ABSTRACT

Total Syntheses of (+)- and (–)-Tetrapetalones A and C

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The total syntheses of polyketide natural products (–)-/(+)-tetrapetalone A and (–)-/(+)-tetrapetalone C are described. In 2003, during their pursuit for novel lipoxygenase inhibitors, Hirota and coworkers reported the isolation and characterization of tetrapetalone A from *Streptomyces* sp. USF-4727 found growing in a soil sample in Yada, Shizouka City, Japan. Subsequent studies in 2004 led to the discovery of three new members of the tetrapetalone family that are each thought to be biosynthetically derived from tetrapetalone A. Common to this family of polyketide natural products, is a unique architecture containing a tetracyclic aglycone that possesses a tetramic acid, an azepine ring fused to a *p*-quinol, and 5-membered ring linked to a ß-rhodinose moiety.

Synthetically, our approach toward the tetrapetalones involves early preparation of a masked tetramic acid unit that is elaborated by way of a Lewis acid promoted conjugate addition. Further oxidation and a Friedel-Crafts acylation reaction lead to an azepine containing intermediate. A variety of strategies were explored to elaborate this versatile compound, with ultimate success hinging upon a key C-H activation that produces a substrate suitable for advancement to the tetracyclic aglycone by way of a classical Heck

cyclization reaction. A chiral resolution utilizing an enantiopure glycosyl donor permits not only ß-selective installation of the rhodinose moiety, but also sets the stage for access to enantiopure natural products. The synthesis concludes with an aryl oxidation reaction followed by unveiling the tetramic acid to deliver tetrapetalone A. Further oxidation gives access to tetrapetalone C.

Total Syntheses of (+)- and (–)- Tetrapetalones A and C

by

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A Dissertation

Approved by the Department of Chemistry and Biochemistry

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LIST OF ABBREVIATIONS

ACP	acyl carrier protein
AIBN	2,2'-azobis(2-methylpropionitrile)
Ar	aromatic
BBN	borabicyclo[3.3.1]nonane
BINAP	1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Boc	*tert*-butyloxycarbonyl
Bu	n-butyl
Bz	benzoyl
Cat.	catalyst
CBS	Corey-Bakshi-Shibata
CD	circular dichroism
CO	carbon monoxide
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DAMP	diazomethylphosphonate
DBU	1,8-diazabicycloundec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine (aka Hünig's base)
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMAPP	dimethyl allyl diphosphate
DMDO	dimethyldioxirane
DMEA	dimethylethanolamine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
ECD	electronic circular dichroism
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ent	enantiomer(ic)
epi	epimer(ic)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FTIR	fourier transform infrared spectroscopy
HMBC	heteronuclear multiple-bond correlation

HMPA	hexamethylphosphoramide
Hex	hexanes
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
hv	irradiation by light
imid.	imidazole
i-Pr	iso-propyl
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamine
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MeCN	acetonitrile
MS	molecular sieves
Ms	methanesulfonyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
n-Pr	linear propyl
Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PDP	*N*,*N*'-bis(2-pyridylmethyl)]-2,2'-bipyrrolidinebis(acetonitrile)
Ph	phenyl
PMB	4-methoxybenzyl
PMP	1,2,2,6,6-pentamethylpiperidine
PPTS	pyridinium p-toluenesulfonate
Pro	proline
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	tert-butyldiphenylsilyl chloride
TBS	tert-butyldimethylsilyl
t-Bu	tert-butyl
TCC	trans-2-cumylcyclohexanol
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	tri-isopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tf	trifluoromethanesulfonate
Tr	triphenylmethyl
Ts	4-toluenesulfonyl
Trp	tryptophan
UV	ultra violet

ACKNOWLEDGMENTS

I often like to ask those who have trekked this path before me, what was it in graduate school that you valued the most? While many synthetic chemists I have spoken to would go on to describe techniques mastered, knowledge gleaned, compounds conquered, or methods developed, I, as with any endeavors or undertakings in my life, would answer with what for me has always been, and I imagine will always continue to be my answer: the people. I have had the great fortune of being surrounded by extraordinary people who have no doubt propelled me to where I am now and to whom I am forever indebted. No doubt, a few simple paragraphs will not do justice to the sheer number of people let alone any individual that has inspired and influenced me to this point in my life.

My parents have no doubt demonstrated a level of patience with me that is rivalled by two others who will be mentioned in the words to follow. From my younger years until now, Naina and Hansraj Dhanjee have been my biggest role models. All too often I find myself asking, "what would mom and dad do?" My parents have gone through great lengths to ensure the availability of opportunity both in my life and in my brother's, and the sacrifices they have made will pale in comparison to anything I do or will ever do. My mother's contagious childlike sense of wonder and father's ability to successfully make comedy out of nearly any situation is challenged only by my brother, Shimal Dhanjee. My brother Shimal and sister-in-law Nicolette have been so supportive of me and have no doubt expended much effort to ensure my inclusion in the lives of three of the most

complex and beautiful concoction of molecules, dare I say, ever synthesized: Keio, Rieen, and Ryer Dhanjee.

When it comes to the tetrapetalone team, I often think of one of my favorite quotes from none other than Rocky. Not Rocky 1, or 2, or 3…. But 6. "It ain't about how hard you hit, it's about how hard you can get hit and keep moving forward." As a team, we took a lot of hits in the tetrapetalone project, and it was the collective experiences of the early members that taught me how to pick myself up when knocked down. I thank all those before me who entrusted this project to me and those who worked alongside me. The support Jennifer Howell offered from a simple conference meeting in my early days on the tetrapetalone project taught me a lot about a new kind of family that was adopting me. This type of support was only reinforced on meeting Matthew Haley, who, even from a one-hour conversation, offered a lot of sage advice that I carry with me today. Jonas Buergler and Travis McMahon, it has been my honor to have trained and worked alongside you during my early days as a graduate student. I'm not sure I can ever live up to 'being like Travis," it's perhaps too big a set of shoes for me to fill. I would not be where I am now without the wisdom and guidance Jonas and Travis imparted on me during our time together at Colorado State. When we were a small collection of people declaring ourselves the Wood group when moving to Baylor, there was no one who taught me more about work ethic and duty than Yutaka Kobayashi. I have not met, nor am I convinced it is possible to meet, someone who worked harder than he. Koichi Fujiwara, you are one of the most creative chemists I have worked with. Your fearlessness to go after ideas, even if it meant hitting the reset button, will no doubt break down that barrier of fear in my future endeavors.

My early days of sanity at Baylor were kept in line primarily due to two rather astonishing individuals, Roy and Nancy Dominguez. For you to have openly taken a stranger onto your APA pool team mimics closely the risk two others to be mentioned later would take. Being a part of your team is an experience I will cherish for the rest of my life. The nervousness when we almost made nationals was one of the most conflicting set of emotions I had ever felt (Thanks John!). The honor of you having voted me team MVP meant the world to me and kept me afloat in rough seas.

When we moved to Baylor, there were two critical individuals who taught me a lot about the chemical world, how to conduct myself, and how to navigate treacherous waters: Aaron Bedermann and Monica McCallum. You both were an integral part of this chapter of my life, and I thank you for sharing this time with me and expelling energy to elevate me. I can only hope to do the same for people in the future.

Michael Tudesco, you no doubt kept me balanced during my time in graduate school. Most importantly, you know what you are, so I need not waste words here to express it.

Josh Cox, I think you are just about the funniest person I have ever met. You're an endless source of observational humor that is second to none and always made the lab more cheerful to be in.

Yu-Wen Huang, your thoughtfulness and insight into not only managing a laboratory, but also into chemistry have been a revelation during my later years in the Wood group. You have no doubt spent much effort to improve all members of the Wood group to where they are now and I am very thankful to have had the opportunity to work alongside you.

Aoi, you are no doubt an exceptional chemist and I will miss our conversations about life and chemistry. Your perspective on things always provided me with food for thought.

Perhaps no person in this endeavor or this time in my life was more important than Joyce Leung. Professionally, you taught me a lot about organization and efficiency. More importantly however, you've been one of my greatest friends and advocates, I'm not sure I would have been able to conclude this chapter of my life without your encouragement and support.

There are many people in my life to whom I owe a debt of gratitude, not the least of which is mentioned on these few pages. During my time in graduate school there were, among many, three notably astonishing individuals who went out of their way to keep me grounded: Zach Theis, Michael Pettit, and Graham Carlson. I'm reminded of what my nephews would say if one were to ask them what the most valuable thing someone can give them is: time. Zach, Mike, and Graham, I thank you for your time, this dissertation would not be possible without you.

What can I say about Marilyn Pierce, aka Marilyn Rajaratnam that would do her justice? Your presence has not only constantly raised my spirits, raised the Wood group, but has certainly done wonders for the department and university. Mrs. Solve-it-all. If ever there were a problem, Marilyn could fix it! Need an ear to listen? Marilyn's there! Need advice? Ask Marilyn! Want to chat about the latest happenings in Waco? Bam, Marilyn! Without you, I'm afraid our group would devolve into a flock of raised-arm Spongebob's running around with the house on fire.

I am extraordinary grateful that Professor Daniel Romo moved his team to join as at Baylor University. The opportunity and expertise your group brought to our department has been invaluable. I cannot imagine graduate school without the likes of Khoi Van, Paul Gladen, Sreekumar Vellalath, and the rest of the clan. I am also thankful to Professor Romo for having served on my committee.

Khoi, the kind of infrastructure building skills you brought with you have no doubt made easier our research lives, not just among the people who were lucky enough to work alongside you, but also for those in the generations to come. I am glad we crossed paths during our time at Baylor.

Professor Charles Garner, I am grateful to you for having served on my committee, on your last day at Baylor no less! It was a challenge having moved to Baylor, but it was no doubt made easier by your presence in the department. All too often, it's easy to overlook the foundations that have been set-up to facilitate growth, education, and research and I know you had a critical role in setting up the infrastructure that allowed me to excel while at Baylor. It is upon your shoulders that I have stood and seen the department grow even further, I am honored that you served on my committee.

I am also thankful to Professor Michael Trakselis who, on such short notice agreed to serve on my committee. You're kindness and demeanor lend to the already growing culture and sense of community at Baylor's burgeoning chemistry program. They are lucky to have you and I'm excited for what changes may come during your tenure as the Director of Graduate Affairs.

Professor Kenneth Park, thank you for having served on my committee. I would not be where I am without you. Your support alleviated a great deal of stress in those chaotic days leading up my defense.

Now, for the two people I was saving for the end: first, Professor Thomas Minehan. The opportunity to be introduced to scientific research, and more specifically total synthesis was an experience that profoundly changed the entire course of my life. I am endlessly thankful to you for having taken a chance on someone who studied math and biology and had almost no business being in a synthesis lab. It was your laboratory that provided me with a forum to grow and explore the things that drove me, and it was you who steered me in the direction to someone only the most astute of audience members would be able to guess is, the other person to be named later: Professor John Louis Wood.

"What? No chemistry degree!?! We might as well put up a sign saying we'll take anyone!" Working with you John, aka cPops, has provided me endless opportunities for growth and, even in the short period I had known you at the time, moving with you to Baylor was a brainless choice. The number of grey hairs I've grown under your tutelage is no doubt a symbol of the endless amount of wisdom you have imparted onto me, and I hope the ones I've given you are likewise a symbol of my attempted reciprocation. As my captain, it should go without say that I would follow you to hell and back, as following you to the scorching temperatures of Texas should trump all of that.

What is my Ph.D…. it's the time Joyce Leung brought me a box of fried rice when the grey hair production was at its highest, it's when Zach Theis invited me to his house and made me some sushi while we watched the Packers, it's waking up to a cool breeze at Michael Pettit's from a day of late night stories and adventures, it's Graham Carlson taking

me to a fancy Austin restaurant and a road-stop near Zilker park, it's not waiting in line at Franklin BBQ with Yutaka Kobayashi and Yasuhiro Shimamoto because we got there too late (but we did get some awesome La Barbeque instead!), it's spending late-night time meeting interesting neighbors with Tarik Ozumerzifon, it's losing to Michael Tudesco in basketball 11-7, it's getting embarrassed by Casey Maguire in a late night pool shootout, it's trading hours of time for an invaluable conversation with Ricardo Francis in a chance run-in on the street, it's Sam Yruegas lifting the spirits of an entire department with a Thanksgiving bash and baking a Cup of Noodles or Paradise (aka "Nervous John") cake, it's sharing a meal with Nancy, Roy, Carl, and Julia, it's Monica McCallum coercing me to try a vegan diet that lasted all of three weeks, it's joining Aaron Bedermann at a Foo Fighters concert, it's when Jacob and Lauren Timmerman joined me on a free steak adventure, it's… many things.

I've always considered myself a bit of a plastic bag in the wind. Maybe in another life it would have been someone or something else, but in this life it was a very special person who got me to start blowing my own wind to propel myself in a direction. To this person I am also endlessly thankful – the brightest planet in the night-sky that inspired me to places I never thought myself capable of going.

What follows is the narrative detailing the synthesis of tetrapetalone A, the MacGuffin that guided this chapter of my life.

DEDICATION

To my friends and family

CHAPTER ONE

Introduction to the Tetrapetalones

1.1 Isolation, Characterization, and Biosynthesis

1.1.1 The Tetrapetalones: Isolation and Characterization

In 2003, during their pursuit to find novel lipoxygenase inhibitors, Hirota and coworkers isolated tetrapetalone A from a culture filtrate of *Streptomyces* sp. USF-4727, found growing in a soil sample in Yada, Shizouka City, Japan.[i] A variety of NMR spectroscopic analyses including ^{1}H, ^{13}C, DEPT, ^{1}H-^{1}H, HMQC, 2D-INADEQUATE, and HMBC were conducted on the compound in CD_3OD, leading to the proposed structural assignment of tetrapetalone A as **1.05** (Figure 1.1). While the relative stereochemistry of the glycosyl unit was determined by NOESY spectrum, coupling constants, and analogy to known β-rhodinose moieties, its absolute stereochemistry was determined by the modified Mosher's method on the C(4') hydroxyl group. Subsequent hydrolysis of the glycosyl unit followed by application of the modified Mosher's method to the resulting aglycone provided the absolute stereochemical assignment of the carbinol C-O linkage at C(9). The relative stereochemistry at the adjacent C(8) and C(7) stereocenters was assigned as illustrated. During the time of this publication, the relative stereochemistry at C(4) and C(15) was still under active investigation.

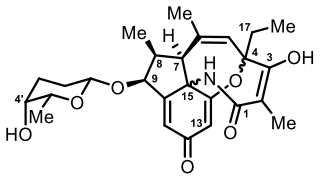
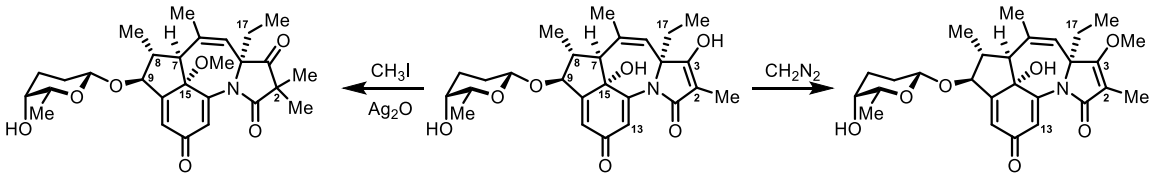


Figure 1.1. Initially proposed structure of tetrapetalone A

Studies performed later in the same year indicated, predominantly based on ^{1}H-^{15}N HMBC data, that not only was the nitrogen atom present as part of an amide functional group (based on chemical shift), but it was also revealed that there was a long-range coupling from H(13) and H(17) to the nitrogen atom. This indicated that these hydrogen atoms were within 2-3 bonds of the nitrogen atom and not in agreement with the structure depicted in figure 1.1.[ii] Based on these results and derivative studies (*vide infra*), they reassigned the structure of tetrapetalone A to be as that depicted in Scheme 1.1 (**1.01**).



Scheme 1.1. Derivatization and structural reassignment of tetrapetalone A (**1.01**)

With evidence of exchangeable protons in the molecule, they further performed derivatization studies by exposure of the isolated natural product to diazomethane to give tetrapetalone A-Me (**1.07**). The resulting methylated compound gave cross-peaks in the ^{1}H-^{13}C HMBC spectrum between the newly introduced methyl group and C(3). This led to the assignment of an acidic hydroxyl unit at the C(3) position. Lastly, exposure to iodomethane in the presence of silver (I) oxide yielded tetrapetalone A-Me2 (**1.06**), whose

methoxy unit showed an NOE correlation between the newly introduced *p*-quinol ether methyl group and H(9). Further NOE analysis of **1.06** as well as detailed analysis of the coupling constants led to the reassigned relative stereochemistries as depicted in the aglycone.

Shortly thereafter, further investigation of the same culture filtrate led to the discovery of three new members of the tetrapetalone family, namely tetrapetalones B (**1.02**), C (**1.03**), and D (**1.04**) which differ in their oxidation states at the angular ethyl group, the tetramic acid moiety, or both, respectively (Figure 1.2).[iii] These newly discovered members of the family of tetrapetalones were assigned through NMR analyses, as well as by similarity to **1.01**.

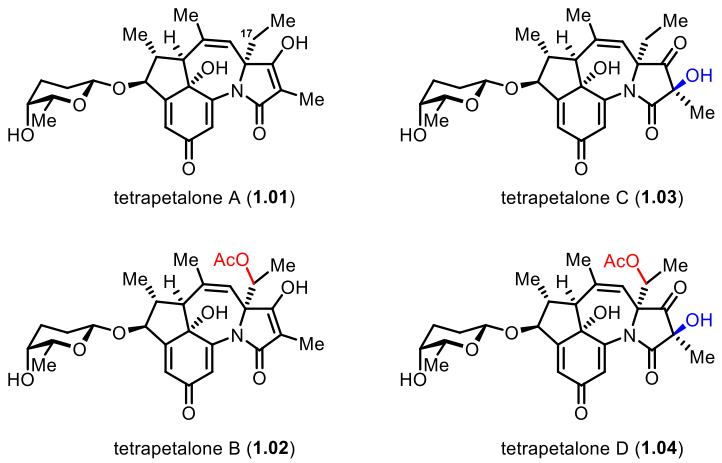
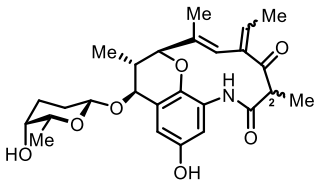


Figure 1.2. The tetrapetalones

1.1.2 Ansaetherone and the Biogenesis of the Tetrapetalones

Several years later, while analyzing the same *Streptomyces* strain (*Streptomyces* sp. USF-4727) for radical scavengers, Hirota and coworkers identified ansaetherone (**1.08**, Figure 1.3) whose structure was determined by 1D- and 2D-NMR data (^{1}H, ^{13}C, DEPT, ^{1}H-^{1}H COSY, HMQC, HMBC, NOE).[iv] They went on to speculate that **1.08** was

biosynthetically related to the tetrapetalone family and thus assigned the absolute stereochemistry based on the assignments that had been made for the tetrapetalones which were done by the modified Mosher's method.

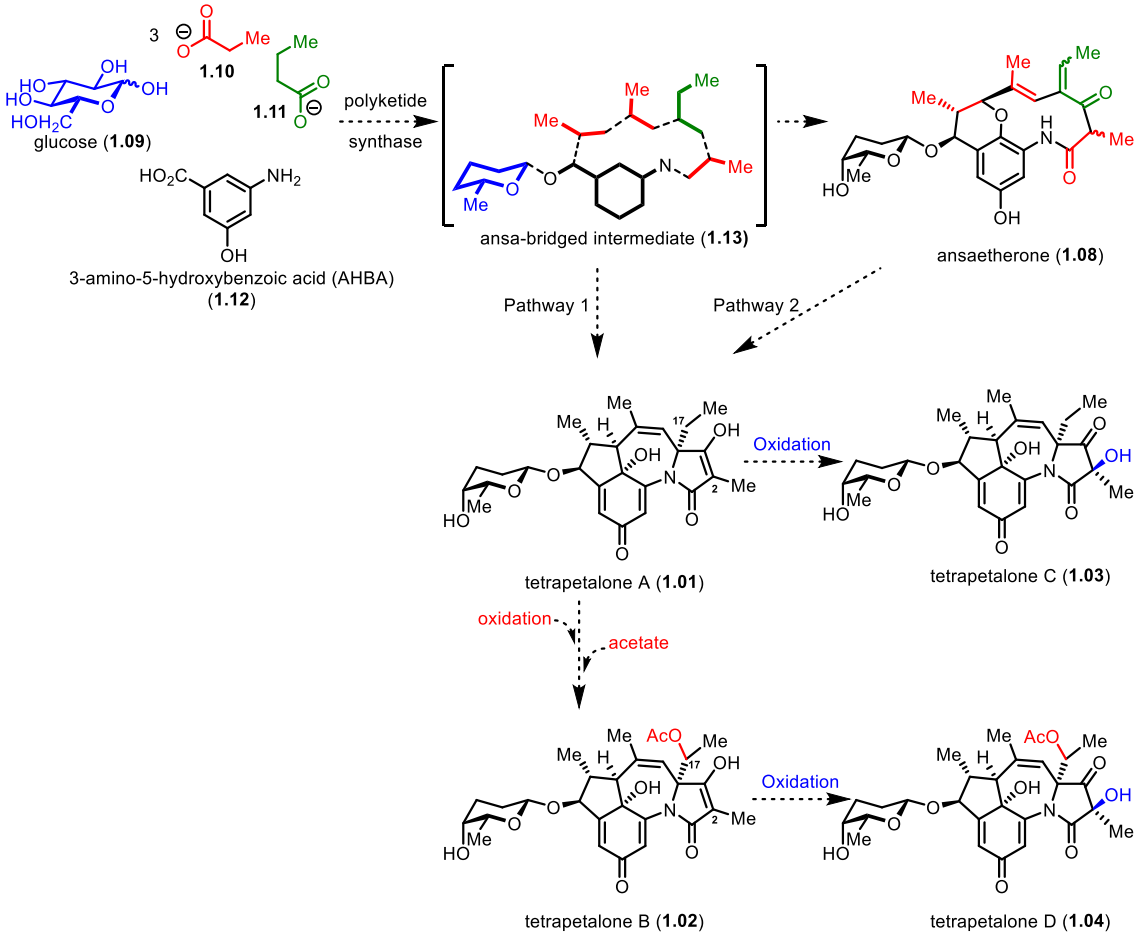


ansaetherone (**1.08**)

Figure 1.3. Ansaetherone

Prior to the isolation and characterization of ansaetherone, deuterium labeling studies into the biosynthetic origins of the tetrapetalones had revealed that these natural products likely derive via a polyketide synthase pathway involving three molecules of propanoate (**1.10**), butanoate (**1.11**), glucose (**1.09**), and 3-amino-5-benzoic acid (**1.12**), which combine to make an ansa-bridged intermediate (**1.13**) (a benzene derivative whose *para* or *meta* positions are bridged by a chain).[v] The isolation of ansaetherone provided evidence that the carbon skeleton present in the aglycone of the tetrapetalones is likely formed after the installation of the β-rhodinose unit. However, it is currently unclear where ansaetherone lies within this biosynthetic scheme. One possibility is that further modification of the ansa-bridged intermediate **1.13** forms ansaetherone (**1.08**), which then undergoes subsequent alterations to form tetrapetalone A (**1.01**) (Pathway 2, Scheme 1.2). Alternatively, as illustrated by Pathway 1, tetrapetalone A may derive by a biosynthetic route not involving ansaetherone (**1.08**). Nevertheless, once tetrapetalone A (**1.01**) is formed, oxidation of the tetramic acid moiety at C(2) then furnishes tetrapetalone C (**1.03**). Alternatively, oxidation at the angular ethyl group at C(17) followed by acetylation gives

tetrapetalone B (**1.02**) that, in a similar transformation from A to C, undergoes oxidation to deliver tetrapetalone D (**1.04**).



Scheme 1.2. The biogenesis of ansaetherone and the tetrapetalones

1.2 Previous Synthetic Efforts

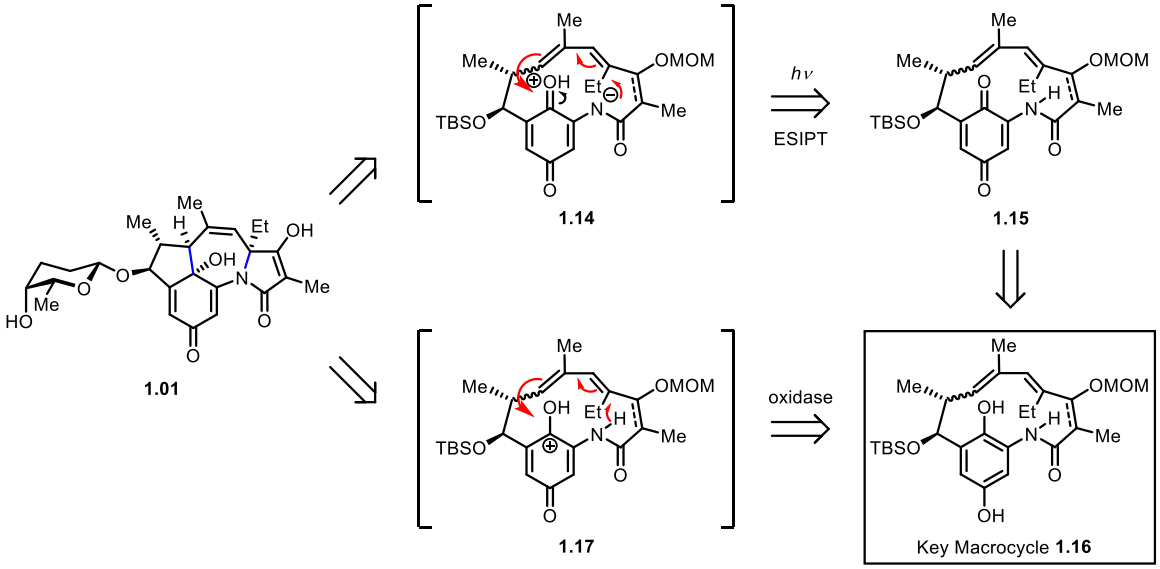
In the 15 years since their isolation, a large number of research groups have reported efforts to prepare members of tetrapetalone family via total synthesis. Of these latter efforts the most notable includes work from the groups of Porco,[vi] Hong,[vii] Sarpong,[viii] Pettus,[ix] and Frontier[x] that describe progress toward the total synthesis of tetrapetalone A (**1.01**). Syntheses of biosynthetically related compounds and proposals regarding their potential

conversion to **1.01** have emanated from Chen and Yang.[xi] Additional efforts from the groups of Kobayashi[xii] and Hosokawa[xiii] can be found outside the realm of peer-reviewed publications. The latter will not be discussed here, as adequate information about their approaches have yet to be disclosed.

1.2.1 Porco's Efforts Toward Tetrapetalone A

Prior to the appearance of publications describing the proposed biogenesis of the tetrapetalones, Porco and coworkers postulated that the tetrapetalones derived, biosynthetically, from a macrocyclic intermediate which they envisioned as an ansamycin analogue akin to **1.16** (Scheme 1.3).[vi] As illustrated, Porco proposed two synthetic hypotheses. The first involves transannular [4+3] cyclization of an intermediate oxonium (**1.17**), which would arise via oxidation of a parent hydroquinone (**1.16**). Trapping of the intermediate oxonium ion by the macrocyclic diene and quenching of the resulting carbocation by the amide functionality would forge, through a single oxidative step, the tetracyclic core of the tetrapetalones. Alternatively, Porco proposed that quinone **1.16** would undergo oxidation to quinone **1.15** followed by excited-state intramolecular proton transfer (ESIPT) under UV irradiation to deliver dipole **1.14** and, in turn, tetrapetalone A (**1.01**) via a [4+3] cyclization process.

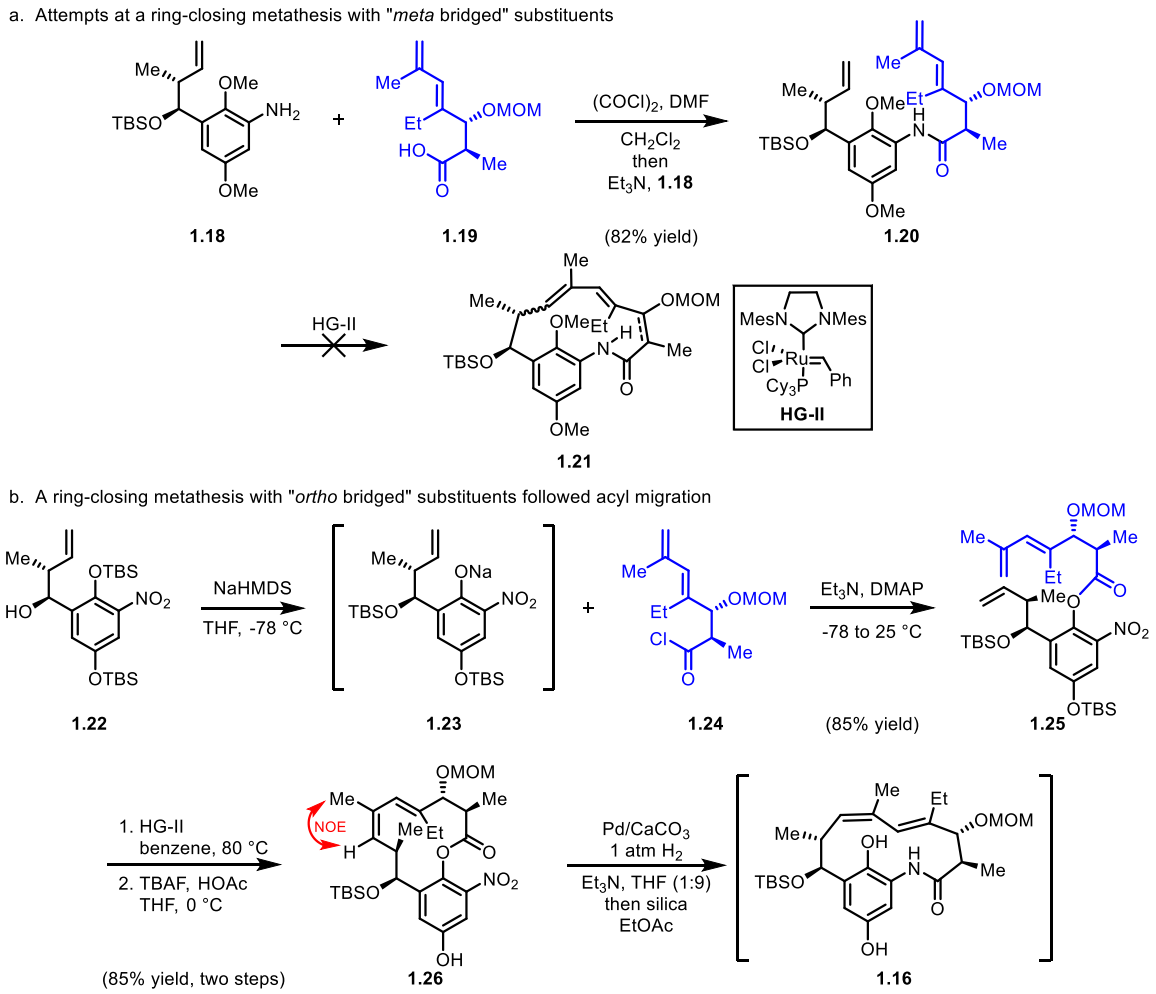
Thus, to test their proposed biosynthetic hypotheses for the formation of the tetrapetalones, they targeted macrocyclic lactam **1.16** for synthesis.



Scheme 1.3. Porco's [4+3] annulation strategy toward tetrapetalone A

Initial efforts toward the preparation of **1.16** were met with failure (Scheme 1.4, top). Acylation of aniline **1.18** with the acid chloride generated from carboxylic acid **1.19** gave **1.20** in 82% yield. The subsequent efforts to effect a ring-closing metathesis (RCM) on compound **1.20** failed to deliver the desired macrocyclic lactam. Conformational analysis of the metathesis substrate suggested that failure was due to the two terminal olefins being too far away due to "*meta* bridging" of the aromatic substituents. In light of this observation the Porco Group opted to pursue an "*ortho* bridged" substrate wherein the increased propinquity of the two relevant olefin moieties would help promote RCM (Scheme 1.4, bottom). In accordance with this strategy, bis-TBS ether **1.22** was treated with NaHMDS to promote selective intramolecular silyl migration thereby unmasking the phenol which, upon exposure to acid chloride **1.24**, delivered ester **1.25** in 85% yield. In contrast to the previous system, **1.25** was found to undergo smooth RCM to furnish an intermediate which, upon TBS deprotection, gave hydroquinone **1.26**. Selective reduction of the nitro group in **1.26** followed by exposure to silica gel, provided the macrolactam

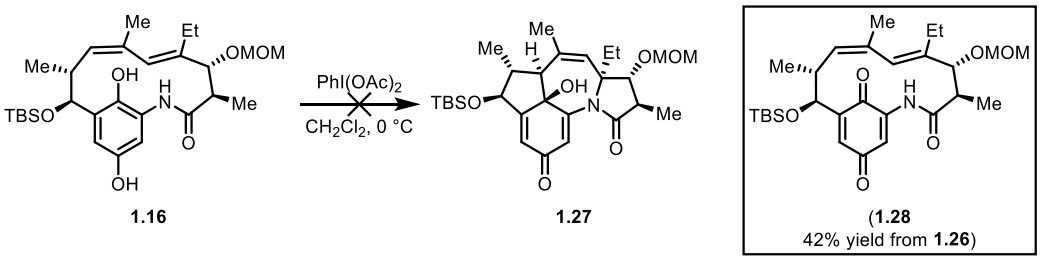
1.16. Evidence for the desired *Z* olefin in **1.16** stemmed from NOE data on the newly formed olefin of **1.26** in the RCM reaction.



Scheme 1.4. Attempted formation of **1.21** and Ring-closing metathesis to secure **1.16**

With the desired macrolactam **1.16** in hand, they began to explore the proposed transannular, biomimetic [4+3] cyclization. After much experimentation, exposure to PIDA was originally thought to give tetracycle **1.27** as product (Scheme 1.5), a result which was published in 2005.[via] However, after further analysis, the product obtained from this transformation was determined to actually be **1.28** (42% yield from **1.26**). Thus none of

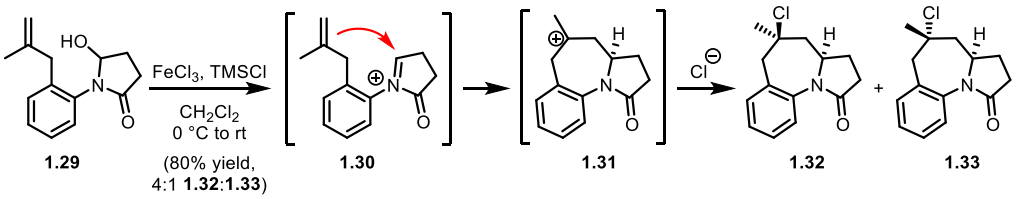
the desired tetracycle had been produced, a result which the Porco group dutifully corrected in a subsequent corrigendum.[vib]



Scheme 1.5. Porco's attempted [4+3] transannular cyclization

1.2.2 Hong's Efforts Toward Tetrapetalone A

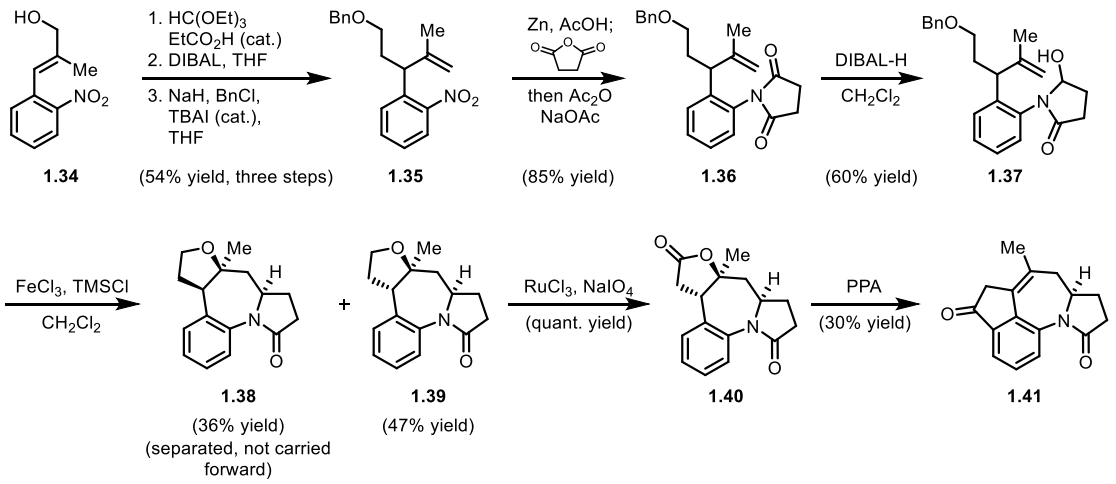
Primarily motivated by an *N*-acyliminium ion cyclization originally developed by Speckamp and Hiemstra,[xiv] Hong and coworkers sought to use this method for the formation and stereochemical analysis of benzazepine intermediates.[vii] In their initial exploration (Scheme 1.6), they prepared a readily accessible substrate **1.29** and then identified optimal conditions for efficiently cyclizing it to tricycles **1.32** and **1.33** (80% yield).



Scheme 1.6. Optimized conditions for benzazepine formation via Speckamp cyclization

Having developed optimized conditions for this transformation, Hong continued by moving to a more functionalized intermediate suitable for advancement to the tetracyclic skeleton of tetrapetalone A. As illustrated in Scheme 1.7, this strategy began with allylic

alcohol **1.34** which, in a three-step sequence involving Johnson-Claisen rearrangement, reduction, and benzyl protection furnished **1.35** in 54% yield. A one-pot reduction and condensation of **1.35** with succinic anhydride gave imide **1.36** which was desymmetrized with DIBAL to give **1.37**. Employing their optimized conditions for the key Speckamp cyclization, however, gave a diastereomeric mixture of furan products **1.38** and **1.39**.



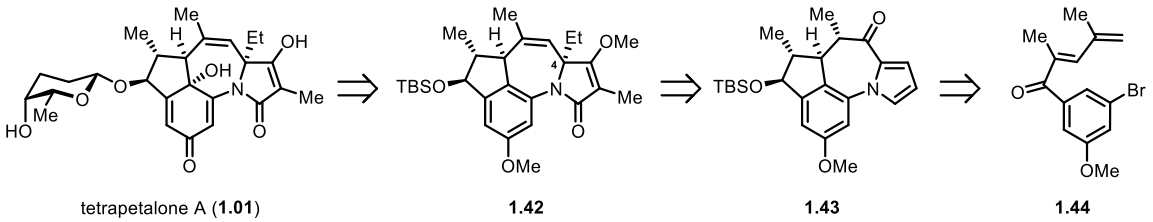
Scheme 1.7. Hong's carbocyclic framework synthesis of the tetrapetalone A aglycone

After separation of the two diastereomers, only the major diastereomer **1.39** was advanced by oxidation to the lactone **1.40** which underwent an elimination/Friedel-Crafts acylation sequence to provide tetracycle **1.41** in modest yield. While this 10-step sequence provides the skeleton of the tetrapetalone aglycone, a considerable amount of work remains for conversion of this intermediate to tetrapetalone A.

1.2.3 Sarpong's Efforts Toward Tetrapetalone A

As illustrated retrosynthetically in Scheme 1.8, Sarpong and Marcus envisioned tetrapetalone A as arising from late-stage glycosylation, aryl oxidation, and unmasking of the tetramic acid. The requisite advanced tetracycle (**1.42**) was seen as arising from **1.43**

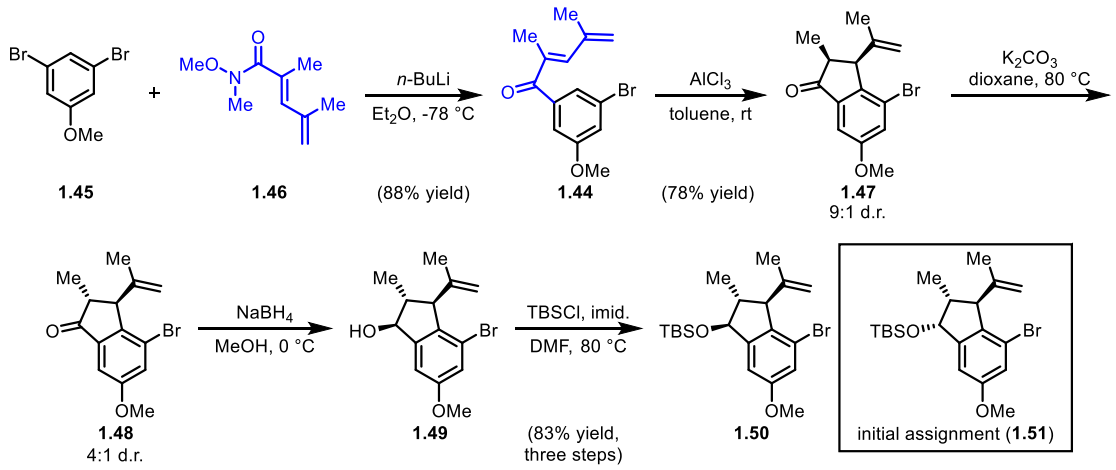
via a sequence wherein the azepine alkene ultimately derives from a ketone and reductive alkylation of a pyrrole allows installation of the tetramic acid and angular ethyl group at C(4).[viii] Building on prior work in their group, Sarpong and Marcus were intrigued by the possibility of employing a Nazarov cyclization reaction at an early stage to deliver the AB ring system of tetrapetalone A, thus **1.43** was seen as accessible from aryl dienone **1.44**.



Scheme 1.8. Sarpong and Marcus' retrosynthesis of tetrapetalone A

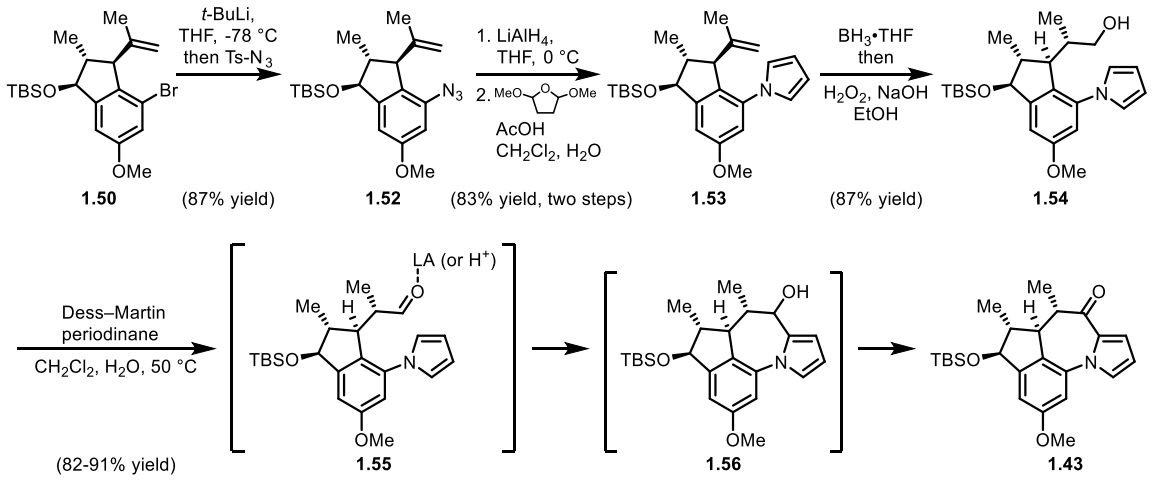
In the synthetic sense, aryl dienone **1.44** was accessed in 88% yield from 3,5-dibromoanisole (**1.45**) via lithium-halogen exchange followed by exposure to the Weinreb amide **1.46** (Scheme 1.9). Utilizing the knowledge that they had gleaned in earlier studies, exposure of the derived ketone (**1.44**) to a stoichiometric quantity of $AlCl_3$ induced the Nazarov reaction which occurred with excellent regiocontrol (13:1). However, the stereochemical outcome of the transformation gave, as the major diastereomer, a product (**1.47**) possessing a *syn* relationship between the methyl group and adjacent isopropenyl unit. Epimerization with K_2CO_3 in dioxane at 80 °C provided the *trans* isomer **1.48** as the major component in a 4:1 mixture that was subsequently silylated to **1.50** after separation of the minor diastereomer. In their initial studies, the borohydride reduction of **1.48** was assigned as proceeding via hydride delivery to the face opposite the methyl group thus leading to silyl ether **1.51**. A correction to this stereochemical assignment was later

published which reassigned the relative stereochemistry of this product to **1.49** and the corresponding silyl ether (**1.50**).



Scheme 1.9. Sarpong's preparation of indane **1.50**

With aryl bromide **1.50** in hand, attempts were made to effect *N*-arylation employing Buchwald-Hartwig conditions, however these efforts proved fruitless. As an alternative, Sarpong and Marcus were able to advance **1.50** using lithium halogen exchange followed by exposure to tosyl azide (Scheme 1.10). The resulting azide **1.52** was subjected to reduction and condensation with 2,5-dimethoxyfuran to produce pyrrole **1.53**. To construct the 7-membered ring, hydroboration-oxidation of the terminal olefin in **1.53** was followed by oxidation of the resultant alcohol (**1.54**) with Dess-Martin periodinane. The latter conditions led directly to the cyclized product, presumably via the intermediacy of aldehyde **1.55** and Friedel-Crafts alkylation product **1.56**, which undergoes a second oxidation to the corresponding ketone **1.43**.

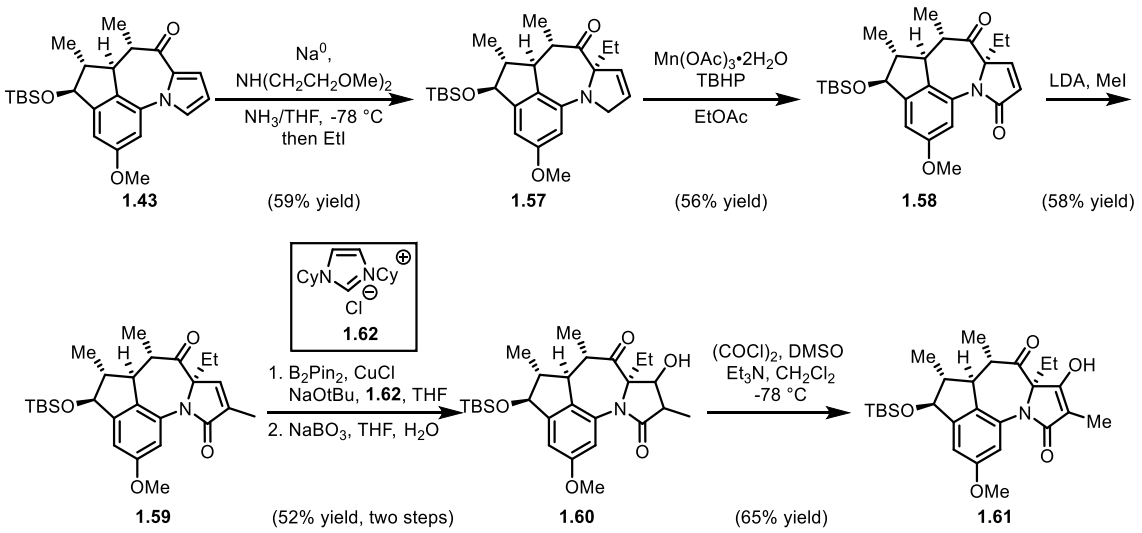


Scheme 1.10. Sarpong's oxidative cyclization to tetracycle **1.43**

With the tetracyclic scaffold now in place, the Sarpong group turned attention to elaborating the pyrrole moiety into the fully functionalized tetramic acid (Scheme 1.11). To this end, building on precedent from Donohoe and coworkers, they were able to remarkably diversify this substrate scope into not only a compound bearing an aromatic ring, but also one that contains a ketone functional group. Utilizing sodium in ammonia/THF with bis(methoxyethyl)amine as additive followed by exposure to iodoethane, not only were they able to effect a reductive alkylation of the pyrrole, this transformation also occurred with the correct regioselectivity and facial selectivity to deliver the ethyl group on the α-face of the molecule (**1.57**).

Following the reductive pyrrole alkylation to **1.57**, allylic oxidation with $Mn(OAc)_3 \cdot 2H_2O$ in the presence of *t*-butylhydroperoxide gave amide **1.58**. From there, a four-step sequence involving methylation, borylation, and two oxidations provided the requisite tetramic acid moiety (**1.61**). This compound represents the most advanced intermediate thus far reported by Sarpong and Marcus and significant challenges remain to advance it to the natural product, including: installation of the azepine alkene from the

ketone, aryl oxidation of the anisole unit, and installation of the β-rhodinose unit on the unmasked benzylic alcohol.

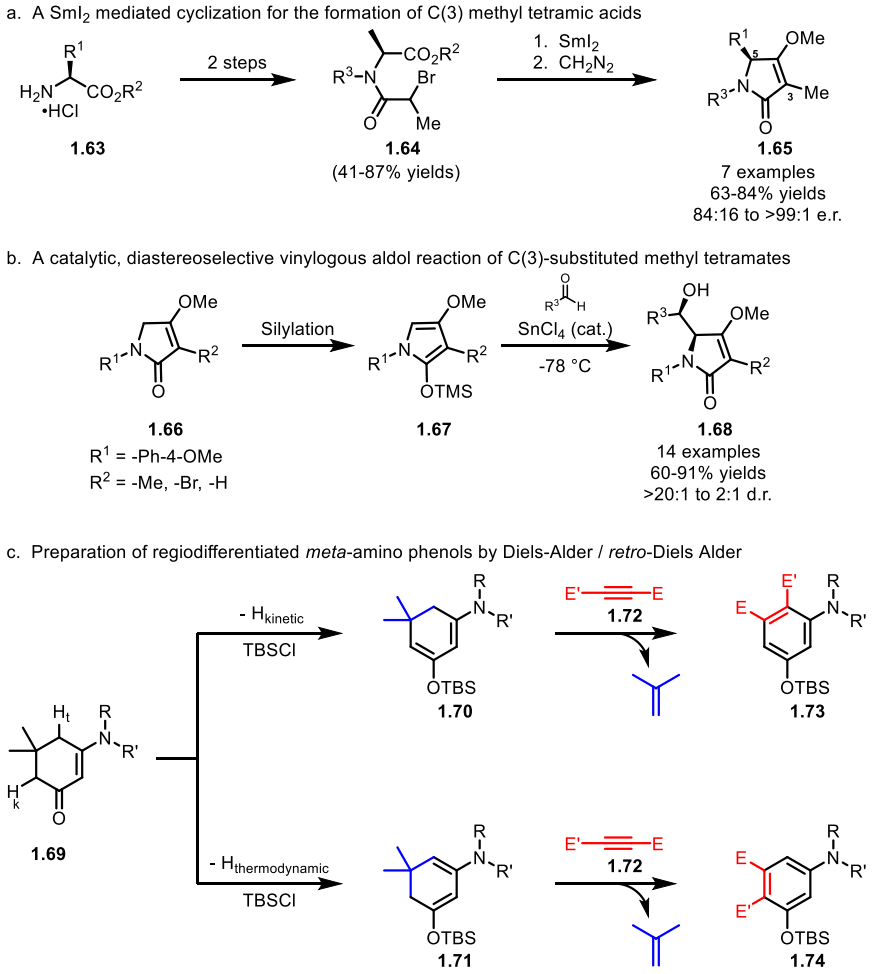


Scheme 1.11. A reductive pyrrole alkylation and oxidation to a tetramic acid.

1.2.4 Pettus' Efforts Toward Tetrapetalone A

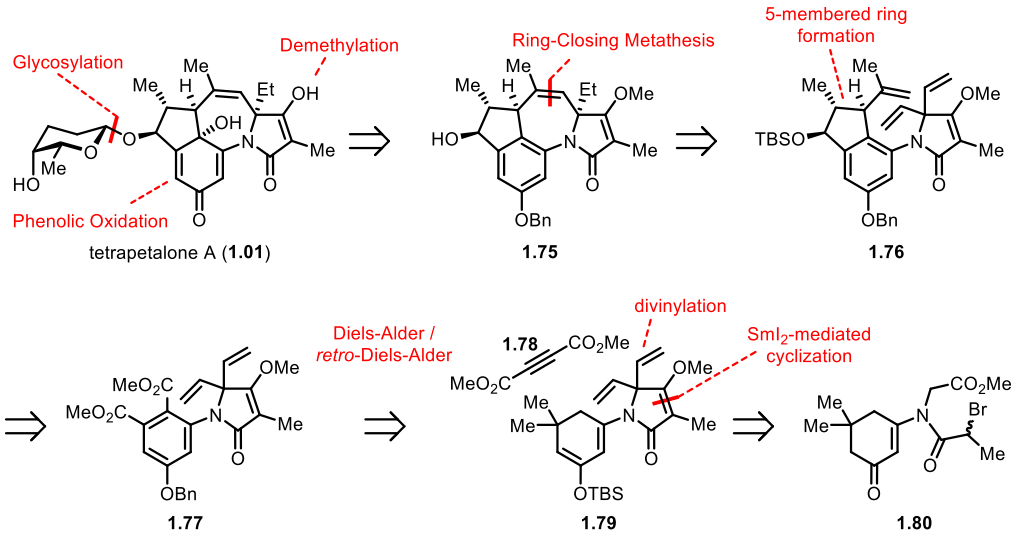
The Pettus group has published three methodological papers that were inspired by structural motifs present in the tetrapetalones. The rare C(3)-methyl tetramic acid present in the natural product led to an effort that culminated in a mild samarium diiodide (SmI_2) mediated cyclization to provide chiral C(3)-methyl tetramic acids (**1.65**, Scheme 1.12, top).[ixa] In addition, Pettus extended the use of the vinylogous Mukaiyama aldol reaction to give the C(5) substituted pyrrolidinones **1.68** from the unsubstituted analogues **1.66** (Scheme 1.12, middle).[ixb] A third method inspired by the tetrapetalone structure, is a novel preparation of *meta*-amino phenols.[ixc] Limitations associated with strategies that would form the *N*-aryl bond (*vide infra*, Frontier's efforts) led the Pettus group to consider the construction of these motifs by way of a Diels-Alder/*retro*-Diels-Alder reaction (Scheme 1.12, bottom). Exposure of **1.69** to kinetic or thermodynamic conditions to generate silyl

enol ethers **1.70** and **1.71**, respectively, led to the regio-differentiated *meta*-amino phenols **1.73** or **1.74**, respectively, with loss of isobutylene gas.



Scheme 1.12. Tetrapetalone A inspired methods development from the Pettus group

Outside of these three publications, no further detail or progress have been reported in the open literature. What follows next are strategies and progress outlined in the dissertations of two graduate students of the Pettus group, Marissa Weaver and Wen-Ju Bai, that were made available in mid-2017.[xv]

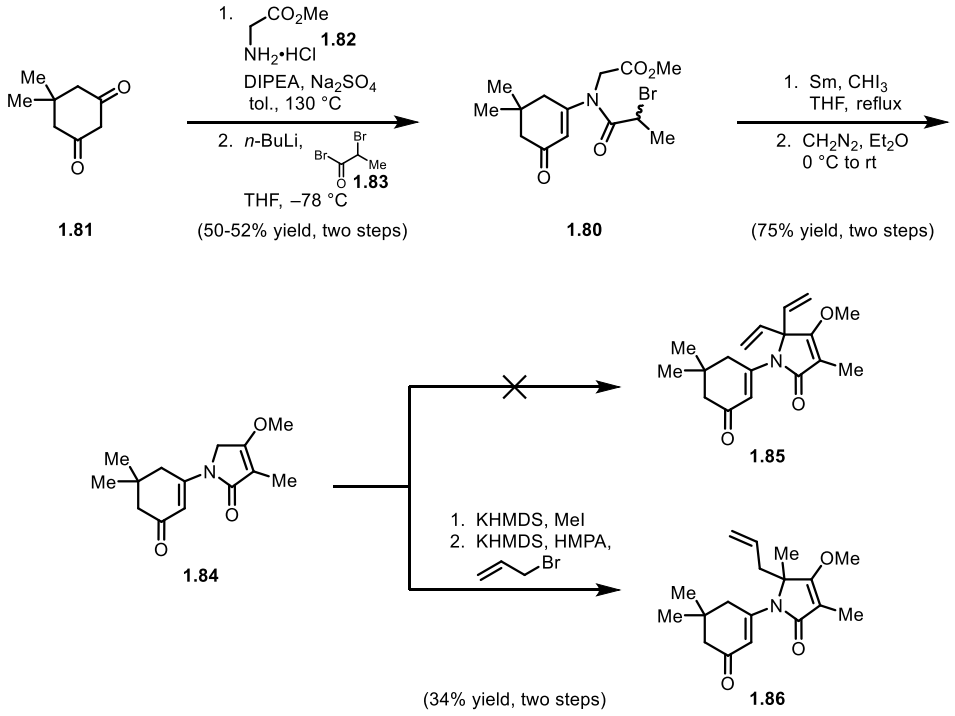


Scheme 1.13. Pettus' initial retrosynthetic analysis of tetrapetalone A.

In an initial retrosynthetic analysis of tetrapetalone A (**1.01**, Scheme 1.13), Pettus and coworkers proposed to employ the aforementioned methods and envisioned **1.01** as arising from a late-stage glycosylation, phenolic oxidation, and demethylation of RCM product **1.75**. The precursor for this ring-closing metathesis reaction (**1.76**) would derive from diester **1.77**, a compound they hoped to access using their developed methods. Specifically, they hoped that **1.77** would arise from a Diels-Alder/*retro*-Diels-Alder reaction of silyl enol ether **1.79** whose tetramate functionality would be installed by way of a divinylation sequence applied to a parent tetramic acid, which itself would be accessible using their SmI_2 mediated cyclization from bromide **1.80**.

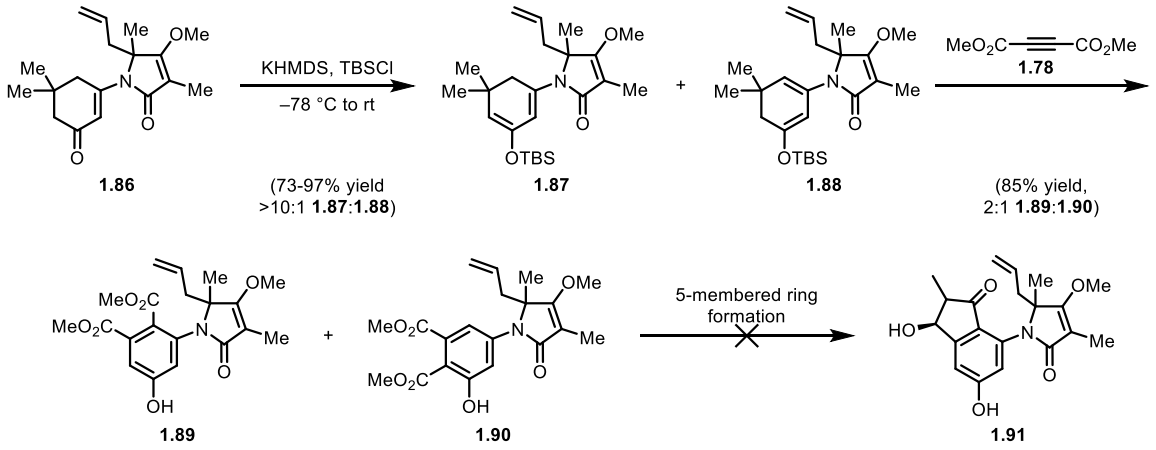
The synthesis began with commercially available dimedone (**1.81**, Scheme 1.14) which, through simple condensation and amidation, provided enamine **1.80** in 45% yield over two steps. Exposure of **1.80** to *in situ* generated SmI_2 followed by methylation resulted in methyl tetramate **1.84**. Unfortunately, subsequent efforts to convert **1.84** to the

desired divinylation intermediate **1.85** failed and their synthetic efforts were diverted along an alternative path involving methylation and allylation to furnish model system **1.86**.



Scheme 1.14. Preparation of model substrate **1.86**

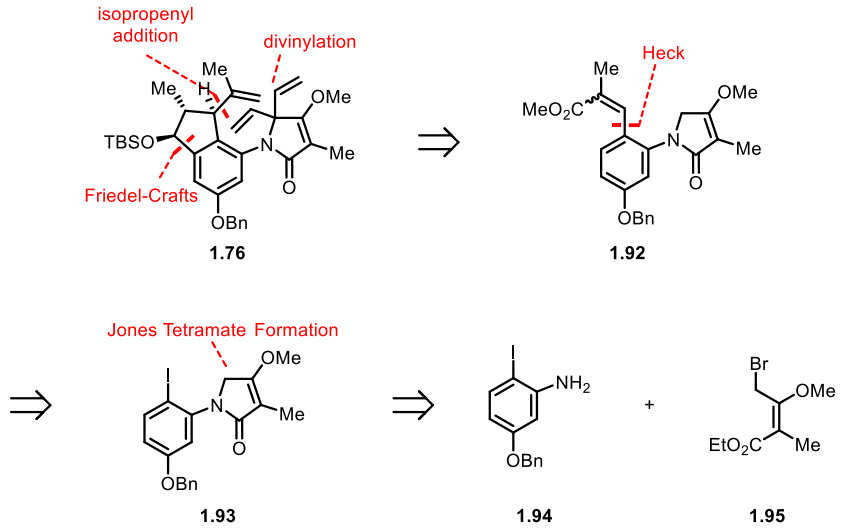
With model substrate **1.86** in hand attention turned to completion of the diene. In the event, deprotonation under kinetic conditions and trapping of the intermediate enolate provided silyl enol ethers **1.87** and **1.88** in >10:1 ratio. Despite this excellent regiochemical outcome, the high temperature required in the subsequent step unfortunately led to erosion of this regioselectivity and ultimately gave a 2:1 mixture of Diels-Alder/*retro*-Diels-Alder products **1.89**:**1.90** upon reaction with DMAD (**1.78**). This erosion was attributed to 1,5-sigmatropic shift which converted **1.87** to **1.88** during the reaction sequence.



Scheme 1.15. Implementation of the Diels-Alder strategy

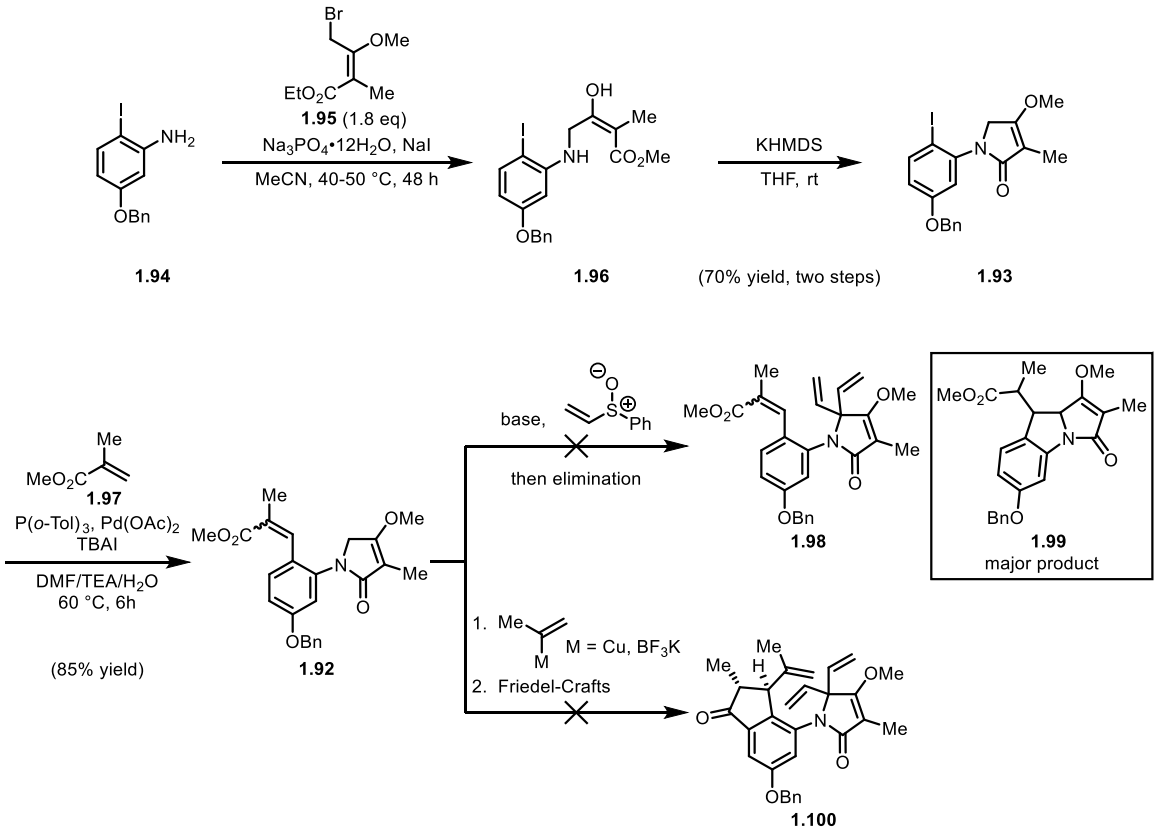
Despite this loss of selectivity in the Diels-Alder/*retro*-Diels-Alder strategy, an effort was made to elaborate **1.89** to an intermediate containing the 5-membered ring of tetrapetalone A (i.e., **1.91**) , however, this proved unsuccessful. Given the low selectivity, and inability to advance **1.89** to a suitable compound containing the 5-membered ring of tetrapetalone A, this route was abandoned and the Pettus group sought an alternative strategy.

In considering the poor regiochemical outcomes in the formation of their desired *N*-aryl tetramate, the Pettus group began to consider a redesigned route that would introduce the aryl unit from the outset of the synthesis. While the latter stages of their synthetic plan remained the same, access to the RCM precursor was re-envisioned as ultimately arising from aniline **1.94** and allylic bromide **1.95** (Scheme 1.16). A single step amine alkylation/intramolecular amidation was seen as delivering **1.93** that would then be advanced by way of a Heck reaction to deliver intermediate ester **1.92**. Advancing this to the RCM precursor would entail divinylation, intramolecular Friedel-Crafts acylation, and isopropenyl addition.



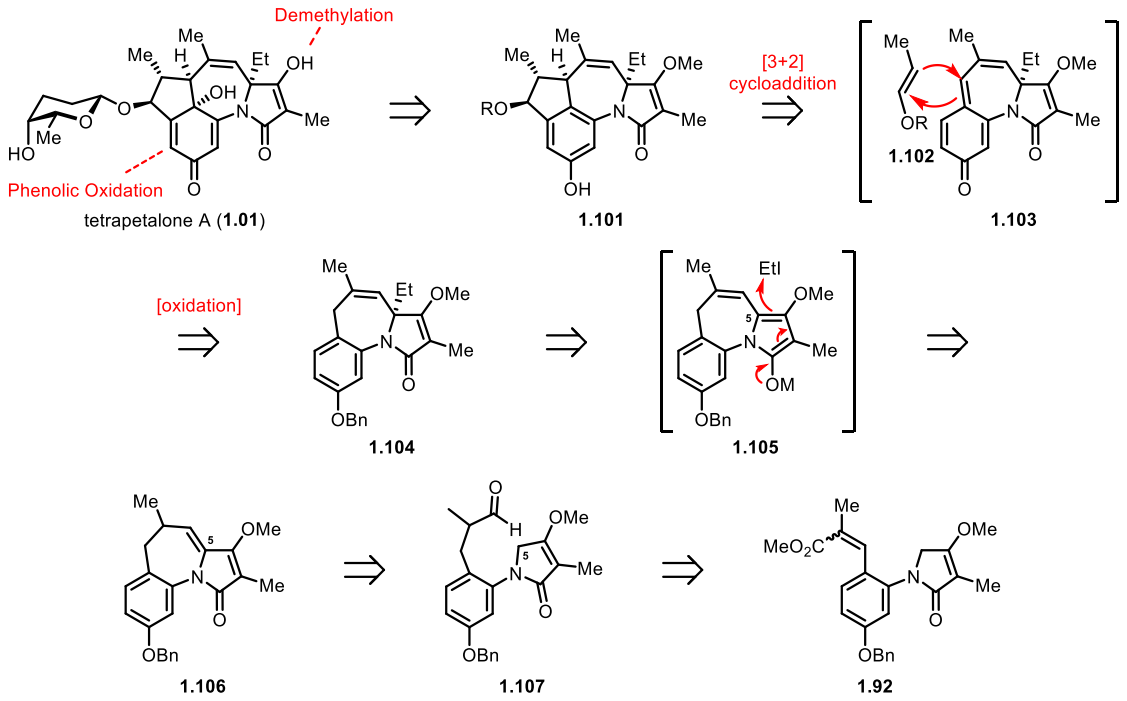
Scheme 1.16. Revised retrosynthesis of RCM precursor **1.76**

Moving forward, **1.94** was advanced via benzyl protection and exposure to modified Jones conditions employing allylic bromide **1.95** to afford **1.93** in 70% yield over two steps (Scheme 1.17). A subsequent Heck reaction with methyl methacrylate (**1.97**) yielded coupled product **1.92** in 85% yield as a mixture of isomers. Unfortunately, exposure of **1.92** to any type of base was found to induce intramolecular Michael addition to produce **1.99** as a major byproduct. Any attempts to trap the presumed intermediate enolate were unsuccessful. Alternatively, attempts to perform an intermolecular Michael addition on **1.92** to deliver **1.100** also proved futile. Faced with yet another failed attempt to introduce the requisite 5-membered ring, the Pettus group began considering approaches focusing on initial installation of the 7-membered ring, a strategy that represents their most current disclosed route to tetrapetalone A.



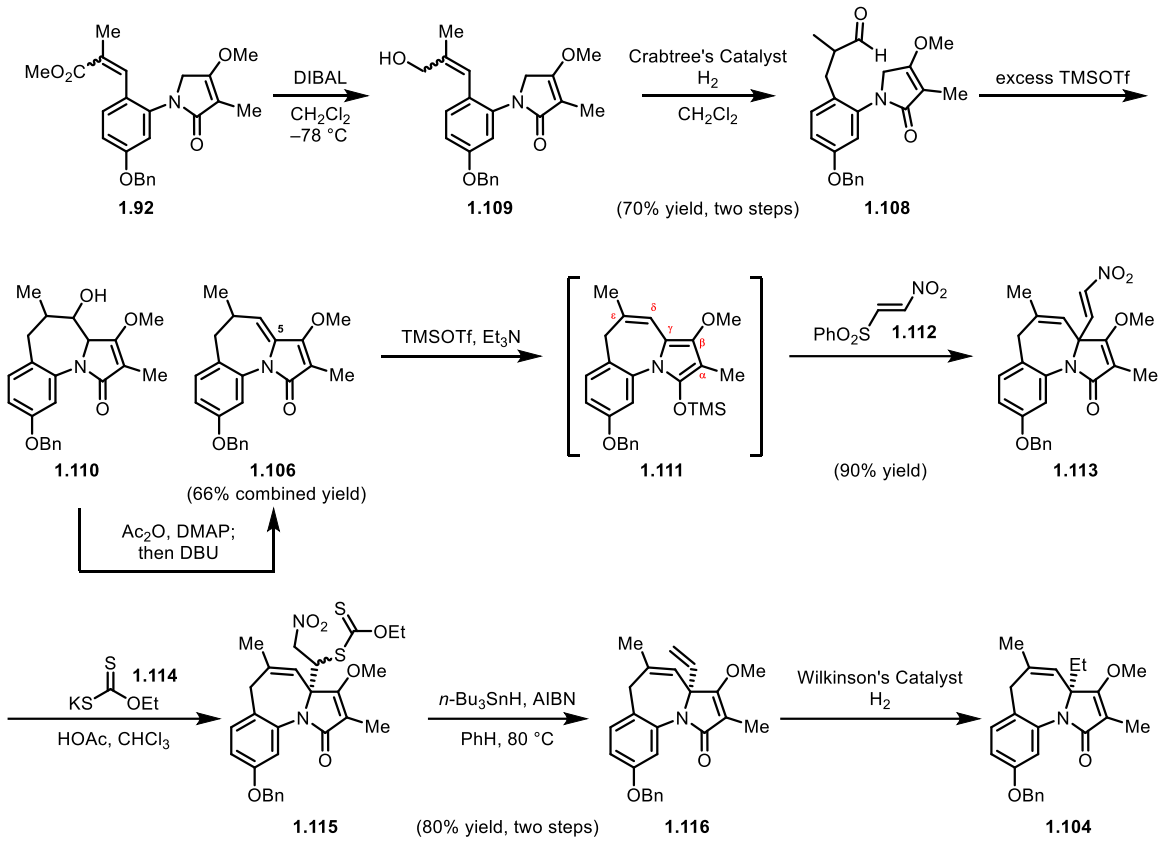
Scheme 1.17. Pettus' attempts to install the 5-membered ring

In this most recent approach, the Pettus group designed a strategy that calls for the same end-game (Scheme 1.16) and takes advantage of forward progress leading to **1.92** (Scheme 1.17). As illustrated in more detail in Scheme 1.18, this latter strategy envisions **1.01** as arising from a late-stage demethylation and phenolic oxidation of tetracycle **1.101** which would, in turn, derive from a formal [3+2] cycloaddition reaction of enol ether **1.102** and *para*-quinone methide **1.103**. This latter reactive intermediate was seen as being accessible from oxidation of parent azepine **1.104**, an intermediate that would arise from regioselective alkylation of the extended enolate (**1.105**) derived from deprotonation of **1.106**. An intramolecular aldol condensation of the aldehyde (**1.107**) produced upon reduction of **1.92** was planned for construction of the azepine ring.



Scheme 1.18. A revised retrosynthetic analysis of tetrapetalone A

In the synthetic sense, the ester of Heck adduct **1.92** was reduced with DIBAL to afford allylic alcohol **1.109** which fortuitously underwent redox isomerization in the presence of Crabtree's catalyst and hydrogen gas to deliver aldehyde **1.108** (Scheme 1.19). Exposure of **1.108** to excess TMSOTf produced a mixture of aldol products that were converged to a single condensation product (**1.106**). The extended enol ether **1.111** was prepared under soft-enolization conditions (TMSOTf, Et_3N) and was regioselectively alkylated using vinyl sulfone **1.112** to deliver **1.113**.



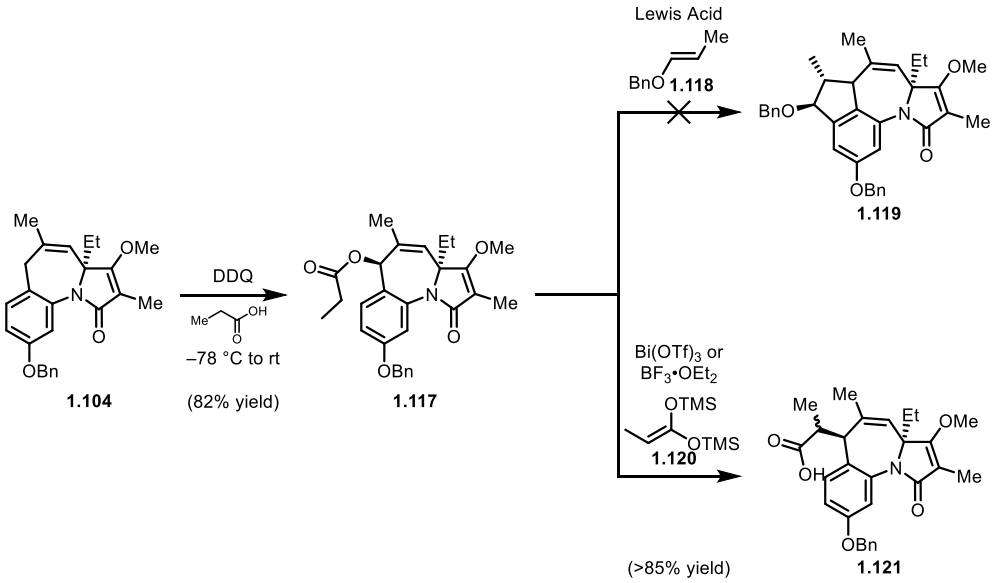
Scheme 1.19. Pettus' preparation of azepine **1.104** utilizing an aldol/vinylation strategy

The remarkable vinylation of **1.111** warrants some discussion. In the case of generating the intermediate enolate, several positions could potentially undergo alkylation, notably at the α, γ, or ε positions (intermediate **1.111**). Pettus and coworkers attributed the observed selectivity to sterics, noting that the α and ε positions are flanked by sp^3 hybridized carbons whereas the γ position is flanked by two sp^2 carbons, and to electronics, that the γ position is the most electron rich amongst the three positions due to the adjacent methyl ether.

In advancing **1.113**, the Pettus group took inspiration from the work of Samir Zard and employed potassium xanthate (**1.114**) in a Michael addition that furnished intermediate **1.115**.[xvi] Reductive elimination of **1.115** produced vinylated intermediate **1.116** which,

upon selective reduction of the vinyl moiety, then completed installation of the ethyl group to give **1.104**.

Efforts to generate a *para*-quinone methide intermediate from **1.104** culminated in a DDQ oxidation in the presence of propionic acid to deliver benzylic propionate derivate **1.117** (Scheme 1.20). While a [3+2] was thwarted by polymerization of the vinyl ether **1.118** prior to reaction with the substrate, the Pettus group was able to effect a nucleophilic addition at the benzylic position with bis-silyl ketene acetal **1.120** to deliver carboxylic acid **1.121**. Although this dissertation was made available in 2017, this work presumably represents work in the Pettus group up until 2015 when Wen-Ju Bai's dissertation was submitted. Any further progress has yet to be disclosed as of this writing.

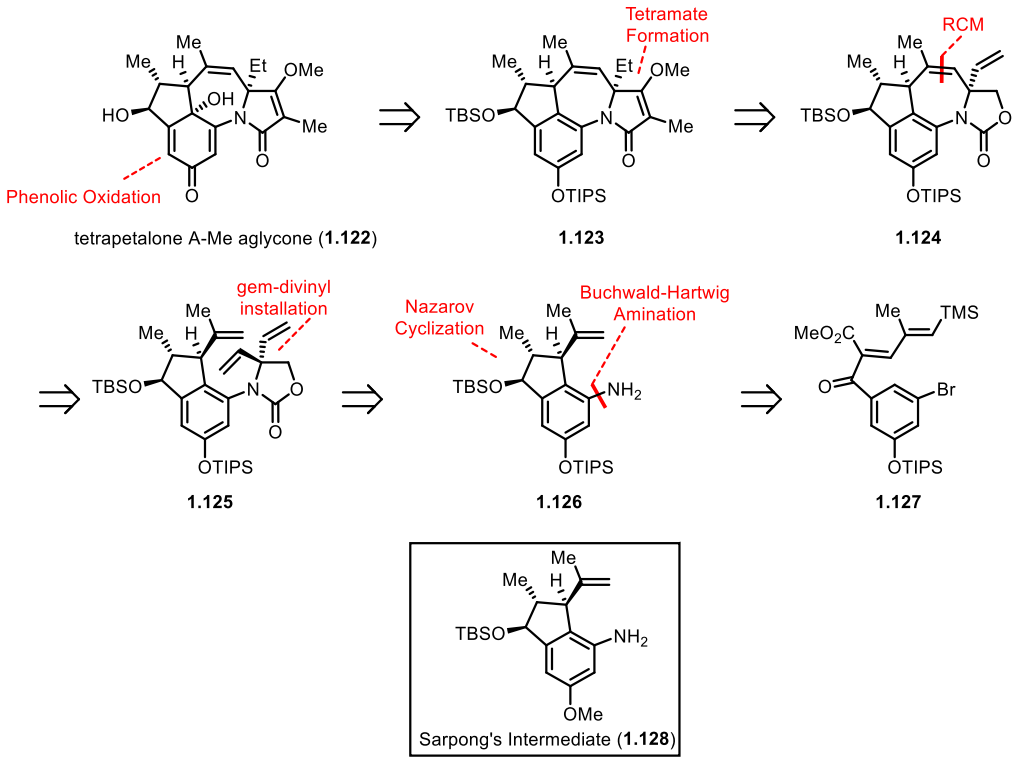


Scheme 1.20. The most advanced Pettus intermediate

1.2.5 Frontier's Efforts Toward Tetrapetalone A

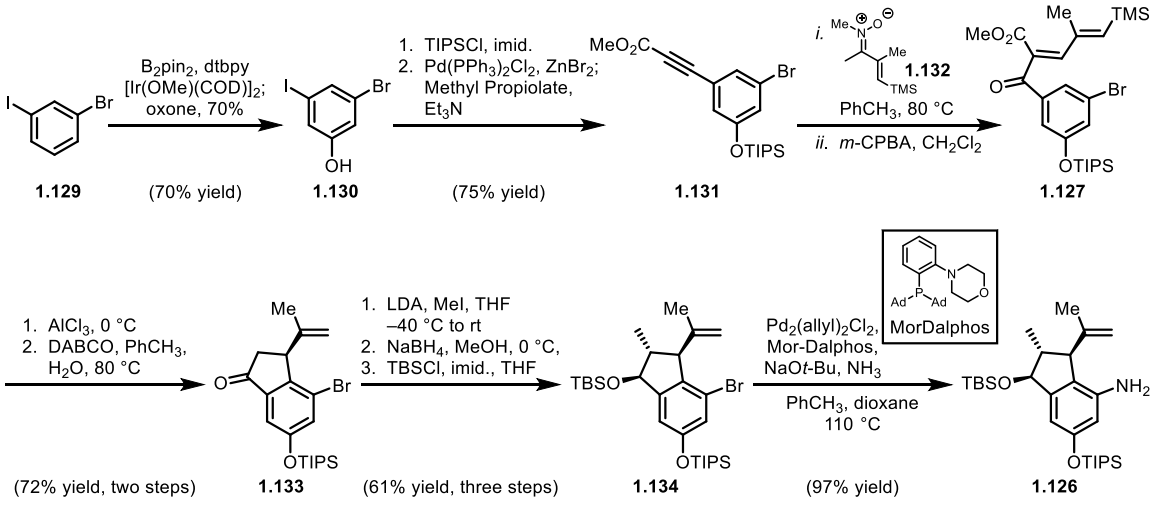
Of all the efforts toward the tetrapetalones published prior to the writing of this thesis, Frontier's paper on the synthesis of the tetrapetalone A-Me aglycone described most advanced intermediate to date.[x] While three graduate students' dissertations from the

University of Rochester were dedicated toward the total synthesis of the tetrapetalones, only the most recently published work is discussed here.[xvii] This landmark synthesis confirmed the structures of the aglycone of tetrapetalone A using X-Ray crystallographic data. Retrosynthetically, like many of the strategies toward the tetrapetalones, Frontier prepared **1.122** by way of a late stage oxidative dearomatization from parent tetracycle **1.123** (Scheme 1.21). The key steps in this synthesis entailed a diastereoselective ring-closing metathesis reaction to deliver **1.124** that would be further elaborated to methyl tetramate **1.123**. The geminal divinyl group of **1.125** would be installed on Buchwald-Hartwig amination product (**1.126**), a compound first established by the Sarpong group as being accessible by way of a Nazarov reaction (**1.128**).[viii]



Scheme 1.21. Frontier's retrosynthetic analysis of tetrapetalone A-Me aglycone.

Although Sarpong first established a preparation of a compound analogous to **1.126** via Nazarov cyclization, Frontier employed alternative tactics in its preparation with a TIPS protected phenol as opposed to Sarpong's methyl ether variant (Scheme 1.22). Using technology developed in the Hartwig lab, 3-bromoiodobenzene underwent a one-pot *meta*-selective borylation-oxidation sequence to deliver phenol **1.130** whose hydroxyl group was protected as a triisopropylsilyl (TIPS) ether. Selective cross-coupling of **1.130** via with the more reactive iodo- functional group under Negishi-type conditions gave alkynoate ester **1.131**. Due to its availability and ease of access, nitrone **1.132** was selected for use in a [3+2] dipolar cycloaddition reaction with **1.31** which, following oxidative extrusion of nitrosomethane, gave aryl dienone **1.127**. Subsequent exposure of **1.127** to a stoichiometric quantity of Lewis Acid ($AlCl_3$) promoted a Nazarov cyclization which was followed by a mild Krapcho decarboxylation reaction to deliver indanone **1.133**.

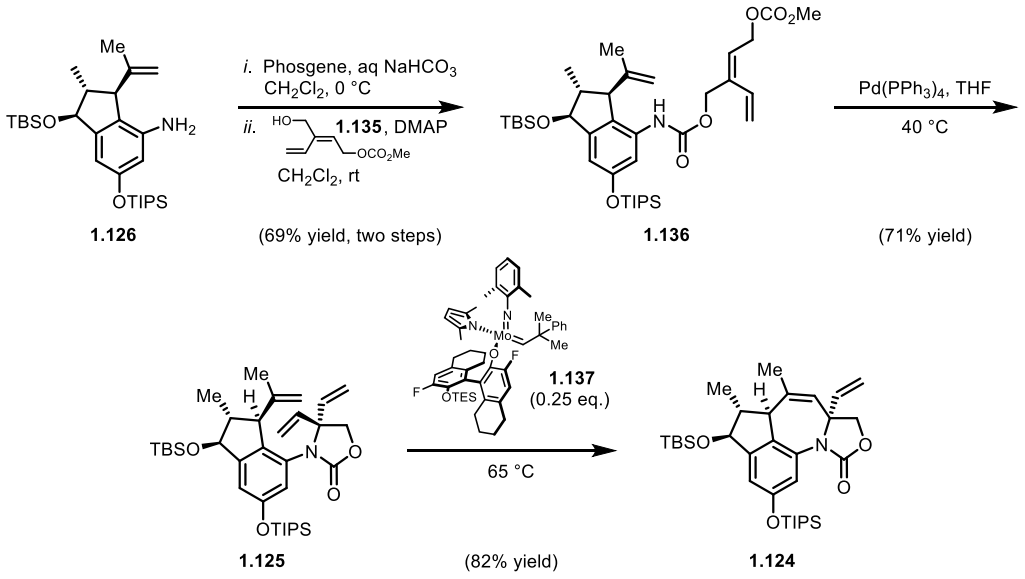


Scheme 1.22. Frontier's synthesis of indane **1.126**

The hopes of diastereoselective alkylation on the face opposite the isopropenyl unit were realized by simple deprotonation of **1.133** with LDA and alkylation of the

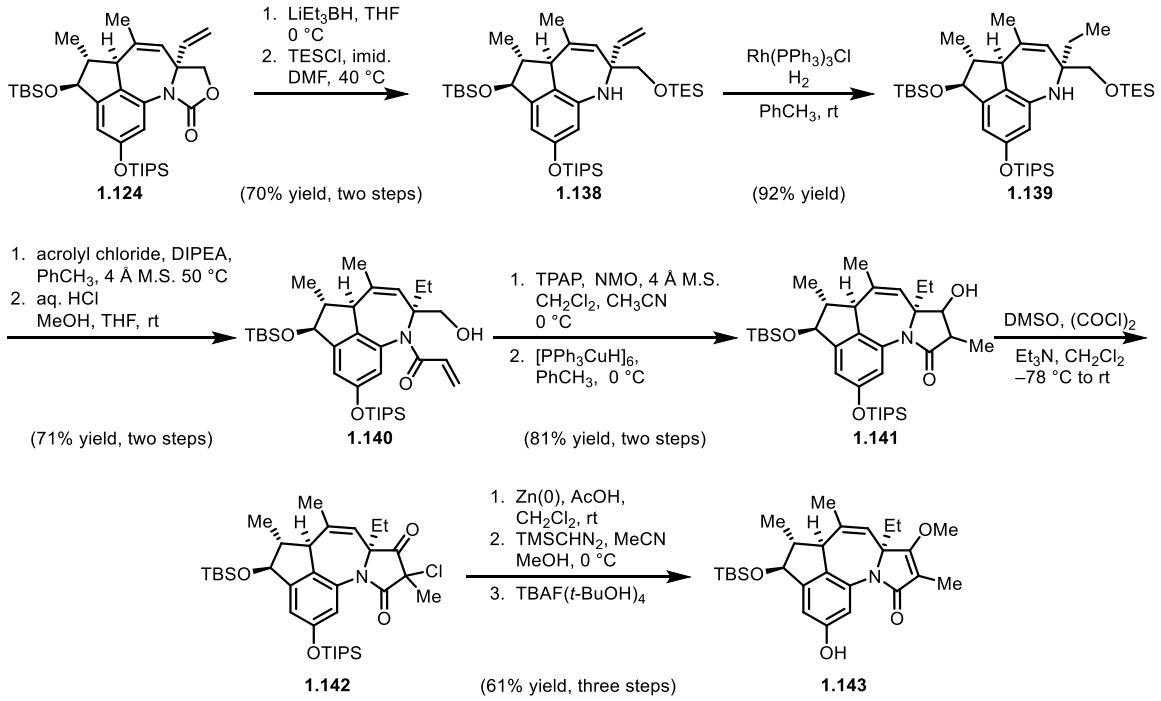
intermediate enolate with iodomethane. Diastereoselective reduction of the intermediate ketone and TBS protection yielded the indane motif with all the relative stereochemistry set as needed in the natural product (**1.134**). As was observed by the Sarpong group, the venerable Buchwald-Hartwig coupling with any type of bulky amine/amide nucleophiles failed to deliver any desired coupling products, which the authors attributed to steric considerations. While Sarpong and coworkers solved this problem with lithium-halogen exchange followed by azidation with tosyl azide, Frontier circumvented this problem by coupling of **1.134** with a sterically unencumbered amine nucleophile, ammonia. Thus, Frontier was able to access intermediate amine **1.126** in 10 steps from commercial materials.

With amine **1.126** in hand, the Frontier group turned attention to the installation of the divinyl moiety required for the proposed RCM reaction (Scheme 1.23). This was achieved by the formation of carbamate **1.136** followed by Pd-catalyzed intramolecular allylic amination to deliver gem-divinyl RCM substrate **1.125**. It is worth noting the diastereotopic nature of the vinyl moieties and the requirement of diastereotopic group selectivity for the planned RCM reaction to successfully lead to the natural product. Initial efforts using HG-II and other typical commercially available RCM catalysts gave, at best, a 2.4:1 dr (favoring the desired isomer **1.124**) with a 58% yield (not depicted). Furthermore, catalyst turnover was poor and required near stoichiometric quantities of reagent in order for the reaction to proceed. With these limitations, the Frontier group turned to a collaborative effort with Professor Amir Hoveyda who found that 25 mol% loading of a molybdenum based catalyst **1.137**, gave a >25:1 dr favoring the desired product **1.124** in 82% yield.



Scheme 1.23. A ring closing metathesis to deliver azepine **1.124**.

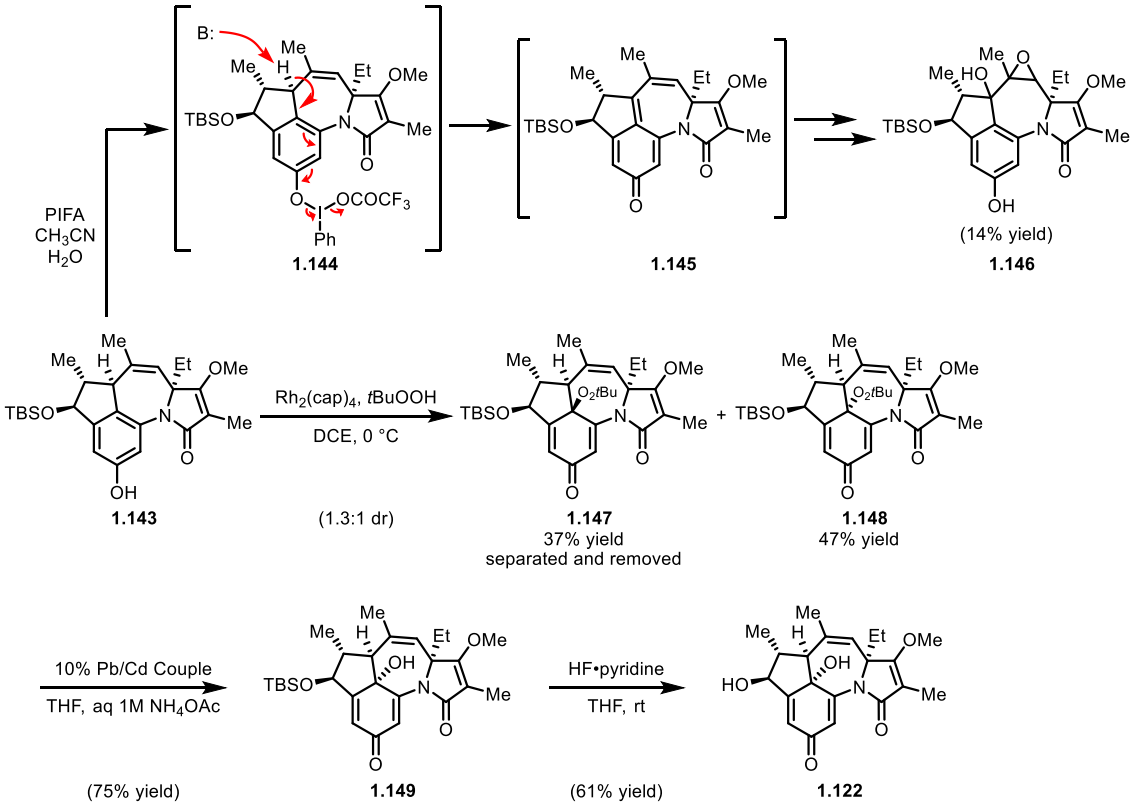
With the phenol, 5-membered ring, and azepine ring in place, what remained for the completion of the aglycone skeleton was the formation of the tetramic acid moiety (Scheme 1.24). To this end, the carbamate functionality of **1.124** was reduced with $LiEt_3BH$ and the resulting primary alcohol was protected as the triethylsilyl (TES) ether to give **1.138**. Selective reduction of the terminal alkene, acylation of the nitrogen, and removal of the TES group afforded primary alcohol **1.140**. Subsequently oxidation of **1.140** under Ley oxidation conditions gave an intermediate aldehyde that was captured via intramolecular aldol reaction upon reduction of the α, β-unsaturated amide to produce tetracycle **1.141**. Oxidation of **1.141** under Swern conditions unfortunately resulted in over oxidation to tertiary halide **1.142**. Reduction of **1.142** followed by methylation with TMS-diazomethane furnished, in roughly 10 steps from **1.124**, the methyl ether variant of the tetramic acid moiety. Lastly, silyl deprotection to give **1.143** set the stage for the remainder of the synthesis.



Scheme 1.24. Installation of the tetramic acid moiety

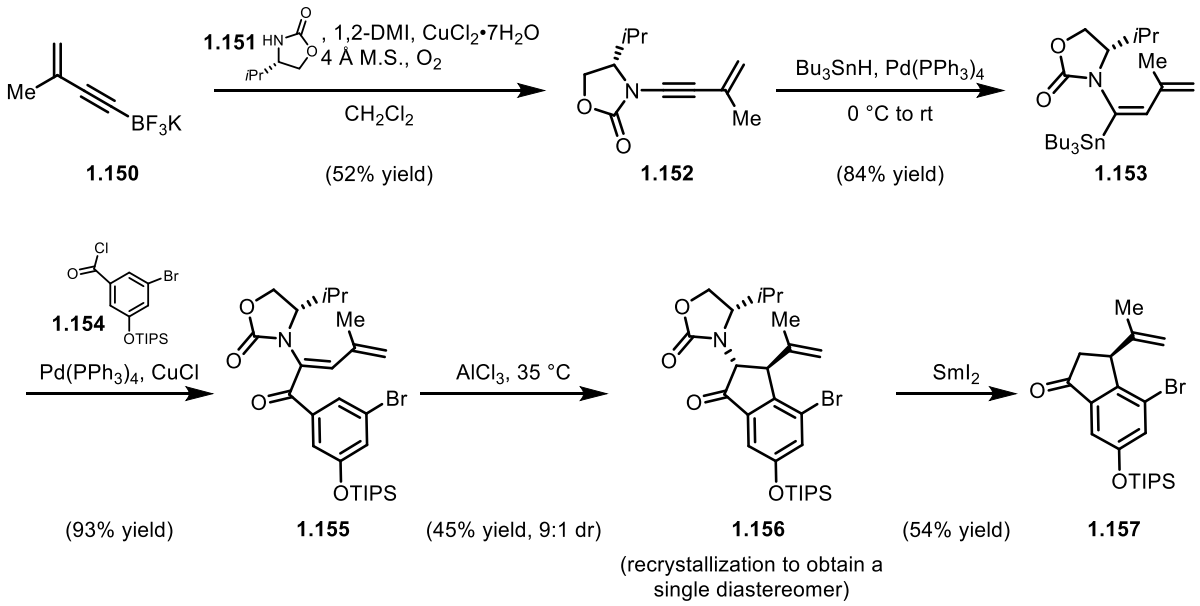
What remained to complete the preparation of tetrapetalone A-Me aglycone, was oxidation of the phenol moiety to the *para*-quinol and deprotection of the TBS ether to the corresponding alcohol (Scheme 1.25). A myriad of conditions were explored for oxidizing phenol **1.143** to the corresponding *para*-quinol. However, under typical oxidation conditions, with oxidants such as DDQ, CAN, or hypervalent iodine reagents, none of the desired product was observed. In the case of the hypervalent iodine reagent PIFA, the interesting benzylic alcohol **1.146** was produced (Scheme 1.25, top). This problem was ultimately solved by using conditions developed by Doyle for the preparation of *para*-quinol peroxide ethers. Under the latter radical conditions **1.143** was found to undergo conversion to a mixture of diastereomers **1.147** and **1.148**. The desired diastereomer, **1.148**, was separated and reduced in the presence of Pb/Cd couple to deliver the *para*-quinol **1.149** in 35% yield over two steps. Finally, deprotection of the TBS ether furnished

the tetrapetalone A-Me aglycone (**1.122**), in approximately 27 steps and ~0.3% overall yield.



Scheme 1.25. Frontier's completion of the synthesis of the tetrapetalone A-Me aglycone via late stage aryl oxidation

Lastly in the dissertation of Peter Carlsen,[xviic] the Frontier group has reported preliminary efforts toward developing their route into an enantioselective synthesis by employing a chiral auxiliary in their Nazarov cyclization (Scheme 1.26). In this strategy, Evans' auxiliary (**1.151**) was coupled to alkyne **1.150** to produce **1.152** which, upon subsequent hydrostannylation, was converted to stannane **1.153**. Stille coupling of **1.153** followed by Nazarov cyclization formed adduct **1.156** as a 9:1 mixture of diastereomers, which could be further enriched by crystallization. To intersect their published route, reductive cleavage of the auxiliary with SmI_2 gave indanone **1.157**.



Scheme 1.26. Preliminary efforts toward an enantioselective synthesis by Frontier

1.2.6 Conclusion

While there has been a large amount of effort directed toward developing a tetrapetalone total synthesis, prior to efforts recently reported in our group, no completed total synthesis has been described. Porco's original biomimetic approach, while building the macrocyclic skeleton of the aglycone of tetrapetalone A, unfortunately led to a macrocyclic quinone, instead of the desired [4+3] cascade cyclization that was to deliver the tetracyclic core. Hong's approach, utilizing an *N*-acyl iminium ion cyclization to furnish benzazepine derivatives, provided the basic skeleton of the tetrapetalone aglycone but much work needs to be done to elaborate these intermediates to the natural product. Work emanating from the Pettus group has led to several novel developments in synthetic methods that were inspired by the tetrapetalone structure, but details to elaborate a tricyclic azepine intermediate have yet to be delineated.

Sarpong was the first to report an approach that diastereoselectively installed the indane motif by way of a Nazarov cyclization reaction. However, this group's attempts to

advance toward the natural product were thwarted due to what can be inferred as an inability to elaborate a 7-membered ring ketone into the trisubstituted alkene present in the natural product. Taking advantage of a nearly identical early stage approach, Frontier was able to advance a Nazarov product via Buchwald-Hartwig coupling with ammonia and subsequent diastereoselective ring-closing metathesis to a fully functionalized azepine. This RCM product was then carried into a 10 step sequence that orchestrated installation of the tetramic acid moiety. These efforts culminated in the first completed total synthesis of the vinylogous methyl urethane derivative of the natural product aglycone, a known derivative from the isolation studies.

Notably, all reports toward the tetrapetalone family of natural products outlined racemic syntheses, with the exception of the Frontier group, who went on to demonstrate the viability of early stage enantioinduction using a chiral auxiliary. In addition, there are no reports disclosing significant advancement toward the β-rhodinose moiety on advanced tetrapetalone intermediates, an unmet challenge that certainly remained to be addressed.

1.3 References

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CHAPTER TWO

Previous Approaches Toward Tetrapetalone A in the Wood Group

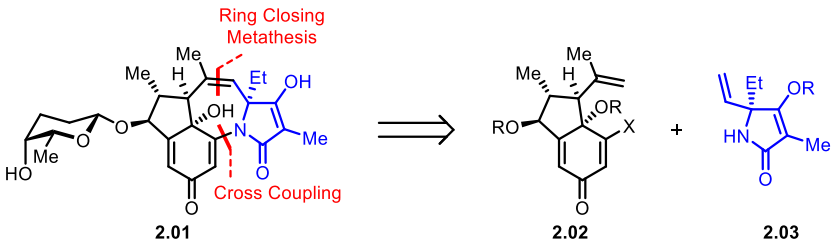
2.1 Background

The tetrapetalones have a long-standing history in the Wood group and a variety of approaches/strategies have been explored by both former graduate students as well as post-doctoral researchers. Prior to my arrival to the Wood group, former graduate student Dr. Jennifer Howell explored a variety of strategies toward the preparation of a functionalized aglycone core.[1] Chief among the paths explored were a ring-closing metathesis strategy to prepare the azepine ring, as well as a convergent *N*-arylation to install a masked tetramic acid unit. Issues with these efforts motivated post-doctoral scholar Dr. Matthew Haley to revise our strategy to one that involves an early installation of the tetramic acid moiety. It was former graduate student Dr. Travis McMahon as well as post-doctoral scholar Jonas Buergler who continued efforts to advance this strategy toward the tetrapetalone core.[2] While Dr. Jennifer Howell's work is summarized in the dissertation of Dr. Travis McMahon, for the sake of completeness it is re-summarized here along with the work of Dr. Matthew Haley, Dr. Travis McMahon, and Dr. Jonas Buergler. Many of the schemes are reproduced from Dr. McMahon's dissertation.

2.2 A Ring-Closing Metathesis / N-Arylation Approach

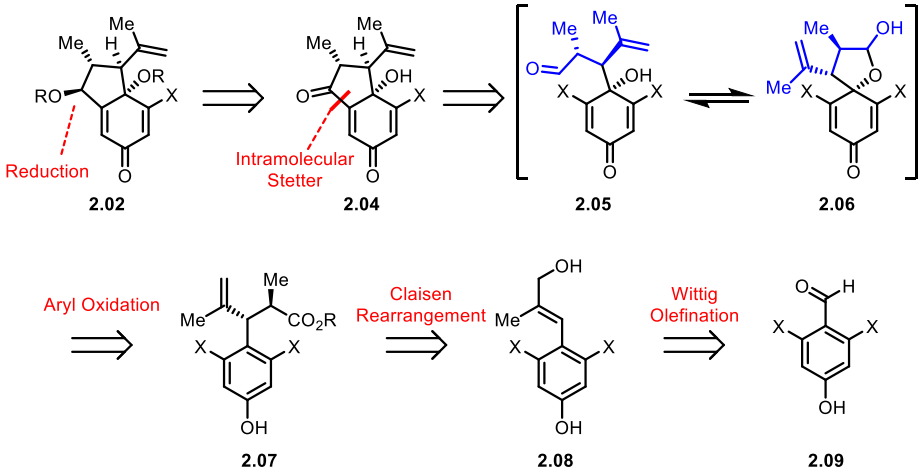
The initial analysis of tetrapetalone A involved deconstructing the natural product into two halves (Scheme 2.1). By cleaving the trisubstituted double bond in the azepine ring and the depicted *N*-C bond (**2.01**), Dr. Howell envisioned taking the natural product

back to vinyl halide **2.02** and tetramic acid **2.03**. Thus, the two key critical bonds would be formed by a ring-closing metathesis and Buchwald-Hartwig amidation cross-coupling reaction.



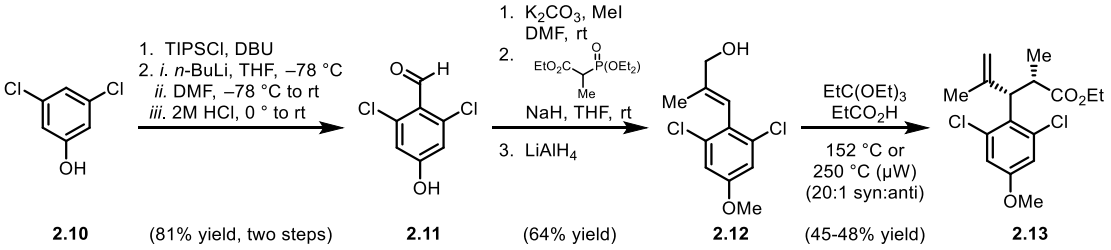
Scheme 2.1. Initial retrosynthetic analysis of tetrapetalone A.

Early efforts in the group were thus directed toward the preparation of vinyl halide **2.02** (Scheme 2.2). This *para*-quinol-containing halide was envisioned as arising from reduction and protection/glycosylation from the parent ketone **2.04**. In considering the aldehyde/lactol equilibrium mixtures **2.05** and **2.06** respectively, Dr. Howell speculated that the ring open form (**2.06**) could be captured in an intramolecular Stetter reaction to deliver the desired ketone. The lactol **2.06** in turn would derive from an aryl oxidation of phenol **2.07**. To set the two stereocenters present in **2.07**, a Claisen rearrangement would be employed on a substrate derived from allylic alcohol **2.08** which was thought to be accessible from aldehyde **2.09**.



Scheme 2.2. Retrosynthetic analysis of vinyl halide **2.02** involving Stetter rearrangement

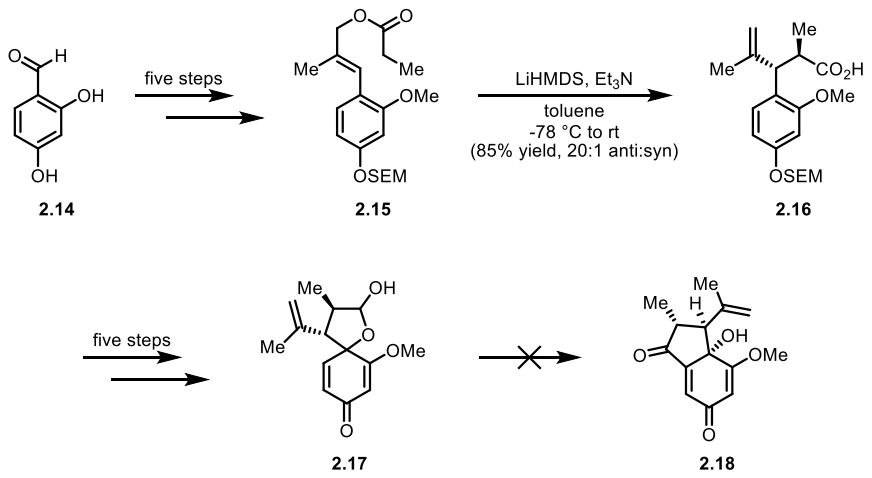
In the forward sense, aldehyde **2.11** was prepared from 3,5-dichlorophenol through a known two-step sequence (Scheme 2.3).[3] A subsequent three-step sequence involving methylation, Wittig olefination, and reduction furnished allylic alcohol **2.12** from which a Johnson-Claisen rearrangement delivered **2.13**. Unfortunately, the wrong relative stereochemistry was the major component of a >20:1 mixture of products.



Scheme 2.3. Johnson-Claisen rearrangement furnishes the wrong relative stereochemistry

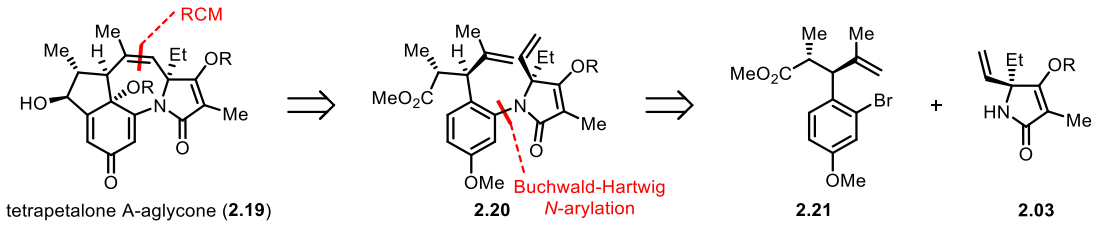
In an effort to overcome this stereochemical problem a literature search for alternate conditions commenced and revealed a report from Collum and Godenschwager that noted the stereochemical outcome could be altered by controlling the enolate geometry in the transition state of the Claisen rearrangement.[4] Thus, this lithium enolate variant was

employed on propionate **2.15** (Scheme 2.4), available in five steps through a similar sequence outlined above in Scheme 2.3. The Collum and Godenschwager conditions indeed delivered acid **2.16** in excellent yield with a 20:1 *anti*:*syn* relationship now favoring the desired product. Acid **2.16** was readily converted into lactol **2.17** through another five-step sequence. Unfortunately, attempts to promote an intramolecular Stetter rearrangement proved unsuccessful. Based on additional model studies, it became apparent that any type of additional substitution adjacent to the aldehyde functional group prevented the Stetter reaction from taking place and thus conversion of **2.17** to **2.18** was never achieved.

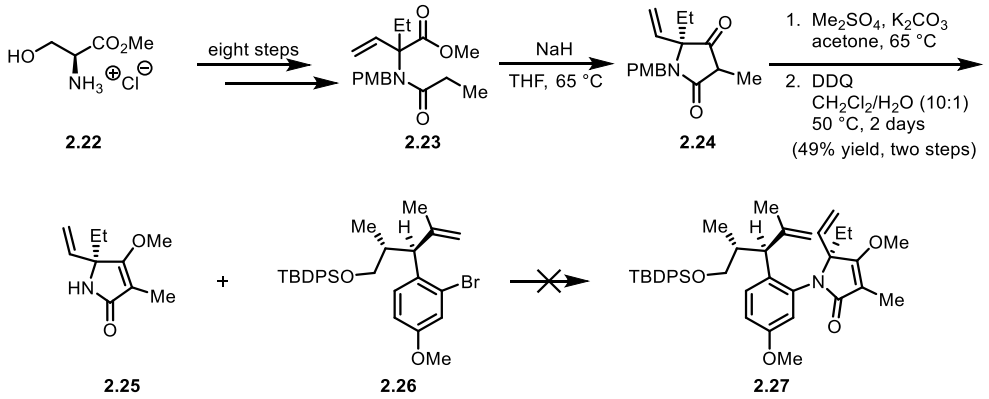


Scheme 2.4. Lactol formation and attempted Stetter rearrangement

Given the poor substrate scope of the Stetter reaction, focus was drawn to formation of the *N*-C bond present in the natural product instead of elaboration to the indane motif (Scheme 2.5). That is, a new strategy was pursued to the tetrapetalone A-aglycone that focused on delivering the azepine ring through a ring-closing metathesis of intermediate **2.20**, itself foreseen as being available from aryl bromide **2.21** and methyl tetramate **2.03** by way of a Buchwald-Hartwig amidation reaction.



Scheme 2.5. An alternative strategy involving RCM from an *N*-arylated precursor **2.20**.

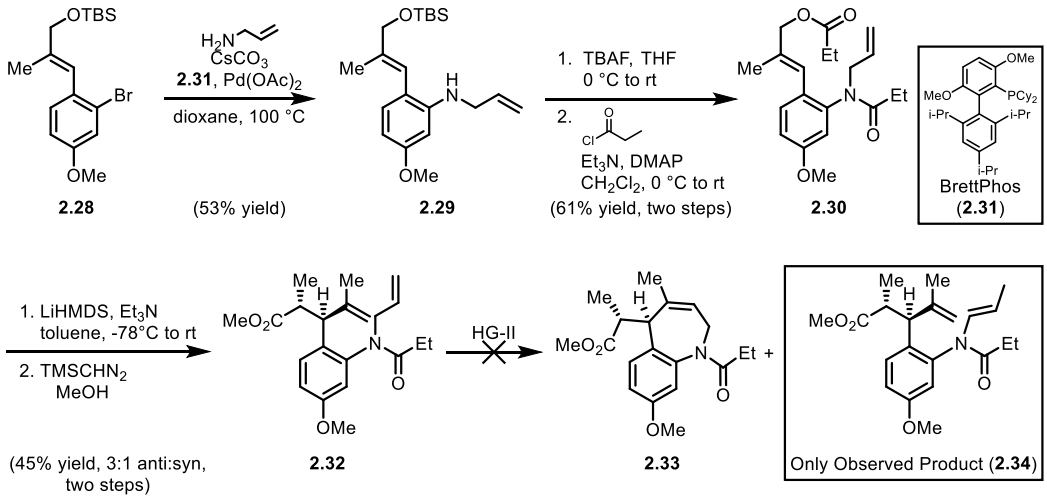


Scheme 2.6. Preparation of methyl tetramate **2.25** and attempted Buchwald-Hartwig coupling.

Prior to examining the feasibility of the Buchwald-Hartwig *N*-arylation reaction, methods for the synthesis of tetramate derivative **2.03** were explored (Scheme 2.6). These efforts culminated in the preparation of Dieckmann cyclization precursor **2.23**, which smoothly underwent cyclization to **2.24** upon treatment with NaH. Formation of a masked tetramic acid unit in the form of a vinylogous methyl urethane and PMB deprotection delivered vinylated methyl tetramate **2.25**. Bromide **2.26** was available utilizing a similar strategy outlined in Schemes 2.3 and 2.4 involving a lithium enolate derived Claisen rearrangement and subsequent advancement to **2.26**. Unfortunately, numerous attempts to form the *N*-aryl bond failed to afford any of the desired product **2.27**. Tests on model systems minimizing the steric environment around the bromide gave indication that any

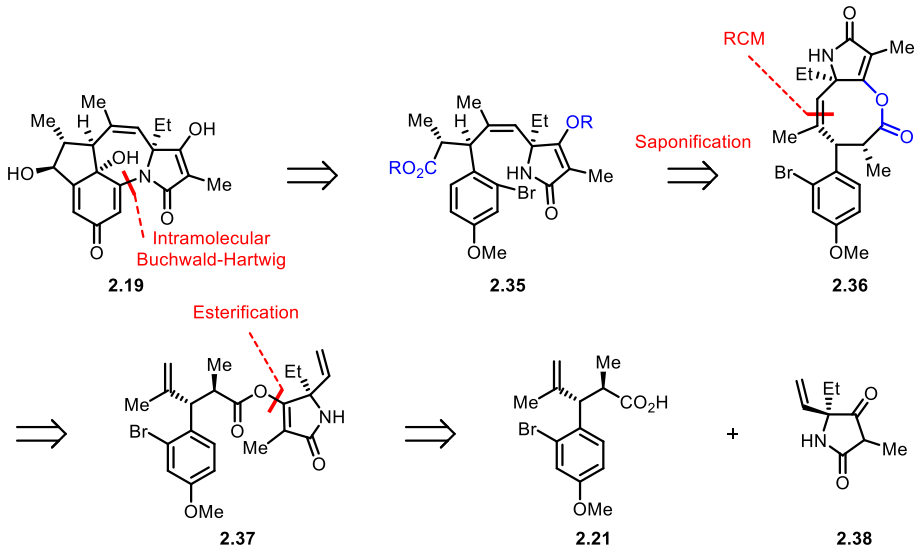
type of *ortho*-substitution to the bromide results in little to no product formation. These results, coupled with with the fact that **2.25** possesses a tetrasubstituted carbon adjacent to the nitrogen atom, indicated that the transformation was likely unproductive due to steric considerations.

Attributing the poor reactivity of the cross-coupling to sterics, the substitution of the aryl bromide coupling partner was reduced to that found in allylic TBS ether **2.28**, and the amine partner was replaced by allylamine (Scheme 2.7). With these changes, the Buchwald-Hartwig cross-coupling reaction proceeded in modest yield to give the corresponding *N*-arylated allylamine **2.29**. With this substrate in hand, silyl deprotection and bis-acylation was employed to access amide **2.30** which, upon Claisen rearrangement followed by methylation furnished **2.32**. However, attempts to use **2.32** as a model to test forming the azepine ring via RCM did not deliver any of the desired product **2.33**, instead, olefin isomerization product **2.34** was observed.



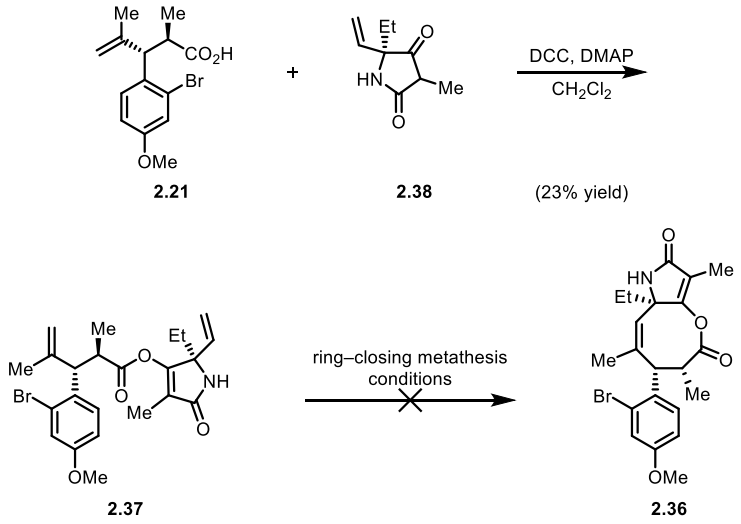
Scheme 2.7. *N*-arylation with sterically reduced coupling partners.

Failing to install the azepine via RCM, Dr. Howell reinvestigated the Buchwald-Hartwig amidation strategy. However, in this next generation approach she planned to employ **2.35** in an intramolecular variation in hope of overcoming the recalcitrance of the amidation reaction (Scheme 2.8). The requisite amide was expected to arise from hydrolysis of the eight-membered lactone **2.36**, the product of an alternative intramolecular RCM reaction applied to intermediate **2.37** which, in turn, would derive from the condensation of acid **2.21**, available through the Claisen rearrangement strategy described above, and tetramic acid **2.38**.



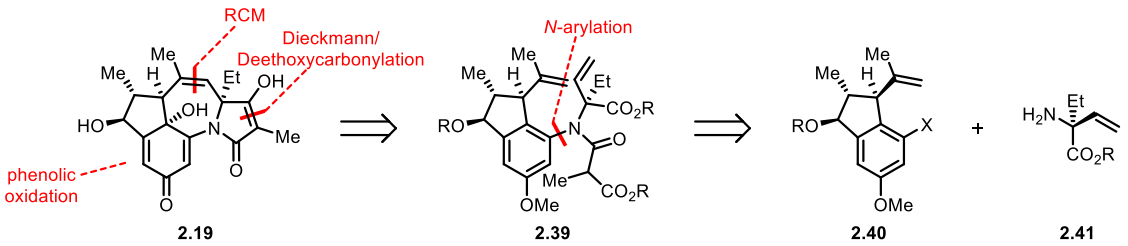
Scheme 2.8. An intramolecular Buchwald-Hartwig *N*-arylation strategy.

In accord with the plan outlined above, Claisen rearrangement product **2.21** was coupled with **2.38** via a DCC mediated esterification. Unfortunately, despite numerous attempts, the derived product (**2.37**) failed to undergo RCM to furnish the eight-membered lactone **2.36**; thus, the viability of the proposed intramolecular Buchwald-Hartwig amidation reaction could not be addressed.



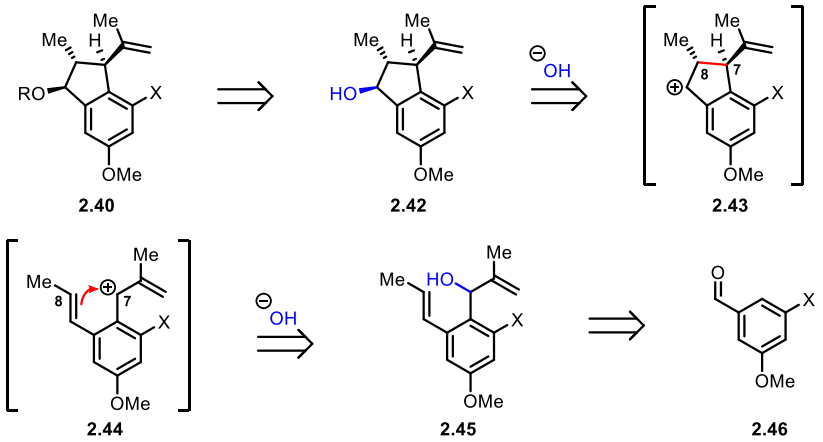
Scheme 2.9. Attempted RCM to form eight-membered lactone **2.36**

Unable to assess the viability of intramolecular Buchwald-Hartwig reactions, efforts turned toward constructing an intermediate containing a preformed aryl-nitrogen bond on an intermediate indane. In this revised strategy, much of the initial effort focused on developing an efficient approach for the preparation of amidation substrate **2.40** (Scheme 2.10). The latter intermediate was envisioned as being employed in a strategy wherein the natural product aglycone **2.19** would derive from **2.39** via RCM and phenolic oxidation followed by a late-stage Dieckmann cyclization/deethoxycarbonylation reaction that would deliver the tetramic acid moiety and complete the synthesis.



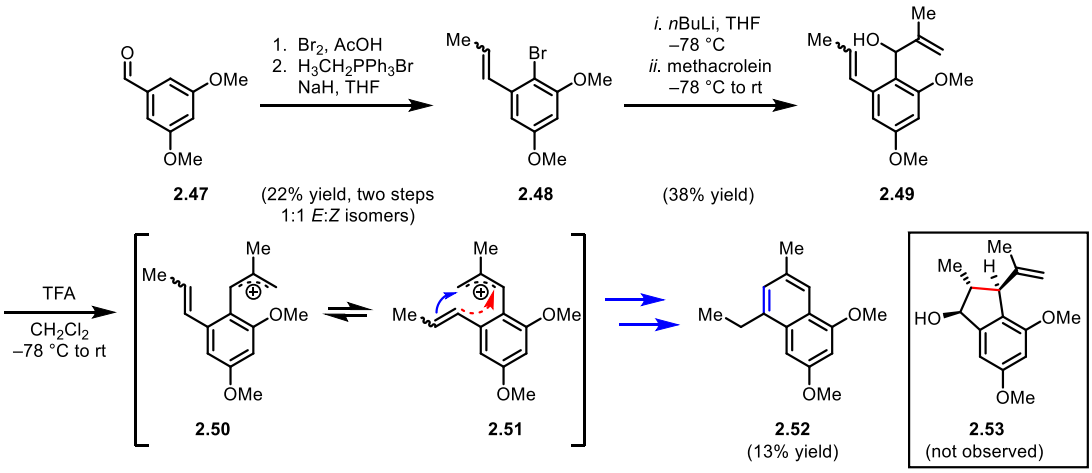
Scheme 2.10. A revised retrosynthesis with renewed focus on indane **2.40**

As depicted in Scheme 2.11, indane **2.40** was seen as arising from protection of **2.42**, the alcohol derived from cation-π cyclization product **2.43**. This cascade reaction sequence was envisioned to begin with the ionization of benzylic alcohol **2.45** to create an intermediate cation **2.44**. Cyclization to forge the C(7)-C(8) bond of **2.43** would be followed by trapping of the cation with the released hydroxide to deliver **2.42**. Benzylic alcohol **2.45** would, in turn, be derived from *meta*-anisaldehyde derivative **2.46**.

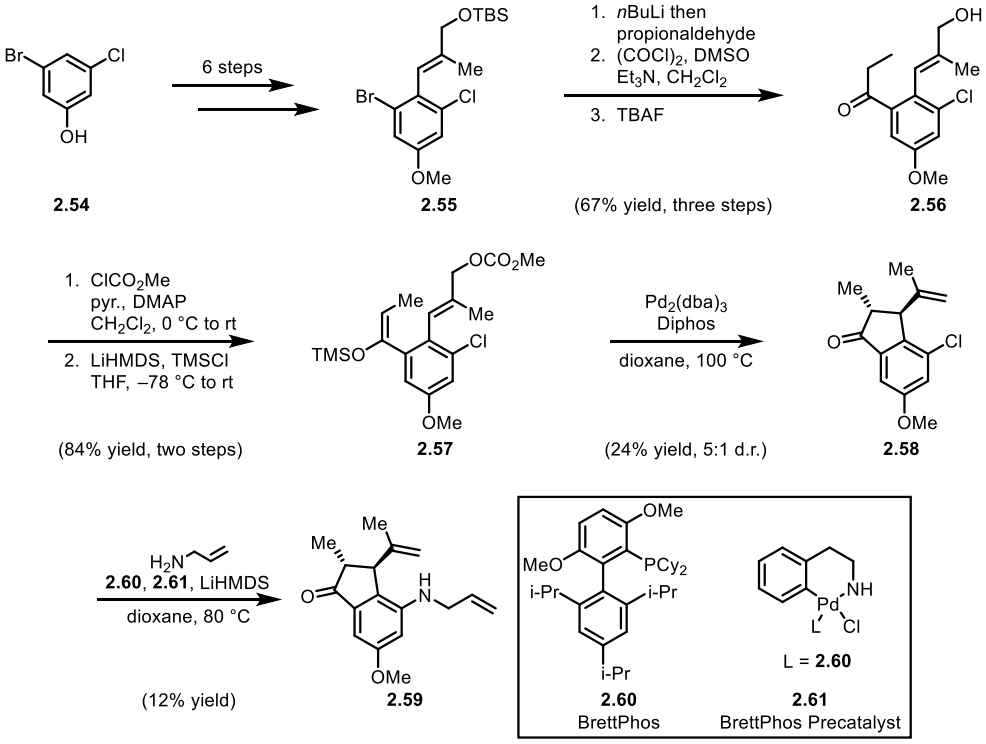


Scheme 2.11. Proposed cascade sequence leading to indane **2.40** from alcohol **2.45**

The modified strategy began with bromination of aldehyde **2.47** followed by Wittig olefination to deliver ß-methyl styrene derivative **2.48** as a mixture of *E*- and *Z*-isomers (Scheme 2.12). Lithium-halogen exchange of **2.48** followed by trapping with methacrolein delivered the substrate required for the cation-π cyclization sequence (**2.49**). In the event, cation formation by exposure to Brønsted acid generated presumed intermediate **2.50**. However, instead of trapping the cation in a 5-*exo* fashion as desired (red, **2.51**), the only isolated product was produced via a 6-*endo* cyclization mode (blue, **2.51**) to ultimately deliver **2.52** in 13% yield, with none of **2.53** detected.



Scheme 2.12. Attempted cation-π cyclization to deliver indanol **2.53**



Scheme 2.13. Preparation of indanone intermediate **2.59**

Despite the lack of success in this cation-π cyclization approach, Dr. Howell went on to consider alternative nucleophilic/electrophilic tethers that would result in this same bond of the indane motif. In accordance with this strategy, silyl enol ether **2.57** was

constructed from phenol **2.54** (Scheme 2.13). Phenol **2.54** was advanced in a similar sequence to that depicted earlier to give, after six steps, TBS-protected allylic alcohol **2.55**. Lithiation of **2.55** and exposure to propionaldehyde gave rise to an alcohol intermediate that was oxidized via Swern oxidation and then subjected to TBAF mediated TBS deprotection to deliver allylic alcohol **2.56**. Conversion of **2.56** to the corresponding carbonate enabled further conversion to silyl enol ether **2.57** which, upon exposure to $Pd_2(dba)_3$ underwent intramolecular Tsuji-Trost allylation to furnish an intermediate indane (**2.58**) for which stereochemistry was assigned via correlation to an intermediate generated in Sarpong's efforts toward tetrapetalone A. Subsequent *N*-arylation of **2.58** took place in 12% yield to give amino-indanone **2.59**. Although this route provided promising results in accessing some of the key bonds in the tetrapetalone framework, this is where Dr. Jennifer Howell's work ended.

2.3 Building From an N-Aryl Masked Tetramic Acid

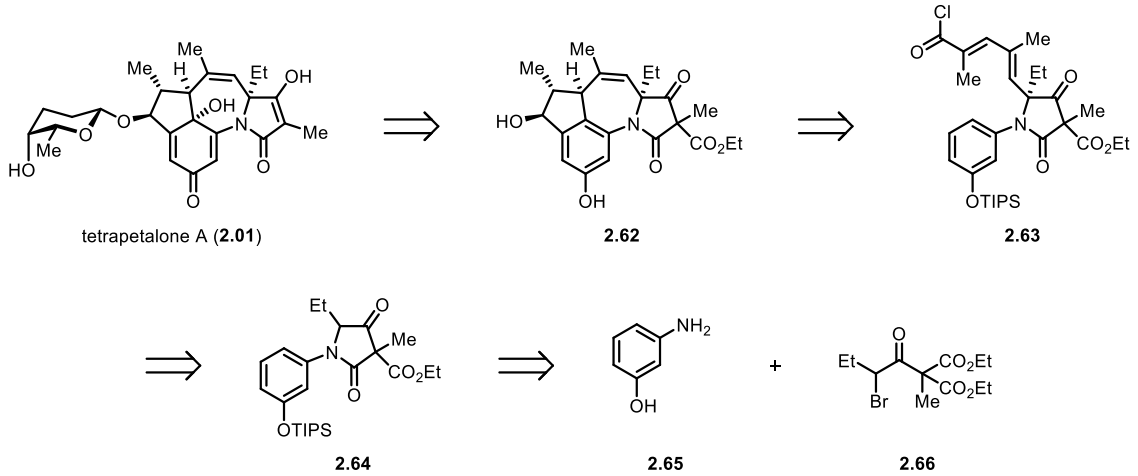
The following section summarizes the combined efforts from post-doctoral fellows Dr. Matthew Haley and Dr. Jonas Buergler as well as graduate student Dr. Travis McMahon.

Although the efforts Dr. Howell had defined a route that was beginning to show promise, concerns over efficiency led to consideration of a new approach wherein the tetramic acid moiety would be installed at an early stage in the synthesis.

2.3.1 A Cascade Tandem Intramolecular Friedel-Crafts Strategy

As illustrated in Scheme 2.14, interest in preparing a masked *N*-aryl tetramic acid unit early in the synthesis led to the design of a strategy wherein tetrapetalone A (**2.01**)

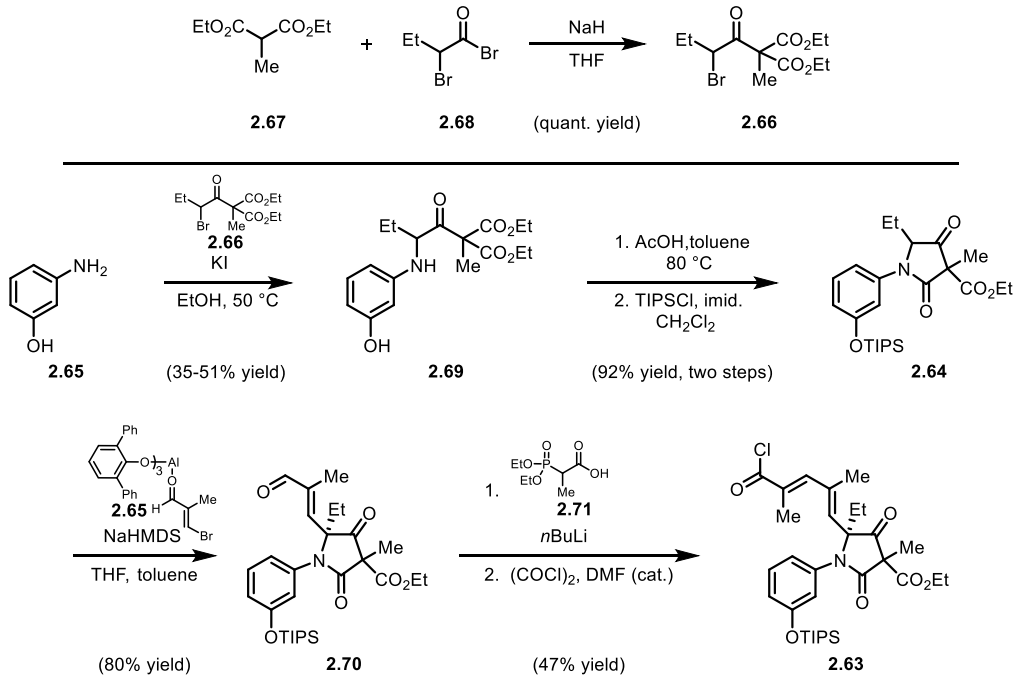
would be accessed from **2.62** via a sequence involving late-stage aryl oxidation, glycosylation, and decarboalkoxylative unmasking of the tetramic acid. The requisite phenol (**2.62**) was envisioned as arising from a cascade Friedel-Crafts reaction that would forge two C-C bonds in a single step from acid chloride **2.63**. This dienyl acid chloride **2.63** would be prepared from the masked tetramic acid **2.64**, which itself would derive from commercially available **2.65** and readily prepared bromide **2.66**.



Scheme 2.14. A cascade Friedel-Crafts strategy to a tetracyclic intermediate

To implement this new strategy, 3-aminophenol **2.65** was alkylated with α-bromo ketone **2.66** (itself available in a single step from diethyl methyl malonate (**2.67**), Scheme 2.15, top), to give **2.69** in variable yields. With **2.69** in hand, smooth cyclization occurred in the presence of catalytic acid to give an intermediate lactam which, upon exposure to TIPS-Cl underwent smooth conversion to silyl ether **2.64**. Thus, in a short four step sequence, the masked tetramic acid unit was installed. Importantly, the strategy of producing a tetramic acid possessing a quaternary carbon between the two carbonyls allowed for ready functionalization of the resident ketone by employing standard enolate technology. Efforts in the latter area led to the development of a Michael addition reaction

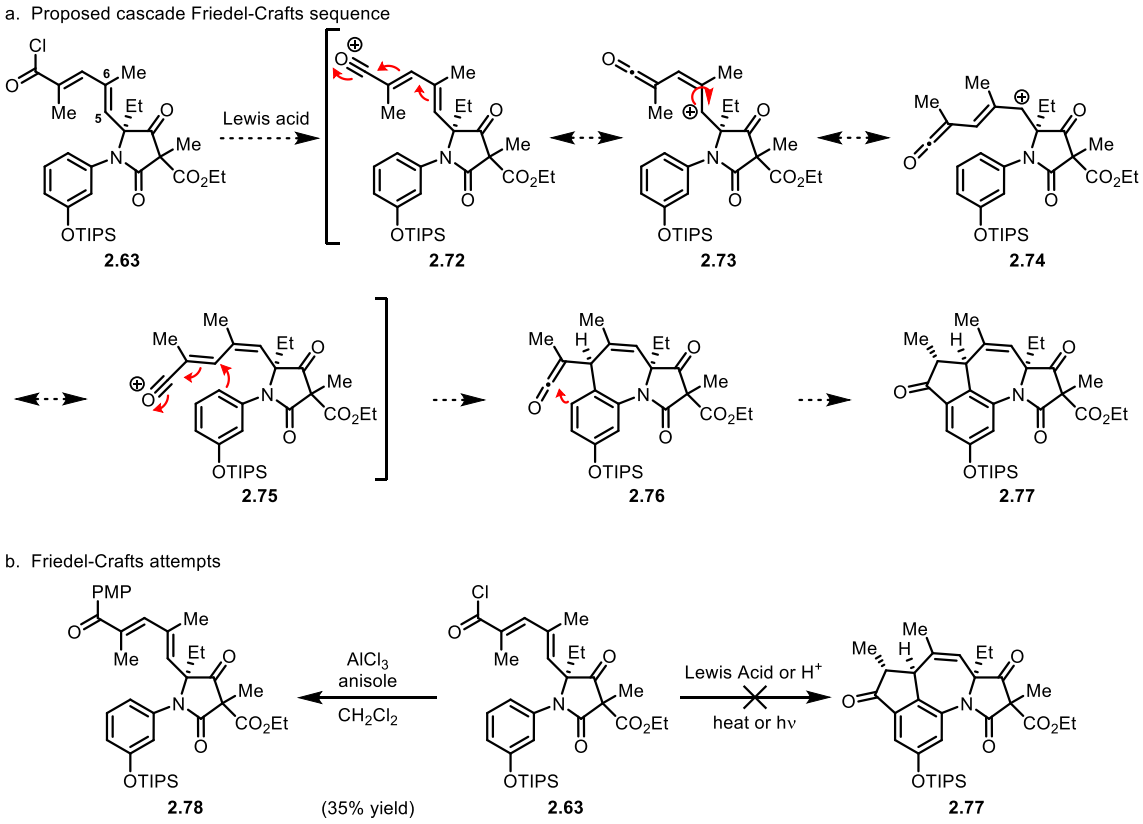
wherein incorporation of technology developed by Yamamoto was found to effectively eliminate problematic 1,2-addition reactions and enable and delivery of Michael addition adduct **2.70** in excellent yield.[5] A subsequent Horner-Wadsworth-Emmons olefination produced an intermediate acid which, upon conversion to the corresponding acid chloride (**2.63**) set the stage for the planned Friedel-Crafts chemistry.



Scheme 2.15. Preparation of acid **2.63** from a masked *N*-aryl tetramic acid

Critical to the success of this Friedel-Crafts reaction was the isomerization ability of the C(5)-C(6) olefin (Scheme 2.16, top). Given that the synthesis had provided ready access to the *E*-olefin geometry, a prerequisite of cyclization to the azepine was isomerization to the *Z*-olefin geometry. Hope for success in this reaction rested on the acylium ion intermediate (**2.72**) isomerizing to *Z*-olefin **2.75** via the illustrated pathway and undergoing the indicated ring closure. The derived intermediate ketene **2.76** would then be poised to undergo further trapping by the aromatic ring to form the tetracyclic

ketone **2.77**. Unfortunately, in practice none of the desired product **2.77** was observed (Scheme 2.16, bottom). To address the question of the suitability of whether or not **2.63** was capable of engaging in Friedel-Crafts chemistry, similar conditions were explored in the presence of the intermolecular trapping agent anisole. In the event, successful acylation and production of **2.78** was observed, albeit in low yield. These observations caused concern over the ability to induce olefin isomerization and thus a new strategy to address this was devised.

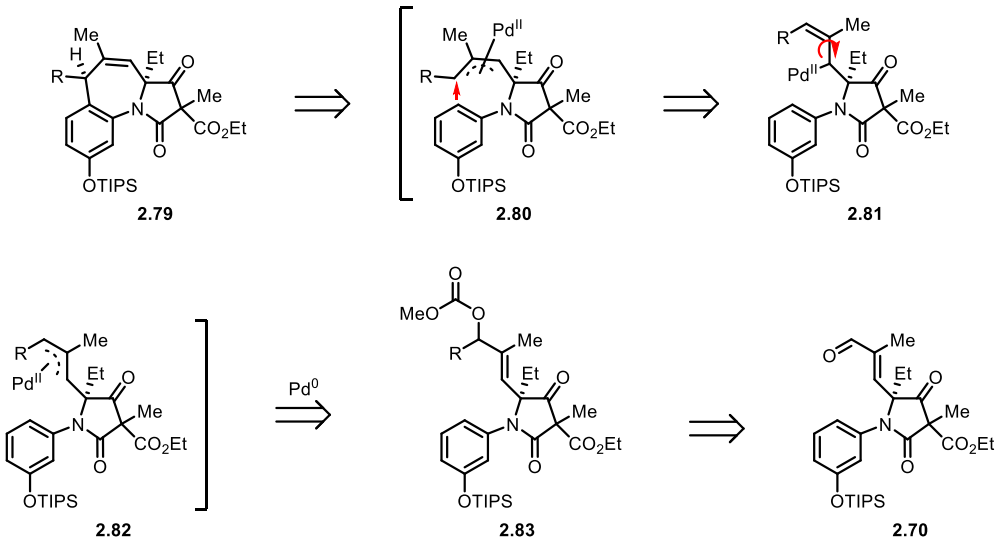


Scheme 2.16. A proposed cascade Friedel-Crafts reaction and attempt

2.3.2 An Intramolecular Pd-π allyl Cacade Sequence

Although the cascade Friedel-Crafts strategy discussed above failed to deliver the desired product, alternatives were considered wherein the overall strategy would remain

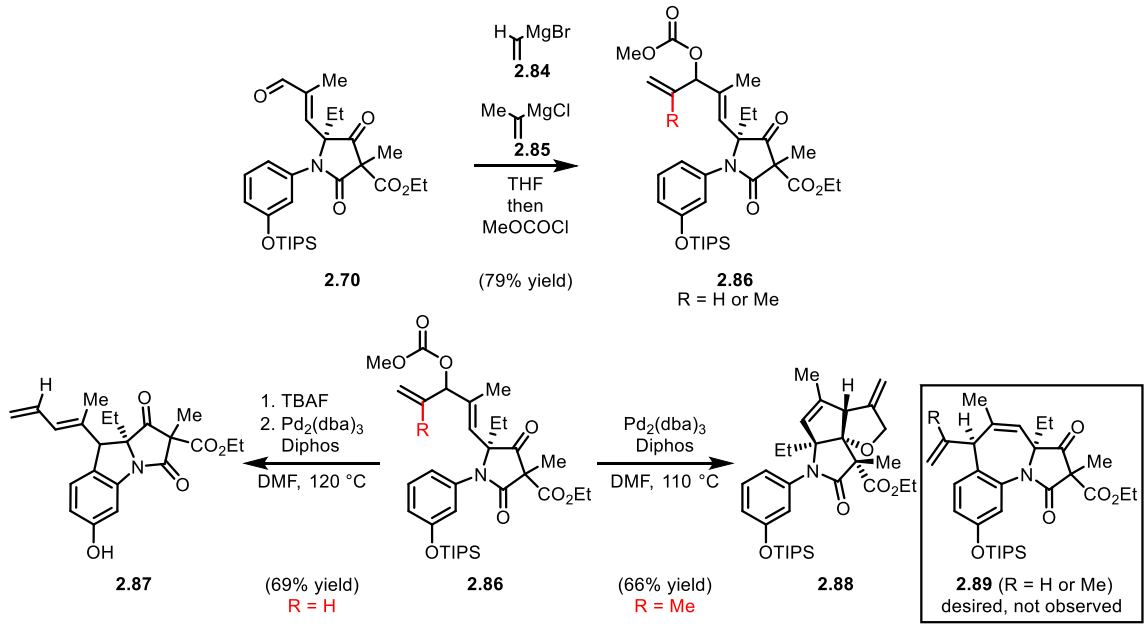
the same: thus, building from aldehyde **2.70** (Scheme 2.17) and simply modifying the nature of the tethered electrophile that would be trapped by the aromatic ring. Considerations over olefin isomerization led to the designing of a modified approach wherein a Pd-π allyl intermediate would serve as the electrophile.[6] As depicted in Scheme 2.17, tricycle **2.79** would be the result of intramolecular trapping of an electrophilic π-allyl by the adjacent aromatic ring (**2.80**). This π-allyl intermediate could be formed as a result of different *eta*-3 and *eta*-1 haptomers (**2.81**, and **2.82**) ultimately arising from allylic carbonate **2.83** which, in turn, would be accessed from aldehyde **2.70**.



Scheme 2.17. A proposed π-allyl cascade reaction to deliver azepine **2.79**

In moving this latter approach forward, aldehyde **2.70** was advanced by simple Grignard addition into the aldehyde followed by trapping of the intermediate alkoxide with methyl chloroformate to deliver allyl carbonates **2.86** (Scheme 2.18). Unfortunately, attempts to advance **2.86** (R = Me) led to fused tricycle **2.88**. After considering the possible mechanistic pathway leading to **2.88**, the same reaction was applied to a substrate (**2.86**, R = H) wherein the vinyl methyl had been removed and desilylation preceded exposure to

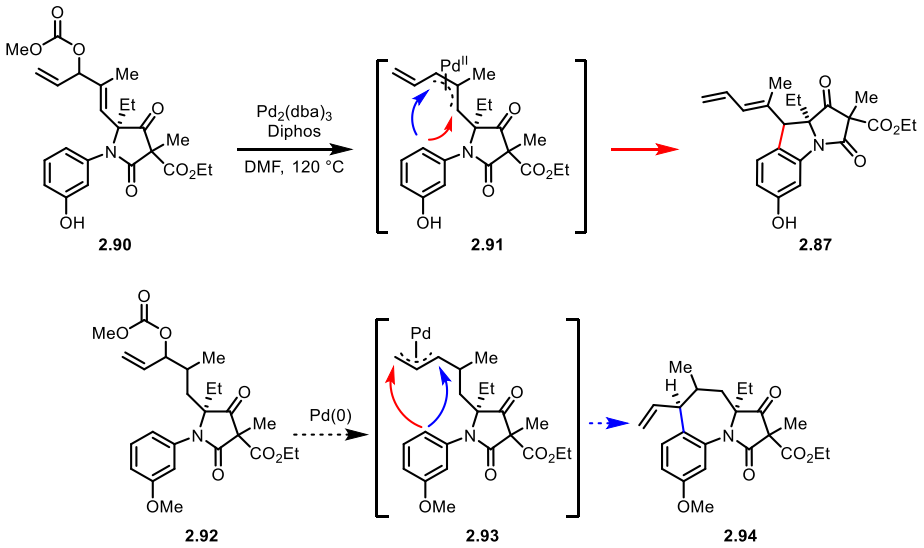
the palladium catalyst. In this latter scenario a different but equally undesireable product (**2.87**) was delivered. These observations provided valuable insights into these transformations. Not only could the olefin isomerization take place in the π-allyl cascade, as evidenced by the *Z*-olefin in **2.88**, but also trapping of the intermediate π-allyl species by the aromatic ring was also feasible; however, the undesired five-membered ring was formed preferentially instead of the desired azepine (**2.89**).



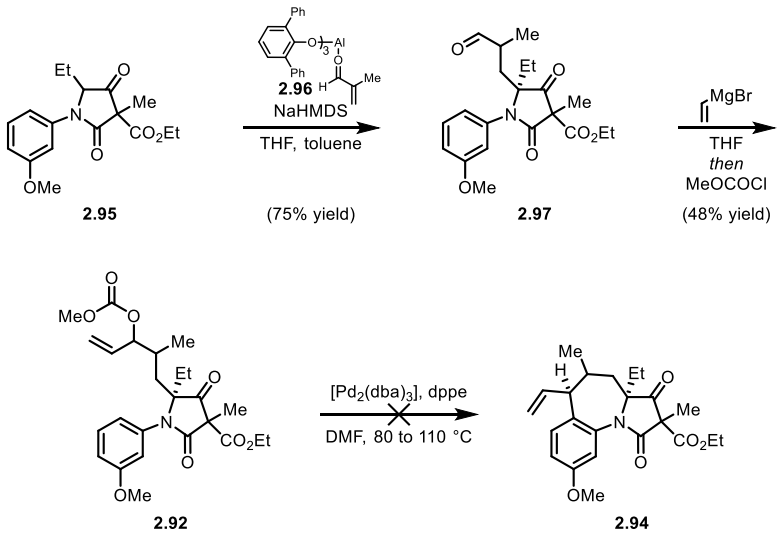
Scheme 2.18. A substrate dependent chemo-differentiated π-allyl cascade

With proof that the π-allyl chain could be trapped by the aromatic ring, efforts were devoted toward developing a substrate that would preferentially close to form the requisite seven-membered ring. The design changes were governed by the likely mechanism leading from **2.90** to **2.87** (Scheme 2.19, top). In this substrate, at least two modes of cyclization were possible, and the goal was to eliminate the possibility of five-membered ring formation (red arrow, **2.91**) and instead, enforce the pathway that leads to seven-membered

ring formation (blue arrow, **2.91**). To promote the latter, substrate **2.92** was proposed as the resultant π-allyl intermediate (**2.93**) was expected to render the desired seven-membered ring product **2.94** (blue arrow) over the corresponding nine-membered ring isomer (red arrow).



Scheme 2.19. Effort to push the π-allyl cascade toward seven-membered ring formation

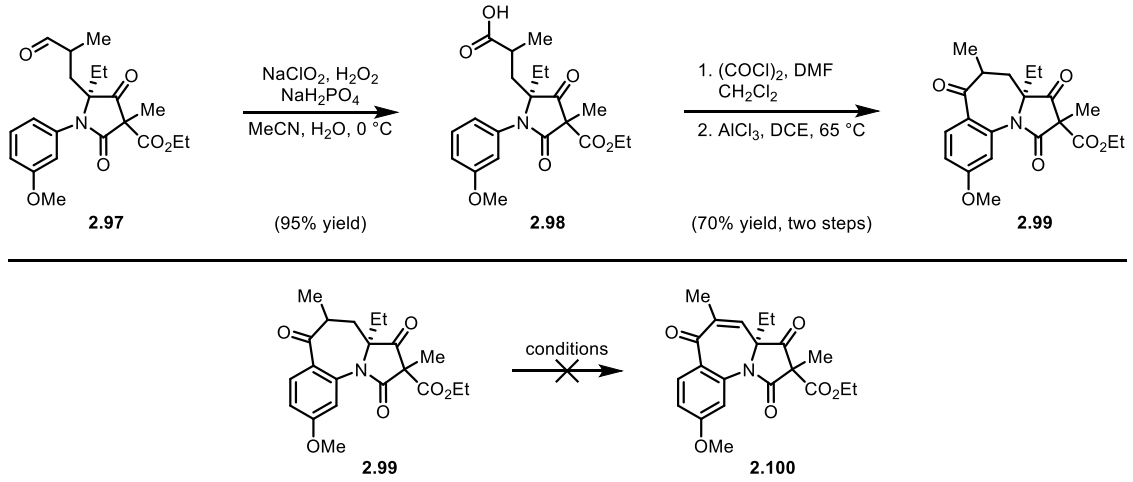


Scheme 2.20. Modified attempts to promote a Pd-catalyzed cyclization

As illustrated in Scheme 2.20, preparation of the modified π-allyl substrate began with masked tetramic acid **2.95** (prepared in a manner analogous to the preparation of TIPS variant **2.64**) which was advanced in similar fashion employing the Yamamoto modified Michael reaction and simple Grignard addition. Unfortunately, exposure of the derived substrate (**2.92**) to a variety of catalytic Pd(0) sources failed to deliver the desired azepine **2.94**.

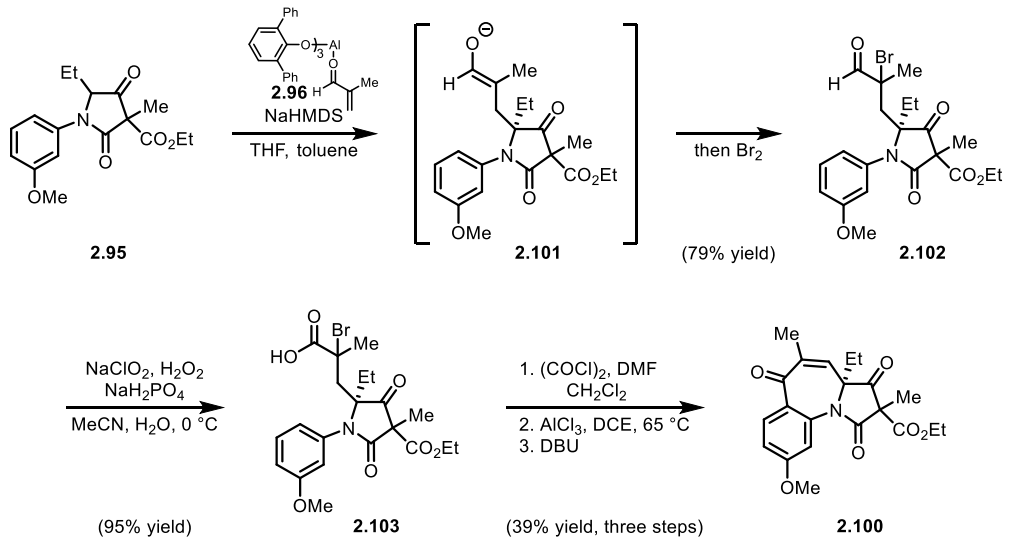
2.3.3 Azepine Formation by Intramolecular Friedel-Crafts Acylation

Despite the lack of success forming the seven-membered ring via a Pd-π allyl cascade reaction, we nevertheless explored alternative electrophilic tethers that could accommodate formation of the seven-membered ring. As illustrated in Scheme 2.21, this exploration led to a Pinnick oxidation of **2.97**, followed by acid chloride formation and intramolecular Friedel-Crafts acylation to deliver tricycle **2.99**. Unfortunately, attempts to further oxidize this compound to **2.100** wherein the trisubstituted bond is in place were unsuccessful.



Scheme 2.21. An intramolecular Friedel-Crafts to deliver the seven-membered ring.

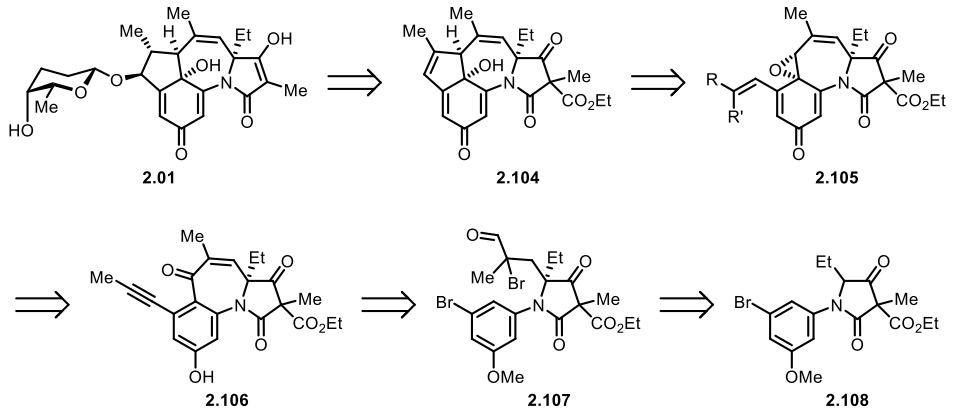
Based on what was becoming an extensive body of preliminary results, a successful route to tricyclic enone **2.100** was eventually developed (Scheme 2.22). Key to this sequence was the formation of α-bromo aldehyde **2.102**, wherein capturing the intermediate enolate (**2.101**) with bromine serves to preserve the olefin oxidation level present in azepine **2.100**. The derived α-bromo ketone (**2.102**) was advanced via the intermediacy of acid **2.103** in a sequence similar to that outlined in Scheme 2.21.



Scheme 2.22. Installing an α-bromo functional handle suitable for elimination.

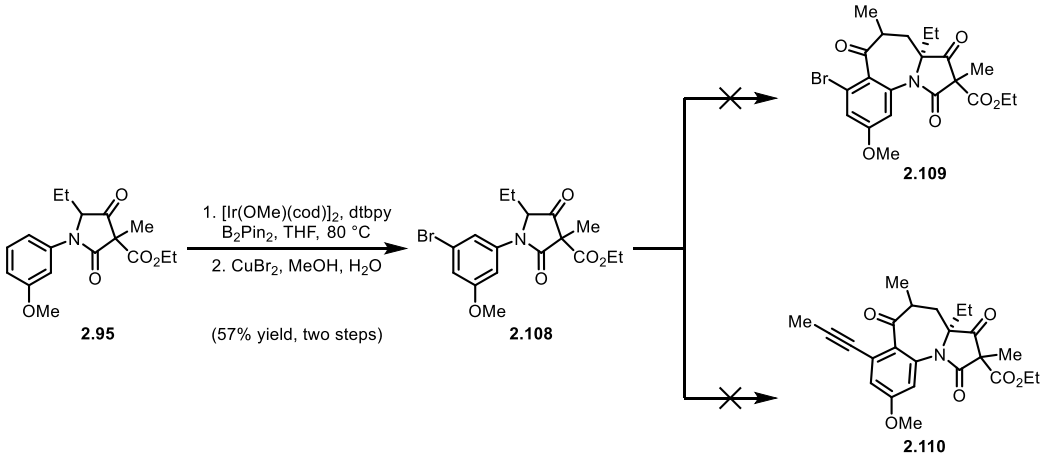
Having finally accessed a fully functionalized azepine and appended tetramic acid, a retrosynthetic plan evolved that called for incorporation of a functional handle on the aromatic ring adjacent to the newly installed ketone. As illustrated in Scheme 2.23, in this modified retrosynthetic plan, tetrapetalone A (**2.01**) was seen as arising from skipped diene **2.104** which would be accessed by way of spiroepoxide **2.105**, the product of an aryl-oxidation/reductive alkylation sequence applied to **2.106**. In accord with recent advances,

2.106 was seen as deriving from bromide **2.107** via an intramolecular Friedel-Crafts acylation reaction similar to that outlined in scheme 2.22.



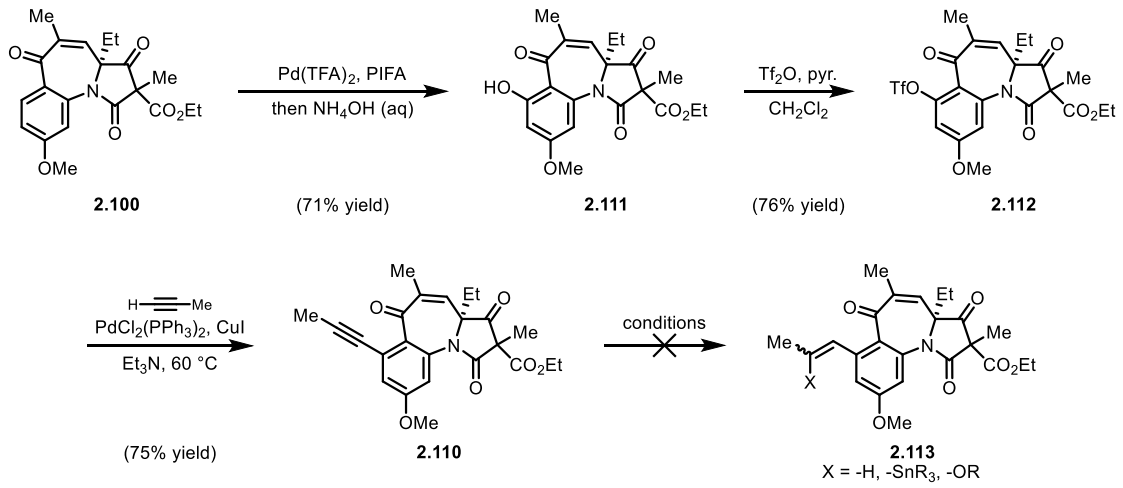
Scheme 2.23. Revised retrosynthetic analysis via spiro-epoxide formation.

To access **2.108** for investigation of the revised strategy shown in scheme 2.23, a *meta*-selective borylation/bromination sequence developed by Hartwig was applied to lactam **2.95** (Scheme 2.24).[7] Unfortunately, the derived bromide (**2.108**) could not be advanced to either **2.109** or **2.110** in a manner analogous to that depicted in Scheme 2.21 as the presence of any additional substitution on the aromatic ring appeared to prevent the Friedel-Crafts acylation.



Scheme 2.24. Installing a functional handle for oxidative addition.

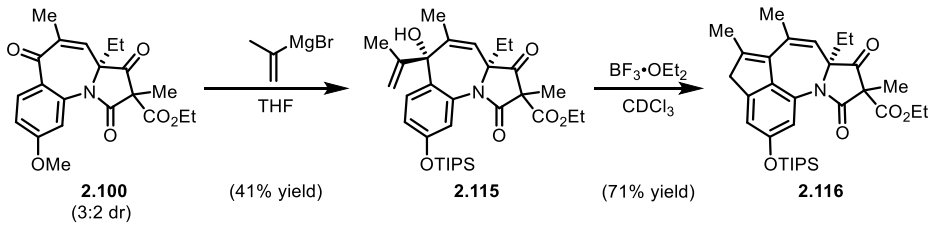
Based on the previous results it became clear that additional functionalization of the aromatic ring would necessarily need be completed after the formation of the azepine. To this end, we became intrigued by recent chemistry, developed in the Dong and Yu labs,[8] wherein aryl C-H activation is controlled by an adjacent benzylic ketone. As illustrated in Scheme 2.25, application of this chemistry to **2.100** resulted in ready access to phenol **2.111** which was subsequently advanced to Sonogashira product **2.110** via the intermediacy of the corresponding triflate **2.112** (Scheme 2.25). Attempts to functionalize alkyne **2.110** to compounds such as **2.113** were unproductive.



Scheme 2.25. Application of Dong's C-H activation and advancement via Sonogashira chemistry.

In an alternative approach, Dr. Buergler had established the viability of nucleophilic addition into the benzylic ketone to give adduct **2.115** upon exposure to isopropenylmagnsium bromide (Scheme 2.26). Advancement of this material to tetracyclic diene **2.116** utilizing BF_3•OEt_2 as Lewis acid gave a compound that contains all the carbons present in the tetrapetalone A aglycone, but no further advancement of this material was

attempted. This marked the end of Dr. Travis McMahon's and Dr. Jonas Buergler's efforts on the tetrapetalone project.



Scheme 2.26. Formation of a tetracyclic diene.

2.4 Conclusion

Much of Dr. Howell's work focused on a convergent synthesis involving a ring-closing metathesis and Buchwald-Hartwig amidation reaction. Although these efforts were met with only limited success they did demonstrate that available technologies for introducing the tetramic acid were limited as was the potential utility of ring closing metathesis chemistry. These observations guided Dr. Matt Haley to redesign the synthesis to one that was less convergent but, as will become evident in subsequent chapters, enabled completion of synthesis. Key elements of this revised approach were the early and efficient installation of a masked tetramic acid unit and the development, by Dr.'s McMahon and Buergler, an intramolecular Friedel-Crafts acylation reaction that enabled subsequent installation of the azepine ring. While these preliminary efforts showed promising results, considerable reaction engineering and troubleshooting would be required in order for this chemistry to serve as a solid foundation for the total synthesis. These efforts as well as the development of a viable engame strategy will be the focus of subsequent chapters of this thesis.

2.5 References

[1] Howell, J. M. Synthetic Strategies Toward the Total Synthesis of Tetrapetalone A. Ph.D. Dissertation, Colorado State University, Fort Collins, CO, 2012.

[2] The works of Dr. Matthew Haley as well Dr. Jonas Buergler are disclosed in the dissertation of graduate student Dr. Travis McMahon: McMahon, T. C. Part One: The Formal Total Synthesis of Dehydrogliotoxin and the First Synthesis of an Epidiselenoketopiperazine and Part Two: Towards the Total Synthesis of the Tetrapetalones. Ph.D. Dissertation, Colorado State University, Fort Collins, CO, 2013.

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[7] (a) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056-3058. (b) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. .Chem. Soc.* **2007**, *129*, 15434-15435.

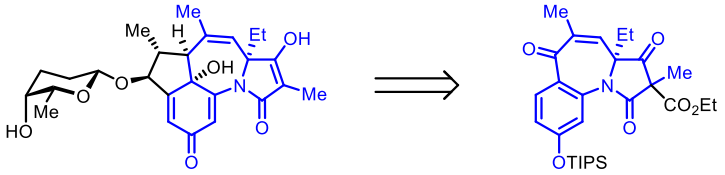
[8] (a) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 13070-13074. (b) Mo, F.; Trzepkowski, L.J.; Dong, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 13075-13079. (c) Mo, F.; Trzepkowski, L.J.; Dong, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 5425.

CHAPTER THREE

A Scalable Preparation of a Tricyclic Enone[1]

3.1 Overview

Although it took a number of years, the synthetic route toward tetrapetalone was beginning to show promise and tricyclic enone **3.02** had emerged as a potentially accessible and versatile intermediate from which a variety of endgame strategies could be launched (Scheme 3.1). As in any multistep synthesis, reaction efficiency eventually becomes a critical issue and there were certainly many concerns about our ability to access tricyclic enone **3.02** in quantities needed to address the many issues that would no doubt arise during efforts to explore further chemistry.

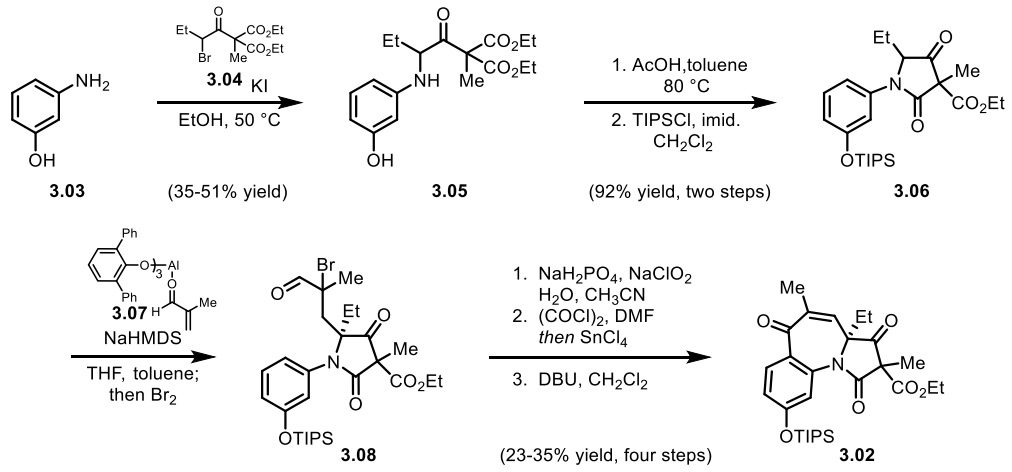


tetrapetalone A (**3.01**) **3.02**

Scheme 3.1. Targeting key intermediate **3.02** en route to tetrapetalone A

At the outset of these optimization studies we discovered that the first step, alkylation of 3-aminophenol (**3.03**) with α-bromo ketone **3.04**, was problematic on large scale, giving low and varying yields (Scheme 3.2). Additionally, the conjugate addition of **3.06** to **3.07** would need to be optimized to provide improved access to aldehyde product **3.08** and the TIPS variant was proving sensitive to the Lewis acid employed in the

intramolecular Friedel-Crafts acylation. Although we had already determined the need to employ $SnCl_4$, the reaction suffered from diminished and often variable yields.

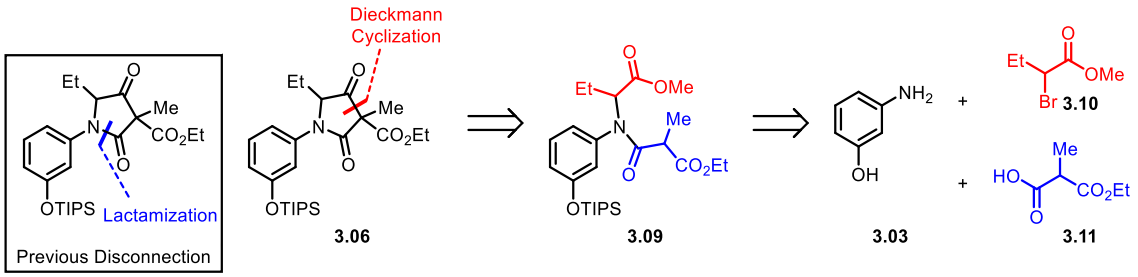


Scheme 3.2. Original preparation of lactam **3.06** and advancement to a tricyclic enone

3.2 An Alternative Preparation of a Masked N-Aryl Tetramic Acid

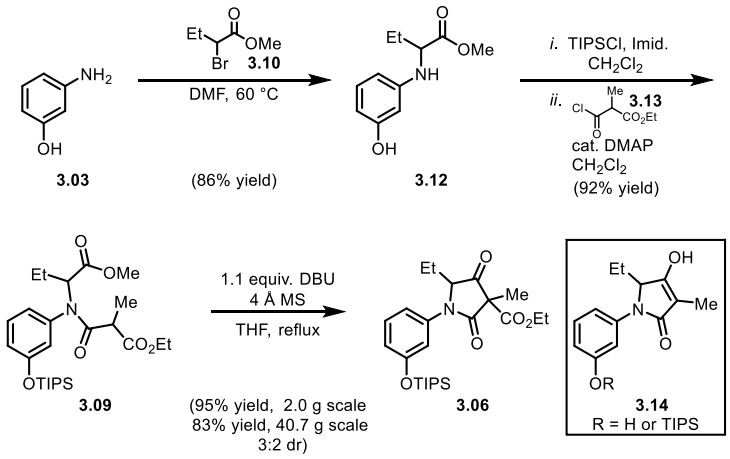
In considering options for improving the preparation of **3.02** it was reasonable to consider both slight variations in strategy and optimization of the current route. Given that some of the latter had been done during the initial investigations, we began to consider slight variations and turned attention to improving the aniline alkylation that had previously furnished **3.05**. As illustrated in Scheme 3.3, we decided to explore a slight variation wherein lactam **3.06** arsises from Dieckmann cyclization of intermediate derivative **3.09** instead of ring closure via amide bond formation (inset). Importantly, **3.09** was seen as arising from readily available materials (i.e., **3.03**, **3.10** and **3.11**).

In investigating this revised strategy, we explored the alkylation of 3-aminophenol **3.03** with α-bromo ester **3.10** (Scheme 3.4). A screen of solvents revealed DMF to be the most suitable. In addition, it was discovered that using excess aniline minimized the production of overalkylation byproducts and improved yields to the high



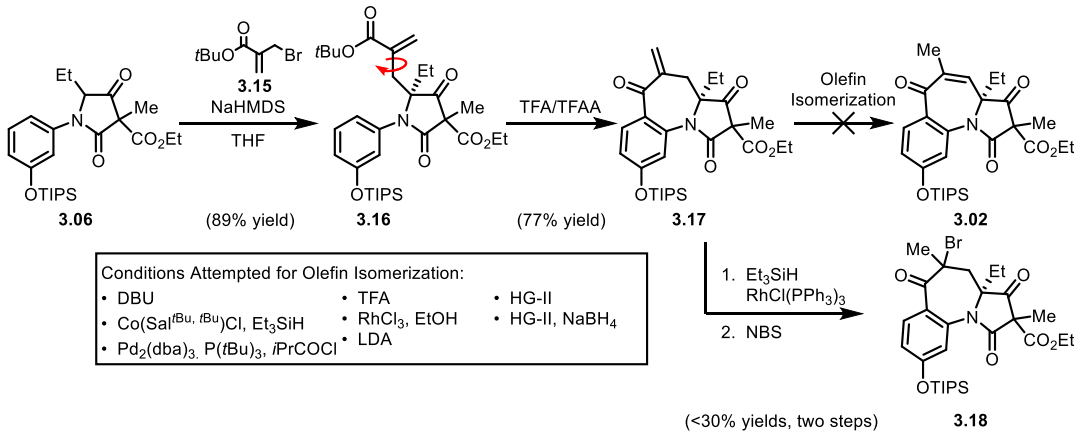
Scheme 3.3. A Dieckmann cyclization strategy toward lactam **3.06**

80's. Moving forward in the synthesis, it was critical to first protect the alcohol functionality to prevent *O*-acylation in the subsequent exposure to acid chloride **3.13**. Furthermore, we could, in a single one-pot transformation, sequentially protect and effect amidation to give **3.09** in a 92% yield. Dieckmann cyclization of **3.09** initially proved problematic, with reactions plagued by formation of byproducts **3.14**. Speculating that these products were arising due to the formation of methoxide, the reaction was modified to include 4 Å molecular sieves. This latter modification presumably sequesters any methanol produced and enabled the large-scale production of **3.06** in excellent yields. It should be noted that **3.06** is produced as a 3:2 mixture of diastereomers which, due to the upcoming stereoconvergent enolization, is inconsequential.



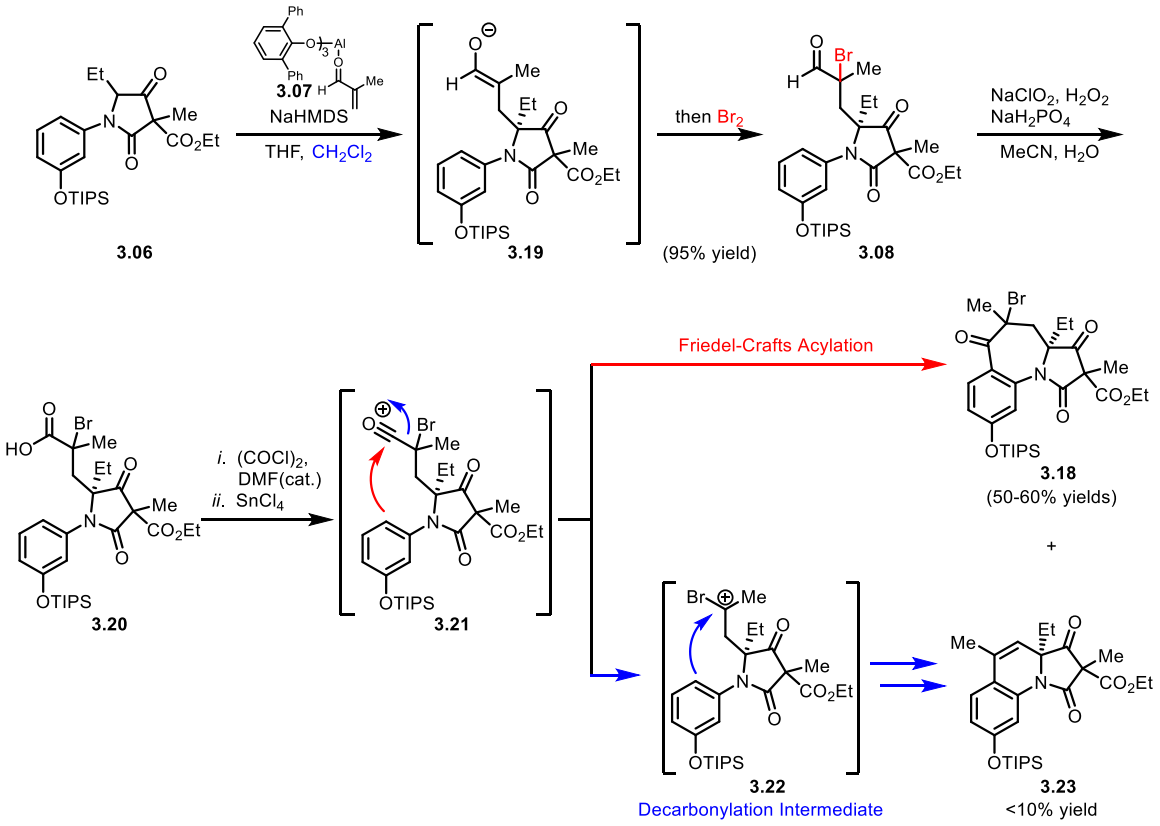
Scheme 3.4. A revised route to masked N-aryl tetramic acid 3.06

Armed with ample quantities of lactam **3.06**, we began considering alternative electrophiles that could be used en route to the key tricyclic enone intermediate **3.02**. As depicted in Scheme 3.5, we speculated that tricyclic enone **3.02** might arise from olefin isomerization of *exo*-methylene **3.17** which, in turn, would arise via intramolecular Friedel-Crafts acylation of **3.16**, an intermediate that would be available from simple allylation of **3.06** with known bromide **3.15**.[2] An important feature of this electrophile is that it delivers an alkylation product residing in the proper oxidation level for direct conversion to **3.02**. Moreover, permuting the double bond to the *exo*-position enables free rotation about the depicted C-C bond (**3.16**) thereby permitting efficient trapping by the aromatic ring, a problem that had plagued our earlier studies. In practice, this chemistry worked quite nicely and advancing **3.16** by *in situ* deprotection and Friedel-Crafts acylation under the modified conditions of Corby (i.e., TFA/TFAA) delivered tricycle **3.17** in 5 steps from commercial materials in excellent yield.[3] Unfortunately, we were unable to induce isomerization of the olefin into the endocyclic position.[4] Although conditions for converting **3.17** to the previously prepared α-bromo ketone (**3.18**) were established, this chemistry diminished not only the yield but also the step efficiency.



Scheme 3.5. Attempt to access tricyclic enone 3.02 by olefin isomerization.

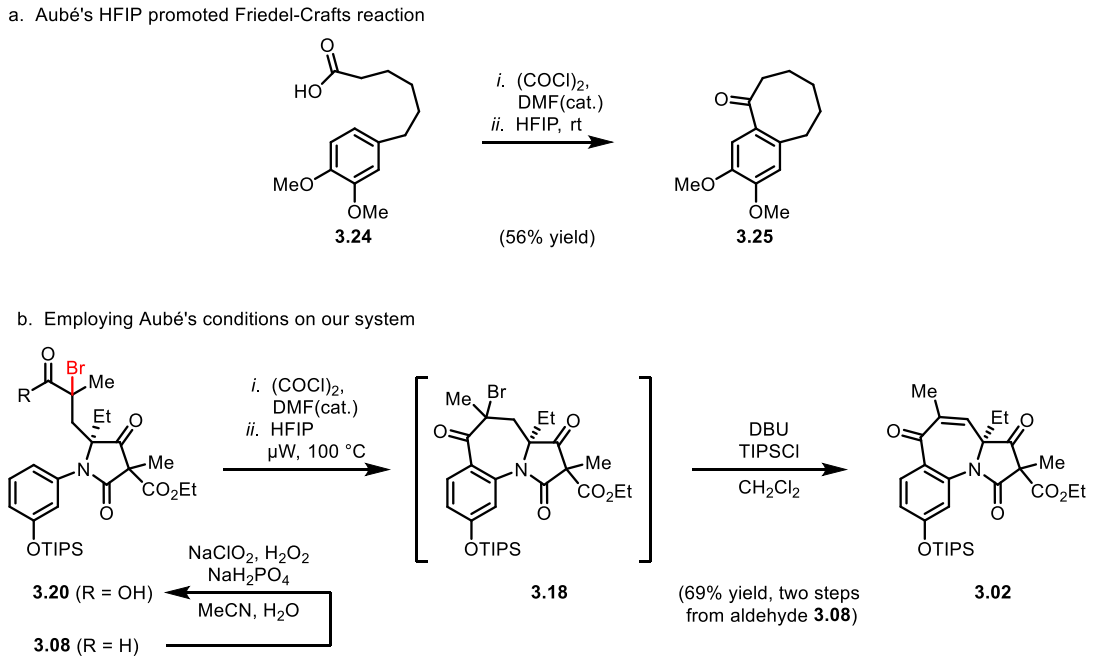
With the lack of success in inducing olefin isomerization, we turned our attention to optimizing the original sequence involving Yamamoto's Lewis Acid promoted conjugate addition reaction (Scheme 3.6). In examining the original report by Yamamoto and coworkers that detailed the scope and optimization, they found that in many cases switching the co-solvent from toluene to CH_2Cl_2 further improved the selectivity of the transformation.[5] In addition, 2D-TLC studies of our reaction indicated the instability of the aldehyde product **3.08** to prolonged silica gel exposure, thus an alternative purification method was warranted. As depicted in Scheme 3.6, changing the solvent from toluene to CH_2Cl_2 resulted a marked improvement in the yield to 95%. The



Scheme 3.6. An optimized conjugate addition reaction and Friedel-Crafts byproduct

instability of the derived product to purification conditions was solved by rapid elution of the 2,6-diphenylphenol ligand with a 1:1 hexane:CH_2Cl_2 mixture followed by rapid flushing of the silica gel column to elute the α-bromo aldehyde product **3.08**.

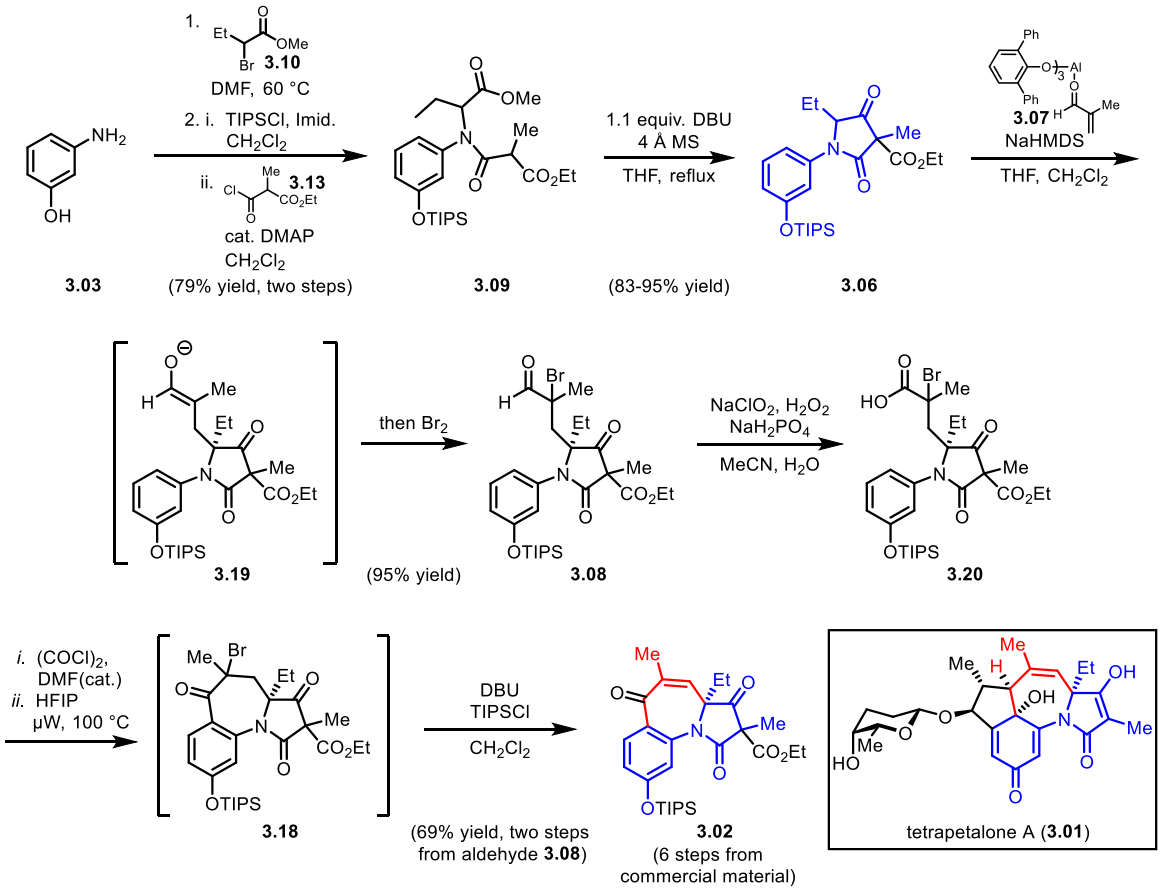
With the α-bromo aldehyde in hand, Pinnick oxidation delivered carboxylic acid **3.20** that could be used in the next step without further purification. Conversion of **3.20** to the corresponding acid chloride followed by exposure to $SnCl_4$, conditions we had initially established for the Friedel-Crafts reaction, gave variable yields (50-60%) of the desired enone **3.18**. Further inspection of the reaction byproducts revealed the formation of **3.23** in <10% yield, presumably as a byproduct by way of decarbonylation to **3.22** followed by trapping of the resulting carbonium. Based on this latter observation we speculated that alternative methods using Brønsted acid catalysis might minimize the formation of byproduct **3.23**. In exploring this latter alternative, we initially turned to the TFA/TFAA conditions that had proven successful in our earlier studies.[3] Although these latter efforts were somewhat successful, the rather harsh nature of these conditions led us to consider alternative procedures and we became intrigued by a report from the Aubé laboratory where dissolution of acid chlorides in hexafluoroisopropanol (HFIP) solvent was found to promote Friedel-Crafts reactions, often at room temperature (Scheme 3.7, top).[6] To our delight, we found that applying Aubé's conditions to the acid chloride derived from **3.20** led to clean formation of **3.18** in yields that were improved over other methods. Moreover, the volatility of the reagents employed in these conditions permitted a very facile solvent exchange thereby enabling subsequent treatment with DBU and the production of tricyclic enone **3.02** (69% yield) in a one-pot transformation (Scheme 3.7, bottom).



Scheme 3.7. Optimized Friedel-Crafts acylation reaction to deliver tricyclic enone **3.02**

3.3 Conclusion and Summary

Re-examining the strategy and conditions for the production of **3.02** led to the improved route summarized in Scheme 3.8. In developing this route, we coupled pot-economical and telescoping methods with modern variations of classical reactions to produce tricyclic enone **3.02** in only six-steps that can all be readily performed on multi-gram scales. The ability to produce multigram quantities of this key intermediate (**3.02**), which possesses the azepine ring, the complete tetramic acid in masked form, and an aryl moiety poised for eventual oxidation, was a critical step forward in developing this synthesis.



Scheme 3.8. Entire optimized route to tricyclic enone **3.02**.

3.4 Experimentals

General

Unless otherwise stated, reactions were magnetically stirred in flame or oven dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Diethyl ether, tetrahydrofuran, toluene, benzene, dichloromethane, and acetonitrile were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. ACS grade acetone (Fisher) was purchased from Fisher-Scientific and used as received. Dimethyl formamide and 1,2-dichloroethane (DCE) were purchased from Sigma-Aldrich and used as received.

$Pd(PPh_3)_4$ was purchased from Sigma-Aldrich and stored under nitrogen in a -20°C freezer. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Millipore glass-backed 60Å plates (indicator F-254s, 150-180 µm thickness) (Millipore, catalogue #1164850001). Column or flash chromatography was performed with the indicated solvents using Millipore Silica Gel 60 (0.040-0.063 mm, 230-400 mesh ASTM) as the stationary phase. MPLC purifications were performed on a Telodyne Isco Combi*Flash*® *Rf*+ (Model: RF + UV-VIS MS COMP), used with standard Telodyne Isco normal phase disposable columns for flash chromatography and monitored at wavelengths of 254 and 280 nm. All melting points were obtained on a Chemglass Life Sciences melting point device (Model: DMP100) and are uncorrected. Infrared spectra were obtained using a Bruker Alpha ATR-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, Varian 500, or Bruker 600. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million (ppm) relative to internal residual solvent peaks from the indicated deuterated solvents (^{1}H: For $CDCl_3$, $CHCl_3$ 7.26; For Methanol-d_4, CD_2HOD 3.31; For Acetone-d_6, Acetone-D5H 2.05). Chemical shifts (δ) for ^{13}C spectra were referenced from the indicated solvent peaks (^{13}C: $CDCl_3$ 77.16, Methanol-d_4 49.00, Acetone-d_6 29.84). Chemical shifts in ^{19}F spectra were taken in $CDCl_3$ doped with fluorobenzene and referenced to -113.15. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as s = singlet, br.s = broad singlet, d = doublet, br. d = broad doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app =

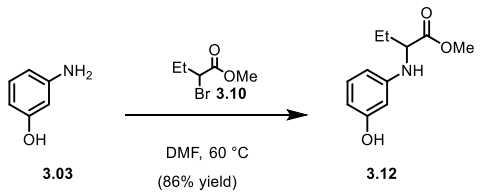
apparent, par = partial. High resolution mass spectra were performed on a Thermo LTQ Orbitrap Discovery with direct injection followed by electro-spray ionization (ESI). Microwave reactions were carried out using a CEM Discover SP Microwave system. Single crystal X-ray diffraction studies were collected on a Bruker Apex II-CCD detector using Mo-K_α radiation (λ = 0.71073 Å). Structures were solved and refined using SHELXTL. Optical rotations were obtained on a Rudolph Research Analytical Autopol IV Automatic Polarimeter.

High-Performance Liquid Chromatography (HPLC): All HPLC purifications were carried out on a Waters HPLC system (consisting of a Waters 1525 binary HPLC pump with direct injection port and monitored at 254 nm unless otherwise specified with a Waters 2489 UV-Visible detector). All purifications utilized a normal-phase Sunfire, Silica Prep 10 µm, 10 x 250 mm column.

Ultra Performance Liquid Chromatography (UPLC)-Mass Spectrometry (MS): All UPLC-MS experiments were carried out on a Waters Acquity H UPLC Class system using the indicated solvent systems as eluents. All separations were performed on a reverse phase Acquity UPLC BEH C18 1.7 µm, 2.1 x 50 mm column.

^{1}H and ^{13}C NMR spectra are included for all previously unreported compounds.

Alkylated amine **3.12**



Experimental: 3-aminophenol **3.03** (11.7g, 107 mmol) was dissolved in DMF (33.7 mL). Methyl 2-bromobutyrate **3.10** (6.0 mL, 50.6 mmol) was then added and the reaction was placed in a preheated oil bath at 60°C. The reaction was stirred for 12 hours, after which

it was cooled to room temperature and diluted with water and extracted four times with ethyl acetate. The combined organics were washed with saturated brine solution and dried over Na_2SO_4. The solvent was then removed in vacuo to yield the crude material as a brown oil. The residue was purified by column chromatography (30% EtOAc/Hexanes) to provide **3.12** as an off-white solid (9.1 g, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (t, J = 8.0 Hz, 1H), 6.22-6.19(m, 2H), 6.09 (t, J = 2.3 Hz, 1H), 5.16 (br s, 1H), 4.19 (br s, 1H), 4.00 (t, J = 6.3 Hz, 1H), 3.74 (s, 3H), 1.92-1.75(m, 2H), 0.99 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 174.9, 156.9, 148.5, 130.5, 106.3, 105.5, 100.5, 57.8, 52.3, 26.2, 10.1.

IR (thin film): cm^{-1} 3390, 2968, 2877, 1727, 1598, 1516, 1497, 1436, 1339, 1194, 1161, 982, 831, 764, 688.

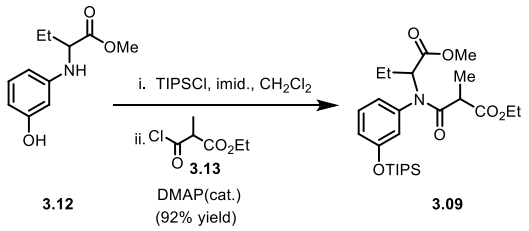
HRMS (ESI+): calculated for $C_{11}H_{16}NO_3$ $[M+H]^+$ 210.1125, found: 210.1163.

TLC: R_f = 0.53 (50% EtOAc/hexanes).

m.p.: 60.9-62.8 °C.

Physical Appearance: Off white/beige solid.

Amide **3.09**



Experimental: To a flame dried 100 mL round-bottomed flask containing **3.12** (1.00 g, 4.8 mmol) was added CH_2Cl_2 (7.2 mL), imidazole (0.488 g, 7.17 mmol), and TIPS-Cl (1.06 mL, 5.02 mmol). The reaction was stirred at room temperature for 12 hours to give a pink

suspension (The reaction was monitored by TLC for the disappearance of starting material, silyl intermediate R_f = 0.57, 20% EtOAc/hexanes). The flask was then cooled in an ice water bath and to this was added pyridine (2.32 mL, 28.7 mmol) and DMAP (29 mg, 0.239 mmol). The crude acid chloride **3.13** (1.56g, 9.5 mmol) (see below) was dissolved in 10 mL CH_2Cl_2 and added to the aniline mixture. The flask containing the crude acid chloride was rinsed twice with 5 mL portions of CH_2Cl_2 and each added to the aniline mixture. The reaction was left stirring until TLC indicated consumption of the intermediate secondary amine (approx. 5h). The reaction was then quenched by the addition of 1M aqueous HCl, and extracted three times with CH_2Cl_2. The combined organics were then washed with saturated brine and dried with Na_2SO_4. The crude orange oil was purified by MPLC (linear gradient from 0% to 30% EtOAc/hexanes, 15 minutes, 40mL/min) to give **3.09** as a colorless oil (2.16g, 4.37 mmol, 92% yield) [mixture of diastereomers/tautomeric forms].

Preparation of acid chloride **3.13**: To a solution of 3-ethoxy-2-methyl-3-oxopropanoic acid[7] (1.39 g, 9.5 mmol) in CH_2Cl_2 (19 mL) cooled in an ice water bath was added $(COCl)_2$ (1.66 mL, 19.0 mmol) followed by a catalytic quantity of DMF (1 drop from a pipette). The reaction was stirred for 6 hours and subsequently concentraed on rotovap to dryness and azeotroped with anhydrous CH_2Cl_2 (10 mL x 2).

Note: Alternatively, one may employ the potassium salt of the above carboxylic acid (potassium 3-ethoxy-2-methyl-3-oxopropanoate)[8] which was found to be equally effective.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.23 (m, 1.7H, overlap with solvent signal), 7.02 (br s, 0.9H), 6.95-6.89 (m, 3.1H), 4.97 (dd, *J* = 8.9, 6.2 Hz, 0.3H), 4.47 (t, *J* = 7.6 Hz, 1H), 4.13~4.08 (m, 2.7H), 3.75 (s, 3H), 3.73 (s, 1H), 3.36 (q, *J* = 7.0 Hz, 1.3H), 1.97-1.89 (m,

2.2H), 1.85-1.78 (m, 0.4H), 1.63 (s, 0.5H), 1.29-1.22 (m, 12.7H), 1.10-1.08 (m, 25.5H), 1.02-0.96 (m, 4.4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.9, 171.4, 171.1, 170.7, 170.6, 157.2, 142.4, 140.5, 130.4, 122.1, 121.9, 121.6, 121.1, 120.8, 120.6, 63.5, 61.3, 61.0, 52.21, 52.18, 44.0, 22.8, 22.6, 18.0, 14.19, 14.16, 14.1, 13.9, 12.7, 11.4, 11.3.

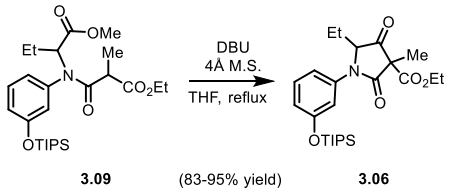
IR (thin film): cm^{-1} 2945, 2868, 1743, 1667, 1592, 1485, 1460, 1383, 1337, 1304, 1236, 1198, 1092, 1005, 923, 882, 790, 706, 685.

HRMS (ESI+): calculated for $C_{26}H_{43}NO_6SiNa$ $[M+Na]^+$ 516.2752, found: 516.2754.

TLC: R_f = 0.25 (20% EtOAc/hexanes).

Physical Appearance: Colorless oil.

Lactam **3.06**



Experimental: In a 250 mL round-bottomed flask was added amide **3.09** (2.02 g, 4.08 mmol). This material was azeotroped 2x with toluene and placed under hi-vac for 1h. To this was added 4Å M.S. (2.05 g, powdered and flame dried under hi-vac). This was placed under hi-vac and backfilled with nitrogen three times and the mixture subsequently suspended in THF (41 mL). This was stirred for 15 minutes, a water cooled reflux condensor attached, and then placed in a preheated 80°C bath. To this was then added DBU (0.67 mL, 4.4 mmol) and stirred vigorously. The reaction was monitored by TLC for consumption of the starting material (~20h). The reaction was then cooled to room temperature, and 10g SiO_2 was added to the reaction mixture with stirring. The reaction was then immediately filtered through a dry pad of 14g SiO_2. The flask was rinsed with

100 mL Et_2O (25 mL x 4). This filtrate was concentrated in vacuo to a colorless oil. 3 mL of hexanes was added to the oil, swirled, and placed in a freezer for 15 minutes until a precipitate began to form. Once the precipitate formed, the suspension was concentrated in vacuo to give **3.06** as a white waxy solid (1.8 g, 95% yield, 1.2:1 dr).

Note: On large scale, the procedure above was followed with **3.09** (52.2 g, 106 mmol), 4Å M.S. (39.8 g), THF (1000 mL), and DBU (17.5 mL, 116 mmol). 52 g SiO_2 was added to the reaction and filtered through a dry pad of 69g SiO_2 and washed with an additional 350 mL Et_2O to give **3.06** (40.7 g, 83% yield, 1.2:1 dr)

The characterization data is in agreement with our previously reported method for the preparation of **3.06**.[9] This data is reproduced below.

Higher R_f diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (t, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 2.4 Hz, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 4.76 (dd, *J* = 5.2, 2.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.97 (dqd, *J* = 14.8, 7.3, 2.7 Hz, 1H), 1.82-1.73 (m, 1H), 1.57 (s, 3H), 1.30-1.21 (m, 6H), 1.10 (d, *J* = 7.4 Hz, 18H), 0.74 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 205.6, 168.8, 165.3, 156.9, 136.9, 130.0, 118.6, 116.8, 116.3, 67.9, 62.9, 59.7, 21.4, 18.0, 15.0, 14.0, 12.8, 8.1.

IR (thin film): cm^{-1} 2966, 2945, 2893, 2869, 1780, 1749, 1709, 1598, 1490, 1463, 1449, 1388, 1297, 1221, 1183, 1158, 1126, 1107, 1073, 1048, 1005.

HRMS (ESI+): calculated for $C_{25}H_{40}NO_5Si$ $[M+H]^+$ 462.2676, found: 462.2676.

TLC: R_f = 0.43 (20% EtOAc/hexanes).

Physical Appearance: White waxy solid.

Lower R_f diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (t, *J* = 8.1 Hz, 1H), 7.02 (t, *J* = 2.2 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.80 (dd, *J* = 6.8 Hz, 1H), 4.49 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.28-4.21 (m, 2H), 1.98 (ddd, *J* = 14.6, 7.4, 3.6 Hz, 1H), 1.86 (dt, *J* = 14.5, 7.3 Hz, 1H), 1.61 (s, 3H), 1.31-1.22 (m, 6H), 1.11 (d, *J* = 7.3 Hz, 18H), 0.88 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 205.3, 168.8, 165.7, 156.9, 136.7, 130.0, 118.5, 116.4, 116.2, 67.4, 62.8, 59.7, 22.6, 18.0, 17.3, 14.0, 12.8, 8.8.

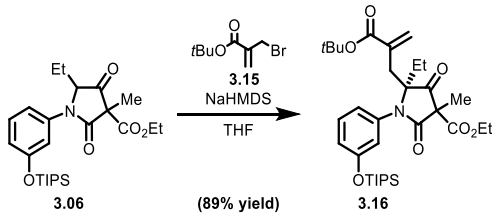
IR (thin film): cm^{-1} 2945, 2894, 2869, 1775, 1732, 1702, 1599, 1496, 1447, 1395, 1306, 1255, 1232, 1160, 1127, 1107, 1052, 1005.

HRMS (ESI+): calculated for $C_{25}H_{40}NO_5Si$ $[M+H]^+$ 462.2676, found: 462.2671.

TLC: R_f = 0.37 (20% EtOAc/hexanes).

Physical Appearance: White waxy solid.

Ester **3.16**



Experimental: To a flame dried round-bottomed flask containing lactam **3.06** (1.9 g, 4.1 mmol) was added THF (54.9 mL) and cooled in a dry ice acetone bath. After cooling, to this was added NaHMDS (2.68 mL, 5.35 mmol, 2.0 M solution in THF) over the course of ~1 min. After 20 minutes, to this was added allyl bromide **3.15** (1.001 g, 4.53 mmol) dropwise over ~ 1 min. The reaction was stirred for 10 min in the dry ice acetone bath after which it was warmed in an ice water bath and stirred for an additional 20 minutes. The reaction was then quenched by the addition of sat aqueous $NaHCO_3$ and diluted with Et_2O. The resulting emulsion was filtered through a cotton plug and the organic layer separated. The aqueous layer was then extracted with EtOAc (3x), dried with $MgSO_4$,

filtered and concentrated to a yellow oil. The mixture was purified by MPLC (15 g column, 35 mL/min, 10 minutes, linear gradient from 0% to 30% EtOAc in hexanes) to give **3.16** (2.2 g, 89% yield, 1.4:1 dr) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.25 (m, 1.9H), 6.98 – 6.88 (m, 3H), 6.90 – 6.83 (m, 2H), 6.82 (t, *J* = 2.2 Hz, 0.8H), 6.15 (d, *J* = 1.3 Hz, 1.1H), 6.13 (d, *J* = 1.4 Hz, 0.8H), 5.47 (d, *J* = 1.2 Hz, 1H), 5.37 (d, *J* = 1.3 Hz, 0.8H), 4.33 (q, *J* = 7.2 Hz, 1.6H), 4.29 – 4.13 (m, 2.2H), 3.17 (d, *J* = 12.9 Hz, 0.8H), 2.95 (d, *J* = 13.4 Hz, 1.1H), 2.59 (d, *J* = 13.5 Hz, 1.1H), 2.44 (d, *J* = 13.1 Hz, 0.8H), 2.15 – 1.99 (m, 1.9H), 1.72 (s, 3.3H), 1.64 – 1.50 (m, 4.9H), 1.47 (s, 10.2H), 1.43 (s, 7.6H), 1.37 (t, *J* = 7.1 Hz, 2.6H), 1.32 – 1.18 (m, 10.5H), 1.10 (d, *J* = 7.2 Hz, 35.8H), 0.93 (t, *J* = 7.3 Hz, 3.6H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 206.4, 205.6, 170.8, 170.7, 166.0, 165.9, 165.8, 165.2, 157.0, 156.9, 136.6, 136.3, 135.9, 135.7, 130.2, 130.1, 128.4, 128.3, 121.3, 121.1, 120.7, 120.6, 120.4, 120.3, 81.5, 81.1, 75.8, 75.6, 63.1, 62.6, 58.9, 58.8, 40.0, 38.9, 28.1, 28.0, 27.7, 26.8, 18.5, 18.0, 15.7, 14.0, 12.7, 8.8, 8.7.

IR (thin film): 2944, 2868, 1774, 1745, 1708, 1597, 1488, 1285, 1151 cm^{-1}

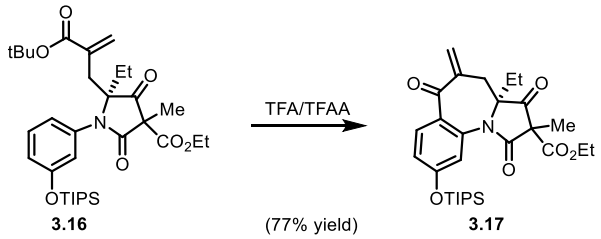
HRMS (ESI+): calculated for $C_{33}H_{51}NNaO_7Si$ $[M+Na]^+$ 624.3332, found: 624.3324.

TLC: R_f = 0.56 (20% EtOAc/hexanes)

m.p.: 67.1-73.7 °C.

Physical Appearance: White solid.

Exo-olefin **3.17**



Experimental: To a 250 mL rbf containing *t*butyl ester **3.16** (437 mg, 0.726 mmol, 1.4:1 dr) was added TFA (10 mL) and CH_2Cl_2 (5.0 mL) and the reaction let stir open to air for 20 min after which the solution had turned pink and TLC indicated all the starting material had been consumed. To this was then added TFAA (1.0 mL, 7.1 mmol) and placed in a preheated oil bath at 60 °C, a vigreux column was attached with a calcium chloride drying tube. After 1 h, an additional TFAA (1.0 mL, 7.1 mmol) was added and the vigreux column replaced with a polyethylene cap. The reaction was stirred for 11 h after which the blue/green solution was cooled to room temperature and concentrated under reduced pressure to a brown oil. The crude residue was azeotroped 2x with anhydrous CH_2Cl_2 and placed under hi-vac. The crude residue was purified by MPLC (0%→30% EtOAc in hexanes, 10 min, 12 g column, 50 mL/min then flushed with pure EtOAc) to give Friedel-Crafts product **3.17** (193 mg, 0.366 mmol) along with recovered carboxylic acid (176 mg). The carboxylic acid was re-subjected to the reaction conditions to give additional **3.17** (105 mg, 0.199 mmol) thus giving a total of **3.17** (298 mg, 0.565 mmol, 77% yield, ca. 1.5:1 dr) as a faint yellow oil.

Alternate Procedure: To a 10 mL microwave reactor vial was added **3.16** (98 mg, 0.16 mmol, 1.4:1 dr) and dissolved in TFA (1.0 mL). The reaction was stirred open to air for 15 min to give a faint orange solution. To this was then added TFAA (1.0 mL) and the reaction heated under microwave irradiation for 2 h at 80 °C to give a brown/yellow solution. The solution was concentrated under reduced pressure and then purified by MPLC (4g column, 30 mL/min, 10 min runtime, 0%→30% EtOAc in hexanes) to give cyclized product **3.17** (57 mg, 0.11 mmol, 66% yield, 1.2:1 dr).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.6 Hz, 1.2H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.00 (app. td, *J* = 9.1, 2.4 Hz, 2.3H), 6.87 (d, *J* = 2.4 Hz, 1.2H), 6.84 (d, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 1.7 Hz, 1H), 6.10 (d, *J* = 1.5 Hz, 1.2H), 5.36 (s, 1H), 5.30 (s, 1.2H), 4.27 (q, *J* = 7.1 Hz, 2.4H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.05 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.26 (d, *J* = 14.6 Hz, 1H), 3.21 (d, *J* = 14.3 Hz, 1.2H), 2.43 (dd, *J* = 14.7, 1.4 Hz, 1H), 2.39 (dd, *J* = 14.3, 1.2 Hz, 1.2H), 2.07 – 1.99 (m, 1H, overlap with H_2O), 1.96 – 1.82 (m, 2.4H), 1.71 (s, 3H), 1.72 – 1.65 (m, 1H), 1.43 (s, 3H), 1.33 – 1.27 (m, 11.6H), 1.16 (t, *J* = 7.1 Hz, 3.6H), 1.12 (d, *J* = 7.5 Hz, 41H), 0.98 (t, *J* = 7.5 Hz, 3.6H), 0.96 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 206.3, 205.7, 191.2, 191.1, 169.3, 169.1, 165.44, 165.38, 161.4, 161.1, 142.9, 140.9, 136.0, 135.4, 133.0, 132.9, 128.8, 128.2, 127.5, 126.3, 121.5, 121.3, 121.2, 121.0, 76.6, 76.1, 63.0, 62.6, 58.5, 38.9, 38.4, 32.2, 31.0, 18.6, 17.98, 17.96, 17.94, 15.7, 14.1, 14.0, 12.80, 12.78, 8.7, 8.1.

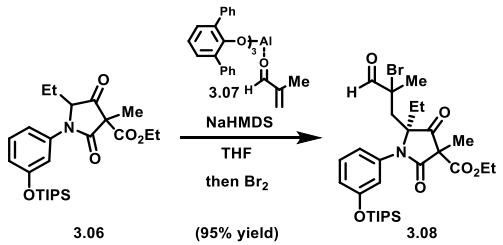
IR (thin film): 2944, 2868, 1775, 1745, 1712, 1671, 1595, 1493, 1463, 1378, 1291, 1230, 1213, 1123, 1107 cm^{-1}

HRMS (ESI+): calculated for $C_{29}H_{41}NO_6SiNa^+$ $[M+Na]^+$ 550.2595 found: 550.2597.

TLC: 0.44 (20% EtOAc in hexanes)

Physical Appearance: Faint yellow oil.

α-bromo aldehyde **3.08**



Experimental: Lactam **3.08** (12.7 g, 27.5 mmol) was dissolved in THF (260 mL) in a 1 L round-bottomed flask and cooled in a dry ice acetone bath. After cooling for 30 minutes,

to this was added NaHMDS (2.0 M in THF, 15.1 mL, 30.2 mmol) to give a faint yellow solution. (After this addition was complete, the preparation of Lewis acid complex **3.07** was started, see below). The solution was stirred for 2 hours after which the solution of the enolate was cannulated using nitrogen pressure into the flask containing Lewis acid complex **3.07** over the course of 20 minutes. The flask was washed with THF (20 mL each) and each rinse cannulated into the the methacrolein mixture. The reaction was stirred for 1h35min and the dry ice/acetone bath removed to let the reaction slowly warm to room temperature. After 1h50min, the beige suspension was again cooled in a dry ice acetone bath. After 1h35min, Br_2 (2.55 mL, 49.5 mmol) was added over the course of 3 minutes to give a yellow suspension and stirred for 15 minutes after which the dry ice/acetone bath was removed and the reaction let warm in air. After 2h, the beige suspension was quenched by the addition of saturated aqueous Rochelle's salt (300 mL), aqueous $NaHSO_3$ (1 M aqueous solution, 20 mL), and diluted with diethyl ether (300 mL). The reaction was stirred for 4h after which 1L of EtOAc was added and the layers separated. The aqueous layer was extracted three times with EtOAc, the combined organics were washed with saturated aqueous brine, dried over $MgSO_4$, filtered through very short pad of celite and concentrated in vacuo to give a yellow/pink solid.

The crude residue was suspended in 150 mL hexanes and stirred vigorously for 1h. After 1h, the suspension was filtered through a Kiriyama filter and the solids washed with ice cold hexanes. The solids were again suspended in hexanes, and stirred vigorously for 30min and the filtration repeated. The combined filtrates were concentrated to a yellow oil which was dry loaded onto 35 g SiO_2. A column was loaded with 200 g SiO_2 and wetted with 50% CH_2Cl_2 / hexanes (1 L). After the compound was loaded onto the column, 50%

CH_2Cl_2/hexanes (2.5 L) was passed through the column followed by 30% EtOAc/hexanes (4.0 L). (Fractions were collected as follows, 1 L, 500 mL x 4, 1 L x 4). Fractions 1,2 contained residual 2,6-diphenylphenol. Fractions 5, 6, and 7 contained the product and were collected and concentrated to give **3.08** (15.9 g, 26.0 mmol, 95% yield) as a yellow oil. (By integrating the aldehyde peaks at 9.13:9.10 ppm, a 2:1 dr was determined). The combined solids and residual 2,6-diphenylphenol can be recrystallized from boiling hexanes to recover the 2,6-diphenylphenol.

*Preparation of Lewis Acid Complex **3.07**:* 2,6-diphenylphenol (34.5 g, 140 mmol) was added to a flame dried 2 L round-bottomed flask and dissolved in CH_2Cl_2 (260 mL). After stirring for 20 minutes, a vent needle was placed on the reaction mixture during the addition of $AlMe_3$ (2.0 M in toluene, 24.8 mL, 49.6 mmol) was added slowly over a period of 5 minutes. The solution goes turned faint yellow then orange. After 15 minutes, this solution was placed in a dry ice acetone bath and stirred for 18 minutes at which point methacrolein (90% pure, 3.8 mL, 41.0 mmol) was added over the course of 3 minutes to give a yellow solution.

Note: The reaction mixture typically provides a 3:2 mixture of diastereomers. A middle fraction containing a 1:1.4 dr was used for characterization purposes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1H), 9.10 (s, 1.4H), 7.36-7.31 (m, 2.7H), 6.99-6.91 (m, 3.8H), 6.87 (t, J = 2.2 Hz, 1H), 6.81-6.78 (m, 1.6H), 6.77 (t, J = 2.2 Hz, 1.5H), 4.32 (q, J = 7.2 Hz, 3.1H), 4.28-4.17 (m, 2.4H), 3.05 (d, J = 15.2 Hz, 1.5H), 2.68 (m, 2H), 2.63 (d, J = 15.3 Hz, 1.7H), 1.96-1.84 (m, 12.3H), 1.67 (s, 3.4H), 1.54 (s, 4.6H), 1.53-1.46 (m, 2.3H), 1.38 (t, J = 7.2 Hz, 4.8H), 1.30-1.21 (m, 12H), 1.11-1.09 (m, 48.9H), 0.94-0.89 (q, J = 7.2 Hz, 8.8H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.2, 205.9, 190.7, 189.7, 169.9, 169.8, 165.3, 165.0, 157.2, 157.1, 135.5, 134.8, 130.5, 130.3, 121.2, 121.1, 121.0, 120.8, 120.7, 120.5, 76.1, 75.0, 66.9, 65.6, 63.3, 63.1, 58.8, 58.6, 45.2, 43.0, 31.7, 28.4, 24.61, 24.56, 18.1, 18.0, 17.4, 15.9, 14.2, 14.0, 12.73, 12.71, 8.9, 8.8.

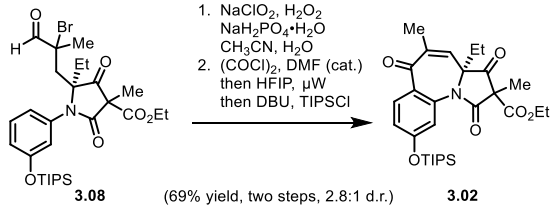
IR (thin film): cm^{-1} 2945, 2868, 1777, 1746, 1705, 1596, 1487, 1463, 1446, 1380, 1282, 1205, 1157, 1120, 1041, 1005, 975, 911, 882, 860, 840, 783, 703, 688.

HRMS (ESI+): calculated for $C_{29}H_{45}BrNO_6Si$ $[M+H]^+$ 610.2194, found: 610.2188.

TLC: R_f = 0.40 (20% EtOAc/Hexanes).

Physical Appearance: Yellow oil.

Enone **3.02**

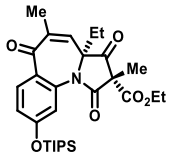


Experimental: To a solution of **3.08** (9.6 g, 15.7 mmol) in CH_3CN (79 mL) cooled in an ice water bath was added dropwise by addition funnel over the course of 1 minute a solution of NaH_2PO_4•H_2O (1.106 g, 8.02 mmol) and H_2O_2 (35% aqueous solution, 1.45 mL, 16.5 mmol) in H_2O (39.3 mL). The addition funnel was washed with 5mL H_2O. To the addition funnel was then added a solution of $NaClO_2$ (80% by weight, 3.64 g, 32.2 mmol) dissolved in H_2O (39.3 mL) and this added to the reaction mixture over the course of 5 minutes dropwise. The addition funnel was washed with an additional 5 mL H_2O. The ice water bath was removed after 5 minutes and the reaction stirred at room temperature for 2 hours after which it was diluted with saturated aqueous NH_4Cl and extracted with EtOAc (3x). The combined organics were washed with saturated aqueous brine, dried over Na_2SO_4,

filtered and concentrated to give the carboxylic acid mixture **3.20** (9.6 g, 15.3 mmol, 97% yield) that was used in the next step without further purification.

To a solution of the carboxylic acid mixture **3.20** (1.005 g, 1.596 mmol) in CH_2Cl_2 (8.0 mL) was added $(COCl)_2$ (0.55 mL, 98% pure, 6.28 mmol) followed by the addition of a catalytic quantity of DMF (1 drop). The reaction was stirred for 1h then concentrated on rotovap and azeotroped 2x with anhydrous CH_2Cl_2. The crude mixture was transferred to a 35 mL microwave reaction vial containing a stirbar using HFIP (16 mL total, 4 x 4 mL). The reaction was heated in a microwave reactor with stirring at 90°C for 6h followed by 18h at 100°C. The black mixture was then transferred to a round-bottomed flask and concentrated in vacuo and azeotroped with toluene two times. After placing under hi-vac for 1h, the residue was dissolved in CH_2Cl_2 (32.0 mL), cooled in an ice water bath, followed by the addition of TIPS-Cl (0.34 mL, 1.6 mmol) and the dropwise addition of DBU (0.96 mL, 6.4 mmol). The reaction was stirred for 3h after which the yellow/brown solution was diluted with 1N aqeuous HCl and extracted three times with CH_2Cl_2. The combined organics were dried with Na_2SO_4, filtered, and concentrated to a dark brown oil. The residue was purified by MPLC (40 g column, linear gradient from 0% to 15% EtOAc/hexanes, 40 mL/min flowrate, 15 minute runtime) to give **3.02** (603.5 mg, 1.14 mmol, 71% yield, 2.8:1 dr) as a faint yellow oil.

The major isomer was separated by dissolving the crude mixture in a minimal amount of hexanes then cooling in a -20°C freezer overnight to precipitate the major diastereomer. This process was repeated three times until the NMR showed a >20:1 dr The mother liquor containing a mixture of diastereomers can be furthered separated using column chromatograpy (0% to 2% ether/toluene).



3.02
(Major isomer)

Major Diastereomer

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.47 (q, *J* = 1.4 Hz, 1H), 4.34-4.22 (m, 2H), 2.09-2.03 (m, 1H), 2.01 (d, *J* = 1.4 Hz, 3H), 1.70 (dq, 14.8, 7.4 Hz, 1H), 1.59 (s, 3H), 1.33-1.27 (m, 6H), 1.11 (dd, *J* = 7.5, 1.7 Hz, 18H), 0.84 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.3, 187.6, 168.7, 165.3, 160.6, 139.4, 138.8, 134.2, 133.6, 128.2, 120.7, 118.6, 76.4, 62.9, 58.1, 28.2, 21.2, 19.1, 17.9, 14.0, 12.7, 8.6.

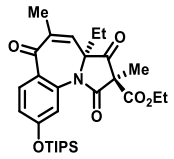
IR (thin film): cm^{-1} 2945, 2868, 1781, 1751, 1715, 1633, 1596, 1498, 1452, 1430, 1378, 1360, 1291, 1258, 1103, 1058, 1016, 985, 900, 882, 851, 768, 688.

HRMS (ESI+): calculated for $C_{29}H_{41}NO_6SiNa$ $[M+Na]^+$ 550.2595, found: 550.2593.

TLC: R_f = 0.33 (5% Et_2O/Toluene)

m.p.: 92.7-94.3 °C.

Physical Appearance: White solid.



3.02
(Minor isomer)

Minor Diastereomer

^{1}H NMR (500 MHzm $CDCl_3$): δ 7.87 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.94 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.50 (s, 1H), 4.20 – 3.99 (m, 2H), 2.05 – 1.97 (m, 4H), 1.66-1.60 (m, 1H), 1.63 (s, 3H), 1.34-1.23 (m, 3H), 1.11 (m, 21H), 0.76 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.5, 188.6, 168.3, 164.5, 160.4, 140.0, 137.1, 133.8, 133.4, 129.0, 120.4, 118.7, 77.2, 63.1, 57.9, 27.7, 21.1, 18.00, 17.96, 15.4, 13.9, 12.8, 8.6.

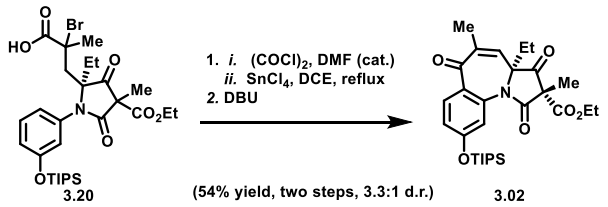
IR (thin film): cm^{-1} 2493, 2868, 1780, 1750, 1712, 1632, 1595, 1358, 1229, 849, 687.

HRMS (ESI+): calculated for $C_{29}H_{41}NO_6SiNa$ $[M+Na]^+$ 550.2595, found: 550.2596.

TLC: R_f = 0.38 (5% Et_2O/Toluene).

Physical Appearance: Colorless oil.

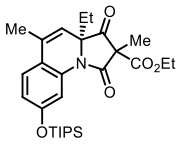
Alternative Preparation of Enone **3.02**



Note: While the above microwave transformation was utilized to streamline the synthesis, for larger scale preparations a stepwise process was initially used. The procedure is as follows:

Experimental: To a solution of the crude carboxylic acid **3.02** (7.22 g, 11.52 mmol) in CH_2Cl_2 (50 mL) was added oxalyl chloride (1.95 mL, 23.05 mmol) followed by three drops of DMF. The solution was stirred for 30 minutes and then concentrated by rotary evaporation. The residue was then dissolved in 1,2-dichloroethane (80 mL) and $SnCl_4$ (0.5 mL, 4.25 mmol) was added and the suspension heated at 90 °C for 11 hours. The dark mixture was then cooled to room temperature and filtered over a short plug of celite which was washed with CH_2Cl_2 (50 mL) and the CH_2Cl_2 was removed by rotary evaporation. The crude material was purified by flash chromatography (6% → 17% EtOAc/Hexanes) to provide the diastereomeric mixture of α-bromo ketones **3.18** (4.25 g, 61% yield) as yellow oil.

To a solution of α-bromo ketone **3.18** (4.25 g, 7.00 mmol) in CH_2Cl_2 (50 mL) was added DBU (2.1 mL, 14.01 mmol) and the dark solution stirred for 2 hours at ambient temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and the aqueous phase extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (16% → 20% EtOAc/Hexanes) to give enone **3.02** (3.31 g, 89% yield, d.r. 3.3:1) as a faint yellow oil. The characterization data is as described above.



3.23
<10% yield

***Friedel-Crafts Byproduct* 3.23**

Note: Analytically pure material was obtained by HPLC using a gradient from 0% to 50% EtOAc in hexanes and characterized as a mixture of diastereomers (9.8:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 2.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.68 (q, *J* = 1.4 Hz, 1H), 4.33 – 4.21 (m, 2H), 2.08 (d, *J* = 1.4 Hz, 3H), 1.90 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.73 – 1.63 (m, 2H), 1.57 (s, 3H), 1.56 (H_2O, 2H), 1.36 – 1.24 (m, 6H), 1.13 (d, *J* = 7.4 Hz, 18H), 0.81 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.7, 169.0, 166.1, 156.6, 133.4, 132.5, 125.1, 121.3, 119.9, 117.3, 115.7, 71.2, 62.9, 58.4, 30.7, 18.8, 18.5, 18.1, 14.0, 12.8, 7.8.

IR (thin film): 2493, 2867, 1776, 1746, 1708, 1604, 1495, 1238, 1217cm^{-1}

HRMS (ESI+): calculated for $C_{28}H_{41}NNaO_5Si$ $[M+Na]^+$ 522.2646, found: 522.2651.

TLC: R_f = 0.27 (10% EtOAc/Hex).

Physical Appearance: Colorless oil.

3.5 References

[1] Dhanjee, H. H.; Kobayashi, Y.; Buergler, J. F.; McMahon, T. C.; Haley, M. W.; Howell, J. M.; Fujiwara, K.; Wood, J. L. *J. Am. Chem. Soc.* **2017**, *139*, 14901-14904.

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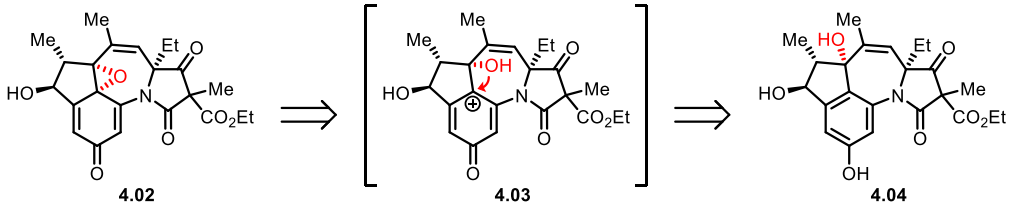
[9] Dhanjee, H. H.; Haley, M. W.; McMahon, T. C.; Buerger, J. F.; Howell, J. M.; Kobayashi, Y.; Fujiwara, K.; Wood, J. L. *Tetrahedron* **2016**, *72*, 3673-3677.

CHAPTER FOUR

A Spiro-Epoxide Strategy for Diastereoselective *para*-Quinol Formation

4.1 Overall Strategy

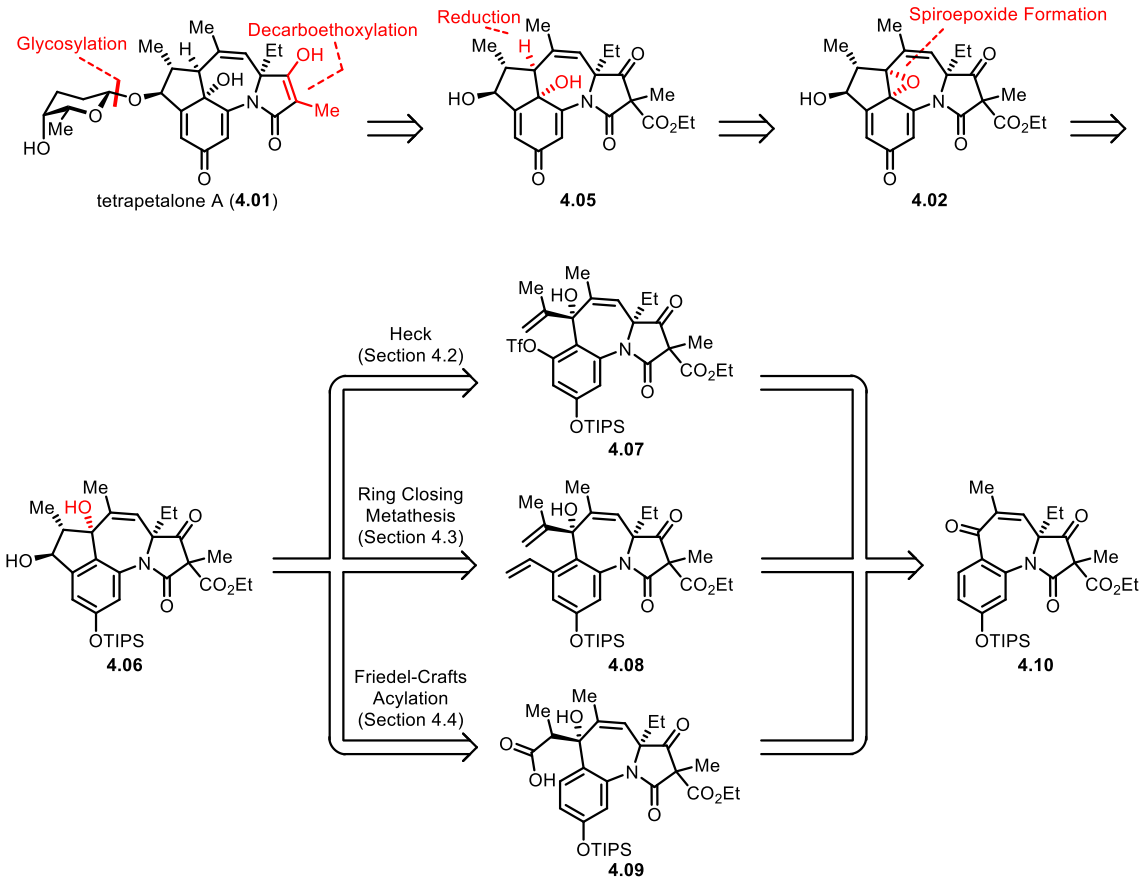
From the outset of our synthesis we noted the inherent challenges associated with not only introducing the *para*-quinol but doing so with control of stereochemistry. In considering methods to stereoselectively introduce the *para*-quinol, we were captivated by the possibility of forming spiroepoxide **4.02** through intramolecular trapping of a carbonium ion by an adjacent alcohol as portrayed in intermediate **4.03** (Scheme 4.1). Thus, in the course of our retrosynthetic analysis we considered **4.04** as a possible intermediate.



Scheme 4.1. Targeting a spiroepoxide for diastereoselective *para*-quinol formation

As illustrated in Scheme 4.2, incorporating this design element led to an overall plan wherein tetrapetalone A (**4.01**) was envisioned as arising from a late-stage glycosylation and deethoxycarbonylation sequence applied to *para*-quinol **4.05**. The *para*-quinol (**4.05**) would be delivered by way of a regio- and diastereo- selective reduction of the spiroepoxide moiety present in **4.02**. A critical intermediate in our strategy would be the stereoselective preparation of tetracyclic diol **4.06** wherein the tertiary alcohol would

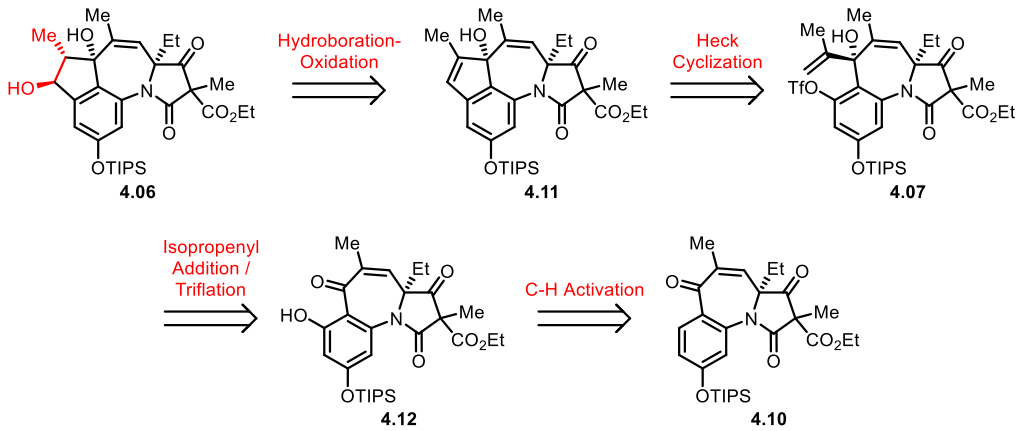
be used to deliver the spiroepoxide **4.02**. Importantly there was considereable flexibility in the way one could imagine constructing **4.06** from tricyclic enone **4.10**. These strategies are discussed in the following sections and include: a Heck cyclization via intermediate **4.07** (section 4.2), a ring-closing metathesis strategy via intermediate **4.08** (section 4.3) and an intramolecular Friedel-Crafts acylation strategy via acid **4.09** (section 4.4).



Scheme 4.2. Retrosynthesis of tetrapetalone A via a key spiroepoxide intermediate **4.02** from tricyclic enone **4.10**

4.2 A Heck Cyclization Strategy Toward a Spiroepoxide

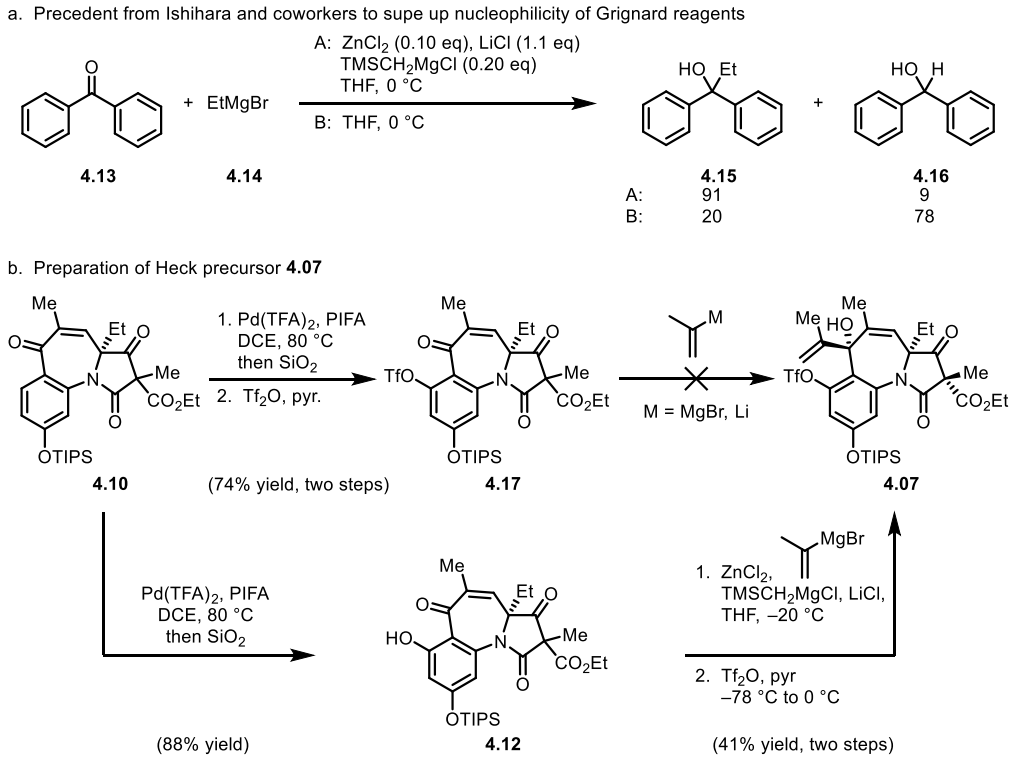
As illustrated in Scheme 4.3, the Heck cyclization strategy calls for producing tetracyclic alcohol **4.06** via a late-stage hydroboration/oxidation reaction applied to intermediate **4.11**. Importantly, this transformation was expected to not only give the desired regiochemical outcome, but also provide the desired *trans*-stereochemistry between the secondary alcohol and adjacent methyl group (Scheme 4.3). The indene motif in tetracycle **4.11** was envisioned to arise by way of an intramolecular Heck cyclization[1] from triflate **4.07**, itself made available from tricyclic enone **4.10** via a sequence involving C-H activation, isopropenyl addition and triflation.



Scheme 4.3. A Heck cyclization strategy to deliver tetracyclic **4.06.**

In the forward sense, triflate **4.17** was accessed from key intermediate **4.10** via initial conversion to an intermediate phenol, using Dong's C-H activation method (Scheme 4.4, bottom), followed by sulfonylation.[2] It is worth noting that in initial studies workup conditions were employed wherein NH_4OH served to hydrolyze an intermediate trifluoroacetate group. Switching to conditions originally reported by Dong, using SiO_2 to cleave the trifluoroacetate, markedly improved the yield of the reaction and further minimized purification efforts.

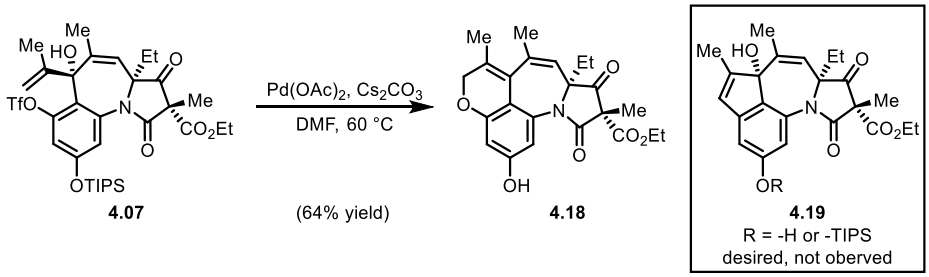
Initial attempts to convert **4.17** to **4.07** using a metalated isopropenyl unit as nucleophile gave only trace yields of the desired adduct. Searching the literature for methods that would increase the nucleophilicity of the Grignard reagent revealed a report by Ishihara and co-workers wherein Zinc(II) was identified as an effective additive in Grignard additions to hindered ketones (Scheme 4.4, top).[3] Interestingly, these studies, in which benzophenone (**4.13**) was employed as an electrophile and ethyl magnesium bromide (**4.14**) as a nucleophile, revealed a dramatic difference in product ratios for experiments run in the presence of Zn(II) (91% yield of the desired adduct **4.15**) and absence of any additives (78% yield of a ß-hydride transfer product **4.16**). To our delight, applying Ishihara's conditions to the addition of isopropenyl Grignard to alcohol **4.12** led, following tiflation, to Heck cyclization precursor **4.07** as a single diastereomer,



Scheme 4.4. Accessing Heck precursor **4.07** via Ishihara nucleophilic addition

the stereochemistry of which was presumed to be as illustrated based on the propensity of these systems to react on the ß-face of the molecule (*vida infra*, Chapter 5).

Although delighted to finally obtain triflate **4.07**, we were soon disappointed to discover that its exposure to numerous Heck cyclization conditions failed to produce **4.19** and resulted only in the formation of benzopyran **4.18** (Scheme 4.5). Presumably this latter product was arising due to the inherent propensity of the bisallylic and benzylic tertiary alcohol (**4.07**) to ionize and undergo 5-endo cyclization. Fearing that we would never overcome this inherent reactivity our efforts shifted to alternative approaches to tetracycle **4.19**.

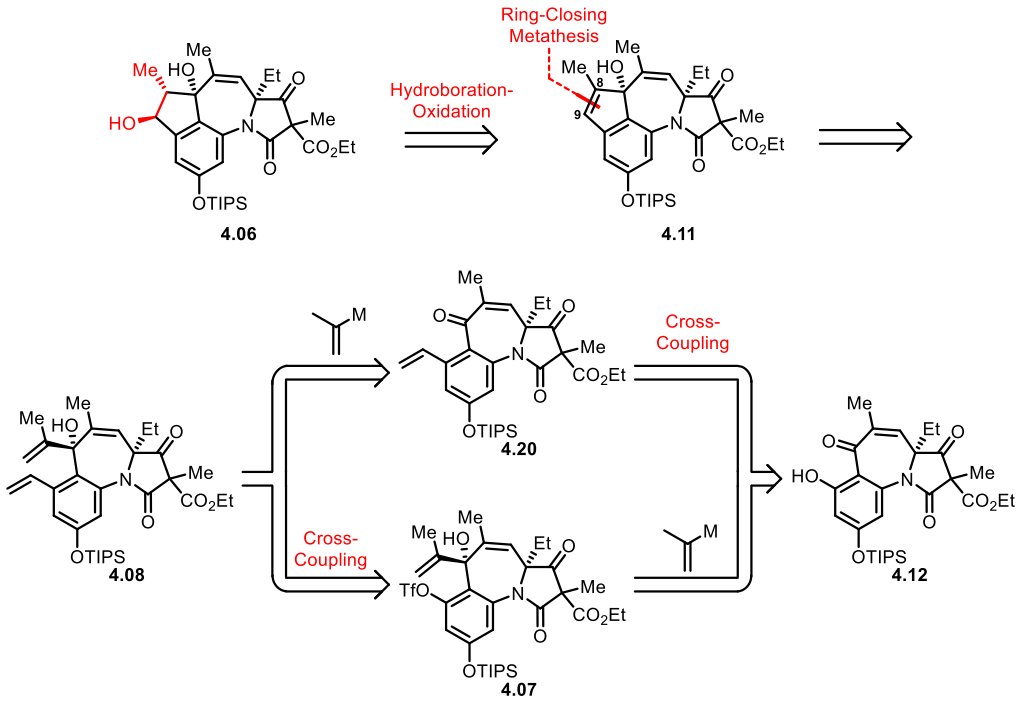


Scheme 4.5. Attempted Heck cyclization resulting in formation of benzopyran **4.18**.

4.3 A Ring-Closing Methathesis Strategy Toward a Spiroepoxide

Having failed to produce the desired tetracyclic alcohol via Heck cyclization, we turned our attention to an alternative disconnection at the C(8)-C(9) bond (**4.11**, Scheme 4.5). In an identical endgame to that described above for the Heck strategy, we envisioned tetracycle **4.06** as arising from a hydroboration-oxidation of intermediate **4.11**; however, in this revised approach **4.11** was envisioned as arising via a RCM reaction and the requisite precursor (**4.08**) seen as deriving from one of two possible pathways from C-H activation product **4.12**. These latter two pathways are a simple permutation of two events. The first

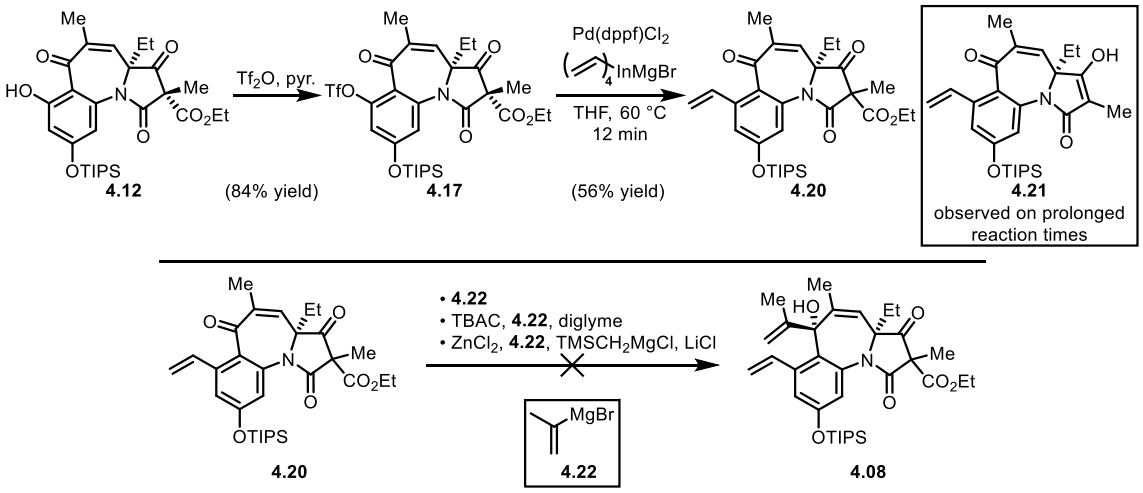
involves cross-coupling to provide styrene derivative **4.20** followed by isopropenyl addition into the azepine ketone. Alternatively, isopropenyl addition could be done first to provide intermediate **4.07** which, upon subsequent subjection to cross-coupling conditions with an appropriate vinyl unit would deliver **4.08**.



Scheme 4.6. A ring-closing metathesis strategy to deliver benzylic alcohol **4.06**.

With ample access to triflate **4.17**, we first looked to explore the viability of cross-coupling chemistry (Scheme 4.7). Initial efforts using classical Stille coupling conditions failed to provide the desired cross-coupling adducts. Familiarity with indium mediated cross-coupling chemistry from my previous experiences in the Minehan Lab (unpublished work) along with precedent from the Lee and Sarandeses labs prompted our investigation into tetraorganoindate chemistry.[4] Initial efforts to effect this cross-coupling reaction with Lee's conditions gave low yields of the desired adduct, with evidence of the formation of

a major side product derived from decarboalkoxylation (i.e., **4.21)**. Gratifyingly, employing a modification of Lee's conditions, wherein reaction times were decreased, proved effective and delivered cross-coupled product **4.20** in good yield.

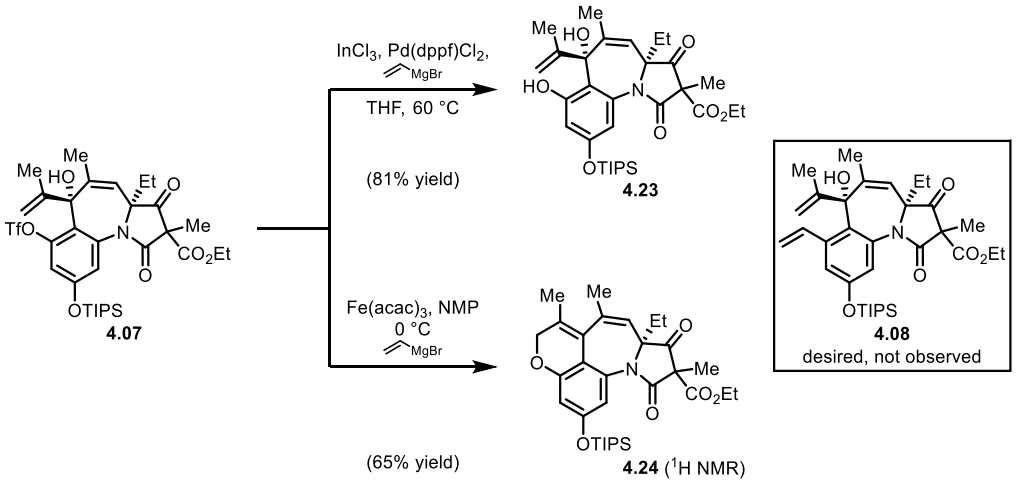


Scheme 4.7. Tetraorganoindate cross-coupling to deliver styrene **4.20**

With styrene derivative **4.20** in hand, efforts focused on elaborating it to the desired RCM precursor **4.08**. Unfortunately, attempts to introduce the isopropenyl unit via nucleophilic addition to the carbonyl proved futile. Faced with the poor reactivity of the *ortho*-substituted ketone toward nucleophilic addition, we decided to change the order of events. Thus, instead of employing cross-coupling followed by isopropenyl addition, we would reverse the order and perform isopropenyl addition first followed by cross-coupling. From our efforts exploring the Heck cyclization reaction, we had already obtained triflate **4.07** (Scheme 4.8) via nucleophilic addition conditions developed in the Ishihara lab.[3]

Moving forward, attempts to cross-couple triflate **4.07** with a vinyl equivalent were ineffective (Scheme 4.8). Under numerous conditions, including the quite mild classical Stille cross-coupling, these efforts failed to deliver the desired styrene **4.08**. Typically,

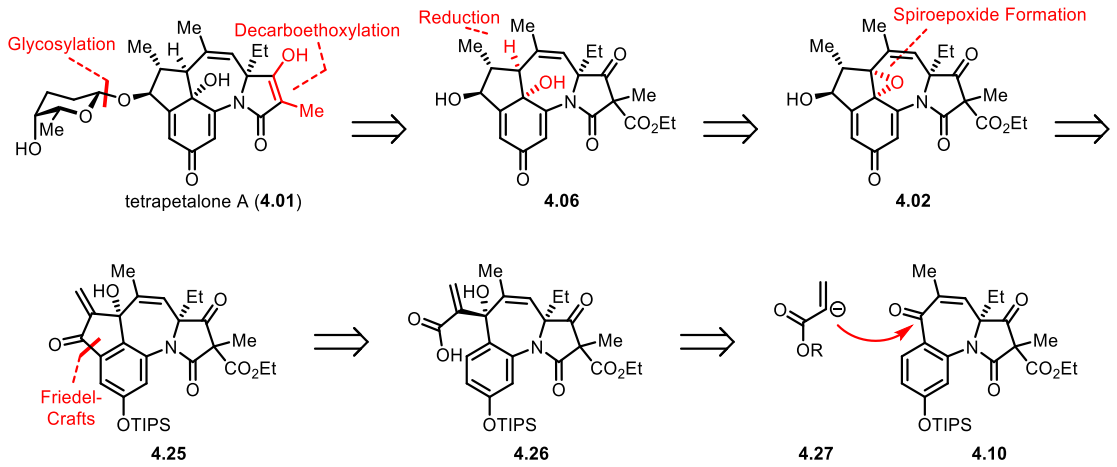
reactions resulted in either triflate hydrolysis to **4.23** or formation of a product possessing ^{1}H NMR data consistent with that of benzopyran **4.24**. Once again thwarted by subsrate instability we abandonded efforts to produce a RCM precursor possessing a tertiary benzylic alcohol.[5]



Scheme 4.8. Attempted cross-coupling after isopropenyl addition to access **4.08**

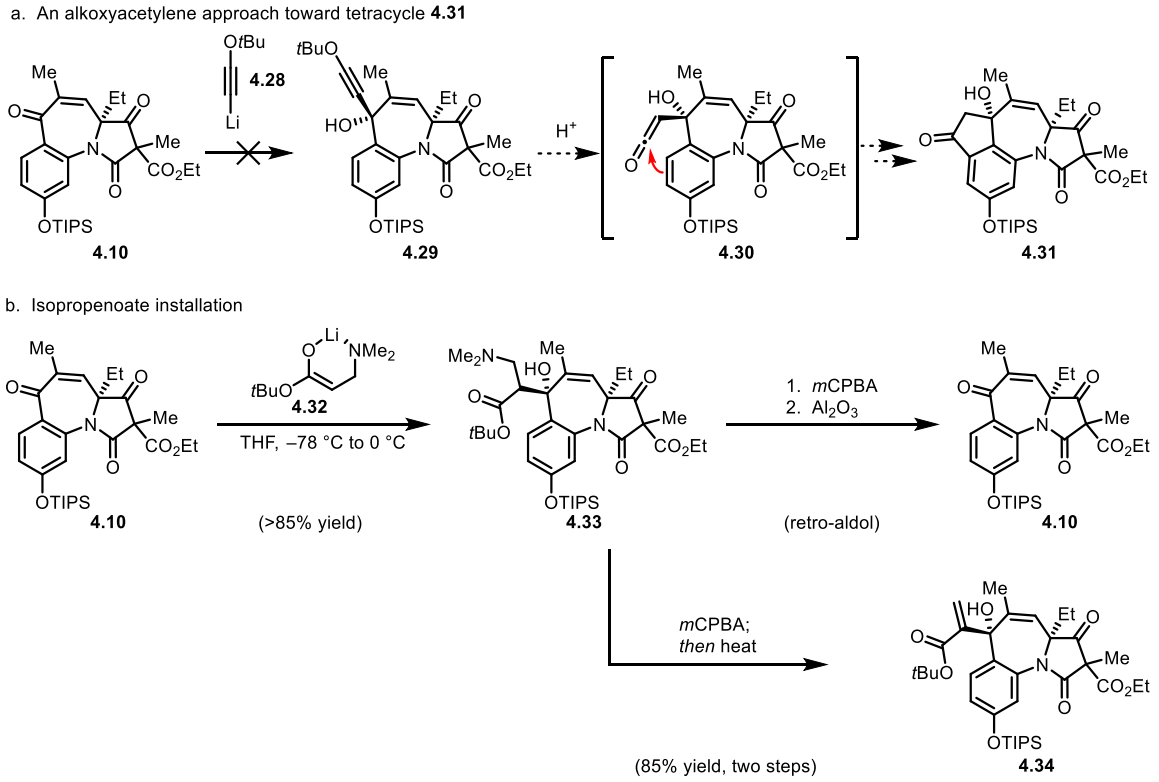
4.4 An Intramolecular Friedel-Crafts Acylation Strategy Toward a Spiroepoxide

With the Heck and RCM approaches looking bleak, we began reflecting upon the method by which we were able to install the azepine ring and thus considered the possibility of using another intramolecular Friedel-Crafts acylation reaction to deliver the desired tetracycle (Scheme 4.9). Accordingly, we revised the retrosynthetic analysis to one wherein the requisite spiroepoxide (**4.02**) would derive from bis-reduction of enone **4.25**, itself available from an intramolecular Friedel-Crafts acylation reaction of acid **4.26**. Acid **4.26** was seen as arising from the addition of a vinyl-anion equivalent (e.g., **4.27**) into our key tricycle enone intermediate (**4.10**).



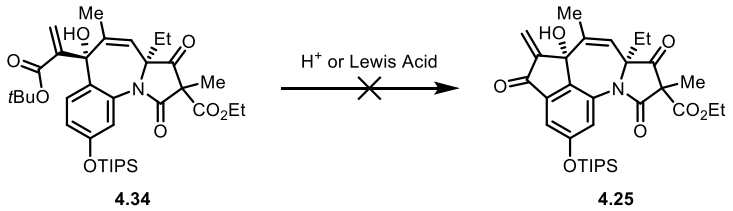
Scheme 4.9. An intramolecular Friedel-Crafts acylation strategy to build a tetracyclic with benzylic alcohol in place

In an initial effort to implement this revised strategy, we hoped to employ alkoxyacetylene **4.28** as an equivalent of ketene that would be unmasked following addition to **4.10** (Scheme 4.10, top). However, this approach failed from the outset with our inability to effect the addition of the **4.28** to the enone.[6] Subsequent efforts to add lithiated *t*butyl propenoate (not depicted) were also unproductive but did lead us to consider nucleophiles similar to those under study in our laboratory's ongoing synthesis of the phomoidrides. In this latter regard, we attempted the addition of ester enolate **4.32**,[7] which proved to be an effective nucleophile and delivered **4.33** in excellent yields. However, initial attempts to effect Cope-elimination resulted in clean retro-aldol reaction and regenerated the starting tricyclic enone **4.10**. Fortunately, simple modification of the conditions such that oxidation was followed by gentle heating was found to promote Cope elimination and produce ester **4.34** in good yield.



Scheme 4.10. Preparation of a Friedel-Crafts precursor.

Despite having formed ester **4.34**, challenges associated with unveiling the acid to set the stage for Friedel-Crafts cyclization proved insurmountable. These efforts were found to produce complex mixtures of products that appeared to lack the azepine alkene and none of the desired azepine **4.25** (Scheme 4.11). As was observed in attempts to perform either the Heck cyclization or the RCM, the allylic and benzylic tertiary alcohol was again proving to be unstable to both acidic and basic conditions, thus making advancement difficult. It was upon this realization that we abandoned the notion of employing strategies involving the intermediacy of benzylic alcohols poised to trap an intermediate carbocation and began to consider alternative strategies.



Scheme 4.11. Attempted intramolecular Friedel-Crafts acylation reaction

4.5 Experimental

General

Unless otherwise stated, reactions were magnetically stirred in flame or oven dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Diethyl ether, tetrahydrofuran, toluene, benzene, dichloromethane, and acetonitrile were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. ACS grade acetone (Fisher) was purchased from Fisher-Scientific and used as received. Dimethyl formamide and 1,2-dichloroethane (DCE) were purchased from Sigma-Aldrich and used as received. $Pd(PPh_3)_4$ was purchased from Sigma-Aldrich and stored under nitrogen in a -20°C freezer. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Millipore glass-backed 60Å plates (indicator F-254s, 150-180 μm thickness) (Millipore, catalogue #1164850001). Column or flash chromatography was performed with the indicated solvents using Millipore Silica Gel 60 (0.040-0.063 mm, 230-400 mesh ASTM) as the stationary phase. MPLC purifications were performed on a Telodyne Isco Combi*Flash*® *Rf*+ (Model: RF + UV-VIS MS COMP), used with standard Telodyne Isco normal phase disposable columns for flash chromatography and monitored at wavelengths of 254 and 280 nm. All melting points were obtained on a Chemglass Life Sciences

melting point device (Model: DMP100) and are uncorrected. Infrared spectra were obtained using a Bruker Alpha ATR-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, Varian 500, or Bruker 600. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million (ppm) relative to internal residual solvent peaks from the indicated deuterated solvents (^{1}H: For $CDCl_3$, $CHCl_3$ 7.26; For Methanol-d_4, CD_2HOD 3.31; For Acetone-d_6, Acetone-D5H 2.05). Chemical shifts (δ) for ^{13}C spectra were referenced from the indicated solvent peaks (^{13}C: $CDCl_3$ 77.16, Methanol-d_4 49.00, Acetone-d_6 29.84). Chemical shifts in ^{19}F spectra were taken in $CDCl_3$ doped with fluorobenzene and referenced to -113.15. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as s = singlet, br.s = broad singlet, d = doublet, br. d = broad doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High resolution mass spectra were performed on a Thermo LTQ Orbitrap Discovery with direct injection followed by electro-spray ionization (ESI). Microwave reactions were carried out using a CEM Discover SP Microwave system. Single crystal X-ray diffraction studies were collected on a Bruker Apex II-CCD detector using Mo-K_α radiation (λ = 0.71073 Å). Structures were solved and refined using SHELXTL. Optical rotations were obtained on a Rudolph Research Analytical Autopol IV Automatic Polarimeter.

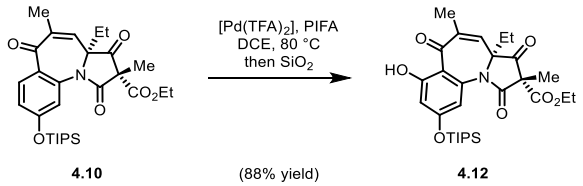
High-Performance Liquid Chromatography (HPLC): All HPLC purifications were carried out on a Waters HPLC system (consisting of a Waters 1525 binary HPLC pump with direct injection port and monitored at 254 nm unless otherwise specified with a Waters

2489 UV-Visible detector). All purifications utilized a normal-phase Sunfire, Silica Prep 10 µm, 10 x 250 mm column.

Ultra Performance Liquid Chromatography (UPLC)-Mass Spectrometry (MS): All UPLC-MS experiments were carried out on a Waters Acquity H UPLC Class system using the indicated solvent systems as eluents. All separations were performed on a reverse phase Acquity UPLC BEH C18 1.7 µm, 2.1 x 50 mm column.

^{1}H and ^{13}C NMR spectra are included for all previously unreported compounds.

Phenol **4.12**



Note: ***4.12*** *was prepared as a single diastereomer using a single diastereomer of* ***4.10*** *in the follow procedure. See chapter 7 for the preparation of the minor diastereomer. Diastereomeric mixtures of* ***4.10*** *have been used in this procedure to give nearly identical yields.*

Experimental: To a 100 mL round-bottomed flask was added **4.10** (1.77 g, 3.35 mmol). This was then dissolved in DCE (25 mL) followed by the addition of PIFA (2.96 g, 6.88 mmol) and $Pd(TFA)_2$ (56 mg, 0.17 mmol). A water-cooled reflux condenser is attached, the reaction placed in a preheated aluminum block at 80°C, and stirred for 3.5h. The reaction was then cooled in an ice water bath and filtered through a plug of SiO2 and washed with CH_2Cl_2. This was then concentrated in vacuo to a yellow oil. The yellow residue was then azeotroped twice with 30% methanol/toluene to ensure removal of the trifluoroacetoxy group, and lastly twice with toluene. The residue was dried under hi-vac overnight to provide **4.12** (1.6 g, 88% yield) as a yellow oil.

Note: An analytically pure sample was prepared by purification of a small aliquot of the crude material by column chromatography (0% →10% EtOAc in hexanes) and this characterization data is described below.

^{1}H NMR (500 MHz, $CDCl_3$): δ 13.30 (s, 1H), 6.61 (d, *J* = 2.5 Hz, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.47-6.46 (m, 1H), 4.35-4.20 (m, 2H), 2.11-2.05 (m, 1H), 2.03 (d, *J* = 1.4 Hz, 3H), 1.75 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.59 (s, 3H), 1.33-1.27 (m, 6H), 1.11 (d, *J* = 7.5, 1.9 Hz, 18H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.0, 191.4, 168.8, 167.0, 165.2, 162.4, 140.6, 139.8, 135.4, 113.0, 112.5, 108.6, 75.8, 63.0, 58.0, 27.4, 21.3, 18.9, 17.92, 17.90, 14.0, 12.8, 8.2.

IR (thin film): cm^{-1} 2944, 2868, 1781, 1752, 1715, 1613, 1574, 1458, 1426, 1367, 1345, 1244, 1194, 1178, 1144, 1122, 1099, 1057, 1037, 1017, 997, 882, 857, 814, 775, 688, 665.

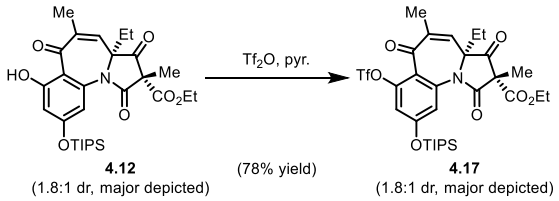
HRMS (ESI+): calculated for $C_{29}H_{41}NO_7SiNa$ $[M+Na]^+$ 566.2545, found: 566.2543.

TLC: R_f = 0.23 (20% EtOAc/hexanes).

m.p.: 80.4-81.9 °C.

Physical Appearance: Yellow oil that solidifies upon standing.

Triflate **4.17**



Experimental: To a 250 mL rbf containing **4.12** (833.4 mg, 1.533 mmol, 1.8:1 mixture of diastereomers, major depicted) was added CH_2Cl_2 (11.0 mL) and cooled to –78 °C in a dry-ice acetone bath. After cooling, to this was added pyridine (0.53 mL, 6.6 mmol) followed by the dropwise addition of Tf_2O (0.55 mL, 3.3 mmol) dropwise over the course of ~15 seconds. The reaction was stirred in a dry-ice acetone bath for 20 min, then warmed

in an ice water bath and stirred for 1.5 h in the ice-water bath until TLC indicated consumption of the starting material (*Note*: the product R_f and starting material R_f were very similar. Consumption of the starting material was gauged by the disappearance of the yellow color of the starting material on TLC). The reaction was then quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3x). The combined organics were then dried over Mg_2SO_4 filtered and concentrated to a faint yellow oil. The product was purified by flash column chromatography on silica gel to give triflates **4.17** (811.7 mg, 1.201 mmol, 78% yield, 1.8:1 dr, major depicted) as a faint yellow oil.

Note: When the reaction was quenched by the addition of saturated aqueous $NaHCO_3$, partial TIPS deprotection was observed and the resulting product had to be re-exposed to TIPSCl, imid. A middle fraction was used for characterization of the diastereomeric mixture whose dr is ca. 3.5:1 (major depicted).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.05 (d, *J* = 2.3 Hz, 3H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.87 – 6.82 (m, 4H), 6.40 (d, *J* = 1.5 Hz, 3H), 6.36 (d, *J* = 1.5 Hz, 1H), 4.35 – 4.21 (m, 7H), 4.15 – 4.00 (m, 2H), 3.48 (q, *J* = 7.0 Hz, 3H), 2.09 – 1.98 (m, 19H), 1.71 (dq, *J* = 15.1, 7.5 Hz, 4H), 1.61 (s, 11H), 1.56 (s, 3H), 1.33 – 1.25 (m, 24H), 1.20 (t, *J* = 7.0 Hz, 6H), 1.12 (dd, *J* = 7.5, 2.2 Hz, 79H), 0.85 (t, *J* = 7.4 Hz, 11H), 0.78 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (151 Hz, $CDCl_3$): δ 204.1, 203.9, 188.5, 187.7, 168.9, 168.6, 165.0, 164.0, 159.4, 159.3, 148.3, 147.9, 138.6, 138.2, 138.0, 137.5, 134.5, 134.2, 125.4, 124.9, 119.7, 119.4, 119.2, 117.6, 115.3, 115.0, 77.9, 66.0, 63.4, 63.1, 57.9, 28.6, 27.9, 20.7, 20.5, 19.1, 19.1, 17.8, 17.8, 17.8, 15.4, 15.2, 14.0, 13.8, 12.7, 12.6, 12.4, 8.5.

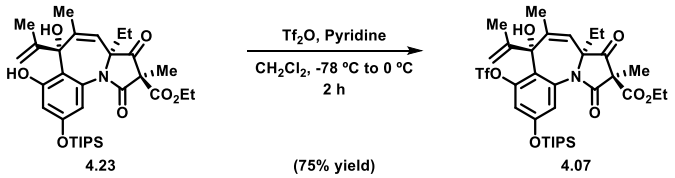
IR (thin film): 2496, 2870, 1782, 1752, 1718, 1659, 1607, 1561, 1482, 1427, 1360, 1307, 1290, 1242, 1206, 1140, 1111, 1014 cm^{-1}.

HRMS (ESI+): calculated for $C_{30}H_{40}F_3NO_9SSiNa$ $[M+Na]^+$ 698.2037, found: 698.2038.

TLC: 0.50 (20% EtOAc in hexanes).

Physical Appearance: Faint yellow oil.

Triflate **4.07**



Experimental: To a flame dried round-bottomed flask was added phenol **4.23** (90 mg, 0.15 mmol) and dissolved in CH_2Cl_2 (0.060 M, 2.56 mL). The solution was cooled to -78 ºC for 10 min. After the addition of pyridine (6.0 eq., 75 µL, 0.92 mmol), trifluoromethanesulfonic anhydride (3.0 eq., 78 µL, 0.46 mmol) was added slowly and the reaction mixture was stirred for 30 min at the same temperature. The mixture was then allowed to warm to 0 ºC. After being stirred for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the aqueous mixture was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 10:1) to afford the triflate **4.07** as a white solid (83.0 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, J = 2.7 Hz, 1H), 6.86 (d, J = 2.7 Hz, 1H), 5.64 (d, J = 1.2 Hz, 1H), 5.49 (s, 1H), 5.18 (m, 1H), 4.25 (m, 2H), 3.08 (s, 1H), 1.98 (dt, J = 14.8, 7.4 Hz, 1kH), 1.83 (d, J = 1.1 Hz, 3H), 1.75 (dt, J = 14.6, 7.3 Hz, 1H), 1.58 (s, 3H), 1.54 (s, 3H), 1.27 (m, 6H), 1.10 (dd, J = 7.3, 0.95 Hz, 18H), 0.88 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 205.9, 169.1, 165.3, 156.2, 150.3, 141.6, 140.6, 134.8, 127.2, 124.9, 121.2, 118.5 (q, J = 320 Hz) 115.7, 115.5, 80.3, 75.4, 62.8, 58.3, 28.0, 22.1, 20.5, 18.9, 17.80, 17.78, 14.0, 12.6, 9.0.

IR (thin film): 3313, 2946, 2869, 1781, 1680, 1609, 1562, 1425, 1236, 1197, 1142, 884, 779, 672 cm^{-1}.

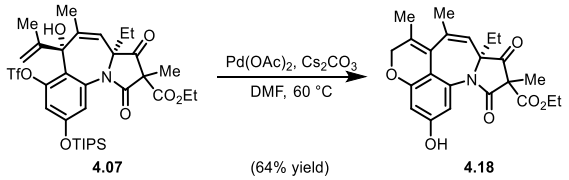
HRMS (ESI+): calculated for $C_{33}H_{46}F_3NO_9SSiNa$ $[M+Na]^+$ 740.2507, found: 740.2495.

TLC: R_f=0.61 (20% EtOAc/Hexanes).

m.p.: 150.3-150.9 °C.

Physical Appearance: White solid.

Benzopyran **4.18**



Experimental: To a flame dried round-bottomed flask equipped with a magnetic stir bar were added palladium (II) acetate (2.8 mg, 0.013 mmol), triphenylphosphine (6.6 mg, 0.025 mmol), and cesium carbonate (27.2 mg, 0.084 mmol). The flask was left under hi-vac for 30 min then back filled with N_2. A solution of triflate **4.07** (30 mg, 0.042 mmol) in DMF (836 µL) was added and immediately placed in a pre-heated oil bath at 60 °C. After stirring for 12 h at 60 °C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the aqueous mixture extracted twice with a 1:1 solution of hexane:EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (18% to 25% EtOAc in hexanes) to provide benzopyran **4.18** as a pale yellow solid (11.0 mg, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (d, *J* = 2.6 Hz, 1H), 6.41 (d, *J* = 2.6 Hz, 1H), 6.04 (br. s, 1H), 5.64 (d, *J* = 1.32 Hz, 1H), 4.42-4.28 (m, 2H), 4.28-4.15 (m, 2H), 2.15-2.06 (m,

2H), 2.05 (d, J = 1.4 Hz, 3H), 1.88 (s, 3H), 1.64 (s, 3H), 1.25 (t. J = 7.2 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 205.8, 170.0, 165.4, 156.1, 136.9, 134.9, 131.2, 129.0, 127.4, 113.6, 108.7, 104.0, 75.6, 70.2, 62.9, 58.9, 29.9, 29.4, 27.0, 26.1, 19.1, 14.1, 9.0.

IR (thin film): 3271, 2931, 1776, 1666, 1610, 1427, 1398, 1203, 1174, 1143, 1012, 884, 832, 676 cm^{-1}.

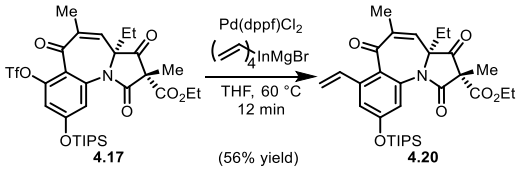
HRMS (ESI+): calculated for $C_{23}H_{25}NO_6Na^+$ $[M+Na]^+$ 434.1574, found: 434.1571.

TLC: 0.22 (20% EtOAc in hexanes)

m.p.: decomp.

Physical Appearance: Pale yellow amorphous solid.

Styrene **4.17**



Experimental: To a flame dried round-bottomed flask was added anhydrous $InCl_3$ (66.1 mg, 0.299 mmol) and the powder heated under hi-vac with heatgun for ~2 min then cooled to room temperature. After cooling, this was placed under an atmosphere of N_2 and to this was added THF (2.16 mL). The suspension was cooled to –78 °C in a dry ice/acetone bath for 15 min followed by the addition of vinylmagnesium bromide (1.36 mL, 0.886 M solution in THF) over the course of 2 min. After stirring for 30 min, the dry ice/acetone bath was removed and the reaction let go to room temperature. The reaction was stirred for another 30 minutes at room temperature to give the tetraorganoindate solution (0.085 M in THF)

In a separate flame-dried round-bottomed flask was added triflate **4.17** (220 mg, 0.326 mmol) and this azeotroped twice with toluene and left under hi-vac for 30 min. After 30 min, the triflate was dissolved in THF (6.5 mL) and the solution cooled to 0 °C in an ice water bath. After cooling, to this was added $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ adduct (0.033 mmol, 26.9 mg) followed by the addition of the tetraorganoindate solution (1.69 mL, 0.085 M solution in THF). The flask was immediately placed in a pre-heated oil bath at 70 °C. The reaction was stirred until TLC analysis indicated consumption of the starting material (12-15 min) and the reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (hexanes:EtOAc 8:1) to give styrene **4.20** (104 mg, 56% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.72 (dd, *J* = 17.3, 10.9 Hz, 1H), 6.28 (d, *J* = 1.4 Hz, 1H), 5.64 (dd, *J* = 17.3, 0.9 Hz, 1H), 5.31 (dd, *J* = 10.9, 0.8 Hz, 1H), 4.27 (m, 2H), 2.01 (m, 4H), 1.68 (m, 1H), 1.54 (s, 3H), 1.28 (m, 6H), 1.12 (d, *J* = 7.2 Hz, 18H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 204.6, 192.7, 169.0, 165.3, 158.5, 141.4, 138.7, 136.9, 134.7, 133.5, 130.3, 118.82, 118.80, 117.1, 76.8, 62.9, 58.0, 28.0, 20.9, 19.2, 17.9, 14.0, 12.7, 8.4.

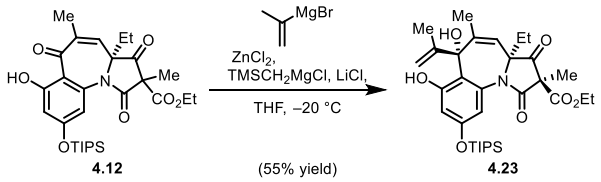
IR (thin film): 2943, 2867, 1777, 1743, 1713, 1636, 1594, 1561, 1433, 1382, 1371, 1244, 1205, 1116 cm^{-1}.

HRMS (ESI+): calculated for $C_{31}H_{43}NO_6SiNa^+$ $[M+Na]^+$ 576.2752, found: 576.2748.

TLC: 0.62 (17% EtOAc in hexanes)

Physical Appearance: Colorless oil.

Tertiary alcohol **4.23**



Experimental: To a flame dried round-bottomed flask equipped with a stirbar was added Magnesium turnings (42.8 mg, 1.76 mmol). After placing this under N_2, dry Et_2O (1.76 mL) was added along with a catalytic amount of I_2 at room temperature. Half an equivalent of trimethylsilylmethyl chloride was added (100 µL, 0.735 mmol) was added in one shot. Subsequently, the remaining trimethylsilylmethyl chloride was added dropwise over the course of ~2 min (100 µL, 0.735 mmol) after which the suspension had turned into a clear, colorless solution.

In a separate flame dried round-bottomed flask equipped with a stirbar was added $ZnCl_2$ (8.5 mg, 0.063 mmol). This was melted under hi-vac by heatgun. Subsequently, LiCl (29.2 mg, 0.688 mmol) was added to the same flask and melted under hi-vac by heatgun. After cooling to room temperature, this was placed under an atmosphere of N_2 followed by the addition of trimethylsilylmethyl magnesium chloride (125 µL, 0.125 mmol) and the suspension vigorously stirred for 15 min at room temperature. Subsequently, isopropenylmagnesium bromide was added (1.38 mL, 0.688 mmol, 0.5 M solution in THF) and the reaction stirred for 45 min. This was then cooled to –20 °C in a controlled dry-ice/acetone bath for 10 min followed by the addition of a solution of phenol **4.12** (170 mg, 0.313 mmol) in THF (6.25 mL) over the course of 10 min. After stirring for 30 min at this temperature, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the aqueous mixture extracted with EtOAc (3x). The combined

organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified by flash column chromatography on silica gel (20:1 to 10:1 hexanes:EtOAc) to give the tertiary alcohol **4.23** (101 mg, 55% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1H), 6.45 (d, *J* = 2.8 Hz, 1H), 6.39 (d, *J* = 2.8 Hz, 1H), 5.67 (m, 1H), 5.60 (d, *J* = 1.3 Hz, 1H), 5.29 (m, 1H), 4.23 (m, 3H), 1.96 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.76 (m, 4 H), 1.56 (s, 3H), 1.37 (s, 3H), 1.25 (m, 6H), 1.08 (d, *J* = 7.1 Hz, 18H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 206.7, 169.4, 165.4, 159.1, 156.6, 146.6, 139.9, 133.2, 128.2, 116.8, 115.0, 113.1, 109.6, 80.3, 75.6, 62.6, 58.5, 27.4, 21.5, 20.2, 18.7, 17.9, 14.0, 12.7, 8.9.

IR (thin film): 3470, 3270, 2943, 2867, 1778, 1615, 1566, 1293, 1236, 1142, 992, 814, 777, 665 cm^{-1}.

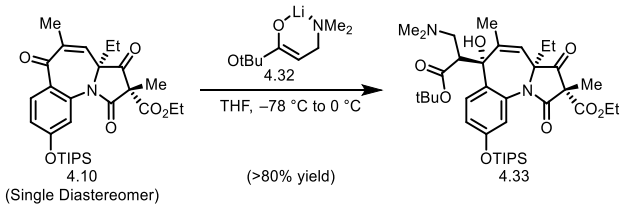
HRMS (ESI+): calculated for $C_{32}H_{47}NO_7SiNa^+$ $[M+Na]^+$ 608.3014, found: 608.3011.

TLC: 0.52 (20% EtOAc in hexanes).

m.p.: 150.1-151.0 °C.

Physical Appearance: White solid.

Amine **4.33**



Experimental: To a flame dried 25 mL round-bottomed flask with stirbar was added *t*Butyl 3-(dimethylamino)propanoate (81.1 mg, 0.468 mmol) and dissolved in THF (1.6 mL). This was then cooled to –78 °C in a dry-ice/acetone bath for 10 min after which LDA (1.1 mL, 0.54 mmol, 0.491 M in THF) was added over the course of ~1 min. The solution

was stirred for 15 min and subsequently warmed to 0 °C in an ice water bath. After stirring for 30 min in the ice water bath, the reaction was cooled back to –78 °C in a dry-ice/acetone bath. After 5 min, this solution of enolate **4.32** (0.173 M in THF) was ready for use.

In a separate flame-dried 25 mL round-bottomed flask was added **4.10** (108.2 mg, 0.205 mmol, single depicted diastereomer) and dissolved in THF (2.0 mL) followed by cooling to –78 °C in a dry-ice/acetone bath. After 10 min, to this was added **4.32** (1.6 mL, 0.28 mmol, 0.173 M in THF) dropwise over the course of ~45 seconds. The reaction was stirred in the dry-ice/acetone bath for 2 h 30 min after which it was quenched by the addition of saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to to give **4.33** (144.3 mg, 100% yield, >80% pure as judged by ^{1}H NMR, >10:1 dr) as a crude yellow oil.

Note: This material was pure enough for subsequent reactions. A small amount of this material was purified by flash column chromatography on silica gel (10% → 20% → 50% EtOAc in hexanes) to give the product **4.33** as a colorless oil. The cleanest fraction is as characterized below.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (d, *J* = 9.1 Hz, 1H), 6.95-6.90 (m, 2H), 5.49 (s, 1H), 5.30 (CH_2Cl_2), 5.20 (br. s, 1H), 4.34 – 4.18 (m, 2H), 2.90 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.57 (t, *J* = 12.0 Hz, 1H), 1.98 (s, 6H), 1.92 (s, 3H), 1.79 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.73 (s, 3H), 1.56 – 1.44 (m, 3H), 1.42 (s, 9H), 1.32 – 1.21 (m, 6H), 1.10 (dd, *J* = 7.4, 1.7 Hz, 18H), 0.77 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.6, 175.5, 168.5, 165.7, 155.9, 142.7, 133.0, 131.5, 128.4, 123.7, 121.0, 120.3, 82.6, 76.0, 74.0, 62.8, 58.3, 58.0, 52.8, 45.8, 30.6, 28.1, 24.2, 18.1, 18.03, 18.00, 14.0, 12.7, 8.4.

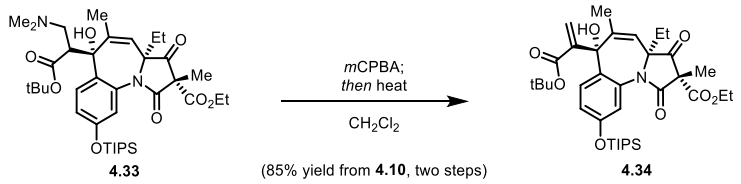
IR (thin film): 3448, 2946, 2869, 1779, 1751, 1712, 1607, 1501, 1459, 1384, 1368, 1239, 1155 cm^{-1}.

HRMS (ESI+): calculated for $C_{38}H_{61}N_2O_8Si^+$ $[M+H]^+$ 701.4192 , found: 701.4193.

TLC: 0.41 (20% EtOAc in hexanes)

Physical Appearance: Colorless oil.

Exo-olefin **4.34**



Experimental: To a round-bottomed flask was added crude amine **4.33** (125.1 mg, 0.178 mmol) and dissolved in CH_2Cl_2 (7.1 mL). This was placed under an atmosphere of N_2 and cooled to –78 °C in a dry-ice/acetone bath. After 10 min, *m*CPBA (44.2 mg, 77% pure, 0.197 mmol) was added as a solid. The suspension was stirred for 5 min in the dry ice acetone bath. The bath was subsequently removed and the reaction was stirred for an additional 15 min. After 15 min, a vigreux column was placed on the flask, placed under N_2, and placed in a preheated oil bath at 50 °C. The reaction was stirred for 2 h, then cooled to room temperature and diluted with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude residue. The crude residue was then purified by flash column chromatography on silica gel (10%→15%→20% EtOAc in hexanes) to give exo-olefin **4.34** (113.8 mg, 0.174 mmol, 85% yield from **4.10**, two steps) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.7 Hz, 1H), 6.94 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 5.78 (d, *J* = 0.7 Hz, 1H), 5.71 (d, *J* = 1.5 Hz, 1H), 5.46 (d, *J* = 1.0 Hz, 1H), 5.30 (CH_2Cl_2), 4.95 (s, 1H), 4.30 – 4.19 (m, 2H), 2.01 (d, *J* = 1.4 Hz, 3H), 1.72

(q, J = 7.5 Hz, 2H), 1.50 (s, 3H), 1.33 – 1.21 (m, 15H), 1.09 (dd, J = 7.5, 1.0 Hz, 18H), 0.74 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.2, 168.0, 167.4, 165.8, 156.0, 143.8, 139.4, 133.3, 132.4, 127.9, 123.5, 122.2, 120.4, 119.8, 82.9, 73.6, 62.9, 57.7, 32.1, 27.8, 27.8, 23.2, 18.0, 16.4, 14.0, 12.7, 8.5.

IR (thin film): 3477, 2691, 2944, 2868, 1776, 1747, 1713, 1606, 1499, 1367, 1232, 1147, 1110, 855 cm^{-1}.

HRMS (ESI+): calculated for $C_{36}H_{53}NO_8SiNa^+$ $[M+Na]^+$ 678.3433, found: 678.3441.

TLC: 0.54 (20% EtOAc in hexanes)

Physical Appearance: Yellow oil.

4.6 References

[1] (a) Liron, F.; Knochel, P. *Tetrahedron Lett.* **2007**, *48*, 4943-4946. (b) Mahender, L.; Satyanarayana, G. *J. Org. Chem.* **2014**, *79*, 2059-2074.

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[3] Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *J. Org. Chem.* **2010**, *75*, 5008-5016.

[4] (a) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963-4966. (b) Pérez, I.; Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155-4160.

[5] Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc*. **2002**, *124*, 13856.

[6] For an overview of reactivity of 1-alkynyl ethers, see: Minehan, T. G. *Acc. Chem. Res.* **2016**, *49*, 1168-1181 and references therein.

[7] (a) Bedermann, A. A. Synthetic Studies Toward the Total Syntheses of Scholarisine A and Phomoidride D. Ph.D. Dissertation. Baylor University, Waco, TX, 2015. (b) Murphy, G. K.; Shirahata, T.; Hama, N.; Bedermann, A.; Dong, P.; McMahon, T. C.; Twenter, B. M.; Spiegel, D. A.; McDonald, I. M.; Taniguchi, N.; Inoue, M.; Wood, J. L. *J. Org. Chem.* **2013**, *78*, 477-489.

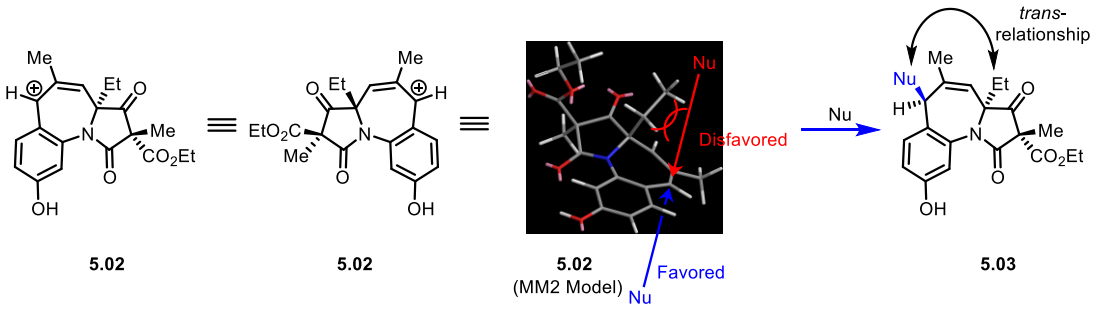
CHAPTER FIVE

Setting a Benzylic Stereocenter and Intramolecular Friedel-Crafts

5.1 Overall Strategy

Our efforts to advance key tricyclic enone **5.08** via a spiroepoxide met with failure due to the deleterious reactivity of various benzylic alcohol intermediates. This unanticipated reactivity also prevented us from adequately assessing the viability of the Heck, RCM and Friedel-Crafts strategies that we had hoped to employ for constructing the final five-membered ring. In a more positive sense, the deleterious reactivity of the benzylic alcohol had served to highlight the facility with which one could generate an intermediate carbonium ion in this system; an observation that certainly brought other strategies to mind that would involve harnessing this reactivity in a more productive fashion. In considering this latter reactivity we recognized that an intermediate carbonium akin to **5.02** could provide a means of introducing the carbon bonds needed to introduce the five-membered ring. Important to this strategy would be the ability to achieve stereoselectivity in the bond forming event. As illustrated in Scheme 5.1, an MM2 guided analysis of the likely conformation adopted by the intermediate carbonium ion suggested that the angular ethyl group would have a significant impact and hinder nucleophilic addition from the *syn*-face, thereby directing preferential nucleophilic addition on the face opposite the ethyl group (i.e., **5.03**). Given that the latter stereochemical outcome would be what is needed for the synthesis, we began developing strategies that featured cations akin to **5.02**. It is important to note that compound **5.02** possesses two stereogenic centers

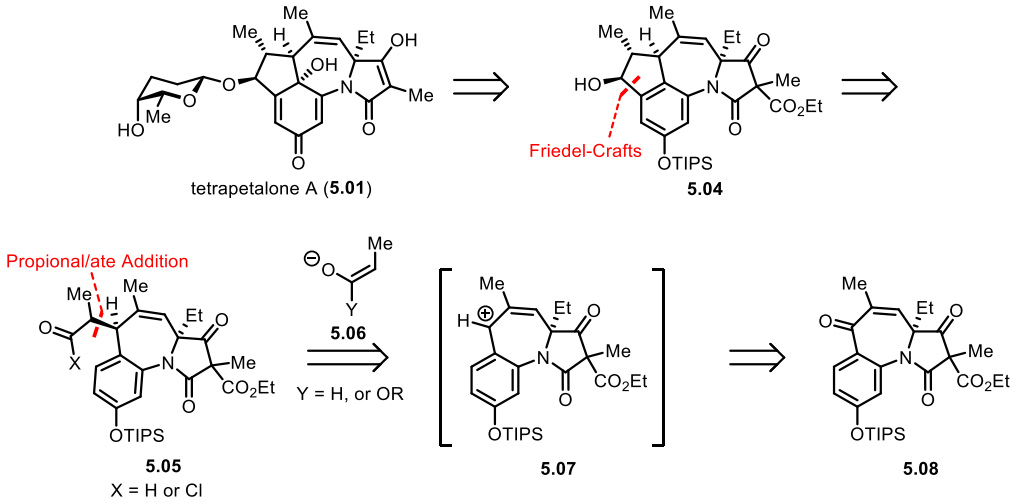
and is produced as a mixture of diastereomers. To facilitate our synthetic efforts this diastereomeric mixture was separated and subsequent chemistry was done on a single isomer and is illustrated accordingly (see experimental section for details on separation).



Scheme 5.1. Proposed stereochemical rationale to set a benzylic stereocenter

5.2 An Intramolecular Friedel-Crafts Approach

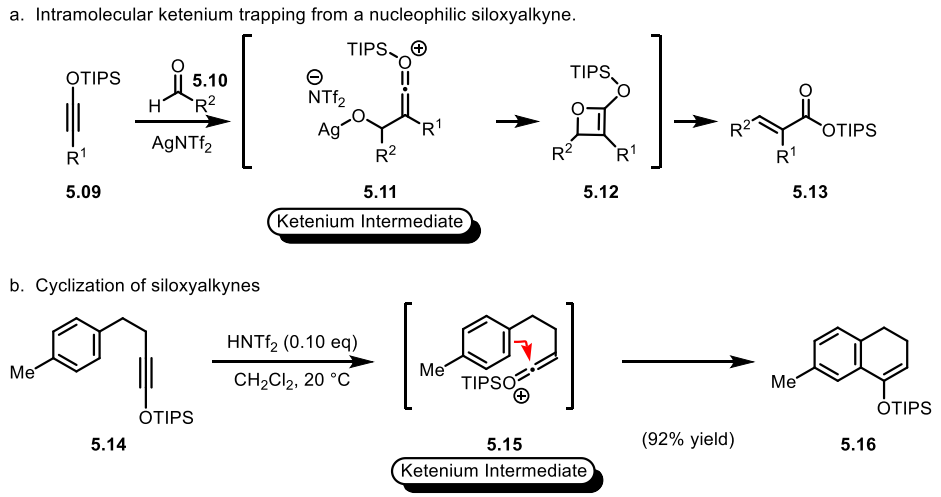
As outlined in retrosynthetic fashion in Scheme 5.2, tetrapetalone A (**5.01**) was seen as arising from tetracyclic alcohol **5.04** which would be delivered by way of an intramolecular Friedel-Crafts alkylation or acylation reaction from the corresponding aldehyde or acid chloride **5.05**. Access to **5.05** would be permitted from our readily prepared tricyclic enone by nucleophilic addition of a propion-al/-ate unit (**5.06**) at the benzylic position of intermediate carbonium **5.07**.



Scheme 5.2 Retrosynthesis of tetrapetalone A with an intramolecular Friedel-Crafts strategy.

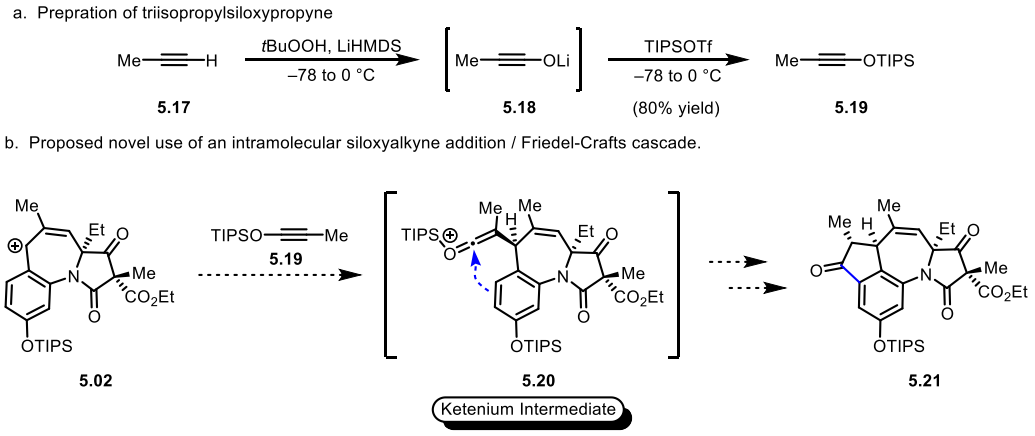
5.2.1. A Siloxypropyne Strategy for Single Step Carbocycle Formation

In implementing the plan outlined above, we took inspiration from work by Kozmin and coworkers wherein siloxyalkynes (e.g., **5.09**, Scheme 5.3) were successfully employed as nucleophiles in aldehyde additions to generate intermediate ketenium ions (e.g., **5.11**) that would undergo intramolecular nucleophilic attack to an intermediate oxatene (e.g., **5.12**) capable of ring opening to an enoate (**5.13**).[1] More specifically, Kozmin and coworkers were able to treat siloxyalkynes **5.14** under Brønsted acid catalysis to deliver a ketenium intermediate (**5.15**) that would intramolecularly trap a tethered nucleophile, in this case an aromatic ring, to give dihydronaphthalene **5.16**.[2]



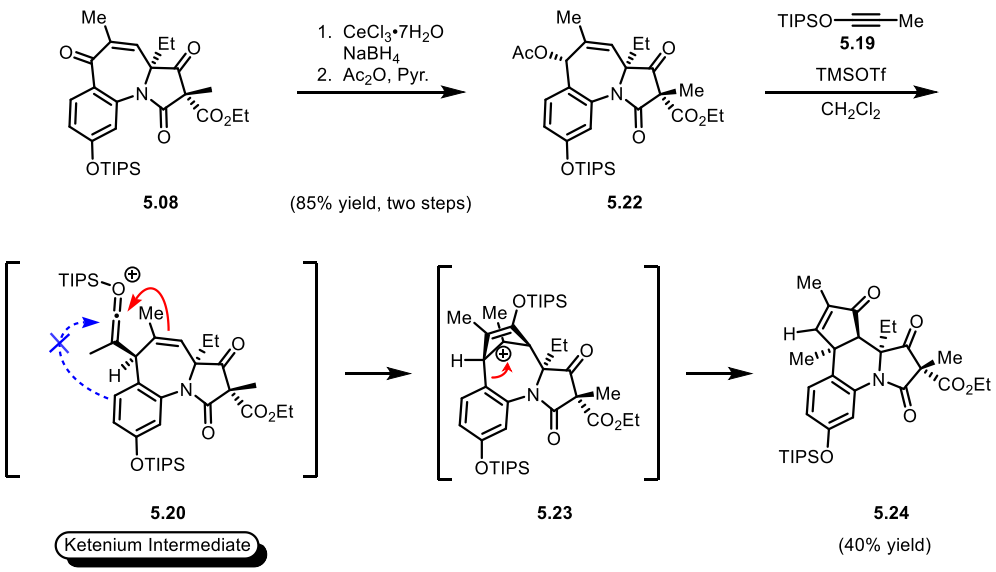
Scheme 5.3. Precedent set forth from the Kozmin laboratory using siloxyalkynes.

In considering Kozmin's work, we proposed a novel cascade sequence that would take advantage of these nucleophilic siloxyalkynes and their intermediate electrophilic ketenium intermediates. The plan was to employ siloxypropyne **5.19**, readily prepared in a single pot transformation (Scheme 5.4a, top),[1,3] as a nucleophile that would add to carbonium **5.02** and generate ketenium **5.20**. The generated ketenium would then be trapped by the tethered nucleophilic aromatic ring to provide tetracycle **5.21** in a single step.



Scheme 5.4. Preparation of siloxypropyne and proposed cascade sequence to deliver a tetracycle via a ketenium intermediate

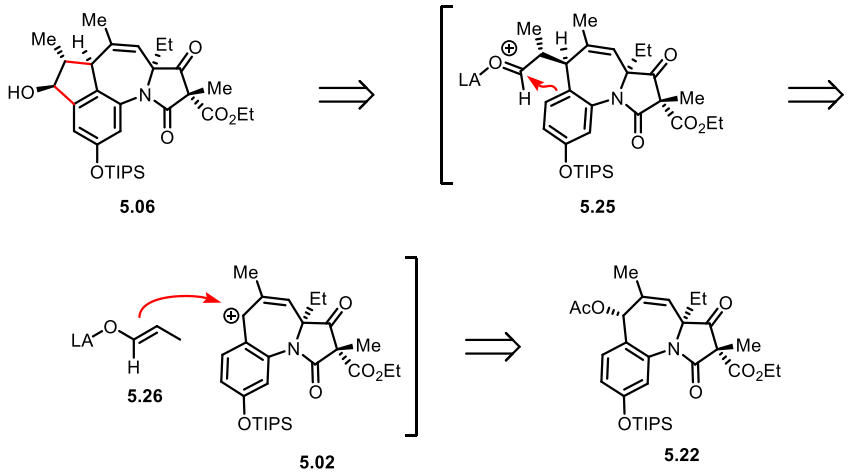
To put this plan into practice we first accessed carbonium precursor **5.22** by way of Luche reduction and acetylation from tricyclic enone **5.08** (Scheme 5.5). Ionization of **5.22** with TMSOTf in the presence of siloxypropyne (**5.19**) successfully forged the desired benzylic C-C bond to make the presumed ketenium intermediate **5.20**. However, this ketenium unexpectedly reacted with the azepine trisubstituted double bond to make carbonium **5.23** which subsequently underwent aryl migration to furnish fused tetracycle **5.24**. Though a remarkable reaction in its own right, it failed to give us the desired reactivity (blue, **5.20**). In considering this reaction, we began to contemplate why the reaction did not proceed as desired and needed to address two questions: (1) is the aromatic ring suitable electronically to undergo a Friedel-Crafts reaction? and (2) can the molecule adopt a conformation suited to the desired reactivity? To address these issues we turned to reactions that would be expected to proceed in a more stepwise fashion.



Scheme 5.5. A chemoselectivity problem to give a fused tetracycle via ketenium formation.

5.2.2. A Formal [3+2] Cycloaddition Strategy

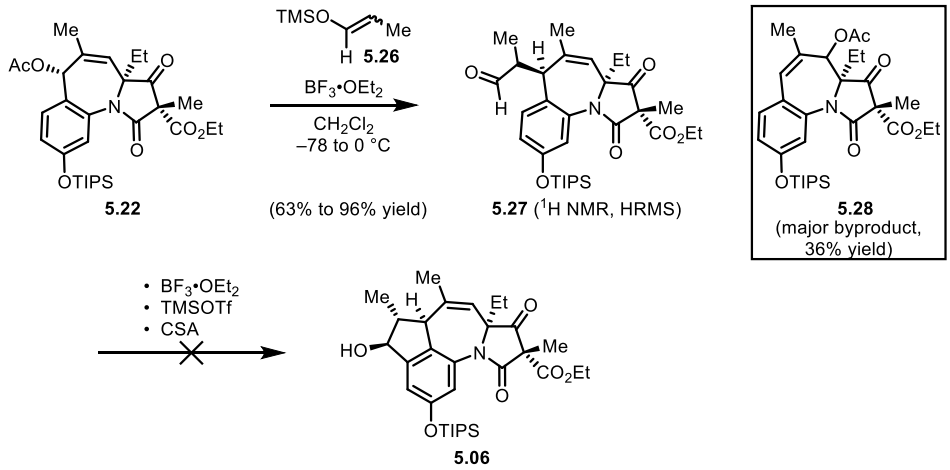
As illustrated in Scheme 5.6, our initially planned foray into more stepwise additions involved a formal [3+2] cycloaddition reaction wherein a propionaldehyde enolate equivalent would, in a single step, react to deliver tetracycle **5.06**. In the course of this reaction it was expected that ionization of benzylic acetate **5.22** in the presence of an enolate equivalent **5.26** would deliver an intermediate oxonium (**5.25**) that would undergo addition by the pendant aromatic ring to furnish tetracycle **5.06**. One key difference here, compared to the ketenium strategy presented above, is the presence of sp^3 hybridization adjacent to the C=O group, which makes for a more conformationally flexibile intermediate that would be perhaps be better suited to undergo the desired C-C bond formation.



Scheme 5.6. Proposed access to tetracycle **5.06** via formal [3+2] cycloaddition

In putting the above plan into practice benzylic acetate **5.22** (Scheme 5.7) was ionized by treatment $BF_3{\bullet}OEt_2$, in the presence of silylenol ether **5.26**. Under these conditions we were delighted to find that ^{1}H NMR analysis was consistent with the formation of the desired product **5.27**, albeit in somewhat low and variable yield. Based on a significant by-product, which was identified as the product of acetate transposition

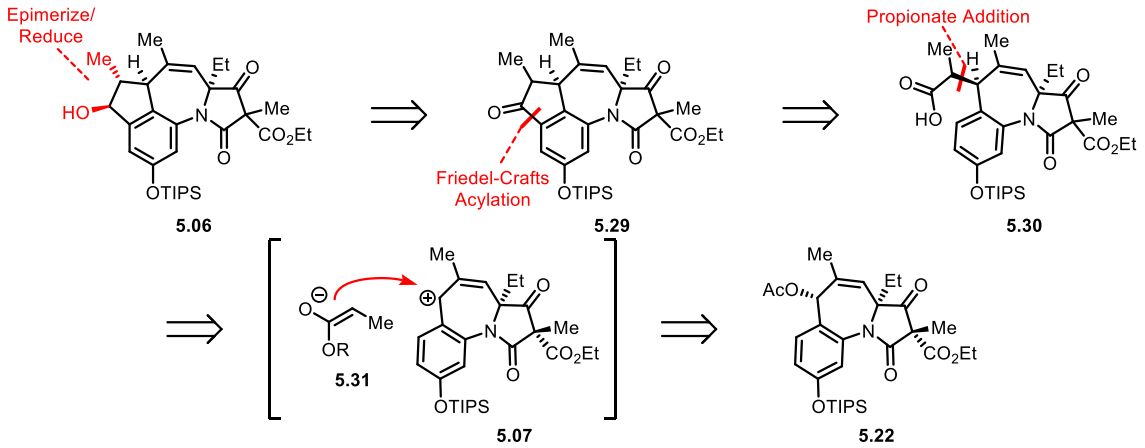
(i.e., **5.28**) we attributed the low yields to poor nucleophilicity of the propionaldehyde-derived silyl enol ether. Though no evidence of the single-step formal [3+2] cycloaddition product was observed, we nevertheless attempted to cyclize aldehyde **5.27** in a second step but were unsuccessful.



Scheme 5.7. Attempted [3+2] cycloaddition

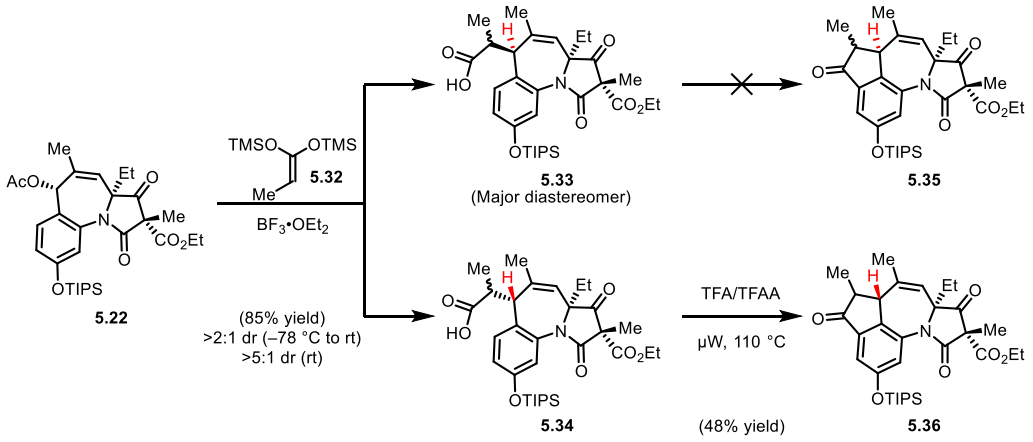
5.2.3. An Intramolecular Friedel-Crafts Acylation Strategy

In hopes of improving the efficiency of nucleophilic attack and set the stage for subsequent Friedel-Crafts acylation chemistry, we next turned to an approach (Scheme 5.8) that would deliver **5.29** from carboxylic acid **5.30** which, in turn, would derive from addition of a propionate equivalent (e.g., **5.31**) onto carbonium **5.07**, an intermediate we knew was accessible from benzylic acetate **5.22**

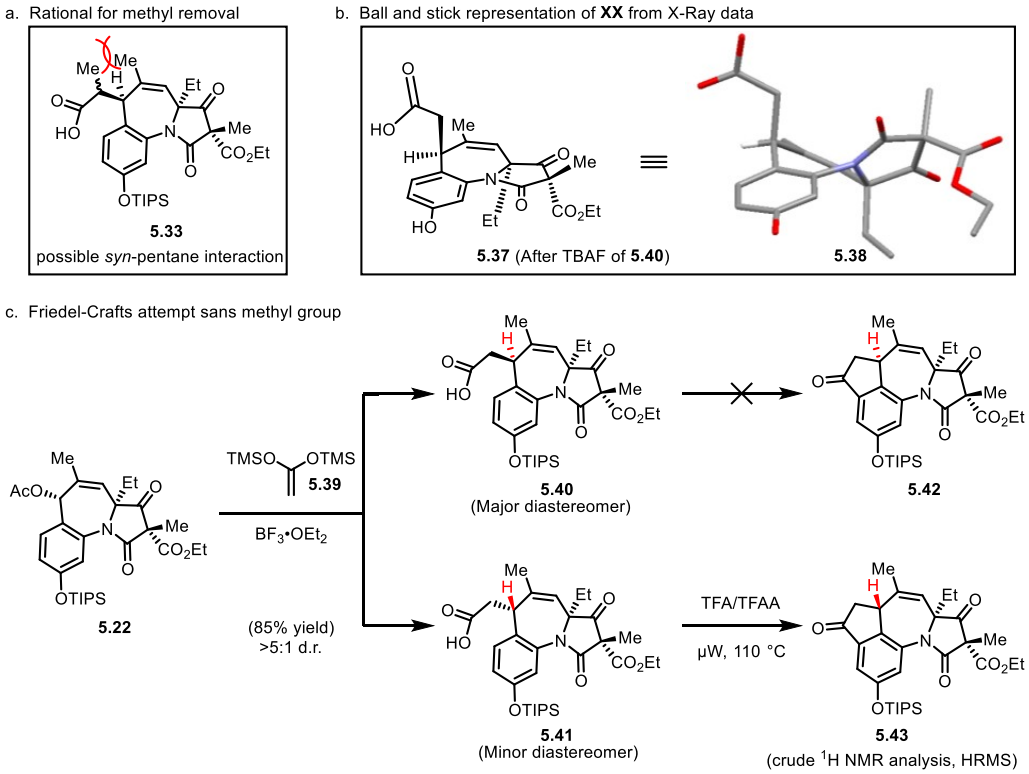


Scheme 5.8. Proposed synthesis of tetracycle **5.06** via Friedel-Crafts acylation

As in our previous studies, we employed a soft nucleophile, in this case bis-silyl ketene acetal **5.32**,[4] which delivered the carboxylic acid **5.33** as the major component of a >2:1 diastereomeric mixture with **5.34**. Although a considerable amount of effort was expended attempting to advance acid **5.33** to tetracyclic ketone **5.35** using a plethora of Friedel-Crafts acylation tactics, all attempts were, sadly, unsuccessful.[5] In contrast, the undesired diastereomer (**5.34**) was found to readily undergo ring closure to give Friedel-Crafts product **5.36**. As evidenced by the formation of **5.36**, and in considering our two posed questions from our ketenium studies, it seemed that our aromatic ring was indeed capable of forging the desired C-C bond via Friedel-Crafts acylation and we took this as mounting evidence that a conformational issue was prohibiting this reaction in the correct diasteromeric series. Of note is the ready decomposition of **5.36** upon exposure to $CDCl_3$ or air. As a result of this reactivity, while **5.36** was fully characterized, the sample after characterization was not recoverable nor were the products of decomposition fully characterized; however, due to the apparent loss of the azepine alkene, a decomposition pathway akin to that outlined for compound **7.09a** is proposed, see chapter 7, Scheme 7.7.



Scheme 5.9. Attempted intramolecular Friedel-Crafts Acylation.

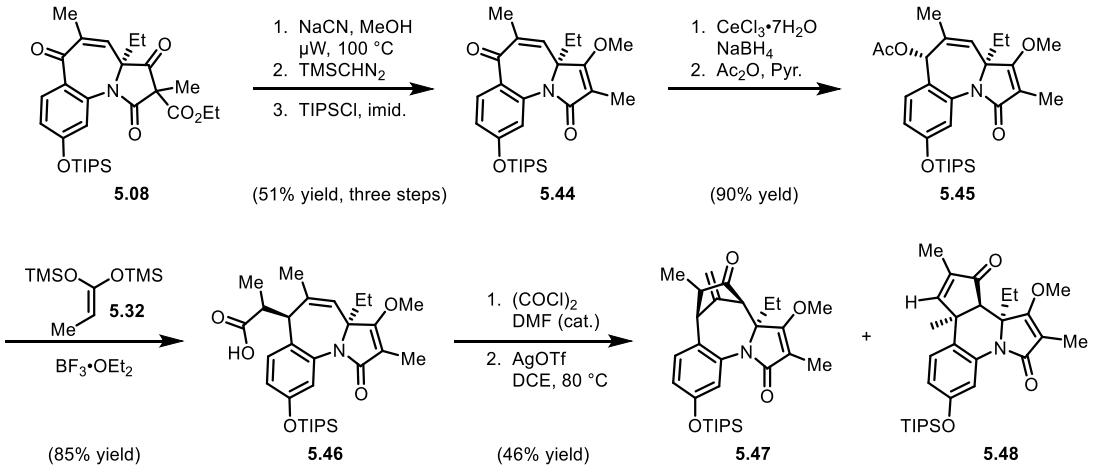


Scheme 5.10. A less sterically bulky substrate in an intramolecular Friedel-Crafts acylation and confirmation of the benzylic stereocenter via X-Ray

In considering potential conformational issues leading to the disparate reactivity of diastereomers **5.33** and **5.34**, we began to suspect that an undesirable *syn*-pentane

interaction (Scheme 5.10a, top left) was at fault. Thus, we prepared the analogous substrate (**5.37**), which lacks one of the offending methyl groups, by employing bis-silyl ketene acetal **5.39** (Scheme 5.10c, bottom).[6] Not surprisingly, we observe a similar stereochemical outcome in the silyl ketene acetal addition; however, much to our chagrin, the similarities also extended to the subsequent Friedel-Crafts acylation. Thus, the correct diastereomer (**5.40**) failed to cyclize whereas the incorrect diastereomer (**5.41**) gave ^{1}H NMR and HRMS data consistent with the formation of **5.43**. Our efforts to purify **5.43** however, proved unsuccessful, which we attributed to the instability of this compound (see chapter 7, Scheme 7.7a). Interestingly, single crystal X-ray analysis of compound **5.37** clearly showed a preference in the solid state for a conformation wherein the pendant acid adopts a pseudoaxial orientation.

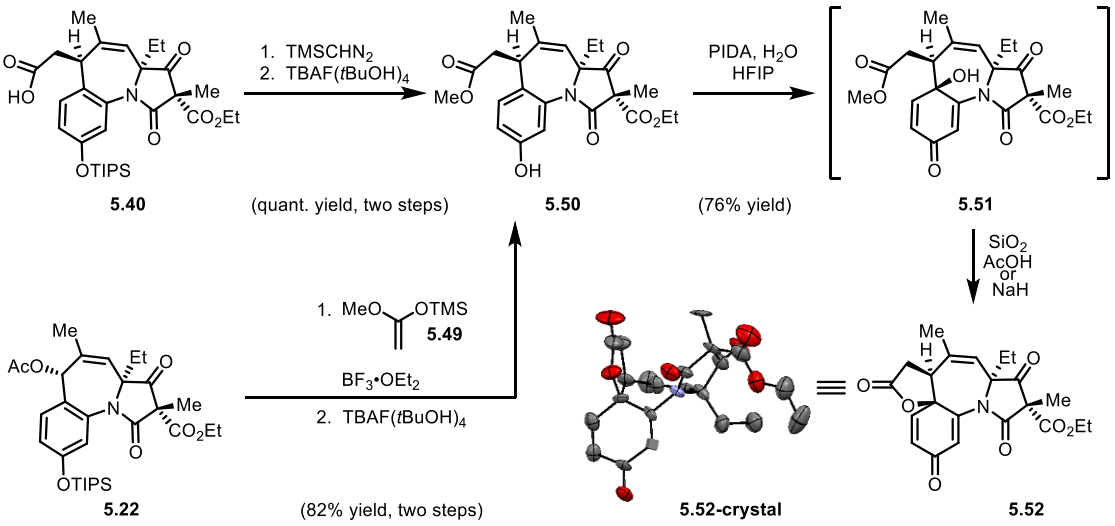
In further consideration of factors impacting the conformational preferences of these reactive intermediates, we decided that it would be important to examine influence of the quaternary center resident in the masked tetramic acid unit. Thus, to generate a compound that might be more analogous to the natural product, we prepared ionization substrate **5.45**, which contains a vinylogous methyl urethane, in five steps from enone **5.08** (Scheme 5.11). Exposure of this substrate to Lewis Acid promoted ionization in the presence of silyl ketene acetal **5.32** furnished acid **5.46** with excellent diastereoselectivity. Generation of an acyl triflate was then found to produce an inseparable mixture of structurally rearranged tetracycles (**5.47** and **5.48**) akin to those we had seen in our siloxypropyne adventures.[7]



Scheme 5.11. Preparation of a vinylogous methyl urethane and attempted Friedel-Crafts.

5.3 Oxidative Dearomatization to Deliver a para-Quinol

With the outlook of making the desired C-C bond by intramolecular electrophilic aromatic substitution starting to look bleak, we took a step back and began to consider approaches where other synthetic challenges *en* route to tetrapetalone A would be addressed first. To this end, we turned our attention to effecting oxidative dearomatization of acid **5.40** (Scheme 5.12). After considerable experimentation, we



Scheme 5.12. Aryl oxidation to deliver a *para*-quinol and subsequent lactonization.

found that formation of methyl ester **5.50** by methylation with TMS-diazomethane and unveiling the phenol permitted efficient oxidative dearomatization. Further, we later found we could directly access **5.50** by employing mixed alkyl, silyl-ketene acetal **5.49** as a nucleophile.[8] After screening a variety of solvents (HFIP, TFE, AcOH, CH_3NO_2, THF, MeOH) Access to **5.51** was obtained by PIDA promoted oxidation of phenol **5.50** in a HFIP:H_2O solvent mixture. *Para*-quinol **5.51** however was found to be unstable to purification and readily lactonized to give spirolactone **5.52**. The stereochemistry of **5.51** was assigned based on observation that treatment of **5.51** under acidic or basic conditions cleanly delivered **5.52**. While a variety of strategies were considered to advance this intermediate, such as the intramolecular Stetter transformation Dr. Howell had explored, issues with redox manipulation and inverting the *para*-quinol center led us to abandoning this approach in favor of other strategies.

5.4 Experimental

General

Unless otherwise stated, reactions were magnetically stirred in flame or oven dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Diethyl ether, tetrahydrofuran, toluene, benzene, dichloromethane, and acetonitrile were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. ACS grade acetone (Fisher) was purchased from Fisher-Scientific and used as received. Dimethyl formamide and 1,2-dichloroethane (DCE) were purchased from Sigma-Aldrich and used as received.

$Pd(PPh_3)_4$ was purchased from Sigma-Aldrich and stored under nitrogen in a -20°C freezer. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Millipore glass-backed 60Å plates (indicator F-254s, 150-180 µm thickness) (Millipore, catalogue #1164850001). Column or flash chromatography was performed with the indicated solvents using Millipore Silica Gel 60 (0.040-0.063 mm, 230-400 mesh ASTM) as the stationary phase. MPLC purifications were performed on a Telodyne Isco Combi*Flash*® *Rf*+ (Model: RF + UV-VIS MS COMP), used with standard Telodyne Isco normal phase disposable columns for flash chromatography and monitored at wavelengths of 254 and 280 nm. All melting points were obtained on a Chemglass Life Sciences melting point device (Model: DMP100) and are uncorrected. Infrared spectra were obtained using a Bruker Alpha ATR-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, Varian 500, or Bruker 600. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million (ppm) relative to internal residual solvent peaks from the indicated deuterated solvents (^{1}H: For $CDCl_3$, $CHCl_3$ 7.26; For Methanol-d_4, CD_2HOD 3.31; For Acetone-d_6, Acetone-D5H 2.05). Chemical shifts (δ) for ^{13}C spectra were referenced from the indicated solvent peaks (^{13}C: $CDCl_3$ 77.16, Methanol-d_4 49.00, Acetone-d_6 29.84). Chemical shifts in ^{19}F spectra were taken in $CDCl_3$ doped with fluorobenzene and referenced to -113.15. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as s = singlet, br.s = broad singlet, d = doublet, br. d = broad doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app =

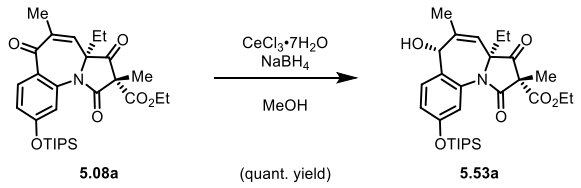
apparent, par = partial. High resolution mass spectra were performed on a Thermo LTQ Orbitrap Discovery with direct injection followed by electro-spray ionization (ESI). Microwave reactions were carried out using a CEM Discover SP Microwave system. Single crystal X-ray diffraction studies were collected on a Bruker Apex II-CCD detector using Mo-K_α radiation (λ = 0.71073 Å). Structures were solved and refined using SHELXTL. Optical rotations were obtained on a Rudolph Research Analytical Autopol IV Automatic Polarimeter.

High-Performance Liquid Chromatography (HPLC): All HPLC purifications were carried out on a Waters HPLC system (consisting of a Waters 1525 binary HPLC pump with direct injection port and monitored at 254 nm unless otherwise specified with a Waters 2489 UV-Visible detector). All purifications utilized a normal-phase Sunfire, Silica Prep 10 µm, 10 x 250 mm column.

Ultra Performance Liquid Chromatography (UPLC)-Mass Spectrometry (MS): All UPLC-MS experiments were carried out on a Waters Acquity H UPLC Class system using the indicated solvent systems as eluents. All separations were performed on a reverse phase Acquity UPLC BEH C18 1.7 µm, 2.1 x 50 mm column.

^{1}H and ^{13}C NMR spectra are included for all previously unreported compounds.

Benzylic alcohol **5.53**



Experimental: To a 50 mL rbf was added **5.08a** (527.9 mg, 1.000 mmol) followed by MeOH (10.0 mL) to create a white suspension. To this was added CH_2Cl_2 (~3.0 mL) to create a homogenous solution. This was then cooled to 0 °C in an ice-water bath followed

by the addition of $CeCl_3 \cdot 7H_2O$ (447 mg, 1.20 mmol) and stirred for 5 min until most of the cerium (III) chloride had dissolved. To this was then added $NaBH_4$ (41.6 mg, 1.10 mmol) in two portions separated by ~20 seconds apart. The solution at this point had turned to a clear yellow solution. The reaction was stirred until TLC indicated consumption of the starting material (~10 min) at which point the stirbar was removed and rinsed with Et_2O and the reaction mixture diluted with saturated aqueous NH_4Cl (15 mL). The mixture was concentrated in vacuo by rotary evaporation with a bath temperature maintained between 30 to 40 °C. The residue was then dissolved in diH_2O and extracted with EtOAc (3x). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give **5.53a** (530 mg, 100% yield) as a white solid that was of characterizable purity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 8.5, 0.7 Hz, 1H), 6.93 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 5.44 (s, 1H), 5.22 – 5.15 (m, 1H), 4.33 – 4.20 (m, 2H), 2.51 (d, *J* = 4.6 Hz, 1H), 1.91 (t, *J* = 1.3 Hz, 3H), 1.90 – 1.79 (m, 1H), 1.61 (s, 3H), 1.45 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.33 – 1.18 (m, 6H), 1.10 (d, *J* = 7.1 Hz, 18H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 205.5, 169.7, 165.8, 155.7, 141.4, 135.1, 131.9, 124.8, 121.6, 120.5, 120.2, 74.6, 68.1, 62.8, 58.4, 29.7, 21.1, 19.1, 18.0, 14.0, 12.7, 8.1.

.**IR** (thin film): 3442, 2944, 2867, 1776, 1749, 1694, 1608, 1579, 1497, 1386, 1231, 1110 cm^{-1}.

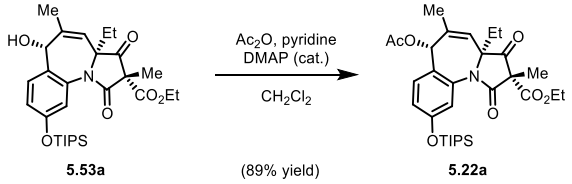
HRMS (ESI+): calculated for $C_{29}H_{44}NO_6Si^+$ $[M+H]^+$ 530.2932, found: 530.2933.

TLC: 0.48 (30% EtOAc in hexanes).

m.p.: 146.7-151.6 °C.

Physical Appearance: White solid.

Benzylic acetate **5.22a**



Experimental: To a 250 mL rbf containing **5.53a** (530 mg, 1.00 mmol) was added CH_2Cl_2 (20 mL) followed sequentially by the addition of pyridine (0.41 mL, 5.1 mmol), acetic anhydride (0.38 mL, 4.0 mmol), and DMAP (catalytic quantity, tip of pipette). The reaction was stirred for 90 min and subsequently concentrated under vacuum by rotary evaporation at 40 °C. The mixture was azeotroped toluene (2x) to remove any residual solvents. The crude residue was purified by flash column chromatography on silica gel to give benzylic acetate **5.22a** (507 mg, 0.89 mmol, 89% yield, two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 8.3 Hz, 1H), 6.97 – 6.89 (m, 2H), 6.62 (s, 1H), 5.27 (s, 1H), 4.33 – 4.21 (m, 2H), 2.23 (s, 3H), 1.88 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H), 1.49 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.31 – 1.20 (m, 6H), 1.10 (d, *J* = 7.4 Hz, 18H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 Hz, $CDCl_3$): δ 205.4, 169.7, 169.4, 165.8, 156.1, 138.1, 132.4, 131.0, 124.6, 122.9, 120.7, 120.4, 74.3, 69.7, 62.7, 58.5, 30.0, 20.8, 20.8, 19.2, 18.0, 14.0, 12.7, 8.1.

IR (thin film): 2944, 2868, 1776, 1749, 1713, 1611, 1500, 1291, 1226 cm^{-1}.

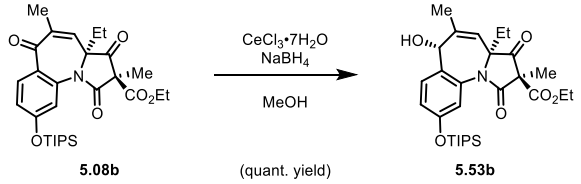
HRMS (ESI+): calculated for $C_{31}H_{45}NO_7SiNa^+$ $[M+Na]^+$ 594.2858, found: 594.2851.

TLC: 0.40 (20% EtOAc in hexanes).

m.p.: 110.6-115.5 °C.

Physical Appearance: White solid.

Benzylic alcohol **5.53b**



Experimental: A procedure identical to that reported for **5.08a** can be used. An alternative procedure is as follows: To a rbf was added **5.08b** (240 mg, 0.455 mmol) was dissolved in MeOH (9.1 mL) followed by the addition of $CeCl_3$•$7H_2O$ (254 mg, 0.682 mmol). The solution was cooled to –50 °C for 15 min after which $NaBH_4$ (15.5 mg, 0.409 mmol) was added. After stirring for 20 min, the solution nwas poured into a biphasic solution of saturated aqueous NH_4Cl and EtOAc. The organic layer was separated and the aqueous layer extracted again with EtOAc (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (10%→20% EtOAc in hexanes) to give benzylic alcohol **5.53b** (196 mg, 81% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 1H), 6.93 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 5.78 (s, 1H), 5.15 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.12 (tq, *J* = 10.8, 7.1 Hz, 1H), 3.97 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.71 (d, *J* = 5.1 Hz, 1H), 1.88 (s, 3H), 1.79 (dt, *J* = 14.7, 7.3 Hz, 1H), 1.58 (s, 3H), 1.35-1.16 (m, 4H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 18H), 0.78 (t, *J* = 0.74, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 205.8, 169.5, 165.2, 155.5, 141.3, 136.1, 131.5, 124.6, 121.2, 120.5, 119.9, 75.6, 67.8, 62.9, 58.3, 29.4, 20.8, 18.0, 15.6, 13.8, 12.7, 8.2.

IR (thin film): 3457, 2944, 2867, 1774, 1606, 1579, 1216 cm^{-1}.

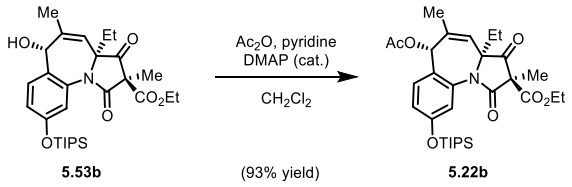
HRMS (ESI+): calculated for $C_{29}H_{43}NO_6SiNa^+$ $[M+Na]^+$ 552.2752, found: 552.2751.

TLC: 0.38 (20% EtOAc in hexanes).

m.p.: 138.9-140.1 °C.

Physical Appearance: White solid.

Benzylic Acetate **5.22b**



Experimental: An identical procedure to that for **5.22a** was used in the preparation of **5.22b**. In this instance **5.53b** (180 mg, 0.34 mmol), CH_2Cl_2 (6.8 mL), pyridine (110 µL, 1.36 mmol), acetic anhydride (96 µL, 1.02 mmol), and DMAP (4.2 mg, 0.034 mmol) were used. Purification by flash chromatography on silica gel (8:1 hexanes:EtOAc) gave **5.22b** (181 mg, 93% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 1H), 6.90 (m, 3H), 5.31 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.36 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.25 (dq, *J* = 10.6, 7.1 Hz, 1H), 2.23 (s, 3H), 1.89-1.77 (m, 1H), 1.78 (t, *J* = 1.3 Hz, 3H), 1.61 (s, 3H), 1.40-1.21 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 18H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 205.7, 169.5, 169.0, 165.1, 155.9, 137.1, 132.1, 131.4, 124.7, 123.0, 120.4, 120.3, 75.1, 69.9, 63.2, 58.2, 29.8, 20.9, 20.9, 18.0, 15.5, 14.0, 12.7, 8.2.

IR (thin film): 2944, 2867, 1776, 1744, 1710, 1609, 1499, 1378, 1291, 1222, 1107, 1039, 977, 852 cm^{-1}.

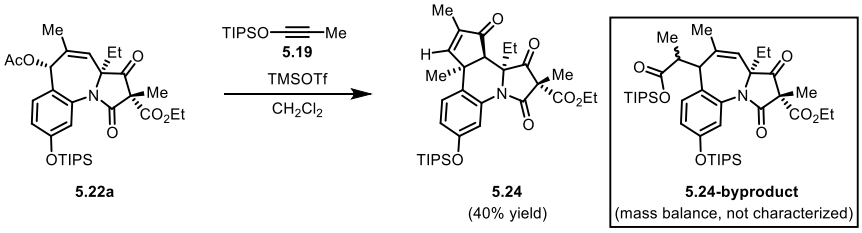
HRMS (ESI+): calculated for $C_{31}H_{45}NO_7SiNa^+$ $[M+Na]^+$ 594.2858, found: 594.2858.

TLC: 0.51 (20% EtOAc in hexanes).

m.p.: 108.8-109.9 °C.

Physical Appearance: White solid.

Fused tetracycle **5.24**



Experimental: To a flame dried vial was added **5.22a** (6.0 mg, 10 µmol) and this was dissolved in CH_2Cl_2 (0.5 mL) followed by the addition of **5.19** (10 mg, 47 µmol) and lastly by TMSOTf (3 µL, 17 µmol). The vial was sealed and the reaction let stir overnight. The reaction was then quenched by the addition of diH_2O and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a faint yellow oil. The residue was purified by pipette column to give **5.24** (2.4 mg, 40% yield).

Note: The crude NMR analysis gave an estimated yield much higher than 40%, however some of the material was lost during attempted HPLC purification. In addition, ^{1}H NMR and HRMS analysis of the remaining products were in agreement with **5.24-byproduct** above.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 2.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.74 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.24 (s, 1H), 1.98 (q, *J* = 7.5 Hz, 2H), 1.82 (s, 3H), 1.73 (s, 3H), 1.62 (d, *J* = 1.4 Hz, 3H), 1.33 – 1.21 (m, 6H, overlap with grease), 1.10 (d, *J* = 7.4 Hz, 18H), 0.95 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 206.0, 203.4, 168.0, 166.3, 165.0, 155.5, 136.7, 132.2, 127.7, 123.9, 117.9, 114.6, 70.2, 62.8, 60.7, 59.8, 44.2, 28.0, 26.9, 18.08, 18.06, 17.6, 14.0, 12.8, 10.0, 8.0.

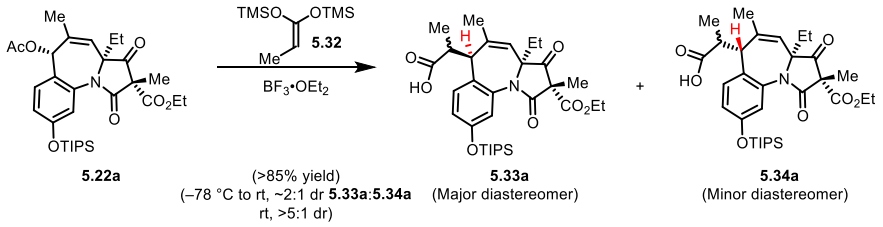
IR (thin film): 2944, 2867, 1776, 1737, 1708, 1605, 1496, 1463, 1427, 1376, 1303, 1222, 1120, 1017, 982 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{45}NO_6SiNa^+$ $[M+Na]^+$ 590.2908, found: 590.2908.

TLC: 0.40 (20% EtOAc in hexanes)

Physical Appearance: Colorless oil.

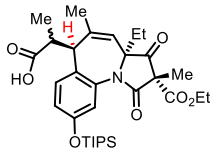
Carboxylic acid **5.33a**



Experimental: Representative procedure: To a 200 mL rbf was added **5.22a** (356.7 mg, 0.624 mmol) and this azeotroped with toluene (3x) and placed under hi-vac for 1 h. After 1 h, this was dissolved in CH_2Cl_2 (8.0 mL) followed by the addition of **5.32** (0.700 mL, 2.72 mmol, calculated density 0.85 g/mL). This was then cooled to –78 °C in a dry-ice/acetone bath. After stirring for 5 min, to this was added BF_3•OEt_2 (0.13 mL, 1.0 mmol). The reaction was stirred for 15 min in the dry-ice/acetone bath and subsequently warmed in an ice-water bath. This was then quenched by the addition of saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was then purified by flash column chromatography on silica gel (80:19:1 hexanes:EtOAc:AcOH) to give the two diastereomeric products **5.33a** and **5.34a** (365 mg, 99% combined yield, 2:1 **5.33a**:**5.34a** dr).

Note 1: When the reaction was conducted at low temperature (–78 °C, dry-ice/acetone bath, a ~2:1 dr was obtained favoring **5.33a**). When the reaction was conducted at room temperature however, a >5:1 dr was observed still favoring **5.33a**).

Note 2: Analytically pure material was obtained by HPLC separation using an isochratic solution of 80:19:1 hexanes:EtOAc:AcOH, 10 mL/min. The compound **5.33a** is characterized as a mixture of homobenzylic methyl diastereomers (1:1 dr).



5.33a
(Major diastereomer)

Major Diastereomer

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.87 (d, *J* = 2.5 Hz, 1H), 6.84 (t, *J* = 2.7 Hz, 1H), 6.82 (t, *J* = 2.7 Hz, 1H), 5.45 (q, *J* = 1.3 Hz, 1H), 5.42 (q, *J* = 1.3 Hz, 1H), 4.35 – 4.20 (m, 4H), 3.28 (d, *J* = 10.7 Hz, 1H), 3.15 (d, *J* = 10.6 Hz, 1H), 2.65 – 2.54 (m, 2H), 1.98 (d, *J* = 1.4 Hz, 3H), 1.89 – 1.77 (m, 5H), 1.70 (s, 3H), 1.60 (s, 3H), 1.58 – 1.48 (m, 2H), 1.32 – 1.19 (m, 17H), 1.09 (td, *J* = 7.6, 1.4 Hz, 36H), 0.83 – 0.80 (m, 6H), 0.78 (t, *J* = 7.5 Hz, 3H).

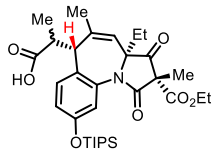
^{13}C NMR (151 Hz, $CDCl_3$): δ 205.6, 204.9, 181.1, 177.1, 170.9, 169.1, 165.8, 165.1, 156.3, 156.1, 137.8, 137.3, 134.4, 133.7, 132.1, 131.7, 131.0, 130.0, 125.2, 124.9, 121.5, 121.14, 121.08, 120.1, 74.7, 74.3, 63.0, 62.7, 58.18, 58.16, 53.4, 52.1, 47.4, 45.1, 30.6, 29.9, 29.4, 27.8, 18.3, 18.0, 17.95, 17.92, 17.1, 16.3, 14.0, 12.68, 12.66, 8.5, 8.4.

IR (thin film): 3121, 2943, 2867, 1776, 1744, 1706, 1607, 1503, 1455, 1432, 1385, 1333, 1291, 1230, 1169, 1106, 1013, 1106, 1013, 980, 897, 859, 731, 685, 646 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_7SiNa^+$ $[M+Na]^+$ 608.3014, found: 608.3017.

TLC: 0.29 (60:39:1 Hexanes:EtOAc:AcOH)

Physical Appearance: Colorless oil.



5.34a
(Minor diastereomer)

Minor Diastereomer

Note: The compound **5.34a** is characterized as a mixture of homobenzylic methyl diastereomers (1.7:1 dr)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.4 Hz, 1H), 6.96 – 6.87 (m, 6H), 6.82 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.16 – 5.12 (m, 1H), 5.02 – 4.98 (m, 1.7H), 4.35 – 4.22 (m, 5.5H), 3.93 (d, *J* = 11.9 Hz, 1.7H), 3.85 (d, *J* = 11.4 Hz, 1H), 3.20 – 3.11 (m, 2.7H), 1.91 – 1.81 (m, 2.7H), 1.81 (s, 3H), 1.77 (s, 5.2H), 1.72 (s, 8.2H), 1.51 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.40 (dq, *J* = 14.8, 7.5 Hz, 2H), 1.35 (d, *J* = 6.5 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 8.7H), 1.28 – 1.20 (m, 15.7H), 1.09 (app. dd, *J* = 13.1, 7.4 Hz, 49H), 0.93 – 0.88 (m, 8.6H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 206.03, 206.00, 181.6, 178.8, 170.4, 169.9, 166.1, 165.9, 155.1, 155.1, 140.3, 139.1, 135.5, 134.8, 134.3, 132.8, 124.72, 124.66, 123.8, 123.2, 121.54, 121.47, 120.20, 120.18, 74.6, 74.5, 62.8, 62.7, 58.8, 58.6, 42.6, 41.6, 39.1, 37.8, 31.5, 30.5, 21.0, 20.5, 18.9, 18.8, 18.5, 18.00, 17.98, 17.8, 14.0, 12.74, 12.70, 7.93, 7.91.

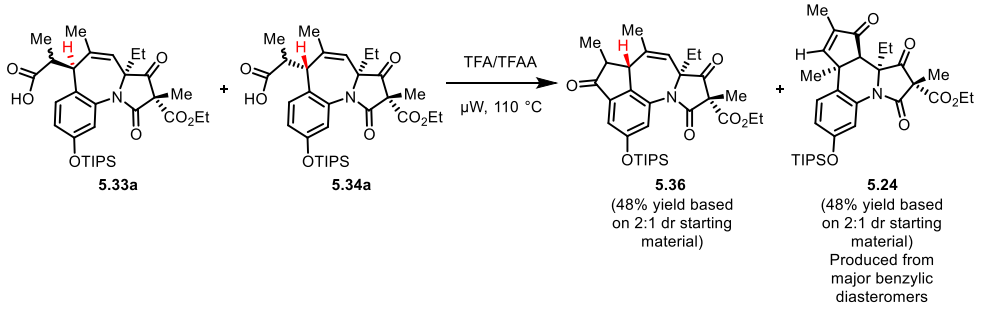
IR (thin film): 3134, 2944, 2867, 1774, 1742, 1709, 1608, 1496, 1460, 1381, 1289, 1230, 1177, 1109, 976, 881, 854, 733, 686, 647 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_7SiNa^+$ $[M+Na]^+$ 608.3014, found: 608.3016.

TLC: 0.14 (60:39:1 hexanes:EtOAc:AcOH)

Physical Appearance: Colorless oil.

Tetracyclic ketone **5.36**



Experimental: To a 10 mL reaction vial was added **5.34** (5.2 mg, 8.9 μmol, ca 2:1 dr at the benzylic position, highlighted in red, minor diastereomers depicted) and this dissolved in TFA/TFAA (2:1, 1.25 mL) and heated to 110 °C in a microwave reactor for 2 h. This was then concentrated under reduced pressure, filtered through a plug of SiO_2 with EtOAc as eluent and then concentrated. This was then purified by HPLC purification (0%→30% EtOAc in hexanes, 10 mL/min flow rate, 10 min) to give **5.36** (0.8 mg, 48% yield based on theoretical 2:1 dr) along with **5.24** (2.2 mg, 65% yield based on 2:1 dr of starting material, characterized above).

Note: In a separate experiment, inspection of the crude NMR after exposing pure minor benzylic diastereomers **5.34** to the reaction conditions exclusively gave **5.36** as product. Unfortunately, on the smaller scales the product **5.34** could not be isolated likely due to its instability in air.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (d, J = 2.3 Hz, 1H), 7.23 (d, J = 2.3 Hz, 1H), 5.48 (s, 1H), 4.36 – 4.23 (m, 2H), 3.69 (s, 1H), 2.70 (dq, J = 12.7, 7.1 Hz, 1H), 1.99 (d, J = 1.5 Hz, 3H), 1.92 (dq, J = 14.9, 7.4 Hz, 1H), 1.64 (s, 3H), 1.55 – 1.47 (m, 1H), 1.46 (d, J = 7.3 Hz, 3H), 1.33 – 1.24 (m, 6H), 1.11 (dd, J = 7.5, 2.3 Hz, 18H), 0.81 (t, J = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.8, 205.2, 168.7, 165.6, 157.3, 141.3, 138.3, 135.3, 134.0, 126.4, 125.5, 113.7, 74.9, 62.8, 58.4, 48.9, 48.1, 30.7, 25.2, 19.3, 18.0, 17.0, 14.0, 12.7, 8.6.

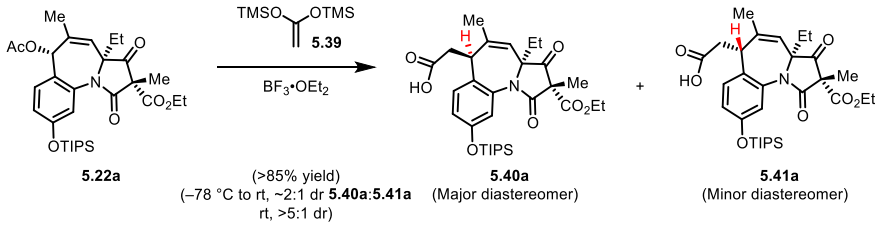
IR (thin film): 2945, 2868, 1778, 1748, 1715, 1611, 1485, 1464, 1392, 1371, 1311, 1238, 1099 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{45}NO_6SiNa^+$ $[M+Na]^+$ 590.2908, found: 590.2908.

TLC: 0.35 (20% EtOAc in hexanes).

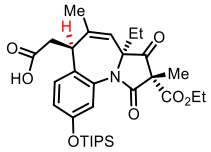
Physical Appearance: Colorless oil.

Carboxylic acid **5.40a** *and* **5.41a**



Experimental: To a rbf was added **5.22a** (78.4 mg, 0.137 mmol) and this dissolved in CH_2Cl_2) followed by the addition of bis-silyl ketene acetal **5.39** (0.09 mL, 77 mg, 0.38 mmol). This was stirred for ~1 min followed by the addition of BF_3•OEt_2 (0.030 mL, 0.24 mmol). The reaction was stirred for 20 min at which point TLC indicated consumption of the starting material. The faint yellow solution was quenched by the addition of saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was separated and the aqueous layer extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered and concentrated to give a crude colorless oil. The crude residue was purified by flash colum chromatography on silica gel (isochratic 80:19:1 Hexanes:EtOAc:AcOH) to give carboxylic acid **5.40a** (69.1 mg, 0.121 mmol, 88% yield) along with an additional mixture of acids **5.40a** and **5.41a** (8.3 mg, 0.015 mmol, 11% yield). Inspection of the crude NMR gave a dr of 8.5:1 favoring **5.40a**. Further purification of the mixture permitted access to an analytically pure sample of the minor diastereomer **5.41a**.

When the reaction was performed using **5.22a** (50.2 mg, 0.088 mmol) at -78 °C then allowed to warm after adding all the reagents, a 2:1 dr was obtained still favoring **5.40a**.



Major Diastereomer **5.40a**

^{1}H NMR (500 MHz, CDCl3): δ 7.11 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.38 – 5.34 (m, 1H), 4.34 – 4.20 (m, 2H), 3.55 (dd, *J* = 9.9, 4.6 Hz, 1H), 2.59 (dd, *J* = 15.3, 4.6 Hz, 1H), 2.46 (dd, *J* = 15.4, 9.9 Hz, 1H), 1.90 (d, *J* = 1.4 Hz, 3H), 1.83 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.63 (s, 3H), 1.49 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.33 – 1.20 (m, 6H), 1.08 (d, *J* = 7.4 Hz, 18H), 0.80 (t, *J* = 7.5 Hz, 3H).

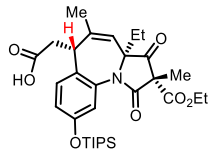
^{13}C NMR (126 Hz, $CDCl_3$): δ 205.6, 175.4, 169.5, 165.5, 156.1, 138.2, 134.1, 131.8, 130.9, 124.6, 121.1, 120.6, 74.7, 62.8, 58.2, 45.8, 40.7, 29.7, 26.5, 18.7, 17.9, 14.0, 12.7, 8.5.

IR (thin film): 3118, 2943, 2867, 1775, 1746, 1707, 1608, 1579, 1504, 1449, 1434, 1388, 1292, 1228, 1106, 881, 855 cm^{-1}.

HRMS (ESI+): calculated for $C_{31}H_{45}NO_7SiNa^+$ $[M+Na]^+$ 594.2858, found: 594.2853.

TLC: 0.20 (76:19:5 Hexanes:EtOAc:AcOH).

Physical Appearance: Colorless oil.



Minor Diastereomer **5.41a**

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.17 (s, 1H), 4.34 – 4.20 (m, 3H), 3.07 (dd, *J* = 17.2, 11.4 Hz,

1H), 2.79 (dd, J = 17.2, 4.0 Hz, 1H), 1.87 (dt, J = 14.7, 7.4 Hz, 1H), 1.76 (s, 3H), 1.74 (s, 3H), 1.46 (dq, J = 14.9, 7.5 Hz, 1H), 1.32 – 1.21 (m, 6H), 1.10 (d, J = 7.4 Hz, 18H), 0.91 (t, J = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.8, 176.9, 170.2, 166.0, 155.4, 138.6, 134.7, 134.3, 124.6, 124.0, 121.1, 120.4, 74.6, 62.7, 58.8, 34.7, 33.7, 30.3, 22.0, 18.9, 18.0, 14.0, 12.7, 8.0.

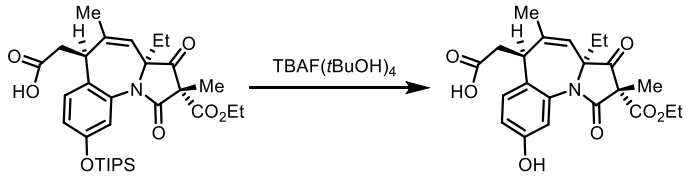
IR (thin film): 3119, 2943, 2867, 1774, 1744, 1707, 1609, 1499, 1432, 1382, 1290, 1231, 1110, 979, 881, 855, 731, 685, 646 cm^{-1}.

HRMS (ESI+): calculated for $C_{31}H_{45}NO_7SiNa^+$ $[M+Na]^+$ 594.2858, found: 594.2850.

TLC: 0.16 (76:19:5 Hexanes:EtOAc:AcOH).

Physical Appearance: Colorless oil.

phenol **5.37**



5.40a (87% yield) **5.37**

Experimental: To a rbf containing **5.40a** (22.7 mg, 0.040 mmol) dissolved in THF (3.0 mL) was added TBAF(tBuOH)$_4$ (31 mg, 0.056 mmol) and stirred for ~ 2 min to give a faint yellow solution. The reaction was then quenched by the addition of 1 N aqueous HCl and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to give the crude product. The crude residue was purified by MPLC (isochratic 95:5:1.5 CH_2Cl_2:MeOH:AcOH, 4g column, 18 mL/min, 10 min runtime) to give phenol **5.37** (14.3 mg, 87% yield) as a white solid. Crystals suitable for X-Ray diffraction were obtained by slow evaporation from methanol.

^{1}H NMR (500 MHz, CD_3OD): δ 7.16 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.76 (dd, *J* = 8.4, 1.9 Hz, 1H), 5.37 (t, *J* = 1.3 Hz, 1H), 4.33 – 4.20 (m, 2H), 3.62 (dd, *J* = 9.8, 4.3 Hz, 1H), 2.62 (dd, *J* = 15.5, 4.3 Hz, 1H), 2.40 (dd, *J* = 15.4, 9.8 Hz, 1H), 1.94 (t, *J* = 1.2 Hz, 3H), 1.86 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.59 (s, 3H), 1.53 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.30 (t, *J* = 6.9 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 Hz, CD_3OD): δ 206.5, 174.7, 171.1, 166.9, 158.6, 140.4, 135.1, 133.1, 130.9, 124.9, 117.1, 116.8, 76.1, 63.8, 59.4, 47.1, 41.9, 30.8, 26.5, 18.9, 14.3, 8.8.

IR (thin film): 3294, 2981, 2938, 1775, 1744, 1707, 1677, 1616, 1596, 1508, 1453, 1409, 1297, 1232, 1113 cm^{-1}.

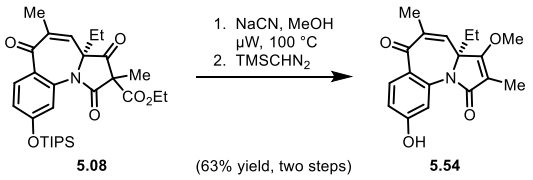
HRMS (ESI+): calculated for $C_{22}H_{25}NO_7Na$ $[M+Na]^+$ 438.1523, found: 438.1524.

TLC: 0.35 (95:5:1.5 CH_2Cl_2:MeOH:AcOH).

m.p.: 202 °C (decomposition, charring).

Physical Appearance: White amorphous solid. Colorless crystalline solid after crystallization.

Phenol **5.54**



Experimental:

WARNING: Both of the following procedures utilize reagents that are highly toxic in nature, and caution should be exercised at all times when performing these reactions. All reactions, workups, purifications, and rotary evaporations were all carried out in a well ventilated fume food.

***Part 1*:** To an 8 mL microwave reactor vial was added a mixture of diasteromers **5.08** (436 mg, 0.826 mmol) and dissolved in MeOH (7 mL) followed by the addition of KCN (192 mg, 2.95 mmol). The reaction turns bright yellow. The reaction was heated under microwave irradiation for a total of 6 min at 100 °C to give an orange/brown solution. In a well ventilated fume hood, the mixture was poured into a flask containing 15 mL diH_2O and concentrated to remove MeOH by rotary evaporation under vacuum (also in a well ventilated fume hood). The residue was then diluted with 10 mL diH_2O, and to this was slowly added 2 mL 6 N aqueous HCl. The aqueous solution was extracted with EtOAc (3x), dried over Na_2SO_4, filtered, and concentrated to a crude residue. The crude residue was then crudely purified using flash column chromatography on silica gel (~25 g SiO_2, 15 mL fractions, 5%→10% MeOH in CH_2Cl_2 and all spots were collected and concentrated by rotary evaporation) to give a semi-crude tetramic acid (276 mg) as yellow, sticky foam.

Part 2: To a rbf containing the aforementioned crude tetramic acid (276 mg, crude) was added Acetone (12 mL). With the flask open to air, $TMSCHN_2$ (0.5 mL, 1.000 mL, 2.0 M solution in Et_2O) was added dropwise over the course of ~2 min until the yellow color of the reaction persisted. The reaction was stirred for an additional 5 min then quenched by the dropwise addition of 1 mL AcOH. The mixture was then concentrated by rotary evaporation under reduced pressure and azeotroped with toluene (2x) to remove any residual acetic acid. The crude residue was purified by MPLC (12 g column, 15 mL/min, 0% →100% EtOAc in hexanes) to give **5.54** (163 mg, 63% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (br. s, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.56 (s, 1H), 4.21 (s, 3H), 2.11 (s, 3H), 1.99 (d, *J*

= 1.2 Hz, 3H), 1.83 (dq, J = 14.6, 7.2 Hz, 1H), 1.73 – 1.63 (m, 1H), 1.64 (H_2O), 0.60 (t, J = 7.3 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 188.3, 172.1, 167.0, 161.8, 138.7, 137.5, 135.8, 134.1, 125.4, 115.2, 112.6, 103.1, 69.8, 59.6, 26.8, 21.2, 8.5, 7.4.

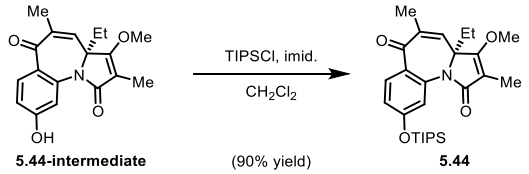
IR (thin film): 3223, 2970, 2931, 1655, 1600, 1459, 1389, 1363, 1338, 1323, 1265, 1234, 1159, 1005, 903, 731 cm^{-1}.

HRMS (ESI+): calculated for $C_{18}H_{19}NO_4Na^+$ $[M+Na]^+$ 336.1206, found: 336.1211.

TLC: 0.24 (50% EtOAc in hexanes).

Physical Appearance: Yellow oil.

Vinylogous methyl urethane **5.44**



Experimental: To a rbf containing **5.54** (130 mg, 0.415 mmol) was added CH_2Cl_2 (5.0 mL) followed by the addition of TIPSCl (0.10 mL, 0.47 mmol) and imidazole (57 mg, 0.84 mmol). After 5 min, the reaction went from a colorless solution to a white suspension. The reaction was stirred for 8 h after which it was quenched by the addition of 0.5 N aqueous HCl and extracted with CH_2Cl_2 (3x). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to a colorless oil. The crude residue was purified by MPLC (12 g column, 18 mL/min, linear gradient from 0%→50% EtOAc in hexanes, 15 min) to give **5.44** (176 mg, 90% yield) as a colorless oil. A small amount of starting material **5.54** (9.2 mg, 7% recovery) was recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 8.8, 2.4 Hz, 1H), 6.59 (q, J = 1.4 Hz, 1H), 4.18 (s, 3H), 2.09 (s, 3H), 1.97 (d, J =

1.3 Hz, 3H), 1.81 (dq, J = 14.6, 7.3 Hz, 1H), 1.62 (dq, J = 14.4, 7.2 Hz, 1H), 1.36 – 1.20 (m, 3H), 1.10 (d, J = 7.1 Hz, 18H), 0.57 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 188.7, 170.8, 165.8, 160.7, 139.8, 137.1, 136.5, 133.3, 126.5, 118.3, 117.4, 103.3, 69.1, 59.4, 26.7, 21.0, 18.0, 12.8, 8.6, 7.3.

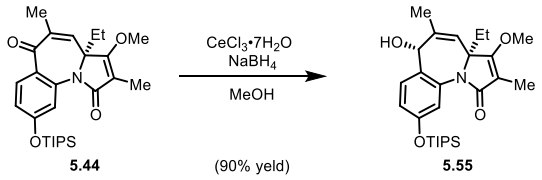
IR (thin film): 2945, 2867, 1702, 1669, 1625, 1590, 1488, 1451, 1285, 1252, 1218, 914 cm^{-1}.

HRMS (ESI+): calculated for $C_{27}H_{40}NO_4Si^+$ $[M+H]^+$ 470.2721, found: 470.2722.

TLC: 0.46 (30% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Benzylic alcohol **5.55**



Experimental: To a 100 mL rbf containing **5.44** (172.5 mg, 0.367 mmol) was added MeOH (7.5 mL) and cooled in an ice water bath. After cooling for 10 min, to this was added $CeCl_3$•$7H_2O$ (180 mg, 0.483 mmol) and stirred for 5 min after which was added $NaBH_4$ (15.6 mg, 0.412 mmol). The reaction was stirred for a total of 5 min after which TLC indicated consumption of the starting material. At this point, the reaction had turned into a white suspension and was quenched by the addition of saturated aqueous NH_4Cl and concentrated by rotary evaporation under reduced pressure at 40 °C to remove methanol. The solids were then dissolved in water and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give **5.55** (156 mg, 90% yield) as a crude white solid that was of characterizable purity.

^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 8.9 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 5.25 (br. s, 1H), 5.16 – 5.10 (m, 1H), 4.09 (s, 3H), 3.19 (br. d, *J* = 3.2 Hz, 1H), 2.05 (s, 3H), 1.84 (t, *J* = 1.4 Hz, 3H), 1.57 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.32 – 1.17 (m, 4H), 1.08 (d, *J* = 7.2 Hz, 18H), 0.63 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 171.8, 168.8, 155.2, 139.9, 136.6, 133.4, 124.4, 121.6, 120.9, 119.2, 101.6, 68.2, 67.6, 59.0, 28.8, 21.1, 18.0, 12.7, 8.5, 6.9.

IR (thin film): 3391, 2944, 2866, 1654, 1604, 1449, 1382, 1335, 1317, 1215, 921 cm^{-1}.

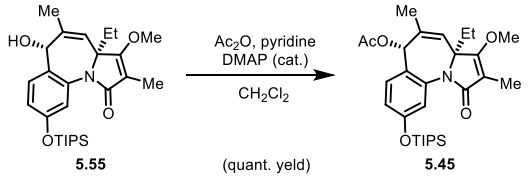
HRMS (ESI+): calculated for $C_{27}H_{42}NO_4Si^+$ $[M+H]^+$ 472.2878, found: 472.2879.

TLC: 0.27 (30% EtOAc in hexanes).

m.p.: 166.3-169.2 °C.

Physical Appearance: White solid.

Benzylic acetate **5.45**



Experimental: To a 100 mL rbf containing **5.55** (156 mg, 0.331 mmol) was placed under N_2 followed by the addition of CH_2Cl_2 (6.6 mL). To this was sequentially added pyridine (0.27 mL, 3.34 mmol), acetic anhydride (0.13 mL, 1.4 mmol), and DMAP (2.0 mg, 0.016 mmol). The reaction was stirred at room temperature for 45 min then concentrated by rotary evaporation (20 °C, 60 torr) to ~¼ the original volume. This was then diluted with EtOAc (30 mL) and saturated aqueous $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer washed with EtOAc (2x more). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (15 mL), then 5% aqueous $CuSO_4$ (15 mL x

3), bring (15 mL x 2), then dried over Na_2SO_4, filtered and concentrated to give **5.45** (179 mg, quant. yield) as a white solid and of characterizable purity.

Note: The product **5.45** appeared unstable to column chromatography and thermally decomposed at elevated temperature (40 °C, rotary evaporation).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.66 – 6.61 (m, 1H), 5.31 – 5.25 (m, 1H), 4.09 (s, 3H), 2.19 (s, 3H), 2.07 (s, 3H), 1.71 (t, *J* = 1.4 Hz, 3H), 1.60 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.35 – 1.17 (m, 4H, overlap with grease), 1.08 (d, *J* = 7.3 Hz, 18H), 0.64 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 171.4, 169.7, 168.1, 155.8, 135.7, 134.2, 131.9, 124.3, 123.9, 121.3, 119.2, 102.1, 70.8, 67.3, 59.1, 29.1, 21.0, 18.1, 18.1, 12.8, 8.6, 7.1.

IR (thin film): 2944, 2867, 1747, 1696, 1663, 1606, 1501, 1436, 1370, 1335, 1317, 1290, 921 cm^{-1}.

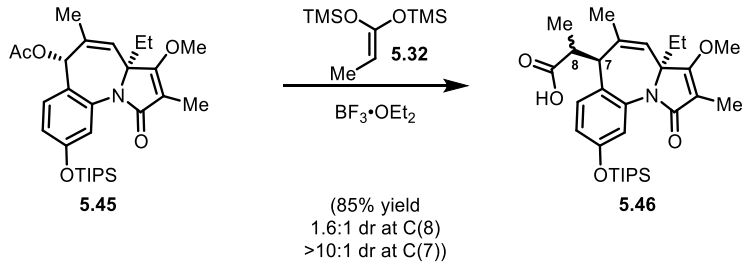
HRMS (ESI+): calculated for $C_{29}H_{44}NO_5Si^+$ $[M+H]^+$ 514.2983, found: 514.2982.

TLC: 0.35 (30% EtOAc in hexanes).

m.p.: 150.3 °C (decomposition).

Physical Appearance: White solid.

Carboxylic acid **5.46**



Experimental: To a rbf was added **5.45** (69.7 mg, 0.136 mmol) and this azeotroped with toluene (3x) (20 °C, 60 torr). This was then placed under hi-vac for 30 min and subsequently redissolved in CH_2Cl_2 (3 mL) and cooled in an ice-water bath. After cooling

for 5 min, to this was added **5.32** (0.18 mL, 0.70 mmol) followed by the dropwise addition of BF_3•OEt_2 (0.03 mL, 0.24 mmol). The reaction was stirred in the ice-water bath for 10 min after which TLC indicated consumption of the starting material. The reaction was then quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude residue. The crude residue was purified by flash column chromatography on silica gel (20%→30%→40% EtOAc in hexanes doped with 1% AcOH) to give **5.46** (60.7 mg, 85% yield, 1.6:1 dr C(8)) as a white sticky foam.

Note: Acid **5.46** is characterized as a 1.6:1 mixture of homobenzylic methyl epimers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (t, *J* = 7.9 Hz, 2.6H), 6.85 (d, *J* = 2.5 Hz, 1.6H), 6.77 (dd, *J* = 8.2, 2.5 Hz, 1.2H), 6.73 (dd, *J* = 3.6, 2.6 Hz, 1.8H), 6.71 (d, *J* = 2.6 Hz, 0.8H), 5.37 – 5.33 (m, 2.5H), 4.15 (s, 3H), 4.10 (s, 4.6H), 3.13 (d, *J* = 9.8 Hz, 1.6H), 3.00 (d, *J* = 10.8 Hz, 1H), 2.65 (dq, *J* = 9.8, 6.9 Hz, 1.6H), 2.49 (dq, *J* = 10.8, 6.5 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 4.8H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.83 (d, *J* = 1.4 Hz, 4.7H), 1.72 – 1.53 (m, 3H), 1.41 – 1.16 (m, 16.8H), 1.11 – 1.04 (m, 50H), 0.79 (d, *J* = 6.9 Hz, 4.7H), 0.68 (t, *J* = 7.3 Hz, 3H), 0.61 (t, *J* = 7.3 Hz, 4.7H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 181.3, 176.2, 174.9, 171.7, 170.6, 168.6, 156.2, 155.8, 136.9, 136.0, 135.6, 134.3, 132.4, 131.4, 131.1, 130.8, 125.3, 125.0, 122.1, 122.0, 120.4, 118.7, 101.8, 101.2, 68.3, 67.5, 59.3, 59.1, 53.2, 52.9, 48.1, 45.4, 29.5, 29.0, 27.8, 18.0, 18.0, 16.9, 16.8, 12.7, 12.7, 8.5, 7.3, 7.2.

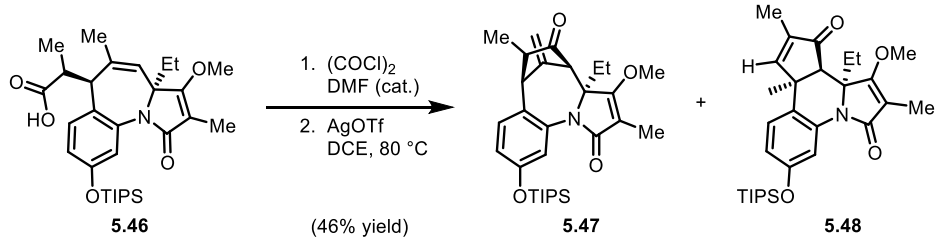
IR (thin film): 3111, 2944, 2867, 1696, 1647, 1604, 1504, 1452, 1386, 1336, 1319, 1289, 1243, 1218, 1190, 1063, 981, 921 cm^{-1}.

HRMS (ESI+): calculated for $C_{30}H_{46}NO_5Si$ $[M+H]^+$ 528.3140, found: 528.3141.

TLC: 0.26/0.22 (60:39:1 hexanes:EtOAc:AcOH) [two diastereomers]

Physical Appearance: White sticky foam.

Fused tetracycles **5.47** *and* **5.48**



Experimental: To a flame dried 50 mL rbf was added **5.46** (24.7 mg, 0.047 mmol) and this was azeotroped with toluene (2x) and placed under hi-vac for 1 h. After placing this under an atmosphere of N_2, this was dissolved in CH_2Cl_2 (2.0 mL) followed by the addition of $(COCl)_2$ (0.10 mL, 1.1 mmol) and a catalytic quantity of DMF (1 drop DMF in 1 mL CH_2Cl_2, 1 drop of this solution was used). This was stirred for 30 min after which TLC indicated complete formation of the methyl ester upon quenching the TLC spotter with MeOH. The reaction was concentrated by rotary evaporation under reduced pressure (25 °C, 60 torr) and azeotroped with anhydrous CH_2Cl_2 (3x). This was then placed under hi-vac for 1 h.

In a separate flame dried flask was added AgOTf (26.3 mg, 0.102 mmol) and this azeotroped with toluene (3x, 45 °C bath temperature, ~60 torr). This was then placed under hi-vac for and heated gently with heat-gun for ~1 min to give a fine white powder. This was then dissolved in DCE (2.0 mL) and 1.5 mL of this suspension transferred to a flame dried 25 mL Schlenk flask. This Schlenk flask was then placed in a preheated oil bath set at 90 °C.

After 5 min, the crude acid chloride was dissolved in DCE (1.0 mL) and 0.8 mL of this solution was transferred dropwise to the AgOTf suspension over the course of 3 min.

The reaction was stirred for an additional 30 min at 90 °C where the white suspension slowly turned into a pink suspension. This was then cooled in an ice-water bath followed by the addition of 0.03 mL Et_3N immediately followed by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated. After concentrated, the crude residue was dissolved in Et_2O and filtered through a Kim-wipe and concentrated to give 29 mg of a crude brown oily suspension. This was then purified by pipette column to give **5.47** and **5.48** (8.8 mg, 46% yield) as an inseparable mixture and as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): ONLY MAJOR PEAKS LISTED (corresponding to **5.48**) δ 7.63 (d, *J* = 2.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 6.89 – 6.86 (m, 1H), 6.64 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.25 (s, 3H), 2.65 (s, 1H), 2.06 (s, 3H), 1.77 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.72 – 1.63 (m, 4H), 1.63 – 1.57 (m, 3H, overlap with H_2O), 1.31 – 1.20 (m, 3H, overlap), 1.09 (dd, *J* = 7.5, 3.8 Hz, 18H, overlap), 0.51 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): MAJOR PEAKS (corresponding to **5.48**): δ 205.0, 170.6, 168.4, 165.0, 155.5, 137.1, 133.4, 127.0, 122.6, 115.9, 112.5, 103.7, 64.8, 60.1, 58.8, 44.0, 28.5, 27.1, 18.1, 12.8, 10.0, 8.4, 6.4.

ALL PEAKS: δ 214.9, 213.9, 205.0, 171.0, 170.9, 170.6, 168.4, 167.3, 167.3, 165.0, 155.5, 155.3, 155.1, 145.9, 145.5, 137.1, 134.7, 133.8, 133.4, 132.1, 130.8, 129.2, 127.5, 127.0, 122.6, 120.9, 120.6, 118.2, 118.0, 115.9, 113.8, 112.8, 112.5, 105.6, 105.1, 103.7, 74.6, 69.2, 68.7, 64.8, 62.4, 61.5, 60.3, 60.1, 59.3, 59.3, 58.8, 58.0, 55.0, 49.6, 48.3, 44.0, 34.3, 34.2, 33.4, 32.1, 31.9, 30.1, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 29.4, 29.2, 28.5, 27.1, 25.5, 25.4, 25.0, 24.9, 24.5, 24.2, 22.8, 22.7, 21.5, 21.1, 20.9, 18.1, 18.0, 18.0, 18.0, 18.0, 17.5, 14.3, 14.2, 13.0, 12.8, 12.8, 12.7, 12.6, 10.4, 10.0, 8.6, 8.6, 8.4, 7.0, 6.9.

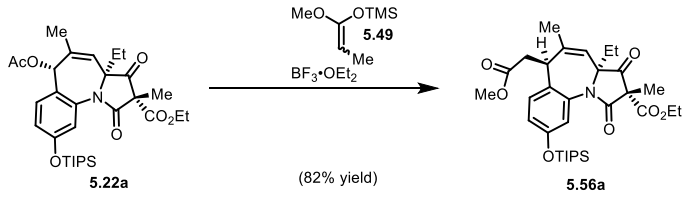
IR (thin film): 29334, 2869, 1746, 1698, 1665, 1602, 1498, 1438, 1373, 1346, 1300, 1217, 932 cm^{-1}.

HRMS (ESI+): calculated for $C_{30}H_{43}NO_4SiNa^+$ $[M+Na]^+$ 532.2854, found: 532.2855.

TLC: 0.34 (30% EtOAc in hexanes).

Physical Appearance: Yellow oil.

Methyl ester **5.56a**



Experimental: To a flame dried vial was added **5.22a** (40 mg, 0.070 mmol). This was placed under hi-vac for 10 min and subsequently dissolved in CH_2Cl_2 (4.0 mL). To this was added, at room temperature, **5.49** (0.16 mL, 0.21 mmol). After stirring for ~ 1 min, to this was added BF_3•OEt_2 (0.020 mL, 0.16 mmol) at which point the reaction turned orange then immediately faded to colorless. The reaction was stirred for an additional 30 min and quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to give a crude residue. The crude residue was purified by flash column chromatography on silica gel (0%→10%→20%→30% EtOAc in hexanes) to give **5.56a** (43 mg, 82% yield) as a colorless oil and >10:1 dr, major diasteromer depicted).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.40 – 5.34 (m, 1H), 4.34 – 4.19 (m, 2H), 3.59 (dd, *J* = 9.1, 5.0 Hz, 1H), 3.53 (s, 3H), 2.58 – 2.44 (m, 2H), 1.89 (d, *J* = 1.3 Hz, 3H), 1.83 (dq, *J* = 14.9, 7.4 Hz, 1H), 1.63 (s, 3H), 1.49 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.33 – 1.17 (m, 6H), 1.08 (dd, *J* = 7.5, 1.2 Hz, 18H), 0.80 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 206.1, 172.1, 168.8, 165.8, 155.9, 138.1, 134.3, 131.7, 131.2, 124.7, 121.2, 120.3, 74.5, 62.7, 58.2, 51.9, 46.1, 40.7, 29.9, 26.5, 18.9, 18.0, 14.0, 12.7, 8.5.

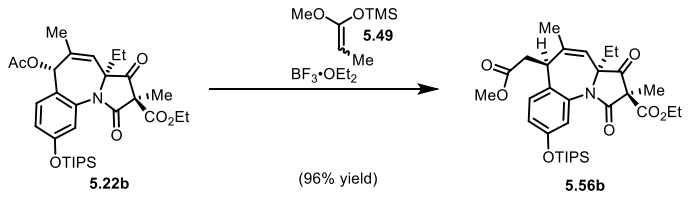
IR (thin film): 2944, 2868, 1776, 1742, 1708, 1608, 1504, 1435, 1388, 1337, 1293, 1231, 1170, 1106, 1056, 1015, 986, 946, 918, 882, 856, 686 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_7SiNa^+$ $[M+Na]^+$ 608.3014, found: 608.3013.

TLC: 0.50 (10% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Methyl ester **5.56b**



Experimental: To a flame dried 50 mL rbf was added **5.22b** (54 mg, 0.094 mmol). This was then placed under hi-vac for 10 min and subsequently dissolved in CH_2Cl_2 (4.4 mL). To this was added at room temperature **5.49** (0.020 mL, 0.28 mmol). After stirring for ~ 1 min, BF_3•OEt_2 (0.026 mL, 0.21 mmol) was added. The reaction instantly turned orange then rapidly faded to colorless. The reaction was stirred for an additional 2 h and the reaction then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by pipette column (0%→5%→10%→20% EtOAc in hexanes) to give **5.56b** (53 mg, 96% yield, >10:1 dr at benzylic position) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 2.5 Hz, 1H), 6.78 (dd, J = 8.3, 2.5 Hz, 1H), 5.42 – 5.37 (m, 1H), 4.33 – 4.10 (m, 2H), 3.60 (dd, J = 10.3, 3.7 Hz, 1H), 3.50 (s, 3H), 2.74 (dd, J = 15.9, 10.4 Hz, 1H), 2.60 (dd, J = 15.9, 3.7 Hz, 1H),

1.91 (d, J = 1.4 Hz, 3H), 1.79 (dq, J = 14.7, 7.4 Hz, 1H), 1.65 (s, 3H), 1.38 – 1.26 (m, 1H), 1.26 – 1.18 (m, 6H), 1.08 (dd, J = 7.3, 2.6 Hz, 18H), 0.74 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 206.5, 172.5, 168.4, 165.5, 155.8, 136.9, 134.1, 132.1, 131.0, 124.7, 120.9, 119.9, 75.3, 62.8, 58.0, 51.8, 46.3, 40.4, 29.7, 26.1, 18.0, 16.6, 14.1, 12.7, 8.8.

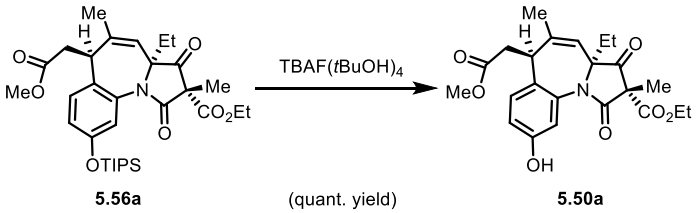
IR (thin film): 2944, 2867, 1776, 1742, 1708, 1608, 1579, 1504, 1462, 1434, 1386, 1364, 1337, 1291, 1225, 1170, 1138, 1123, 1103, 985, 909, 882, 852, 687 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_7SiNa^+$ $[M+Na]^+$ 608.3014, found: 608.3010.

TLC: 0.49 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Phenol **5.50a**



Experimental: To a solution of **5.56a** (8.3 mg, 0.014 mmol) in THF (2.0 mL) was added TBAF(tBuOH)$_4$ (12.7 mg, 0.023 mmol). The reaction turns a faint yellow and is stirred for ~2 min then quenched by the addition of 0.5 N aqueous HCl and extracted with CH_2Cl_2 (3x). The combined organics are dried over $MgSO_4$, filtered, and concentrated to a colorless oil. The crude residue is purified by pipette column (0%→10%→30%→50% EtOAc in hexanes) to give phenol **5.50a** (6.1 mg, quantitative yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.08 (d, J = 8.4 Hz, 1H), 6.88 (br. s, 1H), 6.79 (d, J = 2.5 Hz, 1H), 6.60 (dd, J = 8.4, 2.5 Hz, 1H), 5.37 (s, 1H), 4.36 – 4.16 (m, 2H), 3.64 – 3.56 (m, 4H), 2.58 – 2.47 (m, 2H), 1.89 (s, 3H), 1.82 (dq, J = 14.8, 7.5 Hz, 1H), 1.67 (s, 3H), 1.55

(dq, J = 14.8, 7.5 Hz, 1H), 1.26 (t, J = 6.9 Hz, 3H, overlap with grease), 0.79 (t, J = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.4, 172.0, 170.1, 165.5, 156.6, 138.5, 133.7, 132.1, 129.8, 124.1, 116.5, 116.4, 74.9, 62.9, 58.4, 52.0, 45.8, 40.6, 30.0, 26.6, 18.8, 14.0, 8.5.

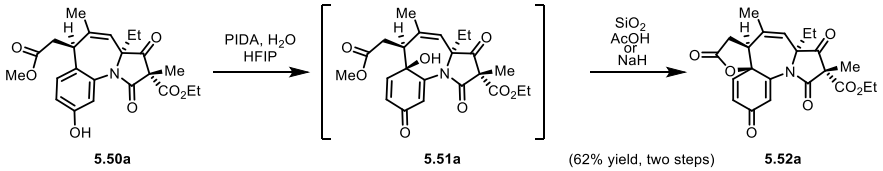
IR (thin film): 3336, 2982, 2925, 2854, 1775, 1741, 1705, 1679, 1617, 1508, 1453, 1392, 1294, 1233, 1166, 1119 cm^{-1}.

HRMS (ESI+): calculated for $C_{23}H_{27}NO_7Na^+$ $[M+Na]^+$ 452.1680, found: 452.1681.

TLC: 0.46 (50% EtOAc in hexanes).

Physical Appearance: Colorless oil.

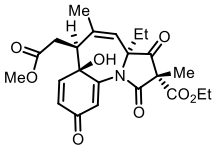
p-Quinol **5.51a**
Spirolactone **5.52a**



Experimental: To a 2 dr vial was added phenol **5.50a** (9.5 mg, 0.022 mmol) and this dissolved in HFIP:H_2O (2:1, 0.33 mL) to which was added PIDA (8.9 mg, 0.028 mmol) and stirred for 15 min. The reaction turns into a grey solution which then turns orange. The reaction is then diluted with H_2O and extracted with EtOAc (3x). The combined organics are dried over $MgSO_4$, filtered, and concentrated to a yellow oily residue/powder. The crude residue is azeotroped with toluene (1x). The crude reaction mixture is rapidly flashed via pipette column (0%→20%→50%→70%→100% EtOAc in hexanes) to give a mixture of products **5.51a** and **5:52a** as an inseparable mixture (~1:1 mixture, 6.1 mg, ca 62% yield).

To a vial containing the above mixture of *para*-quinol **5.51a** and spirolactone **5.52a** (6.1 mg) was added Hexanes:EtOAc (1:1, 2 mL) and stirred with SiO_2 (35.4 mg) for 4 h after

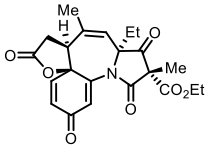
which it was filtered through a kimwipe and washed with EtOAc. This was then purified by pipette column (20%→40%→60%→80%→100% EtOAc in hexanes) to give pure spirolactone **5.52a** (5.7 mg, 62% yield, two steps). Crystals suitable for X-Ray diffraction studies were grown by slow evaporation from Et_2O.



Para-quinol 5.51a **5.51a** An NMR spectra is attached in the appendix pertaining to a mixture of *para*-quinol **5.51a** and spirolactone **5.52a**.

HRMS (ESI+): calculated for $C_{23}H_{27}NO_8Na^+$ $[M+Na]^+$ 468.1629, found: 468.1628.

TLC: 0.31 (70% EtOAc in hexanes).



spirolactone 5.52a **5.52a**

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.81 (d, *J* = 10.1 Hz, 1H), 6.44 (d, *J* = 1.8 Hz, 1H), 6.37 (dd, *J* = 10.0, 1.8 Hz, 1H), 5.60 (s, 1H), 4.32 – 4.17 (m, 2H), 3.27 – 3.14 (m, 2H), 2.49 (dd, *J* = 17.3, 5.0 Hz, 1H), 2.03 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.94 (dq, *J* = 14.7, 7.5 Hz, 1H), 1.86 (s, 3H), 1.60 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 202.9, 184.3, 172.3, 168.0, 164.9, 146.3, 145.5, 133.9, 133.8, 128.9, 123.4, 82.9, 75.1, 63.2, 58.3, 47.6, 36.9, 32.7, 28.3, 19.2, 14.0, 8.7.

IR (thin film): cm^{-1} 2984, 2941, 1781, 1741, 1717, 1679, 1449, 1379, 1362, 1278, 1230, 1108, 1007.

HRMS (ESI+): calculated for $C_{22}H_{23}NO_7Na$ $[M+Na]^+$ 436.1367, found: 436.1368.

TLC: 0.41 (70% EtOAc in hexanes).

m.p.: 188.1-189.2 °C.

Physical Appearance: White amorphous solid. Thin colorless needles after crystallization.

5.5 References

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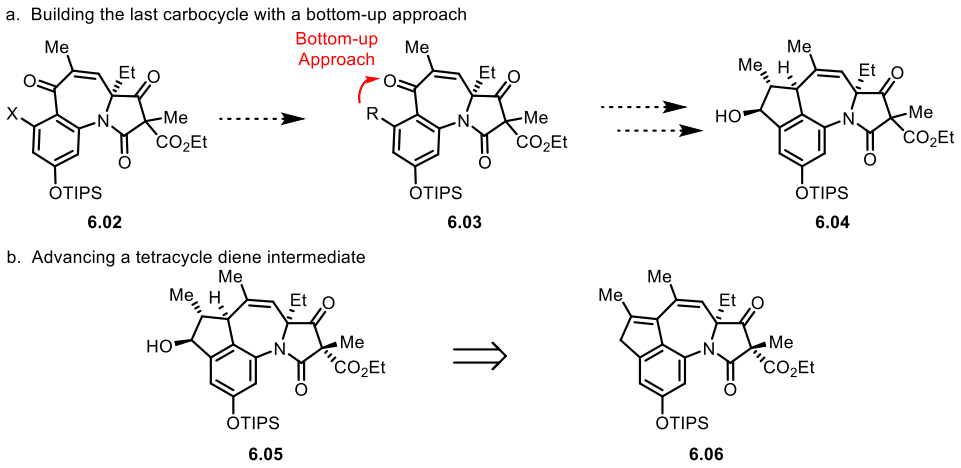
CHAPTER SIX

A Bottom-Up Approach Toward the Last Carbocycle: From Cross-Coupling to 4π Cyclization

6.1 Overall Strategy

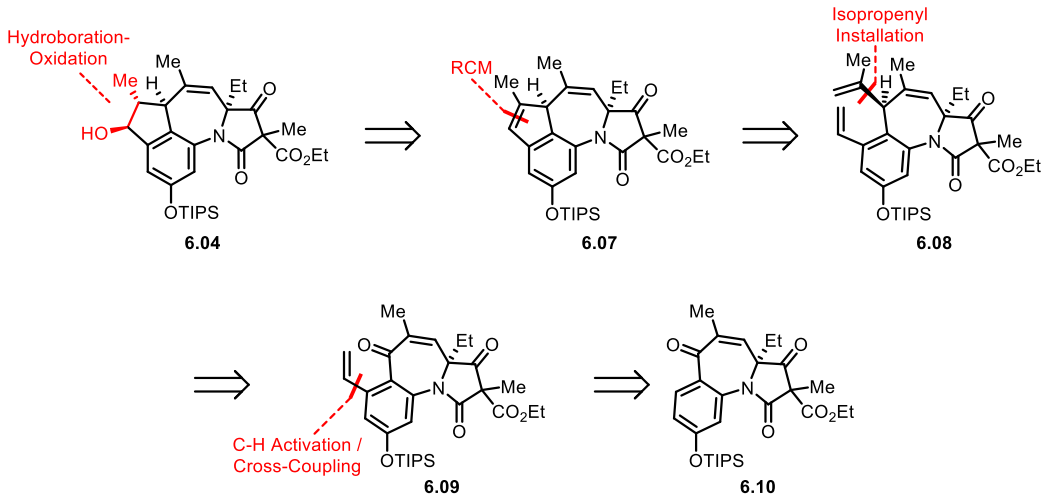
Given that we were unable to build the last carbocycle employing what can be considered "top-down" strategies (see chapter 5), we contemplated the possibility of building this ring instead from a bottom-up strategy (Scheme 6.1a, top). In other words, instead of appending an alkyl chain off the benzylic position and attempting to form an aryl C-C bond in a top down fashion, we considered an approach to tether an alkyl chain (R, **6.03**) on the side of the aromatic ring and later forge the benzylic C-C bond in a bottom-up approach to deliver tetracycle **6.04**. As will be delineated in this chapter, efforts to implement this strategy were found to deliver tetracyclic diene **6.06** and various routes were explored in attempts to advance to this material to **6.05** (Scheme 6.1a, bottom).



Scheme 6.1. General Strategy: A Bottom-up approach and a 4π cyclization approach

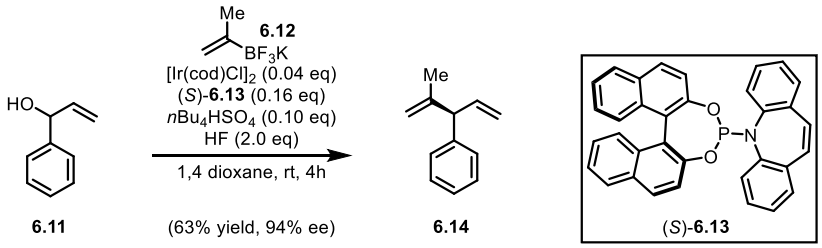
6.2 A Ring-Closing Metathesis Approach

Having previously accessed styrene derivative **6.09** utilizing a tetraorganoindate cross-coupling reaction, we planned for the preparation of tetracycle **6.04** by way of a hydroboration-oxidation sequence on RCM product **6.07**. The diene substrate for this RCM (**6.08**) would be available by a vinylation of styrene **6.09**.



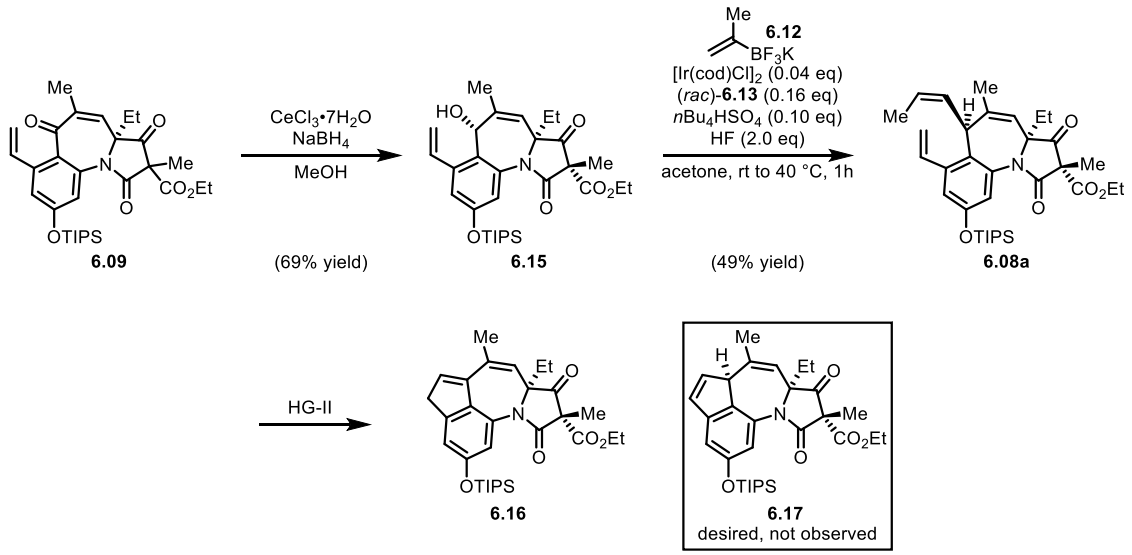
Scheme 6.2. A ring-closing metathesis strategy

In searching the literature for methods to effect allylic vinylation, we came across a report by Carreira and coworkers that described the use of allylic alcohols as substrates (e.g., **6.11**) in coupling reactions with potassium trifluoroborate salts (e.g., **6.12**) under iridium catalysis to deliver the vinylated product (**6.14**).[1]

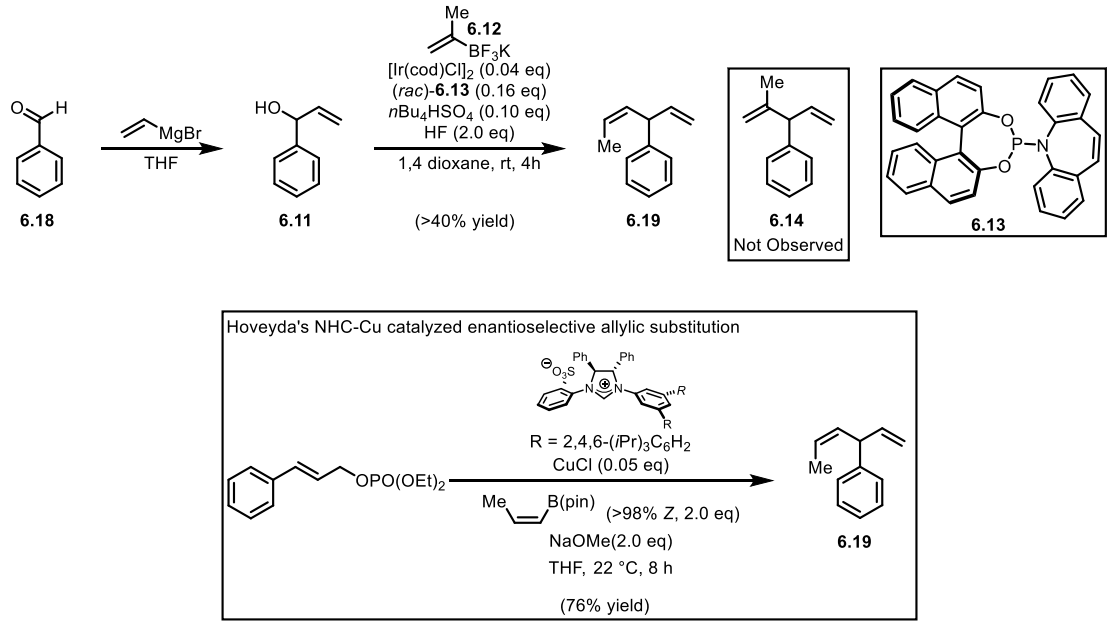


Scheme 6.3. Carreira's allylic vinylation precedent

Thus, looking toward applying Carreira's method to our system, we prepared allylic alcohol **6.15** from cross-coupled product **6.09** (Scheme 6.4). Of note here is that the major isomer of **6.09**, possessing a *syn*-relationship between the angular ethyl group and ethyl ester in the masked tetramic acid, preferentially underwent reduction to give the corresponding diastereomer **6.15**. Surprisingly, as confirmed by preliminary X-Ray crystallographic analysis as well as phase-sensitive HSQC data, *cis*-alkene product **6.08a** was produced upon exposure to Carreira's conditions. Despite this odd result (*vide infra*), we attempted to push forward and prepare skipped diene **6.17** via RCM reaction. Although we were delighted to finally see a ring closed product, spectroscopic analysis clearly indicated that the initially formed diene (**6.17**) had isomerized to the less desired but thermodynamically preferred isomer **6.16**. The seemingly unavoidable migration of the olefin to deliver product **6.08a** deterred us from any further pursuit of a RCM strategy and we thus began considering alternative approaches.



Scheme 6.4. Application of Carreira's allyic vinylation toward a RCM precursor.



Scheme 6.5. A mis-assigned allylic vinylation product

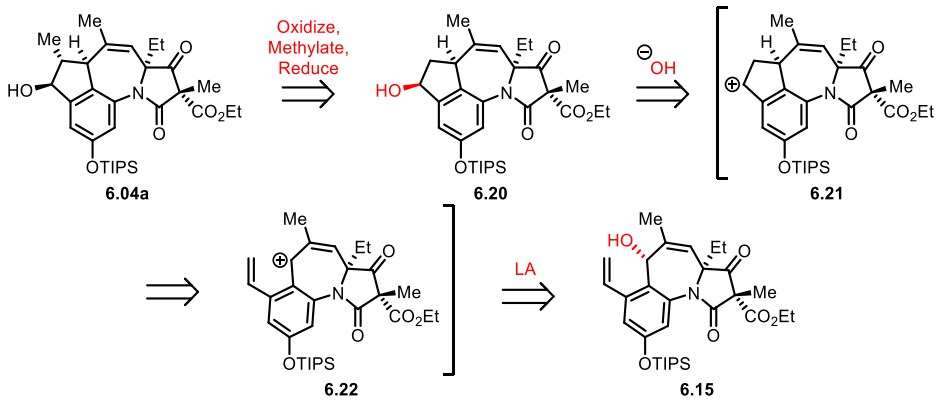
Prior to moving forward with the synthesis, we briefly returned to the odd result obtained in applying Carreira's coupling chemistry. Based on the reagents employed in Scheme 6.4, our expectation in the coupling of **6.11** with **6.12** was an isopropenyl product akin to **6.14** (Scheme 6.5) and not the *n*-propenyl product **6.08a**. After confirming the identity of trifluoroborate salt **6.12** and the fact that we had indeed been using the correct starting materials, we went back to reexamine Carreira's identification of product **6.14** (Scheme 6.5). In the latter event, we reproduced Carreira's chemistry employing *rac*-**6.13** and found that it produced a product possessing spectral data identical to that reported, however further analysis employing 2D NMR techniques revealed that the product was in fact **6.19** (Scheme 6.5). Using an alternative method, as depicted in Scheme 6.5 (bottom, inset), Hoveyda has reported the intentional preparation of **6.19** using *N*-heterocyclic carbene (NHC)-Cu catalyzed enantioselective allylic substitution to give a product whose NMR spectroscopic data is in agreement with the product obtained via Carreira's method (inset).[2] At present there is not a clear mechanistic rational for why Carreira's method

produces a *cis-n*-propene instead of the expected isopropene and thus further investigation of this interesting transformation is warranted.

6.3 A Cation-π Cyclization Approach

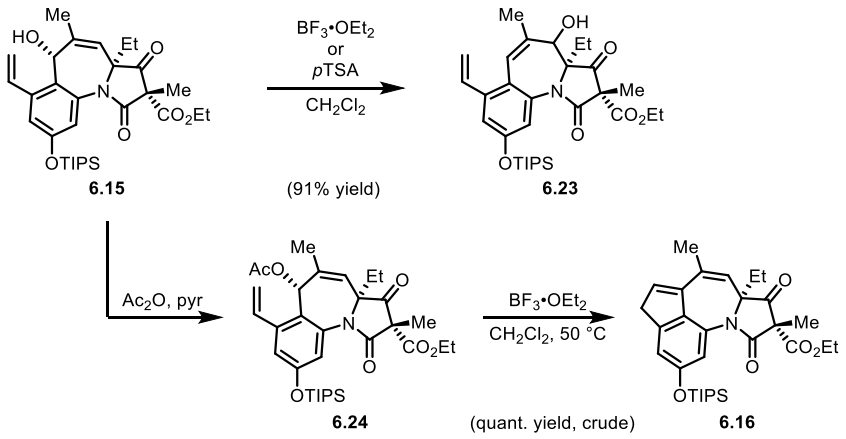
6.3.1. A Cation-π Strategy Based on Late-Stage Methylation

Having established the viability of aryl-CH functionalization for the preparation of various styrene derivatives and conditions for producing reactive benzylic carbonium ions, our efforts turned toward combining these techniques and we thus devised a cation-π strategy to deliver tetracycle **6.20** in a single step from **6.15** (Scheme 6.6). We anticipated that this product would enable the preparation of tetracyclic alcohol **6.04a** via a subsequent oxidation, methylation, and reduction sequence. As illustrated, the course of the proposed cascade cation-π cyclization would involve ionization of benzylic alcohol **6.15** to benzyl cation **6.22** which, following C-C bond creation and formation of cation **6.21** would undergo trapping of the originally released hydroxide to furnish **6.20**. Alternatively, one could imagine employing an external nucleophile, such as rhodinose, for trapping intermediate cation **6.21** to directly deliver the glycosylated product.



Scheme 6.6. A cation-π cyclization strategy toward the last carbocycle

In exploring this chemistry, we found that exposure of **6.15** to a variety of Lewis or Brønsted acids resulted predominantly in transposition of the hydroxyl group to produce **6.23** as the only isolable product. To avoid the deleterious trapping of the incipient carbonioum ion by nucleophilic hydroxide we prepared the corresponding acetate (**6.24**) which upon ionization would give rise to a much less nucleophilic acetate leaving group and thereby better allow for the desired C-C bond formation. In the event, were delighted to find that this change in substrate had indeed redirected the course of this reaction toward a cyclization that cleanly produced tetracyclic diene **6.16**. Unfortunately, this was the same compound that we had observed earlier in our RCM studies, the product we assumed from skipped diene formation followed by facile 1,5-hydride shift.



Scheme 6.7. Attempted cation-π cyclization

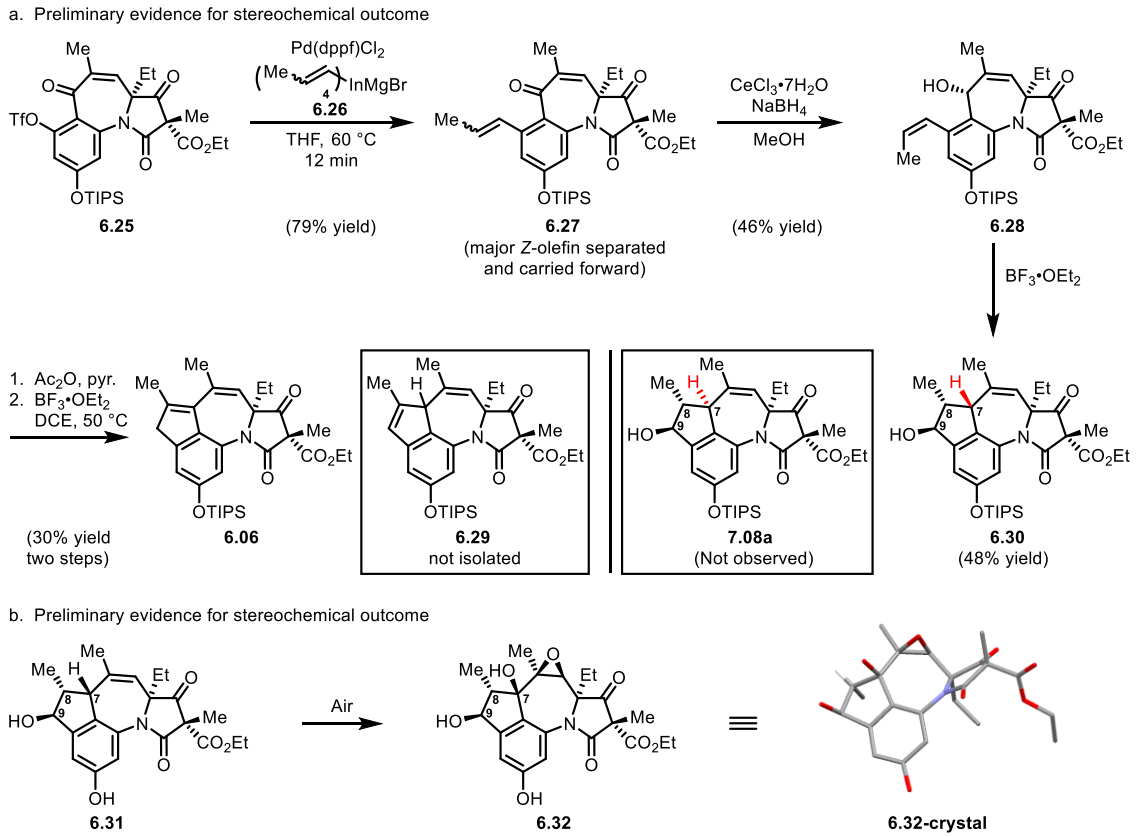
6.3.2. Preparation of a ß-Methyl Styrene Derivative for Cation-π Cyclization

Although our initial investigations into the cation-π cyclization studies were somewhat disappointing, as they had failed to produce the desired skipped diene, we were encouraged by the reaction's efficiency and began to consider other possible substrates. To this end, we envisioned that a ß-methyl styrene derivative would be more suitable to

advancement via this cascade sequence. Not only would the ß-methyl styrene alkene unit be more nucleophilic, but it would install the desired methyl group from the outset as opposed to late-stage alkylation and redox manipulation.

In moving forward, we prepared ß-methyl styrene derivative **6.27** as a mixture of alkene isomers via coupling of tetraorganoindate **6.26** with triflate **6.25** (Scheme 6.8). Luche reduction and separation of the major *cis*-alkene isomer gave the desired alcohol substrate (**6.28**) that was prone to reoxidize back to ketone **6.27** in air. It is worth noting that tetraorganoindate **6.26** was prepared from a mixture of *cis*- and *trans*- 1-propenylmagnesium bromide whose ratio was not determined. Earlier efforts to prepare this ß-methyl styrene derivative (**6.27**) via reduction of a propynyl functionality to avoid olefin isomers proved to be unsuccessful (see Scheme 2.25, Chapter 2). In a fashion similar to that employed in Scheme 6.7, **6.28** was converted to an intermediate acetate and then exposed to BF_3•OEt_2. Unfortunately, this cation π-cyclization again gave rise to a tertracyclic product (**6.06**) lacking the desired skipped diene olefin configuration (30% yield, two-steps). In contrast to previous studies, inspection of the crude ^{1}H NMR gave some indication of skipped diene **6.29**, however, attempts to isolate this material were unsuccessful.

Given that increased olefin substitution results in greater electron density and hence nucleophilicity, we speculated that the olefin in **6.28** may capable of competing with nucleophilic hydroxide and in contrast to **6.15** (*vide supra*) undergo cyclization without conversion to the corresponding acetate. To explore this possibility we exposed **6.28** to BF_3•OEt_2 and were delighted to find that it not only underwent successful



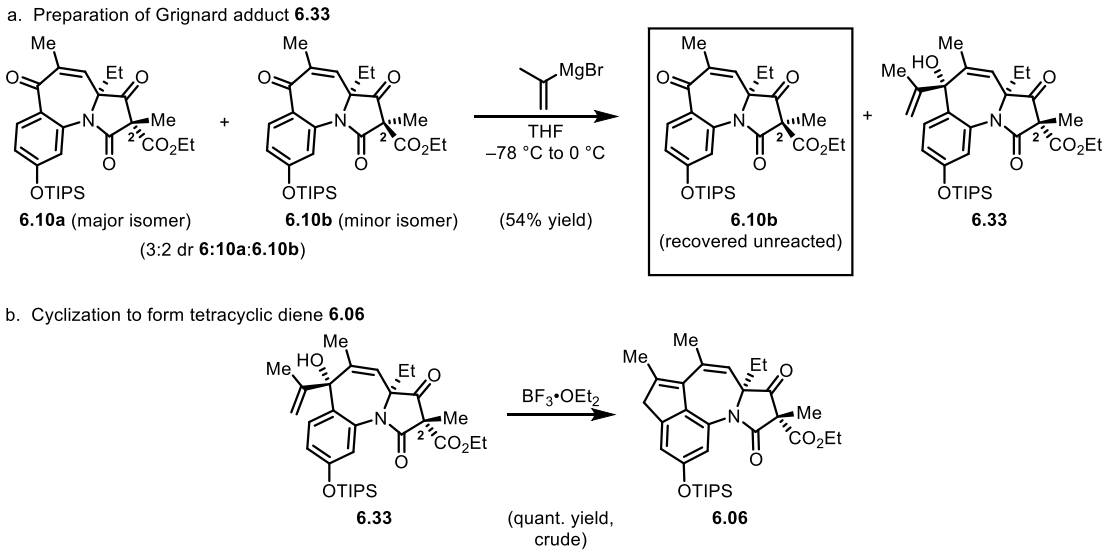
Scheme 6.8. Attempted cation-π cyclization with a more nucleophilic ß-methyl styrene

tetracycle formation but also trapped hydroxide to give the corresponding alcohol **6.30**, a compound that proved to be unstable in air and prone to oxidation. Unfortunately, comparison of ^{1}H-NMR chemical shift values to **6.35** (Scheme 6.10) indicated that the incorrect stereochemistry had been obtained at the benzylic methine stereocenter. Efforts to obtain X-Ray crystal structure data on **6.31**, whose identity was determined through ^{1}H, ^{13}C, HRMS, and IR data, resulted in X-Ray crystallographic data corresponding to the oxidized product **6.32**, likely due to oxidation in air during the time it took to grow crystals. NMR data on this decomposed material was consistent with the epoxide observed in the X-ray study and was absent any of the starting alcohol (**6.31**). Assuming configurational stability at the C(8) and C(9) positions of **6.32** during deprotection and oxidation, these

respective stereocenters have tentatively been assigned as depicted in **6.30**. An NMR mismatch with **7.08a** (see Scheme 7.12 for preparation) a compound later prepared, confirmed **6.30** as possessing the illustrated stereochemistry at the benzyilic methine C(7).

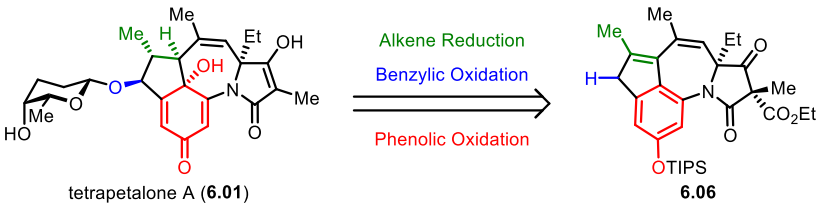
6.4 Advancing a Tetracyclic Diene

The cation-π reaction of **6.28** was remarkable but unfortunately failed to deliver the desired benzylic stereochemistry. In light of this result and in the absence of methods for inverting the benzylic methine stereocenter, we were forced to consider alternatives and thus turned to developing strategies for advancing tetracyclic diene **6.06**. However, for this to be a viable approach we needed to improve the efficiency by which we were accessing this material. To this end, we took note of preliminary investigations by Dr.'s McMahon and Buergler who had established the feasibility of advancing isopropenyl Grignard adduct **2.115** to tetracycle **2.116** (Scheme 2.26, chapter 2). Applying a similar protocol to substrate **6.10** did indeed provide an alternative means of accessing tetracycle **6.06** in adequate yield to move forward (Scheme 6.9). As an aside, these studies also revealed some rather interesting reactivity of the diastereomeric mixture of **6.10a** and **6.10b** used in the initial Grignard reaction. In this transformation it was clear that the major isomer was preferentially undergoing nucleophilic attack by the Grignard reagent as evidenced the enrichment of recovered material in **6.10b**.



Scheme 6.9. A more efficient route to tetracyclic diene **6.06**

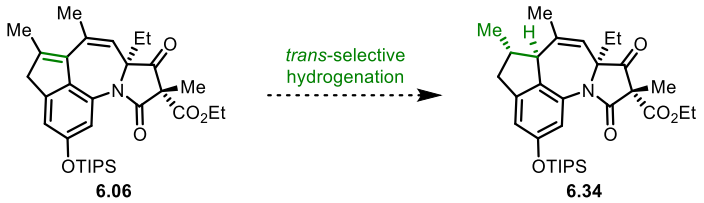
Having improved access to **6.06**, there remained three major challenges regarding its advancement. (Scheme 6.10). First, we would have to effect a *trans*-selective hydrogenation of the indenyl alkene to set the relative stereochemistry of the benzylic and homobenzylic methines (green). Second, a benzylic oxidation or redox isomerization would be necessary to install an alcohol functional handle for glycosylation (blue). Third, installation of the *para*-quinol unit would be necessary from the parent phenol (red). In addressing each of these challenges a variety of regio- and diastereo- selectivity issues would need be overcome. The remainder of this chapter is dedicated to addressing these three challenges in advancing **6.06**.



Scheme 6.10. Remaining challenges in advancing tetracyclic diene **6.06**

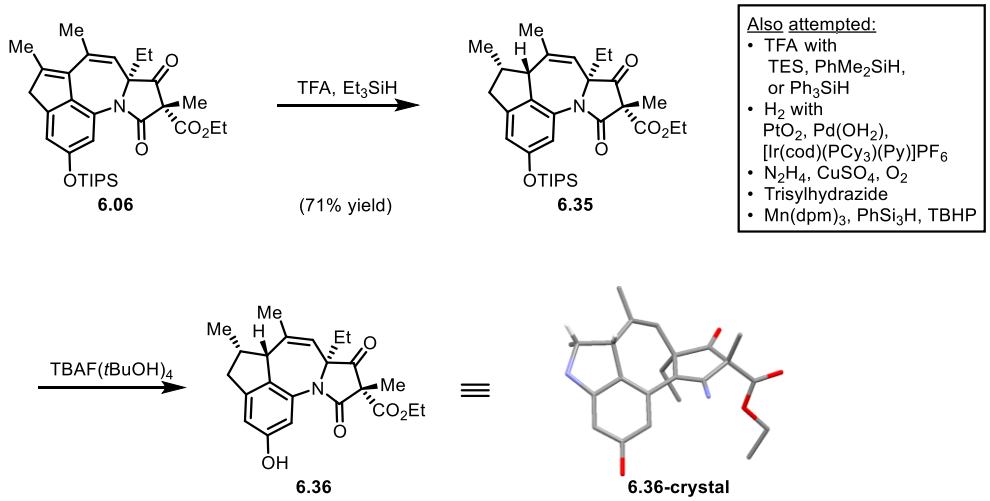
6.4.1. Advancing a Tetracyclic Diene by Alkene Manipulation

With the wide variety of alkene hydrogenation techniques available to us, and setting the benzylic stereocenter being one of the foremost challenges, we focused our initial efforts to advance **6.06** on setting the benzylic stereocenter by alkene hydrogenation (Scheme 6.11).



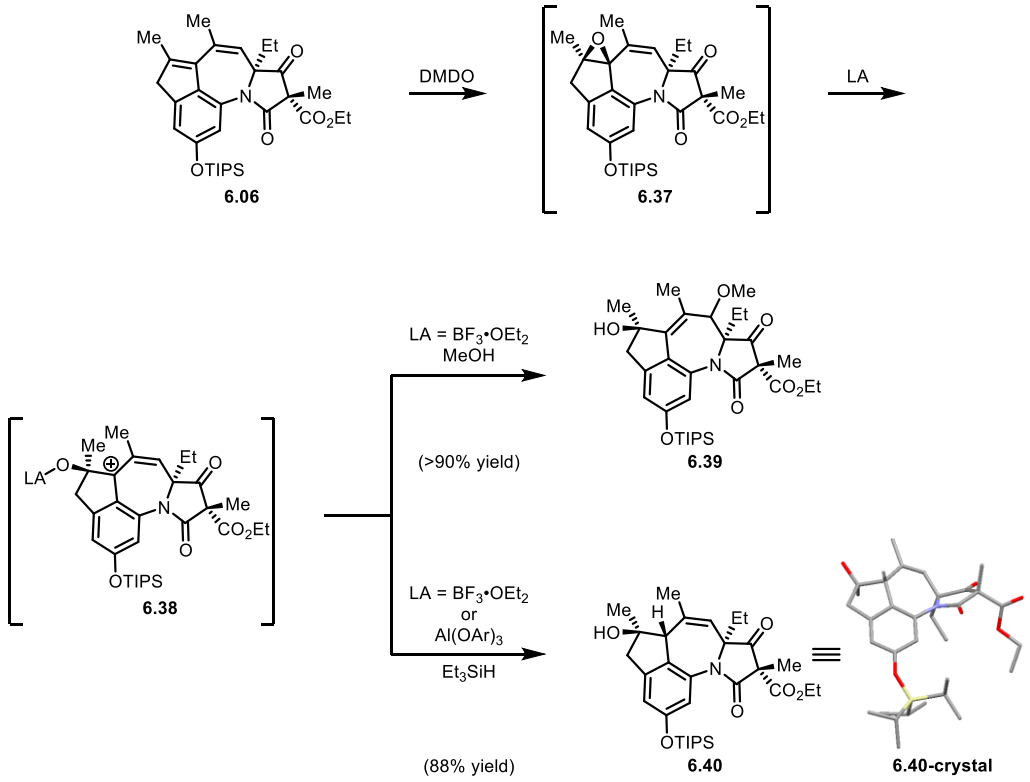
Scheme 6.11. Advancing tetracyclic diene **6.06** by alkene reduction

While many hydrogenation conditions and techniques were attempted,[3] we were unsuccessful in our ability to isolate any reduced products with the correct benzylic stereocenter. As was becoming evident in general, many of the advanced substrates in this synthesis were proving to be quite prone to oxidation in air thus making advancement and isolation of intermediates challenging. As illustrated in Scheme 6.12, the most efficient of the reduction techniques explored was the ionic reduction of **6.06** with TFA in the presence of Et_3SiH which gave *cis*-hydrogenation product **6.35** whose identity was firmly established via single crystal X-Ray analysis of the corresponding deprotected phenol **6.36**. Attempts to alter the stereochemical outcome by employing alternative silyl-hydrides invariably led to **6.35** or non-isolable products. Attempts to take these crude reduced materials forward via oxidation were also plagued with complex mixtures.[4]



Scheme 6.12. An undesired stereochemical outcome in indene reduction

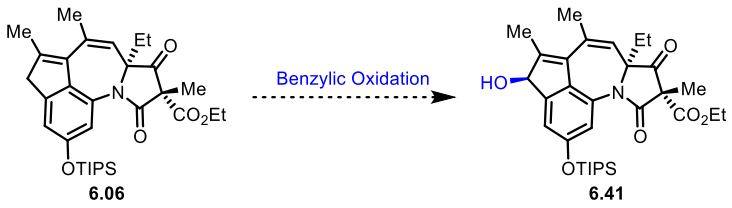
As an alternative to direct hydride delivery, we explored conversion to the corresponding epoxide in hopes of perhaps effecting a subsequent reductive opening (Scheme 6.13). In this event, exposure of **6.06** to DMDO furnished an intermediate epoxide (**6.37**);[5] however, efforts to effect ring opening by Lewis Acid coordination on the ß-face and nucleophilic attack on the α-face resulted in epoxide opening either with transposition of the alkene (e.g., **6.39**) or with the incorrect stereochemistry (i.e., **6.40**). The latter result was confirmed by single crystal X-ray analysis. Attempts to coordinate a Lewis acid, even Yamamoto's bulky ATPH complex,[6] in the presence of triethylsilane invariably gave products with the incorrect benzylic stereocenter.



Scheme 6.13. Attempts to bias stereochemical outcomes via an intermediate epoxide

6.4.2. Advancing a Tetracyclic Diene via Benzylic Oxidation

Our inability to set the benzylic stereocenter led us to abandon hydrogenation techniques in favor of pursuing the challenge of benzylic oxidation (Scheme 6.14).

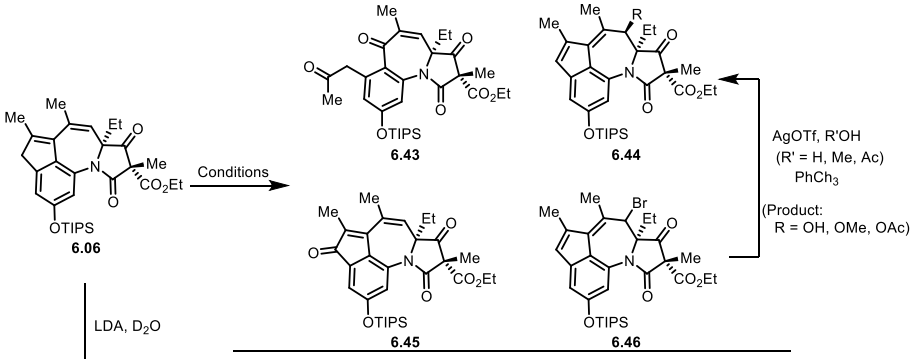


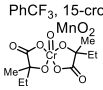
Scheme 6.14. Advancing tetracyclic diene **6.06** by benzylic oxidation

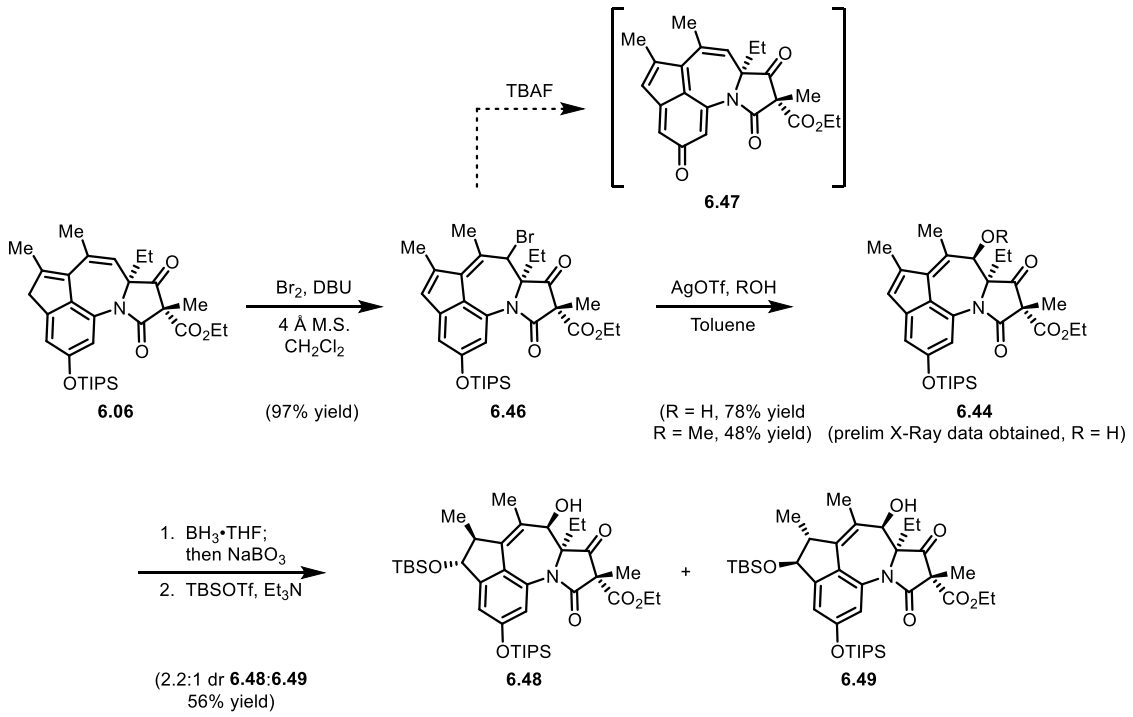
In investigating methods for benzylic oxidation (Scheme 6.14), a myriad of techniques were again available to us. Unfortunately, attempts to oxidize **6.06** often led to oxidative cleavage product **6.43**, as was the case with *m*CPBA or PCC[7] (Entries 1, 2, Table

6.1). Classical SeO_2 promoted allylic oxidation of **6.06** delivered benzylic alcohol **6.44** (R = OH, Entry 3).[8] Of note was a "Cr(V)" reagent popularized by the Baran laboratory which gave only trace quantities of tetracyclic ketone **6.45** (Entry 4).[9] Despite numerous attempts we were unable redirect the reaction away from the pathway leading to **6.44** (R = OH). The most efficient of these procedures however, was formation of allylic bromide **6.46** obtained upon exposure to Br_2 and DBU (entry 6), a compound less productively prepared by alternative methods (entries 7, 8). This bromide could be converted, in the presence of AgOTf and alcohol nucleophiles, to compounds **6.44** (R = OH, OMe, OAc) in excellent yields. It is also interesting to note that exposure of **6.06** to deuterated acids results in the formation of **6.42**, a diene configuration that acts as a thermodynamic sink with both olefins in conjugation with the aromatic ring.

Table 6.1. Efforts toward benzylic oxidation.



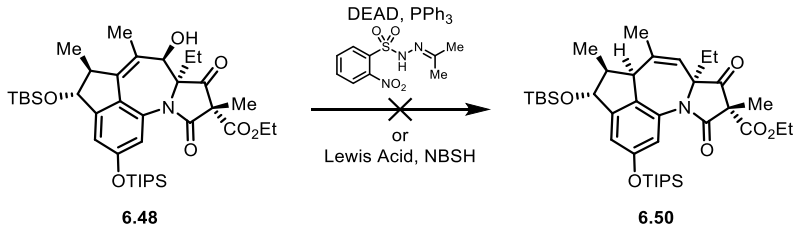
Entry	Reagent	Temperature	Result (%yield)
1	*m*CPBA, CH_2Cl_2	–78 °C to 0 °C	**6.43** (22%)
2	PCC, CH_2Cl_2	rt	**6.43** (33%)
3	SeO_2, dioxane	80 °C	**6.44** (R = OH) (12%)
4	$PhCF_3$, 15-crown-5, MnO_2  **"Cr(V)"**	80 °C	**6.45** (10%), **6.44** (R = OH) (18%)
5	NaHMDS, MoOPh, THF	–100 °C	**6.44** (R = H) (<10%)
6	Br_2, DBU	0 °C	**6.46** (97%)
7	KBr, Oxone, $MeNO_2$	50 °C	**6.46** (~40%)
8	LDA, NBS	–78 °C to 0 °C	**6.46** (<10%, determined by ^{1}H NMR)



Scheme 6.15. A hydroboration-oxidation to deliver a tetracyclic benzylic alcohol

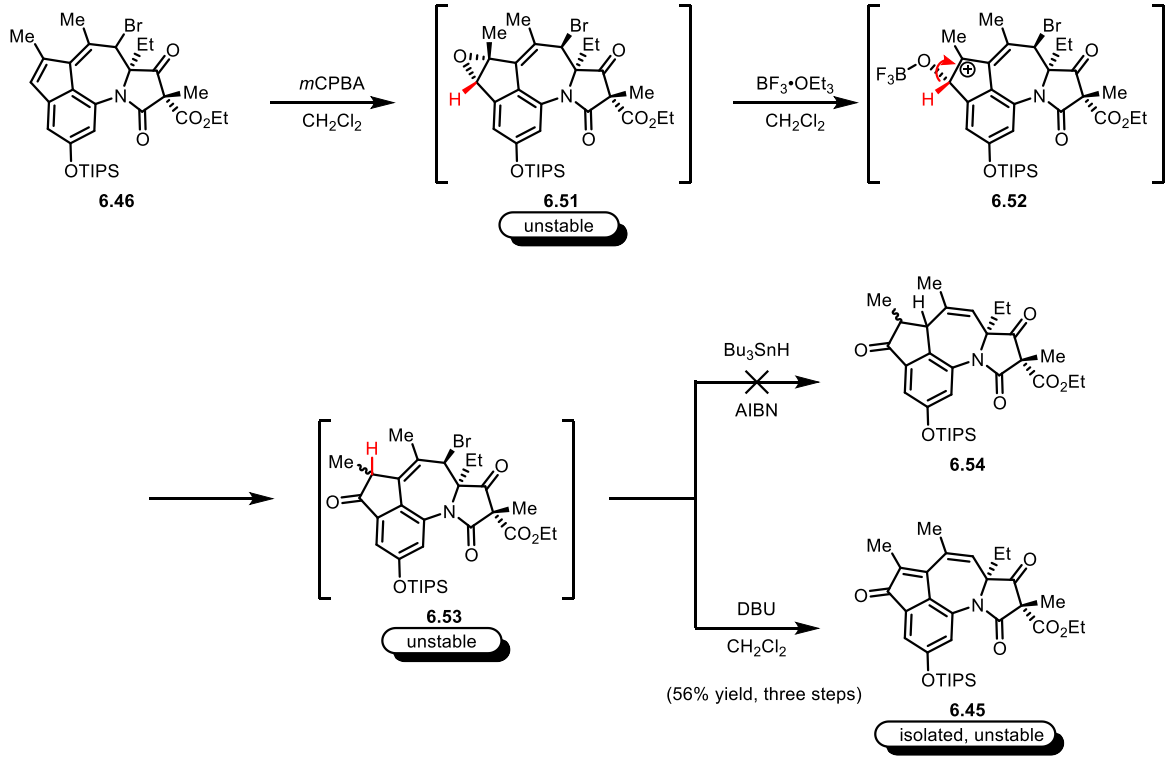
Although we were unable to directly oxidize **6.06** at the benzylic position, its conversion to allylic bromide **6.46** was highly efficient. Thus, as illustrated in Scheme 6.15 we began to explore a number of strategies for advancing this material. To this end, we attempted to form pentadienyl compound **6.47** by TBAF mediated removal of the TIPS group. While these conditions did furnish a product consistent with the desired quinone methide, it proved highly unstable and poorly soluble and thus was not further explored. Attempts to advance **6.46** by treatment with AgOTf in the presence of water or methanol efficiently gave **6.44** (R = H or CH_3) which was found to undergo hydroboration-oxidation[10] to deliver, after TBS protection, silyl ethers **6.48** and **6.49** as a 2.2:1 mixture of diastereomers. Stereochemical assignment of these compounds were made on the basis of ^{1}H NMR similarities to the identified isomers **6.61** and **6.62** (see Scheme 6.19) whose

stereochemistry were unambiguously determined by X-Ray analysis. Unfortunately, this analysis indicated that the major isomer possessed the incorrect stereochemistry at the newly generated benzylic and homobenzylic stereogenic centers. Nevertheless, we attempted to advance **6.48** via a reductive transposition of the allylic alcohol to give tetracycle **6.50**, but were unable to effect this transformation (scheme 6.16).[11]



Scheme 6.16. Attempts to effect reductive transposition of an allylic alcohol

In examining the hydroboration oxidation of indene **6.44** to TBS-ethers **6.48** and **6.49**, we surmised that we could exploit this α-face selectivity to deliver the desired methyl stereocenter preferentially by 1,2-hydride shift (Scheme 6.17). Accordingly, we exposed allylic bromide **6.46** to *m*CPBA which gave unstable epoxide **6.51** as a mixture of diastereomers that rearranged to ketone **6.53** with Lewis acid.[12] Attempts at a reductive transposition of allylic bromide **6.53** to **6.54** were unsuccessful, and gave evidence of *ipso* reduction. Alternatively, we could access tetracyclic dienyl ketone **6.45** by elimination of the bromide which gave us sufficient quantities of **6.45** for characterization.



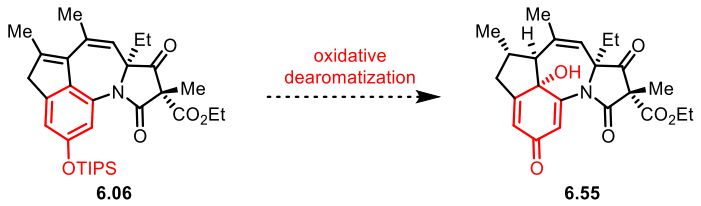
Scheme 6.17. A strategy to flip selectivity in indene oxidation

With **6.45** in hand, we were again faced with the problem of setting the benzylic methine stereocenter, possibly through 1,4-reduction. However, based on our previous studies we were skeptical of our ability to bias a favorable stereochemical outcome in the requisite nucleophilic addition. Some preliminary investigations were carried out on substrate **6.45** involving Luche reduction and hydroxy-directed hydrogenation, but these compounds all proved too unstable for further advancement (including **6.45**) and this route was abandoned.

6.4.3. Advancing a Tetracyclic Diene via Aryl Oxidation

With the grim outlook in both reduction and oxidation attempts, we turned our attention to the last of the three critical motifs that still needed to be installed: the *para*-

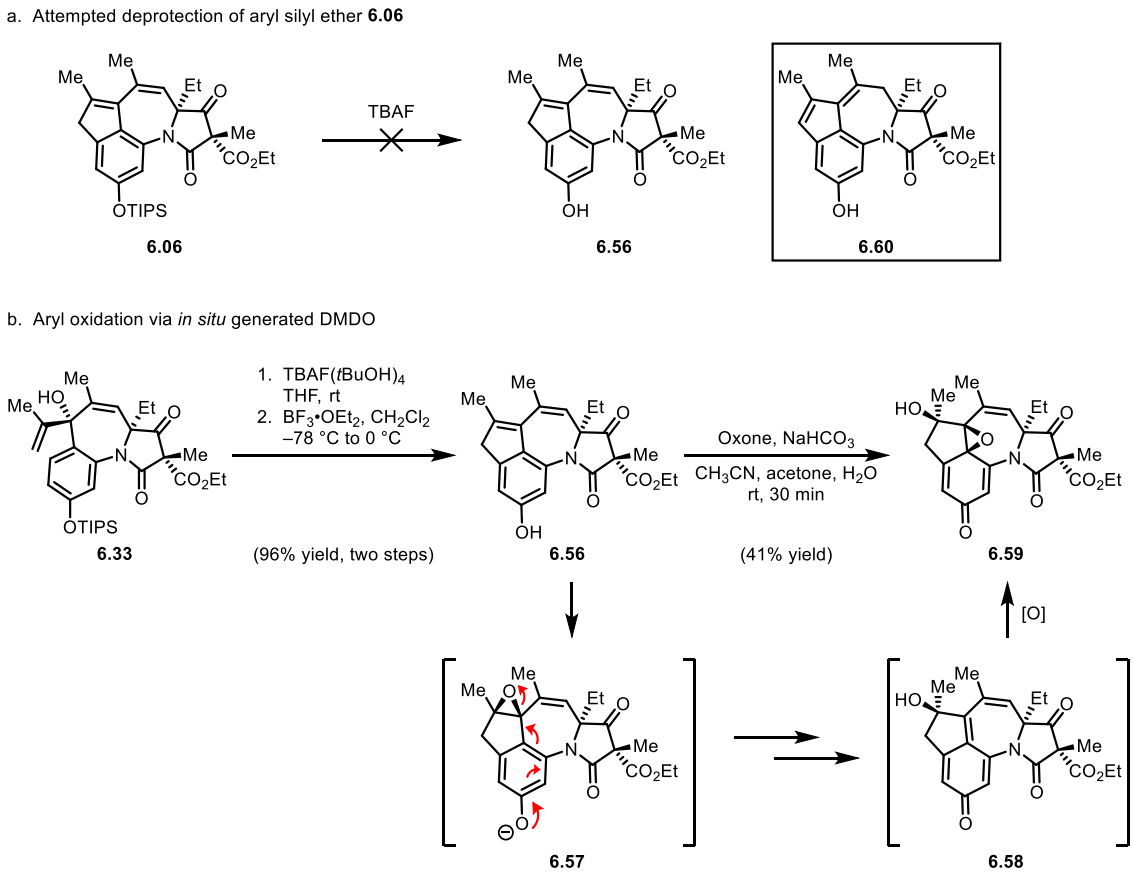
quinol moiety. Thus, we next explored an avenue for accessing *para*-quinol **6.55** from tetracyclic diene **6.06** (Scheme 6.18).



Scheme 6.18. Advancing tetracyclic diene **6.06** by aryl oxidation

Initial efforts to remove the TIPS protecting group and access the phenol required for aryl oxidation were plagued with the formation of **6.60** (Scheme 6.19a, top) whose azepine olefin had migrated out of the desired position. However, simply adjusting the order of events by removing the TIPS group on isopropenyl adduct **6.33** and then effecting the cation-π cyclization successfully provided phenol **6.56** in excellent yield (Scheme 6.19b, bottom). At this stage a variety of strategies to access a *para*-quinol were attempted, including: singlet oxygen generated *in situ* or with photosensitizers,[13] hypervalent iodine,[14] DDQ, CAN, or even Doyle's protocol.[15] Unfortunately, all these latter efforts led to complex mixtures that lacked evidence of the desired *para*-quinol. However, initial efforts to employ Carreño's protocol[16] for singlet oxygen formation led us to consider the use of *in situ* generated DMDO. Carreño's protocol discloses the decomposition of oxone into singlet oxygen under basic conditions ($NaHCO_3$) with acetonitrile and water as solvents. The lack of reactivity in this mixed solvent system was attributed to poor solubility, at which point a small amount of acetone was added. Rapid formation of a new product prompted reconsideration of the reaction conditions and the possible role of in situ

generated DMDO which led to the use of acetone as a co-solvent. Thus, under these new conditions, we found that **6.56** undergoes rapid conversion to spiroepoxide **6.59**.



Scheme 6.19. Novel formation of a spiroepoxide

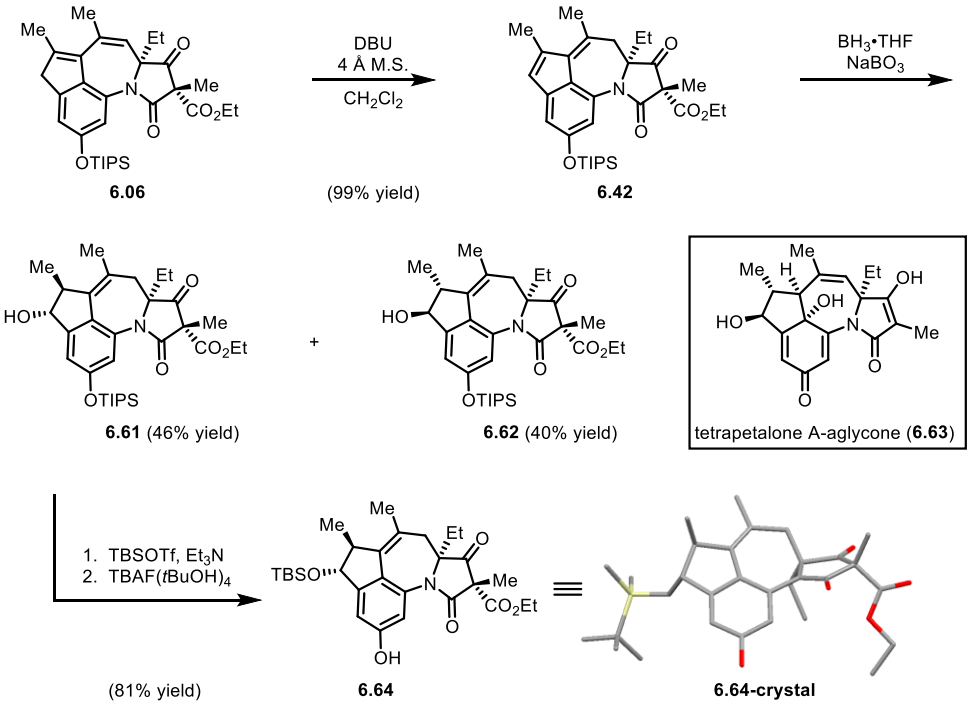
Mechanistically we envision the spiroepoxide as forming via epoxidation of the electron-rich indenyl double bond to furnish intermediate **6.57** which, following base promoted opening, generates an intermediate *para*-quinone methide **6.58**. Subsequent oxidation of **6.58** then delivers spiroepoxide **6.59**. Control experiments using distilled acetone solutions of DMDO in the presence of $NaHCO_3$ gave **6.59**, albeit in lower yields. Although this transformation certainly represented yet another remarkable reaction and delivered a complex spiroepoxide product, much like all of our earlier observations,

oxidation always occurred preferentially from the ß-face delivering the wrong stereochemical outcome and thereby a C-O bond that would be useless with regard to preparation the natural product.

6.5 An Olefin Isomerization Approach: Hydroboration-Oxidation and Spiroepoxide Formation

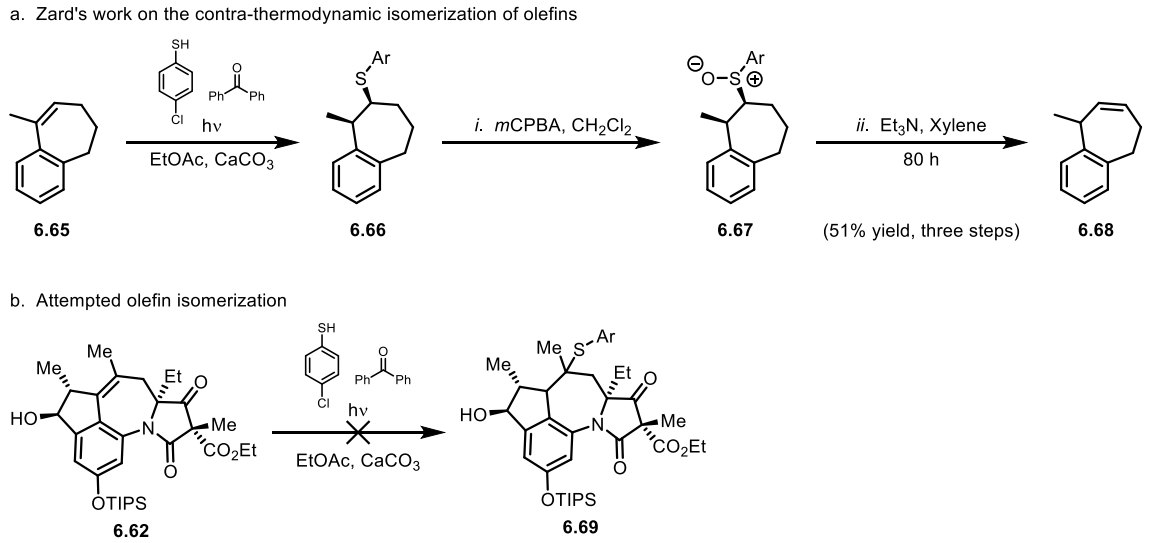
Our efforts to advance the tetracyclic diene **6.06** were consistently troubled by stability issues and thwarted by our inability to set the benzylic stereocenter. To access a more stable intermediate, and to capitalize on the knowledge we had gleaned in the previous section (section 6.4), we thought both about an olefin-isomerization technique and a possible hydroxy-directed spiroepoxidation.

Along these lines, as illustrated in Scheme 6.20, we were able to effect thermodynamic olefin isomerization to give stable diene **6.42** which underwent hydroboration-oxidation in excellent yield to provide diastereomeric products **6.61** and **6.62** in a near 1:1 ratio. Both products had the correct *trans*- configuration of the newly installed alcohol and adjacent methyl stereocenter, but one possesses the incorrect relative stereochemistry at the angular ethyl group (**6.61**, whose stereochemistry was unambiguously determined after X-ray analysis of derivative **6.64**) and one possesses the correct stereochemistry (**6.62**). In the context of the total synthesis all that was needed to advance tetracyclic alcohol **6.62** was a contra-thermodynamic isomerization of the alkene to the trisubstituted position in the 7-membered ring.



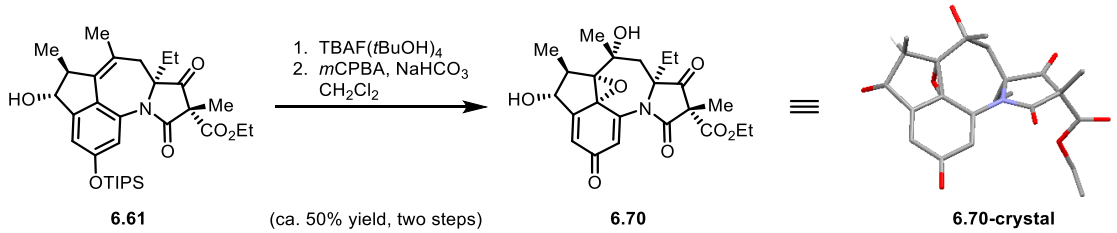
Scheme 6.20. Thermodynamic diene isomerization and advancing via hydroboration-oxidation

After surveying the literature for such a reaction we became intrigued by a report from Zard and coworkers describing the use of *para*-chlorothiophenol to induce contra-thermodynamic olefin isomerization (Scheme 6.21a, top).[17] As exemplified by substrate **6.65**, photochemical addition of the thiophenol across the double bond preferentially delivers *syn*- substituted product **6.66**. Oxidation with *m*CPBA followed by thermally induced elimination affords **6.68** selectively as a result of the required *syn*- elimination. Unfortunately, our attempts to employ a similar strategy on our substrate **6.62** failed to deliver the desired product **6.69**.



Scheme 6.21. Attempts to effect contra-thermodynamic olefin isomerization

In a last-ditch effort to advance a cation-π derived intermediate, we returned to the notion of advancing a spiroepoxide. To this end, we reasoned that an advanced substrate such as **6.61** (Scheme 6.22) was poised to deliver the desired *para*-quinol C-O bond with the proper stereochemistry via the use of a haptophilic reagent like *m*CPBA. Moreover, in this particular substrate the homobenzylic methyl group was expected to further bias this epoxidation away from the ß-face of the molecule. Indeed, upon exposure of the parent phenol derived from **6.61** to *m*CPBA under mildly basic conditions, we were able to obtain spiroepoxide **6.70** with the correct C-O bond stereochemistry present in the *para*-quinol motif. To advance this compound however, we would have to overcome significant challenges in what would be a lengthy sequence. Though this spiroepoxide formation was certainly a novel and fascinating transformation, and tetracyclic diene **6.06** has the appearance of promise toward advancing toward tetrapetalone A, we abandoned this approach and strategy in favor of alternatives.



Scheme 6.22. Substrate alteration to deliver the desired spiroepoxide stereochemistry

6.6 Experimental

General

Unless otherwise stated, reactions were magnetically stirred in flame or oven dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Diethyl ether, tetrahydrofuran, toluene, benzene, dichloromethane, and acetonitrile were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. ACS grade acetone (Fisher) was purchased from Fisher-Scientific and used as received. Dimethyl formamide and 1,2-dichloroethane (DCE) were purchased from Sigma-Aldrich and used as received. $Pd(PPh_3)_4$ was purchased from Sigma-Aldrich and stored under nitrogen in a -20°C freezer. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Millipore glass-backed 60Å plates (indicator F-254s, 150-180 µm thickness) (Millipore, catalogue #1164850001). Column or flash chromatography was performed with the indicated solvents using Millipore Silica Gel 60 (0.040-0.063 mm, 230-400 mesh ASTM) as the stationary phase. MPLC purifications were performed on a Telodyne Isco Combi*Flash*® *Rf*+ (Model: RF + UV-VIS MS COMP), used with standard Telodyne Isco normal phase disposable columns for flash chromatography and monitored at wavelengths

of 254 and 280 nm. All melting points were obtained on a Chemglass Life Sciences melting point device (Model: DMP100) and are uncorrected. Infrared spectra were obtained using a Bruker Alpha ATR-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, Varian 500, or Bruker 600. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million (ppm) relative to internal residual solvent peaks from the indicated deuterated solvents (^{1}H: For $CDCl_3$, $CHCl_3$ 7.26; For Methanol-d_4, CD_2HOD 3.31; For Acetone-d_6, Acetone-D5H 2.05). Chemical shifts (δ) for ^{13}C spectra were referenced from the indicated solvent peaks (^{13}C: $CDCl_3$ 77.16, Methanol-d_4 49.00, Acetone-d_6 29.84). Chemical shifts in ^{19}F spectra were taken in $CDCl_3$ doped with fluorobenzene and referenced to -113.15. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as s = singlet, br.s = broad singlet, d = doublet, br. d = broad doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High resolution mass spectra were performed on a Thermo LTQ Orbitrap Discovery with direct injection followed by electro-spray ionization (ESI). Microwave reactions were carried out using a CEM Discover SP Microwave system. Single crystal X-ray diffraction studies were collected on a Bruker Apex II-CCD detector using Mo-K_α radiation (λ = 0.71073 Å). Structures were solved and refined using SHELXTL. Optical rotations were obtained on a Rudolph Research Analytical Autopol IV Automatic Polarimeter.

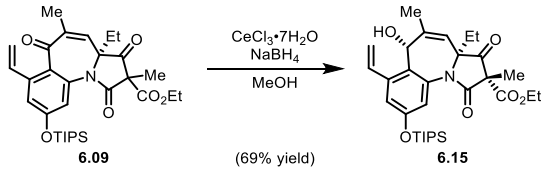
High-Performance Liquid Chromatography (HPLC): All HPLC purifications were carried out on a Waters HPLC system (consisting of a Waters 1525 binary HPLC pump

with direct injection port and monitored at 254 nm unless otherwise specified with a Waters 2489 UV-Visible detector). All purifications utilized a normal-phase Sunfire, Silica Prep 10 µm, 10 x 250 mm column.

Ultra Performance Liquid Chromatography (UPLC)-Mass Spectrometry (MS): All UPLC-MS experiments were carried out on a Waters Acquity H UPLC Class system using the indicated solvent systems as eluents. All separations were performed on a reverse phase Acquity UPLC BEH C18 1.7 µm, 2.1 x 50 mm column.

^{1}H and ^{13}C NMR spectra are included for all previously unreported compounds.

Benzylic alcohol **6.15**



Experimental: To a rbf was added **6.09** (90.0 mg, 0.163 mmol) and this dissolved in MeOH (3.25 mL) followed by the addition of $CeCl_3$•$7H_2O$ (79.0 mg, 0.211 mmol). The solution was then cooled to –20 °C in a dry-ice/acetone bath. After stirring for 15 min, $NaBH_4$ (8.6 mg, 0.23 mmol) was added and the reaction mixture was stirred at this same temperature for 30 min. The reaction was then diluted with saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography on silica gel (10:1→8:1 hexanes:EtOAc) to afford benzylic alcohol **6.15** (61.9 mg, 69% yield) as a white, sticky, amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.95 (d, *J* = 2.5 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 5.77 (s, 1H), 5.40 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.23 (d, *J* = 11.0 Hz, 1H), 5.11 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.77 (m, 1H), 1.94 (s, 3H), 1.80 (dq, *J* = 14.7,

7.4 Hz, 1H), 1.55 (s, 3H), 1.50-1.38 (m, 1H), 1.32-1.18 (m, 6H), 1.10 (d, J = 7.2 Hz, 18H), 0.82 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 205.4, 169.7, 165.7, 155.1, 142.1, 137.5, 136.8, 132.8, 132.1, 120.3, 120.0, 119.6, 115.5, 74.9, 69.8, 62.7, 58.5, 30.1, 20.4, 18.8, 18.0, 14.0, 12.7, 7.9.

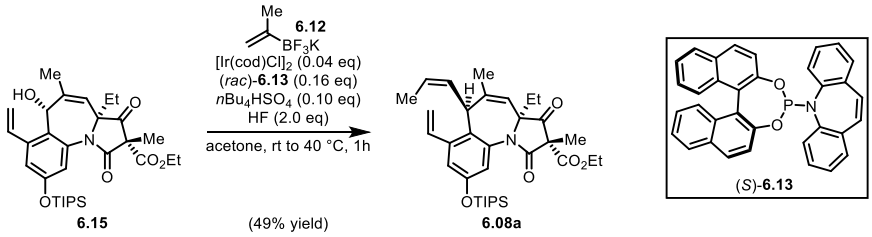
IR (thin film): 3742, 2944, 2867, 1775, 1688, 1597, 1567, 1460, 1387, 1303, 1232, 1210, 1108, 998 cm^{-1}.

HRMS (ESI+): calculated for $C_{31}H_{46}NO_6Si^+$ $[M+H]^+$ 556.3089, found: 556.3085.

TLC: 0.43 (5:1 Hexanes:EtOAc)

Physical Appearance: White amorphous, sticky solid.

Z-olefin containing styrene **6.08a**



Experimental: To a screw cap vial was added bis(1,5-cyclooctadiene)diiridium (I) dichloride (0.5 mg, 0.7 μmol) and (*rac*)-**6.13** (1.5 mg, 2.9 μmol). The vial was left under hi-vac for 30 min the backfilled with N_2. To the vial was then added degassed acetone (0.5 mL) and the solution was stirred vigorously for 15 min at room temperature. To the resulting orange solution were then added a solution of alcohol **6.15** (10.0 mg, 0.018 mmol) in acetone (0.3 mL), potassium trifluoroborate salt **6.12** (5.3 mg, 0.036 mmol), tetra *n*butyl ammonium hydrogen sulfate (0.6 mg, 1.8 μmol), and hydrogen fluoride (2.0 μL, 0.054 mmol, 48% in H_2O). The reaction mixture was placed in a preheated oil bath at 40 °C and stirred for 1 h. The solvent was subsequently removed under reduced pressure, and the

crude residue purified by flash column chromatography on silica gel (20:1 hexanes:EtOAc) to give *Z*-olefin product **6.08a** (5.1 mg, 49% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (dd, *J* = 17.2, 10.9 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 5.49 (app. dd, *J* = 17.2, 1.4 Hz, 1H), 5.45 - 5.23 (m, 4H), 4.45 (d, *J* = 9.8 Hz, 1H), 4.26 (qd, *J* = 7.1, 3.3 Hz, 2H), 1.93 – 1.80 (m, 4H), 1.71 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.61 (s, 3H), 1.59 - 1.48 (m, 1H), 1.31-1.20 (m, 6H), 1.10 (d, *J* = 7.0 Hz, 18H), 0.83 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 206.5, 168.9, 165.9, 154.9, 139.5, 139.0, 135.2, 134.8, 130.2, 130.0, 124.7, 123.4, 120.7, 119.5, 118.5, 74.5, 62.6, 58.2, 42.6, 29.7, 26.4, 18.8, 18.0, 14.0, 13.6, 12.8, 8.7.

IR (thin film): 2942, 2867, 1775, 1748, 1706, 1600, 1573, 1461, 1383, 1300, 1237, 1164, 1112, 1002 cm^{-1}.

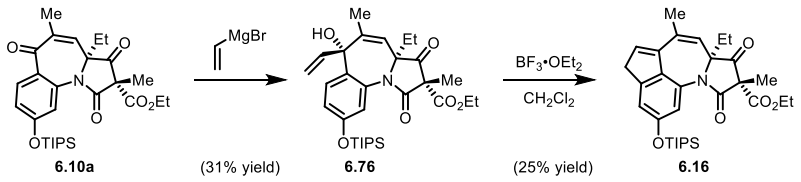
HRMS (ESI+): calculated for $C_{34}H_{50}NO_5Si^+$ $[M+H]^+$ 580.3453, found: 580.3452.

TLC: 0.75 (5:1 hexanes:EtOAc)

Physical Appearance: Colorless oil.

Tetracyclic diene **6.16**

Note: In order to obtain sufficient quantities of analytically pure material for characterization, the following protocol was used to make material (**6.16**) whose ^{1}H NMR and HRMS were identical to the other procedures listed below.



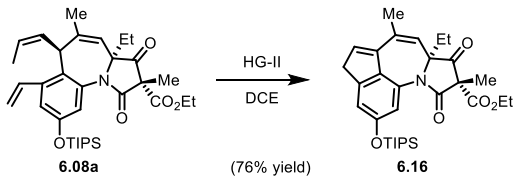
Experimental: **Preparation of 6.76**: To a rbf containing enone **6.10a** (44 mg, 0.083 mmol) dissolved in THF (2.0 mL) cooled to –78 °C in a dry-ice acetone bath was added

vinyl magnesium bromide (0.13 mL, 0.13 mmol, 1.0 M solution in THF). The reaction was stirred for 45 min in the dry-ice acetone bath then warmed in an ice water bath, stirred for an additional 10 min, then quenched by pouring into a separatory funnel containing saturated aqueous $NaHCO_3$ and Et_2O. The aqueous layer was extracted with Et_2O (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude residue that was purified by MPLC (0%→30% EtOAc in hexanes, 30 mL/min, 10 min run time, 4g column) to give benzylic alcohol **6.76** (14.4 mg, 31% yield). The mass balance mostly entailed recovered starting material.

Preparation of 6.16 from 6.76:

A rbf containing **6.76** (7.2 mg, 0.013 mmol) was azeotroped with with toluene (2x) and placed under hi-vac for 3 h. After 3 h, this was dissolved in CH_2Cl_2 (2.0 mL) and cooled to –78 °C in a dry-ice acetone bath. After cooing, to this was added BF_3•OEt_2 (4 µL). The reaction was stirred for 15 min at –78 °C then 10 min at 0 °C during which time the reaction turns to an orange solution. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a blue oil. The crude residue was purified by pipette column (0%→5%→10%→20% EtOAc in hexanes) to give unstable tetracyclic diene **6.16** (1.8 mg, 3.3 µmol, 26% yield) as an orange oil.

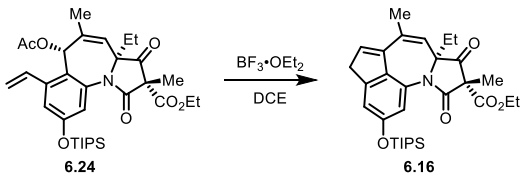
Alternative Preparation of 6.16 via RCM:



Experimental: To a rbf containing diene **6.08a** (5.7 mg, 9.8 µmol) was dissolved in degassed DCE (0.2 mL). After the addition of Grubbs 2nd generation catalyst (0.8 mg, 0.98

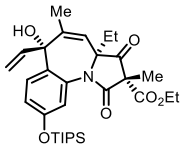
μmol) the mixture was heated to 40 °C. After 6 h, the reaction mixture was heated to 60 °C and let stir overnight. The solvent was then removed and the crude residue purified by pipette column (isochratic 9% EtOAc in hexanes) to give tetracyclic diene **6.16** (4.0 mg, 7.4 μmol, 76% yield). The ^{1}H and HRMS data were identical to those as described above in the alternate preparation of **6.16**.

Alternative Preparation of 6.16 via cation-π cyclization:



Experimental: To a rbf containing benzylic acetate **6.24** (2.3 mg, 3.9 μmol) was added xylenes (~0.4 mL) and this concentrated under hi-vac. The resulting residue was dissolved in DCE (1.0 mL) and placed in an oil bath preheated to 50 °C. After 3 min, BF_3•OEt_2 (0.1 mL, solution prepared by the addition of 0.01 mL neat BF_3•OEt_2 in 1.0 mL DCE) was added in one shot. The reaction turned red/orange for a moment which dissipated to give a faint orange solution. This was stirred for 10 min, cooled to room temperature, and quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude orange oil whose ^{1}H NMR and HRMs were identical to the compounds prepared by the above two methods.

Benzylic alcohol 6.76



^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69 – 7.66 (m, 1H), 6.96 – 6.92 (m, 2H), 5.93 (dd, *J* = 17.1, 10.3 Hz, 1H), 5.54 (d, *J* = 1.6 Hz, 1H), 5.08 – 4.98 (m, 2H), 4.32 – 4.20 (m, 2H), 2.00 (br. s, 1H), 1.97 (d, *J* = 1.4 Hz, 3H), 1.80 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.57 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.53 (s, 3H), 1.32 – 1.22 (m, 6H), 1.10 (dd, *J* = 7.5, 1.7 Hz, 18H), 0.78 (t, *J* = 7.5 Hz, 3H).

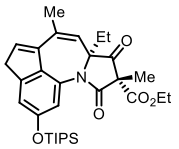
^{13}C NMR (151 Hz, $CDCl_3$): δ 205.8, 168.0, 165.8, 156.1, 141.8, 140.5, 134.1, 132.7, 127.2, 124.2, 120.8, 120.3, 113.9, 77.1, 74.1, 62.7, 58.1, 30.5, 22.4, 18.0, 17.7, 14.0, 12.7, 8.5.

IR (thin film): 3467, 2944, 2868, 1776, 1748, 1710, 1695, 1606, 1574, 1499, 1456, 1429, 1382, 1297, 1236, 1110, 986, 856 cm^{-1}.

HRMS (ESI+): calculated for $C_{31}H_{45}NO_6SiNa^+$ $[M+Na]^+$ 578.2908, found: 578.2905.

TLC: 0.27 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.



Tetracyclic diene 6.16 **6.16**

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (d, *J* = 2.2 Hz, 1H), 6.97 – 6.93 (m, 1H), 6.43 (t, *J* = 2.5 Hz, 1H), 5.61 (s, 1H), 4.31 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.22 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.50 – 3.36 (m, 2H), 2.08 – 2.01 (m, 4H), 1.79 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.61 (s, 3H), 1.34 – 1.26 (m, 6H), 1.13 (dd, *J* = 7.5, 2.3 Hz, 18H), 0.77 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 207.5, 168.3, 165.9, 154.7, 146.8, 141.3, 134.0, 131.2, 129.3, 129.1, 127.5, 115.5, 115.1, 76.1, 62.6, 58.8, 38.1, 29.5, 22.4, 18.8, 18.09, 18.07, 14.0, 12.8, 8.6.

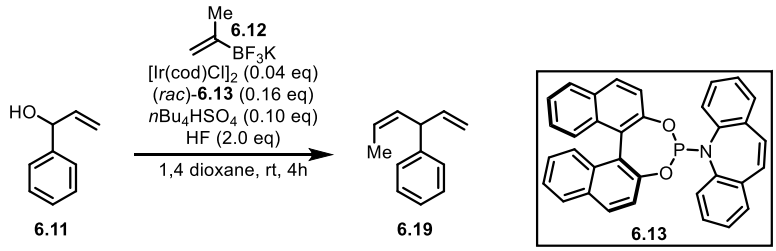
IR (thin film): 2943, 2867, 1777, 1748, 1708, 1608, 1589, 1466, 1385, 1289, 1385, 1289, 1230, 1131, 996 883 cm^{-1}.

HRMS (ESI+): calculated for $C_{31}H_{43}NO_5SiNa^+$ $[M+Na]^+$ 560.2803, found: 560.2799.

TLC: 0.33 (10% EtOAc in hexanes).

Physical Appearance: Faint orange oil.

Tetracyclic diene **6.16**



Experimental: A procedure with identical starting materials were used as reported by Carreira. However, (*rac*)-**6.13** was used as ligand instead of an enantiopure variant.

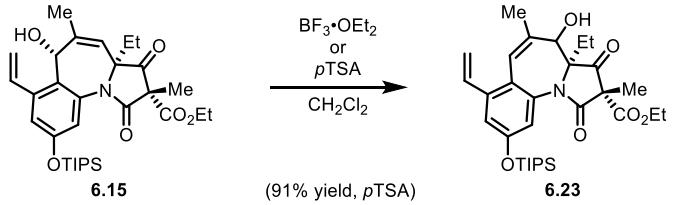
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 2H), 7.28 – 7.16 (m, 3H), 6.06 – 5.93 (m, 1H), 5.70 – 5.53 (m, 2H), 5.17 – 5.10 (m, 1H), 5.10 (br. s, 1H), 4.38 (t, *J* = 7.5 Hz, 1H), 1.74 – 1.68 (m, 3H).

Literature Report: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 2H), 7.26 – 7.18 (m, 3H), 6.05 – 5.95 (m, 1H), 5.68 – 5.54 (m, 2H), 5.14 (dt, *J* = 7.4, 1.5 Hz, 1H), 5.10 (d, *J* = 1.5 Hz, 1H), 4.38 (t, *J* = 7.4 Hz, 1H), 1.76 – 1.67 (m, 3H)

^{13}C NMR (101 Hz, $CDCl_3$): δ 143.8, 140.5, 131.8, 128.6, 127.8, 126.3, 124.7, 114.7, 46.8, 13.2 (referenced to $CDCl_3$ at 77.16 ppm)

Literature Report: **^{13}C NMR** (100 Hz, $CDCl_3$): δ 143.6, 140.4, 131.6, 128.5, 127.6, 126.2, 124.6, 114.5, 46.6, 13.0 (referenced to $CDCl_3$ at 77.0 ppm).

Allylic alcohol **6.23**



Experimental: To a rbf was added **6.15** (5.3 mg, 9.5 μmol) was added CH_2Cl_2 (1.0 mL) and to this was added *p*TSA•H_2O (2.2 mg, 11 μmol). The reaction turns faint yellow and was stirred for 10 min then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a cololess oil. The crude residue was purified by pipette column (0%→10%→20%→30% EtOAc in hexanes) to give **6.23** (4.8 mg, 91% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (d, *J* = 2.5 Hz, 1H), 7.00 (dd, *J* = 17.2, 10.8 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.56 (s, 1H), 5.50 (d, *J* = 17.2 Hz, 1H), 5.39 (d, *J* = 10.9 Hz, 1H), 4.30 (d, *J* = 8.5 Hz, 1H), 4.30 – 4.18 (m, 2H), 2.07 (s, 3H), 2.01 (d, *J* = 9.0 Hz, 1H), 1.77 (dq, *J* = 14.8, 7.3 Hz, 1H), 1.69 (s, 3H), 1.59 – 1.51 (m, 1H, overlap with H_2O), 1.33 – 1.24 (m, 6H), 1.12 (d, *J* = 7.5 Hz, 18H), 0.73 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 207.7, 171.5, 165.6, 155.7, 141.2, 136.1, 135.3, 134.1, 123.2, 120.6, 118.6, 118.5, 118.1, 77.3, 62.9, 59.9, 25.1, 23.5, 18.0, 18.0, 17.4, 14.1, 12.8, 8.6.

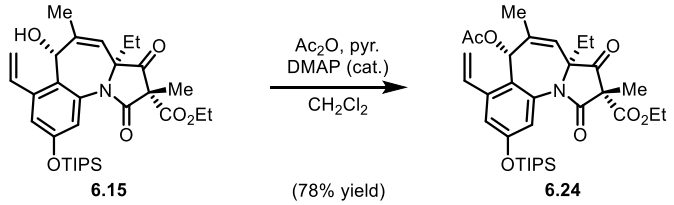
IR (thin film): cm^{-1} 339, 2944, 2867, 1777, 1744, 1694, 1595, 1563, 1460, 1380, 1300, 1242, 1202, 1124, 1000, 882, 768, 688.

HRMS (ESI+): calculated for $C_{31}H_{45}NO_6SiNa^+$ $[M+Na]^+$ 578.2908, found: 578.2914.

TLC: 0.28 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Allylic acetate **6.24**



Experimental: To a rbf was added benzylic alcohol **6.15** (5.0 mg, 9.0 μmol) and dissolved in CH_2Cl_2 (1.0 mL). To this was added pyridine (20 μL, 0.25 mmol), acetic anhydride (0.015 mL, 0.16 mmol), and DMAP (catalytic quantity, tip of pipette). The reaction was stirred at room temperature for 4 h then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were washed with 5% aqueous $CuSO_4$, dried over $MgSO_4$, filtered, and concentrated to a colorless oil. This was concentrated under reduced pressure to give a crude residue that was purified by pipette column (0%→10%→20% EtOAc in hexanes) to give benzylic acetate **6.24** (4.2 mg, 78% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 17.2, 10.8 Hz, 1H, overlap with $CHCl_3$), 6.97 (d, *J* = 2.5 Hz, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.75 (s, 1H), 5.42 (d, *J* = 17.3 Hz, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 5.21 (s, 1H), 4.33 – 4.21 (m, 2H), 2.15 – 2.12 (m, 3H), 1.90 – 1.81 (m, 1H), 1.79 (s, 3H), 1.75 (s, 3H), 1.47 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.32 – 1.23 (m, 6H), 1.11 (d, *J* = 7.4 Hz, 18H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.4, 169.6, 169.6, 165.9, 155.5, 138.8, 137.3, 136.8, 133.3, 128.5, 122.0, 120.1, 115.4, 74.7, 70.8, 62.7, 58.7, 30.3, 20.9, 20.3, 19.0, 18.0, 14.0, 12.8, 7.9.

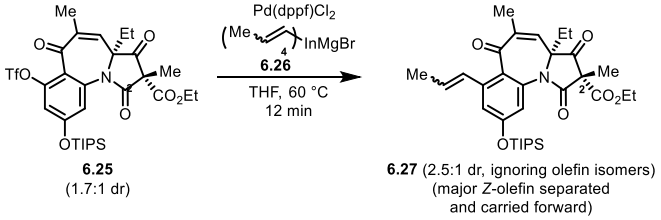
IR (thin film): 2945, 2868, 1776, 1749, 1713, 1599, 1464, 1380, 1367, 1229, 1183, 1046 cm^{-1}.

HRMS (ESI+): calculated for $C_{33}H_{47}NO_7SiNa^+$ $[M+Na]^+$ 620.3014, found: 620.3009.

TLC: 0.35 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

ß-Methyl Styrene **6.27**

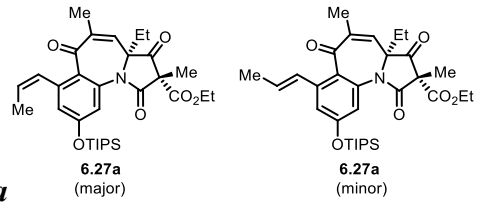


Experimental: To a 50 mL pear flask was added $InCl_3$ (98.6 mg) and this heated by heat-gun under hi-vac. After cooling to room temperature, this was reweighed as having $InCl_3$ (94.2 mg, 0.426 mmol). To this was added THF (0.85 mL) and cooled to –78 °C in a dry-ice/acetone bath. After cooling, 1-propenylmagnesium bromide (3.40 mL, 1.70 mmol, 0.5 M solution in THF) was added dropwise over the course of 2 min. This was stirred for an additional 30 min in the dry-ice/acetone bath to create a 0.1 M solution of the tetraorganoindate complex **6.26**.

In a separate flame dried 100 mL rbf was added $PdCl_2(dppf)\bullet CH_2Cl_2$ (82.0 mg, 0.100 mmol) and the flask then purged with a stream of N_2 for 10 min. After 10 min, to this was added triflate **6.25** (652.9 mg, 0.966 mmol, 1.7:1 dr, major depicted) as a solution in THF (8.5 mL) by syringe to create and orange suspension. After 5 min, the tetraorganoindate solution **6.26** (4.26 mL, 0.44 mmol, 0.1 M solution in THF) was transferred into the solution of triflate by syringe and the reaction then placed immediately in a pre-heated oil bath at 63 °C. Upon addition of the indate complex, the solution turns red then into a red/orange clear solution. Careful monitoring of the reaction mixture by TLC shows the reaction was complete when the reaction had turned sharply black (~12 min). The reaction was immediately cooled in an ice-water bath and quenched by pouring

the reaction mixture into a 125 mL separatory funnel containing saturated aqueous $NaHCO_3$ (40 mL) and EtOAc (40 mL). The aqueous layer was extracted with EtOAc (3x), the combined organics washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subject to purification by flash column chromatography on silica gel (75:20:5 hexanes:CH_2Cl_2:EtOAc) to give ß-methyl styrene **6.27** (433.4 mg, 79% yield, 2.5:1 dr neglecting olefin isomers) as a colorless oil.

Note: To obtain analytically pure samples for characterization, the mixture was subject to HPLC purification (10 mL/min, isochratic 5% EtOAc in hexanes). Only the major diastereomers **6.27a** are characterized below.



Major Diastereomers 6.27a

Note: Only the major (*Z*)-olefin isomer peaks are listed (as determined by coupling constants).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.88 – 6.83 (m, 2H), 6.45 – 6.39 (m, 1H), 6.27 (q, *J* = 1.4 Hz, 1H), 5.76 (dq, *J* = 11.6, 7.1 Hz, 1H), 4.34 – 4.21 (m, 2H), 2.04 – 1.95 (m, 1H), 2.00 (d, *J* = 1.4 Hz, 3H), 1.75 – 1.64 (m, 1H), 1.70 (dd, *J* = 7.1, 1.8 Hz, 3H), 1.57 (s, H_2O), 1.55 (s, 3H), 1.32 – 1.23 (m, 6H), 1.12 (dd, *J* = 7.5, 2.0 Hz, 18H), 0.89 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 204.8, 192.4, 169.0, 165.4, 158.0, 140.8, 138.7, 136.7, 133.5, 130.8, 128.5, 127.4, 122.7, 117.9, 76.8, 62.9, 58.1, 28.1, 21.0, 19.2, 17.9, 14.4, 14.0, 12.8, 8.5.

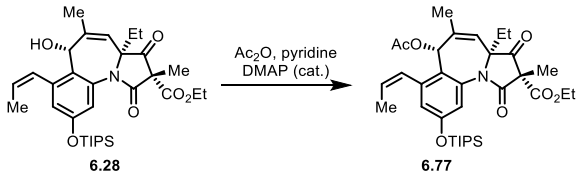
IR (thin film): 2945, 2868, 1780, 1750, 1716, 1654, 1594, 1463, 1371, 1293, 1237 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{45}NO_6SiNa^+$ $[M+Na]^+$ 590.2908, found: 590.2910.

TLC: 0.26 (75:22:3 hexanes:CH_2Cl_2:EtOAc).

Physical Appearance: Colorless oil.

Benzylic acetate **6.77**



Experimental: To a rbf containing benzylic alcohol **6.28** (10 mg, 0.018 mmol) was added pyridine (0.2 mL, 2.47 mmol), acetic anhydride (0.2 mL, 2.12 mmol), and lastly DMAP (catalytic quantity, not measured, tip of pipette). The reaction was stirred for 2 h after which the reaction was concentrated under reduced pressure and azeotroped with toluene (1x, 25 °C bath temperature, ~60 torr). This was then placed under hi-vac followed by purification by pipette column (0%→5%→10%→20% EtOAc in hexanes) to give **6.77** (8.9 mg, 83% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.84 (d, *J* = 2.6 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 6.67 (s, 1H), 6.65 – 6.60 (m, 1H), 5.71 (dq, *J* = 11.4, 7.0 Hz, 1H), 5.22 – 5.17 (m, 1H), 4.33 – 4.21 (m, 2H), 2.09 (s, 3H), 1.86 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.77 – 1.75 (br. m, 3H), 1.74 (s, 3H), 1.65 (dd, *J* = 7.0, 1.8 Hz, 3H), 1.58 (s, H_2O), 1.49 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.32 – 1.21 (m, 6H), 1.10 (d, *J* = 7.4 Hz, 18H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.5, 169.7, 169.5, 165.9, 155.0, 139.0, 135.6, 133.3, 130.4, 129.2, 124.7, 123.0, 121.9, 119.4, 74.6, 70.6, 62.7, 58.7, 30.3, 20.8, 20.5, 19.0, 18.0, 14.2, 14.0, 12.7, 7.9.

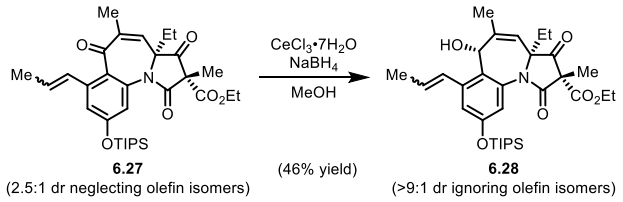
IR (thin film): 2943, 2867, 1775, 1747, 1712, 1599, 1464, 1379, 1304, 1228, 1180, 1010, 883 cm^{-1}.

HRMS (ESI+): calculated for $C_{34}H_{49}NO_7SiNa^+$ $[M+Na]^+$ 634.3171, found: 634.3171.

TLC: 0.39 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

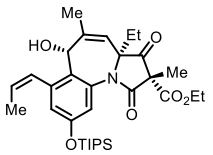
Benzylic alcohol **6.28**



Experimental: A rbf containing ß-methyl styrene mixture **6.27** (112.8 mg, 0.199 mmol, 2.5:1 dr neglecting olefin isomers, major depicted) was azeotroped with toluene (2x) and placed under hi-vac for 1 h. This was then placed under an atmosphere of N_2 followed by the addition of MeOH (2.65 mL). To this was then added $CeCl_3$ (53.9 mg, 0.219 mmol, anhydrous) and cooled to 0 °C in an ice-water bath. After cooling, $NaBH_4$ (8.3 mg, 0.219 mmol) was added in one shot. After stirring for 1 h at 0 °C, an additional $CeCl_3$ (26 mg, 0.11 mmol) and $NaBH_4$ (4.0 mg, 0.11 mmol) was added and stirred for an additional 1 h. The reaction was then quenched by the addition of saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography on silica gel (5%→10%→20% EtOAc in hexanes) to give benzylic alcohol **6.28** (52.2 mg, 46% yield containing >90% of the depicted isomers) as a colorless oil along with recovered **6.27** (12.4 mg, 11% recovery enriched in the minor lactam diastereomer, i.e. the ethyl and ethyl ester are trans, ~1:7).

Note: The product **6.28** was found to be prone to oxidation back to **6.27** in air which diminished the yield. In addition, the use of strictly anhydrous conditions is not necessary and in one instance was found empirically to slightly improve the yield and hence is the condition reported here. This slight increase in yield could possibly be attributed to

variation due to the instability of the product. In addition, the sample was purified by HPLC (10%→20% EtOAc in hexanes, 10 mL/min, 10 min run time, normal phase) to obtain the major isomer which is characterized below. The olefin geometry was determined by coupling constants.



6.28a

Major diastereomer 6.28a

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.84 (d, *J* = 2.5 Hz, 1H), 6.79 (d, *J* = 11.2 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 5.89 (dq, *J* = 11.2, 6.7 Hz, 1H), 5.74 (d, *J* = 6.8 Hz, 1H), 5.18 (s, 1H), 4.32 – 4.21 (m, 2H), 2.67 (d, *J* = 6.9 Hz, 1H), 1.90 (s, 3H), 1.84 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.68 – 1.62 (m, 6H), 1.48 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.31 – 1.21 (m, 6H), 1.10 (d, *J* = 7.4 Hz, 18H), 0.84 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.6, 169.5, 165.8, 154.9, 142.1, 134.9, 133.1, 132.3, 129.7, 128.5, 122.6, 120.8, 119.4, 74.8, 70.4, 62.8, 58.5, 30.2, 20.8, 18.9, 18.0, 14.3, 14.0, 12.7, 8.0.

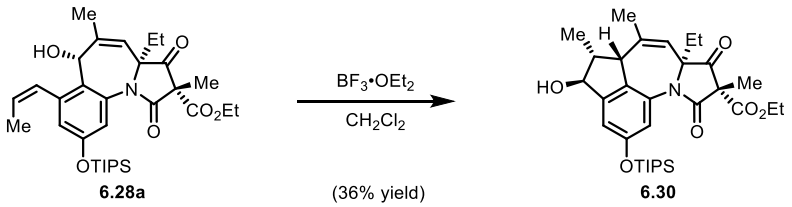
IR (thin film): 3468, 2944, 2867, 1775, 1748, 1710, 1692, 1597, 1571, 1463, 1304, 1231, 1110, 1010 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_6SiNa^+$ $[M+Na]^+$ 592.3065, found: 592.3065.

TLC: 0.34 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Tetracyclic alcohol **6.30**



Experimental: To a rbf was added **6.28a** (13.0 mg, 0.023 mmol) and dissolved in CH_2Cl_2 (1.0 mL) followed by the addition of BF_3•OEt_2 (30 µL). The reactino was stirred under argon for 20 min after which the initial dark red/brown solution turned orange/red. To this was added MeOH (1.0 mL, hydrous) and stirred for 5 min (turns faint orange). This was then quenched by the addition of diH_2O and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a faint red oil. This was then filtered through a plug of SiO_2, eluting with Et_2O, concentrated, then purified by HPLC (10 mL/min, linear gradient from 0% to 100% EtOAc in hexanes, 12 min runtime) to give **6.30** (4.7 mg, 36% yield) as a faint orange oil.

Note: Analysis of the crude NMR and mass indicates excellent conversion to **6.30**, however the low recovery from purification has been attributed to the poor stability of **6.30** which readily oxidized in air.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 2.2 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 5.59 – 5.55 (m, 1H), 4.69 – 4.64 (m, 1H), 4.34 – 4.17 (m, 3H), 2.74 – 2.65 (m, 1H), 1.90 (dq, *J* = 14.4, 7.1 Hz, 1H), 1.80 (s, 3H), 1.61 (s, 3H), 1.51 – 1.40 (m, 1H), 1.33 – 1.23 (m, 6H, overlap with grease), 1.11 (d, *J* = 7.0 Hz, 18H), 0.79 – 0.71 (m, 6H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 207.3, 168.4, 165.8, 156.2, 146.2, 136.3, 133.5, 129.0, 127.1, 119.0, 117.2, 79.6, 75.3, 62.6, 58.6, 50.6, 46.2, 30.9, 24.0, 19.1, 18.0, 13.9, 13.2, 12.7, 8.9.

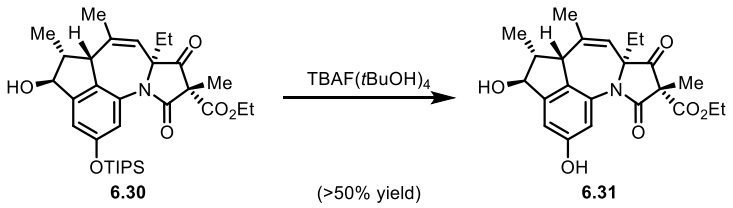
IR (thin film): 3427, 2942, 2867, 1776, 1748, 1704, 1591, 1478, 1392, 1372, 1232, 1014, 882, 731 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{48}NO_6Si^+$ $[M+H]^+$ 570.3245, found: 570.3244.

TLC: 0.33 (30% EtOAc in hexanes).

Physical Appearance: Faint yellow oil (air sensitive, turns red/orange over time when exposed to air).

Phenol **6.31**



Experimental: To a vial containing **6.30** (3.3 mg, 5.8 μmol) was added THF (0.5 mL) followed by the addition of TBAF(*t*BuOH)$_4$ (3.1 mg, 6.6 μmol). The reaction turns yellow/brown, is stirred for 5 min, then quenched by the addition of 0.5 N aqueous HCl and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered,and concentrated to an orange/red oil. The crude residue was purified by pipette column (0%→20%→50%→100% EtOAc in hexanes) to give **6.31**.

Note: Crude ^{1}H NMR and mass analysis indicated near quantitative conversion to **6.31**. Mass after purification (ca 1.8 mg) was not accurately obtained. This material was used for characterization and attempts to obtain crystalline material were done by vapor diffusion using Et_2O and hexanes. The crystalline material from this process was used to obtain data in agreement with **6.32**.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 (br. s, 1H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 5.54 (s, 1H), 4.58 (s, 1H), 4.32 – 4.21 (m, 3H), 2.71 – 2.60 (m, 1H), 1.88 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.80 (s, 3H), 1.64 (s, 3H), 1.50 – 1.41 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.75 (t, *J* = 7.4 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 206.7, 169.6, 165.6, 156.5, 145.9, 136.8, 132.6, 128.1, 126.7, 115.0, 114.1, 79.4, 75.9, 62.9, 58.9, 50.5, 46.1, 30.6, 24.0, 19.1, 14.1, 13.2, 9.0.

IR (thin film): cm^{-1} 3340, 2963, 2927, 2855, 1776, 1747, 1681, 1600, 1454, 1403, 1374, 1229, 1216, 1101, 1014, 730.

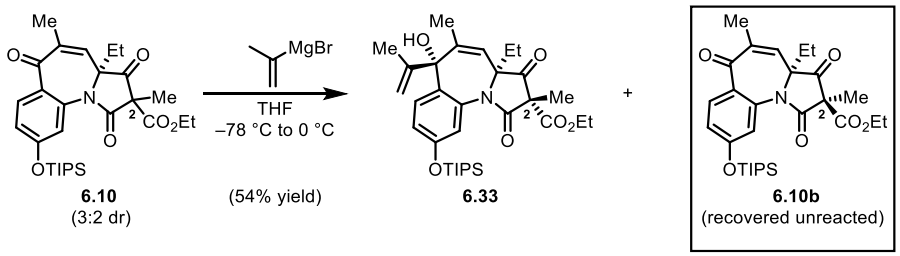
HRMS (ESI+): calculated for $C_{23}H_{27}NO_6Na^+$ $[M+Na]^+$ 436.1731, found: 436.1733.

TLC: 0.18 (50% EtOAc in hexanes).

mp: 195 °C (decomposition).

Physical Appearance: White solid.

Benzylic alcohol **6.33**



Experimental: To a flame dried rbf was added enone **6.10** (500 mg, 0.947 mmol, 3:2 dr, minor component is **6.10b**). This was dissolved in THF (18.9 mL) and cooled to –78 °C in a dry-ice/acetone bath. After cooling, to this was added isopropenylmagnesium bromide (2.27 mL, 1.14 mmol, 0.5 M solution in THF) dropwise over the course of 2 min. After stirring for 30 min in the dry-ice/acetone bath, the bath was replaced with a dry-ice/acetonitrile bath at –40 °C. The reaction was then stirred for 1 h after which the bath was removed and immediately quenched by the addition of a solvent mixture of saturated aqueous NH_4Cl and Et_2O. The aqueous layer was extracted with Et_2O (3x) and the combined organics dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography on silica gel (10:1→8:1 hexanes:EtOAc) to give tertiary alcohol **6.33** (290 mg, 54% yield) as white, sticky solid along with recovered starting enone enriched in **6.10b** (160 mg, 32% recovery).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.7 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 5.66 (d, *J* = 1.4 Hz, 1H), 4.87 (s, 1H), 4.83 (m, 1H), 4.33 - 4.16 (m, 2H), 2.00 (d, *J* = 1.3 Hz, 3H), 1.97 (s, 1H), 1.81 – 1.63 (m, 2H), 1.48 (s, 3H), 1.45 (br. m, 3H), 1.34 – 1.18 (m, 6H), 1.09 (dd, *J* = 7.4, 1.8 Hz, 18H), 0.76 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 205.6, 167.6, 165.8, 155.9, 148.2, 140.6, 134.0, 132.7, 127.8, 123.7, 120.7, 120.0, 113.0, 79.2, 73.7, 62.7, 57.9, 31.3, 23.9, 18.4, 18.0, 16.5, 13.9, 12.7, 8.5.

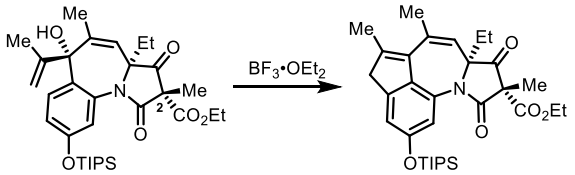
IR (thin film): 3467, 2943, 2867, 1775, 1693, 1606, 1498, 1430, 1379, 1296, 1229, 1108, 984, 898 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_6SiNa^+$ $[M+Na]^+$ 592.3065, found: 592.3060.

TLC: 0.52 (25% EtOAc in hexanes).

Physical Appearance: White sticky solid.

Tetracyclic diene **6.06**



6.33 (98% yield) **6.06**

Experimental: To a flame dried flask was added tertiary alcohol **6.33** (55 mg, 0.097 mmol) and dissolved in CH_2Cl_2(2.44 mL). The solution was then cooled to –78 °C in a dry-ice/acetone bath for 10 min after which BF_3•OEt_2 (31.0 µL) was added in one shot. After stirring for 10 min in the dry-ice/acetone bath, the reaction mixture was warmed to 0 °C in an ice water bath and stirred for an additional 10 min. The faint orange solution was then quenched by the addition of saturated aqueous $NaHCO_3$ extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under

reduced pressure to yield tetracyclic diene **6.06** (52.0 mg, 98% yield) as a colorless foam that was of characterizable purity.

Note: This compound was found to be unstable and would gradually oxidize in air to complex mixtures.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 2.3 Hz, 1H), 6.87 – 6.81 (m, 1H), 5.55 (s, 1H), 4.36 – 4.13 (m, 2H), 3.40 (s, 2H), 2.29 (s, 3H), 2.16 (d, *J* = 1.3 Hz, 3H), 2.03 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.86 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.62 (s, 3H), 1.35 – 1.21 (m, 6H), 1.11 (dd, *J* = 7.4, 1.3 Hz, 18H), 0.72 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 207.7, 168.0, 165.9, 153.7, 144.0, 142.9, 136.2, 133.9, 130.5, 128.4, 128.1, 115.1, 114.3, 75.7, 62.5, 58.8, 45.8, 28.4, 25.5, 18.7, 18.1, 18.1, 17.9, 13.9, 12.7, 8.7.

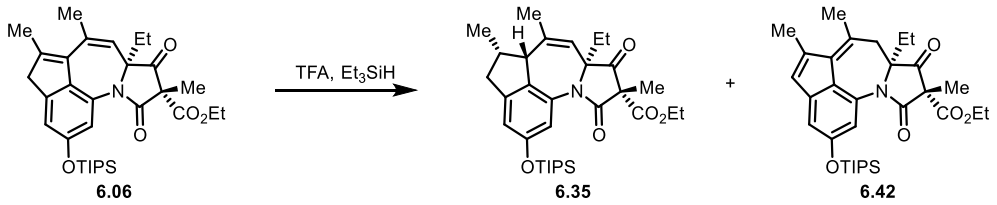
IR (thin film): 2942, 2866, 1776, 1747, 1701, 1613, 1465, 1383, 1286, 1222, 1126, 1003, 986, 882 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{45}NO_6SiNa^+$ $[M+Na]^+$ 574.2959, found: 574.2957.

TLC: 0.63 (25% EtOAc in hexanes).

Physical Appearance: Colorless foam.

Indane **6.35**



Experimental: To a vial was added tetracyclic diene **6.06** (35.1 mg, 0.064 mmol) and dissolved in CH_2Cl_2 (2.0 mL) followed by the addition of triethylsilane (0.34 mL, 2.1 mmol) and TFA (0.11 mL, 1.4 mmol, distilled) at which point the reaction turns yellow. The vial was sealed and placed in a pre-heated oil bath at 60 °C and stirred for 1 h. The

reaction was then cooled to room temperature and concentrated to approximately 1/3 of the original volume. This was then diluted with CH_2Cl_2 and poured into a separatory funnel containing saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3x), dried over $MgSO_4$, filtered, and concentrated to give a crude yellow/orange oil. Inspection of the crude NMR shows an ~5:1 mixture of **6.35**:**6.42**. The crude residue was purified by pipette column (0%→5%→10% EtOAc in hexanes) to give **6.35** and **6.42** (30.7 mg, 87% yield, 5:1 mixture **6.35**:**6.42**).

Note: On larger scales, a 3rd compound was obtained which appeared to be a diastereomer of **6.35**. However, efforts to isolate this compound or advance via benzylic oxidation were unsuccessful.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.89 (s, 1H), 6.76 (s, 1H), 5.55 (s, 1H), 4.34 – 4.16 (m, 2H), 3.79 (d, *J* = 5.5 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H, Et_2O), 2.94 (dd, *J* = 15.2, 5.9 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.48 (d, *J* = 15.4 Hz, 1H), 1.96 – 1.88 (m, 2H), 1.80 – 1.77 (m, 3H), 1.60 (s, 3H), 1.57 (s, 3H, H_2O), 1.55 – 1.47 (m, 1H), 1.32 – 1.23 (m, 6H), 1.21 (t, *J* = 7.0 Hz, 1.5H, Et_2O), 1.13 – 1.08 (m, 18H), 0.77 (t, *J* = 7.3 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$) (Only peaks corresponding to the major component **6.35** are listed): δ ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.7, 168.3, 165.9, 155.6, 146.1, 136.7, 132.8, 128.1, 126.8, 116.9, 116.3, 75.4, 66.0, 62.6, 58.7, 54.0, 39.1, 37.8, 30.6, 24.3, 19.0, 18.0, 14.8, 12.7, 8.9.

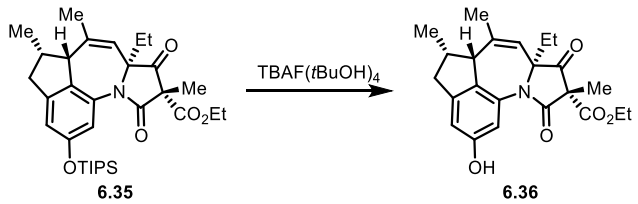
IR (thin film): 2943, 2868, 1776, 1748, 1707, 1614, 1590, 1465, 1392, 1289, 1233, 1120, 998 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_5SiNa^+$ $[M+Na]^+$ 576.3116, found: 576.3113.

TLC: 0.18 (10% EtOAc in hexanes).

Physical Appearance: Faint orange oil.

Phenol **6.36**



Experimental: To a rbf containing **6.35** (13.3 mg, 0.024 mmol) was added THF (0.5 mL) and cooled in a dry ice acetone bath. After cooling, to this was added TBAF (0.026 mL, 0.026 mmol, 1 M solution in THF). The reaction turns bright yellow and was stirred for 5 min. After 5 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a yellow/orange oil. The crude residue was purified by pipette column (10%→20%→30%→40% EtOAc in hexanes) to give **6.36** as a faint yellow solid. Crystals suitable for X-ray analysis were obtained by slow evaporation from CH_2Cl_2 in a smal vial contained with a large vial with hexanes and sealed.

Note: Analysis of the crude ^{1}H NMR and mass indicated near quantitative conversion to **6.36**. A mass after purification was not obtained and the products after purification were in agreement with those in the crude NMR.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.89 (d, *J* = 2.2 Hz, 1H), 6.66 (s, 1H), 5.54 (s, 1H), 4.28 – 4.13 (m, 2H), 3.78 (d, *J* = 5.6 Hz, 1H), 2.93 (dd, *J* = 15.4, 6.1 Hz, 1H), 2.80 – 2.72 (m, 1H), 2.47 (d, *J* = 15.4 Hz, 1H), 1.95 – 1.87 (m, 2H), 1.80 (s, 3H), 1.62 (s, 3H), 1.59 – 1.52 (m, 1H), 1.20 (t, *J* = 9.1 Hz, 3H, overlap with grease), 0.77 (t, *J* = 7.3 Hz, 3H, overlap with grease), 0.73 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): (major peaks listed) δ 207.0, 169.4, 165.7, 165.6, 156.3, 146.4, 145.7, 137.0, 137.0, 132.5, 126.8, 126.4, 124.2, 113.1, 113.1, 112.8, 111.8, 75.8, 75.8, 62.8, 58.9, 53.9, 39.1, 37.8, 30.6, 24.3, 19.0, 14.8, 14.0, 14.0, 8.9.

IR (thin film): cm^{-1} 3325, 2975, 2936, 1775, 1748, 1702, 1677, 1597, 1452, 1407, 1291, 1229, 1116, 732.

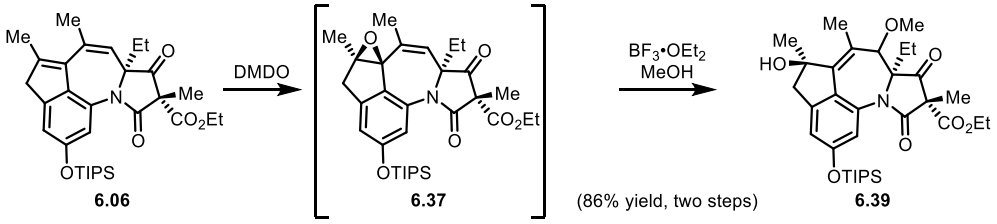
HRMS (ESI+): calculated for $C_{23}H_{27}NO_5Na^+$ $[M+Na]^+$ 420.1781, found: 420.1782.

TLC: 0.59 (50% EtOAc in hexanes).

mp: decomposition.

Physical Appearance: Faint yellow solid.

Allyl methyl ether **6.39**



Experimental: To a vial was added tetracyclic diene **6.06** (17.9 mg, 0.032 mmol). This was cooled to –78 °C in a dry-ice acetone bath followed by the addition of DMDO (1.08 mL, 0.036 mmol, 33 mM solution in acetone). The reaction was stirred for 15 min then concentrated under reduced pressure by rotary evaporation (20 °C, ~50 torr). This was then placed under hi-vac for 1 h to give a intermediate epoxide **6.37** as a white foam. This was then cooled to 0 °C in an ice-water bath followed by the addition of MeOH (1.0 mL, distilled). This was stirred for 5 min followed by the addition of BF_3•EOt_2 (8.0 μL, 0.063 mmol). The reaction was stirred for 50 min in the ice-bath after which H_2O (0.1 mL) was added and the reaction concentrated under reduced pressure by rotary evaporation. The crude residue was then partitioned between brine and Et_2O and the aqueous layer extracted

with Et_2O (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude residue that was purified by flash column chromatography on silica gel to provide **6.39** (16.7 mg, 86% yield over two steps).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 2.3 Hz, 1H), 6.66 (s, 1H), 4.28 (dq, *J* = 10.7, 7.2 Hz, 1H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.00 (s, 1H), 3.30 (s, 3H), 3.20 – 3.06 (m, 2H), 2.38 (s, 3H), 1.85 (br. s, 1H), 1.63 (s, 3H), 1.60 – 1.53 (m, 1H, overlap with H_2O), 1.50 (s, 3H), 1.35 – 1.19 (m, 7H), 1.14 – 1.10 (m, 18H), 0.70 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 208.9, 170.5, 165.8, 156.7, 146.7, 144.0, 132.2, 127.5, 122.0, 115.8, 114.1, 88.2, 80.9, 73.0, 62.7, 58.9, 57.2, 50.0, 27.3, 23.4, 23.1, 18.09, 18.07, 17.7, 14.0, 12.8, 8.1.

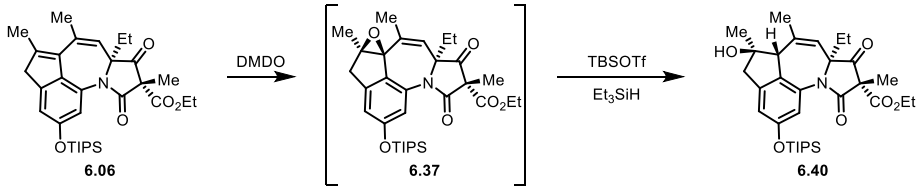
IR (thin film): 3484, 2945, 2866, 1776, 1710, 1606, 1572, 1469, 1384, 1296, 1234, 1135, 1093, 1002, 882 cm^{-1}.

HRMS (ESI+): calculated for $C_{33}H_{49}NO_7SiNa^+$ $[M+Na]^+$ 622.3171, found: 622.3169.

TLC: 0.46 (20% EtOAc in hexanes).

Physical Appearance: Yellow oil.

Indanol **6.40**



Experimental: To a vial was added tetracyclic diene **6.06** (4.4 mg, 8.0 μmol) and this cooled in an ice water bath. After cooling, to this was added DMDO (0.7 mL, 10.5 μmol, 15 mM solution in acetone) and the reaction stirred for 10 min after which TLC indicated consumption of the starting material. The reaction was concentrated under reduced pressure and azeotroped with toluene (1x, 40 °C, ~60 torr) and placed under hi-vac for 30

min to give the crude intermediate epoxide **6.37**. This was then dissolved in DCE (1.0 mL) followed by placing the reaction in a preheated oil bath at 70 °C. Triethylsilane (0.040 mL, 0.25 mmol) was added followed by TBSOTf (5 µL, 0.02 mmol). Upon addition of the TBSOTf the reaction turned orange then quickly faded to a lighter orange in color and finally a faint green solution. The solution was stirred for a total of 5 min after addition of the TBSOTf. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a red/brown oil. This was purified by pipette column to give indanol **6.40** (4.0 mg, 88% yield) as a colorless oil.

Crystals suitable for X-Ray diffraction studies were obtained by dissolving the compound in a minimal amount of Et_2O and layered with hexanes. This was then placed in a -20 °C freezer overnight to give pink crystals.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.92 – 6.89 (m, 1H), 6.70 (s, 1H), 5.62 – 5.58 (m, 1H), 4.33 – 4.17 (m, 2H), 3.78 (s, 1H), 2.98 (d, *J* = 15.2 Hz, 1H), 2.88 (d, *J* = 15.2 Hz, 1H), 1.97 (s, 3H), 1.91 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.60 (s, 3H), 1.48 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.30 – 1.24 (m, 6H), 1.18 (s, 3H), 1.11 (dd, *J* = 7.5, 1.2 Hz, 18H), 0.77 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.4, 168.2, 165.8, 155.8, 142.4, 136.1, 132.6, 127.8, 127.3, 116.8, 116.1, 83.8, 75.1, 62.6, 58.7, 58.6, 48.6, 30.4, 25.1, 22.5, 19.0, 18.0, 13.9, 12.7, 8.9.

IR (thin film): 3473, 2926, 2867, 1777, 1750, 1707, 1688, 1619, 1588, 1478, 1399, 1371, 1328, 1273, 1234, 1120, 1002, 883, 687 cm^{-1}.

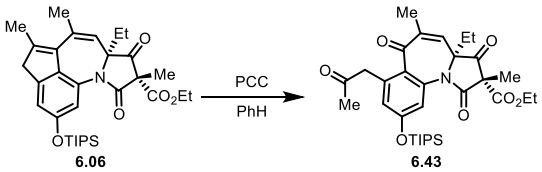
HRMS (ESI+): calculated for $C_{32}H_{47}NO_6SiNa^+$ $[M+Na]^+$ 592.3065, found: 592.3064.

TLC: 0.65 (50% EtOAc in hexanes).

m.p.: 103.1 – 107.2 °C.

Physical Appearance: Pink crystalline solid.

Diketone **6.43**



Experimental: To a flame dried 100 mL rbf was added celite (762 mg) and sodium acetate (319 mg, 3.89 mmol) and this was heated under hi-vac with heat-gun for ~20 seconds. In a separate flask was added PCC (762 mg, 3.53 mmol) and this placed under hi-vac for 30 min. The PCC was then transferred to the flask containing the celite/sodium acetate mixture at which point tetracyclic diene **6.06** (65 mg, 0.12 mmol) dissolved in benzene (2.5 mL) was cannulated into the PCC suspension. The flask containing the tetracyclic diene was rinsed with an additional portion of benzene (2.5 mL). The reaction was stirred for 21 h 30 min at which point the reaction was sonicated and the reaction mixture passed through a plug of SiO_2 wetted with EtOAc. The flask was repeatedly washed with aliquots of EtOAc and the yellow filtrate concentrated under reduced pressure and azeotroped with toluene (1x). The crude residue was purified by flash chromatography on silica gel to give diketone **6.43** (23 mg, 33% yield) as a yellow oil.

Note: Exposure of the substrate **6.06** to *m*CPBA in CH_2Cl_2 affords the same product in lower yields.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (d, *J* = 2.4 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.29 (s, 1H), 4.36 (d, *J* = 17.8 Hz, 1H), 4.35 – 4.19 (m, 2H), 3.54 (d, *J* = 17.7 Hz, 1H), 2.19 (s, 3H), 2.03 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.94 (s, 3H), 1.76 (dq, *J* = 14.9, 7.6 Hz, 1H), 1.54 (s, 3H), 1.32 – 1.21 (m, 6H), 1.11 (d, *J* = 7.3 Hz, 18H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 Hz, $CDCl_3$): δ 205.2, 204.8, 193.5, 169.0, 165.4, 158.2, 138.8, 137.4, 136.8, 133.5, 131.2, 124.2, 117.9, 77.0, 62.9, 58.0, 48.6, 30.2, 28.2, 21.1, 19.1, 18.0, 14.0, 12.7, 8.5.

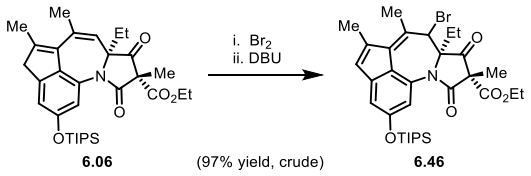
IR (thin film): 2946, 2928, 2869, 1781, 1751, 1718, 1653, 1604, 1385, 1251 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{45}NO_7SiNa^+$ $[M+Na]^+$ 606.2858, found: 606.2863.

TLC: 0.33 (20% EtOAc in hexanes)

Physical Appearance: Yellow oil.

Allylic bromide **6.46**



Experimental: To a 50 mL rbf was added **6.06** (113.9 mg, 0.206 mmol) and this azeotroped with toluene (2x) (22 °C, ~60 torr). After placing this under hi-vac for 1 h, this was then dissolved in CH_2Cl_2(4.12 mL) and cooled to –78 °C in a dry-ice/acetone bath. After cooling for 5 min, to this was added bromine (1.05 mL, 0.210 mmol, 0.20 M solution in CH_2Cl_2) dropwise until the brown color of the reaction persisted at which point the addition of bromine was ceased. The reaction was stirred for 2 min after which the dry-ice/acetone bath was removed and the reaction stirred in air for 20 min. The reaction was then placed back in the dry-ice/acetone bath and to the yellow/brown solution was added DBU(0.065 mL, 0.43 mmol). The reaction was stirred for 30 min in the dry-ice/acetone bath after which the bath was removed, and the reaction let stir in air for 30 min. The reaction was then quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to

give allylic bromide **6.46** (126 mg, 97% yield) as a crude orange oil that was sufficiently pure to be used in further steps without further purification.

An analytically pure sample was obtained by flash chromatography on silica gel for characterization.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 2.2 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.52 – 6.47 (m, 1H), 4.99 (s, 1H), 4.33 – 4.17 (m, 2H), 2.42 (s, 3H), 2.29 (d, *J* = 1.5 Hz, 3H), 1.97 – 1.85 (m, *J* = 6.9 Hz, 2H), 1.82 (s, 3H), 1.34 – 1.25 (m, 6H), 1.13 (d, *J* = 7.4 Hz, 18H), 0.79 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (126 Hz, $CDCl_3$): δ 205.0, 169.3, 165.1, 156.8, 144.6, 139.7, 139.6, 135.7, 133.2, 131.6, 118.0, 111.9, 110.7, 74.2, 63.2, 62.9, 59.5, 25.8, 21.6, 19.7, 18.2, 18.1, 18.1, 14.0, 12.8, 8.7.

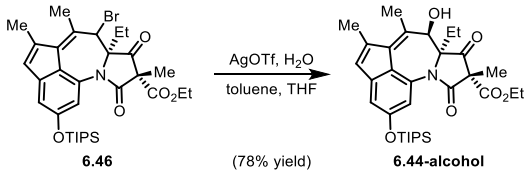
IR (thin film): 2944, 2869, 1781, 1736, 1719, 1613, 1465, 1396, 1302, 1225, 1204, 1131, 692 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{44}BrNO_5SiNa^+$ $[M+Na]^+$ 652.2064, found: 652.2059.

TLC: 0.49 (20% EtOAc in hexanes)

Physical Appearance: Yellow/brown oil.

Allyl alochol **6.44-alcohol**



Experimental: To a 50 mL rbf open to air was added toluene (7.0 mL), AgOTf (133 mg, 0.518 mmol), and H_2O (1.0 mL). The resulting biphasic mixture was stirred vigorously during which time allyl bromide **6.46** (109 mg, 0.173 mmol) as a solution in THF (2 mL) was added dropwise by pipette. The substrate flask was rinsed with THF (2 x 2 mL) and

both transferred to the AgOTf mixture. An additional THF (9 mL) was added to the mixture. The reaction was stirred for 1 h at room temperature at which point the originally yellow/white suspension that, when allowing the layers to settle, turned into a grey suspension in the aqueous layer and a clear yellow organic phase. The crude reaction mixture was diluted with brine and Et_2O and filtered through a plug of celite. This was then extracted with Et_2O (3x) and the combined organics dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude yellow oil. The compound was rapidly flashed by silica gel chromatography (100% CH_2Cl_2 then 30% EtOAc in hexanes) to give allylic alcohol **6.44-alcohol** (80 mg, 78% yield) as a yellow amorphous solid. Crystals suitable for X-Ray diffraction studies were obtained by vapor diffusion (Et_2O/hexanes) to give yellow crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 2.2 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 6.55 (s, 1H), 4.46 (d, *J* = 9.3 Hz, 1H), 4.30 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.45 (s, 3H), 2.33 (d, *J* = 1.6 Hz, 3H), 1.86 (d, *J* = 9.5 Hz, 1H), 1.72 (s, 3H), 1.64 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.57 (s, 3H), 1.49 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.35 – 1.25 (m, 6H), 1.13 (dd, *J* = 7.5, 0.9 Hz, 18H), 0.70 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): (Major peaks corresponding to the product are listed, minor peaks are unknown impurities) δ 208.2, 170.7, 165.6, 156.5, 144.4, 140.0, 138.9, 138.2, 132.9, 131.0, 118.4, 112.4, 110.9, 81.5, 75.4, 62.8, 59.5, 23.6, 22.4, 19.8, 18.10, 18.07, 17.9, 14.0, 12.8, 8.8.

IR (thin film): 3431, 2944, 2867, 1776, 1692, 1612, 1461, 1399, 1224, 1203, 1132, 994, 882 cm^{-1}.

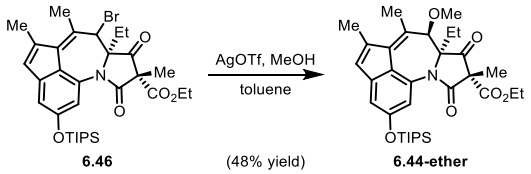
HRMS (ESI+): calculated for $C_{32}H_{45}NO_6SiNa^+$ $[M+Na]^+$ 590.2908, found: 590.2911.

TLC: 0.33 (20% EtOAc in hexanes).

mp: 155.3 – 158.1 °C.

Physical Appearance: Yellow crystalline solid.

Allyl methyl ether **6.44-ether**



Experimental: A rbf containing allylic bromide **6.46** (31.5 mg, 0.050 mmol) was placed under hi-vac for 3 h after which it was dissolved in toluene (5.0 mL). To this was added MeOH (0.3 mL) and cooled to –78 °C in a dry-ice/acetone bath. In a separate rbf was added AgOTf (33 mg) and this azeotroped with toluene (2x) and placed under hi-vac. This was then dissolved in toluene (1.0 mL) and this solution of AgOTf was added dropwise over ~ 30 sec to the solution of the bromide. The reaction was let stir for 1 h without maintaining the dry-ice/acetone bath after which TLC indicated consumption of the starting material. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to give allyl methyl ether **6.44-ether** (14.0 mg, 48% yield) as a faint yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, J = 2.2 Hz, 1H), 6.64 (d, J = 2.3 Hz, 1H), 6.56 (s, 1H), 4.35 – 4.14 (m, 3H), 3.31 (s, 3H), 2.48 (s, 3H), 2.34 (d, J = 1.5 Hz, 3H), 1.66 (s, 3H), 1.60 – 1.52 (m, 1H, overlap with H_2O), 1.41 – 1.33 (m, 1H), 1.33 – 1.24 (m, 6H), 1.12 (d, J = 7.4 Hz, 18H), 0.68 (t, J = 7.5 Hz, 3H).

^{13}C NMR (126 Hz, $CDCl_3$): δ 209.0, 170.1, 165.8, 156.1, 144.3, 140.7, 139.7, 136.0, 132.8, 131.0, 118.5, 112.9, 110.7, 89.2, 73.4, 62.7, 59.3, 57.3, 25.2, 23.6, 19.8, 18.1, 18.1, 17.8, 14.0, 12.8, 8.4.

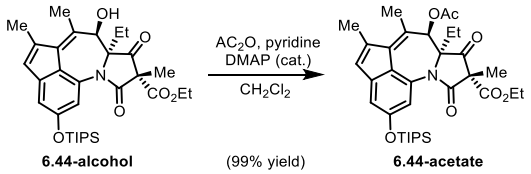
IR (thin film): 2944, 2867, 1776, 1741, 1711, 1611, 1573, 1461, 1397, 1302, 1226, 1132, 1094, 883, 685 cm^{-1}.

HRMS (ESI+): calculated for $C_{33}H_{47}NO_6SiNa^+$ $[M+Na]^+$ 604.3065, found: 604.3068.

TLC: 0.24 (10% EtOAc in hexanes).

Physical Appearance: Faint yellow oil.

Allylic acetate **6.44-acetate**



Experimental: To a tbf was added alcohol **6.44-alcohol** (12.6 mg, 0.022 mmol) followed by the addition of CH_2Cl_2 (2.0 mL), pyridine (1.00 mL, 12.4 mmol), acetic anhydride (1.00 mL, 10.6 mmol), and DMAP (catalytic quantity, tip of pipette, not measured) in that order. The reaction went from yellow to slightly blue/green upon the addition of DMAP. The reaction was let stir overnight and concentrated under reduced pressure. The reaction mixture was then azeotroped with toluene (2x, 35 °C, ~60 torr) and the crude residue then purified by pipette column to give acetate **6.44-acetate** (13.4 mg, 99% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 2.2 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H), 6.56 (s, 1H), 5.75 (s, 1H), 4.36 – 4.14 (m, 2H), 2.47 (s, 3H), 2.31 (d, J = 1.3 Hz, 3H), 1.96 (s, 3H), 1.73 – 1.60 (m, 1H), 1.59 (s, 3H), 1.59 – 1.46 (m, 1H, overlap with H_2O), 1.36 – 1.24 (m, 6H), 1.13 (d, J = 7.3 Hz, 18H), 0.74 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 206.9, 169.5, 169.4, 165.2, 156.5, 144.5, 141.3, 140.1, 135.3, 133.1, 131.0, 118.1, 112.5, 110.8, 81.2, 72.6, 63.1, 59.0, 24.7, 23.7, 21.3, 19.8, 18.1, 18.1, 17.4, 14.0, 12.8, 8.3.

IR (thin film): 2944, 2867, 1779, 1749, 1714, 1611, 1461, 1396, 1204, 1133, 1014, 997 cm^{-1}.

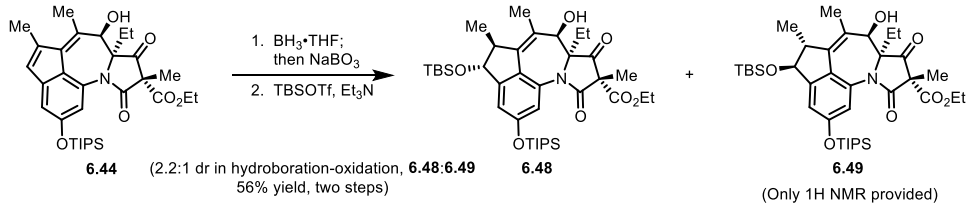
HRMS (ESI+): calculated for $C_{34}H_{47}NO_7SiNa^+$ $[M+Na]^+$ 632.3014, found: 632.3010.

TLC: 0.39 (20% EtOAc in hexanes)

m.p.: 143.8 – 144.9 °C.

Physical Appearance: Yellow solid.

TBS Ether **6.48** *and* **6.49**

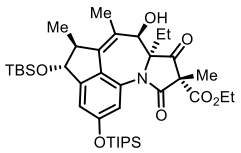


Experimental: A flask containing allylic alcohol **6.44** (40.6 mg, 0.072 mmol) was azeotroped with toluene (3x). This was then placed under hi-vac for 30 min after which to this was added THF (2.0 mL). Subsequently, in one shot, was directly added a solution of BH_3•THF (0.72 mL, 0.36 mmol, 0.5 M solution in THF). The yellow solution was stirred for 1 h after which the intensity of the yellow color had faded. This was then cooled in an ice-water bath, stirred for 22 min, followed by the addition of diH_2O (0.15mL, 8.3 mmol, strong effervescence) then $NaBO_3$•7H_2O (55.0 mg, 0.358 mmol). The reaction was stirred for 2 h then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude residue was left on hi-vac overnight to give the crude hydroboration-oxidation products (49 mg) as a 2.2:1 mixture of diastereomers (favoring the compound that leads to

6.48). This was purified by MPLC (4g column, 18 mL/min, 0%→10% EtOAc in hexanes) to give the intermediate hydroboration-oxidation products (28.2 mg, 67% combined yield) as a colorless oil.

A mixture of the aforementioned hydroboration-oxidation products (17.6 mg, 0.030 mmol, ~1:1 dr) was dissolved in CH_2Cl_2 (3.0 mL) and cooled to –78 °C in a dry-ice/acetone bath. After cooling for 15 min, triethylamine (0.10 mL, 0.72 mmol) was added, stirred for 2 min, followed by the addition of TBSOTf (0.020 mL, 0.093 mmol). The reaction was stirred for 2 h after which the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The compounds were purified by flash column chromatography on silica gel (10% Et_2O in toluene) to give TBS ethers **6.48** and **6.49** (17.4 mg, 83% combined yield). Pure **6.48** was obtained by HPLC purification (normal phase, linear gradient 10%→30% EtOAc in hexanes, 10 mL/min). Only a ^{1}H NMR is provided for diastereomer **6.49**.

Note: Stereochemistry was confirmed by obtaining preliminary X-Ray crystallographic data on the TIPS deprotected phenol derivative of **6.48**.



6.48 (major diastereomer)

***Major Diasteromer* (6.48)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 4.61 (s, 1H), 4.34 – 4.25 (m, 2H), 4.19 (dq, J = 10.8, 7.1 Hz, 1H), 2.88 (q, J = 7.3 Hz, 1H), 2.05 (s, 3H), 1.73 (s, 3H), 1.71 – 1.62 (m, 2H), 1.57 (s, H_2O), 1.47 (dq, J = 14.9, 7.5 Hz, 1H), 1.34

– 1.23 (m, 6H), 1.12 (dd, J = 7.5, 1.4 Hz, 18H), 1.02 (d, J = 7.3 Hz, 3H), 0.86 (s, 9H), 0.67 (t, J = 7.4 Hz, 3H), 0.10 (d, J = 14.8 Hz, 6H).

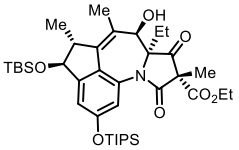
^{13}C NMR (151 Hz, $CDCl_3$): δ ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.9, 171.1, 165.7, 157.1, 149.3, 142.9, 132.4, 126.7, 123.5, 116.9, 116.2, 80.0, 79.4, 76.3, 62.8, 59.6, 48.1, 25.9, 23.3, 20.7, 18.4, 18.2, 18.03, 18.00, 17.9, 14.0, 12.8, 8.4, -4.1, -4.2.

IR (thin film): 3454, 2946, 2929, 2867, 2361, 2338, 1777, 1747, 1696, 1608, 1473, 1390, 1251, 1222, 1069, 837 cm^{-1}.

HRMS (ESI+): calculated for $C_{38}H_{61}NO_7Si_2Na^+$ $[M+Na]^+$ 722.3879, found: 722.3878.

TLC: 0.40 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

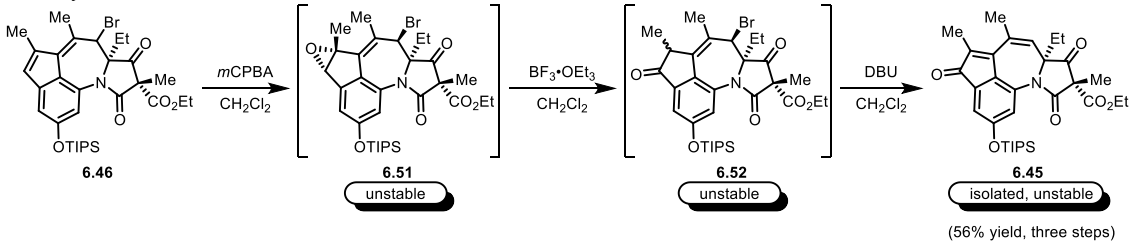


6.49 (minor diastereomer)

Minor Diasteromer* (6.49)*, only ^{1}H provided

^{1}H NMR (400 MHz, $CDCl_3$): 7.53 (d, J = 2.3 Hz, 1H), 6.80 (dd, J = 2.2, 0.6 Hz, 1H), 4.63 (s, 1H), 4.34 – 4.14 (m, 3H), 2.87 (q, J = 7.3 Hz, 1H), 2.07 (s, 3H), 1.74 (d, J = 8.9 Hz, 1H), 1.71 (s, 3H), 1.65 – 1.58 (m, 1H), 1.56 (s, H_2O), 1.41 – 1.24 (m, 7H, overlap with unknown impurities), 1.12 (s, 18H), 1.10 (d, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.73 (t, J = 7.5 Hz, 3H), 0.15 (app. d, J = 4.3 Hz, 6H).

Tetracyclic dienone **6.45**



Experimental: *Note*: Each of the compounds **6.51**, **6.52**, and **6.45** are all unstable and readily decompose and were thus rapidly put through this synthetic sequence. Enough of the material **6.45** was prepared for characterization, but advancing from this intermediate proved difficult.

To a rbf containing allylic bromide **6.46** (50.2 mg, 0.080 mmol) was added CH_2Cl_2 (2.0 mL) followed by the addition of *m*CPBA (81.0 mg, 0.361 mmol, 77% purity). The reaction was stirred for 20 min at room temperature and then quenched by the addition of saturated aqueous thiosulfate/saturated aqueous $NaHCO_3$ mixture (1:1). This was extracted with CH_2Cl_2 (3x) and the combined organics dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude epoxide **6.51** (~3.7:1 dr) as a yellow oil. This was immediately taken on to the next step.

To the rbf containing the crude epoxide mixture **6.51** was added CH_2Cl_2 (20 mL) and cooled to –78 °C in a dry-ice/acetone bath. After cooling, to this was added BF_3•OEt_2 (10 μL, 0.079 mmol) after which the reaction immediately turns from yellow to brown/yellow. The reaction was stirred for 15 min until TLC indicated the reaction was complete. The reaction was then quenched by pouring into a separatory funnel containing saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2x). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude ketone **6.52** (~3:1 dr) as a yellow oil that was used immediately in the next reaction.

To the rbf containing crude ketone **6.52** was added CH_2Cl_2 (10 mL) and cooled to –78 °C in a dry-ice/acetone bath. After cooling, to this was added DBU (0.024 mL, 0.160 mmol) at which point the reaction goes from a faint yellow to a deep orange color. The

reaction was stirred for 30 min in the dry-ice/acetone bath after which it was quenched by the addition of 0.5 N aqueous HCl and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude orange oil. The crude residue was purified by MPLC (0%→40% EtOAc in hexanes, 16 minutes, 4g column, 18 mL/min) to give the produce dienone **6.45** (25.2 mg, 56% yield over three steps) as a bright orange oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, *J* = 2.3 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 5.82 (s, 1H), 4.30 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.22 (d, *J* = 1.5 Hz, 3H), 2.16 – 2.09 (m, 1H), 2.07 (d, *J* = 0.7 Hz, 3H), 1.91 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.63 (s, 3H), 1.33 – 1.23 (m, 6H), 1.11 (d, *J* = 7.4 Hz, 18H), 0.76 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 206.6, 196.8, 168.4, 165.3, 157.1, 150.0, 135.8, 134.8, 133.3, 132.0, 129.6, 127.3, 120.2, 115.2, 75.3, 62.8, 58.6, 29.4, 24.8, 19.0, 18.00, 17.98, 14.0, 12.7, 10.8, 9.3.

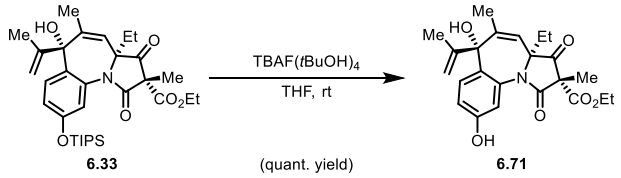
IR (thin film): 2943, 2867, 1779, 1749, 1703, 1614, 1467, 1395, 1291, 1241, 1125, 896, 882 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{43}NO_6SiNa^+$ $[M+Na]^+$ 588.2752, found: 588.2752.

TLC: 0.60 (20% EtOAc in hexanes), orange band.

Physical Appearance: Bright orange oil.

Phenol **6.71**



Experimental: To a rbf containing **6.33** (35.0 mg, 0.061 mmol) was added THF (1.2 mL). At room temperature, to this was added TBAF(*t*BuOH)$_4$ (37.7 mg, 0.068 mmol). The

solution turned yellow, was stirred for 5 min, and the reaction mixture subsequently quenched by the addition of 1 N aqueous HCl. The aqueous layer was extracted with EtOAc (3x) and the combined organics washed with brine, dried over Na2SO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (25% EtOAc in hexanes) to give phenol **6.71** (25.4 mg, quant. yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br. s, 1H), 7.68 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.87 – 6.80 (m, 2H), 5.69 – 5.63 (m, 1H), 4.87 (s, 1H), 4.86-4.81 (m, 1H), 4.25 – 4.06 (m, 2H), 2.05 (br. s, 1H), 1.99 (d, *J* = 1.3 Hz, 3H), 1.94 (br. s, 1H, H_2Ok), 1.81 – 1.64 (m, 2H), 1.52 (s, 3H), 1.51 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 204.6, 169.3, 165.4, 156.7, 148.1, 141.0, 132.4, 131.9, 128.1, 122.9, 116.2, 115.9, 112.8, 79.2, 74.1, 63.1, 58.3, 31.3, 23.8, 18.3, 16.4, 13.9, 8.4.

IR (thin film): 3550, 3249, 2983, 1771, 1747, 1671, 1615, 1452, 1407, 1304, 1227, 1108, 1015, 911 cm^{-1}.

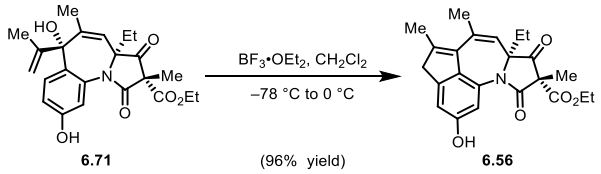
HRMS (ESI+): calculated for $C_{23}H_{27}NO_6Na$ $[M+Na]^+$ 436.1731, found: 436.1730.

TLC: 0.47 (50% EtOAc in hexanes)

m.p.: 192.4 - 193.3 ° C.

Physical Appearance: White solid.

Tetracyclic diene **6.56**



Experimental: To a rbf was added tertiary alcohol **6.71** (30.0 mg, 0.073 mmol) and dissolved in CH_2Cl_2(1.45 mL). This solution was cooled to –78 °C in a dry-ice/acetone

bath for 10 min followed by the addition of BF_3•OEt_2 (23.0 μL). The reaction was stirred for 10 min after which the dry-ice/acetone bath was removed and warmed to 0 °C in an ice-water bath. The reaction was stirred for another 10 min after which it was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tetracyclic diene **6.56** (27.5 mg, 96% yield) as a pale yellow solid that was of characterizable purity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 2.3 Hz, 1H), 7.03 (br. s, 1H), 6.81 – 6.76 (m, 1H), 5.54 (s, 1H), 5.30 (CH_2Cl_2), 4.32 – 4.09 (m, 2H), 3.39 (s, 2H), 2.29 (s, 3H), 2.18 (d, *J* = 1.4 Hz, 3H), 2.10 – 1.96 (m, 1H), 1.87 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.65 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 207.2, 169.1, 165.6, 154.3, 144.6, 142.9, 136.5, 133.8, 129.5, 128.1, 127.7, 110.6, 110.6, 76.1, 62.8, 59.1, 45.8, 28.5, 25.5, 18.8, 18.0, 14.0, 8.8.

IR (thin film): 3245, 2980, 2933, 1774, 1741, 1666, 1594, 1451, 1401, 1388, 1366, 1193, 1126, 977 cm^{-1}.

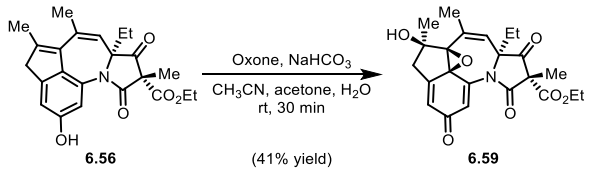
HRMS (ESI+): calculated for $C_{23}H_{25}NO_5Na^+$ $[M+Na]^+$ 418.1625, found: 418.1626.

TLC: 0.24 (20% EtOAc in hexanes)

m.p.: decomposition.

Physical Appearance: Pale yellow solid.

Spiroepoxide **6.59**



Experimental: To a rbf was added tetracyclic diene **6.56** (13.1 mg, 0.033 mmol) and the flask capped with a septa and empty balloon. To this flask was subsequently added CH_3CN/acetone/H_2O (1.95 mL, 2:2:5) at room temperature. The solution was stirred vigorously for 5 min after which a mixture of oxone (50.9 mg, 0.166 mmol) and $NaHCO_3$ (41.7 mg, 0.497 mmol) were added. The suspension was stirred for 30 min after which the reaction mixture was diluted with diH_2O and extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (2:1→1:1 hexanes:EtOAc) to give spiroepoxide **6.59** (5.8 mg, 41% yield) as a white solid.

To obtain crystals suitable for X-Ray diffraction, the material was suspended in MeOH and gently heated until the compound dissolved. The methanol was subsequently allowed to slowly evaporate to give yellow crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, *J* = 1.8 Hz, 1H), 6.38 (q, *J* = 1.7 Hz, 1H), 5.75 (d, *J* = 1.5 Hz, 1H), 4.24 (qd, *J* = 7.1, 1.2 Hz, 2H), 2.66 (s, 2H), 2.35 (s, 1H), 2.21 (d, *J* = 1.5 Hz, 3H), 2.02 (dq, 14.8, 7.4 Hz, 1H), 1.69 – 1.57 (m, 4H), 1.57 (s, H_2O), 1.35 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.2, 185.2, 168.5, 165.0, 155.9, 142.4, 134.0, 133.0, 132.6, 127.1, 79.9, 78.1, 74.4, 66.3, 63.1, 58.1, 43.1, 31.2, 23.9, 23.8, 18.9, 14.0, 8.5.

IR (thin film): 3445, 2975, 1775, 1744, 1698, 1641, 1607, 1442, 1385, 1362, 1322, 1284, 1207, 1166 cm^{-1}.

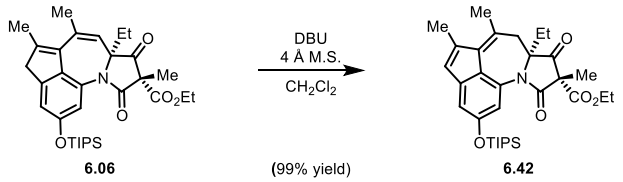
HRMS (ESI+): calculated for $C_{23}H_{25}NO_7Na^+$ $[M+Na]^+$ 450.1523, found: 450.1524.

TLC: 0.44 (50% EtOAc in hexanes).

m.p.: 192.9 – 194.0 °C.

Physical Appearance: Yellow crystalline solid (after crystallization).

Diene shift product **6.42**



Experimental: To a rbf containing tetracyclic diene **6.06** (314.7 mg, 0.570 mmol) was added DCE (50 mL) followed by the addition of 4 Å molecular sieves (2.0 g, crushed/powdered, thoroughly flame-dried). This was stirred for 15 min then placed in a preheated oil bath at 50 °C after which DBU (0.20 mL, 1.3 mmol) was added. After 45 min, TLC showed no starting material (TLC conditions: 75:20:5 hexanes:EtOAc:CH_2Cl_2). The reaction was then cooled to room temperature and filtered through a short plug of SiO_2 via vacuum filtration through a fritted funnel. This was washed with Et_2O:hexanes mixture (1:1, ~200 mL). The filtrate was washed with 0.5 N aqueous HCl, brine, and dried over $MgSO_4$, filtered, and concentrated to a yellow foam. This was azeotroped with CH_2Cl_2 to remove any residual DCE and placed under hi-vac for 1 h to give diene shift product **6.42** (310.0 mg, 99% yield) as a yellow foam contaminated with TIPSOH carried over from a previous reaction.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 2.3 Hz, 1H, overlap with $CHCl_3$), 6.62 (d, J = 2.3 Hz, 1H), 6.47 (d, J = 1.6 Hz, 1H), 4.30 (dq, J = 10.8, 7.1 Hz, 1H), 4.19 (dq, J = 10.8, 7.1 Hz, 1H), 2.97 (d, J = 18.0 Hz, 1H), 2.75 (d, J = 18.1 Hz, 1H), 2.33 (d, J = 1.4 Hz, 3H), 2.25 (d, J = 1.5 Hz, 3H), 1.91 (dq, J = 14.9, 7.5 Hz, 1H), 1.80 (dq, J = 14.7, 7.3 Hz, 1H),

1.63 (s, 3H), 1.35 – 1.23 (m, 6H), 1.11 (dd, J = 7.5, 1.0 Hz, 18H), 1.04 (s, TIPSOH), 0.73 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 208.4, 168.4, 165.7, 155.6, 144.3, 139.7, 137.9, 136.8, 130.9, 130.5, 120.3, 112.2, 110.3, 71.4, 62.7, 58.4, 50.5, 24.5, 23.5, 20.0, 18.6, 18.08, 18.05, 17.8 (TIPSOH), 13.9, 12.7, 12.4 (TIPSOH), 8.6.

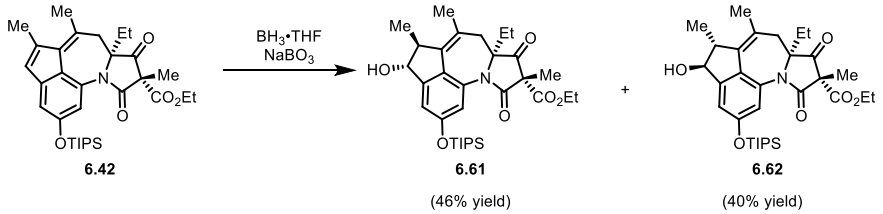
IR (thin film): 2946, 2869, 1776, 1747, 1707, 1614, 1464, 1395, 1236, 1193, 1132, 821, 686 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{45}NO_5SiNa^+$ $[M+Na]^+$ 574.2959, found: 574.2956.

TLC: 0.18 (10% EtOAc in hexanes).

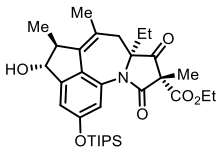
Physical Appearance: Yellow foam.

Tetracyclic alcohols **6.61** *and* **6.62**



Experimental: To a rbf was added diene **6.42** (302.9 mg, 0.549 mmol) and this azeotroped with toluene (2x) then placed under hi-vac for 1 h. To the yellow oil was then directly added BH_3•THF (11 mL, 11 mmol, 1.0 M solution in THF). The reaction was monitored by TLC for disappearance of the starting material. Once the starting material had been consumed (~7 min) the reaction was cooled in an ice-water bath and stirred for an additional 10 min. To the faint yellow solution was then added diH_2O (0.86 mL, 48 mmol) dropwise over the course of 1 min (*caution*: strong effervescence). Immediately after the completion of the addition, $NaBO_3$•7H_2O (253 mg, 1.65 mmol) was added and the reaction stirred for 1 h. The reaction was diluted with diH_2O and extracted with Et_2O (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The credue residue

was then azeotroped with MeOH (5x, 25 °C, ~60 torr). The crude residue was subject to purification by MPLC (0%→20% Et_2O in CH_2Cl_2) to give the higher R_f diastereomer **6.61** (144.9 mg, 46% yield) as a colorless foam and the lower R_f diastereomer **6.62** (124.6 mg, 40% yield) as a colorless oil.



Higher R_f diastereomer **6.61**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 2.2 Hz, 1H), 6.89 (d, *J* = 2.3 Hz, 1H), 4.58 (s, 1H), 4.29 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.99 (q, *J* = 7.2 Hz, 1H), 2.65 (dt, *J* = 17.4, 1.6 Hz, 1H), 2.52 (d, *J* = 17.5 Hz, 1H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.80 (qd, *J* = 7.4, 1.6 Hz, 2H), 1.64 (s, 3H), 1.35 – 1.21 (m, 6H), 1.11 (dd, *J* = 7.5, 1.0 Hz, 18H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.70 (t, *J* = 7.4 Hz, 3H).

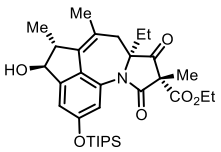
^{13}C NMR (101 Hz, $CDCl_3$): δ 208.0, 168.9, 165.7, 156.3, 148.1, 138.4, 131.9, 124.8, 124.1, 117.3, 115.9, 79.7, 72.1, 62.7, 58.3, 47.5, 47.3, 25.0, 22.1, 18.7, 18.5, 18.01, 17.99, 13.9, 12.7, 8.5.

IR (thin film): 3463, 2943, 2867, 1774, 1747, 1705, 1607, 1579, 1474, 1386, 1299, 1234 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_6SiNa^+$ $[M+Na]^+$ 592.3065, found: 592.3067.

TLC: 0.65 (40:40:20 hexanes:Et_2O:CH_2Cl_2)

Physical Appearance: Colorless foam.



Lower R_f diastereomer **6.62**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 2.3 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 4.58 (s, 1H), 4.29 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.00 (q, *J* = 7.2 Hz, 1H), 2.69 (dt, *J* = 16.9, 1.5 Hz, 1H), 2.52 (d, *J* = 17.1 Hz, 1H), 1.90 (d, *J* = 1.3 Hz, 3H), 1.83 – 1.65 (m, 3H), 1.59 (s, 3H), 1.36 – 1.22 (m, 6H), 1.11 (dd, *J* = 7.5, 1.1 Hz, 18H), 1.08 (d, *J* = 7.3 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 208.4, 168.9, 165.7, 156.4, 148.5, 140.0, 131.8, 125.1, 124.1, 117.5, 115.5, 79.6, 71.2, 62.7, 58.1, 47.1, 47.0, 24.1, 22.9, 18.8, 18.4, 18.03, 18.01, 13.9, 12.7, 8.4.

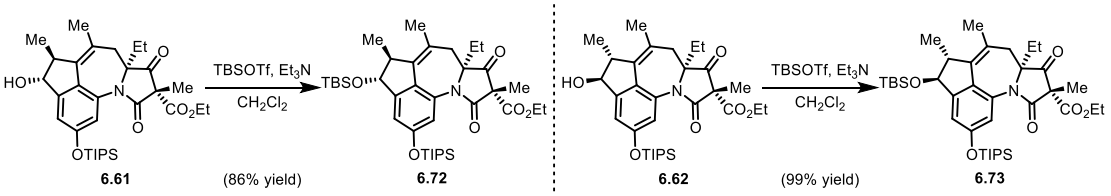
IR (thin film): 3488, 2943, 2867, 1775, 1747, 1705, 1607, 1574, 1474, 1384, 1353, 1298, 1234 cm^{-1}.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_6SiNa^+$ $[M+Na]^+$ 592.3065, found: 592.3065.

TLC: 0.53 (40:40:20 hexanes:Et_2O:CH_2Cl_2)

Physical Appearance: Colorless oil.

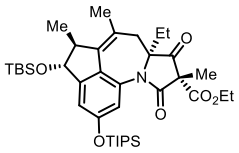
TBS ethers **6.72** *or* **6.73**



Experimental: To a rbf containing benzylic alcohol **6.60** (79 mg, 0.14 mmol) was added CH_2Cl_2 (4.5 mL) and cooled to –78 °C in a dry-ice/acetone bath. After cooling for 10 min, to this was added triethylamine (0.31 mL, 2.2 mmol) followed 2 min later by TBSOTf (0.070 mL, 0.30 mmol). The reaction was stirred for 1 h in the dry-ice/acetone bath then 1 h at room temperature. An additional TBSOTf (0.020 mL) was added dropwise over~ 10 seconds. This was stirred for an additional 20 min then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers

were dried over $MgSO_4$, filtered, and concentrated to a yellow oil that was purified by MPLC (linear gradient 0%→100% EtOAc in hexanes, 4g column, 18 mL/min, 15 min) to give TBS ether **6.72** (81.5 mg, 86% yield) as a colorless oil.

6.73 was obtained using analogous procedure using benzylic alcohol **6.61** (77.1 mg, 0.135 mmol), triethylamine (0.31 mL, 2.2 mmol), TBSOTf (0.07 mL, 0.3 mmol) to give TBS ether **6.73** (91.2 mg, 99% yield) as a colorless oil.



6.72

***Data for* 6.72**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 2.3 Hz, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 4.57 (s, 1H), 4.29 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.86 (q, *J* = 7.2 Hz, 1H), 2.64 (dt, *J* = 17.4, 1.5 Hz, 1H), 2.50 (d, *J* = 17.4 Hz, 1H), 1.88 – 1.74 (m, 5H), 1.64 (s, 3H), 1.33 – 1.20 (m, 6H), 1.10 (dd, *J* = 7.4, 1.6 Hz, 18H), 1.01 (d, *J* = 7.3 Hz, 3H), 0.85 (s, 9H), 0.70 (t, *J* = 7.4 Hz, 3H), 0.08 (d, *J* = 9.8 Hz, 6H).

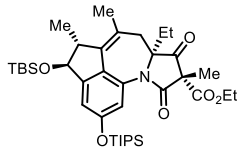
^{13}C NMR (101 Hz, $CDCl_3$): δ 208.3, 168.9, 165.8, 156.0, 148.7, 139.2, 131.6, 125.1, 123.0, 117.0, 116.2, 80.3, 72.2, 62.7, 58.3, 48.0, 47.4, 25.9, 24.9, 22.1, 18.7, 18.5, 18.3, 18.01, 17.98, 13.9, 12.7, 8.5, -4.1, -4.2.

IR (thin film): 2946, 2867, 1775, 1748, 1707, 1608, 1473, 1386, 1298, 1235, 837 cm^{-1}.

HRMS (ESI+): calculated for $C_{38}H_{61}NO_6Si_2Na^+$ $[M+Na]^+$ 706.3930, found: 706.3932.

TLC: 0.25 (10% EtOAc in hexanes)

Physical Appearance: Colorless oil.



6.73

***Data for* 6.73**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 2.3 Hz, 1H), 6.78 (d, *J* = 1.9 Hz, 1H), 4.60 (s, 1H), 4.29 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.88 (q, *J* = 7.2 Hz, 1H), 2.71 (dt, *J* = 17.0, 1.5 Hz, 1H), 2.50 (d, *J* = 17.0 Hz, 1H), 1.88 (d, *J* = 1.3 Hz, 3H), 1.75 (q, *J* = 7.4 Hz, 2H), 1.59 (s, 3H), 1.36 – 1.21 (m, 6H), 1.12 (d, *J* = 7.1 Hz, 18H), 1.08 (d, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.75 (t, *J* = 7.4 Hz, 3H), 0.14 (d, *J* = 4.5 Hz, 6H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 208.7, 168.7, 165.9, 156.1, 148.7, 140.6, 131.7, 124.5, 124.3, 117.5, 115.8, 80.3, 71.4, 62.7, 58.2, 47.5, 47.0, 26.0, 24.1, 22.9, 19.0, 18.5, 18.4, 18.0, 18.0, 14.0, 12.7, 8.5, -4.0, -4.3.

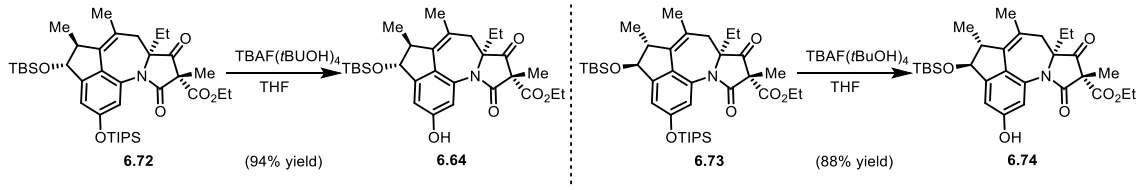
IR (thin film): cm^{-1}.

HRMS (ESI+): calculated for $C_{38}H_{61}NO_6Si_2Na^+$ $[M+Na]^+$ 706.3930, found: 706.3927.

TLC: 0.29 (10% EtOAc in hexanes)

Physical Appearance: Colorless oil.

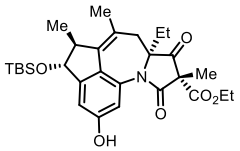
Phenols **6.64** *or* **6.74**



Experimental: To a rbf containing TBS ether **6.72** (81.5 mg, 0.119 mmol). This was then dissolved in THF (4.0 mL) and cooled in an ice-water bath, stirred for 10 min, followed by the addition of TBAF(*t*BuOH)$_4$ (73.1 mg, 0.131 mmol). The solution turned bright yellow, was stirred for 5 min, then quenched by the addition of 0.5 N aqueous HCl (turns colorless) and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered,

and concentrated under reduced pressure to give a white solid. The crude residue was purified by MPLC (0%→100% EtOAc in hexanes, 4g column, 18 mL/min, 15 min run time) to give **6.64** (59.2 mg, 94% yield) as a beige solid. Crystals suitable for X-Ray crystallographic analysis were obtained by vapor diffusion (CH_2Cl_2/pentane).

6.74 was obtained using analogous procedure using TBS ether **6.73** (92.1 mg, 0.133 mmol), THF (4.0 mL), and TBAF(*t*BuOH)$_4$ (82 mg, 0.147 mmol) to give **6.74** (62.0 mg, 88% yield) as a white solid.



6.64

***Data for* 6.64**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (br. s, 1H), 7.44 (d, *J* = 2.3 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 4.58 (s, 1H), 4.23 – 4.01 (m, 2H), 2.87 (q, *J* = 7.2 Hz, 1H), 2.66 (dt, *J* = 17.5, 1.6 Hz, 1H), 2.53 (d, *J* = 17.5 Hz, 1H), 1.96 – 1.73 (m, 5H), 1.69 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.70 (t, *J* = 7.4 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 207.5, 170.3, 165.3, 157.0, 149.1, 139.2, 131.2, 124.0, 122.3, 112.7, 112.5, 80.3, 72.9, 63.0, 58.7, 48.0, 47.2, 26.0, 24.9, 22.0, 18.7, 18.5, 18.3, 13.9, 8.6, -4.1, -4.1.

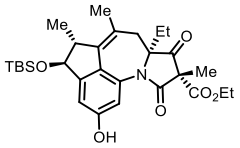
IR (thin film): 3269, 2955, 2930, 2886, 2857, 1775, 1748, 1704, 1675, 1617, 1453, 1389, 1296, 1257, 1227, 1062, 836 cm^{-1}.

HRMS (ESI+): calculated for $C_{29}H_{41}NO_6SiNa^+$ $[M+Na]^+$ 550.2595, found: 550.2600.

TLC: 0.37 (30% EtOAc in hexanes).

mp: 166.9 °C (decomposition)

Physical Appearance: Beige solid / colorless crystalline solid (after crystallization).



6.74

***Data for* 6.74**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (br. s, 1H), 7.63 (d, *J* = 2.3 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 4.61 (s, 1H), 4.21 – 4.07 (m, 2H, overlap with EtOAc), 2.88 (q, *J* = 7.2 Hz, 1H), 2.73 (dt, *J* = 17.0, 1.6 Hz, 1H), 2.52 (d, *J* = 17.1 Hz, 1H), 2.04 (s, EtOAc), 1.89 (s, 3H), 1.83 – 1.71 (m, 2H), 1.64 (s, 3H), 1.25 (t, *J* = 7.1 Hz, EtOAc), 1.13 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.73 (t, *J* = 7.4 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 207.7, 171.4 (EtOAc), 170.4, 165.2, 157.0, 149.4, 140.8, 131.2, 123.4, 112.8, 112.1, 80.2, 71.9, 63.1, 60.6 (EtOAc), 58.5, 47.5, 46.8, 26.0, 24.1, 22.9, 21.2 (EtOAc), 18.9, 18.5, 18.4, 13.9, 8.5, -4.1, -4.2.

IR (thin film): 3251, 2954, 2928, 2883, 2856, 1775, 1745, 1705, 1673, 1616, 1453, 1389, 1362, 1296, 1258, 1229, 1061, 835 cm^{-1}.

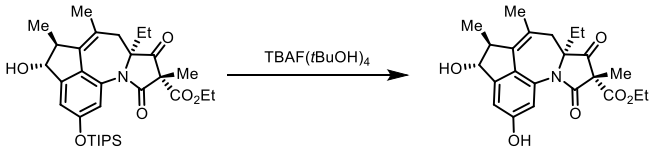
HRMS (ESI+): calculated for $C_{29}H_{41}NO_6SiNa^+$ $[M+Na]^+$ 550.2595, found: 706.3927.

TLC: 0.38 (30% EtOAc in hexanes).

mp: 214.8 °C (decomposition)

Physical Appearance: White solid.

Phenol **6.75**



6.61 (quant. yield) 6.75

Experimental: To a vial containing alcohol **6.61** (165 mg, 0.290 mmol) was added THF (10 mL) and cooled in an ice water bath followed by the addition of TBAF(*t*BuOH)$_4$ (176

mg, 0.315 mmol). Over the course of 5 min, the reaction went from yellow, to dark brown, and finally yellow/orange in color at which point it was quenched by the addition of 0.5 N aqueous HCl and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to a crude residue. The crude residue was purified by silica gel flash column chromatography to give phenol **6.75** (120 mg, quant. yield) as a beige amorphous solid. An analytically pure sample was obtained by HPLC purification (linear gradient 0%→100% EtOAc in hexanes, 10 mL/min, 10 min runtime).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 2.2 Hz, 1H), 7.30 (br. s, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 4.60 (s, 1H), 4.25 – 4.13 (m, 2H), 3.01 (q, *J* = 7.2 Hz, 1H), 2.67 (d, *J* = 17.4 Hz, 1H), 2.55 (d, *J* = 17.5 Hz, 1H), 1.88 (s, 3H), 1.89 – 1.76 (m, 2H), 1.68 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.71 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.4, 170.0, 165.5, 157.0, 148.5, 138.5, 131.8, 124.1, 123.8, 113.2, 112.2, 79.6, 72.6, 63.0, 58.6, 47.5, 47.2, 25.1, 22.1, 18.8, 18.5, 14.0, 8.6.

IR (thin film): 3293, 2976, 2928, 2872, 1773, 1744, 1678, 1615, 1480, 1452, 1391, 1295, 1227, 1017, 730 cm^{-1}.

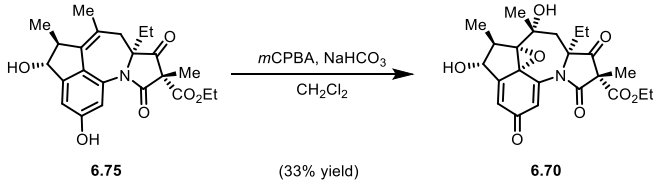
HRMS (ESI+): calculated for $C_{23}H_{27}NO_6Na^+$ $[M+Na]^+$ 436.1731, found: 436.1737.

TLC: 0.23 (50% EtOAc in hexanes).

m.p.: 114.5 – 132.8 °C.

Physical Appearance: Beige amorphous solid.

Spiroepoxide **6.70**



Experimental: To a vial containing phenol **6.75** (29.1 mg, 0.070 mmol) was added CH_2Cl_2 (2.0 mL) and cooled to 0 °C in an ice water bath. After cooling, to this was added $NaHCO_3$ (141 mg, 1.68 mmol) and *m*CPBA (40.1 mg, 0.179 mmol, 77% purity). The reaction turns slightly orange and is stirred for 5 h 20 min and then quenched by the addition of saturated aqueous thiosulfate. The mixture is extracted with CH_2Cl_2 (3x) and the combined organics are dried over $MgSO_4$, filtered, and concentrated. Repeated flash chromatography gave a spiroepoxide **6.70** (estimated yield based on inspection of the crude NMR: ~40%). A crystal suitable for X-Ray diffraction studies was obtained by the slow evaporation from Et_2O solvent.

On **6.75** (37 mg, 0.089 mmol) scale, **6.70** (13.6 mg, 0.029 mmol, 33% yield) was obtained.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 (d, *J* = 1.6 Hz, 1H), 6.60 (dd, *J* = 1.7, 0.8 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.10 (br. s, 1H), 2.79 (q, *J* = 7.6 Hz, 1H), 2.52 (d, *J* = 14.0 Hz, 1H), 2.31 – 2.12 (m, 3H), 1.60 (s, 3H, overlap with H_2O), 1.36 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H, overlap with grease), 1.21 (d, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H, overlap with grease).

^{13}C NMR (151 MHz, $CDCl_3$): δ 206.8, 186.8, 169.8, 164.4, 157.5, 139.1, 131.8, 129.1, 83.0, 76.4, 73.6, 71.3, 63.5, 62.7, 57.9, 48.9, 46.8, 33.3, 27.0, 18.5, 15.9, 14.0, 8.5.

IR (thin film): 3427, 2982, 2941, 2882, 1776, 1718, 1674, 1637, 1454, 1377, 1274, 1234, 1111, 1046, 905, 732 cm^{-1}.

HRMS (ESI+): calculated for $C_{23}H_{27}NO_8Na^+$ $[M+Na]^+$ 468.1629, found: 468.1630.

TLC: 0.11 (70% EtOAc in hexanes).

mp: Decomp.

Physical Appearance: White crystalline solid.

6.7 References

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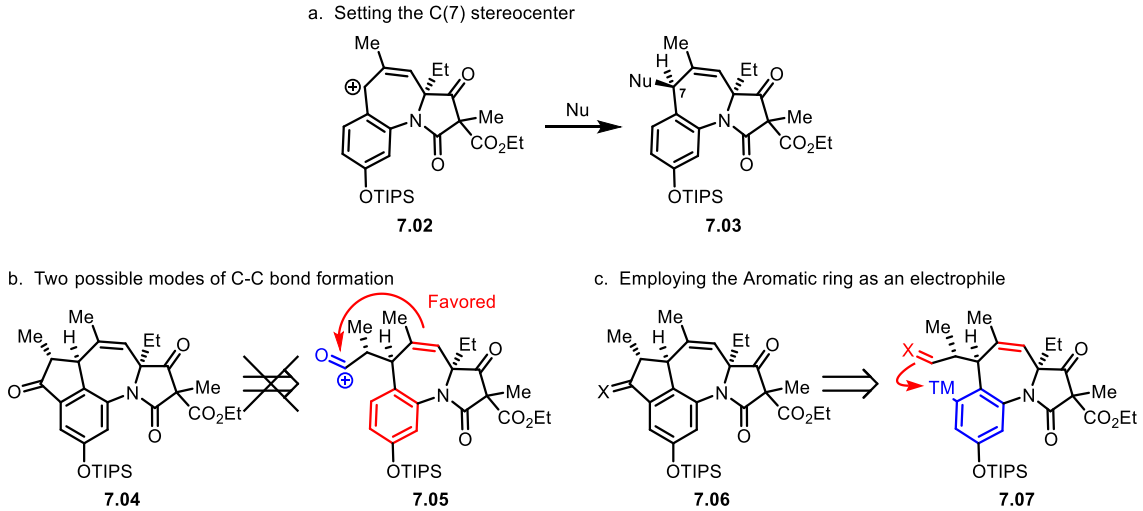
CHAPTER SEVEN

Access to The Tetracyclic Aglycone Core via Heck Cyclization[1]

7.1 Overall Strategy

So far, our efforts to install the final five-membered ring residing in the core structure of tetrapetalones had involved top-down intramolecular Friedel-Crafts approaches (Chapter 5) and bottom-up strategies employing RCM and cation-π cyclization reactions (Chapter 6). Overall, some of these strategies had delivered the final ring system however efficiency was often low and products were either unstable or possessed functional group arrays that were recalcitrant towards further advancement. Nonetheless, these efforts had provided valuable insight into possible ways forward. In particular, we had learned from our Friedel-Crafts efforts that nucleophiles would add to the ß-face of the molecule on intermediate carbonium ions (e.g., **7.02**→**7.03**) to set the C(7) stereocenter (Scheme 7.1a, top). However, these top-down efforts were unsuccessful in delivering the carbocycle (e.g., **7.04,** Scheme 7.1b, left) from intermediates akin to **7.05** due to competing reaction with the azepine alkene. Additionally, our explorations into the methods for bottom-up type pathways had revealed a number of aryl C-H activation strategies that could be used to introduce functional handles ortho to the azepine fusion. In considering these successes our efforts next turned toward examining the possibility of using transition metals to directly mediate formation of the key C-C bond (see **7.07** Scheme 7.1c, right). More specifically, we reasoned that olefin insertion via an intramolecular Heck reaction might enable construction of the last carbocycle. In addition to templating the two reacting

carbons in the cyclization reaction, we reasoned that the Heck cyclization would prevent any type of reaction with the azepine alkene.



Scheme 7.1. General Approach and the Evolution of a Heck Approach

As a general note, for the remainder of this chapter a majority of the compounds pertaining to the advancement of intermediates directed toward the tetrapetalones have an **a** or **b** designation (Figure 7.1). At the outset of these studies, the diastereomeric mixture of **7.12a** and **7.12b** were separated and the corresponding products from each respective series are designated as **a** and **b** accordingly (Figure 7.1, middle and right respectively). Only a subset of the transformations described in this chapter were carried out on what are designated as the **b**-series (Section 7.3). Any reactions whose starting substrates lack an **a** or **b** designation imply a ~3:2 diastereomeric mixture (Figure 7.1, left).

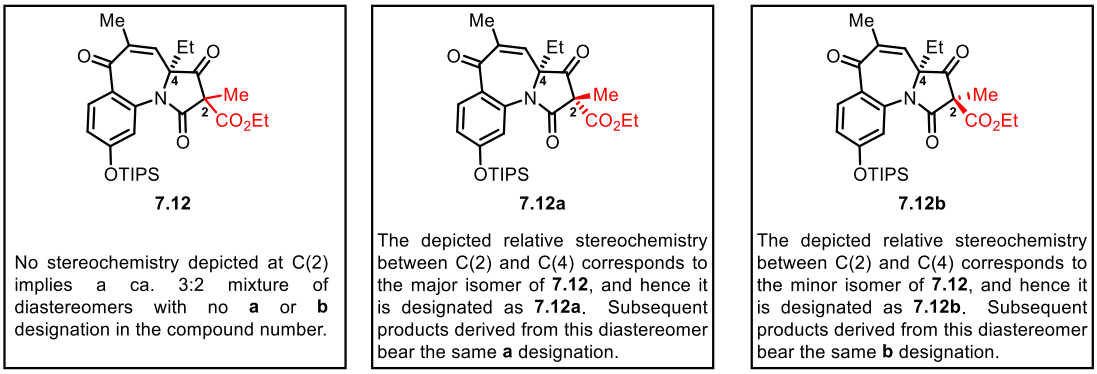
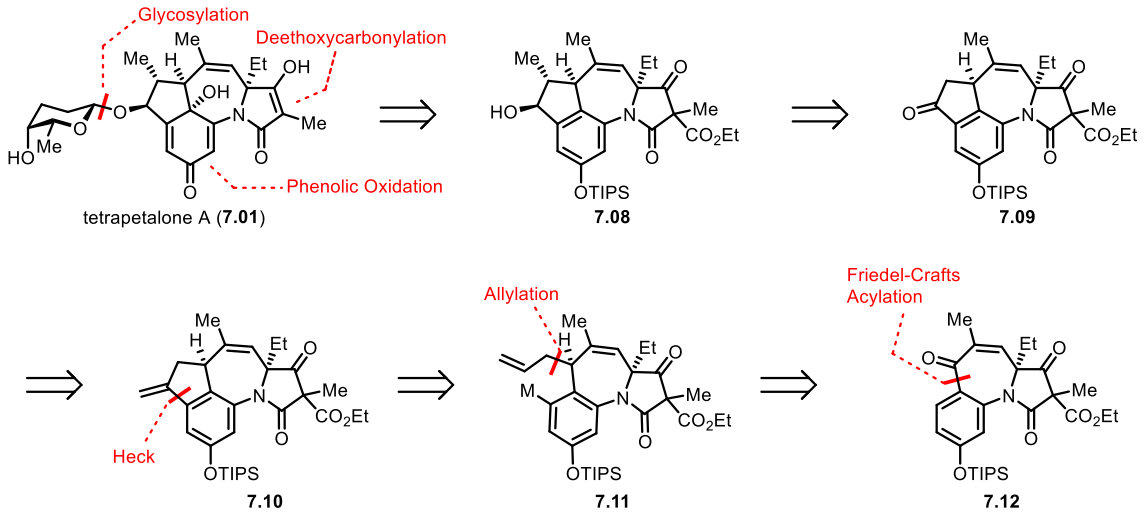


Figure 7.1. Nomenclature: **a** and **b** designations used in the remainder of this chapter

7.2 A Heck Approach to Build the Last Carbocycle

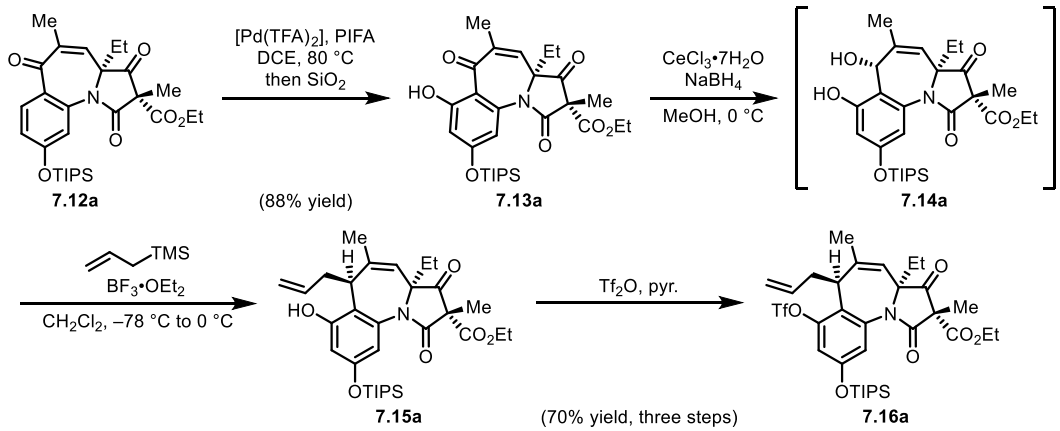
7.2.1. Relying on a Late-Stage Methylation

In accord with the notions outlined above we redesigned the synthesis as illustrated retrosynthetically in Scheme 7.2. Thus, it was envisioned that tetrapetalone A (**7.01**) would be delivered from tetracyclic alcohol **7.08** via a late stage glycosylation, phenolic oxidation, and deethoxycarbonylation sequence. Tetracyclic alcohol **7.08** would arise from diastereoselective methylation and ketone reduction of **7.09**, itself accessed by oxidative cleavage of the *exo*-olefin in **7.10**. The critical Heck product (**7.10**) would arise from a 5-exo trig cyclization of intermediate **7.11**, which we envisioned as being available from our tricyclic enone **7.12** via allylation of an intermediate carbonium ion. Based on prior experience the latter was expected to be selective for the illustrated diastereomer.



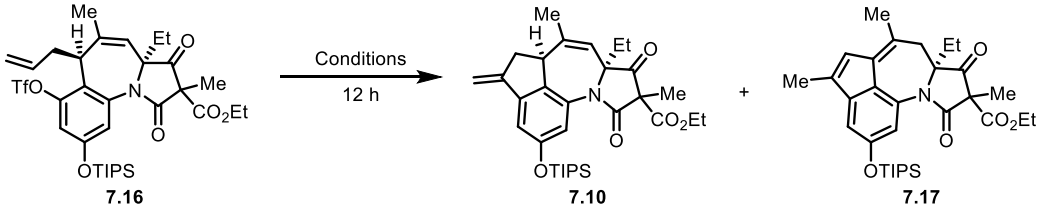
Scheme 7.2. Building the last carbocycle via Heck cyclization

In accessing the requisite Heck substrate (**7.16a**, Scheme 7.3), we were delighted to find that subjecting a single diastereomer of our key azepine intermediate (**7.12a**) to Dong's ketone directed hydroxylation furnished phenol **7.13a** in excellent yield (88% yield).[2] Luche reduction of **7.13a** gave a very unstable *ortho*-hydroxy benzylic alcohol (**7.14a**) which, in the presence of BF_3•OEt_2 and allyltrimethylsilane underwent diastereoselective allylation to **7.15a**. Triflation of **7.15a** then afforded our Heck precursor (**7.16a**) in excellent yield over these three steps.



Scheme 7.3. Preparation of a Heck precursor

Table 7.1. Optimizing the Heck cyclization



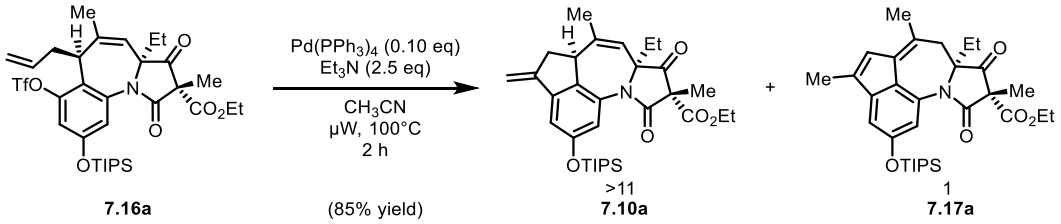
Entry	Catalyst	(mol%)	Ligand	(mol%)	Base	(mol %)	Solvent	Additive	(mol%)	Temp. (°C)	Product (**7.10**:**7.17**:**7.16**)[a]
1	$Pd(OAc)_2$	5.5	PPh_3	11	Et_3N	500	DMF	Et_4NCl	210	90	-
2	$Pd(PPh_3)_4$	10	-	-	Et_3N	150	MeCN	-	-	90	5 : 1 : 12
3	$Pd(PPh_3)_4$	10	-	-	K_2CO_3	100	MeCN	-	-	90	-
4	$Pd(PPh_3)_4$	10	-	-	KOAc	100	MeCN	-	-	90	1.34 : 1 : 1.5
5	$Pd(PPh_3)_4$	10	-	-	Et_3N	500	MeCN	-	-	90	3 : 1 : 0
6	$Pd(PPh_3)_4$	10	-	-	Et_3N	500	THF	-	-	90	1.4 : 1 : 2
7	$Pd(PPh_3)_4$	10	-	-	Et_3N	500	Toluene	-	-	90	2.85 : 1 : 0.87
8	$Pd(PPh_3)_4$	10	-	-	Et_3N	3000	MeCN	-	-	90	3 : 1 : 1
9	$Pd(PPh_3)_4$	10	-	-	Et_3N	250	MeCN	-	-	90	>11 : 1 : 0

[a] In the course of these studies, the only observed compounds on analysis of the crude NMR was compounds **7.10**, **7.17**, and recovered **7.16**. Thus focus was paid only to the optimization of the ratio of **7.10**:(**7.17**, **7.16**) and analyzed by crude ^{1}H NMR.

In planning the current approach, we had done a rather extensive review of the literature on Heck reactions and realized that cyclizations of this type could be plagued with alkene isomerization events and typical conditions often give products derived from alkene migration to the endocyclic position. Since we hoped to produce the exomethylene product **7.10**, in initial efforts (entry 1, table 7.1) we employed conditions developed in the Blechert and Shinde groups where additives such as Et_4NCl had been shown to minimize alkene isomerization.[3] Although applying these conditions failed to give any of the desired product, standard Heck cyclization conditions in acetonitrile (entry 2) did produce the desired cyclization product. Screening these standard conditions employing a variety of organic and inorganic basis revealed that triethylamine gives the best conversion and ratio of **7.10**:**7.17** (entry 5). Further refining these conditions by variation of solvents found acetonitrile to be the most competent solvent, and it was finally by altering the equivalents

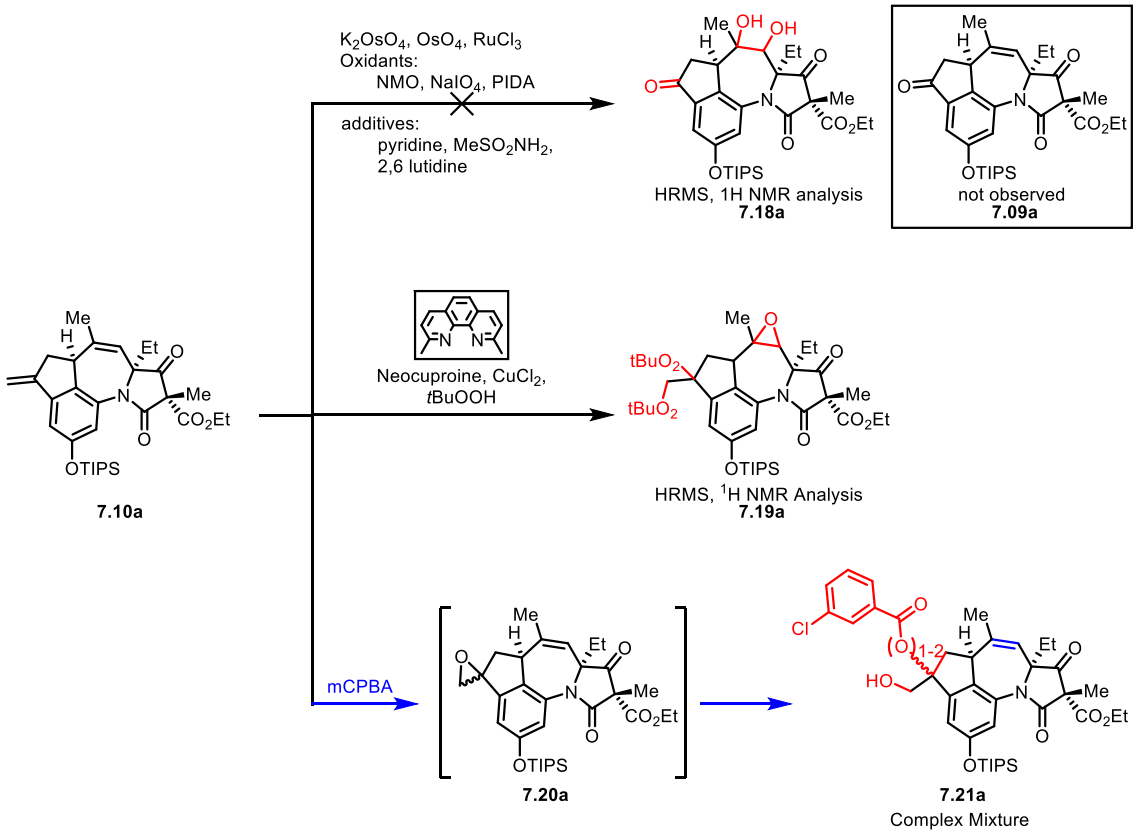
of base employed in the reaction that we were able to find conditions that gave excellent conversion and an excellent **7.10**:**7.17** ratio (entry 9).

Even better, by employing microwave irradiation to apply thermal energy, we were able to effect Heck cyclization of substrate **7.16a** in 85% yield, with minimal amount of olefin isomerization product **7.17a** detected (Scheme 7.4). Now with sufficient access to **7.10a**, we looked to explore oxidative cleavage of the *exo*-olefin.



Scheme 7.4. Optimized Heck cyclization

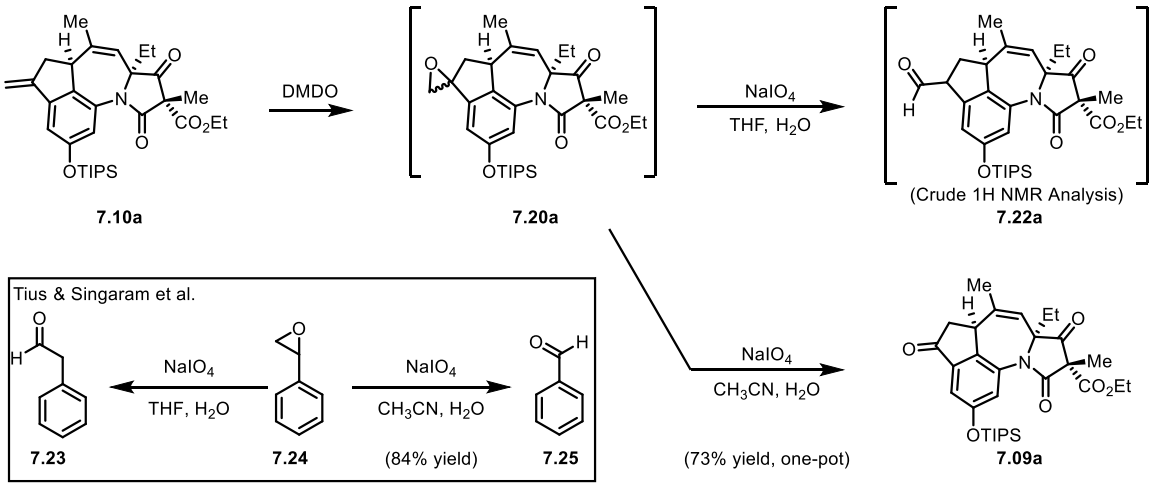
Toward the latter end, surveying the reactivity of 7.10a under conditions found in the literature involving Lemieux-Johnson oxidation, or stepwise Upjohn dihydroxylation followed by cleavage failed to give any of the desired product and resulted in complex mixtures of what appeared to be over-oxidation products by HRMS and ^{1}H-NMR analyses (e.g., **7.18a**, Scheme 7.5, top).[4] Moving on from the traditional approaches, we considered more recently developed radical based methods, however, ^{1}H NMR analysis of isolated products gave evidence of over oxidation and the formation of epoxide **7.19a** with no **7.09a** detected.[5] Although some selectivity in the oxidation of **7.10a** was seen when *m*CPBA was used as oxidant, the reaction furnished a complex mixture of what appeared to be hydroxy-esters **7.21a**, which presumably formed via ring opening of intermediate epoxide **7.20a** by the *m*-chlorobenzoic acid by-product.[6]



Scheme 7.5. Attempts to effect oxidative cleavage of an *exo*-olefin

Given some hope that electrophilic epoxidizing agents could be employed to selectively target the electron rich styrenyl double bond we next explored the use of DMDO (Scheme 7.6).[7] Unlike *m*-CPBA, the byproduct from this reagent (acetone) was not expected to promote epoxide opening and would thus enable our exploration of several conditions found in the literature for inducing a one-step epoxide hydrolysis/cleavage reaction (Scheme 7.6). In initial studies, treatment of **7.10a** with DMDO followed by aqueous sodium periodate gave complex mixtures including the formation of aldehyde products, presumably via the formation of **7.22a** by Meinwald rearrangement.[8] In a further search of the literature, we found a report by Tius and Singaram that indicated rearrangement problems could be avoided by employing acetonitrile as solvent (Scheme

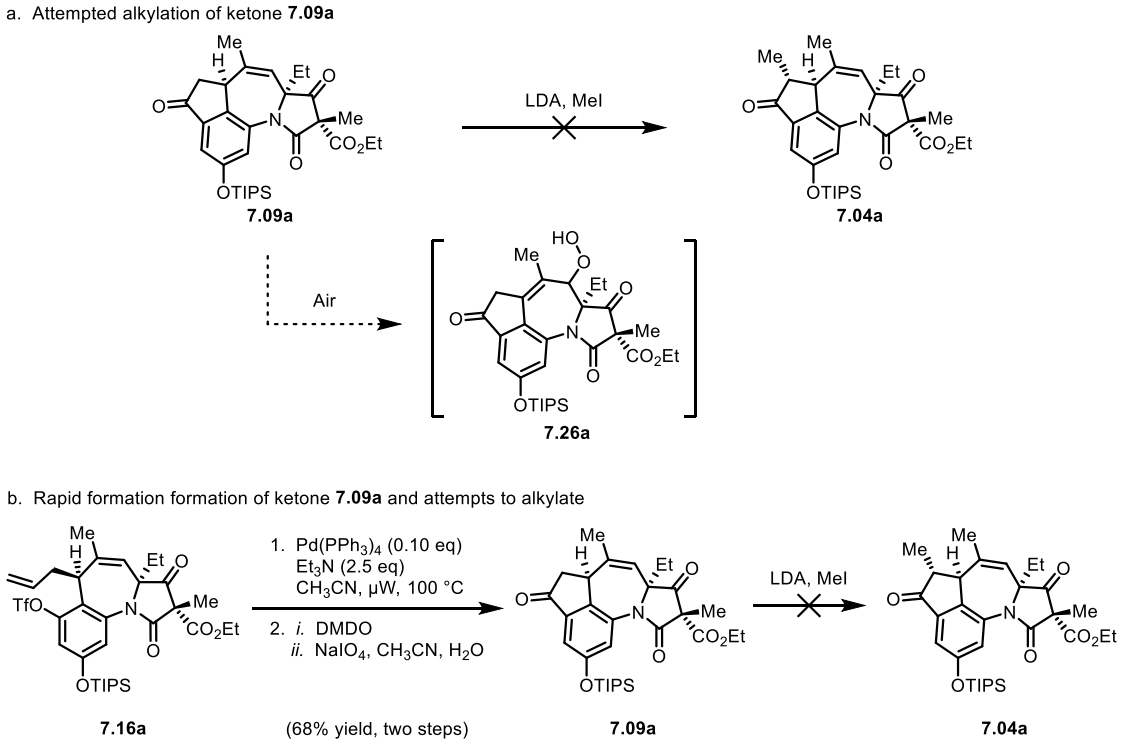
7.6, inset).[9] We were delighted to find that applying a slight modification of these conditions permitted access to tetracyclic ketone **7.09a** in excellent yield, and in one-pot from Heck product **7.10a**.



Scheme 7.6. Successful oxidative cleavage to access a tetracyclic ketone

Having developed a robust method for introducing the final carbocyclic ring attention was now turned to introducing the methyl group α to the newly installed carbonyl. Much to our surprise, preliminary efforts to alkylate were unsuccessful,[10] primarily due to the instability of the ketone **7.09a** which appeared to be the result of air oxidation to allylic peroxide **7.26a** (Scheme 7.7a, top). Inspection of samples left under argon in the freezer showed the disappearance of the azepine alkene which we have tentatively attributed to the formation of allyl peroxide **7.26a** via ene reaction with oxygen. With this insight into the instability of our tetracyclic compounds, we attempted rapid Heck cyclization, ketone formation, and alkylation over the course of a single afternoon but were still unsuccessful in our attempts to alkylate (Scheme 7.7b, bottom). As has been a common element in many

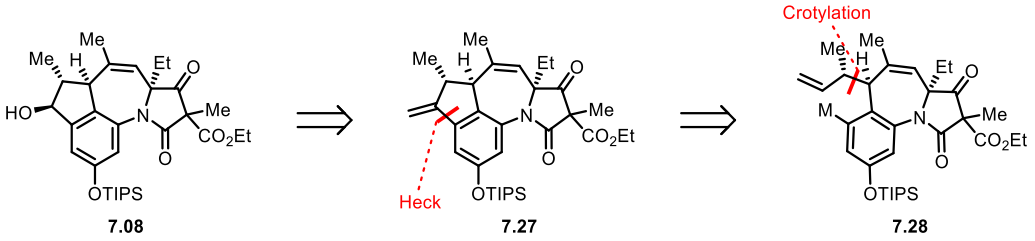
of the tetracycles we had prepared, the instability of not only ketone **7.09a**, but also of Heck product **7.10a**, caused us to re-evaluate the synthesis.



Scheme 7.7. Preliminary efforts to effect α-methylation

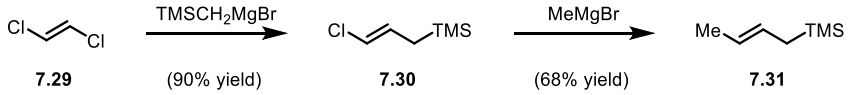
7.2.2. A Crotylation Reaction for Early Methyl Installation

Based upon an increasing number of observations indicating that many advanced intermediates in the tetrapetalone synthesis are sensitive to towards oxidation and even purification conditions, convergency was becoming a necessity. In this regard we recognized that early introduction of the methyl group would certainly save late stage steps and could possibly provide additional stability to the intermediates. Thus, instead of relying on a late stage methylation and reduction to deliver **7.08**, we would attempt to employ crotylation to give **7.28**, which could then be advanced via a similar Heck reaction sequence (Scheme 7.8).



Scheme 7.8. A Heck strategy on a crotylated substrate

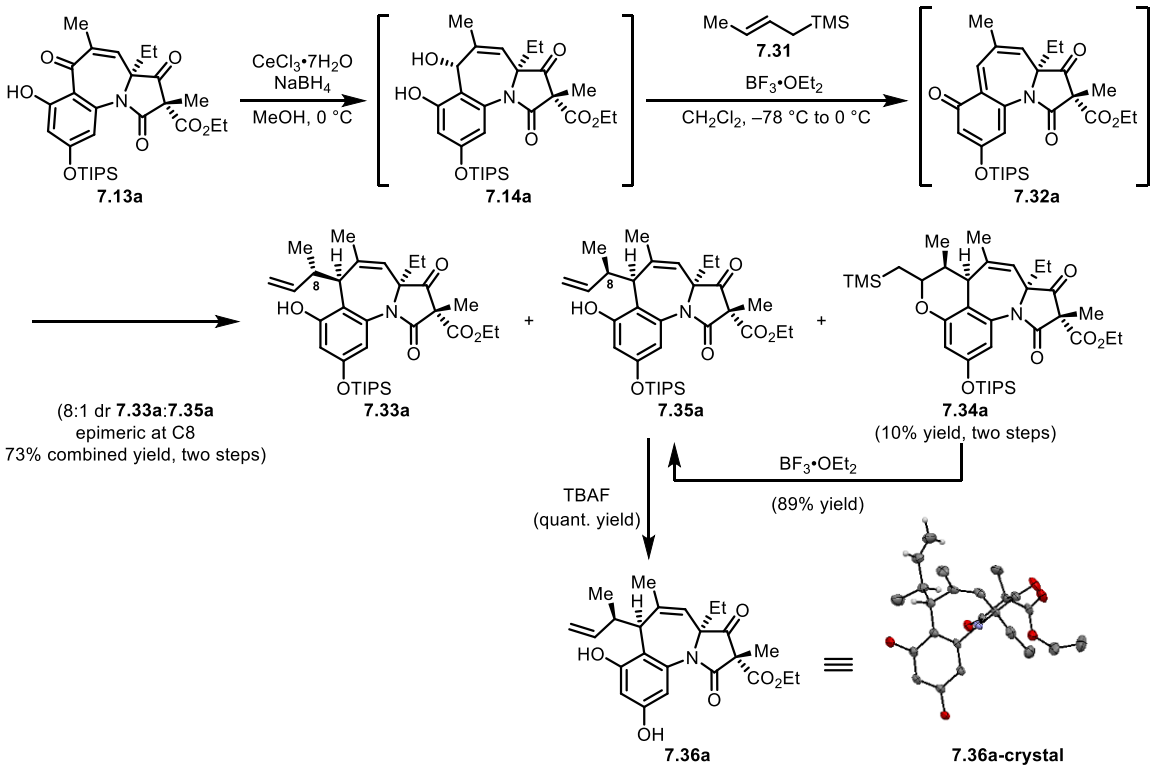
It should be noted that our initial foray into the Heck cyclization on a substrate lacking the methyl group was predominantly guided by the ease with which we could access allyltrimethylsilane (commercially available) and initial problems encountered in the preparation of crotyltrimethylsilane. After exploring a number of tedious strategies for the preparation of **7.31**, we finally settled on a procedure that was readily scalable and gave isomerically pure *trans*-crotylsilane **7.31** by two sequential Kumada couplings from *trans*-dichloroethene **7.29** (Scheme 7.9).[11]



Scheme 7.9. Accessing crotylsilane

In a sequence nearly identical to that employed previously (i.e., Scheme 7.3), phenol **7.13a** was subject to Luche reduction to give an unstable intermediate alcohol which, without purification was treated with BF_3•OEt_2 and crotyl silane **7.31** (Scheme 7.10). These latter conditions presumably generate an *ortho*-quinone methide (**7.32a**) which undergoes reaction with **7.31** to furnish a mixture of three products **7.33a**, **7.35a**, and **7.34a**. The relative stereochemistry of the diastereomeric crotyl addition products (**7.33a** and **7.35a**) was assigned as illustrated via crystallographic analysis (*vide infra*). The

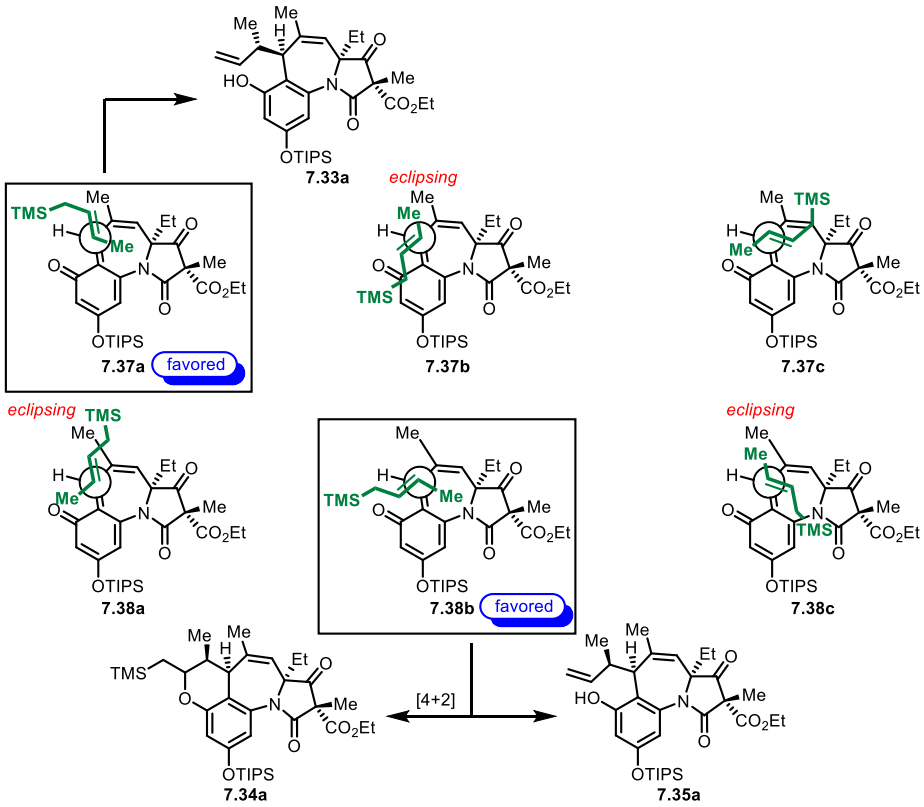
third component in the reaction mixture was spectroscopically accordant with chromane **7.34a**. Interestingly, re-exposure of this latter product to the reaction conditions at higher temperature, gave exclusively the wrong homobenzylic stereochemistry product **7.35a**. Confirmation of the structures and stereochemical assignments for the compounds produced in the crotylation reaction followed from single crystal X-ray analysis of the phenol derived from TBAF mediated TIPS deprotection of **7.35a**. After realizing that adduct **7.34a** was forming exclusively the undesired C(8) epimer, we began employing careful temperature control to trap as much of this [4+2] adduct as possible and thereby facilitate removal of the unwanted diastereomer.



Scheme 7.10. Accessing a crotylated substrate

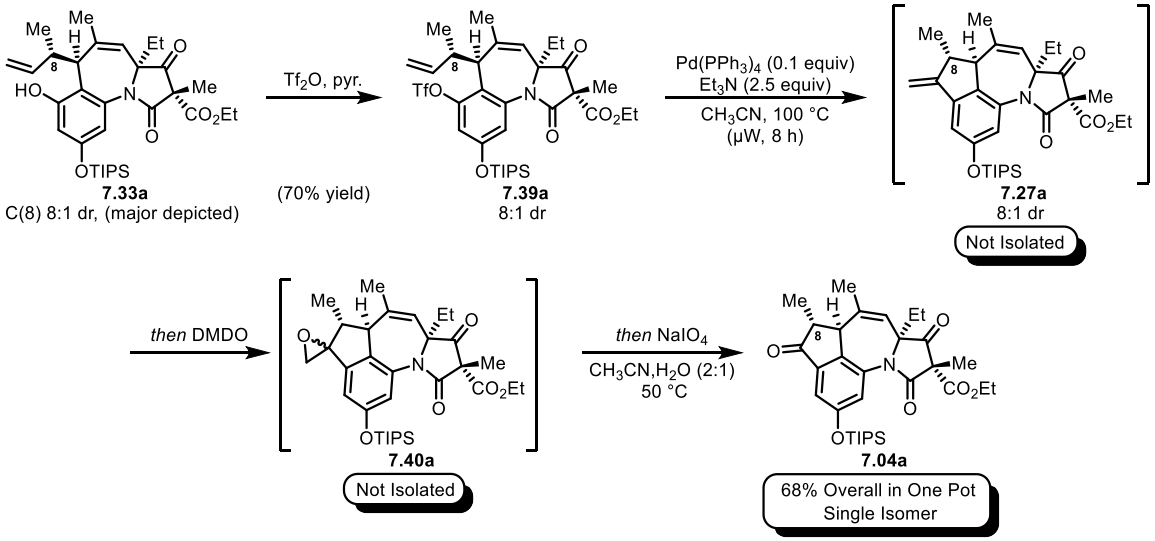
The transformation from **7.14a** to **7.33a/7.35a** warrants further discussion as it is likely that competing mechanistic pathways are operative. In one scenario, if the reaction

proceeds by way of an open transition state, one can envision six different transition state models as depicted by the Newman projections in Scheme 7.11, three staggered positions for each face of the silane (**7.37a-c** and **7.38a-c**, respectively). Considering the various steric interactions that would occur in each, one might expect reaction via **7.37a** and **7.38b** (boxed). Notably the remaining transition structures experience unfavorable syn-pentane-like interactions (e.g., **7.37b**, **7.38c**, and **7.38a**) or steric clashes between the bulky methylene-TMS moiety and resident ring system (e.g., **7.37c** and **7.38c**) . In examining **7.38b**, on can envision a mechanistic pathway wherein the *o*-quinone methide and crotyl silane could undergo a Diels-Alder [4+2] cycloaddition reaction. This type of reactivity is certainly evidenced by the formation of **7.34a** wherein the observed stereochemical outcome would be consistent with illustrated transition structure.



Scheme 7.11 Transition state models rationalizing the crotylation stereochemical outcome

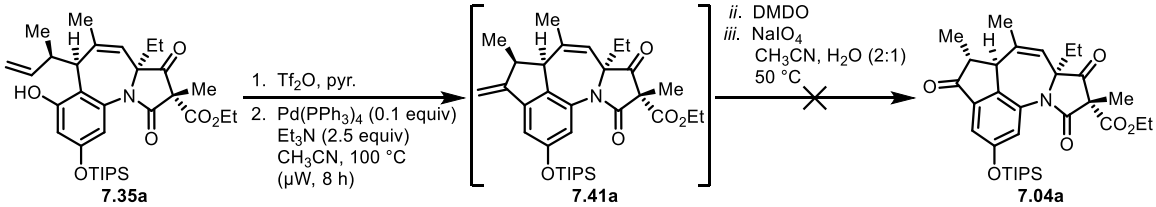
Regardless of the mechanistic underpinnings, having successfully accessed **7.33a** we next explored the Heck reaction and employed the protocol we had established earlier for the des-methyl series (Scheme 7.12). To our delight, triflation of **7.33a** followed by Heck reaction of the resultant triflate (**7.39a**), under the previously optimized conditions, resulted in smooth conversion to **7.27a**. Moreover, solvent exchange and treatment of **7.27a** with an acetone solution of DMDO provided an intermediate spiroepoxide (**7.40a**) which, following yet another solvent exchange and treatment with $NaIO_4$ in CH_3CN and H_2O, furnished **7.04a** as the sole isolable diastereomer. It's notable that this single-pot transformation begins with an ~8:1 mixture of diastereomers that are epimeric at the homobenzylic methyl group and ends with the isolation of a single ketone product.



Scheme 7.12. Successful Heck cyclization and preparation of tetracyclic ketone **7.04a**

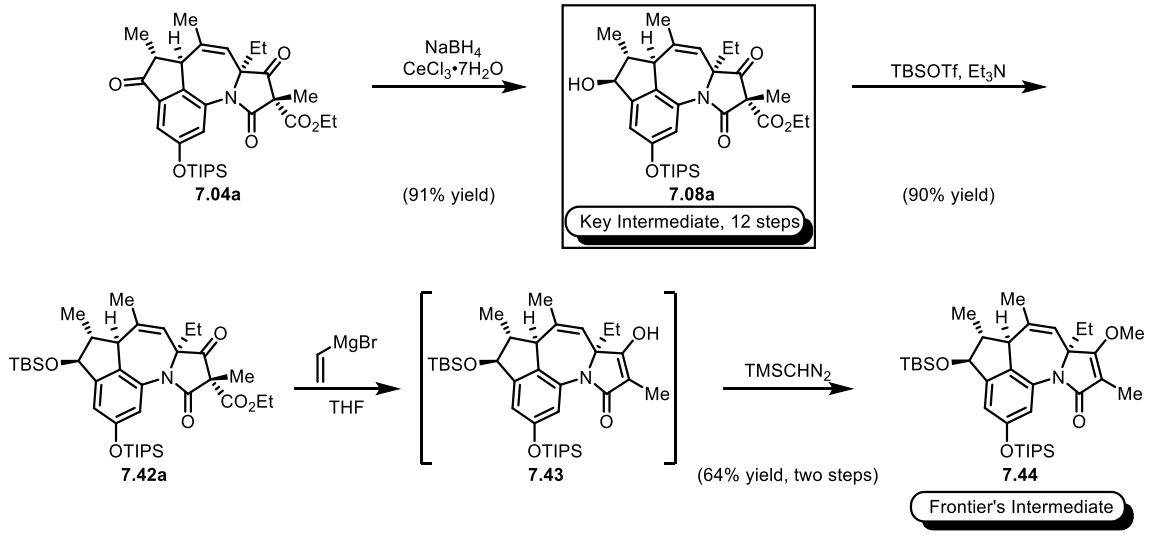
To clarify this seemingly stereoconvergent outcome and address the possibility of epimerization during the reaction sequence, we separately took diastereopure compound **7.35a** and exposed it to the same one-pot Heck/oxidative cleavage protocol (Scheme 7.13). While the Heck reaction proceeded smoothly to give intermediate **7.41a**, issues with the

oxidation prevented success in the formation of **7.04a** and none of it was detected in the crude NMR. Although a complete understanding of why **7.41a** fails to undergo further reaction is lacking, we can offer two possible explanations. (1) Empirical data of the DMDO oxidation shows lower selectivity for the styrenyl double bond over the azepine alkene when the methyl group is on the ß-face of the molecule. (2) As noted earlier, compounds in which the methyl group and the benzylic methine C-H are *trans* to one another were found to be unstable in air, and it's possible that during the course of the reaction, **7.41a** and any subsequent intermediates may have undergone oxidative decomposition.



Scheme 7.13. Addressing the single diastereomeric product observation of **7.04a**

Preparation of key tetracyclic alcohol **7.08a** was achieved by borohydride reduction of ketone **7.04a** (Scheme 7.14). It should be noted, initial studies into the reduction of various tricyclic enones (e.g., **7.12**, Scheme 7.2) revealed that in the absence of cerium additives the substrates undergo competitive reduction of the ketone present in the lactam ring, thus for the reduction of **7.04a** we only explored conditions involving cerium trichloride as an additive.



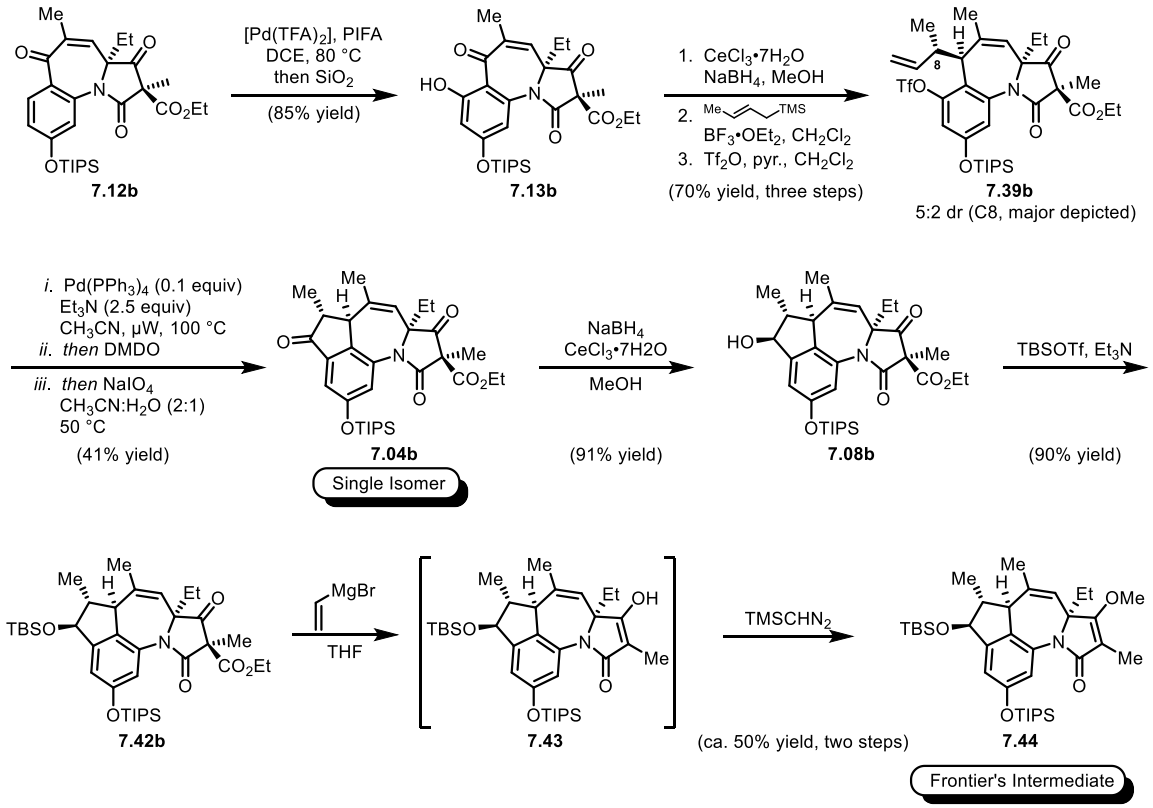
Scheme 7.14. Successful preparation of a tetracyclic alcohol and confirmation of the stereochemistry

Having completed construction of the key tetracycle **7.08a**, we diverted some of this material to a chemical correlation study and prepared an intermediate that had been produced in Frontier's synthetic studies (i.e., **7.44**, Scheme 7.14)). This chemical correlation commenced with TBS protection of **7.08a** to furnish **7.42a** which, in turn, was subjected to vinyl Grignard induced deethoxycarbonylation and methylation to produce **7.44**. The derived material was found to be in complete accord with that previously reported by Frontier; a result that confirmed our relative stereochemical assignments and enabled, via analogy, the stereochemical assignment of several previous structures.

7.3 Successfully Advancing the Opposite Masked Tetramic Acid Diastereomer

To minimize the complexity of the spectral data we had, throughout the studies described above, been employing a single diastereomer of our tricyclic enone (**7.12a**) and not advanced the corresponding isomer **7.12b**. To demonstrate that this Heck strategy could be employed on both **7.12a** and **7.12b**, we began studies to advance the latter to the

analogous tetracyclic alcohol **7.08b** (Scheme 7.15). As illustrated, tricyclic enone **7.12b** was elaborated to Heck precursor **7.04b** through the analogous crotylation, triflation, Heck, and oxidative cleavage sequence and found to behave similarly with regard to yield and diastereochemical outcome. Reduction of **7.04b** under Luche conditions gave **7.08b** whose relative stereochemistry was again confirmed by advancement to Frontier's intermediate **7.44**.



Scheme 7.15. Advancing the opposite masked tetramic acid diastereomer

7.4 Experimental

General

Unless otherwise stated, reactions were magnetically stirred in flame or oven dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and

methanol were dried over calcium hydride and freshly distilled. Diethyl ether, tetrahydrofuran, toluene, benzene, dichloromethane, and acetonitrile were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. ACS grade acetone (Fisher) was purchased from Fisher-Scientific and used as received. Dimethyl formamide and 1,2-dichloroethane (DCE) were purchased from Sigma-Aldrich and used as received. $Pd(PPh_3)_4$ was purchased from Sigma-Aldrich and stored under nitrogen in a -20°C freezer. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Millipore glass-backed 60Å plates (indicator F-254s, 150-180 µm thickness) (Millipore, catalogue #1164850001). Column or flash chromatography was performed with the indicated solvents using Millipore Silica Gel 60 (0.040-0.063 mm, 230-400 mesh ASTM) as the stationary phase. MPLC purifications were performed on a Telodyne Isco Combi*Flash*® *Rf*+ (Model: RF + UV-VIS MS COMP), used with standard Telodyne Isco normal phase disposable columns for flash chromatography and monitored at wavelengths of 254 and 280 nm. All melting points were obtained on a Chemglass Life Sciences melting point device (Model: DMP100) and are uncorrected. Infrared spectra were obtained using a Bruker Alpha ATR-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, Varian 500, or Bruker 600. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million (ppm) relative to internal residual solvent peaks from the indicated deuterated solvents (^{1}H: For $CDCl_3$, $CHCl_3$ 7.26; For Methanol-d_4, CD_2HOD 3.31; For Acetone-d_6, Acetone-D5H 2.05). Chemical shifts (δ) for ^{13}C spectra were referenced from the indicated solvent peaks (^{13}C: $CDCl_3$ 77.16, Methanol-d_4 49.00, Acetone-d_6 29.84). Chemical shifts in ^{19}F spectra were taken in $CDCl_3$ doped with

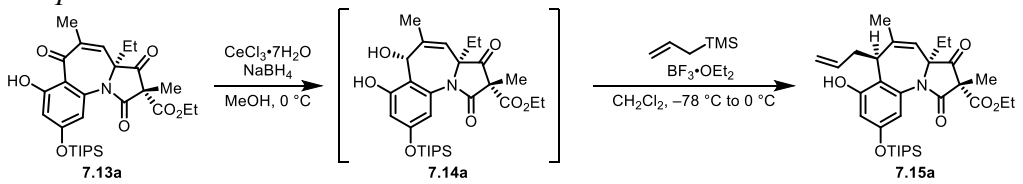
fluorobenzene and referenced to -113.15. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as s = singlet, br.s = broad singlet, d = doublet, br. d = broad doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High resolution mass spectra were performed on a Thermo LTQ Orbitrap Discovery with direct injection followed by electro-spray ionization (ESI). Microwave reactions were carried out using a CEM Discover SP Microwave system. Single crystal X-ray diffraction studies were collected on a Bruker Apex II-CCD detector using Mo-K_α radiation (λ = 0.71073 Å). Structures were solved and refined using SHELXTL. Optical rotations were obtained on a Rudolph Research Analytical Autopol IV Automatic Polarimeter.

High-Performance Liquid Chromatography (HPLC): All HPLC purifications were carried out on a Waters HPLC system (consisting of a Waters 1525 binary HPLC pump with direct injection port and monitored at 254 nm unless otherwise specified with a Waters 2489 UV-Visible detector). All purifications utilized a normal-phase Sunfire, Silica Prep 10 µm, 10 x 250 mm column.

Ultra Performance Liquid Chromatography (UPLC)-Mass Spectrometry (MS): All UPLC-MS experiments were carried out on a Waters Acquity H UPLC Class system using the indicated solvent systems as eluents. All separations were performed on a reverse phase Acquity UPLC BEH C18 1.7 µm, 2.1 x 50 mm column.

^{1}H and ^{13}C NMR spectra are included for all previously unreported compounds.

Allylated phenol **7.15a**



Experimental: To a rbf was added **7.13a** (65.0 mg, 0.114 mmol) and this dissolved in MeOH (2.0 mL). To this was added $CeCl_3$•$7H_2O$ (142 mg, 0.381 mmol) and cooled in an ice water bath. After cooling, to this was added $NaBH_4$ (5.7 mg, 0.15 mmol) after which the initially yellow suspension turned into a yellow solution and finally went almost colorless. The reactino was stirred for 10 min in the ice-water bath after which TLC indicated no starting material present. The faint yellow solution was then quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a pink oil. This was then held under hi-vac for 15 minutes.

After placing under hi-vac for 15 min, the crude residue was dissolved in CH_2Cl_2 (4.0 mL) and cooled to –78 °C in a dry-ice acetone bath to give a pink solution. To this was added allyltrimethylsilane (0.24 mL, 1.5 mmol) and the reaction let stir for 2 min after which was added BF_3•OEt_2 (0.04 mL, 0.32 mmol). The reaction turns dark orange/brown in color. This color quickly subsides after ~20 seconds to give a faint yelow solution. The reaction was stirred for an additional 5 min in the dry-ice acetone bath after which the bath was removed and the reaction allowed to slowly warm to room temperature. The reaction was stirred for an additional 10 min after the removal of the dry-ice/acetone bath and subsequently quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a crude yellow oil that was purified by MPLC (4g column, 30 mL/min, 10 min run

time, linear gradient from 0% to 30% EtOAc in hexanes) to give **7.15a** (56 mg, 85% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.53 (d, *J* = 2.1 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 5.68 – 5.58 (m, 1H), 5.33 (s, 1H), 4.92 (s, 1H), 4.87 (d, *J* = 17.0 Hz, 1H), 4.83 (d, *J* = 10.1 Hz, 1H), 4.33 – 4.18 (m, 2H), 3.69 (dd, *J* = 10.4, 4.4 Hz, 1H), 2.45 – 2.38 (m, 1H), 2.20 – 2.11 (m, 1H), 1.92 (s, 3H), 1.84 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.61 (s, 3H), 1.53 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.30 – 1.21 (m, 6H), 1.09 (d, *J* = 7.4 Hz, 18H), 0.81 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 206.5, 168.7, 165.9, 155.2, 154.0, 139.4, 135.7, 123.7, 119.6, 117.4, 114.2, 107.7, 74.8, 62.6, 58.2, 40.6, 40.4, 29.8, 27.1, 18.8, 18.0, 13.9, 12.7, 8.7.

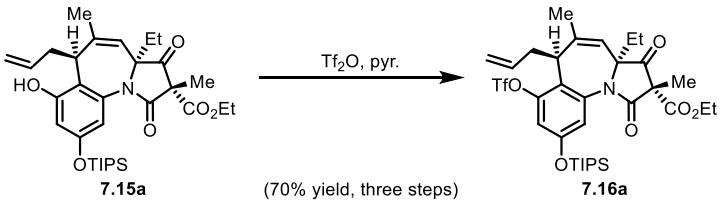
IR (thin film): cm^{-1} 3291, 2943, 2866, 1776, 1718, 1674, 1614, 1592, 1436, 1321, 1259, 1229, 1164, 1134, 1017, 866, 830, 733, 691, 644.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_6SiNa$ $[M+Na]^+$ 592.3070, found: 592.3061.

TLC: 0.36 (30% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Allylated phenol **7.16a**



Experimental: To a rbf containg **7.15a** (265 mg, 0.465 mmol) was added CH_2Cl_2 (9.3 mL) and cooled to –78 °C in a dry-ice acetone bath. After cooling, to this was added pyridine (0.19 mL, 2.3 mmol) followed by the dropwise addition of Tf_2O (0.12 mL, 0.70 mmol) over the course of ~15 seconds. The reaction was stirred for 1 h in the dry-ice acetone bath and subsequent warmed in an ice-water bath. The reaction was stirred for an

additional 30 min after which TLC showed no starting material. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a crude residue that was purified by MPLC (12g column, 36 mL/min, 15 min runtime, linear gradient from 0%→30% EtOAc in hexanes) to give **7.16a** (319.7 mg, 98% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.98 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 5.59 – 5.49 (m, 1H), 5.39 (s, 1H), 4.87 – 4.78 (m, 2H), 4.34 – 4.21 (m, 2H), 3.49 (dd, *J* = 10.6, 4.3 Hz, 3H), 2.50 – 2.43 (m, 1H), 2.16 – 2.08 (m, 1H), 1.94 (s, 3H), 1.86 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.62 (s, 3H), 1.51 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.31 – 1.22 (m, 7H), 1.09 (dd, *J* = 7.5, 3.3 Hz, 15H), 0.77 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 205.6, 168.9, 165.6, 155.7, 147.6, 138.0, 136.4, 134.3, 125.3, 123.9, 121.7, 118.8, 118.7 (q, *J* = 320.1 Hz), 113.5, 74.8, 62.8, 58.0, 42.4, 40.2, 30.2, 26.5, 18.7, 17.85, 17.83, 14.0, 12.6, 8.5.

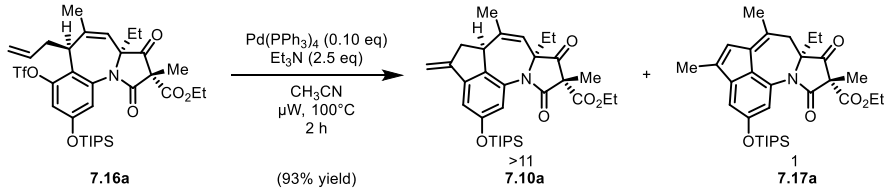
IR (thin film): cm^{-1} 2945, 2869, 1778, 1750, 1711, 1616, 1570, 1487, 1423, 1384, 1303, 1243, 1213, 1160, 1140, 1109. (*Note*: the IR was obtained on material that was a ~3:1 mixture of diastereomers, epimeric at the tetramic acid quaternary carbon).

HRMS (ESI+): calculated for $C_{33}H_{46}F_3NO_8SSiNa$ $[M+Na]^+$ 724.2558, found: 724.2557.

TLC: 0.56 (30% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Tetracyclic exo-olefin **7.10a**



Experimental: To a microwave reactor vial was added **7.16a** (69 mg, 0.098 mmol) and $Pd(PPh_3)_4$ (11.4 mg, 9.8 μmol). This was placed under hi-vac and backfilled with nitrogen (3x). This was then purged with argon with a vent needle for ~ 2 min after which CH_3CN (4.9 mL) and triethylamine (35 μL, 0.25 mmol). This was then placed in a microwave reaction vessel and heated to 100 °C for 2 h after which the reaction was quenched by the addition of diH_2O, saturated brine, and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to give a crude black/orange oil. This was then purified by MPLC (4g column, 30 mL/min, 10 min run time, linear gradient 0%→20% EtOAc in hexanes) to give **7.10a** (46.1 mg, 85% yield) as a colorless oil.

7.10a:

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 2.2 Hz, 1H), 6.91 (d, *J* = 2.2 Hz, 1H), 5.51 – 5.47 (m, 1H), 5.40 (d, *J* = 2.8 Hz, 1H), 5.10 (d, *J* = 2.3 Hz, 1H), 4.34 – 4.15 (m, 3H), 2.89 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.81 (ddt, *J* = 13.9, 10.9, 3.0 Hz, 1H), 2.24 (dq, *J* = 14.7, 7.4 Hz, 1H), 2.15 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.84 (s, 3H), 1.63 (s, 3H), 1.34 – 1.23 (m, 6H), 1.13 (dd, *J* = 7.5, 1.7 Hz, 18H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 207.7, 168.8, 165.8, 155.6, 146.7, 143.1, 143.1, 133.5, 126.9, 125.2, 117.2, 110.4, 104.0, 75.3, 62.6, 58.8, 46.4, 39.0, 25.2, 22.9, 19.0, 18.11, 18.09, 14.0, 12.8, 8.9.

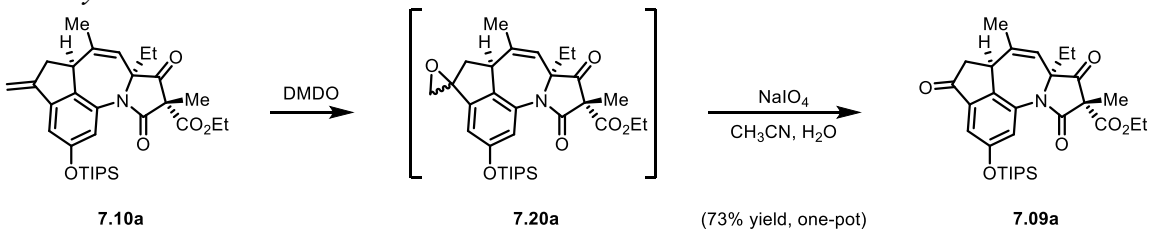
IR (thin film): cm^{-1} 2961, 2944, 2867, 1777, 1748, 1704, 1606, 1465, 1378, 1363, 1285, 1224, 1115, 882.

HRMS (ESI+): calculated for $C_{32}H_{45}NO_5SiNa$ $[M+Na]^+$ 574.2959, found: 574.2958.

TLC: 0.56 (30% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Tetracyclic ketone **7.09a**



Experimental: To a rbf containing **7.10a** (45 mg, 0.082 mmol) was added acetone (2.3 mL) and cooled to –78 °C in a dry-ice acetone bath. After cooling, to this was added DMDO (2.3 mL, ca. 35 mM in acetone) and the reaction stirred for 15 min in the dry-ice acetone bath then warmed in an ice-water bath until TLC showed no SM (ca. 15 min). The reaction was then concentrated under reduced pressure by rotary evaporation to give crude epoxide **7.20a**. This was then dissolved in a solution of $NaIO_4$ in CH_3CN:H_2O (3.65 mL, 2:1, 48 mg/mL $NaIO_4$) and placed in a preheated aluminum block at 50 °C. The reaction was stirred for 30 min and then quenched by cooling to room temperature and diluting with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3x) and the combined organics dried over $MgSO_4$, filtered, and concentrated to give a crude residue that was purified by MPLC (4g column, 30 mL/min, 10 min run time, linear gradient 0%→30% EtOAc in hexanes) to give **7.09a** (33 mg, 73% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (d, *J* = 2.4 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 5.61 – 5.55 (m, 1H), 4.66 – 4.58 (m, 1H), 4.30 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.91 (dd, *J* = 17.1, 6.9 Hz, 1H), 2.82 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.35 – 2.22 (m, 2H), 1.89 (t, *J* = 1.6 Hz, 3H), 1.64 (s, 3H), 1.35 – 1.24 (m, 6H), 1.11 (dd, *J* = 7.5, 2.0 Hz, 18H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 206.9, 202.1, 169.0, 165.4, 156.4, 142.0, 138.7, 134.8, 134.6, 125.6, 123.6, 112.1, 74.9, 62.8, 58.7, 42.8, 41.9, 25.5, 23.6, 19.0, 18.03, 18.01, 14.0, 12.7, 8.9.

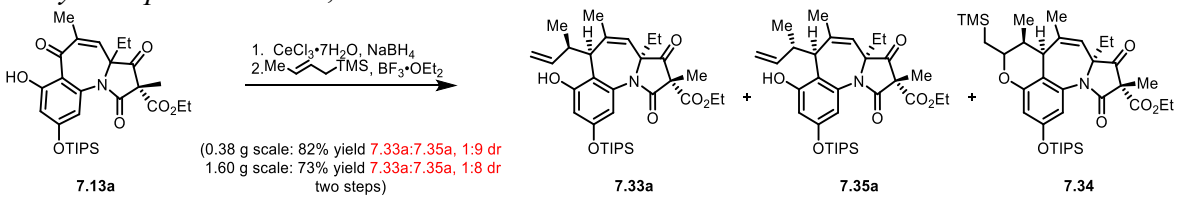
IR (thin film): cm^{-1} 2944, 2868, 1778, 1748, 1708, 1609, 1476, 1377, 1360, 1288, 1241, 1093, 882.

HRMS (ESI+): calculated for $C_{31}H_{43}NO_6SiNa$ $[M+Na]^+$ 576.2752, found: 576.2750.

TLC: 0.33 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

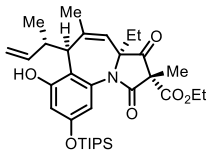
Crotylated phenols **7.33a**, **7.35** *and chromane* **7.34**



Experimental: To phenol **7.13a** (1.60 g, 2.95 mmol) in MeOH (29.5 mL) cooled in an ice water bath was added $CeCl_3$•$7H_2O$ (4.40 g, 11.8 mmol) to give a yellow suspension. To this yellow suspension was added $NaBH_4$ (138 mg, 3.65 mmol) was added in three portions spaced 5min apart. The reaction was monitored by TLC and when complete, the reaction had turned to a faint yellow solution at which point the reaction was quenched by the addition of saturated aqueous NH_4Cl and diluted with EtOAc. Saturated brine was added to the mixture until the aqueous layer turned clear. The organic layer was separated and the aqueous layer extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo and the unstable pink residue was placed under hi-vac for 20min. The pink residue was then dissolved in CH_2Cl_2 (59.0 mL) under nitrogen atmosphere and subsequently cooled in a dry ice acetone bath. To the red solution was added *trans*-crotyl silane[12] (2.55 mL, 14.8 mmol), stirred for 5min then followed by

the dropwise addition of BF_3•OEt_2 (0.56 mL, 4.4 mmol). The reaction turned a deep red/brown color and the reaction stirred in the dry ice acetone bath for 10min. The dry ice acetone bath was then removed and the reaction let warm in air. After 10min, the deep red color began to dissipate at which point the reaction was stirred in an ice water bath for 20min during which time the reaction turned into a faint yellow solution. The reaction was then quenched by the addition of saturated aqueous NH_4Cl/brine mixture, extracted with CH_2Cl_2 three times, the combined organics dried over Na_2SO_4, filtered and concentrated to give a yellow oil. The crude residue was purified by MPLC (linear gradient from 0% to 20% EtOAc/hexanes, 80g column, 60mL/min flow, 30min runtime) to give chromane **7.34** (193 mg, 0.29 mmol, 10% yield) as a colorless oil, and crotylated phenols **7.33a, 7.35a** (1.26 g, 2.16 mmol, 73% yield, dr (**7.33a:7.35a**) = 1:8) as a white foam. Early fractions of purified material were taken to characterize the major diastereomer. Pure minor diastereomer was obtained by exposure of chromane **7.34** to BF_3•OEt_2 (see below). Additional phenol **7.13a** (86 mg, 0.16 mmol, 5% recovery) was recovered.

Note: When the reaction was performed on smaller scale of **7.13a** (380 mg, 0.70 mmol) using the procedure outlined above, crotylated phenols **7.33a, 7.35a** (333 mg, 0.57 mmol, 82% yield, dr (**7.33a:7.35a**) = 1:9) was obtained along with chromane **7.34** (56 mg, 0.086 mmol, 12% yield).



7.33a

***Major Diastereomer* 7.33a**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.51 (d, *J* = 2.4 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 5.48 (ddd, *J* = 17.0, 10.1, 8.5 Hz, 1H), 5.41 (d, *J* = 1.5 Hz, 1H), 5.17 (s, 1H), 4.73 (dd, *J* = 17.1,

1.8 Hz, 1H), 4.65 (dd, J = 10.1, 1.8 Hz, 1H), 4.32 – 4.18 (m, 2H), 3.45 (d, J = 10.2 Hz, 1H), 2.39 – 2.28 (m, 1H), 1.95 (d, J = 1.4 Hz, 3H), 1.81 (dq, J = 14.7, 7.4 Hz, 1H), 1.59 (s, 3H), 1.53 (dq, J = 14.8, 7.5 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.26 – 1.16 (m, 3H), 1.10-1.04 (m, 21H), 0.80 (t, J = 7.5 Hz, 3H).

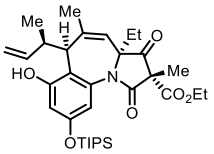
^{13}C NMR (151 MHz, $CDCl_3$): δ 206.4, 168.9, 165.9, 154.9, 154.1, 141.6, 138.7, 135.4, 124.4, 120.5, 115.4, 114.0, 107.5, 74.5, 62.7, 58.2, 45.1, 45.0, 30.4, 29.4, 19.1, 18.5, 18.0, 13.9, 12.7, 8.6.

IR (thin film): cm^{-1} 3320, 2964, 2944, 2868, 1776, 1749, 1708, 1679, 1611, 1591, 1514, 1435, 1376, 1314, 1233, 1165, 1114, 1068, 1016, 948, 919, 883, 857, 687.

HRMS (ESI+): calculated for $C_{33}H_{49}NO_6SiNa$ $[M+Na]^+$ 606.3221, found: 606.3219.

TLC: R_f = 0.41 (20% EtOAc/hexanes).

Physical Appearance: White Foam.



***Minor Diastereomer* 7.35a** **7.35a**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.52 (d, J = 2.3 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 5.78 (ddd, J = 17.1, 10.3, 8.1 Hz, 1H), 5.38 (s, 1H), 5.37-5.35 (m, 1H), 4.94–4.87 (m, 2H), 4.32 – 4.19 (m, 2H), 3.46 (d, J = 10.3 Hz, 1H), 2.37 – 2.26 (m, 1H), 1.87 (d, J = 1.4 Hz, 3H), 1.80 (dq, J = 14.8, 7.4 Hz, 1H), 1.64 (s, 3H), 1.56 (dq, J = 14.8, 7.5 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.27 – 1.17 (m, 3H), 1.08 (d, J = 7.4 Hz, 18H), 0.79 (t, J = 7.5 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 206.1, 168.9, 165.8, 155.2, 154.4, 143.1, 139.6, 135.5, 123.5, 119.9, 113.9, 113.7, 107.6, 74.4, 62.7, 58.1, 45.6, 44.8, 30.6, 29.2, 18.6, 18.3, 18.0, 13.9, 12.7, 8.6.

IR (thin film): cm^{-1} 3301, 2943, 2868, 1776, 1750, 1709, 1679, 1610, 1591, 1515, 1436, 1377, 1351, 1316, 1231, 1161, 1114, 1055, 1015, 948, 910, 883, 857, 773, 733, 685, 559.

HRMS (ESI+): calculated for $C_{33}H_{49}NO_6SiNa$ $[M+Na]^+$ 606.3221, found: 606.3220.

TLC: R_f = 0.40 (20% EtOAc/hexanes).

Physical Appearance: White Foam.

***Chromane* 7.34**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (d, *J* = 2.5 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 1H), 5.64 – 5.59 (m, 1H), 4.33 – 4.16 (m, 2H), 3.53 (br s, 1H), 3.45-3.41 (m, 1H), 2.47-2.41 (m, 1H), 2.02 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.82 (s, 3H), 1.72 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.58 (s, water), 1.56 (s, 3H), 1.30 – 1.20 (m, 7H), 1.12 – 1.02 (m, 19H), 0.84 (t, *J* = 7.3 Hz, 3H), 0.58 (d, *J* = 6.9 Hz, 3H), 0.11 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 168.2, 165.9, 158.9, 155.1, 136.3, 133.9, 129.0, 118.4, 114.2, 109.2, 84.8, 76.1, 62.5, 58.5, 44.0, 43.2, 29.3, 25.6, 24.9, 19.0, 18.01, 17.99, 15.1, 13.9, 12.7, 8.8, -0.6.

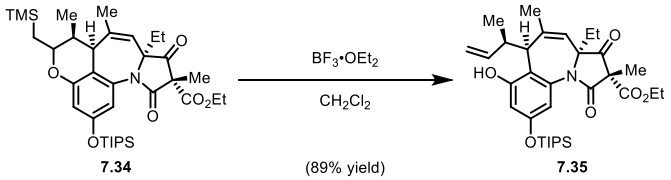
IR (thin film): cm^{-1} 2947, 2868, 1778, 1750, 1709, 1614, 1246, 1161, 860, 838.

HRMS (ESI+): calculated for $C_{36}H_{57}NO_6SiNa$ $[M+Na]^+$ 678.3617, found: 678.3617.

TLC: R_f = 0.31 (10% EtOAc/Hexanes).

Physical Appearance: Colorless oil.

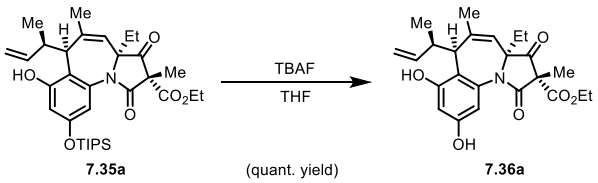
Crotylated phenol **7.35** *(via reaction of chromane* **7.34** *with BF_3•OEt_2)*



Experimental: To a solution of **7.34** (156 mg, 0.238 mmol) in CH_2Cl_2 (4.8 mL) cooled in an ice water bath was added BF_3•OEt_2 (60 µL, 0.48 mmol). The reaction was stirred in the ice water bath for 5 minutes, after which the ice bath was removed and the reaction allowed to stir at room temperature for 45 minutes. The reaction was then quenched by the addition of saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3x), the combined organics were dried over Na_2SO_4, filtered, and concentrated to a yellow solid. The crude mixture was then purifiedy by MPLC (0% to 20% EtOAc/hexanes, 12 g column, 30 mL/min flow rate, 18 minute runtime) to give crotylated phenol **7.35** (124 mg, 0.212 mmol, 89% yield) as a white foam.

The characterization data of crotylated phenol **7.34** is as described above.

Diol **7.36a**



Experimental: To a vial containing **7.35a** (8.0 mg, 0.014 mmol) dissolved in THF (0.3 mL) was added at room temperature TBAF (~1.0 M in THF, 14 µL, 0.014 mmol) to make a yellow solution. The reaction was stirred for 2min then quenched by the addition of 1N aqueous HCl and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to a colorless oil. The crude residue was then purified by flash chromatography (20%→40%→70%→100% EtOAc/hexanes) to give diol **7.36a** (5.9 mg, 0.014 mmol, quant. yield) as a white solid. A single crystal suitable for X-Ray

crystallographic analysis was prepared by vapor diffusion using MeOH/pentane as solvent system.

^{1}H NMR (500 MHz, acetone-d_6): δ 8.69 (br. s, 1H, -OH), 8.45 (br. s, 1H, -OH), 6.49 (d, J = 2.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 5.88 (ddd, J = 17.1, 10.4, 8.2 Hz, 1H), 5.39 (s, 1H), 4.96 – 4.87 (m, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.60 (d, J = 10.5 Hz, 1H), 2.40-2.30 (m, 1H), 1.88 (m, 3H), 1.81 (dq, J = 14.8, 7.5 Hz, 1H), 1.65 (dq, J = 14.9, 7.6 Hz, 1H), 1.54 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H, overlap with grease), 0.81 (t, J = 7.5 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, acetone-d_6): δ 206.9, 168.8, 166.6, 157.3, 156.9, 144.5, 140.8, 136.6, 124.0, 119.0, 113.6, 109.1, 103.2, 74.7, 63.1, 58.4, 45.9, 45.7, 31.5, 29.4, 19.2, 18.3, 14.3, 8.8.

IR (thin film): cm^{-1} 3348, 2977, 2936, 1775, 1678, 1619, 1518, 1321, 1233.

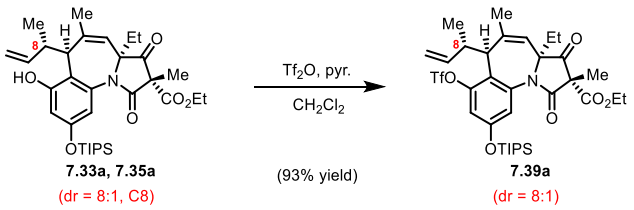
HRMS (ESI+): calculated for $C_{24}H_{29}NO_6Na$ $[M+Na]^+$ 450.1887, found: 450.1890.

TLC: R_f = 0.27 (50% EtOAc/hexanes).

m.p.: decomposition ~191 °C.

Physical Appearance: White solid.

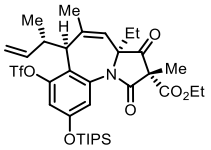
Triflates **7.39a**



Experimental: A solution of crotylated phenols **7.33a**, **7.35a** (1.105 g, 1.893 mmol, 8:1 **7.33a**:**7.35a**) in CH_2Cl_2 (37.9 mL) was cooled in a dry ice acetone bath followed by the addition of pyridine (1.53 mL, 18.9 mmol) then by triflic anhydride (0.96 mL, 5.7 mmol). The mixture was stirred in the dry ice acetone bath for 10min, then warmed in air for 5min,

followed by stirring in an ice water bath for 15min after which TLC no longer indicated the presence of any starting material. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$, extracted three times with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated to an orange oil. The crude residue was purified by MPLC (linear gradient from 0% to 20% EtOAc/hexanes, 40g column, 40 mL/min, 18min runtime) to give triflates **7.39a** (1.26 g, 1.76 mmol, 93% yield, 8:1 **7.39a-major**:**7.39-minor**) as a colorless oil.

Note: To obtain pure major/minor triflate isomers, the purified samples of **7.33a**, **7.35a** were individually subjected to the reaction conditions to deliver the corresponding triflates.



Major Triflate Diastereomer **7.39a - major diastereomer**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 5.48 (q, *J* = 1.3 Hz, 1H), 5.41 – 5.30 (m, 1H), 4.66 (s, 1H), 4.64 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.36 – 4.19 (m, 2H), 3.22 (d, *J* = 10.4 Hz, 1H), 2.37-2.26 (m, 1H), 1.97 (d, *J* = 1.4 Hz, 3H), 1.86 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.62 – 1.47 (m, 4H), 1.57 (br s, water), 1.32 – 1.19 (m, 6H, overlap with grease), 1.13 – 1.05 (m, 21H), 0.77 (t, *J* = 7.5 Hz, 3H).

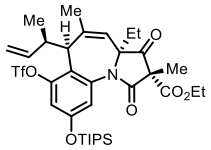
^{13}C NMR (151 MHz, $CDCl_3$): δ 205.5, 168.9, 165.6, 155.4, 147.5, 140.6, 137.1, 136.1, 126.7, 124.8, 121.7, 118.7 (q, 320 Hz), 116.7, 113.2, 74.6, 62.8, 58.0, 47.1, 45.7, 30.7, 29.9 (grease), 28.8, 19.1, 18.4, 17.86, 17.84, 14.0, 12.6, 8.5.

IR (thin film): cm^{-1} 2944, 2869, 1778, 1751, 1711, 1616, 1423, 1302, 1212, 1141, 1109, 1012, 988, 862, 756.

HRMS (ESI+): calculated for $C_{34}H_{48}F_3NO_8Na$ $[M+Na]^+$ 738.2714, found: 738.2712.

TLC: R_f = 0.37 (10% EtOAc/hexanes).

Physical Appearance: Colorless oil.



Minor Triflate Diastereomer **7.39a - minor diastereomer**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 2.5 Hz, 1H), 5.76 (ddd, *J* = 17.0, 10.3, 8.0 Hz, 1H), 5.43 (d, *J* = 1.5 Hz, 1H), 5.01 – 4.88 (m, 2H), 4.34-4.22 (m , 2H), 3.23 (d, *J* = 10.3 Hz, 1H), 2.33 (dq, *J* = 16.8, 7.0 Hz, 1H), 1.89 (d, *J* = 1.3 Hz, 3H), 1.83 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.64 (s, 3H), 1.57 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.32 – 1.22 (m, 6H), 1.10 (dd, *J* = 7.5, 2.9 Hz, 18H), 0.75 (t, *J* = 7.5 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.2, 168.8, 165.5, 155.7, 147.7, 141.7, 138.0, 136.4, 125.8, 123.8, 121.9, 118.7 (q, *J* = 320 Hz), 114.7, 113.4, 74.4, 62.9, 57.8, 47.8, 44.8, 31.0, 28.6, 18.9, 18.2, 17.9, 17.8, 14.0, 12.6, 8.5.

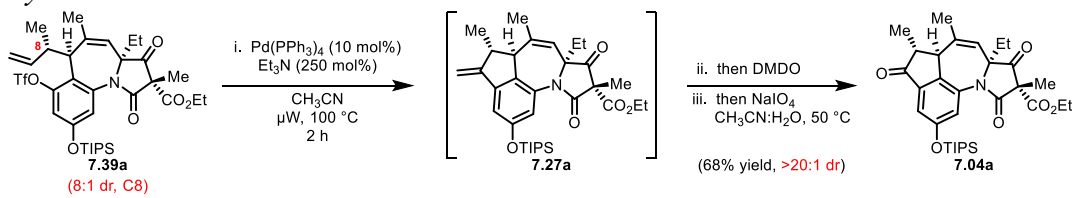
IR (thin film): cm^{-1} 2946, 2869, 1779, 1750, 1713, 1615, 1569, 1486, 1425, 1382, 1304, 1244, 1214, 1141, 1110, 1058, 1013, 988, 918, 864, 821, 783, 756, 687, 607.

HRMS (ESI+): calculated for $C_{34}H_{48}F_3NO_8Na$ $[M+Na]^+$ 738.2714, found: 738.2707.

TLC: R_f = 0.37 (10% EtOAc/hexanes).

Physical Appearance: Colorless oil.

Benzylic ketone **7.04a**



Experimental: In a 35mL microwave reactor vial was added triflates **7.39a** (1.02 g, 1.42 mmol) and placed under hi-vac for 30min. This was backfilled with nitrogen and to this

was added $Pd(PPh_3)_4$ (164 mg, 0.14 mmol). The vial was placed under vacuum and backfilled with nitrogen then purged using a balloon of argon. To the vial was added CH_3CN (22.0 mL) followed by triethylamine (0.50 mL, 3.56 mmol). The vial was capped and placed in a microwave reactor for 8 h at 100°C with stirring. After cooling to room temperature, the solution was diluted with acetone and concentrated in a round-bottomed flask to a red/orange oil. The crude Heck product **7.27a** was then dissolved in acetone (52.0 mL) and cooled in a dry ice acetone bath. After cooling, a solution of DMDO (40.0 mL, 45.8 mM solution in acetone, 1.83 mmol) was added and the reaction stirred for 10 minutes in the dry ice acetone bath. The reaction was then warmed by placing in an ice water bath and stirred for 20 minutes. The reaction was monitored by TLC and additional DMDO was added when the reaction appeared to stall. In this instance, an addition of 7.0 mL, then 7.0 mL, and lastly 2.5 mL DMDO was added with the reaction stirred for 5min between additions. When TLC indicated consumption of the starting material, the reaction was concentrated in air to dryness in vacuo to give a red/brown foam. This was then dissolved in a CH_3CN/H_2O solution of $NaIO_4$ (63 mL of a 2:1 v/v $CH_3CN:H_2O$ containing 3.04 g solid $NaIO_4$) and placed in a preheated aluminum block at 50°C. The reaction was stirred for 50 minutes and subsequently cooled in an ice water bath, diluted by the addition of saturated aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered through a short plug of SiO_2, and concentrated to a yellow oil. The crude mixture was purified by MPLC (linear gradient from 0% to 20% EtOAc/hexanes, 24 g column, 45 mL/min, 16min run time) to give tetracyclic ketone **7.04a** (552.5 mg, 0.972 mmol, 68% yield, >20:1 dr) as a beige/off-white solid.

Note: Attempts to perform the same sequence on pure minor diastereomer **7.39a – minor diastereomer** did not lead to any of the desired product. While the Heck reaction proceeded smoothly, products after the oxidation and cleavage steps no longer contained the azepine alkene upon inspection of the crude NMR.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 2.4 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 5.60-5.55 (m, 1H), 4.30 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19-4.15 (m, 1H), 2.82 (p, *J* = 7.0 Hz, 1H), 2.39 – 2.24 (m, 2H), 1.97 (t, *J* = 1.6 Hz, 3H), 1.64 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.36-1.25 (m, 6H), 1.11 (dd, *J* = 7.5, 1.4 Hz, 18H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.0, 204.6, 169.0, 165.4, 156.4, 142.4, 137.9, 134.8, 132.4, 125.8, 123.7, 112.2, 74.6, 62.9, 58.7, 49.6, 47.5, 25.1, 22.8, 19.1, 18.05, 18.02, 15.5, 14.0, 12.7, 8.9.

IR (thin film): cm^{-1} 2944, 2868, 1778, 1708, 1476, 1377, 1360, 1288, 1238, 899.

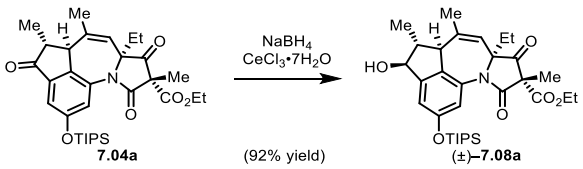
HRMS (ESI+): calculated for $C_{32}H_{45}NO_6SiNa$ $[M+Na]^+$ 590.2908, found: 590.2906.

TLC: R_f = 0.46 (20% EtOAc/hexanes).

m.p.: 135.3-138.0 °C.

Physical Appearance: Beige/off-white solid.

Benzylic alcohol (±)–**7.08a**



Experimental: To **7.04a** (200 mg, 0.300 mmol) was added MeOH (7.0 mL) and sonicated to create a uniform white suspension. This was cooled in an ice water bath and $CeCl_3$•$7H_2O$ (447 mg, 1.20 mmol) was added. The suspension was stirred for 5min followed by the

addition of $NaBH_4$ (15 mg, 0.387 mmol) and stirred for 10min. After TLC indicated no starting material remained (see *Note* below), the reaction was then quenched by the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was separated and the aqueous layer extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated to a colorless oil. The crude residue was purified by MPLC (linear gradient from 0% to 30% EtOAc/hexanes, 12 g column, 30 mL/min, 15min runtime) to give (±)–**7.08a** (184 mg, 0.323 mmol, 92% yield, >20:1 dr) as a colorless oil.

Note: The reduction with $NaBH_4$ was observed to be a rapid reaction. If the reaction at all appeared stalled after 10 min, 2.5 mg portions of $NaBH_4$ were added, stirred for 5min and monitored by TLC until the reaction was complete.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 (d, *J* = 2.3 Hz, 1H), 6.81 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.49–5.45 (m, 1H), 4.49 (t, *J* = 7.2 Hz, 1H), 4.28 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.81 (d, *J* = 11.1 Hz, 1H), 2.29 (dq, *J* = 14.7, 7.4 Hz, 1H), 2.24–2.16 (m, 2H), 1.89 (t, *J* = 1.6 Hz, 3H), 1.86 (br d, *J* = 8.1 Hz, 1H), 1.62 (s, 3H), 1.43 (d, *J* = 6.3 Hz, 3H), 1.33–1.26 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.11 (dd, *J* = 7.5, 1.7 Hz, 18H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.6, 168.7, 165.7, 155.9, 146.5, 143.3, 133.3, 125.4, 121.7, 116.4, 113.1, 81.0, 74.7, 62.7, 58.8, 50.7, 50.4, 24.5, 22.5, 19.1, 18.4, 18.11, 18.08, 14.0, 12.8, 8.9.

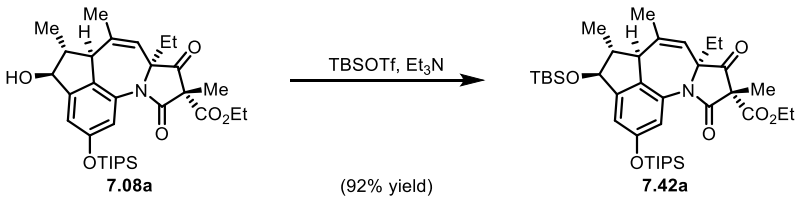
IR (thin film): cm^{-1} 3470, 2943, 2867, 1777, 1748, 1702, 1473, 1381, 1289, 1237, 920, 686.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_6SiNa$ $[M+Na]^+$ 592.3065, found: 592.3064.

TLC: $R_f = 0.24$ (20% EtOAc/hexanes).

Physical Appearance: Colorless oil.

TBS Ether **7.42a**



Experimental: To a vial was added **7.08a** (22.3 mg, 0.0391 mmol) and this dissolved in CH_2Cl_2 (2.0 mL) and cooled to –78 °C in a dry-ice acetone bath. After cooling, to this was added triethylamine (0.05 mL, 0.36 mmol) followed by the addition of TBSOTf (0.05 mL, 0.22 mmol) and the reaction let warm to room temperature overnight. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to give a crude residue that was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to give **7.42a** (24.7 mg, 92% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.70 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.48 – 5.44 (m, 1H), 4.54 (d, *J* = 8.3 Hz, 1H), 4.27 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.79 (d, *J* = 10.9 Hz, 1H), 2.38 – 2.25 (m, 2H), 2.20 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.89 (s, 3H), 1.62 (s, 3H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.32 – 1.22 (m, 6H, overlap with grease), 1.11 (dd, *J* = 7.5, 1.2 Hz, 18H), 0.96 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.22 (s, 3H), 0.17 (s, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 207.8, 168.6, 165.8, 155.5, 147.2, 143.6, 133.3, 125.2, 121.4, 116.4, 113.3, 81.2, 74.6, 62.6, 58.9, 50.3, 49.3, 26.0, 24.4, 22.4, 19.1, 18.6, 18.12, 18.09, 18.07, 14.0, 12.8, 8.9, -3.6, -3.8.

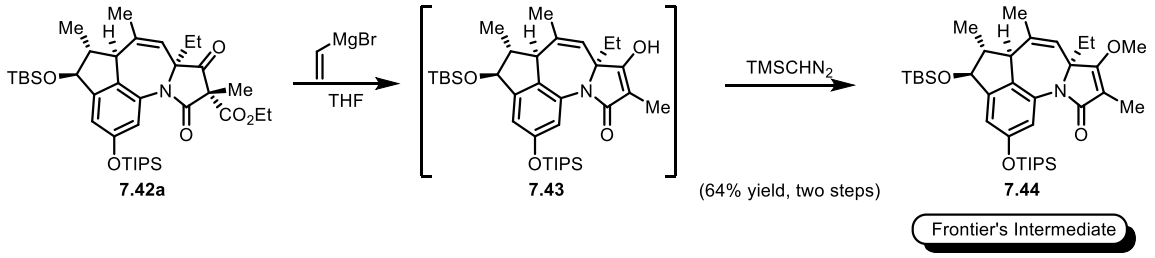
IR (thin film): cm^{-1} 2930, 2865, 1777, 1749, 1703, 1611, 1471, 1376, 1363, 1236, 1104, 882, 841.

HMS (ESI+): calculated for $C_{38}H_{61}NO_6Si_2Na$ $[M+Na]^+$ 709.3635, found: 709.3936.

TLC: 0.56 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Tetracyclic vinylogous methyl urethane **7.44** *(Frontier's Intermediate)*



Experimental: To a vial was added **7.42a** (3.8 mg, 5.6 μmol) and this dissolved in THF (0.5 mL) and cooled in an ice-water bath after which vinylmagnesium bromide (0.056 mL, 0.056 mmol, 1.0 M solution in THF) was added. The reaction was stirred for 20 minutes in the ice-water bath after which it was warmed to room temperature. The reaction was cooled bath in the ice-water bath after which additional vinylmagnesium bromide solution was added(4.6 μL) and warmed to room temperature. This was repeated one more time with one more addition of vinylmagnesium bromide (20 μL). After warming to room temperature and stirring for an additional 30 min, the reaction was quenched by the addition of 0.5 N aqueous HCl and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered and concentrated to give crude **7.43**. This crude material was used in the next step without further purification.

The crude residue was dissolved in $CHCl_3$:MeOH (3:1, 0.8 mL) and to this was added dropwise TMS-Diazomethane (0.2 mL, 0.12 mmol, 0.6 M solution in Et_2O) until the yellow color persisted. The reaction was stirred for an additional 30 minutes and then

quenched by the addition of 1 drop of AcOH after which the reaction bubbled and the yellow color dissipated. The reaction was concentrated under reduced pressure and purified by pipette column (0%→5%→10%→15%→20% EtOAc in hexanes) to give **7.44** (2.2 mg, 63% yield) as a colorless oil.

The ^{1}H and ^{13}C NMR data were in agreement with that reported by Frontier.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 2.3, 0.8 Hz, 1H), 6.55 (dd, *J* = 2.4, 1.0 Hz, 1H), 5.63 – 5.58 (m, 1H), 4.51 (d, *J* = 8.8 Hz, 1H), 4.12 (s, 3H), 3.84 (d, *J* = 10.5 Hz, 1H), 2.37 – 2.21 (m, 2H), 2.05 (s, 3H), 1.86 (t, *J* = 1.5 Hz, 3H), 1.86 – 1.75 (m, 1H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.31 – 1.24 (m, 3H, overlap with grease), 1.11 (dd, *J* = 7.4, 3.0 Hz, 18H), 0.97 (s, 9H), 0.60 (t, *J* = 7.3 Hz, 3H), 0.20 (s, 3H), 0.16 (s, 3H).

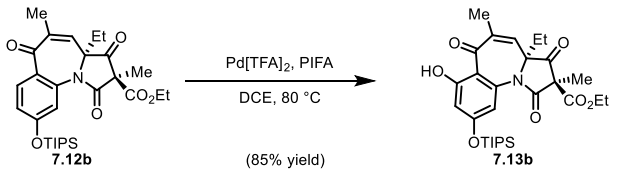
^{13}C NMR (151 Hz, $CDCl_3$): δ 171.2, 168.9, 155.6, 146.7, 140.9, 135.6, 125.5, 119.2, 113.8, 110.5, 102.0, 81.4, 67.5, 59.1, 49.9, 49.1, 29.8, 26.0, 23.7, 22.0, 18.7, 18.2, 12.9, 8.6, 7.7, 1.2, -3.7, -3.8.

IR (thin film): cm^{-1} 2927, 2864, 1677, 1607, 1579, 1469, 1376, 1305, 1218, 1101, 1004, 881, 838, 775, 674.

HRMS (ESI+): calculated for $C_{36}H_{59}NO_4Si_2Na$ $[M+Na]^+$ 648.3880, found: 648.3871.

Physical Appearance: Colorless oil.

Phenol **7.13b**



Experimental: To a 100 mL rbf was added **7.12b** (240 mg, 0.455 mmol) followed by the addition of DCE (4.5 mL), PIFA (401 mg, 0.932 mmol), $Pd(TFA)_2$ (7.6 mg, 0.023 mmol) in that order. The reaction goes from faint yellow to brown in color. This was the placed

in a preheated oil bath set at 80 °C and a water cooled reflux condenser attached. The reaction was stirred for 3 h after which NMR of an aliquot of the reaction mixture showed no starting material present. The reaction was concentrated to dryness, dissolved in CH_2Cl_2 and filtered through a pad of SiO_2 (12.5 g) under vacuum filtration. An additional 200 mL CH_2Cl_2 were used to rinse the flash and washed the pad of SiO_2. After concentrating the filtrate under reduced pressure by rotary evaporation, it was dissolved in MeOH and concentrated under reduced pressure (this was performed twice). This gave **7.13b** (210 mg, 0.386 mmol, 85% yield, >95% pure) as a yellow oil that was pure for use in subsequent steps. A small amount of this sample was purified by MPLC to give analytically pure material for characterization.

^{1}H NMR (600 MHz, $CDCl_3$): δ 13.21 (s, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 6.54 – 6.50 (m, 1H), 6.49 (d, *J* = 2.5 Hz, 1H), 4.18 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.07 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.07 – 2.00 (m, 4H), 1.70 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.63 (s, 3H), 1.35 – 1.26 (m, 3H, overlap with grease), 1.15 (t, *J* = 7.1 Hz, 3H), 1.11 (dd, *J* = 7.5, 1.9 Hz, 18H), 0.77 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.3, 191.8, 168.4, 166.8, 164.6, 162.2, 141.4, 138.1, 135.1, 113.1, 112.8, 108.3, 76.6, 63.1, 57.7, 29.8 (grease), 27.0, 21.3, 17.9, 15.7, 14.0, 12.8, 8.2.

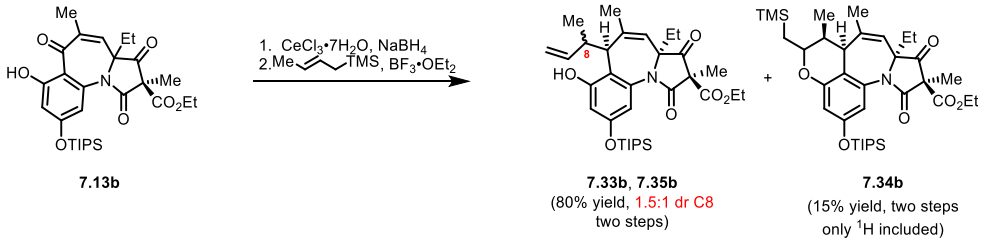
IR (thin film): cm^{-1} 2944, 2868, 1781, 1751, 1713, 1611, 1573, 1424, 1368, 1342, 1286, 1261, 1232, 1176, 1121, 1014, 881, 855, 807.

HRMS (ESI+): calculated for $C_{29}H_{41}NO_7SiNa$ $[M+Na]^+$ 566.2545, found: 566.2541

TLC: R_f = 0.23 (20% EtOAc/hexanes).

Physical Appearance: Yellow oil.

Crotylated phenols **7.33b**



Experimental: To a solution of **7.13b** (90 mg, 0.17 mmol) in MeOH (1.65 mL) was cooled in an ice-water bath under an atmosphere of argon. This was degassed by bubbling argon for 10 min with a balloon. Subsequently, to this was added $CeCl_3$•$7H_2O$ (247 mg, 0.662 mmol), stirred for 5 min, followed by the addition of $NaBH_4$ (6.9 mg. 0.182 mmol). To this was then added additional $NaBH_4$ (1.2 mg, 0.031 mmol). The reaction was stirred for another 2 min after which TLC indicated no SM. The reaction was then quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a red/pink oil and held under hi-vac for 5 min. After 5 min, this was then dissolved in CH_2Cl_2 (4.15 mL) and cooled to –78 °C in a dry-ice acetone bath. After cooling, to this was added *E*-crotyl silane (143 µL, 0.830 mmol). The reaction was stirred for 2 min followed by the addition of BF_3•OEt_2 (32 µL, 0.25 mmol). The reaction turned a deep red/burgundy color and the reaction was stirred for 10 min in the dry-ice acetone bath after which the bath was removed and the reaction stirred in air for another 10 min. During this time the deep red color began to fade and the reaction was stirred for an additional 20 min in an ice-water bath to give a faint yellow solution. The reaction was quenched by the addition of saturated aqueous NH_4Cl and brine, extracted with CH_2Cl_2 (3x), and the combined organics dried over Na_2SO_4, filtered, and concentrated to give a crude yellow oil. This was purified by MPLC

(4g column, 30 mL/min flow, 0%→30% EtOAc in hexanes) to give **7.33b** (78 mg, 0.13 mmol, 80% yield, 1.5:1 dr) and **7.34b** (16.4 mg, 0.025 mmol, 15% yield).

Note: The stereochemical assignment of **7.34b** was made by an analogous outcome in the isolation of **7.34a** whose benzylic and homobenzylic methyl stereochemistries were determined by X-Ray crystallographic data on a derivative of **7.34a**. In addition, the lower dr in this reaction has tentatively been attributed to a lower reaction scale whose temperature is more difficult to control. In work with the preparation of **7.33a**, it was determined that careful control of the temperature would permit isolation of **7.33a** in >8:1 dr. Further investigation into the diastereoselectivity in the preparation of **7.33b** has not been investigated. In addition, only a ^{1}H spectrum of byproduct **7.34b** is included for reference (see appendix).

The compounds **7.33b** are characterized as a mixture of homobenzylic methyl epimers.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.49 (d, *J* = 2.3 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1.5H), 6.36 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1.5H), 5.96 – 5.87 (m, 1H), 5.50 – 5.40 (m, 4.5H), 5.22 (br. s, 1H), 5.10 – 5.00 (m, 2.5H), 4.97 (dt, *J* = 10.6, 1.4 Hz, 1H), 4.71 (dd, *J* = 16.9, 1.8 Hz, 1.5H), 4.61 (dd, *J* = 10.2, 1.8 Hz, 1.5H), 4.26 – 4.14 (m, 5H), 3.43 (d, *J* = 10.8 Hz, 2.5H), 2.71 – 2.56 (m, 2.5H), 1.98 (s, 4.5H), 1.90 (s, 3H), 1.82 – 1.71 (m, 3H), 1.67 (s, 3H), 1.66 (s, 4.5H), 1.37 (ddd, *J* = 14.5, 7.4, 5.5 Hz, 4.3H), 1.25 – 1.17 (m, 21H), 1.13 – 1.05 (m, 59H), 0.78 – 0.72 (m, 12H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 206.9, 206.7, 168.5, 168.4, 165.9, 165.8, 155.0, 154.8, 154.3, 153.9, 143.6, 141.8, 138.9, 138.0, 135.3, 135.2, 124.3, 123.4, 120.9, 119.9, 115.3, 113.7, 113.3, 107.4, 107.3, 75.0, 74.9, 62.8, 62.8, 57.8, 57.8, 45.9, 45.3, 45.1, 43.0, 30.7, 30.5, 29.5, 29.1, 20.0, 18.0, 17.6, 17.3, 17.1, 14.2, 14.1, 12.7, 12.7, 8.9, 8.9.

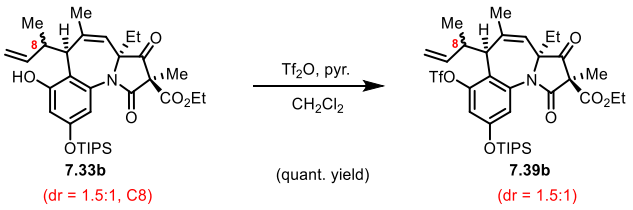
IR (thin film): cm^{-1} 3339, 2965, 2944, 2867, 1774, 1727, 1677, 1610, 1590, 1513, 1462, 1433, 1377, 1309, 1219, 1164, 1021, 855

HRMS (ESI+): calculated for $C_{33}H_{49}NO_6SiNa$ $[M+Na]^+$ 606.3221, found: 606.3220

TLC: 0.27 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Triflates **7.39b**



Experimental: To a rbf containing **7.33b** (60 mg, 0.10 mmol, 1.5:1 dr) was added CH_2Cl_2 (2.05 mL) and cooled to –78 °C in a dry ice acetone bath. After cooling, to this was added pyridine (50 µL, 0.62 mmol) followed by the dropwise addition of Tf_2O (35 µL, 0.21 mmol) over the course of ~15 seconds. The reaction was stirred for 10 min in the dry-ice acetone bath then warmed by placing in an ice-water bath. The reaction was stirred for an additional 10 min after which TLC showed no starting material. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a crude colorless oil that was purified by MPLC (4g column, 8 min runtime, 0%→20% EtOAc in hexanes, 30 mL/min) to give triflates **7.39b** (74 mg, quant. yield, 1.5:1 dr) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.97 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1.5H), 6.82 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1.5H), 5.91 – 5.83 (m, 1H), 5.52 (s, 1.5H), 5.48 (s, 1H), 5.34 (ddd, J = 17.0, 10.1, 9.3 Hz, 1.5H), 5.09 (dt, J = 17.3, 1.5 Hz, 1H), 5.02 (dt, J = 10.5, 1.3 Hz, 1H), 4.67 – 4.58 (m, 3H), 4.27 – 4.15 (m, 5.2H), 3.22 (dd, J = 14.4, 10.4 Hz,

2.5H), 2.75 – 2.55 (m, 2.5H), 2.00 (d, J = 1.3 Hz, 4.7H), 1.92 (d, J = 1.4 Hz, 3H), 1.80 (dqd, J = 14.8, 7.4, 2.1 Hz, 2.7H), 1.68 (d, J = 4.0 Hz, 8H), 1.35 (dqd, J = 14.7, 7.4, 4.5 Hz, 3H), 1.29 – 1.17 (m, 17.5H), 1.14 – 1.05 (m, 52.7H), 0.72 (td, J = 7.4, 2.7 Hz, 8H), 0.69 (d, J = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.8, 205.7, 168.6, 168.5, 165.5, 165.5, 155.5, 155.3, 147.7, 147.4, 142.2, 140.9, 137.4, 136.4, 136.1, 135.9, 126.9, 125.9, 124.7, 123.7, 121.5, 121.4, 116.5, 114.3, 113.2, 112.9, 75.1, 74.9, 63.0, 63.0, 57.7, 57.7, 48.0, 47.2, 45.7, 42.9, 31.1, 30.9, 28.8, 28.5, 20.0, 17.8, 17.6, 17.5, 17.3, 14.2, 14.1, 12.6, 12.6, 8.8.

^{19}F NMR (470 MHz, $CDCl_3$): δ -73.6.

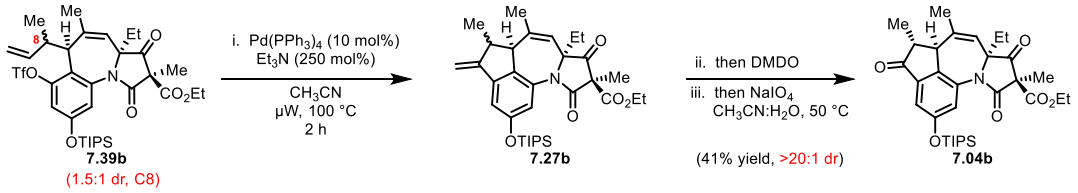
IR (thin film): 2947, 2870, 1778, 1750, 1712, 1616, 1569, 1484, 1424, 1300, 1215, 1141, 1012, 982, 864 cm^{-1}

HRMS (ESI+): calculated for $C_{34}H_{48}F_3NO_8Na$ $[M+Na]^+$ 738.2714, found: 738.2710.

TLC: R_f = 0.28 (10% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Benzylic ketone **7.04b**



Experimental: In a 10mL microwave reactor vial was added triflates **7.39b** (72 mg, 0.10 mmol) and placed under hi-vac for 30min. This was backfilled with nitrogen and to this was added $Pd(PPh_3)_4$ (17.4 mg, 0.015 mmol). The vial was placed under vacuum and backfilled with nitrogen then purged using a balloon of argon. To the vial was added CH_3CN (2.0 mL) followed by triethylamine (35 µL, 0.25 mmol). The vial was capped and placed in a microwave reactor for 7 h at 100°C with stirring. After cooling to room

temperature, the solution was quenched by the addition of saturated aqueous $NaHCO_3$, extracted with EtOAc (3x), the combined organics dried over Na_2SO_4, filtered and concentrated to a crude grey oil. This was purified by MPLC (4g column, 30 mL/min, 0%→20% EtOAc in hexanes) to give **7.27b** (52.2 mg, 92% yield) as a faint yellow oil.

The Heck product **7.27b** (52.2 mg, 0.092 mmol) was then dissolved in acetone (1.48 mL) and cooled in a dry ice acetone bath. After cooling, a solution of DMDO (1.7 mL, 62.4 mM solution in acetone, 0.106 mmol) was added and the reaction stirred for 10 minutes in the dry ice acetone bath. The reaction was then warmed by placing in an ice water bath and stirred for 25 minutes at which point TLC indicated consumption of the starting material. The reaction was concentrated in air to dryness in vacuo to give a crude white foam. This was then dissolved in a CH_3CN/H_2O solution of $NaIO_4$ (4.1 mL of a 2:1 v/v $CH_3CN:H_2O$ containing 197 mg solid $NaIO_4$, 0.92 mmol) and placed in a preheated aluminum block at 50°C. The reaction was stirred for 45 minutes and subsequently cooled in an ice water bath, diluted by the addition of saturated aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered through a short plug of SiO_2, and concentrated to a yellow oil. The crude mixture was purified by MPLC (linear gradient from 0% to 20% EtOAc/hexanes, 4 g column, 30 mL/min, 10min run time) to give tetracyclic ketone **7.04b** (21.3 mg, 0.038 mmol, 41% yield, >20:1 dr) as a colorless oil from **7.39b**.

Note: The single-pot procedure from **7.39b** to **7.04b** was developed after this stepwise sequence, and the single-pot procedure was not attempted on this diastereomeric series. In addition, the lower yield is attributed to the lower dr of the starting material. As was evidenced in the case of diastereomer **7.39a**, the compound containing the wrong

homobenzylic methyl stereocenter did not go on to the desired product, thus the lower dr of the starting material is expected to have a lower yield of tetracyclic ketone **7.04b**.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 5.75 – 5.70 (m, 1H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 – 4.18 (m, 1H), 4.10 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.84 (p, *J* = 6.9 Hz, 1H), 2.37 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.19 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.97 (s, 3H), 1.65 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.30 (h, *J* = 7.4 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.5 Hz, 18H), 0.81 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.5, 204.8, 168.8, 165.2, 156.5, 140.6, 137.9, 135.3, 132.7, 126.7, 123.5, 111.8, 75.5, 62.9, 58.7, 49.7, 47.5, 25.3, 22.6, 18.1, 16.6, 15.5, 14.0, 12.7, 9.3.

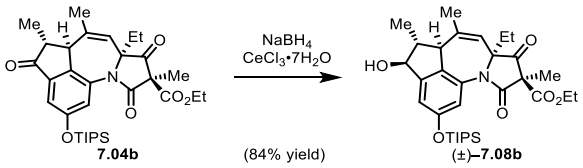
IR (thin film): cm^{-1} 2943, 2892, 2868, 1779, 1749, 1720, 1705, 1609, 1476, 1377, 1359, 1289, 1234, 1159, 1129, 882

HRMS (ESI+): calculated for $C_{32}H_{45}NO_6SiNa$ $[M+Na]^+$ 590.2908, found: 590.2904

TLC: R_f = 0.39 (20% EtOAc/hexanes).

Physical Appearance: Colorless oil.

Benzylic alcohol (±)–**7.08b**



Experimental: To **7.04b** (21.3 mg, 0.038 mmol) was added MeOH (0.75 mL) and cooled in an ice water bath. After stirring for 5 min, $CeCl_3$•$7H_2O$ (55.9 mg, 0.150 mmol) was added. The suspension was stirred for 5min followed by the addition of $NaBH_4$ (1.6 mg, 0.041 mmol). An additional $NaBH_4$ (0.6 mg x 2) was added when the reaction appeared to stall. The reaction was stirred for a total of 15 min after which TLC indicated no starting

material remained (see *Note* below). The reaction was then quenched by the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was separated and the aqueous layer extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated to a colorless oil. The crude residue was purified by pipette column (0%→20%→30% EtOAc in hexanes) to give (±)–**7.08b** (18.0 mg, 0.032 mmol, 84% yield, >20:1 dr) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 2.3, 0.8 Hz, 1H), 6.79 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.66 – 5.59 (m, 1H), 4.50 (d, *J* = 8.4 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.16 – 4.02 (m, 1H), 3.84 (d, *J* = 10.9 Hz, 1H), 2.34 (dq, *J* = 14.6, 7.3 Hz, 1H), 2.30 – 2.16 (m, 1H), 2.16 – 2.05 (m, 1H), 1.90 (t, *J* = 1.5 Hz, 3H), 1.61 (s, 3H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.33 – 1.18 (m, 6H), 1.11 (d, *J* = 7.4 Hz, 18H), 0.74 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.1, 168.5, 165.5, 155.9, 146.5, 141.5, 133.8, 126.3, 121.9, 116.2, 112.8, 81.0, 75.5, 62.8, 58.8, 50.7, 50.3, 24.8, 22.4, 18.5, 18.1, 16.7, 14.0, 12.8, 9.2.

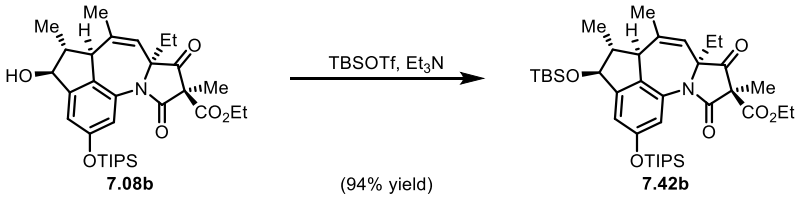
IR (thin film): cm^{-1} 3468, 2943, 2868, 1778, 1748, 1700, 1610, 1579, 1473, 1379, 1360, 1288, 1224, 1192, 1175.

HRMS (ESI+): calculated for $C_{32}H_{47}NO_6SiNa$ $[M+Na]^+$ 592.3065, found: 592.3061.

TLC: R_f = 0.40 (30% EtOAc/hexanes).

Physical Appearance: Colorless oil.

TBS Ether **7.42b**



Experimental: To a 25 mL rbf was added **7.08b** (11.5 mg, 0.020 mmol) and, under an atmosphere of argon, was added CH_2Cl_2 (1.0 mL) and cooled to –78 °C in a dry-ice acetone bath. After cooling, to this was added triethylamine (0.028 mL, 0.20 mmol) followed by the dropwise addition of TBSOTf (0.028 mL, 0.121 mmol) over the course of ~15 seconds. This was stirred for 10 min in the dry-ice acetone bath after which the bath was removed and the reaction allowed to slowly warm to room temperature. After 1 h, TLC showed no starting material after which the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a crude faint yellow oil that was purified by MPLC (4g column, 18 mL/,min, 0%→15% EtOAc in hexanes, 15 min runtime) to give **7.42b** (13.0 mg, 0.019 mmol, 94% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.68 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.65 – 5.58 (m, 1H), 4.54 (d, *J* = 8.2 Hz, 1H), 4.22 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.09 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.82 (d, *J* = 10.0 Hz, 1H), 2.41 – 2.29 (m, 2H), 2.10 (dq, *J* = 14.5, 7.2 Hz, 1H), 1.90 (s, 3H), 1.61 (s, 3H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.32 – 1.24 (m, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.11 (dd, *J* = 7.4, 1.1 Hz, 18H), 0.97 (s, 9H), 0.75 (t, *J* = 7.3 Hz, 3H), 0.22 (s, 3H), 0.18 (s, 3H).

^{13}C NMR (101 Hz, $CDCl_3$): δ 208.3, 168.4, 165.5, 155.6, 147.2, 141.9, 133.8, 126.1, 121.5, 116.2, 113.0, 81.2, 75.5, 62.7, 58.8, 50.3, 49.2, 26.0, 24.7, 22.2, 18.7, 18.1, 16.7, 14.0, 12.8, 9.3, -3.6, -3.9.

IR (thin film): cm^{-1} 2944, 2866, 1778, 1749, 1702, 1610, 1578, 1471, 1376, 1362, 1282, 1251, 1222, 1195, 1174, 1148, 1130, 1103, 1062, 882.

HRMS (ESI+): calculated for $C_{38}H_{61}NO_6Si_2Na$ $[M+Na]^+$ 706.3930, found: 706.3926.

TLC: 0.31 (10% EtOAc in hexanes).

Physical Appearance: Colorless oil.

7.5 References

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[11] While a number of procedures are found in the literature for the preparation of *trans*-crotyl silane, we found the method developed by Okamoto utilizing *trans*-1,2-dichloroethane permitted the ready preparation of large quantities of isomerically pure material (a) Kamachi, T.; Kuno, A.; Matsuno, C.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 4677-4679. For a representative procedure for the reaction of *trans*-1,2-

dichloroethane with TMSMeMgCl, see (b) Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, *39*, 6159-6162. Procedure for the reaction of (*E*)-(3-chloroallyl)trimethylsilane with MeMgI adapted from (c) Kumada, M.; Tamao, K.; Sumitani, K. *Org. Synth.* **1978**, *58*, 127.

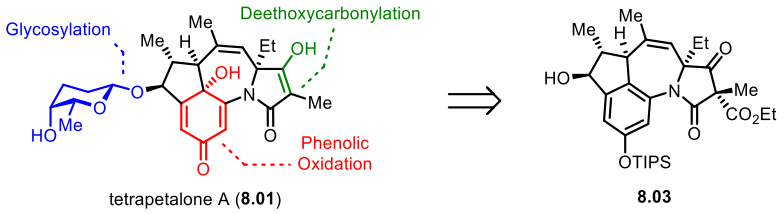
CHAPTER EIGHT

ß-Selective Glycosylation and Completion of the Total Syntheses of Tetrapetalones A and C[1]

8.1 End Game Strategy

Much like lightning from the clouds above to the target below, one can imagine an endless number of starting points and branching points as they navigate their way through a synthesis. As we come closer to the end however, the number of challenges narrows, and with it the number of paths one can take.

As we came to consider the end-game strategy of our tetrapetalone synthesis, three significant architectural features remained to be addressed (Scheme 8.1). We would need to (1) install the ß-rhodinose moiety, (2) effect an oxidative dearomatization to deliver the *para*-quinol, and (3) unmask the tetramic acid moiety by way of deethoxycarbonylation. If one were to simply consider these three features, one can imagine a total of six possible permutations that could lead us to the natural product. From the outset, it was unclear as to which of these paths would be the most likely to succeed.



Scheme 8.1. Three remaining challenges to completion of the total synthesis

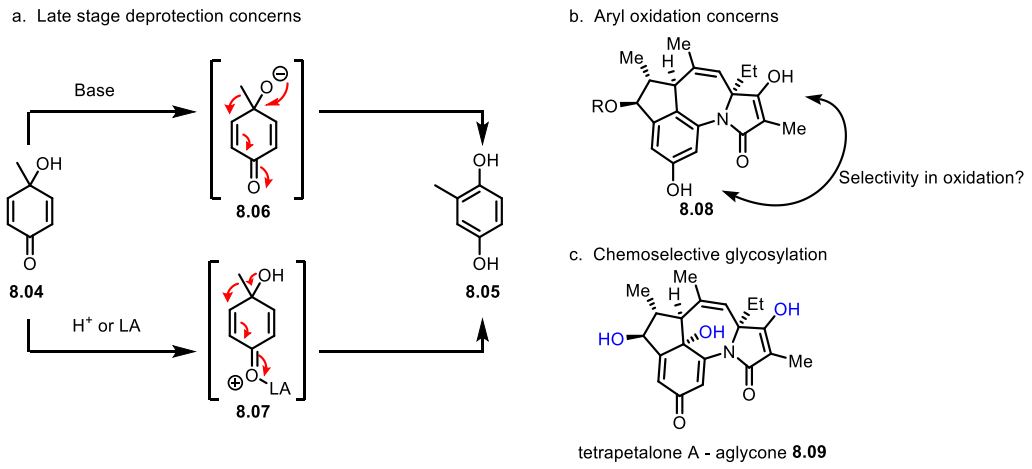


Figure 8.1. Consideration of obstacles that guided our end-game strategy

Of many potential pitfalls, concerns over well-known acid or base promoted aromatization of *para*-quinols (**8.04** to **8.05**) made us uneasy about unveiling the natural product from a penultimate masked tetramic acid (Figure 8.1a, left).[2] The conditions likely necessary to promote this transformation would be basic or acidic in nature. Preliminary probing of aryl oxidation conditions that would be required to advance intermediates such as **8.08** led to competitive oxidation of the tetramic acid, so oxidation after unmasking was out (Figure 8.1b, top right). Lastly, we looked to employ an electrophilic glycosyl donor to install the β-rhodinose moiety which meant if we were to attempt this chemistry on the parent tetrapetalone A-aglycone (**8.09**), there would be potential selectivity issues among the three different nucleophilic sites (Figure 8.1c, blue).

Taken together, these concerns pointed to a single pathway that would involve glycosylation, followed by aryl oxidation and, finally, deethoxycarbonylation of the tetramic acid with the hope that the rigid skeleton of the core of the molecule would prevent migrations akin to those depicted in Figure 8.2a (left).

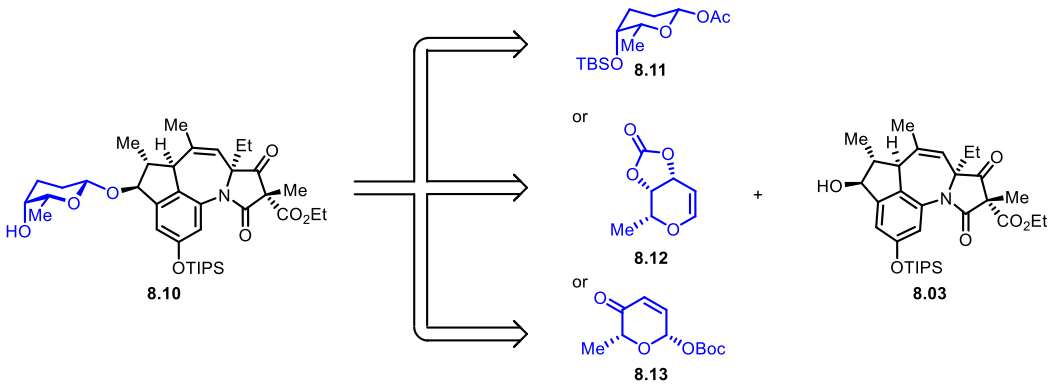
8.2.1. Three Successful Model Studies for ß-Rhodinose Installation

Our initial excursion into glycosylation began with model systems. In combing the literature, we came up with three possible avenues by which we could effect glycosylation (Scheme 8.2).

(A) Based on precedent from Roush, rhodinose donor **8.11** could be employed using classical Lewis acid promoted glycosylation methods to couple with acceptor **8.03**, though in Roush's precedent, the α-linked anomer was exclusively furnished.[3]

(B) Precedent set forth by Trost led us to consider a double invertive mechanism with allylic carbonate **8.12** which should provide exclusively the ß-linkage. Subsequent hydrogenation of an intermediate alkene (not depicted) would deliver the ß-rhodinose moiety, a strategy employed by Frontier in preliminary efforts.[4,16]

(C) Inspired by an *Organic Syntheses* procedure we had the opportunity to check in our laboratory,[5] we recognized that we could employ O'Doherty's stereospecific ß-exclusive glycosylation protocol with allylic carbonate **8.13** to deliver an intermediate ß-linked enone moiety that would require further reduction.[6]

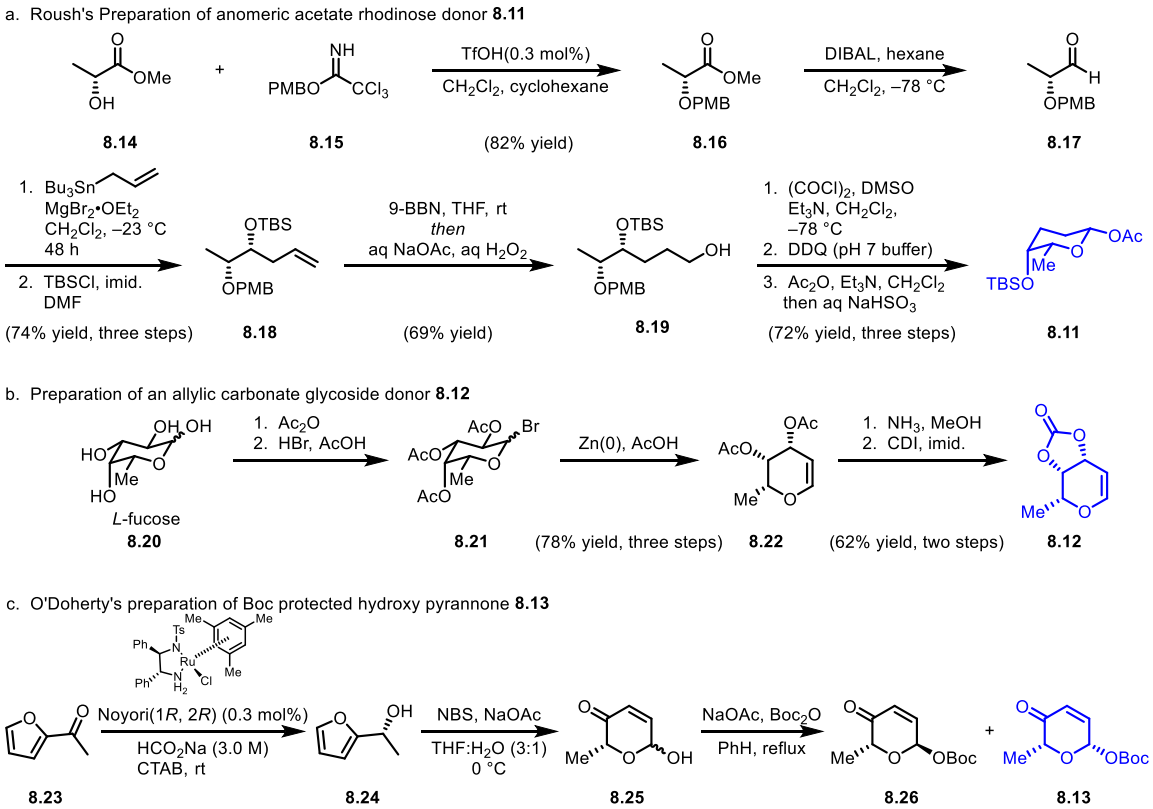


Scheme 8.2. Three ideas for ß-rhodinose installation

To test these three approaches, we had to first prepare each glycosyl donor (Scheme 8.3). Access to **8.11** was gained through a straightforward synthesis starting with PMB protection of methyl lactate (**8.14**, Scheme 8.2a, top).[3] Reduction of the ester in **8.16** followed by diastereoselective allylation of the resultant aldehyde gave TBS ether **8.18** after silylation. A three-step sequence involving Swern oxidation, PMB deprotection, and acetylation gave **8.11** interestingly as only the ß-anomer. (The possibility to exploit this property was contemplated in section 6.3).

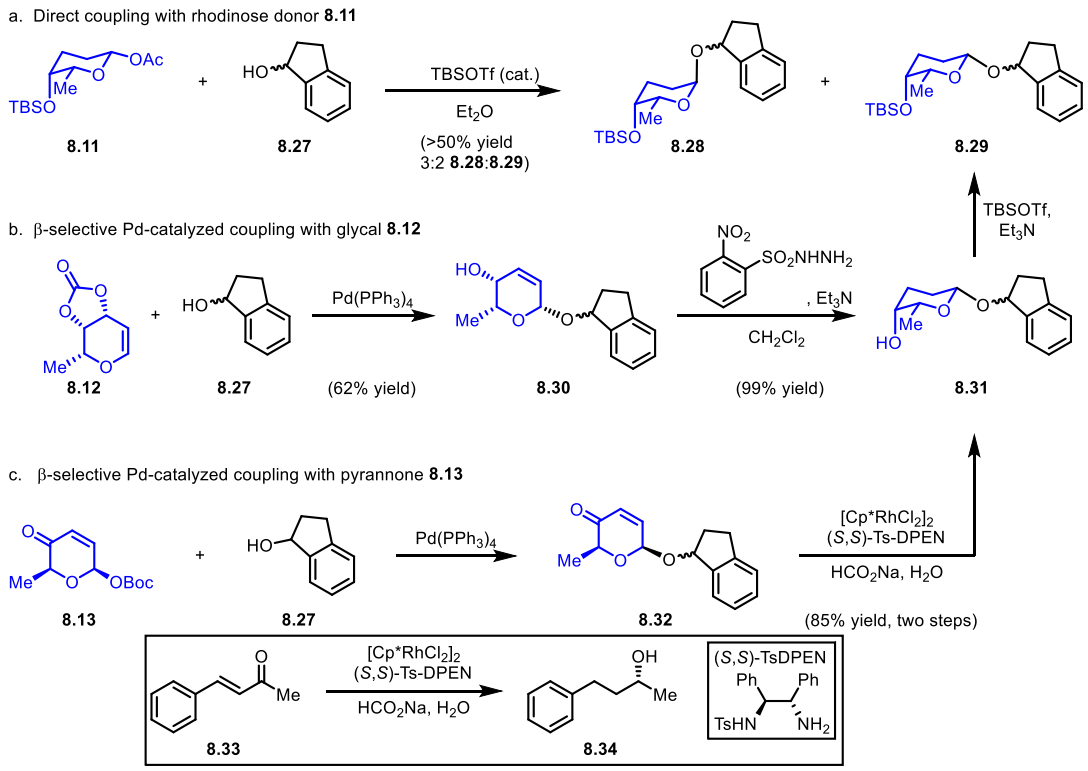
To access bicyclic allylic carbonate **8.12**, simple acetylation of *L*-fucose (**8.20**) and treatment with HBr gave anomeric bromide **8.21** (Scheme 8.2b, middle).[7] Reduction of **8.21** in the presence of metallic Zinc to give glycal **8.22** was then followed by deacetylation and CDI to give **8.12**.[8]

Lastly, as per O'Doherty's method, Noyori transfer hydrogenation of 2-acetyl furan (**8.23**) gave **8.24** in >98% ee (Scheme 8.2c, bottom).[9] Subsequent NBS promoted Achmatowicz rearrangement of **8.24** to **8.25** was followed by carbonate formation with Boc_2O under thermodynamic conditions[10] to give enantioenriched ß-Boc protected hydroxy pyrannone **8.13** as a single diastereomer after separation of the minor α-anomer (**8.26**) by column chromatography.



Scheme 8.3. Preparation of three glycosyl donors

With the three glycosyl donors precursors in hand, we explored the strategies outlined above using a model indanol (**8.27**) as substrate (Scheme 8.4). In the event, with Roush's rhodinose donor, the best we could achieve in this direct coupling under Lewis acid promoted conditions was a 3:2 mixture of α:ß anomers **8.28**:**8.29** respectively (Scheme 8.4a, top).



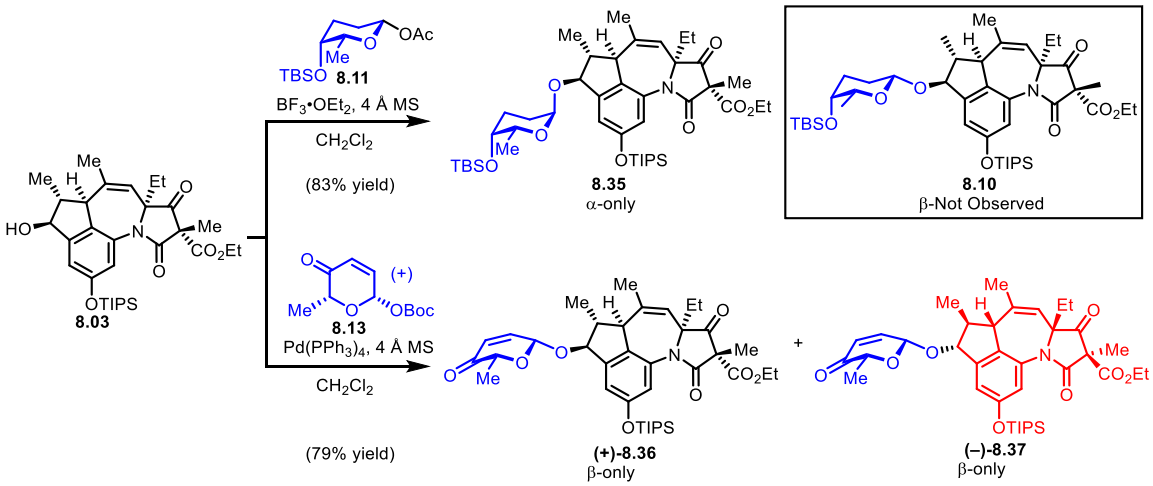
Scheme 8.4. Successful installation of ß-rhodinose on a model system: three possible solutions

Turning to the Trost procedure, we were able to successfully access the ß-linked anomer via the Pd catalyzed coupling of **8.27** with glycosyl donor **8.12** (Scheme 8.4b, middle).[4] Subsequent reduction of the derived product (**8.30**) using conditions employed by O'Doherty on a similar sugar derivative gave **8.31** exclusively.[11] Conversion to **8.29** was also achieved by exposure to TBSOTf to confirm the convergency of the methods. In both of the model systems, stereochemistry at the anomeric position was confirmed by characteristic coupling constant data obtained in the ^{1}H-NMR and comparison to similar data reported for the tetrapetalone A.

Lastly, we explored O'Doherty's Pd catalyzed stereospecific coupling conditions employing ß-Boc pyrannone **8.13** and indanol **8.27**. The conditions cleanly furnished coupled product **8.32** exclusively with the ß-linkage.[6] Taking note of conditions developed

in the Deng Laboratory, we reduced **8.32** under modified Noyori conditions to **8.31** in excellent yield.[12] It should be noted however, that both **8.11**, **8.12**, and **8.13** were all prepared as enantiopure glycosyl donors whereas indanol **8.27** was racemic. Thus the products produced in our model studies were mixtures at the indanol. As will become evident below, the resolving power of the rhodinose moiety will be applied when coupling with the racemic tetrapetalone aglycone as will the catalyst controlled asymmetric reduction chemistry developed by Deng.

8.2.2. ß-Exclusive Rhodinose Formation and Chiral Resolution

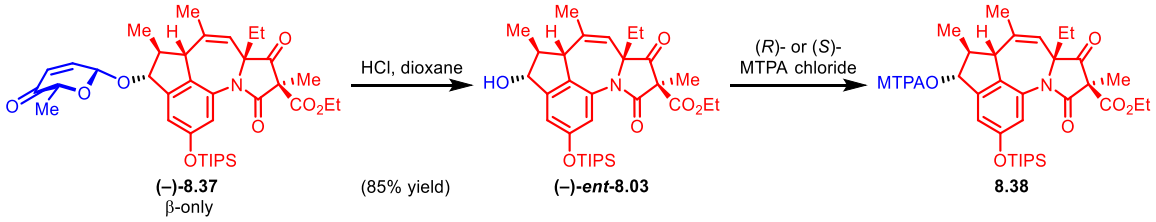


Scheme 8.5. ß-selective glycosylation and chiral resolution

Concerns over the selectivity in the diimide reduction (of the glycosyl unit versus the azepine alkene) led us to consider using only **8.11** and **8.13** as glycosyl donors. Given that glycosylation of **8.03** using **8.11** and classical methods produced exclusively the undesired α-linked product (**8.35**, Scheme 8.5) our choice of methods was quickly reduced to the use of Pd-catalysis in conjunction with (+)-**8.13**. To our delight, exposure of **8.03** to **8.13** under O'Doherty's conditions resulted in clean formation of a mixture of two

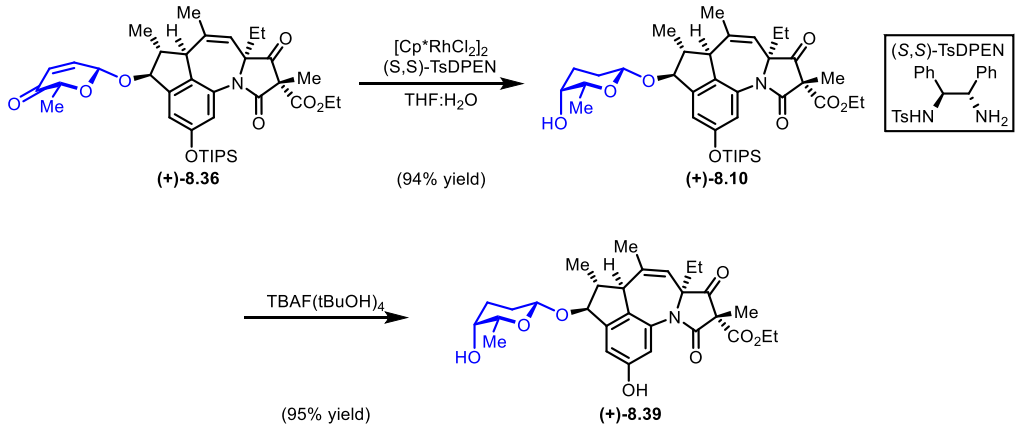
diasteromeric products ((+)-**8.36** and (–)-**8.37**). Separation of these diastereomers by standard column chromatography followed by ^{1}H-NMR analysis indicated that both possess the desired ß-linked glycosyl unit and hence differing absolute configurations about the aglycone core.

Difficulties in determining which diastereomer had the correct relative configuration by NOE analysis, and lacking a crystal structure, prompted us to conduct a modified Mosher ester analysis on the aglycone derived from hydrolysis of (–)-**8.37** (Scheme 8.6). In the event, exposure of (–)-**8.37** to anhydrous HCl gave (–)-*ent*-**8.03** whose Mosher ester derivative permitted assignment of the carbinol carbon as that being opposite as that assigned for the natural product (hence our designation here as *ent*).[13] With this information, we were able to assign (+)-**8.36** as the compound which had the same configurations as that of the natural product.



Scheme 8.6. Identifying the correct glycosylated diastereomer

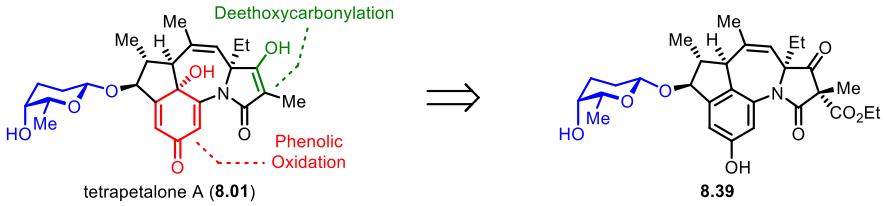
Completing the introduction of the rhodinose moiety required transfer hydrogenation to (+)-**8.10** and set the stage for silyl deprotection and aryl oxidation. With regard to the former of these latter events, treatment of (+)-**8.10** with TBAF furnished the aryl oxidation substrate (+)-**8.39** in excellent yield (Scheme 8.7).



Scheme 8.7. Completion of the installation of the ß-rhodinose

8.3 Completion of the Synthesis: Aryl Oxidation and Deethoxycarbonylation

With installation of the rhodinose moiety completed and the phenol unmasked, we turned to next major step in our end-game sequence, oxidative dearomatization to the *para*-quinol (Scheme 8.8, red).



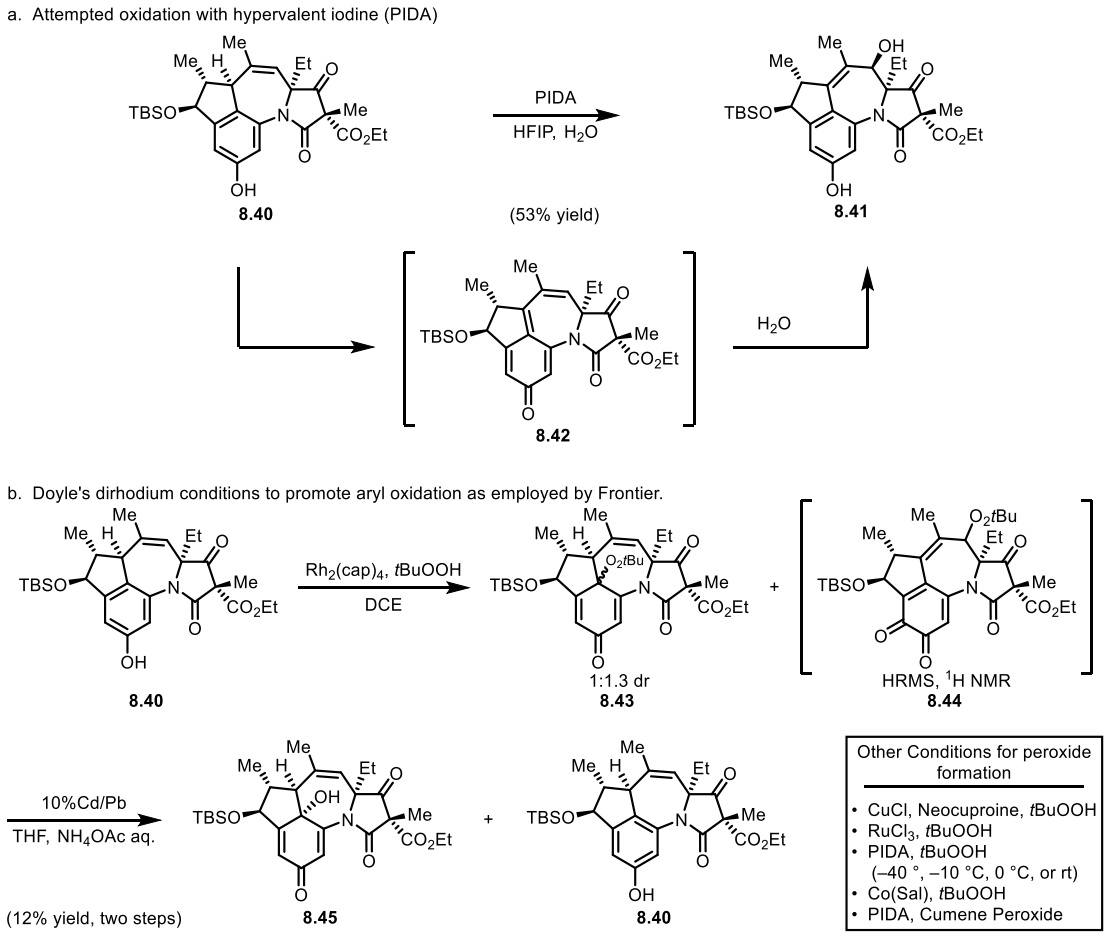
Scheme 8.8. Two remaining challenges for completion of the synthesis

8.3.1. Successful para-Quinol Installation by Oxidative Dearomatization

Prior to advancing the glycosylated material, we explored the aryl-oxidation sequence on a number of advanced intermediates. These studies proved to be quite informative and also served to highlight the potential difficulties of the late-stage sequence. Of particular note from these studies is the fact that many of the oxidative dearomatization conditions attempted were fraught with elimination problems. As exemplified by

hypervalent iodine chemistry (Scheme 8.9a, top), model aglycone **8.40** was exposed to bis-acetoxyiodobenzene (PIFA) to give allylic alcohol **8.41** whose NMR correlated well to that which we had earlier prepared (**6.49**, scheme 6.15).[14] Building a model of tetracycle **8.40** indicates a near perfect anti-periplanar geometry of the benzylic methine proton thus making it prone to elimination to *para*-quinone methide **8.42**. Subsequent addition of water to this electrophilic intermediate at the position adjacent to the angular ethyl group gives **8.41**.

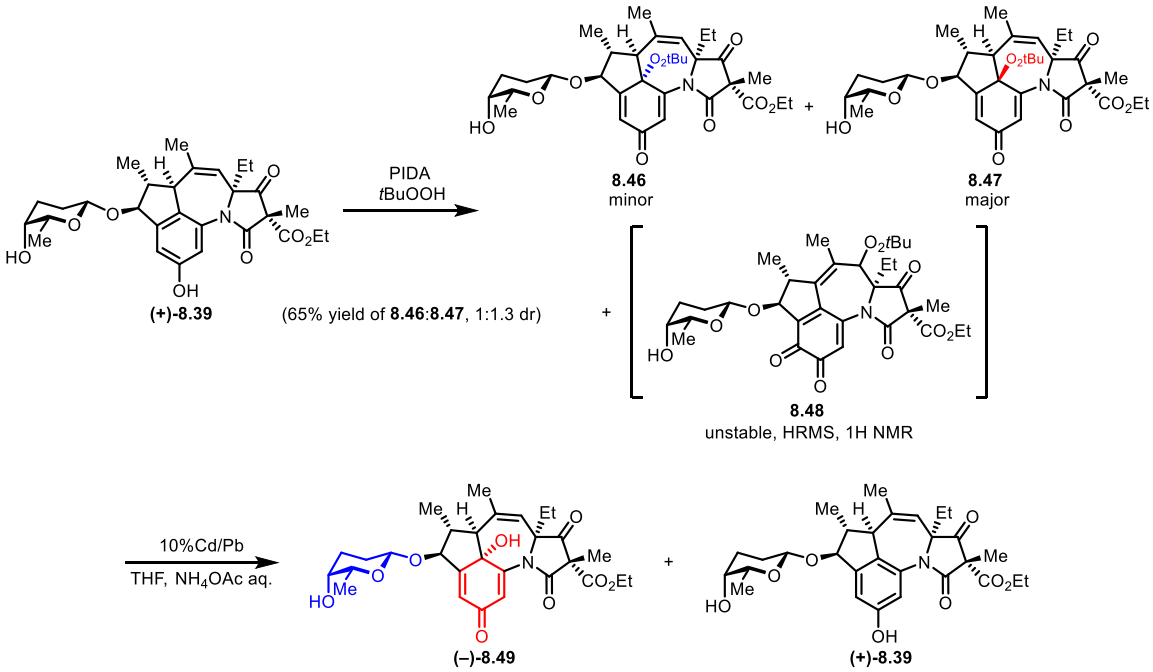
Turning to Doyle's dirhodium promoted oxidation[15] as employed by Frontier,[16] we were able to convert **8.40** to the corresponding *para*-quinol peroxide ethers **8.43** as a



Scheme 8.9. Oxidative dearomatization studies on a model system

1:1.3 mixture of diastereomers (Scheme 8.9b, bottom). Alongside these products was obtained an *ortho*-quinone byproduct assigned as **8.44** which proved unstable and hence not fully characterizable. Of note is that Doyle's conditions generate *t*BuOO• thus, in an effort to influence the diastereoselectivity, a variety of conditions were attempted that generate the same *t*BuOO• (inset).[17,18] However, none of these latter efforts proved to be at all superior to the initially attempted conditions employed by Frontier. Reduction of the diastereomeric mixture of peroxide ethers (**8.43**) then gave **8.45** as the sole *para*-quinol isomer isolated from the reaction mixture along with rearomatized material (**8.40)**.[16]

Having developed what we deemed satisfactory conditions for the aryl oxidation, we turned next to the glycosylated substrate (+)-**8.39**. For ease of set up, we switched to hypervalent iodine mediated generation of *t*BuOO• on substrate (+)-**8.39** (Scheme 8.10).[18] To our delight, oxidation of (+)-**8.39** under these slightly modified conditions generated a 1:1.3 mixture of peroxide ether diastereomers **8.46**:**8.47**, wherein the respective stereochemistry was assigned based on NMR correlation to the natural product. Again, alongside the formation of the desired adduct was unstable *ortho*-quinone **8.48**. In a result that was similar to that observed in the model study, exposure of the **8.46**/**8.47** mixture to reduction with Cd/Pb furnished *para*-quinol (**–)-8.49** along with rearomatized material ((+)-**8.39**). As before, the diastereomer possessing the stereochemical configuration needed for advancement to the natural product (**8.46**) withstood the reduction conditions whereas the undesired isomer (**8.47**) underwent aromatization.

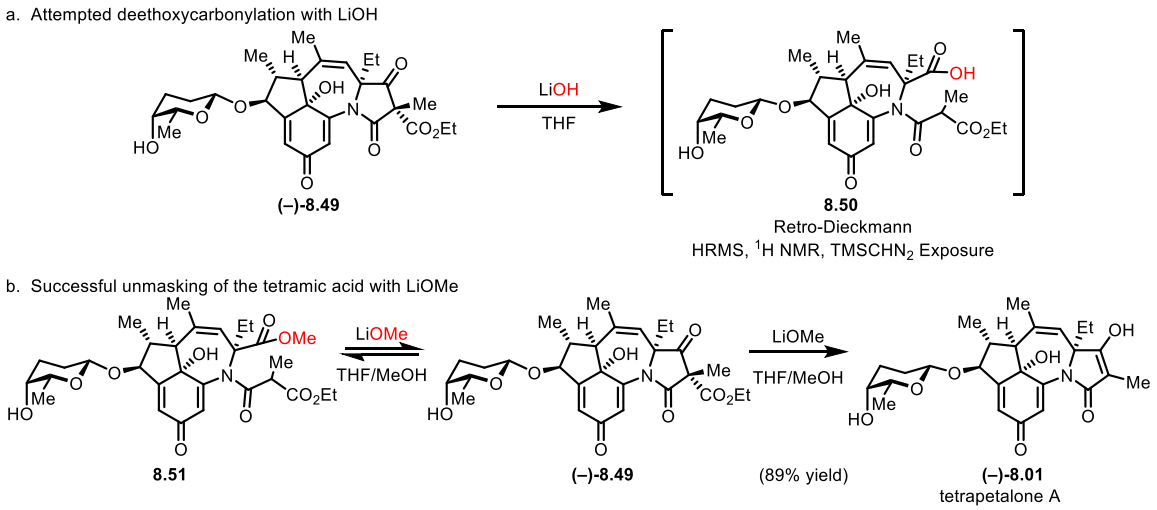


Scheme 8.10. Preparation of a late-stage *para*-quinol

8.3.2. Unveiling the Tetramic Acid, Preparation of Tetrapetalone C, and the Unnatural Enantiomers

At this point in our synthesis, all that remained was unmasking of the tetramic acid moiety by deethoxycarbonylation. Although a variety of saponification conditions would be amenable in this regard, in initial studies we simply exposed (–)-**8.49** to lithium hydroxide. Much to our disappointment, LCMS, HRMS, and preliminary ^{1}H NMR data obtained on the crude reaction mixture indicated that these conditions were inducing a retro-Dieckmann reaction leading to product **8.50** (Scheme 8.11a, top). In addition, exposure of this crude product to diazomethane furnished a compound that was spectroscopically consistent with **8.51** (Scheme 8.11b, bottom). In evaluating this result, we reasoned that the terminal retro-Dieckmann reaction could be avoided by performing the decarboethoxylation with LiOMe. Under these latter conditions ring opening would furnish **8.51**, an intermediate capable of undergoing reclosure to (–)-**8.49**, thus enabling

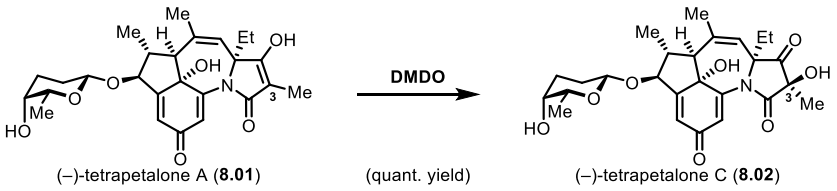
eventual decarboethyoxylation to deliver tetrapetalone ((–)-**8.01**). Gratifyingly, these conditions cleanly delivered a product whose mass was identical to that of the natural product. However, the ^{1}H and ^{13}C NMR however failed to satisfactorily match with the reported spectra of tetrapetalone A. Suspecting keto-enol tautomerism as the issue, we titrated our NMR sample with a dilute solution of formic acid until the spectral data matched. Indeed, we had successfully accessed tetrapetalone A (**8.01**) in this manner. A result which constituted the first reported total synthesis of tetrapetalone A and the first reported optical rotation of the natural product.



Scheme 8.11. Synthesis completion by unmasking the tetramic acid via deethoxycarbonylation

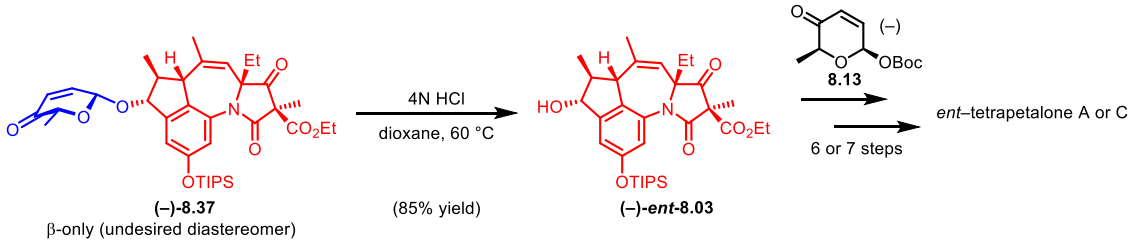
With an eye toward accessing other members of the tetrapetalone family, we evaluated conditions that would be able to oxidize the tetramic acid at C(2) while leaving other alcohol and alkene functional groups untouched (Scheme 8.12). Thinking back to our Heck cyclization studies, wherein we had observed only very slow oxidation of the azepine alkene with DMDO, led us to consider this reagent as a potential oxidant. To our

delight exposure of (–)-**8.01** to DMDO followed by evaporation of the solvent was found to produce tetrapetalone C ((–)-**8.02**) in quantitative yield and of characterizable purity.



Scheme 8.12. Successful oxidation to tetrapetalone C

Lastly, earlier in our efforts we had done a resolution of our racemic aglycone with a single enantiomer glycosyl donor. Hydrolyzing the incorrect diastereomer (–)-**8.37** and advancing this material in an analogous manner except employing (–)-**8.13** as coupling partner gave *ent*-tetrapetalones A and C ((+)-**8.01** and (+)-**8.02** respectively).



Scheme 8.13. Accessing the enantiomers of the natural products

8.4 Experimental

General

Unless otherwise stated, reactions were magnetically stirred in flame or oven dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Diethyl ether, tetrahydrofuran, toluene, benzene, dichloromethane, and acetonitrile were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. ACS grade acetone

(Fisher) was purchased from Fisher-Scientific and used as received. Dimethyl formamide and 1,2-dichloroethane (DCE) were purchased from Sigma-Aldrich and used as received. $Pd(PPh_3)_4$ was purchased from Sigma-Aldrich and stored under nitrogen in a -20°C freezer. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Millipore glass-backed 60Å plates (indicator F-254s, 150-180 µm thickness) (Millipore, catalogue #1164850001). Column or flash chromatography was performed with the indicated solvents using Millipore Silica Gel 60 (0.040-0.063 mm, 230-400 mesh ASTM) as the stationary phase. MPLC purifications were performed on a Telodyne Isco Combi*Flash*® *Rf*+ (Model: RF + UV-VIS MS COMP), used with standard Telodyne Isco normal phase disposable columns for flash chromatography and monitored at wavelengths of 254 and 280 nm. All melting points were obtained on a Chemglass Life Sciences melting point device (Model: DMP100) and are uncorrected. Infrared spectra were obtained using a Bruker Alpha ATR-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, Varian 500, or Bruker 600. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million (ppm) relative to internal residual solvent peaks from the indicated deuterated solvents (^{1}H: For $CDCl_3$, $CHCl_3$ 7.26; For Methanol-d_4, CD_2HOD 3.31; For Acetone-d_6, Acetone-D5H 2.05). Chemical shifts (δ) for ^{13}C spectra were referenced from the indicated solvent peaks (^{13}C: $CDCl_3$ 77.16, Methanol-d_4 49.00, Acetone-d_6 29.84). Chemical shifts in ^{19}F spectra were taken in $CDCl_3$ doped with fluorobenzene and referenced to -113.15. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as s = singlet, br.s = broad singlet, d = doublet, br. d = broad doublet, t = triplet, q = quartet, m = multiplet, dd =

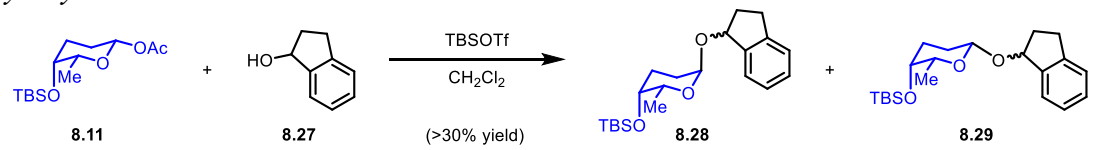
doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High resolution mass spectra were performed on a Thermo LTQ Orbitrap Discovery with direct injection followed by electro-spray ionization (ESI). Microwave reactions were carried out using a CEM Discover SP Microwave system. Single crystal X-ray diffraction studies were collected on a Bruker Apex II-CCD detector using Mo-K_α radiation (λ = 0.71073 Å). Structures were solved and refined using SHELXTL. Optical rotations were obtained on a Rudolph Research Analytical Autopol IV Automatic Polarimeter.

High-Performance Liquid Chromatography (HPLC): All HPLC purifications were carried out on a Waters HPLC system (consisting of a Waters 1525 binary HPLC pump with direct injection port and monitored at 254 nm unless otherwise specified with a Waters 2489 UV-Visible detector). All purifications utilized a normal-phase Sunfire, Silica Prep 10 µm, 10 x 250 mm column.

Ultra Performance Liquid Chromatography (UPLC)-Mass Spectrometry (MS): All UPLC-MS experiments were carried out on a Waters Acquity H UPLC Class system using the indicated solvent systems as eluents. All separations were performed on a reverse phase Acquity UPLC BEH C18 1.7 µm, 2.1 x 50 mm column.

^{1}H and ^{13}C NMR spectra are included for all previously unreported compounds.

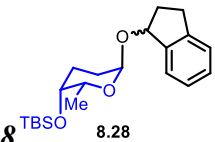
Glycosylated TBS ethers **8.28** *and* **8.29**



Experimental: To a 25 mL rbf was added **8.27** (10.0 mg, 0.075 mmol) and **8.11** (27.9 mg, 0.097 mmol) and this azeotroped with benzene (1x). To this was added 4 Å molecular

sieves (crushed/powdered, ~20 mg, freshly flame-dried) and a stir bar. This was placed under hi-vac for ~2 min then suspended in CH_2Cl_2 (1.49 mL) and stirred for 20 min. This was then cooled to –78 °C in a dry-ice acetone bath and stirred for an additional 10 min after which TBSOTf (0.9 µL, 4 µmol) was added. The reaction was stirred in the dry-ice acetone bath for 1.5 h after which it was quenched at this temperature by the addition of Et_3N (0.1 mL) and subsequently diluted with saturated aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organics dried over $MgSO_4$, filtered, and concentrated to give a crude colorless oil. This was then purified by MPLC (4g column, 18 mL/min, 15 min, 0%→10% EtOAc in hexanes) to give **8.28** (9.4 mg, 35% yield) along with **8.29** contaminated with an unknown impurity. The yield of the ß anomer was not obtained due to significant contamination with this unknown impurity. Inspection of the crude NMR gave a ca. 5:1 mixture of diastereomers at the anomeric position [the α:ß ratio was determined by integration one of the α-anomer diastereomer 5.06 ppm (d, J = 3.3 Hz) and one of the ß-anomer diastereomer peaks at 4.62 ppm (dd, J = 8.9, 2.1 Hz)].

Note: The conditions which gave the highest percentage of ß-anomer utilized Et_2O as solvent (0.05 M) with BF_3•OEt_2 (0.05 mol %) as catalyst at –78 °C for 1 h, then warmed to 5 °C in an ice-water bath. Inspection of the crude NMR gave a 3:2 mixture of α:ß anomers.

α-anomer 8.28 

(characterized as a mixture of diastereomers)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 – 7.36 (m, 1H), 7.28 – 7.17 (m, 3H, overlap with $CHCl_3$), 5.32 – 5.27 (m, 0.4H), 5.13 – 5.05 (m, 1.5H), 4.05 (qd, J = 6.5, 1.5 Hz, 0.4H), 3.96

(qd, J = 6.5, 1.5 Hz, 0.5H), 3.63 (d, J = 2.9 Hz, 0.4H), 3.59 (dt, J = 3.4, 1.9 Hz, 0.5H), 3.14 – 3.01 (m, 1H), 2.88 – 2.75 (m, 1H), 2.49 – 2.36 (m, 1H), 2.18 – 1.93 (m, 3H), 1.65 – 1.54 (m, 1.4H, overlap with H_2O), 1.53 – 1.41 (m, 1H), 1.17 (t, J = 6.9 Hz, 3H), 0.94 (d, J = 2.3 Hz, 9H), 0.07 (dd, J = 4.9, 2.3 Hz, 6H).

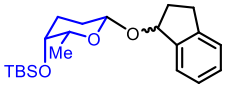
^{13}C NMR (151 Hz, $CDCl_3$): δ 143.8, 143.7, 143.5, 143.4, 128.3, 128.2, 126.6, 126.4, 125.1, 125.0, 124.94, 124.89, 97.2, 95.1, 81.0, 78.7, 68.2, 67.5, 67.3, 34.4, 32.1, 30.4, 30.2, 26.5, 26.4, 26.0, 24.1, 24.0, 18.4, 17.9, 17.9, -4.45, -4.46, -4.72, -4.74.

IR (thin film): cm^{-1} 2950, 2930, 2885, 2856, 1472, 1461, 1443, 1383, 1368, 1339, 1252, 1208, 1120, 1076, 1013, 935

HRMS (ESI+): calculated for $C_{21}H_{34}O_3SiNa$ $[M+Na]^+$ 385.2169, found: 385.2173.

TLC: 0.50 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.



ß-anomer 8.29 **8.29** (mixture of diastereomers)

Note: The ß-anomer coeluted with some unknown impurity and no effort was made to separate this impurity. However, the important anomeric peak could be identified to determine the linkage at the anomeric center. In addition, TBS protection of **8.31** gave a crude spectra which correlated well **8.29**, giving further evidence to the identity of this compound. ^{1}H and ^{13}C spectra of this material is attached in the appendix.

^{1}H NMR (500 MHz, $CDCl_3$): Anomeric protons:

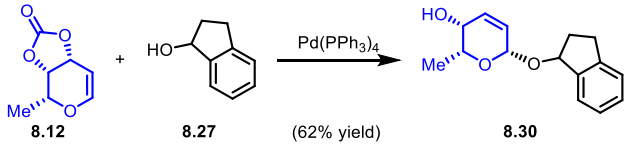
Diastereomer 1: δ 4.62 (dd, J = 9.0, 2.2 Hz, 1H)

Diastereomer 2: δ 4.57 (dd, J = 9.0, 2.1 Hz, 1H).

TLC: 0.46 (20% EtOAc in hexanes).

Physical Appearance: Colorless oil.

Glycosylated allylic alcohol **8.30**



Experimental: To a vial was added **8.12** (24.8 mg, 0.159 mmol), **8.27** (63.9 mg, 0.477 mmol), and $Pd(PPh_3)_4$ (18.4 mg, 0.016 mmol). This was placed under hi-vac and backfilled with nitrogen (3x). This was then capped with a septa and purged with argon with a vent needle after which the solids were dissolved in THF (1.3 mL) and placed in a preheated aluminum block at 40 °C. This was stirred for 5 h, after which the reaction was concentrated and purified by MPLC (linear gradient from 0%→40% EtOAc in hexanes, 12g column, 36 mL/min, 15 min runtime) to give **8.30** (24.3 mg, 0.099 mmol, 62% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.0 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.30 – 7.19 (m, 6H, overlap with $CHCl_3$), 6.18 – 6.10 (m, 2H), 5.84 (dt, *J* = 10.0, 1.0 Hz, 1H), 5.80 (dt, *J* = 10.1, 0.9 Hz, 1H), 5.41 (dd, *J* = 6.9, 5.1 Hz, 1H), 5.31 (dd, *J* = 6.6, 3.9 Hz, 1H), 5.27 – 5.22 (m, 2H), 3.82 – 3.75 (m, 2H), 3.71 – 3.63 (m, 2H), 3.14 – 3.02 (m, 2H), 2.86 – 2.76 (m, 2H), 2.47 – 2.37 (m, 2H), 2.28 – 2.21 (m, 1H), 2.16 – 2.07 (m, 1H), 1.80 (d, *J* = 11.2 Hz, 1H), 1.75 (d, *J* = 11.2 Hz, 1H), 1.69 (s, 2H), 1.36 (dd, *J* = 6.5, 5.2 Hz, 6H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 142.7, 142.3, 131.4, 131.4, 131.2, 128.7, 128.5, 126.7, 126.3, 125.8, 125.5, 125.2, 124.8, 97.0, 96.9, 82.1, 82.0, 71.7, 71.6, 65.0, 64.9, 34.4, 32.8, 30.4, 30.1, 16.9, 16.9.

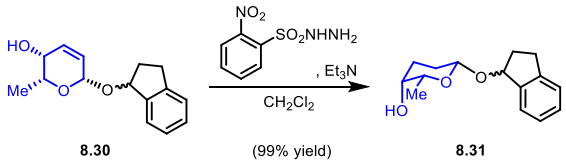
IR (thin film): cm^{-1} 3408, 3041, 2976, 2933, 2850, 1477, 1459, 1402, 1379, 1320, 1180, 1138, 1110, 1056, 1010, 749.

HRMS (ESI+): calculated for $C_{15}H_{18}O_3Na^+$ $[M+Na]^+$ 269.1148, found: 269.1151.

TLC: 0.20 (30% EtOAc in hexanes).

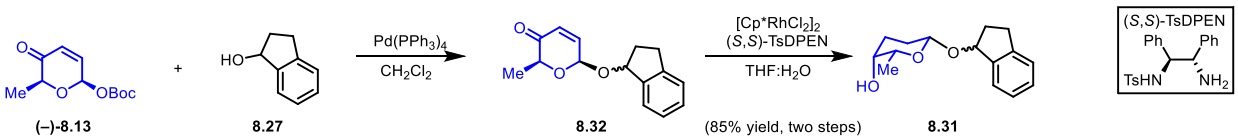
Physical Appearance: Colorless oil that solidifies to a sticky solid over time.

Model ß-rhodinose **8.31**
Method 1: Diimide reduction of an alkene



Experimental: To a vial was added **8.30** (3.0 mg, 0.012 mmol) and dissolved in CH_2Cl_2 (0.12 mL). To this was added triethylamine (14 µL, 0.10 mmol) and 2-nitrobenzenesulfonohydrazide (15.9 mg, 0.073 mmol). The reaction was sealed and stirred at room temperature for 12 h. The reaction was monitored by UPLC/MS (95:5 to 20:80 H_2O:CH_3CN, product retention time ca. 4 min). After 12 h, an additional quantity of triethylamine and 2-nitrobenzenesulfonohydrazide were added equal to the portions originally added. The reaction was stirred for an additional 12 h then quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organics were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated to a yellow oil. This was purified by pipette column (0%→10%→20%→30%→40%→50% EtOAc in hexanes) to give **8.31** (3.0 mg, 99% yield) as a colorless oil. The ^{1}H and HRMS data were in agreement to that obtained by the procedure described in Method 2.

Method 2: Transfer Hydrogenation of an Enone



Experimental (Preparation of 8.32): To a 20 dr vial was added 1-indandol **8.27** (117 mg, 0.872 mmol), (–)-**8.13** (436 mg, 1.97 mmol), and $Pd(PPh_3)_4$ (153 mg, 0.133 mmol). This was placed under hi-vac then backfilled with nitrogen (3x). This was then put under an atmosphere of argon and purged for ~3 min with a vent needle. After dissolved in CH_2Cl_2 (4.0 mL), the solution was stirred for 3 h then concentrated under reduced pressure by rotary evaporation. The crude residue was purified by MPLC (12 g column, 48 mL/min, 10 min, linear gradient from 0%→50% EtOAc in hexanes) to give **8.32** along with an unknown impurity (277 mg). Partial separation of the two daistereomers of the product occurred. Two ^{1}H NMR of this material is included in the appendix for reference corresponding to an NMR of early fractions of this material and an NMR corresponding to latter fractions. This material was used as is in the next step which proved easier to separate from the unknown impurity.

Experimental (Preparation of 8.31): To a vial was added (*S*, *S*)-TsDPEN (3.0 mg, 8.2 μmol) and $[Cp^*RhCl_2]_2$ (2.0 mg, 3.2 μmol). This was placed under hi-vac and backfilled with nitrogen (3x). This was then suspended in H_2O (2.0 mL) and placed in a preheated aluminum block at 60 °C while argon bubbled through the suspension with a vent needle in place for 10 min. After 10 min, the vent needle was removed, and the solution stirred for an additional 30 min at 40 °C.

In a separate vial, **8.32** (60 mg, 0.22 mmol, containing an unknown impurity, see previous step in the preparation of **8.32**) and $NaHCO_2$ (295 mg, 4.34 mmol) were added followed by the addition of THF (1.0 mL). To this was then added the solution of the above prepared catalyst (2.0 mL) and the biphasic mixture stirred vigorously at 40 °C for 1 h under an atmosphere of argon until TLC indicated no starting material remained. The

reaction was then diluted with brine, and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a crude yellow oil that was purified by MPLC (4g column, 30 mL/min, 10 min, linear gradient of 0%→70% EtOAc in hexanes) to give **8.31** mixed with an unknown impurity (54 mg). This material was subject to MPLC purification again (4g column, 30 mL/min, linear gradient from 0%→20% EtOAc in CH_2Cl_2, 10 min runtime) to give pure **8.31** (39 mg, 0.16 mmol, 85% yield over two steps).

Characterized as a mixture of diastereomers (epimeric at the benzylic position):

^{1}H NMR (600 MHz, $CDCl_3$): δ δ 7.53 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.30 – 7.17 (m, 6H, overlap with $CHCl_3$), 5.38 (t, *J* = 6.1 Hz, 1H), 5.27 (dd, *J* = 6.7, 3.7 Hz, 1H), 4.68 – 4.61 (m, 2H), 3.66 (p, *J* = 6.2 Hz, 2H), 3.50 (s, 2H), 3.14 – 3.01 (m, 2H), 2.87 – 2.74 (m, 2H), 2.45 – 2.33 (m, 2H), 2.28 – 2.19 (m, 1H), 2.14 – 2.03 (m, 3H), 2.03 – 1.94 (m, 2H), 1.81 – 1.56 (m, 7H), 1.34 – 1.26 (m, 6H)

^{13}C NMR (151 Hz, $CDCl_3$): δ 144.9, 143.7, 142.9, 142.3, 128.6, 128.4, 126.7, 126.2, 125.8, 125.3, 125.2, 124.7, 100.8, 100.7, 81.6, 81.4, 74.1, 74.0, 66.9, 66.9, 34.4, 32.5, 30.4, 30.1, 30.0, 29.9, 25.9, 25.6, 17.4, 17.4.

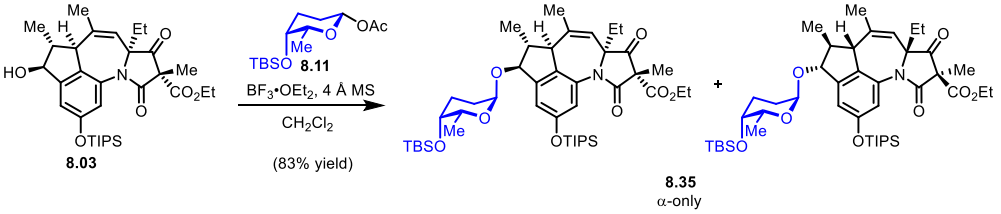
IR (thin film): cm^{-1} 3432, 2934, 2852, 1478, 1447, 1395, 1319, 1209, 1166, 1121, 1061, 1017, 972, 748.

HRMS (ESI+): calculated for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1305, found: 271.1305.

TLC: 0.20 (30% EtOAc in hexanes)

Physical Appearance: Colorless oil.

α-rhodinose derivatives **8.35**



Experimental: In a vial was added **8.03** (3.0 mg, 5.3 μL) and **8.11** (3.04 mg, 10.5 μL) and azeotroped with benzene (1x). To this was added 4 Å molecular sieves (35 mg, powdered/crushed, flame dried) and a flame dried stirbar. This was placed under hi-vac for 20 min after which the vial was placed under a balloon of argon and dissolved in CH_2Cl_2 (0.2 mL). This was stirred for 30 min at room temperature then cooled to –78 °C in a dry-ice acetone bath. After cooling, to this was added TBSOTf (0.04 mL, 5.8 mg/mL neat TBSOTf in CH_2Cl_2). This was let stir for 2 h after which the temperature of the bath had reached ca. 5 °C. The reaction was diluted with CH_2Cl_2 and triethylamine added (10 μL). The reaction was then diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3x) and the combined organics dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a colorless oil. This was purified by pipette column (0%→5%→10%→15%→20% EtOAc in hexanes doped with 2% triethylamine) to give **8.35** (3.5 mg, 83% yield) as a mixture of the depicted diastereomers as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 – 7.52 (m, 2H), 6.80 (dd, J = 2.4, 1.1 Hz, 1H), 6.64 (dd, J = 2.4, 1.0 Hz, 1H), 5.48 – 5.44 (m, 2H), 5.20 (d, J = 3.5 Hz, 1H), 5.15 (d, J = 2.7 Hz, 1H), 4.67 – 4.63 (m, 1H), 4.56 (d, J = 8.1 Hz, 1H), 4.31 – 4.24 (m, 2H), 4.23 – 4.12 (m, 3H), 4.10 – 4.05 (m, 1H), 3.83 (app. dd, J = 21.1, 10.3 Hz, 2H), 3.63 (app. d, J = 12.2 Hz, 2H), 2.59 – 2.50 (m, 1H), 2.45 – 2.38 (m, 1H), 2.35 – 2.25 (m, 2H), 2.25 – 1.97 (m, 7H), 1.93 – 1.86 (m, 6H), 1.70 – 1.64 (m, 3H), 1.62 (d, J = 2.0 Hz, 7H), 1.57 (s, 9H), 1.42 (d, J = 6.3 Hz, 3H), 1.40 (d, J = 6.4 Hz, 3H), 1.32 – 1.23 (m, 20H), 1.19 (d, J = 6.5 Hz, 3H),

1.16 (d, J = 6.5 Hz, 3H), 1.11 (ddd, J = 7.4, 2.5, 1.8 Hz, 39H), 0.94 (d, J = 4.6 Hz, 18H), 0.90 – 0.82 (m, 11H), 0.08 (d, J = 3.4 Hz, 11H).

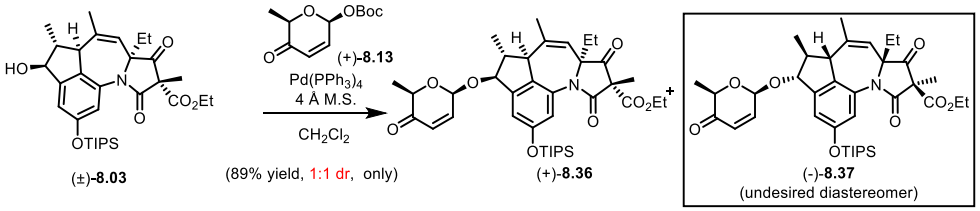
^{13}C NMR (151 Hz, $CDCl_3$): δ 207.7, 168.6, 168.6, 165.7, 155.7, 155.6, 145.8, 145.1, 143.7, 143.6, 133.3, 125.2, 125.2, 121.9, 121.6, 116.4, 116.4, 114.0, 113.2, 99.1, 97.2, 87.2, 86.3, 74.7, 68.1, 68.0, 67.7, 62.7, 62.6, 58.9, 51.2, 50.8, 47.1, 46.9, 29.8, 26.4, 26.4, 26.0, 24.6, 24.5, 24.5, 22.2, 19.6, 19.1, 18.8, 18.4, 18.1, 18.1, 17.8, 14.0, 12.8, 12.7, 8.9, -4.4, -4.5, -4.7.

IR (thin film): cm^{-1} 2930, 2866, 1778, 1749, 1704, 1610, 1472, 1378, 1361, 1283, 1251, 1221, 1124, 1079, 1015, 874, 838, 773, 682.

HRMS (ESI+): calculated for $C_{44}H_{71}NO_8Si_2Na$ $[M+Na]^+$ 820.4616, found: 820.4607.

Physical Appearance: Colorless oil.

Glycosylated diastereomers **8.36** *and* **8.37**



Experimental: To a vial was added (±)-**8.03** (58 mg, 0.10 mmol) and (+)-**8.13** (116 mg, 0.509 mmol). To this was added 4Å M.S. (~60 mg) and the vial placed under hi-vac and backfilled with nitrogen. CH_2Cl_2 (2.0 mL) was then added followed by the addition of $Pd(PPh_3)_4$ (5.9 mg, 5.09 μmol). The reaction was capped and let stir for 24h. The reaction was monitored by UPLC-MS until the reaction was complete (see below for conditions) After 24h, the reaction was filtered through a pad of celite/SiO_2, washed with CH_2Cl_2 and Et_2O then concentrated to a yellow oil. The crude residue was purified by MPLC (linear gradient from 0% to 15% EtOAc/hexanes then isochratic 15% until the first UV active peak is off, the gradient is then increased linearly to 20% EtOAc/hexanes after which the

lower R_f diastereomer elutes, 12 g column, 30 mL/min, 15min runtime) to give (+)-**8.36** (30.5 mg, 0.045 mmol, 44% yield) as a white solid and a lower R_f diastereomer with coelutes with <5% of the starting tetracyclic alcohol (31.4 mg, 0.046 mmol, 45% yield). To obtain an analytically pure sample of the lower R_f diastereomer (-)-**8.37**, the material was further purified by HPLC (linear gradient from 0%→30% EtOAc in hexanes over 15 minutes, 6 mL/min flowrate) to give (-)-**8.37** as a white solid.

Note: The ^{1}H, ^{13}C, and HRMS data were in agreement for both enantiomeric series.

UPLC-MS Conditions: Gradient from 80:20→10:90 H_2O:CH_3CN, ESI+, wavelength = 280 nm. Retention time product: 5.7 minutes, starting material: 4.7 minutes.

Desired diastereomer 8.36

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 2.3 Hz, 1H), 7.02 (dd, *J* = 10.3, 1.5 Hz, 1H), 6.79–6.75 (m, 1H), 6.21 (dd, *J* = 10.3, 1.7 Hz, 1H), 5.72–5.68 (m, 1H), 5.49–5.45 (m, 1H), 4.71 (d, *J* = 8.2 Hz, 1H), 4.33–4.14 (m, 3H), 3.87 (d, *J* = 10.3 Hz, 1H), 2.55–2.43 (m, 1H), 2.37–2.16 (m, 2H), 1.89 (t, *J* = 1.5 Hz, 3H), 1.63 (s, 3H), 1.50 (d, *J* = 6.7 Hz, 3H), 1.46 (d, *J* = 6.4 Hz, 3H), 1.35–1.21 (m, 6H), 1.12 (dd, *J* = 7.5, 2.4 Hz, 18H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.5, 196.5, 168.7, 165.6, 155.7, 147.4, 144.4, 143.4, 133.5, 129.2, 125.3, 121.7, 116.6, 113.4, 97.1, 88.3, 75.5, 74.6, 62.7, 58.9, 50.9, 46.9, 24.5, 22.2, 19.1, 18.5, 18.13, 18.10, 16.5, 14.0, 12.7, 8.9.

IR (thin film): cm^{-1} 2942, 2867, 1777, 1747, 1700, 1611, 1473, 1375, 1223, 1053, 883, 686.

HRMS (ESI+): calculated for $C_{38}H_{53}NO_8SiNa$ $[M+Na]^+$ 702.3433, found: 702.3428.

TLC: R_f = 0.38 (20% EtOAc/hexanes).

m.p.: 128.7-131.1 °C.

Natural Enantiomeric Series (using (+)-8.13 to give (+)-8.36): $[\alpha]_D^{25}$: (c = 0.45, $CHCl_3$), +57°

***ent*-tetrapetalone A Series (using (-)-8.13 to give (-)-8.36): $[\alpha]_D^{25}$**: (c = 0.29, $CHCl_3$), -57°

Physical Appearance: White solid.

^{1}H, ^{13}C, and HRMS data for both (+)-**8.36** and (-)-**8.36** were in agreement.

Undesired diastereomer 8.37

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 2.3 Hz, 1H), 7.02–6.95 (m, 2H), 6.18 (dd, *J* = 10.3, 1.7 Hz, 1H), 5.61–5.57 (m, 1H), 5.51–5.46 (m, 1H), 4.73 (d, *J* = 8.6 Hz, 1H), 4.33–4.14 (m, 3H), 3.84 (d, *J* = 10.5 Hz, 1H), 2.63–2.52 (m, 1H), 2.35–2.14 (m, 2H), 1.90 (t, *J* = 1.5 Hz, 3H), 1.63 (s, 3H), 1.50 (d, *J* = 6.7 Hz, 3H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.32–1.21 (m, 6H), 1.10 (d, *J* = 7.4 Hz, 18H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.6, 196.6, 168.7, 165.7, 155.8, 147.6, 144.0, 143.2, 133.3, 128.9, 125.5, 121.7, 116.8, 114.5, 96.7, 88.7, 75.4, 74.6, 62.7, 58.9, 50.5, 47.1, 24.5, 22.3, 19.1, 18.9, 18.11, 18.08, 16.5, 14.0, 12.7, 8.9.

IR (thin film): cm^{-1} 2943, 2867, 1777, 1747, 1701, 1474, 1377, 1224, 1054, 883, 686.

HRMS (ESI+): calculated for $C_{38}H_{53}NO_8SiNa$ $[M+Na]^+$ 702.3433, found: 702.3429.

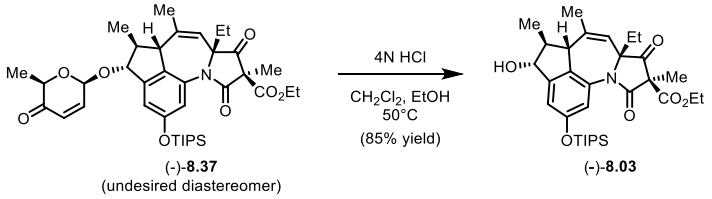
TLC: R_f = 0.31 (20% EtOAc/hexanes).

m.p.: 125.5-127.8 °C.

Natural Enantiomeric Series (using (+)-8.13 to give (-)-8.37): $[\alpha]_D^{25}$: (c = 0.89, $CHCl_3$), -8.5°

Physical Appearance: White solid.

Benzylic alcohol (-)-**8.03**



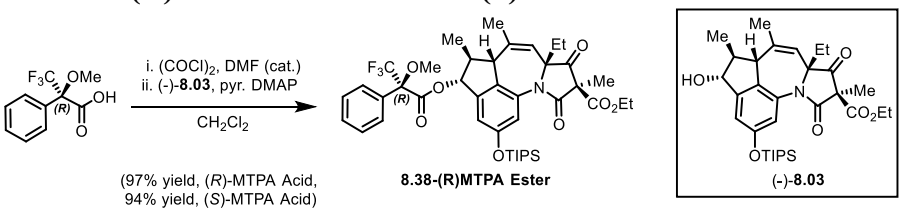
Experimental: A 2 dram vial containing **(-)-8.37** (26.1 mg, 0.0384 mmol) was dissolved in a 1:1 mixture of EtOH:CH_2Cl_2 (1.84 mL). To this was added HCl (4N solution in dioxane, 0.37 mL, 1.5 mmol) and placed in an aluminum block preheated to 50°C. The reaction was monitored by LCMS (Acquity UPLC BEH C18 1.7µm column, 2.1 x 50 mm, gradient from 80:20→5:95 H_2O:CH_3CN over 3 minutes, then isochratic 5:95 for a total runtime of 5 minutes, retention time starting material: 4.26/4.48 min (isomerization of starting material), product: 4.88 min). The reaction was stirred for a total of 12min after which the reaction was cooled in an ice water bath folowed by the dropwise addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a crude yellow residue. The residue was purified by MPLC (4g column, linear gradient from 0%→25% EtOAc/hexanes, 18 mL/min flow rate, 15 minute runtime) to provide (-)-**8.03** (18.7 mg, 0.0328 mmol, 85% yield) as a colorless oil.

The spectral data of the compound (^{1}H, ^{13}C, HRMS) were in agreement with those of (±)-**7.08a**.

$[\alpha]_D^{25}$: (c = 0.310, $CHCl_3$), -68°

Physical Appearance: Colorless oil.

Mosher esters **8.38-(R)MTPA Ester** *and* **8.38-(S)MTPA Ester**



Experimental: To a vial was added **(*R*)-MTPA acid** (32 mg, 0.132 mmol) and dissolved in CH_2Cl_2 (0.5 mL). To this was added $(COCl)_2$ (0.04 mL, 0.46 mmol) and a DMF (catalytic quantity). This was stirred for 30 minutes and subsequently concentrated on rotovap and azeotroped with anhydrous CH_2Cl_2 (2x). This was then placed under hi-vac. In a separate vial was added (-)-**6** (6.1 mg, 11 μmol) and dissolved in CH_2Cl_2 (0.5 mL) followed by the addition of pyridine (0.04 mL, 0.49 mmol) and DMAP (catalytic quantity). The crude acid chloride was dissolved in CH_2Cl_2 (0.5 mL) and transferred to the vial containing (-)-**6**. The reaction was stirred for 8 hours after which it was diluted with H_2O, and extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to a colorless oil. The crude residue was purified by flash chromatography (0%→10% EtOAc/hexanes) to give **8.38-(*R*)MTPA Ester** (8.2 mg, 10 μmol, 97% yield) as a colorless oil. Utilizing the protocol outlined by Hoye et. al.,[19] the absolute stereochemistry of the (-)-**8.03** was assigned as depicted above.

8.38-(R)MTPA Ester

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 – 7.57 (m, 2H), 7.55 (br. d, *J* = 2.3, 1H), 7.46 – 7.37 (m, 3H), 6.66 (dd, *J* = 2.4, 1.0 Hz, 1H), 6.00 (d, *J* = 8.3 Hz, 1H), 5.51 – 5.46 (m, 1H), 4.34 – 4.15 (m, 2H), 3.94 (br. d, *J* = 10.8 Hz, 1H), 3.59 (s, 3H), 2.62 – 2.50 (m, 1H), 2.35 – 2.15 (m, 2H), 1.86 (s, 3H), 1.62 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.28-1.21 (m, 6H), 1.08 (d, *J* = 7.4 Hz, 18H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.3, 168.8, 167.3, 165.6, 156.0, 142.6, 141.3, 133.6, 132.2, 129.9, 128.7, 127.5, 125.7, 123.5 (q, *J* = 288.8 Hz), 122.4, 117.6, 113.9, 84.9 (q, *J* = 27.3 Hz), 84.1, 74.6, 62.8, 58.8, 55.7, 50.7, 45.5, 24.6, 22.3, 19.1, 18.5, 18.02, 18.01, 14.0, 12.7, 8.9.

^{19}F NMR (470 MHz, $CDCl_3$): δ -71.3

HRMS (ESI+): calculated for $C_{42}H_{54}F_3NO_8SiNa$ $[M+Na]^+$ 808.3463, found: 808.3457.

TLC: R_f = 0.45 (20% EtOAc/Hex).

Physical Appearance: Colorless oil.

8.38-(*S*)MTPA Ester

The (*S*)-MTPA Ester was prepared in analogous fashion. Using (-)-**8.03** (5.4 mg, 9.5 μmol), **8.38-(*S*)MTPA Ester** (7.0 mg, 8.9 μmol, 94% yield) was obtained as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 – 7.59 (m, 2H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.47 – 7.40 (m, 3H), 6.49 – 6.45 (m, 1H), 6.07 (d, *J* = 8.3 Hz, 1H), 5.51 – 5.46 (m, 1H), 4.33 – 4.14 (m, 2H), 3.96 (d, *J* = 10.1 Hz, 1H), 3.58 (s, 3H), 2.67 – 2.56 (m, 1H), 2.35 – 2.15 (m, 2H), 1.89 (s, 3H), 1.62 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.31 – 1.17 (m, 6H), 1.07 (d, *J* = 7.4 Hz, 18H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.3, 168.8, 167.2, 165.6, 155.9, 142.6, 141.2, 133.5, 132.0, 130.0, 128.7, 127.5, 125.8, 123.5 (q, *J* = 288.5 Hz), 122.1, 117.4, 113.7, 84.9 (q, *J* = 27.3 Hz), 83.7, 74.6, 62.7, 58.8, 55.6, 50.9, 45.9, 24.6, 22.3, 19.1, 18.8, 18.0, 14.0, 12.7, 8.9.

^{19}F NMR (470 MHz, $CDCl_3$): δ -71.5

HRMS (ESI+): calculated for $C_{42}H_{54}F_3NO_8SiNa$ $[M+Na]^+$ 808.3463, found: 808.3456.

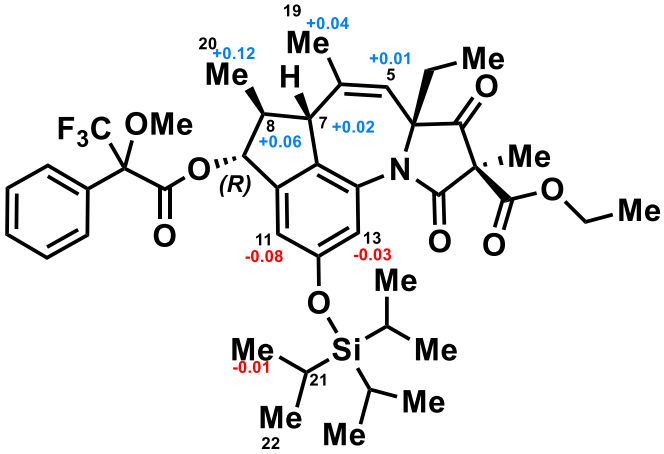
TLC: $R_f = 0.50$ (20% EtOAc/Hex).

Physical Appearance: Colorless oil.

Table 8.1: $\Delta\delta$ ($=\delta_S - \delta_R$) data for the (*S*)- and (*R*)-MTPA Esters **8.38-R** and **8.38-S**

C	(*S*)-MTPA Ester	(*R*)-MTPA Ester	(*S*)-(*R*) (ppm)
C5	5.49	5.48	0.01
C7	3.96	3.94	0.02
C8	2.62	2.56	0.06
C9	6.08	6.00	0.08
C11	6.47	6.65	-0.18
C13	7.52	7.55	-0.03
C16	1.62	1.62	0.00
C17	2.25	2.25	0.00
C18	0.87	0.87	0.00
C19	1.90	1.86	0.04
C20	1.42	1.30	0.12
C21	N.D. *	N.D.	-
C22	1.07	1.08	-0.01

* = Not determined due to overlapping signals



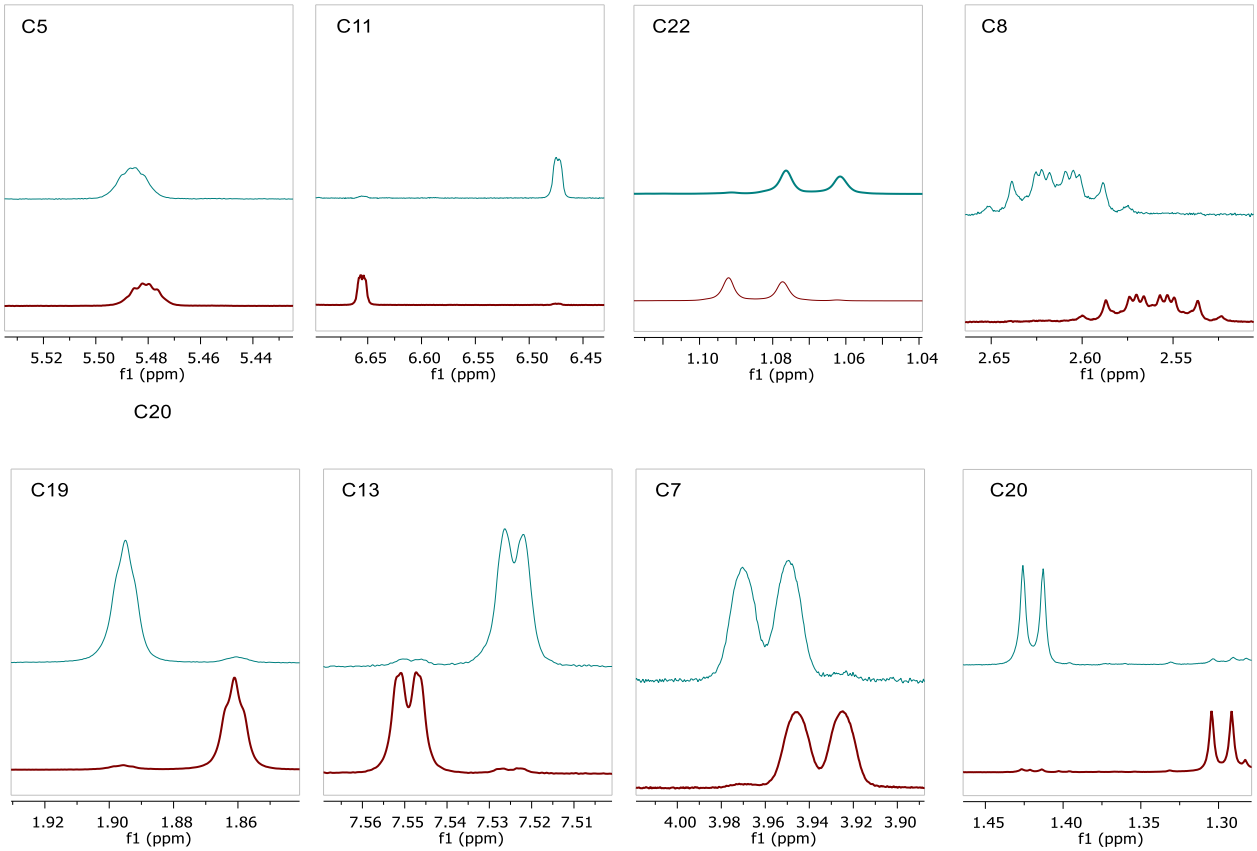
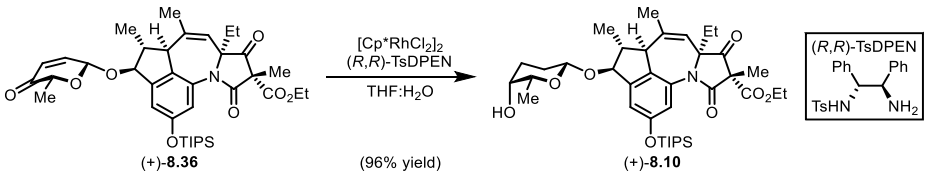


Figure 8.2. Mosher Ester Analysis. TOP RIGHT: Figure representing $\Delta\delta$ ($=\delta_S - \delta_R$) data for the *S*- and *R*-MTPA mosher esters SI-4a and SI-4b; BOTTOM: ^{1}H NMR of pertinent peaks in Mosher ester analysis. Upper spectra (blue) corresponds to the (*S*)-Mosher ester derivative. Bottom spectra (red) corresponds to the (*R*)-Mosher ester derivative.

ß-rhodinose derivative **8.10**



Experimental: To a vial was added (*R*, *R*)-TsDPEN (1.2 mg, 2.9μmol) and $[Cp^*RhCl_2]_2$ (0.8 mg, 1.1 μmol). This was vacuum and backfilled with nitrogen three times. After this, H_2O (2.0 mL) was added, a vent needle placed on the vial, and argon gas bubbled through the solution while stirring in a preheated aluminum block at 60°C. After 10min, the vent needle was removed, and the aluminum block let cool to 40°C. This was stirred for an additional 50min, after which the catalyst solution was ready for use.

In a separate vial a solution of enone (+)**-8.36** (29 mg, 0.043 mmol) in THF (0.7 mL) was prepared followed by the addition of solid $NaHCO_2$ (58 mg, 0.85 mmol). To the vial containing the substrate was added the catalyst solution (1.4 mL) and the reaction placed in a preheated aluminum block at 40°C and stirred vigorously for 20min, after which TLC showed completion of the reaction. The reaction was then diluted by the addition of saturated aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated to a yellow oil. The compound was purified by flash chromatography (0%→20%→25%→30%→40% EtOAc/hexanes) to provide rhodinose derivative (+)**-8.10** (27.9 mg, 0.041 mmol, 96% yield) as a colorless oil. *Note*: The preparation of **(–)-8.10** utilized (*S*, *S*)-TsDPEN as ligand in the transfer hydrogenation.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, *J* = 2.3 Hz, 1H), 6.70–6.65 (m, 1H), 5.48–5.43 (m, 1H), 4.74 (dd, *J* = 8.2, 3.4 Hz, 1H), 4.59 (d, *J* = 8.4 Hz, 1H), 4.33–4.14 (m, 2H), 3.82 (d, *J* = 10.5 Hz, 1H), 3.67 (q, *J* = 6.5 Hz, 1H), 3.52 (br s, 1H), 2.49–2.37 (m, 1H), 2.38–2.15 (m, 2H), 2.11–2.01 (m, 1H), 1.88 (t, *J* = 1.5 Hz, 3H), 1.86–1.70 (m, 3H), 1.63 (s, 3H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.34–1.21 (m, 9H, overlap with grease), 1.12 (dd, *J* = 7.5, 2.8 Hz, 18H), 0.86 (t, *J* = 7.3 Hz, 3H, overlap with grease).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.7, 168.6, 165.7, 155.6, 145.1, 143.8, 133.4, 125.0, 121.6, 116.3, 113.1, 103.2, 87.8, 74.6, 74.3, 66.7, 62.6, 58.9, 51.0, 47.2, 30.1, 26.0, 24.5, 22.2, 19.1, 18.5, 18.12, 18.10, 17.4, 14.0, 12.7, 8.9.

IR (thin film): cm^{-1} 3468, 2939, 2866, 1777, 1747, 1702, 1473, 1377, 1360, 1235, 1168, 1014, 882, 686.

HRMS (ESI+): calculated for $C_{38}H_{57}NO_8SiNa$ $[M+Na]^+$ 706.3746, found: 706.3741.

TLC: $R_f = 0.29$ (30% EtOAc/hexanes).

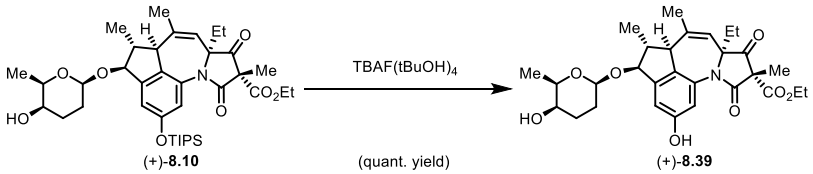
Natural Enantiomeric Series **(using (+)-8.36) to give (+)-8.10: $[\alpha]_D^{25}$**: (c = 0.20, $CHCl_3$), +25°

***ent*-tetrapetalone A Series** **(using (-)-8.36 to give (–)-8.10: $[\alpha]_D^{25}$**: (c = 0.24, $CHCl_3$), -30°

Physical Appearance: Colorless oil.

^1H, ^{13}C, and HRMS data for both (+)-**8.10** and (–)-**8.10** were in agreement.

Phenol **8.39**



Experimental: A solution of (+)-**8.10** (27.9 mg, 0.041 mmol) in THF (2.0 mL) was cooled in an ice water bath followed by the addition of TBAF(*t*BuOH)$_4$ (23.9 mg, 0.043 mmol) to give a yellow solution. The reaction was stirred for 5min after which it was quenched by the addition of saturated aqueous NH_4Cl, diluted with saturated brine and extracted three times with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a yellow residue. The residue was purified by flash chromatography (0%→20%→70% EtOAc/hexanes) to give (+)-**8.39** (22.0 mg, quant. yield) as a white sticky foam.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 2.3 Hz, 1H), 6.94 (br s, 1H), 6.73–6.69 (m, 1H), 5.48–5.43 (m, 1H), 4.75 (dd, *J* = 9.2, 2.3 Hz, 1H), 4.60 (d, *J* = 8.4 Hz, 1H), 4.25–4.13 (m, 2H), 3.82 (d, *J* = 10.4 Hz, 1H), 3.69–3.62 (m, 1H), 3.52 (s, 1H), 2.48–2.39 (m, 1H), 2.37–2.19 (m, 2H), 2.11–1.98 (m, 1H), 1.89 (t, *J* = 1.5 Hz, 3H), 1.89–1.69 (m, 3H), 1.65

(s, 3H), 1.44 (d, J = 6.3 Hz, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 207.1, 169.5, 165.5, 156.0, 145.8, 144.4, 133.3, 124.4, 120.7, 111.8, 109.3, 103.2, 87.5, 74.9, 74.3, 66.8, 62.8, 59.2, 50.9, 47.0, 30.0, 25.9, 24.6, 22.2, 19.2, 18.4, 17.4, 14.1, 8.9.

IR (thin film): cm^{-1} 3360, 2968, 2933, 2360, 1777, 1747, 1699, 1674, 1452, 1383, 1233, 1168, 1130, 1058, 1021, 972.

HRMS (ESI+): calculated for $C_{29}H_{37}NO_8Na$ $[M+Na]^+$ 550.2411, found: 550.2409.

TLC: R_f = 0.18 (50% EtOAc/hexanes).

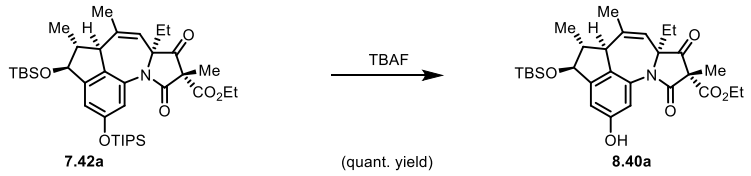
Natural Enantiomeric Series (using (+)-8.10) to give (+)-8.39: $[\alpha]_D^{25}$: (c = 0.31, $CHCl_3$), +35°

***ent*-tetrapetalone A Series (using (-)-8.10) to give (-)-8.39: $[\alpha]_D^{25}$**: (c = 0.25, $CHCl_3$), -34°

Physical Appearance: White foam.

^{1}H, ^{13}C, and HRMS data for both (+)-**8.39** and (-)-**8.39** were in agreement.

Phenol **8.40a**



Experimental: To a rbf containing **7.42a** (24.7 mg, 0.0361 mmol) was added THF (1.8 mL) and cooled in an ice-water bath. After cooling, to this was added TBAF(tBuOH)$_4$ (21.2 mg, 0.038 mmol) at which point the reaction turns a faint yellow. The reactino was stirred for 5 min after which it was quenched by the addition of 0.5 N aqueous HCl and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and

concentrated to give a crude residue that was purified by flash column chromatography on silica gel (10%→20%→30%→50% EtOAc in hexanes) to give **8.40a** (19.0 mg, quant. yield) as a white amorphous solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 2.2 Hz, 1H), 7.00 (br. s, 1H), 6.68 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.48 – 5.44 (m, 1H), 4.54 (d, *J* = 8.3 Hz, 1H), 4.25 – 4.13 (m, 2H), 3.79 (d, *J* = 10.5 Hz, 1H), 2.39 – 2.27 (m, 2H), 2.23 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.90 (s, 3H), 1.66 (s, 3H, overlap with H_2O), 1.36 (d, *J* = 6.3 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.97 (s, 9H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.24 (s, 3H), 0.17 (s, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 207.2, 169.6, 165.4, 156.1, 147.9, 144.3, 133.1, 124.7, 120.4, 111.5, 109.6, 81.2, 75.0, 62.9, 59.2, 50.2, 49.2, 26.1, 26.0, 24.4, 22.3, 19.3, 18.7, 18.2, 14.0, 8.9, -3.6, -3.7.

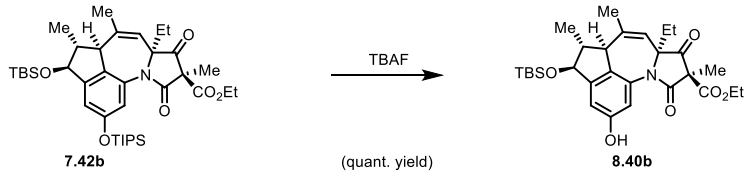
IR (thin film): cm^{-1} 3305, 2956, 2930, 2885, 2856, 1777, 1748, 1670, 1621, 1596, 1472, 1452, 1385, 1362, 1252, 1222, 1129, 1102, 905, 848, 836, 775, 732.

HRMS (ESI+): calculated for $C_{29}H_{41}NO_6SiNa$ $[M+Na]^+$ 550.2595, found: 550.2601.

TLC: 0.21 (20% EtOAc in hexanes).

Physical Appearance: White amorphous solid.

Phenol **8.40b**



Experimental: An experimental procedure identical to the one reported for **8.40a** was used in comparable yield.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.70 (dd, *J* = 2.4, 1.1 Hz, 1H), 6.59 (br. s, 1H), 5.63 – 5.58 (m, 1H), 4.54 (d, *J* = 8.3 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.1

Hz, 1H), 4.12 (dq, J = 10.8, 7.1 Hz, 1H), 3.82 (d, J = 11.0 Hz, 1H), 2.41 – 2.29 (m, 2H), 2.13 (dq, J = 14.5, 7.2 Hz, 1H), 1.90 (t, J = 1.5 Hz, 3H), 1.61 (s, 3H), 1.37 (d, J = 6.3 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H), 0.76 (t, J = 7.3 Hz, 3H), 0.24 (s, 3H), 0.18 (s, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 207.7, 169.4, 165.2, 155.9, 148.0, 142.4, 133.4, 125.7, 120.8, 111.2, 109.5, 81.2, 75.9, 62.9, 59.0, 50.2, 49.2, 26.1, 24.7, 22.2, 18.7, 18.2, 16.5, 14.0, 9.3, -3.6, -3.7.

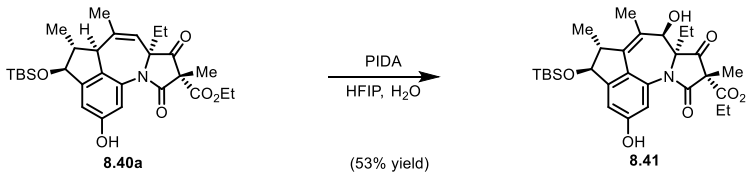
IR (thin film): cm^{-1} 3338, 2929, 2856, 1778, 1748, 1672, 1619, 1595, 1460, 1383, 1364, 1290, 1252, 1221, 1195, 1169, 1130, 1102, 1061, 1009, 901, 879, 835, 774, 670.

HRMS (ESI+): calculated for $C_{29}H_{41}NO_6SiNa$ $[M+Na]^+$ 550.2595, found: 550.2594.

TLC: 0.71 (50% EtOAc in hexanes).

Physical Appearance: White foam.

Allylic alcohol **8.41**



Experimental: To a vial was added **8.40a** (2.0 mg, 3.8 μmol) and this dissolved in HFIP:H_2O (2:1, 0.3 mL) and to this was added PIDA (1.4 mg, 4.6 μmol). The reaction turned yellow, was stirred for 5 min, then quenched by diluting with diH_2O and extracted with EtOAc (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a yellow solid. The crude residue was purified by filtering through a short plug of SiO_2 then purified by HPLC (linear gradient 10%→40% EtOAc in hexanes, 10 mL/min flow rate, 10 min runtime) to give **8.41** (1.1 mg, 53% yield) as a white film.

^{1}H NMR (600 MHz, MeOD-d_4): δ 7.38 (d, J = 2.3 Hz, 1H), 6.78 (d, J = 2.3 Hz, 1H), 4.70 (s, 1H), 4.58 (s, 1H), 4.29 (dq, J = 10.8, 7.1 Hz, 1H), 4.24 – 4.15 (m, 2H), 2.93 (q, J = 7.3 Hz, 1H), 2.06 (s, 3H), 1.68 – 1.57 (m, 4H), 1.46 (dq, J = 14.8, 7.5 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H overlap with grease), 1.12 (d, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.74 (t, J = 7.5 Hz, 3H), 0.18 (d, J = 4.7 Hz, 6H).

^{13}C NMR (151 Hz, MeOD-d_4): δ 209.3, 172.8, 167.2, 159.4, 150.6, 144.3, 133.5, 128.3, 123.4, 113.8, 112.3, 81.3, 79.6, 77.3, 63.8, 60.6, 26.3, 24.5, 21.4, 19.0, 18.9, 17.8, 14.4, 8.8, -4.1, -4.2.

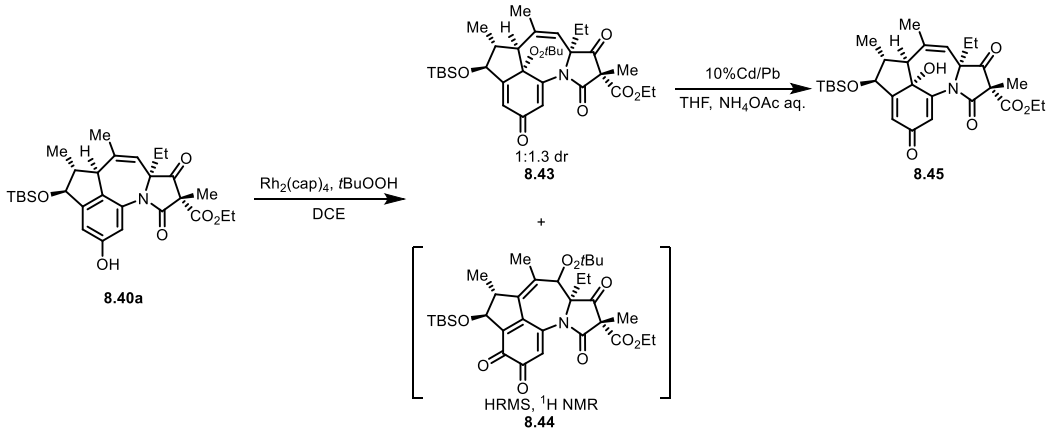
IR (thin film): cm^{-1} 3461, 3198, 2924, 2853, 1782, 1742, 1651, 1615, 1457, 1413, 1386, 1207, 1100, 1011, 849, 832, 777.

HRMS (ESI+): calculated for $C_{29}H_{41}NO_7SiNa$ $[M+Na]^+$ 566.2545, found: 566.2547.

TLC: 0.30 (30% EtOAc in hexanes).

Physical Appearance: White film.

p-Quinol **8.45**



Experimental: To a vial containing **8.40a** (31.0 mg, 0.059 mmol) was added DCE (1.18 mL) and $Rh_2(cap)_4$ (0.4 mg, 0.6 μmol) and this was sonicated for ca. 30 seconds until all the catalyst had dissolved to make a pink solution. This was then cooled to 0 °C in an ice-water bath after which *t*BuOOH (80 μL, 0.59 mmol, 70% solution in H_2O) was added. The

reaction turns red and was stirred in the ice-water bath for 1.5 h and subsequently placed directly into a pipette column (0%→10%→20%→30% EtOAc in hexanes) to give **8.43** (18 mg, 1:1.3 dr, >80% pure).

To this semi-impure material **8.43** (3.0 mg, 4.9 μmol) was added THF (0.2 mL) and aqueous NH_4OAc (0.2 mL, 1.0 M solution). To this was added 10% Cd/Pb couple (56 mg) and stirred vigorously for 3 h. This was then diluted with EtOAc and filtered through a plug of celite. The filtrate was then washed with H_2O and the aqueous layer extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to a faint yellow oil. This crude residue was filtered through a small plug of SiO_2 eluting with EtOAc and concentrated under reduced pressure. This was then purified by HPLC (linear gradient from 0% to 20% EtOAc in hexanes over 2.5 min, then linear gradient from 20% to 50% EtOAc in hexanes for 12.5 min) to give **8.45** (1.1 mg, ca. 20% yield over two steps).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.59 (d, *J* = 1.7 Hz, 1H), 6.06 (t, *J* = 1.8 Hz, 1H), 5.66 – 5.61 (m, 1H), 4.71 (dd, *J* = 9.5, 2.0 Hz, 1H), 4.30 – 4.21 (m, 2H), 3.40 (dq, *J* = 15.1, 7.5 Hz, 1H), 3.04 (d, *J* = 9.6 Hz, 1H), 2.61 (s, 1H), 2.02 – 1.94 (m, 1H), 1.91 – 1.82 (m, 1H), 1.82 (s, 3H), 1.63 (s, 3H), 1.29 (d, *J* = 7.4 Hz, 3H, overlap with grease), 0.97 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (151 Hz, $CDCl_3$): δ 202.1, 186.4, 170.5, 166.3, 165.4, 148.8, 141.6, 122.0, 121.3, 116.7, 76.6, 73.7, 72.8, 63.3, 58.0, 53.5, 42.5, 29.8, 25.9, 25.8, 22.3, 19.9, 19.1, 18.3, 14.0, 8.5, -4.4, -4.7.

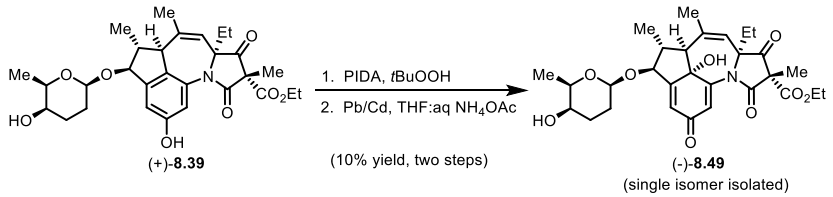
IR (thin film): cm^{-1} 3390, 2921, 2851, 1781, 1710, 1653, 1462, 1378, 1222, 1100.

HRMS (ESI+): calculated for $C_{29}H_{41}NO_7SiNa$ $[M+Na]^+$ 566.2550, found: 566.2545.

TLC: 0.20 (20% EtOAc in hexanes).

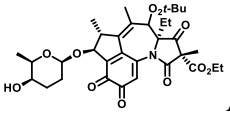
Physical Appearance: White/grey film.

p-quinol **8.49**



Experimental: To a vial was added (+)-**8.39** (20.0 mg, 0.0379 mmol) and this dissolved in DCE (0.95 mL). The solution was then placed in an acetone bath cooled to -18°C with dry ice. After stirring for 5min, to the solution was added TBHP (5.5M in decane, 0.14 mL, 0.76 mmol). The solution was stirred for ~1 minute followed by the addition of PIDA (36.6 mg, 0.114 mmol). The reaction was stirred for 15 minutes while the temperature was maintained between -18°C and -11°C. After 15min, the red solution was placed directly onto a silica gel column wetted with hexanes. The compound was rapidly filtered through the pipette column using a gradient from 0%→10%→20%→30%→40% EtOAc in hexanes. The fractions containing the crude products **8.46** and **8.47** were concentrated on rotovap and transferred to a 2 dram vial and dissolved in a 1:1 mixture of THF:1M aq NH_4OAc (4.4 mL). With the solution vigorously stirring, 10% Cd/Pd couple was added (136 mg, fine powder). Yellow mixture quickly turns colorless then a faint orange-red color. The mixture is stirred for 2.5h after which the suspension is diluted with EtOAc and filtered through a plug of celite and washed with EtOAc (5 x 2 mL) and brine (2 x 1 mL). The layers were separated and the aqueous layer washed with EtOAc (2 mL x 2) and the combined organics dried over Na_2SO_4, filtered through a short plug of SiO_2, and concentrated in vacuo. The residue was purified by HPLC (linear gradient from 30% to 100% EtOAc/hexanes over 12 minutes) to give *p*-quinol (+)-**8.49** (2.1 mg, 3.9 μmol, 10%

yield, two steps) and recovered phenol (+)-**8.39** (5.0 mg, 9.5 μmol mmol, 25% recovery, two steps).

Note:  After the *t*-BuOOH procedure and filtration, a separate red oil was obtained whose NMR indicated the formation of the *o*-quinone pictured to the left (ca. 40% yield). This compound was unstable and was therefore not characterized.

***p*-quinol 8.49**

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.60 (d, *J* = 1.7 Hz, 1H), 6.06 (t, *J* = 1.8 Hz, 1H), 5.66–5.62 (m, 1H), 4.82 (dd, *J* = 9.7, 2.0 Hz, 1H), 4.57 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.31–4.22 (m, 2H), 3.66 (qd, *J* = 6.5, 1.2 Hz, 1H), 3.53 (br s, 1H), 3.40 (dq, *J* = 15.1, 7.5 Hz, 1H), 3.10–3.04 (m, 1H), 2.16–2.02 (m, 2H), 1.88 (dq, *J* = 14.8, 7.3 Hz, 1H), 1.84–1.67 (m, 6H), 1.63 (s, 3H), 1.36 (d, *J* = 6.5 Hz, 3H), 1.31–1.25 (m, 6H), 0.85 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 202.0, 186.4, 170.9, 165.4, 164.6, 149.3, 141.8, 122.0, 121.1, 116.8, 102.0, 81.8, 74.3, 73.8, 73.0, 66.7, 63.2, 58.0, 54.3, 40.5, 29.9, 25.9, 25.5, 22.4, 19.8, 19.2, 17.3, 14.0, 8.4.

IR (thin film): cm^{-1} 3388, 2973, 2933, 2876, 1777, 1718, 1638, 1450, 1374, 1275, 1229, 1167, 1105, 1059, 1023, 975.

HRMS (ESI+): calculated for $C_{29}H_{37}NO_9Na$ $[M+Na]^+$ 566.2361, found: 566.2359.

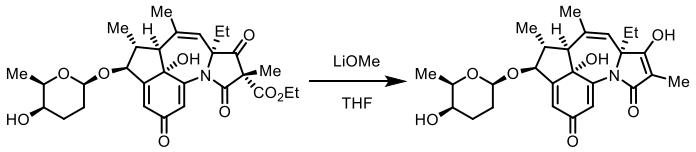
TLC: $R_{f=}$ 0.39 (70% EtOAc/hexanes).

Natural Enantiomeric Series (using (+)-8.39 to give (-)-8.49): [α]$_D^{24}$: (c = 0.20, $CHCl_3$), -198°

***ent*-tetrapetalone A Series (using (-)-8.39 to give (+)-8.49): [α]$_D^{24}$** : (c = 0.23, $CHCl_3$), +195°

Physical Appearance: Faint yellow oil.

Tetrapetalone A **8.01**



(-)-**8.39** (86% yield) (-)-tetrapetalone A (**8.01**)

Experimental: A solution of (-)-**8.39** (2.0 mg, 3.7 μmol) in THF (0.5 mL) was placed under a balloon of argon to give a faint yellow solution. To this was added LiOMe (1.0 M in MeOH, 15 μL, 15 μmol). The solution turned to a darker shade of yellow. The reaction was stirred for 1h20min after which LCMS indicated no starting material remained in the reaction (see below for conditions). The reaction was diluted with Et_2O and filtered through a short plug of celite. The reaction vial and celite were then washed with MeOH to give a yellow solution. The filtrate was concentrated on rotovap to give a yellow residue. The residue was then purified by silica gel chromatography (SiO_2 prewashed with MeOH then saturated with CH_2Cl_2. The compound was loaded with a 5% MeOH in CH_2Cl_2 solution and subsequently 5% MeOH in CH_2Cl_2 followed by 20% MeOH in CH_2Cl_2 was passed through the column) to give (-)-**tetrapetalone A** (**8.01**) (1.5 mg, 3.2 μmol, 86% yield) as a yellow oily residue.

UPLC-MS Conditions: 0.5 mL/min flowrate, linear gradient 80:20→10:90 H_2O:CH_3CN (0.2% formic acid) over 4 minutes, then isochratic for 1 minute, wavelength = 265 nm, Retention times: product: 1.62 min, starting material: 2.32 min

Note: The initially yellow oily form of the compound directly after chromatography did not match with the reported spectra of the natural product. Upon analysis of the spectral data, those protons away from the tetramic acid moeity matched well with the reported spectra, however those within proximity to the tetramic acid moeity showed a range of

differences to the natural product. Thus, by titrating the compound with a dilute solution of formic acid, a spectra in agreement with that of the natural product was obtained. Both spectra are reported here:

Directly After Column Chromatography:

^{1}H NMR (500 MHz, Methanol-d_4): δ 6.59 (d, J = 1.8 Hz, 1H), 5.89 (t, J = 1.9 Hz, 1H), 5.72-5.70 (m, 1H), 4.82 (dd, J = 9.8, 2.0 Hz, 1H), 4.61 (dd, J = 9.1, 2.0 Hz, 1H), 3.65 (qd, J = 6.5, 1.2 Hz, 1H), 3.49 – 3.46 (br. s, 1H), 3.29-3.27 (br. s, 1H, partial overlap with solvent peak), 2.97 (dq, J = 14.1, 7.1 Hz, 1H), 2.01 – 1.93 (m, 2H), 1.90 – 1.73 (m, 3H), 1.76-1.75 (s, 3H), 1.74-1.67 (m, 1H), 1.64 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H), 1.26 (d, J = 6.4 Hz, 3H), 0.69 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Methanol-d_4): δ 192.5, 189.8, 181.4, 167.0, 158.4, 139.4, 128.4, 116.2, 112.8, 103.4, 97.6, 83.1, 75.4, 74.3, 71.1, 67.2, 55.8, 49.9 (methanol), 41.6, 30.9, 26.7, 25.5, 22.2, 20.2, 17.6, 7.8, 5.9.

IR (thin film): cm^{-1} 3386, 2964, 2927, 2870, 1686, 1561, 1361, 1251, 1056.

HRMS (ESI+): calculated for $C_{26}H_{33}NO_7Na$ $[M+Na]^+$ 494.2149, found: 494.2148.

TLC: R_f = 0.36 (20% MeOH in CH_2Cl_2).

Natural Enantiomer (using (-)-27 to give (-)-tetrapetalone A (1)): $[\alpha]_D^{25}$: (c = 0.12, MeOH), -378°

***ent*-tetrapetalone A (using (+)-27 to give (+)-tetrapetalone A (1)): $[\alpha]_D^{24}$**: (c = 0.10, MeOH), +200°

Note: The observed range in optical rotations was attributed to changes in the keto-enol equilibrium of the tetramic acid moeity in solution.

Physical Appearance: Yellow oily residue.

Note: Diluting the oily residue in ethyl acetate and washing with saturated aqueous ammonium chloride provided a faint yellow solid that contained some unknown impurities.

Acidification with dilute formic acid:

To an NMR tube containing tetrapetalone A (~1.1 mg) in methanol-d_4 (~0.2 mL) was added 5 µL aliquots of a solution of formic acid in methanol-d_4 (5 µL formic acid in 1.0 mL methanol-d_4). After the addition of 10 µL of this solution, the following spectral data was obtained:

^{1}H NMR (500 MHz, Methanol-d_4): δ 8.15 (s, 7H, formic acid), 6.74 (d, J = 1.8 Hz, 1H), 5.92 (t, J = 1.9 Hz, 1H), 5.74 – 5.70 (m, 1H), 4.82 (dd, J = 9.9, 2.0 Hz, 1H, partial overlap with water), 4.61 (dd, J = 9.4, 2.1 Hz, 1H), 3.64 (qd, J = 6.5, 1.3 Hz, 1H), 3.49-3.46 (m, 1H), 3.30 (br. s, 1H, overlap with solvent signal), 3.12 (dq, J = 14.1, 7.1 Hz, 1H), 2.02 – 1.93 (m, 2H), 1.91 – 1.72 (m, 7H), 1.71 (s, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.26 (d, J = 6.5 Hz, 3H), 0.70 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Methanol-d_4): δ 189.9, 178.2, 178.1, 167.2, 165.4 (formic acid), 156.4, 141.0, 125.9, 116.2, 114.6, 103.3, 102.2, 82.8, 75.4, 73.9, 69.5, 67.2, 56.0, 49.8 (methanol), 41.7, 30.9, 26.7, 24.8, 22.2, 20.2, 17.6, 7.4, 5.7.

Table 8.2: ^{1}H data for tetrapetalone A as reported by Hirota and co-workers and synthetic tetrapetalone A.

C	Natural	Observed (After chromatography)	Delta	Observed (Formic Acid Titrated)	Delta
C1	-	-	-	-	-
C2	-	-	-	-	-
C3	-	-	-	-	-
C4	-	-	-	-	-
C5	5.72 (br. s)	5.71 (m)	0.01	5.72 (m)	0.00
C6	-	-	-	-	-
C7	ca. 3.3	3.29	0.01	3.30	0.00
C8	ca. 2.0	ca. 1.97	0.03	ca. 1.98	0.02
C9	4.82 (dd, *J* = 10.0, 2.0 Hz)	4.82 (dd, *J* = 9.8, 2.0 Hz)	0.00	4.82 (*J* = 9.9, 2.0 Hz)	0.00
C10	-	-	-	-	-
C11	5.95 (t, *J* = 2.0 Hz)	5.89 (t, *J* = 1.9 Hz)	0.06	5.92 (t, *J* = 1.9 Hz)	0.03
C12	-	-	-	-	-
C13	6.75 (*J* = 2.0 Hz)	6.59 (d, *J* = 1.8 Hz)	0.16	6.74 (*J* = 1.8 Hz)	0.01
C14	-	-	-	-	-
C15	-	-	-	-	-
C16	1.70 (s, 3H)	1.64 (s, 3H)	0.06	1.70 (m, 3H)	0.00
C17a	1.85 (m)	1.71 (m)	0.14	*	*
C17b	3.14 (m)	2.97 (dq, *J* = 14.1, 7.1 Hz)	0.17	3.12 (dq, *J* = 14.1, 7.1 Hz)	0.02
C18	0.70 (t, *J* = 7.6 Hz)	0.69 (t, *J* = 7.1 Hz)	0.01	0.70 (t, *J* = 7.1 Hz)	0.00
C19	1.80 (s, 3H)	1.75 (m, 3H)	0.05	1.78 (s, 3H)	0.02
C20	1.35 (d, *J* = 6.4 Hz, 3H))	1.33 (d, *J* = 6.5 Hz, 3H)	0.02	1.35 (d, *J* = 6.4 Hz, 3H)	0.00
C1'	4.60 (dd, *J* = 9.2, 2.0 Hz)	4.61 (dd, *J* = 9.2, 2.0 Hz)	0.01	4.61 (dd, *J* = 9.4, 2.1 Hz)	0.01
C2'a	1.75 (m)	*	*	*	*
C2'b	1.87 (m)	*	*	*	*
C3'a	1.78 (m)	*	*	*	*
C3'b	1.95 (m)	*	*	*	*
C4'	3.47 (br. s)	3.47 (m)	0.00	3.48 (m)	0.01
C5'	3.65 (q, *J* = 6.4 Hz)	3.65 (qd, *J* = 6.5, 1.2 Hz)	0.00	3.64 (qd, 6.5, 1.3 Hz)	0.01
C6'	1.25 (d, *J* = 6.4 Hz)	1.26 (dd, *J* = 6.4 Hz)	0.01	1.26 (d, *J* = 6.5 Hz)	0.01

* = overlapping multiplets were observed in the range from 2.02-1.72 ppm

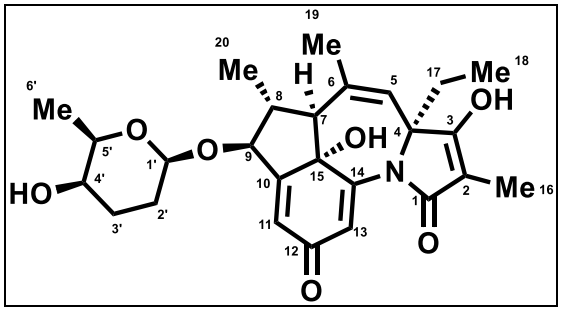
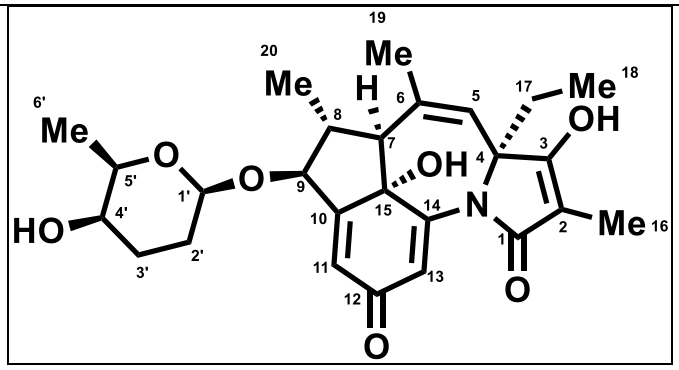
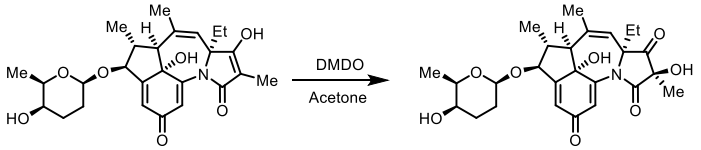


Table 8.3: ^{13}C data for tetrapetalone A as reported by Hirota and co-workers and synthetic tetrapetalone A.

C	Natural	Observed (After chrom.)	Delta ppm	delta ppm (>1.0)	Observed (Formic Acid Titrated)	Delta	delta ppm (>0.2)
C1	177.6	181.4	3.8	3.8	178.1	0.5	0.5
C2	103.0	97.6	5.4	5.4	102.2	0.8	0.8
C3	176.0	192.5	16.5	16.5	178.2	2.2	2.2
C4	69.3	71.1	1.8	1.8	69.5	0.2	0.2
C5	125.6	128.4	2.8	2.8	125.9	0.3	0.3
C6	141.2	139.4	1.8	1.8	141.0	0.2	-
C7	56.0	55.8	0.2	-	56.0	0.0	-
C8	41.8	41.6	0.2	-	41.7	0.1	-
C9	82.8	83.1	0.3	-	82.8	0.0	-
C10	167.2	167.0	0.2	-	167.2	0.0	-
C11	116.3	116.2	0.1	-	116.2	0.1	-
C12	189.6	189.8	0.2	-	189.9	0.3	0.3
C13	114.9	112.8	2.1	2.1	114.6	0.3	0.3
C14	156.1	158.4	2.3	2.3	156.4	0.3	0.3
C15	73.9	74.3	0.4	-	73.9	0.0	-
C16	5.6	5.9	0.3	-	5.7	0.1	-
C17	24.8	25.5	0.7	-	24.8	0.0	-
C18	7.3	7.8	0.5	-	7.4	0.1	-
C19	22.1	22.2	0.1	-	22.2	0.1	-
C20	20.2	20.2	0.0	-	20.2	0.0	-
C1'	103.3	103.4	0.1	-	103.3	0.0	-
C2'	26.7	26.7	0.0	-	26.7	0.0	-
C3'	30.9	30.9	0.0	-	30.9	0.0	-
C4'	67.2	67.2	0.0	-	67.2	0.0	-
C5'	75.4	75.4	0.0	-	75.4	0.0	-
C6'	17.5	17.6	0.1	-	17.6	0.1	-



Tetrapetalone C **8.02**



(-)-**tetrapetalone A** (**8.01**) (quant. yield) (-)-**tetrapetalone C** (**8.02**)

Experimental: A solution of (-)-**tetrapetalone A (1)** (1.0 mg, 2.1 μmol) in acetone (0.3 mL) cooled in an ice water bath (yellow solution) was added a solution of DMDO (68 mM in acetone, 31 μL, 2.1 μmol). The yellow color rapidly faded to a colorless solution. The solution was stirred for 2min in the ice water bath and subsequently placed on a rotovap and concentrated in air under vacuum to dryness, azeotroped with acetone (2x) and subsequently placed under hi-vac to afford (-)-**tetrapetalone C (3)** (1.0 mg, 2.1 μmol quant. yield) as a white amorphous solid that was of characterizable quality.

Note: Attempts to obtain spectral data in the methanol-d_4 lead to the partial decomposition of the material to an as yet undetermined compound. In one instance, the partially decomposed material was purified by HPLC (normal phase, gradient from 30% to 100% EtOAc in hexanes over 15 minutes, then isochratic 100% EtOAc for 10 minutes) to give (-)-**tetrapetalone C (3)** (0.9 mg, 1.8 μmol, 87% yield) as a white amorphous solid.

^{1}H NMR (500 MHz, methanol-d_4): δ 6.72 (d, J = 1.7 Hz, 1H), 5.99 (t, J = 1.9 Hz, 1H), 5.67 (br. s, 1H), 4.86 (d, J = 2.1 Hz, 1H, overlap with HDO), 4.62 (dd, J = 9.3, 1.9 Hz, 1H), 3.68 – 3.59 (m, 2H), 3.48 (br. s, 1H), 3.09 (br. d, J = 9.1 Hz, 1H), 2.16 (s, 0.3H, acetone), 2.15 – 2.06 (m, 1H), 2.00 – 1.94 (m, 1H), 1.89-1.67 (m, 4H), 1.82 (s, 3H), 1.59 (s, 3H), 1.35 (d, J = 6.5 Hz, 3H), 1.26 (d, J = 6.4 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H).

^{1}H NMR (500 MHz, acetone-d_6): δ 6.57 (d, J = 1.7 Hz, 1H), 5.92 (t, J = 1.9 Hz, 1H), 5.68 (s, 1H, -OH), 5.61 (br. s, 1H), 5.41 (s, 1H, -OH), 4.88 (dd, J = 9.7, 2.0 Hz, 1H), 4.62 (d, J = 8.6 Hz, 1H), 3.68 – 3.57 (m, 2H), 3.54 (d, J = 6.6 Hz, 1H, -OH), 3.47 (br. s, 1H), 3.11

(br. d, J = 9.1 Hz, 1H), ca. 2.06 (m, 1H, overlap with solvent signal), 1.98 – 1.67 (m, 5H), 1.83 (s, 3H), 1.57 (s, 3H), 1.35 (d, J = 6.5 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, Acetone-d_6): δ 209.9, 186.8, 174.3, 165.8, 150.8, 141.9, 129.2 (benzene), 122.7, 121.9, 116.6, 102.7, 82.1, 74.8, 74.1, 71.7, 70.8, 66.5, 55.6, 41.2, 30.8, 30.3 (grease), 27.1, 26.3, 23.8, 22.2, 20.0, 17.6, 8.8.

IR (thin film): cm^{-1} 3360, 2922, 2852, 1777, 1709, 1627, 1452, 1377, 1279, 1169, 1155, 1127, 1059, 1026, 974.

HRMS (ESI+): calculated for $C_{26}H_{33}NO_8Na$ $[M+Na]^+$ 510.2098, found: 510.2098.

TLC: R_f = 0.47 (100% EtOAc).

Natural Enantiomeric Series (using (-)-tetrapetalone A (1) to give (-)-tetrapetalone C (3)): $[\alpha]_D^{24}$: (c = 0.05, acetone), -280°

***ent*-tetrapetalone A Series (using (+)-tetrapetalone A (1) to give (+)-tetrapetalone C (3)):** $[\alpha]_D^{24}$: (c = 0.03, acetone), +267°

Physical Appearance: White amorphous solid.

Table 8.4: ^{1}H data for tetrapetalone C as reported by Hirota and co-workers and synthetic tetrapetalone C.

C	Natural	1H - methanol-*d*4 (500 MHz)	Delta (ppm)	1H - Acetone-*d*6	Delta
C1	-	-	-	-	-
C2	-	-	-	-	-
C3	-	-	-	-	-
C4	-	-	-	-	-
C5	5.72 (br. s)	5.67 (br. s)	0.05	5.61 (br. s)	0.11
C6	-	-	-	-	-
C7	3.09 (br. d, *J* = 8.8 Hz)	3.09 (br. d, *J* = 9.1 Hz)	0.00	3.11 (br. d, *J* = 9.1 Hz)	0.02
C8	ca. 2.1 (m)	2.13-2.07 (m)	0.00	ca. 2.06, overlap with solvent)	/
C9	4.86 (br. d, *J* = 10.0 Hz)	4.86 (d, *J* =2.0 Hz, overlap with solvent signal)	0.00	4.88 (dd, *J* = 9.7, 2.0 Hz)	0.02
C10	-	-		-	-
C11	5.99 (t, *J* = 2.0 Hz)	6.00 (t, *J* = 1.9 Hz)	0.01	5.92 (t, *J* = 1.9 Hz)	0.07
C12	-	-	-	-	-
C13	6.71 (d, *J* = 2.0 Hz)	6.72 (d, *J* = 1.7 Hz)	0.01	6.57 (d, *J* = 1.7 Hz)	0.14
C14	-	-	-	-	-
C15	-	-	-	-	-
C16	1.59 (s, 3H)	1.59 (s, 3H)	0.00	1.57 (s, 3H)	0.02
C17a	ca. 1.7 (m)	*	*	*	*
C17b	ca. 3.6 (m)	3.68-3.59 (m), overlap with C5'	/	3.68-3.57 (m, overlap with C5')	/
C18	0.85 (t, *J* = 6.4 Hz)	0.86 (t, *J* = 7.5 Hz)	0.01	0.84 (t, *J* = 7.5 Hz)	0.01
C19	1.81 (s, 3H)	1.82 (s, 3H)	0.01	1.83 (s, 3H)	0.02
C20	1.35 (d, *J* = 6.8 Hz, 3H)	1.35 (d, *J* = 6.5 Hz, 3H)	0.00	1.35 (d, *J* = 6.5 Hz)	0.00
C1'	4.61 (br. d, *J* = 9.2 Hz)	4.62 (dd, *J* = 9.3, 1.9 Hz)	0.01	4.62 (br. d, 8.6 Hz)	0.01
C2'a	ca. 1.8 (m)	*	*	*	*
C2'b	ca. 1.9 (m)	*	*	*	*
C3'a	ca. 1.9 (m)	*	*	*	*
C3'b	ca. 2.0 (m)	*	*	*	*
C4'	3.47 (br.s)	3.48 (br. s)	0.01	3.47 (br. s)	0.00
C5'	3.62 (q, *J* = 6.4 Hz)	3.68-3.59 (m), overlap with C17b	/	3.68-3.57 (m, overlap with C17b)	/
C6'	1.25 (d, *J* = 6.4 Hz)	1.26 (d, *J* = 6.4 Hz)	0.01	1.23 (d, *J* = 6.5 Hz)	

* = overlapping multiplets were observed in the range from 1.89-1.66 ppm (methanol-*d*4), 1.98-1.67 (acetone-*d*6)

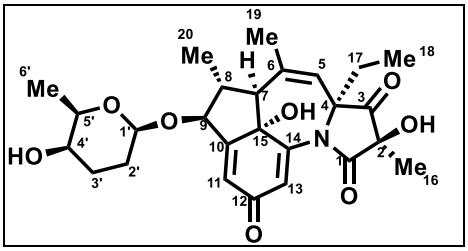
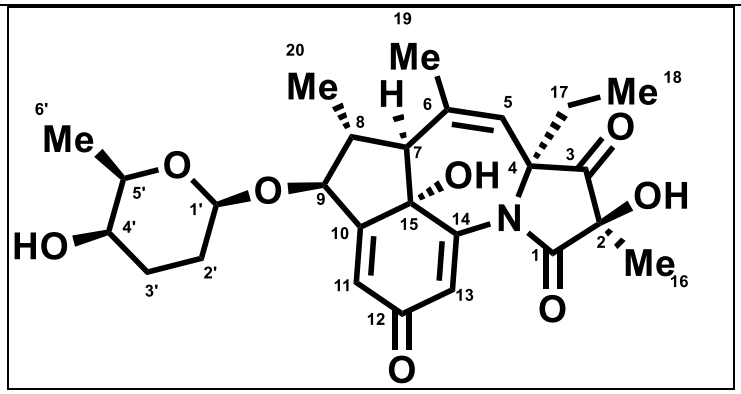


Table 8.5: ^{1}H data for tetrapetalone C as reported by Hirota and co-workers and synthetic tetrapetalone C.

C	13C - Natural (methanol-*d*4, 100Mhz)	13C - (acetone-*d*6, 151 MHz)	Delta (ppm)
C1	175.7	174.3	1.4
C2	72.2	71.7	0.5
C3	210.2	209.9	0.3
C4	71.7	70.8	0.9
C5	122.8	122.7	0.1
C6	142.7	141.9	0.8
C7	56.1	55.6	0.5
C8	41.7	41.2	0.5
C9	83.0	82.1	0.9
C10	168.1	165.8	2.3
C11	116.7	116.6	0.1
C12	189.1	186.8	2.3
C13	122.0	121.9	0.1
C14	152.8	150.8	2.0
C15	74.2	74.1	0.1
C16	23.7	23.8	0.1
C17	27.4	27.1	0.3
C18	8.8	8.8	0.0
C19	22.2	22.2	0.0
C20	20.2	20.0	0.2
C1'	103.4	102.7	0.7
C2'	26.7	26.3	0.4
C3'	30.9	30.8	0.1
C4'	67.1	66.5	0.6
C5'	75.4	74.8	0.6
C6'	17.6	17.6	0.0



8.5 References

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APPENDICES

APPENDIX A

Spectra Relevant to Chapter Three

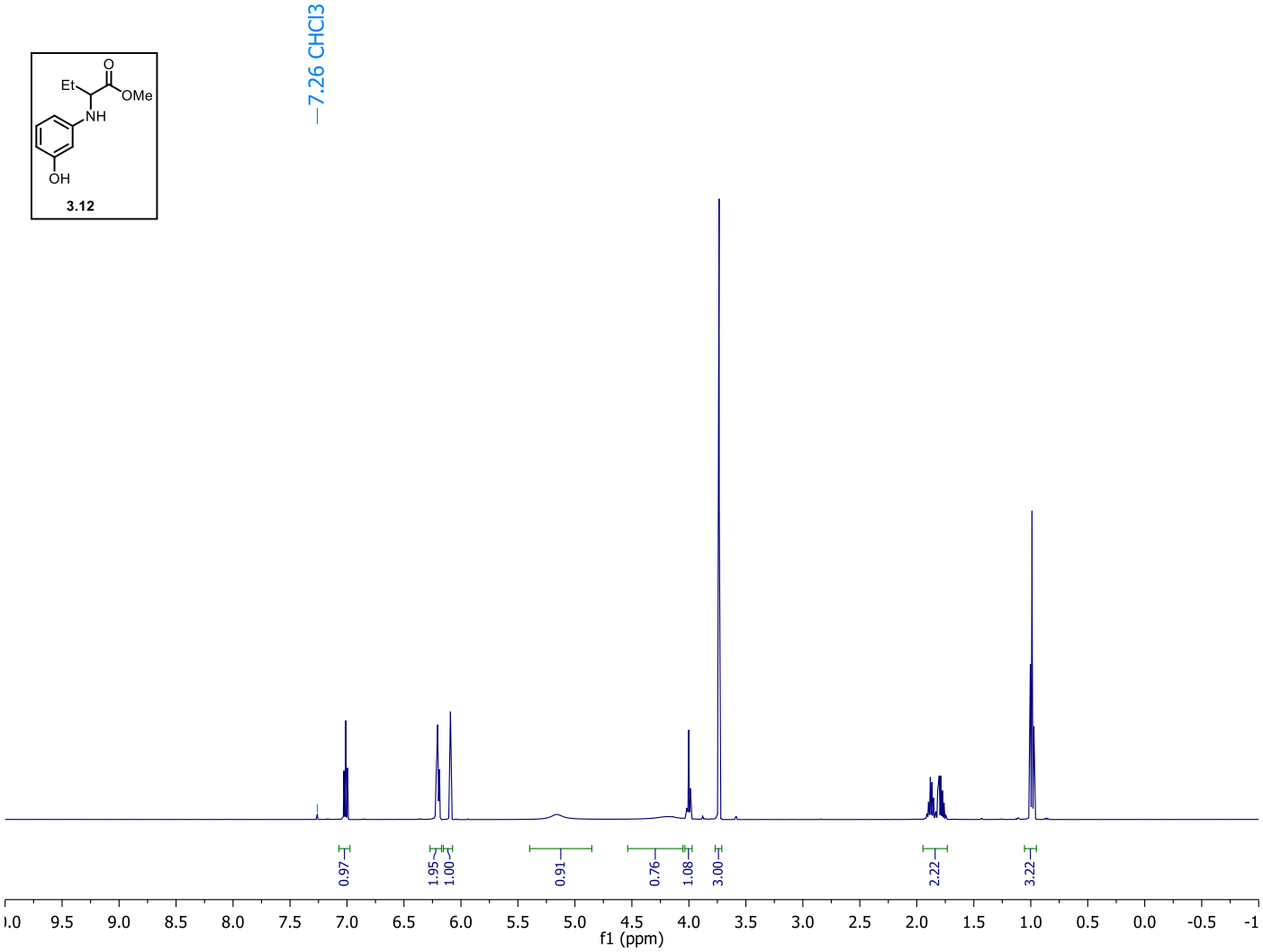


Figure A.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.12**

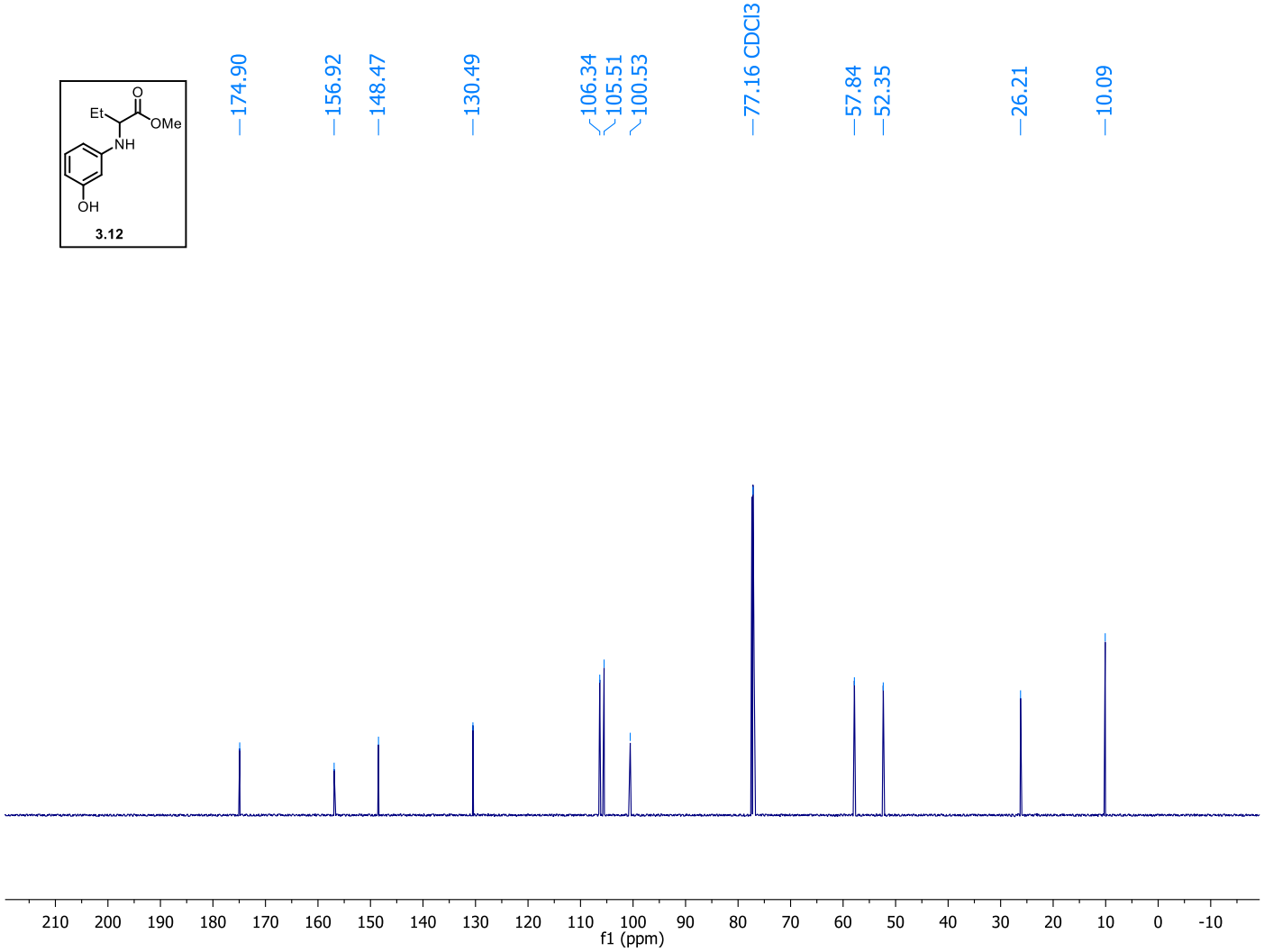


Figure A.2. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **3.12**

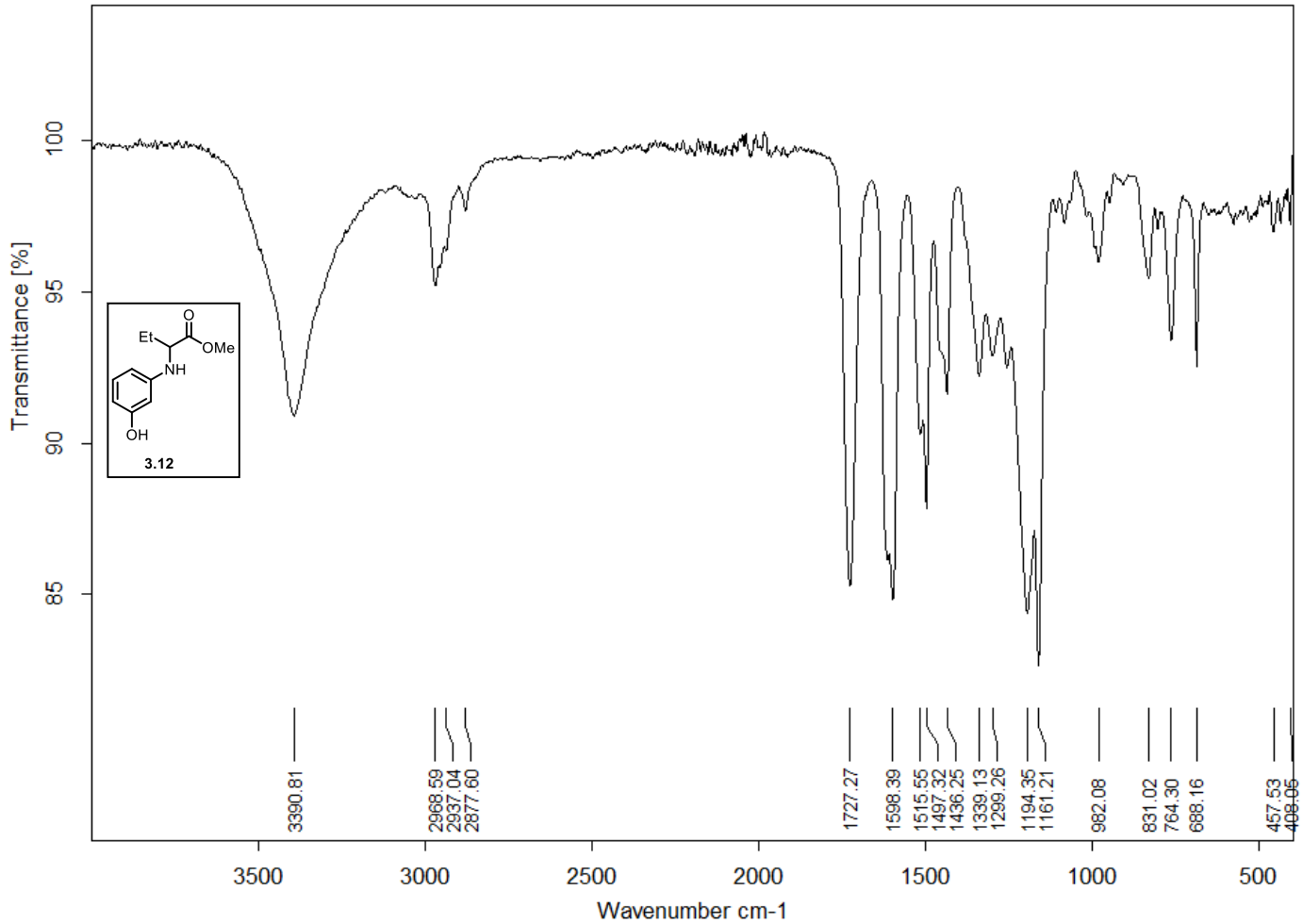


Figure A.3. FTIR spectrum (neat) of compound **3.12**

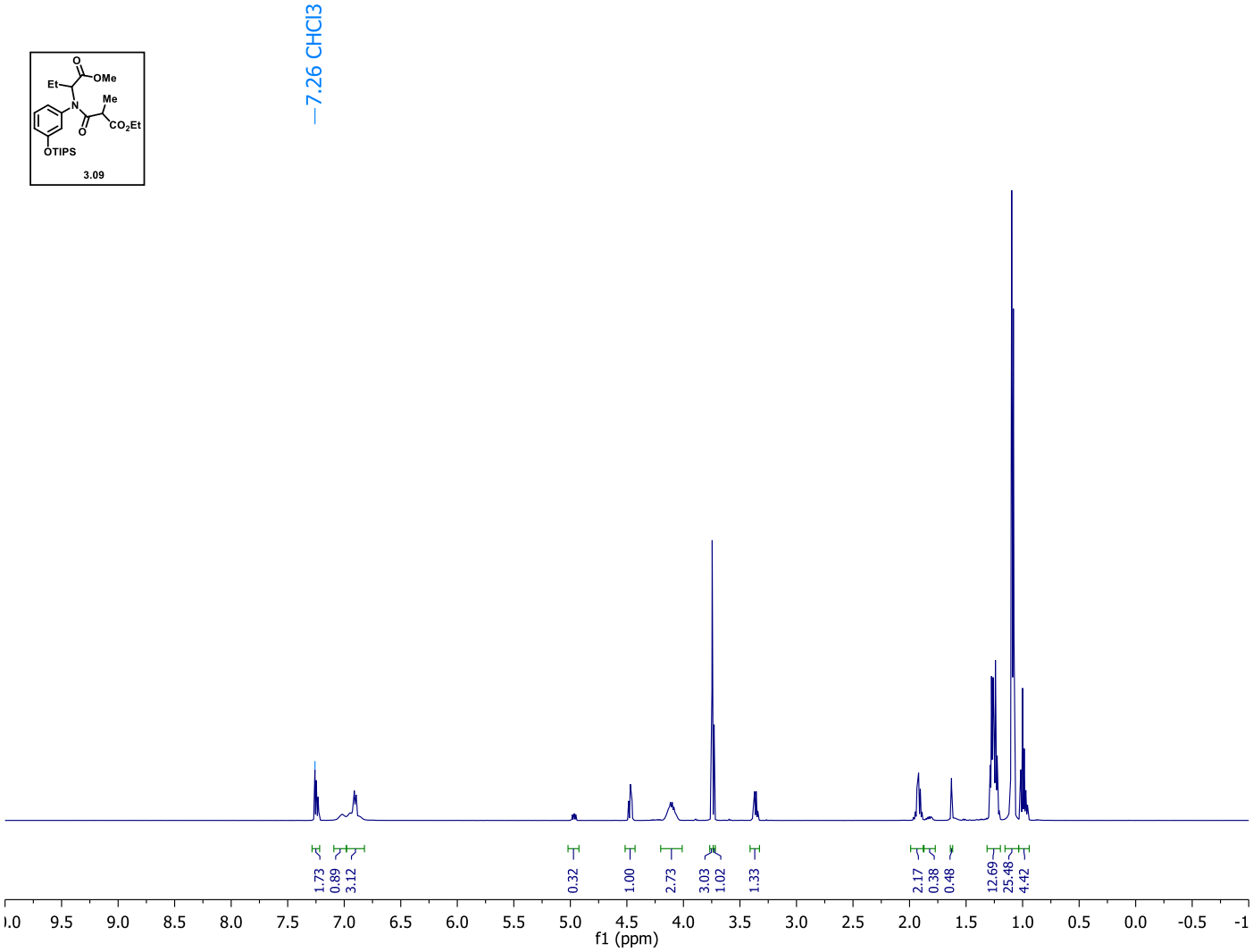


Figure A.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.09**

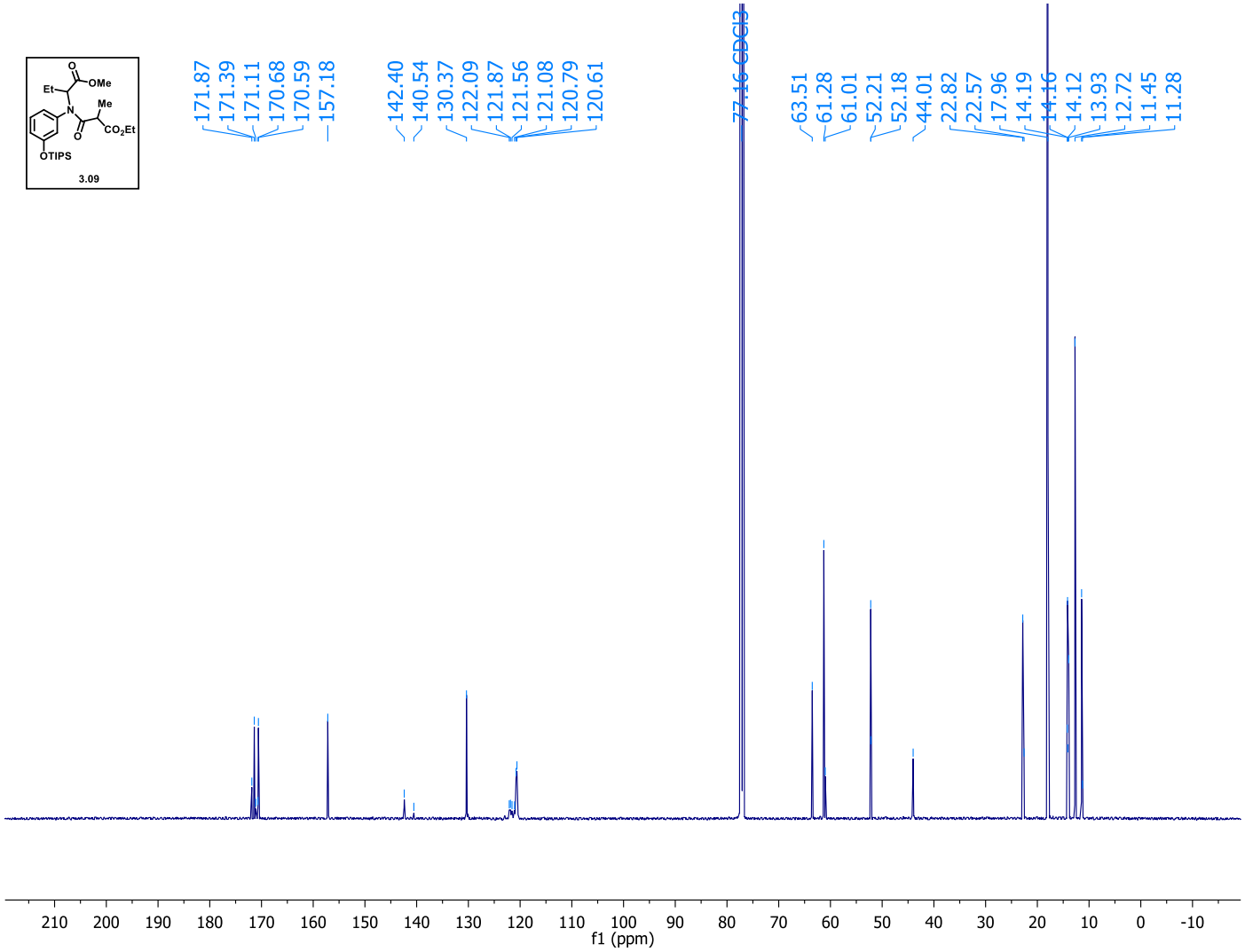


Figure A.5. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **3.09**

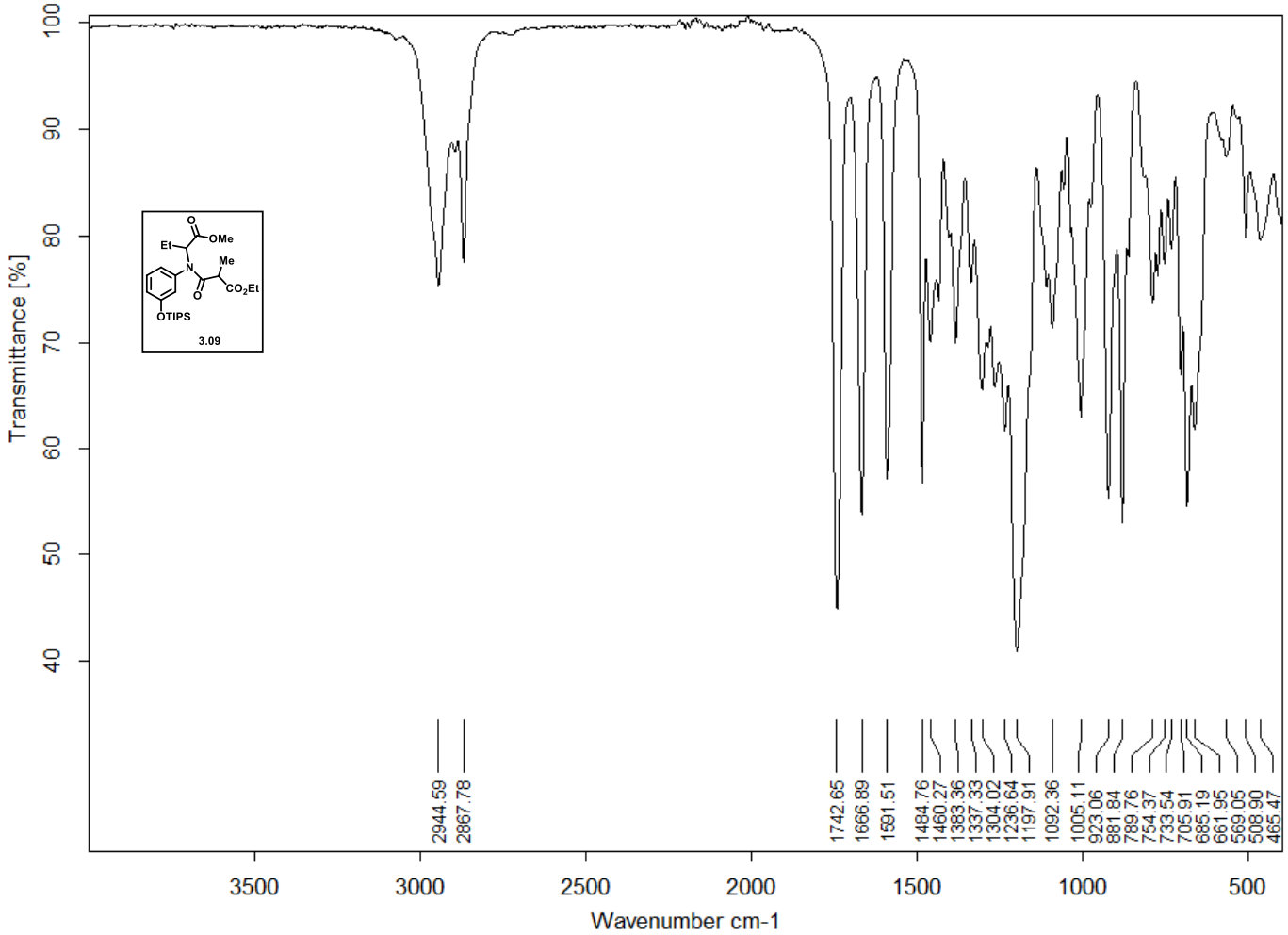


Figure A.6. FTIR spectrum (neat) of compound **3.09**

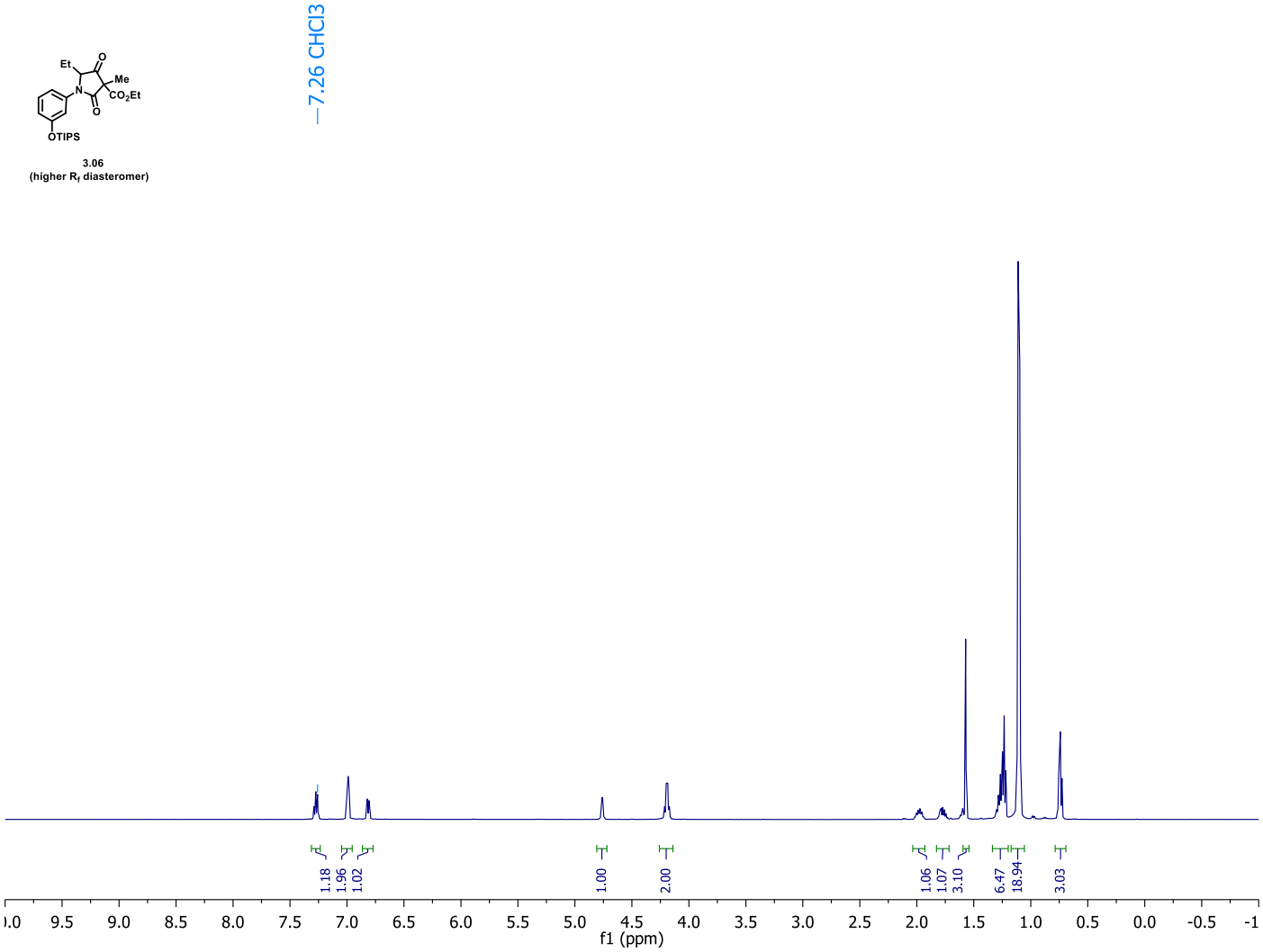


Figure A.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.06** (higher R_f diastereomer)

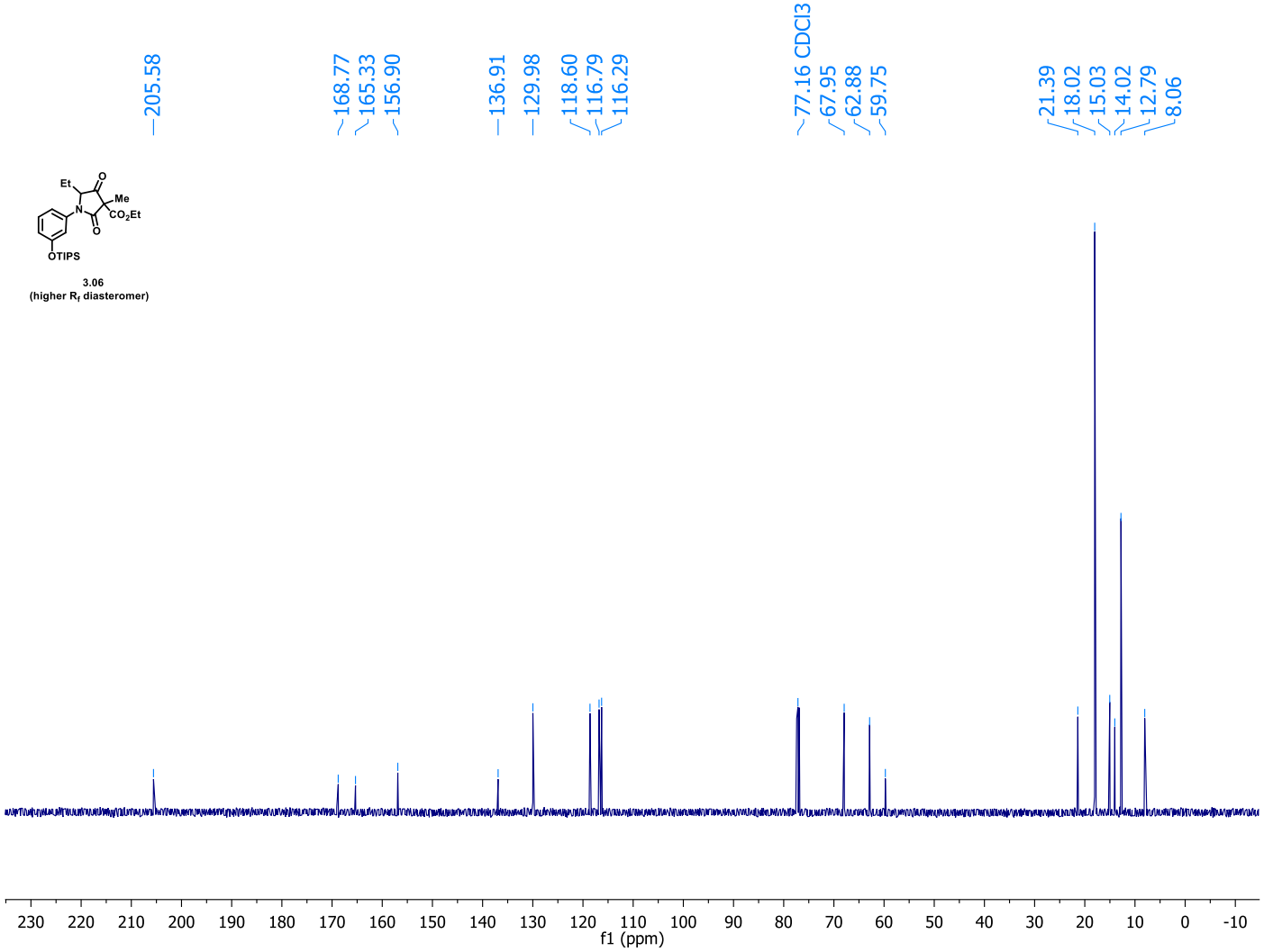


Figure A.8. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3.06** (higher R_f diastereomer)

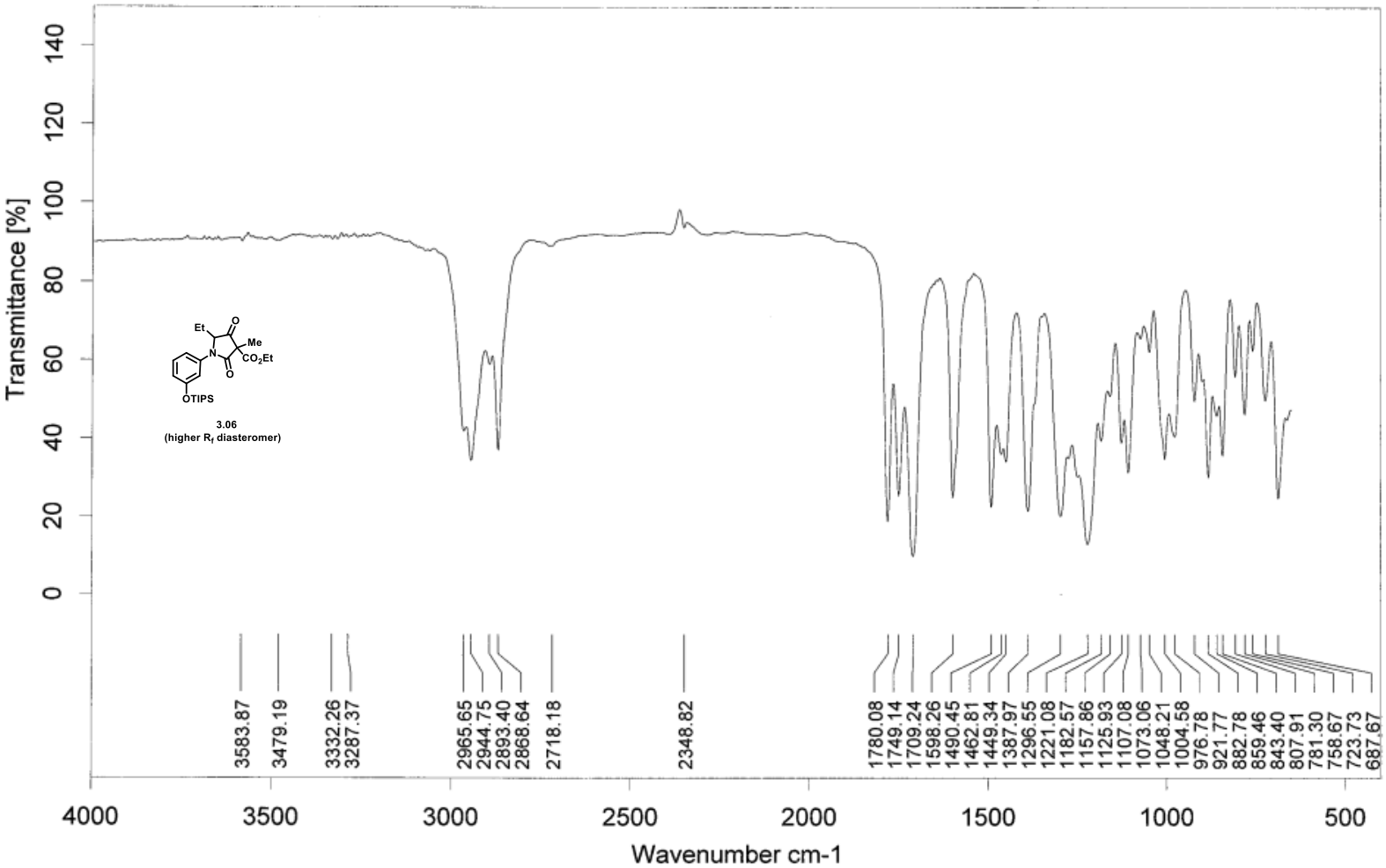


Figure A.9. FTIR spectrum (neat) of compound **3.06** (higher R_f diastereomer)

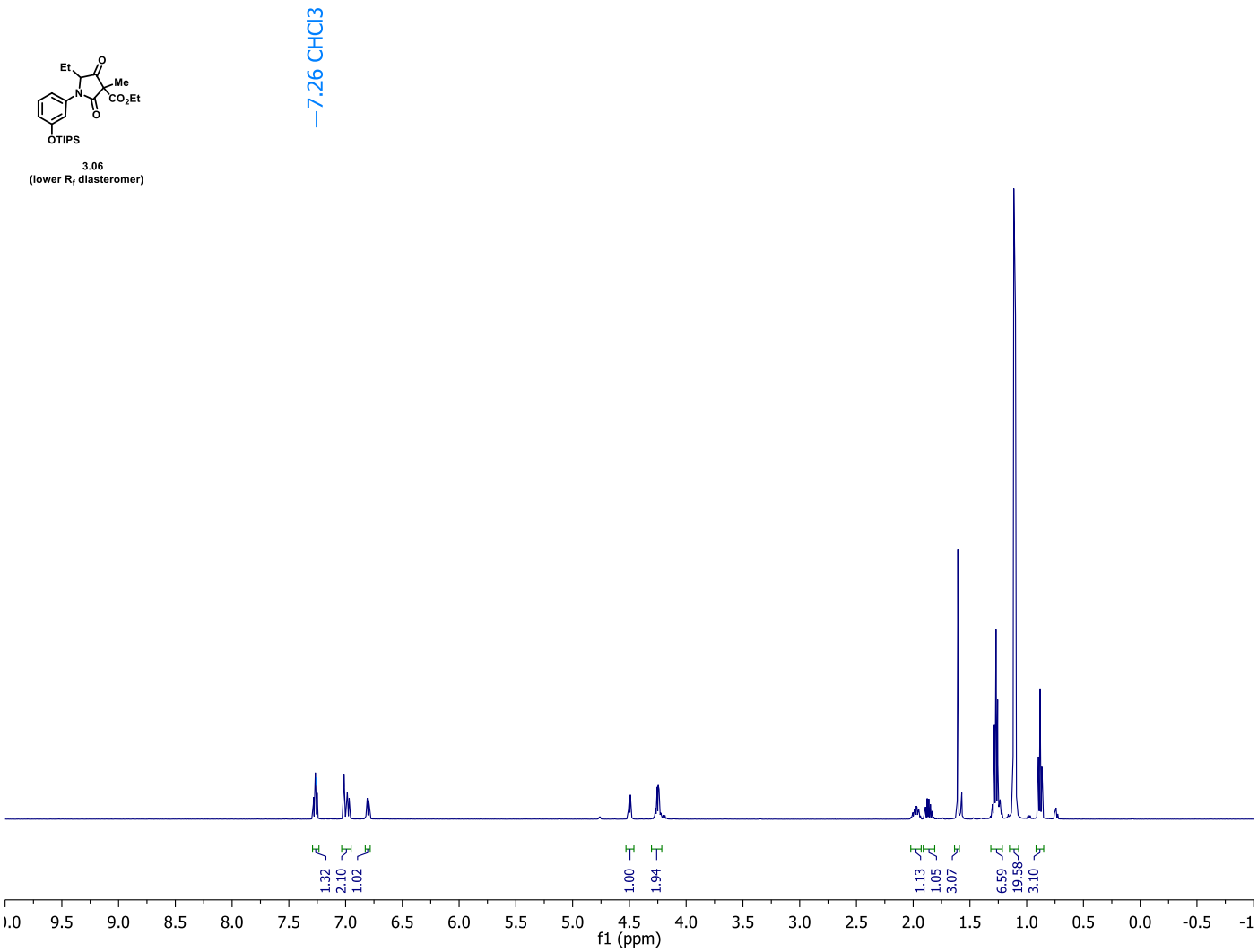


Figure A.10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.06** (Lower R_f diastereomer)

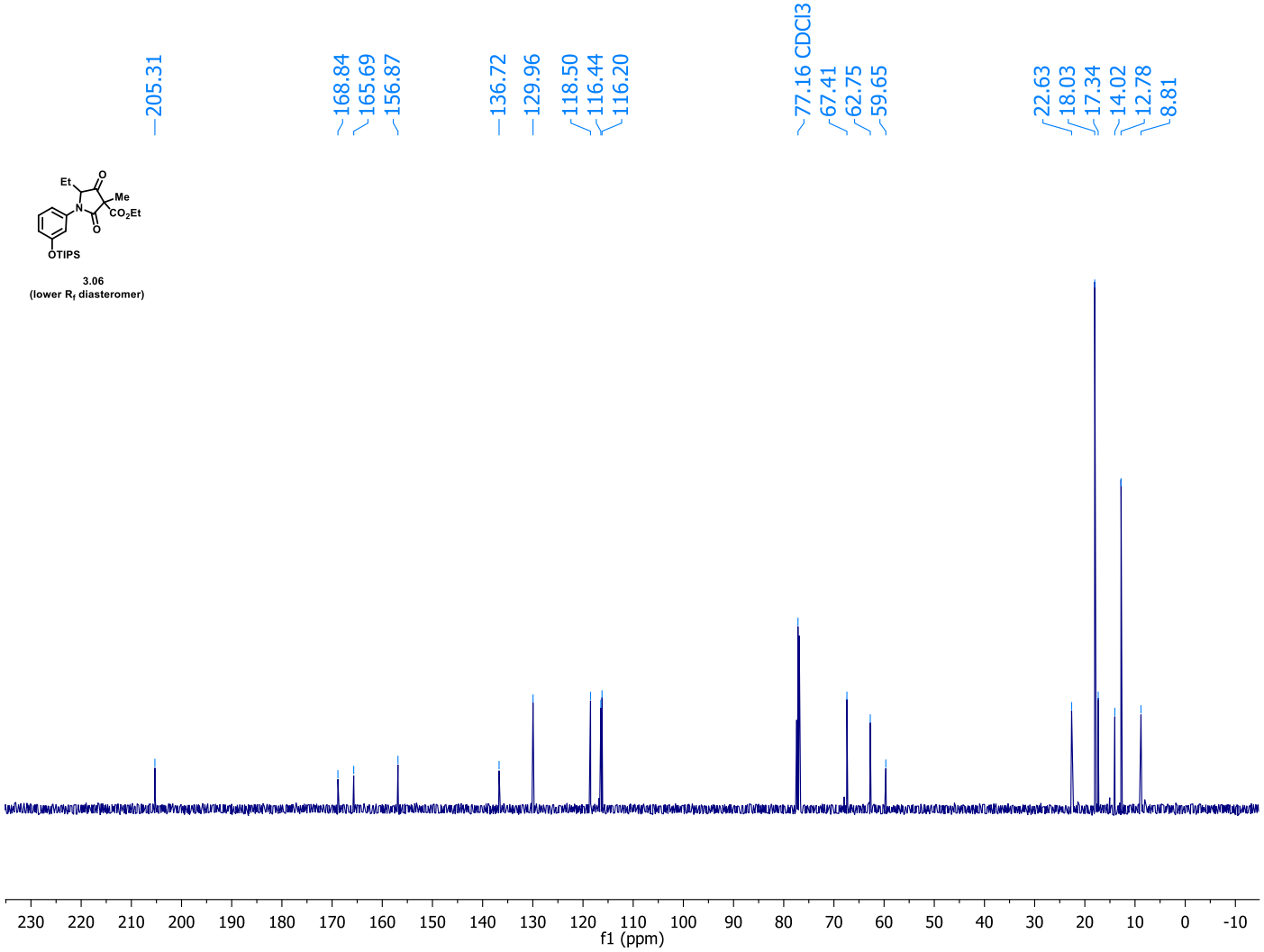


Figure A.11. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3.06** (Lower R_f diastereomer)

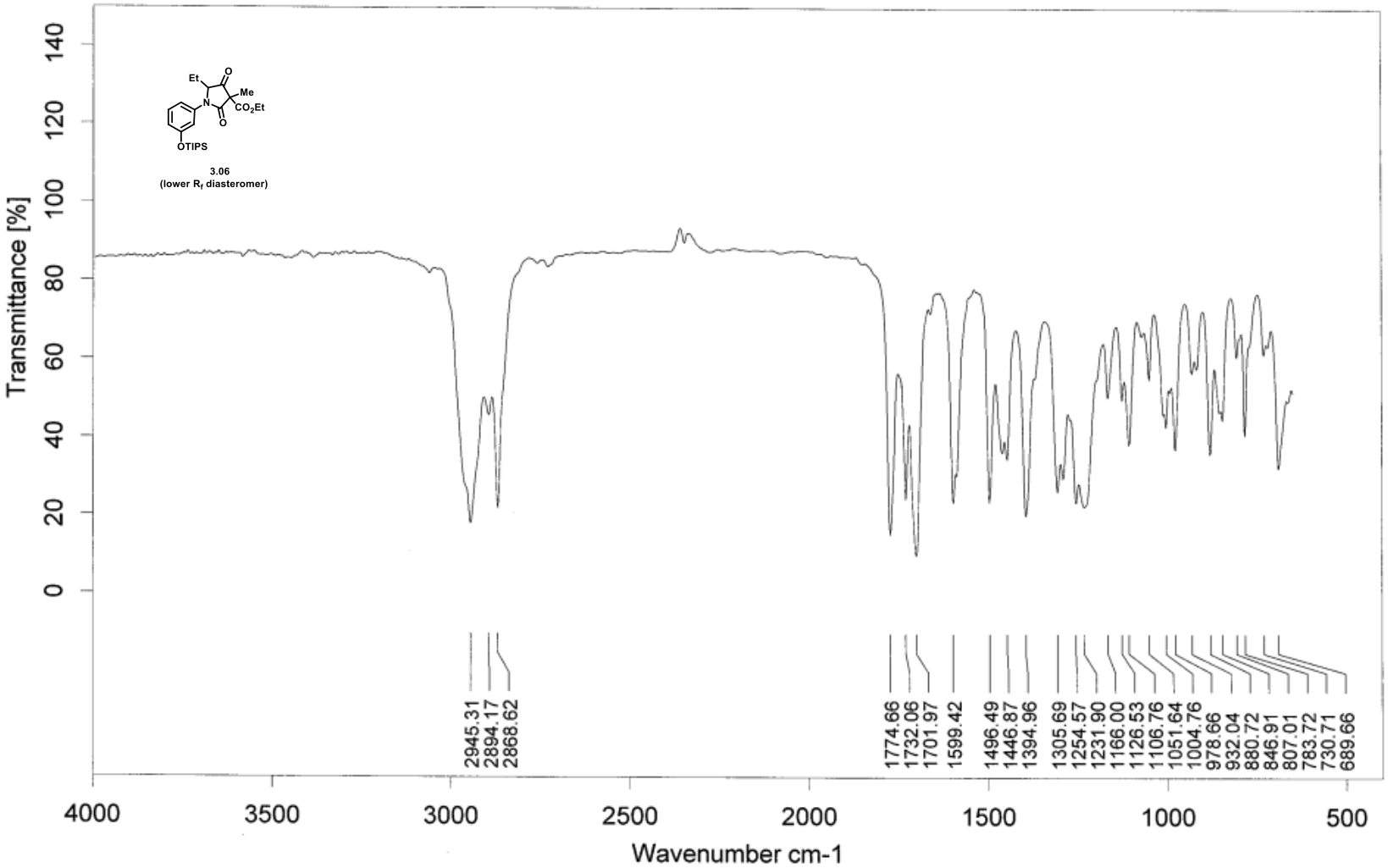


Figure A.12. FTIR spectrum (neat) of compound **3.06** (Lower R_f diastereomer)

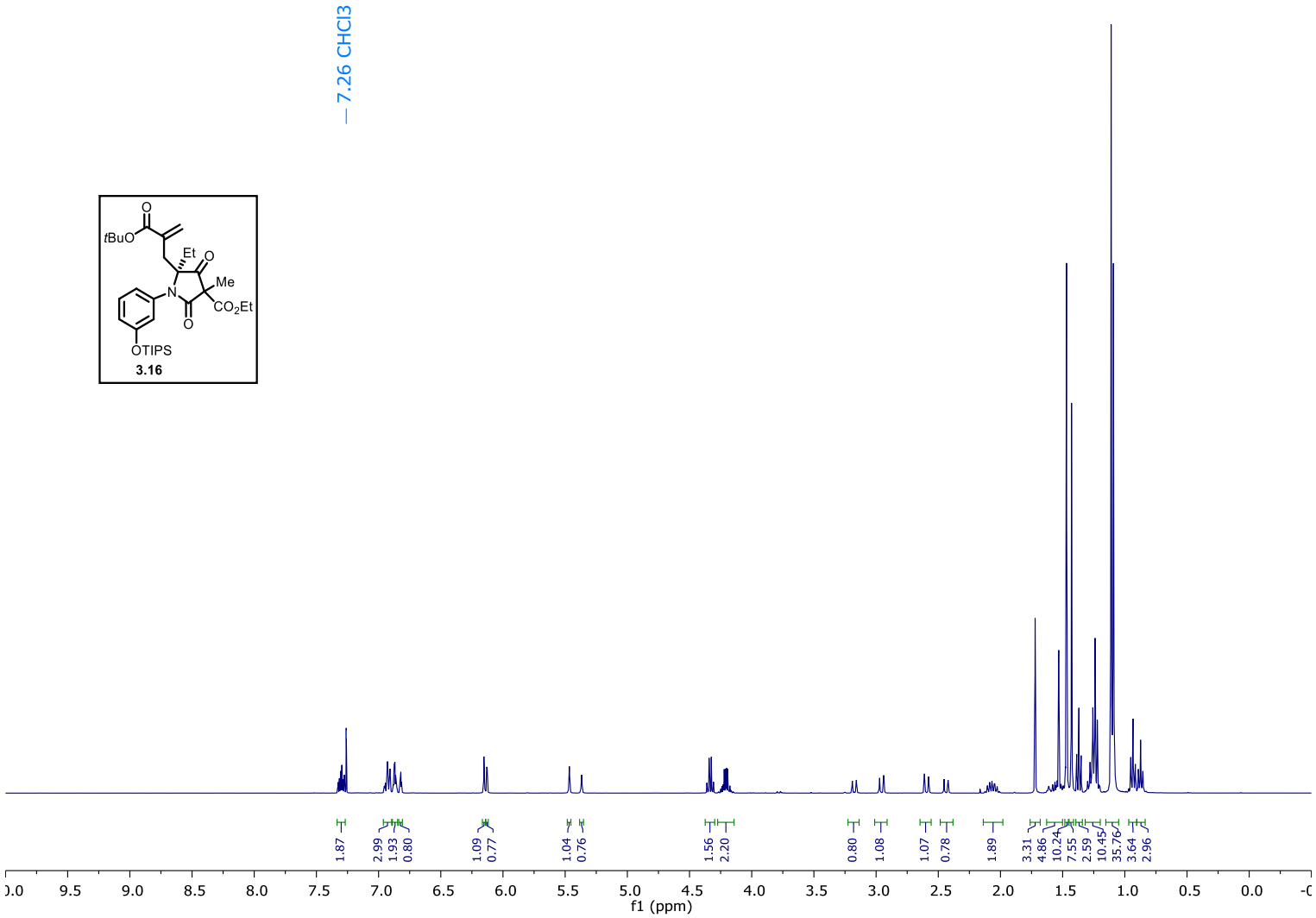


Figure A.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.16**

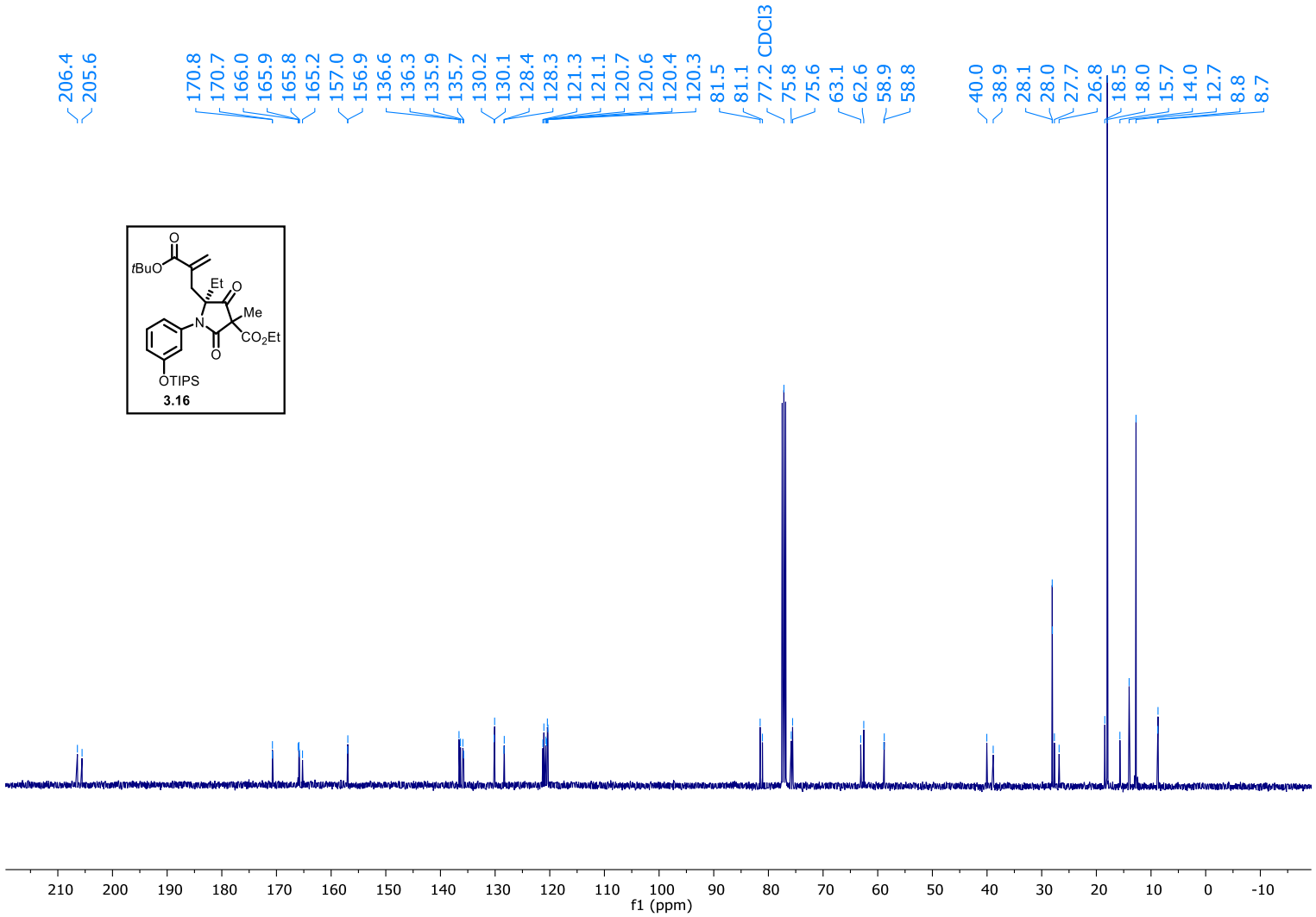


Figure A.14. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **3.16**

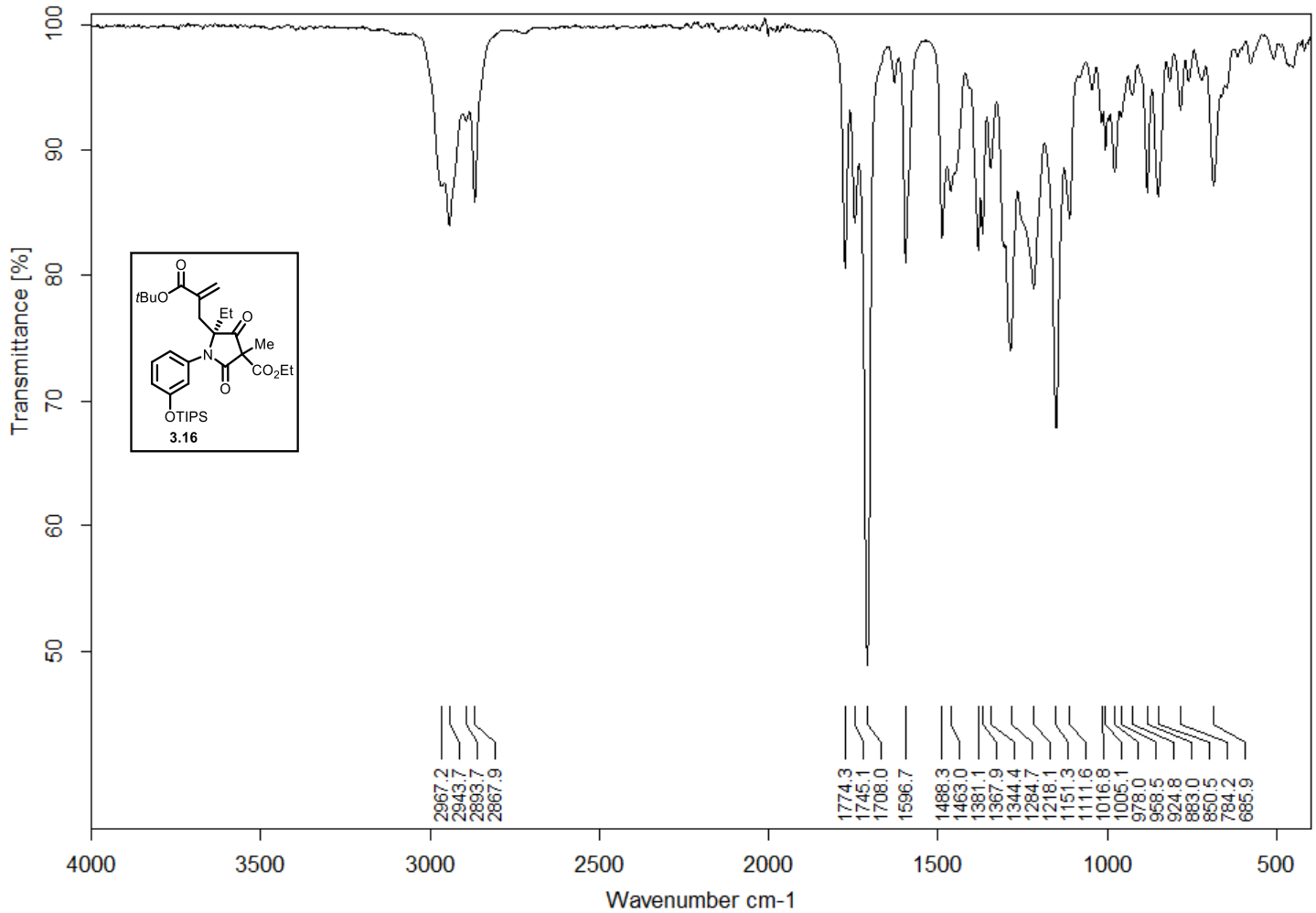


Figure A.15. FTIR spectrum (neat) of compound **3.16**

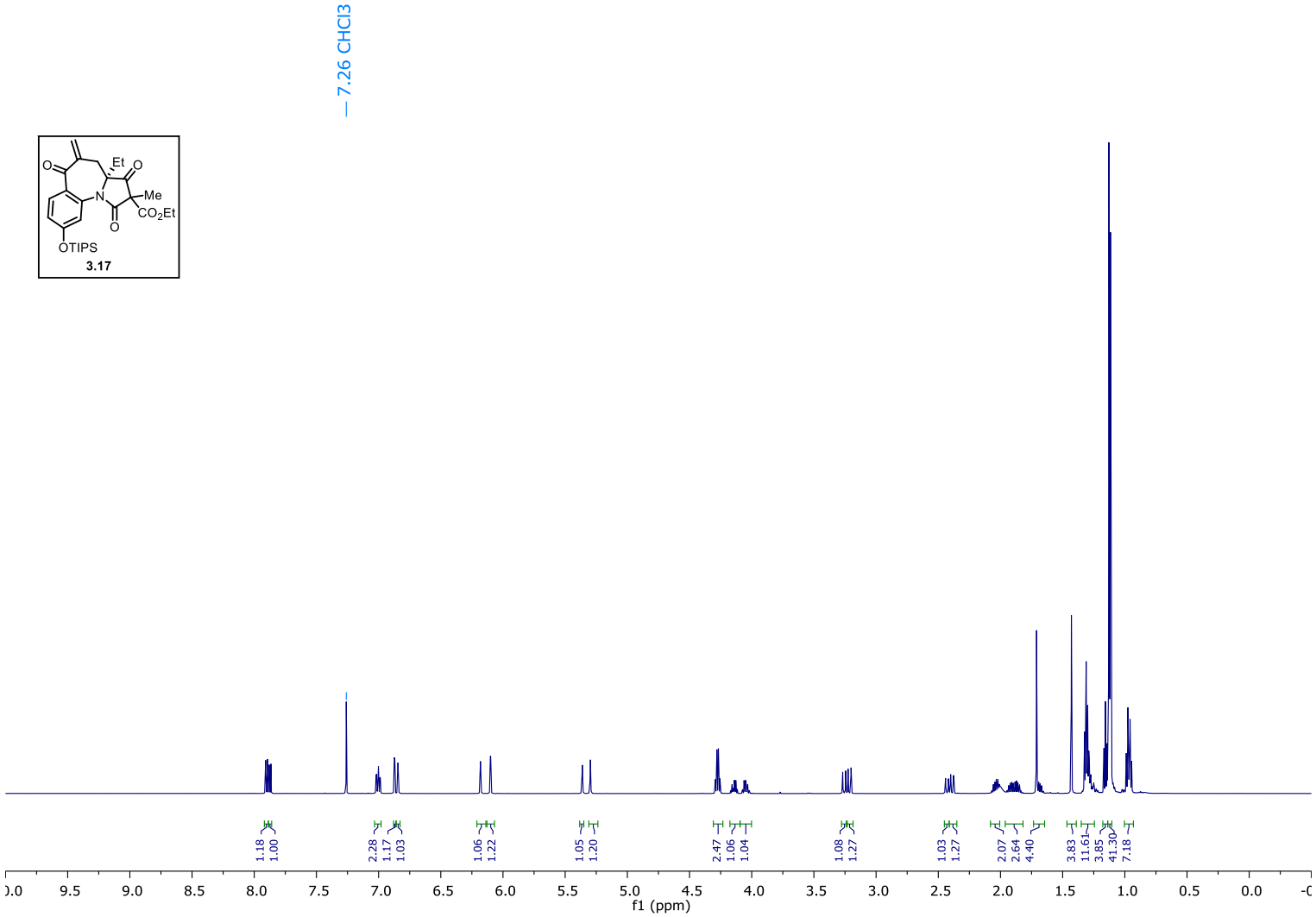


Figure A.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.17**

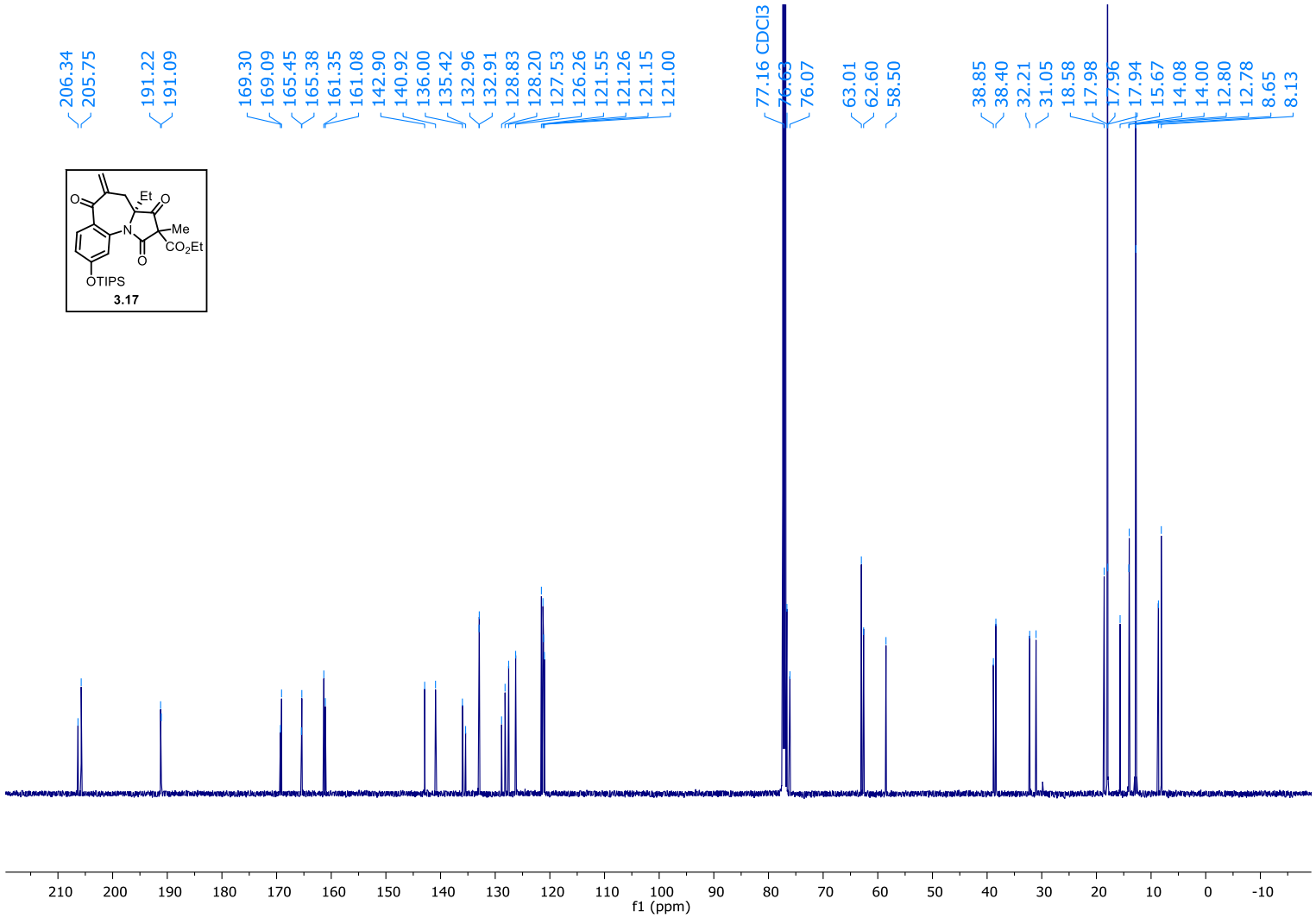


Figure A.17. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **3.17**

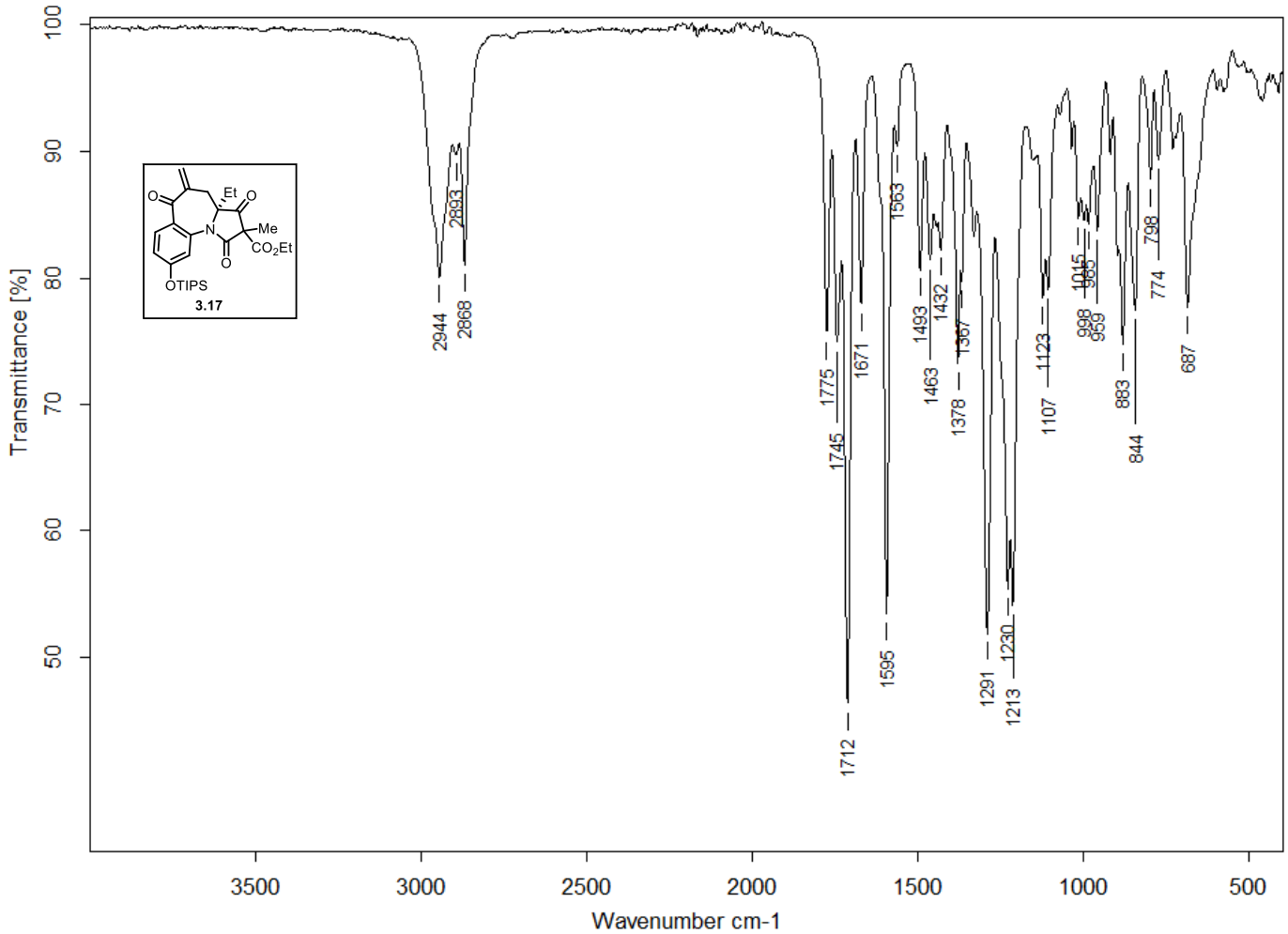


Figure A.18. FTIR spectrum (neat) of compound **3.17**

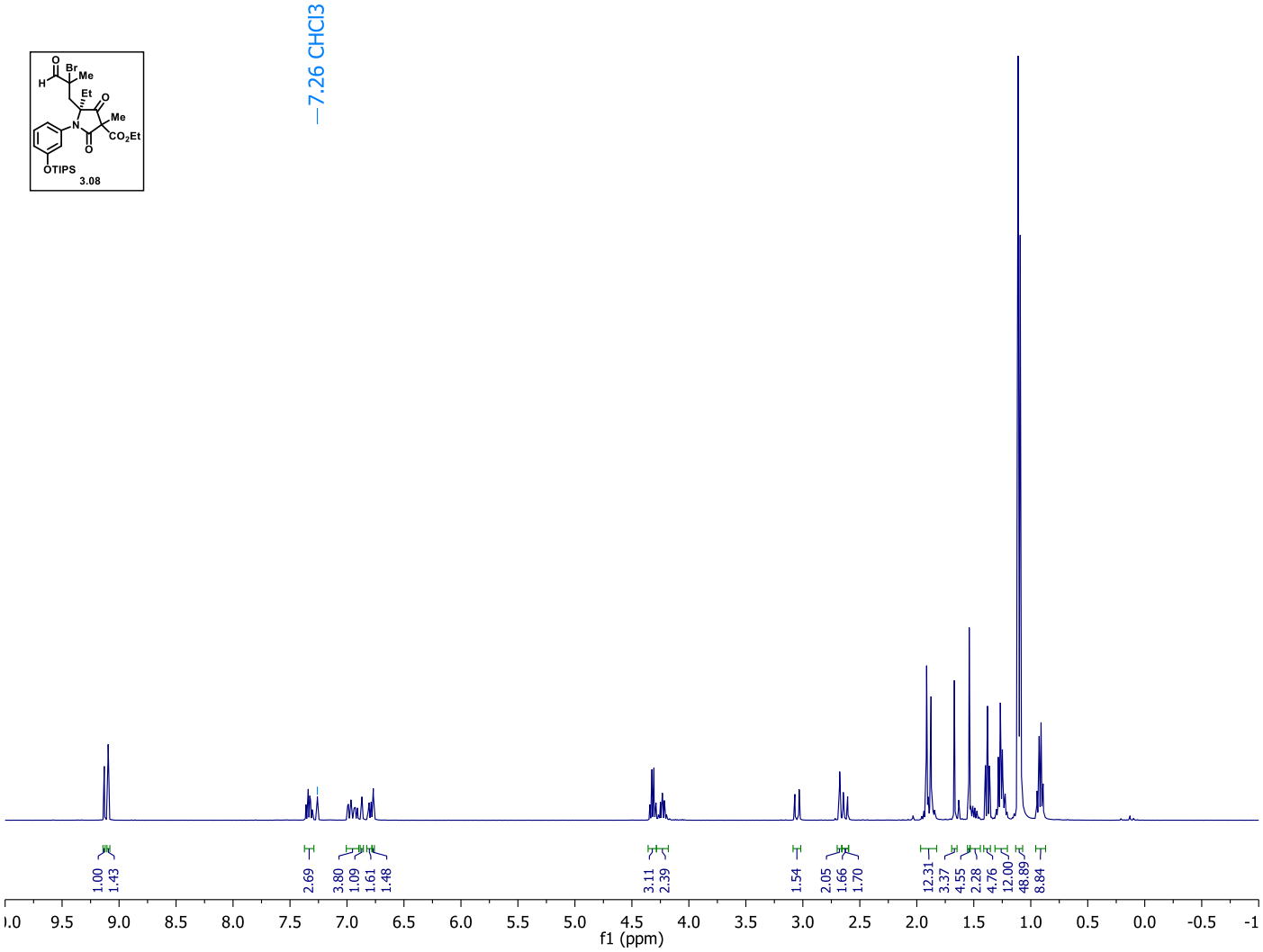


Figure A.19. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **3.08**

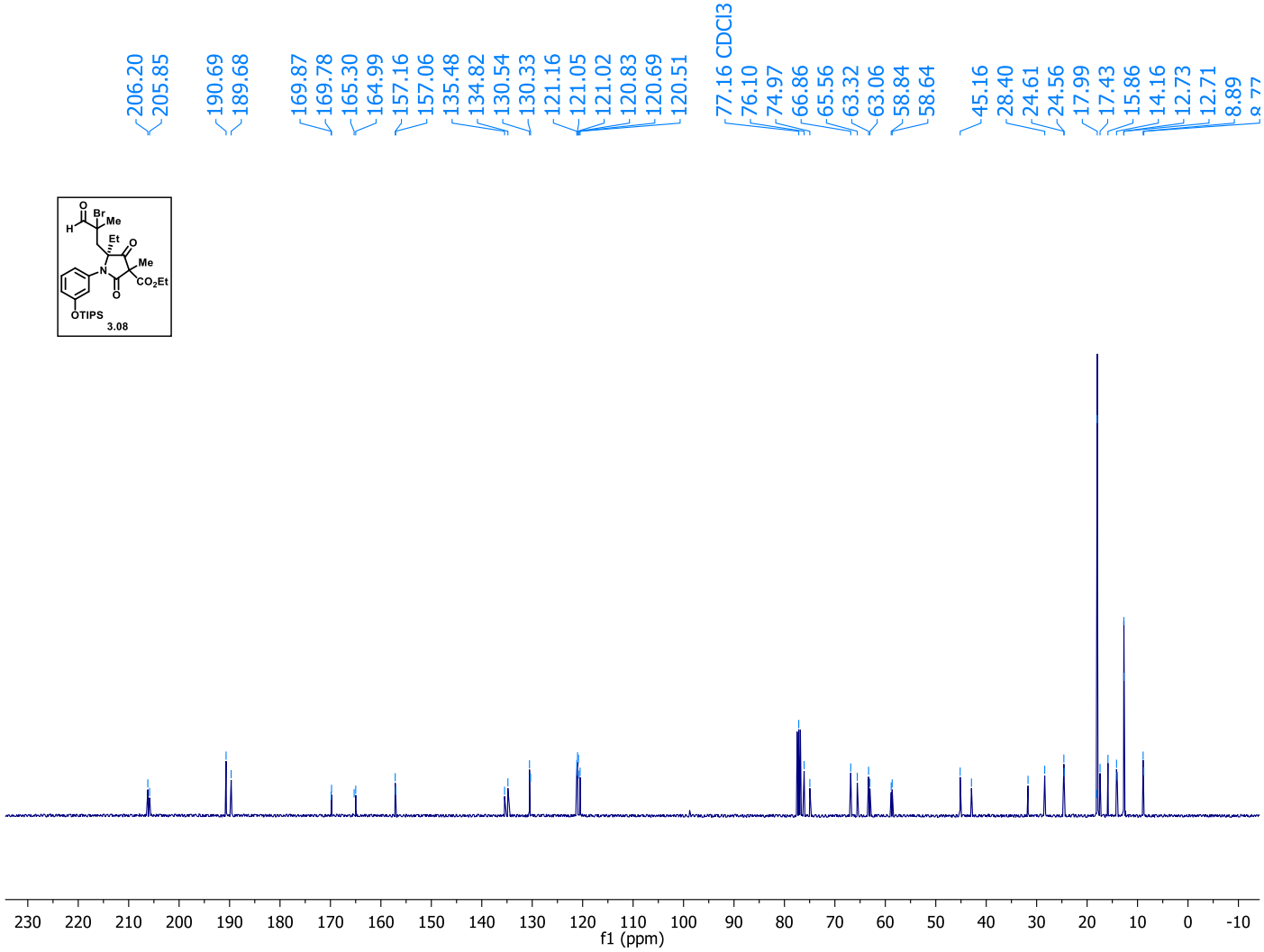


Figure A.20. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **3.12**

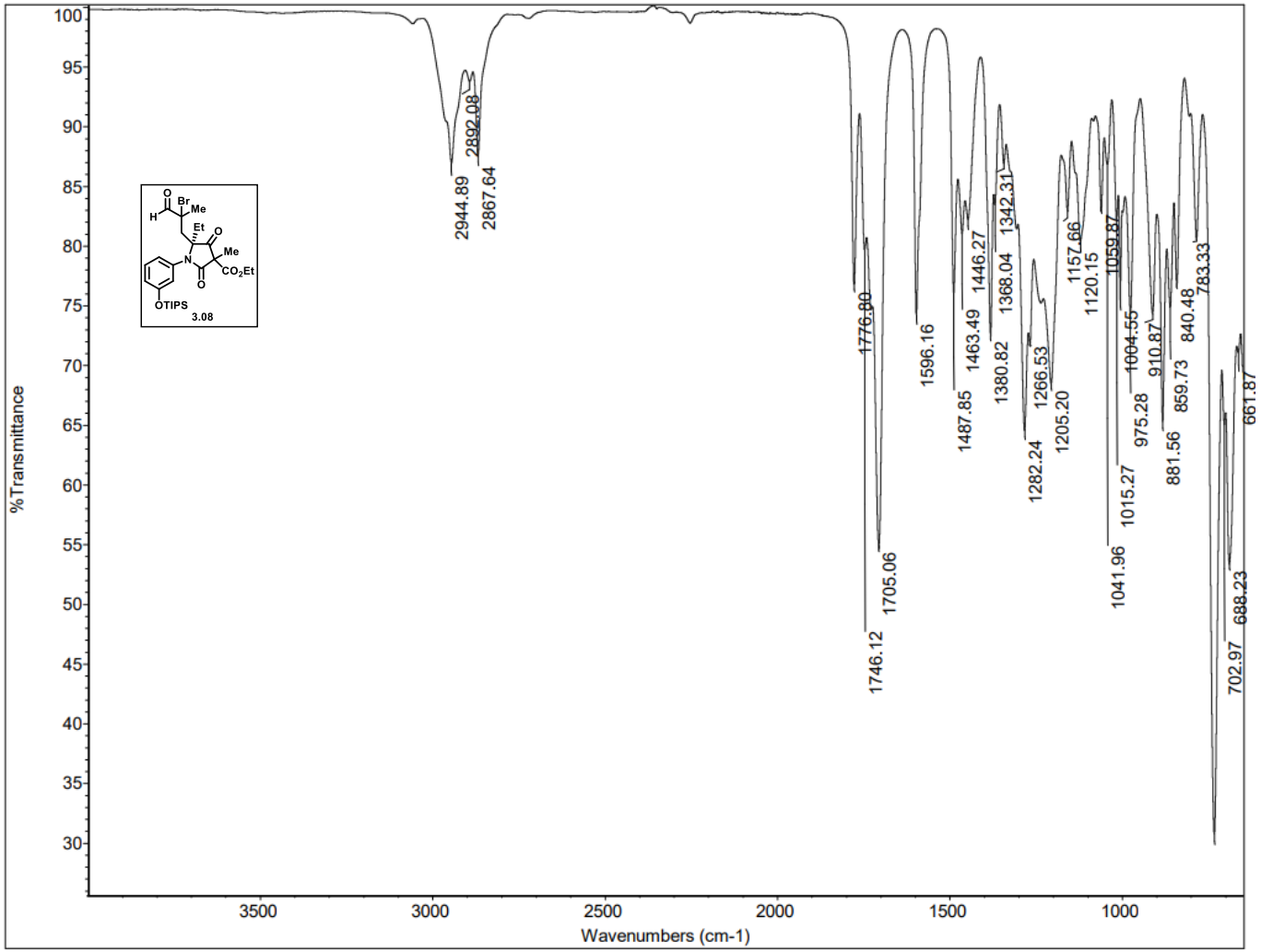


Figure A.21. FTIR spectrum (neat) of compound **3.12**

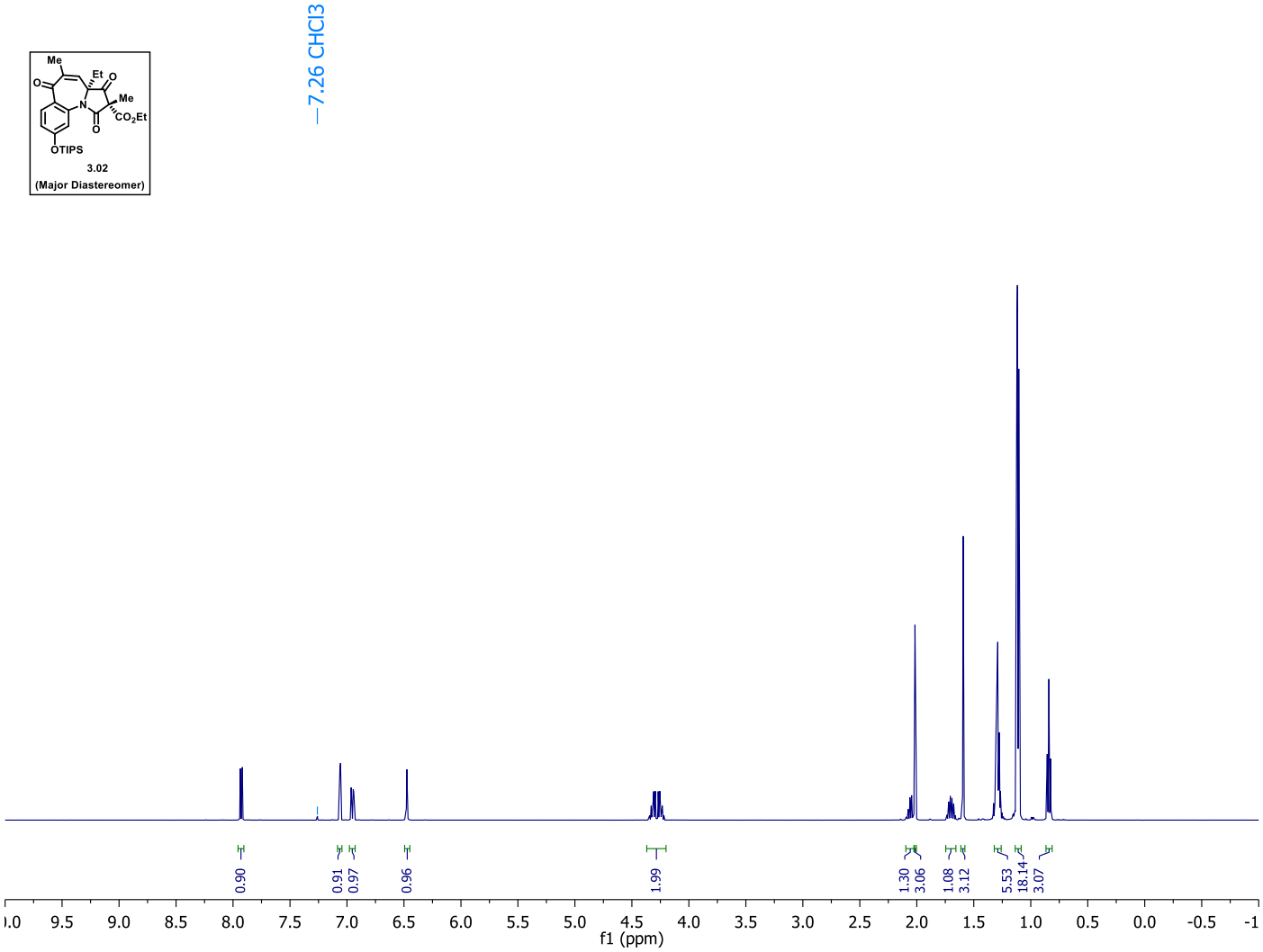


Figure A.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.02** (major diastereomer)

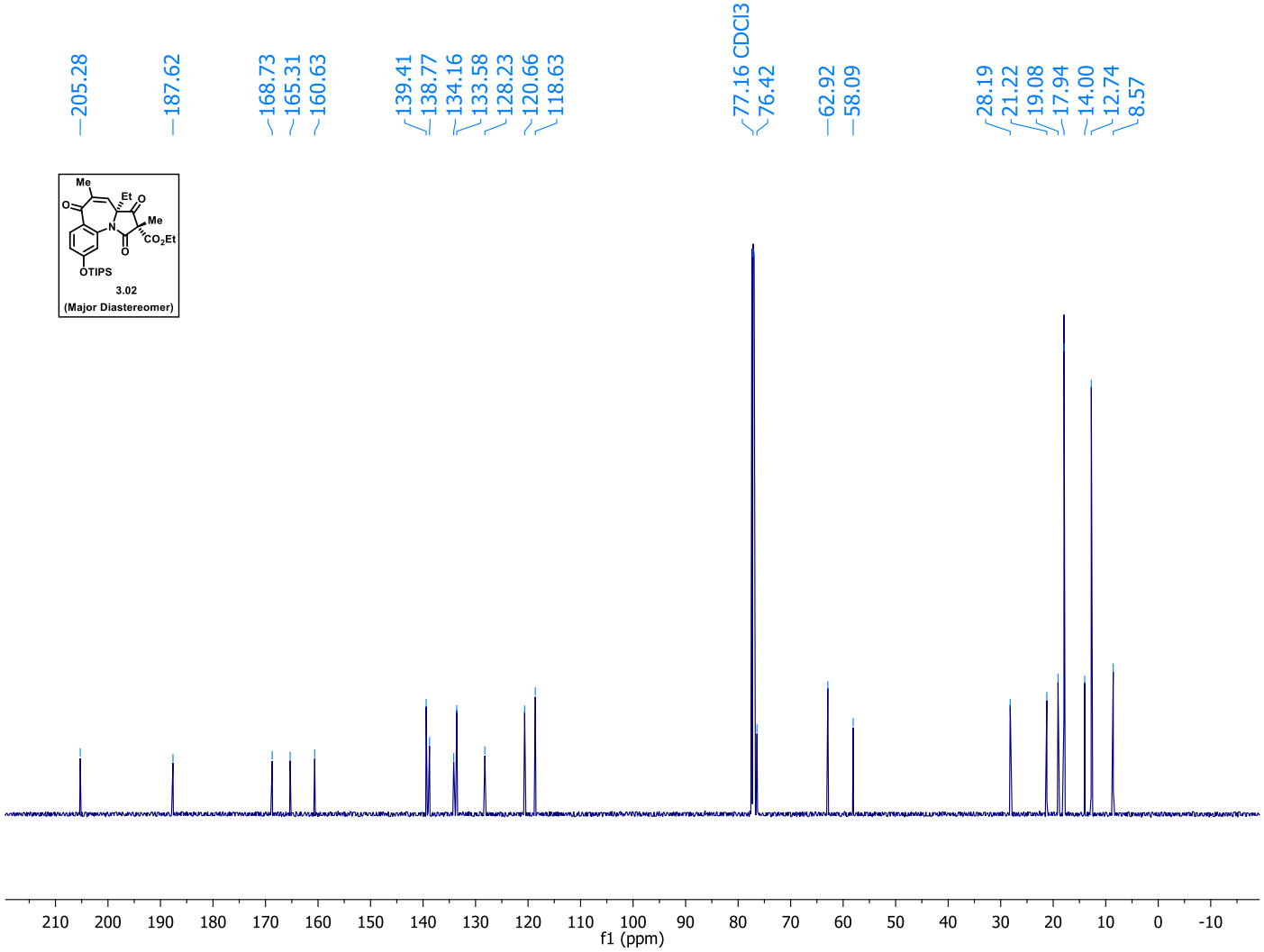


Figure A.23. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **3.02** (major diastereomer)

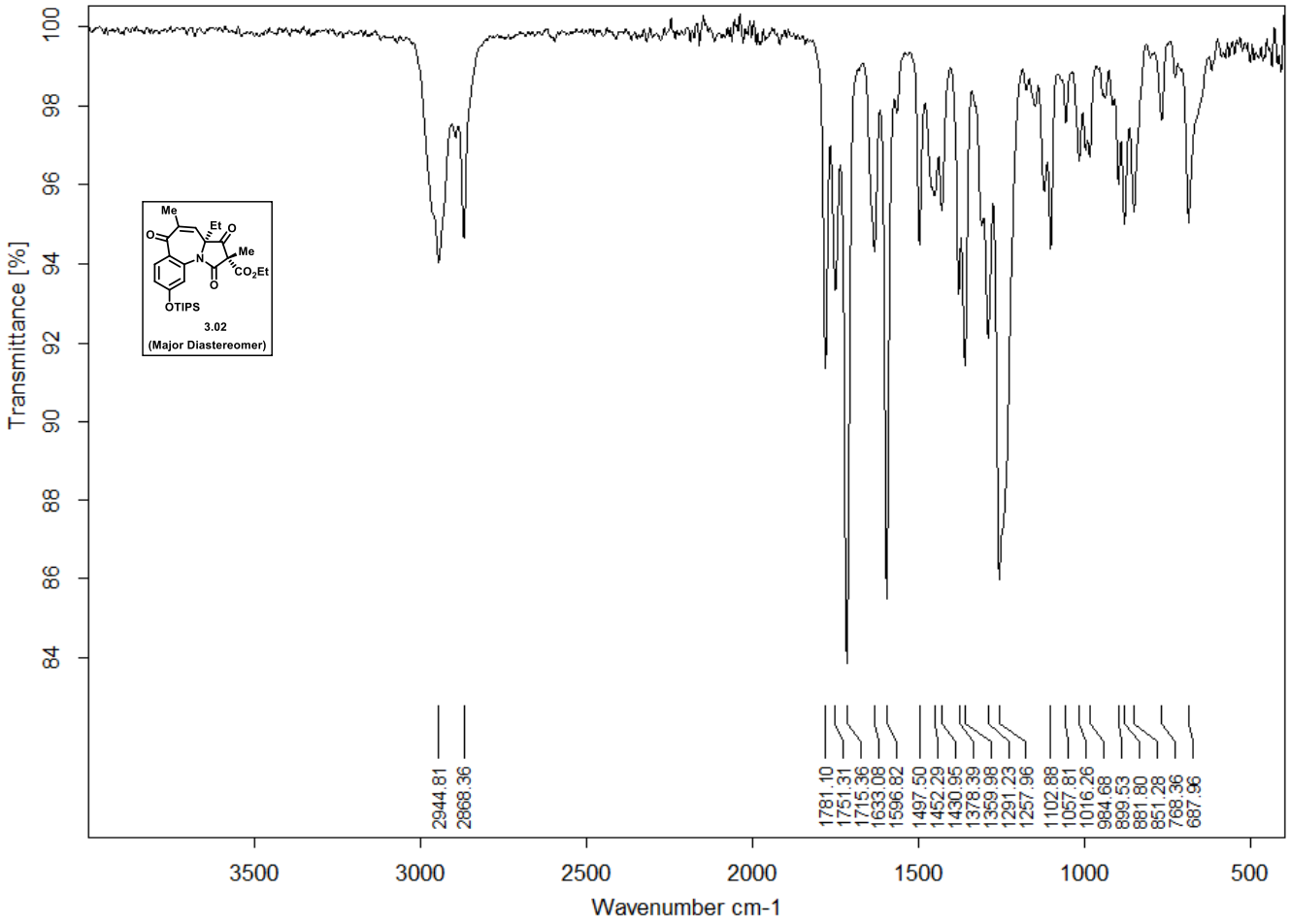


Figure A.24. FTIR spectrum (neat) of compound **3.02** (major diastereomer)

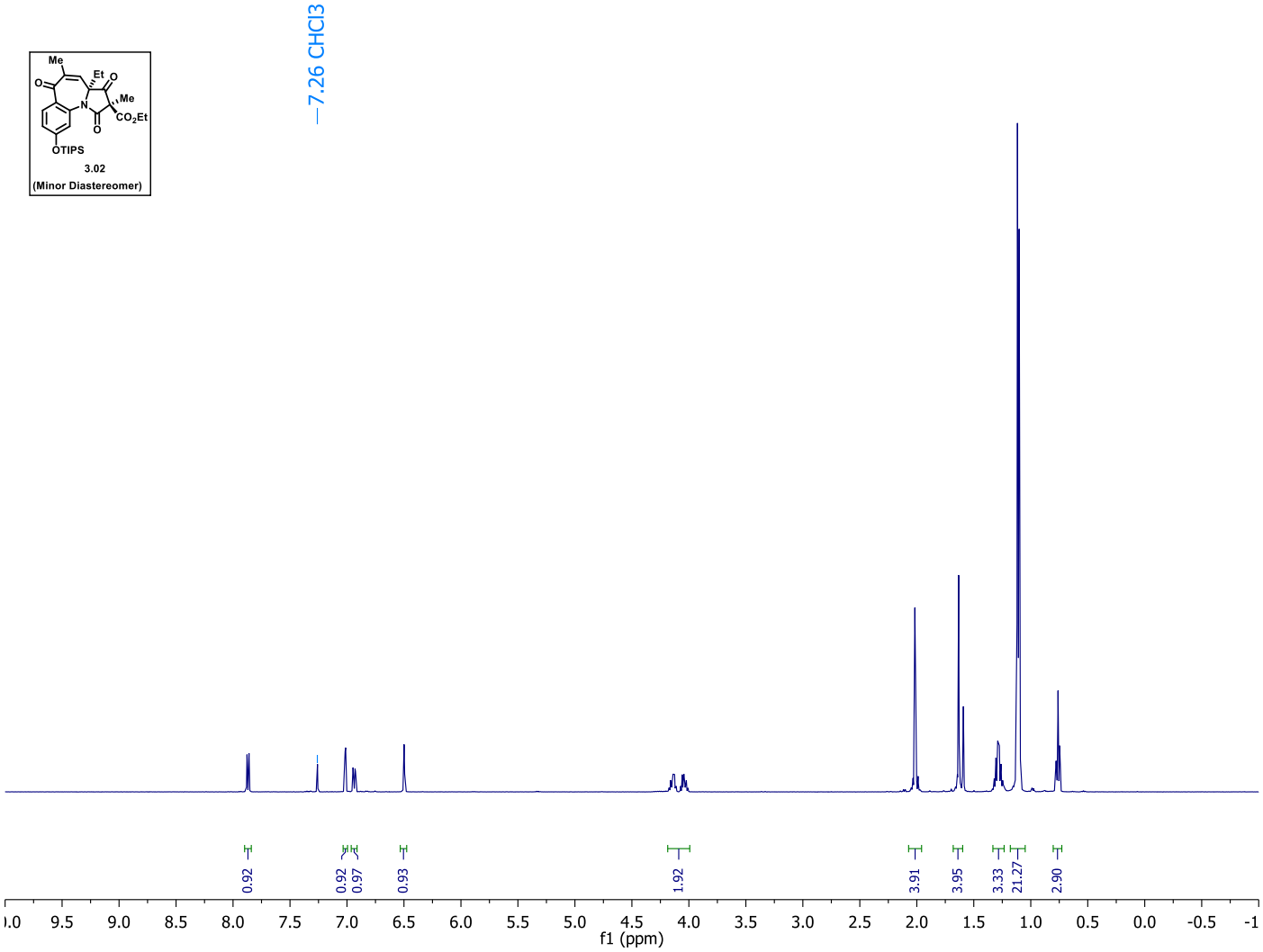


Figure A.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.02** (minor diastereomer)

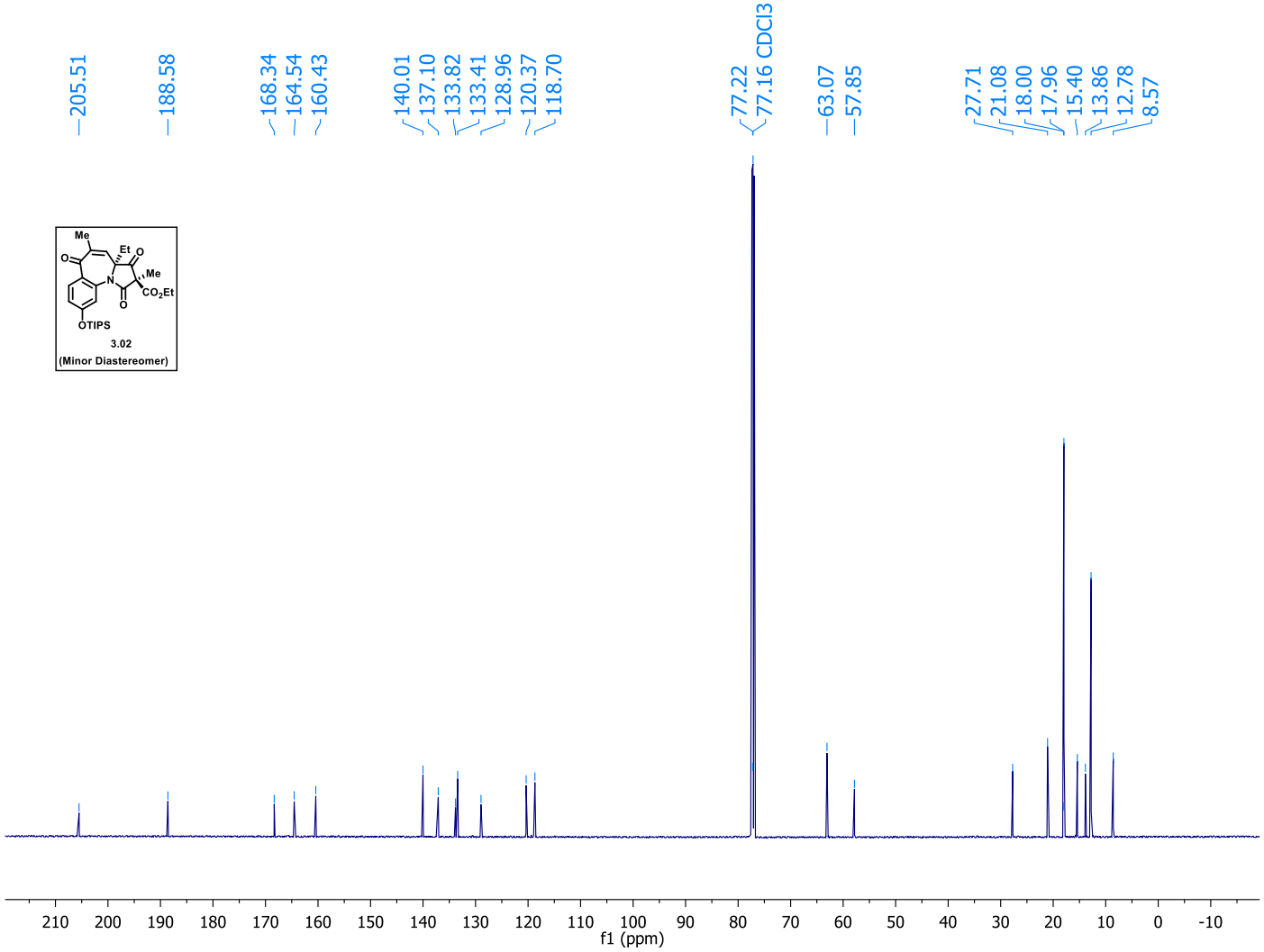


Figure A.26. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **3.02** (minor diastereomer)

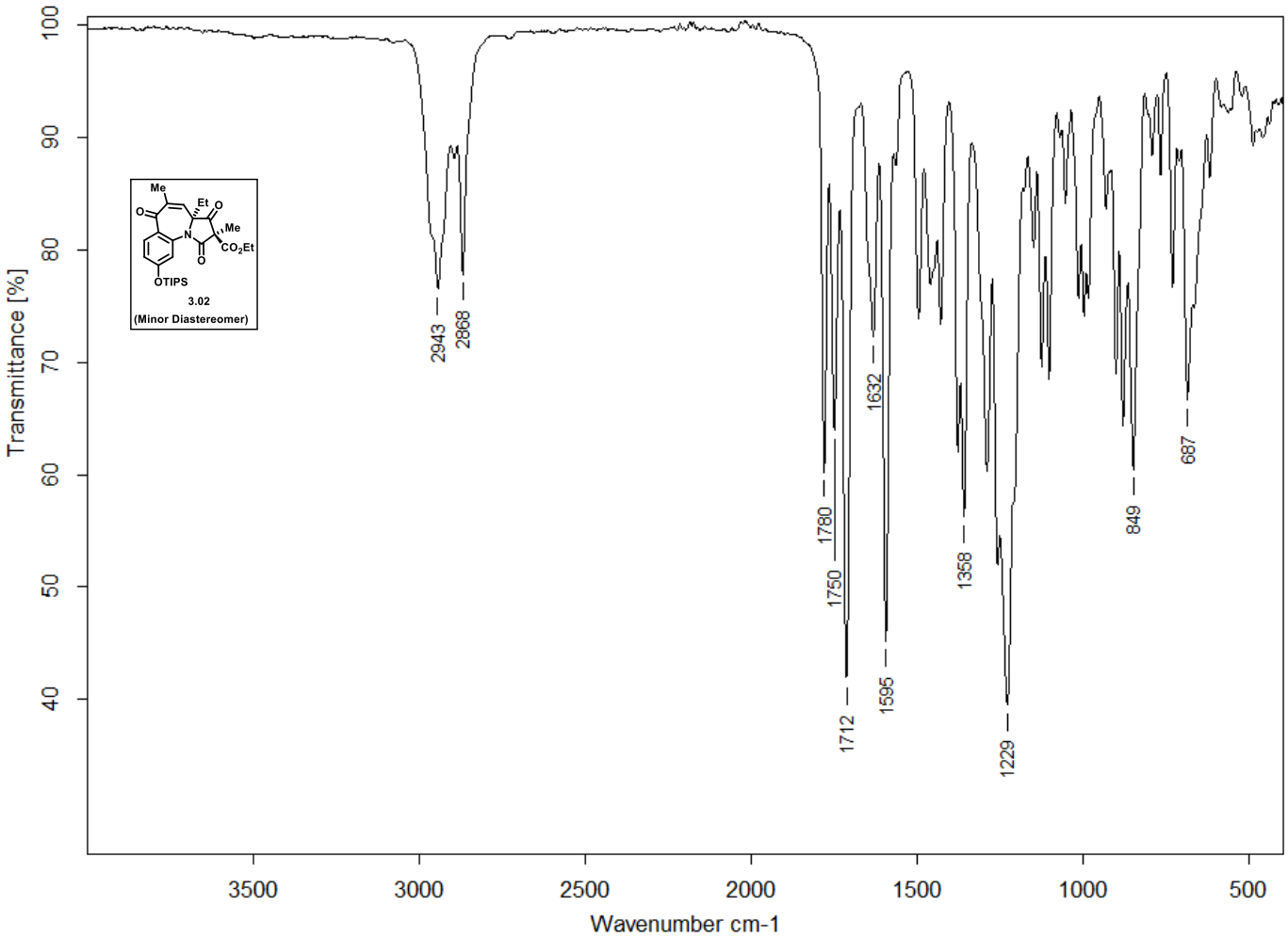


Figure A.27. FTIR spectrum (neat) of compound **3.02** (minor diastereomer)

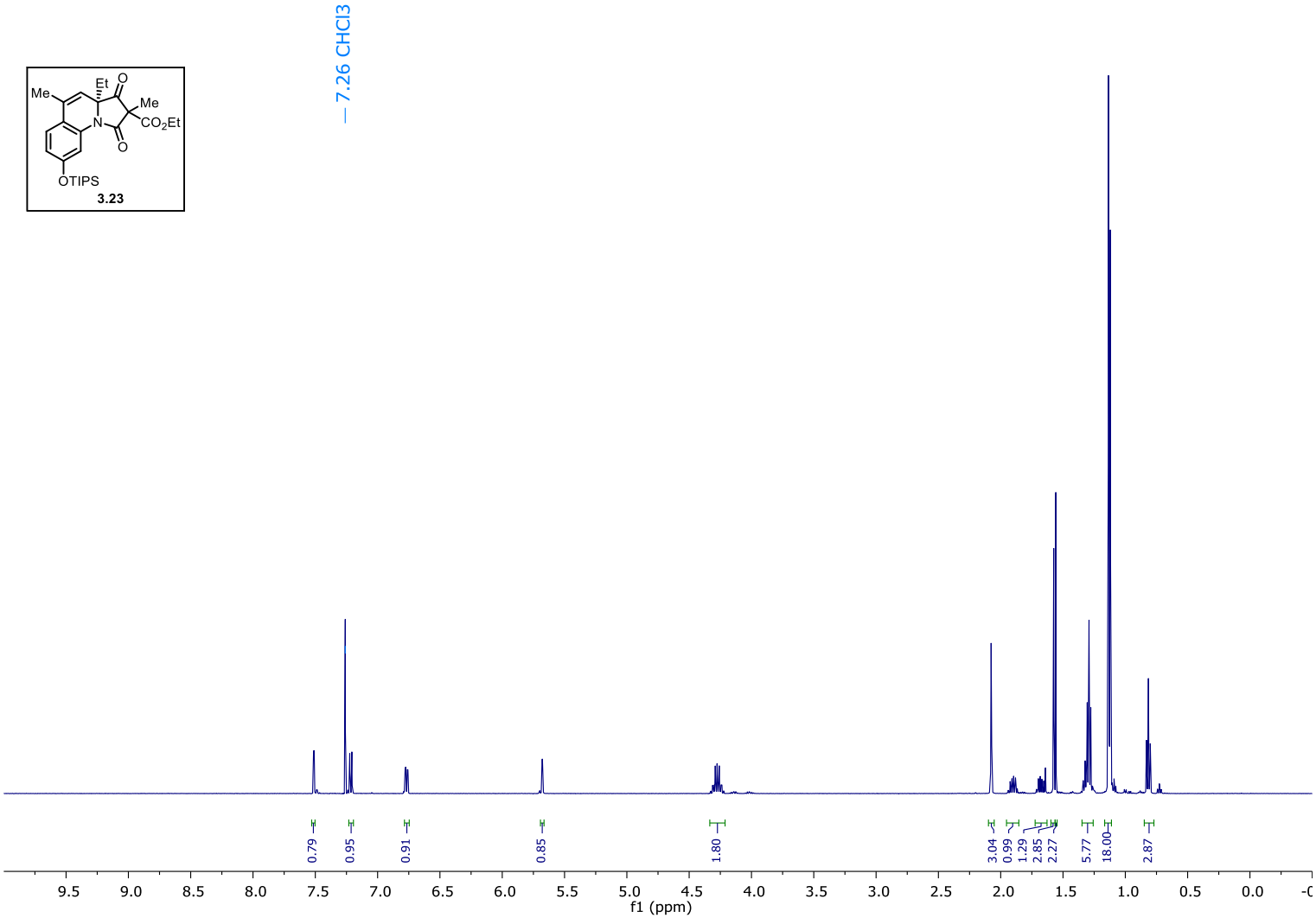


Figure A.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3.23**

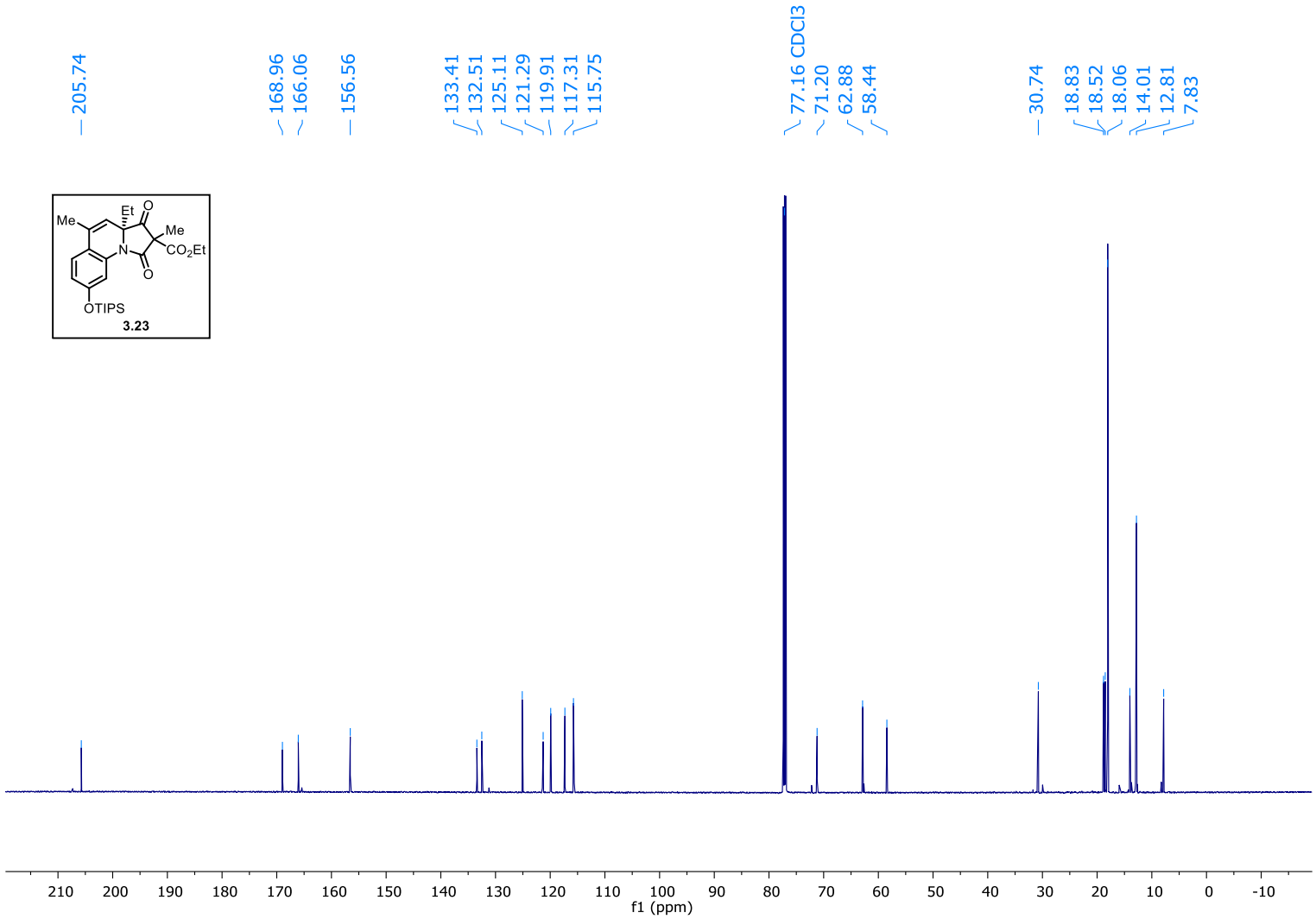


Figure A.29. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **3.23**

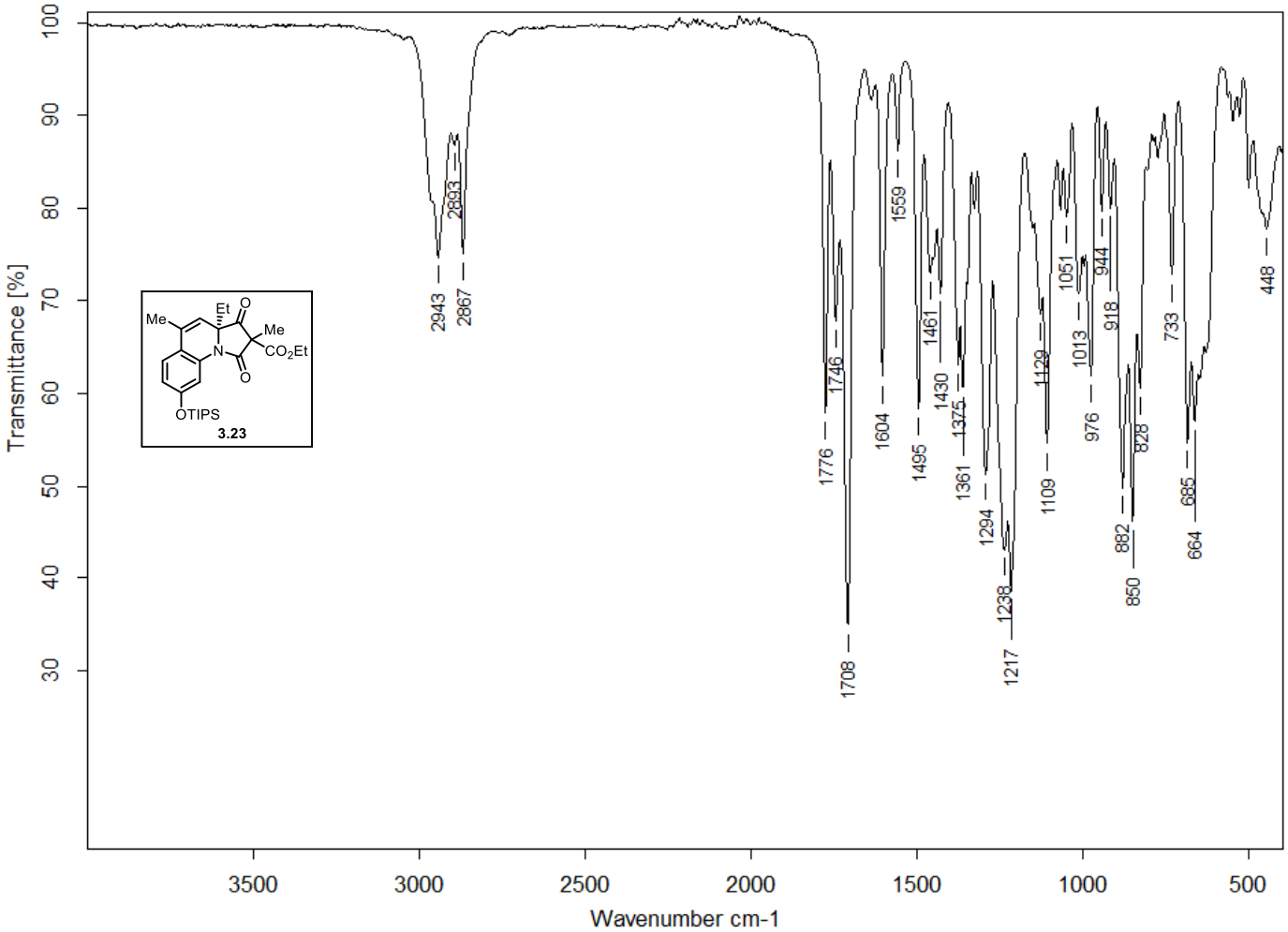


Figure A.30. FTIR spectrum (neat) of compound **3.23**

APPENDIX B

Spectra Relevant to Chapter Four

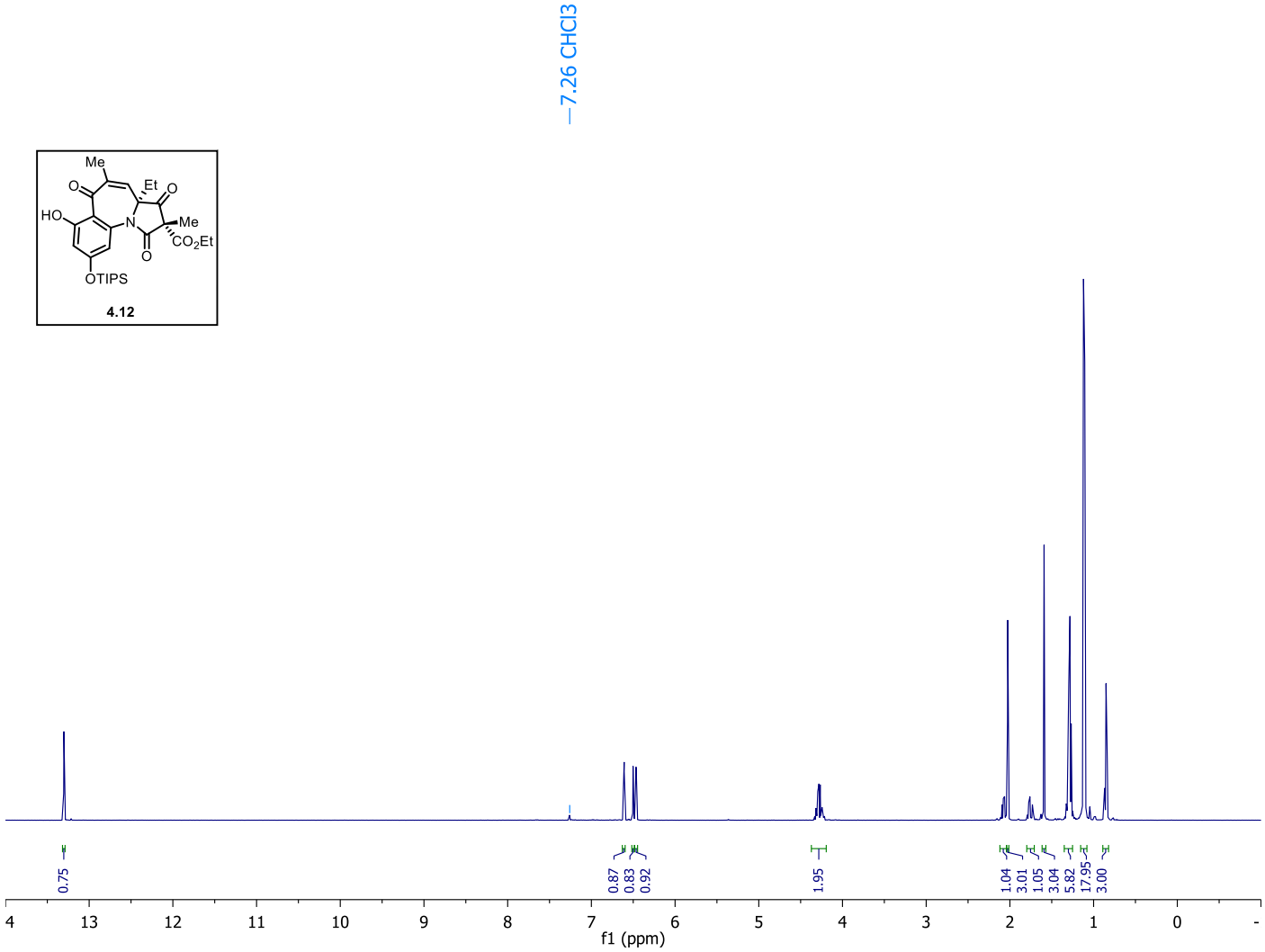


Figure B.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.12**

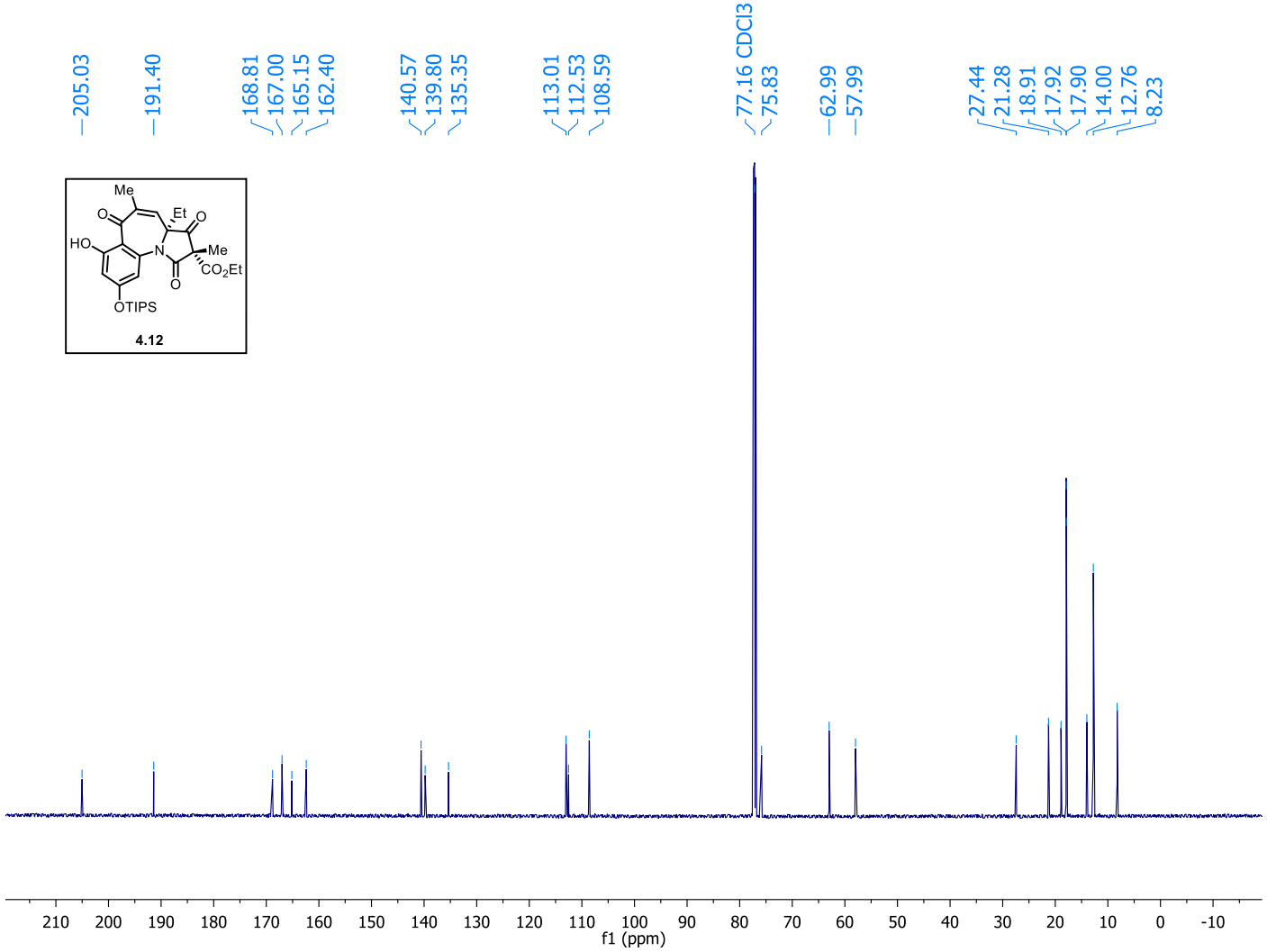


Figure B.2. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **4.12**

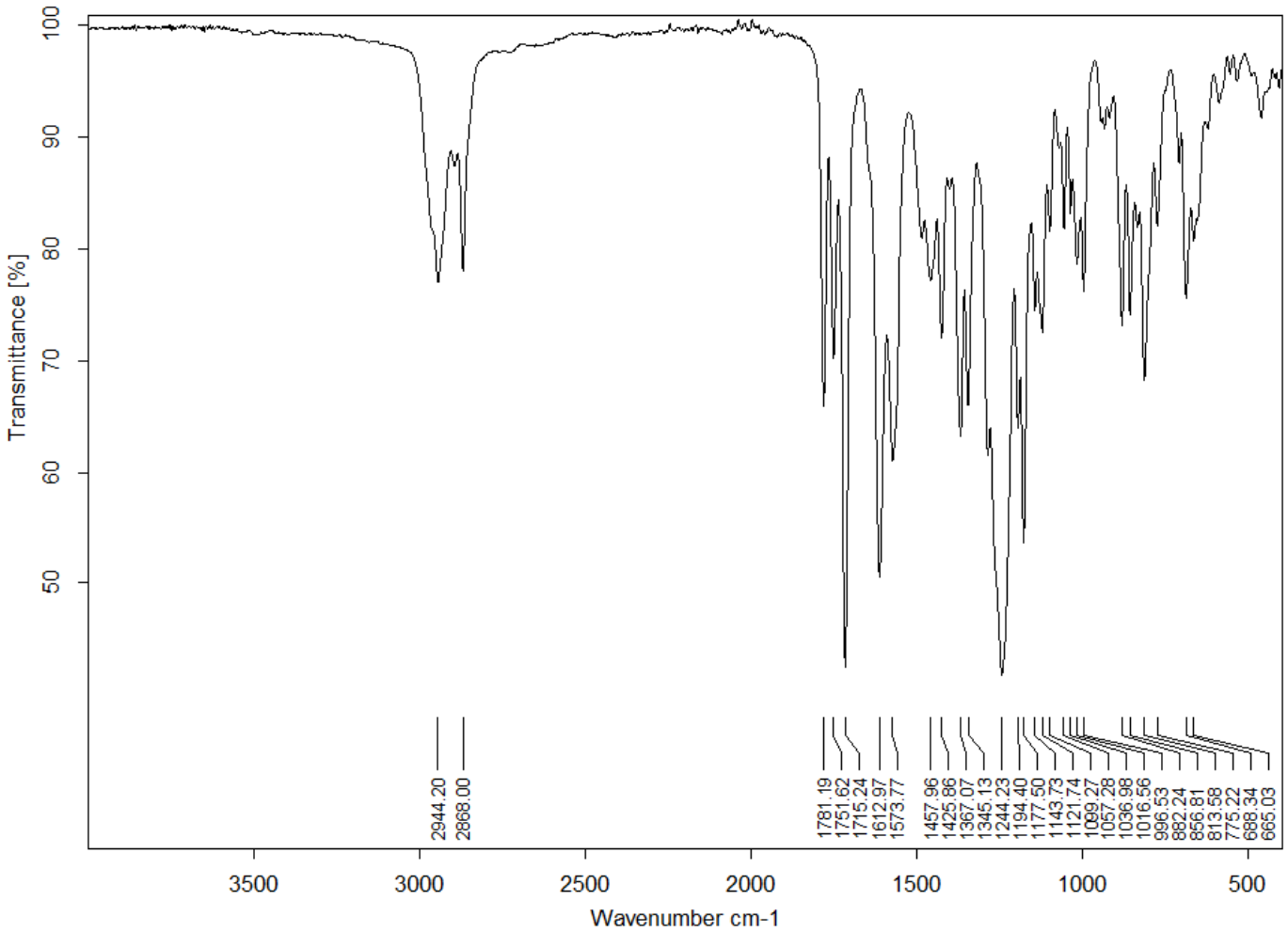


Figure B.3. FTIR spectrum (neat) of compound **4.12**

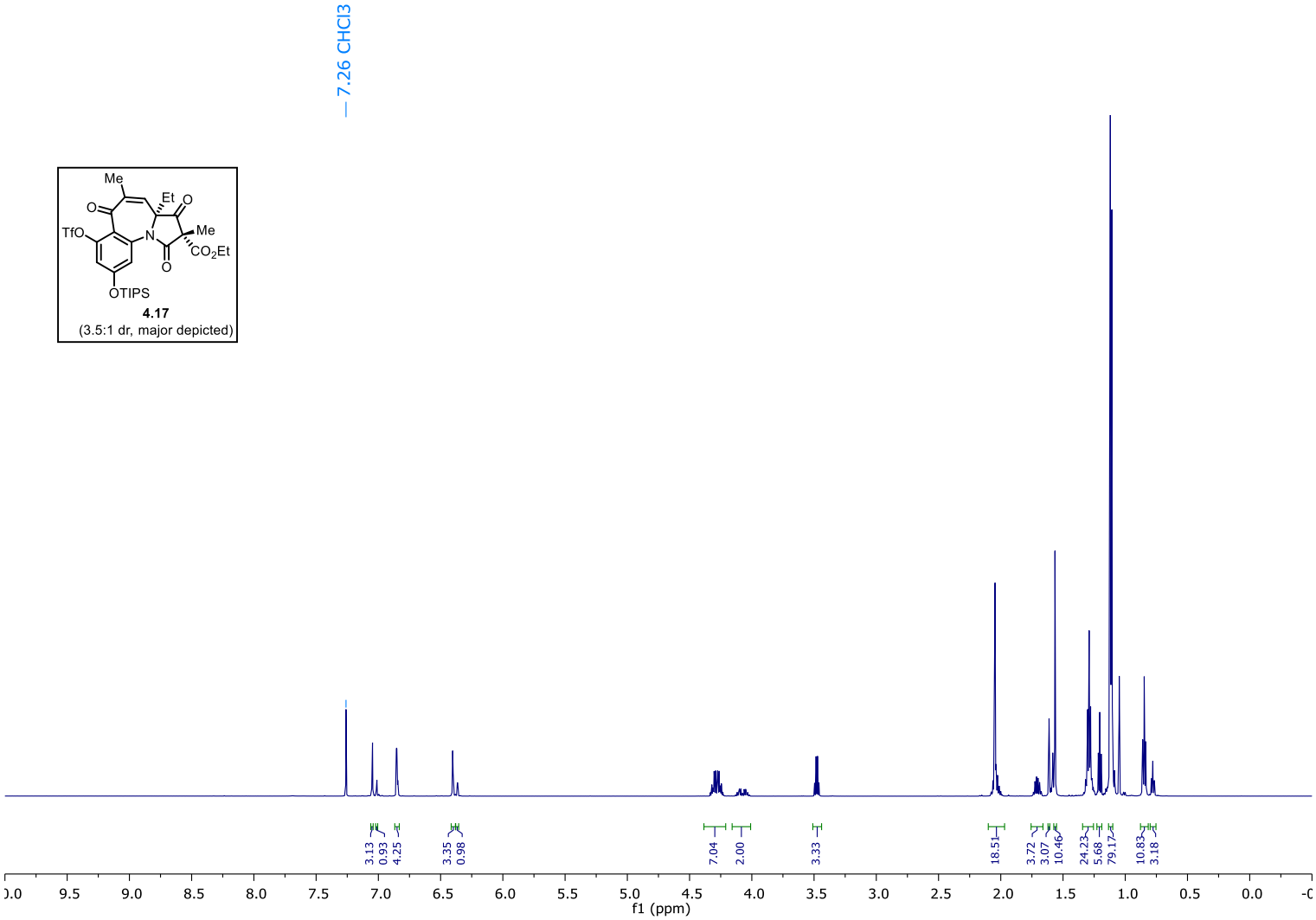


Figure B.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4.17**

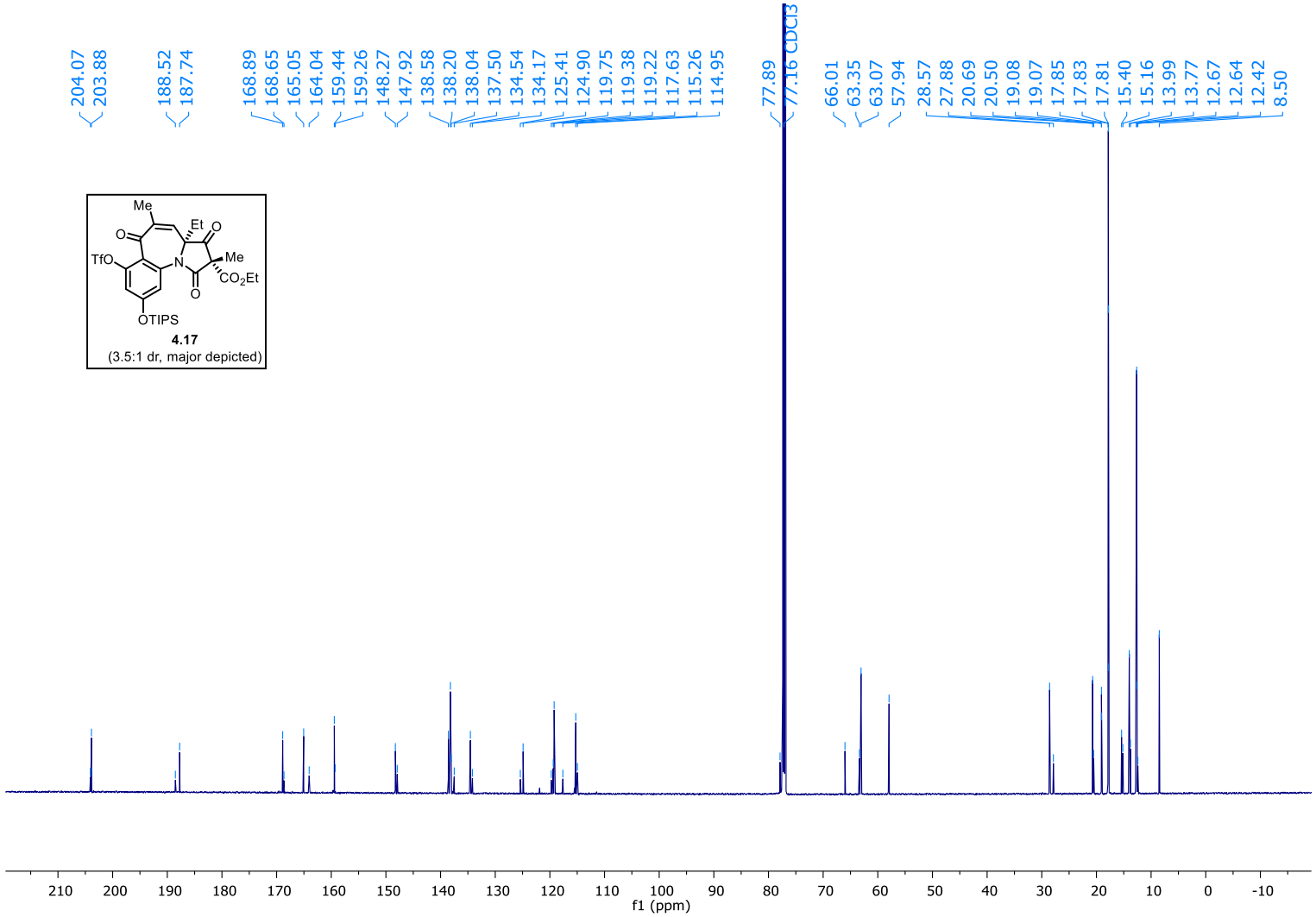


Figure B.5. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **4.17**

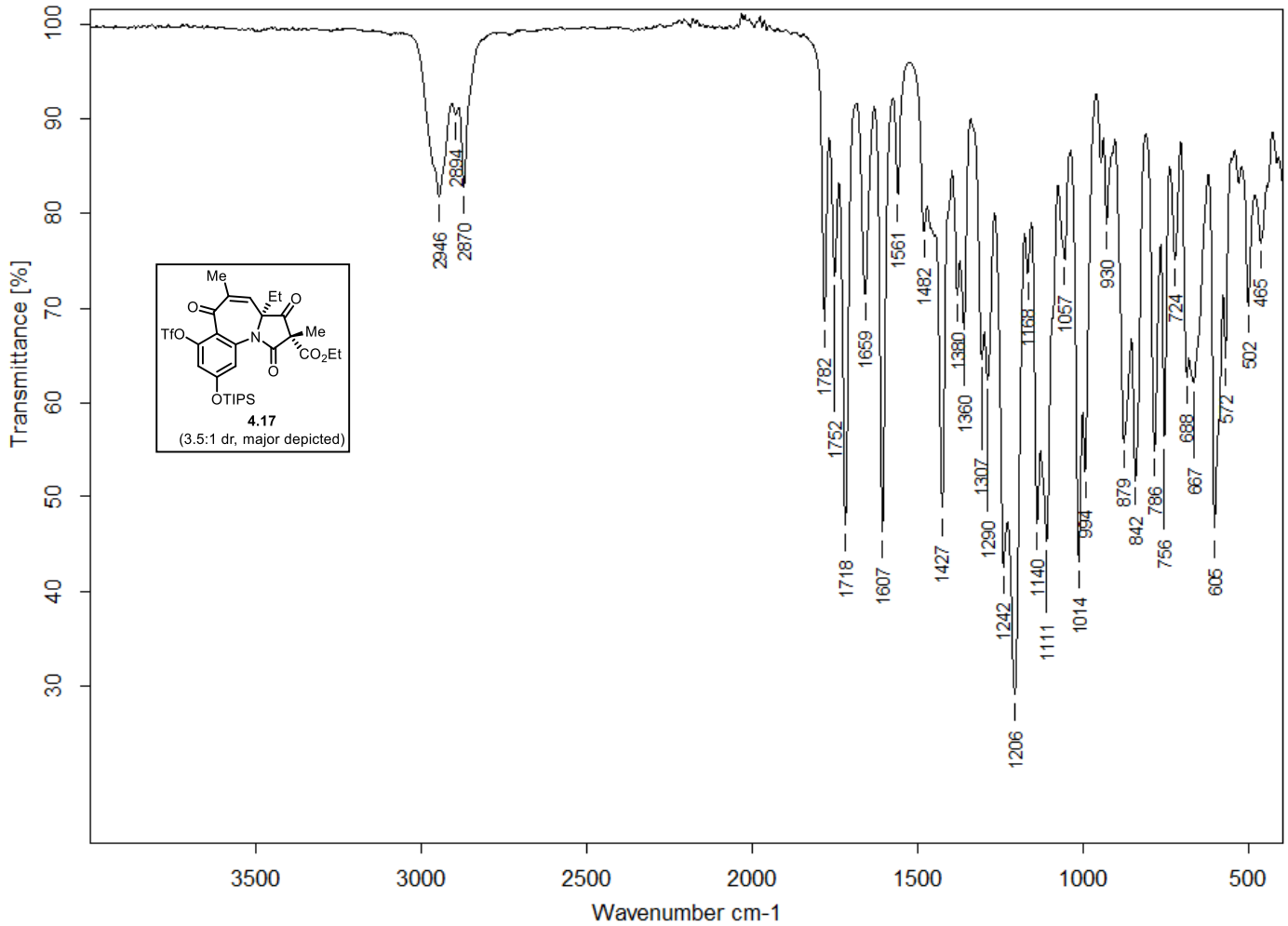


Figure B.6. FTIR spectrum (neat) of compound **4.17**

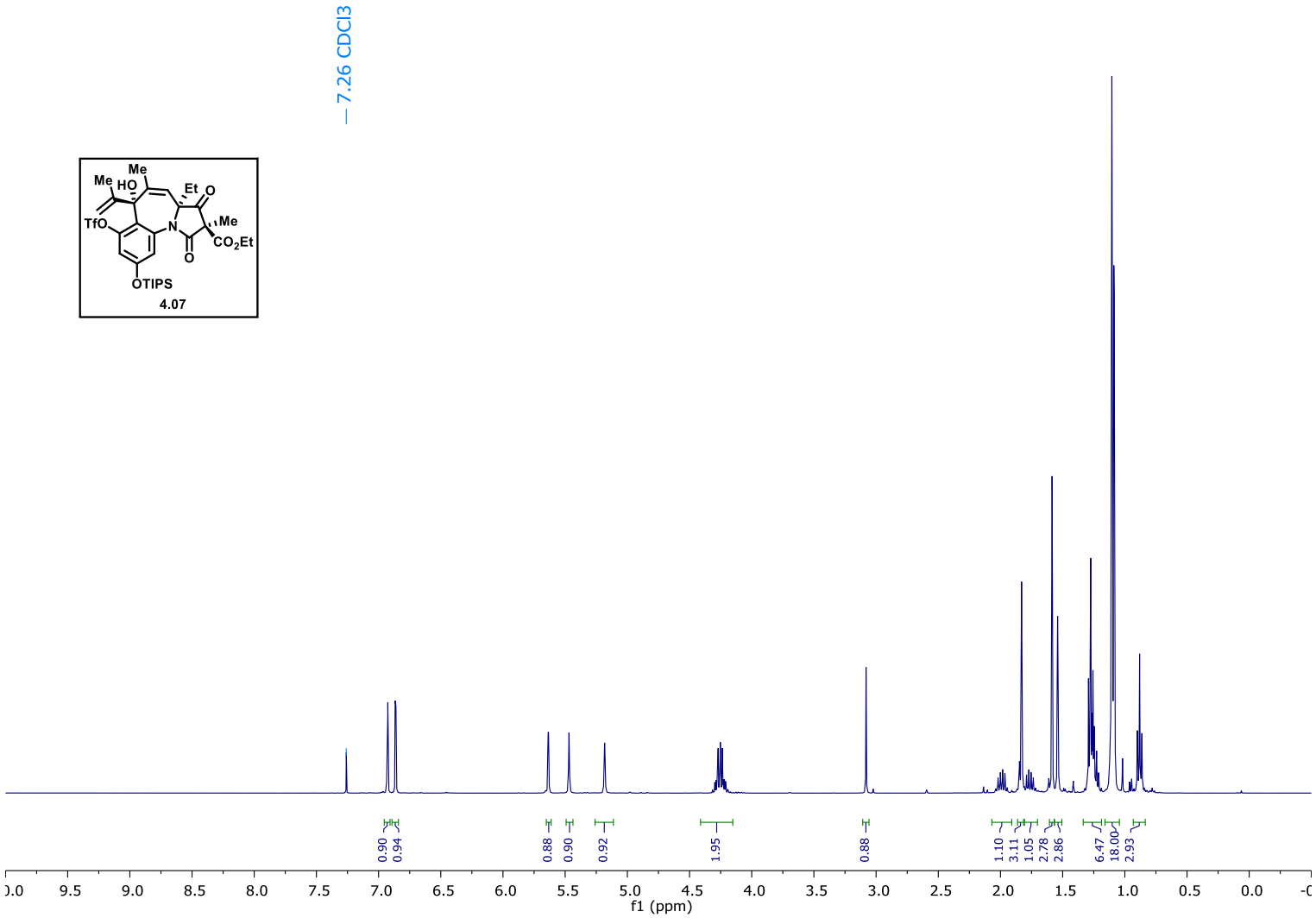


Figure B.7. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.07**

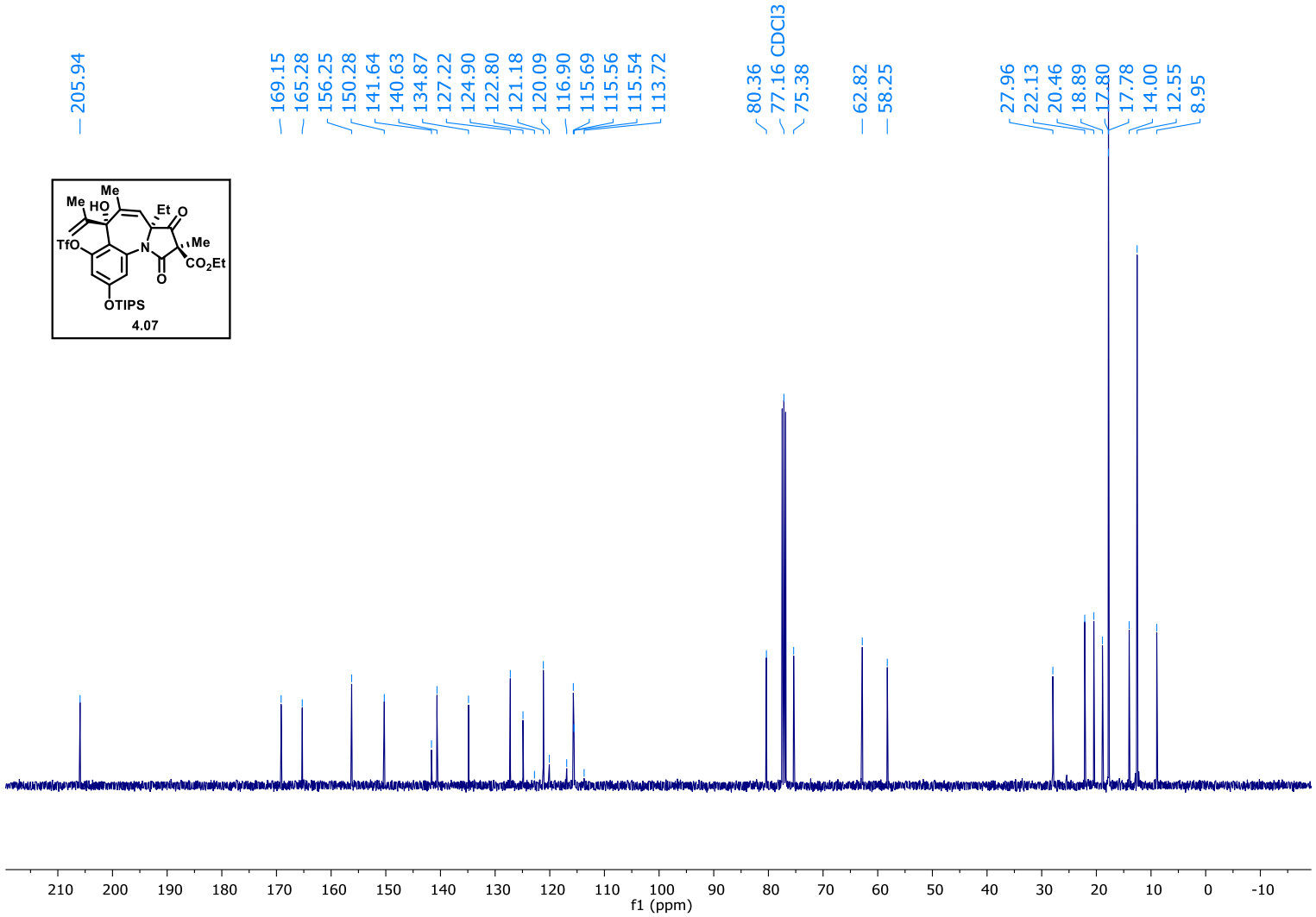


Figure B.8. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **4.07**

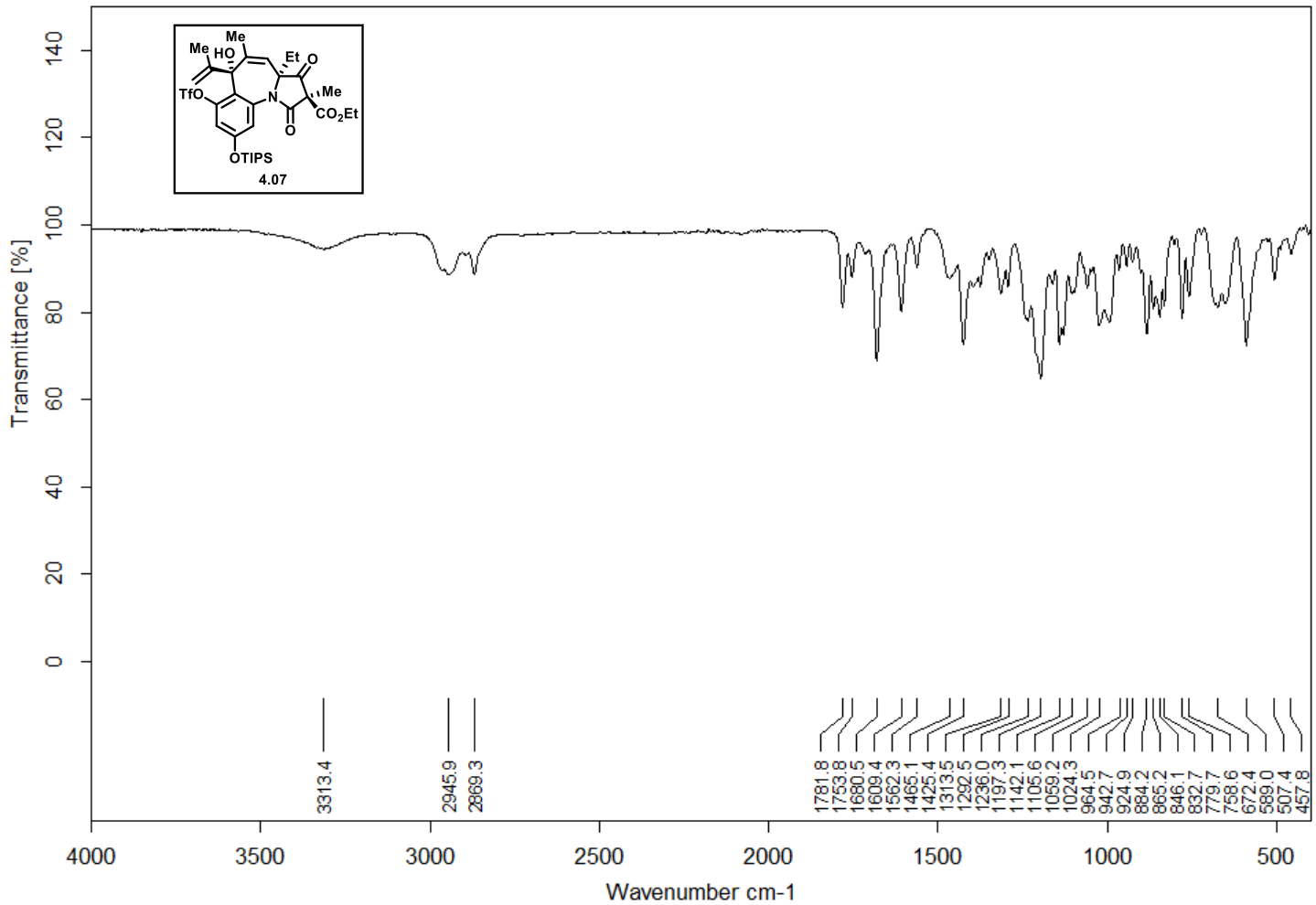


Figure B.9. FTIR spectrum (neat) of compound **4.07**

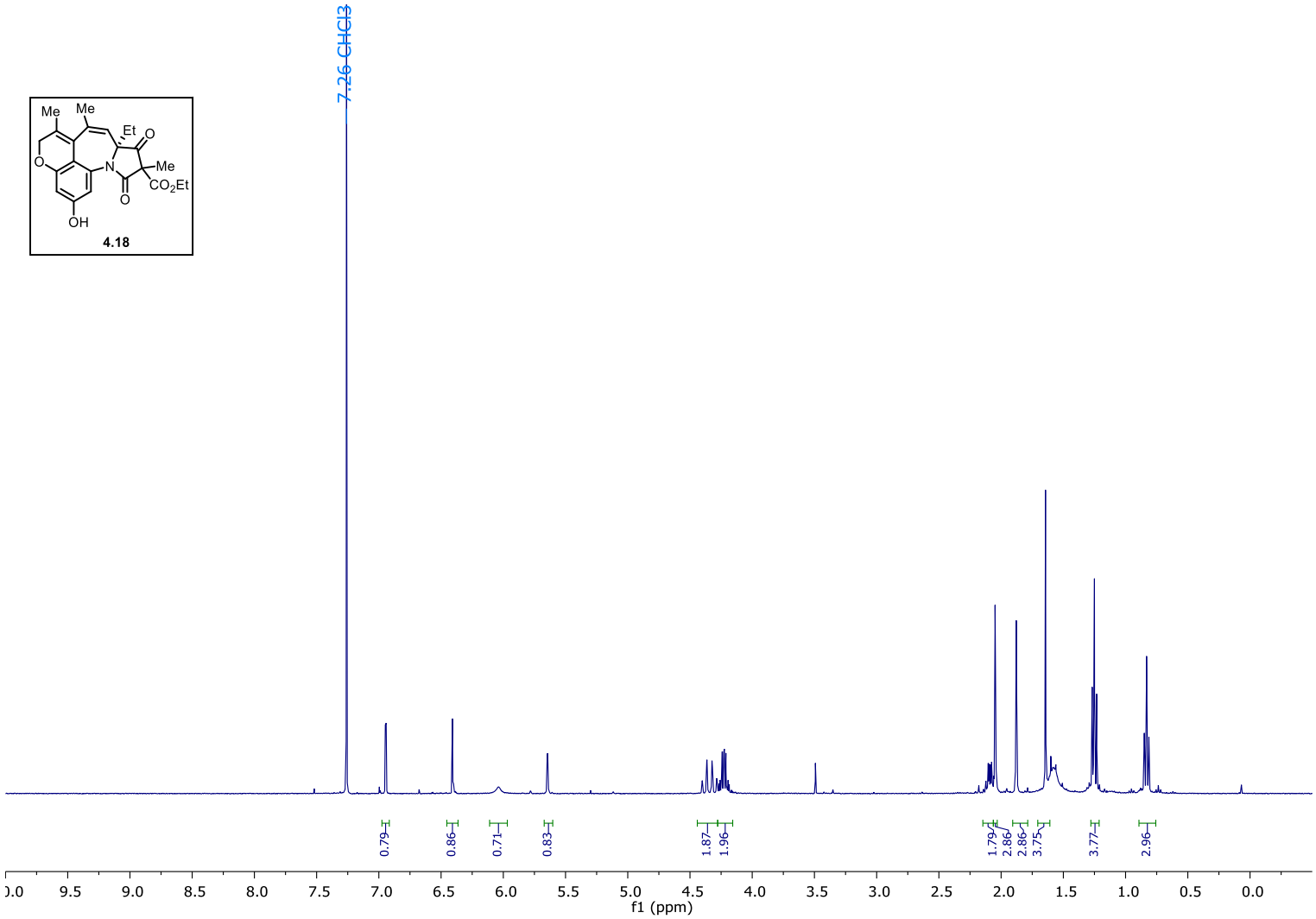


Figure B.10. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.18**

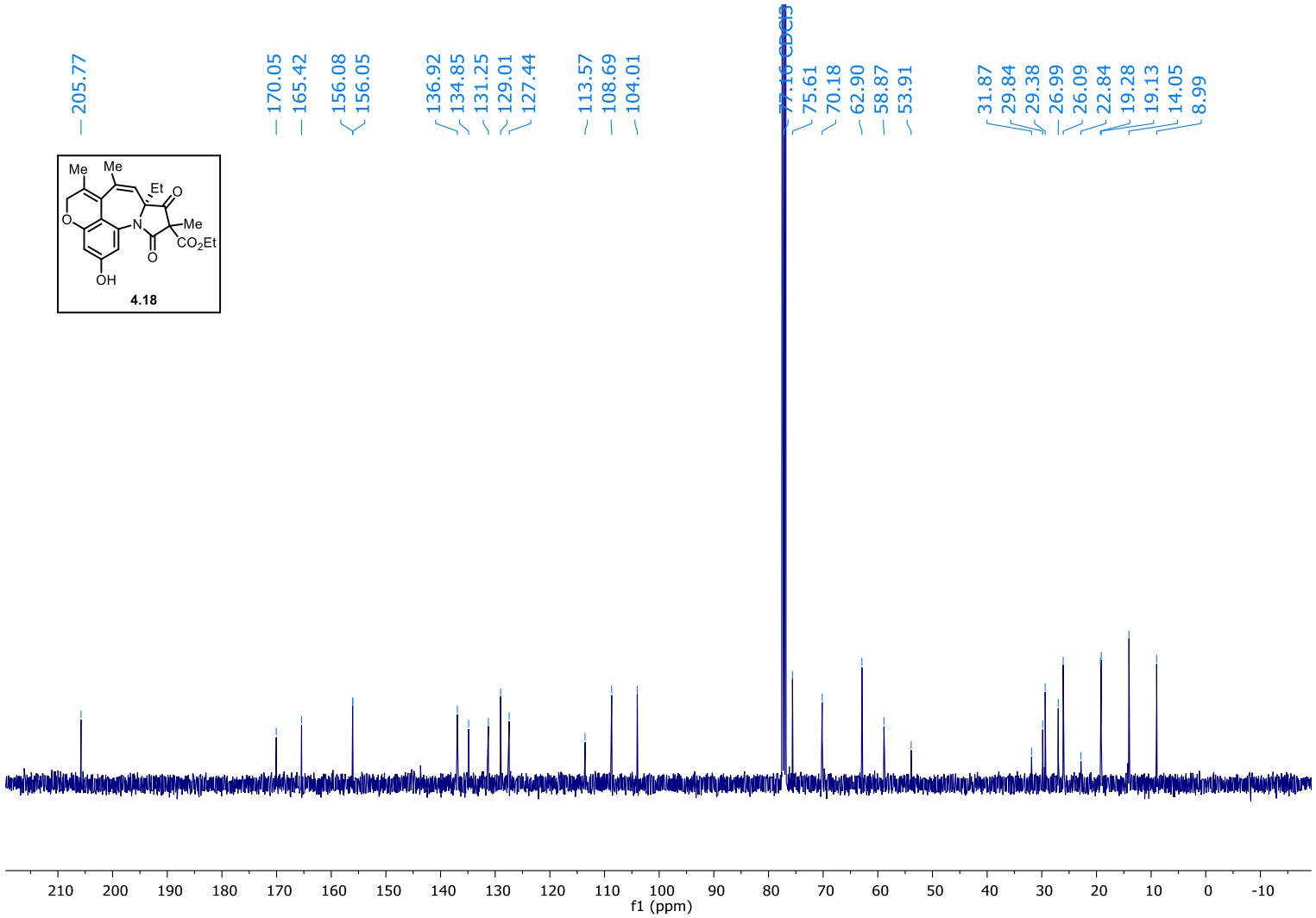


Figure B.11. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **4.18**

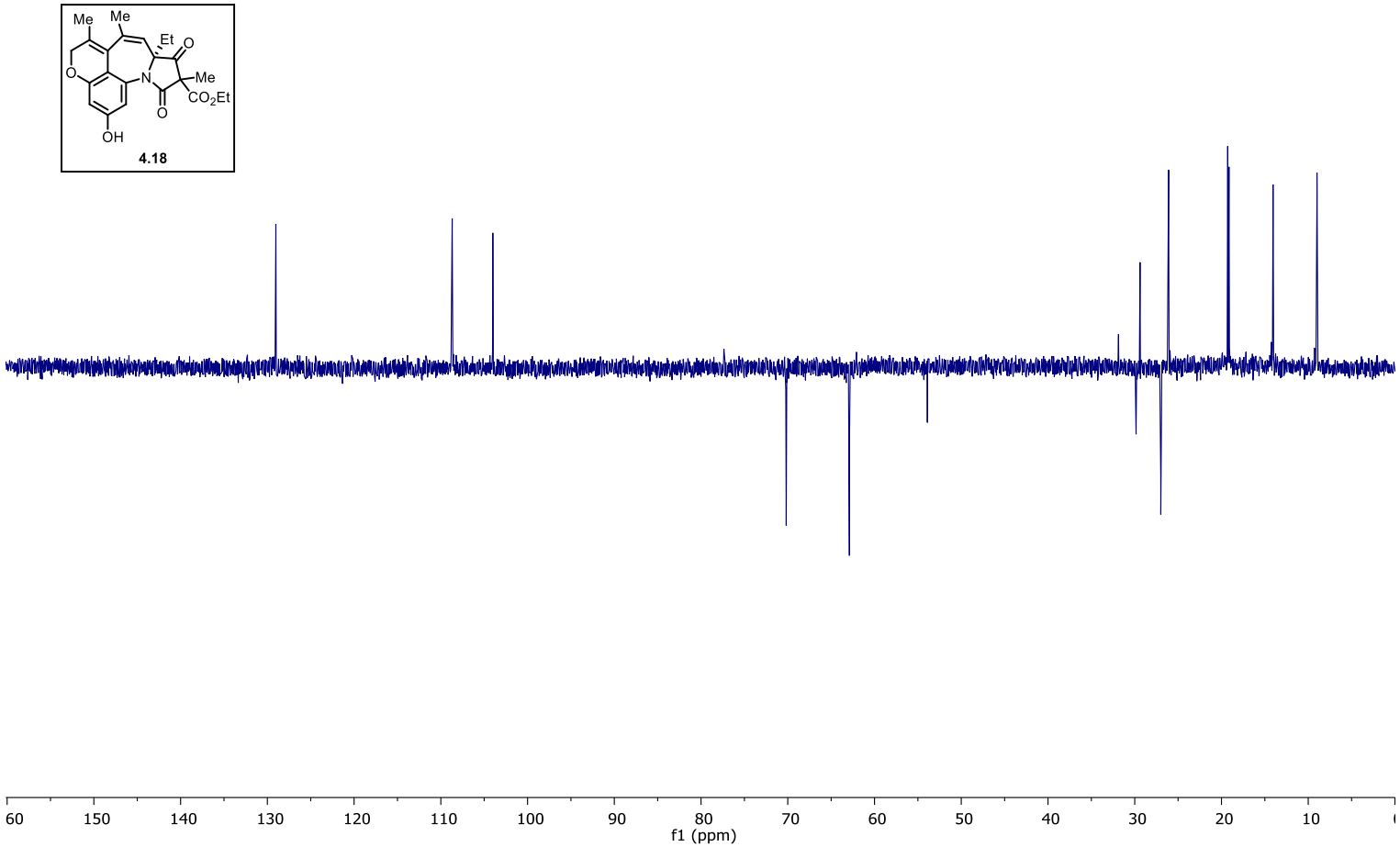


Figure B.12. DEPT spectrum of compound **4.18**

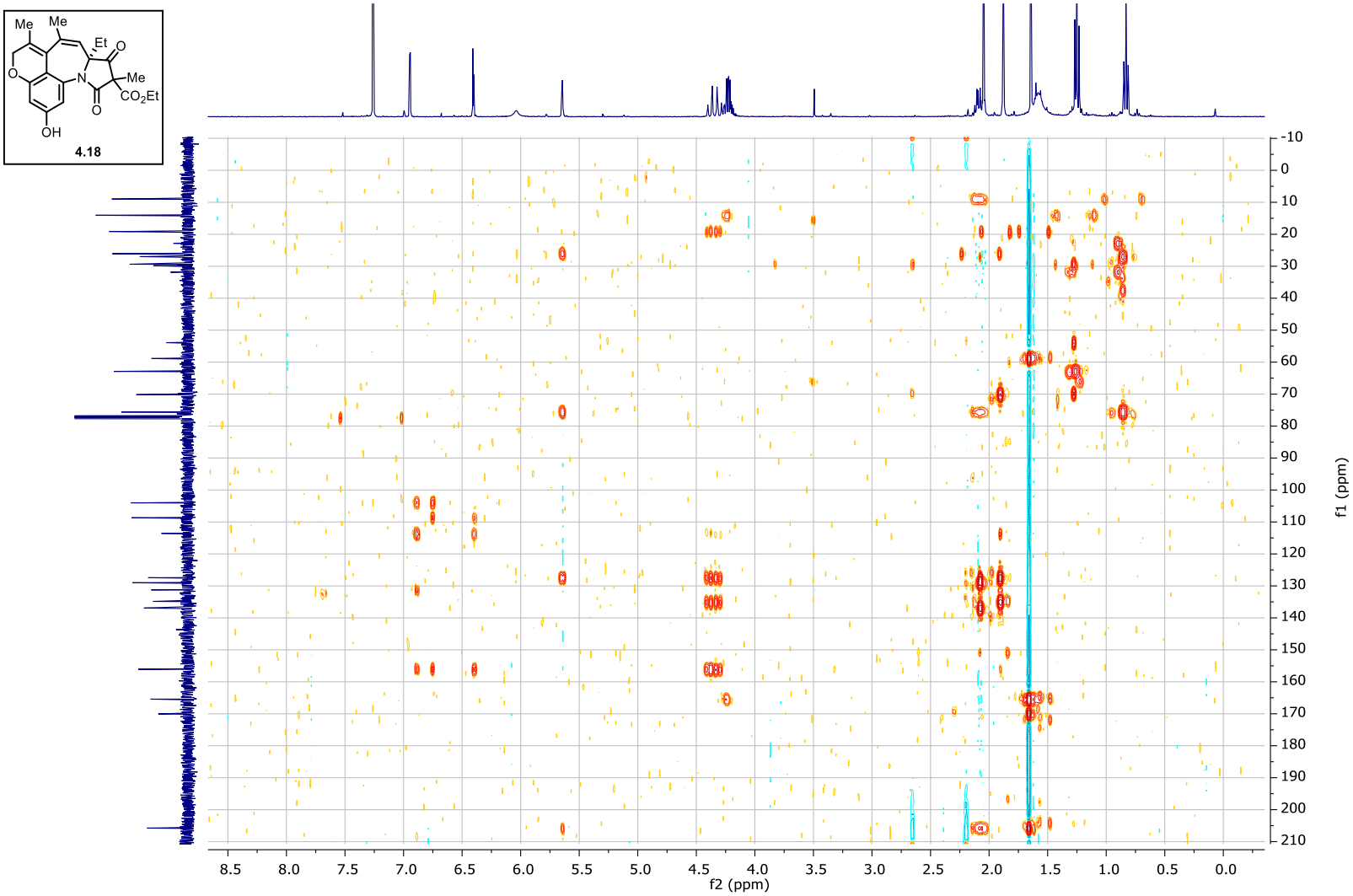


Figure B.13. HMBC spectrum of compound **4.18**

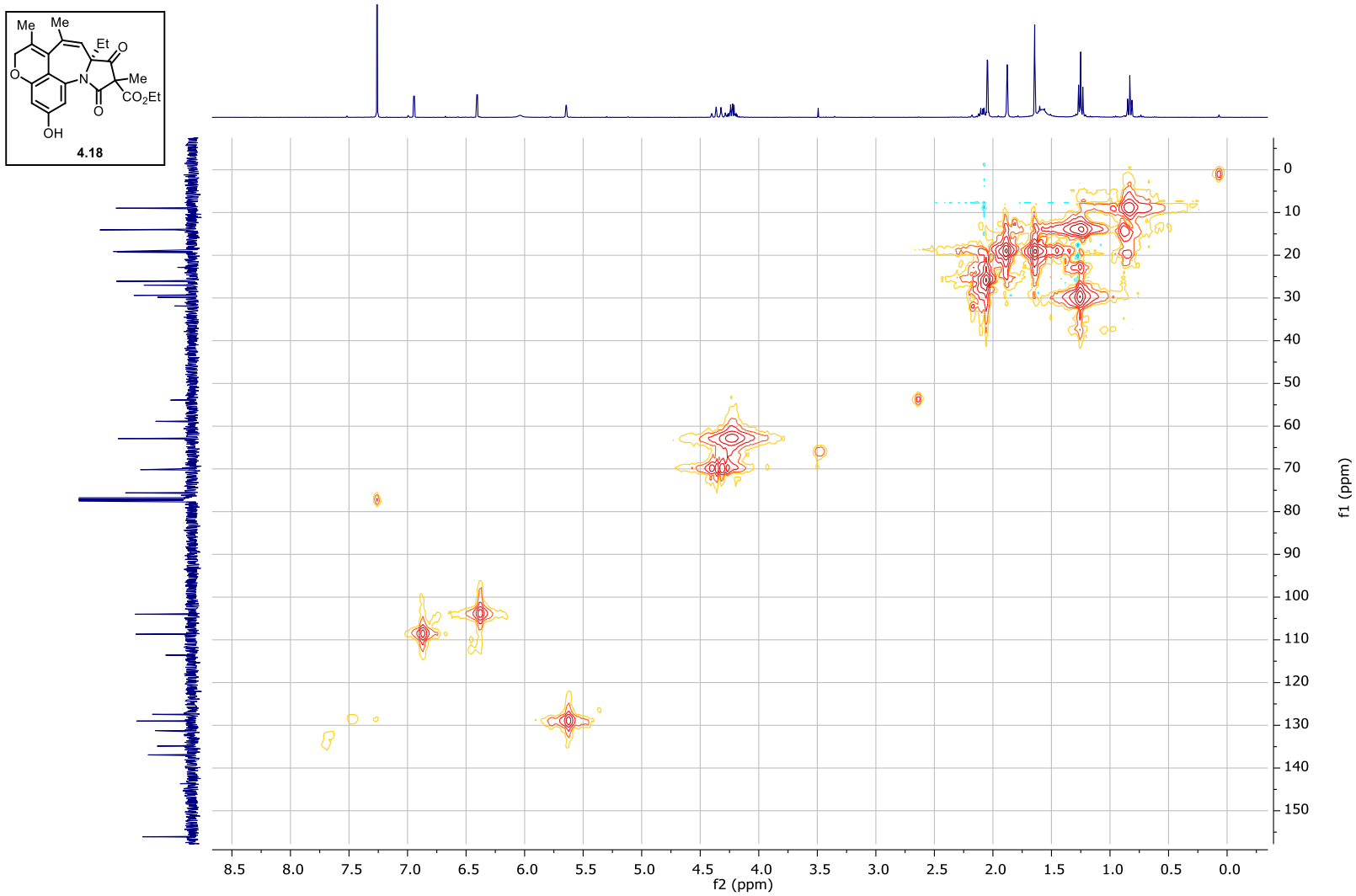


Figure B.14. HMQC spectrum of compound **4.18**

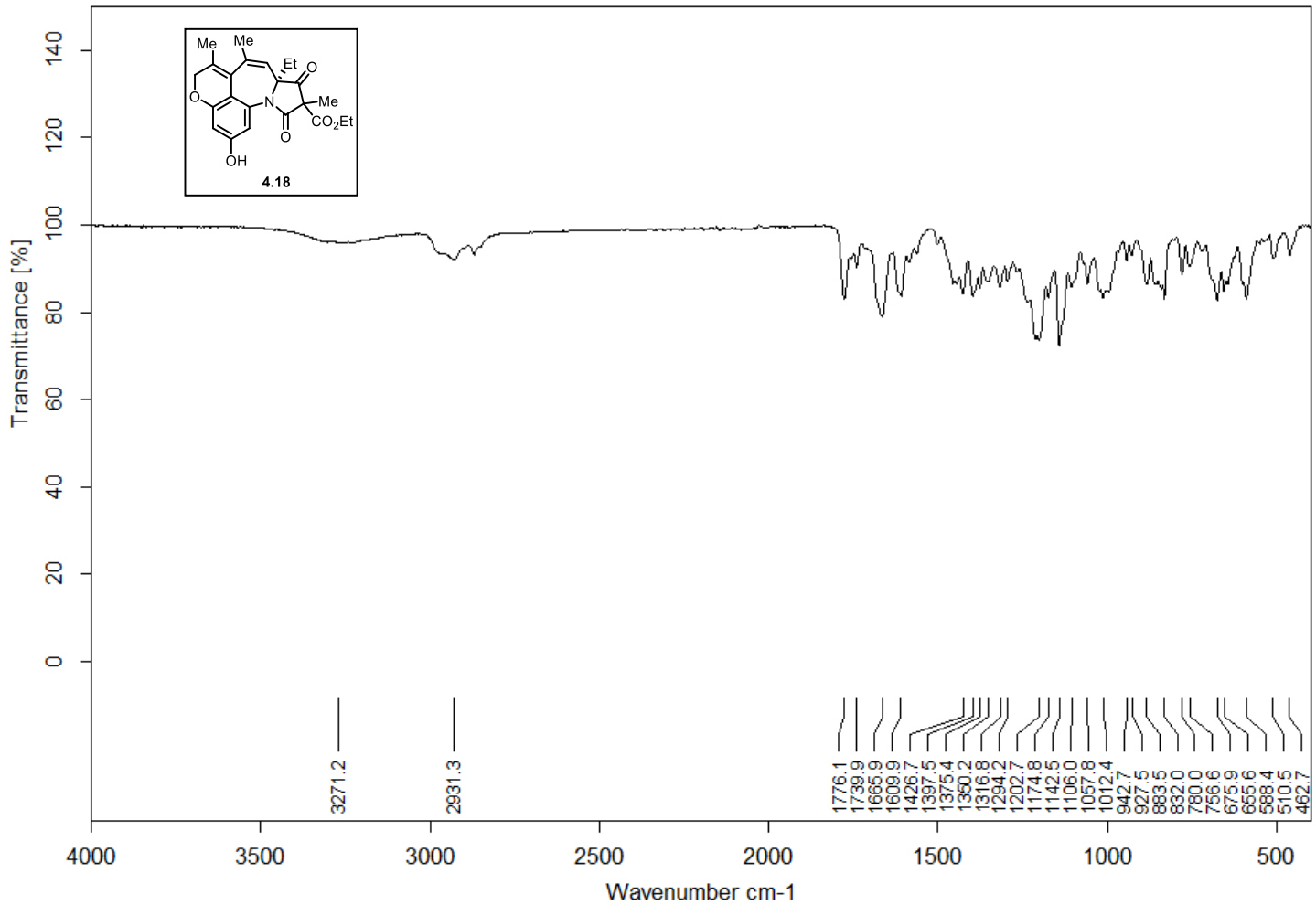


Figure B.15. FTIR spectrum (neat) of compound **4.18**

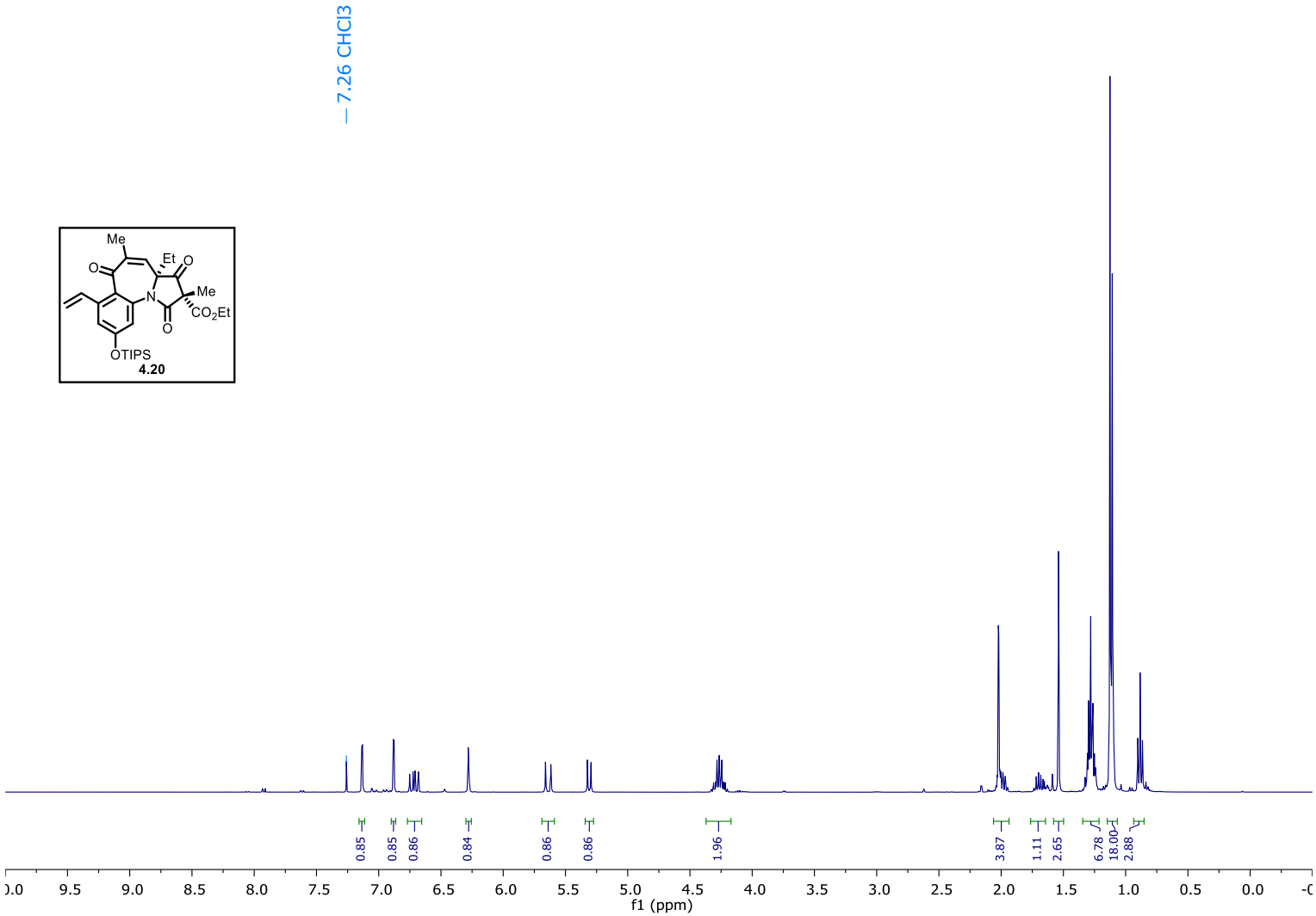


Figure B.16. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.20**

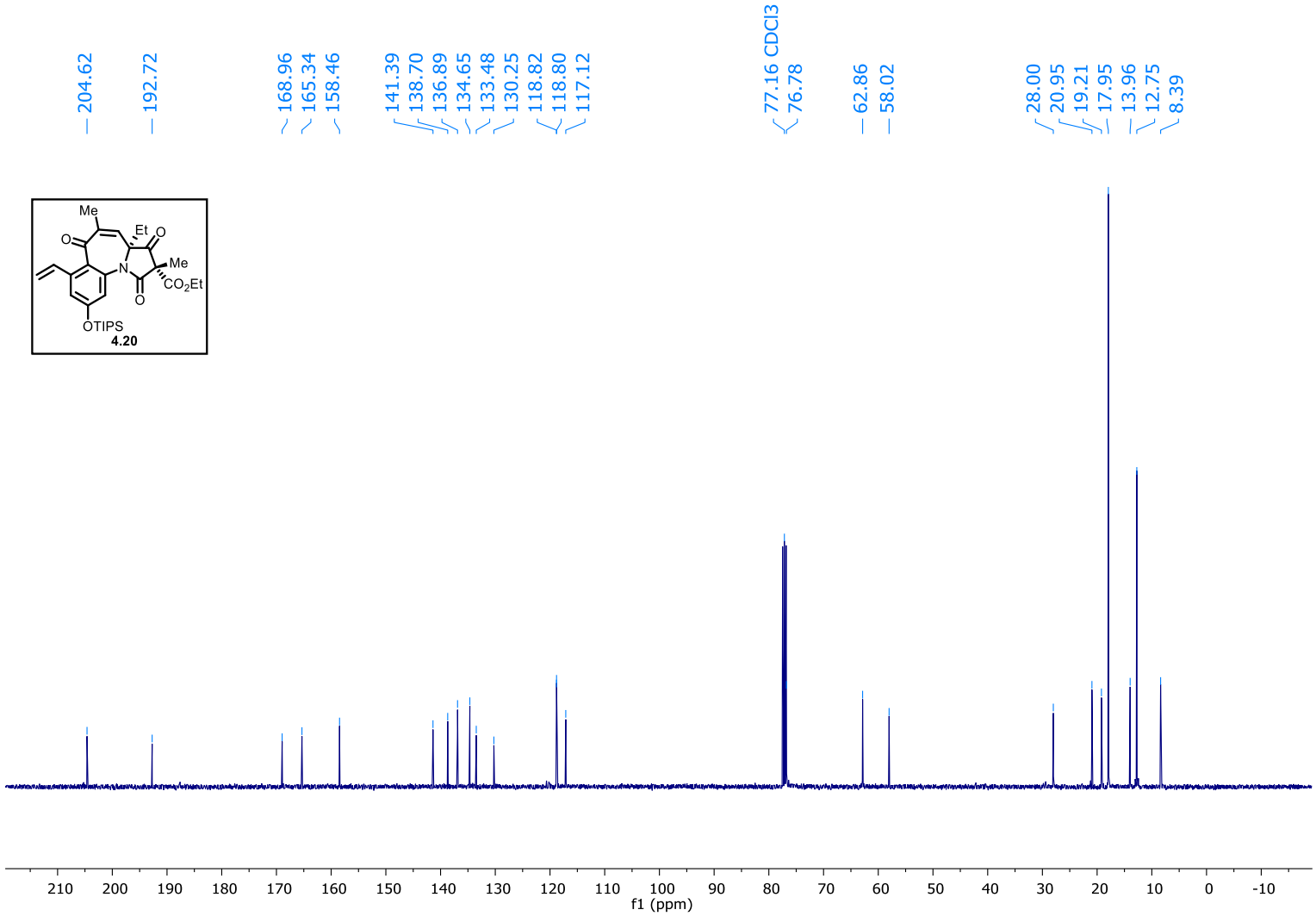


Figure B.17. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **4.20**

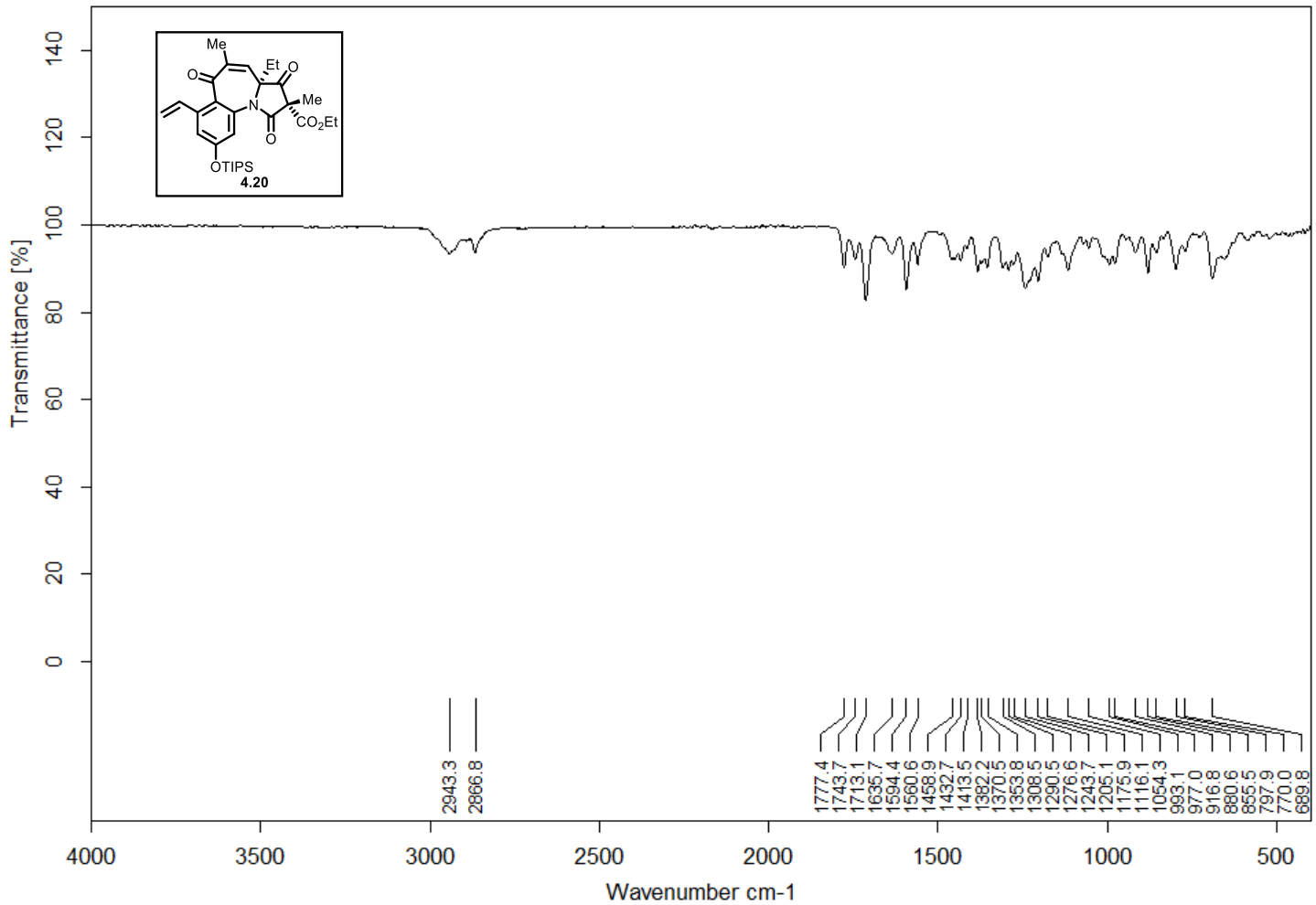


Figure B.18. FTIR spectrum (neat) of compound **4.20**

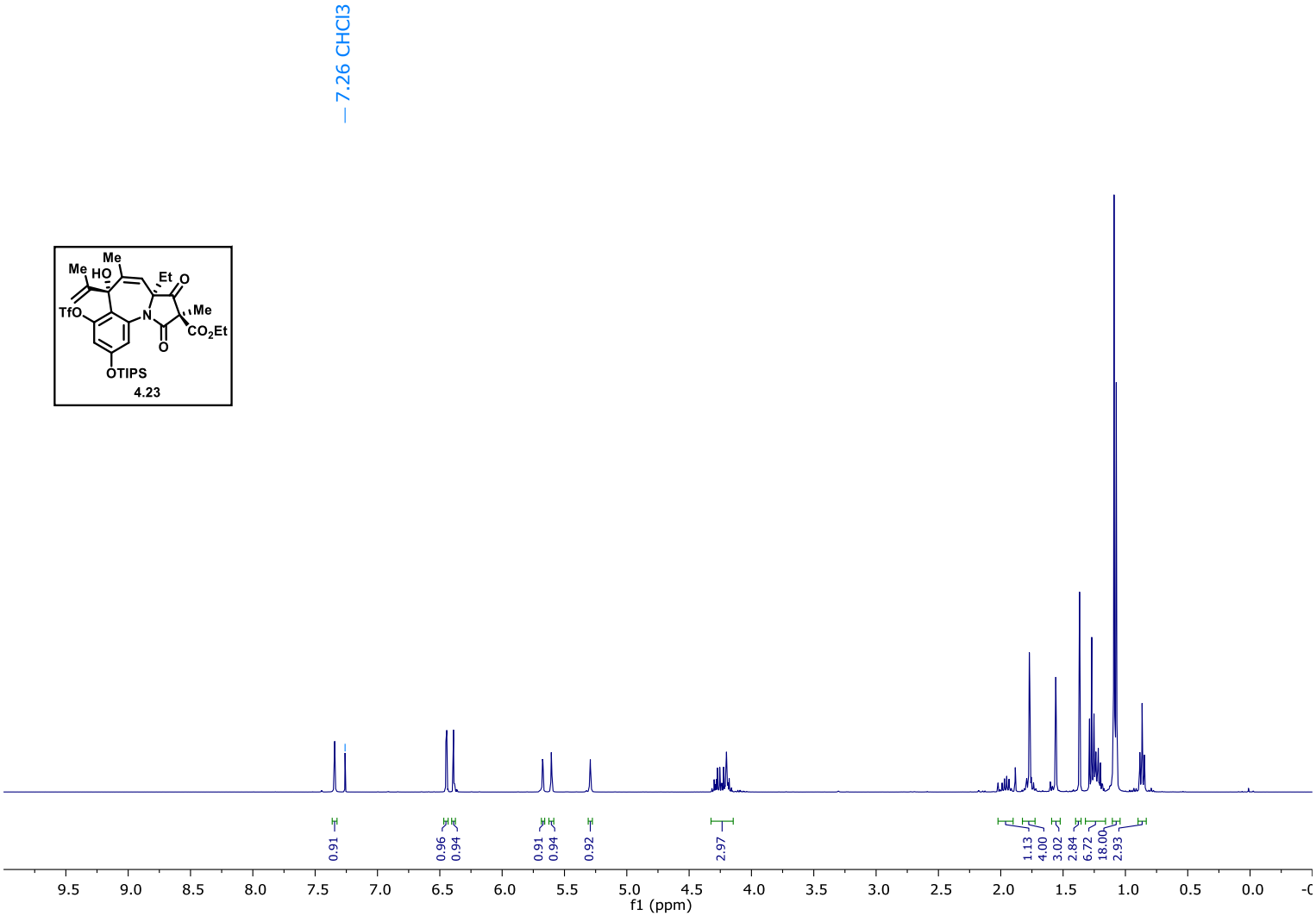


Figure B.19. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **4.23**

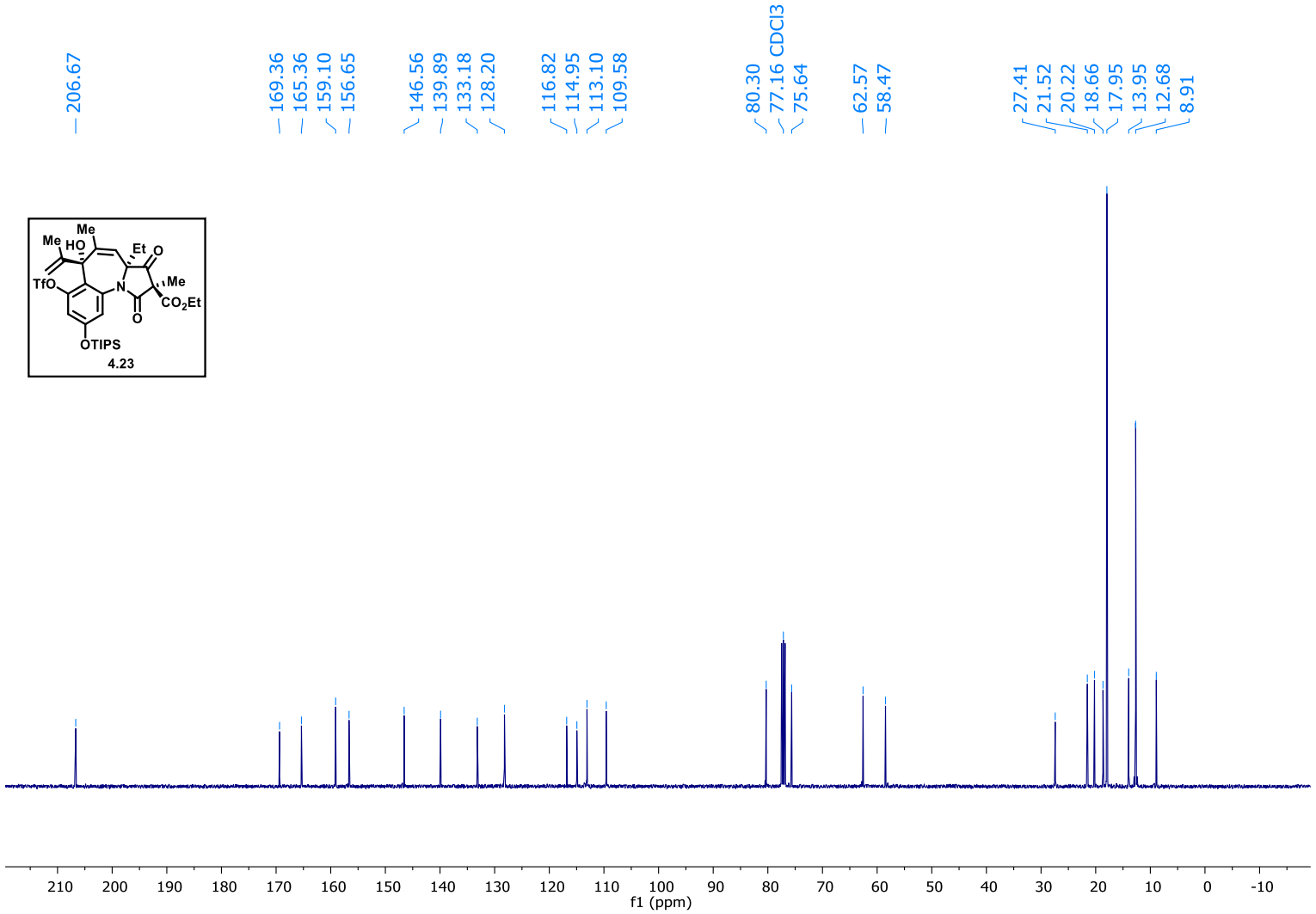


Figure B.20. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **4.23**

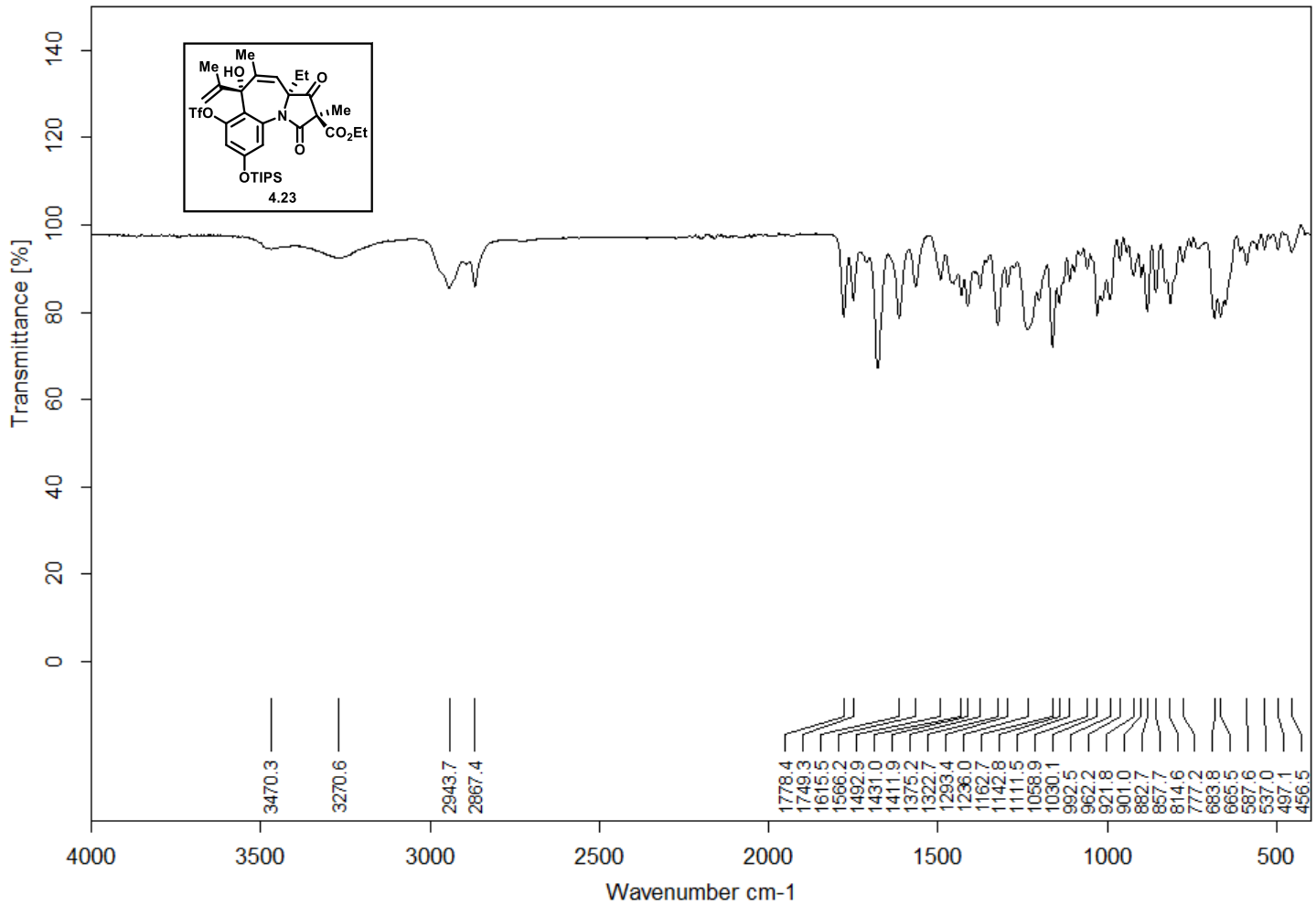


Figure B.21. FTIR spectrum (neat) of compound **4.23**

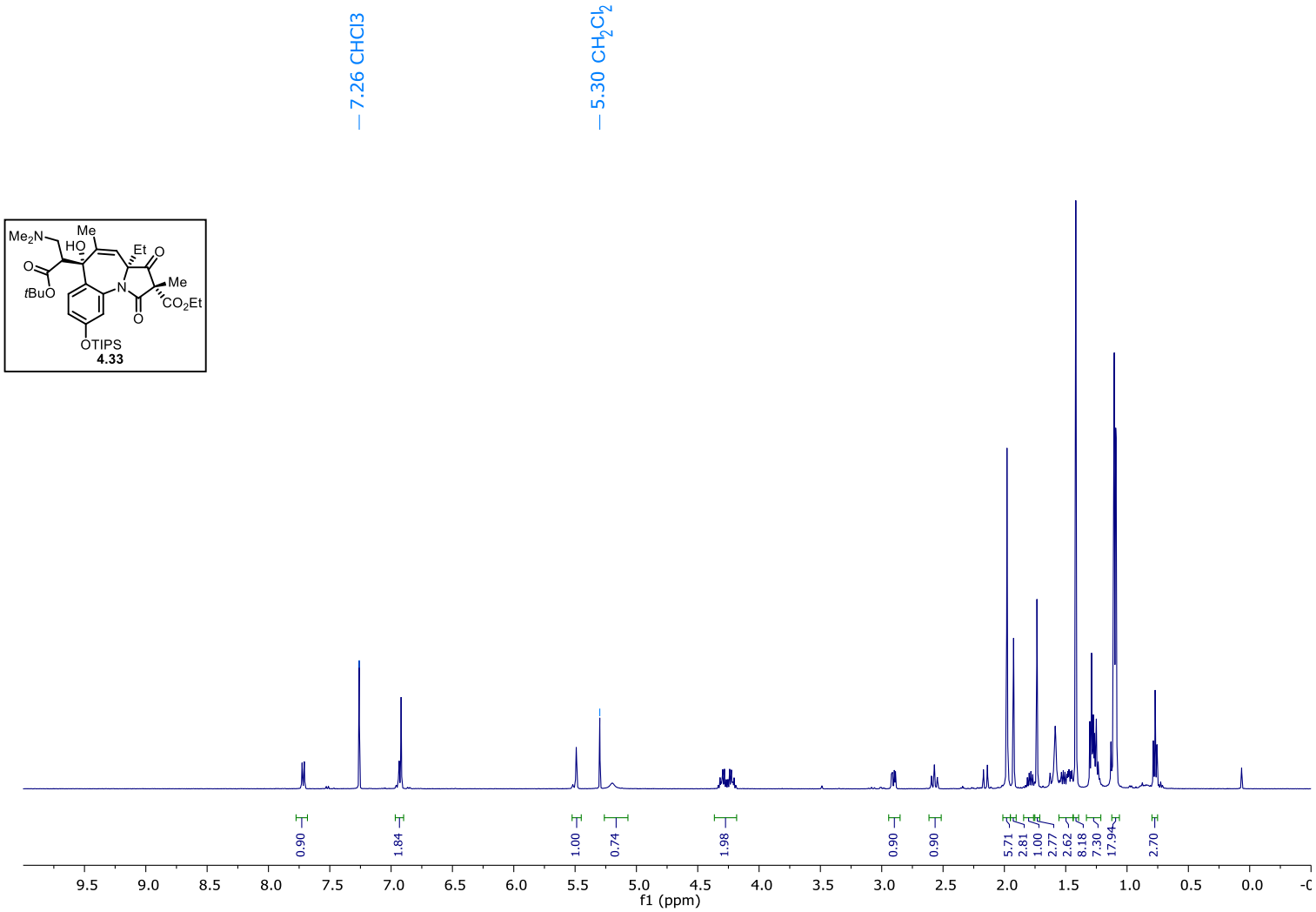


Figure B.22. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **4.33**

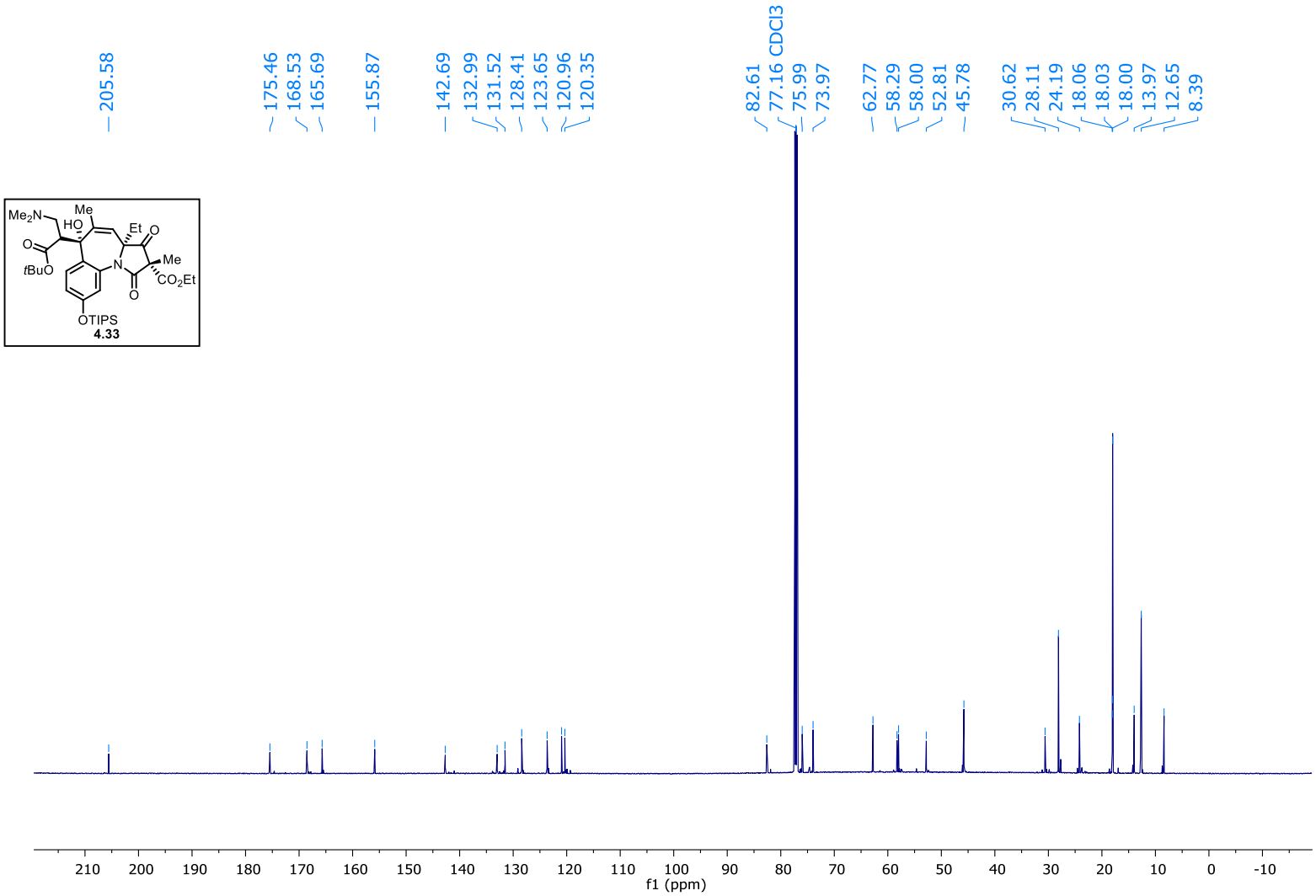


Figure B.23. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **4.33**

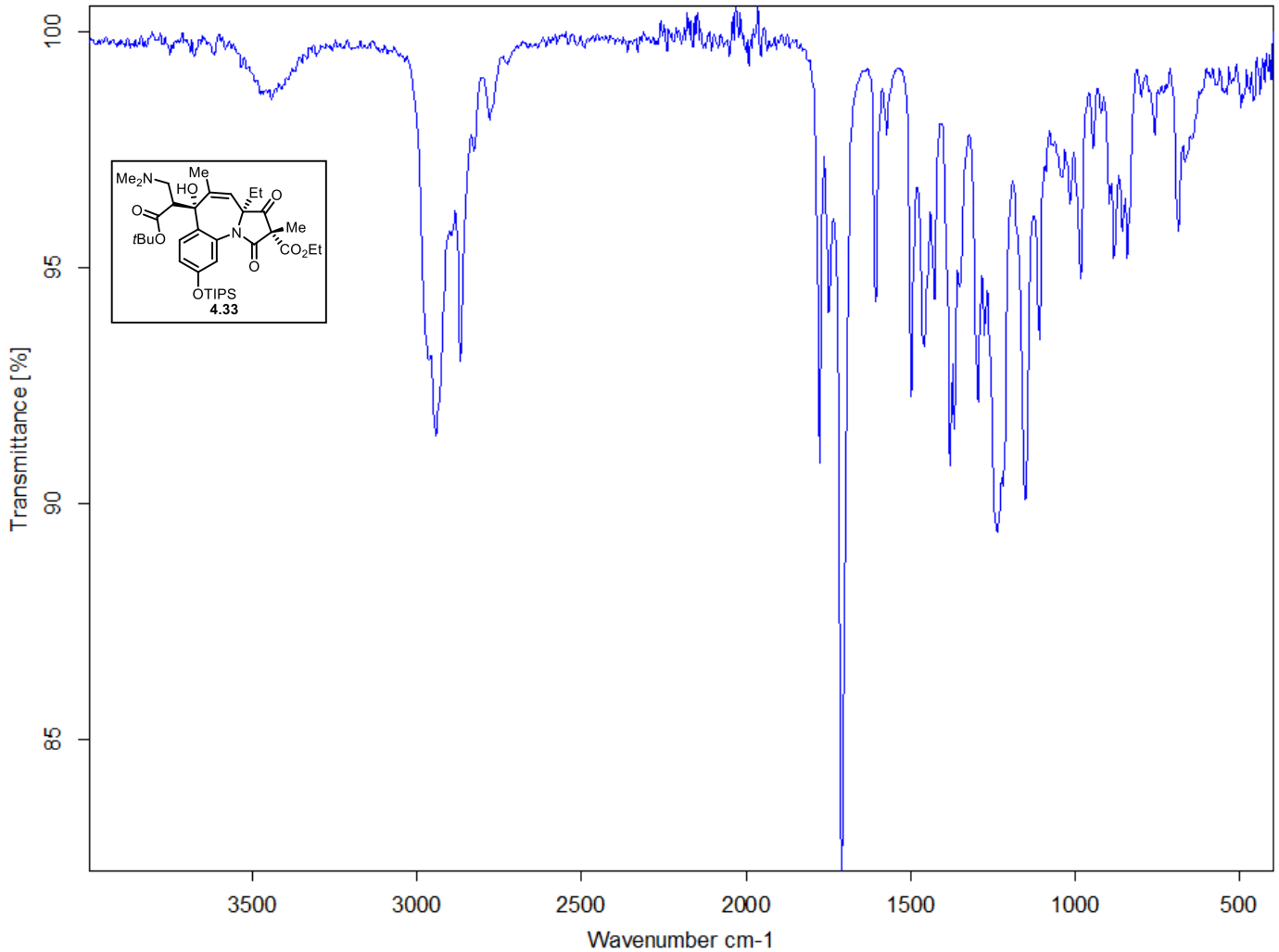


Figure B.24. FTIR spectrum (neat) of compound **4.33**

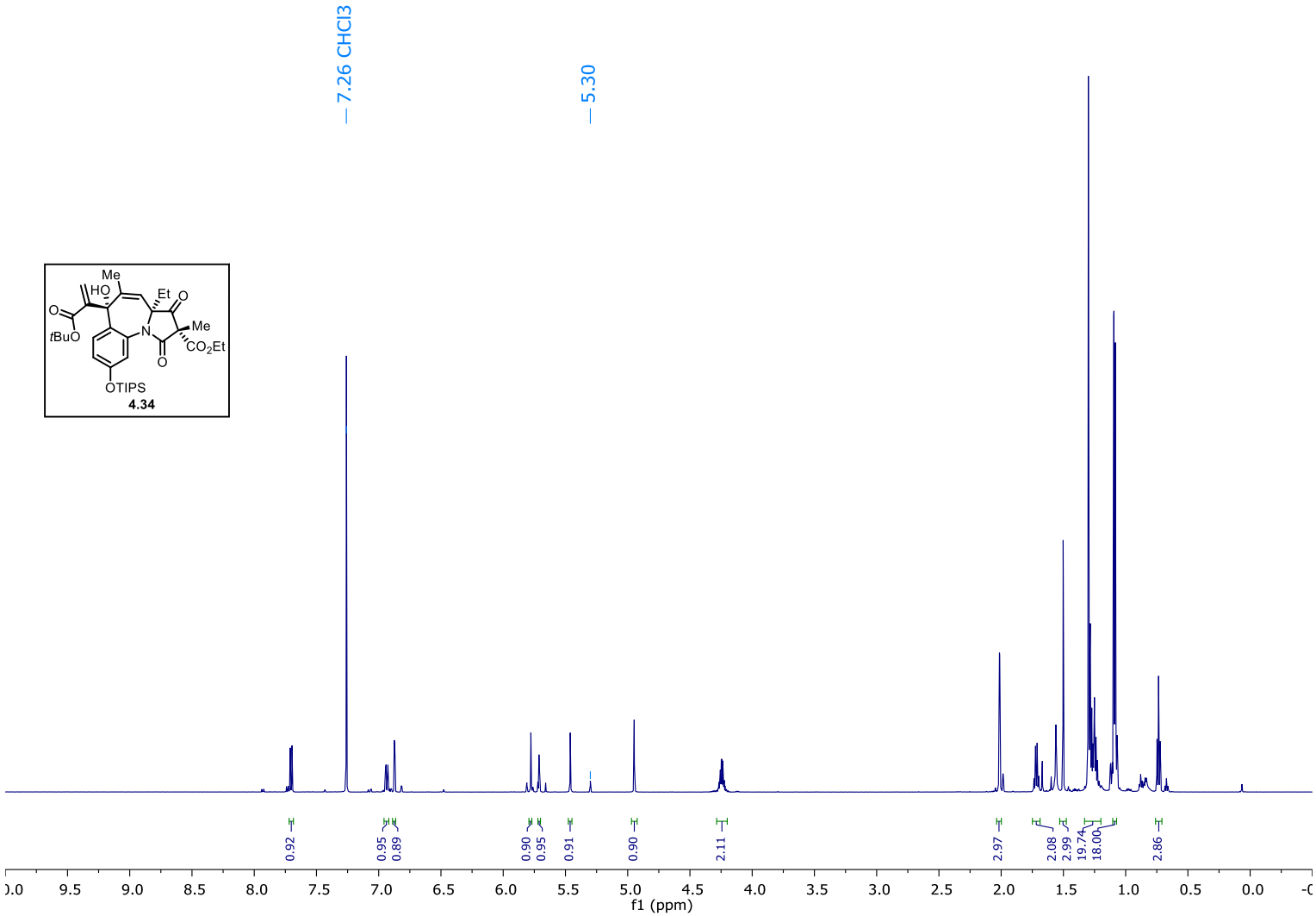


Figure B.25. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **4.34**

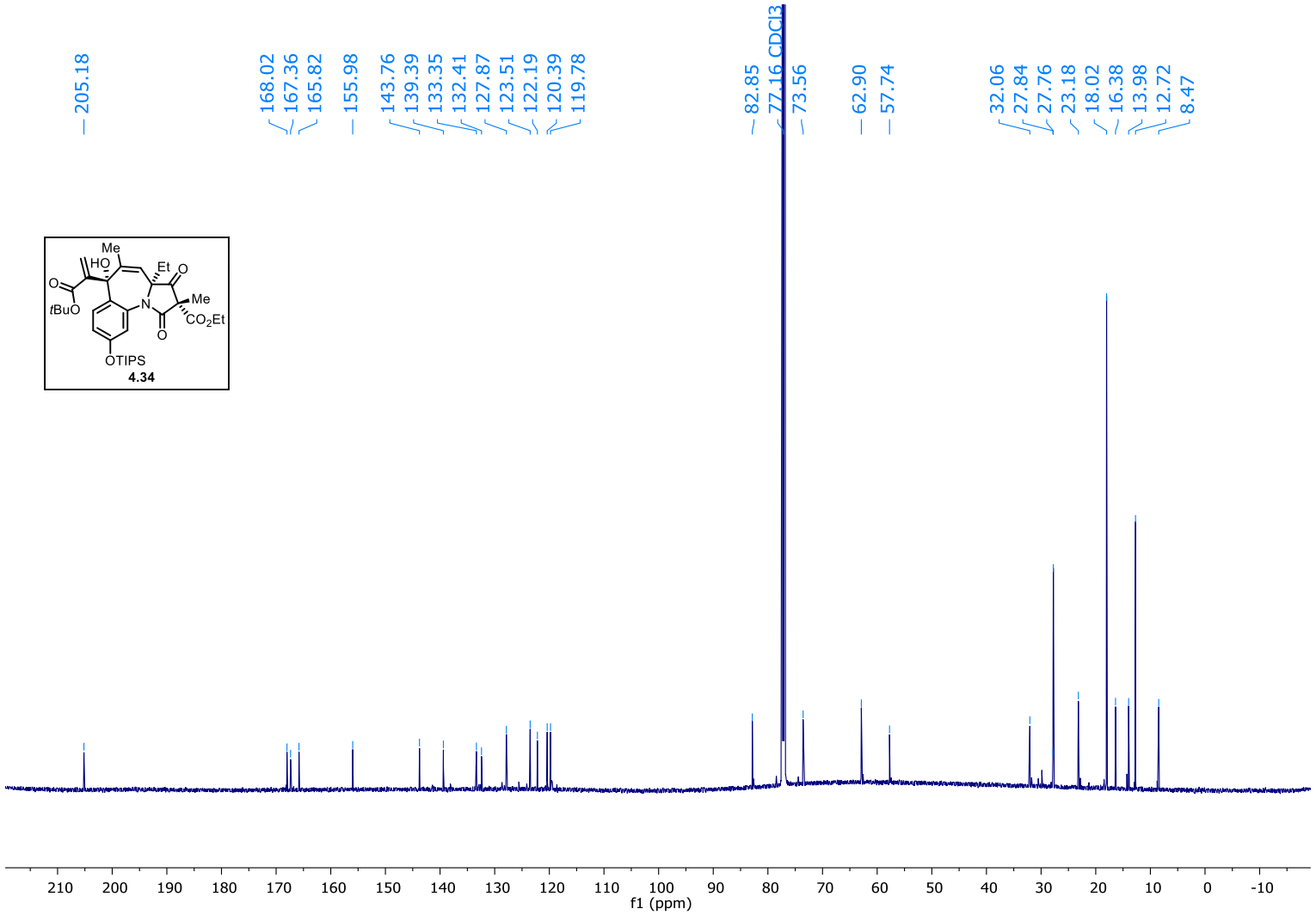


Figure B.26. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **4.34**

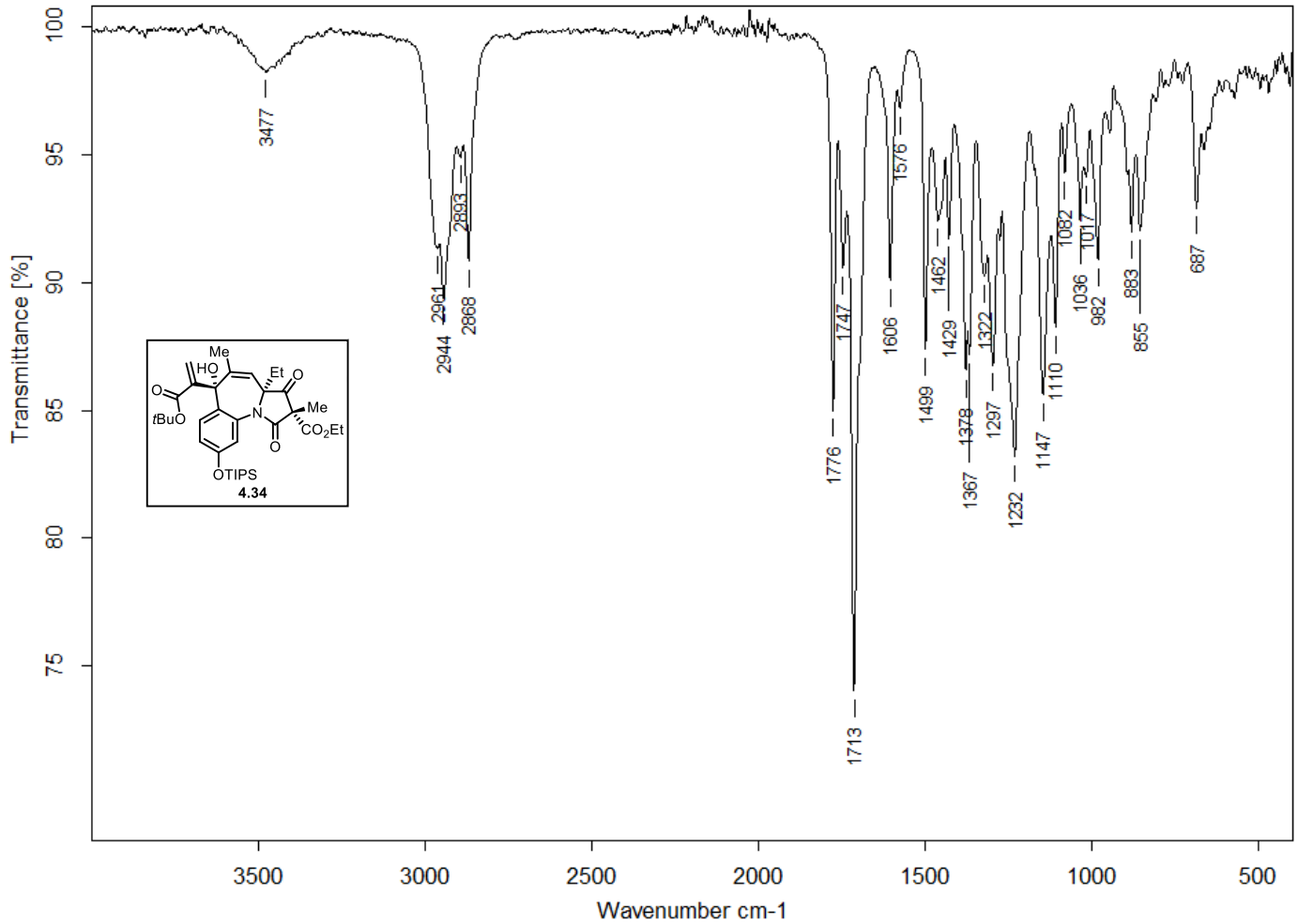


Figure B.27. FTIR spectrum (neat) of compound **4.34**

APPENDIX C

Spectra Relevant to Chapter Five

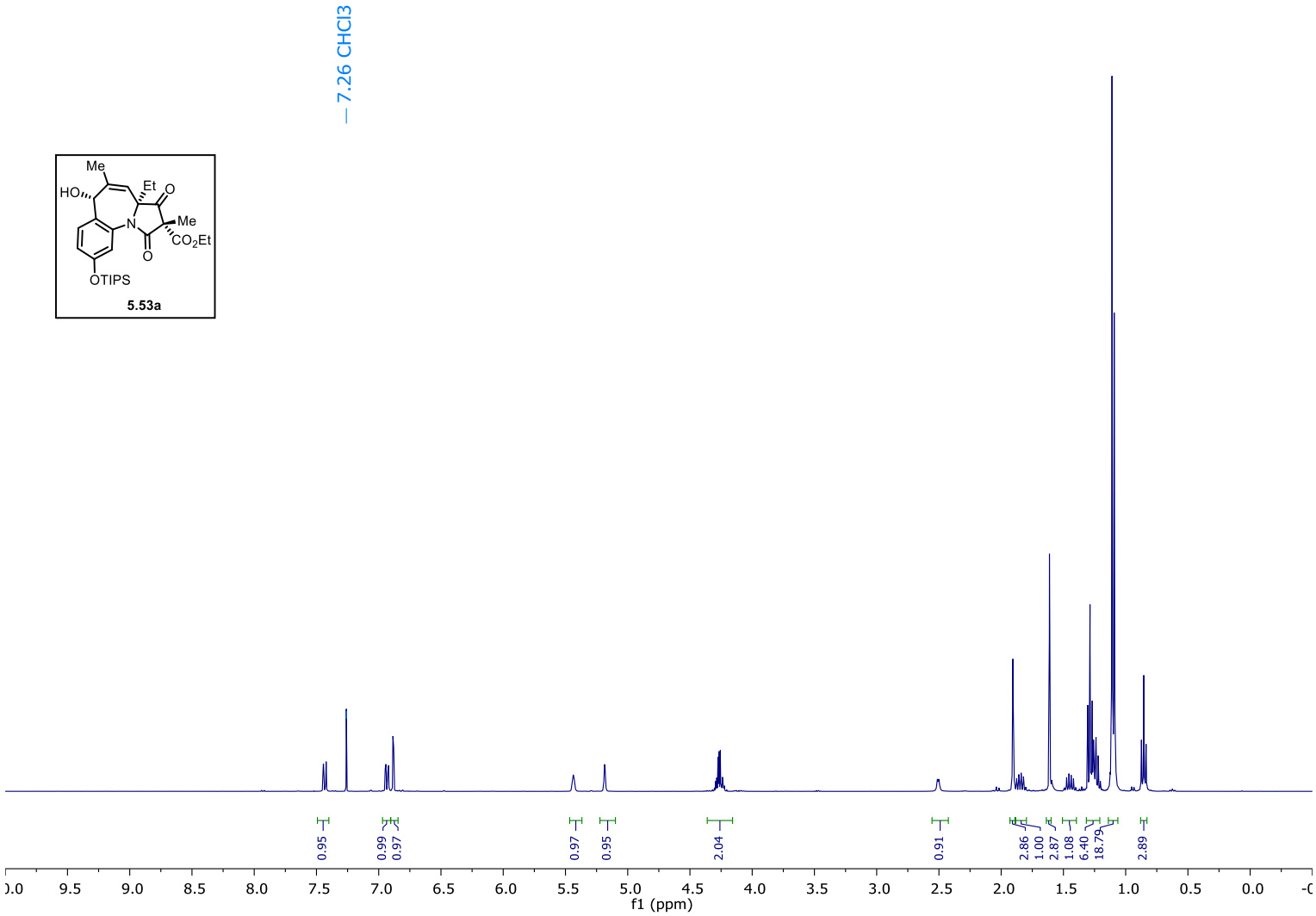


Figure C.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.53a**

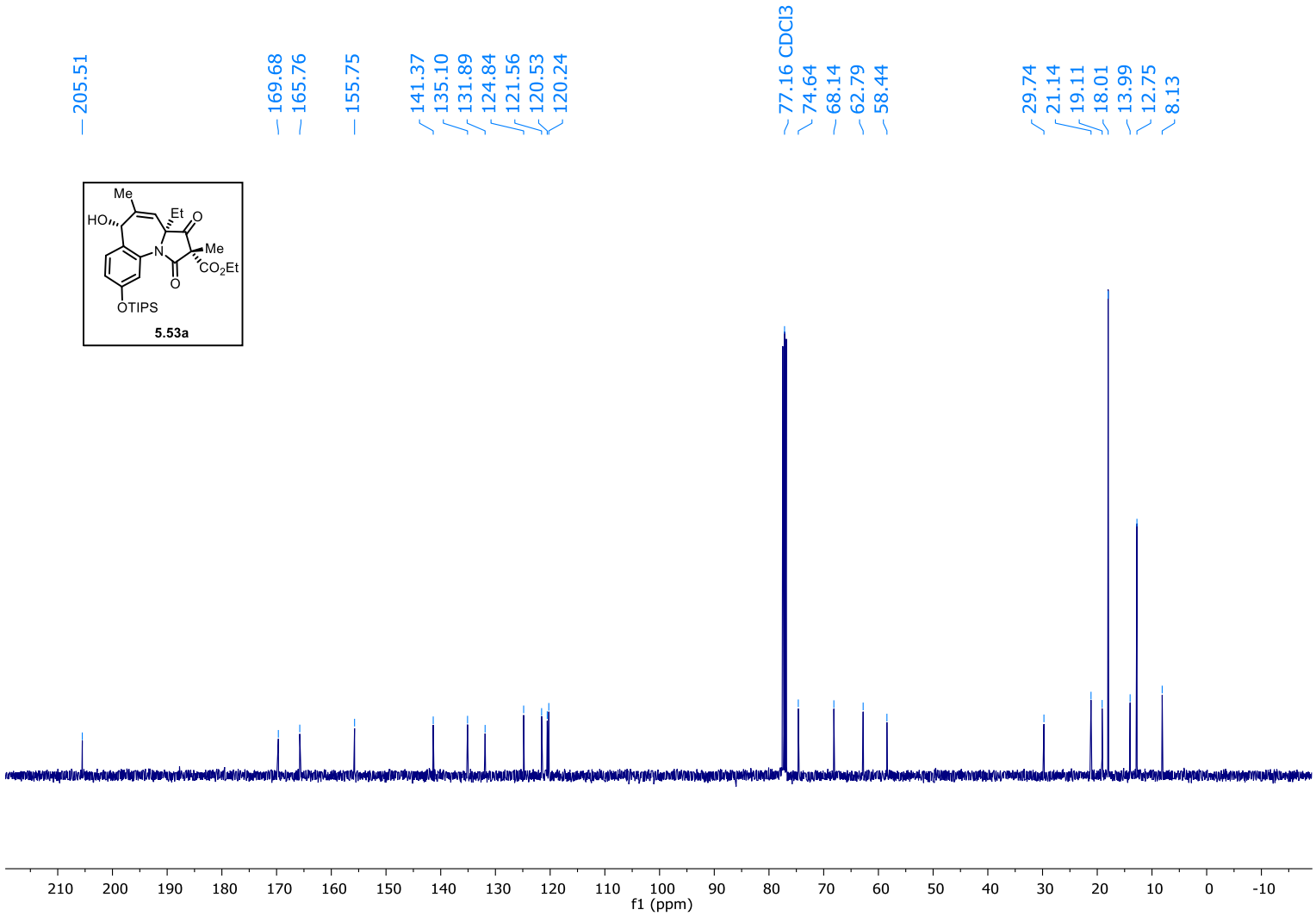


Figure C.2. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.53a**

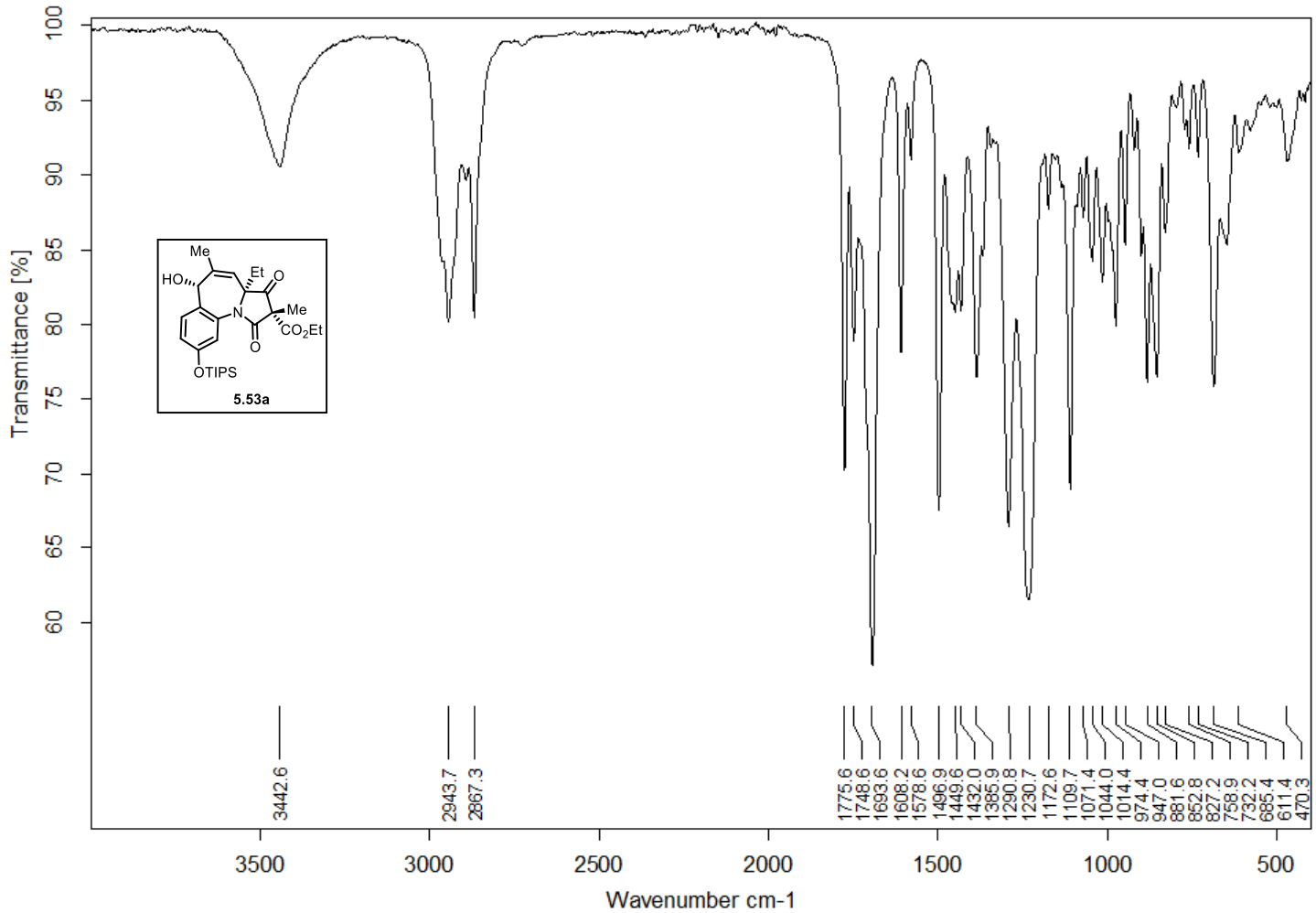


Figure C.3. FTIR spectrum (neat) of compound **5.53a**

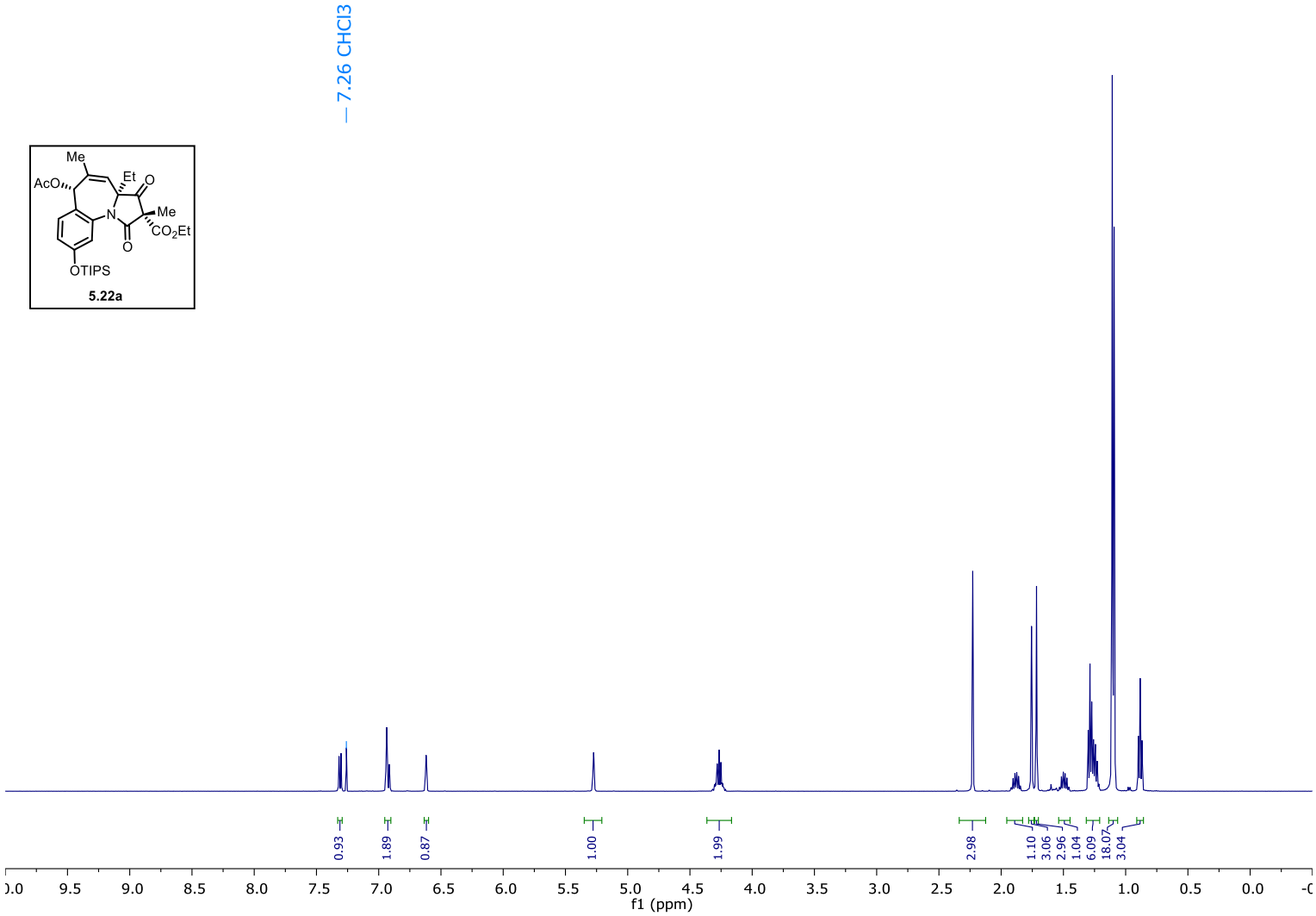


Figure C.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.22a**

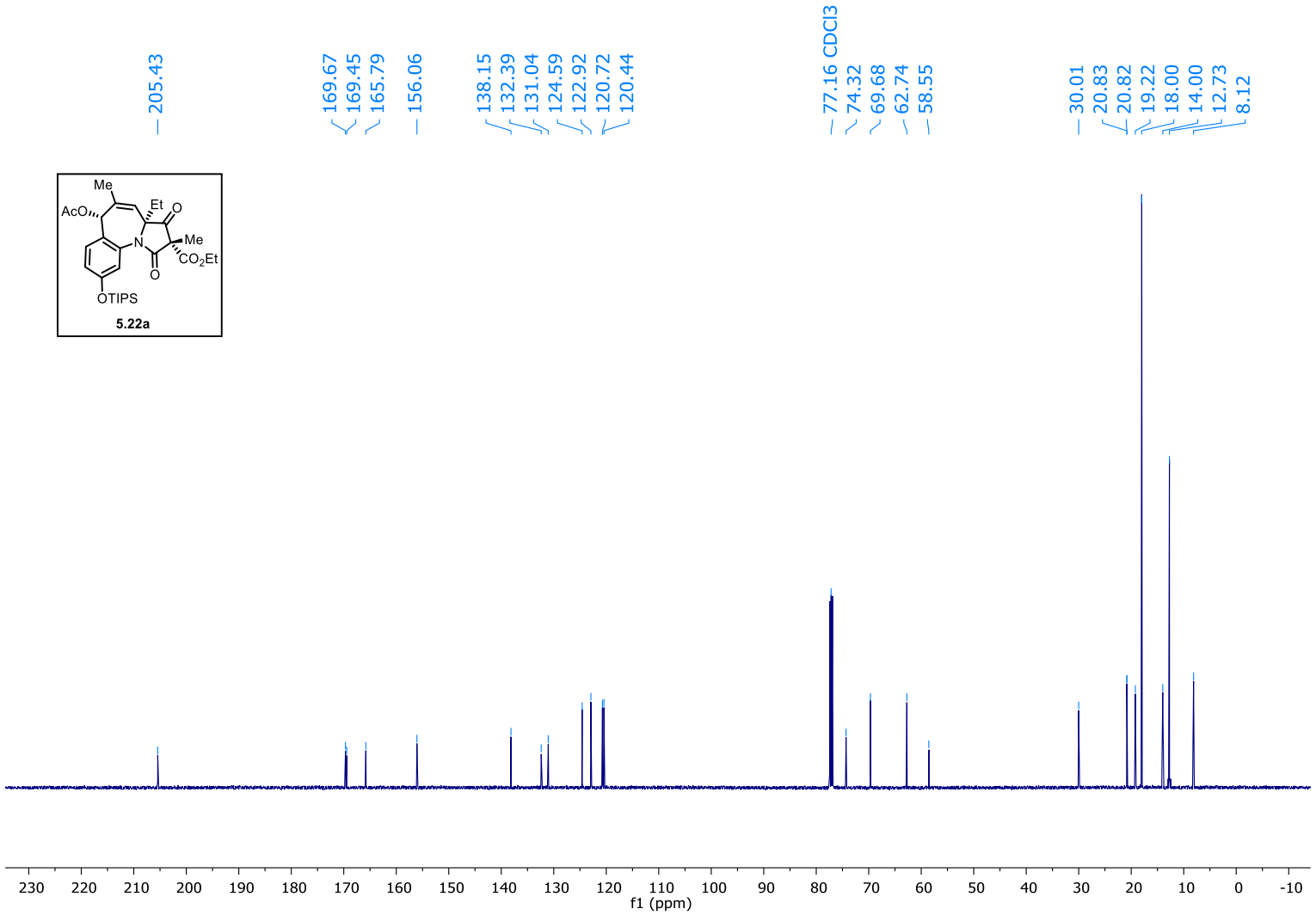


Figure C.5. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **5.22a**

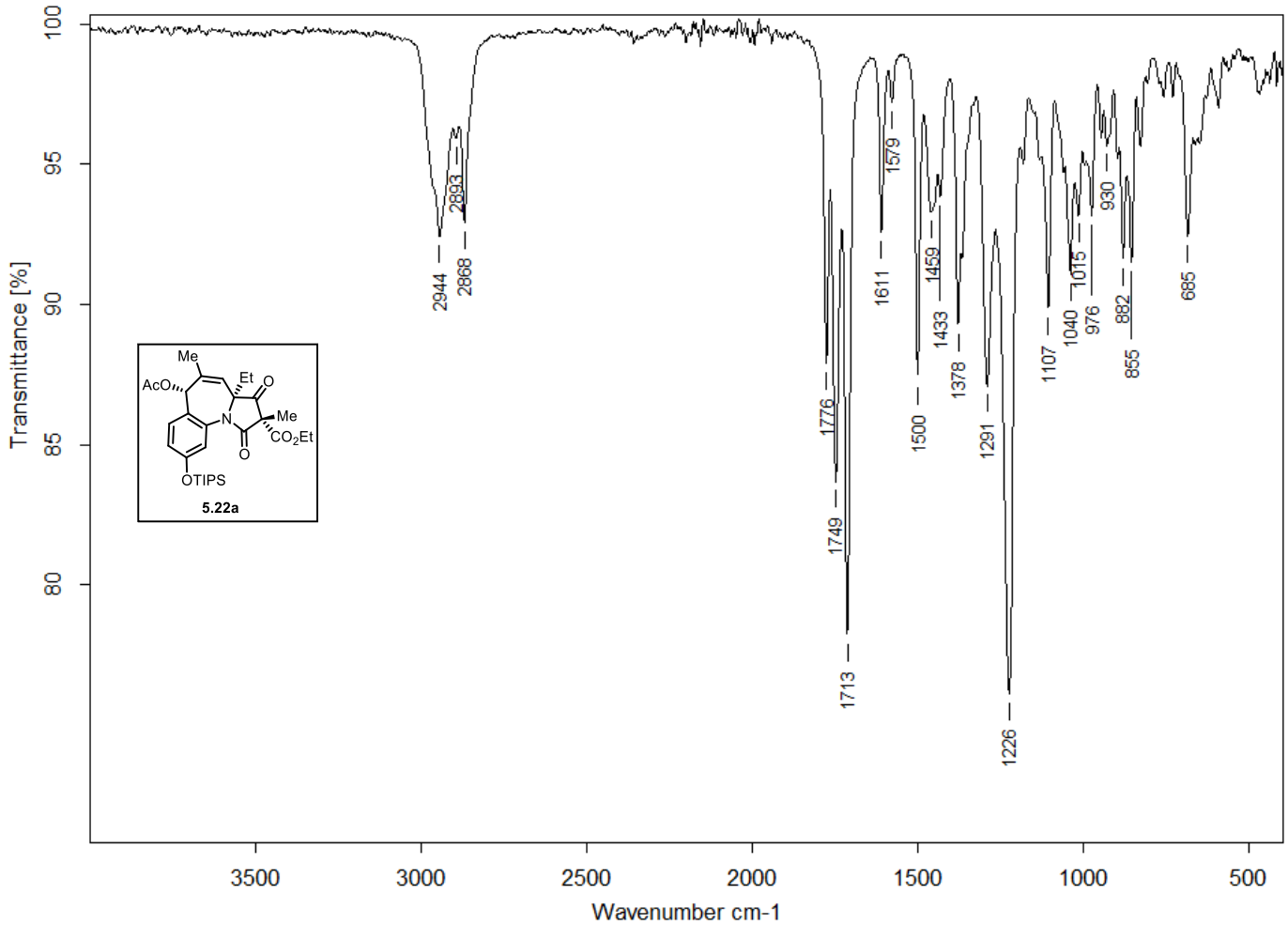


Figure C.6. FTIR spectrum (neat) of compound **5.22a**

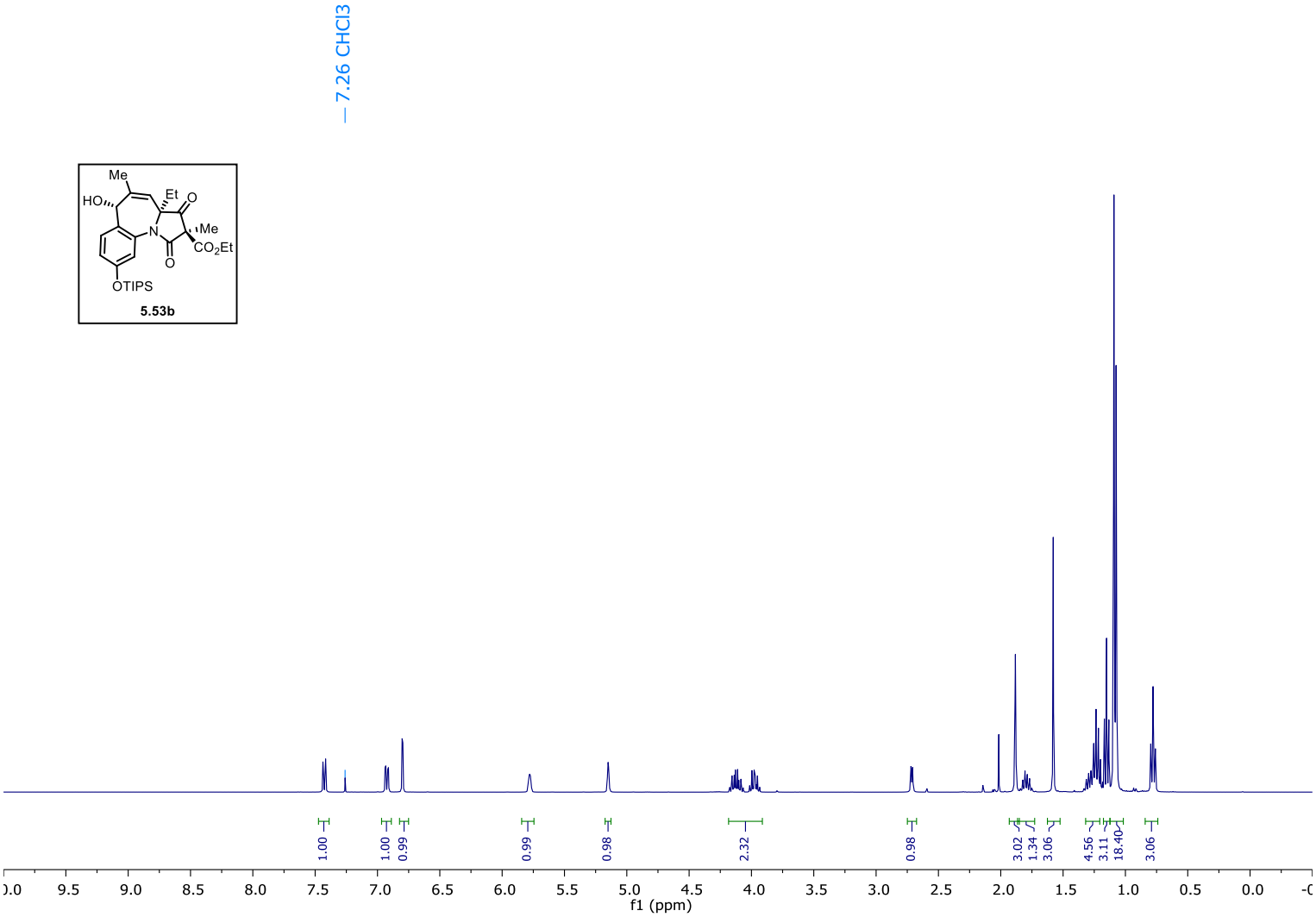


Figure C.7. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.53b**

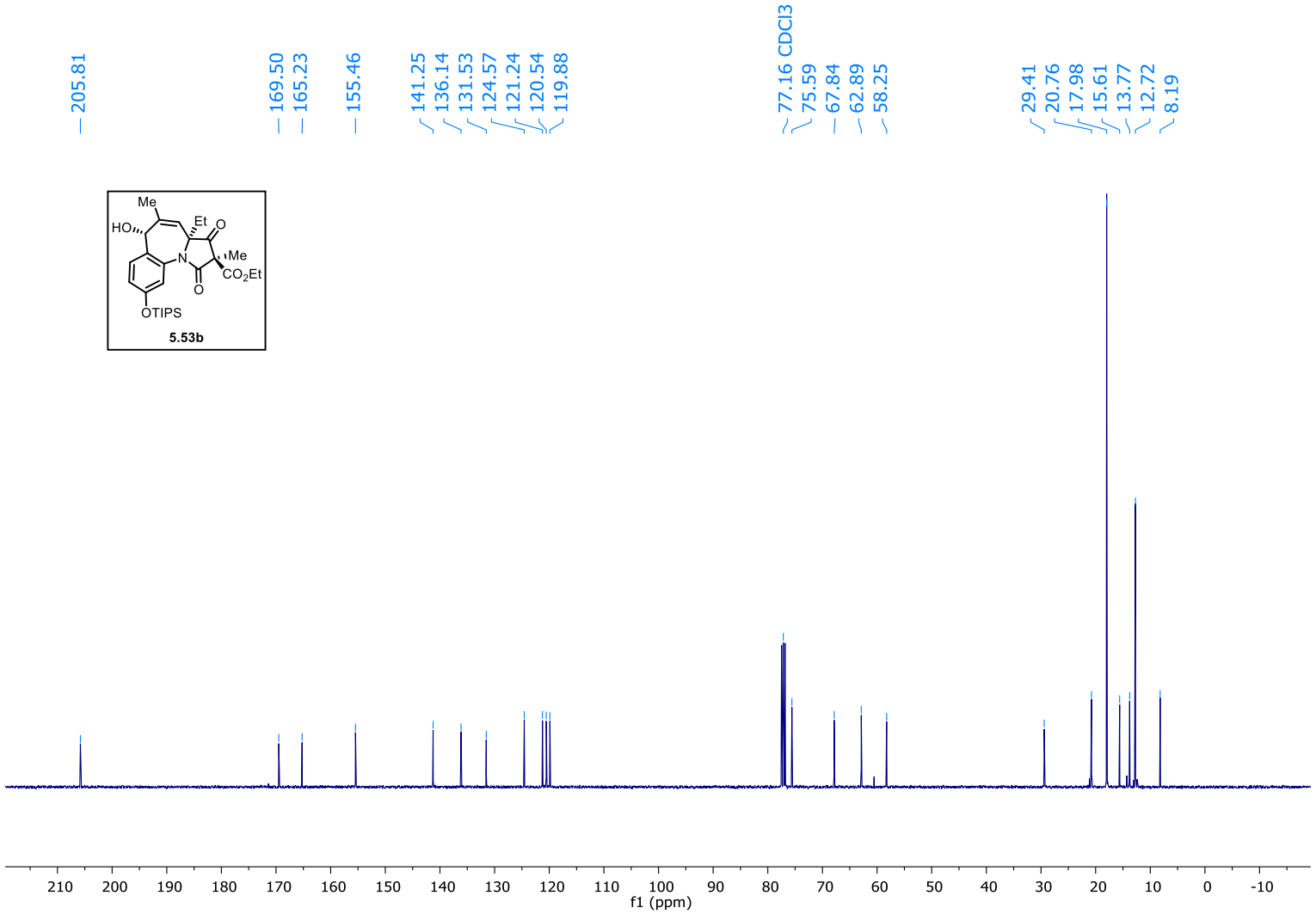


Figure C.8. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.53b**

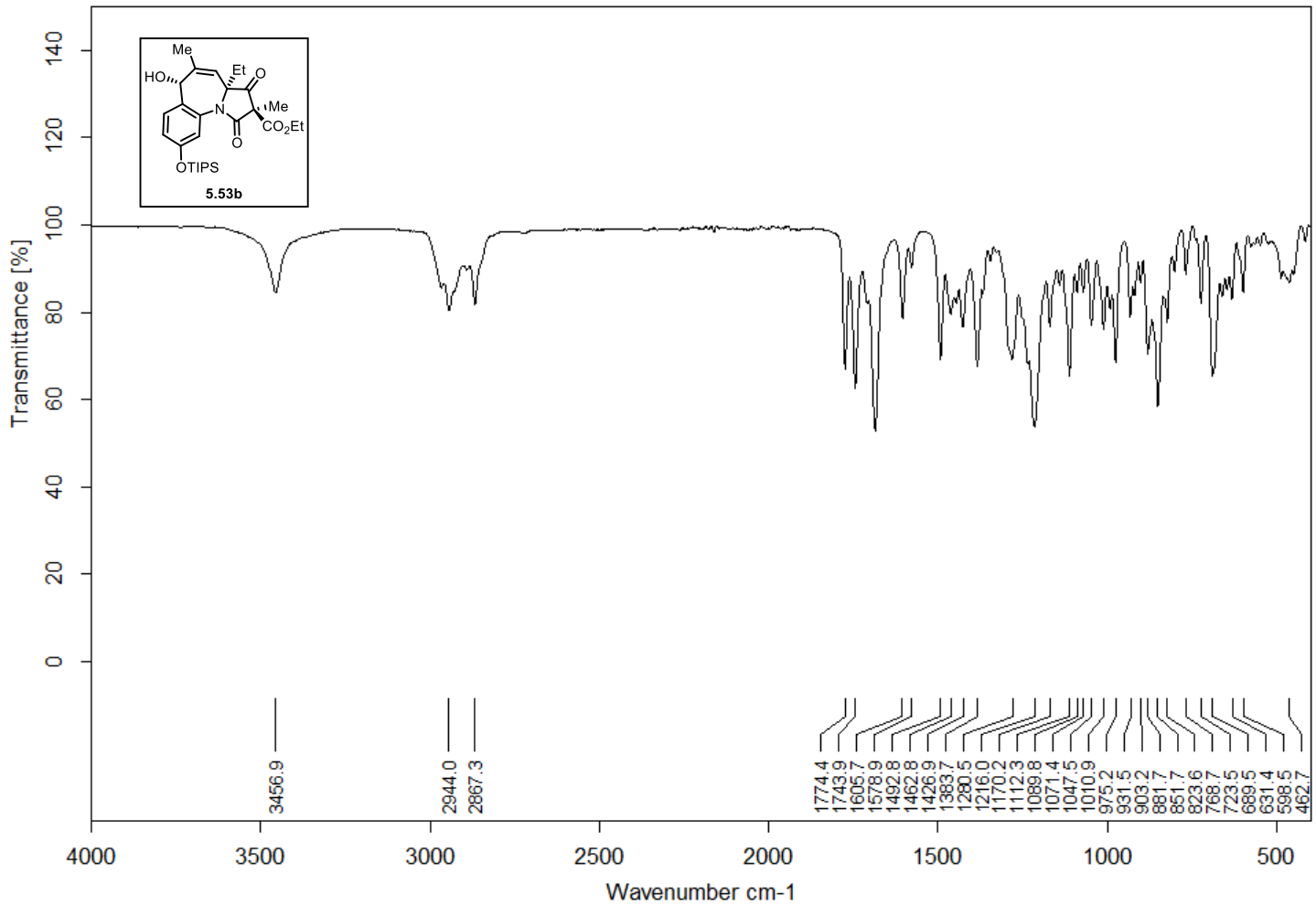


Figure C.9. FTIR spectrum (neat) of compound **5.53b**

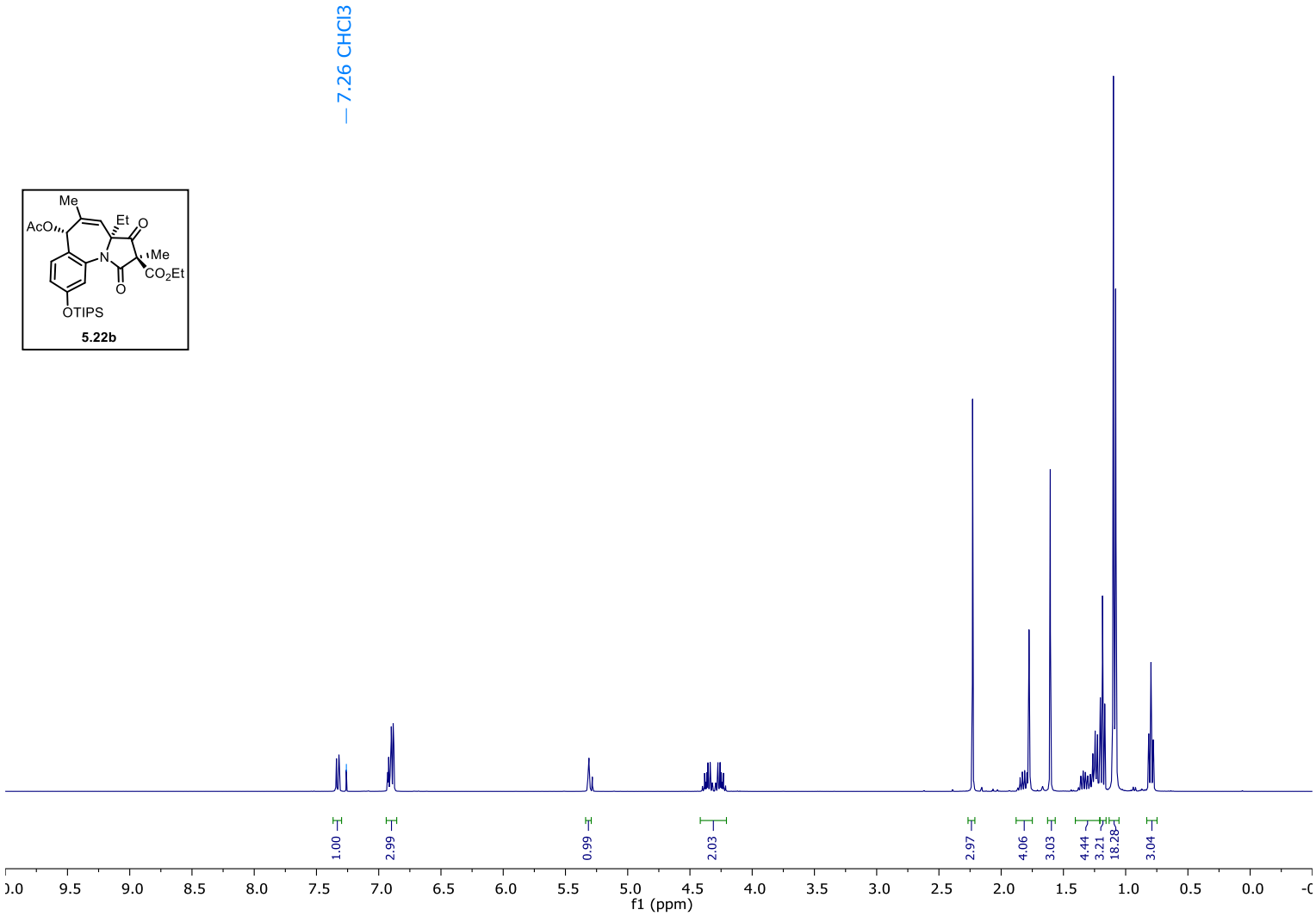


Figure C.10. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.22b**

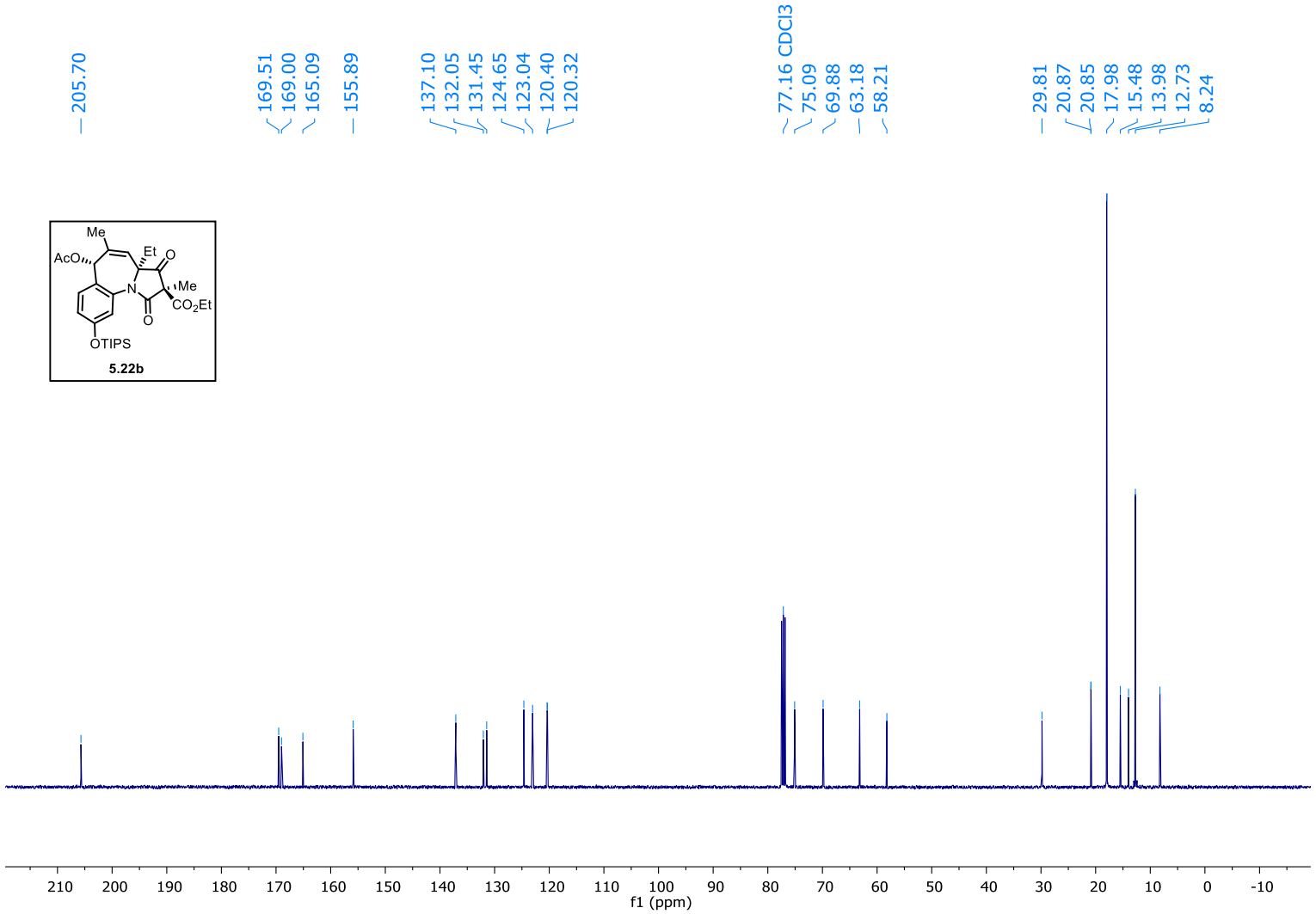


Figure C.11. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.22b**

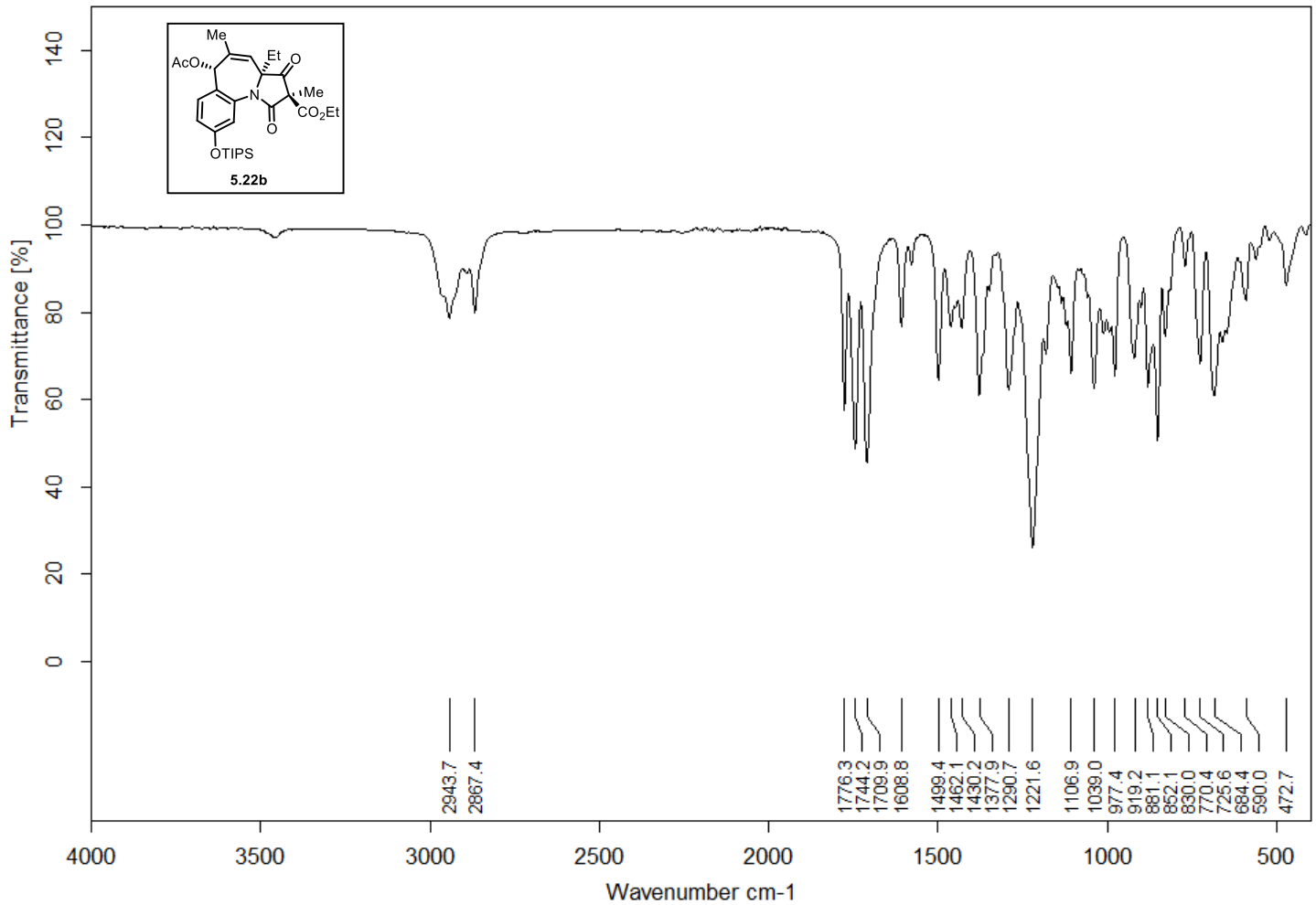


Figure C.12. FTIR spectrum (neat) of compound **5.22b**

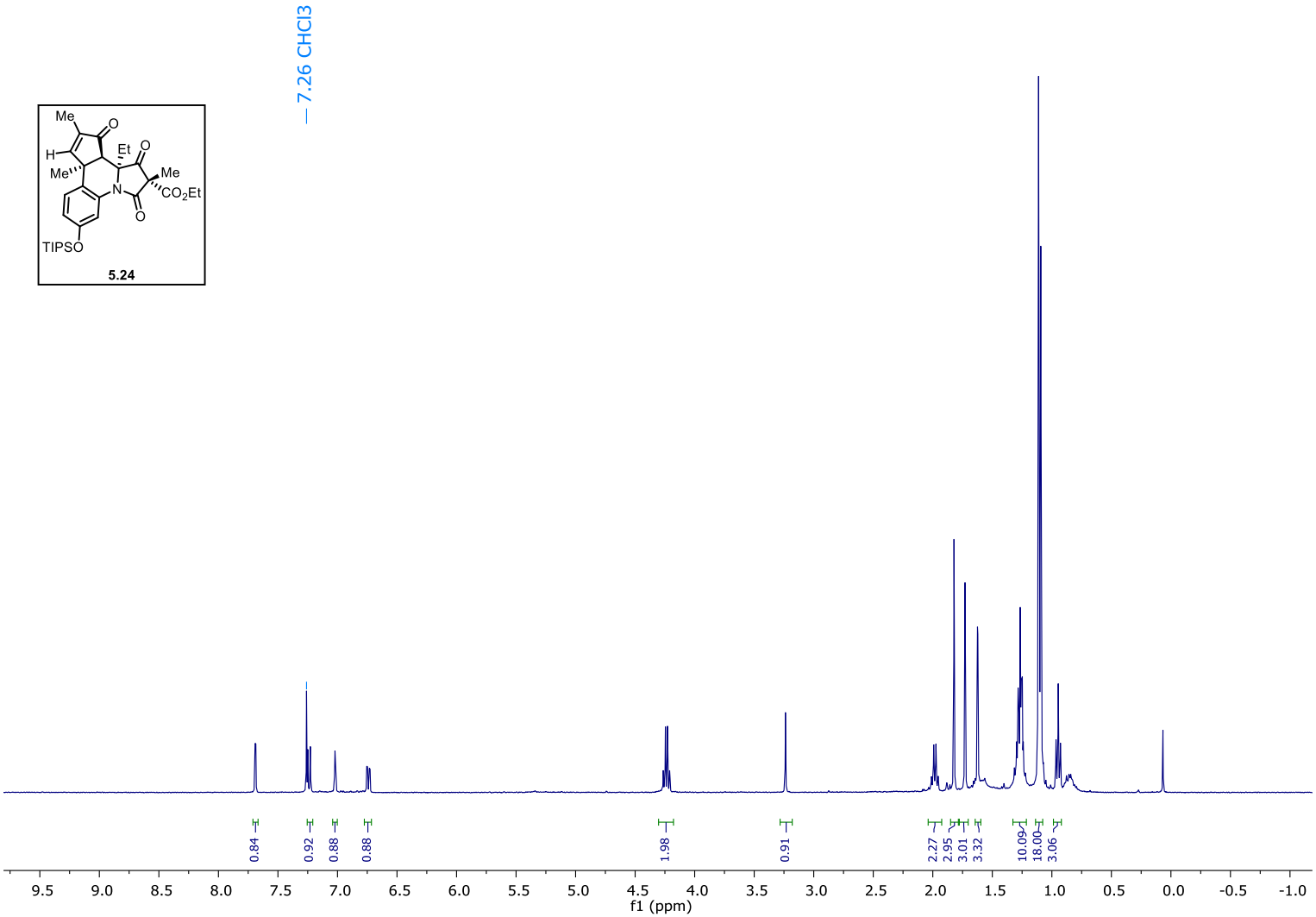


Figure C.13. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.24**

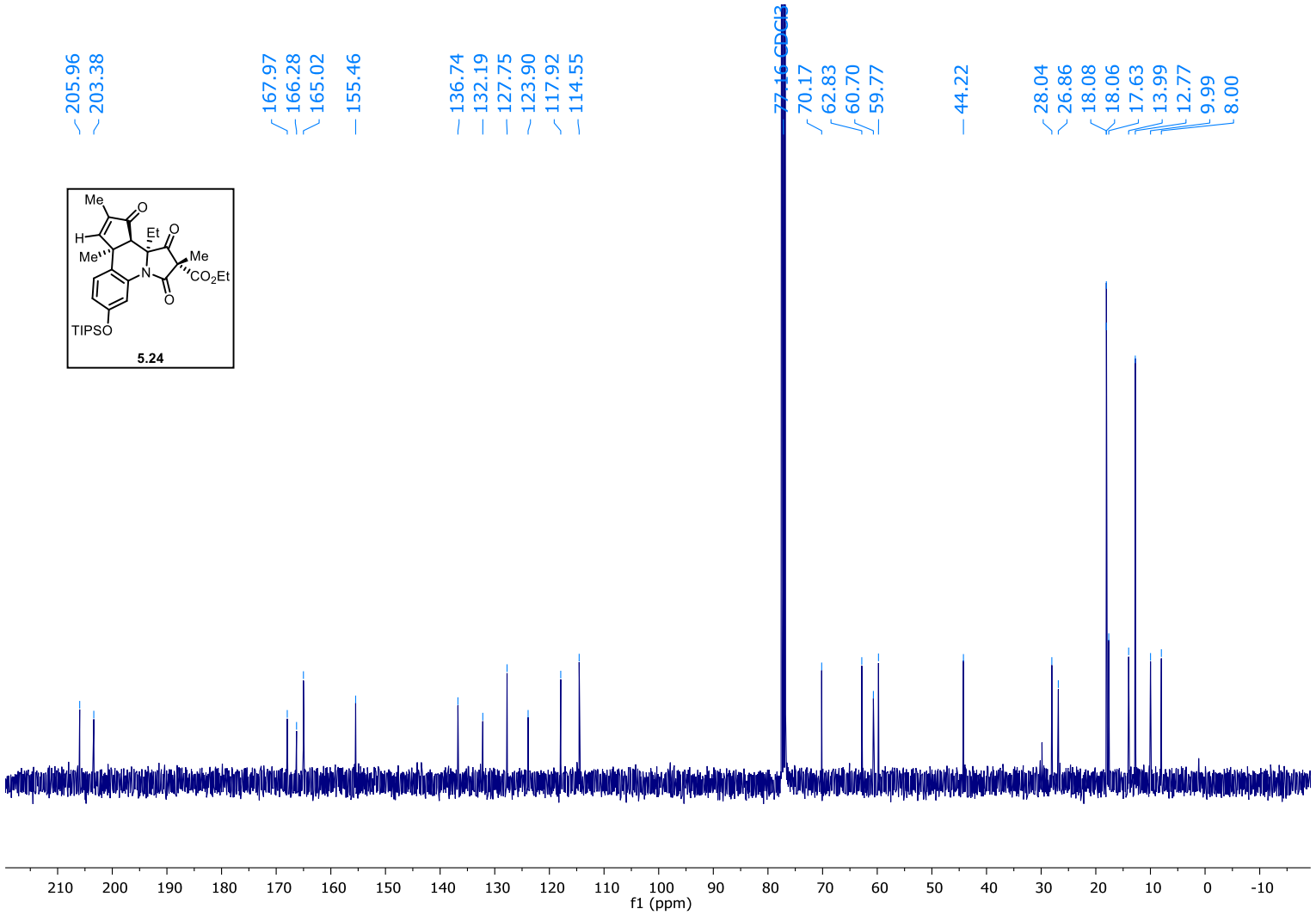


Figure C.14. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.24**

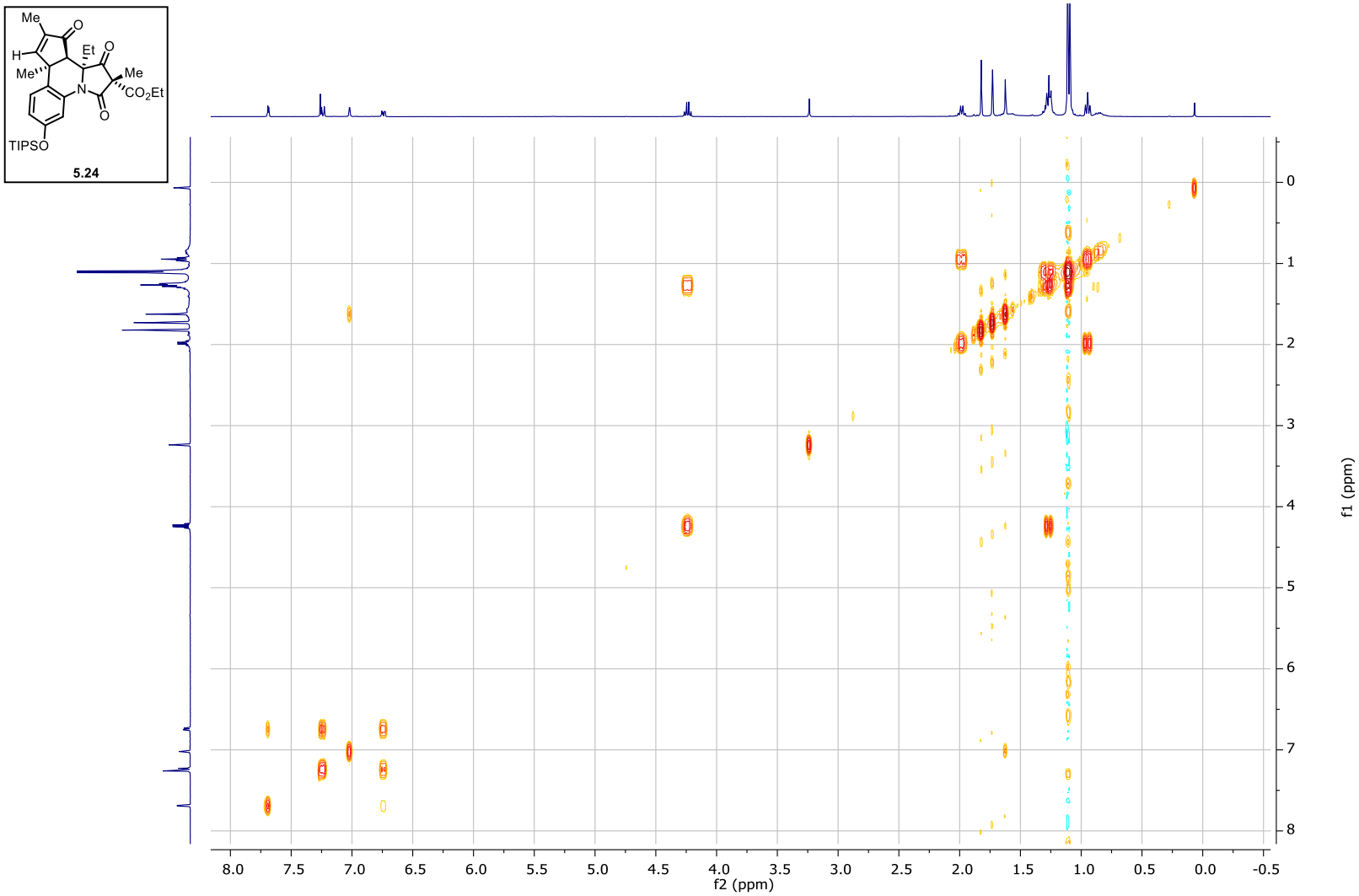


Figure C.15. COSY of compound **5.24**

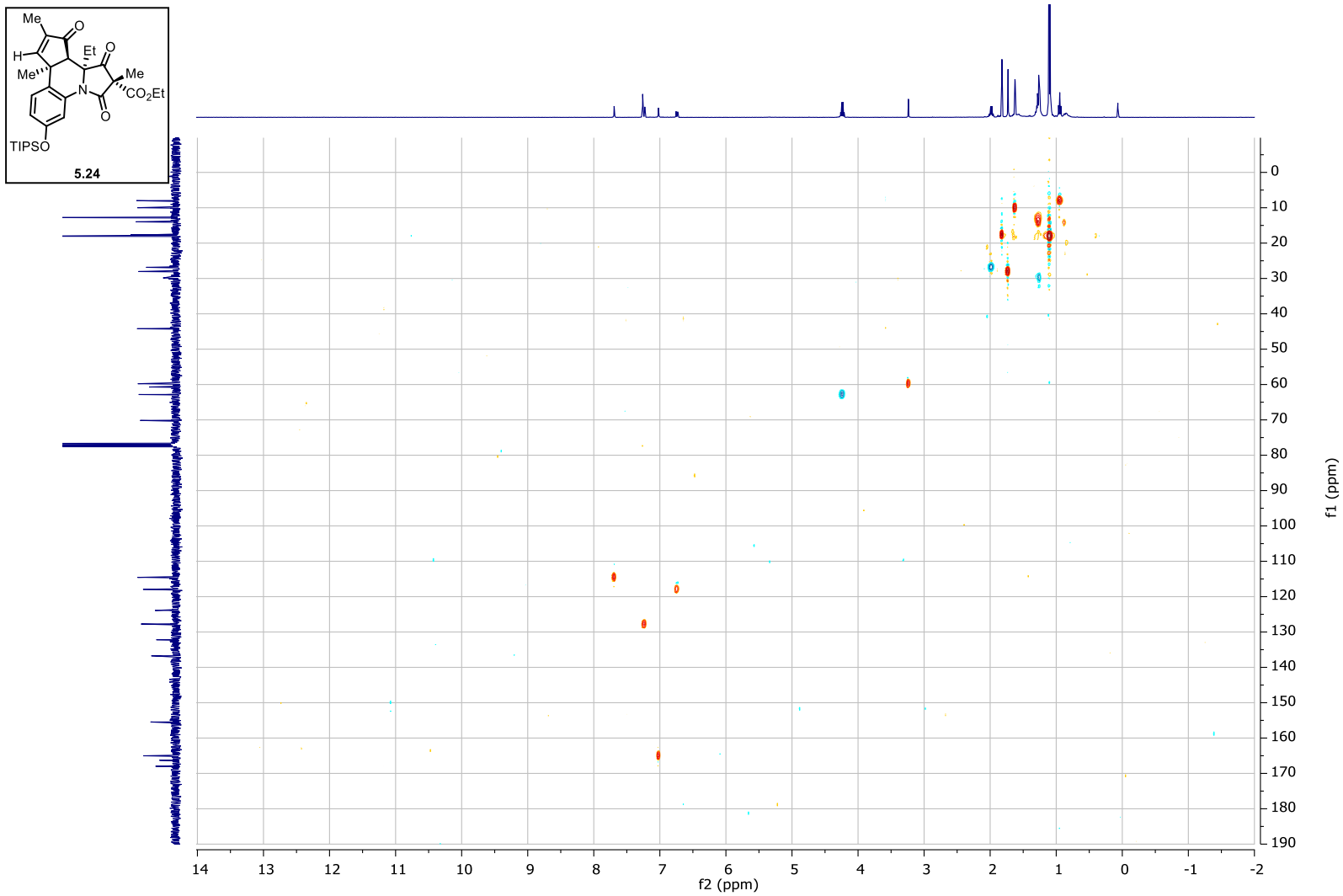


Figure C.16. HSQC of compound **5.24**

Figure C.17. HMBC of compound **5.24**

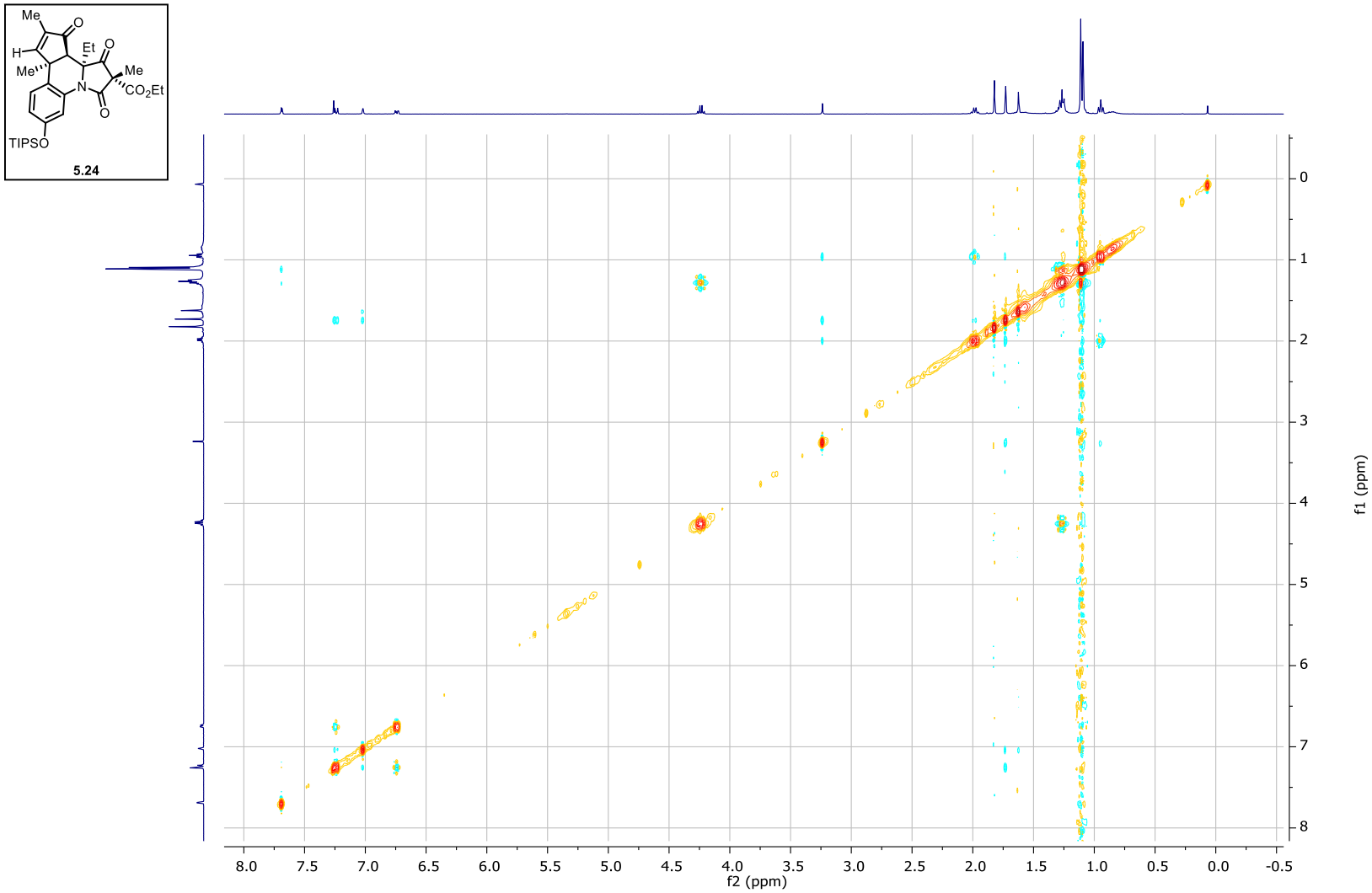


Figure C.18. NOESY of compound **5.24**

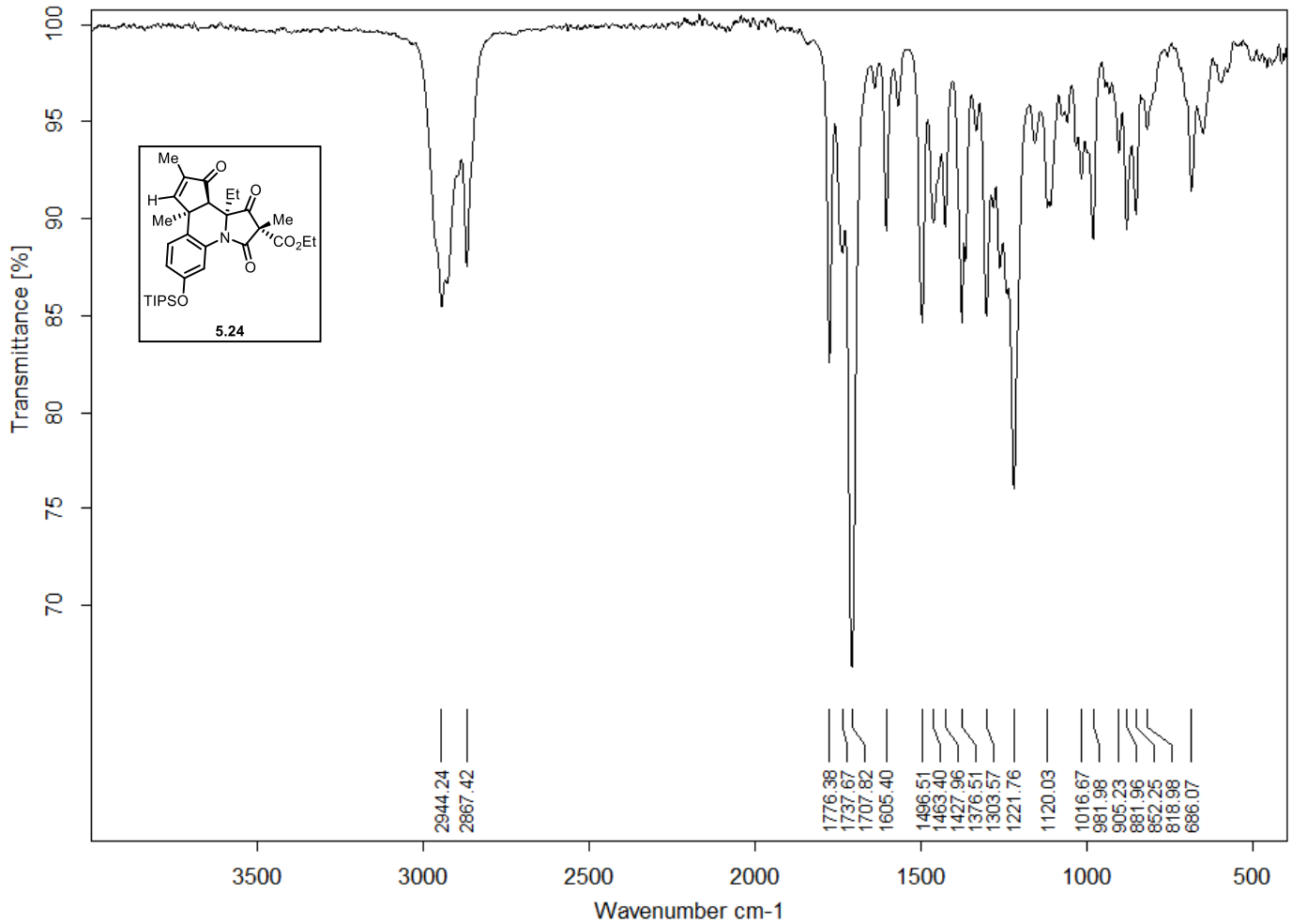


Figure C.19. FTIR spectrum (neat) of compound **5.24**

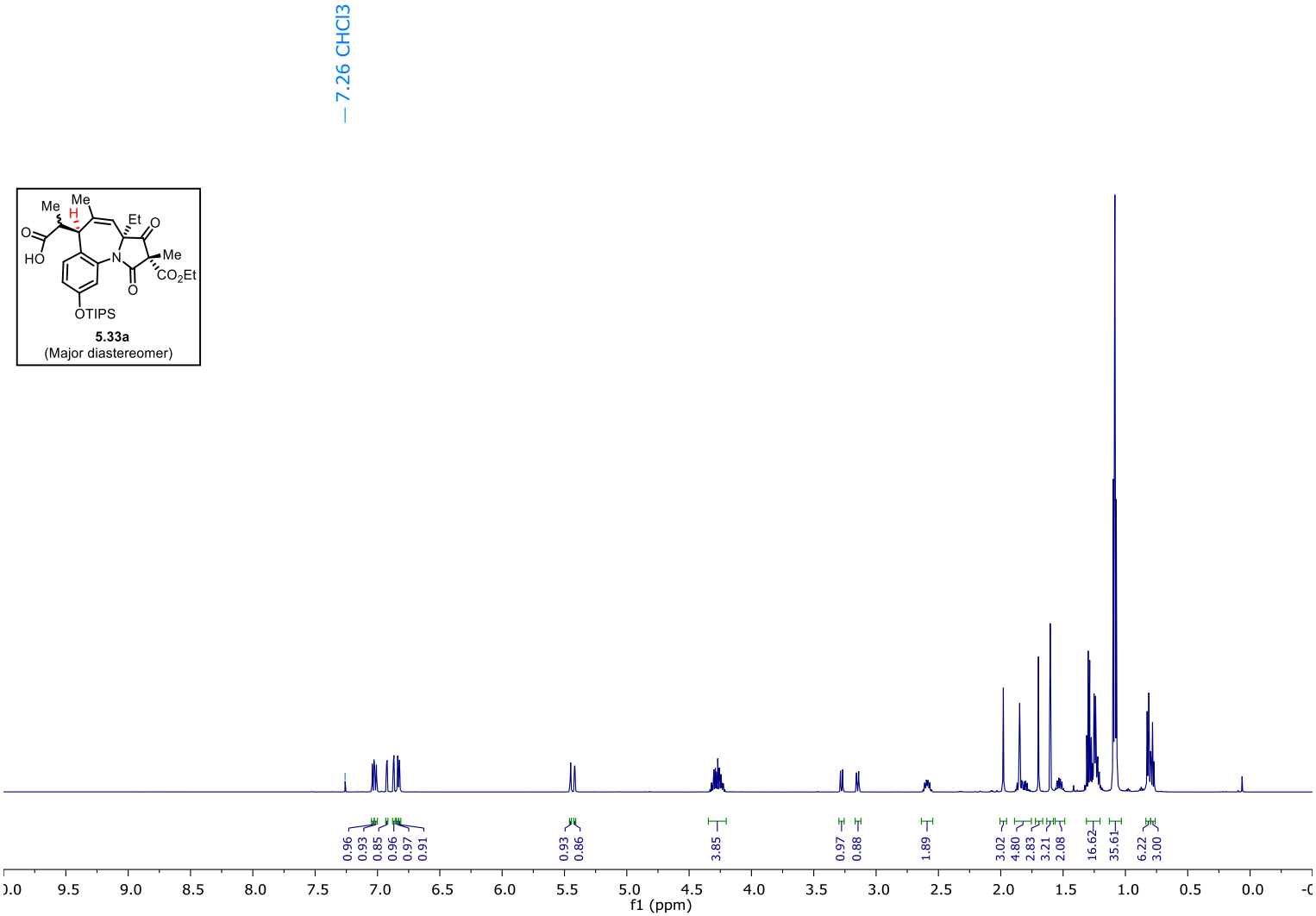


Figure C.20. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **5.33a**

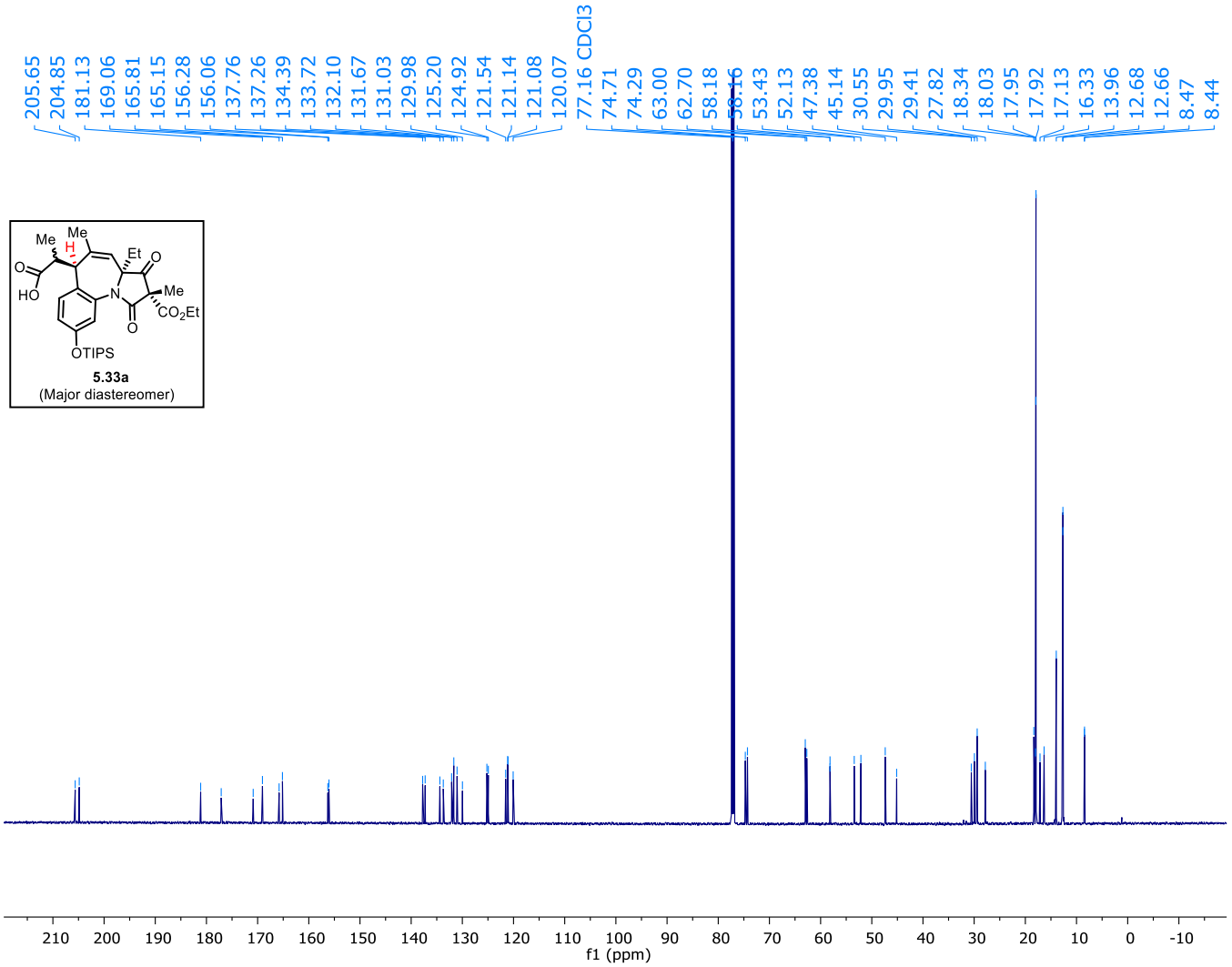


Figure C.21. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.33a**

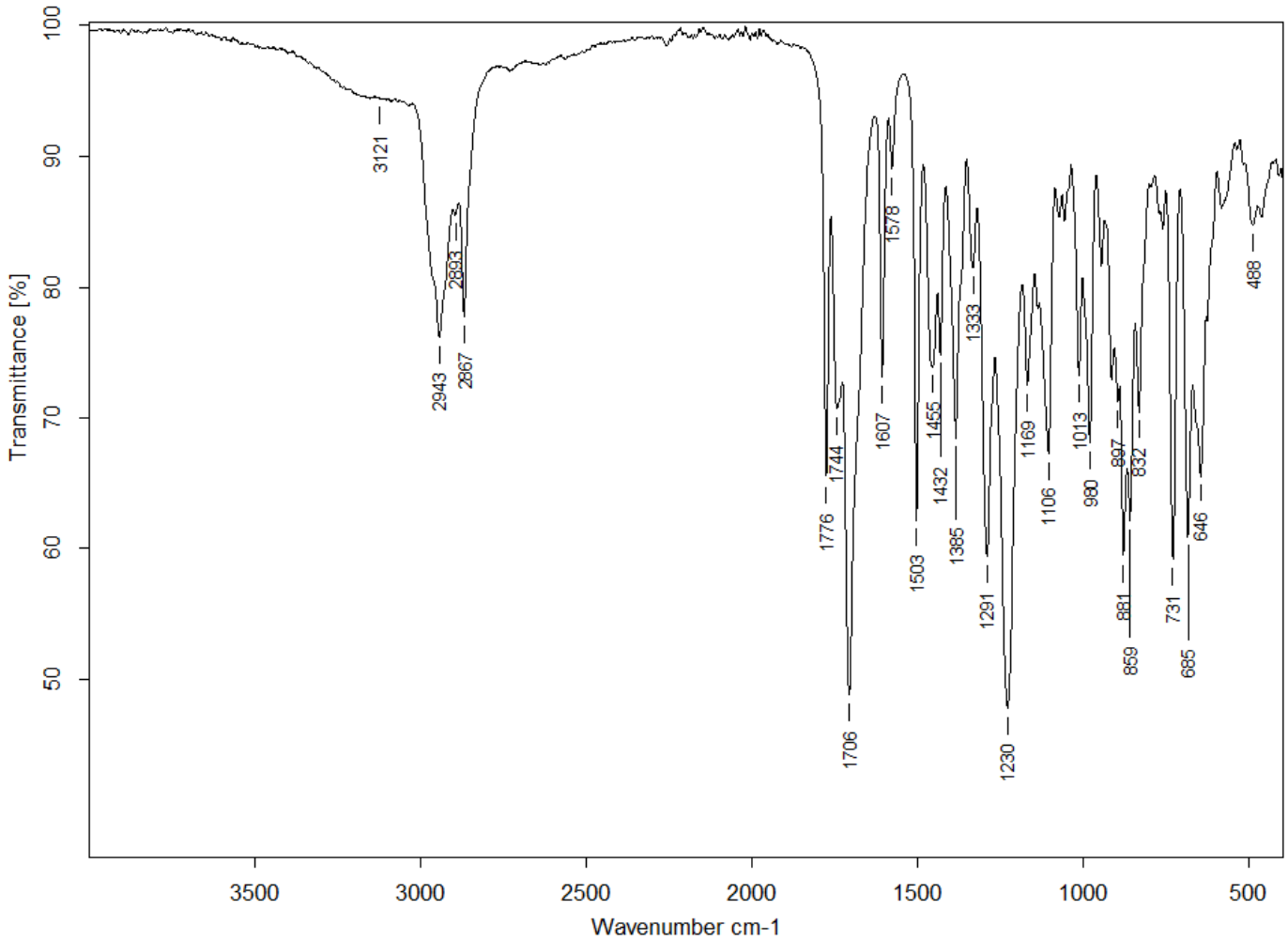


Figure C.22. FTIR spectrum (neat) of compound **5.33a**

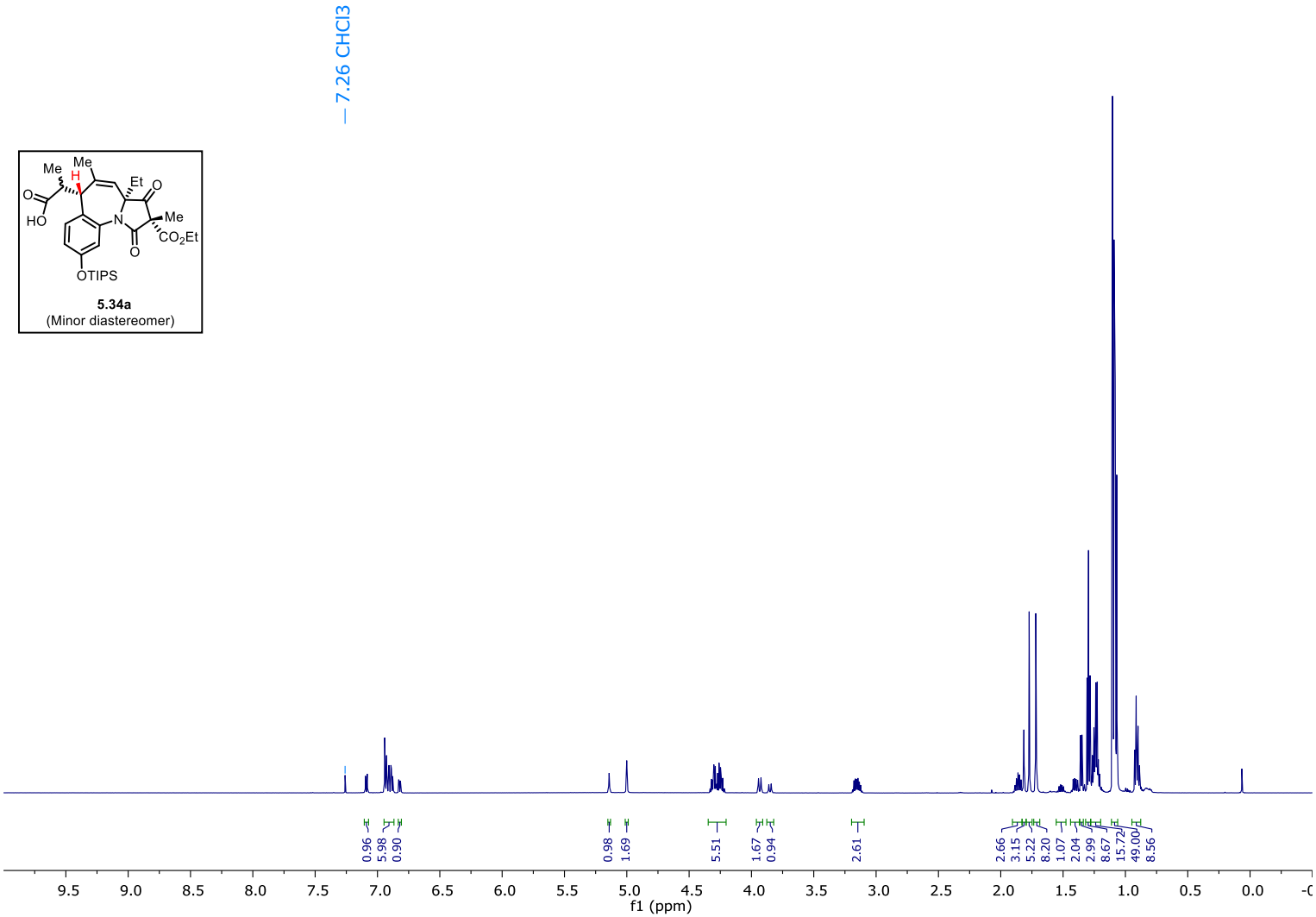


Figure C.23. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **5.34a**

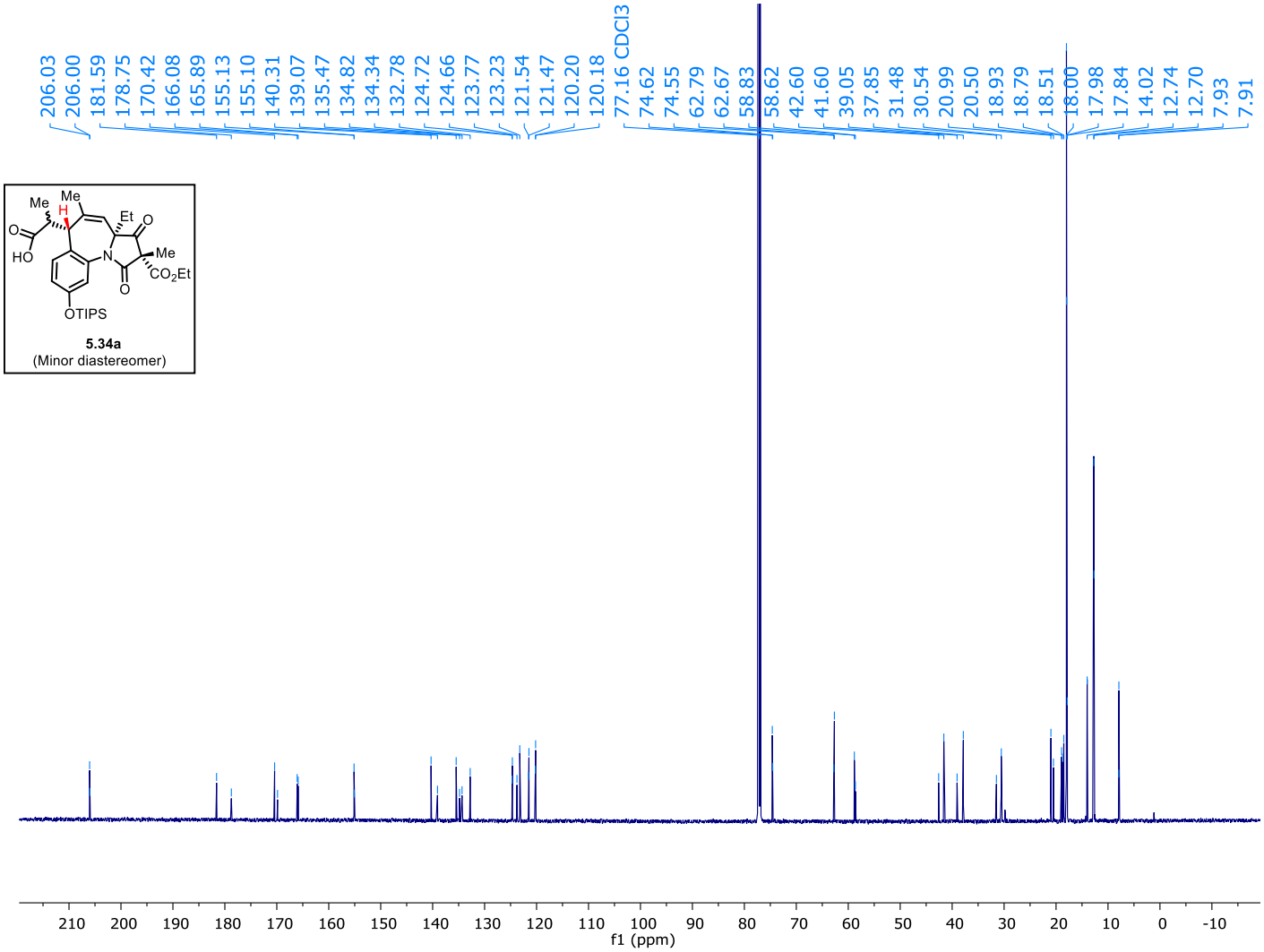


Figure C.24. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.34a**

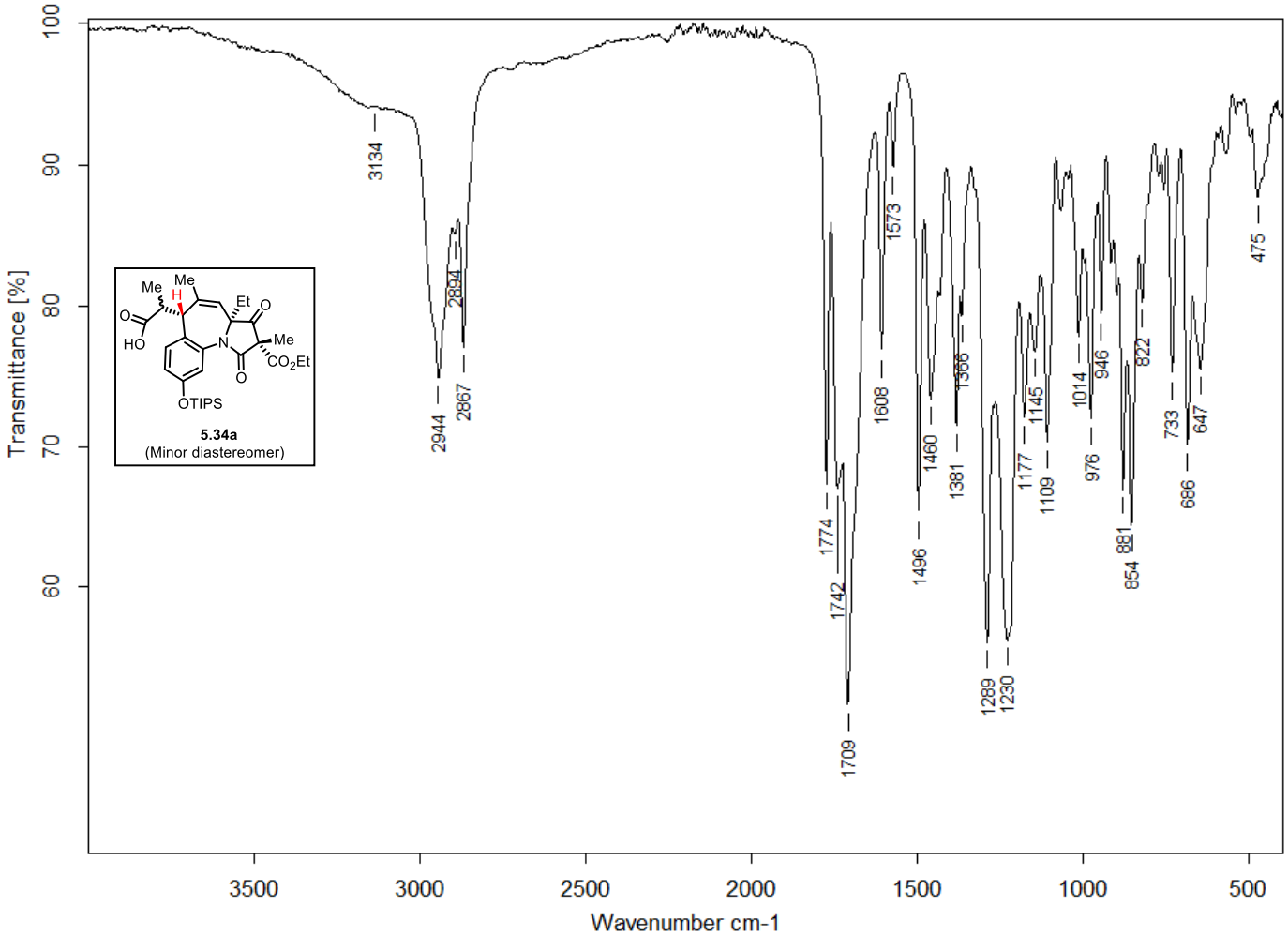


Figure C.25. FTIR spectrum (neat) of compound **5.34a**

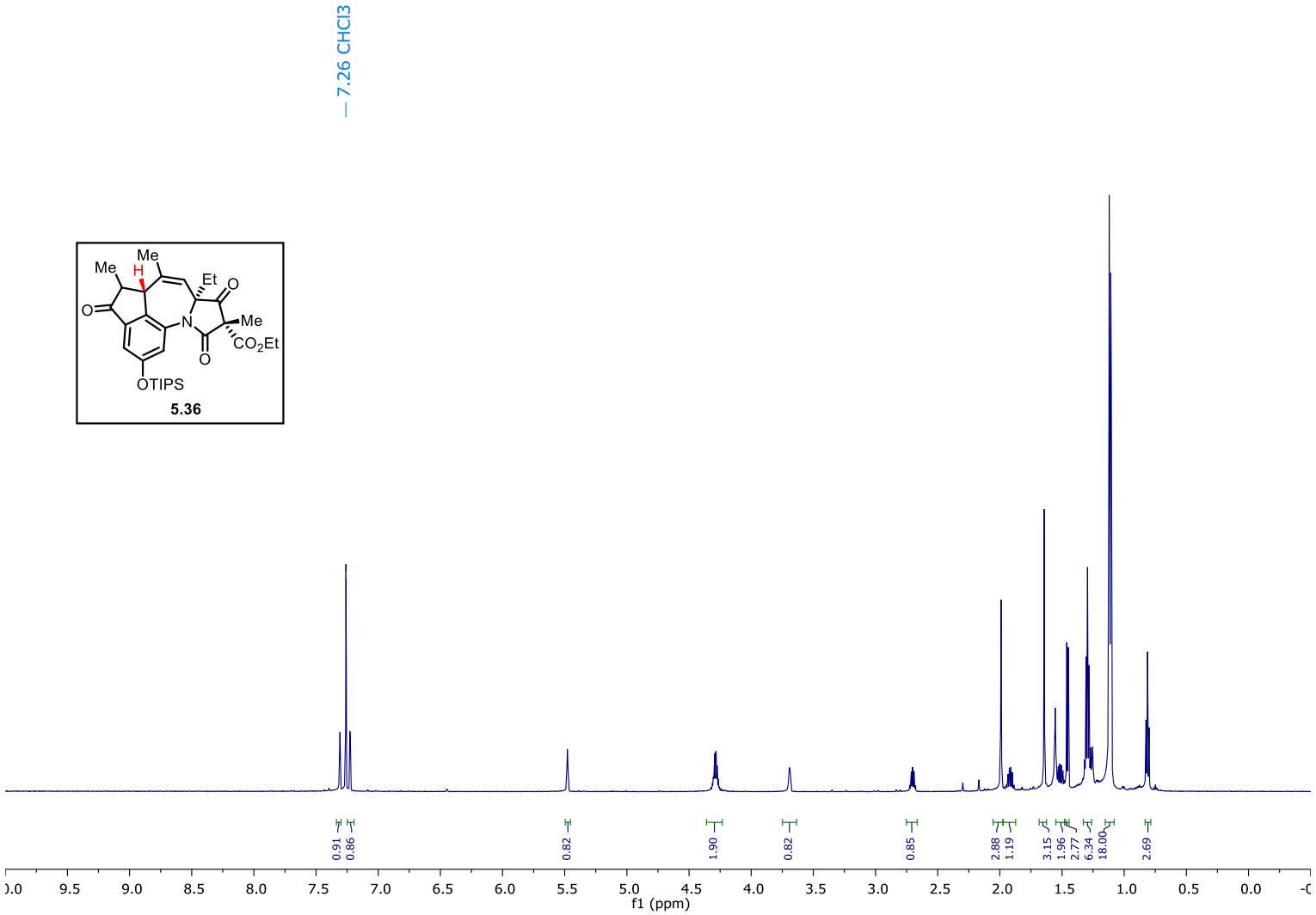


Figure C.26. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **5.36**

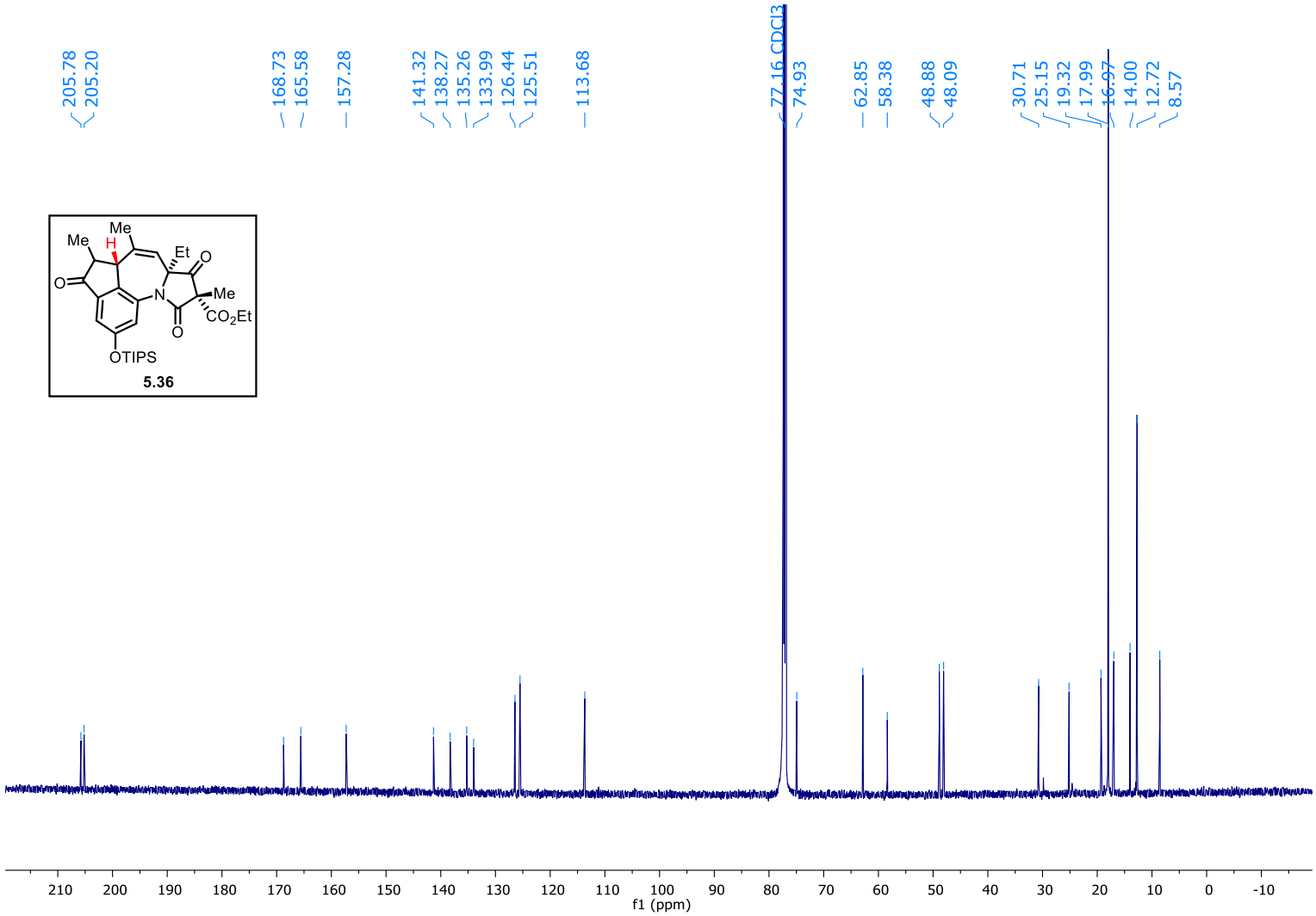


Figure C.27. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.36**

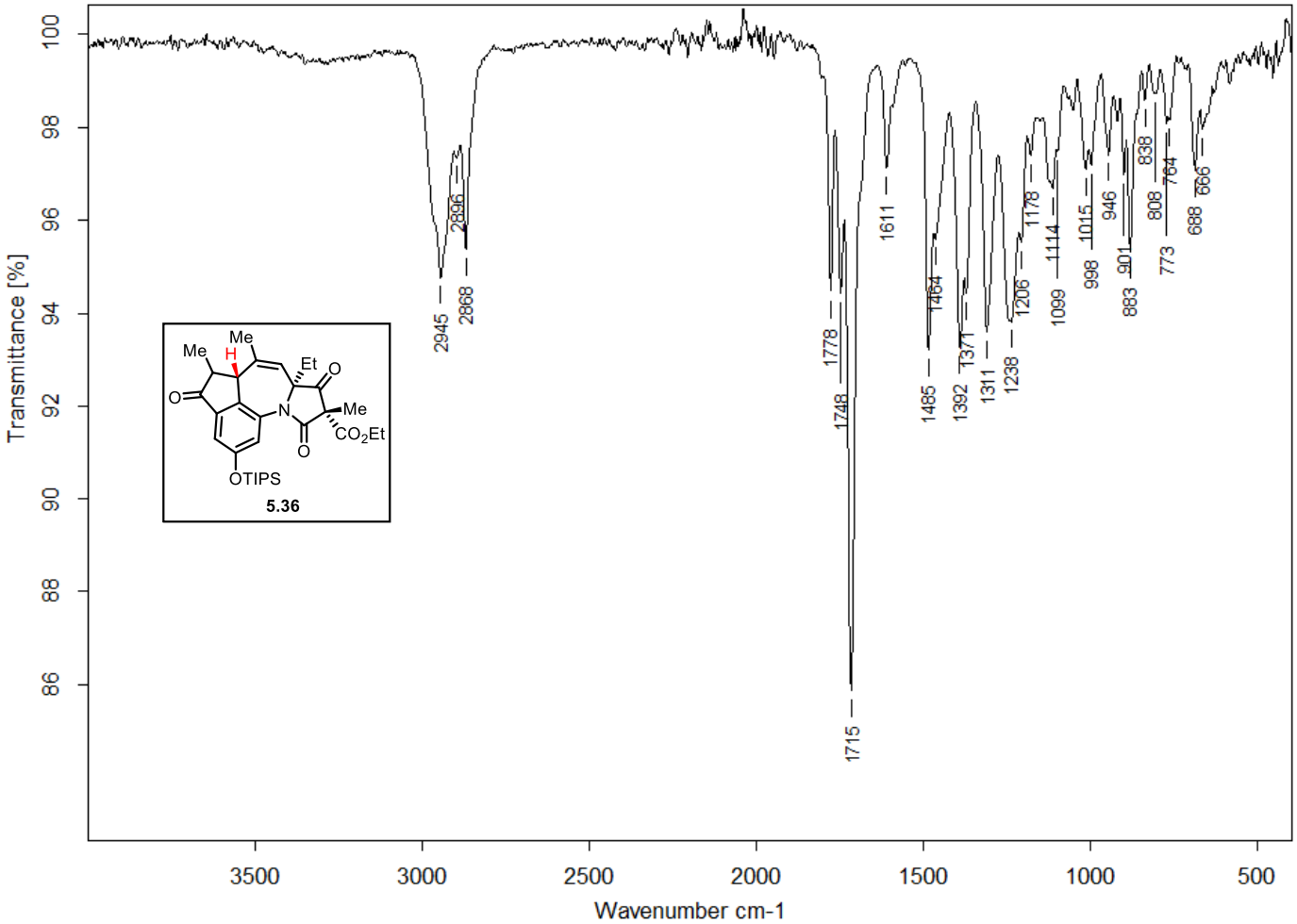


Figure C.28. FTIR spectrum (neat) of compound **5.36**

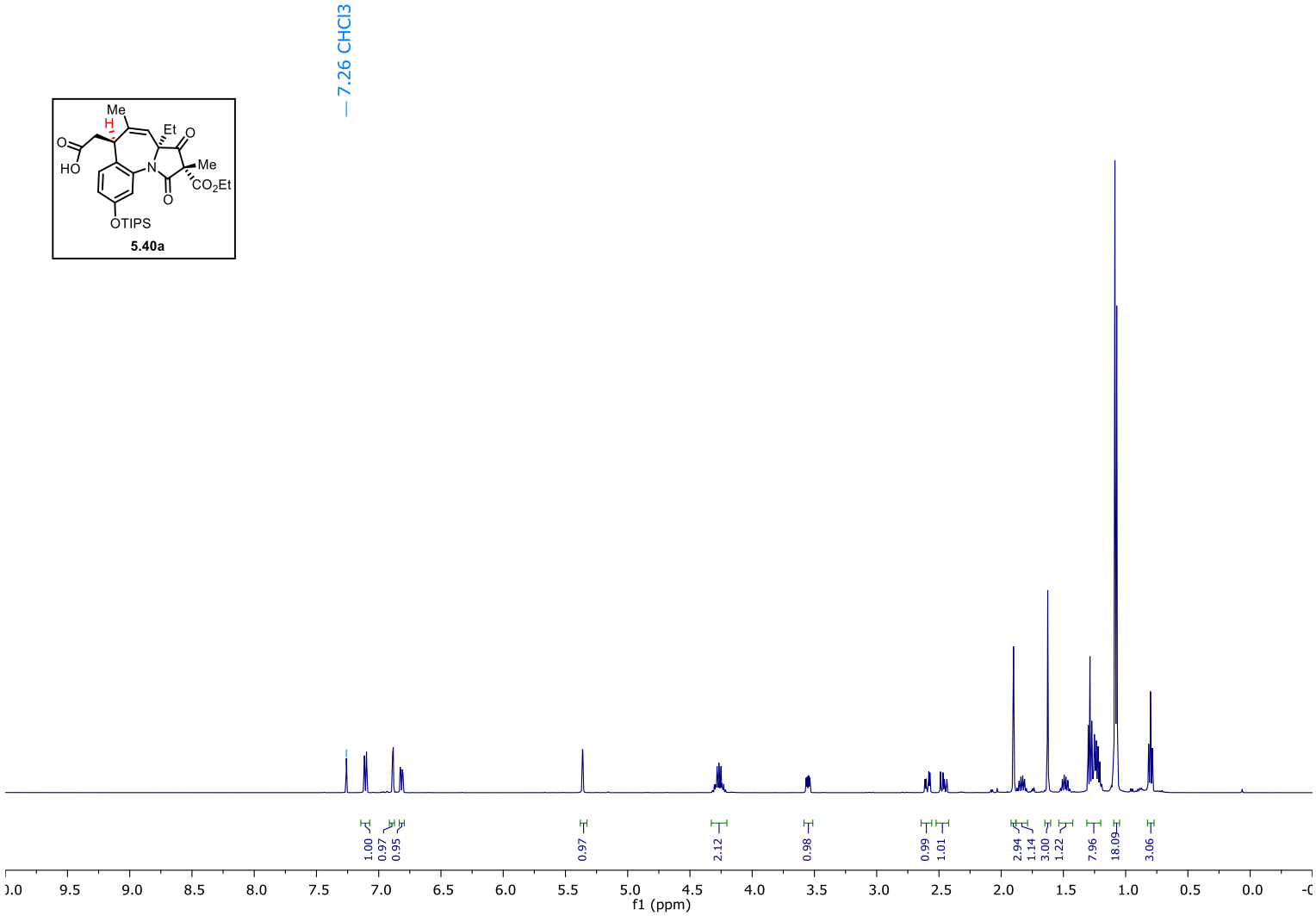


Figure C.29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.40a**

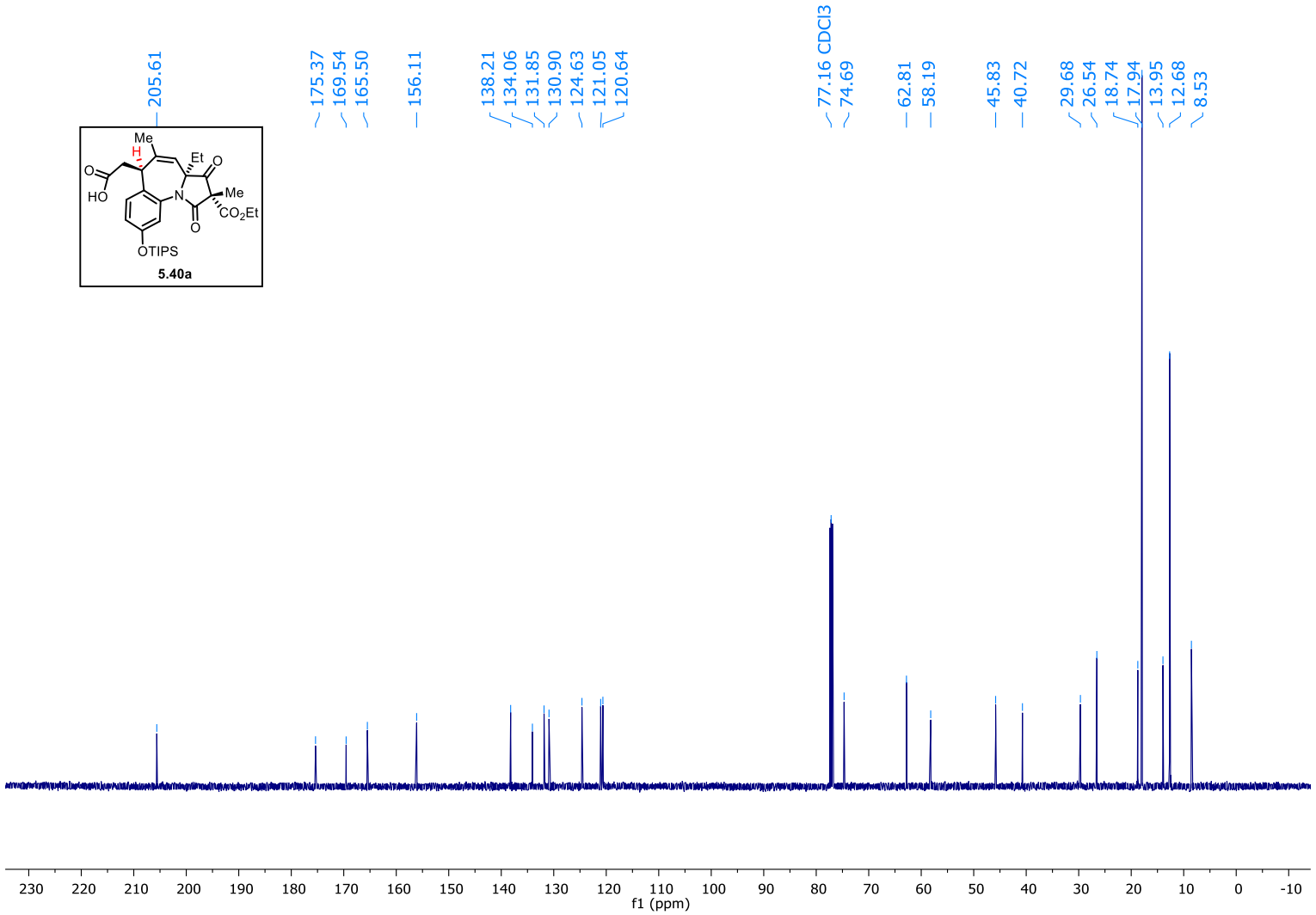


Figure C.30. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **5.40a**

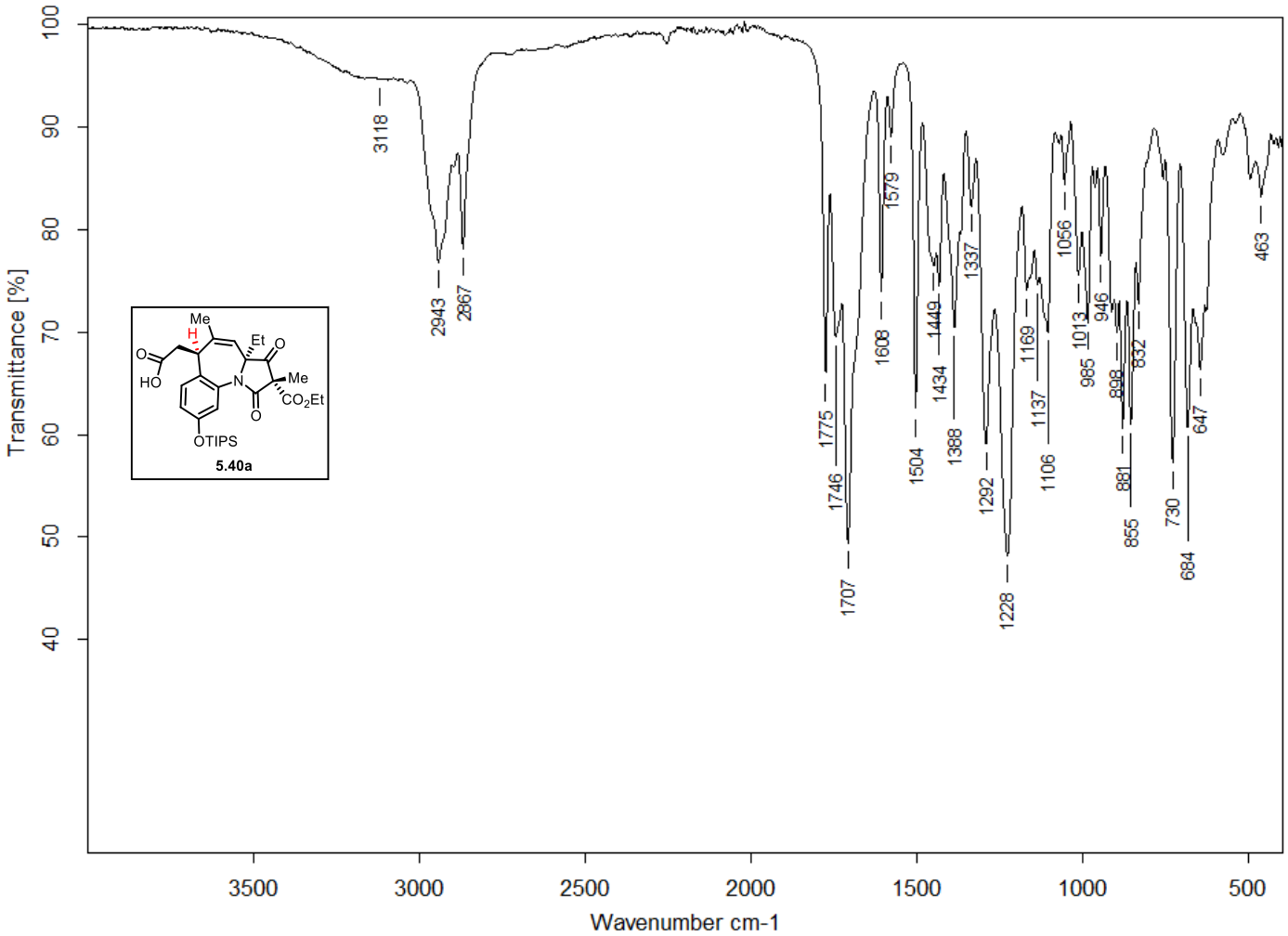


Figure C.31. FTIR spectrum (neat) of compound **5.40a**

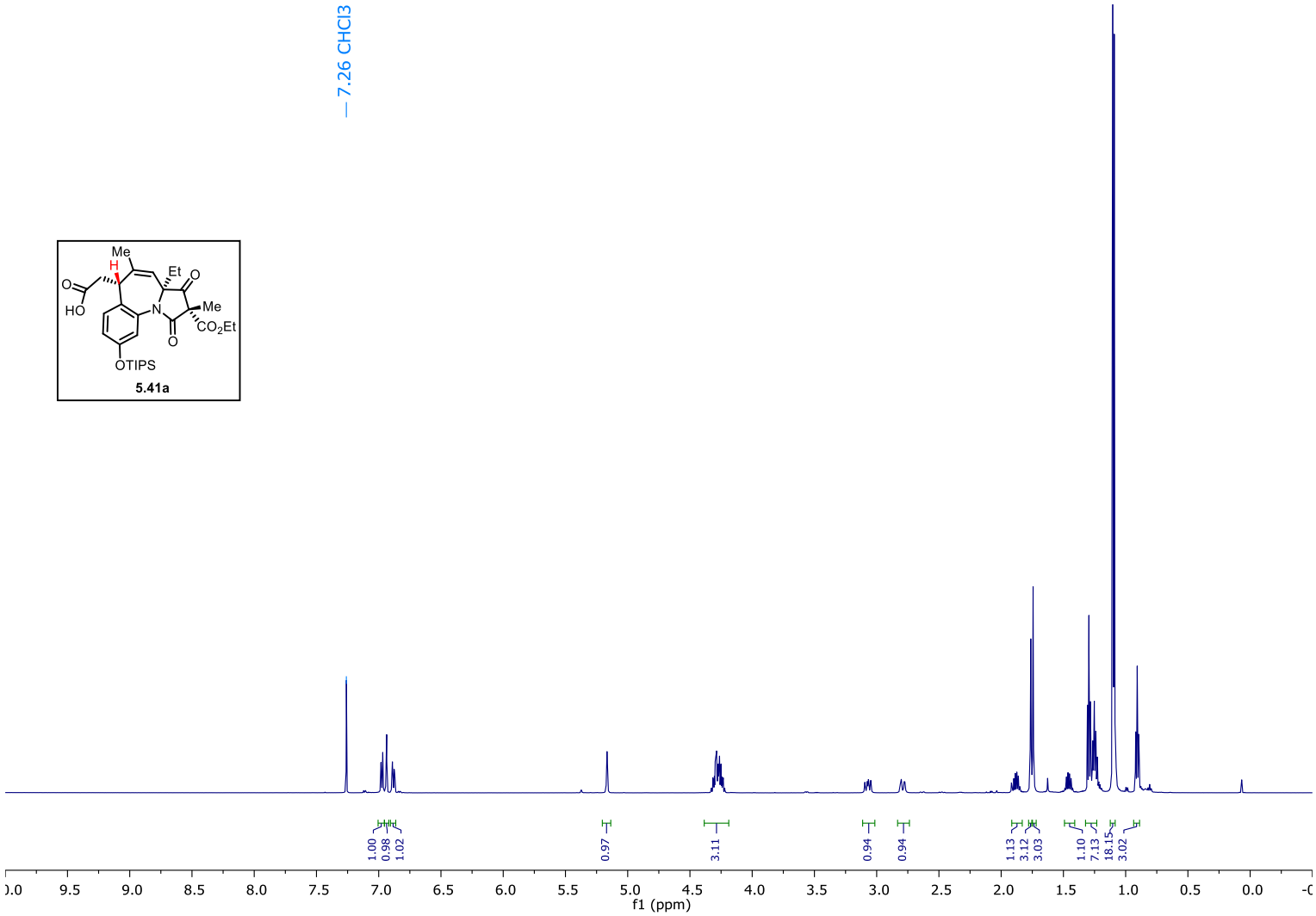


Figure C.32. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **5.41a**

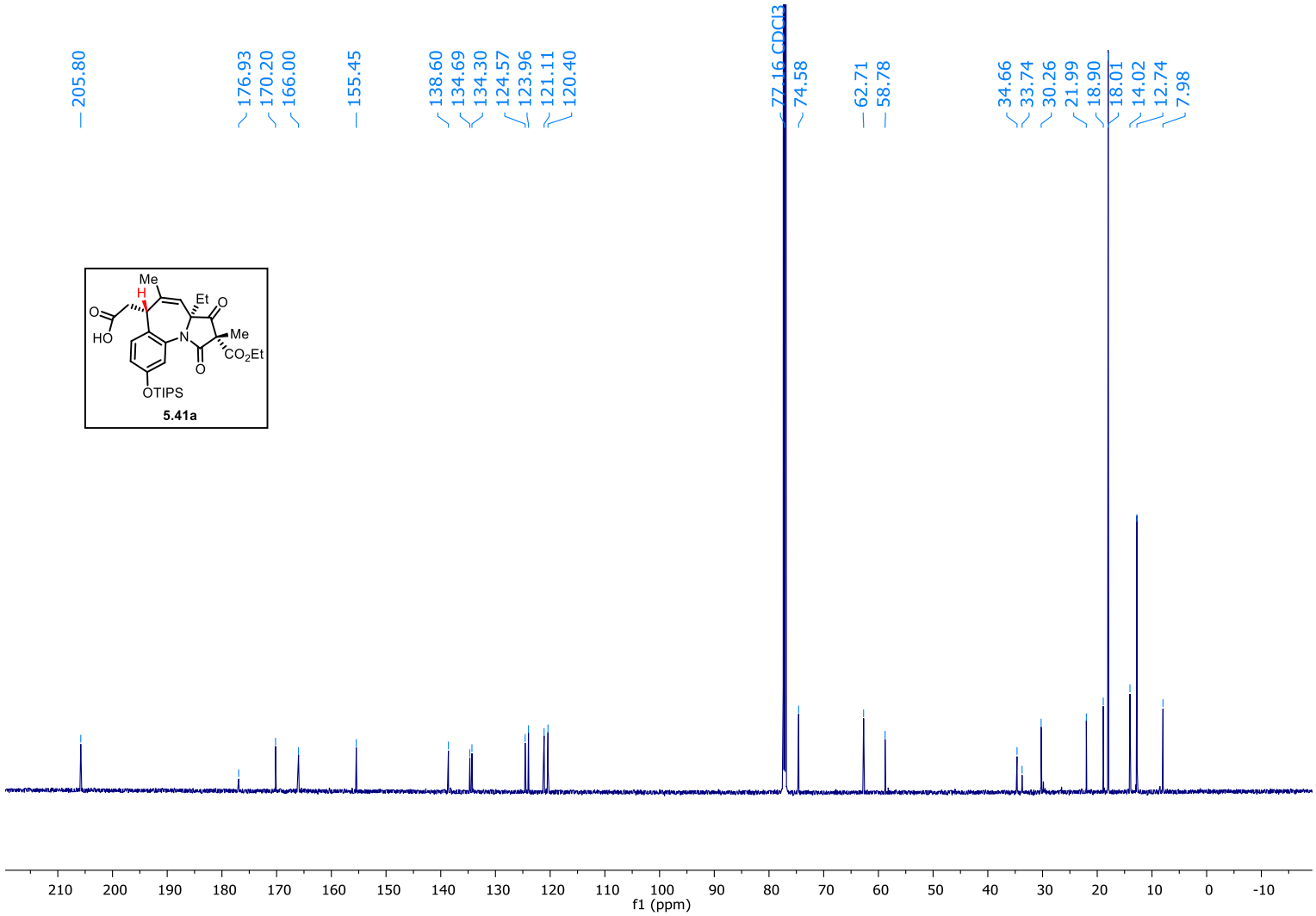


Figure C.33. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.41a**

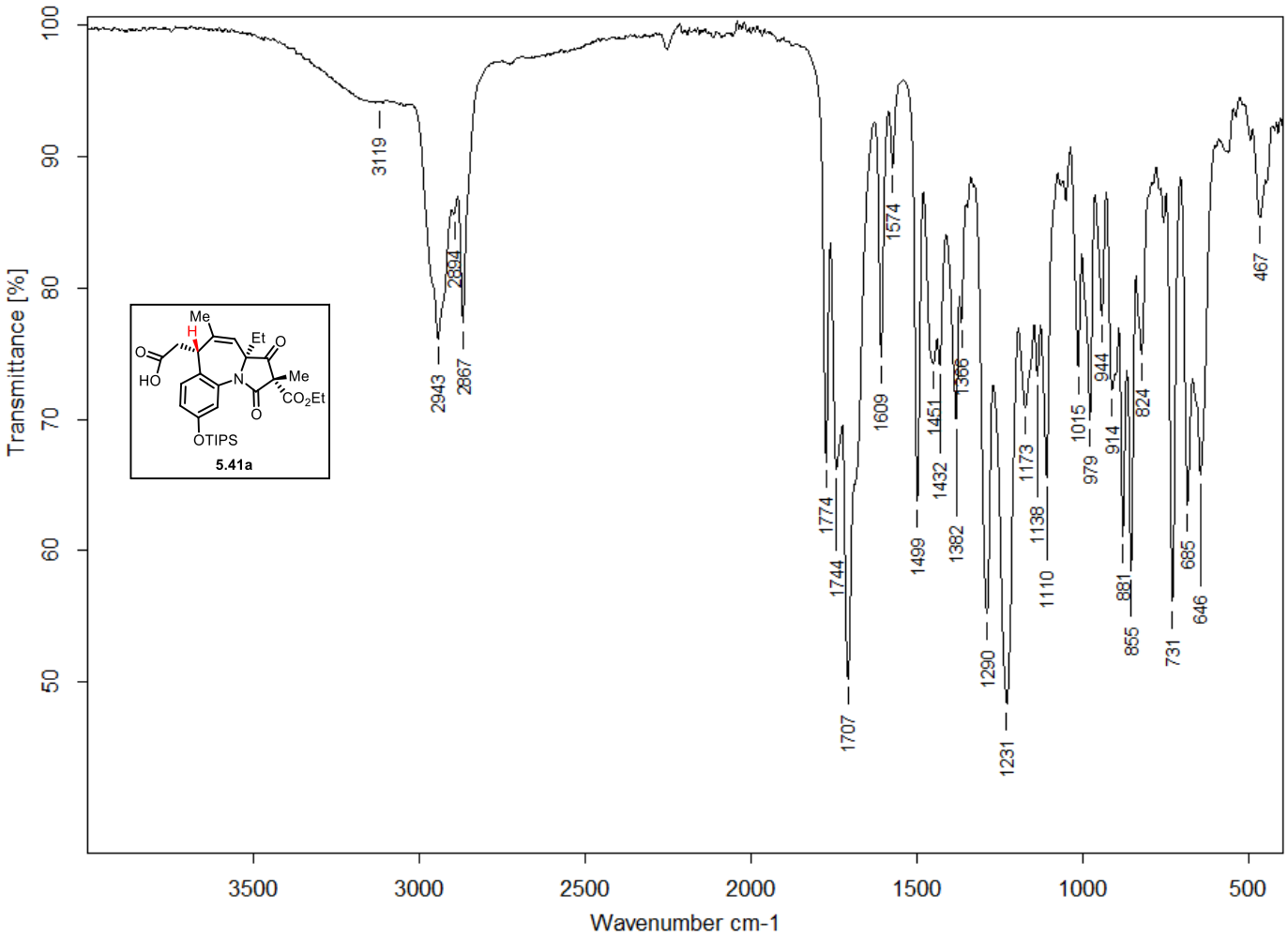


Figure C.34. FTIR spectrum (neat) of compound **5.41a**

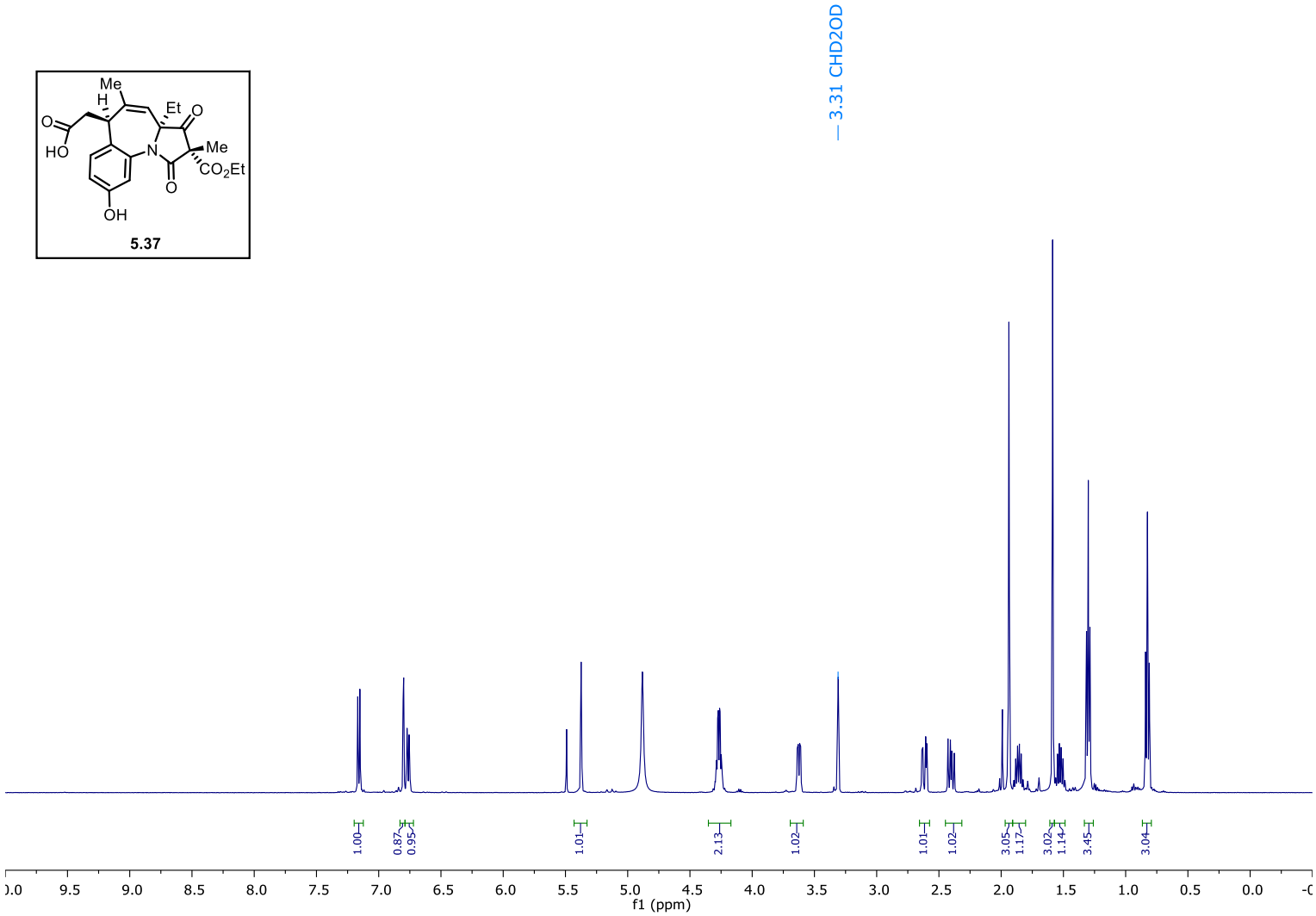


Figure C.35. ^{1}H NMR (500 MHz, CD_3OD) of compound **5.37**

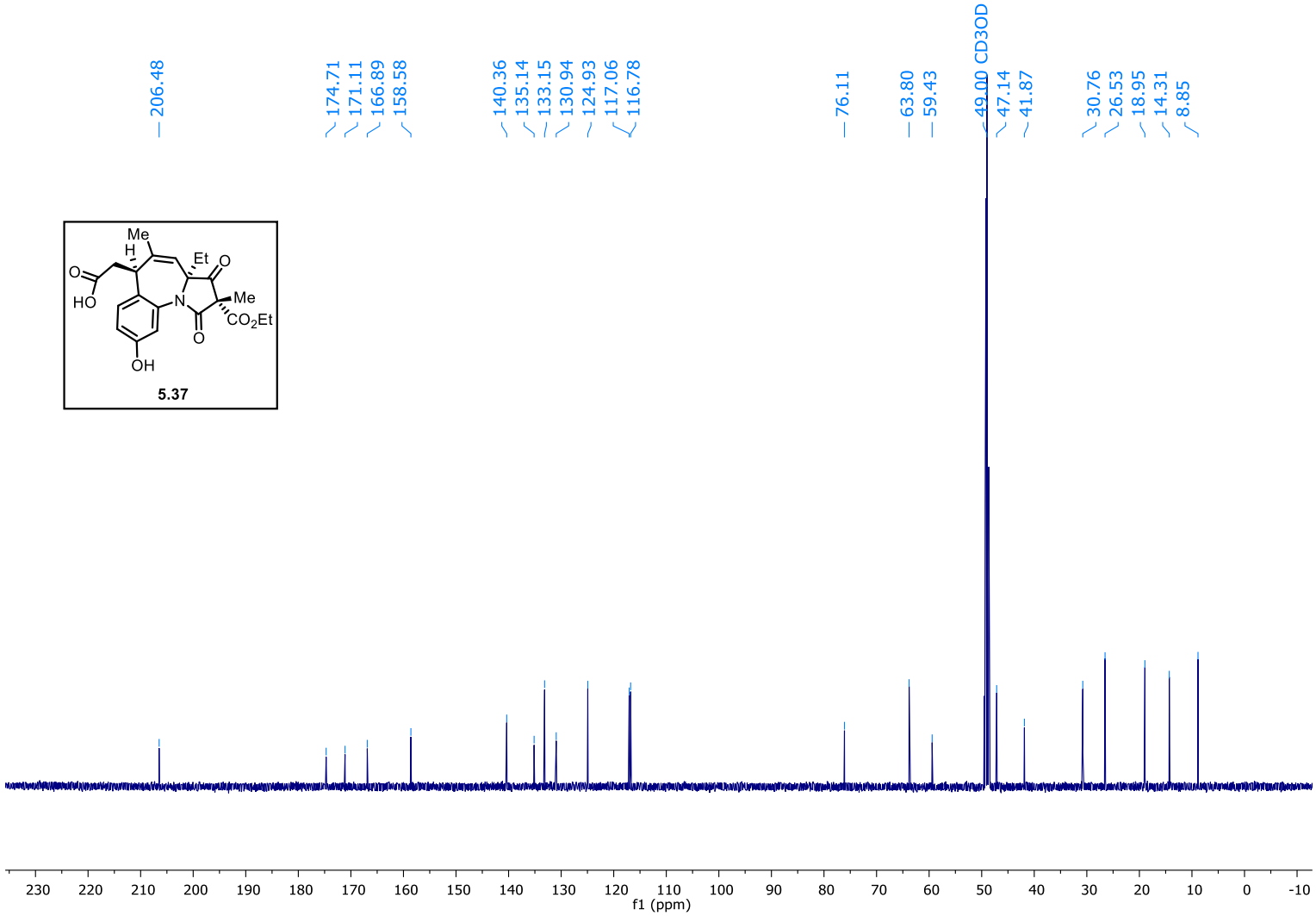


Figure C.36. ^{13}C NMR (151 MHz, CD_3OD) of compound **5.37**

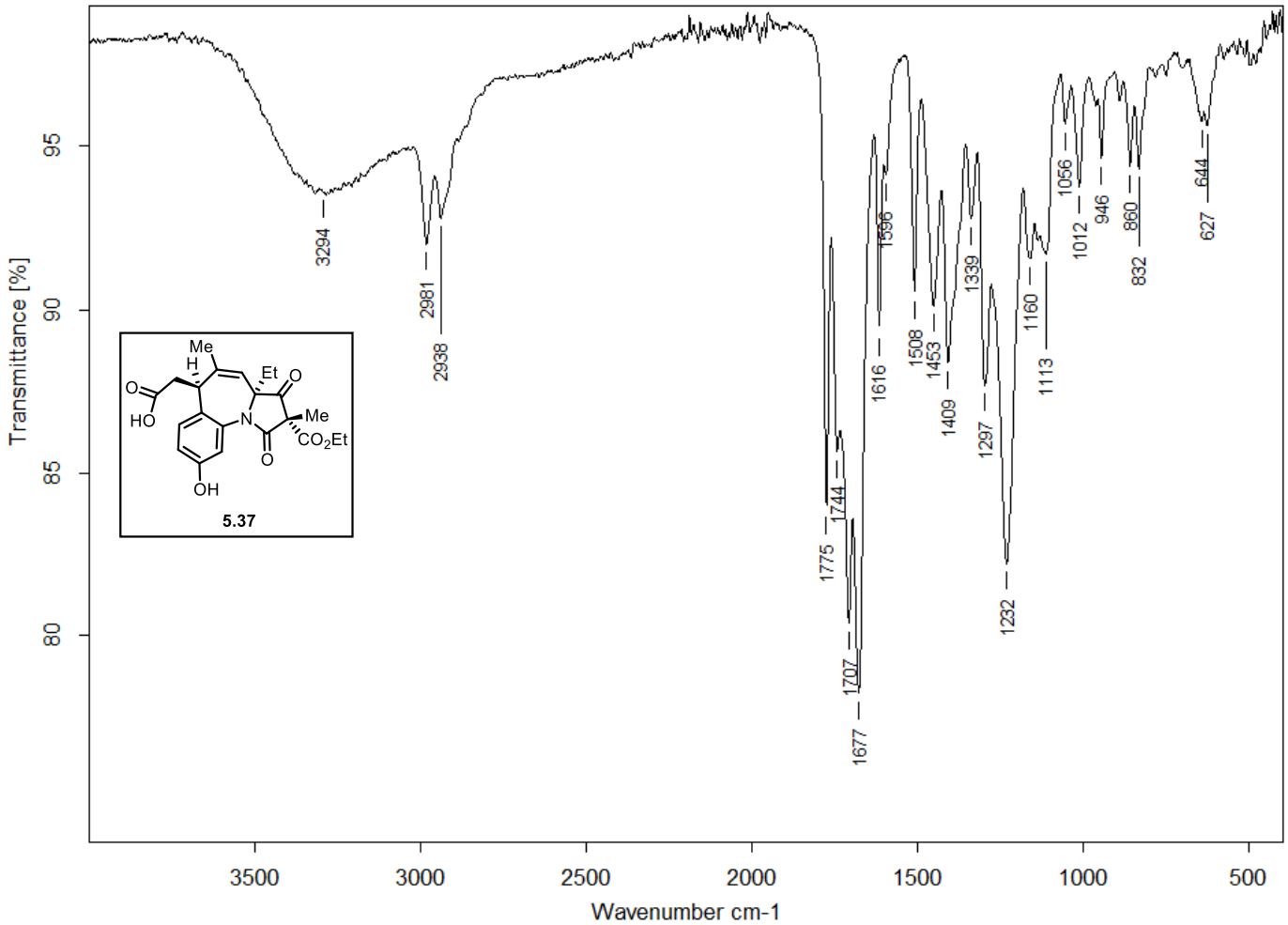


Figure C.37. FTIR spectrum (neat) of compound **5.37**

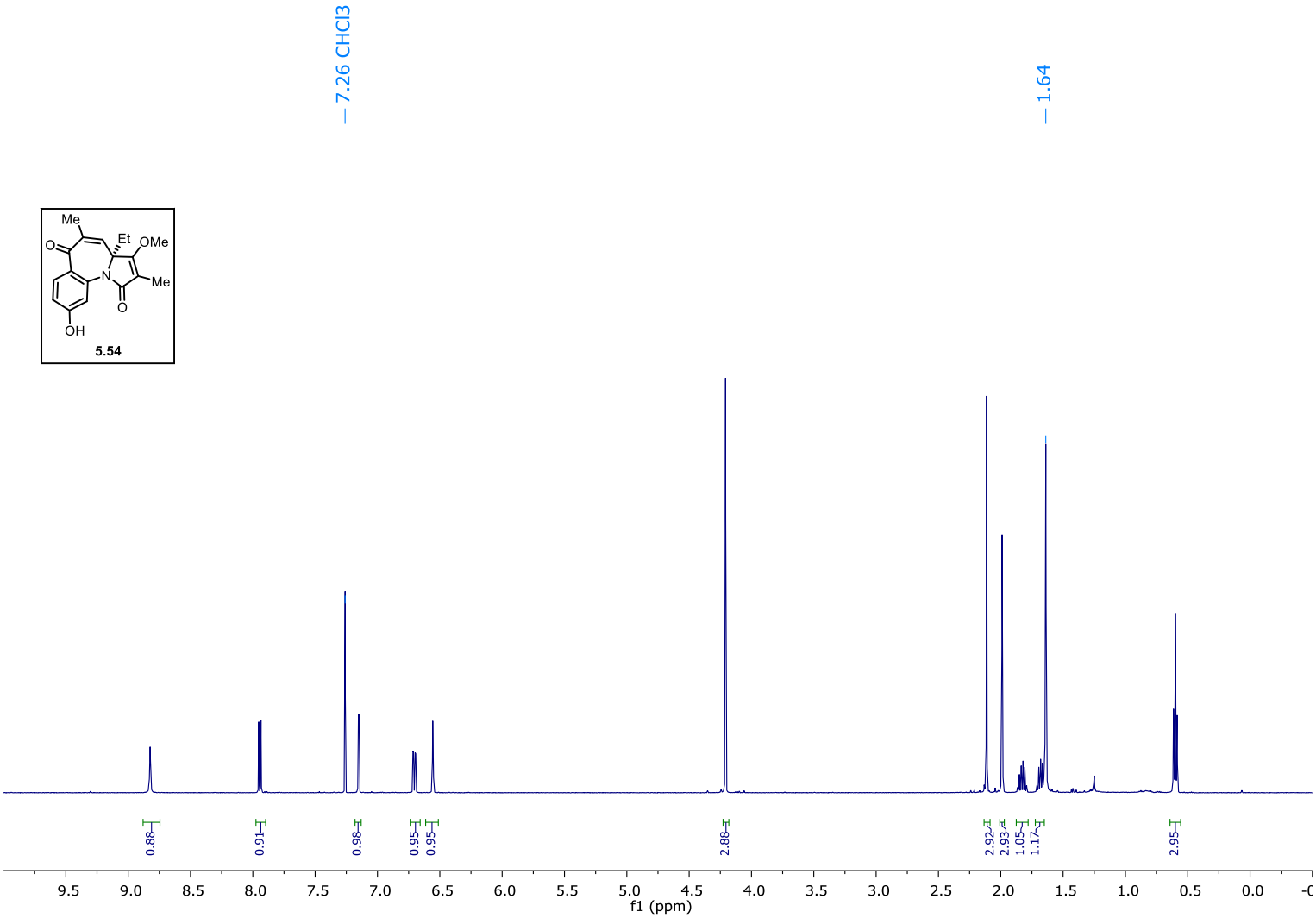


Figure C.38. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5.54**

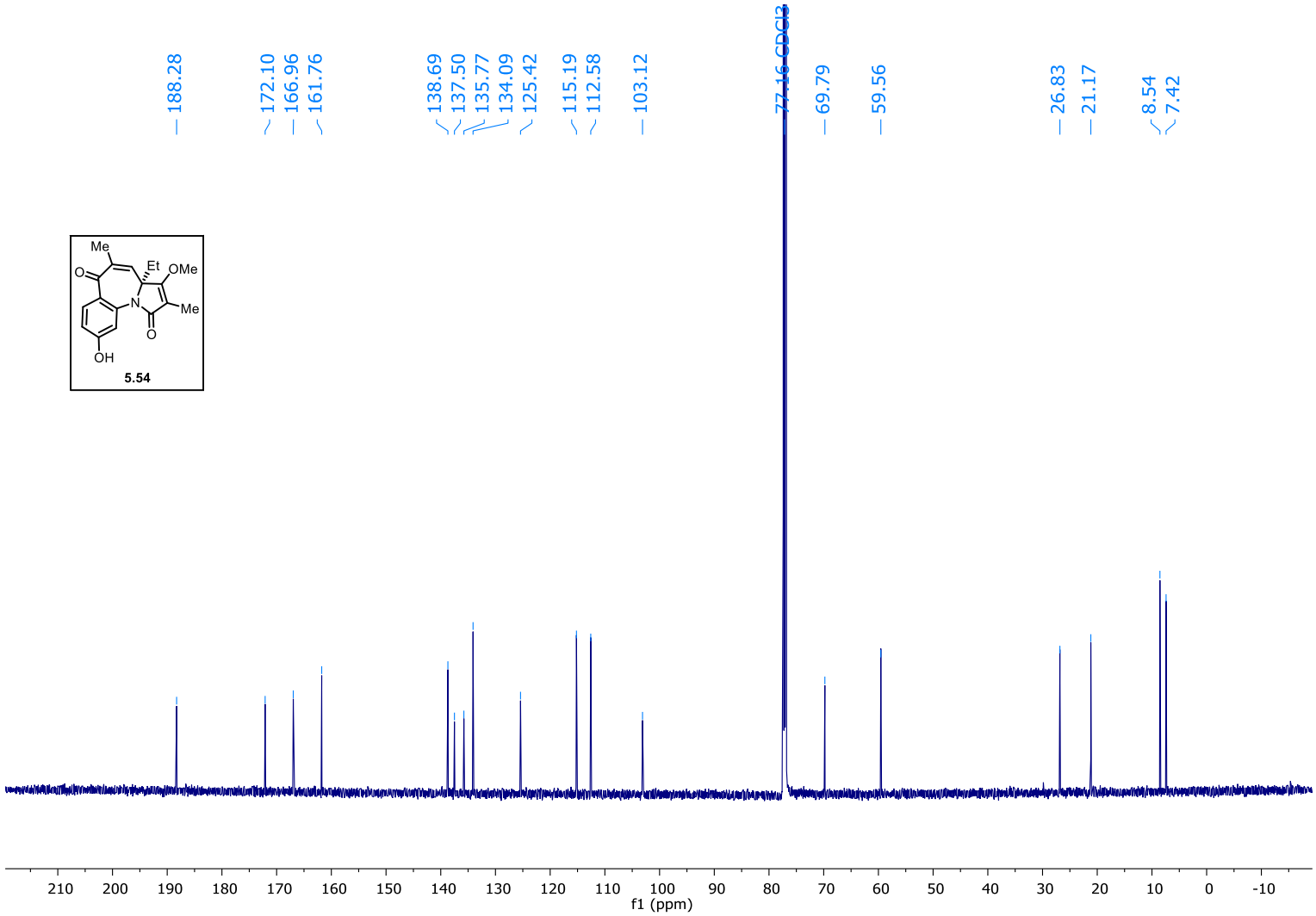


Figure C.39. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.54**

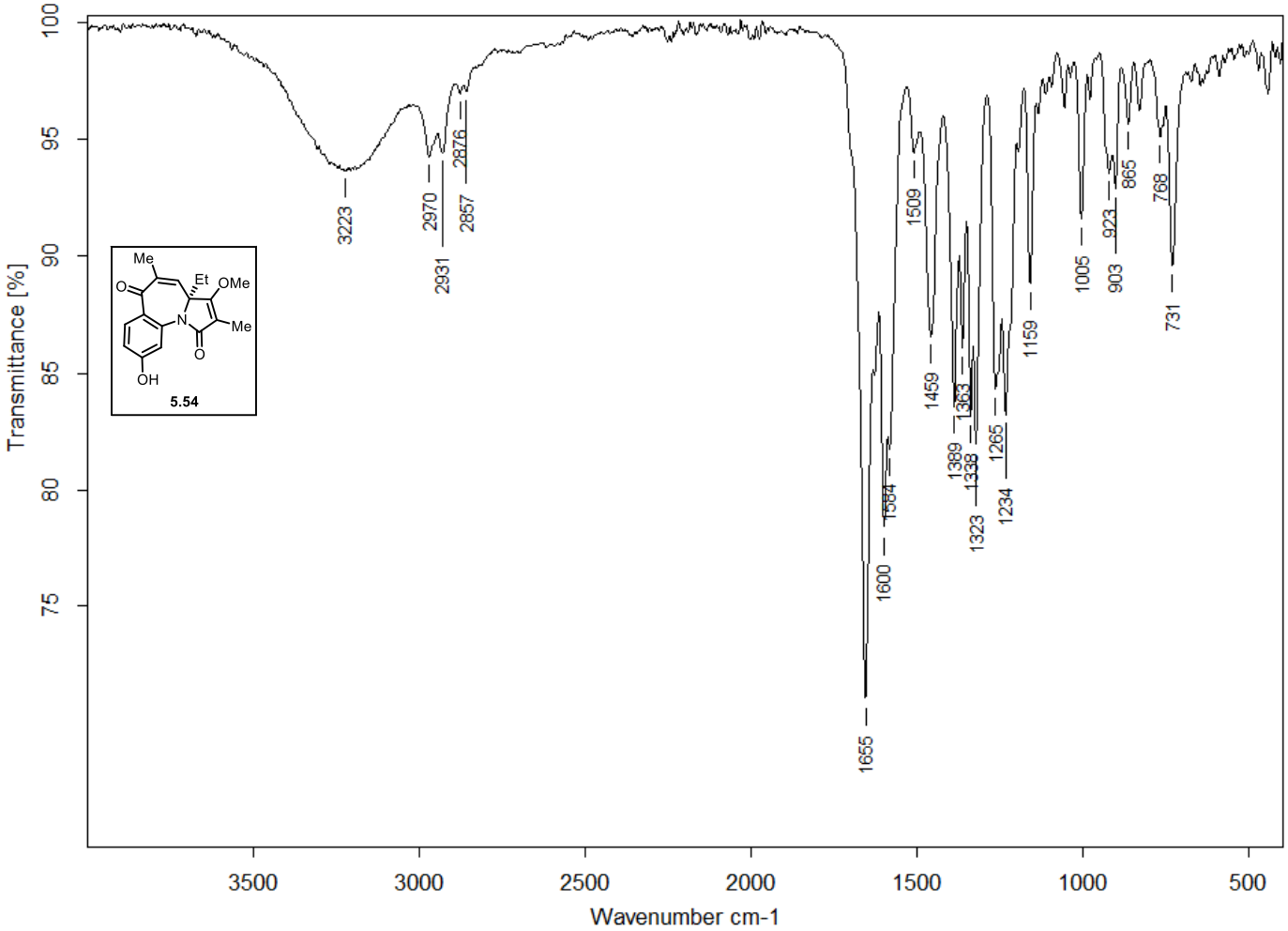


Figure C.40. FTIR spectrum (neat) of compound **5.54**

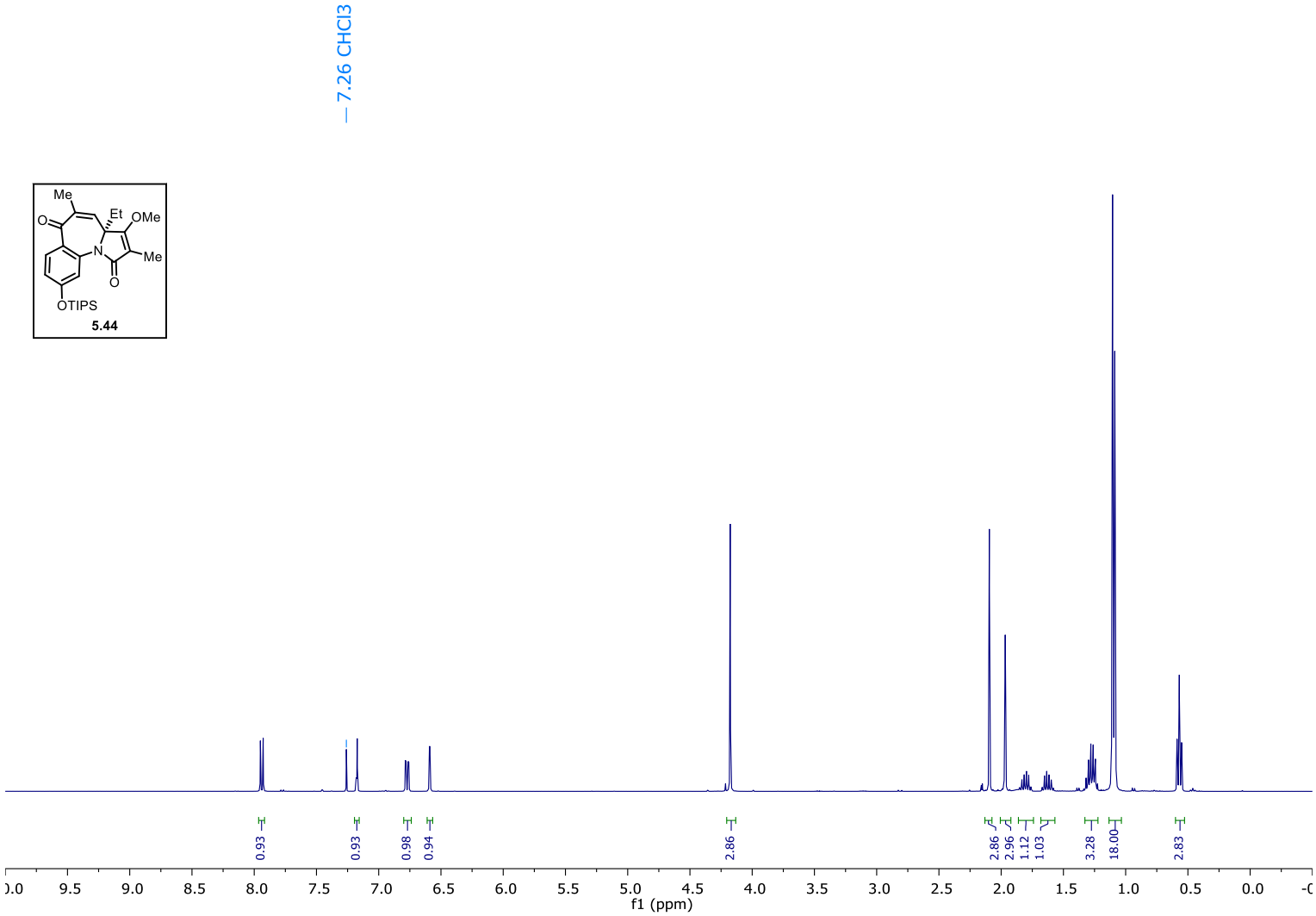


Figure C.41. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.44**

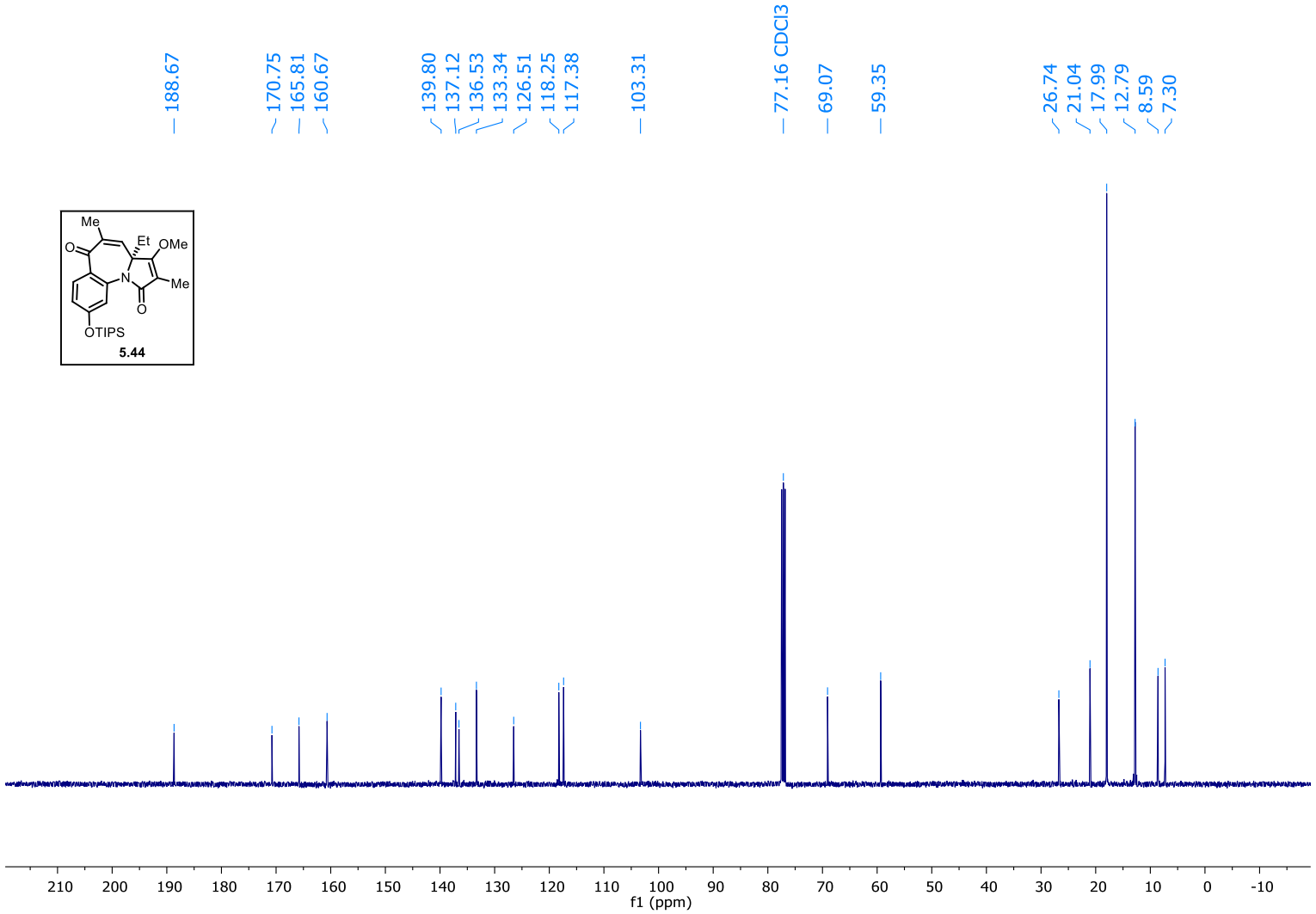


Figure C.42. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.44**

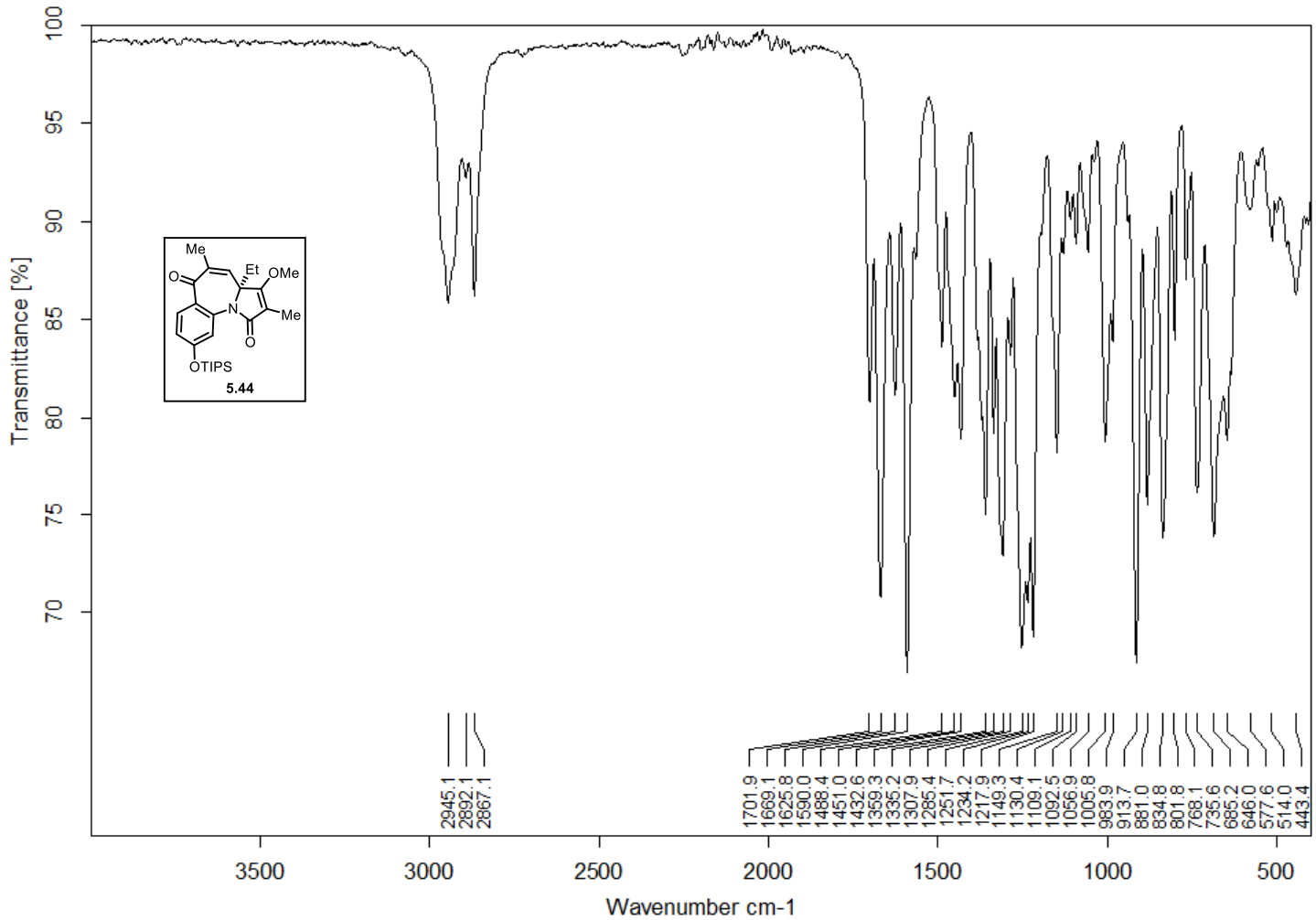


Figure C.43. FTIR spectrum (neat) of compound **5.44**

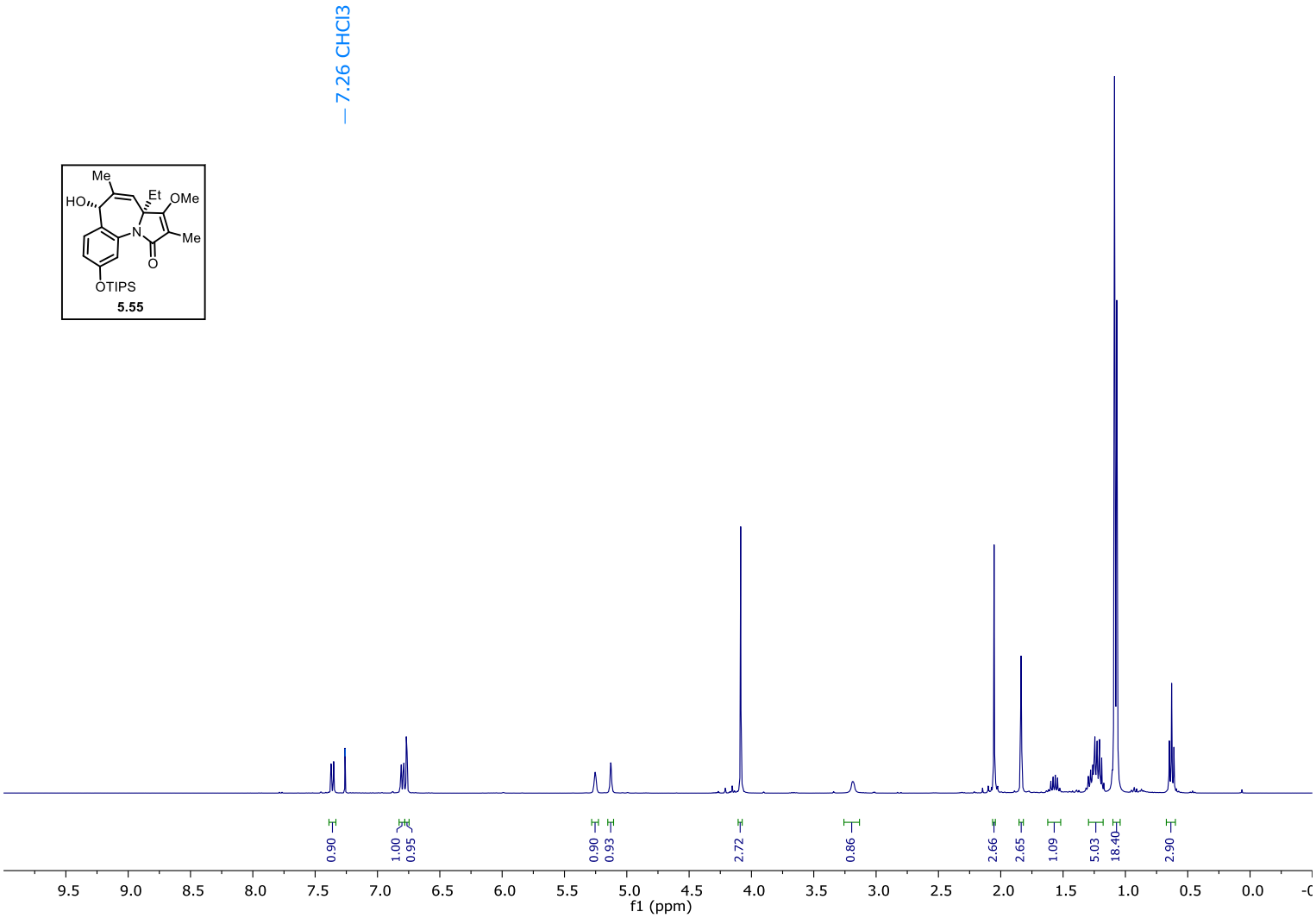


Figure C.44. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.55**

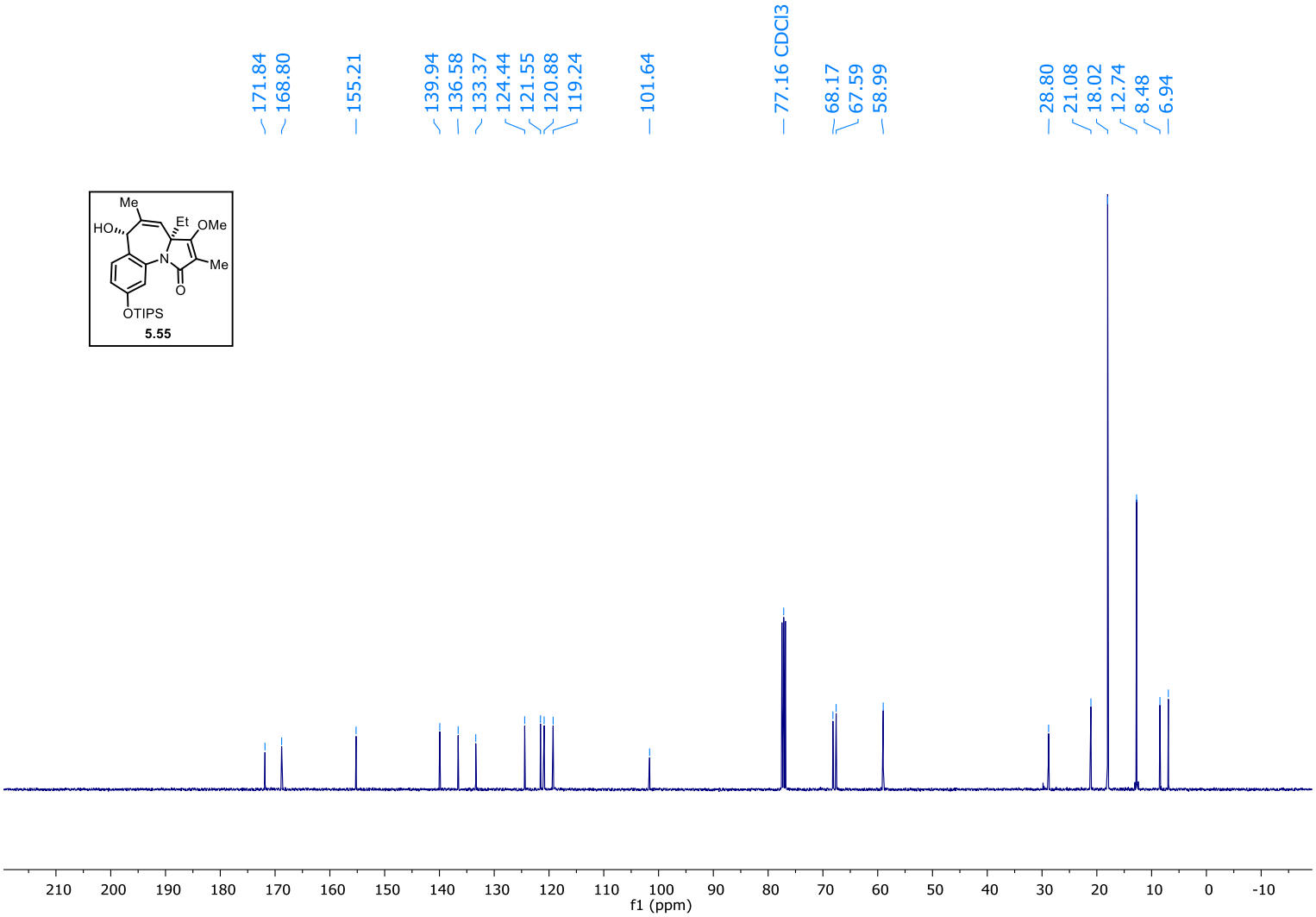


Figure C.45. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.55**

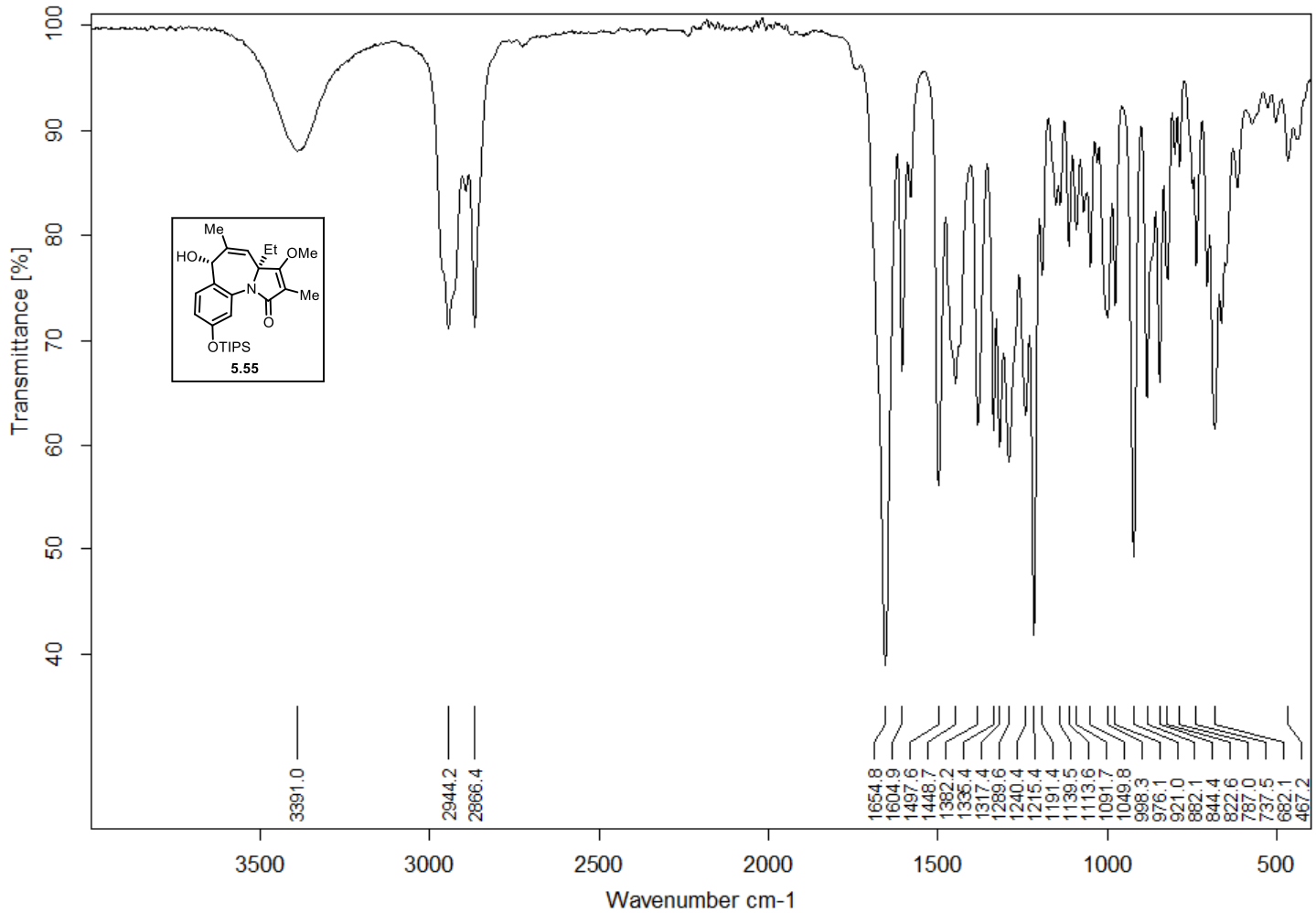


Figure C.46. FTIR spectrum (neat) of compound **5.55**

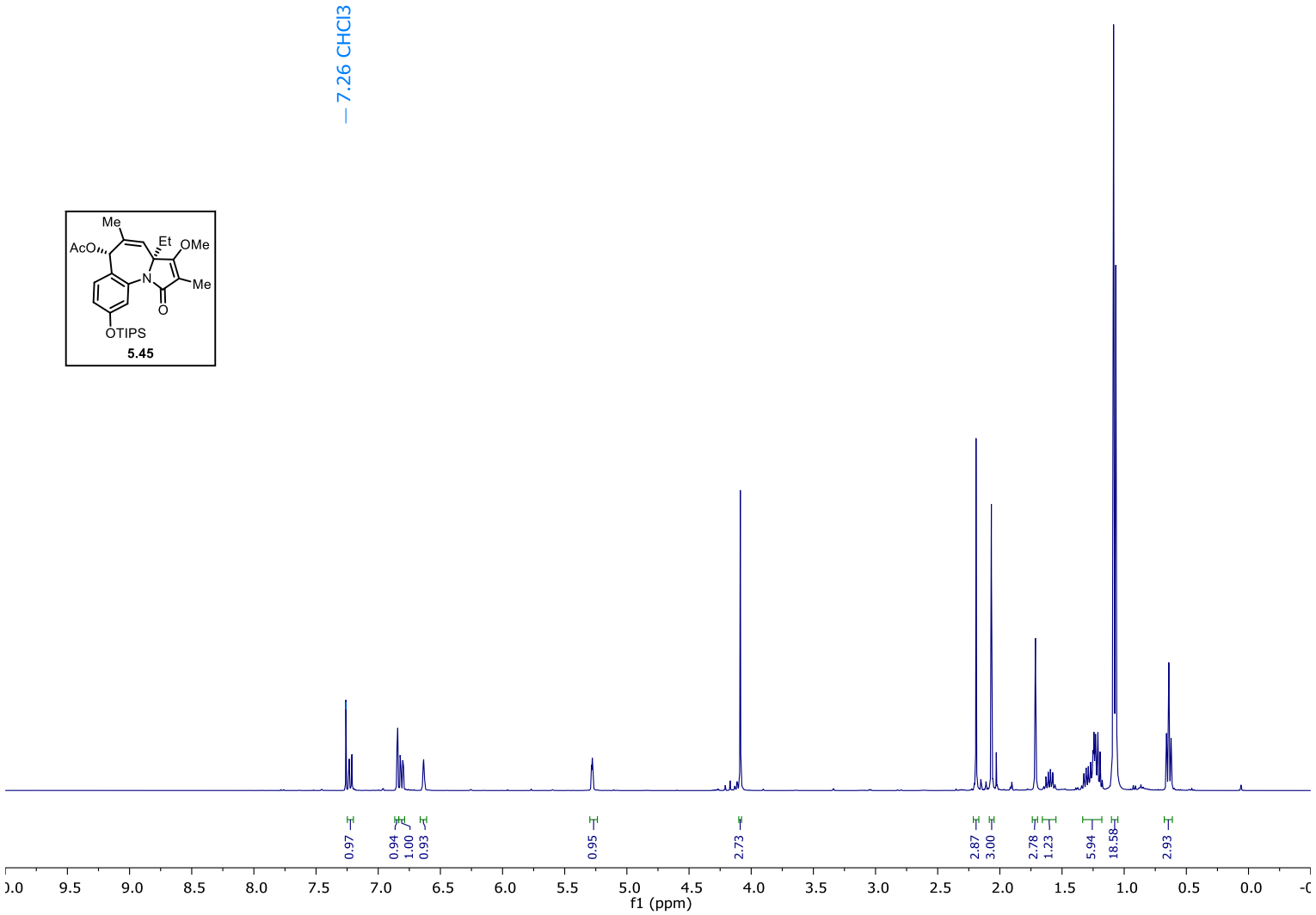


Figure C.47. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.45**

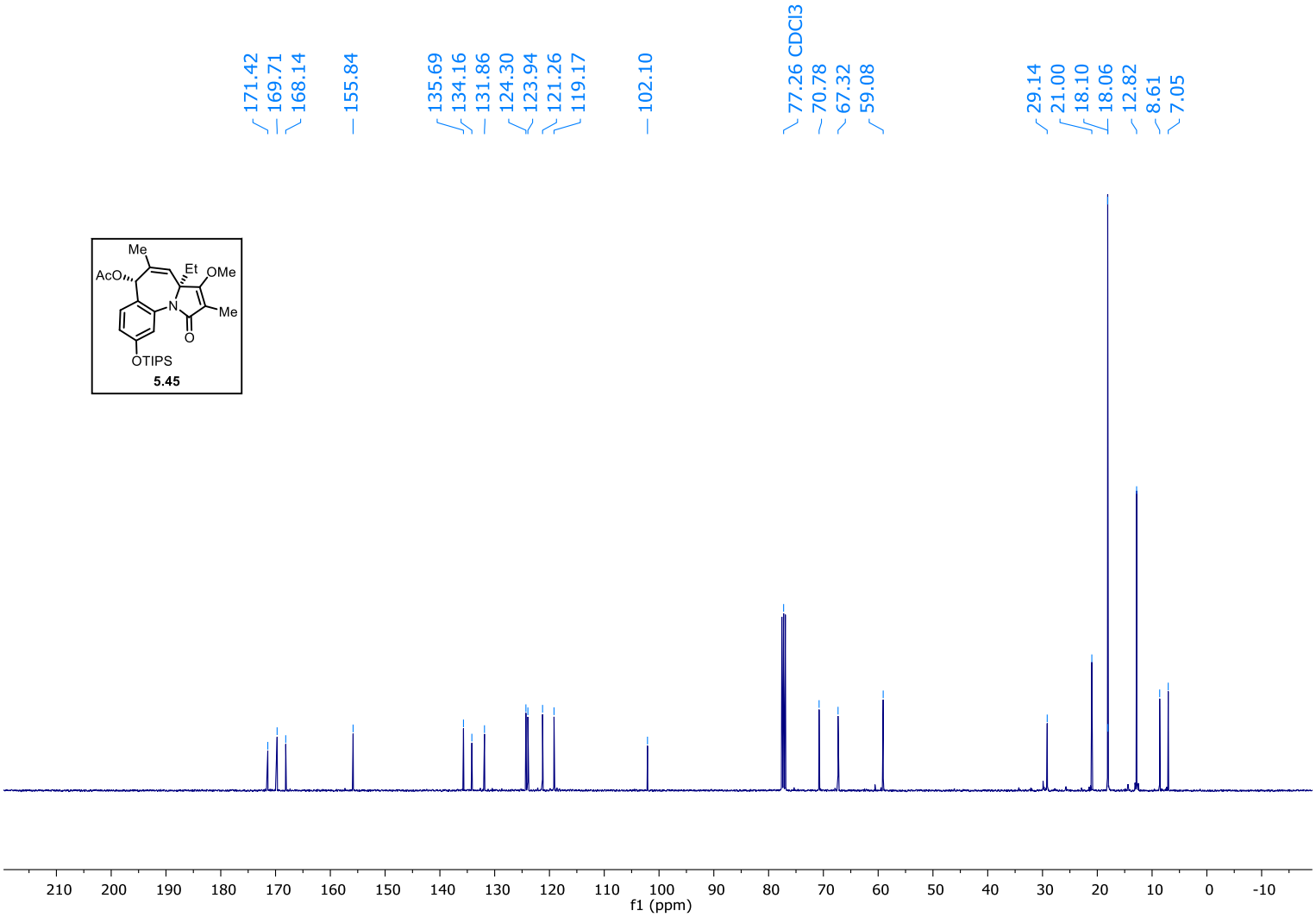


Figure C.48. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.45**

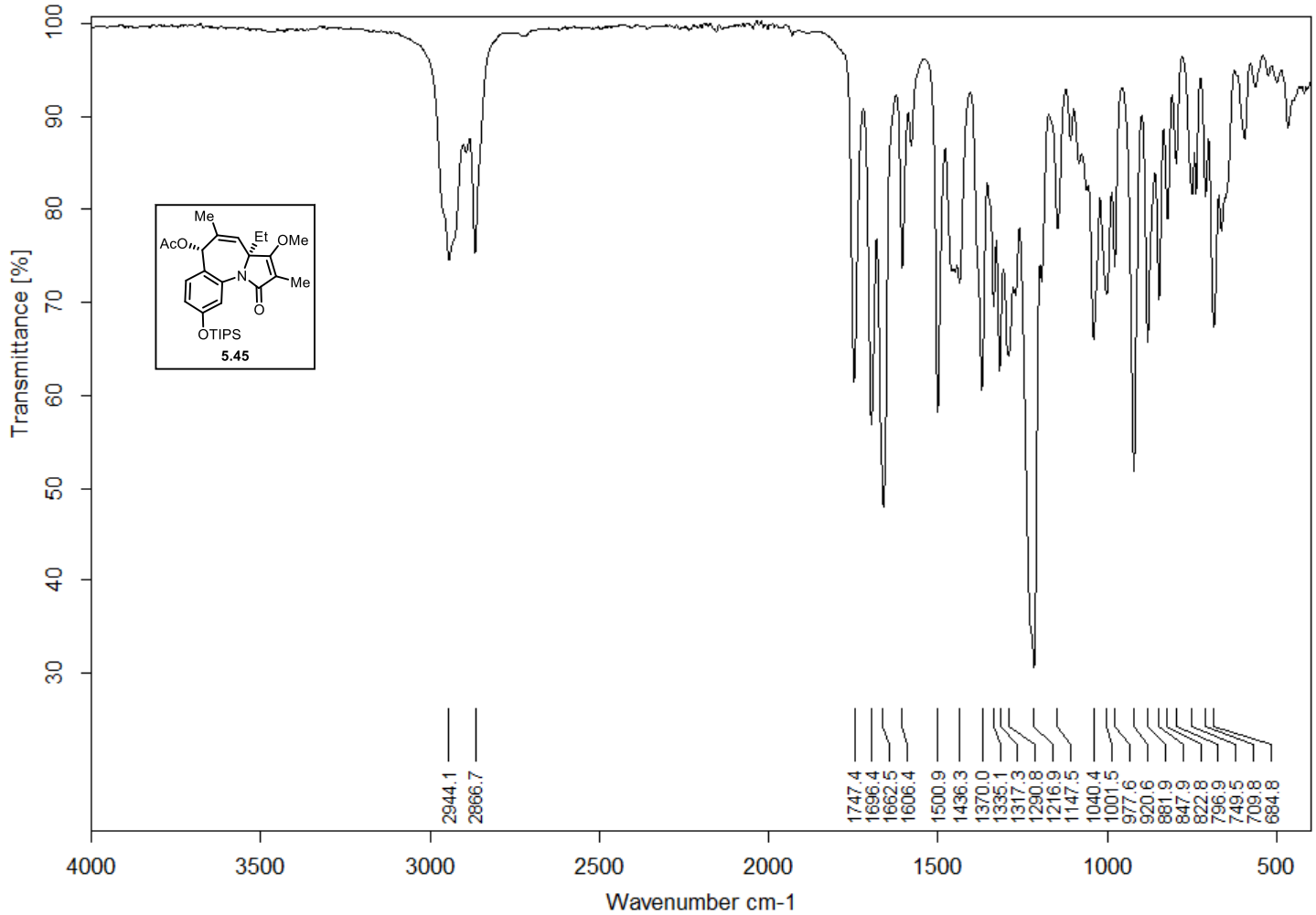


Figure C.49. FTIR spectrum (neat) of compound **5.45**

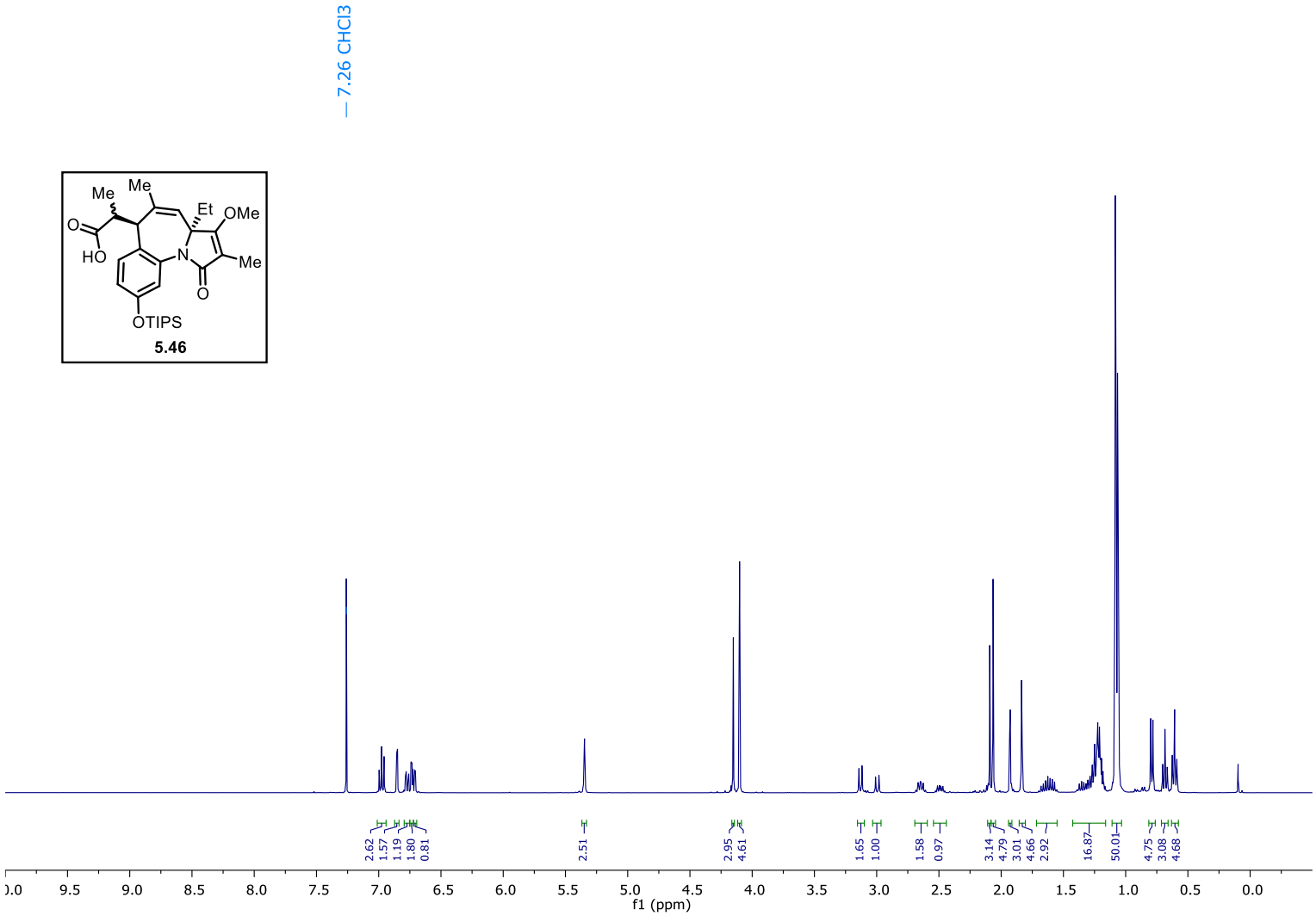


Figure C.50. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.46**

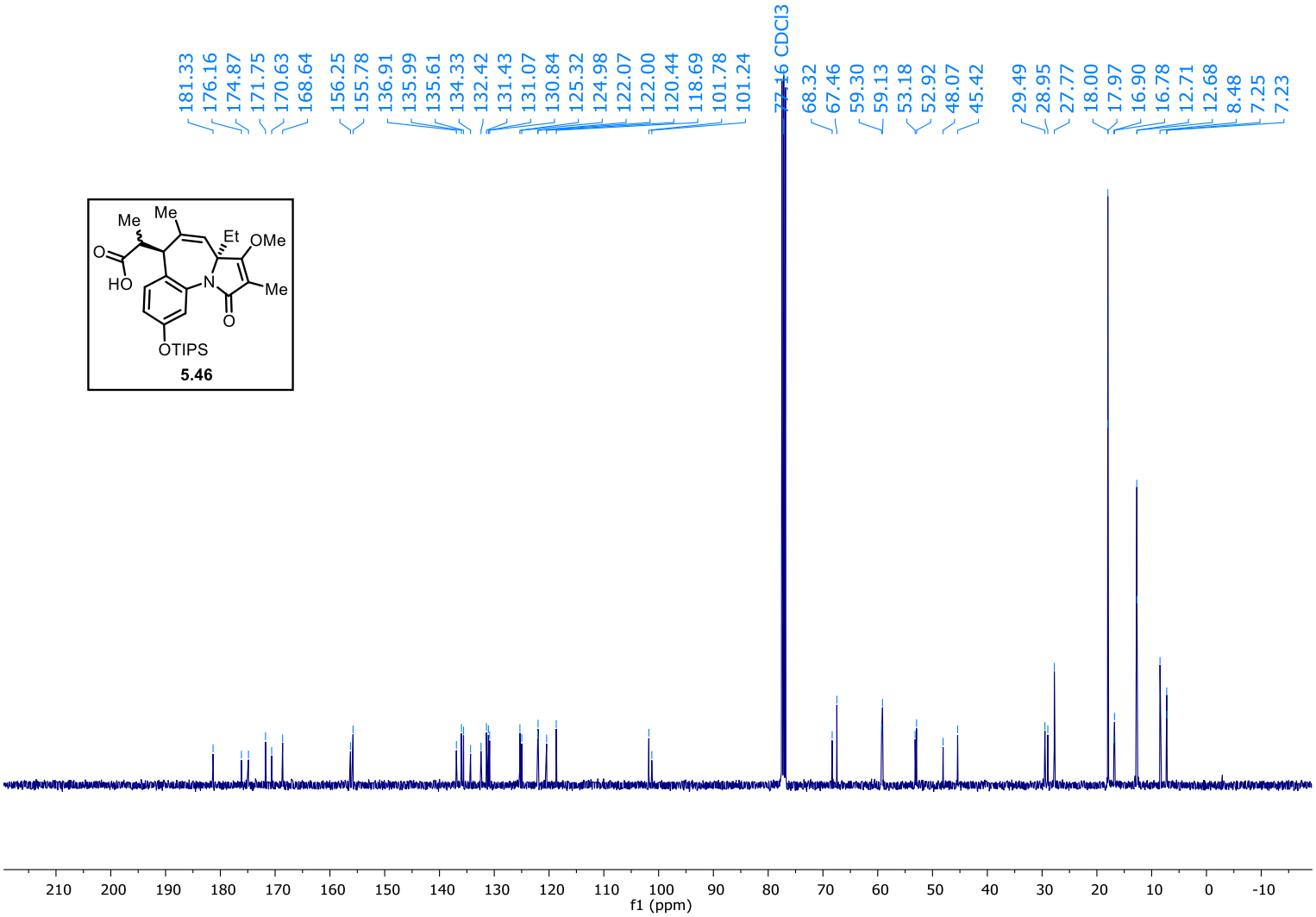


Figure C.51. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.46**

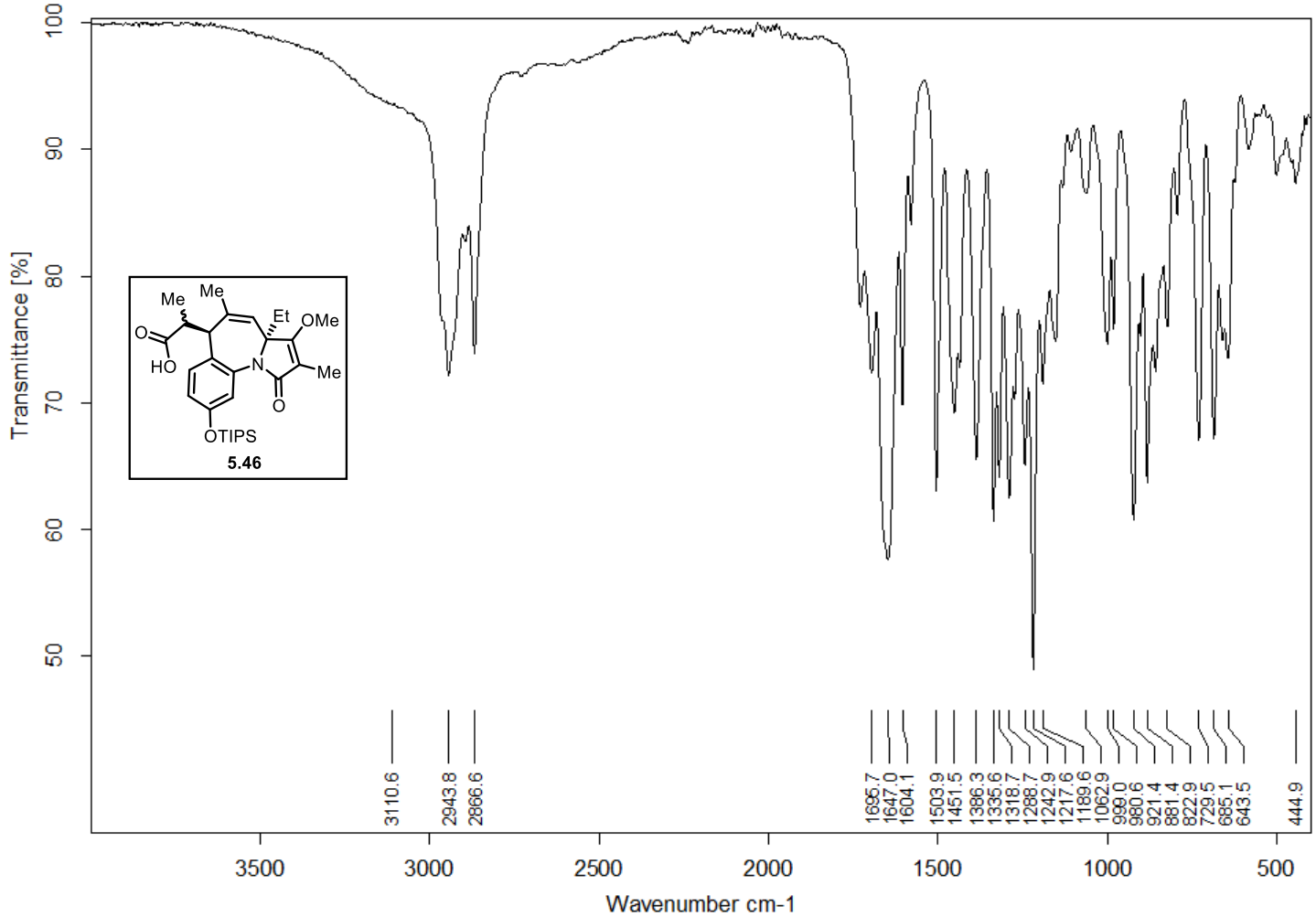


Figure C.52. FTIR spectrum (neat) of compound **5.46**

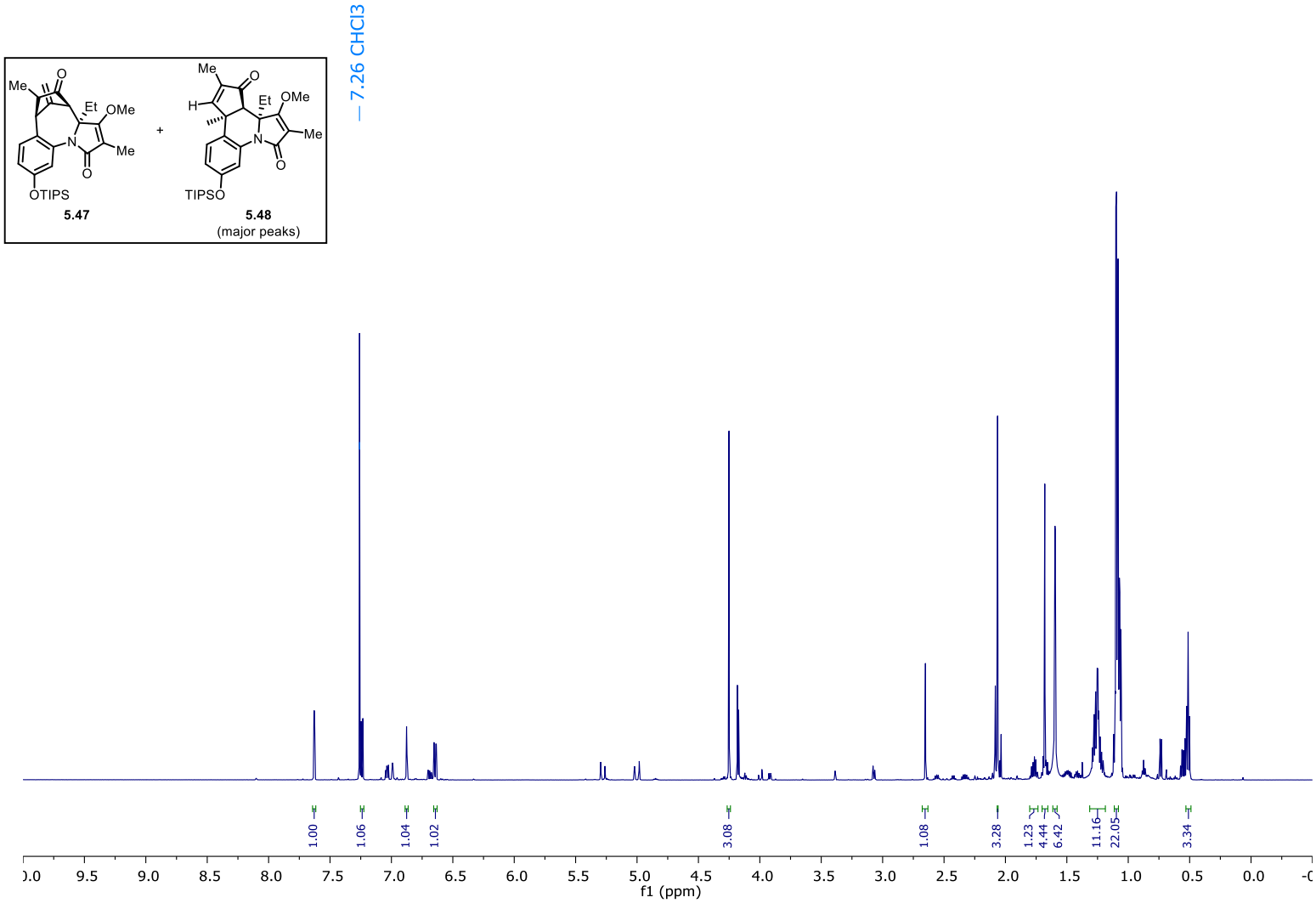


Figure C.53. ^{1}H NMR (600 MHz, $CDCl_3$) of compounds **5.47** and **5.48**

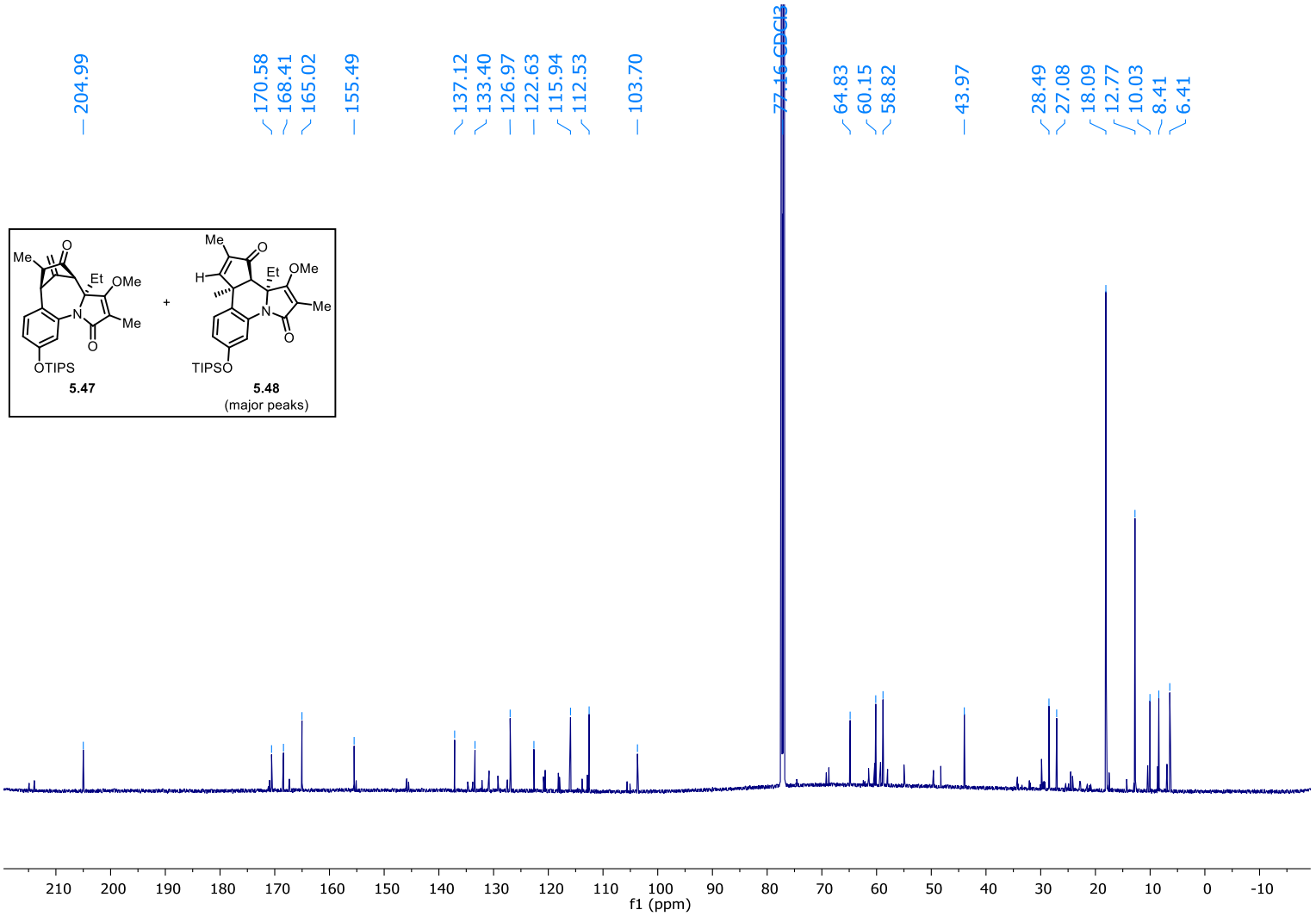


Figure C.54. ^{13}C NMR (151 MHz, $CDCl_3$) of compounds **5.47** and **5.48** (major peaks)

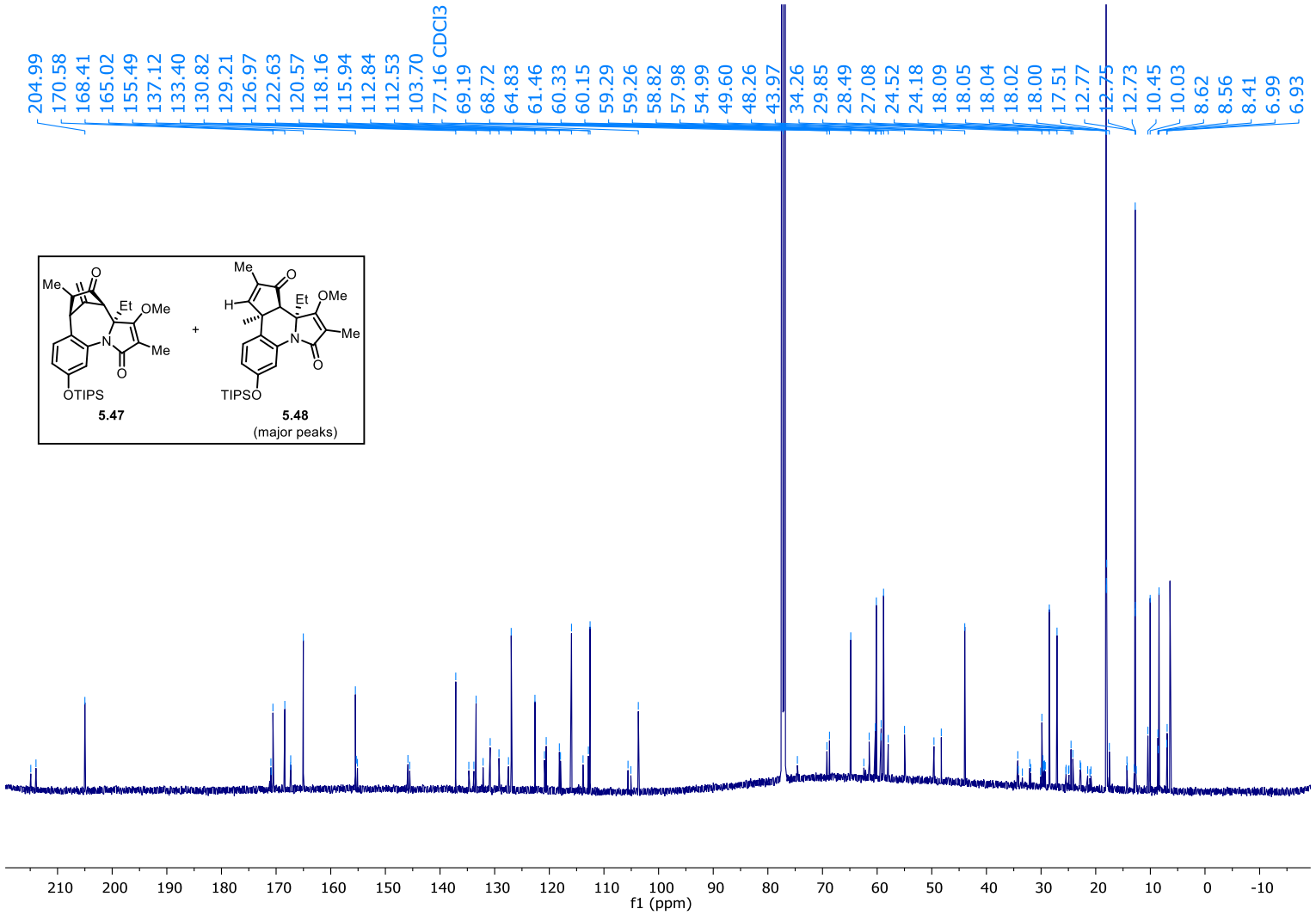


Figure C.55. ^{13}C NMR (151 MHz, $CDCl_3$) of compounds **5.47** and **5.48** (all peaks)

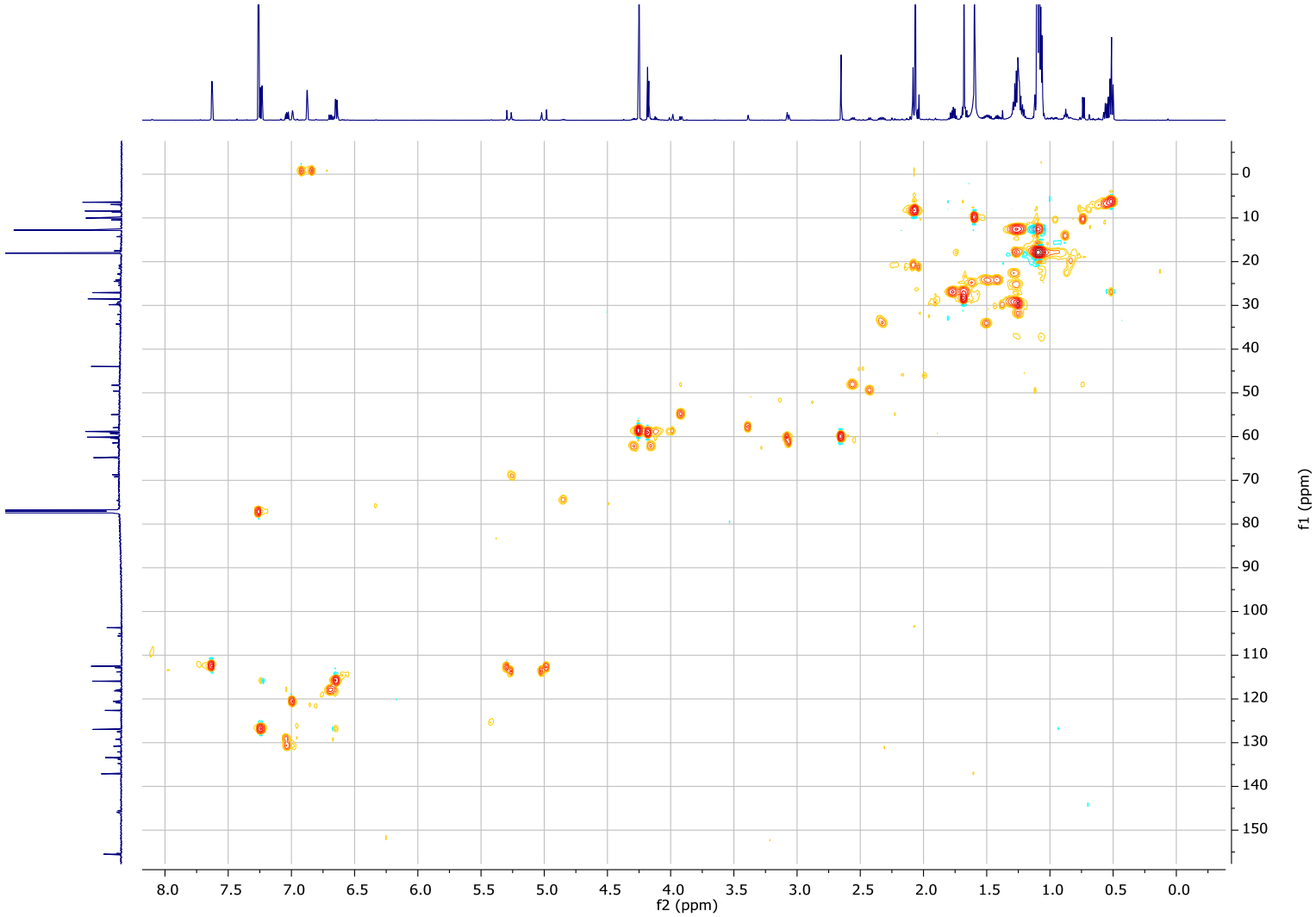


Figure C.56. HSQC of compounds **5.47** and **5.48**

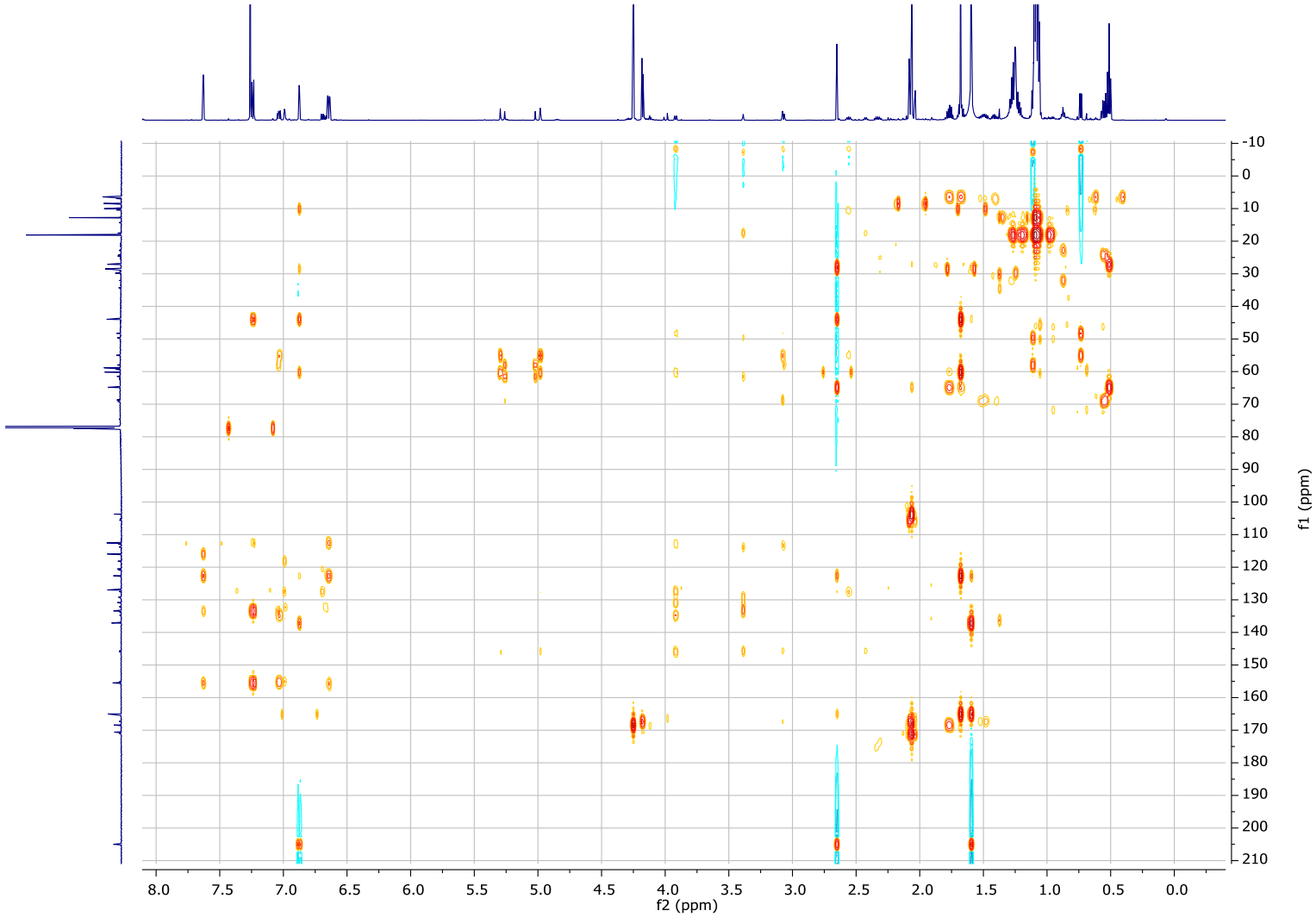


Figure C.57. HMBC of compounds **5.47** and **5.48**

Figure C.58. COSY of compounds **5.47** and **5.48**

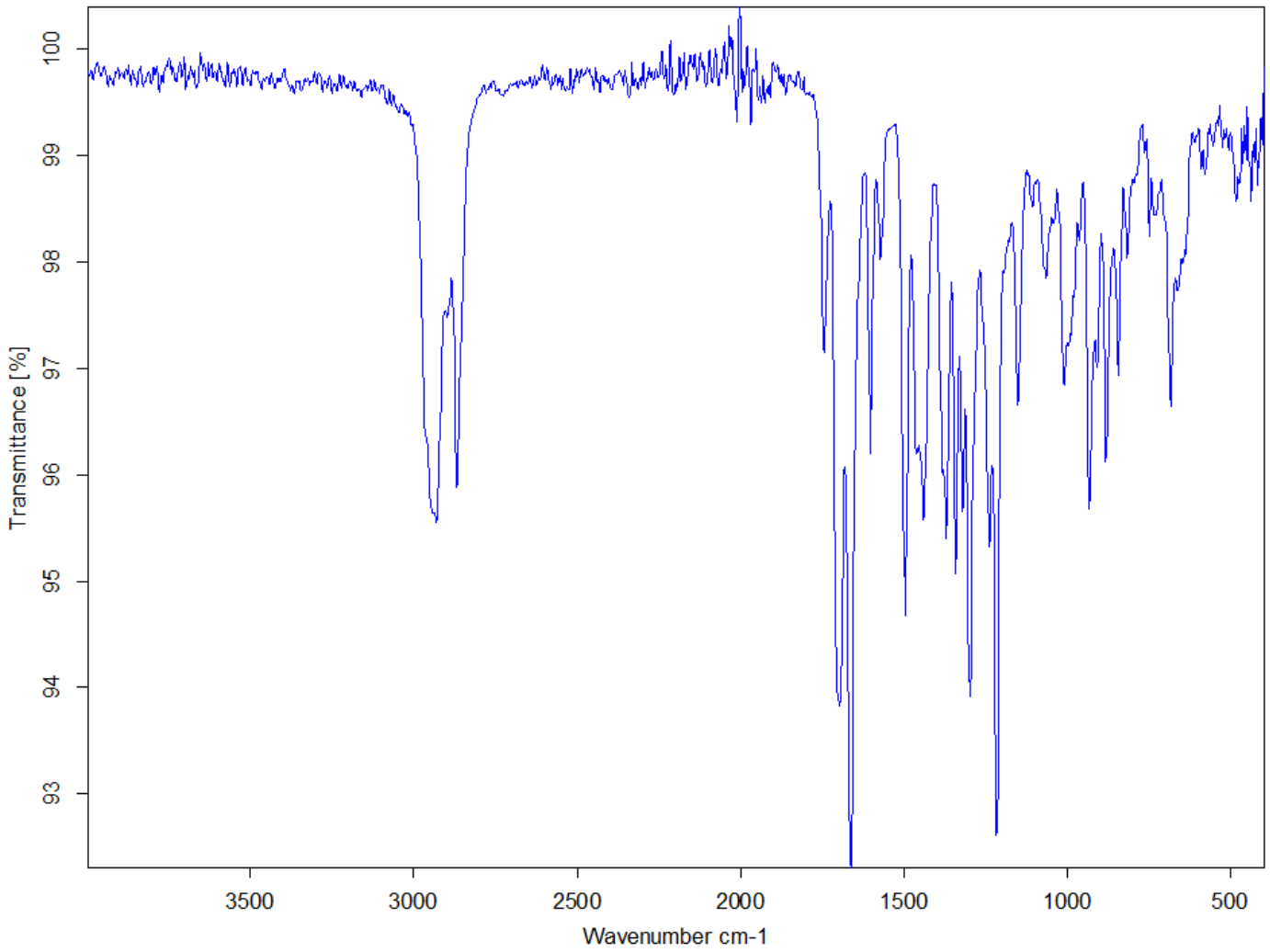


Figure C.59. FTIR spectrum (neat) of compounds **5.47** and **5.48**

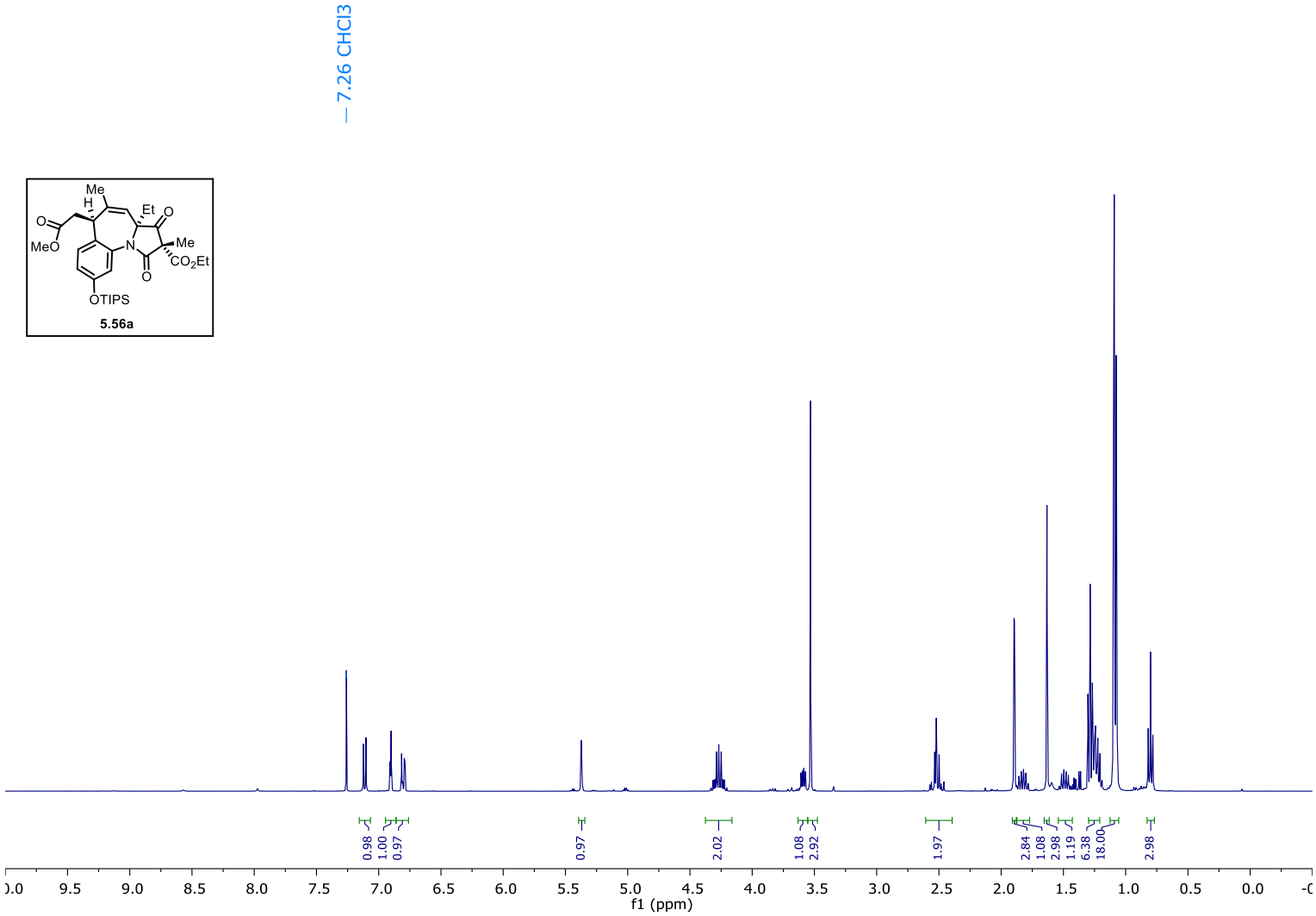


Figure C.60. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.56a**

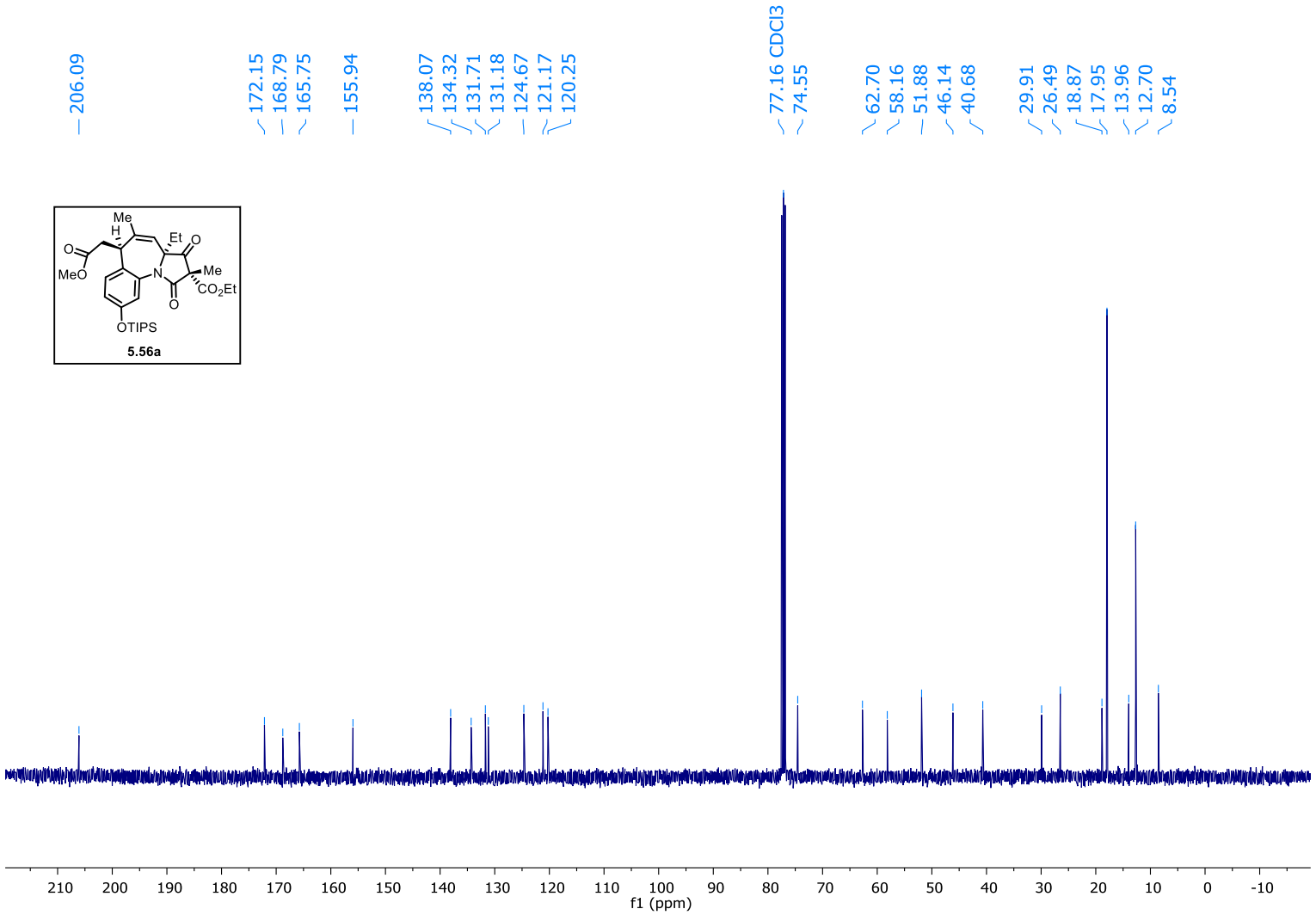


Figure C.61. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **5.56a**

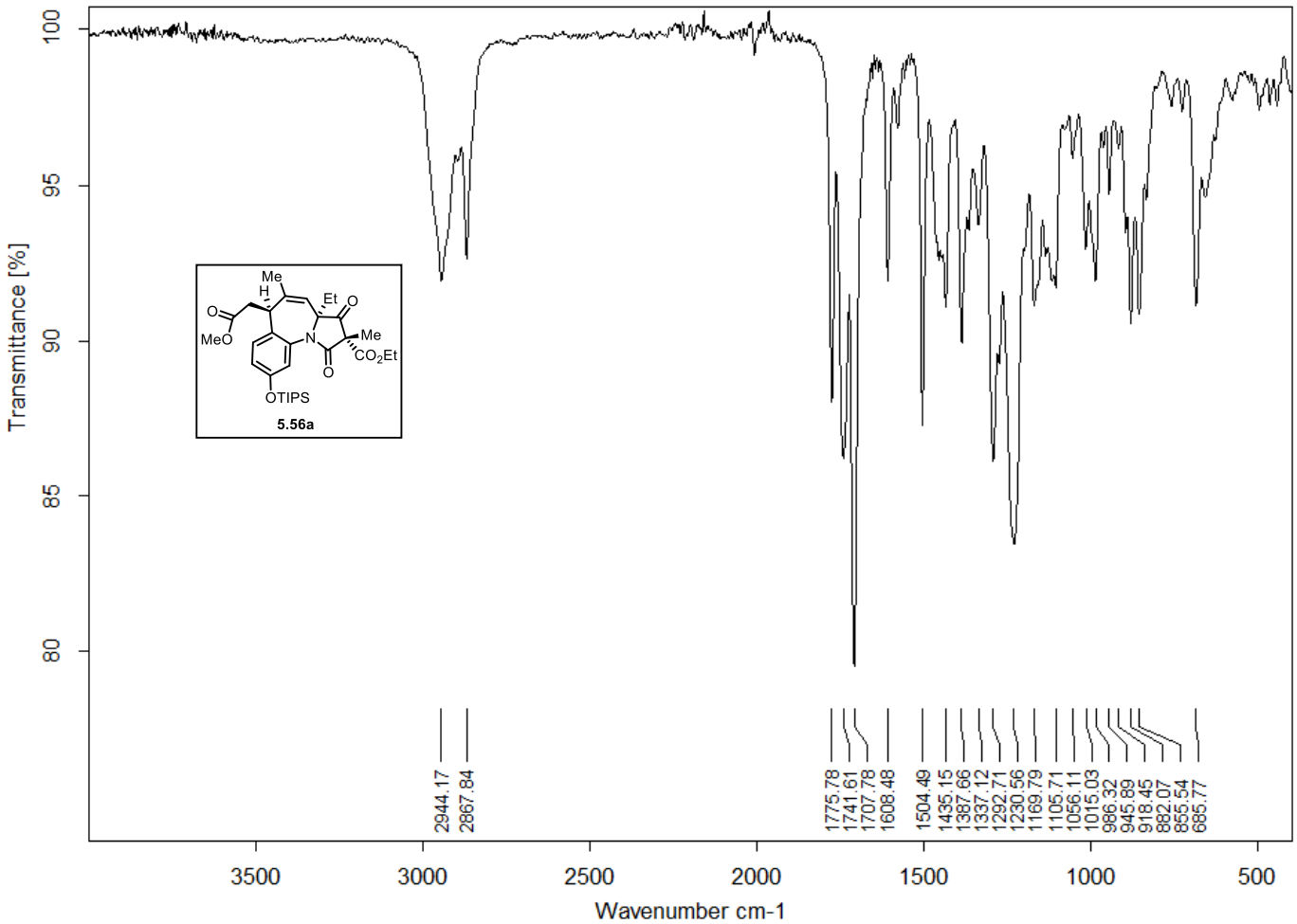


Figure C.62. FTIR spectrum (neat) of compound **5.56a**

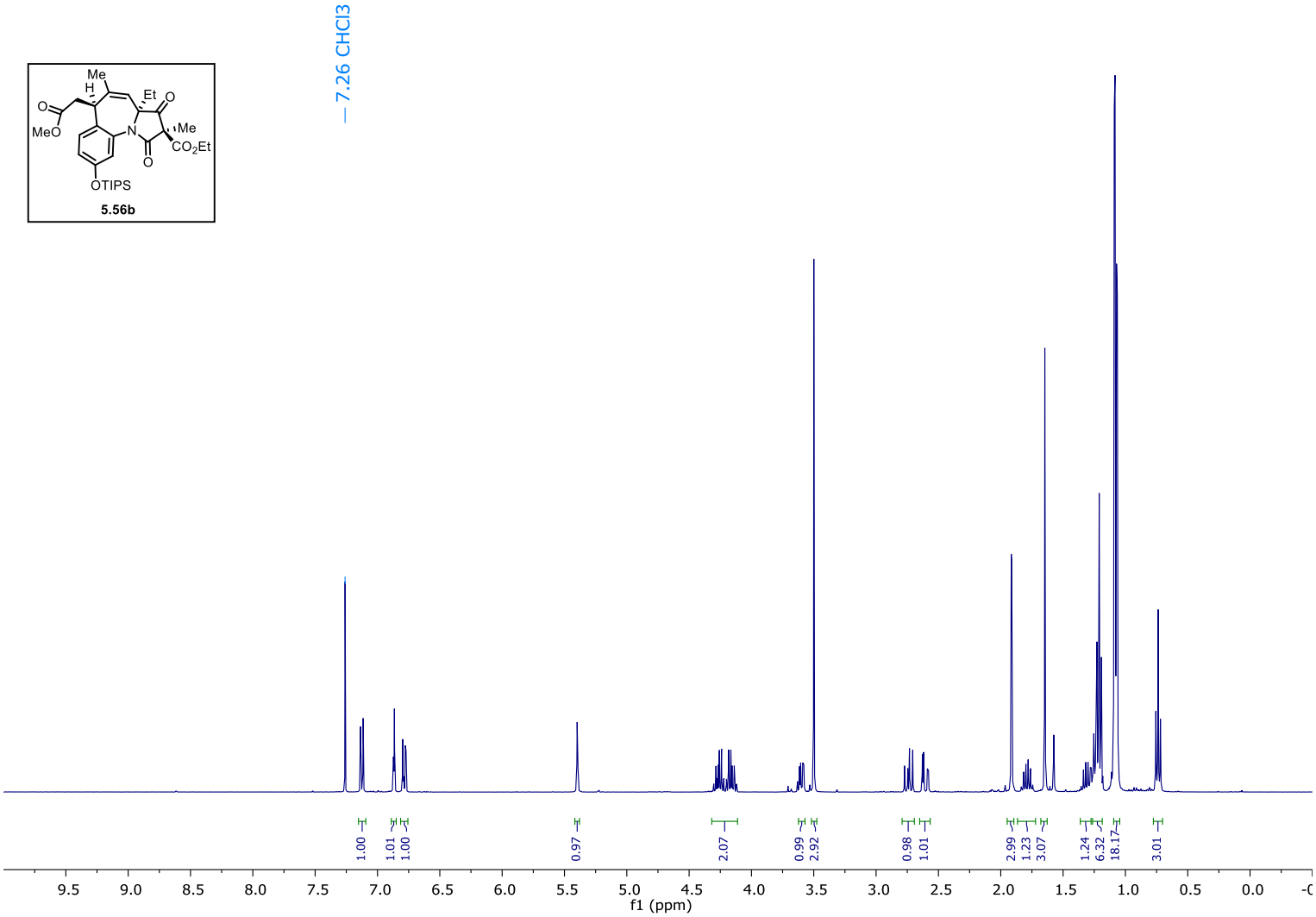


Figure C.63. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.56b**

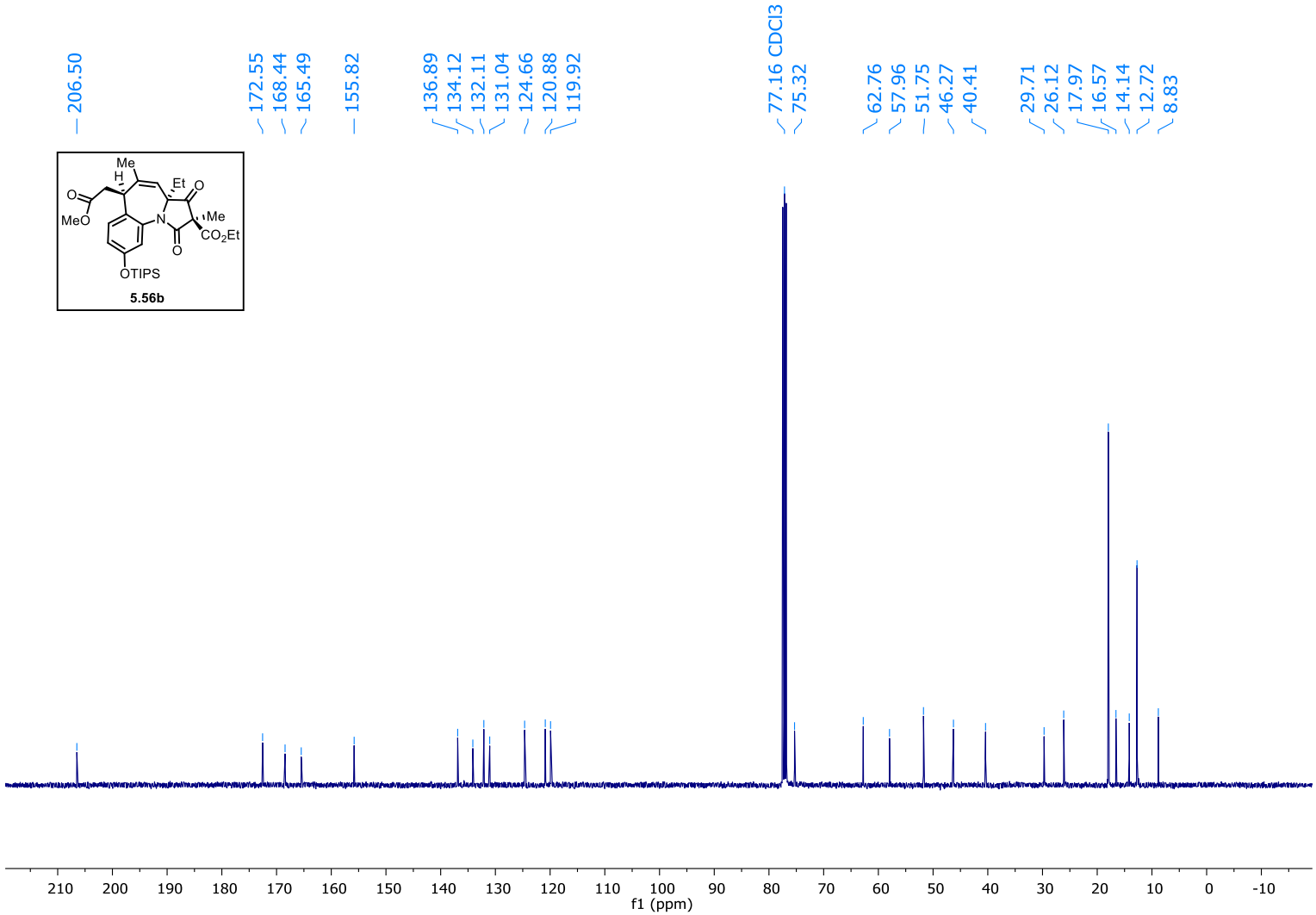


Figure C.64. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.56b**

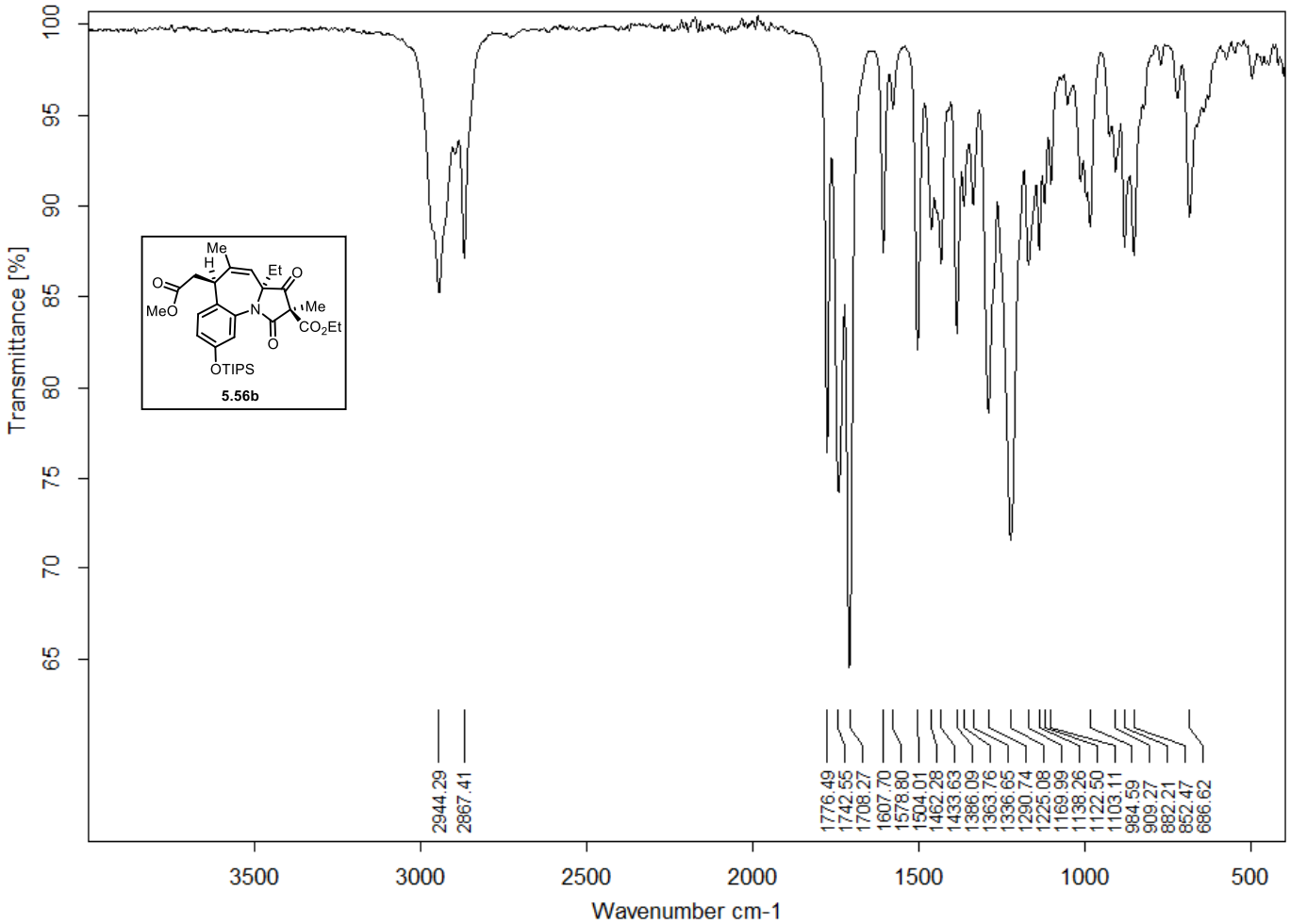


Figure C.65. FTIR spectrum (neat) of compound **5.56b**

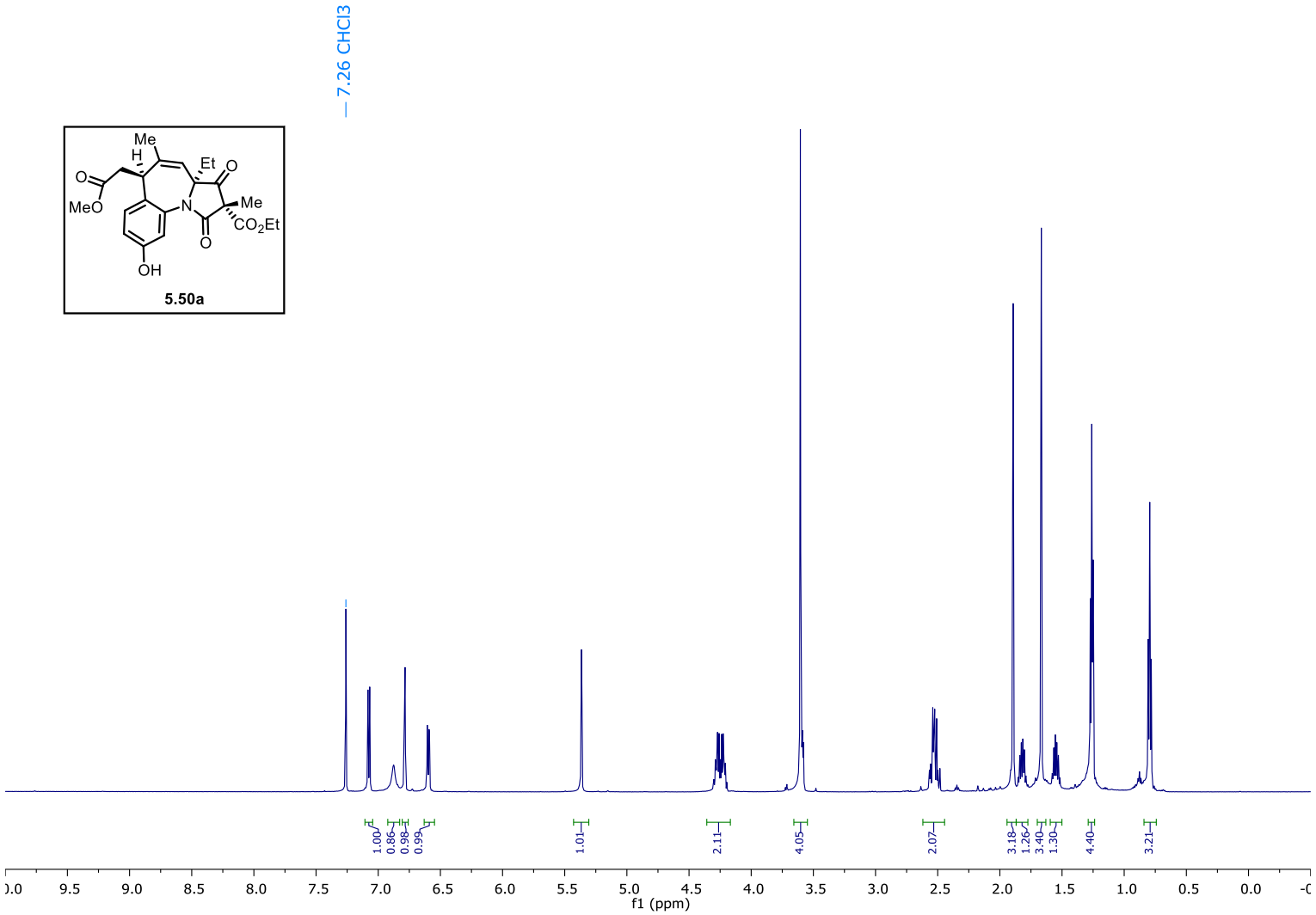


Figure C.66. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **5.50a**

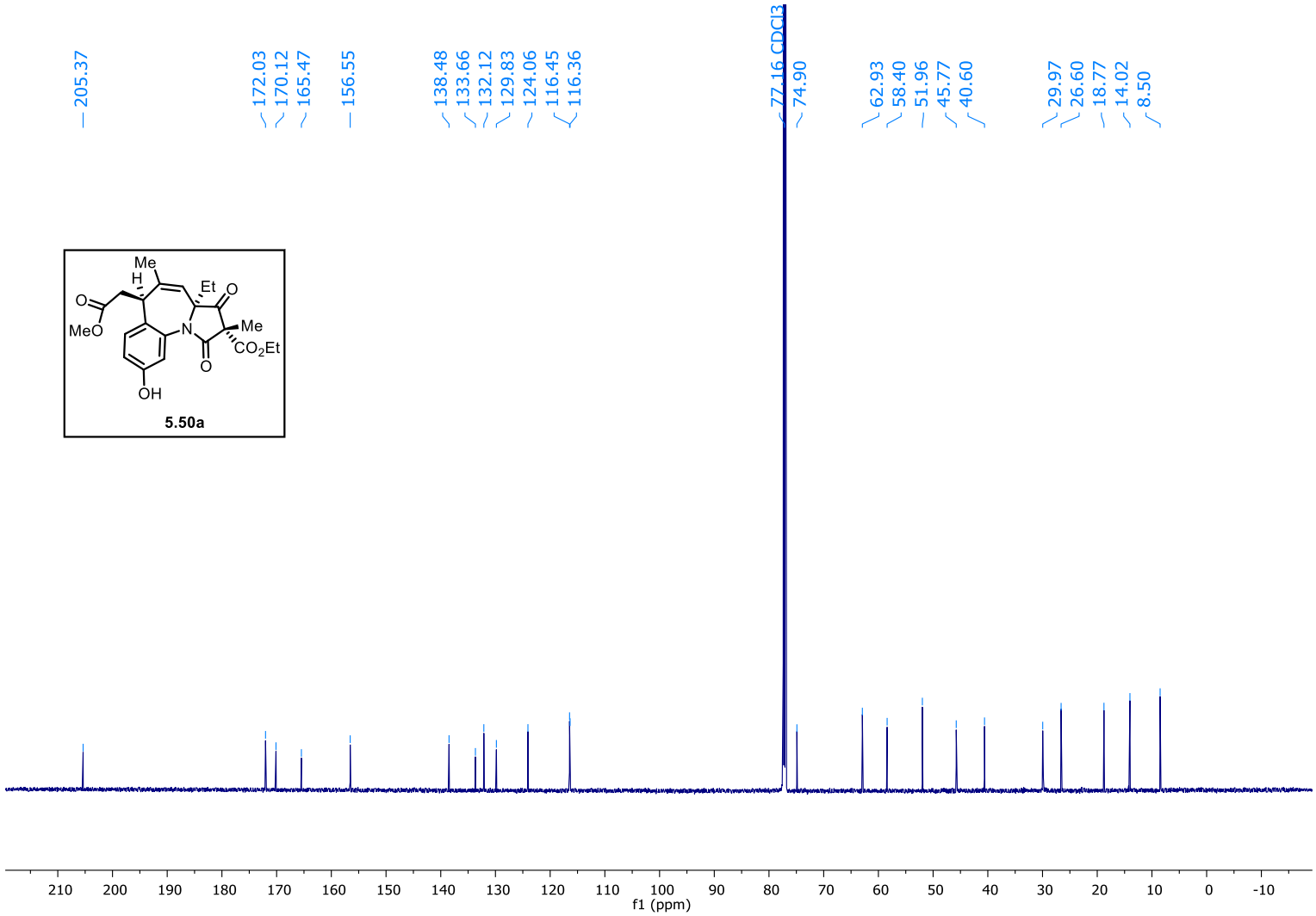


Figure C.67. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.50a**

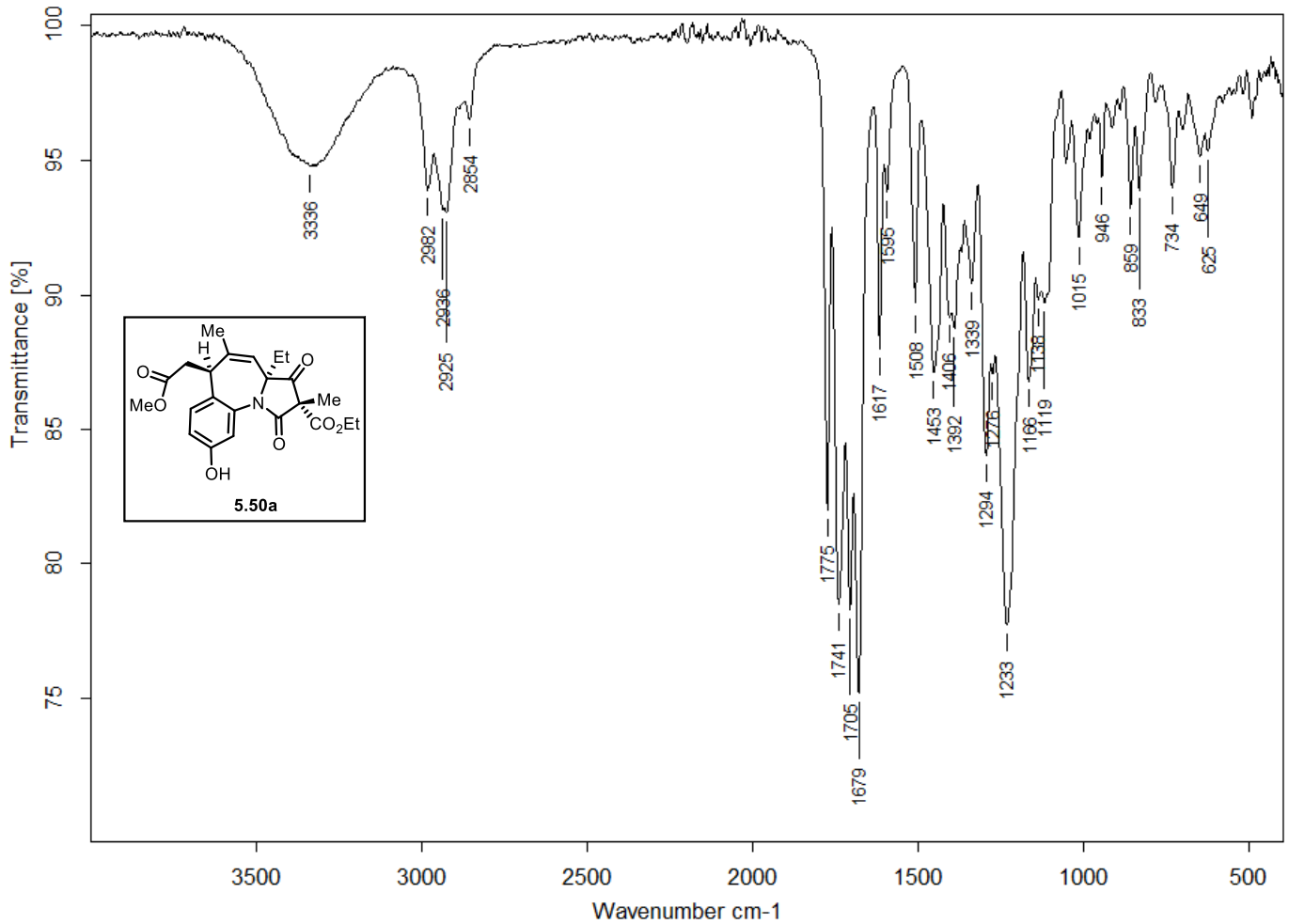


Figure C.68. FTIR spectrum (neat) of compound **5.50a**

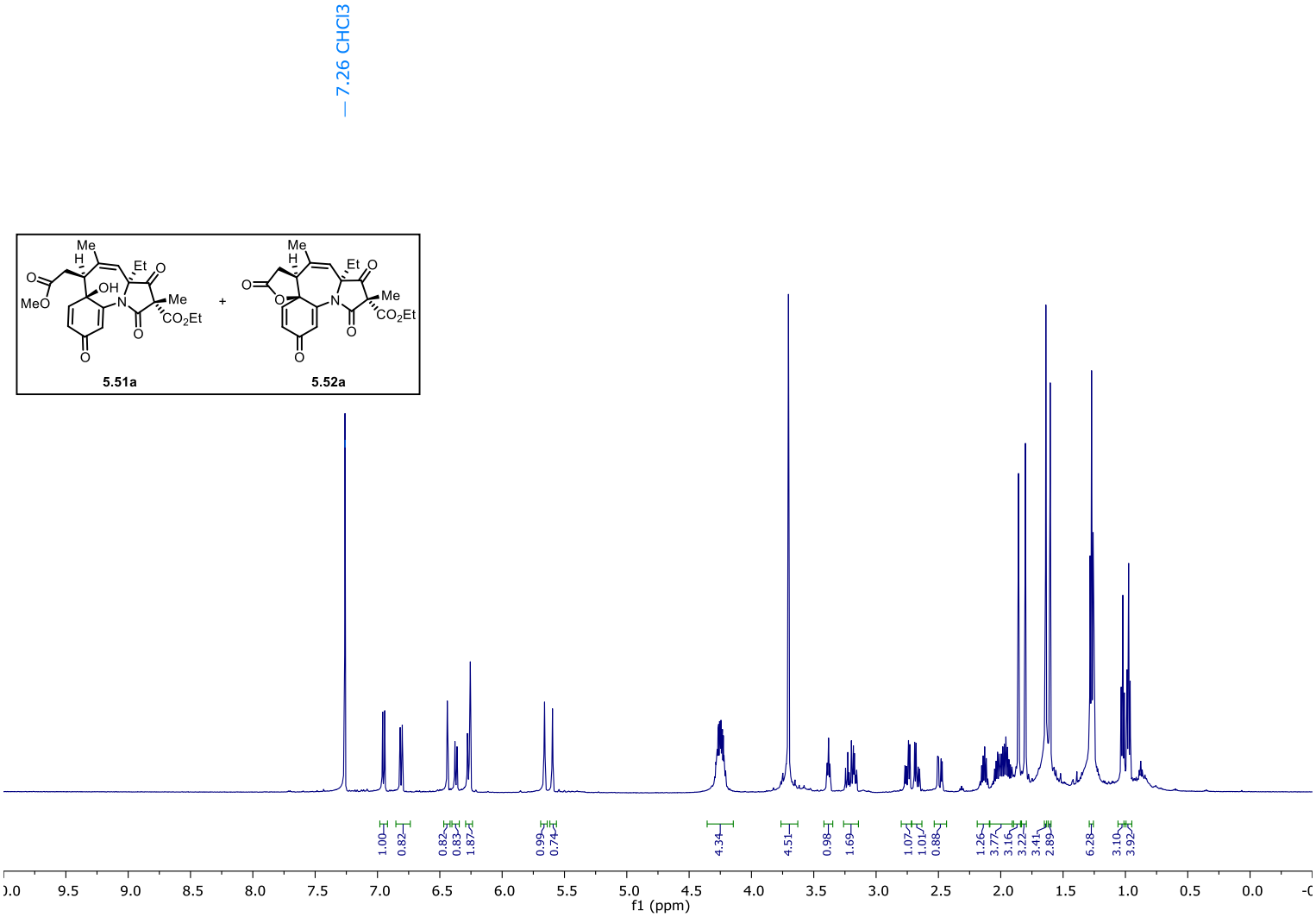


Figure C.69. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **5.51a** + **5.52a**

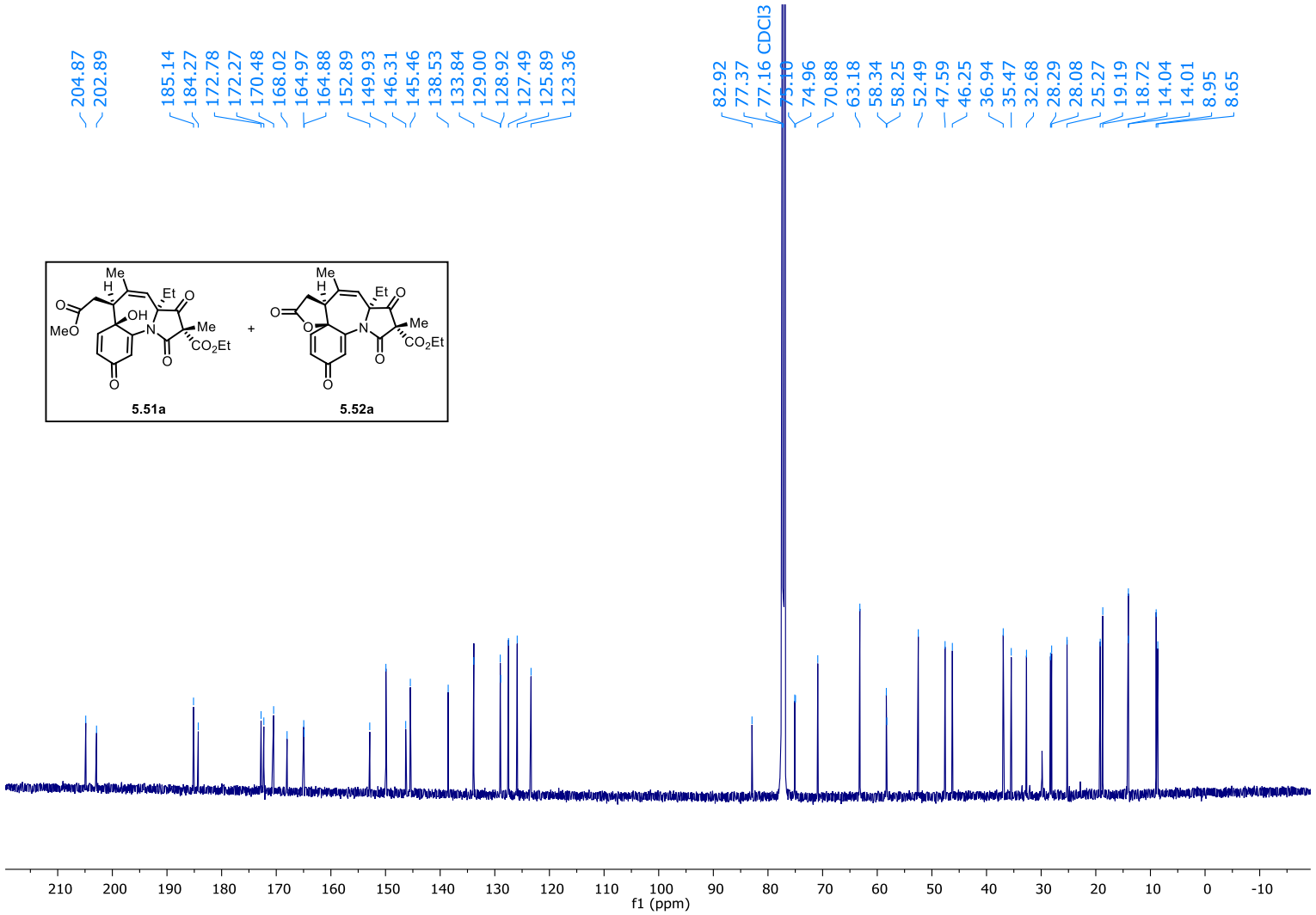


Figure C.70. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.51a** + **5.52a**

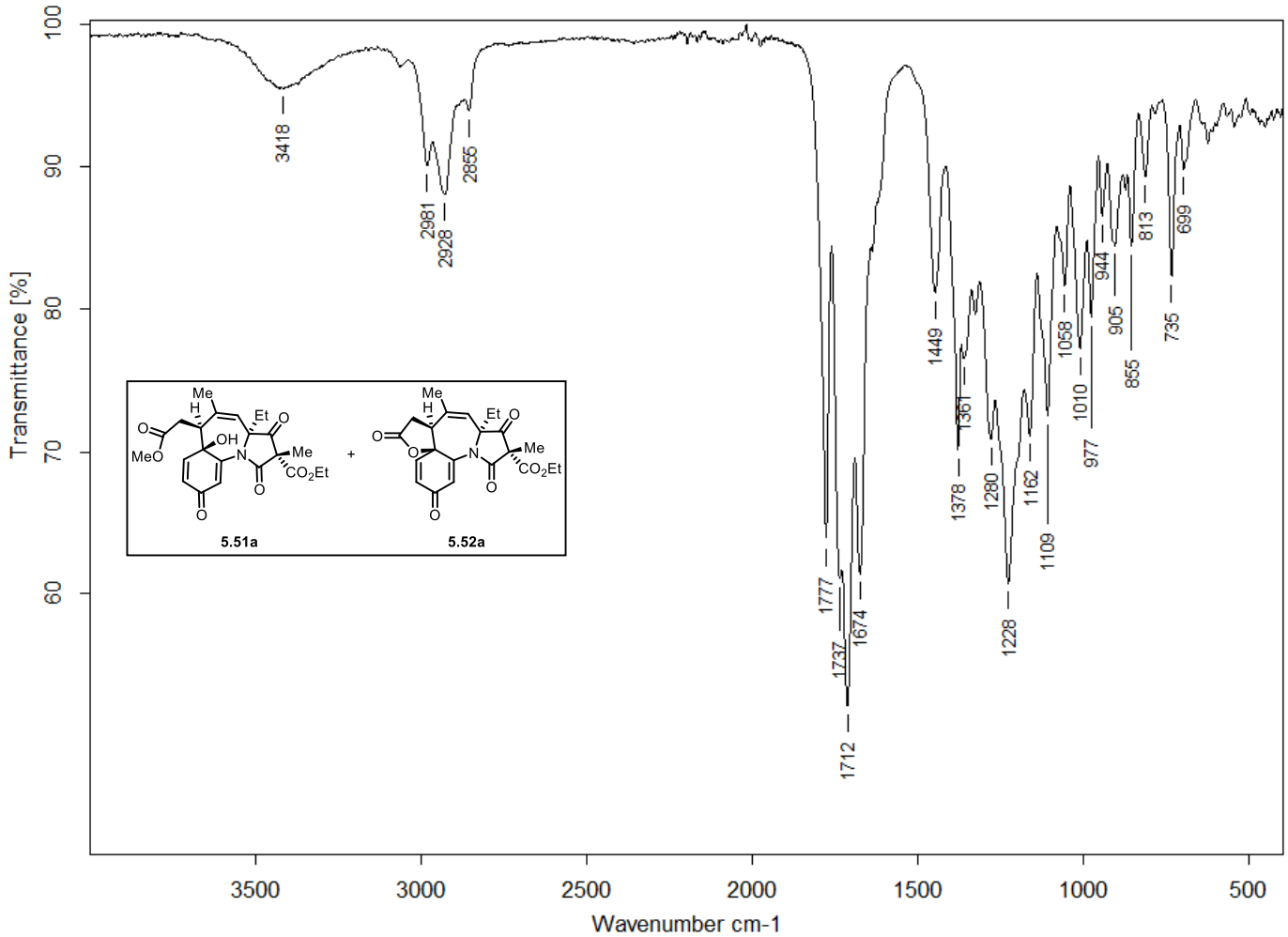


Figure C.71. FTIR spectrum (neat) of compound **5.51a** + **5.52a**

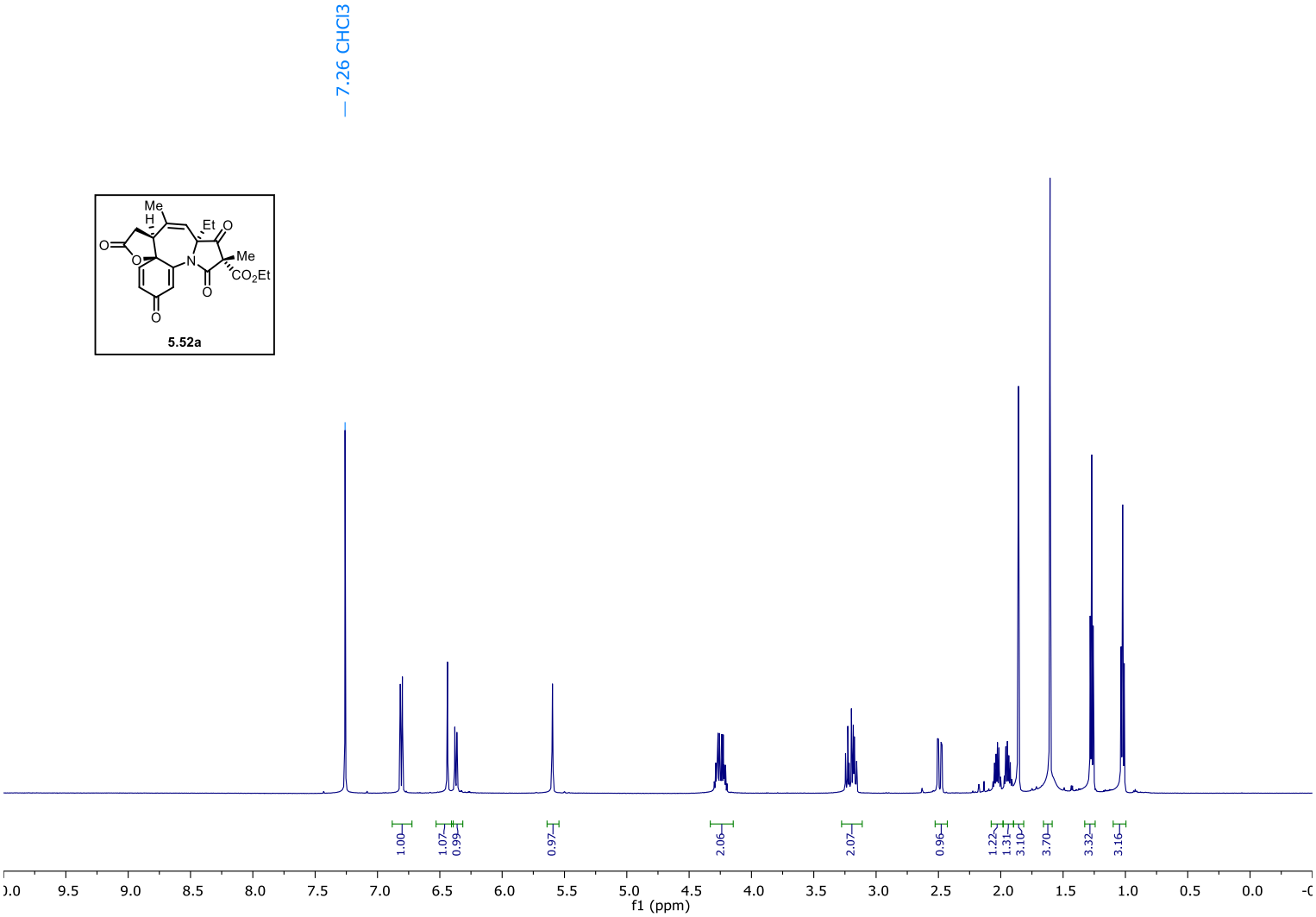


Figure C.72. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **5.52a**

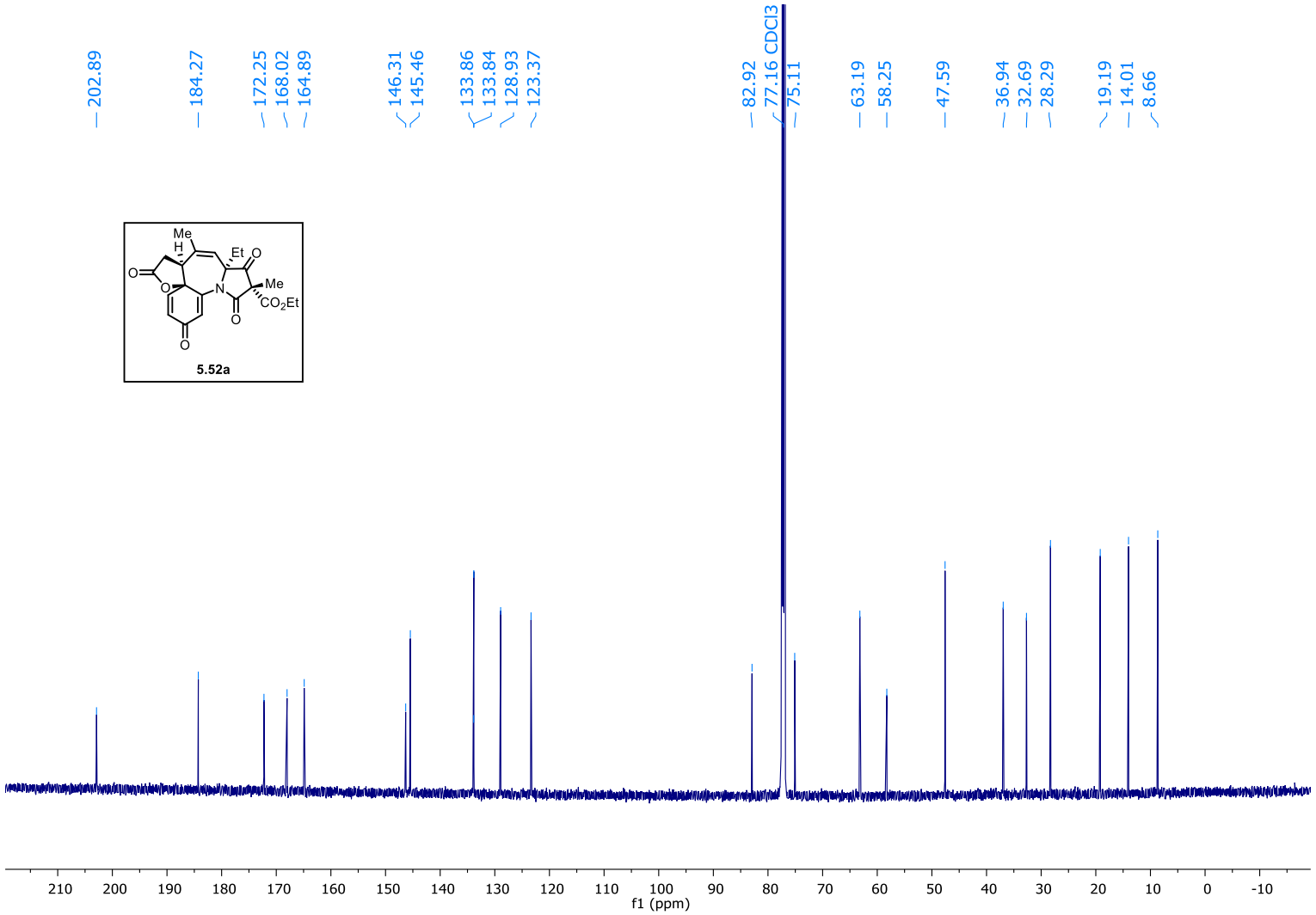


Figure C.73. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **5.52a**

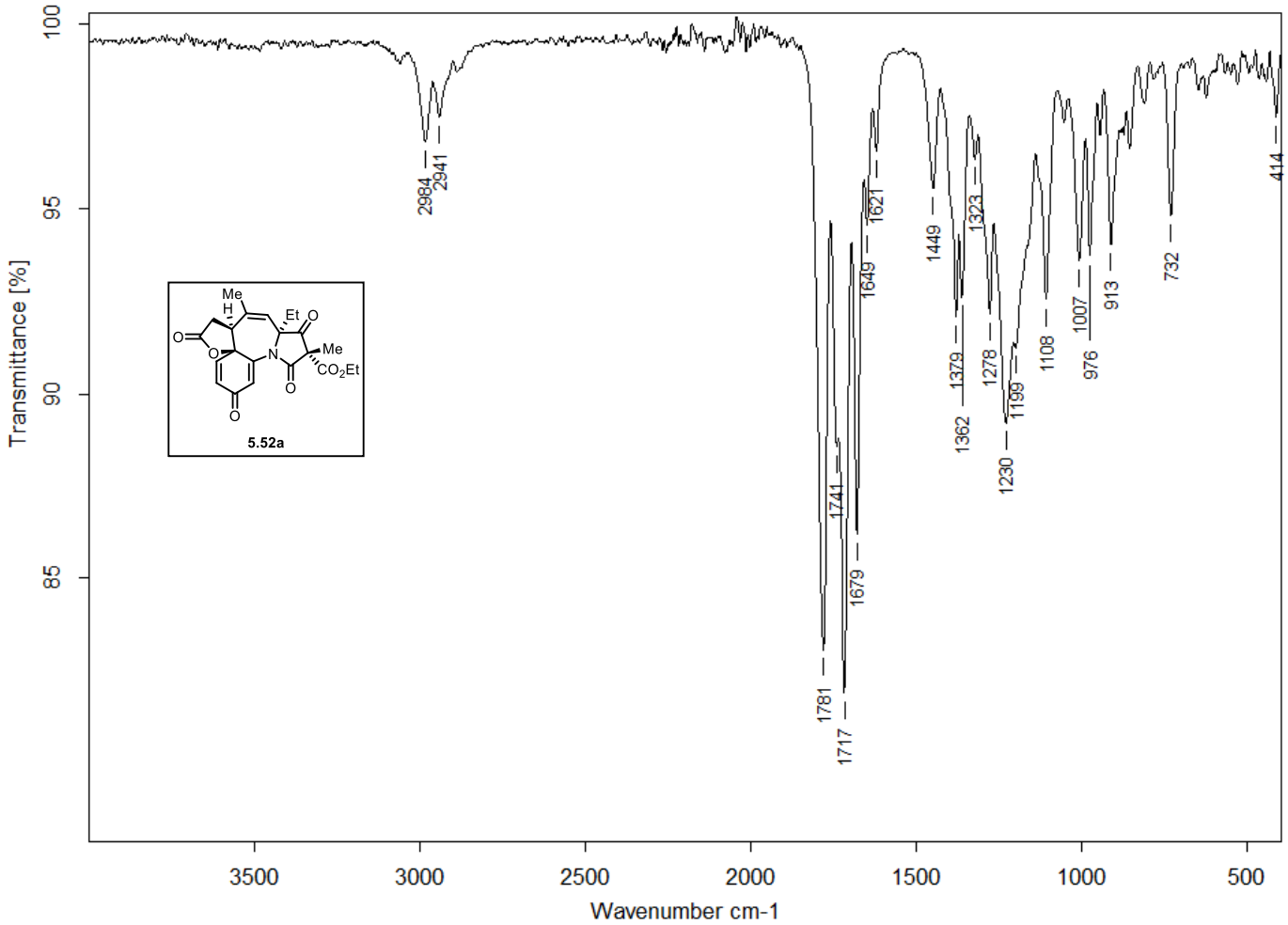


Figure C.74. FTIR spectrum (neat) of compound **5.52a**

APPENDIX D

Spectra Relevant to Chapter Six

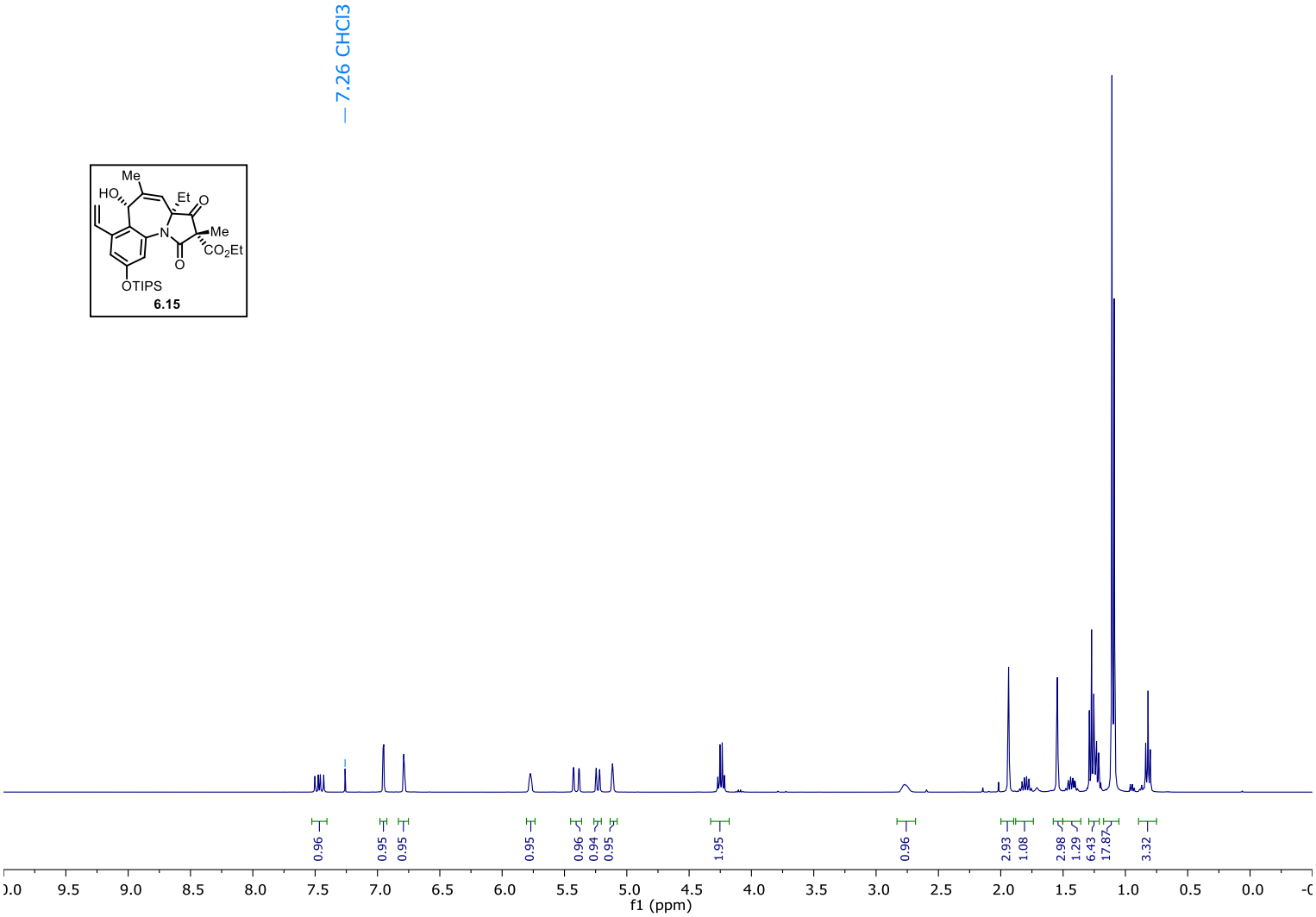


Figure D.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.15**

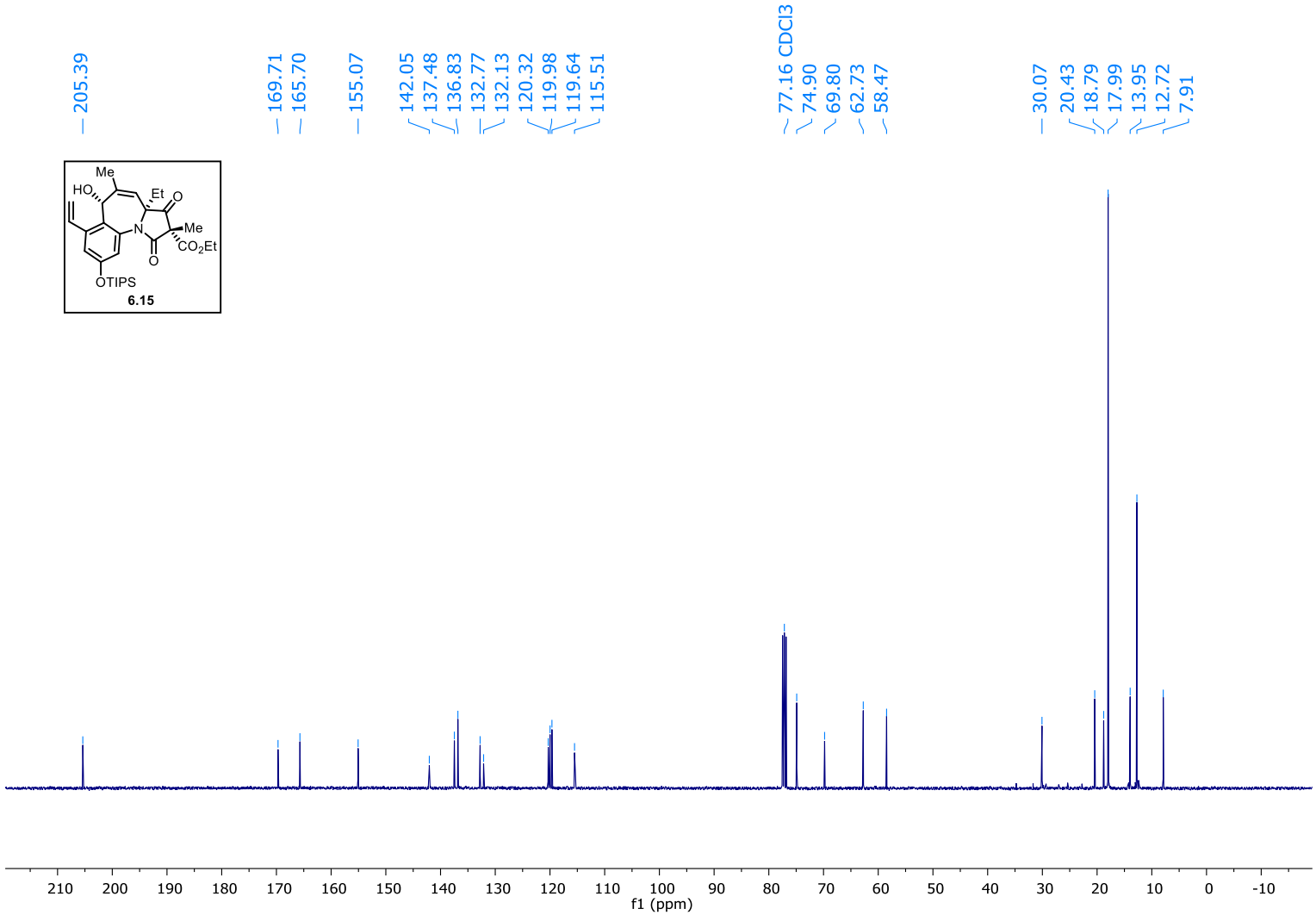


Figure D.2. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.15**

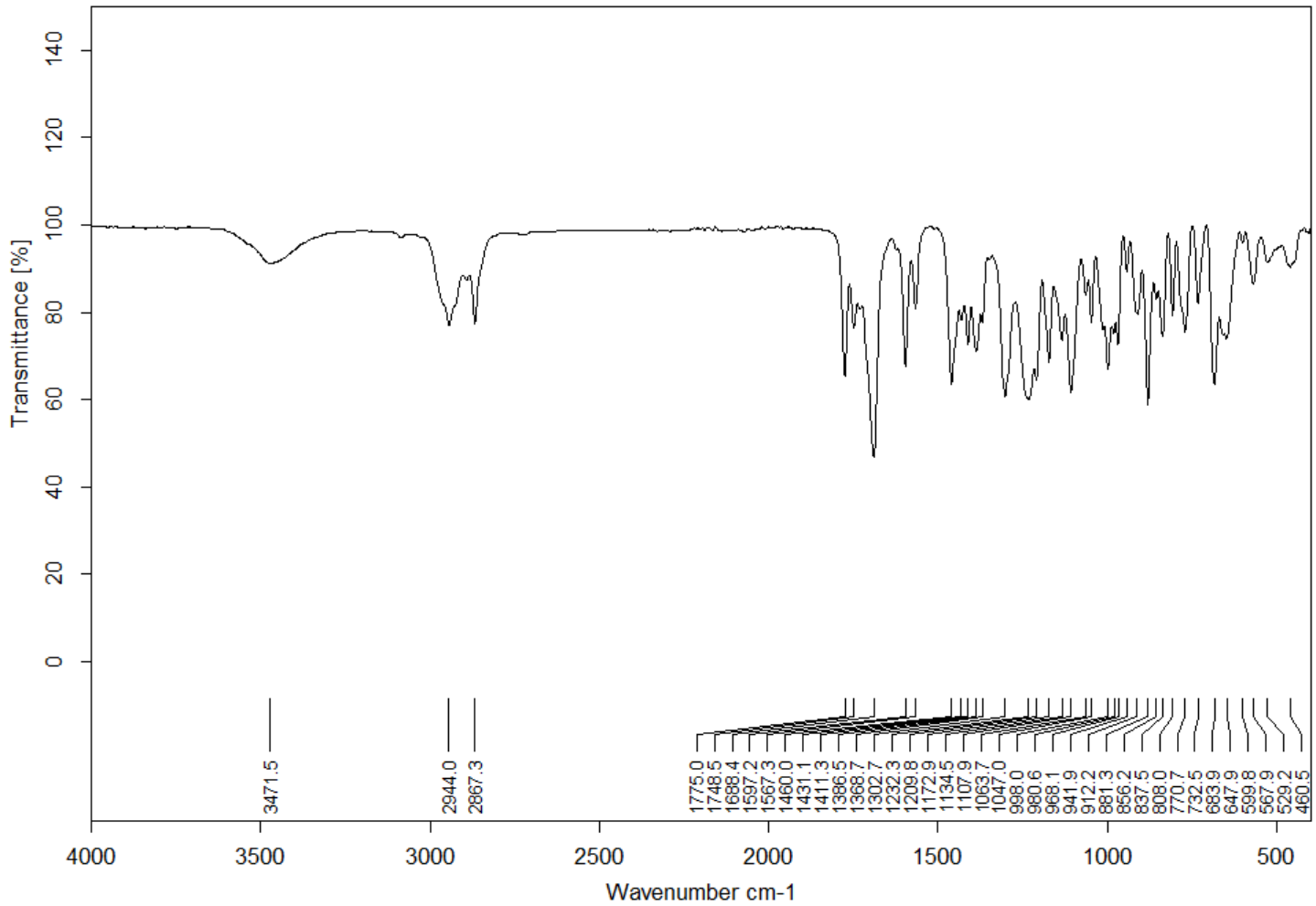


Figure D.3. FTIR spectrum (neat) of compound **6.15**

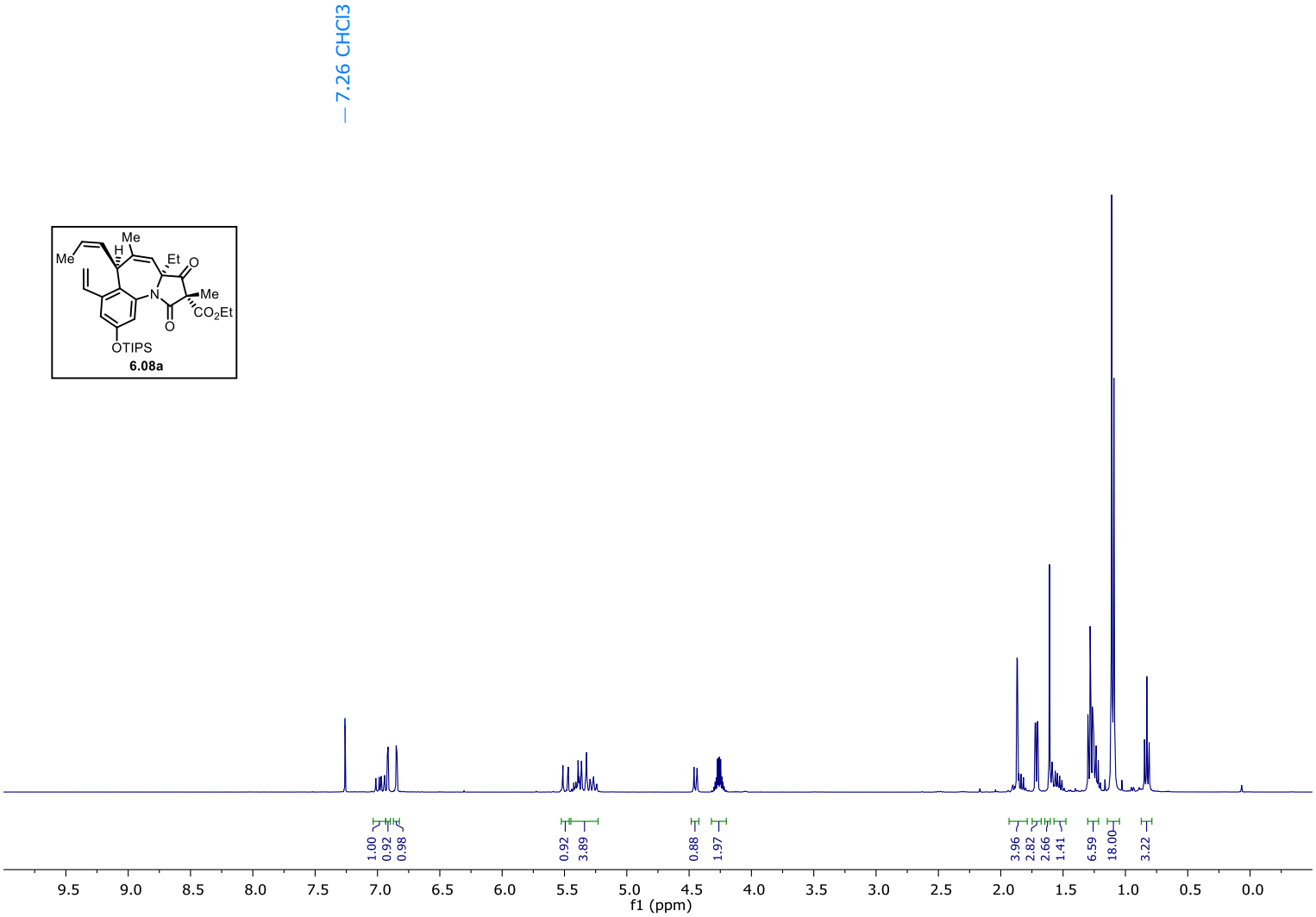


Figure D.4. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.08a**

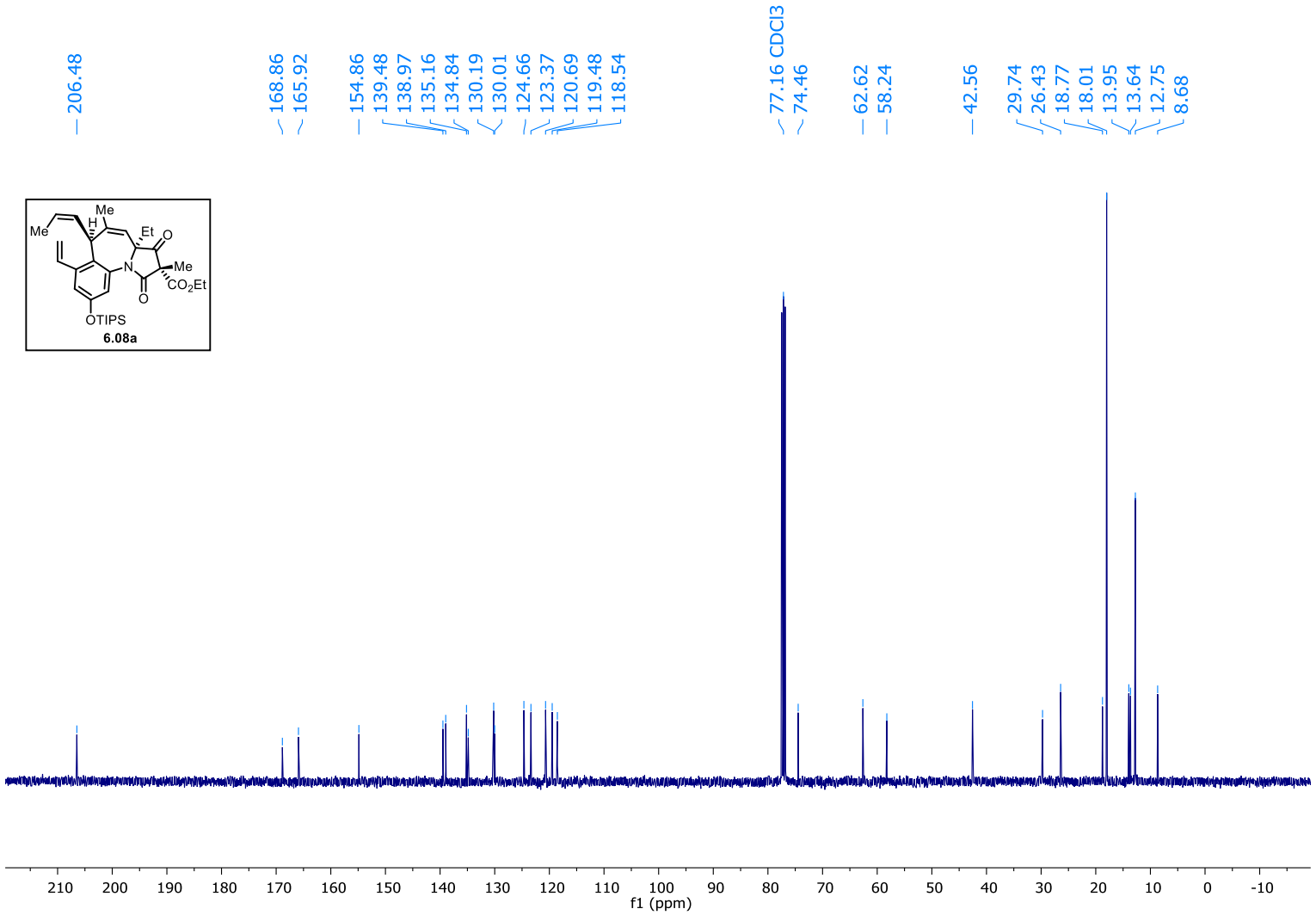


Figure D.5. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.08a**

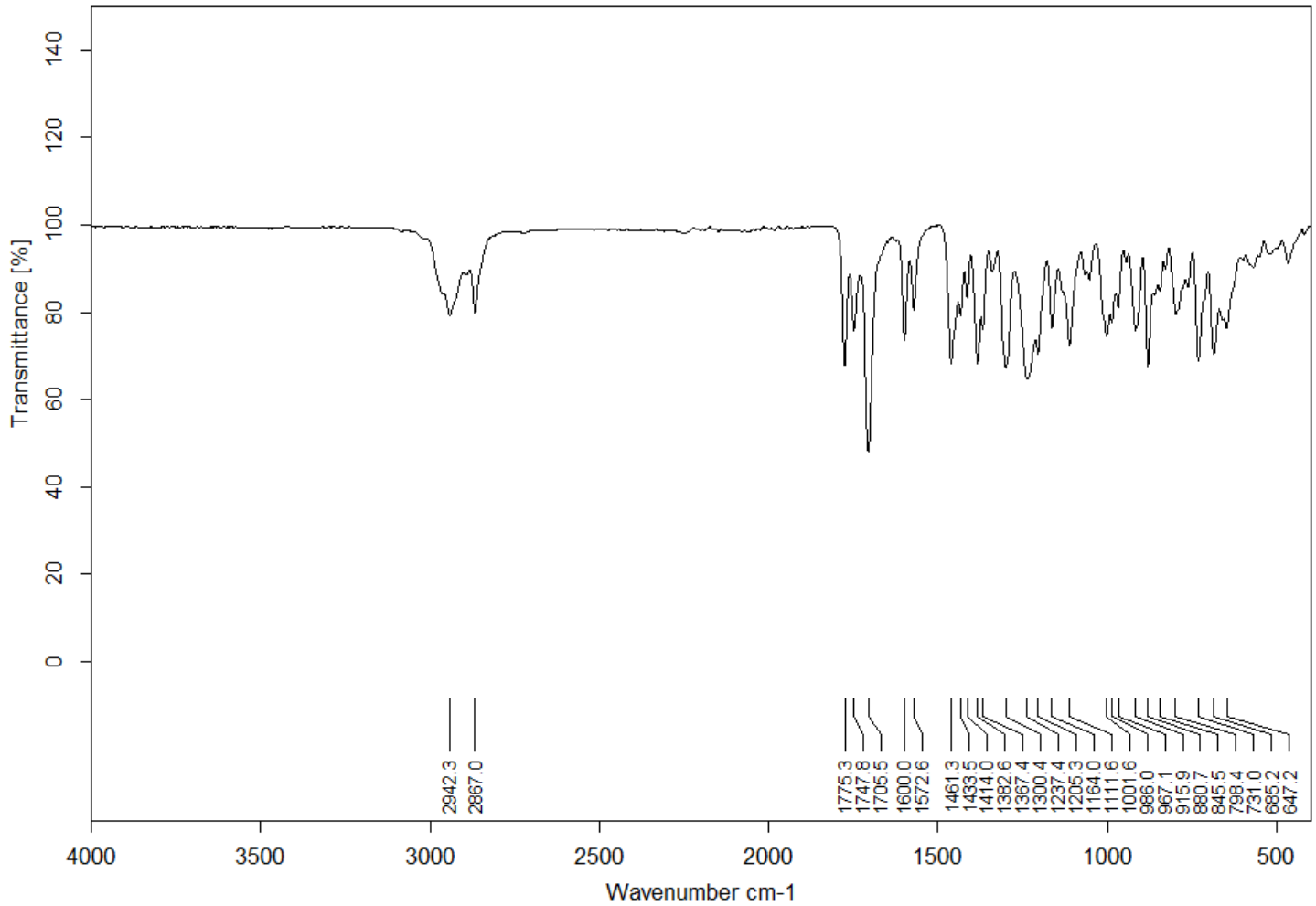


Figure D.6. FTIR spectrum (neat) of compound **6.08a**

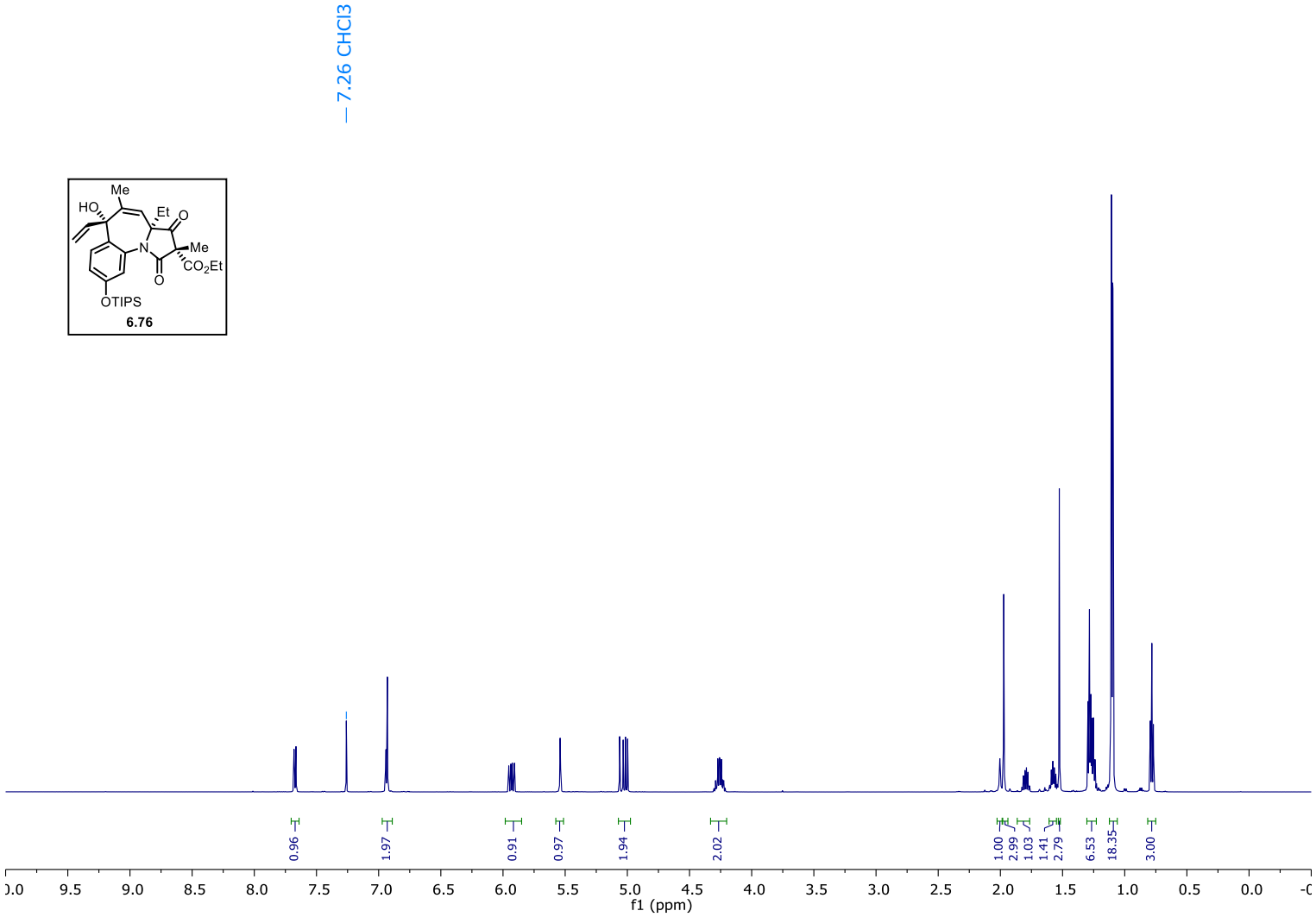


Figure D.7. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.76**

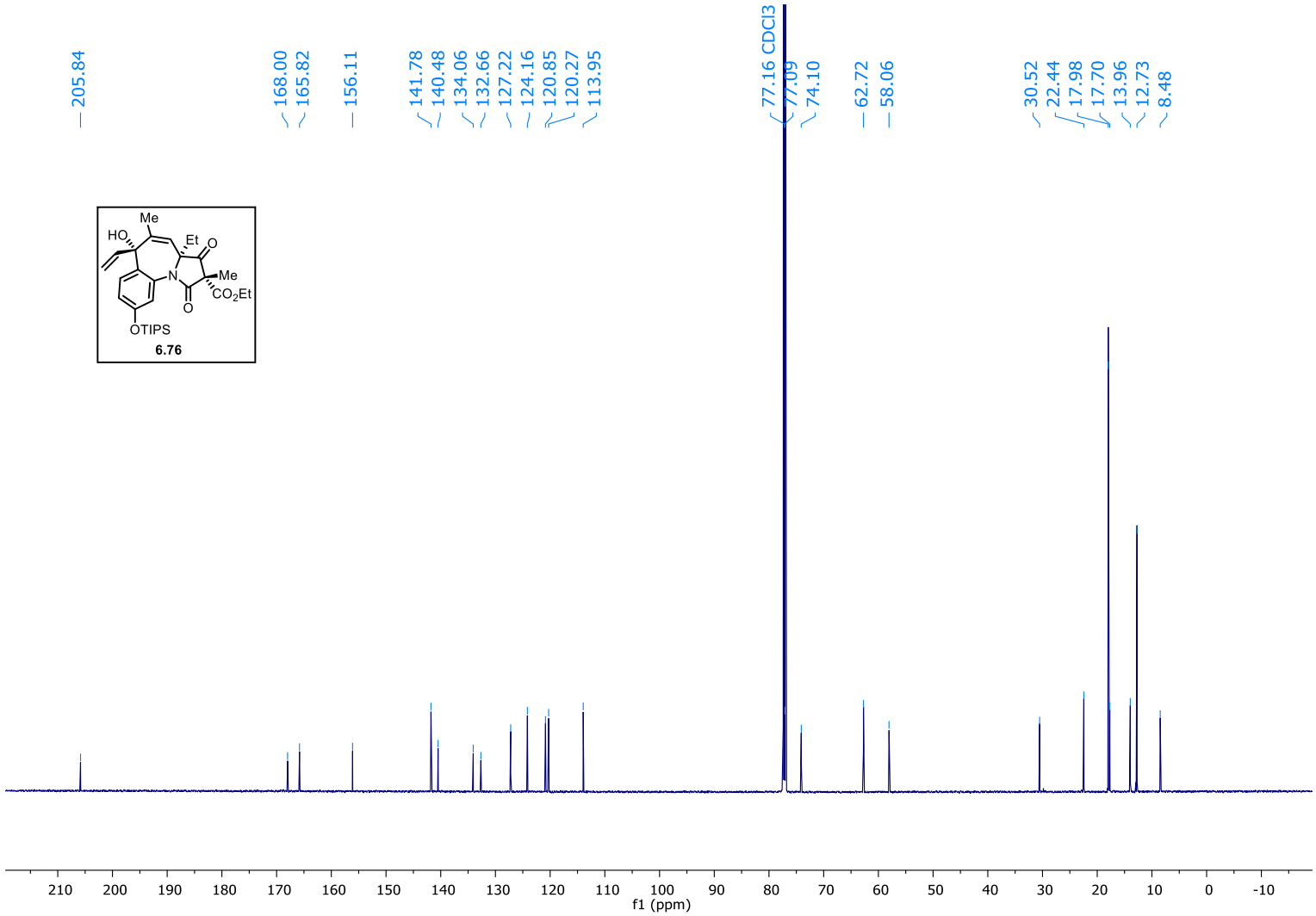


Figure D.8. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.76**

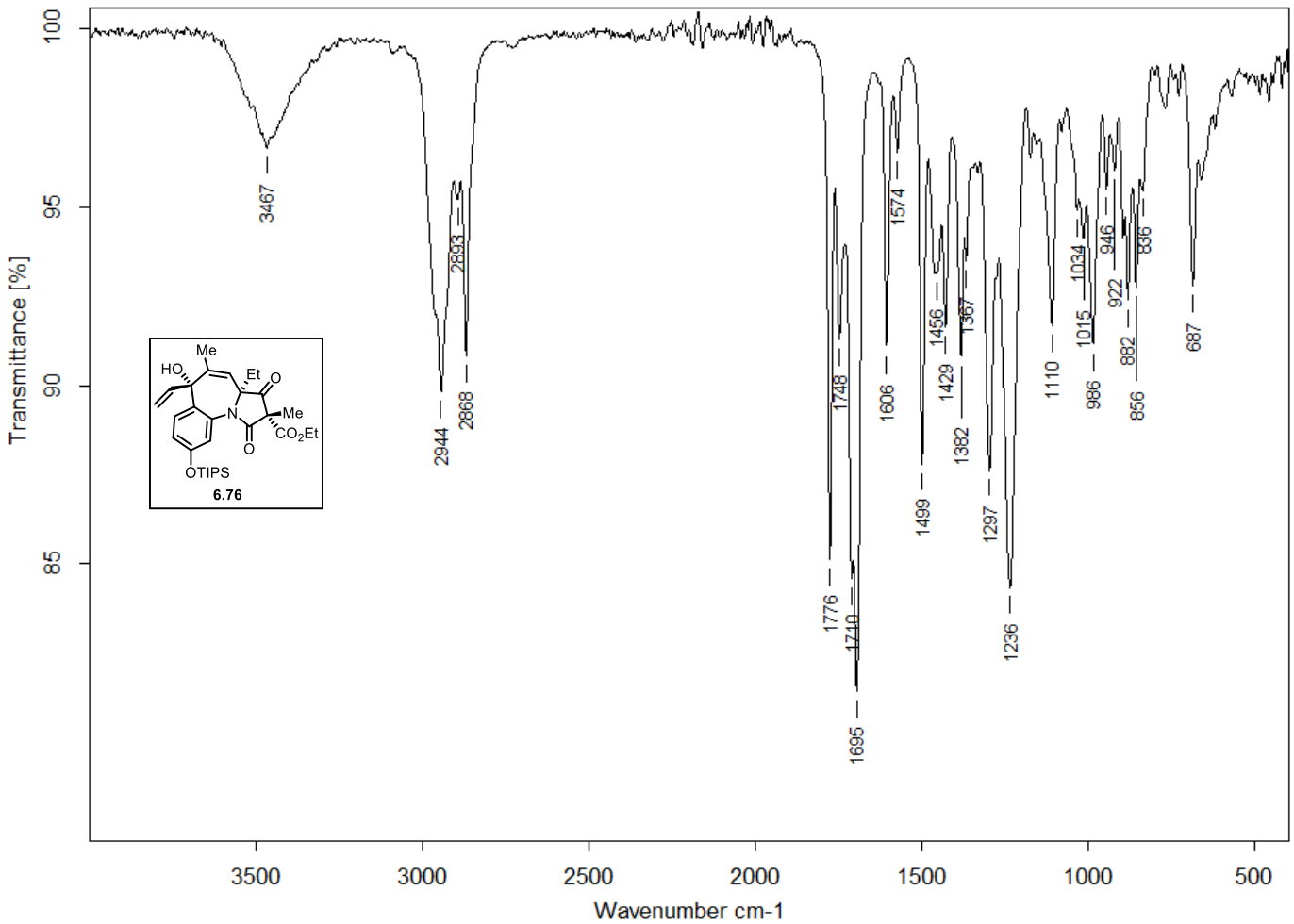


Figure D.9. FTIR spectrum (neat) of compound **6.76**

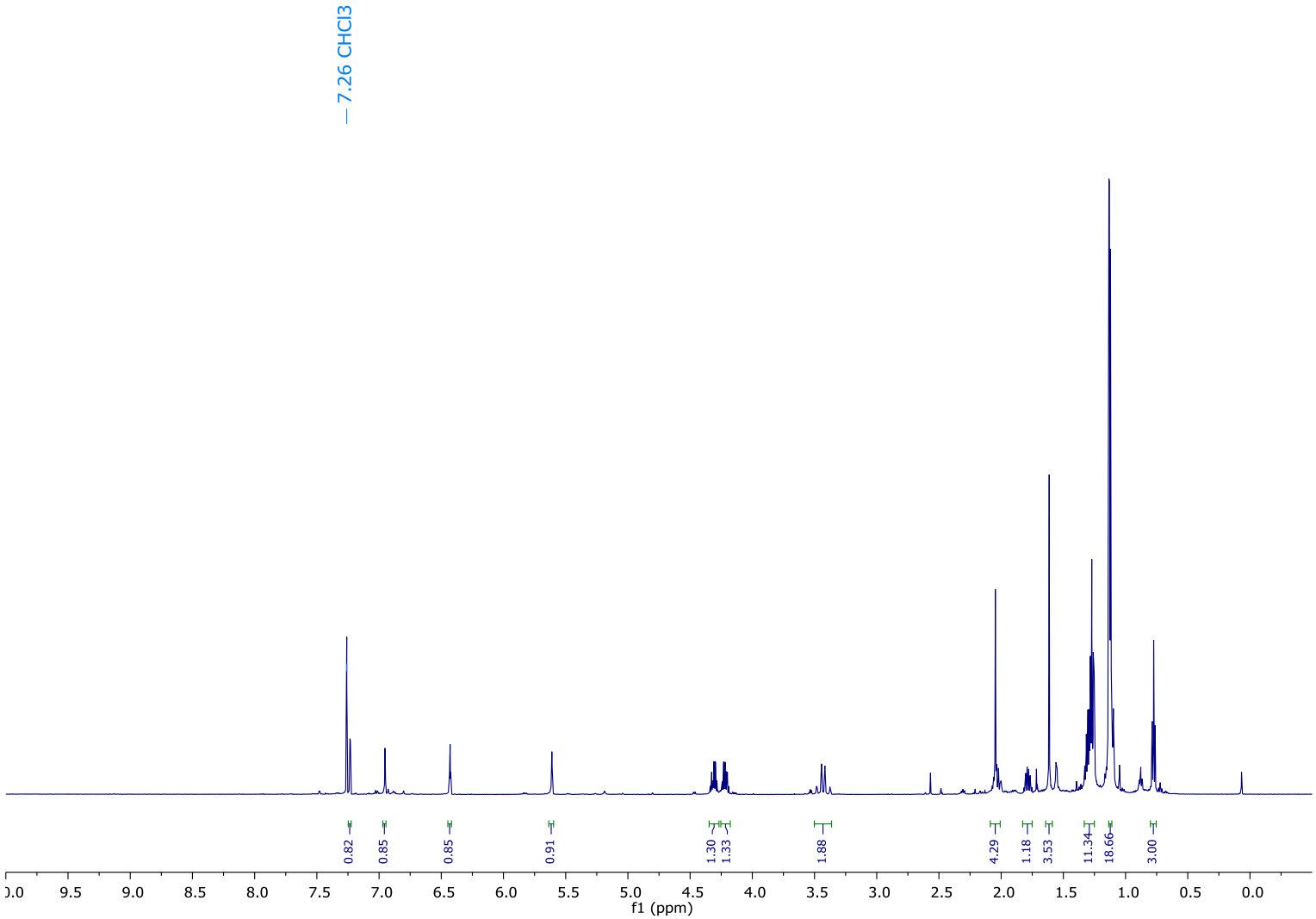


Figure D.10. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.16**

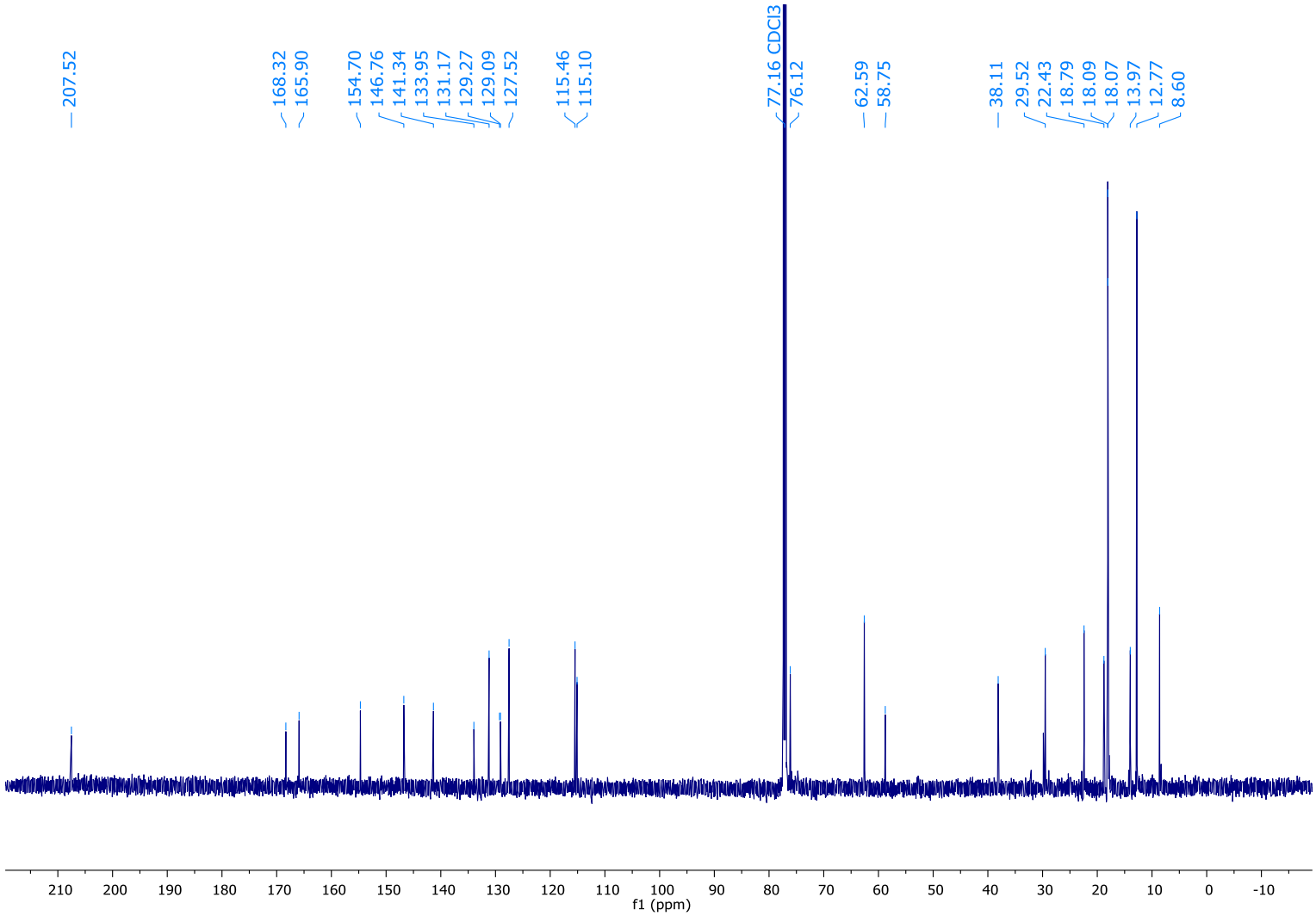


Figure D.11. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.16**

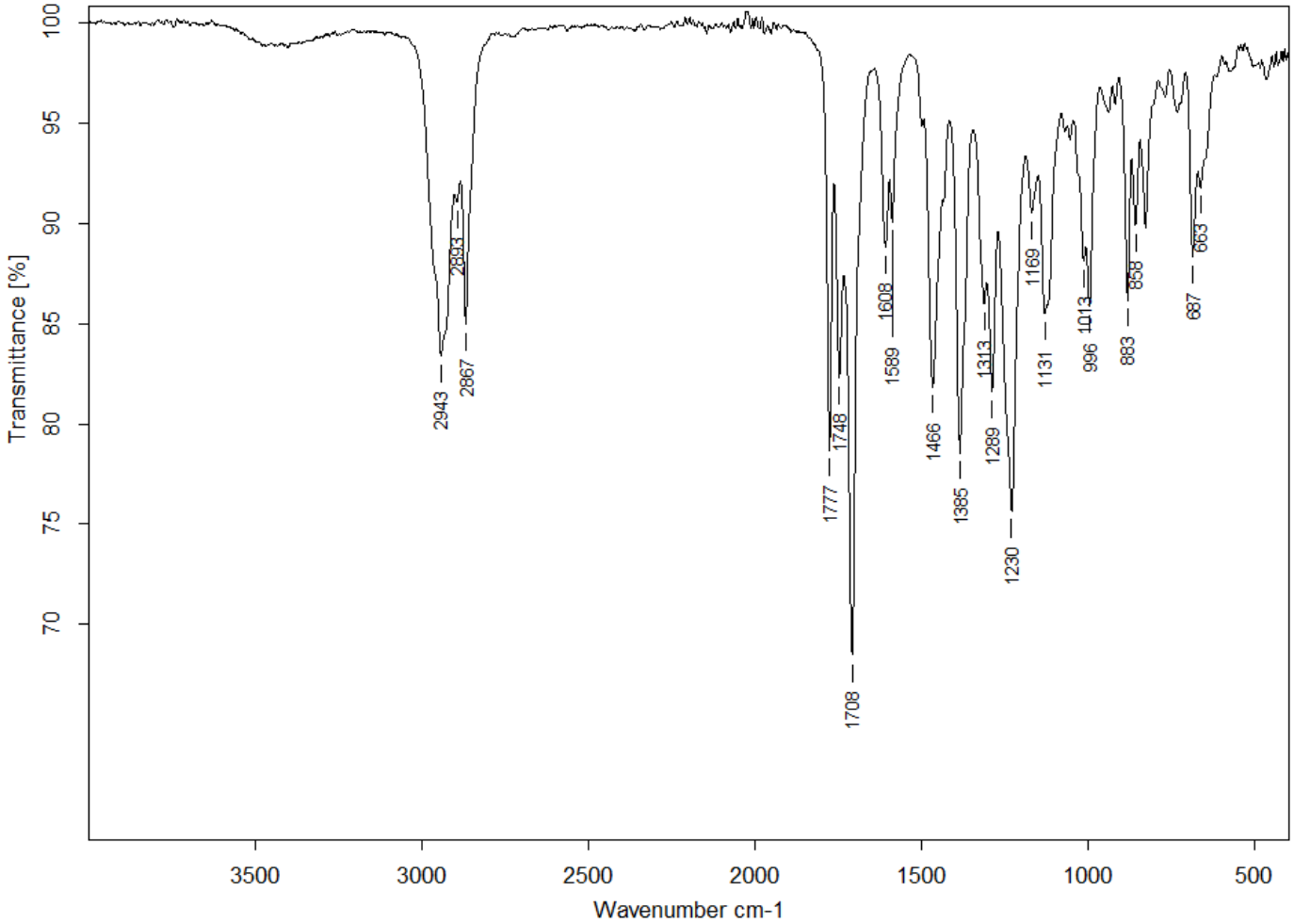


Figure D.12. FTIR spectrum (neat) of compound **6.16**

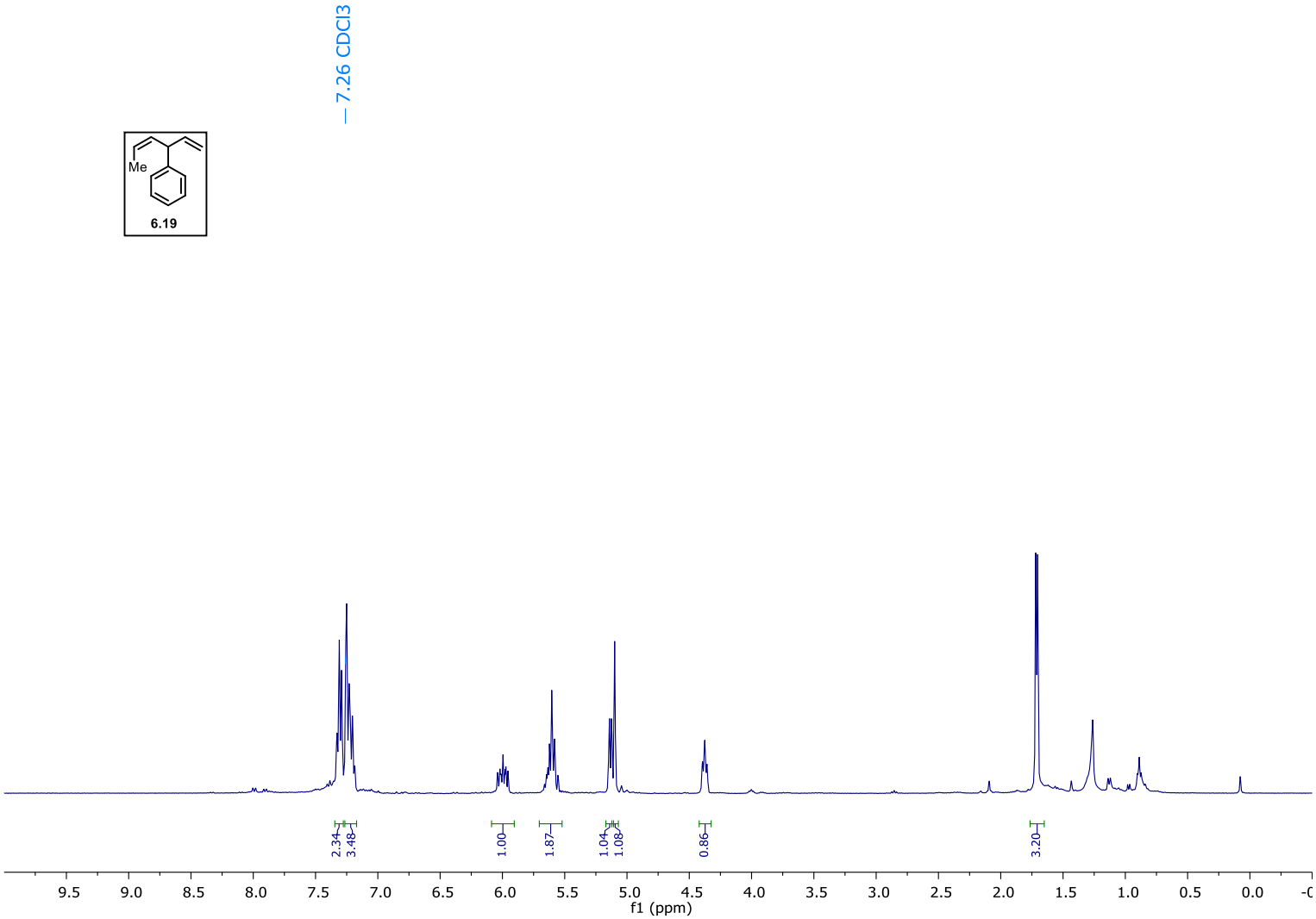


Figure D.13. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.19**

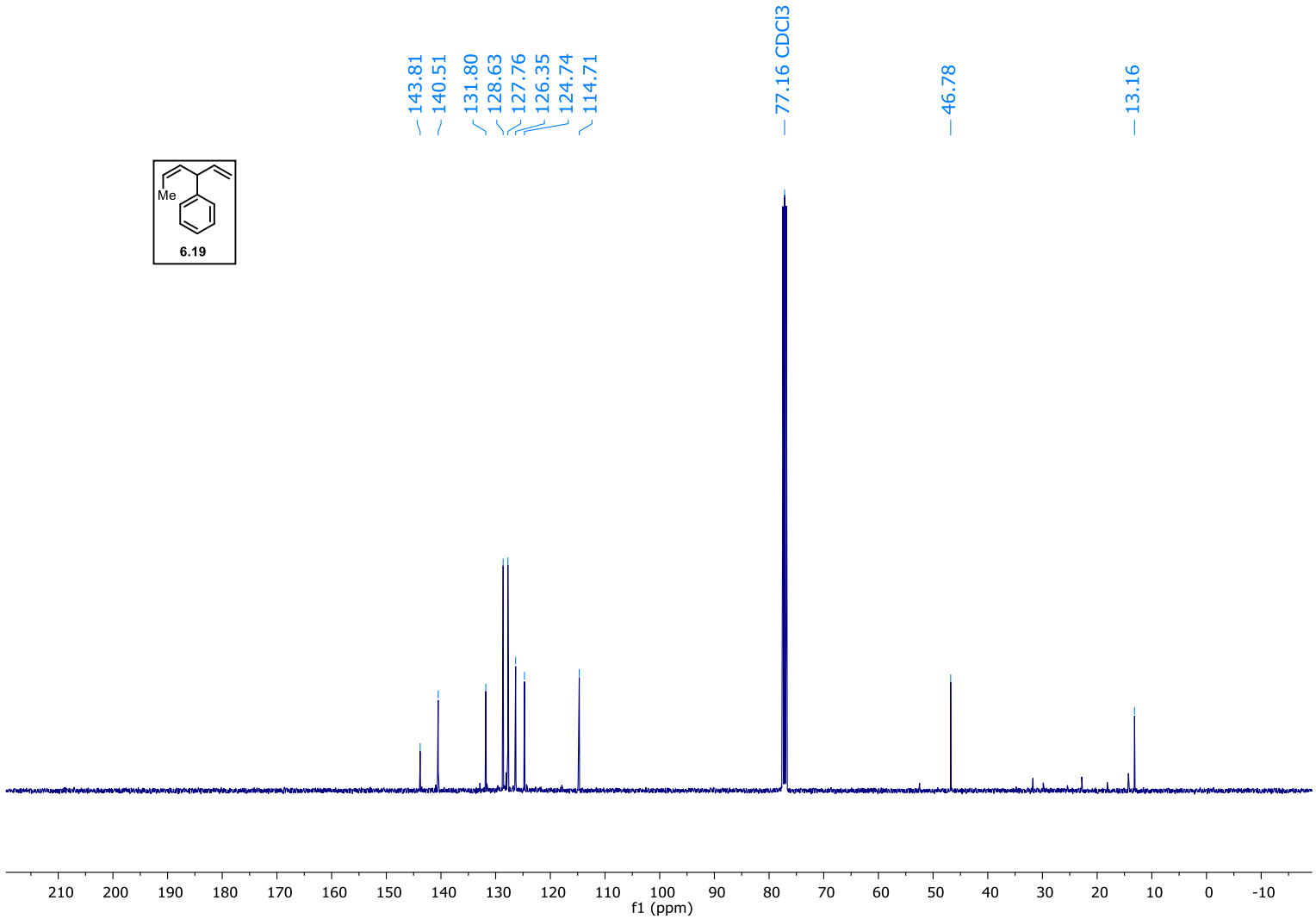


Figure D.14. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.19**

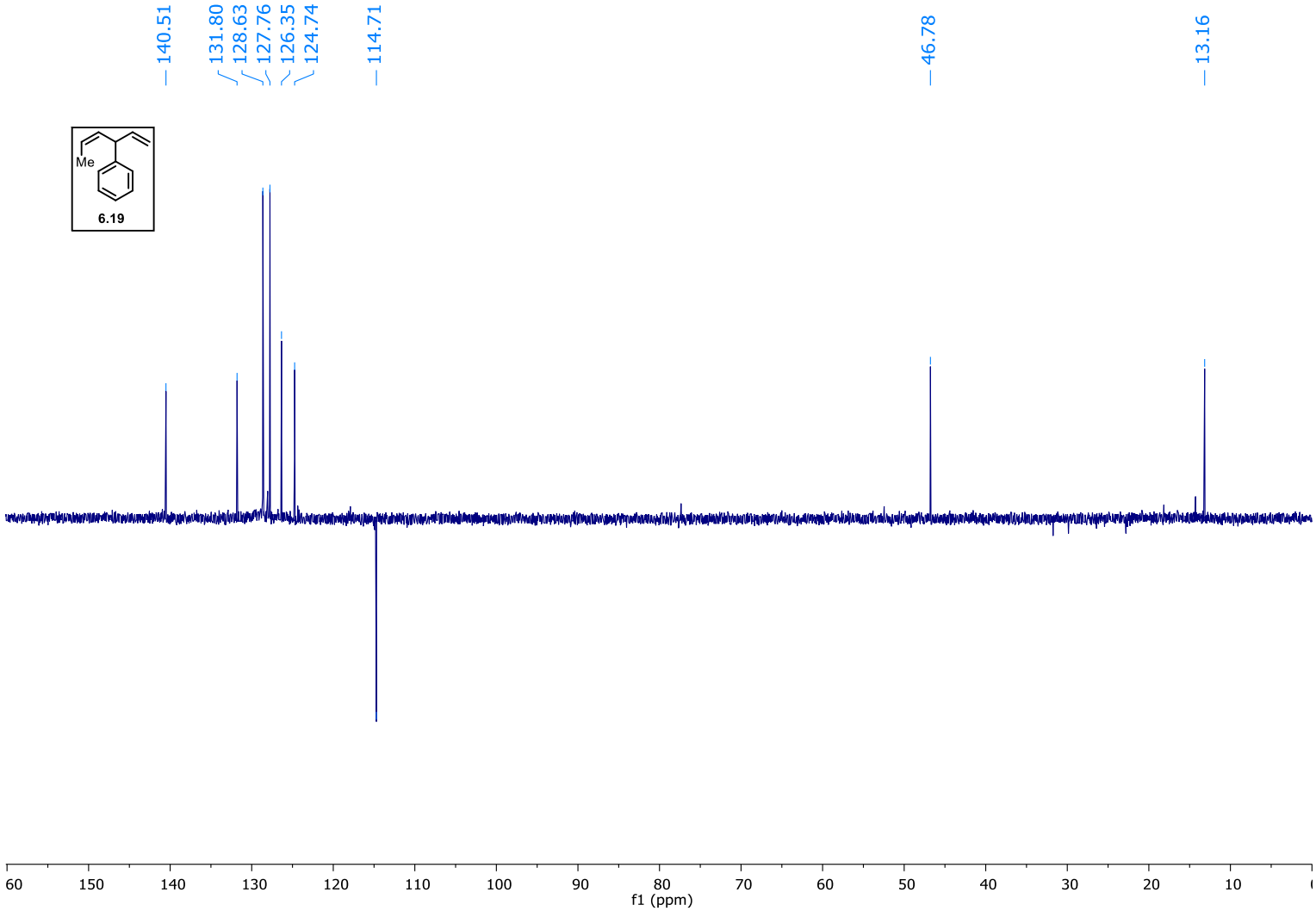


Figure D.15. DEPT-135 of (101 MHz, $CDCl_3$) of compound **6.19**

Figure D.16. HMQC of (400 MHz, $CDCl_3$) of compound **6.19**

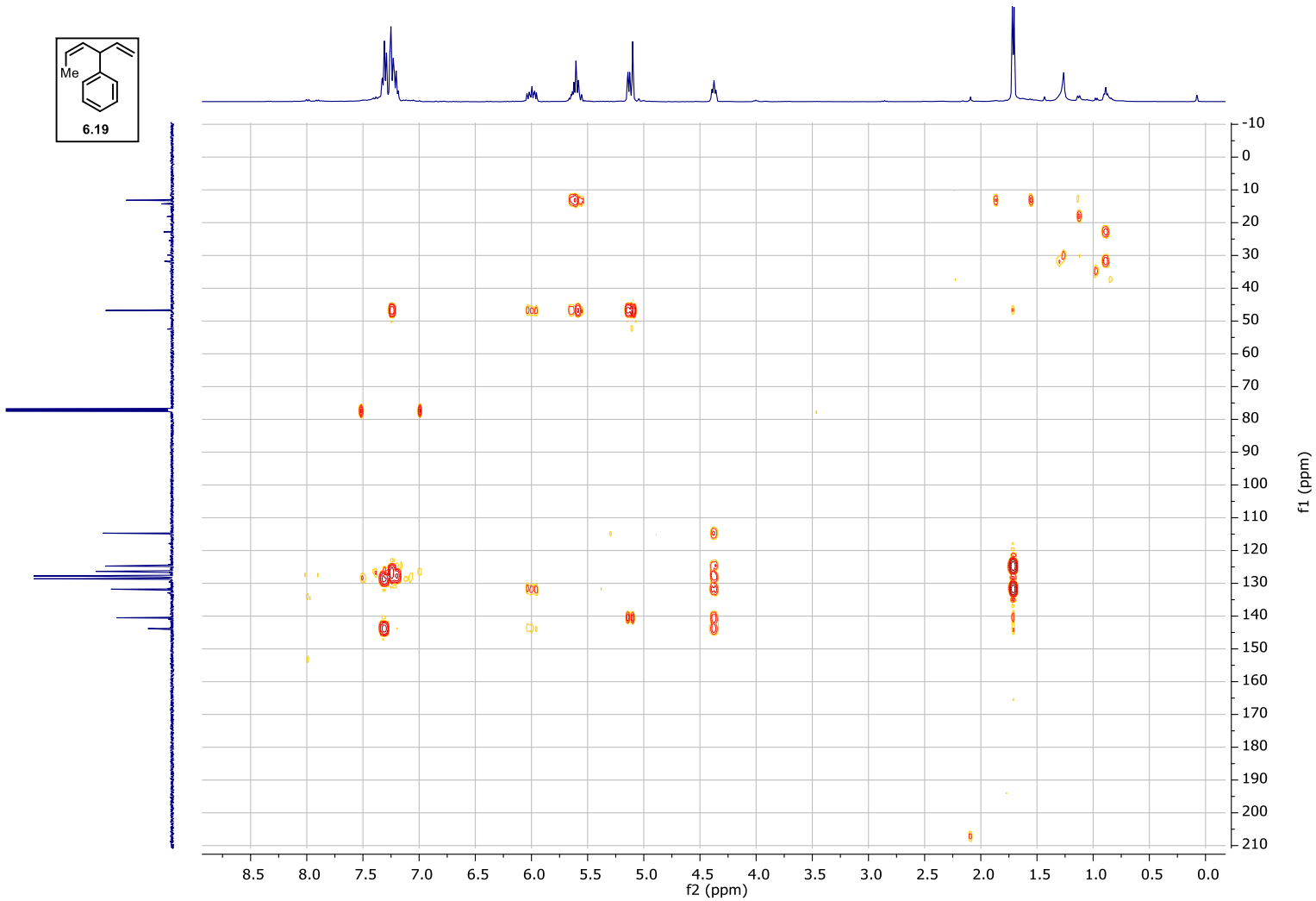


Figure D.17. HMBC of (400 MHz, $CDCl_3$) of compound **6.19**

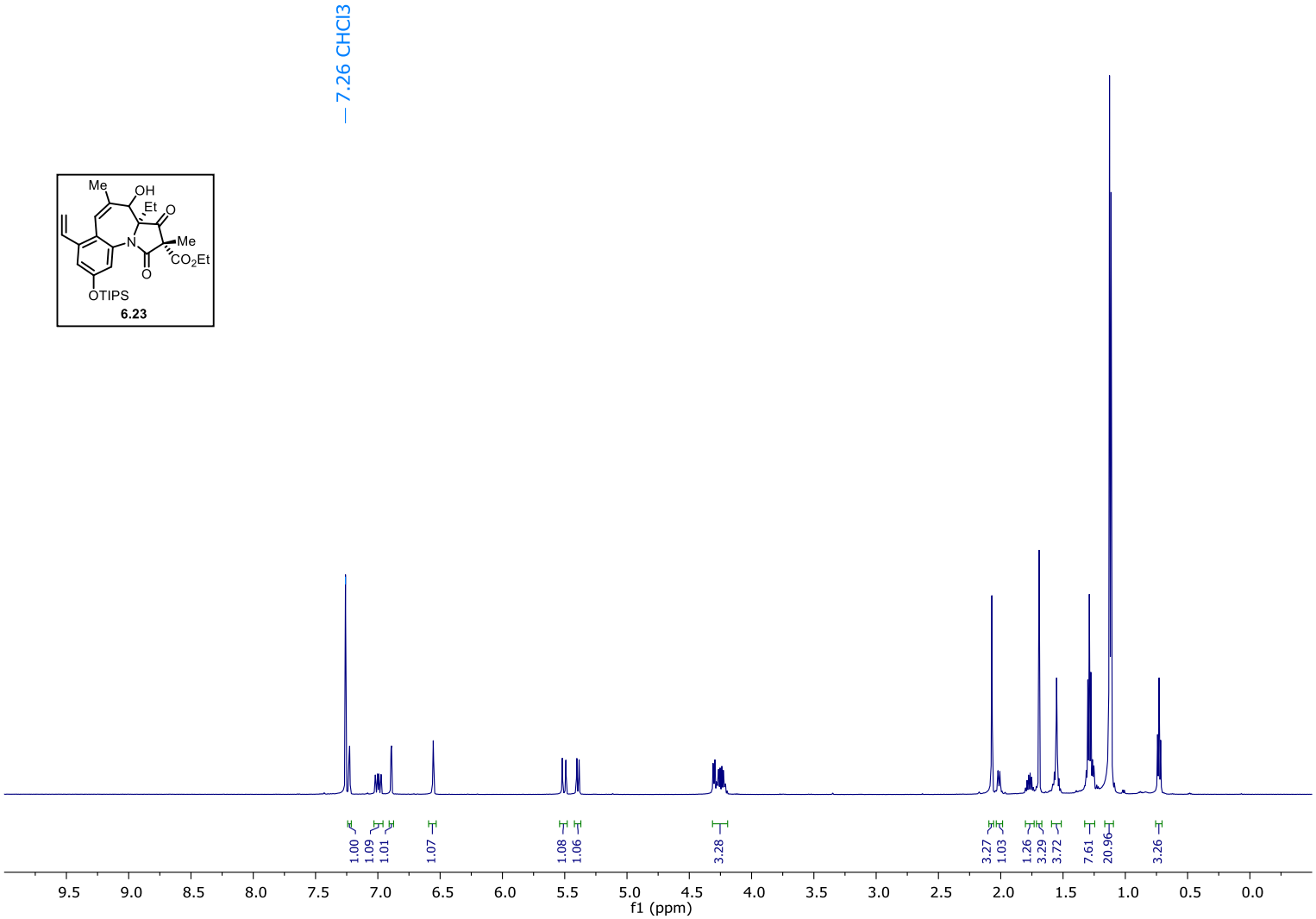


Figure D.18. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.23**

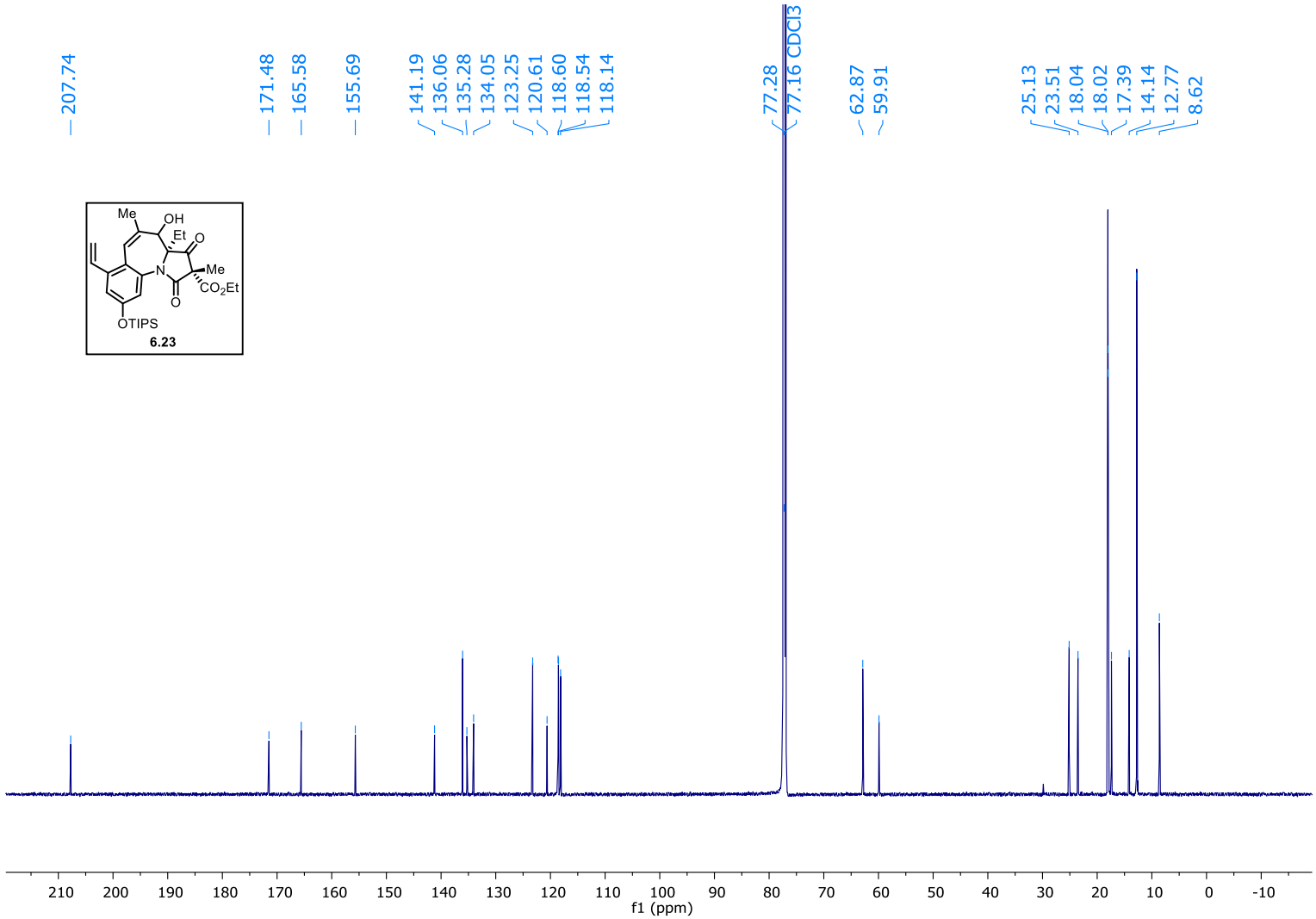


Figure D.19. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.23**

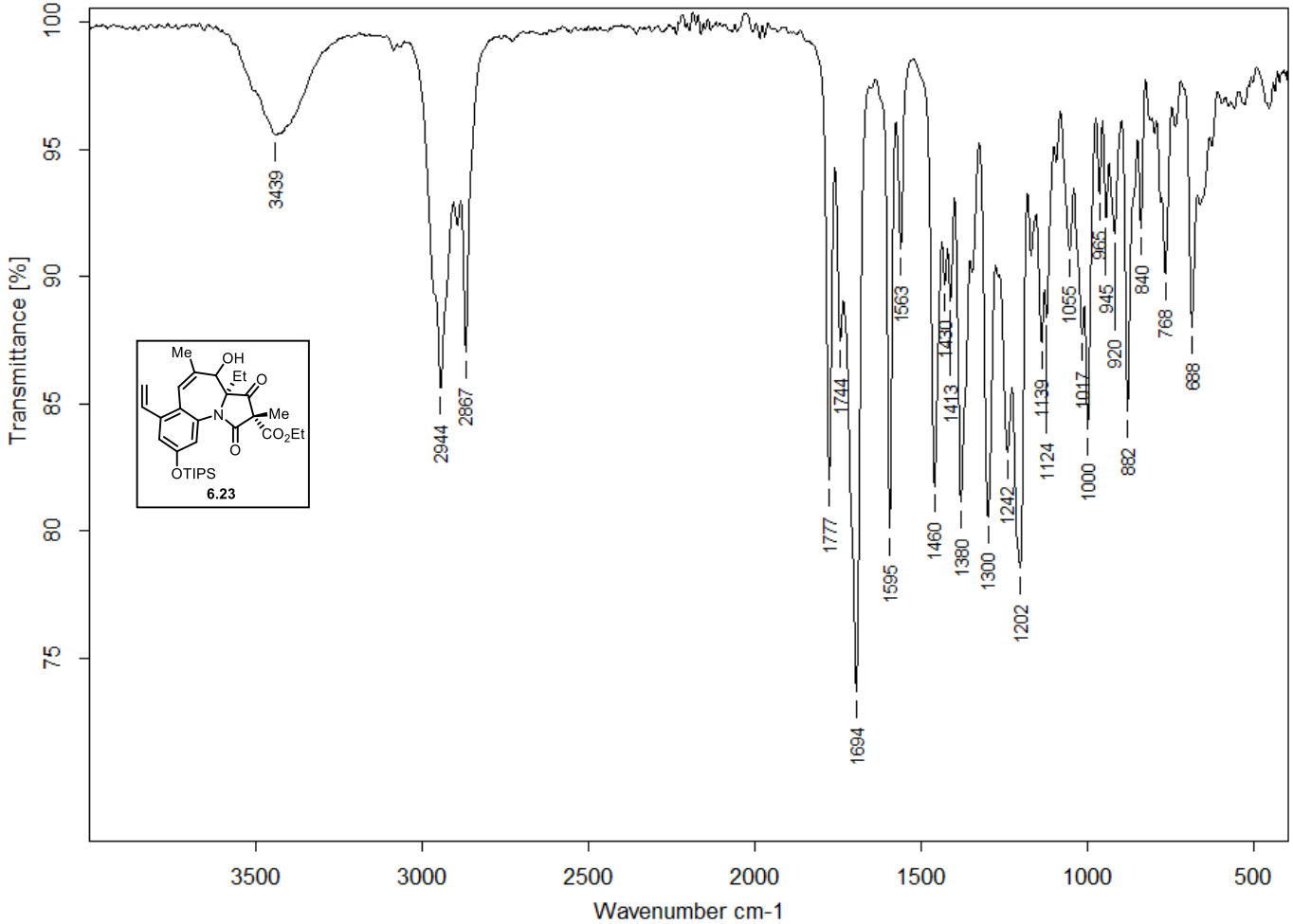


Figure D.20. FTIR spectrum (neat) of compound **6.23**

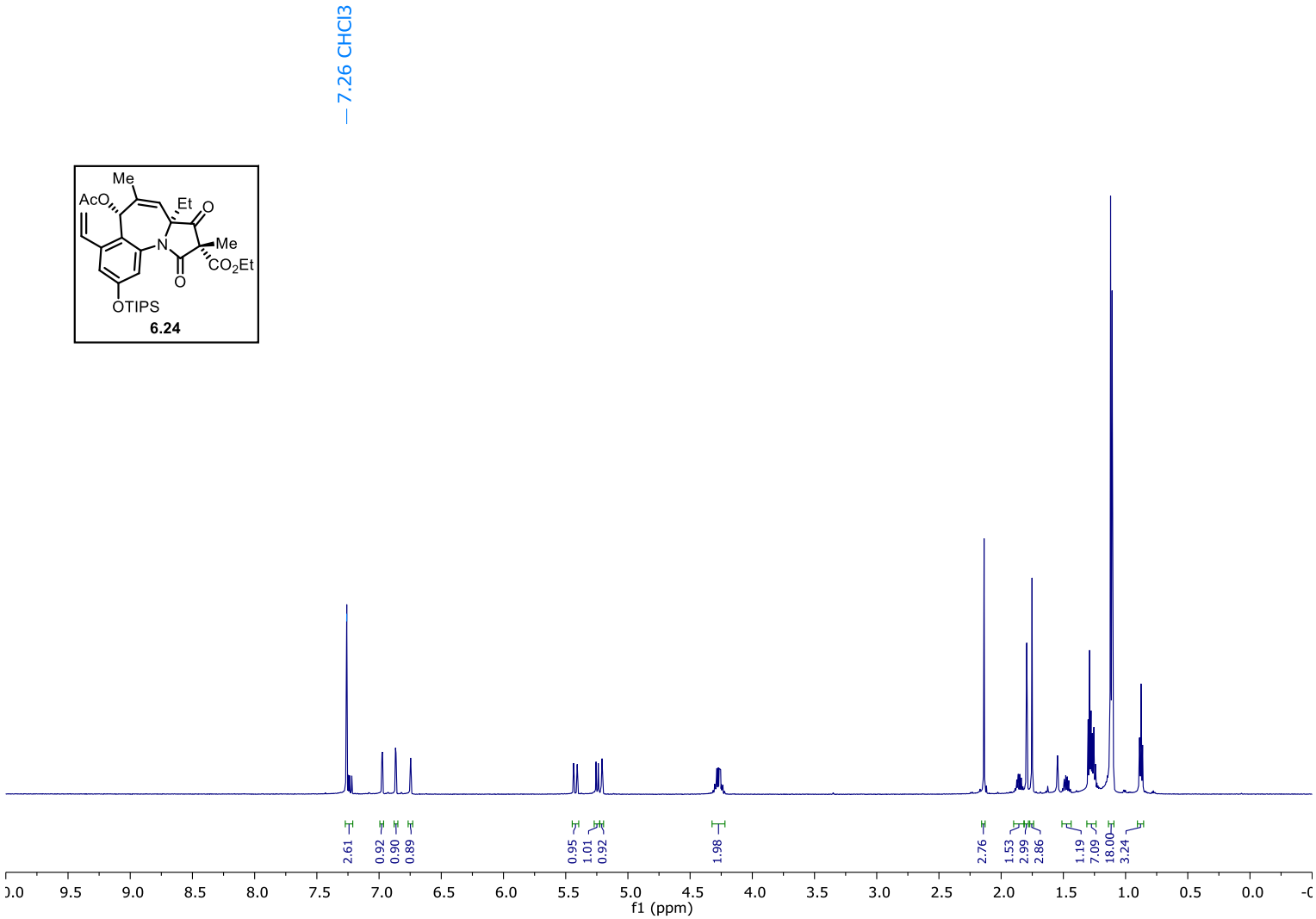


Figure D.21. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.24**

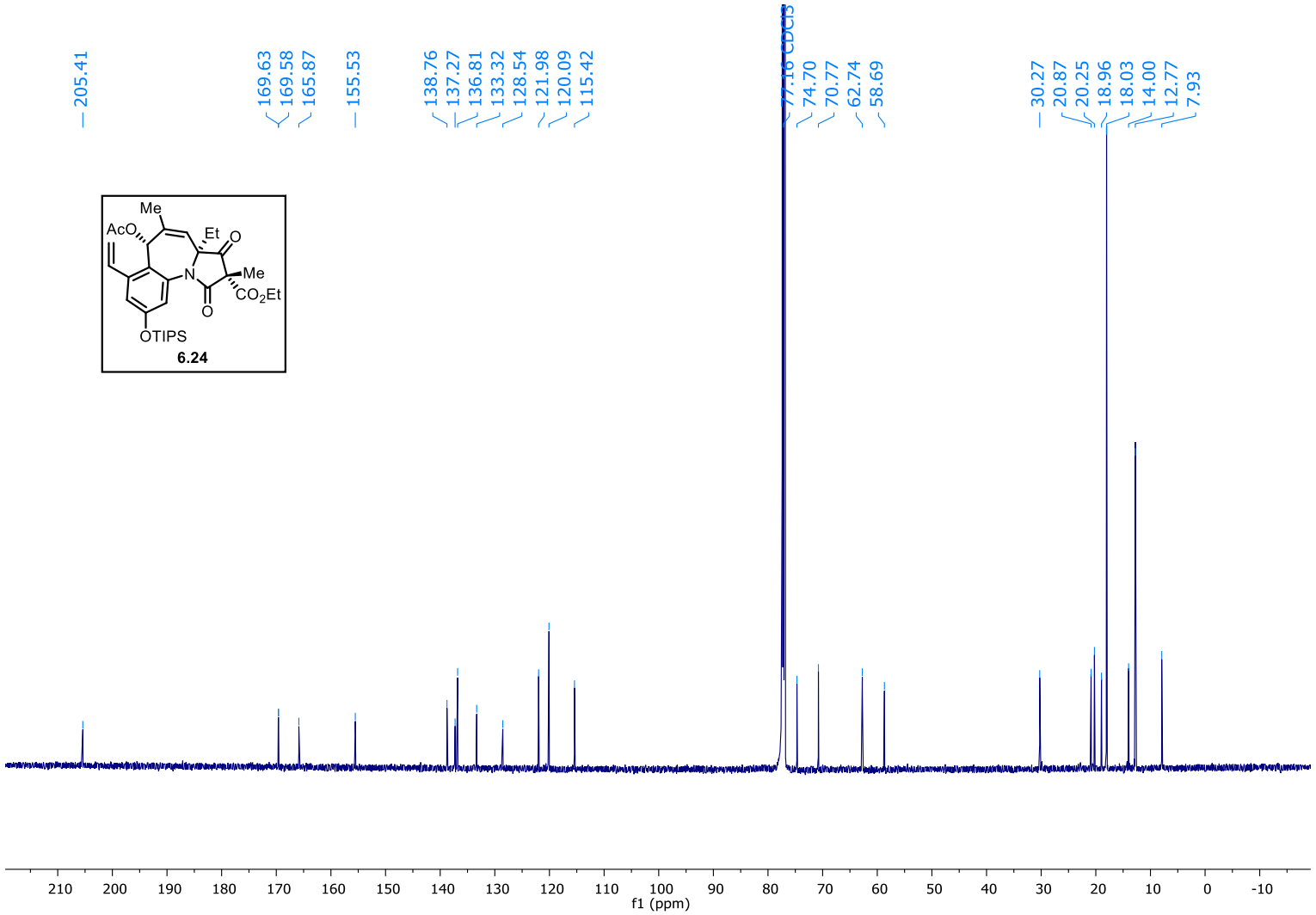


Figure D.22. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.24**

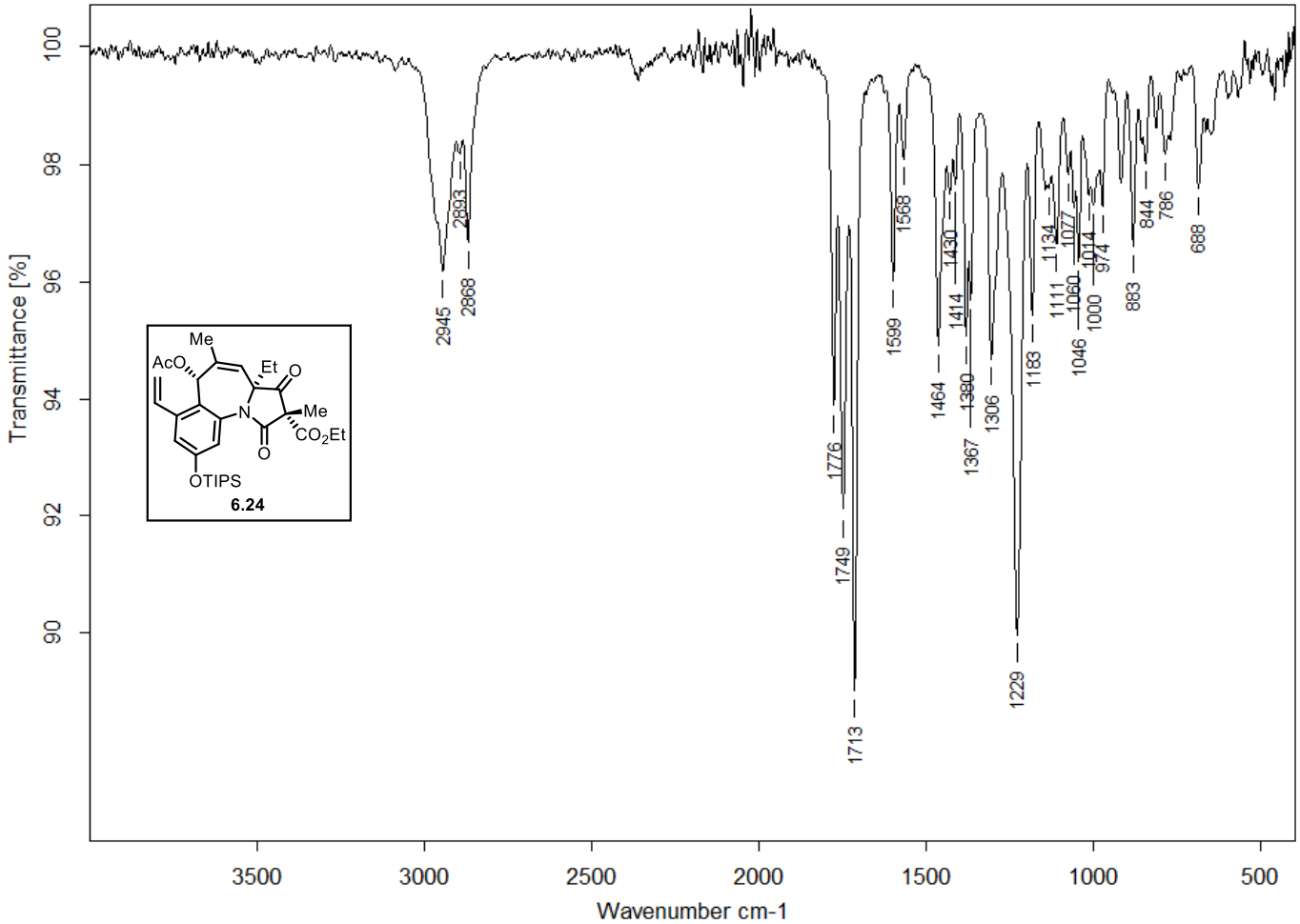


Figure D.23. FTIR spectrum (neat) of compound **6.24**

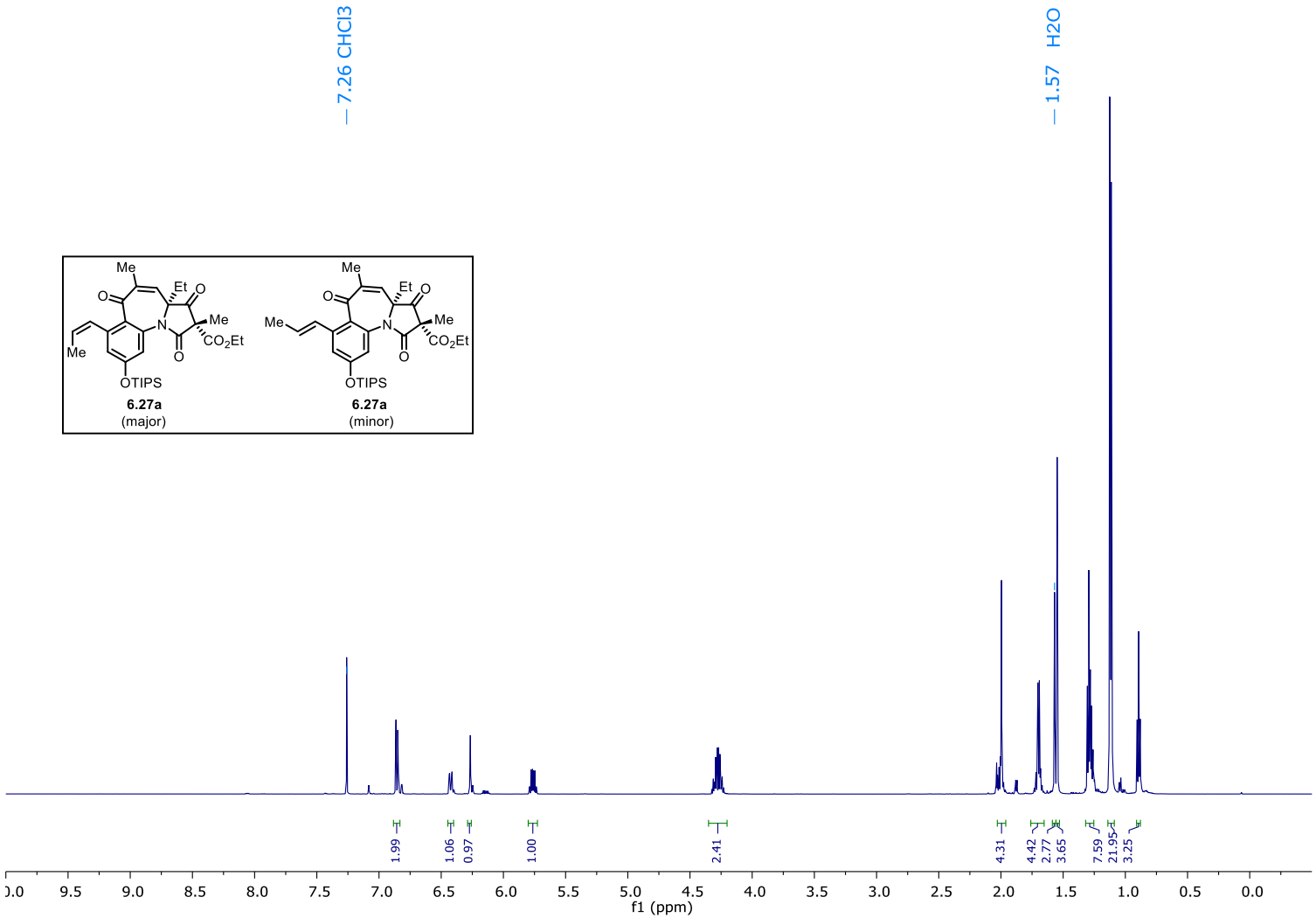


Figure D.24. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.27a**

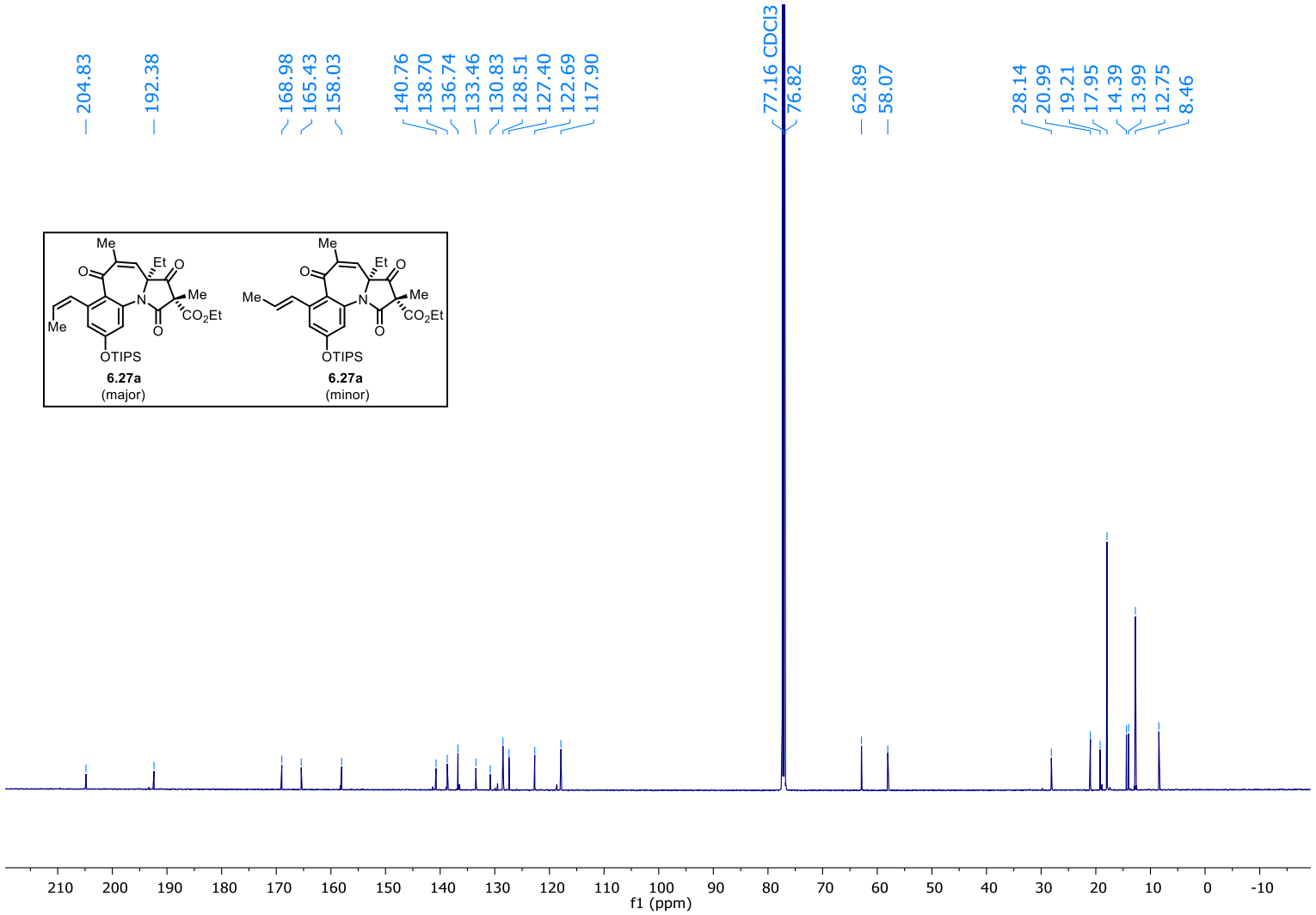


Figure D.25. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.27a**

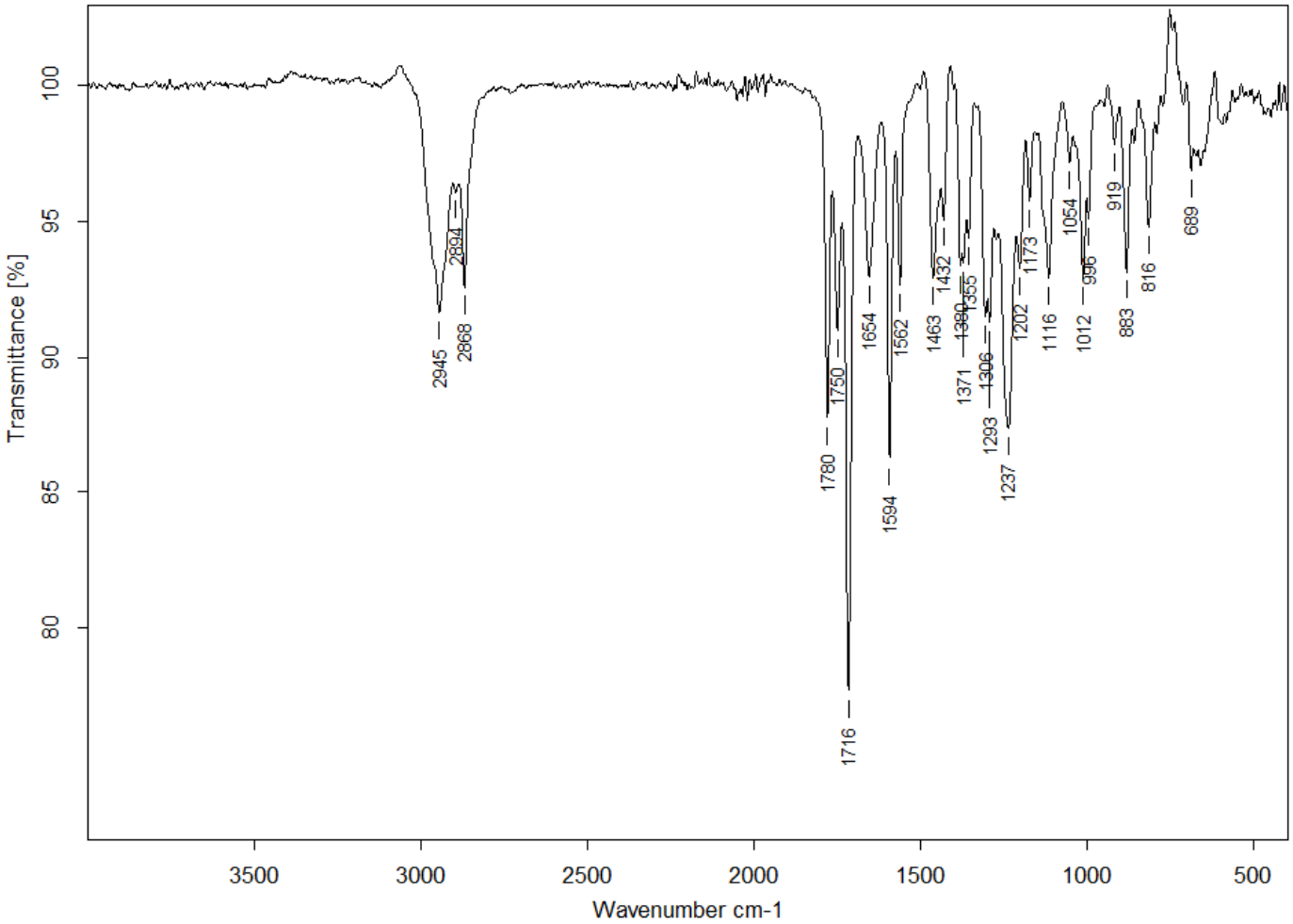


Figure D.26. FTIR spectrum (neat) of compound **6.27a**

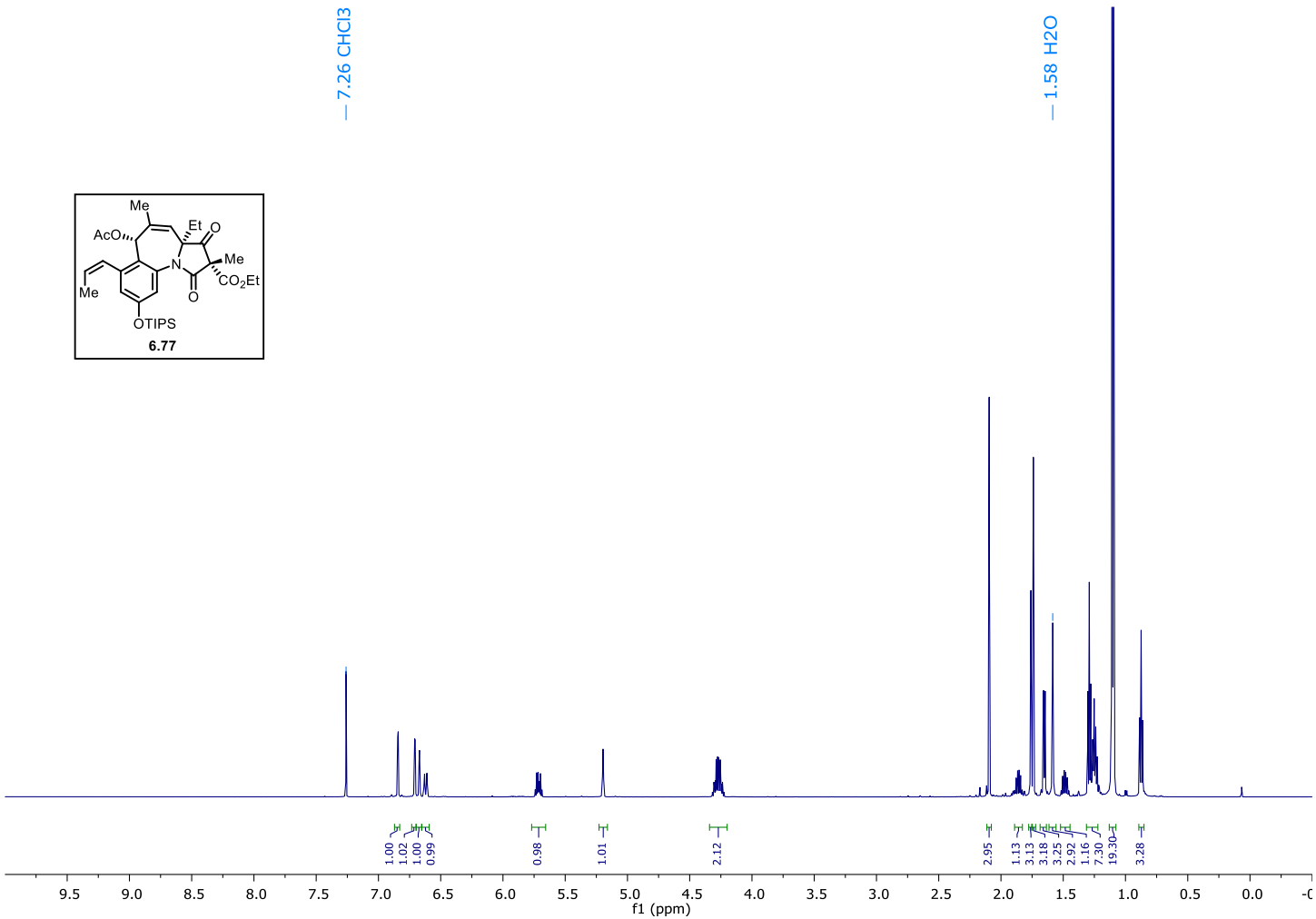


Figure D.27. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.77**

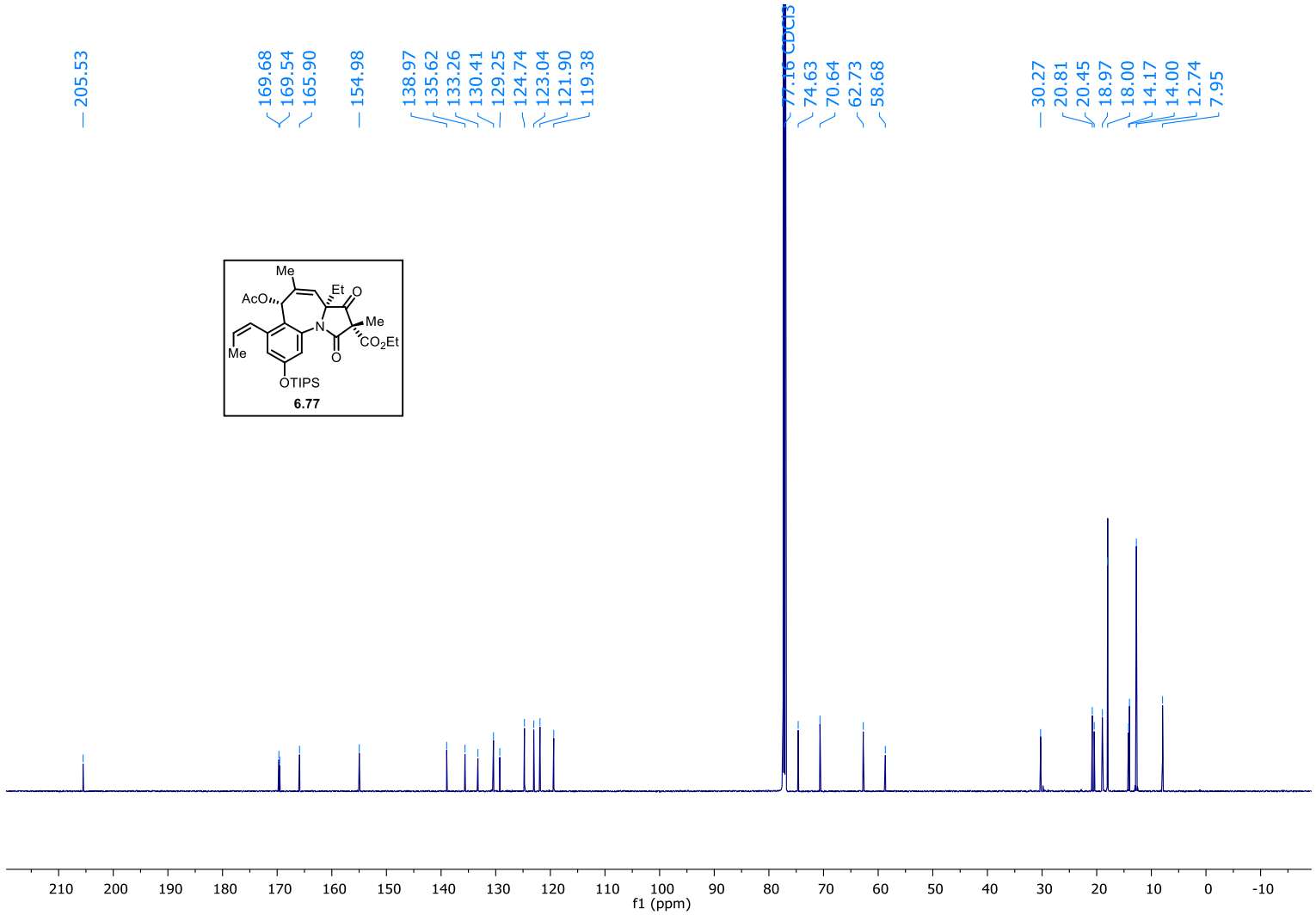


Figure D.28. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.77**

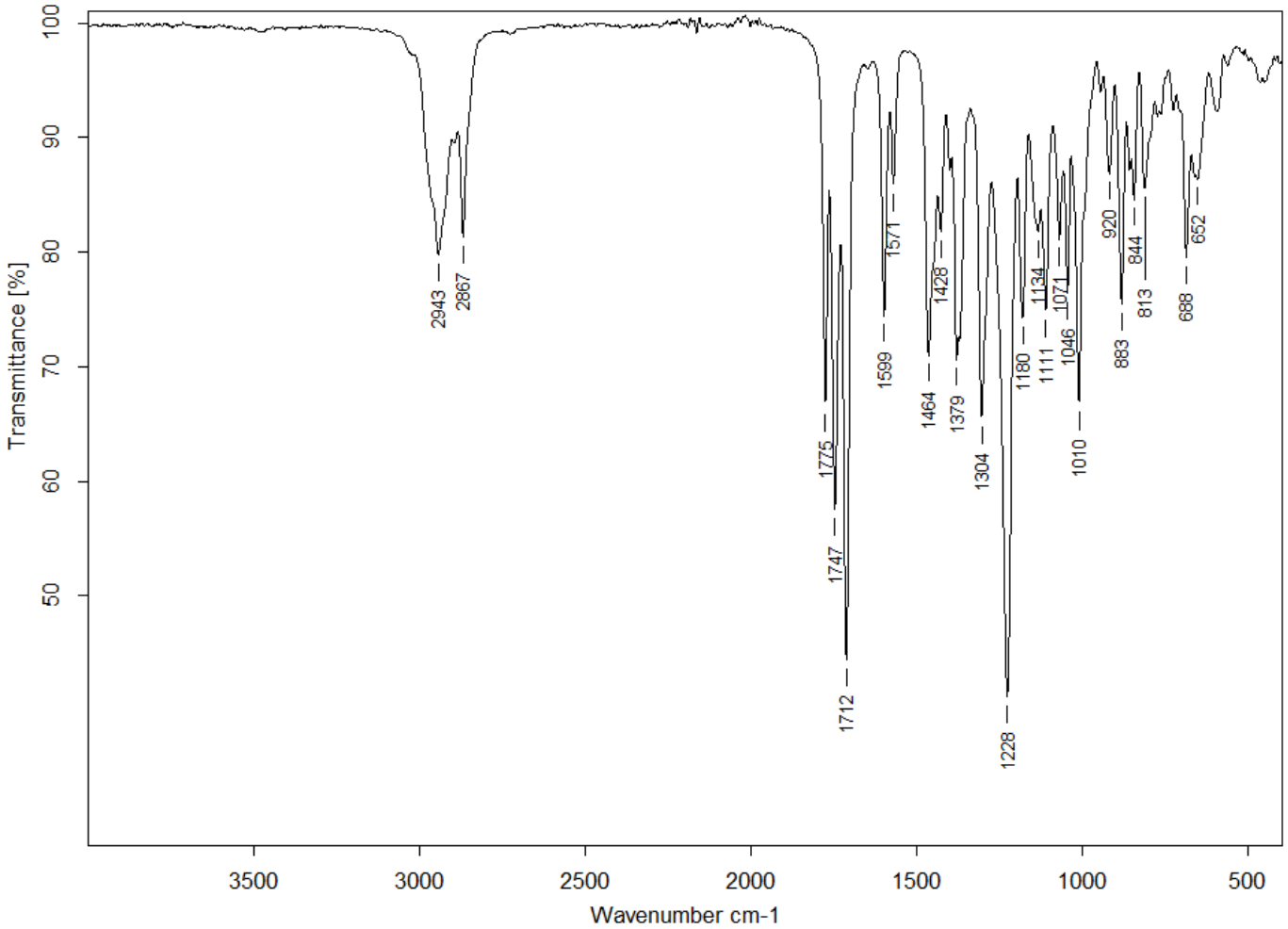


Figure D.29. FTIR spectrum (neat) of compound **6.77**

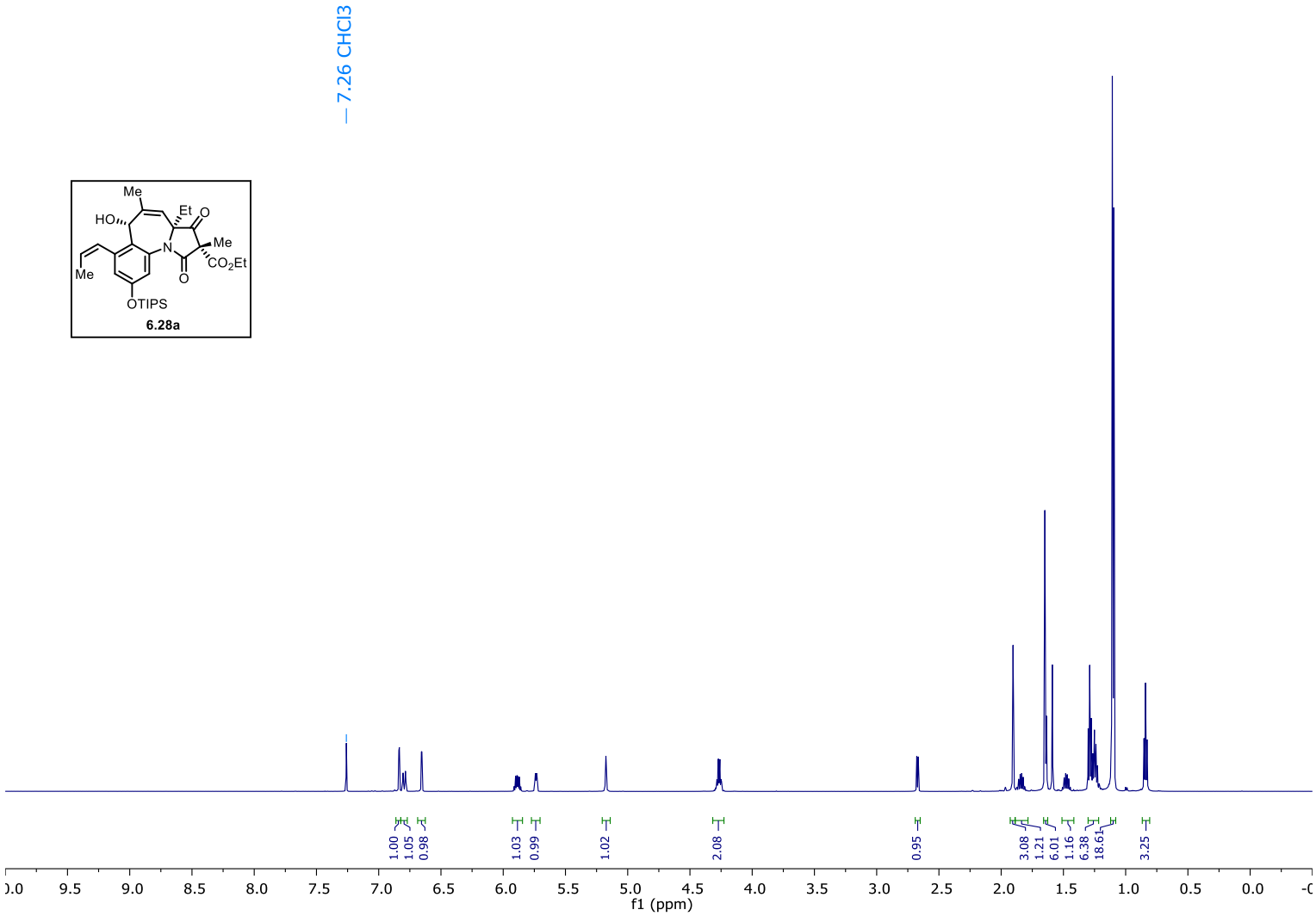


Figure D.30. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.28a**

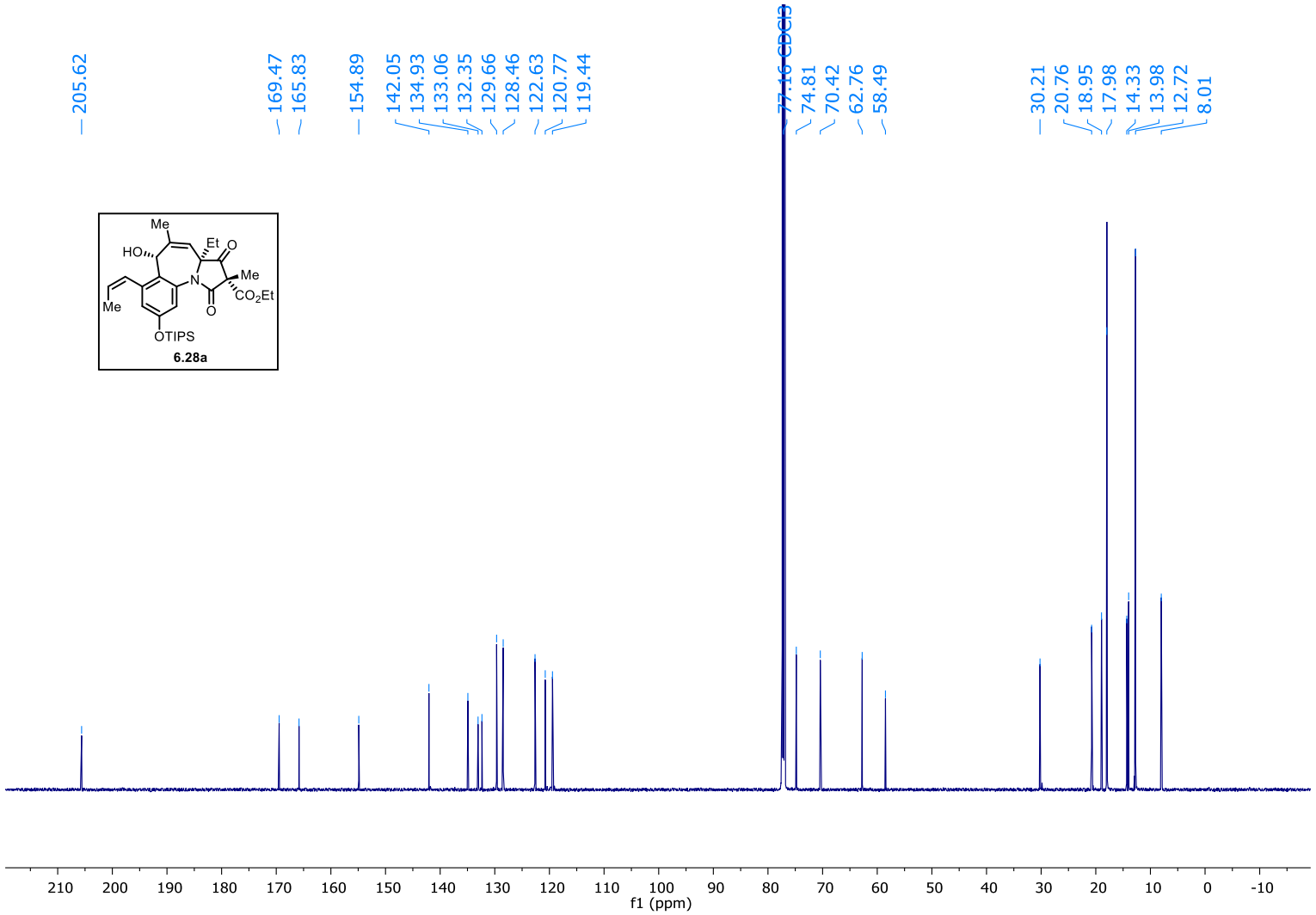


Figure D.31. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.28a**

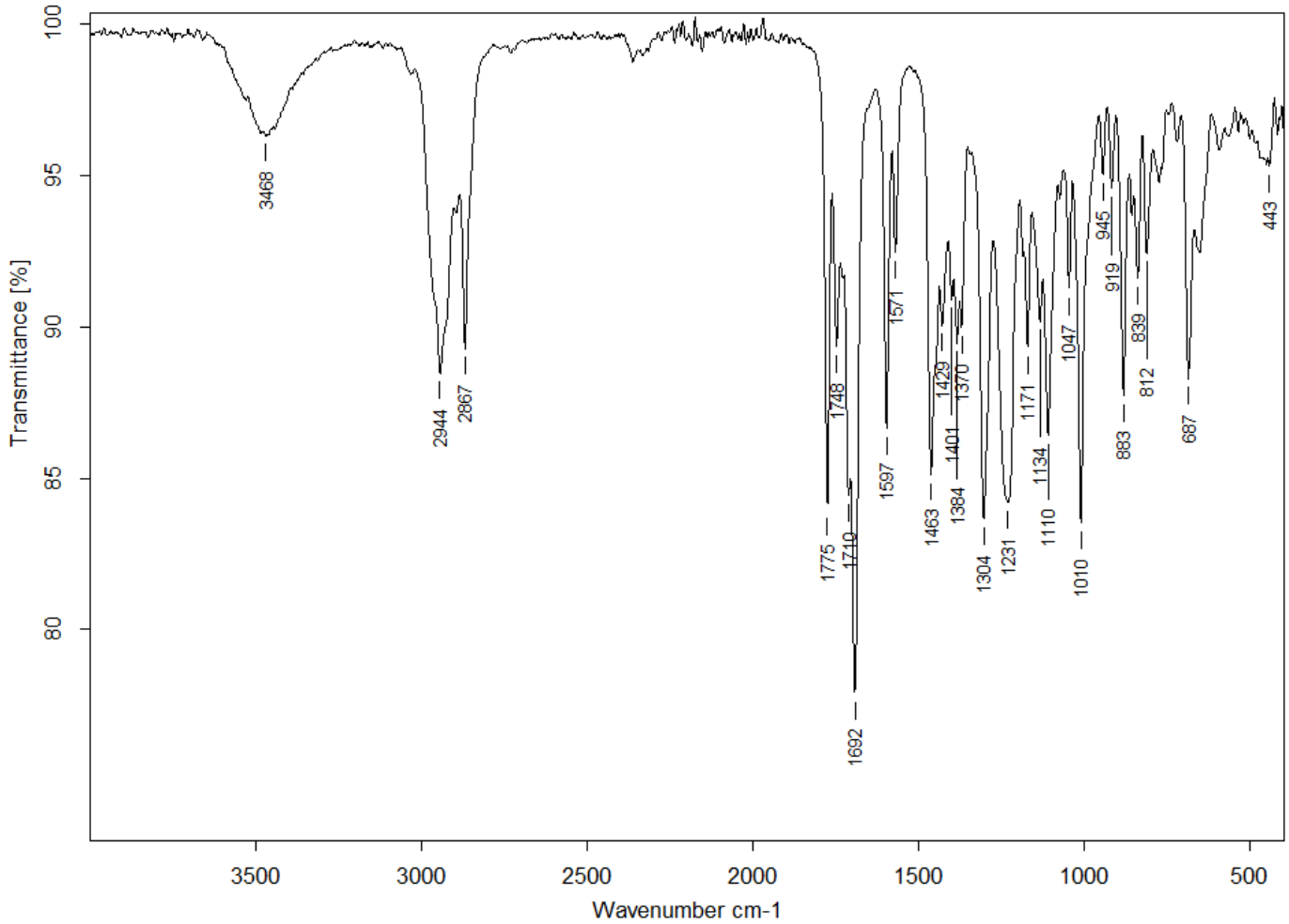


Figure D.32. FTIR spectrum (neat) of compound **6.28a**

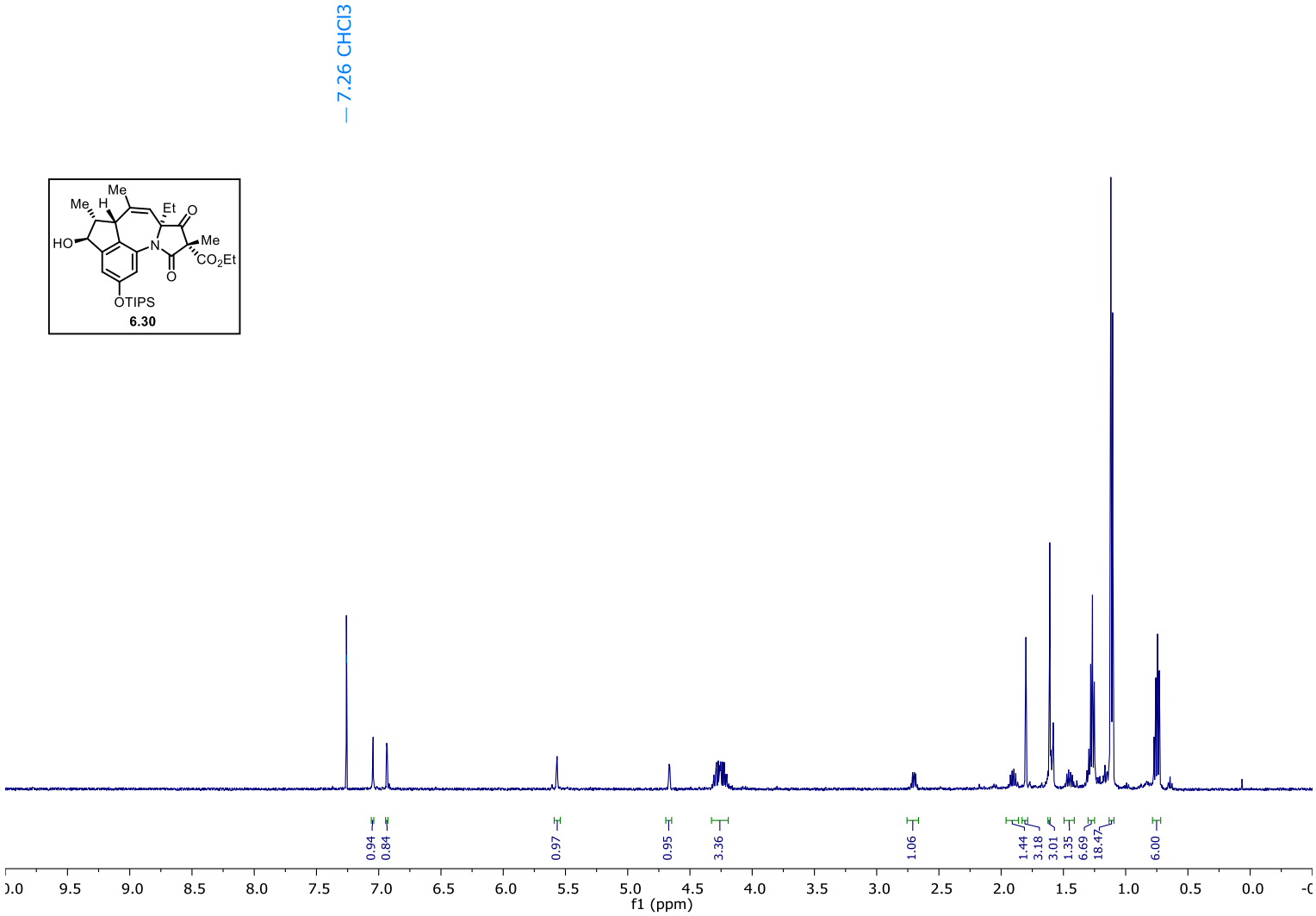


Figure D.33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6.30**

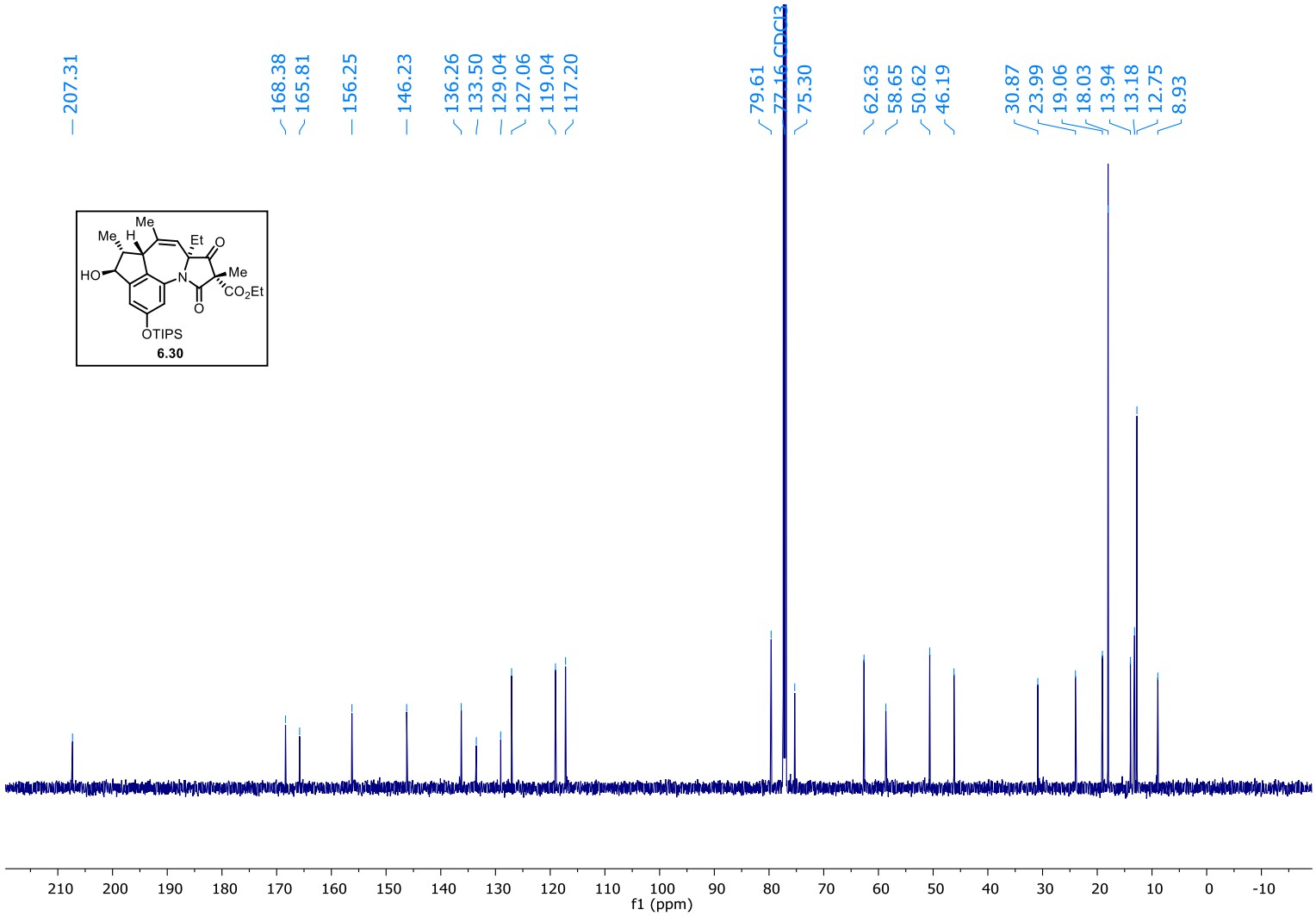


Figure D.34. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.30**

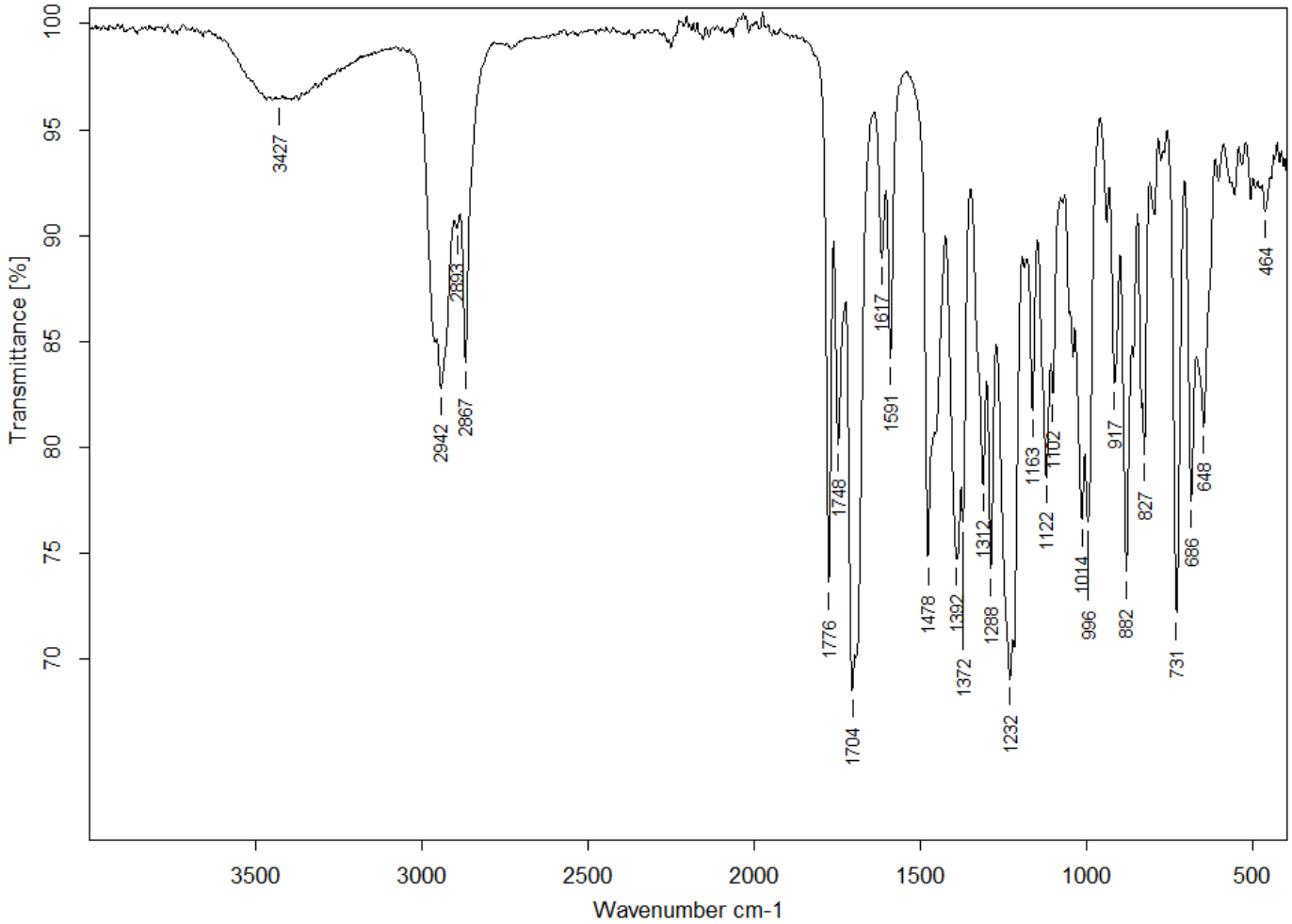


Figure D.35. FTIR spectrum (neat) of compound **6.30**

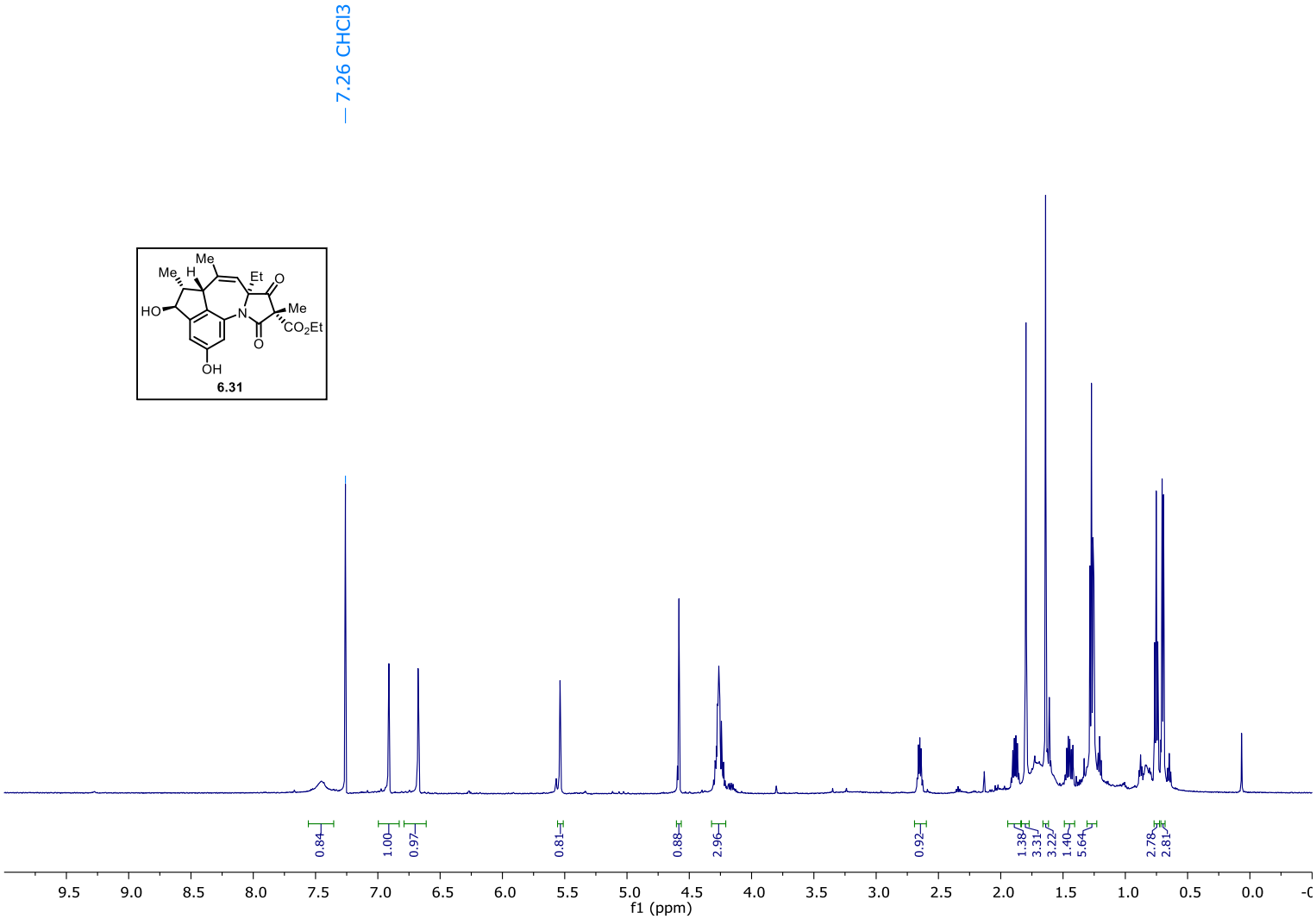


Figure D.36. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.31**

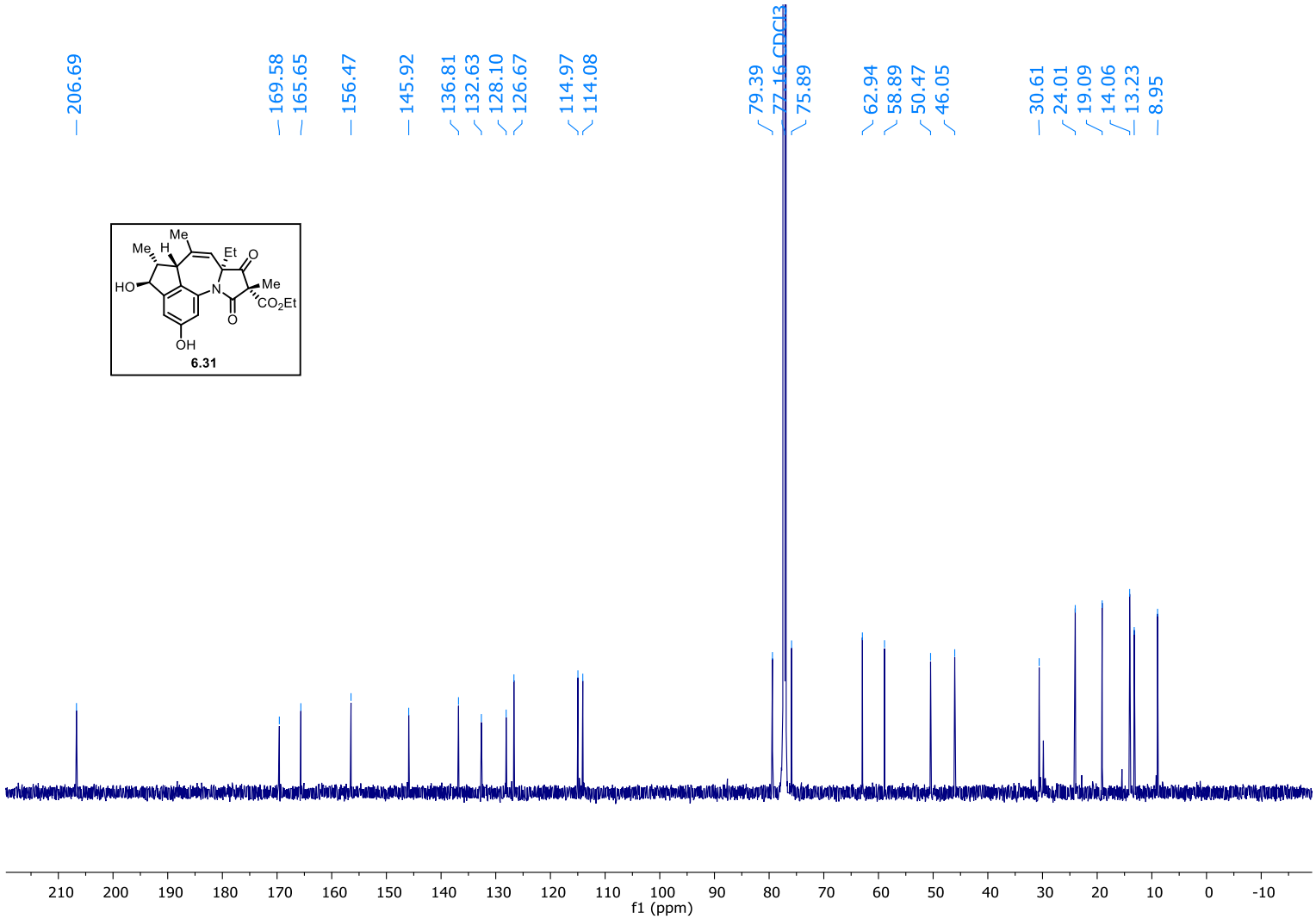


Figure D.37. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.31**

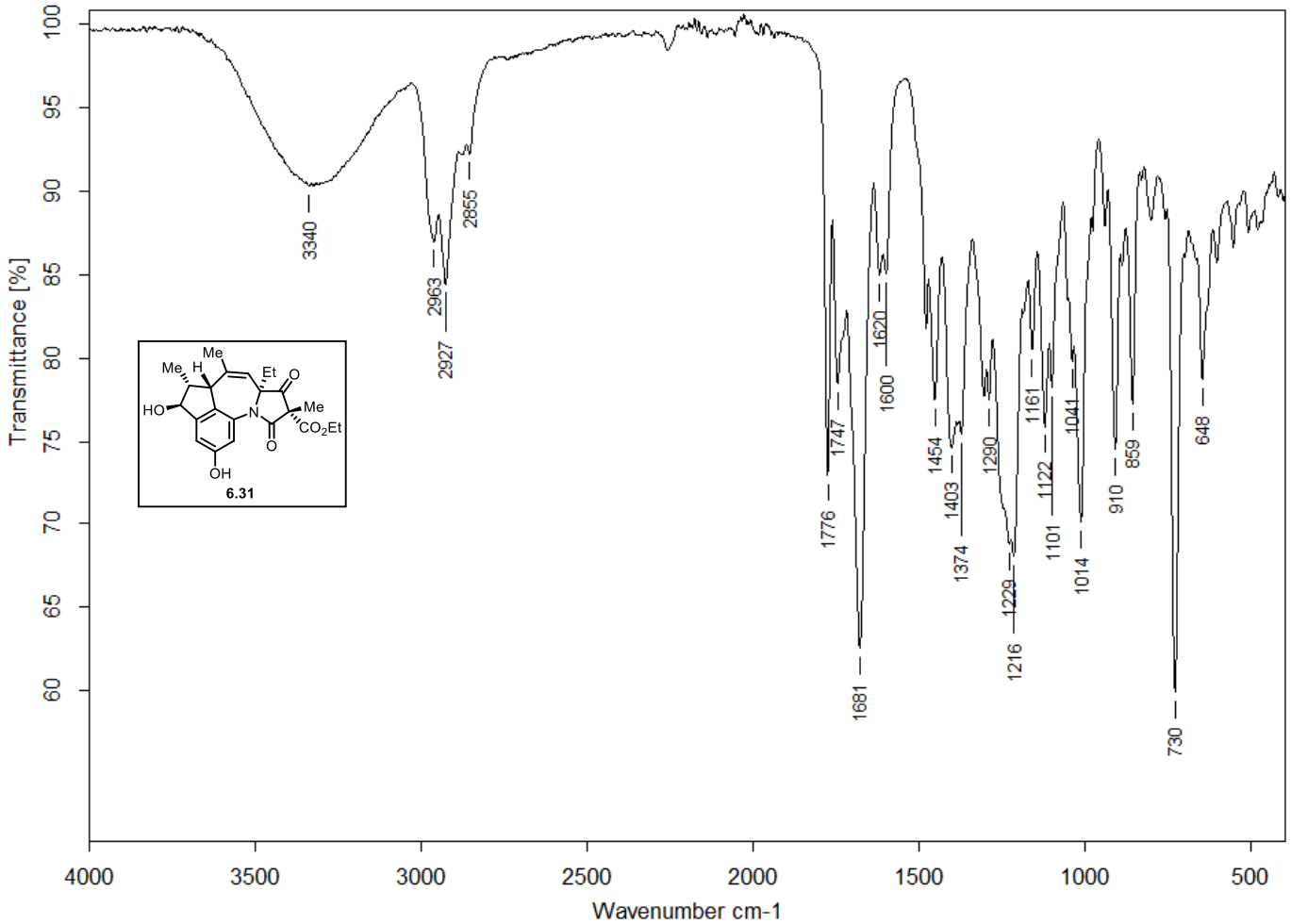


Figure D.38. FTIR spectrum (neat) of compound **6.31**

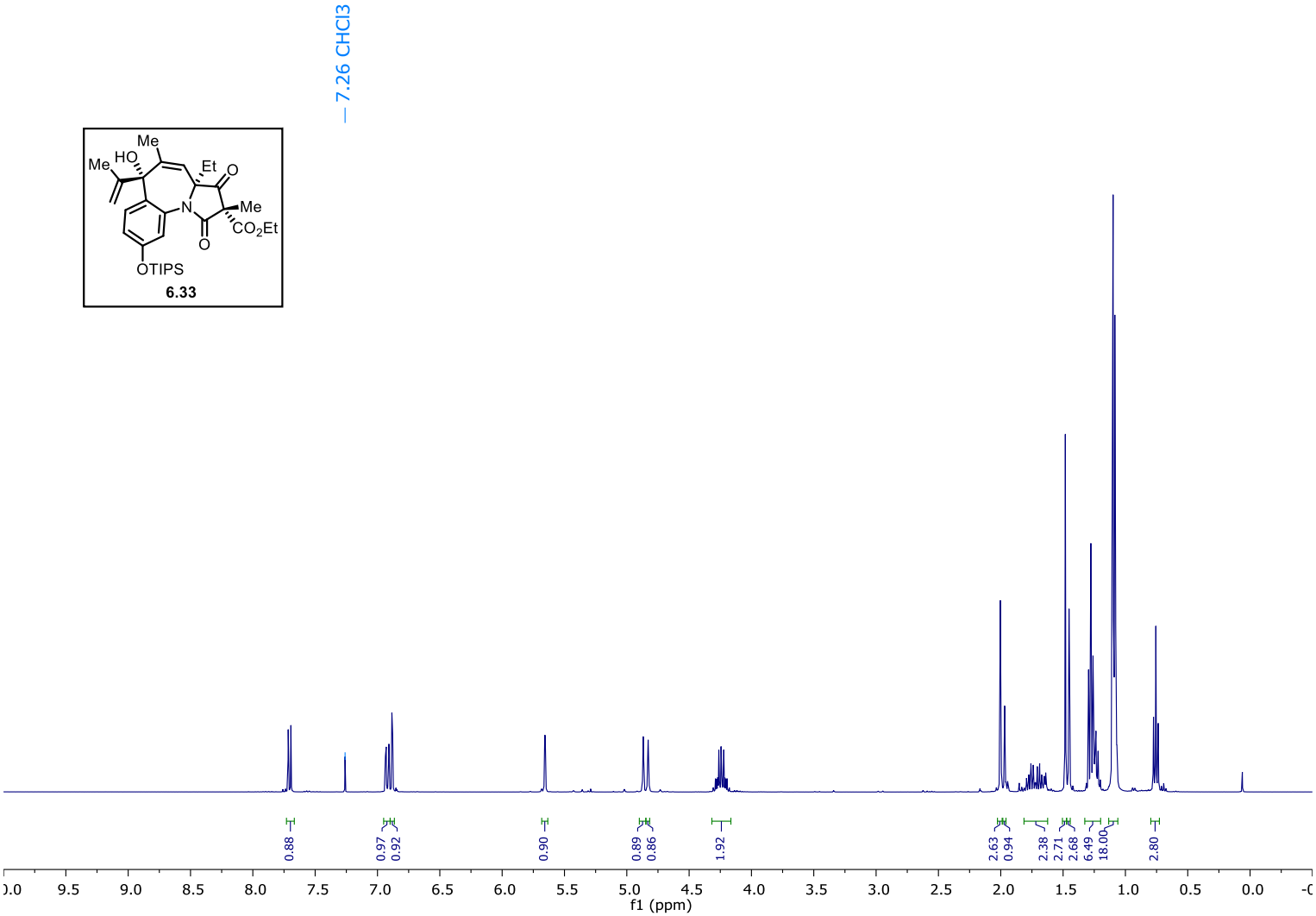


Figure D.39. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.33**

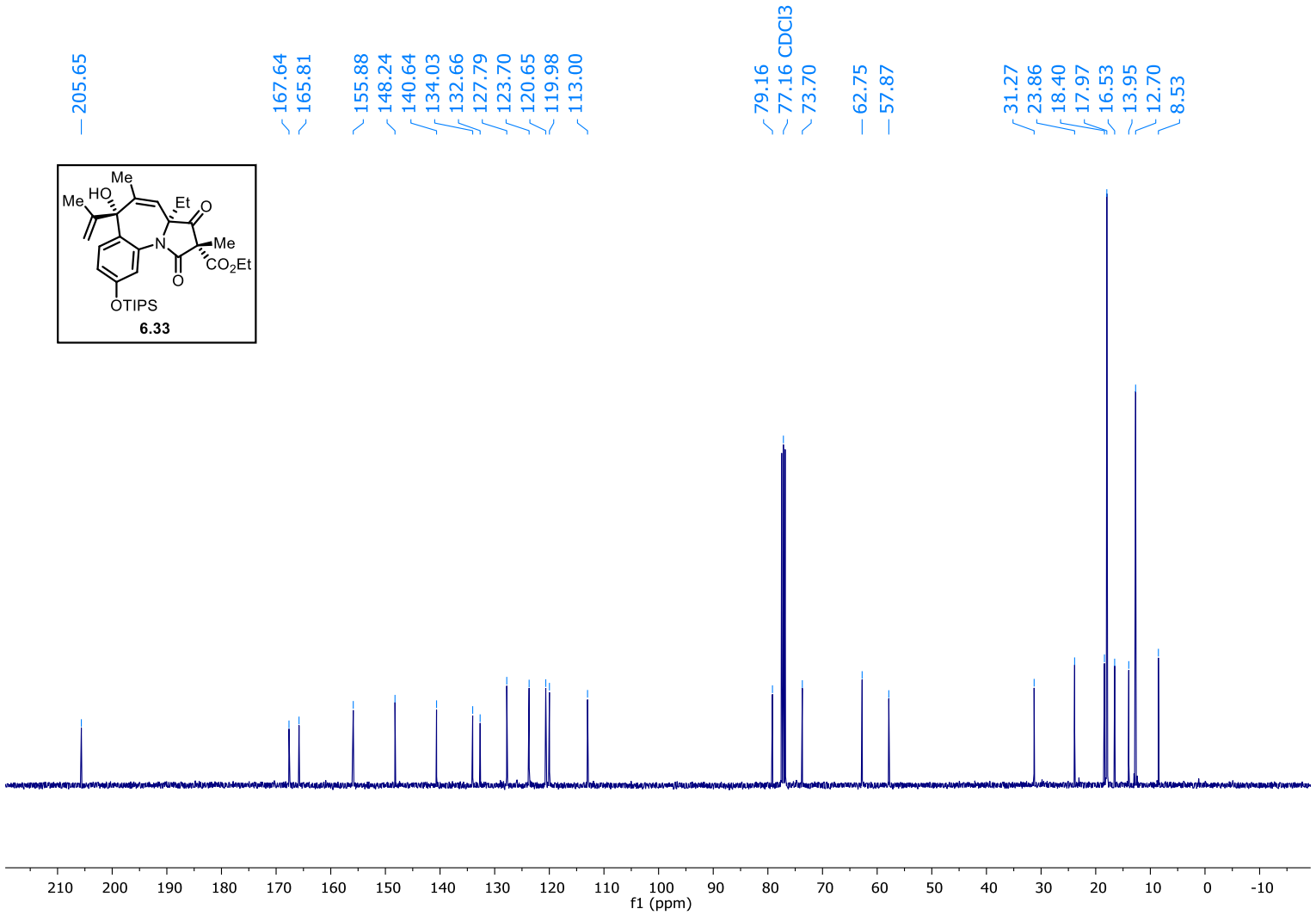


Figure D.40. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.33**

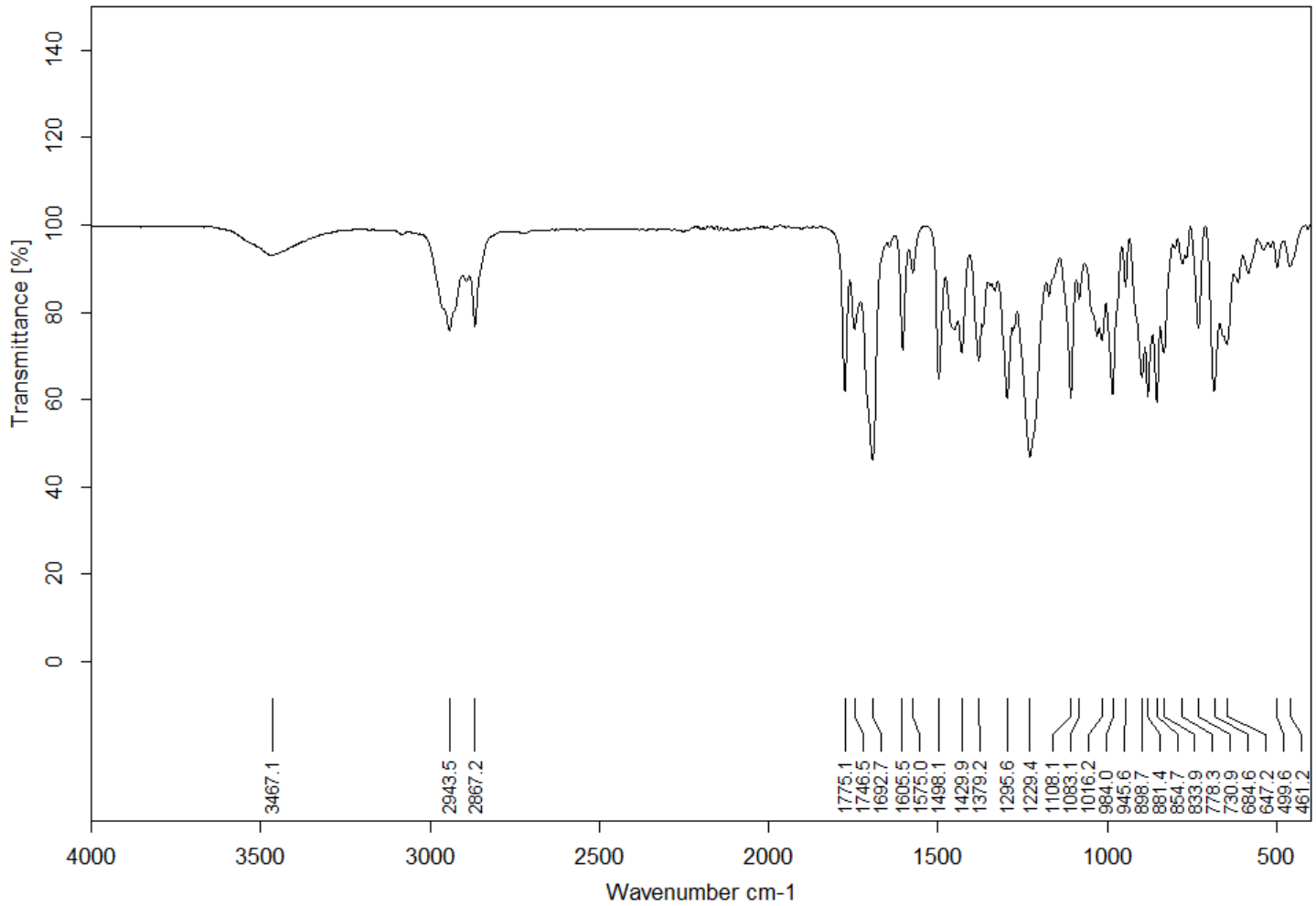


Figure D.41. FTIR spectrum (neat) of compound **6.33**

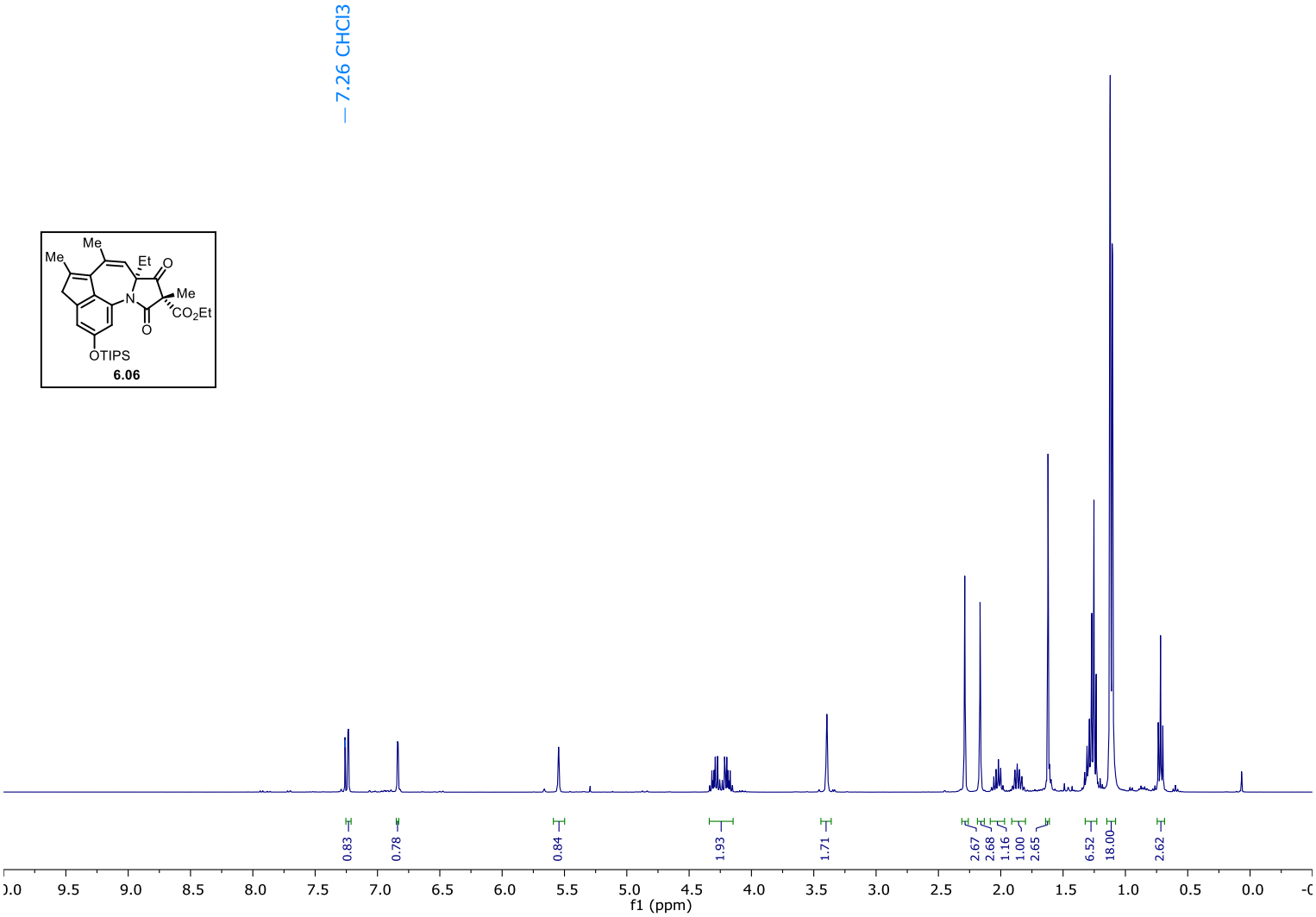


Figure D.42. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.06**

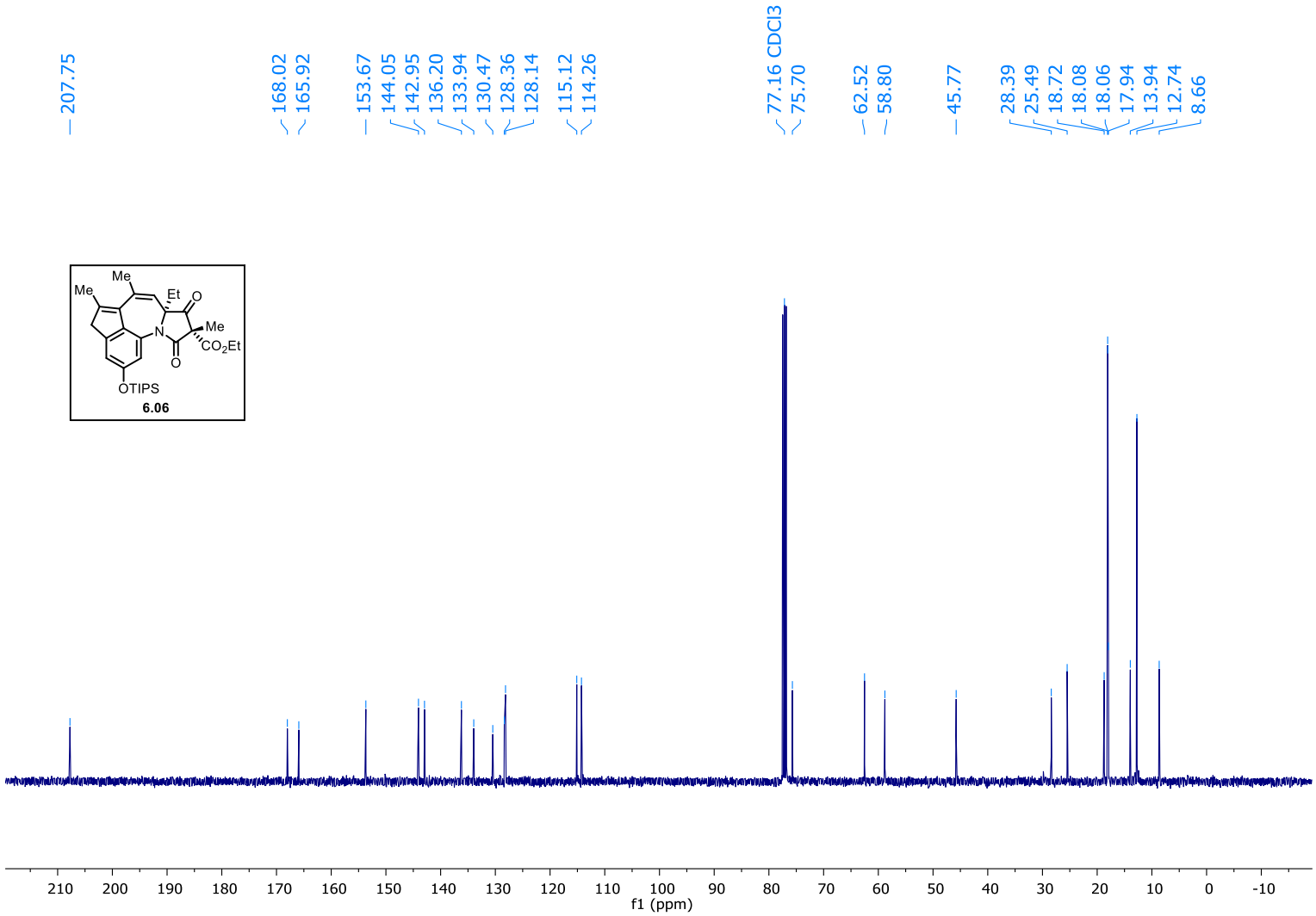


Figure D.43. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.06**

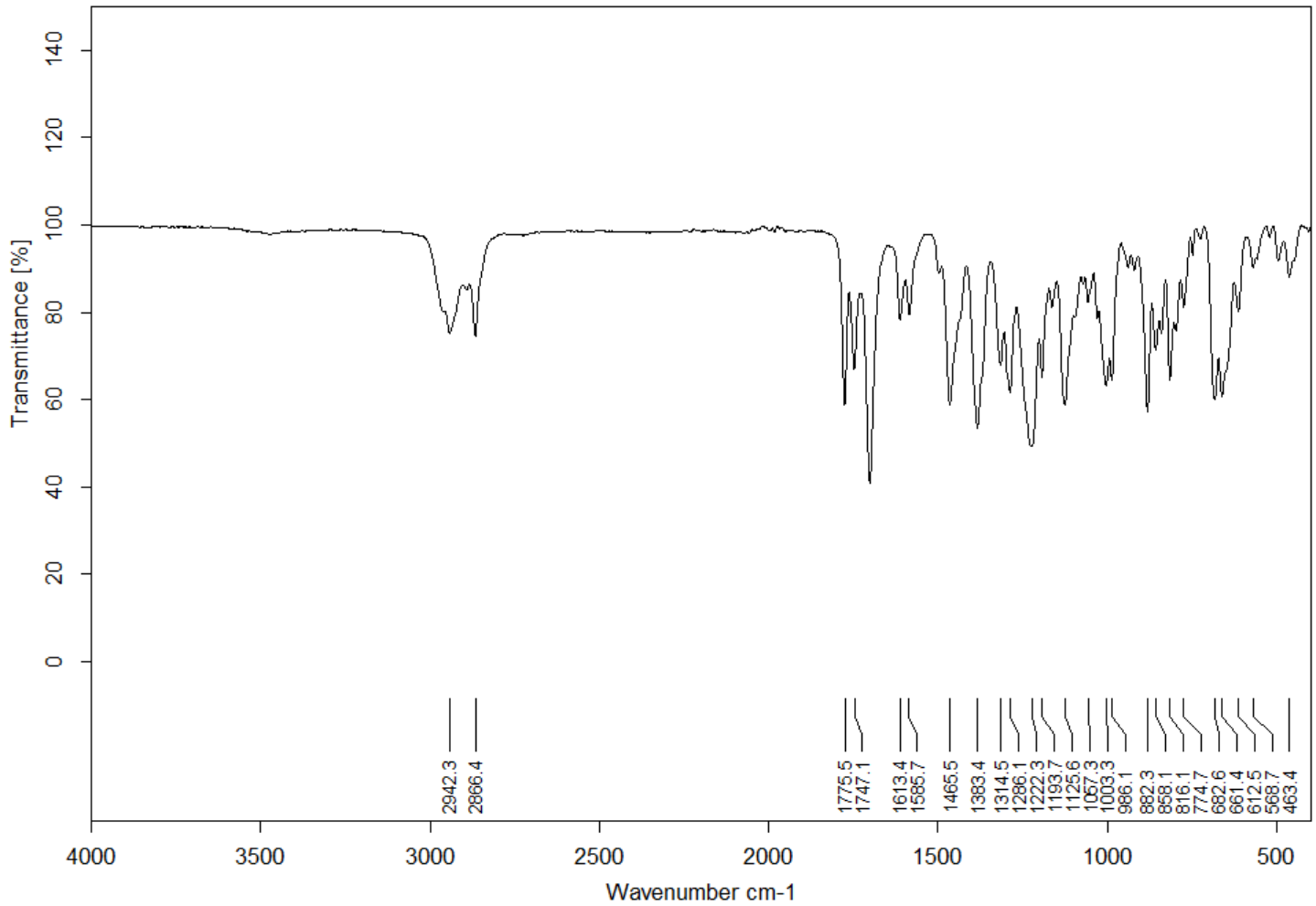


Figure D.44. FTIR spectrum (neat) of compound **6.06**

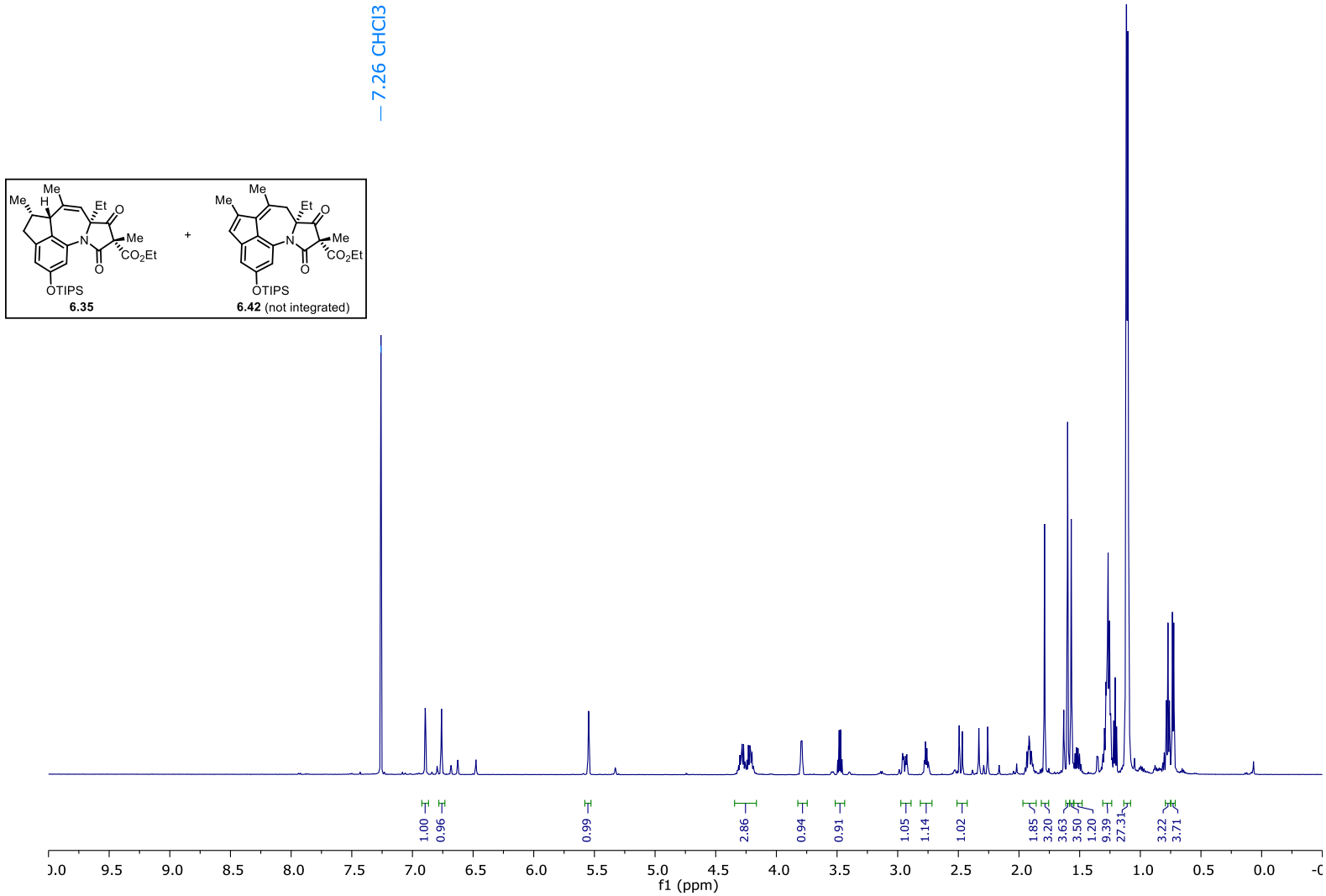


Figure D.45. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.35**

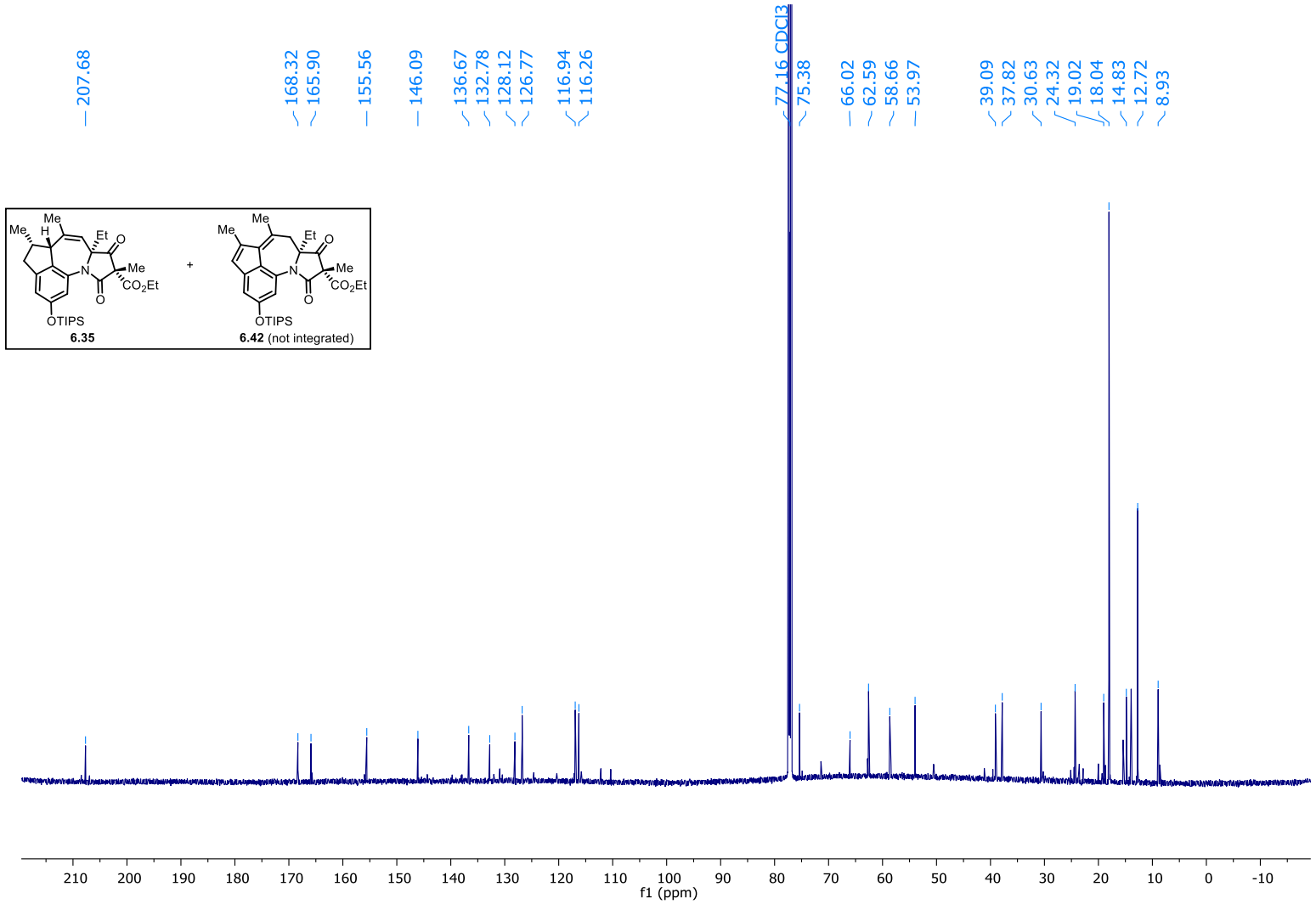


Figure D.46. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.35**

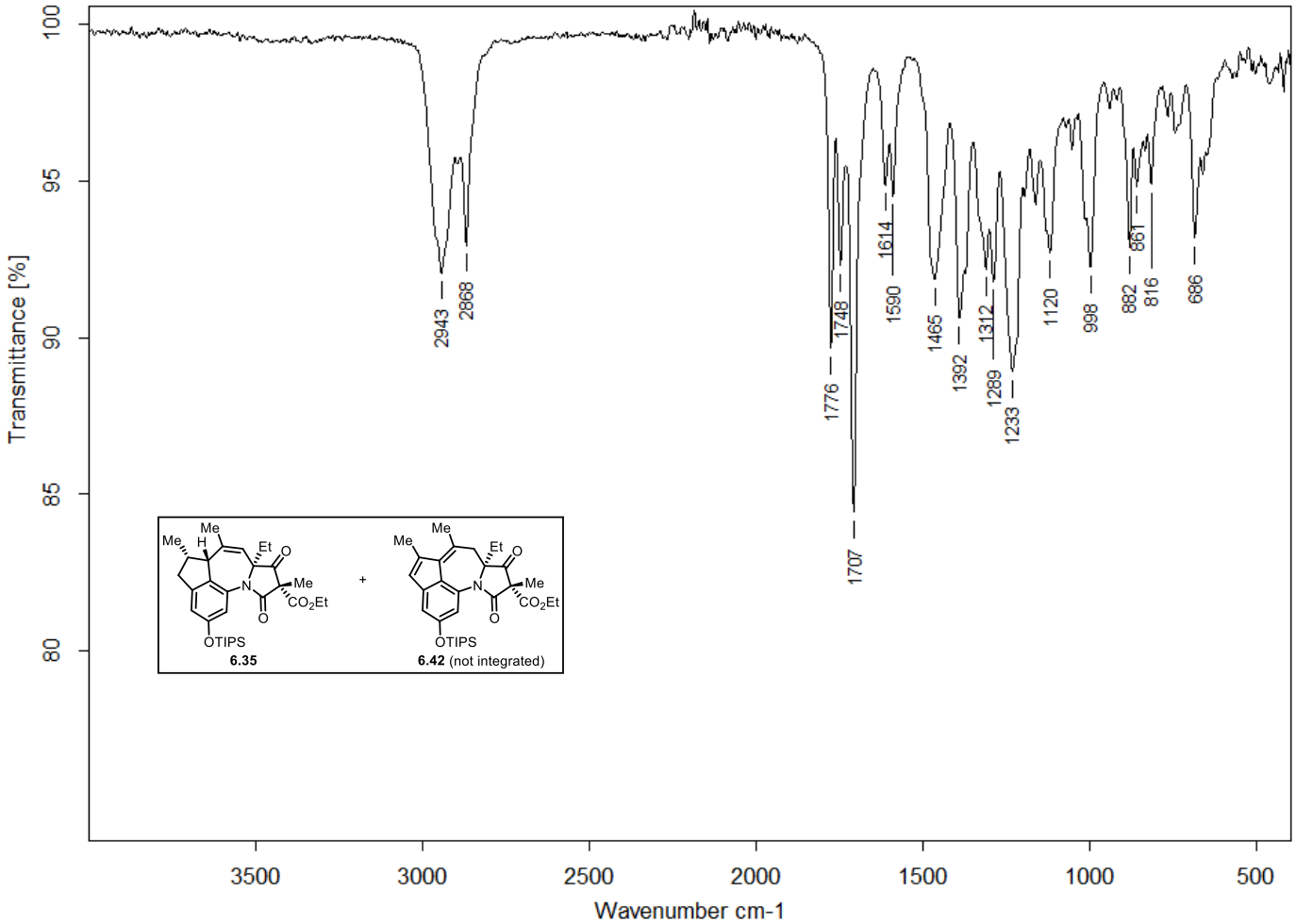


Figure D.47. FTIR spectrum (neat) of compound **6.35**

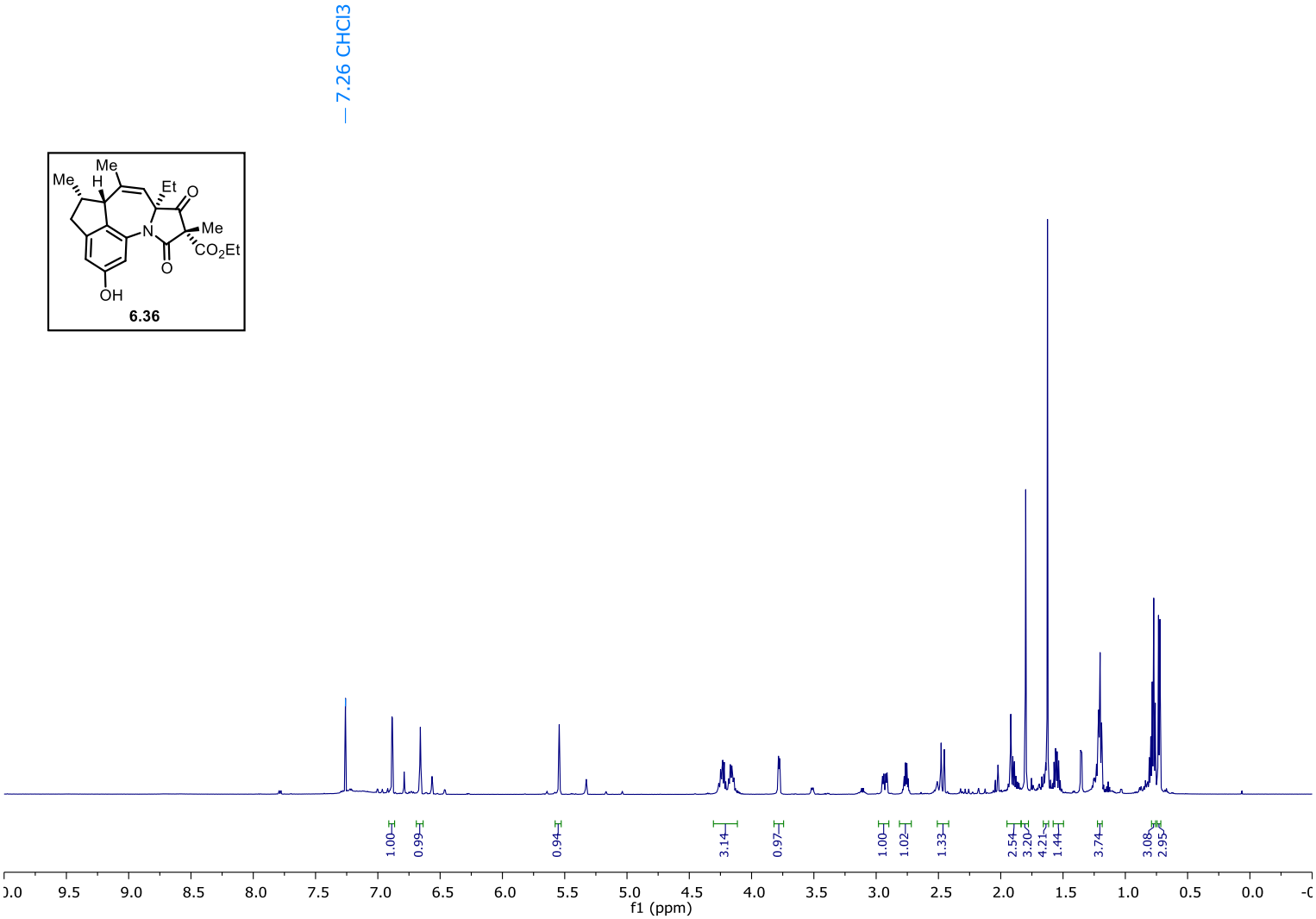


Figure D.48. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.36**

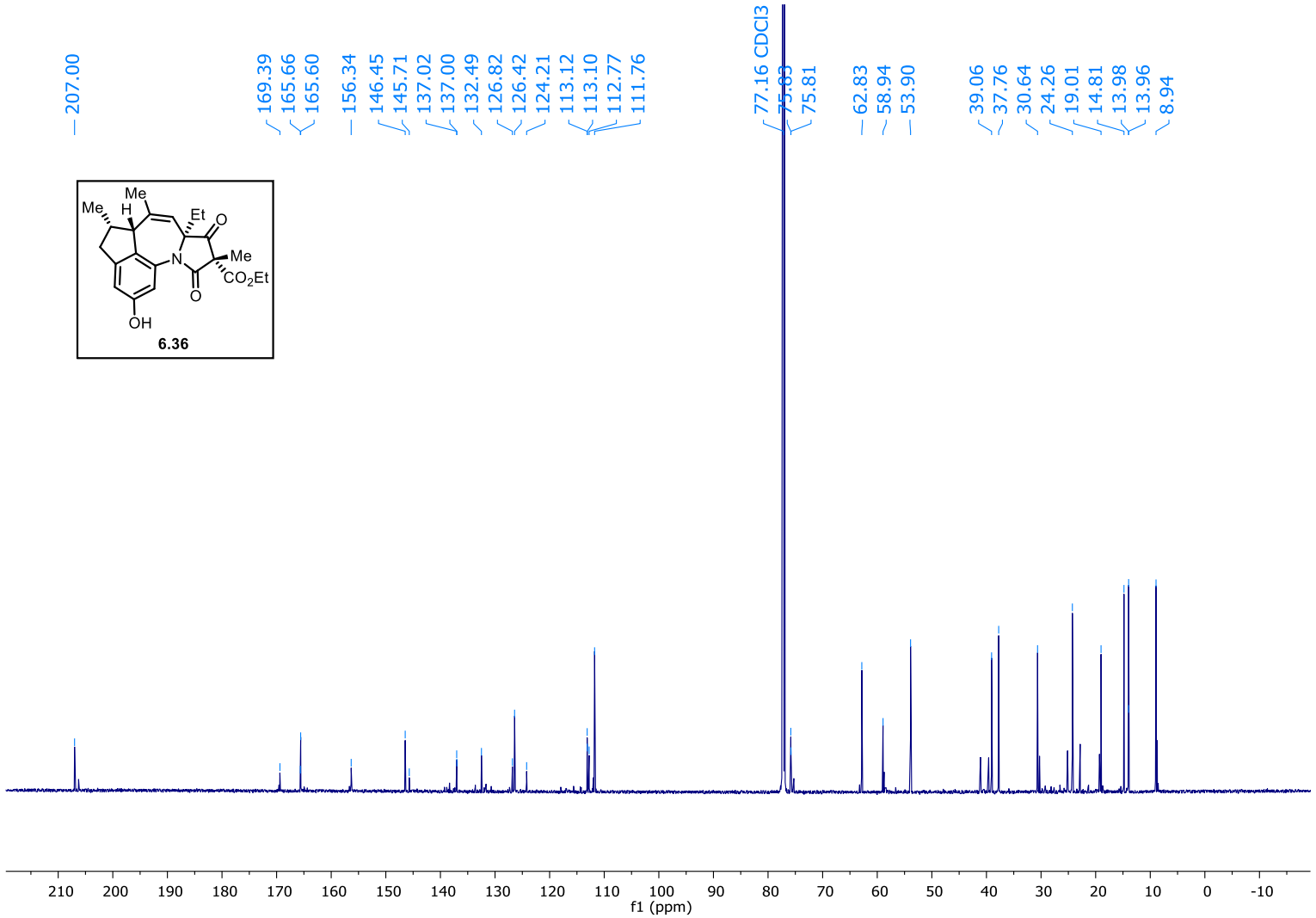


Figure D.49. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.36**

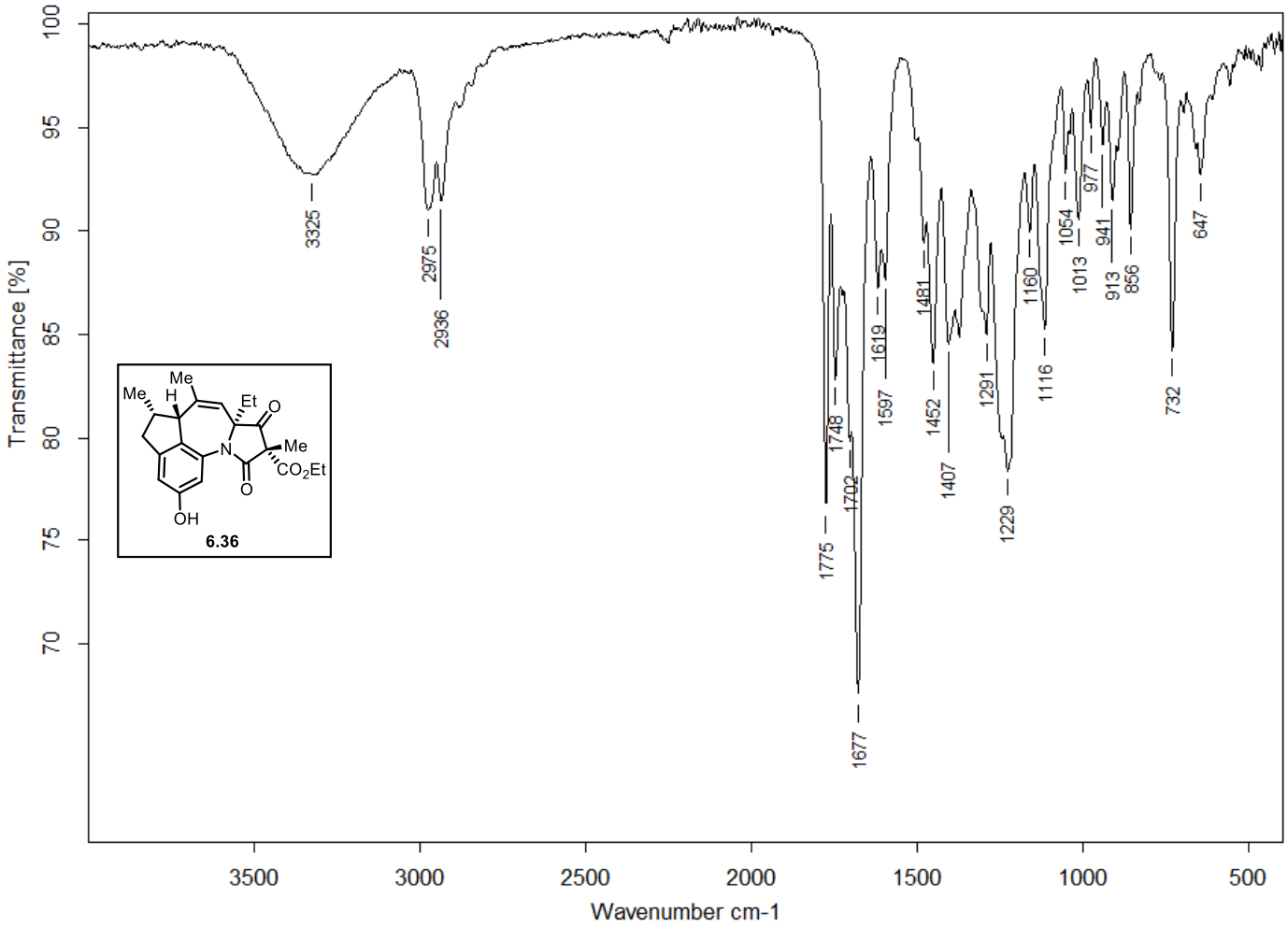


Figure D.50. FTIR spectrum (neat) of compound **6.36**

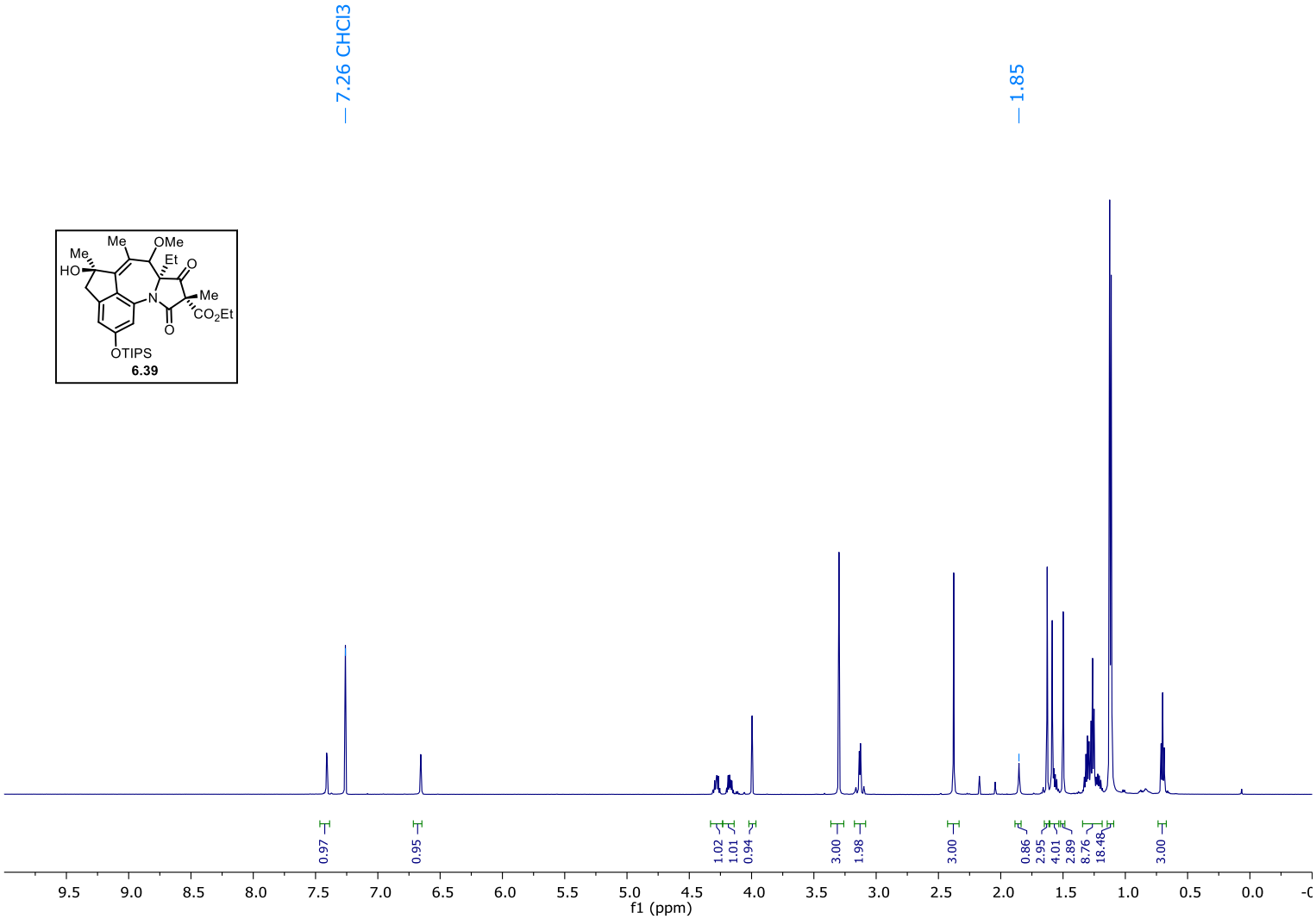


Figure D.51. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.39**

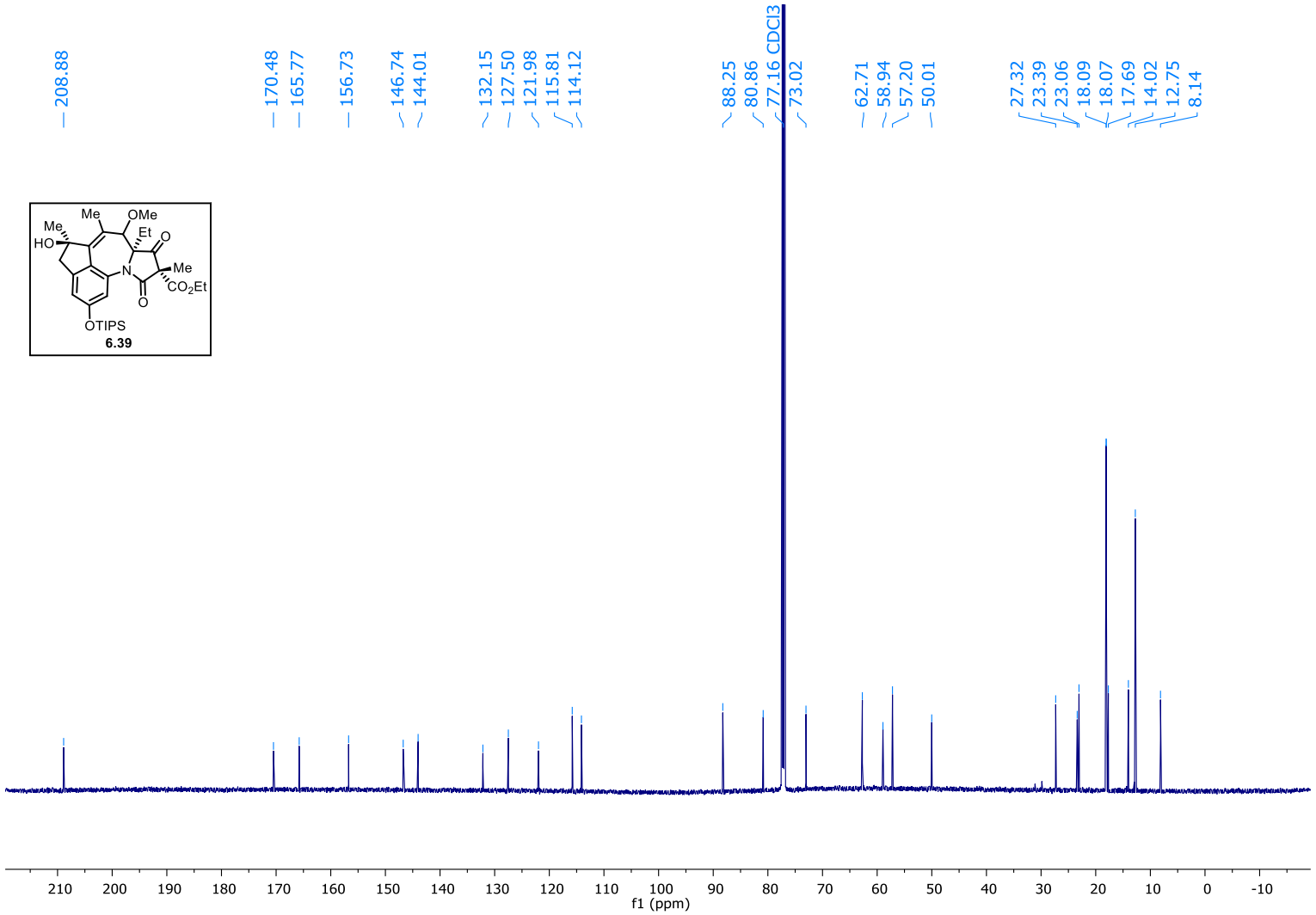


Figure D.52. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.39**

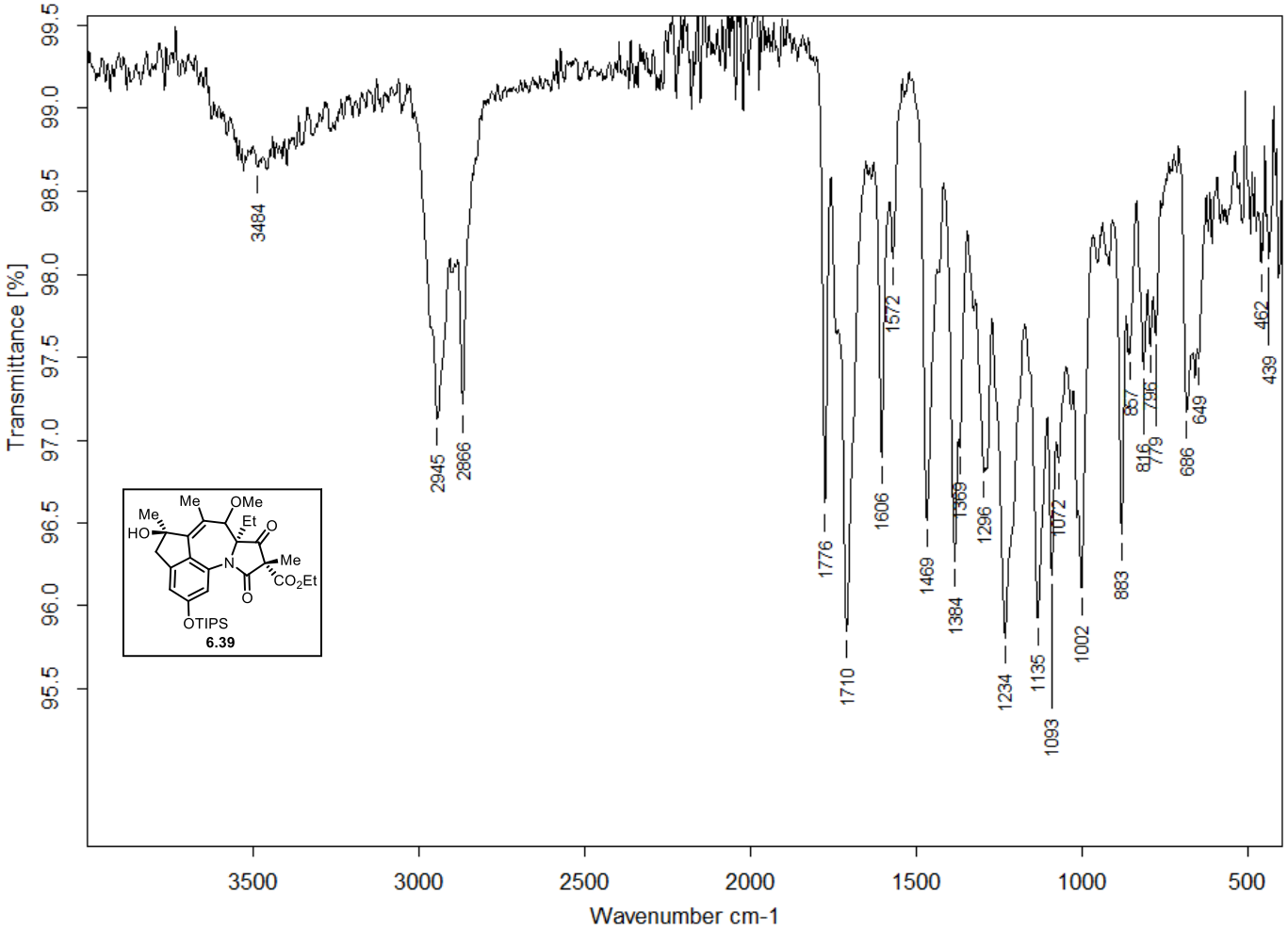


Figure D.53. FTIR spectrum (neat) of compound **6.39**

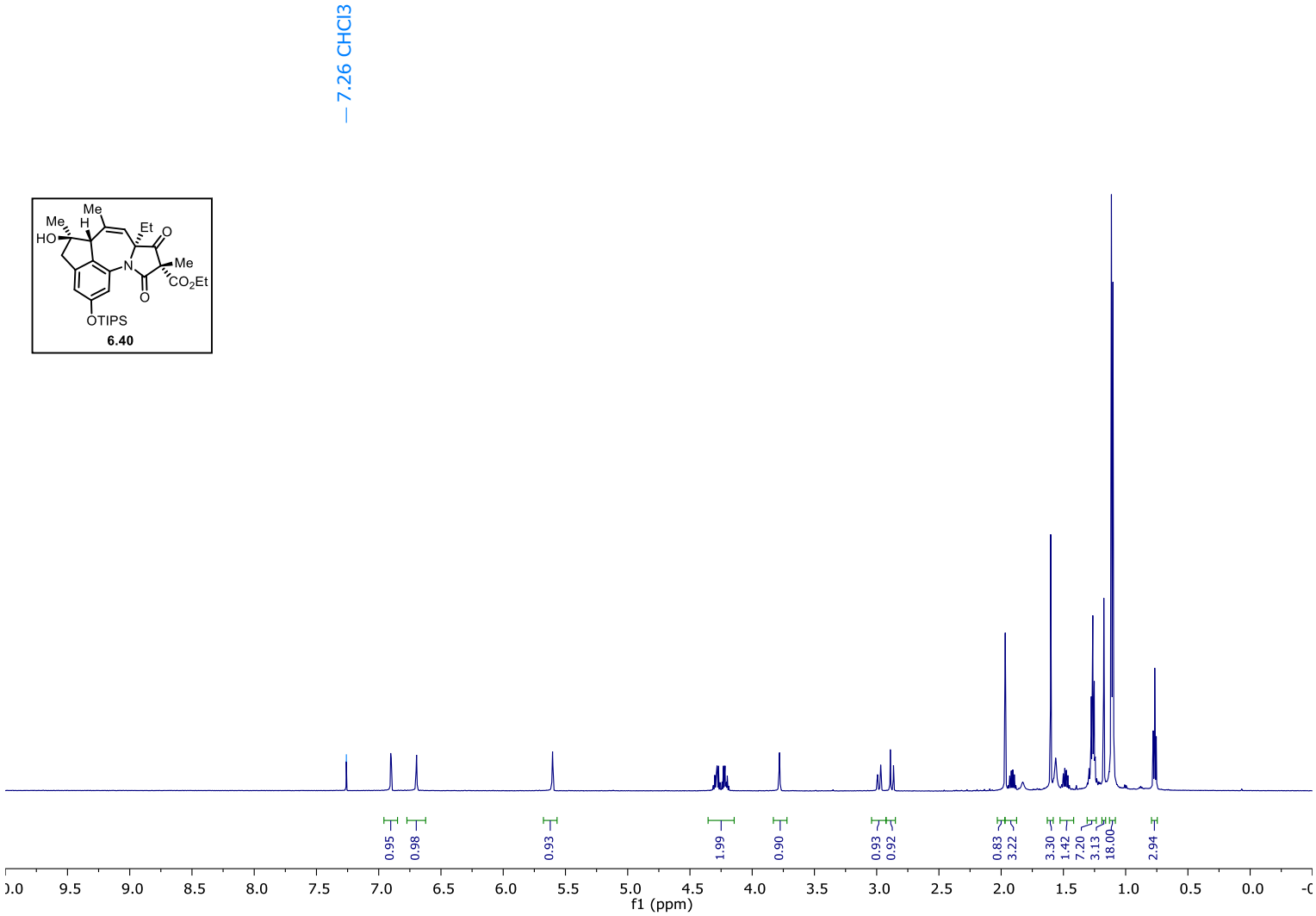


Figure D.54. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.40**

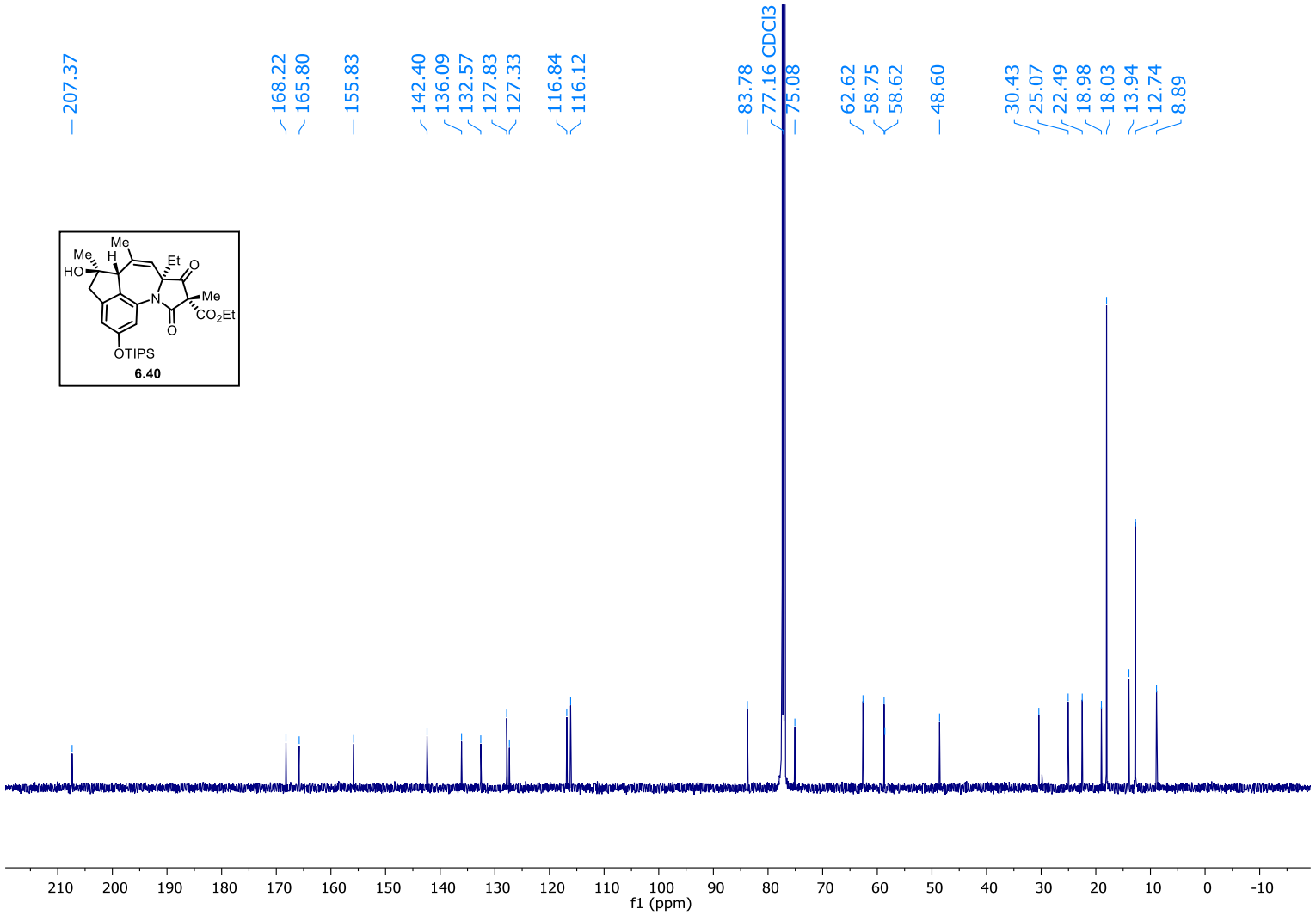


Figure D.55. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.40**

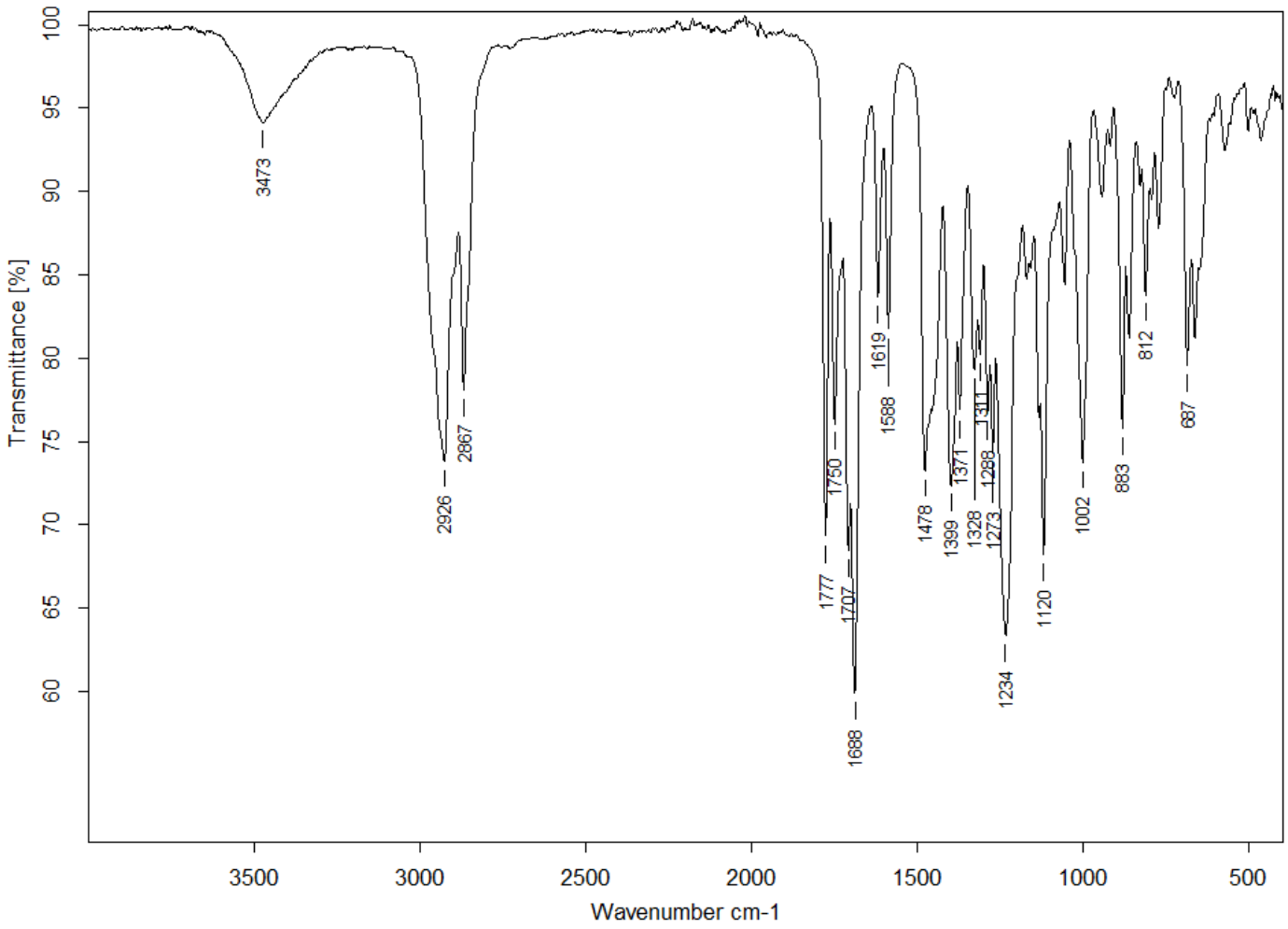


Figure D.56. FTIR spectrum (neat) of compound **6.40**

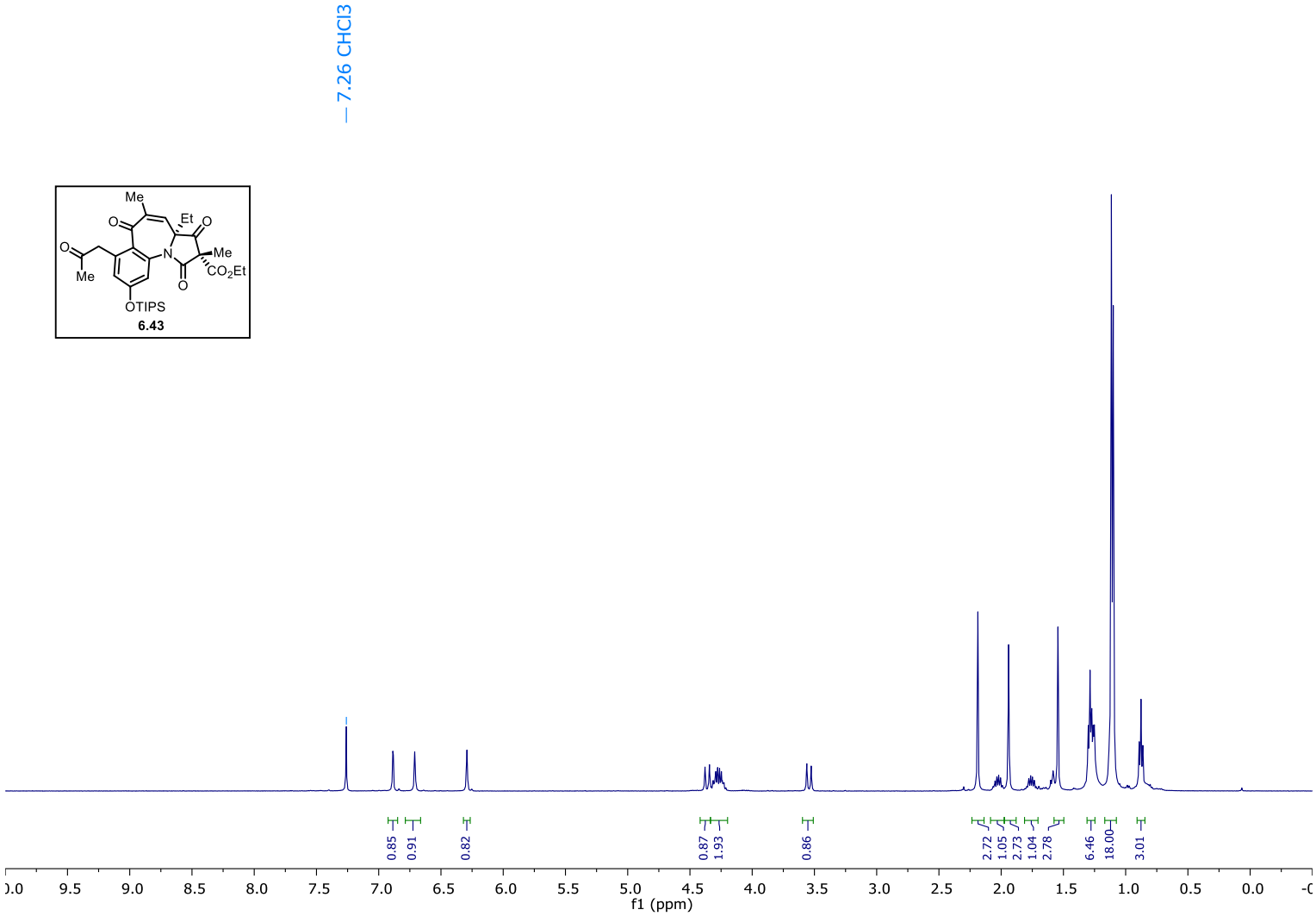


Figure D.57. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6.43**

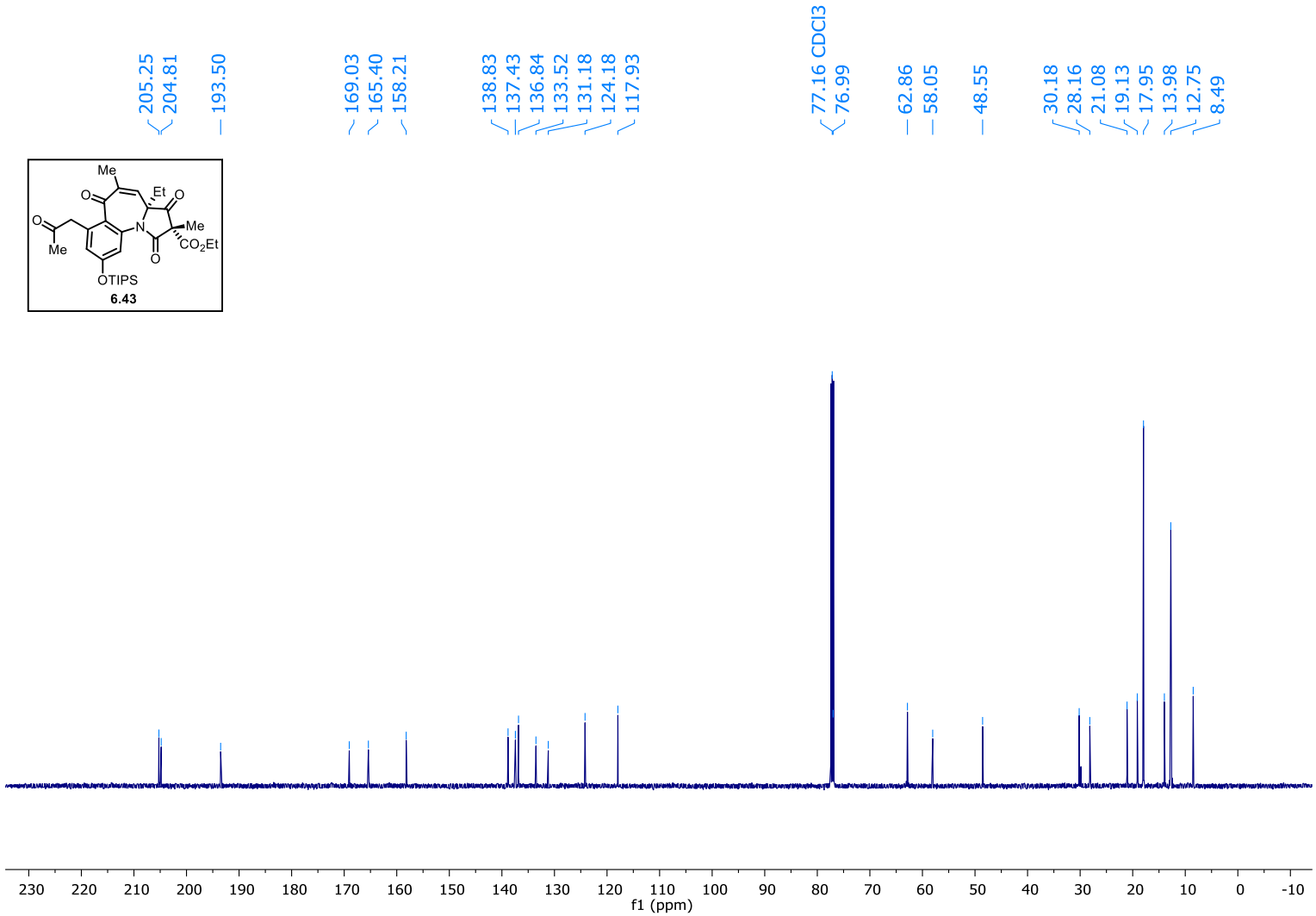


Figure D.58. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **6.43**

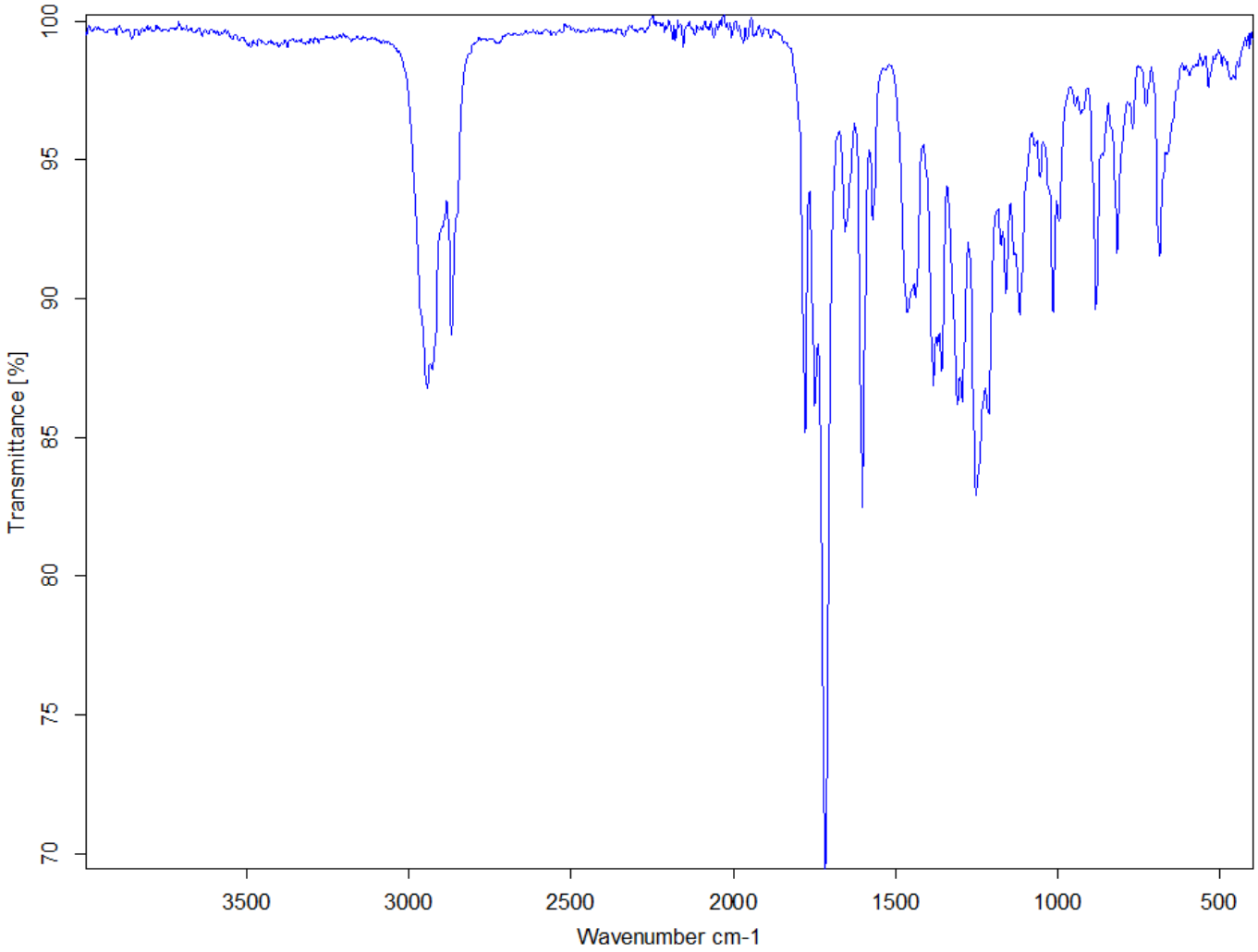


Figure D.59. FTIR spectrum (neat) of compound **6.43**

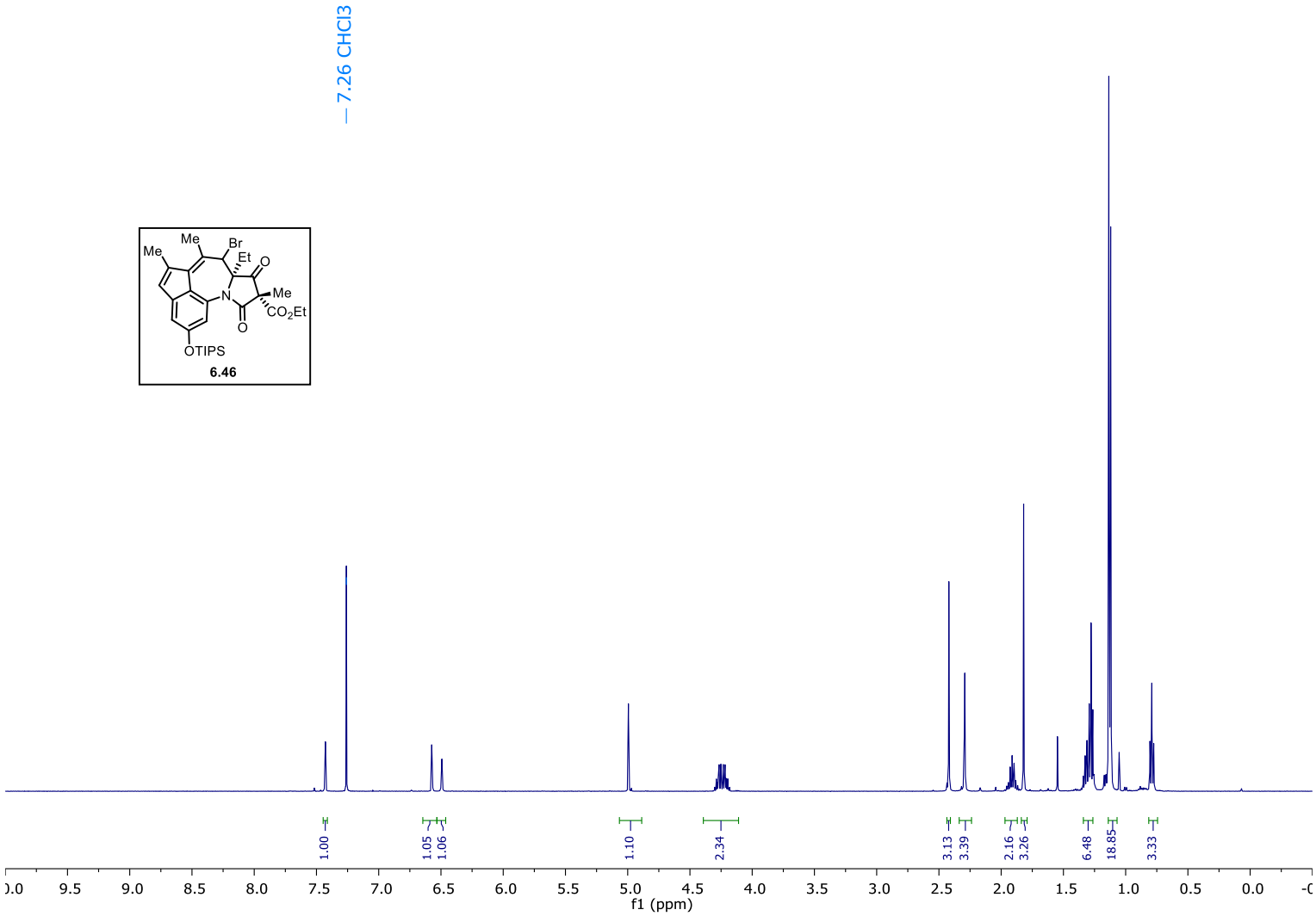


Figure D.60. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6.46**

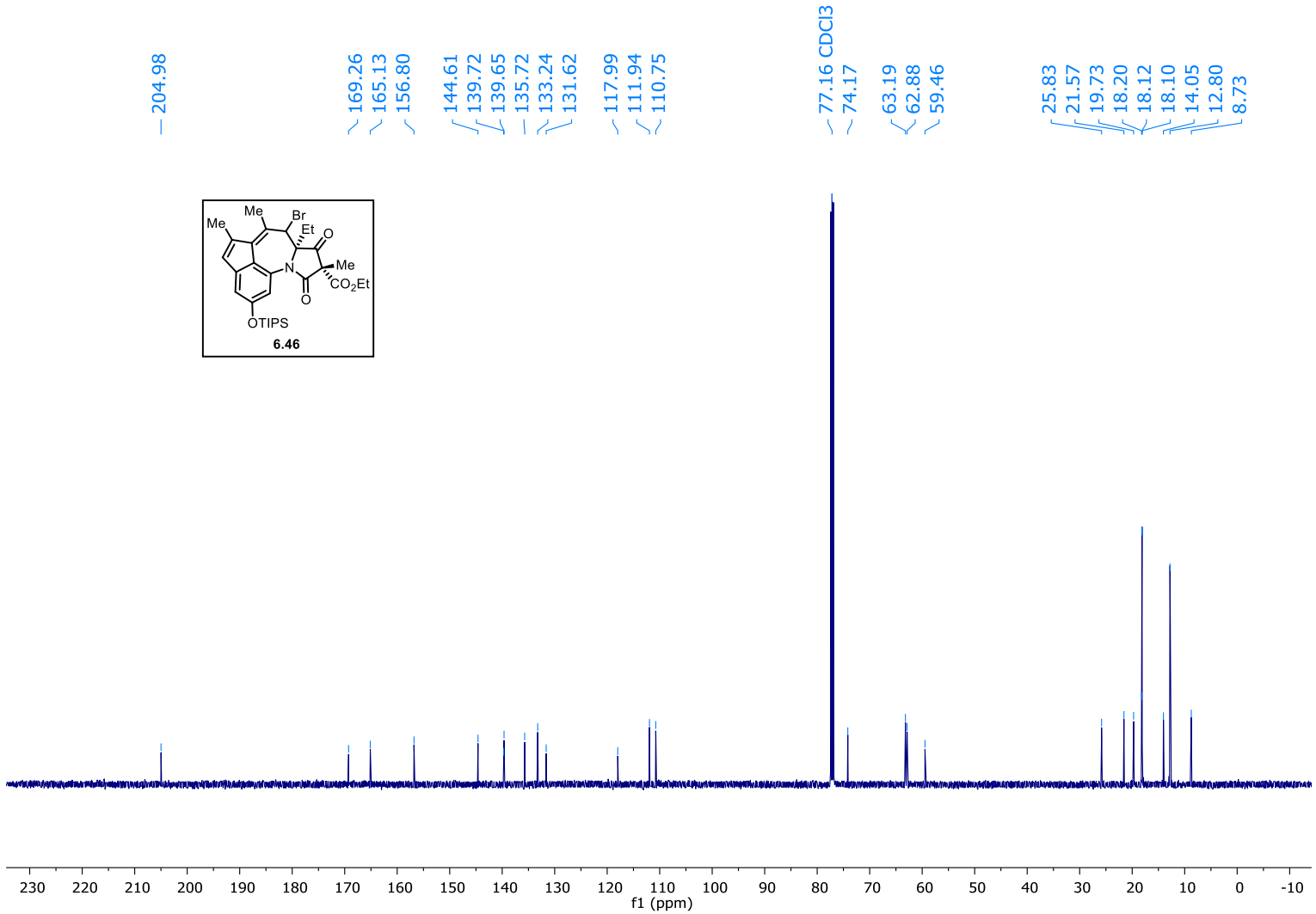


Figure D.61. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **6.46**

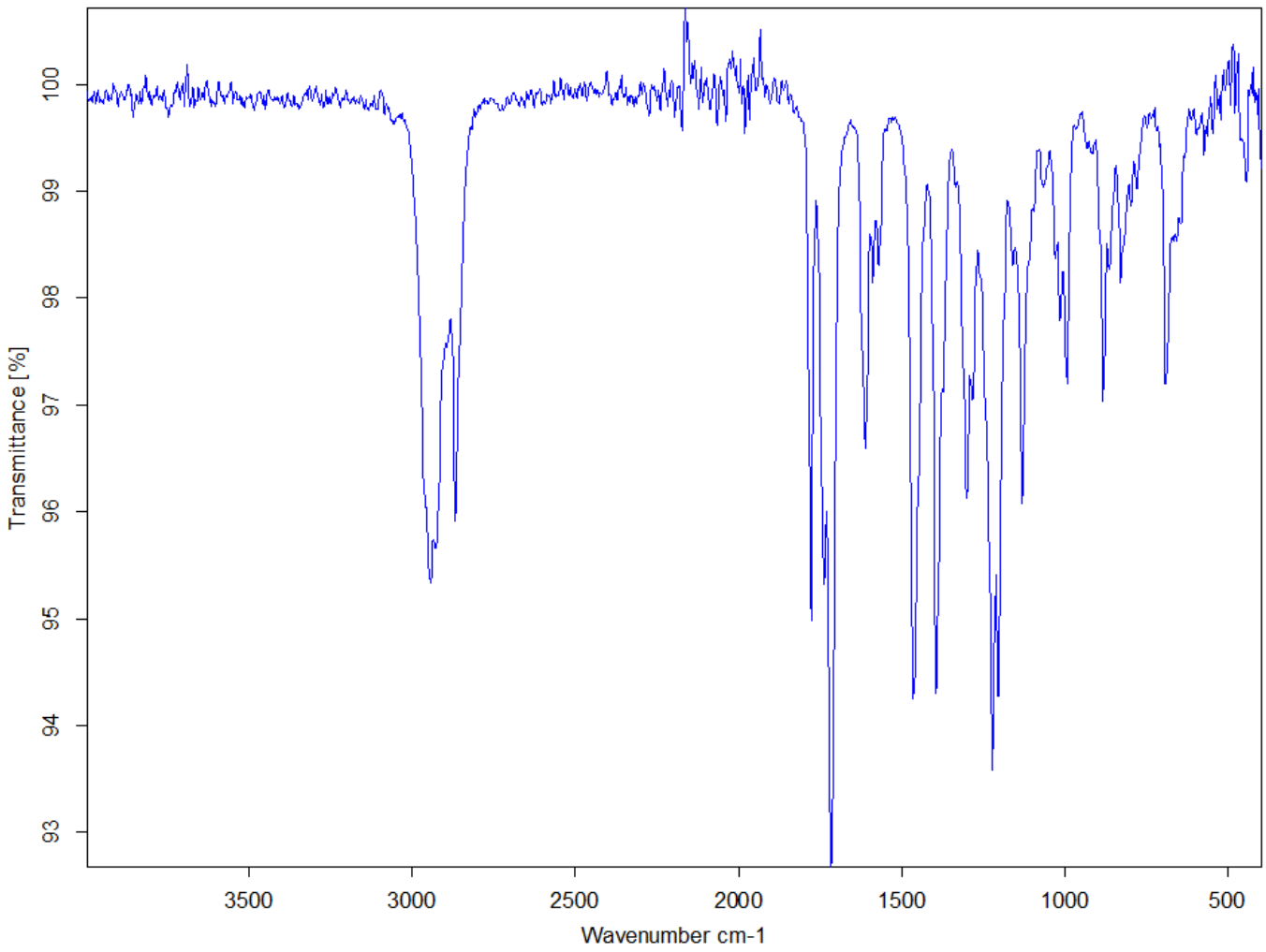


Figure D.62. FTIR spectrum (neat) of compound **6.46**

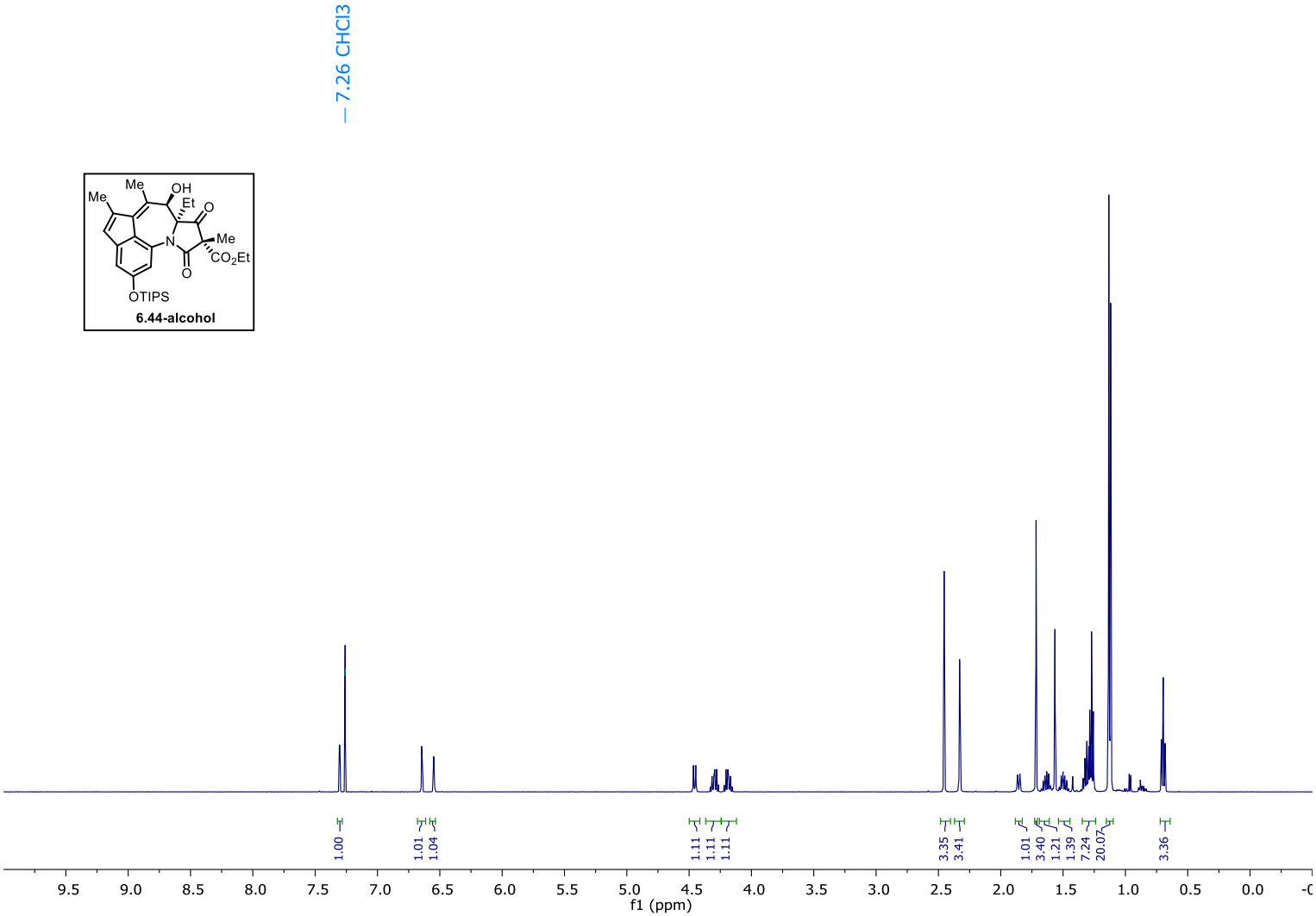


Figure D.63. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6.44-alcohol**

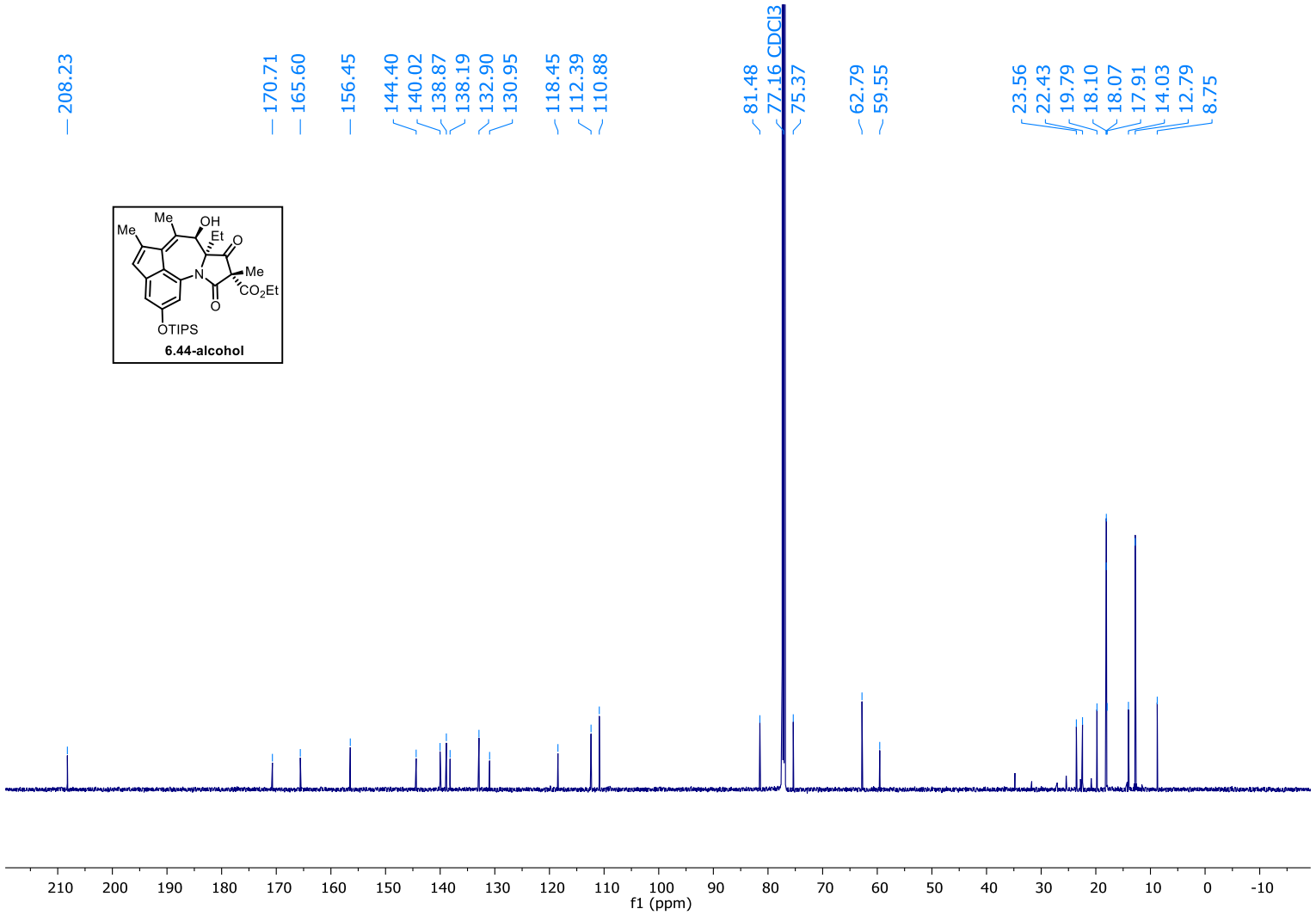


Figure D.64. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.44-alcohol**

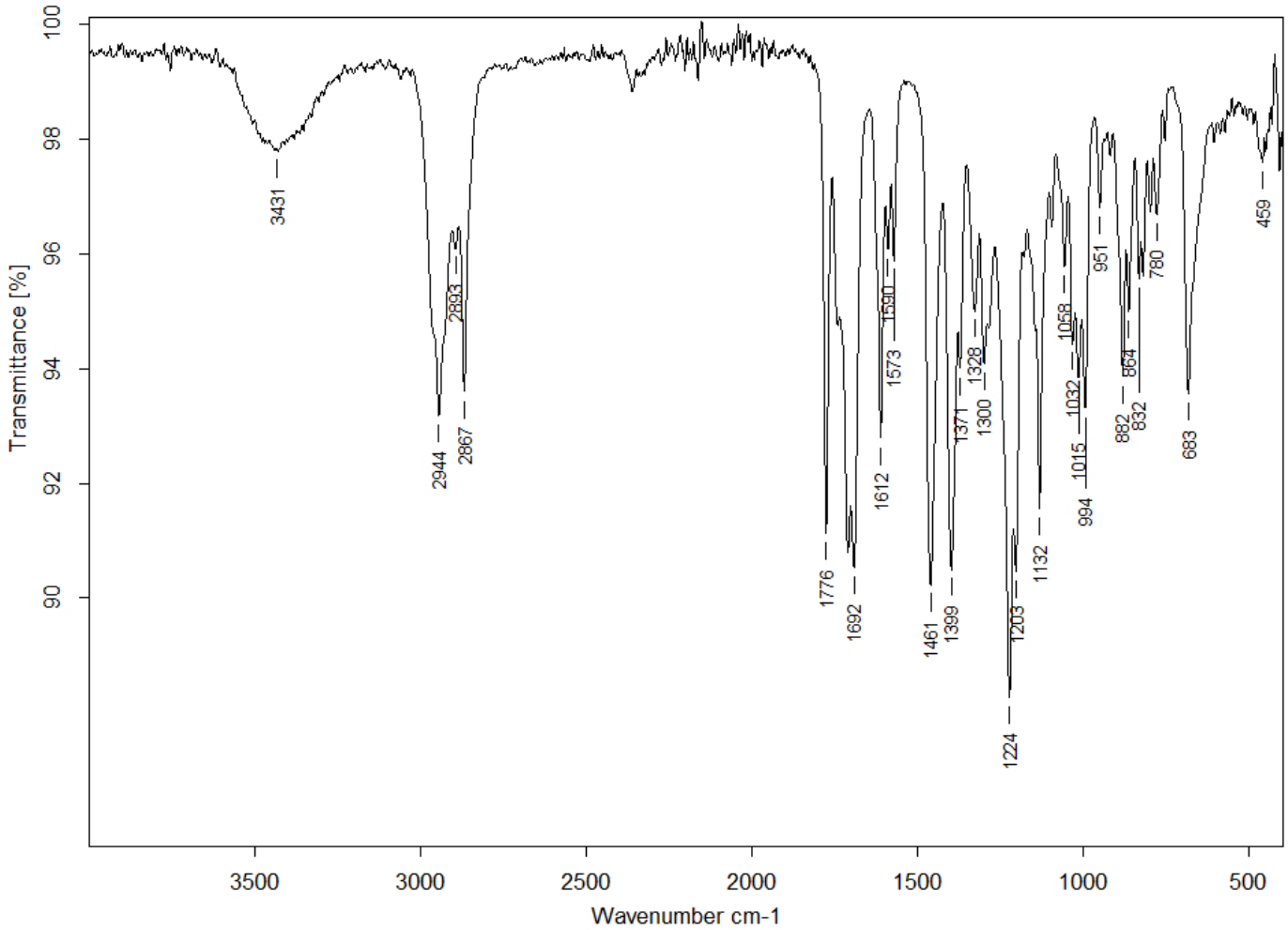


Figure D.65. FTIR spectrum (neat) of compound **6.44-alcohol**

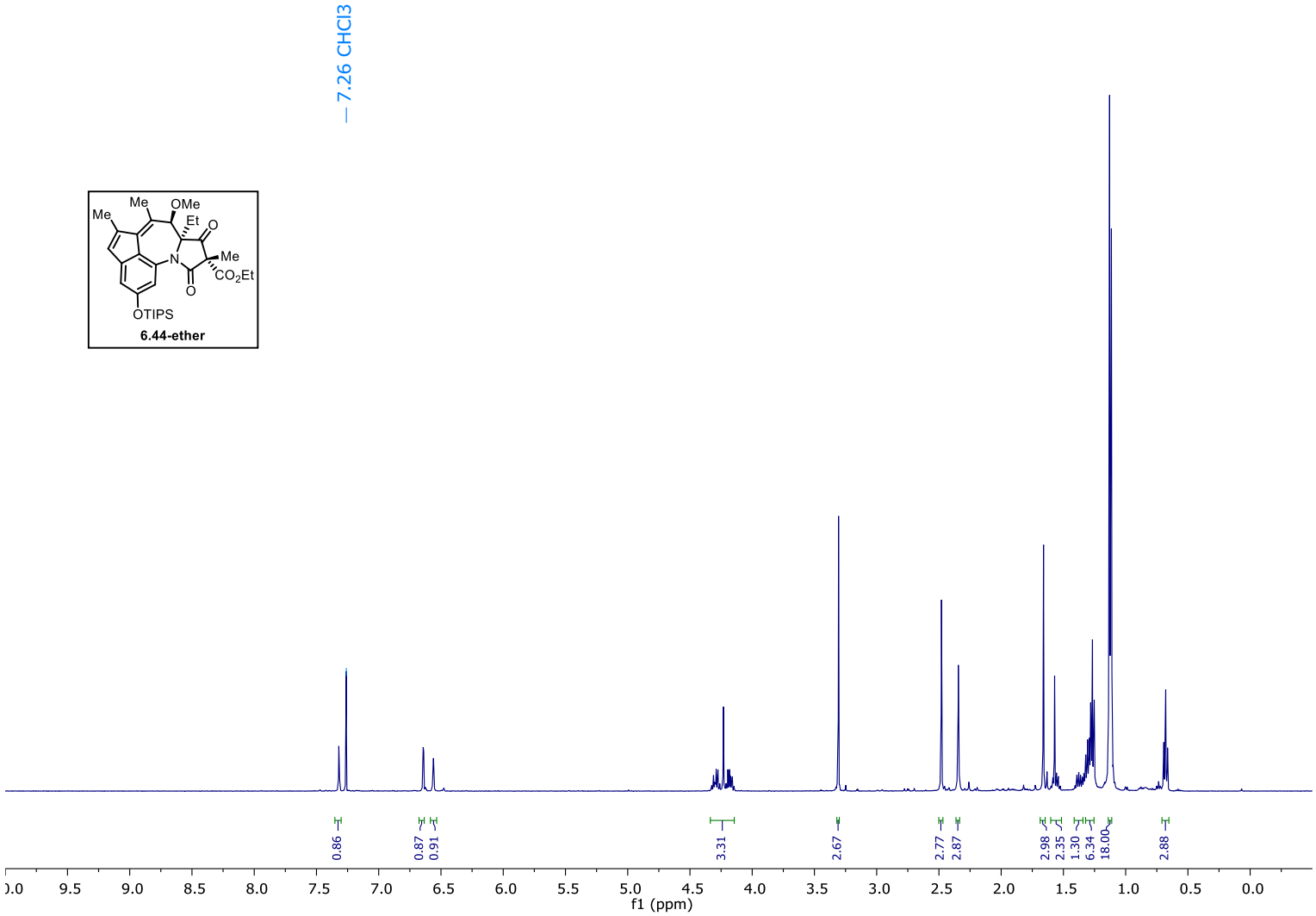


Figure D.66. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6.44-ether**

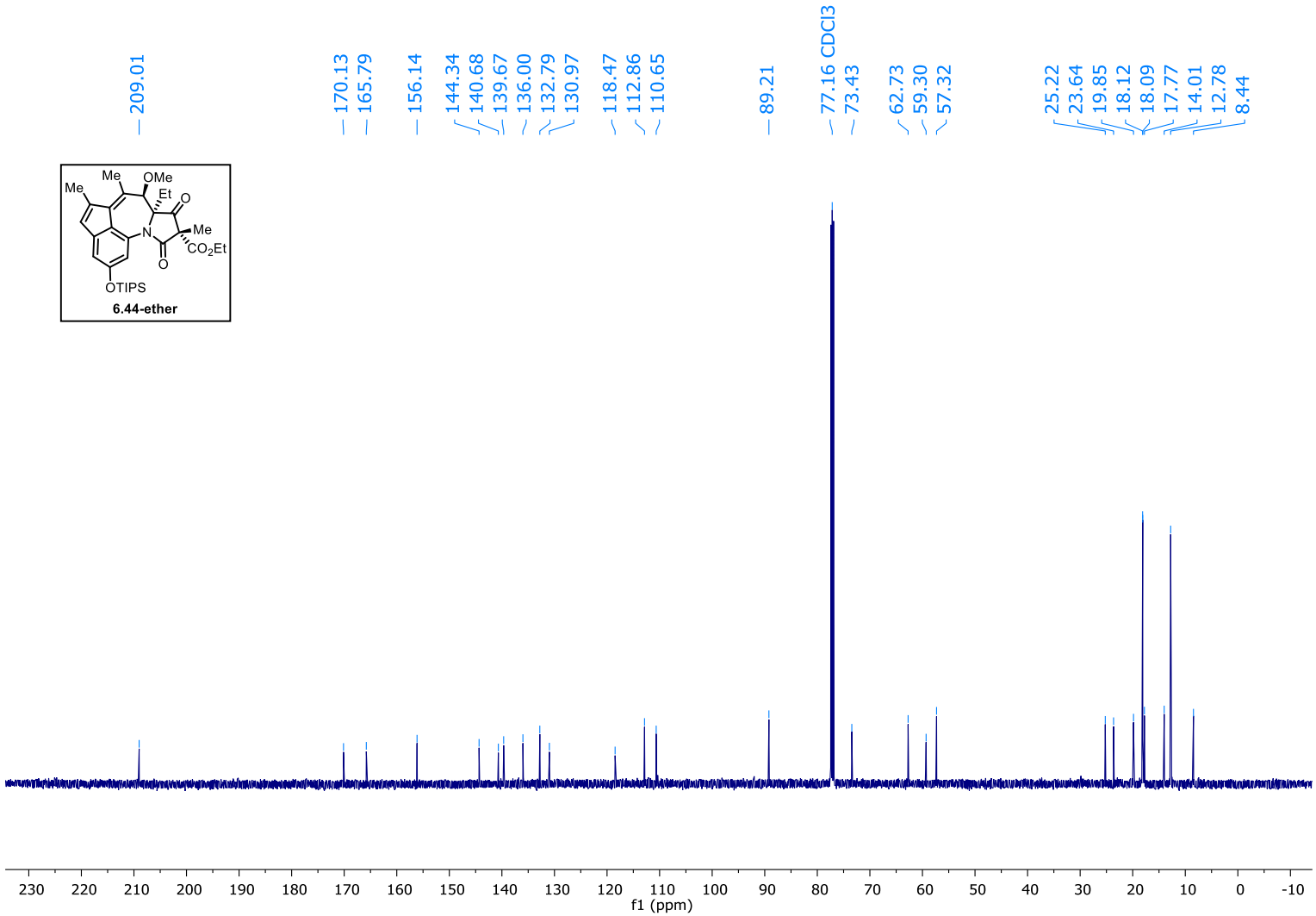


Figure D.67. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **6.44-ether**

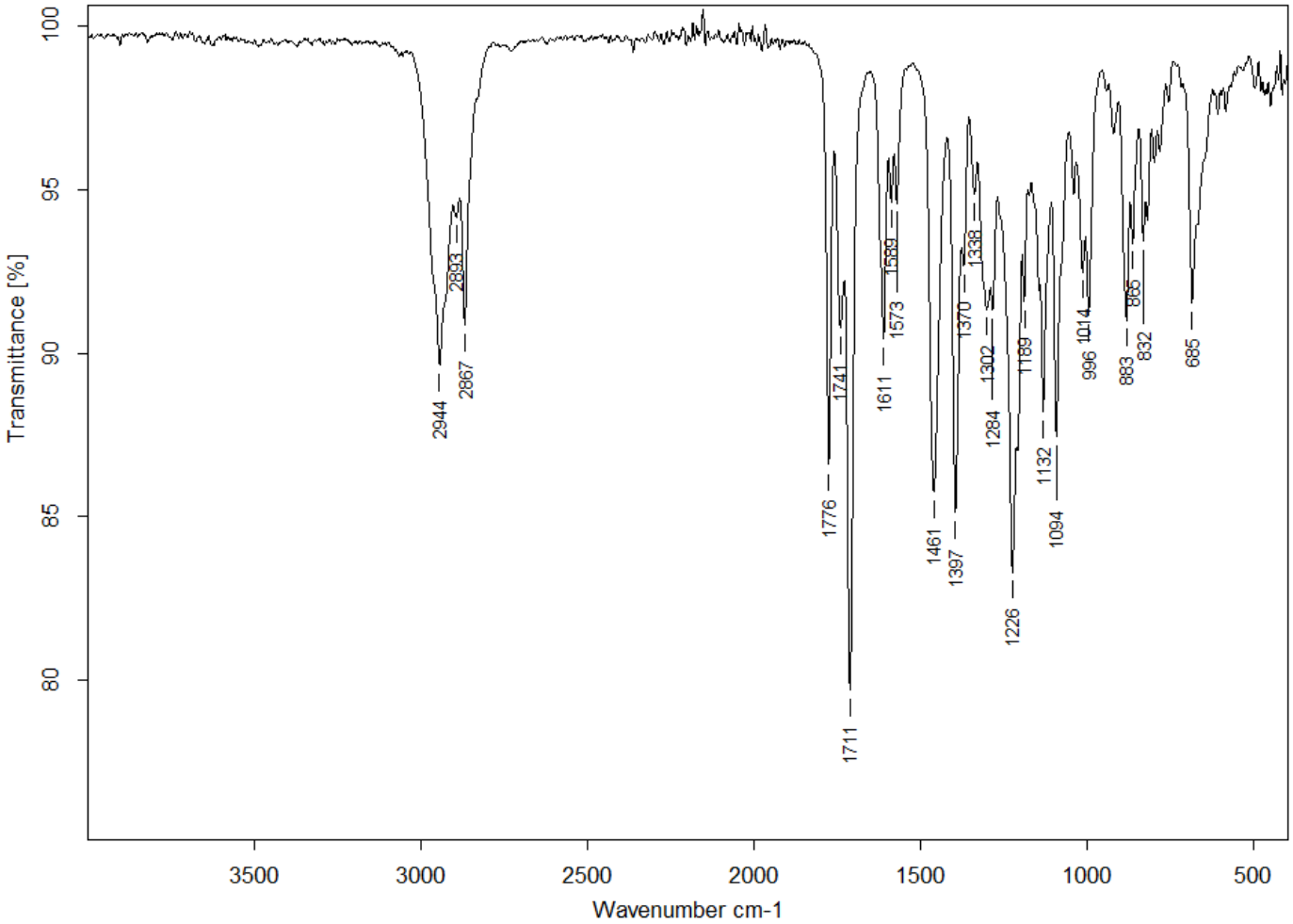


Figure D.68. FTIR spectrum (neat) of compound **6.44-ether**

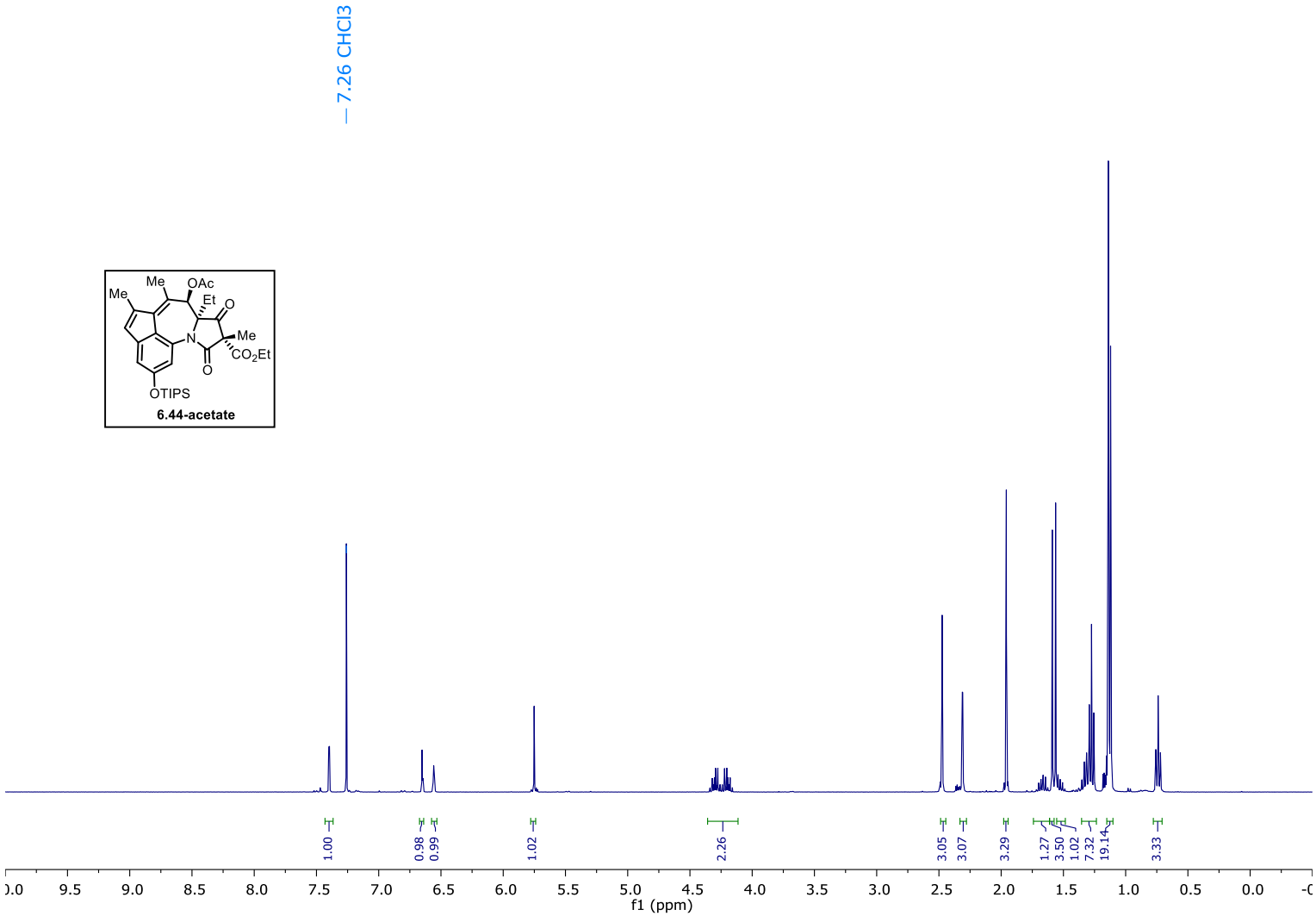


Figure D.69. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.44-acetate**

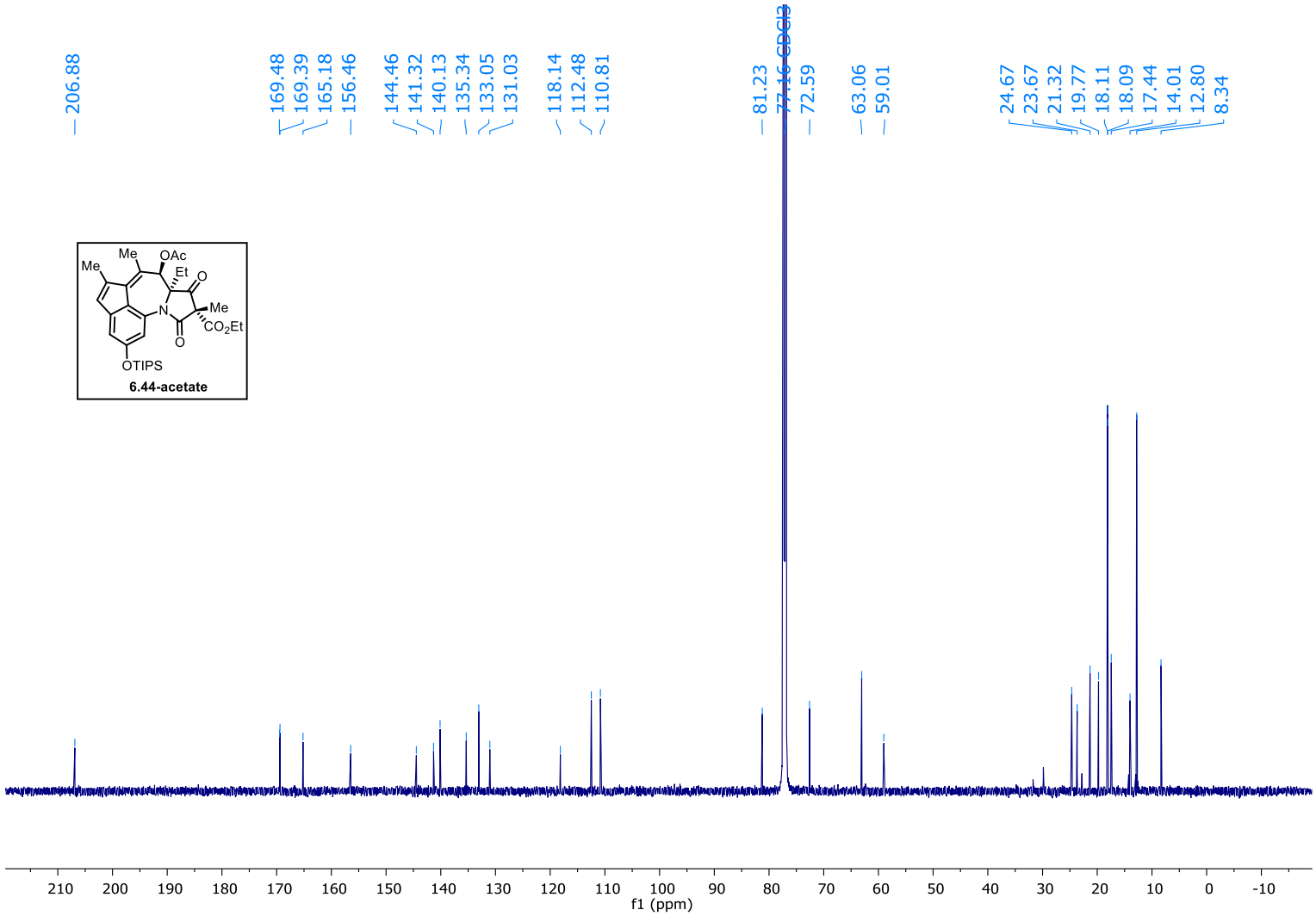


Figure D.70. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.44-acetate**

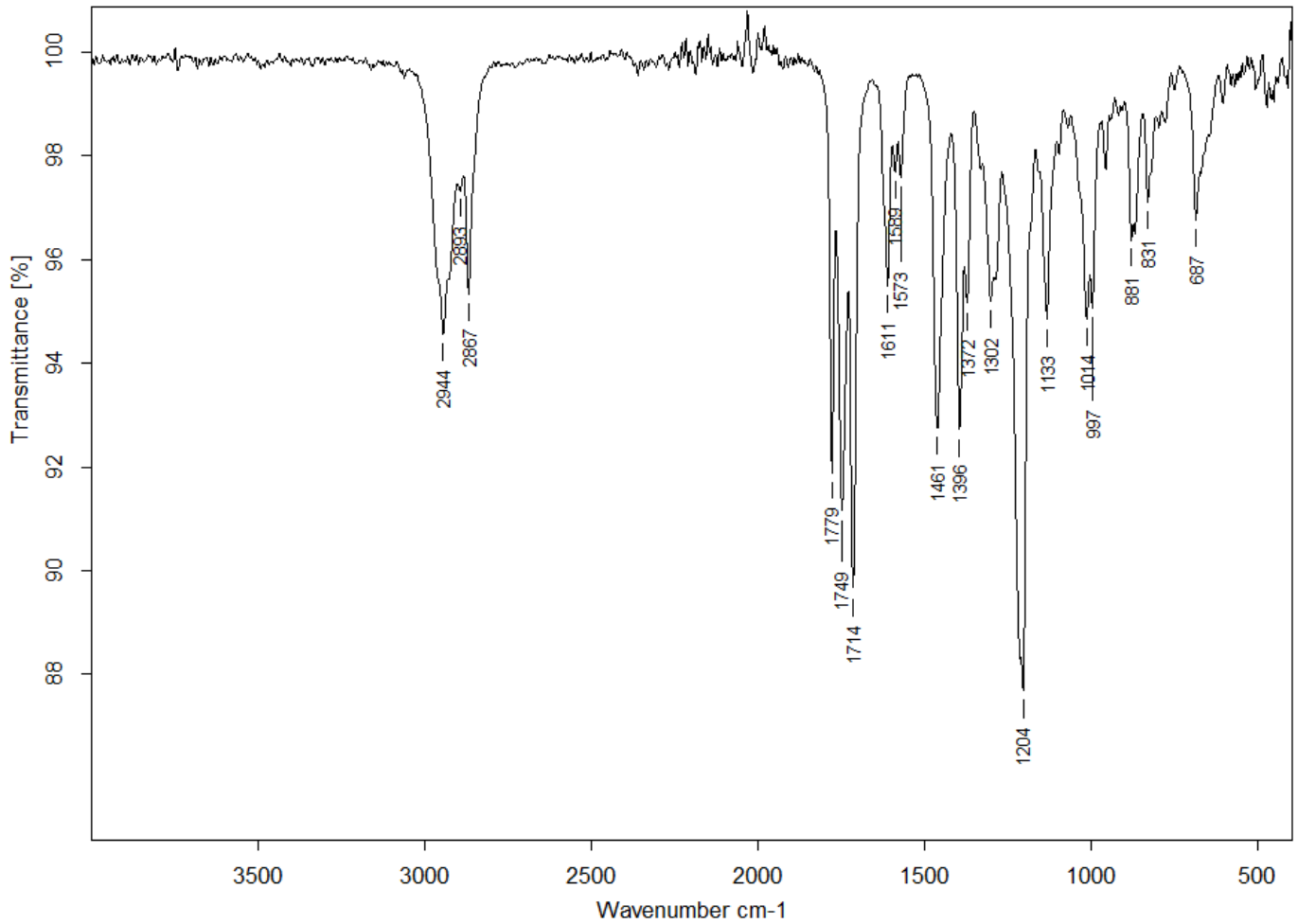


Figure D.71. FTIR spectrum (neat) of compound **6.44-acetate**

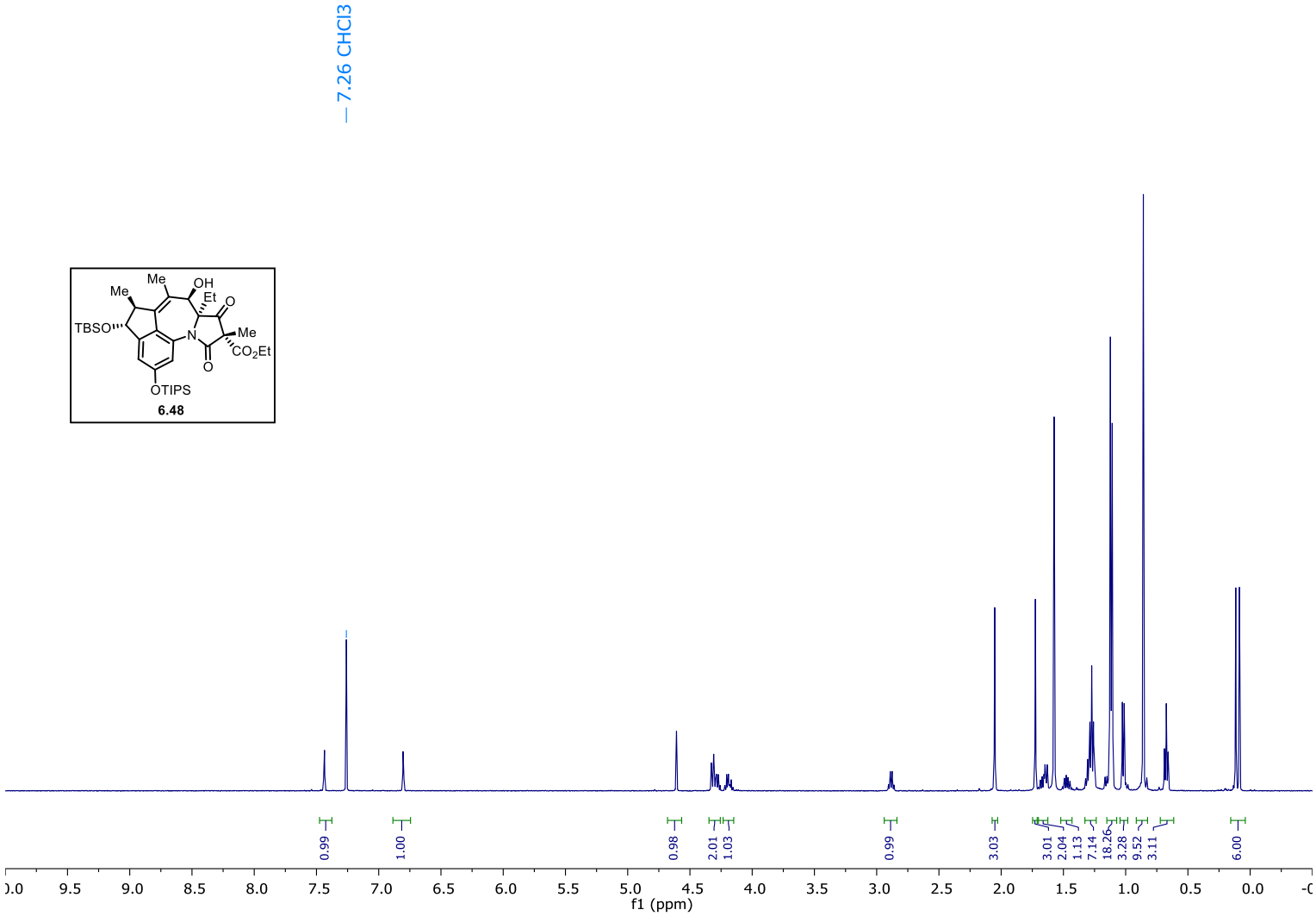


Figure D.72. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6.48**

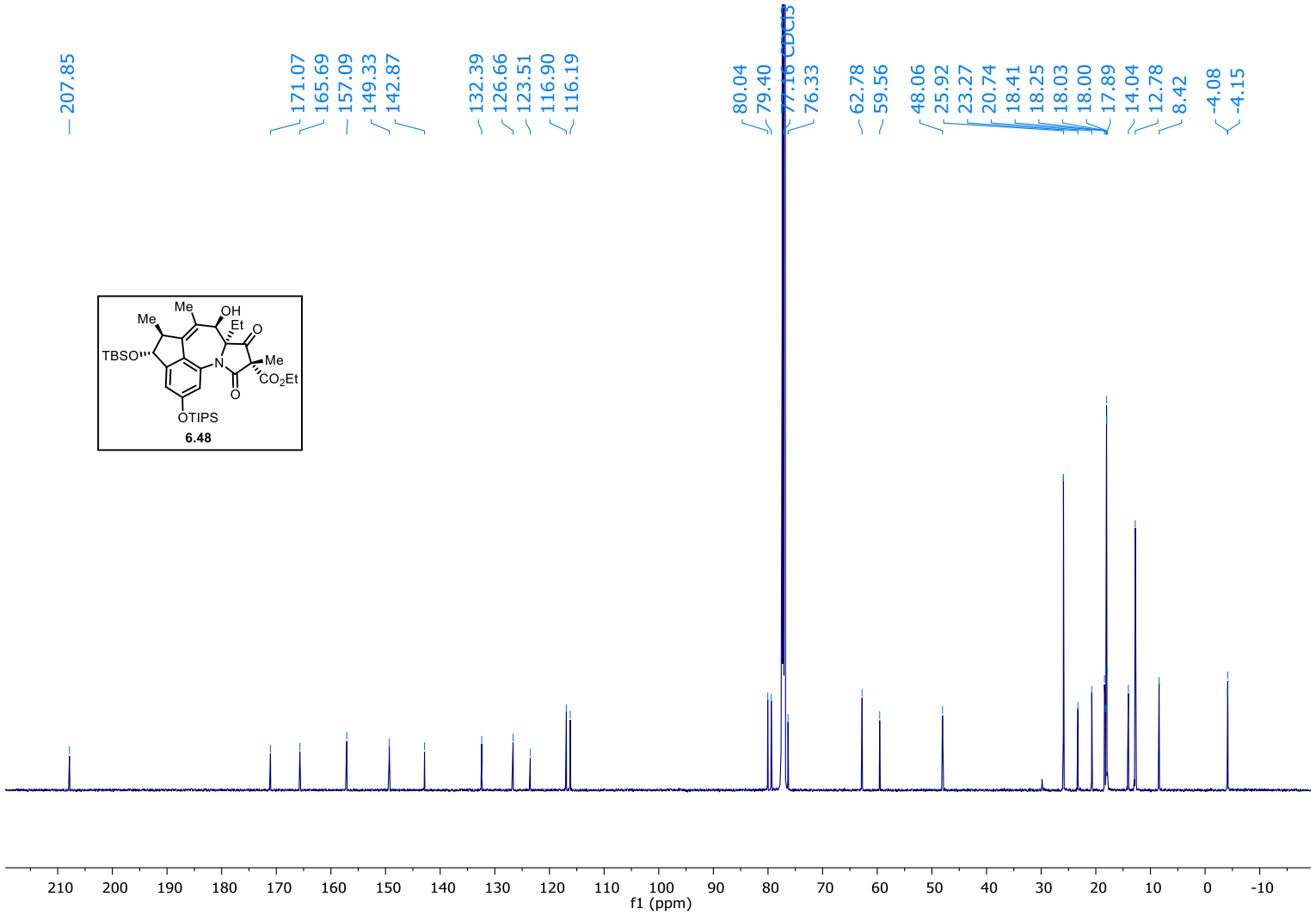


Figure D.73. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.48**

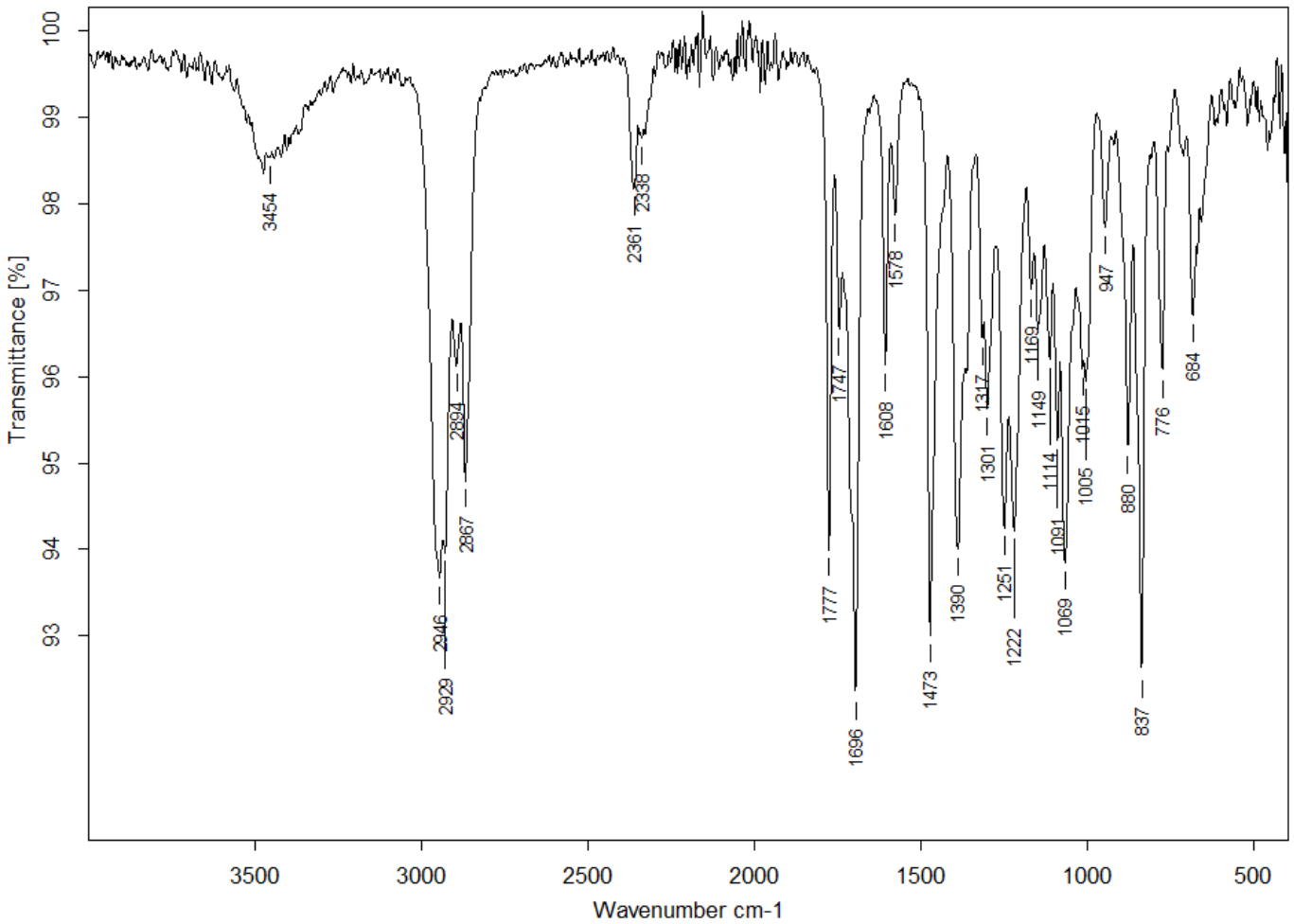


Figure D.74. FTIR spectrum (neat) of compound **6.48**

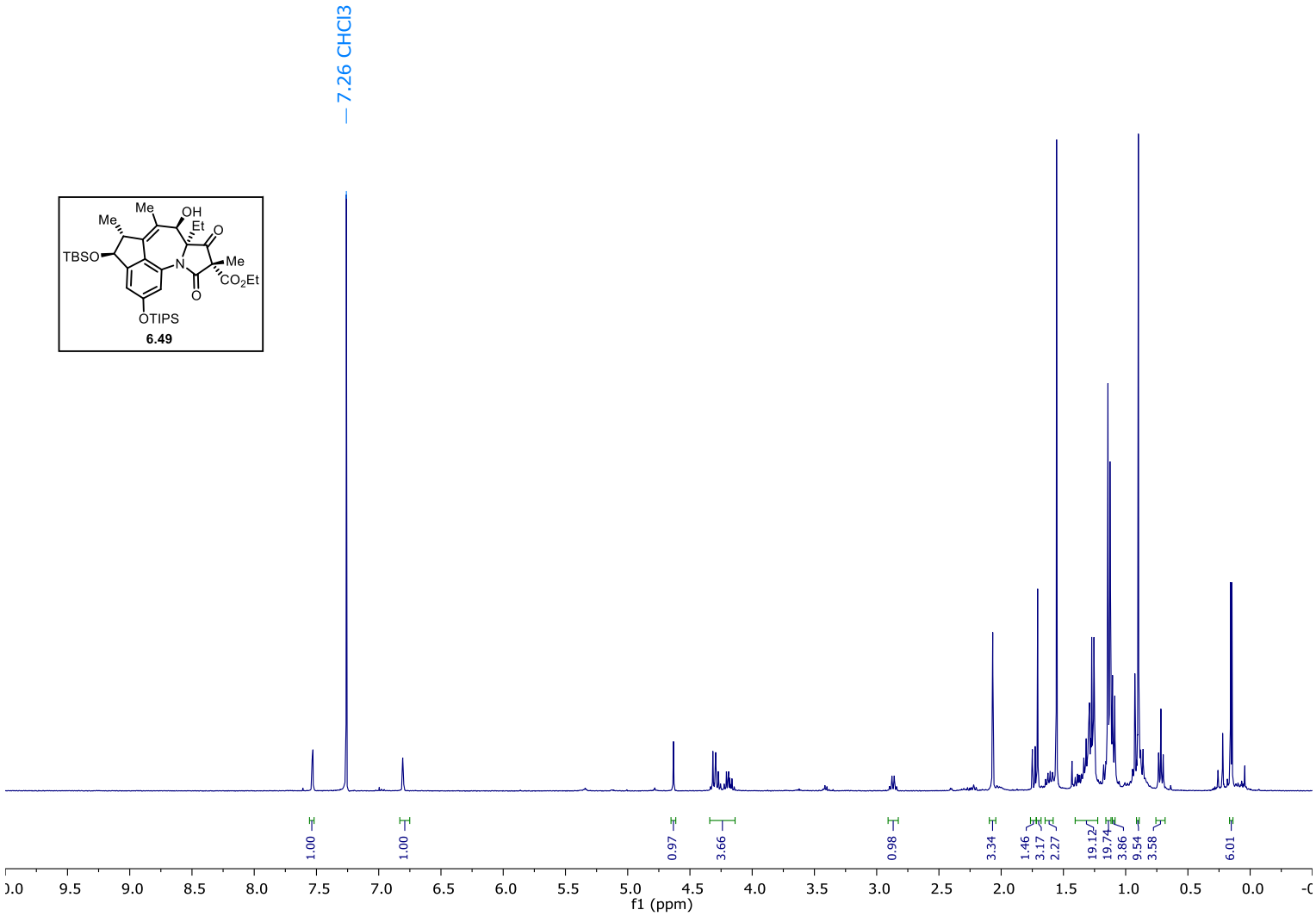


Figure D.75. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.49**

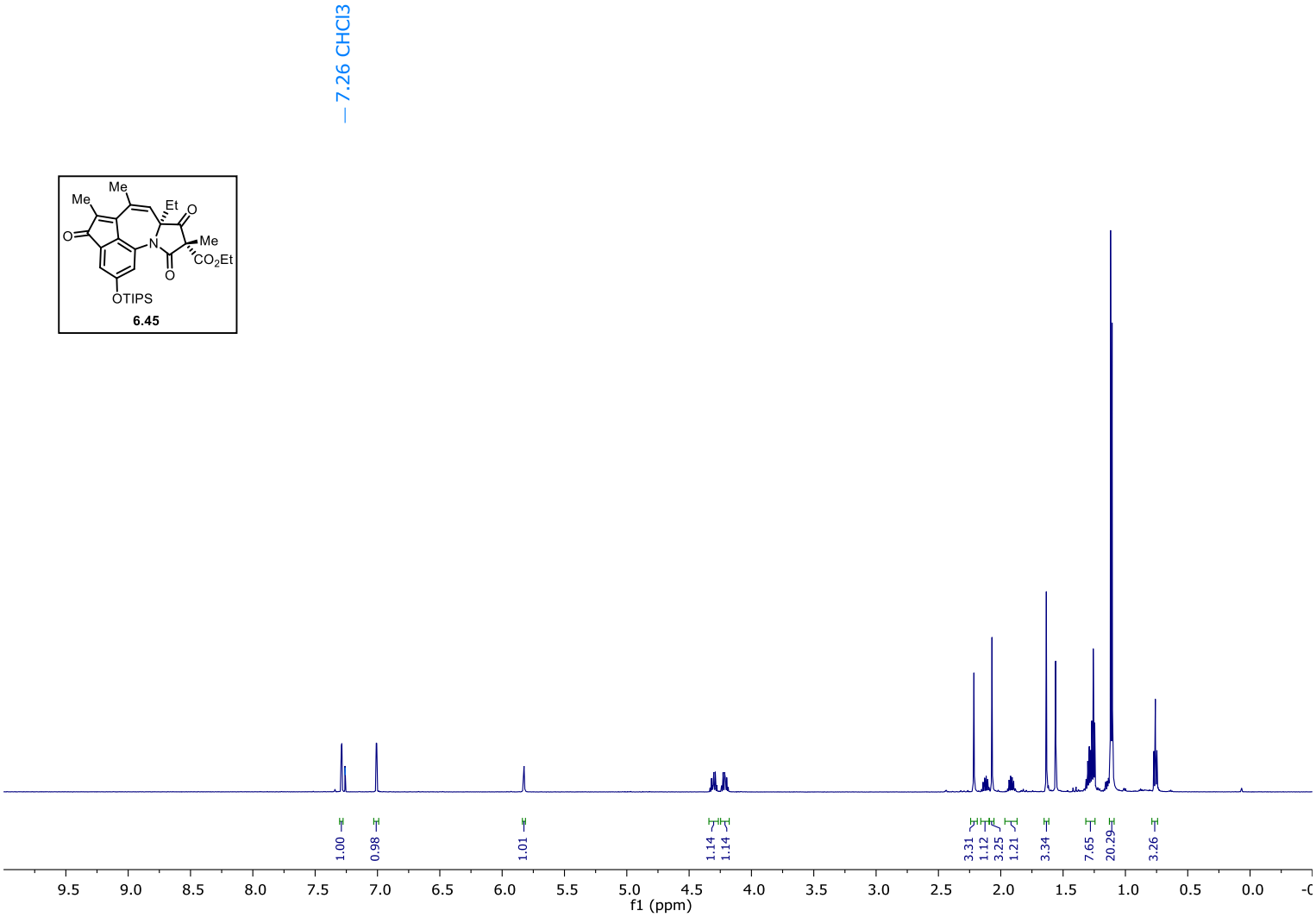


Figure D.76. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.45**

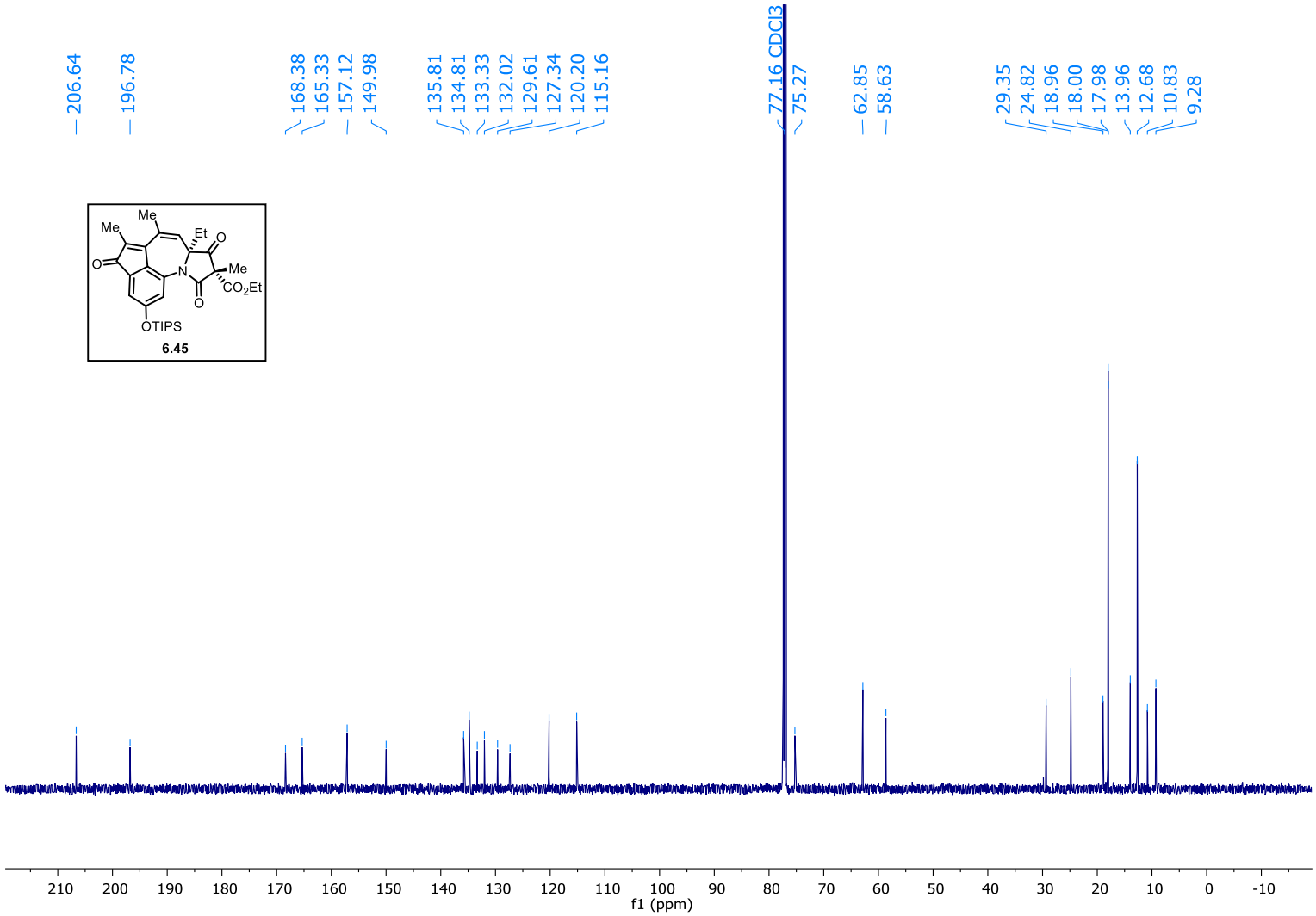


Figure D.77. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.45**

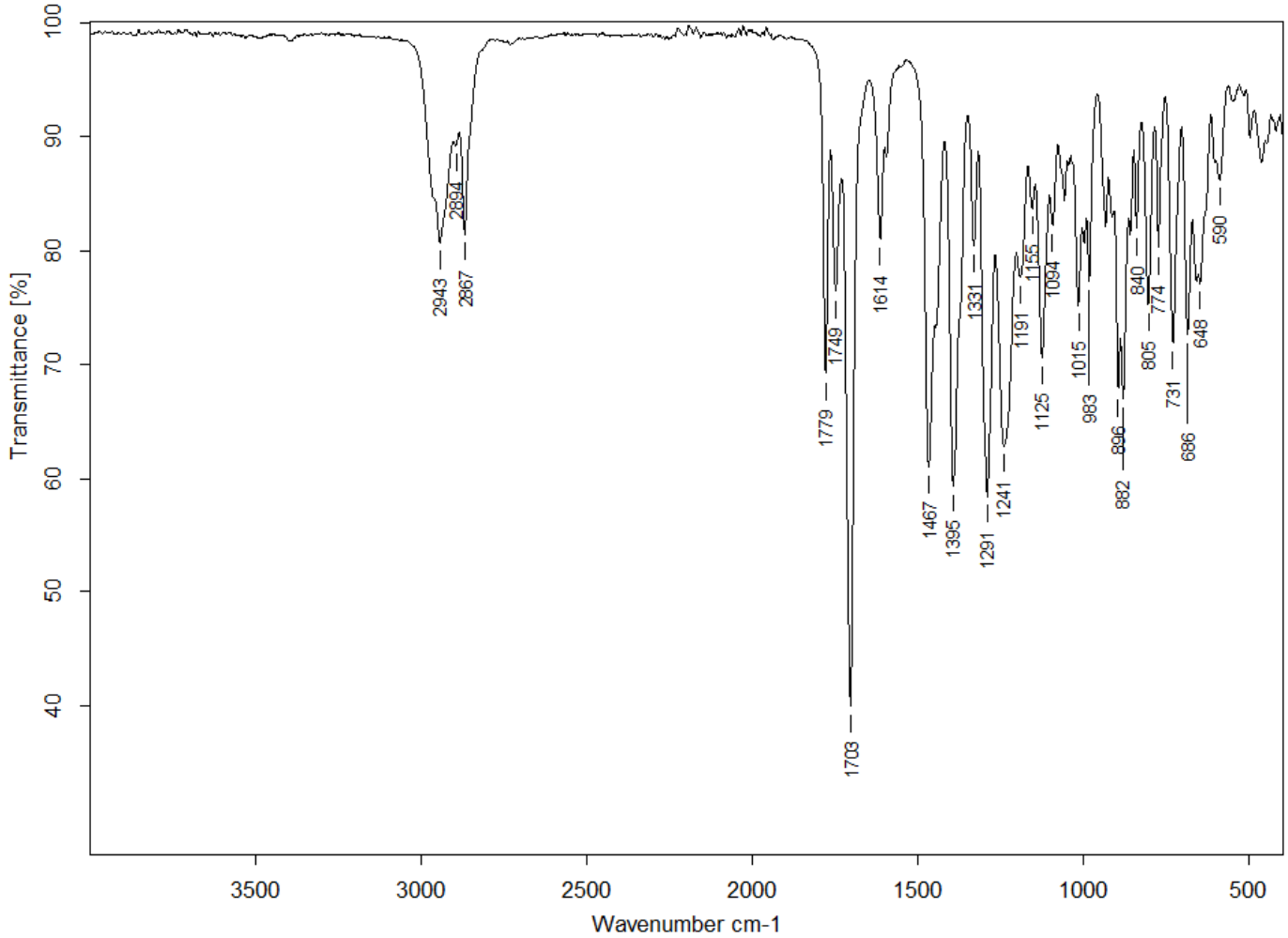


Figure D.78. FTIR spectrum (neat) of compound **6.45**

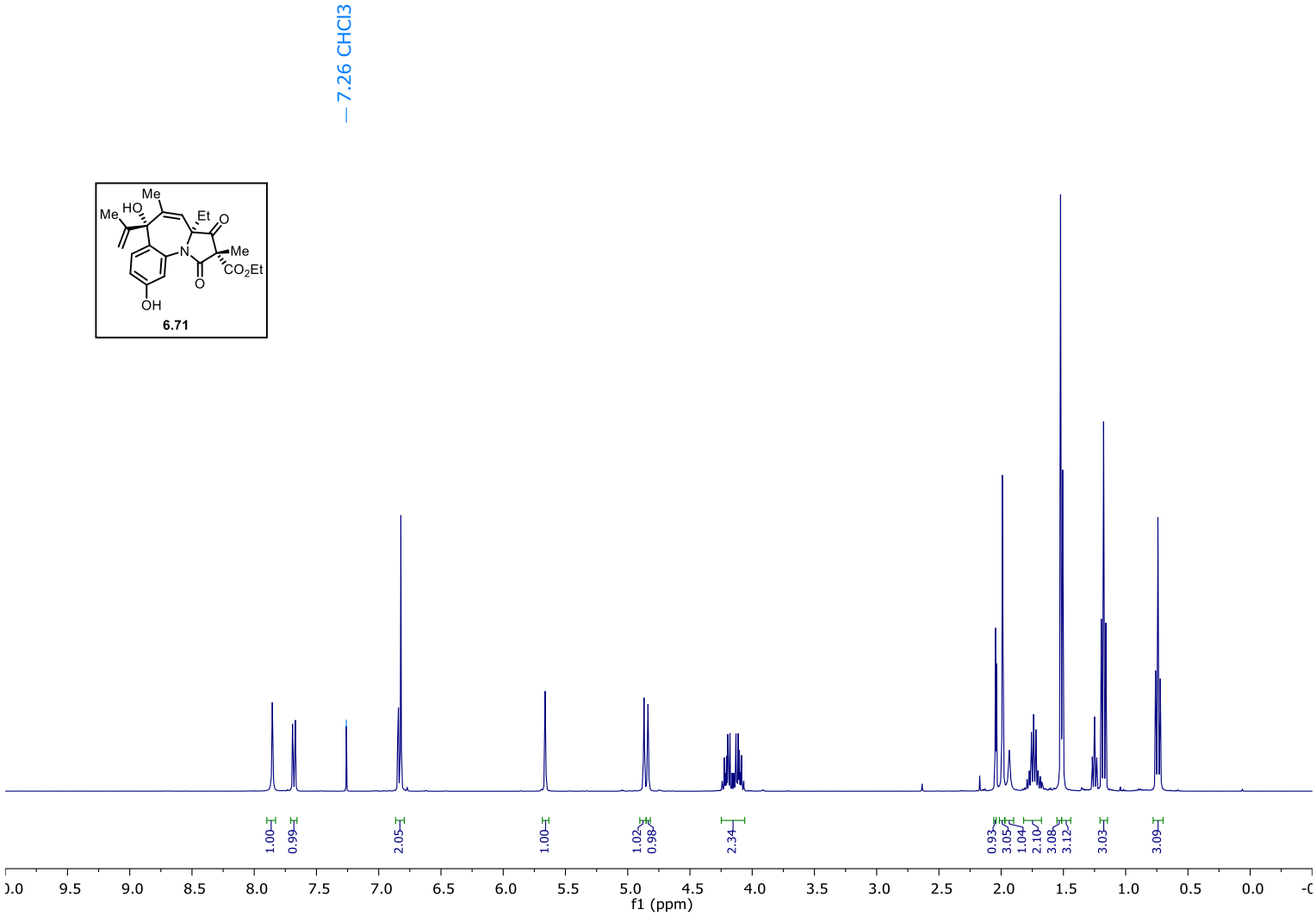


Figure D.79. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.71**

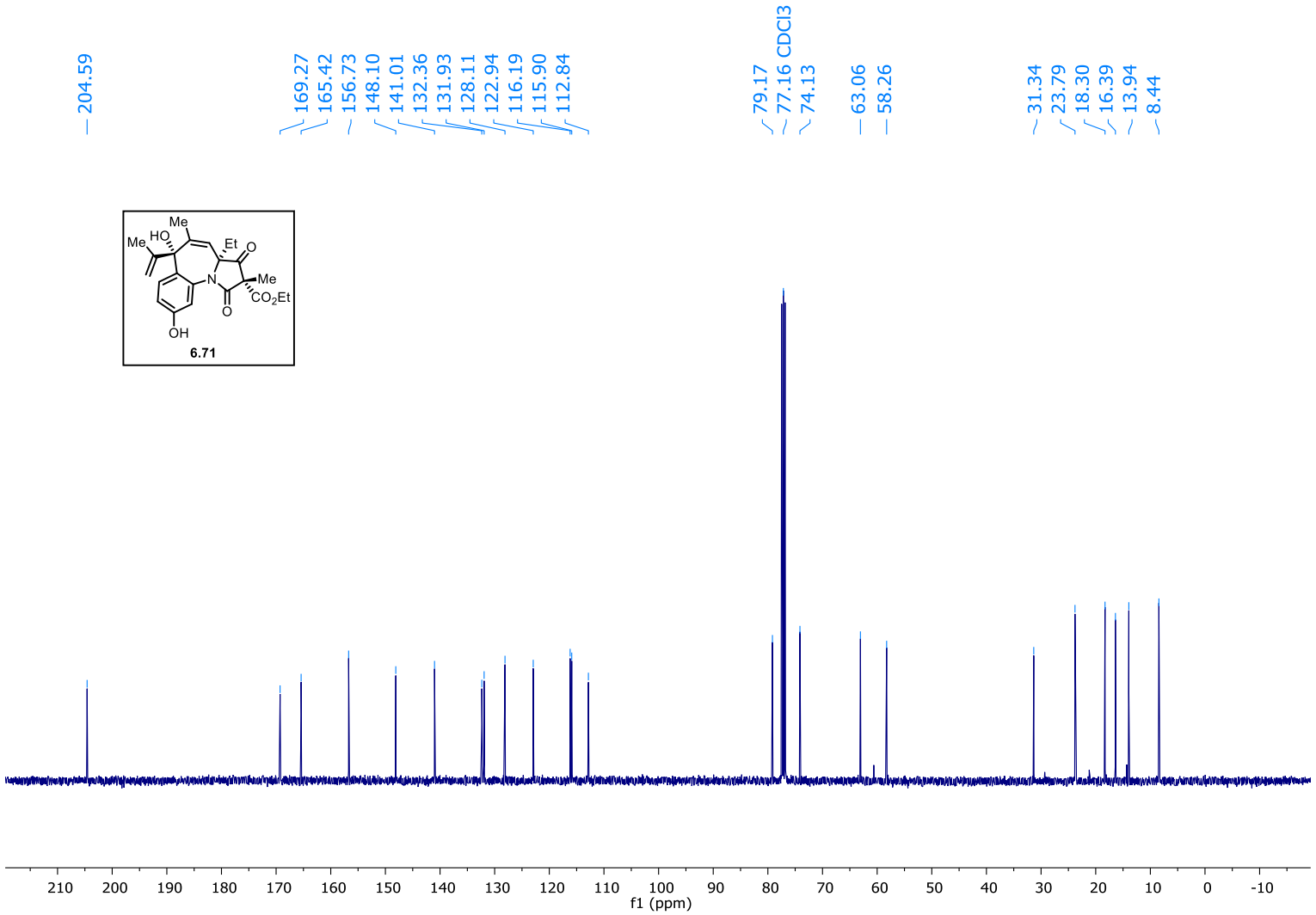


Figure D.80. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.71**

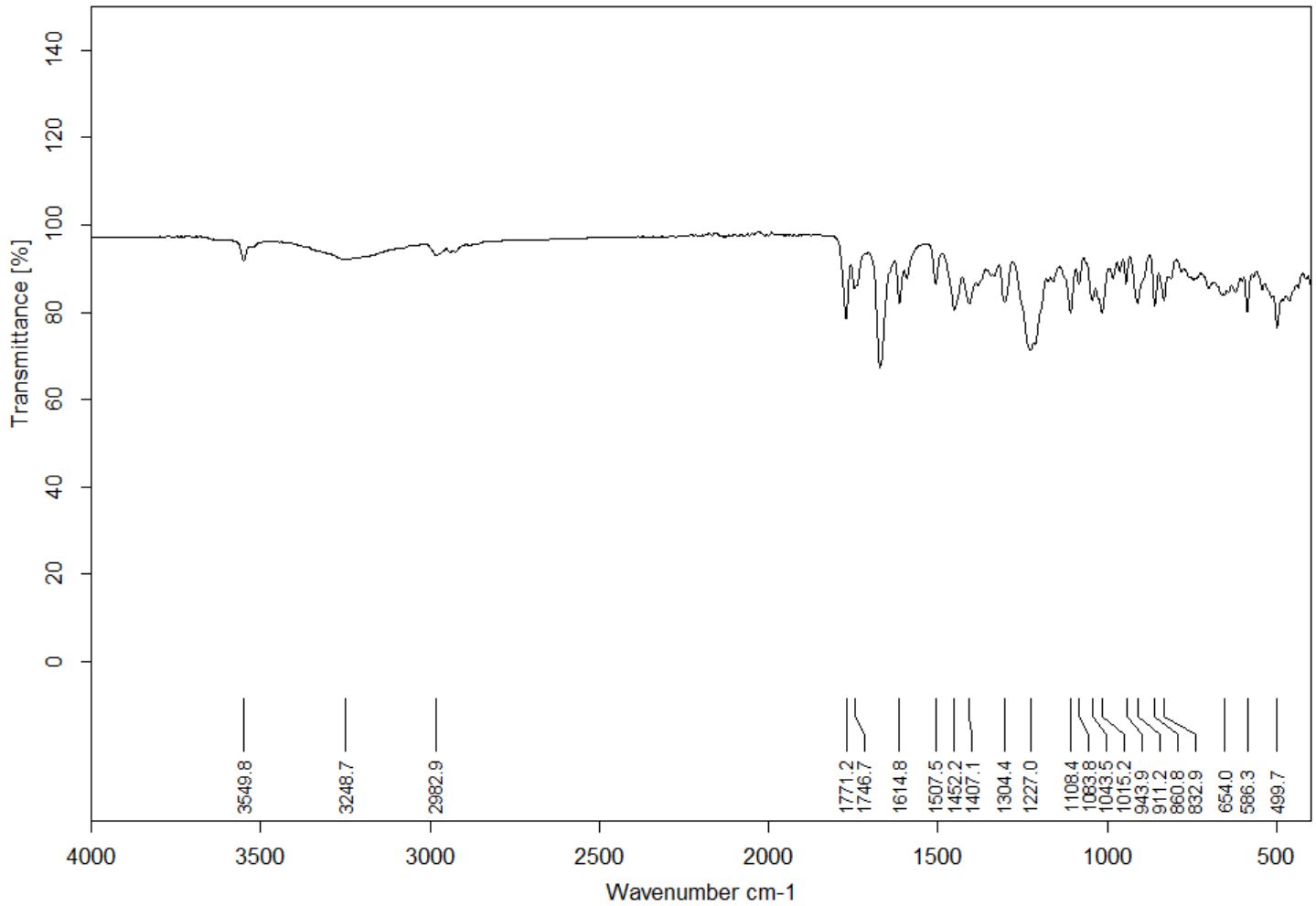


Figure D.81. FTIR spectrum (neat) of compound **6.71**

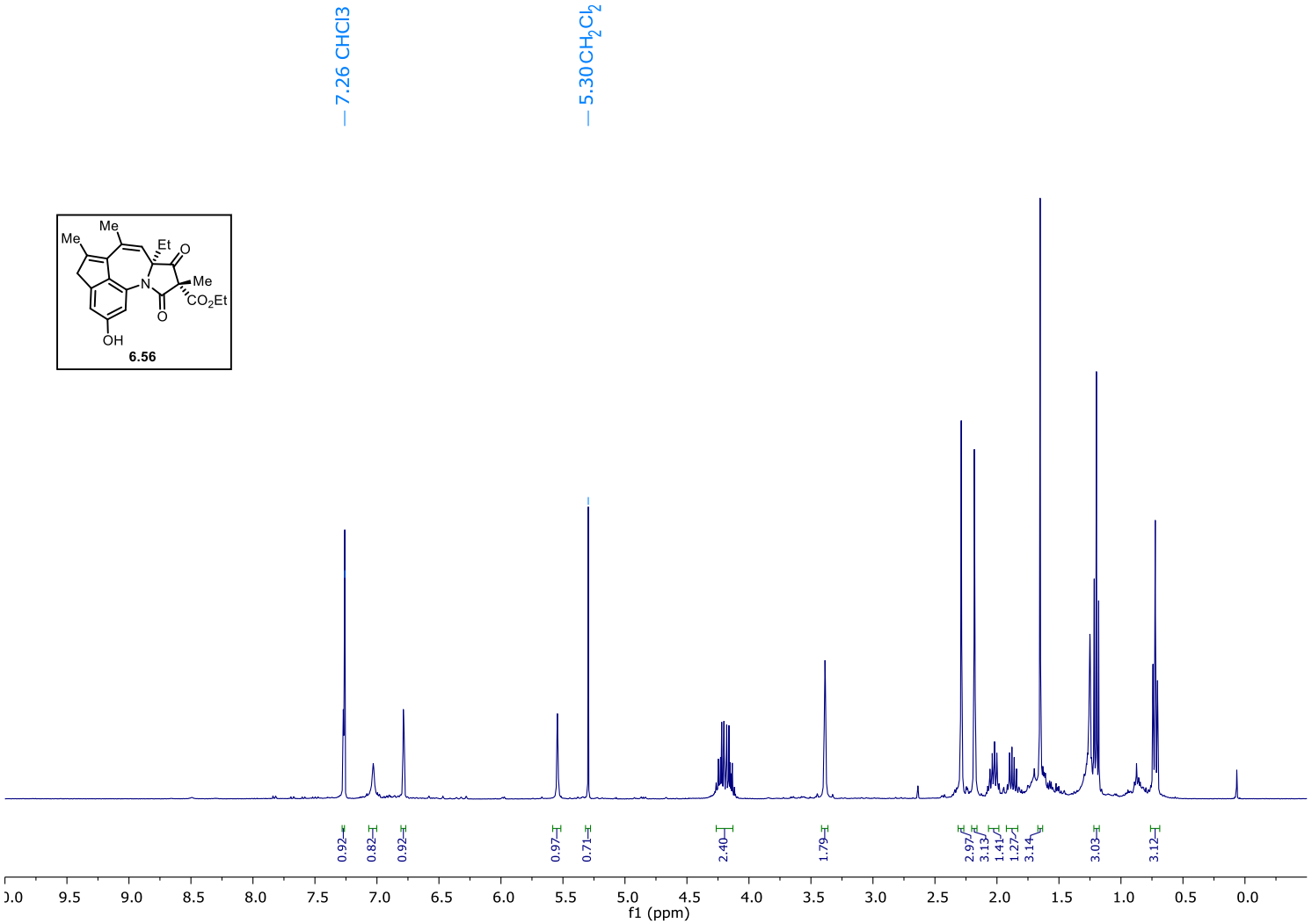


Figure D.82. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.56**

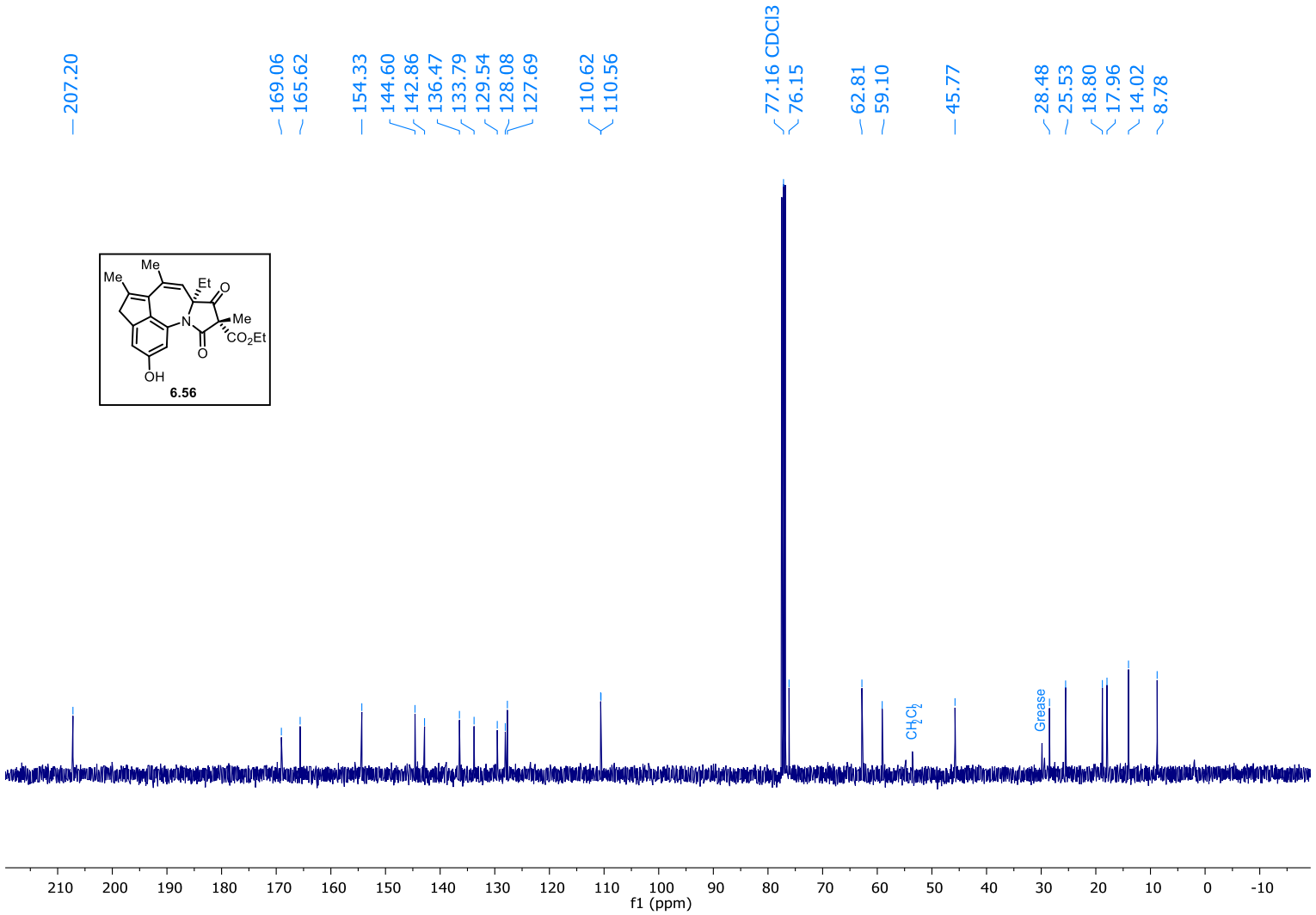


Figure D.83. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.56**

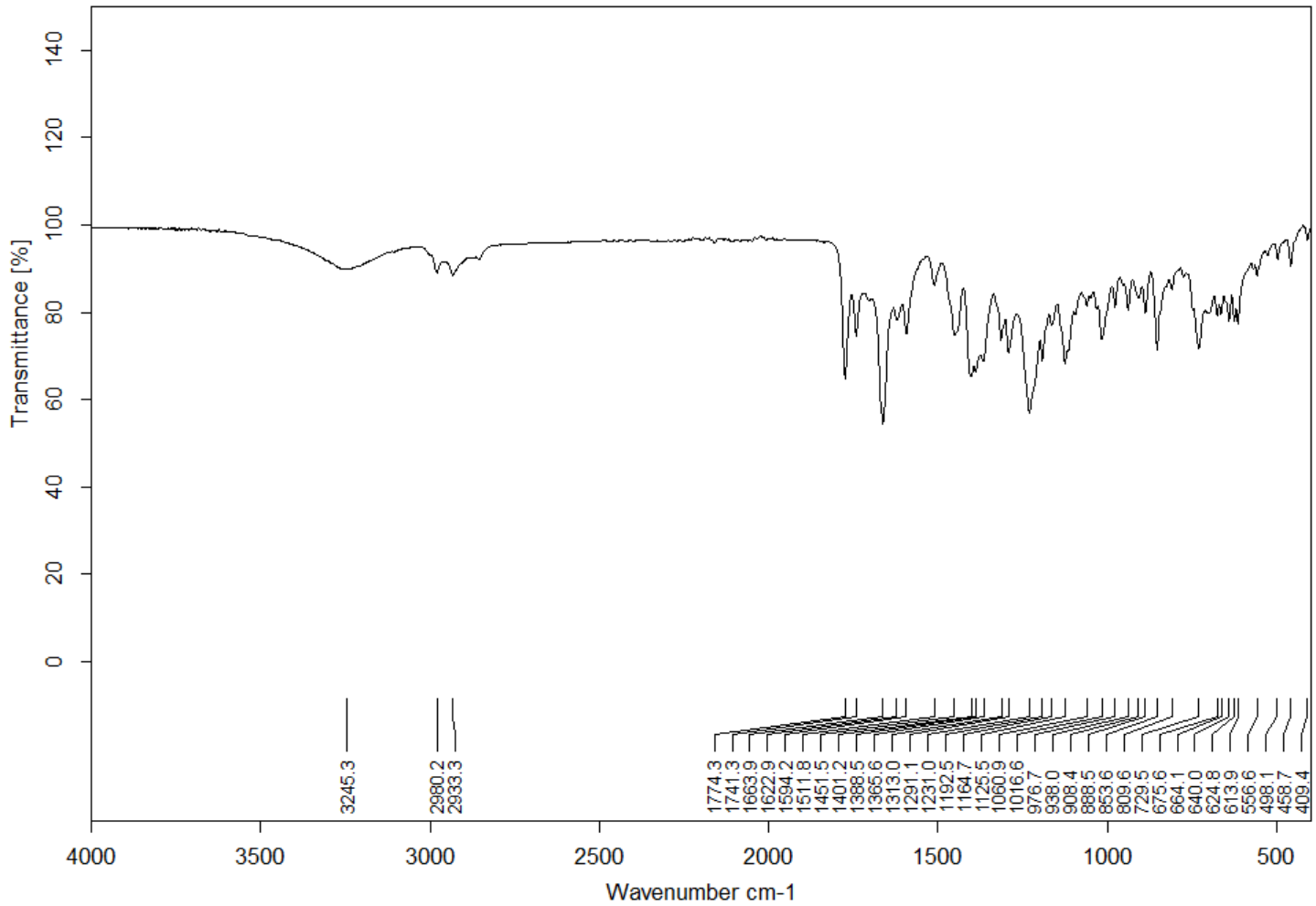


Figure D.84. FTIR spectrum (neat) of compound **6.56**

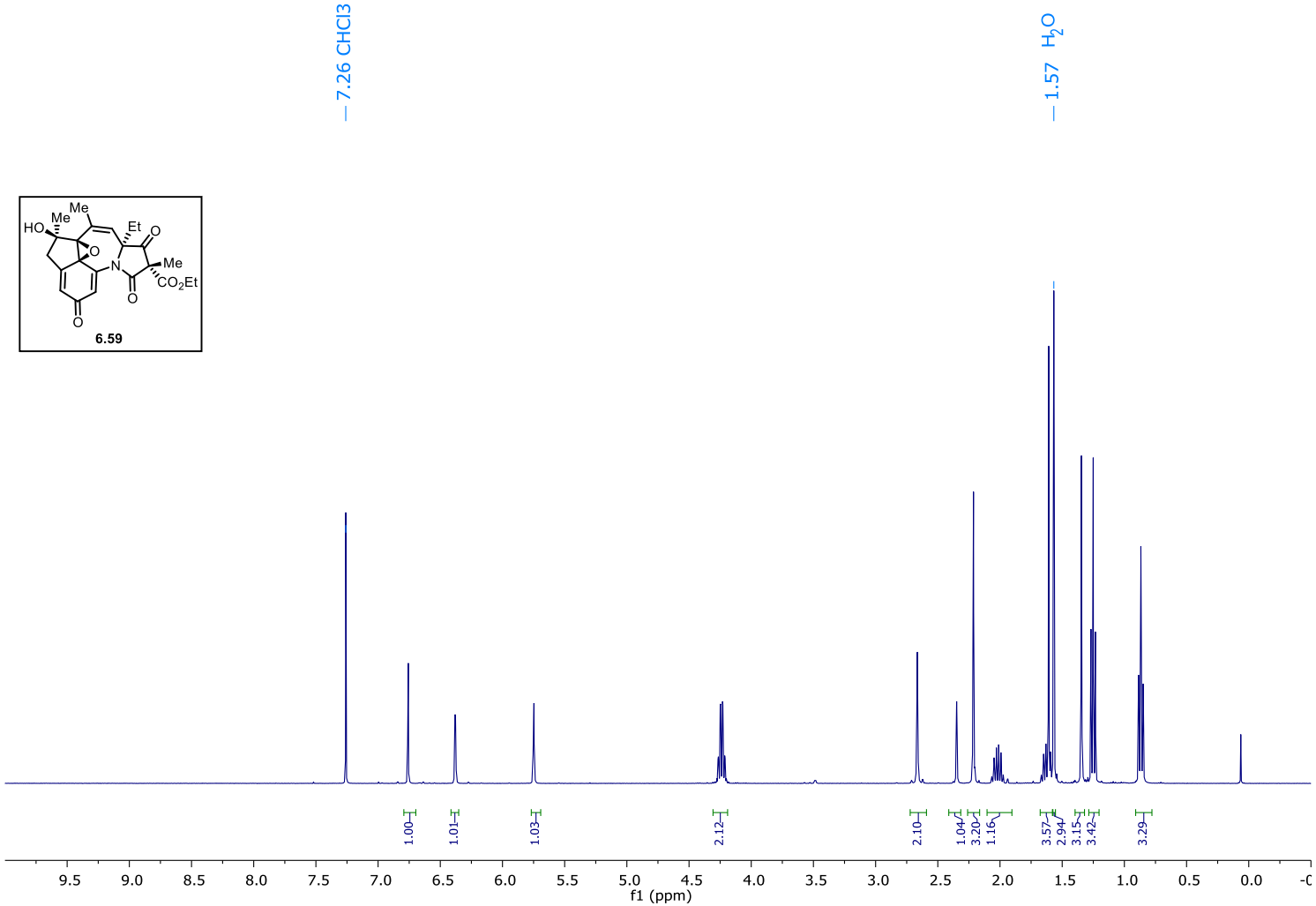


Figure D.85. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.59**

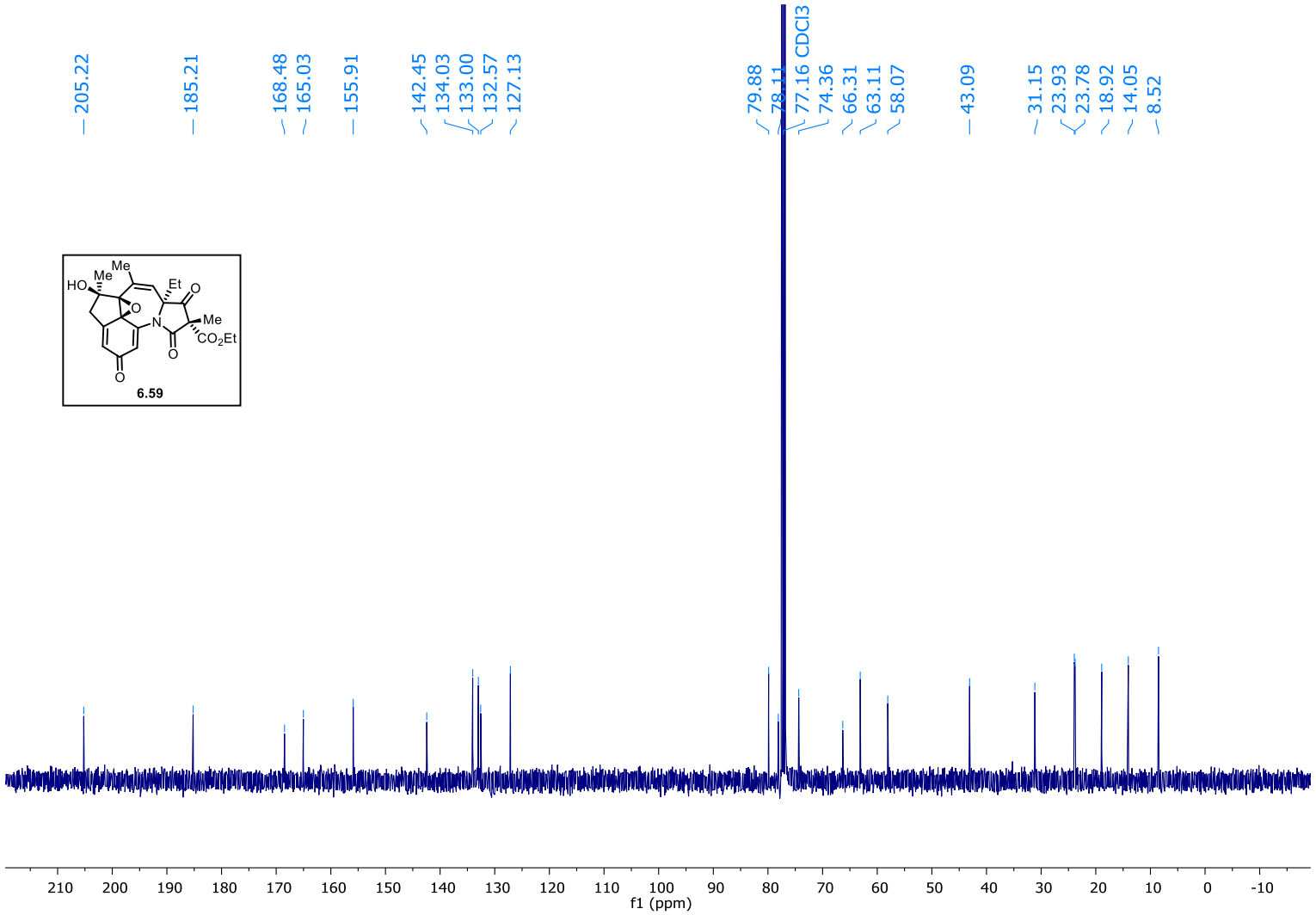


Figure D.86. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.59**

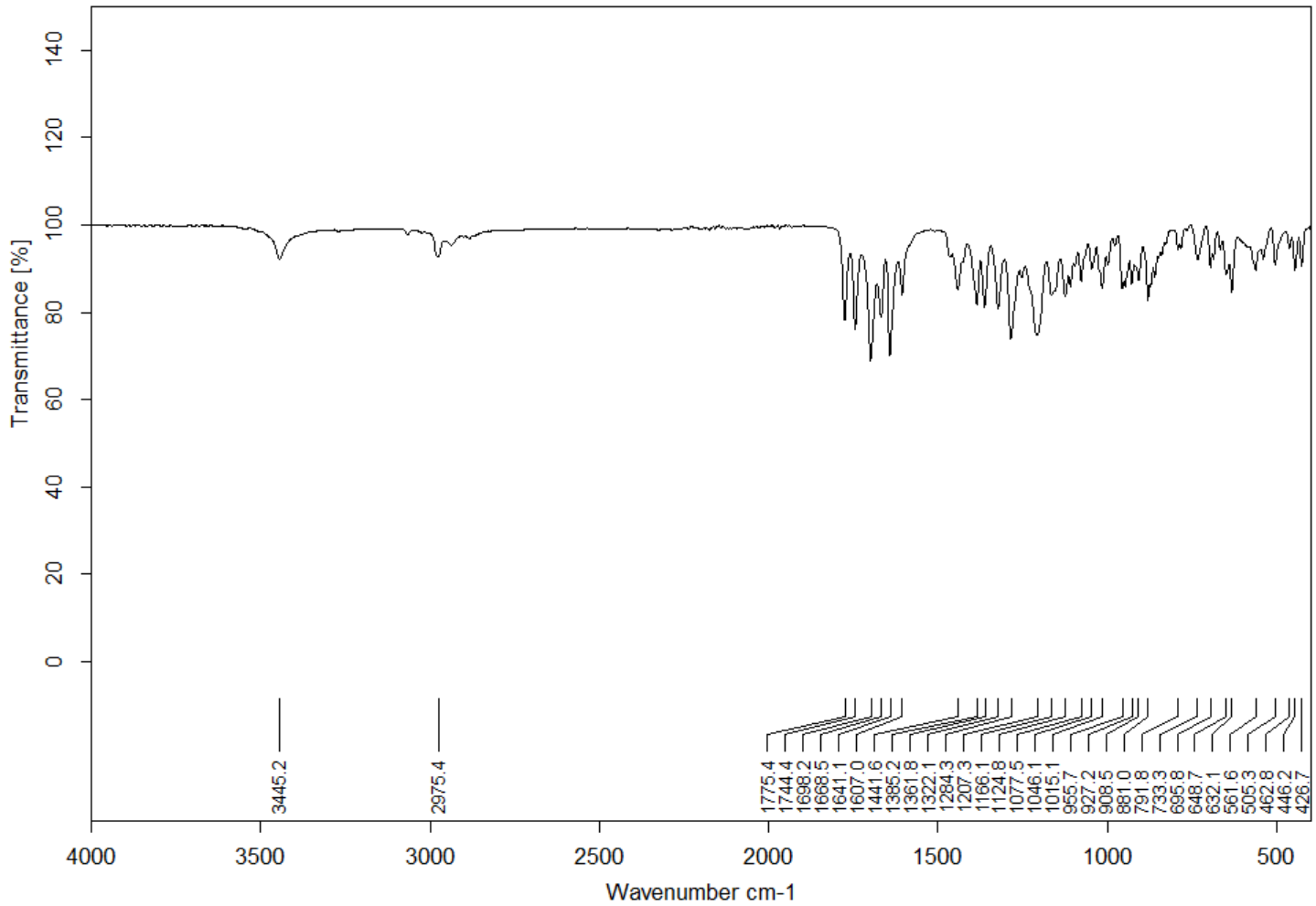


Figure D.87. FTIR spectrum (neat) of compound **6.59**

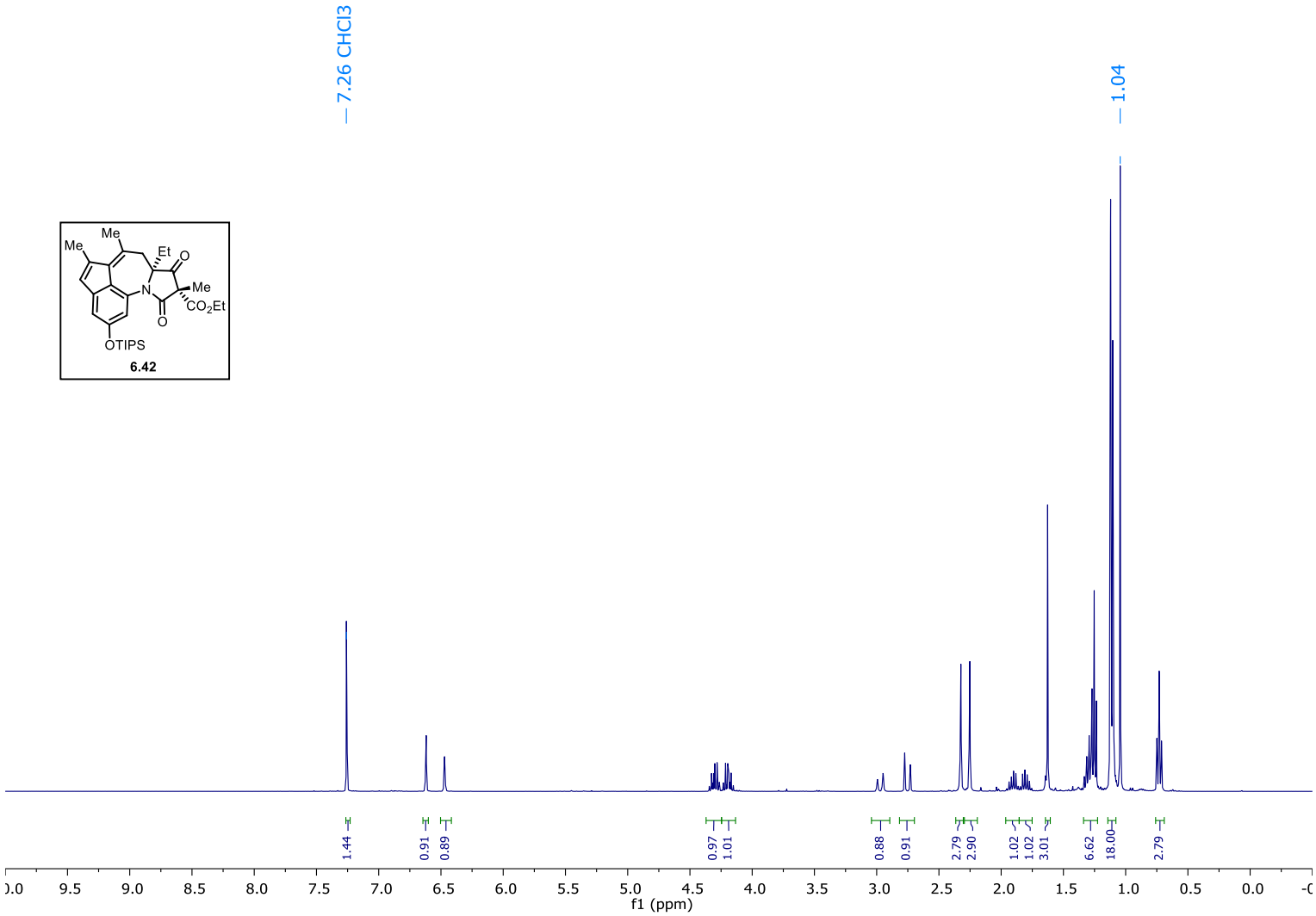


Figure D.88. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.42**

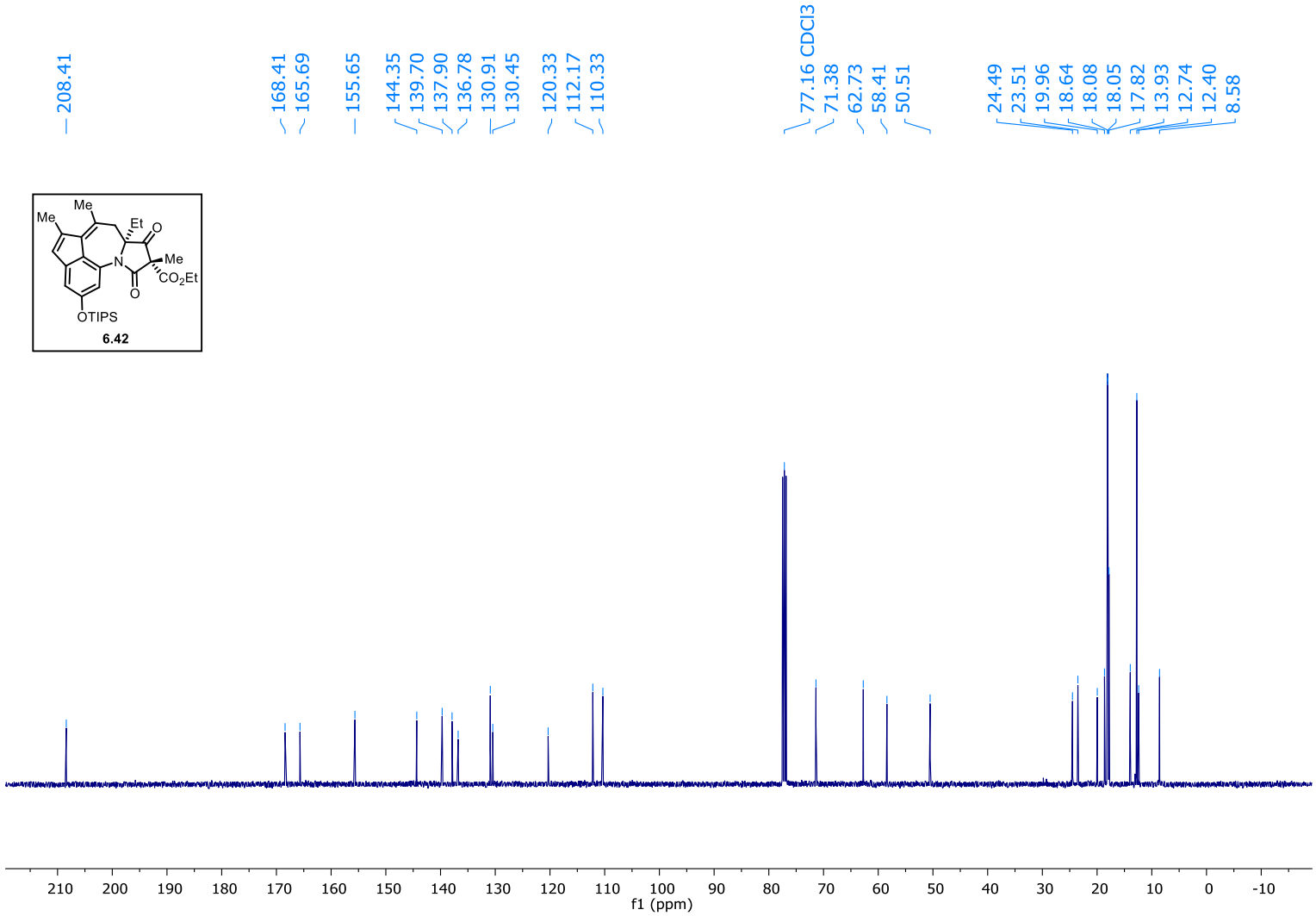


Figure D.89. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.42**

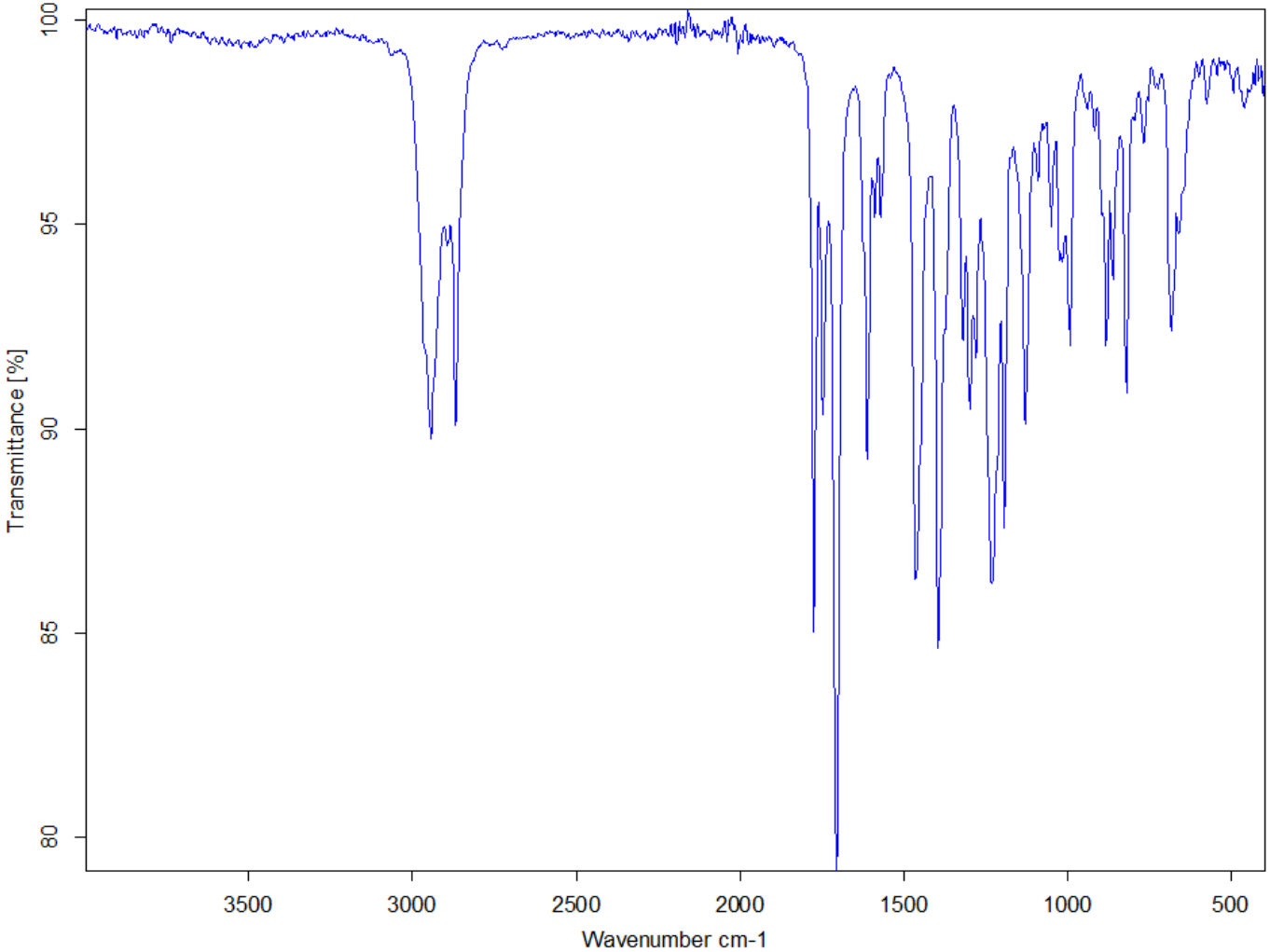


Figure D.90. FTIR spectrum (neat) of compound **6.42**

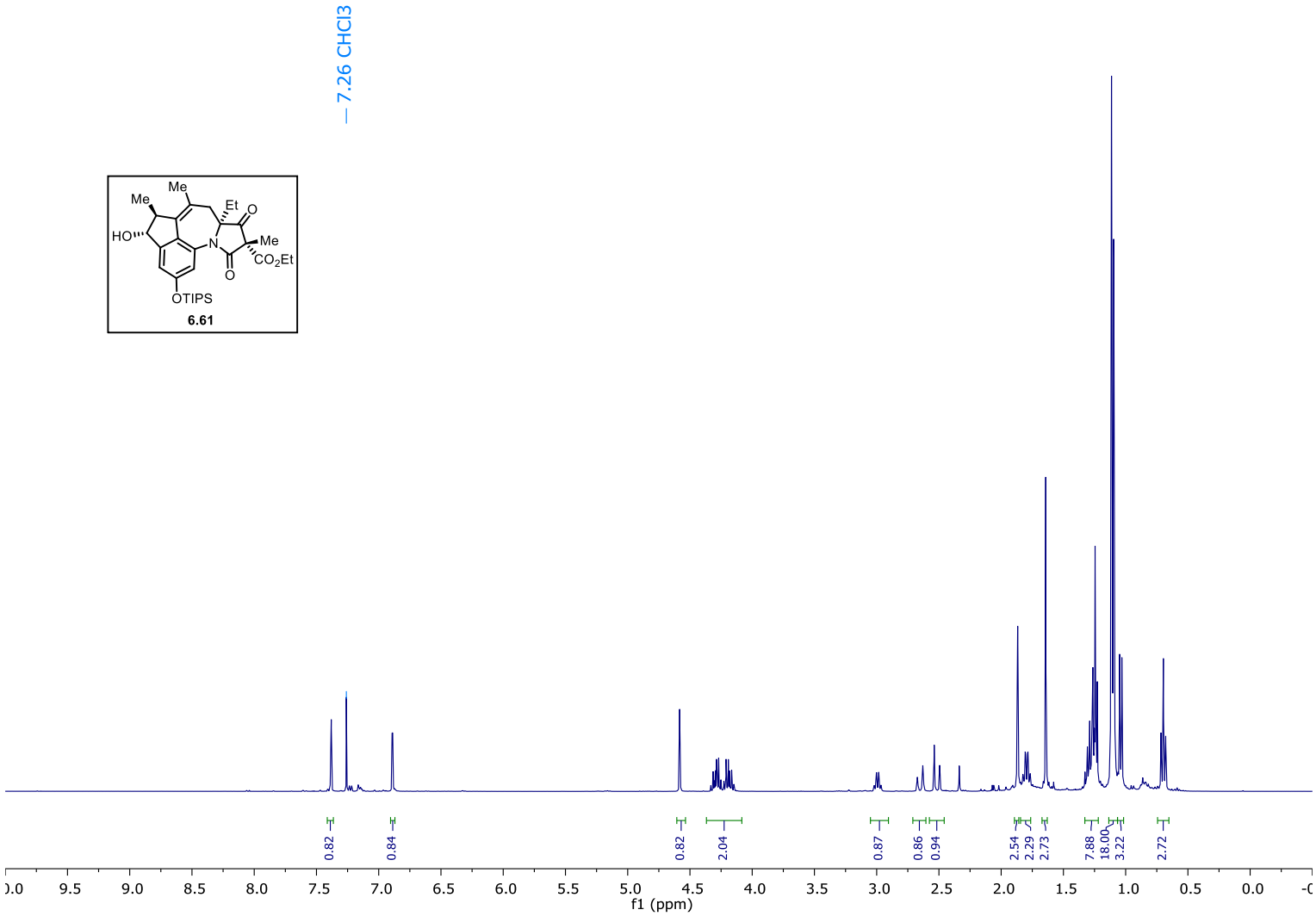


Figure D.91. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.61**

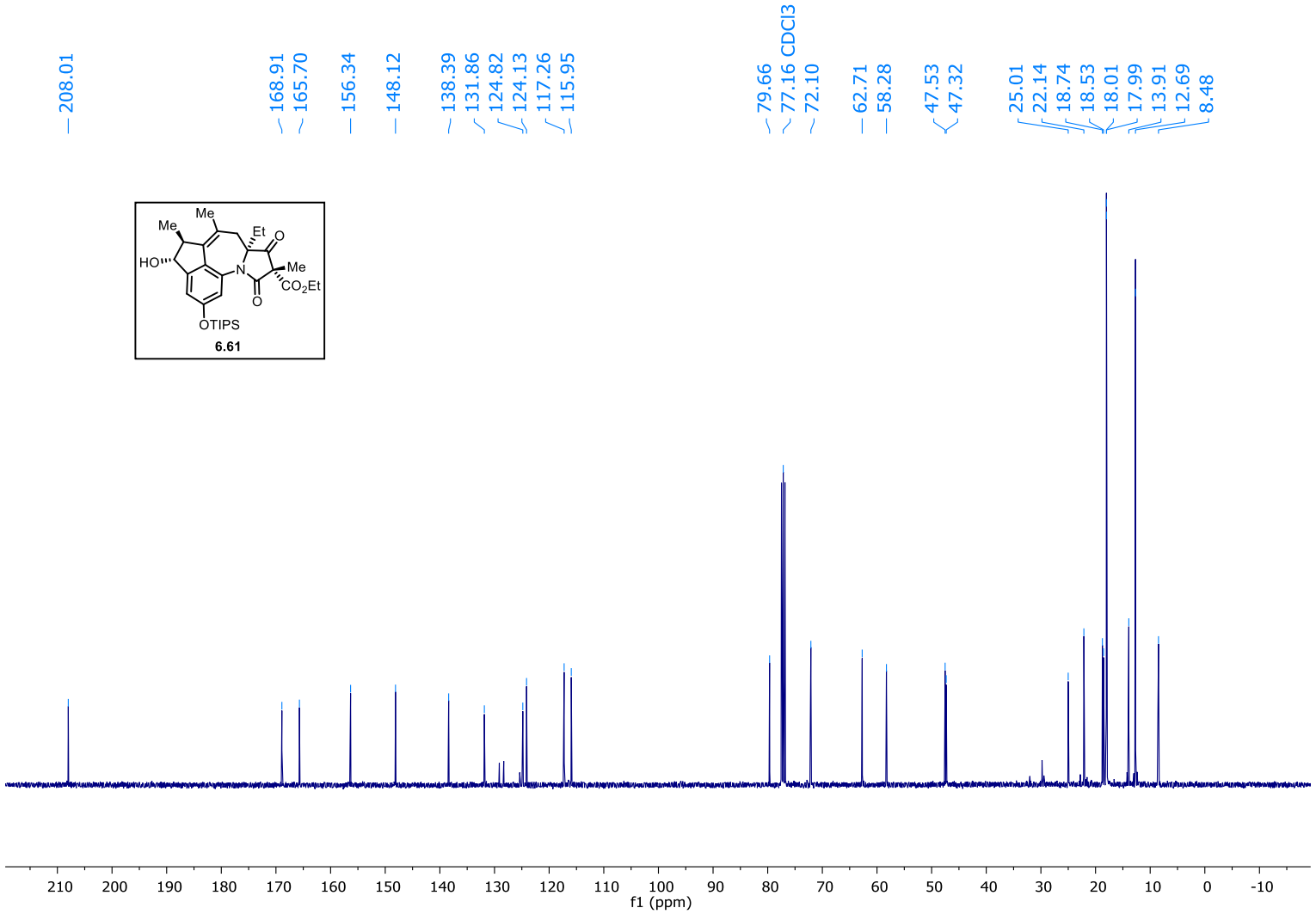


Figure D.92. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.61**

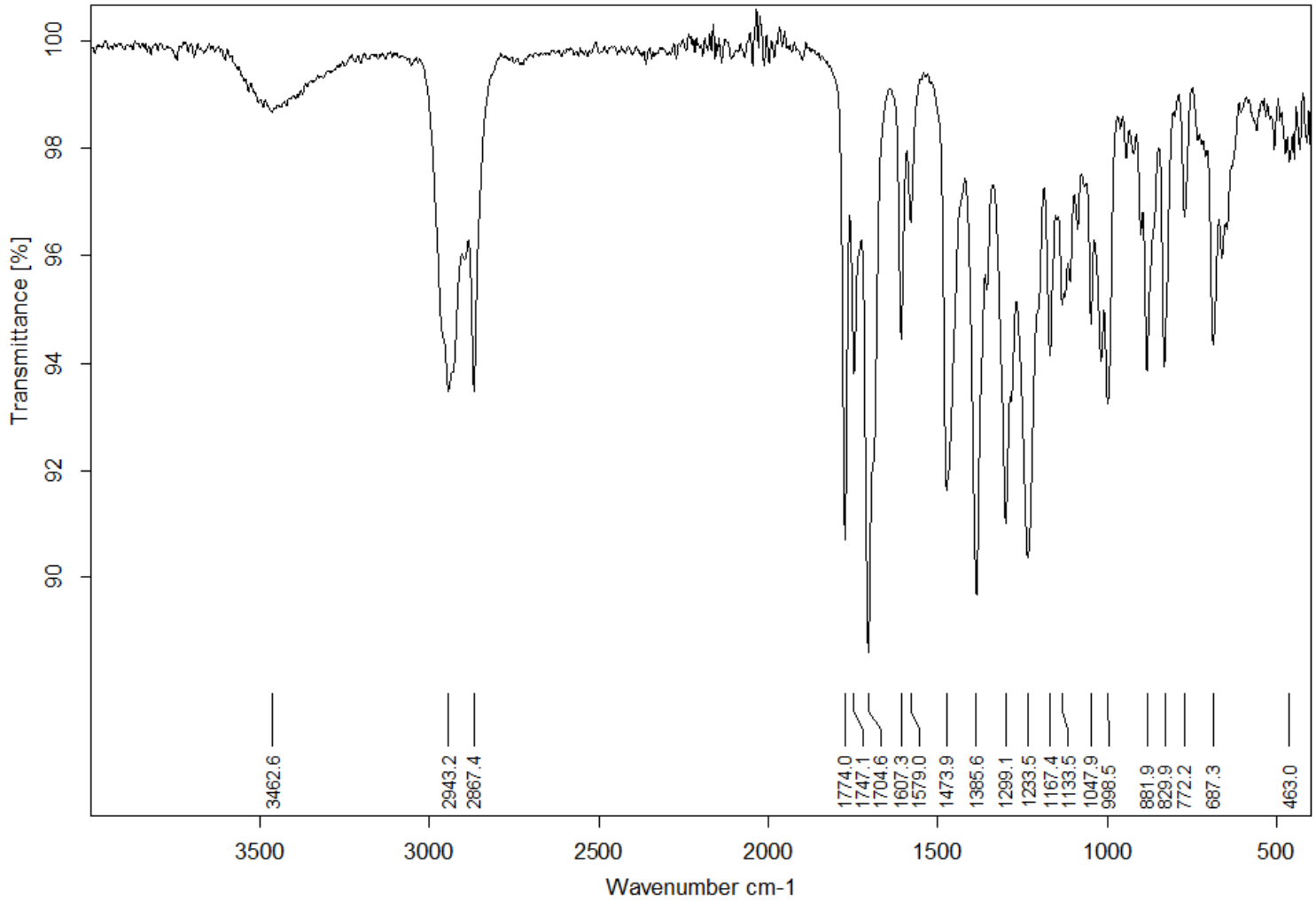


Figure D.93. FTIR spectrum (neat) of compound **6.61**

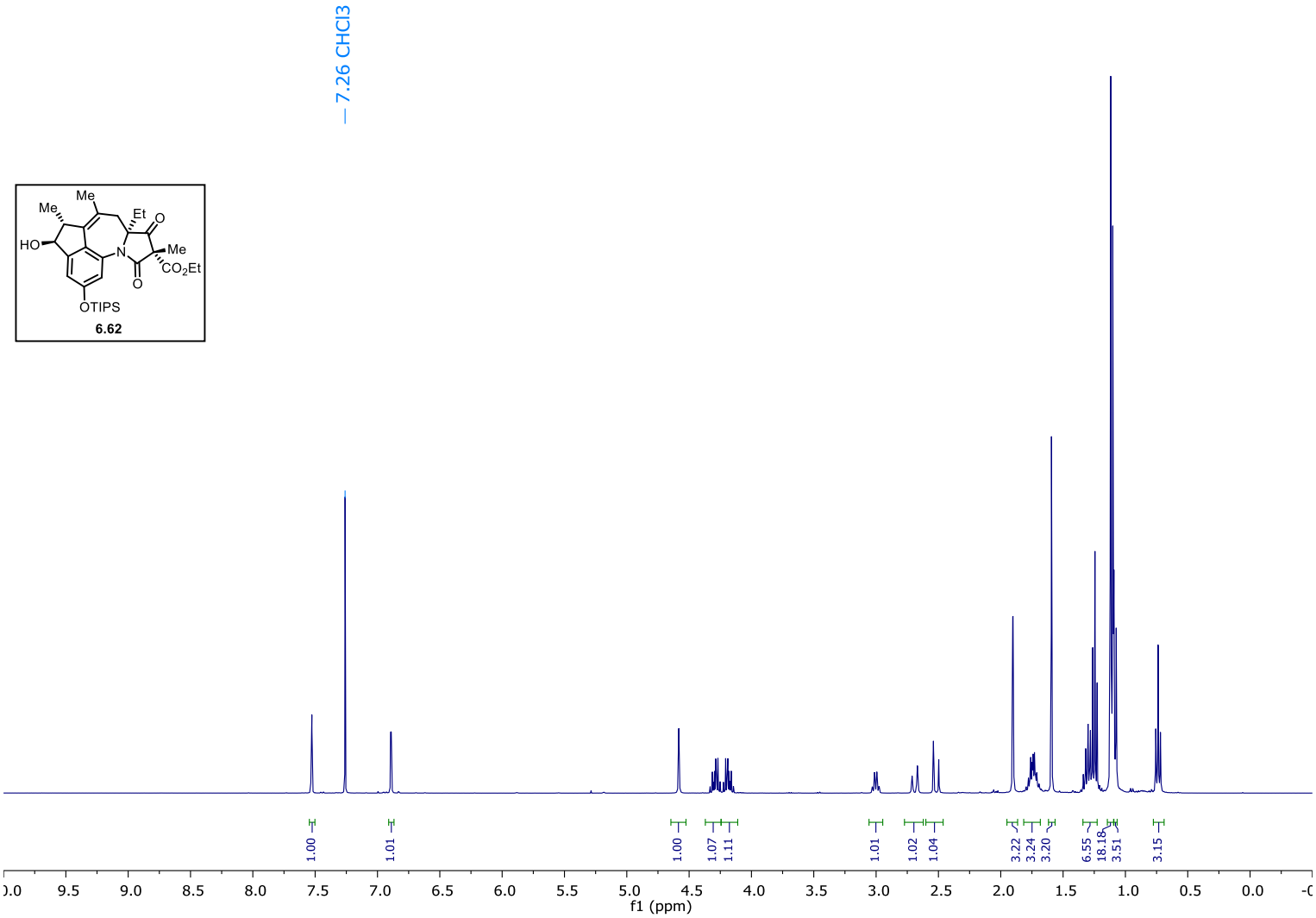


Figure D.94. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.62**

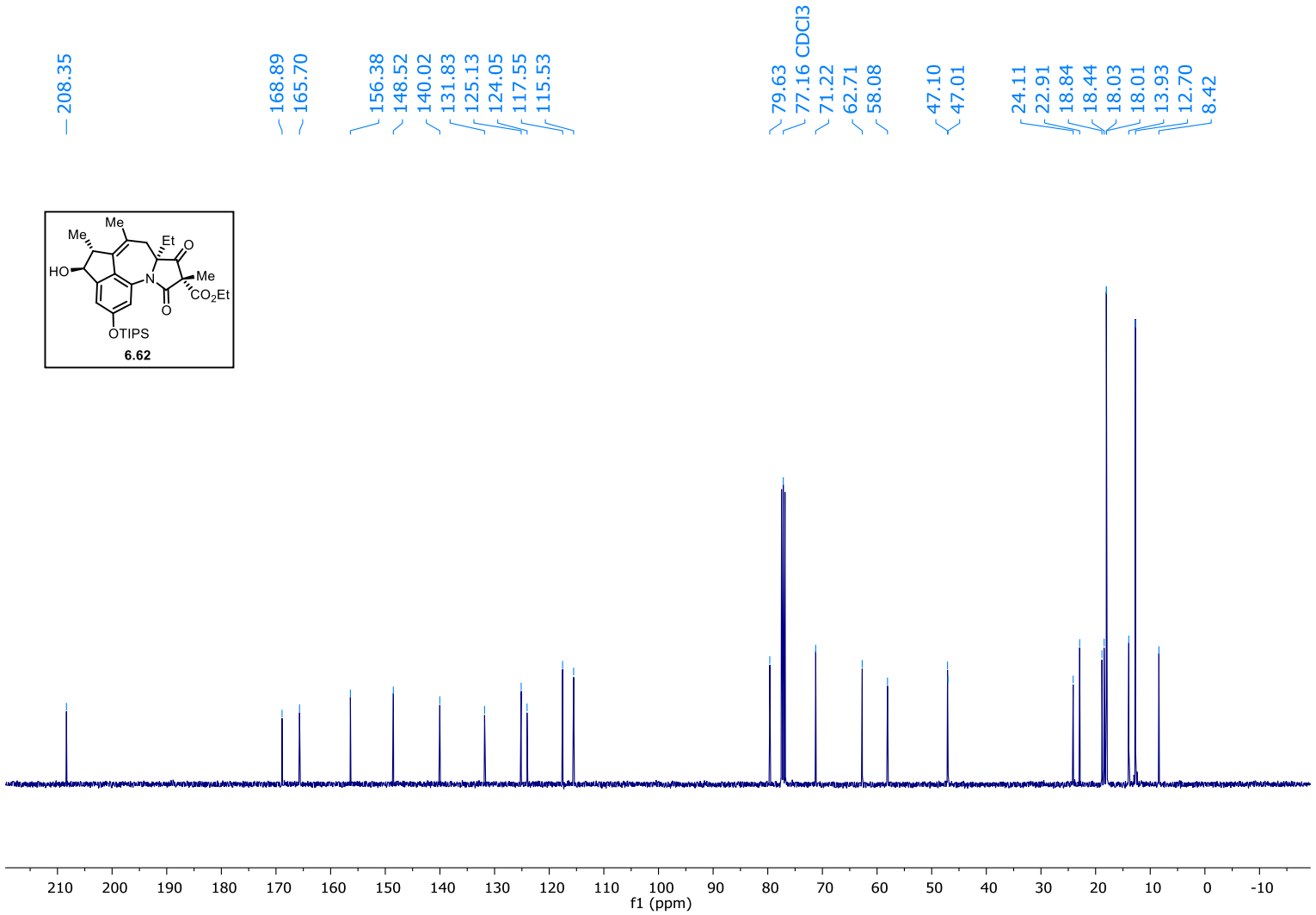


Figure D.95. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.62**

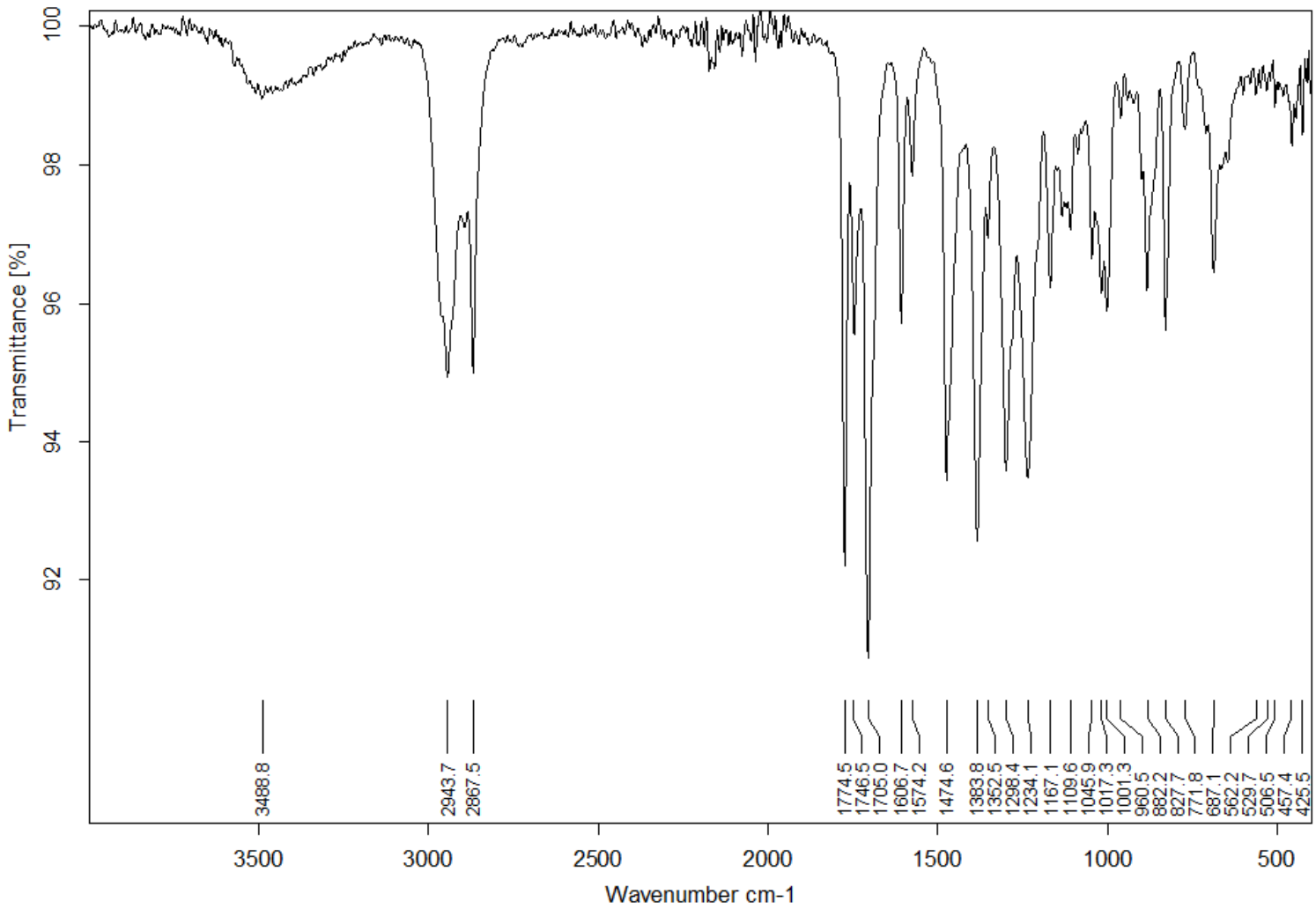


Figure D.96. FTIR spectrum (neat) of compound **6.62**

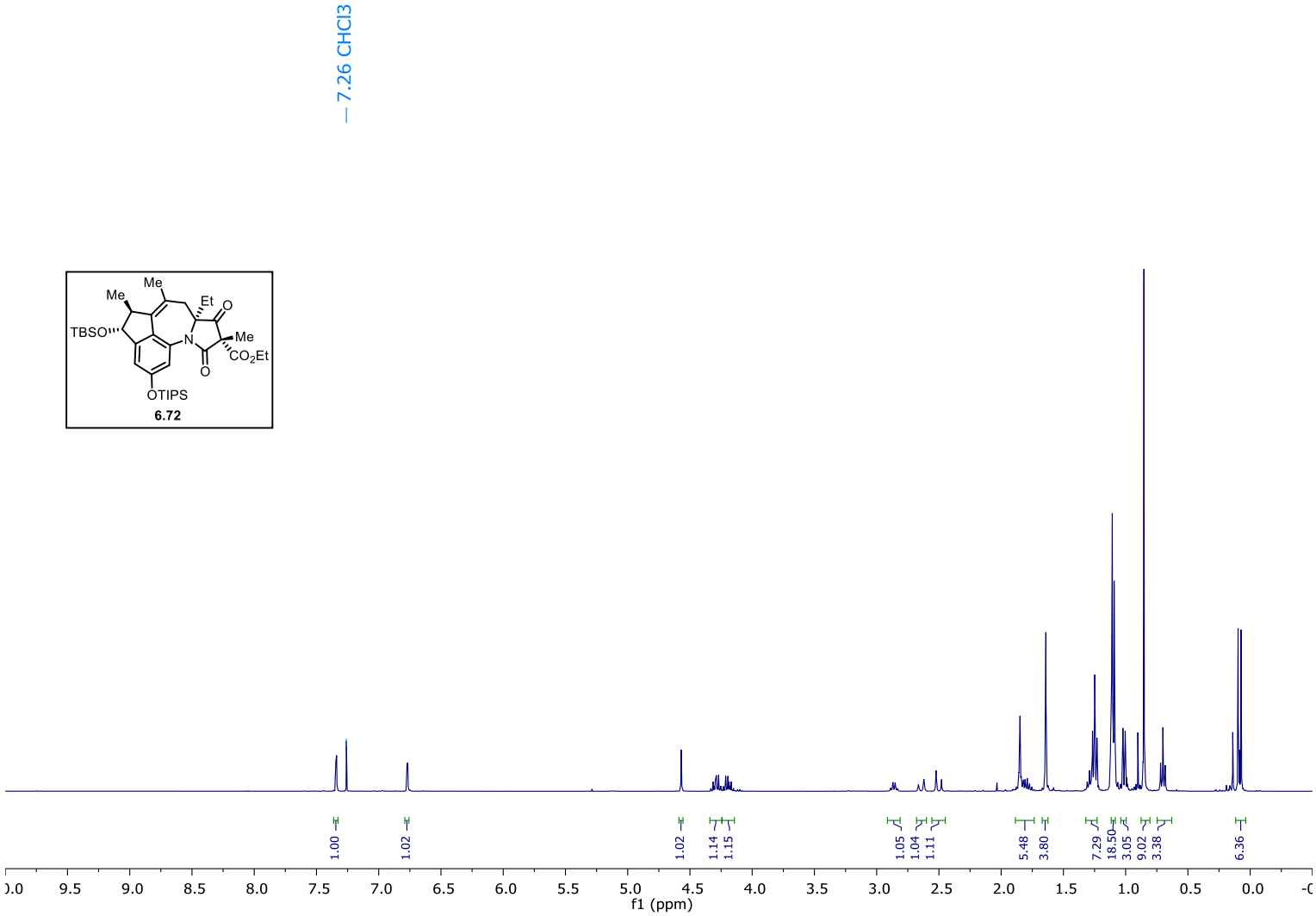


Figure D.97. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.72**

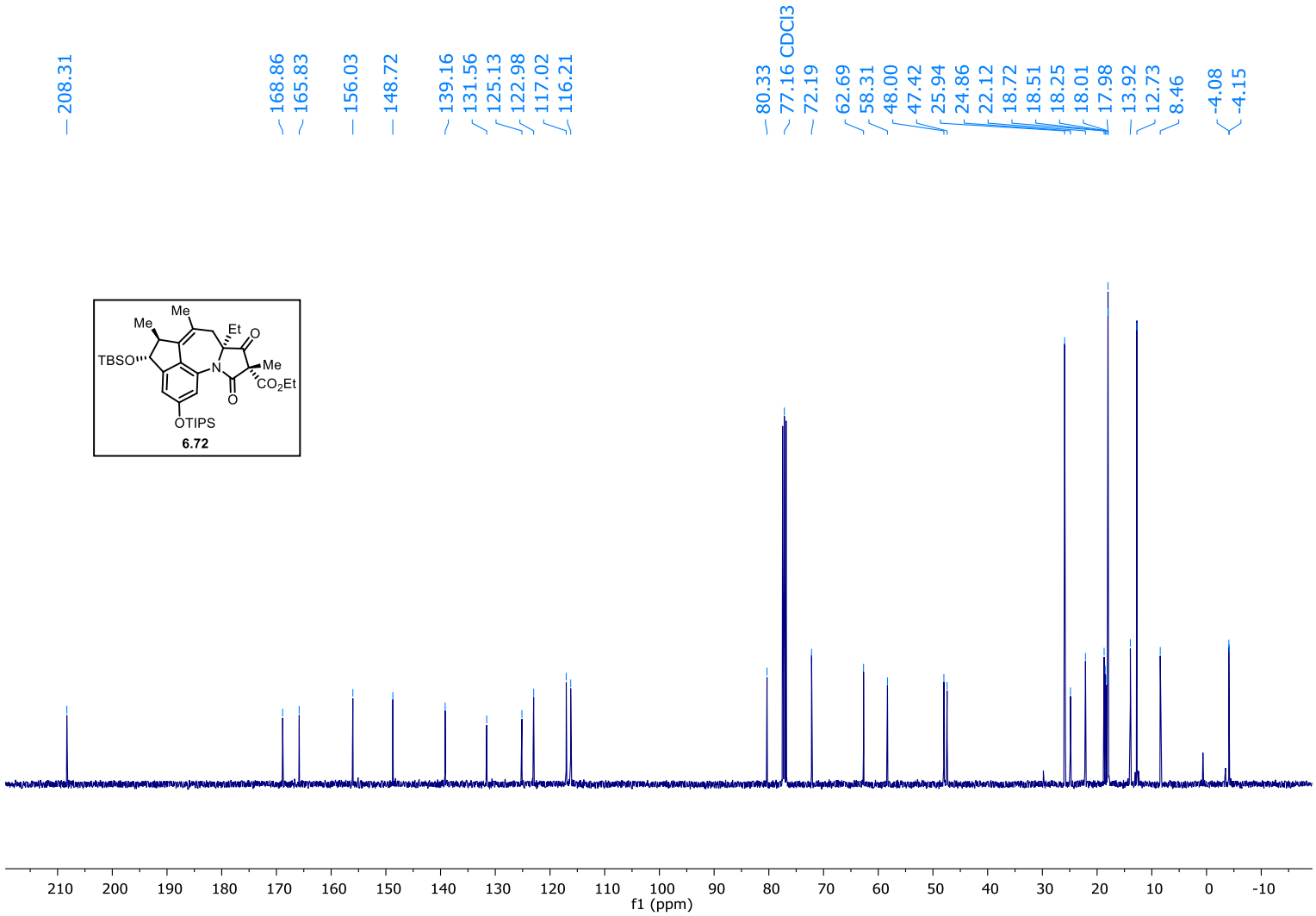


Figure D.98. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.72**

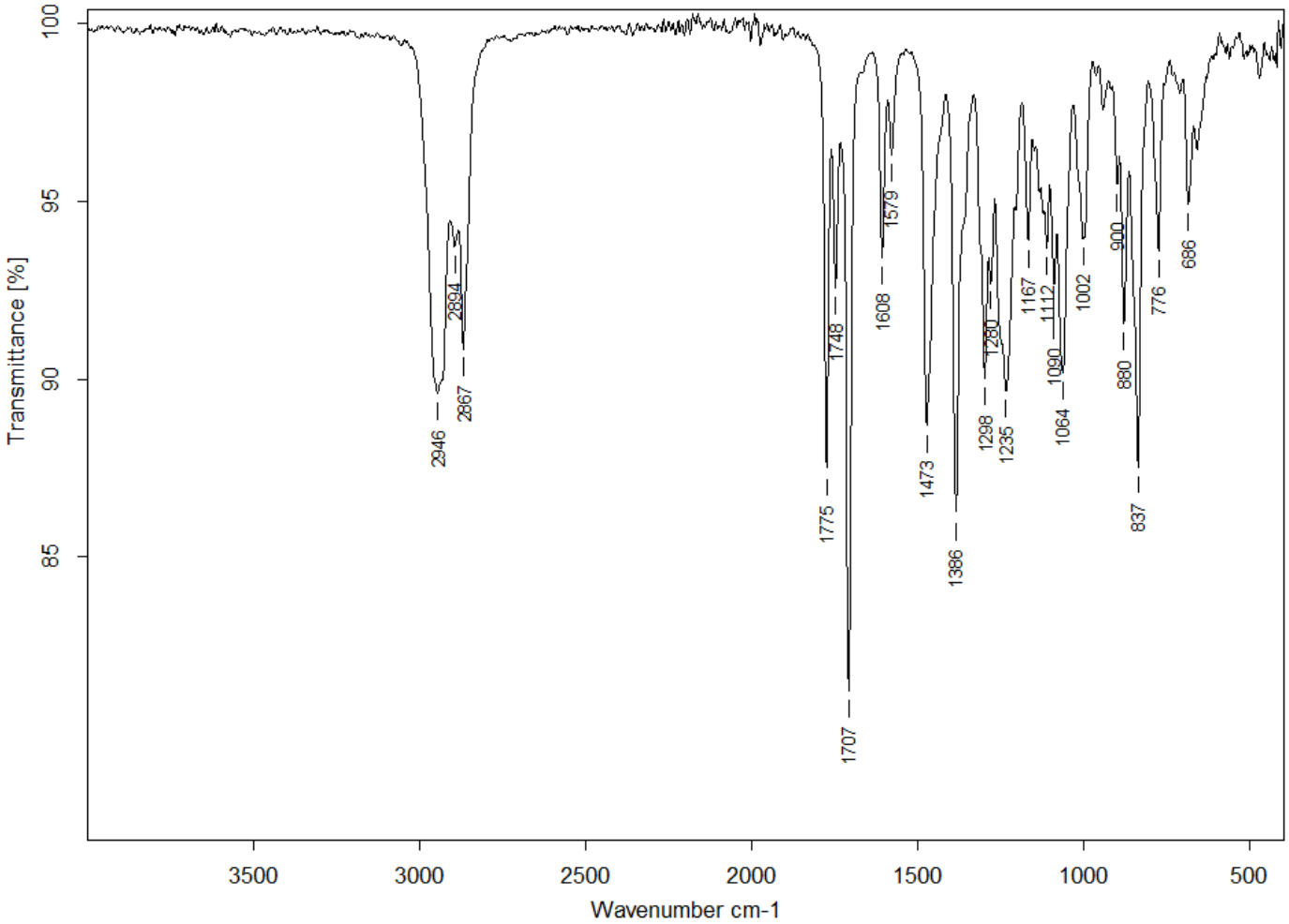


Figure D.99. FTIR spectrum (neat) of compound **6.72**

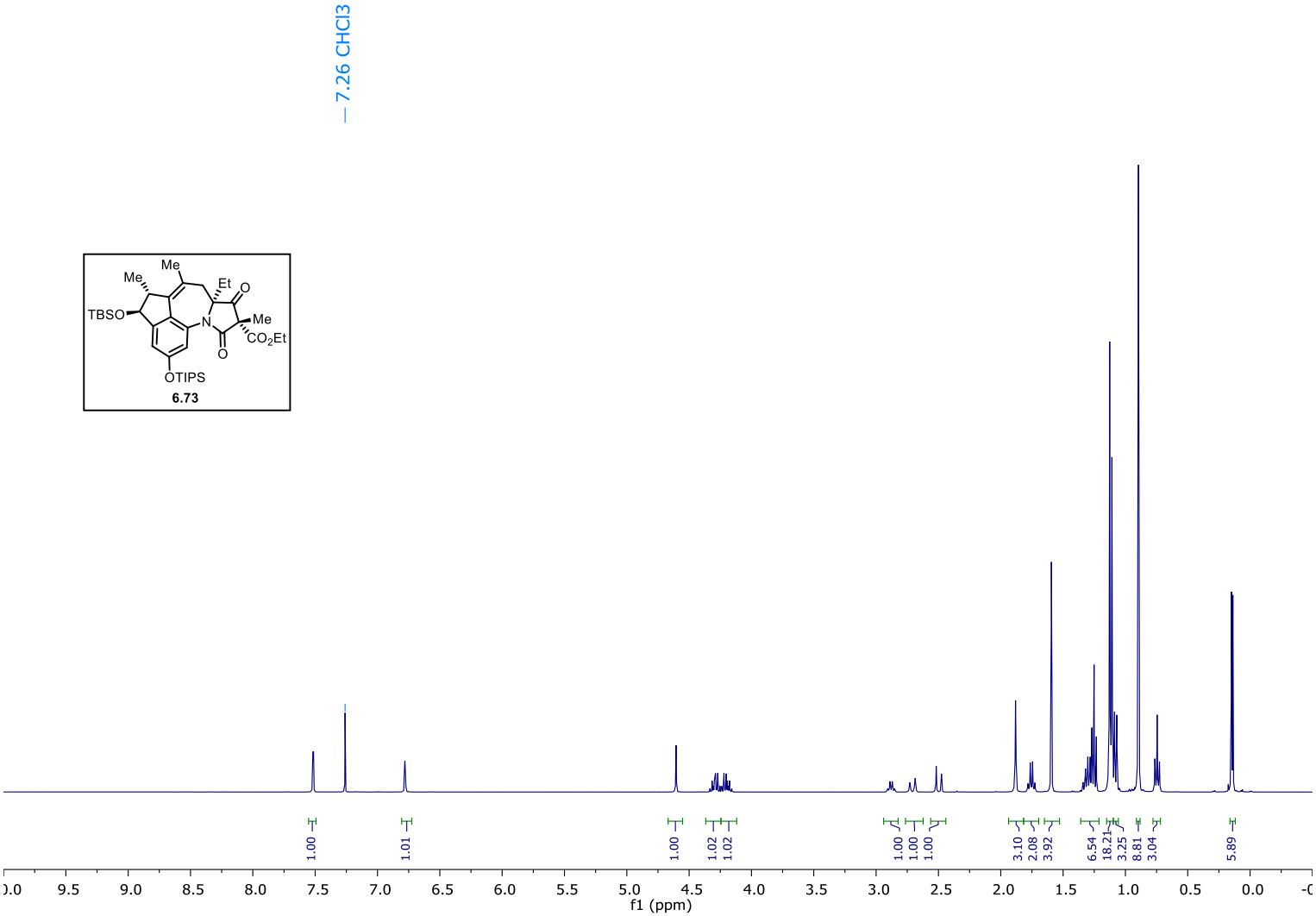


Figure D.100. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.73**

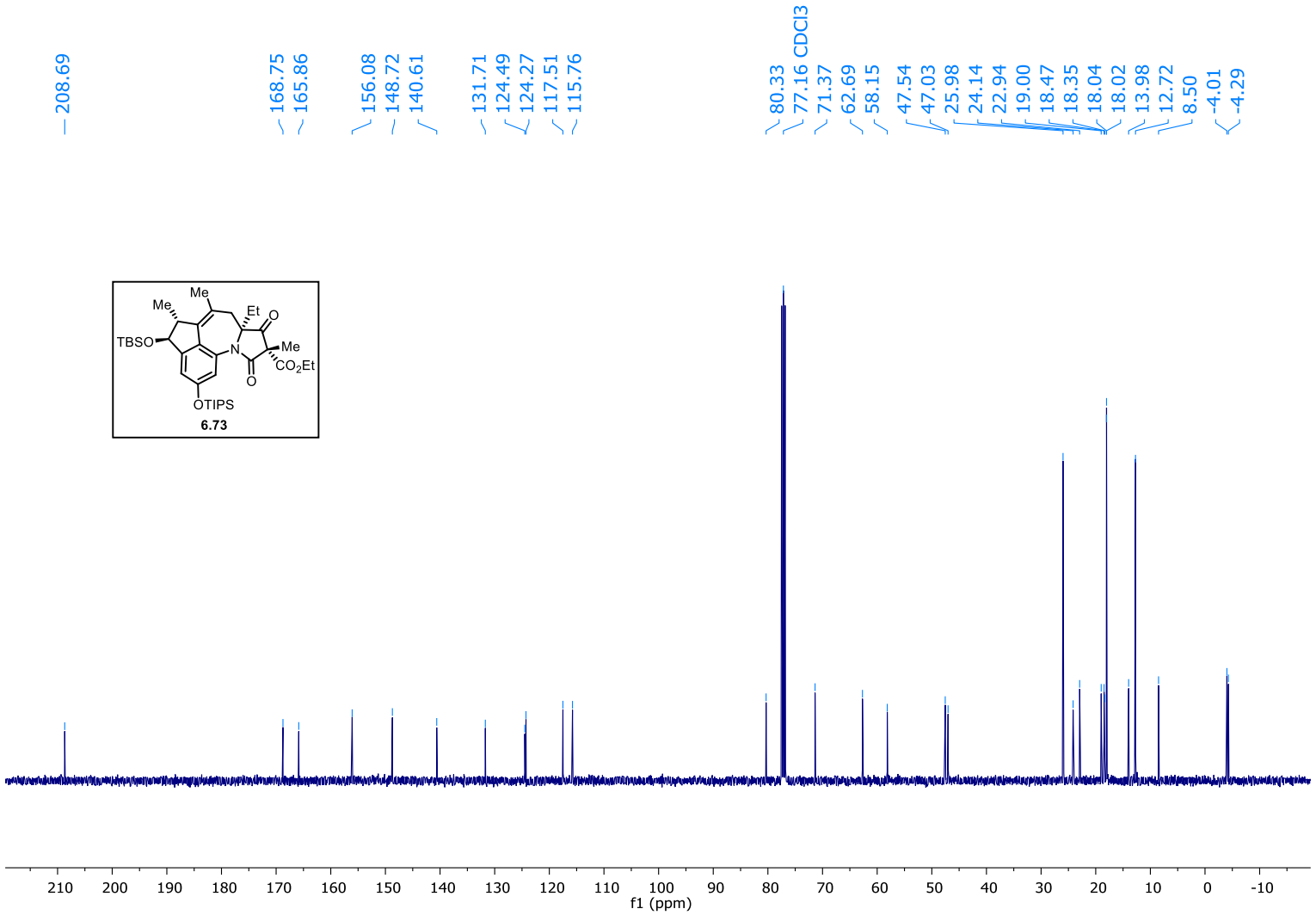


Figure D.101. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.73**

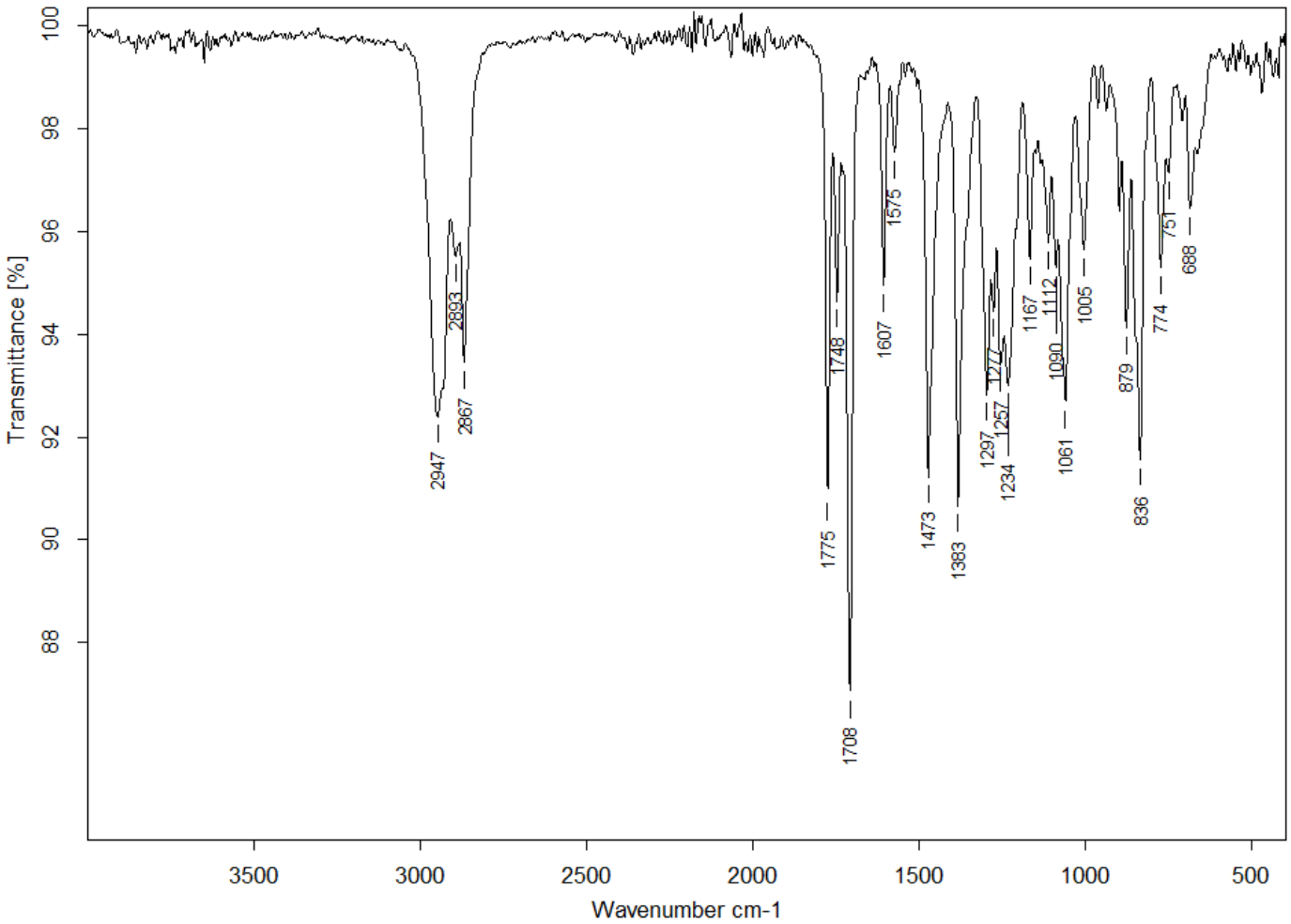


Figure D.102. FTIR spectrum (neat) of compound **6.73**

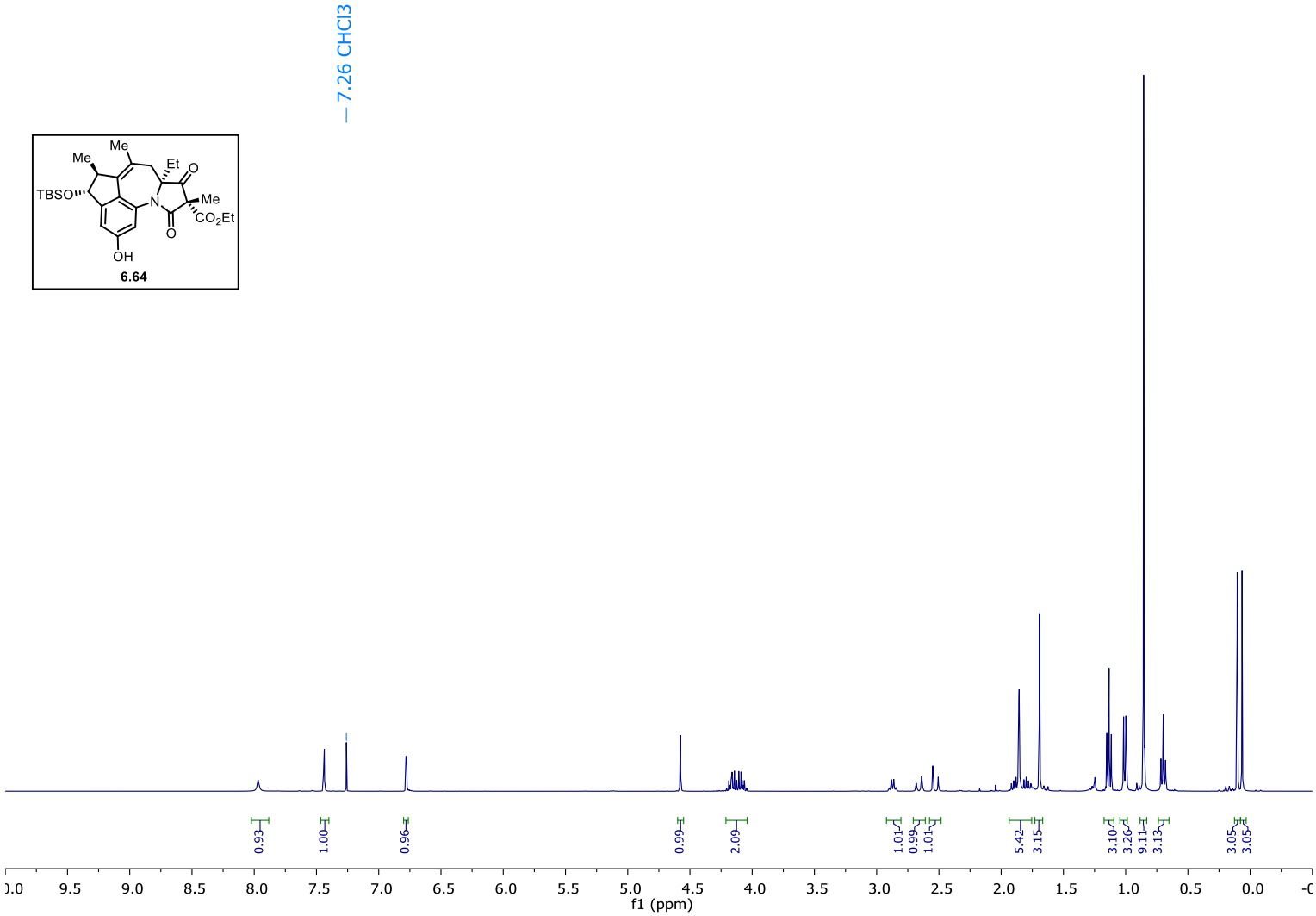


Figure D.103. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.64**

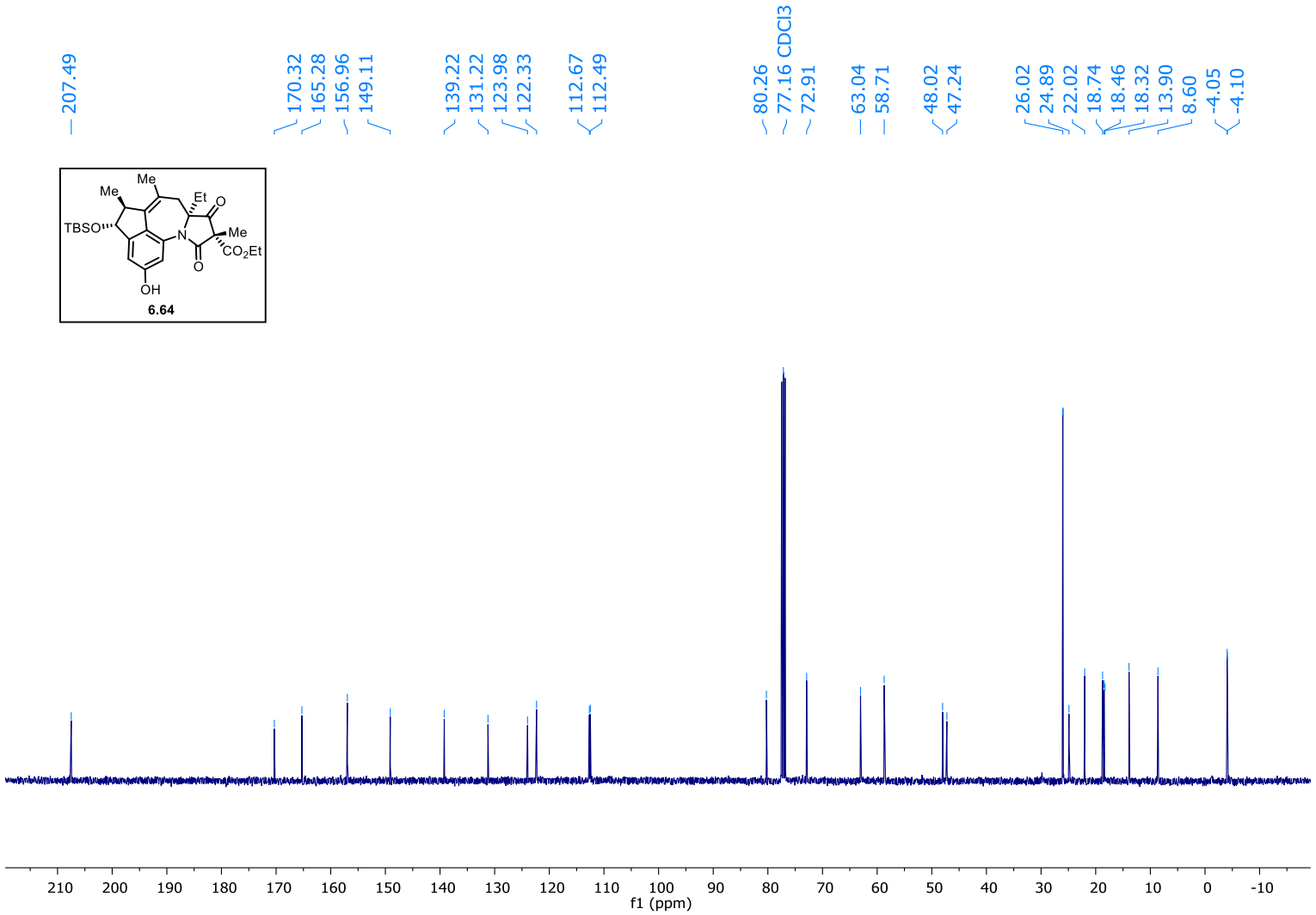


Figure D.104. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.64**

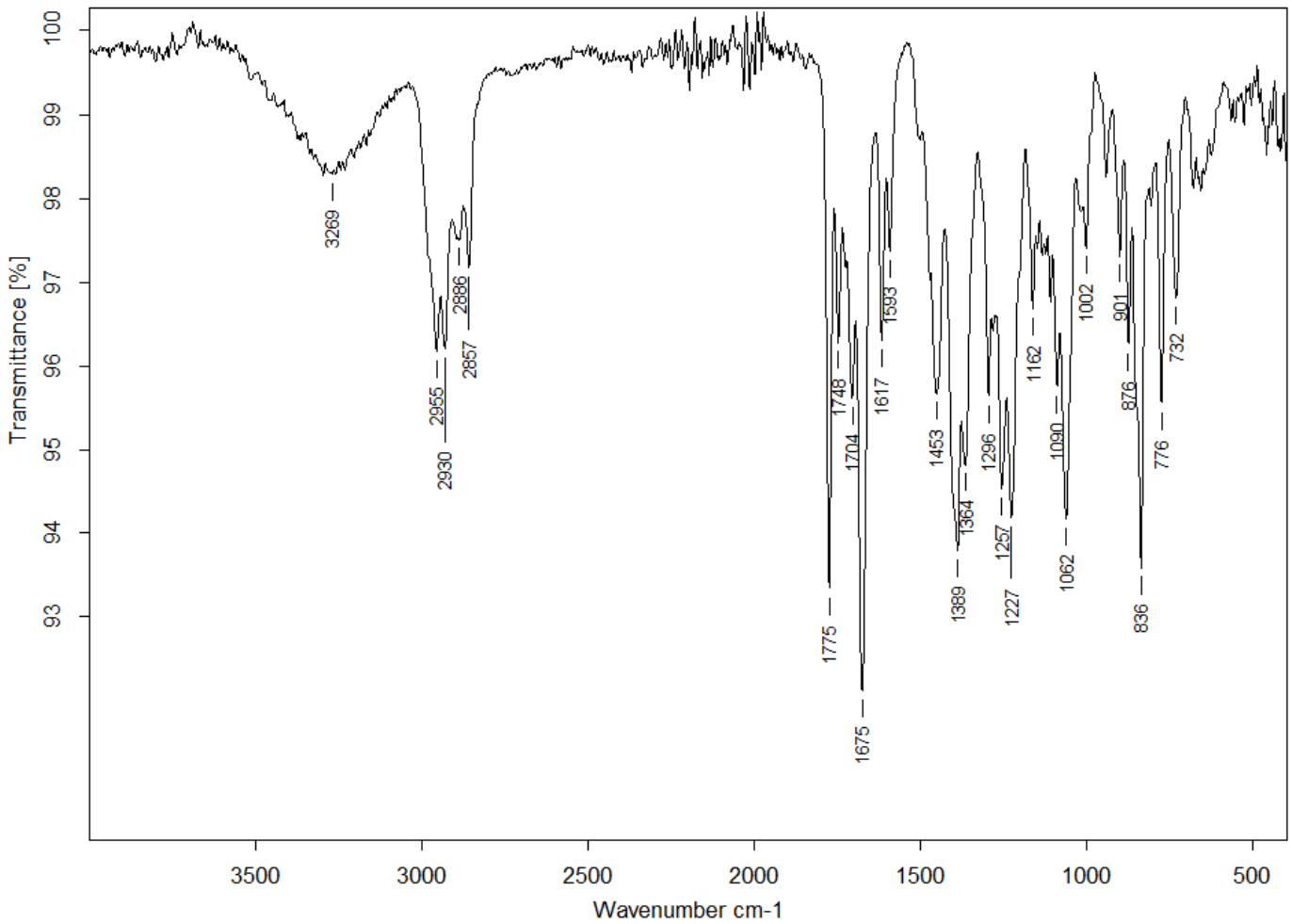


Figure D.105. FTIR spectrum (neat) of compound **6.64**

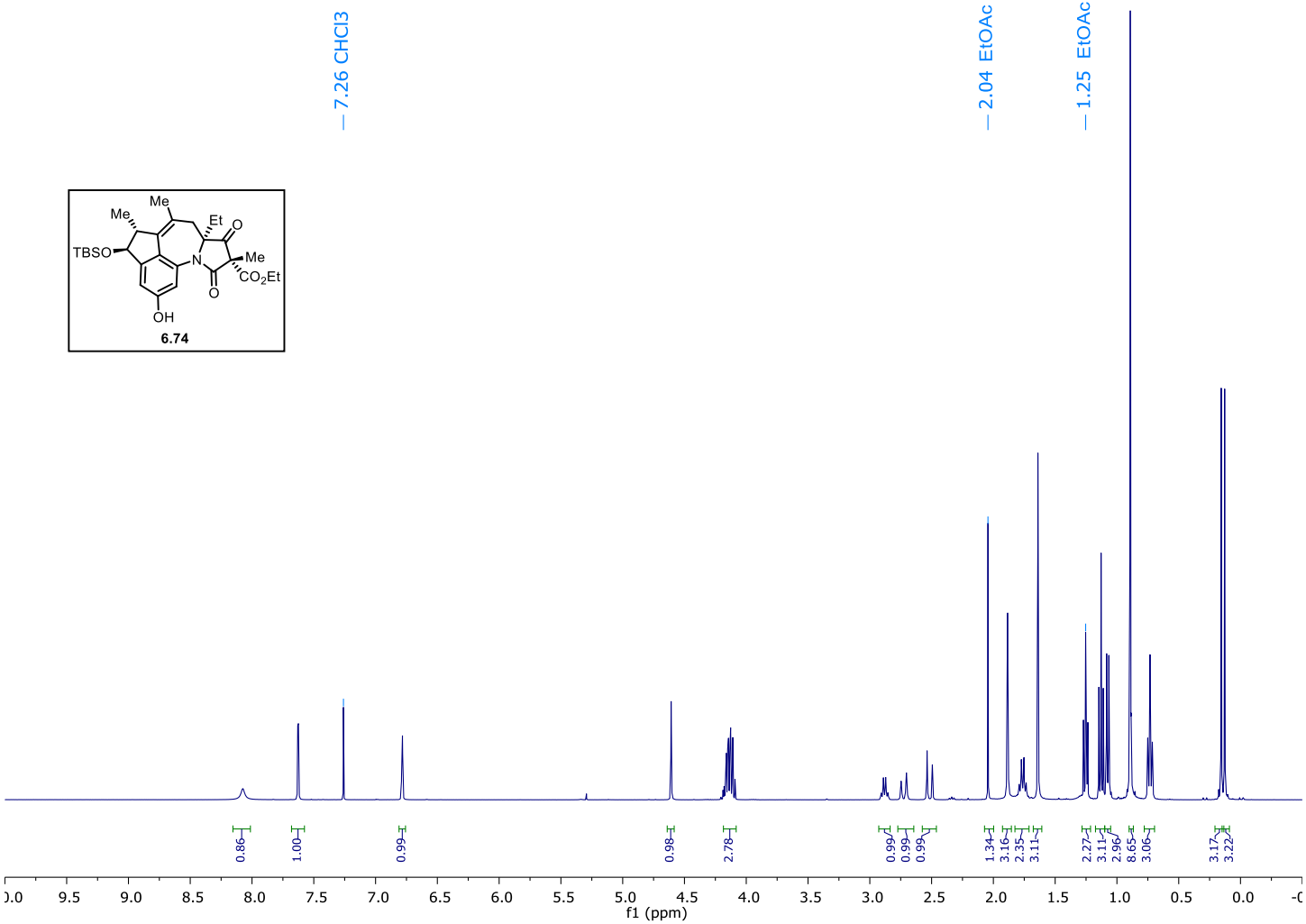


Figure D.106. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.74**

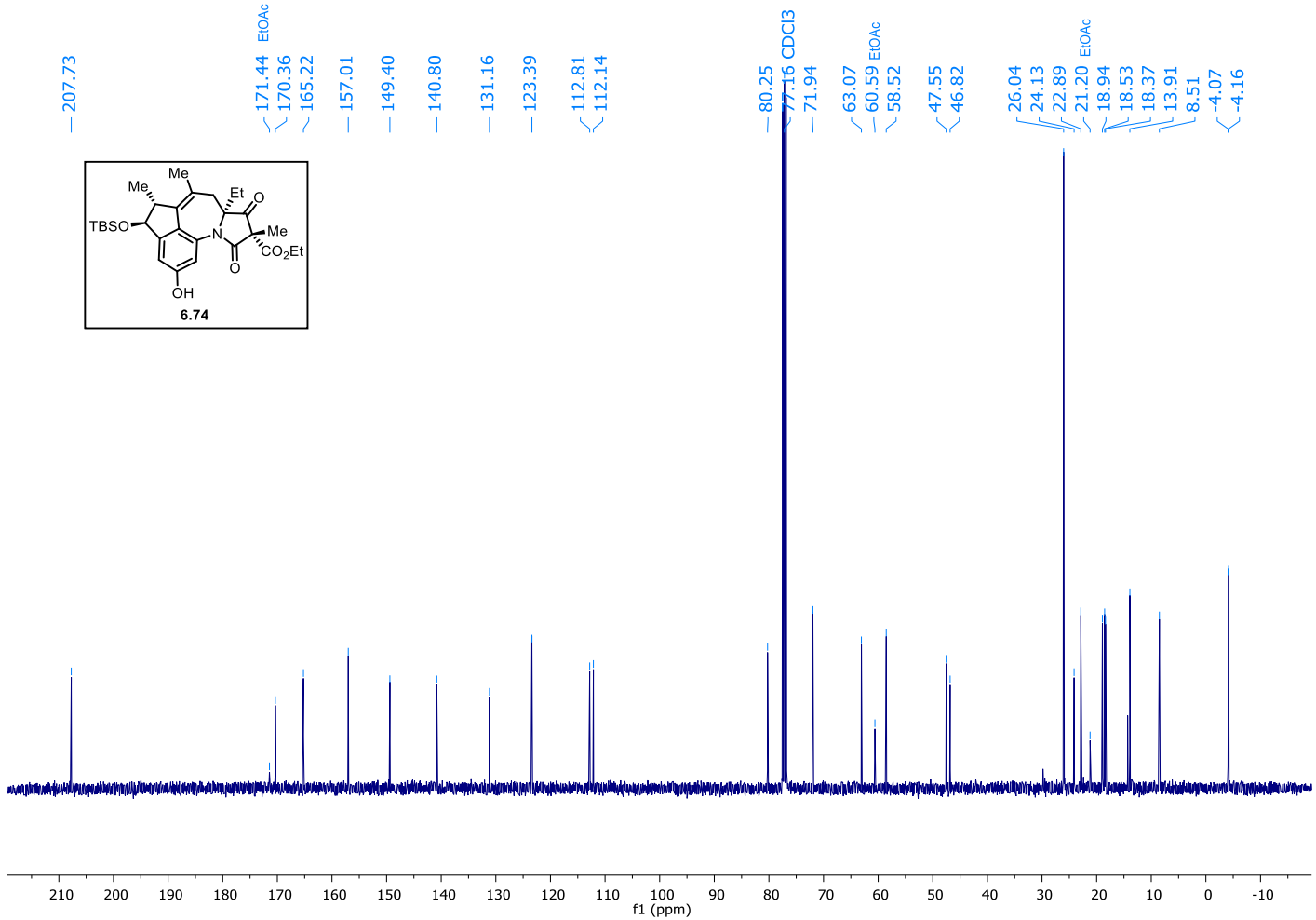


Figure D.107. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **6.74**

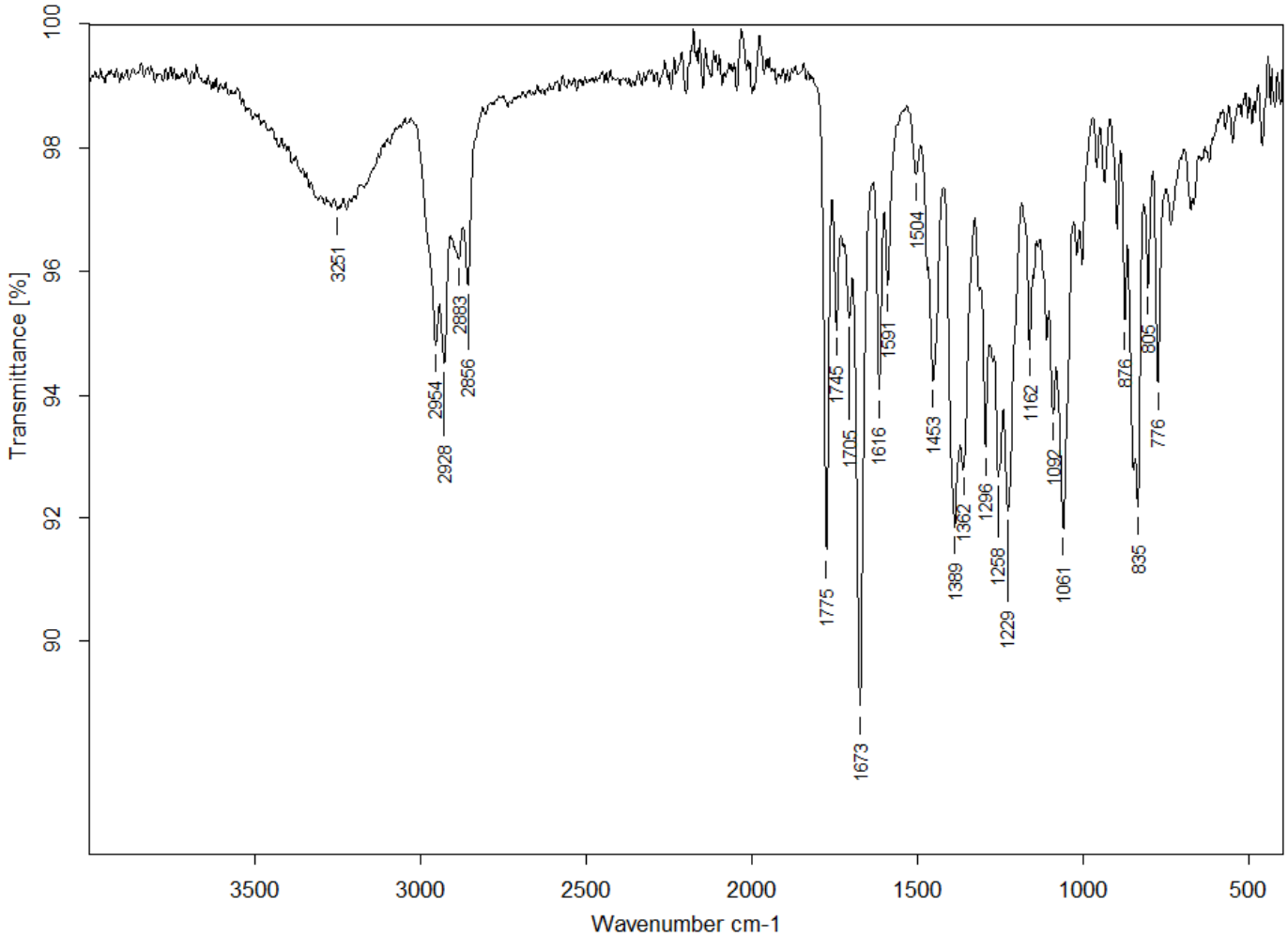


Figure D.108. FTIR spectrum (neat) of compound **6.74**

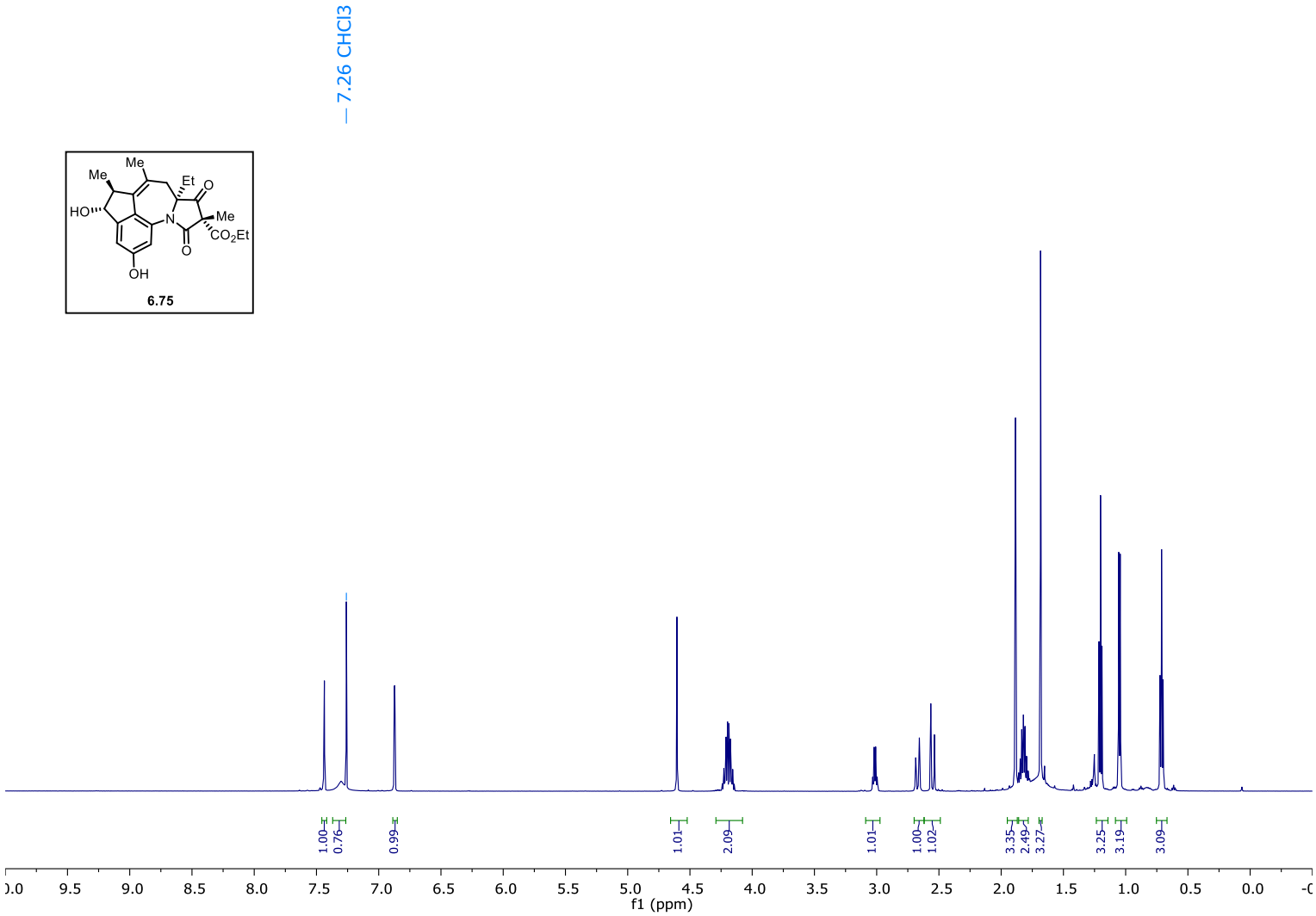


Figure D.109. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **6.75**

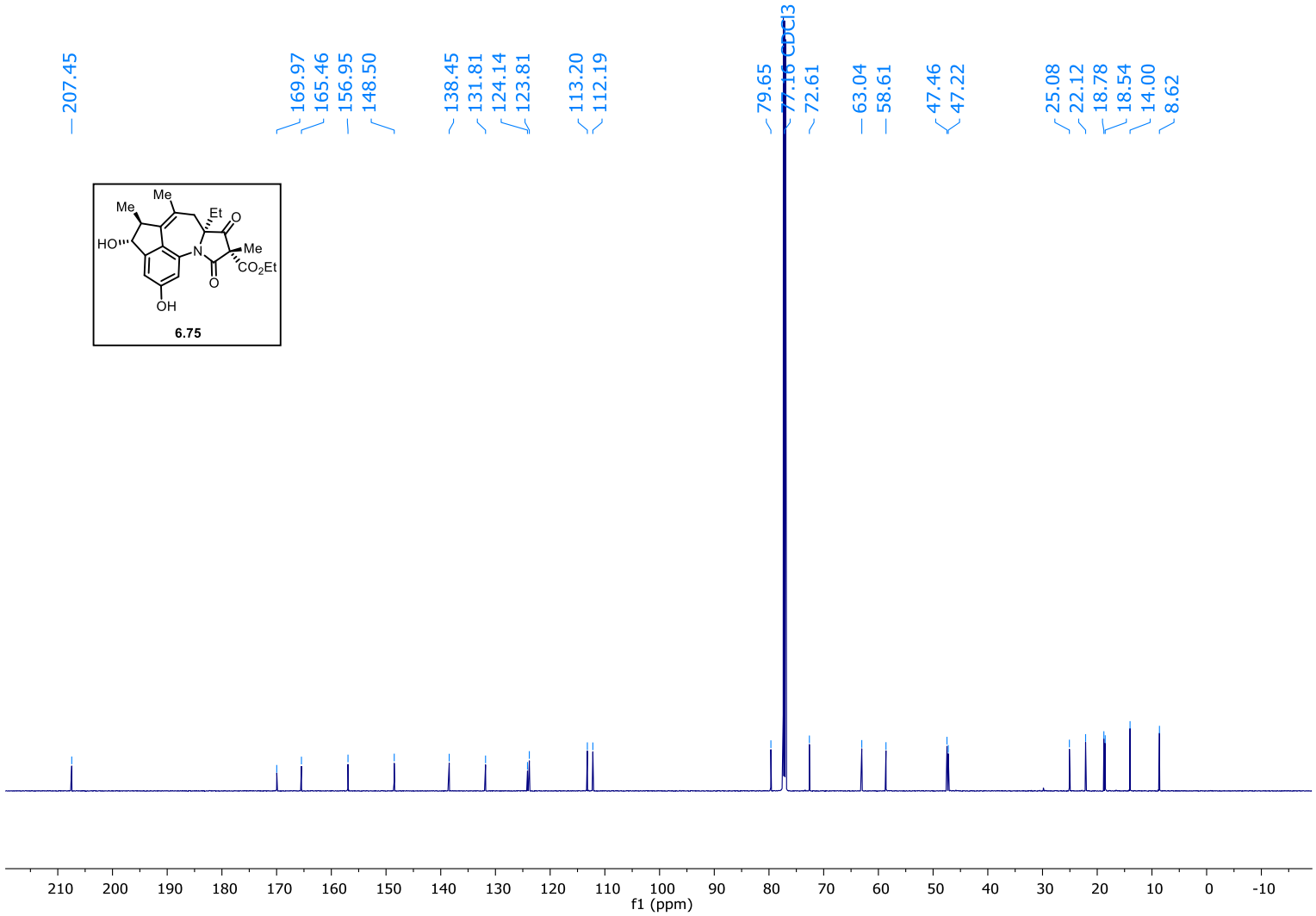


Figure D.110. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.75**

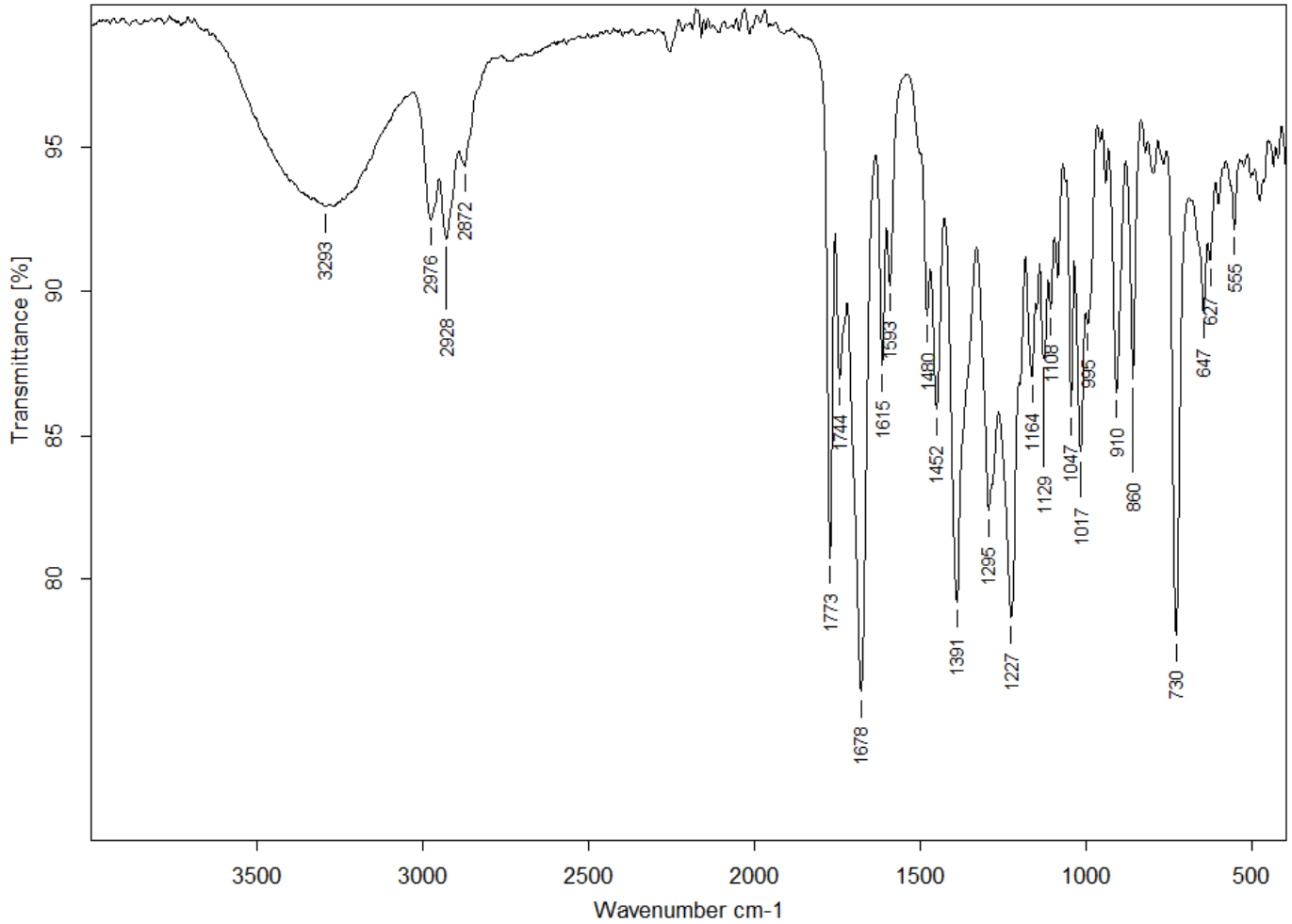


Figure D.111. FTIR spectrum (neat) of compound **6.75**

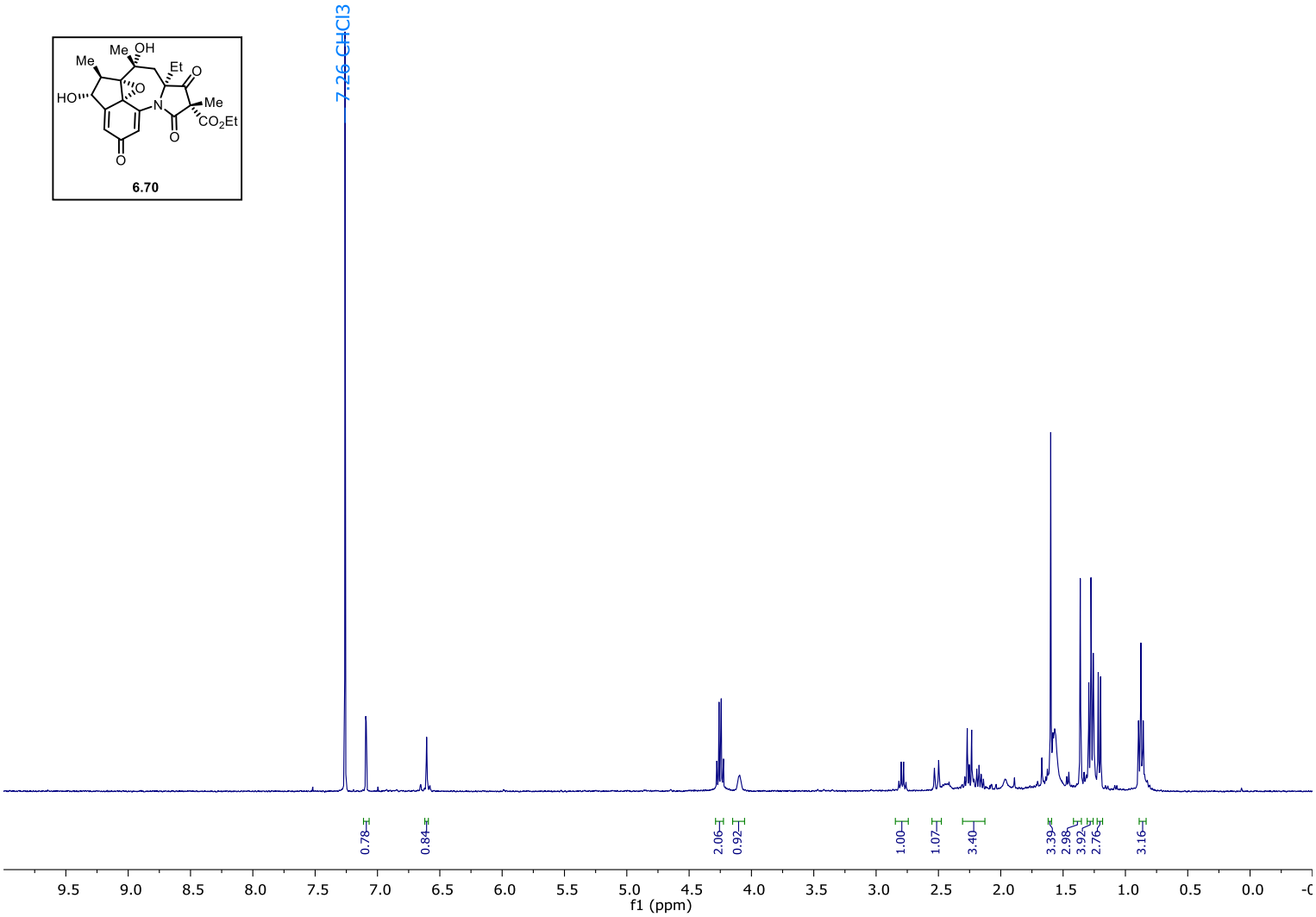


Figure D.112. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **6.70**

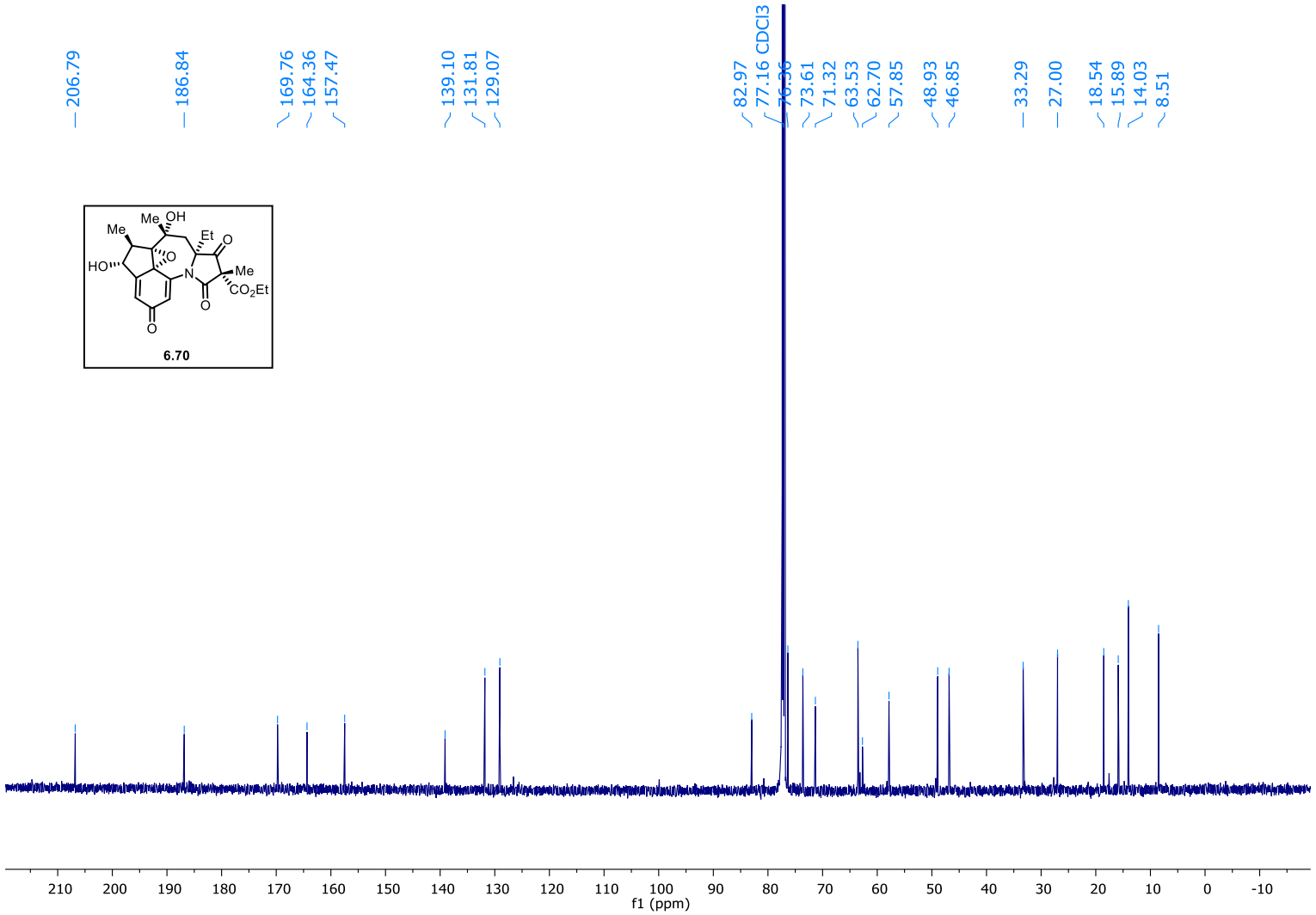


Figure D.113. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **6.70**

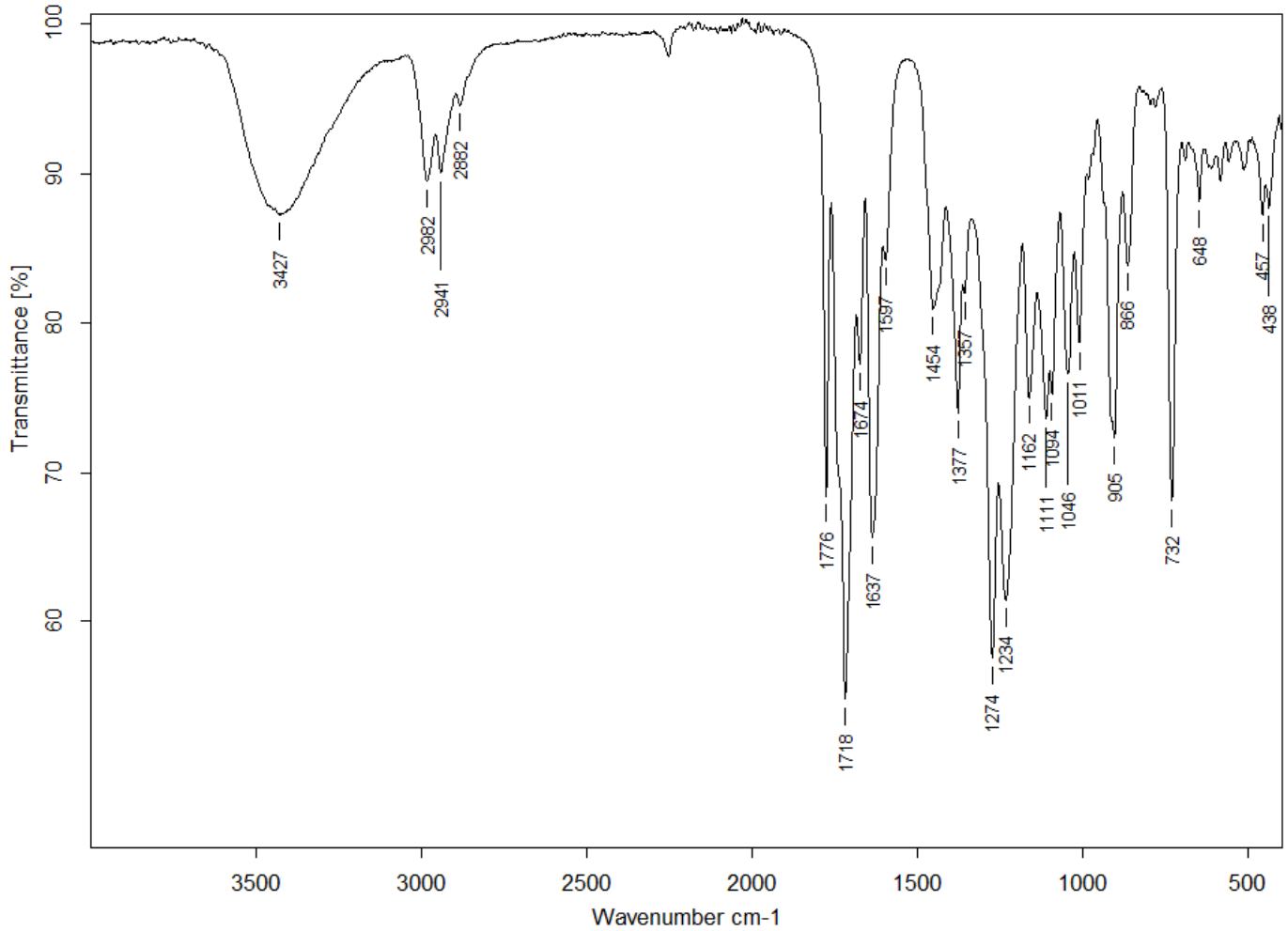


Figure D.114. IR spectra (neat) of compound **6.70**

APPENDIX E

Spectra Relevant to Chapter Seven

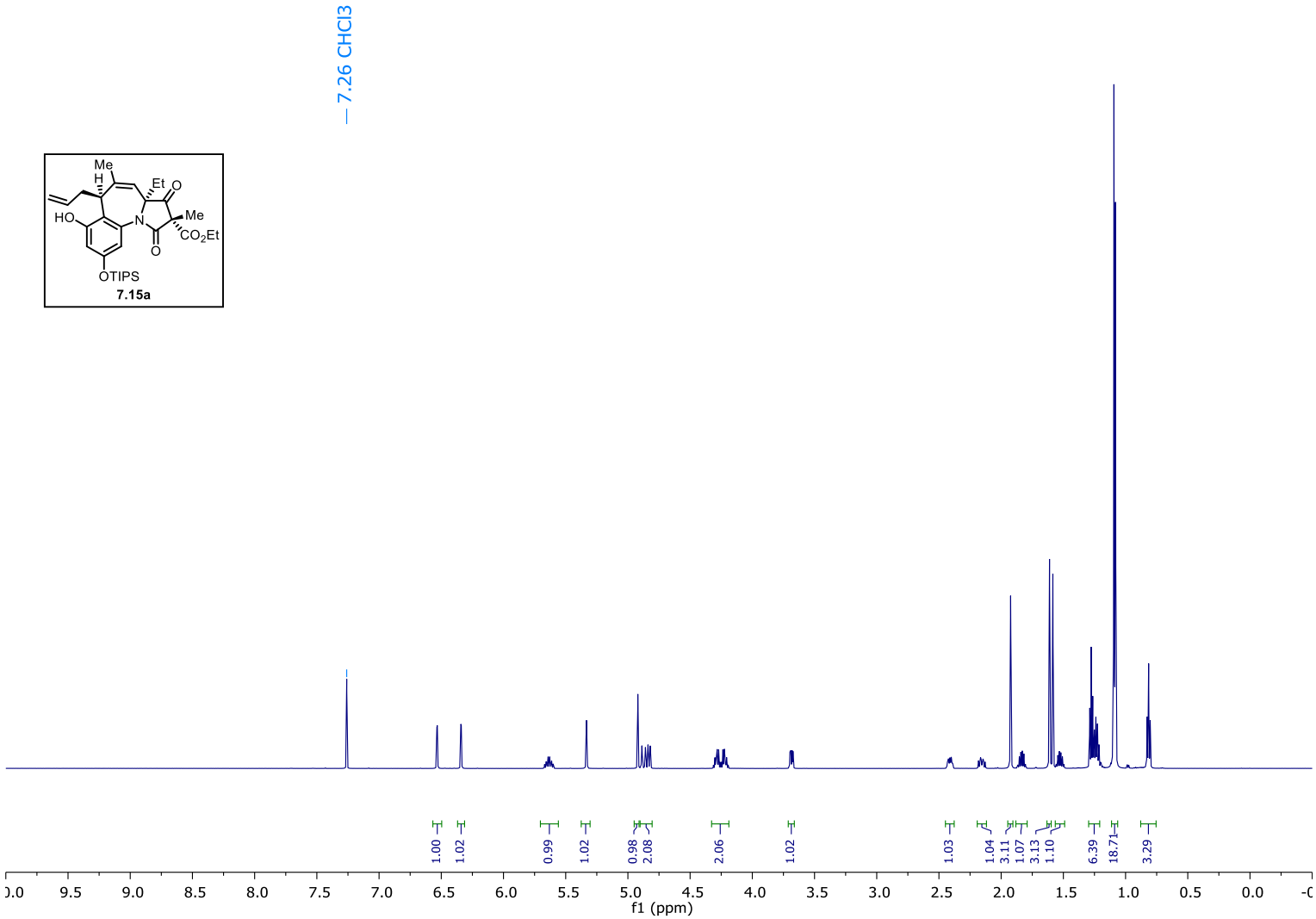


Figure E.1. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.15a**

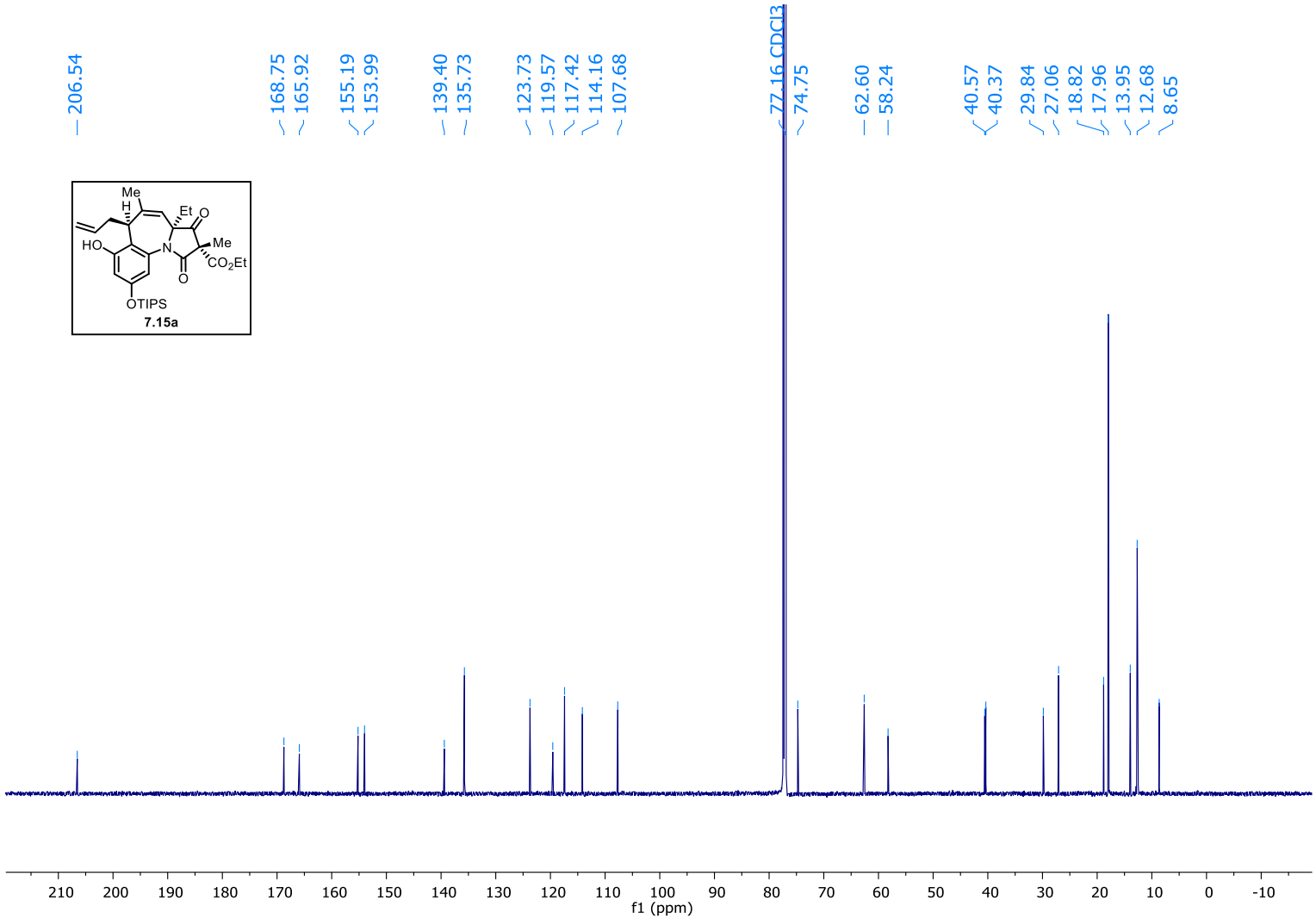


Figure E.2. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.15a**

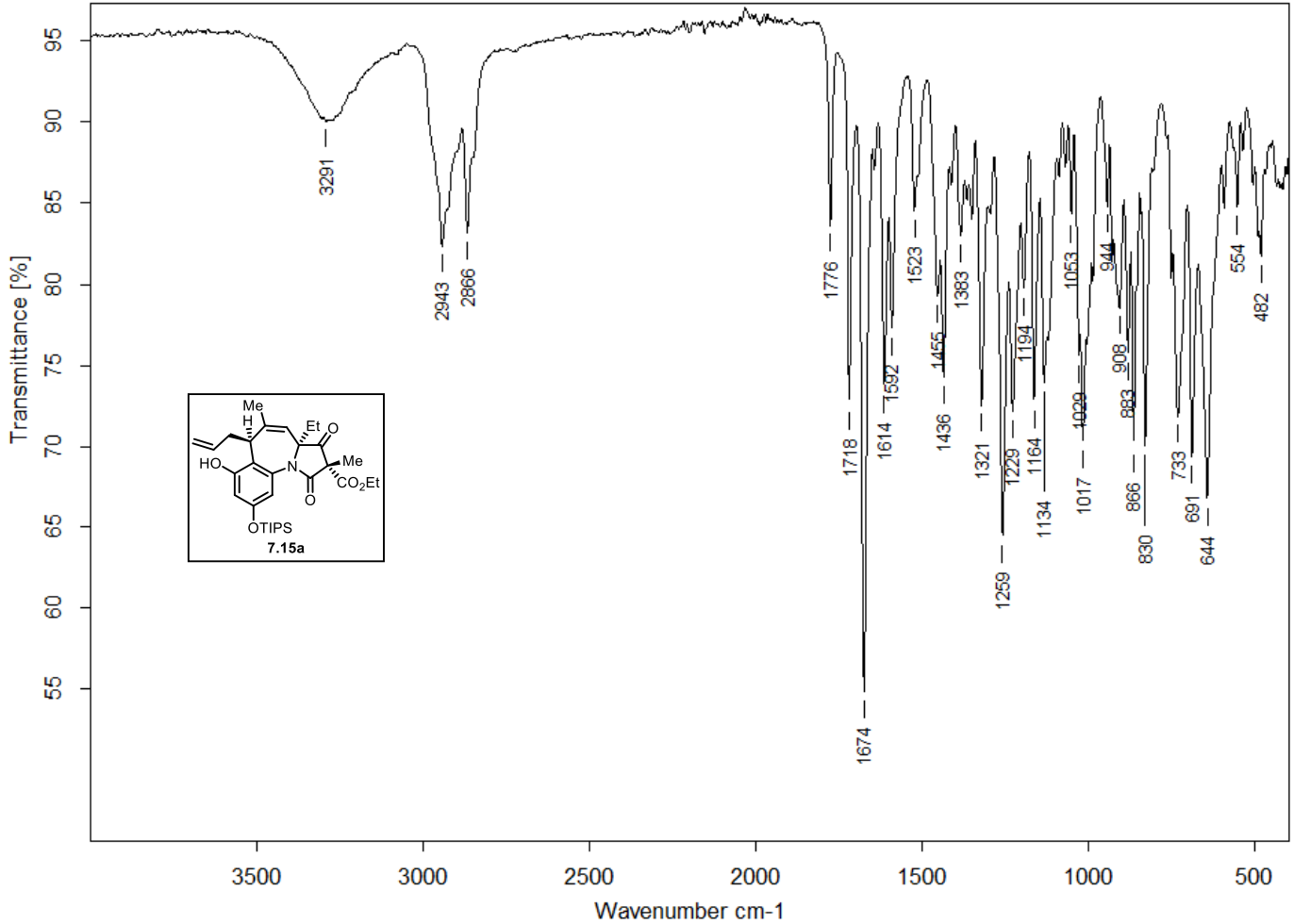


Figure E.3. FTIR spectrum (neat) of compound **7.15a**

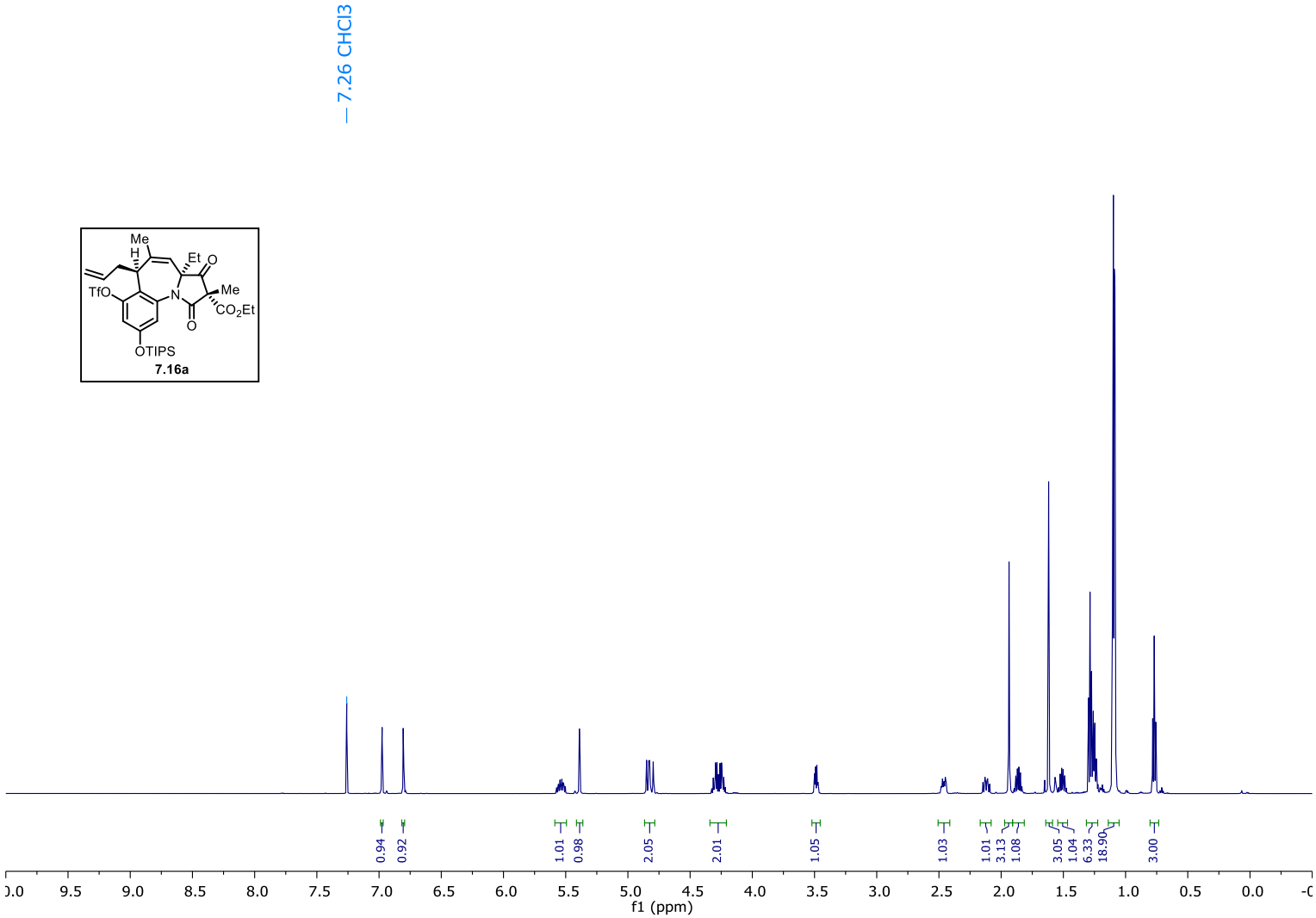


Figure E.4. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.16a**

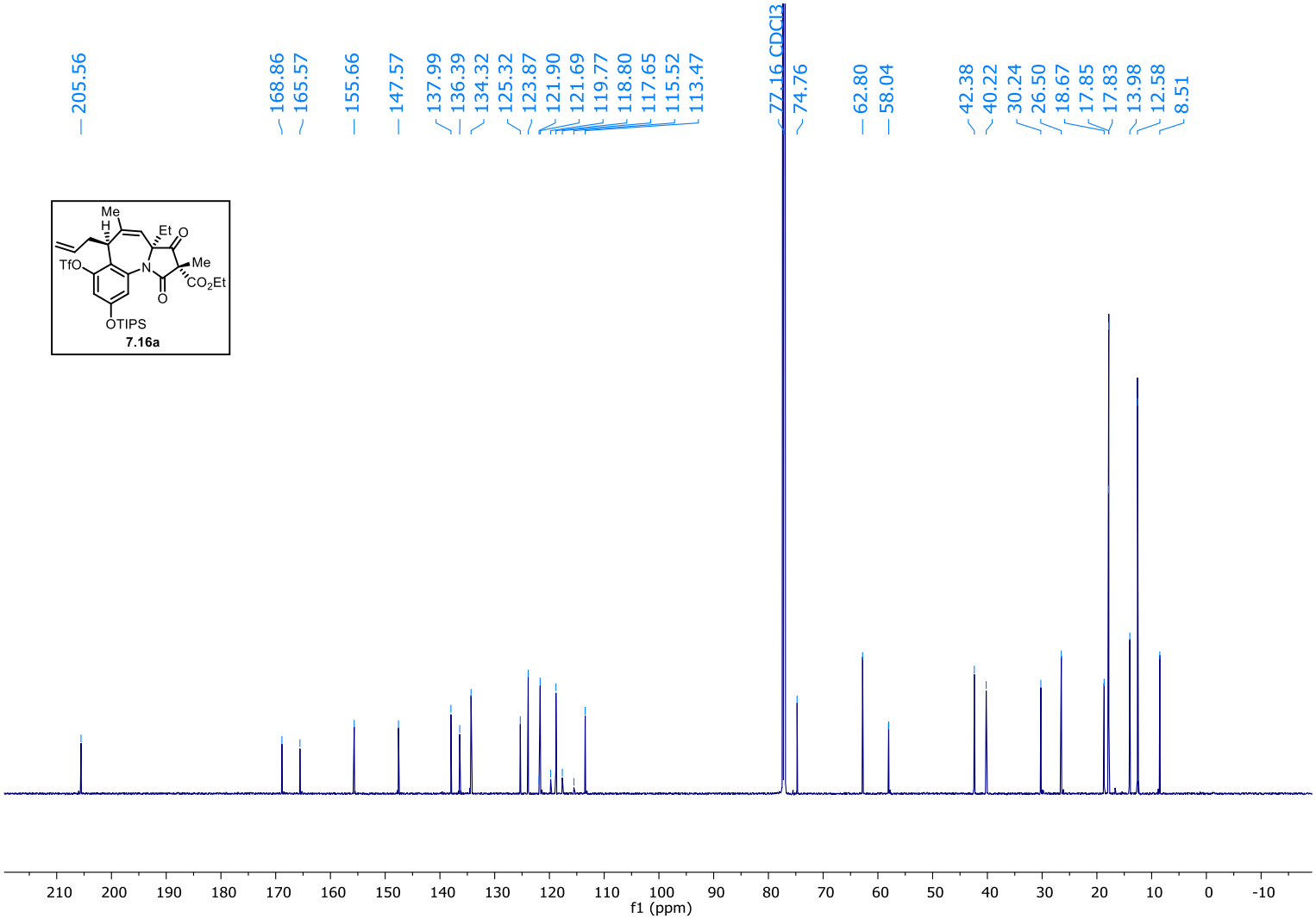


Figure E.5. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.16a**

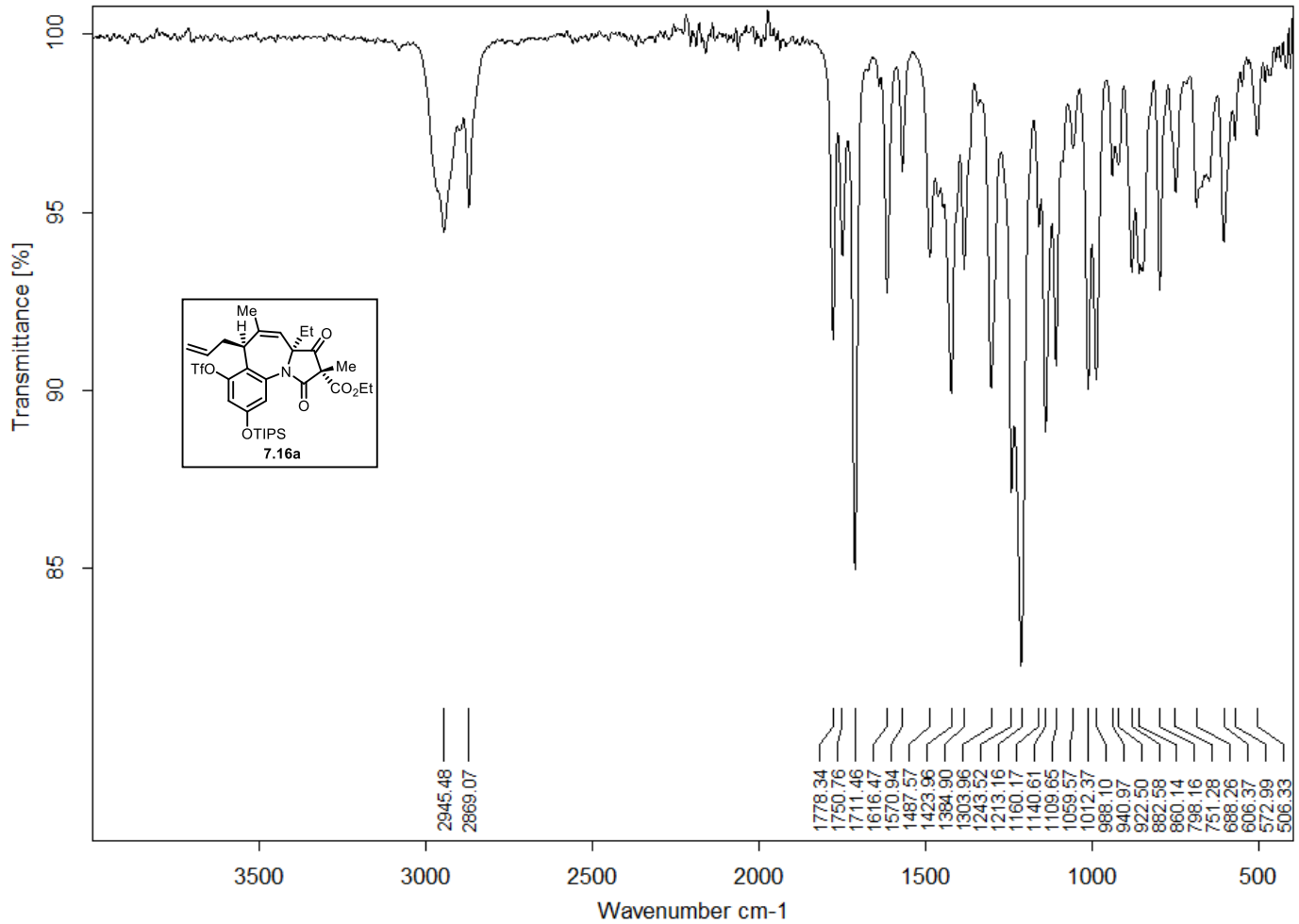


Figure E.6. FTIR spectrum (neat) of compound **7.16a**

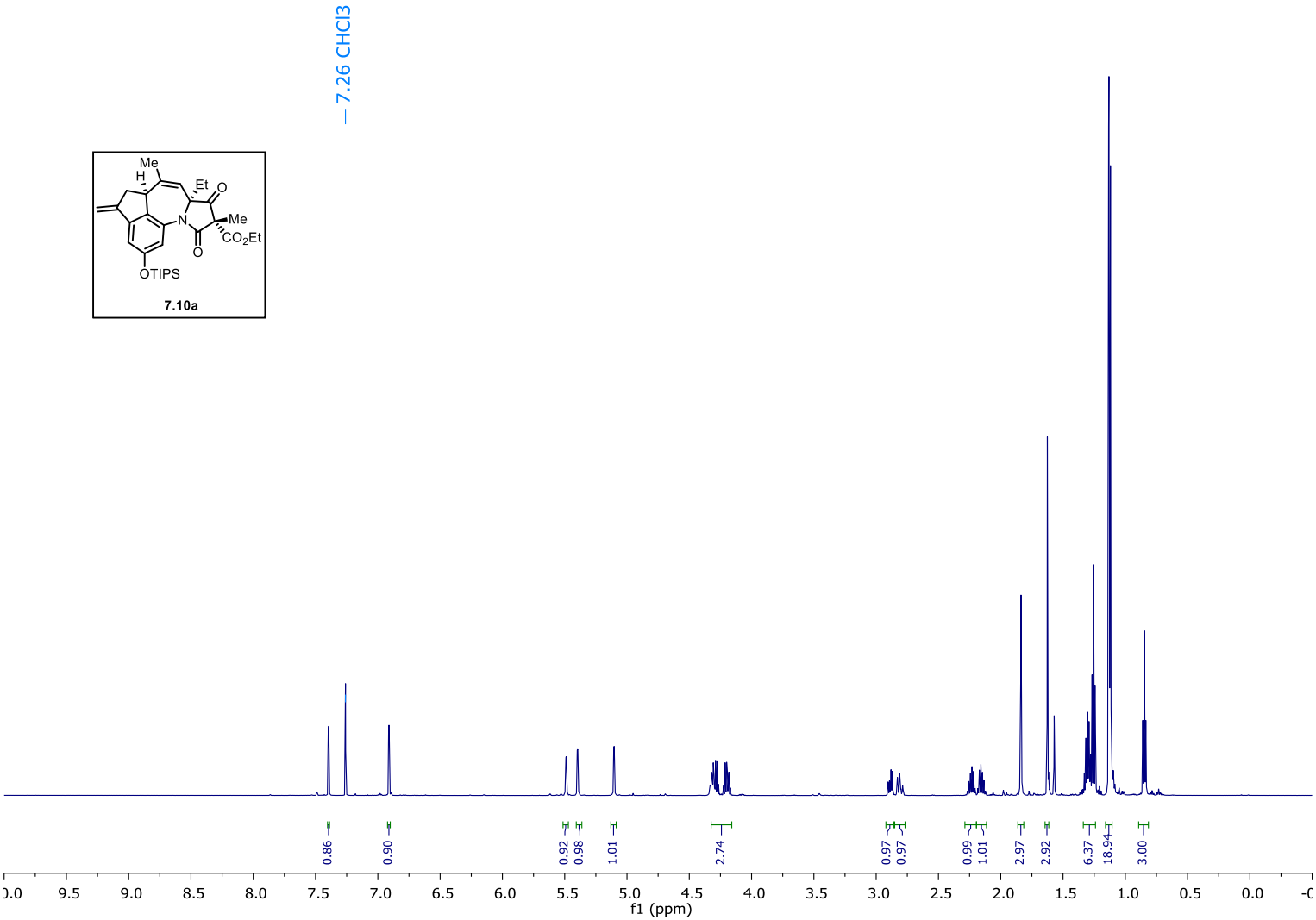


Figure E.7. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.10a**

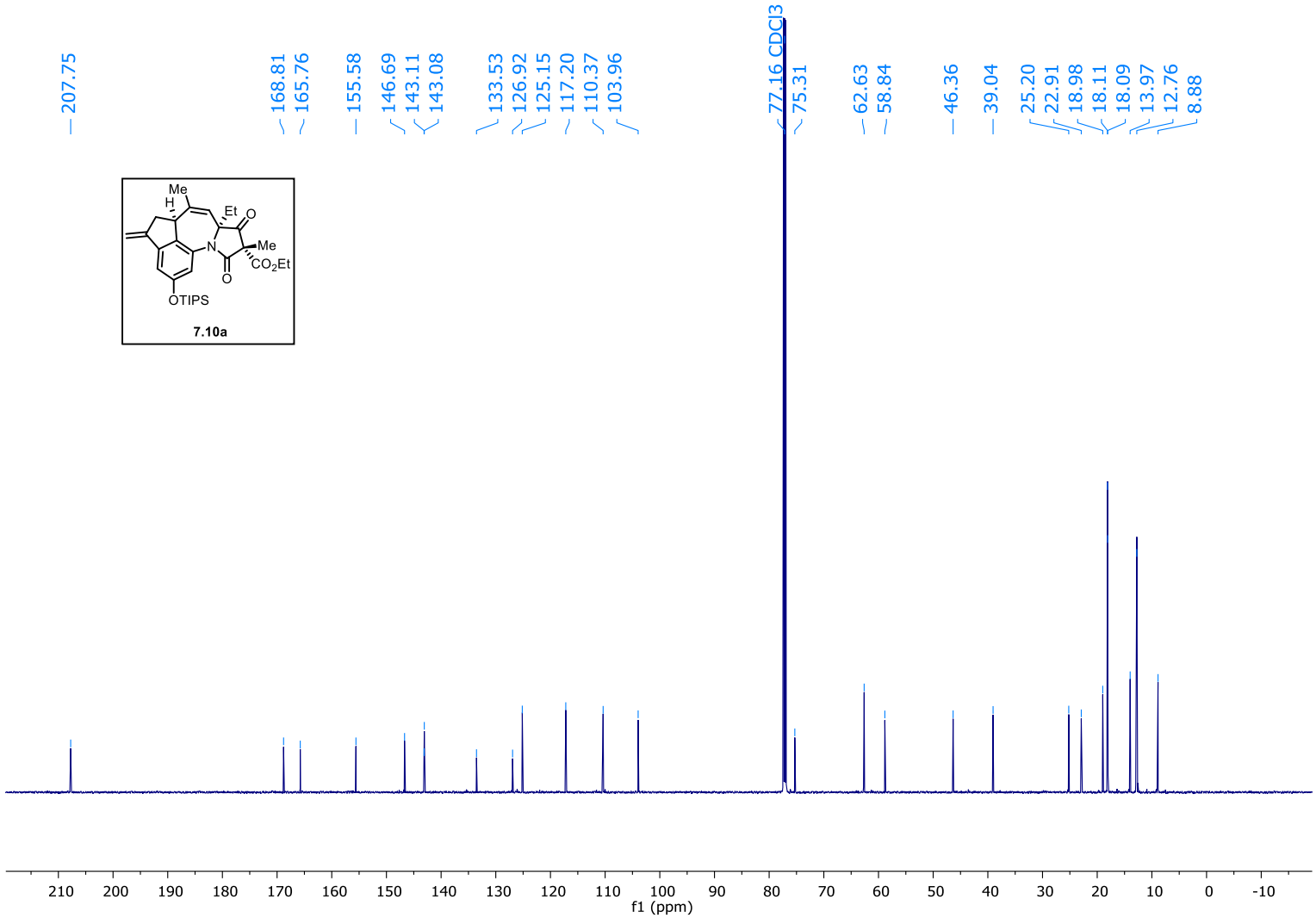


Figure E.8. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.10a**

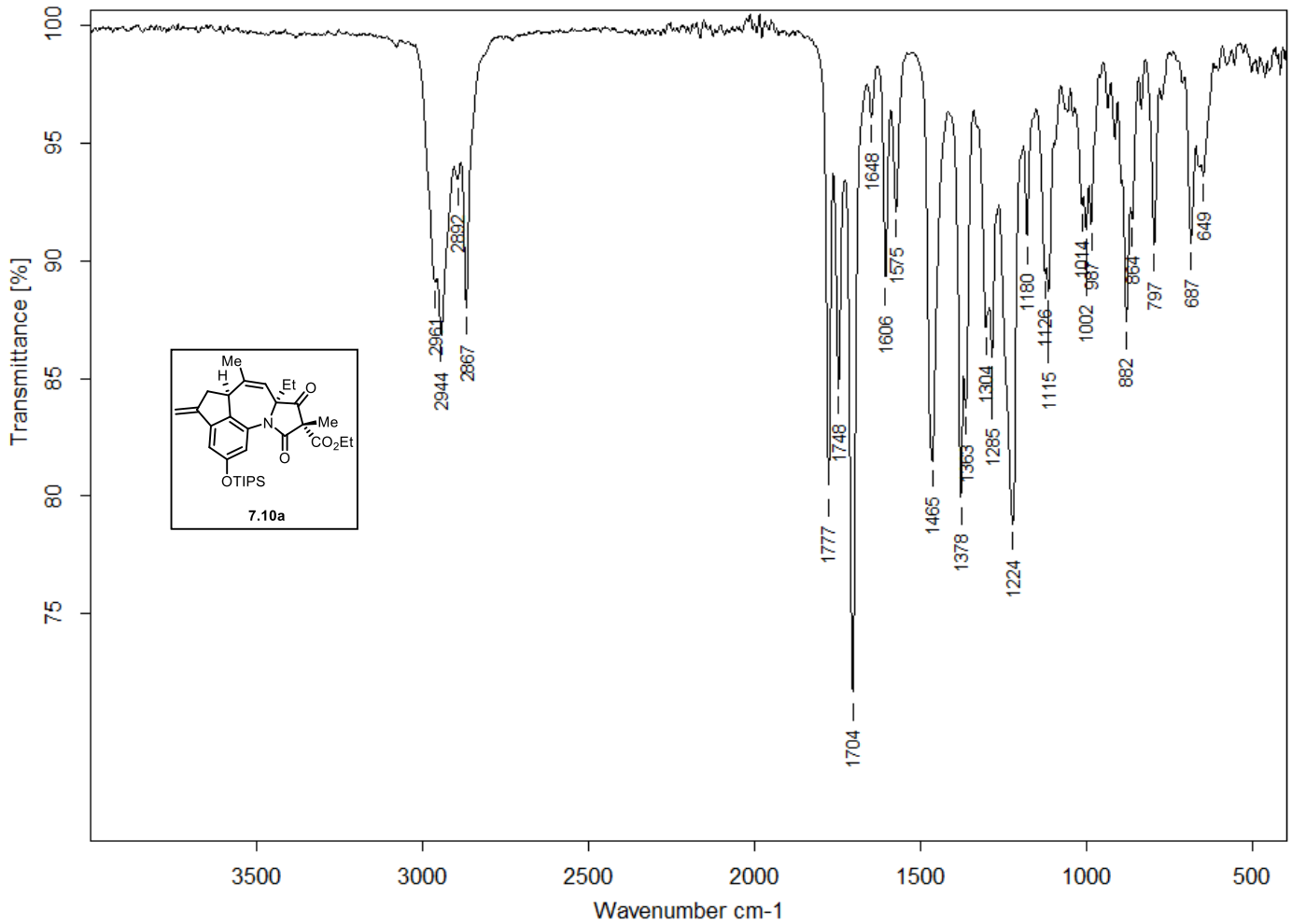


Figure E.9. FTIR spectrum (neat) of compound **7.10a**

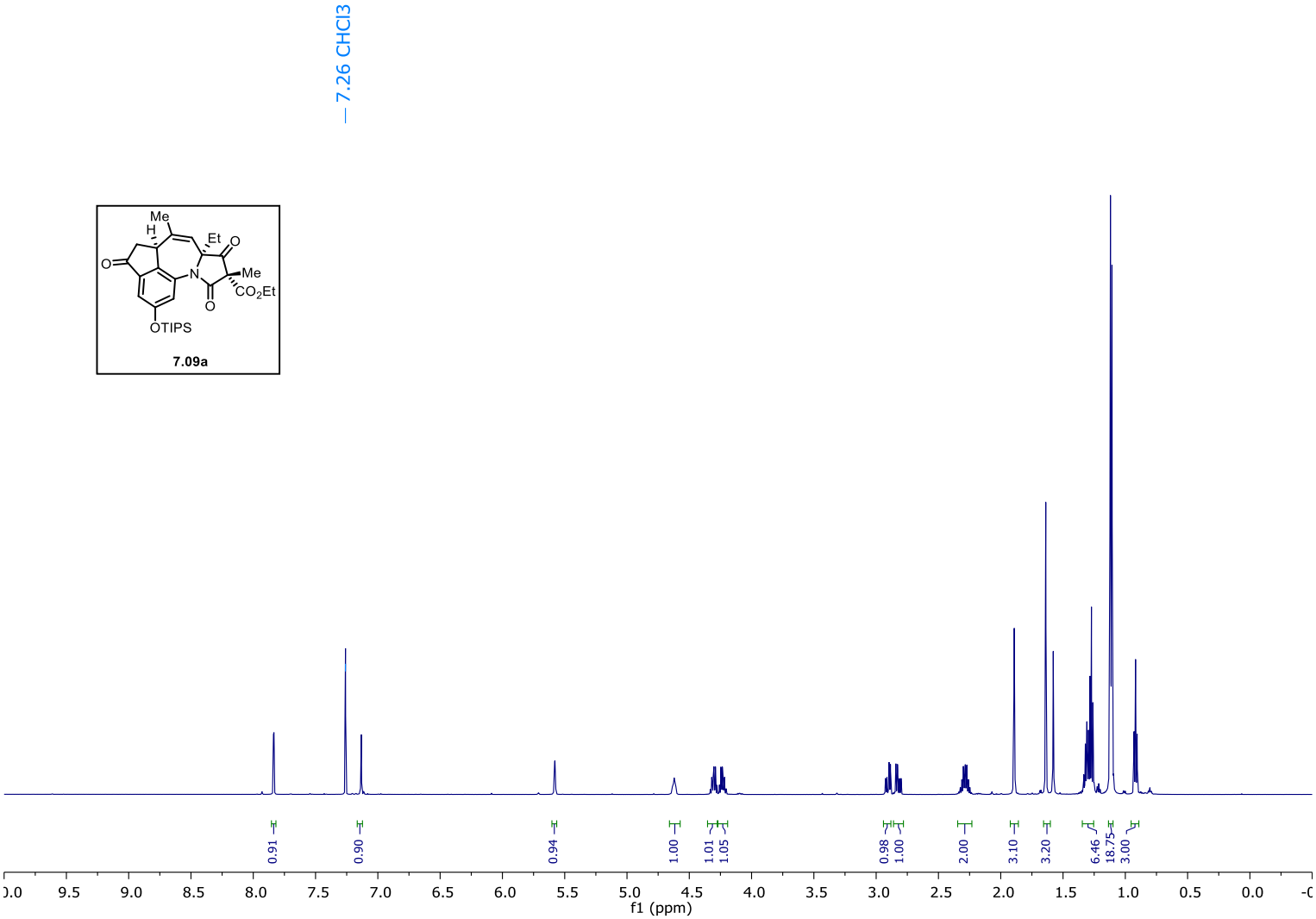


Figure E.10. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.09a**

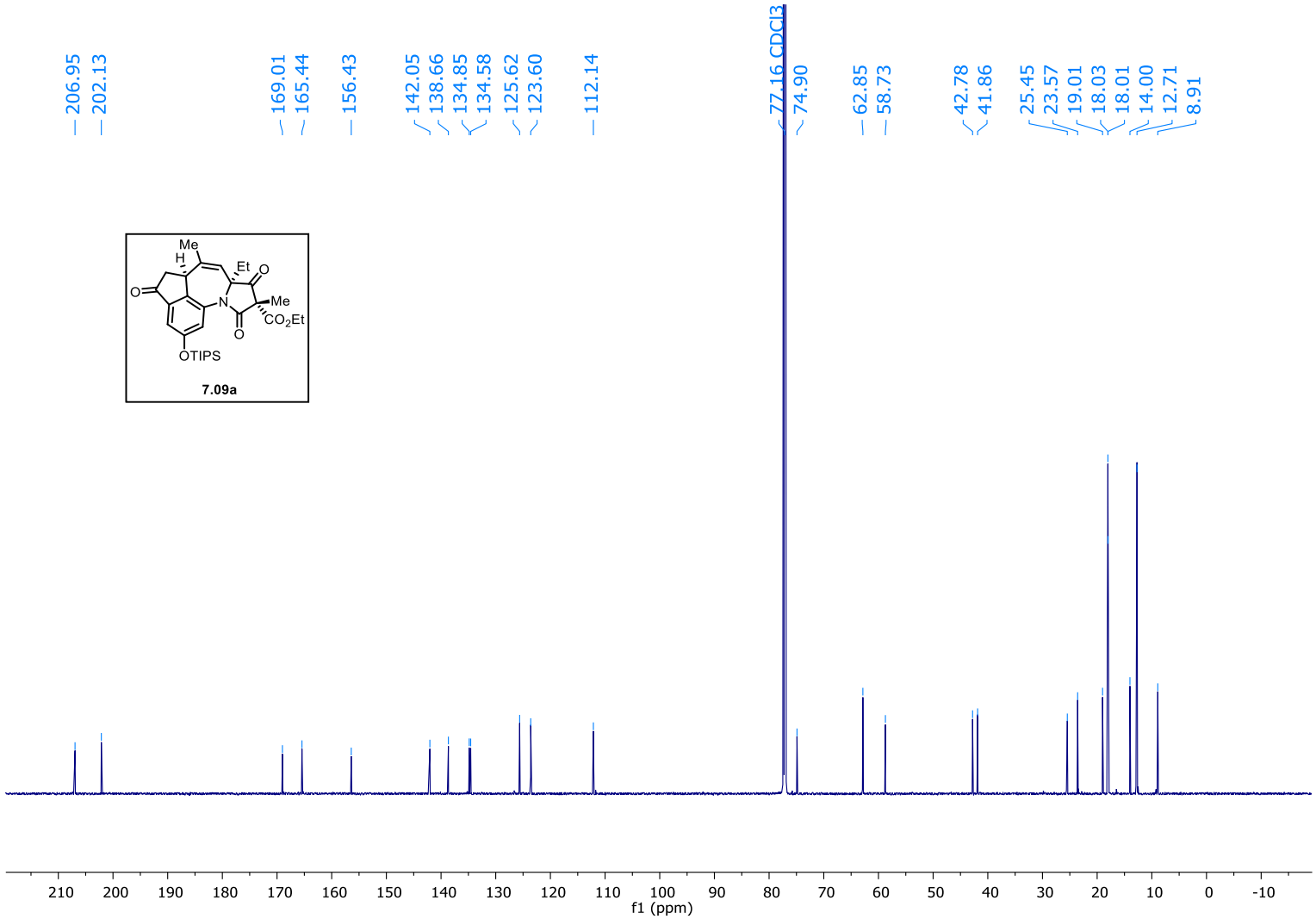


Figure E.11. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.09a**

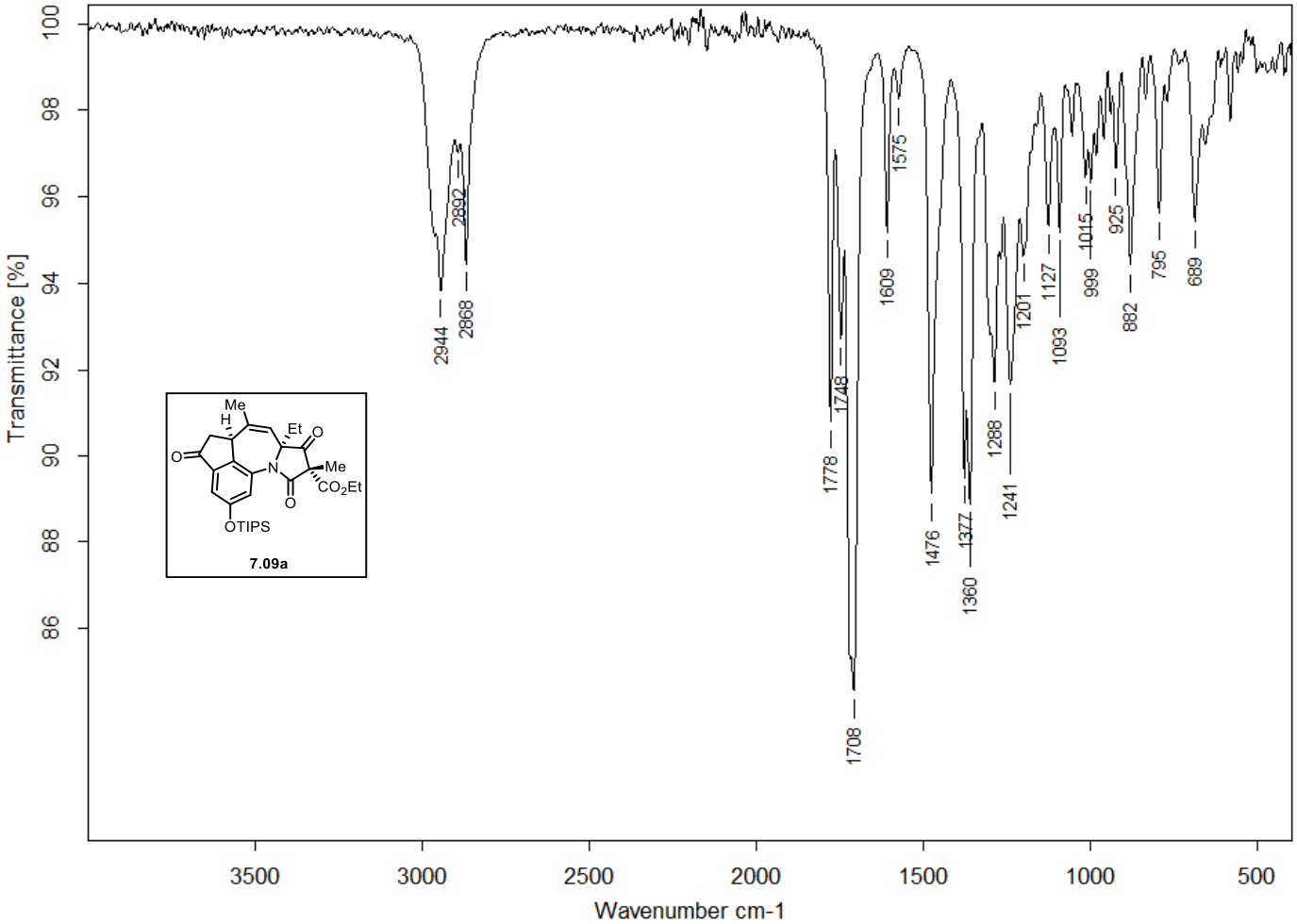


Figure E.12. FTIR spectrum (neat) of compound **7.09a**

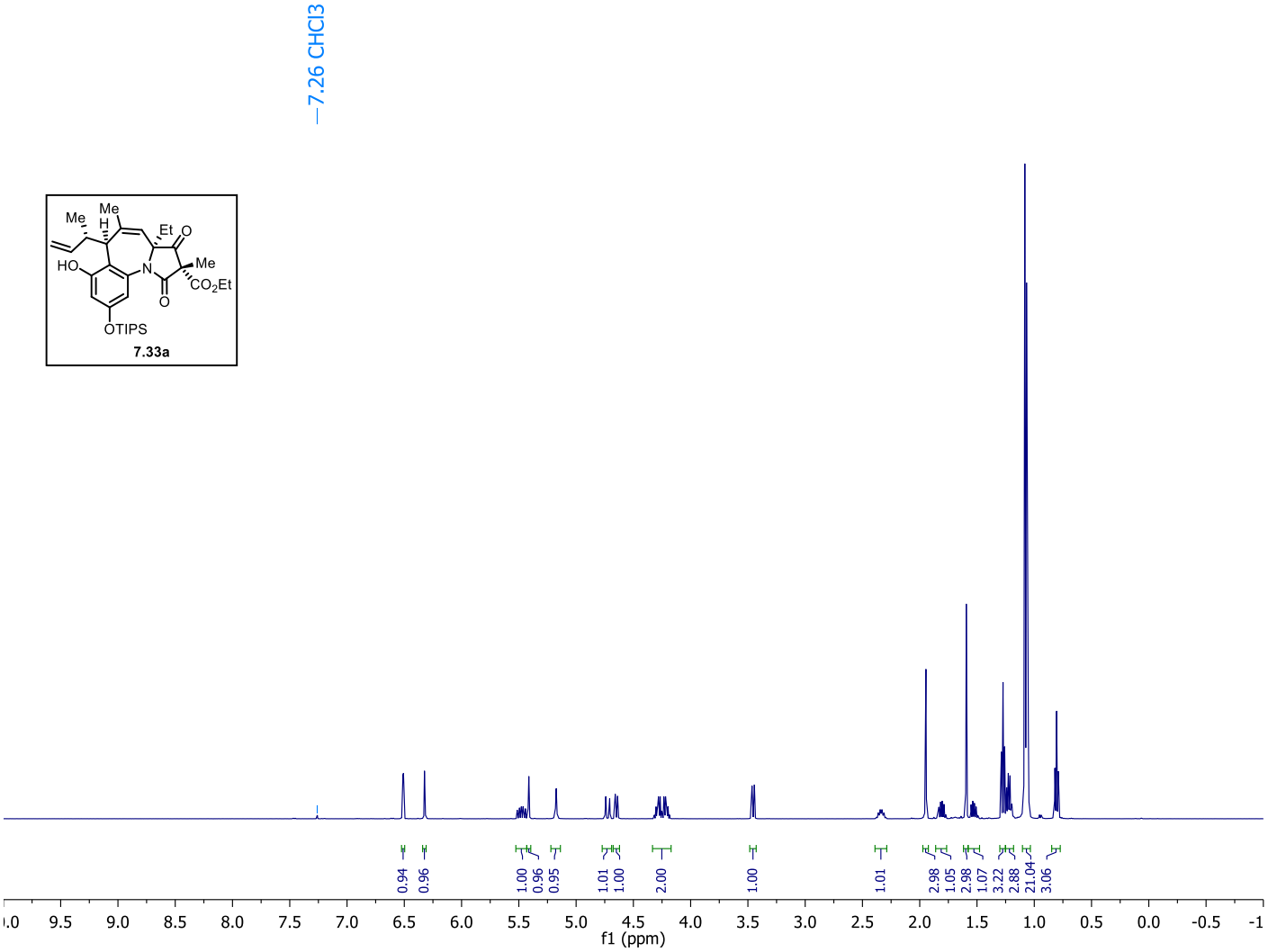


Figure E.13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.33a**

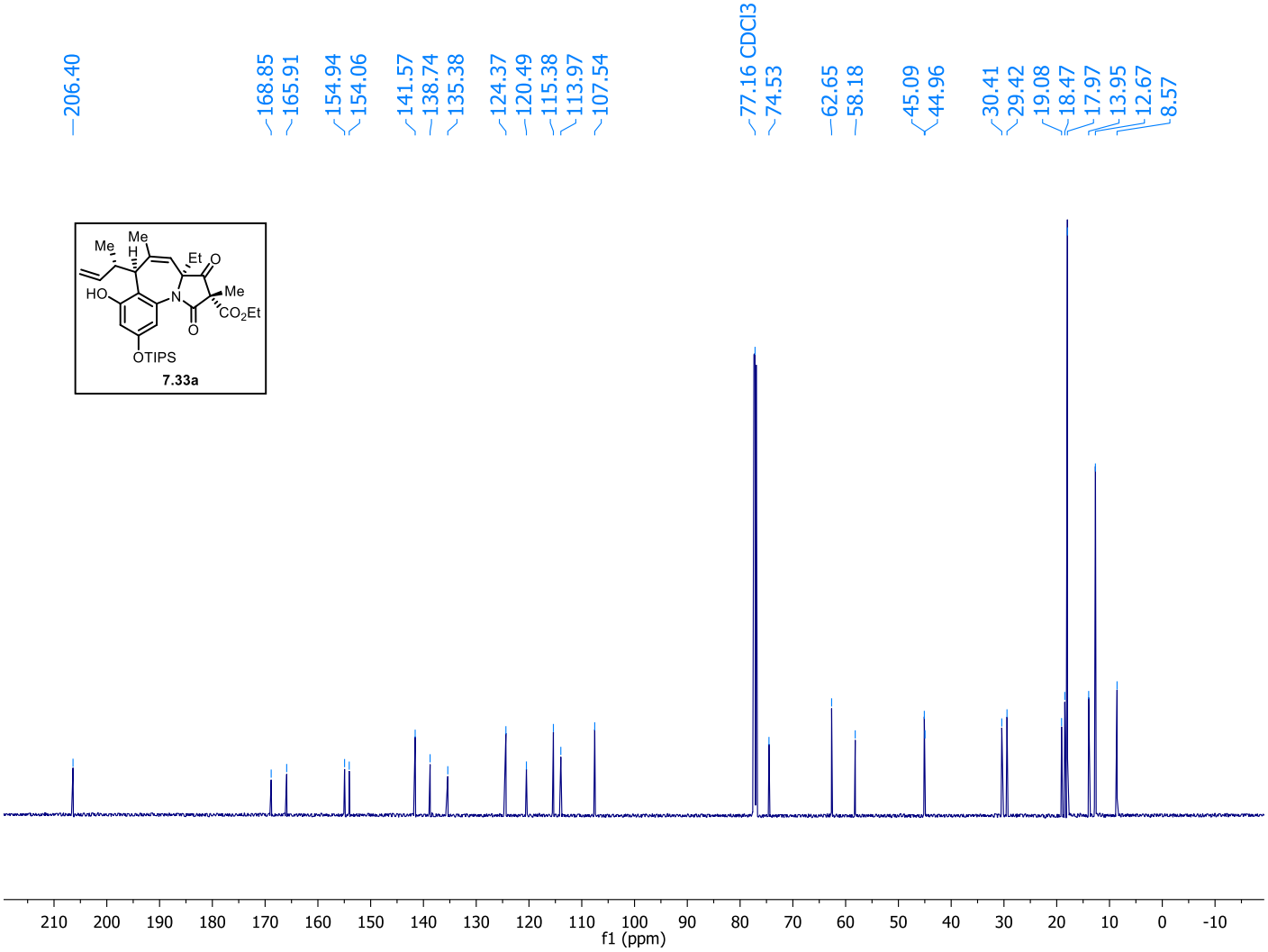


Figure E.14. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.33a**

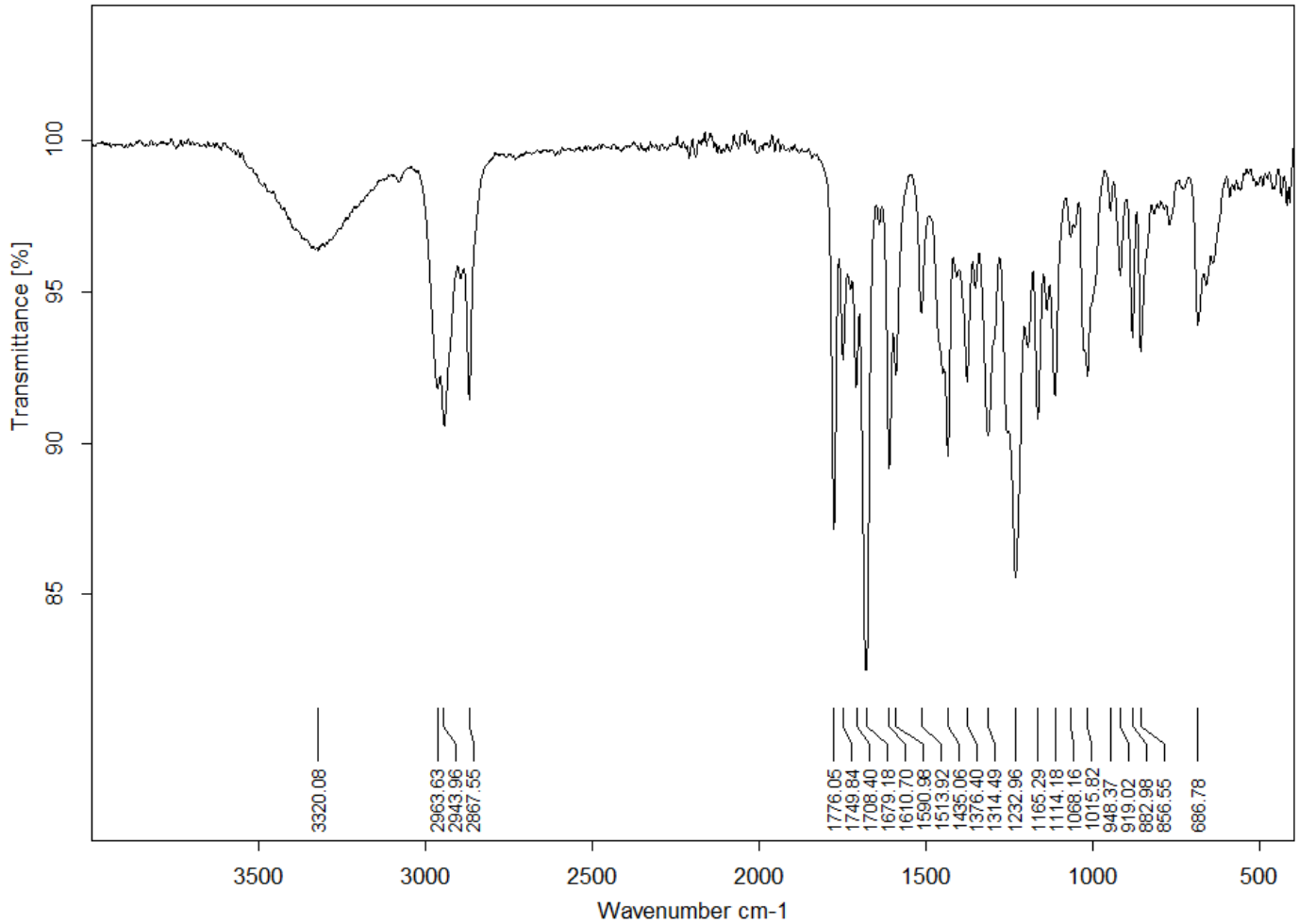


Figure E.15. FTIR spectrum (neat) of compound **7.33a**

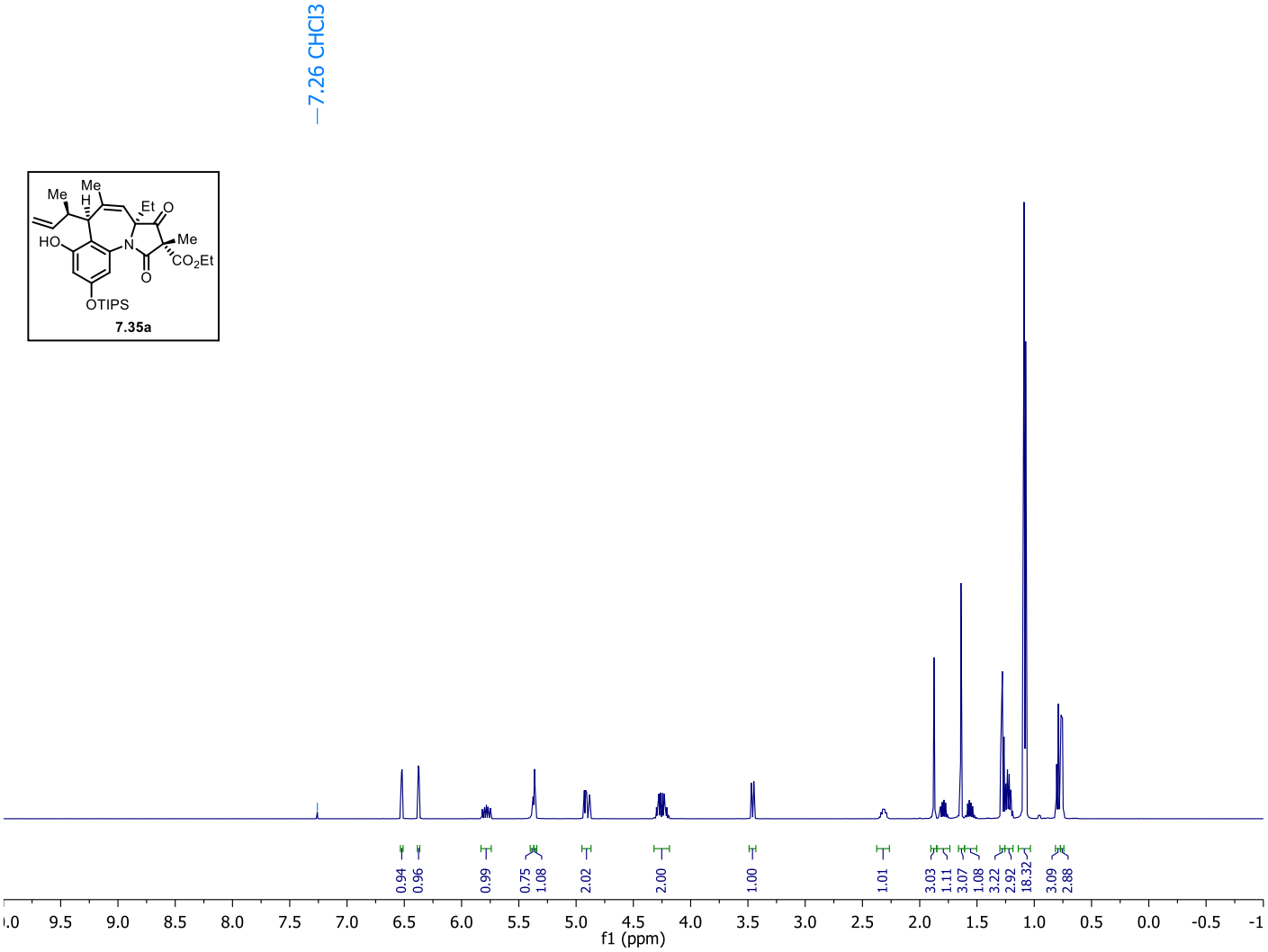


Figure E.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.35a**

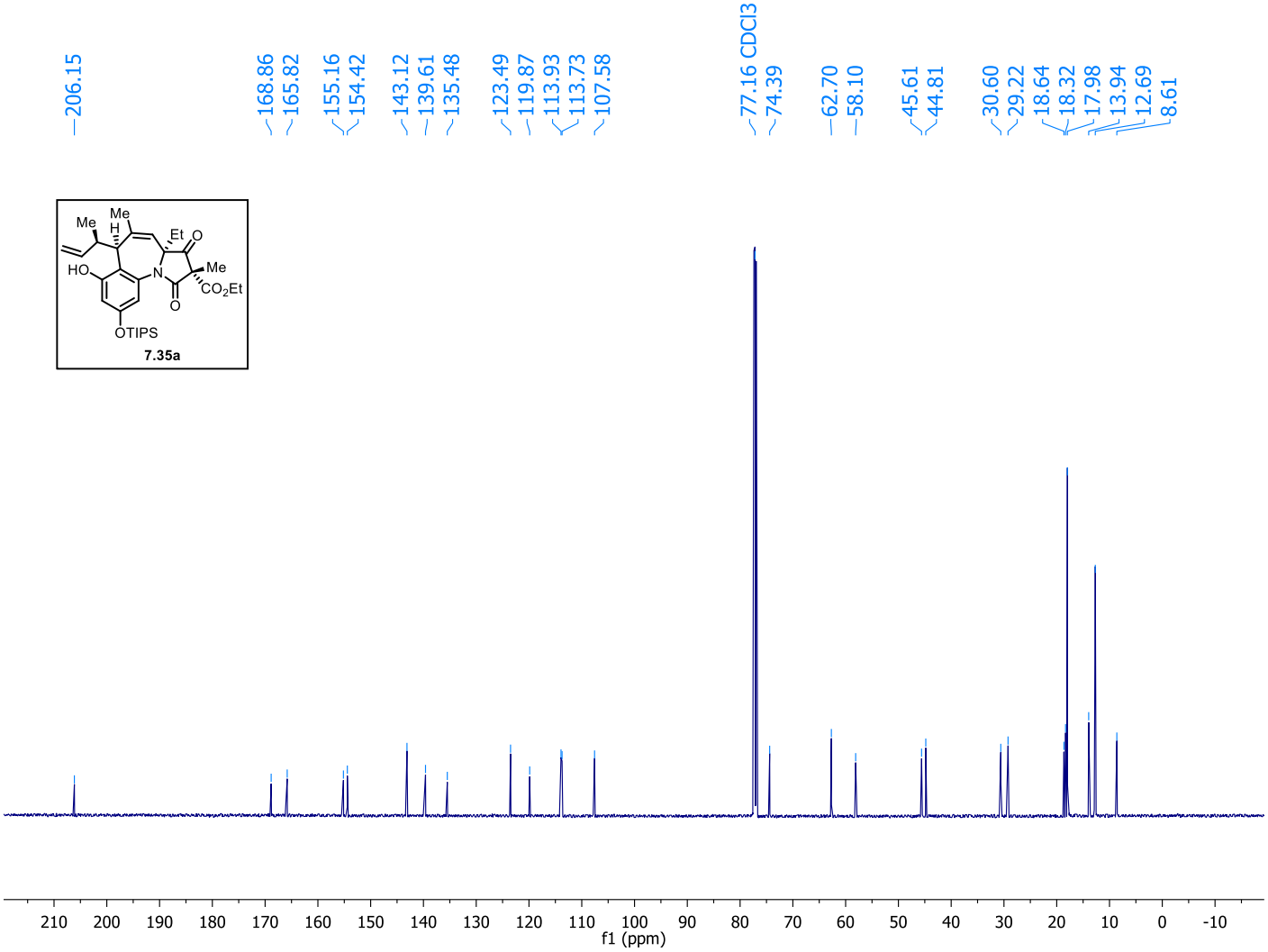


Figure E.17. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.35a**

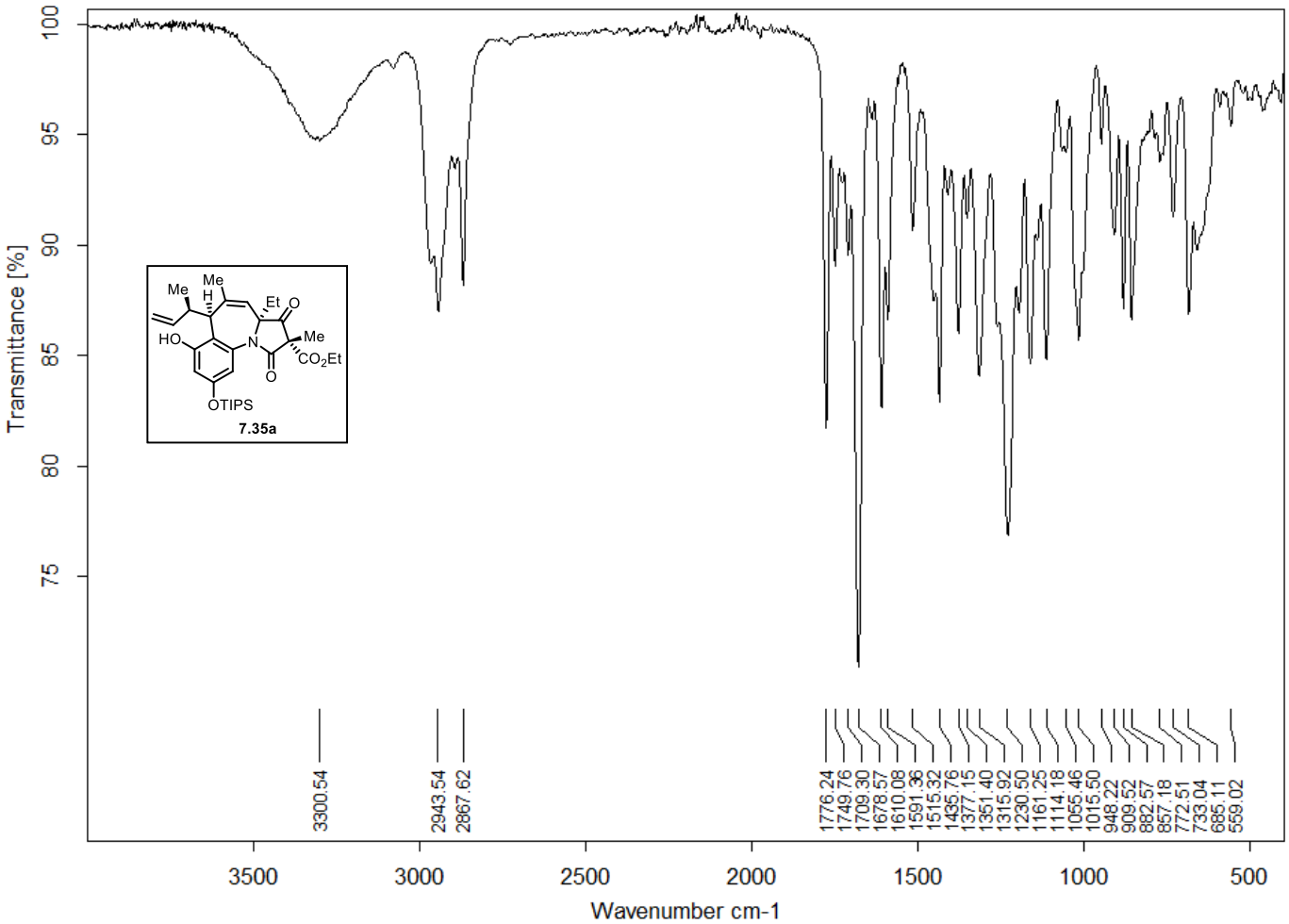


Figure E.18. FTIR spectrum (neat) of compound **7.35a**

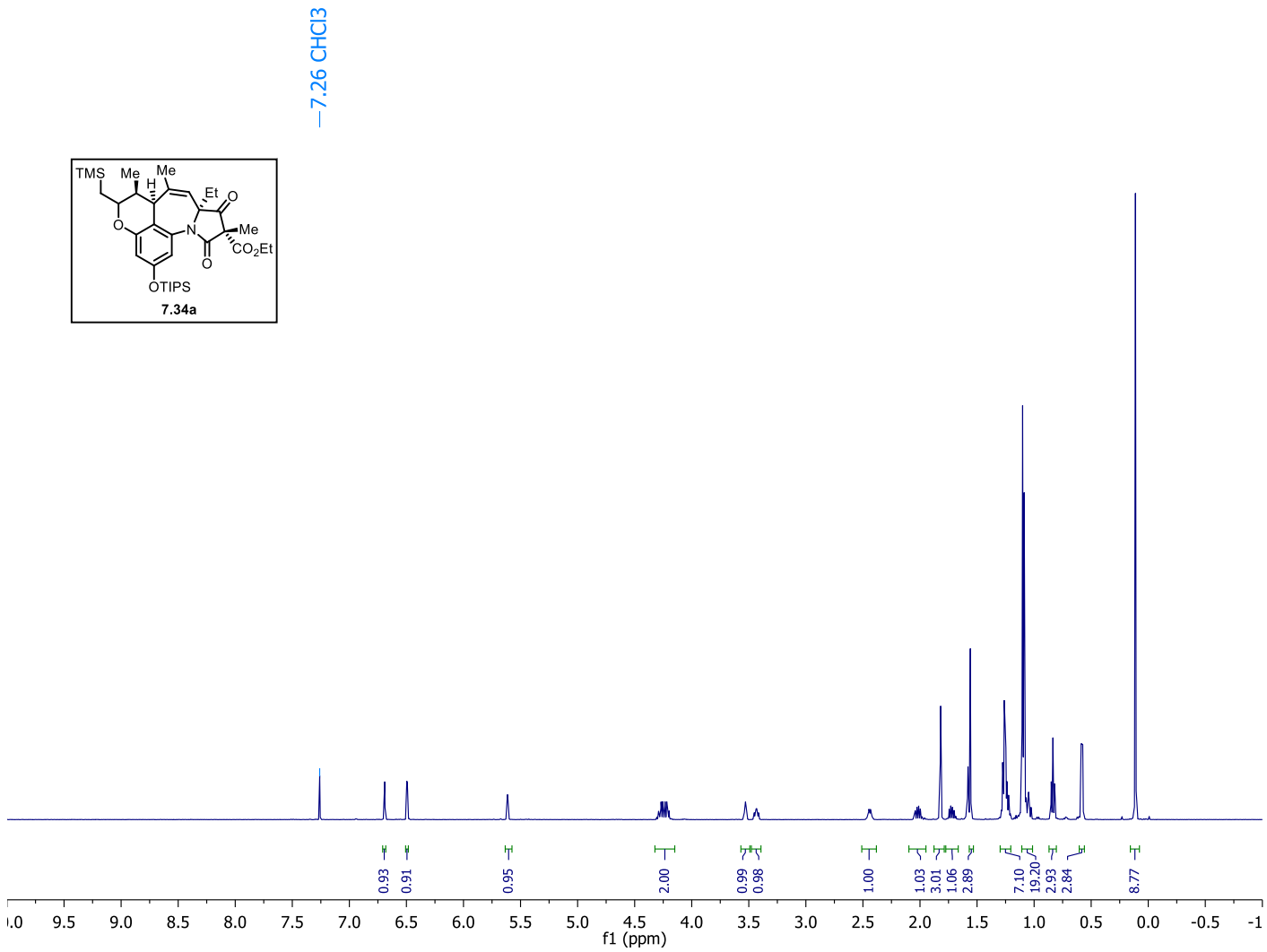


Figure E.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.34a**

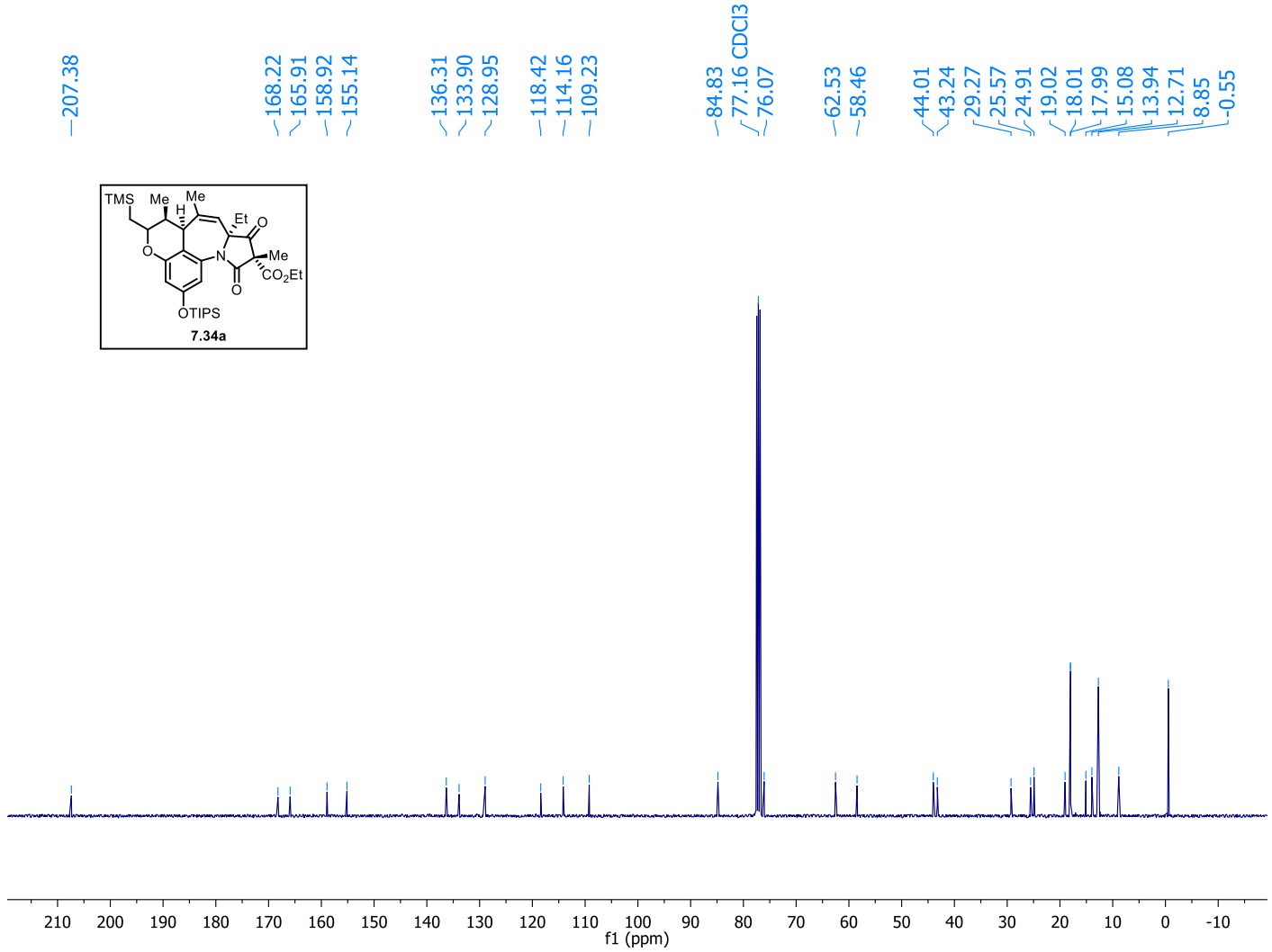


Figure E.20. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.34a**

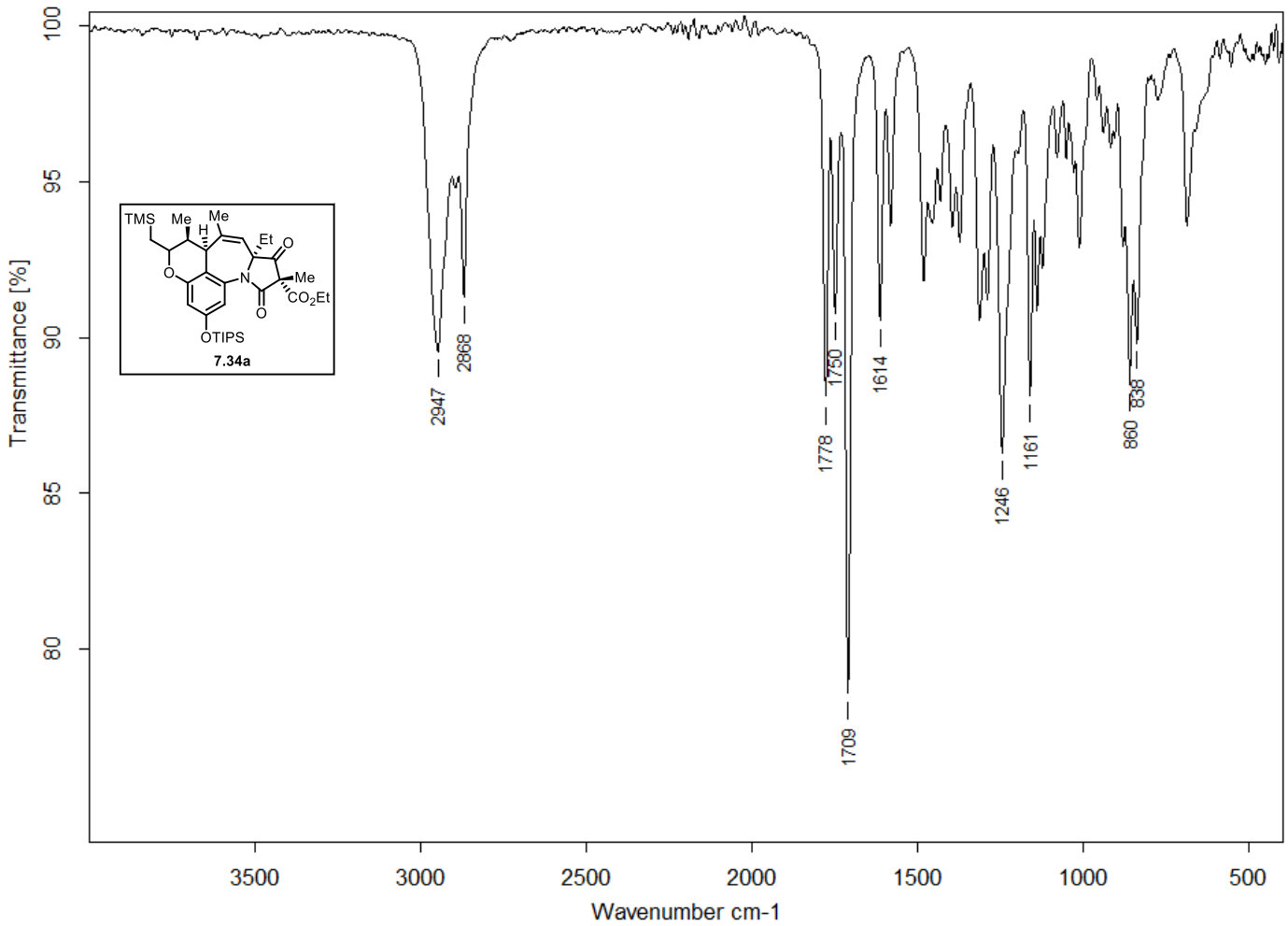


Figure E.21. FTIR spectrum (neat) of compound **7.34a**

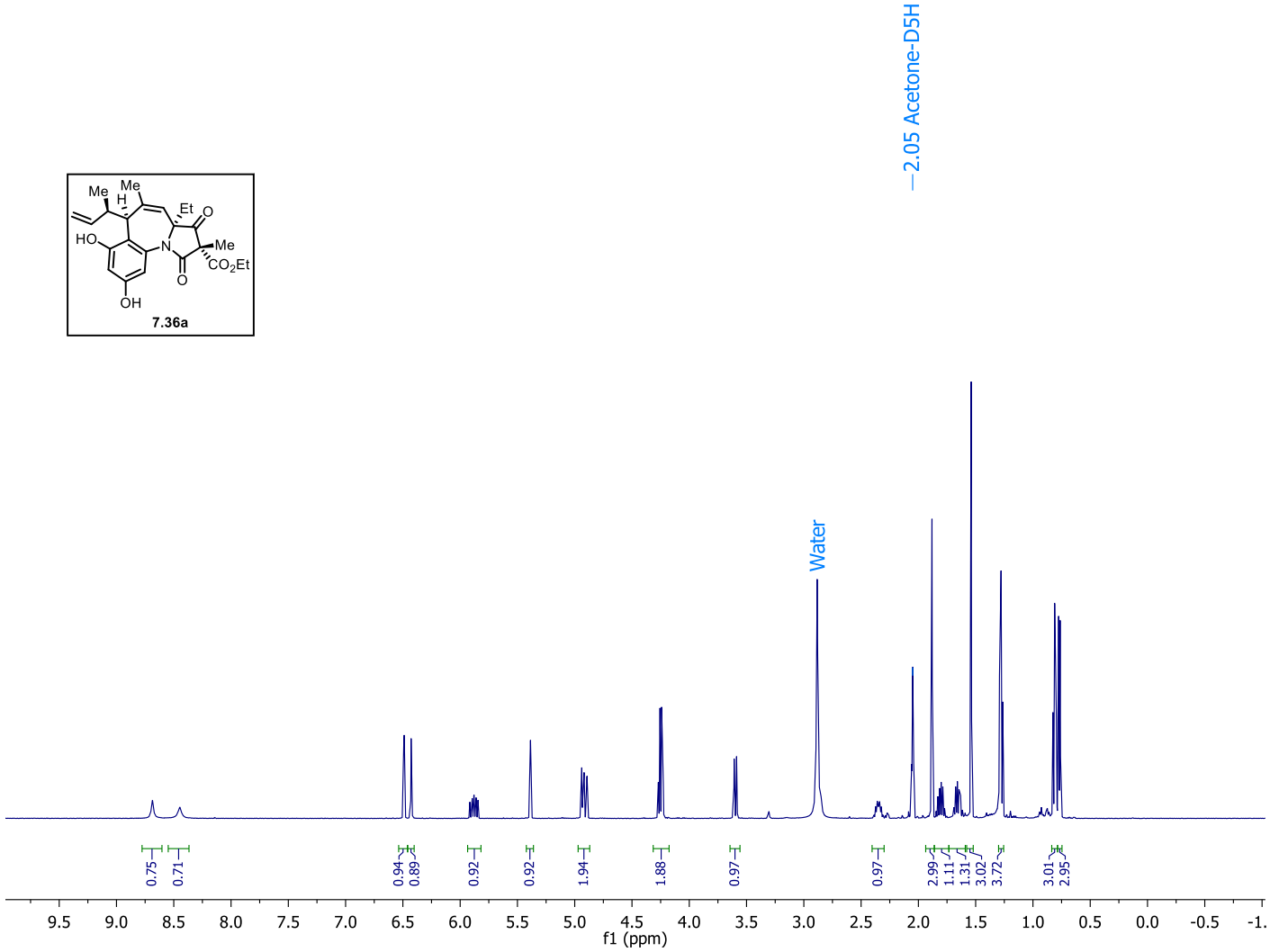


Figure E.22. ^{1}H NMR (500 MHz, acetone-d_6) of compound **7.36a**

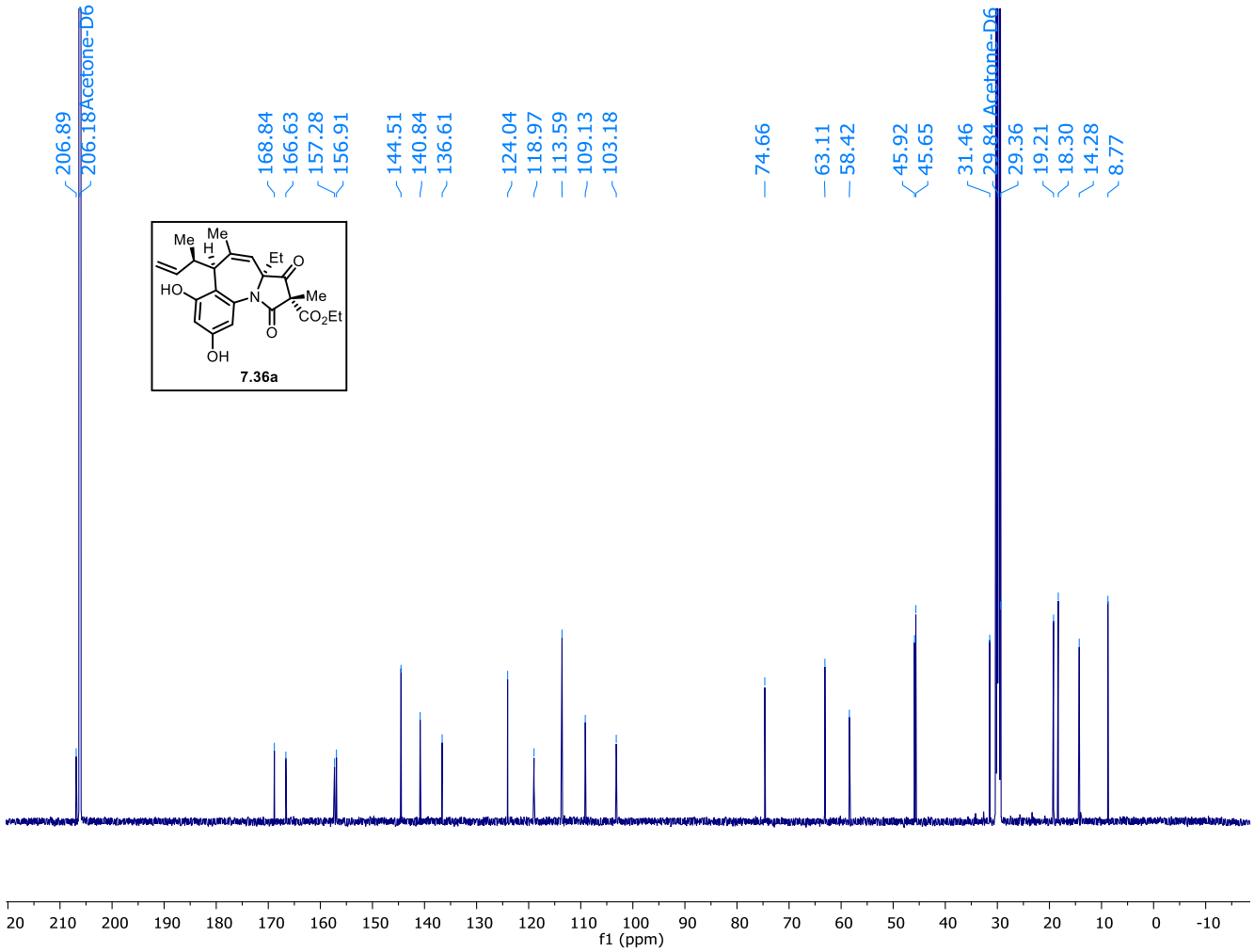


Figure E.23. ^{13}C NMR (151 MHz, acetone-d_6) of compound **7.36a**

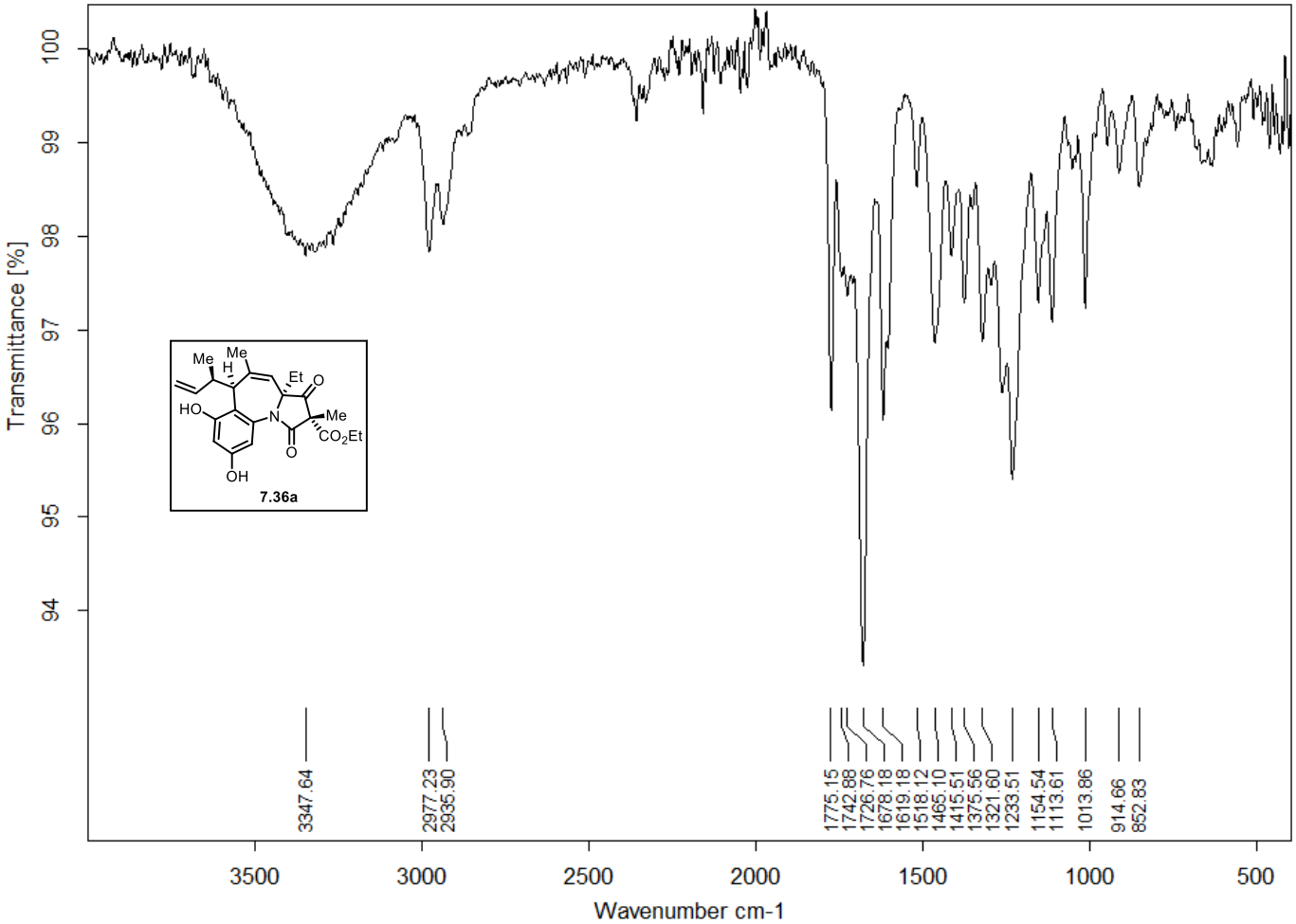


Figure E.24. FTIR spectrum (neat) of compound **7.36a**

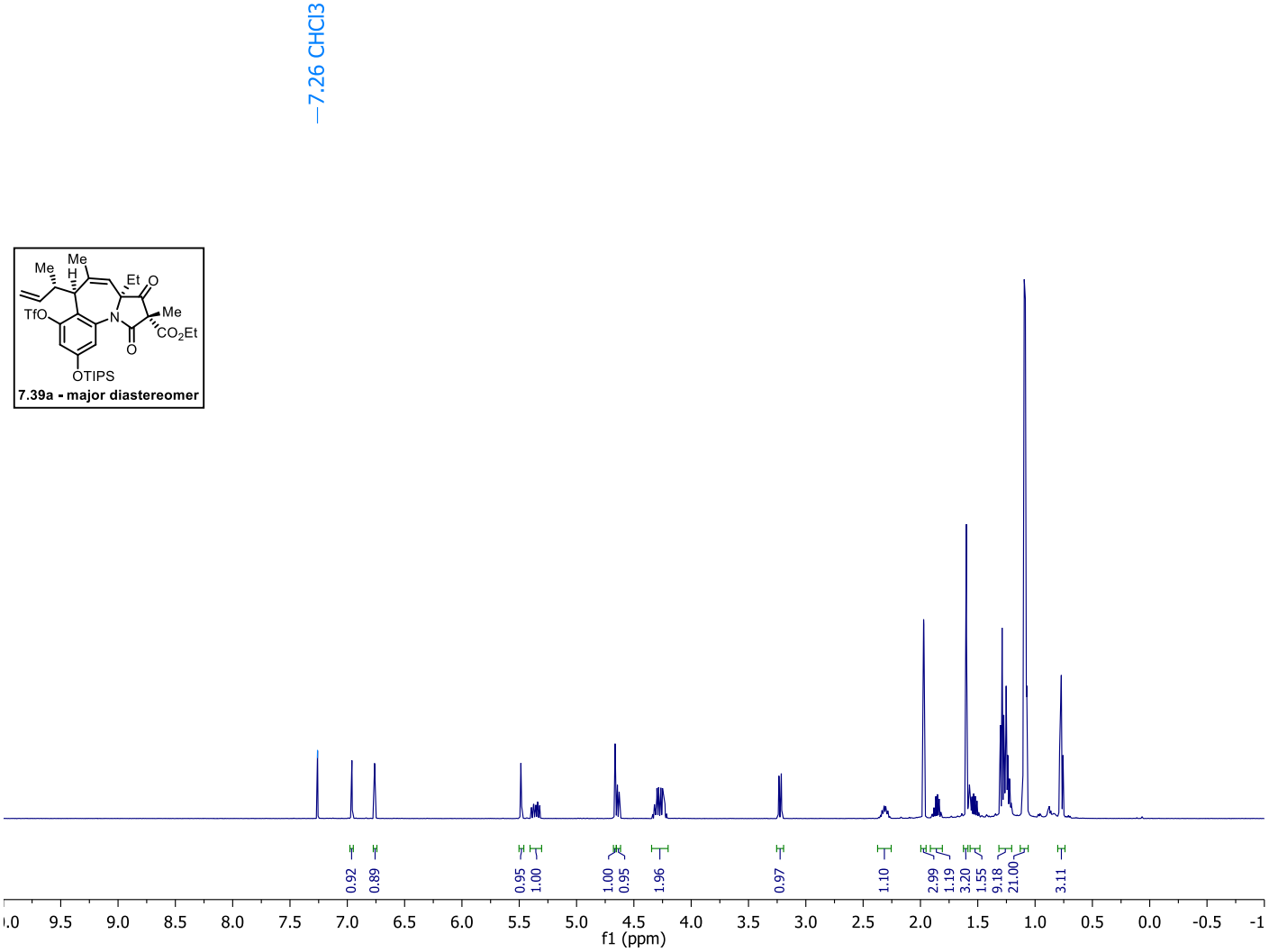


Figure E.25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.39a – major diastereomer**

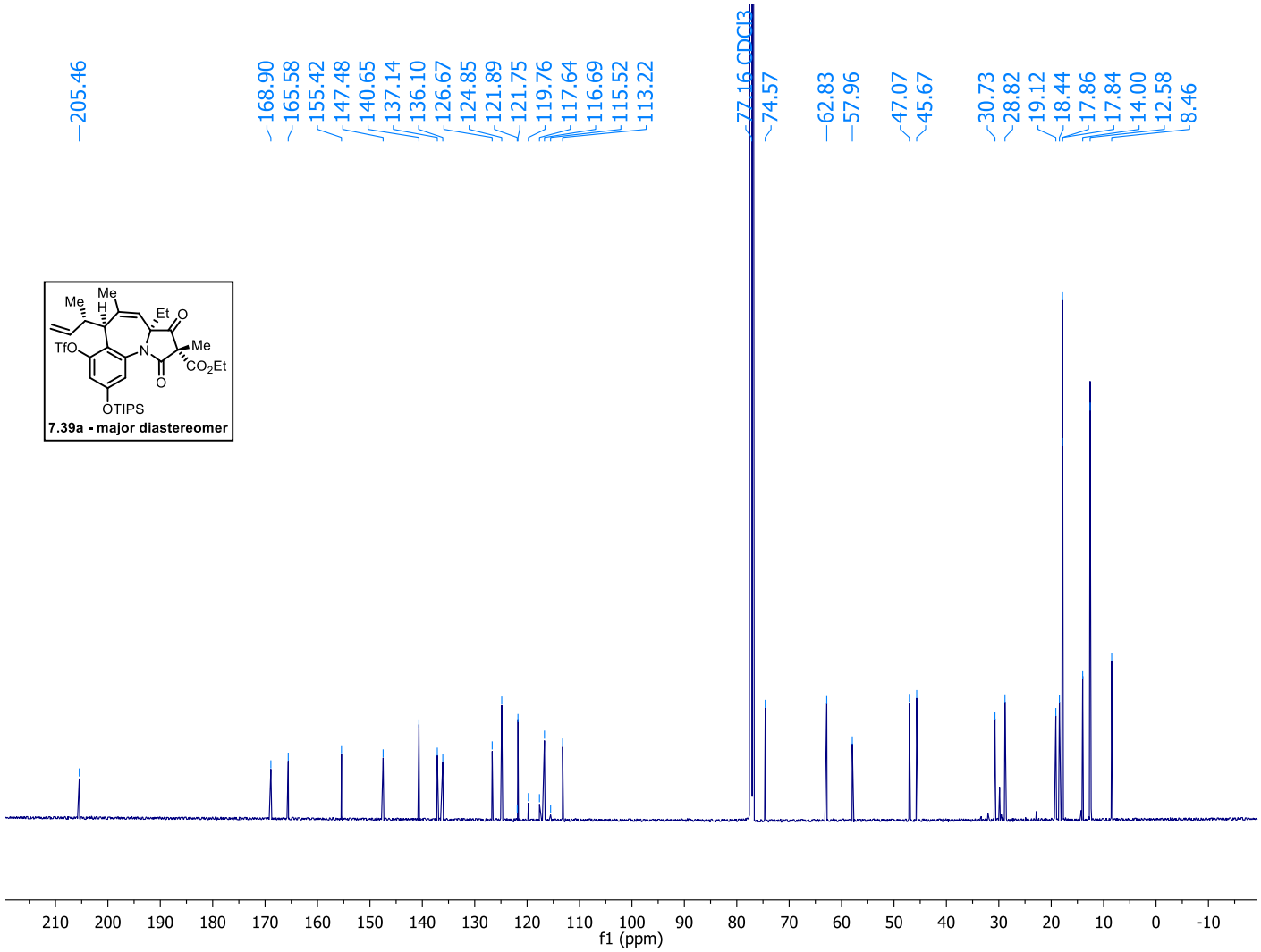


Figure E.26. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.39a – major diastereomer**

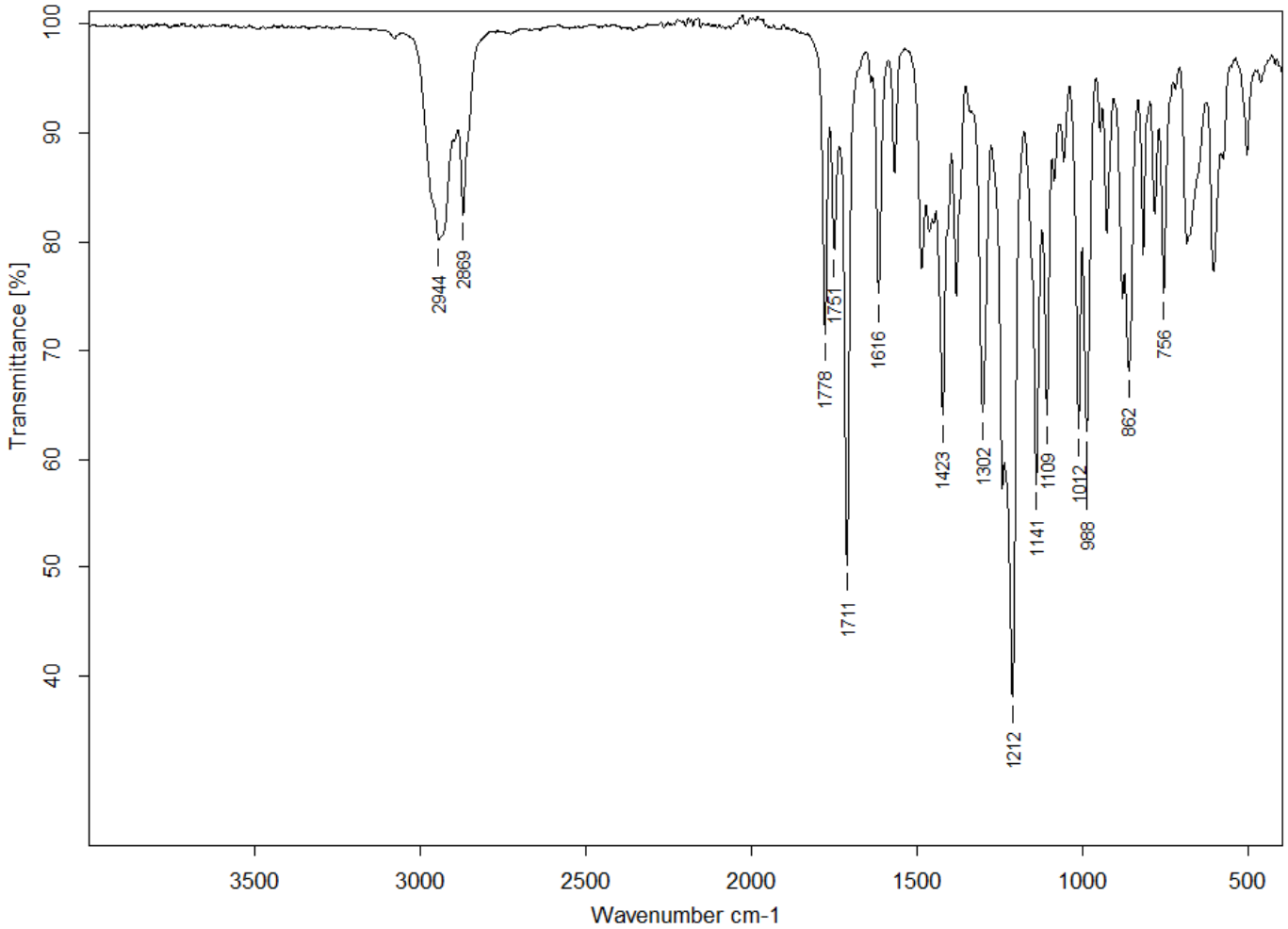


Figure E.27. FTIR spectrum (neat) of compound **7.39a – major diastereomer**

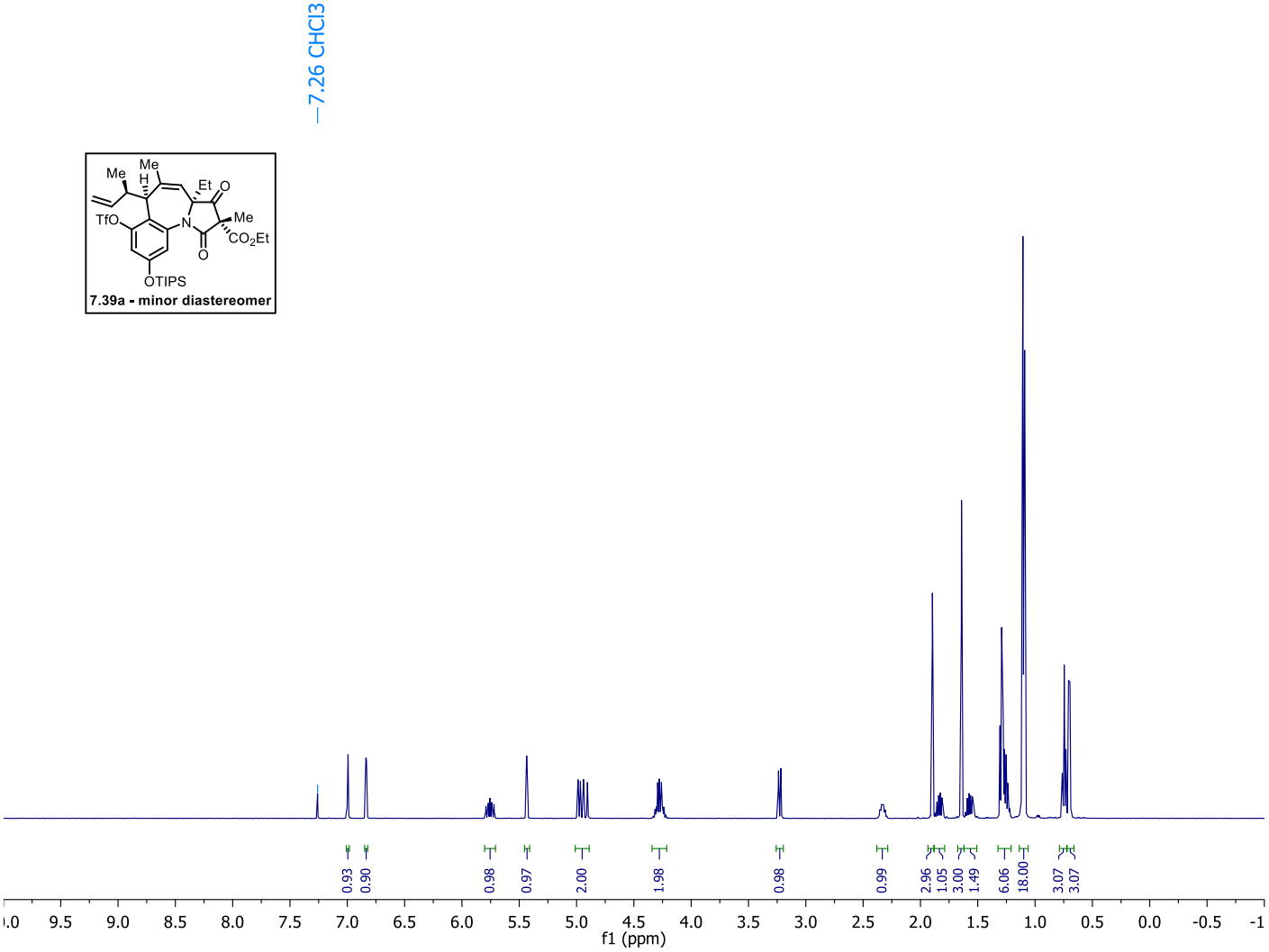


Figure E.28. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.39a – minor diastereomer**

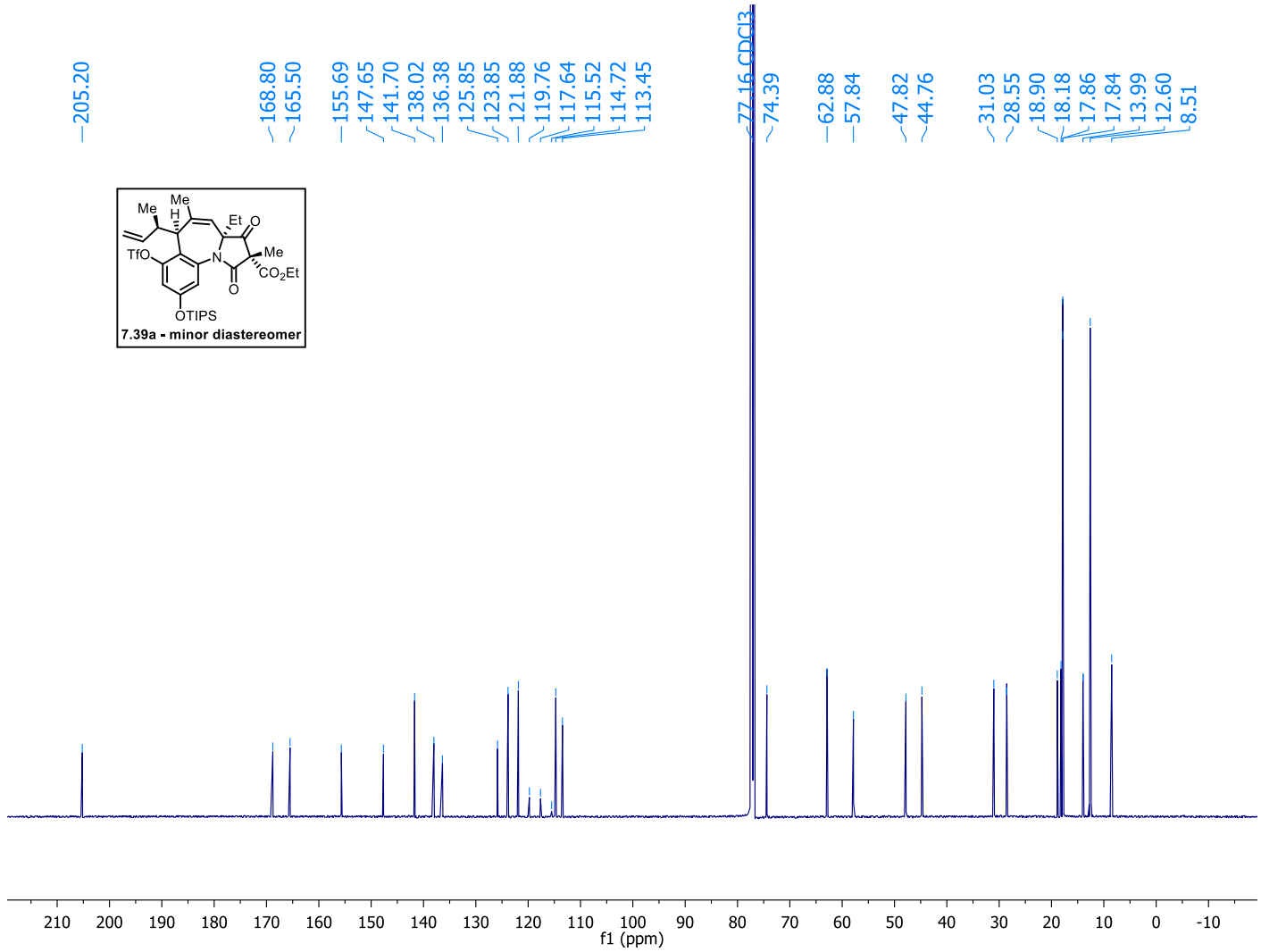


Figure E.29. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.39a – minor diastereomer**

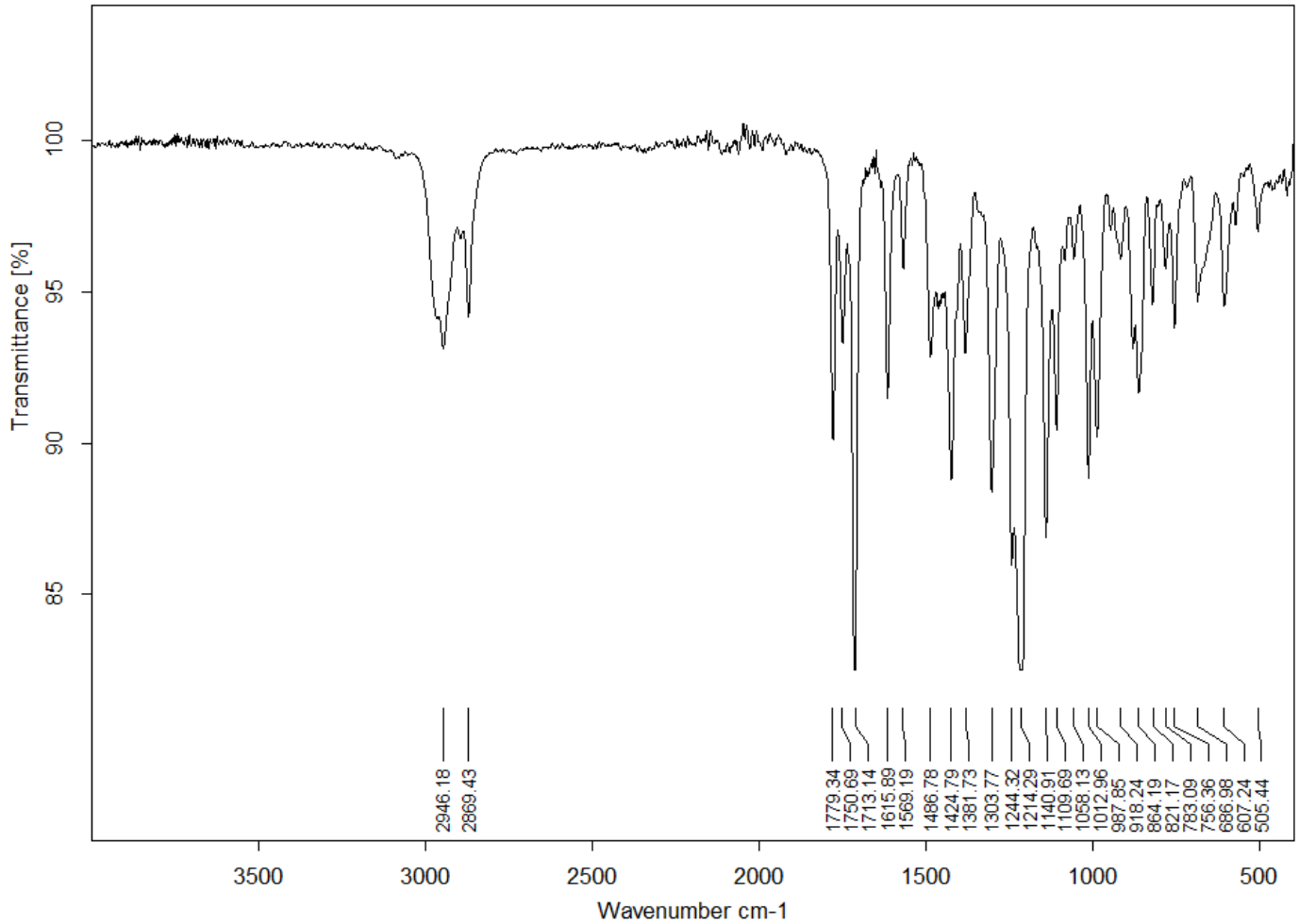


Figure E.30. FTIR spectrum (neat) of compound **7.39a – minor diastereomer**

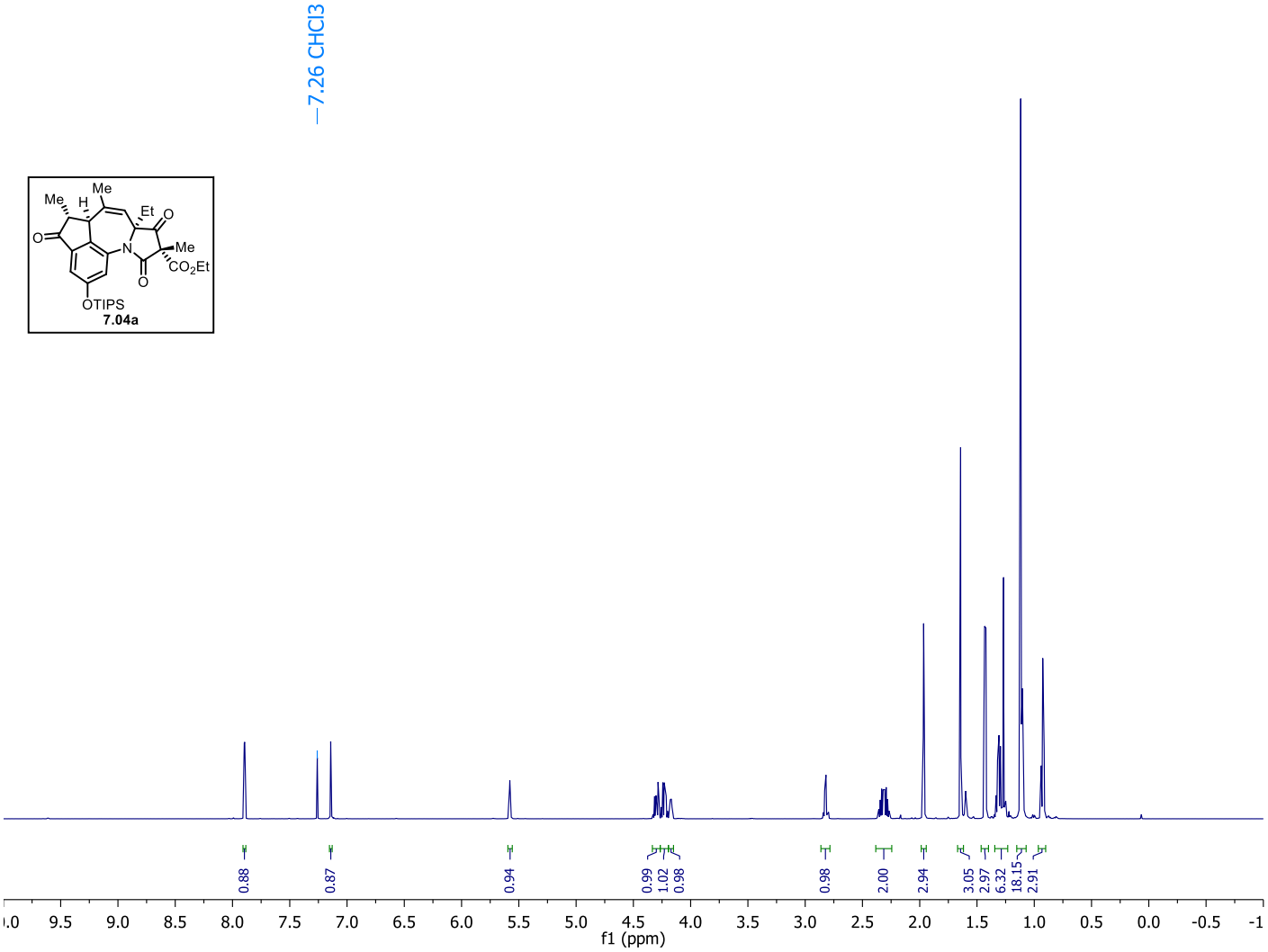


Figure E.31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.04a**

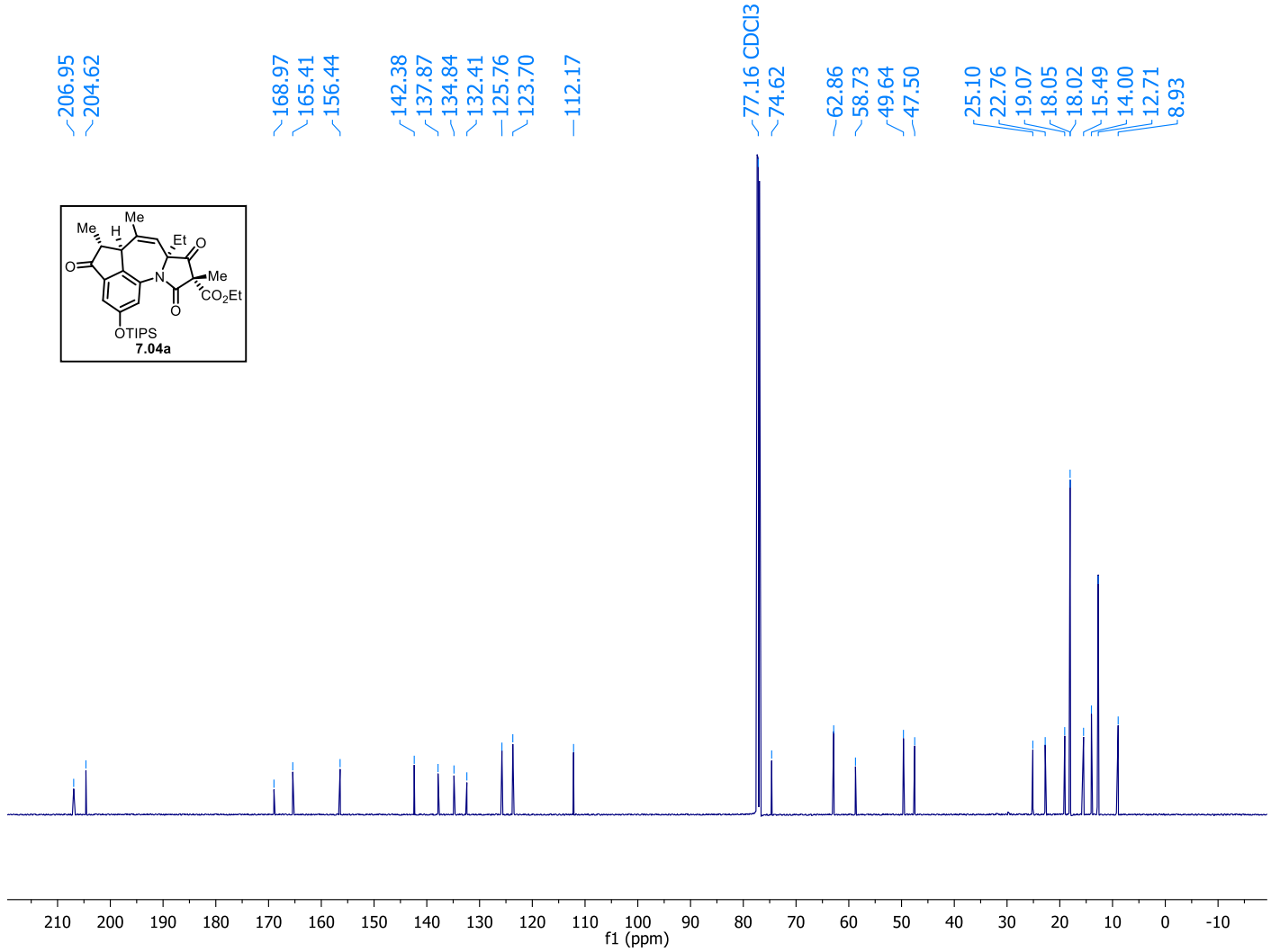


Figure E.32. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.04a**

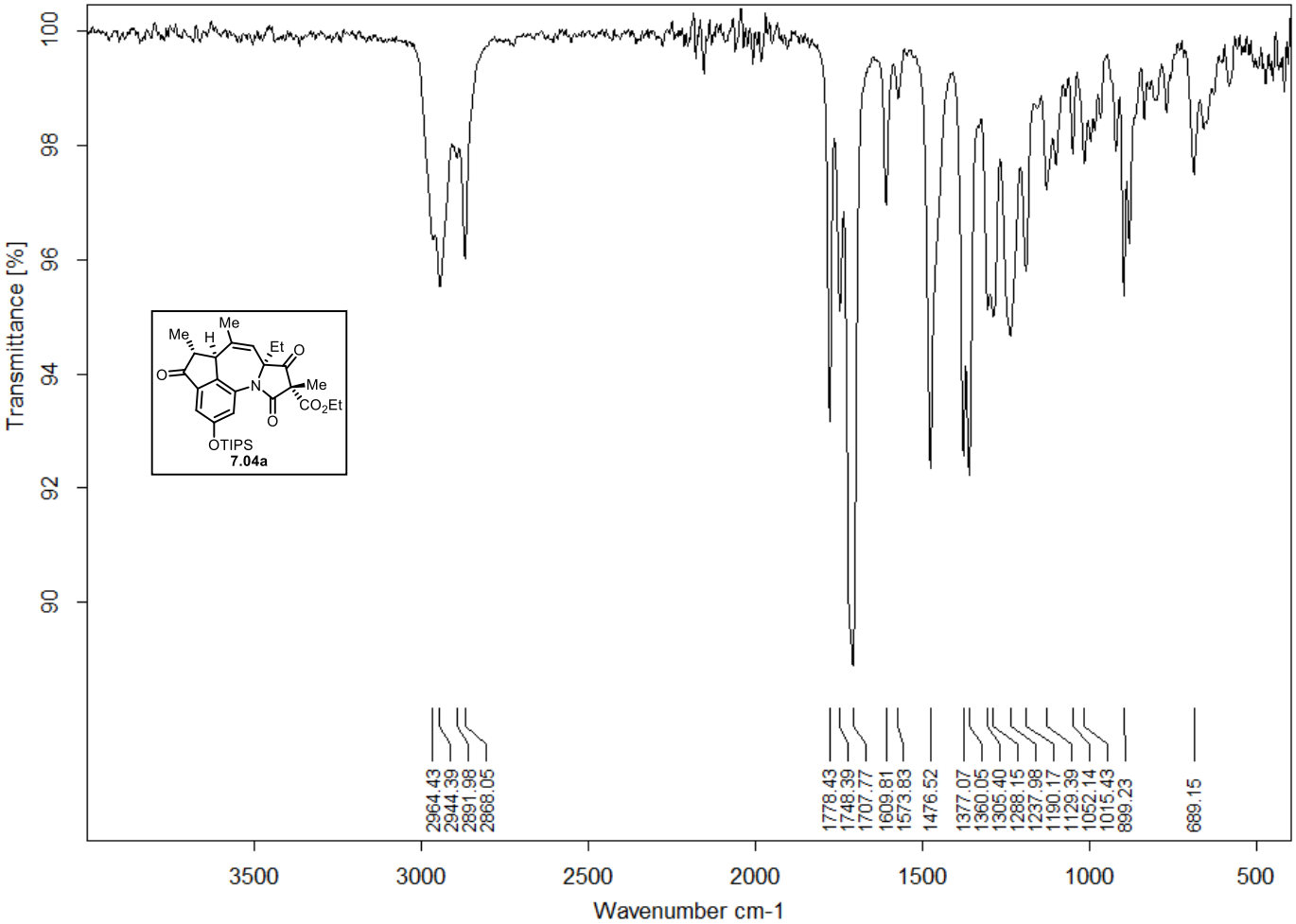


Figure E.33. FTIR spectrum (neat) of compound **7.04a**

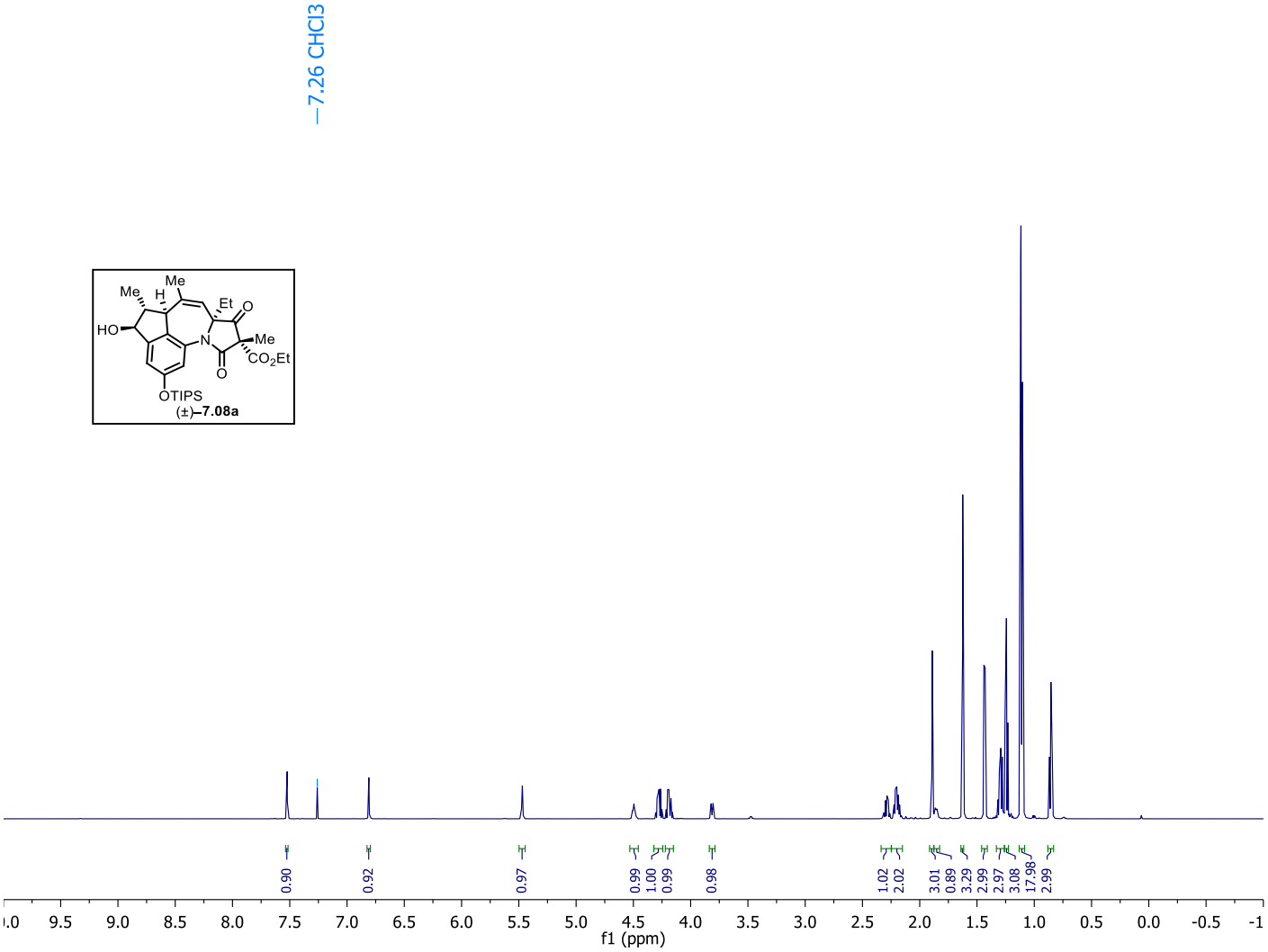


Figure E.34. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **(±)–7.08a**

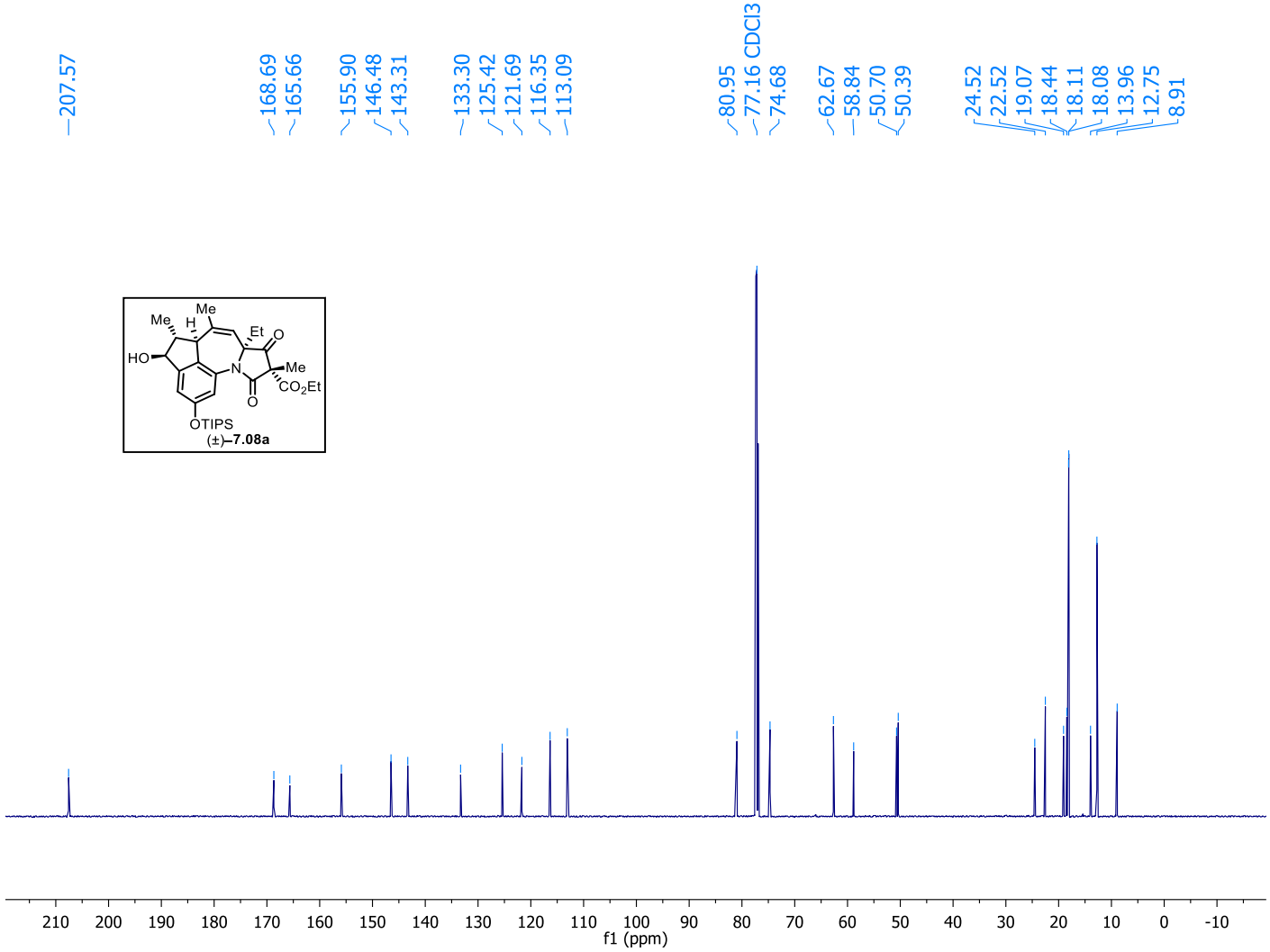


Figure E.35. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **(±)–7.08a**

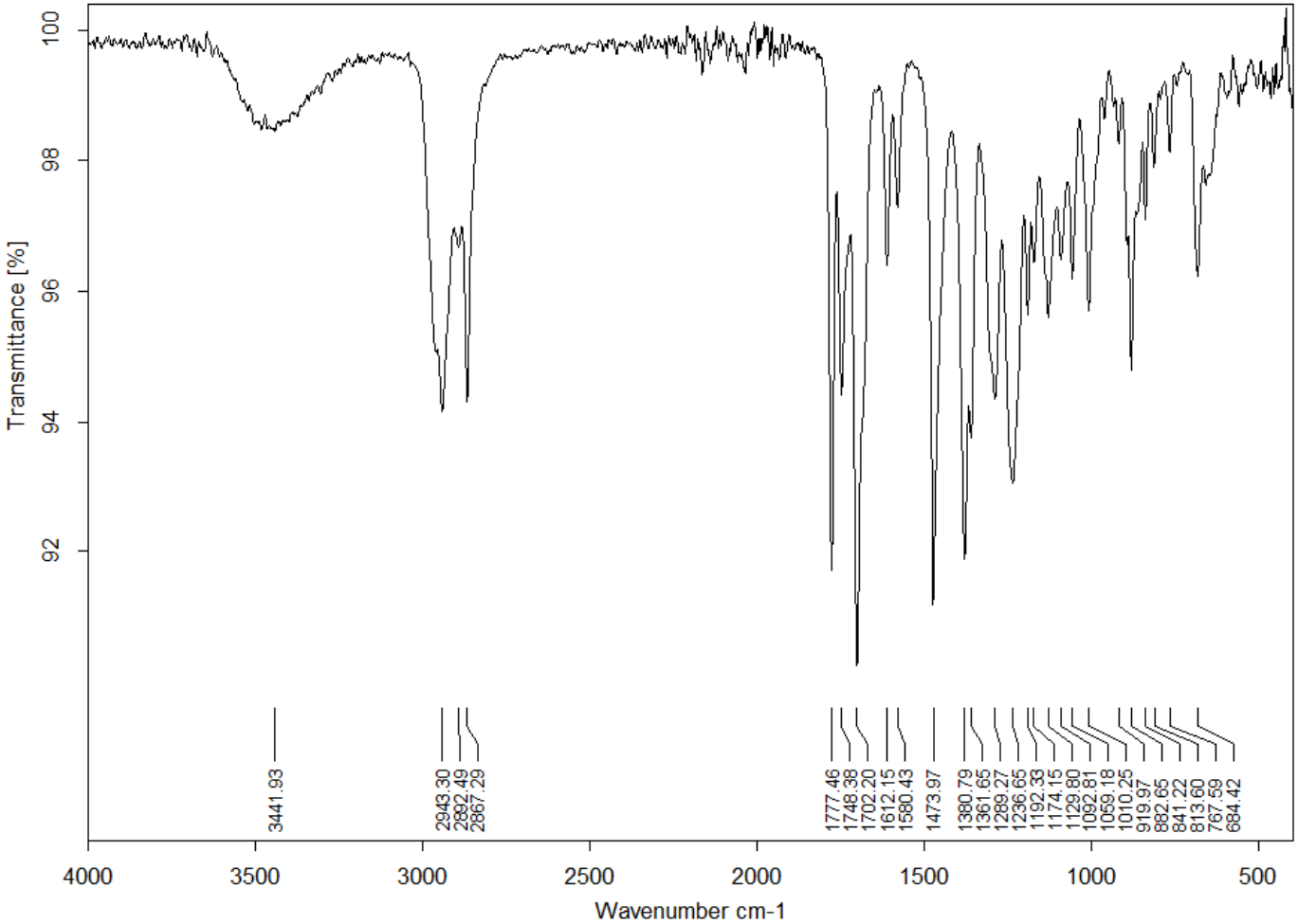


Figure E.36. FTIR spectrum (neat) of compound **(±)–7.08a**

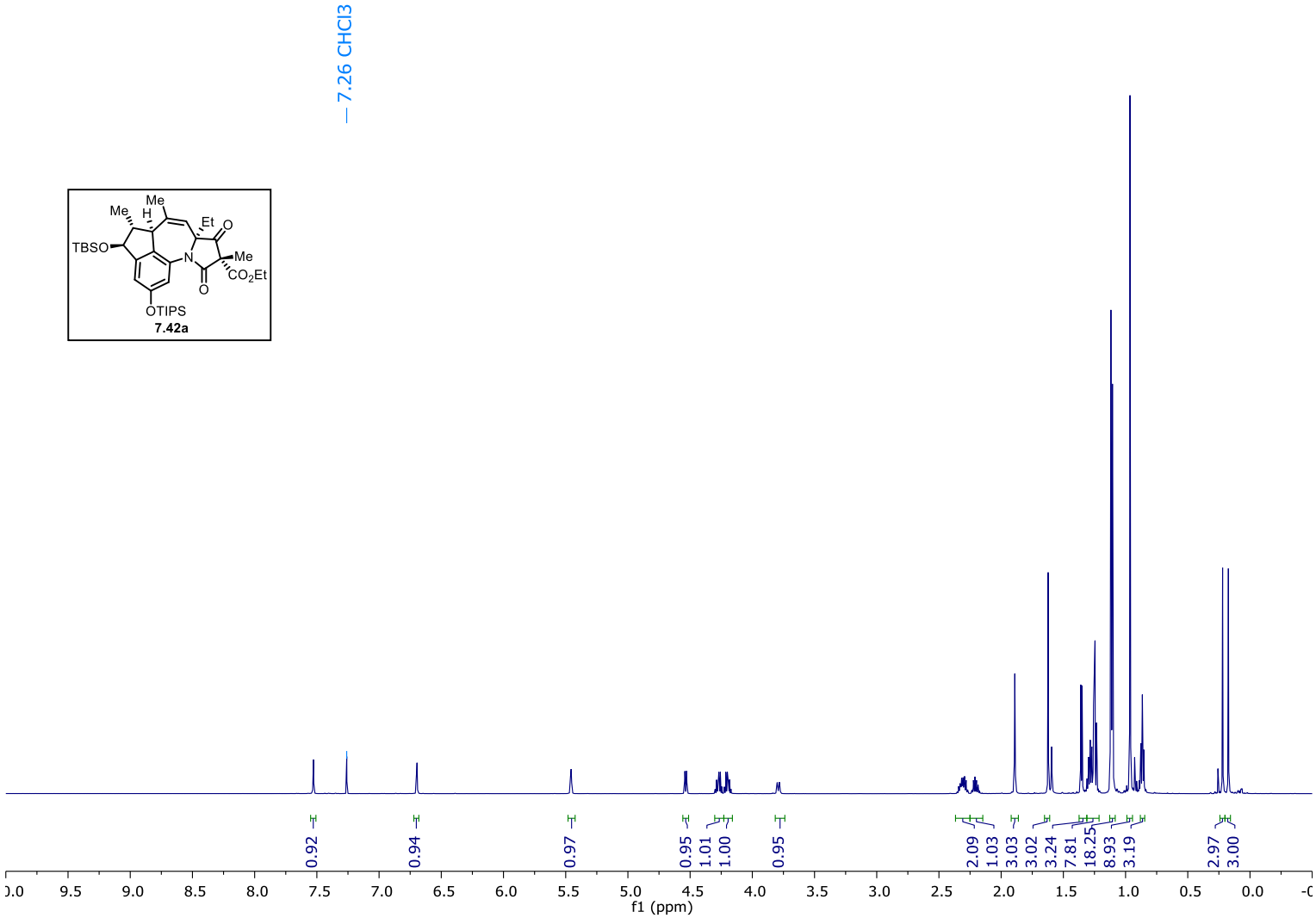


Figure E.37. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.42a**

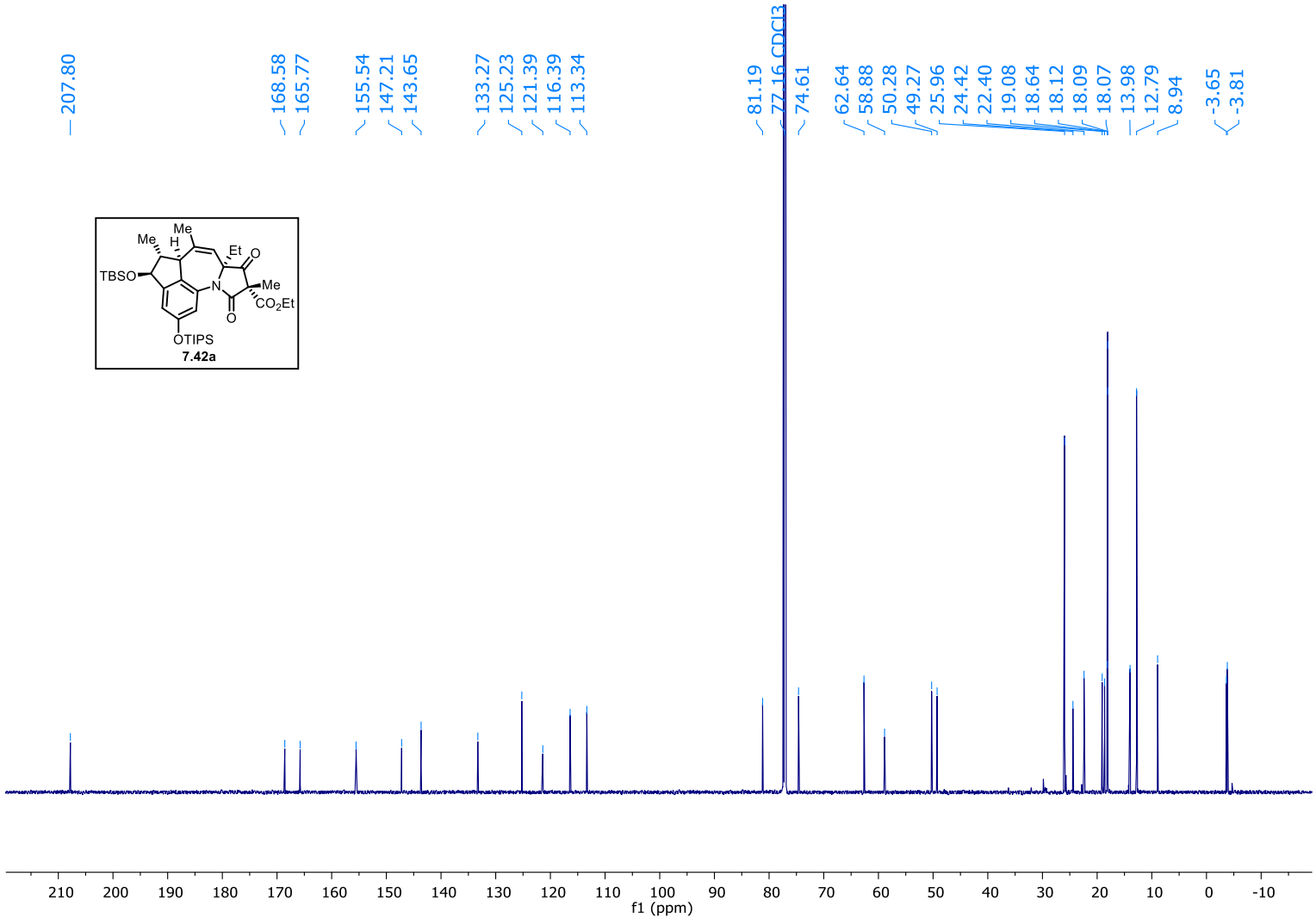


Figure E.38. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.42a**

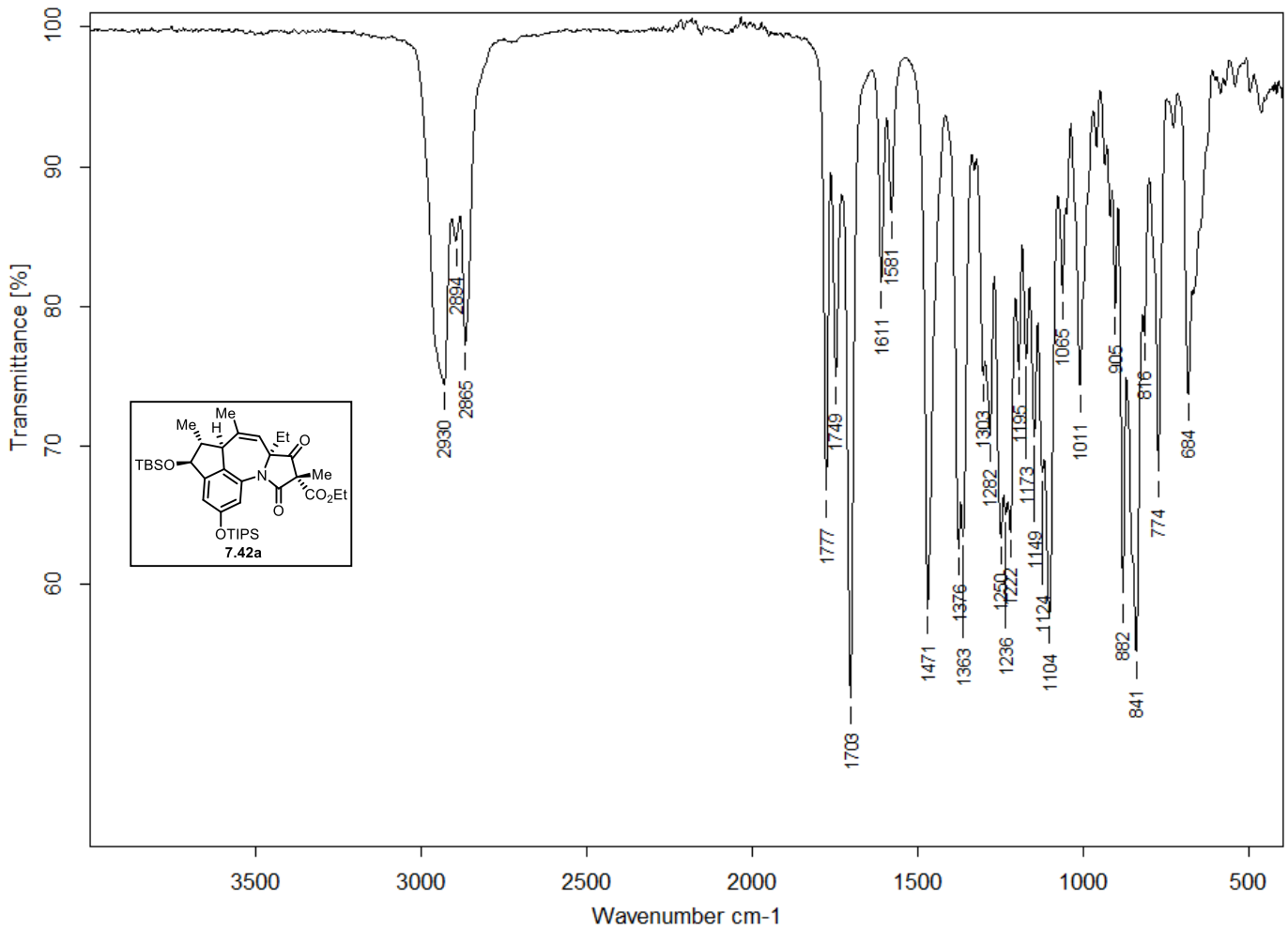


Figure E.39. FTIR spectrum (neat) of compound **7.42a**

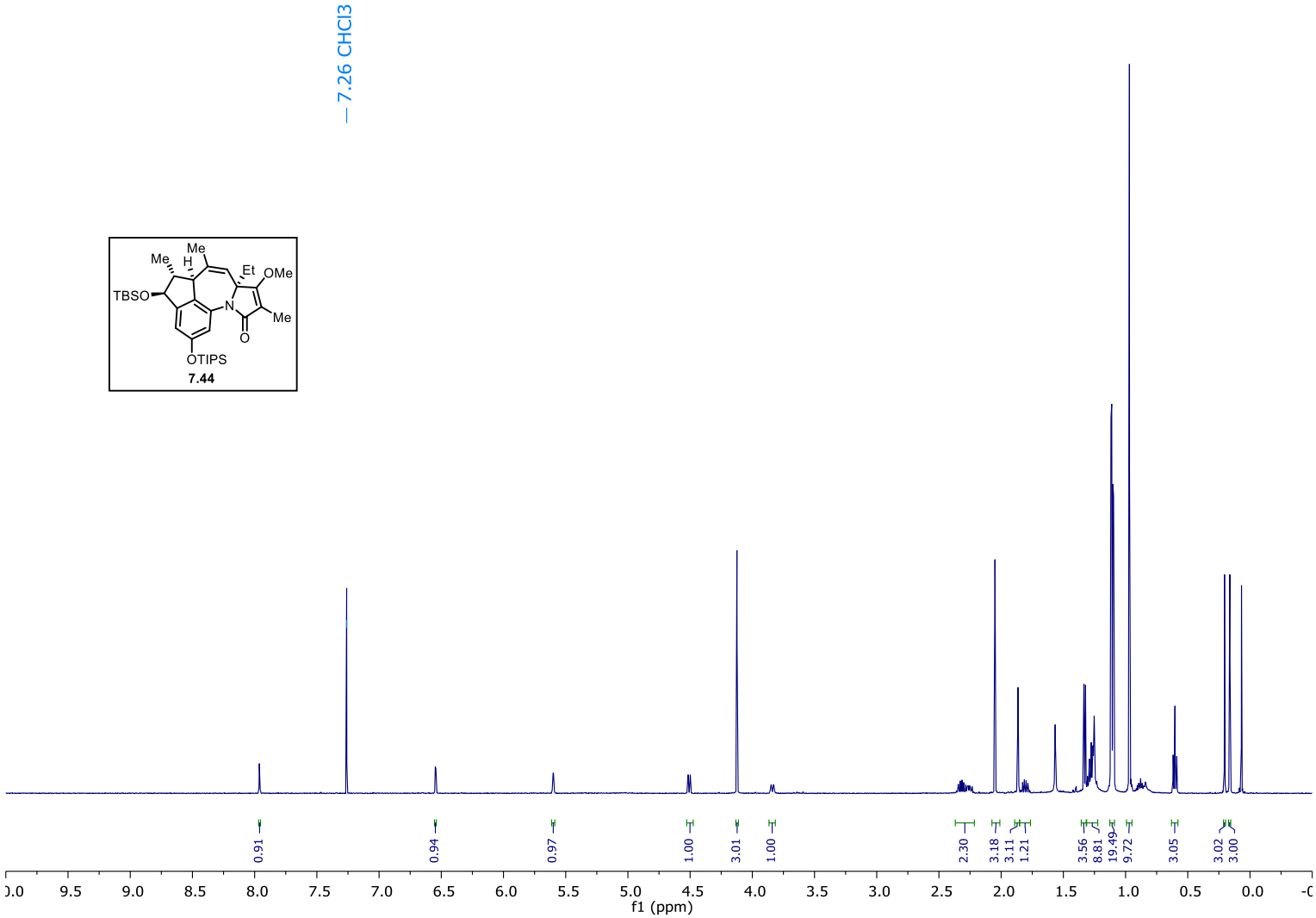


Figure E.40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.44**

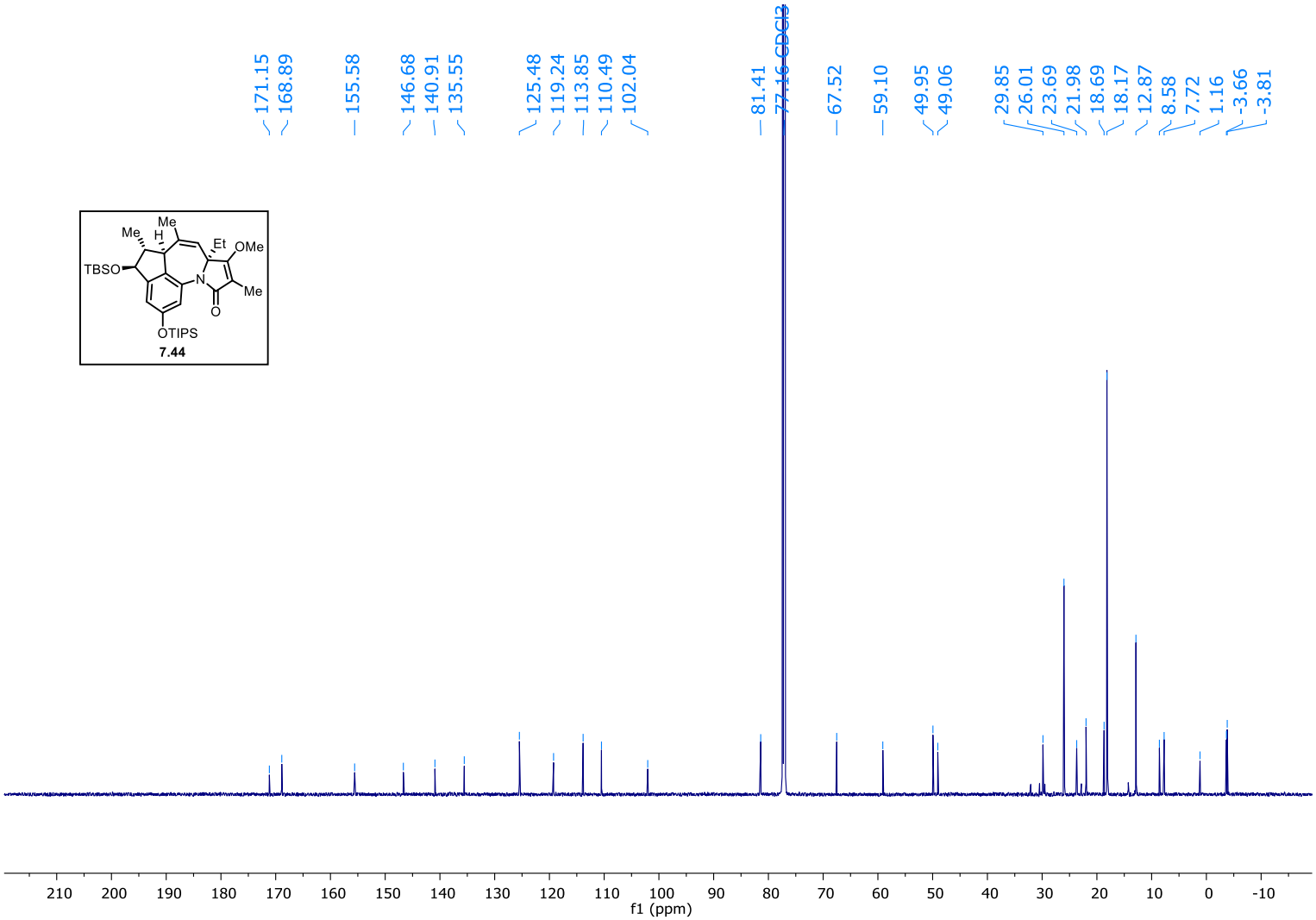


Figure E.41. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.44**

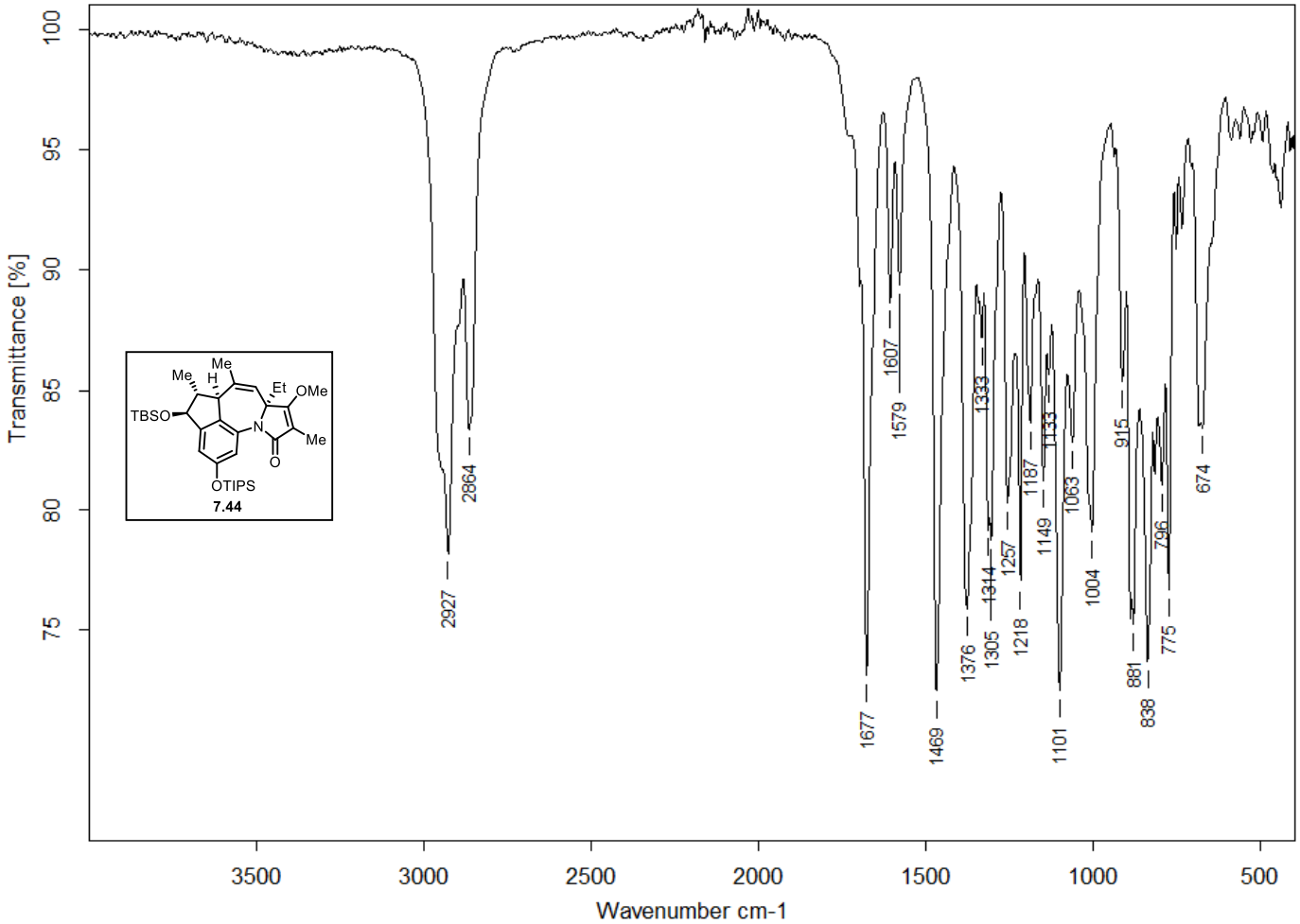


Figure E.42. FTIR spectrum (neat) of compound **7.44**

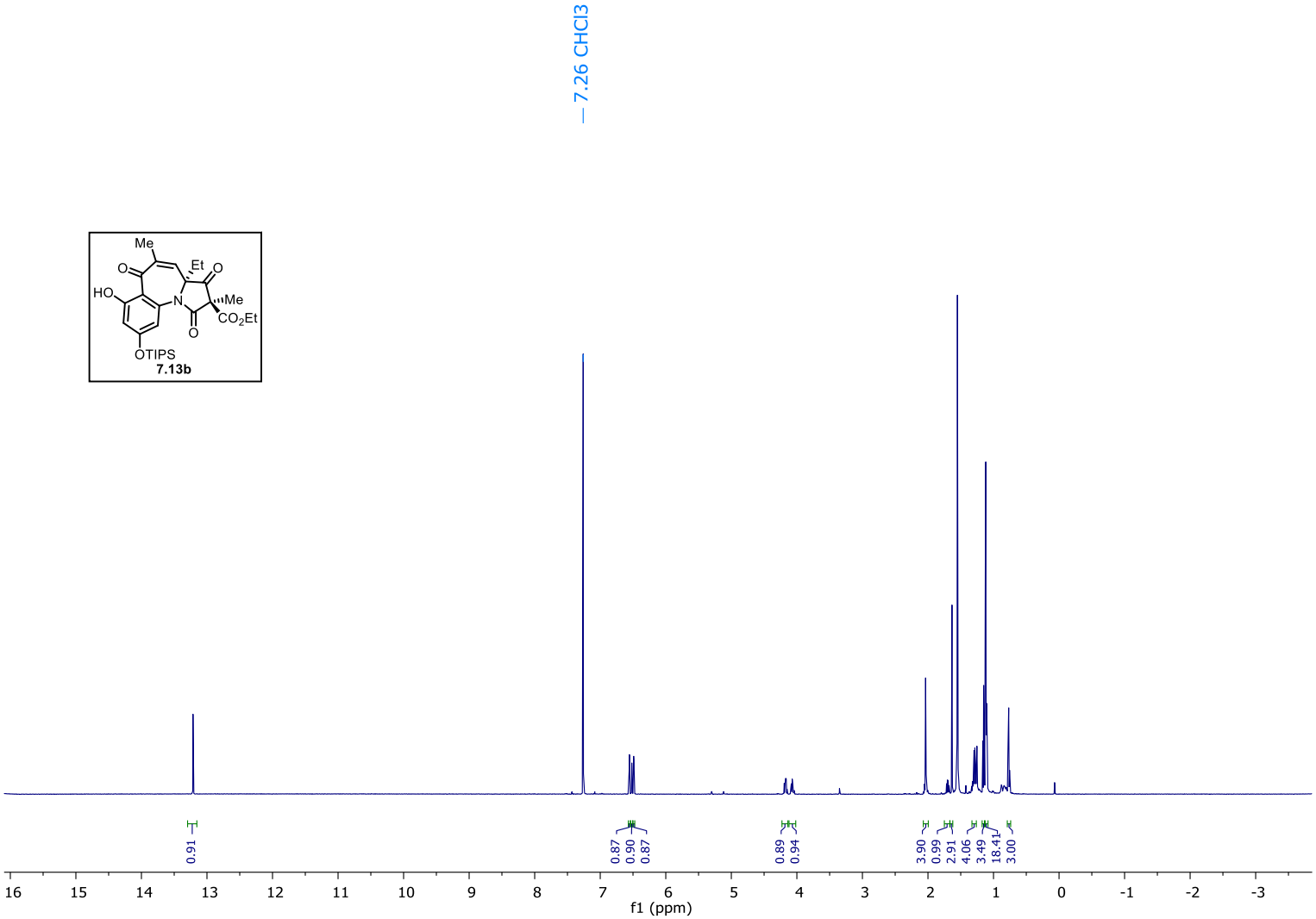


Figure E.43. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.13b**

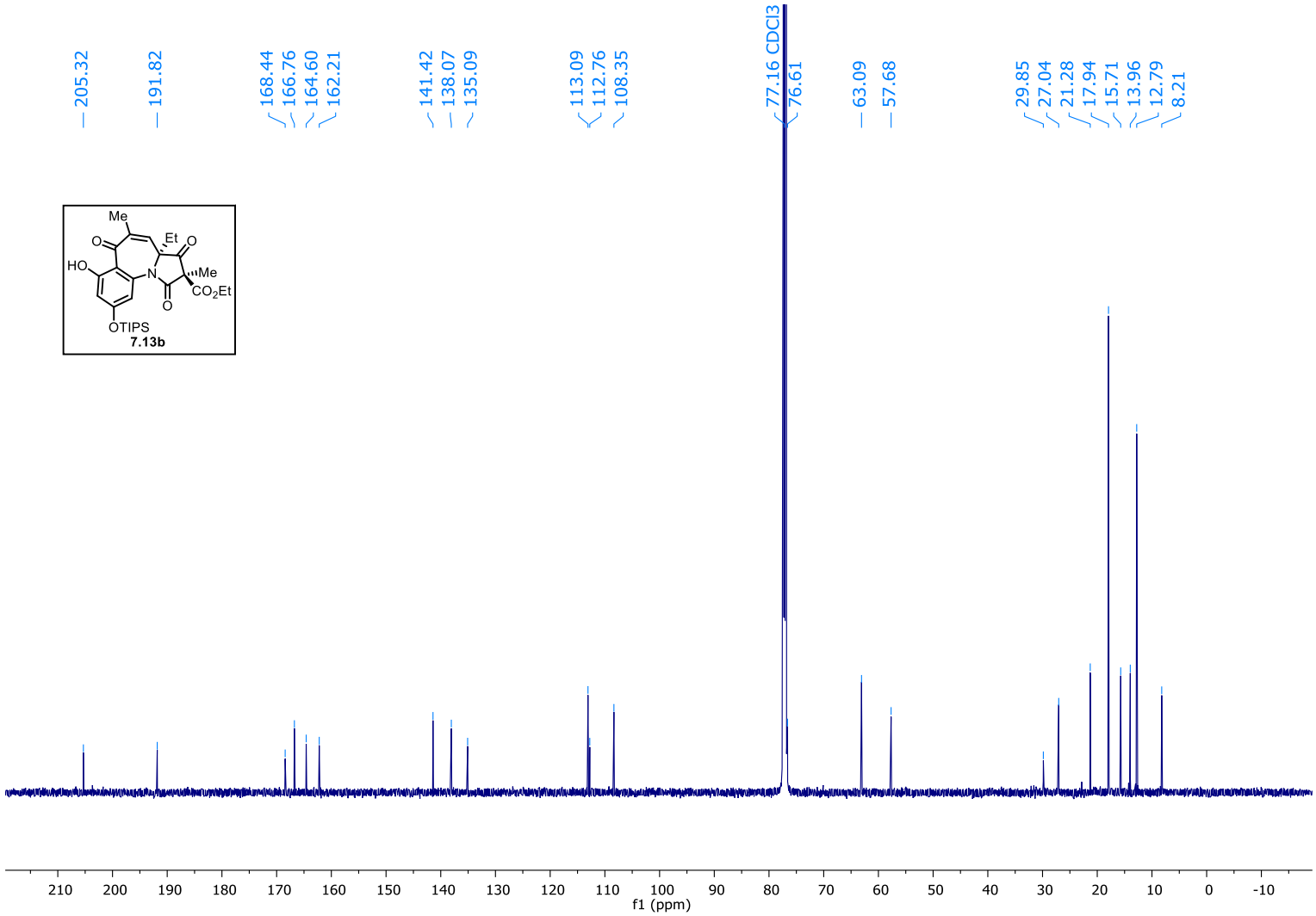


Figure E.44. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.13b**

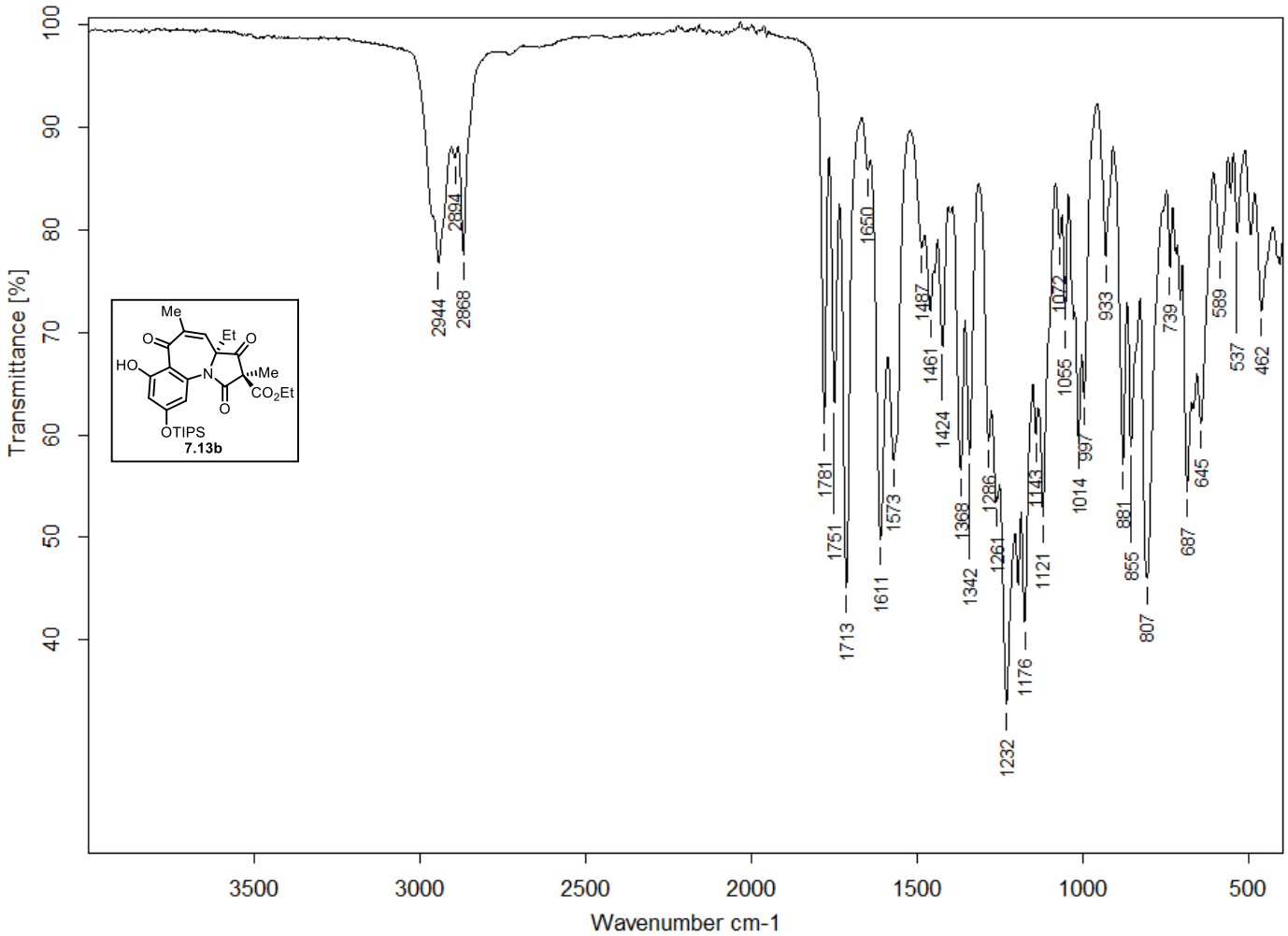


Figure E.45. FTIR spectrum (neat) of compound **7.13b**

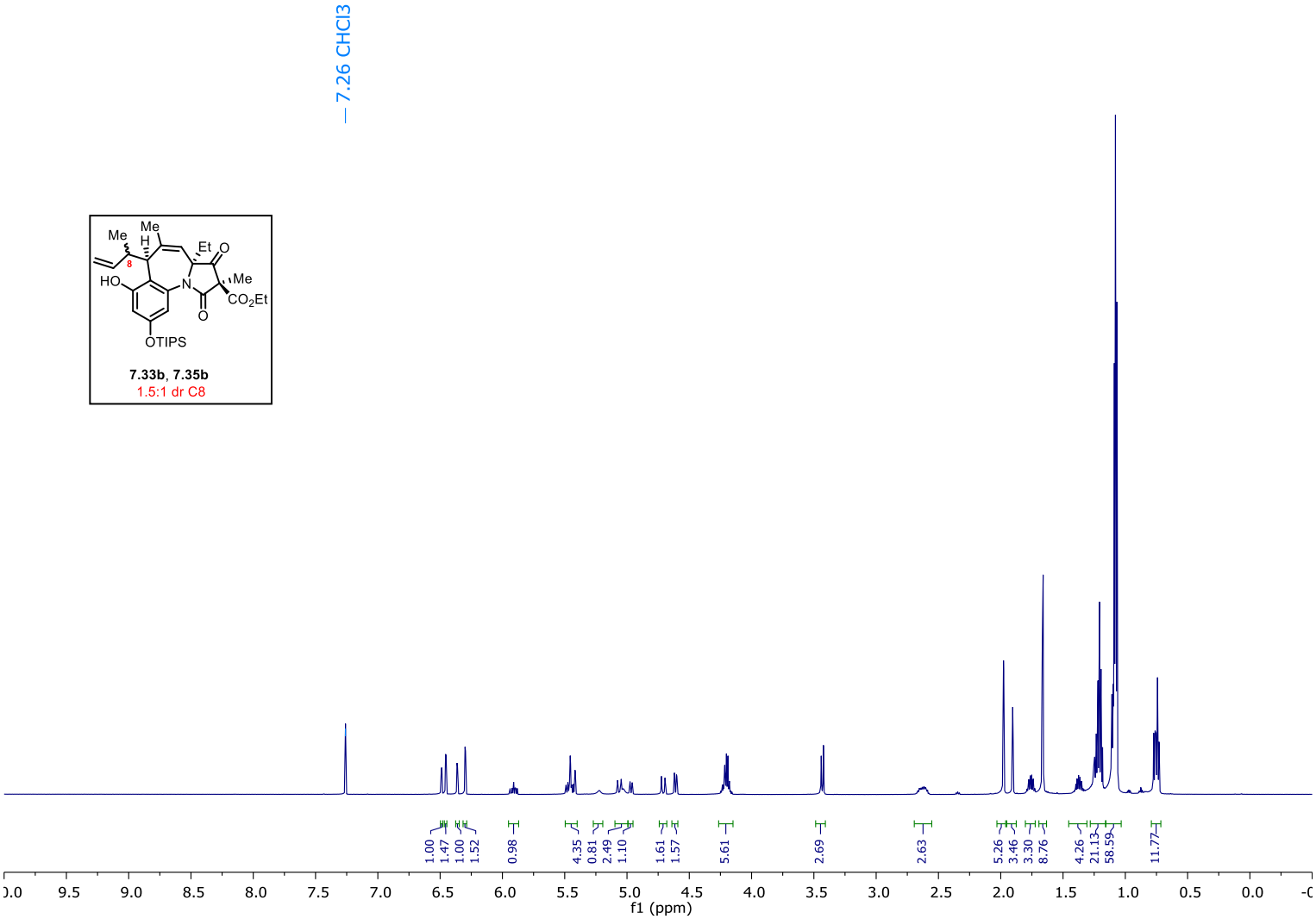


Figure E.46. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.33b**, **7.35b**

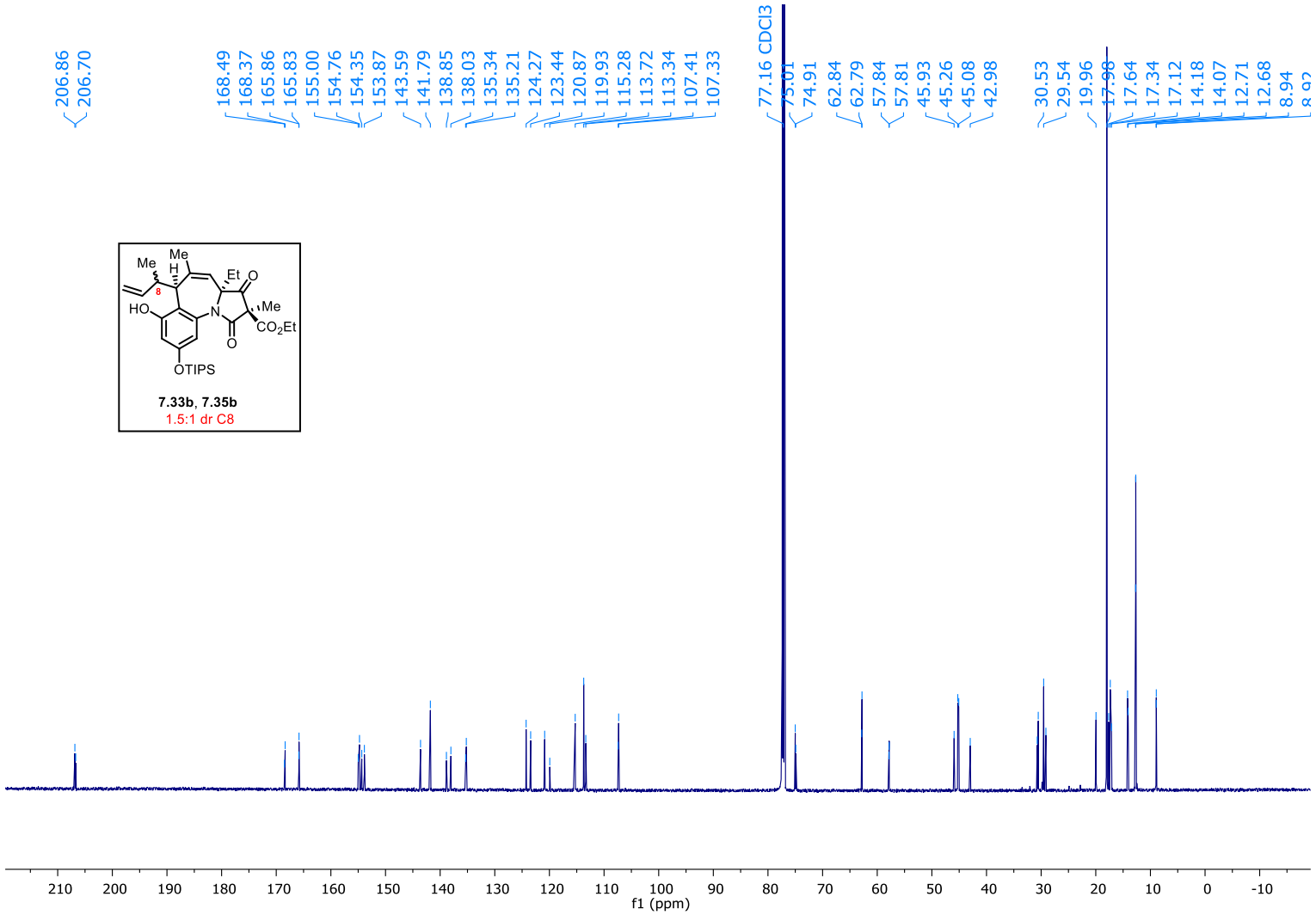


Figure E.47. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.33b**, **7.35b**

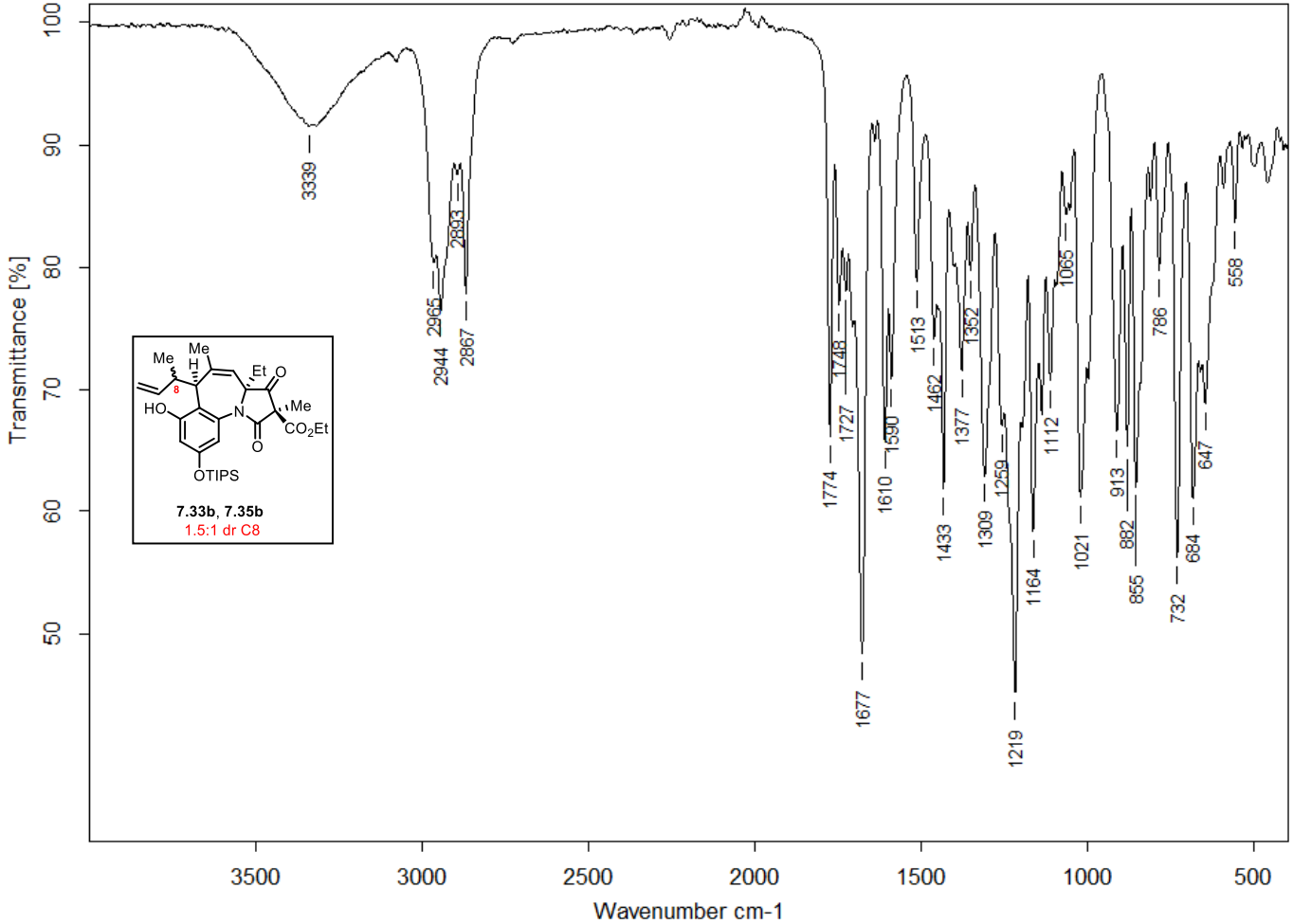


Figure E.48. FTIR spectrum (neat) of compound **7.33b**, **7.35b**

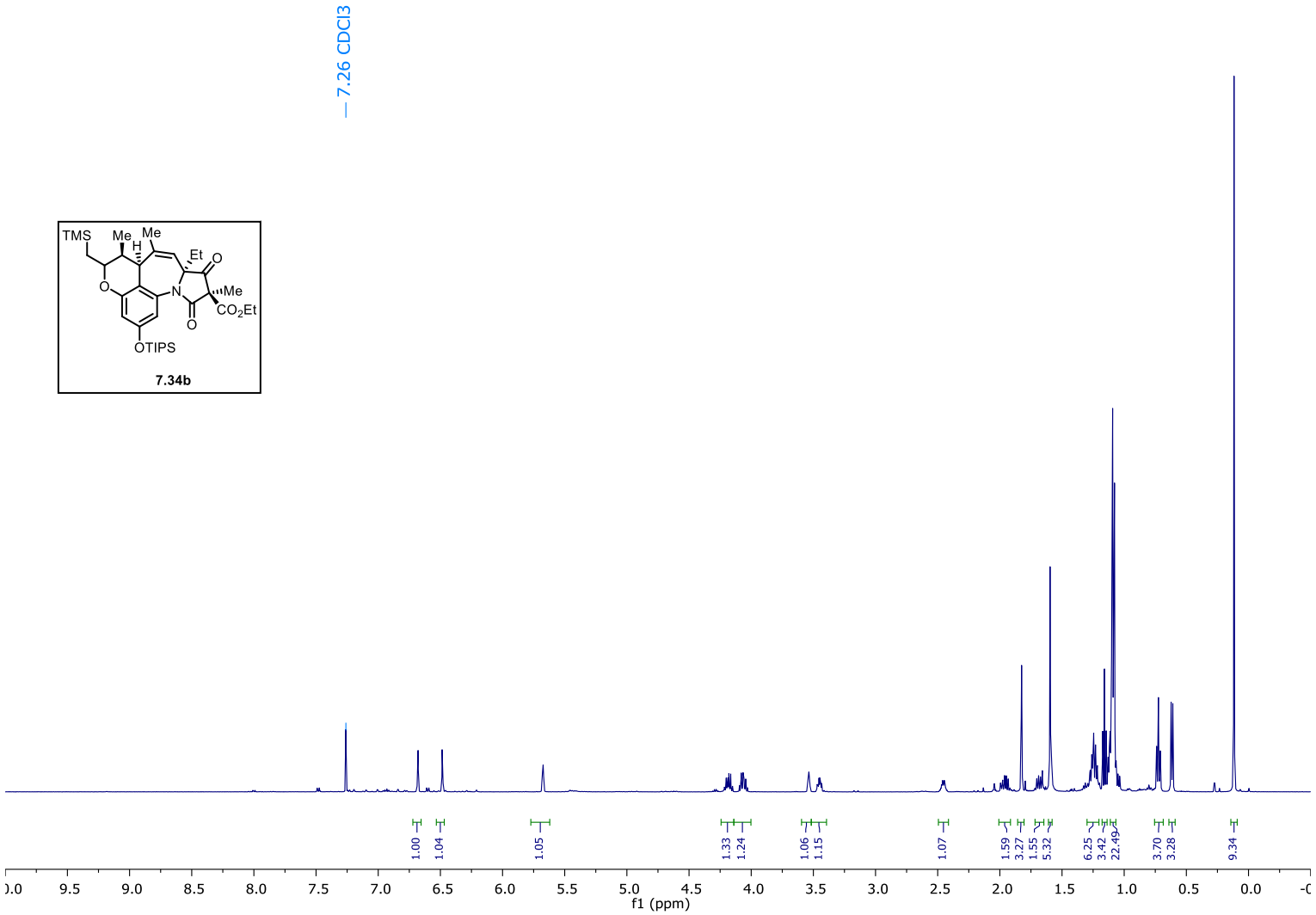


Figure E.49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.34b** (tentative assignment)

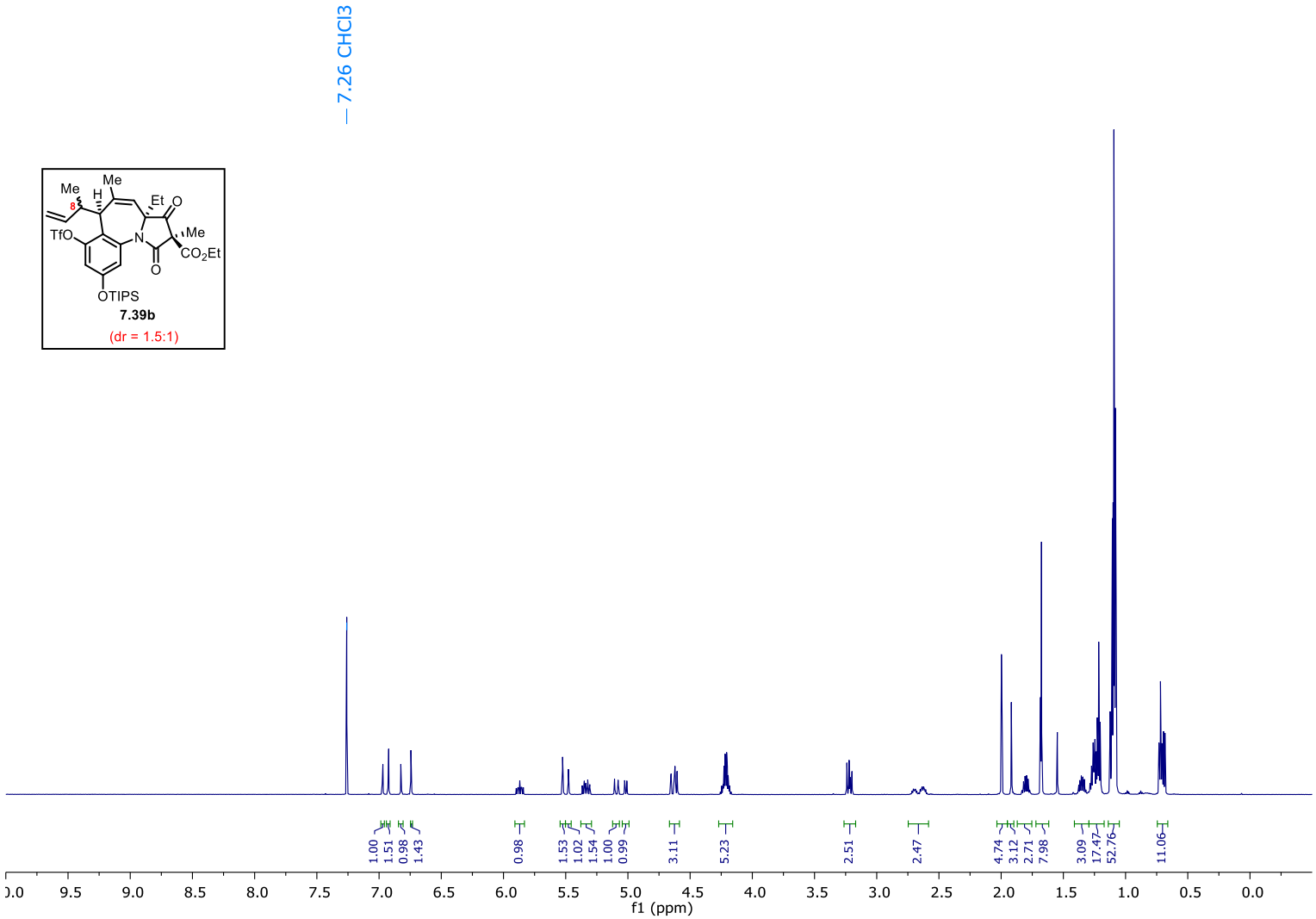


Figure E.50. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.39b**

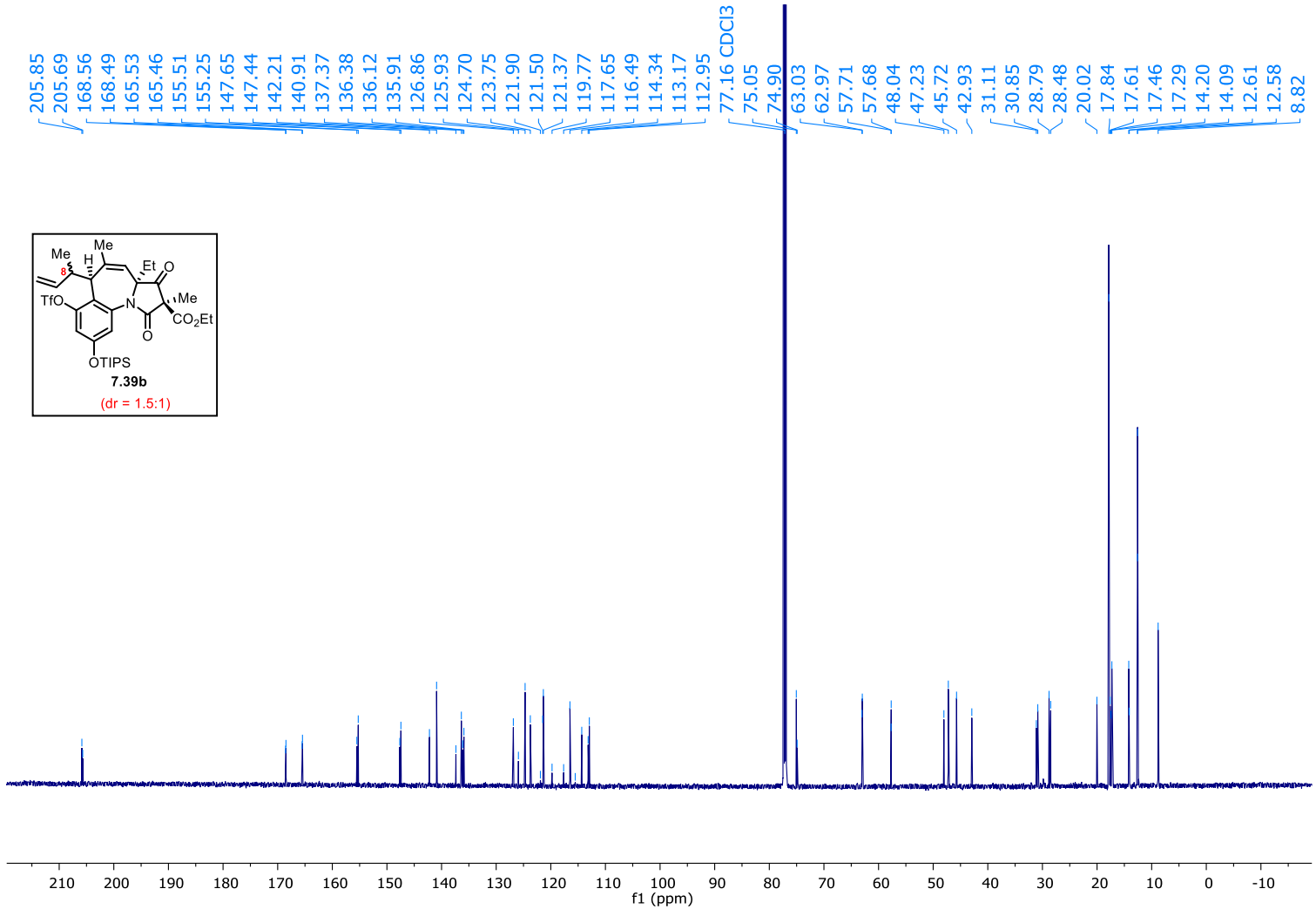


Figure E.51. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.39b**

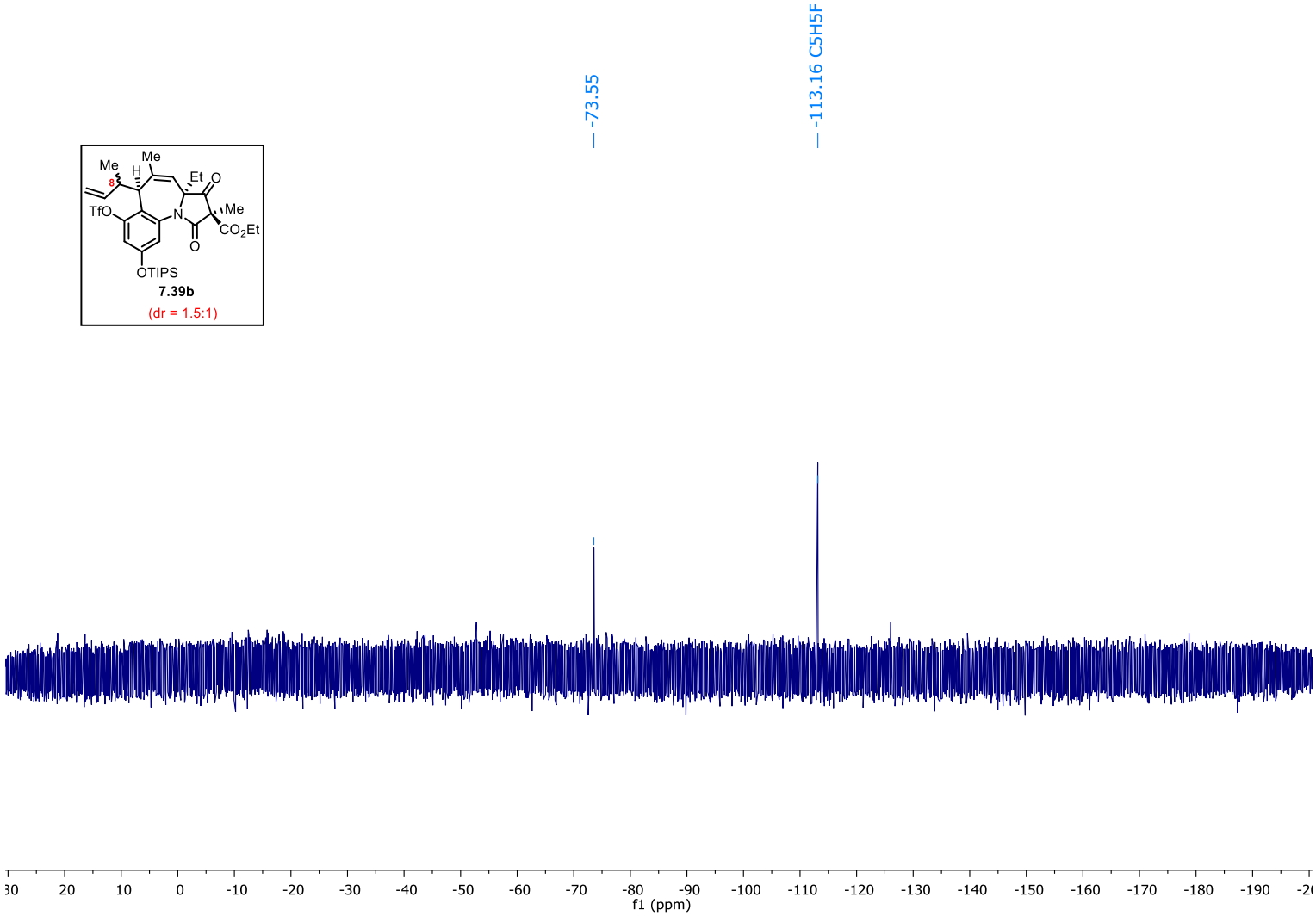


Figure E.52. ^{19}F NMR (470 MHz, $CDCl_3$) of compound **7.39b**

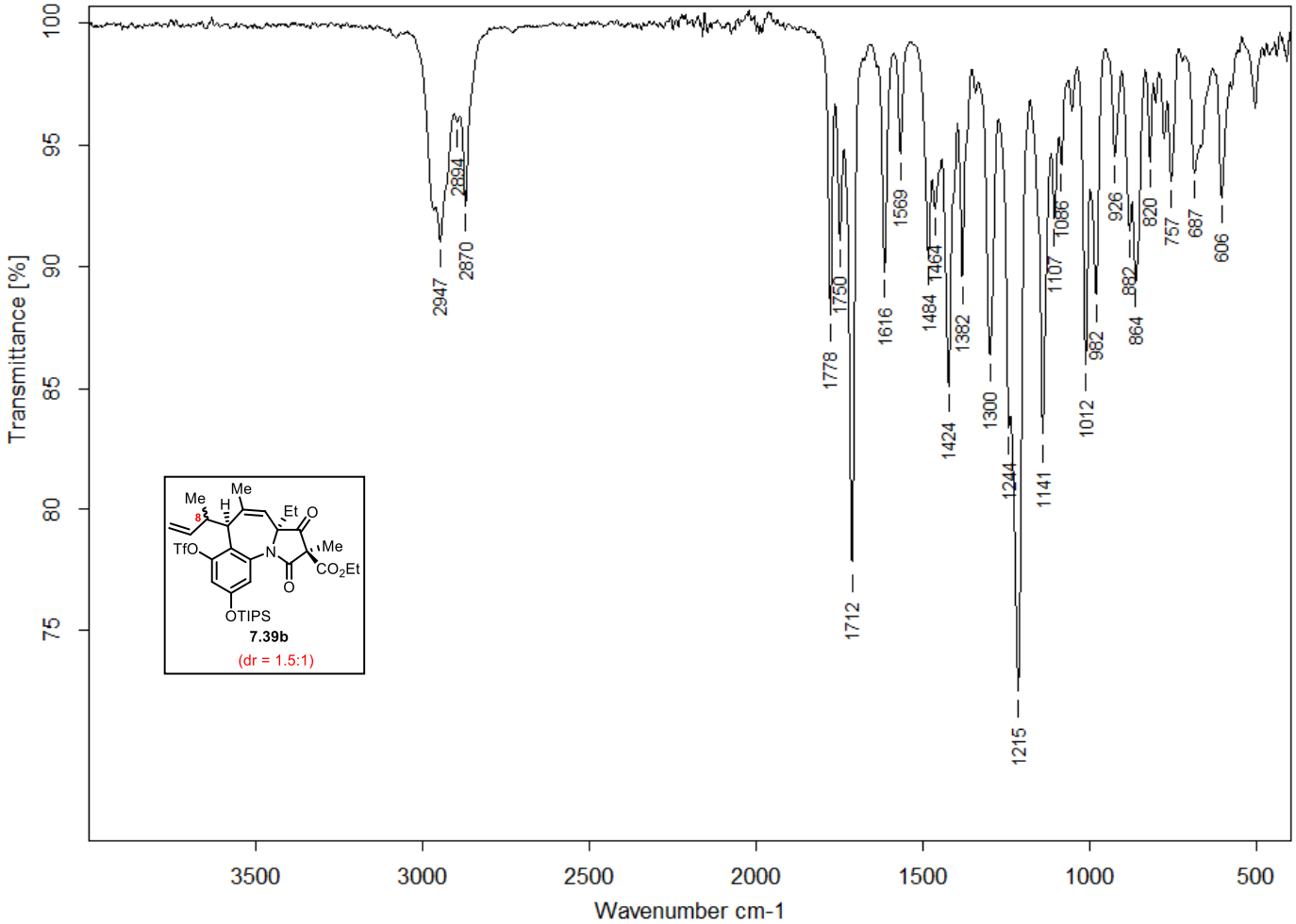


Figure E.53. FTIR spectrum (neat) of compound **7.39b**

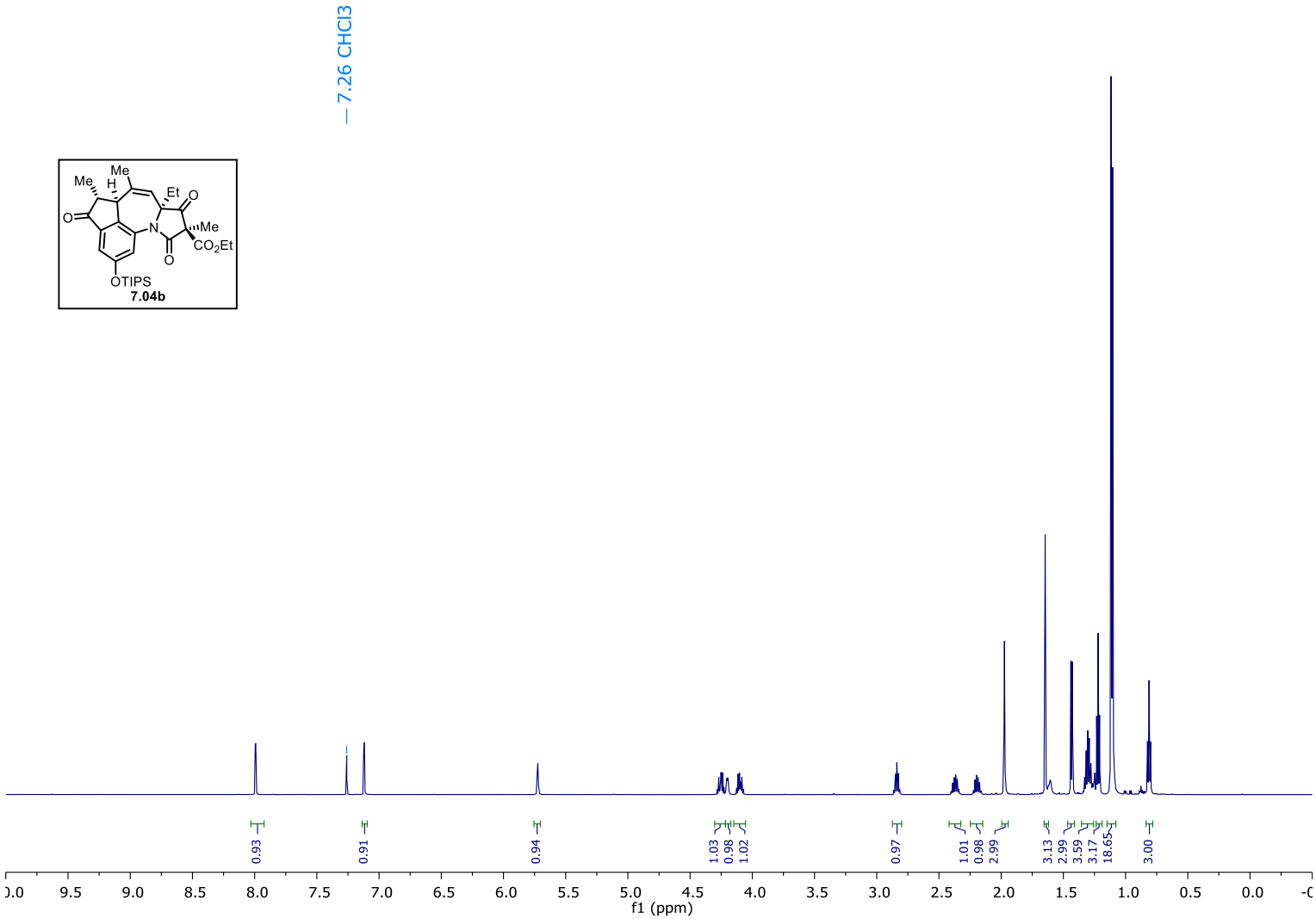


Figure E.54. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7.04b**

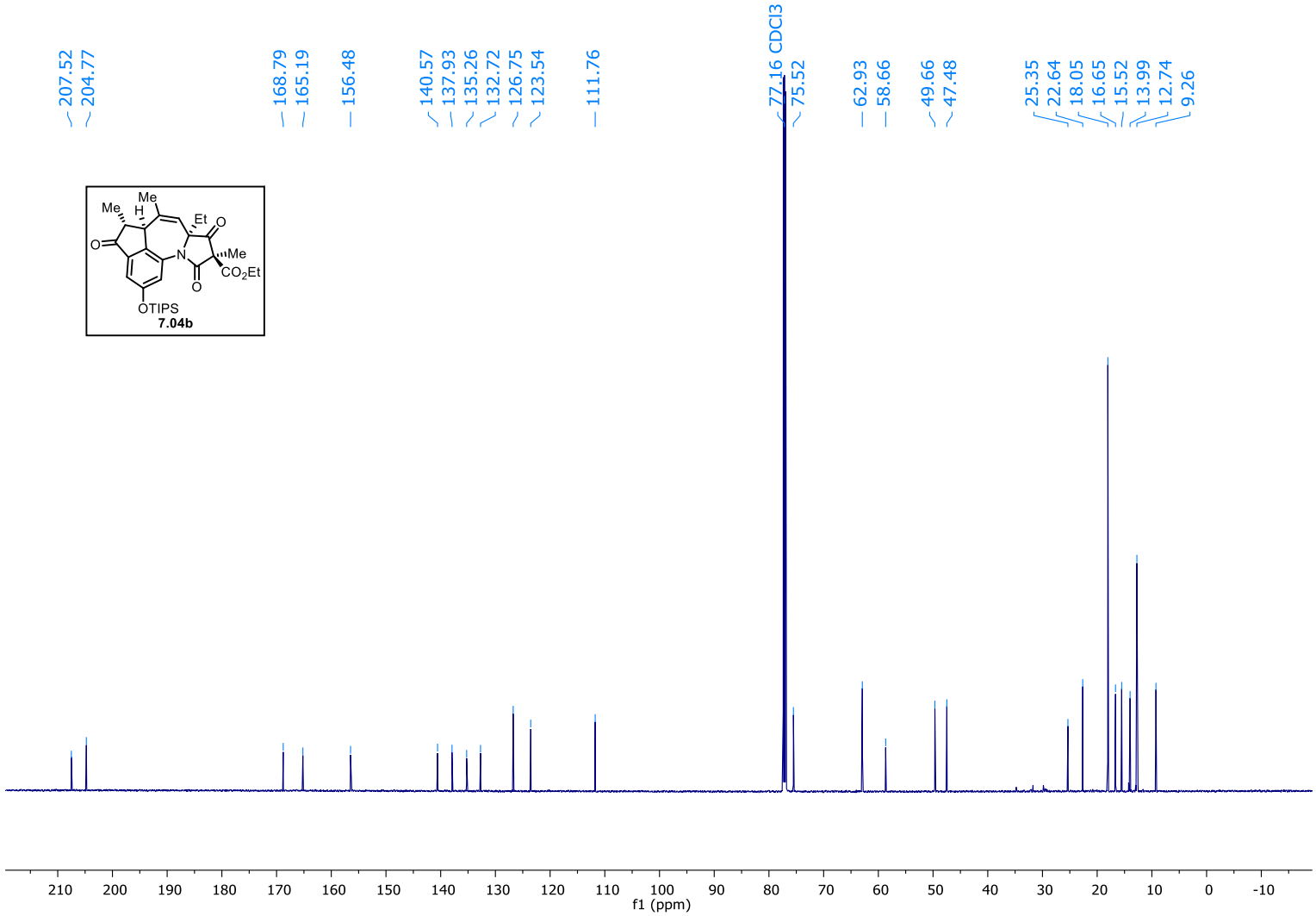


Figure E.55. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **7.04b**

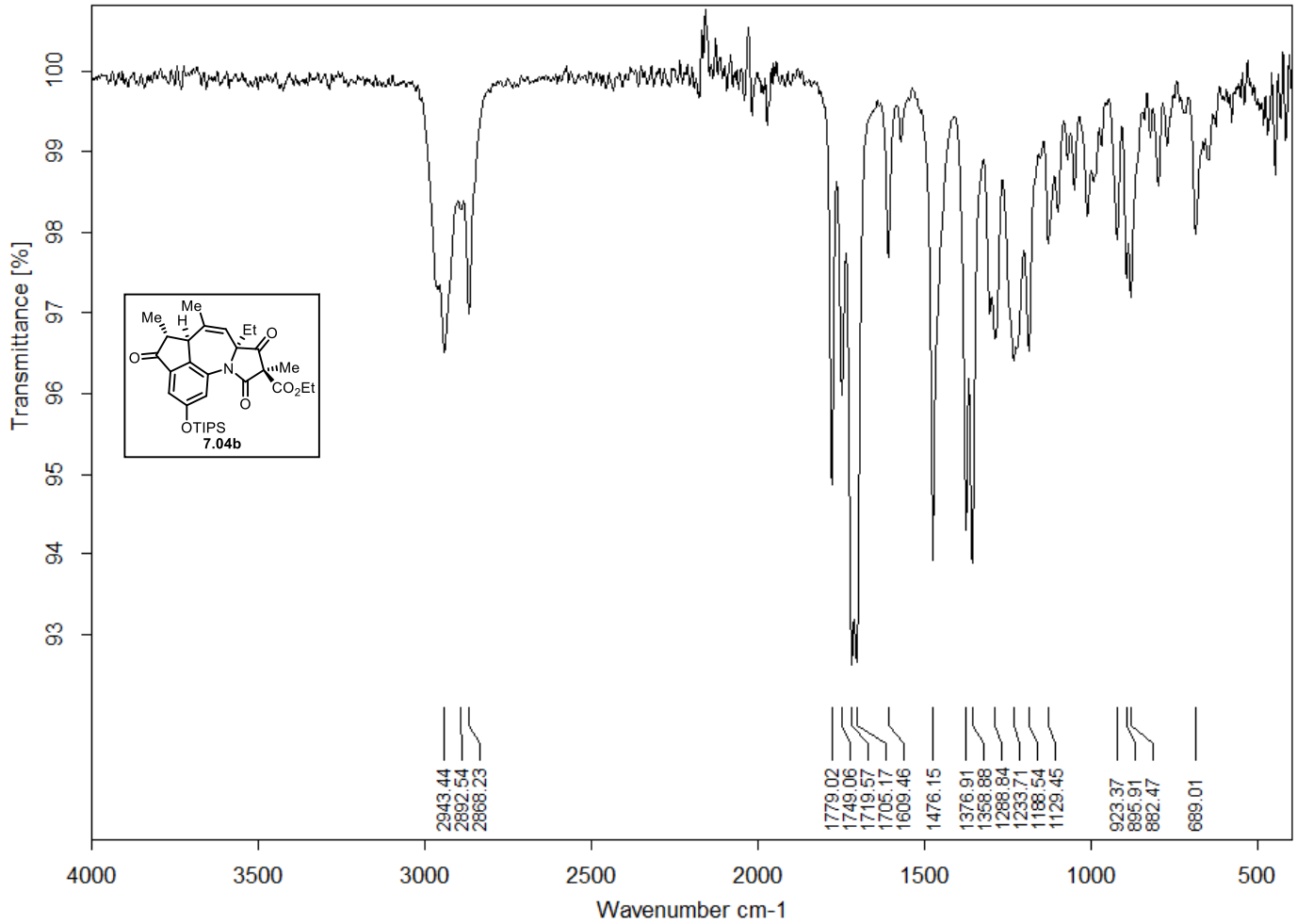


Figure E.56. FTIR spectrum (neat) of compound **7.04b**

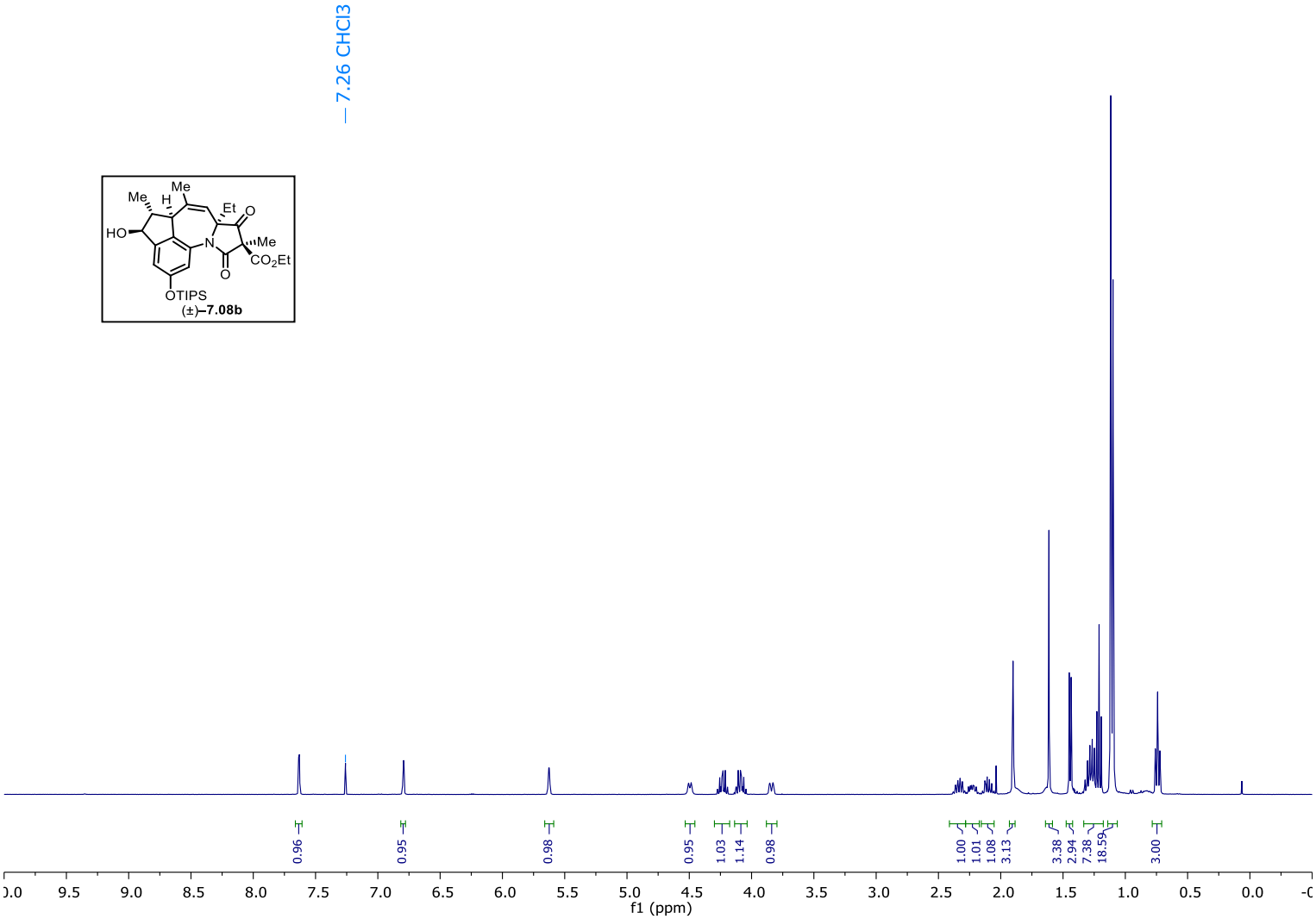


Figure E.57. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **(±)–7.08b**

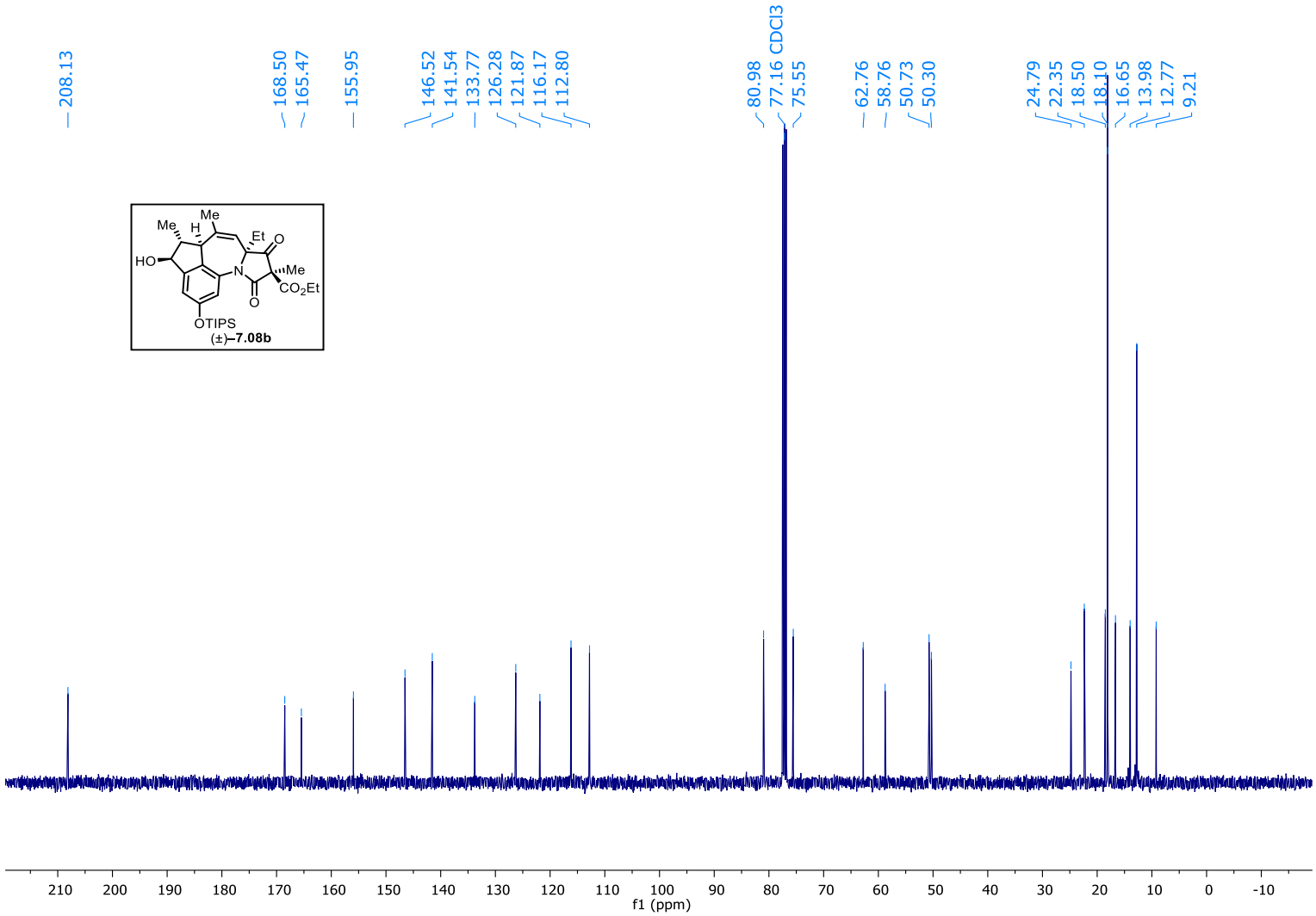


Figure E.58. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **(±)–7.08b**

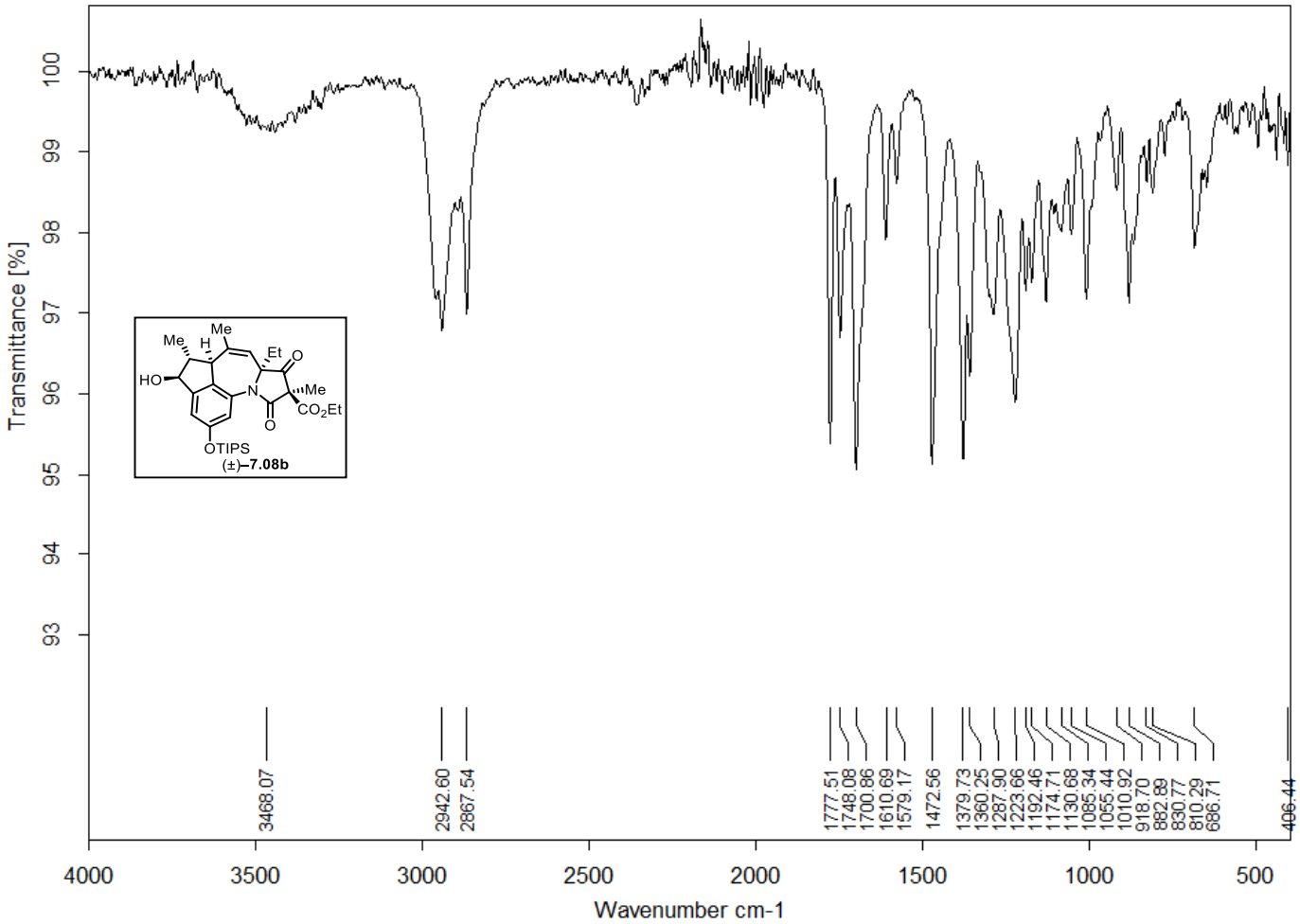


Figure E.59. FTIR spectrum (neat) of compound **(±)–7.08b**

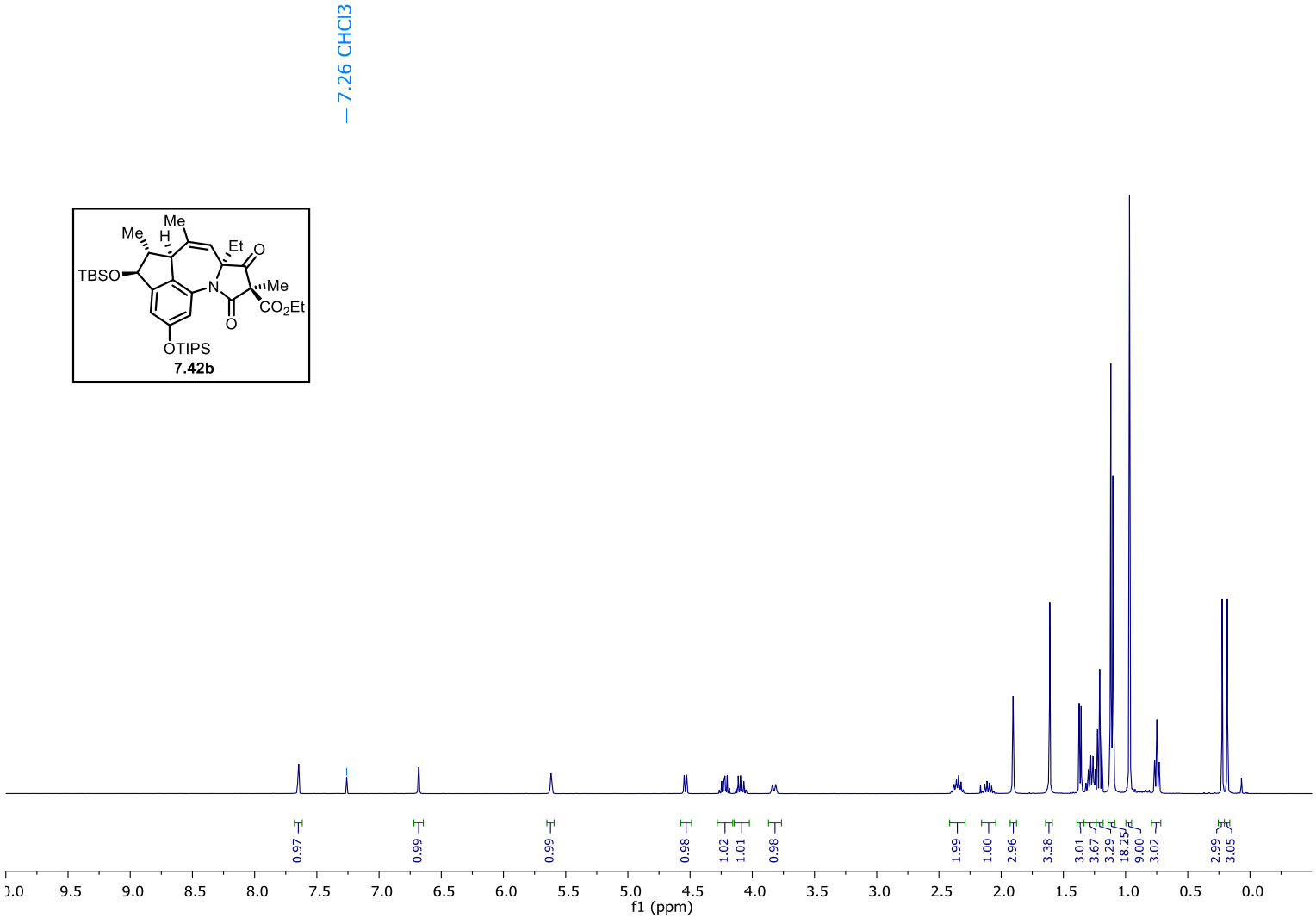


Figure E.60. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **7.42b**

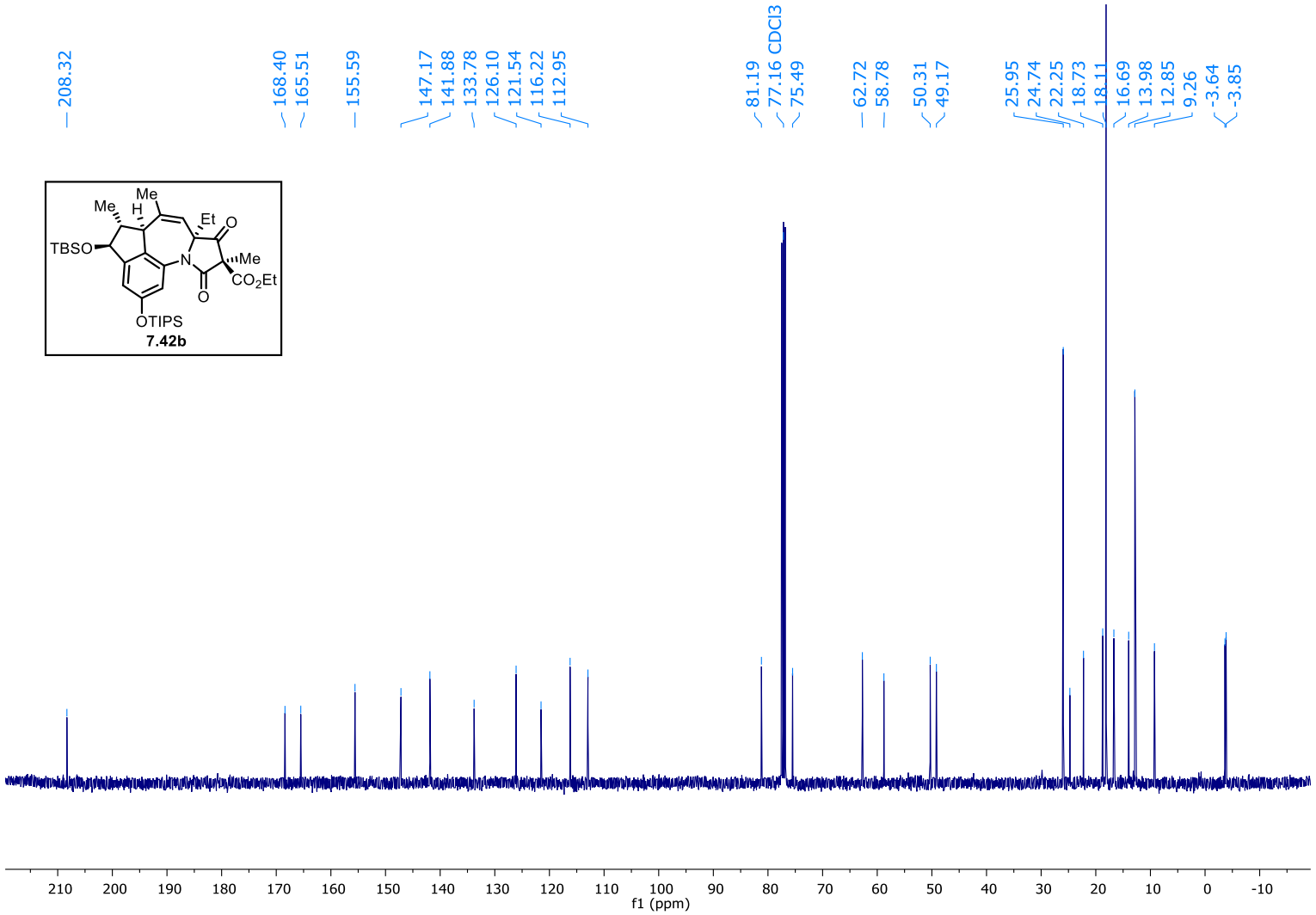


Figure E.61. ^{13}C NMR (101 MHz, $CDCl_3$) of compound **7.42b**

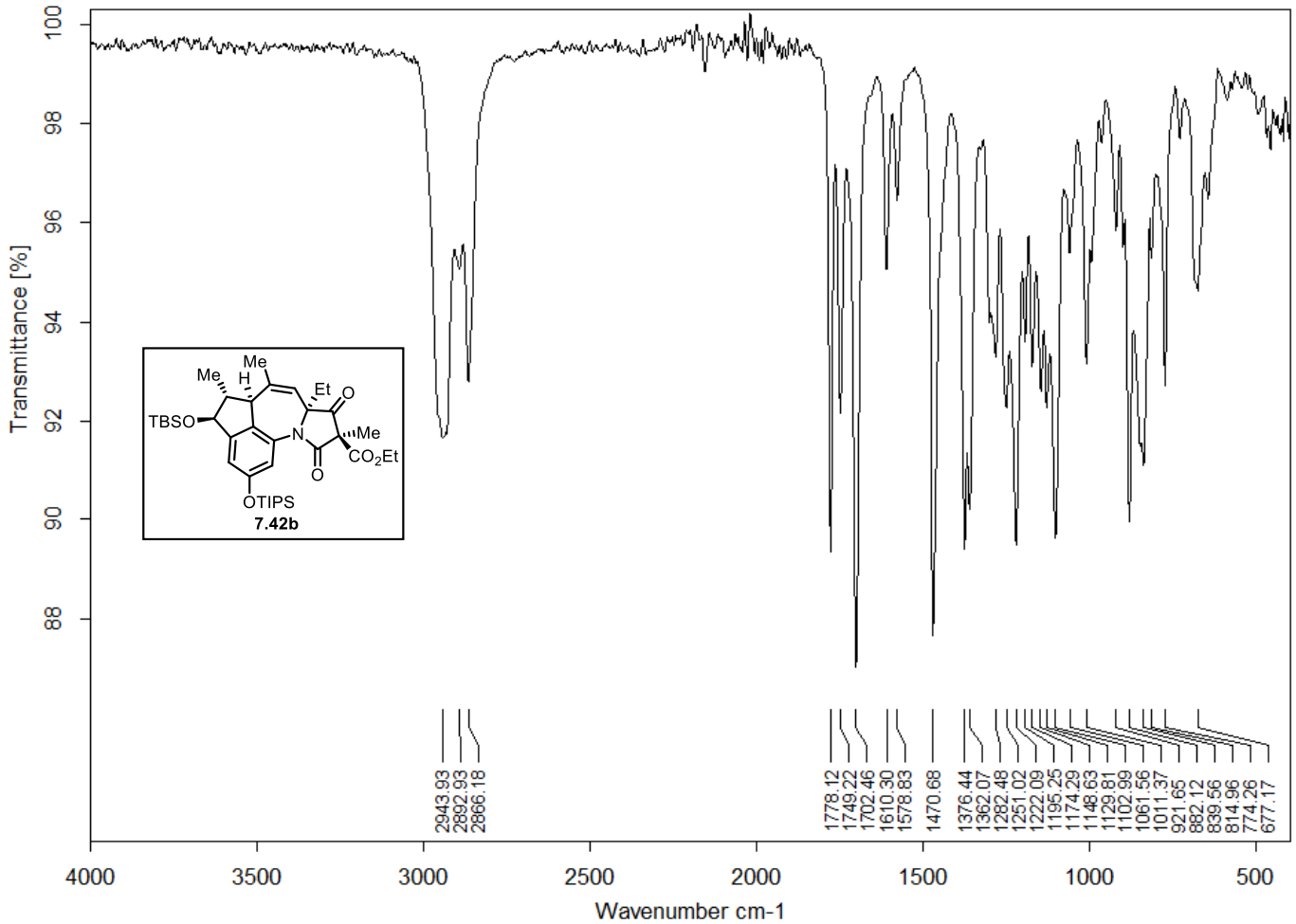


Figure E.62. FTIR spectrum (neat) of compound **7.42b**

APPENDIX F

Spectra Relevant to Chapter Eight

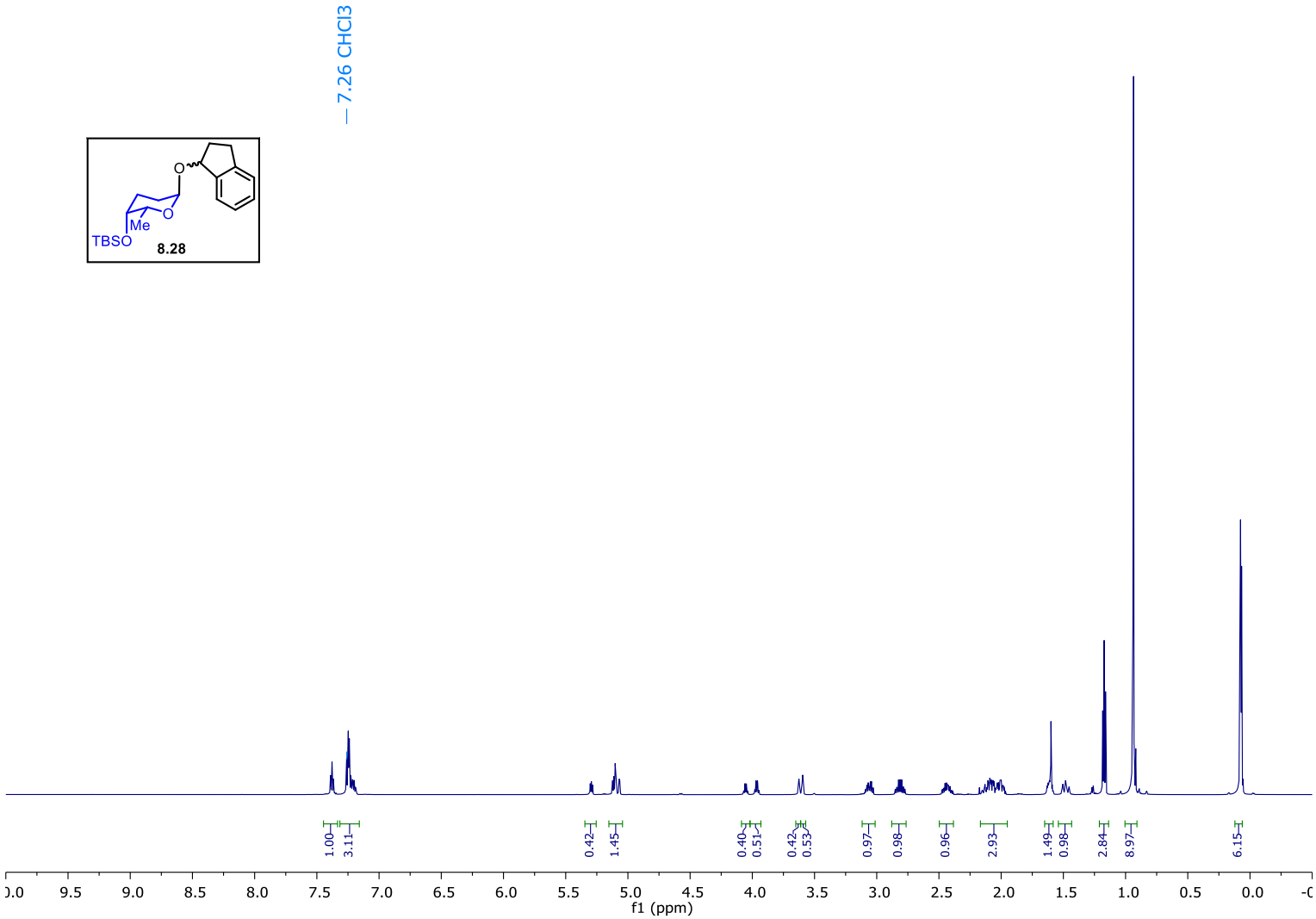


Figure F.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.28**

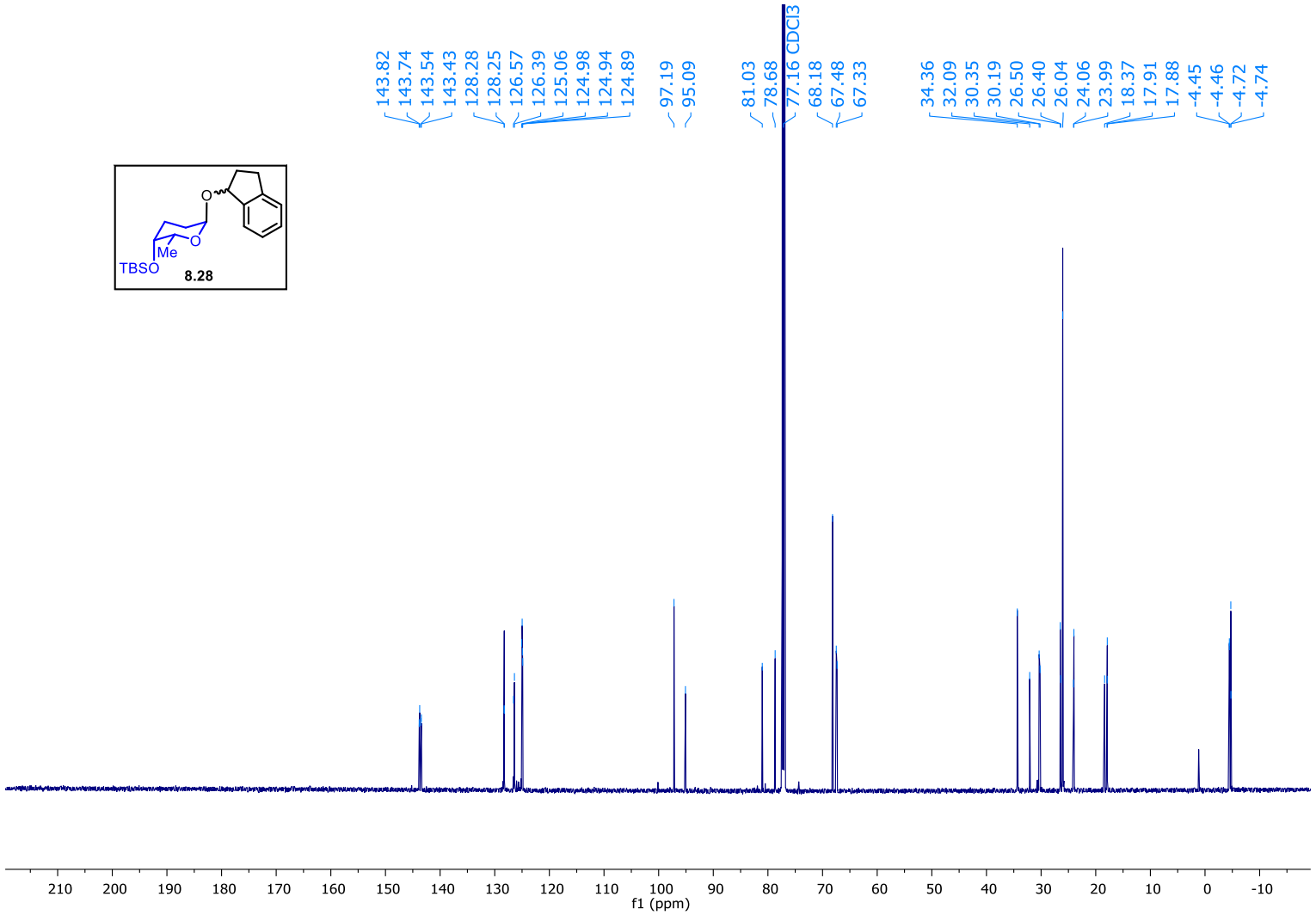


Figure F.2. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.28**

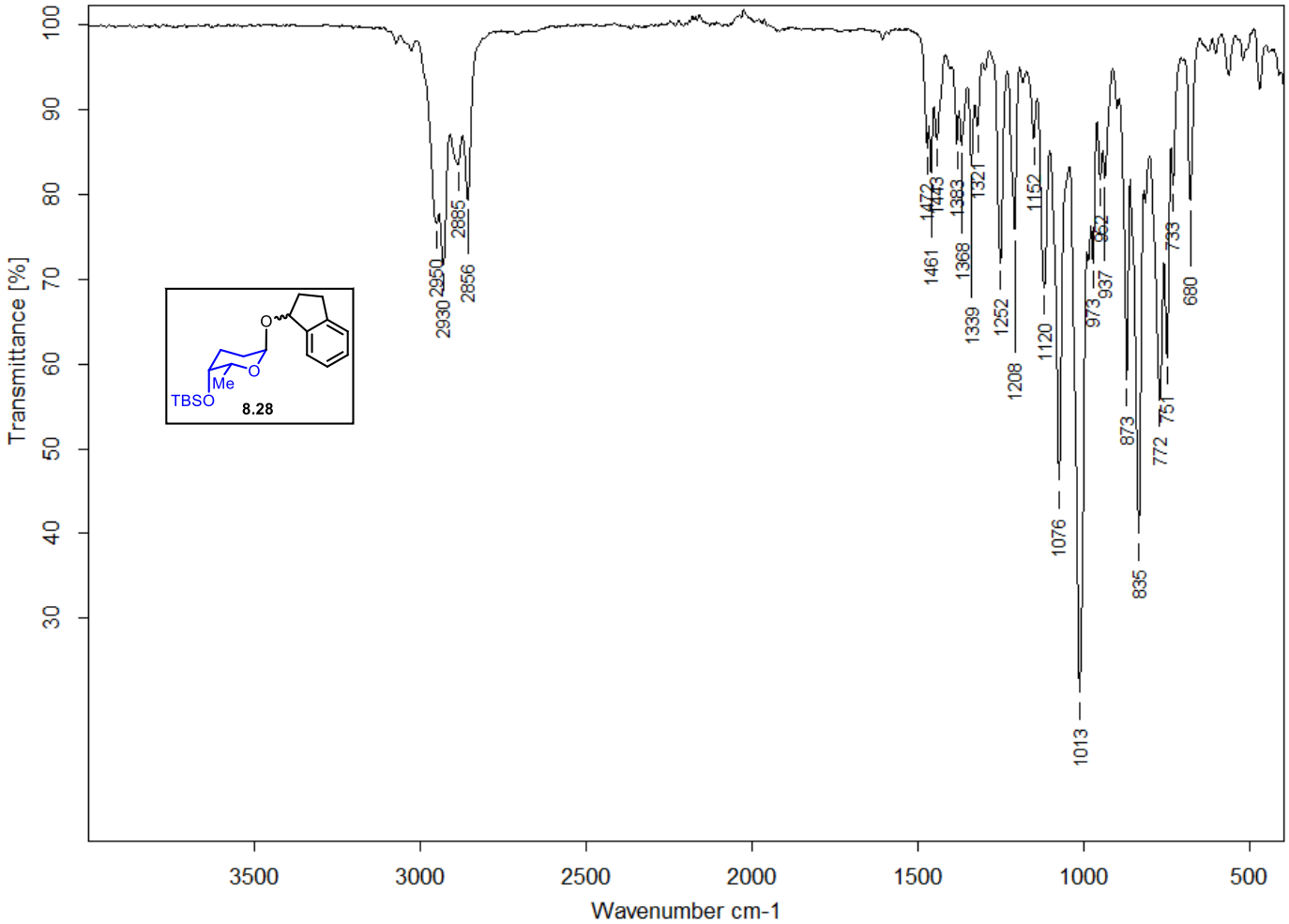


Figure F.3. FTIR spectrum (neat) of compound **8.28**

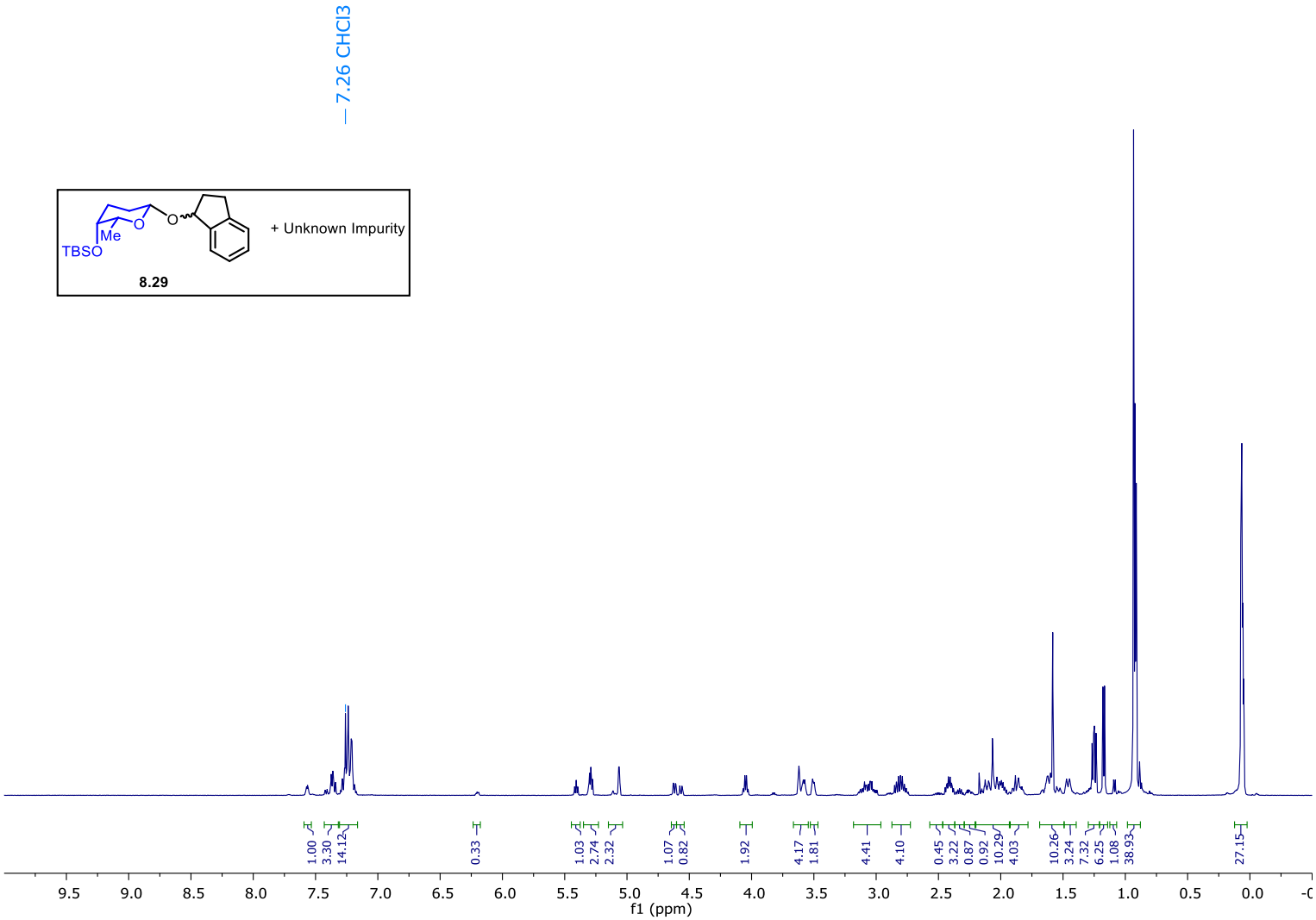


Figure F.4. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.29**

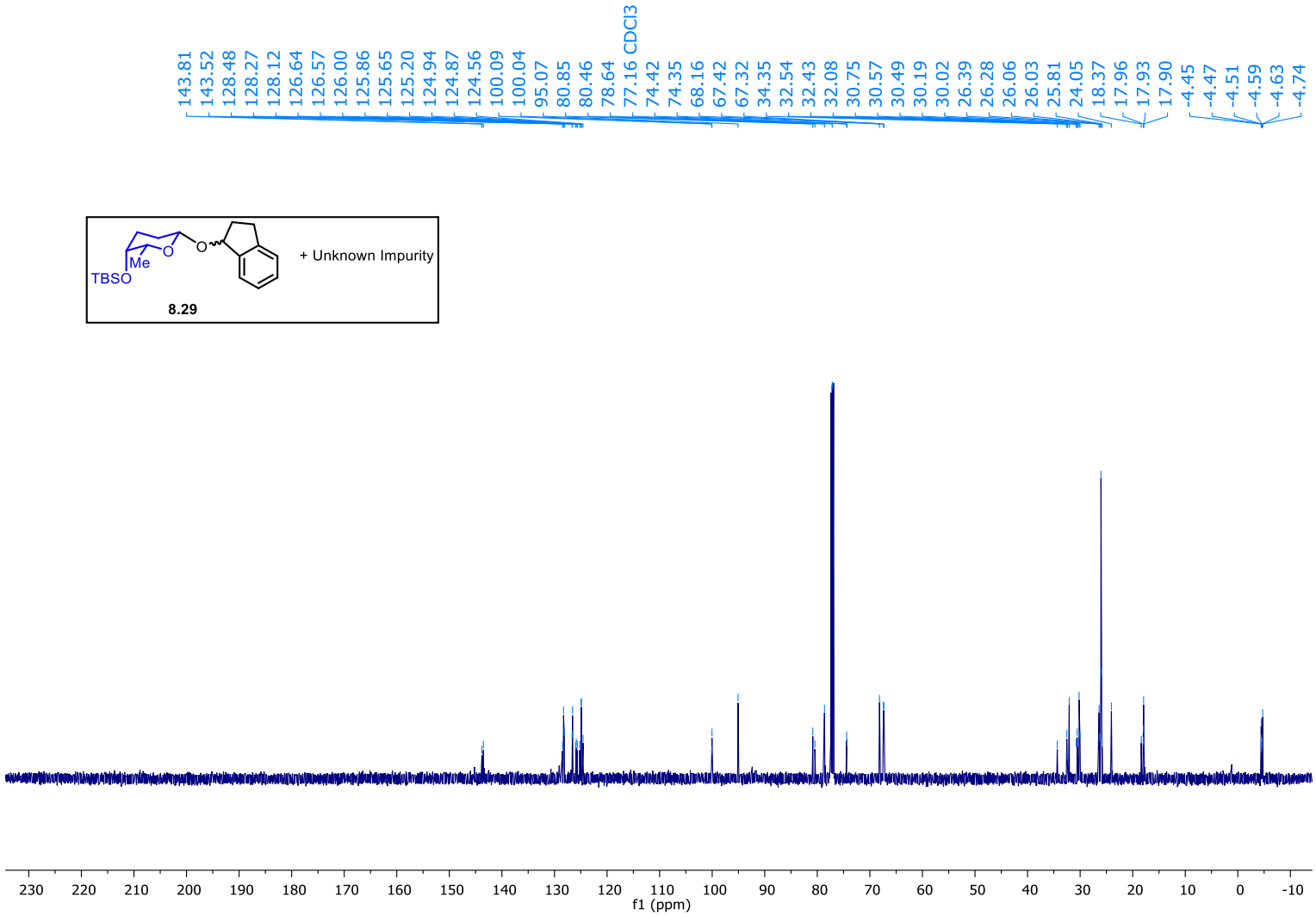


Figure F.5. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.29**

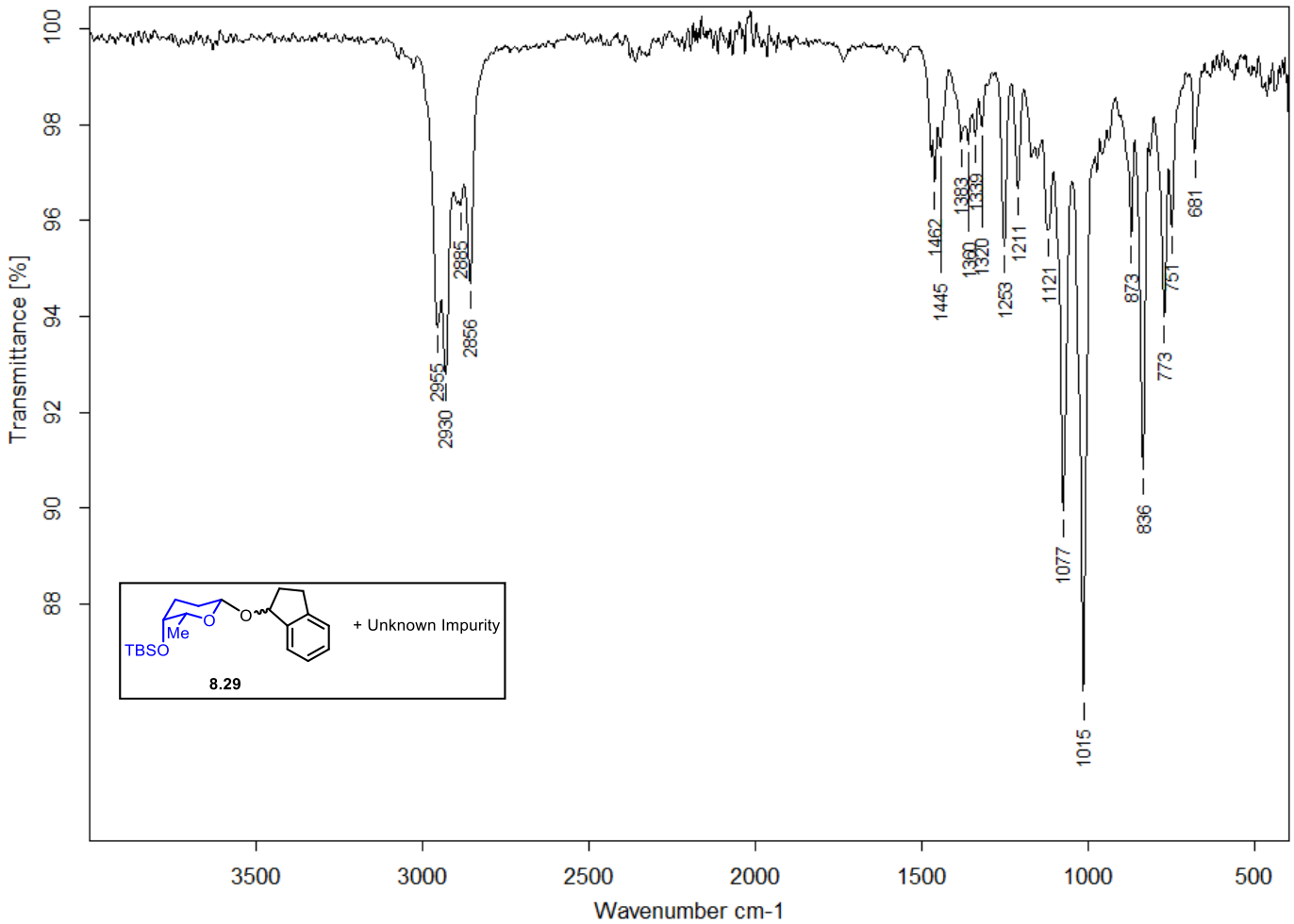


Figure F.6. FTIR spectrum (neat) of compound **8.29**

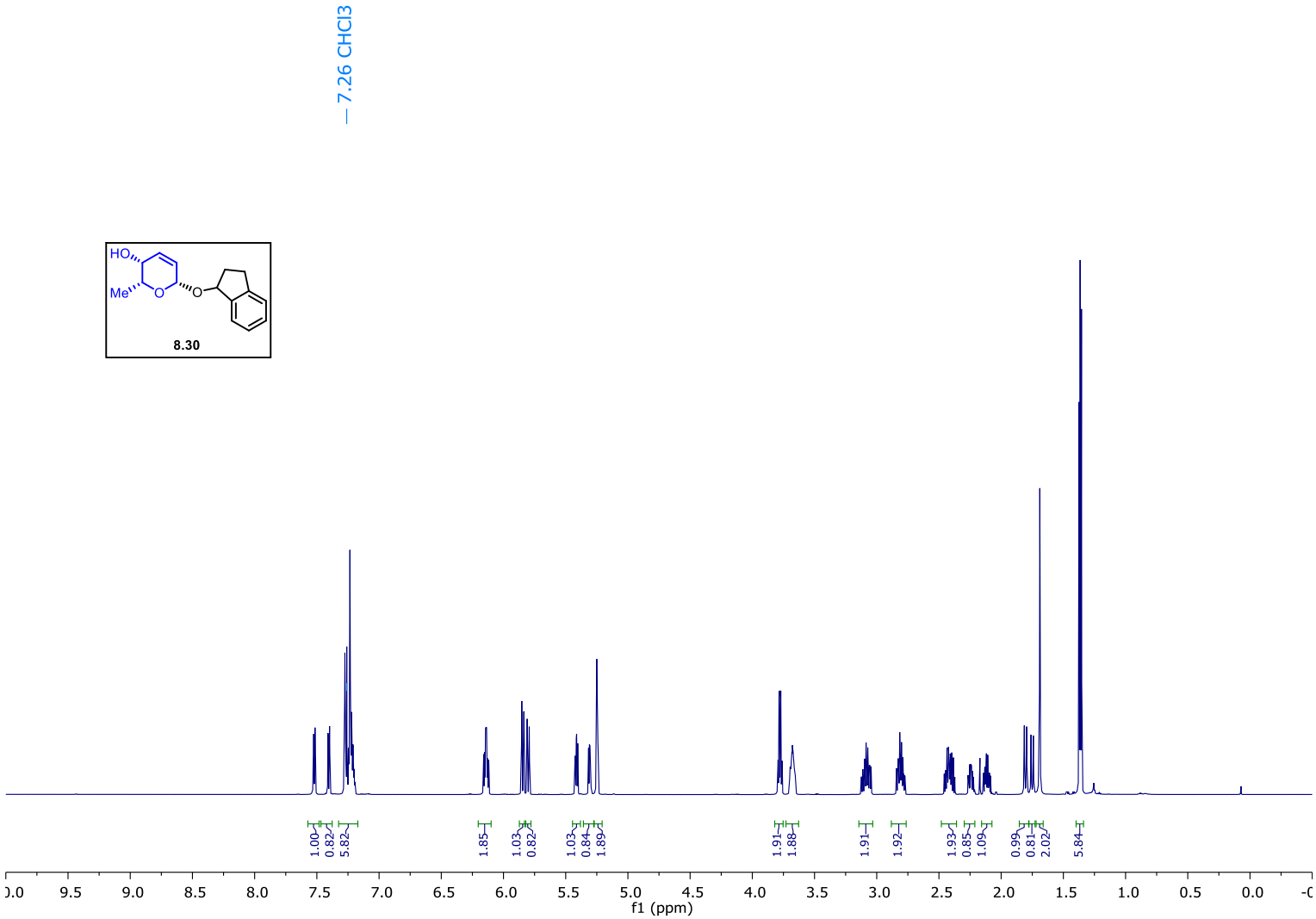


Figure F.7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.30**

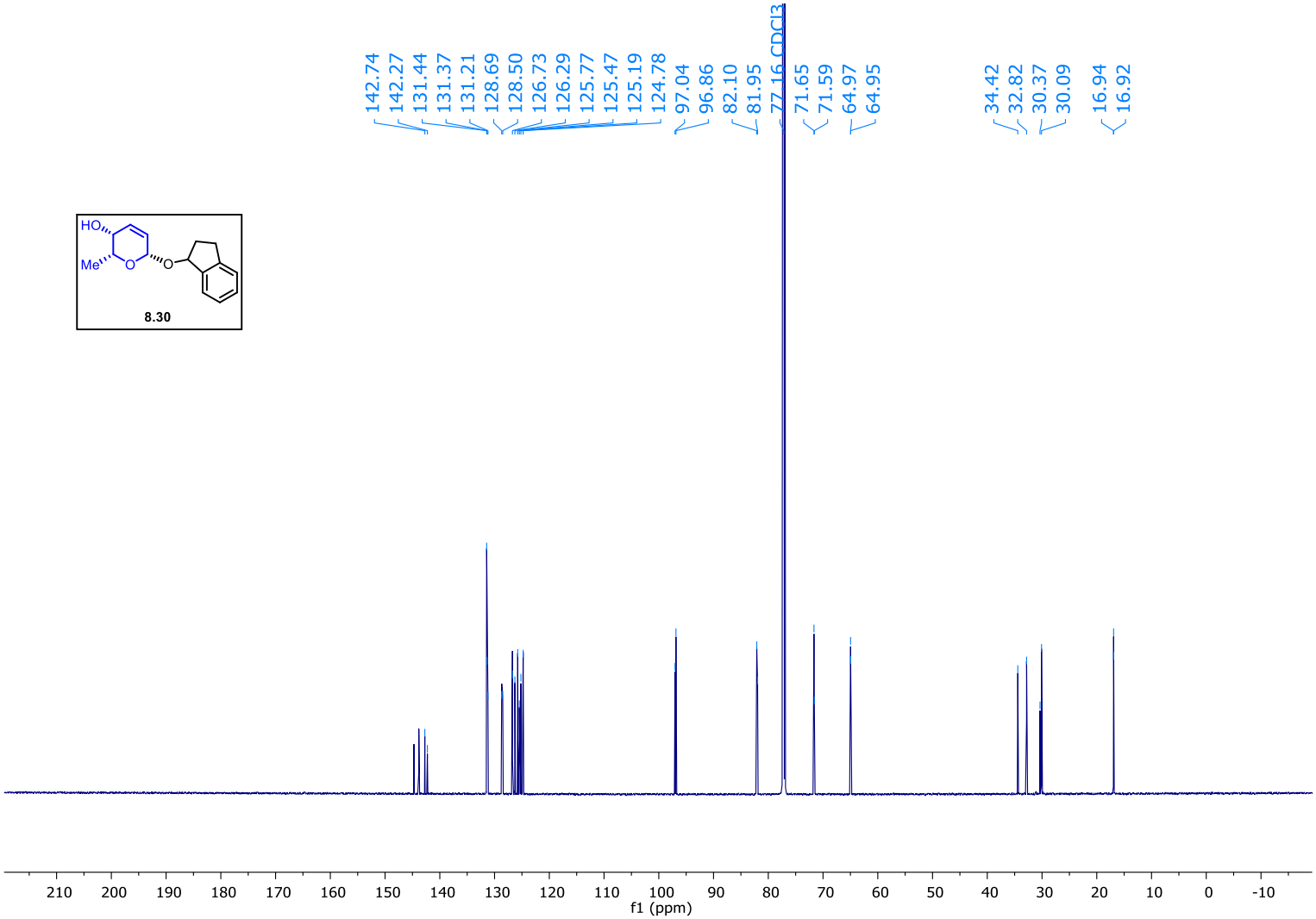


Figure F.8. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.30**

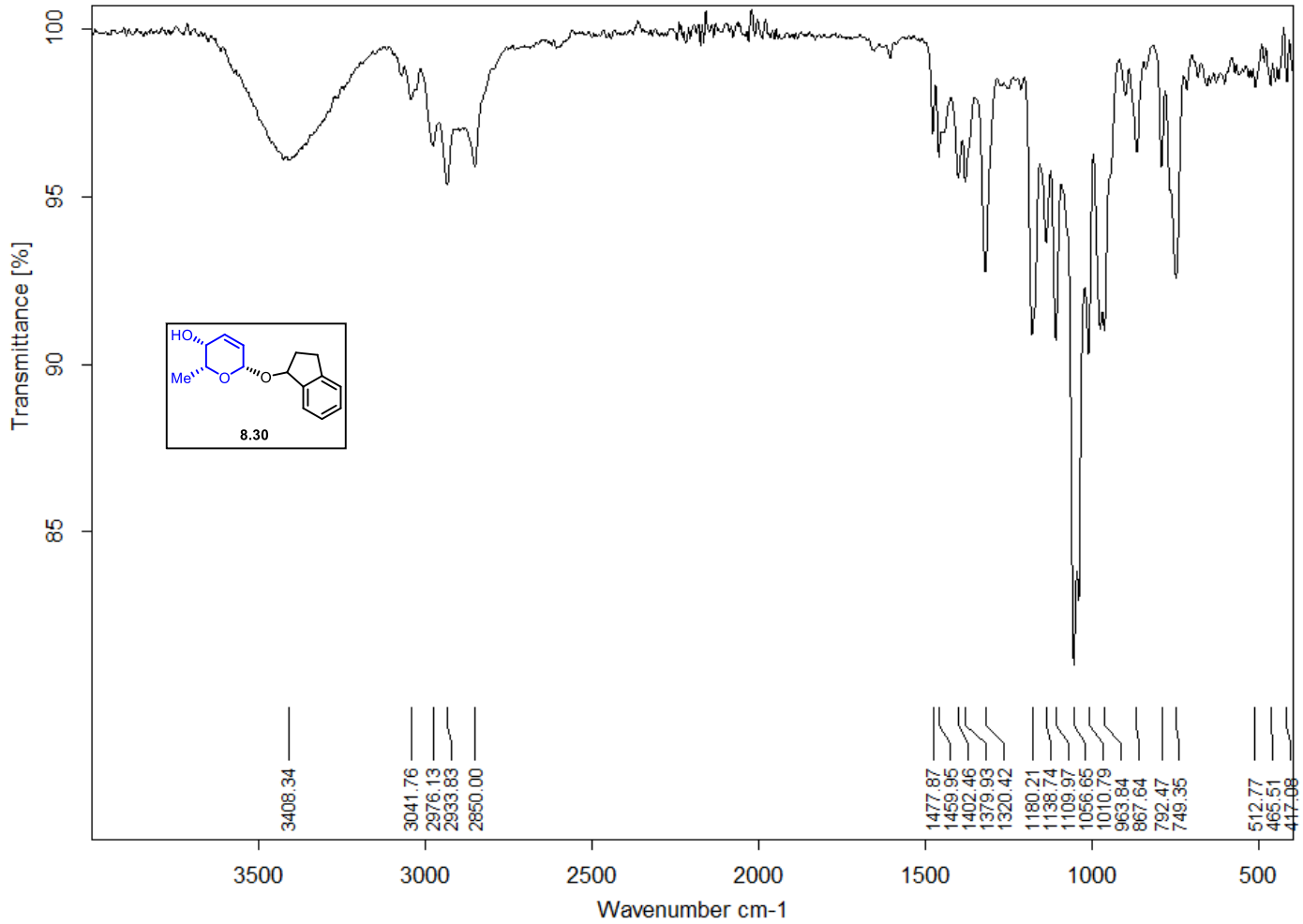


Figure F.9. FTIR spectrum (neat) of compound **8.30**

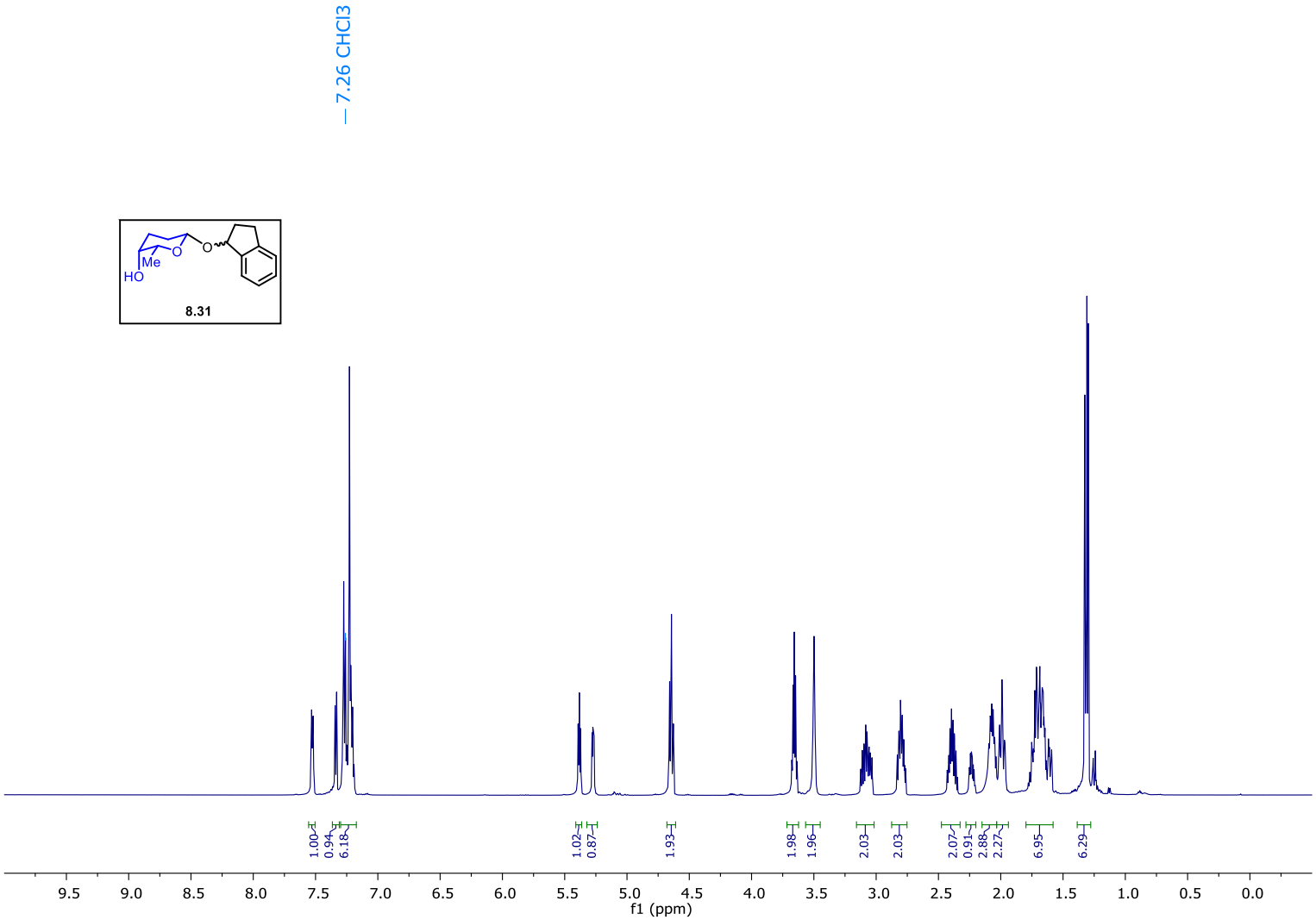


Figure F.10. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.31**

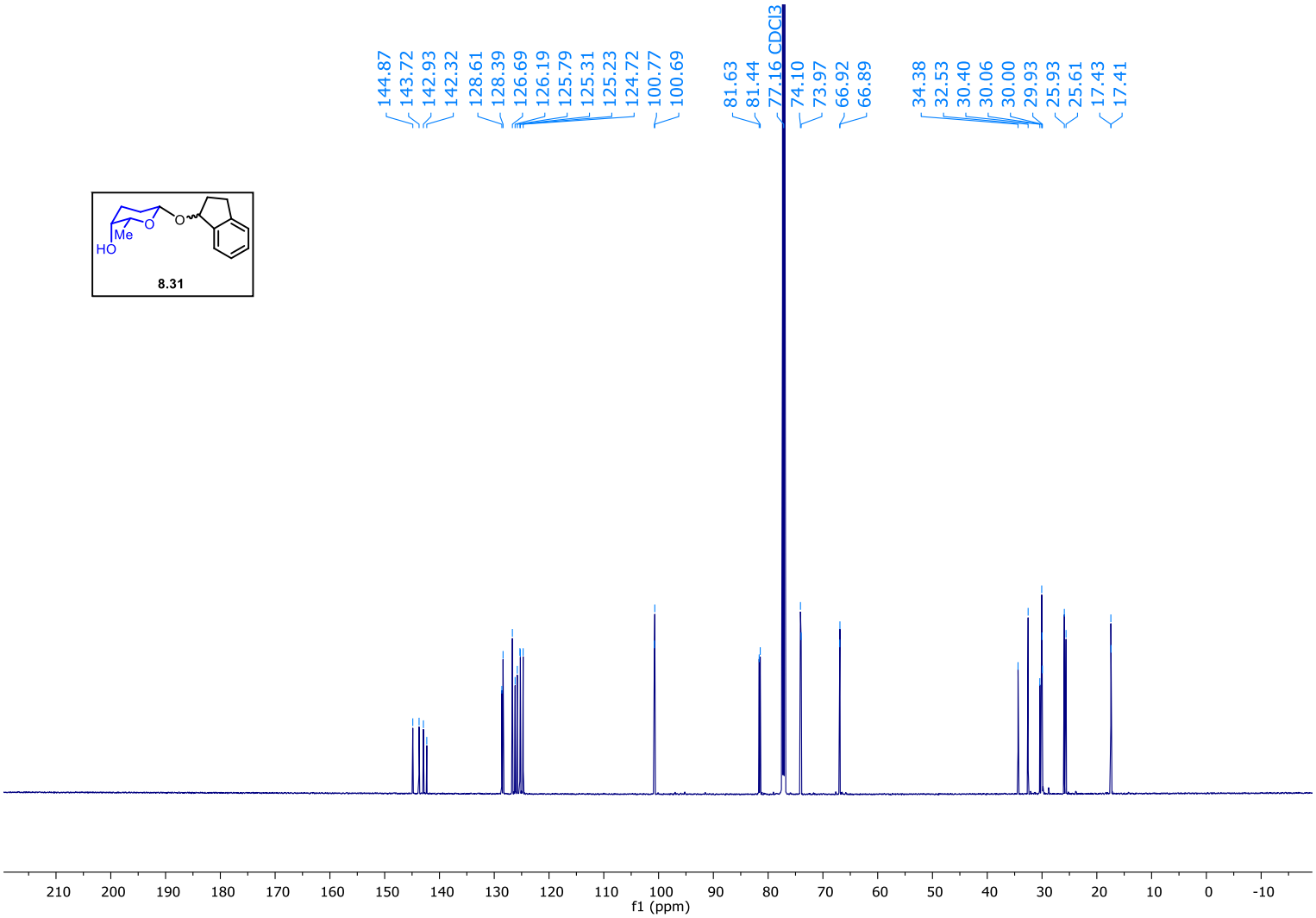


Figure F.11. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.31**

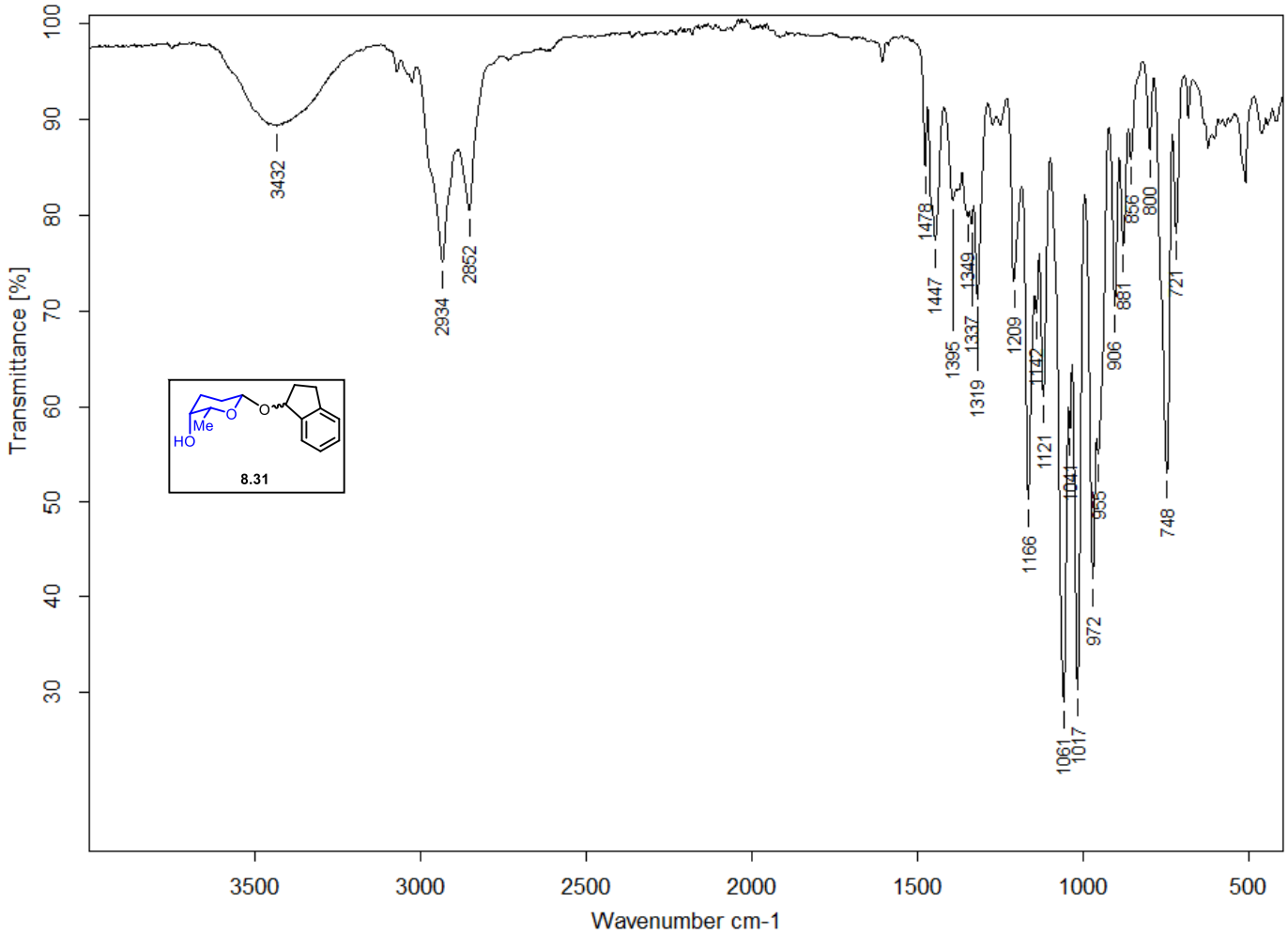


Figure F.12. FTIR spectrum (neat) of compound **8.31**

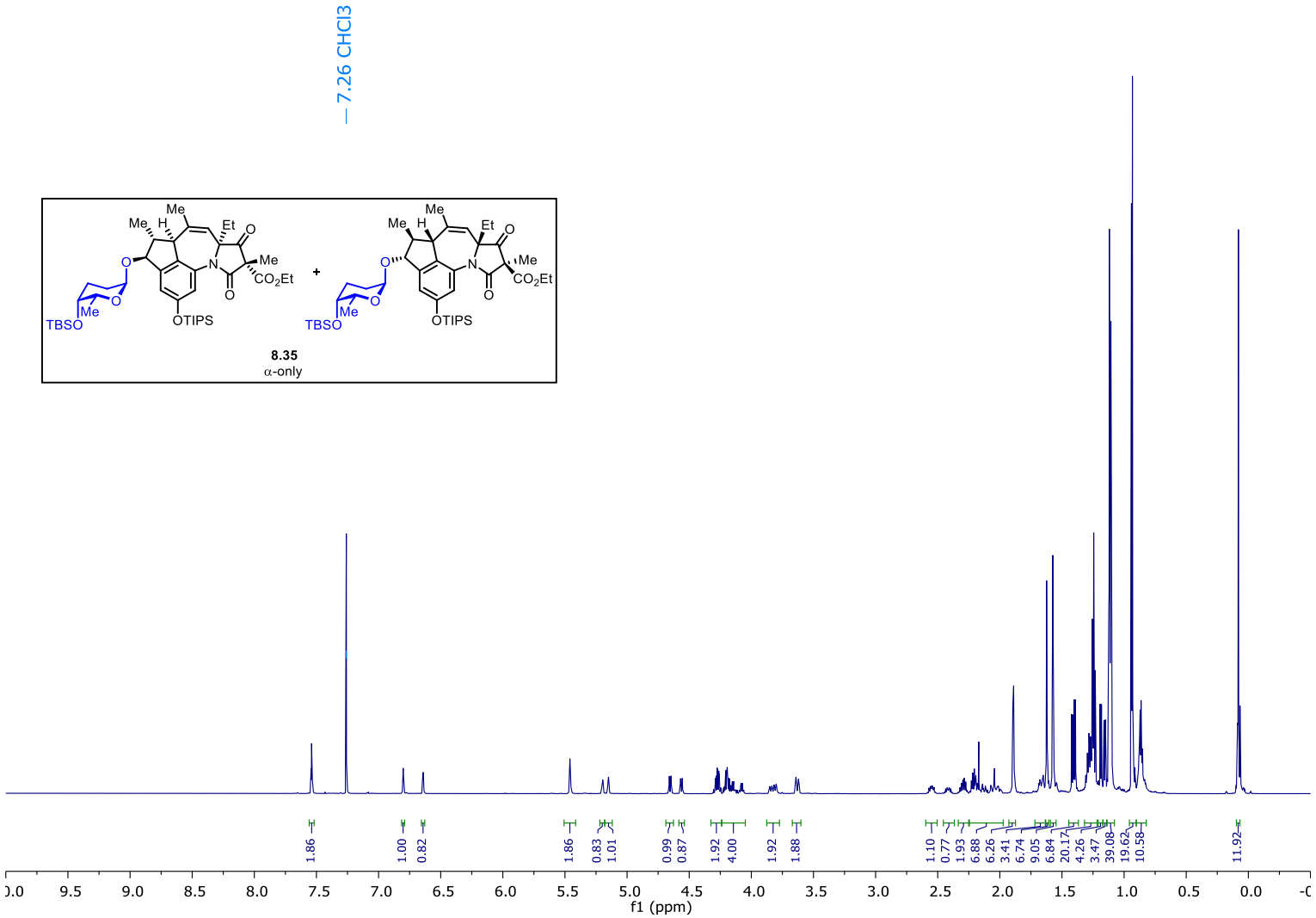


Figure F.13. ^{1}H NMR (00 MHz, $CDCl_3$) of compound **8.35**

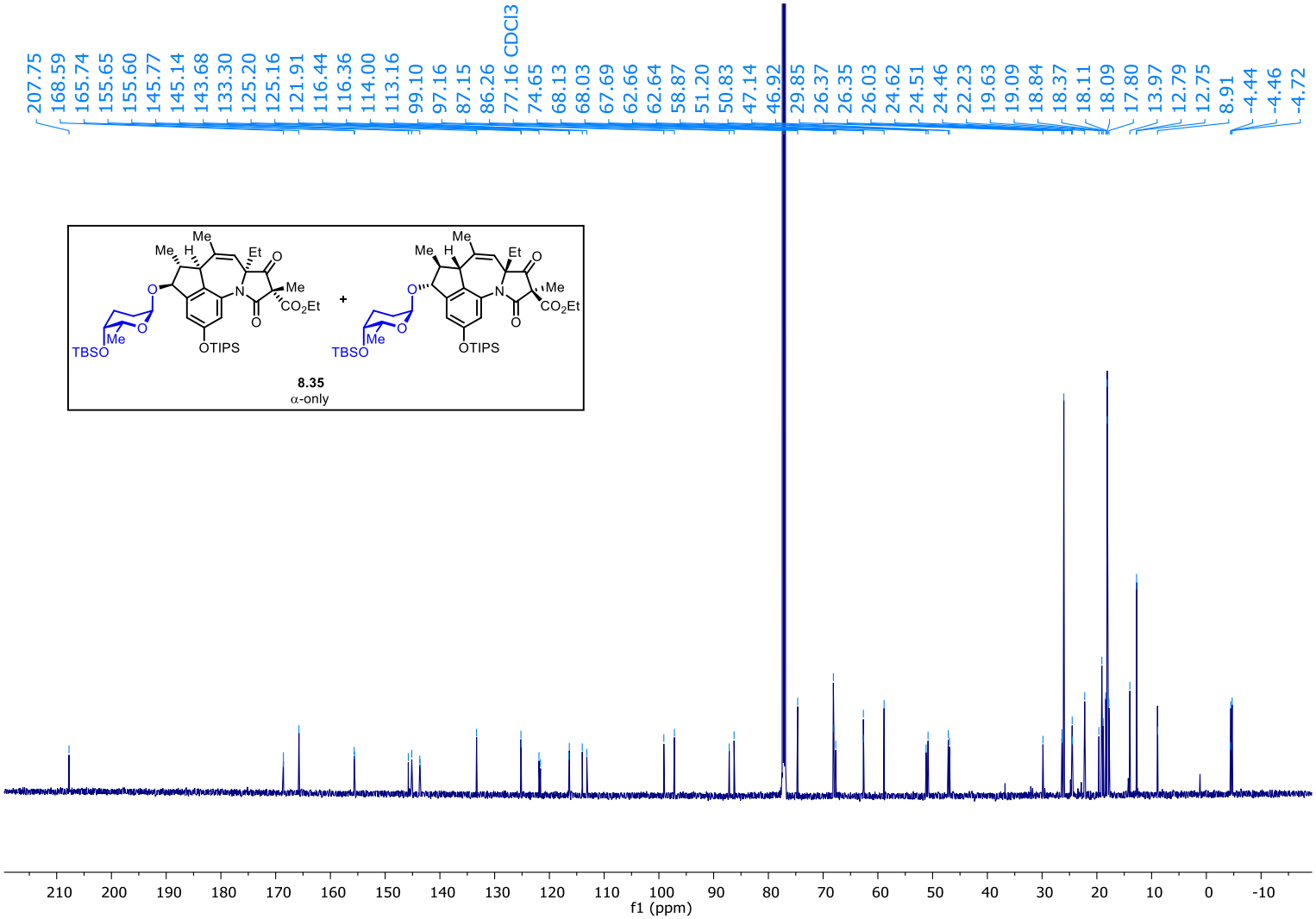


Figure F.14. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.35**

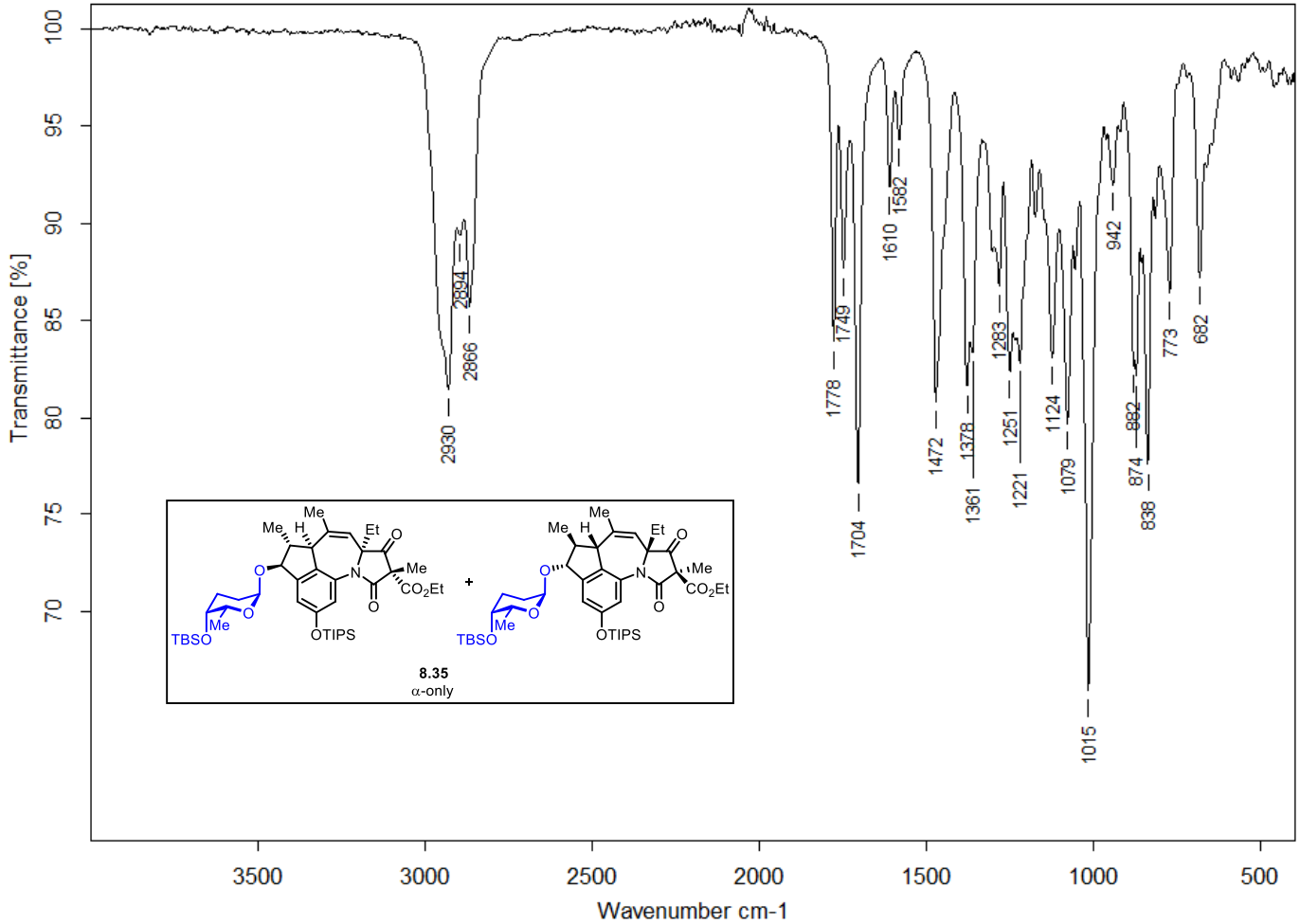


Figure F.15. FTIR spectrum (neat) of compound **8.35**

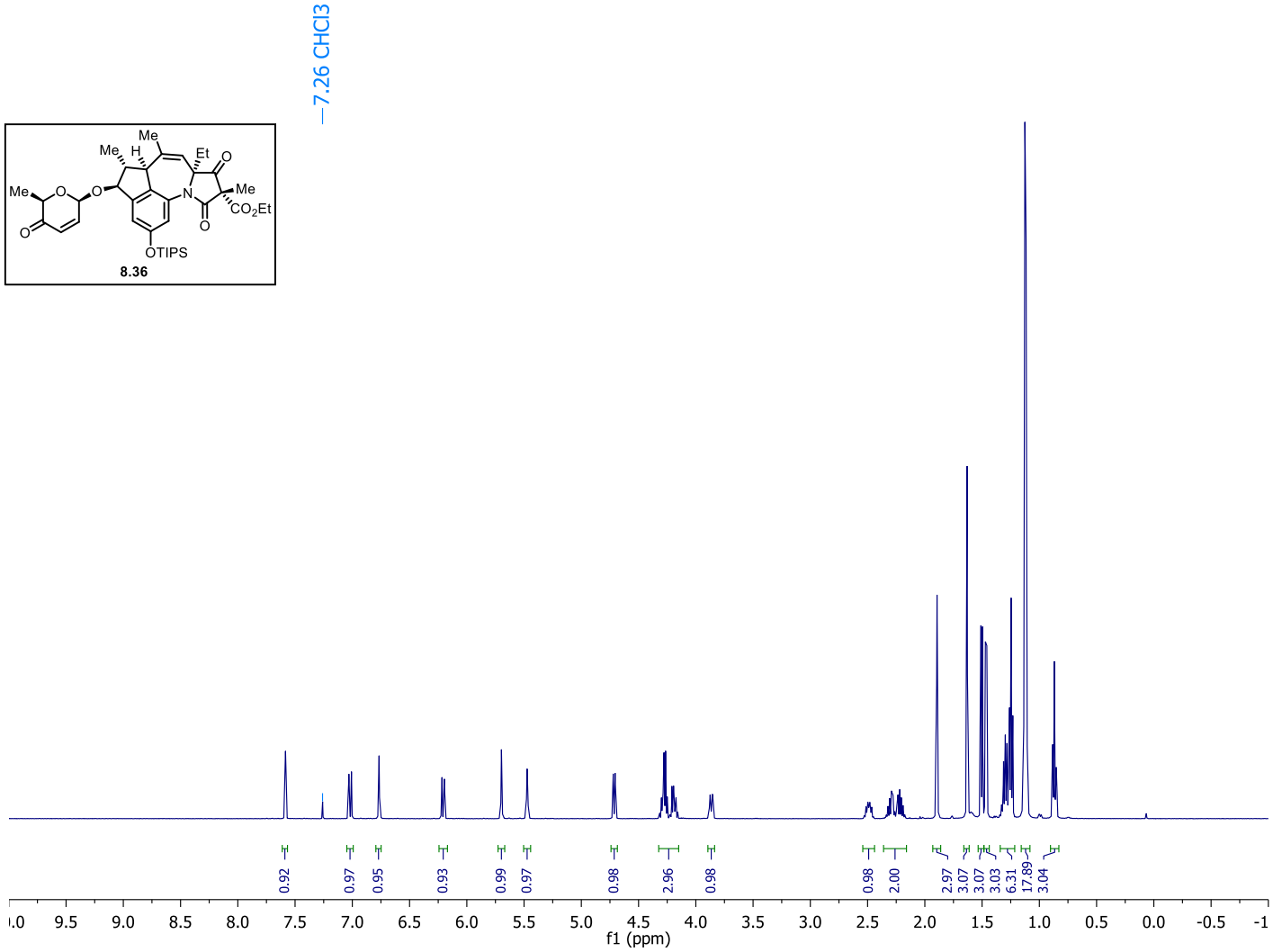


Figure F.16. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.36** (higher R_f diastereomer)

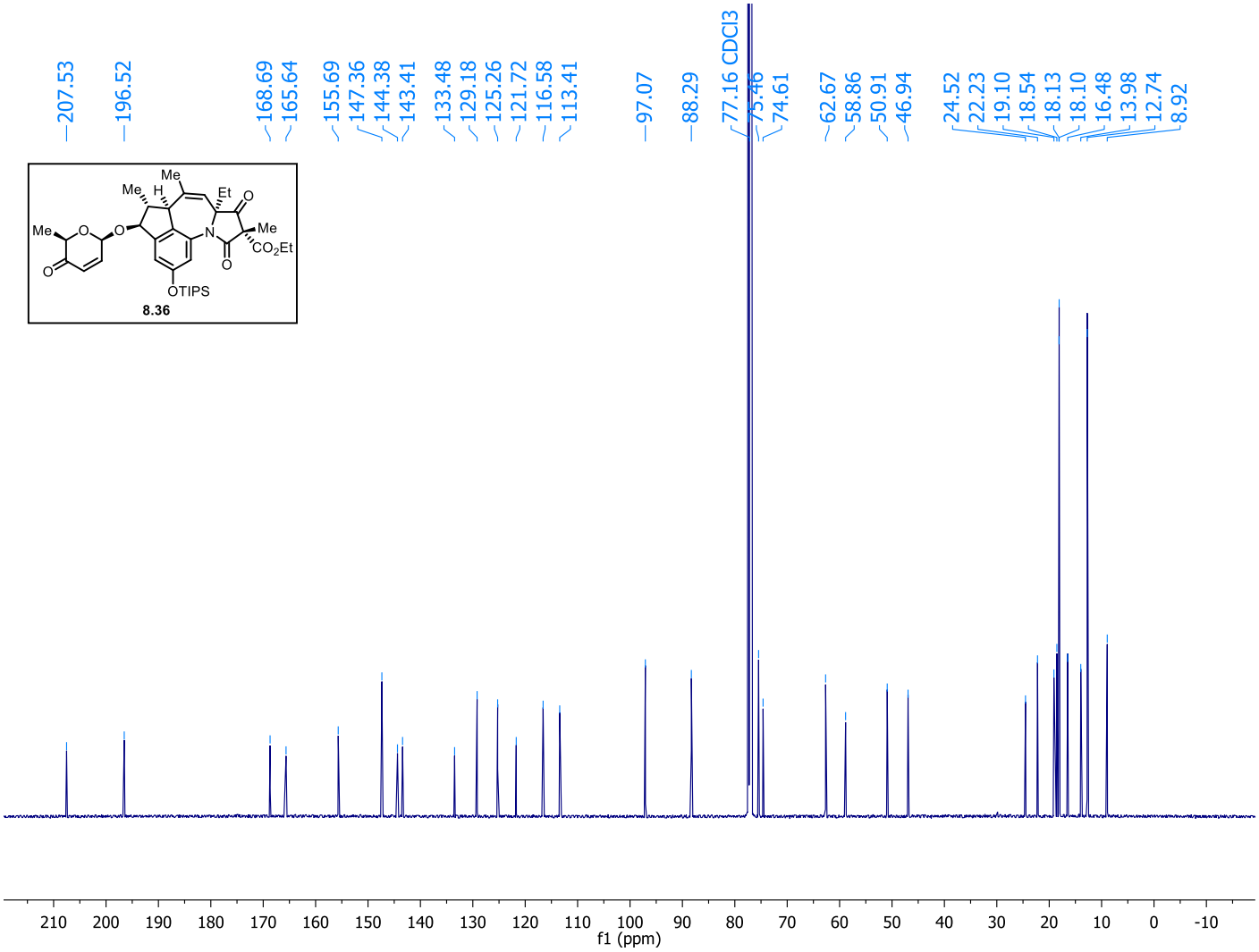


Figure F.17. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.36** (higher R_f diastereomer)

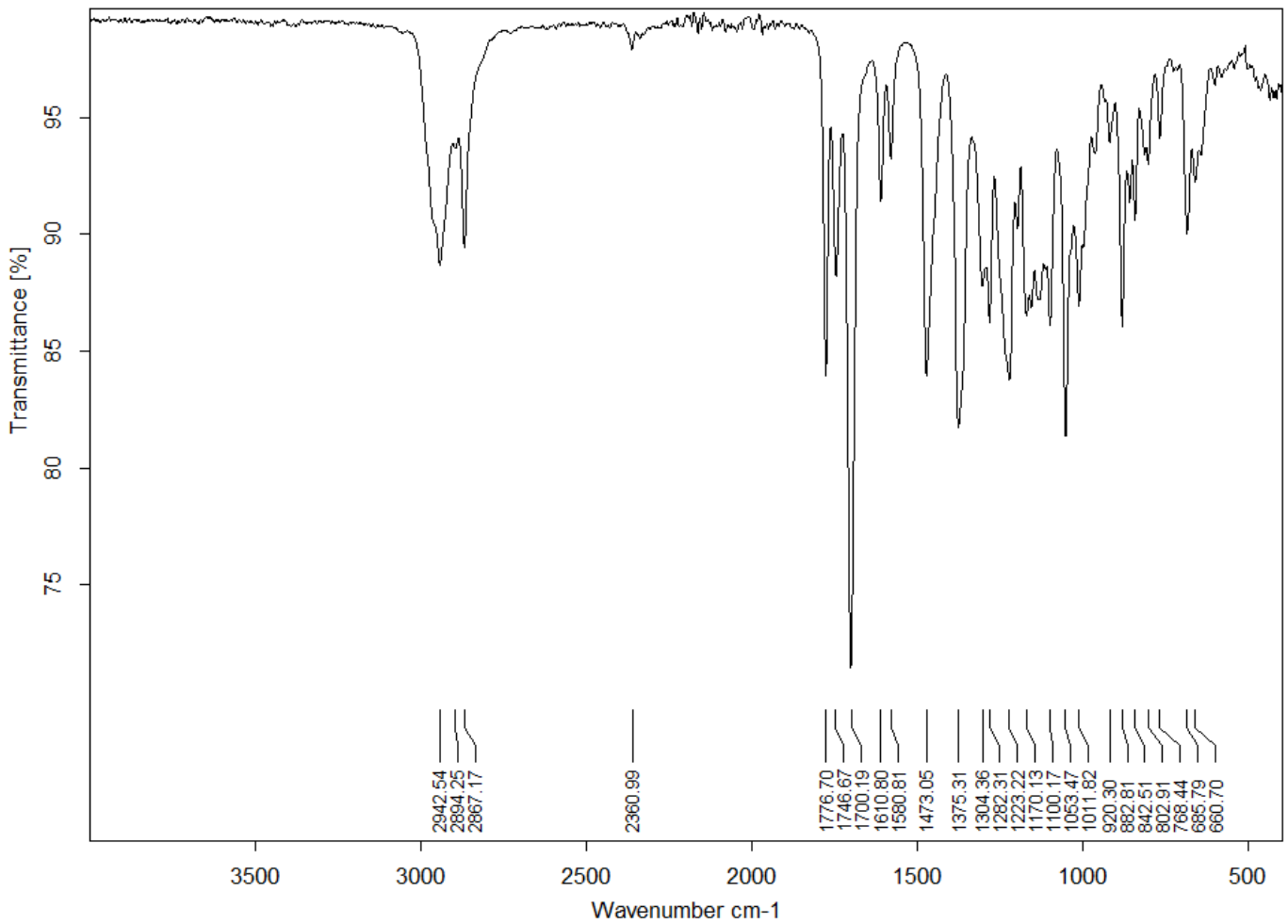


Figure F.18. FTIR spectrum (neat) of compound **8.36** (higher R_f diastereomer)

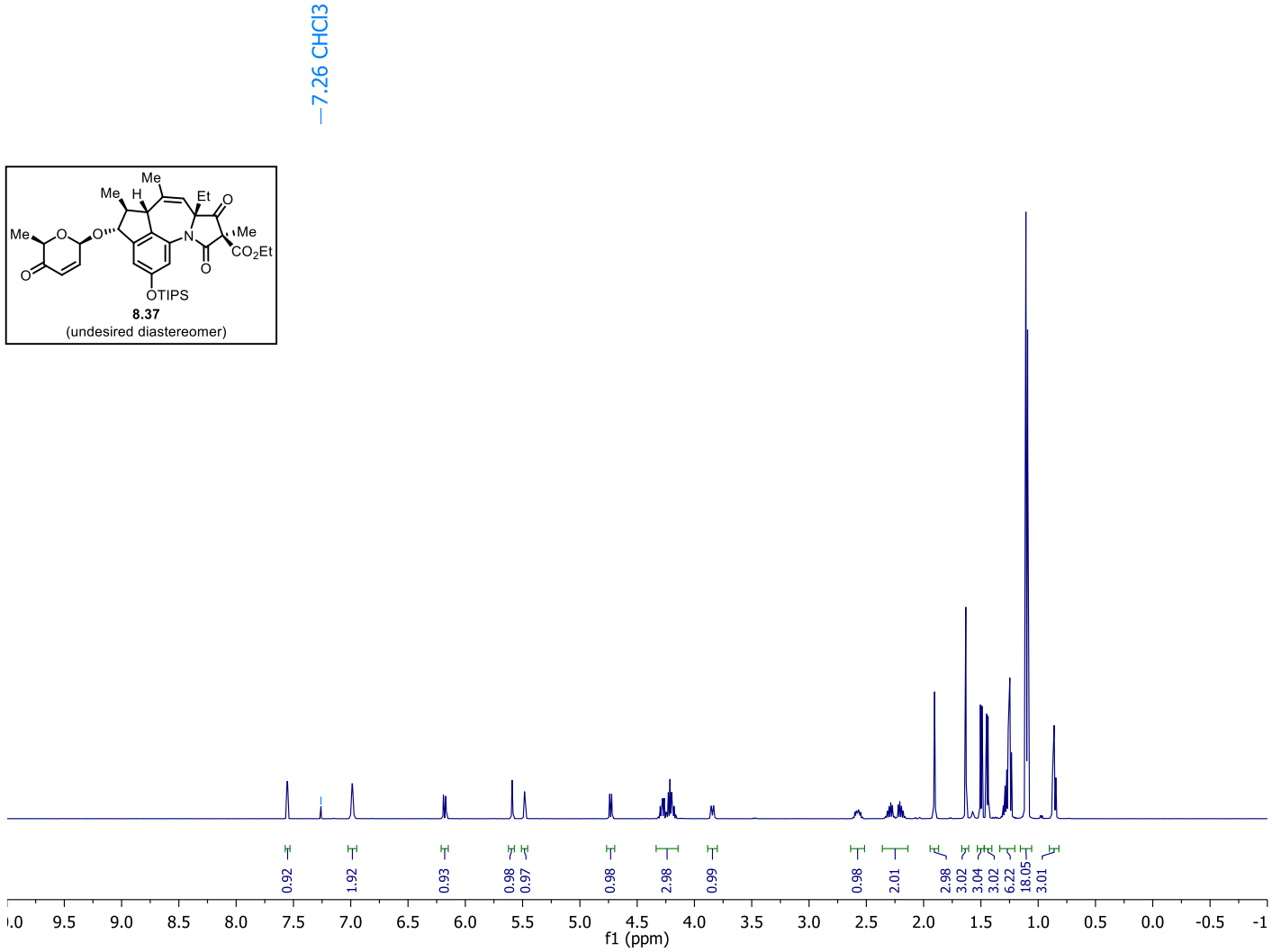


Figure F.19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.37** (lower R_f diastereomer)

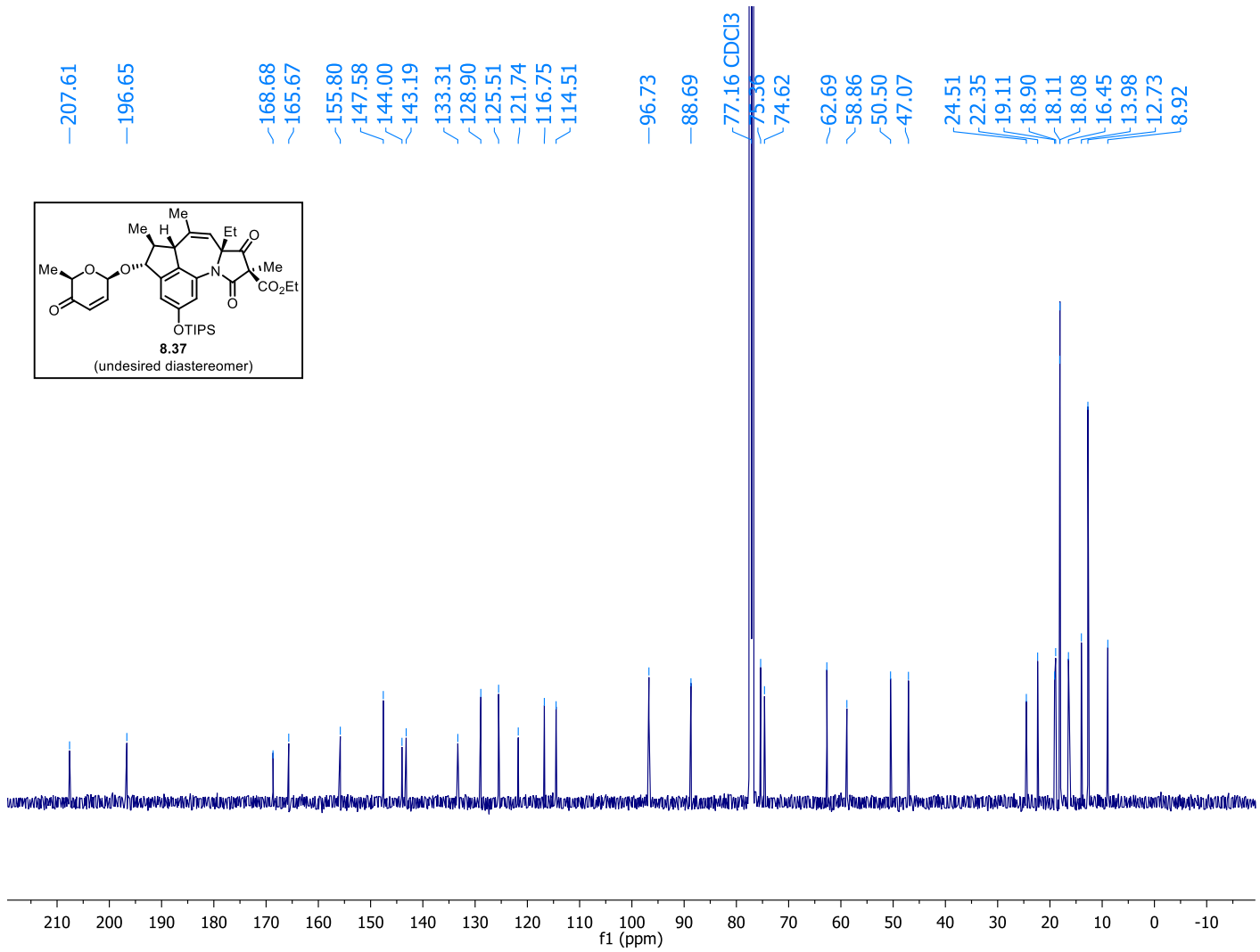


Figure F.20. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.37** (lower R_f diastereomer)

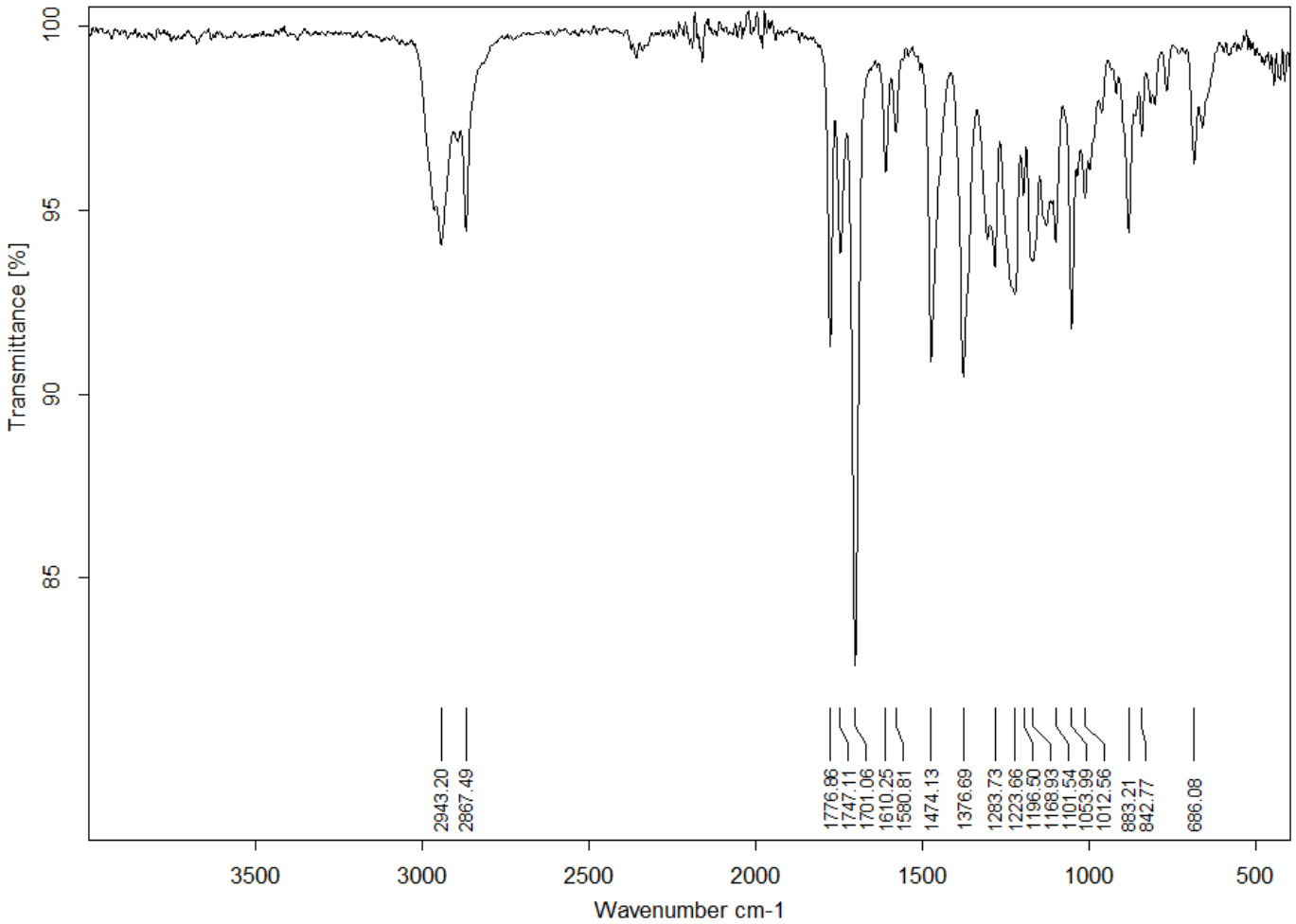


Figure F.21. FTIR spectrum (neat) of compound **8.37** (lower R_f diastereomer)

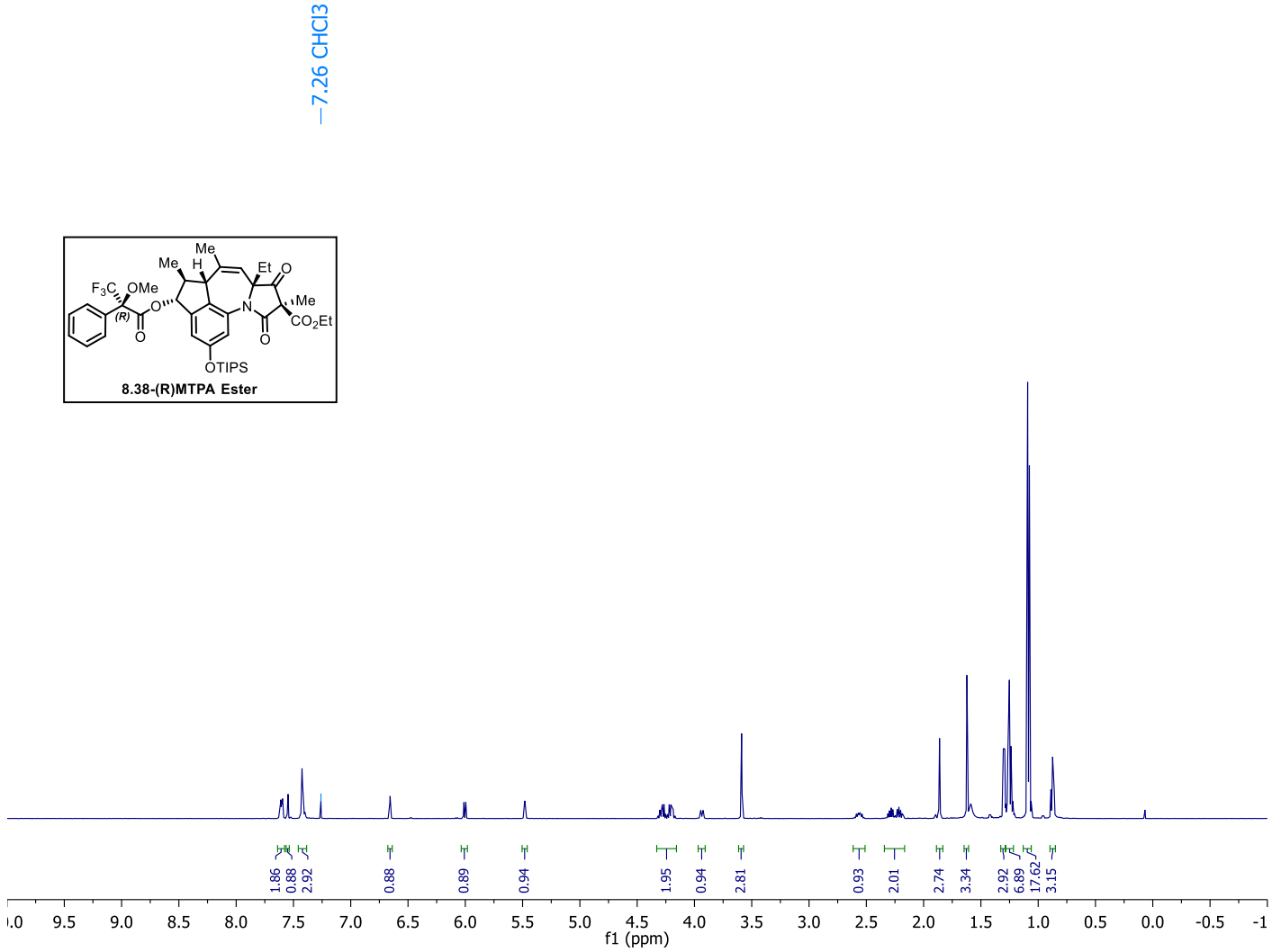


Figure F.22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.38-(*R*)MTPA Ester**

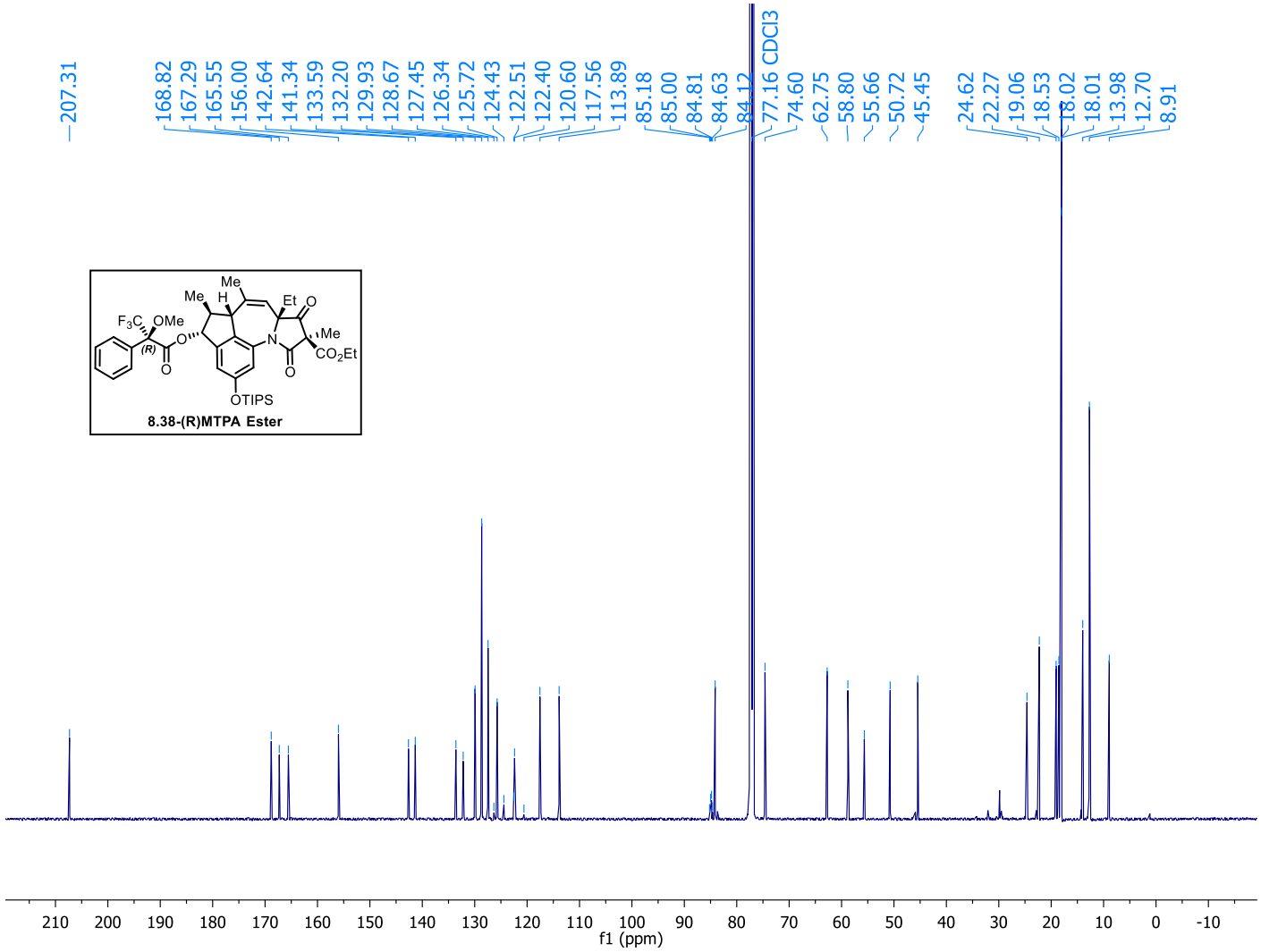


Figure F.23. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.38-(*R*)MTPA Ester**

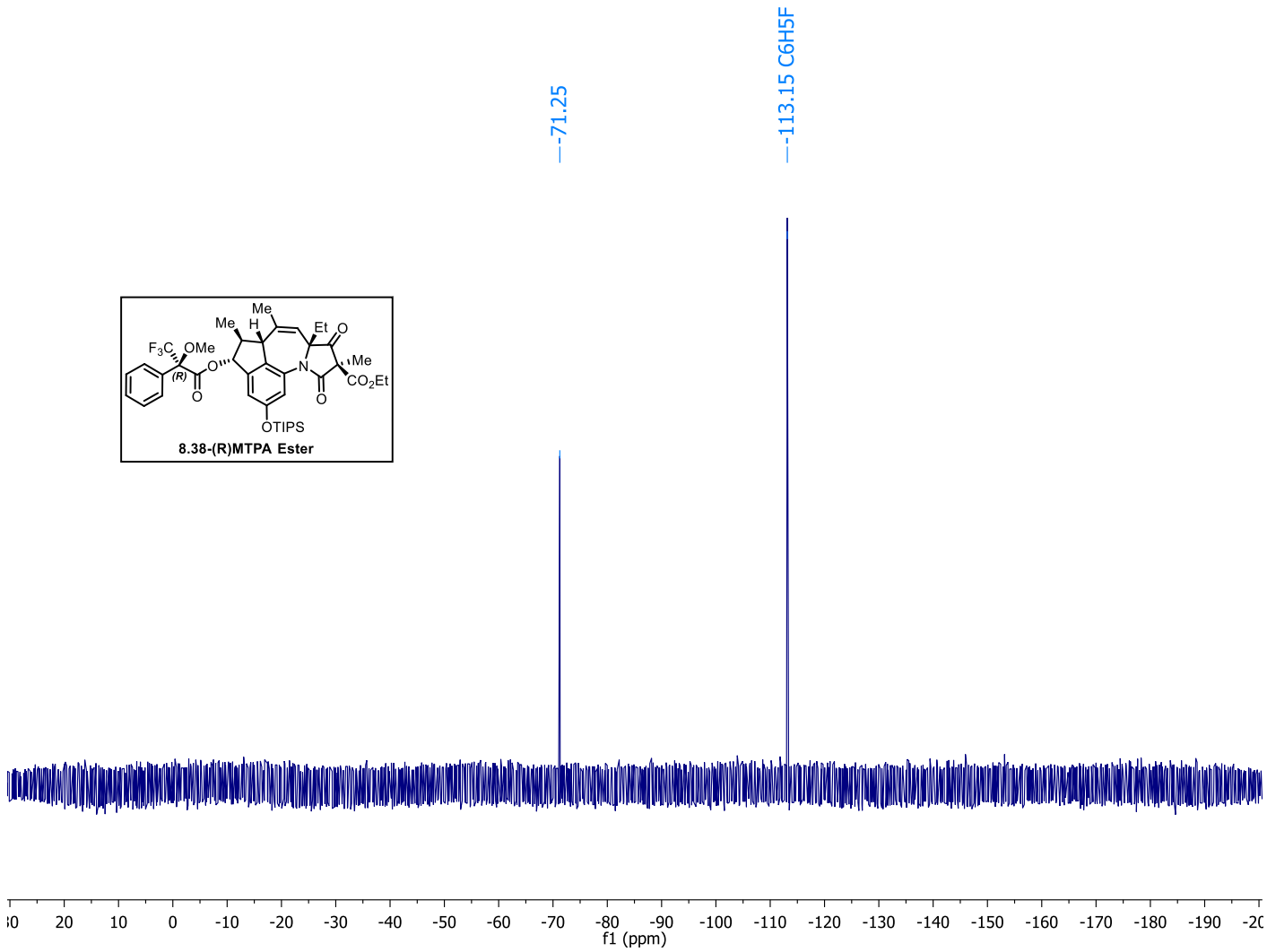


Figure F.24. ^{19}F NMR (470 MHz, $CDCl_3$) of compound **8.38-(*R*)MTPA Ester**

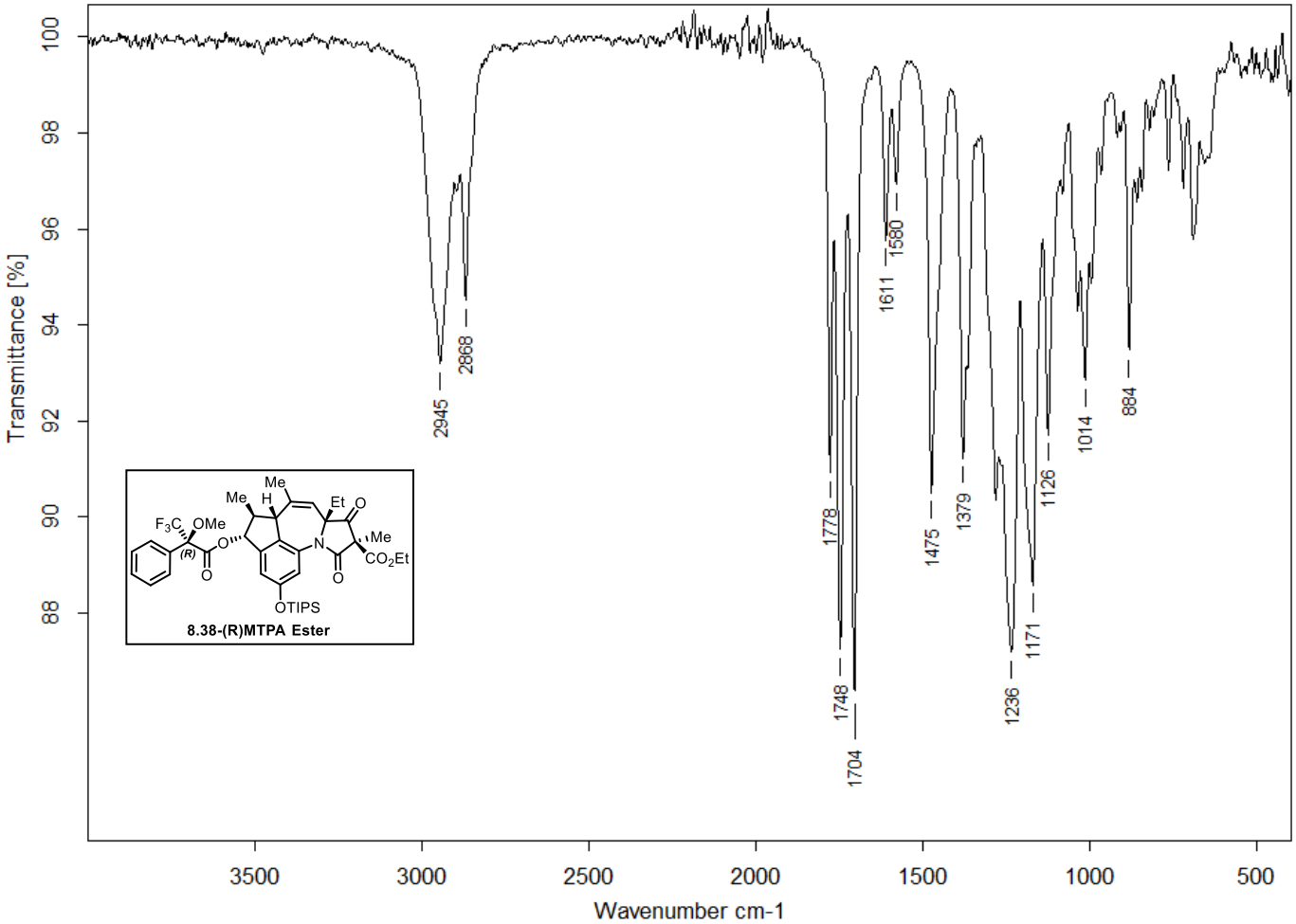


Figure F.25. FTIR spectrum (neat) of compound **8.38-(*R*)MTPA Ester**

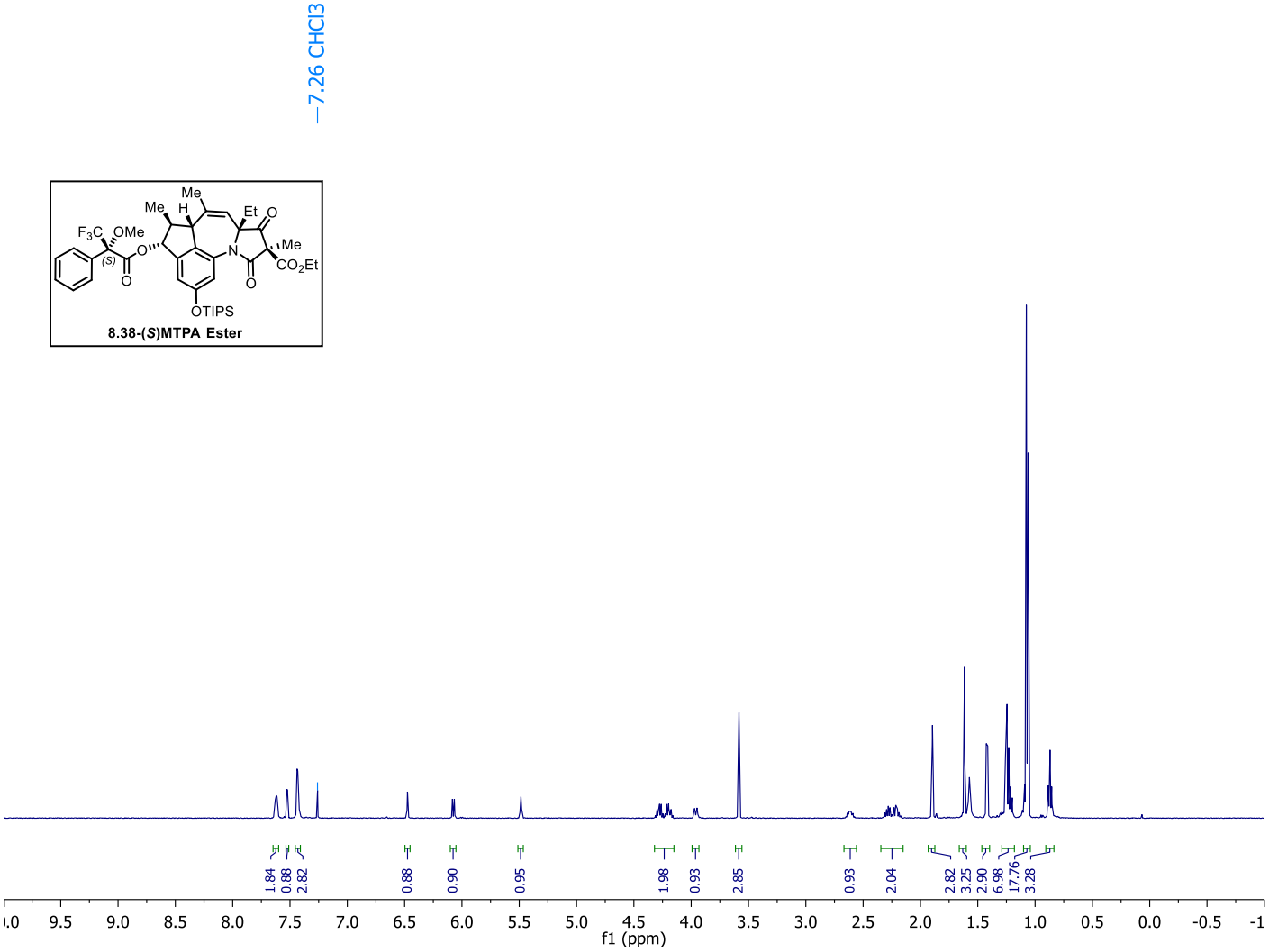


Figure F.26. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.38-(*S*)MTPA Ester**

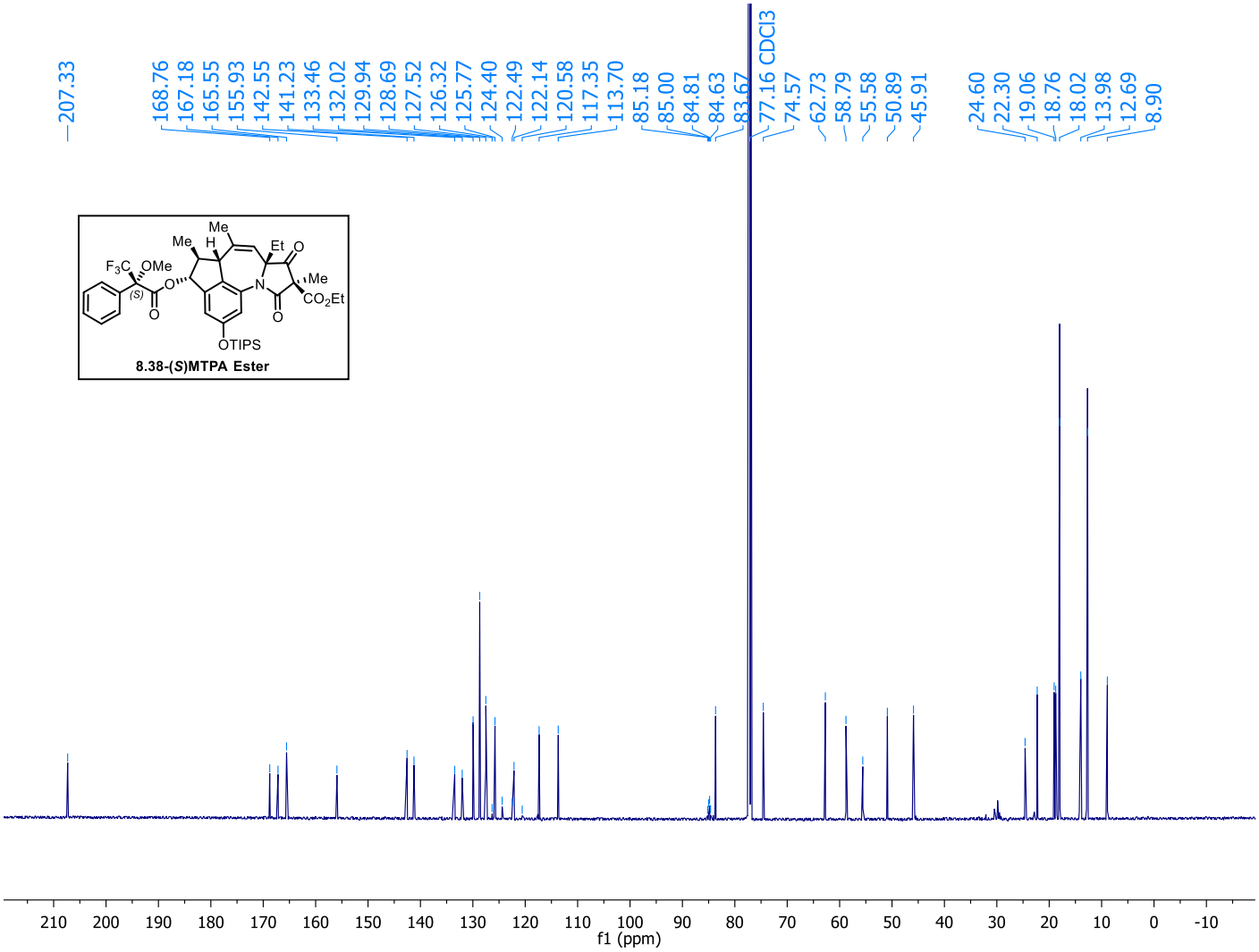


Figure F.27. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.38-(*S*)MTPA Ester**

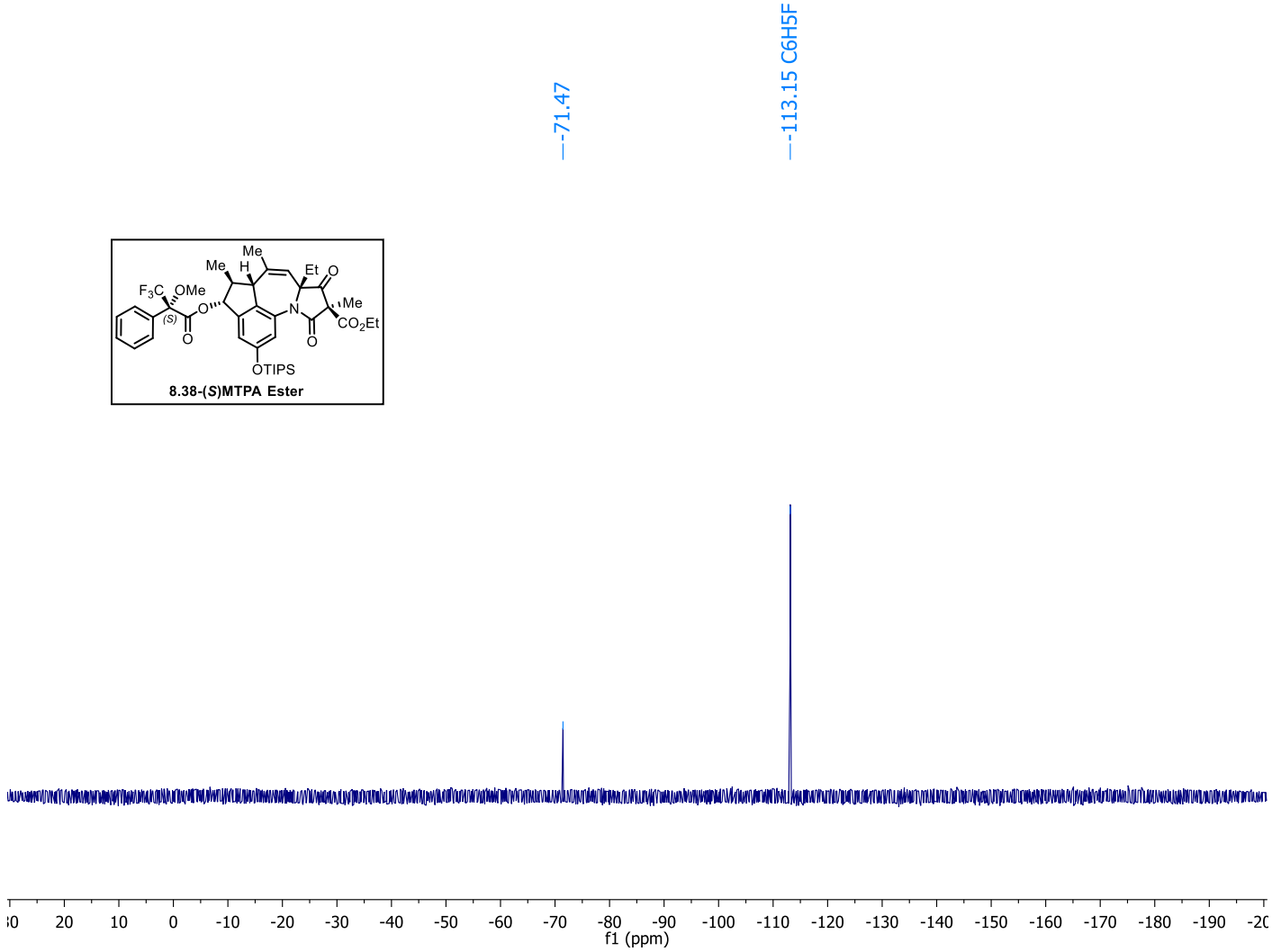


Figure F.28. ^{19}F NMR (470 MHz, $CDCl_3$) of compound **8.38-(*S*)MTPA Ester**

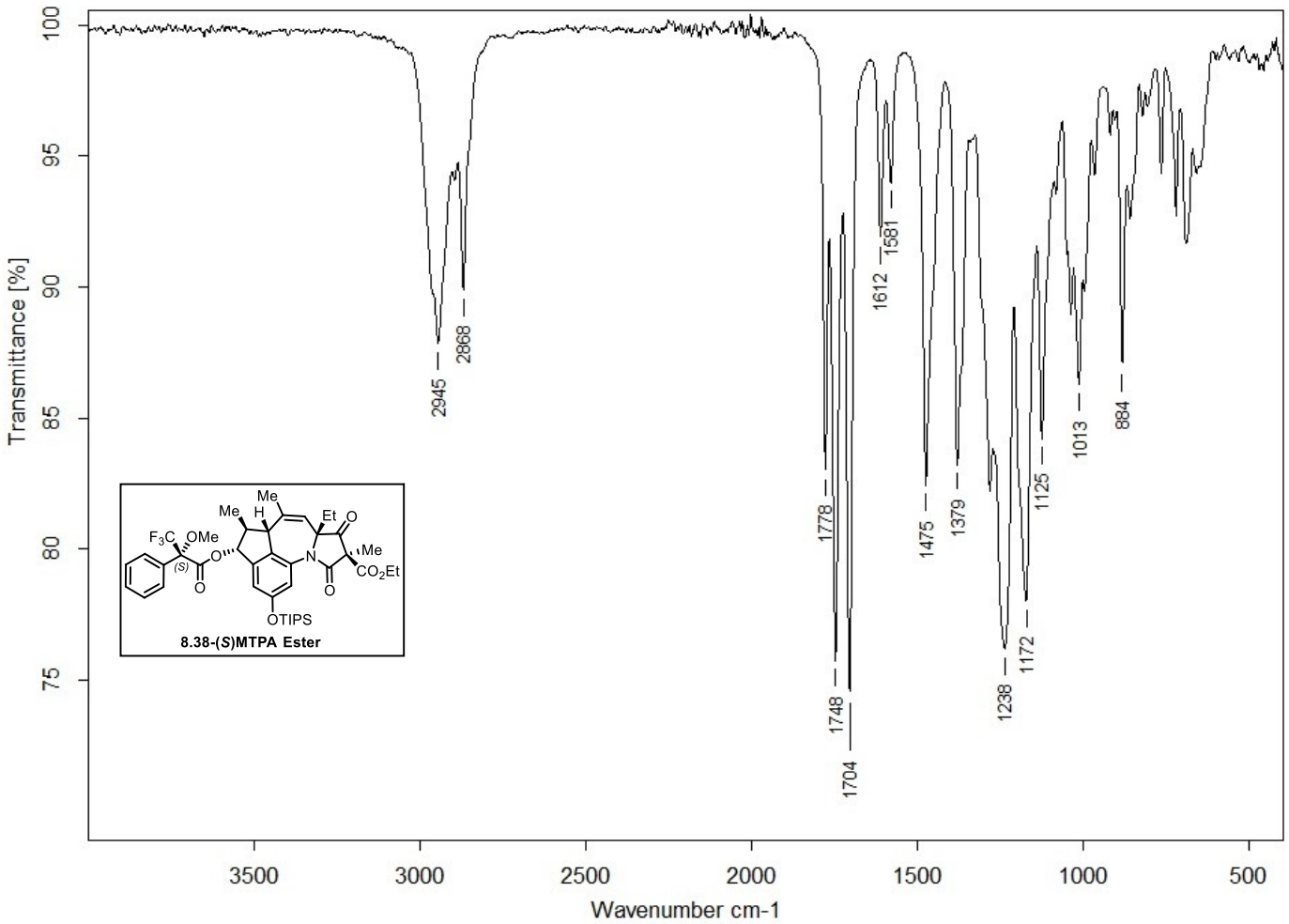


Figure F.29. FTIR spectrum (neat) of compound **8.38-(*S*)MTPA Ester**

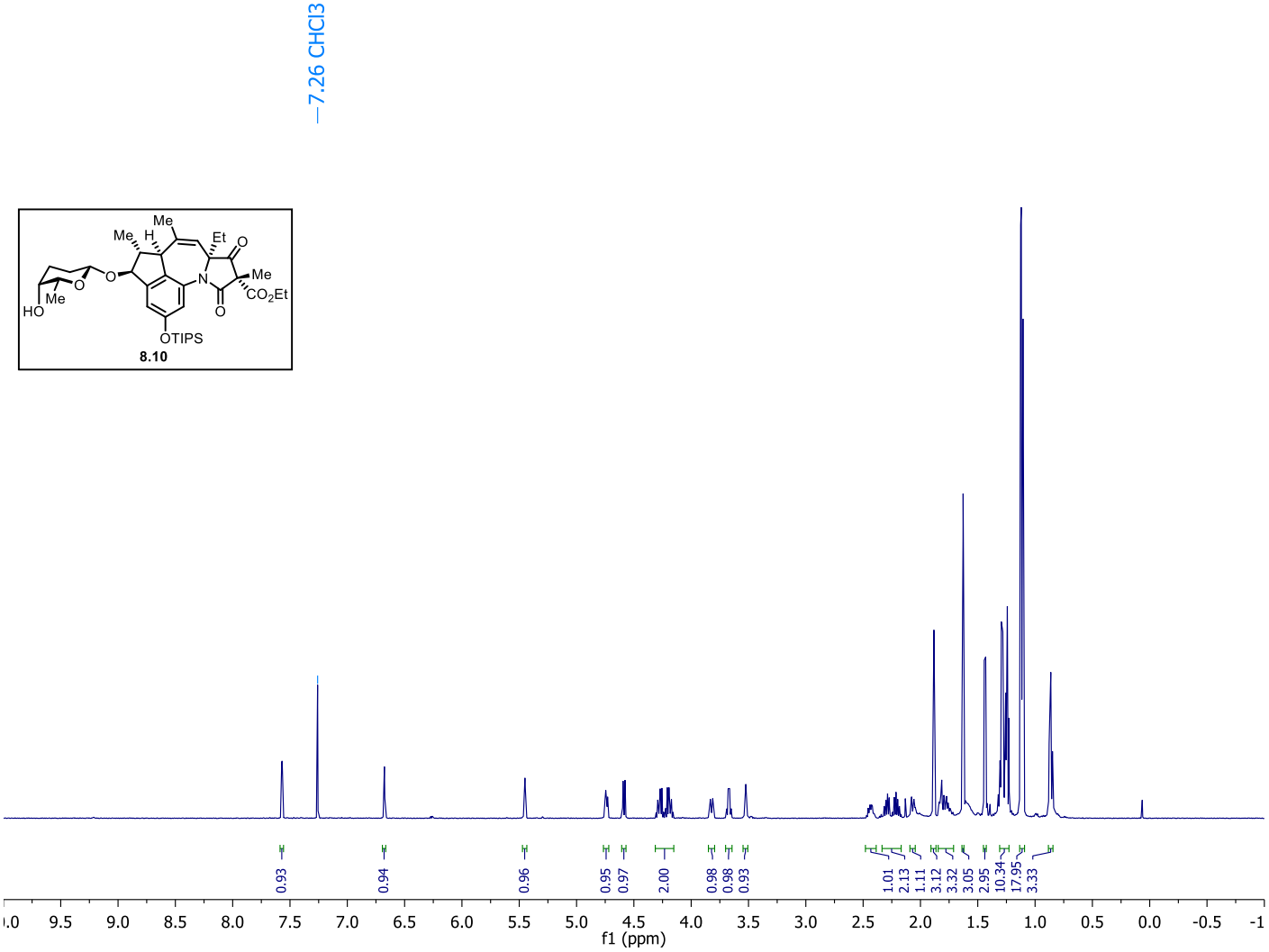


Figure F.30. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.10**

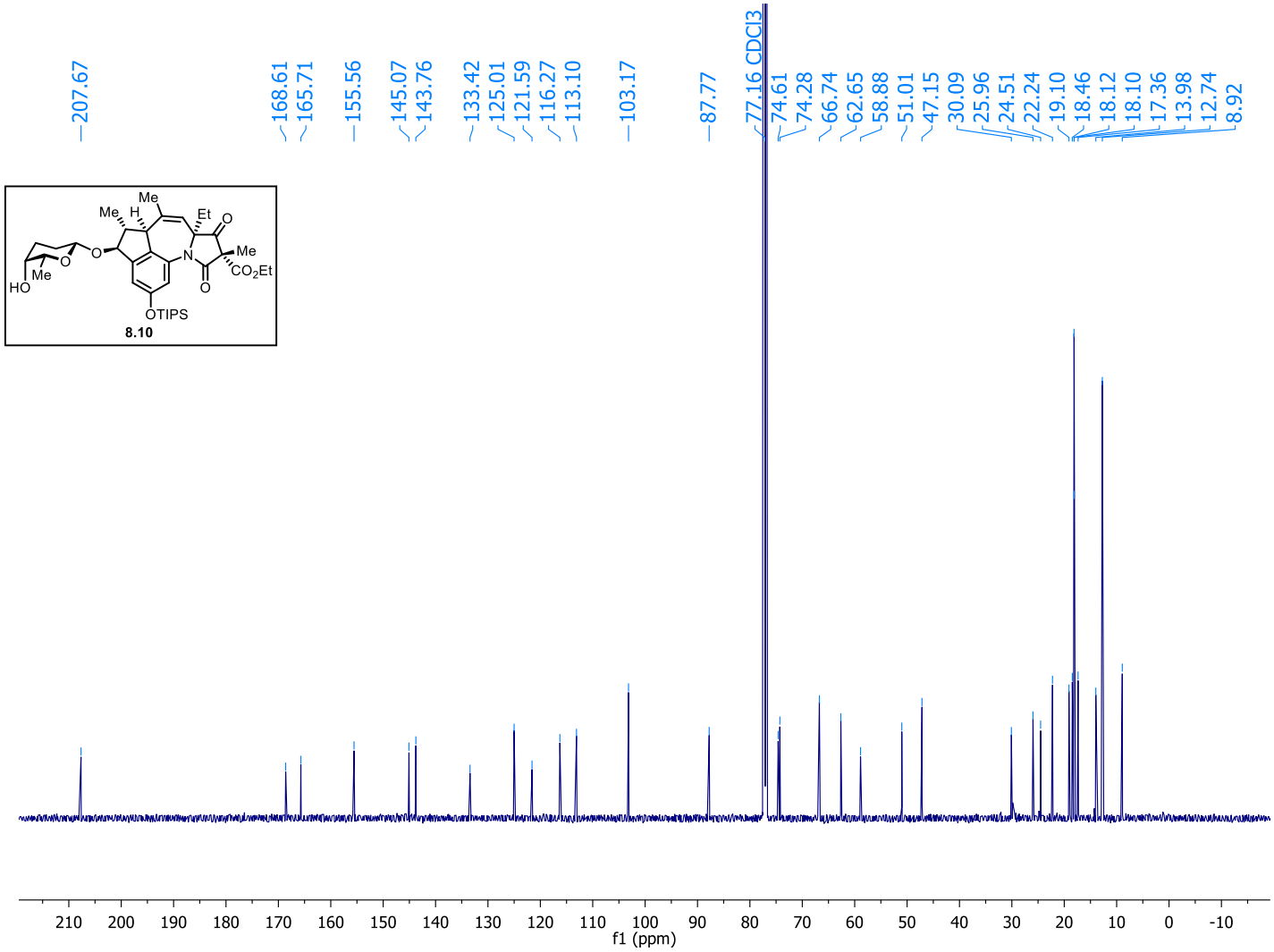


Figure F.31. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.10**

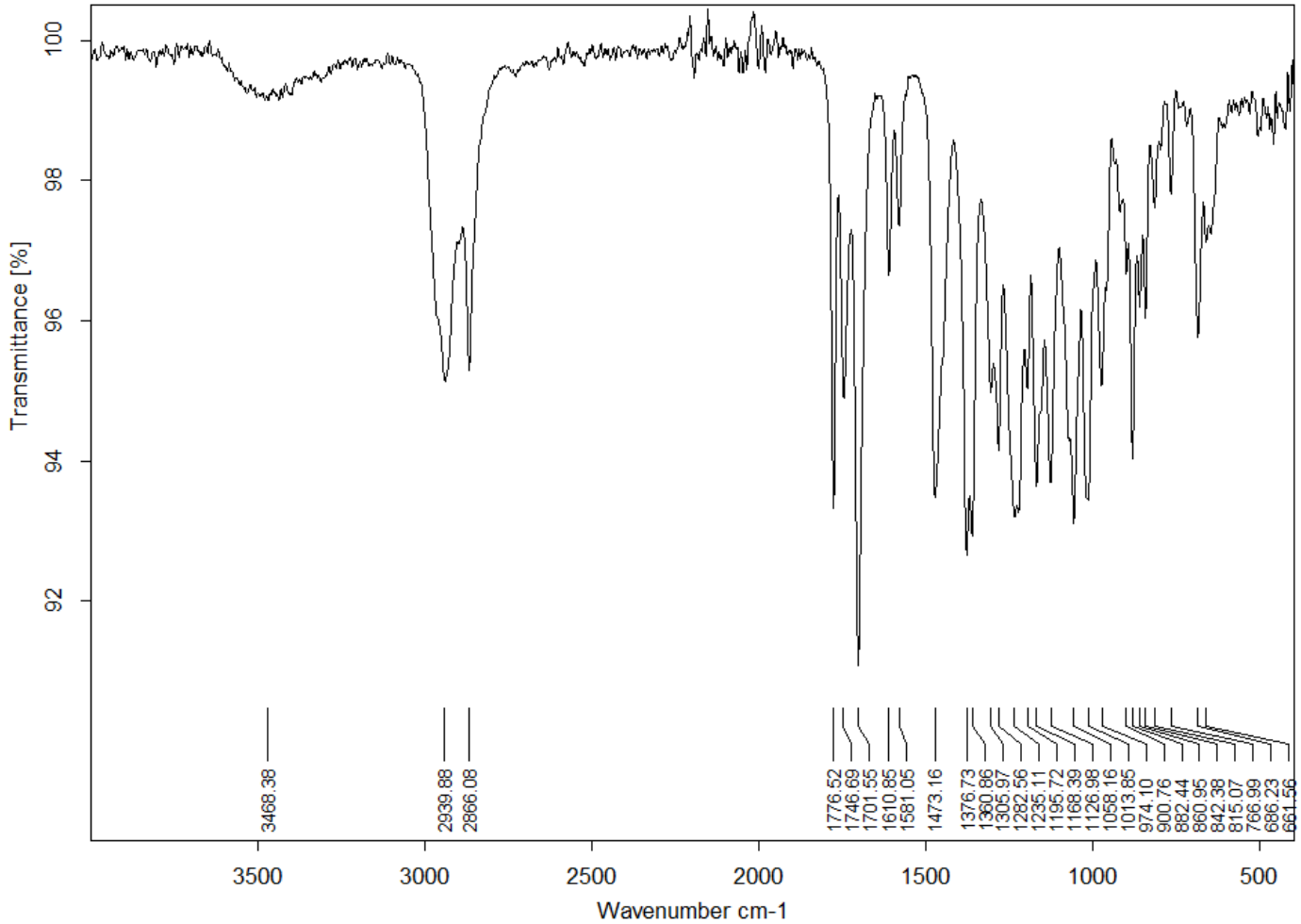


Figure F.32. FTIR spectrum (neat) of compound **8.10**

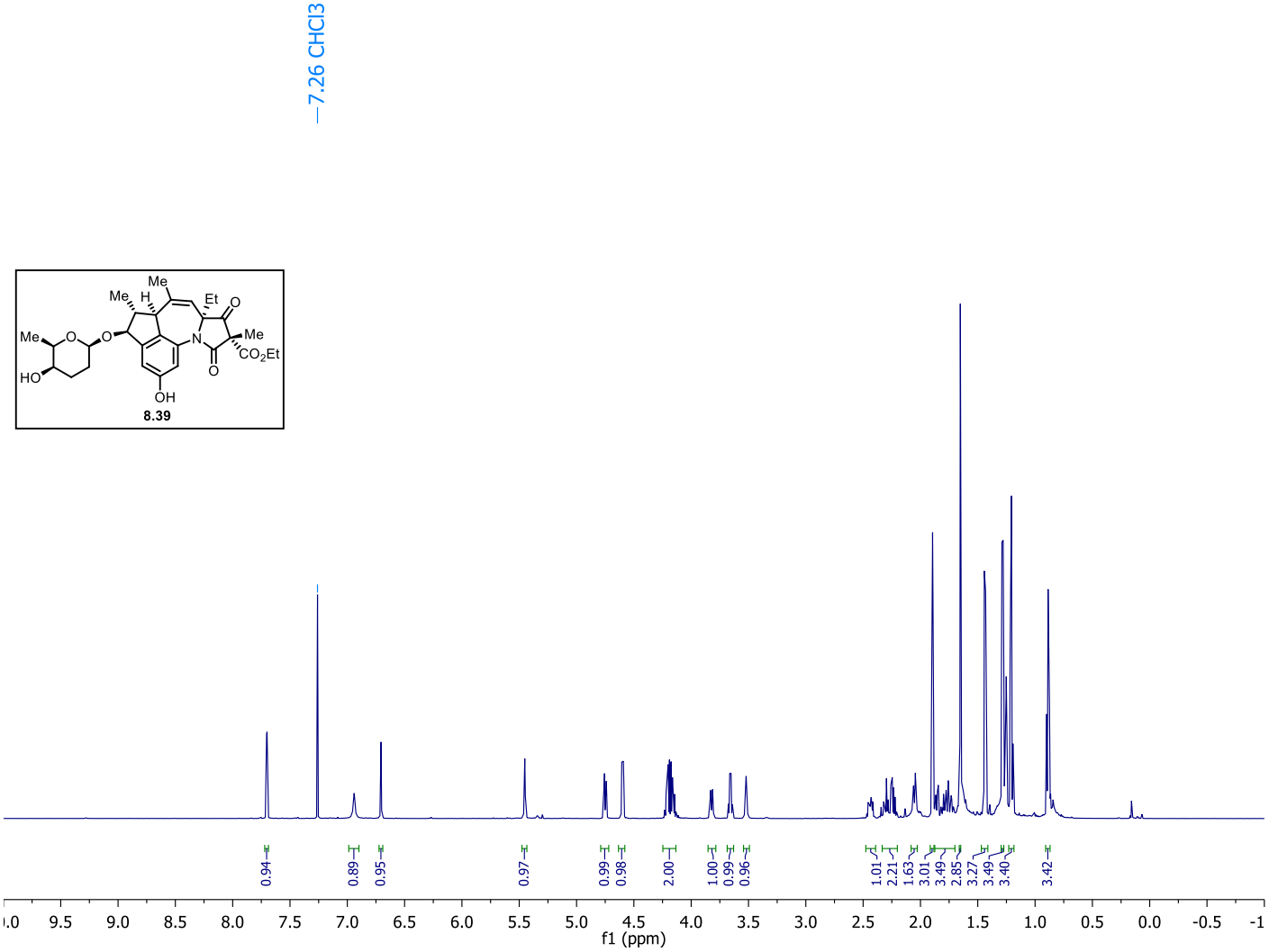


Figure F.33. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **8.39**

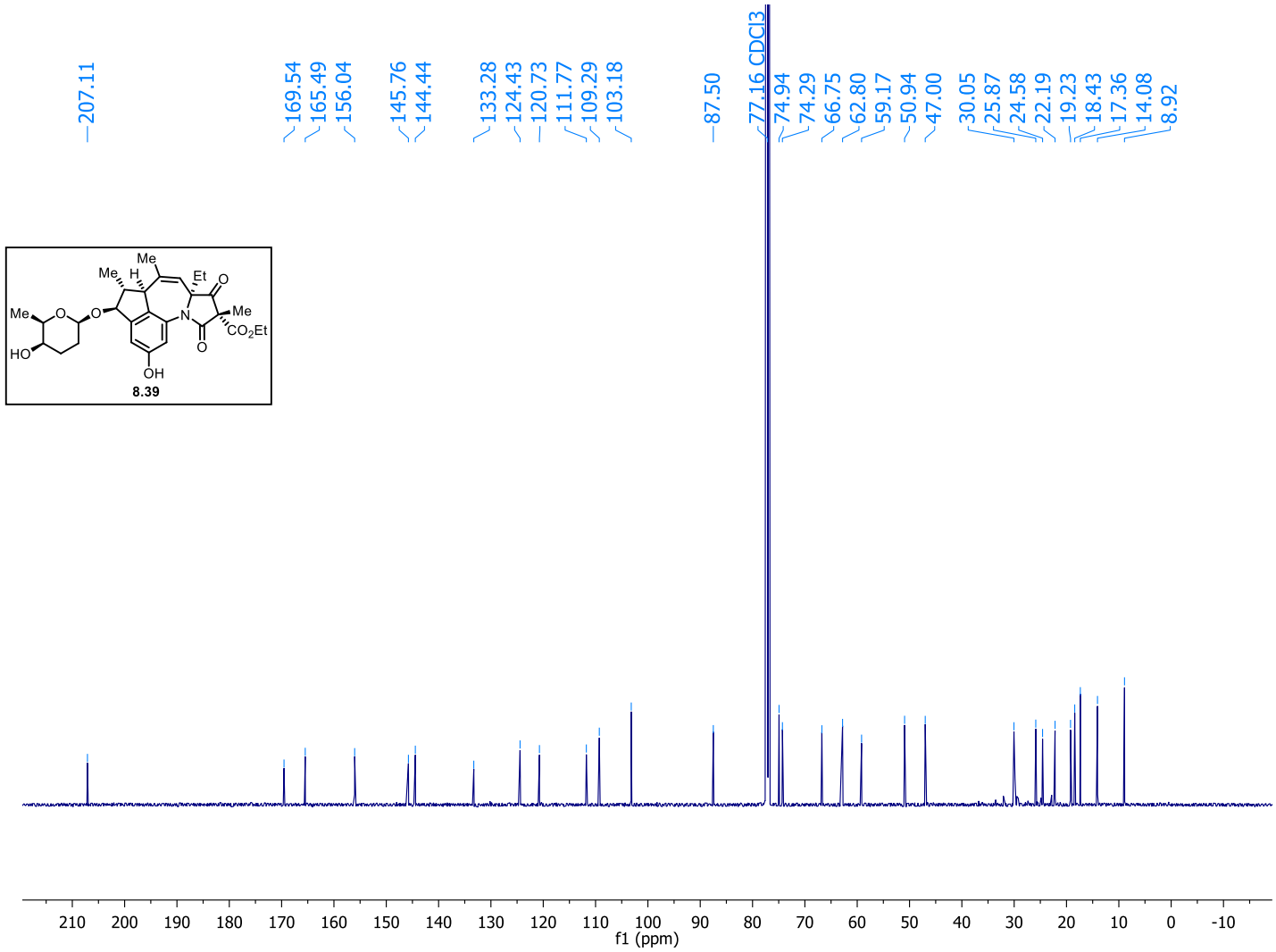


Figure F.34. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.39**

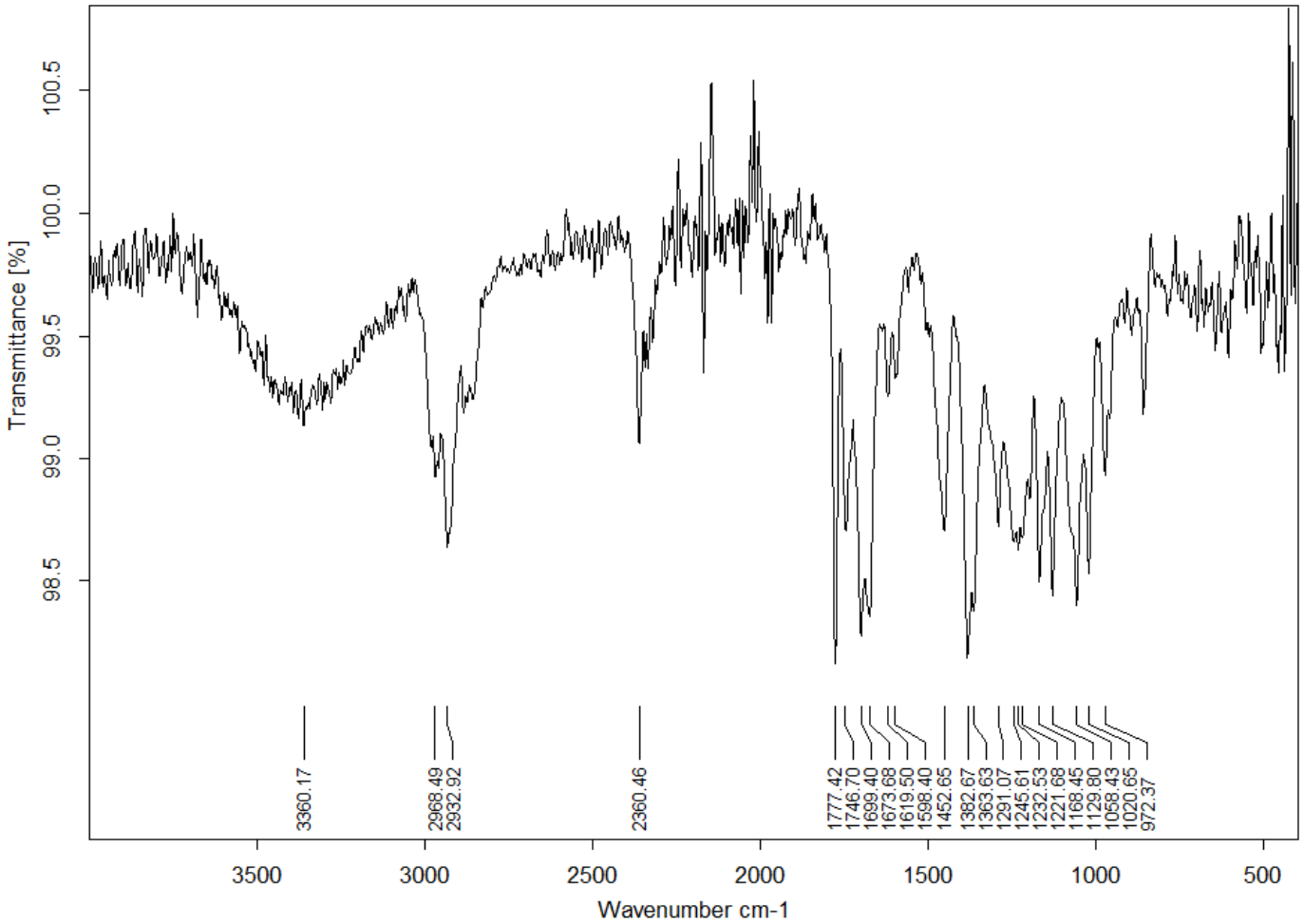


Figure F.35. FTIR spectrum (neat) of compound **8.39**

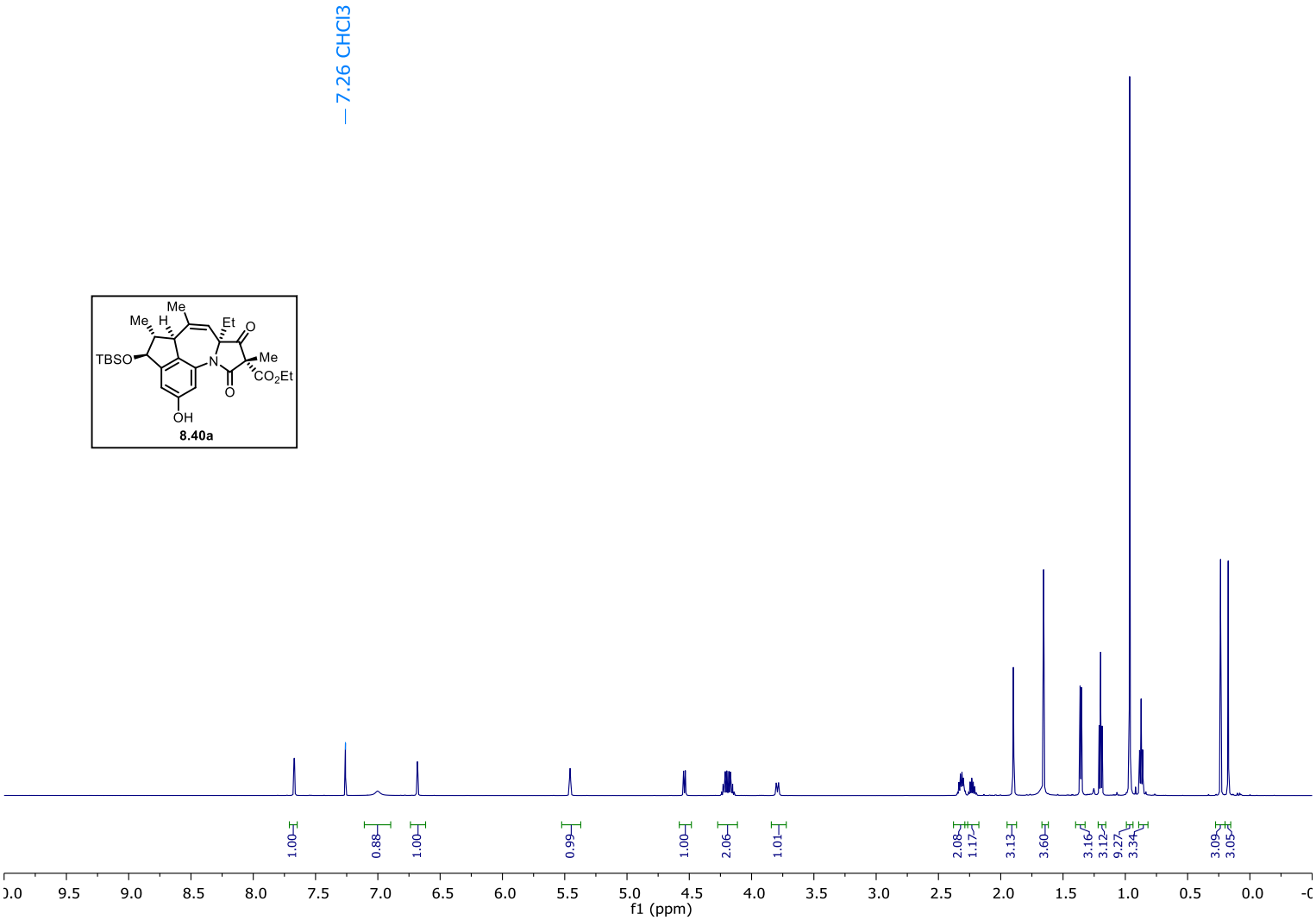


Figure F.36. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **8.40a**

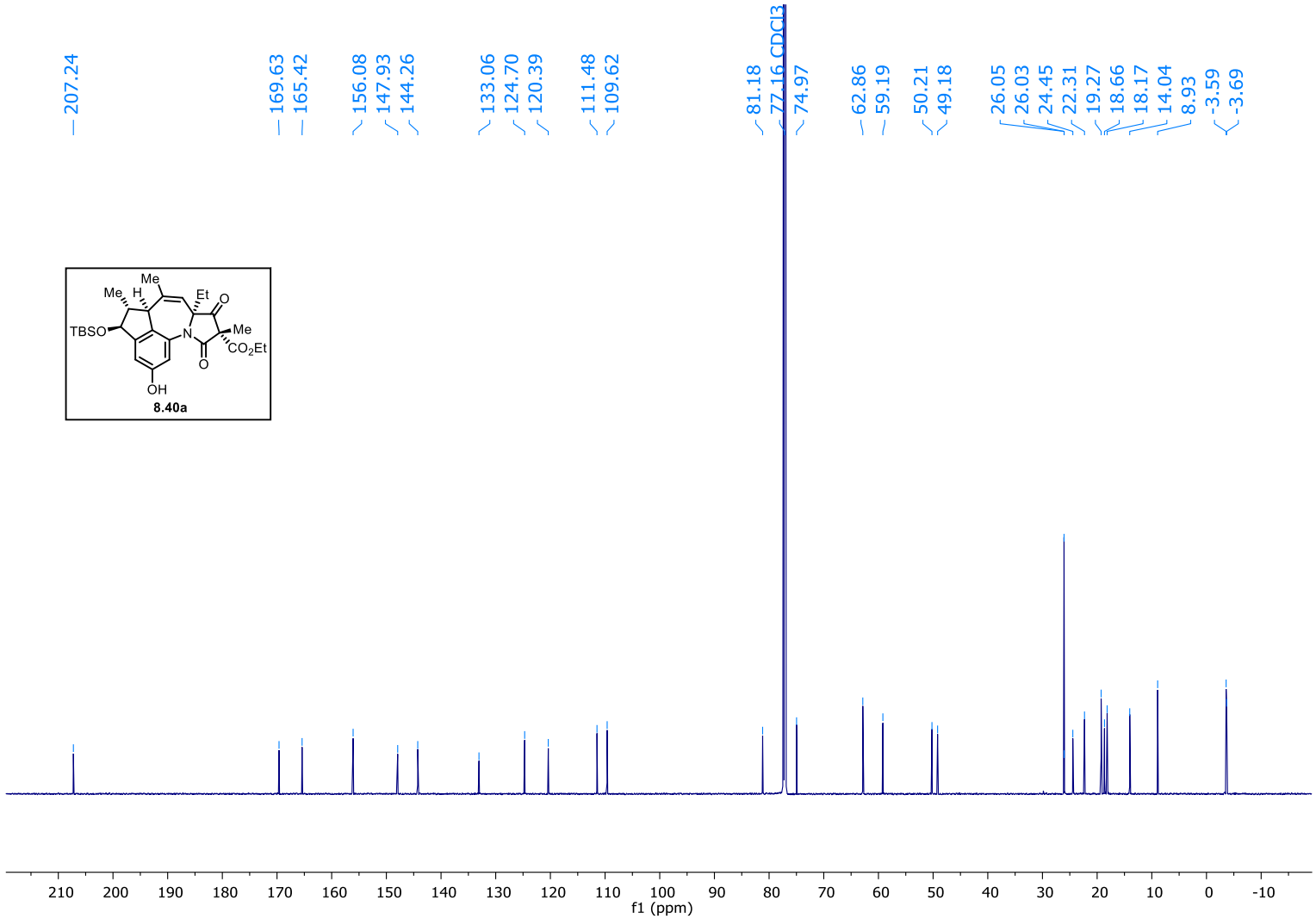


Figure F.37. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.40a**

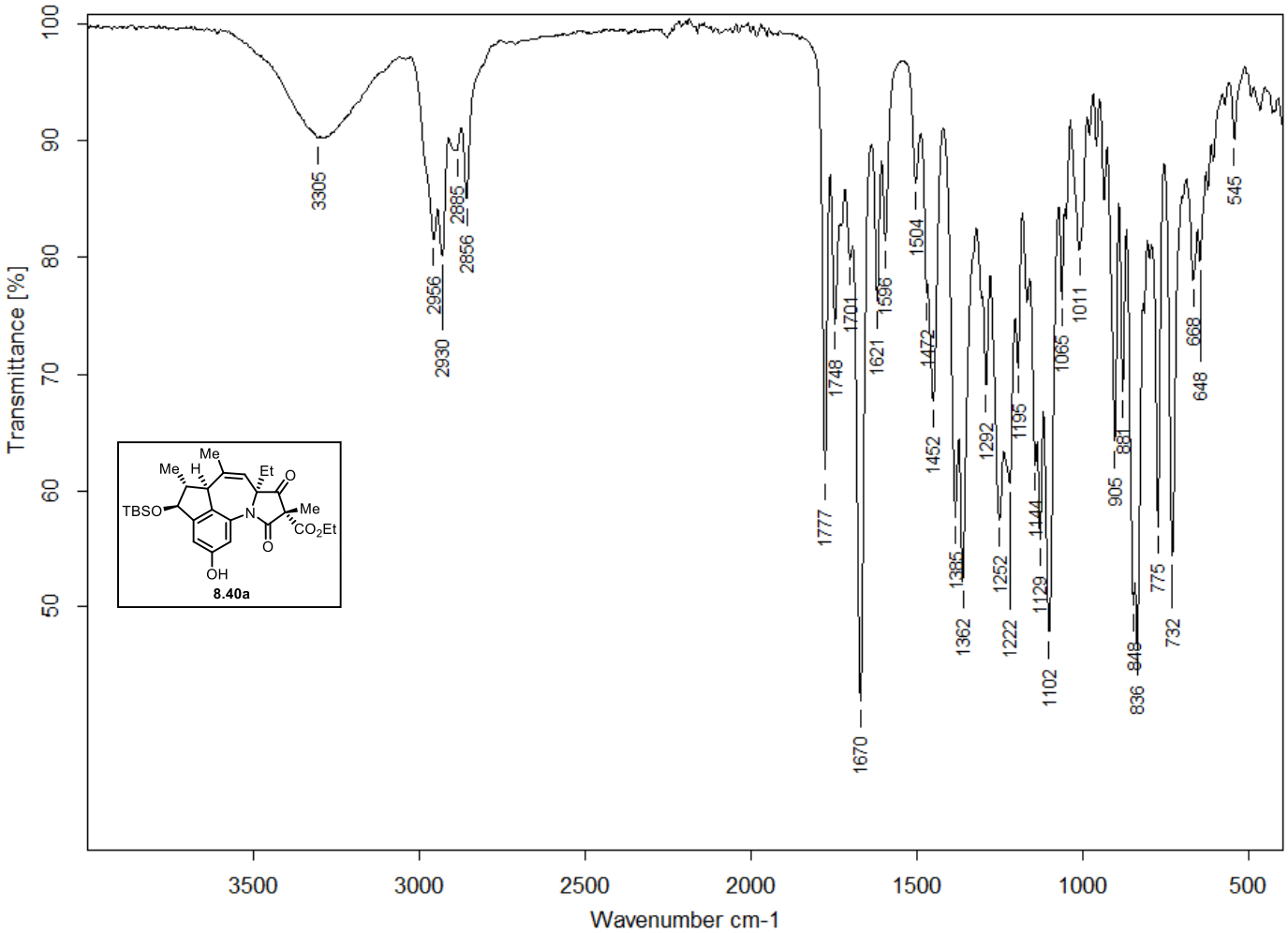


Figure F.38. FTIR spectrum (neat) of compound **8.40a**

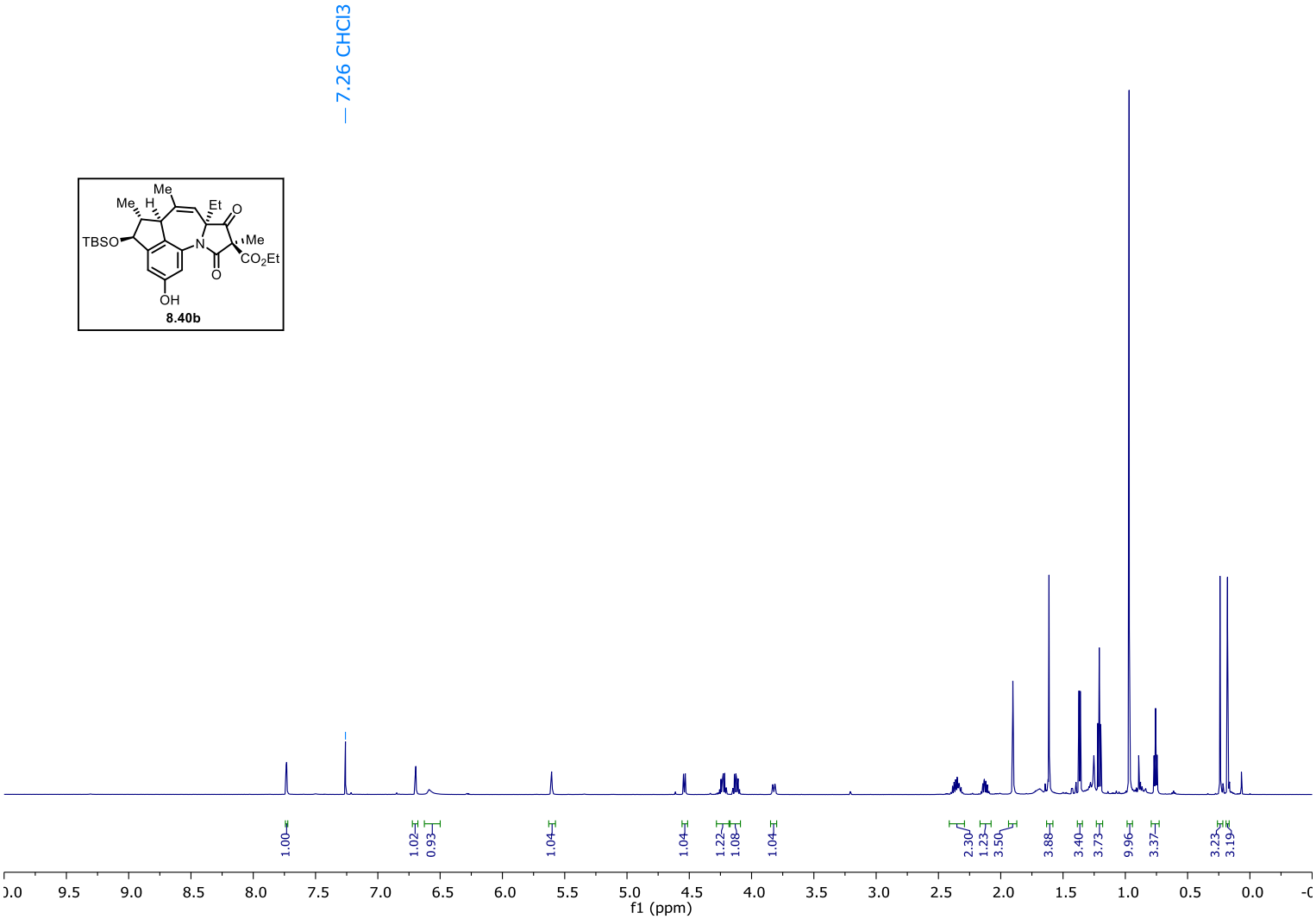


Figure F.39. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **8.40b**

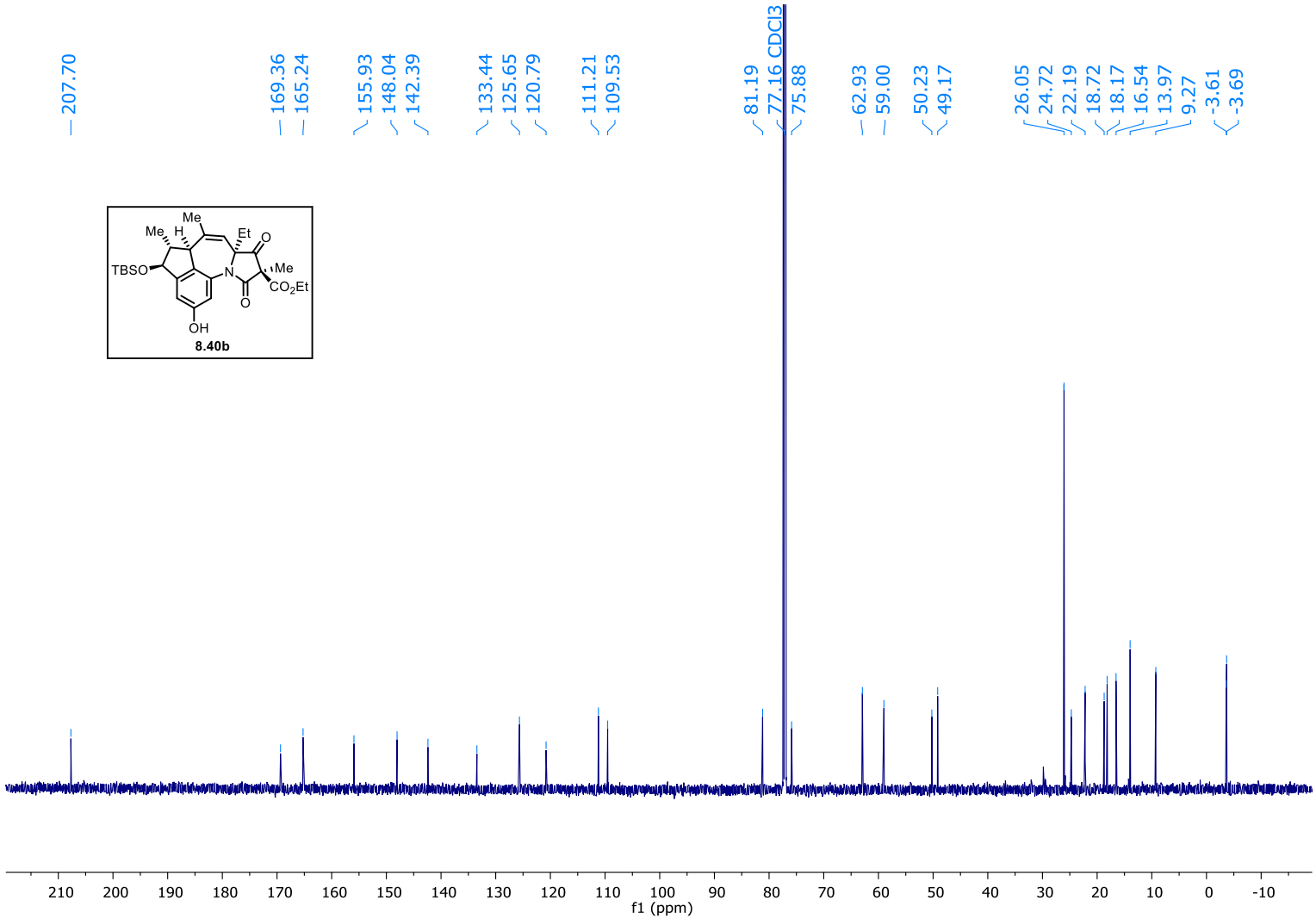


Figure F.40. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.40b**

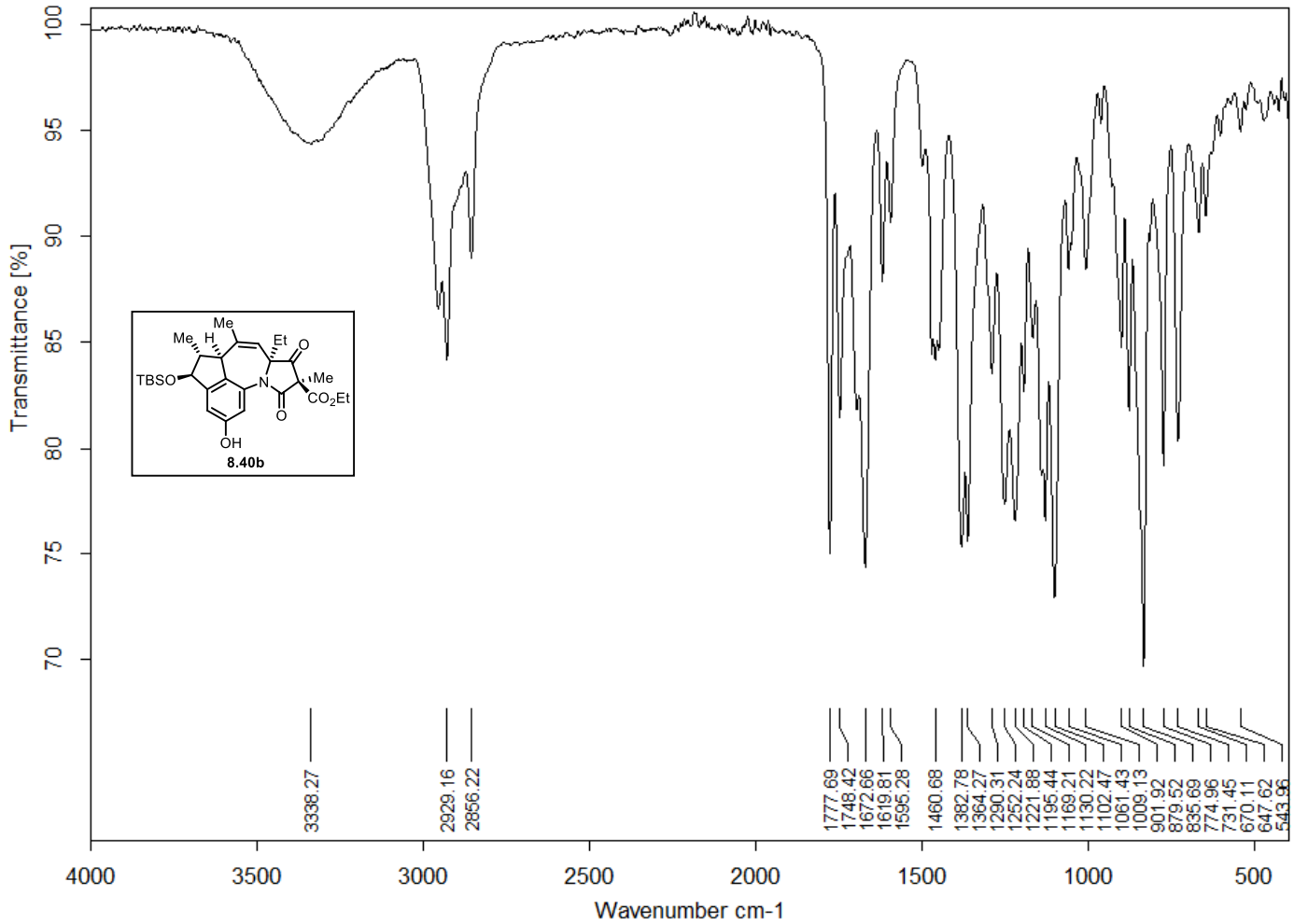


Figure F.41. FTIR spectrum (neat) of compound **8.40b**

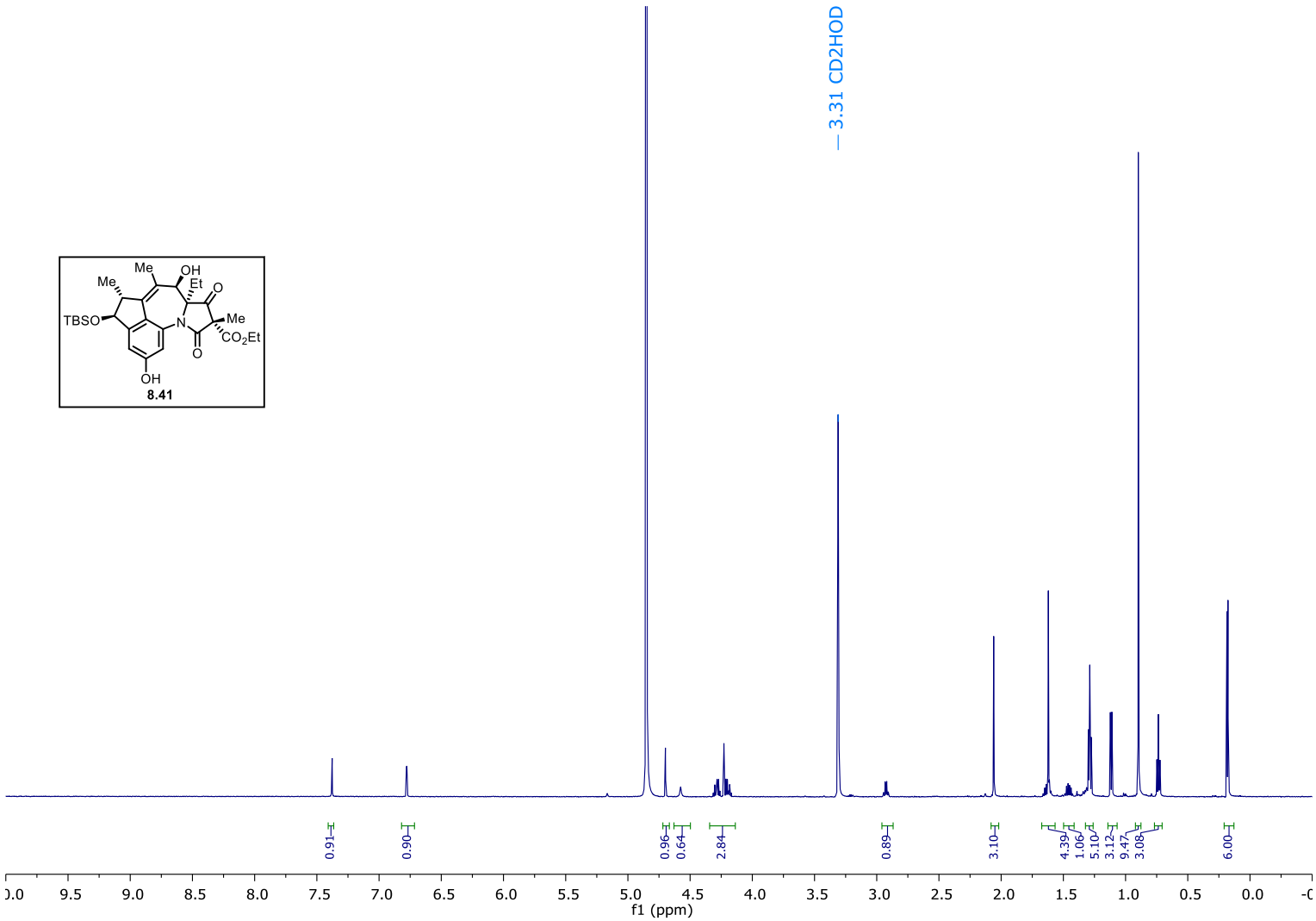


Figure F.42. ^{1}H NMR (600 MHz, MeOD-d_4) of compound **8.41**

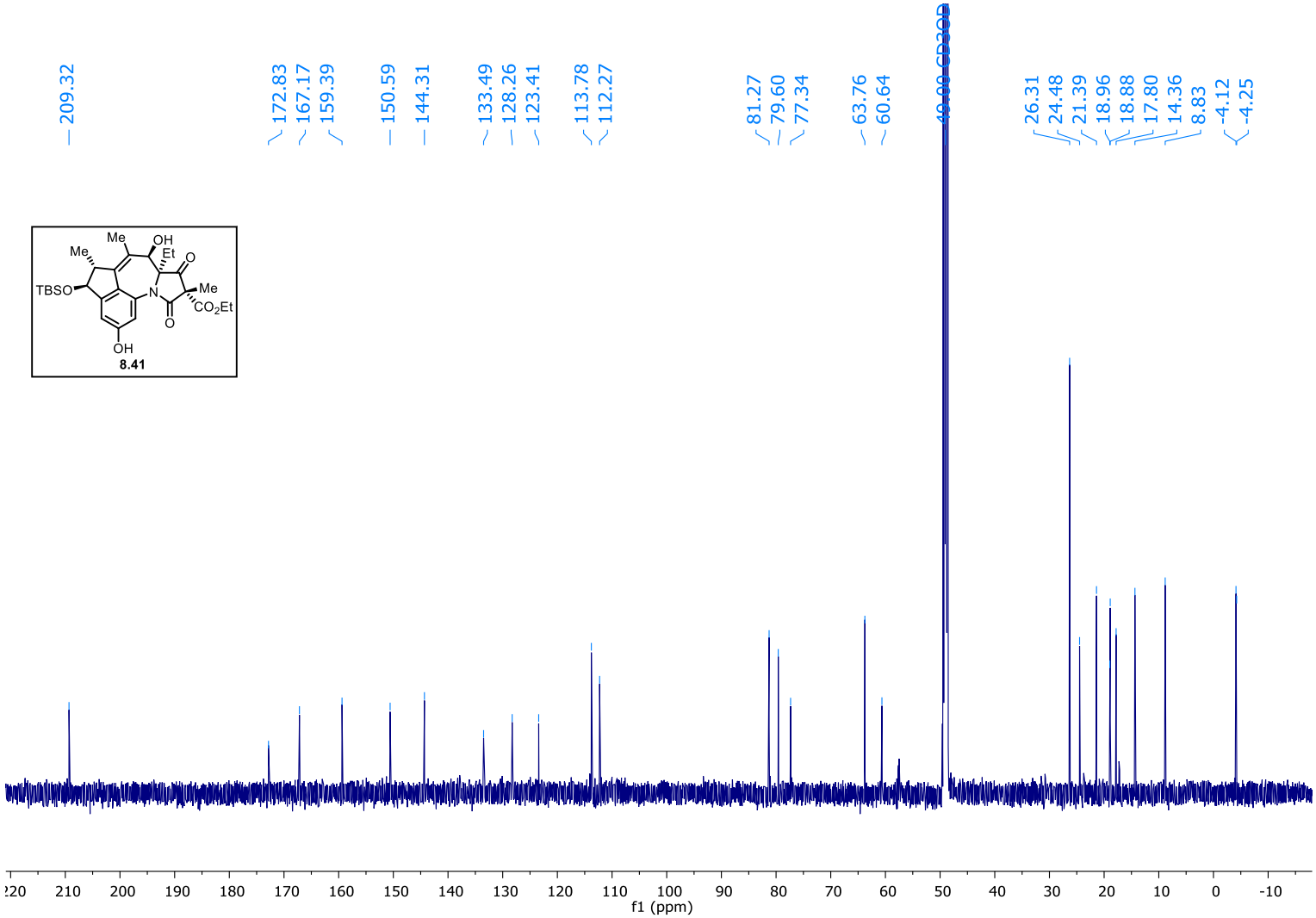


Figure F.43. ^{13}C NMR (151 MHz, MeOD-d_4) of compound **8.41**

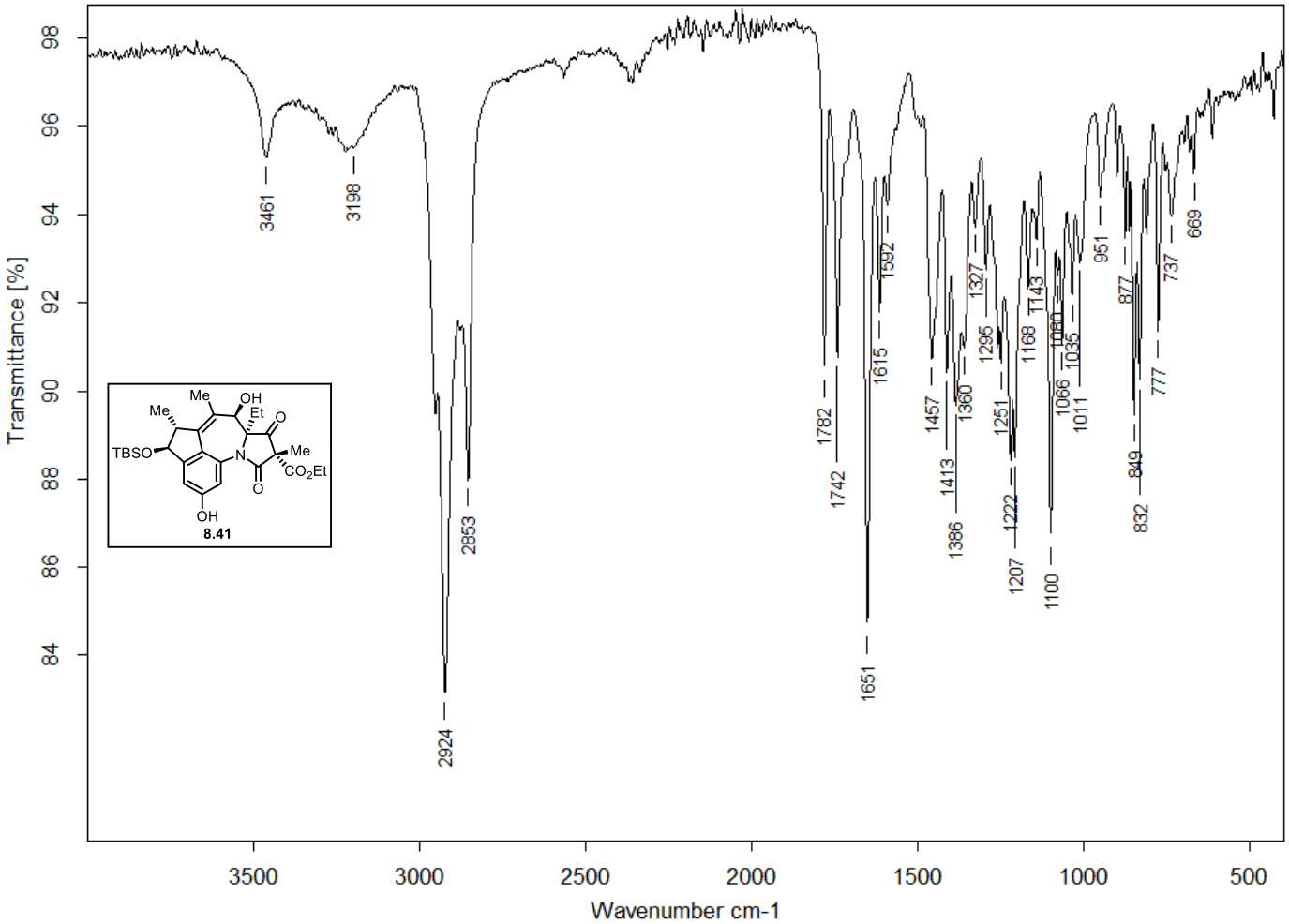


Figure F.44. FTIR spectrum (neat) of compound **8.41**

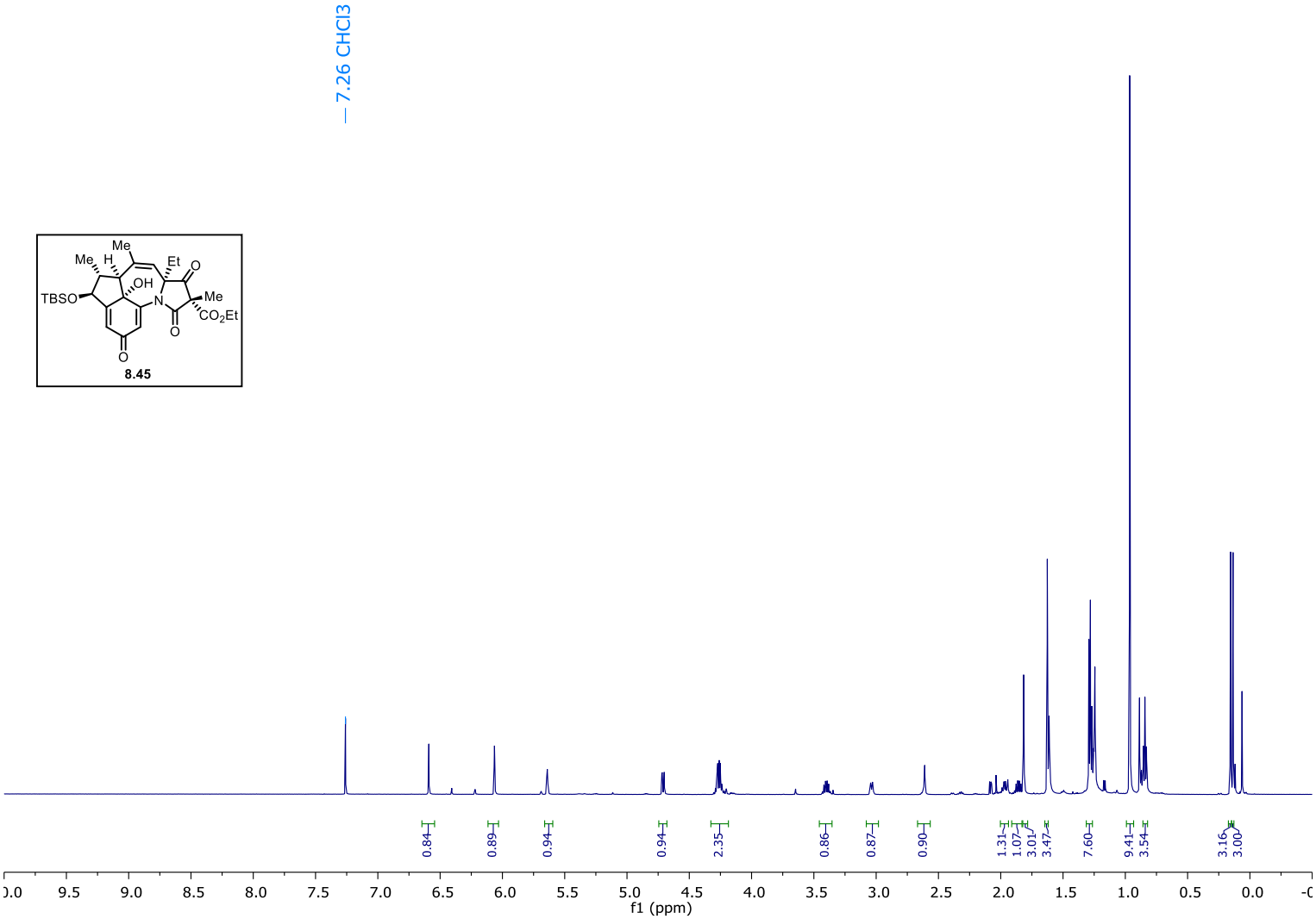


Figure F.45. ^{1}H NMR (600 MHz, $CDCl_3$) of compound **8.45**

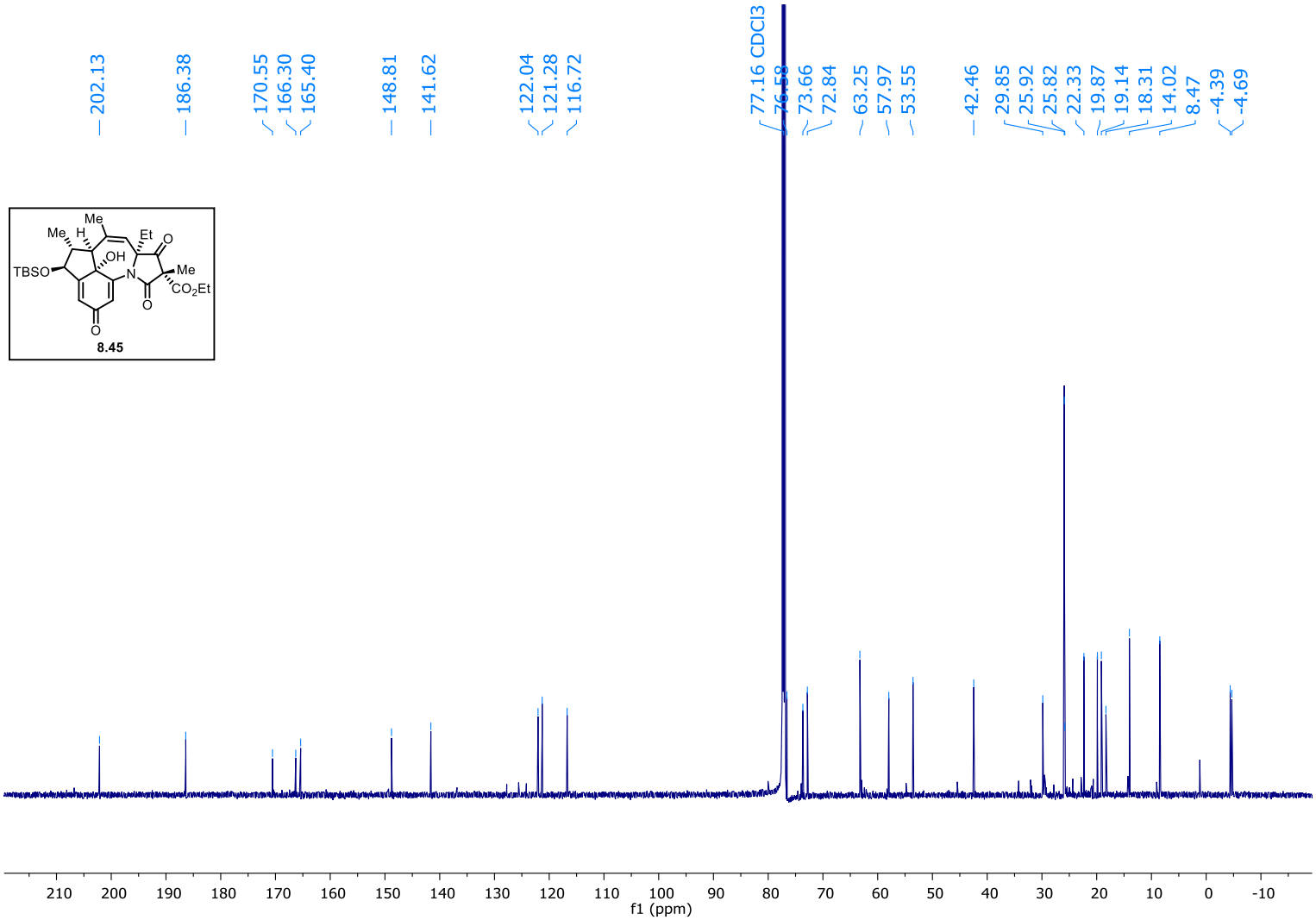


Figure F.46. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.45**

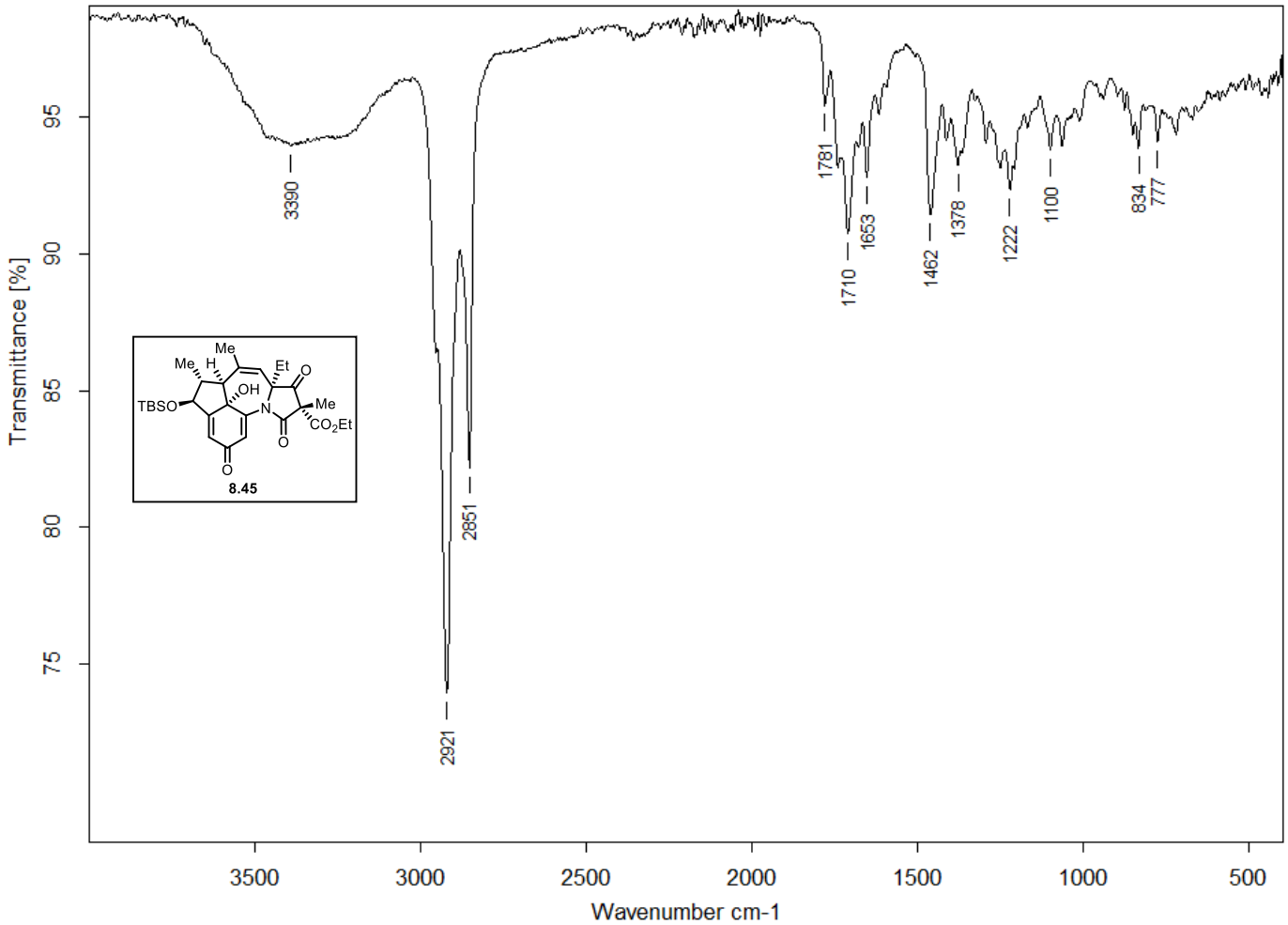


Figure F.47. FTIR spectrum (neat) of compound **8.45**

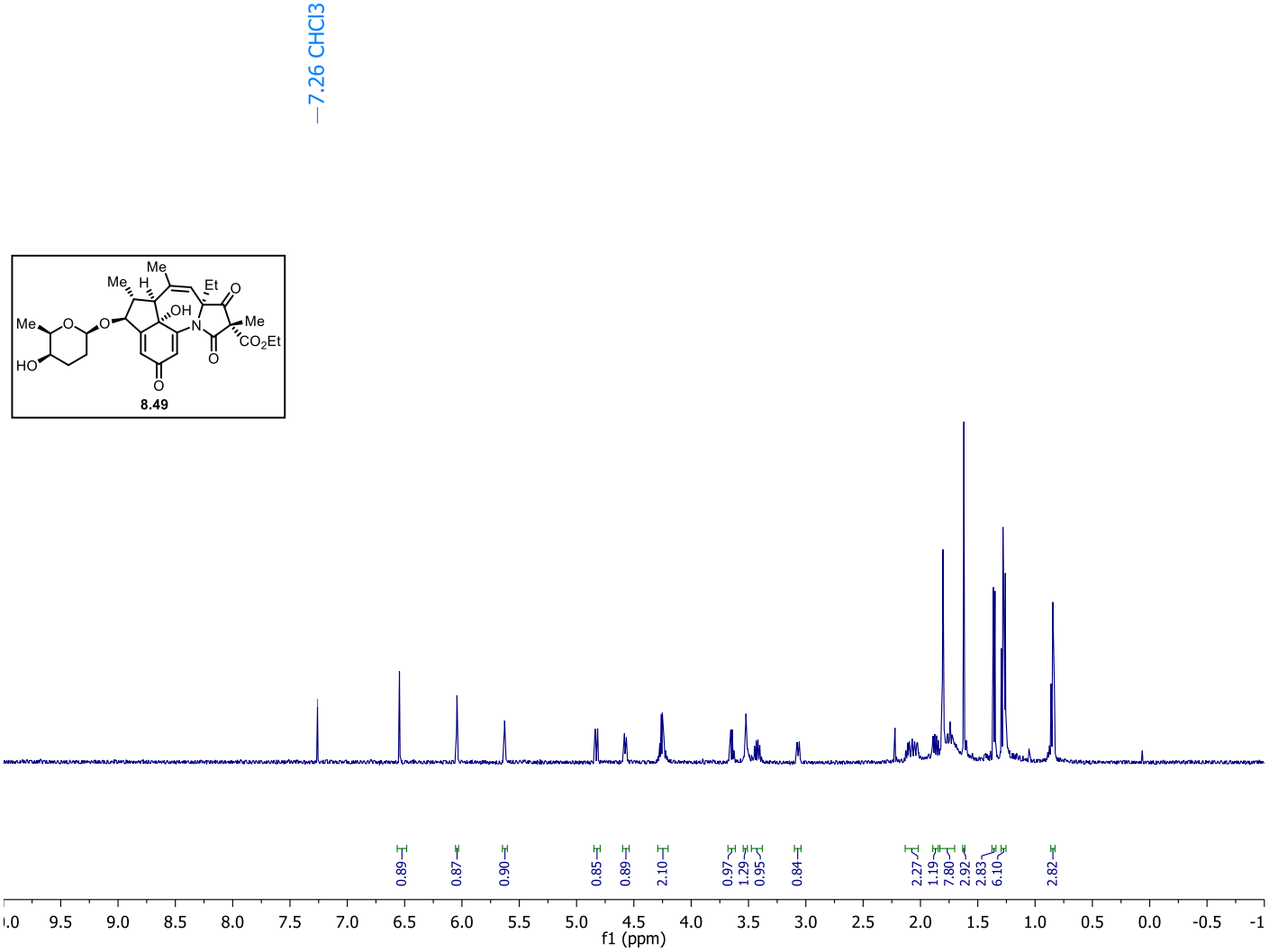


Figure F.48. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8.49**

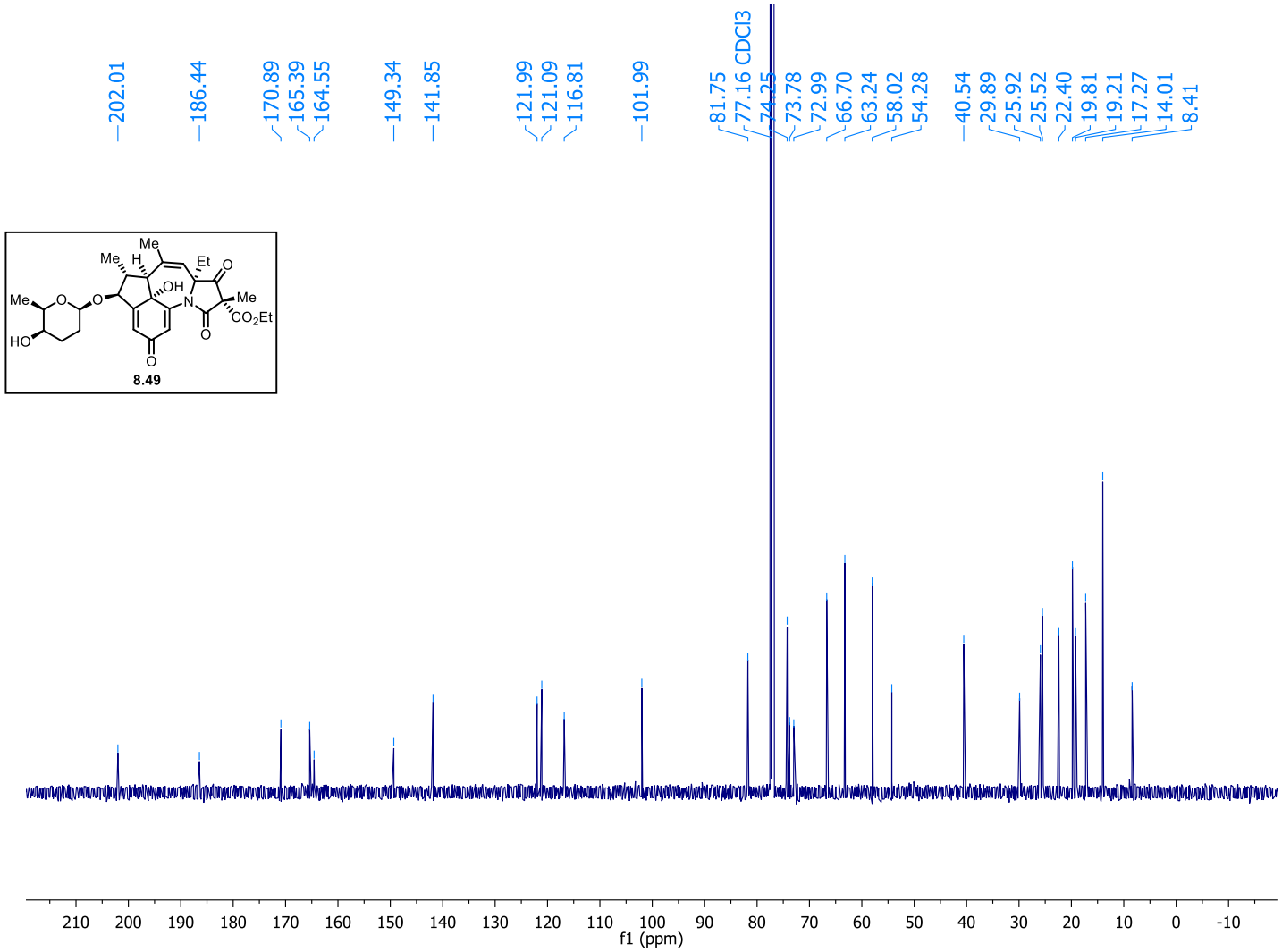


Figure F.49. ^{13}C NMR (151 MHz, $CDCl_3$) of compound **8.49**

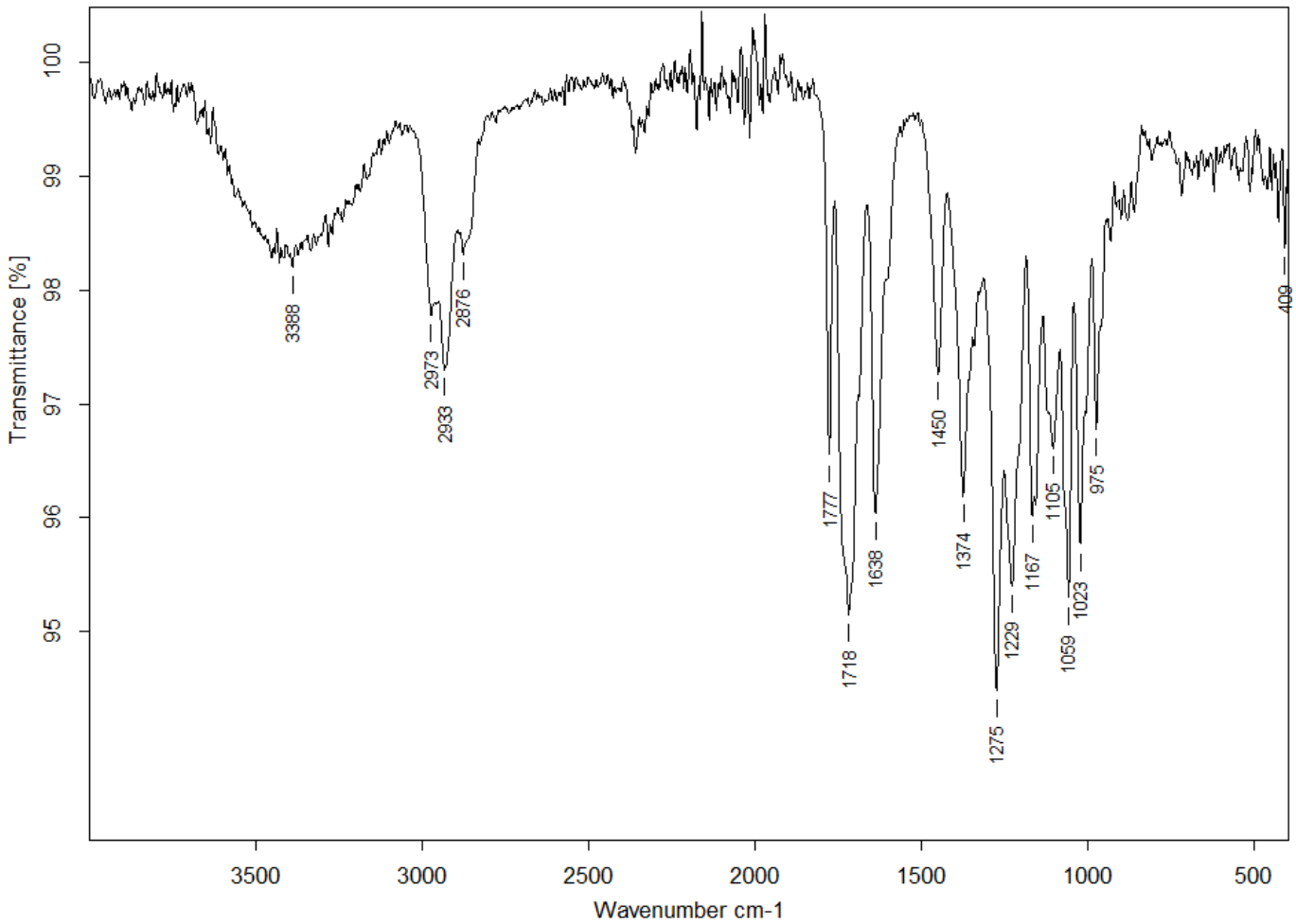


Figure F.50. FTIR spectrum (neat) of compound **8.49**

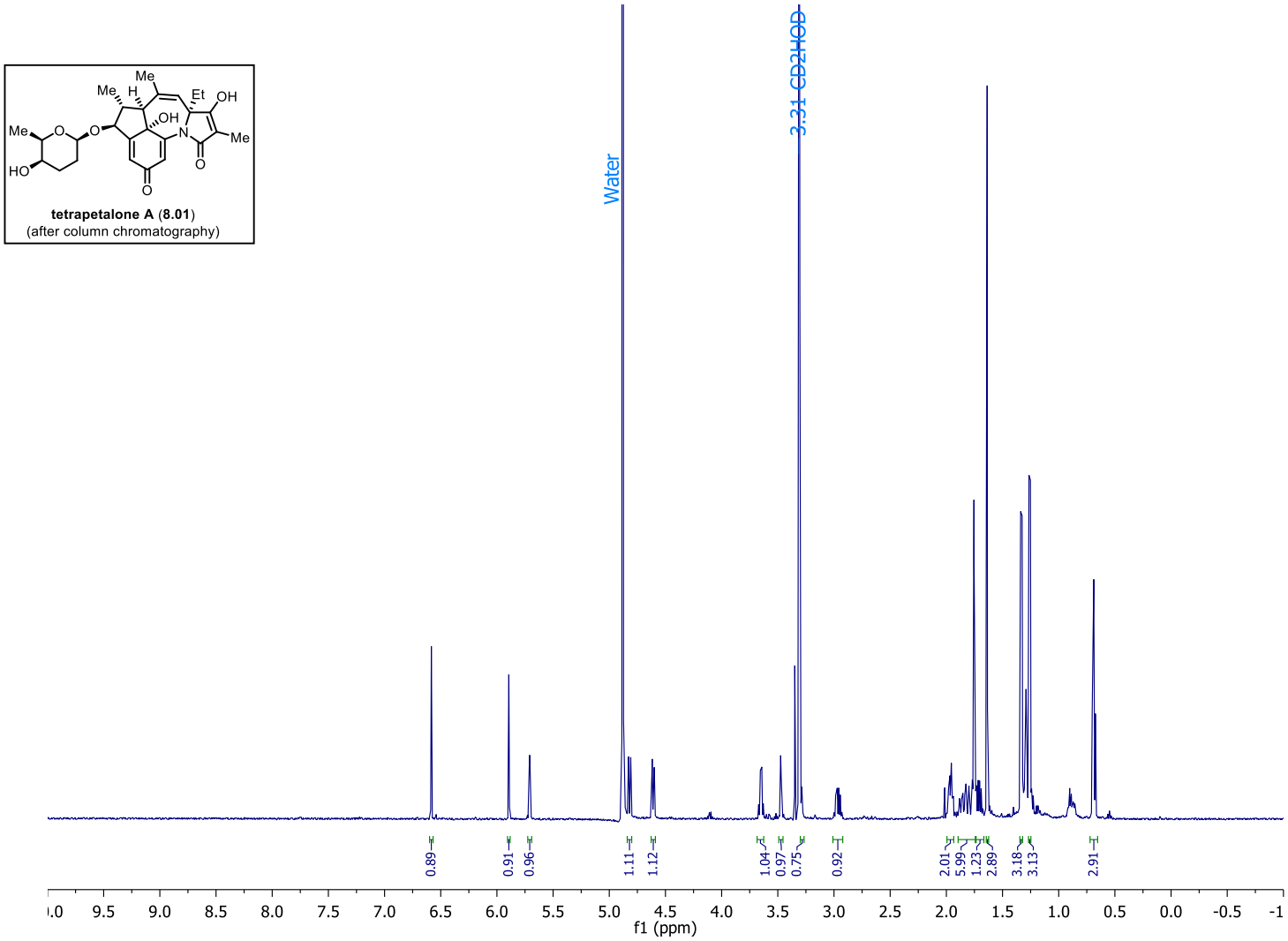


Figure F.51. ^{1}H NMR (500 MHz, methanol-d_4) of compound **8.01** (after column chromatography)

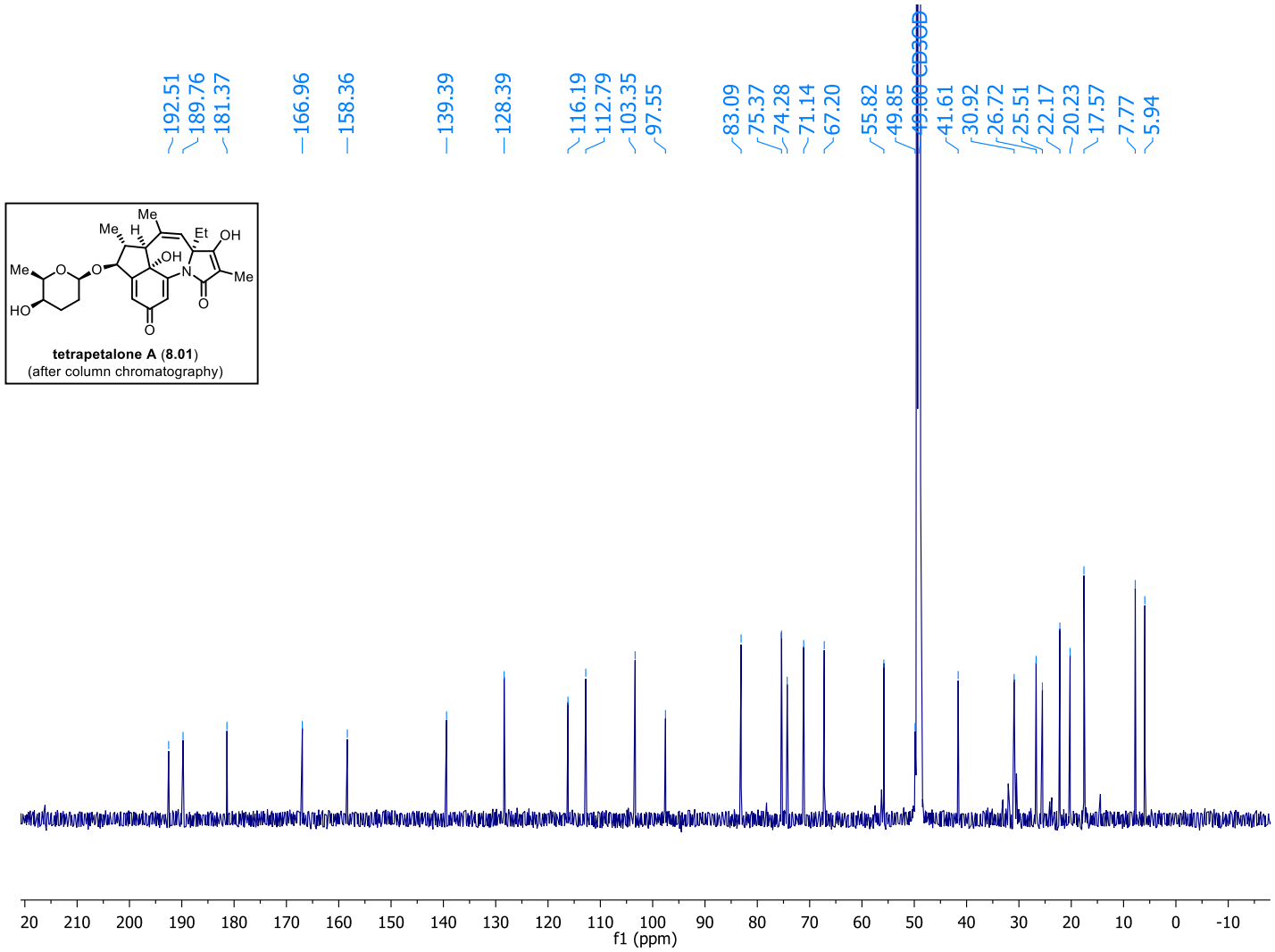


Figure F.52. ^{13}C NMR (151 MHz, methanol-d_4) of compound **8.01** (after column chromatography)

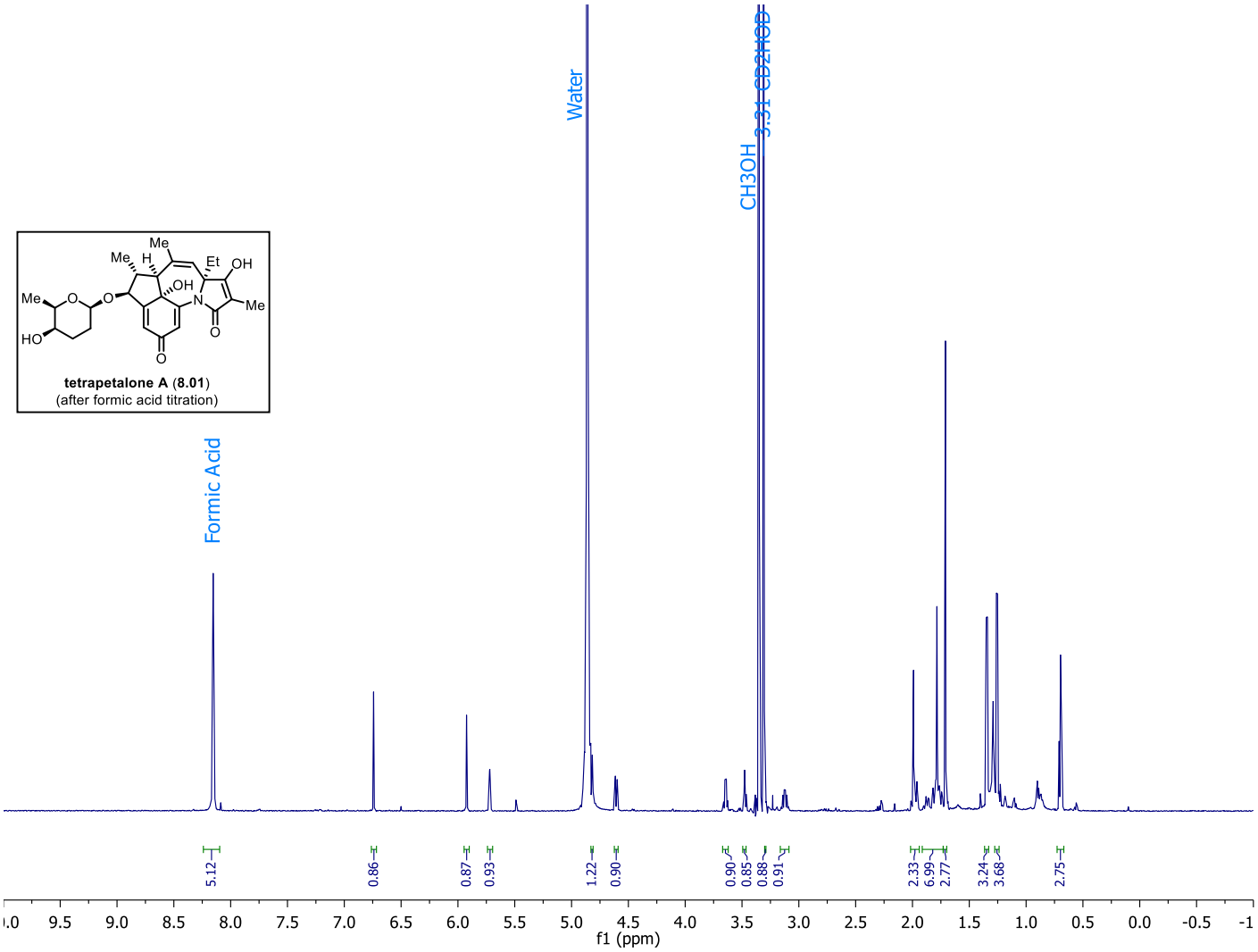


Figure F.53. ^{1}H NMR (500 MHz, methanol-d_4) of compound **8.01** (after formic acid titration)

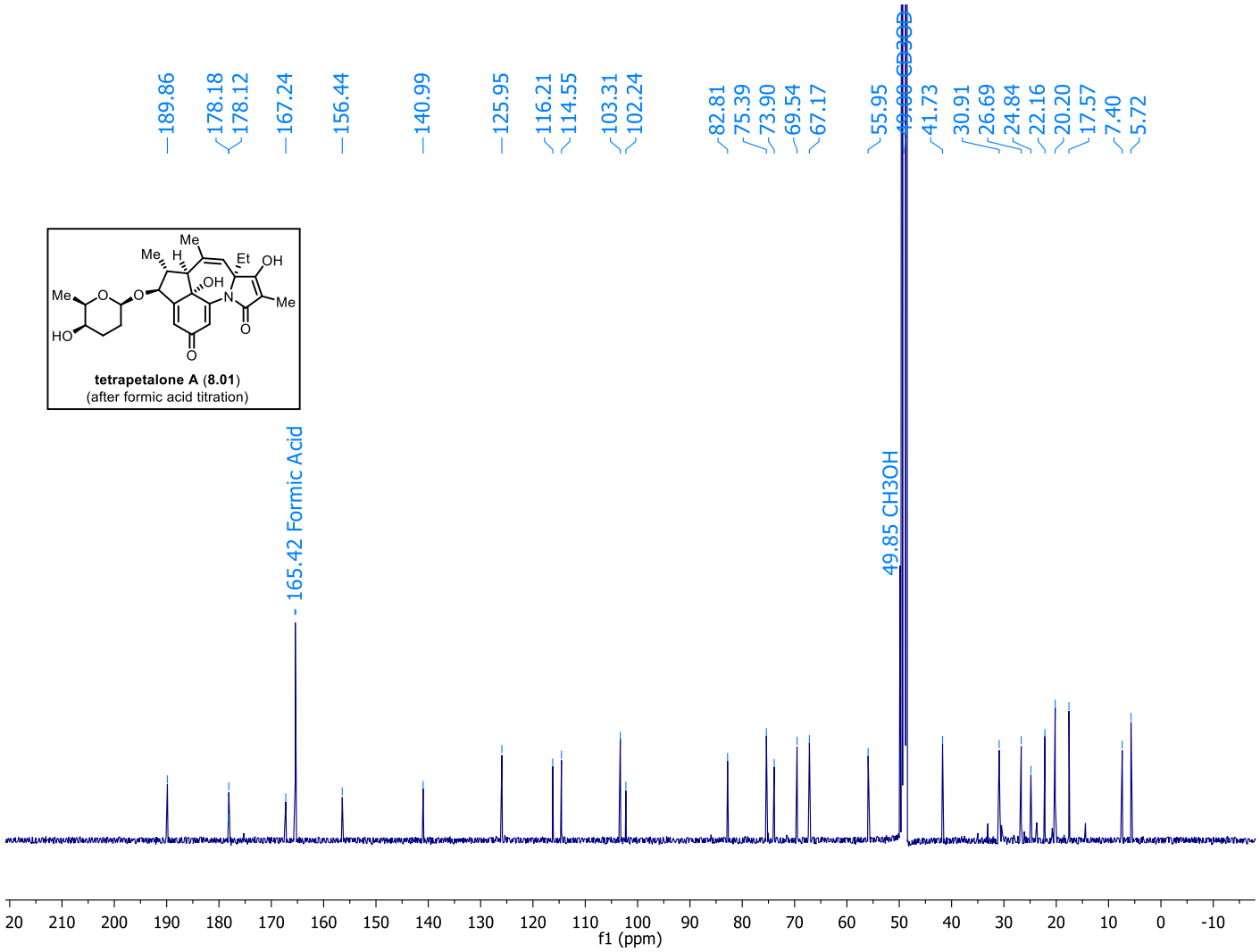


Figure F.54. ^{13}C NMR (151 MHz, methanol-d_4) of compound **8.01** (after formic acid titration)

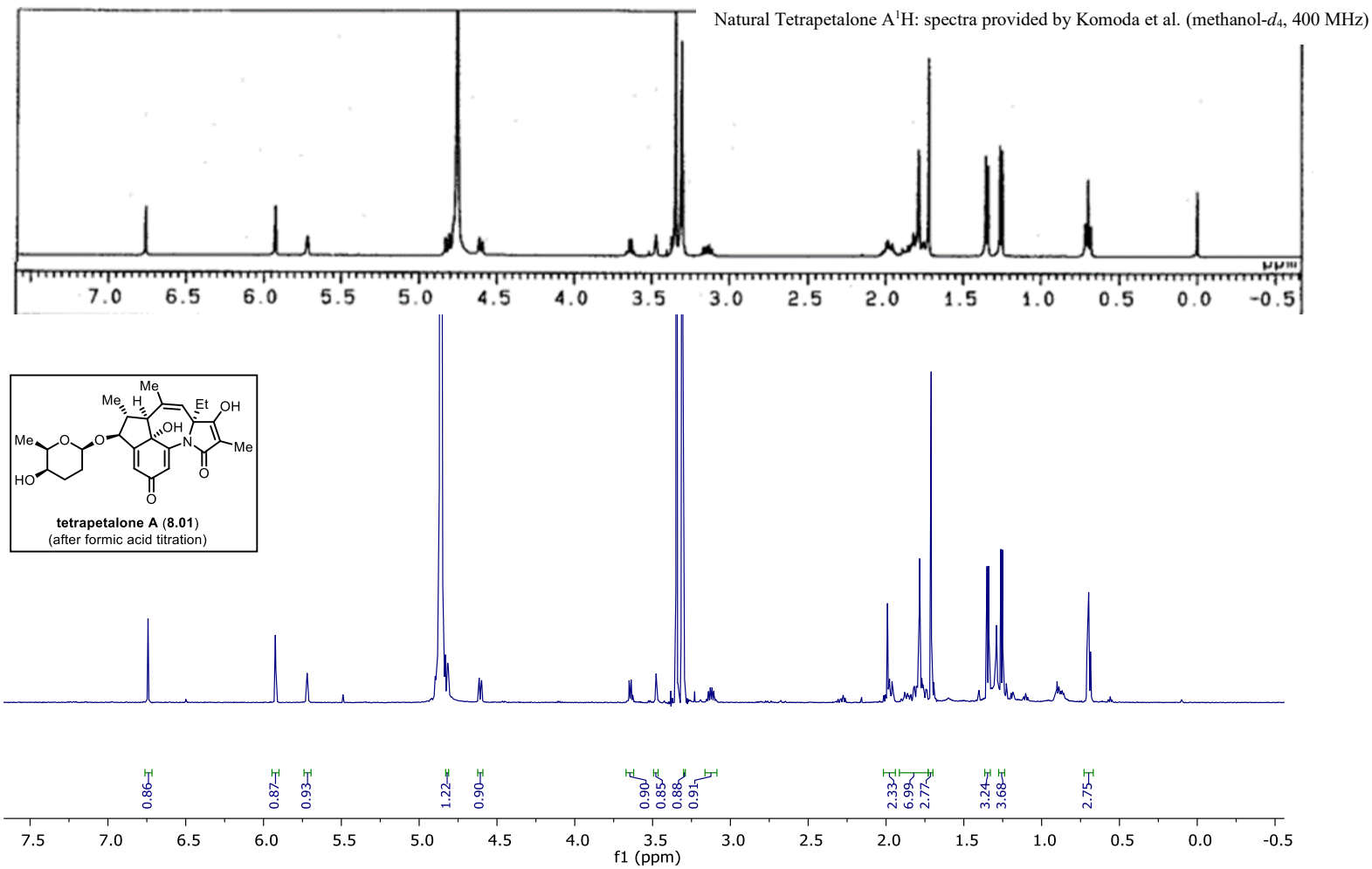


Figure F.55. Comparison ^{1}H-NMR spectra of natural (provided by Komoda et al., methanol-d_4, 400 MHz) and synthetic (titrated with dilute formic acid, methanol-d_4, 500 MHz) **tetrapetalone A** (**8.01**)

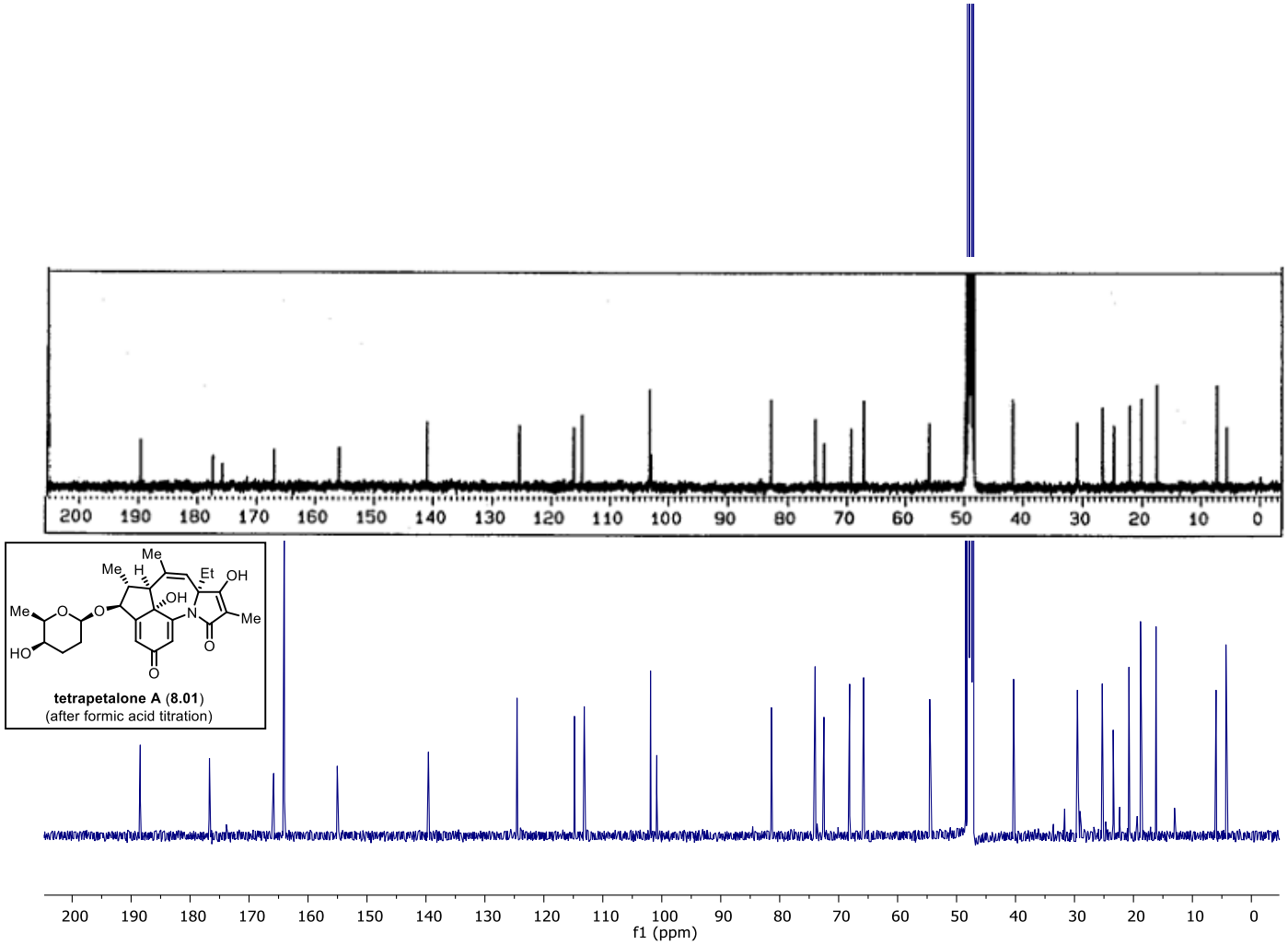


Figure F.56. Comparison ^{13}C-NMR spectra of natural (provided by Komoda et al., methanol-d_4, 100 MHz) and synthetic (titrated with dilute formic acid, methanol-d_4, 151 MHz) **tetrapetalone A** (**8.01**)

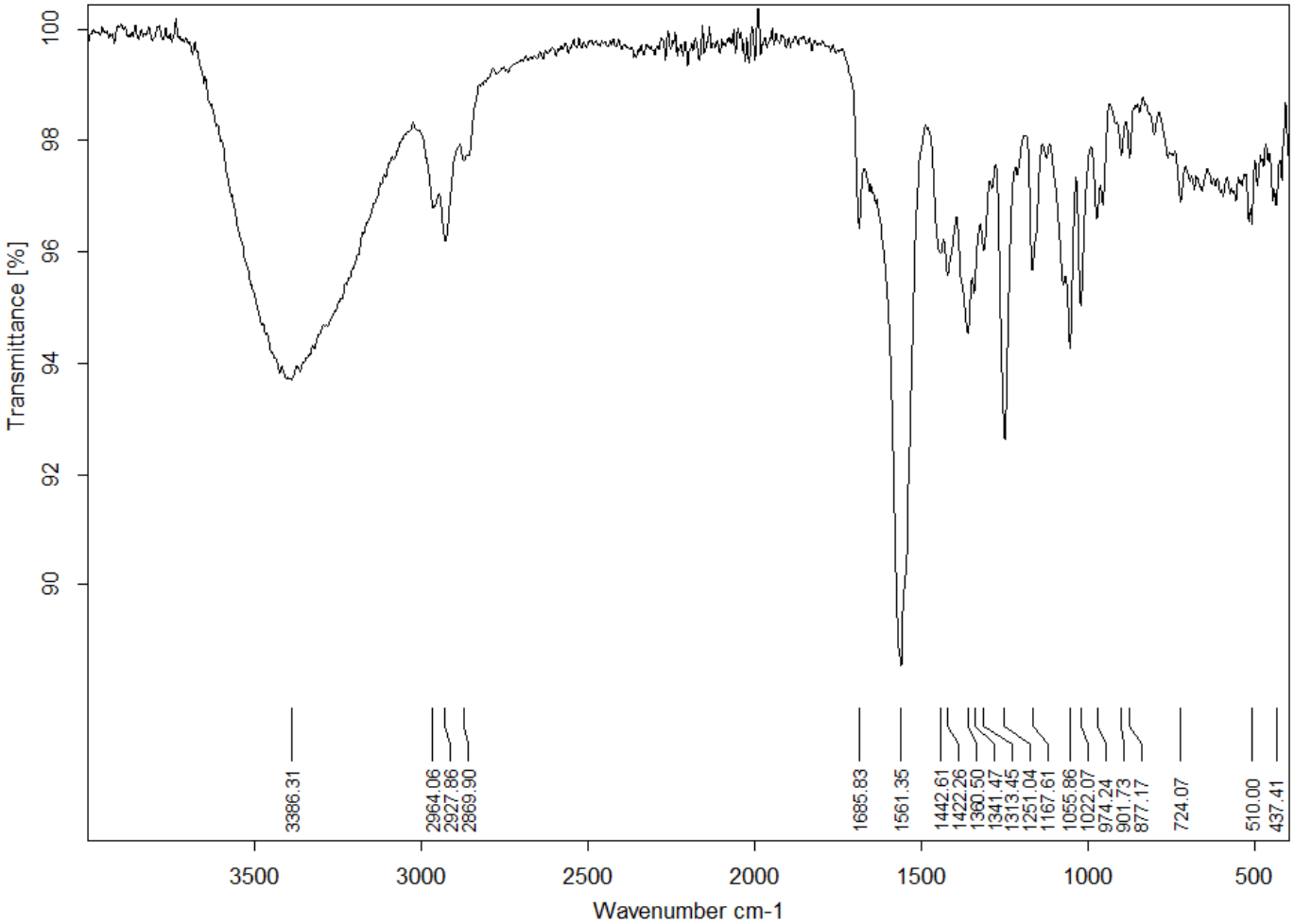


Figure F.57. FTIR spectrum (neat) of compound **8.01** (after column chromatography)

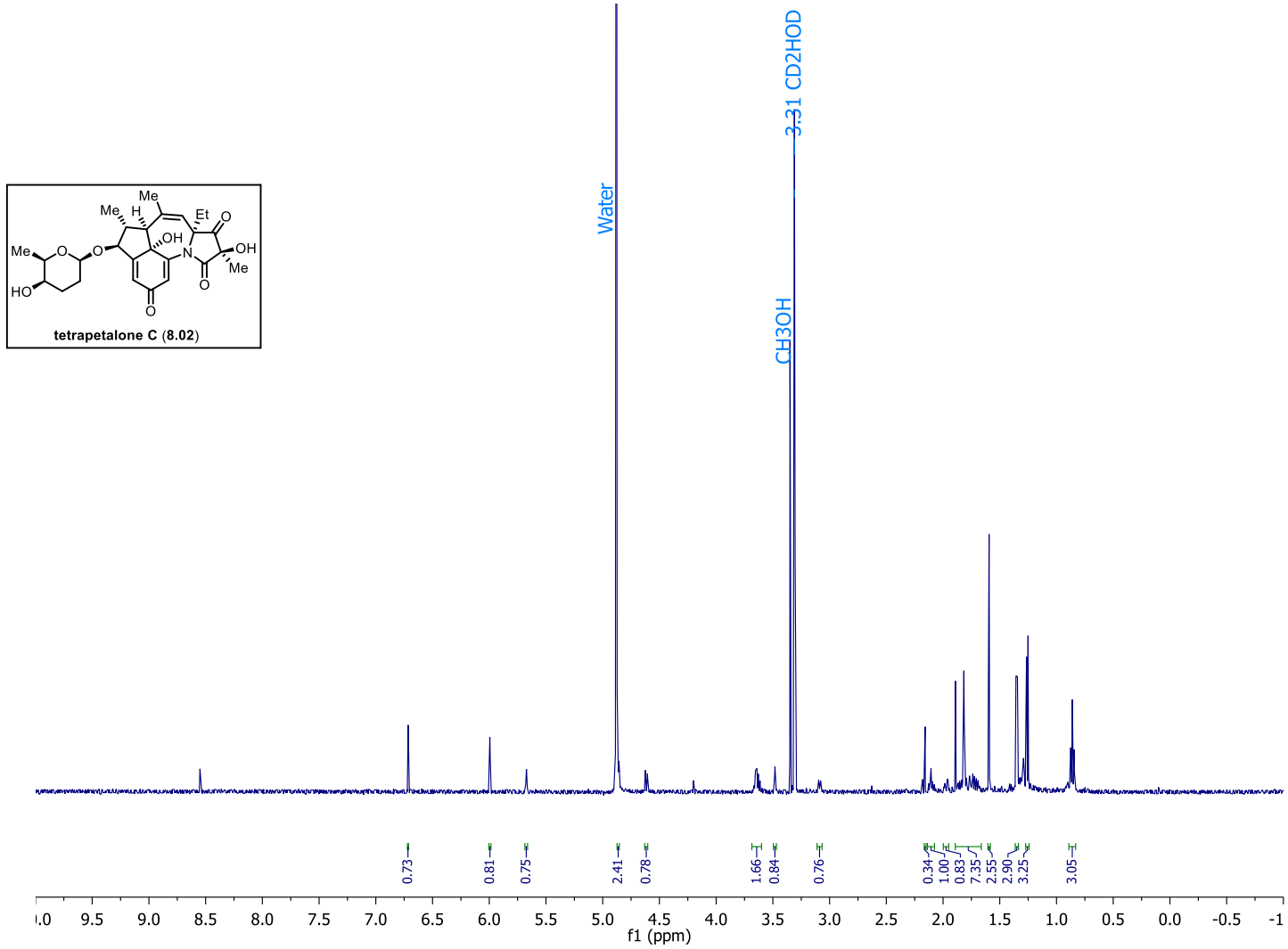


Figure F.58. ^{1}H NMR (500 MHz, methanol-d_4) of compound **8.02**

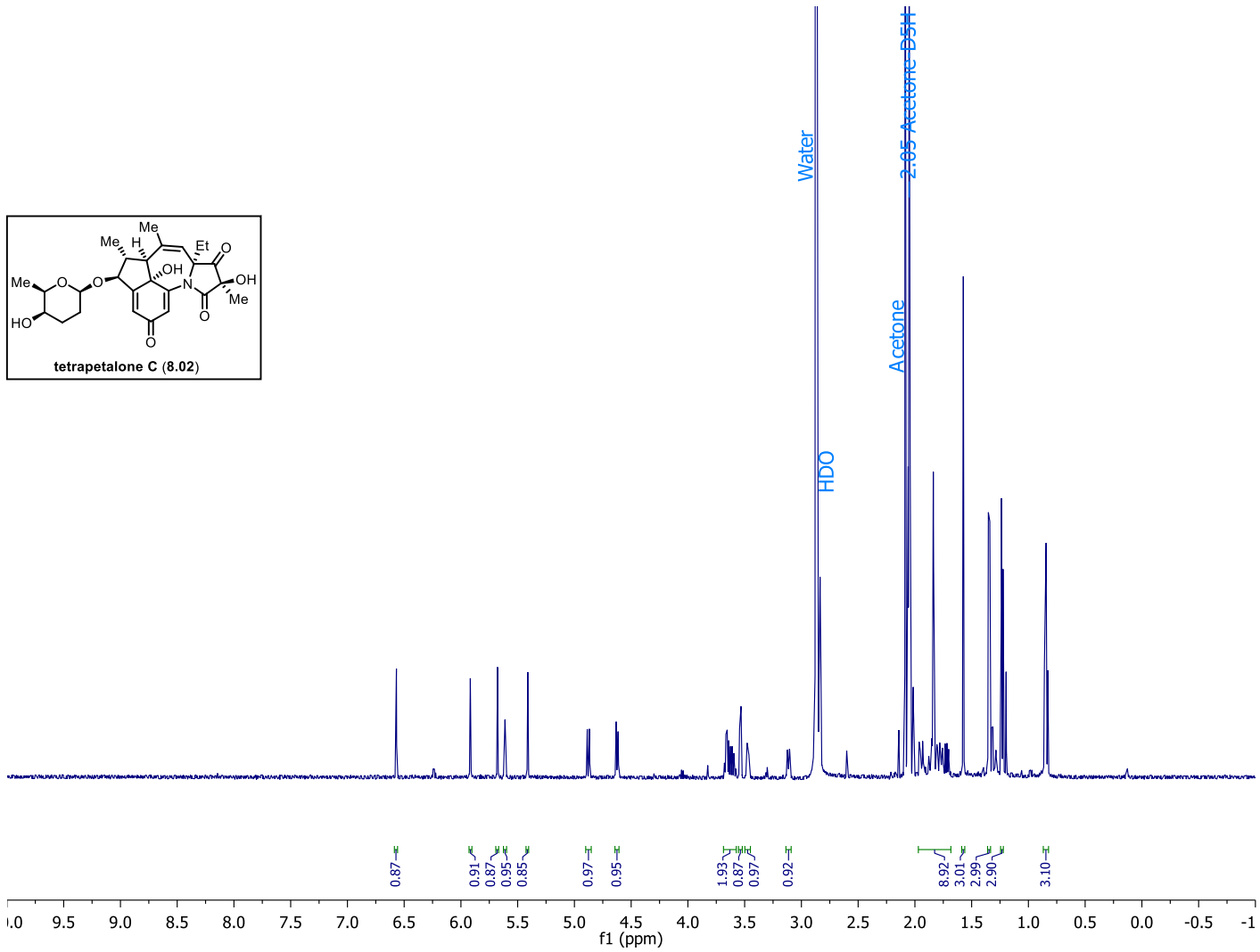


Figure F.59. ^{1}H NMR (500 MHz, acetone-d_6) of compound **8.02**

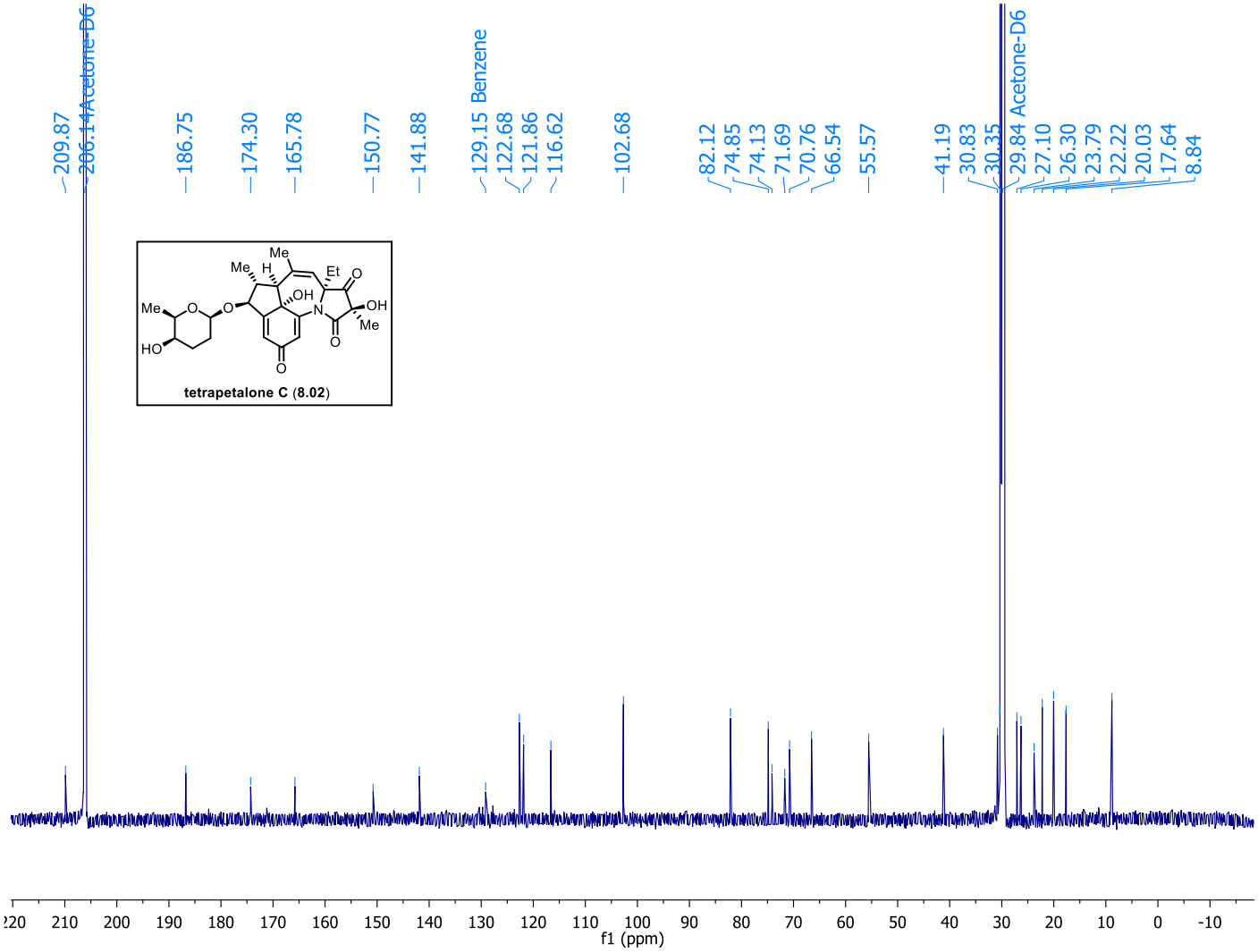


Figure F.60. ^{13}C NMR (151 MHz, acetone-d_6) of compound **8.02**

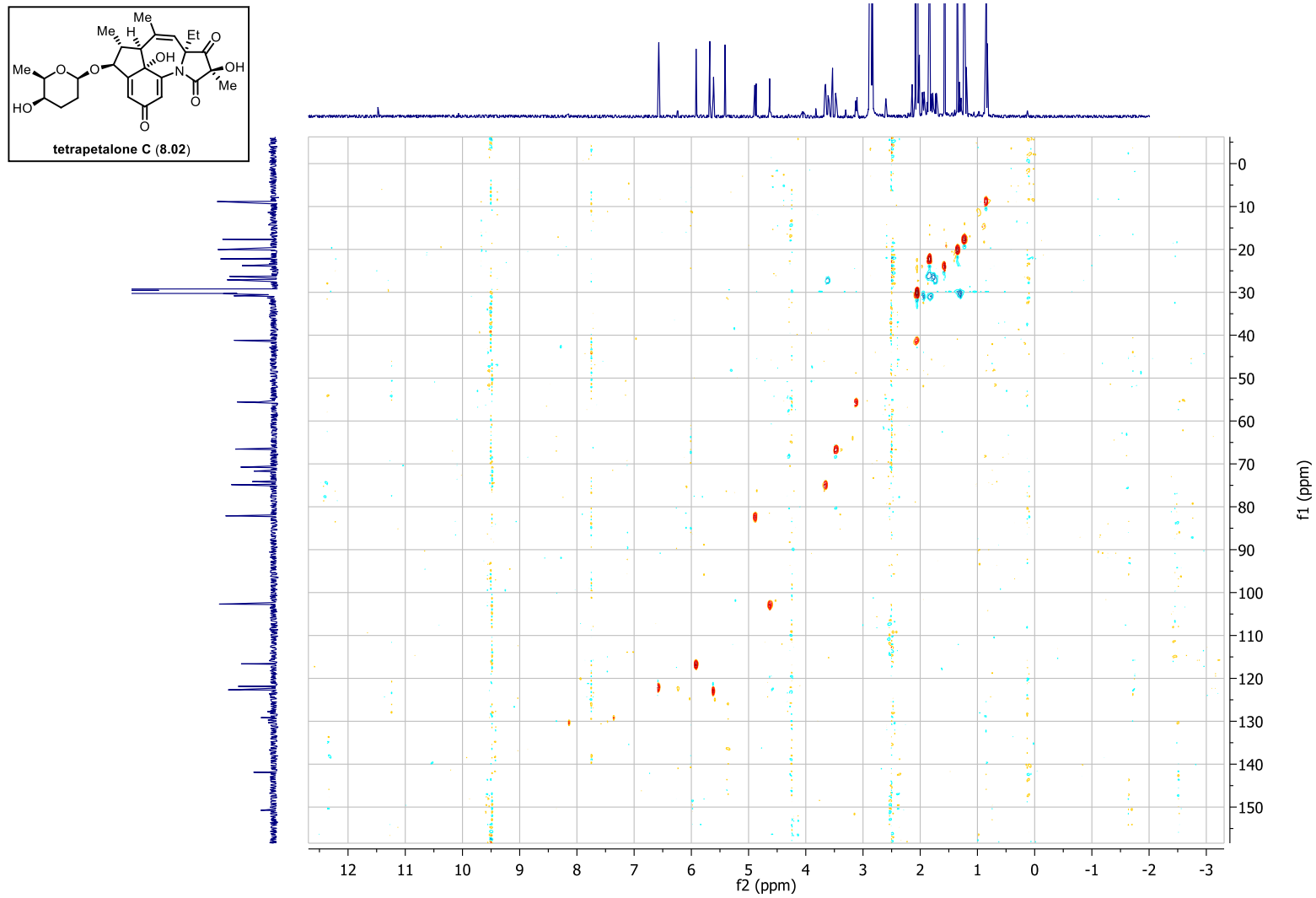


Figure F.61. HSQC (acetone-d_6) of tetrapetalone C **8.02**

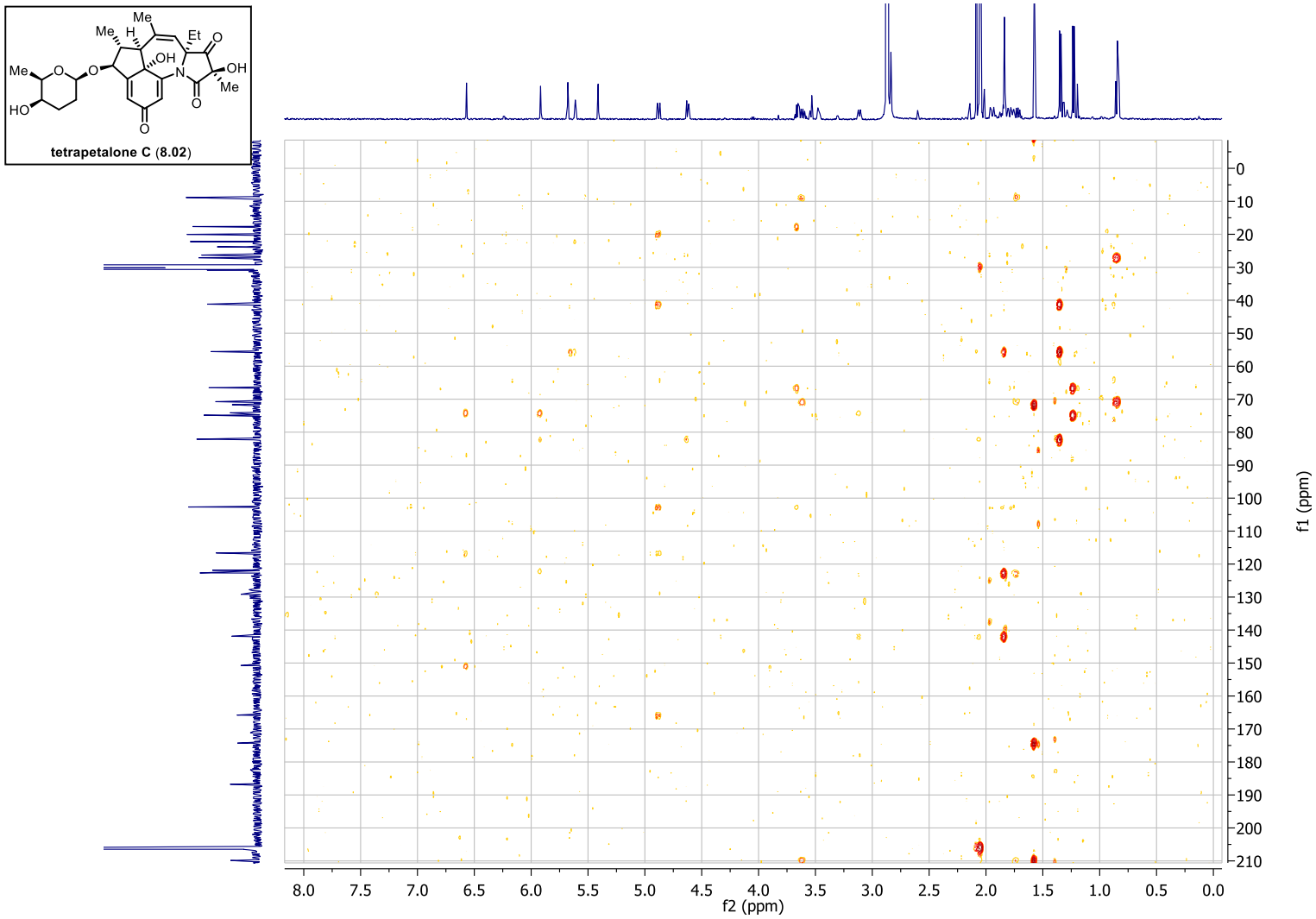


Figure F.62. HMBC (acetone-d_6) of tetrapetalone C **8.02**

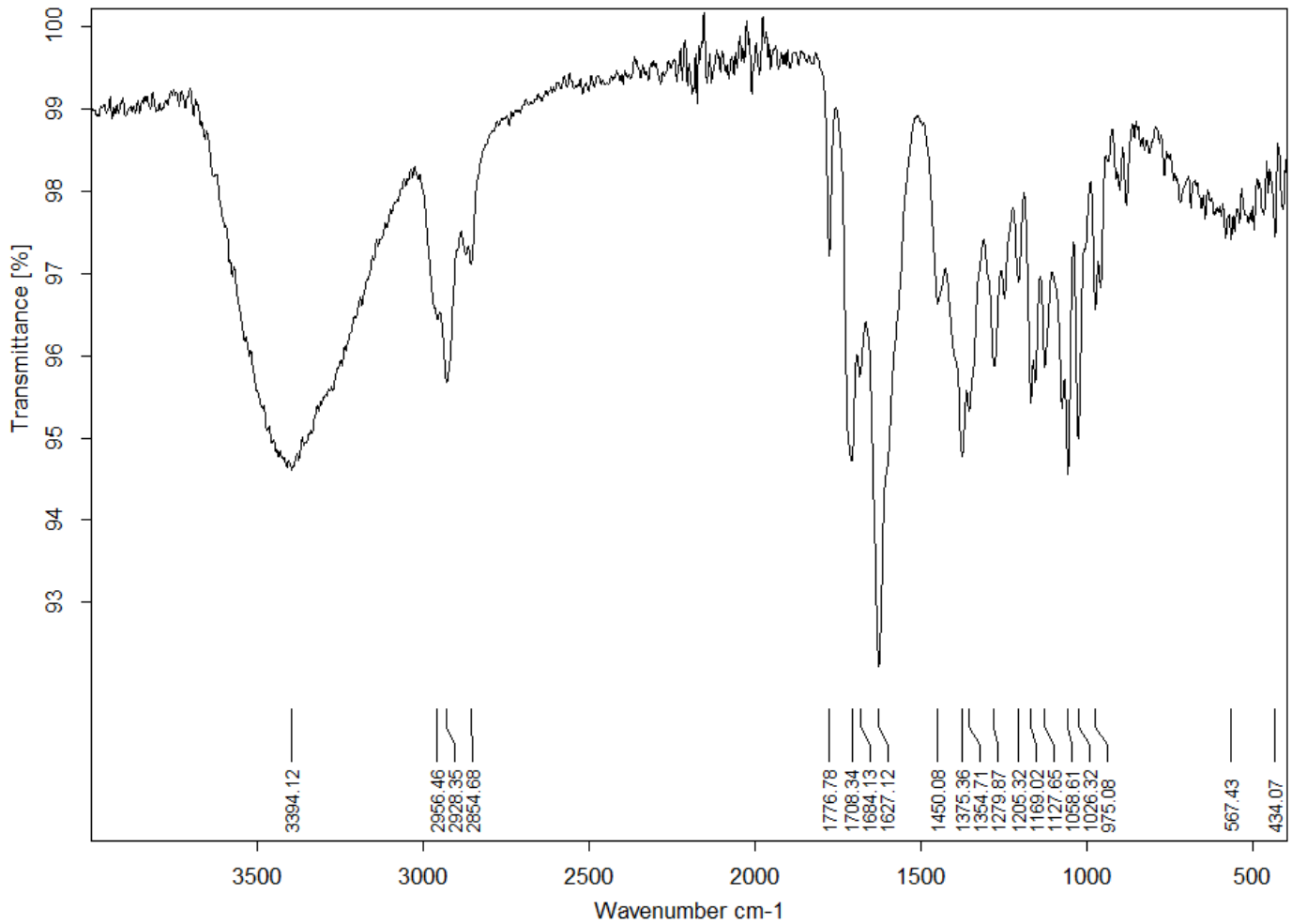


Figure F.63. FTIR spectrum (neat) of compound **8.02**

APPENDIX G

Crystal Structure Data

G.1. Crystal Structure Data of **7.39a**

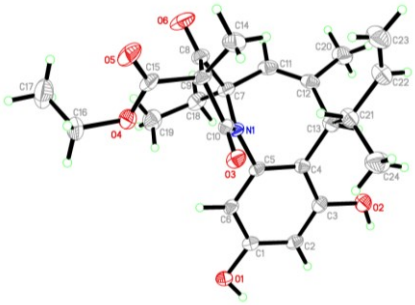


Table G.1. Crystal data and structure refinement for diol **7.36a**

Identification code	JLW67	
Empirical formula	C24 H29 N O6	
Formula weight	427.48	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 11.2630(6) Å	α= 90°.
	b = 11.6823(4) Å	β= 90°.
	c = 20.3071(7) Å	γ = 90°.
Volume	2671.96(19) $Å^3$	
Z	4	
Density (calculated)	1.063 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	912	
Crystal size	0.386 x 0.240 x 0.176 mm^3	
Theta range for data collection	2.512 to 28.310°.	
Index ranges	-12<=h<=15, -15<=k<=13, -25<=l<=27	
Reflections collected	26054	
Independent reflections	6624 [R(int) = 0.0358]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.945 and 0.929	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6624 / 0 / 293	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.0440, wR2 = 0.1190	
R indices (all data)	R1 = 0.0534, wR2 = 0.1234	
Absolute structure parameter	-0.4(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.249 and -0.227 e.$Å^{-3}$	

Table G.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **7.36a** (JLW67). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	11750(2)	2718(1)	2406(1)	31(1)
O(2)	8573(2)	4111(1)	1030(1)	33(1)
O(3)	8734(1)	-488(1)	1867(1)	26(1)
O(4)	10759(2)	-2351(1)	1572(1)	31(1)
O(5)	9437(2)	-3703(1)	1302(1)	39(1)
O(6)	10075(2)	-2087(2)	-140(1)	42(1)
N(1)	9731(2)	165(1)	966(1)	20(1)
C(6)	10730(2)	1480(2)	1693(1)	22(1)
C(4)	9153(2)	2167(2)	967(1)	21(1)
C(2)	10158(2)	3458(2)	1728(1)	24(1)
C(3)	9312(2)	3253(2)	1246(1)	24(1)
C(5)	9878(2)	1306(2)	1216(1)	21(1)
C(1)	10877(2)	2572(2)	1948(1)	24(1)
C(10)	9176(2)	-645(2)	1323(1)	20(1)
C(9)	9141(2)	-1763(2)	925(1)	25(1)
C(7)	10096(2)	-152(2)	299(1)	24(1)
C(8)	9818(2)	-1443(2)	293(1)	26(1)
C(14)	7867(2)	-2115(2)	751(2)	39(1)
C(15)	9780(2)	-2730(2)	1289(1)	26(1)
C(16)	11488(3)	-3193(2)	1924(1)	41(1)
C(17)	12251(3)	-3868(3)	1458(2)	56(1)
C(11)	9385(2)	462(2)	-224(1)	28(1)
C(20)	8153(3)	1874(2)	-795(1)	37(1)
C(12)	8635(2)	1341(2)	-170(1)	26(1)
C(23)	5558(2)	187(3)	170(2)	45(1)
C(18)	11432(2)	64(2)	178(1)	31(1)
C(19)	12277(2)	-566(2)	627(1)	38(1)
C(13)	8200(2)	1940(2)	453(1)	25(1)
C(21)	7087(2)	1353(2)	770(1)	28(1)
C(22)	6106(2)	1160(2)	280(1)	35(1)
C(24)	6601(3)	2067(3)	1338(2)	47(1)

Table G.3. Bond lengths [Å] for diol **7.36a** (JLW67)

Atoms	Bond Length	Atoms	Bond Length
O(1)-C(1)	1.363(3)	C(16)-C(17)	1.503(4)
O(1)-H(1A)	0.85(4)	C(16)-H(16A)	0.9900
O(2)-C(3)	1.375(3)	C(16)-H(16B)	0.9900
O(2)-H(2A)	0.87(3)	C(17)-H(17A)	0.9800
O(3)-C(10)	1.225(3)	C(17)-H(17B)	0.9800
O(4)-C(15)	1.320(3)	C(17)-H(17C)	0.9800
O(4)-C(16)	1.468(3)	C(11)-C(12)	1.334(3)
O(5)-C(15)	1.200(3)	C(11)-H(11)	0.9500
O(6)-C(8)	1.193(3)	C(20)-C(12)	1.515(3)
N(1)-C(10)	1.346(3)	C(20)-H(20A)	0.9800
N(1)-C(5)	1.436(2)	C(20)-H(20B)	0.9800
N(1)-C(7)	1.463(3)	C(20)-H(20C)	0.9800
C(6)-C(5)	1.379(3)	C(12)-C(13)	1.526(3)
C(6)-C(1)	1.387(3)	C(23)-C(22)	1.312(4)
C(6)-H(6)	0.9500	C(23)-H(23A)	0.9500
C(4)-C(5)	1.390(3)	C(23)-H(23B)	0.9500
C(4)-C(3)	1.402(3)	C(18)-C(19)	1.510(4)
C(4)-C(13)	1.520(3)	C(18)-H(18A)	0.9900
C(2)-C(3)	1.386(3)	C(18)-H(18B)	0.9900
C(2)-C(1)	1.388(3)	C(19)-H(19A)	0.9800
C(2)-H(2)	0.9500	C(19)-H(19B)	0.9800
C(10)-C(9)	1.535(3)	C(19)-H(19C)	0.9800
C(9)-C(15)	1.529(3)	C(13)-C(21)	1.568(3)
C(9)-C(14)	1.534(3)	C(13)-H(13)	1.0000
C(9)-C(8)	1.540(3)	C(21)-C(22)	1.503(3)
C(7)-C(11)	1.511(3)	C(21)-C(24)	1.525(4)
C(7)-C(8)	1.541(3)	C(21)-H(21)	1.0000
C(7)-C(18)	1.546(3)	C(22)-H(22)	0.9500
C(14)-H(14A)	0.9800	C(24)-H(24A)	0.9800
C(14)-H(14B)	0.9800	C(24)-H(24B)	0.9800
C(14)-H(14C)	0.9800	C(24)-H(24C)	0.9800

Table G.4. Bond angles [°] for diol **7.36a** (JLW67)

Atoms	Bond Angle	Atoms	Bond Angle
C(1)-O(1)-H(1A)	102(3)	C(17)-C(16)-H(16B)	109.4
C(3)-O(2)-H(2A)	112(2)	H(16A)-C(16)-H(16B)	108.0
C(15)-O(4)-C(16)	117.02(19)	C(16)-C(17)-H(17A)	109.5
C(10)-N(1)-C(5)	121.11(17)	C(16)-C(17)-H(17B)	109.5
C(10)-N(1)-C(7)	116.79(16)	H(17A)-C(17)-H(17B)	109.5
C(5)-N(1)-C(7)	121.95(16)	C(16)-C(17)-H(17C)	109.5
C(5)-C(6)-C(1)	118.75(19)	H(17A)-C(17)-H(17C)	109.5
C(5)-C(6)-H(6)	120.6	H(17B)-C(17)-H(17C)	109.5
C(1)-C(6)-H(6)	120.6	C(12)-C(11)-C(7)	130.0(2)
C(5)-C(4)-C(3)	115.64(19)	C(12)-C(11)-H(11)	115.0
C(5)-C(4)-C(13)	122.58(18)	C(7)-C(11)-H(11)	115.0
C(3)-C(4)-C(13)	121.70(19)	C(12)-C(20)-H(20A)	109.5
C(3)-C(2)-C(1)	120.02(18)	C(12)-C(20)-H(20B)	109.5
C(3)-C(2)-H(2)	120.0	H(20A)-C(20)-H(20B)	109.5
C(1)-C(2)-H(2)	120.0	C(12)-C(20)-H(20C)	109.5
O(2)-C(3)-C(2)	121.07(19)	H(20A)-C(20)-H(20C)	109.5
O(2)-C(3)-C(4)	116.96(19)	H(20B)-C(20)-H(20C)	109.5
C(2)-C(3)-C(4)	121.96(19)	C(11)-C(12)-C(20)	118.3(2)
C(6)-C(5)-C(4)	123.92(18)	C(11)-C(12)-C(13)	128.7(2)
C(6)-C(5)-N(1)	117.66(18)	C(20)-C(12)-C(13)	113.04(19)
C(4)-C(5)-N(1)	118.41(18)	C(22)-C(23)-H(23A)	120.0
O(1)-C(1)-C(6)	117.1(2)	C(22)-C(23)-H(23B)	120.0
O(1)-C(1)-C(2)	123.20(18)	H(23A)-C(23)-H(23B)	120.0
C(6)-C(1)-C(2)	119.7(2)	C(19)-C(18)-C(7)	115.99(19)
O(3)-C(10)-N(1)	124.64(18)	C(19)-C(18)-H(18A)	108.3
O(3)-C(10)-C(9)	126.20(18)	C(7)-C(18)-H(18A)	108.3
N(1)-C(10)-C(9)	109.11(18)	C(19)-C(18)-H(18B)	108.3
C(15)-C(9)-C(14)	110.70(19)	C(7)-C(18)-H(18B)	108.3
C(15)-C(9)-C(10)	111.29(18)	H(18A)-C(18)-H(18B)	107.4
C(14)-C(9)-C(10)	111.9(2)	C(18)-C(19)-H(19A)	109.5
C(15)-C(9)-C(8)	110.43(19)	C(18)-C(19)-H(19B)	109.5
C(14)-C(9)-C(8)	109.6(2)	H(19A)-C(19)-H(19B)	109.5
C(10)-C(9)-C(8)	102.67(16)	C(18)-C(19)-H(19C)	109.5
N(1)-C(7)-C(11)	112.48(18)	H(19A)-C(19)-H(19C)	109.5
N(1)-C(7)-C(8)	101.43(17)	H(19B)-C(19)-H(19C)	109.5
C(11)-C(7)-C(8)	110.59(18)	C(4)-C(13)-C(12)	114.96(19)
N(1)-C(7)-C(18)	112.26(18)	C(4)-C(13)-C(21)	111.08(17)
C(11)-C(7)-C(18)	109.05(18)	C(12)-C(13)-C(21)	113.32(18)
C(8)-C(7)-C(18)	110.89(18)	C(4)-C(13)-H(13)	105.5
O(6)-C(8)-C(9)	125.6(2)	C(12)-C(13)-H(13)	105.5
O(6)-C(8)-C(7)	125.0(2)	C(21)-C(13)-H(13)	105.5
C(9)-C(8)-C(7)	109.35(17)	C(22)-C(21)-C(24)	108.6(2)
C(9)-C(14)-H(14A)	109.5	C(22)-C(21)-C(13)	112.49(19)
C(9)-C(14)-H(14B)	109.5	C(24)-C(21)-C(13)	111.0(2)
H(14A)-C(14)-H(14B)	109.5	C(22)-C(21)-H(21)	108.2
C(9)-C(14)-H(14C)	109.5	C(24)-C(21)-H(21)	108.2
H(14A)-C(14)-H(14C)	109.5	C(13)-C(21)-H(21)	108.2
H(14B)-C(14)-H(14C)	109.5	C(23)-C(22)-C(21)	126.0(2)
O(5)-C(15)-O(4)	125.2(2)	C(23)-C(22)-H(22)	117.0
O(5)-C(15)-C(9)	124.0(2)	C(21)-C(22)-H(22)	117.0
O(4)-C(15)-C(9)	110.78(17)	C(21)-C(24)-H(24A)	109.5
O(4)-C(16)-C(17)	111.3(2)	C(21)-C(24)-H(24B)	109.5
O(4)-C(16)-H(16A)	109.4	H(24A)-C(24)-H(24B)	109.5
C(17)-C(16)-H(16A)	109.4	C(21)-C(24)-H(24C)	109.5
O(4)-C(16)-H(16B)	109.4	H(24A)-C(24)-H(24C)	109.5
		H(24B)-C(24)-H(24C)	109.5

Table G.5. Anisotropic displacement paramaters ($Å^2 x 10^3$) for diol **7.36a** (JLW67). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	35(1)	25(1)	33(1)	-11(1)	-12(1)	4(1)
O(2)	40(1)	14(1)	43(1)	-1(1)	-12(1)	3(1)
O(3)	39(1)	18(1)	21(1)	3(1)	3(1)	2(1)
O(4)	38(1)	20(1)	36(1)	1(1)	-7(1)	2(1)
O(5)	55(1)	14(1)	49(1)	-2(1)	4(1)	-2(1)
O(6)	71(1)	25(1)	30(1)	-10(1)	6(1)	-1(1)
N(1)	28(1)	14(1)	19(1)	-2(1)	-2(1)	-2(1)
C(6)	29(1)	16(1)	23(1)	-1(1)	-1(1)	2(1)
C(4)	26(1)	17(1)	21(1)	1(1)	-1(1)	-3(1)
C(2)	31(1)	15(1)	25(1)	-4(1)	2(1)	-2(1)
C(3)	28(1)	15(1)	28(1)	1(1)	2(1)	0(1)
C(5)	28(1)	13(1)	20(1)	-1(1)	3(1)	-1(1)
C(1)	27(1)	22(1)	21(1)	-4(1)	1(1)	-1(1)
C(10)	27(1)	12(1)	22(1)	1(1)	-5(1)	1(1)
C(9)	34(1)	14(1)	26(1)	-3(1)	-3(1)	-2(1)
C(7)	34(1)	18(1)	22(1)	-4(1)	2(1)	-1(1)
C(8)	36(1)	20(1)	24(1)	-3(1)	-3(1)	1(1)
C(14)	38(1)	30(1)	49(2)	-7(1)	-11(1)	-8(1)
C(15)	37(1)	14(1)	27(1)	-3(1)	5(1)	1(1)
C(16)	53(2)	32(1)	39(1)	5(1)	-11(1)	15(1)
C(17)	53(2)	50(2)	64(2)	5(2)	2(2)	23(2)
C(11)	42(1)	23(1)	19(1)	0(1)	0(1)	-6(1)
C(20)	51(2)	34(1)	26(1)	6(1)	-8(1)	-1(1)
C(12)	34(1)	21(1)	24(1)	1(1)	-6(1)	-8(1)
C(23)	36(1)	49(2)	50(2)	-2(1)	-10(1)	-9(1)
C(18)	36(1)	27(1)	30(1)	0(1)	10(1)	-1(1)
C(19)	31(1)	42(2)	42(1)	-2(1)	6(1)	4(1)
C(13)	30(1)	18(1)	26(1)	3(1)	-7(1)	-2(1)
C(21)	28(1)	27(1)	29(1)	4(1)	-5(1)	-3(1)
C(22)	32(1)	37(1)	35(1)	5(1)	-6(1)	-3(1)
C(24)	36(1)	62(2)	43(2)	-13(1)	3(1)	-8(1)

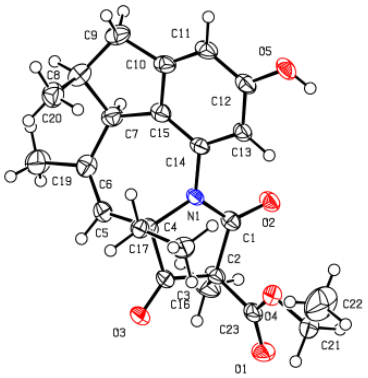
Table G.6. [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1A)...O(3)#1	0.85(4)	1.82(4)	2.622(2)	156(4)
O(2)-H(2A)...O(5)#2	0.87(3)	1.94(3)	2.788(2)	163(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y+1/2,-z+1/2 #2 x,y+1,z

G.2. Crystal Structure Data for **6.36** *(Preliminary Data)* [JLW8]



Note: Preliminary X-ray data obtained, data unrefined.

Bond precision: C-C = 0.0059 A Wavelength=0.71073

Cell: a=9.2085(7) b=12.3926(8) c=12.4704(9)
alpha=96.248(2) beta=111.570(2) gamma=109.873(2)

Temperature: 150 K

	Calculated	Reported
Volume	1199.32(15)	1199.32(15)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C23 H27 N O5, C H2 Cl2 ?	
Sum formula	C24 H29 Cl2 N O5	C24 H29 Cl2 N O5
Mr	482.38	482.38
Dx,g cm-3	1.336	1.336
Z	2	2
Mu (mm-1)	0.306	0.306
F000	508.0	508.0
F000'	508.81	
h,k,lmax	11,15,15	11,15,15
Nref	5271	5262
Tmin,Tmax	0.919,0.932	0.976,0.980
Tmin'	0.918	

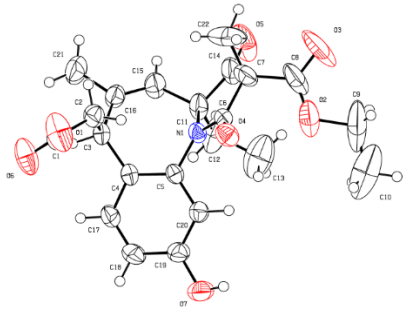
Correction method= # Reported T Limits: Tmin=0.976 Tmax=0.980
AbsCorr = MULTI-SCAN

Data completeness= 0.998 Theta(max)= 27.102

R(reflections)= 0.0827(3507) wR2(reflections)= 0.2384(5262)

S = 1.039 Npar= 289

G.3. Crystal Structure Data for **5.37** *(Preliminary Data)* [JLW10]



Note: Preliminary X-ray data obtained, data unrefined.

Bond precision: C-C = 0.0043 A Wavelength=0.71073

Cell: a=7.7722(4) b=19.5965(8) c=14.4404(7)

alpha=90 beta=99.430(2) gamma=90

Temperature: 254 K

	Calculated	Reported
Volume	2169.67(18)	2169.67(18)
Space group	P 21/n	P 21/n
Hall group	-P 2yn	-P 2yn
Moiety formula	C22 H24 N O7	?
Sum formula	C22 H24 N O7	C22 H25 N O7
Mr	414.42	415.43
Dx,g cm-3	1.269	1.272
Z	4	4
Mu (mm-1)	0.095	0.095
F000	876.0	880.0
F000'	876.50	
h,k,lmax	10,25,18	10,25,18
Nref	4988	4978
Tmin,Tmax		
Tmin'		

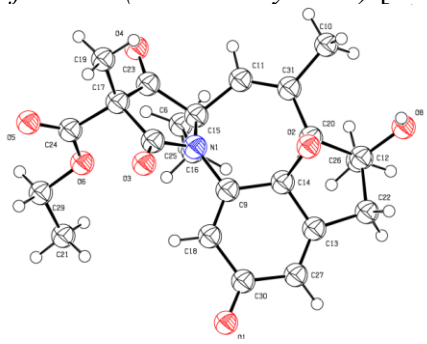
Correction method= Not given

Data completeness= 0.998 Theta(max)= 27.521

R(reflections)= 0.0764(2857) wR2(reflections)= 0.2345(4978)

S = 1.411 Npar= 271

G.4. Crystal Structure Data for **6.59** *(Preliminary Data)* [JLW19]



Note: Preliminary X-ray data obtained, data unrefined.

Bond precision: C-C = 0.0038 A Wavelength=0.71073

Cell: a=8.9282(5) b=11.6524(5) c=19.7604(10)
alpha=90 beta=92.848(2) gamma=90

Temperature: 150 K

	Calculated	Reported
Volume	2053.23(18)	2053.23(18)
Space group	P 21/n	P 21/n
Hall group	-P 2yn	-P 2yn
Moiety formula	C23 H25 N O7	?
Sum formula	C23 H25 N O7	C23 H N O7
Mr	427.44	403.25
Dx,g cm-3	1.383	1.304
Z	4	4
Mu (mm-1)	0.103	0.100
F000	904.0	808.0
F000'	904.51	
h,k,lmax	11,14,25	11,14,25
Nref	4550	4542
Tmin,Tmax	0.971,0.979	
Tmin'	0.971	

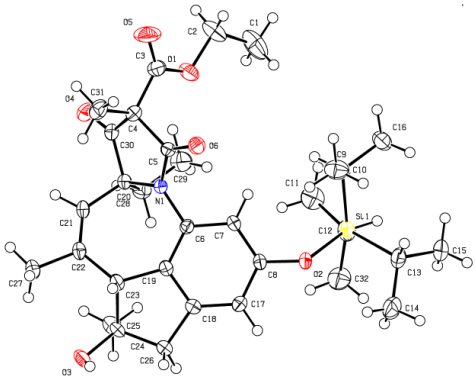
Correction method= Not given

Data completeness= 0.998 Theta(max)= 27.151

R(reflections)= 0.0798(3236) wR2(reflections)= 0.2372(4542)

S = 1.606 Npar= 105

G.5. Crystal Structure Data for **6.40** *(Preliminary Data)* [JLW15]



Note: Preliminary X-ray data obtained, data unrefined.

Bond precision: C-C = 0.0029 A Wavelength=0.71073

Cell: a=11.9759(6) b=12.3507(6) c=13.4860(6)
alpha=91.391(2) beta=112.511(2) gamma=116.604(2)

Temperature: 150 K

	Calculated	Reported
Volume	1600.71(14)	1600.71(14)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C32 H47 N O6 Si	C32 H47 N O6 Si
Sum formula	C32 H47 N O6 Si	C32 H47 N O6 Si
Mr	569.80	569.79
Dx,g cm-3	1.182	1.182
Z	2	2
Mu (mm-1)	0.115	0.115
F000	616.0	616.0
F000'	616.44	
h,k,lmax	15,15,17	15,15,17
Nref	7148	7118
Tmin,Tmax	0.971,0.981	
Tmin'	0.969	

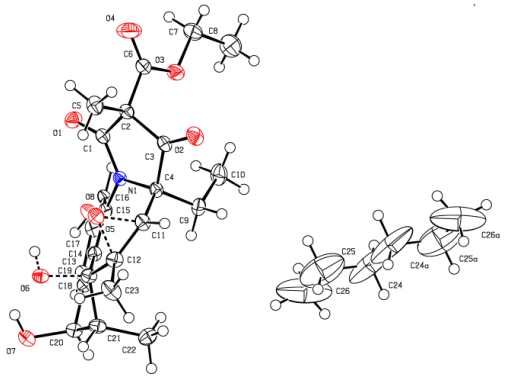
Correction method= Not given

Data completeness= 0.996 Theta(max)= 27.204

R(reflections)= 0.0454(5152) wR2(reflections)= 0.1525(7118)

S = 1.050 Npar= 375

G.6. Crystal Structure Data for **6.32** *(Preliminary Data)* [JLW77]



Note: Preliminary X-ray data obtained, data unrefined.

Bond precision: C-C = 0.0022 A Wavelength=0.71073

Cell: a=11.4259(10) b=11.5156(10) c=11.8502(10)
alpha=67.470(3) beta=62.893(3) gamma=63.925(2)

Temperature: 150 K

	Calculated	Reported
Volume	1213.62(18)	1213.62(19)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C23 H26.42 N O6.85, 0.447(C6 H14)	?
Sum formula	C25.69 H32.69 N O6.85	C25.69 H32.69 N O6.85
Mr	464.97	465.02
Dx,g cm-3	1.272	1.273
Z	2	2
Mu (mm-1)	0.092	0.092
F000	497.1	497.0
F000'	497.40	
h,k,lmax	15,16,16	15,16,16
Nref	6857	6773
Tmin,Tmax	0.981,0.991	0.951,0.960
Tmin'	0.981	

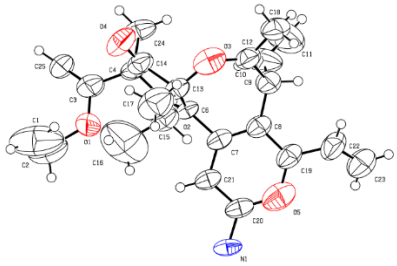
Correction method= # Reported T Limits: Tmin=0.951 Tmax=0.960
AbsCorr = MULTI-SCAN

Data completeness= 0.988 Theta(max)= 29.664

R(reflections)= 0.0514(5698) wR2(reflections)= 0.1312(6773)

S = 1.066 Npar= 336

G.7. Crystal Structure Data for **6.08a** *(Preliminary Data)* [JLW32]



Note: Preliminary X-ray data obtained, data unrefined.

Bond precision: C-C = 0.0081 A Wavelength=0.71073

Cell: a=12.7082(5) b=10.5988(4) c=16.9359(6)
alpha=90 beta=91.399(1) gamma=90

Temperature: 150 K

	Calculated	Reported
Volume	2280.45(15)	2280.44(15)
Space group	P 21/n	P 21/n
Hall group	-P 2yn	-P 2yn
Moiety formula	C25 H25 N O5	C25 H25 N O5
Sum formula	C25 H25 N O5	C25 H25 N O5
Mr	419.46	419.46
Dx,g cm-3	1.222	1.222
Z	4	4
Mu (mm-1)	0.085	0.085
F000	888.0	888.0
F000'	888.45	
h,k,lmax	16,14,22	16,14,22
Nref	5529	5515
Tmin,Tmax	0.983,0.992	
Tmin'	0.968	

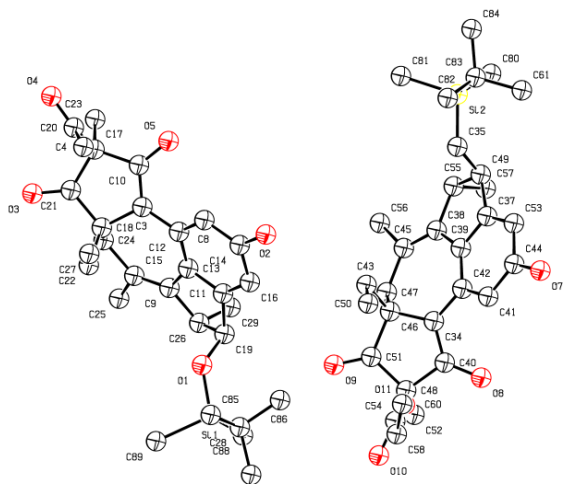
Correction method= Not given

Data completeness= 0.997 Theta(max)= 28.049

R(reflections)= 0.1836(3410) wR2(reflections)= 0.5086(5515)

S = 3.511 Npar= 284

G.8. Crystal Structure Data for **6.64** *(Preliminary Data)* [JLW20]



Note: Preliminary X-ray data obtained, data unrefined.

Bond precision: C-C = 0.0130 A Wavelength=0.71073

Cell: a=8.5339(9) b=16.458(2) c=22.983(3)
alpha=109.196(3) beta=96.949(3) gamma=95.023(3)

Temperature: 296 K

	Calculated	Reported
Volume	2998.1(6)	2998.1(6)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C31 O5 Si, C29 O5 Si	?
Sum formula	C60 O10 Si2	C29 H41 N O6 Si
Mr	936.78	527.72
Dx,g cm-3	1.038	1.169
Z	2	4
Mu (mm-1)	0.109	0.118
F000	936.0	1136.0
F000'	936.82	
h,k,lmax	10,21,29	10,21,29
Nref	13297	13262
Tmin,Tmax	0.978,0.996	
Tmin'	0.931	

Correction method= Not given

Data completeness= 0.997 Theta(max)= 27.172

R(reflections)= 0.1837(5815) wR2(reflections)= 0.4594(13262)

S = 2.248 Npar= 289

APPENDIX H Notebook

Cross-Reference

Table H.1. Notebook cross-reference for chapter 3

Compound	Notebook
3.02	hhd12160, hhd11017, hhd13073, hhd_VI_094, hhd13073, hhd15006, hhd15010, YK491, YK498, YK415
3.06	HHD_I_269, YK_II_372, HHD_III_067, HHD_IV_001
3.08	hhd11017, hhd13073, HHD_VI_094
3.09	HHD_I_194, hhd13063
3.12	HHD_I_219, HHD_I_196
3.16	HHD_VIII_079, hhd12176, hhd09051
3.17	hhd15118, hhd09054
3.23	HHD_VI_094_r4

Table H.2. Notebook cross-reference for chapter 4

Compound	Notebook
4.07	YK448, YK_VIII_048
4.12	hhd13022
4.17	hhd15047, HHD_II_004, HHD_II_035, HHD_II_052
4.18	YK451, YK458, YK_VIII_045, JLW13 (**crystal**)
4.20	HHD_II_017, YK_VIII_098
4.23	YK442, YK440, YK_VIII_047
4.33	HHD_IV_028, HHD_IV_029
4.34	HHD_IV_032, HHD_IV_034, hhd15127

Table H.3. Notebook cross-reference for chapter 5

Compound	Notebook
5.22a	HHD_V_014
5.22b	YK_VIII_034
5.24	hhd10072
5.27	HHD_V_060, HHD_V_149
5.28	HHD_V_060, HHD_V_149
5.33	HHD_V_009, HHD_IV_085
5.34	HHD_V_009, HHD_IV_085
5.36	hhd15140, hhd11037
5.37	hhd15134, HHD_V_063, JLW10 (**crystal**)
5.40	HHD_V_086, HHD_V_095, HHD_V_062
5.41	HHD_V_086, HHD_V_095, HHD_V_062
5.43	hhd11037
5.44	HHD_VIII_044
5.45	HHD_VIII_051
5.46	HHD_VIII_052

Table H.3 Continued

Compound	Notebook
5.47	HHD_V_147
5.48	HHD_V_147
5.50a	hhd15125, HHD_VIII_142
5.51	hhd15126, HHD_VIII_020, HHD_VIII_012
5.52	hhd15128, HHD_VIII_21, JLW27 (**crystal**, **5.52a**)
5.53a	HHD_VIII_033, HHD_V_012
5.53b	YK_VIII_033
5.54	HHD_VIII_042, hhd15077
5.55	HHD_VIII_049
5.56a	hhd10006
5.56b	hhd10013

Table H.4. Notebook cross-reference for chapter 6

Compound	Notebook
6.06	HHD_II_117, YK723, YK728
6.08a	YK_VIII_100, YK_VIII_068, JLW32 (**crystal**)
6.15	YK_VIII_099
6.16	hhd15132, HHD_V_112 (cation-π), YK_VIII_071 (RCM)
6.19	YK-Carreira
6.23	hhd15121
6.24	hhd15135, HHD_V_110
6.27	hhd15102, HHD_II_038
6.28	HHD_II_107
6.30	hhd15107
6.31 / 6.32	hhd15108, JLW77 (**crystal**, **6.32**)
6.33	YK755, YK779
6.35	HHD_IV_046, HHD_IV_048, hhd15139
6.36	HHD_IV_049, hhd15144, JLW8 (**crystal**)
6.39	HHD_IV_013
6.40	HHD_V_124, JLW15 (**crystal**)
6.42	HHD_VI_148, HHD_VI_139
6.43	HHD_II_129, HHD_III_001, HHD_II_128
6.44-acetate	HHD_VI_117
6.44-alcohol	HHD_VI_082, HHD_VI_106
6.44-ether	HHD_III_058
6.45	HHD_III_049, HHD_VII_116, HHD_VII_117, HHD_VII_118, hhd15092
6.46	HHD_II_135, HHD_II_151, YK_IV_727, HHD_VII_056, HHD_VII_057
6.48	HHD_VI_125, HHD_VI_123, JLW18 (**crystal**)
6.56	YK760, YK_VIII_095

6.59	YK_VIII_096, YK705, JLW19 (**crystal**)
6.61	HHD_VII_001

Table H.4 Continued

Compound	Notebook
6.62	HHD_VII_001
6.64	HHD_VII_004, JLW20 (**crystal**)
6.70	HHD_VII_111, HHD_VII_114, HHD_VI_034
6.71	YK805, YK862, YK_VIII_059
6.72	HHD_VII_002
6.73	HHD_VII_003
6.74	HHD_VII_005
6.75	HHD_VII_108, JLW28 (**crystal**)
6.76	hhd15131
6.77	hhd15080

Table H.5. Notebook cross-reference for chapter 7

Compound	Notebook
7.04a	hhd12113, hhd13061, hhd15044
7.04b	hhd12166r6
7.08a	hhd12137, hhd13038, hhd13030, (enantiopure (–)-**7.08a**, hhd14013)
7.08b	hhd12166r7
7.09a	hhd15110, hhd11109
7.10a / 7.17a	hhd15109, hhd11107 (also contains **7.17a**)
7.12a/b	See **3.02**, JLW26 (**crystal**, **7.12b**)
7.13b	hhd12161
7.15a	hhd15114, hhd11005
7.16a	hhd11104, hhd11006
7.33a	hhd13024, hhd13022
7.33b	hhd12166r2
7.34a	hhd13024, hhd13022
7.35a	hhd13024, hhd13022, hhd13027
7.36a	hhd13067, JLW67 (**crystal**)
7.39a	hhd13026, hhd13025
7.39b	hhd12166r3
7.42a	hhd15096, hhd12174
7.42b	hhd12166r8
7.44	hhd12128

Table H.6. Notebook cross-reference for chapter 8

Compound	Notebook
8.03/*ent*-8.03	hhd14013
8.01	Natural Enantiomer: hhd14011. Unnatural Enantiomer: hhd13055, hhd13059
8.02	Natural Enantiomer: hhd14012. Unnatural Enantiomer: hhd13071, hhd15002
8.10	Natural Enantiomer: hhd14006, hhd15007. Unnatural Enantiomer: hhd12164
8.28	hhd12109, hhd12122
8.29	hhd12109, hhd12122
8.30	hhd12140
8.31	hhd15138, hhd12168
8.32	hhd12146, hhd12136
8.35	hhd12118
8.36	Natural Enantiomer: hhd14005, hhd14008
8.37	Using (+)-**8.13**: hhd14005, hhd14008. Using (–)-**8.13**: hhd12159, hhd13033
8.38 (R and S)	hhd15011 (R), hhd15012 (S)
8.39	Natural Enantiomer: hhd14007, hhd15008. Unnatural Enantiomer: hhd12165
8.40	hhd12166r11 (**8.40b**), hhd15097, hhd12019
8.41	hhd15098
8.45	hhd12178, hhd13012, hhd12177
8.49	Natural Enantiomer: hhd14010. Unnatural Enantiomer: hhd13020, hhd15018

RESPECTIVE CONTRIBUTIONS

Chapter One

Summaries of prior published works on the tetrapetalones were attributed to the appropriate publications throughout.

Chapter Two

Dr. Jennifer Howell, Dr. Matthew Haley, Dr. Travis McMahon, and Dr. Jonas Buergler each contributed to the design and execution of the chemistry presented in this chapter. The contributions in this chapter were attributed to the appropriate indivudals throughout.

Chapter Three

Dhanjee, H. H.; Kobayashi, Y.; Buergler, J. F.; McMahon, T. C.; Haley, M. W.; Howell, J. M.; Fujiwara, K.; Wood, J. L. *J. Am. Chem. Soc.* **2017**, *139*, 14901-14904.

Initial preparation of **3.02** was carried out by Dr.'s McMahon and Buergler. Heemal Dhanjee repeated the preparation of tricyclic enone **3.02**. Optimization and exploration of alternative methods for the preparation of tricyclic enone **3.02** were carried out by Heemal Dhanjee. Parts of this chapter were published in the above listed publication.

Chapter Four

Dr. Yutaka Kobayashi and Heemal Dhanjee collaborated on the design and execution of the ideas carried out in Chapter 4. Dr. Kobayashi discovered the utility of Ishihara's conditions for nucleophilic addition that enabled exploration of subsequent Heck and ring-closing metathesis chemistries.

Chapter Five

Dr. Yutaka Kobayashi and Heemal Dhanjee collaborated on the design and execution of the ideas carried out in Chapter 5. Initial investigation into many of these chemistries were first executed by Heemal Dhanjee and later reproduced by Dr. Kobayashi. Heemal Dhanjee focussed efforts on the advancement of the major diastereomer of **5.08** while Dr. Kobayashi focussed his attention on advancement of the minor diastereomer.

Chapter Six

Dr. Kobayashi designed and executed a ring-closing metathesis strategy for the preparation of the last carbocyclic of the aglycone. In addition, Dr. Kobayashi was the first to discover a novel spiro-epoxide forming reaction (Scheme 6.19). Efforts to further investigate this chemistry on alternative substrates were conducted by Heemal Dhanjee. Unless otherwise noted, all other transformations in this chapter were first carried out by Heemal Dhanjee and a subset of these were later reproduced by Dr. Kobayashi.

Chapter Seven

Dhanjee, H. H.; Kobayashi, Y.; Buergler, J. F.; McMahon, T. C.; Haley, M. W.; Howell, J. M.; Fujiwara, K.; Wood, J. L. *J. Am. Chem. Soc.* **2017**, *139*, 14901-14904.

The reactions described in this chapter, that are not otherwise attributed to previous publications, were carried out by Heemal Dhanjee. Parts of this chapter were published in the above listed publication.

Chapter Eight

Dhanjee, H. H.; Kobayashi, Y.; Buergler, J. F.; McMahon, T. C.; Haley, M. W.; Howell, J. M.; Fujiwara, K.; Wood, J. L. *J. Am. Chem. Soc.* **2017**, *139*, 14901-14904.

The reactions described in this chapter, that are not otherwise attributed to previous publications, were carried out by Heemal Dhanjee. Parts of this chapter were published in the above listed publication.

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ABOUT THE AUTHOR

Heemal was born on the West Coast of the United States in mid-November 1984 to Naina and Hansraj Dhanjee. He spent a majority of the first 17 years of his life in Northridge, CA with his parents and older brother before graduating from Van Nuys High School in 2002. That Fall, Heemal ventured north to begin his undergraduate career at the University of California, Berkeley originally aspiring toward a degree in computer science.

As was the case at an early age, he was captivated by problems and games that had seemingly simple rules, yet were extraordinarily complex. He found himself in the middle of his undergraduate career exploring mathematics, and even further found himself in a position to obtain a degree in the field. Through his undertakings in pursuit of things other than a degree, he also found himself also in position to obtain a degree in Molecular and Cell Biology, naturally with an emphasis in Genetics as it tickled his mathematical inclinations. After having graduated in 2007, he went back south to call Los Angeles home while travelling and contemplating his life.

With the intention of pursuing a higher degree in Mathematics, he enrolled at California State University, Northridge. While research opportunities had eluded him during his time at Berkeley, he found himself in the extraordinary position to do research in the field of total synthesis under the guidance of Professor Thomas Minehan. Over the next two years in the Minehan lab, he would explore the field of total synthesis, a game with simple rules yet extraordinarily complex problems. After catching the total synthesis bug, Heemal applied to graduate school with the primary intention of joining the

laboratories of Professor John L. Wood and thus moved to Colorado State University, Fort Collins. After joining the ongoing tetrapetalone project in the Wood laboratory, Heemal moved to Baylor University with the newly appointed Welch Chair of Chemistry, the one and only Professor John L. Wood. During his time in Waco, Heemal enjoyed playing competitive pool for a brief time while he completed the total synthesis of tetrapetalones A and C. Heemal has accepted a joint post-doctoral position in the laboratories of Professor Stephen L. Buchwald and Bradley L. Pentelute at MIT, which will begin in January of 2018.