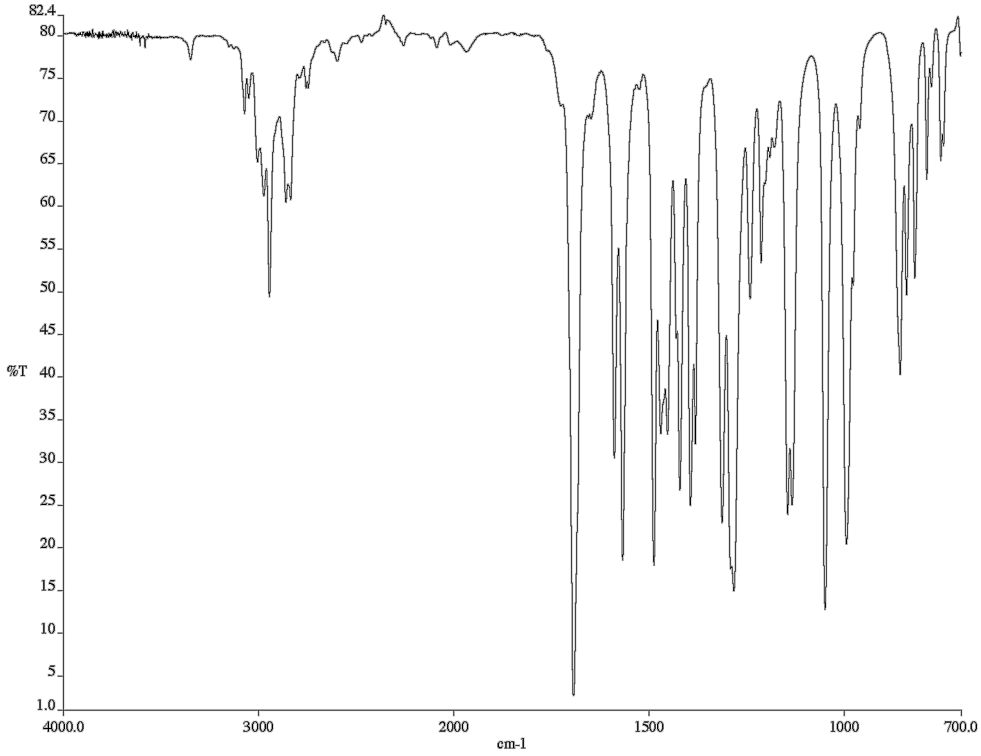


Figure A2.11.2 Infrared spectrum (thin film/NaCl) of compound **622**.

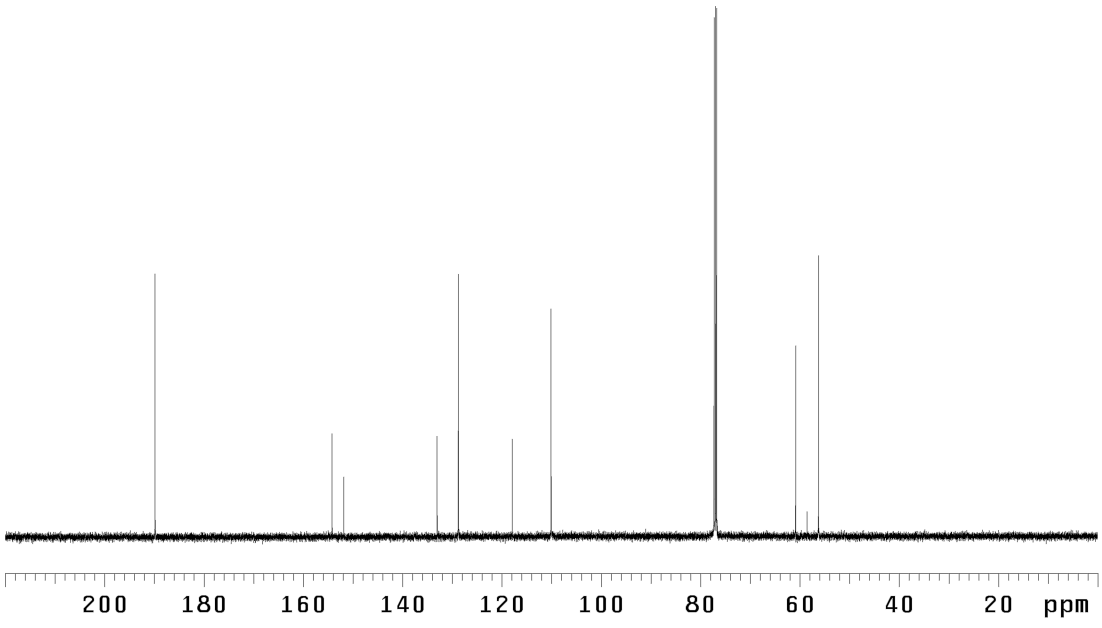


Figure A2.11.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **622**.

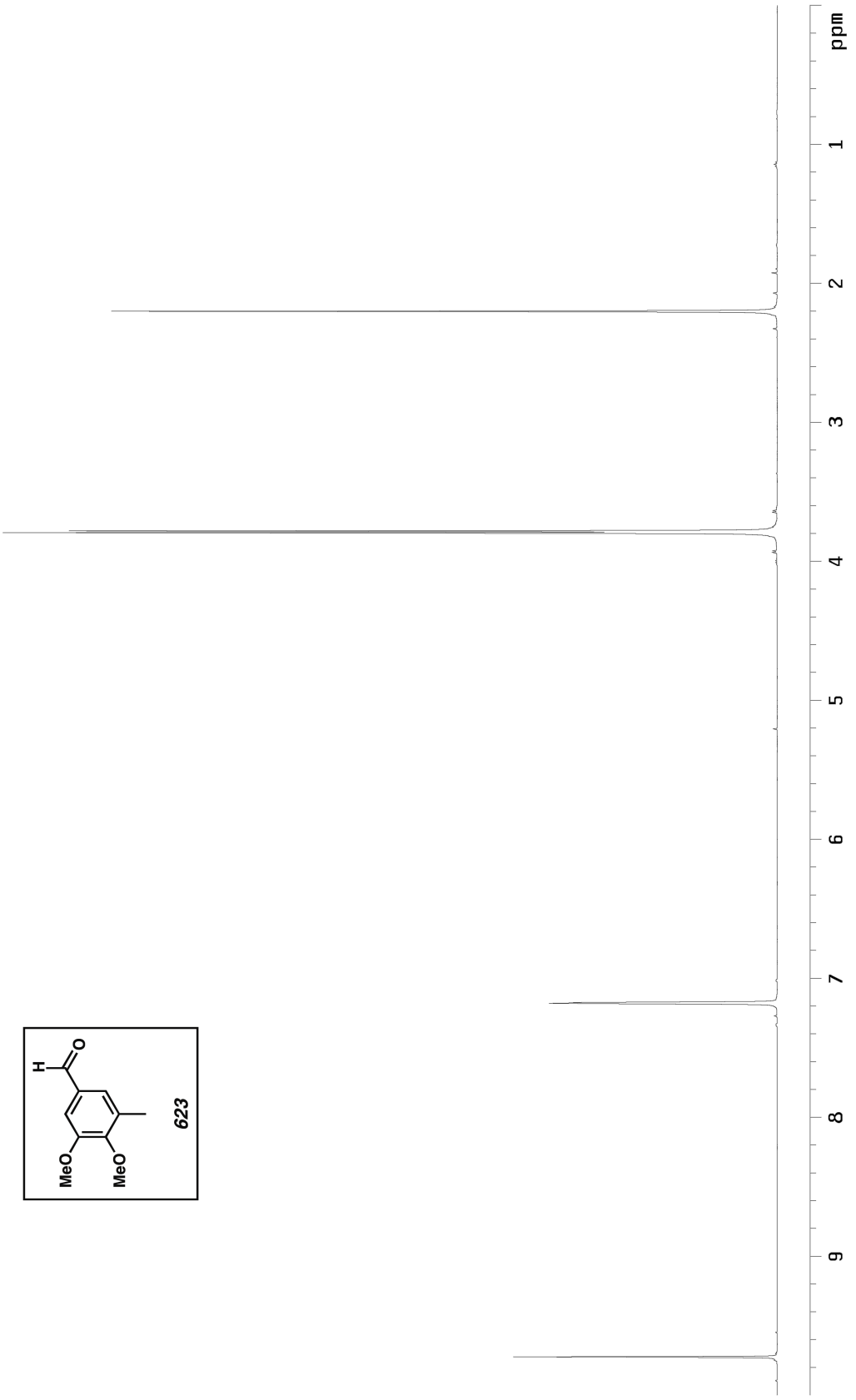


Figure A2.12.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **623**.

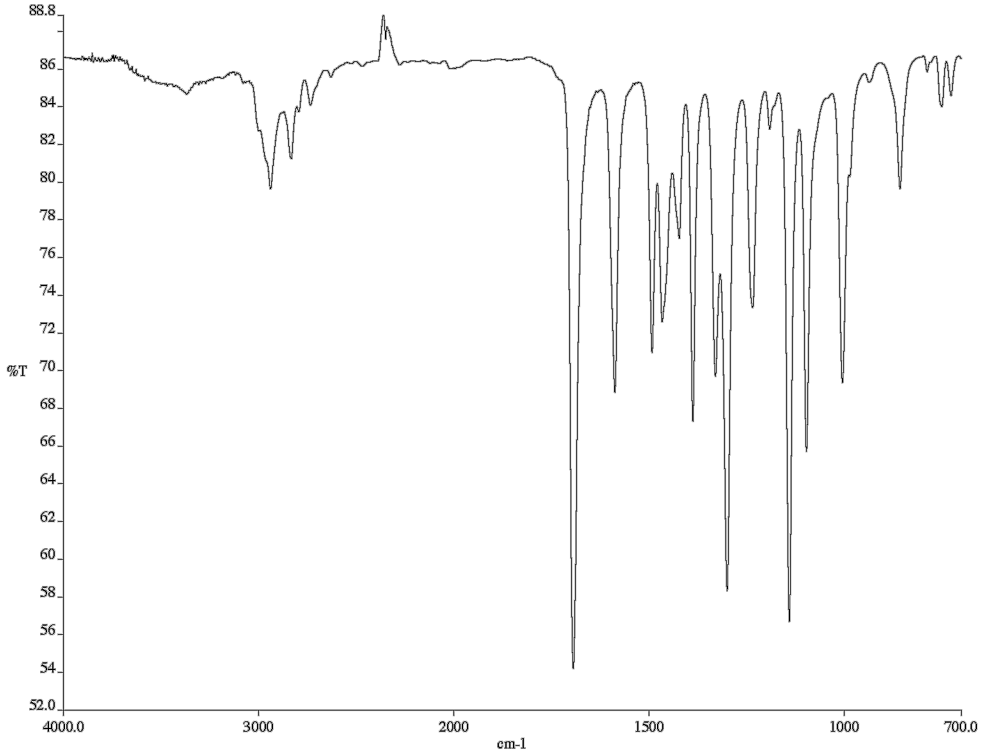


Figure A2.12.2 Infrared spectrum (thin film/NaCl) of compound **623**.

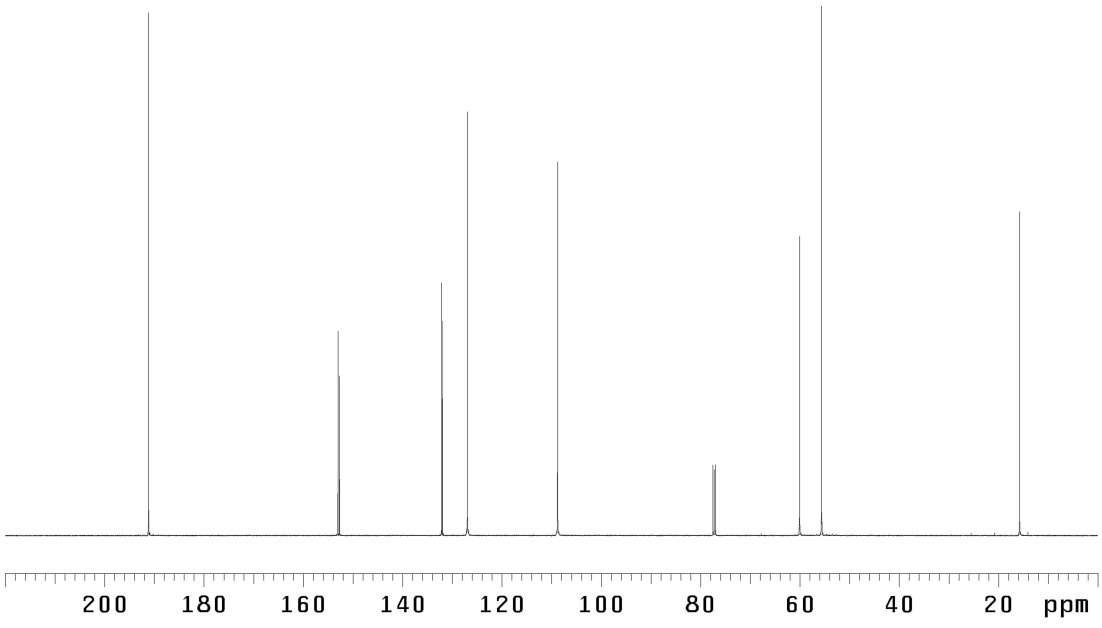


Figure A2.12.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **623**.

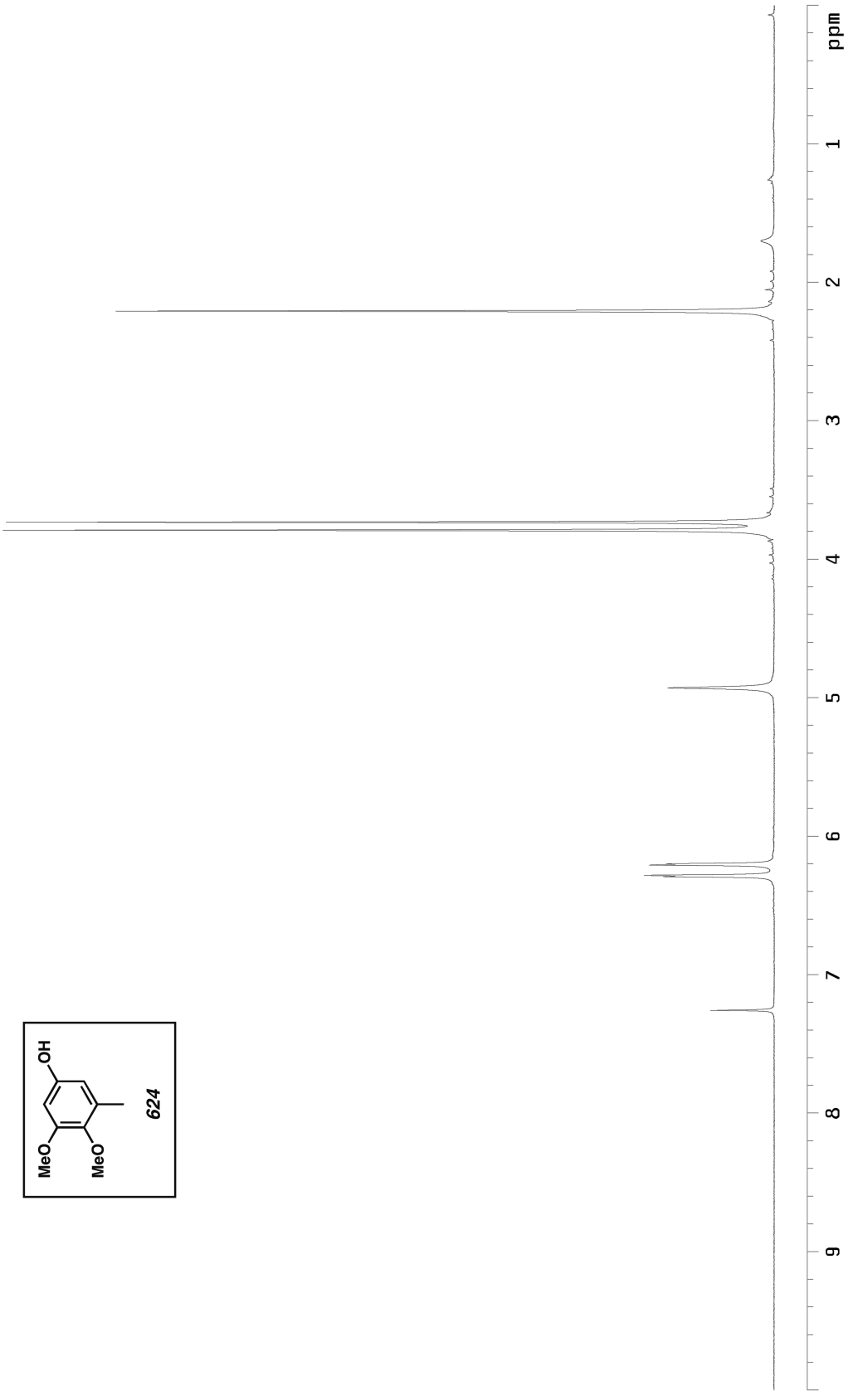


Figure A2.13.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **624**.

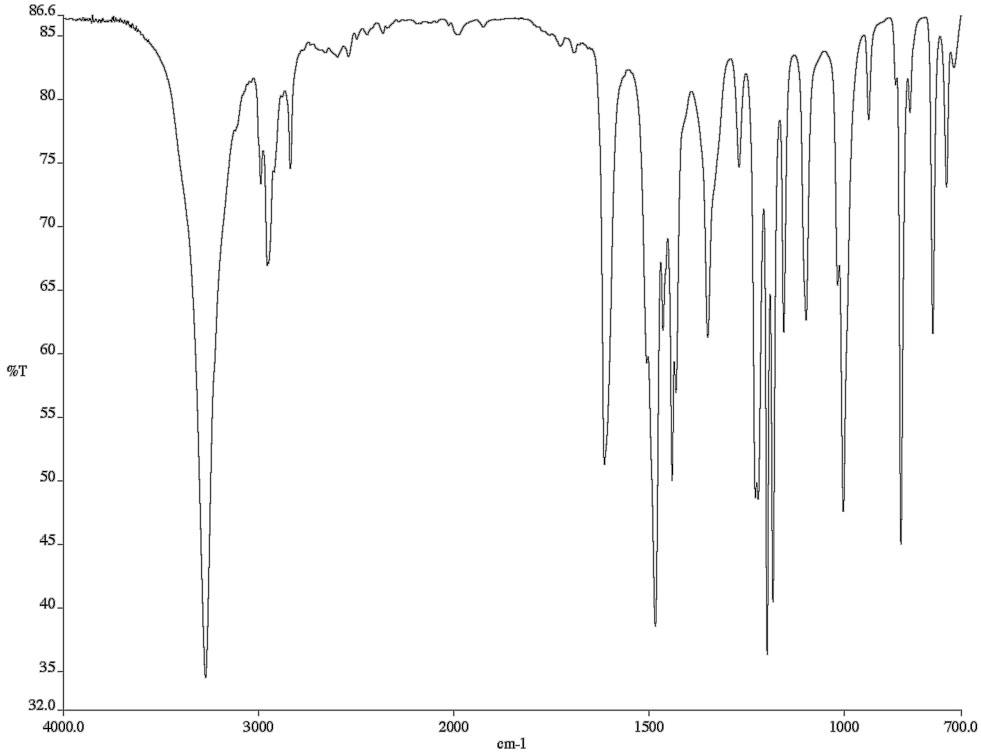


Figure A2.13.2 Infrared spectrum (thin film/NaCl) of compound **624**.

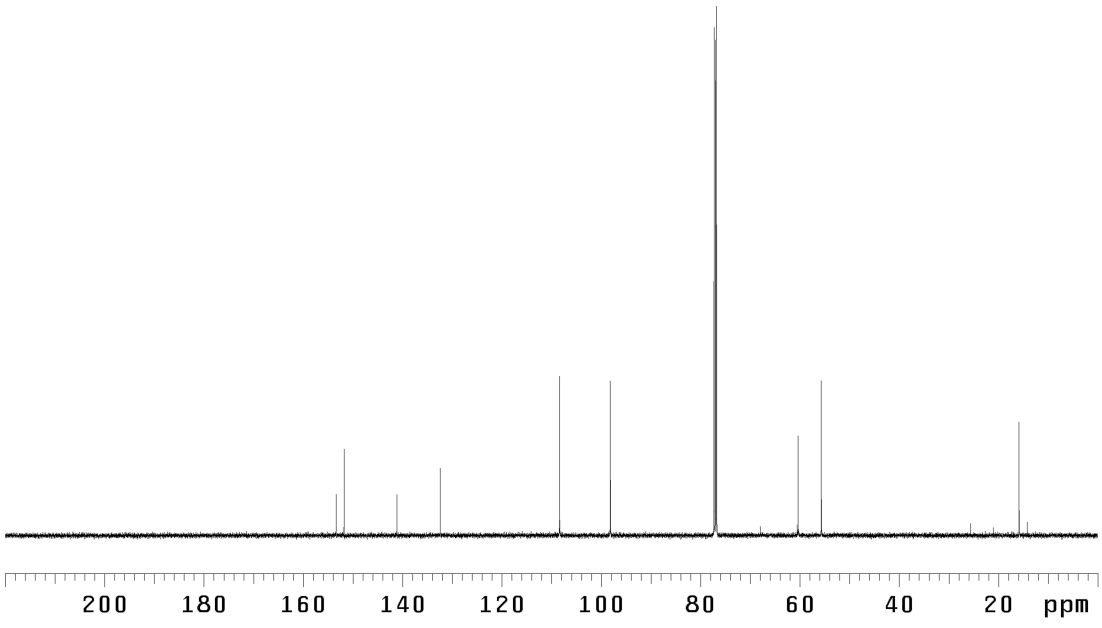


Figure A2.13.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **624**.

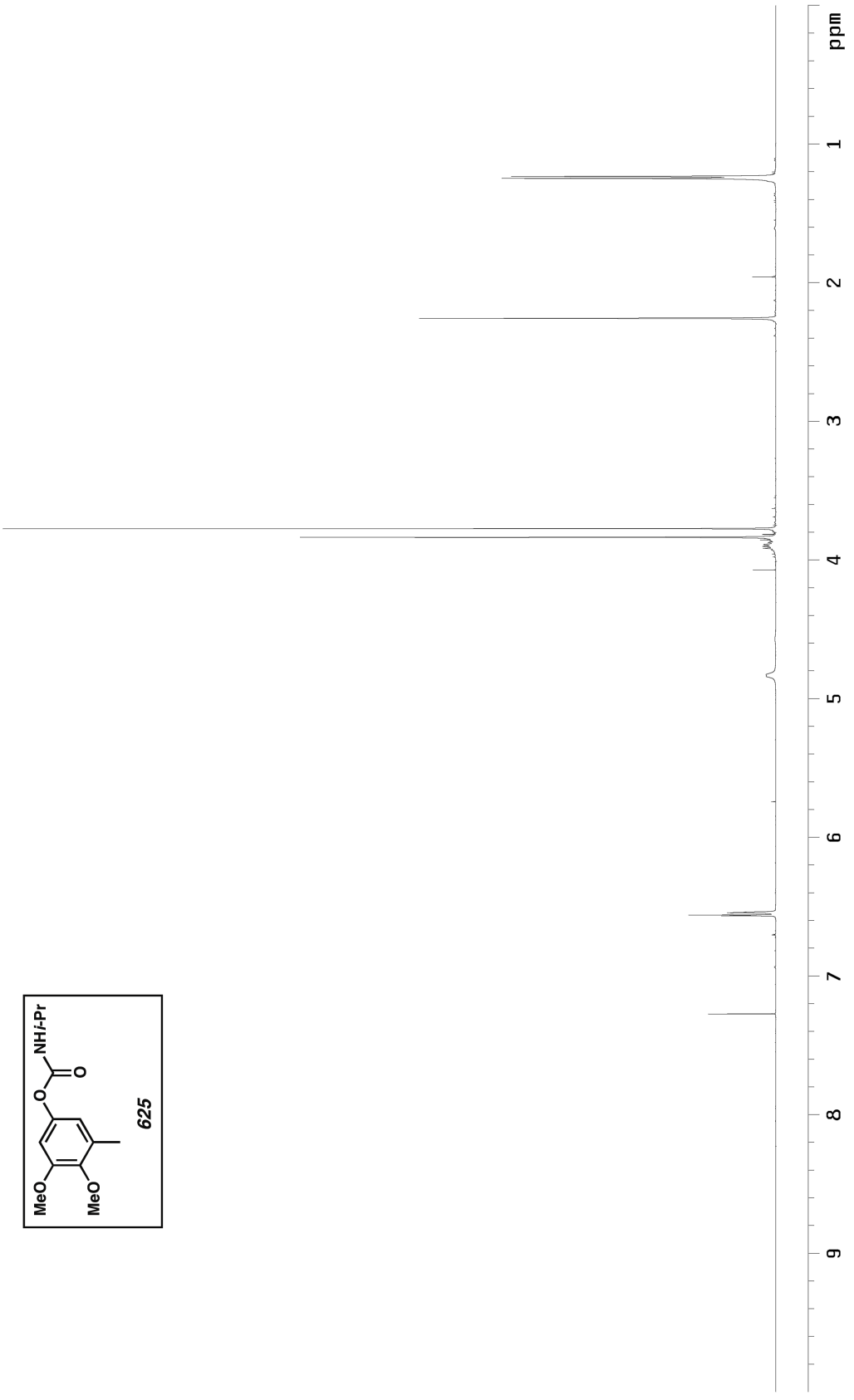


Figure A2.14.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **625**.

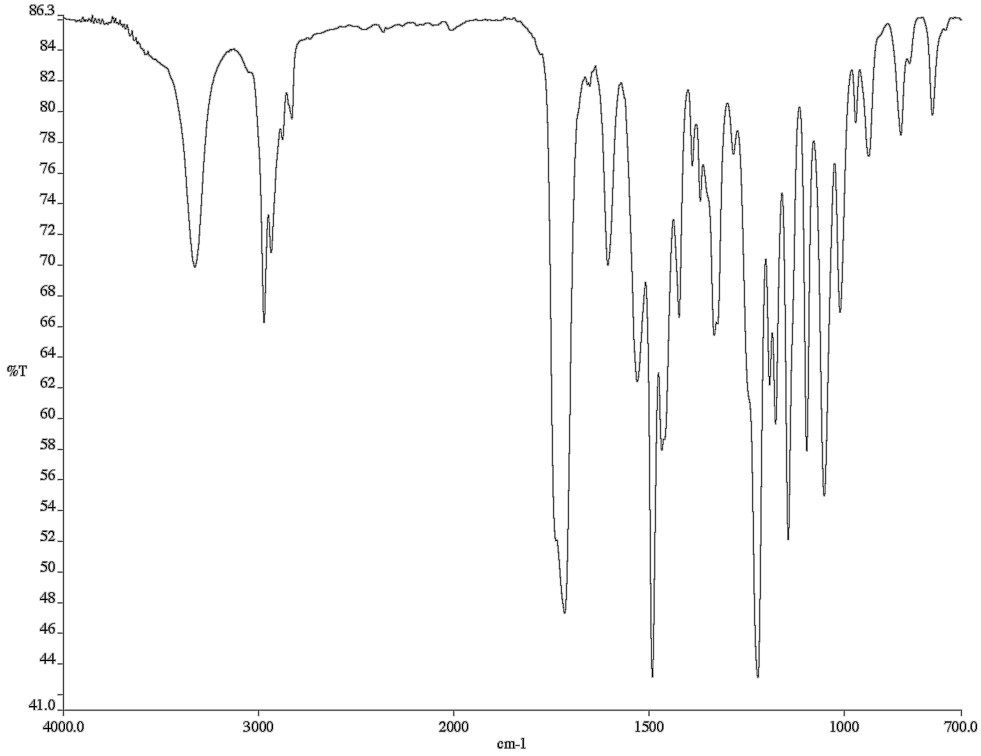


Figure A2.14.2 Infrared spectrum (thin film/NaCl) of compound **625**.

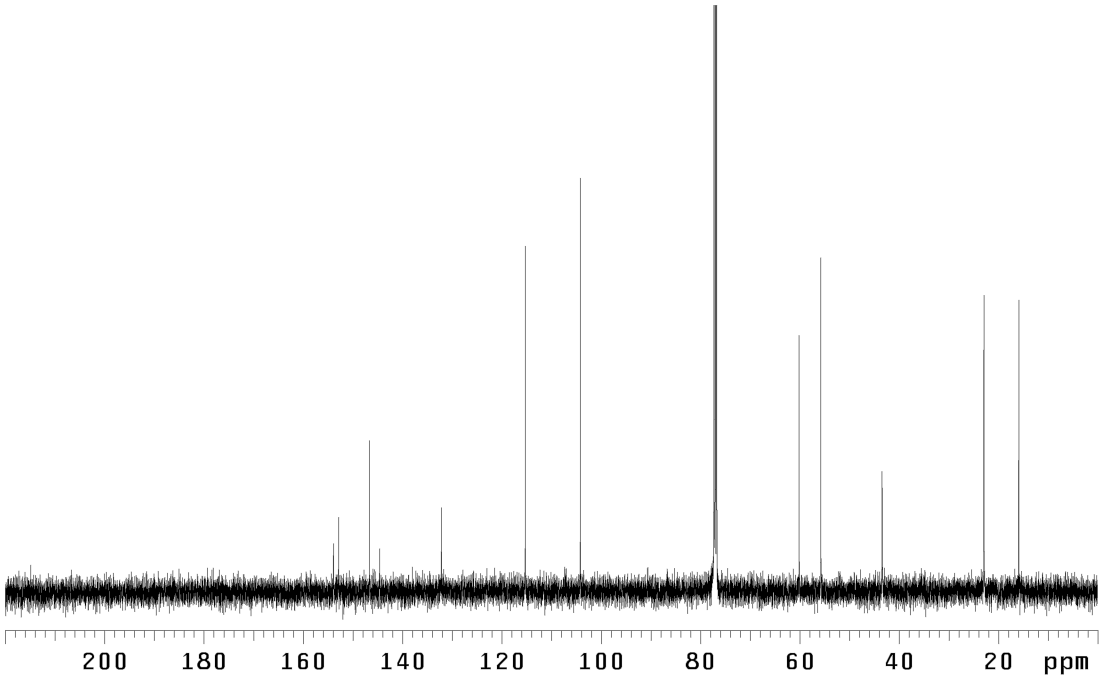


Figure A2.14.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **625**.

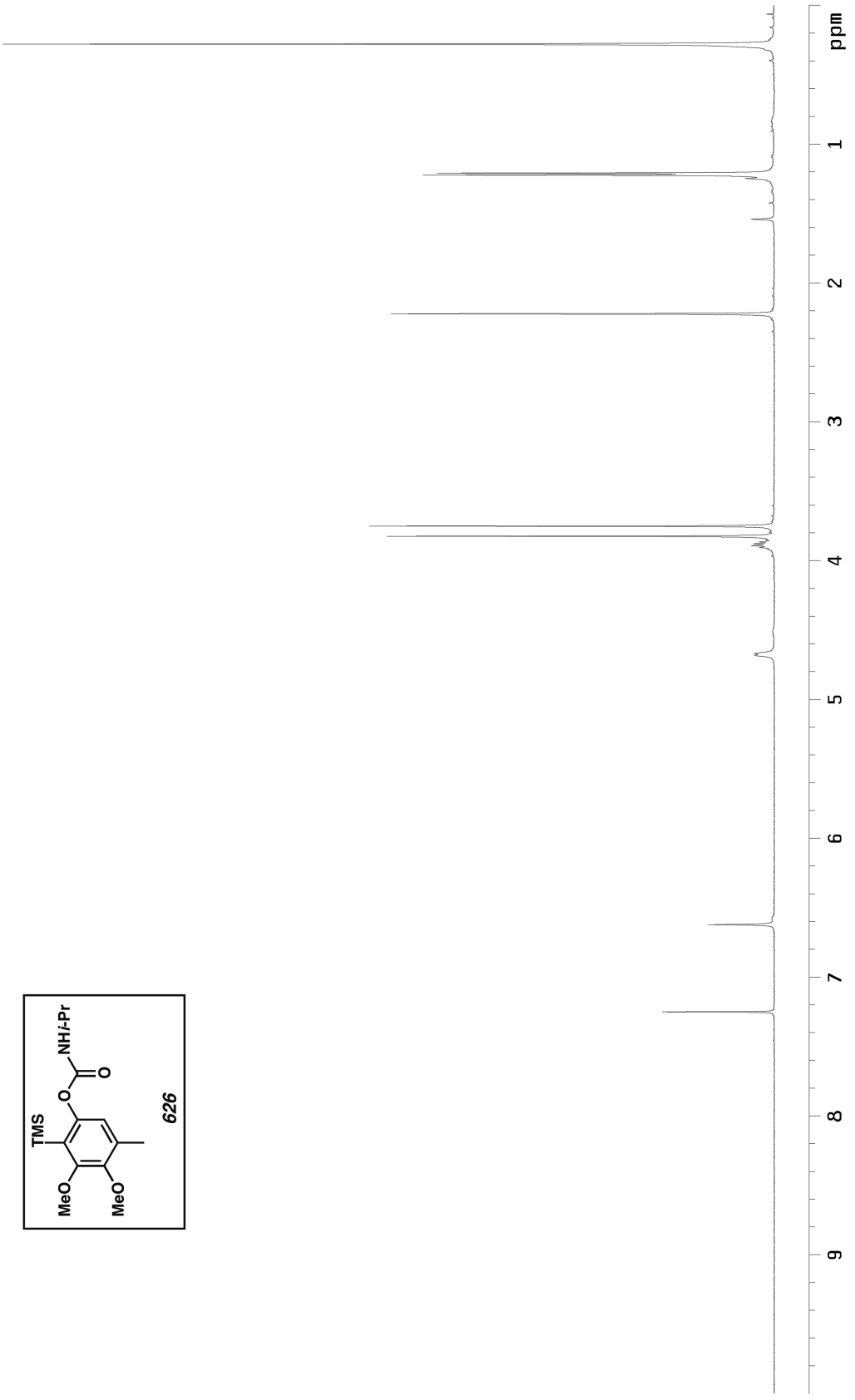


Figure A2.15.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **626**.

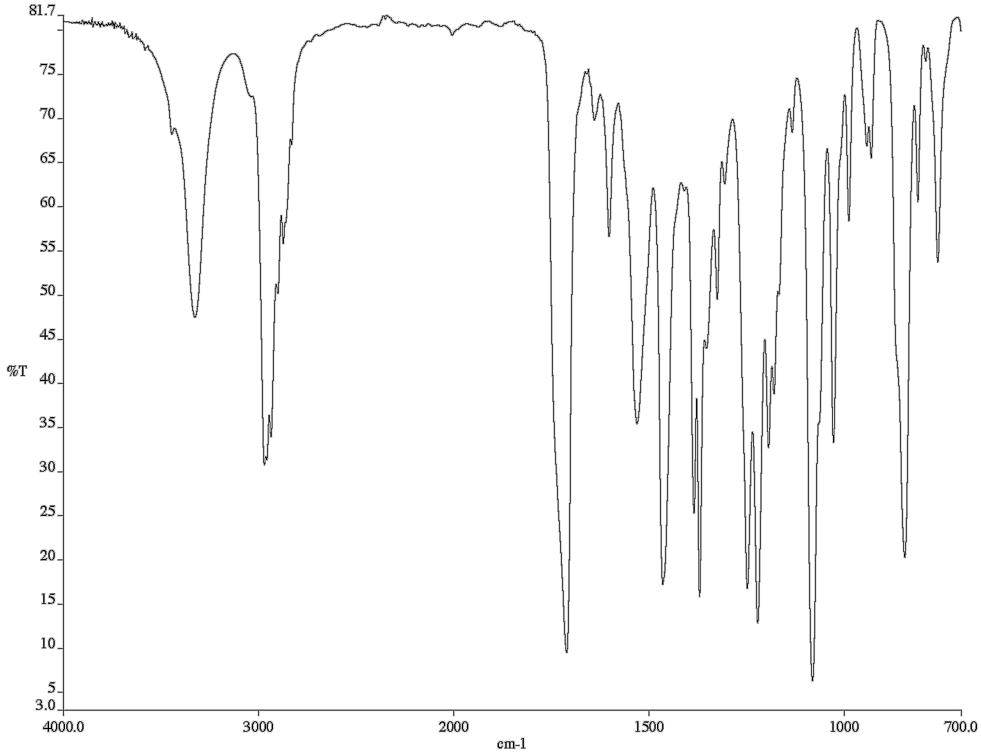


Figure A2.15.2 Infrared spectrum (thin film/NaCl) of compound **626**.

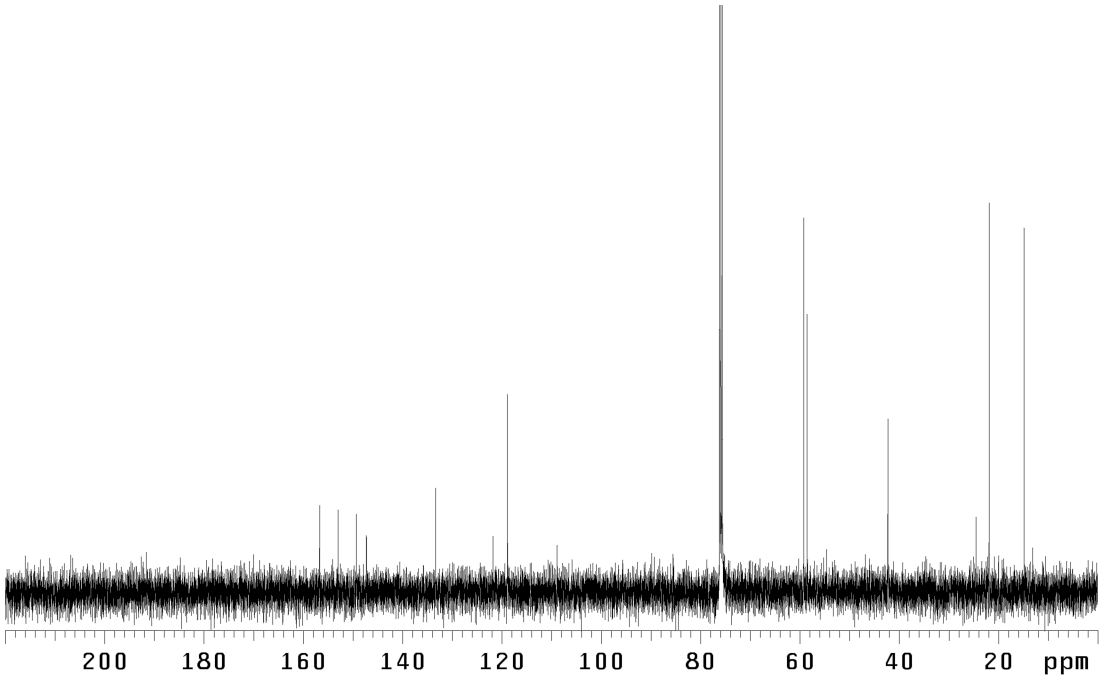


Figure A2.15.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **626**.

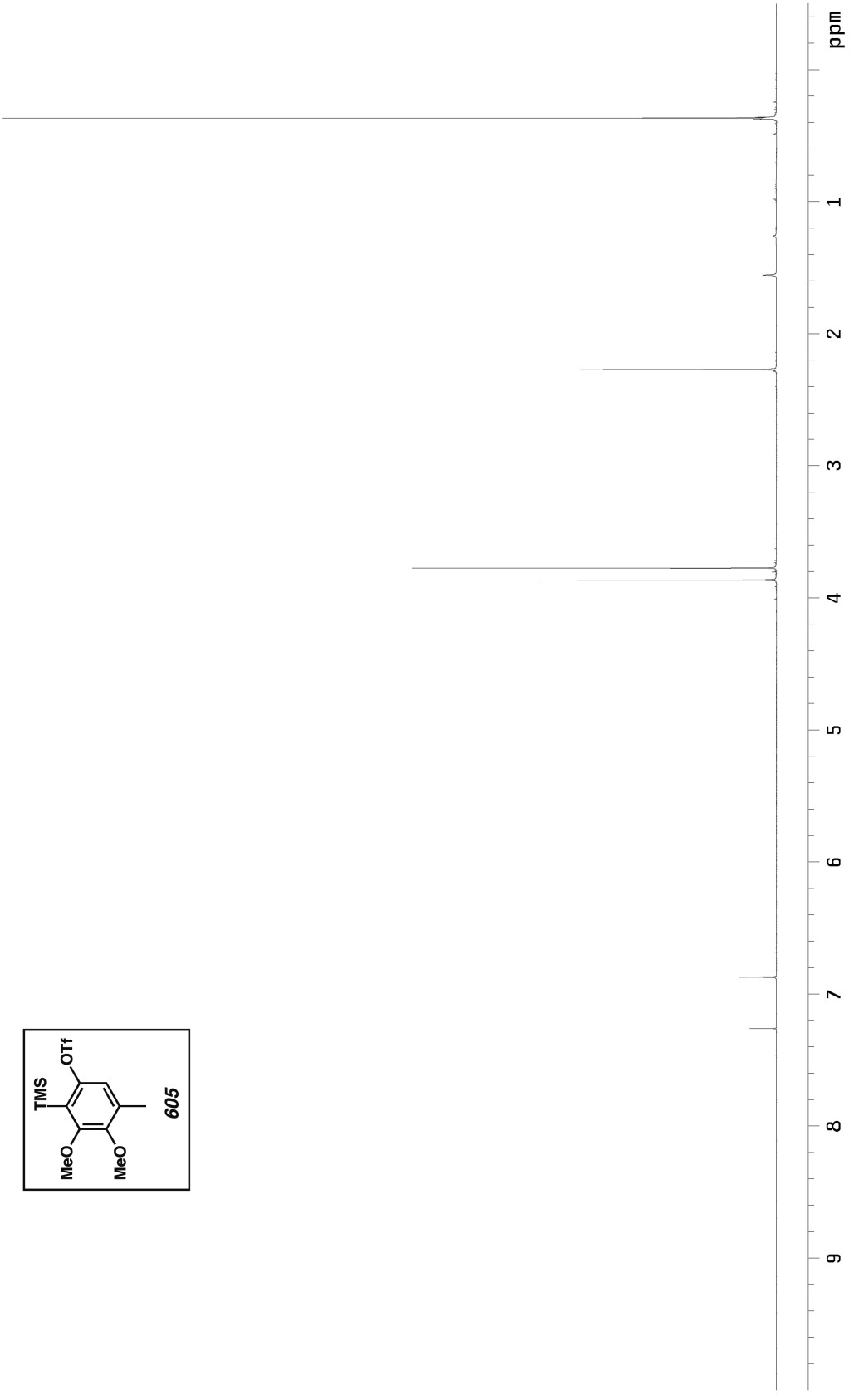


Figure A2.16.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **605**.

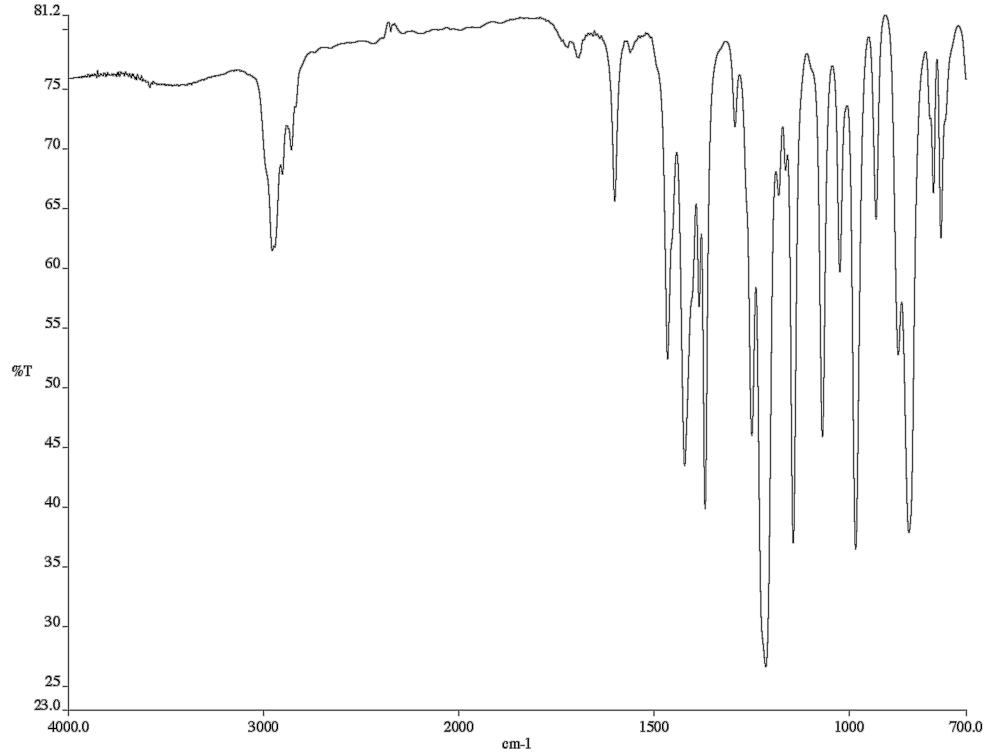


Figure A2.16.2 Infrared spectrum (thin film/NaCl) of compound **605**.

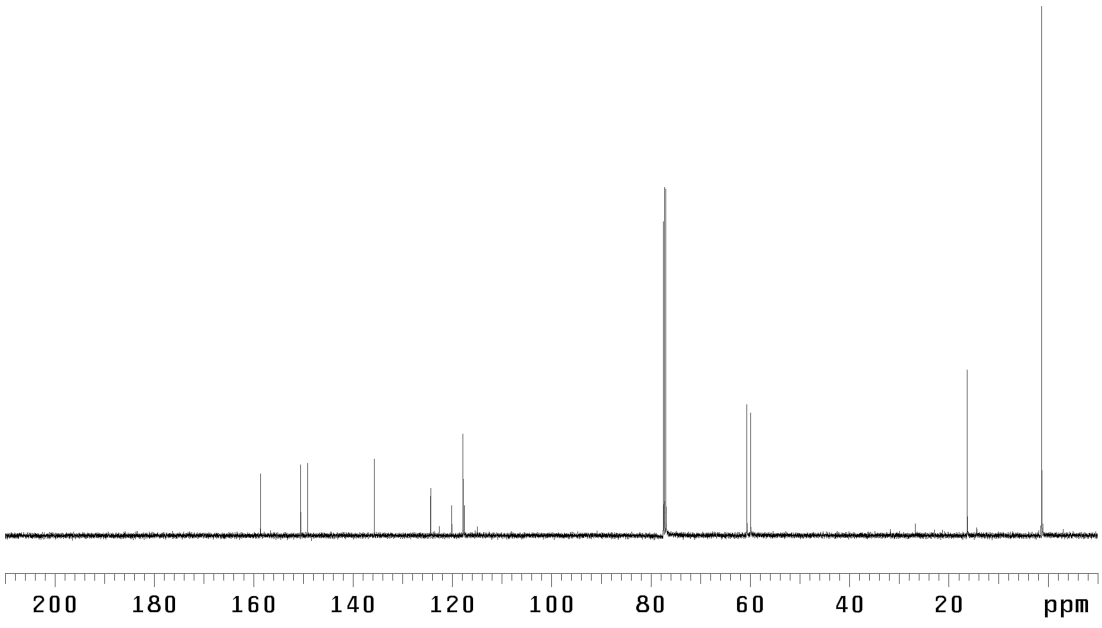


Figure A2.16.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **605**.

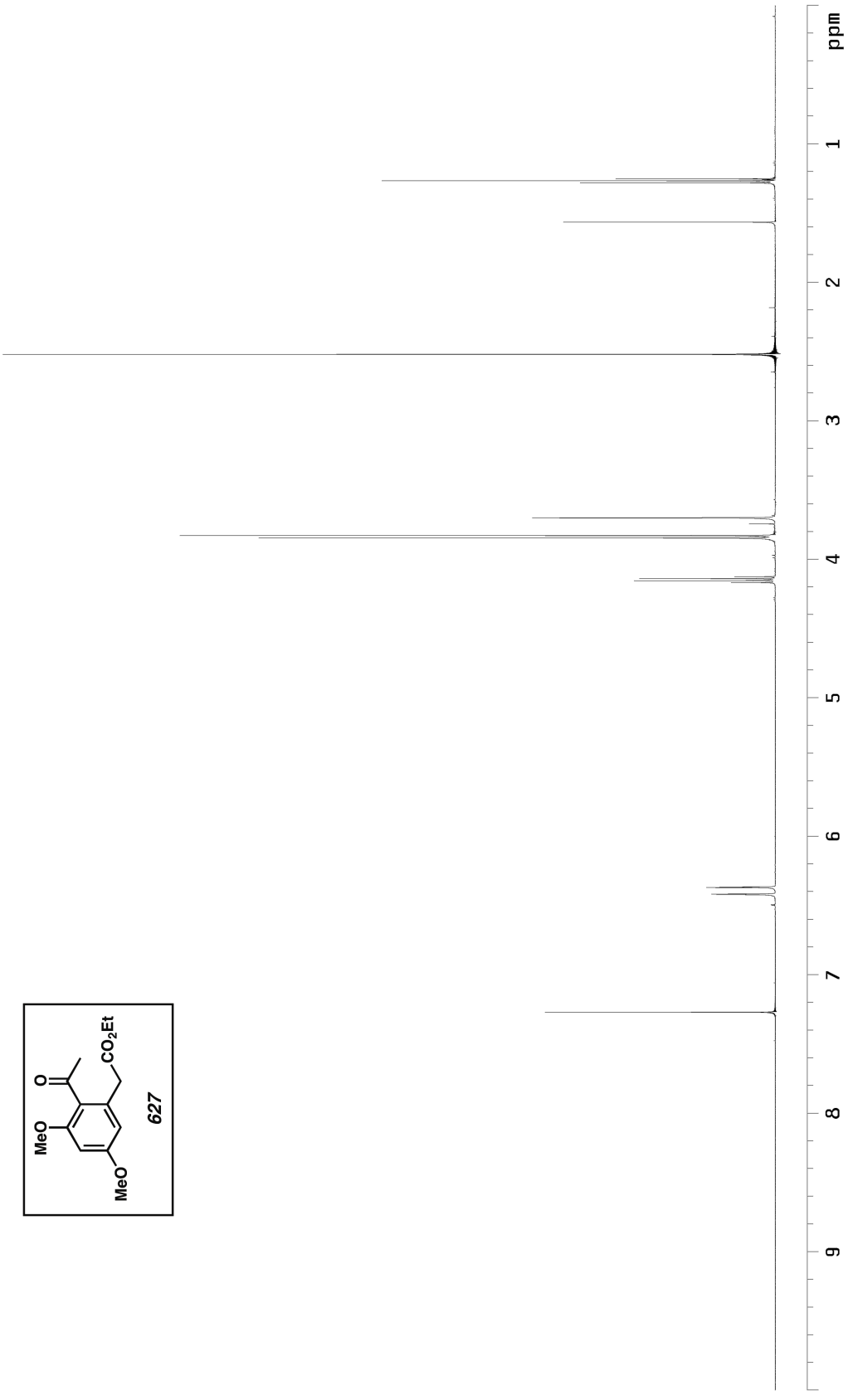


Figure A2.17.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **627**.

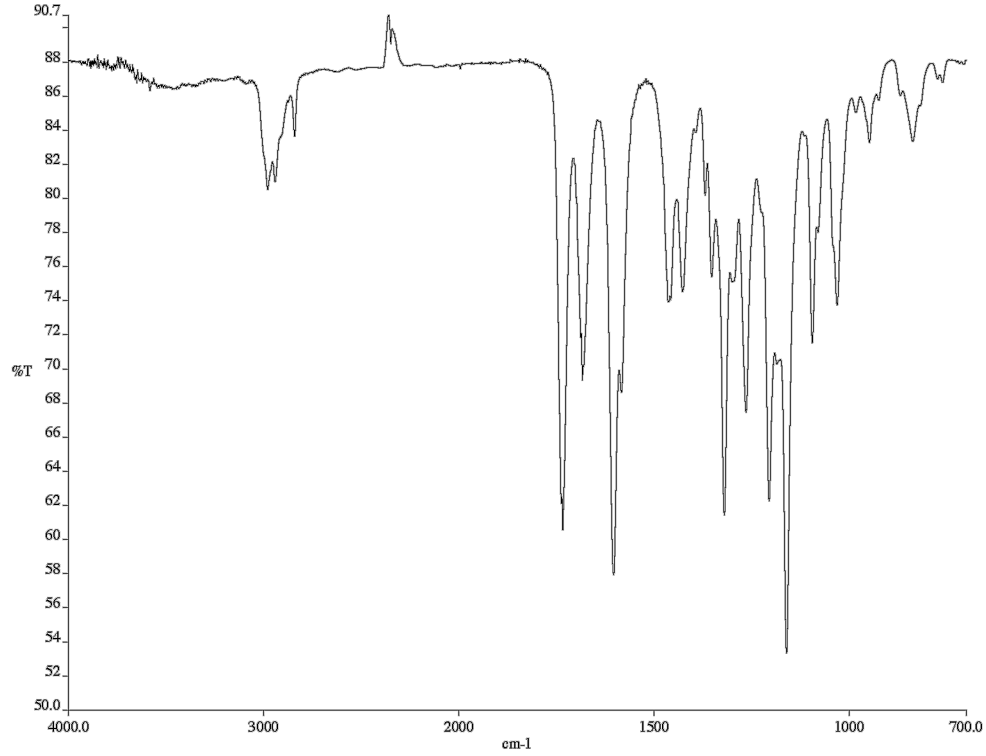


Figure A2.17.2 Infrared spectrum (thin film/NaCl) of compound **627**.

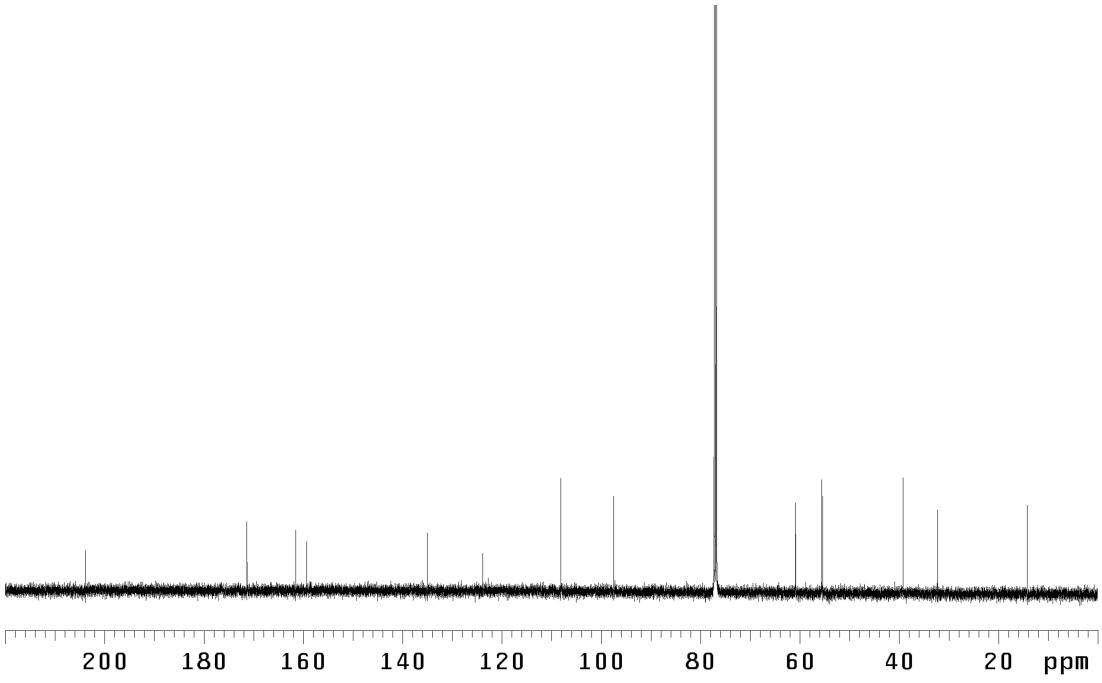


Figure A2.17.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **627**.

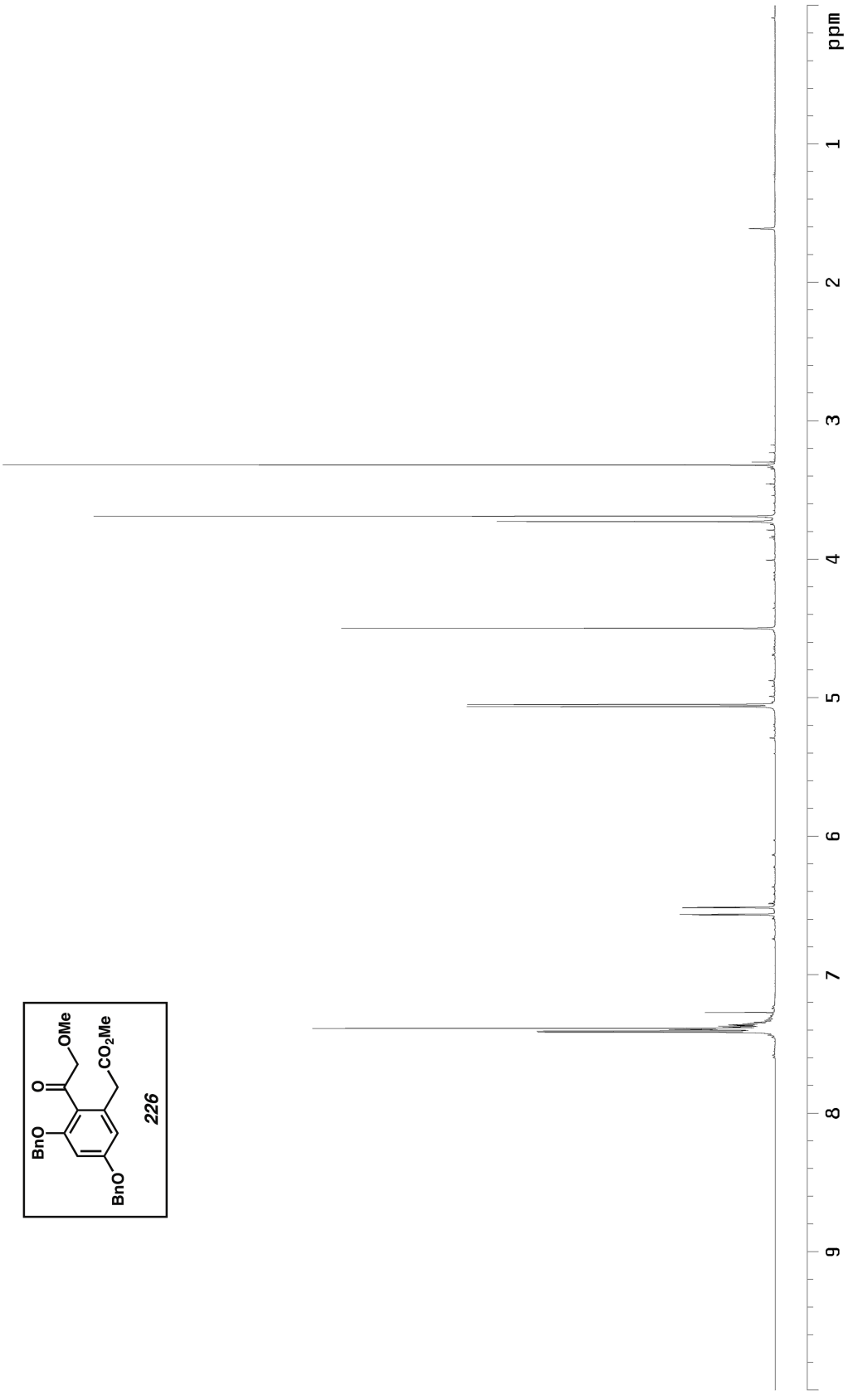


Figure A2.18.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **226**.

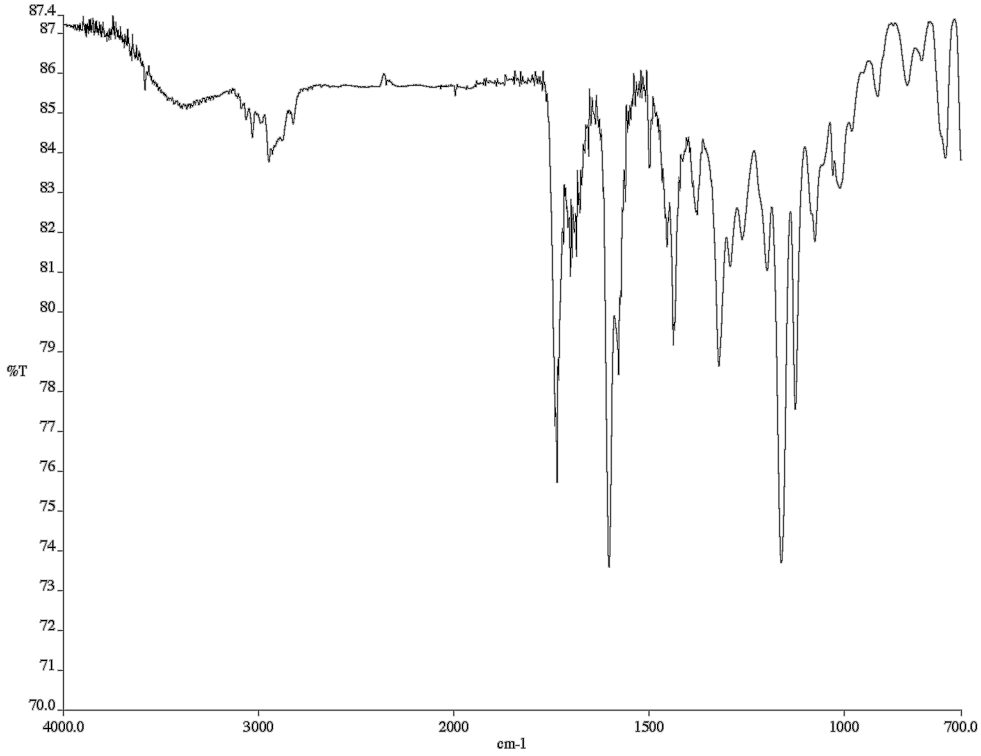


Figure A2.18.2 Infrared spectrum (thin film/NaCl) of compound **226**.

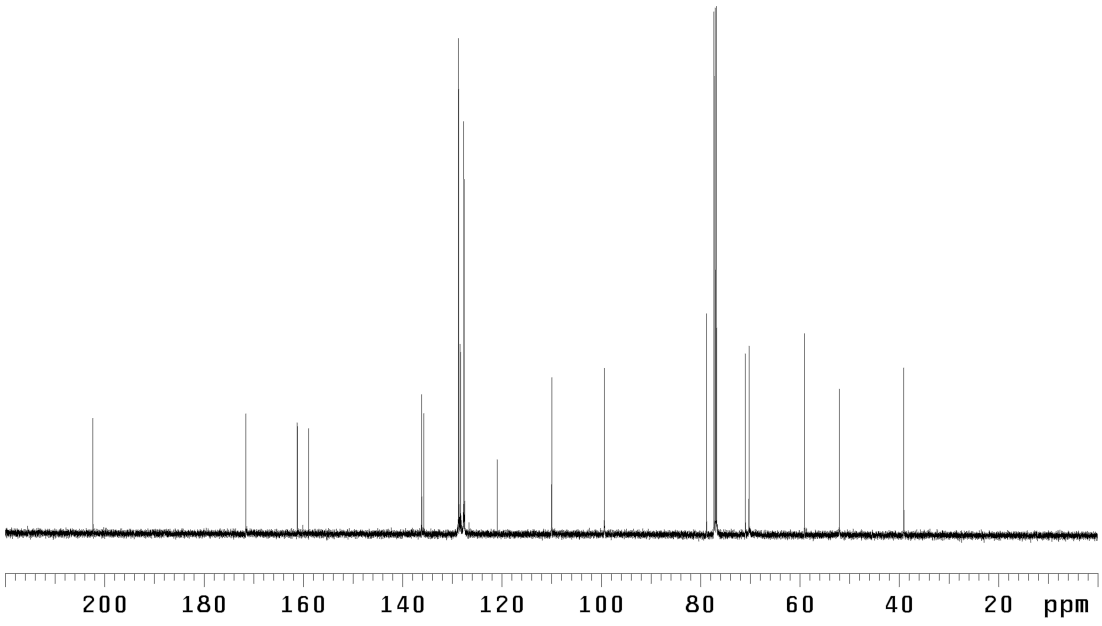


Figure A2.18.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **226**.

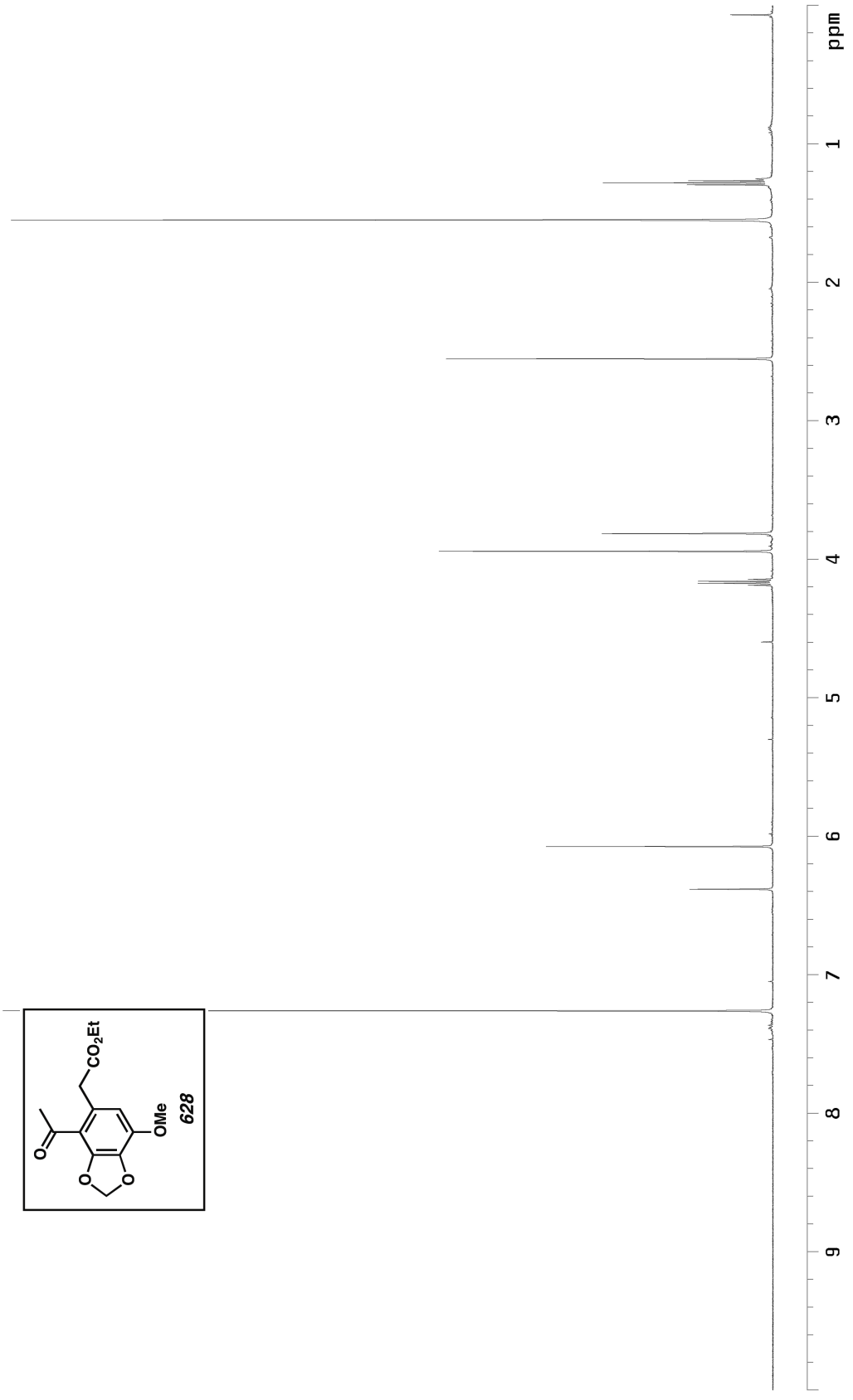


Figure A2.19.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **628**.

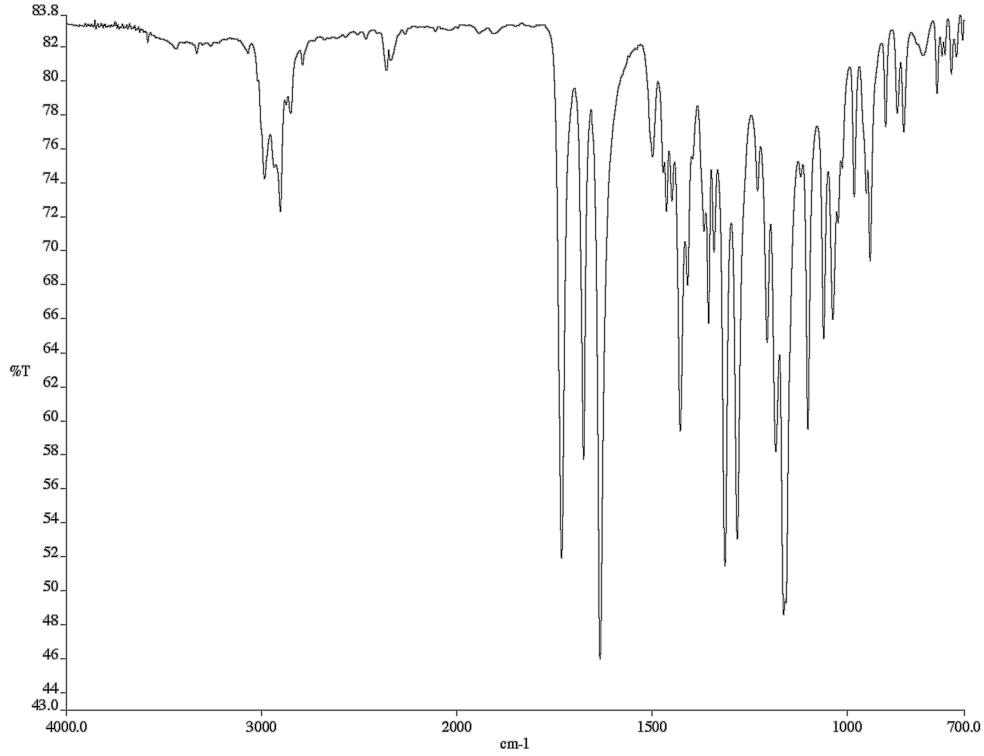


Figure A2.19.2 Infrared spectrum (thin film/NaCl) of compound **628**.

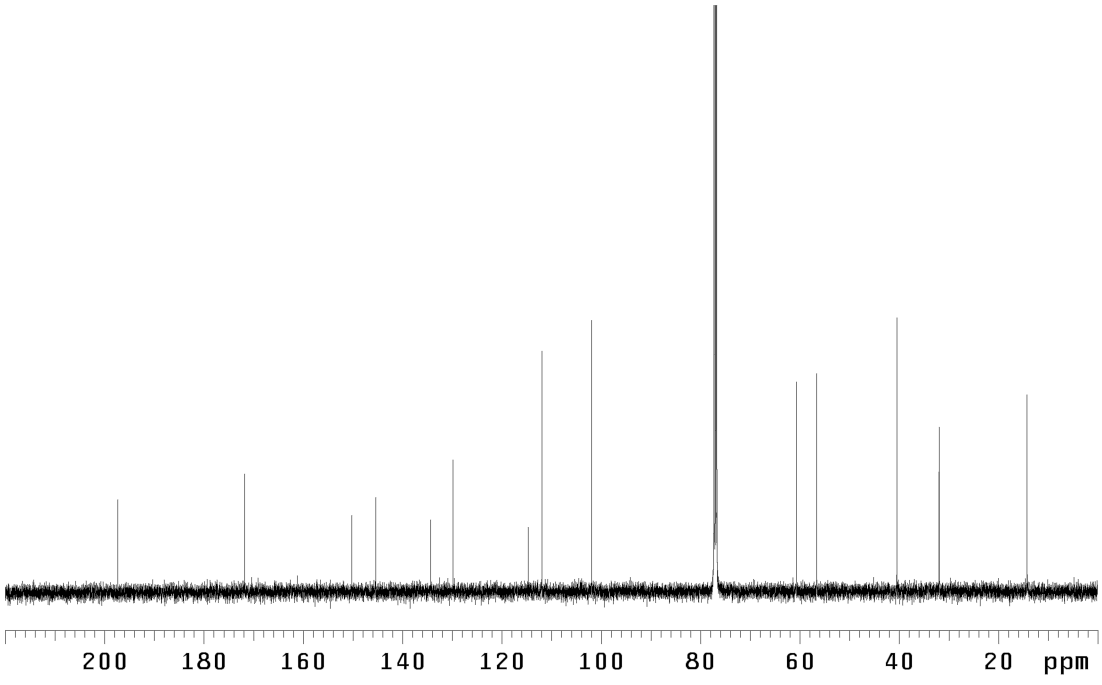


Figure A2.19.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **628**.

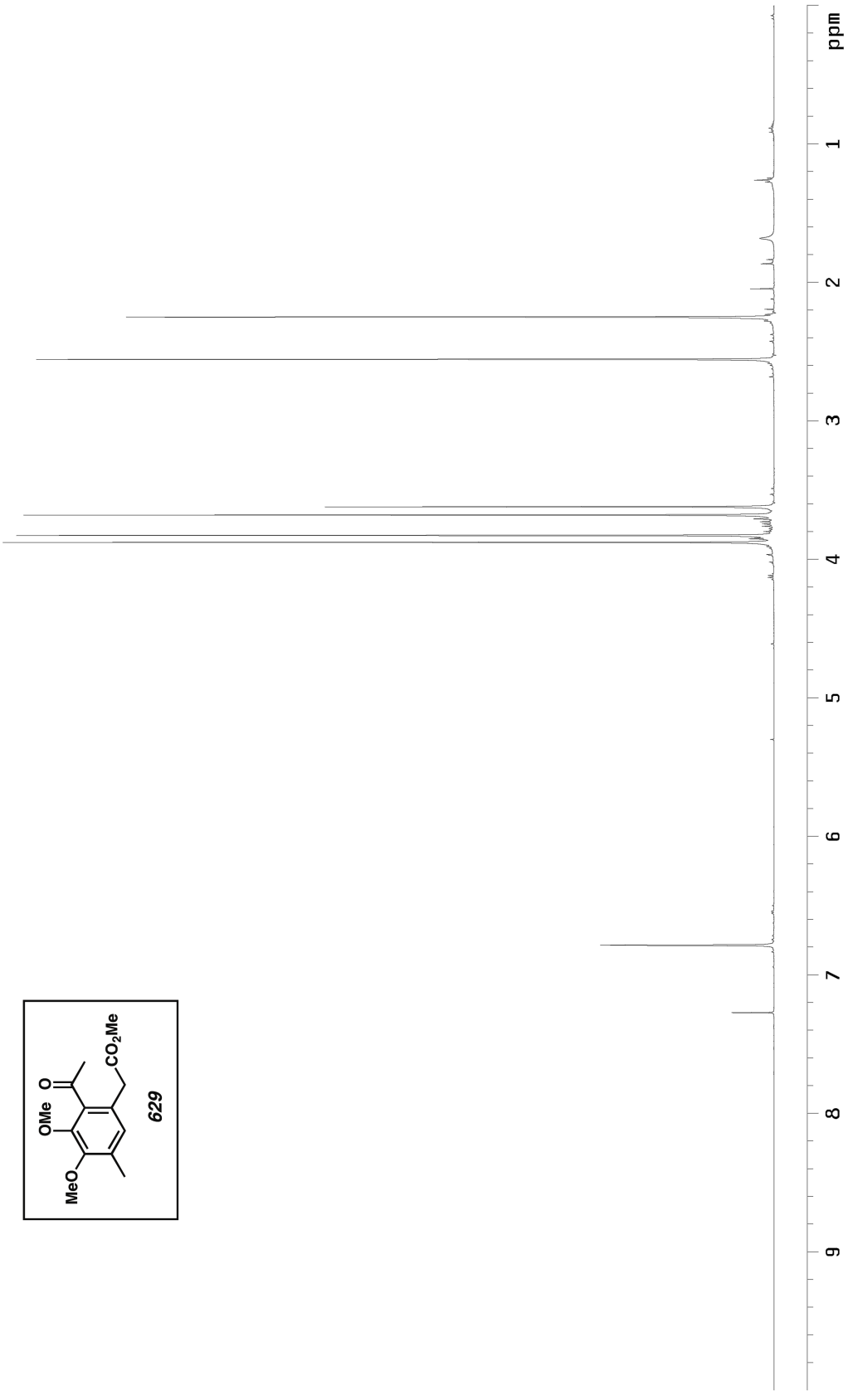


Figure A2.20.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **629**.

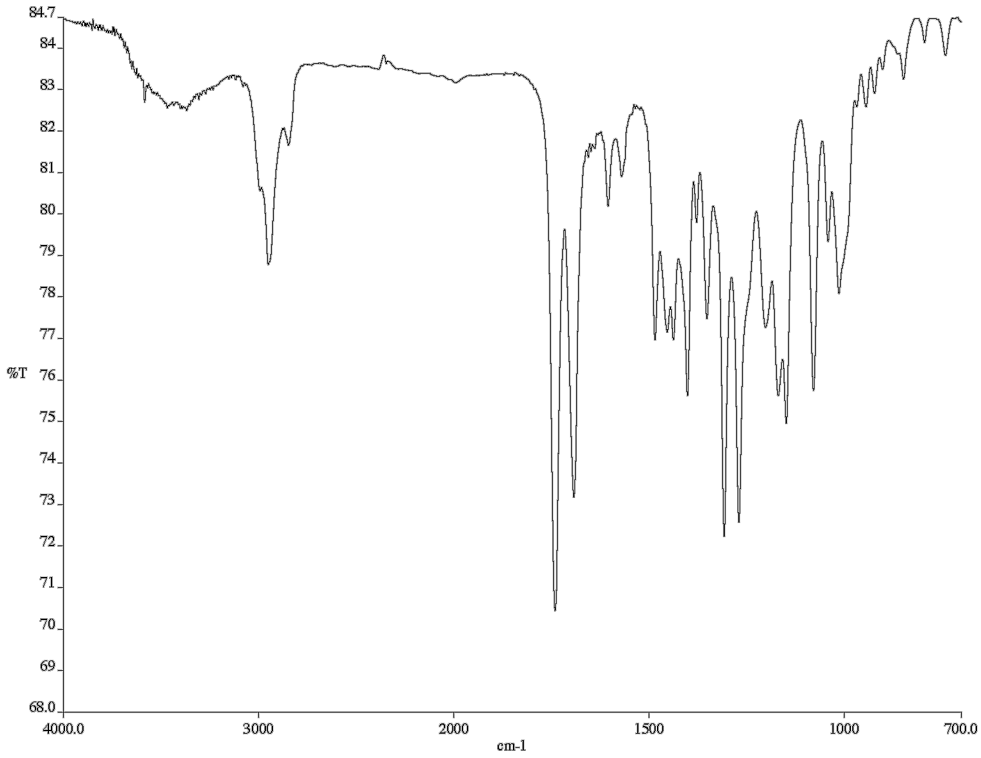


Figure A2.20.2 Infrared spectrum (thin film/NaCl) of compound **629**.

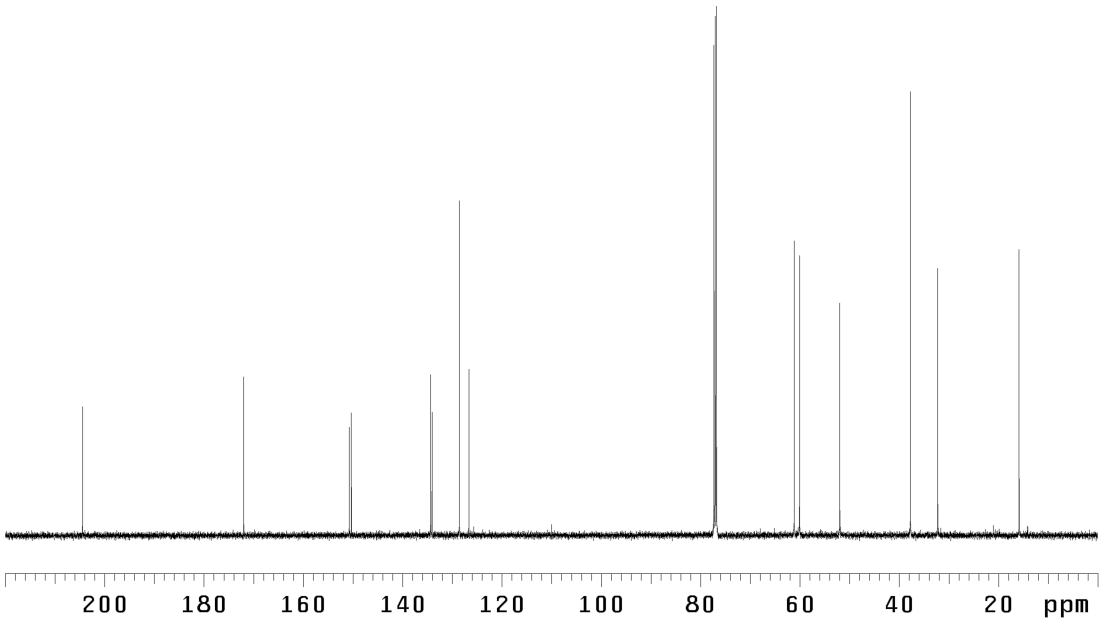


Figure A2.20.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **629**.

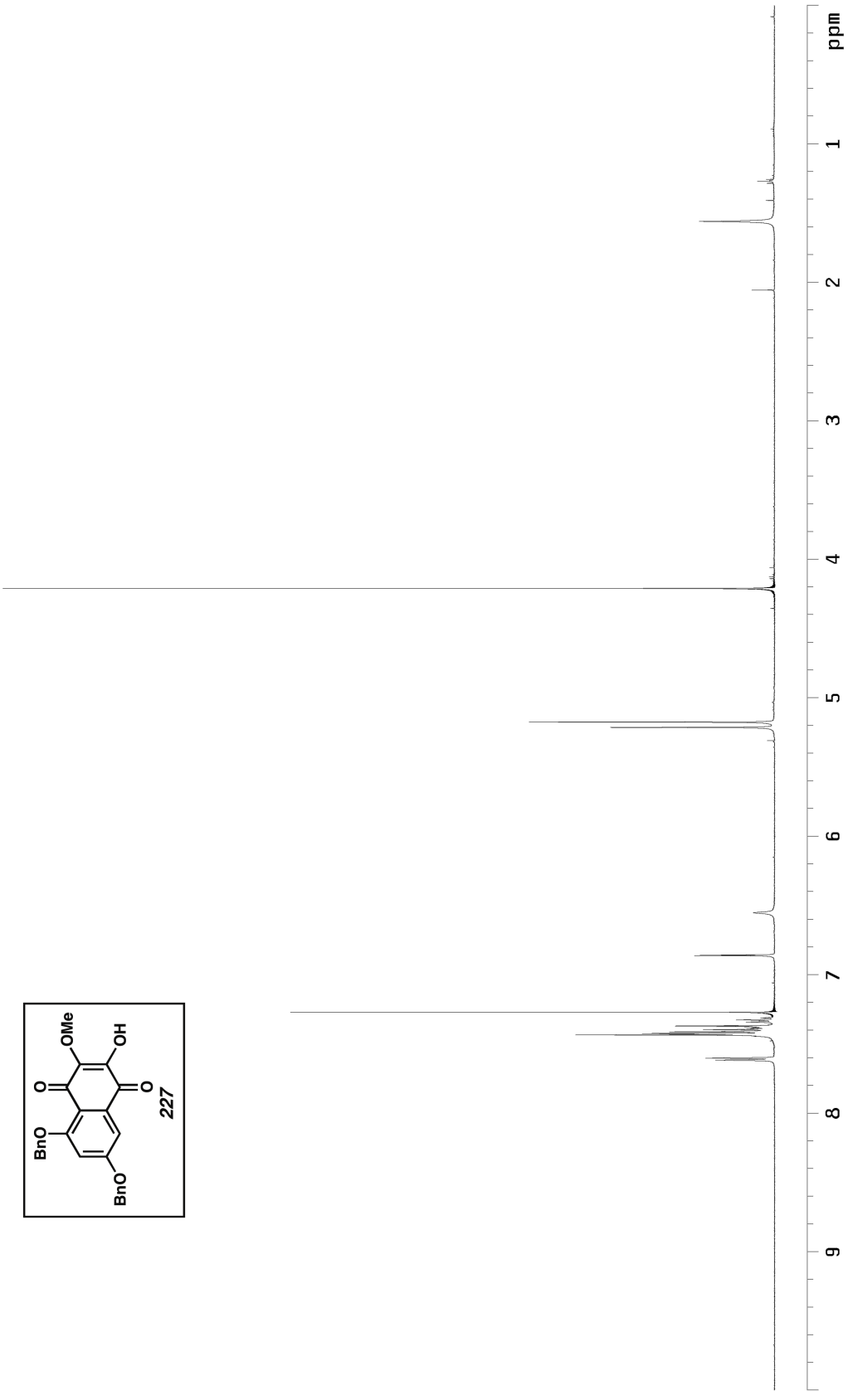


Figure A2.21.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **227**.

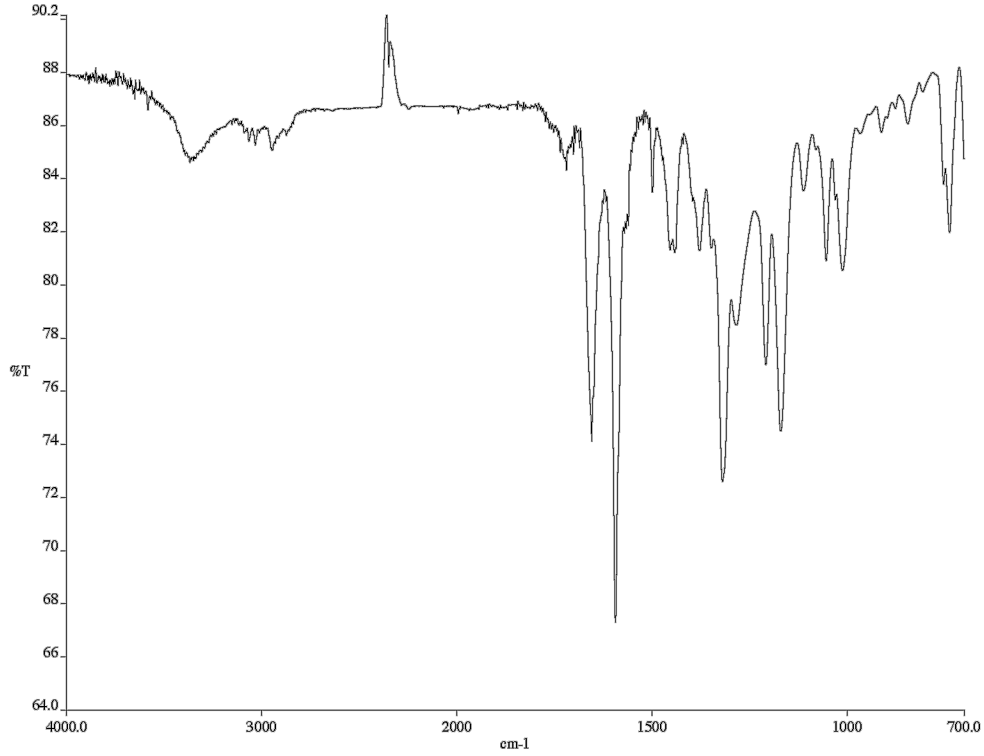


Figure A2.21.2 Infrared spectrum (thin film/NaCl) of compound **227**.

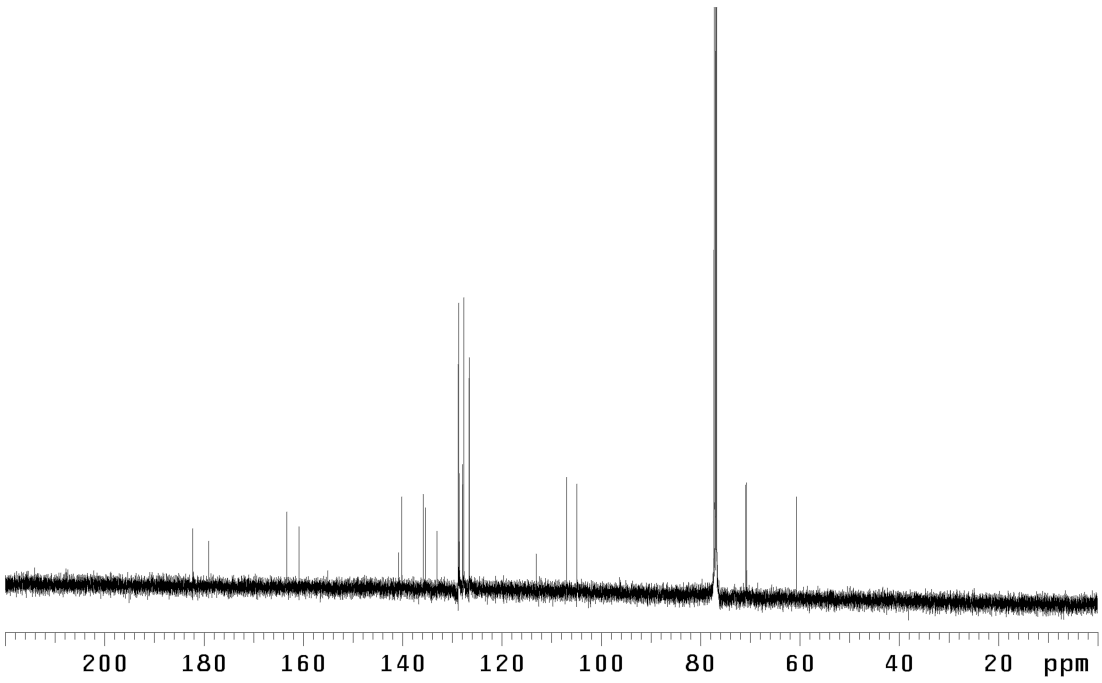


Figure A2.21.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **227**.

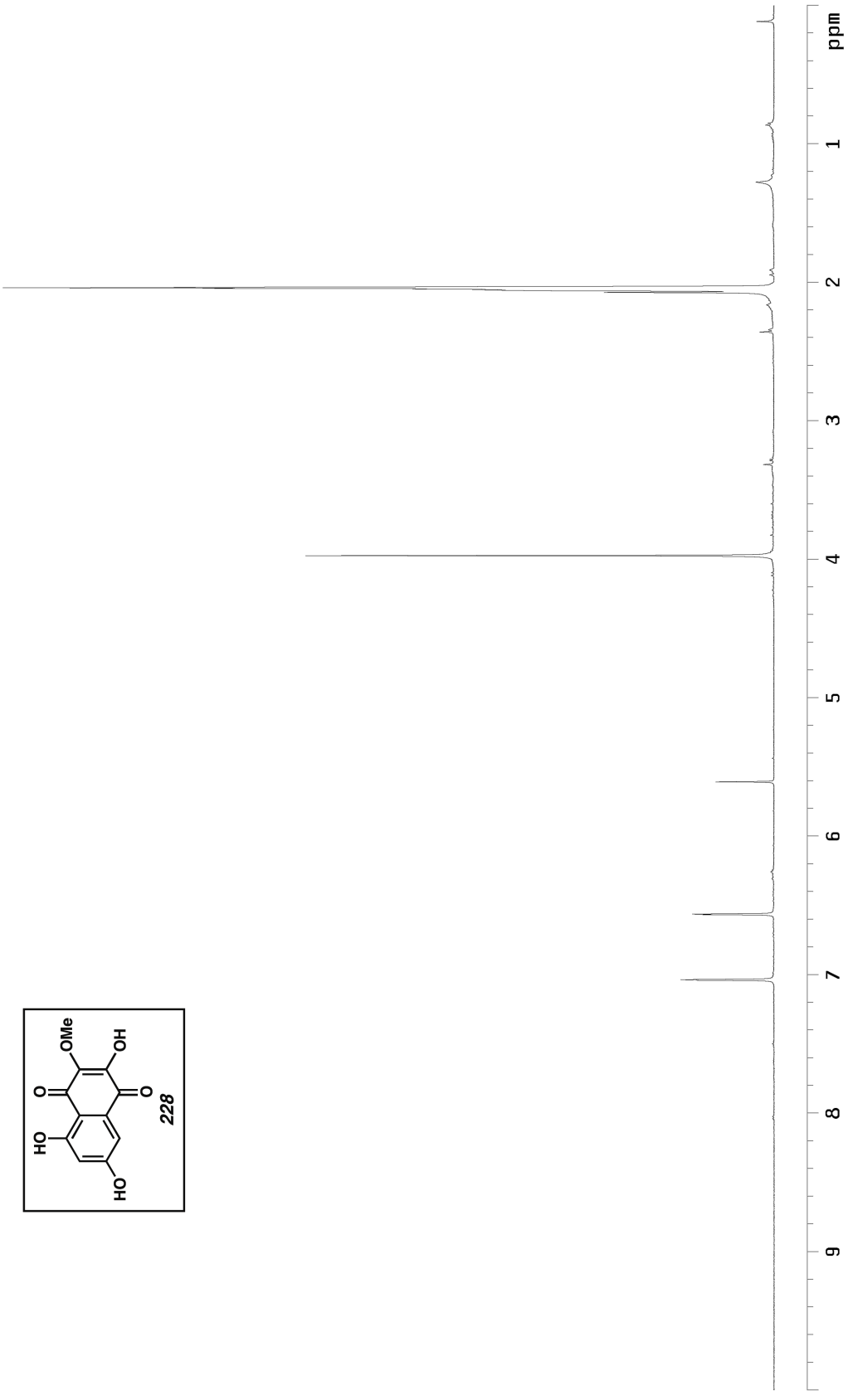


Figure A2.22.1 ^{1}H NMR (500 MHz, acetone-d_6) of compound **228**.

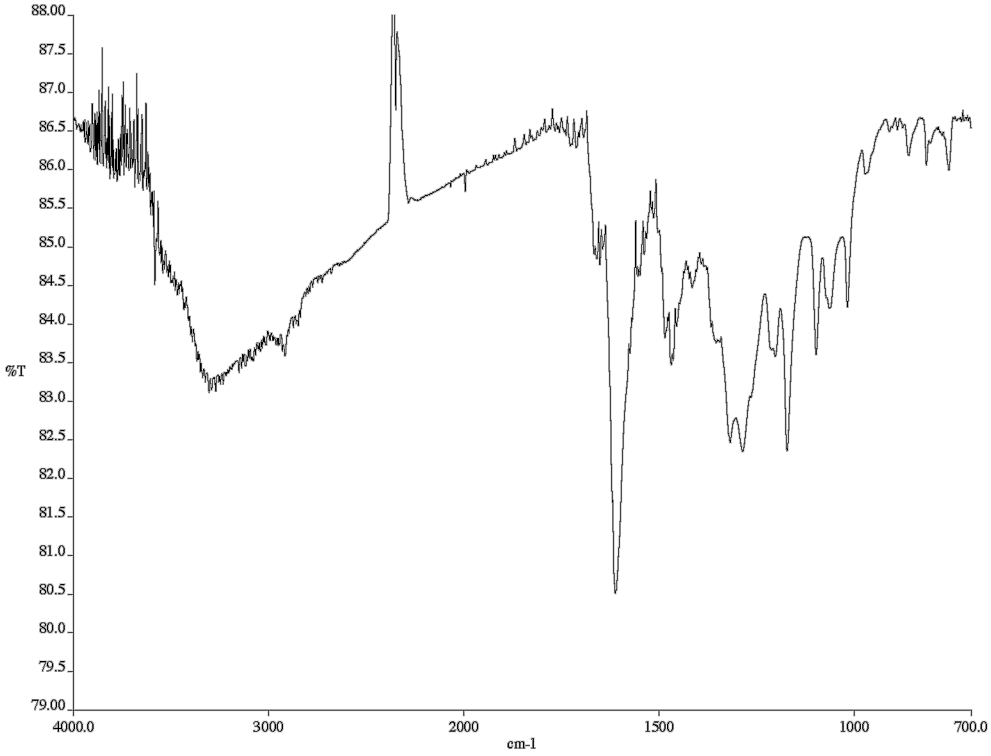


Figure A2.22.2 Infrared spectrum (thin film/NaCl) of compound **228**.

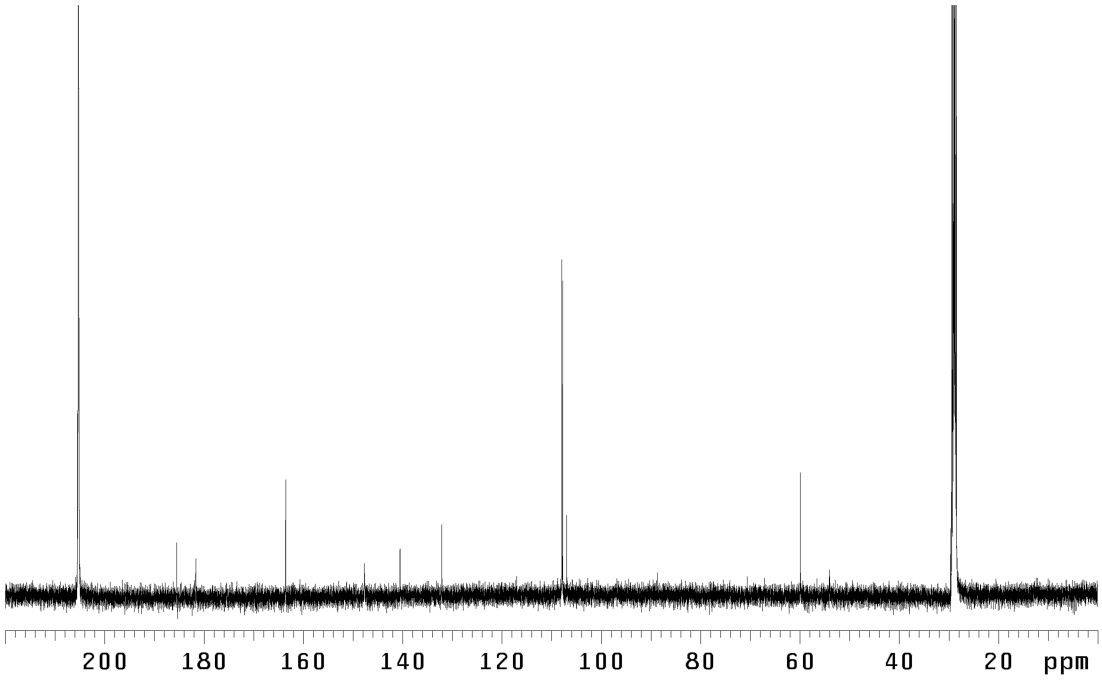


Figure A2.22.3 ^{13}C NMR (125 MHz, acetone-d_6) of compound **228**.

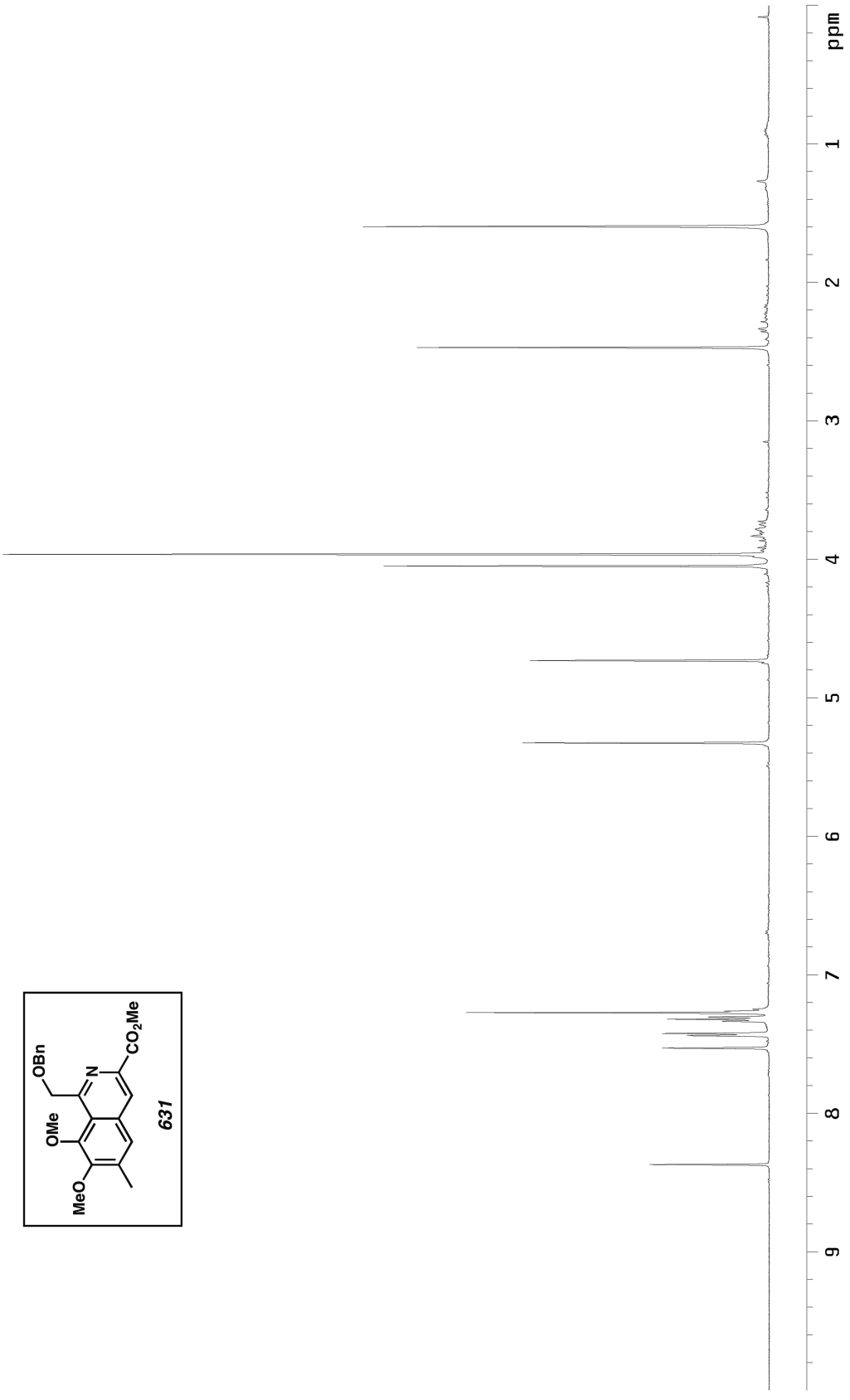


Figure A2.23.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **631**.

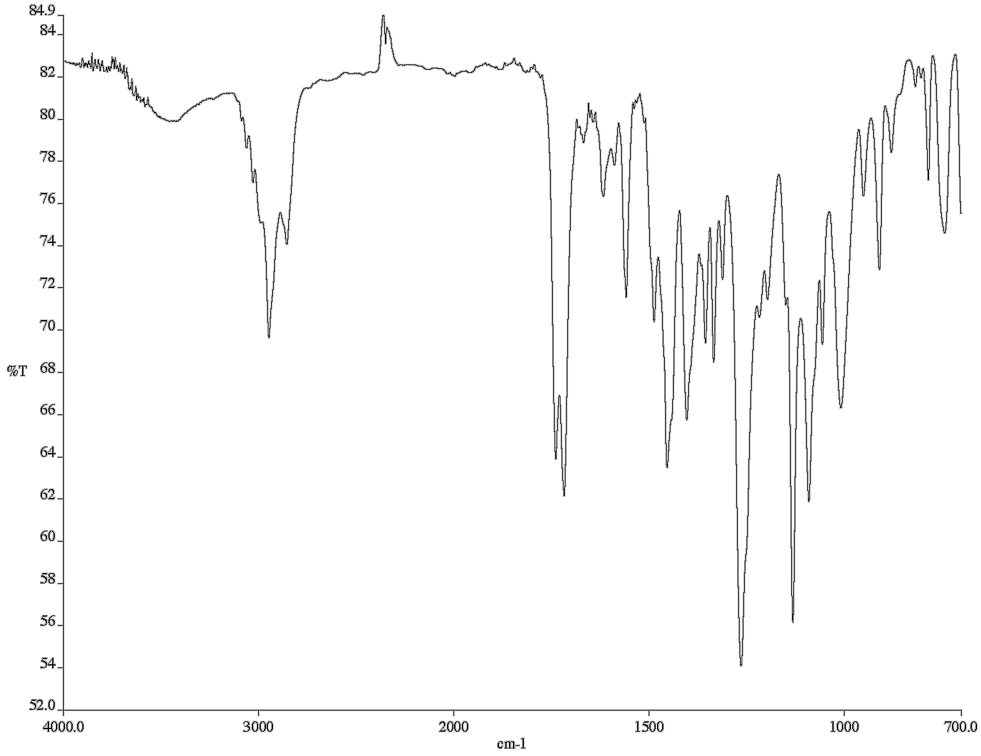


Figure A2.23.2 Infrared spectrum (thin film/NaCl) of compound **631**.

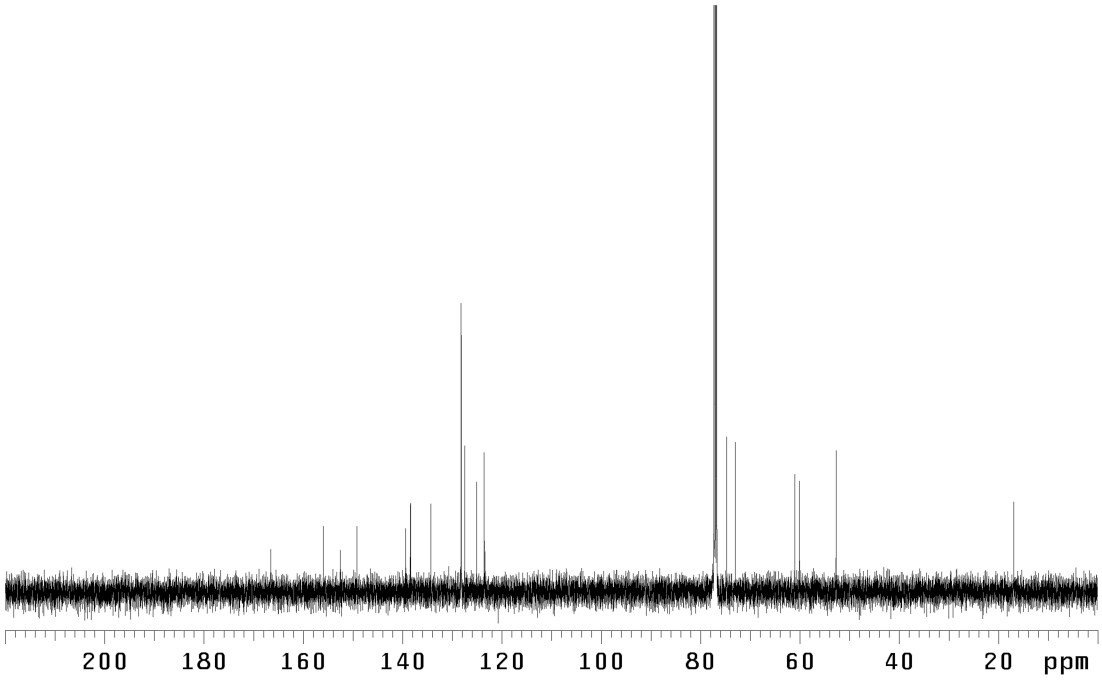


Figure A2.23.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **631**.

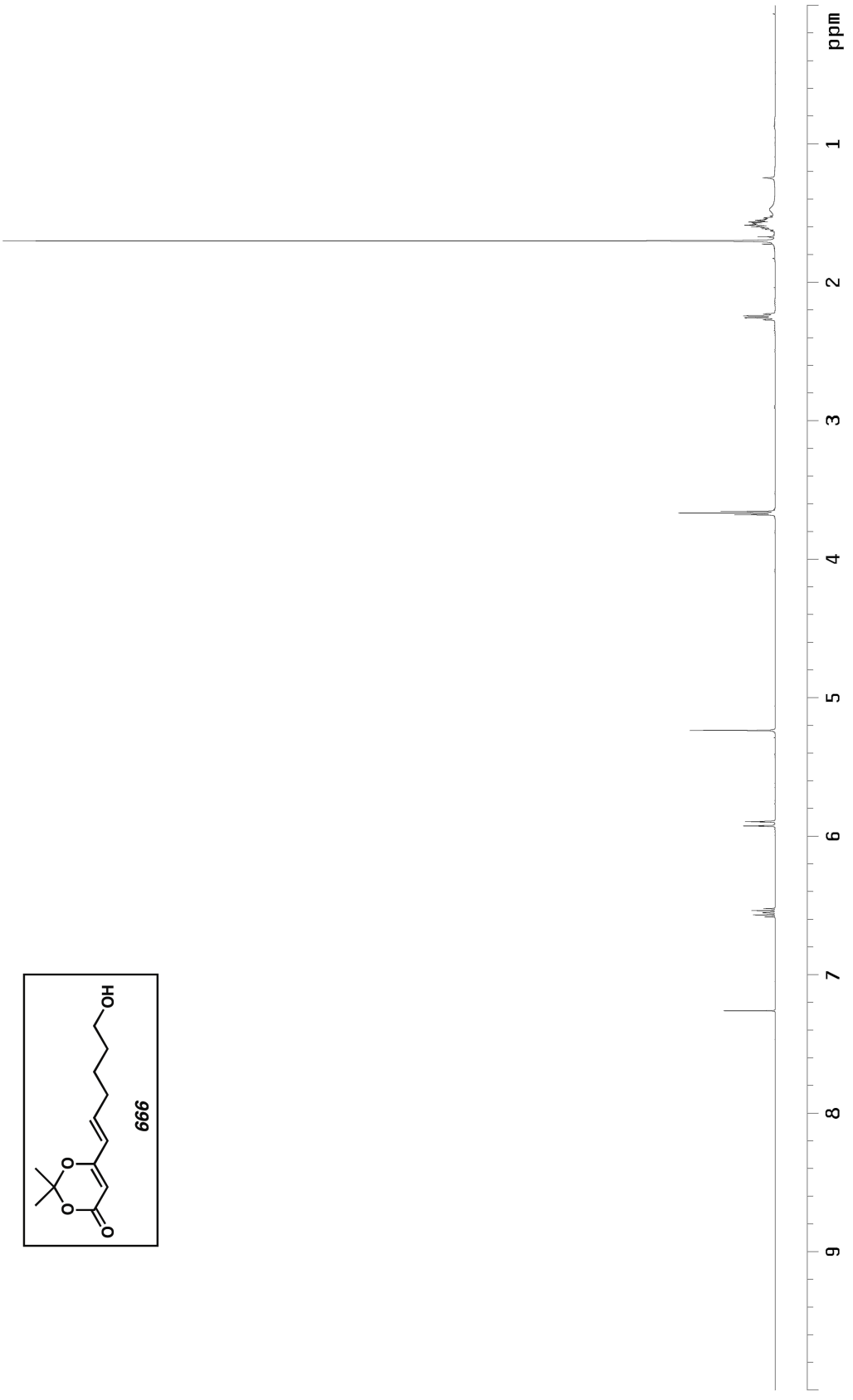


Figure A2.24.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **666**.

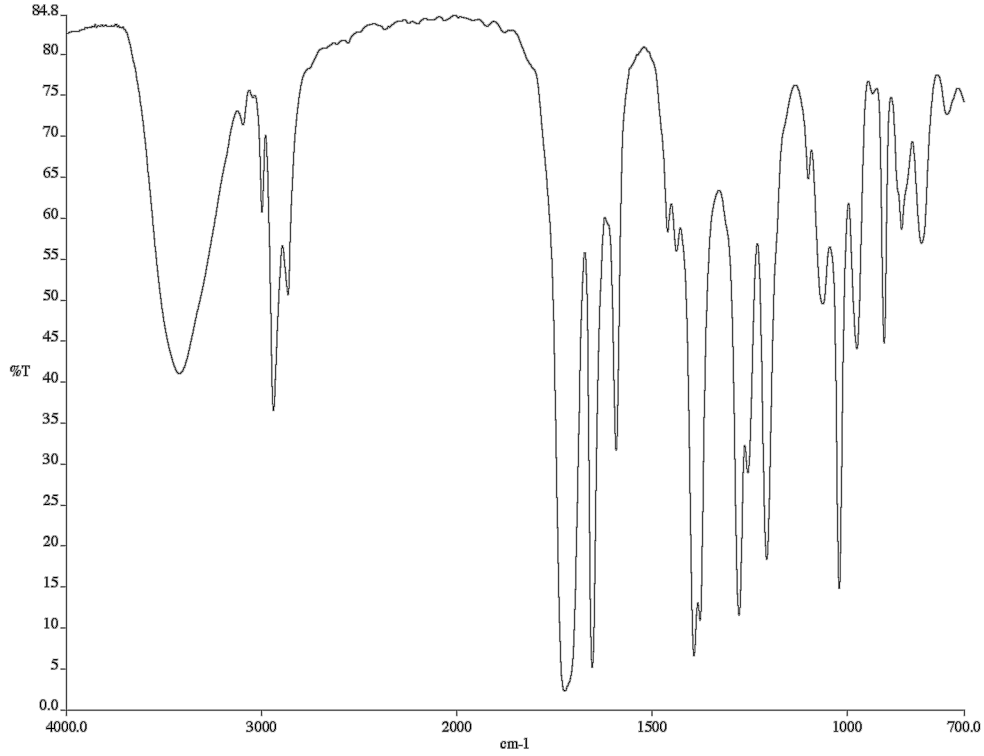


Figure A2.24.2 Infrared spectrum (thin film/NaCl) of compound **666**.

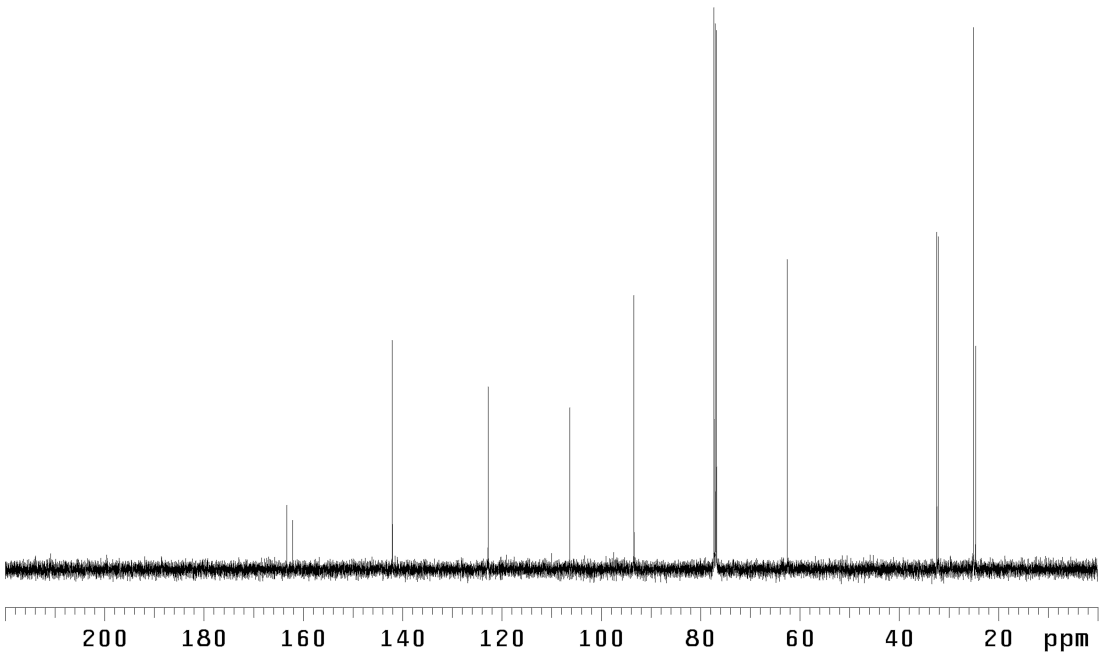


Figure A2.24.3 ^{13}C NMR (500 MHz, $CDCl_3$) of compound **666**.

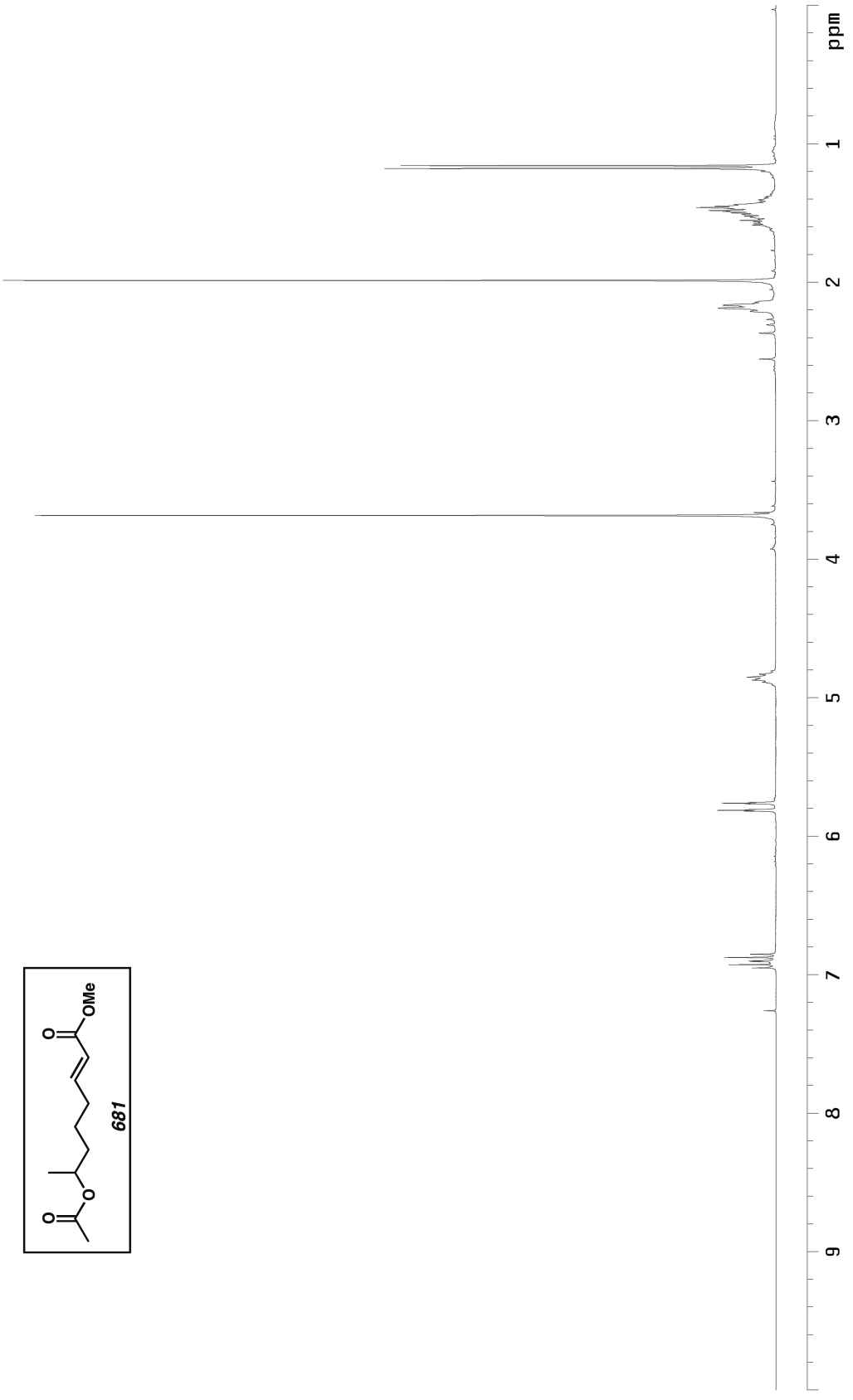


Figure A2.25.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **681**.

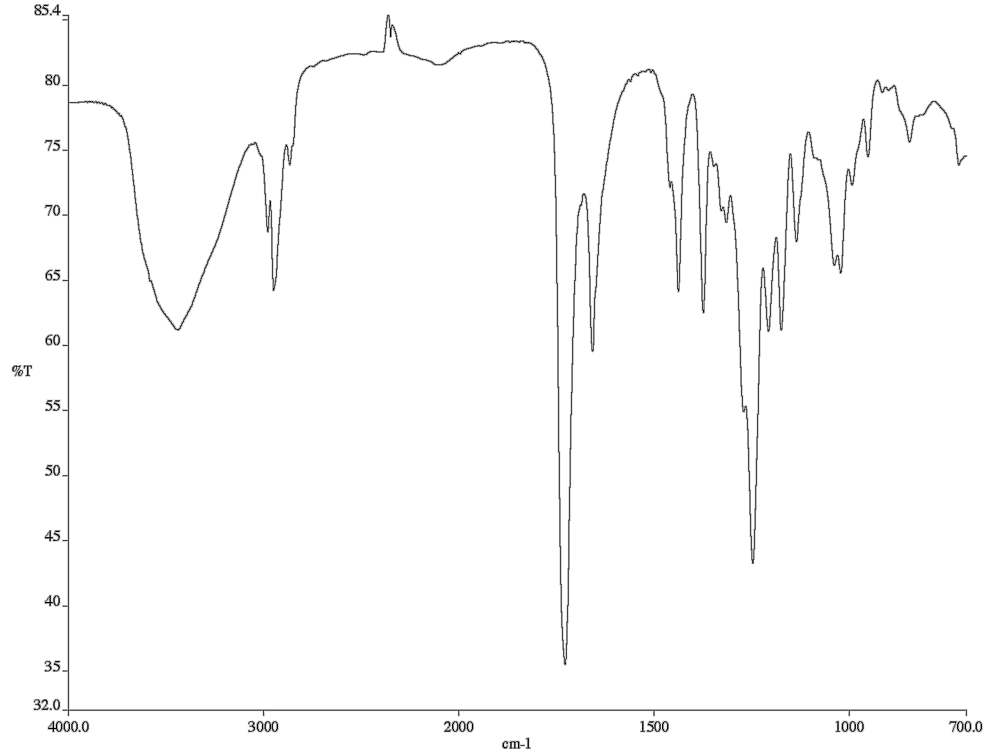


Figure A2.25.2 Infrared spectrum (thin film/NaCl) of compound **681**.

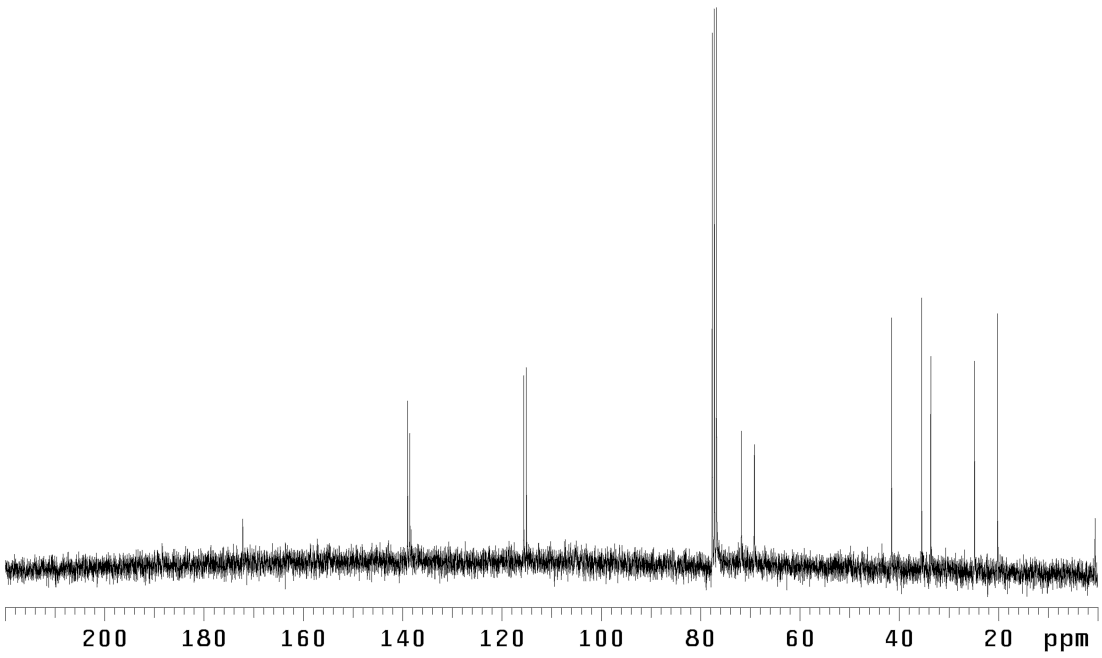


Figure A2.25.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **681**.

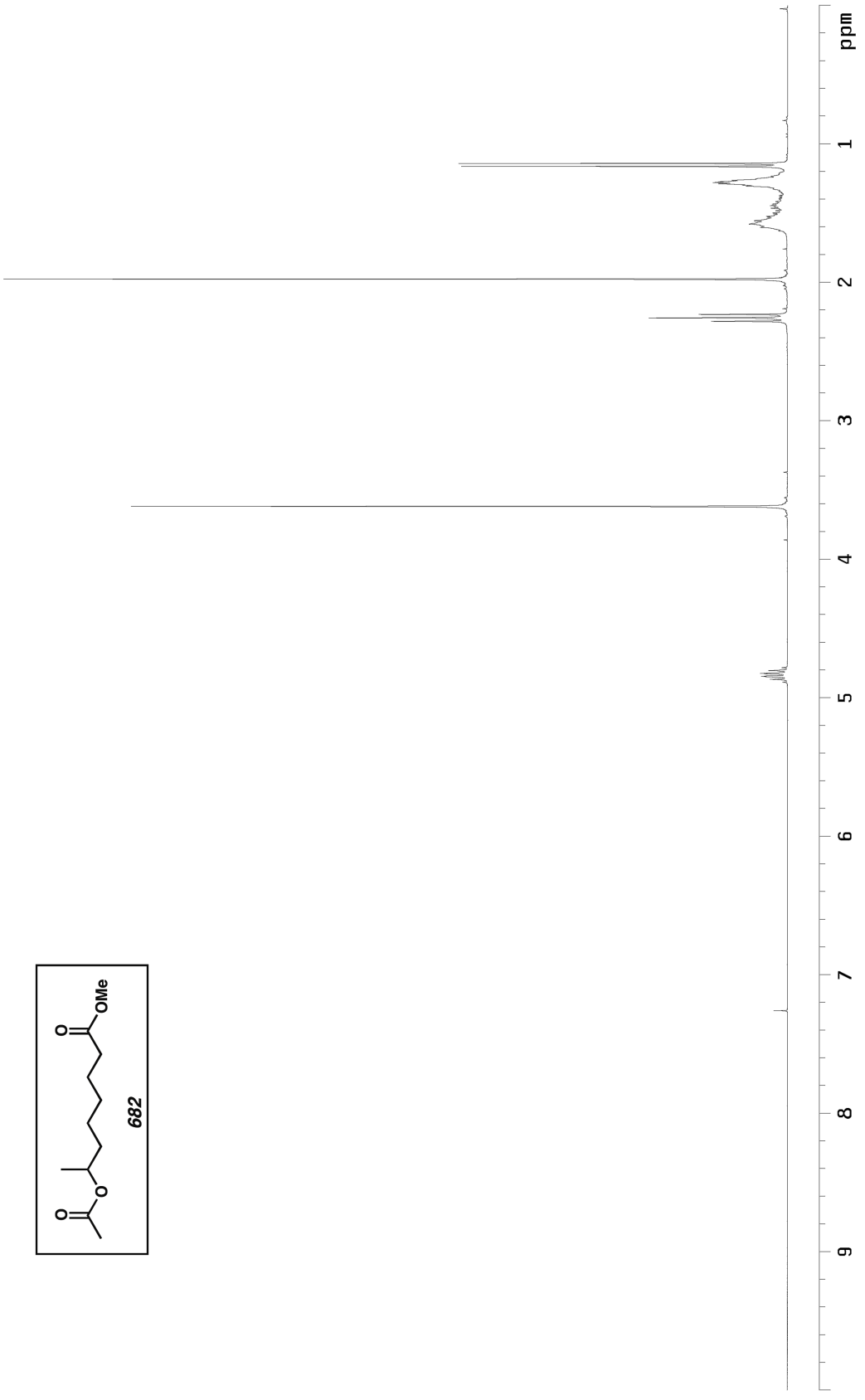


Figure A2.26.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **682**.

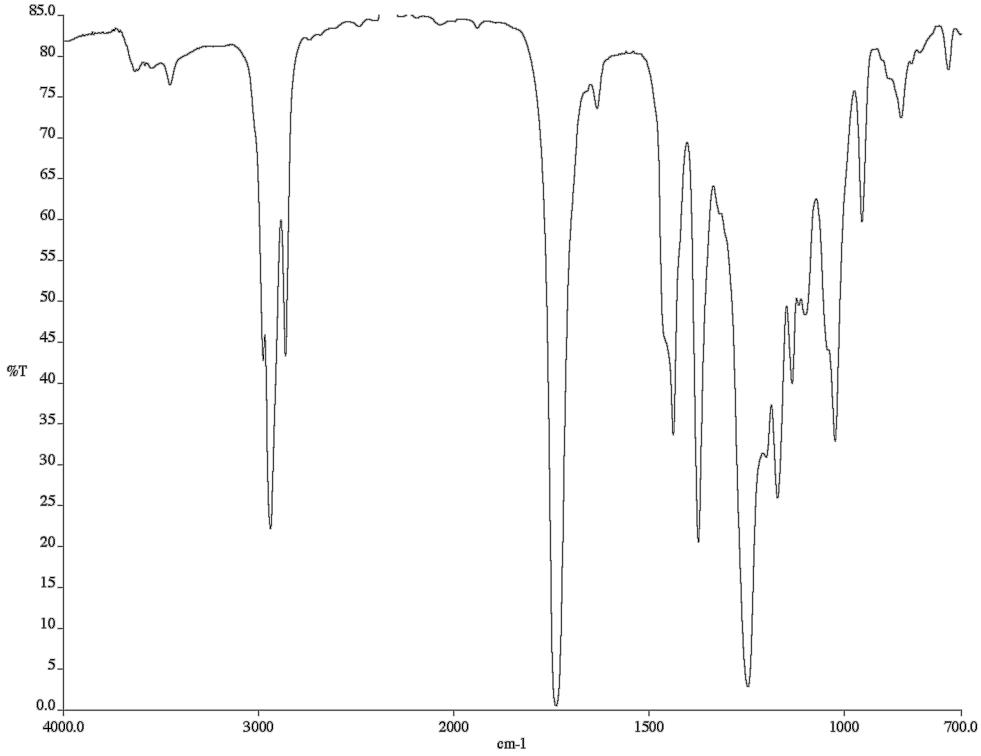


Figure A2.26.2 Infrared spectrum (thin film/NaCl) of compound **682**.

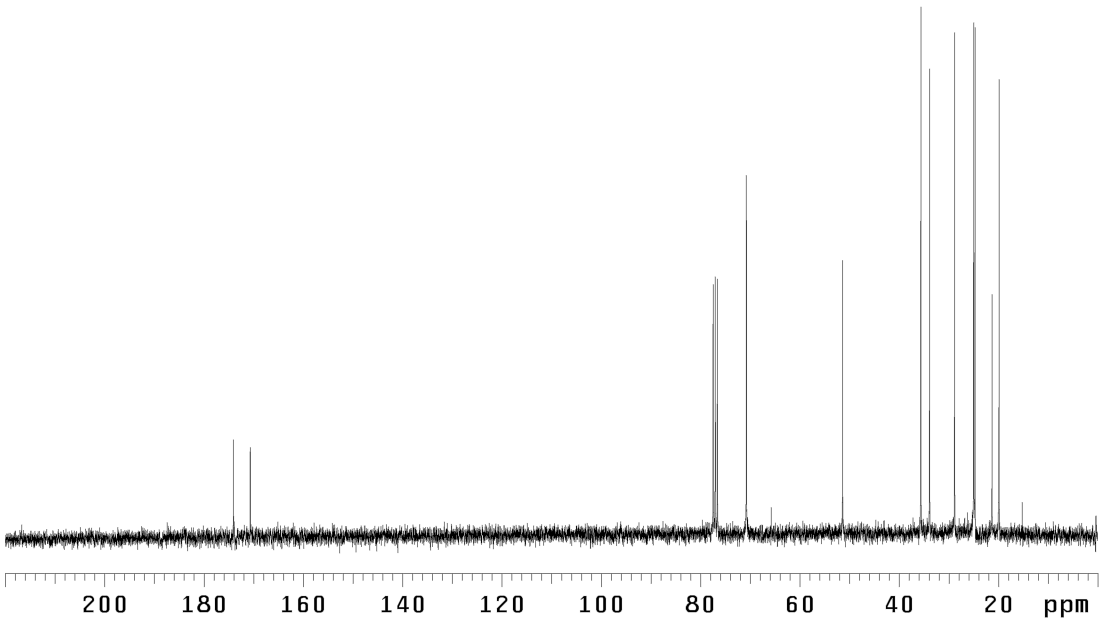


Figure A2.26.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **682**.

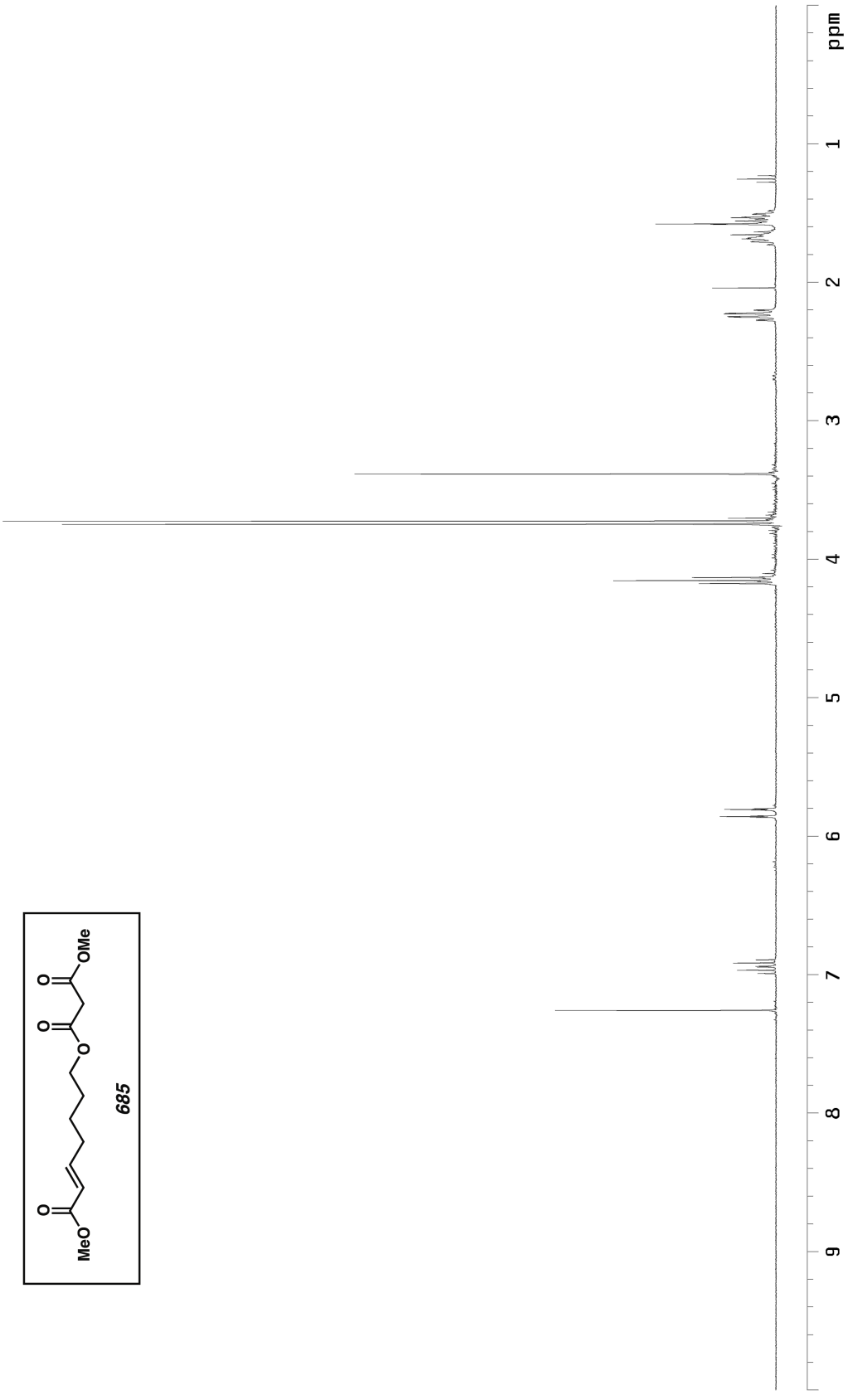


Figure A2.27.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **685**.

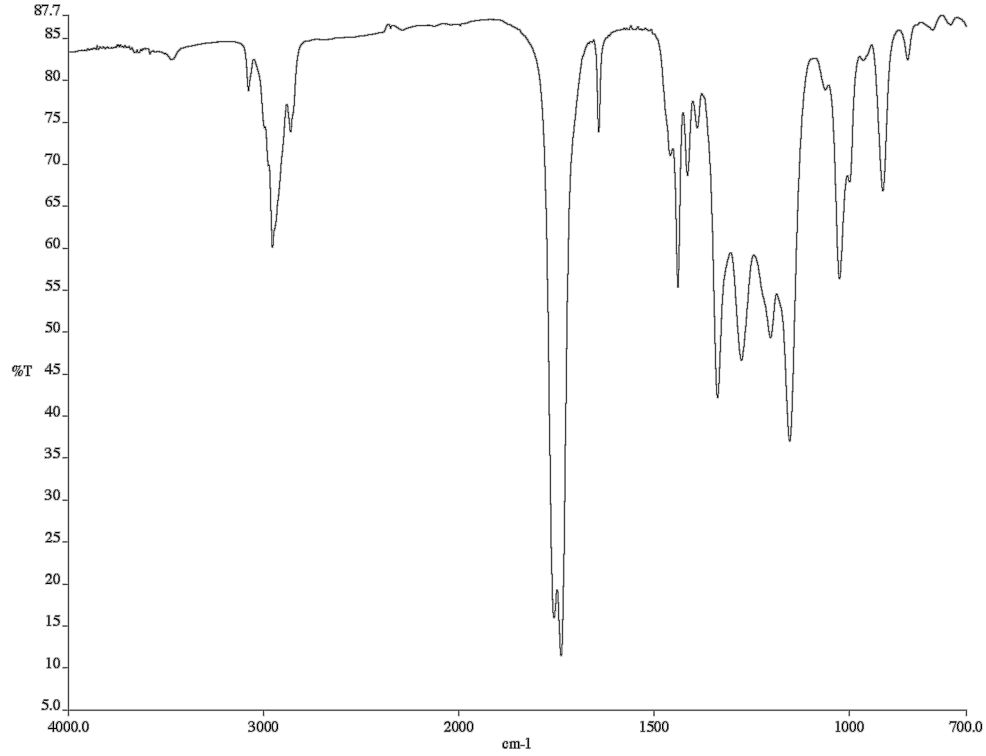


Figure A2.27.2 Infrared spectrum (thin film/NaCl) of compound **685**.

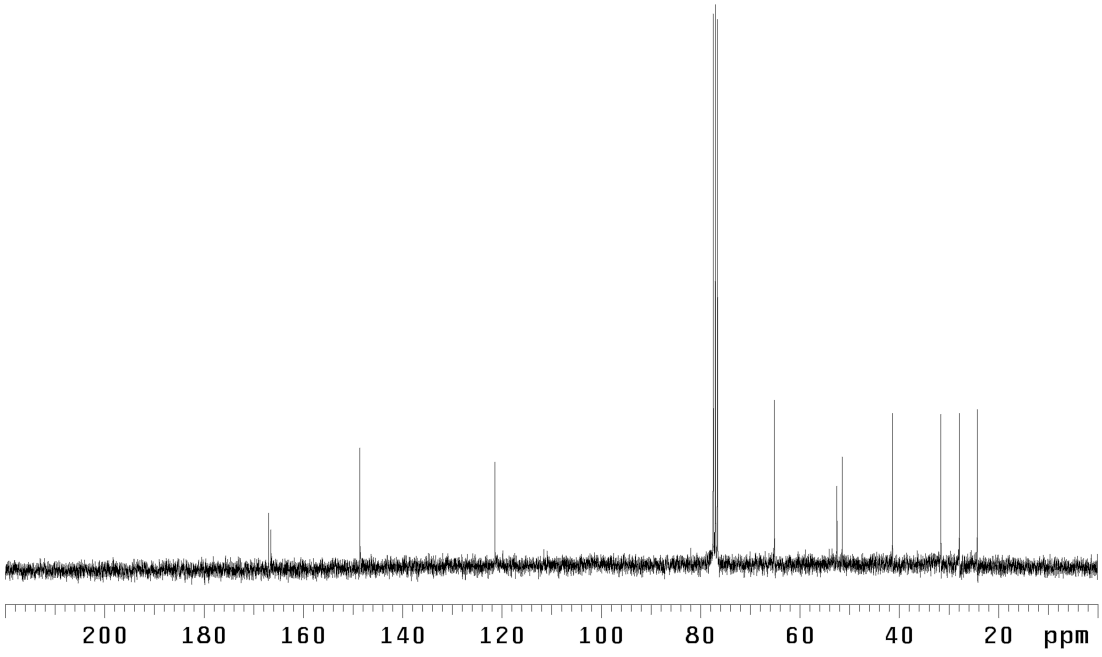


Figure A2.27.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **685**.

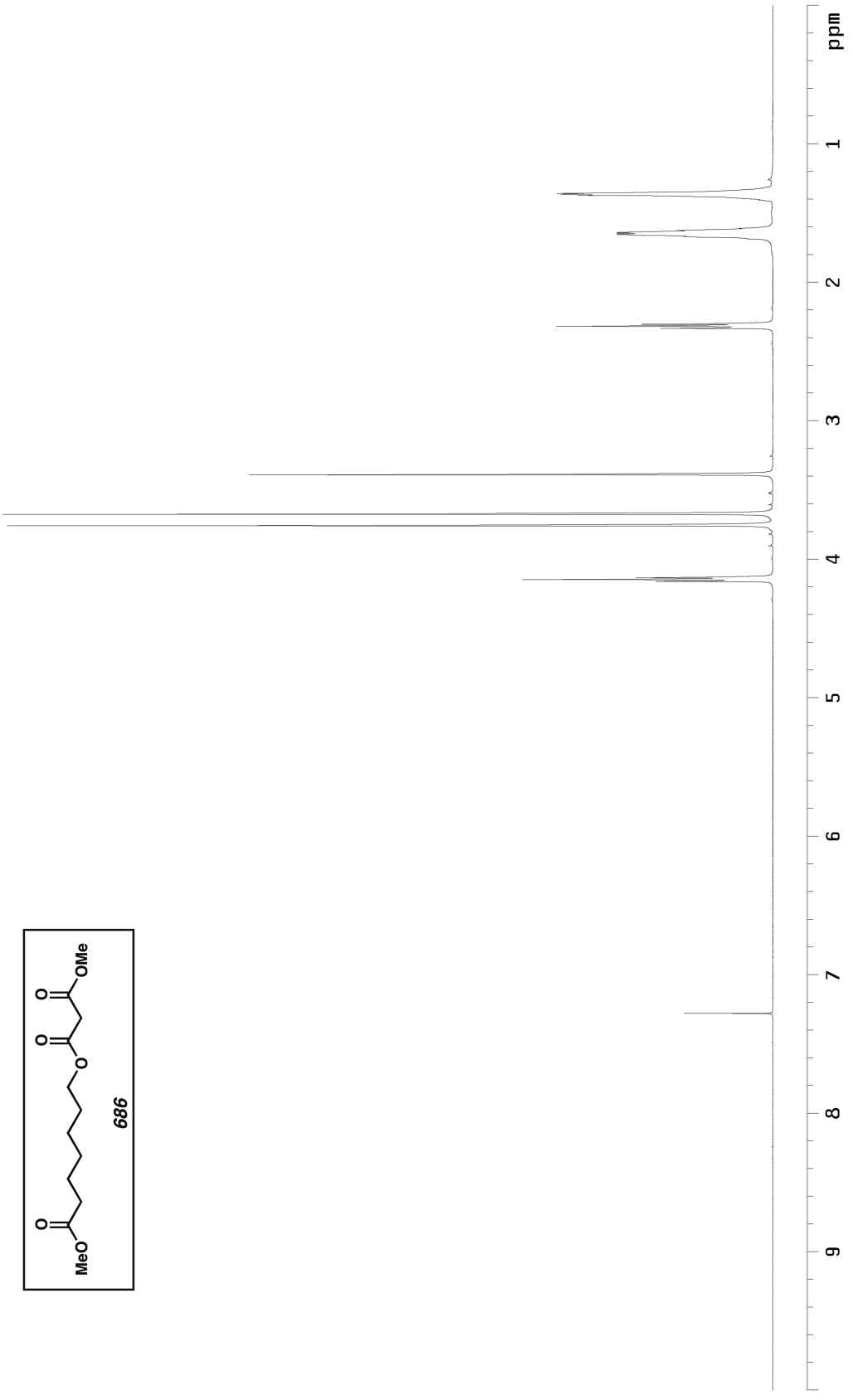


Figure A2.28.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **686**.

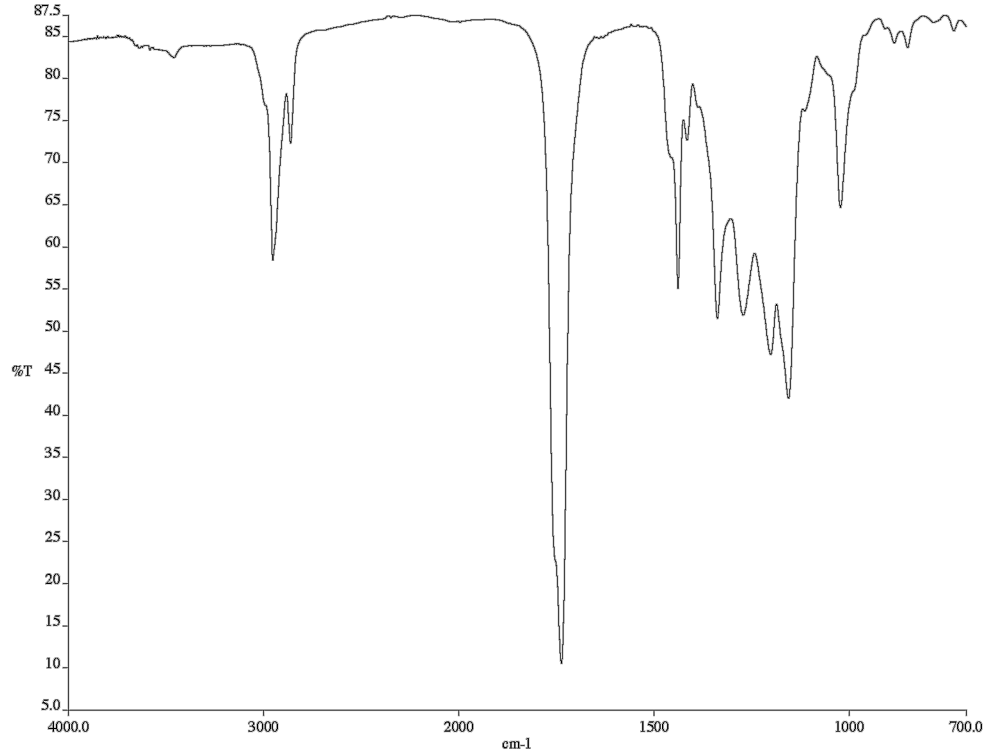


Figure A2.28.2 Infrared spectrum (thin film/NaCl) of compound **686**.

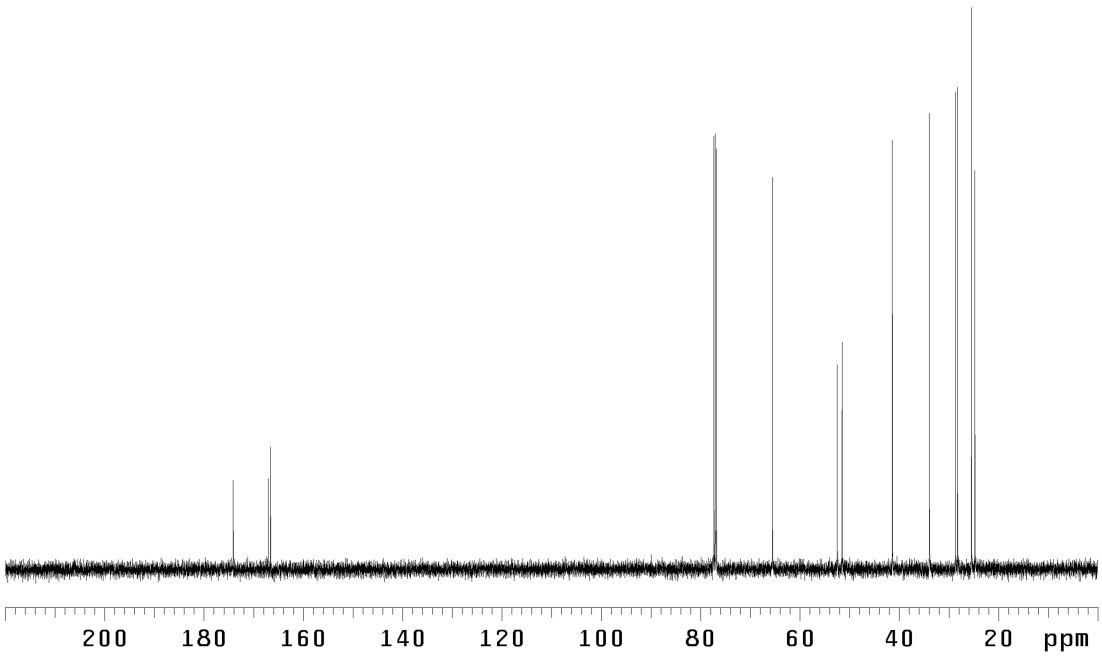


Figure A2.28.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **686**.

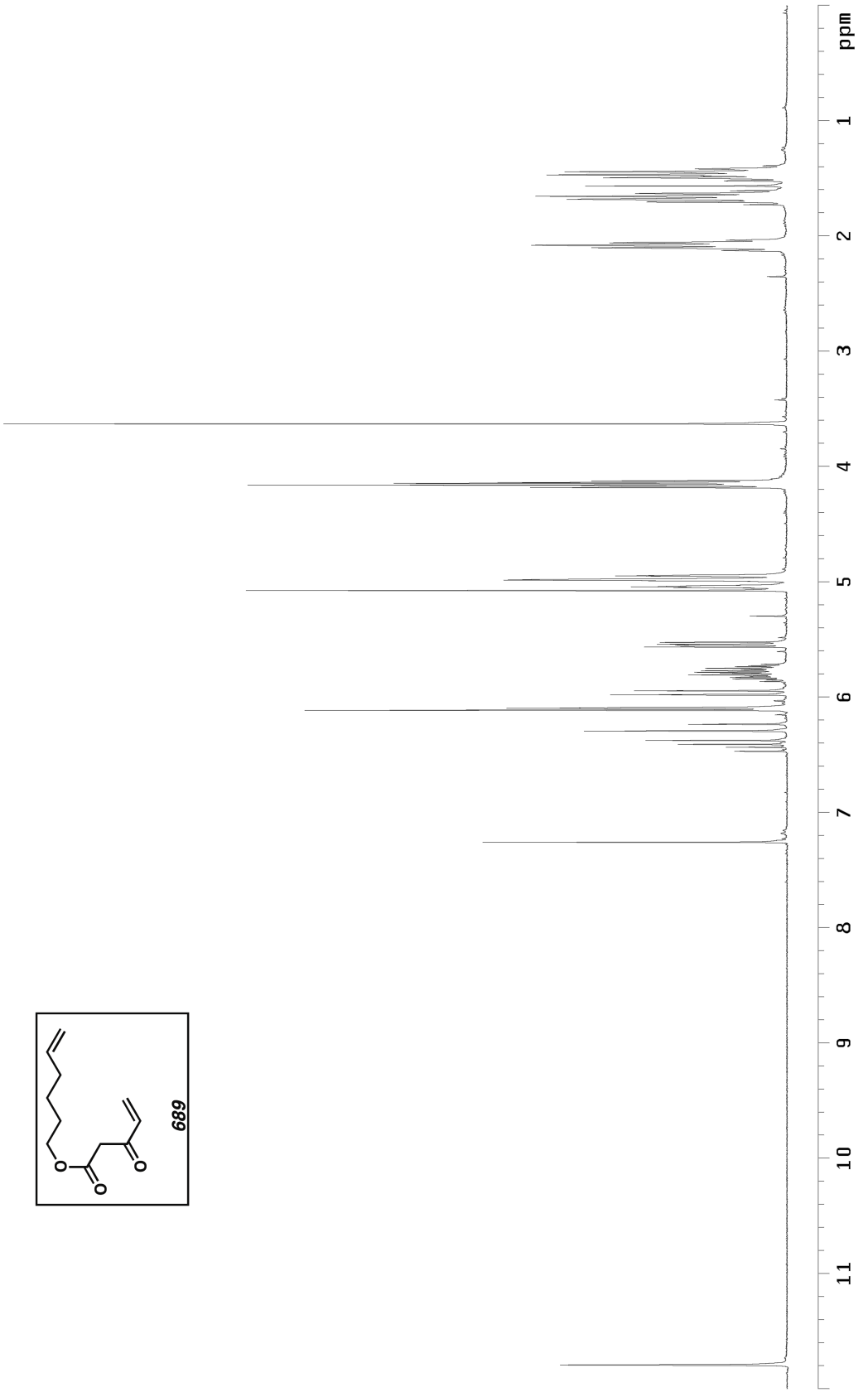


Figure A2.29.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **689**.

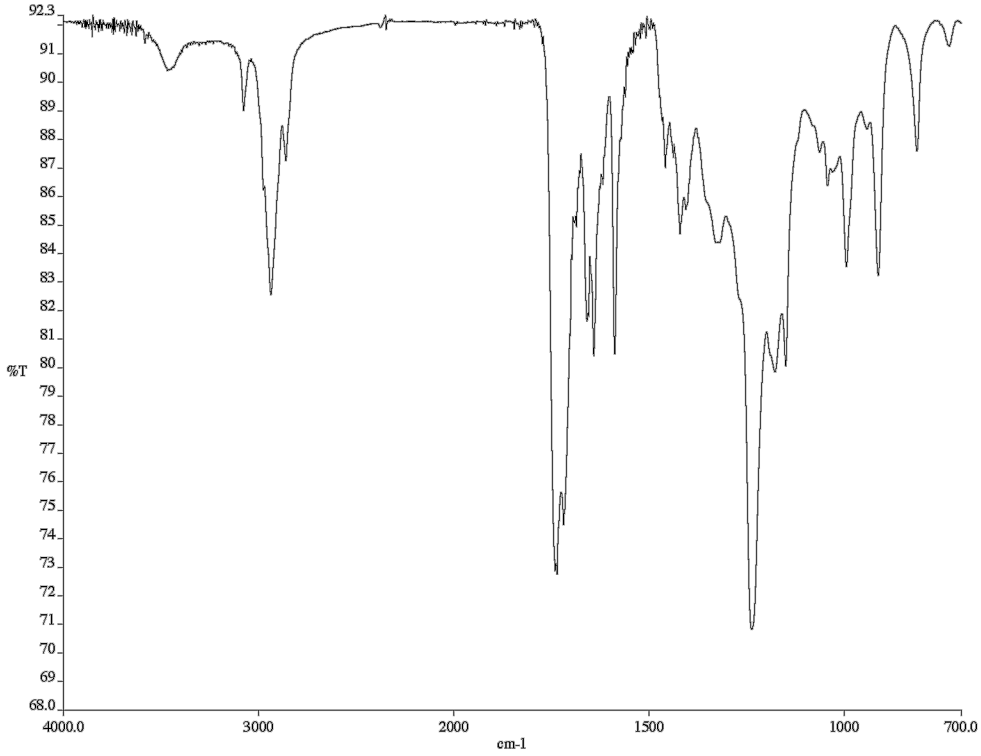


Figure A2.29.2 Infrared spectrum (thin film/NaCl) of compound **689**.

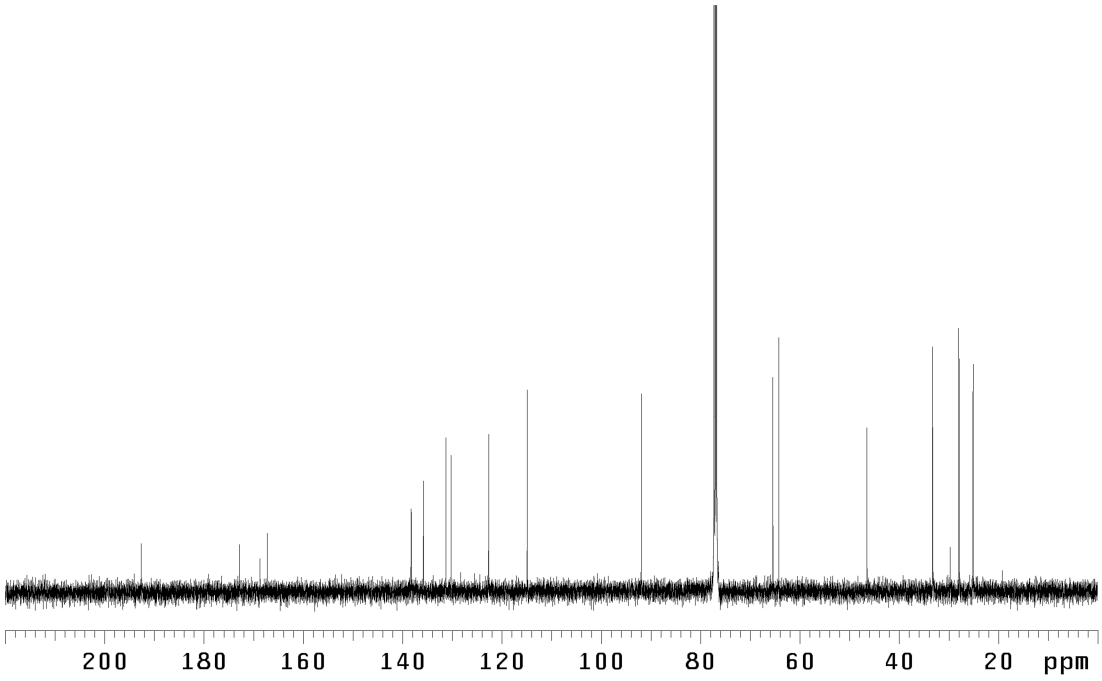


Figure A2.29.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **689**.

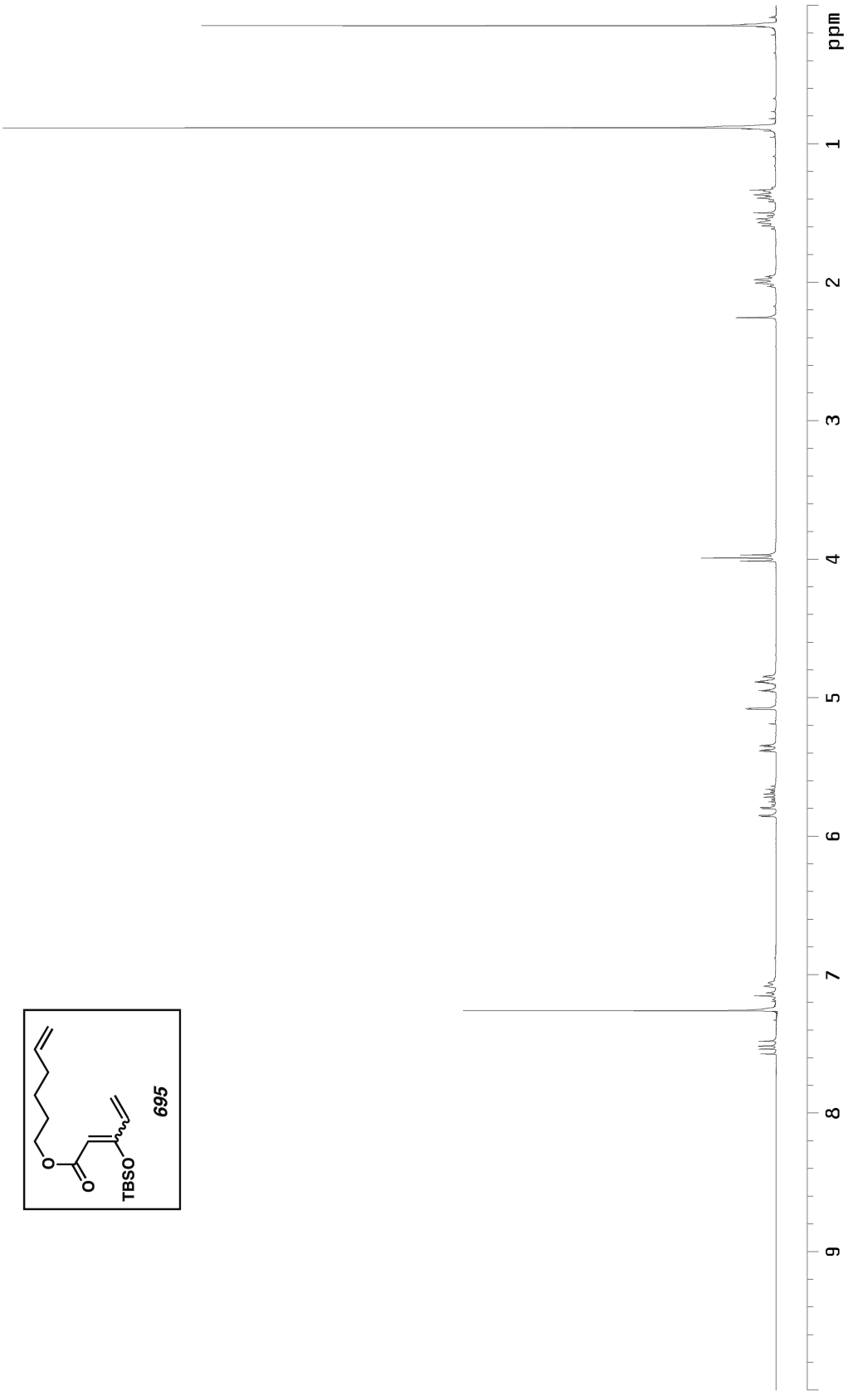


Figure A2.30.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **695**.

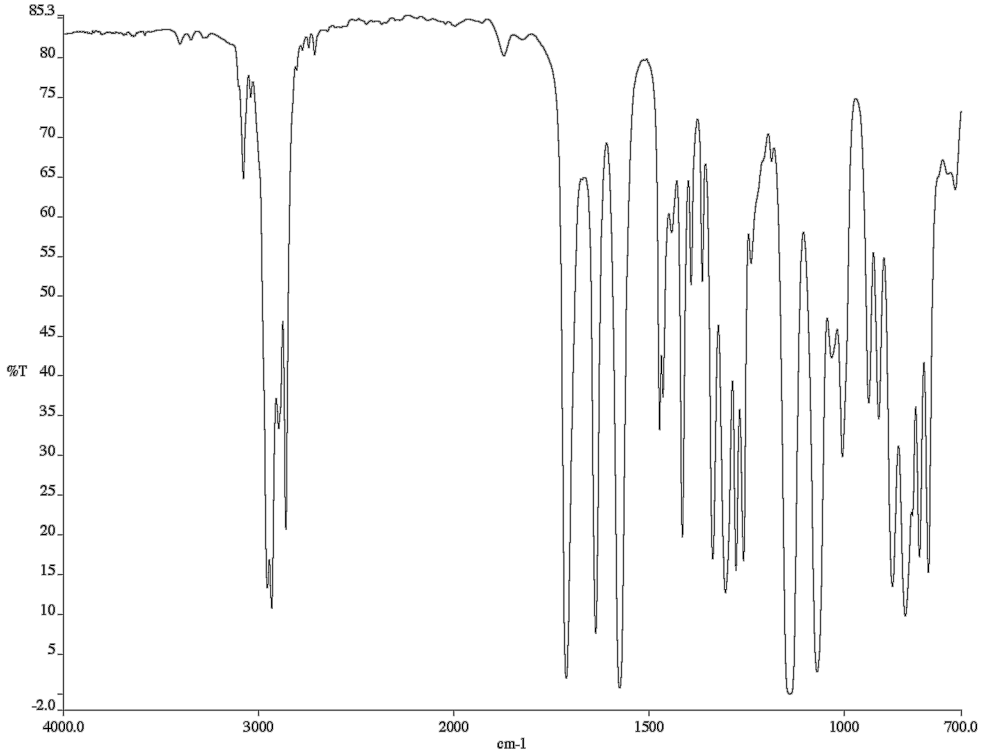


Figure A2.30.2 Infrared spectrum (thin film/NaCl) of compound **695**.

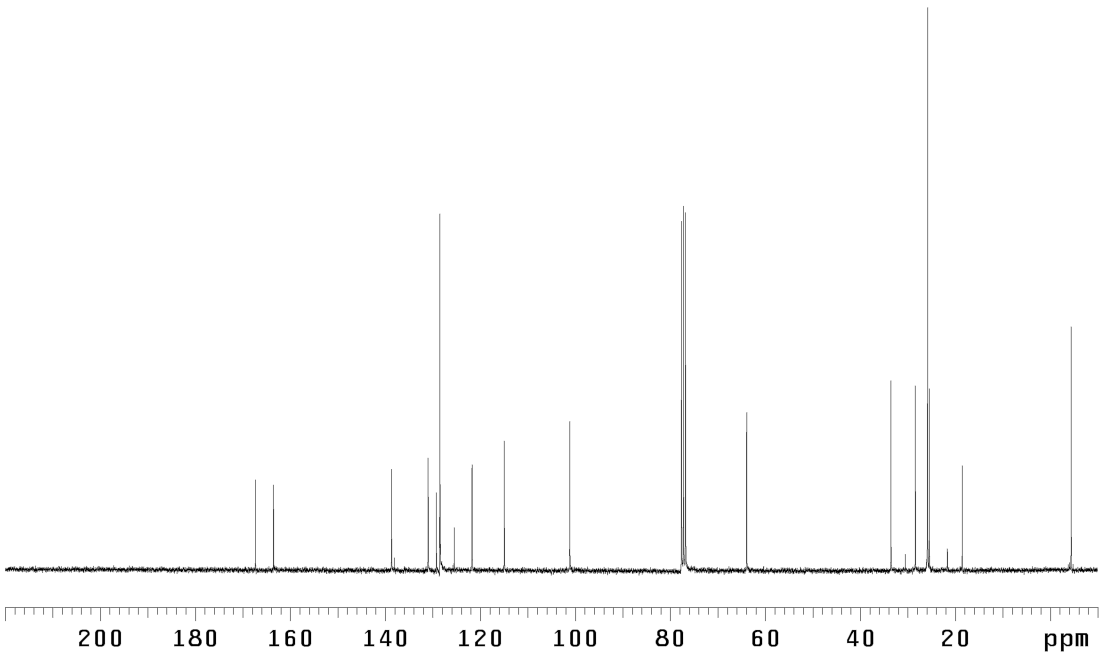


Figure A2.30.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **695**.

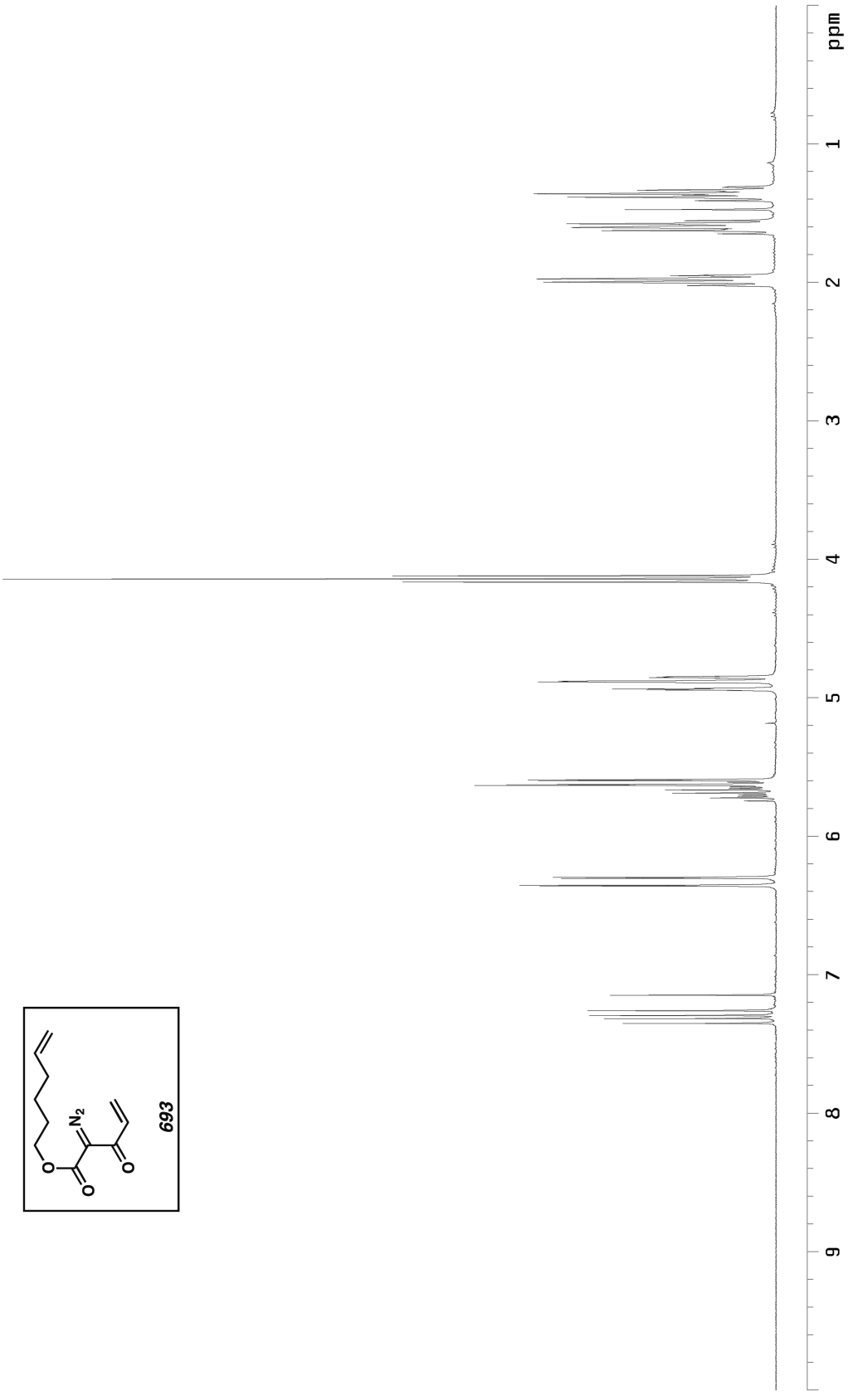


Figure A2.31.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **693**.

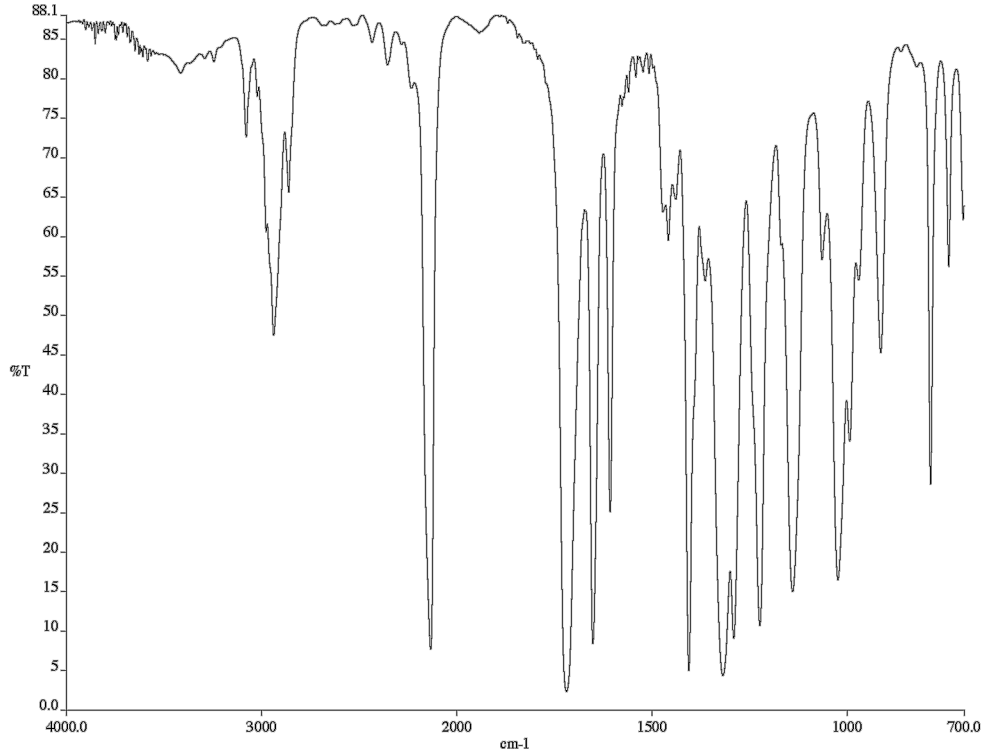


Figure A2.31.2 Infrared spectrum (thin film/NaCl) of compound **693**.

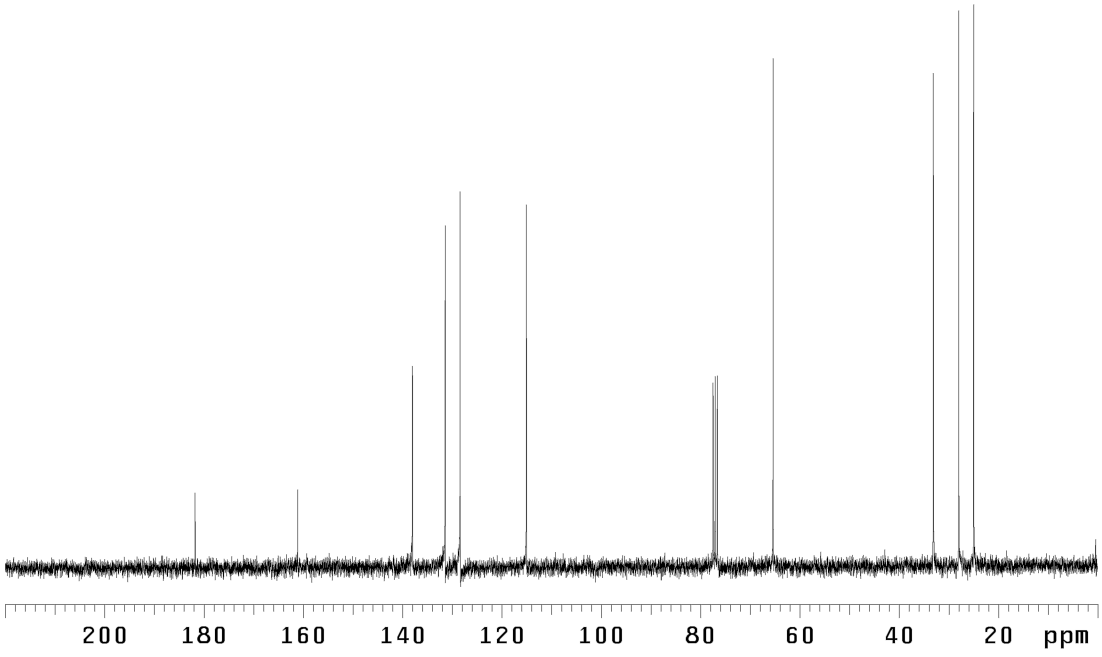


Figure A2.31.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **693**.

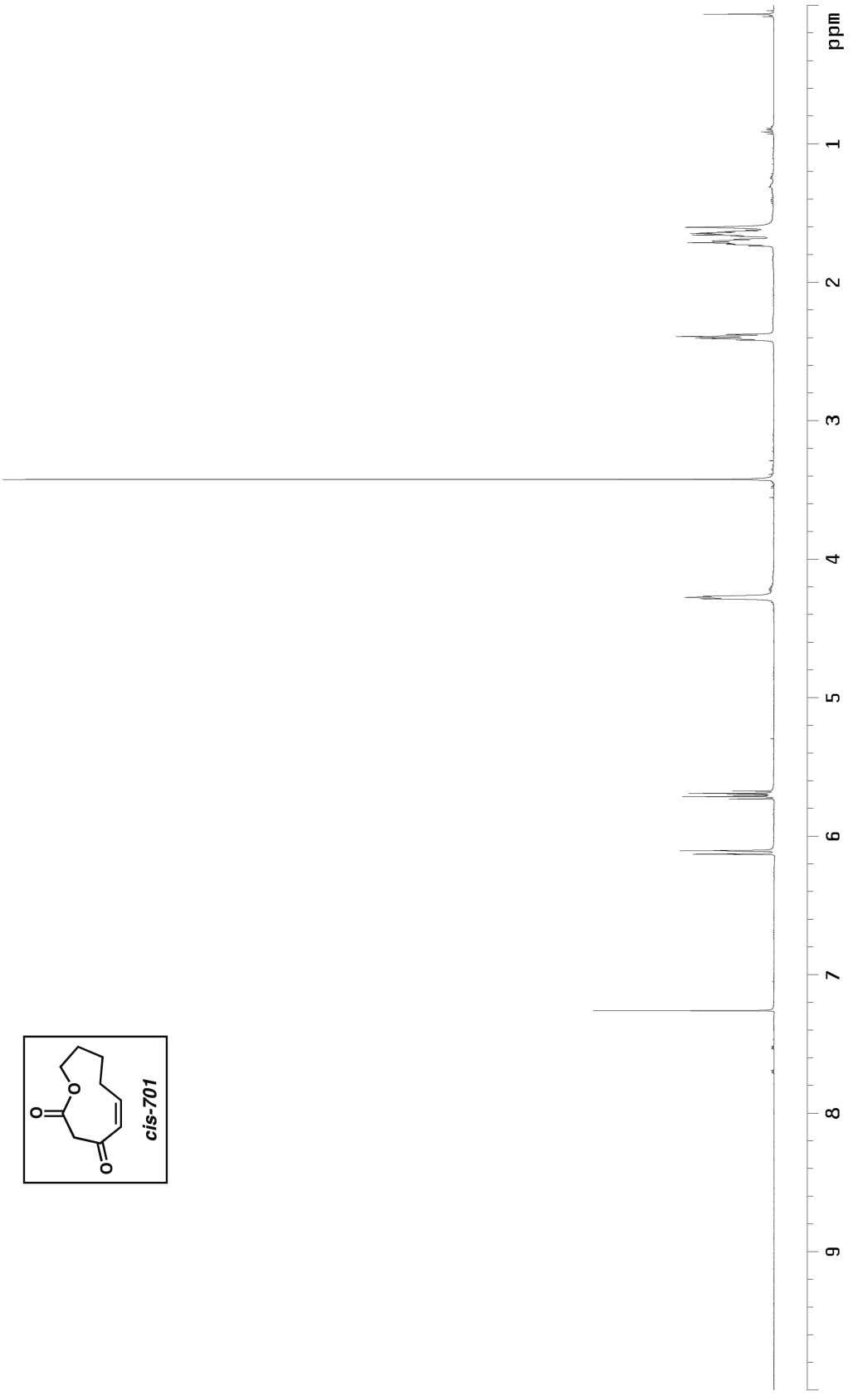


Figure A2.32.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound ***cis*-701**.

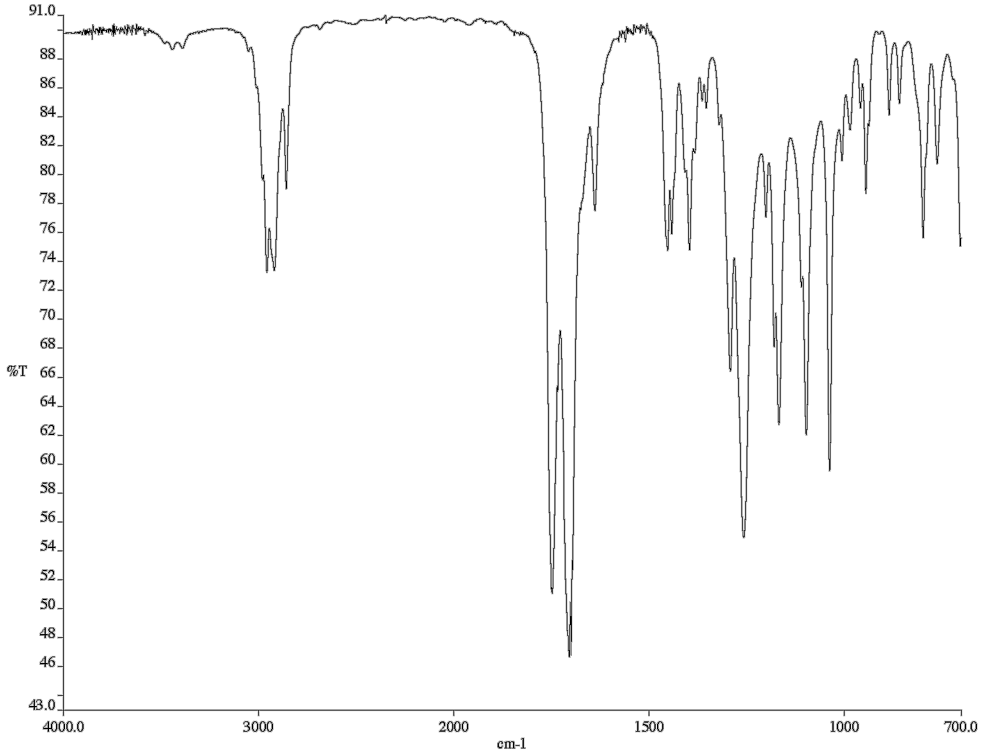


Figure A2.32.2 Infrared spectrum (thin film/NaCl) of compound ***cis*-701**.

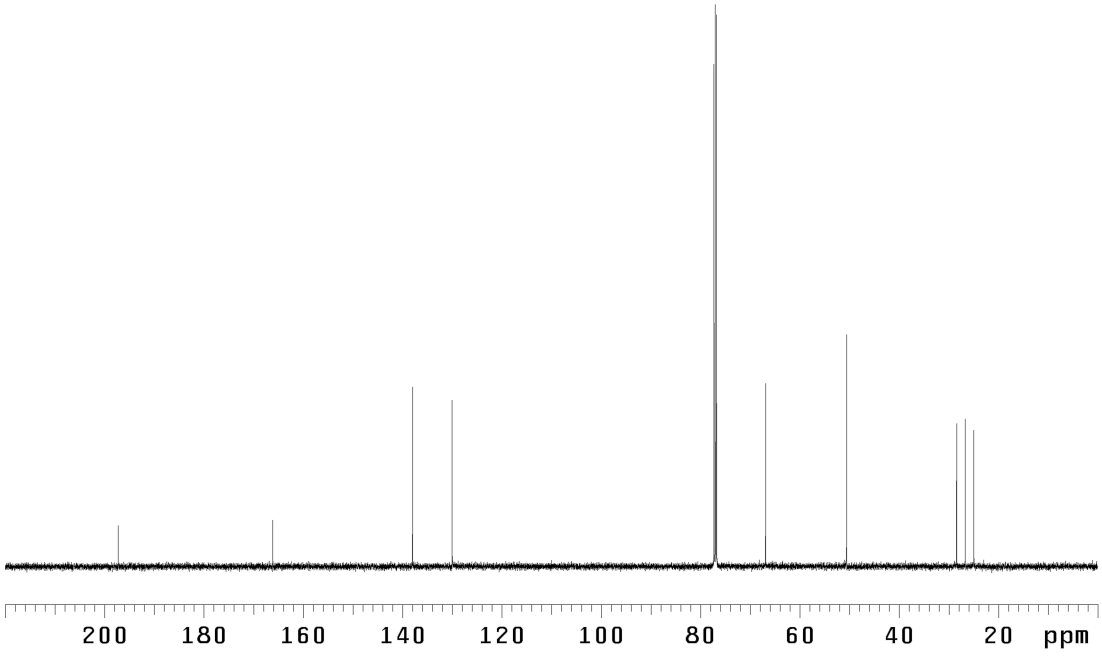


Figure A2.32.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound ***cis*-701**.

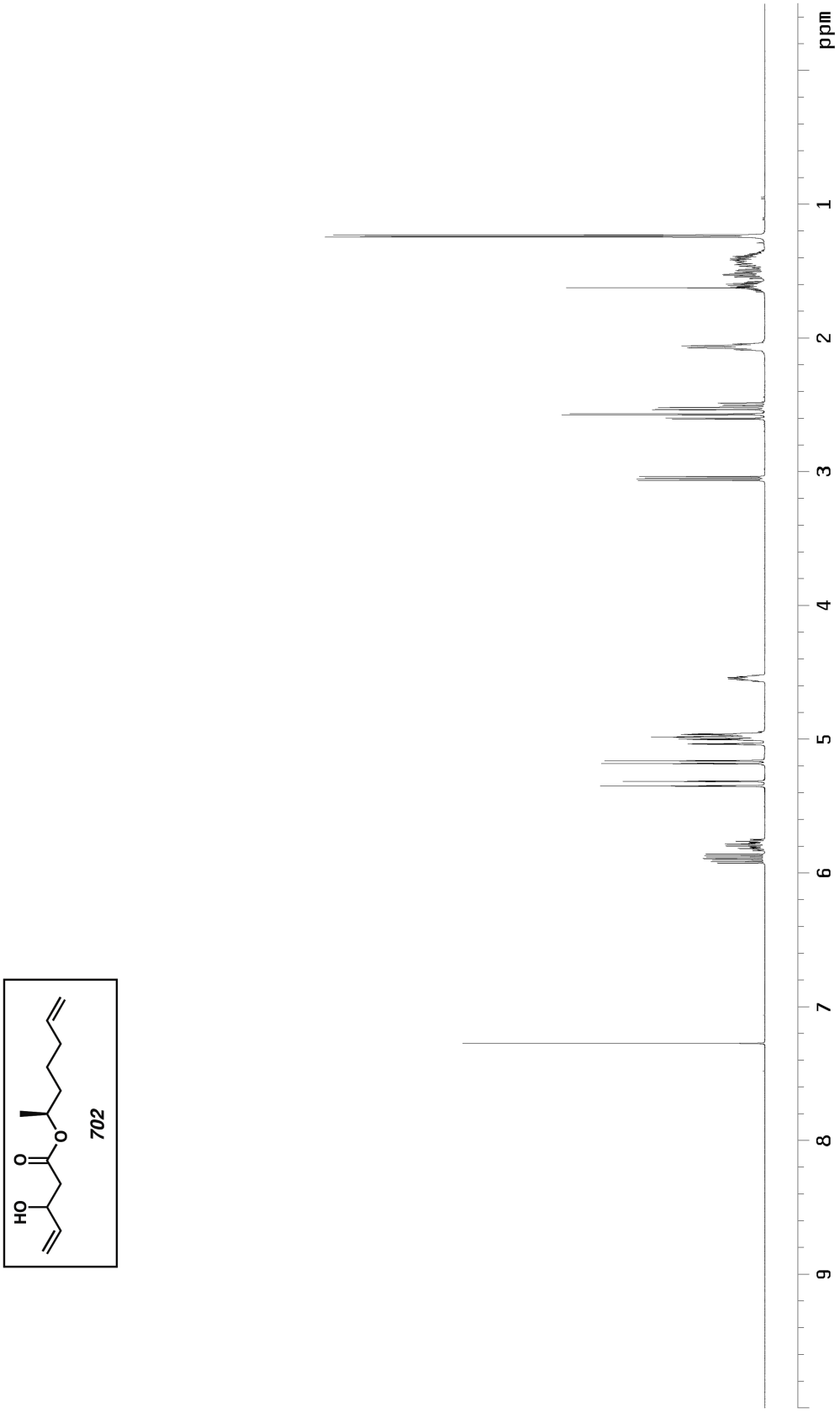


Figure A2.33.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **702**.

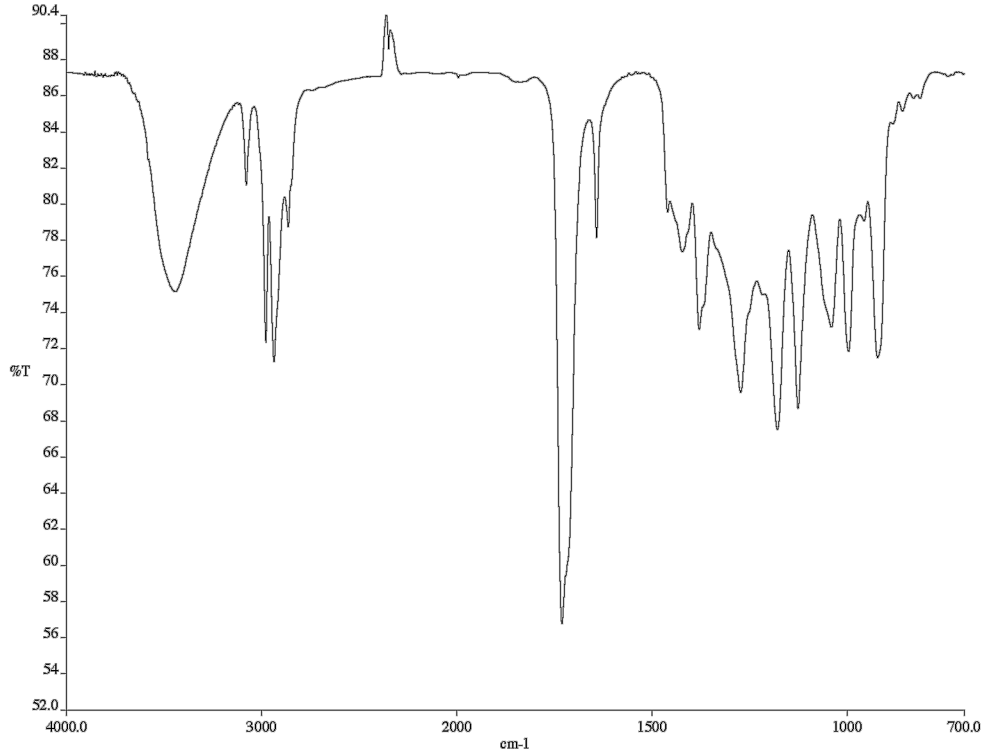


Figure A2.33.2 Infrared spectrum (thin film/NaCl) of compound **702**.

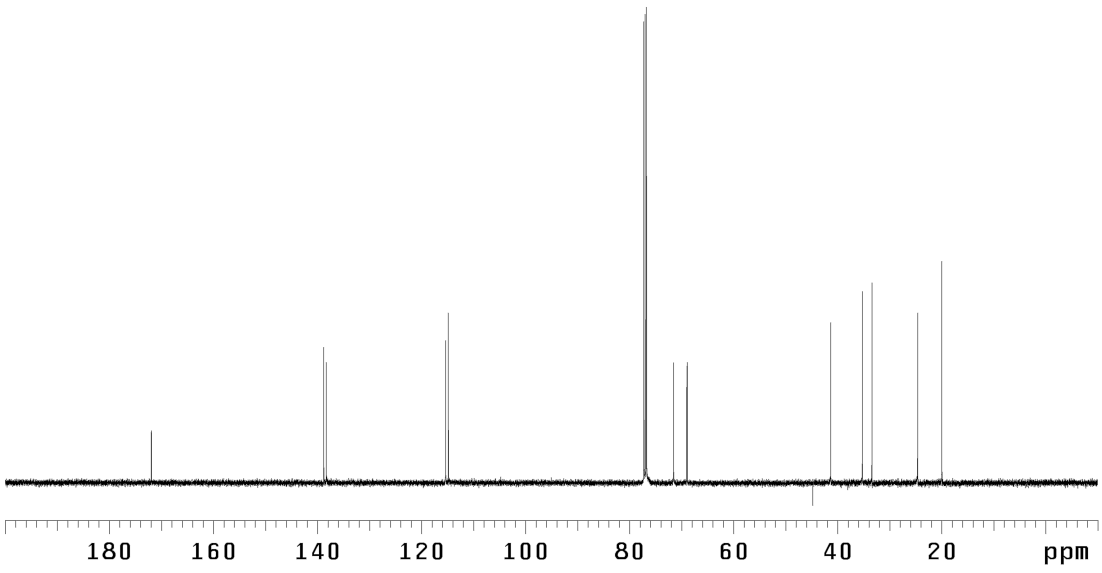


Figure A2.33.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **702**.

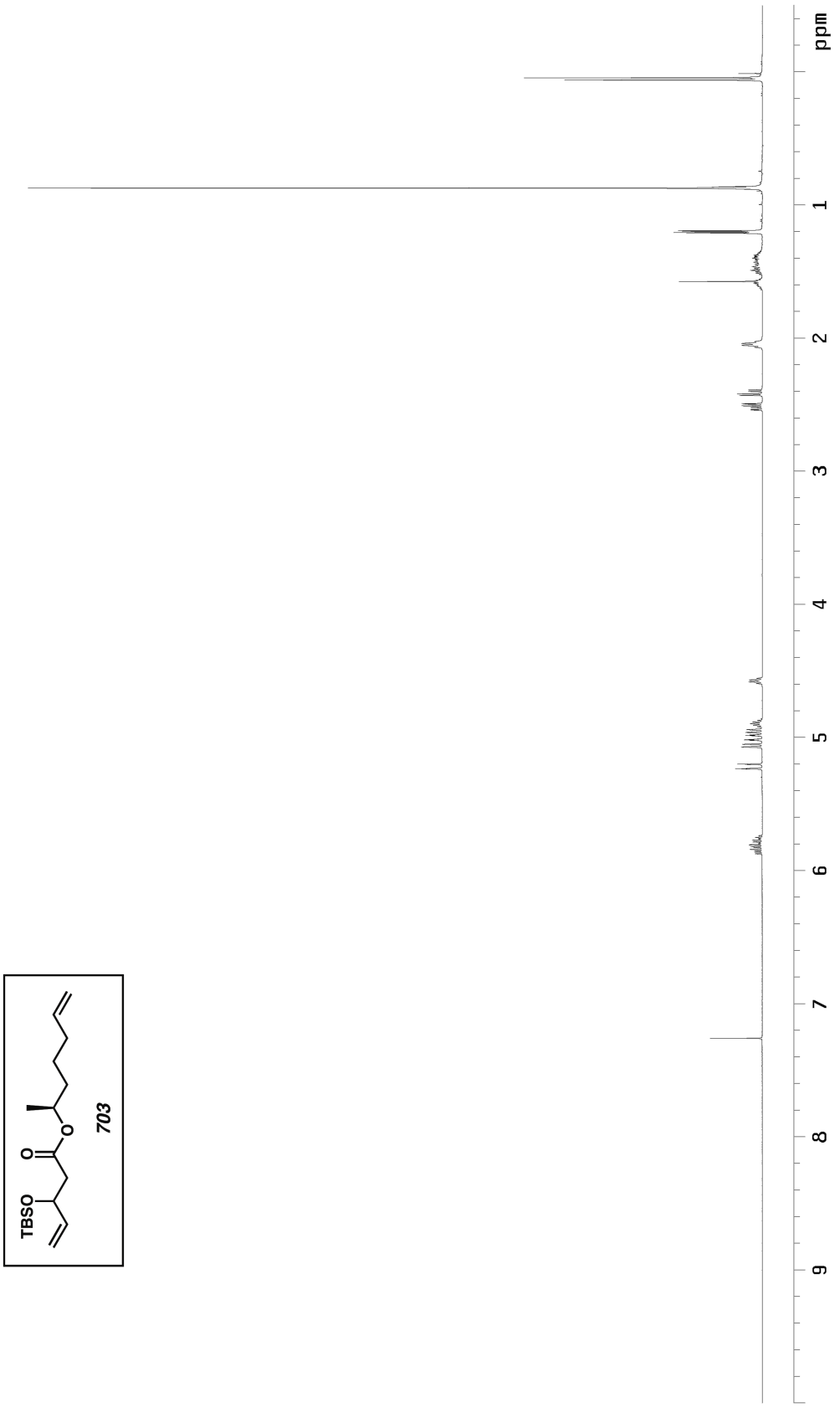


Figure A2.34.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **703**.

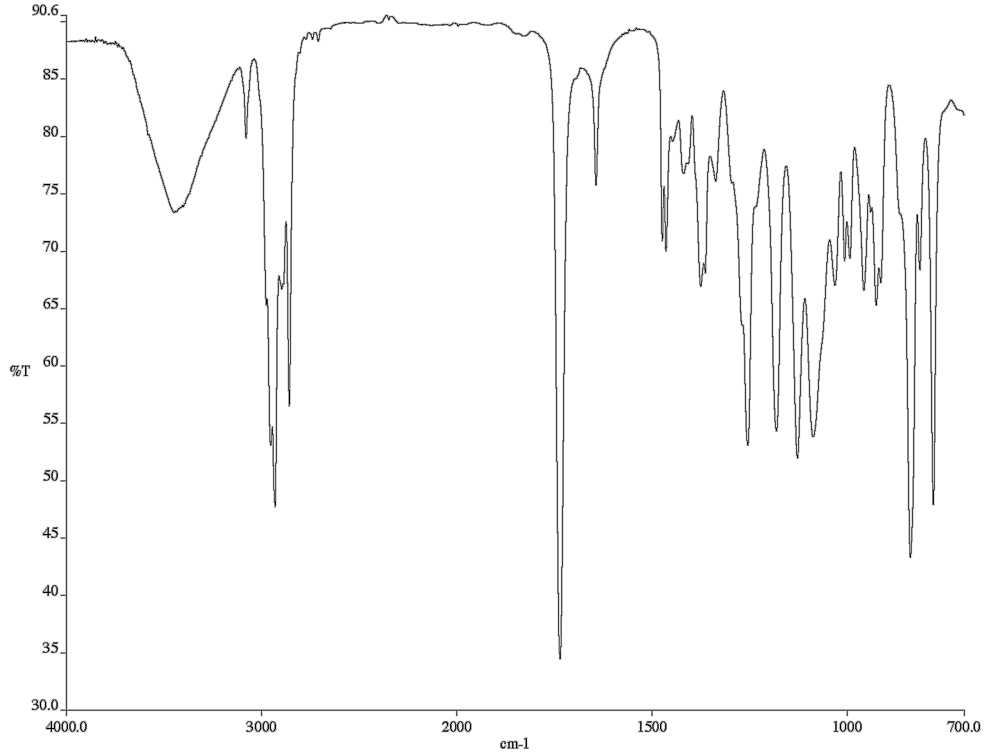


Figure A2.34.2 Infrared spectrum (thin film/NaCl) of compound **703**.

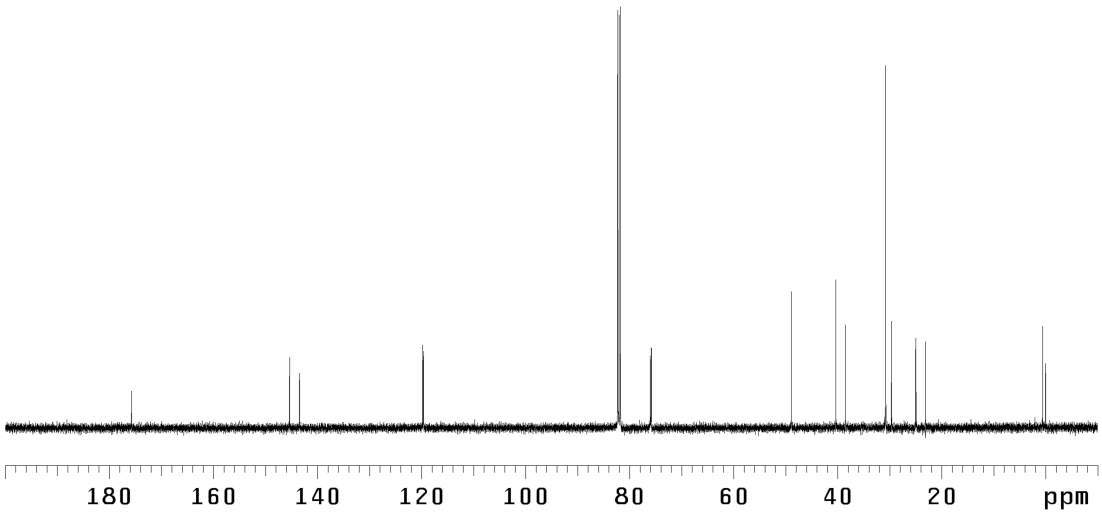


Figure A2.34.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **703**.

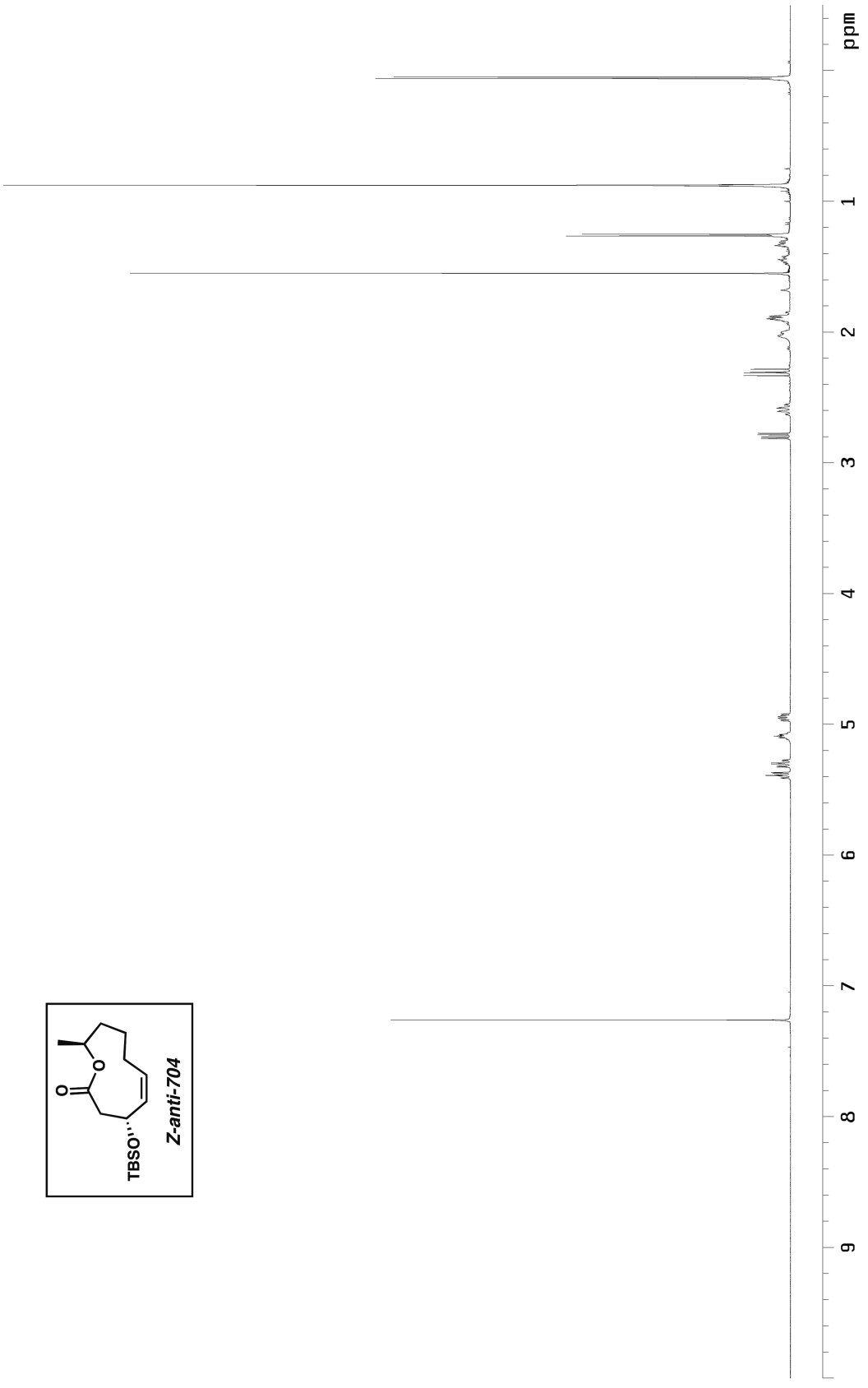


Figure A2.35.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound ***Z-anti-*704**.

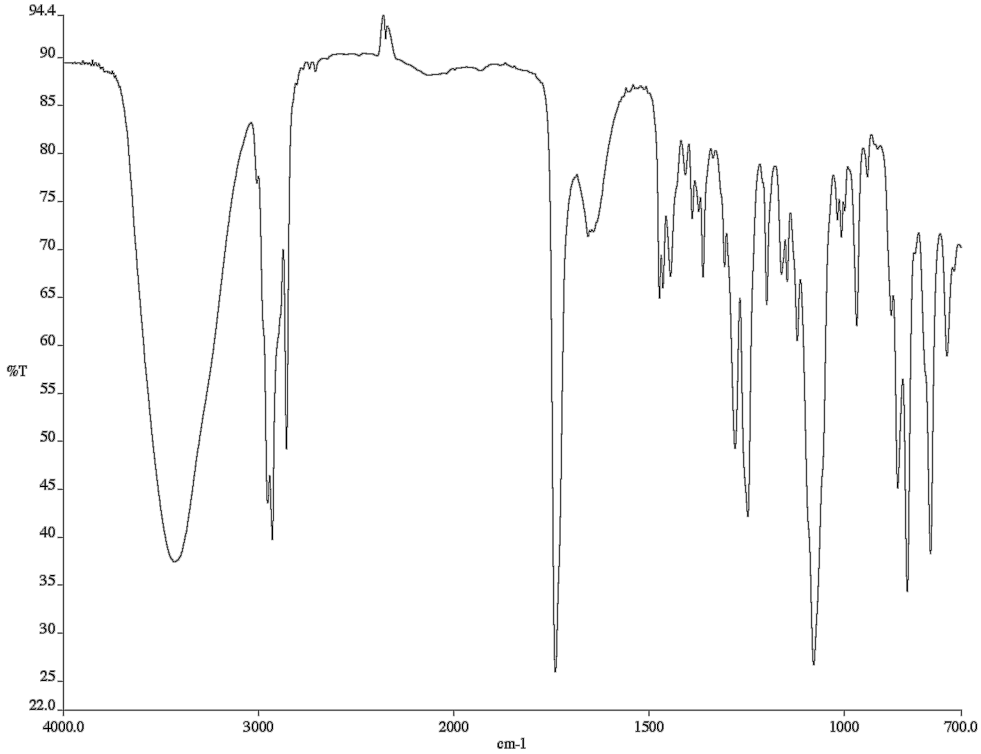


Figure A2.35.2 Infrared spectrum (thin film/NaCl) of compound ***Z-anti-*704**.

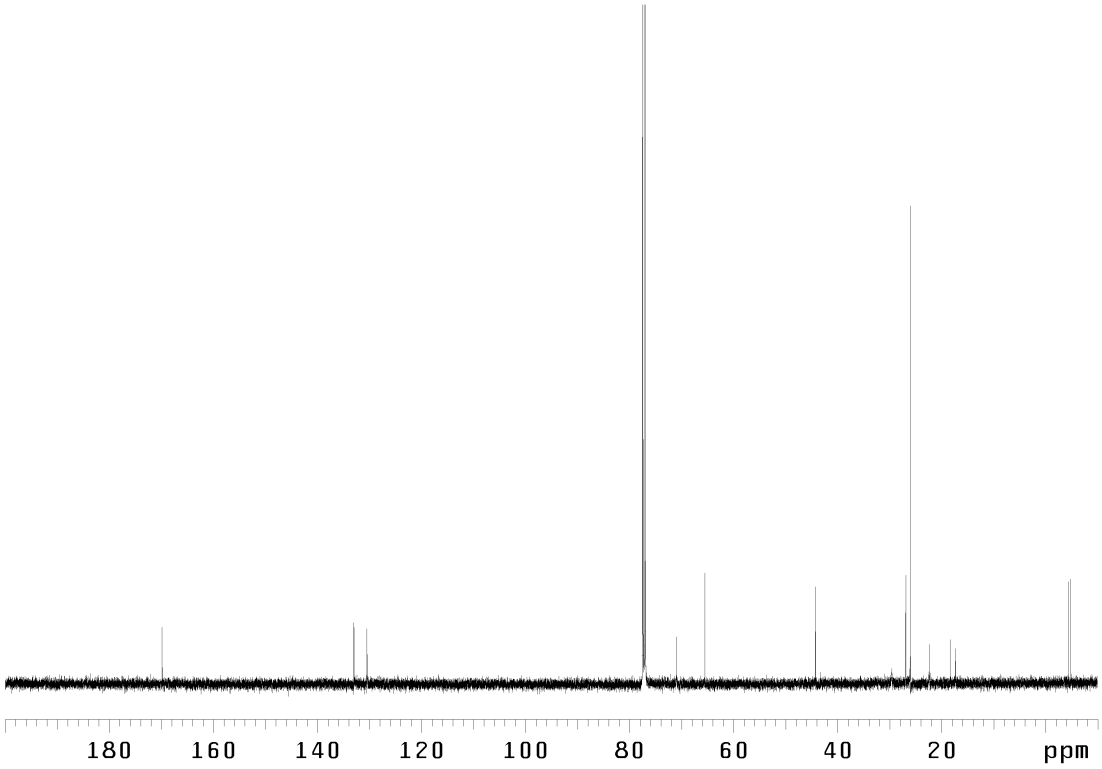
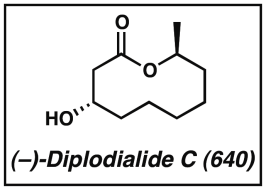


Figure A2.35.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound ***Z-anti-*704**.



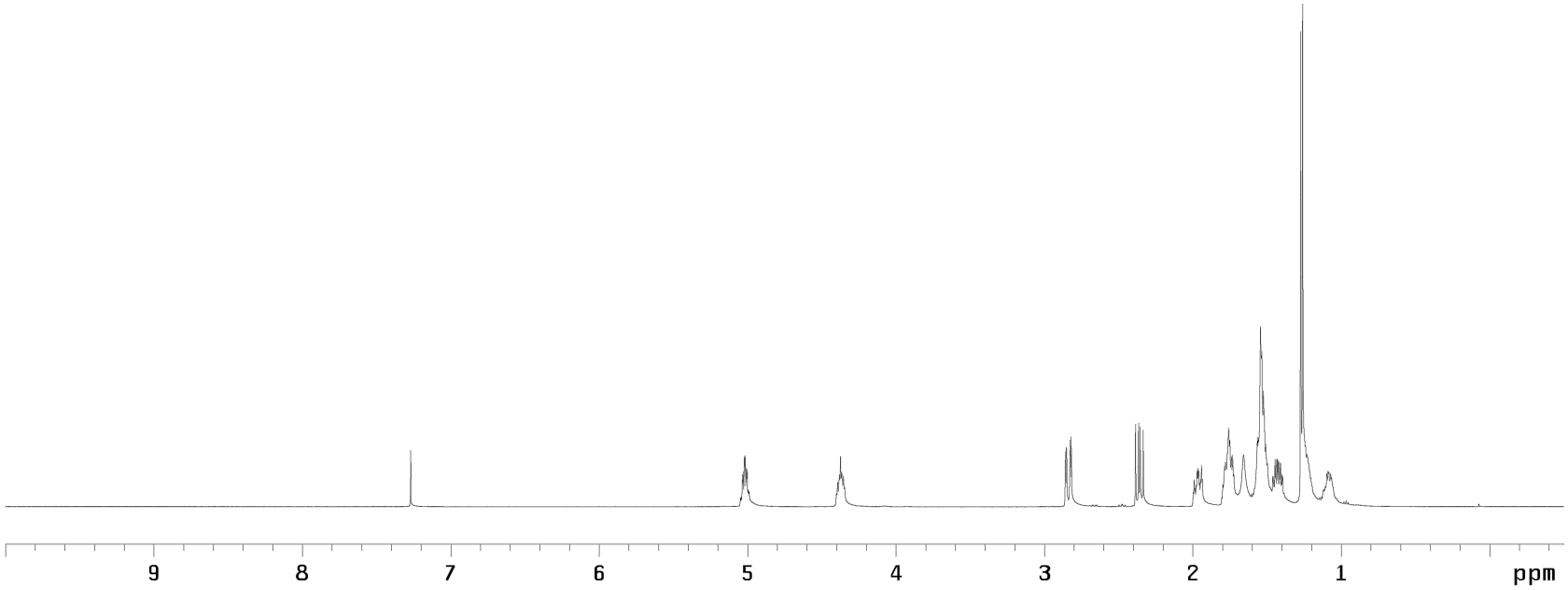


Figure A2.36.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **640**.

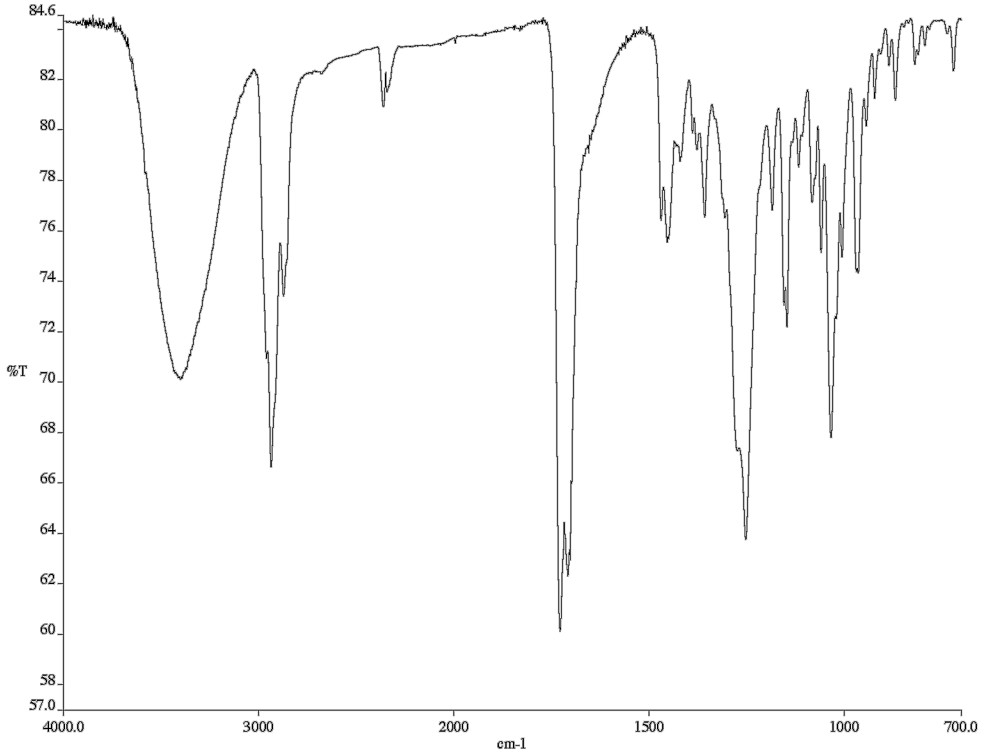


Figure A2.36.2 Infrared spectrum (thin film/NaCl) of compound **640**.

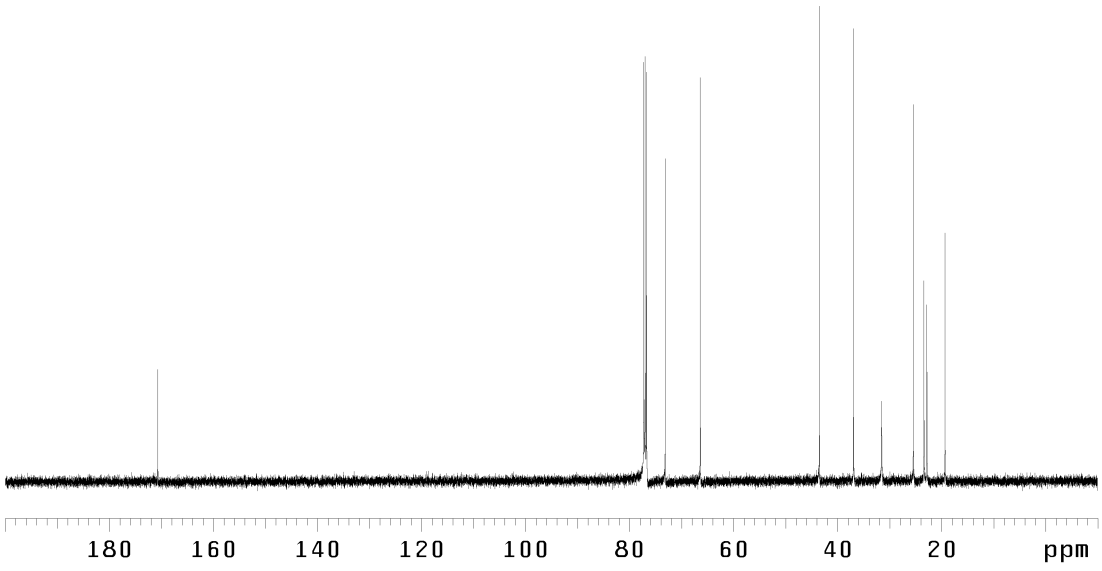


Figure A2.36.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **640**.

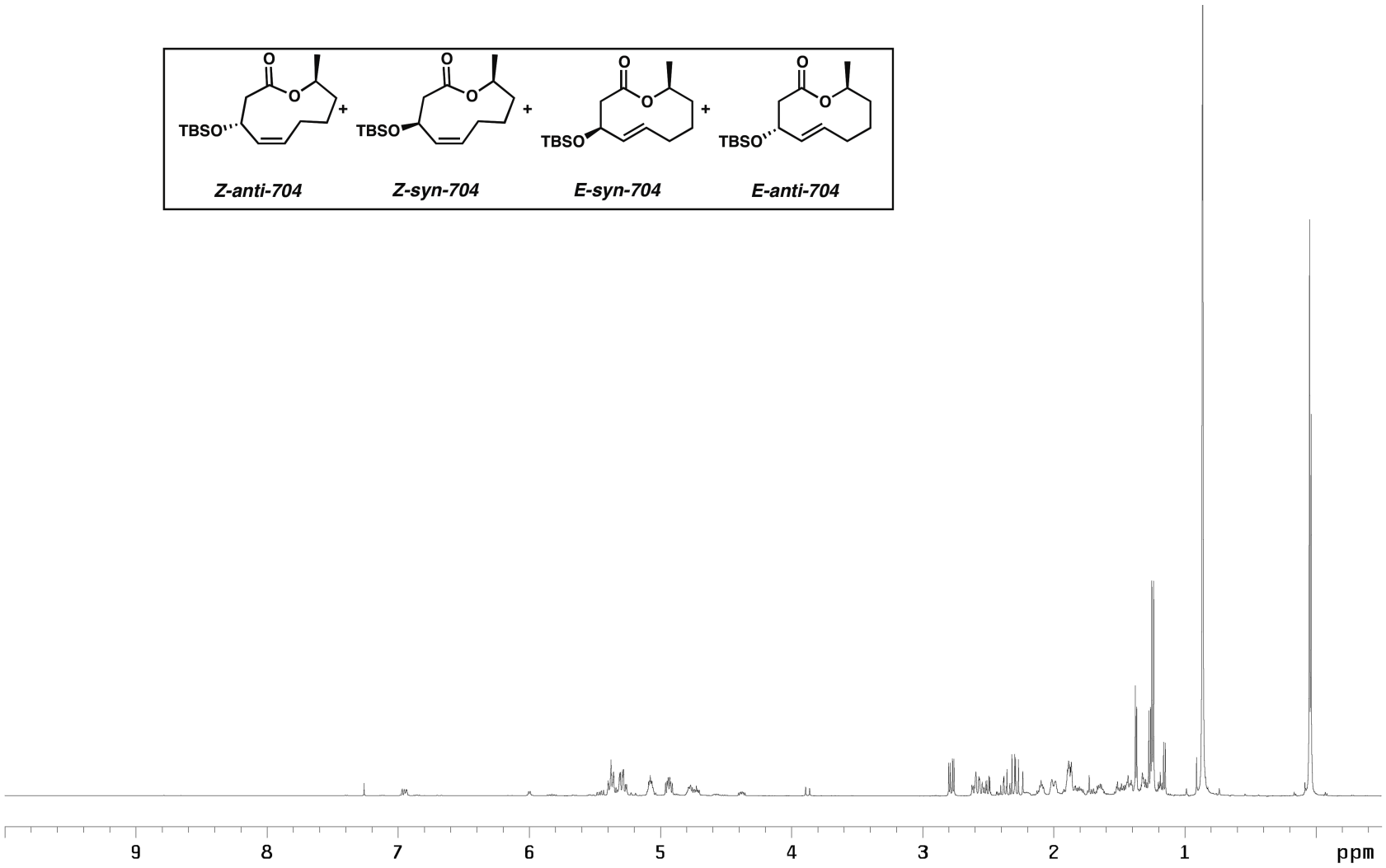


Figure A2.37.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **704**.

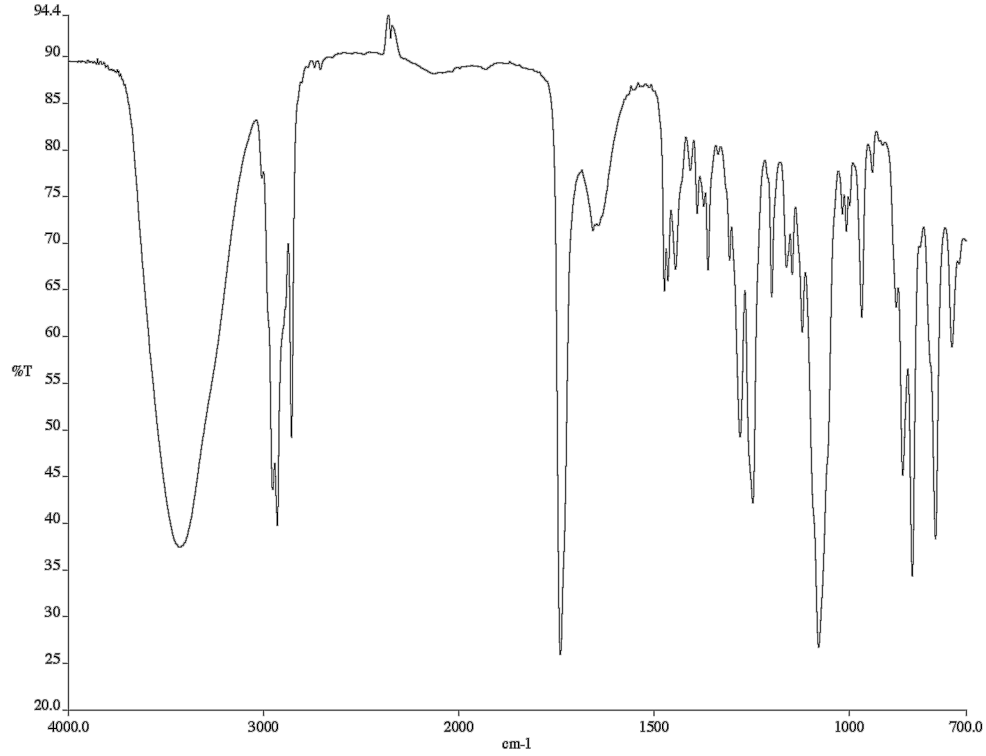


Figure A2.37.2 Infrared spectrum (thin film/NaCl) of compound **704**.

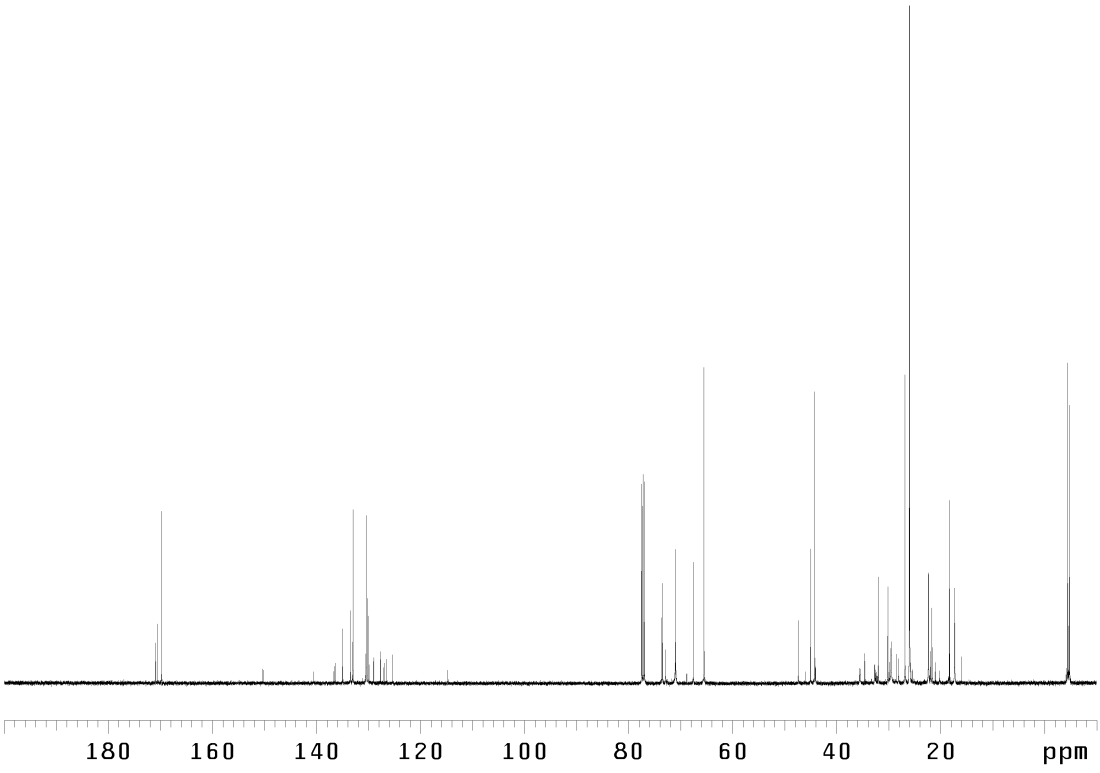


Figure A2.37.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **704**.

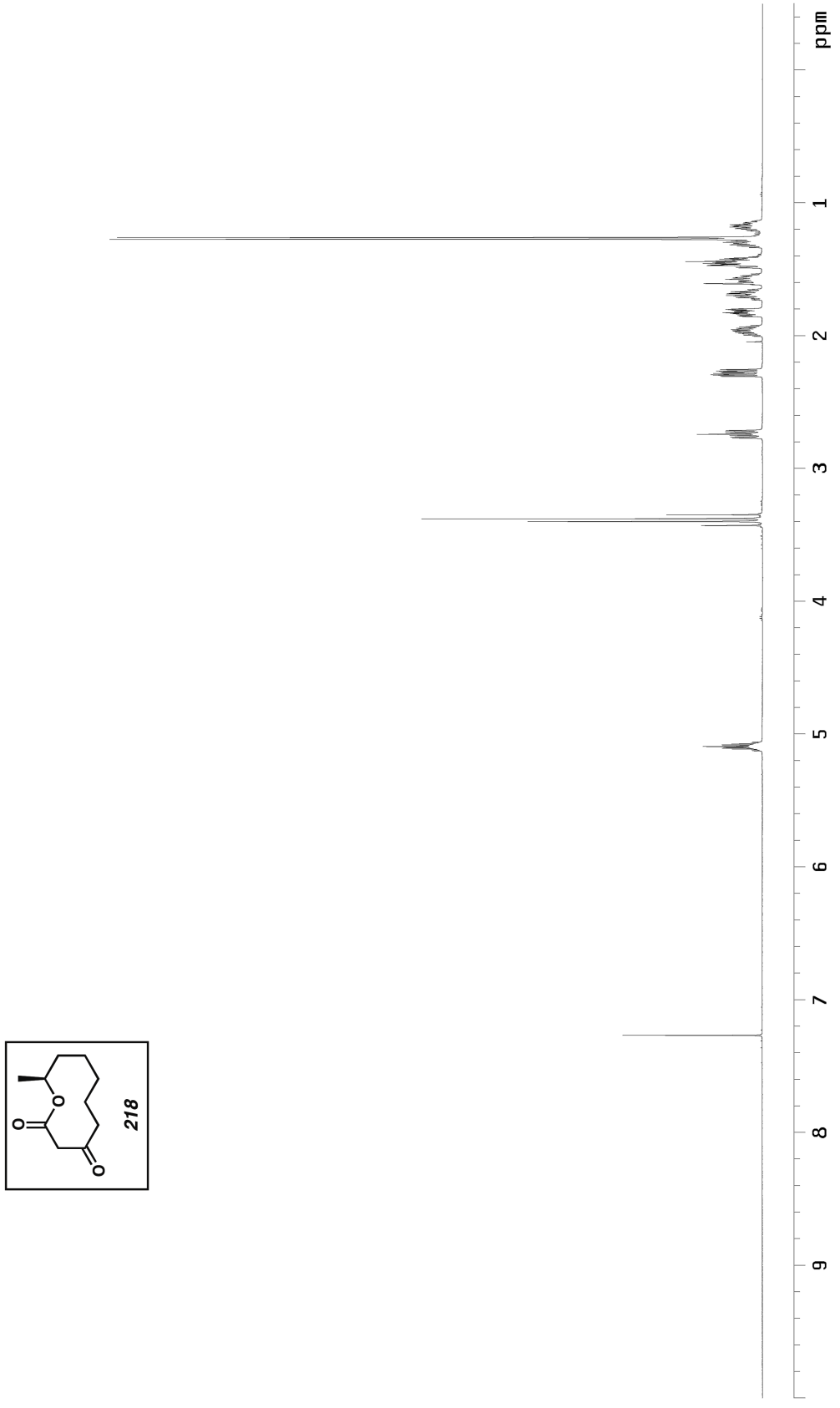


Figure A2.38.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **218**.

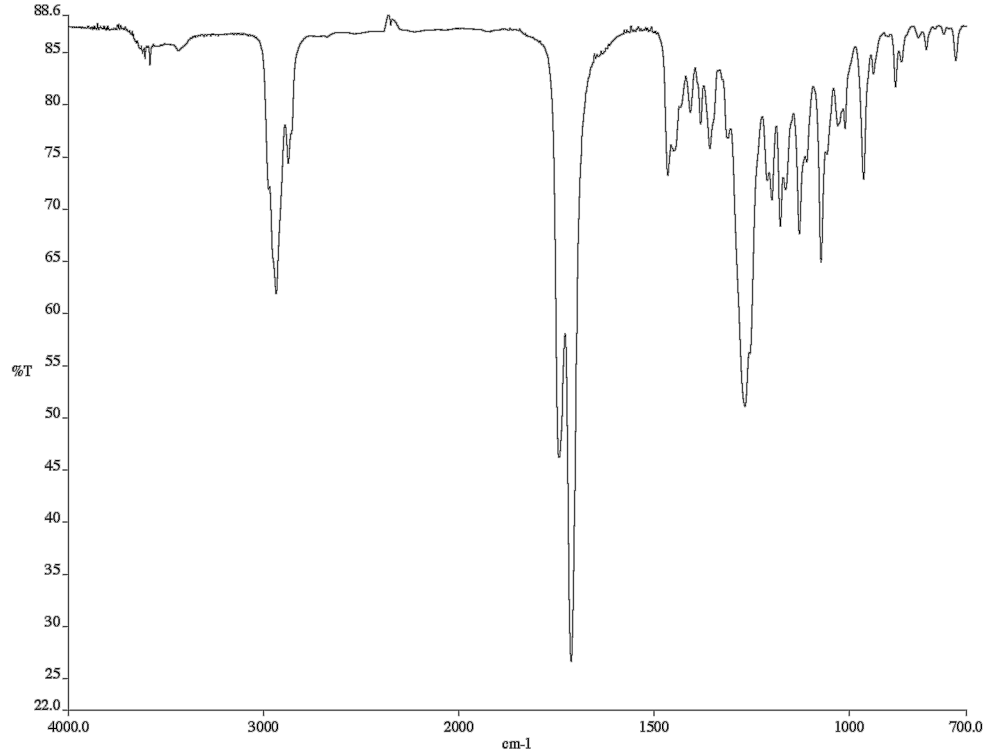


Figure A2.38.2 Infrared spectrum (thin film/NaCl) of compound **218**.

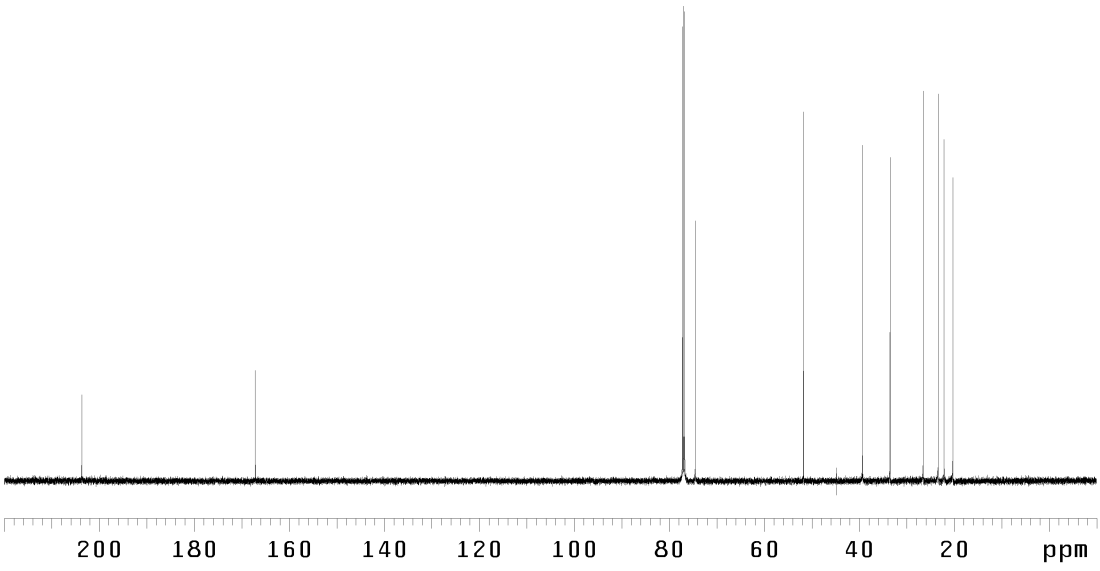


Figure A2.38.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **218**.

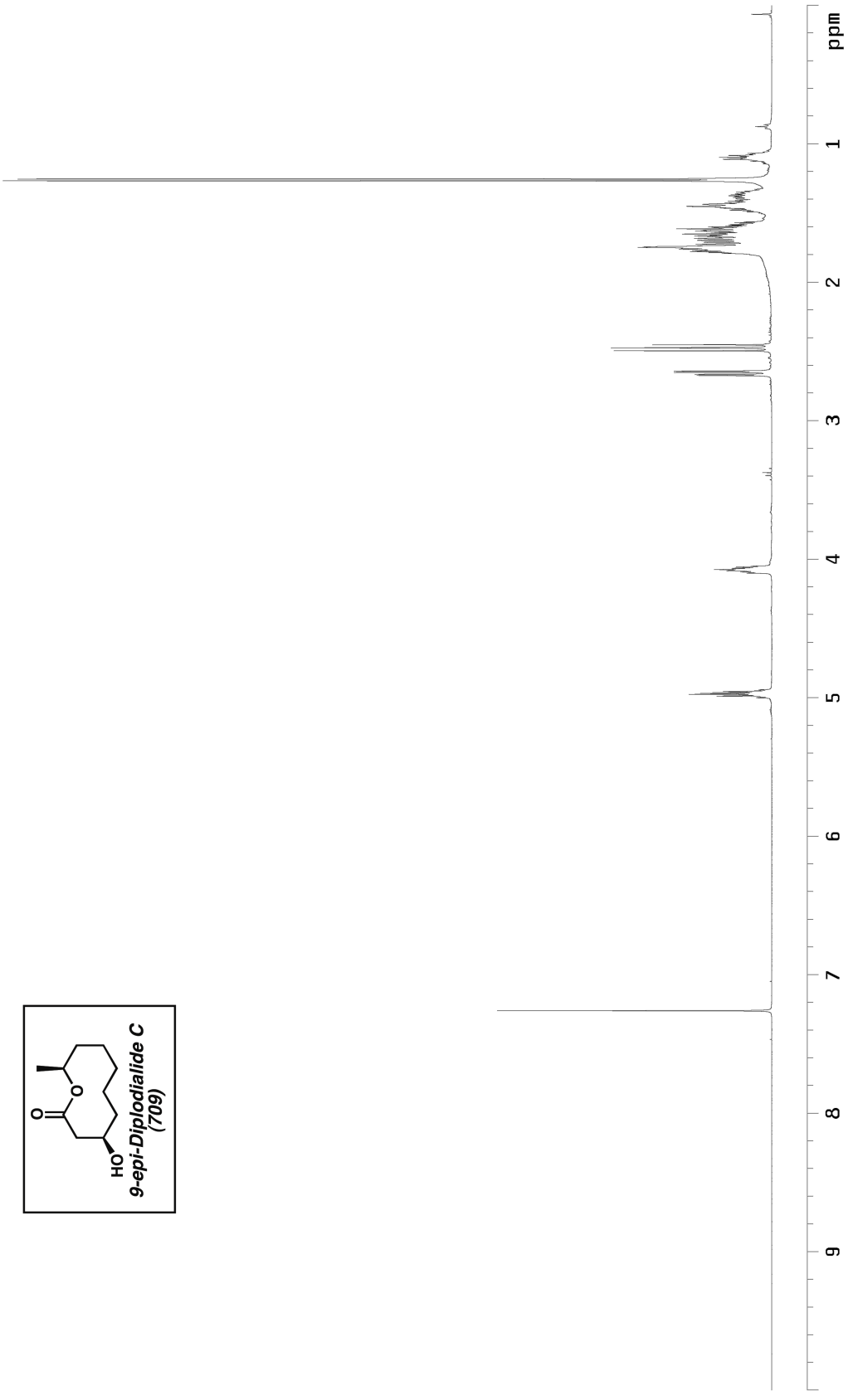


Figure A2.39.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **709**.

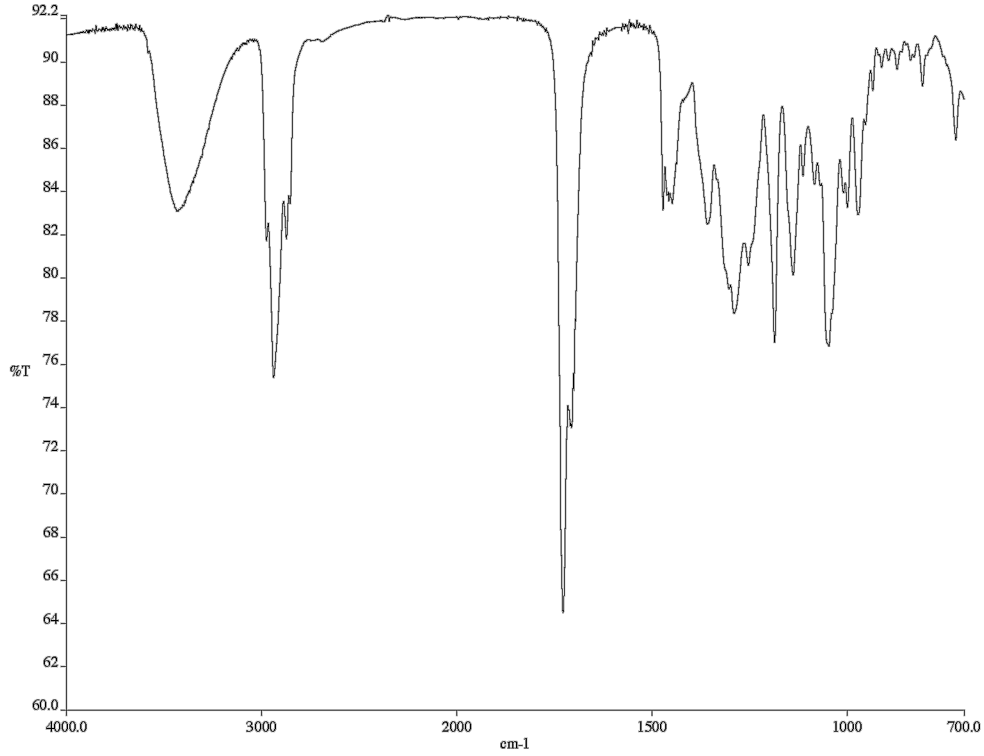


Figure A2.39.2 Infrared spectrum (thin film/NaCl) of compound **709**.

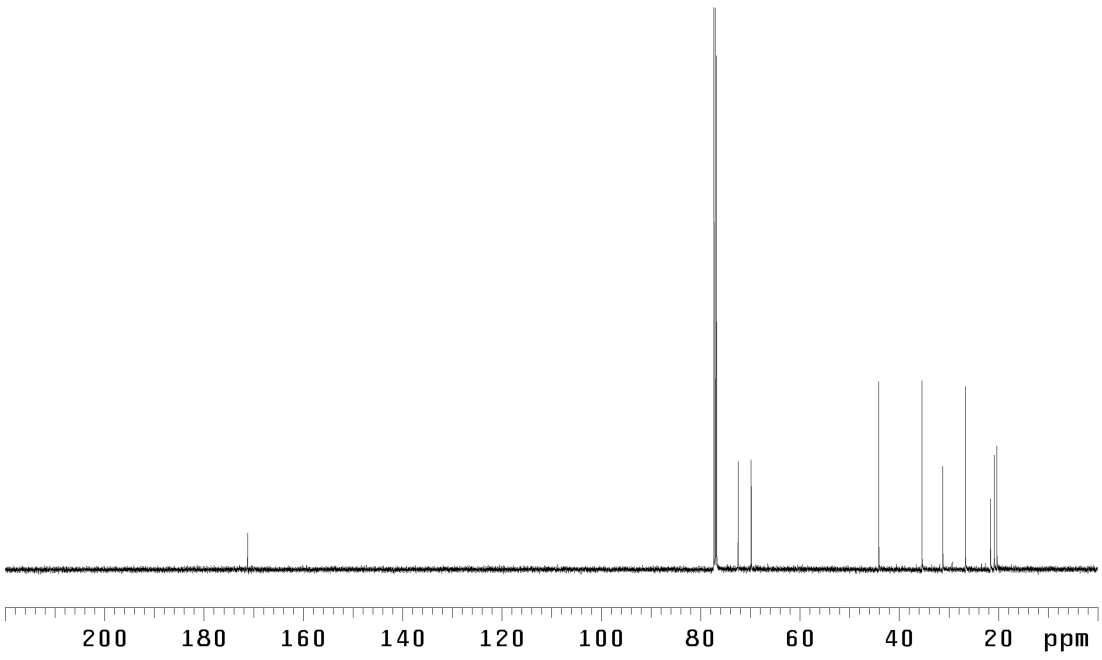


Figure A2.39.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **709**.

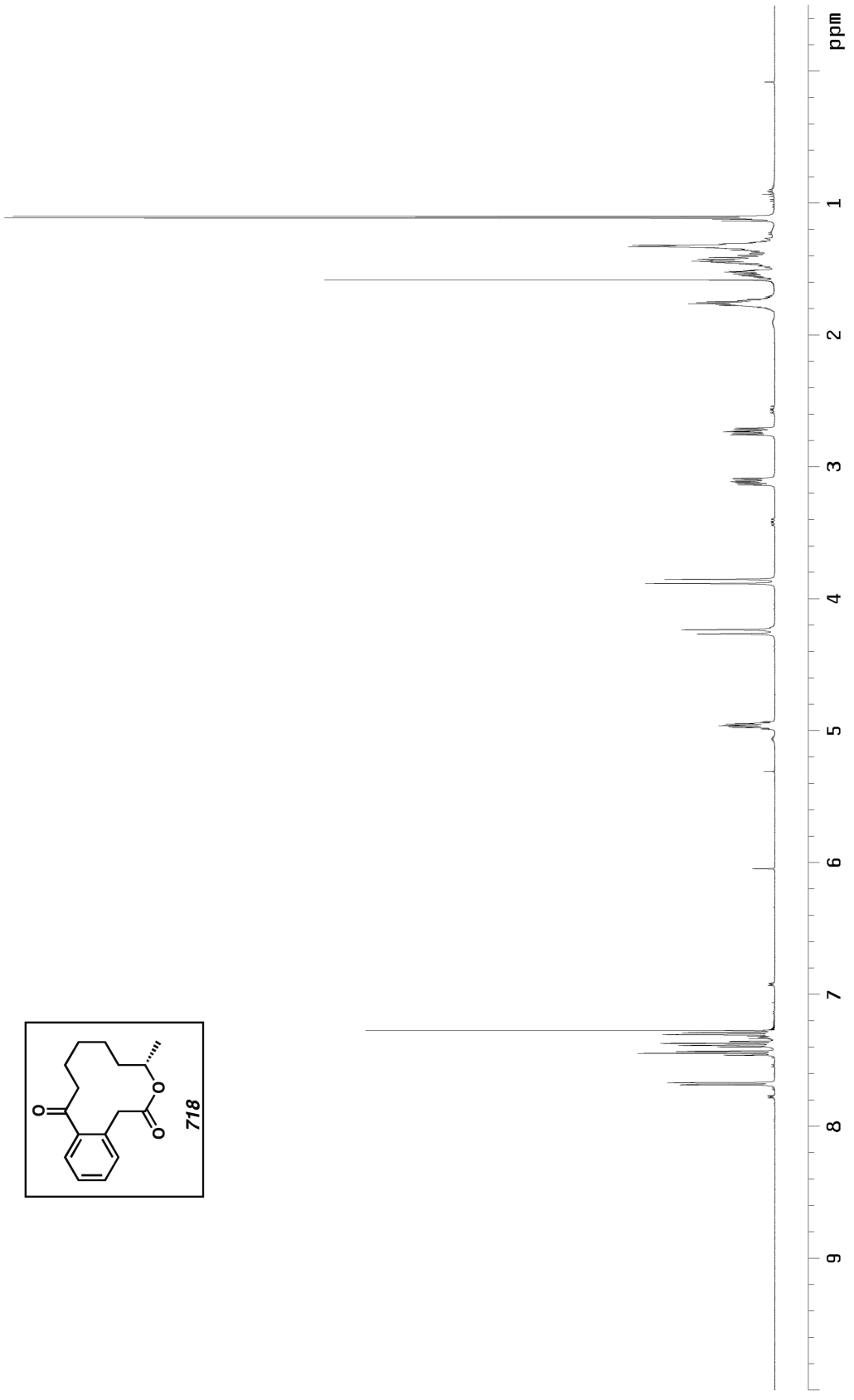


Figure A2.40.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **718**.

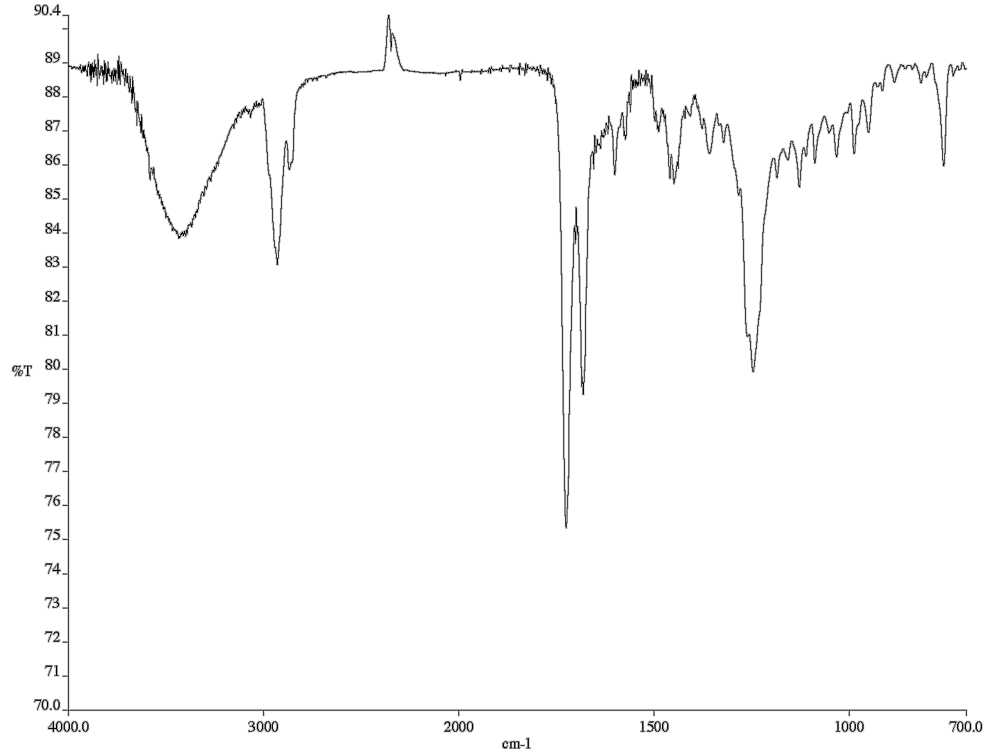


Figure A2.40.2 Infrared spectrum (thin film/NaCl) of compound **718**.

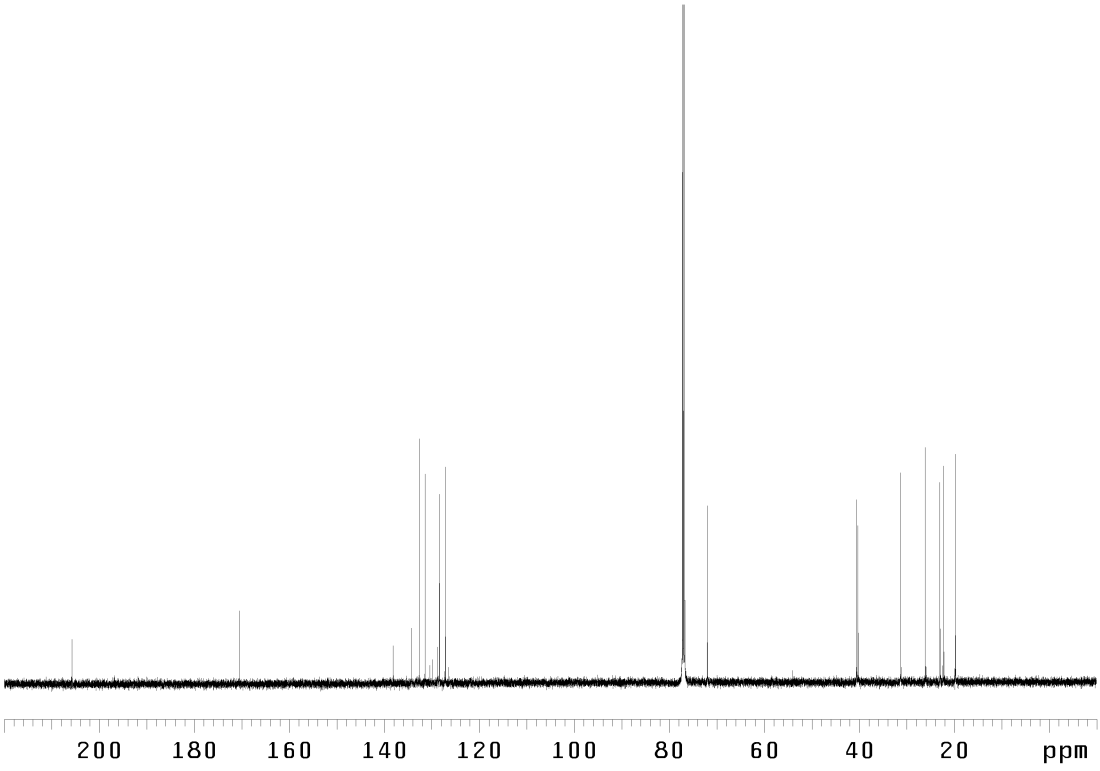


Figure A2.40.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **718**.

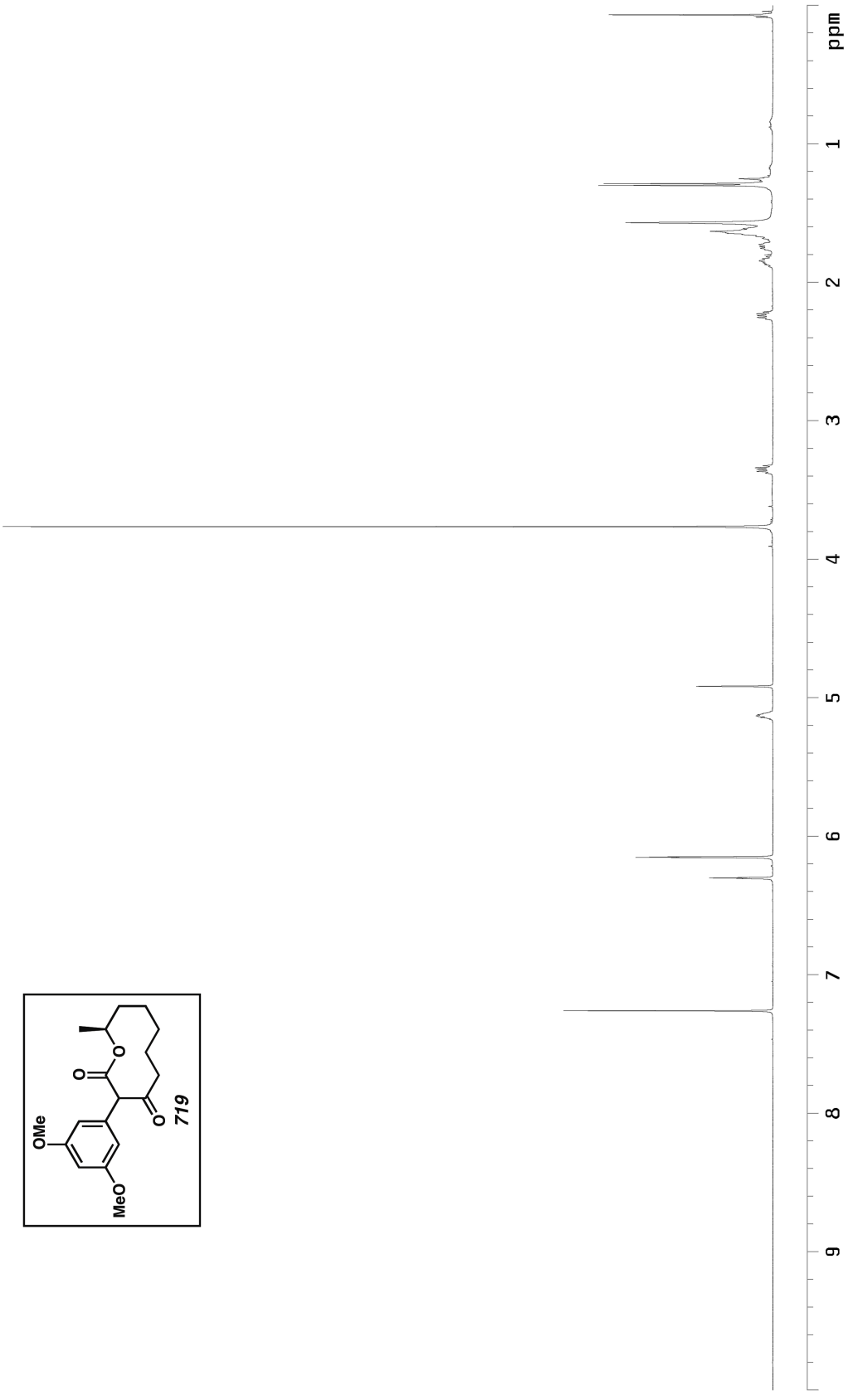


Figure A2.41.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **719**.

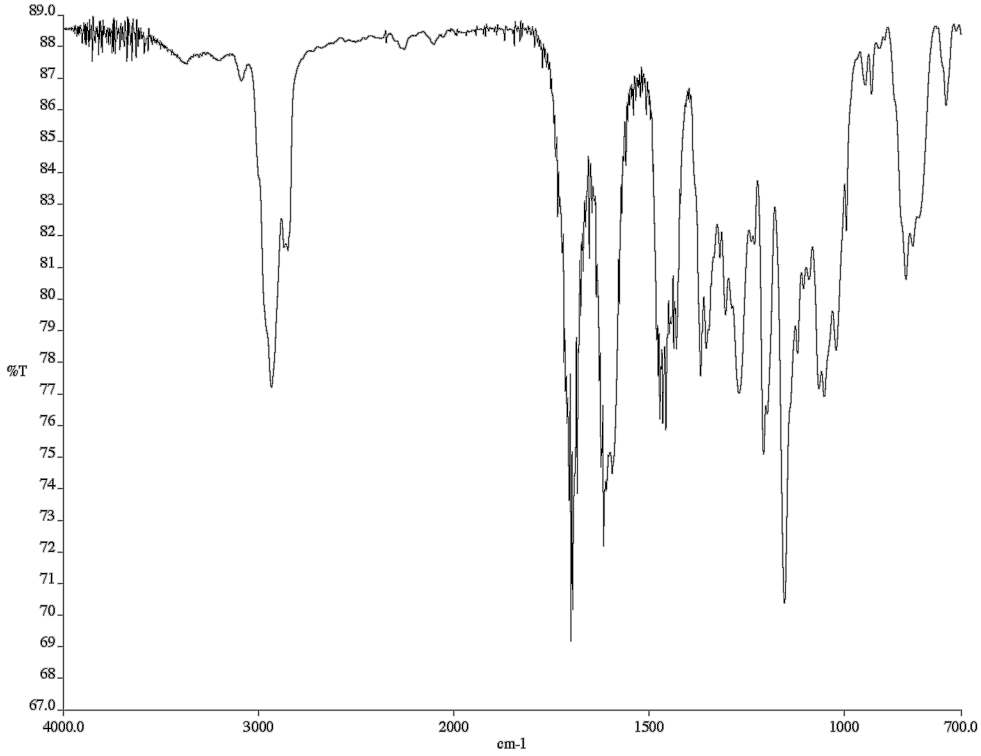


Figure A2.41.2 Infrared spectrum (thin film/NaCl) of compound **719**.

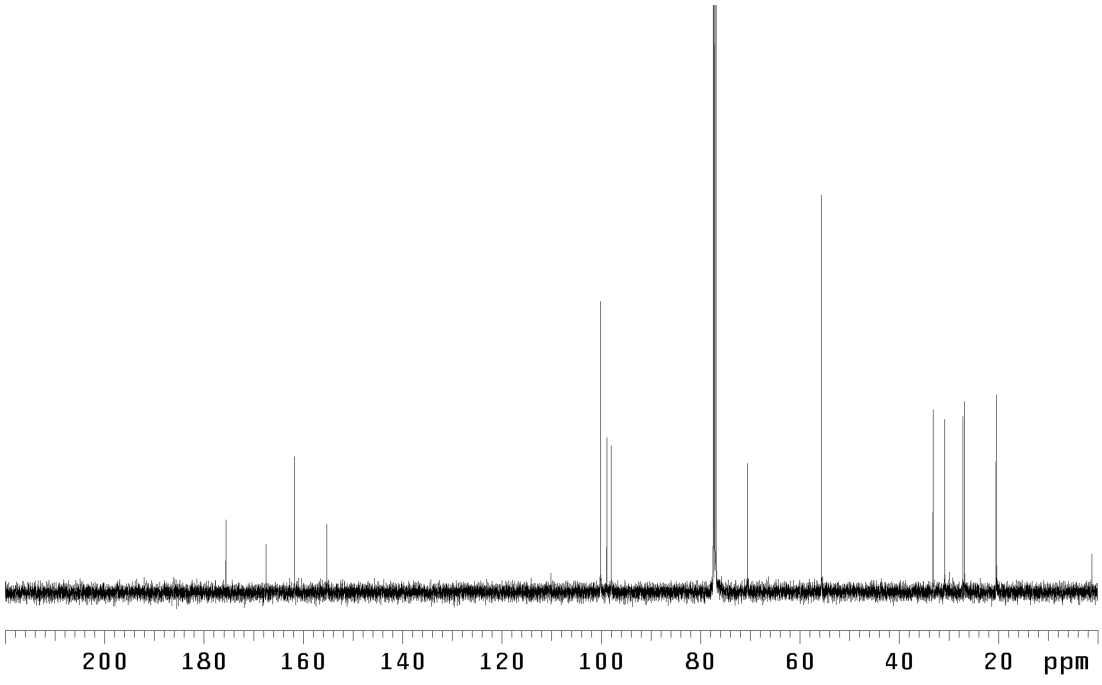


Figure A2.41.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **719**.

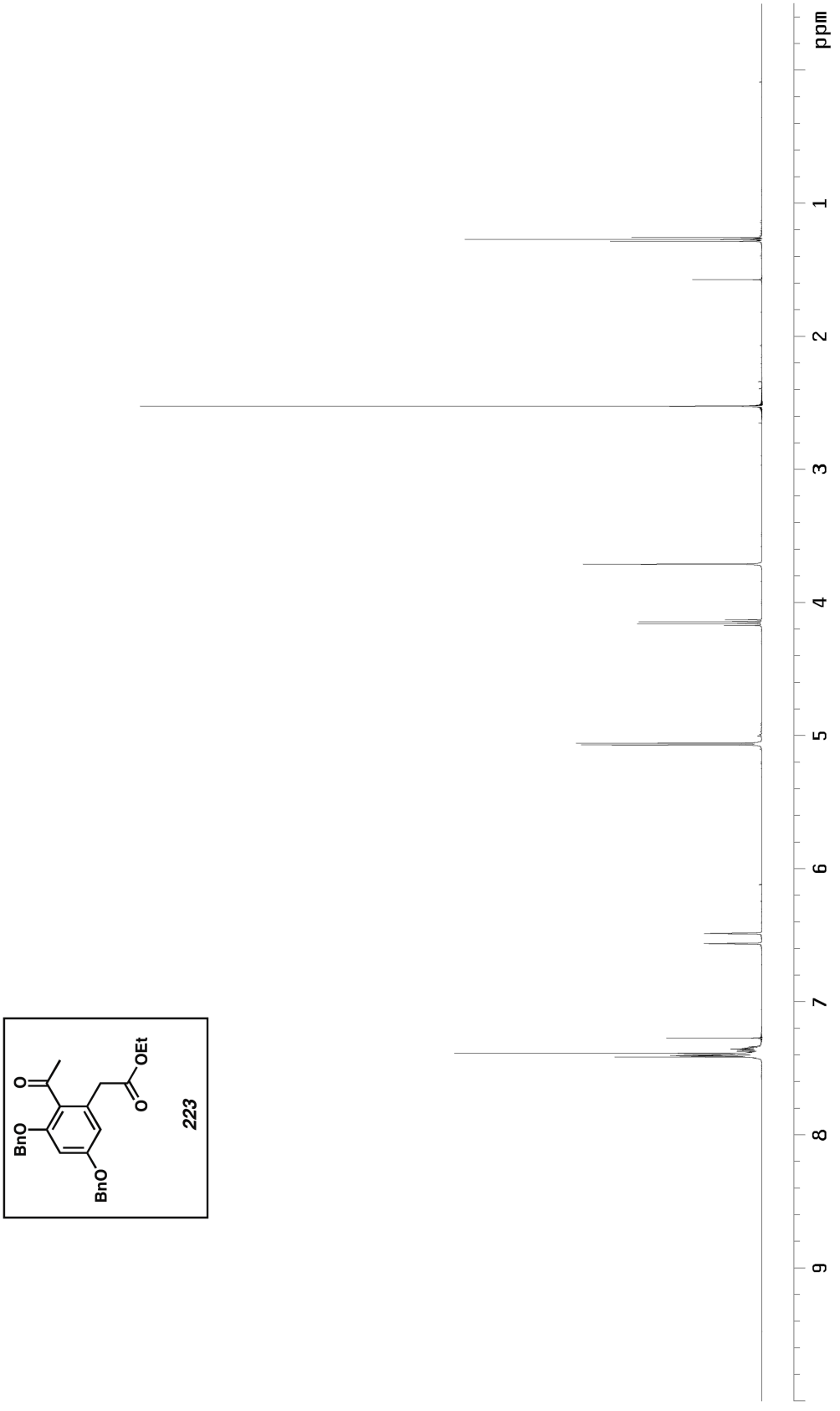


Figure A2.42.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **223**.

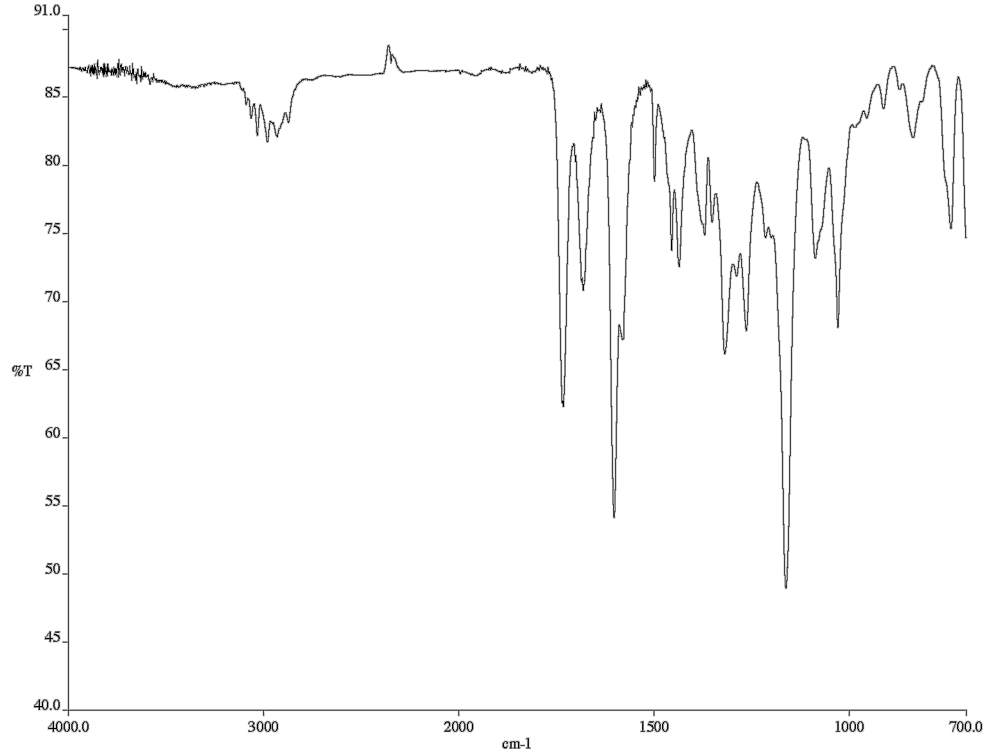


Figure A2.42.2 Infrared spectrum (thin film/NaCl) of compound **223**.

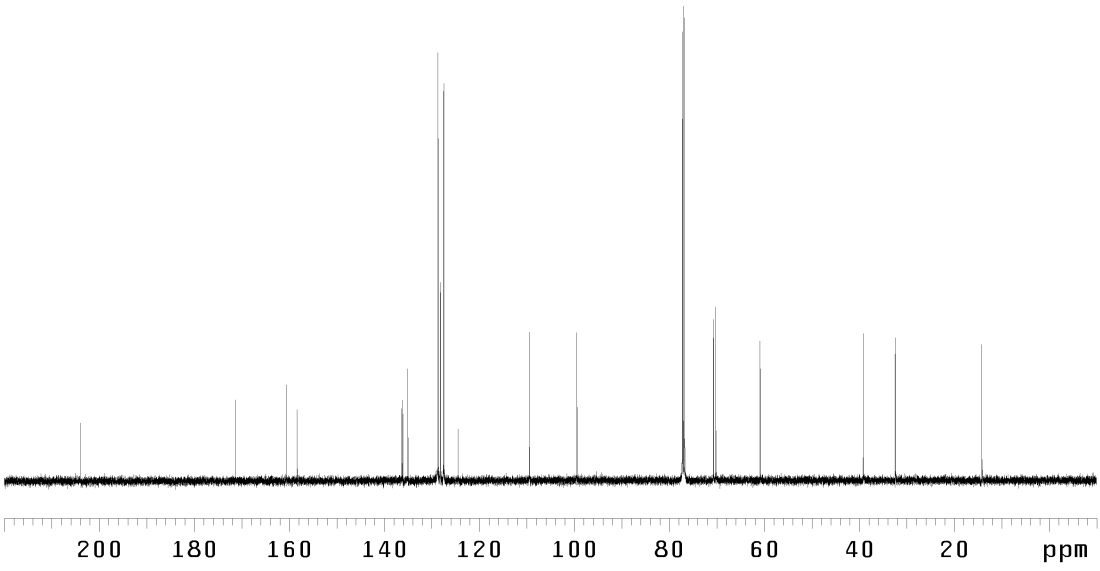


Figure A2.42.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **223**.

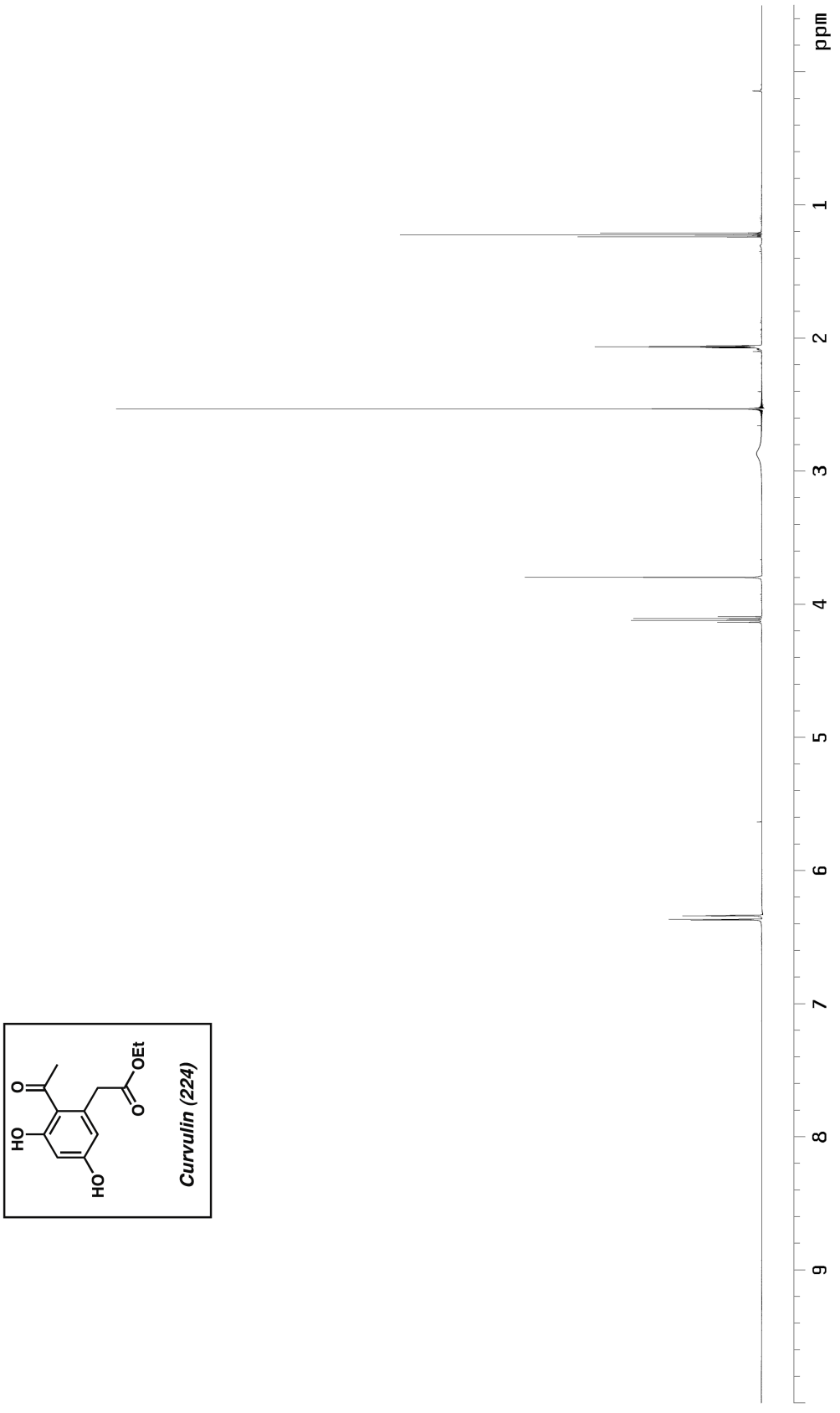


Figure A2.43.1 ^{1}H NMR (500 MHz, acetone-d_6) of compound **224**.

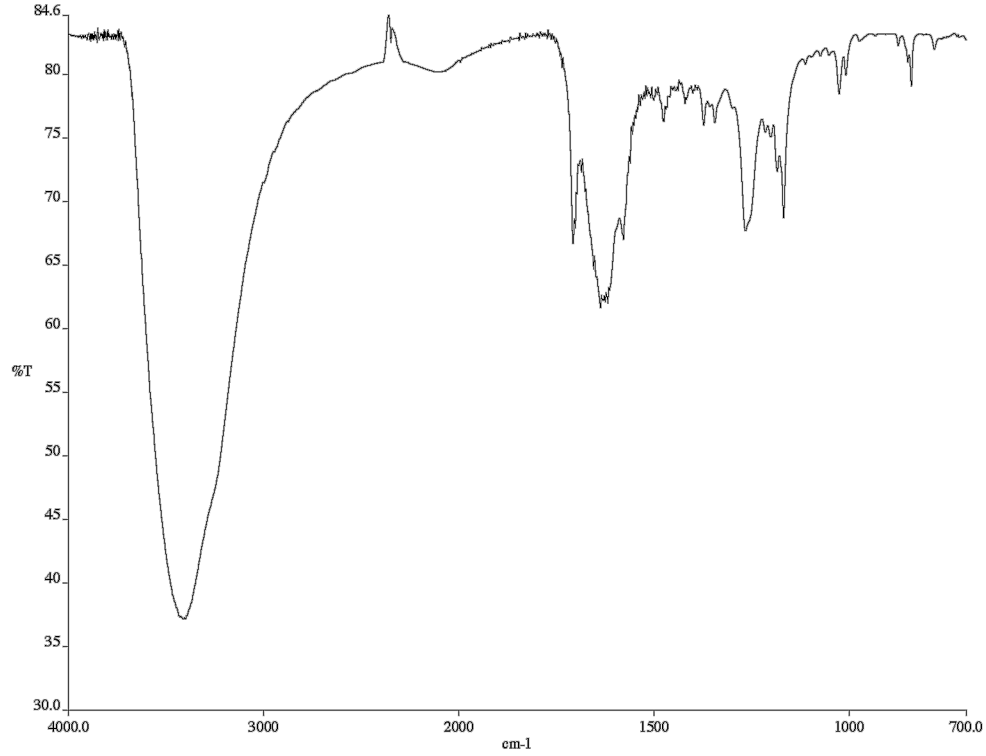


Figure A2.43.2 Infrared spectrum (thin film/NaCl) of compound **224**.

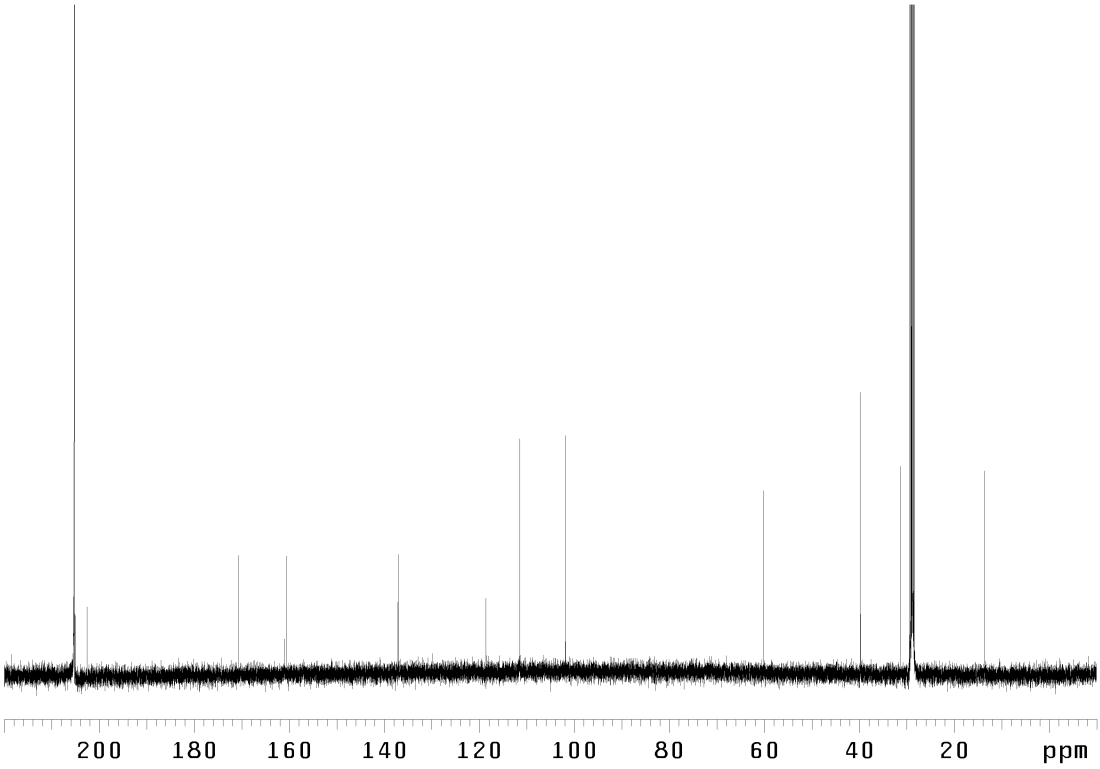


Figure A2.43.3 ^{13}C NMR (125 MHz, acetone-d_6) of compound **224**.

Figure A2.44.1 ^{1}H NMR (500 MHz, acetone-d_6) of compound **221**.

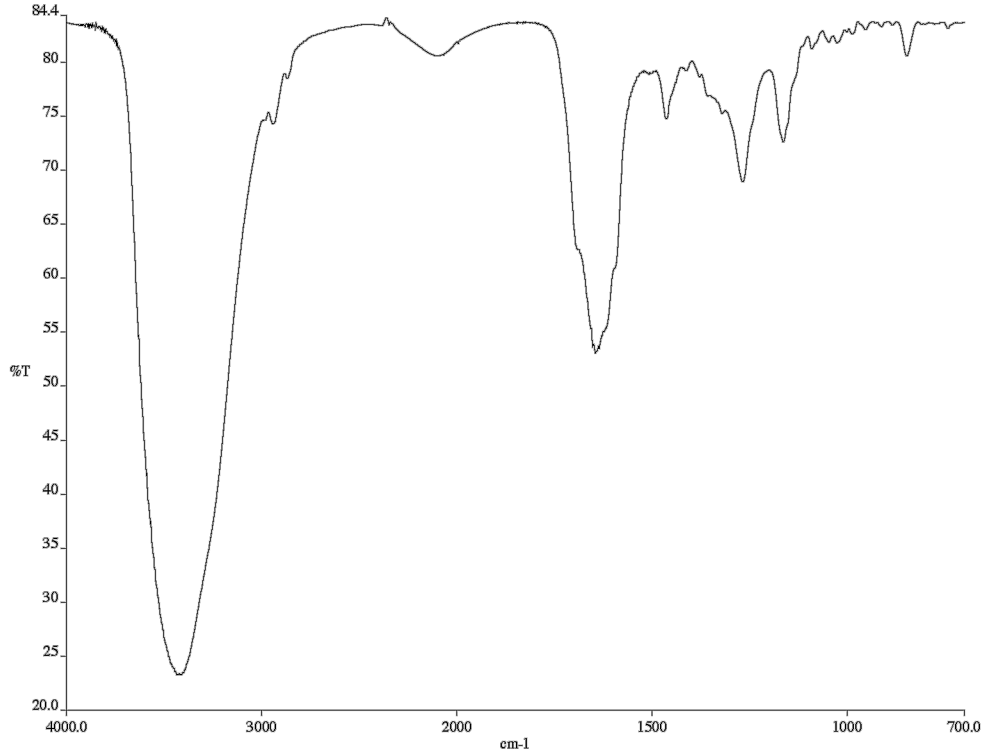


Figure A2.44.2 Infrared spectrum (thin film/NaCl) of compound **221**.

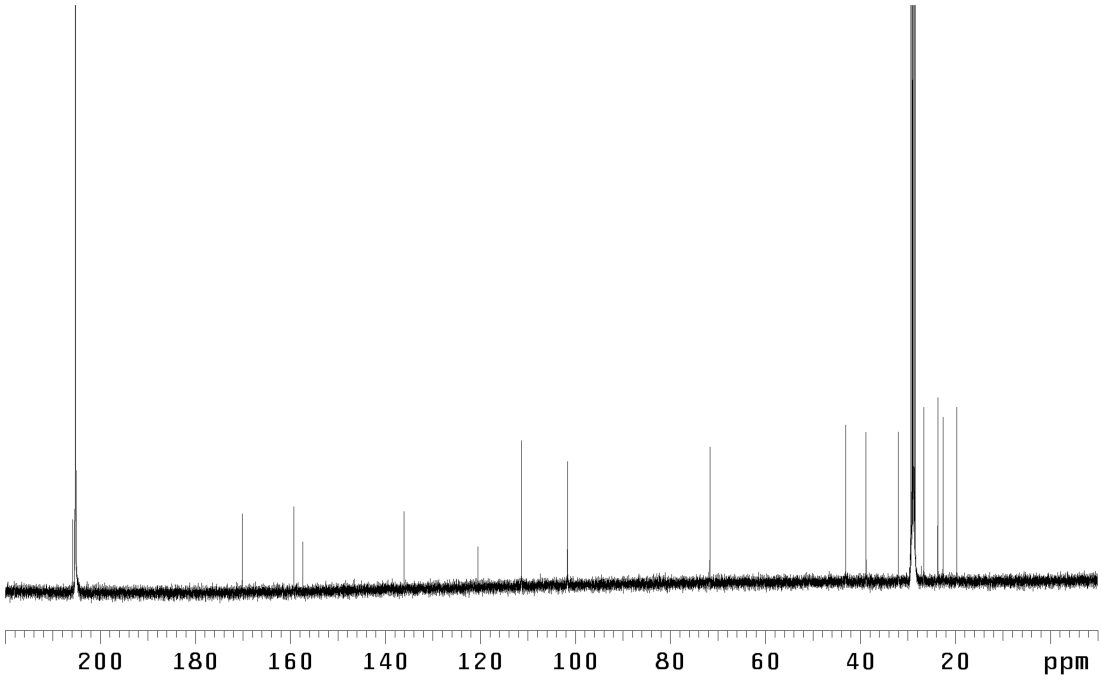


Figure A2.44.3 ^{13}C NMR (125 MHz, acetone-d_6) of compound **221**.

Chapter 3

Efforts Toward the Total Synthesis of Integrastatins A and B[†]

3.1 INTRODUCTION

Since its discovery in 1981, the United Nations and World Health Organization have estimated that HIV/AIDS has claimed more than 25 million lives, placing it among the most destructive pandemics in history.[1] With approximately 39 million people currently living with HIV/AIDS worldwide, the unabated spread of the virus is one of the most pressing issues confronting the scientific community in modern times. In 2006 alone, roughly 4.3 million people were newly infected with HIV and another 2.9 million died of the virus. The urgency of the matter is emphasized by the explosion of research over the past 25 years geared toward the development of new therapies aimed at disabling viral replicative processes. Despite this growth, novel drugs are needed to supplant the use of HIV protease and reverse transcriptase inhibitors known for numerous side effects, while minimizing the potential for the emergence of drug-resistant viral strains.

[†] The work described in this chapter was completed in collaboration with Pradeep Bugga, a former undergraduate researcher in the Stoltz group.

Toward this end, the synthesis and implementation of small molecule inhibitors has become central to the development of new chemotherapeuties. One biological target that holds particular promise for inhibiting viral replication is the enzyme HIV integrase. Because of the potential that integrase inhibitors hold for the advancement of HIV therapy, we sought to synthesize the naturally occurring integrase inhibitors integrastatin A and B, as well as related structural analogs for biological screening.

3.1.1 HIV-1 Integrase Inhibition

Current FDA-approved treatments for HIV target either the viral reverse transcriptase or protease enzymes.[2,3] Though effective, these therapies are prohibitively expensive and often lead to multidrug resistance. Additionally, the presence of equivalents of these viral enzymes within the host cell renders the leading drug regimens toxic because of their interference with normal cellular processes. For example, HAART (Highly Active Antiretroviral Therapy), the leading combination therapy for HIV treatment, is known to cause nausea, anemia, lipodystrophy and diabetes-like problems, forcing many patients to switch medications or cease use entirely.[2,3] For these reasons, there has been an ongoing search for more attractive targets for HIV chemotherapies. Over the past decade, the principle target emerging from this search has been the enzyme HIV integrase.[4]

Importantly, unlike HIV reverse transcriptase and HIV protease, HIV integrase has no host-cell equivalent, diminishing the potential for drug interference with normal cellular processes. An additional benefit of targeting integrase is emerging evidence that

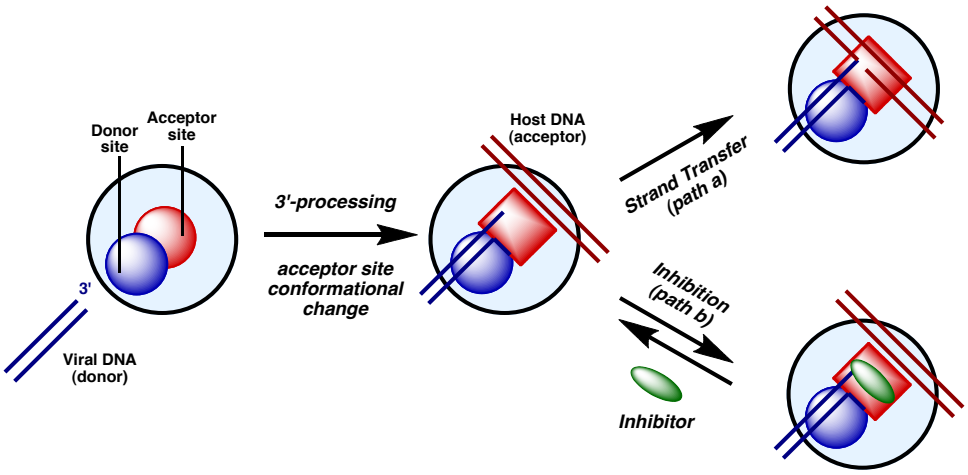
mutated forms of integrase possess reduced viral replicative fitness.[5] Thus, HIV integrase exhibits a decreased likelihood of evolving drug-resistant viral strains.

HIV integrase is responsible for transporting viral cDNA from the cytoplasm into the nucleus of the host cell, and subsequently inserting it into the host genome.[6,7] This complex and highly specialized integration process is essential for retroviral replication because transcription of viral proteins is only possible if the cDNA is fully integrated into a host chromosome. More specifically, integrase has two primary tasks: 3'-processing of viral cDNA and strand transfer of the processed cDNA into the host genome.[8] It has been shown that small-molecule inhibitors can interrupt the 3'-processing and strand-transfer steps, shutting down the HIV replication process.[4e] As a consequence, there have been increasing efforts to develop new inhibitors of integrase for biological assays and in vivo testing.

Studies have produced a general hypothesis concerning the mechanism of integrase inhibition that has aided researchers in discovering new inhibitors (Figure 3.1).[6,9,10] In the absence of an inhibitor, binding and 3'-processing of viral cDNA at the integrase donor (blue) site promotes a conformational change in the acceptor (red) site, which, in turn, allows binding of host DNA.[10] Upon host DNA binding, the strand transfer reaction occurs, inserting the viral cDNA into the host genome (path a). It is believed that some integrase inhibitors intercept the integrase-cDNA complex following the 3'-processing step and subsequent conformational shift (path b). Apparent stabilization of the pre-integration complex prevents the strand transfer reaction from occurring, effectively shutting down the integration pathway. Structural and mechanistic data have indicated that binding of the inhibitor to the pre-integration complex occurs

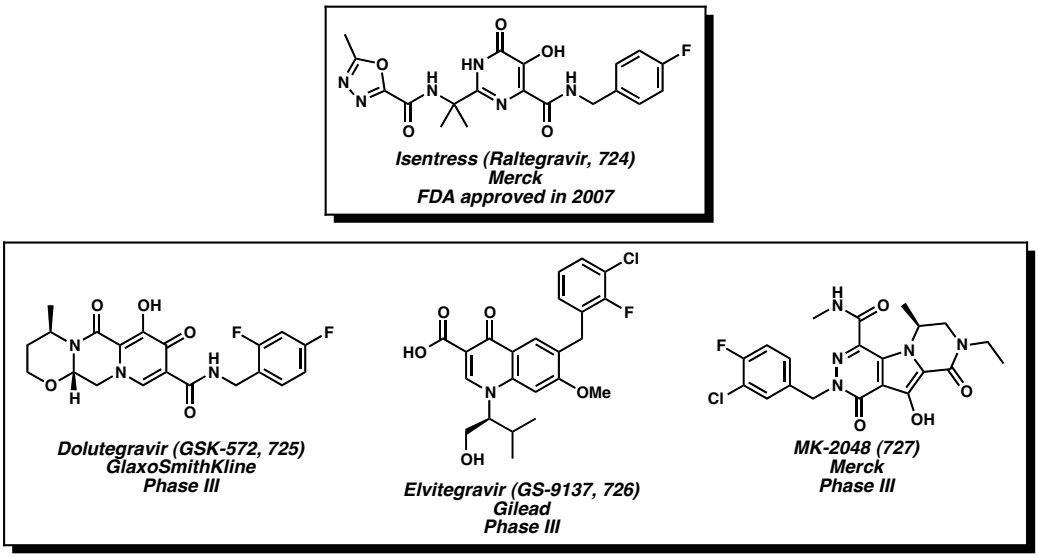
through chelation of divalent metal cofactors in integrase.[9] Since the mechanism of integrase inhibition is relatively well understood, the integrase enzyme represents an excellent target for development of HIV chemotherapy.

Figure 3.1. Proposed mechanism of action of integrase inhibitors.[6]



While there are a number of HIV reverse transcriptase inhibitors and protease inhibitors available as treatments, therapies that target HIV integrase are relatively rare.[2,3] At this time, raltegravir (Isentress, **724**), which was approved by the FDA in 2007, is the only HIV integrase inhibitor on the market (Figure 3.2).[11] Three other integrase inhibitors are currently in Phase 3 clinical trials: dolutegravir (GSK-572, **725**),[12] elvitegravir (GS-9137, **726**),[13] and MK-2048 (**727**).[14]

Figure 3.2. HIV integrase inhibitors approved by the FDA and in Phase III clinical trials.

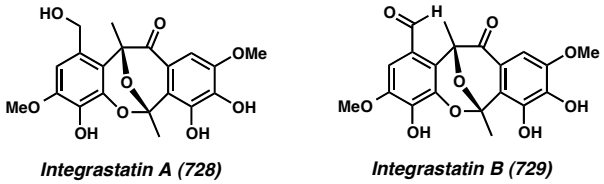


3.1.2 Integrastatins A and B: Naturally Occurring HIV Integrase Inhibitors

Natural products have historically served as excellent sources for the discovery of biologically active agents that act as the basis for lead candidates in drug development.[15] In particular, the naturally occurring compounds integrastatin A and B display inhibitory activity against HIV-1 integrase at micromolar concentrations and are thus attractive targets for new therapeutic development.[16] Synthetic access to these naturally occurring inhibitors would allow for more thorough biological testing as well as structure-activity relationship (SAR) studies to optimize potency and antiviral activity.

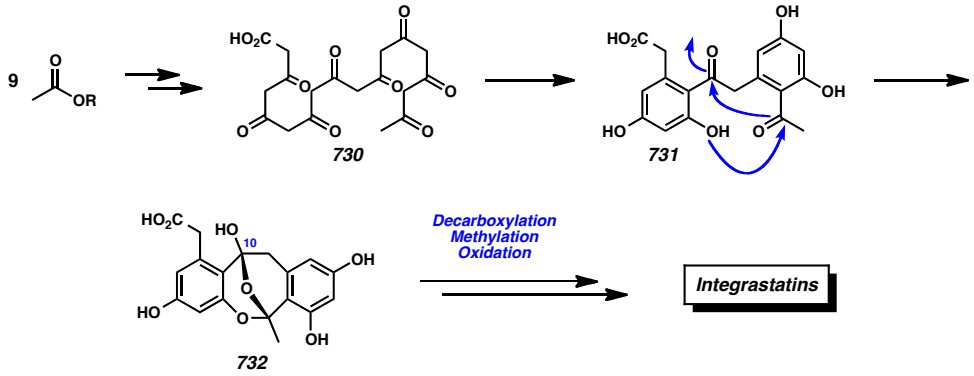
Integrastatins A (**728**) and B (**729**) were isolated as racemic compounds in 2002 from an unidentified fungus found in herbivore dung in New Mexico (Figure 3.3).[16] Both compounds display potent inhibition of the strand transfer reaction of recombinant HIV-1 integrase at micromolar concentrations. IC_{50} values for integrastatin A and B are 1.1 μM and 2.5 μM, respectively.

*Figure 3.3. Integrastatins A (**728**) and B (**729**).*



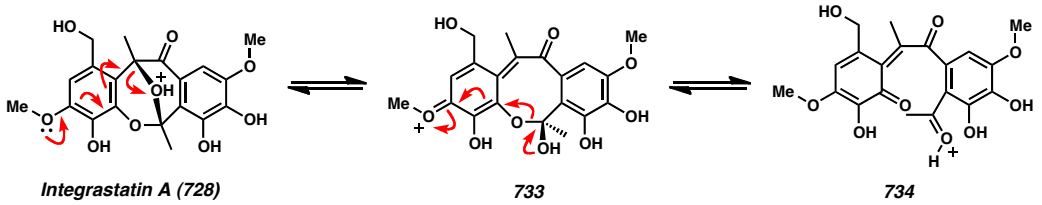
Biosynthetically, the integrastatins are believed to arise from a polyketide pathway by condensation of nine acetate units (Scheme 3.1).[16] Subsequent decarboxylation, methylation at C(10), and oxidation of the putative intermediate (**732**) result in formation of the integrastatins.

Scheme 3.1. Proposed biosynthesis of the integrastatins.

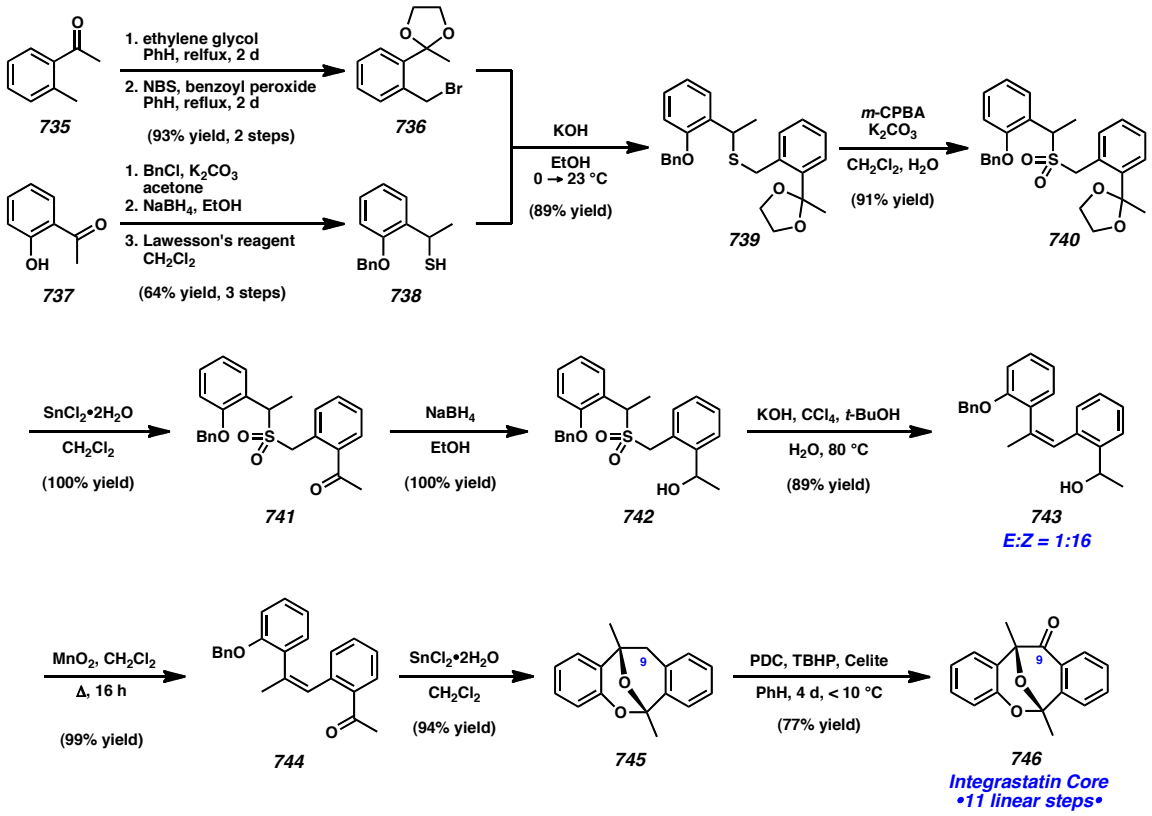


Their isolation as racemic compounds invites the question of whether the integrastatins are biosynthetically produced racemically or whether this racemization occurs in vivo *after* enantioselective biosynthesis. A third possibility is that racemization occurrs in vitro upon isolation. One potential racemization pathway would involve the achiral intermediate **734** (Scheme 3.2). We believe that total syntheses of these compounds will shed more light on this peculiarity.

Scheme 3.2. Potential racemization pathway for integrastatins A and B (only integrastatin A shown).

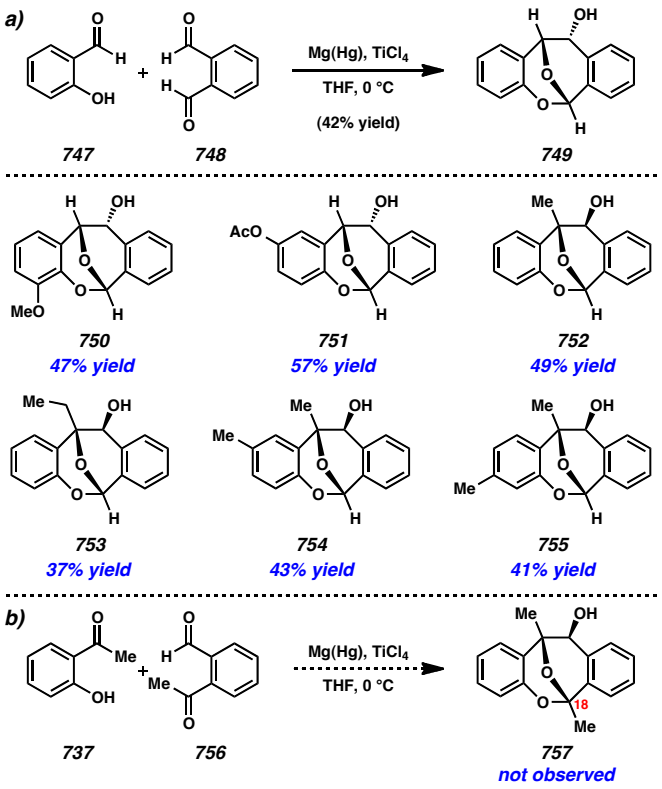

HO
Me
O
OH
Me
OH
OH
OH

*Scheme 3.3. Taylor and co-workers' synthesis of the integrastatin core (**746**).*



Following the efforts of Taylor and co-workers, the Ramana group reported a one-step synthesis of tetracycle **749** that relies upon a pinacol coupling to unite two aromatic fragments (**747** and **748**) (Scheme 3.4a).[18] In the event, treatment of *o*-phthalaldehyde (**748**) and *o*-hydroxybenzaldehyde (**747**) with Mg(Hg) and $TiCl_4$ in THF at 0 °C produced tetracycle **749** in 42% isolated yield. The authors note that the reaction generally results in a complex mixture of compounds, including homocoupled products. While this process permits some variation of substitution around the core structure, use of 2-formylacetophenone (**756**) in the pinacol coupling, which would install the methyl group corresponding to C(18) of integrastatin, failed to provide tetracycle **757** (Scheme 3.4b).

*Scheme 3.4. a) Ramana and co-workers' synthesis of tetracycle **749** and analogs, and b) failed pinacol coupling of 2-formylacetophenone (**756**).*



3.2 AN ARYNE ACYL-ALKYLATION APPROACH TO INTEGRASTATINS A AND B

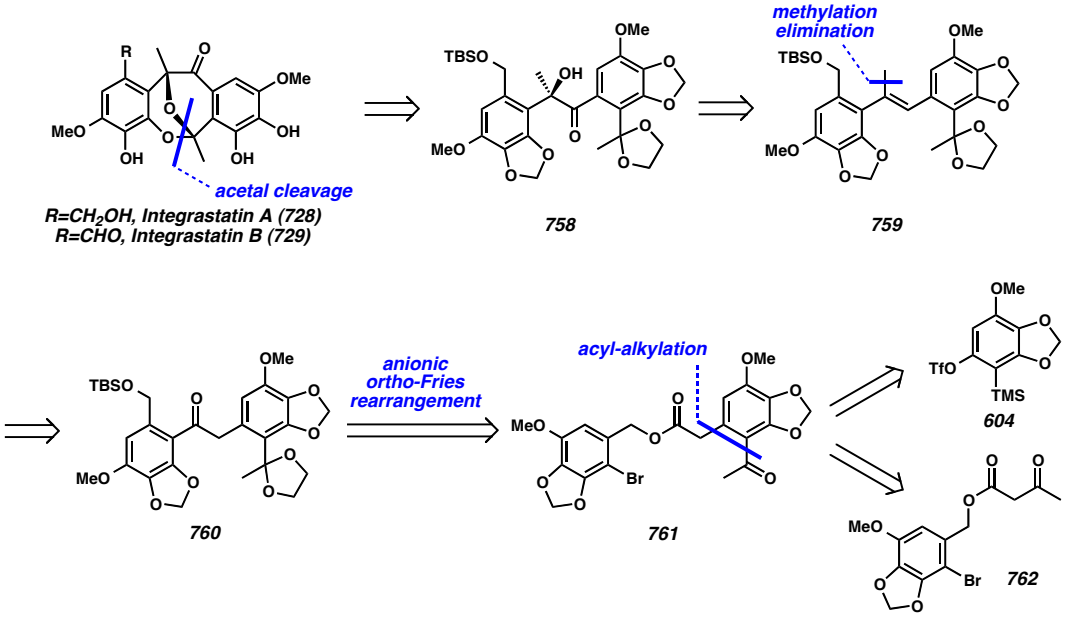
3.2.1 Strategy and Retrosynthesis

Our initial efforts toward a synthesis of integrastatins A and B (**728** and **729**) focused on application of an acyl-alkylation reaction to convergently unify two highly functionalized aromatic fragments. This strategy would allow for a concise synthesis that is amenable to analog synthesis.

Retrosynthetically, disconnection of the natural products along the acetal of the central [3.3.1]-dioxabicycle leads back to α-hydroxyketone **758** containing appropriately protected catechol and ketone groups (Scheme 3.5). We anticipated that the

α-hydroxyketone functionality could be derived from stilbene **759**, which would, in turn, be available from benzyl ketone **760**. In one of the key transformations, benzyl ketone **760** would be the result of an anionic *ortho*-Fries-type rearrangement of acyl-alkylation product **761**. Finally, ketoester **761** could arise from acyl-alkylation of silyl aryl triflate **604** with β-ketoester **762**.

*Scheme 3.5. Retrosynthetic analysis of integrastatins A (**728**) and B (**729**).*

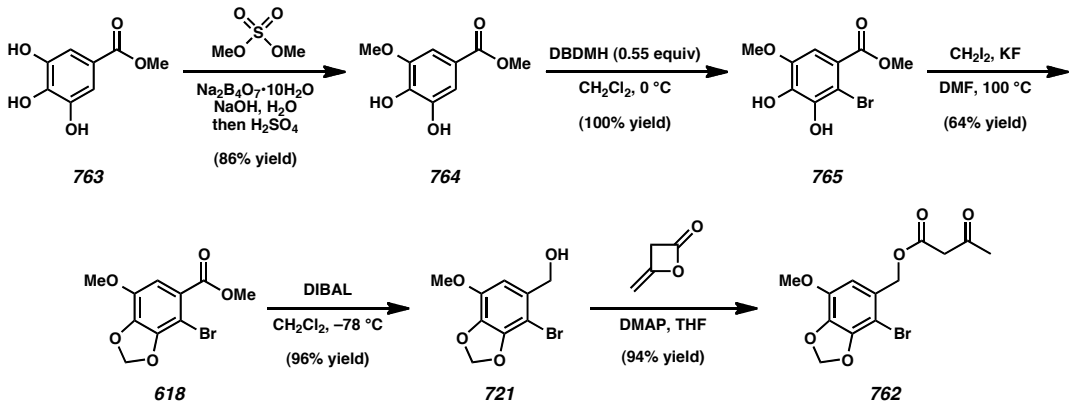


The proposed route tackles a number of the synthetic challenges presented by the integrastatins, such as the acid-sensitive acetal that forms the central [3.3.1]-dioxabicycle. The potential for racemization and the lability of this group will mandate its late installation. Additionally, the phenol moieties on both rings will require appropriate protection throughout the synthesis to avoid unwanted oxidation to *ortho*-quinones. Finally, the unsymmetrical pattern of oxygenation on the aryl rings is a significant difficulty, but will be well addressed by our unique approach.

3.2.2 Aryne Acyl-Alkylation Approach

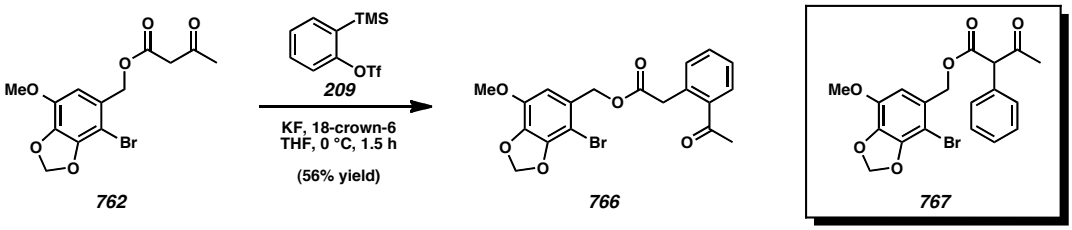
Our synthesis commenced with preparation of β-ketoester **762** beginning with commercially available methyl gallate (**763**) (Scheme 3.6). Mono-methylation using borax with dimethyl sulfate provided the methyl gallate methyl ether (**764**) in 86% yield.[19] Selective bromination of the 6-position of the arene was accomplished in quantitative yield using the mild electrophilic bromine source *N*,*N*'-dibromodimethylhydantoin (DBDMH) to generate bromoarene **765**.[20] At this point, the catechol moiety was protected with diiodomethane using KF as a base, producing methylenedioxy arene **618** in 64% yield. In the final two steps of the sequence, the methyl ester was fully reduced with diisobutyl aluminum hydride (DIBAL) to the primary alcohol, which was subsequently acylated with diketene to give the desired β-ketoester (**762**). Using this optimized procedure, we have been able to carry out this process on 25-gram scale to generate large quantities of β-ketoester **762** for acyl-alkylation studies.

*Scheme 3.6. Synthesis of β-ketoester **762** from methyl gallate (**763**).*



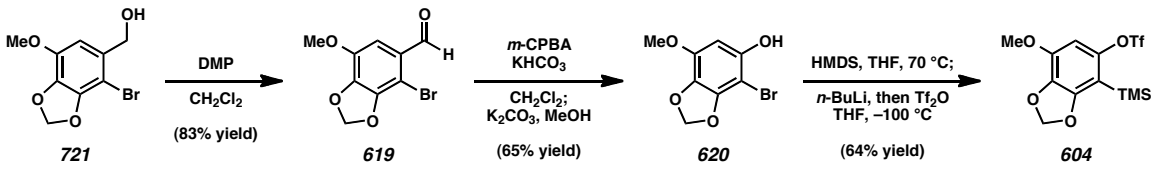
In order to test the viability of β-ketoester **762** in the aryne insertion reaction, we examined a model acyl-alkylation reaction using an unfunctionalized benzyne precursor (**209**) (Scheme 3.7). To our delight, reaction of β-ketoester **762** with aryne precursor **209** in the presence of KF and 18-crown-6 led to formation of aryne insertion product **766** in 56% yield (unoptimized). It is worth noting that the use of KF and 18-crown-6 as the fluoride source significantly suppressed the formation of the α-arylation side product (**767**) in this reaction. Additionally, we found that lower temperatures were required since rapid decomposition of β-ketoester **762** was observed at elevated and room temperatures under the reaction conditions.

*Scheme 3.7. Acyl-alkylation of β-ketoester **762** with silyl aryl triflate **209**.*



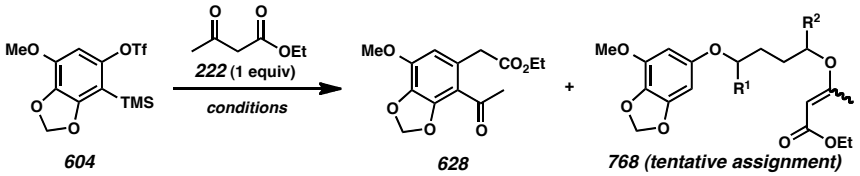
With β-ketoester **762** in hand, we turned our attention to preparation of silyl aryl triflate **604** by a route divergent from the synthesis of β-ketoester **762** (Scheme 3.8). In this way, we can exploit the similar substitution patterns on the aromatic rings of the integrastatins to derive both silyl aryl triflate **604** and β-ketoester **762** from benzyl alcohol **721**. Beginning with benzyl alcohol **721**, oxidation with Dess–Martin periodinane resulted in aldehyde **619**. Subsequent Baeyer–Villiger oxidation of the aldehyde followed by basic methanolysis generated bromophenol **620**, which was then converted to silyl aryl triflate **604** by a known procedure.[21]

*Scheme 3.8. Preparation of silyl aryl triflate **604** from benzyl alcohol **721**.*



Prior to investigating the acyl-alkylation of silyl aryl triflate **604** with β-ketoester **762**, simpler β-ketoester substrates were examined. We first attempted to demonstrate its ability to participate in a model acyl-alkylation with ethyl acetoacetate (**222**) under standard conditions using CsF in MeCN at 80 °C (Table 3.1, entry 1). As has been shown previously in related systems, the acyl-alkylation proceeded regioselectively to give a single isomer (**628**).[2] However, the low isolated yield of **628** prompted us to examine alternative fluoride sources and solvents for this transformation. When using KF/18-crown-6 in THF at room temperature, the only observed product was THF ring-opened enol ether **768** (R^1,R^2 = H, entry 2). Attempts to circumvent this pathway by using 2-Me-THF were also complicated by ring-opened products **768** (R^1 = H, R^2 = Me and R^1=Me, R^2 = H, entry 3). In general, arynes derived from silyl aryl triflates possessing high degrees of oxygenation appear to have a higher propensity for reaction with THF and its substituted variants. In an effort to circumvent this difficulty, we turned our attention to acyclic ethereal solvents that might be less likely to add to the reactive aryne bond (entries 4–7). After much optimization, we found that KF/18-crown-6 in *tert*-butyl methyl ether (TBME) produced the corresponding acyl-alkylation product (**628**) in the best yield and without any ether addition side products (entry 6).

*Table 3.1. Acyl-alkylation reactions of silyl aryl triflate **604** and ethyl acetoacetate (**222**).*



604 ***628*** ***768 (tentative assignment)***

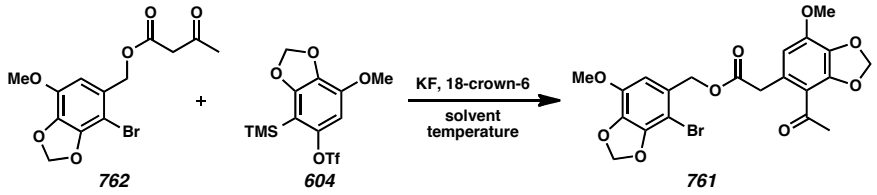
Entry	Fluoride Source[a]	Solvent[b]	Temperature	Yield **628**	Yield **768**[c]
1	CsF	MeCN	80 °C	18%	–
2	KF/18-crown-6	THF	23 °C	–	>60% (R^1, R^2 = H)
3	KF/18-crown-6	2-Me-THF	23 °C	–	28% (R^1 = H, R^2 = Me) 2% (R^1=Me, R^2 = H)
4	KF/18-crown-6	DME	23 °C	–	–
5	KF/18-crown-6	TBME	23 °C	36%	–
6	KF/18-crown-6	TBME	23 °C	45%[d]	–
7	KF/18-crown-6	TBME	40 °C	45%[e]	–

[a] All reactions run with 3.0 equiv of indicated fluoride source and 1.25 equiv **604**. [b] All reactions run 0.1 M **604** in indicated solvent. [c] Isolated as a single unassigned enol ether isomer. [d] Reaction run with 2.0 equiv **604**. [e] Reaction run with 3.0 equiv **604**.

Despite the success of these model reactions, acyl-alkylations of silyl aryl triflate **604** with β-ketoester **762** proved to be a significant challenge (Table 3.2). We were faced initially with the prospect of reconciling the high temperatures required for efficient reaction of silyl aryl triflate **604** with the low reaction temperatures required to prevent decomposition of β-ketoester **762** under the reaction conditions. In all cases, KF and 18-crown-6 served as the fluoride source while the solvent and reaction temperature were varied. In THF at 0 °C (entry 1), decomposition of β-ketoester **762** was not an issue; however, ring-opening of the solvent was problematic. Control experiments showed that β-ketoester **762** was stable to the fluoride source in TBME over a range of temperatures up to 50 °C. However, reactions with silyl aryl triflate **604** in TBME at 0 °C, 23 °C, and 40 °C showed no consumption of β-ketoester **762** (entries 2–4). Similar results were seen

with Et_2O as solvent (entry 5). Ultimately, only traces of the desired acyl-alkylation product (**761**) of silyl aryl triflate **604** and β-ketoester **762** were ever observed.

*Table 3.2. Attempted acyl-alkylations of silyl aryl triflate **604** with β-ketoester **762**.*

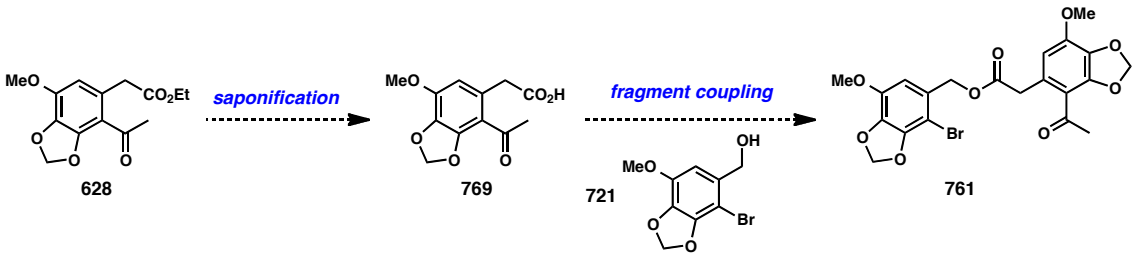


Entry[a]	Solvent[b]	Temperature
1	THF	0 °C
2	TBME	0 °C
3	TBME	23 °C
4	TBME	40 °C
5	Et_2O	23 °C

[a] All reactions run with 3.0 equiv each of KF and 18-crown-6 and 1.25 equiv **604**. [b] All reactions run 0.1 M **604** in indicated solvent.

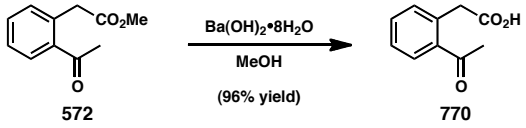
Although ketoester **761** was not available by direct acyl-alkylation of silyl aryl triflate **604** with β-ketoester **762**, we did have an alternative route by which to access this key intermediate. Saponification of ketoester **628**, resulting from reaction of silyl aryl triflate **604** with ethylacetoacetate (**222**), followed by coupling to benzyl alcohol **721** would generate acyl-alkylation product **761** (Scheme 3.9).

*Scheme 3.9. Alternative synthesis of acyl-alkylation product **761**.*



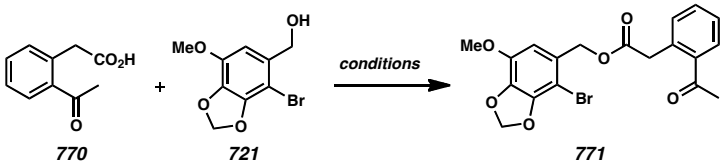
Saponification and coupling were initially investigated on ketoester **572** in order to conserve material. The saponification of acyl-alkylation products, such as ketoester **572**, was somewhat problematic initially due to the propensity of these substrates to undergo Dieckmann cyclizations under basic conditions. Most standard bases for this transformation, including carbonates and many hydroxides, failed to produce carboxylic acid **770**. Following an extensive screen of mild conditions for saponification, we found that $Ba(OH)_2 \bullet 8H_2O$ in methanol produced the corresponding carboxylic acid (**770**) in almost quantitative yield (Scheme 3.10).

*Scheme 3.10. Mild saponification of acyl-alkylation product **572**.*



A number of conditions were examined for coupling of carboxylic acid **770** with benzyl alcohol **721** including acid chloride couplings, Mitsunobu reactions, and standard peptide coupling conditions (Table 3.3). Ultimately, the best results were obtained by treatment of benzylic alcohol **721** with DIAD and PPh_3 followed by addition of the carboxylic acid nucleophile (**770**) to provide ester **771** in a modest 30% yield (entry 4). Unfortunately this success did not translate to preparation of acyl-alkylation product **761** containing the fully elaborated aromatic rings. In fact, even saponification of ketoester **628** was unsuccessful with our optimized conditions.

*Table 3.3. Attempted couplings of carboxylic acid **770** and benzyl alcohol **721**.*



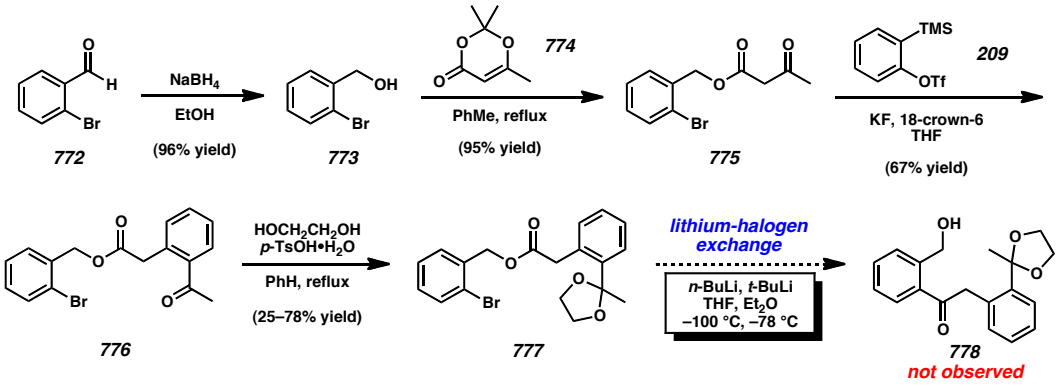
770 ***721*** ***771***

entry	conditions	result
1	acid **770** + $SOCl_2$ in CH_2Cl_2 then alcohol **721**, 40 °C	–
2	acid **770** + $SOCl_2$ and DMF in CH_2Cl_2 then alcohol **721**	< 5%
3	acid **770** + $(COCl)_2$ and DMF in CH_2Cl_2 then alcohol **721**, 40 °C	< 5%
4	alcohol **721** + DIAD and PPh_3 in THF then acid **770**, 65 °C	30%
5	EDC and DMAP in DMF	< 5%
6	acid **770** + isobutyl chloroformate and *N*-methyl morpholine in CH_2Cl_2 then alcohol **721**	< 5%

Concurrent with our efforts to construct ketoester **761**, we investigated the proposed anionic *ortho*-Fries-type rearrangement in the context of a simpler model system lacking the extensive aromatic functionalization (Scheme 3.11). Beginning with 2-bromobenzaldehyde (**772**), reduction with sodium borohydride followed by acylation with the diketene acetone adduct (**774**) provided model β-ketoester **775** in excellent yield. Compared to β-ketoester **762**, this model compound (**775**) exhibits excellent stability over a wide temperature range in the presence of various fluoride sources. Upon treatment of the model β-ketoester (**775**) with the parent silyl aryl triflate (**209**) in the presence of KF and 18-crown-6, acyl-alkylation product **776** was formed in 67% yield. Acetalization of acyl-alkylation product **776** with ethylene glycol was inconsistent and often resulted in variable yield of acetal **777**. While acetal **777** could be rapidly accessed in good quantities, all attempts to effect the anionic *ortho*-Fries-type rearrangement under lithium-halogen exchange conditions failed to produce the desired product (**778**). In most

cases, reactions either returned starting material or butylated side products (when *n*-BuLi was used).

Scheme 3.11. Attempted model anionic ortho-Fries-type rearrangement.



Given the complex difficulties encountered during our investigations into this strategy toward integrastatins A and B, at this juncture we elected to pursue an alternative route toward the natural products. Importantly, this new strategy would make use of many of the valuable intermediates that had already been prepared, some in significant quantity. Furthermore, in devising an alternative approach to the integrastatins, we sought to shorten the synthesis as well.

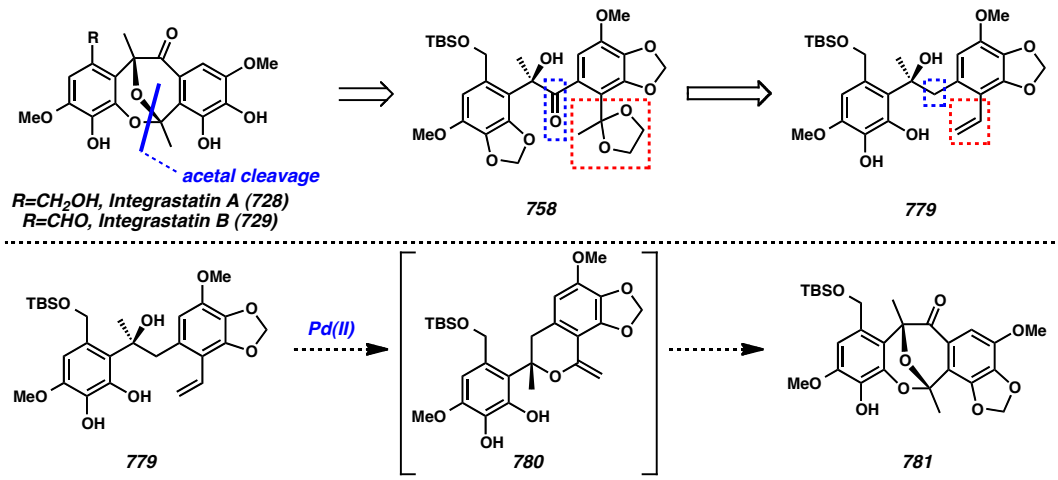
3.3 AN OXIDATIVE CYCLIZATION APPROACH TO INTEGRASTATINS A AND B

3.3.1 Strategy and Retrosynthesis

In redesigning our approach to the integrastatins, we again focused our attention on a key α-hydroxyketone intermediate bearing two fully functionalized aromatic rings (**758**) (Scheme 3.12). Given the difficulty experienced in accessing this structure by an

anionic *ortho*-Fries-type rearrangement, we sought to access intermediates such as these in a more direct manner. Furthermore, in an effort to minimize protecting group manipulation, we opted to mask the protected acetophenone moiety as an olefin. With this modification to α-hydroxyketone **758**, the central [3.3.1]-dioxabicycle could be installed in the late stages of the synthesis by a palladium(II)-catalyzed oxidative cyclization of the α-hydroxyl group onto the olefin followed by ketalization with the pendant phenol. Cyclizations of this type to form bicyclic acetal structures are precedented in the literature.[22] In a final simplification of α-hydroxyketone **758**, the oxidation at C(9) was removed, leading to tertiary alcohol **779** as our key synthetic target. Importantly, this approach would make use of several intermediates already prepared for the acyl-alkylation studies.

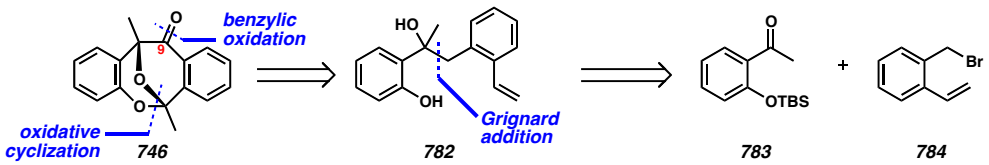
Scheme 3.12. Wacker cyclization approach to integrastatins A and B.



3.3.2 Model System Wacker Cyclization Study[23]

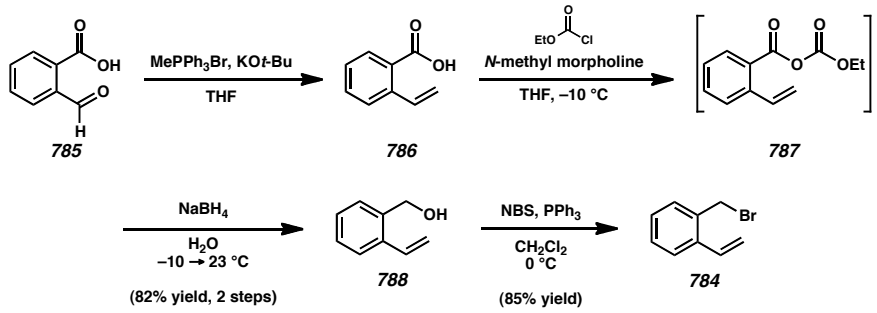
Before exploring this strategy in the fully elaborated system, we turned to a model system to test its feasibility. Toward this end, we disconnected the tetracyclic core of the integrastatins along the two C–O acetal bonds of the central [3.3.1]-dioxabicycle and removed the oxidation at C(9), leading back to diol **782** (Scheme 3.13). Diol **782** could be prepared in turn from two aromatic fragments (**783** and **784**) of similar complexity by a Grignard addition.

*Scheme 3.13. Retrosynthetic analysis of tetracycle **746**.*

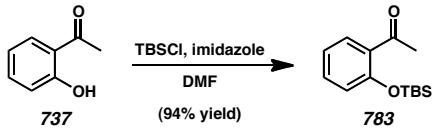


In the forward sense, we began with the synthesis of benzyl bromide **783** from commercially available 2-carboxybenzaldehyde (**785**) (Scheme 3.14). Wittig olefination of benzaldehyde **785** produced styrene **786**,[24] which was subsequently reduced to the primary benzyl alcohol (**788**) through an intermediate mixed anhydride (**787**).[25,26] Moving forward, a number of conditions were examined for the conversion of primary alcohol **788** to the benzyl bromide (**784**); ultimately we found that use of NBS with triphenylphosphine accomplished the transformation in high yield. With benzyl bromide **784** in hand, ketone **783** was prepared in one step from commercially available 2-hydroxyacetophenone (**737**) by protection of the phenol as a silyl ether (Scheme 3.15).[27]

*Scheme 3.14. Preparation of benzyl bromide **784**.*

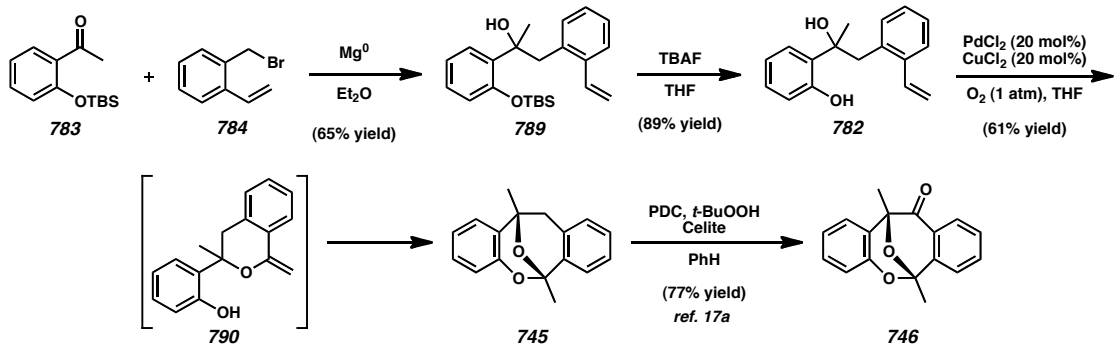


*Scheme 3.15. Preparation of ketone **783**.*



We next turned our attention toward coupling of benzyl bromide **784** with ketone **783** and construction of an appropriate Wacker cyclization substrate. To this end, Grignard addition of the organomagnesium reagent derived from benzyl bromide **784** into ketone **783** furnished tertiary alcohol **789**, which was subsequently desilylated under standard conditions to yield diol **782** (Scheme 3.16). Treatment of diol **782** with catalytic quantities of $PdCl_2$ and $CuCl_2$ under an oxygen atmosphere resulted in cyclization of both the phenol and tertiary alcohol of diol **782** onto the styrenyl olefin to generate the [3.3.1]-dioxabicycle central to the integrastatin core (**745**).[28] This key cyclization reaction likely proceeds first through palladium-catalyzed formation of a 6-membered ring enol ether (**790**). At this point, the pendant phenol can cyclize onto the enol ether, furnishing the ketal moiety. Importantly, Taylor and co-workers have shown that tetracycle **745** can undergo benzyl oxidation when treated with PDC, Celite, and *t*-BuOOH to produce benzyl ketone **746** in good yield.[17a]

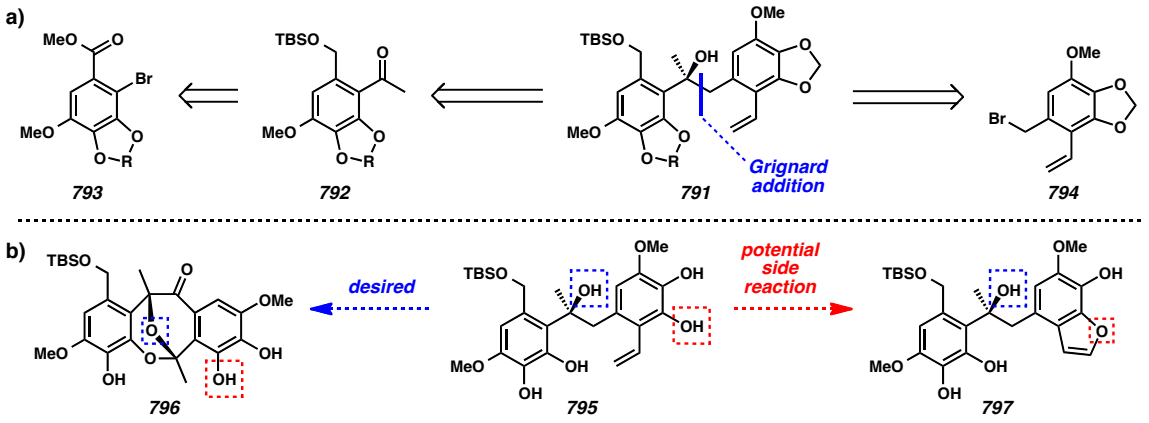
*Scheme 3.16. Coupling of benzyl bromide **784** and ketone **783** and completion of the integrastatin core.*



3.3.3 Attempted Synthesis of Tertiary Alcohol 779: Alkali and Transition Metal Coupling Strategies

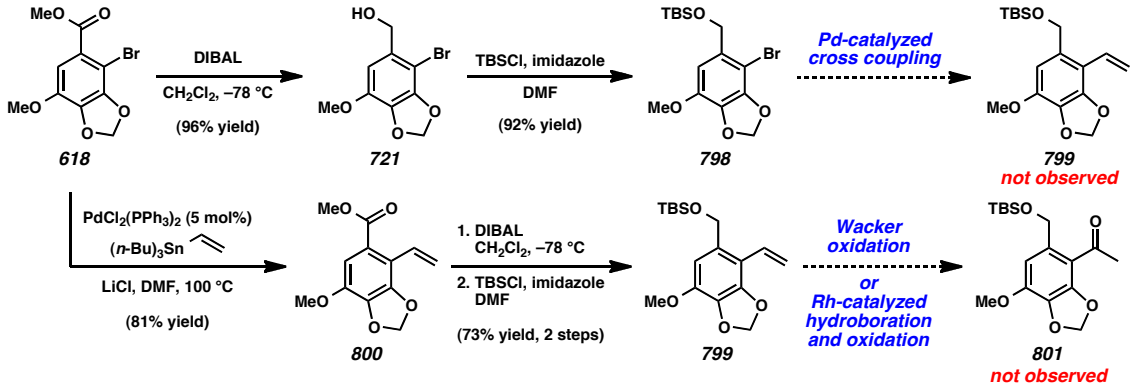
With this key proof of principle result, we focused our efforts on preparation of appropriately functionalized ketone and benzyl bromide fragments (Scheme 3.17a). In a departure from the acyl-alkylation route, the two catechol units must be differentially protected to allow for selective cleavage of the protecting group on the western catechol (**791**, R ≠ CH_2) over that of the eastern catechol. We anticipated that revealing both catechols simultaneously prior to oxidative cyclization would result in preferential benzofuran formation with the proximal hydroxyl group (**795** → **797**) instead of the desired 6-membered ring formation and ketalization (**795** → **796**) (Scheme 3.17b).[29] However, due to the ease of preparing large quantities of protected catechol **618** (i.e., **793**, R = CH_2), the synthesis of a suitable ketone partner (i.e., **792**, R = CH_2) was investigated on this compound. As such, we first sought to convert intermediate bromoarene **793** (R = CH_2) into acetophenone **792** (R = CH_2).

Scheme 3.17. Synthetic strategy for the Wacker cyclization route.



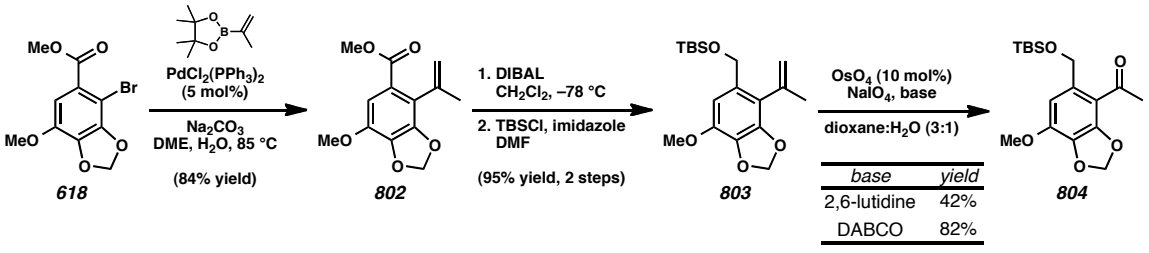
Initially, we targeted acetophenone **801** by a strategy involving reduction and protection of the ester (**618**), Stille coupling of a vinyl stannane, and Wacker oxidation. Benzoate **618** was readily reduced by DIBAL to the primary alcohol (**721**), which was subsequently protected as the silyl ether (**798**) (Scheme 3.18). To our surprise though we were unable to install the vinyl group on this compound by a number of palladium-catalyzed methods, including Stille and Suzuki couplings. We postulated that the extreme electron-rich nature of these compounds, in combination with the dual *ortho* substitution to the bromide, prevent oxidative addition even under very forcing conditions. To circumvent this problem, cross-coupling of tributyl(vinyl)stannane was performed on benzoate **618** to yield styrene **800**, which was subsequently reduced and protected as the silyl ether (**799**). However, to our disappointment, we were unable to convert this intermediate to the acetophenone under a variety of Wacker oxidation conditions.[28b] Furthermore, attempts to install the benzylic oxidation by rhodium-catalyzed hydroboration methods also failed.[30]

*Scheme 3.18. Attempted synthesis of acetophenone **801** by oxidation of styrene **799**.*



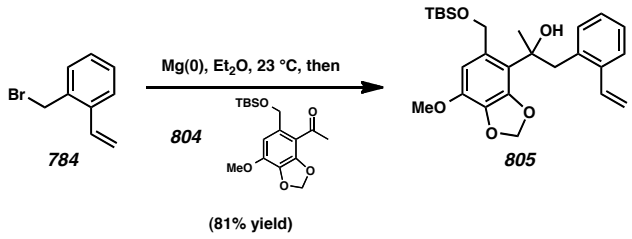
Given the success of the Stille coupling of tributyl(vinyl)stannane to benzoate **618**, we investigated a sequence involving *iso*-propenylation and oxidative olefin cleavage to generate acetophenone **804** (Scheme 3.19). Under highly optimized conditions, palladium-catalyzed Suzuki coupling of *iso*-propenyl boronic ester[31] with benzoate **618** yielded α-methylstyrene **802**, which was then reduced and protected as the silyl ether (**803**). All attempts to produce the ketone by ozonolysis of α-methylstyrene **803** resulted only in complete decomposition of the electron rich substrate. However, oxidative olefin cleavage with catalytic OsO_4, 2,6-lutidine, and $NaIO_4$ yielded acetophenone **804** in 42% yield. Simply switching the base from 2,6-lutidine to DABCO increased the yield of acetophenone **804** to 82%.

*Scheme 3.19. Preparation of acetophenone **804** by oxidative olefin cleavage.*



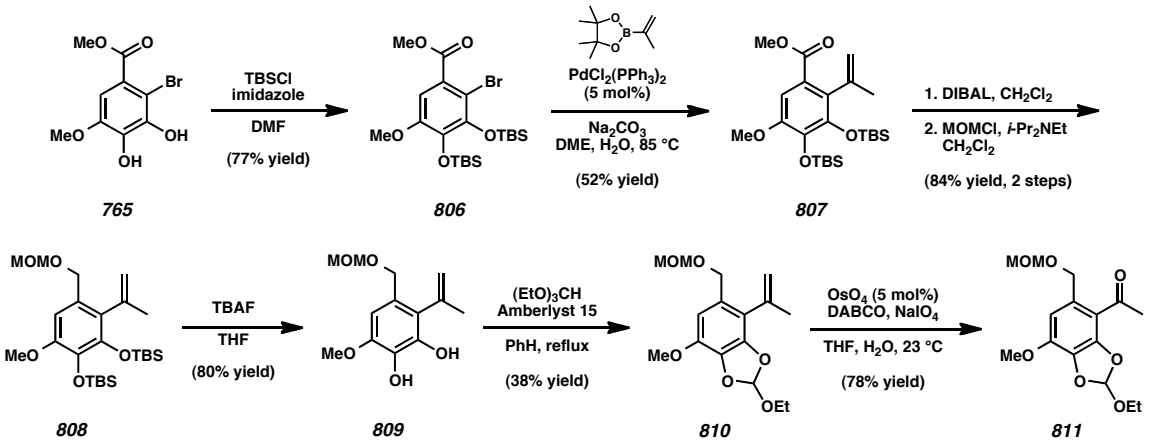
With acetophenone **804** in hand, we sought to test its viability in a Grignard reaction with benzyl bromide **784** as a model system. To our delight, smooth addition of the organomagnesium reagent derived from bromide **784** to acetophenone **804** generated tertiary alcohol **805** in 81% yield (Scheme 3.20).

*Scheme 3.20. Grignard coupling of benzylic bromide **784** with acetophenone **804**.*



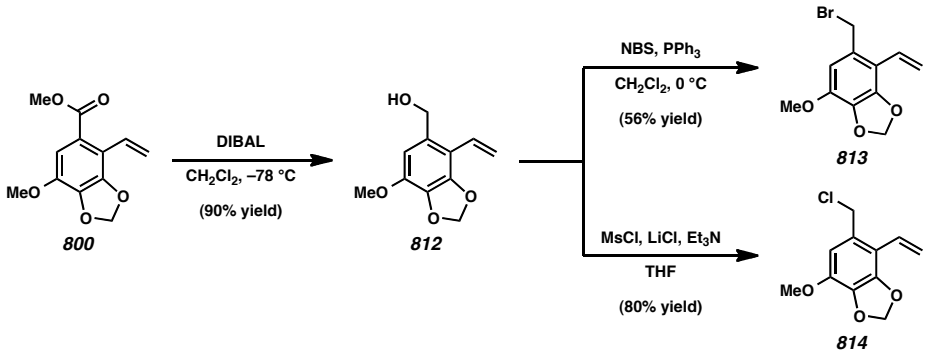
Encouraged by this promising result, we turned next to preparation of a differentially protected ketone (**811**) and the fully functionalized benzyl bromide (**813**). In place of the formaldehyde acetal protecting the catechol of acetophenone **804** we opted to install a more acid labile orthoester functionality. However, due to difficulty with the Suzuki coupling in the presence of an orthoester,[32] early intermediates en route to acetophenone **811** required TBS protective groups (Scheme 3.21). Treatment of catechol **765** with TBSCl generated protected catechol **806**, which underwent facile Suzuki coupling to yield α-methyl styrene **807**. Reduction of the ester and protection of the resultant benzyl alcohol as the methoxymethyl ether (**808**) was followed by removal of the TBS protective groups and reaction of the resulting catechol with triethylorthoformate in the presence of an acidic resin to produce orthoester **810** in moderate yield.[33] Finally, oxidative olefin cleavage using the conditions developed on the model system furnished the desired acetophenone (**811**).

*Scheme 3.21. Synthesis of acetophenone **811** featuring an acid-labile orthoester.*



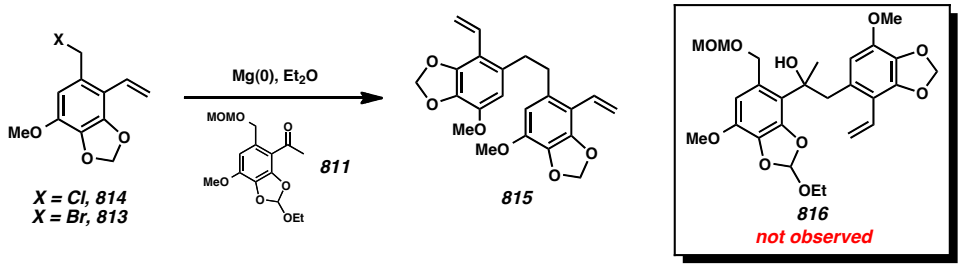
Synthesis of the fully functionalized benzyl bromide (**813**) was readily accomplished by with reduction of Stille coupling product **800** and subsequent bromination with NBS and PPh_3 (Scheme 3.22). Although benzyl bromide **813** could be generated in moderate yield, it was somewhat unstable and underwent decomposition within a period of one day at room temperature. As an alternative, benzyl chloride **814** could be prepared by treatment of the corresponding alcohol (**812**) with mesyl chloride, lithium chloride, and triethylamine in THF. Both the benzyl bromide (**813**) and chloride (**814**) were investigated as coupling partners for acetophenone **811**.

*Scheme 3.22. Synthesis of benzyl bromide **813** and benzyl chloride **814**.*



First attempts to couple the benzyl halides (**813** and **814**) with acetophenone **811** focused on standard Grignard reaction conditions. Treatment of either benzyl bromide **813** or chloride **814** with Mg(0) in ethereal solvents led to rapid and exclusive formation of dimer **815**, with no traces of the desired addition product (**816**) (Scheme 3.23). Furthermore, all attempts to preclude this side reactivity by slow addition or temperature control failed to produce anything but dimer **815**. Efforts to effect a lithium-halogen exchange on benzyl chloride **814** using inverse addition techniques at –100 °C with *t*-BuLi resulted only in several unidentified *t*-butylated products. We reasoned that the highly electron rich nature of benzyl chloride **814** and bromide **813** is likely responsible for the difficulties in effecting metal-halogen exchanges on these compounds.

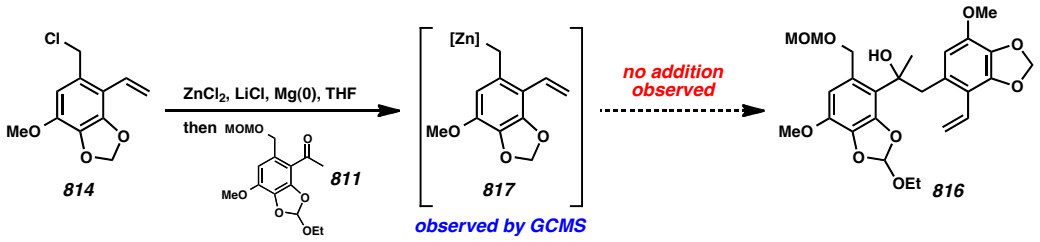
*Scheme 3.23. Attempted Grignard addition reactions with benzyl halides **813** and **814** into acetophenone **811**.*



Throughout the course of our investigations into metallation of benzyl halides **813** and **814**, only one method ever resulted in effective formation of a benzyl organometallic reagent. Treatment of benzyl chloride **814** with $ZnCl_2$, LiCl, and Mg(0) under conditions developed by Knochel[34] led exclusively to formation of the organozinc reagent with no noticeable dimer (Scheme 3.24). However, attempts to add this species into

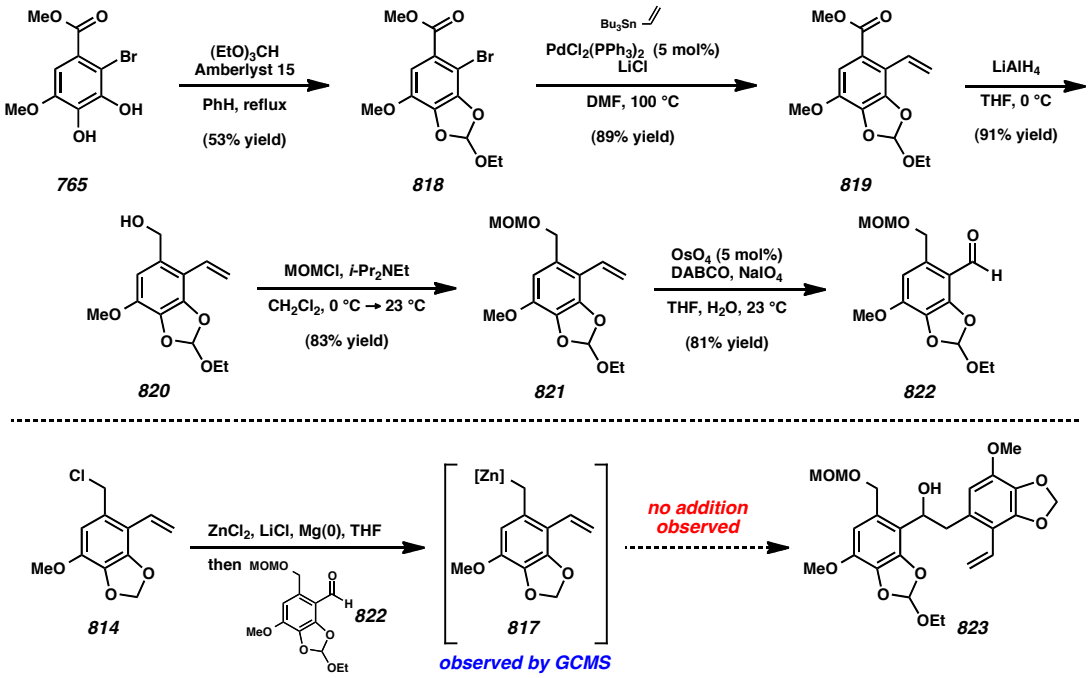
acetophenone **811** failed to produce any product, presumably because the ketone is not electrophilic enough for the less nucleophilic organozinc reagent.

*Scheme 3.24. Successful formation of the oganozinc reagent of benzyl chloride **814** according to Knochel conditions.*



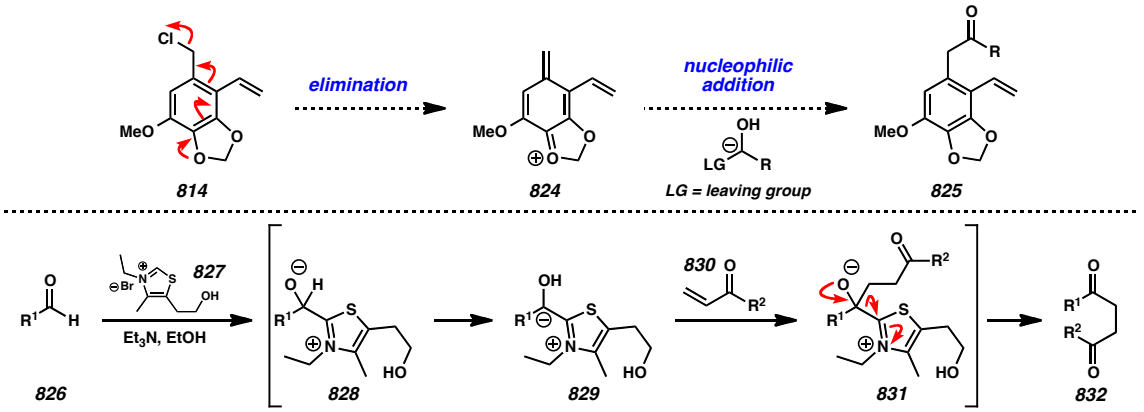
In an effort to take advantage of the success of organozinc reagent formation, we prepared the corresponding aldehyde (**822**) instead of the less electrophilic ketone (**811**) (Scheme 3.25). Stille coupling of a vinyl stannane with orthoester **818**, was followed by reduction of the ester (**819**) and protection of the benzyl alcohol as a methoxymethyl ether (**821**). Finally, oxidative olefin cleavage furnished the desired aldehyde coupling partner (**822**). Unfortunately, all efforts to couple aldehyde **822** with the organozinc reagent (**814**) failed to produce any tractable products.

Scheme 3.25. Synthesis of aldehyde ***822*** *and attempted organozinc reagent coupling.*



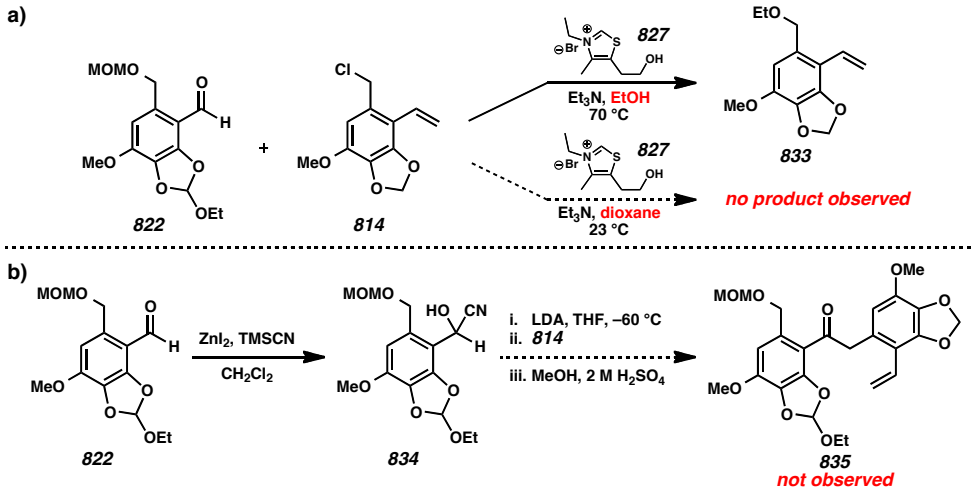
In considering the difficulties experienced trying to functionalize benzyl halides **813** and **814**, we recognized that these structures also possess the ability to directly eliminate their respective halides to generate a *para*-quinonemethide structure (e.g., **824**) (Scheme 3.26). While this elimination pathway was likely contributing to the instability of halides **813** and **814** and hindering our efforts at coupling them to aldehydes and ketones, we considered the potential to take advantage of the ease of this process in an umpolung fashion in which aldehyde **822** serves as a nucleophile and adds into a *para*-quinonemethide (**824**) derived from benzyl chloride **814**. To accomplish this, we turned to thiazolium catalysts such as **827**, which, upon deprotonation by an amine base, form *N*-heterocyclic carbenes. Upon reaction with aldehydes, these carbenes catalyze the formation of an acyl anion (**829**), which have been previously utilized for additions to a range of electrophiles, including enones (**830**).[35]

*Scheme 3.26. Stetter reaction strategy for coupling of benzyl chloride **814** and aldehyde **822**.*



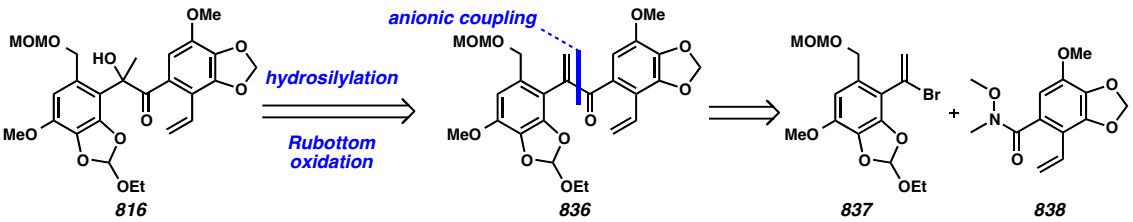
In our initial attempt to couple aldehyde **822** and benzyl chloride **814** by a Stetter reaction with thiazolium catalyst **827** with ethanol as solvent, only ethyl ether **833** was isolated from the reaction (Scheme 3.27a). No traces of coupled products were observed. To avoid reaction with the ethanol, the solvent was changed to dioxane; however, under these conditions, rapid decomposition of benzyl chloride **814** was not accompanied by consumption of aldehyde **822**. As an alternative to thiazolium catalysts, acyl anion generation from the cyanohydrin of aldehyde **822** was investigated (Scheme 3.27b).[36] Unfortunately, this method too yielded none of the desired ketone product (**835**).

*Scheme 3.27. Attempted acyl anion couplings of aldehyde **822** and benzyl chloride **814**.*



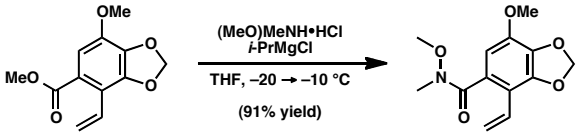
At this juncture, we recognized the significant difficulties in forming the C(8)–C(9) bond of the integrastatins due to a variety of steric and electronic difficulties. As such, we considered disconnecting tertiary alcohol **816** in a somewhat different fashion, instead targeting enone **836** by the coupling of α-bromostyrene (**837**) and Weinreb amide (**838**) (Scheme 3.28). Enone **836** appeared to be an intermediate that could be converted readily to α-hydroxyketone **816** by a number of different methods, including a hydrosilylation/Rubottom oxidation sequence.

*Scheme 3.28. Revised strategy to tertiary alcohol **816** via enone **836**.*

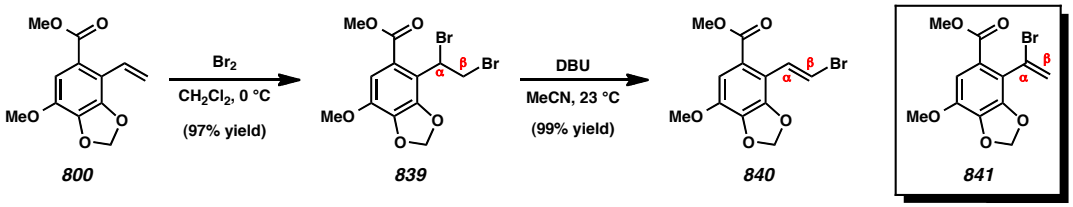


Weinreb amide **838** was readily accessed in one synthetic step from styrene **800**, an intermediate en route to benzyl halides **813** and **814** (Scheme 3.29).[37] The synthesis of α-bromostyrene **837** was investigated on a model system bearing the formaldehyde acetal on the catechol (**800**) (Scheme 3.30). Beginning again with styrene **800**, bromination with Br_2 yielded vicinal dibromide **839**, which was subsequently treated with DBU to effect the elimination of the β-bromide. Among literature reports for this elimination, all examples give exclusively the α-bromostyrene product (**841**).[38] However, it was clear to us that treatment of dibromide **839** with DBU produced exclusively the β-bromostyrene (**840**). We reasoned that the presence of *ortho*- and *para*-alkoxy groups significantly increases the lability of the α-bromide, resulting in more facile elimination of this bromide over the β-bromide.

*Scheme 3.29. Synthesis of Weinreb amide **838**.*

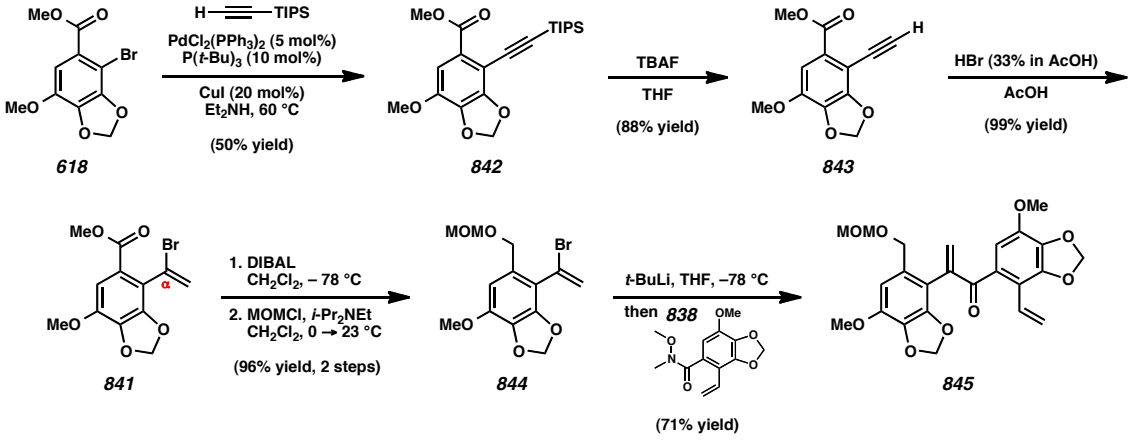


*Scheme 3.30. Selectivity issues in the attempted synthesis of α-bromostyrene **841**.*



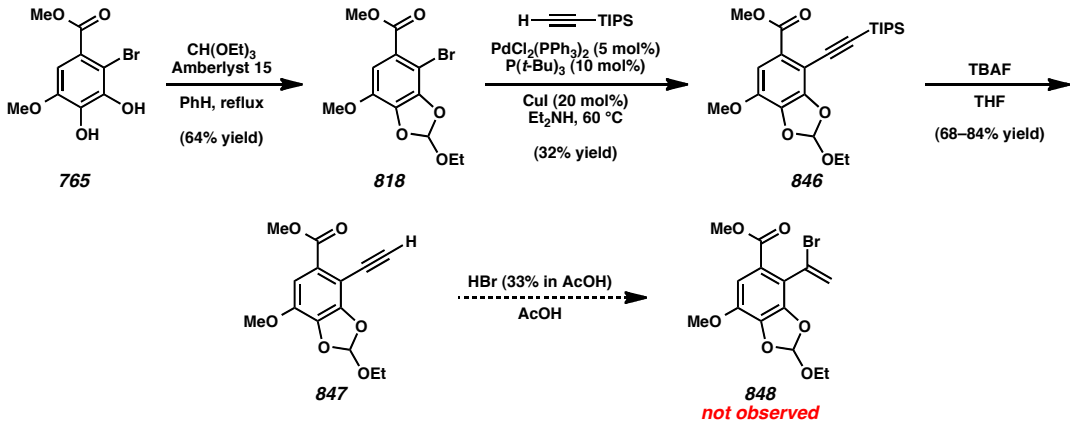
To circumvent this selectivity issue, we reasoned that it might be easier to access α-bromostyrene **841** from acetylene **843** by an acidic bromination (Scheme 3.31). This method would take advantage of the stability of a carbocation at the α-styrenyl position, giving good selectivity for the desired α-bromostyrene. On a model system to test this concept, Sonogashira coupling of aryl bromide **618** with TIPS acetylene produced the corresponding aryl alkyne (**842**) in moderate yield. Interestingly, when using PPh_3 as the ligand, no reaction was ever observed even at elevated temperatures; product was only obtained using the more electron-rich P(*t*-Bu)$_3$ as the ligand for palladium. Aryl alkyne **842** was next desilylated with TBAF, yielding the terminal alkyne (**843**) in preparation for bromination. To our delight, treatment of terminal alkyne **843** with anhydrous HBr in acetic acid produced the desired α-bromostyrene (**841**) in excellent yield.[39] Furthermore, following reduction of the ester and protection of the resulting primary alcohol, α-bromostyrene **844** could be effectively coupled to Weinreb amide **838** to furnish enone **845** in very good yield. This marked the first time that both fully functionalized aromatic rings of integrastatin had been incorporated into a synthetic intermediate.

*Scheme 3.31. Synthesis of α-bromostyrene **844** and successful coupling with Weinreb amide **838**.*



Encouraged by this key result, we turned our attention to the synthesis of an α-bromostyrene with a more labile protective group masking the catechol functionality, such as an orthoester. Beginning with orthoester **818**, an intermediate used en route to aldehyde **822**, Sonogashira coupling to install the TIPS acetylene proceeded in low yield to give aryl alkyne **846**, which was subsequently desilylated to give terminal alkyne **847** (Scheme 3.32). Unfortunately, though, under the acidic bromination conditions, orthoester cleavage was rapid. This forced us to investigate alternative protective groups for the catechol that would remain intact when treated with acetic acid and HBr at room temperature.

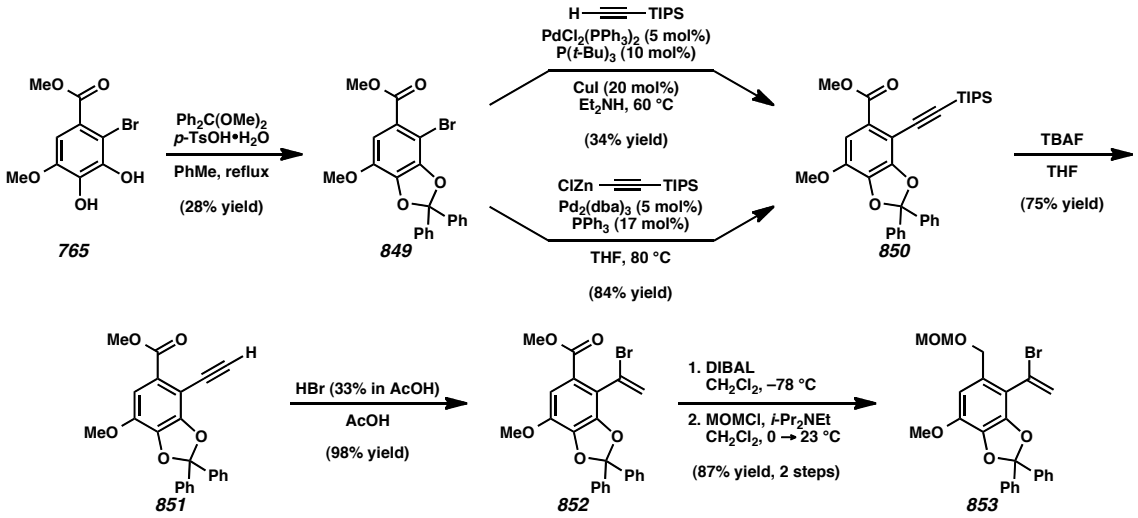
*Scheme 3.32. Attempted synthesis of α-bromostyrene **848**, with an orthoester protective group.*



Eventually, we focused our efforts on a diphenyl acetal protective group for the catechol. The diphenyl acetal was installed by treatment of catechol **765** with acetophenone dimethyl acetal and *p*-TsOH•H_2O in refluxing toluene to provide diphenyl acetal **849**, albeit in quite low yields (Scheme 3.33). A number of different conditions to effect this transformation were investigated, with none offering any improvement over

standard conditions. Furthermore, the Sonogashira coupling of TIPS acetylene with diphenyl acetal **849** was plagued by variable yields and poor conversion, often accompanied by palladium black formation. Fortuitously, we found that use of a Negishi coupling with the zinc reagent of TIPS acetylene remedied this problem and led to very good yields of aryl alkyne **850**.[40] Following desilylation of aryl alkyne **850**, bromination under our optimized conditions cleanly produced the desired α-bromostyrene (**852**) in excellent yield. The synthesis of the fully elaborated coupling partner (**853**) was then achieved by simple DIBAL reduction of the ester and protection of the resultant alcohol as a methoxymethyl ether.

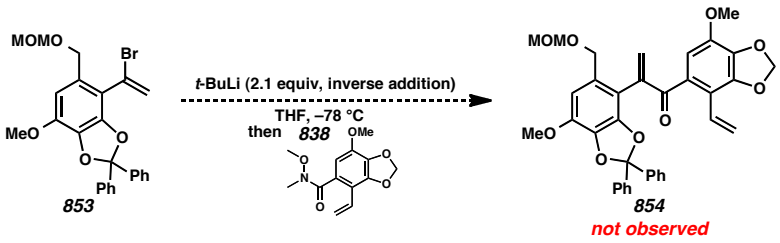
*Scheme 3.33. Synthesis of α-bromostyrene **853**, bearing a diphenyl acetal.*



With α-bromostyrene **853** in hand, we were eager to test the key coupling reaction. Upon inverse addition of α-bromostyrene **853** to a cooled THF solution of *t*-BuLi, the color of the solution turned a deep red, indicating formation of the lithiated species (Scheme 3.34). Furthermore, TLC analysis showed complete consumption of α-

bromostyrene **853**. This behavior was identical to that observed in the model system coupling between α-bromostyrene **844** and this same Weinreb amide (**838**) (i.e., Scheme 3.31). However, unlike in the model system, no consumption of Weinreb amide (**838**) was ever observed upon its addition to the solution of lithiated α-bromostyrene **853** over a range of temperatures. We reasoned that the bulky phenyl substituents on the neighboring acetal significantly hindered the addition of lithiated α-bromostyrene **853** into Weinreb amide **838**, prohibiting coupling of these two components.

*Scheme 3.34. Attempted coupling of α-bromostyrene **853** and Weinreb amide **838**.*

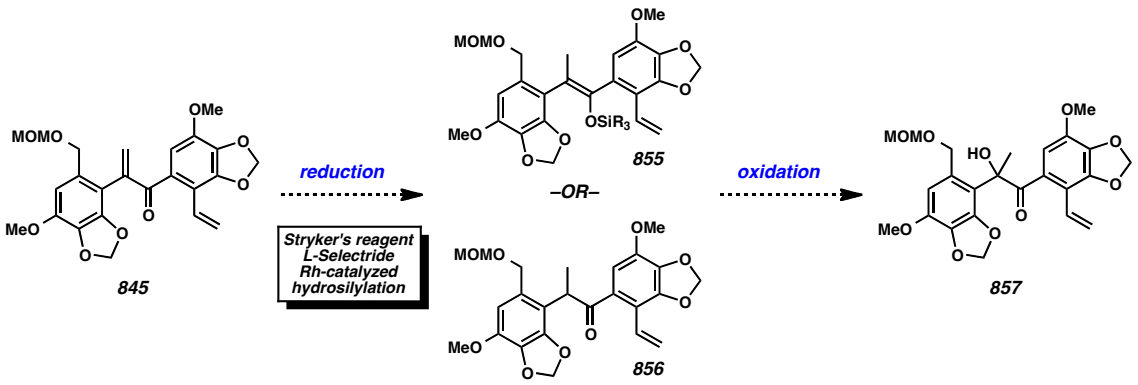


This result was consistent with a pattern throughout our studies toward the integrastatins, in which we routinely found that modifying our substrates in any subtle way usually significantly altered the reactivity of these species. Often, steric and electronic factors were to blame for these differences in reactivity. As such, we were never able to access an intermediate that could be selectively deprotected to allow investigation of the proposed palladium-catalyzed Wacker cyclization.

While we never were able to test the key oxidative cyclization, enone functionalization to install the tertiary alcohol of α-hydroxyketone **857** was briefly examined on model system enone **845** (Scheme 3.35). From attempts at hydrosilylation as well as L-Selectride and Stryker's reagent 1,4-reductions, it appears that enone **845**

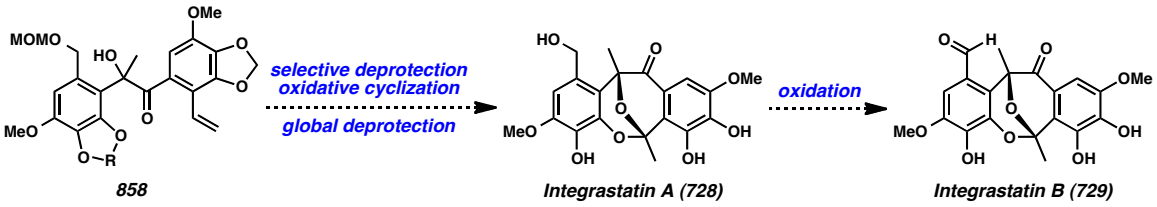
does not exhibit typical enone reactivity. In fact, 1,4-reduction of any type was never observed in these reactions. This is likely due to a conformational preference for enone **845** in which the olefin and ketone moieties are oriented perpendicularly to one another, disrupting the conjugation required for 1,4-reduction of the system. These results cast further doubt on the feasibility of this strategy for accessing a suitable oxidative cyclization precursor.

*Scheme 3.35. Attempted functionalization of enone **845**.*



At this point, it appears that a new strategy aimed at the synthesis of α-hydroxyketone **858** is necessary to circumvent the difficulties encountered in preparing a suitably protected enone (i.e., **845**), as well as the challenges of converting such an enone to the α-hydroxyketone (Scheme 3.36). Upon synthesis of a suitably protected α-hydroxyketone, we anticipate that integastatin A (**728**) will be completed in short order by a sequence involving selective protective group cleavage, palladium-catalyzed oxidative cyclization, and global deprotection. Furthermore, integrastatin B (**729**) will then be obtained by selective oxidation of integrastatin A (**728**).

*Scheme 3.36. Proposed completion of integrastatins A and B (**728** and **729**) from α-hydroxyketone **858**.*



3.4 CONCLUDING REMARKS

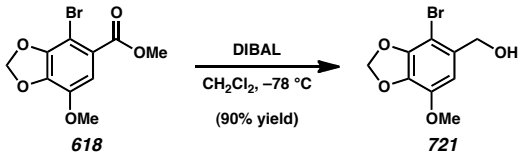
In designing our various approaches to the integrastatin natural products, we always sought to limit the amount of late-stage aromatic functionalization required while maintaining a high level of convergency. In this way, even though we moved on from the acyl-alkylation approach, we have drawn from the core strategic advantages of aryne-based methods in the total synthesis of natural products. While we were able to achieve the synthesis of enone **845**, a molecule containing all the carbon atoms comprising the integrastatins, we were unable to recognize our goal of converting this intermediate to the tetracyclic core of the natural products. Given the success of the model system Wacker oxidative cyclization to produce the [3.3.1]-dioxabicyclic core of the integrastatins, we are confident that upon synthesis of an appropriately protected version of α-hydroxyketone **858**, the natural products will be accessible by this route.

3.5 EXPERIMENTAL SECTION

3.5.1 Materials and Methods

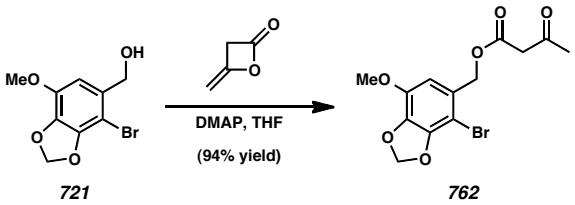
Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 (at 500 MHz and 125 MHz, respectively) 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), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

3.5.2 Preprative Procedures and Spectroscopic Data



Benzyl alcohol 721

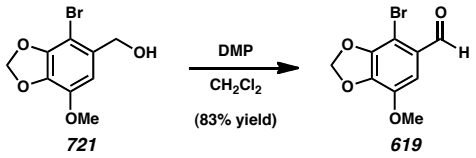
A solution of methyl ester **618** (3.0 g, 10.4 mmol) in CH_2Cl_2 (100 mL) was prepared and cooled to –78 °C. Diisobutylaluminum hydride (DIBAL, 4.1 mL, 22.8 mmol) was added dropwise and the reaction was maintained at –78 °C until methyl ester **618** was consumed by TLC analysis. The reaction was quenched at –78 °C by the addition of saturated aqueous sodium potassium tartrate solution (25 mL) and then warmed to room temperature. The reaction was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield benzylic alcohol **721** (2.6 g, 96% yield): R_f = 0.33 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.05 (s, 2H), 4.66 (d, J = 5.8 Hz, 2H), 3.90 (s, 3H), 1.99 (t, J = 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.00, 142.90, 135.00, 133.49, 108.42, 101.94, 93.34, 64.47, 56.75; IR (NaCl/film) 3187, 2904, 1628, 1486, 1465, 1446, 1343, 1165, 1106, 1038, 968, 931, 824, 701 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_9H_8O_3{}^{79}Br$ $[M–OH]^+$: 242.9651, found 242.9648; m/z calc'd for $C_9H_8O_3{}^{81}Br$ $[M–OH]^+$: 244.9632, found 244.9629.



721 *762*

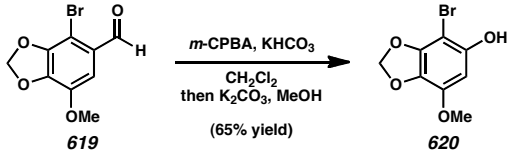
β-Ketoester 762

To a solution of benzylic alcohol **721** (33.3 mg, 0.128 mmol) in THF (0.65 mL) were added DMAP (1.6 mg, 0.013 mmol) and diketene (20 μL, 0.255 mmol). The reaction was maintained with stirring at room temperature until benzylic alcohol **721** was consumed by TLC analysis. Following this time, the reaction was diluted with diethyl ether (25 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried with Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (2:1 hexanes:ethyl acetate eluent) to yield β-ketoester **762** (36.3 mg, 83% yield) as a mixture of keto and enol tautomers (4.5:1 ratio by ^{1}H NMR): R_f = 0.21 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.96 (s, 0.22H), 6.68 (s, 1H), 6.65 (2, 0.22H), 6.05 (s, 2H), 6.05 (s, 0.44H), 5.16 (s, 2H), 5.15 (s, 0.44H), 5.04 (s, 0.22H), 3.90 (s, 3H), 3.89 (s, 0.66H), 3.51 (s, 2H), 2.26 (s, 3H), 1.96 (s, 0.66H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.27, 176.15, 172.04, 166.70, 147.19, 142.76, 142.70, 135.75, 135.62, 128.64, 128.04, 110.37, 110.25, 102.11, 102.05, 94.83, 94.76, 89.44, 66.10, 64.67, 56.85, 49.93, 30.26, 21.27; IR (NaCl/film) 2936, 1745, 1714, 1628, 1488, 1435, 1351, 1319, 1254, 1167, 1149, 1108, 1036, 963, 934, 837 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_8O_3{}^{79}Br$ $[M]^{\cdot+}$: 242.9651, found 242.9645.



Aldehyde 619

A solution of Dess–Martin periodinane (2.94 g, 6.92 mmol) in CH_2Cl_2 (28 mL) was prepared under nitrogen. Alcohol **721** (1.63 g, 6.24 mmol) in CH_2Cl_2 (72 mL) was added and the reaction was maintained under nitrogen until alcohol **721** was fully consumed by TLC analysis. The reaction was quenched by the addition of a 1:1 v/v solution of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (60 mL total volume). The reaction was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL) and subsequently dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (hexanes → 7:3 hexanes:ethyl acetate eluent) to yield aldehyde **619** (1.34 g, 83% yield): R_f = 0.37 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.24 (s, 1H), 6.16 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 147.4, 143.5, 140.9, 127.6, 109.5, 103.0, 98.8, 56.8; IR (NaCl/film) 1683, 1619, 1485, 1446, 1351, 1315, 1169, 1112, 1048, 993, 928, 654 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_9H_8O_4{}^{79}Br$ $[M+H]^+$: 258.96, found 258.9597; *m/z* calc'd for $C_9H_8O_4{}^{81}Br$ $[M+H]^+$: 260.9581, found 260.9578.

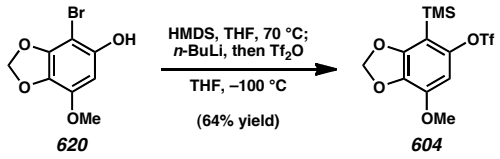


Bromophenol 620

A flask was charged with aldehyde **619** (100 mg, 0.386 mmol) and $KHCO_3$ (4 mg, 0.04 mmol) under a nitrogen atmosphere. To this was added *m*-CPBA (20 mg, 0.116 mmol) as a solution in CH_2Cl_2 (4 mL). Four additional portions of *m*-CPBA (20 mg, 0.116 mmol, each) were added as CH_2Cl_2 solutions (0.25 mL, each) at three-hour intervals. Nine hours following the final *m*-CPBA addition, the reaction was quenched by the addition of saturated $NaHCO_3$ aqueous solution (1 mL) and diluted with CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was further washed with CH_2Cl_2 (10 mL). The combined organic layers were sequentially washed with water (10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), and brine (10 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under vacuum to yield a crystalline solid.

The crude solid (103 mg) was taken up in a 10% (w/v) solution of K_2CO_3 in methanol (7.5 mL). The resultant suspension was maintained with stirring at room temperature until the starting material had been completely consumed by TLC analysis. Following this period, the reaction was concentrated under vacuum, diluted with water (10 mL), and acidified to pH 1.5 with 6 N HCl. **Warning:** vigorous gas evolution. The aqueous solution was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield bromophenol **620** (62 mg, 65% yield) as a white solid: R_f = 0.20 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.99 (s, 2H), 5.18

(s, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.42, 147.02, 143.93, 130.01, 102.37, 95.12, 83.45, 57.12, 57.10.; IR (NaCl/film) 3093, 2899, 1642, 1454, 1350, 1167, 1109, 1051, 971, 935, 874, 797, 700 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_8H_7O_4{}^{79}Br$ $[M]^+$: 245.9522, found 245.9525; *m/z* calc'd for $C_8H_7O_4{}^{81}Br$ $[M]^+$: 247.9502, found 247.9506.

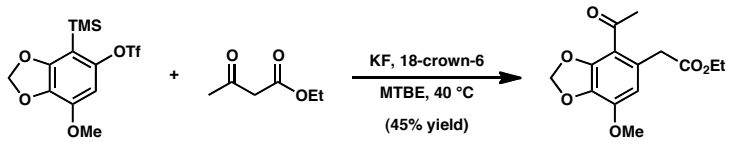


Silyl aryl triflate 604

Bromophenol **620** (149.6 mg, 0.606 mmol) and hexamethyldisilazide (253 μL, 1.21 mmol) were combined in THF (1.2 mL). The solution was heated to 70 °C and maintained for 8 h. The reaction was cooled to room temperature and concentrated under vacuum. The resulting oil was immediately taken on to the next step.

The crude residue was taken up in THF (8 mL) and cooled to –100 °C. *n*-Butyllithium (2.5 M in hexanes, 266 μL, 0.666 mmol) was added slowly and the reaction was allowed to warm to –82 °C. The reaction was cooled again to –100 °C and maintained between –100 °C and –82 °C for 30 minutes. After this period, triflic anhydride (122 μL, 0.727 mmol) was added at –100 °C. The reaction was warmed to –80 °C, quenched by the addition of saturated aqueous sodium bicarbonate solution (4 mL), and subsequently warmed to room temperature. The reaction was diluted with diethyl ether (25 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (50:1 petroleum ether:diethyl ether eluent) to yield silyl aryl triflate **604** (144.6 mg, 64%

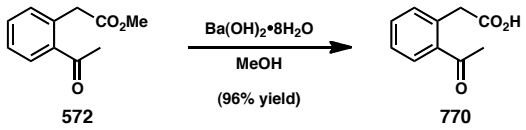
yield): R_f = 0.36 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 1H), 5.99 (s, 2H), 3.89 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.99, 148.40, 144.10, 133.88, 118.76 (q, J = 300.56 Hz), 107.02, 101.78, 101.32, 57.02, 0.23; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.07; IR (NaCl/film) 2058, 2901, 1645, 1487, 1419, 1388, 1294, 1244, 1211, 1140, 1111, 1046, 984, 893, 845, 802 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{15}O_6SiSF_3$ $[M+H]^+$: 372.0311, found 372.0321.



Ketoester 628

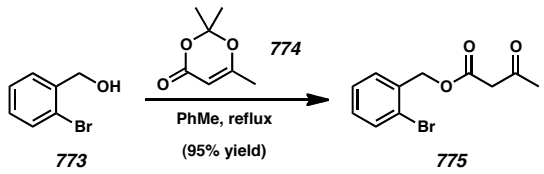
To a solution of silyl aryl triflate **604** (23.8 mg, 0.0639 mmol) and ethyl acetoacetate (**222**, 4.1 mL, 0.0320 mmol) in *tert*-butyl methyl ether (MTBE, 0.32 mL) was added 18-crown-6 (25.3 mg, 0.0959 mmol) and KF (5.6 mg, 0.0959 mmol). The resulting suspension was heated in an oil bath to 40 °C and maintained for a period of 1 hour. Following this time, the reaction was cooled to room temperature, diluted in diethyl ether (25 mL), and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield ketoester **628** (4 mg, 45% yield): R_f = 0.49 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.07 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 3.81 (s, 2H), 2.55 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 147.4, 143.5, 140.9, 127.6, 109.5, 103.0, 98.8, 56.8; IR (NaCl/film) 2985, 2904, 1731, 1674, 1632, 1427, 1312, 1281, 1162,

1100, 940, 854 cm^{-1}; HRMS (MM:ESI-APCI) *m/z* calc'd for $C_{14}H_{16}O_6$ $[M+H]^+$: 281.1020, found 281.1020.



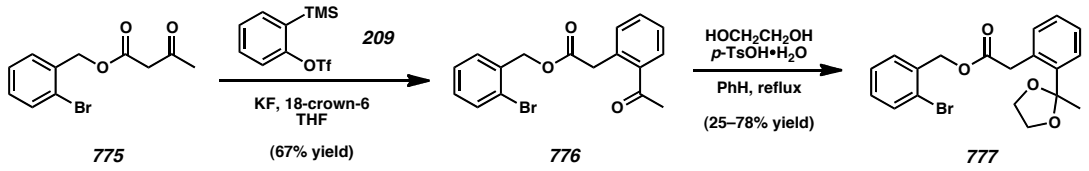
Acid 770

To a solution of ketoester **572** (200 mg, 1.04 mmol) in methanol (5 mL) was added $Ba(OH)_2•8H_2O$ (460 mg, 1.46 mmol). The resulting solution was maintained with stirring at room temperature until complete by TLC analysis (about 12 hours). The reaction was diluted with diethyl ether (25 mL) and sequentially washed with 1 N HCl solution (2 x 10 mL) and brine (10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under vacuum to yield acid **770** (179 mg, 96% yield): R_f = 0.15 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.51 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H), 7.42 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 7.35 (dd, *J* = 7.6, 0.7 Hz, 1H), 3.91 (s, 2H), 2.65 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.93, 174.67, 136.92, 133.78, 132.77, 132.67, 130.17, 127.75, 40.74, 28.79; IR (NaCl/film) 3033, 2916, 1705, 1673, 1424, 1360, 1256, 1232, 930, 766 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{11}O_3$ $[M+H]^+$: 179.0703, found 179.0709.



β-Ketoester 775

To a solution of benzylic alcohol **773** (968 mg, 5.18 mmol) in toluene (21 mL) was added diketene acetone adduct (**774**, 684 μL, 5.18 mmol)) via syringe. The reaction was equipped with a reflux condenser an heated to reflux. After six hours at reflux, the reaction was cooled to room temperature and concentrated under vacuum. The crude residue was purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield β-ketoester **775** (1.33 g, 95% yield) as a mixture of keto and enol tautomers (6.5:1 ratio by ^{1}H NMR): R_f = 0.23 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.97 (s, 0.15H), 7.58 (ddd, J = 8.0, 3.5, 1.2 Hz, 1H), 7.55 (dd, J = 8.0, 1.1 Hz, 0.15H), 7.51–7.47 (m, 0.15H), 7.45–7.38 (m, 1.15H), 7.36–7.29 (m, 1.15H), 7.23–7.14 (m, 1.15H), 5.27 (s, 2H), 5.26 (s, 0.30H), 5.10 (s, 0.15H), 3.54 (s, 2H), 2.28 (s, 3H), 1.98 (s, 0.45H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.25, 176.21, 166.71, 139.74, 135.25, 134.57, 132.89, 132.81, 132.57, 130.18, 130.00, 129.66, 129.61, 129.09, 128.87, 127.64, 127.60, 127.51, 123.54, 123.21, 122.54, 89.43, 66.68, 65.14, 65.06, 62.98, 49.93, 30.23, 21.30; IR (NaCl/film) 2929, 1744, 1717, 1570, 1474, 1441, 1408, 1359, 1314, 1255, 1147, 1027, 752 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{11}O_3{}^{79}Br$ $[M–H]^-$: 268.9819, found 268.9842.

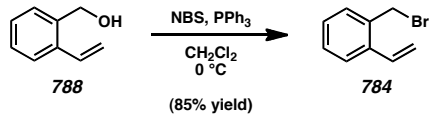


Acetal 777

Silyl aryl triflate **209** (280 μL, 1.15 mmol) and β-ketoester **775** (240 mg, 0.885 mmol) were combined in THF (9 mL). To this solution were sequentially added 18-crown-6 (700 mg, 2.66 mmol) and KF (154 mg, 2.66 mmol). The resulting suspension was maintained at room temperature with stirring until β-ketoester **775** was fully consumed by TLC analysis. Following this time, the reaction was diluted with diethyl ether (25 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield ketoester **776** (182.5 mg, 59% yield).

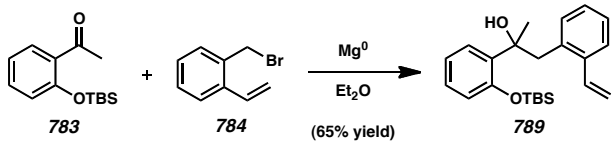
Ketoester **776** (182.5 mg, 0.526 mmol) was taken up in benzene (5 mL). To this were added ethylene glycol (176 μL, 3.15 mmol) and *p*-TsOH•H_2O (1 mg, 0.0053 mmol). The reaction flask was equipped with a Dean–Stark trap (filled with benzene) and reflux condenser and heated to reflux, where it was maintained for 24 hours. Following this time, the reaction was cooled to room temperature, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield acetal **777** (52.2 mg, 25% yield): R_f = 0.30 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.55 (m, 2H), 7.41–7.37 (m, 1H), 7.32–7.21 (m, 4H), 7.18 (m, 1H), 5.24 (s, 2H), 3.97 (s, 2H), 3.92 (dt, J = 6.2, 4.2 Hz, 2H), 3.64 (dt, J = 6.1, 4.2 Hz, 2H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.76, 141.31, 135.47, 132.73, 132.58,

131.31, 129.66, 129.51, 128.18, 127.40, 127.31, 126.39, 123.19, 109.06, 65.79, 64.19, 39.24, 27.57; IR (NaCl/film) 2986, 2890, 1740, 1473, 1442, 1374, 1333, 1240, 1199, 1152, 1034, 950, 869, 754 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{19}O_4{}^{79}Br$ $[M+H]^+$: 391.0539, found 391.0555.



Benzyl bromide 784

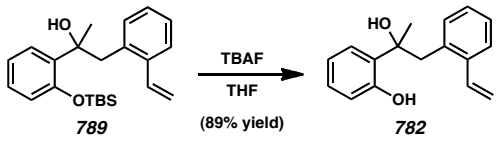
A solution of benzyl alcohol **788** (736 mg, 5.49 mmol) in CH_2Cl_2 (27 mL) was cooled to 0 °C in an ice bath. Triphenylphospine (1.67 g, 6.36 mmol) was added as a solid in one portion and the resulting solution was maintained at 0 °C for 10 minutes with stirring. Following this period, *N*-bromosuccinimide (1.13 g, 6.36 mmol) was added portion-wise as a solid over 5 minutes. The reaction was then maintained with stirring at 0 °C for 20 minutes or until benzyl alcohol **788** was consumed by TLC analysis. The reaction was concentrated under vacuum and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield benzyl bromide **784** (932 mg, 85% yield): R_f 0.56 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.51 (m, 1H), 7.35–7.29 (m, 2H), 7.28–7.23 (m, 1H), 7.11 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.76 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.45 (dd, *J* = 11.0, 1.2 Hz, 1H), 4.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.25, 134.56, 133.36, 130.23, 129.13, 128.11, 126.43, 117.08, 31.63; IR (NaCl/film) 3066, 1847, 1627, 1569, 1486, 1453, 1416, 1223, 1210, 1184, 987, 917, 772, 758 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_9{}^{79}Br$ $[M]^+$: 195.9888, found 195.9897.



Tertiary alcohol 789

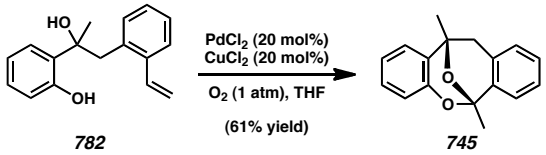
A flame-dried reaction flask was charged with Mg turnings (141 mg, 5.79 mmol). The flask was evacuated and backfilled with nitrogen. Diethy ether (5 mL) was added, followed by 1,2-dibromoethane (20 μL). The suspension was stirred for 15 minutes and then concentrated under vacuum. Next, benzyl bromide **784** (457 mg, 2.32 mmol) was added as a solution in diethyl ether (23 mL), and the resulting suspension was maintained at room temperature with stirring for 2 hours. Following this time, ketone **783** (870 mg, 3.47 mmol) was added to the reaction as a solution in diethyl ether (5 mL). The reaction was maintained for 1 hour with stirring at room temperature and then quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). Water (10 mL) was added and the biphasic solution was extracted with diethyl ether (25 mL). The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude isolate was purified by flash chromatography (30:1 petroleum ether:diethyl ether eluent) to yield tertiary alcohol **789** (556 mg, 65% yield): R_f 0.38 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.18–7.11 (m, 2H), 7.08–7.00 (m, 2H), 6.93 (dd, *J* = 17.3, 10.9 Hz, 1H), 6.88–6.81 (m, 2H), 6.78 (dd, *J* = 7.7, 1.1 Hz, 1H), 5.51 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.13 (dd, *J* = 10.9, 1.4 Hz, 1H), 4.42 (s, 1H), 3.37 (d, *J* = 13.4 Hz, 1H), 3.31 (d, *J* = 13.4 Hz, 1H), 1.56 (s, 3H), 1.08 (s, 9H), 0.42 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.22, 138.25, 135.68, 135.53, 135.46, 132.02, 128.16, 127.97, 127.22, 126.77, 125.89, 121.24, 118.46, 115.23, 76.45, 44.79, 27.07, 26.30, 18.70, –3.36, –3.64;

IR (NaCl/film) 3532, 2931, 2859, 1598, 1577, 1485, 1445, 1255, 1234, 1052, 906, 838, 781, 753 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{33}O_2Si$ $[M+H]^+$: 369.2250, found 369.2260.



Diol 782

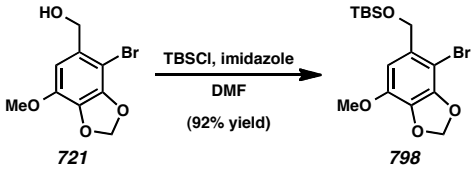
To a solution of silyl ether **789** (475 mg, 1.29 mmol) in THF (3 mL) was added TBAF (1 M solution in THF, 1.41 mL, 1.42 mmol). The resulting solution was then maintained with stirring at room temperature until silyl ether **789** was consumed by TLC analysis (about 1 hour). The reaction was diluted with water (10 mL) and then extracted with diethyl ether (25 mL). The organic phase was washed with water (3 x 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (12:1 → 10:1 hexanes:ethyl acetate eluent) to yield diol **782** (291 mg, 89% yield): R_f 0.22 (10:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.55 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.33–7.25 (m, 1H), 7.25–7.14 (m, 2H), 7.12–6.96 (m, 3H), 6.89 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.87–6.79 (m, 1H), 5.63 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.29 (dd, *J* = 10.9, 1.3 Hz, 1H), 3.36 (d, *J* = 13.9 Hz, 1H), 3.20 (d, *J* = 13.9 Hz, 1H), 2.51 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.81, 138.43, 135.12, 133.51, 132.13, 129.72, 129.09, 127.53, 127.46, 126.37, 126.12, 119.54, 117.76, 116.21, 79.13, 44.54, 28.12; IR (NaCl/film) 3306, 1618, 1582, 1491, 1453, 1374, 1293, 1237, 1154, 1095, 1036, 989, 914, 865, 752 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{17}O$ $[M+H]^+–H_2O$: 237.1279, found 237.1268.



782 *745*

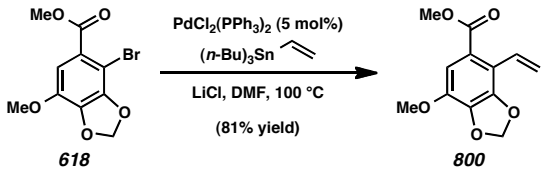
Tetracycle 745

A flame-dried reaction flask was charged with $PdCl_2$ (6.9 mg, 0.0393 mmol) and $CuCl_2$ (5.3 mg, 0.0393 mmol). THF (1.5 mL) was added followed by diol **782** (50 mg, 0.197 mmol) as a solution in THF (500 μL). The reaction was placed under an oxygen atmosphere (1 atm) and maintained at room temperature with vigorous stirring until diol **782** was consumed by TLC analysis (about 24 hours). Upon completion, the reaction solution was passed through a short column of $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (50:1 → 25:1 hexanes:ethyl acetate eluent) to yield tetracycle **745** (30.4 mg, 61% yield): R_f 0.41 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.23–7.12 (m, 2H), 7.11–7.02 (m, 2H), 7.02–6.97 (m, 1H), 6.85 (td, *J* = 7.5, 1.2 Hz, 1H), 6.71 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.29 (d, *J* = 16.0 Hz, 1H), 2.95 (d, *J* = 16.1 Hz, 1H), 1.98 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.06, 135.87, 133.19, 128.20, 128.18, 128.06, 127.42, 126.75, 125.72, 124.58, 120.71, 116.81, 97.66, 73.08, 43.09, 27.62, 26.67; IR (NaCl/film) 2994, 2932, 1607, 1585, 1484, 1452, 1382, 1299, 1275, 1249, 1115, 1081, 978, 899, 879, 760 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{17}O_2$ $[M+H]^+$: 253.1223, found 253.1211.



Silyl ether 798

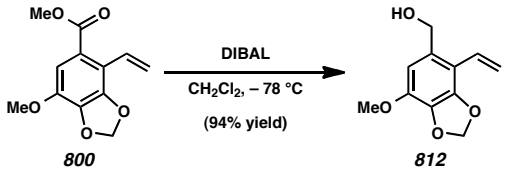
To a solution of benzyl alcohol **721** (1.0 g, 3.83 mmol) in DMF (10 mL) were sequentially added imidazole (0.52 g, 7.66 mmol) and TBSCl (0.86 g, 5.75 mmol). The resulting solution was maintained with stirring at room temperature until benzyl alcohol **721** had been fully consumed by TLC analysis. At this time, the reaction was diluted with diethyl ether (25 mL) and washed with water (3 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (50:1 hexanes:ethyl acetate eluent) to yield silyl ether **798** (1.32 g, 92% yield): R_f = 0.70 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.03 (s, 2H), 4.66 (d, J = 0.9 Hz, 2H), 3.89 (s, 3H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.69, 143.03, 134.40, 134.19, 106.82, 101.92, 91.87, 64.16, 56.65, 26.04, 18.49, -5.17; IR (NaCl/film) 2928, 1628, 1431, 1345, 1253, 1162, 1110, 1045, 937, 836, 775 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_9H_8O_3{}^{79}Br$ $[M–OTBS]^{\cdot+}$: 242.9651, found 242.9653.



Styrene 800

Lithium chloride (367 mg, 8.65 mmol) was flame dried in the reaction flask under vacuum. $PdCl_2(PPh_3)_2$ (61 mg, 0.087 mmol) was added, and the flask was evacuated and

backfilled with nitrogen. In a different flame-dried flask, a solution of aryl bromide **618** (500 mg, 1.73 mmol) and tri-*n*-butyl(vinyl)stannane (1.01 mL, 3.46 mmol) in DMF (17 mL) was sparged with argon for 10 minutes. The DMF solution was transferred to the reaction flask containing the LiCl and palladium catalyst and heated to 100 °C in an oil bath. The reaction was maintained at 100 °C with stirring under nitrogen atmosphere until aryl bromide **618** was fully consumed by TLC analysis. Following this time, the reaction was diluted with diethyl ether (50 mL) and washed with water (4 x 25 mL) and brine (25 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield styrene **800** (329 mg, 81% yield): R_f = 0.33 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.15 (m, 2H), 6.10 (s, 2H), 5.91 (dd, *J* = 17.8, 1.8 Hz, 1H), 5.49 (dd, *J* = 11.7, 1.8 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.17, 147.28, 141.89, 138.47, 129.67, 123.00, 118.95, 116.30, 110.85, 102.15, 56.52, 52.10; IR (NaCl/film) 2976, 2904, 2841, 2797, 1710, 1636, 1589, 1497, 1432, 1323, 1248, 1194, 1167, 1083, 1041, 991, 958, 900, 851, 785, 759 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{13}O_5$ $[M+H]^+$: 237.0757, found 237.0758.

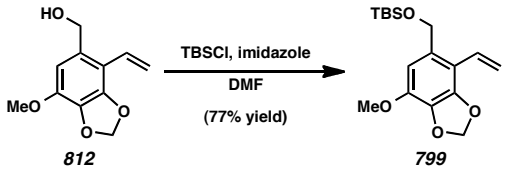


800 ***812***

Benzyl alcohol 812

A solution of styrene **800** (300 mg, 1.27 mmol) in CH_2Cl_2 (13 mL) was cooled to –78 °C. DIBAL (500 μL, 2.79 mmol) was added dropwise, and the reaction was maintained for 15 minutes at –78 °C, until styrene **800** was consumed by TLC analysis.

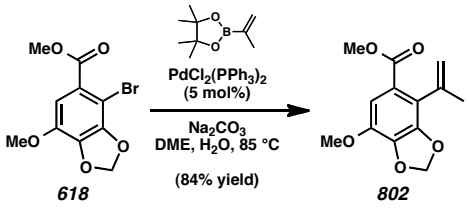
The reaction was quenched at –78 °C by the addition of a saturated solution of Rochelle's salt (5 mL) and subsequently warmed to room temperature over about one hour with vigorous stirring. The biphasic solution was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The organic phase was washed with brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum to yield benzyl alcohol **812** (247 mg, 94% yield): R_f = 0.16 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (dd, J = 17.7, 11.7 Hz, 1H), 6.57 (s, 1H), 6.03 (s, 2H), 5.93 (dd, J = 17.7, 1.8 Hz, 1H), 5.45 (dd, J = 11.7, 1.8 Hz, 1H), 4.66 (s, 2H), 3.90 (s, 3H), 1.77 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.21, 142.43, 134.95, 132.47, 128.15, 118.34, 113.06, 108.10, 101.68, 63.49, 56.54; IR (NaCl/film) 3270, 2910, 1639, 1489, 1432, 1343, 1317, 1289, 1147, 1095, 1038, 994, 942, 908, 830 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{11}H_{11}O_3$ $[M–OH]^{\cdot+}$: 191.0703, found 191.0705.



Silyl ether 799

To a solution of benzyl alcohol **812** (21 mg, 0.101 mmol) in DMF (1 mL) were added imidazole (14 mg, 0.202 mmol) and TBSCl (23 mg, 0.151 mmol). The resulting solution was maintained at room temperature with stirring until benzyl alcohol **812** was completely consumed by TLC analysis. At this time, the reaction was diluted with diethyl ether (25 mL) and washed with water (3 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum and purified by flash chromatography (20:1 hexanes:ethyl acetate eluent) to yield silyl ether **799** (32.5 mg,

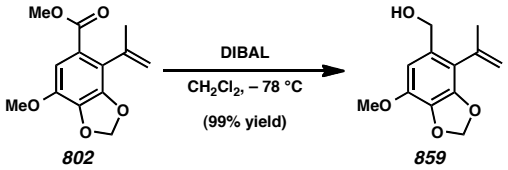
77% yield): R_f = 0.39 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74–6.61 (m, 2H), 6.02 (s, 2H), 5.87 (dd, *J* = 17.7, 1.8 Hz, 1H), 5.40 (dd, *J* = 11.7, 1.8 Hz, 1H), 4.71 (d, *J* = 0.6 Hz, 2H), 3.90 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.11, 142.62, 134.41, 133.25, 128.37, 117.90, 112.36, 106.58, 101.75, 63.40, 56.59, 26.12, 18.58, -5.02; IR (NaCl/film) 2953, 2928, 2855, 1639, 1492, 1462, 1446, 1431, 1346, 1312, 1255, 1154, 1121, 1046, 1005, 947, 910, 836, 775 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{11}O_3$ $[M–OTBS]^{\cdot+}$: 191.0703, found 191.0702.



α-Methyl styrene 802

Aryl bromide **618** (100 mg, 0.346 mmol), $PdCl_2(PPh_3)_2$ (12 mg, 0.0173 mmol), and Na_2CO_3 (110 mg, 1.04 mmol) were combined in a flame-dried reaction flask. To this were added DME (3.5 mL) and water (0.85 mL) (each sparged with argon), followed by the boronic ester (87 mg, 0.519 mmol). The sealed reaction was heated to 85 °C in an oil bath and maintained at 85 °C with stirring until aryl bromide **618** was consumed by TLC analysis (about 5 hours). At this time, the reaction was cooled to room temperature, diluted with ethyl acetate (10 mL), and filtered over a pad of Celite (rinsing with ethyl acetate). The filtrate was washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield α-methyl styrene **802** (73 mg, 84% yield): R_f = 0.13 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14

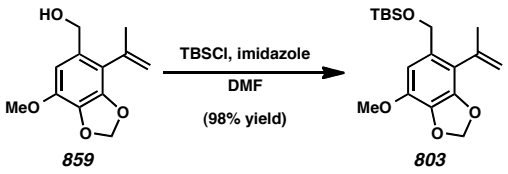
(s, 1H), 6.04 (s, 2H), 5.28–5.15 (m, 1H), 4.86 (dd, J = 1.7, 0.9 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 2.15–1.98 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.25, 146.16, 141.87, 140.11, 137.92, 123.53, 121.15, 115.12, 110.32, 102.11, 56.58, 51.96, 23.41; IR (NaCl/film) 2913, 1711, 1635, 1499, 1427, 1325, 1244, 1194, 1174, 1112, 1049, 1038, 962, 899, 862, 789, 757 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{13}H_{15}O_5$ $[M+H]^+$: 251.0914, found 251.0919.



Benzyl alcohol 859

A solution of α-methyl styrene **802** (25 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was cooled to –78 °C. To this solution was added DIBAL dropwise. The reaction was maintained at –78 °C for 15 minutes, at which time TLC analysis indicated complete consumption of α-methyl styrene **802**. The reaction was quenched at –78 °C by the addition of a saturated solution of Rochelle's salt (1 mL) and subsequently warmed to room temperature over one hour with vigorous stirring. The reaction was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The organic phase was washed with brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum to yield benzylic alcohol **859** (22 mg, 99% yield): R_f = 0.18 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.97 (s, 2H), 5.33 (dd, J = 2.0, 1.6 Hz, 1H), 4.97 (dd, J = 2.0, 1.0 Hz, 1H), 4.58 (d, J = 0.4 Hz, 2H), 3.90 (s, 3H), 2.05 (dd, J = 1.5, 1.0 Hz, 3H), 1.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.74, 142.46, 139.13, 134.20, 132.26, 118.49,

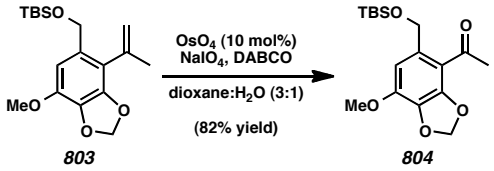
117.21, 107.65, 101.52, 62.93, 56.55, 23.86; IR (NaCl/film) 3358, 2887, 1639, 1596, 1498, 1425, 1338, 1317, 1164, 1115, 1039, 943, 908, 834 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{13}O_3$ $[M–OH]^{\cdot+}$: 205.0859, found 205.0858.



859 ***803***

Silyl ether 803

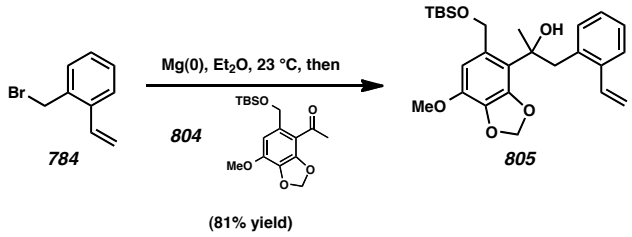
To a solution of benzyl alcohol **859** (22 mg, 0.1 mmol) in DMF (1 mL) were added imidazole (13.6 mg, 0.2 mmol) and TBSCl (22.6 mg, 0.150 mmol). The resulting solution was maintained at room temperature with stirring until TLC analysis indicated complete consumption of benzyl alcohol **859**. At this time, the reaction was diluted with diethyl ether (25 mL) and washed with water (3 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum to yield silyl ether **803** (33 mg, 98% yield): R_f = 0.59 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 5.96 (s, 2H), 5.29 (d, *J* = 1.9 Hz, 1H), 4.91 (dd, *J* = 2.0, 1.0 Hz, 1H), 4.63 (d, *J* = 0.6 Hz, 2H), 3.90 (s, 3H), 2.13–1.89 (m, 3H), 0.94 (s, 9H), 0.09 (s, 6H); 13C NMR; IR (NaCl/film) 2853, 2928, 2855, 1639, 1597, 1497, 1462, 1424, 1343, 1254, 1164, 1119, 1050, 948, 836, 775 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{13}O_3$ $[M–OTBS]^{\cdot+}$: 205.0859, found 205.0859.



803 ***804***

Acetophenone 804

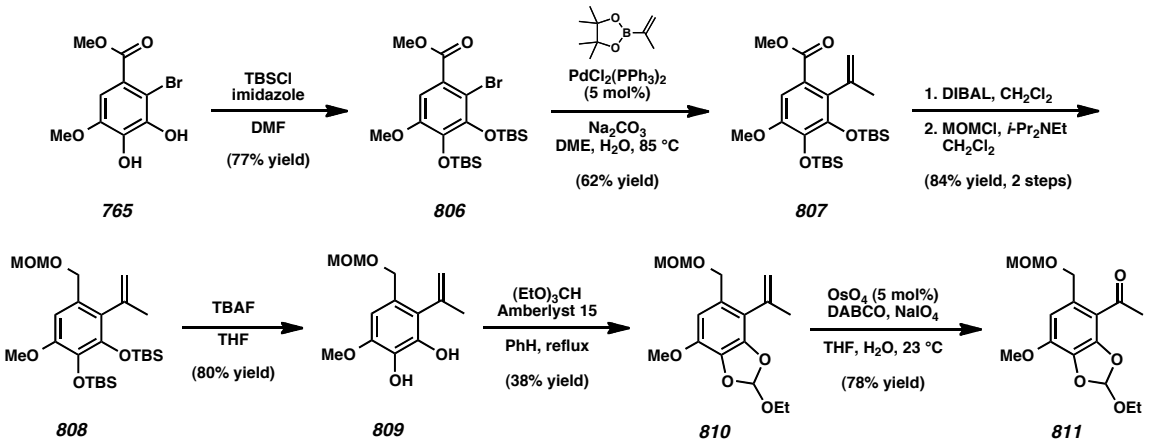
Silyl ether **803** (25 mg, 0.0743 mmol), DABCO (42 mg, 0.393 mmol), and $NaIO_4$ (159 mg, 0.743 mmol) were combined in dioxane (0.75 mL) and water (0.75 mL). Osmium tetroxide (1 mg, 0.00393 mmol) was added and the reaction was maintained with vigorous stirring at room temperature until silyl ether **803** was consumed by TLC analysis. At this time, the reaction was filtered through a Celite plug (rinsing with ethyl acetate). The filtrate was washed with brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (7:1 hexanes:ethyl acetate eluent) to yield acetophenone **804** (21 mg, 82% yield): R_f = 0.26 (10:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (t, J = 1.1 Hz, 1H), 6.07 (s, 2H), 4.96 (d, J = 1.1 Hz, 2H), 3.95 (s, 3H), 2.55 (s, 3H), 0.96 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.18, 150.18, 146.30, 139.41, 133.53, 112.64, 105.34, 102.02, 63.72, 56.39, 32.38, 26.12, 18.49, –5.18; IR (NaCl/film) 2923, 2853, 1657, 1626, 1462, 1423, 1360, 1284, 1259, 1155, 1093, 1049, 1004, 956, 867, 839, 774 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{17}H_{27}O_5Si$ $[M+H]^+$: 339.1622, found 339.1628.



Tertiary alcohol 805

A flame-dried flask was charged with magnesium turnings (106 mg, 4.36 mmol), evacuated, and backfilled with nitrogen. Diethyl ether (1 mL) was added, followed by 1,2-dibromoethane (15 μL). After 15 minutes, benzyl bromide **784** (344 mg, 1.75 mmol) was added as a solution in diethyl ether (5 mL). The suspension was maintained at room temperature with stirring for 2.5 hours, at which time, acetophenone **804** (295 mg, 0.873 mmol) was added dropwise as a solution in diethyl ether (4 mL). The reaction was further maintained for 15 minutes at room temperature with stirring until acetophenone **804** was completely consumed by TLC analysis. The reaction was quenched by the addition of a saturated solution of NH_4Cl (4 mL). The biphasic suspension was then diluted with diethyl ether (25 mL) and washed with saturated $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield tertiary alcohol **805** (321 mg, 81% yield): R_f = 0.42 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 1H), 7.22–7.05 (m, 3H), 6.37 (s, 1H), 5.95 (s, 2H), 5.53 (dd, J = 17.4, 1.5 Hz, 1H), 5.17 (dd, J = 11.0, 1.5 Hz, 1H), 4.80 (s, 1H), 4.65 (dd, J = 40.5, 11.6 Hz, 2H), 3.88 (s, 3H), 3.30 (dd, J = 32.8, 13.9 Hz, 2H), 1.63 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.72, 141.43, 138.29, 136.10, 135.80, 134.84, 132.18, 131.85, 127.01, 126.51, 125.48, 123.04, 114.52, 110.73, 100.97, 76.73, 66.92, 56.69, 43.69, 29.30, 26.03,

18.37, -4.80, -4.94; IR (NaCl/film) 3435, 2953, 2928, 2855, 1639, 1462, 1412, 1382, 1313, 1253, 1139, 1038, 999, 943, 837, 777 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{26}H_{34}O_4Si$ $[M–OH]^{\cdot+}$: 439.2299, found 439.2295.



Acetophenone 811

To a solution of catechol **765** (5.693 g, 20.5 mmol) in DMF (103 mL) were added imidazole (4.20 g, 61.6 mmol), DMAP (251 mg, 2.05 mmol), and TBSCl (9.29 g, 61.6 mmol). The resulting solution was maintained with stirring at room temperature until catechol **765** was fully consumed by TLC. At that time, the reaction was diluted with diethyl ether (150 mL) and washed with water (3 x 50 mL) and brine (50 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (25:1 hexanes:ethyl acetate eluent) to yield bis-silyl ether **806** (7.96 g, 77% yield).

Bis-silyl ether **806** (1.0 g, 1.98 mmol), $PdCl_2(PPh_3)_2$ (76 mg, 0.109 mmol), and Na_2CO_3 (629 mg, 5.93 mmol) were combined in a flame-dried reaction flask. The flask was evacuated and backfilled with nitrogen. To the solids were added DME (20 mL) and water (5 mL) (both sparged with argon), followed by the boronic ester (559 μL, 2.97

mmol). The sealed reaction flask was heated to 85 °C in an oil bath and maintained at 85 °C until bis-silyl ether **806** was fully consumed by TLC analysis. At that time, the reaction was cooled to room temperature and filtered through a Celite plug (washing with ethyl acetate). The filtrate was washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (20:1 hexanes:ethyl acetate eluent) to yield α-methyl styrene **807** (576 mg, 62% yield).

A solution of α-methyl styrene **807** (2.01 g, 4.31 mmol) in CH_2Cl_2 (43 mL) was cooled to –78 °C. To this was added DIBAL (1.69 mL, 9.49 mmol) dropwise, and the reaction was maintained at –78 °C until α-methyl styrene **807** was fully consumed by TLC. At this time, the reaction was quenched by the addition of a saturated solution of Rochelle's salt (15 mL) and subsequently warmed to room temperature over one hour with vigorous stirring. The reaction was diluted with CH_2Cl_2 (25 mL) and washed with water (25 mL) and brine (25 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum to yield the benzyl alcohol (1.59 g, 84% yield), which was immediately taken on to the next step.

A solution of the benzyl alcohol (1.59 g, 3.64 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C in an ice bath. To this were added *i*-Pr_2Net (1.65 mL, 9.46 mmol) and MOMCl (0.581 mL, 7.64 mmol) sequentially. The resulting solution was allowed to warm to room temperature over several hours with stirring and subsequently maintained at room temperature until the benzyl alcohol was consumed by TLC analysis. At this time, the reaction was diluted with CH_2Cl_2 (25 mL) and washed with 10% citric acid

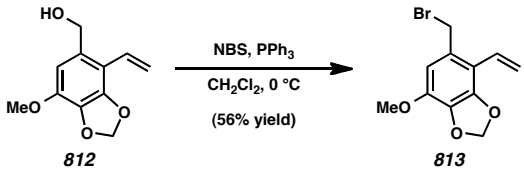
solution (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum to yield methoxymethyl ether **808** (1.76 g, 99% yield).

To a solution of methoxymethyl ether **808** (1.76 g, 3.64 mmol) in THF (12 mL) was added TBAF (8.01 mL, 8.01 mmol, 1.0 M solution in THF). The resulting solution was maintained with stirring at room temperature until methoxymethyl ether **808** was fully consumed by TLC analysis. At that time, the reaction was diluted with diethyl ether (50 mL) and washed with water (2 x 25 mL) and brine (25 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 → 3:1 → 1:1 hexanes:ethyl acetate eluent) to yield catechol **809** (737 mg, 80% yield).

To a solution of catechol **809** (437 mg, 1.72 mmol) in benzene (17 mL) were added triethyl orthoformate (0.86 mL, 5.16 mmol) and Amberlyst 15 (9 mg, 5 mg/mmol). The reaction flask was equipped with a Dean–Stark condenser (empty) and reflux condenser. The reaction was heated to reflux and maintained at reflux with distillation of the ethanol/benzene azeotrope into the Dean–Stark condenser. Benzene was replenished into the reaction flask as needed. After two days, the reaction was cooled to room temperature, filtered through a Celite plug, and concentrated under vacuum. The crude residue was purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield orthoester **810** (200 mg, 38% yield).

Orthoester **810** (200 mg, 0.644 mmol), DABCO (361 mg, 3.22 mmol), and $NaIO_4$ (1.38 g, 6.44 mmol) were combined in THF (6.4 mL) and water (6.4 mL). Osmium tetroxide (8 mg, 0.032 mmol) was added and the resulting suspension was maintained with vigorous stirring until orthoester **810** was consumed by TLC analysis. At that time,

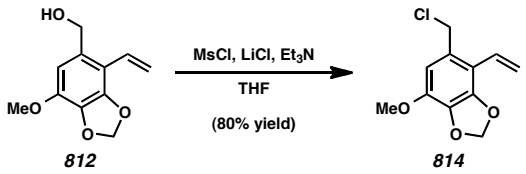
the reaction was filtered through a Celite plug (washing with ethyl acetate). The filtrate was washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (6:1 hexanes:ethyl acetate eluent) to yield acetophenone **811** (140 mg, 70% yield): R_f = 0.17 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.90 (s, 1H), 4.84 (s, 2H), 4.73 (s, 2H), 3.98 (s, 3H), 3.83–3.69 (m, 2H), 3.41 (s, 3H), 2.59 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.00, 147.87, 145.13, 134.57, 132.69, 119.74, 113.24, 107.11, 96.34, 67.82, 59.66, 56.56, 55.49, 32.10, 14.81; IR (NaCl/film) 2982, 2943, 1673, 1634, 1446, 1427, 1360, 1286, 1266, 1149, 1106, 1040, 958, 917, 842, 783 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{15}O_5$ [M–OMOM]$^{\bullet+}$: 251.0914, found 251.0920.



Benzyl bromide 813

A solution of benzyl alcohol **812** (245 mg, 1.18 mmol) in CH_2Cl_2 (6 mL) was cooled to 0 °C in an ice bath. Triphenylphosphine (358 mg, 13.7 mmol) was added, followed by NBS (243 mg, 13.7 mmol), and the reaction was maintained at 0 °C until benzyl alcohol **812** was consumed by TLC analysis. Following this time, the reaction was warmed to room temperature and concentrated under vacuum. The crude residue was purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield benzyl bromide **813** (180.5 mg, 56% yield): R_f = 0.56 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 17.6, 11.7 Hz, 1H), 6.57 (s, 1H), 6.07 (s, 2H), 6.02 (dd, *J* =

17.6, 1.7 Hz, 1H), 5.57 (dd, J = 11.7, 1.7 Hz, 1H), 4.57 (s, 2H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.37, 142.50, 135.99, 129.08, 127.84, 119.06, 113.75, 109.76, 101.92, 56.60, 32.67; IR (NaCl/film) 2901, 1637, 1495, 1456, 1431, 1351, 1319, 1149, 1089, 1045, 947, 919, 834, 768 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{11}H_{11}O_3$ $[M–Br]^+$: 191.0703, found 191.0700.

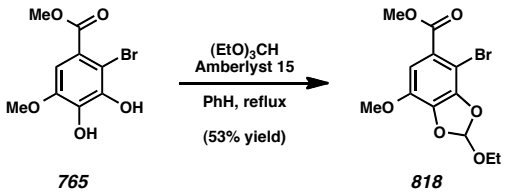


812 ***814***

Benzyl chloride 814

Lithium chloride (61 mg, 1.44 mmol) was flame dried in a reaction flask. Benzyl alcohol **812** (200 mg, 0.961 mmol) was added to the LiCl as a solution in THF (2 mL), and the resulting solution was cooled to 0 °C in an ice bath. Triethylamine (201 μL, 1.44 mmol) was added, followed by MsCl (82 μL, 1.05 mmol), dropwise. The reaction was then allowed to warm to room temperature over one hour, at which point it was maintained at room temperature until benzylic alcohol was consumed by TLC analysis. The reaction was quenched by the addition of a saturated solution of NH_4Cl (3 mL) and extracted with diethyl ether (25 mL). The ether extracts were washed with brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield benzyl chloride **814** (139.6 mg, 64% yield): R_f = 0.10 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (dd, J = 17.6, 11.7 Hz, 1H), 6.56 (s, 1H), 6.06 (s, 2H), 6.04–5.92 (m, 1H), 5.53 (dd, J = 11.7, 1.7 Hz, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 1.60–1.48 (m, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 147.33, 142.45, 135.88, 128.91, 127.79, 119.12, 113.80, 109.84, 101.88, 56.62, 44.94; IR (NaCl/film) 3435, 1639, 1496, 1459, 1431, 1355, 1317, 1262, 1149, 1090, 1046, 1018, 951, 919, 837, 772 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{11}O_3$ $[M–Cl]^{\bullet+}$: 191.0708, found 191.0704.

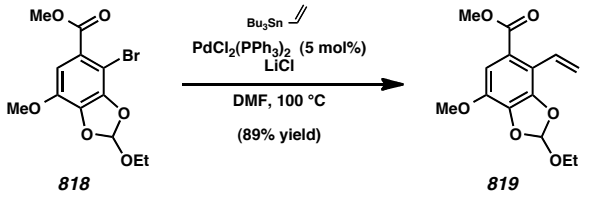


765 ***818***

Orthoester 818

To a solution of catechol **765** (1.94 g, 7.50 mmol) in benzene (70 mL) were added triethyl orthoformate (3.5 mL, 21.0 mmol) and Amberlyst 15 (35 mg, 5 mg/mmol). The reaction flask was equipped with a Dean–Stark condenser (empty) and reflux condenser. The reaction was heated to reflux and maintained at reflux with distillation of the ethanol/benzene azeotrope into the Dean–Stark condenser. Benzene was replenished into the reaction flask as needed. After two days, the reaction was cooled to room temperature, filtered through a Celite plug, and concentrated under vacuum. The crude residue was purified by flash chromatography (7:1 hexanes:ethyl acetate eluent) to yield orthoester **818** (1.25 g, 53% yield): R_f = 0.25 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.01 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.78 (dq, *J* = 7.1, 1.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.55, 146.37, 141.62, 136.77, 124.22, 120.05, 111.89, 93.99, 59.99, 56.77, 52.35, 14.74; IR (NaCl/film) 2981, 2950, 1728, 1629, 1600, 1490, 1436, 1348, 1319, 1249, 1175, 1109, 1092, 1036, 939,

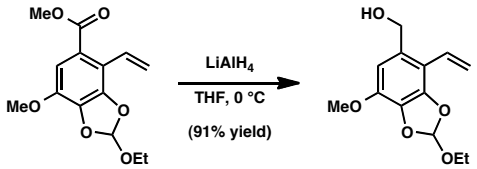
852, 770 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{14}O_6{}^{79}Br$ $[M+H]^+$: 332.9968, found 332.9996.



Styrene 819

Lithium chloride (63.6 mg, 1.50 mmol) was flame dried in the reaction flask under vacuum. $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015 mmol) was added, and the flask was evacuated and backfilled with nitrogen. In a different flame-dried flask, a solution of aryl bromide **818** (100 mg, 0.30 mmol) and tri-*n*-butyl(vinyl)stannane (175 μL, 0.60 mmol) in DMF (3 mL) was sparged with argon for 10 minutes. The DMF solution was transferred to the reaction flask containing the LiCl and palladium catalyst by cannula and heated to 100 °C in an oil bath. The reaction was maintained at 100 °C with stirring under nitrogen atmosphere until aryl bromide **818** was fully consumed by TLC analysis. Following this time, the reaction was diluted with diethyl ether (25 mL) and washed with water (4 x 20 mL) and brine (20 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield styrene **819** (70.5 mg, 84% yield): R_f = 0.33 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.17 (m, 2H), 7.00 (s, 1H), 5.95 (dd, *J* = 17.8, 1.7 Hz, 1H), 5.51 (dd, *J* = 11.7, 1.7 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.74 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.22, 145.52, 141.29, 136.99, 129.45, 122.89, 119.93, 119.27, 115.82, 110.41, 59.44, 56.51, 52.15, 14.79; IR

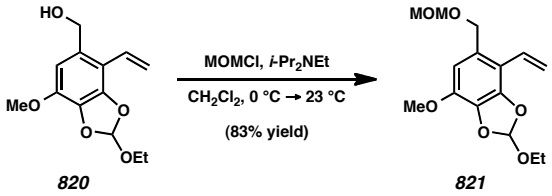
(NaCl/film) 2981, 2951, 1716, 1637, 1590, 1496, 1434, 1346, 1318, 1245, 1192, 1167, 1133, 1089, 1038, 964, 917, 865, 787 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{17}O_6$ $[M+H]^+$: 281.1020, found 281.1032.



819 ***820***

Benzyl alcohol 820

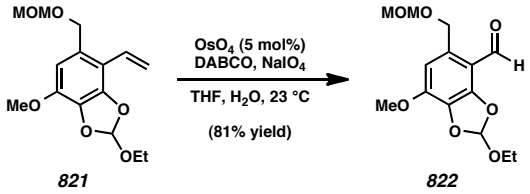
A solution of styrene **819** (70.5 mg, 0.251 mmol) in THF (2.5 mL) was cooled to 0 °C in an ice bath. Lithium aluminum hydride (9.5 mg, 0.251 mmol) was added and the reaction was maintained at 0 °C for 5 minutes, at which time, TLC analysis showed full consumption of styrene **819**. The reaction was quenched at 0 °C by the sequential addition of 10 μL water, 10 μL of 20% NaOH solution, and 30 μL water and then warmed to room temperature with vigorous stirring over one hour. Following this time, the suspension was filtered and the filtrate was concentrated under vacuum to yield benzyl alcohol **820** (58.2 mg, 92% yield): R_f = 0.13 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.78 (dd, *J* = 17.7, 11.7 Hz, 1H), 6.59 (s, 1H), 5.97 (dd, *J* = 17.7, 1.7 Hz, 1H), 5.47 (dd, *J* = 11.7, 1.7 Hz, 1H), 4.67 (s, 2H), 3.91 (s, 3H), 3.74 (q, *J* = 7.1 Hz, 2H), 1.80 (s, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.47, 141.79, 133.61, 132.29, 127.96, 119.59, 118.58, 112.55, 107.90, 63.49, 59.27, 56.54, 14.83; IR (NaCl/film) 3368, 2979, 1642, 1497, 1448, 1437, 1376, 1311, 1154, 1131, 1093, 1034, 1006, 927, 833, 771 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{15}O_4$ $[M–OH]^{\cdot+}$: 235.0965, found 235.0962.



820 *821*

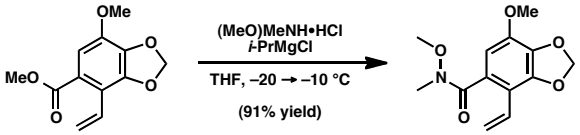
Methoxymethyl ether 821

A solution of benzyl alcohol **820** (58.2 mg, 0.231 mmol) in CH_2Cl_2 (2.3 mL) was cooled to 0 °C in an ice bath. To this were added *i*-Pr_2Net (104 μL, 0.60 mmol) and MOMCl (36.8 μL, 0.484 mmol) sequentially. The resulting solution was allowed to warm to room temperature over several hours with stirring and subsequently maintained at room temperature until benzyl alcohol **820** was consumed by TLC analysis. At this time, the reaction was diluted with diethyl ether (25 mL) and washed with 10% citric acid solution (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum to yield methoxymethyl ether **821** (57.1 mg, 83% yield): R_f = 0.38 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.77 (dd, J = 17.7, 11.7 Hz, 1H), 6.60 (s, 1H), 5.97 (dd, J = 17.7, 1.7 Hz, 1H), 5.46 (dd, J = 11.7, 1.6 Hz, 1H), 4.69 (s, 2H), 4.59 (s, 2H), 3.92 (s, 3H), 3.74 (q, J = 7.1 Hz, 2H), 3.42 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.45, 141.66, 133.82, 129.14, 128.21, 119.57, 118.39, 113.21, 109.05, 95.48, 67.35, 59.11, 56.56, 55.54, 14.83; IR (NaCl/film) 2980, 2841, 1642, 1498, 1448, 1437, 1379, 1312, 1148, 1093, 1038, 916, 831, 770 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{13}H_{15}O_4$ $[M–OMOM]^{\cdot+}$: 235.0965, found 235.0959.



Benzaldehyde 822

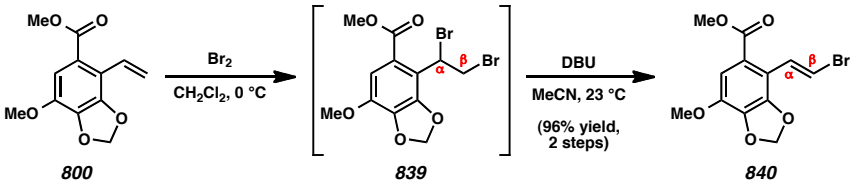
Orthoester **821** (57.1 mg, 0.193 mmol), DABCO (108 mg, 0.963 mmol), and $NaIO_4$ (412 mg, 1.93 mmol) were combined in THF (2 mL) and water (2 mL). Osmium tetroxide (2.4 mg, 0.0096 mmol) was added and the resulting suspension was maintained with vigorous stirring until orthoester **821** was consumed by TLC analysis. Following that time, the reaction was filtered through a Celite plug (washing with ethyl acetate). The filtrate was washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude residue was purified by flash chromatography (4:1 hexanes:ethyl acetate eluent) to yield benzaldehyde **822** (46 mg, 81% yield): R_f = 0.29 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.28–10.19 (m, 1H), 7.01 (s, 1H), 6.83 (s, 1H), 5.02–4.82 (m, 2H), 4.75 (s, 2H), 4.00 (s, 3H), 3.78 (qd, J = 7.1, 1.2 Hz, 2H), 3.41 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.69, 151.11, 146.81, 135.09, 133.00, 120.72, 110.87, 107.18, 96.23, 67.11, 59.98, 56.75, 55.57, 14.75; IR (NaCl/film) 2942, 1684, 1635, 1502, 1448, 1387, 1291, 1130, 1037, 916, 774 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{14}H_{19}O_7$ $[M+H]^+$: 299.1125, found 299.1115.



800 ***838***

Weinreb amide 838

A slurry of ester **800** (1.08 g, 4.57 mmol) and (MeO)MeNH•HCl (691 mg, 7.08 mmol) in THF (9 mL) was cooled to –20 °C. The *i*-PrMgCl (8.36 mL, 13.7 mmol, 1.64 M solution in THF) was added very slowly over 5–10 minutes. Following addition, the reaction was maintained with stirring between –10 °C and –20 °C for 20 minutes, at which point it was quenched by the addition of a saturated solution of NH_4Cl (10 mL). The reaction was then warmed to room temperature, diluted with diethyl ether (25 mL), and washed with water (25 mL) and brine (25 mL). The organic phase was dried with Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (1:1 hexanes:ethyl acetate eluent) to yield Weinreb amide **838** (1.10 g, 91% yield): R_f = 0.27 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (m, 2H), 6.07 (s, 2H), 5.93 (dd, *J* = 17.7, 1.2 Hz, 1H), 5.39 (d, *J* = 11.6 Hz, 1H), 3.89 (s, 3H), 3.57 (br s, 3H), 3.27 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.64, 142.60, 135.97, 128.70, 118.35, 112.20, 106.37, 101.95, 61.09, 56.62; IR (NaCl/film) 2935, 1648, 1633, 1493, 1461, 1430, 1379, 1303, 1156, 1074, 1040, 982, 938, 839, 800 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{16}O_5N$ $[M+H]^+$: 266. 1023, found 266.1027.

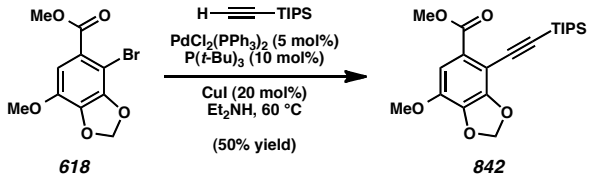


β-Bromo styrene 840

A solution of styrene **800** (31 mg, 0.131 mmol) in CH_2Cl_2 (1.3 mL) was cooled to 0 °C. Bromine (7.1 μL, 0.138 mmol) was added dropwise to the styrene solution, and the resulting solution was maintained with stirring at 0 °C until styrene **800** was consumed by TLC analysis. At that time, the reaction was concentrated under vacuum at 0 °C. Dichloromethane (2 x 1 mL) was added to the concentrated residue and evaporated under vacuum at 0 °C to remove excess bromine.

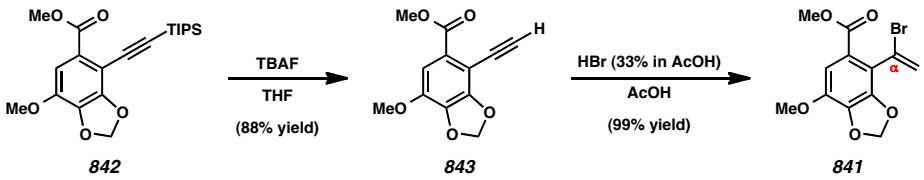
The concentrated residue was warmed to room temperature and acetonitrile (1.6 mL) was added to the concentrated mixture, followed by DBU (39.2 μL, 0.262 mmol). The resulting solution was maintained with stirring until dibromide **839** was fully consumed by TLC analysis. The reaction was then quenched by the addition of a 1 N HCl solution (1.5 mL). The reaction was diluted with ethyl acetate (25 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield β-bromo styrene **840** (39.6 mg, 96% yield): R_f = 0.29 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 14.0 Hz, 1H), 7.23 (s, 1H), 7.11 (d, J = 14.0 Hz, 1H), 6.11 (s, 2H), 3.94 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.69, 147.00, 142.18, 138.52, 129.70, 122.01, 113.99, 111.79, 111.28, 102.33, 56.57, 52.29; IR (NaCl/film) 2909, 1705, 1631, 1583, 1490, 1432, 1323, 1246,

1189, 1164, 1060, 1038, 965, 937, 926, 888, 862, 760 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{12}O_5{}^{79}Br$ $[M+H]^+$: 314.9863, found 314.9862.



Aryl TIPS acetylene 842

Aryl bromide **618** (50 mg, 0.173 mmol), $PdCl_2(PPh_3)_2$ (6.0 mg, 0.00865 mmol), and CuI (6.6 mg, 0.0346 mmol) were combined in a flame-dried reaction tube. The tube was evacuated and transferred to a glove box, where P(*t*-Bu)$_3$ (3.5 mg, 0.0173 mmol) was added. The flask was sealed and removed from the glove box and placed under an atmosphere of nitrogen in the hood. Diethylamine (1 mL, degassed) was added, followed by TIPS acetylene (46.6 μL, 0.208 mmol). The reaction tube was sealed and heated to 60 °C in an oil bath, where it was maintained for 12 hours with stirring. Following this time, the reaction was cooled to room temperature and concentrated under vacuum. The crude residue was purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield aryl TIPS acetylene **842** (34 mg, 50% yield): R_f = 0.53 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 1H), 6.12 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 1.15 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.34, 152.10, 142.79, 138.09, 126.10, 111.00, 102.75, 100.04, 99.33, 98.35, 56.61, 52.12, 18.66, 11.33; IR (NaCl/film) 2940, 2863, 2148, 1720, 1638, 1589, 1495, 1430, 1327, 1248, 1195, 1173, 11131, 1048, 993, 961, 882, 773 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{31}O_5Si$ $[M+H]^+$: 391.1935, found 391.1947.

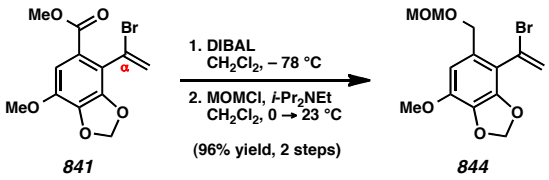


α-Bromo styrene 841

To a solution of aryl TIPS acetylene **842** (34 mg, 0.0871 mmol) in THF (1 mL) was added TBAF (104 μL, 0.104 mmol, 1.0 M solution in THF). The resulting solution was maintained at room temperature with stirring until aryl TIPS acetylene **842** was fully consumed by TLC analysis. At that time, the reaction was diluted with diethyl ether (25 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum to yield aryl acetylene **843** (18 mg, 88% yield).

To a solution of aryl acetylene **843** (18 mg, 0.0769 mmol) in acetic acid (1 mL) was added HBr in acetic acid (14 μL, 0.0769 mmol, 33% solution of HBr in acetic acid). The resulting solution was maintained at room temperature until aryl acetylene **843** was consumed by TLC analysis. At that time, water (2 mL) and CH_2Cl_2 (3 mL) were added and the biphasic solution was stirred vigorously for 5 minutes. The layers were separated and the organic phase was washed with saturated $NaHCO_3$ solution (10 mL), dried with $MgSO_4$, and concentrated under vacuum to yield α-bromo styrene **841** (24.1 mg, 99% yield): R_f = 0.36 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.10 (s, 2H), 5.92 (s, 1H), 5.80 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.20, 146.75, 142.99, 138.10, 123.55, 121.94, 121.07, 117.29, 110.94, 102.73, 56.73, 52.33; IR (NaCl/film) 2948, 1718, 1641, 1591, 1496, 1430, 1358, 1320,

1249, 1192, 1171, 1136, 1044, 959, 899, 870, 784, 757 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{12}O_5{}^{79}Br$ $[M+H]^+$: 314.9863, found 314.9868.

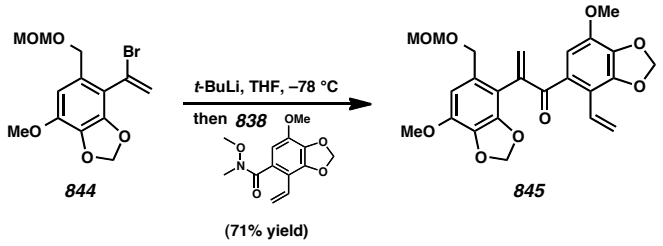


Methoxymethyl ether 844

A solution of α-bromo styrene **841** (118.2 mg, 0.375 mmol) in CH_2Cl_2 (4 mL) was cooled to –78 °C. To this was added DIBAL (154 μL, 0.863 mmol) dropwise, and the reaction was maintained at –78 °C until α-bromo styrene **841** was fully consumed by TLC. At this time, the reaction was quenched by the addition of a saturated solution of Rochelle's salt (15 mL) and subsequently warmed to room temperature over one hour with vigorous stirring. The reaction was diluted with CH_2Cl_2 (25 mL) and washed with water (25 mL) and brine (25 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum. The crude isolate was immediately taken on to the next step.

A solution of the crude product in CH_2Cl_2 (15 mL) was cooled to 0 °C in an ice bath. To this were added *i*-Pr_2NEt (229 μL, 1.31 mmol) and MOMCl (85.5 μL, 1.12 mmol) sequentially. The resulting solution was allowed to warm to room temperature over several hours with stirring and subsequently maintained at room temperature until the starting material was consumed by TLC analysis. At this time, the reaction was diluted with CH_2Cl_2 (25 mL) and washed with 10% citric acid solution (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield

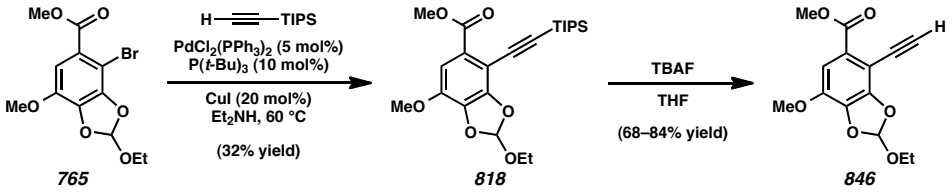
methoxymethyl ether **844** (118.9 mg, 95% yield, 2 steps): R_f = 0.27 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.05 (s, 2H), 6.02 (d, *J* = 1.5 Hz, 1H), 5.89 (d, *J* = 1.5 Hz, 1H), 4.73 (s, 2H), 4.59 (s, 2H), 3.94 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.31, 143.78, 134.48, 129.82, 124.14, 120.62, 115.81, 108.16, 102.14, 95.96, 66.43, 56.61, 55.54; IR (NaCl/film) 2941, 2885, 1644, 1628, 1498, 1432, 1381, 1315, 1210, 1147, 1101, 1041, 948, 916, 834, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_3{}^{79}Br$ [M–OMOM]$^{\bullet+}$: 268.9808, found 268.9810.



Enone 845

In a flame-dried reaction flask under nitrogen, THF (7 mL) was cooled to –78 °C. To this was added *t*-BuLi (741 μL, 0.963 mmol, 1.3 M solution in pentane), followed by α-bromo styrene **844** (151.9 mg, 0.459 mmol) dropwise as a solution in THF (1.5 mL). The resulting solution was maintained at –78 °C for 10 minutes. Following this time, Weinreb amide **838** (146 mg, 0.550 mmol) was added dropwise as a solution in THF (1.5 mL). The reaction was maintained at –78 °C for 10 minutes, after which time, it was allowed to warm to room temperature, where it was maintained for three hours with stirring. Following that time, the reaction was quenched by the addition of a saturated solution of NH_4Cl (6 mL) and stirred vigorously for 10 minutes. The reaction was then diluted with ethyl acetate (25 mL) and washed with water (25 mL) and brine (25 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by

flash chromatography (3:1 hexanes:ethyl acetate eluent) to yield enone **845** (149.3 mg, 71% yield): R_f = 0.40 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83–6.74 (m, 2H), 6.67 (s, 1H), 6.20 (d, *J* = 1.0 Hz, 1H), 6.19 (d, *J* = 1.0 Hz, 1H), 6.10 (s, 2H), 6.00–5.91 (m, 3H), 5.40 (dd, *J* = 11.7, 1.6 Hz, 1H), 4.62 (s, 2H), 4.46 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.12, 147.18, 146.95, 143.15, 142.89, 141.69, 137.22, 134.47, 132.97, 132.10, 130.02, 129.32, 118.52, 114.39, 113.20, 109.79, 109.31, 102.10, 101.66, 95.33, 67.03, 56.62, 56.60, 55.49; IR (NaCl/film) 2942, 2888, 1653, 1632, 1590, 1491, 1430, 1317, 1156, 1123, 1037, 920, 837 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{22}H_{19}O_7{}^{79}Br$ [M–OMOM]$^{\bullet+}$: 395.1125, found 395.1140.

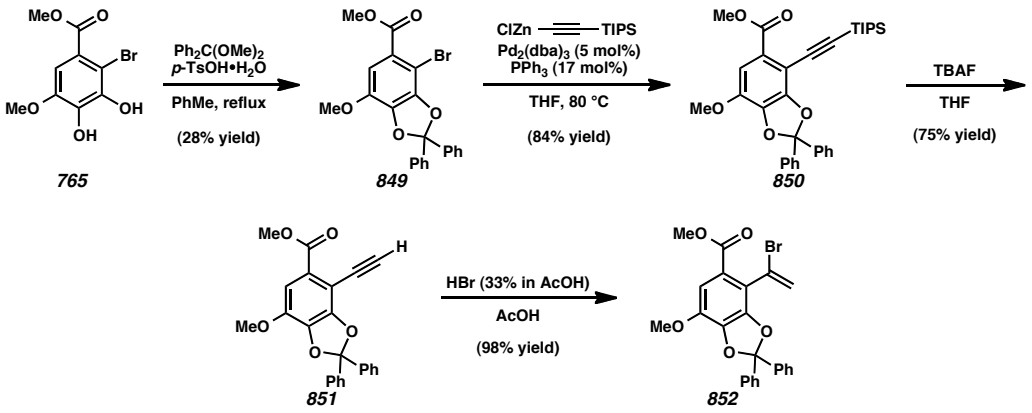


Aryl acetylene 846

Aryl bromide **765** (50 mg, 0.150 mmol), $PdCl_2(PPh_3)_2$ (5.3 mg, 0.0075 mmol), and CuI (5.7 mg, 0.030 mmol) were combined in a flame-dried reaction tube. The tube was evacuated and transferred to a glove box, where P(*t*-Bu)$_3$ (3.0 mg, 0.015 mmol) was added. The flask was sealed and removed from the glove box and placed under an atmosphere of nitrogen in the hood. Triethylamine (250 μL, degassed) and DMF (500 μL, degassed) were added, followed by TIPS acetylene (40.3 μL, 0.180 mmol). The reaction tube was sealed and heated to 100 °C in an oil bath, where it was maintained for 12 hours with stirring. Following this time, the reaction diluted with diethyl ether (25

mL) and washed with 10% citric acid (15 mL), water (3 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography (15:1 hexanes:ethyl acetate eluent) to yield aryl TIPS acetylene **818** (21.2 mg, 32% yield).

To a solution of aryl TIPS acetylene **818** (21.2 mg, 0.0488 mmol) in THF (500 μL) was added TBAF (53.6 μL, 0.054 mmol, 1.0 M solution in THF). The resulting solution was maintained at room temperature with stirring until aryl TIPS acetylene **818** was fully consumed by TLC analysis. At that time, the reaction was diluted with diethyl ether (25 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum to yield aryl acetylene **846** (18 mg, 88% yield): R_f = 0.22 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.03 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.78 (qd, *J* = 7.1, 2.7 Hz, 2H), 3.54 (s, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.58, 150.30, 142.51, 136.75, 126.07, 120.54, 110.89, 98.36, 85.07, 75.72, 59.88, 56.68, 52.17, 14.73; IR (NaCl/film) 3280, 2981, 2950, 1723, 1637, 1590, 1499, 1435, 1364, 1320, 1249, 1192, 1171, 1124, 1092, 1035, 966, 901, 860, 778, 753 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{15}O_6$ $[M+H]^+$: 279.0863, found 279.0872.



α-Bromo styrene 852

Catechol **765** (100 mg, 0.361 mmol), $Ph_2C(OMe)_2$ (87 mg, 0.379 mmol), and *p*-TsOH•H_2O (1 mg, 0.00361 mmol) were combined in toluene (4 mL). The reaction flask was equipped with a Dean–Stark trap (filled with toluene) and reflux condenser. The reaction was heated to reflux and maintained for 16 hours. After that time, the reaction was cooled to room temperature and washed with saturated $NaHCO_3$. The toluene solution was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield diphenyl acetal **849** (44.3 mg, 28%yield).

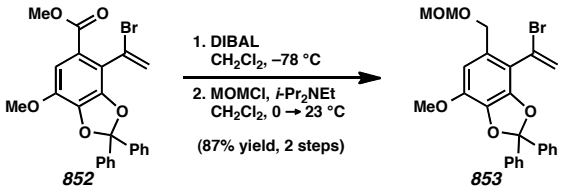
A solution of TIPS acetylene (500 mg, 2.74 mmol) in diethyl ether (3 mL) was cooled to –78 °C. To this was added *n*-BuLi (1.34 mL, 3.01 mmol, 2.25 M solution in hexanes). The resulting solution was maintained for one hour at –78 °C. In the meantime, $ZnCl_2$ (523 mg, 3.84 mmol) was flame dried under vacuum and cooled to room temperature under nitrogen. The lithium acetylide solution was transferred to the flask containing $ZnCl_2$ by cannula, and the resulting suspension was stirred at room temperature for one hour before use. Immediately prior to use, stirring was stopped to allow salts to settle. Only the supernatant was used for subsequent transformations.

A flame-dried reaction tube was charged with $Pd_2(dba)_3$ (5.2 mg, 0.00567 mmol) and PPh_3 (5.1 mg, 0.0193 mmol), evacuated, and backfilled with nitrogen. Diphenyl acetal **849** (50 mg, 0.113 mmol) was added as a THF solution (0.6 mL), followed by the zinc acetylene solution (231 mL, 0.136 mmol, 0.59 M solution in diethyl ether). The sealed reaction tube was then heated to 80 °C, where it was maintained with stirring until complete by TLC analysis. After that time, the reaction was cooled to room temperature, diluted with diethyl ether (25 mL), and washed with saturated NH_4Cl solution (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate eluent) to yield aryl TIPS acetylene **850** (52.8 mg, 84% yield).

To a solution of aryl TIPS acetylene **850** (204.5 mg, 0.377 mmol) in THF (4 mL) was added TBAF (414 μL, 0.414 mmol, 1.0 M solution in THF). The resulting solution was maintained at room temperature with stirring until aryl TIPS acetylene **850** was fully consumed by TLC analysis. At that time, the reaction was diluted with diethyl ether (25 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum to yield aryl acetylene **851** (110 mg, 75% yield).

To a solution of aryl acetylene **851** (110 mg, 0.285 mmol) in acetic acid (3 mL) was added HBr in acetic acid (77 μL, 0.427 mmol, 33% solution of HBr in acetic acid). The resulting solution was maintained at room temperature until aryl acetylene **851** was consumed by TLC analysis. At that time, toluene (3 mL) was added and the reaction was sparged with air for 5 minutes to remove any excess HBr. The solution was then concentrated from toluene three times. The crude residue was purified by flash

chromatography (10:1 hexanes:ethyl acetate eluent) to yield α-bromo styrene **852** (130.7 mg, 98% yield): R_f = 0.42 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.54 (m, 4H), 7.43–7.31 (m, 6H), 7.18 (s, 1H), 5.95 (d, *J* = 1.7 Hz, 1H), 5.83 (d, *J* = 1.7 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H); $_{13}$C NMR (125 MHz, $CDCl_3$) δ 166.34, 146.44, 142.98, 139.32, 137.73, 129.42, 128.32, 126.38, 123.40, 121.90, 121.27, 119.07, 117.30, 110.78, 56.69, 52.22; IR (NaCl/film) 2948, 1724, 1641, 1582, 1494, 1449, 1431, 1360, 1323, 1202, 1133, 1044, 1019, 974, 948, 906, 778 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{24}H_{20}O_5{}^{79}Br$ $[M+H]^+$: 467.0489, found 467.0486.



Methoxymethyl ether 853

A solution of α-bromo styrene **852** (130.7 mg, 0.280 mmol) in CH_2Cl_2 (3 mL) was cooled to –78 °C. To this was added DIBAL (115 μL, 0.643 mmol), dropwise, and the reaction was maintained at –78 °C until α-bromo styrene **852** was fully consumed by TLC. At this time, the reaction was quenched by the addition of a saturated solution of Rochelle's salt (3 mL) and subsequently warmed to room temperature over one hour with vigorous stirring. The reaction was diluted with diethyl ether (25 mL) and washed with water (25 mL) and brine (25 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum. The crude isolate was immediately taken on to the next step.

A solution of the crude product in CH_2Cl_2 (3 mL) was cooled to 0 °C in an ice bath. To this were added *i*-Pr_2Net (94.5 μL, 0.543 mmol) and MOMCl (30.9 μL, 0.407

mmol) sequentially. The resulting solution was allowed to warm to room temperature over several hours with stirring and subsequently maintained at room temperature until the starting material was consumed by TLC analysis. At this time, the reaction was diluted with diethyl ether (25 mL) and washed with 10% citric acid solution (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes:ethyl acetate) to yield methoxymethyl ether **853** (118.2 mg, 90% yield, 2 steps): R_f = 0.43 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.57 (m, 4H), 7.47–7.33 (m, 6H), 6.65 (s, 1H), 6.04 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.5 Hz, 1H), 4.72 (s, 2H), 4.59 (s, 2H), 3.96 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.06, 143.69, 139.81, 134.24, 129.51, 129.18, 128.19, 126.51, 124.05, 120.85, 118.24, 115.87, 108.29, 95.96, 66.53, 56.67, 55.53; IR (NaCl/film) 2934, 1644, 1495, 1446, 1433, 1382, 1317, 1265, 1208, 1140, 1042, 1020, 947, 915, 833, 777 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{25}H_{24}O_5{}^{79}Br$ $[M+H]^+$: 483.0802, found 483.0807.

3.6 NOTES AND REFERENCES

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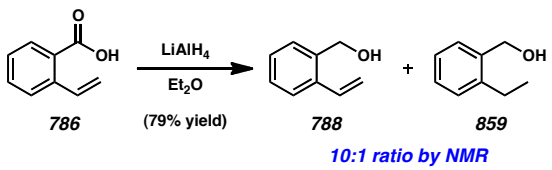
(26) All attempts to reduce the acid directly (e.g., with $LiAlH_4$) resulted in significant quantities of the fully reduced product (**859**), lacking the key terminal olefin.



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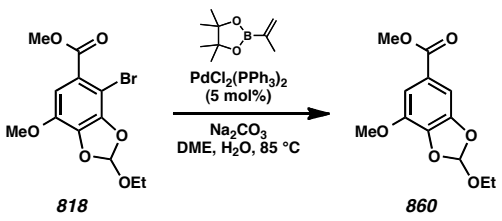

818 ***860***

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APPENDIX 3

Spectra Relevant to Chapter 3:

Efforts Toward the Total Synthesis of Integrastatins A and B

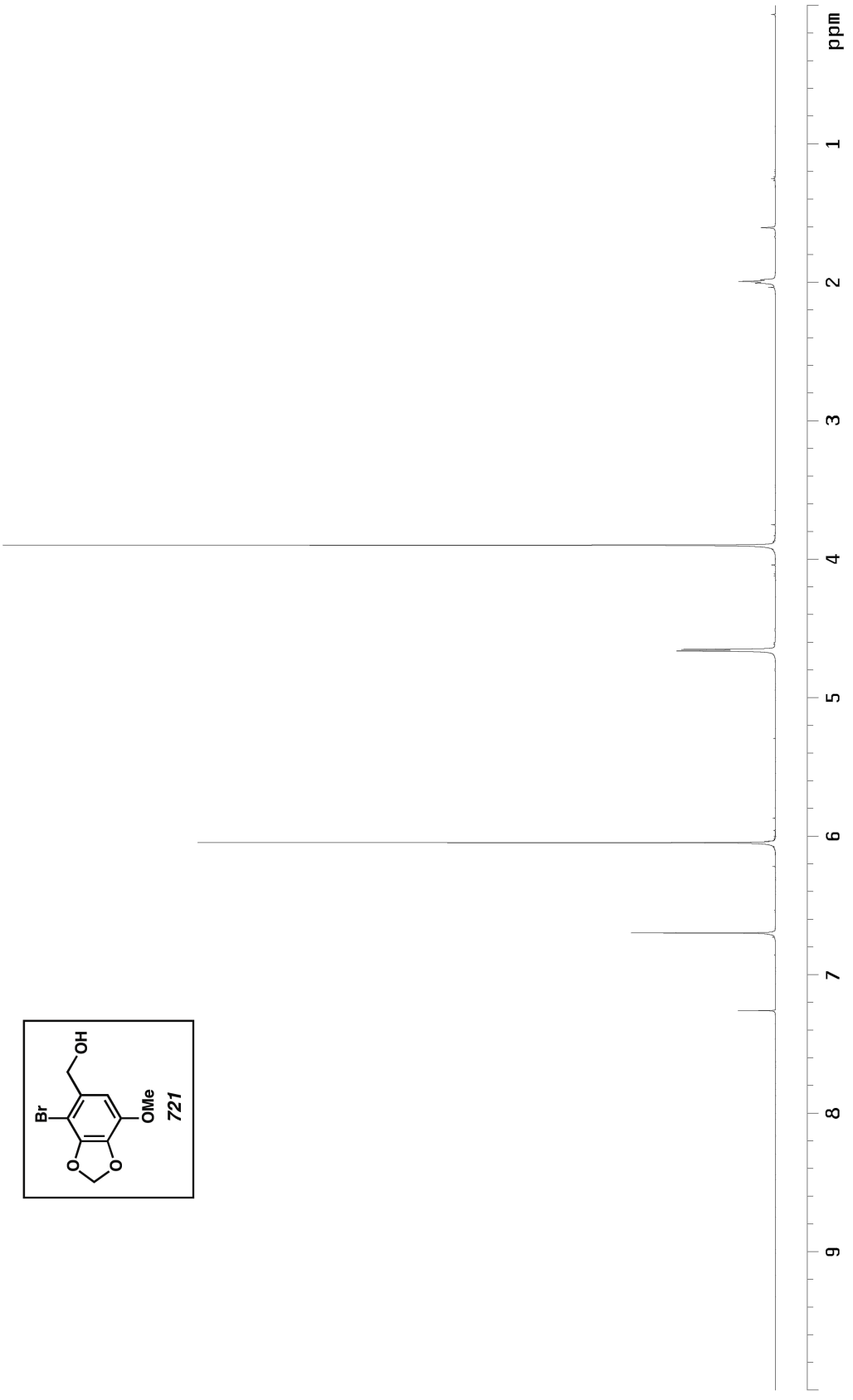


Figure A3.1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **721**.

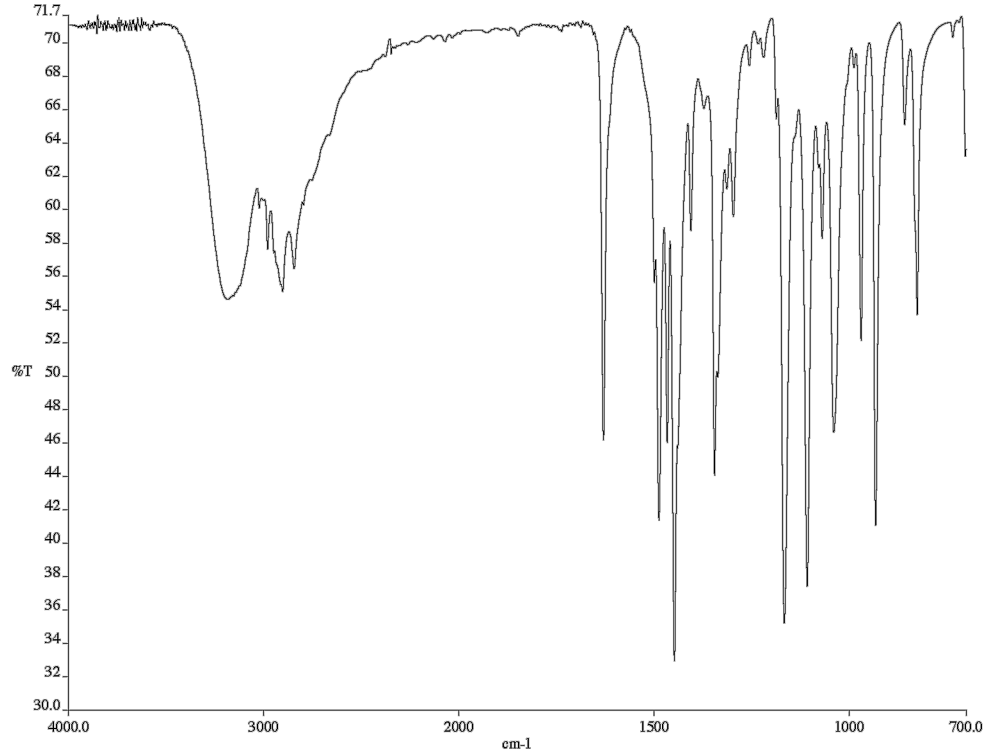


Figure A3.1.2 Infrared spectrum (thin film/NaCl) of compound **721**.

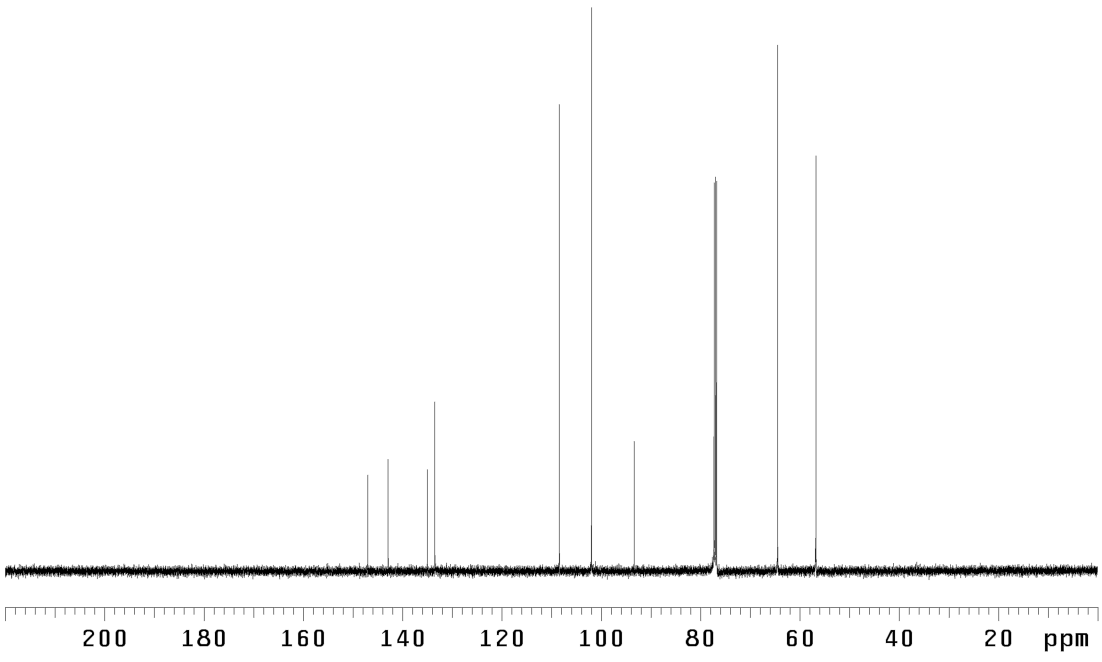


Figure A3.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **721**.

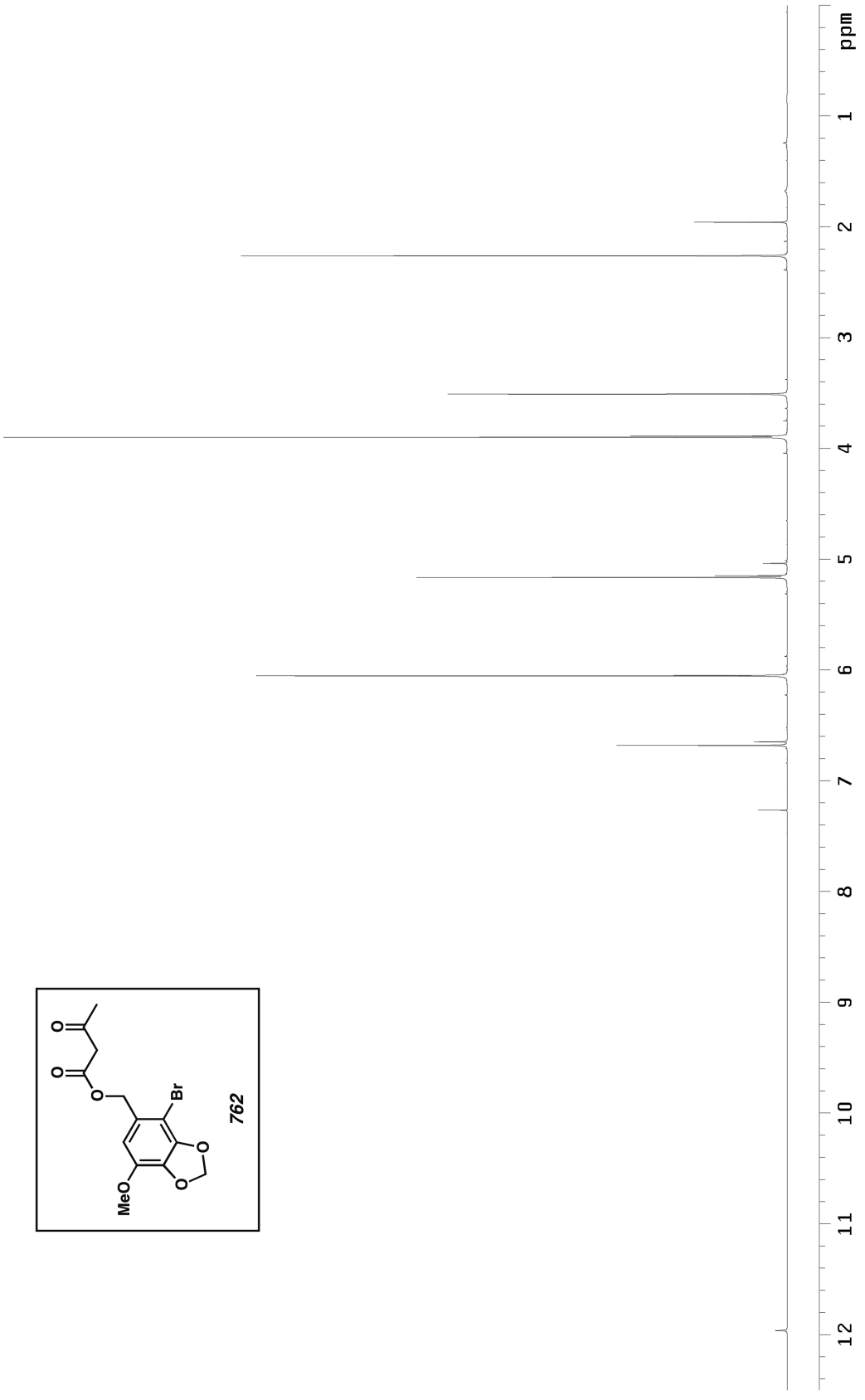


Figure A3.2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **762**.

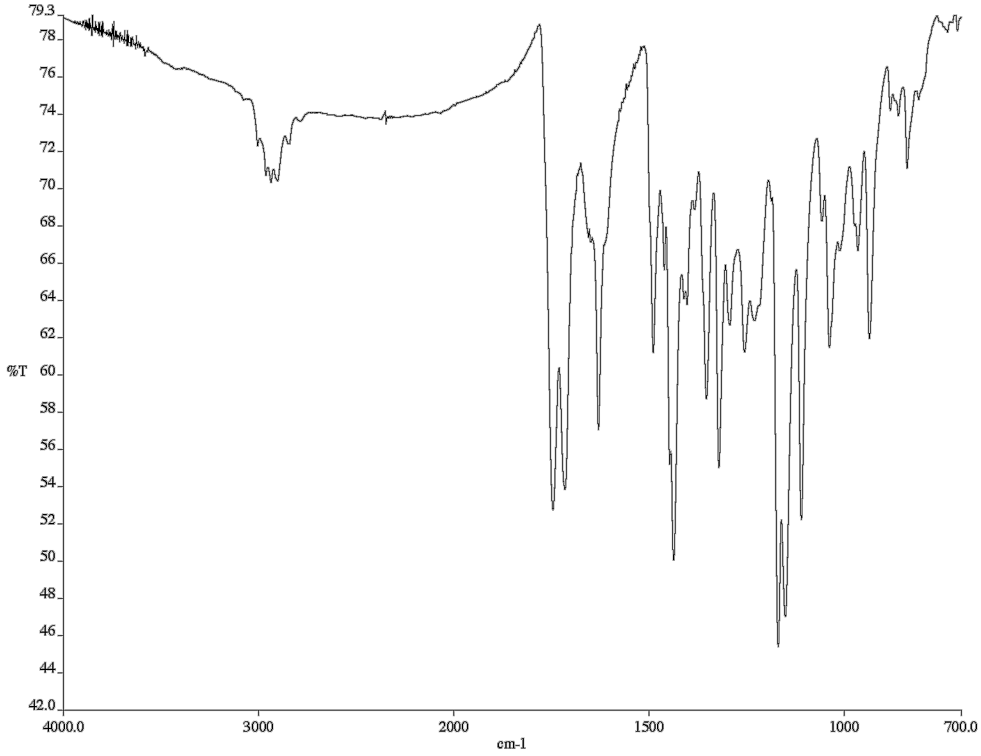


Figure A3.2.2 Infrared spectrum (thin film/NaCl) of compound **762**.

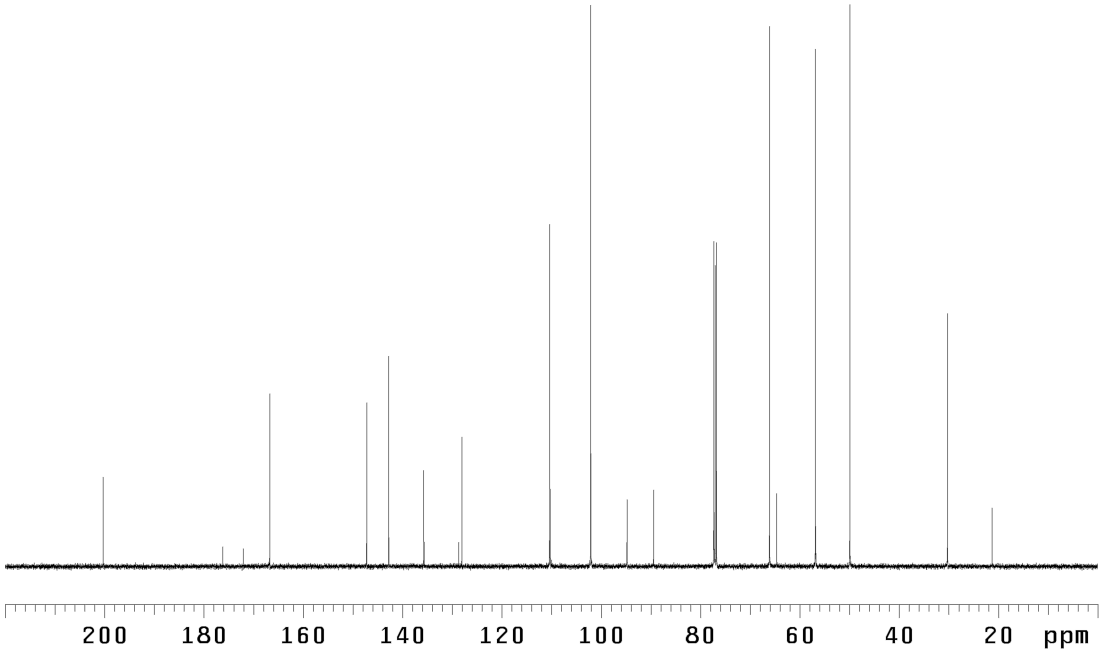


Figure A3.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **762**.

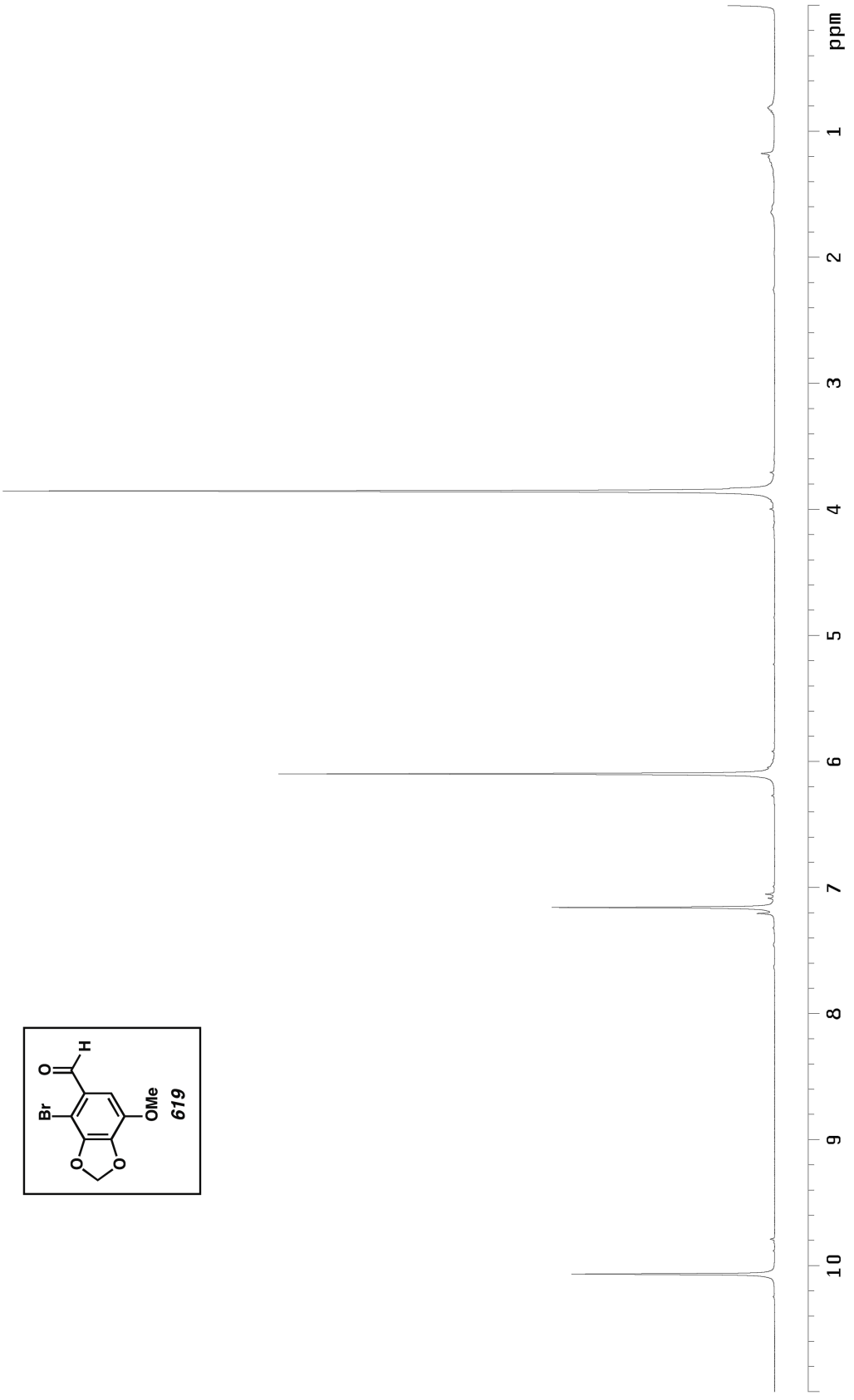


Figure A3.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **619**.

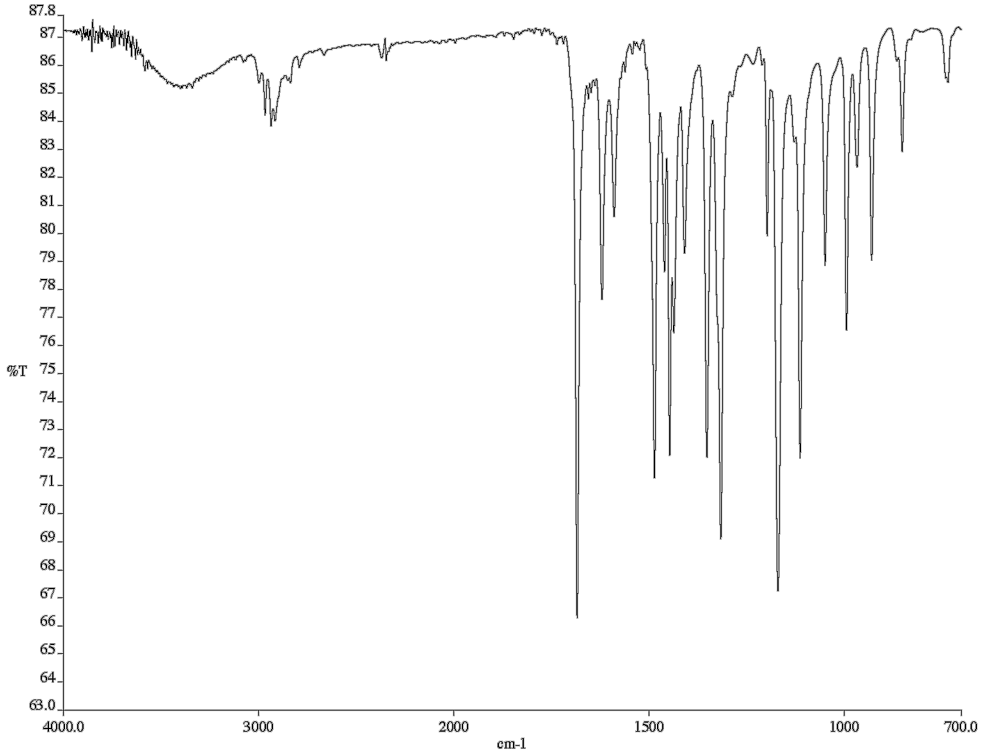


Figure A3.3.2 Infrared spectrum (thin film/NaCl) of compound **619**.

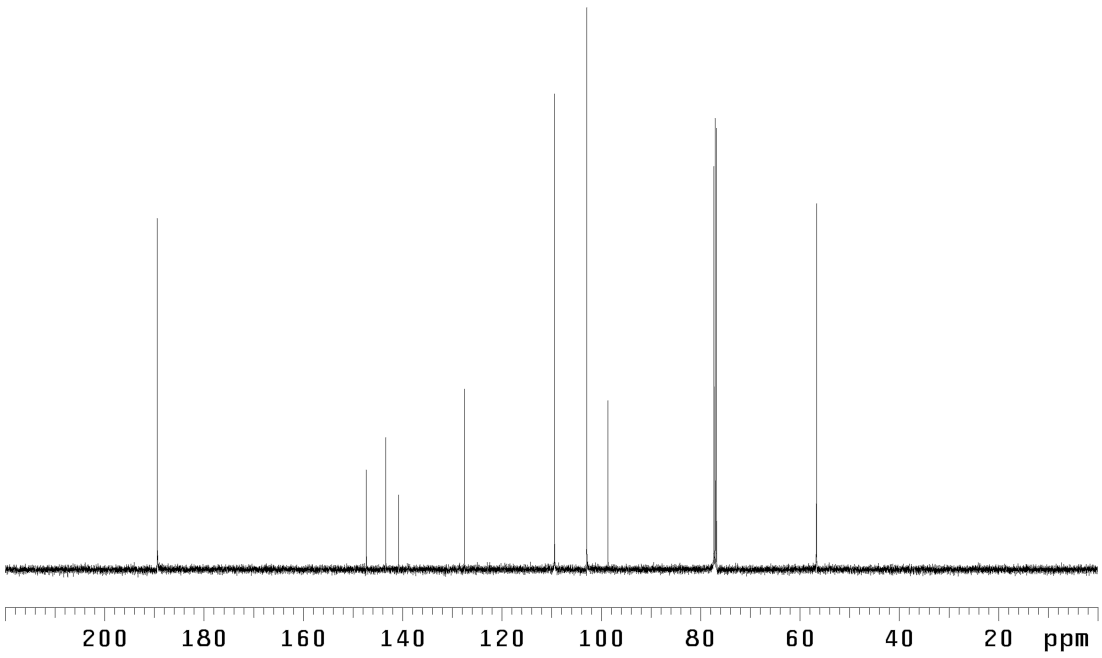


Figure A3.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **619**.

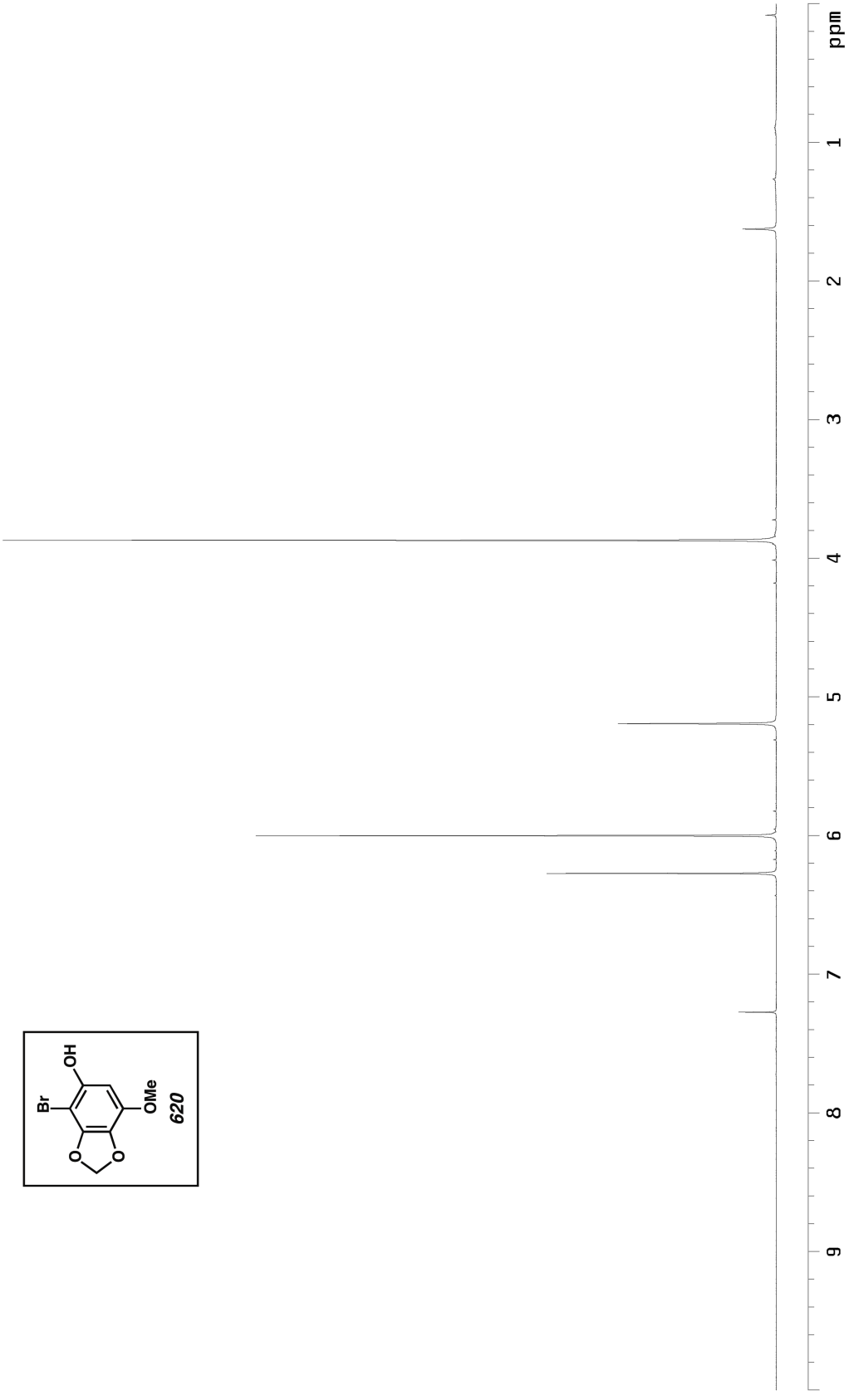


Figure A3.4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **620**.

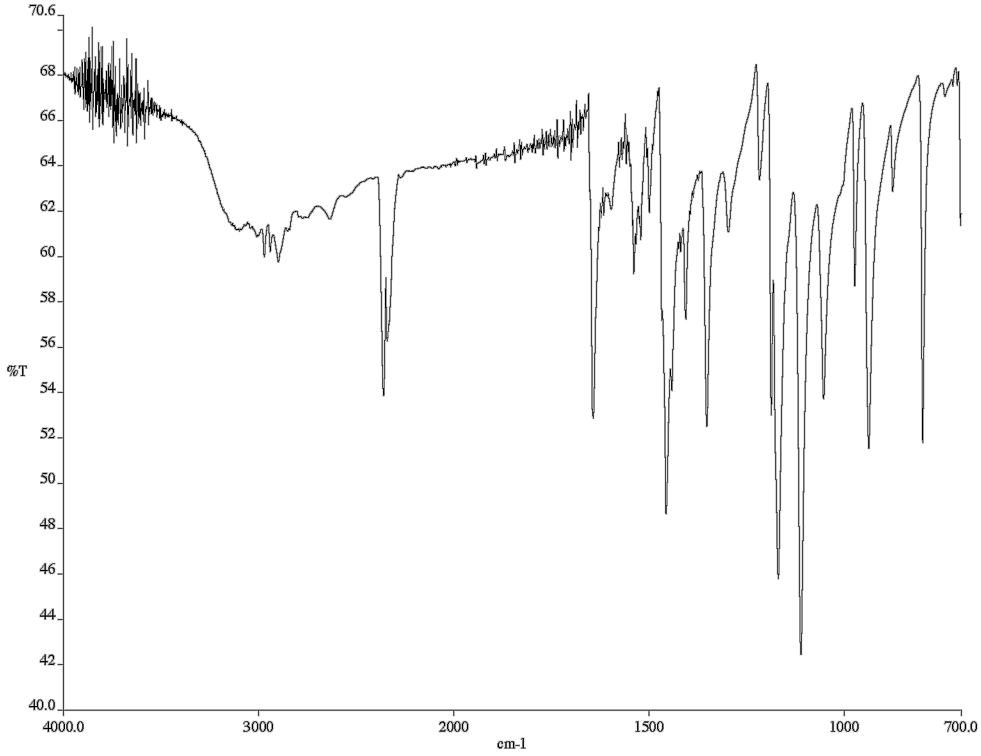


Figure A3.4.2 Infrared spectrum (thin film/NaCl) of compound **620**.

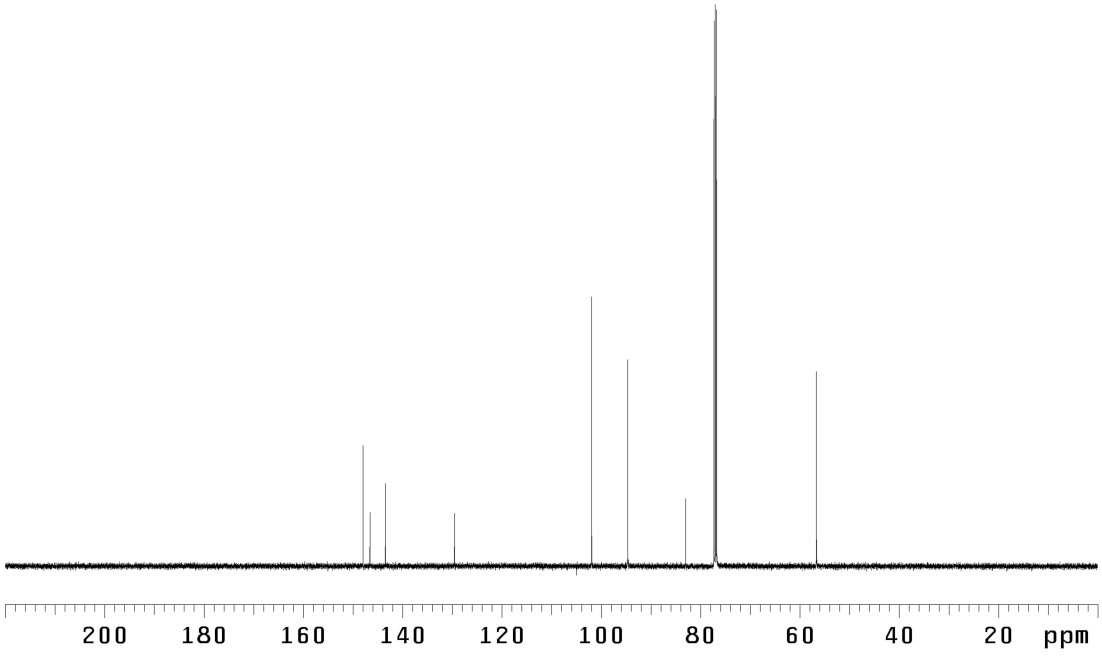


Figure A3.4.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **620**.

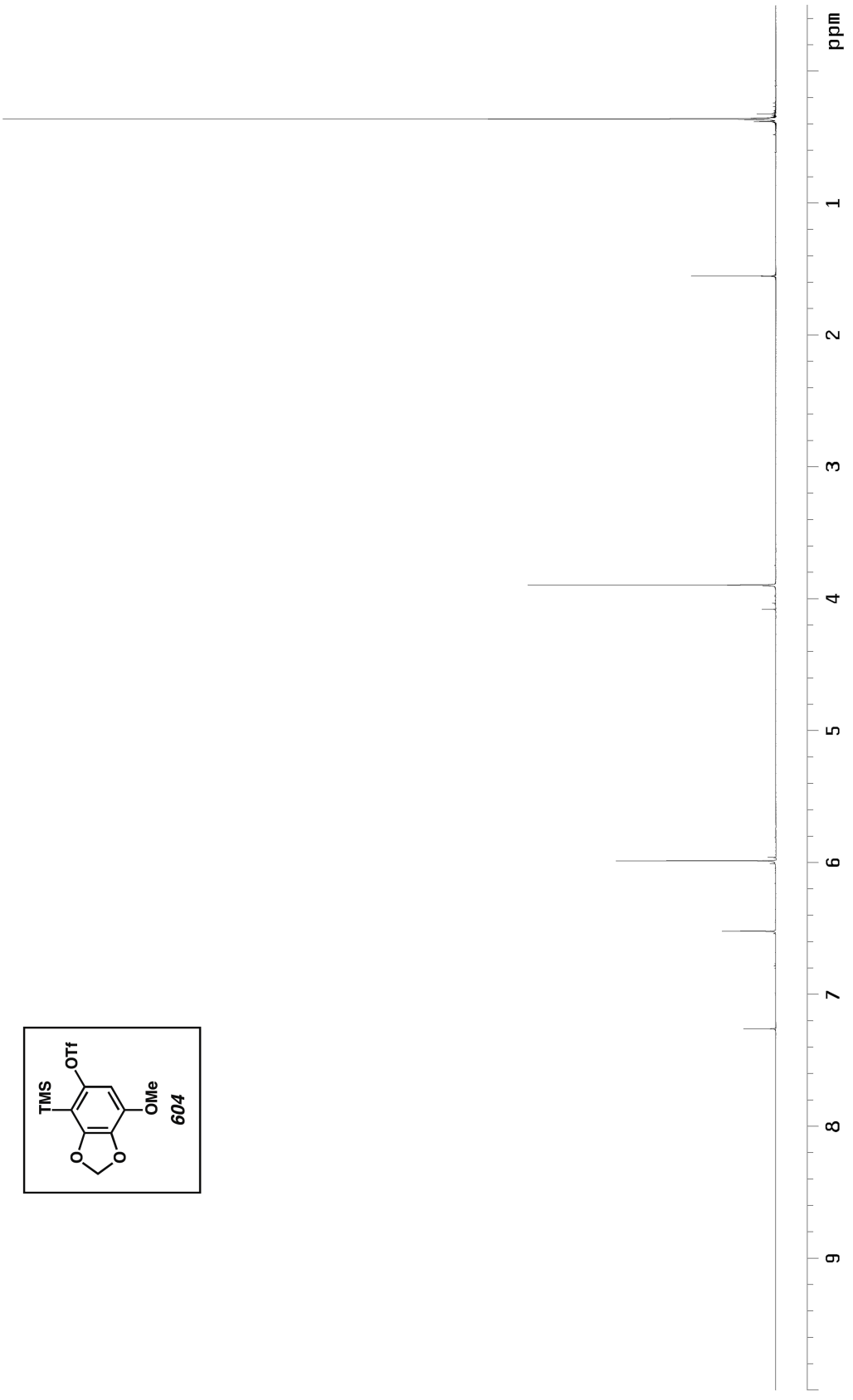


Figure A3.5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **604**.

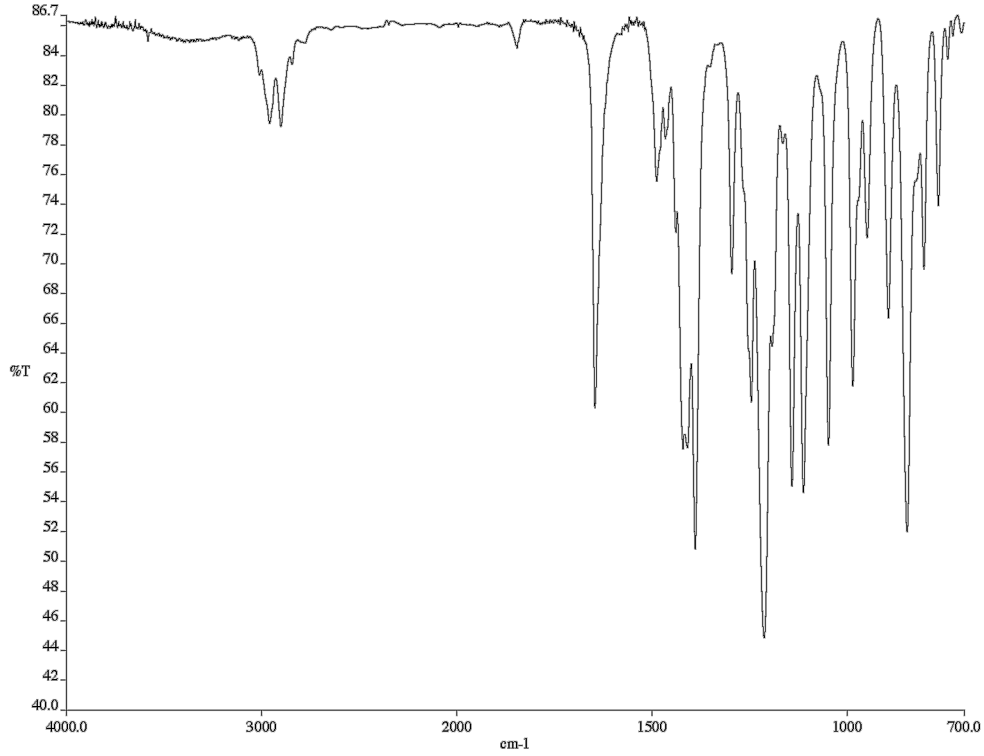


Figure A3.5.2 Infrared spectrum (thin film/NaCl) of compound **604**.

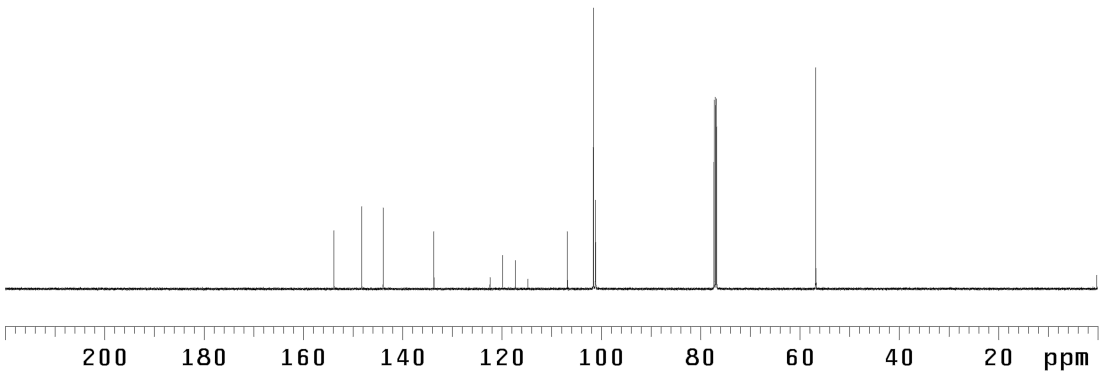


Figure A3.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **604**.

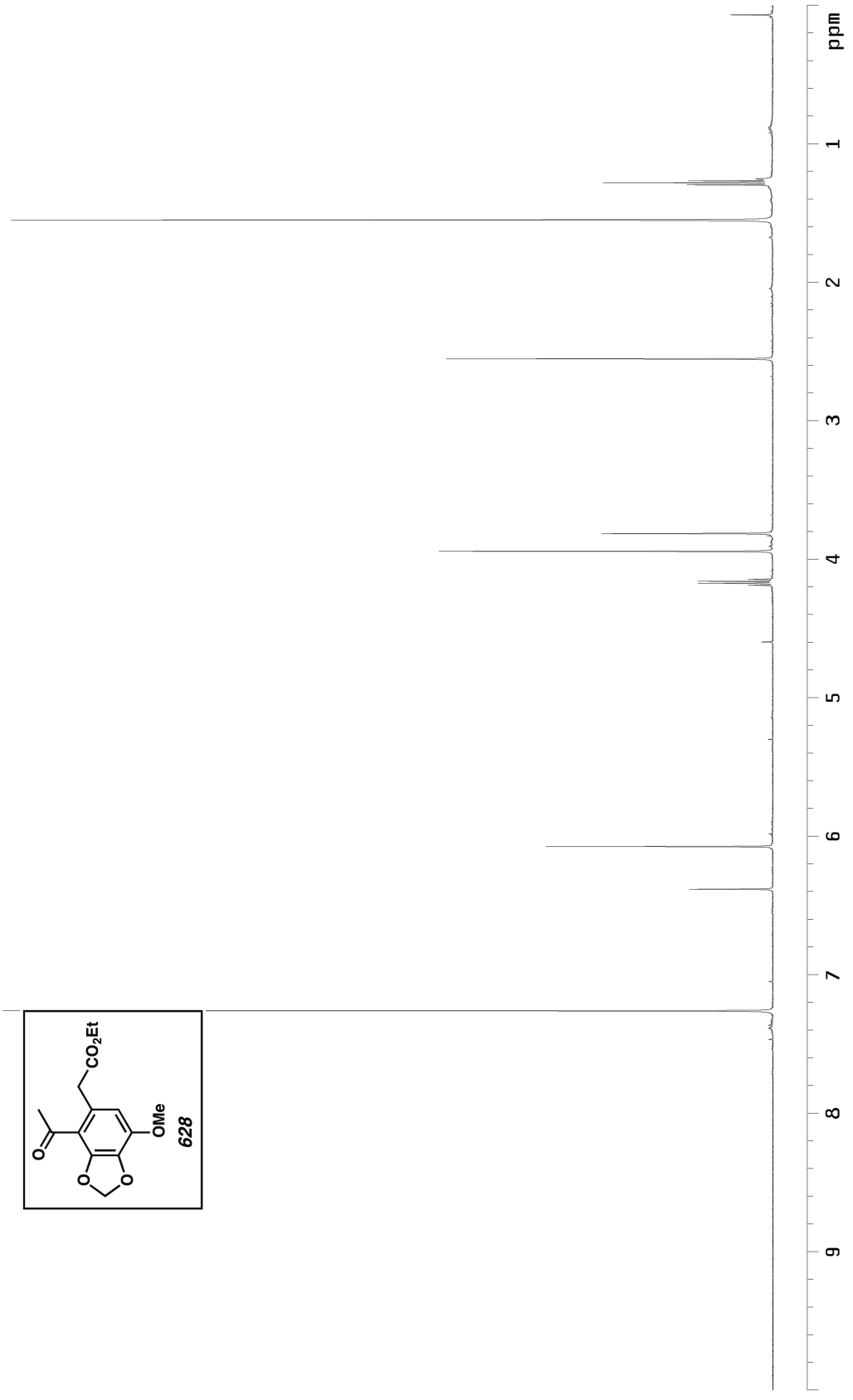


Figure A3.6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **628**.

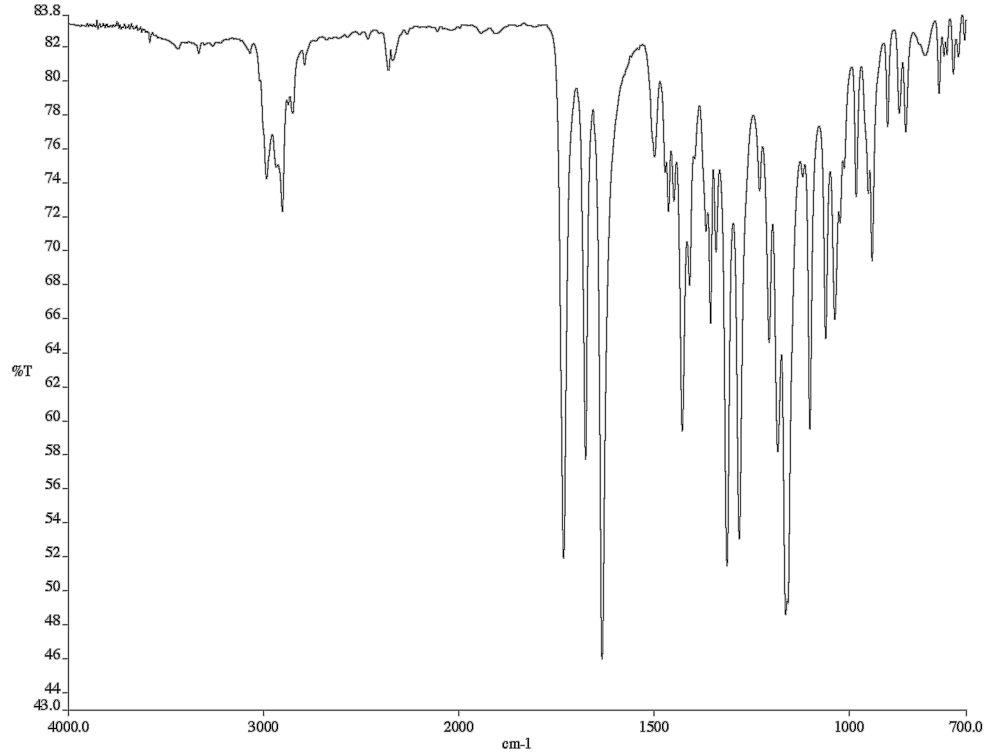


Figure A3.6.2 Infrared spectrum (thin film/NaCl) of compound **628**.

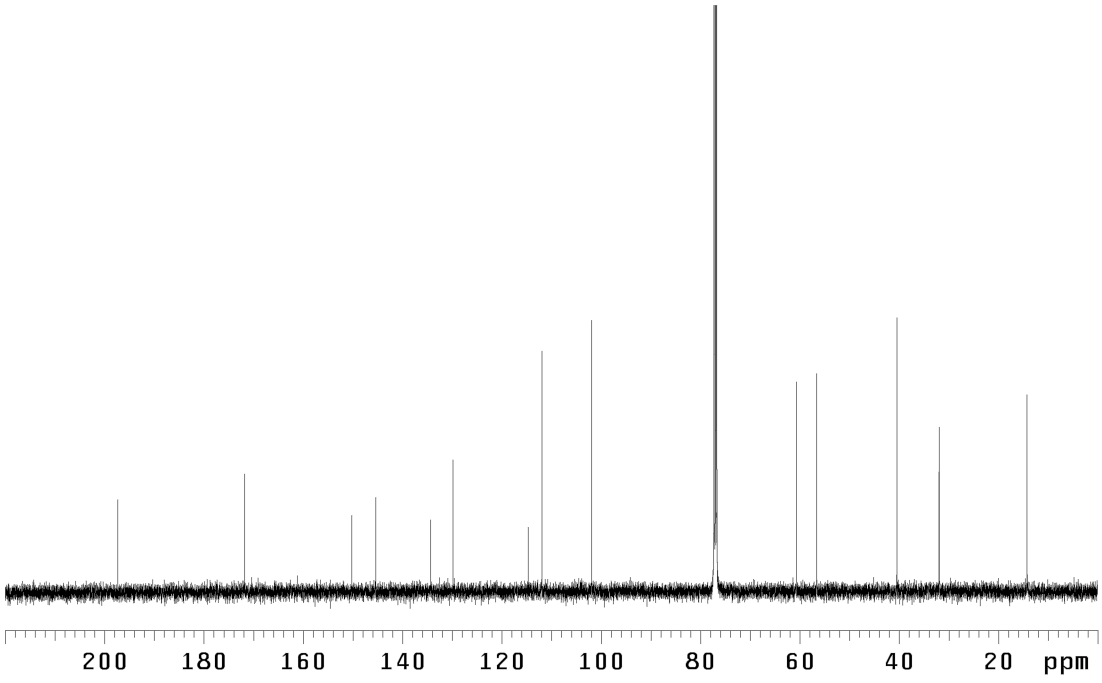


Figure A3.6.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **628**.

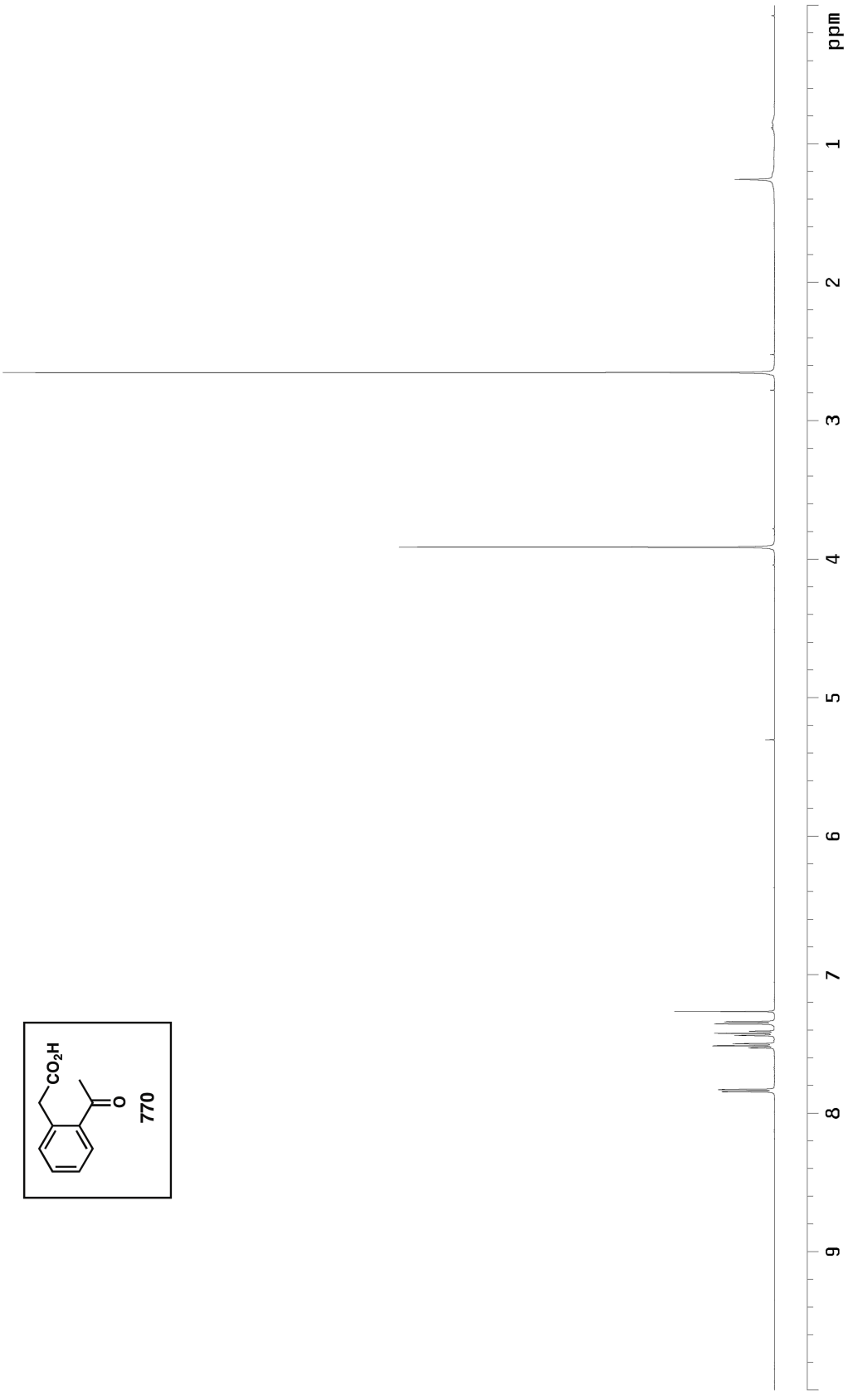


Figure A3.7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **770**.

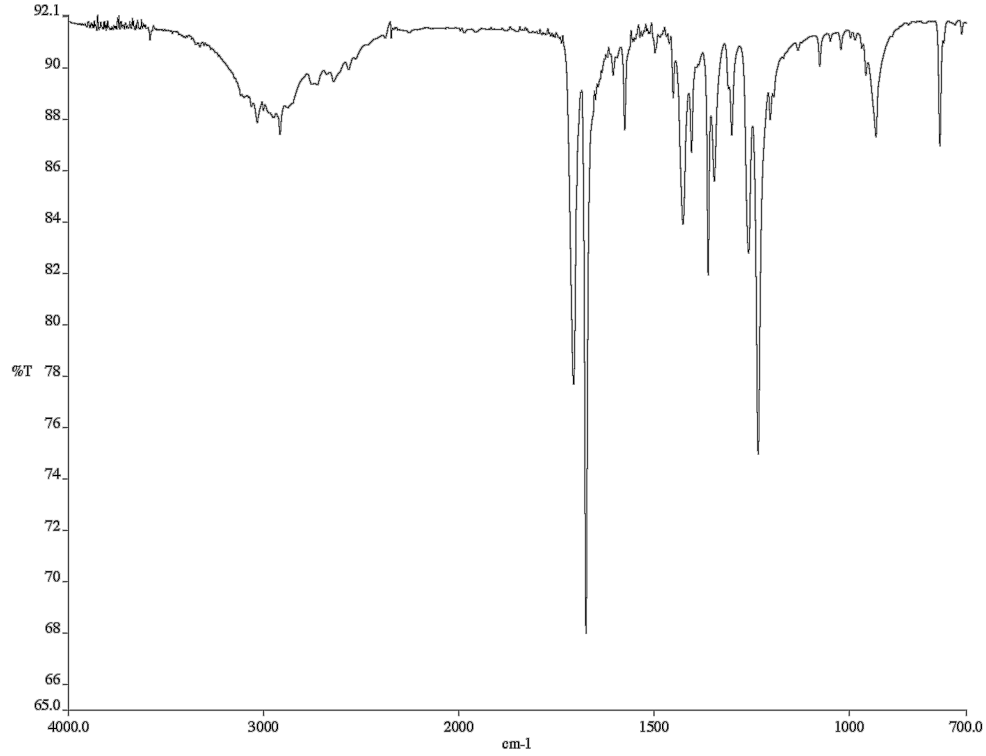


Figure A3.7.2 Infrared spectrum (thin film/NaCl) of compound **770**.

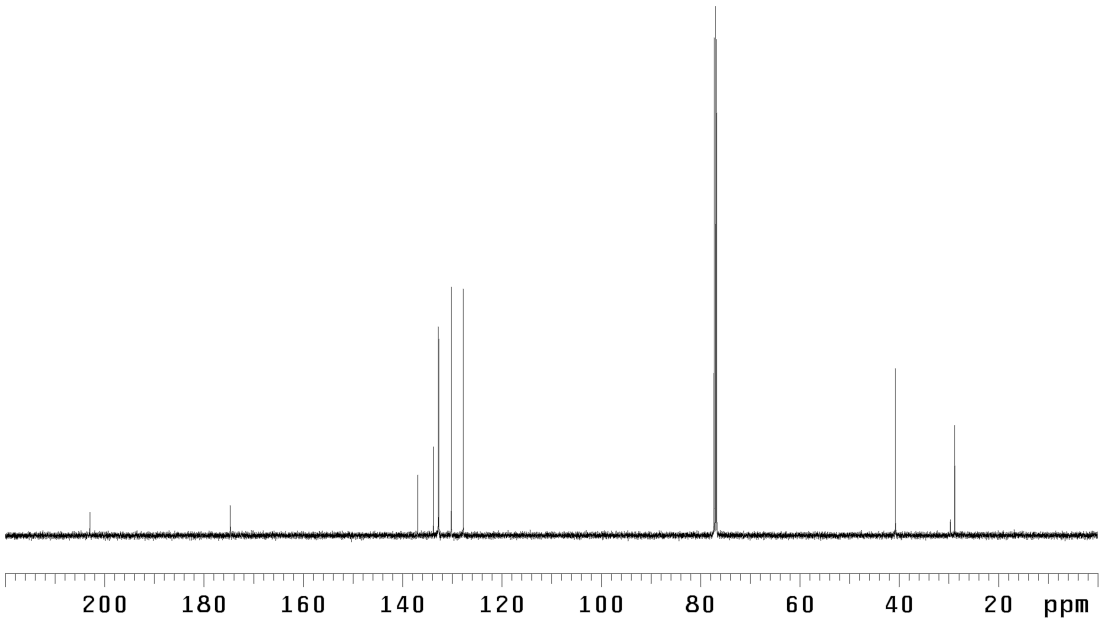


Figure A3.7.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **770**.

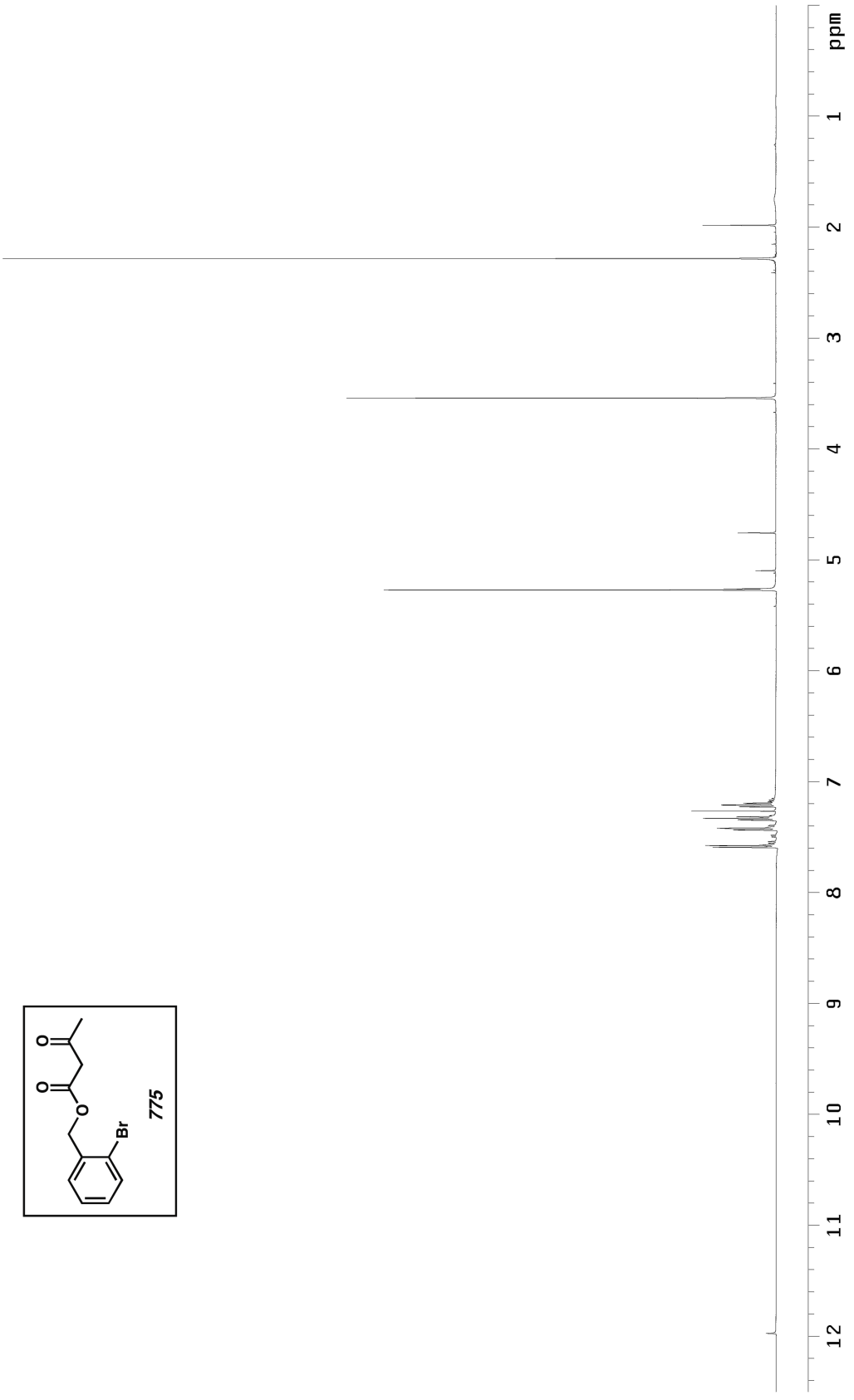


Figure A3.8.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **775**.

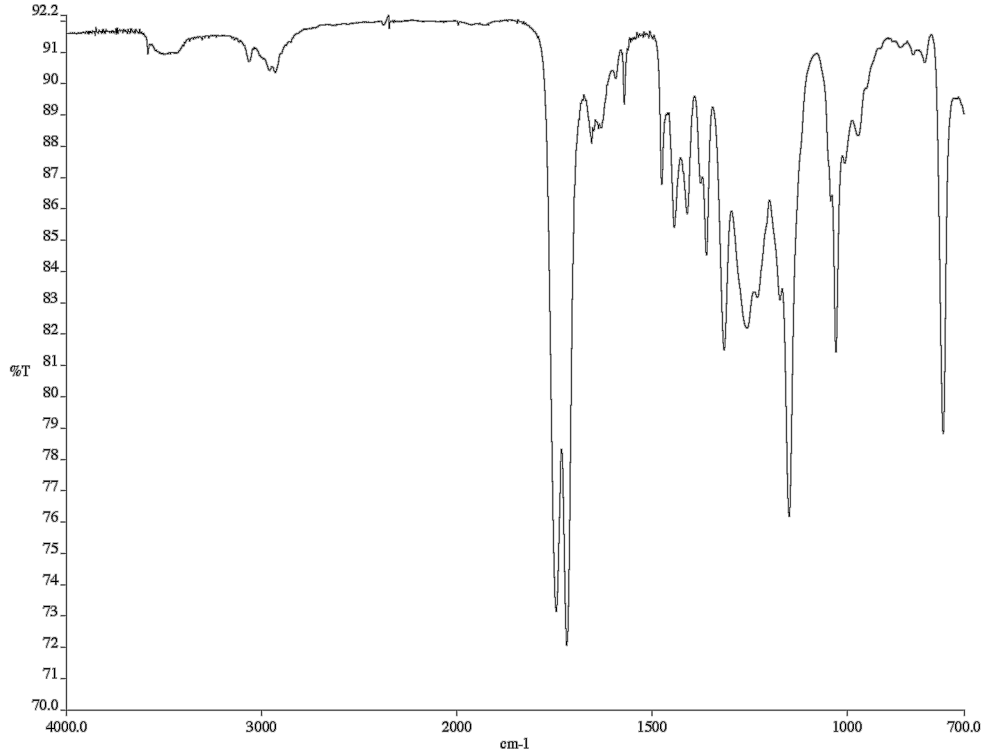


Figure A3.8.2 Infrared spectrum (thin film/NaCl) of compound **775**.

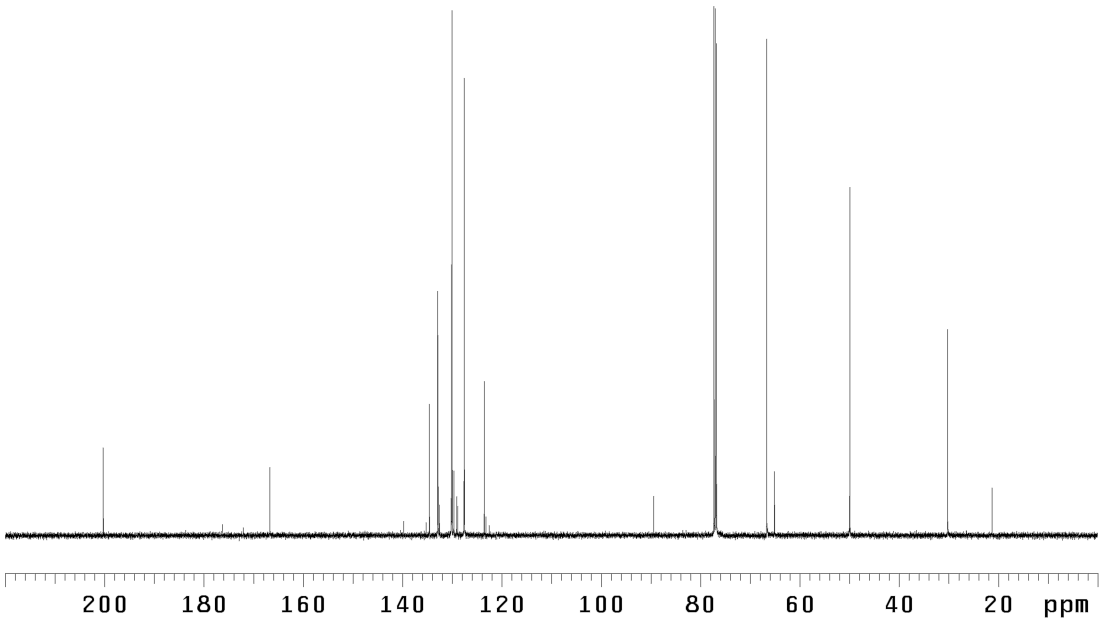


Figure A3.8.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **775**.

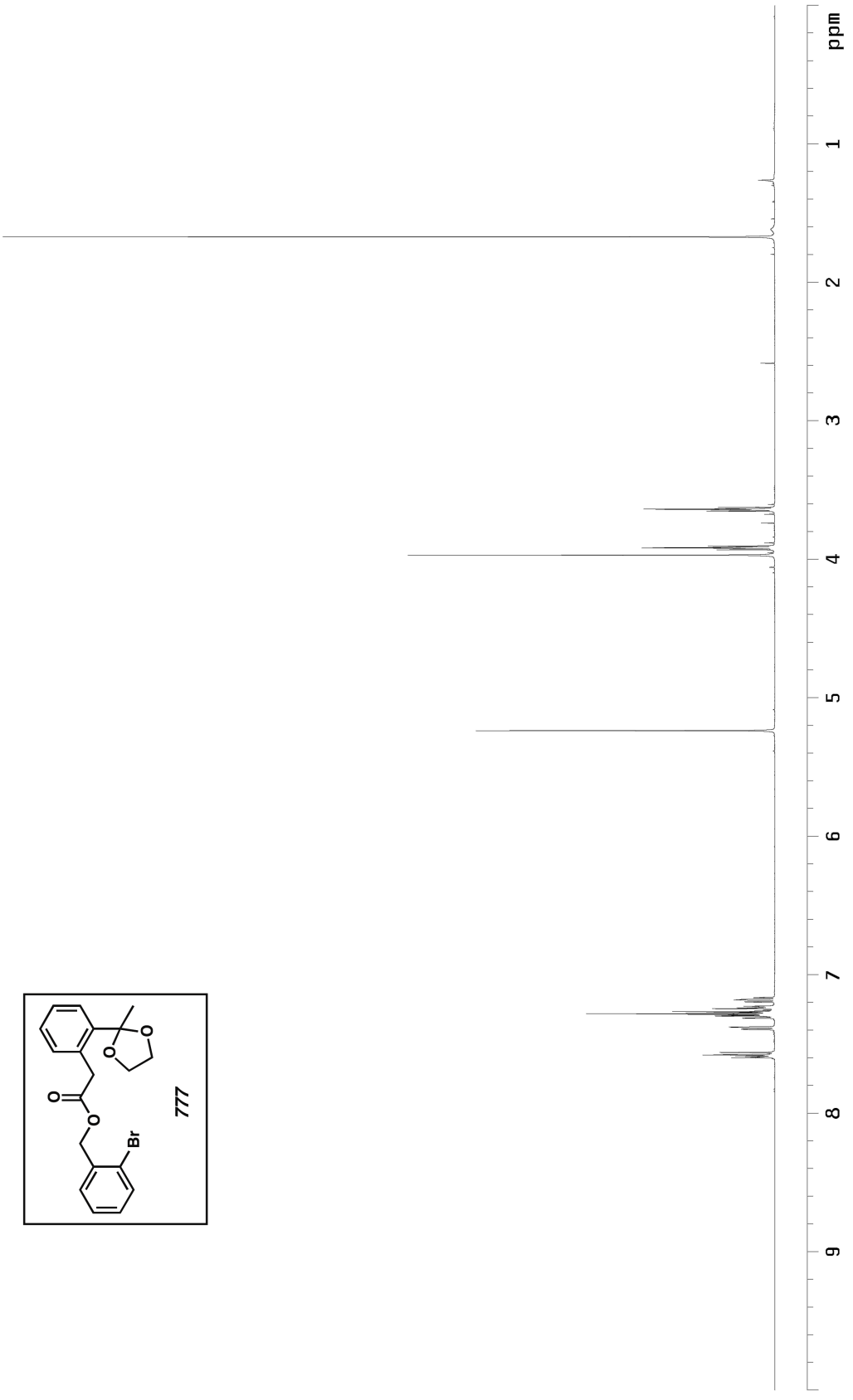


Figure A3.9.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **777**.

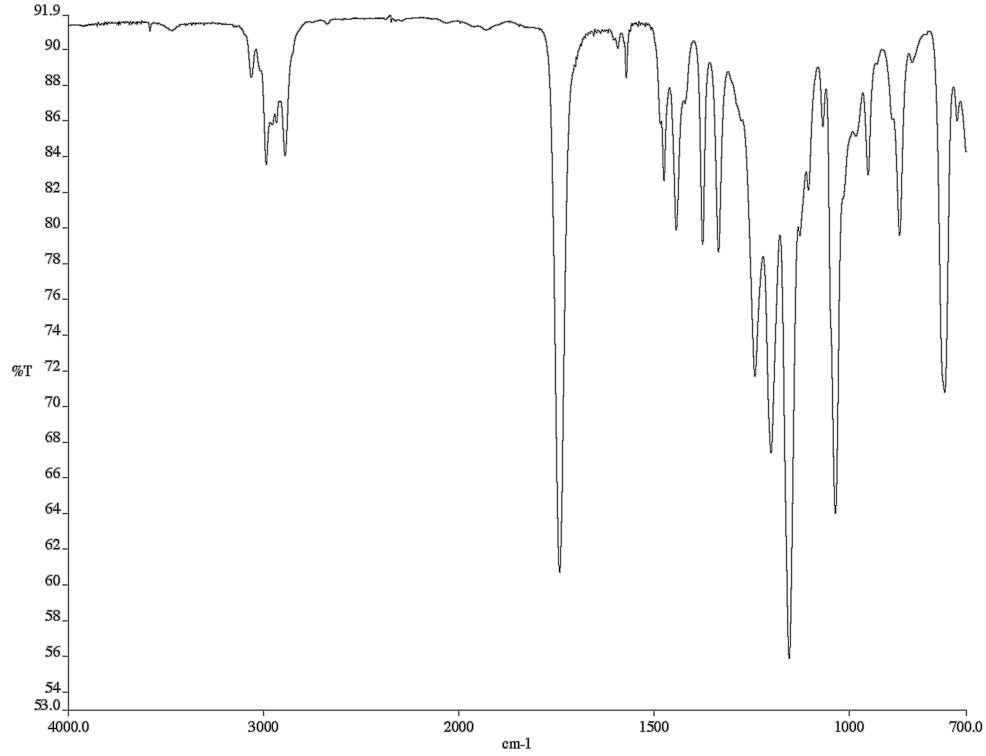


Figure A3.9.2 Infrared spectrum (thin film/NaCl) of compound **777**.

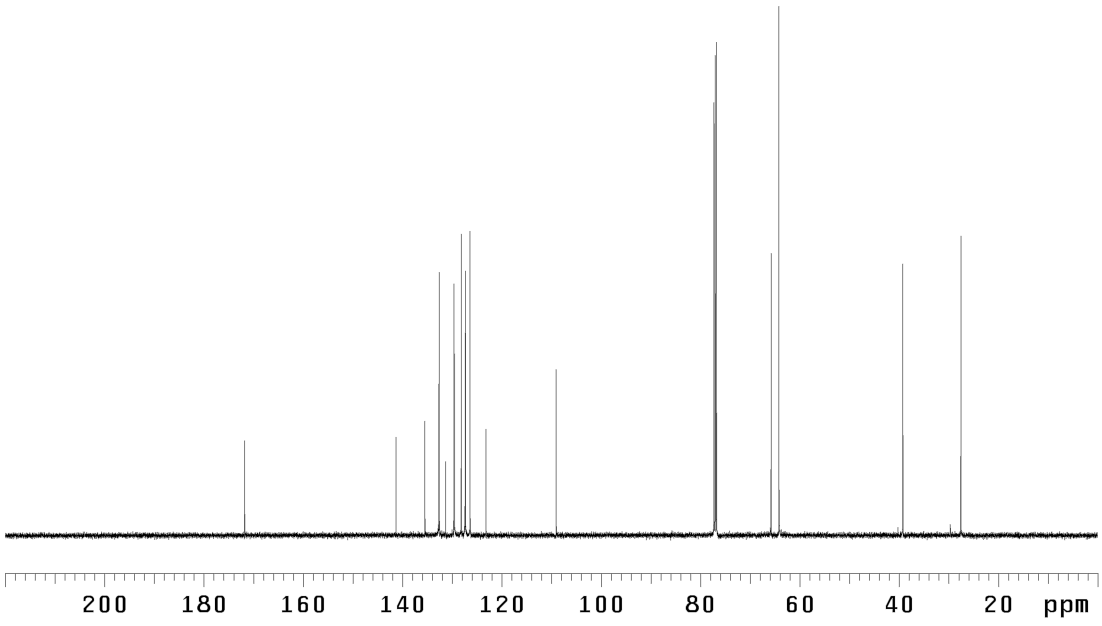


Figure A3.9.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **777**.

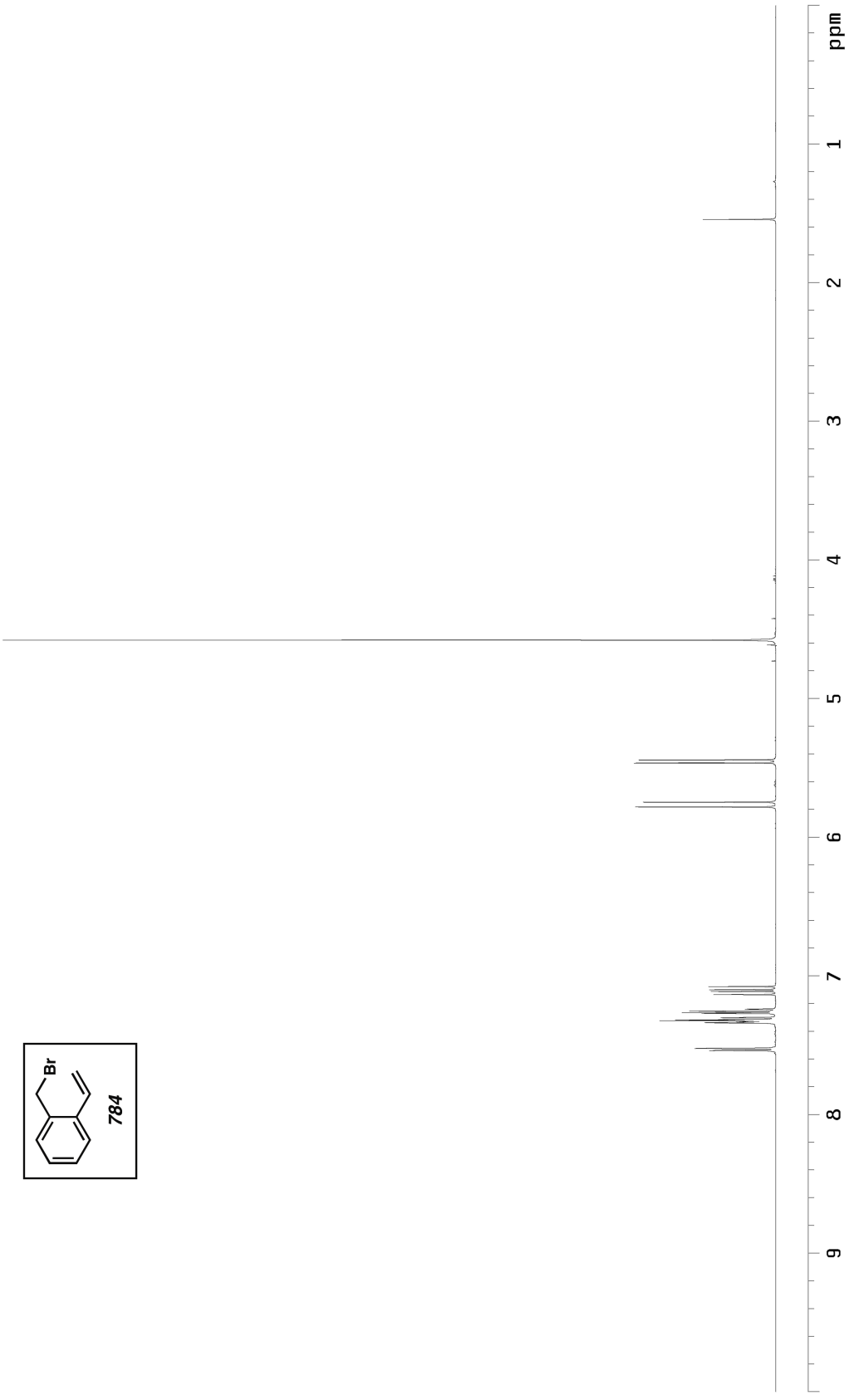


Figure A3.10.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **784**.

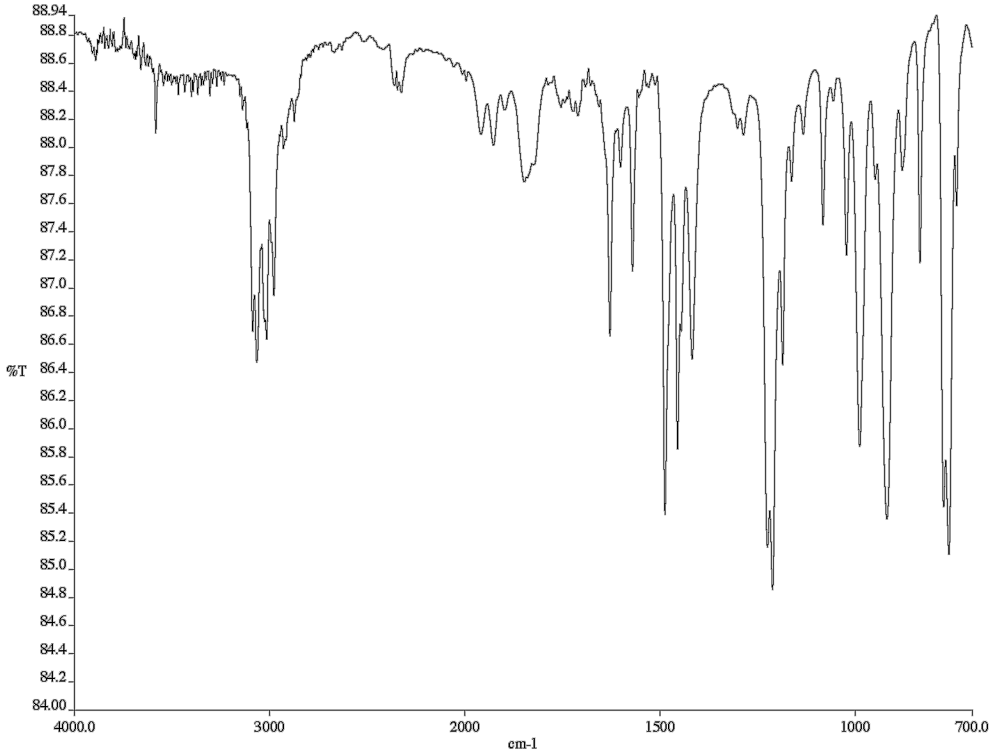


Figure A3.10.2 Infrared spectrum (thin film/NaCl) of compound **784**.

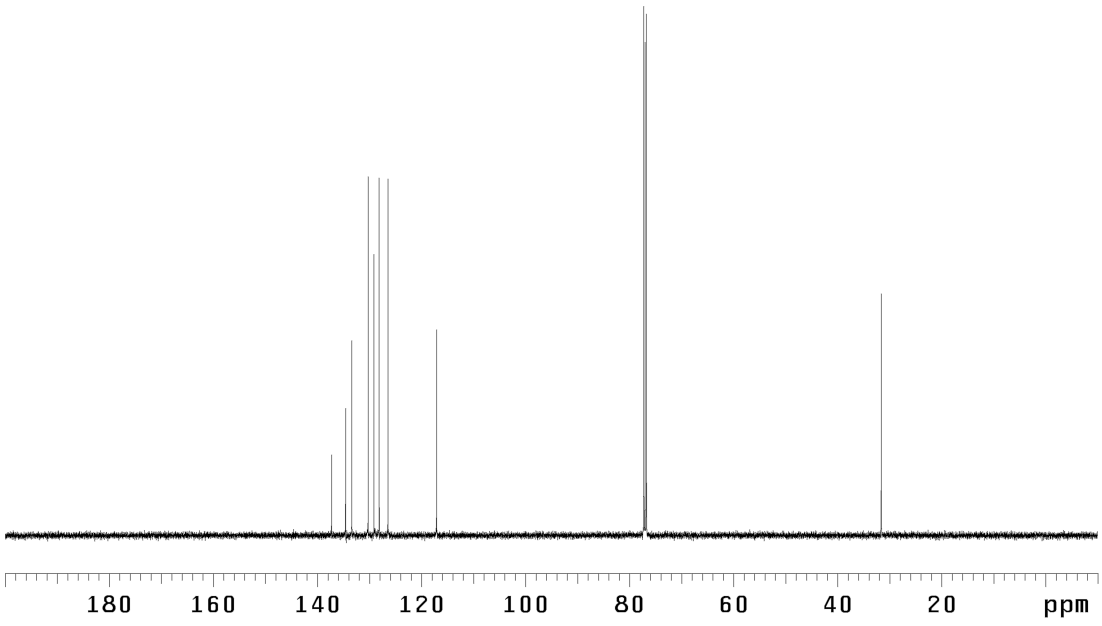


Figure A3.10.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **784**.

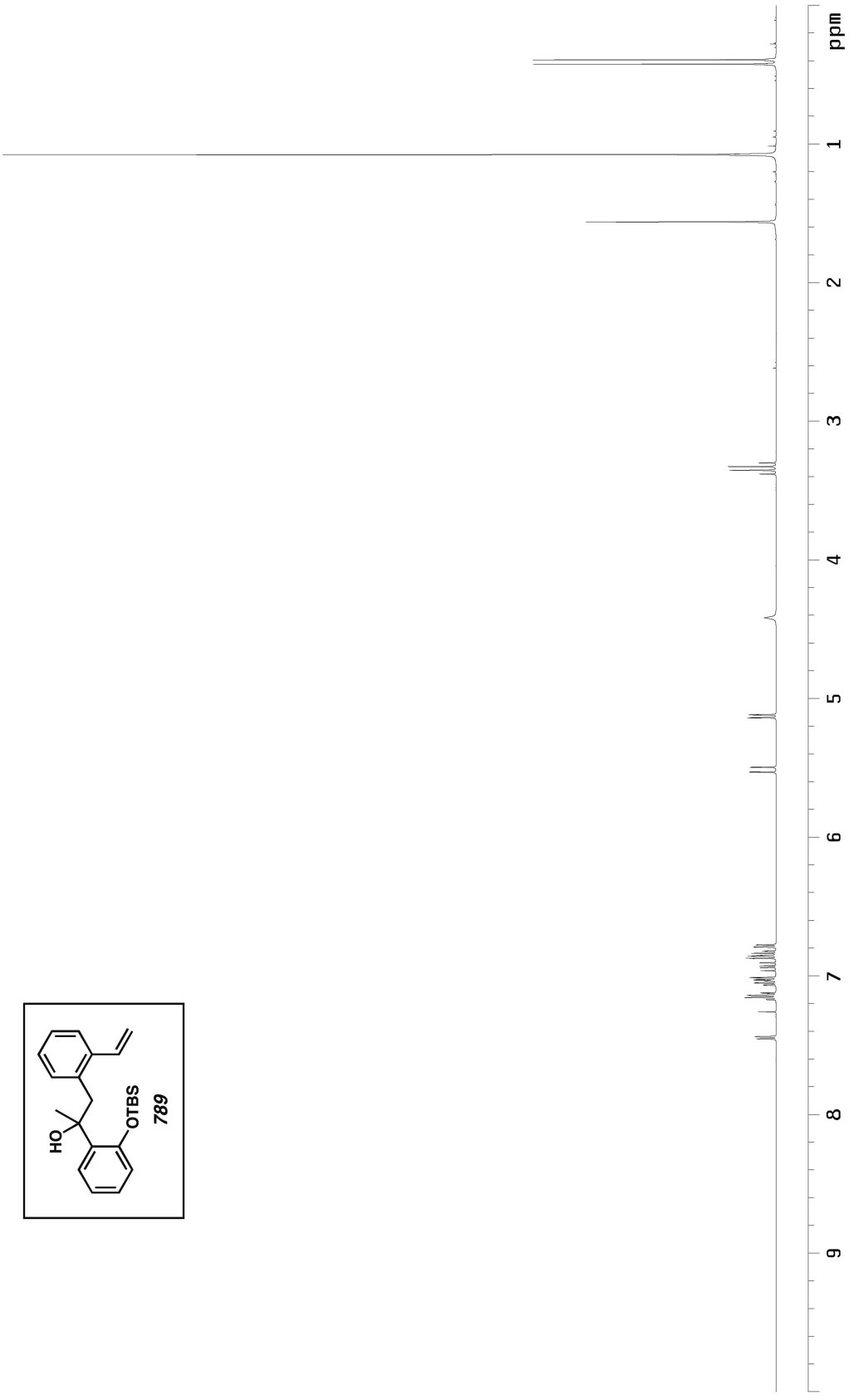


Figure A3.11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **789**.

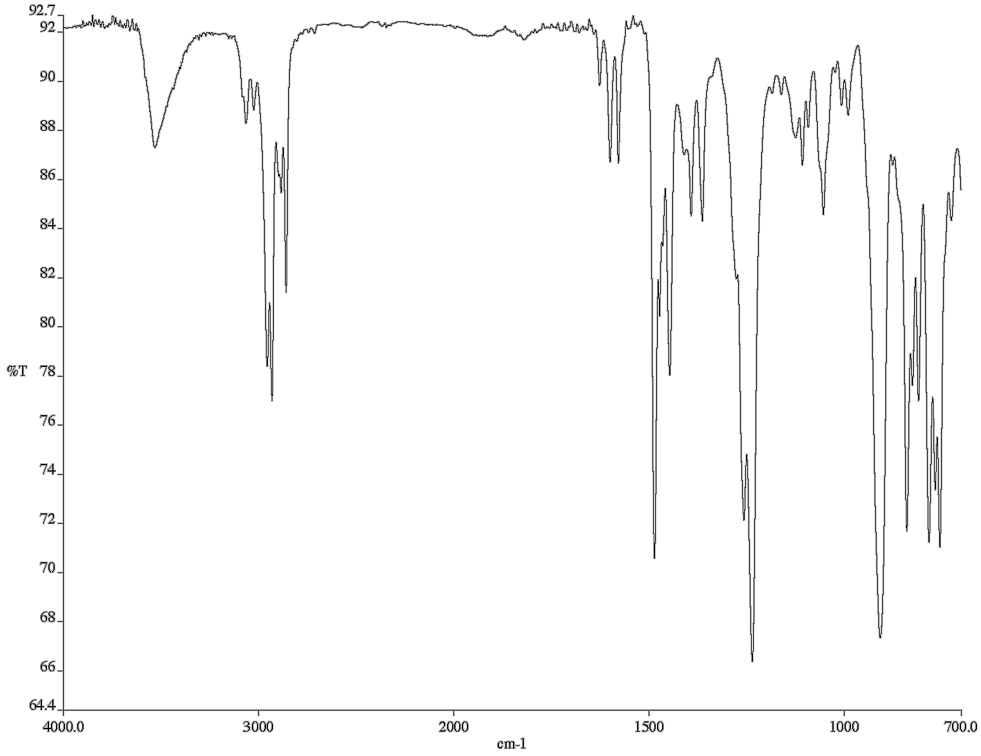


Figure A3.11.2 Infrared spectrum (thin film/NaCl) of compound **789**.

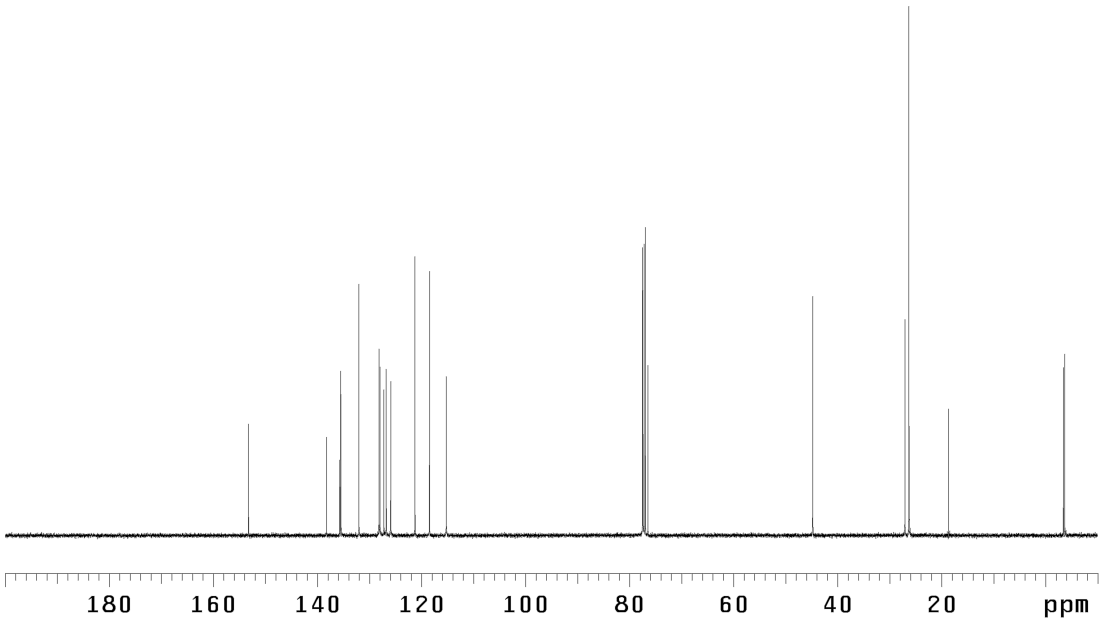


Figure A3.11.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **789**.

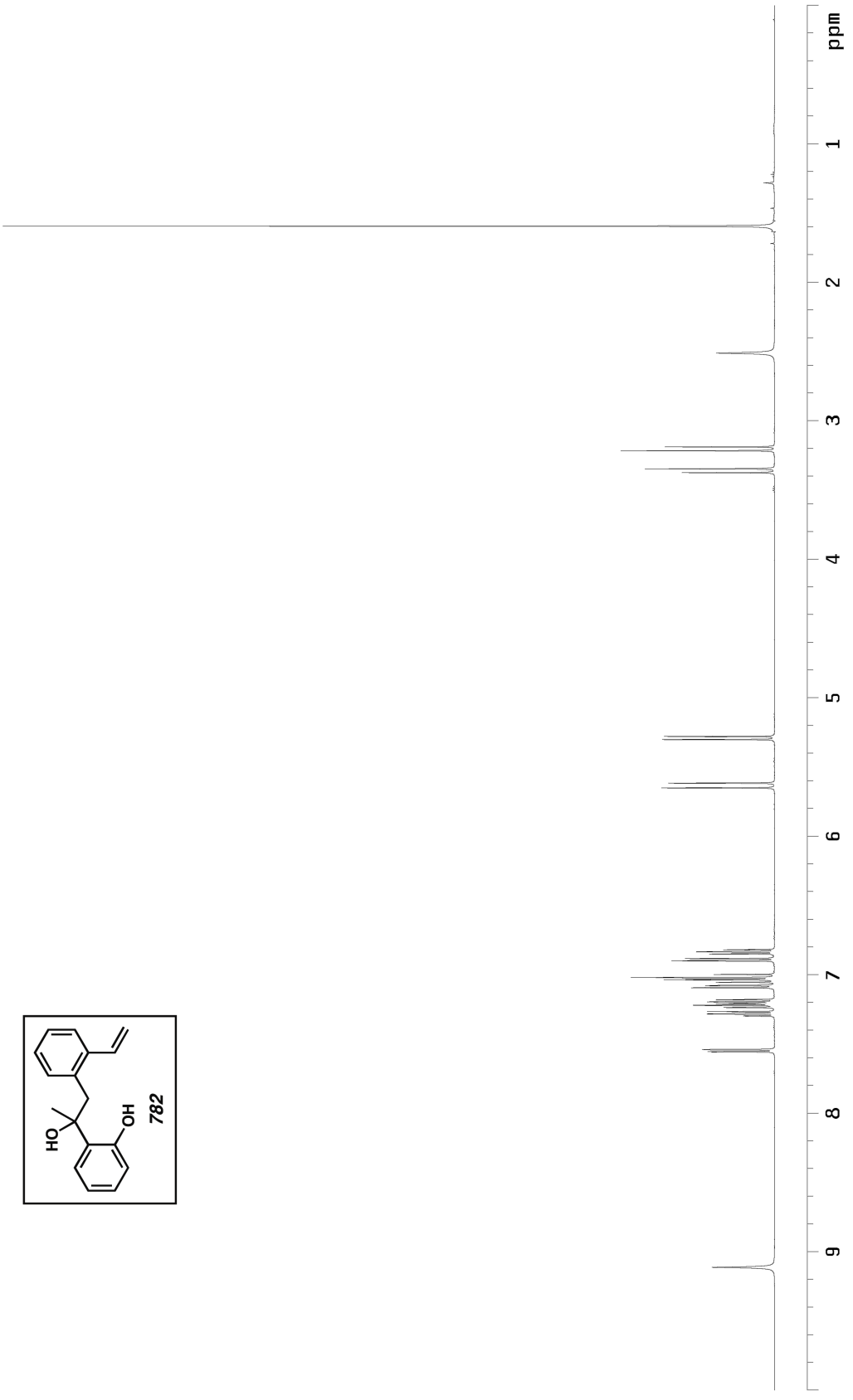


Figure A3.12.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **782**.

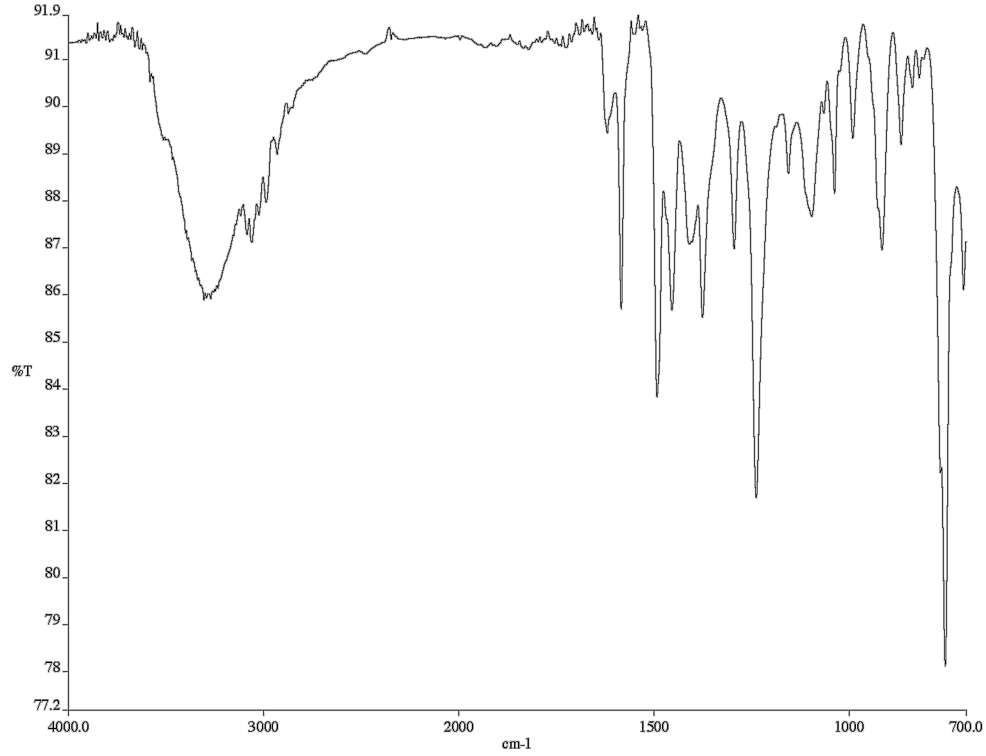


Figure A3.12.2 Infrared spectrum (thin film/NaCl) of compound **782**.

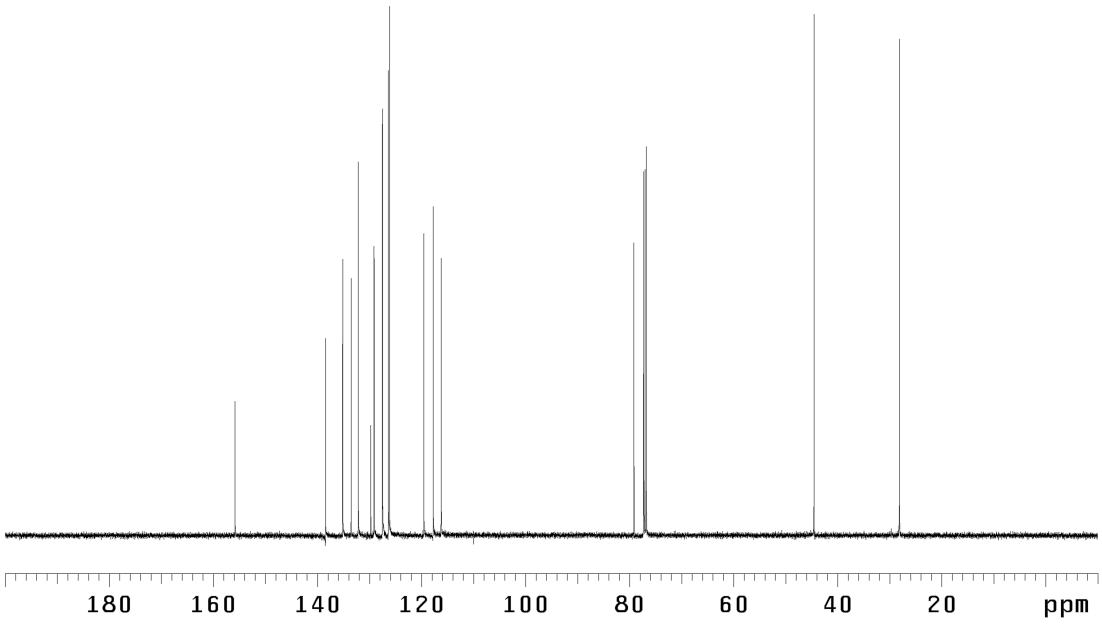


Figure A3.12.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **782**.

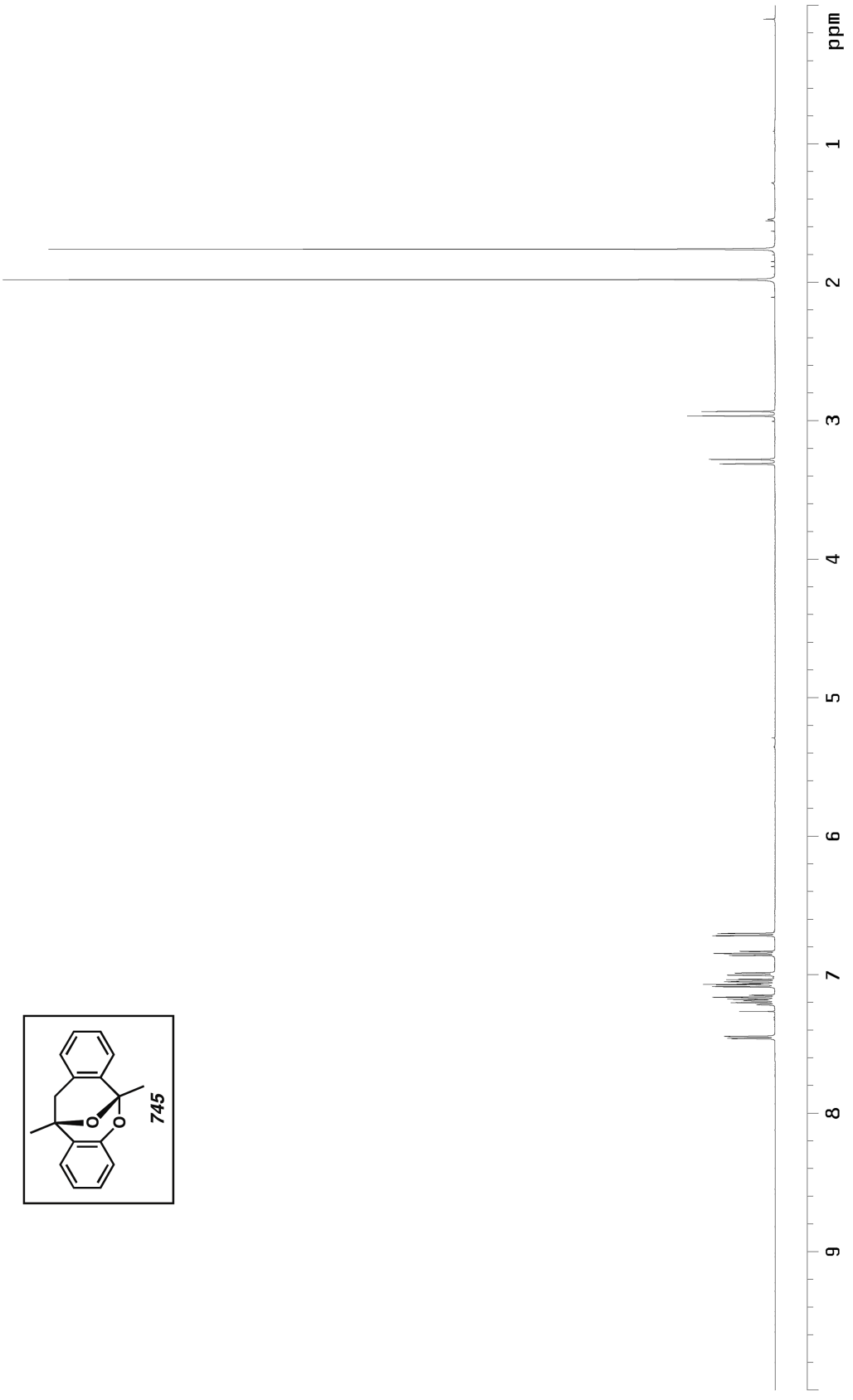


Figure A3.13.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **745**.

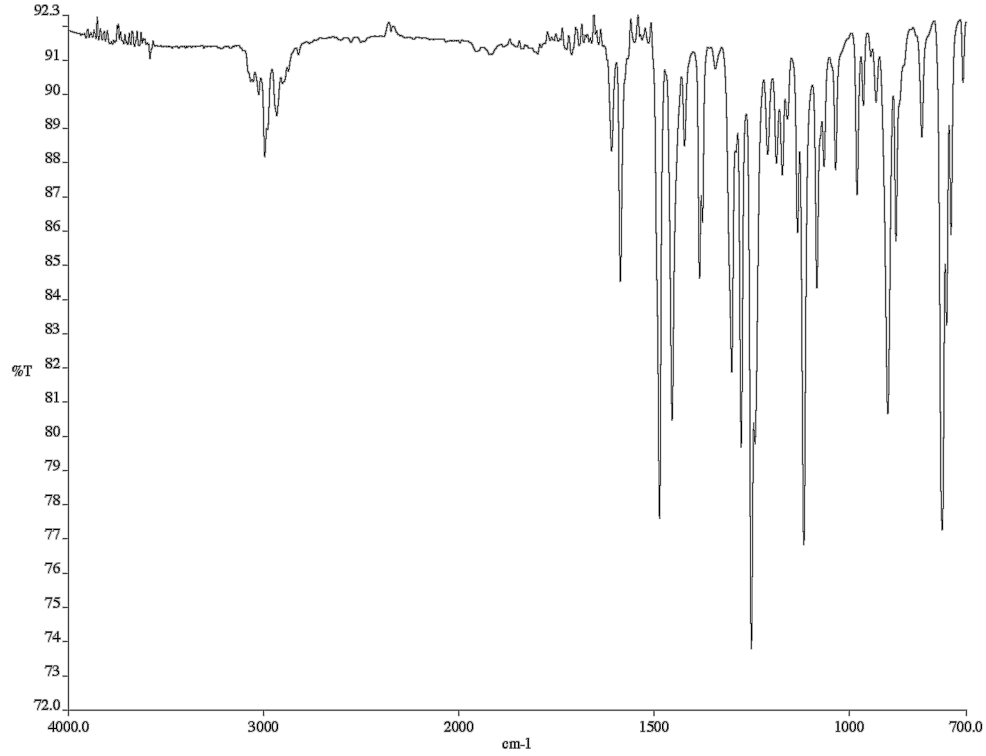


Figure A3.13.2 Infrared spectrum (thin film/NaCl) of compound **745**.

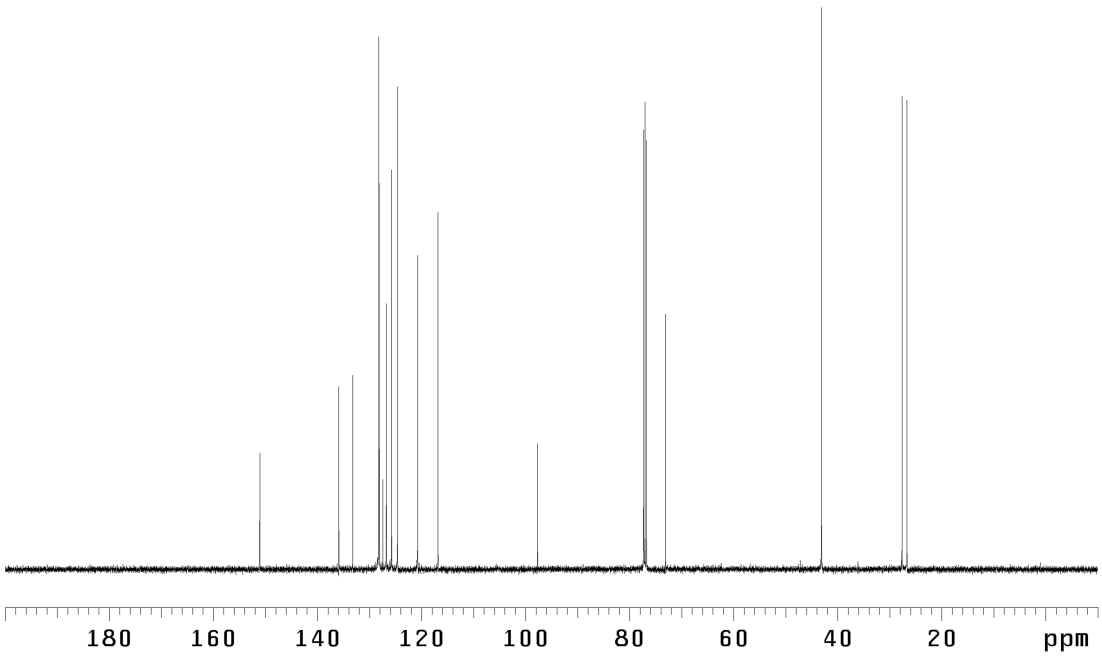


Figure A3.13.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **745**.

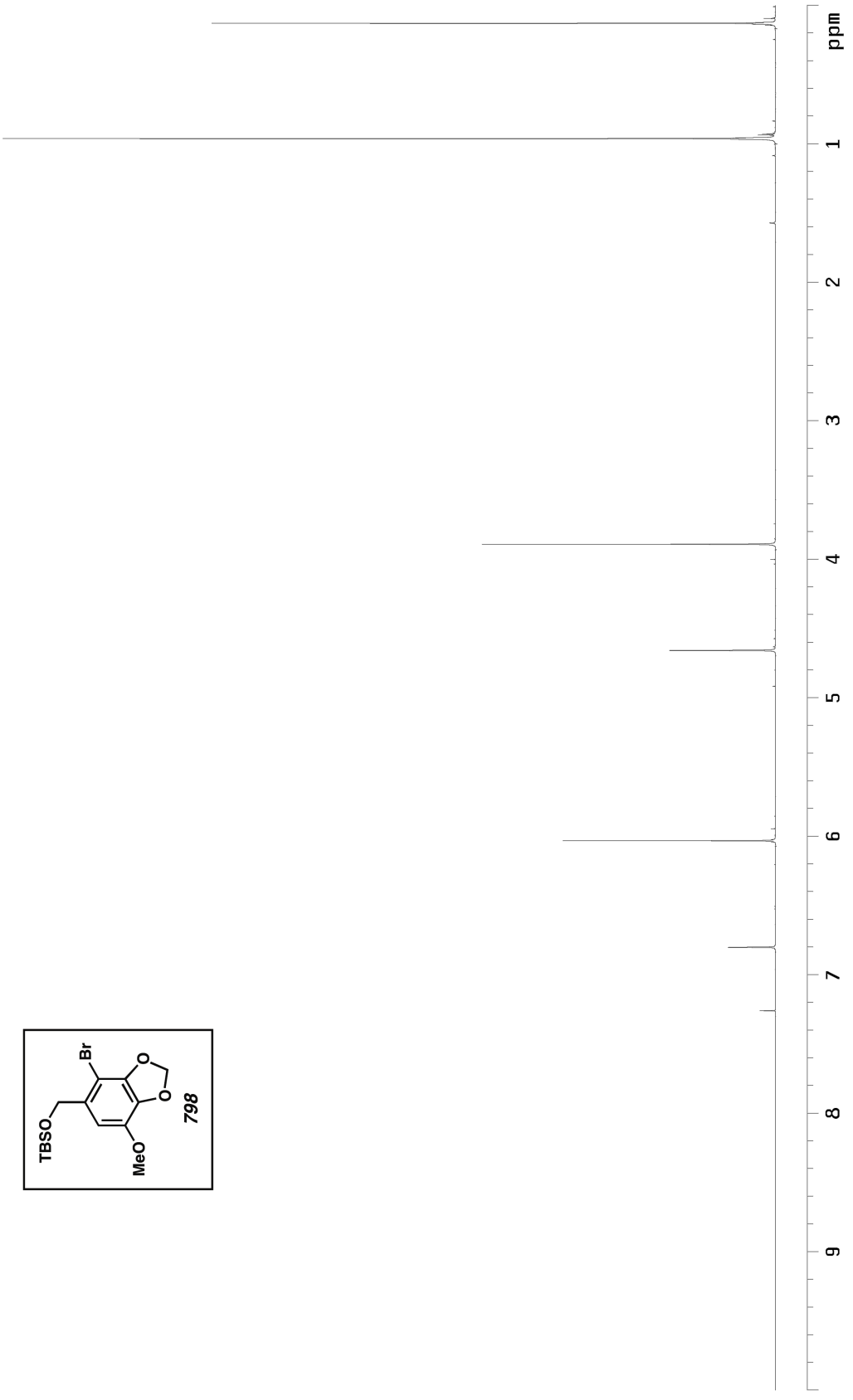


Figure A3.14.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **798**.

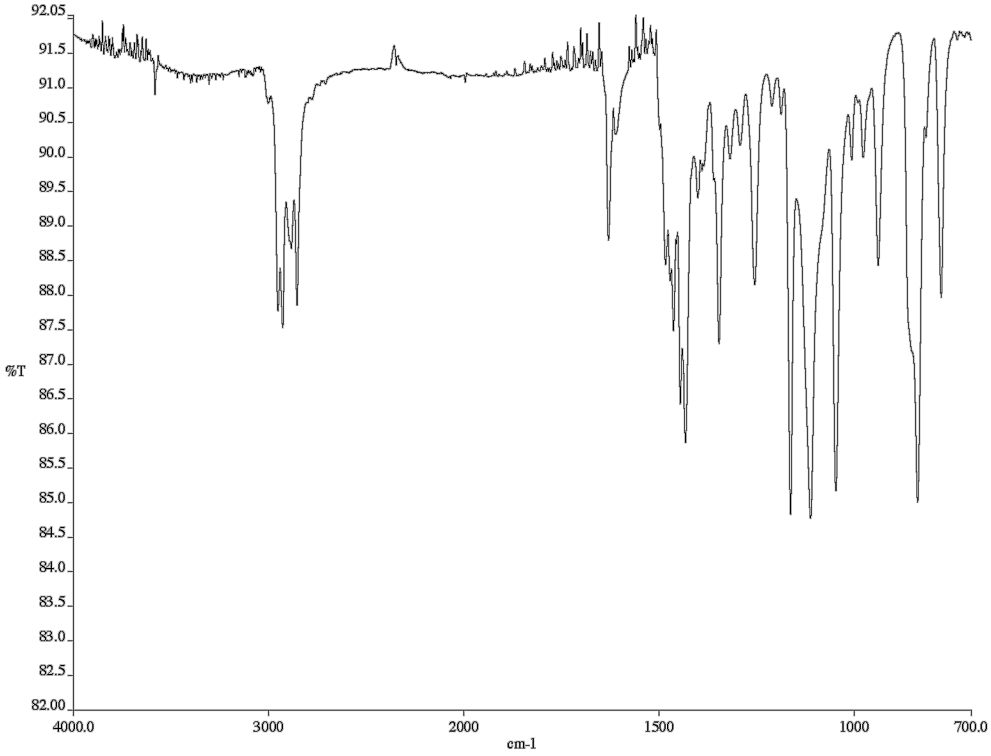


Figure A3.14.2 Infrared spectrum (thin film/NaCl) of compound **798**.

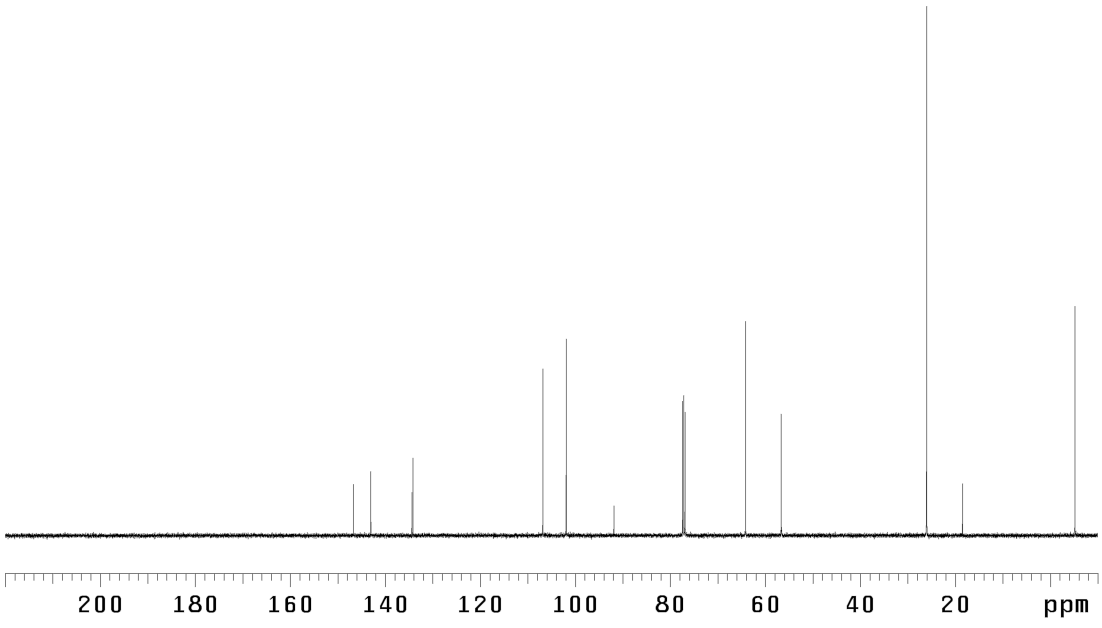


Figure A3.14.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **798**.

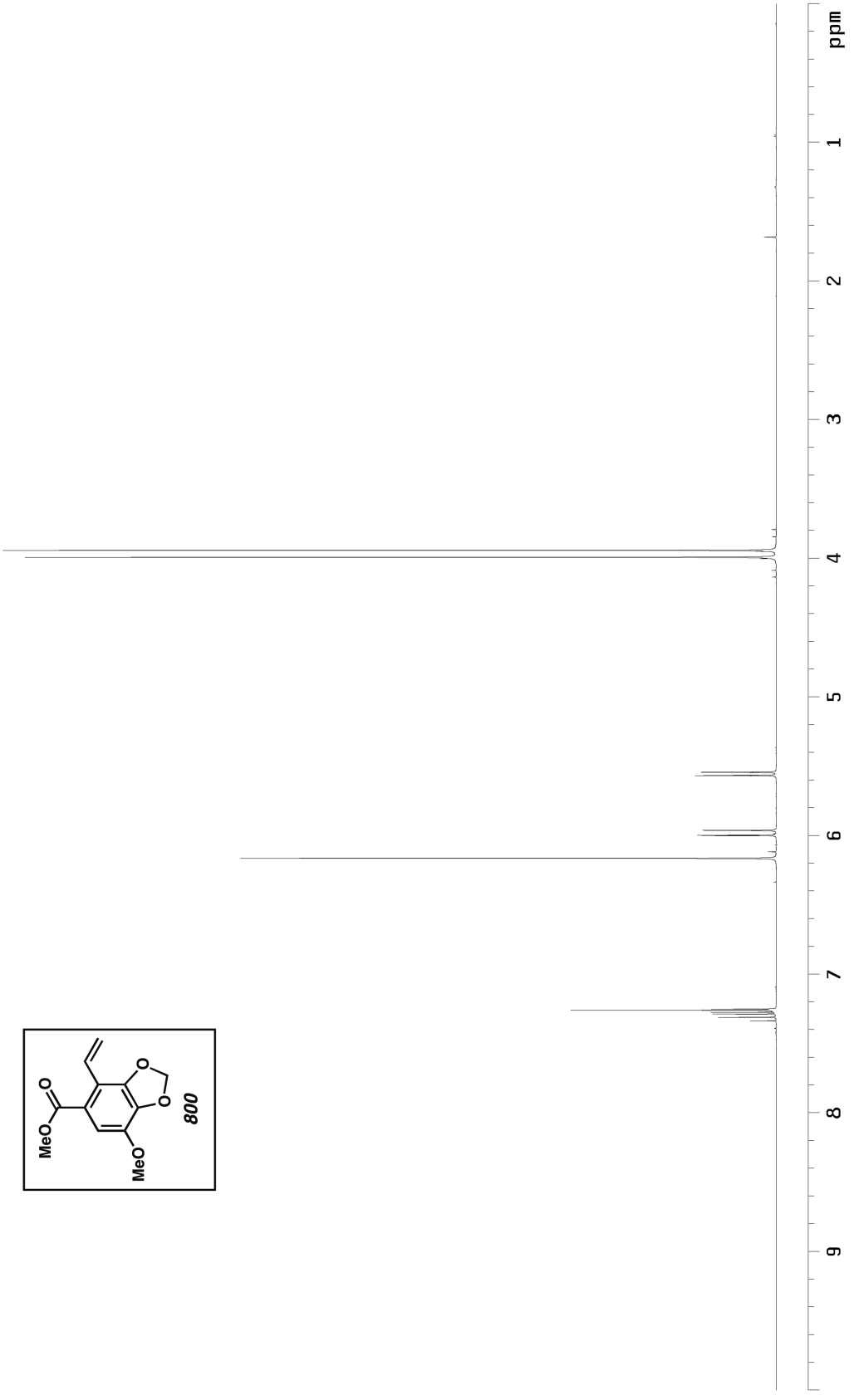


Figure A3.15.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **800**.

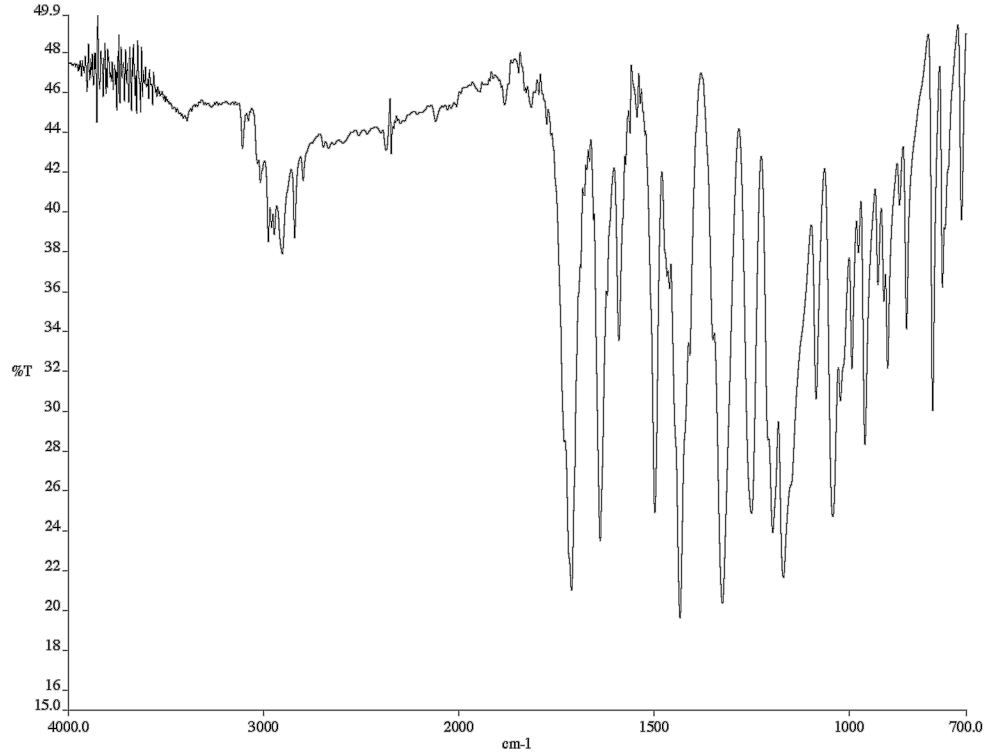


Figure A3.15.2 Infrared spectrum (thin film/NaCl) of compound **800**.

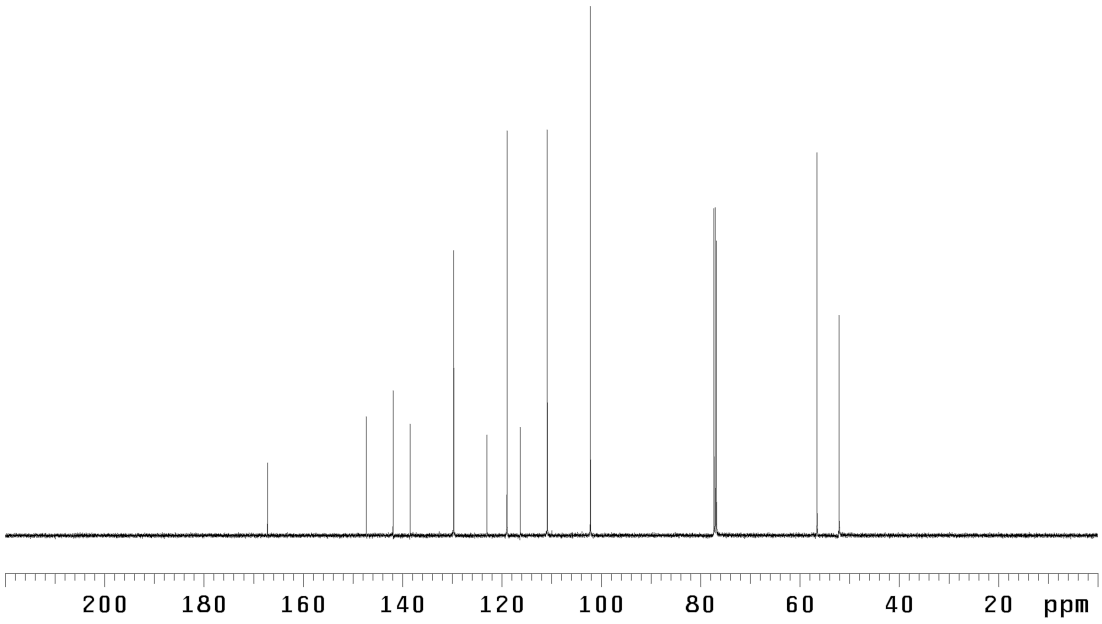


Figure A3.15.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **800**.

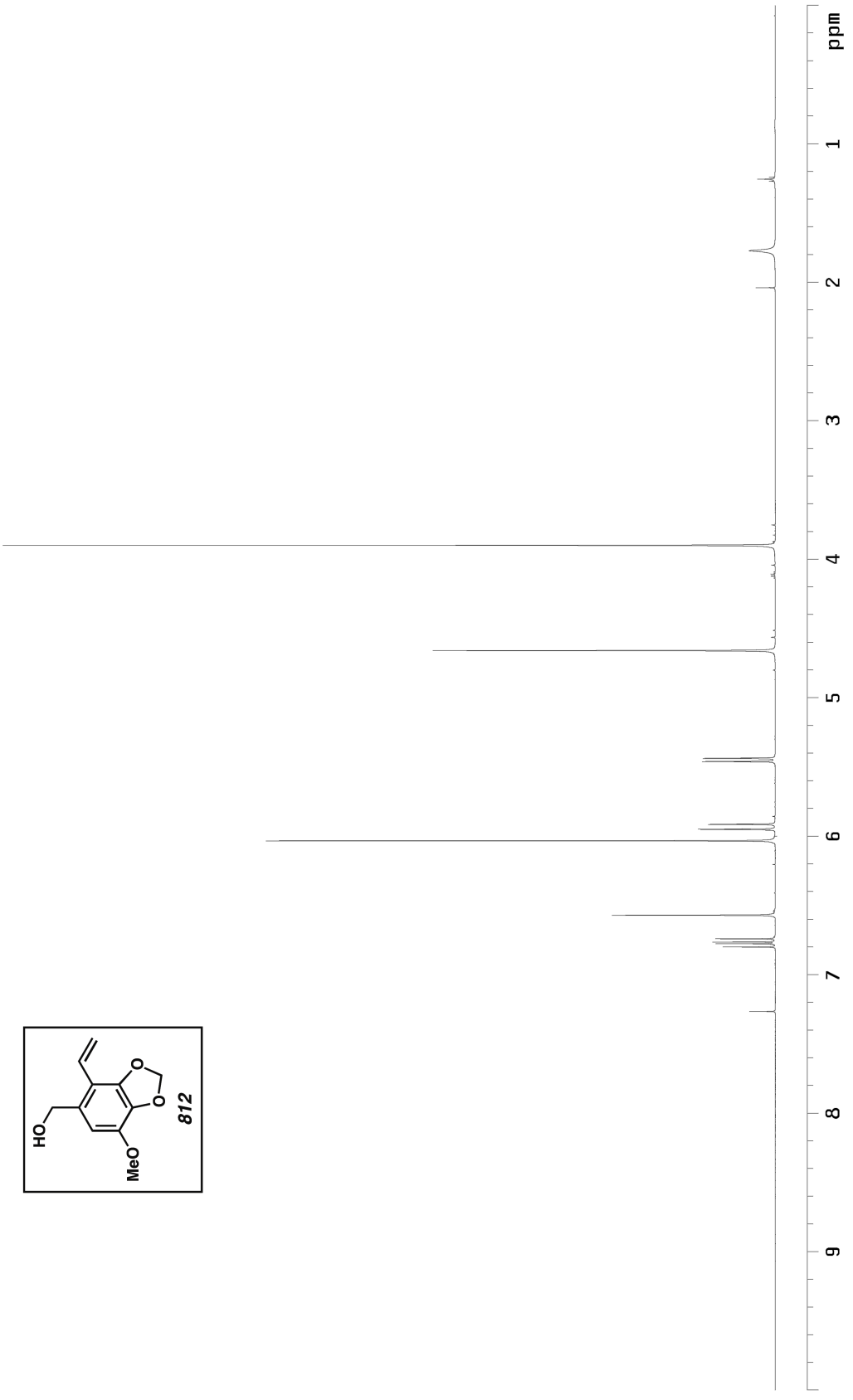


Figure A3.16.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **812**.

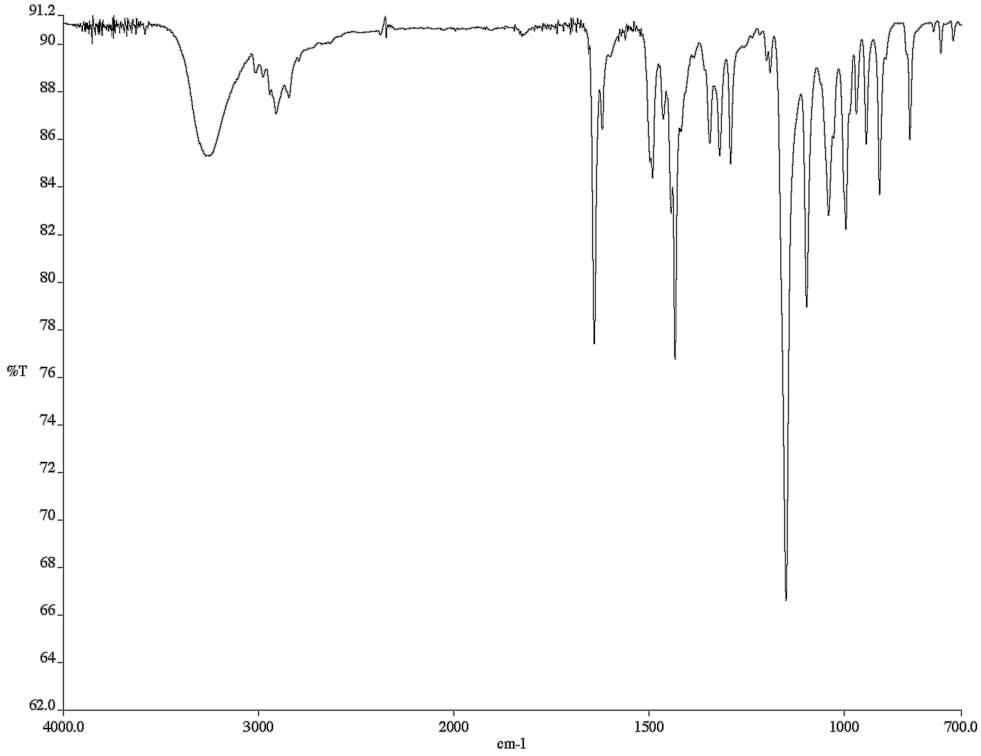


Figure A3.16.2 Infrared spectrum (thin film/NaCl) of compound **812**.

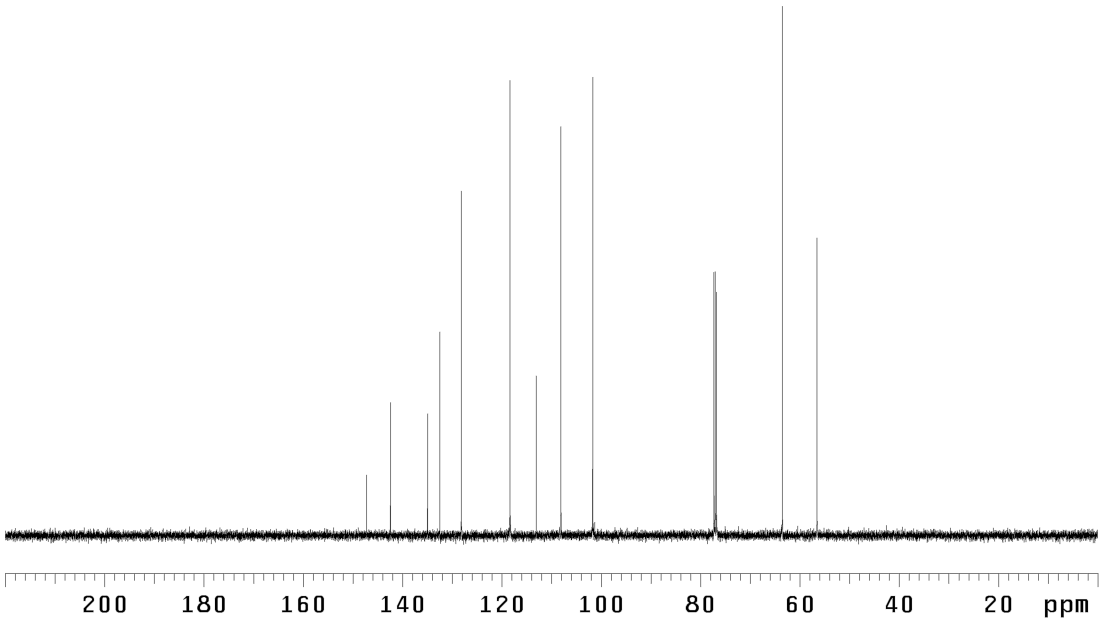


Figure A3.16.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **812**.

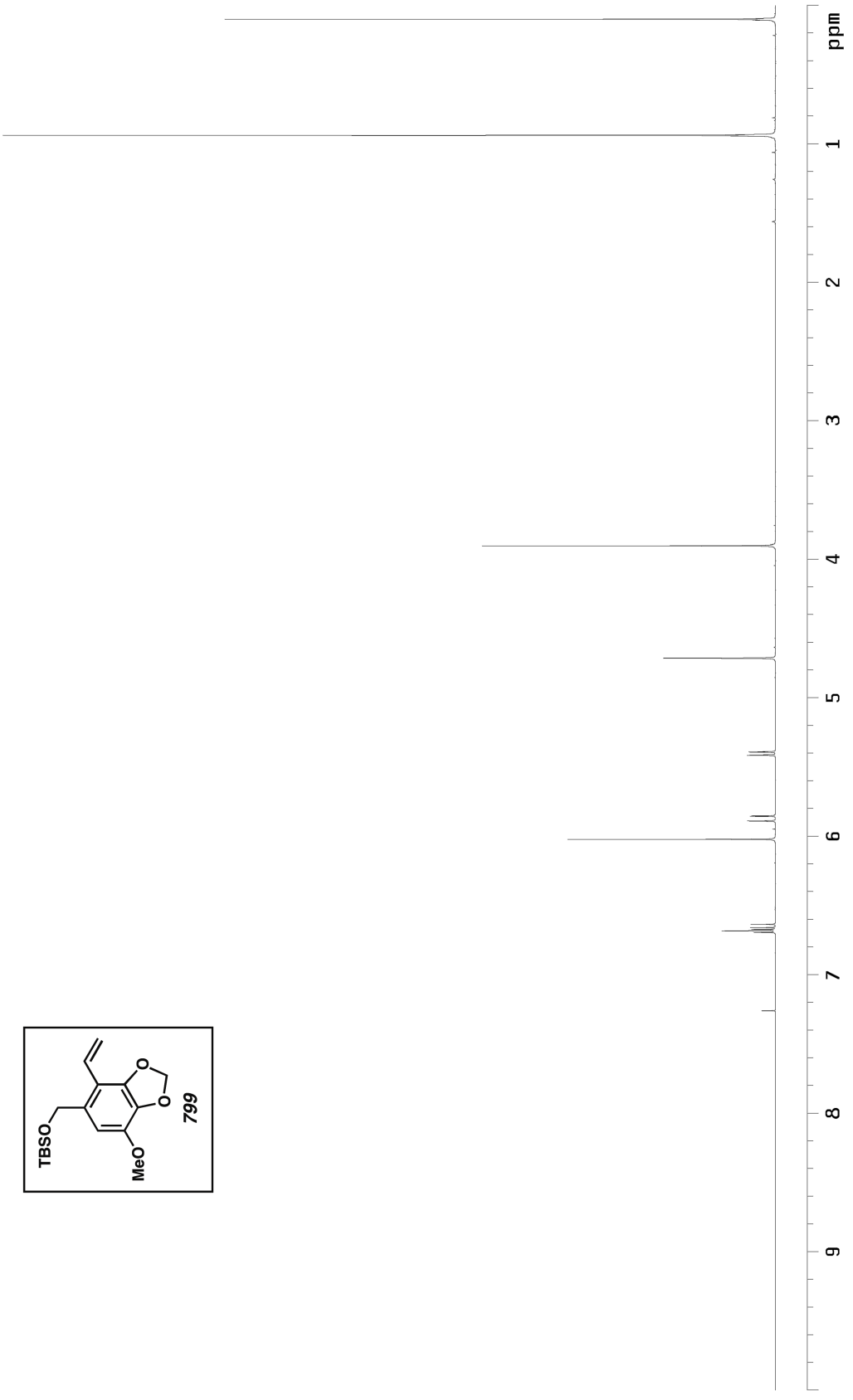


Figure A3.17.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **799**.

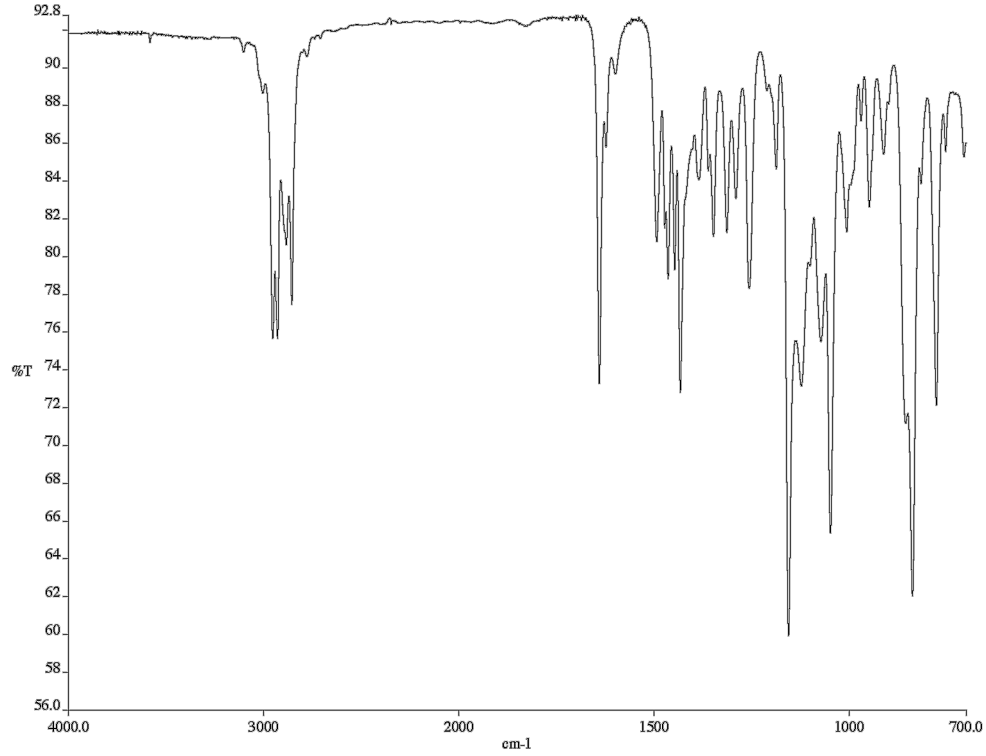


Figure A3.17.2 Infrared spectrum (thin film/NaCl) of compound **799**.

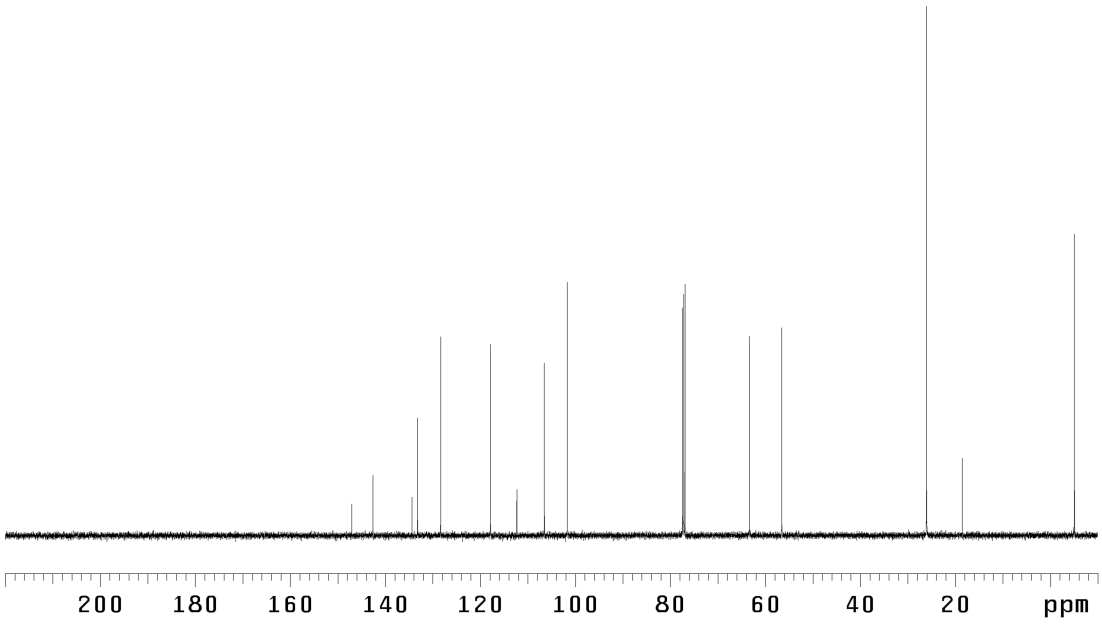


Figure A3.17.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **799**.

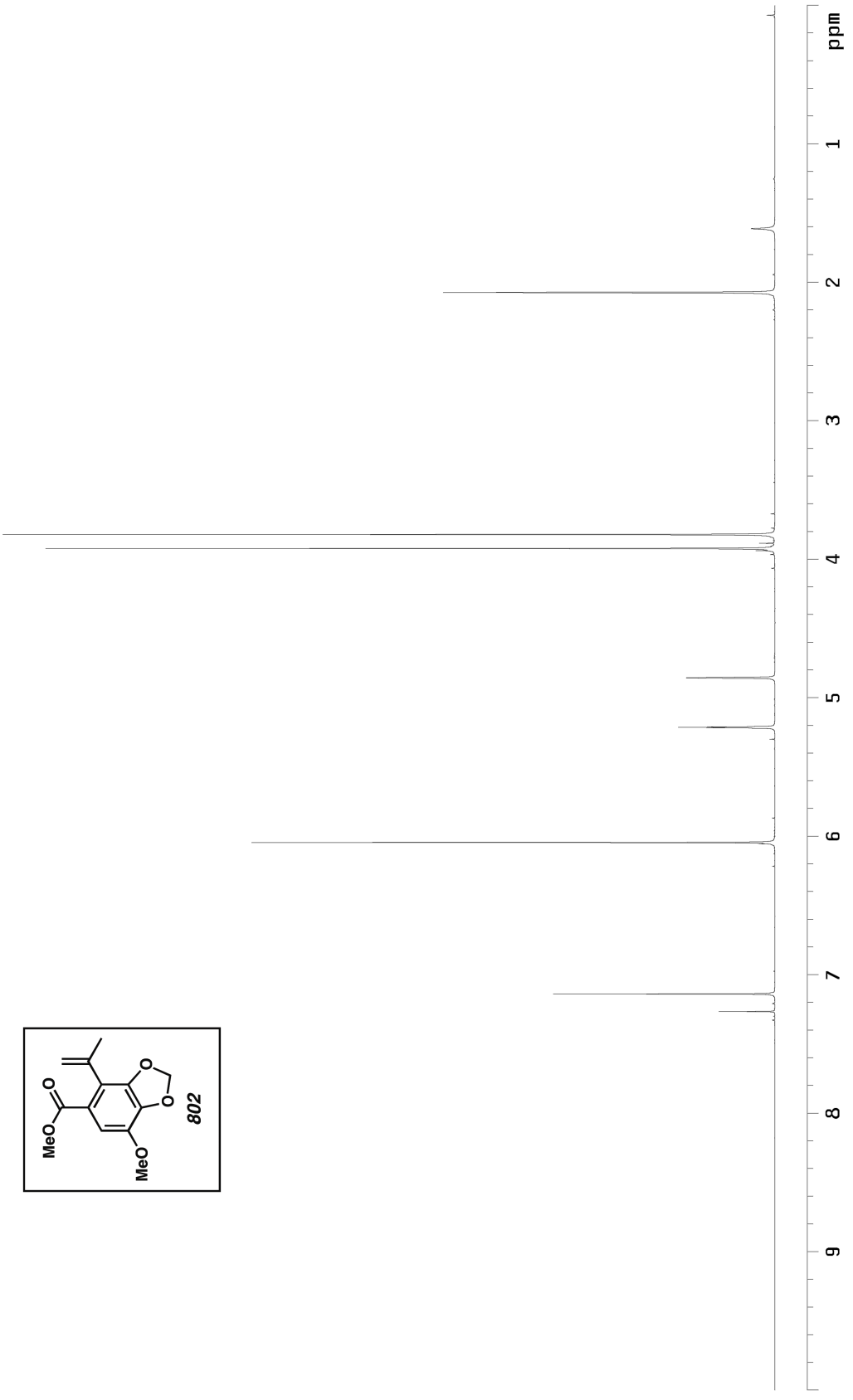


Figure A3.18.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **802**.

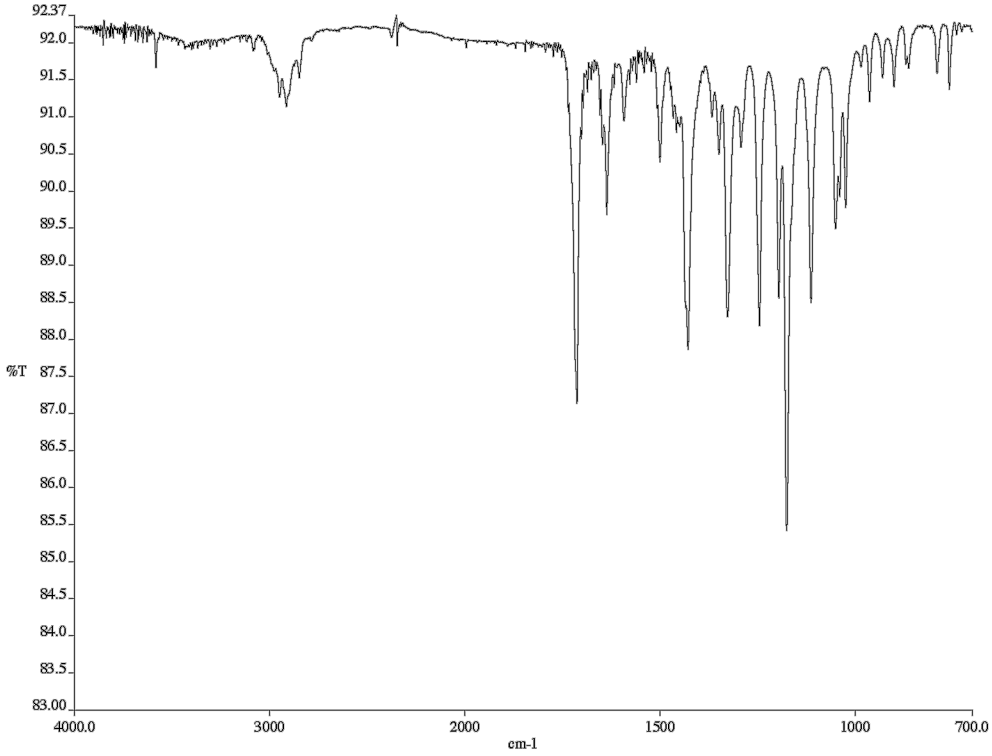


Figure A3.18.2 Infrared spectrum (thin film/NaCl) of compound **802**.

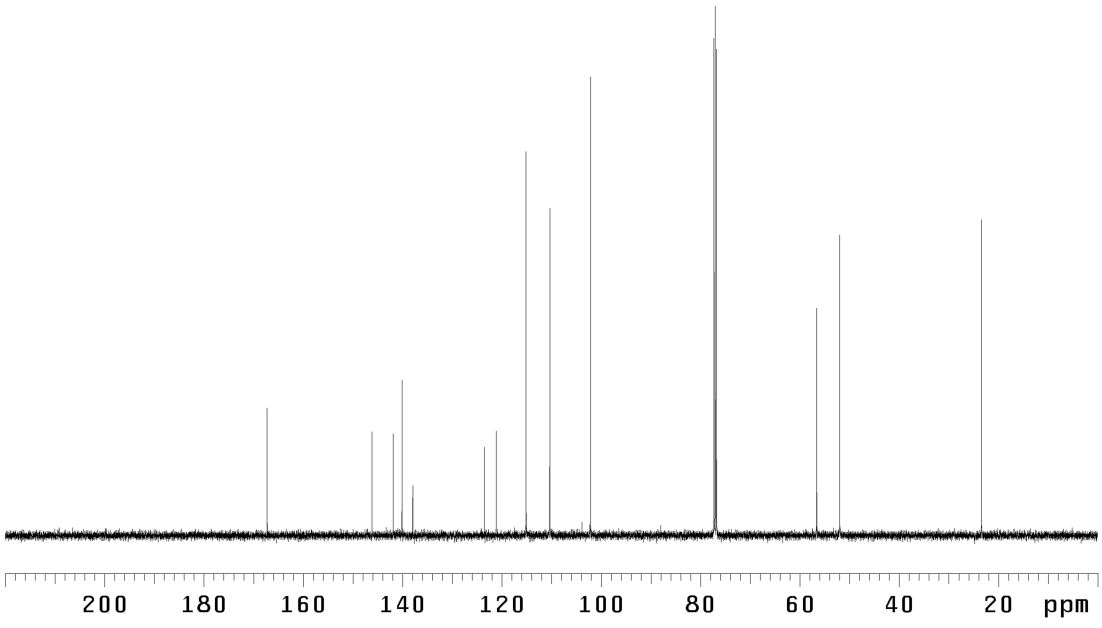


Figure A3.18.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **802**.

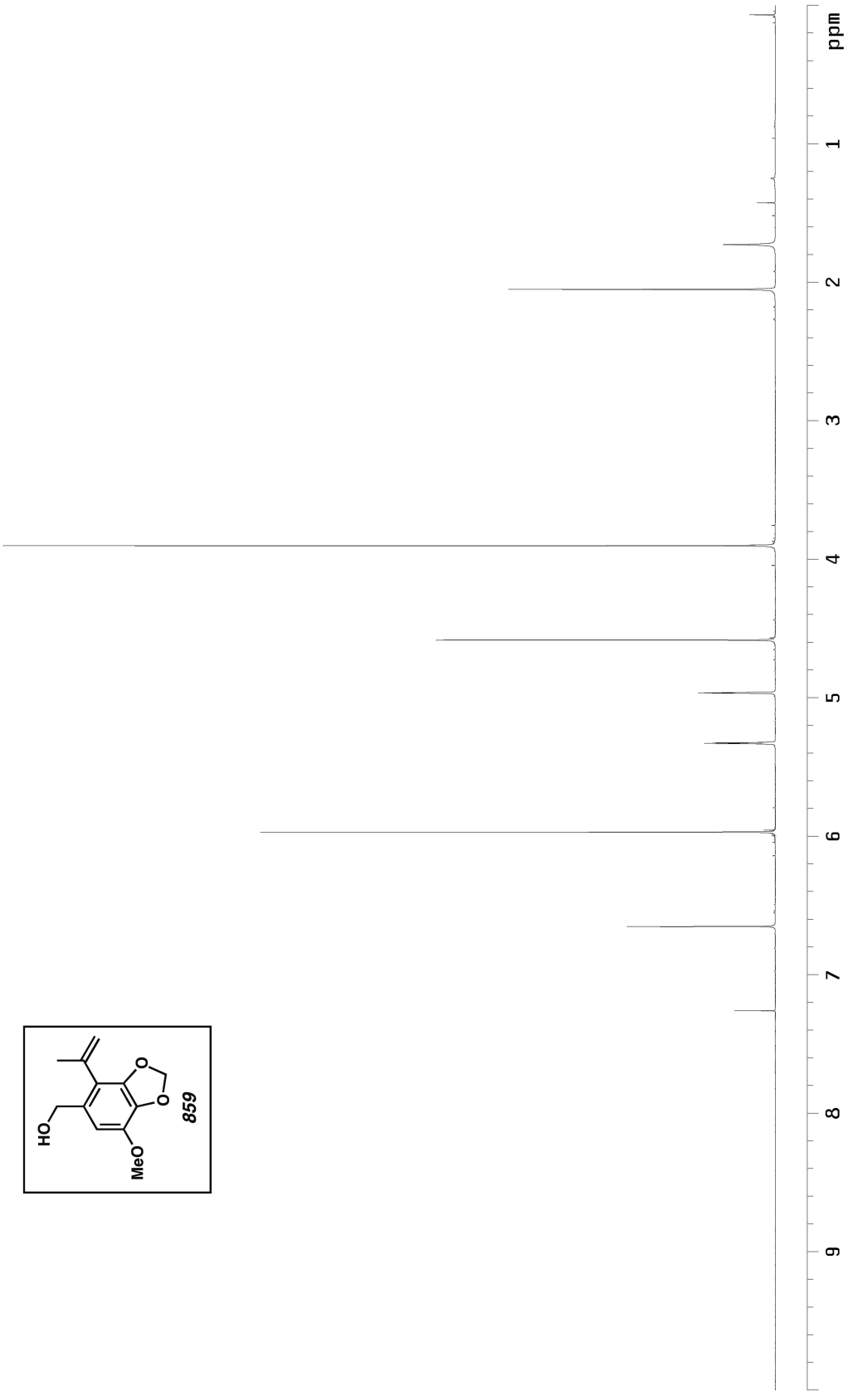


Figure A3.19.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **859**.

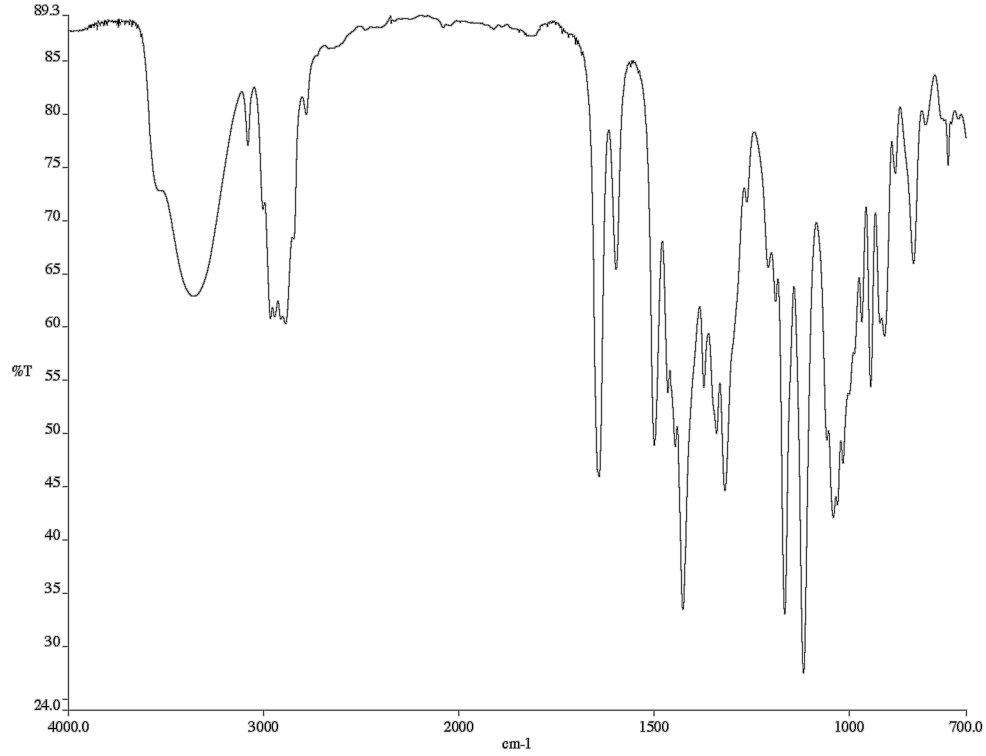


Figure A3.19.2 Infrared spectrum (thin film/NaCl) of compound **859**.

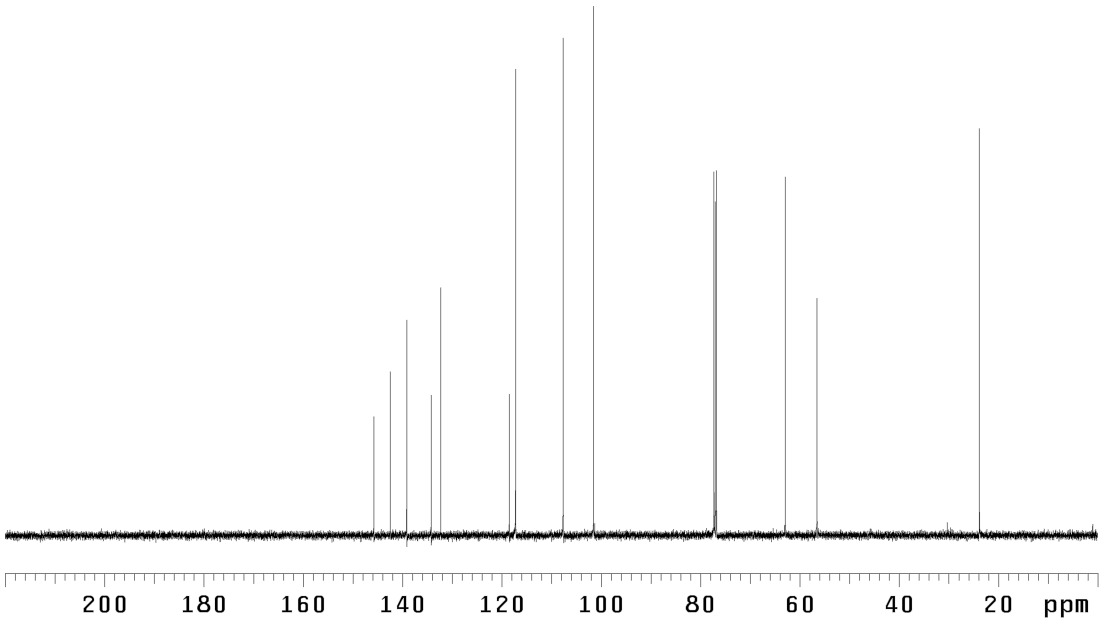


Figure A3.19.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **859**.

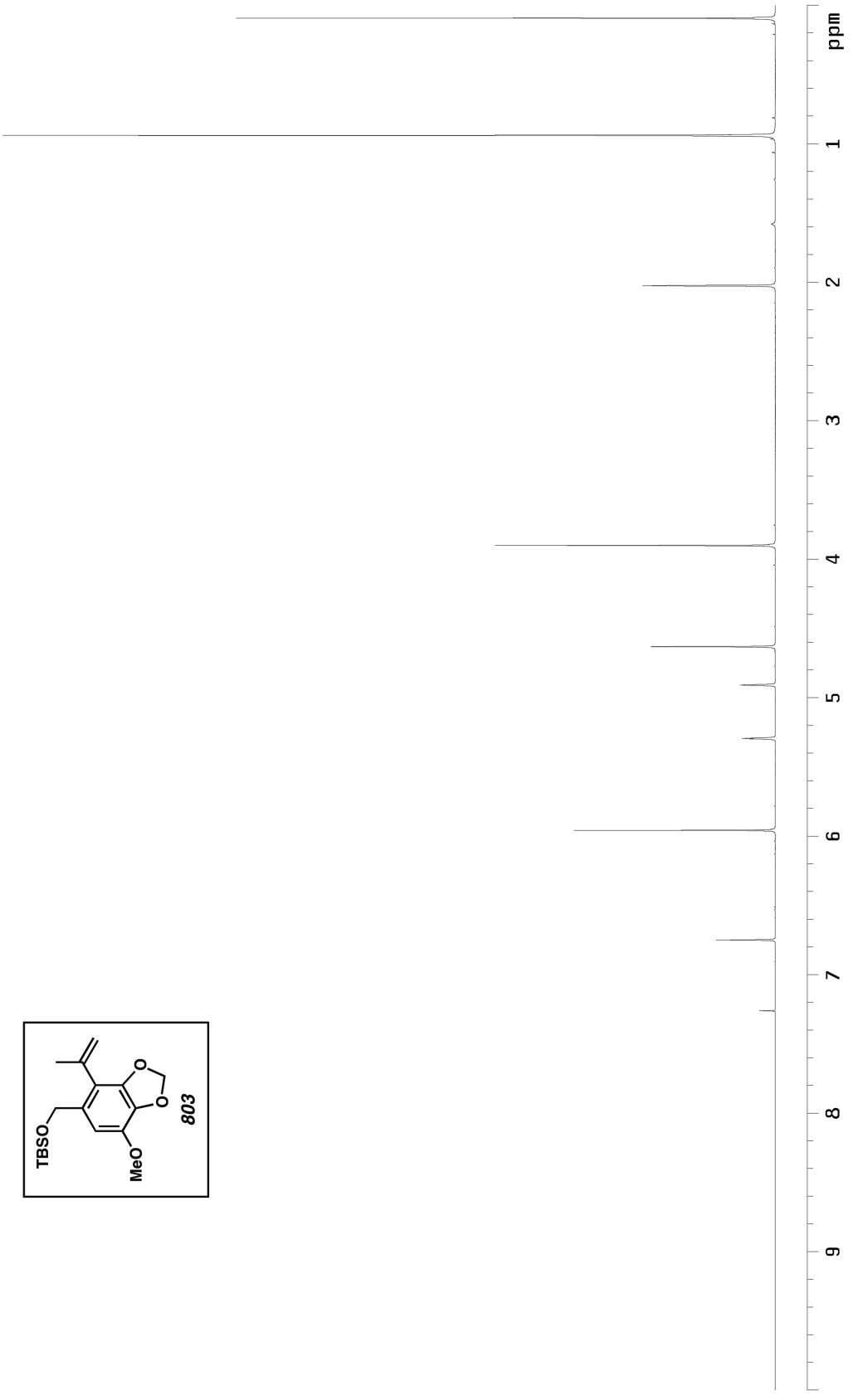


Figure A3.20.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **803**.

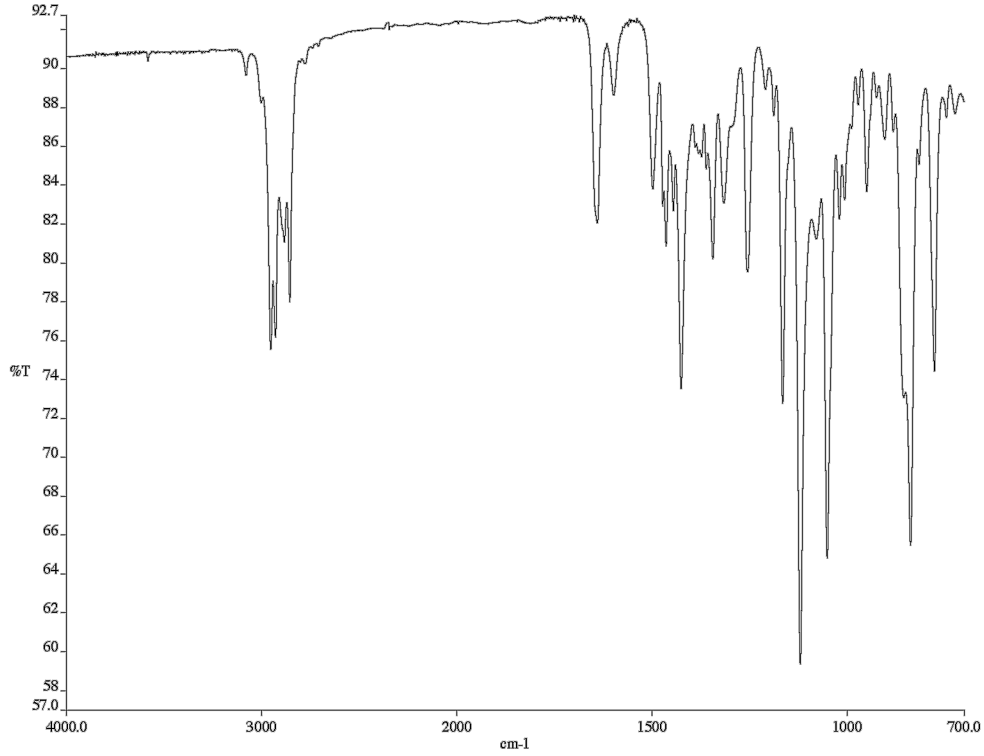


Figure A3.20.2 Infrared spectrum (thin film/NaCl) of compound **803**.

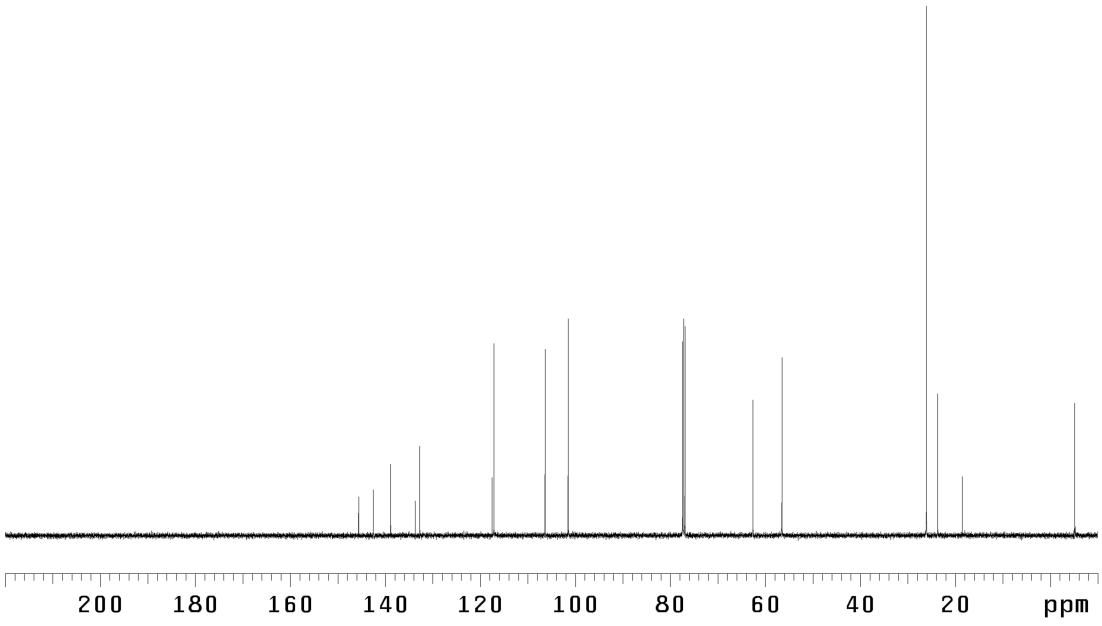


Figure A3.20.3 ^{13}C NMR (500 MHz, $CDCl_3$) of compound **803**.

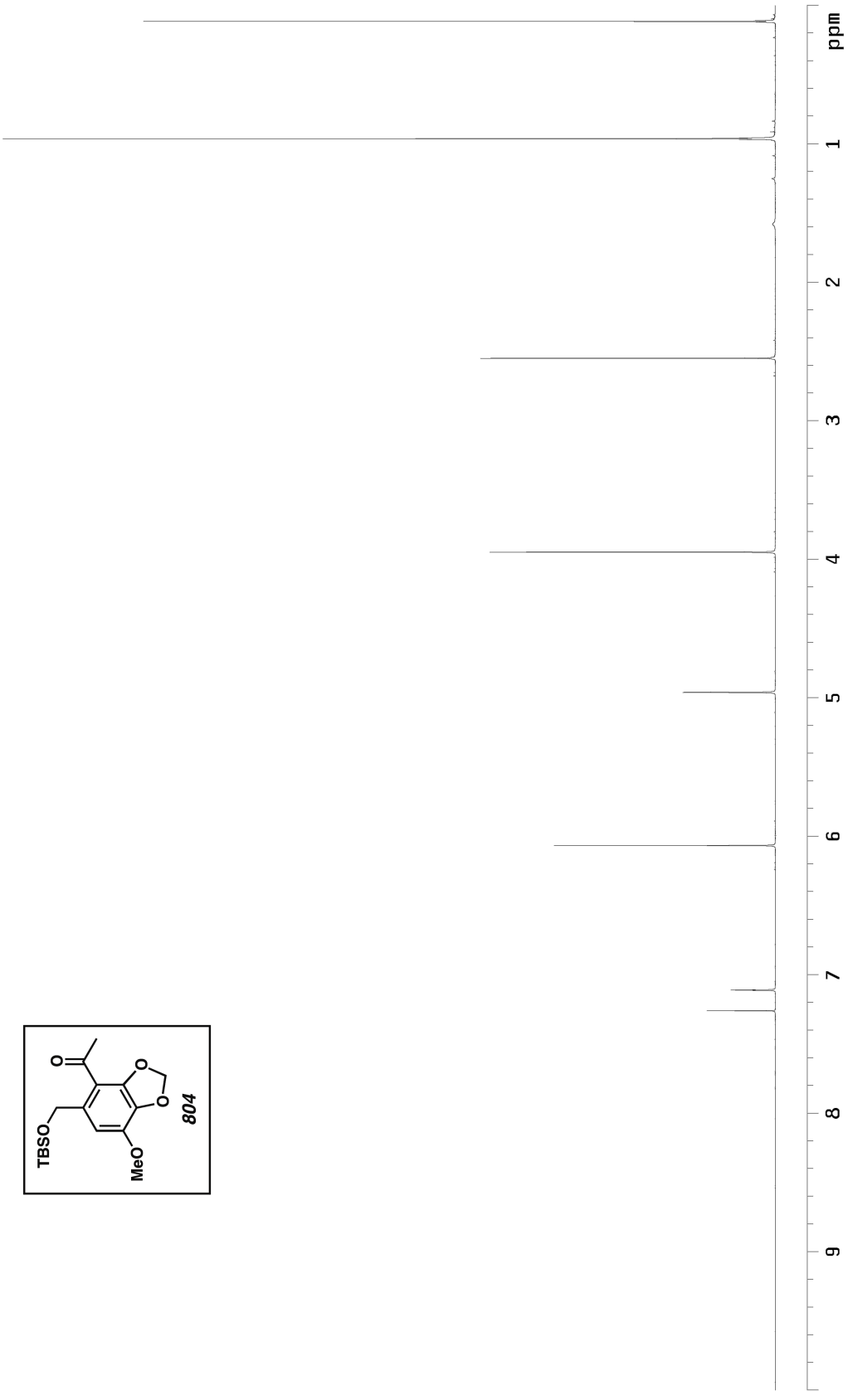


Figure A3.21.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **804**.

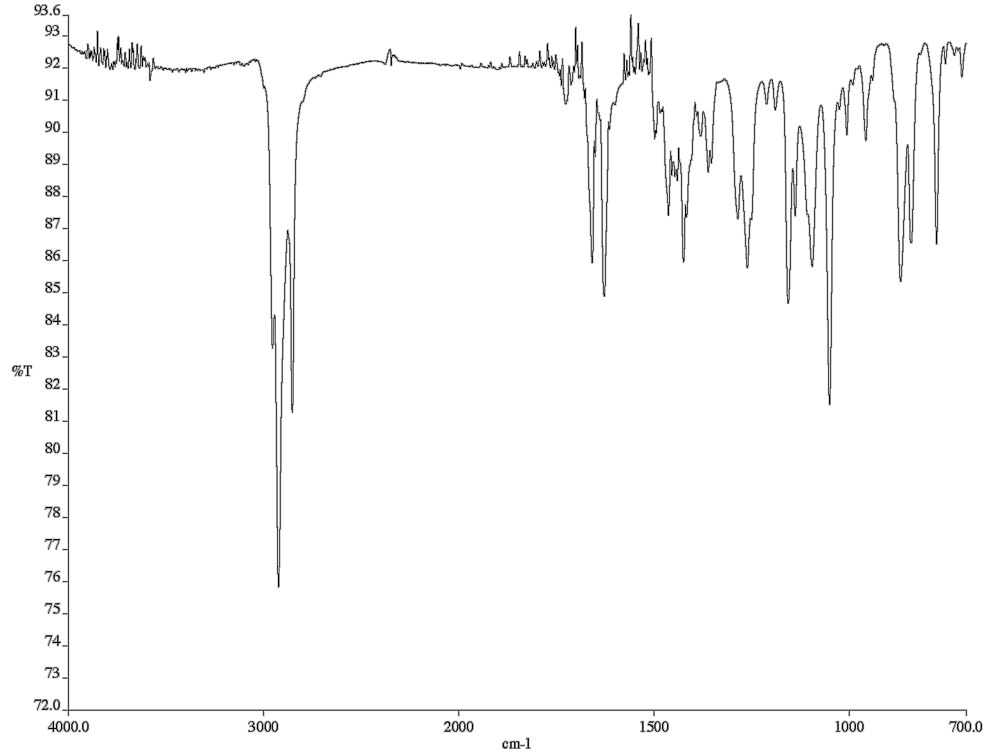


Figure A3.21.2 Infrared spectrum (thin film/NaCl) of compound **804**.

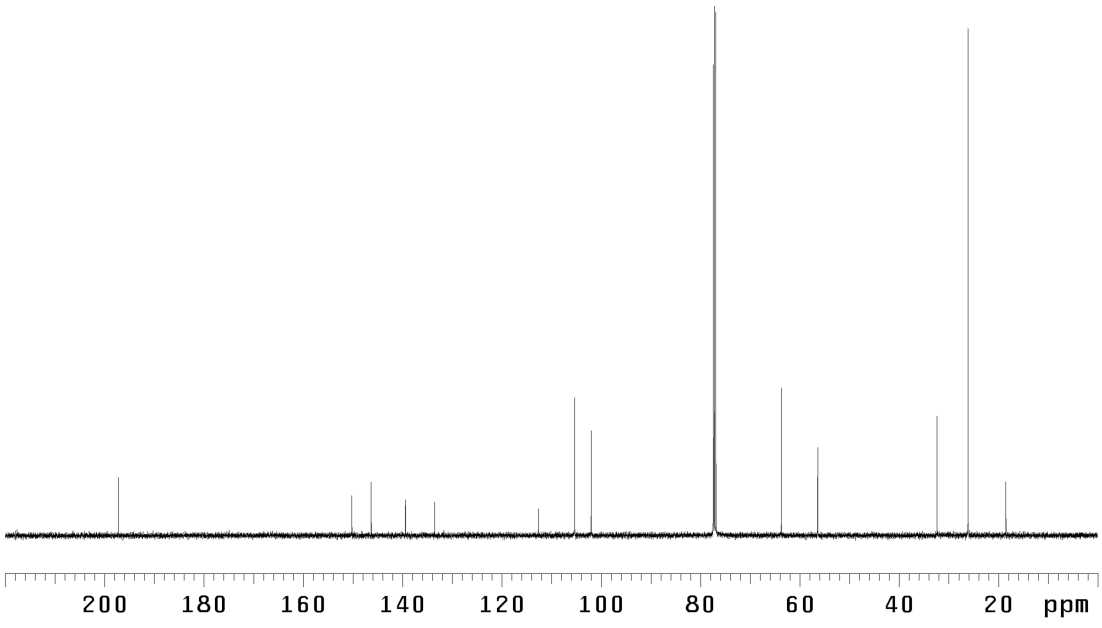


Figure A3.21.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **804**.

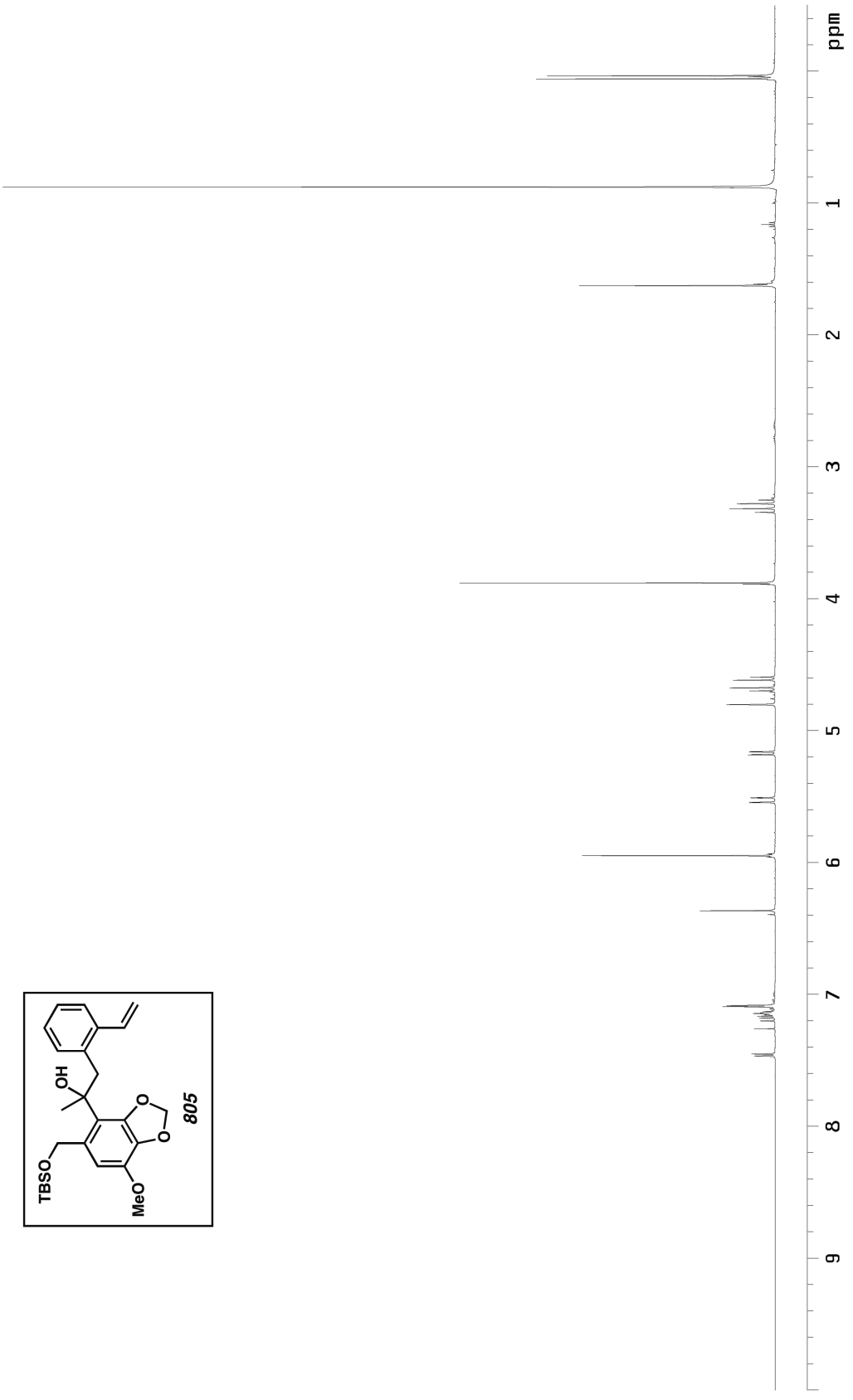


Figure A3.22.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **805**.

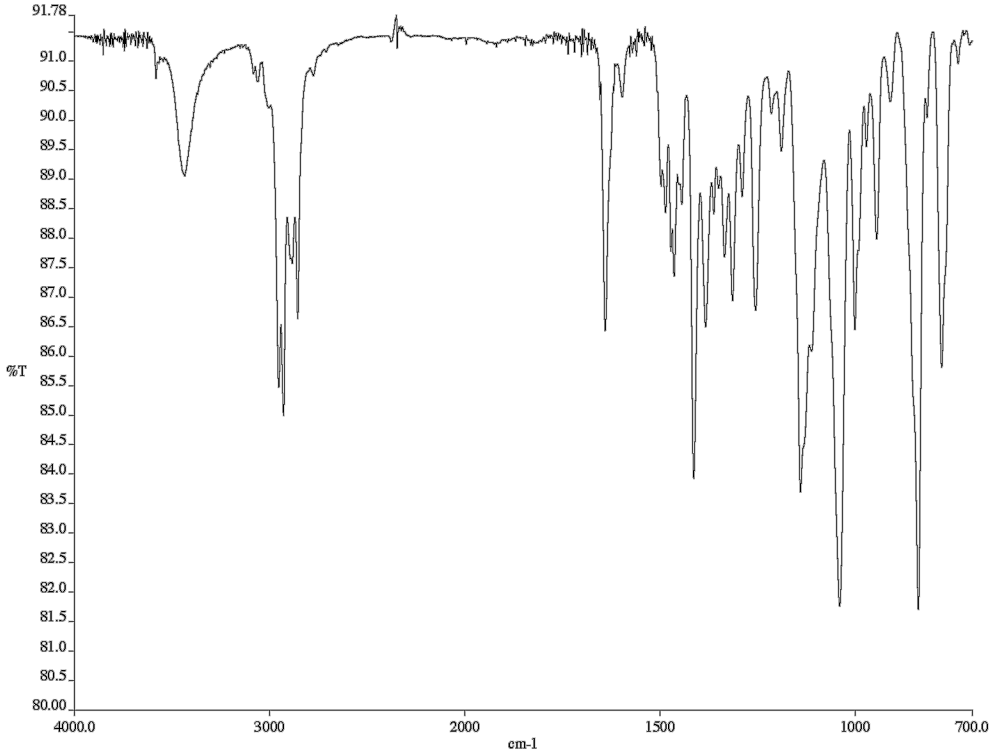


Figure A3.22.1 Infrared spectrum (thin film/NaCl) of compound **805**.

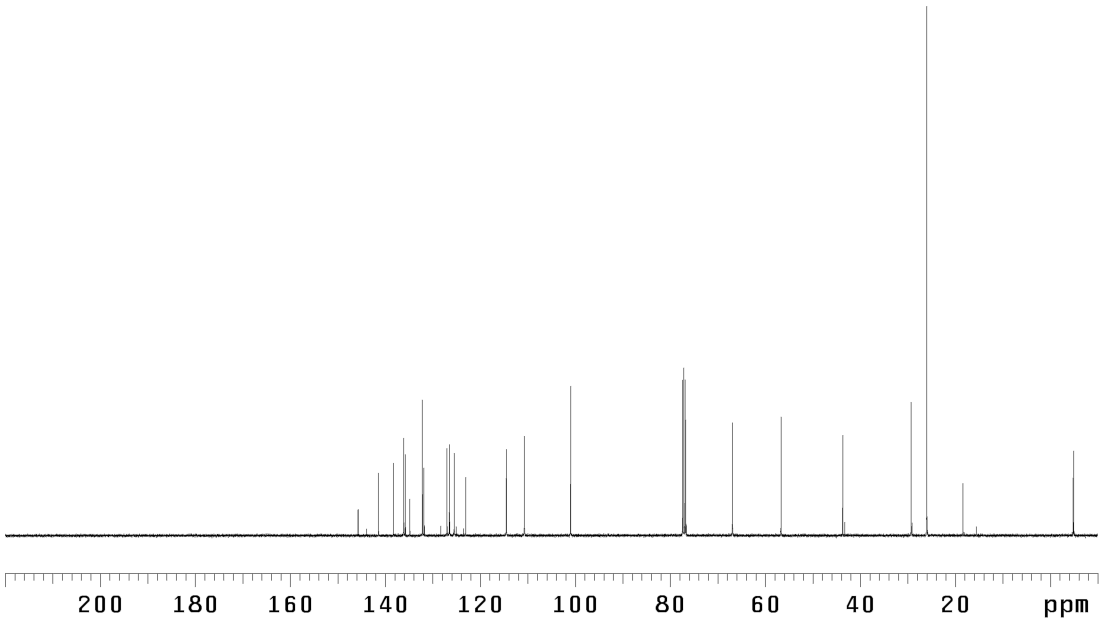


Figure A3.22.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **805**.

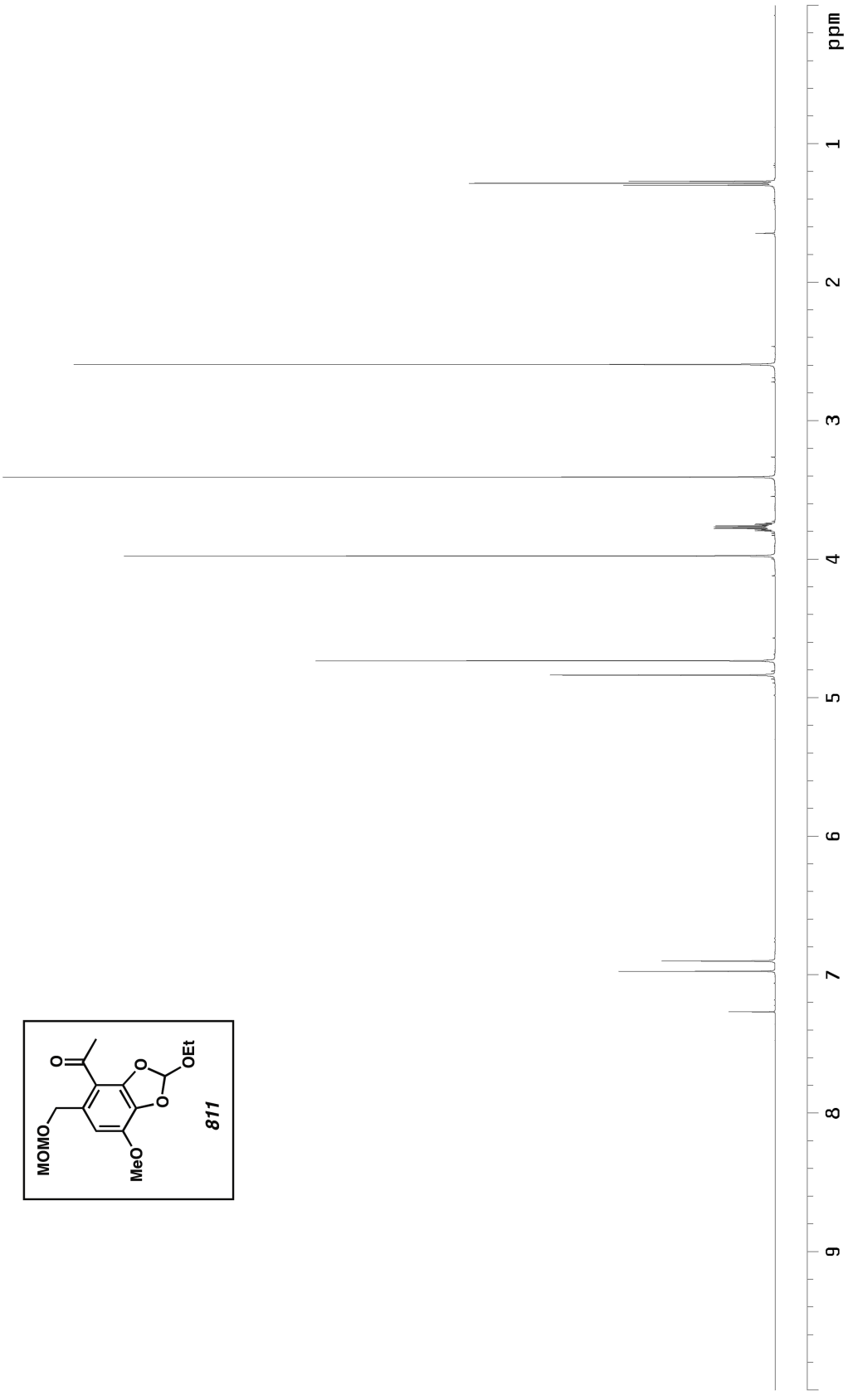


Figure A3.23.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **811**.

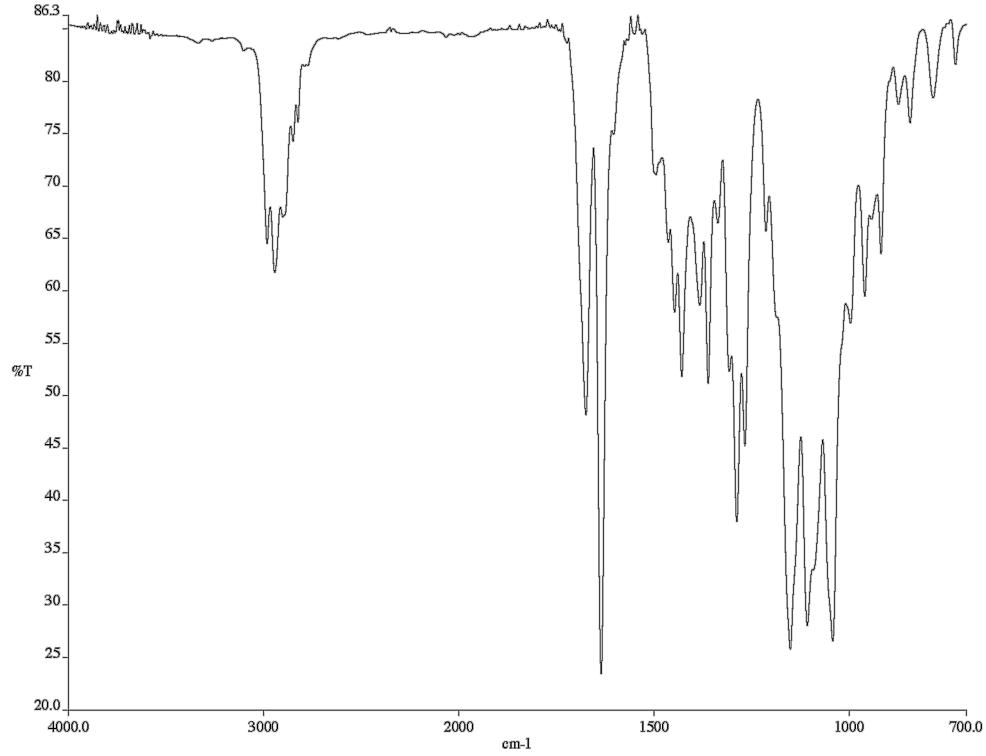


Figure A3.23.2 Infrared spectrum (thin film/NaCl) of compound **811**.

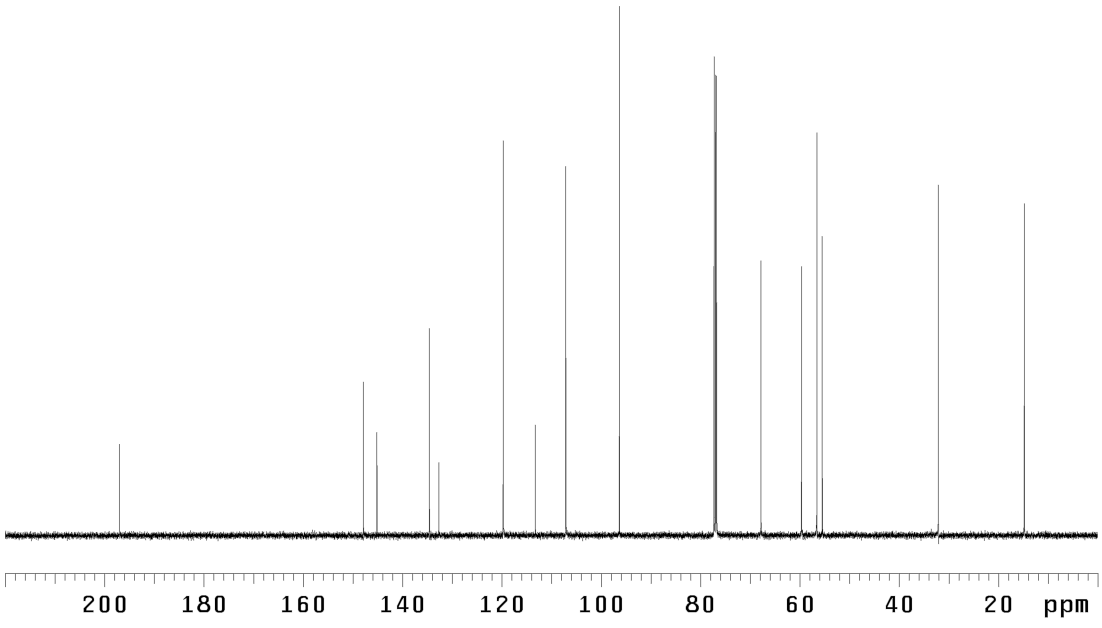


Figure A3.23.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **811**.

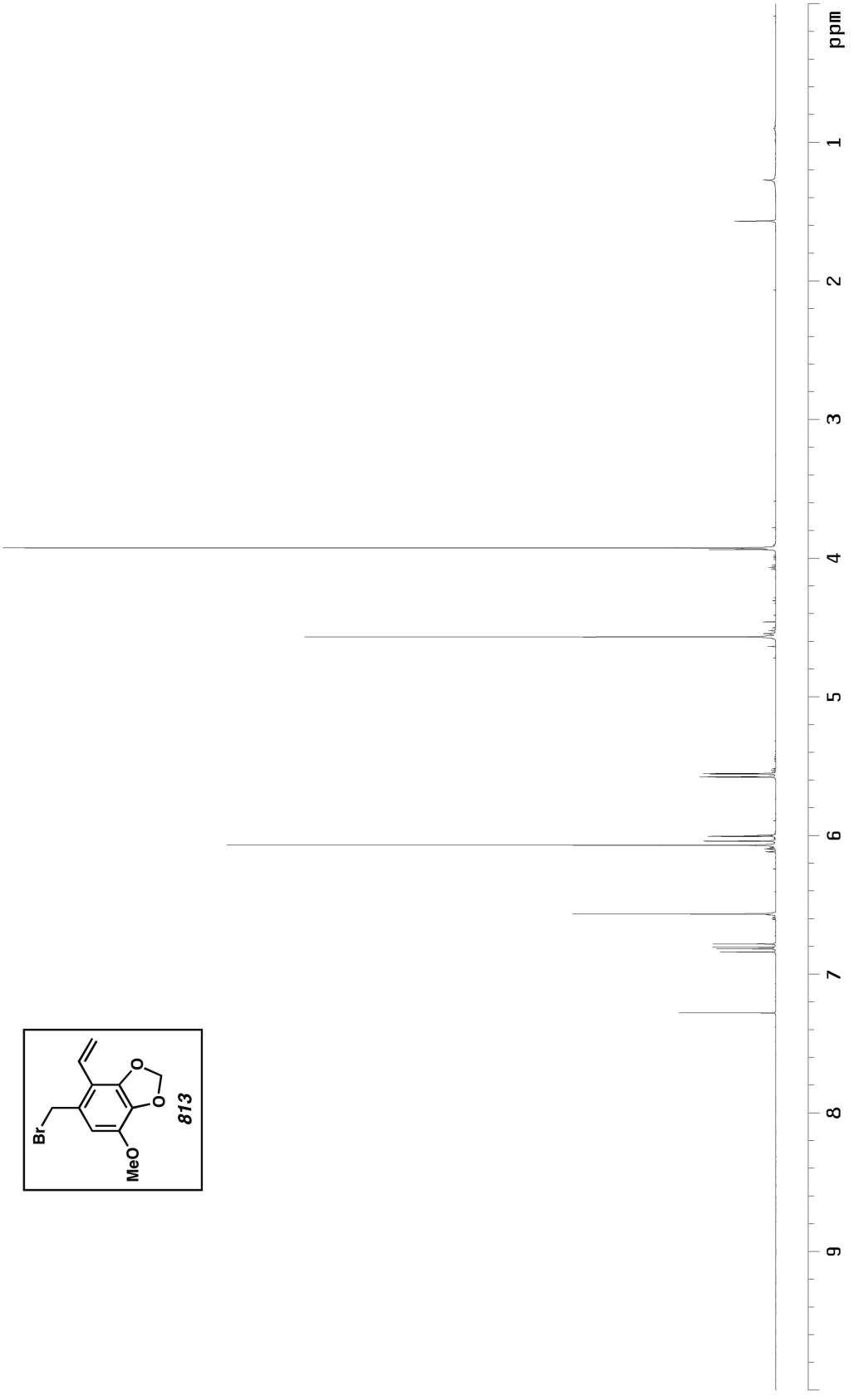


Figure A3.24.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **813**.

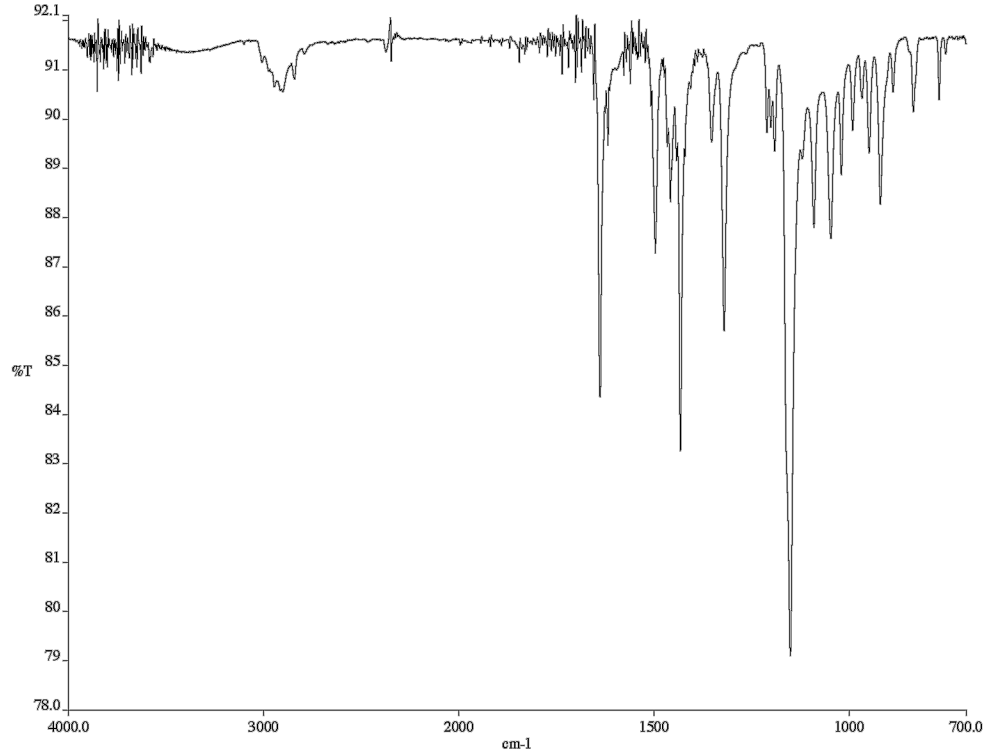


Figure A3.24.2 Infrared spectrum (thin film/NaCl) of compound **813**.

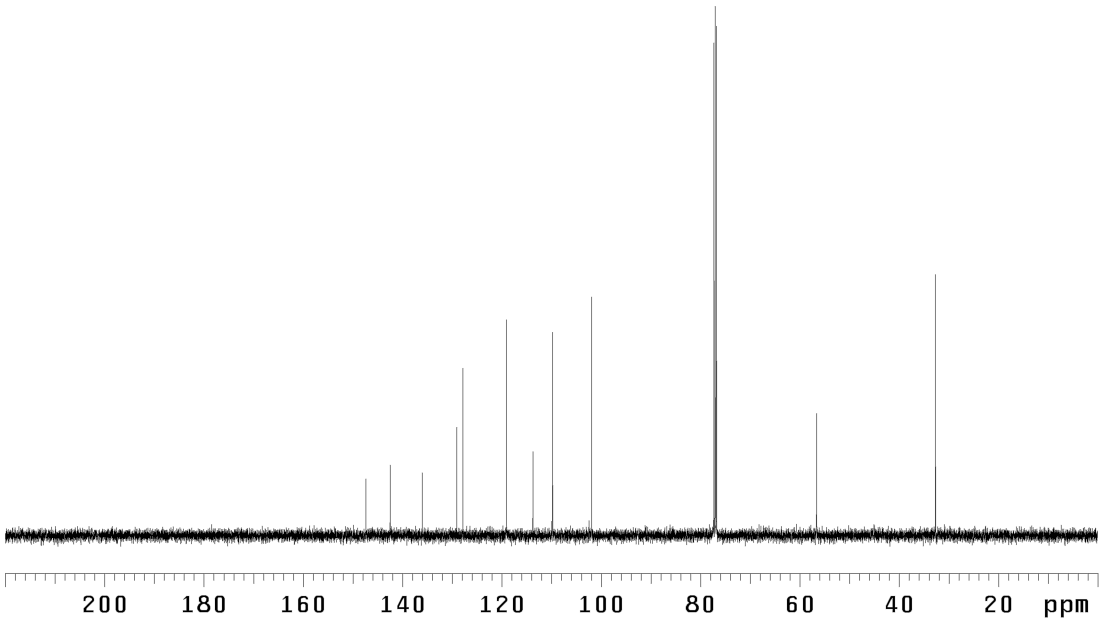


Figure A3.24.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **813**.

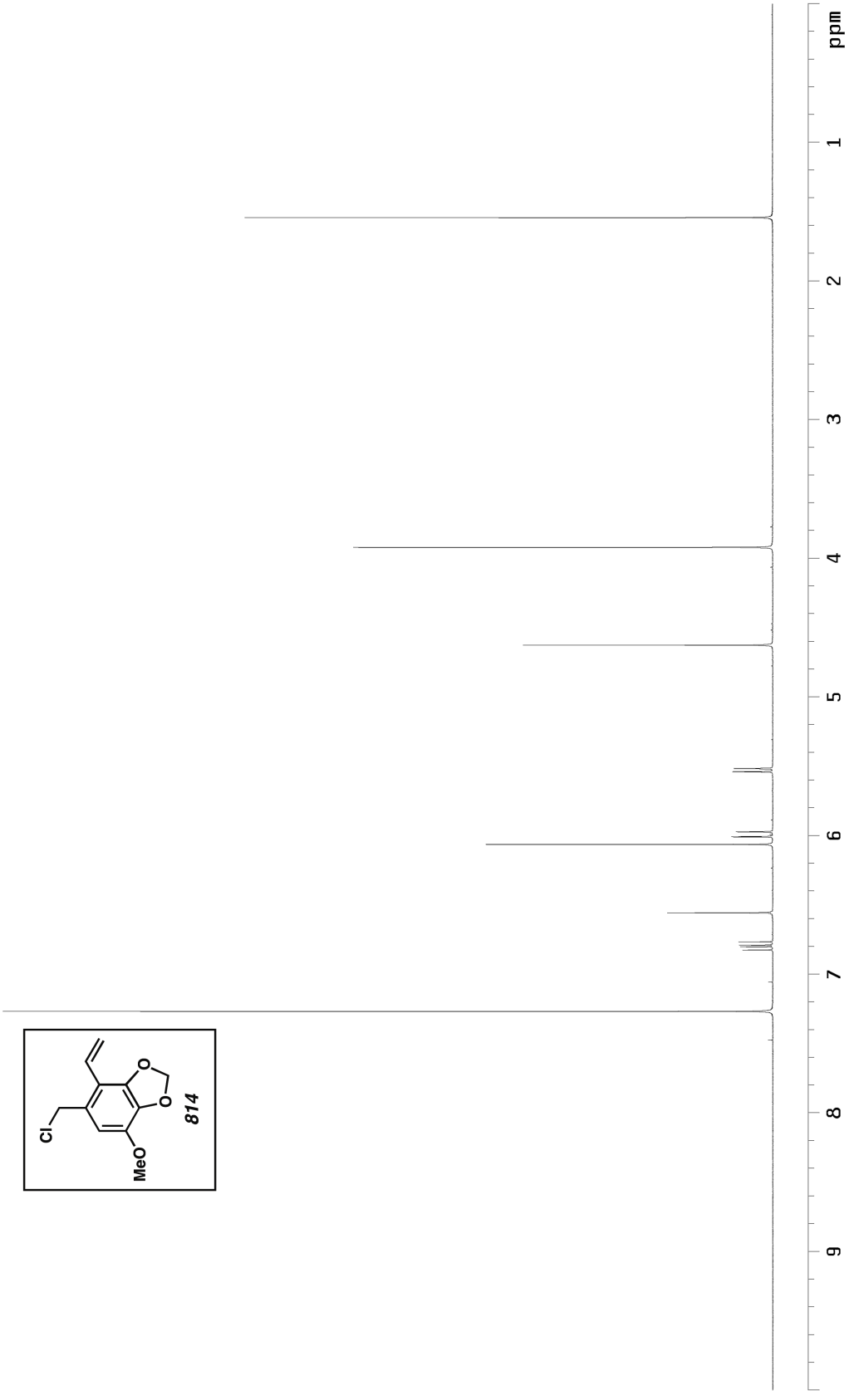


Figure A3.25.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **814**.

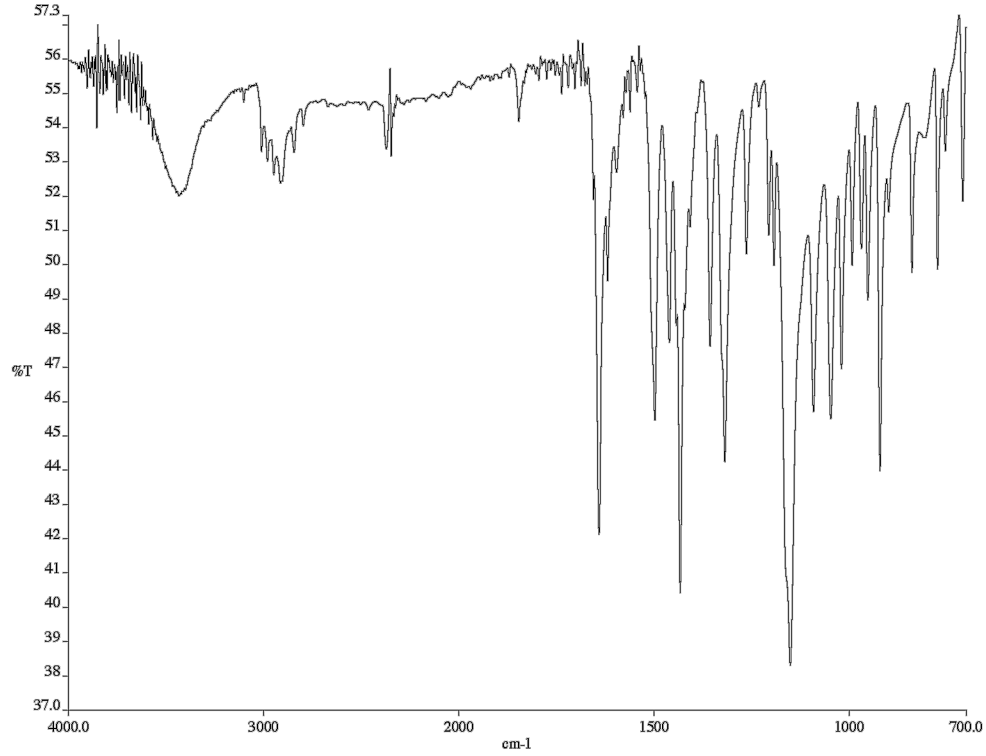


Figure A3.25.2 Infrared spectrum (thin film/NaCl) of compound **814**.

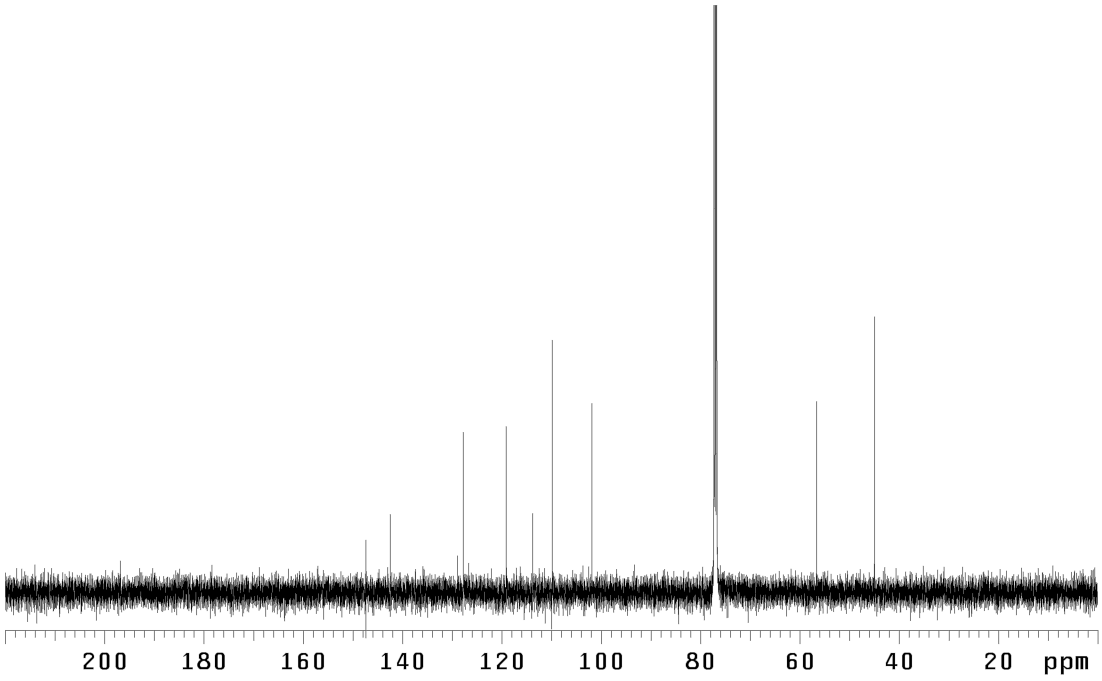


Figure A3.25.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **814**.

Figure A3.26.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **818**.

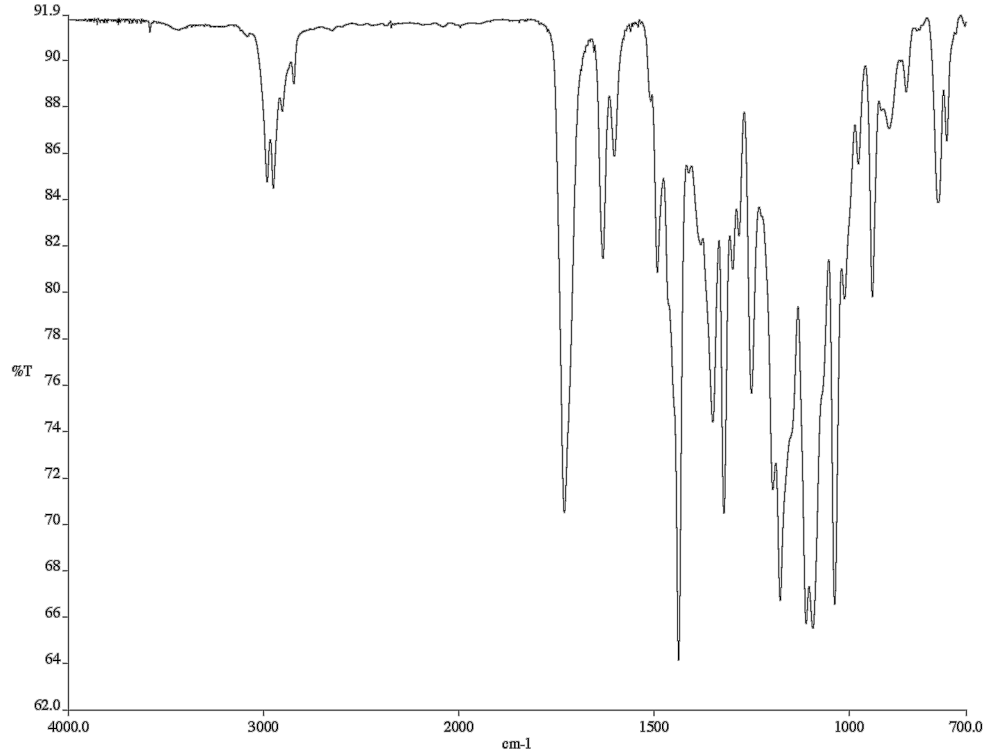


Figure A3.26.2 Infrared spectrum (thin film/NaCl) of compound **818**.

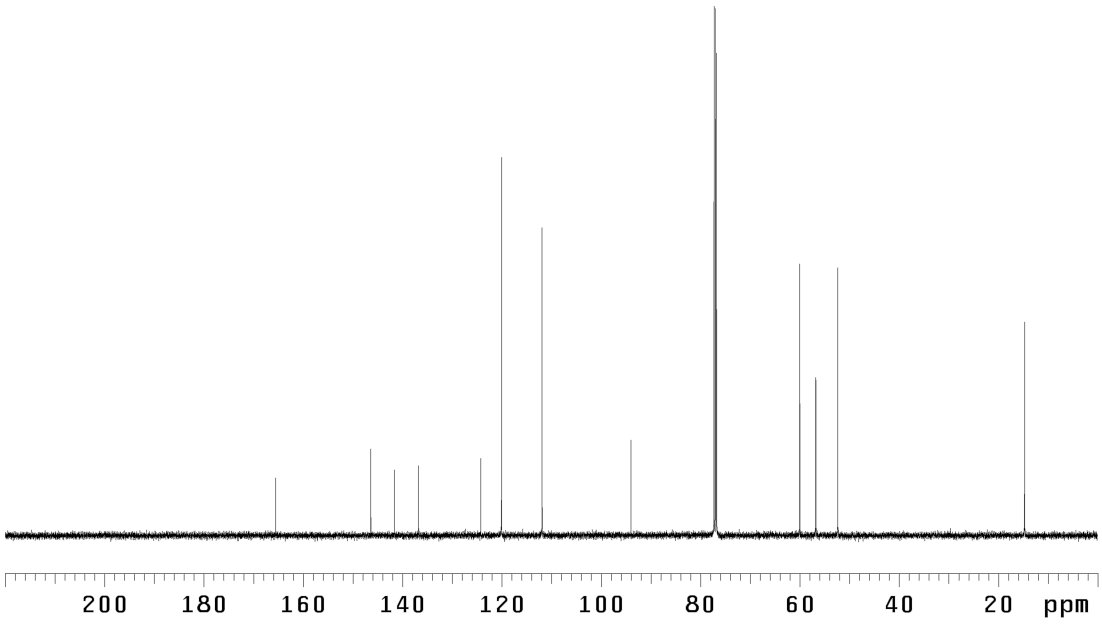


Figure A3.26.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **818**.

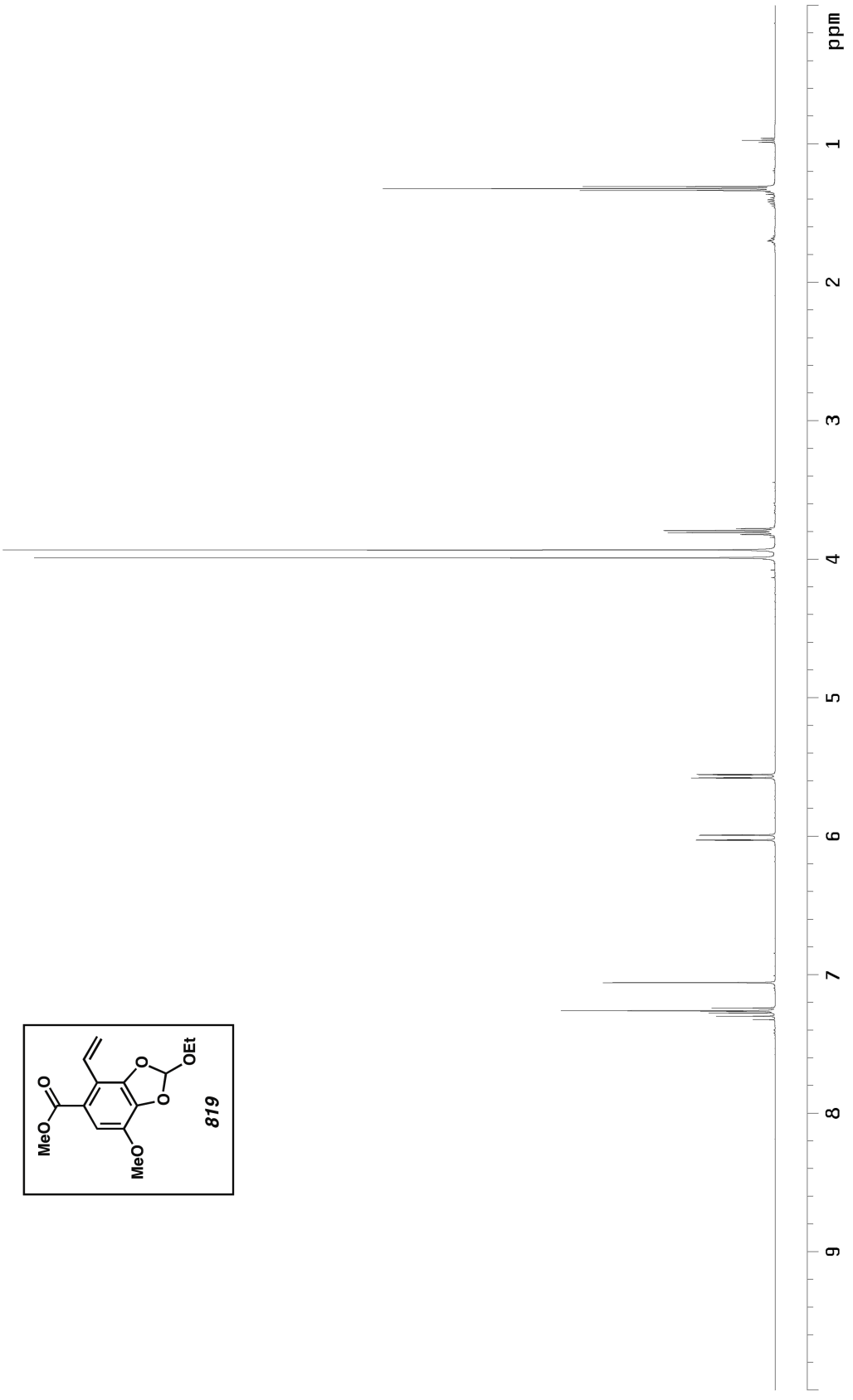


Figure A3.27.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **819**.

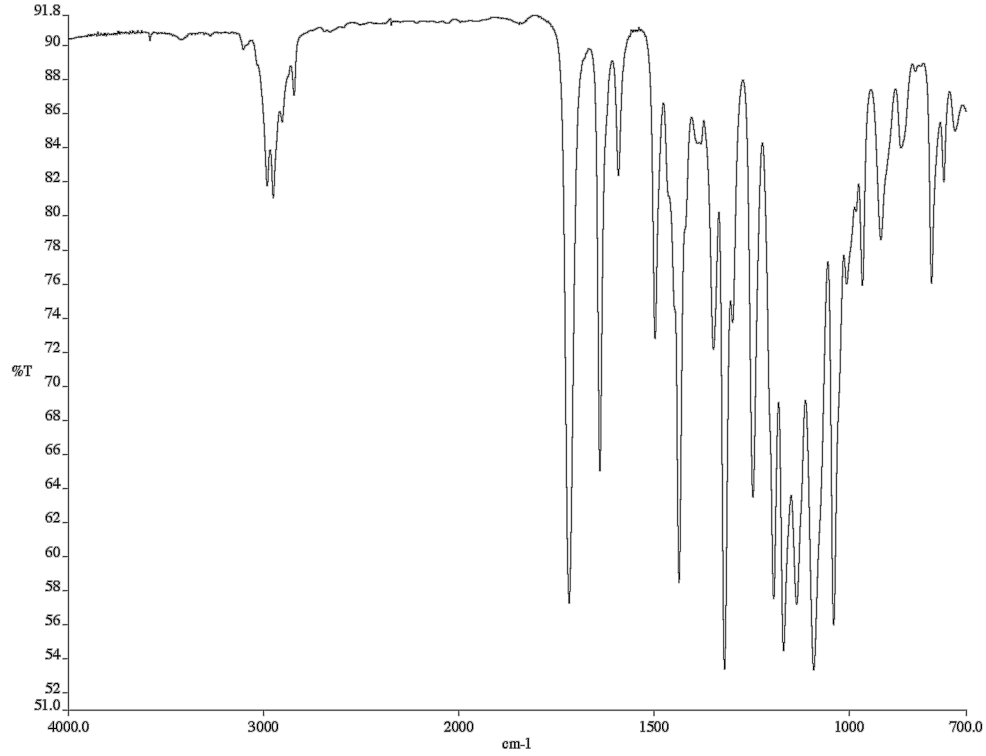


Figure A3.27.2 Infrared spectrum (thin film/NaCl) of compound **819**.

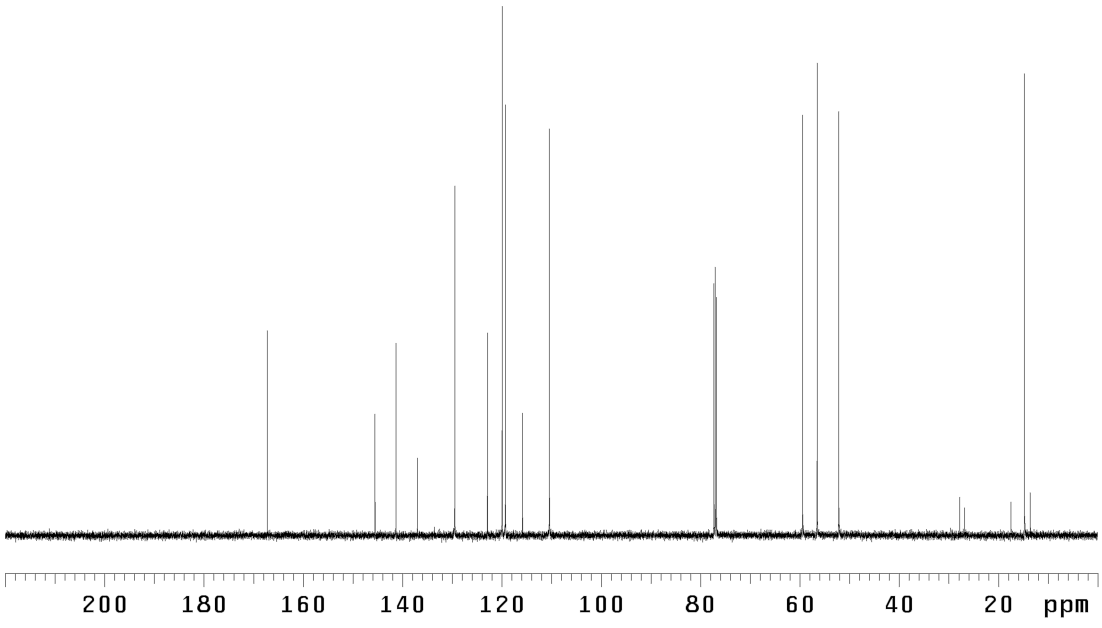


Figure A3.27.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **819**.

Figure A3.28.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **820**.

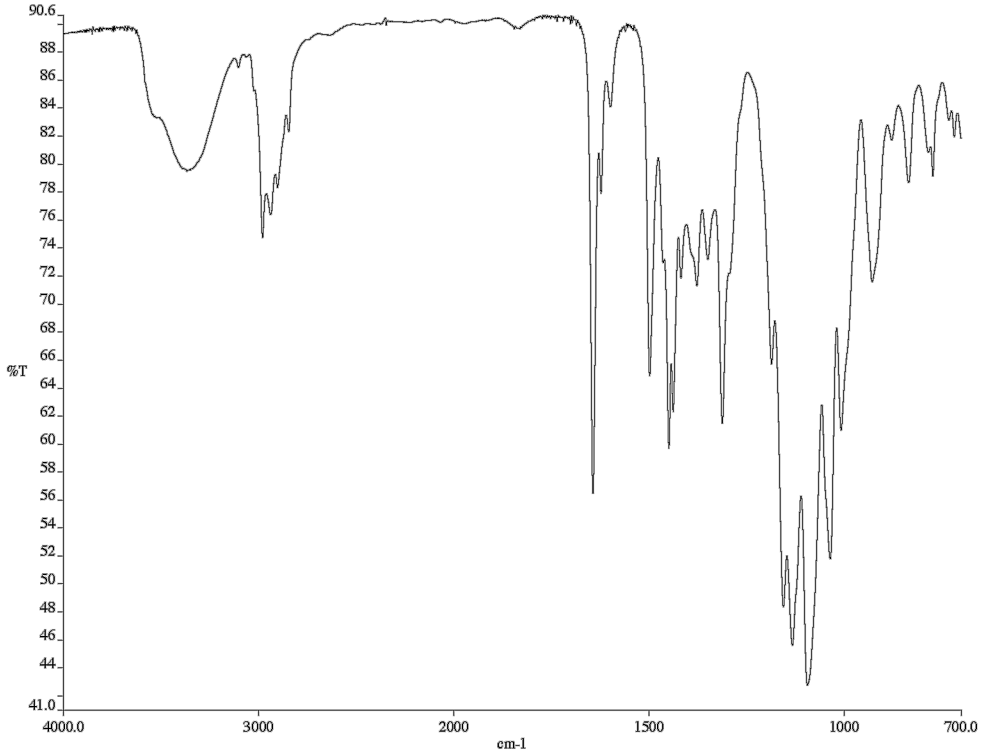


Figure A3.28.2 Infrared spectrum (thin film/NaCl) of compound **820**.

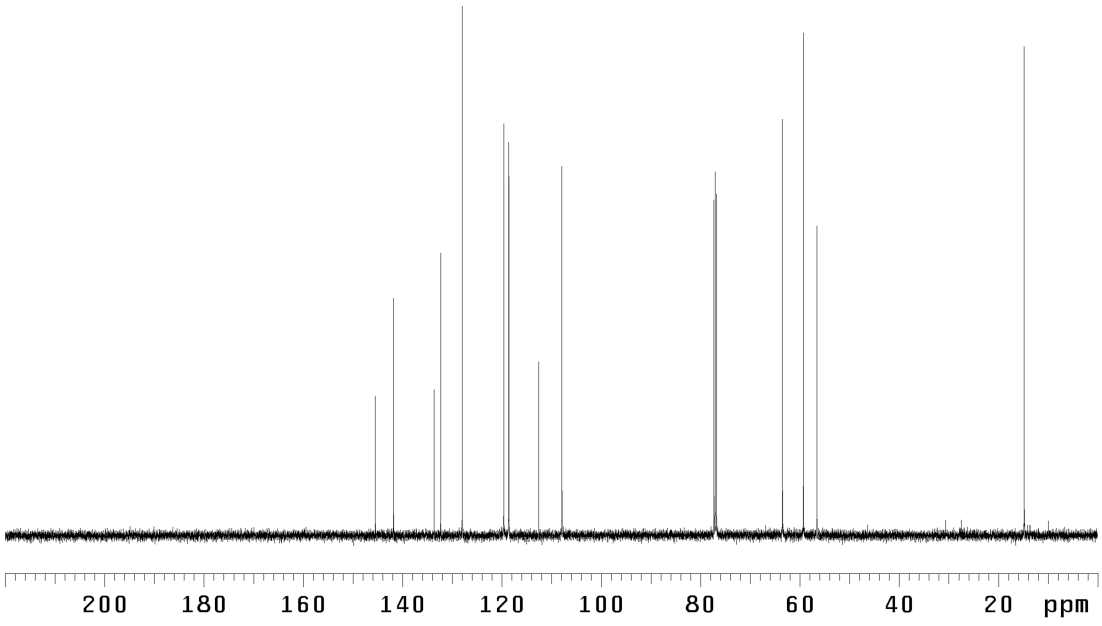


Figure A3.28.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **820**.

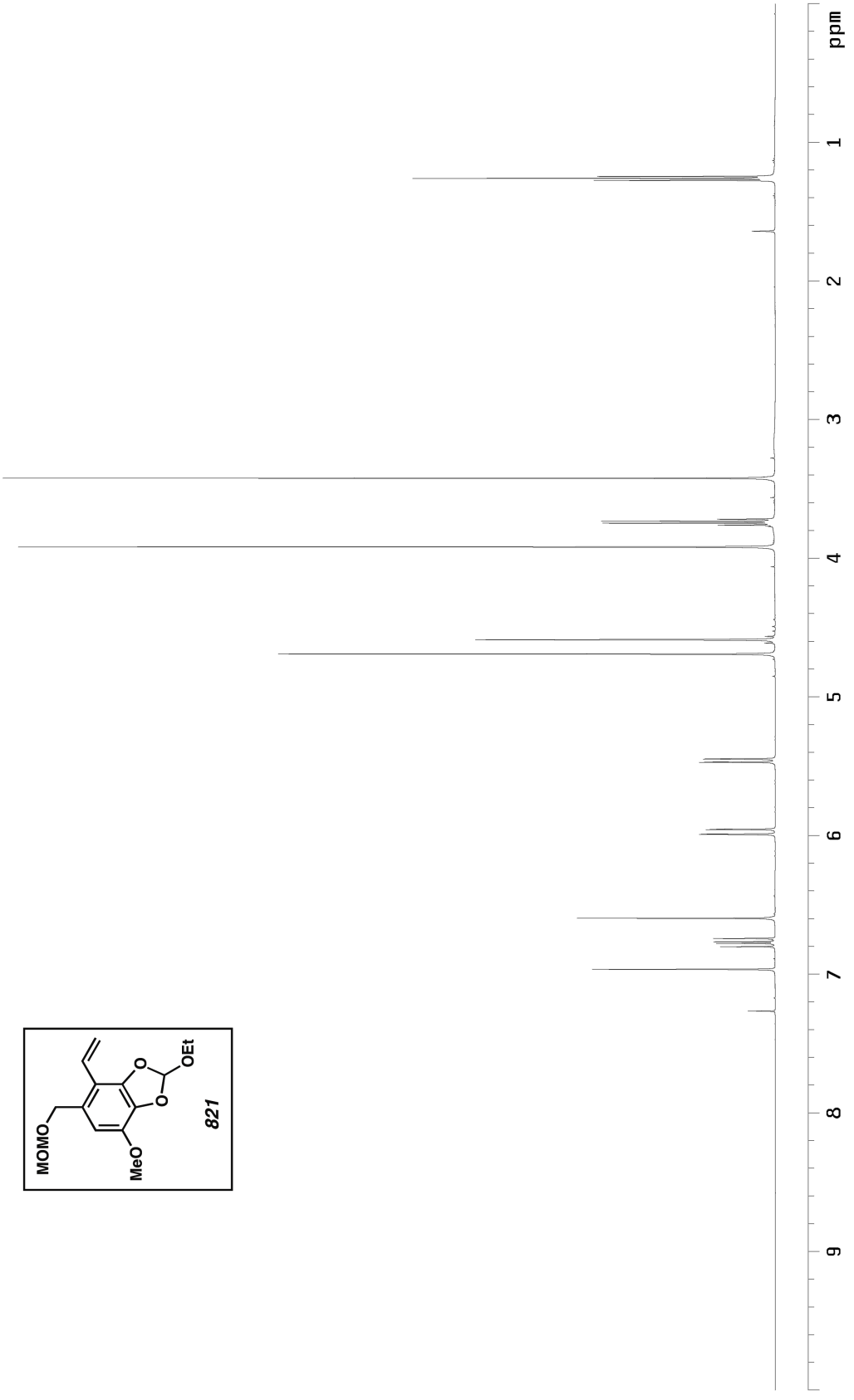


Figure A3.29.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **821**.

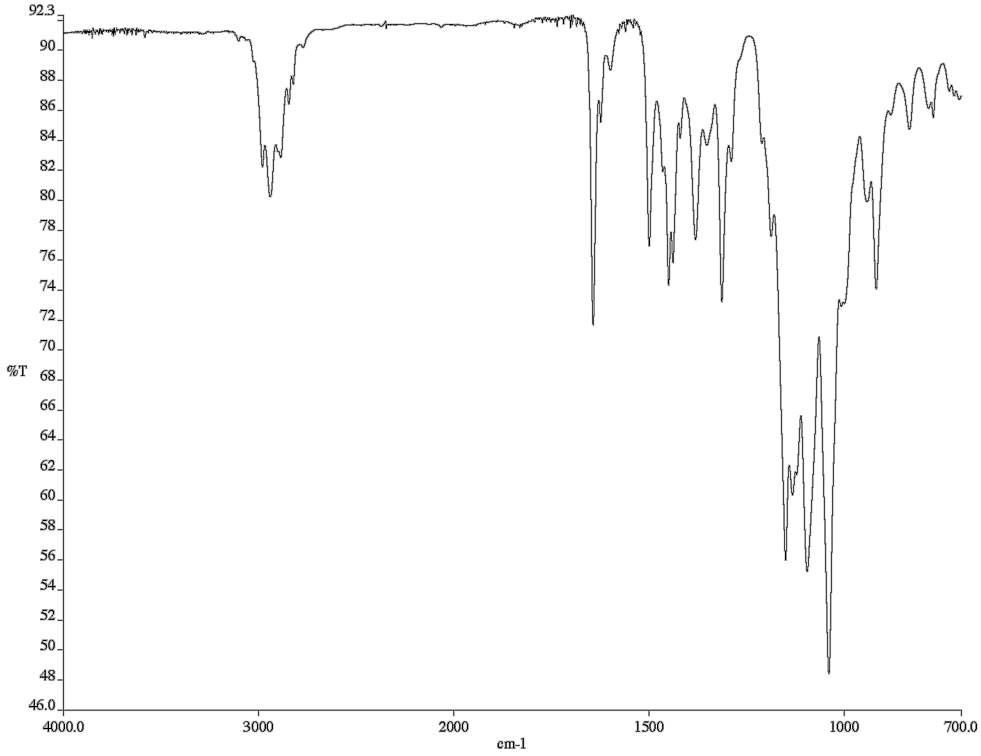


Figure A3.29.2 Infrared spectrum (thin film/NaCl) of compound **821**.

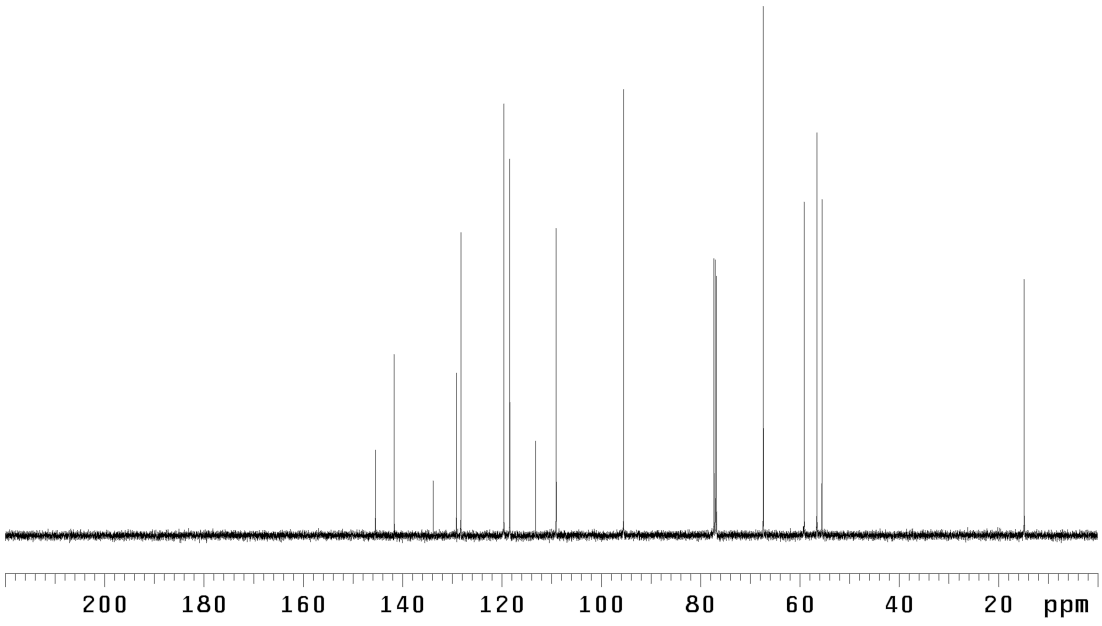


Figure A3.29.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **821**.

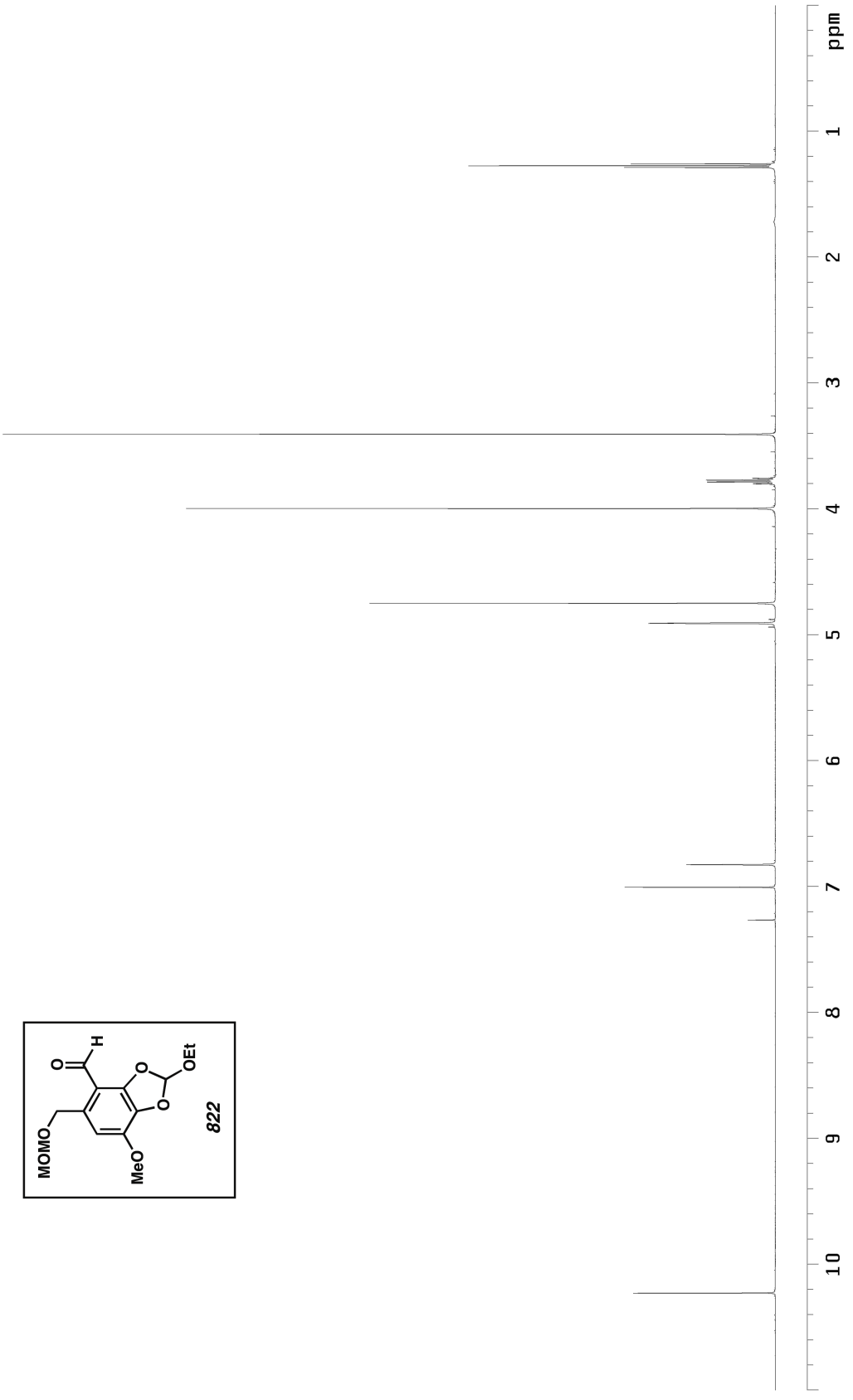


Figure A3.30.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **822**.

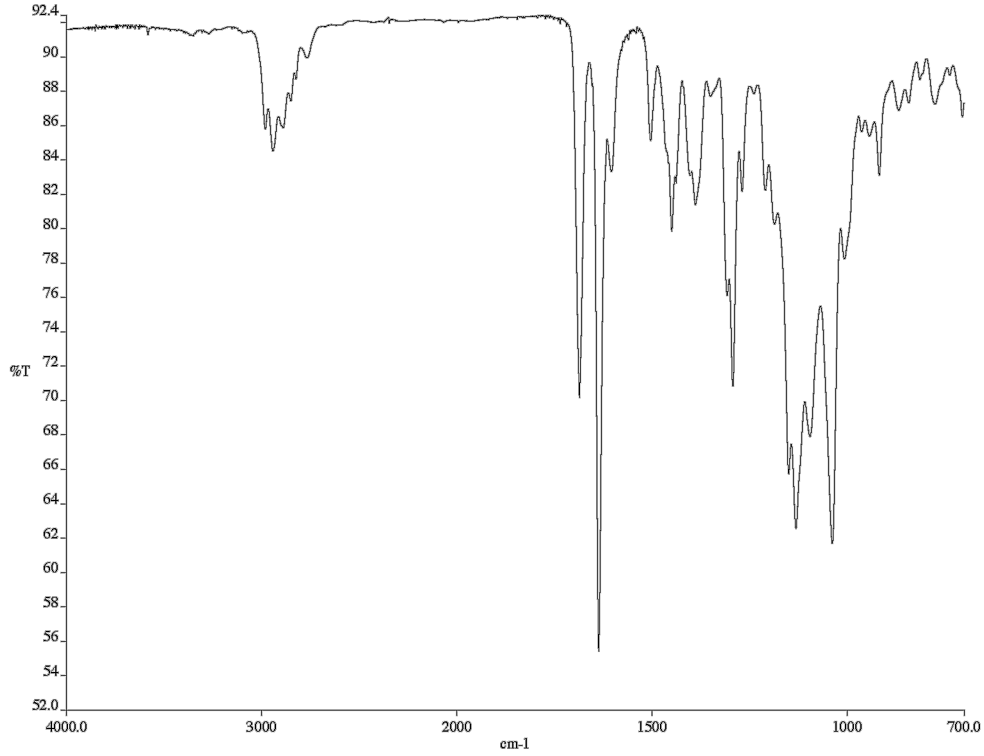


Figure A3.30.2 Infrared spectrum (thin film/NaCl) of compound **822**.

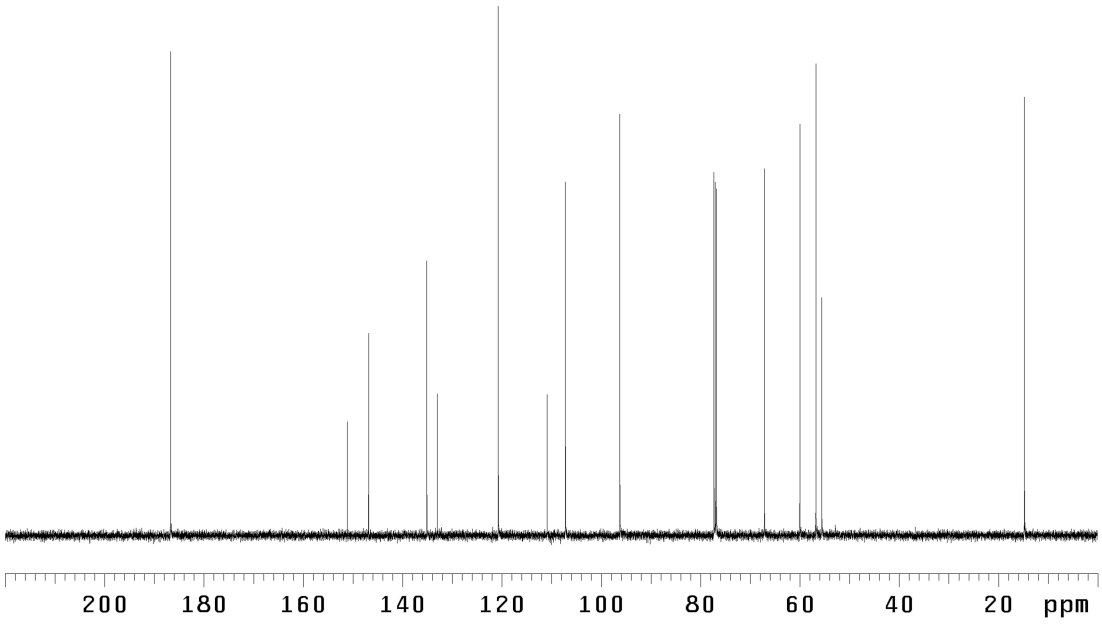


Figure A3.30.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **822**.

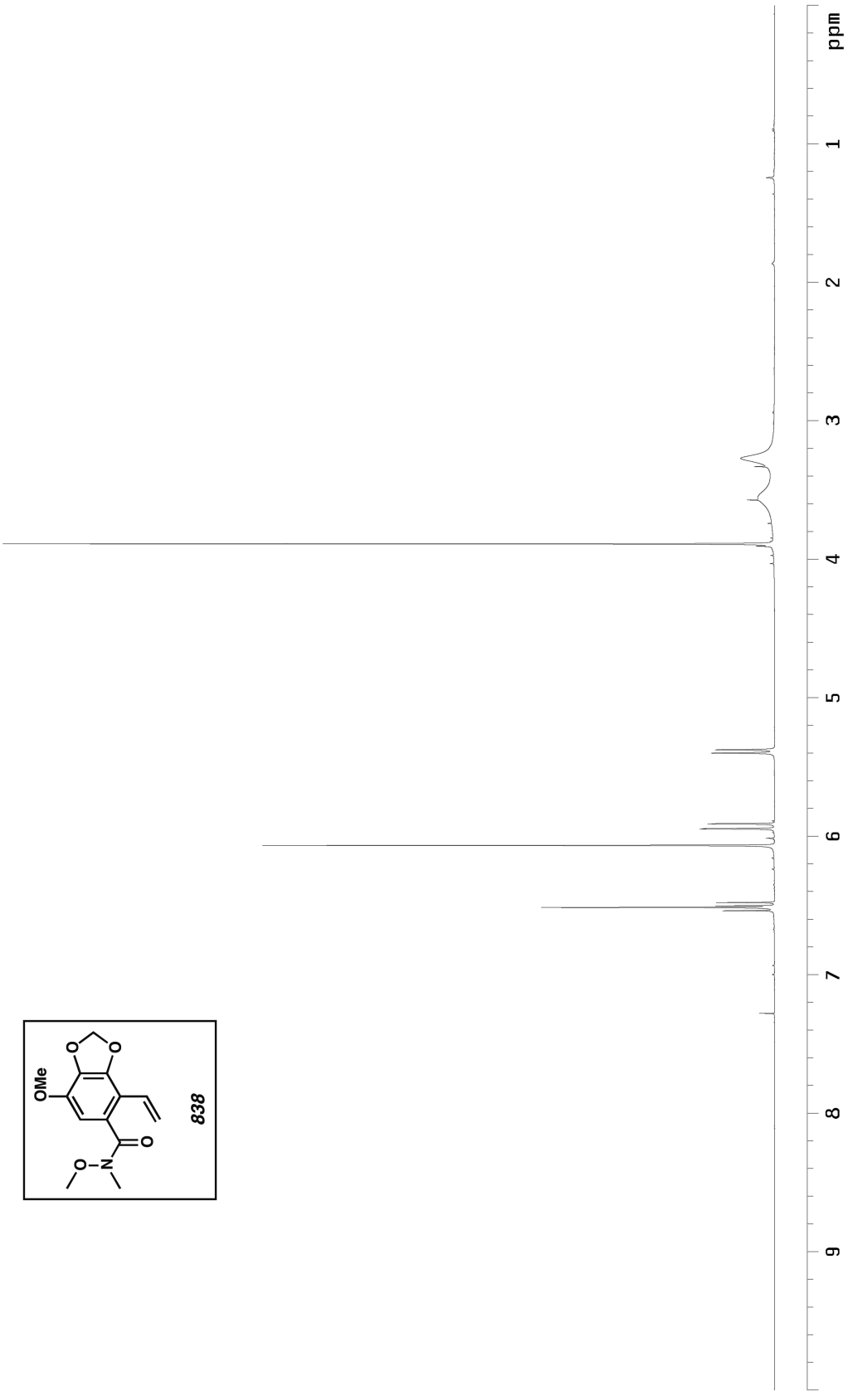


Figure A3.31.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **838**.

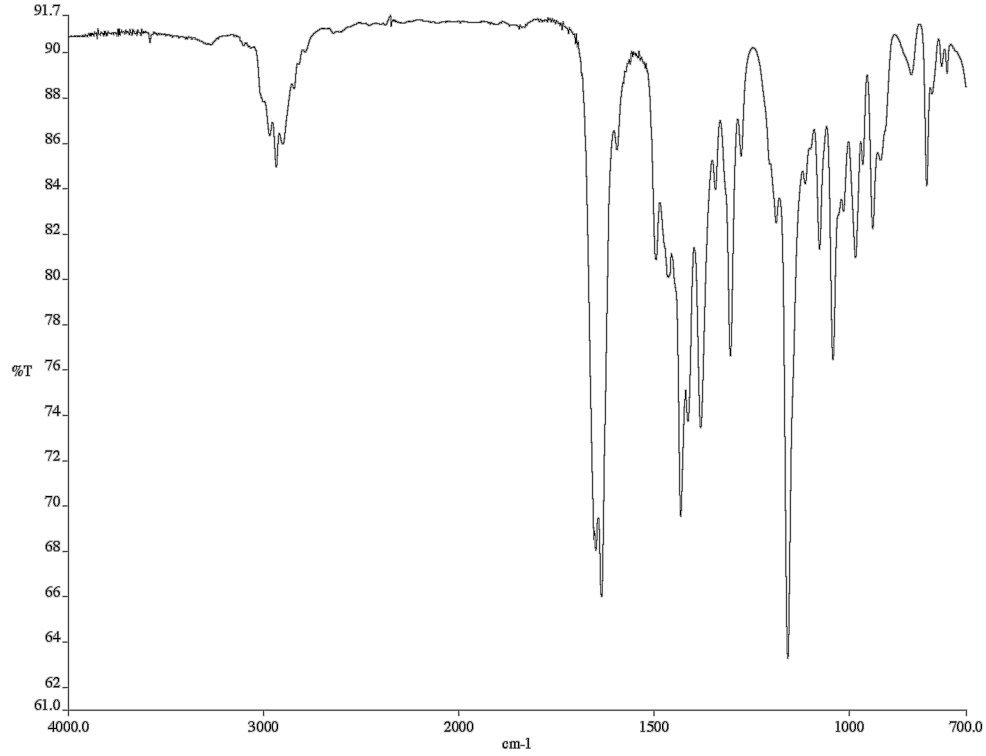


Figure A3.31.2 Infrared spectrum (thin film/NaCl) of compound **838**.

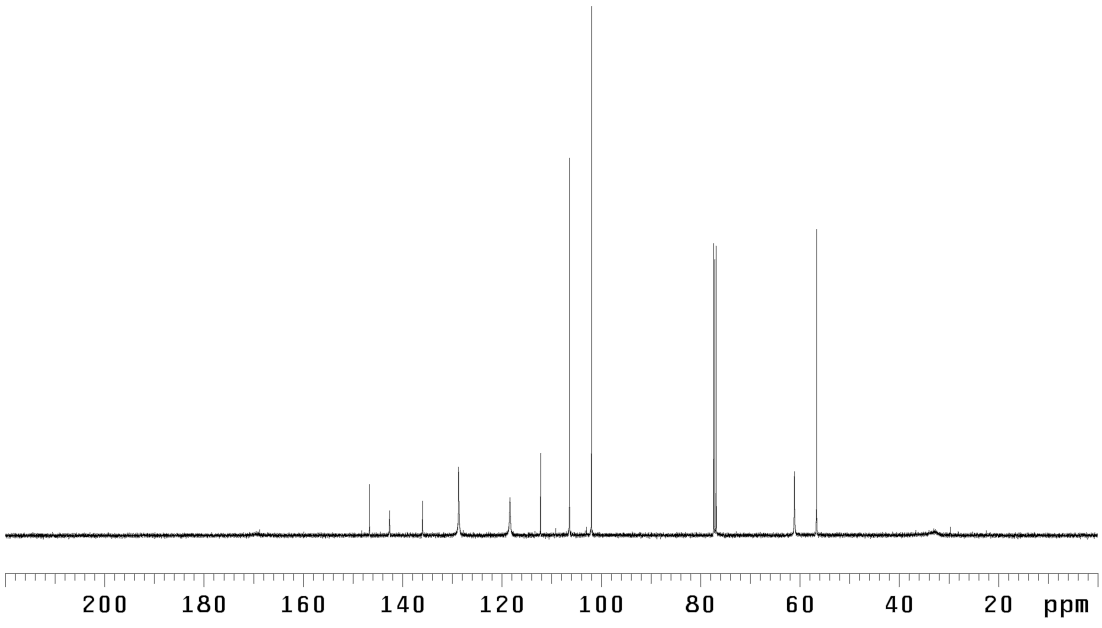


Figure A3.31.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **838**.

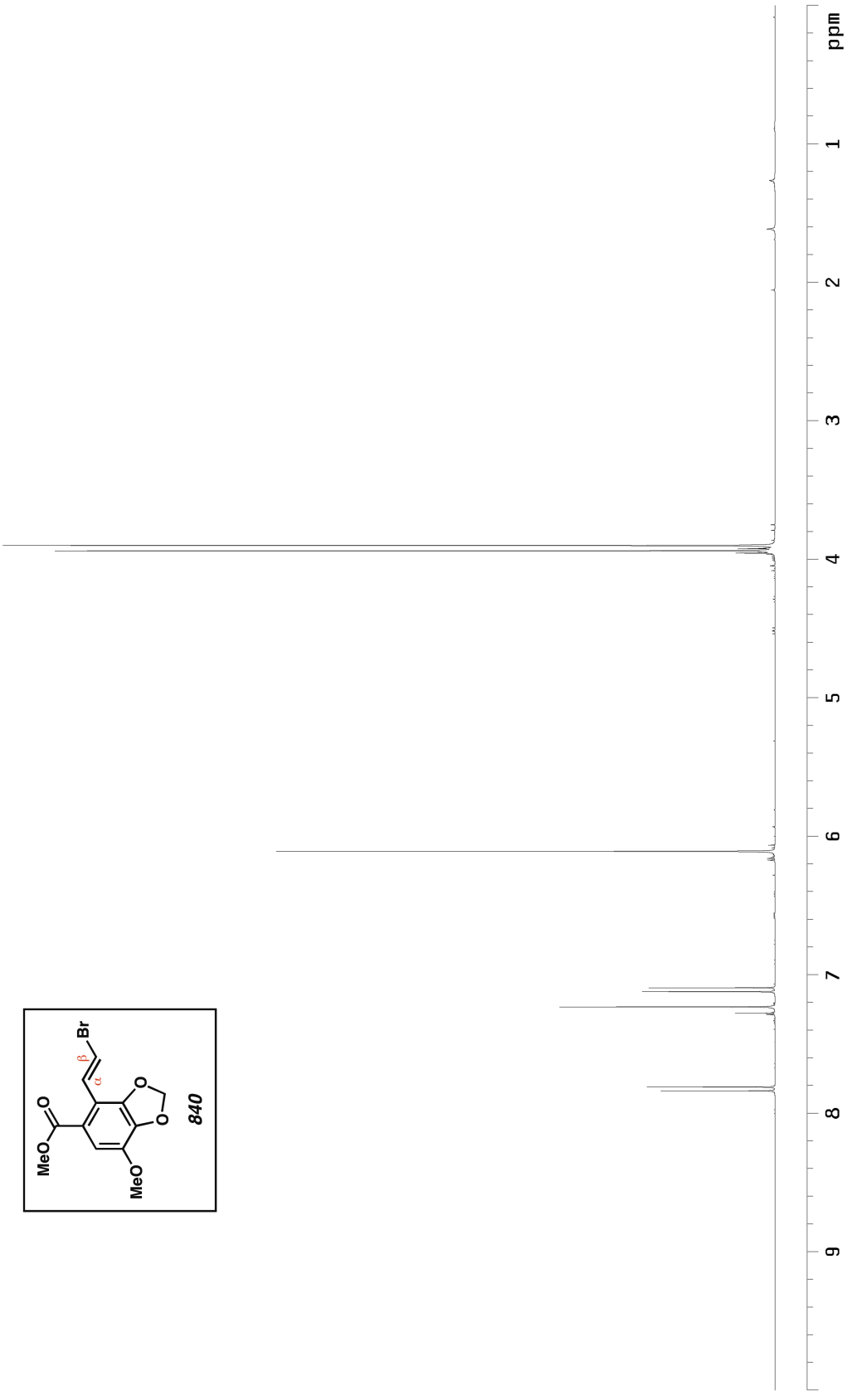


Figure A3.32.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **840**.

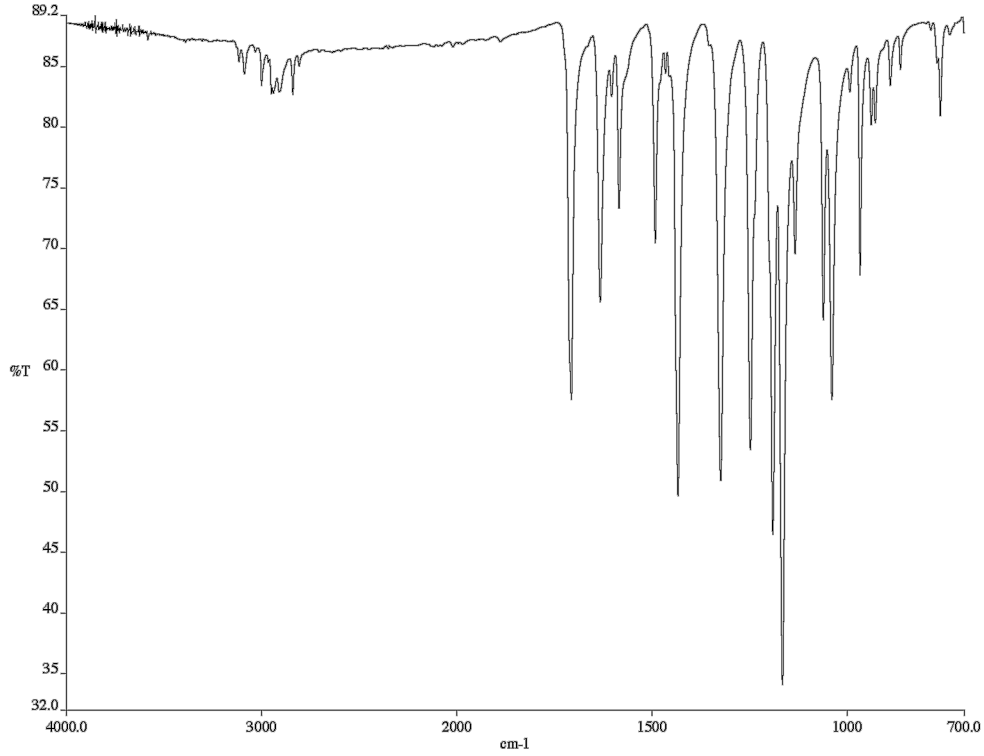


Figure A3.32.2 Infrared spectrum (thin film/NaCl) of compound **840**.

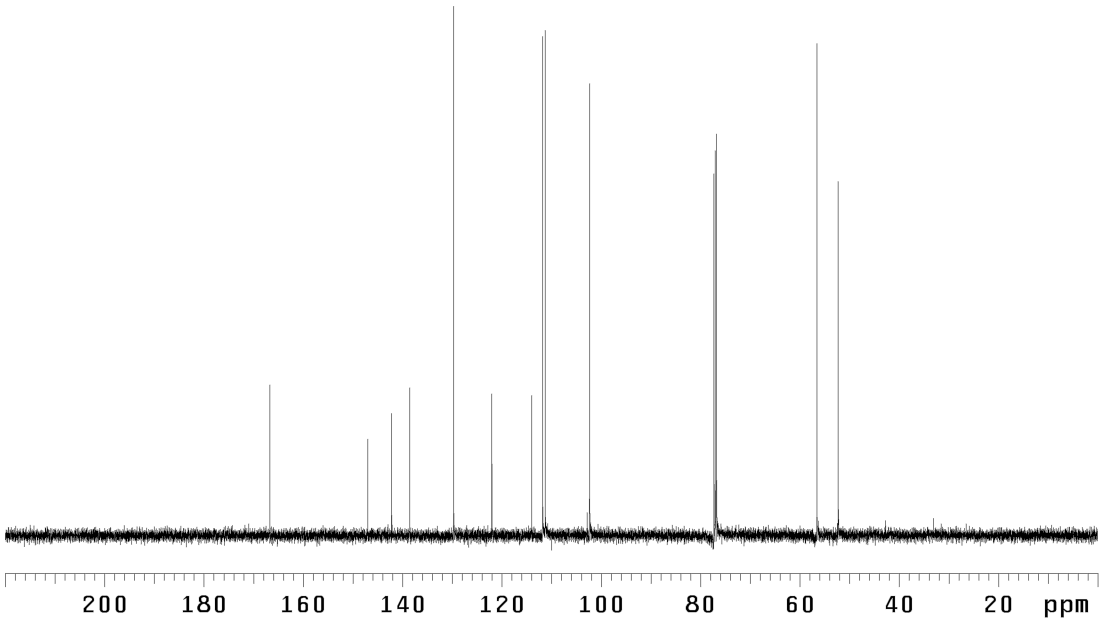


Figure A3.32.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **840**.

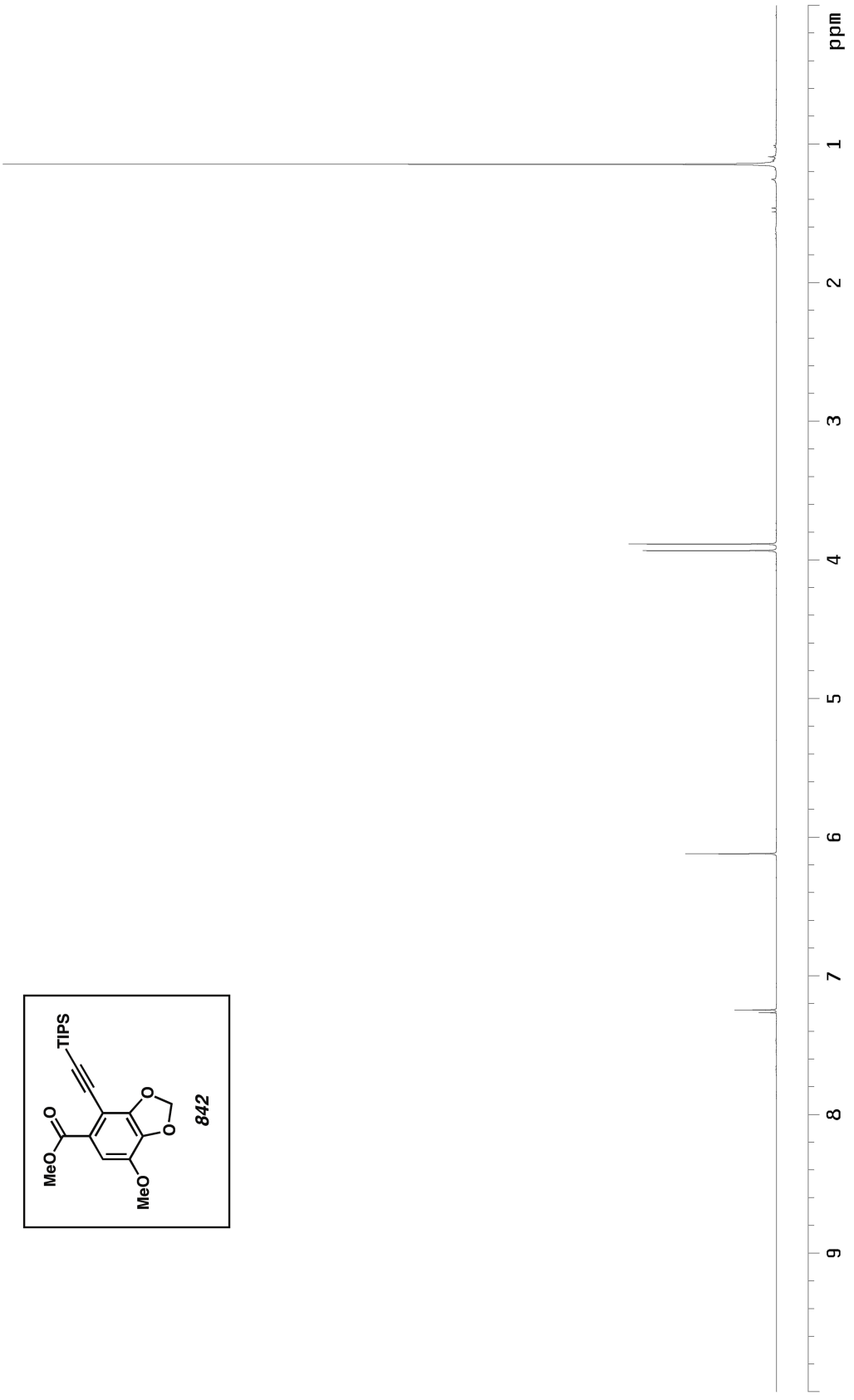


Figure A3.33.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **842**.

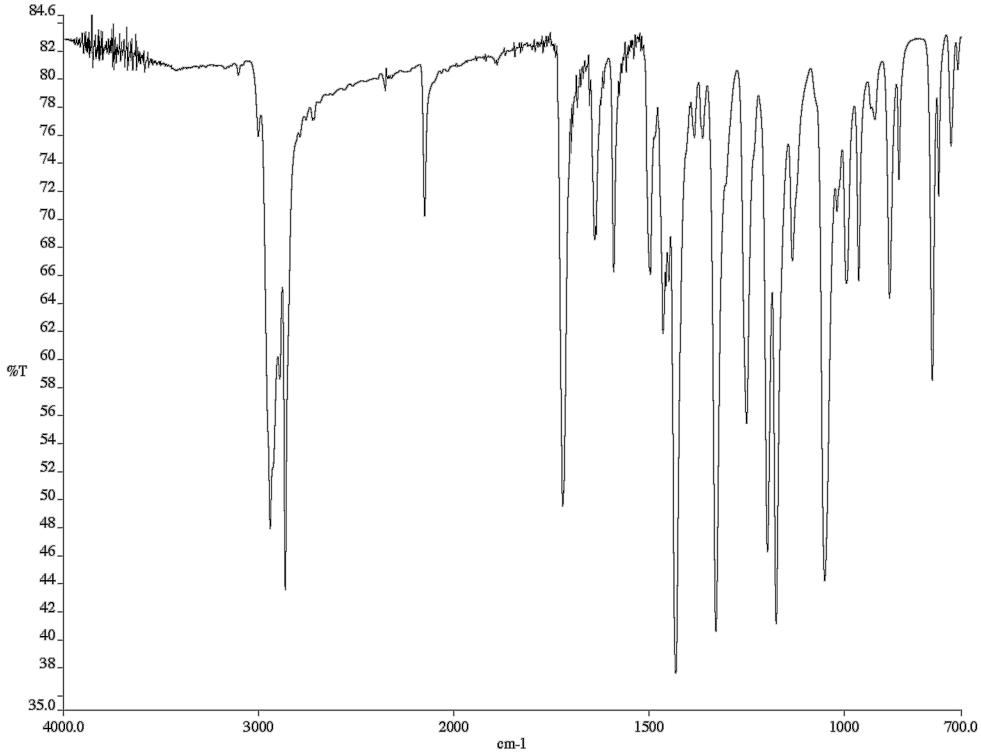


Figure A3.33.2 Infrared spectrum (thin film/NaCl) of compound **842**.

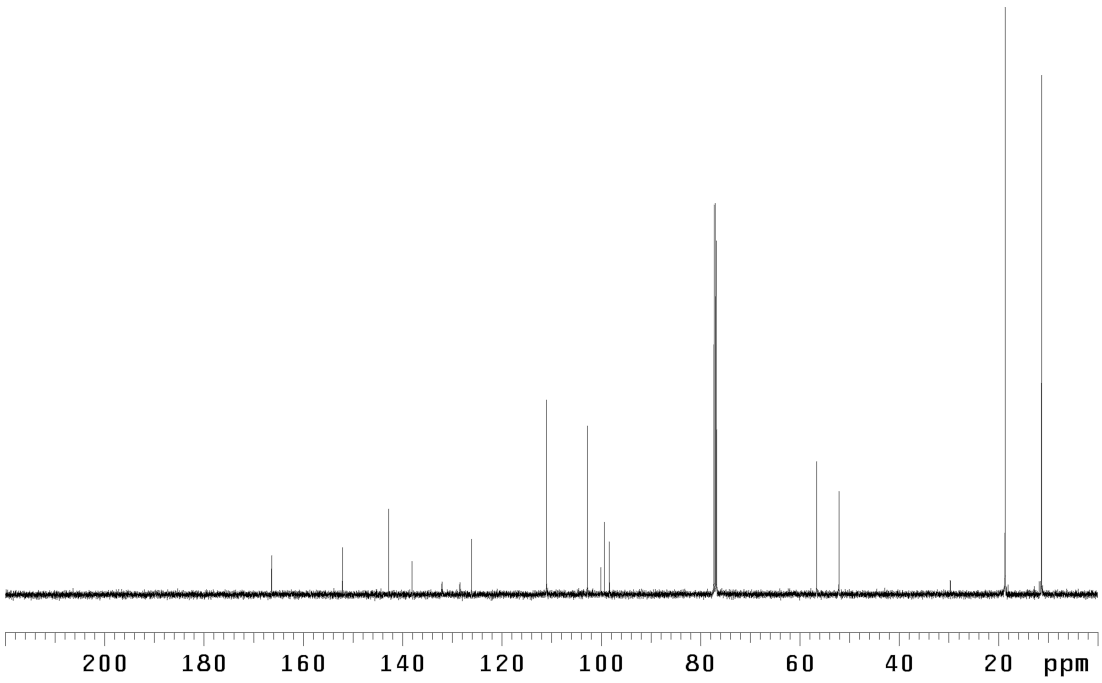


Figure A3.33.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **842**.

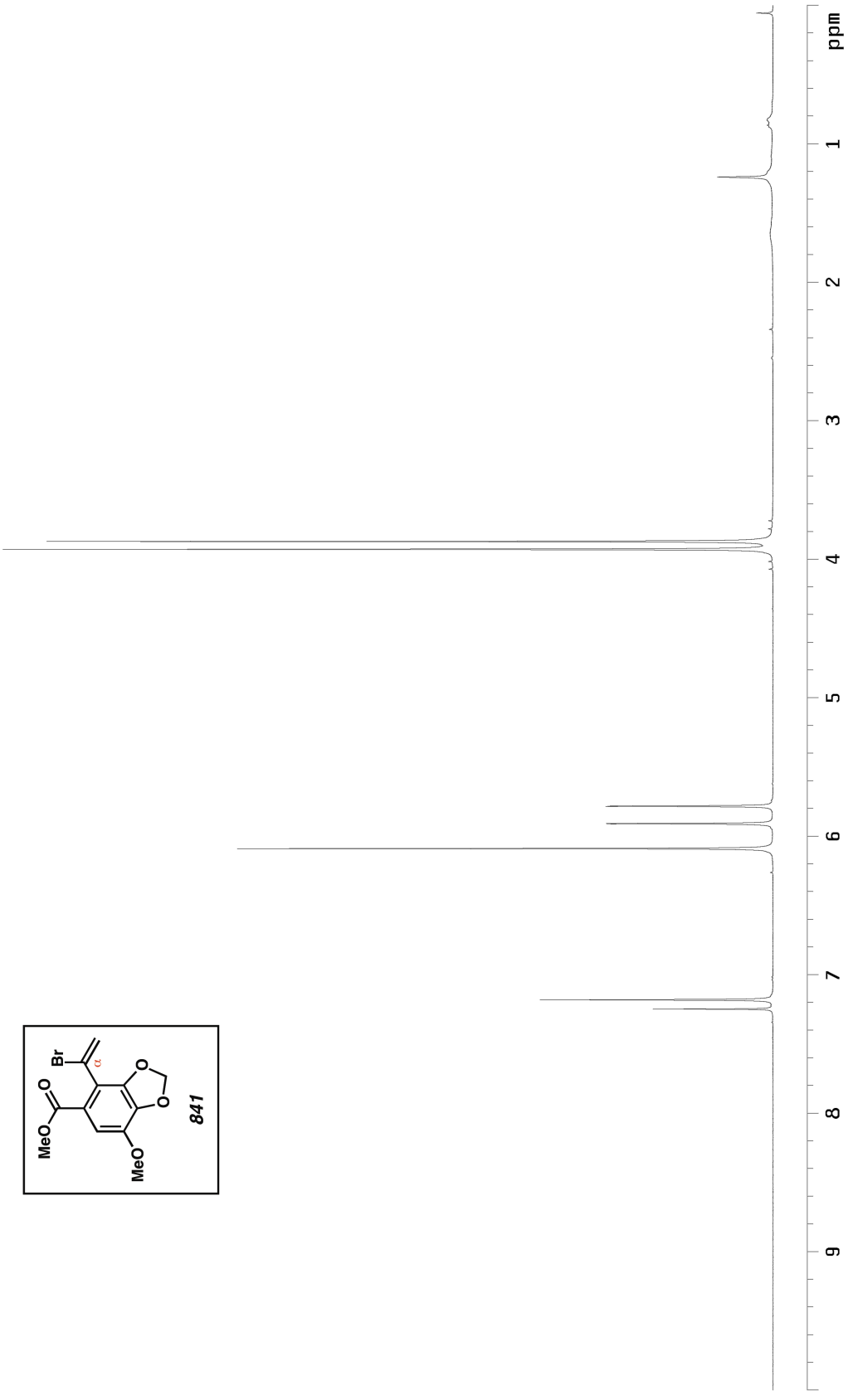


Figure A3.34.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **841**.

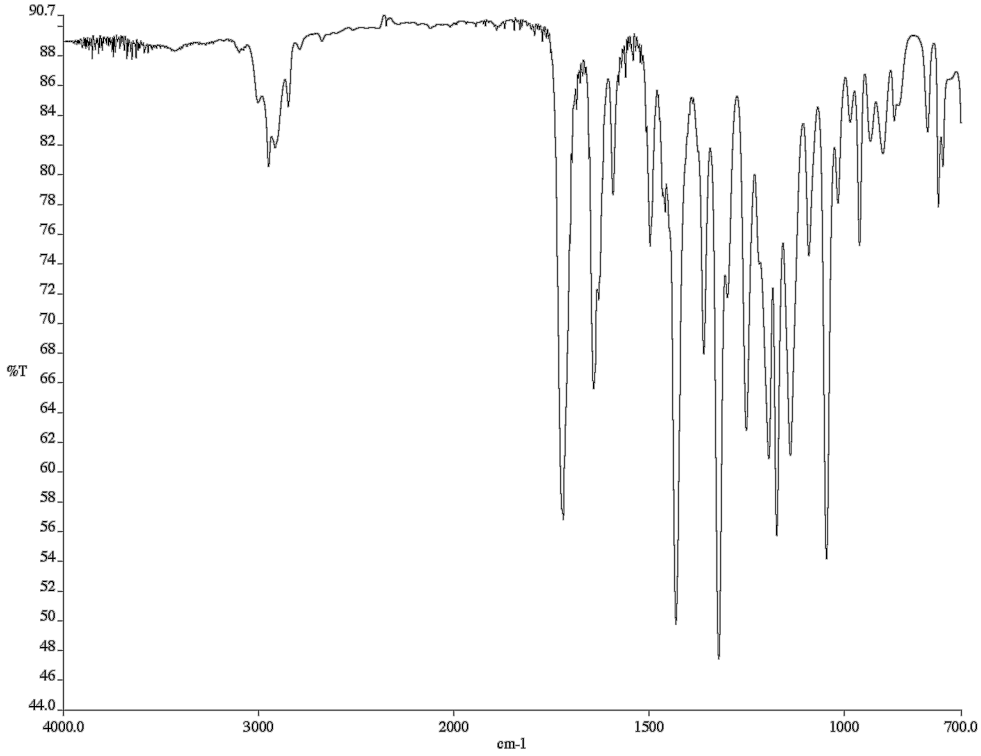


Figure A3.34.2 Infrared spectrum (thin film/NaCl) of compound **841**.

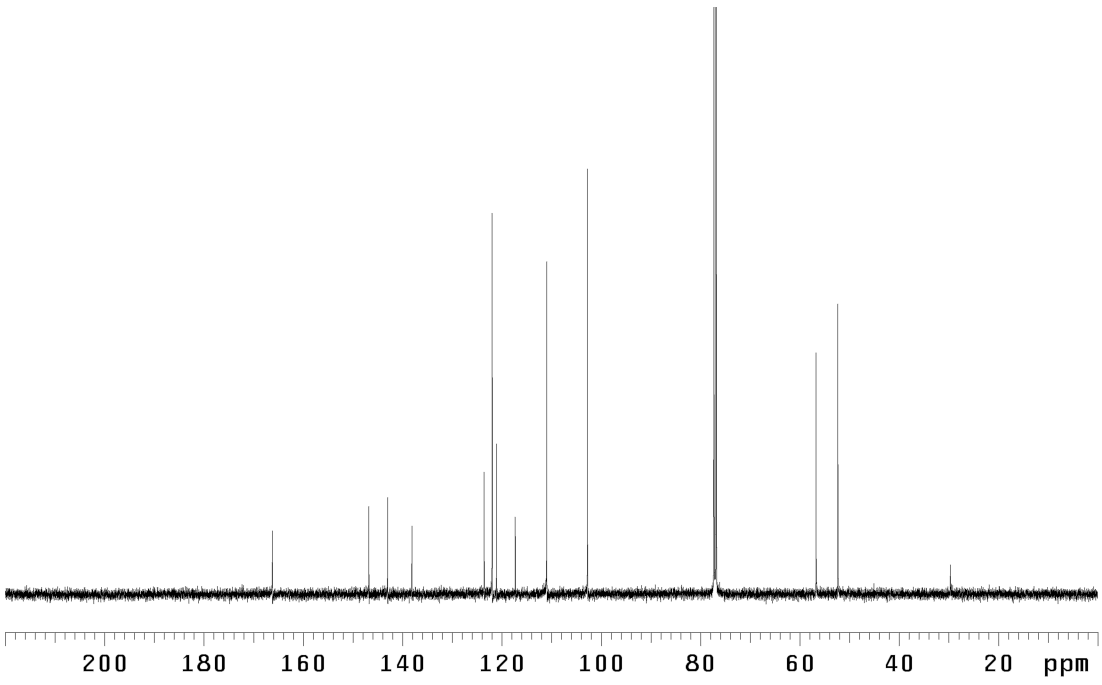


Figure A3.34.3 ^{13}C NMR (125 MHz, CDCl3) of compound **841**.

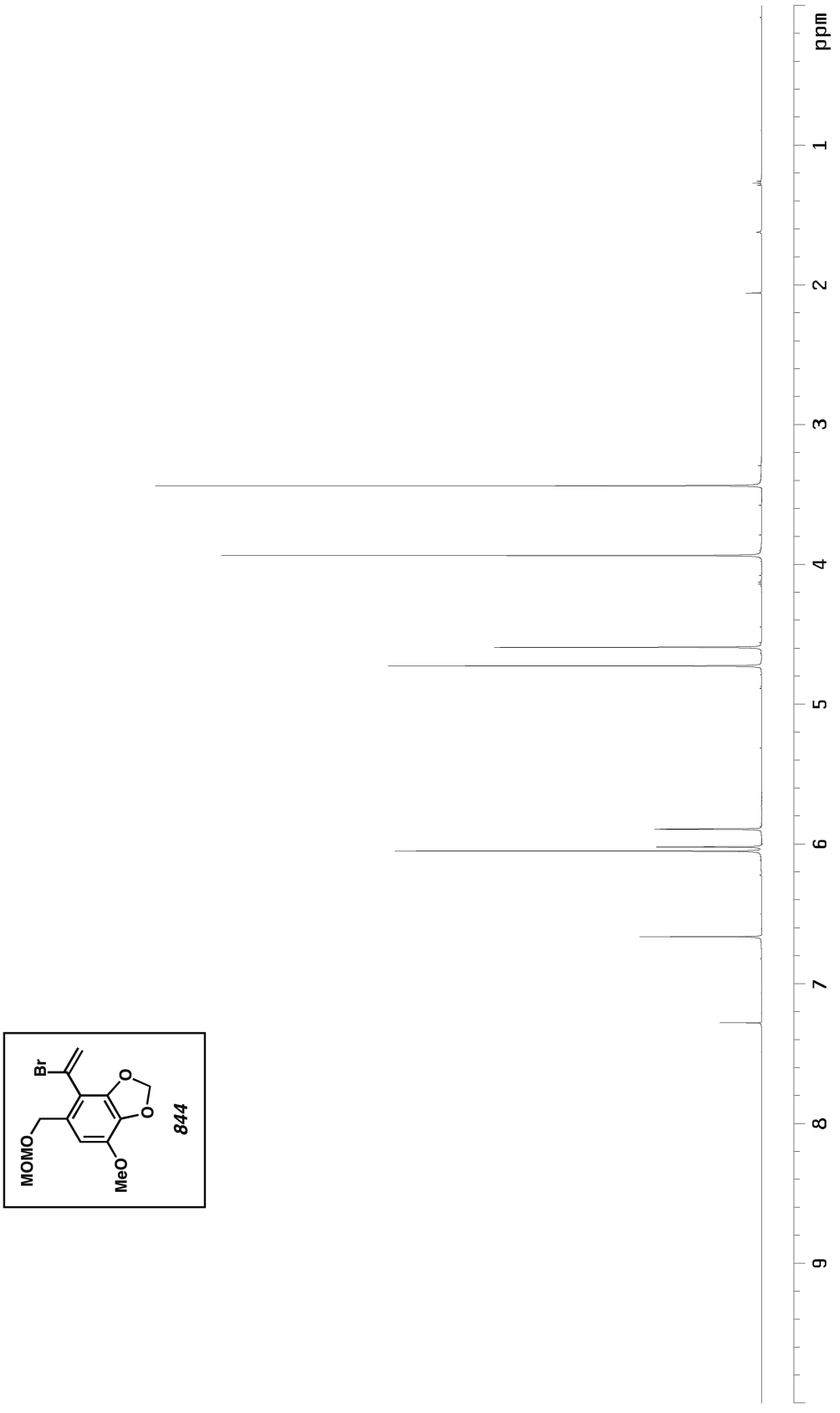


Figure A3.35.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **844**.

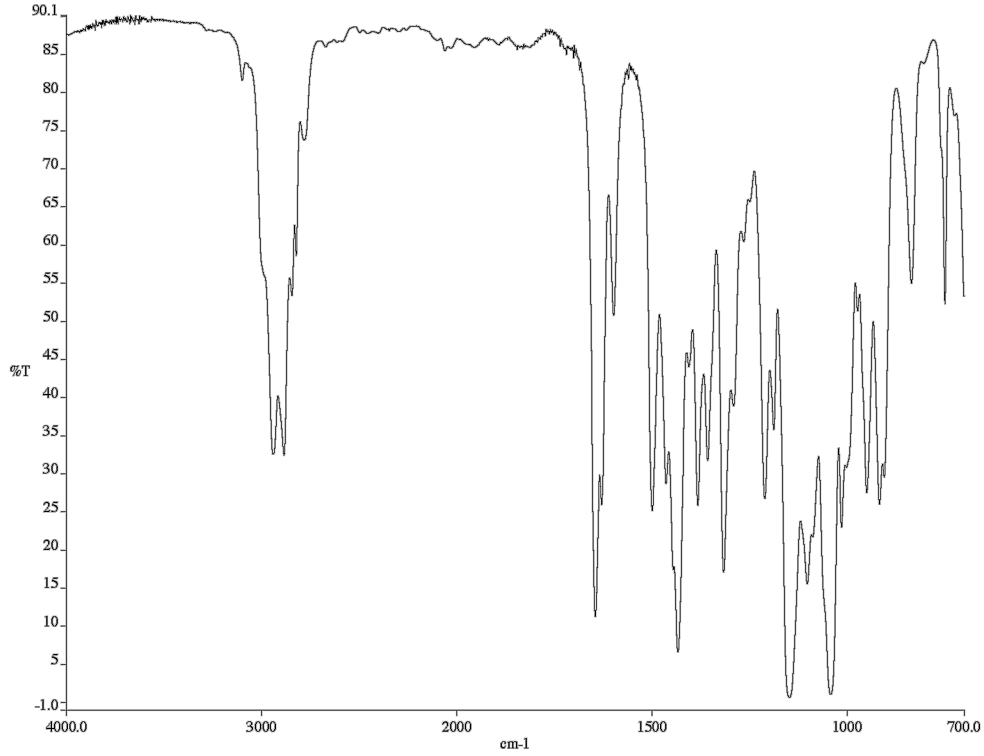


Figure A3.35.2 Infrared spectrum (thin film/NaCl) of compound **844**.

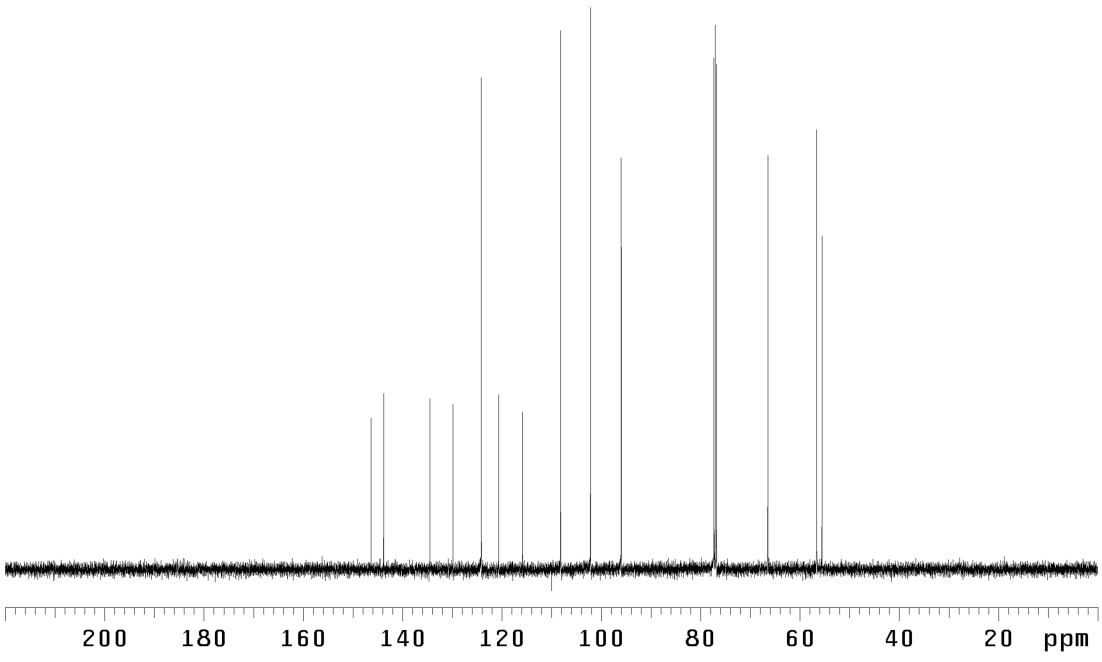


Figure A3.35.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **844**.

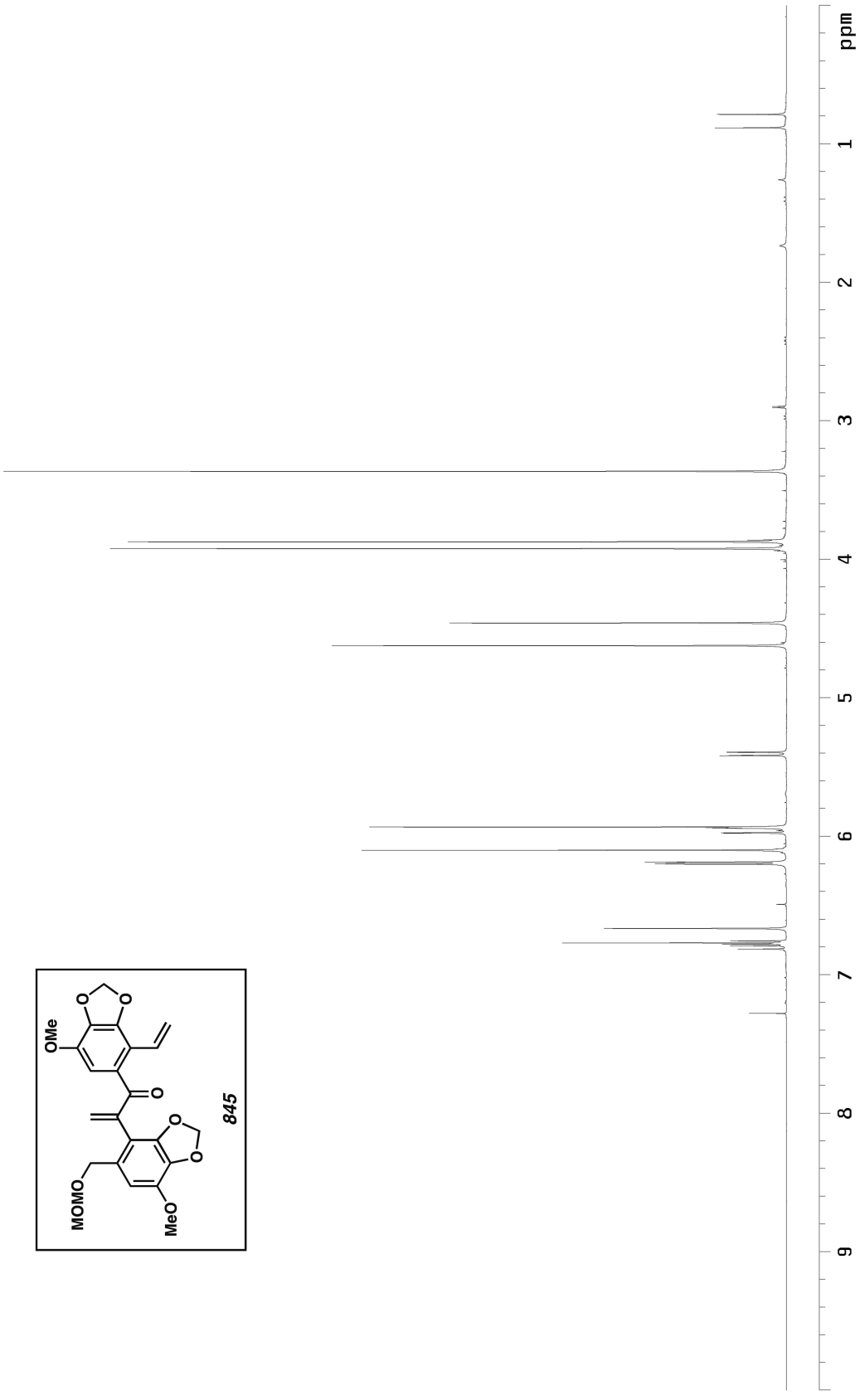


Figure A3.36.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **845**.

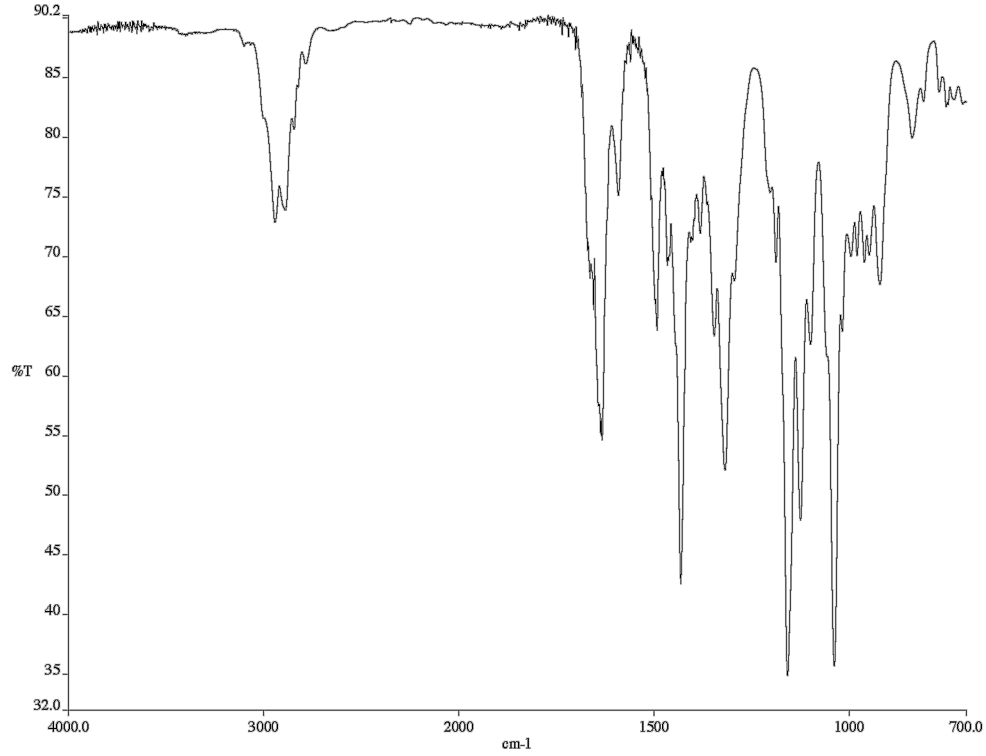


Figure A3.36.2 Infrared spectrum (thin film/NaCl) of compound **845**.

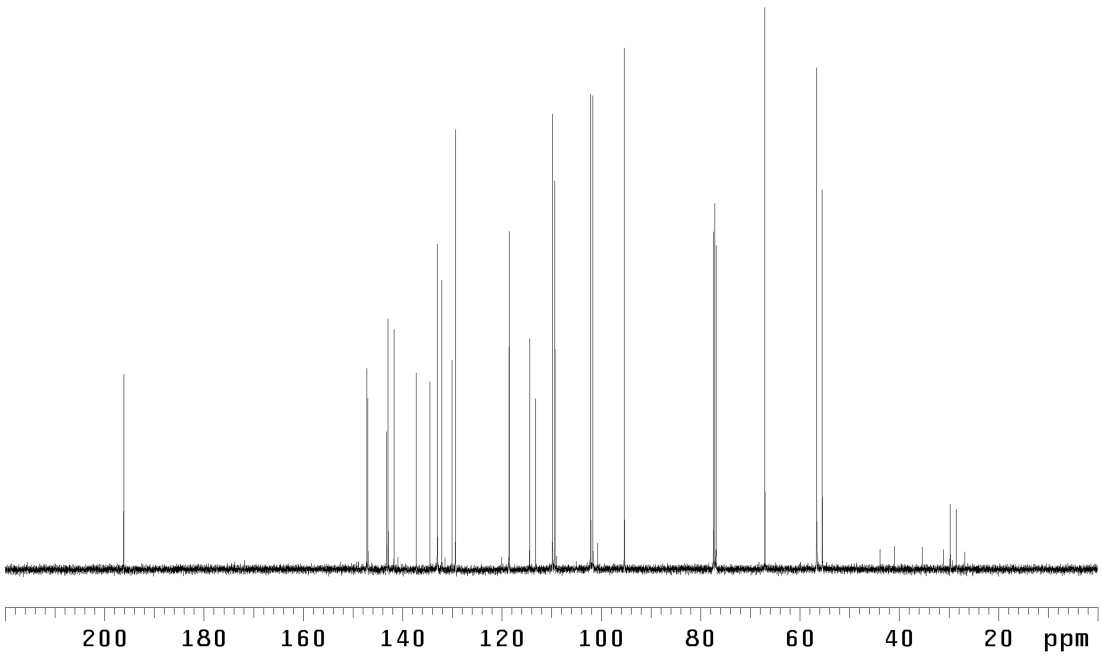


Figure A3.36.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **845**.

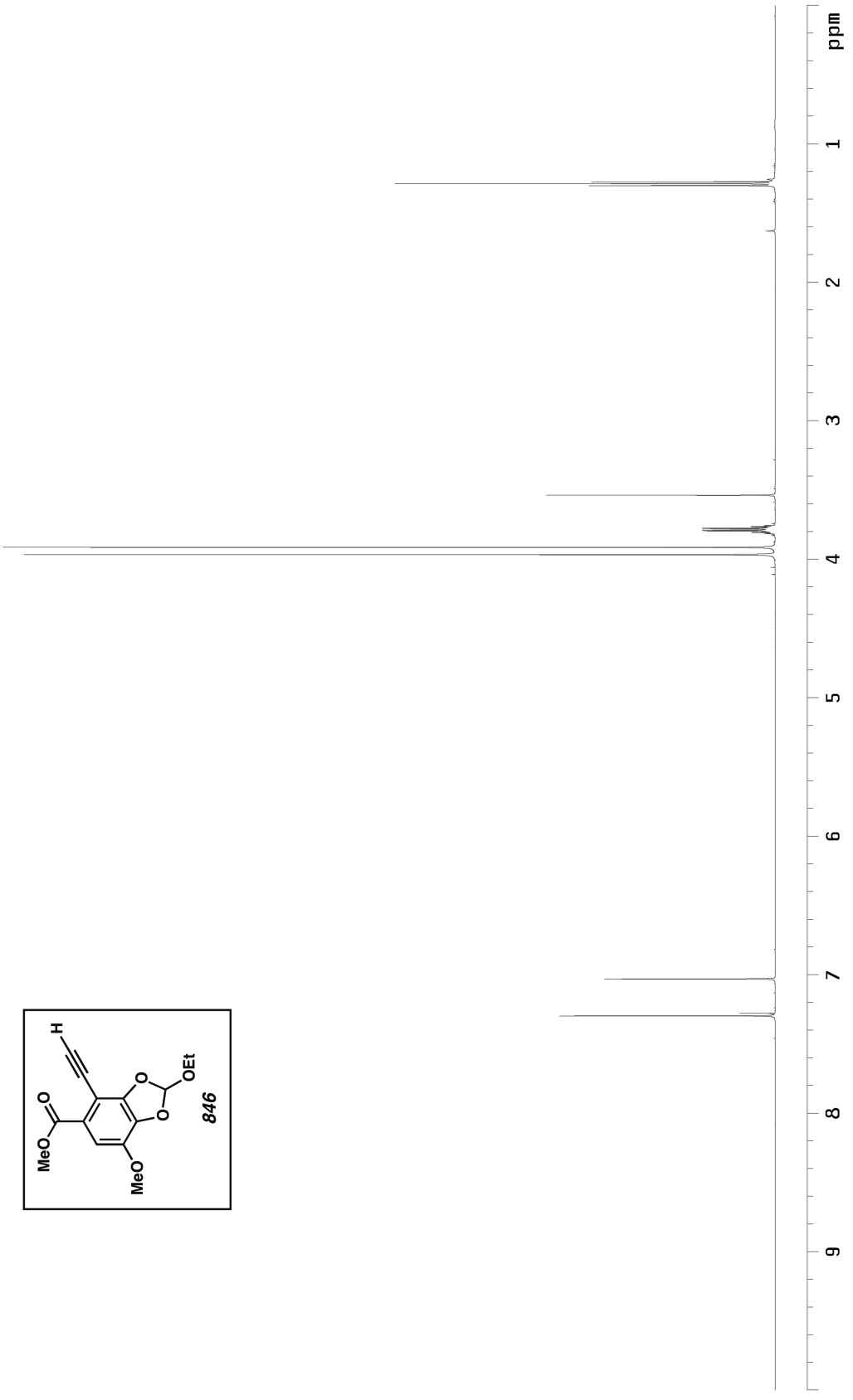


Figure A3.37.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **846**.

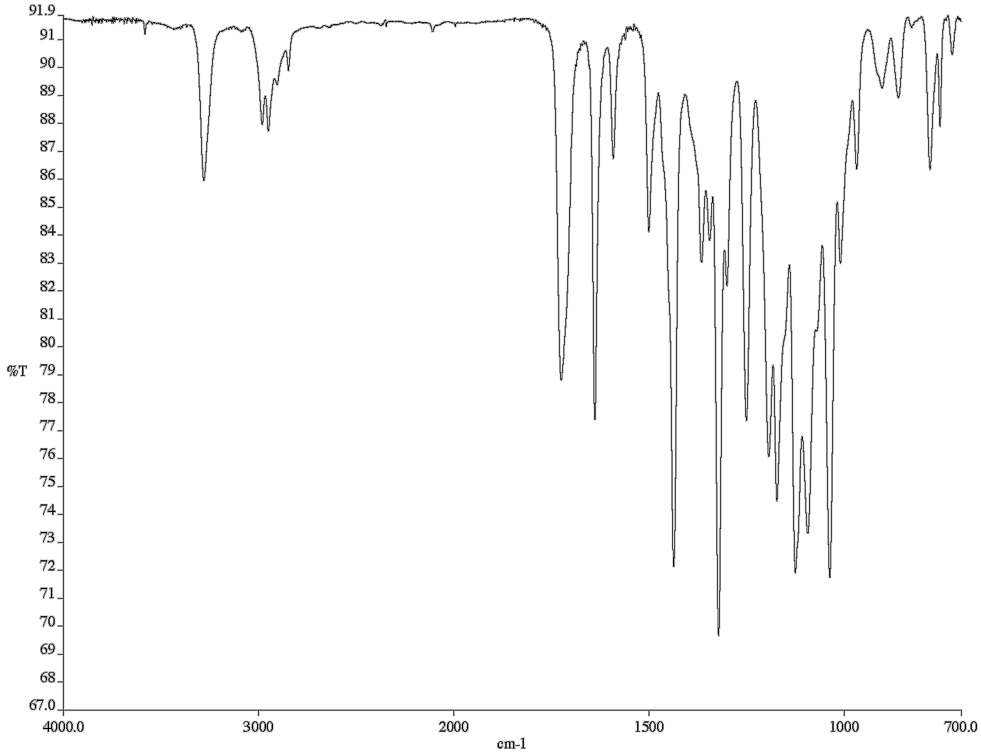


Figure A3.37.2 Infrared spectrum (thin film/NaCl) of compound **846**.

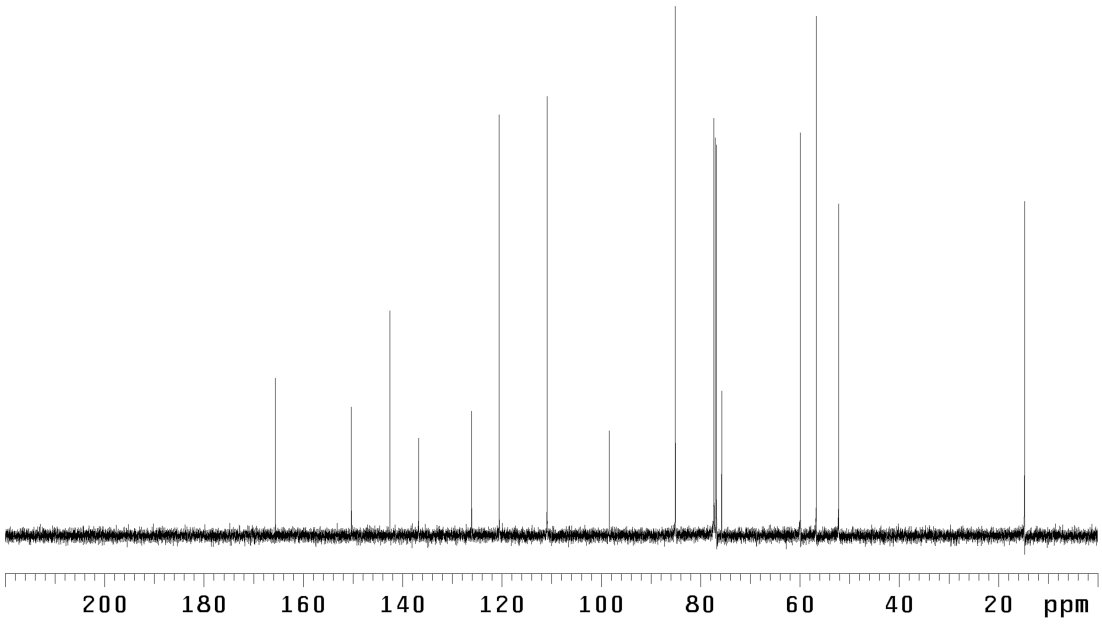


Figure A3.37.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **846**.

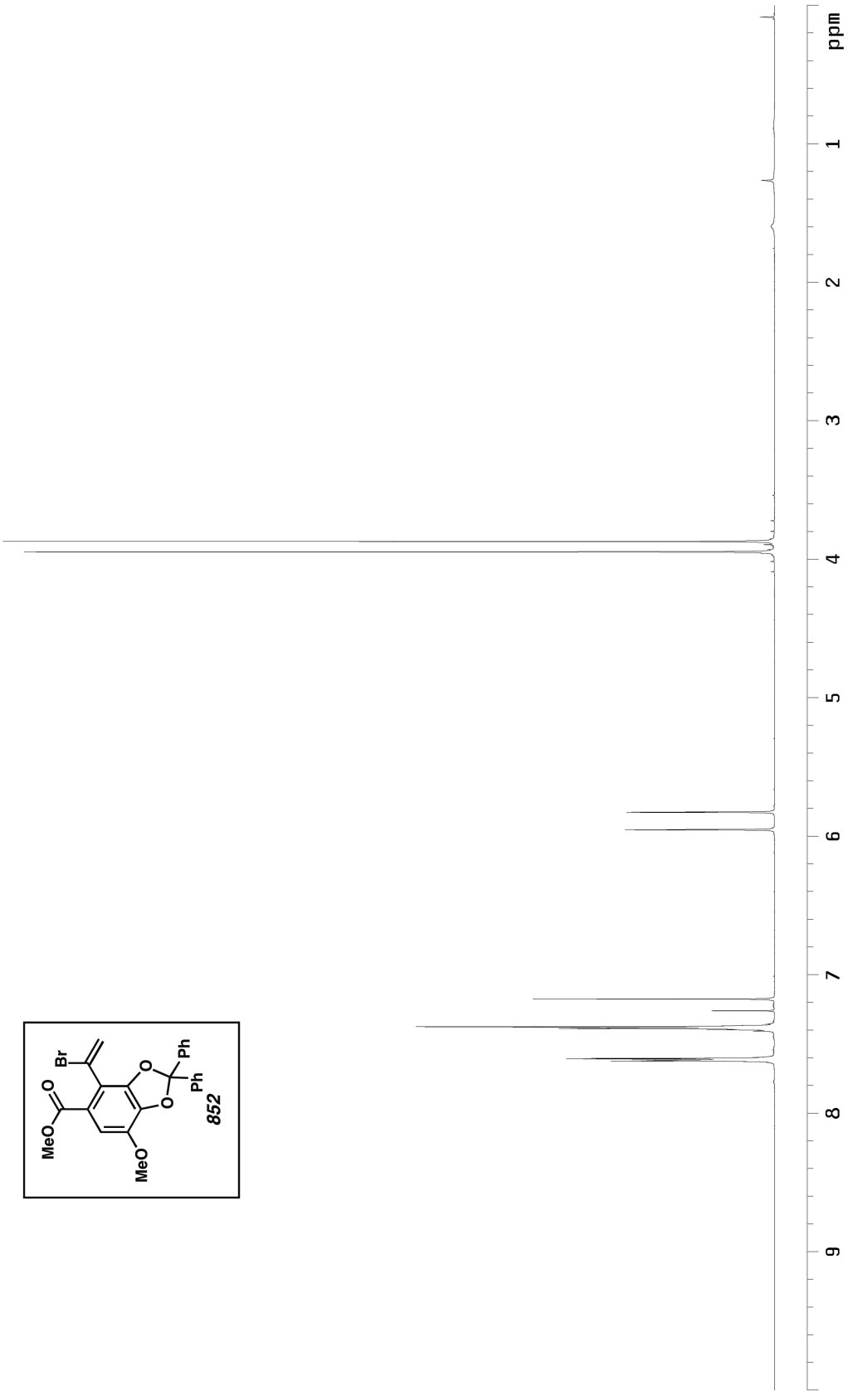


Figure A3.38.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **852**.

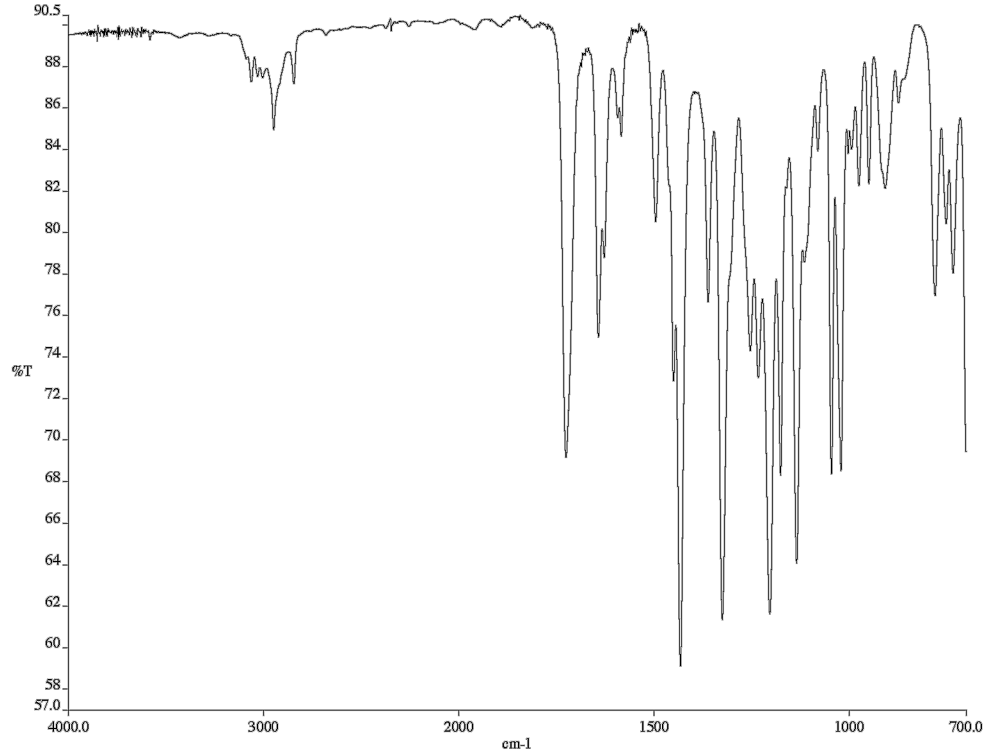


Figure A3.38.2 Infrared spectrum (thin film/NaCl) of compound **852**.

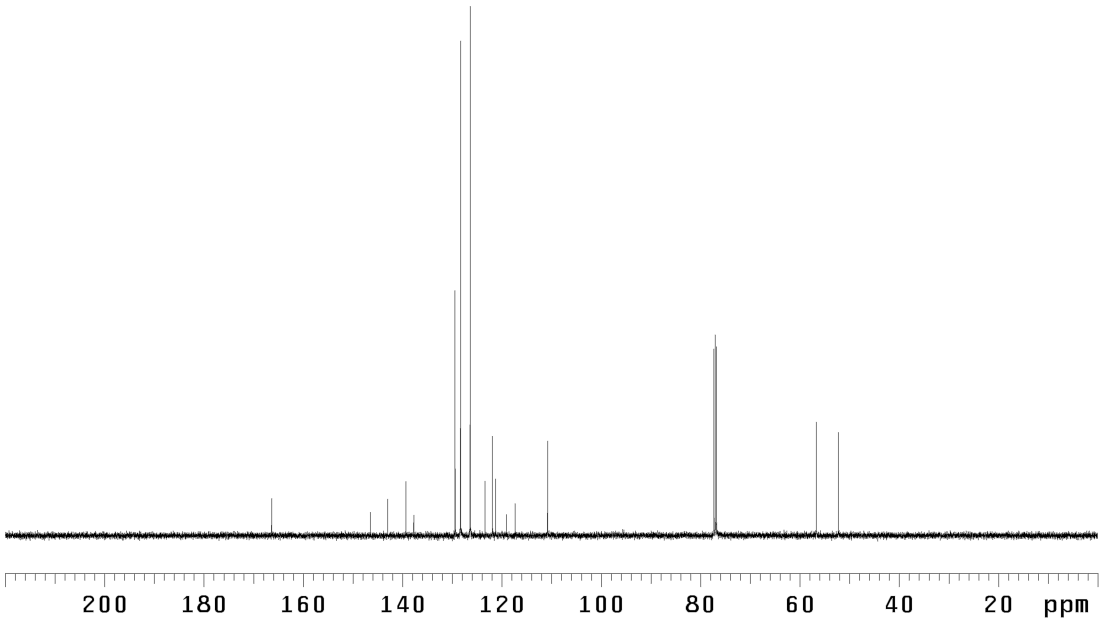


Figure A3.38.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **852**.

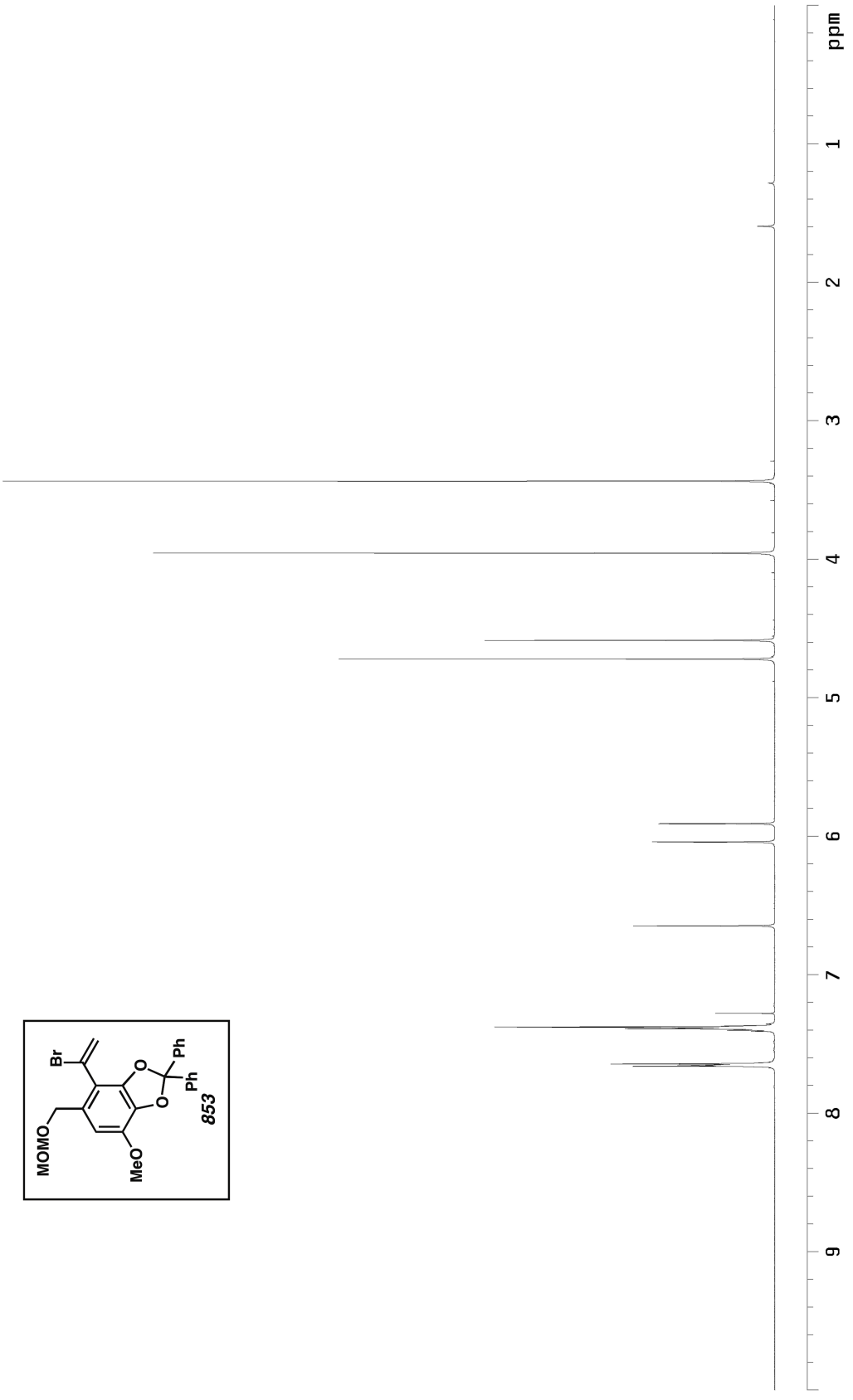


Figure A3.39.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **853**.

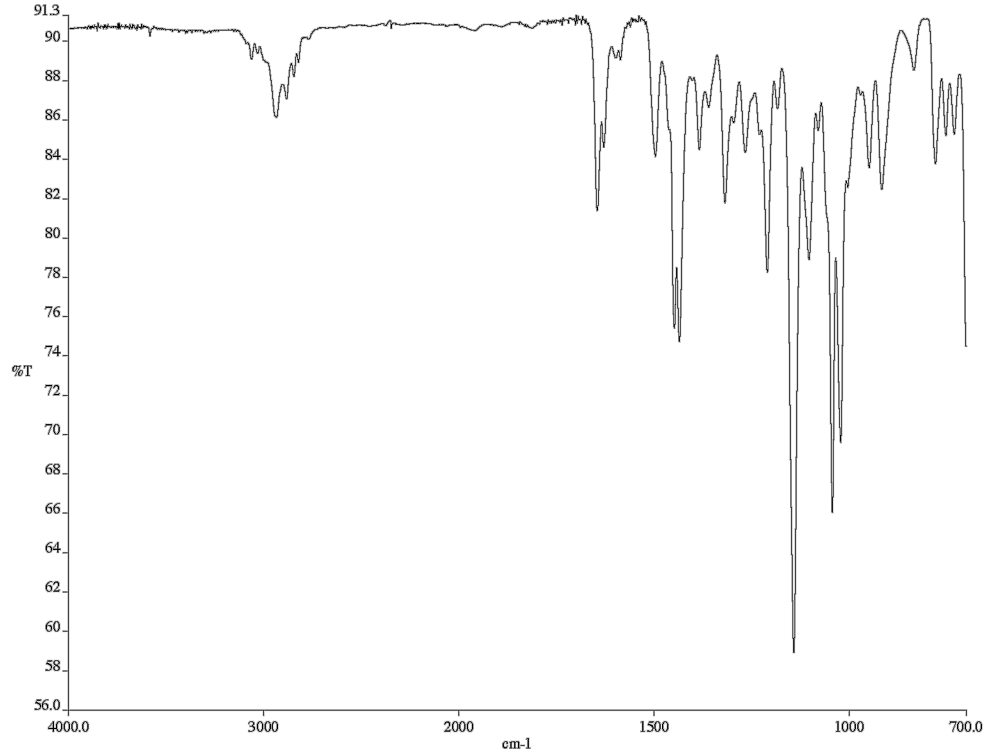


Figure A3.39.2 Infrared spectrum (thin film/NaCl) of compound **853**.

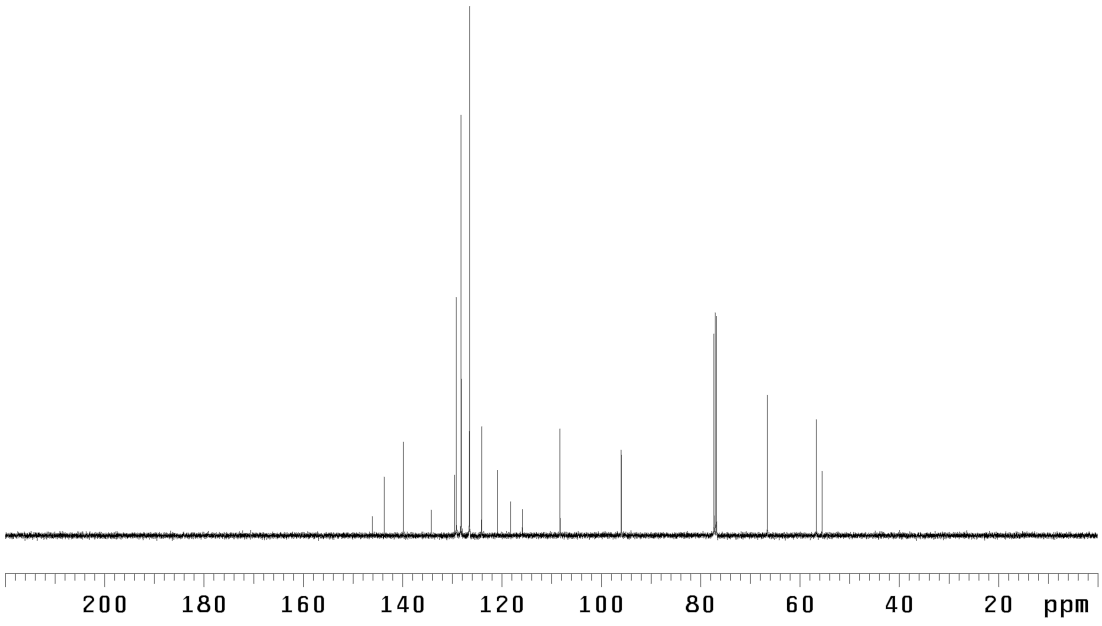


Figure A3.39.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **853**.

Chapter 4

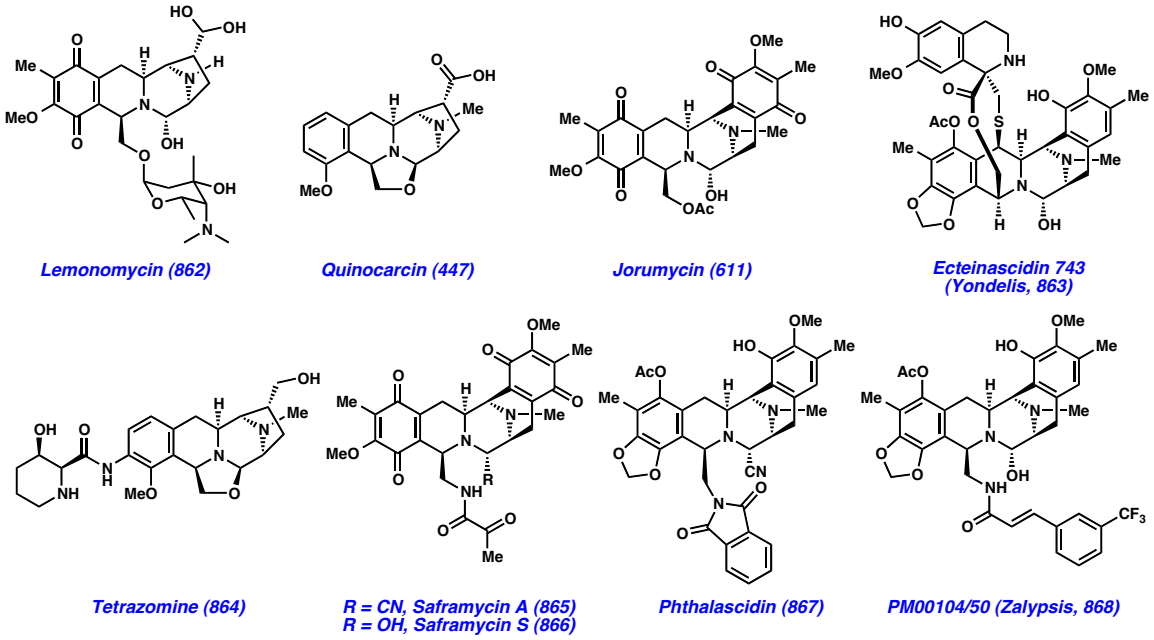
Progress Toward the Total Synthesis of Jorumycin

4.1 INTRODUCTION

In recent years, the tetrahydroisoquinoline (THIQ) alkaloids have garnered attention from both the chemical and biological communities for because of their complex molecular architectures, novel biochemical modes of action, and potent biological activity.[1] With over 60 naturally occurring members, the THIQ alkaloids display a remarkable amount of structural diversity that is reflected by their wide variety of anticancer activities (Figure 4.1). For example, saframycins A (**865**) and S (**866**) display nanomolar cytotoxicity toward L1210 leukemia cell lines (IC_{50} = 5.6, 5.3 nM, respectively).[2] Jorumycin (**611**) inhibits the growth of A549 human lung carcinoma and HT29 human colon carcinoma cell lines at extremely low concentrations (IC_{50} = 0.24 nM).[3] Lemonomycin (**862**) shows activity against colon cancer HCT 116 (IC_{50} = 0.65 μM).[4] KW2152 (the citrate salt of quinocarcin, **447**) has been clinically tested against non-small cell lung cancer,[5] P-388 leukemia (IC_{50} = 0.11 μM),[6] and several types of melanoma.[7] In fact, the therapeutic potential of these molecules is perhaps best conveyed by those members that have advanced through human clinical trials. Ecteinascidin 743

(Trabectedin, Yondelis, **863**) is approved in Europe and Japan for the treatment of soft tissue sarcomas and is currently undergoing Phase III trials within the U.S. as a treatment for ovarian cancer.[8] The synthetic ecteinascidin analog, PM00104/50 (Zalypsis, **868**), is currently entering Phase II trials to treat solid tumors.[9] In addition to their various anticancer properties, the THIQ alkaloids also possess broad-spectrum antibiotic activity against the Gram-positive and Gram-negative bacterial strains responsible for infectious diseases such as meningitis, pneumonia, strep throat, and diphtheria.[10] Furthermore, these compounds provide promising leads for alternatives to current drugs such as vancomycin and methicillin in cases of bacterial drug resistance.[4]

Figure 4.1. Representative THIQ antitumor antibiotics.



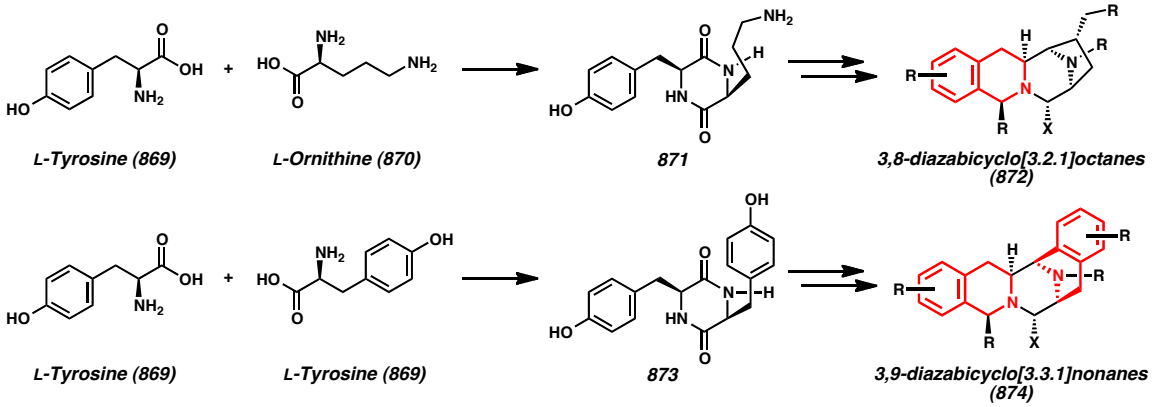
While the numerous biological properties of the THIQ alkaloids make them ideal targets for pharmaceutical development, the isolation of material from natural sources is

often expensive and low yielding.[1] Fortunately, in such cases, chemical synthesis can provide an alternative means to produce the quantities necessary for clinical testing. It is therefore of utmost importance to develop synthetic methods that assemble these important molecules in a concise and efficient manner. In pursuit of this goal, we have sought to devise a general strategy to rapidly construct the core structures of the THIQ alkaloids while providing avenues to introduce the varying peripheral functionality that makes this such a large and diverse class of natural products.

4.1.1 Biosynthetic Origins

The THIQ alkaloids can be divided into two structural subclasses based on the nature of the central diazabicycle: those featuring a 3,8-diazabicyclo[3.2.1]octane (**872**) biosynthetically derived from the condensation of the amino acids tyrosine (**869**) and ornithine (**870**),[11] and those featuring a 3,9-diazabicyclo[3.3.1]nonane (**874**) derived from two equivalents of tyrosine (**869**) (Scheme 4.1).[12] These two groups of natural products can be further distinguished by the presence of either one (as in the 3,8-diazabicyclo[3.2.1]octanes) or two (as in the 3,9-diazabicyclo[3.3.1]nonanes) embedded tetrahydroisoquinolines (highlighted in red).

Scheme 4.1. Biosynthetic origins of the THIQ alkaloids.



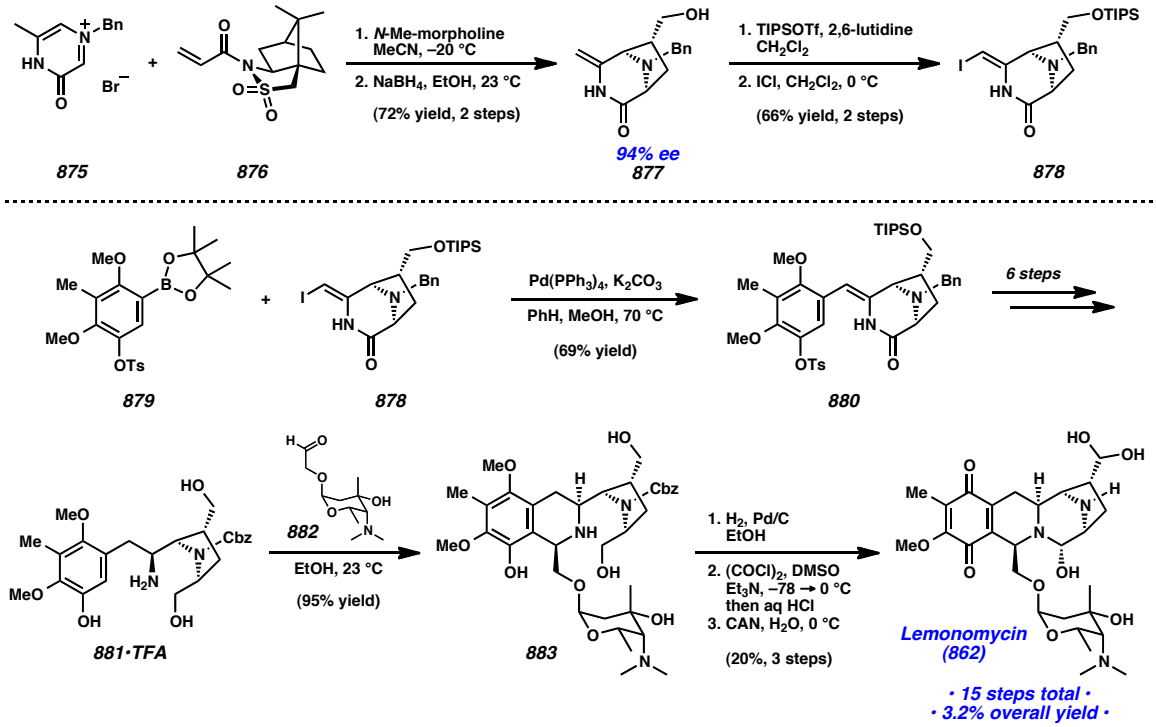
4.1.2 The Enantioselective Total Synthesis of (–)-Lemonomycin[†,13]

Focusing on the mono-THIQ alkaloids, our group reported the first total synthesis of (–)-lemonomycin,[14,4] a compound that has demonstrated potent activity against both *Staphylococcus aureus* and *Bacillus subtilis* in addition to its antitumor properties. We initiated our efforts by investigating an auxiliary-controlled diastereoselective dipolar cycloaddition between oxidopyrazinium bromide **875**[15] and the acrylamide of Oppolzer's sultam (**876**) (Scheme 4.2).[16] Following reductive removal of the auxiliary, alcohol **877** was isolated in 94% ee, thus setting the absolute stereochemistry. Silylation and iodination provided iodoenamide **878**, which was then coupled with boronic ester **879** under Suzuki–Miyaura conditions. This intermediate was carried forward to aminotriol **881**, at which point the tetrahydroisoquinoline ring system was generated by a highly diastereoselective Pictet–Spengler cyclization with aldehyde **882**, simultaneously introducing the fully elaborated glycoside. Protecting group removal, ring closure, and

[†] The total synthesis of (–)-lemonomycin was completed by Dr. Eric Ashley, a former graduate student in the Stoltz lab.

oxidation provided (–)-lemonomycin (**862**), completing the first, and to date only, total synthesis of this natural product in a total of 15 linear steps.[17]

*Scheme 4.2. The total synthesis of (–)-lemonomycin (**862**).*



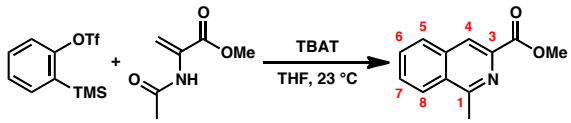
4.1.3 The Aryne Annulation for the Synthesis of Isoquinolines[18] and the Total Synthesis of (–)-Quinocarcin[19,†]

Following the successful completion of our first target within the 3,8-diazabicyclo[3.2.1]octane subclass, we began exploring other methods with the potential for general applicability to the assembly of the THIQ architecture. Toward this end, we reported a method to generate highly substituted isoquinolines (e.g., **885**) by the fluoride-

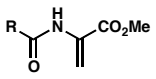
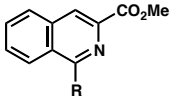
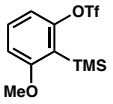
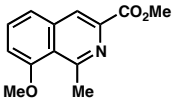
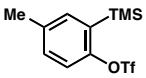
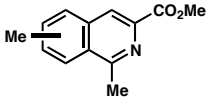
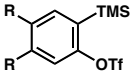
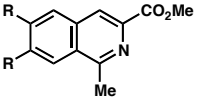
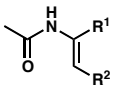
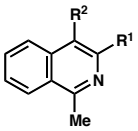
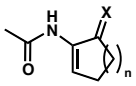
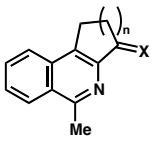
† The work toward development of the aryne annulation described in this section was performed by Christopher D. Gilmore, a graduate student in the Stoltz group, and Dr. Kevin M. Allan, a former graduate student in the Stoltz group. The total synthesis of quinocarcin was completed by Dr. Kevin M. Allan.

induced cyclocondensation of *N*-acyl dehydroamino esters (e.g., **884**) with arynes generated in situ from *o*-silyl aryl triflates (e.g., **209**) (Table 4.1).[18,20] Throughout the development of this transformation, it has proven to be remarkably tolerant of substitution on both the silyl aryl triflate (**209**) and *N*-acyl dehydroamino ester (**884**) reaction partners. More specifically, variation of the *N*-acyl moiety resulted in isoquinoline products bearing alkyl, aryl, and heteroatom substituents at C(1) (entries 1–9). Importantly, the groups in a range of oxidation states may be featured at C(1). Incorporation of substitution on the silyl aryl triflate (**209**) afforded isoquinolines functionalized at C(6), C(7), and C(8) (entries 10–14). Furthermore, the ester of enamine **884** can be replaced with various alkyl substituents and substitution can be added to the β-position of the enamine to furnish products bearing alternative groups at C(3) and C(4) (entries 15 and 16). The enamine may even be incorporated within a carbocycle to generate tricyclic isoquinoline products (entries 17–19).

Table 4.1. Synthesis of functionalized isoquinolines by aryne annulation.



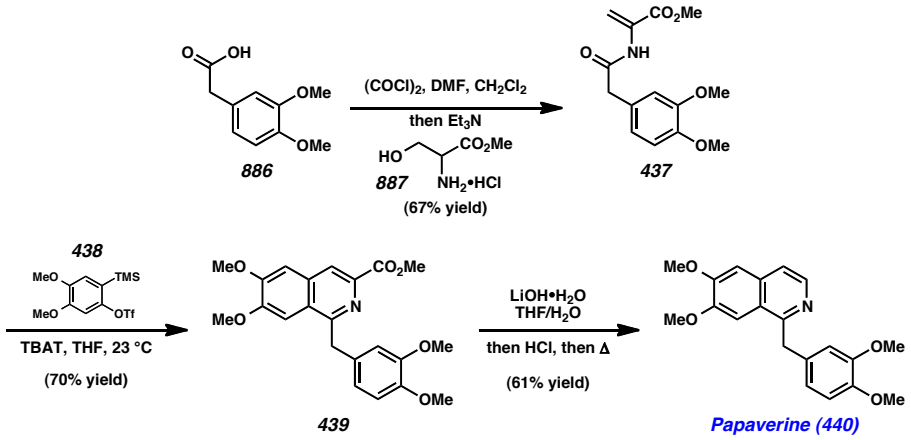
209 ***884*** ***885***

entry	*substrate*	*product*		*yield*
1			R = Me	87%
2			R = *n*-Bu	76%
3			R = cyclohexyl	65%
4			R = *i*-Pr	66%
5			R = Bn	72%
6			R = Ph	55%
7			R = CF_3	57%
8			R = CO_2Me	51%
9			R = CH_2OMe	68%
10				66%
11				59% (1:1)
12			R = $O(CH_2)O$	63%
13			R = OMe	60%
14			R = F	78%
15			R^1 = Et, R^2 = Me	72%
16			R^1 = *t*-Bu, R^2 = H	83%
17			n = 1 X = H_2	66%
18			n = 2 X = H_2	67%
19			n = 2 X = O	66%

With the development of this versatile method for the synthesis of isoquinolines, we sought to demonstrate its utility in a rapid total synthesis of papaverine (**440**),[21] a clinically used non-narcotic antispasmotic agent that is a biosynthetic precursor of several pavine alkaloids and one of the four major constituents of opium.[22] Beginning with homoveratric acid (**886**), *N*-acyl enamine **437** was prepared by a one-pot procedure

consisting of condensation with serine methyl ester•HCl (**887**) and elimination.[23] In the key step, aryne annulation of silyl aryl triflate **438** with *N*-acyl enamine **437** afforded isoquinoline **439** in 70% yield. Finally, saponification and thermal decarboxylation[24] furnished papaverine (**440**) in 29% overall yield in three steps from commercially available materials, marking the shortest reported synthesis of this alkaloid.[25]

*Scheme 4.3. The total synthesis of papaverine (**440**) by an aryne annulation.*



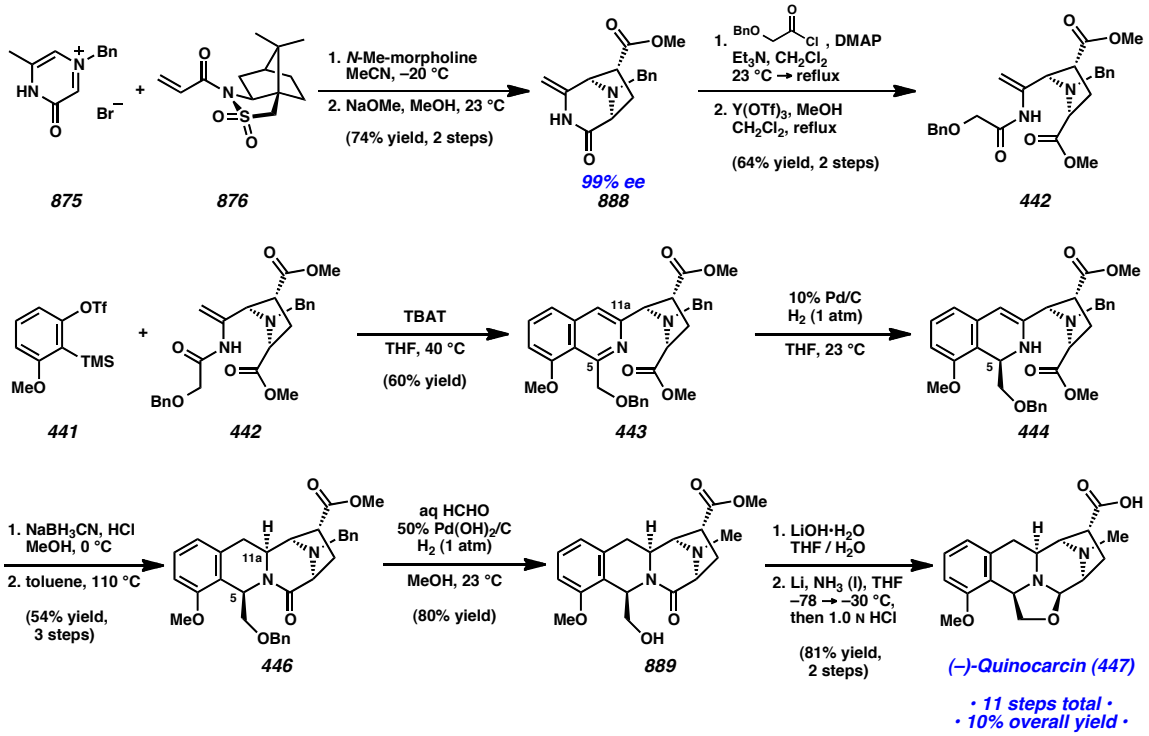
We found ourselves particularly intrigued by the complete regioselectivity of the annulation of an *ortho*-methoxy aryne, which yielded a single product isomer (Table 4.1, entry 10).[26] The similarity of this product to the western half of quinocarcin (**447**)[10b,27]—another member of the 3,8-diazabicyclo[3.2.1]octane subclass—hinted that this method could be employed to generate functionalized isoquinoline intermediates en route to the THIQ alkaloids. To test this hypothesis, we devised a synthetic route toward an asymmetric total synthesis of (–)-quinocarcin using this aryne annulation approach.[19]

Drawing from our synthesis of (–)-lemonomycin, we chose once again to build the bridged bicycle using an auxiliary-controlled diastereoselective dipolar cycloaddition

between oxidopyrazinium salt **875** and chiral acrylamide **876** (Scheme 4.4). Following separation of the major diastereomer, the auxiliary was removed via basic methanolysis to provide diazabicycle **888** in 99% ee. This compound was then acylated and selectively methanolyzed at the lactam carbonyl to generate *N*-acyl enamine **442**, the substrate for the key aryne annulation. To our delight, simple treatment of a mixture of silyl aryl triflate **441**[28] and enamine **442** with TBAT resulted in the formation of isoquinoline **443**. Thus, in only 5 steps, we had constructed an intermediate comprising the entire carbon skeleton of quinocarcin.

Next, a two-step reduction was employed to convert isoquinoline **443** to a tetrahydroisoquinoline. First, 1,2-hydrogenation of the isoquinoline ring system formed a 3.3:1 mixture of diastereomeric dihydroisoquinolines (**444** being the major diastereomer). Based on the stereochemistry at C(5), reduction using sodium cyanoborohydride proceeded with complete diastereoselectivity to produce an equivalent ratio of tetrahydroisoquinolines with a syn relationship between the C(5) and C(11a) substituents. The major diastereomer was purified and heated in toluene to close the lactam, generating tetracycle **446**. The sequence was completed by benzyl group hydrogenolysis, *N*-methylation, saponification, and dissolving metal reduction to furnish (–)-quinocarcin (**447**) in 10% overall yield through 11 linear steps, the shortest route reported to date.[29,30,31]

*Scheme 4.4. The total synthesis of (–)-quinocarcin (**447**).*



4.2 PROGRESS TOWARD THE TOTAL SYNTHESIS OF JORUMYCIN

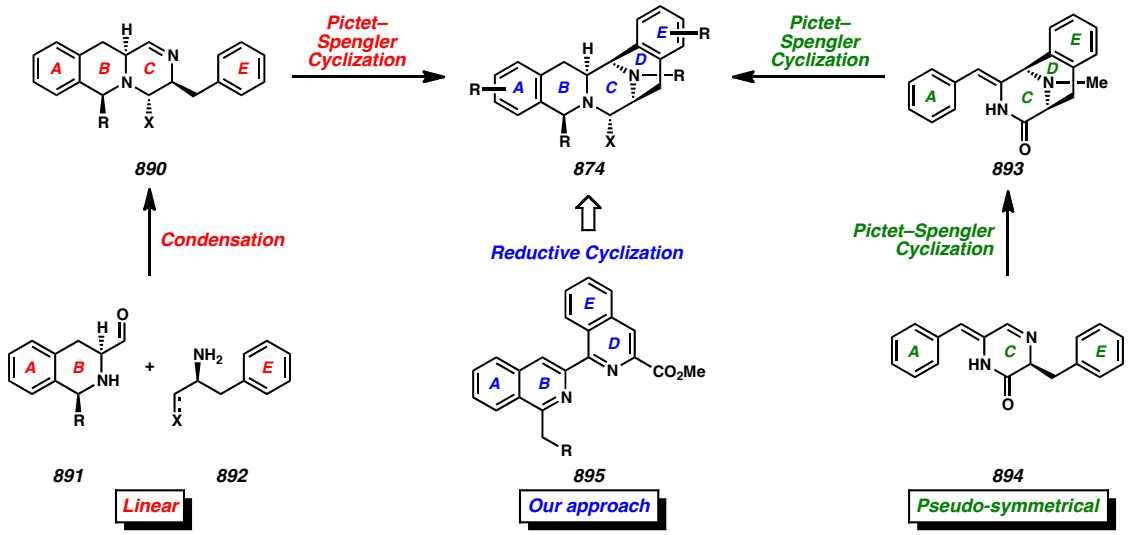
4.2.1 Outline of Approach

With two completed members of the 3,8-diazabicyclo[3.2.1]octane subclass, we have turned our attention toward extending this isoquinoline-based synthetic strategy to THIQ alkaloids featuring the 3,9-diazabicyclo[3.3.1]nonane framework. Unlike lemonomycin (**862**) and quinocarcin (**447**), these natural products contain a second tetrahydroisoquinoline ring system embedded within a pentacyclic core. The majority of reported synthetic approaches to this bis-THIQ scaffold have employed one of two retrosynthetic disconnections (Scheme 4.5). The first joins the A–B tetrahydroisoquinoline (**891**) to an E-ring-containing fragment (**892**) through condensation before cyclizing the D–E tetrahydroisoquinoline to close the [3.3.1]-

diazabicycle (**874**).[32] The second takes advantage of the pseudosymmetry of the core by attaching the A- and E-rings to a central piperazine C-ring (**894**) and performing successive Pictet–Spengler cyclizations.[33] Notably, both of these strategies make heavy use of the Pictet–Spengler reaction, which requires electron-rich aromatic rings and, in some cases, suffers from lack of regio- and stereoselectivity.

In contrast to these approaches, we plan to intercept a highly functionalized bis-isoquinoline intermediate (**895**) using our recently developed aryne annulation methodology. Stereoselective reduction of bis-isoquinoline **895** followed by lactamization will generate the pentacyclic core (**874**), setting four of the five stereocenters of bis-THIQ **874** in the process. Furthermore, unlike Pictet–Spengler-based strategies, the application of the aryne annulation to the synthesis of bis-isoquinoline **895** will allow incorporation of a range of electronically diverse A- and E-ring fragments in a modular fashion. Because of the versatility and flexibility offered by this aryne approach, a number of members of the renieramycins, safframycins, and ecteinascidins can be targeted with few changes to the central strategy. As a demonstration of this concept, we have targeted (–)-jorumycin (**611**) as a representative member of the bis-THIQ class of alkaloids.

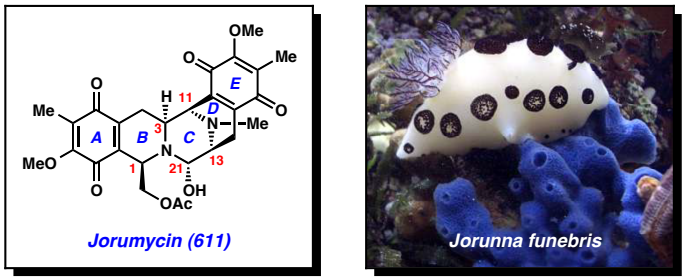
*Scheme 4.5. General approaches to the 3,9-diazabicyclo[3.3.1]nonane framework (**874**).*



4.2.2 Jorumycin: Isolation, Biological Activity, and Mechanism of Action

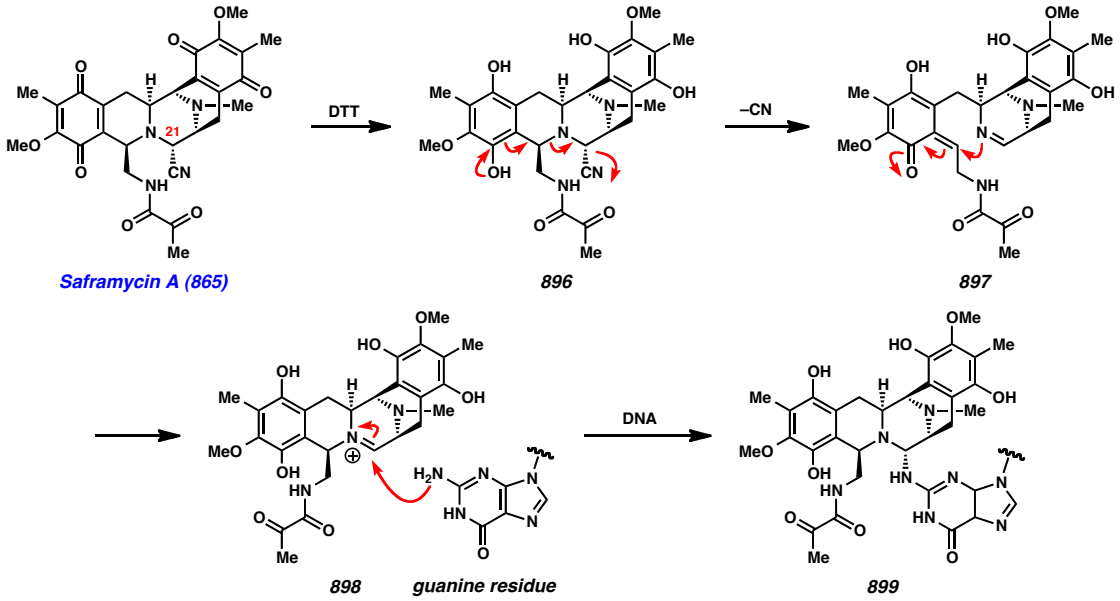
Jorumycin (**611**) was first isolated in 2000 by Fontana and co-workers from the mantle and mucus of the Pacific nudibranch *Jorunna funebris* (Figure 4.2).[3a] Primary assays on jorumycin (**611**) have indicated activity against NIH 3T3 tumor cells (100% of inhibition at 50 ng/mL). More detailed investigations demonstrated that jorumycin (**611**) is cytotoxic (IC_{50} = 12.5 ng/mL) at very low concentrations against several different tumor cell lines, such as P388 mouse lymphoma, A549 human lung carcinoma, HT29 human colon carcinoma, and MEL28 human melanoma cells. Additionally, jorumycin (**611**) inhibits the growth of various Gram-positive bacteria, including *Bacillus subtilis* and *Staphylococcus aureus*, at concentrations lower than 50 ng/mL.

*Figure 4.2. Jorumycin (**611**) and the Pacific nudibranch Jorunna funebris.*[34]



Although the mechanism of action of jorumycin (**611**) has not been studied explicitly, it is likely the same as that of the related saframycins and renieramycins. The antitumor activity of these compounds is derived from their ability to alkylate DNA in the minor groove through the formation of an intermediate iminium ion (**898**) (Scheme 4.6). According to the mechanism proposed by Hill and Remers[35] for alkylation of DNA by saframycin A (**865**), reductants such as dithiothreitol (DTT) in the cell can initially reduce the quinone moieties to the corresponding hydroquinones (**896**). This reduction is essential for DNA alkylation. Following reduction, expulsion of cyanide and scission of the C–N bond of the western THIQ can be assisted by the newly formed phenol, resulting in the formation of an imine and an *o*-quinone methide (**897**). Subsequent addition of the imine into the *o*-quinone methide generates an activated iminium (**898**) that can alkylate guanine-rich sequences of DNA.[36] Experimental support for this mechanism was obtained by ^{14}C labeling studies in which ^{14}C-labeled saframycin was incorporated into DNA in the presence of DTT.[37] Saframycins containing a C(21) hydroxyl group instead of the cyano functionality have the same activity and are believed to operate by the same mechanism.

Scheme 4.6. Hill and Remers' mechanism for DNA alkylation by the saframycins.



The broad bioactivity of the bis-THIQ alkaloids, like jorumycin (**611**), can also be attributed to aerobic oxidative mechanisms in addition to DNA alkylation. There is evidence for the formation of superoxide and hydroxyl radicals in the presence of saframycins in their hydroquinone forms (e.g., **896**), leading to eventual DNA cleavage under aerobic conditions.[38]

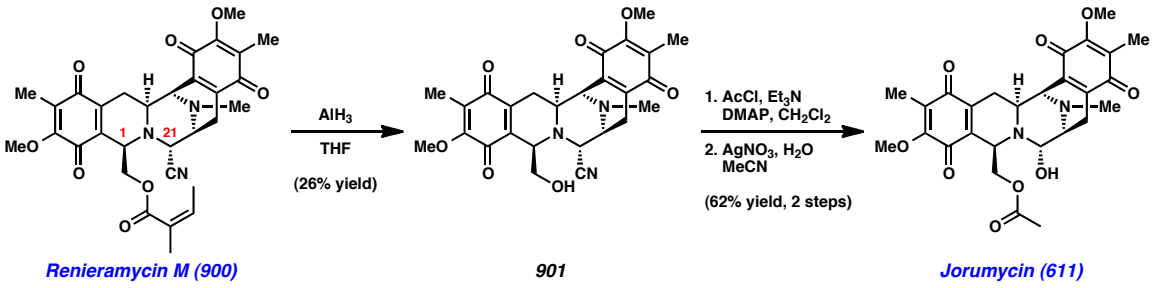
4.2.3 Jorumycin: Previous Total Syntheses

The synthesis of the bis-THIQ natural products such as the saframycins, renieramycins, and ecteinascidins, has been the subject of intense synthetic study since their first isolations. Indeed there have been hundreds of efforts directed at their synthesis reported in the literature; these accounts have been reviewed in detail elsewhere[1] and are beyond the scope of this report. In the 11 years since its isolation,

jorumycin (**611**) has been synthetically prepared on three separate occasions: twice by total synthesis and once by semisynthesis from renieramycin M (**900**).

The first report of the preparation of jorumycin (**611**) came in 2004 from Saito and co-workers and is a semisynthesis beginning with renieramycin M (**900**).[39] The key differences between jorumycin (**611**) and renieramycin M (**900**) are the identity of the ester group appended to C(1) (angelate vs. acetate) and the C(21) leaving group (hydroxyl vs. cyanide) (Scheme 4.7). The conversion of renieramycin M (**900**) to jorumycin (**611**) begins with removal of the angelate ester by reduction with alane, affording alcohol **901**. Acetylation of alcohol **901** was followed by substitution of the C(21) cyano group with a hydroxyl to furnish jorumycin (**611**) in a total of three steps from renieramycin M (**900**).

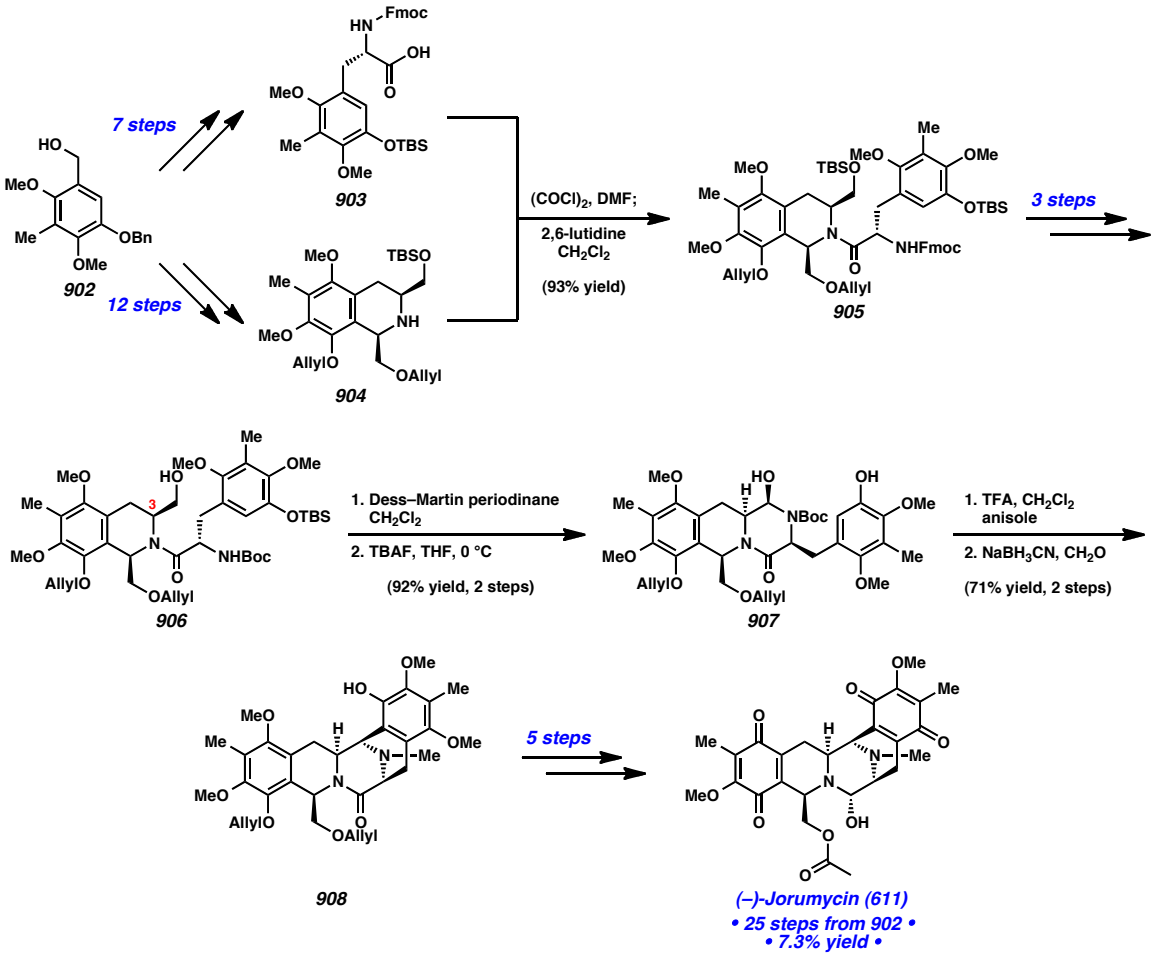
*Scheme 4.7. Saito's semisynthesis of jorumycin (**611**) from renieramycin M (**900**).*



The first total synthesis of (–)-jorumycin (**611**) was reported shortly after Saito's semisynthesis by Williams and co-workers in 2005.[40] Beginning with the coupling of tetrahydroisoquinoline **904** with amino acid **903**, both accessed with the aid of chiral auxiliary methods, amide **905** was advanced over three steps to an intermediate bearing a primary alcohol at C(3) (**906**) (Scheme 4.8). Following oxidation of the alcohol to the

aldehyde and cleavage of the silyl ether of **906**, aminal **907** was treated with TFA to effect an intramolecular Pictet–Spengler reaction to close the final ring of the natural product. From this point, pentacycle **908** was converted over five additional steps to (–)-jorumycin (**611**). Overall, jorumycin (**611**) was completed in 7.3% yield by a longest linear sequence of 25 steps beginning with arene **902**.[41]

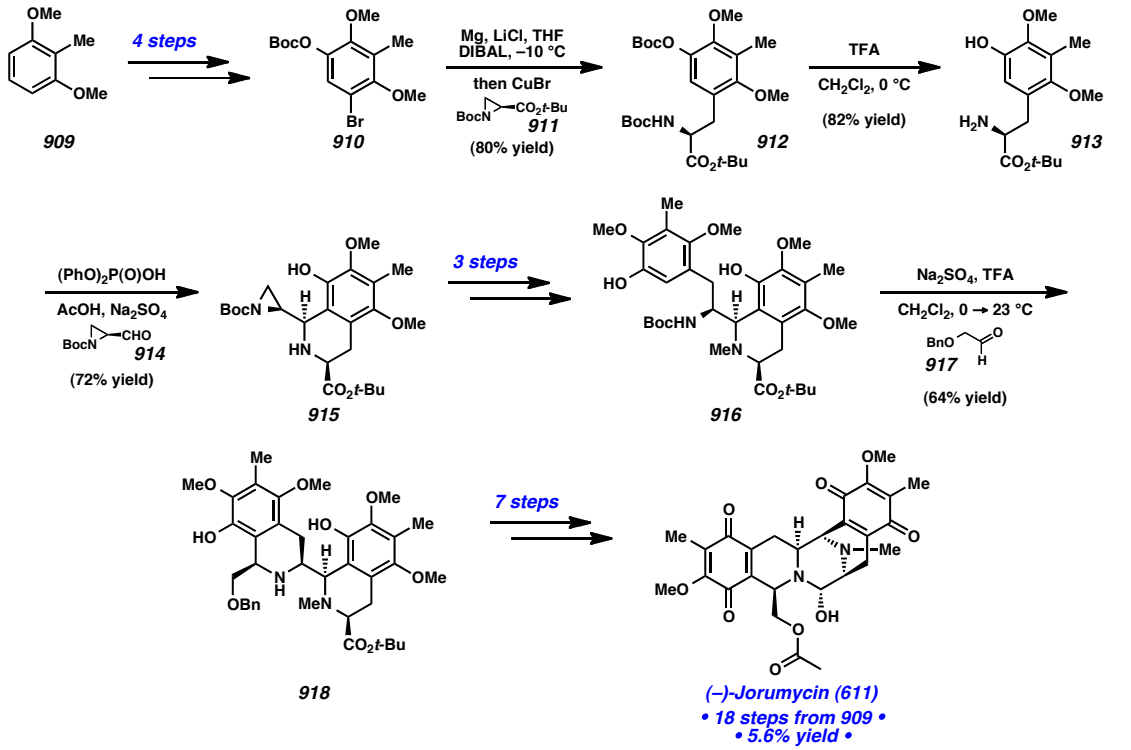
*Scheme 4.8. Williams' total synthesis of (–)-jorumycin (**611**).*



The final and most recent synthesis of (–)-jorumycin was reported by Zhu and co-workers in 2009 and relied upon sequential aziridine ring-opening reactions to build the

pentacyclic core.[42] As in the synthesis reported by Williams, Zhu constructed the two individual tetrahydroisoquinolines of jorumycin (**611**) by Pictet–Spengler cyclizations. Beginning with aryl bromide **910**, which was accessed in four steps from commercially available materials (**909**), nucleophilic ring-opening addition to aziridine **911** produced protected amino acid **912** (Scheme 4.9). Following cleavage of the Boc protecting groups, Pictet–Spengler reaction of aminophenol **913** with aziridine aldehyde **914** furnished the first tetrahydroisoquinoline (**915**). This intermediate (**915**) was advanced over three steps to phenol **916** in preparation for the second Pictet–Spengler cyclization to afford bis-THIQ **918**. Finally, bis-THIQ **918** was converted to (–)-jorumycin (**611**) over an additional seven steps. Overall, Zhu was able to construct (–)-jorumycin (**611**) in 5.6% yield and 18 linear steps from commercially available compounds (**909**).

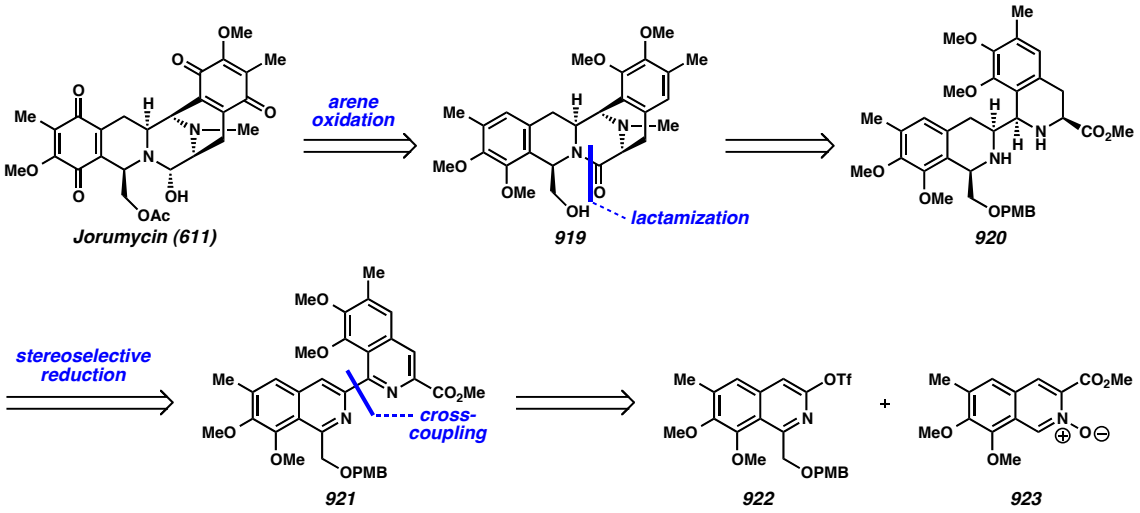
*Scheme 4.9. Zhu's total synthesis of (–)-jorumycin (**611**).*



4.2.4 Retrosynthetic Analysis of Jorumycin

In designing our synthetic strategy toward jorumycin (**611**), we sought a route that would maximize convergency and allow access to related natural products and non-natural analogs in a rapid fashion. As previously described, the pentacyclc bis-THIQ framework (**919**) of jorumycin (**611**) will be accessed by reduction of functionalized bis-isoquinoline **921** via tetracyclic bis-THIQ **920** (Scheme 4.10). This key intermediate (**921**) will be disconnected along the central carbon–carbon bond linking the two discrete isoquinolines to an isoquinoline triflate (**922**) and an isoquinoline *N*-oxide (**923**). We anticipate joining triflate **922** and *N*-oxide **923** by a palladium-catalyzed cross coupling involving a directed C–H functionalization such as that developed by Fagnou and co-workers.[43]

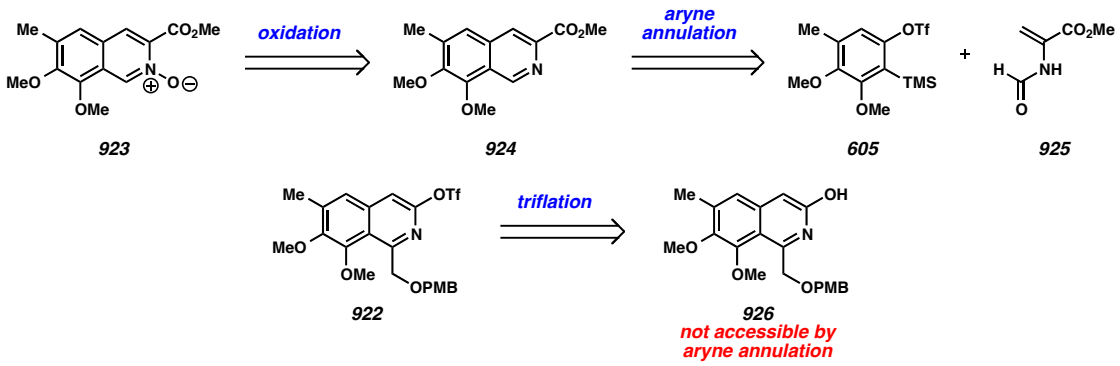
*Scheme 4.10. Retrosynthetic analysis of jorumycin (**611**).*



Each of these building blocks (**922** and **923**) will be prepared by aryne-based methodologies developed in our group. Importantly, the symmetry inherent to jorumycin

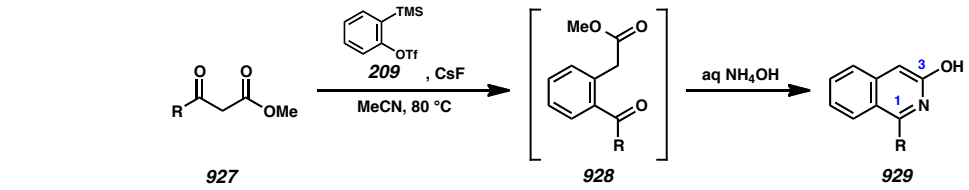
(**611**) can be exploited, requiring only a single aryne precursor to prepare each coupling partner. Retrosynthetically, the isoquinoline *N*-oxide (**923**) can be derived from the parent isoquinoline (**924**), which will in turn be constructed by aryne annulation of silyl aryl triflate **605** with formyl enamide **925** (Scheme 4.11). Isoquinoline triflate **922** will be best prepared from 3-hydroxyisoquinoline **926**, which cannot be accessed by a direct aryne annulation.

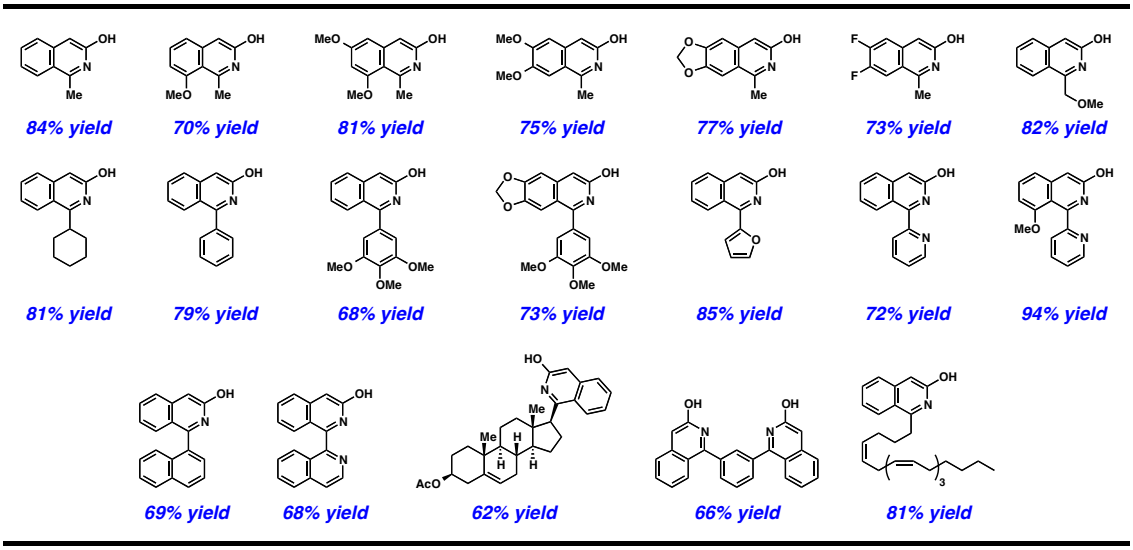
*Scheme 4.11. Retrosynthetic analysis of isoquinoline N-oxide **923** and isoquinoline triflate **922**.*



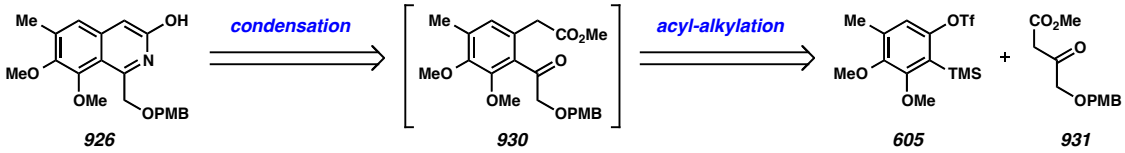
Fortuitously, concurrent with these efforts, we uncovered a method for the synthesis of 3-hydroxyisoquinolines (**929**) by condensation with ammonia[44] with acyl-alkylation products of our previously reported aryne insertion methodology[45] (Table 4.2). This one-pot modification to our acyl-alkylation protocol provides facile access to a variety of C(1)-substituted 3-hydroxyisoquinolines from silyl aryl triflate (e.g., **209**) and β-ketoester (e.g., **927**) starting materials.[46] Furthermore, 3-hydroxyisoquinoline **926**, required for implementation of a cross-coupling strategy to the synthesis of jorumycin (**611**), can be prepared by this method using silyl aryl triflate **605** with β-ketoester **931** (Scheme 4.12).

Table 4.2. Synthesis of C(1)-functionalized 3-hydroxyisoquinolines by the acyl-alkylation/condensation method.





Scheme 4.12. Retrosynthetic analysis of 3-hydroxyisoquinoline ***926****.*



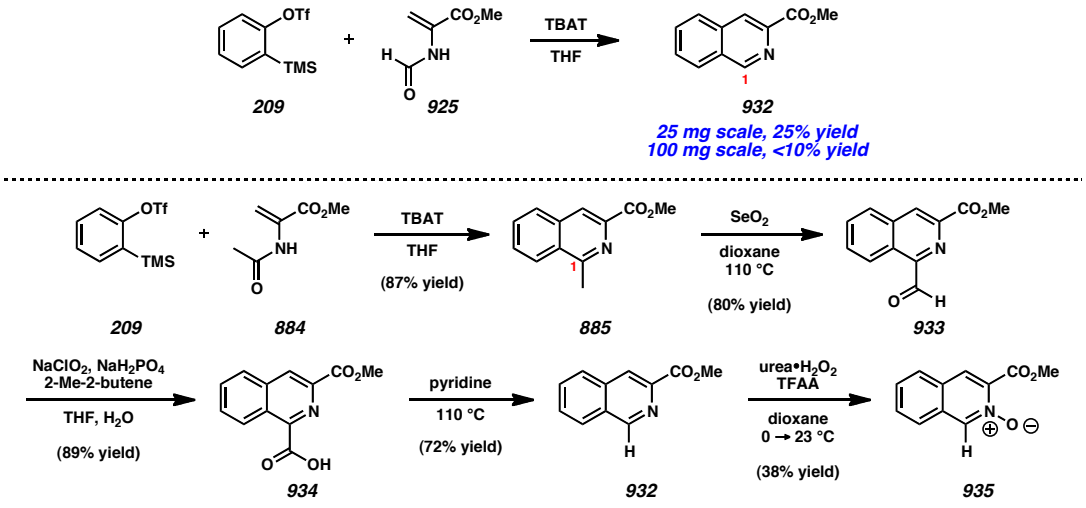
4.2.5 Model System Cross-Coupling and Reduction

Before pursuing the synthesis of jorumycin (**611**) by this route, we sought to test our synthetic strategy of isoquinoline cross-coupling followed by bis-isoquinoline reduction in a model system lacking functionality on the silyl aryl triflate. Initial

attempts to prepare model compounds of both 3-hydroxyisoquinoline **926** and 1-*H*-isoquinoline **924** were met with significant difficulty.

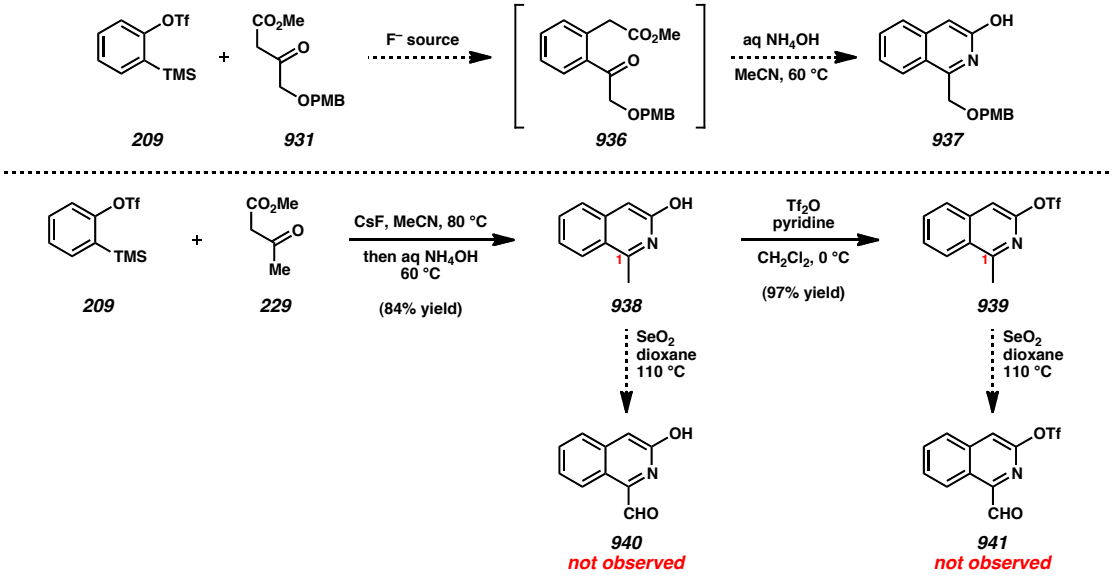
In the synthesis of 1-*H*-isoquinoline **932**, we immediately found that formyl enamide **925** was prone to polymerization and that its reaction with silyl aryl triflate **209** was low yielding (Scheme 4.13). Furthermore, the yield dropped precipitously upon scaling up the annulation. As such, a number of alternative procedures were investigated to install a hydrogen at C(1). The highest yielding and most operationally straightforward of these methods begins with isoquinoline **885**, which is the product of aryne annulation between silyl aryl triflate **209** and methyl 2-acetamidoacrylate (**884**). Oxidation of the C(1) methyl group was readily accomplished by treatment of isoquinoline **885** with selenium dioxide in dioxane,[47] yielding aldehyde **933**. Pinnick oxidation followed by thermal decarboxylation then afforded 1-*H*-isoquinoline **932** in excellent yield. Finally, isoquinoline **932** was oxidized to the corresponding *N*-oxide (**925**) upon treatment with urea•H_2O_2 and trifluoroacetic anhydride (TFAA).[48]

*Scheme 4.13. Synthesis of 1-H-isoquinoline **932** and isoquinoline N-oxide **935**.*



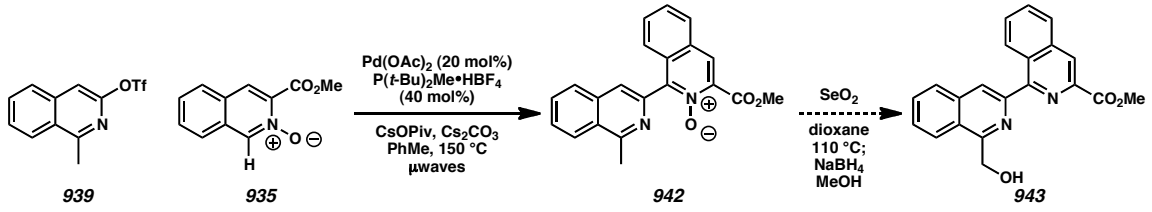
In the synthesis of hydroxyisoquinoline **937**, difficulty was encountered in the acyl-alkylation step with β-ketoesters bearing γ-alkoxy substituents (e.g., **931**) (Scheme 4.14). Generally, yields for this step were low and the desired product was accompanied by significant side product formation. However, we anticipate that we can again rely on the selective selenium dioxide oxidation of the C(1) methyl group of to circumvent this difficulty. Toward this end, 3-hydroxyisoquinoline **938** was prepared from silyl aryl triflate **209** and methyl acetoacetate (**229**) in very good yield and was subsequently triflated under standard conditions. Notably, attempts to oxidize the C(1) methyl group of both the 3-hydroxyisoquinoline (**938**) and the isoquinoline triflate (**939**) failed: treatment of 3-hydroxyisoquinoline **938** with selenium dioxide resulted in rapid decomposition, while isoquinoline triflate **939** failed to react under the same reaction conditions and at more elevated temperatures. We reasoned that C(1) methyl group oxidation could be performed immediately following cross-coupling of isoquinoline *N*-oxide **935** and isoquinoline triflate **939** since the electronic nature of the bis-isoquinoline will more closely resemble that of isoquinoline **885**.

*Scheme 4.14. Synthesis of isoquinoline triflate **939** and attempted C(1) methyl group oxidations.*



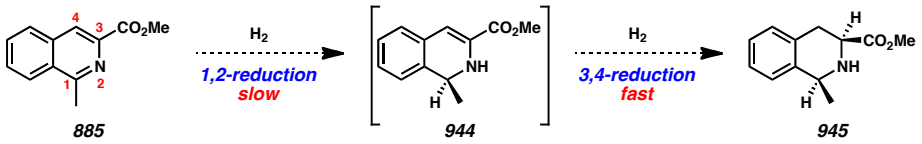
In practice, palladium-catalyzed cross coupling of isoquinoline *N*-oxide **935** and isoquinoline triflate **939** afforded bis-isoquinoline **942** in good yield (Scheme 4.15).[43] We anticipate that oxidation of bis-isoquinoline **942** with SeO_2 and subsequent reduction with sodium borohydride will yield the bis-isoquinoline bearing the required hydroxymethyl group at C(1) (**943**). However, before investigating this step, we were interested in testing the key reduction of bis-isoquinoline **942** to the corresponding bis-THIQ.

*Scheme 4.15. Cross-coupling of isoquinoline triflate **939** and isoquinoline N-oxide **935** and proposed subsequent C(1) methyl group oxidation.*



With bis-isoquinoline **942** in hand, we turned our attention to the key reduction of this intermediate to a tetracyclic bis-THIQ.[49,19] Generally, the reduction of isoquinolines is known to proceed by 1,2-reduction to yield an enamine (**885** → **944**), which then undergoes rapid reduction of the C(3)–C(4) bond (**944** → **945**) (Scheme 4.16).[50,51,49b] Furthermore, the stereochemical outcome of the initial 1,2-reduction is known to strongly influence the stereoselectivity of the subsequent 3,4-reduction,[52,49b,51c] furnishing THIQ products bearing substituents at C(1) and C(3) with cis relative stereochemistry. We believe that this characteristic of isoquinoline reduction can be exploited to effect the all-cis reduction required for the synthesis of a tetracyclic bis-THIQ.

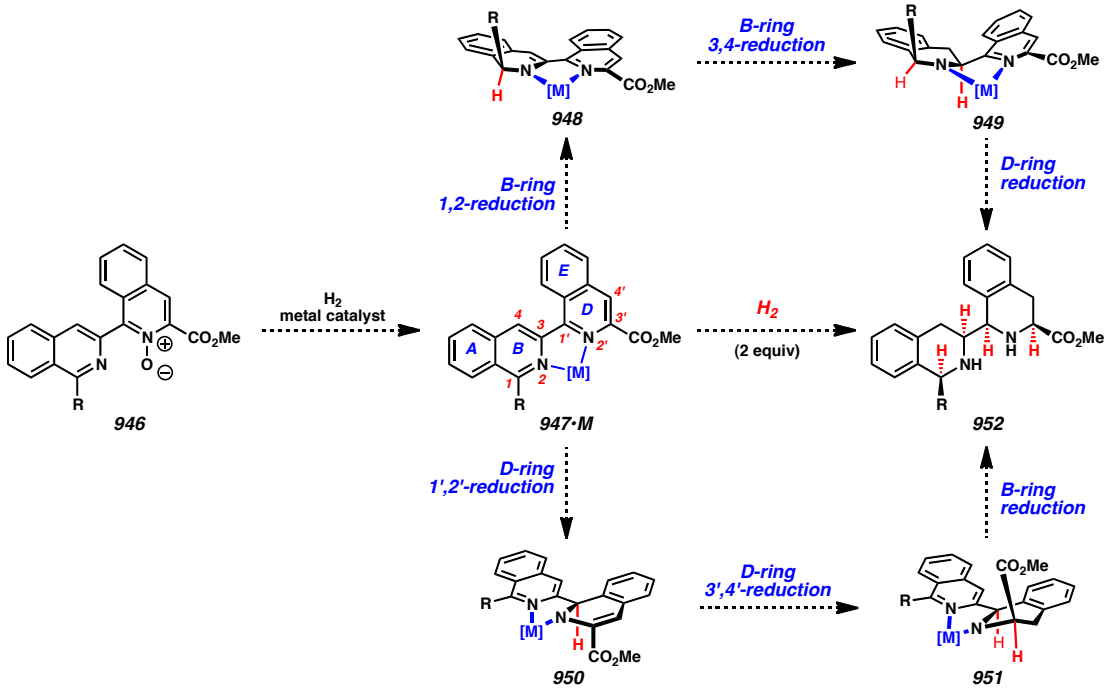
Scheme 4.16. Stereoselectivity in the reduction of isoquinolines.



Upon exposure of bis-isoquinoline **946** to a metal catalyst (homogeneous or heterogeneous) and hydrogen gas, two potential reduction pathways are likely that each lead to the desired bis-THIQ (**952**) (Scheme 4.17). Each pathway will be initiated by reduction of the *N*-oxide and complexation of the bis-isoquinoline to the metal catalyst. This will serve to orient the substrate in a conformation conducive to reduction with the preferred stereoselectivity. In an achiral sense, a reduction cascade can be initiated by 1,2-reduction on either of the two discrete isoquinoline units. If initial 1,2-reduction occurs on the B-ring (**947•M** → **948**), we expect that the newly formed stereocenter at C(1) would impart a concavity on the system, leading to fast 3,4-reduction in a syn

fashion (**948** → **949**). Importantly, the increased concavity of THIQ **949** will further predispose the system toward D-ring reduction from the convex face to produce all-syn bis-THIQ **952**. In this way, the stereochemistry of the C(1)-position can be relayed to the other three stereocenters formed during this reduction process. An alternative pathway would begin with 1,2-reduction of the D-ring, proceeding through intermediates **950** and **951** en route to bis-THIQ **952**. Importantly, in an achiral reduction of bis-isoquinoline **946**, initiation of the reduction cascade on either the B- or D-ring will lead to bis-THIQ **952** with the same relative (all-syn) stereochemistry.

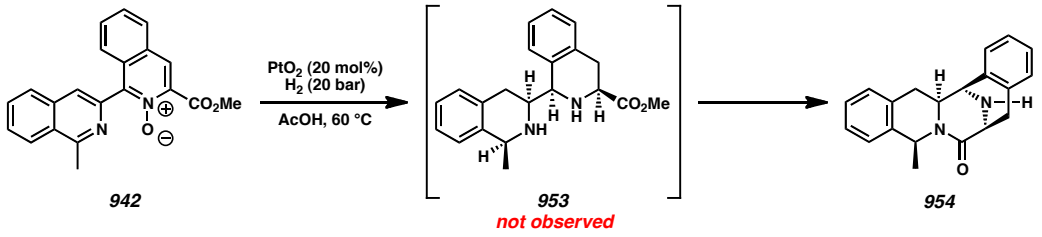
*Scheme 4.17. Expected stereoselectivity in the reduction of bis-isoquinoline **946**.*



While there have been few reported reductions of isoquinolines to THIQs, several heterogeneous catalysts and a recently disclosed Crabtree iridium catalyst have

performed the desired transformation.[53,49] In our initial efforts, treatment of bis-isoquinoline **942** with Adams' catalyst under 20 bar H_2 at 60 °C yielded not the expected tetracyclic bis-THIQ (**953**), but instead afforded the pentacyclic core of the bis-THIQ alkaloids (**954**) directly (Scheme 4.18). Pentacycle **954** is believed to arise by full reduction of the bis-isoquinoline, as anticipated, followed by in situ lactamization of the all-syn tetracyclic bis-THIQ (**953**). With this proof-of-principle result in hand, we turned our attention to preparation of the fully functionalized bis-isoquinoline required for the synthesis of jorumycin.

*Scheme 4.18. Successful reduction of bis-isoquinoline **942** to pentacycle **954**.*

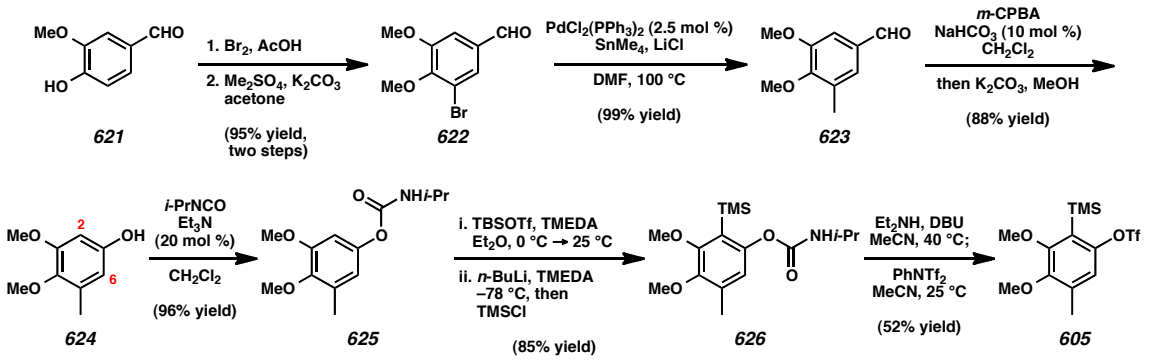


4.2.6 Synthesis of the Jorumycin Aryne Precursor[54]

Before constructing the key bis-isoquinoline desired for the synthesis of jorumcyin, we sought a rapid and scalable synthesis of the functionalized silyl aryl triflate (**605**) aryne precursor from readily available starting materials. We began with a regioselective bromination of vanillin (**621**) to provide exclusively the 5-bromo product, which was methylated to produce bromo dimethoxy benzaldehyde **622** (Scheme 4.19).[55] Next, Stille coupling of the bromoarene (**622**) with tetramethyltin enabled the introduction of the 5-methyl substituent to generate arene **623**.[56] Further elaboration of

this intermediate by one-pot Baeyer–Villiger oxidation and cleavage of the resultant formate ester yielded intermediate phenol **624**. All attempts to install a bromide selectively at C(2) of phenol **624** failed, instead resulting in exclusive bromination at C(6). In order to selectively functionalize phenol **624**, we turned to a recently disclosed 3-step procedure for the general synthesis of *o*-silyl aryl triflates by Garg, et al.[57] Analysis of this approach indicated that conversion of the phenol to a carbamate might facilitate silylation at C(2) over C(6). Application of this sequence to our intermediate (**624**) allowed the direct *ortho*-silylation of carbamate **625** to produce the 2-silyl carbamate (**626**) exclusively. Subsequent cleavage of the carbamate and triflation of the resulting phenoxide furnished the desired aryne precursor (**605**) in 5 steps from known aldehyde **622**.

*Scheme 4.19. Synthesis of silyl aryl triflate **605**.*



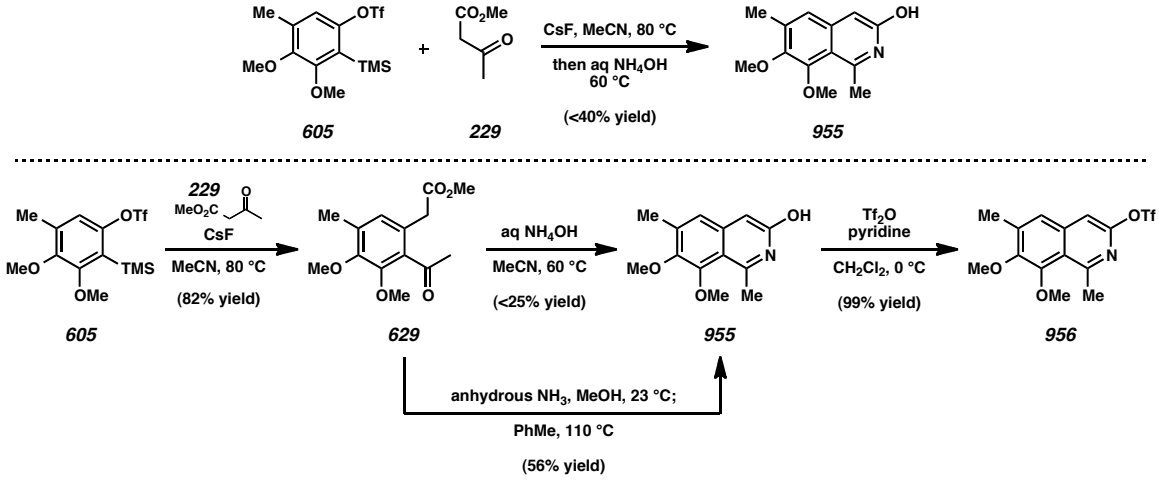
4.2.7 Synthesis and Reduction of a Functionalized Bis-isoquinoline

With silyl aryl triflate **605** in hand, we turned our attention toward the preparation of a bis-isoquinoline appropriately functionalized for the synthesis of jorumycin (**611**). Throughout these efforts we encountered several subtle differences in reactivity

stemming from use of substituted silyl aryl triflate **605** instead of the unsubstituted model system aryne precursor (**209**).

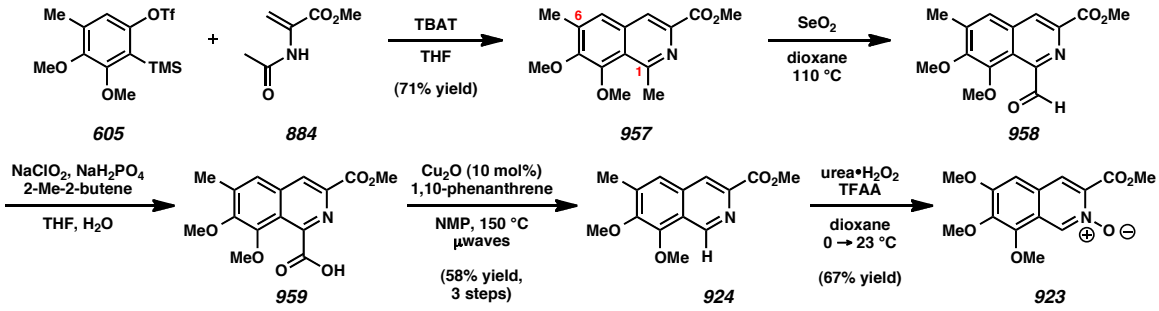
Our synthesis of a bis-isoquinoline commenced with preparation of the isoquinoline triflate (**956**) and isoquinoline *N*-oxide (**923**) coupling partners. Isoquinoline triflate **956** was targeted by a one-pot acyl-alkylation/condensation with silyl aryl triflate **605** and methyl acetoacetate (**229**) (Scheme 4.20).[46] However, despite significant effort to optimize this reaction, yields could not be increased above 40%. Attempts to perform the hydroxyisoquinoline formation in a stepwise manner showed that the acyl-alkylation reaction routinely occurred in 82% yield while the cyclocondensation step was the problematic one. Gratifyingly, condensation of acyl-alkylation product **629** with anhydrous ammonia in methanol followed by heating in toluene afforded the desired 3-hydroxyisoquinoline (**955**) in 56% yield. Finally, triflation of hydroxyisoquinoline **955** with triflic anhydride and pyridine furnished isoquinoline triflate **956**.

*Scheme 4.20. Synthesis of substituted isoquinoline triflate **956**.*



Synthesis of the isoquinoline *N*-oxide coupling partner (**923**) began with aryne annulation of silyl aryl triflate **605** and methyl 2-acetamidoacrylate (**884**) in 71% yield (Scheme 4.21). Importantly, the directed C(1) methyl group oxidation of isoquinoline **957** with selenium dioxide proceeded with perfect selectivity, leaving the C(6) methyl group untouched. Pinnick oxidation and decarboxylation were followed by *N*-oxide formation to yield the desired isoquinoline *N*-oxide (**923**).

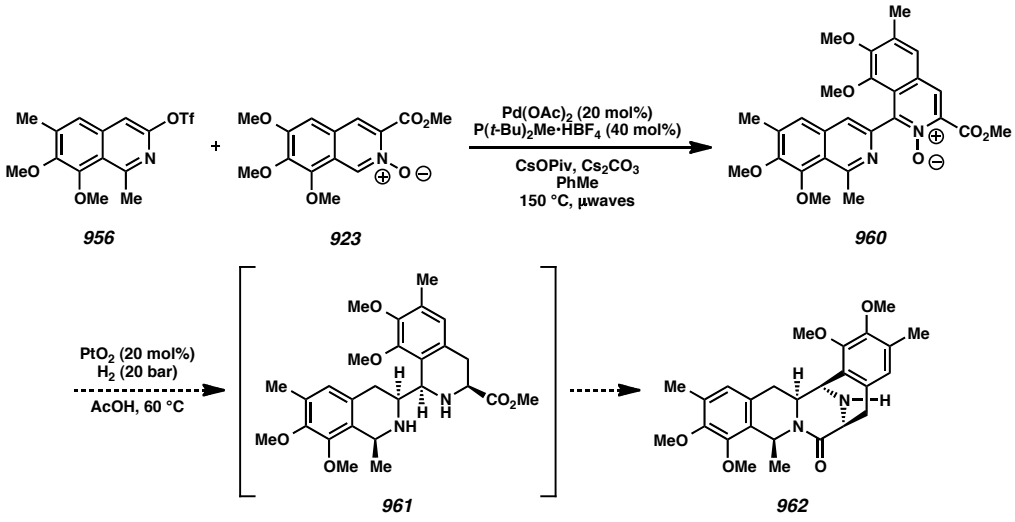
Scheme 4.21. Synthesis of substituted isoquinoline N-oxide ***923****.*



At this point, we were poised to investigate the key cross-coupling of isoquinoline *N*-oxide **923** and isoquinoline triflate **956** (Scheme 4.22). To our delight, the conditions developed for the model system cross-coupling (vide supra) produced the desired bis-isoquinoline (**960**). Currently we are investigating the reduction of bis-isoquinoline **960** to pentacyclic bis-THIQ **962** via tetracyclic intermediate **961** by treatment with Adams' catalyst under a hydrogen atmosphere. This process would set the relative stereochemistry of four of the five stereogenic centers present in jorumycin (**611**) in a single operation. Furthermore, in only two steps the simple isoquinoline trifalte (**956**) and isoquinoline *N*-oxide (**923**) can be stereoselectively transformed into the pentacyclic

core of jorumycin (**962**) and other bis-THIQ alkaloids. This represents the point of furthest progress toward the synthesis of jorumycin (**611**) at this time.

*Scheme 4.22. Cross-coupling of isoquinoline triflate **956** and isoquinoline N-oxide **923** and reduction of bis-isoquinoline **960** to bis-THIQ **962**.*

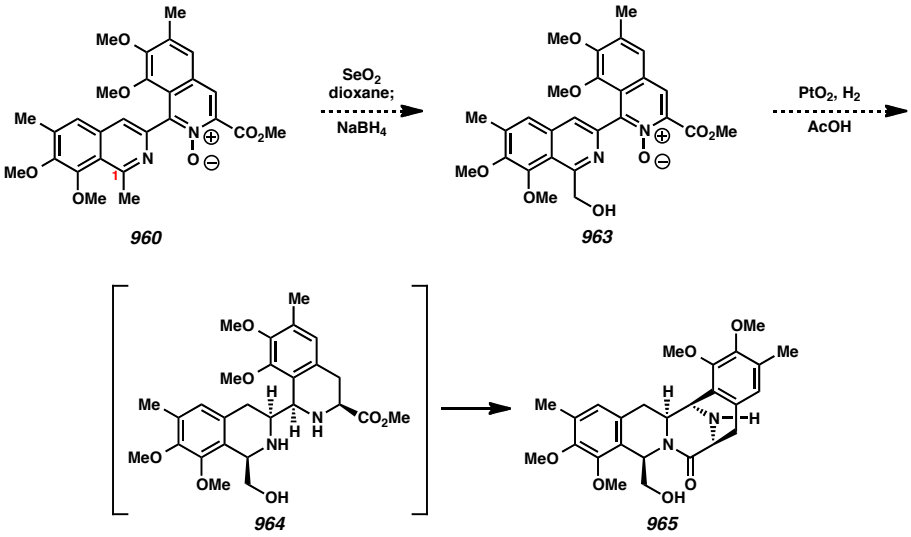


956 923 960 961 962

4.2.8 Strategy for the Completion of Jorumycin

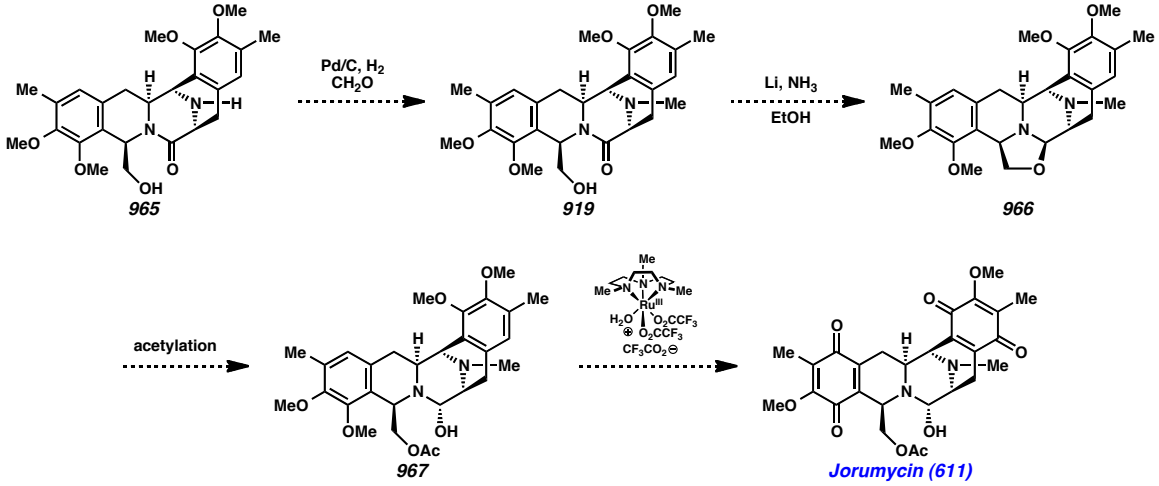
Completion of jorumycin (**611**) will first require the installation of the appropriate oxidation state on the C(1) substituent. Returning to bis-isoquinoline **960**, selenium dioxide oxidation of the C(1) methyl group and subsequent reduction with sodium borohydride will incorporate the oxidation at this position of jorumycin (Scheme 4.23). At this point, reduction of the bis-isoquinoline (**963**) to the bis-THIQ and in situ lactamization will yield the pentacyclic core of the natural product (**965**).

Scheme 4.23. Synthesis of pentacycle ***965*** *following oxidation of the C(1) methyl group of bis-isoquinoline* ***960****.*



From pentacylic bis-THIQ **965**, the synthesis of jorumycin can be completed in potentially four transformations (Scheme 4.24). First, reductive methylation will install the *N*-methyl group on the secondary amine of pentacycle **965**, yielding *N*-methyl pentacycle **919**. Next, the amide (**919**) will be diastereoselectively reduced under dissolving metal conditions, as in many prior syntheses of alkaloids in this class, to the cyclic aminal (**966**).[58,30a,b,e] We anticipate that, upon ring-opening, acetylation of pentacycle **966** will occur selectively at the primary alcohol, leaving the aminal untouched. Finally, oxidation of the arenes to their corresponding quinones will afford jorumycin (**611**).[59] In total, the route described here will furnish jorumycin (**611**) in only 12 linear steps from silyl aryl triflate (**605**) (19 steps from commercially available compounds).

*Scheme 4.24. Strategy for the completion of jorumycin (**611**).*



4.3 CONCLUDING REMARKS

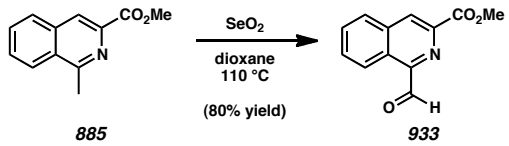
In designing our route to jorumycin we have focused on the development of a highly convergent strategy capable of generating significant complexity in a rapid fashion. Implementation of an aryne-based approach to the synthesis of simple isoquinoline coupling partners has facilitated the progress toward jorumycin, allowing synthesis of the core of the natural product in just three steps from these building blocks. Furthermore, use of a reduction cascade of bis-isoquinolines sets the relative stereochemistry of four of the five stereocenters in jorumycin in a single operation. Given the success of the reduction of bis-isoquinolines to the pentacyclic bis-THIQ core of these alkaloids, we are confident that jorumycin will be completed in due course. Finally, we anticipate that this strategy will be a general one, amenable to the synthesis of many members of the bis-THIQ family of alkaloids as well as non-natural analogs for biological studies.

4.4 EXPERIMENTAL SECTION

4.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. 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 by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 500 (at 500 MHz and 125 MHz, respectively) 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), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

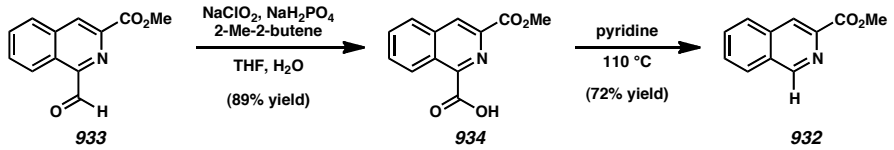
4.4.2 Preparative Procedures and Spectroscopic Data



885 ***933***

Aldehyde 933

Selenium dioxide (206 mg, 1.86 mmol) was added to a solution of isoquinoline **885** (93.5 mg, 0.465 mmol) in dioxane (5 mL). The reaction was sealed and heated to 100 °C, at which temperature it was maintained with stirring until isoquinoline **885** had been completely consumed by TLC analysis. Following this time, the reaction was cooled, filtered, and concentrated under vacuum. The crude residue was purified by flash chromatography (5:1 hexanes:ethyl acetate eluent) to yield aldehyde **933** (80 mg, 80% yield): $R_f = 0.16$ (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.43 (s, 1H), 9.33 (dd, J = 8.3, 1.2 Hz, 1H), 8.73 (s, 1H), 8.02 (dd, J = 7.2, 1.6 Hz, 1H), 7.94–7.73 (m, 2H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.00, 165.39, 149.75, 140.95, 136.90, 132.23, 131.59, 128.41, 128.39, 127.26, 126.10, 53.15; IR (NaCl/film) 2946, 2829, 1751, 1719, 1708, 1452, 1372, 1332, 1299, 1255, 1213, 1150, 1112, 1056, 985, 914, 793, 749 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{12}H_{10}O_3N$ $[M+H]^+$: 216.0655, found 216.0659.

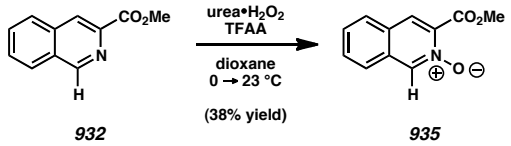


Isoquinoline 932

A solution of $NaClO_2$ (336 mg, 3.72 mmol) and $NaH_2PO_4 \bullet H_2O$ (928 mg, 5.95 mmol) in H_2O (3.7 mL) was added to a suspension of aldehyde **933** (80 mg, 0.372 mmol) and 2-methyl-2-butene (2.36 mL, 22.3 mmol) in *t*-BuOH (3.7 mL). The biphasic suspension was then maintained at room temperature with vigorous stirring until aldehyde **933** was fully consumed by TLC analysis. Following this time, the reaction was diluted with brine (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under vacuum. The crude product (**934**, 76 mg, 89% yield) was used without further purification.

Acid **934** (76 mg, 0.330 mmol) was taken up in pyridine (2 mL) and heated to 110 °C. The solution was maintained at 110 °C until acid **934** had been fully consumed by TLC analysis. At that time, the reaction was cooled to room temperature, diluted with ethyl acetate, and washed sequentially with water (2 x 10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (1:1 hexanes:ethyl acetate eluent) to yield isoquinoline **932** (45 mg, 72% yield): R_f = 0.16 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.52 (s, 1H), 8.05–7.94 (m, 1H), 7.94–7.82 (m, 1H), 7.69 (m, 2H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.36, 152.74, 141.54, 135.53, 131.27, 130.01, 129.71, 128.09, 127.77, 124.14, 52.96; IR (NaCl/film) 2994, 2951, 1726, 1577, 1497, 1452, 1387, 1328,

1291, 1228, 1202, 1139, 1095, 970, 901, 795, 769 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 188.0706, found 188.0709.

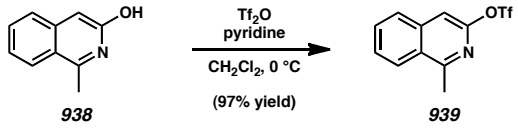


932 ***935***

Isoquinoline *N*-oxide 935

Urea•H_2O_2 (108 mg, 1.14 mmol) and K_2CO_3 (316 mg 2.28 mmol) were combined in dioxane (11 mL) and maintained at room temperature with stirring for 1 hour. Following this time, the suspension was cooled to 0 °C in an ice bath with vigorous stirring. Trifluoroacetic anhydride (161.4 μL, 1.14 mmol) was added and, after 10 minutes at 0 °C, the reaction was allowed to warm to room temperature over 30 minutes. At that time, isoquinoline **932** (21.4 mg, 0.114 mmol) was added and the reaction was heated to 50 °C. The suspension was maintained with vigorous stirring at 50 °C for 24 hours, at which point it was cooled to room temperature and concentrated under vacuum. The crude residue was diluted with CH_2Cl_2 (25 mL) and washed with water (20 mL). The organic phase was dried with $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (1:2:0.15 hexanes:ethyl acetate:Et_3N eluent) to yield isoquinoline *N*-oxide **935** (8.7 mg, 38% yield): R_f = 0.30 (5% Et3N in ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.03 (s, 1H), 7.83 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.75–7.71 (m, 1H), 7.67 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.62 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.25, 139.05, 137.36, 130.82, 130.11, 129.41, 127.77, 127.42, 125.69, 124.70, 53.40; IR (NaCl/film) 2952, 1742, 1630, 1601, 1559,

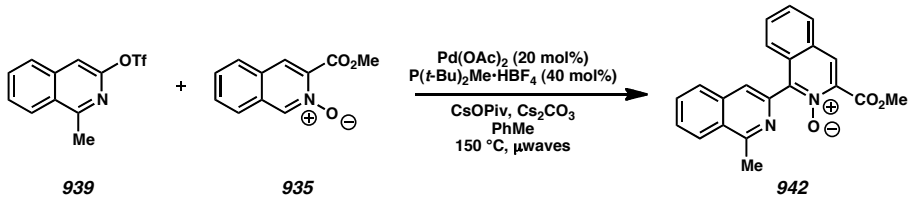
1439, 1320, 1290, 1208, 1180, 1135, 1077, 918, 796, 754 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_3N$ $[M+H]^+$: 204.0655, found 204.0647.



938 *939*

Isoquinoline triflate 939

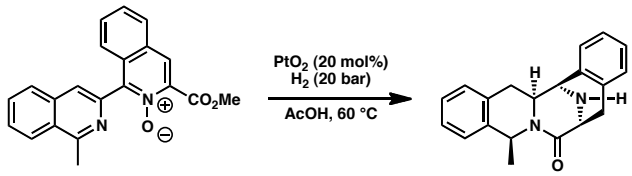
A suspension of 3-hydroxyisoquinoline **938** (250 mg, 1.57 mmol) in CH_2Cl_2 (16 mL) was cooled to 0 °C. Pyridine (1.27 mL, 15.7 mmol) was added, followed by Tf_2O (528 μL, 3.14 mmol). The reaction was maintained at 0 °C until 3-hydroxyisoquinoline **938** was fully consumed by TLC analysis. At that time, the reaction was quenched at 0 °C by the addition of a saturated solution of $NaHCO_3$ (6 mL) and then allowed to warm to room temperature. The reaction was then diluted with diethyl ether (25 mL) and washed sequentially with water (25 mL), saturated NH_4Cl (25 mL), and brine (25 mL). The organics were dried with Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (25:1 hexanes:ethyl acetate eluent) to yield isoquinoline triflate **939** (441.3 mg, 97% yield): R_f = 0.45 (5:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.76 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.66 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.41 (s, 1H), 2.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.12, 151.16, 138.40, 131.34, 128.01, 127.61, 127.47, 125.98, 118.77 (q, *J* = 320.5 Hz), 108.82, 21.99; IR (NaCl/film) 3073, 2961, 2927, 1624, 1600, 1562, 1506, 1421, 1327, 1213, 1139, 1116, 988, 957, 890, 833, 741 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_9O_3NSF_3$ $[M+H]^+$: 292.0250, found 292.0261.



Bis-isoquinoline 942

Palladium acetate (6 mg, 0.027 mmol) was added to a flame-dried microwave vial containing cesium carbonate (87 mg, 0.267 mmol), cesium pivalate (40 mg, 0.177 mmol), and di-*tert*-butylmethylphosphonium tetrafluoroborate (13 mg, 0.053 mmol). The vessel was sealed, and then evacuated and backfilled with an atmosphere of argon three times. Next, toluene (0.5 mL) was added to the reaction vial, which was subsequently heated to 50 °C in an oil bath. The suspension was maintained at this temperature for 30 minutes with vigorous stirring. Concomitant to this step, isoquinoline triflate **939** (26 mg, 0.089 mmol) was added to a flask containing isoquinoline *N*-oxide **935** (36 mg, 0.177 mmol). This flask was sealed with a rubber septum, and evacuated and backfilled with an atmosphere of argon three times. Toluene (0.5 mL) was added to the flask under an argon atmosphere. After the palladium suspension had stirred for 30 minutes at 50 °C, the solution had turned from clear to pale yellow. Upon cooling to room temperature, the isoquinoline solution was added via syringe to the microwave vessel, with care given to prevent exposure to the air. Next, the microwave vial was heated in the microwave at 150 °C for 2 hours. At the completion of this step, the contents filtered over a short plug of celite. The crude residue was purified by preparatory TLC (1:49:50 Et_3N:hexanes:ethyl acetate eluent) to yield bis-isoquinoline **942**: R_f = 0.41 (1:49:50 Et_3N:hexanes:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 8.63–8.51 (m, 2H), 8.19 (s, 1H), 8.16 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H),

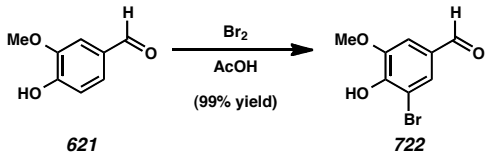
7.77–7.57 (m, 4H), 4.00 (s, 3H), 3.02 (s, 3H); HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{21}H_{17}O_3N_2$ $[M+H]^+$: 345.1234, found 345.1228.



942 ***954***

Pentacycle 954

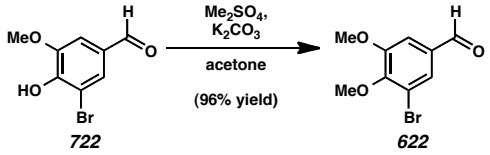
Bis-isoquinoline **942** was dissolved in glacial acetic acid in a 1 dram vial with a stir bar. To this solution was added PtO_2 (20 mol%) and the resulting suspension was stirred vigorously. The reaction vial was placed in a 24-well high-pressure autoclave with H_2 attached via a regulator. The autoclave was pressurized to 20 bar with H_2 and then evacuated to remove O_2. This purging process was repeated twice more. The autoclave was then pressurized to 20 bar with H_2, placed onto a stir plate, and heated at 60 °C for 36 hours. TLC analysis showed complete consumption of bis-isoquinoline **942** at that time. The reaction was cooled to room temperature and filtered over a celite plug while washing with ethyl acetate. The crude product was purified by flash chromatography (1:1 hexanes:ethyl acetate eluent) to provide lactam **954**.



621 *722*

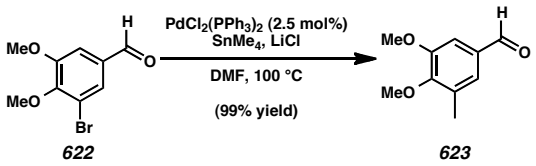
3-Bromovanillin (722)

The following procedure was adopted from a literature report by Rao and Stuber.[55] A single-neck, 2 L round-bottom flask was charged with vanillin (**621**, 50 g, 328.6 mmol). Glacial acetic acid was added (1.1 L, 3.0 M). Following this, a mechanical stirrer was affixed to the flask through the neck and, with vigorous but even stirring, the vanillin dissolved to form a pale yellow solution. At this point, neat bromine (16.84 mL, 361.5 mmol) was added in a rapid dropwise fashion to the stirring solution through the flask neck to produce a deep red-orange solution. Following addition, the reaction was maintained with vigorous stirring for 90 minutes, after which time TLC analysis indicated formation of the product (R_f = 0.32, 15% ethyl acetate in hexanes). The reaction also resulted in the formation of a bright orange-yellow precipitate when nearing completion. Upon completion of the reaction, the mechanical stirrer was disengaged and the contents of the reaction flask were poured onto chilled deionized water (0 °C, 600 mL), resulting in further precipitation of a pale yellow solid from the bright orange aqueous layer. The reaction flask was washed into this flask with more chilled water. While still cooled, the contents of the 1 L Erlenmeyer flask were filtered over a glass frit to separate the desired solid product. The isolated solid product (**722**, 75.25 g, 99% yield) was transferred to a flask and dried under vacuum for a period of 8 hours.



3-bromo-4,5-dimethoxy benzaldehyde (622)

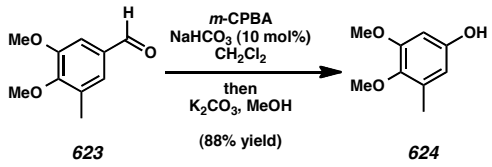
To a 1 L round-bottom flask was added anhydrous K_2CO_3 (113.56 g, 821.6 mmol), followed by a solution of bromobenzaldehyde **722** (75.25 g, 325.66 mmol) in reagent grade acetone (700 mL). A mechanical stirrer was affixed to the reaction flask, and vigorous stirring was required to generate an evenly distributed, maroon suspension. To this stirring mixture was added Me_2SO_4 (77.74 mL, 821.69 mmol) over 1 minute via funnel. The reaction was left to stir vigorously at 25 °C for 8 hours, at which point TLC analysis confirmed the conversion of phenol **722** to a less polar product. The reaction contents were then vacuum filtered over a glass frit to separate residual solid K_2CO_3. The filtered solid was washed with acetone (2 x 100 mL) and methanol (100 mL). The organic filtrate was concentrated to an orange oil and purified by flash chromatography (5% → 50% ethyl acetate in hexanes eluent) to yield bromobenzaldehyde **622** (76.6 g, 96% yield), which was isolated as a white powder: R_f = 0.56 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.67 (d, J = 1.80 Hz, 1H), 7.40 (d, J = 1.85 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.83, 154.17, 151.81, 133.03, 128.77, 117.92, 110.09, 60.83, 56.25; IR (NaCl/film) 2945, 2860, 1692, 1588, 1566, 1486, 1469, 1452, 1420, 1393, 1380, 1312, 1281, 1240, 1212, 1144, 1133, 1048, 993, 855, 840 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_9H_9BrO_3$ $[M]^+$: 243.9735, found 243.9731.



3,4-dimethoxy-5-methylbenzaldehyde (623)

A 250 mL round-bottom flask was charged with lithium chloride (4.32 g, 102.00 mmol) and then flame dried. To this flask was added a solution of benzaldehyde **622** (5.0 g, 20.40 mmol) in *N*,*N*-dimethylformamide (200 mL) that had been rigorously sparged with argon. Next, $PdCl_2(PPh_3)_2$ (0.358 g, 0.51 mmol) was added to the stirring mixture, producing a bright yellow-orange solution that was stirred vigorously. A reflux condenser was affixed to the top of the reaction flask before adding, dropwise, neat tetramethyltin (7.06 mL, 51.0 mmol). The reaction vessel was sealed under an argon atmosphere and heated to reflux in 100 °C oil bath. The reaction was maintained at reflux for 3 hours; during this period the color of the solution changed to dark red-orange.[60] TLC analysis of the reaction after this period showed full consumption of the starting material. The reaction was cooled to room temperature and then quenched by the addition of H_2O (200 mL). The aqueous layer was thoroughly extracted with ethyl acetate (5 x 200 mL), and the combined organic layers were washed with brine (150 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to furnish benzaldehyde **623** as a colorless oil (3.63 g, 99% yield): $R_f = 0.42$ (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.17 (d, J = 1.71 Hz, 1H), 7.16 (d, J = 0.60 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.14, 153.02, 152.70, 126.95, 108.79, 60.05, 55.65, 15.75; IR (NaCl/film) 2939, 2833, 1693, 1586,

1491, 1465, 1422, 1387, 1329, 1299, 1233, 1140, 1096, 1003, 856 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{12}O_3$ $[M]^+$: 180.0786, found 180.0779.

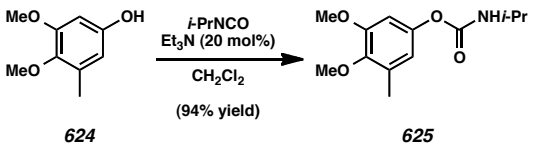


623 *624*

3,4-dimethoxy-5-methylphenol (624)

A 250 mL round-bottom flask was charged with anhydrous $NaHCO_3$ (0.467 g, 0.56 mmol). To this, was added a solution of benzaldehyde **623** (1.00 g, 5.55 mmol) in CH_2Cl_2 (11 mL). This mixture was vigorously stirred until the $NaHCO_3$ fully dissolved. At this point, *m*-CPBA (1.92 g, 11.10 mmol) was added as a solid in a single portion to the pale yellow solution. Immediately, the solution turned bright yellow, and was maintained with stirring at 25 °C under an atmosphere of N_2. Notable accumulation of precipitate resulted in increasing turbidity of the solution, and after 6 hours, TLC analysis indicated formation of a new product (R_f = 0.22, hexanes) and consumption of benzaldehyde **623**. At this time, methanol (110 mL) and anhydrous K_2CO_3 (2.30 g, 16.65 mmol) were added, and the solution turned maroon in color. The reaction was maintained at 25 °C for 12 hours, resulting in formation of a new polar product. The reaction was stopped by concentration under vacuum to yield a dark maroon solid. This solid was dissolved in H_2O (100 mL), and then neutralized with concentrated aqueous HCl (6 mL). **Warning:** vigorous gas evolution. The resulting suspension was extracted with CH_2Cl_2 (5 x 100 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 200 mL) to remove benzoate byproducts. The organic

layers were dried with Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (30% ethyl acetate in hexanes eluent) to provide phenol **624** (0.822 g, 4.89 mmol, 88% yield) as a white solid: R_f = 0.30 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, J = 2.80 Hz, 1H), 6.20 (d, J = 2.80 Hz, 1H), 4.53 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.36, 151.78, 141.12, 132.41, 108.36, 98.17, 60.35, 55.69, 15.85; IR (NaCl/film) 3272, 2957, 1614, 1483, 1463, 1440, 1430, 1348, 1268, 1226, 1219, 1196, 1181, 1154, 1096, 1001, 854, 772, 737 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_9H_{12}O_3$ $[M]^+$: 168.0786, found 168.0753.

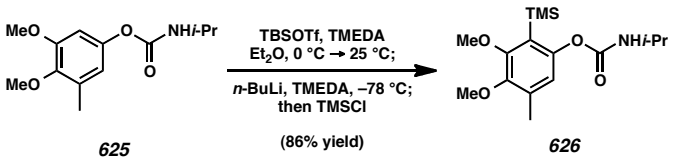


624 ***625***

Isopropyl carbamate 625

This procedure was adopted from the literature procedure reported by Bronner, et al.[57] A 100 mL round-bottom flask was charged with a solution of phenol **624** (1.696 g, 10.08 mmol) in CH_2Cl_2 (35 mL). The solution was stirred at 25 °C under an atmosphere of N_2 before neat isopropyl isocyanate (1.483 mL, 15.12 mmol) was added via syringe. The solution turned orange, and after 5 minutes of stirring, freshly distilled Et_3N (0.281 mL, 2.02 mmol) was added via syringe to effect the formation of a dark purple solution. The reaction was maintained with stirring for 18 hours at 25 °C. Following this period, TLC analysis showed conversion of phenol **624** to a single product. The reaction was concentrated to an orange-brown residue and purified by flash chromatography (5% ethyl acetate in hexanes eluent) to provide isopropyl carbamate **625** as a clear, pale yellow oil

(2.404 g, 94% yield): R_f = 0.48 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, J = 2.65 Hz, 1H), 6.54 (d, J = 2.65 Hz, 1H), 2.79 (s, 1H), 3.87 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.24 (s, 3H), 1.23 (d, J = 7.25 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.92, 152.87, 146.66, 144.62, 115.29, 104.21, 60.15, 55.78, 43.44, 22.93, 15.91; IR (NaCl/film) 3326, 2972, 2936, 1715, 1604, 1529, 1490, 1466, 1422, 1332, 1220, 1190, 1175, 1142, 1095, 1050, 1009, 936, 854, 773 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{13}H_{19}NO_4$ $[M]^+$: 253.1314, found 253.1319.

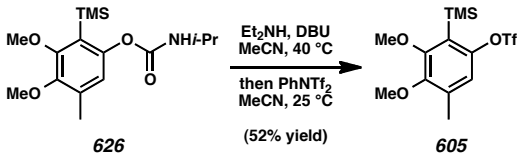


625 ***626***

TMS carbamate 626

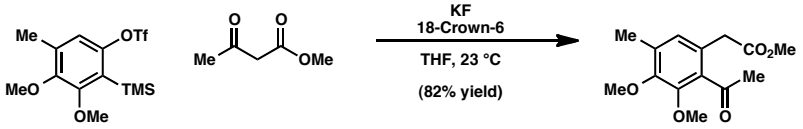
This procedure was adopted from the literature procedure reported by Bronner, et al.[57] To a 25 mL round-bottom flask was added a solution of isopropyl carbamate **625** (2.404 g, 9.49 mmol) in diethyl ether (94 mL), followed by freshly distilled TMEDA (1.56 mL, 10.44 mmol) via syringe. The solution was cooled to 0 °C in an ice water bath. Upon temperature equilibration (15 minutes), neat distilled TBSOTf (2.398 mL, 10.44 mmol) was added. The resulting solution was maintained for 10 minutes at 0 °C and then the flask was allowed to warm to 23 °C over 30 minutes. At this point, TLC analysis showed formation of a less polar product (R_f = 0.81, 15% ethyl acetate in hexanes) corresponding to the *N*-silylated intermediate. Additional TMEDA was added to the mixture via syringe (5.688 mL, 37.964 mmol). The reaction was then cooled to –78 °C in a dry ice and acetone bath with vigorous stirring to avoid aggregation of triflate salts.

Next, *n*-BuLi solution (2.32 M in hexanes, 16.36 mL, 37.96 mmol) was added dropwise down the side of the flask of the cold solution. The solution was maintained with stirring at –78 °C for 4 hours, after which time freshly distilled TMSCl (8.432 mL, 66.437 mmol) was added dropwise to the flask. The reaction vessel, in the cold bath, was allowed to warm to 23 °C over the course of two hours. At this point, TLC analysis indicated the presence of a single, new product. Saturated aqueous $NaHSO_4$ solution (50 mL) was added and stirred with the reaction mixture for 1 hour. The layers were separated and the organic layer was washed with an additional 50 mL of the $NaHSO_4$ solution. The combined aqueous layers were then extracted with diethyl ether (3 x 50mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and then concentrated under vacuum to a colorless crystalline solid. Purification via flash chromatography (5% → 20% ethyl acetate in hexanes eluent) provided pure TMS carbamate **626** (2.63 g, 86% yield): R_f = 0.63 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.69 (d, J = 7.08 Hz, 1H), 3.89 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.23 (s, 3H), 1.23 (d, J = 6.75, 6H), 0.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.69, 153.00, 149.33, 147.28, 133.33, 121.79, 118.88, 59.19, 58.54, 42.27, 21.88, 14.83, 0.13; IR (NaCl/film) 3326, 2971, 2937, 1710, 1601, 1530, 1464, 1384, 1370, 1324, 1247, 1220, 1193, 1179, 1080, 1026, 987, 844, 810, 759 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{27}NO_4Si$ $[M+H]^+$: 326.1734, found 326.1725.



Silyl aryl triflate 605

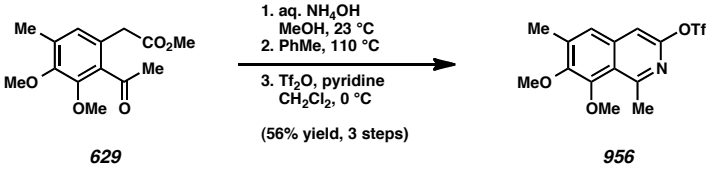
This procedure was adopted from the literature procedure reported by Bronner, et al.[57] A 250 mL round-bottom flask was charged with a solution of TMS carbamate **626** (2.63 g, 8.10 mmol) in acetonitrile (80 mL). To this was added diethylamine (1.01 mL, 9.71 mmol), followed by DBU (1.82 mL, 12.14 mmol). The reaction was carefully monitored by TLC as it was heated to 40 °C in an oil bath. After 10 minutes, TLC anaylsis indicated complete consumption of the starting material and conversion to two spots (R_{f1} = 0.78 and R_{f2} = 0.60).[61] The reaction was immediately removed from the oil bath and a solution of $PhNTf_2$ (4.34 g, 12.14 mmol) in acetonitrile (24 mL) was added via syringe. The reaction was maintained with stirring for 12 hours at 23 °C, after which point the reaction solution was washed with saturated aqueous $NaHSO_4$ (2 x 50 mL) and brine (100 mL). The organic extract was dried over $MgSO_4$, concentrated under vacuum to an orange oil, and purified via flash chromatography (5% ethyl acetate in hexanes eluent) to yield silyl aryl triflate **605** (1.57 g, 52% yield) as a pale yellow oil: R_f = 0.68 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.27 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.72, 150.74, 149.21, 135.84, 117.49 (q, J = 320 Hz), 124.53, 117.96, 60.79, 60.03, 16.43, 1.41; ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.10; IR (NaCl/film) 2956, 2858, 1600, 1464, 1420, 1383, 1368, 1292, 1248, 1213, 1179, 1142, 1068, 1023, 982, 930, 873, 846, 764 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{13}H_{19}F_3O_5SSi$ $[M]^+$: 372.0675, found 372.0674.



605 ***229*** ***629***

Ketoester 629

Silyl aryl triflate **605** (500 mg, 1.34 mmol) was added to a solution of methyl acetoacetate (**229**, 132 μL, 1.22 mmol), KF (160 mg, 2.74 mmol) and 18-crown-6 (758 mg, 2.86 mmol) in THF (15 mL) at 23 °C. The reaction was maintained at this temperature for 16 hours, at which time TLC analysis indicated complete consumption of both silyl aryl triflate **605** and methyl acetoacetate (**229**). The solution was diluted with diethyl ether (50 mL) and washed with saturated aqueous sodium chloride (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated to a yellow oil. Purification of this residue by flash chromatography (10% EtOAc in hexanes eluent) furnished ketoester **629** (295 mg, 82% yield) as a clear, colorless oil: R_f = 0.49 (4:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.61 (s, 2H), 2.55 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.50, 172.03, 150.77, 150.33, 134.38, 134.07, 128.57, 126.65, 61.17, 60.08, 52.00, 37.76, 32.26, 15.89; IR (NaCl/film) 2951, 2849, 1740, 1692, 1604, 1568, 1484, 1451, 1437, 1400, 1351, 1306, 1269, 1200, 1167, 1147, 1078, 1040, 1012 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 267.1227, found 267.1233.



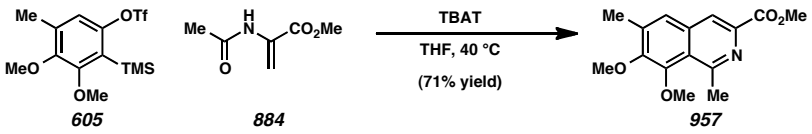
629 ***956***

Isoquinoline triflate 956

Ketoester **629** (50 mg, 0.188 mmol) was dissolved in MeOH (2 mL) in a Schlenk flask with a sealable top. To this was added 28–30% aqueous ammonium hydroxide (10 mL, 80 mmol), and the flask was sealed. The reaction was maintained at 23 °C with vigorous stirring for 30 min. At this point, TLC analysis indicated the complete consumption of the starting material, and the reaction was stopped by concentration under vaccuum. The resulting orange-yellow residue was taken up in PhMe (10 mL) and heated to 110 °C for 18 hours. The reaction was then cooled and concentrated under vaccuum. The crude product was used without further purification in the next step.

The crude starting material was dissolved in dry CH_2Cl_2 (8 mL). To this solution, was added pyridine (1.75 mL, 18.80 mmol), and the reaction was cooled to 0 °C in an ice bath under an atmosphere of nitrogen. Triflic anhydride (63 μL, 0.376 mmol) was added dropwise to the cold solution, which was maintained at 0 °C for 30 minutes. At this time, TLC analysis indicated complete consumption of the starting material. The reaction was quenched at 0 °C by the addition of saturated aqueous $NaHCO_3$ (10 mL) followed by warming to 23 °C. The mixture was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated under vaccuum. The resulting residue was purified by flash chromatography (10% ethyl acetate in hexanes eluent) to furnish isoquinoline triflate **956** (38 mg, 56% yield, 3 steps): $R_f = 0.83$ (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.21 (s, 1H), 3.98

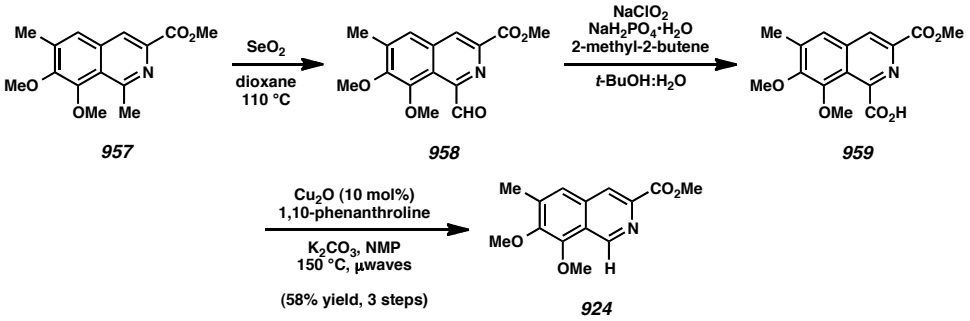
(s, 3H), 3.93 (s, 3H), 3.07 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ158.61, 151.01, 150.42, 149.87, 139.22, 136.77, 123.56, 122.86, 118.73 (q, J = 320 Hz), 107.60, 60.73, 60.13, 26.63, 16.93; IR (NaCl/film) 2961, 2924, 2853, 1604, 1552, 1452, 1413, 1377, 1352, 1332, 1260, 1208, 1094, 1059, 1016, 966, 940, 799, 699 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 366.0618, found 366.0637.



Isoquinoline 957

To a round-bottomed flask containing methyl-2-acetamidoacrylate (**884**, 50 mg, 0.349 mmol) and TBAT (141 mg, 0.262 mmol) stirring in THF (35 mL) at 23 °C was added silyl aryl triflate **605** (66 mg, 0.175 mmol) via syringe. The flask was maintained at 23 °C for 8 hours until amidoacrylate **884** had been fully consumed by TLC analysis. At this point, the reaction was stopped by dilution with methanol (20 mL) and adsorption of the resultant mixture onto silica gel (1 g) under vacuum. The resulting powder was purified by flash chromatography (2.5% → 10% ethyl acetate in CH_2Cl_2 eluent) to furnish isoquinoline **957** (34 mg, 71% yield) as an off-white powder: R_f = 0.35 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.51 (s, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.09 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.62, 157.80, 152.53, 149.72, 139.37, 138.12, 133.88, 125.11, 124.12, 122.20, 60.82, 60.19, 52.80, 27.49, 16.92; IR (NaCl/film) 2948, 2852, 1735, 1715, 1617, 1559, 1487, 1450, 1437, 1396, 1355, 1328, 1261, 1218, 1194, 1131, 1091, 1057, 1010, 998, 907, 874,

782 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 276.1230, found 276.1245.



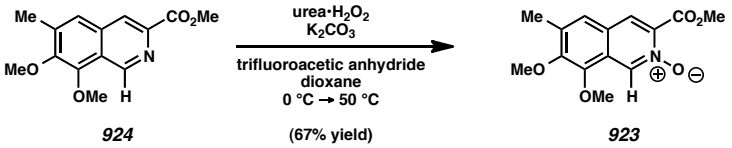
Isoquinoline 924

A solution of isoquinoline **957** (20 mg, 0.073 mmol) in dioxane (1 mL) was added to selenium dioxide (16 mg, 0.146 mmol) in a flame-dried round-bottomed flask containing a stir bar. A reflux condenser was attached, and the colorless suspension was vigorously stirred while heating to reflux (110 °C) under a nitrogen atmosphere. The reaction was maintained for 30 minutes at reflux, by which time the reaction had turned red-orange and appeared complete by TLC analysis. The flask was then cooled to room temperature and diluted with ethyl acetate (20 mL). The suspension was filtered through a short plug of celite to remove residual solids and then concentrated under vacuum. This crude mixture was purified by flash chromatography (25% ethyl acetate in hexanes eluent) to yield aldehyde **958** (19 mg, 88% yield) as a clear oil: R_f = 0.28 (1:1 ethyl acetate:hexanes).

Aldehyde **958** (19 mg, 0.064 mmol) was suspended in a mixture of *t*-BuOH (1.3 mL) and 2-methyl-2-butene (0.406 mL, 3.840 mmol). To this suspension was added a solution of $NaH_2PO_4 \bullet H_2O$ (141 mg, 1.024 mmol) and $NaClO_2$ (58 mg, 0.640 mmol) in

H_2O (1.3 mL). The biphasic solution was vigorously stirred for 28 hours, after which time TLC analysis indicated complete consumption of aldehyde **958**. The reaction was diluted with ethyl acetate (100 mL), and washed with water (150 mL). The aqueous layer was extracted with ethyl acetate (5 x 100 mL), until the persistent yellow color of the aqueous layer disappeared. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to provide isoquinoline carboxylic acid **959** (18 mg, 94% yield), which was used without further purification.

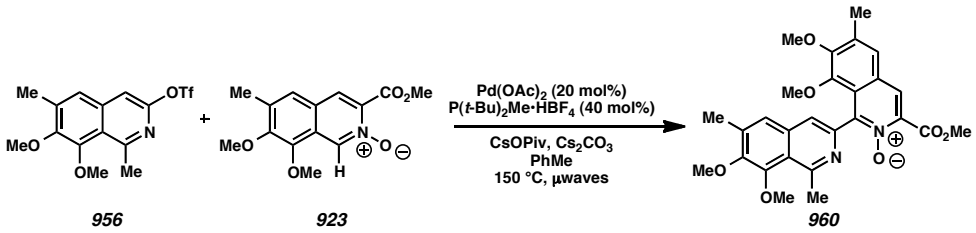
A solution of isoquinoline carboxylic acid **959** (18 mg, 0.060 mmol) in *N*-methyl pyrrolidinone (1 mL) was added to a microwave vial containing cuprous oxide (1 mg, 0.006 mmol), 1,10-phenanthroline (2 mg, 0.012 mmol), and K_2CO_3 (17 mg, 0.120 mmol). The vial was sealed and heated to 150 °C at a maximum power of 400 W for 30 minutes. The resulting brown suspension was diluted with ethyl acetate (10 mL) and filtered through a silica plug. The filtrate was added to brine (25 mL) and extracted with ethyl aetate (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to provide a brown residue. Purification via flash chromatography (30% ethyl acetate in hexanes eluent) yielded isoquinoline **924** (11 mg, 70% yield): $R_f = 0.32$ (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.44 (s, 1H), 7.52 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 4.01 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.55, 147.46, 147.16, 140.85, 139.20, 132.70, 124.82, 124.09, 123.04, 109.98, 61.59, 60.48, 52.81, 17.36; IR (NaCl/film) 2949, 2855, 1738, 1717, 1620, 1570, 1483, 1456, 1418, 1386, 1321, 1285, 1257, 1196, 1141, 1105, 1085, 1006, 984, 906, 818, 802, 777cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 262.1074, found 262.1070.



924 (67% yield) ***923***

Isoquinoline *N*-oxide 923

To a flame-dried round-bottomed flask with a large stirring bar containing urea•H_2O_2 (288 mg, 3.06 mmol) and K_2CO_3 (530 mg, 3.82 mmol) was added dioxane (7.5 mL). The suspension was stirred at 23 °C for 15 minutes before being cooled to 0 °C in an ice/water bath. To this suspension, trifluoroacetic anhydride (0.425 mL, 3.060 mmol) was added dropwise to maintain a consistent internal temperature. The reaction was maintained with stirring for 1 hour at 0 °C before transferring to an oil bath at 50 °C. After maintaining the suspension at 50 °C for 30 minutes, a solution of 1-*H*-isoquinoline **924** (40 mg, 0.153 mmol) in dioxane (7.5 mL) was added, and the reaction was maintained at 50 °C for 12 hours. After this time, TLC analysis indicated complete consumption of the isoquinoline, and the reaction was stopped by dilution with CH_2Cl_2 (100 mL). Water (50 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to a yellow oil. Purification by flash chromatography (1:10:10 NEt_3:ethyl acetate:hexanes eluent) provided the isoquinoline *N*-oxide **923** (28 mg, 67% yield): R_f = 0.12 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.88 (s, 1H), 7.36 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.48, 151.85, 144.27, 137.25, 133.10, 125.59, 124.99, 124.95, 123.53, 61.35, 60.48, 53.33, 30.96, 17.21; IR (NaCl/film) 2951, 2850, 1742, 1623, 1607, 1558, 1475, 1447, 1418, 1374, 1277, 1258, 1209, 1144, 1100, 1073, 1002, 958, 936, 828 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 278.1028, found 278.1034.



Bis-isoquinoline 960

Palladium acetate (0.75 mg, 0.0033 mmol) was added to a flame-dried microwave vial containing cesium carbonate (11 mg, 0.0328 mmol), cesium pivalate (4 mg, 0.0164 mmol), and di-*tert*-butylmethylphosphonium tetrafluoroborate (1.6 mg, 0.0065 mmol). The vessel was sealed, and then evacuated and backfilled with an atmosphere of argon three times. Next, toluene (0.5 mL) was added to the reaction vial, which was subsequently heated to 50 °C in an oil bath. The suspension was maintained at this temperature for 30 minutes with vigorous stirring. Concomitant to this step, isoquinoline triflate **956** (3 mg, 0.0082 mmol) was added to a flask containing isoquinoline *N*-oxide **923** (6 mg, 0.0164 mmol). This flask was sealed with a rubber septum, and evacuated and backfilled with an atmosphere of argon three times. Toluene (0.5 mL) was added to the flask under an argon atmosphere. After the palladium suspension had been stirred for 30 minutes at 50 °C, the solution had turned from clear to pale yellow. Upon cooling to room temperature, the isoquinoline solution was added via syringe to the microwave vessel, with care given to prevent exposure to the air. Next, the microwave vial was heated in the microwave at 150 °C for 2 hours. At the completion of this step, the contents were filtered over a short plug of celite. The crude residue was purified by preparatory TLC (1:49:50 Et_3N:hexanes:ethyl acetate) to yield bis-isoquinoline **960**: R_f =

0.55 (1:49:50 Et_3N:hexanes:ethyl acetate); HRMS (MM: ESI-APCI) *m*/*z* calc'd for $C_{27}H_{29}O_7N_2$ $[M+H]^+$: 493.1969, found 493.1980.

4.5 NOTES AND REFERENCES

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(60) Cessation of the reaction occurs when exposed to air, and large amounts of Pd(0) black deposits result in a grey solution and reduced yields.

(61) R_{f1} corresponds to the 2-TMS phenol, the desired cleavage product. R_{f2} corresponds to undesired des-TMS phenol **624**.

APPENDIX 4

Spectra Relevant to Chapter 4:

Progress Toward the Total Synthesis of Jorumycin

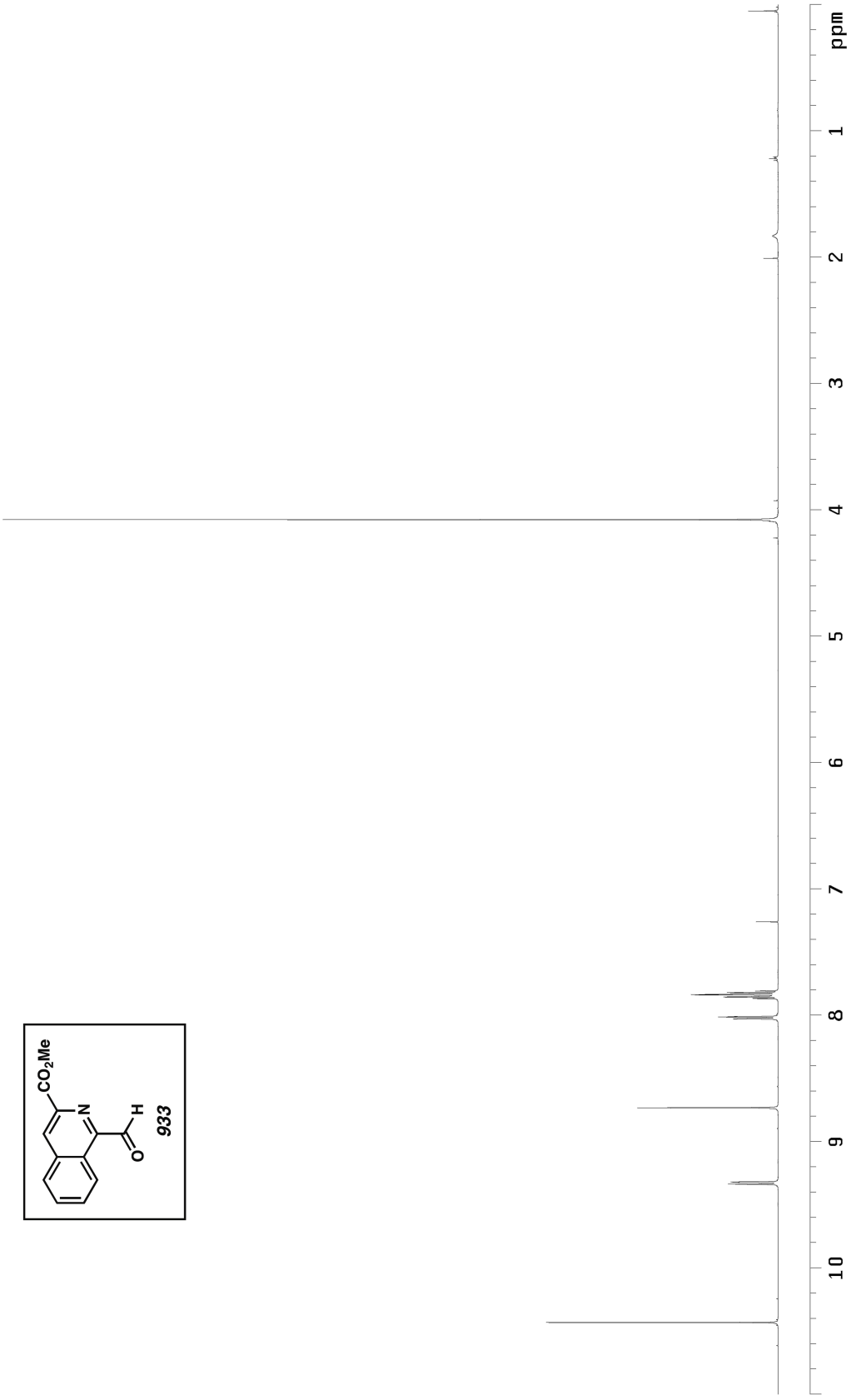

Figure A4.1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **933**.

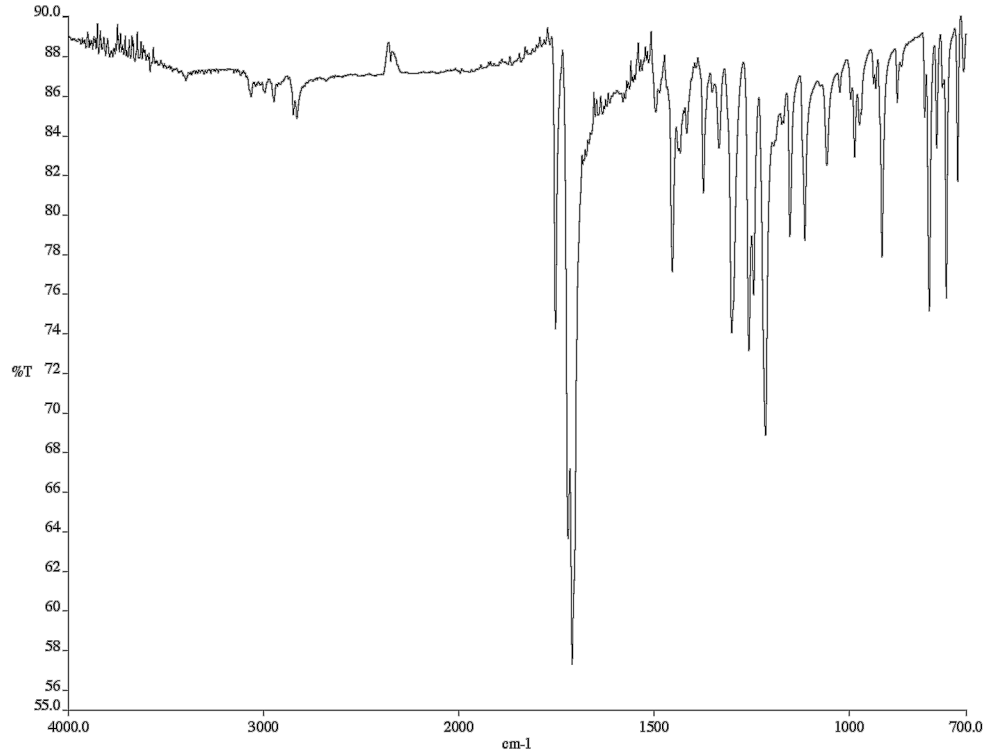

Figure A4.1.2 Infrared spectrum (thin film/NaCl) of compound **933**.

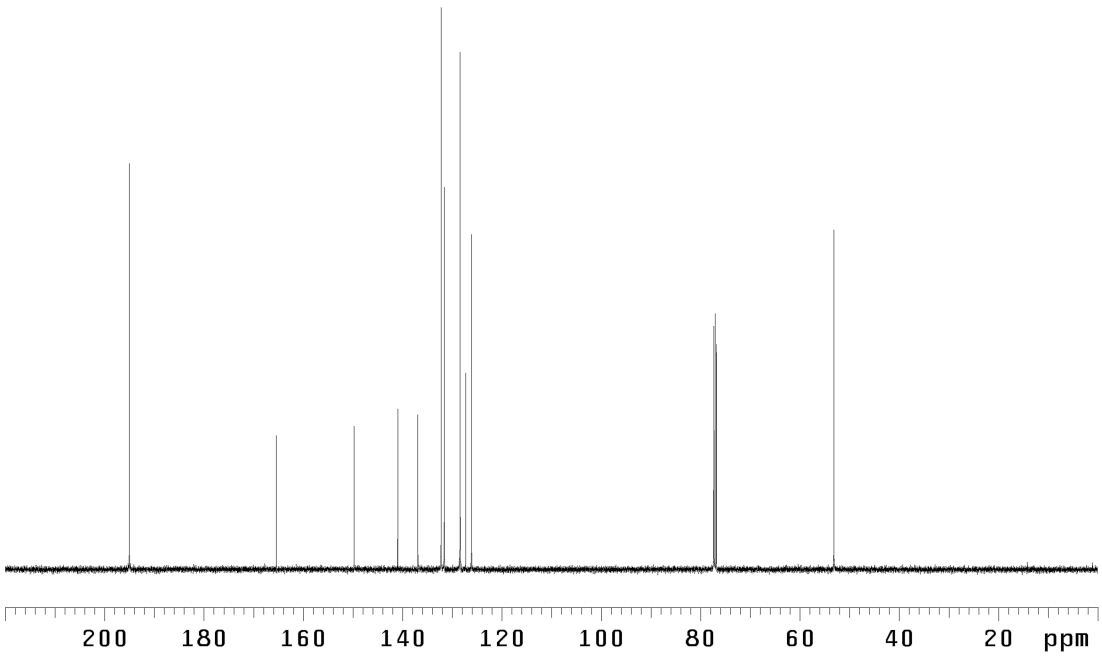

Figure A4.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **933**.

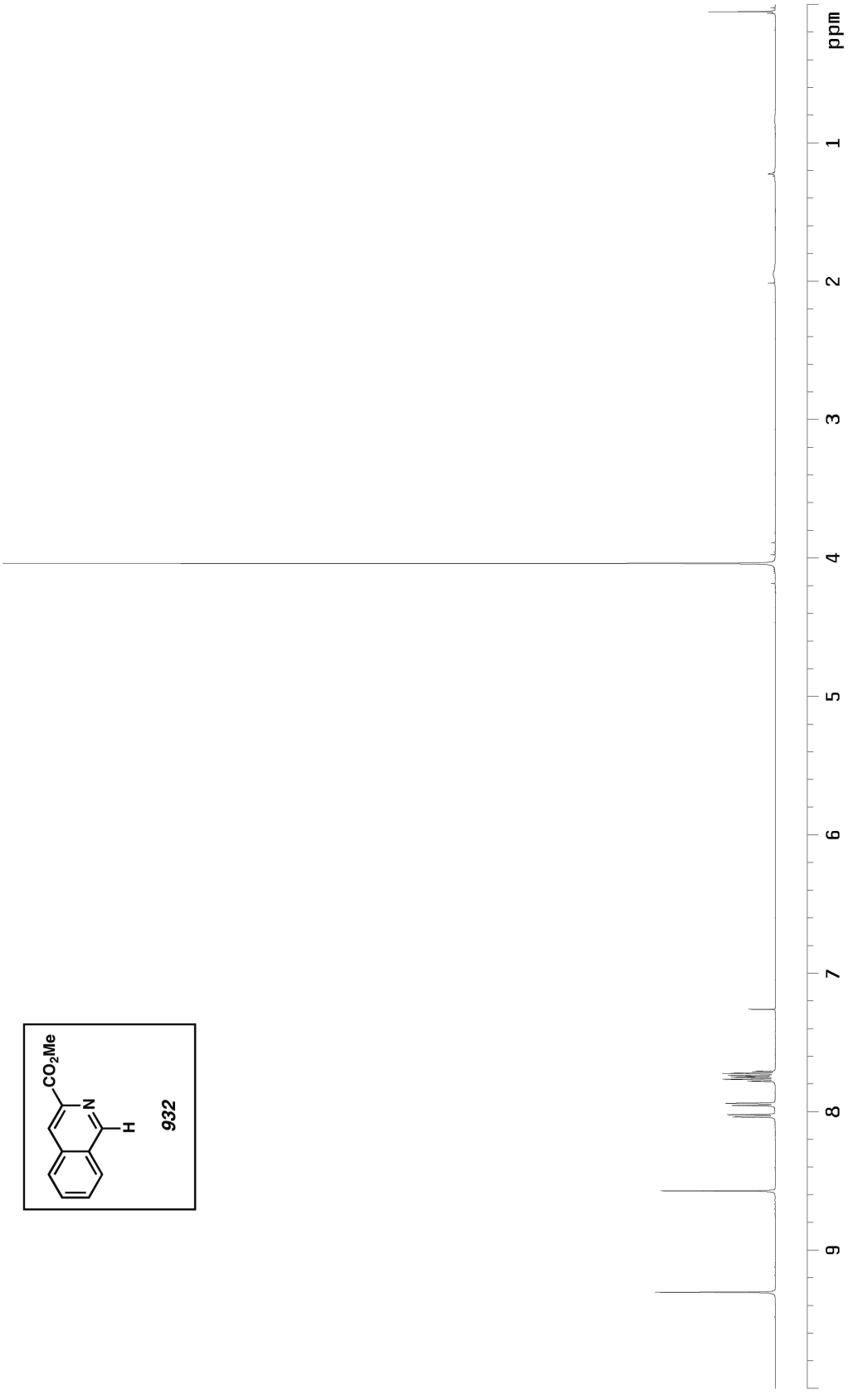

Figure A4.2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **932**.

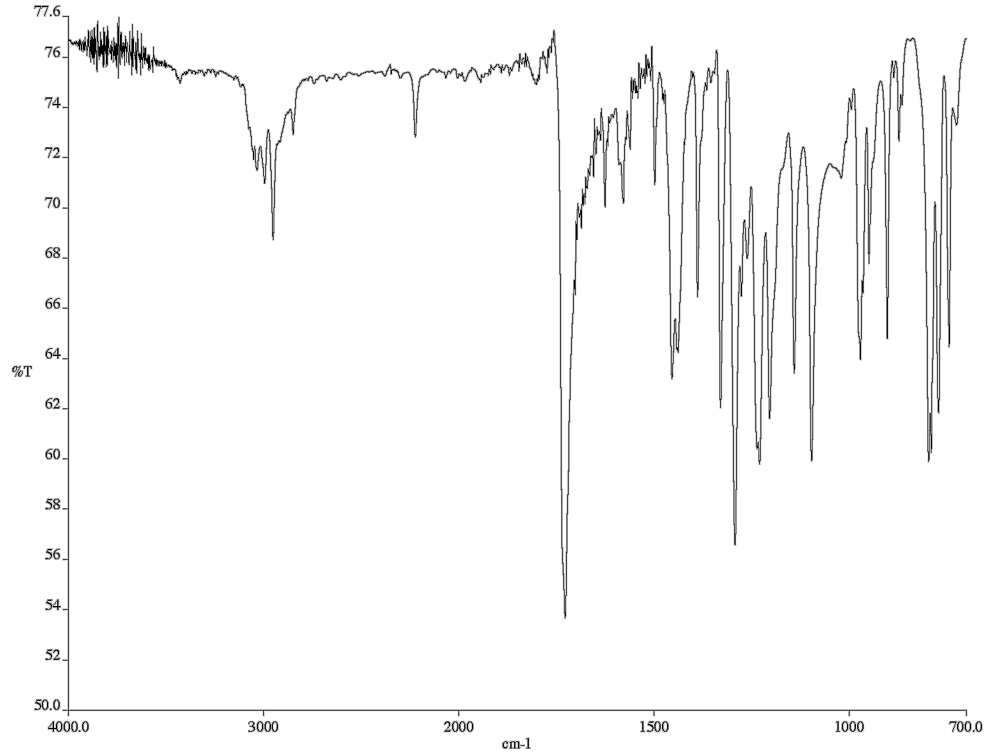

Figure A4.2.2 Infrared spectrum (thin film/NaCl) of compound **932**.

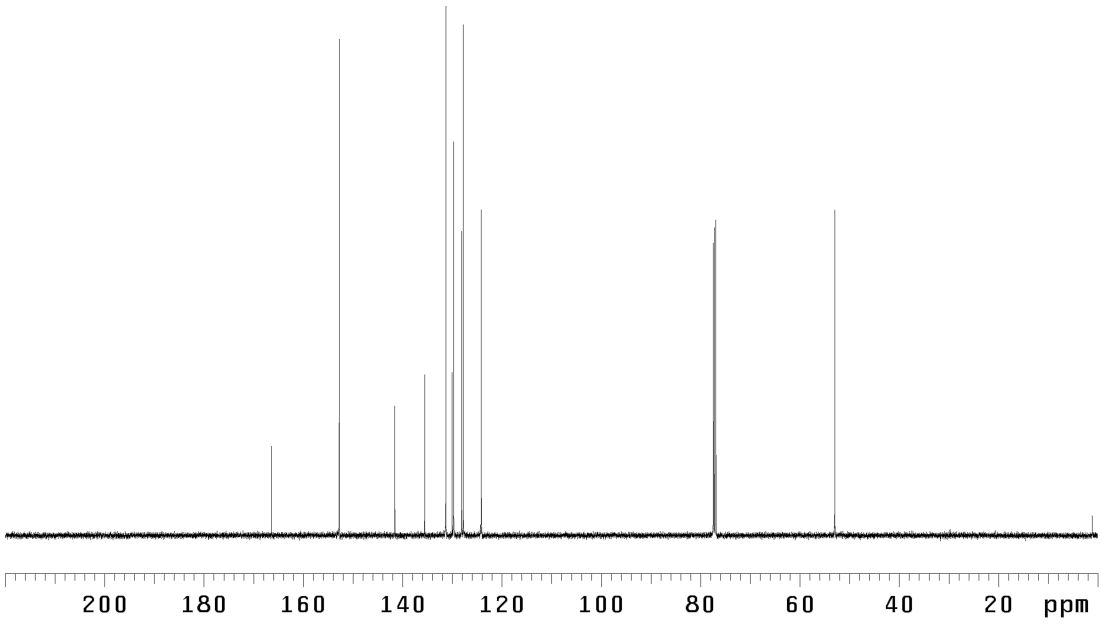

Figure A4.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **932**.

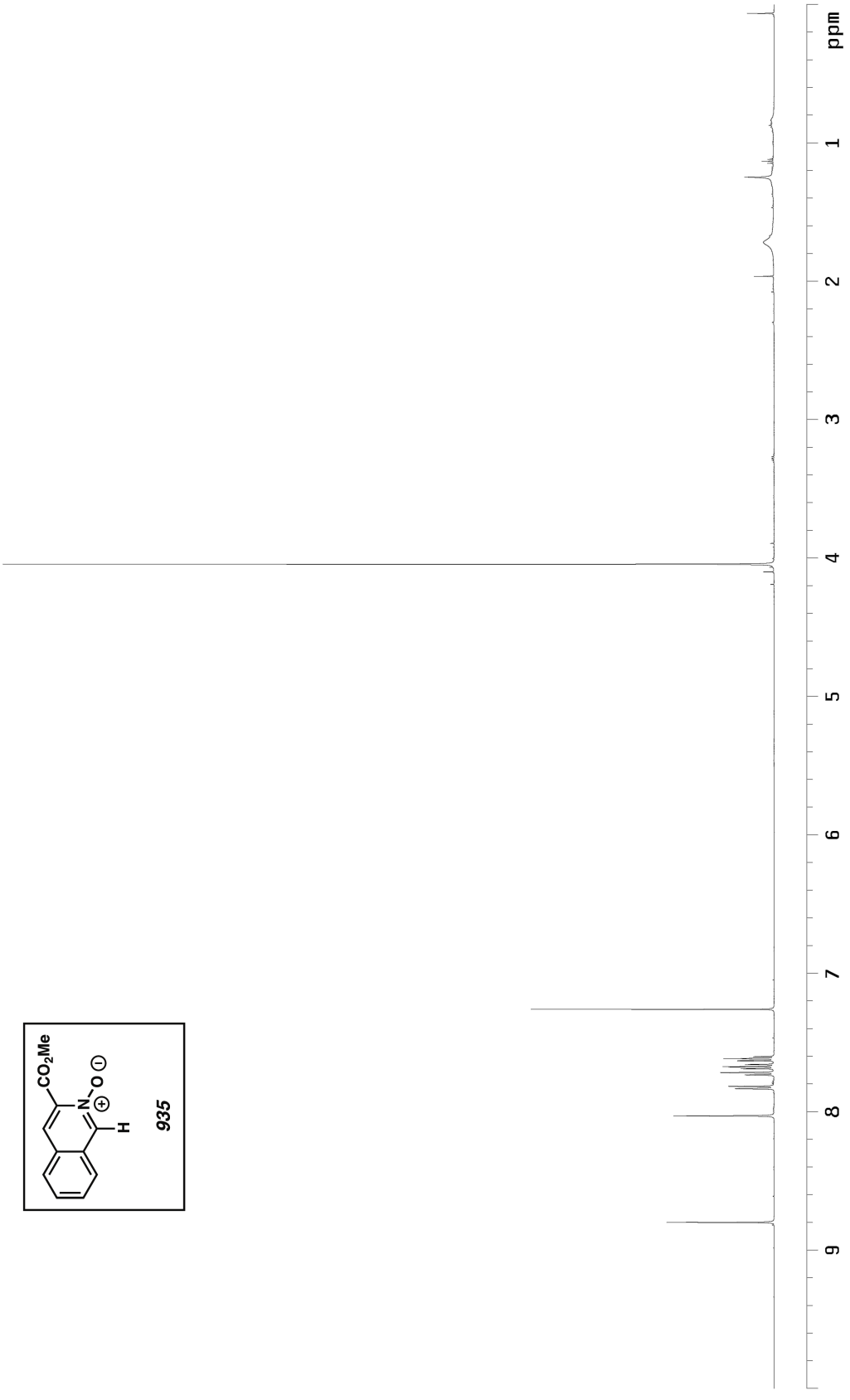

Figure A4.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **935**.

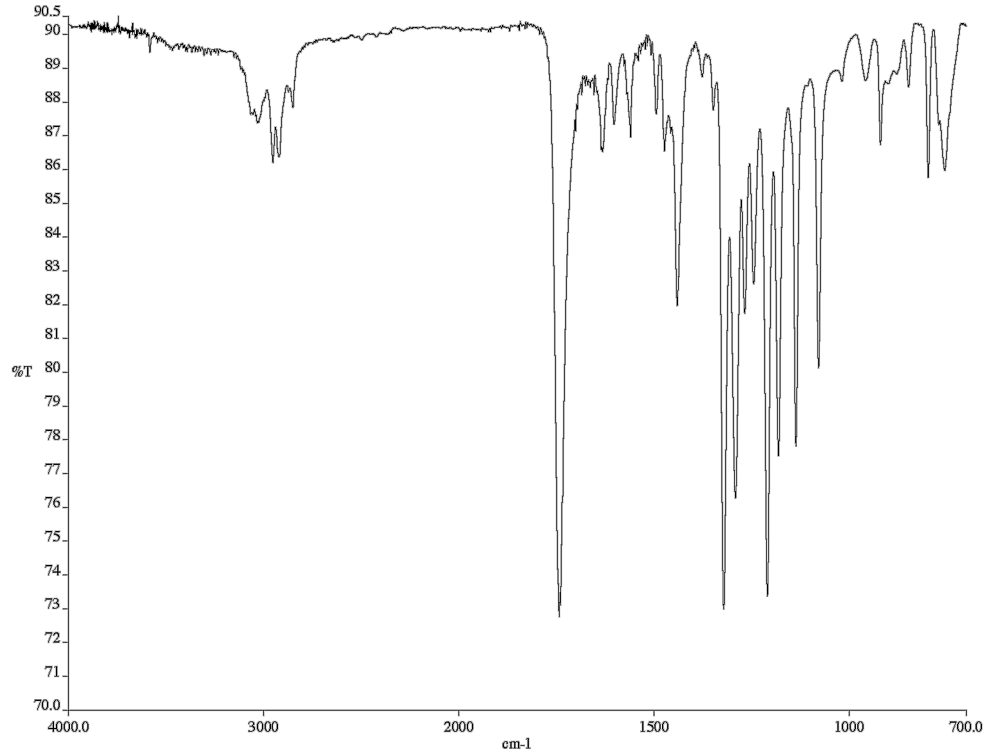

Figure A4.3.2 Infrared spectrum (thin film/NaCl) of compound **935**.

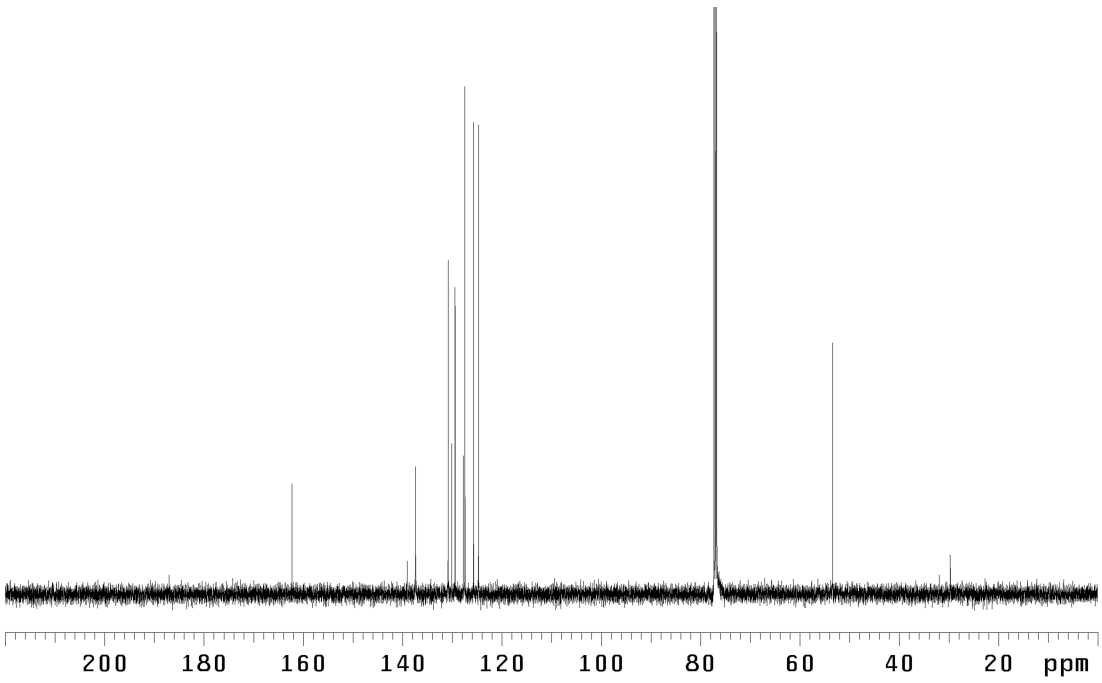

Figure A4.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **935**.

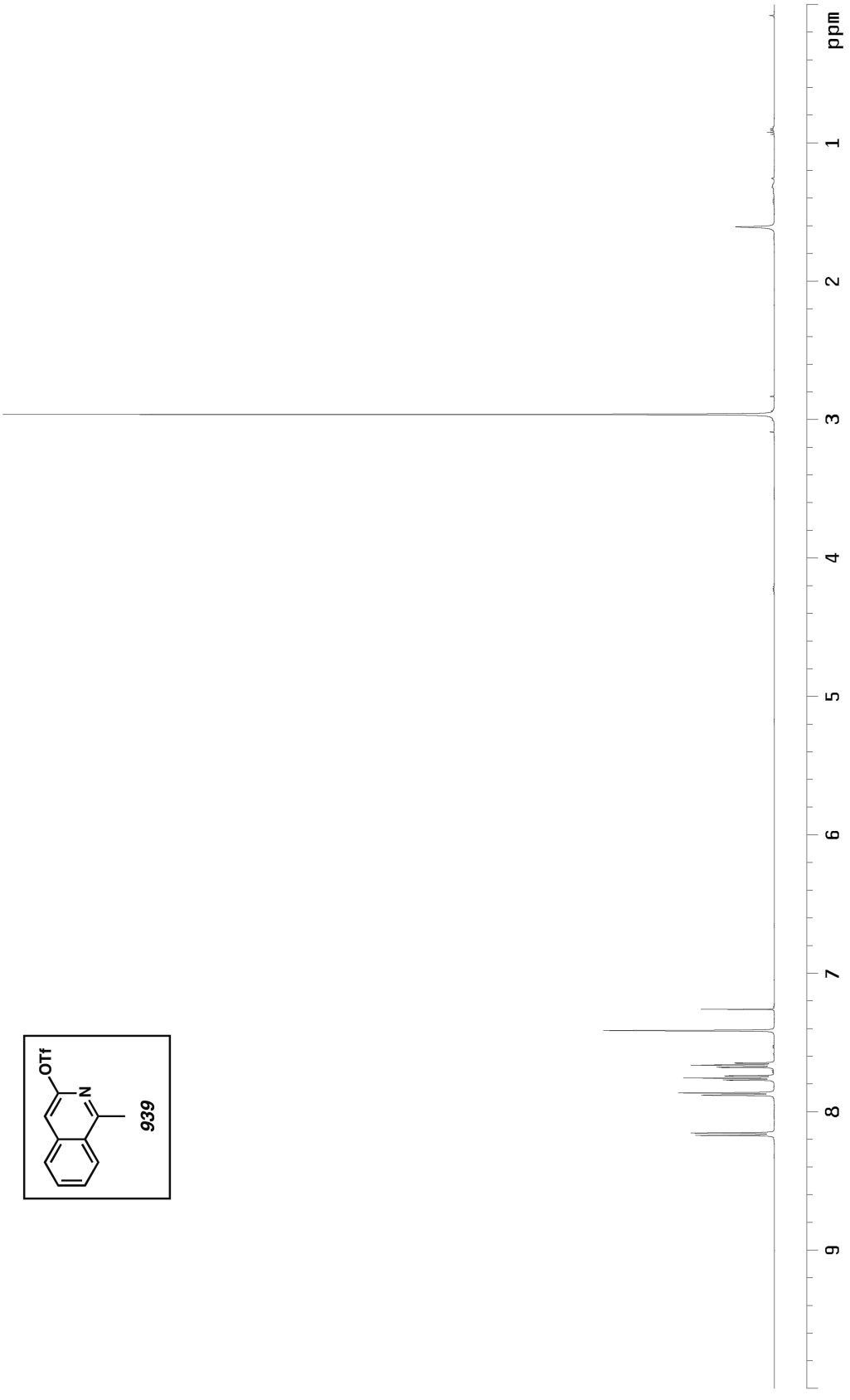

Figure A4.4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **939**.

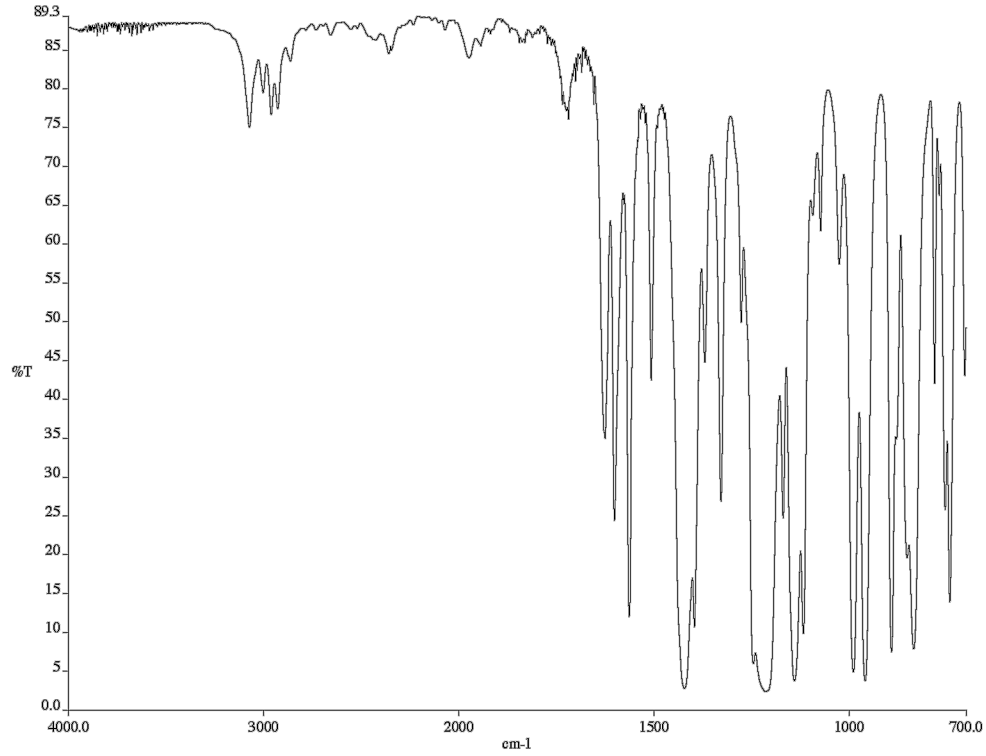

Figure A4.4.2 Infrared spectrum (thin film/NaCl) of compound **939**.

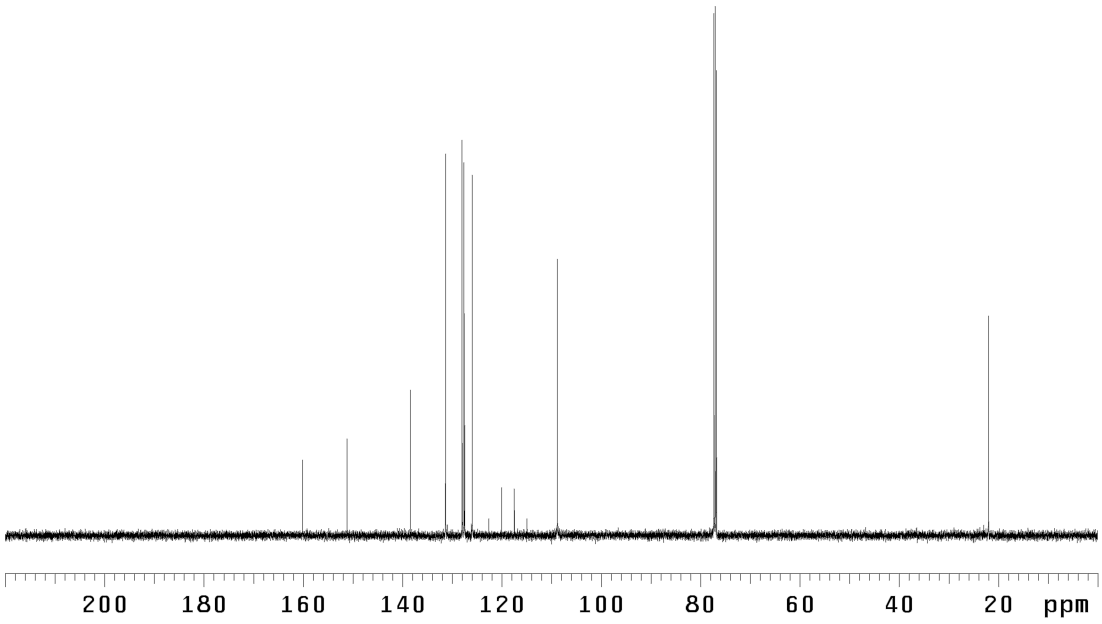

Figure A4.4.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **939**.

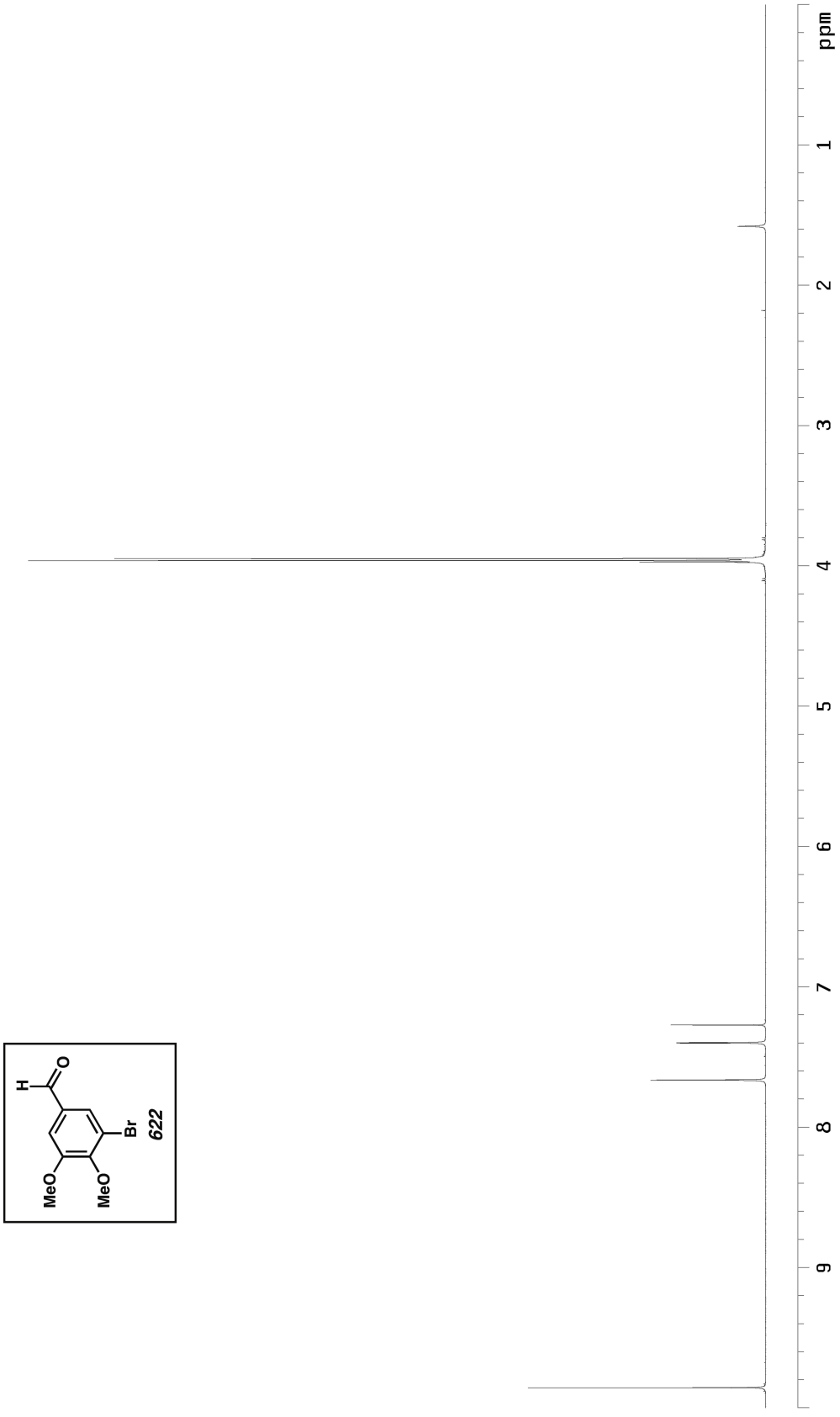

Figure A4.5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **622**.

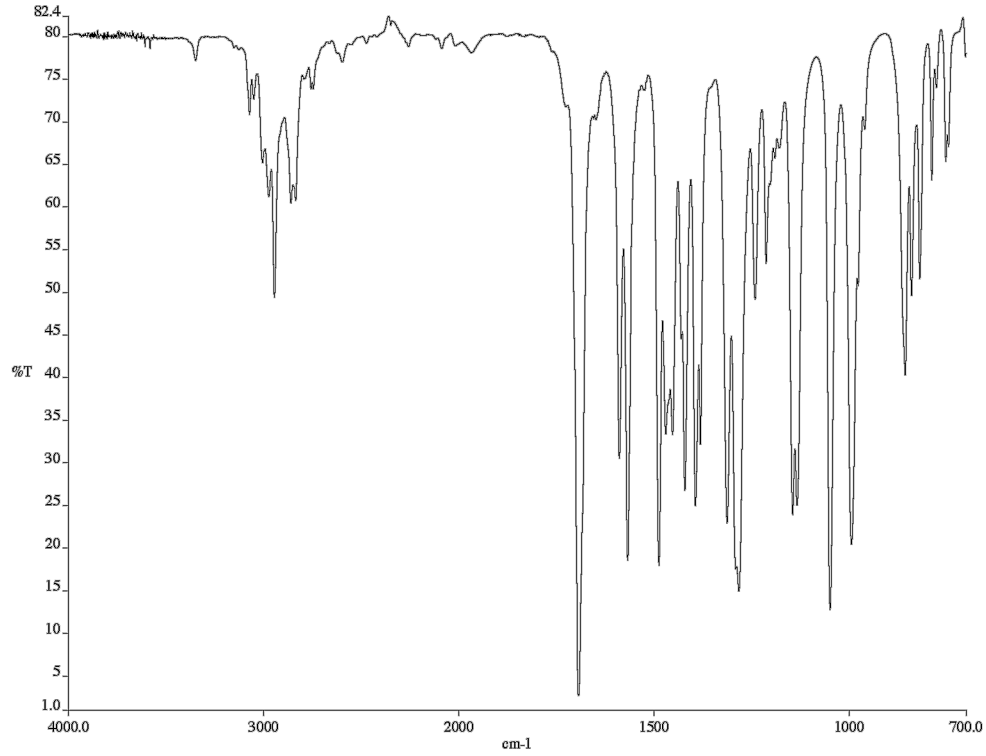

Figure A4.5.2 Infrared spectrum (thin film/NaCl) of compound **622**.

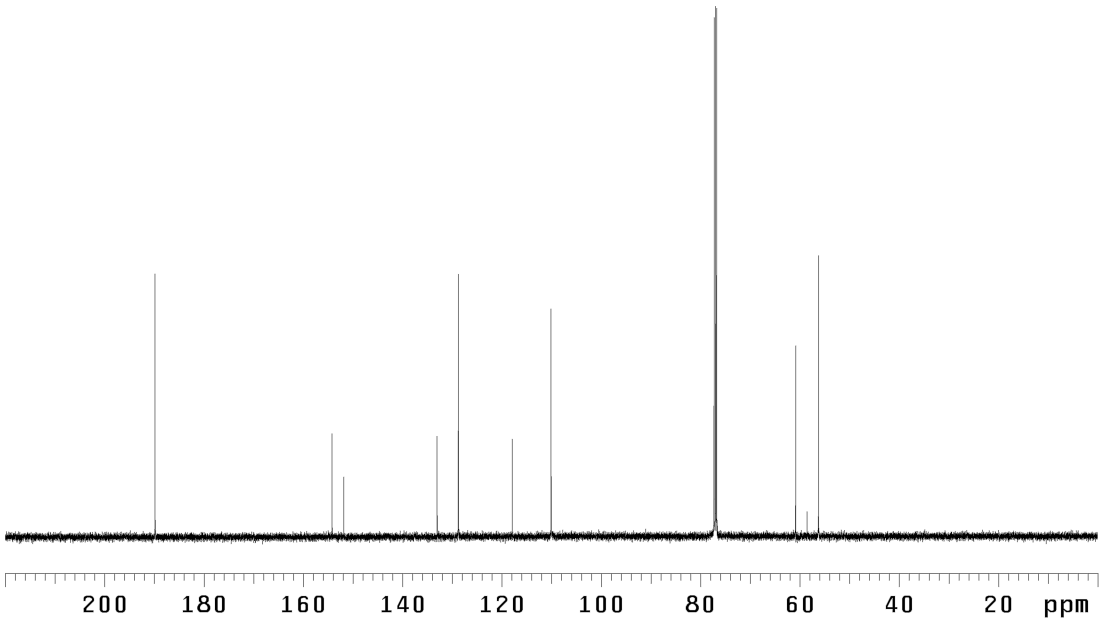

Figure A4.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **622**.

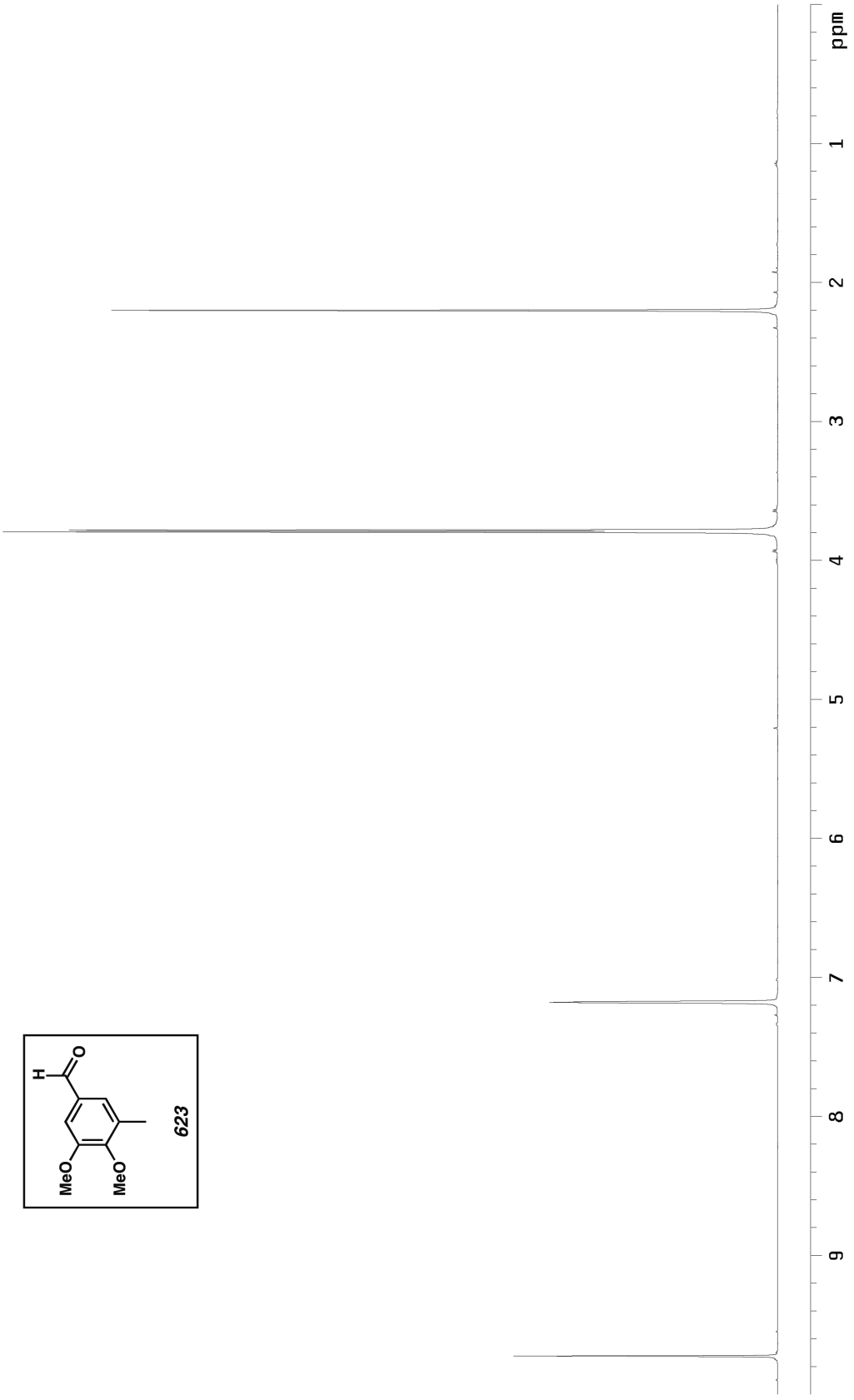

Figure A4.6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **623**.

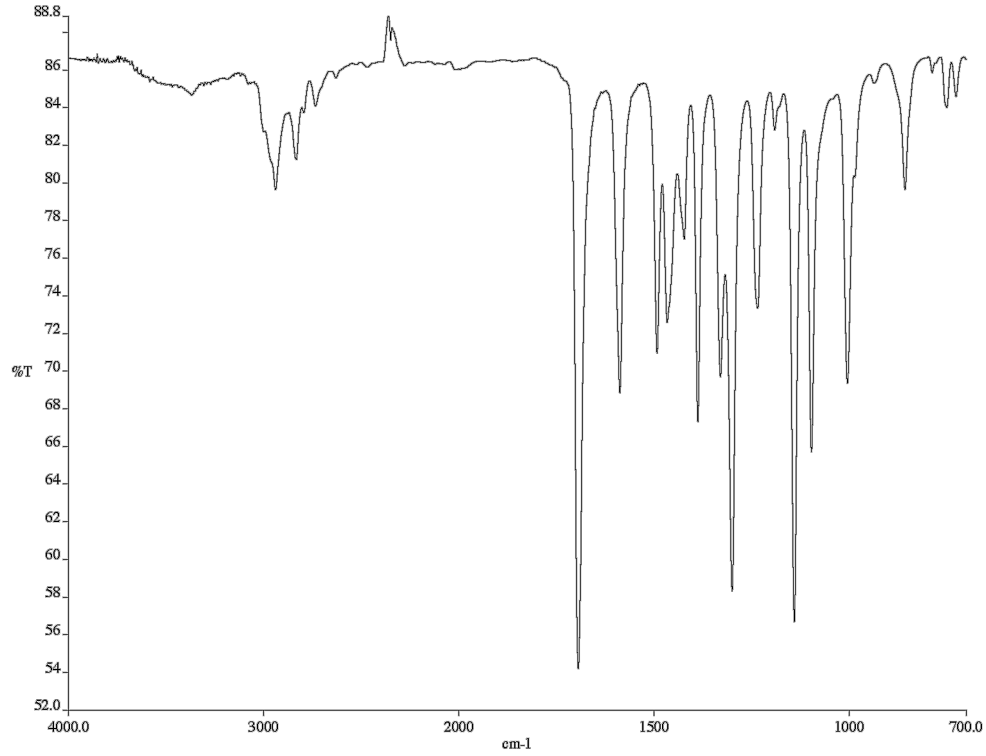

Figure A4.6.2 Infrared spectrum (thin film/NaCl) of compound **623**.

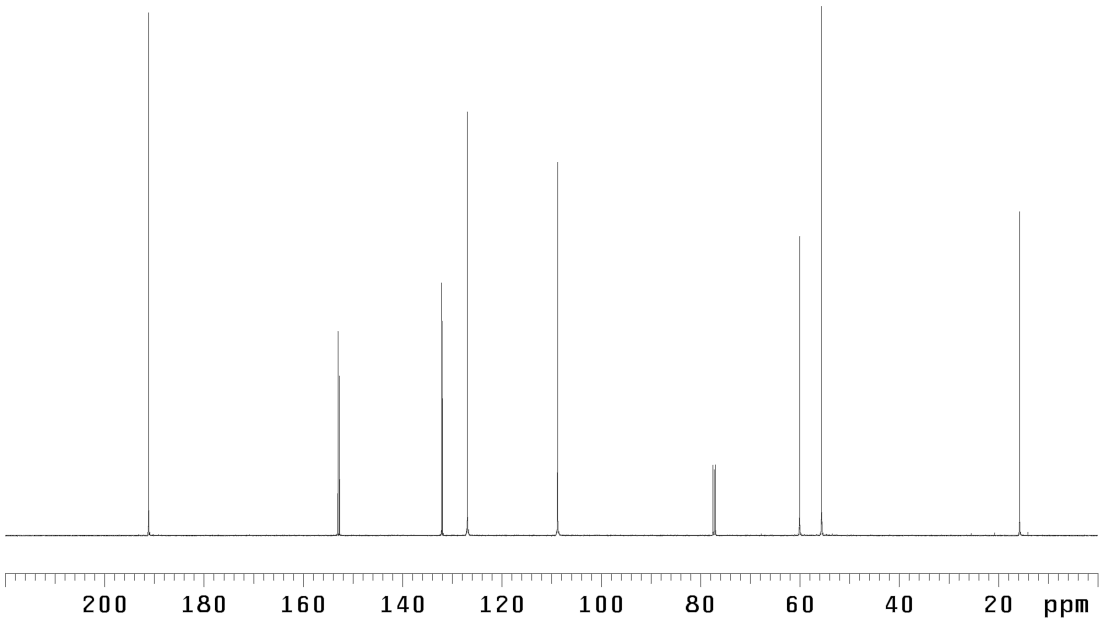

Figure A4.6.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **623**.

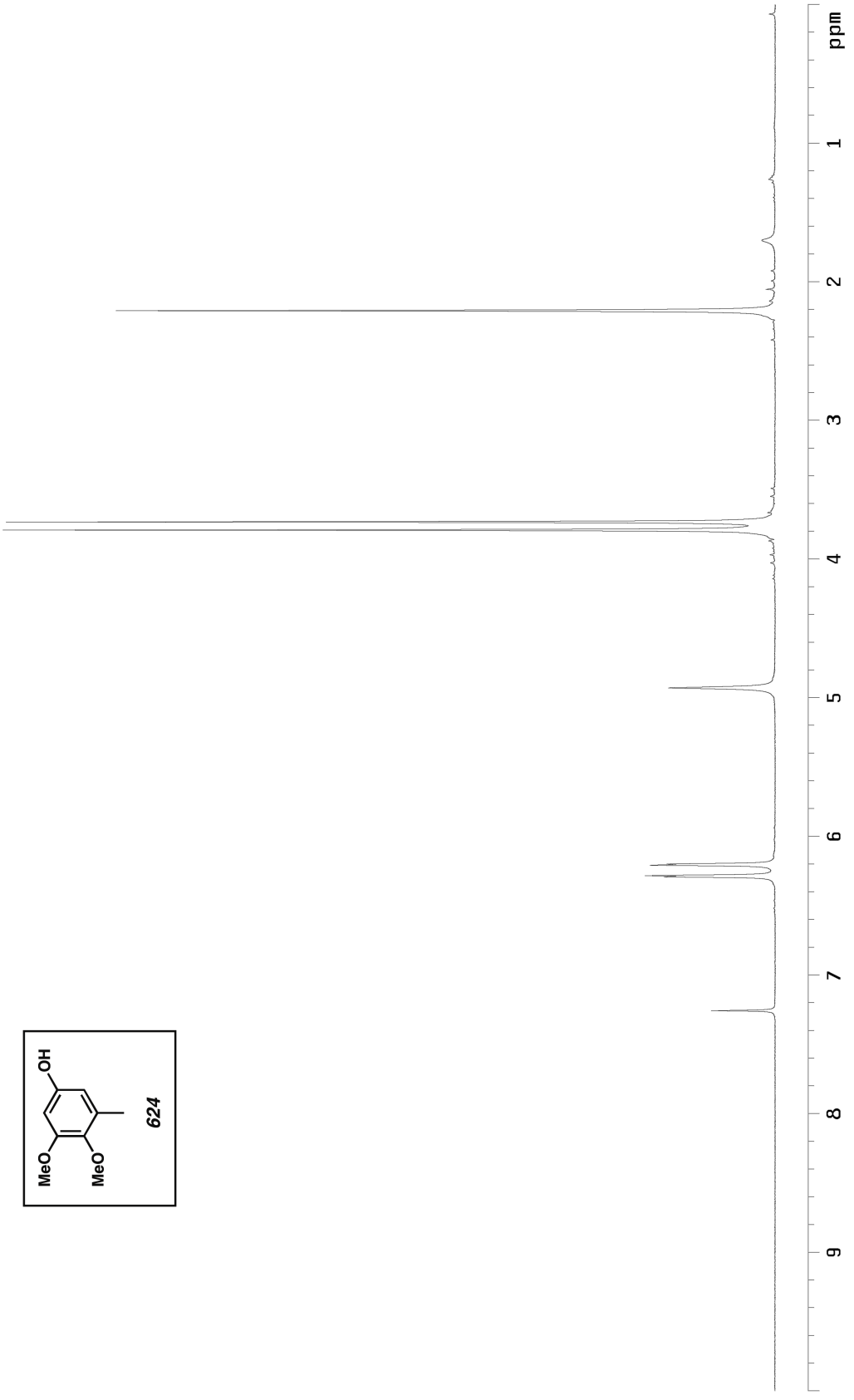

Figure A4.7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **624**.

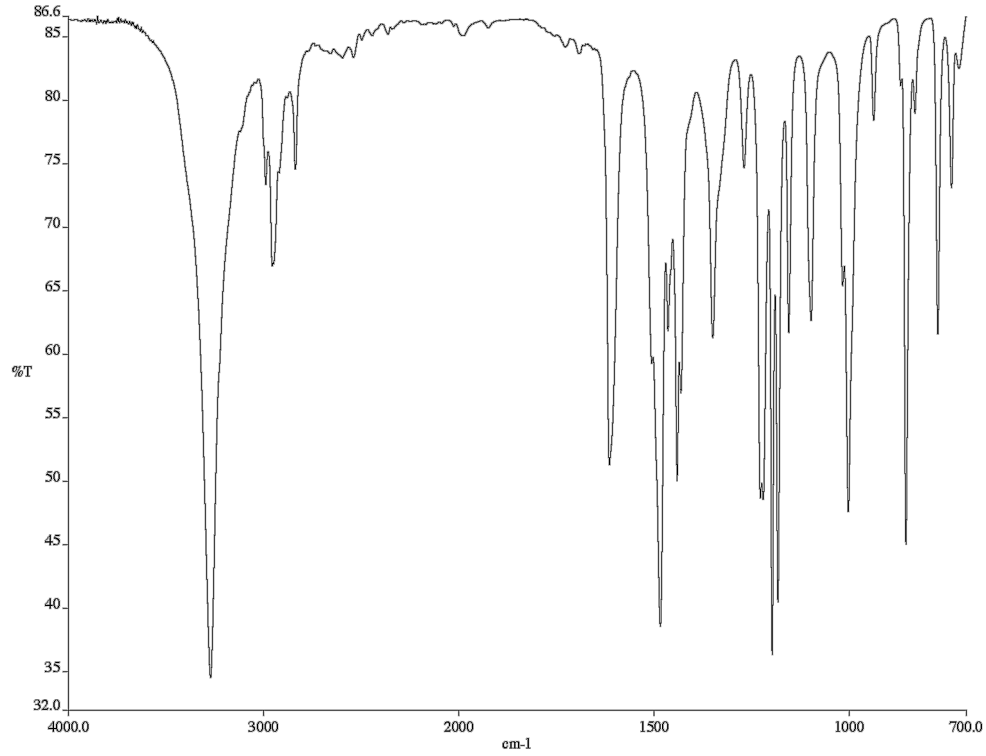

Figure A4.7.2 Infrared spectrum (thin film/NaCl) of compound **624**.

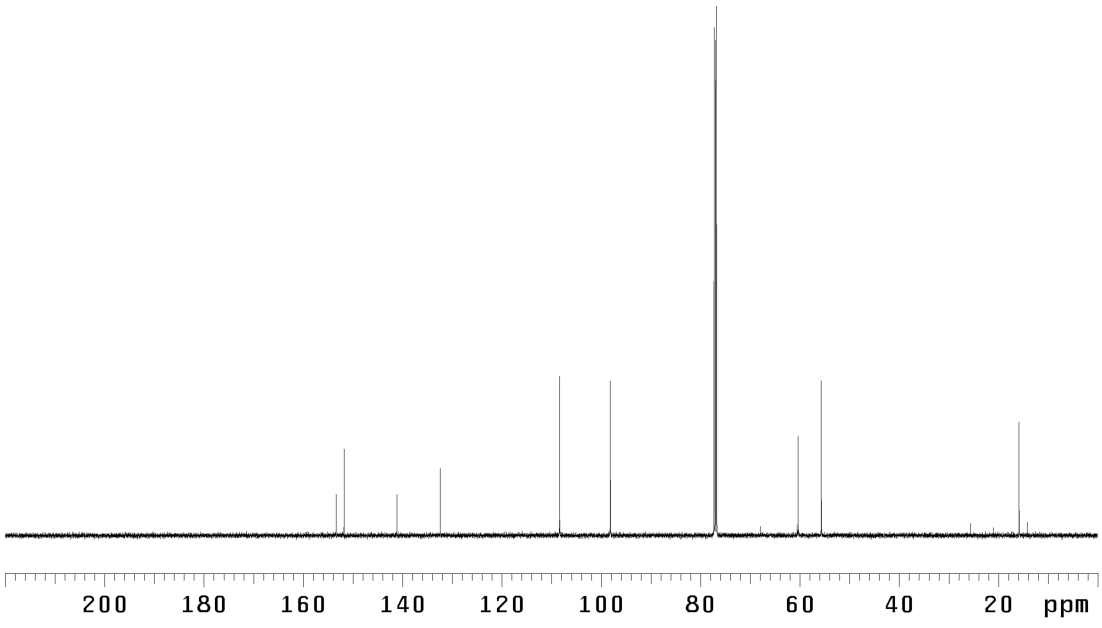

Figure A4.7.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **624**.

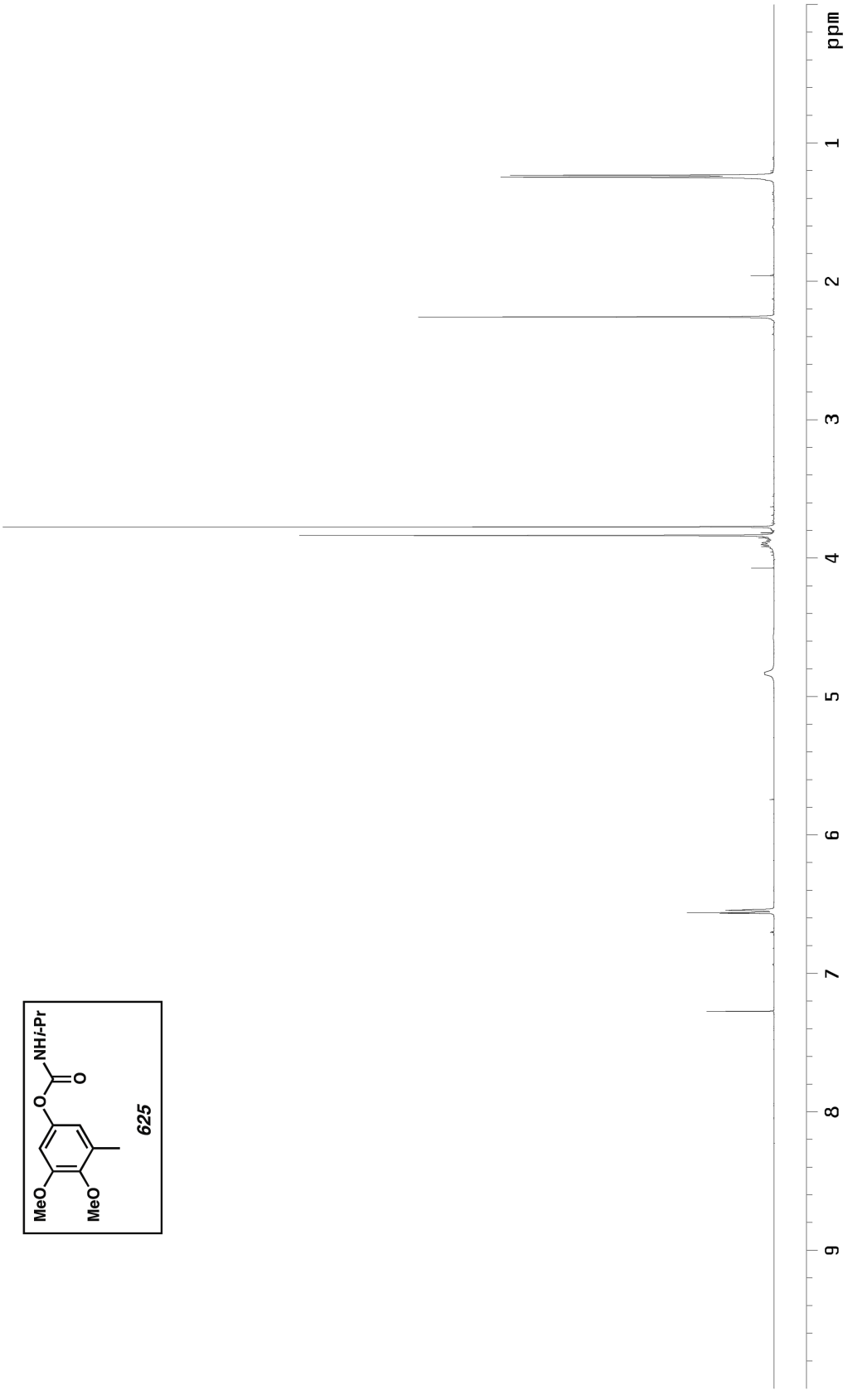

Figure A4.8.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **625**.

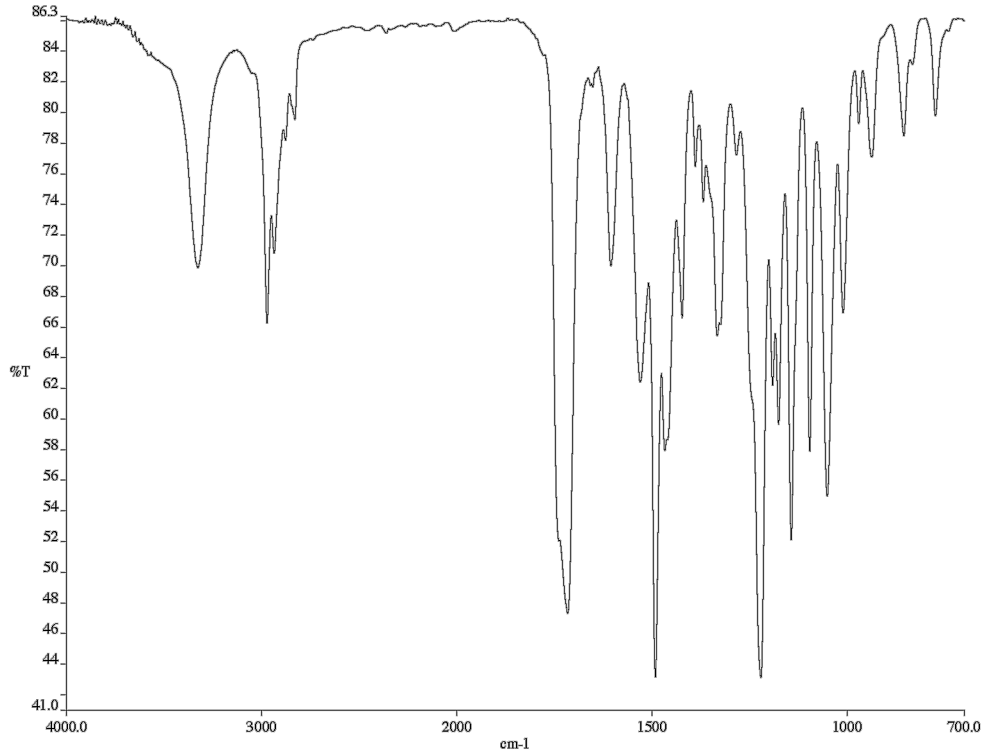

Figure A4.8.2 Infrared spectrum (thin film/NaCl) of compound **625**.

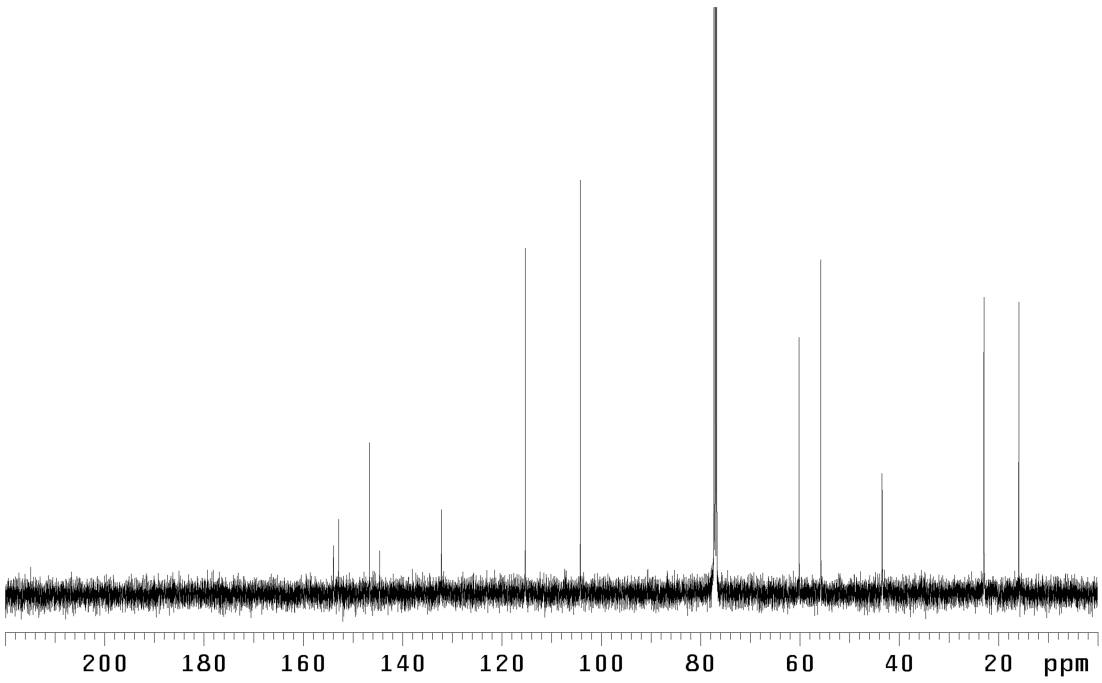

Figure A4.8.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **625**.

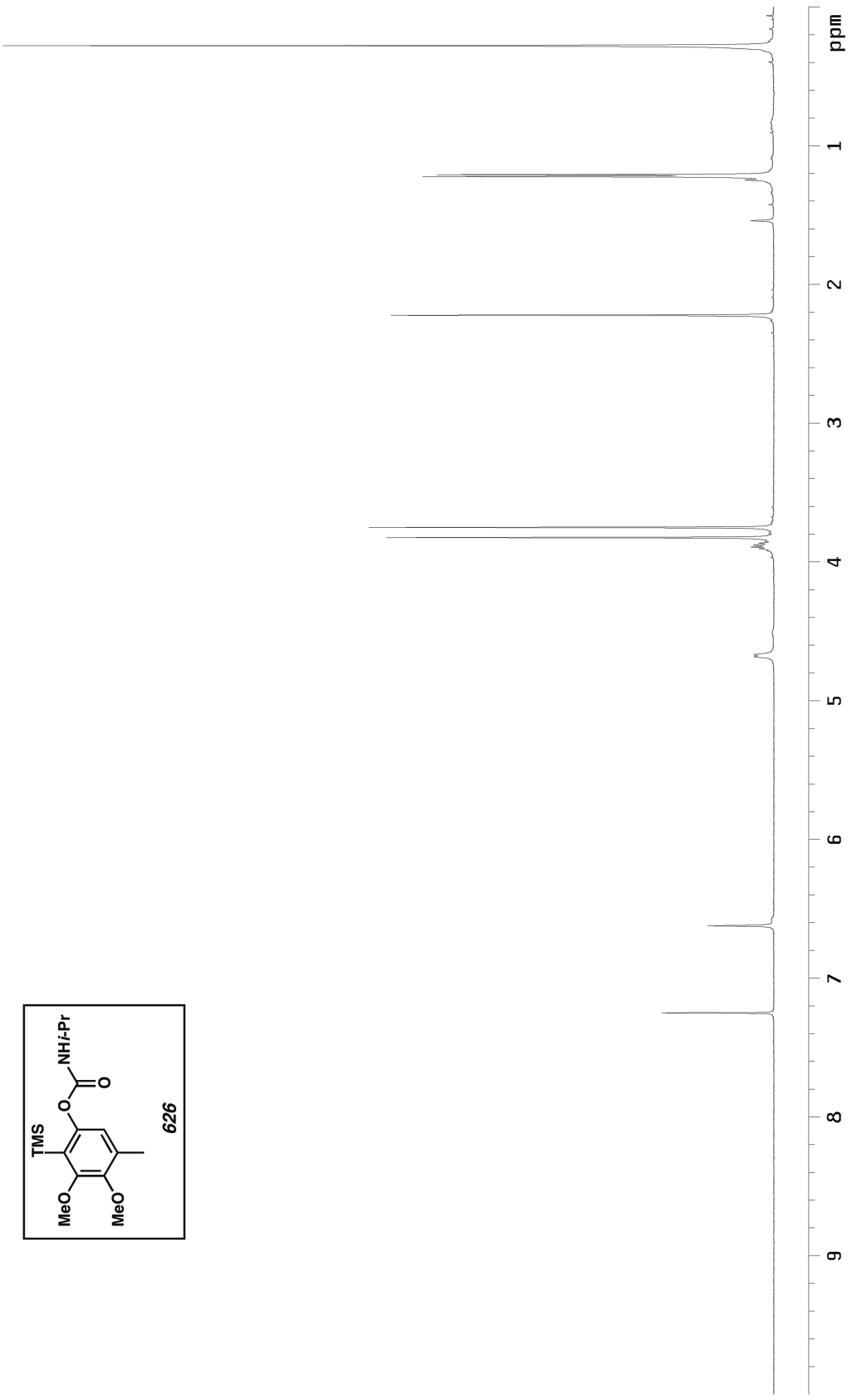

Figure A4.9.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **626**.

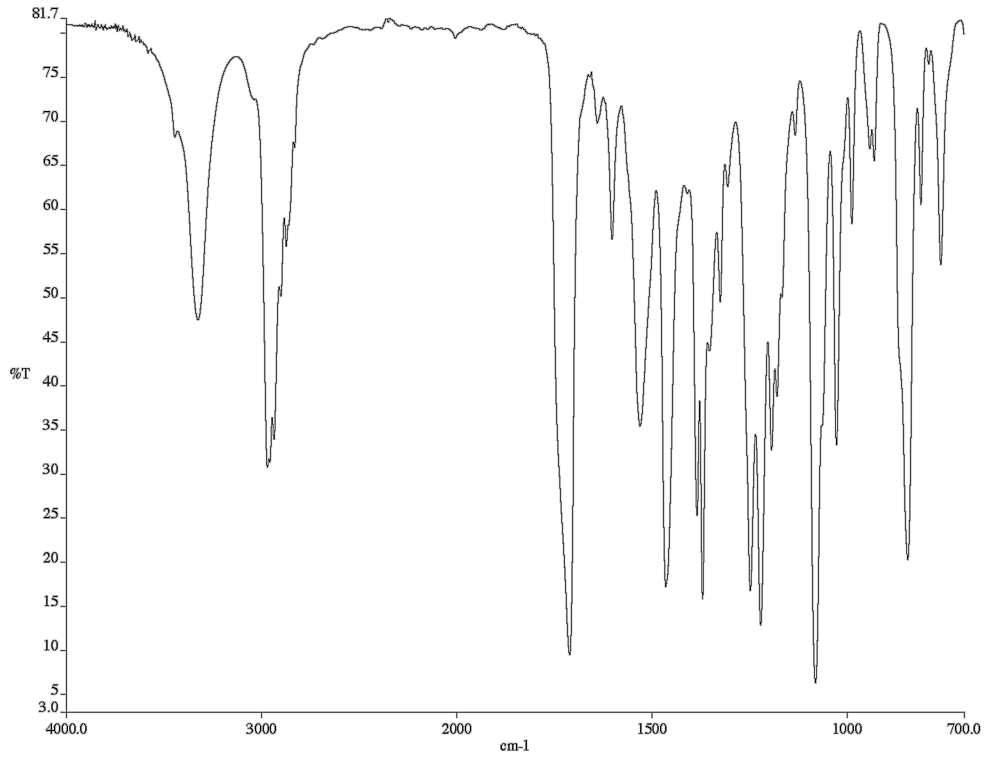

Figure A4.9.2 Infrared spectrum (thin film/NaCl) of compound **626**.

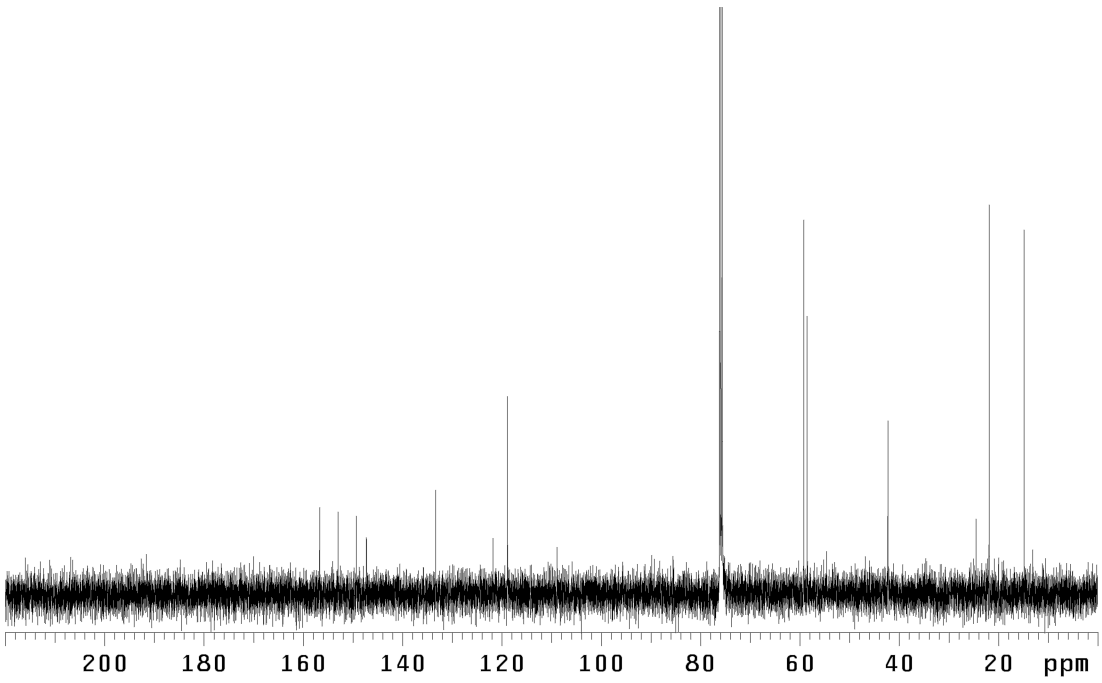

Figure A4.9.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **626**.

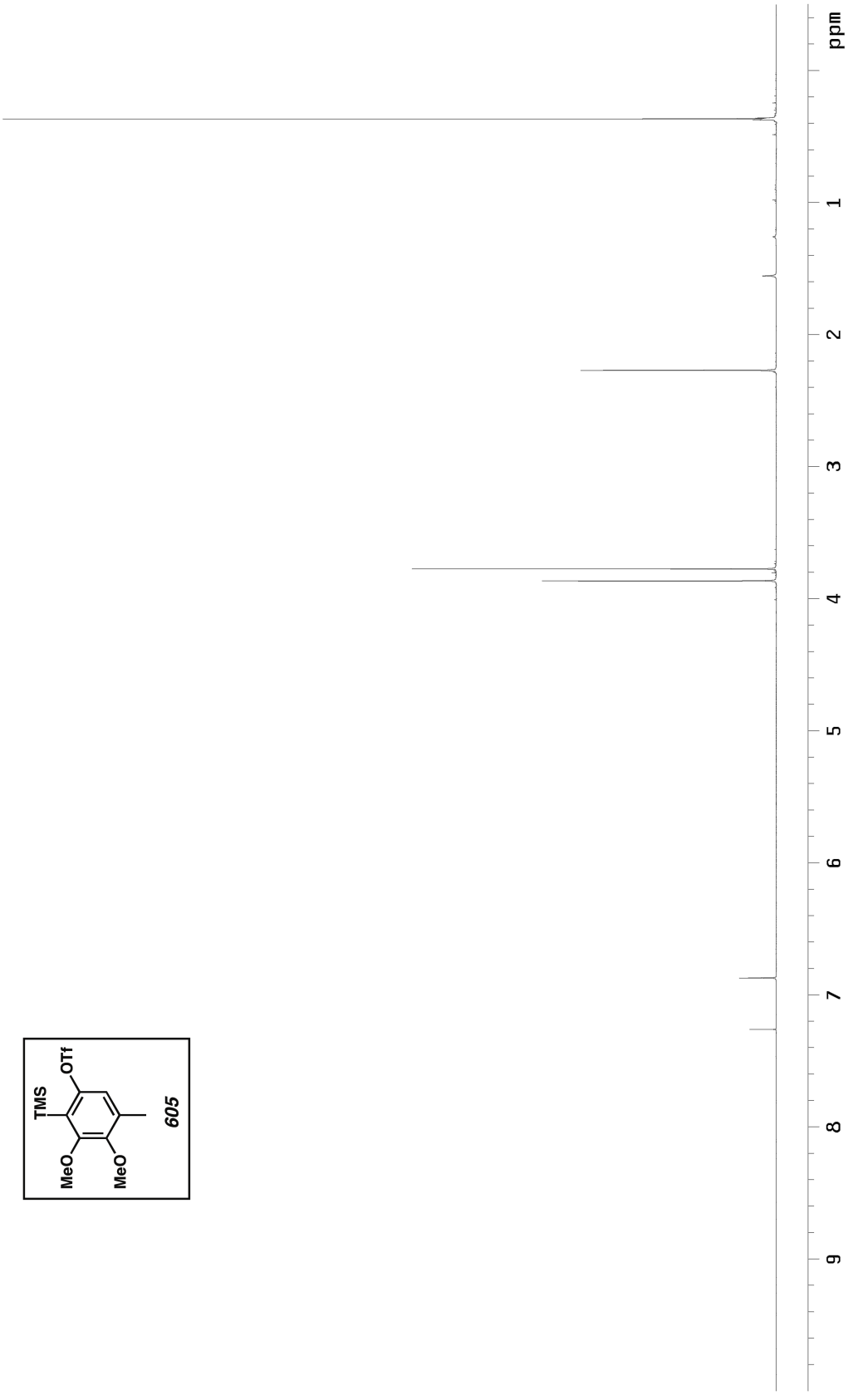

Figure A4.10.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **605**.

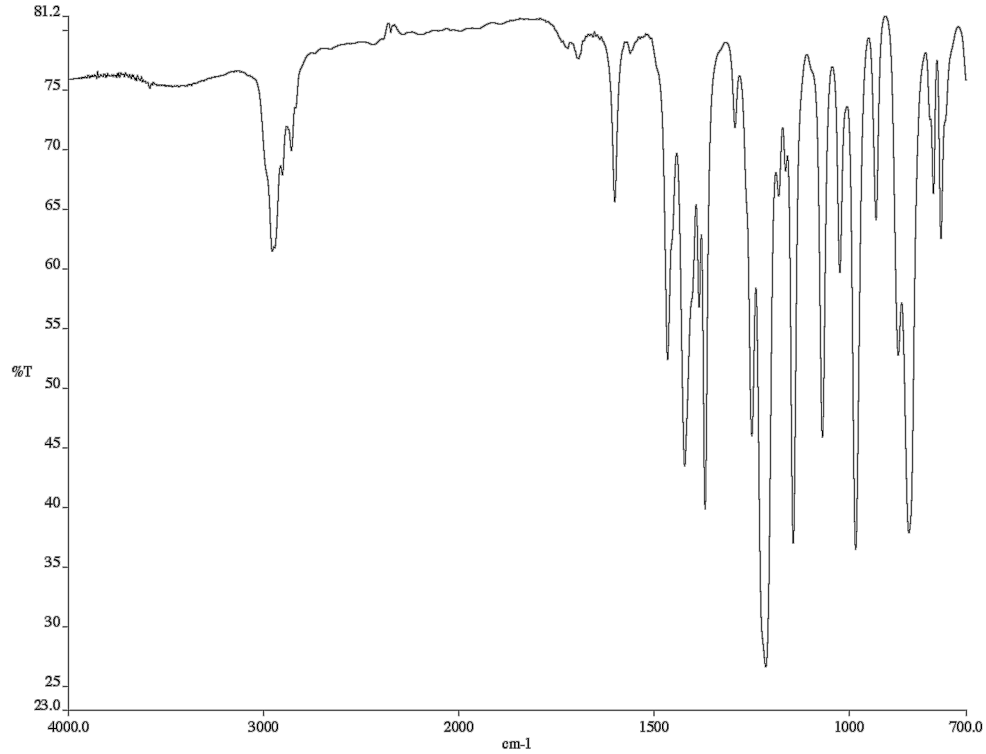

Figure A4.10.2 Infrared spectrum (thin film/NaCl) of compound **605**.

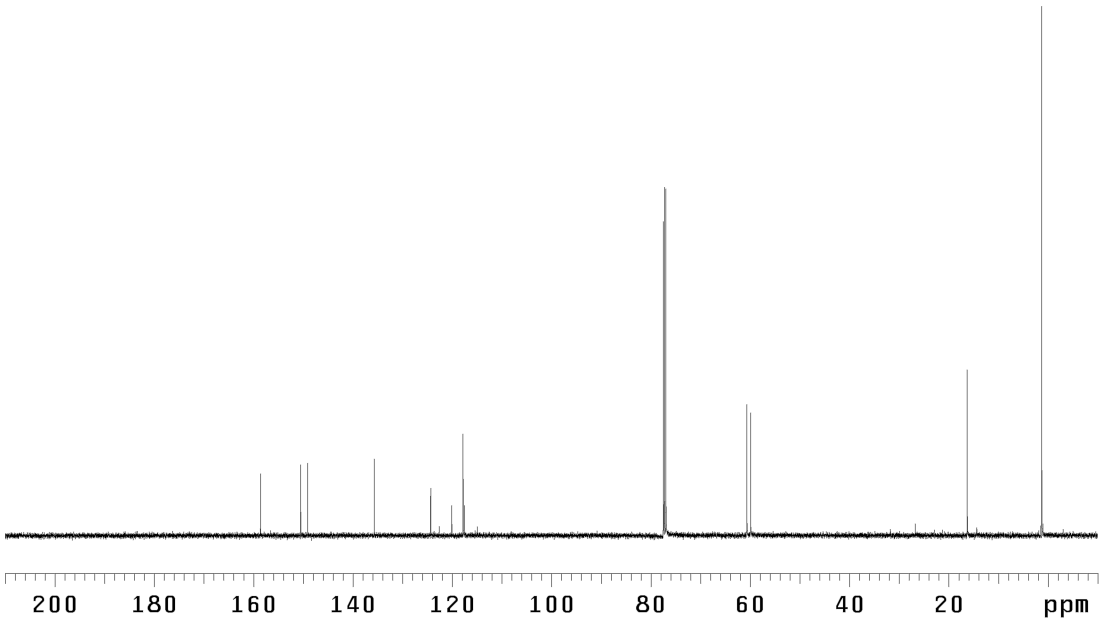

Figure A4.10.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **605**.

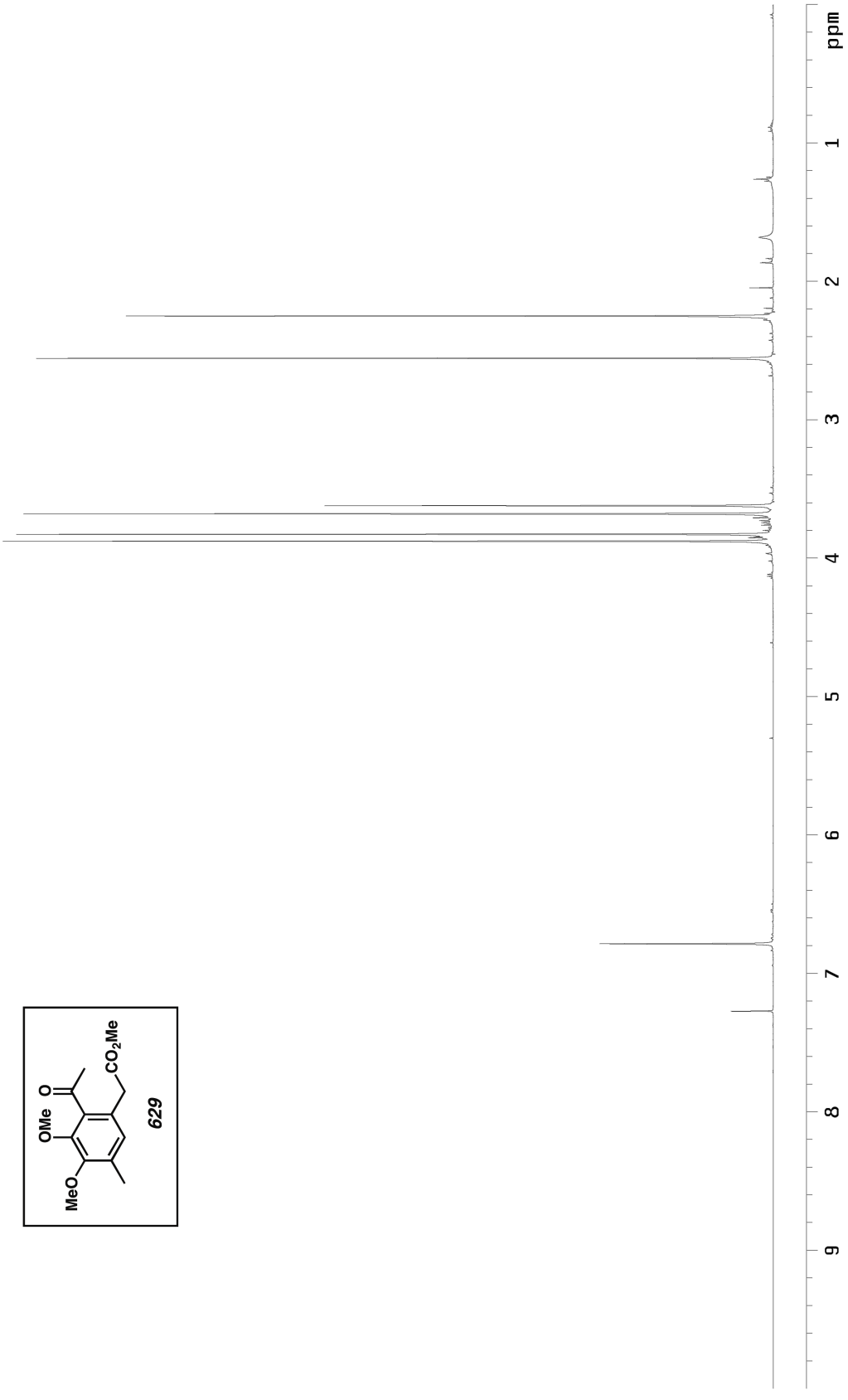

Figure A4.11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **629**.

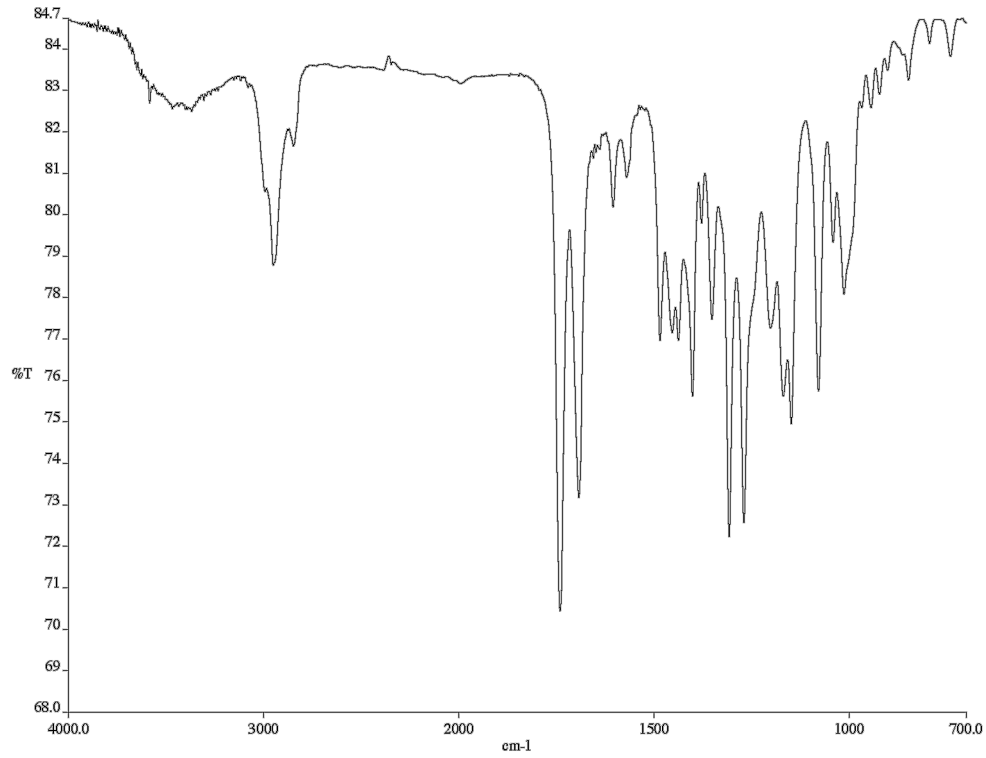

Figure A4.11.2 Infrared spectrum (thin film/NaCl) of compound **629**.

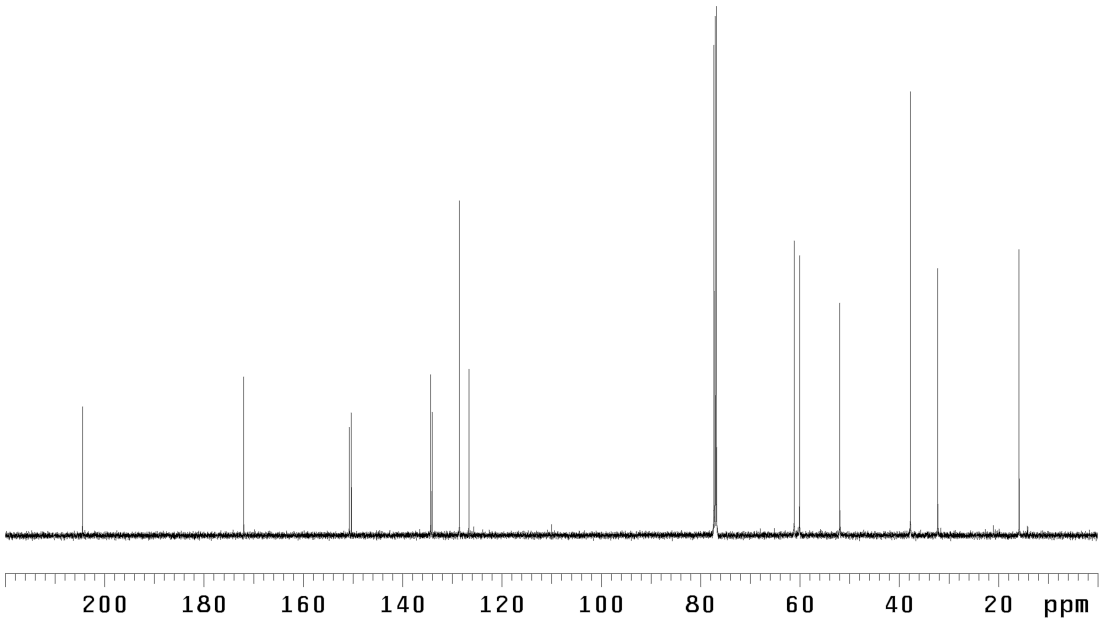

Figure A4.11.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **629**.

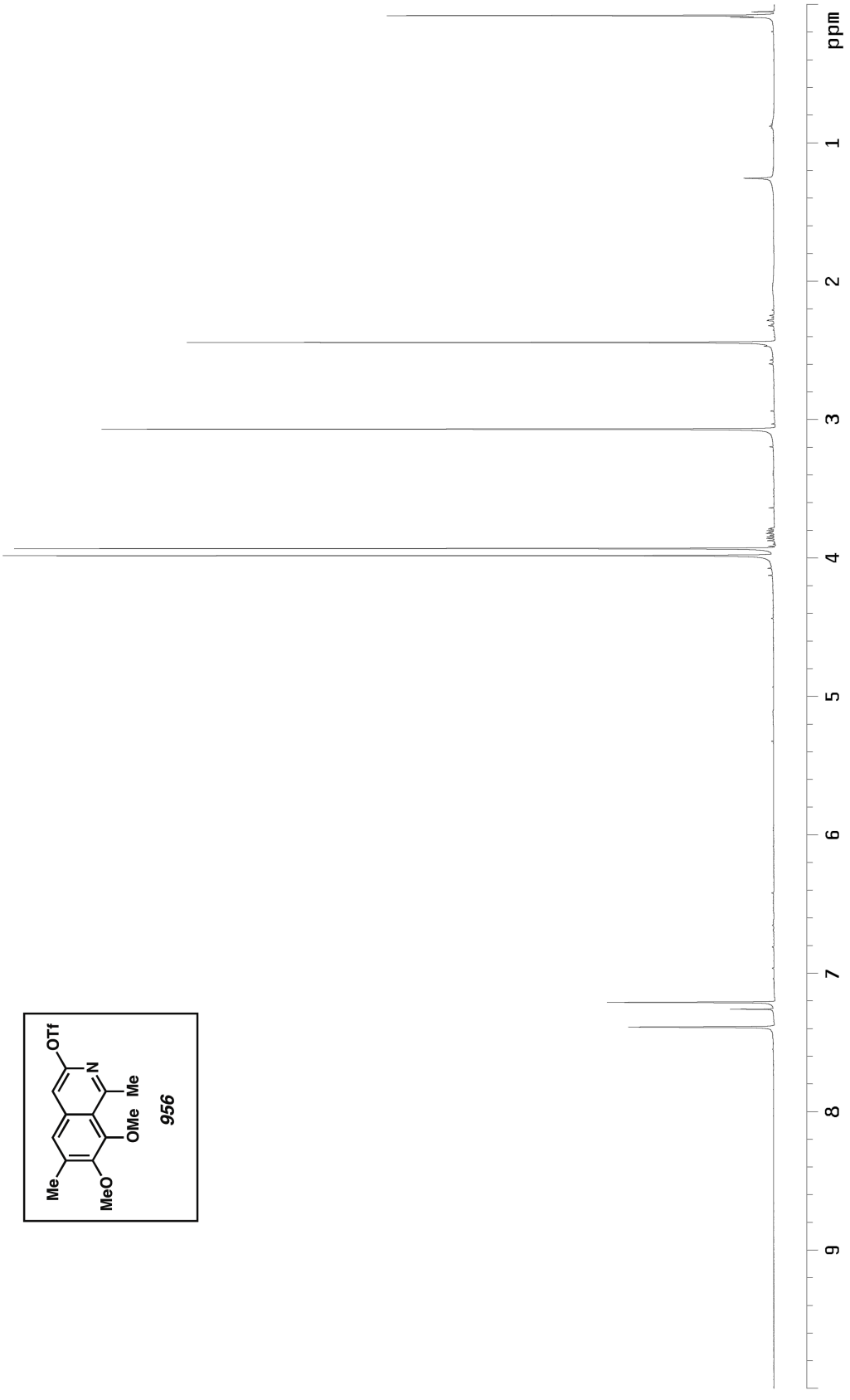

Figure A4.12.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **956**.

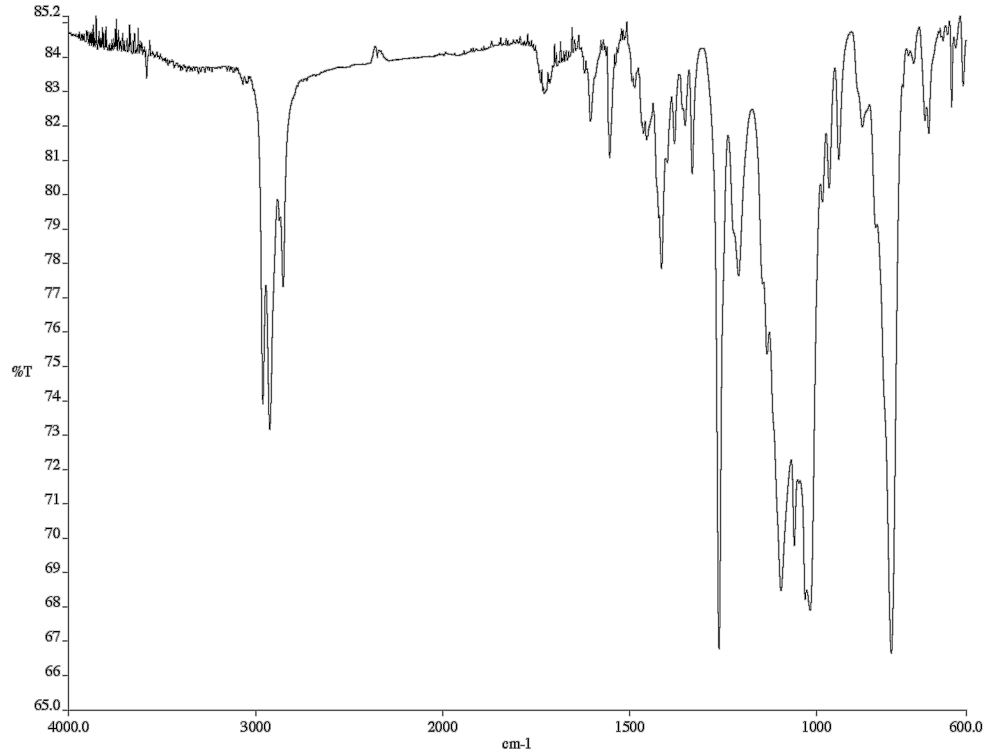

Figure A4.12.2 Infrared spectrum (thin film/NaCl) of compound **956**.

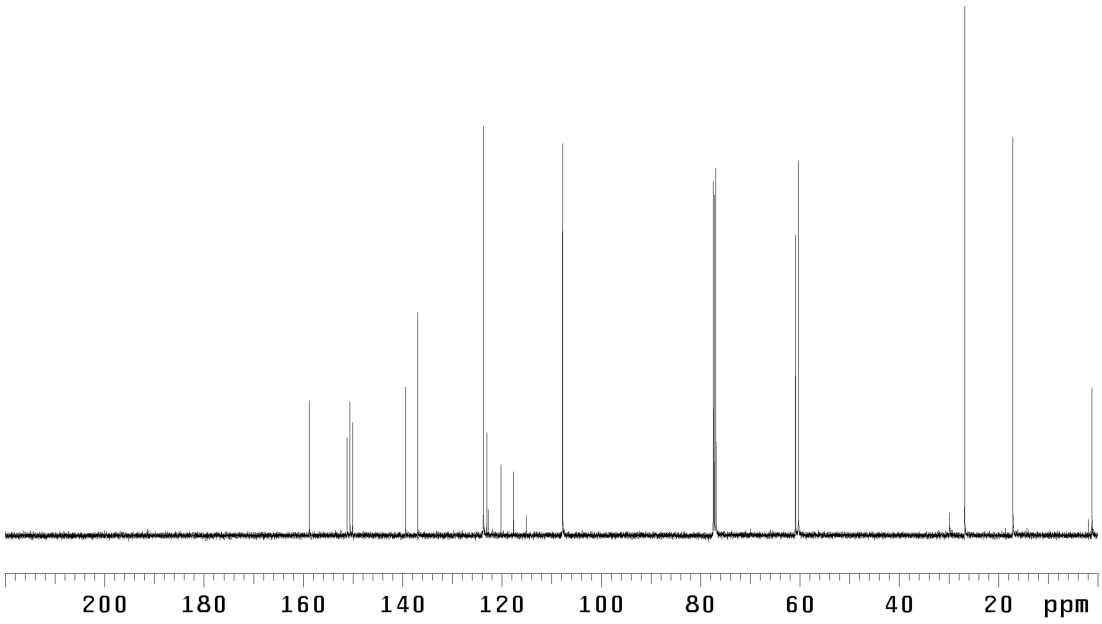

Figure A2.12.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **956**.

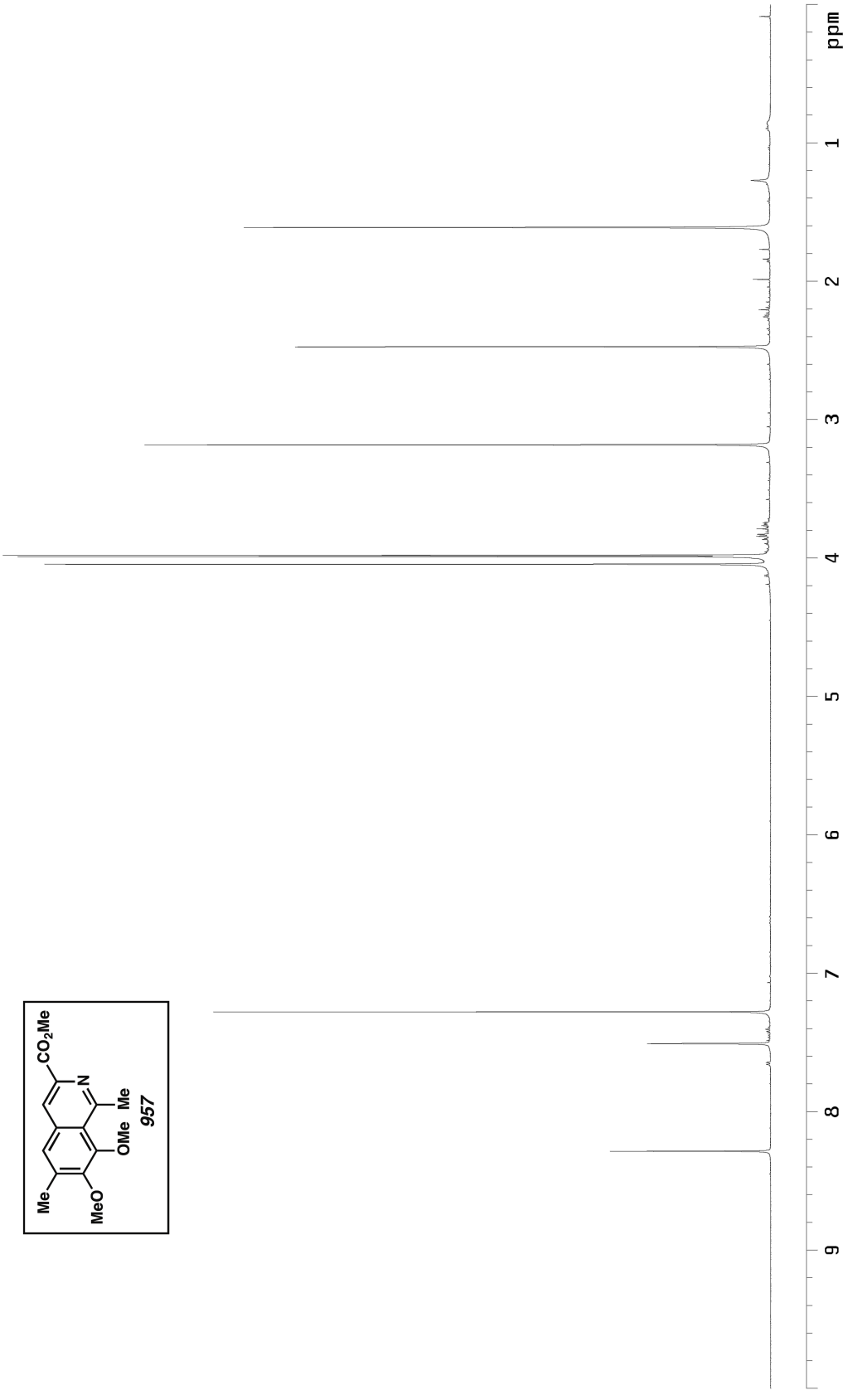

Figure A4.13.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **957**.

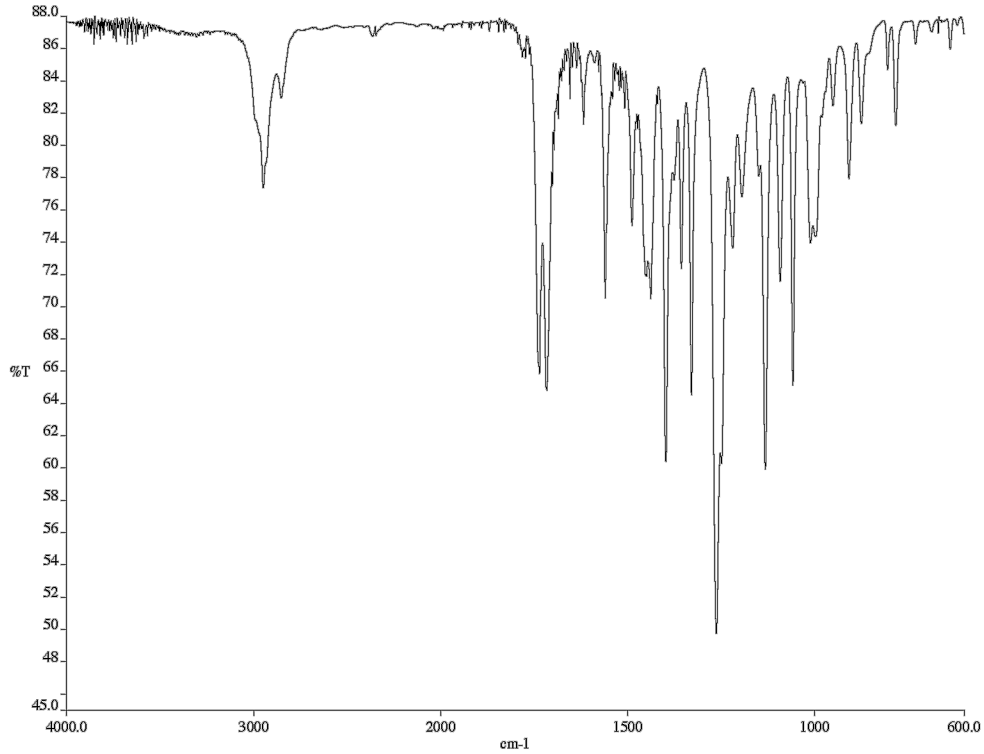

Figure A4.13.2 Infrared spectrum (thin film/NaCl) of compound **957**.

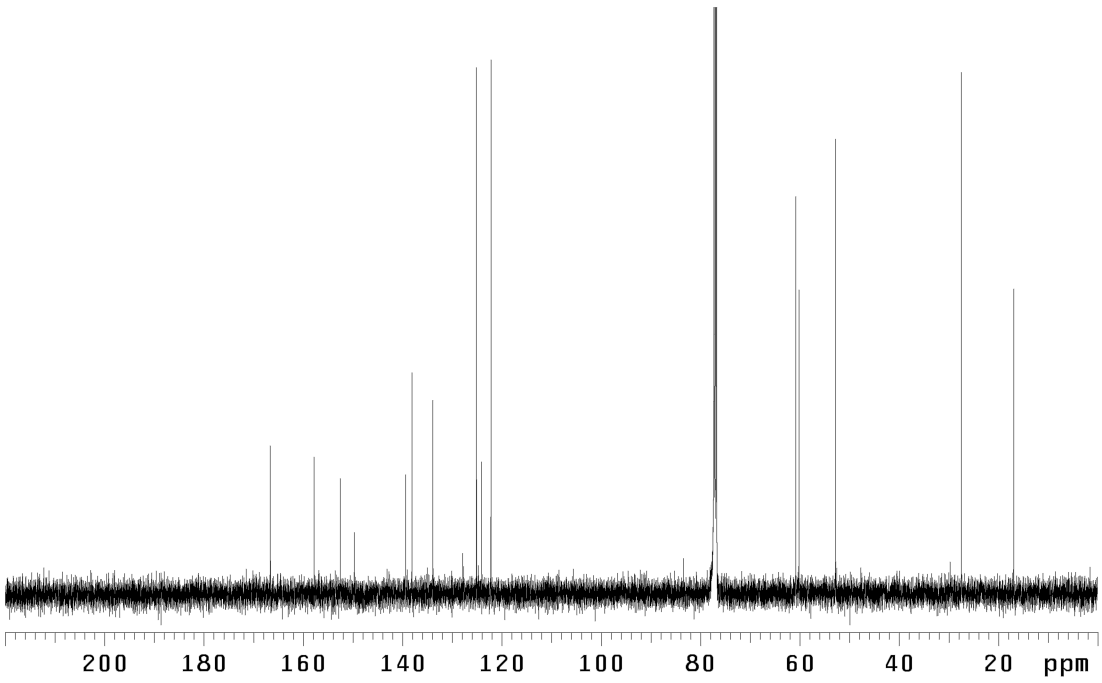

Figure A4.13.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **957**.

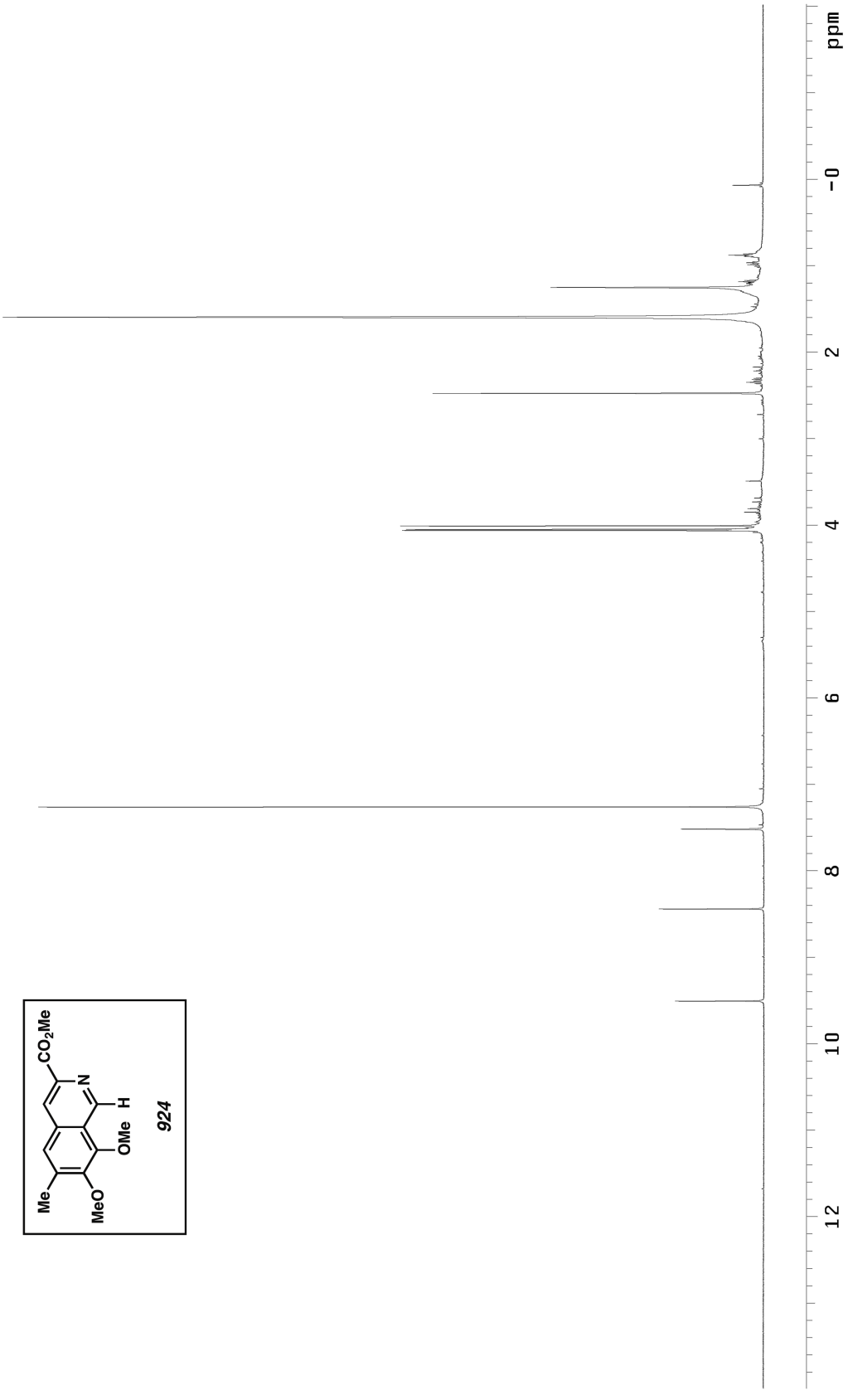

Figure A4.14.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **924**.

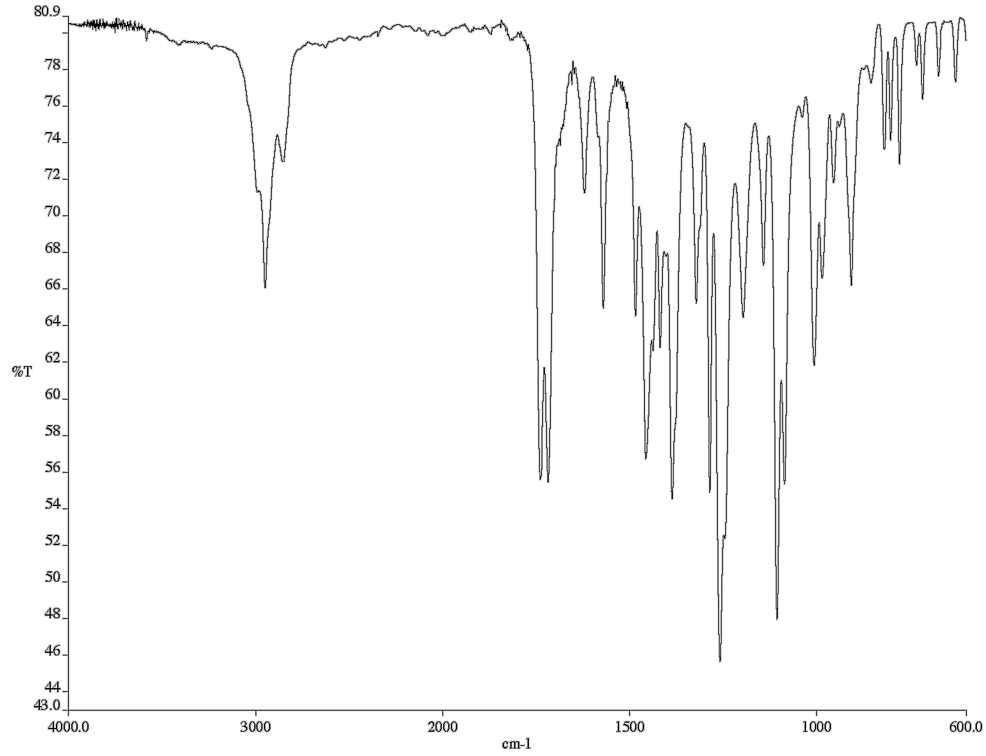

Figure A4.14.2 Infrared spectrum (thin film/NaCl) of compound **924**.

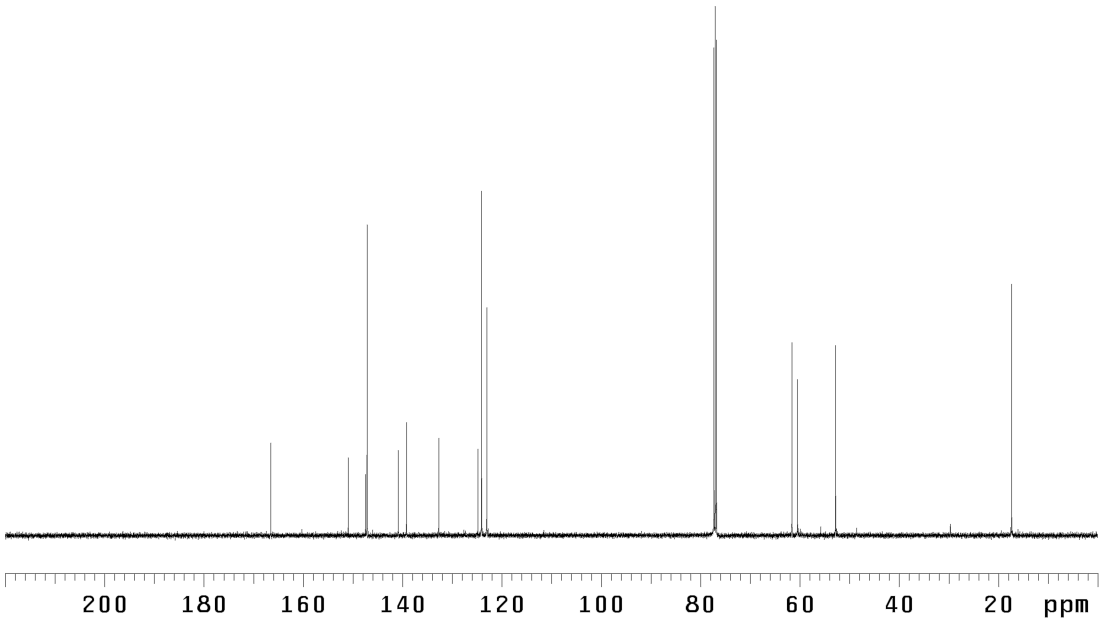

Figure A4.14.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **924**.

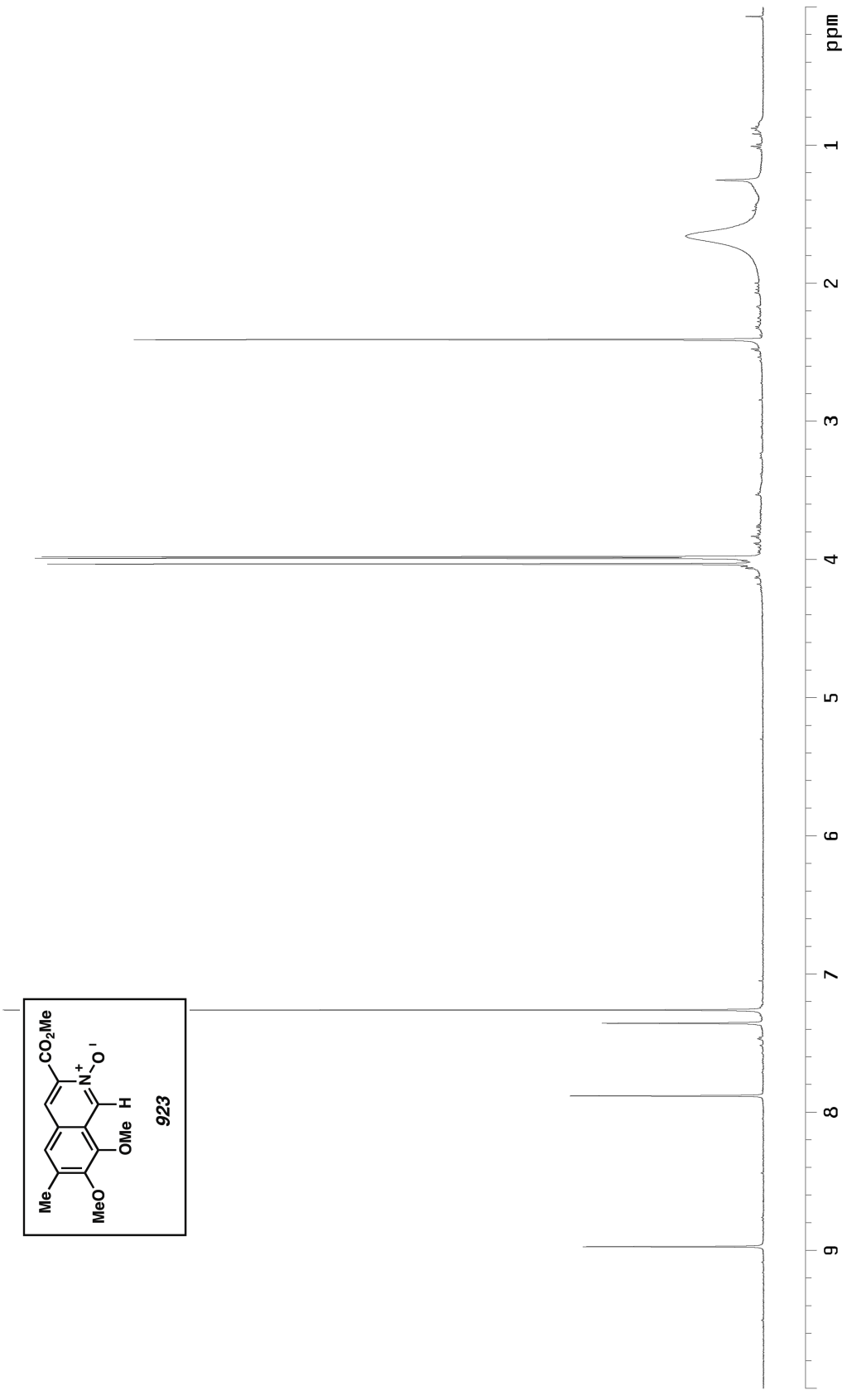

Figure A4.15.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **923**.

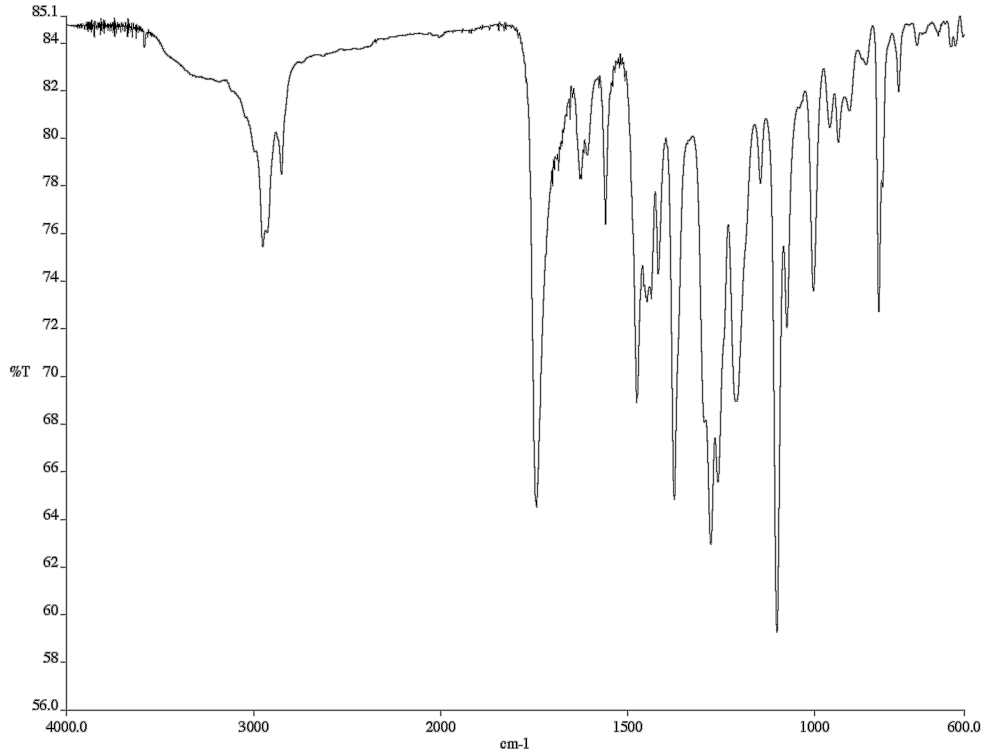

Figure A4.15.2 Infrared spectrum (thin film/NaCl) of compound **923**.

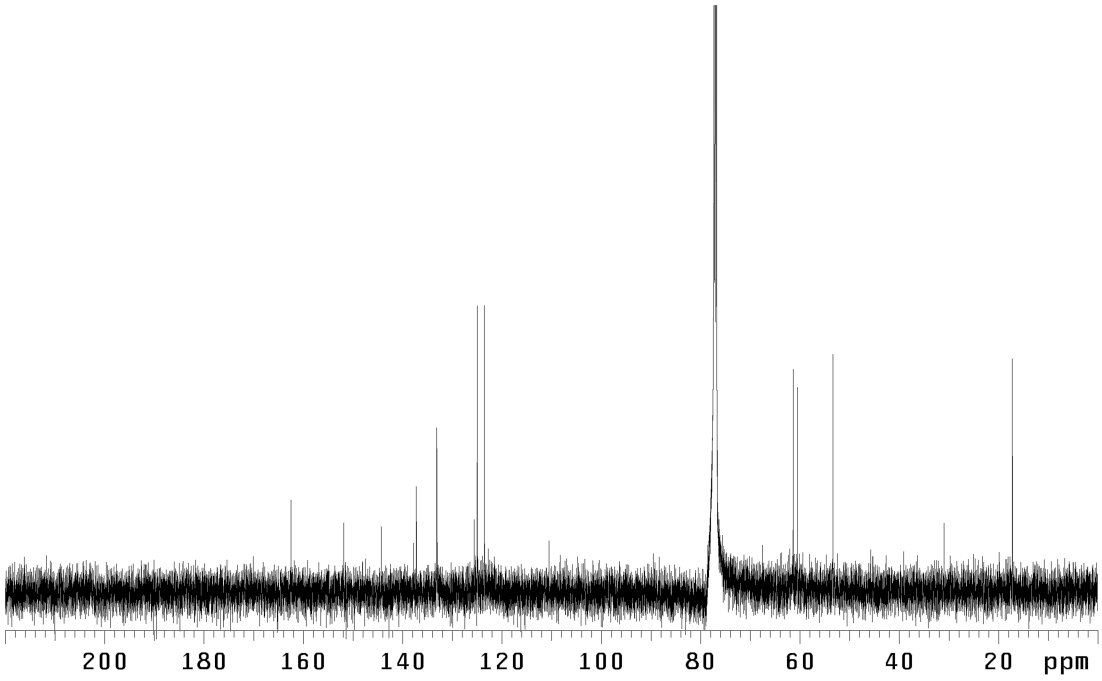

Figure A4.15.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **923**.

APPENDIX 5

Notebook Cross-Reference

NOTEBOOK CROSS-REFERENCE FOR NEW COMPOUNDS

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 hard copy and electronic characterization folders containing the original ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and IR spectra have been created. All notebooks and spectroscopic data are stored in the Stoltz research group archive.

Table A5.1. Compounds in Chapter 2 – The Total Synthesis of (–)-Curvularin

Compound	^{1}H NMR	^{13}C NMR	IR
614	PMT-IX-77-1H	PMT-IX-77-13C	PMT-IX-81
232	PMT-VII-33-1H	PMT-VII-33-13C	PMT-VII-33
720	PMT-VIII-107-1H	PMT-VIII-107-13C	PMT-VIII-107
616	PMT-VIII-121-1H	PMT-VIII-121-13C	PMT-VIII-121
617	PMT-VIII-103-1H	PMT-VIII-103-13C	PMT-VIII-103
217	PMT-VII-273-1H	PMT-VII-273-13C	PMT-VII-273
721	PB-I-179.pur1	PB-I-179.pur1	PB-I-179
619	PB-II-119.2ndpur01	PB-II-119.2ndpurC	PB-I-225 bc
620	PB-II-97.purchar	PB-II-97.purcharC	PB-II-97
604	PMT-IX-85-1H	PMT-VII-189	PMT-IX-85
622	CDG-XII-247	CDG-XII-247	CDG-XII-247
623	CDG-XIV-289C-2	CDG-XIV-289C-2	CDG-XIV-289
624	CDG-XIV-117C	CDG-XIV-117C	CDG-XIV-117
625	CDG-XV-123C-C13	CDG-XV-123C-C13	CDG-XV-123
626	CDG-XV-163C-C13	CDG-XIV-273B-201	CDG-XIV-273
605	CDG-XIV-267B	CDG-XIV-293D-C13	CDG-XIV-293
627	PMT-IX-99-1H	PMT-IX-99-13C	PMT-IX-99
226	PMT-IX-83-1H	PMT-IX-83.13C	PMT-IX-83
628	PB-II-105.3rdpur3	PB-II-105.3rdpur3	PB-II-105.3rdpur3
629	CDG-XIV-299C	CDG-XIV-299C-C13	CDG-XIV-299
227	PMT-IX-91-1H	PMT-IX-91-13C	PMT-IX-91

228	PMT-IX-109	PMT-IX-109	PMT-IX-109
631	CDG-XIV-301C	CDG-XIV-301C-C13	CDG-XIV-301
666	PMT-II-159	PMT-II-159	PMT-II-159
680	PMT-III-209	PMT-III-209-13C	PMT-III-209
681	PMT-III-217	PMT-III-217-13C	PMT-III-217
685	PMT-III-273	PMT-III-273-13C	PMT-III-273
686	PMT-III-275	PMT-III-275	PMT-III-275
689	PMT-II-211	PMT-II-211	PMT-II-211
695	PMT-II-225-1H	PMT-II-225-13C	PMT-II-225
693	PMT-II-205-1H	PMT-II-205-13C	PMT-II-205
***cis*-701**	PMT-III-29	PMT-III-29	PMT-III-29
702	PMT-VIII-135-1H	PMT-VIII-135-13C	PMT-VIII-135
703	PMT-VI-121-1H	PMT-VI-121-13C	PMT-VI-121
***Z-anti*-704**	PMT-IX-33-1H	PMT-IX-33-13C	PMT-IX-33
640	PMT-V-57-1H	PMT-V-57-13C	PMT-V-57
704	PMT-VII-29-1H	PMT-VII-29-13C	PMT-VII-29
709	PMT-IV-301	PMT-IV-301	PMT-IV-301
218	PMT-VII-73-1H	PMT-VII-73-13C	PMT-VII-73
718	PMT-VI-187	PMT-VI-187-13C	PMT-VI-187
719	PMT-VII-55	PMT-VII-55	PMT-VII-55
223	PMT-VIII-285-1H	PMT-VIII-285-13C	PMT-VIII-285
224	PMT-VIII-289-1H	PMT-VIII-289-13C	PMT-VIII-289
221	PMT-IX-31-1H	PMT-IX-31-13C	PMT-IX-31

Table A5.2. Compounds in Chapter 3 – Efforts Toward the Total Synthesis of Integrastatins A and B

Compound	^{1}H NMR	^{13}C NMR	IR
721	PB-I-179.pur1	PB-I-179.pur1	PB-I-179
762	PB-II-133	PB-II-133	PB-II-133
619	PB-II-119.2ndpur01	PB-II-119.2ndpurC	PB-I-225 bc
620	PB-II-97.purchar	PB-II-97.purcharC	PB-II-97
604	PMT-IX-85-1H	PMT-VII-189	PMT-IX-85
628	PB-II-105.3rdpur3	PB-II-105.3rdpur3	PB-II-105.3rdpur3
770	PB-I-171	PB-I-171	PB-I-171

775	PB-II-89	PB-II-89	PB-II-89
777	PB-II-99	PB-II-99	PB-II-99
784	PMT-XI-245	PMT-XI-245	PMT-XI-245
789	PMT-XI-247	PMT-XI-247	PMT-XI-247
782	PMT-XI-251	PMT-XI-251	PMT-XI-251
745	PMT-XI-255.1	PMT-XI-255.1	PMT-XI-255
798	PMT-XII-113	PMT-XII-113	PMT-XII-113
800	PB-III-165.char1H	PB-III-165.char13C	PB-III-165char
812	PMT-X-273	PMT-X-273	PMT-X-273
799	PMT-XII-143	PMT-XII-143	PMT-XII-143
802	PB-II-229	PB-II-229	PB-II-229
859	PMT-XII-115	PMT-XII-115	PMT-XII-115
803	PMT-XII-117	PMT-XII-117	PMT-XII-117
804	PB-II-273	PB-II-273	PB-II-273
805	PB-III-45	PB-III-45	PB-III-45
811	PMT-X-279	PMT-X-279	PMT-X-279
813	PMT-X-217	PMT-X-217	PMT-X-217
814	PMT-X-275	PMT-X-275	PMT-X-275
818	PB-III-117	PB-III-117	PB-III-117
819	PMT-XII-119	PMT-XII-119	PMT-XII-119
820	PMT-XII-125	PMT-XII-125	PMT-XII-125
821	PMT-XII-127	PMT-XII-127	PMT-XII-127
822	PMT-XII-137	PMT-XII-137	PMT-XII-137
838	PMT-XI-51	PMT-XI-51	PMT-XI-51
840	PMT-XII-165	PMT-XII-165	PMT-XII-165
842	PMT-XI-125	PMT-XI-125	PMT-XI-125
841	PMT-XI-151	PMT-XI-151	PMT-XI-151
844	PMT-XII-263	PMT-XII-263	PMT-XII-263
845	PMT-XII-267	PMT-XII-267	PMT-XII-267
846	PMT-XII-171	PMT-XII-171	PMT-XII-171
852	PMT-XI-205	PMT-XI-205	PMT-XI-205
853	PMT-XII-155	PMT-XII-155	PMT-XII-155

Table A5.3. Compounds in Chapter 4 – Progress Toward the Total Synthesis of Jorumycin

Compound	^{1}H NMR	^{13}C NMR	IR
933	PMT-XII-227	PMT-XII-227	PMT-XII-227
932	PMT-XII-241	PMT-XII-241	PMT-XII-241
935	PMT-XII-245	PMT-XII-245	PMT-XII-245
939	PMT-XII-225	PMT-XII-225	PMT-XII-225
622	CDGXII-247	CDGXII-247	CDGXII-247
623	CDGXIV-289C-2	CDGXIV-289C-2	CDGXIV-289
624	CDGXIV-117C	CDGXIV-117C	CDGXIV-117
625	CDGXV-123C-C13	CDGXV-123C-C13	CDGXV-123
626	CDGXV-163C-C13	CDGXIV-273B-201	CDGXIV-273
605	CDGXIV-267B	CDGXIV-293D-C13	CDGXIV-293
629	CDGXIV-299C	CDGXIV-299C-C13	CDGXIV-299
956	CDGXXI-131B-1-C13	CDGXXI-131B-1-C13	CDGXXI-131C
957	CDGXXI-147B-C13	CDGXXI-147B-C13	CDGXXI-135C
924	CDGXII-075-SM-C13	CDG-PMT-12-079	PMT-12-079
923	CDGXXI-107B-2	CDGXXI-107B-2-C13	CDGXXI-107B-2

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ABOUT THE AUTHOR

Pamela Michele Tadross was born in Brooklyn, New York on June 27th, 1983, to Anthony and Karen Tadross. Her younger sister, Victoria, was born four years later. Pam vividly remembers (although not quite as vividly as Vicky) her first encounter with science to be when she performed life-saving surgery on her sister's favorite stuffed animal. In 1997, Pam began high school at Bishop Kearney High School where she swam competitively as captain of the varsity team and played piano both classically and with local orchestras for musical theater. It was at BKHS that Pam first fell in love with chemistry, thanks to her teacher Ms. Denice Gamper. Around this time, she also discovered Latin and, intent on majoring in everyone's favorite dead language, she decided to attend New York University in the fall of 2001, following her graduation as salutatorian of her high school class.

Not long after beginning at NYU, Pam discovered an opportunity to perform undergraduate research in the labs of Professor Marc Walters, an inorganic chemist. During the three and a half years Pam spent in the Walters lab, Prof. Walters encouraged her growth as a chemist, always sharing his enthusiasm for research. In the Walters lab, Pam investigated the effect of hydrogen bonding on electron transfer in metalloenzymes through the encapsulation of iron metalloenzyme mimics in reverse micellar structures. Her research experience with Prof. Walters quickly led Pam to declare chemistry as her major, with minors in Latin and piano performance. Pam graduated from NYU in 2005 summa cum laude as the College of Arts and Science and All-University valedictorian with a Bachelor of Science degree in Chemistry.

In the fall of 2005, Pam left New York for the warmer weather of Pasadena, California, to begin her graduate work at the California Institute of Technology. Although she entered Caltech as an inorganic chemistry student, Pam quickly discovered synthetic organic chemistry and joined the lab of Professor Brian Stoltz. Her research in the Stoltz lab focused on the application of new aryne methodologies developed in the group to the total synthesis of natural products. In November 2011, Pam will be moving to Cambridge, Massachusetts, with her fiancé, Chris Gilmore, to begin a postdoctoral position in the lab of Professor Eric Jacobsen at Harvard University, where she will be an NIH postdoctoral fellow. She will be married to Chris in July 2012 in New York.